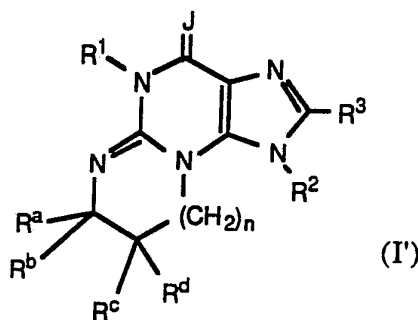
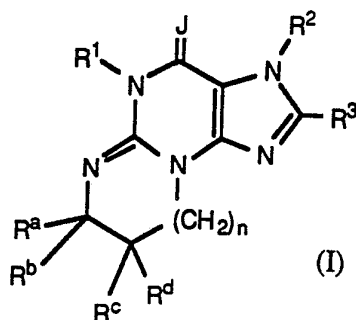




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(54) Title: POLYCYCLIC GUANINE DERIVATIVES



(57) Abstract

Novel polycyclic guanine derivatives of formula (I) and (I'), wherein J is oxygen or sulfur, R¹ is hydrogen, alkyl or alkyl substituted with aryl or hydroxy; R² is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino, or -(CH₂)_mTCOR²⁰ wherein m is an integer from 1 to 6, T is oxygen or -NH- and R²⁰ is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl; R³ is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino; R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7- carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7- carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more of the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and n is zero or one. The compounds of formulas (I) and (I') are useful as antihypertensive, muscle relaxant and bronchodilating agents.

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"POLYCYCLIC GUANINE DERIVATIVES"10 BACKGROUND

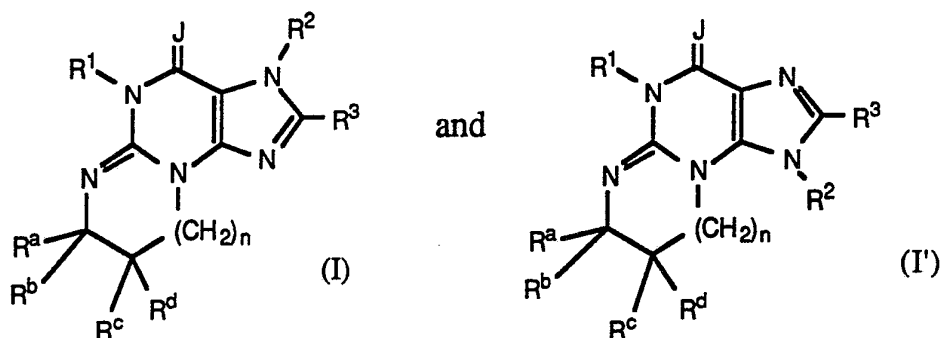
The present invention relates to polycyclic guanine derivatives useful for treating cardiovascular and pulmonary disorders, as well as to their pharmaceutical compositions and methods for using the same.

15

SUMMARY OF THE INVENTION

The present invention is directed to novel polycyclic guanine derivatives of the formula:

20



wherein

J is oxygen or sulfur,

25 R¹ is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

R² is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or $-(CH_2)_mTCOR^{20}$ wherein m is an integer from

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1 to 6, T is oxygen or -NH- and R²⁰ is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;

R³ is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7- carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more of the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and n is zero or one.

Preferred compounds are those of formula (I). Preferably, J is O. Also preferred is that R¹ is alkyl, more preferably methyl. For R², preferred substituents include hydrogen, benzyl, 4-chlorobenzyl, cyclohexylmethyl and trimethylacetoxymethyl. For R³, preferred substituents include hydrogen and alkyl such as methyl or ethyl. Preferably n is zero. Also preferred is that (R^a and R^b) form a saturated 5 membered ring, that (R^b and R^c) form a saturated 5, 6 or 7 membered ring or (R^a and R^b) and (R^b and R^c) each can complete a saturated ring and each ring contains 5 or 6 carbon atoms. When (R^b and R^c) form a saturated 5, 6 or 7 membered ring, generally the preferred stereochemistry is (R) at the carbon atom bearing R^b and the preferred stereochemistry is (S) at the carbon atom bearing R^c.

The compounds of formulas (I) and (I') are useful as antihypertensive, bronchodilating and blood platelet inhibiting agents. Compounds (I) and (I') are also useful in inhibiting phosphodiesterase enzymes. The

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inhibition of vascular phosphodiesterase is believed to induce antihypertensive activity. Compounds (I) and (I') can also serve as smooth muscle relaxants and are therefore useful in the treatment of bronchoconstriction. Such compounds also can inhibit platelet function and are useful in treating conditions benefitting from inhibiting platelet function.

The present invention is also directed toward a pharmaceutical composition containing at least one of compounds (I) and (I') in an amount effective to inhibit phosphodiesterase or relax smooth muscle.

10 The present invention is also directed toward a pharmaceutical composition containing an anti-hypertensive, a bronchodilating or a platelet inhibiting effective amount of the compounds (I) and (I').

The present invention is also directed toward a method for treating hypertension, bronchoconstriction or diseases benefitting from platelet inhibition in a mammal comprising administering to a mammal in need of such treatment an amount of at least one of compounds (I) and (I') effective to treat any of the above diseases. The present invention is also directed toward a method for maintaining guanosine 3':5'-cyclic monophosphate (cGMP) levels in a mammal by administering an amount of compounds (I) and (I') effective to maintain or increase cGMP levels.

DETAILED DESCRIPTION OF THE INVENTION

alkyl - represents a straight chain saturated hydrocarbon moiety having from 1 to 10, preferably from 1 to 6 carbon atoms or a branched hydrocarbon moiety of 3 to 10 carbon atoms, preferably from 3 to 6, such as for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, decyl and the like;

30 alkoxy - represents an alkyl moiety as defined above covalently bonded to an oxygen atom, as for example, methoxy, ethoxy, propoxy, pentyloxy, hexyloxy, decyloxy and the like;

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alkenyl - represents a straight chain hydrocarbon chain hydrocarbon moiety of two to 10 carbon atoms or a branched hydrocarbon moiety of three to 10 carbon atoms having at least one carbon-to-carbon double bond such as ethenyl, 1-propenyl, 1-butenyl, 2-butenyl, isobutenyl, 1-pentenyl, 2-methyl-1-butenyl, 1-hexenyl and the like;

alkynyl - represents a straight chain hydrocarbon moiety of two to 10 carbon atoms or a branched hydrocarbon chain of four to 10 carbon atoms having at least one carbon to carbon triple bond such as for example ethynyl, 1-propynyl, 1-butyne, 1-pentyne, 2-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl and the like;

alkylthio - represents an alkyl moiety as defined above bonded to a sulfur atom;

aryl - represents a carbocyclic moiety containing at least one benzenoid-type ring, with the aryl moiety having from 6 to 14 carbon atoms, with all available substitutable carbon atoms of the aryl moiety being intended as possible points of attachment, for example phenyl, naphthyl, indenyl, indanyl and the like, and wherein said carbocyclic moiety can be optionally substituted with one to three moieties independently selected from the following: halo, alkyl, trifluoromethyl, phenyl, hydroxy, alkoxy, phenoxy, amino, monoalkylamino or dialkylamino;

cycloalkyl - represents a saturated carbocyclic ring containing from 3 to 7 carbon atoms, such as for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like;

halo - represents fluoro, chloro, bromo or iodo;

heteroaryl - represents a cyclic group having at least one O, S and/or N interrupting a carbocyclic ring structure and having a

- 5 -

sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably from 2 to 6 carbon atoms, for example 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 1, 2-, 4- or 5-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3- or 5-[1,2,4-thiadazolyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl and the like;

aminosulfonyl- a sulfonyl moiety bonded to an amino or alkylamino moiety of one to six carbon atoms, e.g. -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂ and the like.;

monoalkylamino - an amino moiety in which one of the hydrogens has been substituted with an alkyl moiety as defined hereinbefore;

dialkylamino - an amino moiety in which each of the hydrogens has been substituted independently with an alkyl moiety;

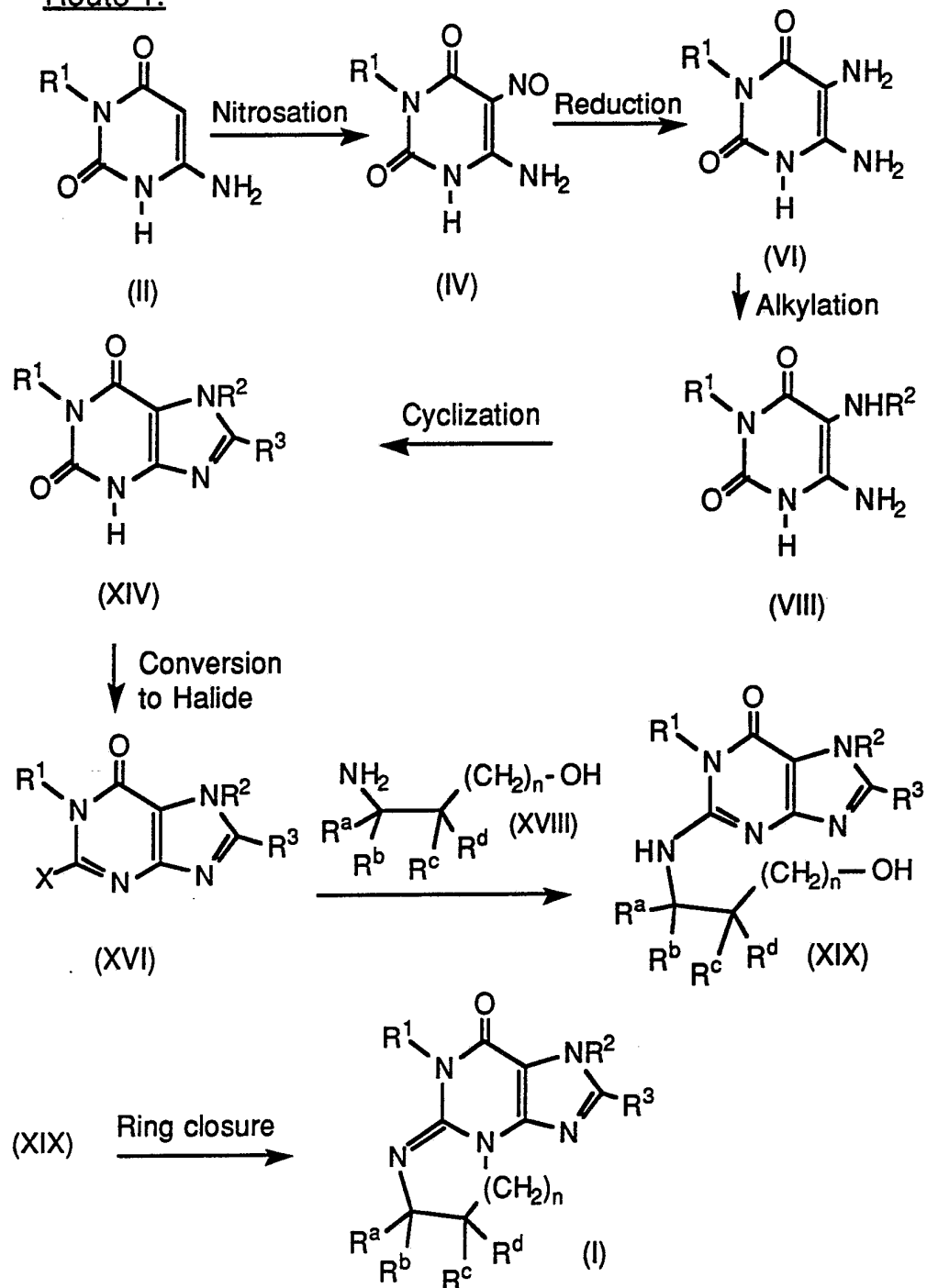
Certain compounds of the invention e.g., those with a basic nitrogen containing moiety, can also form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner.

Certain compounds of the invention will be acidic in nature, e.g., those compounds which possess a carboxy or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkylamines, hydroxyalkylamines, N-methylglucamine and the like.

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The compounds of the present invention can be prepared by several preparative routes as described hereinafter. Variations of these routes can be employed, as well as other routes known to those skilled in the art such as those described in the various references cited
5 throughout the specification, whose preparative teachings are incorporated herein by reference.

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Route 1.

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In Route 1, the compounds of formula (IV) can be prepared by contacting compound (II) with a nitrosating agent such as nitrous acid, as described in Arnold Weissberger (ed.), The Chemistry of
5 Heterocyclic Compounds, A Series of Monographs, The Pyrimidines, Interscience Publishers, John Wiley & Sons, New York (1962), whose preparative teachings are incorporated herein by reference.

The compounds of formula (VI) can be prepared by contacting compound (IV) with a reducing agent such as hydrogen with
10 a catalyst, a metal with an acid, or a sulfur containing reducing agent such as sodium dithionite, as described in Weissberger, supra.

The compounds of formula (VIII) can be prepared by reductive alkylation of compounds (VI) entailing contacting compound (VI) with a carbonyl compound and reducing the intermediate thus
15 obtained by catalytic hydrogenation as described hereinbefore or by reduction with a hydride reducing agent such as sodium cyanoborohydride, as described in Mary Fieser and Louis Fieser, Reagents for Organic Synthesis, Vol. 1-13, John Wiley & Sons, New York (1979-88), whose preparative teachings are incorporated herein by
20 reference.

The compounds of formula (XIV) can be prepared by cyclizing the adduct prepared from compound (VIII) with a carboxylic acid derivative such as an orthoester of the formula $R_3C(OCH_3)_3$ as taught in Weissberger, The Chemistry of Heterocyclic Compounds, A
25 Series of Monographs, The Fused Pyrimidines, Vol. 2, Purines, Interscience Publishers, John Wiley & Sons, New York (1967).

The compounds of formula (XVI) wherein X is Cl or Br can be prepared by converting compounds (XIV) to their halide form with a halide forming reagent such as phosphorus oxychloride ($POCl_3$) as
30 taught in Weissberger, The Fused Pyrimidines, supra.

The compounds of formula (XIX) can be prepared by amination of compounds (XVI) with aminoalcohol (XVIII) optionally in the presence of a suitable acid acceptor such as triethylamine, according to known or analogous procedures such as taught in Weissberger, The

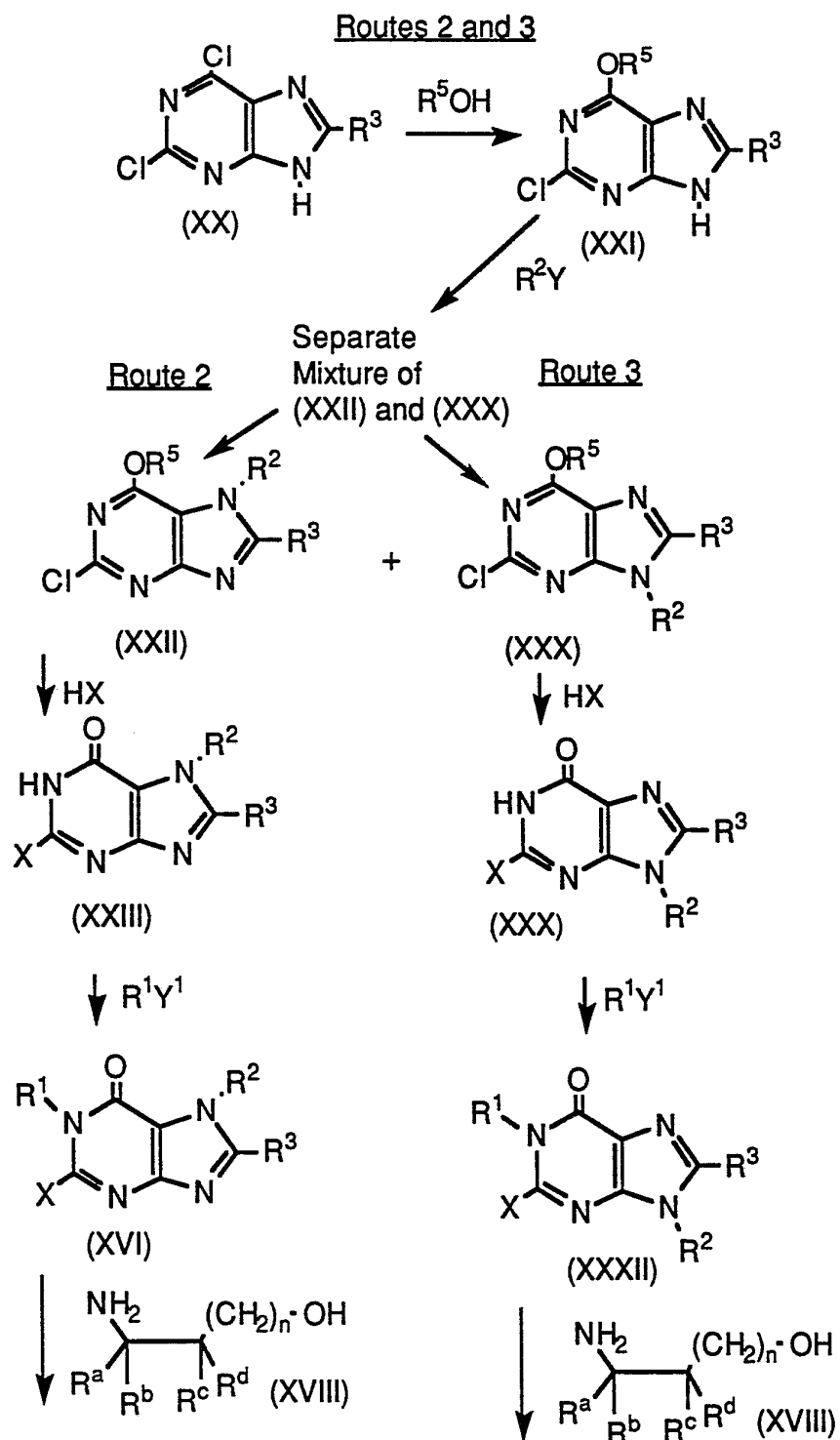
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Fused Pyrimidines, supra. A particularly useful method employs excess diisopropylethylamine in a solvent such as N-methylpyrrolidinone at elevated temperatures of 100 to 150°C.

5 The desired compounds of formula (I) can be prepared by ring closure of compound (XIX) with a suitable dehydrating agent such as thionyl chloride or triphenylphosphine dibromide according to known or analogous procedures as taught in Fieser and Fieser, supra.

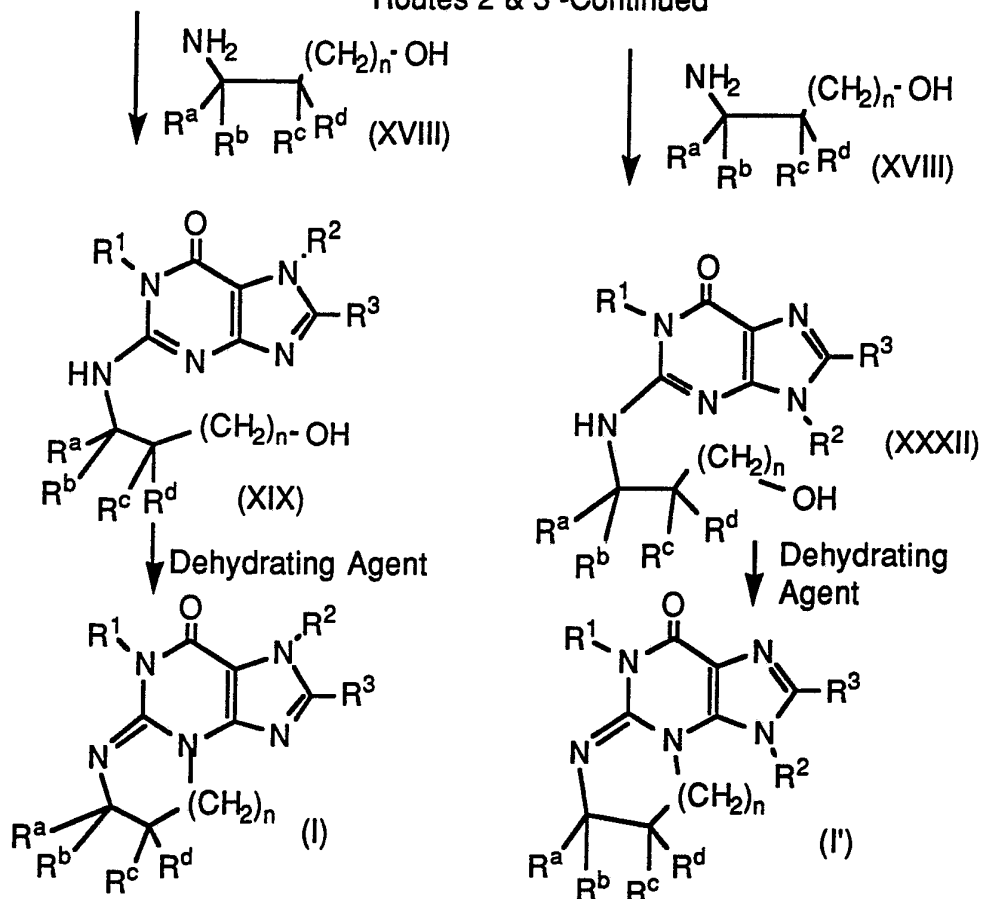
10 The compounds of formula (I) and (I') wherein R¹ or R² is benzyl or substituted benzyl can be converted to the corresponding intermediate compounds (I) and (I') wherein R¹ or R² is hydrogen by hydrogenolysis, as for example, with hydrogen and palladium catalyst. The corresponding intermediate compounds (I) and (I') wherein R¹ or R² is hydrogen can then be converted to compounds (I) and (I') wherein R¹ or R² represents the non-hydrogen substituents for R¹ and R², with an
15 alkylating agent R¹Y or R²Y, wherein Y is a leaving group, e.g., halo or sulfonate such as mesylate or triflate, in the presence of a suitable base.

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Routes 2 & 3 -Continued

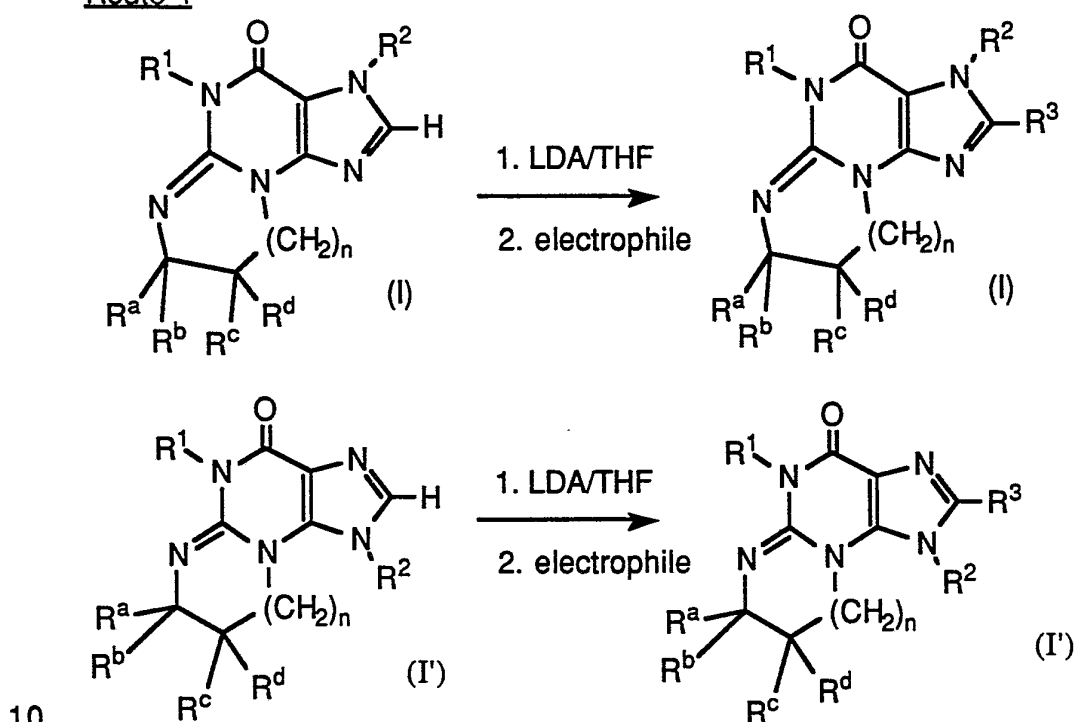


- In Routes 2 and 3, compound (XXI) can be prepared by contacting the 2,6-dichloropurine compound (XX) with a benzylic alcohol of the formula R^5OH , wherein R^5 represents benzyl or substituted benzyl, in the presence of a suitable base such as sodium hydride (NaH) in a solvent such as DMF or THF. Compound (XXI) is contacted with a compound of the formula R^2Y wherein R^2 and Y are as defined hereinbefore in the presence of a base such as potassium carbonate (K_2CO_3) and a solvent such as dimethylformamide (DMF) to give a mixture containing monochlorinated purines (XXII) and (XXX). These compounds are then separated by conventional procedures, such as chromatography or crystallization.

- In Route 2, compound (XXII) can be contacted with an acid such as HX wherein X is chloro or bromo in an organic acid such as acetic acid to give the compound (XXIII). Compound (XXIII) can then be

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- contacted with a compound of formula R^1Y^1 wherein R^1 is defined hereinbefore and Y^1 is a leaving group representing any of the values for Y , in the presence of a base such as lithium hydroxide in dimethylformamide, as described in D. Ranganathan and F. Farooqui, Tet. Lett. 25, 5701 (1984) to give compound (XVI). Compound (XVI) can be converted to the desired compound (I) as described in Route 1. Similarly, in Route 3, desired compounds (I') can be prepared according to the procedures as described in Routes 1 and 2.

Route 4

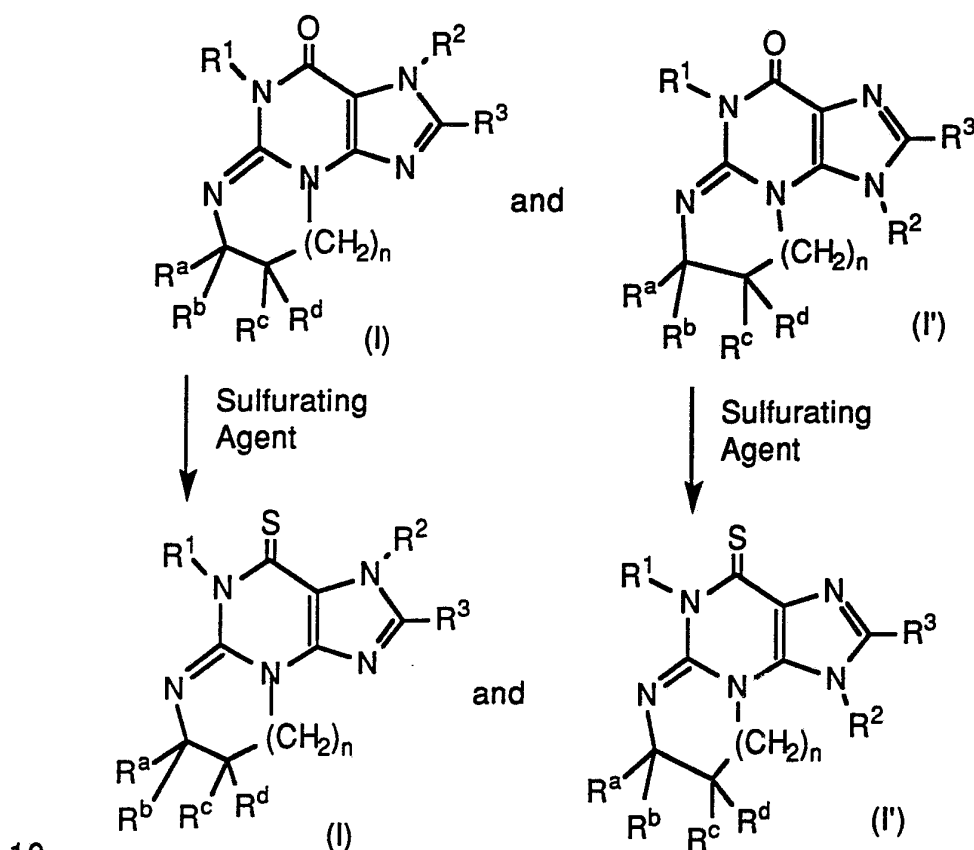
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- In Route 4, the compounds of formula (I) or (I') wherein R^3 is alkyl, halo, alkylthio, carboxy or alkoxy carbonyl, can be prepared by, in step 1, contacting compound (I) or (I') wherein R^3 is hydrogen, with a base such as lithium diisopropylamide (LDA) in a suitable solvent such as THF. In step 2, the adduct from step 1 is treated with a corresponding electrophile giving R^3 , such as halogen, e.g. Br_2 giving $R^3=Br$, a disulfide, e.g. CH_3SSCH_3 giving $R^3=CH_3S$, carbon dioxide (CO_2) giving $R^3=COOH$, methyl iodide (CH_3I) giving $R^3=CH_3$, and the like. See H. Hayakawa, K. Haraguchi, H. Tanaka and T. Miyasaka, Chem. Pharm.

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Bull., 35(1), pp. 72-79 (1987) for analogous procedures. The compounds of formula (I) wherein R^3 is amino, monoalkylamino, dialkylamino, alkylthio or alkoxy can be prepared by contacting a compound of formula (I) wherein R^3 is halogen with an amine, alkyl mercaptide or alkoxide to form the corresponding amino, alkylthio or alkoxy compound (I) as taught in Weissberger, The Fused Pyrimidines, supra.

Route 5.

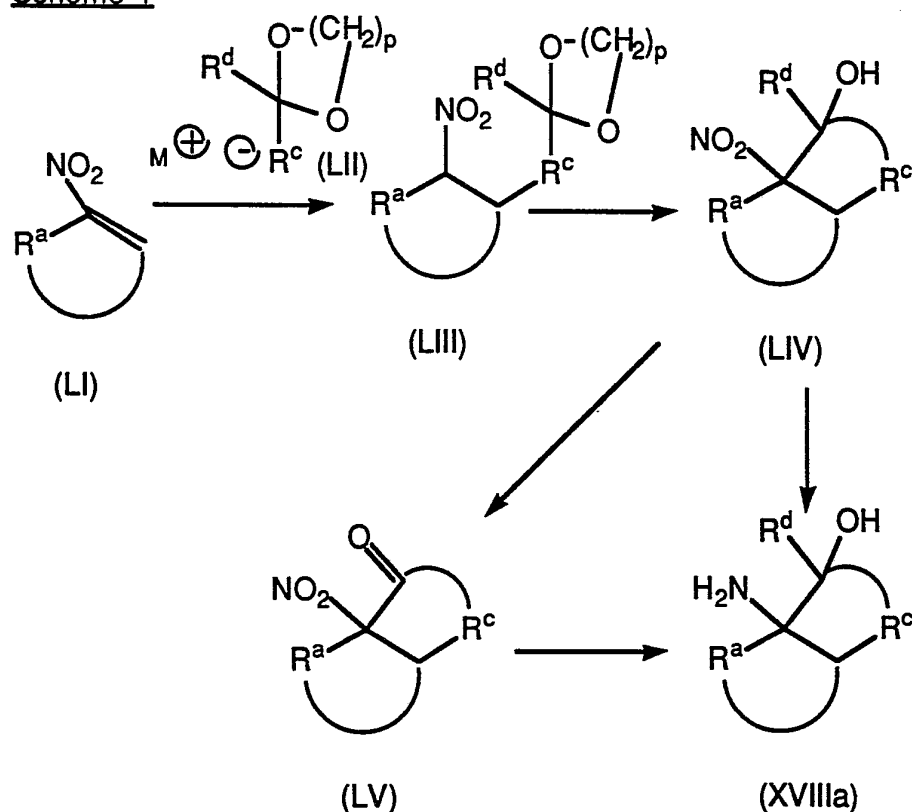
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In Route 5, the sulfur containing compounds (II), and (II') wherein $J=S$, can be prepared by contacting the oxygen containing compounds (I) and (I') wherein $J=O$, with a sulfurating agent such as phosphorus pentasulfide (P_2S_5), or Lawesson's reagent, as taught in J. March, Advanced Organic Chemistry, Reactions, Mechanisms and

15

Structure, 3rd Edition, John Wiley & Sons, New York, (1985), pp. 793-795, whose preparative teachings are incorporated herein by reference.

5 Scheme 1



Aminoalcohols (XVIII) are known or may be prepared by known methods, such as taught in Rodd's Chemistry of Carbon Compounds, 2nd Edition, Vol. 1, Part D., pp 34-37, whose preparative teachings are incorporated herein by reference.

Compounds (XVIIIa) represent the case where (R^a and R^b) and (R^b and R^c) each complete a saturated ring, R^b is CH , and n is 0. These may be prepared according to Scheme 1, where p is 2 or 3, and R^a , R^c , and R^d are as defined hereinbefore. Compound (LIII) can be prepared by treating compound (LI) with an organometallic reagent (LII), ie. grignard reagent or a zinc copper reagent as described in E.J. Corey et al., Journal of American Chemical Society, 1978 page 6294 or

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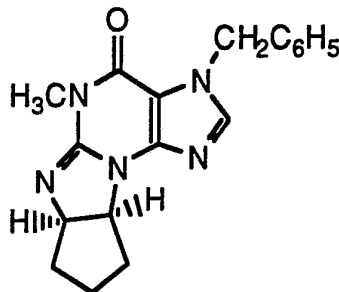
P. Knochel et al., Journal of Organic Chemistry, 1989, pg. 5200, whose preparative teachings are incorporated herein by reference.

Compound (LIV) can be prepared by treating compound (LIII) with a protic acid in alcohol, e.g. toluenesulfonic acid or hydrochloric acid in methanol, at refluxing temperatures, followed by treatment with an aqueous solution of a protic acid in a solvent such as hydrochloric acid in THF. Subsequent treatment with a base, e.g. potassium carbonate in an alcoholic solvent such as methanol, gives compound (LIV).

Compound (XVIIIa) can be prepared by treating compound (LIV) with a reducing agent, e.g. by hydrogenation with Raney nickel or reduction with sodium borohydride in an alcohol solvent, e.g. methanol. Alternatively, when R^d is H, compound (XVIIIa) can be prepared by treating compound (LIV) with an oxidizing agent such as pyridinium chlorochromate (PCC) to give ketone (LV), followed by reduction with a reducing agent such as borohydride in an alcoholic solvent, followed by hydrogenation with a suitable catalyst, eg. Raney nickel, to give the desired compound (XVIIIa).

The following examples are presented to illustrate typical compounds of the present invention, but the scope of the invention is not to be considered limited to such examples.

Example 1: cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4-one



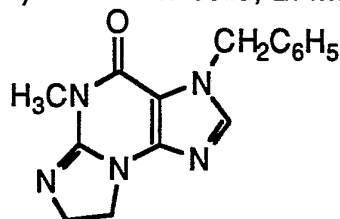
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Add 3.2 g SOCl₂ (27 mmol) to a solution of 2-(trans-2-hydroxycyclopentylamino)-1-methyl-7-(phenylmethyl)purin-6-one (3.0g=8.8mmol) in 150 ml CH₂Cl₂. Stir the solution overnight, wash with cold 2 N NaOH, dry, and solvent strip. Chromatograph the residue

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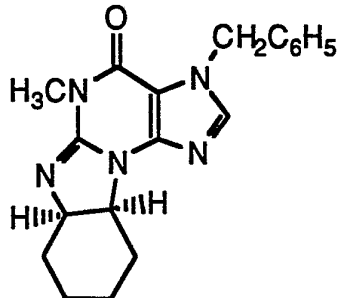
on silica (98:2 CH₂Cl₂/CH₃OH) to give the title compound as a foamed solid. FAB MS: M+1=322.

- Example 2:** 7,8-Dihydro-5-methyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: white solid, EI MS: M+=281.



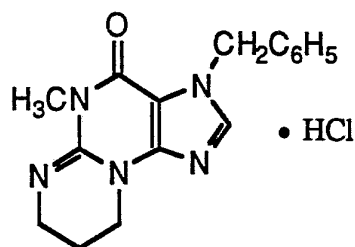
By using 2-(2-hydroxyethylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

- Example 3:** cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b] purin-4(5H)-one: white foam, EI MS: M+=335



- By using 2-(trans-2-hydroxycyclohexylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

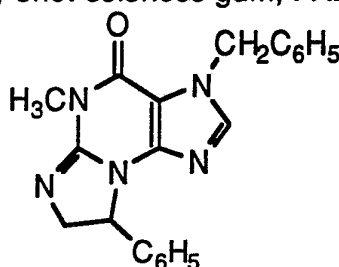
- Example 4:** 5,7,8,9-Tetrahydro-5-methyl-3-(phenylmethyl)pyrimido[2,1-b]purin-4(3H)-one, hydrochloride: white solid, FAB MS: M-HCl=295



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By using 2-(3-hydroxypropylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

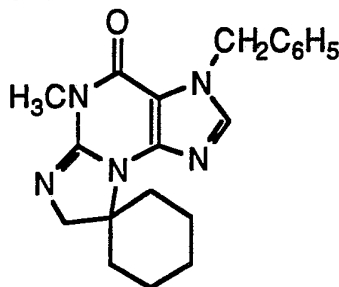
Example 5: 7,8-Dihydro-8-phenyl-5-methyl-3-(phenylmethyl)-
5 3*H*-imidazo[2,1-*b*]purin-4(5*H*)-one: colorless gum, FAB MS: $M+1=358$.



By using 2-(2-hydroxy-2-phenylethylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

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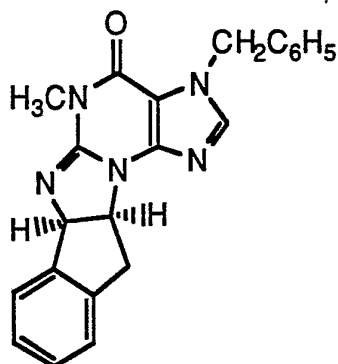
Example 6: 5',7'-Dihydro-5'-methyl-3'-
(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-imidazo[2,1-*b*]purin]-4'(3'*H*)-
one: white solid, CI MS: $M+1=350$.



15 By using 2-(1-(hydroxycyclohexyl)methylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

20 **Example 7:** cis-5,6a,11,11a-Tetrahydro-5-methyl-3-
(phenylmethyl)indeno[1',2':4,5]imidazo[2,1-*b*]purin-4(3*H*)-one: foamed
solid, CI MS: $M+1=374$.

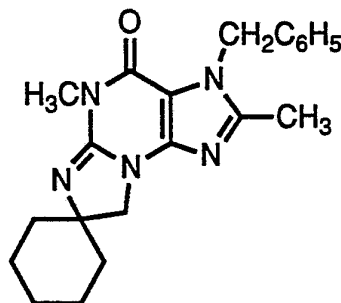
- 18 -



By using 2-(2-hydroxy-1-indanylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

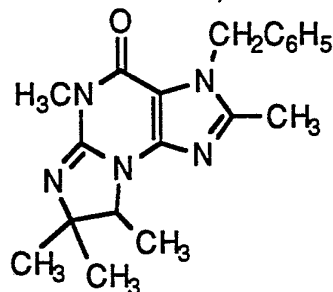
By use of the appropriate amino-alcohol in accordance with
 5 Example 1, the following compounds are obtained:

7A8 5',7'-Dihydro-2',5' dimethyl-3'-(phenylmethyl)spiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one: off-white solid, EI MS: $M^+ = 363$.



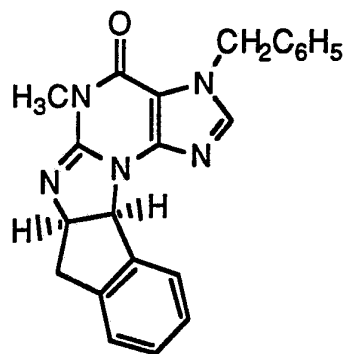
10

7A9 7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one: white solid, EI MS: $M^+ = 247$.



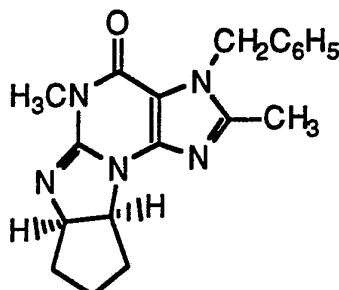
15

Example 8: cis-5,6a,7,11b-Tetrahydro-5-methyl-3-(phenylmethyl)indeno[2',1':4,5]imidazo[2,1-b]purin-4(3*H*)-one: white solid, CI MS: M+1=370.



- 5 By using 2-(1-hydroxy-2-indanylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

Example 9: cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4-(3*H*)-one: off-white solid, CI MS: M+1=336.

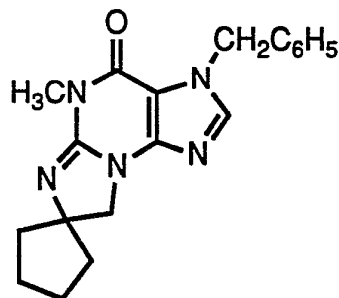


By using 2-(trans-2-hydroxycyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

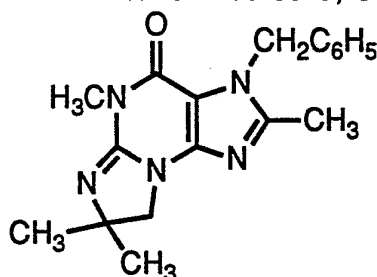
- 15 By use of the appropriate amino-alcohol in accordance with Example 1, the following compounds are obtained:

9A3 5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'*H*)-(3'*H*)-imidazo[2,1-b]purin]-4'(5'*H*)-one: off-white solid, CI MS: M+1=336.

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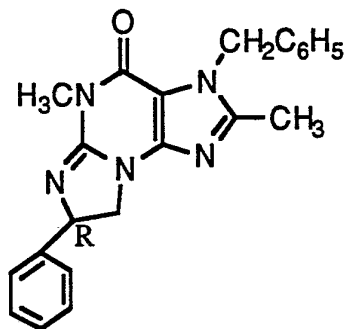


9A4. 7,8-Dihydro-2,5,7,7-tetramethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: white foamed solid, CI MS: $M+1=324$.



5

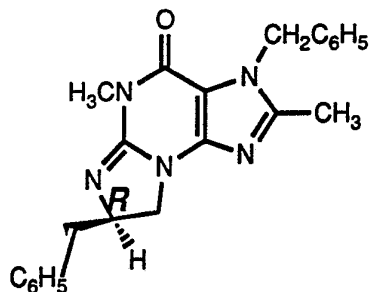
9A5 7,8-Dihydro-7(R)-phenyl-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: off-white solid, CI MS: $M+1=372$. $[\alpha]_D^{26} = +44.4^\circ$.



10

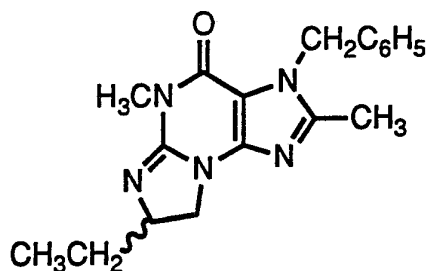
9A6 7,8-Dihydro-2,5-dimethyl-3,7(R)-bis(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: tan solid, EI MS: $M+=385$. $[\alpha]_D^{23.5} = +11.6^\circ$.

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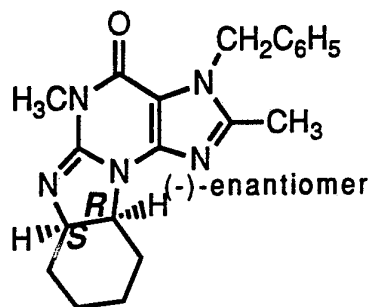
9A7 (±)-7,8-Dihydro-2,5-dimethyl-7-ethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: tan solid, CI MS:

5 M+1=324.



9A8 6a(S)-7,8,9,10,10a(R)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one: tan foam, CI

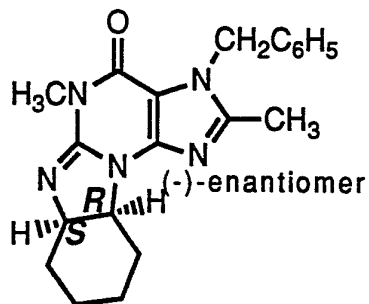
10 MS: M+1=350, $[\alpha]_D^{26} = -79.1^\circ$.



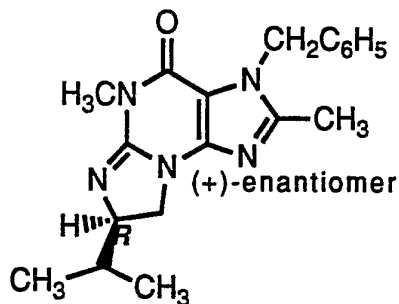
9A9 6a(R)-7,8,9,10,10a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one: off-white

15 foamed solid, CI MS: M+1=350, $[\alpha]_D^{26} = +83.0^\circ$.

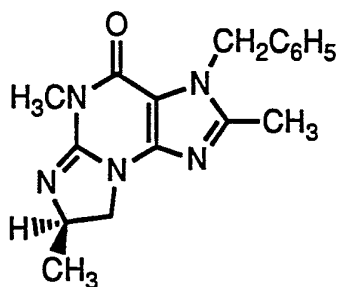
- 22 -



- 9A10 7,8-Dihydro-2,5-dimethyl-7(R)-isopropyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: tan solid, CI MS:
 5 M+1=338, $[\alpha]_D^{26} = +64.8^\circ$.

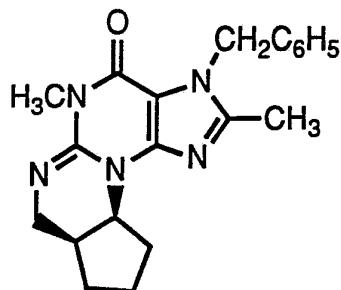


- 9A11 7,8-Dihydro-2,5,7(R)-trimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: white solid, CI MS: M+1=310, $[\alpha]_D^{26} = +79.4^\circ$.
 10

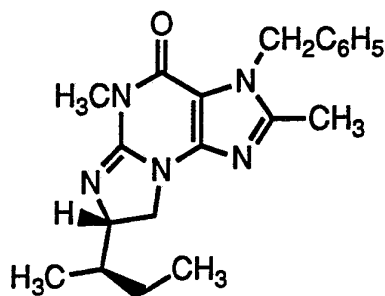


- 9A12 cis-7,7a,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-cyclopenta[5,6]pyrimido[2,1-b]purin-4(5H)-one: tan
 15 foamed solid, CI MS: M+1=350.

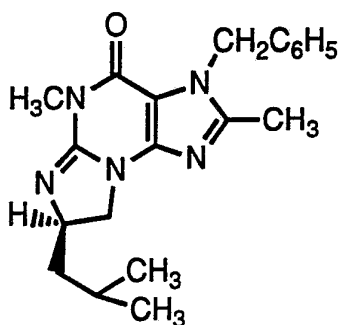
- 23 -



- 9A13 7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: crystalline solid, FAB
 5 MS: $M+1=352$, $[\alpha]_D^{24} = -60.8^\circ$.

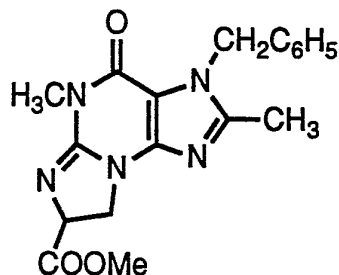


- 9A14 7,8-Dihydro-2,5-dimethyl-7(R)-(2-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: clear gum, CI MS:
 10 $M+1=352$., $[\alpha]_D^{24} = +73.1^\circ$.

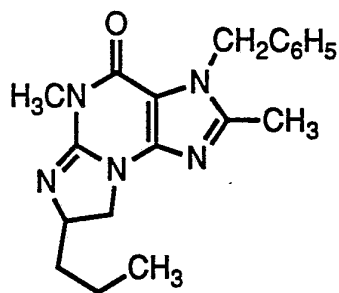


- 9A15 7,8-Dihydro-2,5-dimethyl-7(R,S)-(methoxycarbonyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: tan foam, FAB MS:
 15 $M+1=354$.

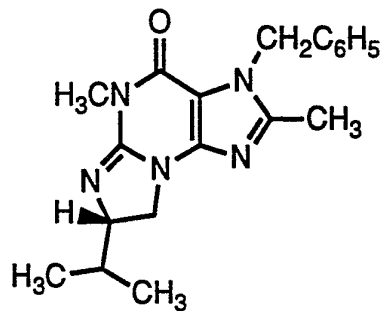
- 24 -



- 9A16 7,8-Dihydro-2,5-dimethyl-7(R,S)-(1-propyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: tan solid, CI MS:
5 M+1=338.

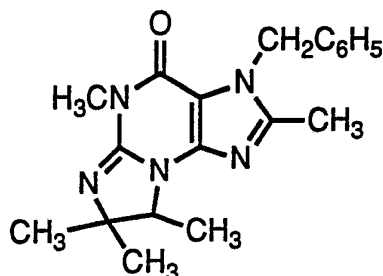


- 9A17 7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: white foamed solid,
10 CI MS: M+1=338, $[\alpha]_D^{23.5} = -65.6^\circ$.

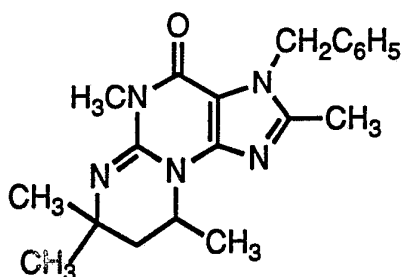


- 9A18 7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: off-white solid, EI
15 MS: M+=337.

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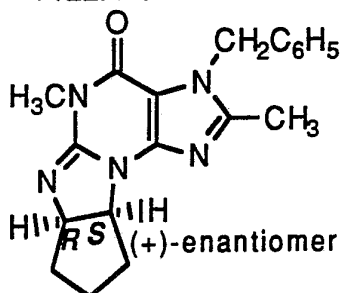


9A19: 5,7,8,9-Tetrahydro-2,5,7,9(R,S)-pentamethyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one: white solid, EI MS: $M^+=351$.



5

Example 10: 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: white solid, CI MS: $M+1=336$, $[\alpha]_D^{26} = +122.4^\circ$.

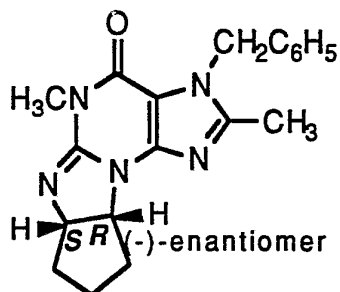


10

By using 2-(2(R)-hydroxy-1(R)-cyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

15 Example 11: 5,6a(S),7,8,9,9a(R)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: white solid, CI MS: $M+1=336$, $[\alpha]_D^{26} = -122.4^\circ$.

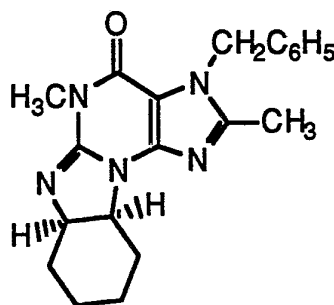
- 26 -



By using 2-(2(*S*)-hydroxy-1(*S*)-cyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

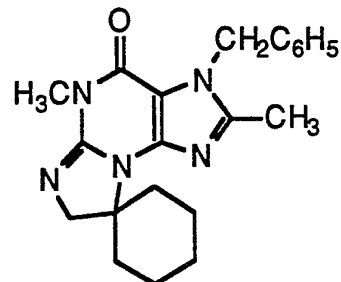
5

Example 12: cis-6a,7,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-*b*]purin-4(5*H*)-one: white solid, CI MS: $M+1=350$.



10 By using 2-(trans-2-hydroxycyclohexylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

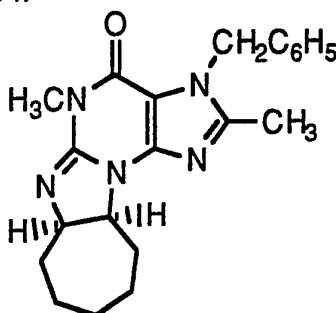
Example 13: 5',7'-Dihydro-2',5'-dimethyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-imidazo[2,1-*b*]purin]-4'(3'*H*)-one: tan foamed solid, CI MS: $M+1=364$.



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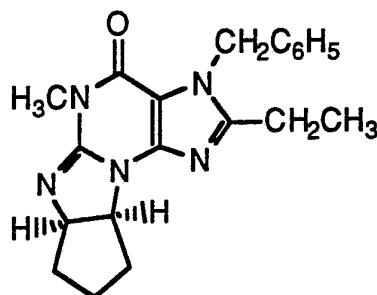
By using 2-(1-(hydroxycyclohexyl)methylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

- 5 **Example 14:** cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclohept[6,7]imidazo[2,1-b]purin-4(3*H*)-one: pale yellow foam, FAB MS: $M+1=364$.



- 10 By using 2-(trans-2-hydroxycycloheptylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

- Example 15:** cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one: tan solid, EI
15 MS: $M+=349$.

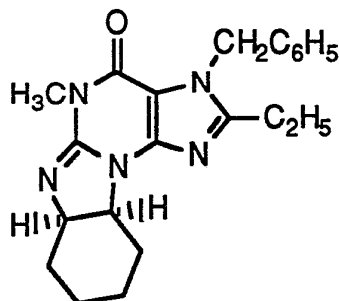


By using 2-(trans-2-hydroxycyclopentylamino)-8-ethyl-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

20

- Example 16:** cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)-one: pale yellow solid, CI MS: $M+1=364$.

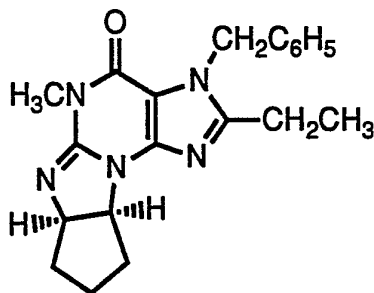
- 28 -



By using 2-(trans-2-hydroxycyclohexylamino)-8-ethyl-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

- 5 By using the appropriate amino-alcohol in accordance with Example 1, the following compounds are obtained:

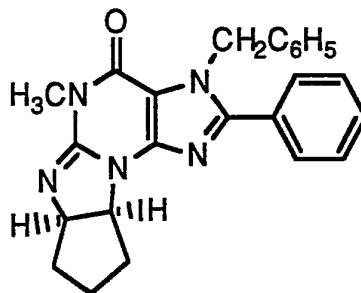
16A1 cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: tan solid, EI MS: $M^+ = 349$.



10

Example 17: cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: white solid, FAB MS: $M^+ = 398$.

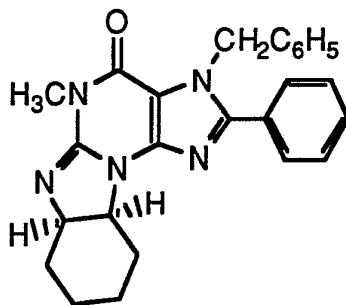
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By using 2-(trans-2-hydroxycyclopentylamino)-1-methyl-8-phenyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

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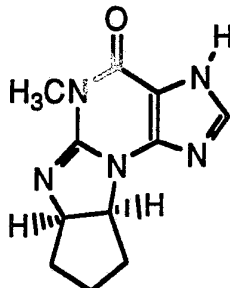
Example 17a cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-*b*]purin-4(5*H*)-one
FAB MS: $M+1=412$.



5

By using 2-(trans-2-hydroxycyclohexylamino)-1-methyl-8-phenyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound, a white foam, is obtained.

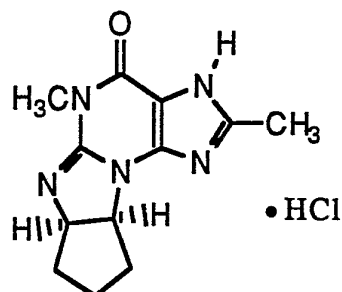
10 Example 18: cis-5,6a,7,8,9,9a-Hexahydro-5-methylcyclopenta[4,5]-imidazo[2,1-*b*]purin-4(3*H*)-one.



Hydrogenate cis-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-*b*]purin-4-one
15 (0.3g=0.93mmol) at room temperature/60psi in EtOH (125ml) containing 0.4g Pearlman catalyst. Filter catalyst, remove solvent, and recrystallize to give the title compound as a white solid. FAB MS: $M+1=232$.

Example 19: cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopenta[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one, hydrochloride:
20 white solid, EI MS: $M-HCl=245$.

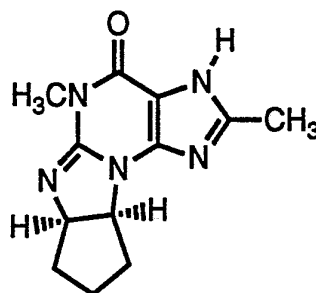
- 30 -



By using cis-5,6a,7,8,9,9a-hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one in accordance with Example 18, the title compound is obtained.

5

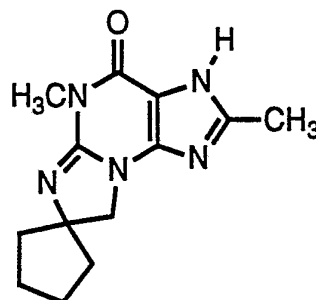
Example 19a. cis-5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-di-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: white solid, CI MS: $M+1=246$, $[\alpha]_D^{23.5} = +153.4^\circ$.



10 By hydrogenating 5,6a(R),7,8,9,9a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one from Example 10 in accordance with Example 18, the title compound is obtained.

15 By hydrogenating the corresponding benzyl derivative, the following compounds are obtained in accordance with Example 18.

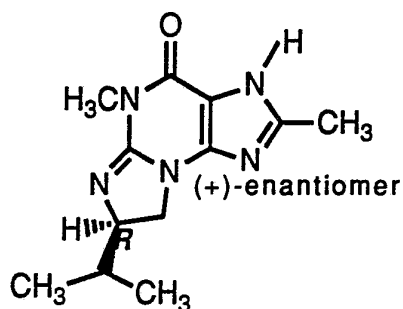
19b 2'-Methyl-3'-spiro{cyclopentane-1,7'(8'H)}-(3'H)-imidazo [2,1-b]purin}-4'(5'H)-one: white solid, CI MS: $M+1=260$.



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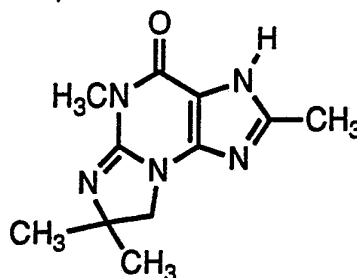
19c 7,8-Dihydro-2,5-dimethyl-7(R)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: off-white solid, CI MS: $M+1=248$. $[\alpha]_D^{26} = +84.4^\circ$.

5



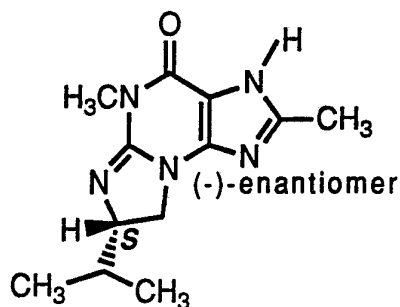
19d 7,8-Dihydro-2,5,7,7-tetramethyl-3H-imidazo[2,1-b]purin-4(5H)-one: white solid, CI MS: $M+1=234$.

10



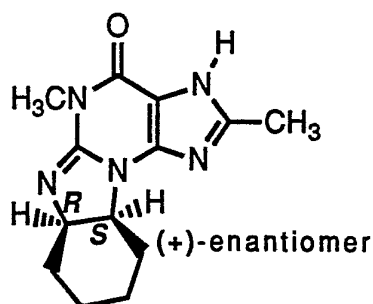
19e 7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: pale yellow solid, CI MS: $M+1=248$. $[\alpha]_D^{23} = -88.4^\circ$.

15

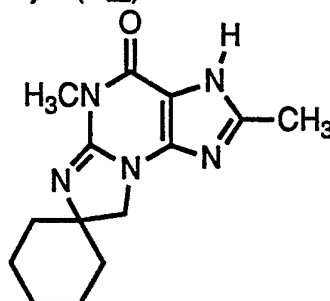


19f 6a(R),7,8,9,10,10a(S)-Hexahydro-2,5-dimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one: off-white solid, CI MS: $M+1=260$. $[\alpha]_D^{22} = +116.3^\circ$.

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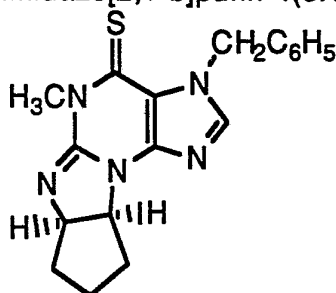


19g 5',7'-Dihydro-2',5'-dimethylspiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one: white solid, CI MS: $M+1=274$.



5

Example 20: cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-thione.

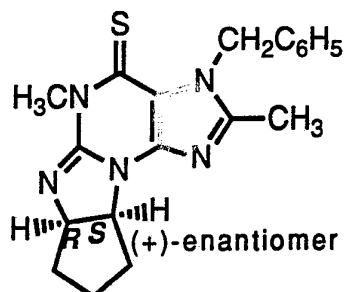


10 Treat cis-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-one (0.16g=0.5mmol) with Lawesson's reagent (0.2g=0.5mmol) in xylene overnight. Remove solvent and chromatograph on silica, eluting with 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give the title compound as a yellow foam. FAB MS: $M+1=338$.

15

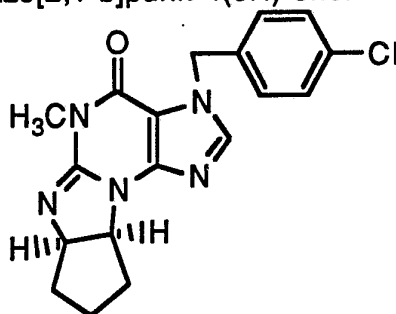
Example 20a: 5,6a(R),7,8,9,9a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-thione FAB MS: $M+=352$.

- 33 -



By treating 5,6a(*R*),7,8,9,9a(*S*)-hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one in accordance with Example 20, the title compound is obtained.

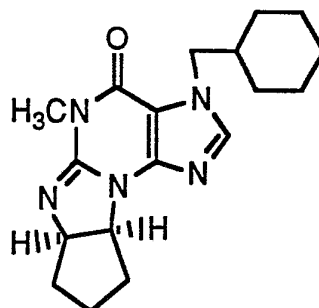
Example 21: *cis*-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(4-chlorophenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-one.



10 Add a solution of *cis*-5,6a,7,8,9,9a-hexahydro-5-methylcyclopenta[4,5]-imidazo[2,1-b]purin-4-one (0.5g=2.2mmol) in DMF drop-wise to a slurry of 60% NaH (0.1g=2.4mmol) in DMF at 30°C. When gas evolution ceases, add 4-chlorobenzyl chloride (0.5g=2.4mmol) in 2 ml DMF. Heat at 50°C. two hours. Remove DMF and partition between EtOAc and
15 water. Dry, solvent strip, and recrystallize from CH₃CN to give the title compound, a white solid. CI MS: M⁺=356.

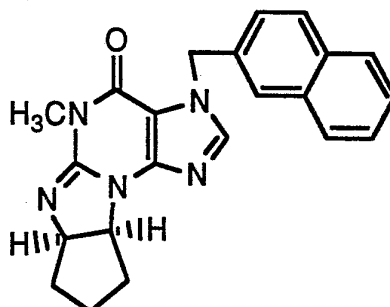
Example 22: *cis*-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one: off-white foam, FAB MS: M+1=328.

- 34 -



By using bromomethylcyclohexane in accordance with Example 21, the title compound is obtained.

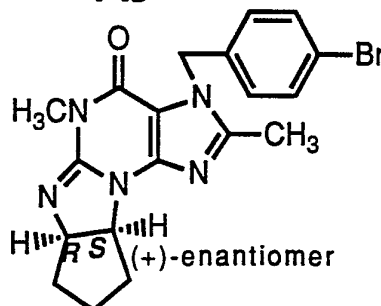
- 5 **Example 23:** cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: white foamed solid, FAB MS: $M+1=372$.



- 10 By using 2-(bromomethyl)naphthalene in accordance with Example 21, the title compound is obtained.

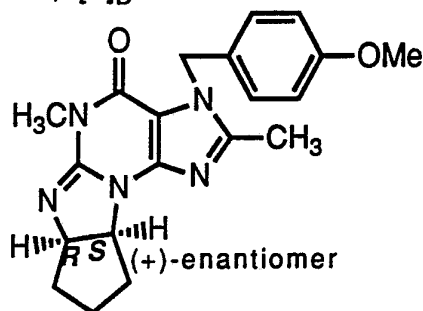
By use of the appropriate alkyl halide in accordance with Examples 21-23, the following compounds are obtained:

- 15 **23A1** 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: yellow crystals, EI MS: $M+=414$, $[\alpha]_D^{26}=+98.6^\circ$.



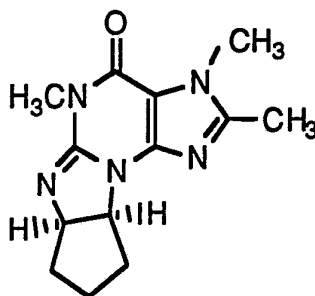
- 35 -

23A2 5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl- 3-(4-methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: yellow solid, CI MS: $M+1=366$, $[\alpha]_D^{26}=+116.7^\circ$.



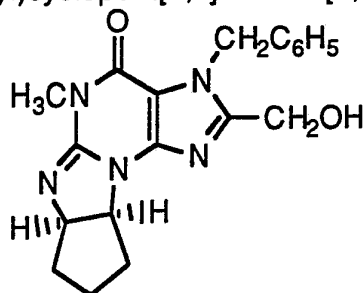
5

Example 24: cis-5,6a,7,8,9,9a-Hexahydro-2,3,5-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: tan solid, FAB MS: $M+1=260$.



- 10 By using cis-5,6a,7,8,9,9a-hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one hydrochloride, and methyl iodide instead of 4-chlorobenzyl chloride in accordance with Example 21, the title compound is obtained.

- 15 Example 25: cis-5,6a,7,8,9,9a-Hexahydro-2-(hydroxymethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one

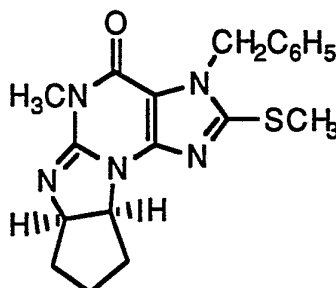


- 36 -

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)-
cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one (0.3gm, 0.93mmol) in THF
(4ml) is added to a solution of LDA (prepared from diisopropylamine
(0.34ml) in THF (2ml) and 2.5 M n-butyllithium (1.0 ml), at -78°C. After 1
5 hr at -78°C, formaldehyde is bubbled into the reaction mixture for 10
min.. The mixture is stirred at -78°C for 30 min., then warmed to room
temperature over 30 min. and acetic acid, brine, and CH₂Cl₂ are added.
The CH₂Cl₂ layer is concentrated in vacuo and purified by flash
chromatography using 5% MeOH in CH₂Cl₂ to give the title compound,
10 a solid, mp 228-229°C.

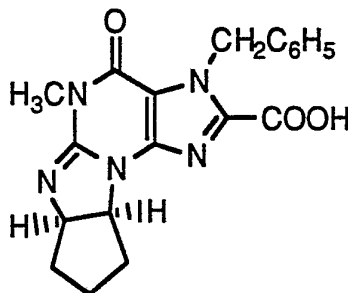
Example 26: cis-5,6a,7,8,9,9a-Hexahydro-2-methylthio-5-methyl-
3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)one
CI MS: M+1=368.

15



By using LDA and 2.5 eq. CH₃SSCH₃ as the electrophile in
accordance with Example 25, the title compound is obtained.

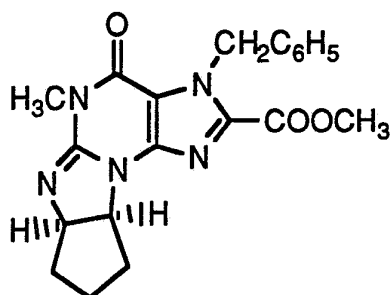
20 Example 27: cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-
(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid,
sodium salt, dihydrate FAB MS:M+1=324.



- 37 -

By using LDA and excess carbon dioxide as the electrophile in accordance with Example 25, the title compound is obtained.

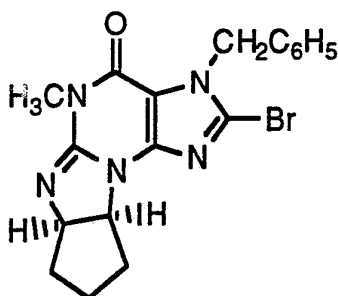
Example 28: cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid, methyl ester, mp 185-186°C.



The title compound of Example 27 is treated with ethereal CH_2N_2 to obtain the title compound.

10

Example 29: cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one
FAB MS: $M+1=402, 400$.



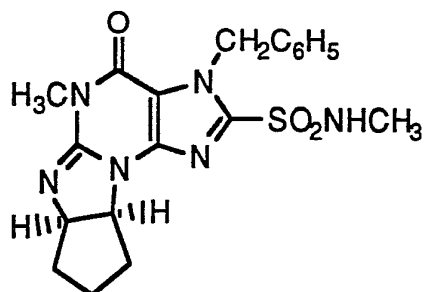
15

By using 2.5 equivalents (eq) LDA and 2.5 bromine as the electrophile in accordance with Example 25, the title compound is obtained.

Example 29a: cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one

20

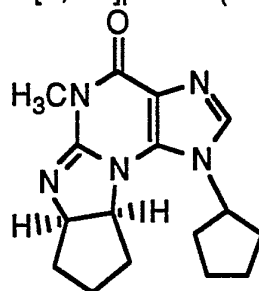
- 38 -



By using LDA, sulfuryl chloride and aqueous methylamine in accordance with Example 25, the title compound is obtained, a solid. EI MS: M=414.

5

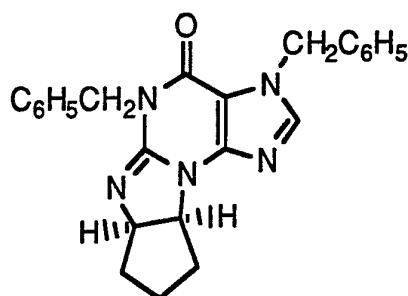
Example 30: cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4(1*H*)one



- 10 A mixture of 2-bromo-1-methyl-9-cyclopentylpurin-6-one and 2-chloro-1-methyl-9-cyclopentylpurin-6-one (1.4 g) is mixed with
(±) trans-2-aminocyclopentanol (1.2g, 11mmol) and triethylamine (1.2ml) in CH₃CN (20ml) and heated to reflux for 12 hr. The resultant mixture is cooled, concentrated in vacuo, and partitioned between
15 EtOAc/THF 1:1 and brine. The organic layers are concentrated in vacuo and the residue is purified by flash chromatography using 6% EtOH in CH₂Cl₂ to give 2-(trans-2-hydroxycyclopentylamino)-1-methyl-9-cyclopentylpurin-6-one, a solid (1.4 gm, MS FAB: M+H=318). The 2-(trans-2-hydroxy cyclopentylamino)-1-methyl-9-cyclopentylpurin-6-one(1.3g, 4.1mm), triphenylphosphine dibromide (prepared from
20 triphenylphosphine (1.2 g) and bromine (0.2ml))in DMF (20 ml) is stirred at room temperature for 18 hr and heated to 70°C for 12hr. Dilute NaOH is added to the cooled reaction mixture to adjust the pH to 10, and the resultant solution is extracted with EtOAc/ THF 1:1. The organic layer is

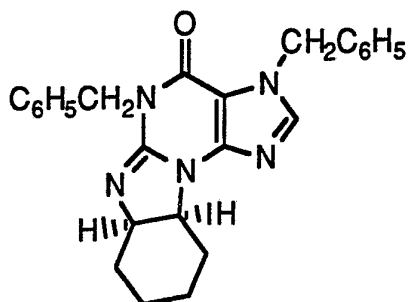
concentrated in vacuo and purified by flash chromatography using 15% EtOH in CH₂Cl₂ and recrystallized from CH₂Cl₂/ hexane, to give the title compound, a solid, mp 194-195°C.

- 5 Example 31:** cis-5,6a,7,8,9,9a-Hexahydro-3,5-bis
(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one



- 10 Cyclize 2-(trans-2-hydroxycyclopentylamino)-1,7-bis(phenylmethyl)purin-6-one in accordance with Example 1 to give the title compound, an off-white foamed solid CI MS: M+1=398.

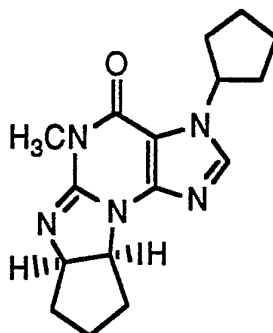
- Example 32:** cis-6a,7,8,9,10,10a-Hexahydro-3,5-bis(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)one



- Cyclize 2-(trans-2-hydroxycyclohexylamino)-1,7-bis(phenylmethyl)purin-6-one in accordance with Example 1 to give the title compound, a tan
20 foam, CI MS: $M + 1 = 412$.

- Example 33:** cis-3-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)one

- 40 -

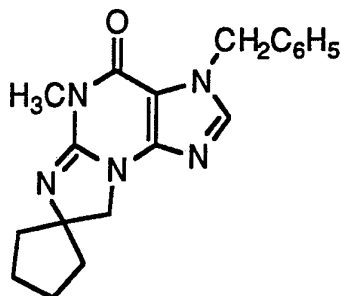


- A mixture of 2-bromo-1-methyl-7-cyclopentylpurin-6-one and 2-chloro-1-methyl-7-cyclopentylpurin-6-one (11.4 g), ($\pm$) trans-2-aminocyclopentanol (1.2g, 11mmol), and triethylamine (1.2ml) in
- 5 CH₃CN (20ml) is heated to reflux for 12 hr. The resultant mixture is cooled, concentrated in vacuo, and partitioned between EtOAc/THF 1:1 and brine. The organic layers are concentrated in vacuo and the residue is purified by flash chromatography using 6% EtOH in CH₂Cl₂ to give
- 10 2-(trans-2-hydroxycyclopentylamino)-1-methyl-7-cyclopentylpurin-6-one, a colorless solid (1.4 gm, MS FAB: M+H=318). A mixture of 2-(trans-2-hydroxycyclopentylamino)-1-methyl-7-cyclopentylpurin-6-one (1.3gm, 4.1mm) and triphenylphosphine dibromide (prepared from triphenylphosphine (1.2g) and 0.2 ml bromine) in DMF (20ml) is stirred at room temperature for 18hr and heated to 70°C for 6hr. Dilute NaOH is
- 15 added to the cooled reaction mixture to adjust the pH to 10, and the resultant solution is extracted with EtOAc/THF (1:1). The organic layer is concentrated in vacuo and purified by flash chromatography using 15% EtOH in CH₂Cl₂ and recrystallized from CH₂Cl₂/ hexane to give the title compound, a solid, mp 133-134°C.

20

Example 34: 5'-Methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'-(8'H)-(3'H)-imidazo[2,1-b]purin]-4'-(5'H)one
EI MS: M+=335

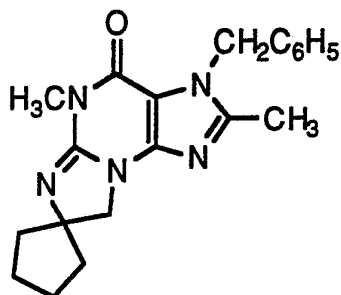
- 41 -



By using 2-(1-hydroxymethylcyclopentylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound, an off-white solid, is obtained.

5

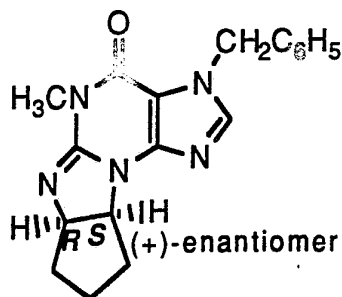
Example 34a: 2', 5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'-(8'*H*)-(3'*H*)-imidazo[2,1-*b*]purin]-4'(5'*H*)one
EI MS: $M^+ = 349$



10

By using 2-(1-hydroxymethylcyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with the procedure of Example 1, the title compound, an off-white solid, is obtained.

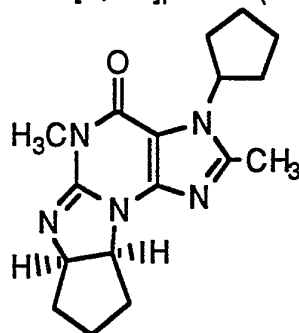
15 **Example 35:** *cis*-5,6a(*R*), 7, 8, 9, 9a(*S*)-Hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one, mp 145-146°C.



- 42 -

By using 2-(2(R)-hydroxy-1(R)-cyclopentylamino)-1-methyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

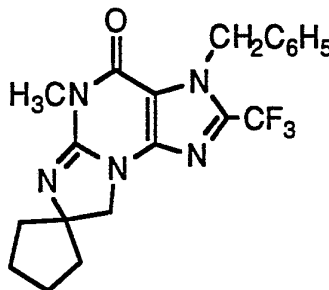
- 5 Example 36: cis-3-Cyclopentyl-5,6a, 7, 8, 9, 9a-hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)one CI MS: M+1=314.



- 10 By using cis-3-cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)one and 2.5 eq. of methyl iodide as the electrophile in accordance with Example 25, the title compound is obtained.

- 15 Example 37 In accordance with Preparative Example 25, treat the appropriate aminoalcohols with SOCl_2 to generate the following cyclic products:

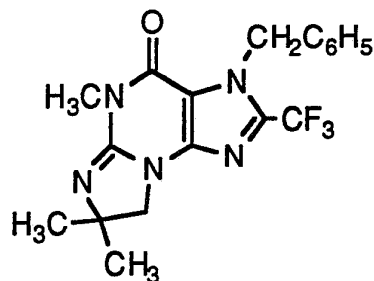
37A1 5'-Methyl-2'-trifluoromethyl-3'-(phenylmethyl)spiro{cyclopentane-1,7'(8'H)-(3'H)imidazo[2,1-b]purin}-4'(5'H)-one: white solid, FAB MS: M+=404.



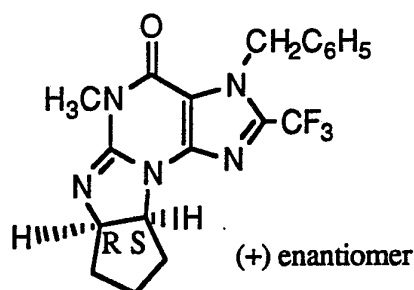
20

37A2 7,8-Dihydro-5,7,7-trimethyl-2-trifluoromethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one: white solid, CI MS: M+1=378.

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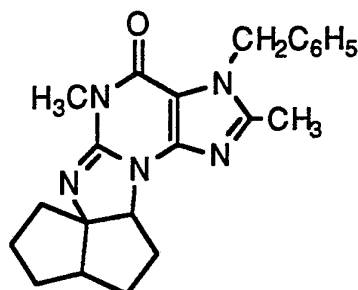
37A3 (+/-)-cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-trifluoromethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one.



5

To a solution of the title aminoalcohol of Preparative Example 25 (0.9g= 2.2mmol) in 40ml CH_2Cl_2 add SOCl_2 (0.7ml=9.2mmol). Stir at room temperature overnight. Wash the diluted solution with cold 2N NaOH, then water. Dry and solvent strip the organic layer. Chromatograph the residue, eluting with 2% CH_3OH in CH_2Cl_2 to give the title compound, 0.61g white solid. CI MS: $M+1=390$.

10 Example 38 (+,-) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-(phenylmethyl)-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one
15 CI MS : $M+1=376$

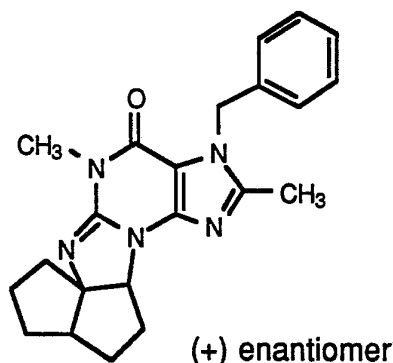


Treat the title compound from Preparative Example 29 with SOCl_2 in accordance with Preparative Example 1 to obtain the title compound. The title compound is resolved by HPLC using a chiral stationary phase

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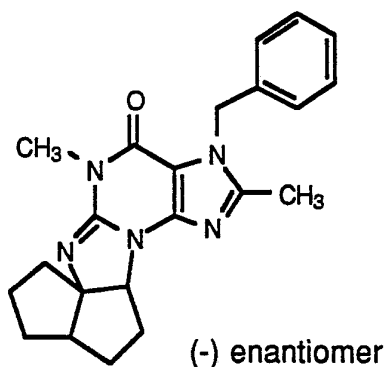
(Daicel Chiralcel OD) to give the (+) and (-) isomers of the title compound, as described in Examples 39 and 40.

Example 39 (+) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one
5 CI MS : M+1=376



The title compound of Example 38 is resolved by HPLC using a chiral stationary phase (Daicel Chiralcel OD). Elute with
10 0.1:20:80 diethylamine:2-propanol:hexane to give the title compound as a solid.

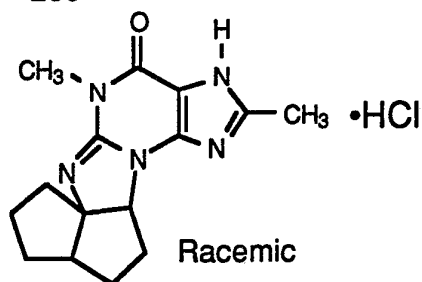
Example 40 (-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b] purin-4(5H)-one
15 CI MS : M+1=376



The title compound of Example 38 is resolved by HPLC using a chiral stationary phase (Daicel Chiralcel OD). Elute with
20 0.1:20:80 diethylamine:2-propanol:hexane to give the title compound as a solid.

- 45 -

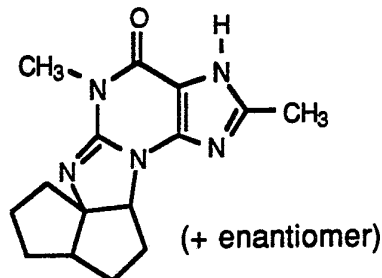
Example 41. (+/-) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one, hydrochloride
FAB MS : M+1= 286



5 Treat the title compound (0.86g) from Example 38 in EtOH (80ml) containing conc HCl (0.7ml) with 20% Pearlman's catalyst (1.0 g) and H₂ (60 PSI). After 48 hr, filtered through celite and concentrate to dryness. The residue is dissolved in water and lyophilized to give the title compound as a colorless powder.

10

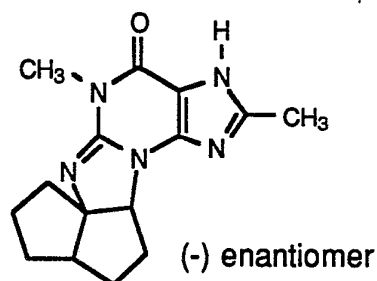
Example 41a (+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one, hydrochloride
[α]_D = +114.3 (3mg/ml EtOH) FAB MS : M+1= 286



15 Treat the title compound from Example 39 in accordance with Example 41 to obtain the title compound as a colorless powder.

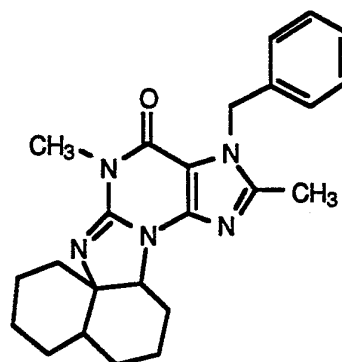
Example 41b (-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one, hydrochloride
20 [α]_D = -122 (1.7mg/ml MeOH) FAB MS : M+1= 286

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Treat the title compound from Example 40 in accordance with Example 41 to obtain the title compound as a colorless powder.

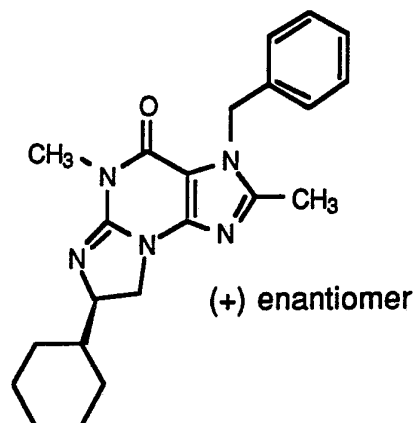
- 5 Example 42 (3-Phenylmethyl)-6a,7,8,9,10,10a,11,12,13,13a-decahydro-2,5-dimethyl-naphth[1,8a-d]imidazo[2,1-b]purin-4(5H)one EI
MS: $M^+=403$



- Treat the title compound from Preparative Example 31 with
10 SOCl_2 in accordance with Preparative Example 1 to give the title compound.

- Example 43 7(R)-cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one: solid, CI MS
15 $M+1=378$

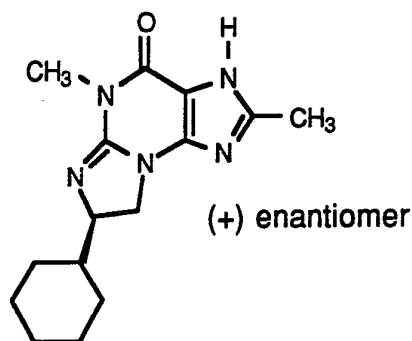
- 47 -



5 Treat 2-[2-hydroxy-1(R)-(cyclohexyl)ethylamino]-1-methyl-7-(phenylmethyl)purin-6-one with triphenylphosphine dibromide in DMF at 65°C for 18hr. Partition the cooled reaction mixture between water and ethyl acetate. Treat the aqueous phase with dilute sodium hydroxide and extract with ethyl acetate: THF 1:1. Concentrate the organic layer and purify by silica gel chromatography using 6% ethanol in dichloromethane to give the title compound as a beige solid.

10

Example 44 7(R)-cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one hydrochloride: solid, FAB MS $M+1=288$, $[\alpha]_D^{23} = +46.2^\circ$ (CH₃OH)

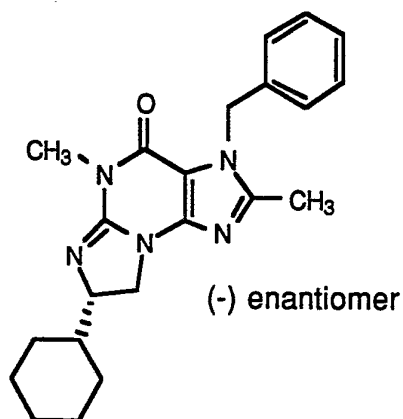


15

Treat the title compound in Example 43 with Pearlman's catalyst in accordance with Example 41 to give the title compound as a powder.

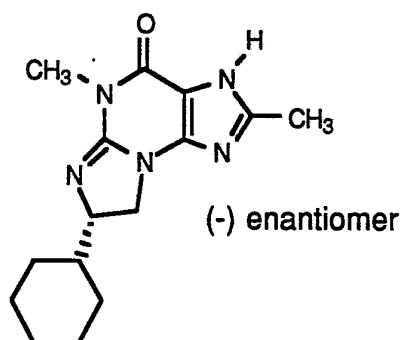
- 48 -

Example 45 7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one: solid, EI MS $M^+=377$, m.p.=99-101°C



5 Treat 2-[2-hydroxy-1- (S)-(cyclohexyl)ethylamino]-1-methyl-7-(phenylmethyl) purin-6-one with triphenylphosphine dibromide in accordance with Example 43 to give the title compound as a solid

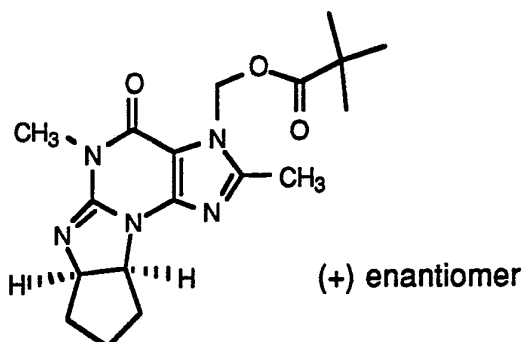
Example 46 7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one hydrochloride: solid, FAB MS $M+1=288$, $[\alpha]_D^{20.5} = -53.1^\circ$ (CH₃OH)



15 Treat the title compound from Example 45 with Pearlman's catalyst in accordance with Example 41 to give the title compound as a powder.

Example 47 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[(trimethylacetoxymethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: solid, FAB MS $M+1=360$

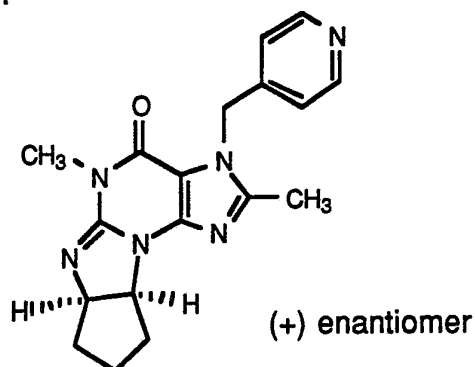
- 49 -



Treat 5,6a(R),7,8,9,9a(S)-hexahydro-2,5-dimethyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one from Example 19a (0.28g, 1.1mmol) in DMF with (4ml) with potassium carbonate (0.24g) and
 5 chloromethylpivalate (0.2ml, 1.4mmol) at 35°C for 6 hr. Cool and filter the reaction mixture. Partition the filtrate with brine and ethyl acetate: THF 1:1. Dry and concentrate the organic layer to give the title compound as a powder.

10

Example 48 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-pyridylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: solid, CI MS $M+1=337$, mp 169-171°C.



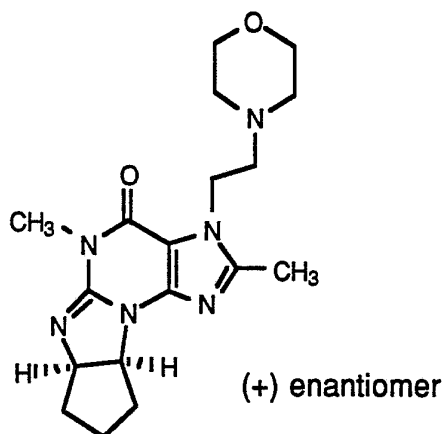
15

Treat 5,6a(R),7,8,9,9a(S)-hexahydro-2,5-dimethyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one from Example 19a with 4-chloromethyl pyridine in accordance with Example 47 to give the title compound as a powder.

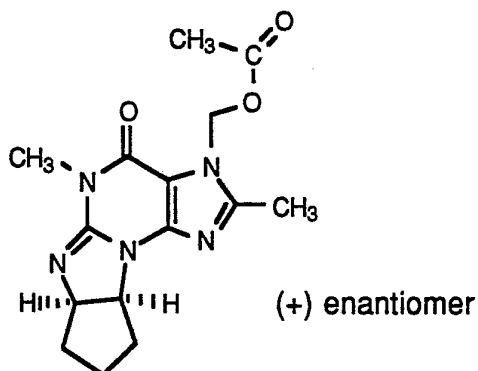
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Example 49 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[2-(1-morpholinyl)ethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: solid, Cl MS $M+1=359$, mp 144-145°C.

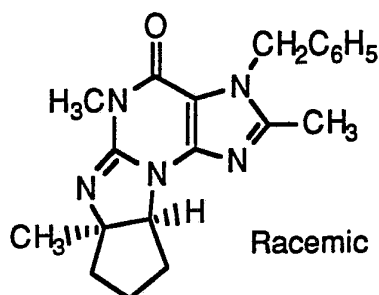


- 5 Treat 5,6a(R),7,8,9,9a(S)-hexahydro-2,5-dimethyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one from Example 19a with 4-(2-chloroethyl)-morpholine in accordance with Example 47 to give the title compound as a powder.
- 10 **Example 50** 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[acetoxymethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: solid, Cl MS $M+1=318$, mp 144-145°C.



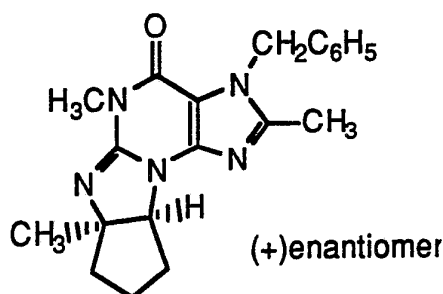
- Treat 5,6a(R),7,8,9,9a(S)-hexahydro-2,5-dimethyl-
- 15 cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one from Example 19a with bromomethyl acetate in accordance with Example 47 to give the title compound as a powder.

Example 51 5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: beige solid, mp 182-4°.



- 5 By using 2-(2 β -hydroxy-1 β -methylcyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

- 10 **Example 52** 5,6a(*R*),7(*S*),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: yellow solid, mp 193-5°, $[\alpha]_D^{23} = +38.0^\circ$ (EtOH).



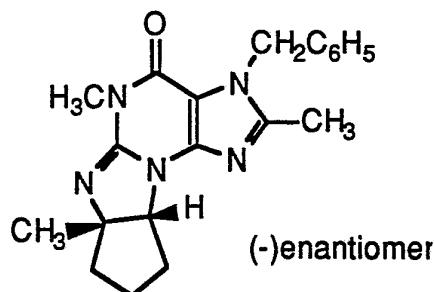
- 15 The compound of Example 51 is separated into the individual enantiomers by HPLC (Daicel chiralcel OD, 80:20:0.1 hexane-isopropanol-diethylamine). The (+)-enantiomer is eluted second.

The title compound is also obtained from 2-(2(*R*)-hydroxy-1(*R*)-methylcyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1.

20

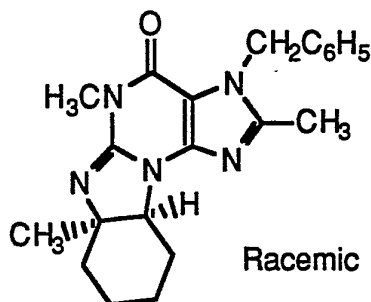
Example 53 5,6a(*S*),7(*R*),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one: yellow solid, mp 194-6°, $[\alpha]_D^{23} = -38.1^\circ$ (EtOH).

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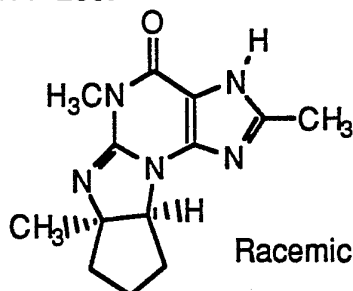
The chiral chromatography described in Example 52 yields the (-)-enantiomer as the first component eluted.

- 5 Example 54 *cis*-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one]: tan solid, mp 159-60°.



- 10 By using 2-(2β-hydroxy-1β-methylcyclohexylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Example 1, the title compound is obtained.

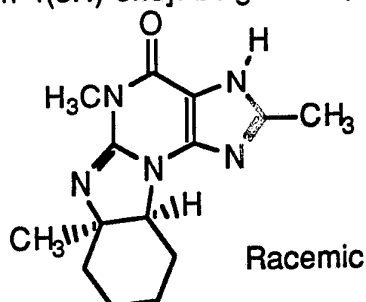
- Example 55 *cis*-5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one] hydrochloride:
15 white solid, FAB MS: M+1=260.



By using *cis*-5,6a,7,8,9,9a-hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one] in accordance with Example 18, the title compound is obtained.

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Example 56 *cis*-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one]: beige solid, mp 262-4°.



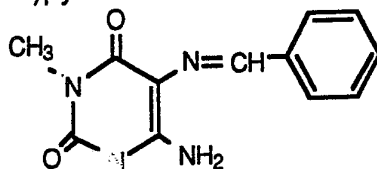
- 5 By using *cis*-6a,7,8,9,10,10a-hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one in accordance with Example 18, the title compound is obtained.

10 Preparation of Starting Materials

The starting materials of formulas (II) and (XX) are well known in the art, as taught, for example, in Weissberger, Pyrimidines, supra and Weissberger, Purines, supra.

- 15 The following preparative examples illustrate various methods for preparing starting materials used to make the present invention.

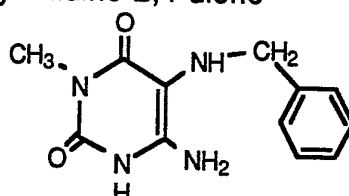
Preparative Example 1: 6-Amino-3-methyl-5-(phenylmethyleneamino)pyrimidine-2,4-dione



- 20 6-amino-3-methyl-5-nitrosopyrimidine-2,4-dione (37.5g=0.22mol) with 10% palladium on carbon (Pd/C) (1.9g) and 25% NaOH (25ml) in 0.75L water. Hydrogenate at 50 psi for 3hr, filter through Celite, and dilute to 1.5L with water. Adjust to pH 4.5 with HOAc and add benzaldehyde (35g=0.34mol). Add 0.5 kg ice, collect the solid, wash with water, then
- 25 acetonitrile, and dry to give the title compound as a yellow powder.

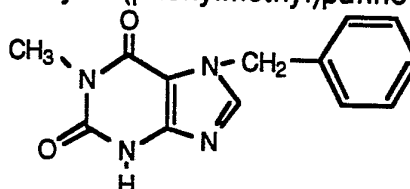
- 54 -

Preparative Example 2: 6-Amino-3-methyl-5-(phenylmethylamino)pyrimidine-2,4-dione



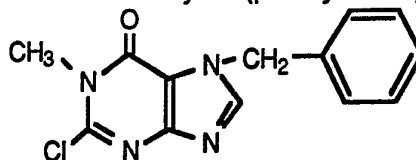
- 5 Add 6-amino-3-methyl-5-(phenylmethylamino)pyrimidine-2,4-dione (85g=0.35mol) to CH_2Cl_2 (1.6L) and MeOH (1.6L). Stir the suspension, add HOAc (21.9ml=0.35mol), then NaCNBH_3 (21.9g=0.35mol). Stir 1.5hr, and add HOAc (2ml) and NaCNBH_3 (2.0g). After another 30min, concentrate to ca. 1.6L on a rotovap (35°C bath). Chill the crystalline mixture, filter, and wash with cold MeOH. Stir the product 15min in 0.5L boiling MeOH, chill, filter, and dry to obtain the title compound, m.p. 206-218°C.

Preparative Example 3: 1-Methyl-7-(phenylmethyl)purine-2,6-dione



- 15 To 6-amino-3-methyl-5-(phenylmethylamino)pyrimidine-2,4-dione (24.6g=0.1mol) in DMF (125ml) at 60°C add triethyl orthoformate (75ml=0.45mol). Heat to 110°C for 5hr, cool in ice, filter, and wash with methanol, then ether, to obtain the title compound, m.p. 268-71°C.
- 20 In a similar manner employ the appropriate orthoester to obtain the following 8-substituted products:
- 3A 1,8-Dimethyl-(7-phenylmethyl)purine-2,6-dione: white solid, m.p. 293-5°C.
- 3B 8-Ethyl-1-methyl-7-(phenylmethyl)purine-2,6-dione: pale yellow solid, CI MS: $M+1=285$.
- 25 3C 1-Methyl-8-phenyl-7-(phenylmethyl)purine-2,6-dione: white solid, CI MS: $M+1=333$.

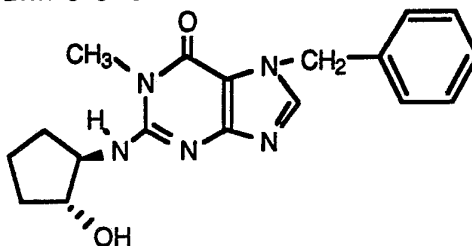
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Preparative Example 4: 2-Chloro-1-methyl-7-(phenylmethyl)purin-6-one

- Heat 1-methyl-7-(phenylmethyl)purine-2,6-dione (8.0g=31mmol) in POCl₃ (80ml) at reflux 7hr. Concentrate in vacuo, partition EtOAc-ice water, wash with water, dry and concentrate. Chromatograph on silica with 98:2 CH₂Cl₂/MeOH to obtain the title compound as a foam, FAB MS: M+1=275.

Similarly, convert the other materials of Preparative Example 3 into the corresponding chloro-compounds:

- 10 4A 2-Chloro-1,8-dimethyl-7-(phenylmethyl)purin-6-one:
off-white solid, EI MS: M+1= 290.
- 4B 2-Chloro-8-ethyl-1-methyl-7-(phenylmethyl)purin-6-one:
one: white solid, FAB MS: M+=303.
- 15 4C 2-Chloro-1-methyl-8-phenyl-7-(phenylmethyl)purin-6-one:
one: white crystals, CI MS: M+1= 351.

Preparative Example 5: 2-(trans-2-Hydroxycyclopentylamino)-1-methyl-7-(phenylmethyl)purin-6-one

- 20 Heat at reflux for 2 days a mixture of 2-chloro-1-methyl-7-(phenylmethyl)purin-6-one (3.14g=11.4mmol), triethylamine (1.7g=16.8mmol), and (±)-trans-2-aminocyclopentanol (4.04g=39.9mmol) in CH₃CN (150ml). Collect the precipitate, wash with water, and dry to give the title compound, a solid, FAB MS: M+1=340.
- 25 Similarly, treat a chloro-compound of Preparative Example 4 with the appropriate amino-alcohol to obtain the following hydroxyalkylamino-purines:

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- 5.1 2-(2-hydroxyethylamino)-1-methyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=300$.
- 5.2 2-(trans-2-hydroxycyclohexylamino)-1-methyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=354$.
- 5 5.3 2-(3-hydroxypropylamino)-1-methyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=314$.
- 5.4 2-(2-hydroxy-2-phenylethylamino)-1-methyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=376$.
- 5.5 2-(1-(hydroxycyclohexyl)methylamino)-1-methyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=368$.
- 10 5.6 2-(2-hydroxy-1-indanylamino)-1-methyl-7-(phenylmethyl)purin-6-one: off-white solid, CI MS: $M+1=388$.
- 5.7 2-(1-hydroxy-2-indanylamino)-1-methyl-7-(phenylmethyl)purin-6-one: off-white solid, CI MS: $M+1=388$.
- 15 5.8 2-(1-hydroxymethylcyclopentylamino)-1-methyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=354$.
- 5.9 2-(trans-2-hydroxycyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one : white solid, CI MS: $M+1=354$.
- 5.10 (+)-isomer : 2-(2(*R*)-hydroxy-1(*R*)-cyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one : white solid, CI MS: $M+1=354$, $[\alpha]_D^{26} = +8.30$.
- 20 5.11 (-)-isomer: 2-(2(*S*)-hydroxy-1(*S*)-cyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, EI MS: $M+=353$, $[\alpha]_D^{26} = -8.20$.
- 25 5A2 2-(trans-2-hydroxycyclohexylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=368$.
- 5A5 2-(1-(hydroxycyclohexyl)methylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=382$.
- 5A9 2-(trans-2-hydroxycycloheptylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=382$.
- 30 5A10 2-(1-hydroxymethylcyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: off-white solid, FAB MS: $M+1=368$.
- 5A11 2-(1-hydroxy-2-methyl-2-propylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: off-white solid, FAB MS: $M+1=341$

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- 5A12 2-(1(R)-phenyl-2-hydroxyethylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: colorless foamed solid, CI MS: $M+1=390$. $[\alpha]_D^{26}=+29.2^\circ$.
- 5 5A13 2-(1-phenyl-3-hydroxy-2(R)-propylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: CI MS: $M+1=404$. $[\alpha]_D^{26}=+80.1^\circ$.
- 5A14 2-(1-hydroxy-2(R,S)-butylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: off-white foamed solid. Thin layer chromatography (10% CH_3OH in CH_2Cl_2): one spot, $R_f=0.5$.
- 10 5A15 2-((1S,2S)-2-hydroxycyclohexylamino)-8-dimethyl-7-(phenylmethyl)purin-6-one: white foamed solid, CI MS: $M+1=368$. $[\alpha]_D^{26}=+20.9^\circ$.
- 15 5A16 2-((1R,2R)-2-hydroxycyclohexylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white foam, CI MS: $M+=368$. $[\alpha]_D^{26}=-21.4^\circ$.
- 5A17 (+)-isomer: 2-(1-hydroxy-3-methyl-2-butylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: CI MS: $M+=356$. $[\alpha]_D^{24}=+57^\circ$.
- 20 5A18 (-)-isomer: 2-(1-hydroxy-2-propylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+=327$. $[\alpha]_D^{26}=-1.9^\circ$.
- 5A19 2-(trans-2-hydroxycyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: tan solid, EI MS: $M+=367$.
- 25 5A20 (-)-isomer: 2-(1-hydroxy-3-methyl-2-pentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=370$. $[\alpha]_D^{26}=-52.1^\circ$.
- 5A21 (+)-isomer: 2-(1-hydroxy-4-methyl-2-pentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=370$. $[\alpha]_D^{26}=+43.7^\circ$.
- 30 5A22 2-(1-methoxycarbonyl-2-hydroxyethylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: tan solid, EI MS: $M+=371$.
- 5A23 2-(1-hydroxy-2-pentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: off-white solid, CI MS: $M+1=356$.

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5A24 (-)-isomer: 2-(1-hydroxy-3-methyl-2-butylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: white solid, EI MS: $M^+=355$.

5A25 2-(2-methyl-3-hydroxy-2-butylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: tan foam, CI MS: $M^+=355$.

5 5A26 2-(2-methyl-4(R,S)-hydroxy-2-pentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: off-white solid, FAB MS: $M+1=370$.

5A27 2-[2-hydroxy-1(R)-(cyclohexyl)ethylamino]-1-methyl-7-(phenylmethyl)purin-6-one, solid $[\alpha]_D^{23.5} = -10.8^\circ$ (CH₃OH)

10 5A28 2-[2-hydroxy-1(S)-(cyclohexyl)ethylamino]-1-methyl-7-(phenylmethyl)purin-6-one, solid, $[\alpha]_D^{23.5} = +12.1^\circ$ (CH₃OH)

5B 2-(trans-2-hydroxycyclopentylamino)-8-ethyl-1-methyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=368$.

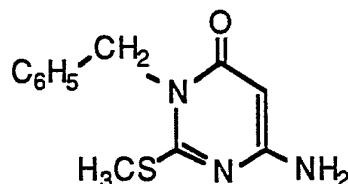
15 5B2 2-(trans-2-hydroxycyclohexylamino)-8-ethyl-1-methyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=382$.

5C 2-(trans-2-hydroxycyclopentylamino)-1-methyl-8-phenyl-7-(phenylmethyl)purin-6-one: white solid, CI MS: $M+1=416$.

20 5C2 2-(trans-2-hydroxycyclohexylamino)-1-methyl-8-phenyl-7-(phenylmethyl)purin-6-one: white solid, FAB MS: $M+1=430$.

5C3 2-(2(R)-hydroxy-1(R)-cyclopentylamino)-1-methyl-7-(phenylmethyl)purin-6-one; mp 158-160°C

25 Preparative Example 6: 6-Amino-3-(phenylmethyl)-2-methylthiopyrimidin-4-(3H)-one

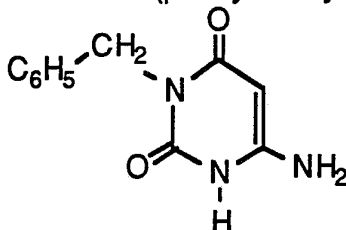


To a slurry of 60% NaH dispersion (1.8 g = 45 mmol) in 25 ml DMF at 10°C. add dropwise a solution of 6-amino-2-methylthio-4-hydroxypyrimidine (6.3 g = 40 mmol) in 150 ml DMF. When gas evolution subsides, add benzyl bromide (7.5 g = 44 mmol). Stir 1.5 hr. at room temperature. Remove DMF
30 and partition the residue between EtOAc and water. Wash the organic

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layer with water, dry and concentrate. Recrystallize the residue from CH_3CN to give the title compound, a white solid. FAB MS: $M+1=248$.

Preparative Example 7: 6-Amino-3-(phenylmethyl)pyrimidine-2,4-dione

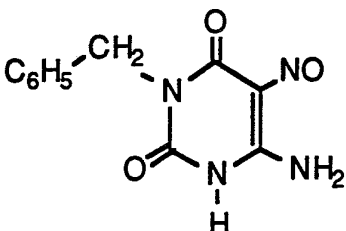


5

Reflux 6-amino-3-(phenylmethyl)-2-methylthiopyrimidin-4(3H)-one (2.5 g = 10 mmol) in 40 ml 10% aqueous NaOH for four hours. Cool, acidify the solution and collect the precipitate. Water wash and dry to give the title compound, a white solid, EI MS: $M+ = 217$.

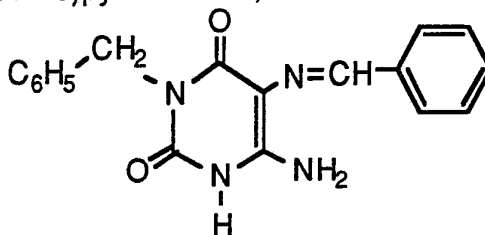
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Preparative Example 8: 6-Amino-3-(phenylmethyl)-5-nitrosopyrimidine-2,4-dione



Slurry 6-amino-3-(phenylmethyl)-pyrimidine-2,4-dione (1.1 g = 5 mmol) in 50 ml water. Add NaNO_2 (0.63 g = 9.1 mmol), warm to 75°C and add acetic acid (2.6 ml = 45 mmol) in 30 ml water over two hours. Collect the product, water wash and dry over P_2O_5 to give title compound as an orange solid. EI MS: $M+ = 246$.

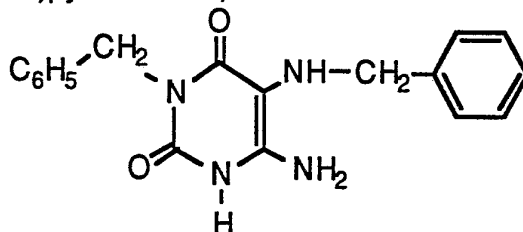
20 Preparative Example 9: 6-Amino-3-(phenylmethyl)-5-(phenylmethyleneamino)pyrimidine-2,4-dione



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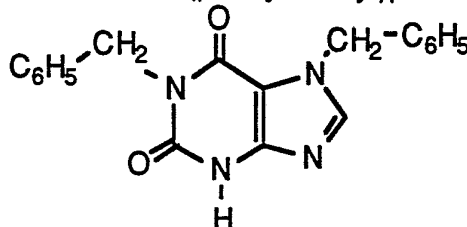
Treat 6-amino-3-(phenylmethyl)-5-nitrosopyrimidine-2,4-dione according to Preparative Example 1 to obtain the title compound, a yellow solid. EI MS: $M^+=320$.

- 5 Preparative Example 10: 6-Amino-3-(phenylmethyl)-5-(phenylmethylanino)pyrimidine-2,4-dione



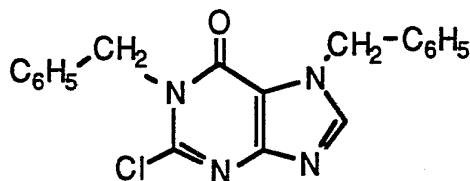
- 10 Reduce 6-amino-3-(phenylmethyl)-5-(phenylmethylanino)pyrimidine according to the procedure of Preparative Example 2 to give the title compound, a white solid. CI MS: $M^+=322$.

- Preparative Example 11: 1,7-Bis(phenylmethyl)purin-2,6-dione



- 15 Cyclize 6-amino-3-(phenylmethyl)-5-(phenylmethylanino)pyrimidine-2,4-dione in accordance with Preparative Example 3 to give the title compound, a tan solid. CI MS: $M^+=333$.

- Preparative Example 12: 2-chloro-1,7-bis(phenylmethyl)purin-6-one



- 20 Treat 1,7-bis(phenylmethyl)purin-2,6-dione with POCl_3 in accordance with Preparative Example 4, to give the title compound, an off-white solid, EI MS: $M^+=350$.

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Preparative Example 13: 2-(trans-2-Hydroxycyclopentylamino)-1,7-bis(phenylmethyl)purin-6-one

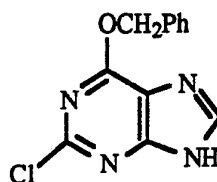
- 5 Treat 2-chloro-1,7-bis(phenylmethyl)purin-6-one with trans-2-aminocyclopentanol as described in Preparative Example 5 to give the title compound, a tan solid. FAB MS: M+1=416.

Preparative Example 14: 2-(trans-2-Hydroxycyclohexylamino)-1,7-bis(phenylmethyl)purin-6-one

- 10 Treat 2-chloro-1,7-bis(phenylmethyl)purin-6-one with trans-2-aminocyclohexanol as described in Preparative Example 5 to give the title compound, a tan foam. FAB MS: M+1=430.

Preparative Example 15: 2-Chloro-6-benzyloxypurine

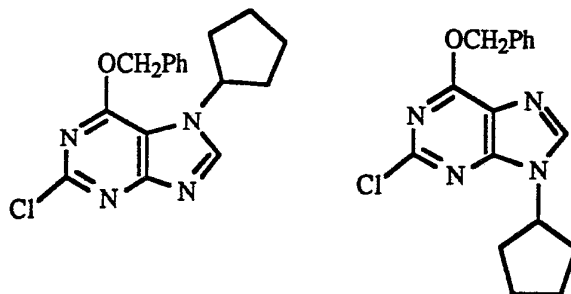
15



- 2,6-dichloropurine (0.30g, 1.6mmol) is added to a mixture of benzyl alcohol (0.19g, 1.8mmol) and 60% sodium hydride (0.13g, 3.3mmol) in DMF (8ml) at room temperature (RT). After 1 hr, the reaction is heated to 60°C for 18 hr, cooled to RT and dilute HCl is added to adjust the pH to 5. The mixture is extracted with EtOAc/THF 1:1, and the organic layer is dried over sodium sulfate, filtered and concentrated to give a solid. This is recrystallized from EtOAc/ hexane to give the title compound, mp. 195-196°C.
- 20
- 25

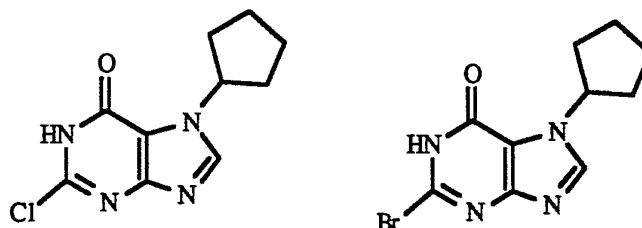
Preparative Example 16: 2-Chloro-6-benzyloxy-7-cyclopentylpurine and 2-Chloro-6-benzyloxy-9-cyclopentylpurine

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A mixture of 2-chloro-6-benzyloxypurine (0.32g, 1.2 mmol) cyclopentyl mesylate (0.24g) and K₂CO₃ (0.25g, 1.8 mm) in DMF (10ml) is heated to 75°C for 18hr. The mixture is cooled to RT and partitioned between brine and EtOAc/THF 1:1. The organic phase is concentrated in vacuo to give a solid, which is purified by flash chromatography. Elution with 40% EtOAc in hexane gives the N-9 isomer of the title compound as a solid. FAB MS : M+1= 329. Further elution gives the N-7 isomer of the title compound, a solid. FAB MS : M+1= 329.

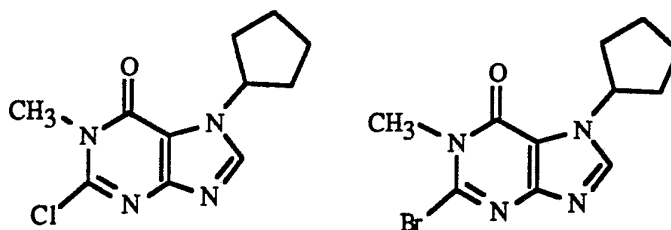
Preparative Example 17: 2-Chloro-7-cyclopentylpurin-6-one and 2-Bromo-7-cyclopentylpurin-6-one



2-Chloro-6-benzyloxy-7-cyclopentylpurine (1.0 g, 3mmol) is treated with 33% HBr in acetic acid (25ml). After 1 hr at RT, the mixture is concentrated in vacuo and triturated with H₂O and hexane to give a mixture of the title compounds, a solid. CI MS M+1=285,283 and 241,239.

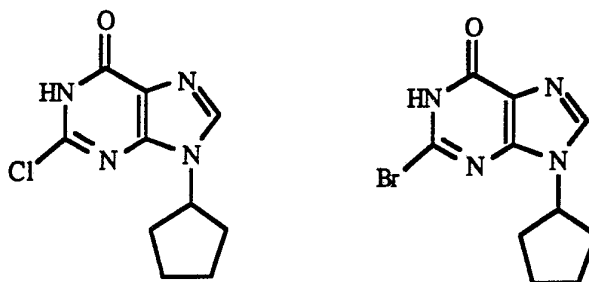
Preparative Example 18: 1-Methyl-2-chloro-7-cyclopentylpurin-6-one and 1-Methyl-2-bromo-7-cyclopentylpurin-6-one

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- 5 Iodomethane (0.95 ml) is added to a mixture of 2-chloro-7-cyclopentylpurin-6-one and 2-bromo-7-cyclopentylpurin-6-one (1.8g) and LiOH (0.38g) in DMF (20ml) at 0°C. After 1 hr at RT, the mixture is partitioned between EtOAC/THF (1:1), and brine. The organic layers are concentrated in vacuo and the residue is purified by flash chromatography using 3% EtOH in CH₂Cl₂ to give a mixture of the title
10 compounds, a solid. mp 140-145°C .

Preparative Example 19: 2-Chloro-9-cyclopentylpurin-6-one and 2-Bromo-9-cyclopentylpurin-6-one



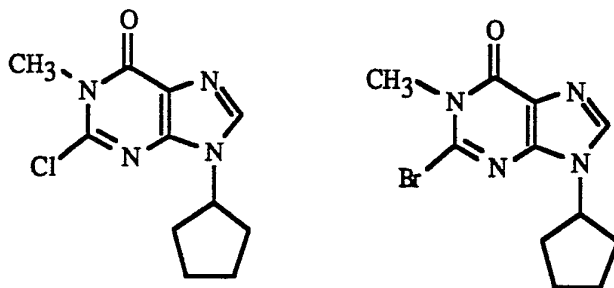
15

Treat 2-chloro-6-benzyloxy-9-cyclopentylpurine with HBr in acetic acid as described in Preparative Example 17 to give a mixture of the title compounds as a solid. CI MS M+1 = 285, 283 and 241,239.

20

Preparative Example 20: 1-Methyl-2-chloro-9-cyclopentylpurin-6-one and 1-methyl-2-bromo-9-cyclopentylpurin-6-one

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5 Treat 2-chloro-9-cyclopentylpurin-6-one and 2-bromo-9-cyclopentylpurin-6-one with methyl iodide as described in Preparative Example 18 to give a mixture of the title compounds, a solid. CI MS $M+1=$ 299, 297 and 255, 253.

Preparative Example 21 6-Amino-3-methyl-5-(N-(phenylmethyl)trifluoroacetamido)-pyrimidine-2,4-dione.

10 Add amine from Preparative Example 2 (1.23g=5mmol) to a mixture of 1.0ml trifluoroacetic anhydride and 10ml trifluoroacetic acid. Reflux overnight. Cool, pour into cold water, collect and water wash the precipitate to give, after drying, 1.45g of the title compound. One spot on thin layer chromatography; FAB MS: $M+=$ 342.

15

Preparative Example 22 1-Methyl-7-(phenylmethyl)-8-trifluoromethylpurine-2,6-dione.

20 To the trifluoroacetamide (3.4g=10mmol) of Preparative Example 21, in 50ml DMF add sodium methoxide (2.7g=50mmol), and heat the mixture, at 130-150° for 3 hours. Pour into water, acidify, collect and dry the precipitate to give 2.5g of the title compound, m.p. 211-213°. CI MS: $M+1=$ 325.

25 Preparative Example 23 2-Chloro-1-methyl-7-(phenylmethyl)-8-trifluoromethylpurin-6-one.

Reflux the trifluoromethylpurine of Preparative Example 22 (10.0g=31mmol) in 100ml POCl_3 10 hours. Remove excess reagent in vacuo, and partition the residue between ice water and ethyl acetate (EtOAc). Wash the the organic layer, dry, and remove solvent.

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Chromatograph on silica; elute with 2% CH₃OH in CH₂Cl₂ to give 5.1g of the title compound. Tan solid, CI MS:M+1=343.

Preparative Example 24 (+/-)-2-(trans-2-Hydroxycyclopentylamino)-1-methyl-7-(phenylmethyl)-8-trifluoromethylpurin-6-one.

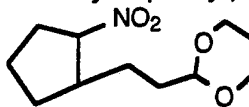
Heat under reflux a mixture of the chloropurine of Preparative Example 23 (0.86g=2.5mmol), (+/-)-trans-2-aminocyclopentanol (1.01g=10mmol), and triethylamine (0.6ml=4.3mmol) in 10 ml CH₃CN overnight. Remove solvent, partition residue between water and EtOAc. Dry the organic layer, remove solvent, and chromatograph the product on silica. Elution with 5% CH₃OH in CH₂Cl₂ gives 0.91g title compound. Tan foam, FAB MS: M+1=408.

Preparative Example 25 2-(1-hydroxymethylcyclopentylamino)-1-methyl-7-(phenylmethyl)-8-trifluoromethylpurin-6-one: tan foam, CI MS: M+1=422.

Treat the chloropurine of Preparative Example 23 with the appropriate amino alcohol to give the title compound. Similarly prepare:

25.1 2-(1-hydroxy-2-methyl-2-propylamino)-1-methyl-7-(phenylmethyl)-8-trifluoromethylpurin-6-one: white foam, CI MS: M+1=396.

Preparative Example 26 2-[2-(2-Nitrocyclopentyl)ethyl]-1,3-dioxane



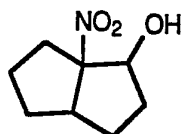
At -78°C, add 1-nitrocyclopentene (1.8ml, 18.4mmol) in THF (20ml) to a THF solution (33ml) of the zinc-copper reagent prepared from 2-(2-iodoethyl)-1,3-dioxane (5.6gm,23mm), zinc powder (1.58 g), CuCN (1.9 g) and LiCl (1.7 g) , according to the general procedure of P. Knochel et. al. (J. Org. Chem. 1989, 54, 5200). After 15min. warm to 0°C for one hour, then recool to -78°C and add AcOH (2.0 ml). Warm to RT, add AcOH:0.1N HCl (15ml, 1:2) and stir for one hr. Partition between EtOAc and brine. Concentrate the organic layer and purify by silica gel

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chromatography using EtOAc/Hex 1:3 to elute the title compound (3.6g 15.7mmol) as an oil. CI MS : $M+1 = 230$.

Preparative Example 27 1-Hydroxy-7-nitrobicyclo[3.3.0]octane

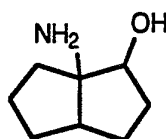
5



- Add toluenesulfonic acid (0.1 g) to a dry MeOH (200ml) solution of the title compound (3.6 g) from Preparative Example 6. Heat to reflux for 6 hr. then cool to room temperature, add NaHCO_3 (0.1 g) and concentrate to dryness. Dissolve the residue in THF (60ml) and 0.5N HCl (30ml). After 13hr, remove the THF in vacuo and partition the residue with Et_2O and brine. Dry the Et_2O layer (MgSO_4), and concentrate. Dissolve the residue (2.0g) in MeOH (50ml) and add anhydrous K_2CO_3 (0.14g). After seven hours add AcOH (0.15ml) and concentrate to dryness.
- 15 Dissolve the residue in Et_2O and wash with brine. Usual workup of the Et_2O layer affords the title compound (2.0 g) CI MS : $M+1 = 172$

Preparative Example 28 1-Hydroxy-7-aminobicyclo[3.3.0]octane

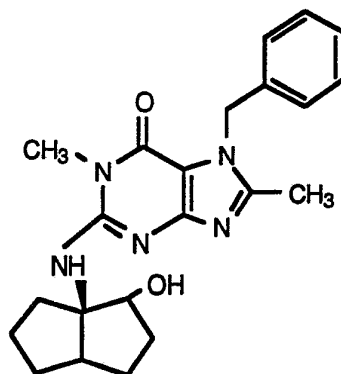
20



- Dissolve the title compound from Example 2 (2.8 g) in EtOH (40ml), add this to Raney nickel (2 g, wet weight) and place under H_2 at 60 psi. After 48 hr, filter through celite and concentrate the filtrate to dryness. Dissolve the resultant oil (2.7 g) in Et_2O . To this add a solution of dry
- 25 HCl in MeOH and collect the title compound as a colorless solid. EI MS $M+ = 141$

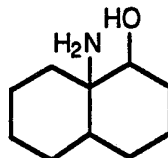
Preparative Example 29 2-(1-Hydroxybicyclo[3.3.0]octyl-7-amino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one

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- Heat a mixture of the title compound from Preparative Example 28 (10.8g, 60.8mmol) , 2-chloro-1-methyl-7(phenylmethyl)purin-6-one (21.5g , 74.4mmol) and diisopropylethylamine (40ml) in 1-methyl-2-pyrrolidinone (35ml) to 140°C for 64hr. Cool the mixture and pour into ice water. Collect the resultant precipitate (22g) and purify this by silica gel chromatography using CH₂Cl₂: EtOH (90:10) to obtain the title compound (14.2 g) as a solid. CI MS M + 1 = 394.

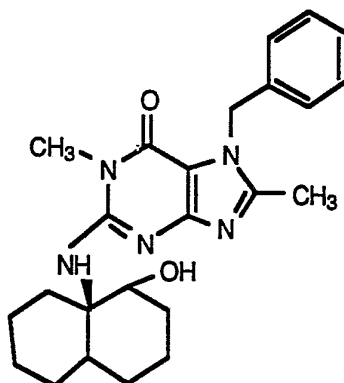
- 10 Preparative Example 30 1-Hydroxy-8a-nitrodecahydronaphthalene hydrochloride



- To a solution of 8a-nitrodecahydronaphthalen-1-one [P. Dampawan and W.W. Zajac Jr. Synthesis,545,1983](1.2g, 6.1mmol) in MeOH (10ml) at 0°C , add sodium borohydride (.09g) and warm to RT. After 0.5hr, add ether and 1 N HCl. Dry and concentrate the organic layer. Dissolve the residue in EtOH (50 ml) and add this to Raney Nickel (1.2g, wet weight) and place under 60 psi of H₂ at 55°C. After 24 hr. , filter though celite and concentrate to dryness. Dissolve the resultant oil in Et₂O add dry HCl in MeOH and collect the title compound as a colorless precipitate EI MS : M+= 169.

- Preparative Example 31 2-(1-Hydroxydecahydronaphthalen-8a-ylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one: FAB MS :
25 M+1=422

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5 Treat the title compound in Preparative Example 30 with 2-chloro-1,8-dimethyl-7-(phenylmethyl)purin-6-one in accordance with Preparative Example 29 to give the title compound.

Preparative Example 32. 2β-Amino-2α-methylcyclopentanol

A. To methyl 1-methyl-2-oxocyclopentanecarboxylate (20.0g=128mmol) in THF (800ml) add portionwise lithium tri-*t*-butoxyaluminumhydride (40.7g=160mmol). Stir 1hr and partition between Et₂O and 1.0N HCl. Dry and concentrate to obtain methyl 1-methyl-2-hydroxycyclopentanecarboxylate, largely the 1β-methyl-2β-hydroxy isomer, as an oil.

15 B. Combine the above ester with 250ml each 1.0N NaOH and MeOH. After 24hr, concentrate and partition with EtOAc and 1.0N HCl (saturated with NaCl). Dry and concentrate to obtain 1-methyl-2-hydroxycyclopentanecarboxylic acid, largely the 1 β -methyl-2 β -hydroxy isomer, as a wet solid.

C. Combine the above acid (5.00g=34.7mmol) with Et₃N (3.68g=36.5mmol) and diphenylphosphoryl azide (10.0g=36.5mmol) in toluene (100ml). Heat at 80° 1hr, allow to cool, add benzyl alcohol (3.93g=36.5mmol), and heat at reflux 18hr. Allow to cool, concentrate, and partition with EtOAc and 1.0N NaHCO₃. Dry and concentrate to obtain an oil. Chromatograph on silica with 1:1 Et₂O-hexane to obtain 2α-methyl-2β-(phenylmethoxycarbonylamino)cyclopentanol as an oil.

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D. Shake the above carbamate (2.50g=10.0mmol) with 10% Pd/C (0.6g) in MeOH (150ml) under 60psi hydrogen. After 2hr, filter and concentrate to obtain 2 β -amino-2 α -methylcyclopentanol as an oil.

5 Preparative Example 33 1(*R*),2(*R*)-2-Amino-2-methylcyclopentanol

- A. Treat the acid of Preparative Example 32B (10.8g) in Et₂O (110ml) with (*R*)-(+)- α -methylbenzylamine (5.42g) in Et₂O (70ml). Collect the precipitate and dissolve in a boiling mixture of 10:1 CH₂Cl₂/MeOH (400ml). Boil down to 200ml volume, allow to cool, and
10 collect the solid. Recrystallize from CH₂Cl₂ (60ml) and MeOH (25ml) by boiling down with addition of CH₂Cl₂ (95ml) to a final volume of 60ml. Allow to cool and collect the (*R*)-(+)- α -methylbenzylamine salt of 1(*R*),2(*R*)-1-methyl-2-hydroxycyclopentanecarboxylic acid as a solid, mp 172-3 $^{\circ}$, [α]_D²³ = -4.9 $^{\circ}$ (EtOH). Partition the salt between Et₂O and 1.0N
15 HCl. Dry and concentrate to obtain (*R*),2(*R*)-1-methyl-2-hydroxycyclopentanecarboxylic acid as a solid, mp 70-1 $^{\circ}$.

B. Treat the above acid in analogous fashion to Preparative Example 32C to obtain 1(*R*),2(*R*)-2-methyl-2-(phenylmethoxycarbonylamino)cyclopentanol as an oil.

- 20 C. Treat the above carbamate in analogous fashion to Preparative Example 32D to obtain 1(*R*),2(*R*)-2-amino-2-methylcyclopentanol as an oil.

Preparative Example 34 2 β -Amino-2 α -methylcyclohexanol

- 25 A. Treat ethyl 1-methyl-2-oxocyclohexanecarboxylate in analogous fashion to Preparative Example 32A to obtain ethyl 1-methyl-2-hydroxycyclohexanecarboxylate, largely the 1 β -methyl-2 β -hydroxy isomer, as an oil.

- B. Combine the above ester (4.97g=26.7mmol) with 80ml each
30 1.0N NaOH and EtOH. After 48hr, concentrate and partition with EtOAc and 1.0N HCl (saturated with NaCl). Dry and concentrate to obtain 1-methyl-2-hydroxycyclohexanecarboxylic acid, largely the 1 β -methyl-2 β -hydroxy isomer, as a beige solid. Recrystallize from Et₂O-hexane to obtain the pure isomer as a white solid, mp 97 $^{\circ}$.

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C. Combine the above acid (2.00g=12.7mmol) with Et₃N (1.40g=13.9mmol) and diphenylphosphoryl azide (3.82g=13.9mmol) in toluene (40ml). Heat at 100° 1hr, allow to cool, and concentrate. Partition with EtOAc and 1.0N NaHCO₃, wash with water, dry and
5 concentrate to obtain a solid. Recrystallize from Et₂O-hexane to obtain 3α,4,5,6,7,7α-hexahydro-3αβ-methyl-2(3H)benzoxazolone as a white solid, mp 107-9°.

D. Heat the above carbamate (1.10g=7.09mmol) with 20% KOH (50ml) at reflux 4hr. Allow to cool, saturate with NaCl, and extract with
10 EtOAc. Dry and concentrate to obtain 2β-amino-2α-methylcyclohexanol as a gum.

Preparative Example 35 2-(2β-Hydroxy-1β-methylcyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one

15 Combine the aminoalcohol of Preparative Example 32 (1.10g=9.6mmol) and 2-chloro-1,8-dimethyl-7-(phenylmethyl)purin-6-one (2.75=9.6mmol) with N-methylpyrrolidinone (5.0g) and diisopropylethylamine (5.2g). Heat in a sealed vessel at 140° for 40hr, allow to cool, and partition with EtOAc and water. Dry and concentrate
20 to obtain an oil. Chromatograph on silica with 4% MeOH/CH₂Cl₂ to obtain the title compound as a foam, FAB MS: M+1=368.

In similar fashion employ the aminoalcohol of Preparative Example 33 to obtain 2-(2(R)-hydroxy-1(R)-methylcyclopentylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one as a foam, FAB MS:
25 M+1=368.

In similar fashion employ the aminoalcohol of Preparative Example 34 to obtain 2-(2β-hydroxy-1β-methylcyclohexylamino)-1,8-dimethyl-7-(phenylmethyl)purin-6-one as a foam, FAB MS: M+1=382.

30 Pharmaceutical Preparations

The compounds of formulas (I) and (I') can be combined with a suitable pharmaceutical carrier to prepare a pharmaceutical preparation or composition suitable for parenteral or oral administration. Such pharmaceutical compositions are useful in the treatment of cardiovascular

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and pulmonary disorders such as mammalian hypertension and bronchoconstriction.

The effective daily antihypertensive dose (ED₅₀) of the present compounds will typically be in the range of about 1 to about 100 mg/kg of mammalian body weight, administered in single or divided doses. The exact dosage to be administered can be determined by the attending clinician and is dependent upon where the particular compound lies within the above cited range, as well as upon the age, weight and condition of the individual.

Generally, in treating humans in need of treatment for hypertension or bronchoconstriction, the present compounds can be administered in a dosage range of about 10 to about 500 mg per patient generally given a number of times per day, providing a total daily dosage of from about 10 to about 2000 mg per day.

The compositions of the present invention can be administered orally or parenterally. Typical injectable formulations include solutions and suspensions. Typical oral formulations include tablets, capsules, syrups, suspensions and elixirs. Also contemplated are mechanical delivery systems, e.g. transdermal dosage forms.

The typical acceptable pharmaceutical carriers for use in the formulations described above are exemplified by sugars such as lactose, sucrose, mannitol and sorbitol; starches such as cornstarch, tapioca starch and potato starch; cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone, polyvinyl alcohol; stearic acid; alkaline earth metal stearates such as magnesium stearate and calcium stearate, stearic acid, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; beta-cyclodextrin; fatty alcohols and hydrolyzed cereal solids; as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents, and the like commonly used in pharmaceutical formulations.

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Following are typical examples of oral and parenteral formulations, wherein the term "Active Ingredient" refers to a compound of formula (I) or (I').

A capsule comprising the Active Ingredient:

- 5 (+)-6a,7,8,9,9a,10,11,11a-octahydro-2,5-dimethyl-3H-pentaleno [6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one, hydrochloride is prepared from the following ingredients:

	<u>Capsule</u>	<u>Amount (mg)</u>	
10	Active Ingredient	250.0	125.0
	Lactose	173.0	86.5
	Corn Starch	75.0	37.5
	<u>Magnesium Stearate</u>	<u>2.0</u>	<u>1.0</u>
	TOTAL	500.0	250.0

15

Blend the active ingredient, lactose and corn starch until uniform; then blend the magnesium stearate into the resulting powder. Encapsulate the mixture into suitably sized two-piece hard gelatin capsules.

20

	<u>Capsule</u>	<u>Amount (mg)</u>	
	Active Ingredient	250.0	125.0
25	Lactose	161.0	80.5
	Corn Starch	12.0	6.0
	Water (per thousand tablets) 120 ml		60 ml
	(evaporates)		
	(evaporates)		
30	Corn Starch	75.0	37.5
	<u>Magnesium Stearate</u>	<u>2.0</u>	<u>1.0</u>
	TOTAL	500.0	250.0

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- Blend the active ingredient with the lactose until uniform. Blend the smaller quantity of corn starch with the water and add the resulting corn starch paste then mix until a uniform wet mass is formed. Add the remaining corn starch to the remaining wet mass and mix until
- 5 uniform granules are obtained. Screen the granules through a suitable milling machine, using a 3/4 inch stainless steel screen. Dry the milled granules in a suitable drying oven until the desired moisture content is obtained. Mill the dried granules through a suitable milling machine using a 16 mesh stainless steel screen. Blend in the magnesium
- 10 stearate and compress the resulting mixture into tablets of desired shape, thickness, hardness and disintegration.

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	<u>Injectable Solution</u>	<u>mg/ml</u>
5	Active Ingredient	5.00
	Methyl p-hydroxybenzoate	0.80
	Propyl p-hydroxybenzoate	0.10
	Disodium Edetate	0.10
	Citric Acid Monohydrate	0.08
10	Dextrose	40.0
	Water for injection qs. ad.	1.0 ml

15 Dissolve the p-hydroxybenzoates in a portion of water for injection at a temperature of between 60°C - 70°C and cool the solution to 20°C - 30°C, Charge and dissolve all other excipients and the active ingredient. Bring the solution to final volume, filter it through a sterilizing membrane and fill into sterile containers.

20

Biological Activity of Polycyclic Guanines

The present compounds are useful in inhibiting the phosphodiesterase enzymes . These phosphodiesterase enzymes are known to hydrolyze cGMP in smooth muscle. High levels of cGMP are associated with the relaxation of vascular smooth muscle, with a consequent subsequent reduction in blood pressure. Thus, it is believed that by inhibiting these phosphodiesterase enzymes, cGMP levels in muscle will be either maintained or increased with a subsequent reduction in blood pressure.

25 *In vivo* antihypertensive activity is determined orally in spontaneously hypertensive rats (SHR).

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Phosphodiesterase inhibition in vitro:

Compounds are evaluated for inhibition of two phosphodiesterase enzymes which hydrolyze cyclic guanosine monophosphate (cGMP). The first enzyme, calcium-calmodulin dependent phosphodiesterase (CaM-PDE), is a partially pure enzyme obtained from bovine aorta homogenates and purified by DEAE-cellulose and calmodulin-affinity chromatography. The enzyme is activated several fold by Ca-calmodulin and is selective for cGMP, although it will also hydrolyze cAMP. The second enzyme, cGMP phosphodiesterase (cGMP-PDE), is a homogeneous enzyme obtained from bovine lung and purified by ion-exchange chromatography, gel filtration, and sucrose gradient centrifugation. cGMP-PDE is highly selective for cGMP. Bovine aorta homogenates and primary cultures of bovine aortic endothelial and vascular smooth muscle cells contain an enzyme with properties very similar to the lung isozyme.

The enzyme assay is performed using a Biomek Automated Pipetting Station. Compounds are dissolved in distilled water or DMSO and diluted with 10% DMSO. Compounds are tested at several concentrations at log intervals, typically 0.1, 1.0, 10, and 100 μ M final concentration.

Assays contain the following components:

1 μ M substrate 3 H-cGMP
50 mM Tris-HCl, pH 7.5, 5 mM magnesium chloride (MgCl₂)
0.5 mg/ml snake venom alkaline phosphatase
0.1 μ M Calmodulin and 1 mM CaCl₂ (for CaM-PDE only)

Assays are initiated by addition of enzyme and stopped by addition of 10 mM isobutylmethylxanthine, a general phosphodiesterase inhibitor. Assays are performed for 25 minutes at room temperature to achieve 5-10% hydrolysis of substrate. The negatively charged substrates are then separated from guanosine by binding to an anion-exchange resin (AG1-X8) and centrifugation or filtration, and the product is quantitated by scintillation counting in counts

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per minute (cpm) of the remaining soluble material. Percent inhibition is calculated as follows:

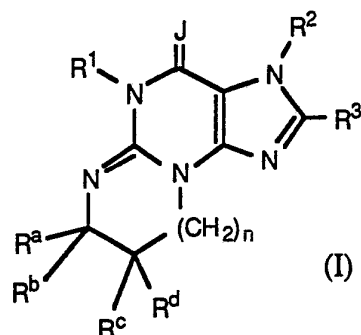
% Inhibition= $100 - [(cpm \text{ compound-blank}) / (cpm \text{ control-blank}) \times 100]$

- 5 Activity is expressed as the IC₅₀ value, ie. the concentration required to inhibit activity of enzyme by 50 per cent.

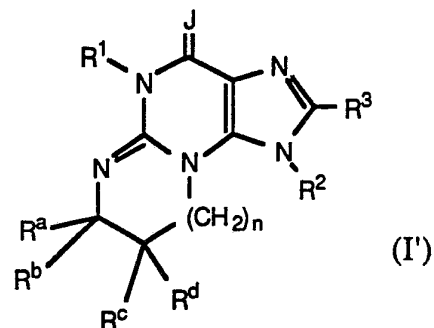
Antihypertensive activity in rats

- 10 The ability of the compounds of the present invention to lower blood pressure can be assessed *in vivo* in conscious spontaneously hypertensive rats (SHR). SHR males are purchased from Taconic Farms, Germantown New York and are approximately 16-18 weeks old when anesthetized with ether. The caudal (ventral tail) artery is
- 15 cannulated with polyethylene tubing (PE50) and blood pressure and heart rate are recorded as described by Baum, T. et. al, J. Cardiovasc. Pharmacol. Vol 5, pp. 655-667, (1983). Rats are placed into plastic cylindrical cages where they rapidly recover consciousness. Blood pressure and heart rate are allowed to stabilize for approximately 90
- 20 minutes prior to compound administration. Compounds are administered orally as solutions or suspensions in 0.4% aqueous methylcellulose vehicle via a feeding needle. The compound or 0.4% aqueous methylcellulose vehicle are given in a volume of 4 ml/kg to SHRs that had been fasted overnight. Activity is expressed as the fall in
- 25 mean blood pressure (MBP) in millimeters of mercury (mm Hg). Compound-induced changes are compared with the changes in an appropriate placebo group.

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and



ACTIVITY OF POLYCYCLIC GUANINES

5

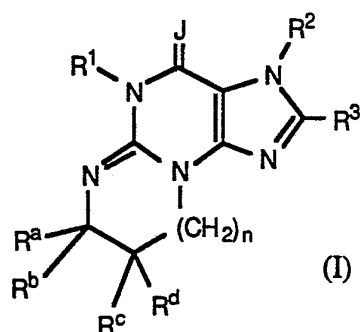
<u>Example Number</u>	<u>PDE IC₅₀</u>		<u>SHR Antihypertensive</u>	
	<u>CaM</u> <u>(μM)</u>	<u>cGMP</u> <u>(μM)</u>	<u>Dose</u> <u>(mpk)</u>	<u>Fall</u> <u>in MBP</u> <u>(mmHg)</u>
1	0.3	0.4	25	30
3	0.1	1.4	25	22
9	0.6	0.2	25	36
10	0.3	1.0	25	45
12	0.2	0.2	25	38
14	0.3	0.9	25	20
16	0.1	3	25	23
19a	3.0	0.3	25	40
20	0.04	0.4	25	6
21	3.3	0.4	25	20
22	0.2	0.2	25	15
28	0.2	0.2	25	19
34	0.1	0.1	25	40
35	0.4	0.3	25	41
34a	0.3	0.8	25	58
39	0.1	0.1	25	40
41a	0.2	0.1	25	67
			10	52
			5	45

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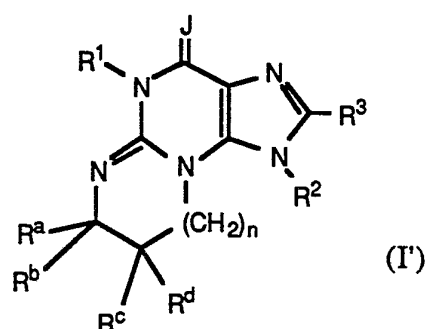
IN THE CLAIMS:

1. A compound of the formula:

5



and



wherein

J is oxygen or sulfur,

10 R¹ is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

R² is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or -(CH₂)_mTCOR²⁰ wherein m is an integer from 1 to 6, T is oxygen or -NH- and R²⁰ is hydrogen, aryl, heteroaryl, alkyl or

15 alkyl substituted with aryl or heteroaryl;

R³ is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino,

20 monoalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7- carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a

25 sulfur or oxygen atom and whose carbon atoms may be optionally

substituted with one or more of the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy

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or alkoxy carbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and

n is zero or one.

- 5 2. A compound according to claim 1 wherein the compound is of formula (I).
3. A compound according to claim 2 wherein J is O.
- 10 4. A compound according to claim 2 wherein R¹ is alkyl, more preferably methyl; R² is hydrogen, benzyl, 4-chlorobenzyl, trimethylacetoxymethyl or cyclohexylmethyl; and R³ is hydrogen, methyl or ethyl and n is zero.
- 15 5. A compound according to claim 2 wherein (R^a and R^b) complete a saturated 5 membered ring, (R^b and R^c) complete a saturated 5, 6 or 7 membered ring or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms.
- 20 6. A compound according to claim 1 which is:
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)-
cyclopenta[4,5]imidazo[2,1-b]purin-4-one;
7,8-Dihydro-5-methyl-3-(phenylmethyl)-3*H*-imidazo[2,1-b]purin-4(5*H*)-
one;
- 25 cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-3-(phenylmethyl)-3*H*-
benzimidazo[2,1-b] purin-4(5*H*)-one;
5,7,8,9-Tetrahydro-5-methyl-3-(phenylmethyl)pyrimido[2,1-b]purin-
4(3*H*)-one;
- 30 7,8-Dihydro-8-phenyl-5-methyl-3-(phenylmethyl)-3*H*-imidazo[2,1-
b]purin-4(5*H*)-one;
5',7'-Dihydro-5'-methyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-
imidazo[2,1-b]purin]-4'(3'*H*)-one;
cis-5,6a,11,11a-Tetrahydro-5-methyl-3-
(phenylmethyl)indeno[1',2':4,5]imidazo[2,1-b]purin-4(3*H*)-one;

- 5',7'-Dihydro-2',5' dimethyl-3'-(phenylmethyl)spiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
- 5 cis-5,6a,7,11b-Tetrahydro-5-methyl-3-(phenylmethyl)indeno[2',1',:4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4-(3H)-one;
5'-Methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]-4'(5'H)-one;
- 10 7,8-Dihydro-2,5,7,7-tetramethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5'H)-one;
7,8-Dihydro-7(R)-phenyl-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
- 15 7,8-Dihydro-2,5-dimethyl-3,7(R)-bis(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(±)-7,8-Dihydro-2,5-dimethyl-7-ethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(S)-7,8,9,10,10a(R)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
- 20 6a(R)-7,8,9,10,10a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-isopropyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
- 25 7,8-Dihydro-2,5,7(R)-trimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-7,7a,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-cyclopenta[5,6]pyrimido[2,1-b]purin-4(5H)-one;
- 30 7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(2-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(methoxycarbonyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;

- 7,8-Dihydro-2,5-dimethyl-7(R,S)-(1-propyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
- 7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
- 5 7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
- 5,7,8,9-Tetrahydro-2,5,7,9(R,S)-pentamethyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
- 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-
- 10 (phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 5,6a(S),7,8,9,9a(R)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- cis-6a,7,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
- 15 5',7'-Dihydro-2',5'-dimethyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8H)-imidazo[2,1-b]purin]-4'(3'H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclohept[6,7]imidazo[2,1-b]purin-4(3H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-
- 20 cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 25 cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-5-methylcyclopenta[4,5]imidazo[2,1-
- 30 b]purin-4(3H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-one;
- cis-5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-di-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

- 2'-Methyl-3'-spiro{cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin}-
4'(5'H)-one;
- 7,8-Dihydro-2,5-dimethyl-7(R)-(1-methylethyl)-3H-imidazo[2,1-b]purin-
4(5H)-one;
- 5 7,8-Dihydro-2,5,7,7-tetramethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3H-imidazo[2,1-b]purin-
4(5H)-one;
- 6a(R),7,8,9,10,10a(S)-Hexahydro-2,5-dimethyl-3H-benzimidazo[2,1-
b]purin-4(5H)-one;
- 10 5',7'-Dihydro-2',5'-dimethylspiro{cyclohexane-1,7'(8'H)-imidazo[2,1-
b]purin}-4'(3'H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-
(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-thione;
- 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-
15 (phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-thione;
- cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(4-chlorophenyl-
methyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)-
cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 20 cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)-
cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-
methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-
25 one;
- cis-5,6a,7,8,9,9a-Hexahydro-2,3,5-trimethylcyclopent[4,5]imidazo[2,1-
b]purin-4(3H)-one;
- cis-5,6a,7,8,9,9a-Hexahydro-2-(hydroxymethyl)-5-methyl-3-
(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 30 cis-5,6a,7,8,9,9a-Hexahydro-2-methylthio-5-methyl-3-(phenylmethyl)-
cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)-
cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid;
- cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)-

- cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid, methyl ester;
 cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)-
 cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
 cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-
 5 (phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
 cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methyl-
 cyclopent[4,5]imidazo[2,1-b]purin-4-(1H)one;
 cis-5,6a,7,8,9,9a-Hexahydro-3,5-bis-(phenylmethyl)
 cyclopent(4,5)imidazo(2,1-b)purin-4(3H)one;
 10 cis-6a,7,8,9,10,10a-Hexahydro-3,5-bis-(phenylmethyl)-3H-
 benzimidazo[2,1-b]purin-4(5H)one;
 cis-3-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methyl-
 cyclopent[4,5]imidazo(2,1-b)purin-4(3H)one;
 5'-Methyl-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'H)-(3'H)-
 15 imidazo[2,1-b]purin]-4'(5'H)one;
 2',5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-
 imidazo[2,1-b]purin]-4'(5'H)one;
 cis-5,6a,(R)7,8,9,9a(S)-Hexahydro-5-methyl-3-
 (phenylmethyl)cyclopent[4,5]imidazo(2,1-b)purin-4(3H)one;
 20 cis-3-Cyclopentyl-5,6a,7,8,9,9a-Hexahydro-2,5-
 dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;36
 5'-Methyl-2'-trifluoromethyl-3'-(phenylmethyl)spiro{cyclo-pentane-
 1,7'(8'H)-(3'H)imidazo[2,1-b]purin}-4'(5'H)-one;
 7,8-Dihydro-5,7,7-trimethyl-2-trifluoromethyl-3-(phenylmethyl)-3H-
 25 imidazo[2,1-b]purin-4(5H)-one;
 (+/-)-cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-trifluoromethyl-3-
 (phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
 (+/-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-(phenylmethyl)-
 3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
 30 (+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-
 pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
 (-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-
 pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;

- (+/-) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
- (+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
- 5 (-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
- 6a,7,8,9,10,10a,11,12,13,13a-Decahydro-2,5-dimethyl-(3-phenylmethyl)naph[1,8a-d]imidazo[2,1-b]purin-4(5H)-one;
- 7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
- 10 7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
- 7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
- 15 7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
- 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[(trimethylacetoxymethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one];
- 20 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-pyridylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[2-(1-morpholinyl)ethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[acetoxymethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 25 5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 5,6a(R),7(S),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
- 30 5,6a(S),7(R),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one];
- cis*-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one];

cis-5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one]; or
cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one].

5

7. A compound according to claim 1 characterized in that
J is O;

R¹ is alkyl, preferably methyl;

10 R² is hydrogen, benzyl, 4-chlorobenzyl, cyclohexylmethyl or
trimethylacetoxymethyl;

R³ is hydrogen, or alkyl such as methyl or ethyl;

n is zero; and

15 (R^a and R^b) forms a saturated 5 membered ring, or (R^b and R^c) forms a
saturated 5, 6 or 7 membered ring, or (R^a and R^b) and (R^b and R^c) each
complete a saturated ring and each ring contains 5 or 6 carbon atoms .

8. A compound according to claim 1 which is:

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-

20 (phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

2', 5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-
imidazo[2,1-b]purin]-4'(5'H)one; or

25 (+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno
[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one.

9. A pharmaceutical composition comprising a compound of formula (I)
or (I') in an amount effective to inhibit phosphodiesterase.

30

10. A pharmaceutical composition comprising a compound of formula
(I) and (I') in an amount effective to relax smooth muscle.

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11. A pharmaceutical composition comprising an anti-hypertensive or a bronchodilating effective amount of the compounds (I) and (I').
- 5 12. A method for treating hypertension or bronchoconstriction in a mammal comprising administering to a mammal in need of such treatment an amount of at least one of compounds (I) and (I') effective to treat any of the above diseases.
- 10 13. A method for maintaining guanosine 3':5'-cyclic monophosphate (cGMP) levels in a mammal by administering an amount of compounds (I) and (I') effective to maintain or increase cGMP.

INTERNATIONAL SEARCH REPORT

International Application

PCT/US 91/04154

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 487/14 C 07 D 487/20 A 61 K 31/52 //

(C 07 D 487/14, 239:00, 239:00, 235:00), (C 07 D 487/14, 239:00, 235:00, 235:00),

(C 07 D 487/20, 239:00, 239:00, 235:00), (C 07 D 487/20, 239:00, 235:00, 235:00)

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
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Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
	No relevant documents have been disclosed. -----	

¹⁰ Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-10-1991	28. 10. 91
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	 Danielle van der Haas