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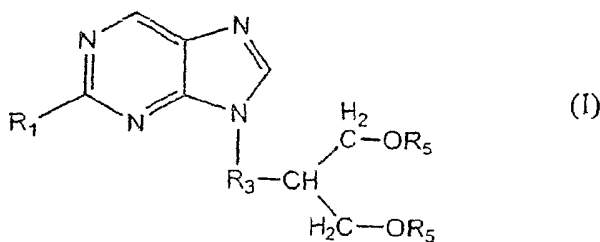
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PREPARATION OF FAMCICLOVIR AND OTHER PURINE DERIVATIVES



(57) Abstract: Purine derivatives substituted at the 9-position of formula (I), are prepared from a chloro substituted purine starting material, first making an alkyl substitution at the 9-position, then forming the desired esterified side chain, reducing this and hydrogenating the resultant diol prior to addition of alkyl carbonyl groups.

PREPARATION OF FAMCICLOVIR AND OTHER PURINE DERIVATIVES

Field of Invention

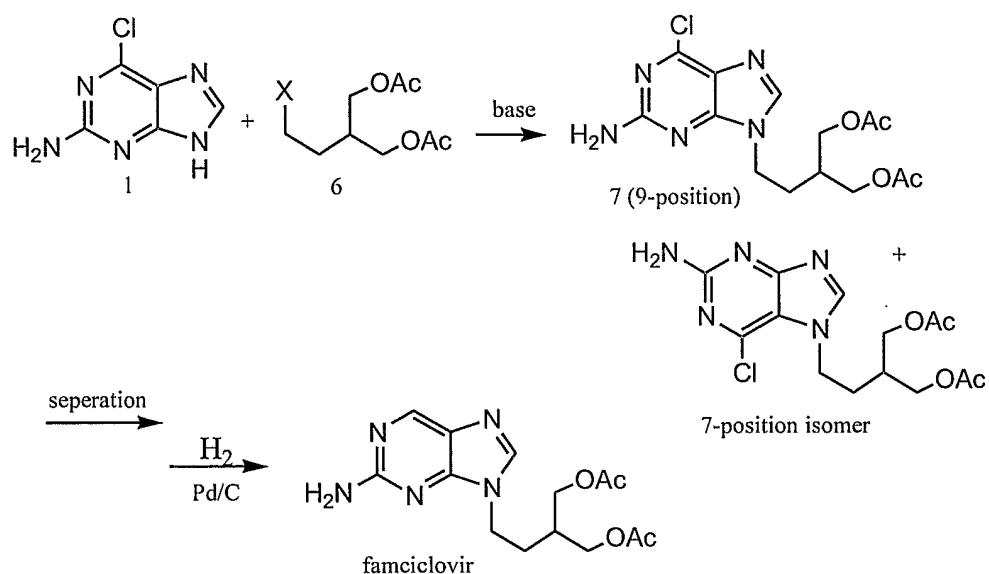
- 5 The present invention relates to the preparation of various 9-substituted purine derivatives, including famciclovir.

Background of the Invention

- 10 Famciclovir (9-[4-acetoxy-3-(acetoxymethyl) but-1-yl]-2-aminopurin) is one of a number of compounds known to have useful antiviral activity and described, for example, in EP 141,927. Famciclovir has antiviral activity relevant for treatment of a number of viral infections, including herpes simplex, varicella-zoster and hepatitis.
- 15 A number of different routes for preparation of purine derivatives such as famciclovir are known, including those described in EP 182,024, US 5,684,153, US 5,138,057, US 5,917,041, US 6,761,767 and WO 2004/110343.

- One method, set out below in Scheme 1, is known from EP 182,024 and US patents
- 20 5,684,153; 5,138,057 and 6,761,767. Here the X on starting compound 6 is either halogen or any other leaving group such as tosyl or mesyl.

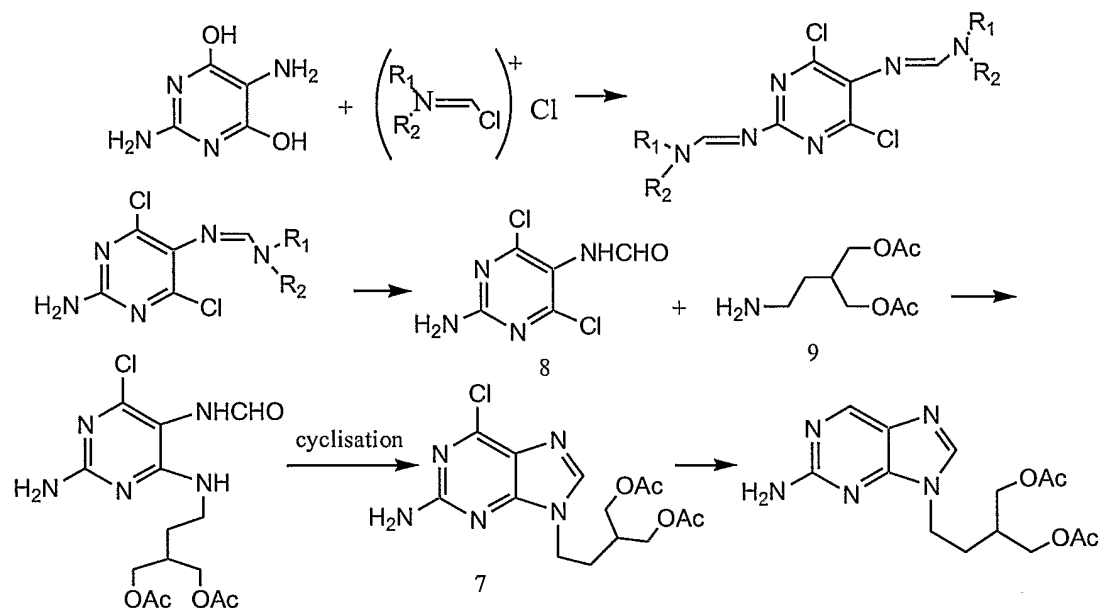
- 2 -



Scheme 1

- 5 The starting material, 2-amino-6-chloro-purine (compound 1), is commercially available at a reasonable price. However, a common problem associated with this process is lack of regioselectivity as the undesired 7-position isomer is generated simultaneously, reducing yield and requiring a separation step to remove this unwanted (inactive) isomer.
- 10 A further method, set out as Scheme 2, is known from US 5,971,041.

- 3 -



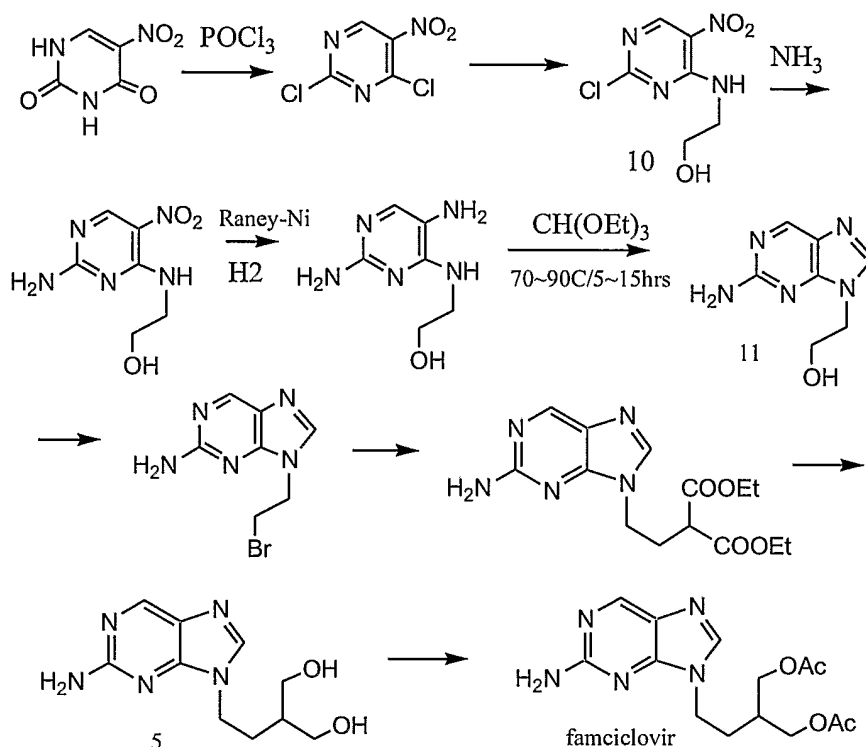
Scheme 2

- 5 The method of Scheme 2 tries to address this problem in order to maximize the percentage of desired 9-substituted compound by carefully controlling the reaction conditions. However, starting compounds 8 and 9 are not commercially available and have to be prepared separately. Also, the overall yield for famciclovir is low, less than 30%.

10

A more recent method, set out as Scheme 3, is described in WO 2004/110343.

- 4 -



Scheme 3

- 5 But this process only produces famciclovir at about 18% overall yield. Again, compound 11 used in this process is not commercially available and has to be prepared from nitroimidazole.

10 The methods described in scheme 2 and 3 provide a solution to the above mentioned regioselectivity problem by introducing the alkyl side-chain first onto the desired 9-position before the formation of fused imidazole ring. Nevertheless, a common drawback in these methods is their lengthy procedure and overall low yield.

15 An object of the present invention is to provide an alternative process for preparation of purine derivatives such as famciclovir.

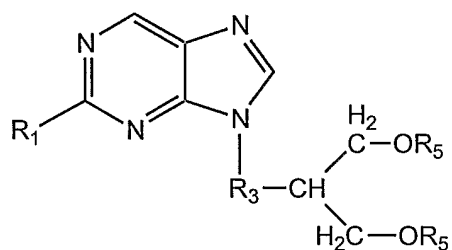
An object of specific embodiments of the invention is to provide a process for preparation of these purine derivatives with improved efficiency, for example with a reduced number of steps and/or improved yield of the desired end product.

- 5 -

Summary of the Invention

According to the present invention, there is provided a method for preparation of a purine derivative of formula I

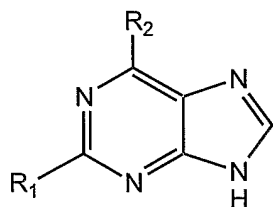
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(I)

10

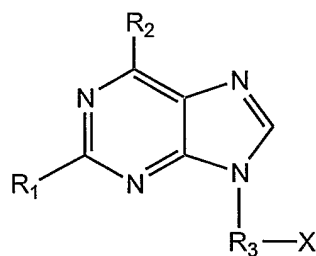
comprising reacting a compound of formula VI



(VI)

15

with X-R₃-X to form a compound of formula V



(V)

20

- 6 -

wherein R_1 is selected from the group consisting of amino, hydroxyl and C_{1-6} alkyl (optionally substituted), R_2 is halo or an electron withdrawing group, R_3 is C_{1-6} alkyl (optionally substituted) and each X is independently a leaving group. All substituents are optionally protected.

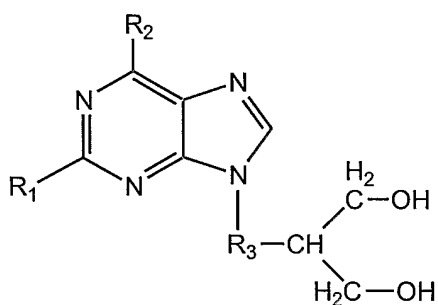
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It has been found that employment of this step results in formation of the 9-substituted compound of formula V with high regioselectivity, the 9-substituted isomer being obtainable in specific embodiments of the invention at a ratio of 15-20:1 compared with the formation of the contaminating 7-substituted isomer. Hence, there is significantly reduced contamination by the unwanted isomer, reduced need for separation of the products of this reaction step and improved yield overall of the desired end product.

10

In a further method of the invention, a desired purine derivative of formula I is obtained in a method comprising hydrogenating an intermediate diol of formula III

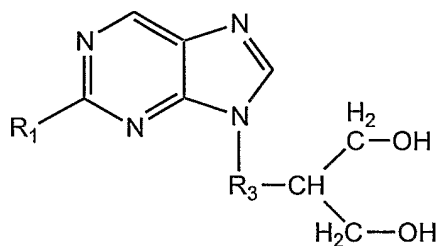
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(III)

so as to yield a compound of formula II.

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(II)

- 7 -

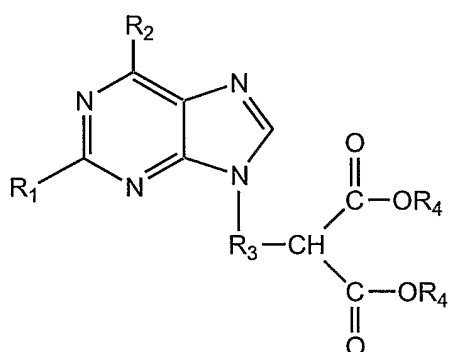
In operation of a method of the invention employing this step, there is high yield of the desired intermediate II and absence of a trans-acetylation side-reaction seen in prior art methods in which the corresponding hydrogenation step is carried out on a diester intermediate.

A preferred method of the invention employs both the steps detailed above, namely reacting a compound of formula VI with $X-R_3-X$ to form a compound of formula V and also hydrogenating an intermediate compound of formula III so as to form a compound of formula II.

Detailed Description of the Preferred Embodiments

A preferred embodiment of the invention provides a five step process for manufacture of a compound of formula I from a starting material of formula VI. Initial formation of compound V and an intermediate hydrogenation step are as described above. Other steps are as follows.

A compound of formula V can be converted to a compound of formula IV



(IV)

by reaction of compound V with $CH_2(COOR_4)_2$ typically under basic conditions, wherein each R_4 is independently a group such that subsequent hydrogenation yields a diol. R_4

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can be C₁₋₆ alkyl (optionally substituted by halo, amino, hydroxyl and/or C₁₋₆ alkyl), preferably C₁₋₃ alkyl. Generally, both R₄ groups are the same.

5 The compound of formula IV can be then subjected to a reduction reaction using a reducing agent to yield a diol compound of formula III.

10 The compound of formula II can be converted into the end product of formula I by reaction with (R₅)₂O, wherein each R₅ is independently selected from C₁₋₆ alkyl carbonyl, preferably C₁₋₃ alkylcarbonyl. Generally, both R₅ groups are the same.

For preparation of famciclovir, in accordance with a preferred embodiment of the invention, R₁ is amino, R₂ is chloro, R₃ is ethyl and R₅ is acetyl.

15 While a process of a specific embodiment has advantageously been used for preparation of the particular compound famciclovir, the process more generally may be employed to obtain other purine derivatives with different side chains located at the 9-position of the purine. For instance, the R₅ group, acetyl of famciclovir, can be replaced by any alkylcarbonyl group, especially C₁₋₆ alkyl carbonyl, preferably C₁₋₃ alkyl carbonyl, optionally substituted by, for example, halo, hydroxyl and/or C₁₋₆ alkyl. Separately, the 2-substituted butyl of famciclovir (R₃CH) can be replaced by another alkyl chain (see
20 further discussion below) such as C₁₋₆ alkyl, preferably C₁₋₄ alkyl, optionally substituted by, for example, halo, amino, hydroxyl and/or C₁₋₆ alkyl. Halo or halogen refers throughout to fluoro, chloro, bromo and iodo, preferably bromo or chloro, more preferably chloro.

25 The 2-amino substituent of famciclovir (R₁) can also, and independently from the variations noted elsewhere, be replaced in other embodiments of the invention by an alternative substituent. One option is for there to be no substituent, i.e. a hydrogen. Another option is for the 2- position to be substituted by a group selected from amino, hydroxyl (both optionally protected) or C₁₋₆ alkyl, preferably C₁₋₃ alkyl, optionally
30 substituted by, for example, amino, hydroxyl and/or C₁₋₆ alkyl.

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The starting material of a specific embodiment is 2-amino-6-chloro-purine, but can generally be a purine substituted at the 2- and 6- positions in accordance with the above.

Substitution of the purine or purine derivative starting material at the 9-position by an
5 alkyl group, as shown for example in step 1 in the example, can be carried out using X-
C₂₋₆ alkyl-X, where each X is independently a leaving group such as halogen, p-tosyl,
mesyl, triflate, alkylcarbonate, preferably halogen. Solvents suitable for this step include
polar solvents such as DMF, DMSO, acetonitrile and mixtures of such. The step is
suitably carried out in the presence of base, which can be an inorganic base such as
10 K₂CO₃ or Na₂CO₃, KOH and/or NaOH or appropriate mixtures of these.

Converting compound V to compound IV (step 2 in the example) is suitably carried out
in the presence of a base, which can be K₂CO₃ or KOH or even a lithium amide like
LDA. The solvent used can be similar to that for step 1. There is not much side reaction
15 at all in this step and yields of about 96% can be obtained.

Converting compound IV to compound III (step 3 in the example) is a reduction of the
ester functionality for which a number of known reducing agents are suitable.

20 The diol on compound III may be hydrogenated to compound II (step 4 in the example)
by any suitable catalyst, such as Pt, Pd, raney Ni. Because hydrogenation was carried out
in alcoholic solvent in the prior art processes, cross acetylation of solvent occurred, which
meant that an acetyl group on the 9-side chain group could be lost to give a 9-substituted
purine alcohol. This side reaction is substantially avoided in the present process.

25 Compound II can be converted to compound I (step 5 in the example) in an inert, organic
solvent such as CH₂Cl₂, CH₃Cl, EtOAc etc, and mixtures thereof. In the example this
step is carried out in the presence of the triethylamine though pyridine or any tertiary
amines may also be used.

30 The process described herein addresses the problems discussed in the background art.
The starting materials and reactants used in the process are all ready available at a

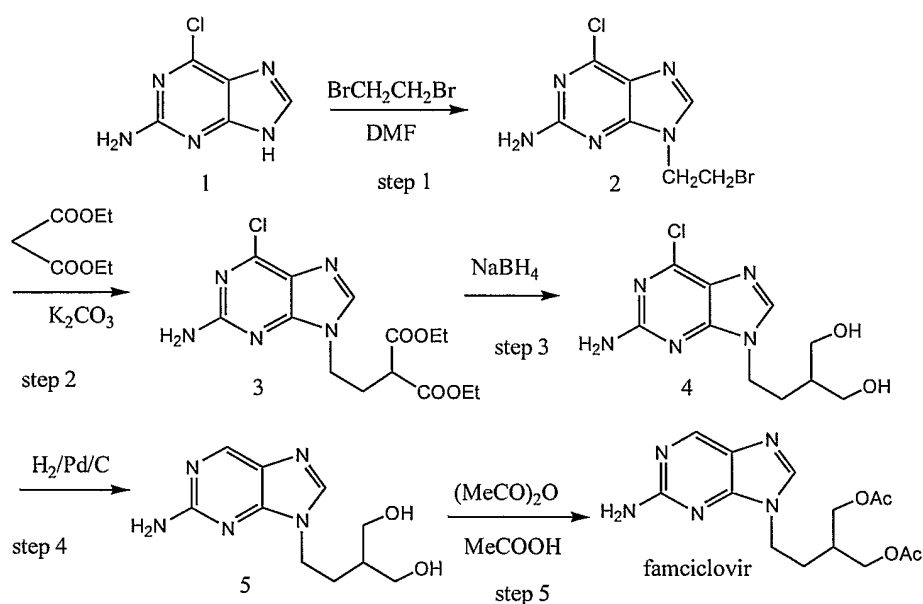
- 10 -

- reasonable price. In the specific embodiment, by using compounds VI and 1,2-dibromoethane, the invention forms the desired 9-position alkylated purine in a ratio of 15~20:1(9-position against 7-position isomer), an improvement over the known methods. The process comprises 5 steps and, as per the example, produced famciclovir with an overall yield of over 40%, again an improvement. Another feature in the process is the operational advantage achieved by hydrogenating a diol instead of a diester, avoiding the trans-acetylation side reactions. Referring to the example, this in turn reduced the potential impurity and increased the yield of the process.
- The invention is now described in more detail with reference to a specific embodiment as set out in the following example.

Example 1

Preparation of Famciclovir

Famciclovir was prepared according to the following synthetic scheme:-



- 11 -

The steps were as follows.

Step 1: preparation of

2-amino-6-9-chloro-(2-bromoethyl) purine (2)

5

A mixture of 2-amino-6-chloropurine (33.9g, 0.2mol), potassium carbonate (69g, 0.5mol) and DMF (340ml) were placed in a 1L 3-neck flask, and heated at 60-65°C for 1hour. Then the 1,2-dibromoethane (112.8g, 0.6mol) was added and the resulting mixture was refluxed for 24 hours. The reaction mixture was then cooled and filtered. The filtrate solution was concentrated by distillation at reduced pressure. The residue was dissolved with methanol (170ml) and cooled down to 0~5°C. The titled compound 2 was obtained in crystalline form (50.3g, yield 91%).

10

¹H NMR (*d*-DMSO): 3.89(t,2H,CH₂CH₂Br), 4.45(t,2H, CH₂CH₂Br), 6.94(s,2H,NH₂), 8.15(s,1H,aromatic)

15

Step 2: preparation of

diethyl 2-[2-(2-amino-6-chloro-9H-purine-9-yl)-ethyl]-1,3-malonate (3)

20

To a dried 1L reaction flask were added sequentially the DMF (380g), anhydrous K₂CO₃ (55g, 0.04mol), intermediate compound 2 (98g, 0.06mol) and diethyl malonate (40g, 0.0145mol). The mixture was heated to 60°C and stirred at 60°C for 50 hours. Then the carbonate salt was removed by filtration. Solvent was then recovered by distillation at reduced pressure (keeping the temperature lower than 95°C at all times). The residue was cooled to room temperature and dissolved with methanol (400g). The title compound 3 was recovered after the methanol solution was kept at 0~4°C for 4 hours (48g, yield 95%).

25

¹H NMR (*d*-DMSO): 1.10(t,6H,CH₂CH₃), 2.33(q,2H, NCH₂CH₂CHCO), 3.52(t,1H,), 3.59(m,4H,OCH₂CH₃), 4.11(t,2H,NCH₂CH₂CHCO), 6.87(s,2H, NH₂), 8.06(s,1H,aromatic)

30

Step 3: preparation of

2-[2-(2-amino-6-chloro-9H-purine-9-yl)-ethyl]-1,3-propanediol (4)

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To a 1L flask was added the dichloromethane (350ml) to dissolve the intermediate compound 3 (50g, 0.013mol), followed by NaBH₄ (17.5g, 0.046mol) and methanol (95ml). The reaction mixture was stirred at 20~25°C for 2 hours, then diluted with water (150ml) and settled at room temperature. The separated organic layer was removed. The aqueous layer (along with the precipitated solid) was cooled down with an ice/water bath, and hydrochloric acid (25-30%) was added slowly till the solution became neutral. The product was obtained by cooling in an ice/water bath. The precipitate was collected by filtration, and then washed with cold brine. The collected diol 4 was dried under vacuum (30g, yield 80%).

¹H NMR (*d*-DMSO): 1.42(t,1H,NCH₂CH₂CH), 1.75(q,2H, NCH₂CH₂CH) 3.35(d,4H,CH₂OH), 4.09(t,2H,NCH₂CH₂CH), 4.45(s,2H,OH), 6.86(s,2H, NH₂), 8.12(s,1H,aromatic)

Step 4: preparation of

2-[2-(2-amino-9H-purine-9-yl)-ethyl]-1,3-propanediol (5)

The diol 4 (25g, 9.2mmol) was dissolved with a mixed solvent of ethyl acetate (200ml) and ethanol (100ml) in a 1L steel autoclave. The palladium charcoal (5g) and triethylamine (12g) were added as well. The reaction mixture was kept at 55°C under hydrogen pressure (0.8Mpa) for 4 hours. The reaction was regarded as completed when no hydrogen intake was observed. The catalyst was removed by filtration after cooling down. The filtrate was concentrated by distillation under reduced pressure. The residue was dissolved by addition of DCM and water. The separated aqueous layer was extracted with more DCM (30ml x 3). The combined organic solution was dried and distilled to remove solvent. The residue was dissolved with ethyl acetate (80ml) and kept at room temperature for 4 hours. The product was collected by filtration and dried under vacuum (18g, yield 82%).

¹H NMR (*d*-DMSO): 1.42(m,1H,NCH₂CH₂CH), 1.75(q,2H, NCH₂CH₂CH) 3.42(d,4H,CH₂OH), 4.09(t,2H,NCH₂CH₂CH), 4.44(s,2H,OH), 6.44(s,2H, NH₂), 8.05(s,1H,aromatic), 8.54(s,1H, aromatic)

Step 5: preparation of famciclovir

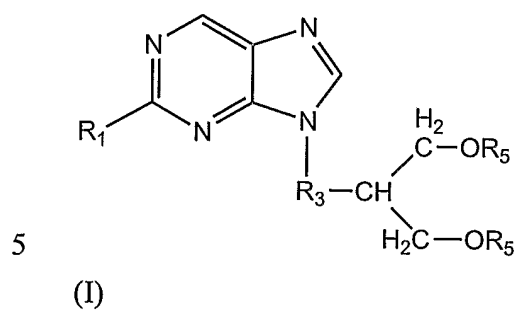
- 13 -

- To a dry 1L flask were added the intermediate diol 5 (50g, 21.5mmol), dichloromethane (500ml), triethylamine (31g, 30.6mmol) and catalytic dimethylaminopyridine (3.1g). The acetic anhydride (120g, 31mmol) was then added dropwise, keeping the solution at 25~30°C. The reaction mixture was stirred at room temperature for 10 hours. Water was added to dilute the reaction mixture, and 5% Sodium hydroxyl solution (5%) was added till the solution turned neutral. The separated organic layer was washed with water (200ml x 2), saturated brine and dried by sodium sulphate. The dichloromethane was then removed under reduced pressure, and residue was dissolved with boiling methanol (180ml). The famciclovir crystallized out by keeping the methanol solution at 0~4°C for 4 hours (60g, yield 90%).
- ¹H NMR (CDCl₃): 1.89(m,2H,NCH₂CH₂CH), 1.98(m,1H NCH₂CH₂CH) 2.03(s,6H,COCH₃), 4.11(d,4H,CH₂OCO), 4.19(t,2H,NCH₂CH₂CH), 5.18(s,2H, NH₂), 7.73(s,1H,aromatic), 8.64(s,1H, aromatic)
- Hence methods for the preparation of purine derivatives, such as famciclovir have been provided.

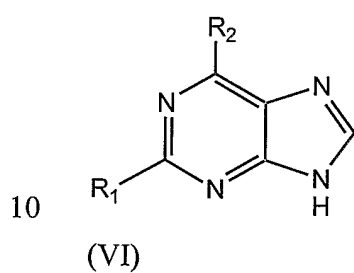
- 14 -

Claims

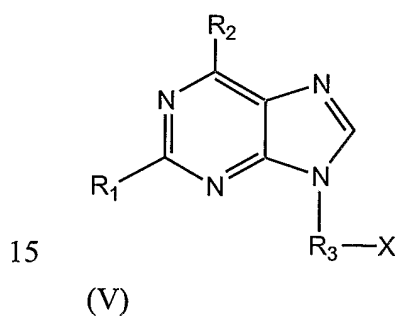
1. A method for preparation of a purine derivative of formula I,



comprising reacting a compound of formula VI



with X-R3-X to form a compound of formula V



wherein

20 R_1 is selected from the group consisting of amino or hydroxyl (both optionally protected, C_{1-6} alkyl (optionally substituted by amino, hydroxyl and/or C_{1-6} alkyl),

R_2 is halo or an electron withdrawing group,

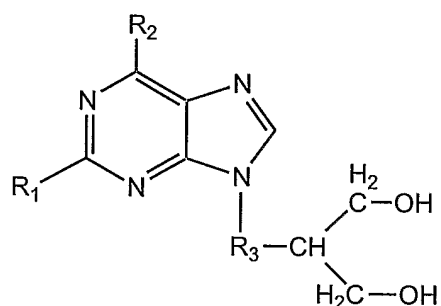
- 15 -

R_3 is C_{1-6} alkyl (optionally substituted by halo, amino, hydroxyl and/or C_{1-6} alkyl),
 each R_5 is independently C_{1-6} alkyl carbonyl (optionally substituted by halo,
 hydroxyl and/or C_{1-6} alkyl), and
 each X is independently a leaving group.

5

2. A method according to claim 1, carried out in a polar solvent in the presence of base.

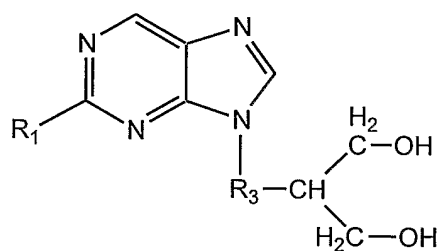
3. A method according to claim 1 or 2, comprising hydrogenating a diol of formula III



10

(III)

so as to yield a compound of formula of II



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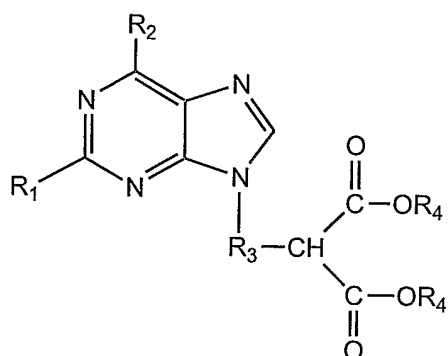
(II)

4. A method according to claim 3, carried out using hydrogen in the presence of a
 20 hydrogenation catalyst.

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5. A method for preparation of a purine derivative of formula I, comprising hydrogenating a diol of formula III so as to yield a compound of formula of II, wherein R_1 , R_2 , R_3 and R_5 are as defined above.

- 5 6. A method according to any previous claim, comprising converting a compound of formula V to a compound of formula IV



(IV)

10

by reacting compound V with $CH_2(COOR_4)_2$, wherein R_4 is selected from C_{1-6} alkyl, optionally substituted by halo, hydroxyl, amino, and/or C_{1-6} alkyl.

15

7. A method according to claim 6, carried out in a polar solvent in the presence of base.

8. A method according to any previous claim, comprising reducing a compound of formula IV to yield a compound of formula III.

20

9. A method according to any previous claim, comprising reacting a compound of formula II with $(R_5)_2O$ to form a compound of formula I.

10. A method according to claim 9, carried out in an inert organic solvent.

11. A method according to claim 10, carried out in the presence of an amine.

25

12. A method according to claim 11, wherein the amine is a tertiary amine.

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13. A method according to any previous claim, for preparation of famciclovir, wherein R₁ is amino, R₂ is chloro, R₃ is butyl and R₅ is acetyl.
- 5 14. A method for preparation of famciclovir, substantially as hereinbefore described with reference to the example.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/001877

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, EMBASE, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CIAPETTI P ET AL: "A Simple Preparation of N-Vinyl Derivatives of DNA Nucleobases" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 37, 10 September 1998 (1998-09-10), pages 11305-11310, XP004132319 ISSN: 0040-4020 Scheme 4 page 11306</p> <p style="text-align: center;">----- -/--</p>	1,2



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

8 August 2006

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25/08/2006

Name and mailing address of the ISA/

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Marzi, E

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/001877

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>BRAND ET AL: "Convenient Synthesis of 9-[4-Hydroxy-3-(hydroxymethylbutyl)]-guanine (penciclovir) and 9-[4-Acetoxy-3-(acetoxymethyl)butyl]2-amino-9H-purine (Famciclovir)" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 55, 1999, pages 5239-5252, XP002126581 ISSN: 0040-4020 Scheme 5 page 5244</p>	6-8
Y	<p>HARNDEN M R ET AL: "Prodrugs of the selective antiherpesvirus agent 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123) with improved gastrointestinal absorption properties" JOURNAL OF MEDICINAL CHEMISTRY 1989 UNITED STATES, vol. 32, no. 8, 1989, pages 1738-1743, XP002390989 ISSN: 0022-2623 Scheme 1 page 1739</p>	3-5,9-14
Y	<p>WO 2004/110343 A (KYUNG DONG PHARM. CO., LTD; LEE, BYOUNG-SUK; SHIN, SANG-HOON; PARK, JON) 23 December 2004 (2004-12-23) cited in the application claim 6 page 19; example 15</p>	6-14
Y	<p>US 5 036 071 A (JOHANSSON ET AL) 30 July 1991 (1991-07-30) column 7, lines 8-55</p>	3-5
Y	<p>WO 95/28402 A (SMITHKLINE BEECHAM PLC; DALES, JOHN, ROBERT, MANSFIELD) 26 October 1995 (1995-10-26) Scheme 2 page 6</p>	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2006/001877

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004110343 A	23-12-2004	AU 2004246958 A1 EP 1636231 A2	23-12-2004 22-03-2006
US 5036071 A	30-07-1991	DE 3575927 D1 EP 0186640 A1 JP 1945763 C JP 6080061 B JP 61171481 A	15-03-1990 02-07-1986 23-06-1995 12-10-1994 02-08-1986
WO 9528402 A	26-10-1995	AP 582 A AP 703 A AT 201209 T AU 691000 B2 AU 2670695 A BG 63464 B1 BG 100926 A BR 9507494 A CA 2188181 A1 CN 1150427 A CZ 9603053 A3 DE 69520945 D1 DE 69520945 T2 DK 756597 T3 DZ 1872 A1 EG 20938 A EP 0756597 A1 ES 2158948 T3 FI 964193 A GR 3036338 T3 HK 1012348 A1 HU 75339 A2 IL 113409 A IN 183830 A1 JP 9512000 T MA 23518 A1 NO 964395 A NZ 287858 A OA 10376 A PL 316943 A1 PT 756597 T RO 118950 B1 RU 2158266 C2 SK 133296 A3 ZA 9503110 A	09-04-1997 04-12-1998 15-06-2001 07-05-1998 10-11-1995 28-02-2002 31-07-1997 12-08-1997 26-10-1995 21-05-1997 11-06-1997 21-06-2001 28-03-2002 20-08-2001 17-02-2002 28-06-2000 05-02-1997 16-09-2001 18-12-1996 30-11-2001 12-04-2002 28-05-1997 17-08-1999 29-04-2000 02-12-1997 31-12-1995 15-10-1996 26-06-1998 20-11-2001 17-02-1997 30-11-2001 30-01-2004 27-10-2000 07-05-1997 20-05-1996