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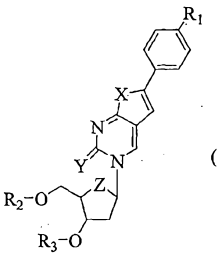
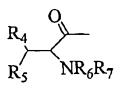
(54) Title: ANTI-VIRAL PYRIMIDINE NUCLEOSIDE DERIVATIVES



(II)



(IV)

(57) Abstract: A compound for use in the treatment or prophylaxis of viral infections such, for example as chicken pox or shingles caused by the Varicella Zoster virus, said compound having the general formula (II): wherein X is O, S, NH or CH_2, Y is O, S or NH, Z is O, S or CH_2, R_1 is C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl, and one of R_2 and R_3 is OH, and the other of R_3 and R_2 is a neutral, non-polar amino acid moiety, or a pharmaceutically acceptable salt or hydrate thereof. Said neutral, non-polar amino acid moiety R_2 or R_3 may be (IV): in which R_4, R_5, R_6 and R_7 are each independently H or C_{1-2} alkyl. In preferred embodiments, one of R_2 or R_3 is valine, leucine, isoleucine or alanine, particularly valine.

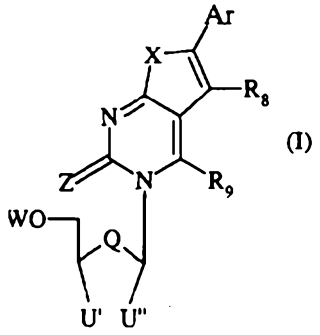
WO 2007/129083 A1

ANTI-VIRAL PYRIMIDINE NUCLEOSIDE DERIVATIVES

[0001] The present invention relates to ester derivatives of certain nucleoside analogues having therapeutic use in the prophylaxis and treatment of viral infections such, for example, as those caused by the Varicella Zoster virus (VZV). Varicella Zoster virus is the aetiological agent in chickenpox and shingles, which can cause considerable human illness and suffering. The invention also provides a pharmaceutical composition comprising such an ester derivative, and a method of treatment or prophylaxis of viral infection by administering such a derivative.

[0001a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[0002] WO 01/83501 A1, the contents of which are incorporated herein by reference, describes certain nucleoside analogues with potent activity against Varicella Zoster virus (VZV), said nucleoside analogues having general formula (I):



(I)

wherein:

Ar is an optionally substituted, aromatic ring system, the aromatic ring system comprising one six-membered aromatic ring or two fused six-membered aromatic rings;

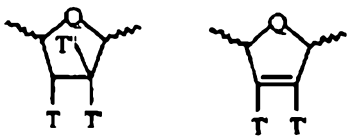
R_8 and R_9 are each independently selected from the group comprising hydrogen, alkyl, cycloalkyl, halogens, amino, alkylamino, dialkylamino, nitro, cyano, alkyoxy, aryloxy, thiol, alkylthiol, arythiol, aryl;

Q is selected from the group comprising O, S and CY_2, where Y may be the same or different and is selected from H, alkyl and halogens;

X is selected from the group comprising O, NH, S, N-alkyl, (CH_2), where m is 1 to 10, and CY_2 where Y may be the same or different and is selected from hydrogen, alkyl and halogens;

Z is selected from the group comprising O, S, NH, and N-alkyl;

U" is H and U' is selected from H and CH_2T, or U' and U" are joined so as to form a ring moiety including Q wherein U'-U" together is respectively selected from the group comprising CTH-CT'T" and CT'=CT', so as to provide ring moieties selected from the group comprising:



wherein T is selected from the group comprising OH, H, halogens, O-alkyl, O-acyl, O-aryl, CN, NH_2 and N_3;

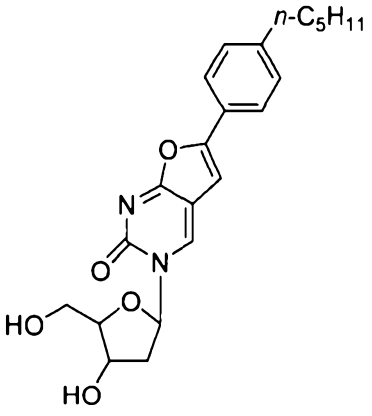
T' is selected from the group comprising H and halogens and, where more than one T' is present, they may be the same or different;

T" is selected from the group comprising H and halogens; and

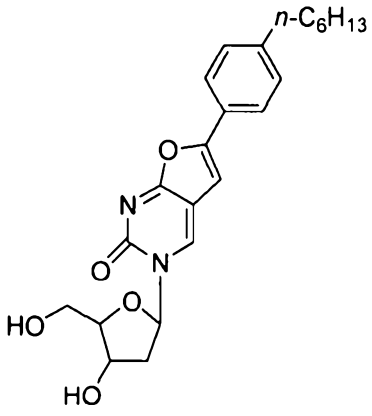
W is selected from the group comprising H, a phosphate group and a pharmacologically acceptable salt, derivative or pro-drug thereof;

with the proviso that when T is OAc and T' and T" are present and are H, Ar is not 4-(2-benzoxazolyl) phenyl.

[0003] Compounds **1** and **2** below are particularly preferred compounds according to WO 01/83501 A1:



Compound **1**



Compound **2**

[0004] In one or more preferred embodiments, the present invention relates to novel compounds for the treatment or prophylaxis of viral infections, especially those caused or exacerbated by the Varicella Zoster virus (VZV).

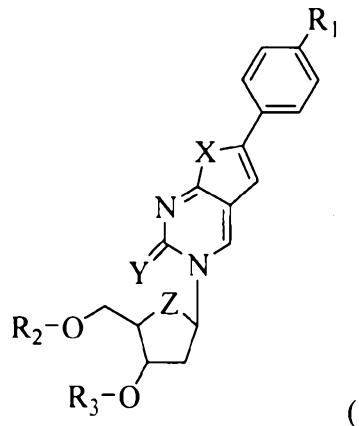
[0005] In one more preferred embodiments, the present invention relates to compounds for the treatment of such viral infections, said compounds having improved bioavailabilities.

[0006] In one or more preferred embodiments the present invention relates to such compounds which have advantageous pharmacokinetic properties.

[0007] In one or more preferred embodiments, the present invention relates to a method of making such compounds.

[0007a] It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

[0008] According to a first aspect of the present invention therefore there is provided a compound of general formula (II):



(II)

wherein X is O, S, NH or CH_2,

Y is O, S or NH,

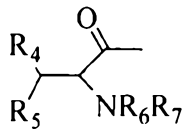
Z is O, S or CH_2,

R_1 is C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl, and

one of R_2 and R_3 is H, and the other of R_3 and R_2 is an amino acid moiety having a neutral, non-polar side chain,

or a pharmaceutically acceptable salt or hydrate thereof.

[0009] Preferably said neutral, non-polar amino acid moiety R_2 or R_3 is:



in which R_4, R_5, R_6 and R_7 are each independently H or C_{1-2} alkyl.

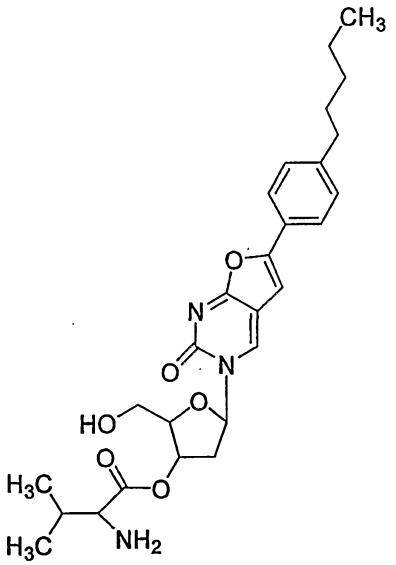
[0010] R_6 and R_7 are preferably both H.

[0011] In some embodiments, one of R_2 or R_3 may be valine, leucine, isoleucine or alanine. Preferably R_2 or R_3 is valine.

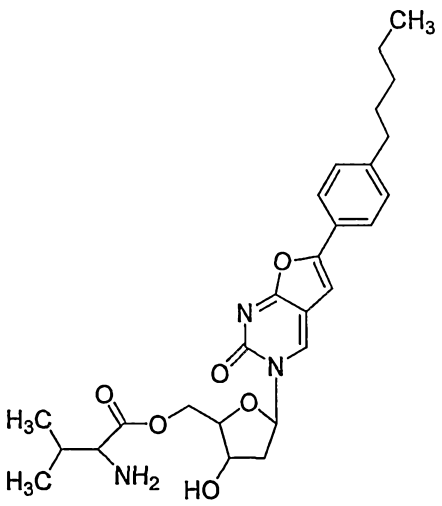
[0012] It is to be understood that the valine ester of the present invention may be either L-valine, D-valine or D,L-valine.

[0013] Further, X, Y and Z are preferably all O.

[0014] Particularly preferred compounds according to the present invention are



Compound **3**



Compound **5**

[0015] It will be appreciated that Compounds **3** and **5** are the valine esters of the 3'- and 5'- hydroxy groups respectively of Compound **1**.

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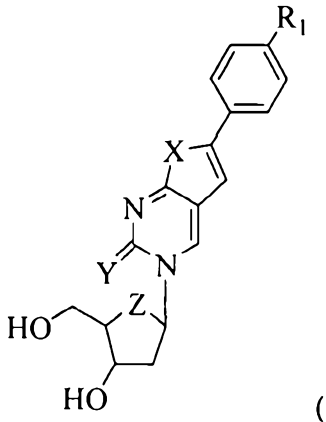
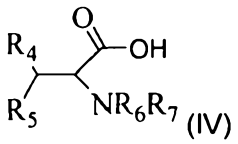
[0016] According to a second aspect of the present invention there is provided a method of synthesising a compound of the invention, said method comprising esterifying a compound of formula (III):



(III)

with a protected amino acid moiety having a neutral, non-polar side chain, wherein R_1, X, Y and Z are as defined in the first aspect, and optionally thereafter reacting the resultant ester with acid to form a pharmaceutically acceptable salt.

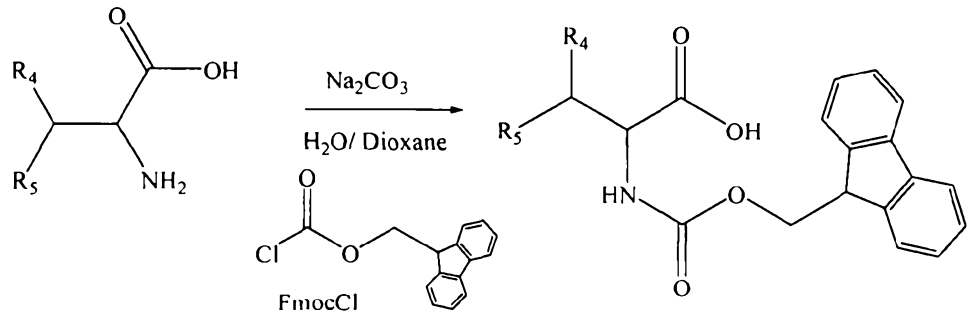
[0017] Preferably, said amino acid has the formula (IV):



(IV)

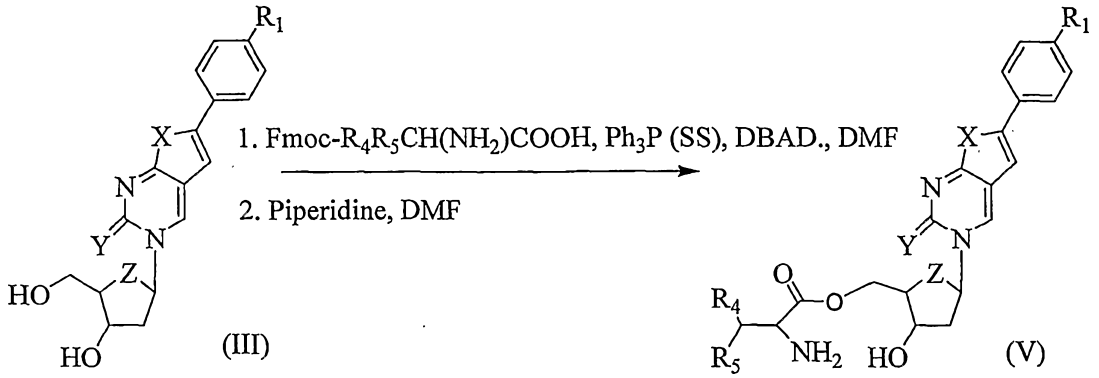
wherein R_4, R_5, R_6 and R_7 are as defined above.

[0018] The α-amino group is suitably protected during the esterification reaction. In some embodiments, where R_6 and R_7 are both H, said amino acid may be protected using a 3.9-fluorenylmethoxycarbonyl (Fmoc) protecting group. Other suitable protecting groups are known and available to those skilled in the art.



[0019] The Fmoc group may be introduced under Schotten-Baumen conditions. It is exceptionally stable towards acid. The cleavage of this group may be base catalysed (ammonia, piperidine, morpholine, DBU) undergoing an E1 β-elimination mechanism.

[0020] The esterification is preferably carried out under Mitsunobu conditions[1]:

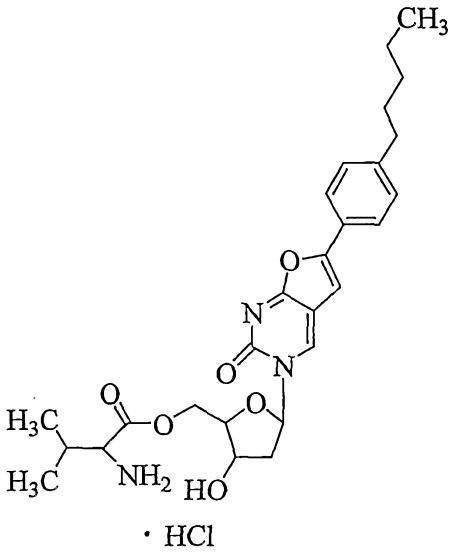


[0021] The hydrochloride salt may be prepared by treatment of the ester (V) with a solution of HCl in THF.

[0022] Preferably, R_1 is *n*-pentyl, X, Y and Z are all O, and R_4 and R_5 are both methyl.

[1] Mitsunobu, Synthesis, January 1981: 1-28

[0023] It has been found that the compounds of the present invention, and their hydrochloride salts, e.g., Compound **6** (see below), have advantageous pharmacokinetic (PK) properties and improved bioavailability as compared to Compound **1** of WO 01/83501 A1.



Compound **6**

[0024] Bioavailability is often a key factor in the practical application of a drug as a therapeutic agent and compounds that demonstrate enhanced PK and/or solubility generally have improved potency in vivo over compounds with less favorable PK properties even though their in vitro potency may be similar. Such compounds, i.e., derivatives of known *in vitro* active compounds, are often referred to as prodrugs. Novel Compound **5** and its hydrochloride salt Compound **6**, are examples of two such prodrugs.

[0025] Compounds **5** and **6** were tested for antiviral activity as described below and found to be active. In addition, a comparative study of the pharmacokinetic behaviour of Compounds **1** and **5** was conducted in a mouse model, demonstrating the improved bioavailability of Compound **5** compared to Compound **1**.

[0026] According to another aspect of the present invention therefore there is provided a compound according to the present invention for use in a method of treatment, particularly the prophylaxis or treatment of a viral infection. In some embodiments, said compound

may be provided for use in the treatment or prophylaxis of an infection with the Varicella Zoster virus.

[0026a] According to a third aspect of the present invention there is provided use of a compound according to the first aspect in the manufacture of a medicament for the prophylaxis or treatment of a viral infection.

[0027] Accordingly, there is provided use of a compound according to the present invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection, especially a viral infection caused by the Varicella Zoster virus, e.g., chicken pox or shingles.

[0028] According to a fourth aspect of the present invention there is provided a method of prophylaxis or treatment of viral infection, said method comprising administration to a human or non-human animal patient in need of such treatment an effective dose of a compound according to the present invention.

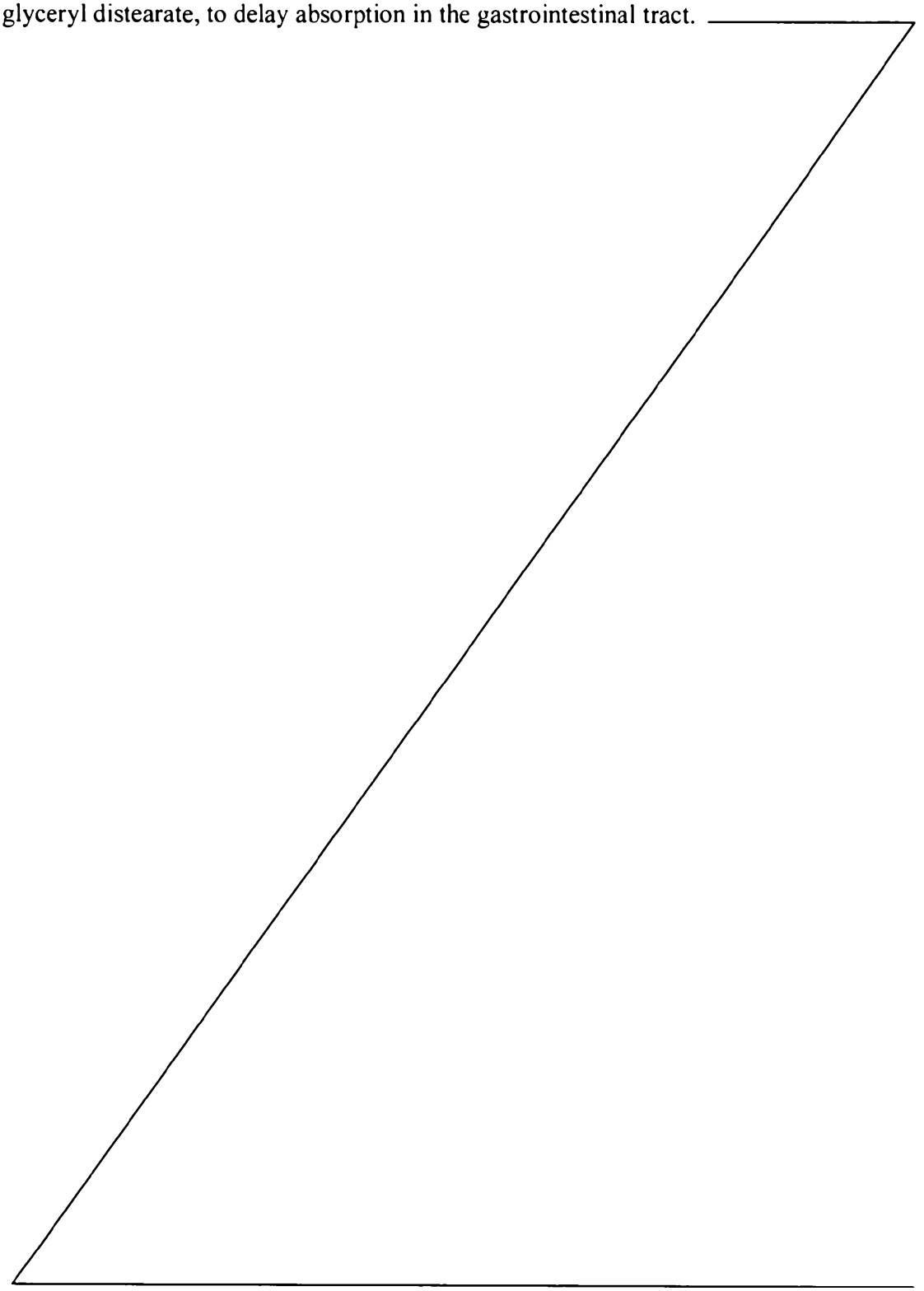
[0029] According to a fifth aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient. Medicaments embodying the present invention can be administered by oral, enteral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

[0030] For oral administration, compounds embodying the present invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

[0031] Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are

suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

5



[0032] Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

[0033] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0034] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0035] For intramuscular, intraperitoneal, subcutaneous and intravenous use, compounds embodying the present invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions embodying the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and *n*-propyl *p*-hydroxybenzoate.

[0036] Compounds embodying the present invention can be presented as liposome formulations.

[0037] In general, a suitable dose will be in the range of 0.001 to 300 mg per kilogram body weight of the recipient per day, preferably in the range of 0.01 to 25 mg per kilogram body weight per day and most preferably in the range 0.05 to 10 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 0.1 to 1500 mg, preferably 0.2 to 1000 mg, and most preferably 0.5 to 700 mg of active ingredient per unit dosage form.

[0038] Following are various examples of the invention with reference to the accompanying drawings, from which examples further advantages and effects of the compounds of the invention will be apparent.

[0039] In the drawings the single Figure is a graph of Mean ± SD Plasma Compound 1 (shown as relative peak area) in Female Mice After a Single Oral Gavage Dose of Compound **1** (25 mg/kg) or Compound **5** (31.25 mg/kg, equivalent to 25 mg/kg of Compound **1**).

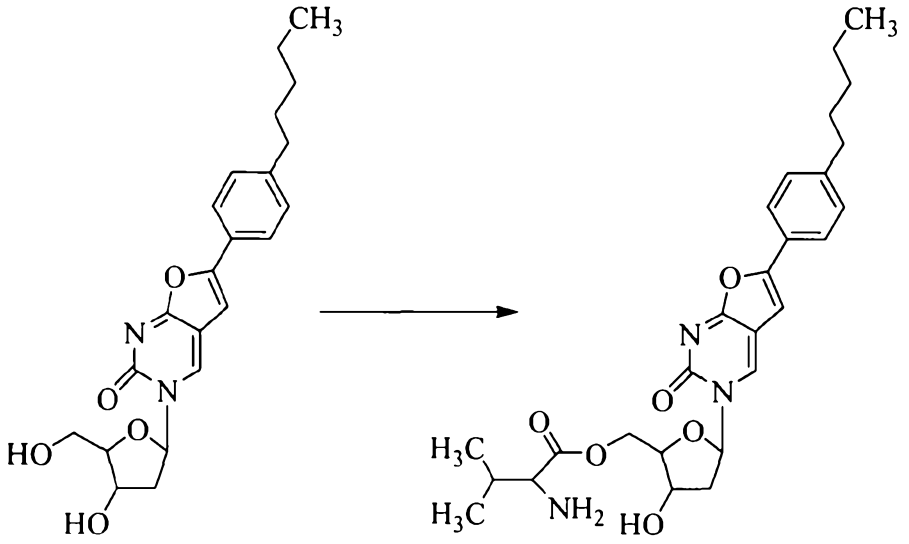
[0039a] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Experimental procedures and biological results

[0040] Preparation of compounds

Example 1

Preparation of Compound **5**; Formation of Valine ester

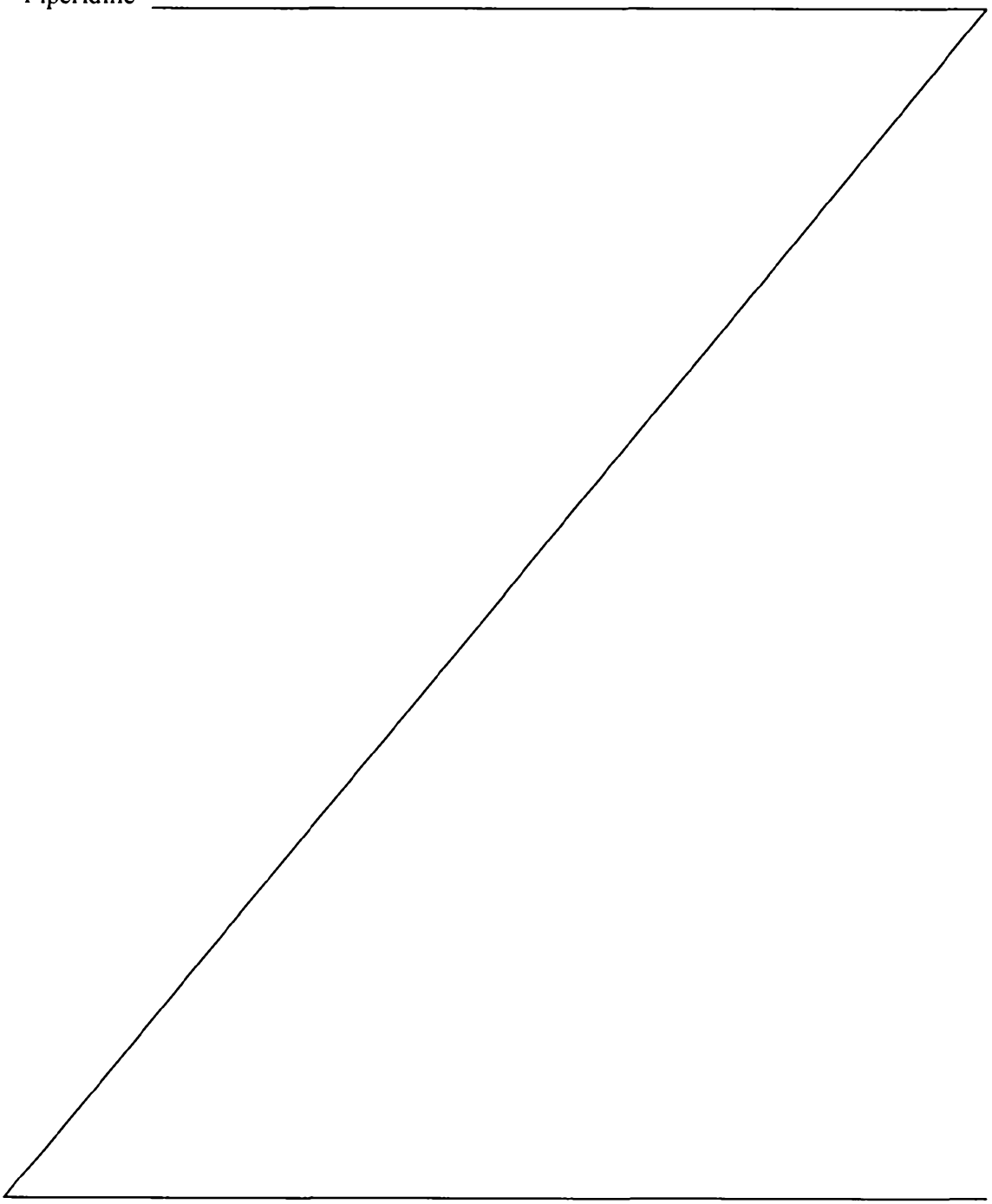


Compound **1** Compound **5**

[0041] Compound **1** (200 mg, 0.5 mmol, prepared as described in WO 01/83501 A1, Example 3, page 15) was dissolved in dry DMF (5mL), followed by the addition of

polymer-bound triphenylphosphine [370 mg, 1.1 mmol, (3 mmol p/g resin)] and di-*tert*-butyl azodicarboxylate (DBAD) (231 mg, 1.0 mmol) to the mixture and stirred for 20 minutes. A solution of Fmoc-Val-OH (340 mg, 1.0 mmol) in DMF (5 mL) was added dropwise over a period of 30 minutes. The reaction mixture was stirred at room temperature under an argon atmosphere until complete disappearance of the starting material (overnight). The resin was filtered off and washed with ethyl acetate.

Piperidine



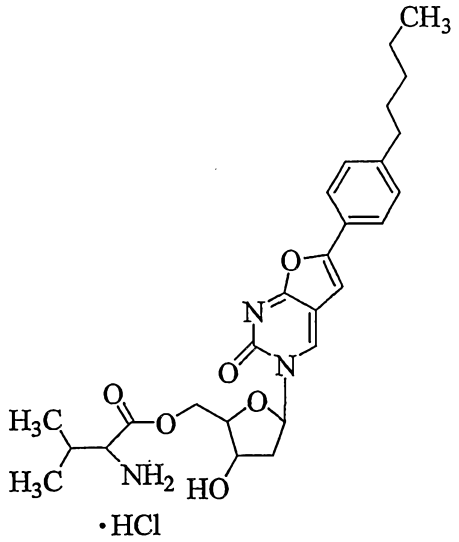
(1 mL, 10 mmol) was added to the solution and stirred for 10 minutes. The solvent was removed under reduced pressure without warming over 35°C and the residue was dissolved in ethyl acetate (20 mL), washed with 10% $NaHCO_3$ (3 x 20 mL) and brine (2 x 20 mL). The final residue was purified by column chromatography (gradient CH_2Cl_2 : MeOH 100% 98% 95% 90%), to give 137 mg of Compound **5** (55% yield) as a yellow solid.

[0042] ^{1}H-NMR ($CDCl_3$) δ : 8.3 (1H, s), 7.55 (2H, d), 7.15 (2H, d), 6.6 (1H, s), 6.25 (1H, t), 4.45-4.30 (4H, m), 3.23 (1H, d), 2.80 (1H, m), 2.53 (2H, t), 2.12 (1H, m), 1.97 (1H, m), 1.60 (2H, m), 1.24 (4H, m), 0.90-0.78 (9H, m).

[0043] ^{13}C-NMR ($CDCl_3$) δ : 175.16, 171.62,156.26, 154.89, 145.19, 135.29, 129.02, 125.69, 124.95, 108.60, 96.82, 88.73, 85.08, 70.90, 64.19, 60.19, 41.91, 35.82, 32.32, 31.44, 30.89, 22.50, 19.30, 17.24, 13.99.

[0044] **Example 2**

Preparation of Compound **6**; Formation of the HCl salt



Compound **6**

[0045] 300 mg of Compound **5** were dissolved in 3 mL of THF. Under vigorous stirring 2 mL of HCl 1M were added at 0 °C and the mixture were stirred for 10 minutes. The solvents were dried under reduce pressure to obtain 322 mg (100%) of yellow oil that solidified with addition of ether.

[0046] ^{1}H-NMR (d_6-DMSO) δ : 8.6 (4H, bs), 7.70 (2H, d), 7.30 (2H, d), 7.20 (1H, s), 6.22 (1H, t), 5.60 (1H, bs), 4.48 (2H, m), 4.30 (1H, m), 4.16 (1H, m), 3.98 (1H, m), 2.61 (2H, t), 2.44 (1H, m), 2.25 (1H, m), 2.18 (1H, m), 1.57 (2H, m), 1.32 (4H, m), 1.00-0.83 (9H, m).

[0047] ^{13}C-NMR (d_6-DMSO) δ : 171.13, 168.88, 153.97, 153.70, 144.18, 137.94, 129.04, 125.77, 124.58, 107.22, 98.75, 87.71, 84.13, 69.73, 65.26, 57.35, 40.18, 34.88, 30.88, 30.39, 29.38, 21.91, 18.26, 17.55, 13.90.

Biological and Pharmacokinetic Studies

[0048] In order to demonstrate the improved exposure profile of Compound **5**, several experiments were run using mouse animal models. Below are representative results

Pilot Comparative Virology Study with Compounds **1** and **5**

[0049] The objective of this pilot study was to compare the antiviral activity of Compounds **1** and **5** in HEL cells inoculated with the Oka VZV strain. Antiviral activity was assessed as the ability of **1** or **5** to reduce viral plaque formation after incubation periods ranging from 3 to 7 days compared to untreated control cultures. Preliminary results of the antiviral efficacy studies showing comparable efficacy between the two compounds are shown in Table 4.2.

[0050] **Table 1: Preliminary Results Comparing Compound 1 and Compound 5 for Anti-Varicella Zoster Virus Activity in HEL Cells**

Compound	EC_{50} in VZV OKA
1	0.007 μM (2.8 ng/mL)
5	0.016 μM (8.0 ng/mL)

Note: The molecular weight of Compound **5** is approximately 1.25 times that of Compound **1** due to the valine ester.

[0051] In conclusion, the results of these comparative pilot *in vitro* studies showed that Compound **5** has comparable *in vitro* antiviral activity to Compound **1**.

Nonclinical Pharmacokinetic Studies with Compound 5

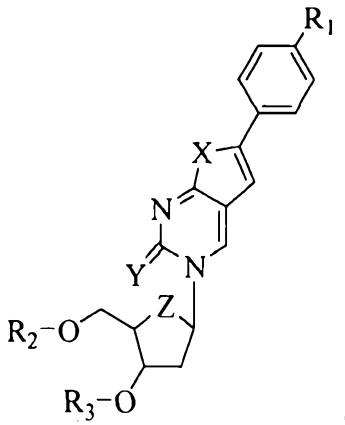
[0052] A pilot study was conducted with Compounds **1** and **5** to compare the relative bioavailability of Compound **1** after oral dosing in mice. Two groups of female mice received equimolar doses of Compound **1** (25 mg/kg) or **5** (31.25 mg/kg; equivalent to 25 mg/kg of Compound **1**) as a single oral gavage dose) formulated in 0.5% carboxymethylcellulose. The mice were serially sacrificed at time-points ranging from 0.25 to 3 hours post dosing (3 mice/time-point), and plasma samples were taken and analyzed for Compound **1** concentration using a non-validated HPLC method with fluorescence detection. Results are reported as relative peak areas for Compound **1**, which assumes that peak area is directly proportional to concentration over these ranges of concentrations.

[0053] The results of this study are shown in the accompanying Figure. Plasma concentrations of Compound **1** were much higher in mice receiving Compound **5** compared to mice receiving Compound **1**. Note that although these data do not provide absolute plasma concentrations of Compound **1**, one can estimate from the peak areas that Compound **5**increases the oral bioavailability of Compound **1** by approximately 8.4 to 10 fold (e.g., the AUC is increased by ~840% and the C_{max} is increased by ~1000%).

[0054] In conclusion, this data supports the hypothesis that Compound **5** is a prodrug of Compound **1**, and greatly increases the oral bioavailability of Compound **1.**

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound of general formula (II):



(II)

wherein X is O, S, NH or CH_2,

Y is O, S or NH,

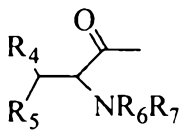
Z is O, S or CH_2,

R_1 is C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl, and

one of R_2 and R_3 is H, and the other of R_3 and R_2 is an amino acid moiety having a neutral, non-polar side chain,

or a pharmaceutically acceptable salt or hydrate thereof.

2. A compound as claimed in claim 1, wherein said amino acid moiety R_2 or R_3 is:



in which R_4, R_5, R_6 and R_7 are each independently H or C_{1-2} alkyl.

3. A compound as claimed in claim 2, wherein R_6 and R_7 are both H.

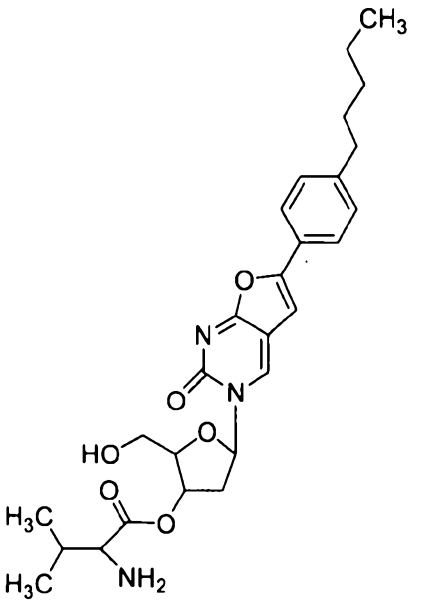
4. A compound as claimed in claim 1, wherein one of R_2 or R_3 is valine, leucine, isoleucine or alanine.

5. A compound as claimed in claim 1 or claim 4, wherein R_2 or R_3 is valine.

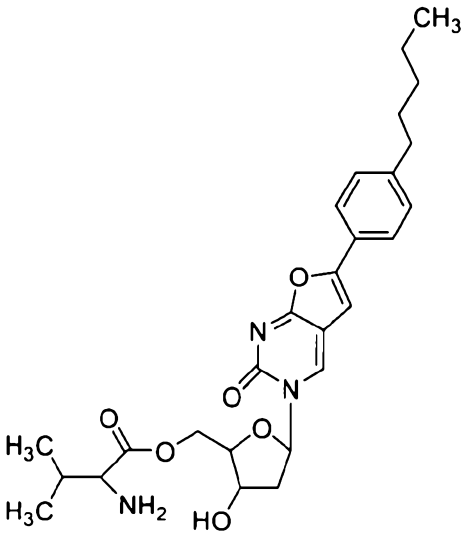
6. A compound as claimed in claim 5, wherein said valine is L-valine, D-valine or D,L-valine.

7. A compound as claimed in any one of the preceding claims, wherein X, Y and Z are preferably all O.

8. A compound as claimed in claim 1, which is:



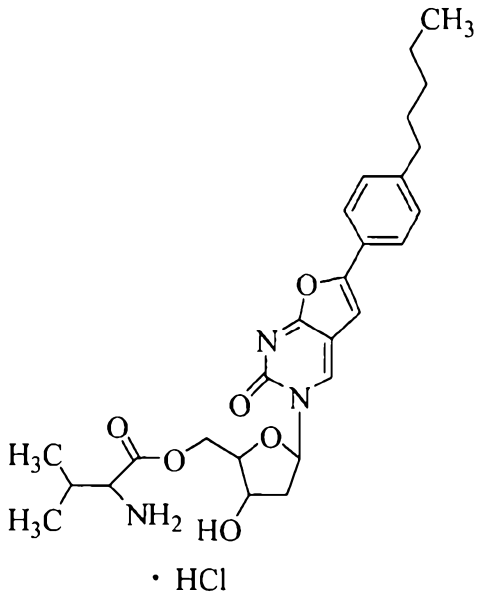
Compound **3,**



Compound **5,**

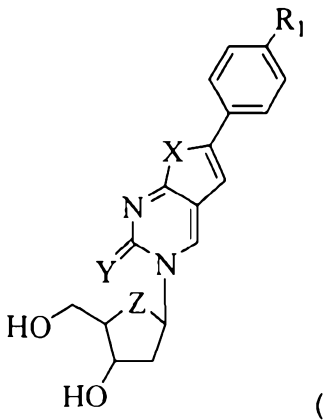
or the hydrochloride salt of Compound **3** or Compound **5**.

9. A compound as claimed in claim 1, which is:



Compound **6**

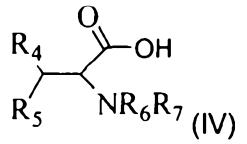
10. A method of synthesising a compound as claimed in any one of claims 1-9, said method comprising esterifying a compound of formula (III):



(III)

with a protected amino acid moiety having a neutral, non-polar side chain, wherein R_1, X, Y and Z are as defined in claim 1, and optionally thereafter reacting the resultant ester with acid to form a pharmaceutically acceptable salt.

11. A method as claimed in claim 10, wherein said amino acid moiety has the formula (IV):



(IV)

wherein R_4, R_5, R_6 and R_7 are as defined in claim 2.

12. A method as claimed in claim 11, wherein R_6 and R_7 are both H, and said α-amino group is protected during the esterification reaction by a 3.9- fluorenylmethoxycarbonyl (Fmoc) protecting group.

13. A method as claimed in claim 10, claim 11 or claim 12, wherein said esterification is carried out under Mitsunobu conditions.

14. A method as claimed in any one of claims 10-13, further comprising treating the ester with a solution of HCl to form the hydrochloride salt.

15. A method as claimed in any one of claims 10-14, wherein R_1 is *n*-pentyl or *n*-hexyl, X, Y and Z are all O, and R_4 and R_5 are both methyl.

16. A compound as claimed in any one of claims 1-9 for use in a method of treatment of the human or animal body.

17. Use of a compound as claimed in any one of claims 1-9 in the manufacture of a medicament for the prophylaxis or treatment of a viral infection.

18. A method of prophylaxis or treatment of viral infection, said method comprising administration to a human or non-human animal patient in need of such treatment an effective dose of a compound as claimed in any one of claims 1-9.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1-9 in combination with a pharmaceutically acceptable excipient.

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20. A compound of claim 1; a method of synthesising a compound according to claim 10; use of a compound according to claim 17; a method according to claim 18; or a pharmaceutical composition according to claim 19, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

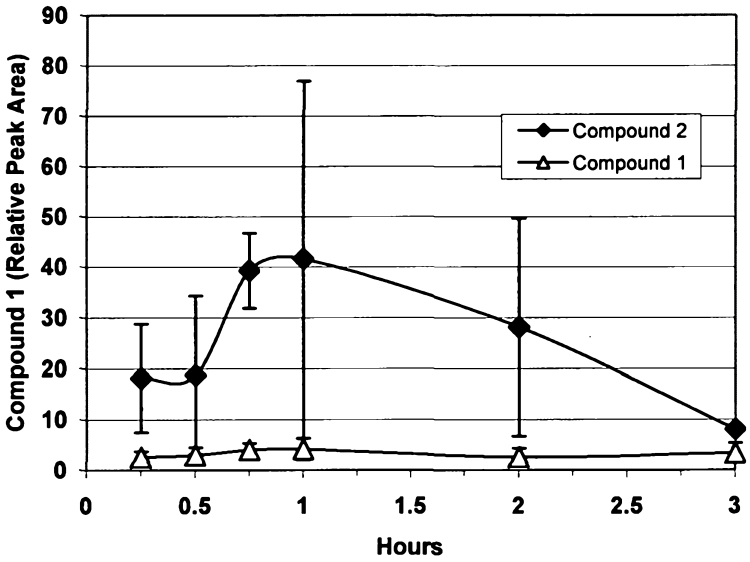
90
80
70
60
50
40
30
20
10
0
Compound 1 (Relative Peak Area)
0
0.5
1
1.5
2
2.5
3
Hours
Compound 2
Compound 1

FIG. 1