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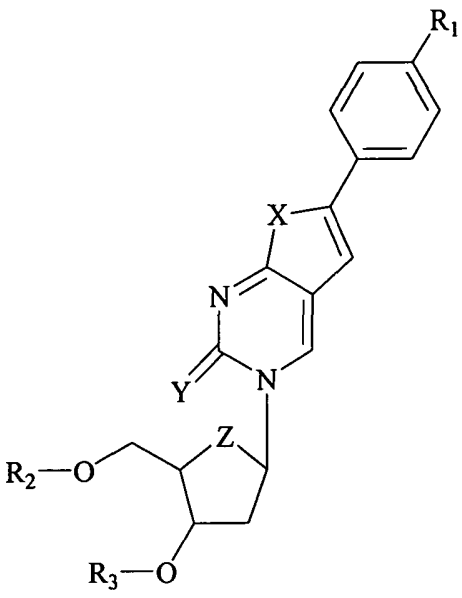
(54) **Title:** IMPROVEMENTS IN OR RELATING TO COMPOSITIONS FOR THE TREATMENT OR PROPHYLAXIS OF VIRAL INFECTIONS



(III)

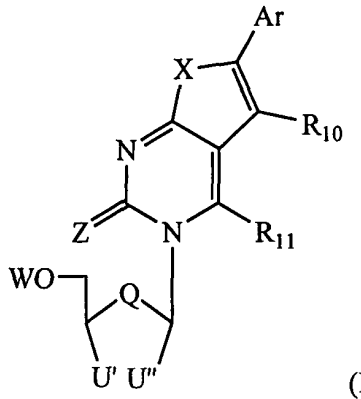
(57) **Abstract:** A compound of the general formula (III): wherein X is O, S, NH or CH_2; Y is O, S or NH; Z is O, S or CH_2; R_1 is C_{1-8} alkyl, especially C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl; at least one of R_2 and R_3 is H-$[R_4$-$R_5]_n$-R_6-, in which: H-$[R_4$-$R_5]_n$- comprises an oligopeptide, R_4 being an amino acid and R_5 being an amino acid selected from proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine, R_6 is a neutral, non-polar amino acid moiety that is bonded to R_5 by a peptide bond, and n is 1, 2, 3, 4 or 5; and the other of R_3 and R_2 is H-$[R_4$-$R_5]$n-R_6- or H; or a pharmaceutically acceptable salt thereof.

WO 2009/030410 A1

Improvements in or Relating to Compositions for the Treatment or Prophylaxis of Viral Infections

[0001] The present invention provides improvements in or relating to compositions for the treatment or prophylaxis of viral infections such, for example, as those caused by the Varicella Zoster virus (VZV). Varicella Zoster virus is the aetiological agent of chickenpox and shingles, which can cause considerable human illness and suffering.

[0002] WO 01/83501 A1, the contents of which are incorporated herein by reference, discloses certain nucleoside analogues with potent activity against Varicella Zoster virus (VZV), said nucleoside analogues having the 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_{10} and R_{11} are each independently selected from the group comprising hydrogen, alkyl, cycloalkyl, halogens, amino, alkylamino, dialkylamino, nitro, cyano, alkyloxy, aryloxy, thiol, alkylthiol, arylthiol, aryl;

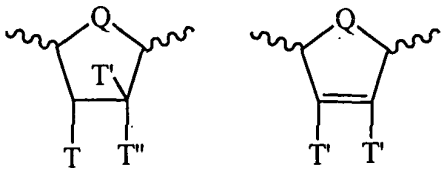
Q is selected from the group comprising O, S and CY_2, where Y may be the same or different and is selected from H, alkyl and halogens;

X is selected from the group comprising O, NH, S, N-alkyl, $(CH_2)_m$ 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;

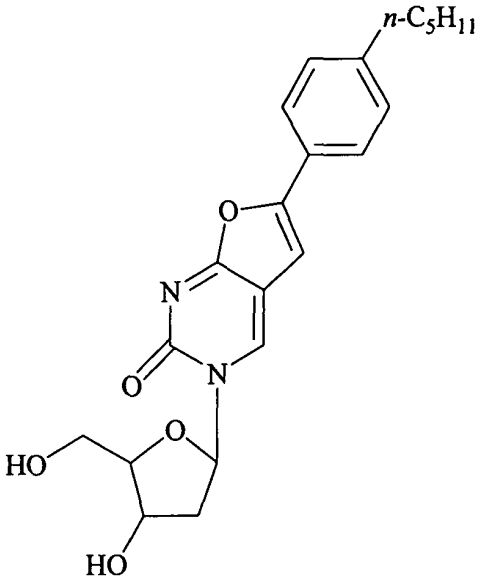
T" is selected from the group comprising H and halogens; and

W is selected from the group comprising H, a phosphate group and a phosphonate group;

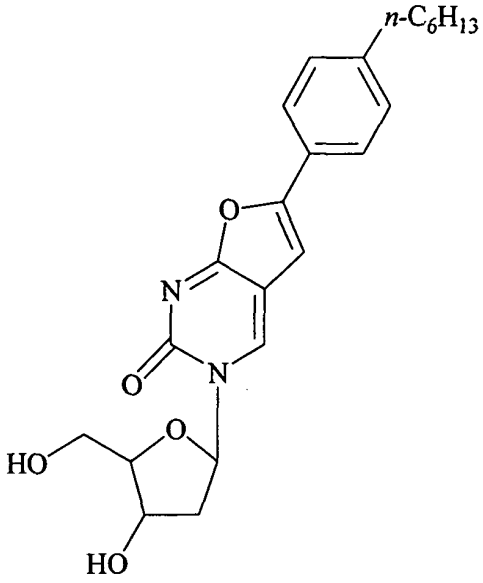
with the proviso that when T is OAc and T' and T" are present and are H, Ar is not 4-(2-benzoxazolyl) phenyl.

[0003] According to WO 01/83501 A1, W may be modified to provide any *pharmacologically acceptable salt or derivative of H, phosphate or phosphonate.* WO 01/83501 A1 further discloses that when W is selected from phosphates and derivatives thereof and phosphonates and derivatives thereof, W may be modified to provide a pro-drug of the compound of formula (I).

[0004] Compounds **1** and **2** below are particularly preferred compounds according to WO 01/83501 A1:



Compound **1**



Compound **2**

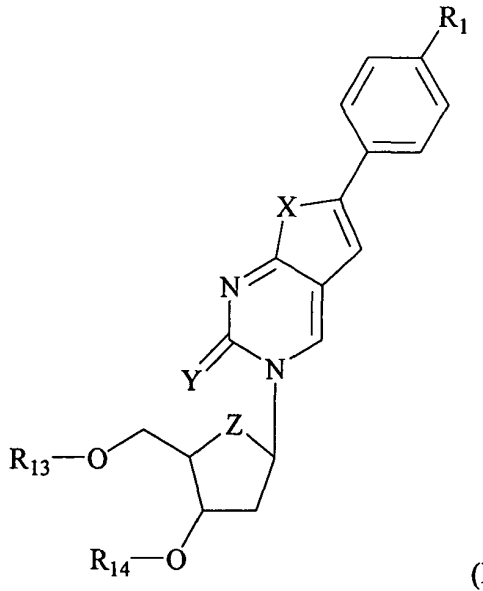
[0005] The development of many promising therapeutic agents is hindered by their poor water solubility.

[0006] WO 2004/098644 A1, the contents of which are also incorporated herein by reference, discloses conjugates of therapeutic agents with a peptidic moiety in which the conjugate is cleavable by a dipeptidyl-peptidase, such as CD26. Such conjugation of the therapeutic agents is calculated to ameliorate their solubility and bioavailability, and may be used to modulate the protein binding of a therapeutic compound and to target specific sites in a mammal.

[0007] By "CD26" as used herein is meant dipeptidyl-peptidase IV (EC 3.4.14.5) in its membrane bound or free form; synonyms for CD26 are DPPIV, DPP4, CD26/DPPIV, or ADCP2 (adenosine deaminase complexing protein 2). A dipeptidyl-peptidase is an enzyme with a dipeptidyl aminopeptidase activity, i.e., removing a dipeptide from the amino-terminal side of a substrate site by cleavage of the second CO-NH amide bond in the substrate. Other enzymes than CD26 with a comparable activity and proteolytic specificity as CD26 (i.e., prolyloligopeptidases) are referred to by "dipeptidyl-peptidase(s)". "Dipeptidylpeptidase IV" refers to CD26.

[0008] According to WO 2004/098644 A1, a therapeutic compound having, or being bound to a linker A_m having an amino group, particularly a terminal primary or secondary amino group, capable of binding with the carboxyl group of an amino acid is linked to an oligopeptide consisting of a general structure H-[X-Y]$_n$, wherein X is an amino acid, n is between 1 and 5 and Y is an amino acid selected from proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine, and wherein the binding between the carboxy terminus of H-[X-Y]$_n$ and the amino group of the therapeutic compound or its linker occurs via an amide. In one embodiment, the peptide has between two to five CD26 cleavable repeats. In another embodiment, the number m of amino acids in the linker A_m is between 1 and 15, more particularly between 1 to 3. A may be any amino acid. More particularly, m is 1 and A is valine.

[0009] International patent application no. PCT/GB2007/001677, which is comprised in the state of the art according to EPCa.54(3) and the contents of which are also incorporated herein by reference, discloses 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

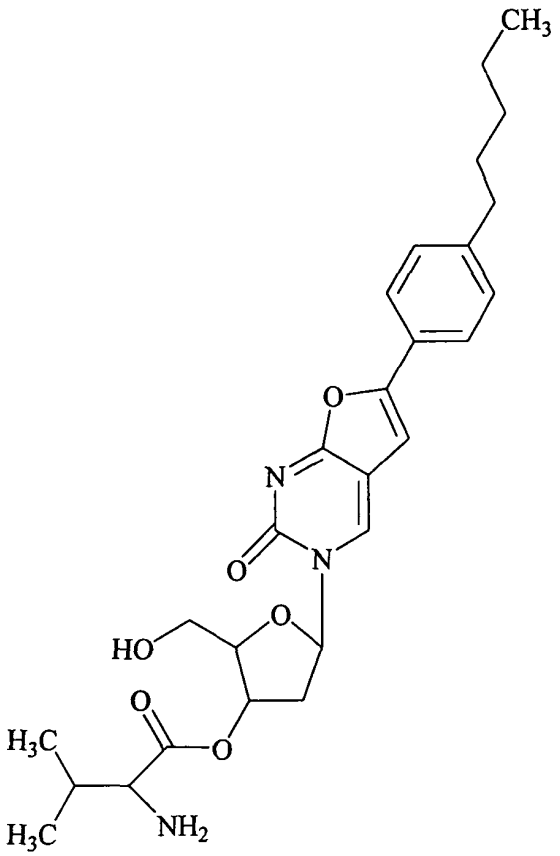
one of R_{13} and R_{14} is OH, and the other of R_{14} and R_{13} is a neutral, non-polar amino acid moiety,

or a pharmaceutically acceptable salt or hydrate thereof.

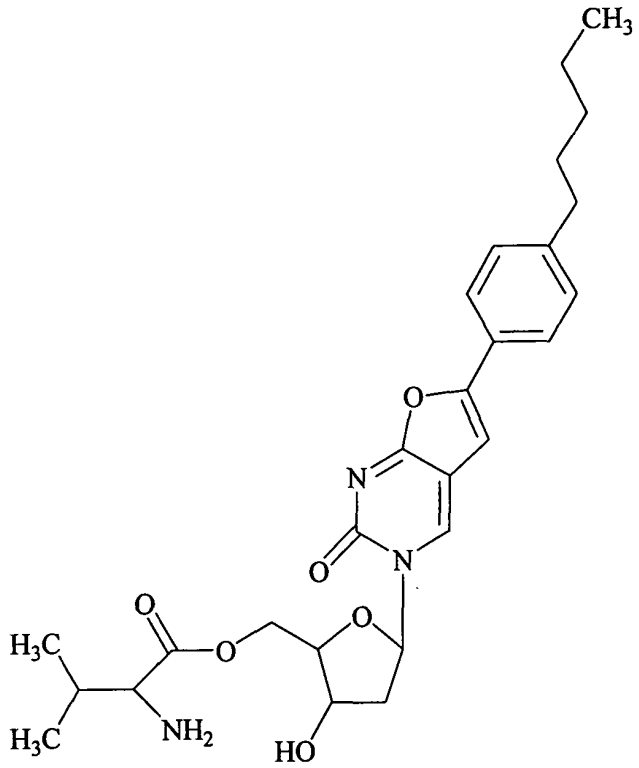
[0010] Preferably R_{13} or R_{14} is valine, especially L-valine.

[0011] The compound of PCT/GB2007/001677 is especially suitable for oral administration. It has been shown that the oral bioavailability of drugs can be mediated by amino acid prodrug derivatives containing an amino acid, preferably in the L-configuration. L-valine seems to have the optimal combination of chain length and branching at the β-carbon of the amino acid for intestinal absorption. hPEPT-1 has been found to be implicated as the primary absorption pathway of increased systemic delivery of L-valine ester prodrugs. The hPEPT-1 transport needs to interact optimally with a free NH_2, a carbonyl group and a lipophylic entity, and may form additional H-bridges with its target molecule.

[0012] Preferred compounds according to PCT/GB2007/001677 are:



Compound **3**

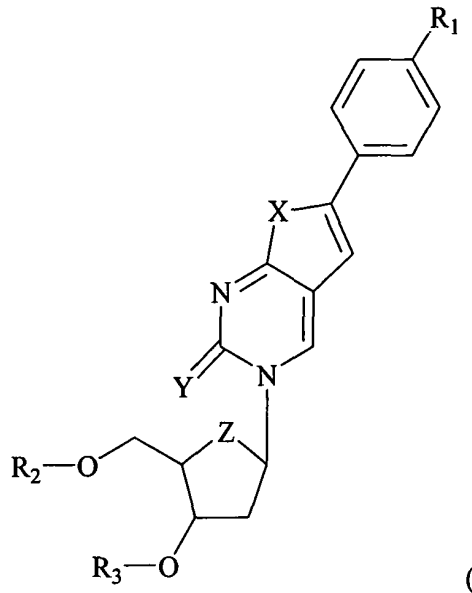


Compound **5**

[0013] Compound **5** was found to have improved bioavailability after oral dosing in mice as compared to Compound **1** of WO 01/83501 A1 (see above).

[0014] It has now been found that by conjugating the compound of PCT/GB2007/001677 with a CD26 cleavable oligopeptide, a surprisingly great improvement in the solubility of the compound as compared with the non-derivatised nucleoside analogue of general formula (I) according to WO 01/83501 A1 may be obtained, without adversely affecting the bioavailability of such compound. Indeed, the bioavailability may even be increased. Further, the conjugated compound retains comparable antiviral activity to the non-derivatised nucleoside analogue of general formula (I).

[0015] According to one aspect of the present invention, therefore, there is provided a compound of the general formula (III):



(III)

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_{1-8} alkyl, especially C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl;

at least one of R_2 and R_3 is H-$[R_4$-$R_5]_n$-R_6-, in which:

H-$[R_4$-$R_5]_n$- comprises an oligopeptide, R_4 being an amino acid and R_5 being an amino acid selected from proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine,

R_6 is a neutral, non-polar amino acid moiety that is bonded to R_5 by a peptide bond, and

n is 1, 2, 3, 4 or 5; and

the other of R_3 and R_2 is H-$[R_4$-$R_5]_n$-R_6- or H; or

a pharmaceutically acceptable salt thereof.

[0016] In some embodiments, one of R_2 and R_3 is H-$[R_4$-$R_5]_n$-R_6- and the other is H. Alternatively, both of R_2 and R_3 may be H-$[R_4$-$R_5]_n$-R_6-. Where both R_2 and R_3 are H-$[R_4$-$R_5]_n$-R_6-, R_4, R_5, R_6 and n are selected independently for R_2 and R_3 respectively. However, in some embodiments, R_2 and R_3 may be the same.

[0017] The compound of the present invention is cleavable by CD26. The H-$[R_4$-$R_5]_n$- has a free amino-terminus, i.e., an unmodified NH_2 group.

[0018] In some embodiments n may be 2-5, and in particular the -$[R_4$-$R_5]_n$- oligopeptide may be a tetrapeptide or a hexapeptide, it being understood that, in each R_4-R_5 unit, R_4 and R_5 are selected independently of the one or more other units.

[0019] Preferably, however, n=1, H-$[R_4$-$R_5]_n$-R_6 thus being a tripeptide moiety.

[0020] One or both of R_4 and R_5 may be L-amino acids, although, in some embodiments, one or both of R_4 and R_5 may be employed in their D-forms. Further, R_4 and R_5 are suitably naturally occurring amino acids.

[0021] Suitably, R_4 may be selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

[0022] Advantageously, R_4 is valine.

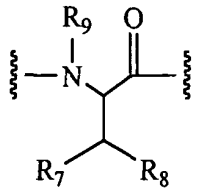
[0023] Suitably, R_5 may be selected from proline, alanine, glycine, serine, valine and leucine.

[0024] Advantageously R_5 is proline or alanine.

[0025] Suitably, the oligopeptide -$[R_4$-$R_5]$- is selected from Val-Pro, Asp-Pro, Ser-Pro, Lys-Pro, Arg-Pro, His-Pro, Phe-Pro, Ile-Pro, Leu-Pro, Val-Ala, Asp-Ala, Ser-Ala, Lys-Ala, Arg-Ala, His-Ala, Phe-Ala, Ile-Ala and Leu-Ala.

[0026] Preferably, said oligopeptide is Val-Pro.

[0027] Preferably said neutral, non-polar amino acid moiety R_6 is:



in which R_7, R_8 and R_9 are each independently H or C_{1-3} alkyl, especially C_{1-2} alkyl.

[0028] R_9 is preferably H.

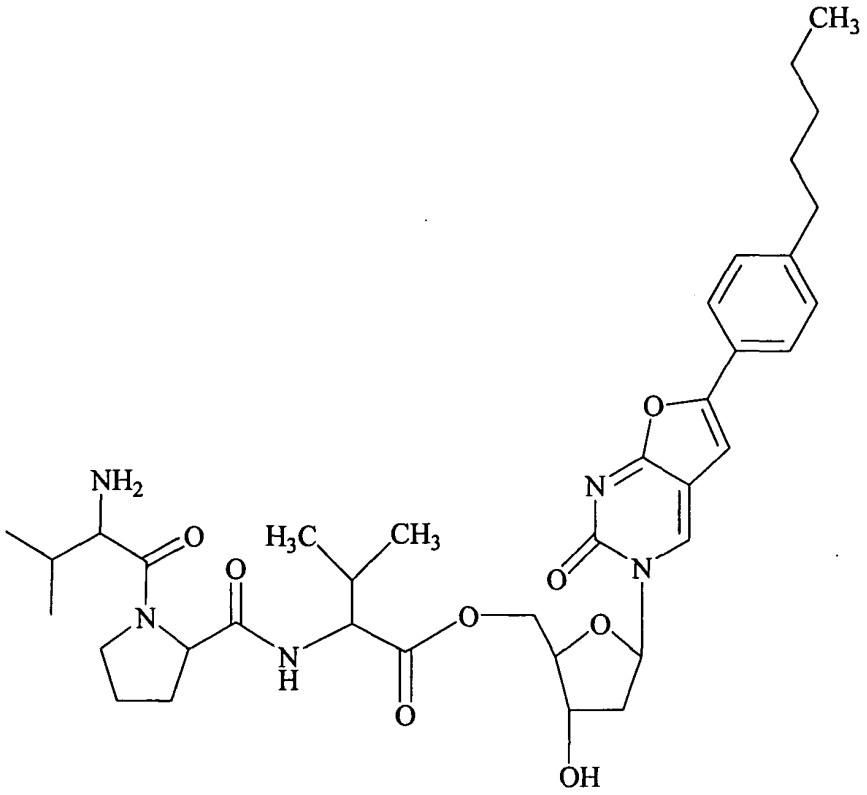
[0029] In some embodiments, R_6 may be valine, leucine, isoleucine or alanine.

[0030] Preferably R_6 is valine. R_6 may be L-valine, D-valine or D,L-valine; preferably R_6 is L-valine.

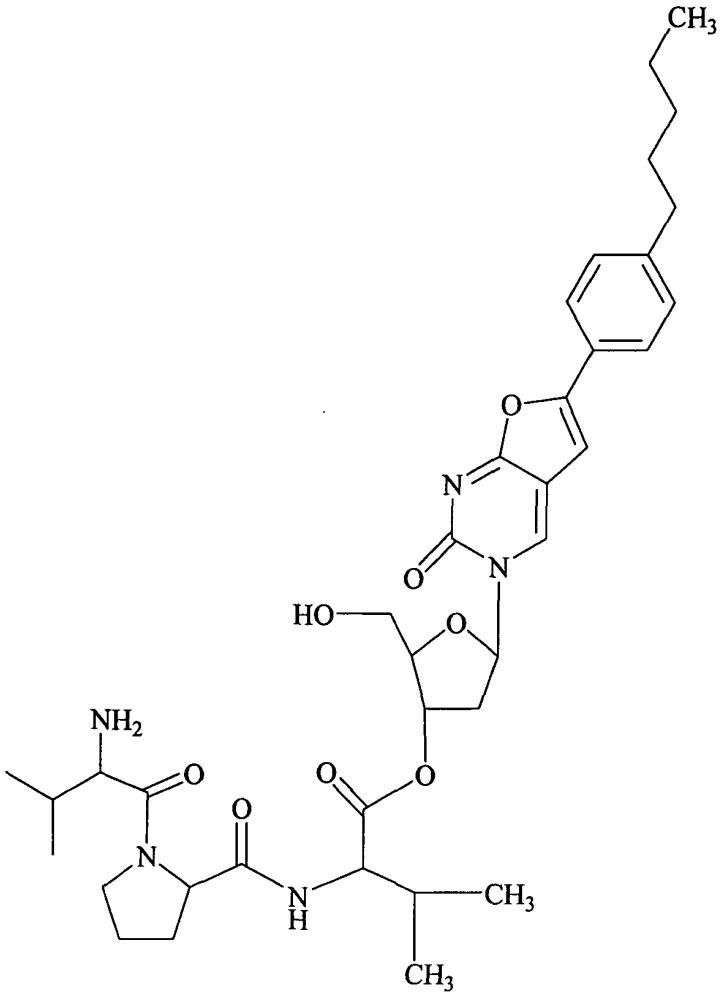
[0031] In some preferred embodiments, R_2 and R_3 are the same, and both are H-Val-Pro-Val- .

[0032] Further, X, Y and Z are preferably all O.

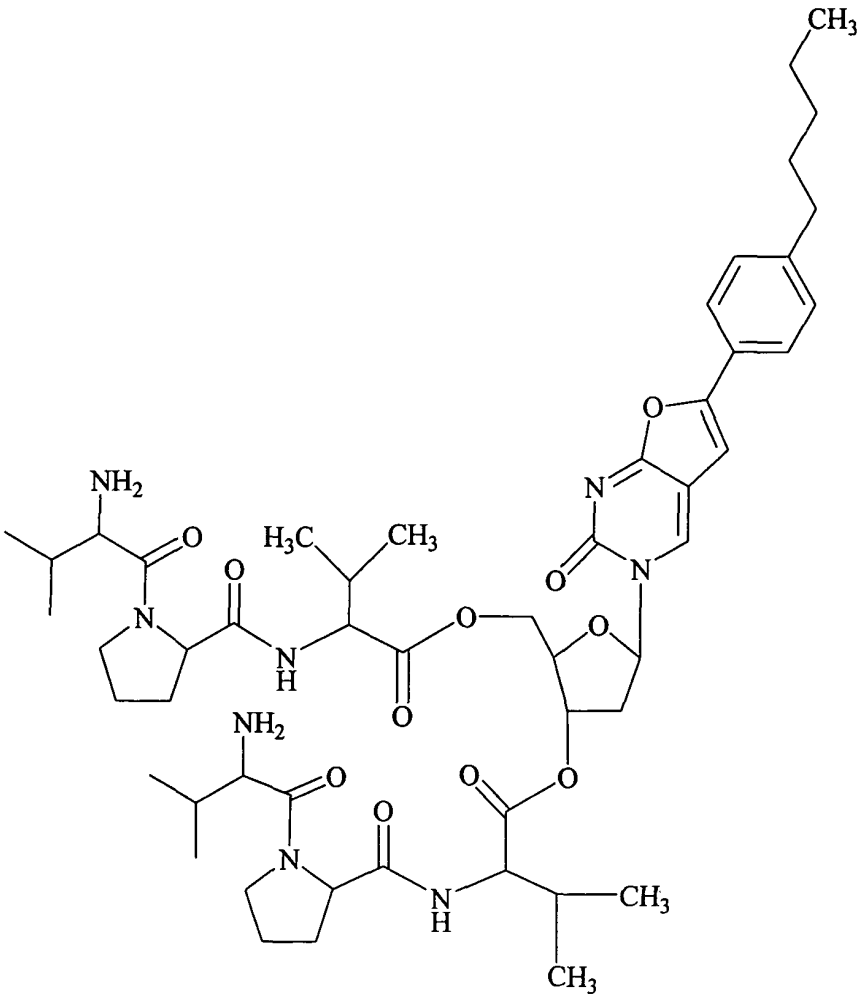
[0033] Particularly preferred compounds according to the present invention are:



Compound 7

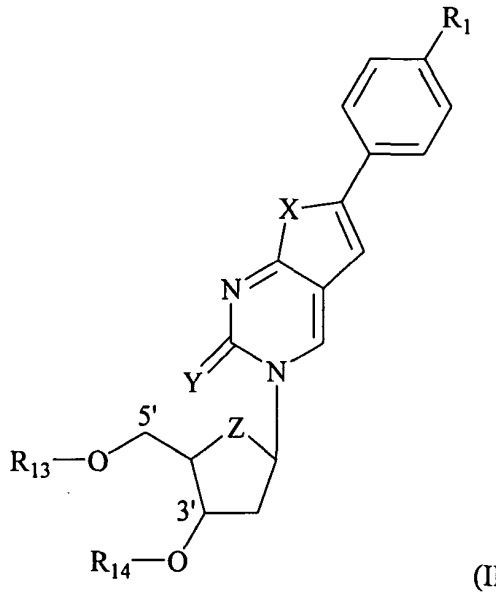


Compound **9**



Compound **11**

[0034] According to another aspect of the present invention there is provided a method of synthesising the compound of the invention, said method comprising conjugating a compound of 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;

at least one of R_{13} and R_{14} is a neutral, non-polar amino acid moiety having a free amino terminus; and

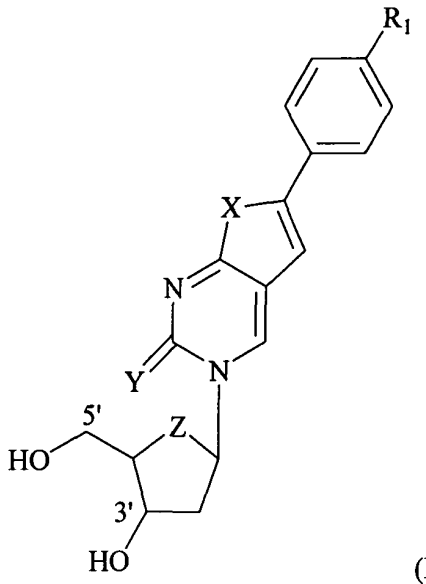
the other of R_{14} and R_{13} is H, the resulting hydroxyl group being optionally protected, or a neutral, non-polar amino acid moiety;

with a protected oligopeptide of formula Z'-$[R_4$-$R_5]_n$-OH to form a peptide bond between R_5 and at least one of R_{13} or R_{14}, wherein R_4 and R_5 are as defined above and Z' is an amino-protecting group to protect the free amino terminus, and thereafter removing said protecting group.

[0035] Said amino-protecting group may comprise a 3. 9- fluorenylmethoxycarbonyl (Fmoc) protecting group, but other, suitable amino-protecting groups are known and available to those skilled in the art.

[0036] When R_{13} is H, the resulting hydroxyl group may be protected with a suitable hydroxyl-protecting group such, for example, as *tert*-butyldimethylsilyl chloride. Other hydroxyl-protecting groups will be known to those skilled in the art. Once the conjugation reaction between the compound of formula (II) and the dipeptide has been completed, the hydroxyl-protecting group may be removed to expose the free 5'-OH group.

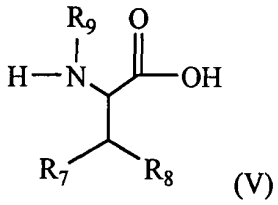
[0037] Said compound of formula (II) may be synthesised by esterifying a compound of formula (IV):



(IV)

with a protected neutral, non-polar amino acid, wherein R_1, X, Y and Z are as defined above to obtain the 3'- or 5'- ester or 3',5'- diester.

[0038] In some embodiments, said amino acid may have the formula (V):

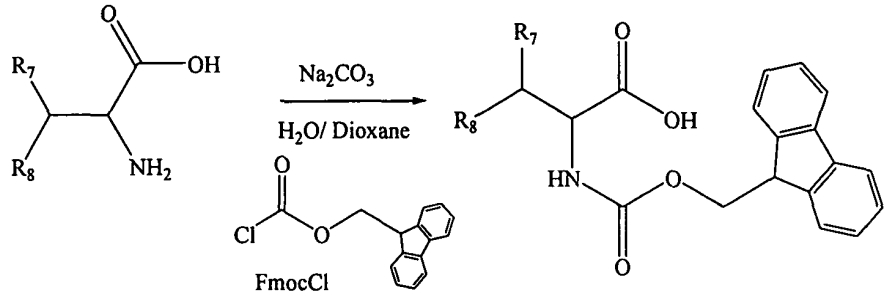


(V)

wherein R_7, R_8 and R_9 are as defined above.

[0039] Preferably R_{13} and/or R_{14} are valine, especially L-valine.

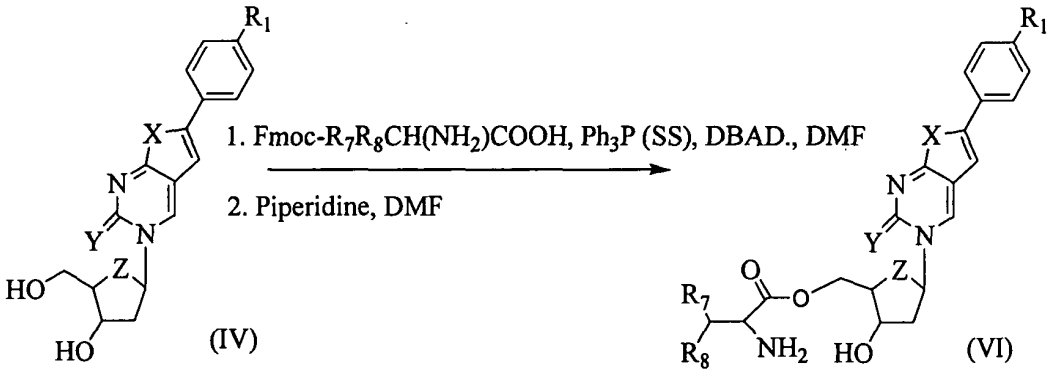
[0040] The α-amino group is suitably protected during the esterification reaction. In some embodiments, where R_9 is H, said amino acid may be protected using a 3. 9-fluorenylmethoxycarbonyl (Fmoc) protecting group. Other suitable protecting groups are known and available to those skilled in the art.



[0041] 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.

[0042] The esterification reaction conditions may be suitably adjusted as desired to obtain the 3'- or 5'- ester or the 3',5'- diester. Where the 3'- (mono) ester is desired, the 5'-OH group may be protected as described above using a suitable hydroxyl-protecting group such, for example, as *tert*-butyldimethylsilyl chloride, which may be removed after completion of the esterification reaction or left *in situ* for the subsequent conjugation reaction with the protected oligopeptide.

[0043] The 5'- esterification is preferably carried out under Mitsunobu conditions[1]:



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

[0044] The hydrochloride salt may be prepared by treatment of the ester (VI) with a solution of HCl in THF.

[0045] The 3'- and 3', 5'- esterification reactions may be carried out using the conventional coupling method (DCC/DMAP) known to those skilled in the art of in acyclic nucleosides[2]. For example, the 3', 5'- diesterification may be performed in DMF by admixing to the compound of formula (IV) 4-dimethylaminopyridine, Fmoc-$R_7R_8CH_9(NH_2)COOH$ and N,N'-dicyclohexyl-carbodiimide DCC in succession, followed by washing the resultant white solid.

[0046] 3'- esterification may be performed in a similar manner by reacting the 5'- protected hydroxyl compound of formula (IV) dissolved in DMF with 4-dimethylaminopyridine, Fmoc-$R_7R_8CH_9(NH_2)COOH$ and N,N' dicyclohexyl-carbodiimide DCC in succession.

[0047] Preferably, R_1 is *n*-pentyl, X, Y and Z are all O, and R_7 and R_8 are both methyl.

[0048] It has been found that the compound of the present invention has advantageous pharmacokinetic (PK) properties and improved bioavailability as compared to Compound 1 of WO 01/83501 A1. The conjugation of a dipeptide moiety to the free amino terminus of the valyl ester of PCT/GB2007/001677 appears not to impair the bioavailability of the compound. Further, it has been found that the compound of the invention exhibits unexpectedly high solubility in water as compared with Compound **1**.

[0049] 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 **7** is an example of such a prodrug.

[0050] Compounds **7** and **9** were tested for antiviral activity as described below and found to be active. In addition, a comparative study of the pharmacokinetic behaviour of

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[2] See, e.g., "Amino acid ester prodrugs of acyclovir," Antiviral Chemistry & Chemotherapy, 1992; 3: 157-164

Compounds **1**, **5** and **7** was conducted in a mouse model, demonstrating the improved bioavailability of Compounds **5** and **7** as compared to Compound **1**.

[0051] Surprisingly, the water-solubility of Compound **7** was found to be more than 57-fold greater than the water-solubility of Compound **1**.

[0052] For therapeutic use, a pharmaceutically acceptable salt of the compound of the invention may comprise a counter-ion that is pharmaceutically physiologically acceptable. The pharmaceutically or physiologically acceptable acid addition salt forms that the compound of the invention is able to form can conveniently be prepared using the appropriate acids such, for example, as inorganic acids such as hydrohalic acids, e.g., hydrochloride or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such, for example, as acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfuric, ethanesulfuric, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-amino-salicylic, pamoic and the like acids.

[0053] Conversely, said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.

[0054] The compound of the invention containing an acidic proton may also be converted into its non-toxic metal or amine addition salt by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, quaternary ammonium salts, the alkali and earth alkaline metal salts, e.g., the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g., the benzathine, N-methyl, -D-glucamine, hydrabamine salts and bases, and salts with amino acids, such as, for example, arginine, lysine and the like.

[0055] Conversely, said base addition forms can be converted by treatment with an appropriate acid into the free acid form.

[0056] The term "salt" as used herein also comprises the hydrate and solvent addition forms that the compound of the invention is able to form. Examples of such forms are, e.g., hydrates, alcoholate and the like. The term "salt" also comprehends the quaternisation of the nitrogen atoms of the compound. A basic nitrogen can be quaternised with any

agent known to those skilled in the art including, for instance, lower alkyl halides, dialkyl sulfates, long chain halides and arylalkyl halides.

[0057] The compound of the invention may also exist in its tautomeric forms. Such forms, although not explicitly indicated in the above formula (III), are intended to be included within the scope of the present invention.

[0058] 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.

[0059] According to a yet another aspect of the present invention 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.

[0060] According to yet another 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 amount of a compound according to the present invention.

[0061] According to a further 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0067] 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.

[0068] 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.

[0069] Compounds embodying the present invention can be presented as liposome formulations.

[0070] 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 may be 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.

[0071] In a particularly preferred embodiment, a dose of 100-500 mg of the compound of the present invention may be administered once per day.

[0072] Following is a description by way of example only with reference to the accompanying drawings of embodiments of the present invention.

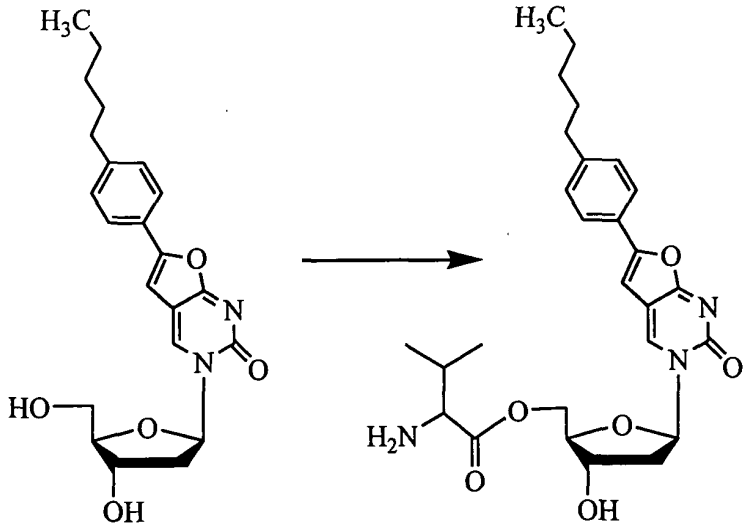
[0073] In the drawings:

[0074] FIG. 1 is a graph showing the bioavailability (in arbitrary units) of Compounds **1**, **5** and **7** at certain times after oral gavage.

[0075] FIG. 2 shows the water-solubility of Compounds **1**, **5** and **7**.

Description 1

[0076] **Preparation of Compound 5; Formation of Valine ester**



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

[0077] 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.

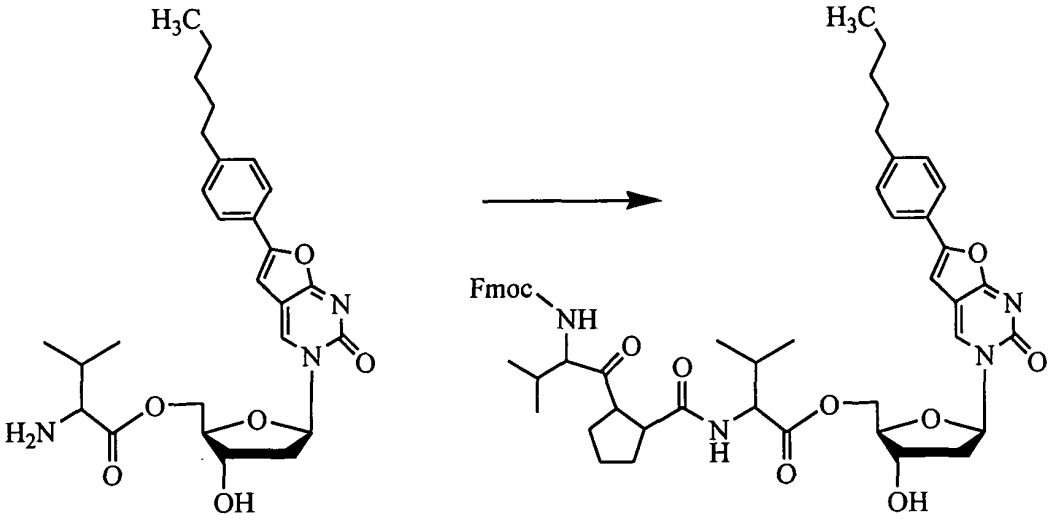
[0078] ^{1}H-NMR ($CDCl_3$) δ : 8.3 (1H, s), 7.55 (2H, d), 7.15 (2H, d), 6.6 (1H, s), 6.25 (1H, t), 4.45-4.30 (4H, m), 3.23 (1H, d), 2.80 (1H, m), 2.53 (2H, t), 2.12 (1H, m), 1.97 (1H, m), 1.60 (2H, m), 1.24 (4H, m), 0.90-0.78 (9H, m).

[0079] ^{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.

Example 1

[0080] **Preparation of Fmoc-Compound 7; Formation of Fmoc-Val-Pro-Val Conjugate**

(3-[2'-Deoxy-5'-*O*-[*N*-(fluorenilmethoxycarbonyl)-valyl-prolyl-valyl]-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidine-2-one)



Compound **5** Fmoc-Compound 7

[0081] A solution of Compound **5** prepared as described above in Description 1 (95 mg, 0.19 mmol) in dichloromethane (5 mL) was successively treated with the commercially available amino-protected dipeptide Fmoc-Val-Pro-OH (100 mg, 0.23 mmol), (benzotriazol-1-yl-oxy)-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) (101 mg, 0.23 mmol) and triethylamine (0.032 mL, 0.23 mmol). The reaction mixture was stirred at room temperature for 15 hours and the solvent was evaporated to dryness. The residue was dissolved in ethyl acetate 26 (50 mL), washed with 10% aqueous citric acid (3 x 20 mL), 10% aqueous $NaHCO_3$ (3 x 20 mL), water (3 x 20 mL) and brine (3 x 20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (dichloromethane-methanol, 25:1) to give the protected derivative Fmoc-Compound 7 (130 mg, 74%) as a white amorphous solid.

[0082] **^{1}H NMR** (300 MHz, acetone-d_6) δ: 0.84-1.04 (m, 15H, 2γ-CH_3, Val_1 y Val_2, CH_3), 1.20-1.41 (m, 4H, CH_2), 1.62 (m, 2H, CH_2), 1.91-2.18 (m, 6H, β-CH, Val_1 y Val_2, β-

CH_2, Pro, γ-CH_2, Pro), 2,37 (m, 1H, H-2'a), 2.62-2.70 (m, 3H, H-2'b, CH_2), 3.69-3.84 (m, 2H, δ-CH_2, Pro), 4.22- 4.72 (m, 11H, CH_2, Fmoc, CH, Fmoc, 2H-5', H-4', H-3', 2α-CH, Val_1 y Val_2, α-CH, Pro, OH), 6.30 (t, 1H, H-1', J = 5.9 Hz), 6.44 (d, 1H, NH, Val_1, J = 8.5 Hz), 7.22 (s, 1H, H-5), 7.35 y 7.81 (AA'BB' system, 4H, Ar, J = 8.5 Hz), 7.30-7.89 (m, 9H, Ar, Fmoc, NH, Val_2), 8.73 (s, 1H, H-4).

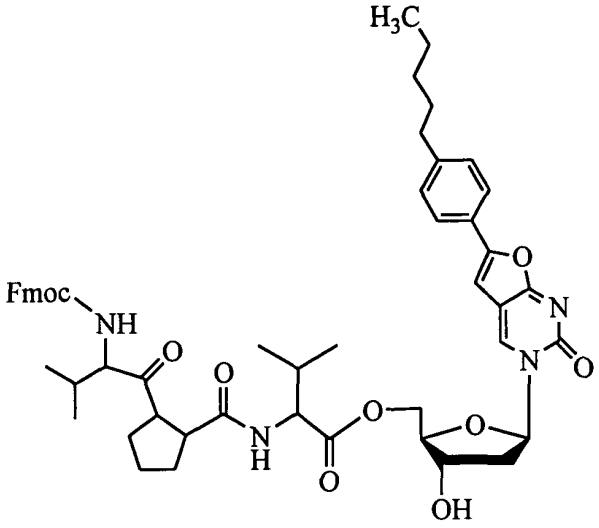
[0083] **^{13}C NMR** (100 MHz, acetone-d_6) δ; 13.6 (CH_3), 17.7, 18.1, 18.7, 19.1 (4C-γ, Val_1 y Val_2), 22.5, 25.1, 28.4, 30.8, 31.1, 31.2 (4CH_2, C-β, Pro, C-γ, Pro), 31.5, 35.7 (2C-β, Val_1 y Val_2), 41.8 (C-2'), 47.4, 47.7 (C-δ, Pro, CH Fmoc), 58.1, 58.6 (C-α, Val_2, C-α, Pro), 59.9 (C-α, Val_1), 64.1 (C-5'), 66.6 (CH_2, Fmoc), 70.5 (C-3'), 85.3, 88.5 (C-1', C-4'), 99.0 (C-5), 107.7 (C-4a), 120.1, 125.0, 125.1, 125.6, 127.3, 127.9 (4C-Ar, Fmoc, C-Hb, *ipso*-C), 129.2 (C-Ha), 137.1 (C-4), 141.4 (C-Ar, Fmoc), 144.4, 144.6 (*para*-C, C-Ar, Fmoc), 154.3, 154.7 (C-6, C=O, Fmoc), 156.5 (C-2), 171.6, 171.7, 172.0, 172.1 (C=O, Val_1, C=O, Val_2, C=O, Pro, C-7a).

[0084] MS (ESI$^+$): m/z 916.3 $(M+1)^+$, 938.0 $(M+Na)^+$. Elemental analysis calcd (%) for $C_{52}H_{61}N_5O_{10}$: C, 68.18; H, 6.71; N, 7.65; found: C, 68.01; H, 6.95; N, 7.79.

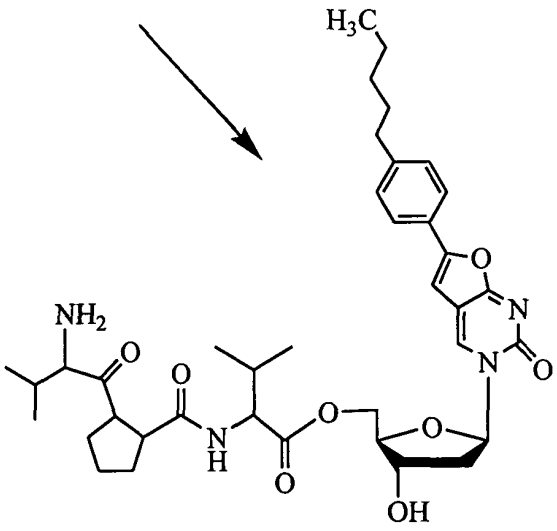
Example 2

[0085] **Preparation of Compound 7; Deprotection of the Fmoc-Val-Pro-Val Conjugate**

3-[2'-Deoxy-5'-*O*-(valyl-prolyl-valyl)-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidine-2-one)



Fmoc-Compound 7



Compound 7

[0086] To a solution of Fmoc-Compound 7 prepared as described in Example 1 above (120 mg, 0.13 mmol) in DMF (3 ml) piperidine (0.15 ml, 1.5 mmol) was added and the

mixture was stirred for 10 minute. The solvent was removed under reduced pressure and the residue was purified by CCTLC on the Chromatotron (ethyl acetate-methanol, 10:1) to give the deprotected derivative Compound 7 (81 mg, 89%) as a white foam.

[0087] **^{1}H NMR** (300 MHz, acetone-d_6) δ: 0.78-0.97 (m, 15H, 2γ-CH_3, Val_1 y Val_2, CH_3), 1.17-1.41 (m, 4H, CH_2), 1.65 (m, 2H, CH_2), 1.83-2.35 (m, 7H, 2β-CH, Val_1 y Val_2, β-CH_2, Pro, γ-CH_2, Pro, H-2'a), 2.59-2.70 (m, 3H, H-2'b, CH_2), 3.51-3.78 (m, 2H, δ-CH_2, Pro), 3.93 (d, 1H, α-CH, Val_1, J = 8.1 Hz), 4.32- 4.58 (m, 7H, 2H-5', H-4', H-3', α-CH, Val_2, α-CH, Pro, OH), 6.31 (t, 1H, H-1', J = 5.8 Hz), 7.25 (s, 1H, H-5), 7.33 (AA'BB' system, 2H, Ar, J = 8.5 Hz), 7.75-7.86 (m, 3H, Ar, NH, Val_2), 8.71 (s, 1H, H-4).

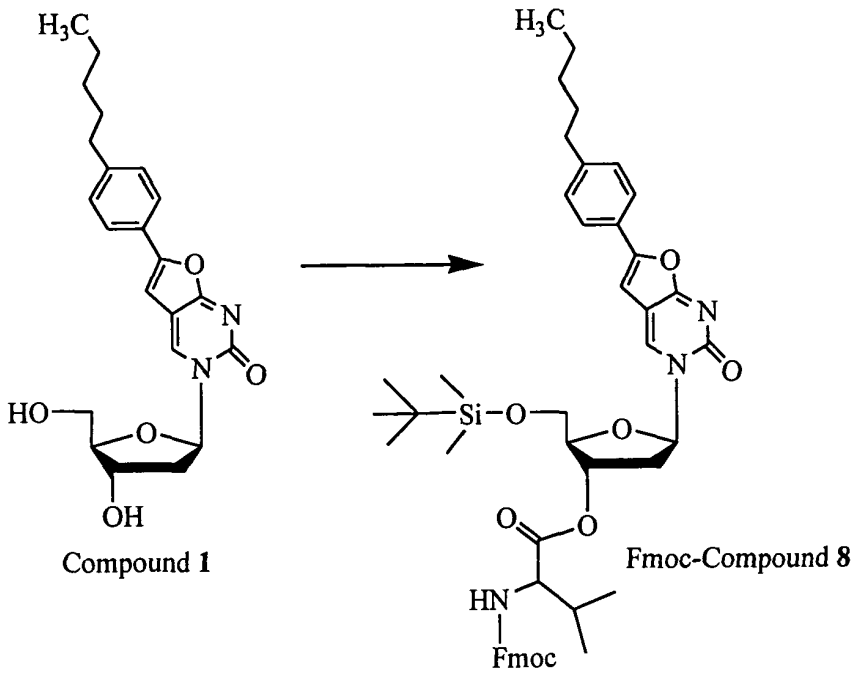
[0088] **^{13}C NMR** (100 MHz, acetone-d_6) δ; 13.9 (CH_3), 18.4, 19.0, 19.1, 19.6 (4C-γ, Val_1 y Val_2), 22.8, 25.4, 28.2, 31.0, 31.4, 31.8 (4CH_2, C-β, Pro, C-γ, Pro), 32.5, 35.9 (2C-β, Val_1 y Val_2), 42.0 (C-2'), 47.6 (C-δ, Pro), 58.8 (C-α, Val_2), 60.1, 60.4 (C-α, Val_1, C-α, Pro), 64.4 (C-5'), 70.8 (C-3') , 85.6, 88.8 (C-1', C-4'), 99.4 (C-5), 108.2 (C-4a), 125.3 (C-Hb), 127.1 (*ipso*-C), 129.5 (C-Ha), 137.5 (C-4), 144.9 (*para*-C), 154.8 (C-6), 155.1 (C-2), 168.9, 172.0, 172.3, 172.7 (C=O, Val_1, C=O, Val_2, C=O, Pro, C-7a).

[0089] MS (ESI^+): m/z 694.3 $(M+1)^+$, 716.5 $(M+Na)^+$, 1387.7 $(2M+1)^+$, 1409.6 $(2M+Na)^+$. Elemental analysis calcd. (%) for $C_{37}H_{53}N_5O_7$: C, 65.37; H, 7.86; N, 10.30; found: C, 65.26; H, 8.01; N, 10.49.

Example 3

[0090] **Preparation of Fmoc-Compound 8; Formation of 3'-valine ester**

3-[2'-Deoxy-3'-*O*-[*N*-(fluorenilmethoxycarbonyl)-valyl]-5'-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Compound **1** Fmoc-Compound **8**

[0091] To a solution of Compound **1** (200 mg, 0.5 mmol) in dry pyridine (4 ml), *tert*-butyldimethylsilyl chloride (302 mg, 2.0 mmol) was added. The reaction mixture was stirred at room temperature under an argon atmosphere for 48 hours. The solvent was removed under reduced pressure. The residue (5'-silyl derivative) was dissolved in DMF (3 ml) and 4-dimethylaminopyridine (12 mg, 0.1 mmol), Fmoc-Val-OH (225 mg, 0.66 mmol) and *N,N'*-dicyclohexyl-carbodiimide (137 mg, 0.66 mmol) were successively added at 0°C. The reaction mixture was stirred at room temperature for 2 hours. The white solid was filtered, washed with DMF and the solvent was evaporated to dryness. The residue, thus obtained, was dissolved in ethyl acetate (50 mL), washed with 10% aqueous citric acid (3 x 20 mL), 10% aqueous $NaHCO_3$ (3 x 20 mL), water (3 x 20 mL) and brine (3 x 20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by flash column chromatography on silica gel (dichloromethane/methanol, 40:1) to give 230 mg (83%) of Fmoc-Compound **8** as a white foam.

[0092] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.14 (s, 3H, CH_3, Si-CH_3), 0.16 (s, 3H, CH_3, Si-CH_3), 0.89 (m, 12H, ^{t}Bu, CH_3), 1.02 (d, 6H, γ-CH_3, Val), 1.27-1.40 (m, 4H, $2CH_2$), 1.63 (m, 2H, CH_2), 1.81 (m, 1H, β-CH, Val), 2.21-2.39 (m, 2H, 2H-2'), 2.66 (t, 2H, CH_2, J = 7.3 Hz), 4.02 (m, 2H, 2H-5'), 4.17-4.40 (m, 5H, CH_2, Fmoc, CH, Fmoc, H-4', α-CH, Val), 5.40 (m, 1H, H-3'), 6.31 (t, 1H, H-1', J = 5.9 Hz), 6.98 (d, 1H, NH, J = 8.8 Hz), 7.03 (s, 1H, H-5), 7.29-7.86 (m, 8H, Ar Fmoc), 7.33 y 7.74 (AA'BB' system, 4H, Ar, J = 8.1 Hz), 8.68 (s, 1H, H-4).

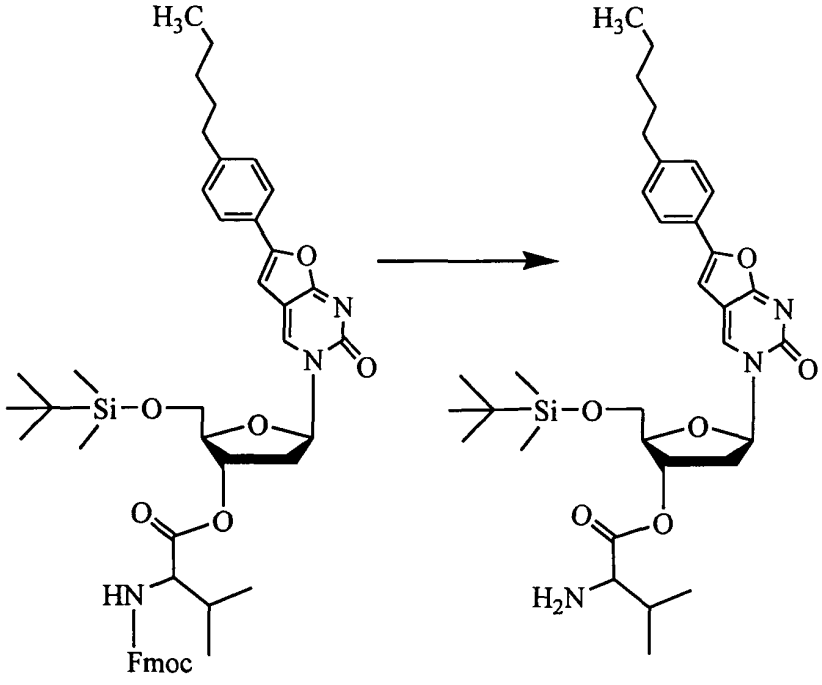
[0093] **MS (ESI+):** m/z 834.3 ($M+1^+$).

[0094] **Elemental analysis:** calcd (%) for $C_{48}H_{61}N_3O_8Si$: C, 68.95; H, 7.35; N, 5.03; found: C, 69.07; H, 7.49; N, 5.58.

Example 4

[0095] **Fmoc-Deprotection of Compound 8**

3-[2'-Deoxy-3'-*O*-valyl-5'-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Fmoc-Compound **8** Compound **8**

[0096] To a solution of Fmoc-Compound **8** (179 mg, 0.22 mmol) in DMF (5 ml), piperidine (0.25 ml, 2.5 mmol) was added and the mixture was stirred for 5 minutes. The solvent was evaporated to dryness. The residue was purified by CCTLC on the Chromatotron (dichloromethane/methanol, 20:1) to afford 122 mg (93%) of Compound **8** as a yellow foam.

[0097] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.16 (s, 3H, CH_3, Si-CH_3), 0.18 (s, 3H, CH_3, Si-CH_3), 0.87-0.99 (m, 18H, ^{t}Bu, γ-CH_3, Val, CH_3), 1.29-1.40 (m, 4H, $2CH_2$), 1.66 (m, 2H, CH_2), 2.03 (m, 1H, β-CH, Val), 2.22-2.37 (m, 2H, 2H-2'), 2.67 (t, 2H, CH_2, J = 7.5 Hz), 3.92 (d, 1H, α-CH, Val, J = 6.8 Hz), 4.05 (m, 2H, 2H-5'), 4.33 (m, 1H, H-4'), 5.37 (m, 1H, H-3'), 6.29 (m, 1H, H-1'), 7.03 (s, 1H, H-5), 7.34 y 7.75 (AA'BB' system, 4H, Ar, J = 8.1 Hz), 8.70 (s, 1H, H-4).

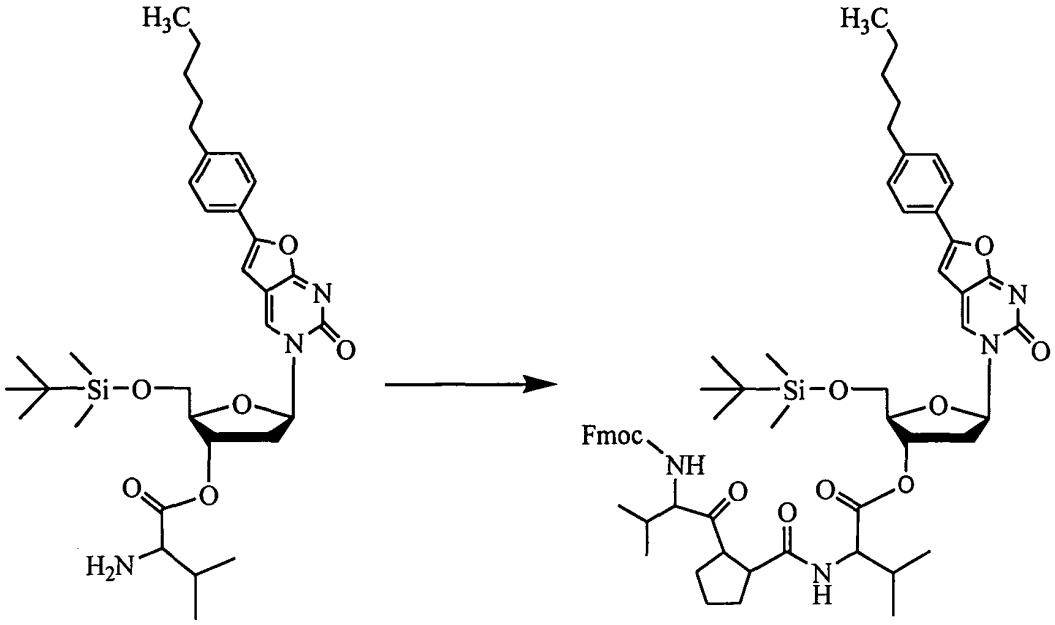
[0098] **MS (ESI+):** m/z 612.4 ($M+1^+$).

[0099] **Elemental analysis:** calcd (%) for $C_{33}H_{51}N_3O_6Si$: C, 64.57; H, 8.37; N, 6.85; found: C, 64.44; H, 8.51; N, 6.89.

Example 5

[0100] **Preparation of Fmoc-Compound 9; Formation of 3'-Fmoc-Val-Pro-Val conjugate**

3-[2'-Deoxy-3'-*O*-[*N*-(fluorenilmethoxycarbonyl)-valyl-prolyl-valyl]-5'-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Compound **8** Fmoc-Compound **9**

[0100] Following the method described in Example 1 for the synthesis of Fmoc-compound 7, a solution of Compound **8** (81 mg, 0.13 mmol) in dichloromethane (2 ml) was successively reacted with Fmoc-Val-Pro-OH (69 mg, 0.16 mmol), BOP (70 mg, 0.16 mmol) and triethylamine (0.022 ml, 0.16 mmol) for 15 hours. After the work-up the final residue was by CCTLC on the Chromatotron (dichloromethane/methanol, 50:1) to afford 109 mg (80%) of Fmoc-Compound **9** as a white foam.

[0101] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.16 (s, 3H, CH_3, Si-CH_3), 0.18 (s, 3H, CH_3, Si-CH_3), 0.86-1.05 (m, 24H, ^{t}Bu, 2γ-CH_3, Val_1, Val_2, CH_3), 1.30-1.36 (m, 4H, $2CH_2$), 1.64 (m, 2H, CH_2), 1.96-2.38 (m, 8H, 2β-CH, Val_1, Val_2, β-CH_2, Pro, γ-CH_2, Pro, 2H-2'), 2.66 (t, 2H, CH_2, J = 7.3 Hz), 3.63-3.82 (m, 2H, δ-CH_2, Pro), 4.06 (m, 2H, 2H-5'), 4.21-4.38 (m, 6H, CH_2, Fmoc, CH, Fmoc, 2α-CH Val_1, Val_2, α-CH, Pro), 4.61 (m, 1H, H-4'), 5.40 (m, 1H, H-3'), 6.45 (m, 1H, H-1'), 6.66 (d, 1H, NH, Val_1, J = 8.3 Hz), 7.03 (s, 1H, H-5), 7.28-

7.86 (m, 9H, Ar, Fmoc, NH Val_2), 7.34 y 7.75 (AA'BB' system, 4H, Ar, J= 8.1 Hz), 8.71 (s, 1H, H-4).

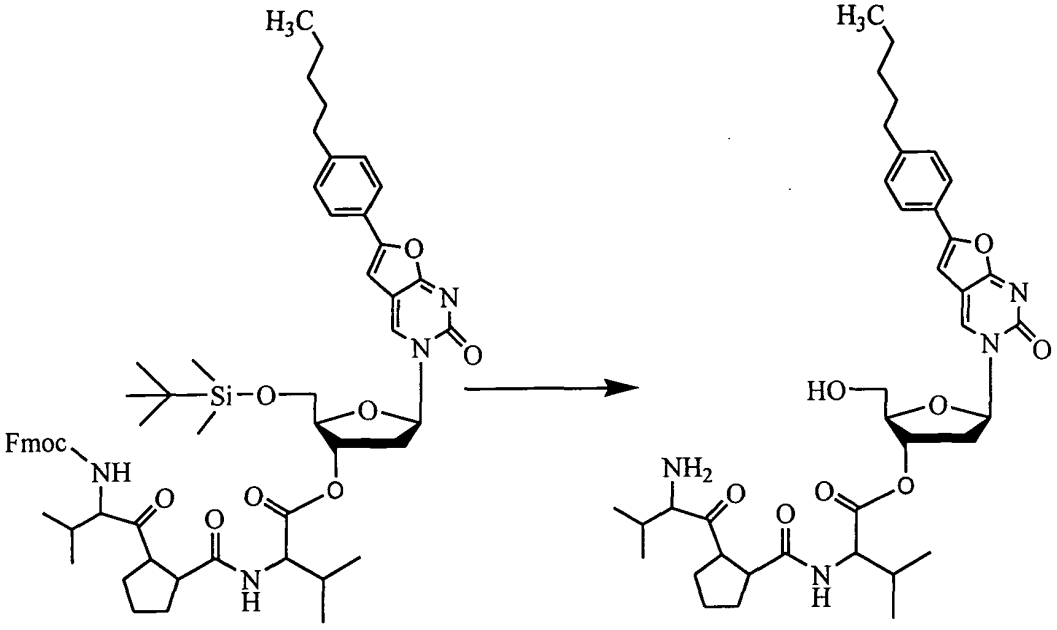
[0102] **MS (ESI+):** m/z 1030.3 ($M+1^+$).

[0103] **Elemental analysis:** calcd (%) for $C_{58}H_{77}N_5O_{10}Si$: C, 67.48; H, 7.52; N, 6.78; found: C, 67.63; H, 7.59; N, 6.81.

Example 6

[0104] **Full Deprotection of Fmoc-Compound 9**

3-[2'-Deoxy-3'-*O*-(valyl-prolyl-valyl)-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Fmoc-Compound **9** Compound **9**

[0105] According to the deprotection method described for Compound **3** (See Example 7 below), a solution of Fmoc-Compound **9** (109 mg, 0.11 mmol) in MeOH (2 ml) was reacted with HCl 0.1N in MeOH (1.1 ml, 0.11 mmol) for 3 hours. The residue obtained after the work-up, was dissolved in DMF (2 mL) and piperidine was added. After 5 minutes at room temperature the solvent was evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (dichloromethane/methanol, 50:1) to afford 40 mg (52%) of the fully deprotected Compound **9** as a yellow foam.

[0106] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.83-1.02 (m, 15H, 2γ-CH_3, Val_1, Val_2, CH_3), 1.29-1.39 (m, 4H, 2CH_2), 1.65 (m, 2H, CH_2), 1.88-2.48 (m, 8H, 2β-CH ,Val_1,Val_2, β-CH_2, Pro, γ-CH_2, Pro, 2H-2'), 2.66 (t, 2H, CH_2, J = 7.5 Hz), 3.53-3.76 (m, 3H, α-CH, Val_1, δ-CH_2, Pro), 3.93-4.55 (m, 6H, 2H-5', H-4', α-CH Val_2, α-CH, Pro, OH), 5.43 (m, 1H, H-3'), 6.37 (m, 1H, H-1'), 7.05 (s, 1H, H-5), 7.34 y 7.74 (AA'BB' system, 4H, Ar, J = 8.5 Hz), 7.69 (d, 1H, NH, Val_2, J = 7.9 Hz), 8.86 (s, 1H, H-4).

[0107] **MS (ESI+):** m/z 694.3 ($M+1^+$).

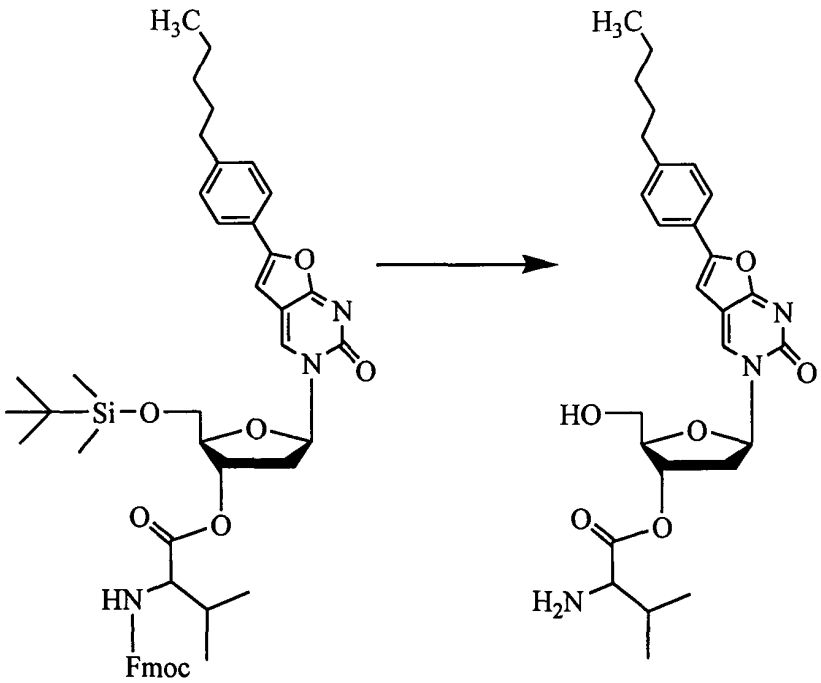
[0108] **Elemental analysis:** calcd (%) for $C_{37}H_{53}N_5O_8$: C, 63.86; H, 7.68; N, 10.06; found: C, 64.01; H, 7.54; N, 10.21.

Example 7

[0101] **Silyl and Fmoc Deprotection of Fmoc-Compound 8**

3-[2'-Deoxy-3'-*O*-valyl-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one

[0109] If desired, Fmoc-Compound **8** may be fully deprotected to form Compound **3** of PCT/GB2007/00167.



Fmoc-Compound **8** Compound **3**

[0102] Fmoc-Compound **8** (128 mg, 0.15 mmol) was dissolved in MeOH (1 ml) and a solution of HCl 0.1N in MeOH (1.85 ml, 0.19 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and the solvent was evaporated to dryness. The residue was dissolved in dichloromethane (40 mL) and washed with a 10% aqueous $NaHCO_3$ (3 x 20 mL). The organic layer was dried, filtered and evaporated to dryness. The residue was dissolved in DMF (3 mL), piperidine (0.15 ml, 1.5 mmol) was added and stirred at room temperature for 5 minutes. The solvent was removed under reduced pressure and the residue was purified by CCTLC on the Chromatotron (dichloromethane/methanol, 20:1) to yield 58 mg (76%) of fully deprotected Compound **3** as a yellow oil.

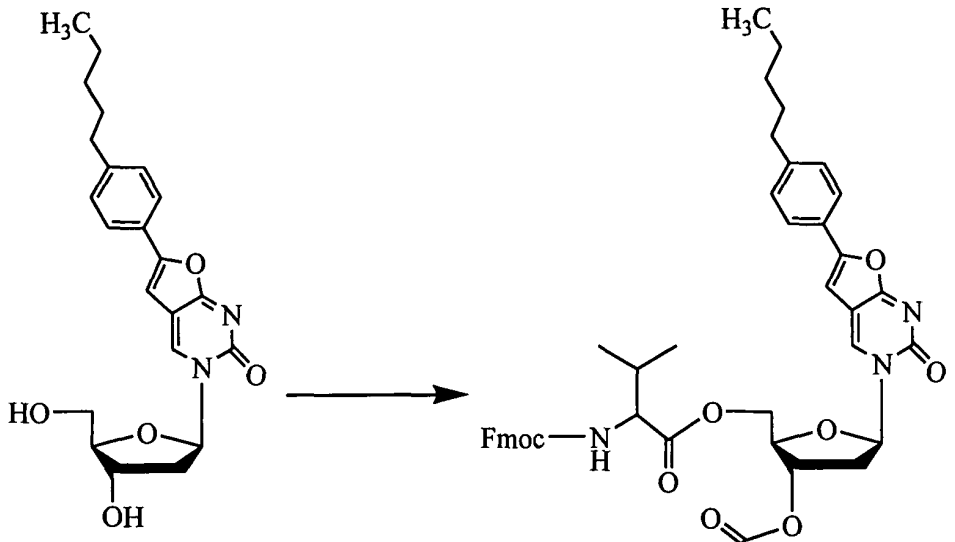
[0103] **^{1}H NMR** (300 MHz, DMSO-d_6): δ 0.80-0.91 (m, 9H, γ-CH_3, Val, CH_3), 1.28 (m, 4H, $2CH_2$), 1.58 (m, 2H, CH_2), 1.87 (m, 1H, β-CH, Val), 2,30 (m, 1H, H-2'a), 2.55-2.72 (m, 3H, CH_2, H-2'b), 3.17-3.73 (m, 3H, 2H-5', α-CH, Val), 4.15 (m, 1H, H-4'), 5.25 (m, 1H, H-3'), 5.32 (t, 1H, 5'-OH, J = 5.2 Hz), 6.22 (t, 1H, H-1', J = 6.1 Hz), 7.21 (s, 1H, H-5), 7.31 y 7.72 (AA'BB' system, 4H, Ar, J = 8.3 Hz), 8.78 (s, 1H, H-4).

[0104] **MS (ESI+):** m/z 498.3 ($M+1^+$).

Example 8

[0110] **Preparation of Fmoc-Compound 10; Formation of 3', 5'- valine ester**

3-[2'-Deoxy-3',5'-bis-*O*-[*N*-(fluorenilmethoxycarbonyl)-valyl]-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Compound **1** Fmoc-Compound **10**

[0111] To a solution of Compound **1** (188 mg, 0.47 mmol) in DMF (4 mL) at 0°C, 4-dimethylaminopyridine (17 mg, 0.14 mmol), Fmoc-Val-OH (481 mg, 1.42 mmol) and N,N'-dicyclohexyl-carbodiimide DCC (292 mg, 1.42 mmol) were successively added. The reaction mixture was stirred at room temperature for 15 hours. The white solid was filtered, washed with DMF and the solvent was evaporated to dryness. The residue, thus obtained, was dissolved in ethyl acetate (40 mL), washed with 10% aqueous citric acid (3 x 20 mL), 10% aqueous $NaHCO_3$ (3 x 20 mL), water (3 x 20 mL) and brine (3 x 20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 3:1) to give 343 mg (70%) of Fmoc-Compound **10** as a white foam.

[0112] **^{1}H NMR** (400 MHz, acetone-d_6): δ 0.88 (t, 3H, CH_3, J = 6.9 Hz), 0.91-1.02 (m, 12H, 2γ-CH_3, Val-3', Val-5'), 1.30-1.34 (m, 4H, $2CH_2$), 1.57-1.64 (m, 2H, CH_2), 2.14-2.27 (m, 2H, β-CH, Val-3', Val-5'), 2.48 (m, 1H, H-2'a), 2.61 (t, 2H, CH_2, J = 7.8 Hz), 2.78-

2.82 (m, 1H, H-2'b), 4.18-4.61 (m, 11H, $2CH_2$, Fmoc-3', Fmoc-5', 2CH, Fmoc-3', Fmoc-5', 2H-5', H-4', 2α-CH, Val-3', Val-5'), 5.45 (m, 1H, H-3'), 6.33 (t, 1H, H-1', J = 5.9 Hz), 6.97-7.03 (m, 2H, NH, Val-3', Val-5'), 7.07 (s, 1H, H-5), 7.24-7.85 (m, 16H, Ar, Fmoc), 7.19 y 7.58 (AA'BB' system, 2H, Ar, J = 8.2 Hz), 8.54 (s, 1H, H-4).

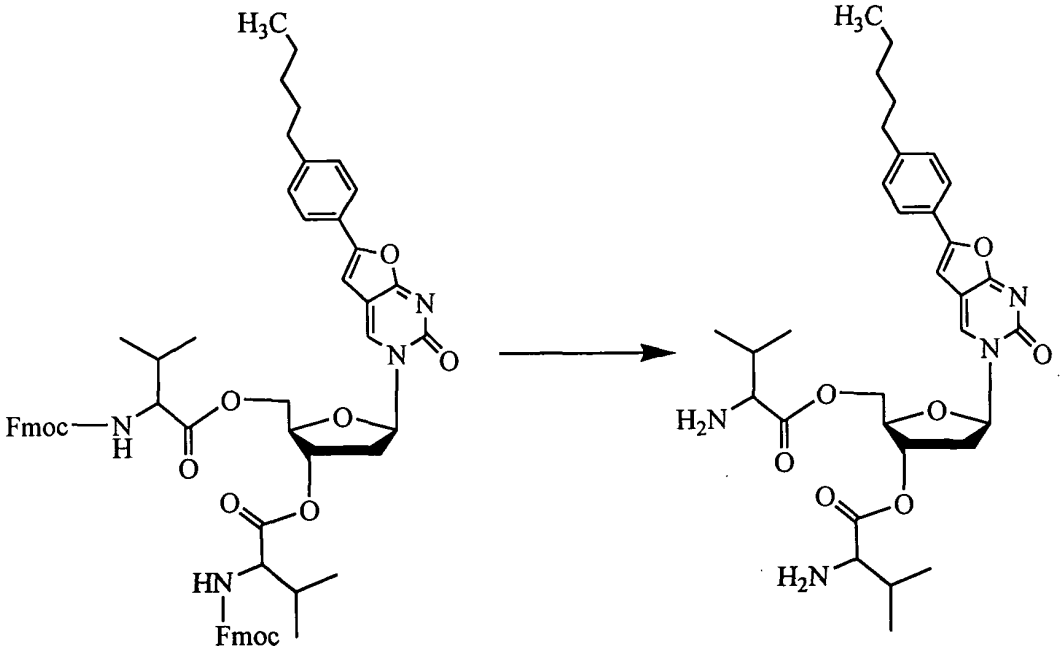
[0113] **MS (ESI+):** m/z 1041.3 ($M+1^+$).

[0114] **Elemental analysis:** calcd (%) for $C_{62}H_{66}N_4O_{11}$: C, 71.38; H, 6.38; N, 5.37; found: C, 71.12; H, 6.51; N, 5.50.

Example 9

[0115] **Deprotection of Fmoc-Compound 10**

3-[2'-Deoxy-3',5'-bis-*O*-valyl]-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Fmoc-Compound **10** Compound **10**

[0116] To a solution of Fmoc-Compound **10** (330 mg, 0.32 mmol) in DMF (12 ml) piperidine (0.6 ml, 6.0 mmol) was added and the mixture was stirred for 5 minutes. The solvent was evaporated to dryness. The residue was purified by CCTLC on the Chromatotron (dichloromethane/methanol, 20:1) to afford 181 mg (95%) of Compound **10** as a yellow oil.

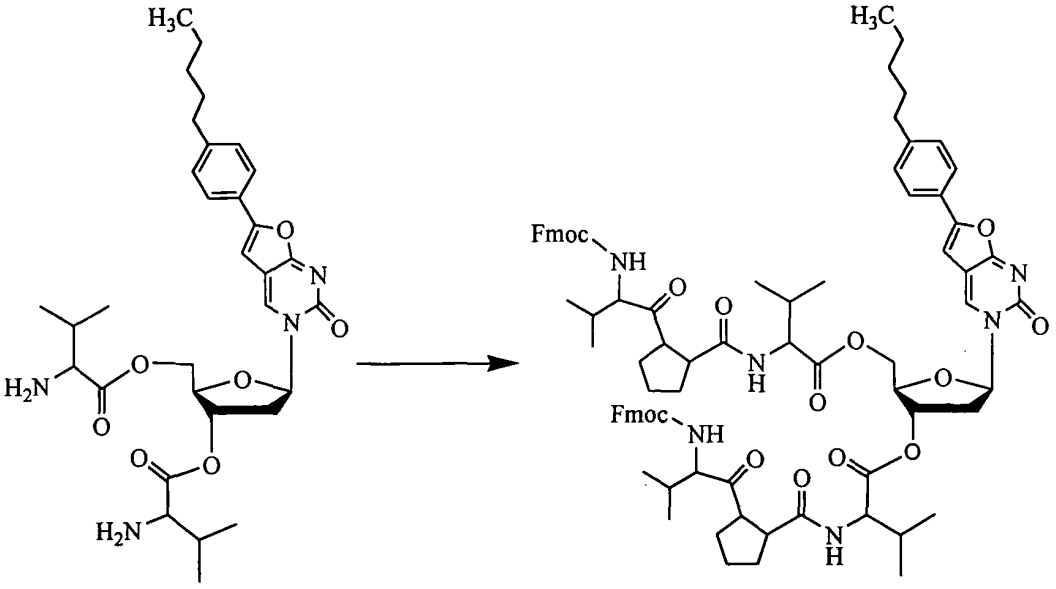
[0117] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.81-0.99 (m, 15H, 2γ-CH_3, Val-3', Val-5', CH_3), 1.29-1.36 (m, 4H, 2CH_2), 1.62-1.67 (m, 2H, CH_2), 1.91-2.07 (m, 3H, 2β-CH, Val-3', Val-5', H-2'a), 2.44 (m, 1H, H-2'b), 2.67 (t, 2H, CH_2, J = 8.1 Hz), 4.31-4.50 (m, 5H, 2H-5', H-4', 2α-CH, Val-3', Val-5'), 5.38 (m, 1H, H-3'), 6.32 (t, 1H, H-1', J = 6.2 Hz), 7.07 (s, 1H, H-5), 7.34 y 7.74 (AA'BB' system, 4H, Ar, J = 8.3 Hz), 8.65 (s, 1H, H-4).

[0118] **MS (ESI+):** m/z 597.3 ($M+1^+$), 1193.7 ($2M+1^+$).

Example 10

[0119] **Preparation of Fmoc-Compound 11; Formation of 3', 5'-Fmoc-Val-Pro-Val conjugate**

3-[2'-Deoxy-3',5'-bis-*O*- [*N*-(fluorenilmethoxycarbonyl)-valyl-prolyl-valyl]-β-D-ribofuranosyl]-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Compound **10** Fmoc-Compound **11**

[0120] Following the method described in Example 1 for the synthesis of Fmoc-compound **7**, a solution of compound **10** (113 mg, 0.19 mmol) in dichloromethane (5 ml) was successively reacted with Fmoc-Val-Pro-OH (198 mg, 0.45 mmol), BOP (201 mg, 0.45 mmol) and triethylamine (0.063 ml, 0.45 mmol). After the work-up the final residue was by CCTLC on the Chromatotron (dichloromethane/methanol, 40:1) to afford 184 mg (68%) of Fmoc-compound **11** as a yellow oil.

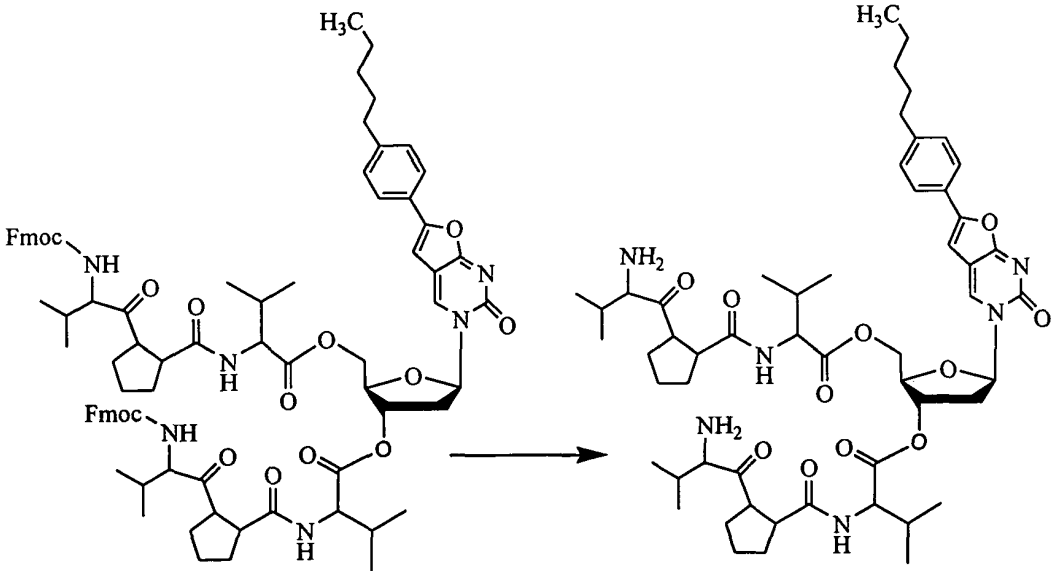
[0121] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.86-1.05 [m, 27H, 4γ-CH_3, (Val_1,Val_2)-3' y (Val_1, Val_2)-5', CH_3], 1.30 (m, 4H, 2CH_2), 1.62 (m, 2H, CH_2), 1.91-2.55 [m, 14H, 2H-2', 4β-CH, (Val_1,Val_2)-3' and (Val_1,Val_2)-5', 2β-CH_2, Pro-3', Pro-5', 2γ-CH_2, Pro-3', Pro-5'], 2.64 (m, 2H, CH_2), 3.58-3.84 (m, 4H, 2δ-CH_2, Pro-3', Pro-5'), 4.24-4.60 (m, 15H, 2CH_2, Fmoc-3', Fmoc-5', 2CH, Fmoc-3', Fmoc-5', 2H-5', H-4', 4α-CH, (Val_1, Val_2)-3' and (Val_1,Val_2)-5', 2α-CH Pro-3', Pro-5'), 5.46 (m, 1H, H-3'), 6.65 (m, 1H, H-1'), 7.19 (s, 1H, H-5), 7.33-7.88 (m, 16H, Ar Fmoc), 7.34 y 7.86 (AA'BB' system, 4H, Ar, J = 7.5 Hz), 8.70 (s, 1H, H-4).

[0122] **MS (ESI+):** m/z 1434.4 ($M+1^+$).

Example 11

[0123] **Preparation of Compound 11; Deprotection of 3', 5'-Fmoc-Val-Pro-Val conjugate**

3-(2'-Deoxy-3',5'-bis-*O*-valyl-prolyl-valyl-β-D-ribofuranosyl)-6-(*p*-pentylphenyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one



Fmoc-Compound **11** Compound **11**

[0124] To a solution of Fmoc-compound **11** (164 mg, 0.11 mmol) in DMF (12 ml), piperidine (0.25 ml, 2.5 mmol) was added and the mixture was stirred for 5 minutes. The solvent was evaporated to dryness. The residue was purified by CCTLC on the

Chromatotron (dichloromethane/methanol, 10:1) to afford 98 mg (87%) of compound **11** as a yellow foam.

[0125] **^{1}H NMR** (300 MHz, acetone-d_6): δ 0.88-1.02 [m, 27H, 4γ-CH_3, (Val_1 ,Val_2)-3', (Val_1, Val_2)-5', CH_3], 1.29-1.40 (m, 4H, $2CH_2$), 1.65 (m, 2H, CH_2), 1.72-2.57 [m, 14H, 2H-2', 4β-CH, (Val_1, Val_2)-3', (Val_1, Val_2)-5', 2β-CH_2, Pro-3', Pro-5', 2γ-CH_2, Pro-3', Pro-5'], 2.67 (t, 2H, CH_2, J = 7.7 Hz), 3.60-4.58 (m, 13H, 2H-5', H-4', 4α-CH, (Val_1, Val_2)-3', (Val_1,Val_2)-5', 2α-CH Pro-3', Pro-5', 2δ-CH_2, Pro-3', Pro-5'), 5.45 (m, 1H, H-3'), 6.35 (m, 1H, H-1'), 7.20 (s, 1H, H-5), 7.34 y 7.70 (AA'BB' system, 2H, Ar, J = 8.1 Hz), 7.75-7.89 (m, 2H, 2NH Val_2-3', Val_2-5'), 8.68 (s, 1H, H-4).

[0126] **MS (ESI+):** m/z 989.5 ($M+1^+$).

[0127] **Elemental analysis:** calcd (%) for $C_{52}H_{76}N_8O_{11}$: C, 63.14; H, 7.74; N, 11.33; found: C, 63.27; H, 7.69; N, 11.50.

Example 12

[0128] **Oral bioavailability of Compound 1, Compound 5 and Compound 7 in mice**

[0129] A study was conducted with Compounds **1, 5** and **7** to compare the relative bioavailability of Compound **1** after oral dosing in mice. Three groups of female mice received equimolar doses of Compound **1** (25 mg/kg), **5** (31.25 mg/kg; equivalent to 25 mg/kg of Compound **1**) or **7** (41.8 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.

[0130] The results of this study are shown in Table 1 below and in FIG. 1 of the accompanying drawings. Plasma concentrations of Compound **1** were much higher in mice receiving Compounds **5** and **7** as 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-fold and Compound 7 by approximately 12-fold (as estimated by the AUC values).

[0131] In conclusion, this data supports the hypothesis that Compound 7 according to the present invention is a prodrug of Compound **1**, and greatly increases the oral bioavailability of Compound **1**.

Table 1

Time (min) after oral gavage	Compound 1 in plasma (area under the curve (HPLC))		
	Compound 7	Compound 5	Compound 1
15	32	18	2.6
30	52	19	2.9
45	87	39	4.0
60	44	42	4.2
120	14	28	2.5
180	6.2	8.1	3.4

In all cases, only Compound **1** was detected in plasma.
Compound **5** was markedly more bioavailable than Compound **1**.
Compound 7 was more bioavailable than Compound **5**.

Example 13

[0132] **Conversion of** Compound 7 **by purified CD26, bovine serum (10%) and human serum (10%)**

[0133] A variety of test compounds have been evaluated for their substrate activity against purified CD26, human serum (HS), and bovine serum (BS) in Eppendorf tubes. The 400 µL reaction mixture contained 50 µM of test compound in PBS (containing 0.1% DMSO). The reaction was started by the addition of purified CD26 (1.5 mU) or 20% of HS (in PBS) or BS (in PBS) at 37°C. At different time points, 100 µL was withdrawn from the reaction mixture, added to 200 µL methanol, and put on ice for ~ 10 min. Then, the mixture was centrifuged at 13,000 rpm for 5 min at 4°C and 250 µL of supernatant was analyzed by HPLC on a reverse phase RP-8 column, using following gradients:

[0134] Gradient A (Buffer A: 50 mM NaH_2PO_4 + 5 mM heptane-sulfonic acid pH 3.2; buffer B: acetonitrile): 2 min 98% A + 2% B; 6 min linear gradient to 80% A + 20% B; 2 min linear gradient to 75% A + 25% B; 2 min linear gradient to 65% A + 35% B; 18 min linear gradient to 50% A + 50 % B; 5 min 50% A + 50% B; 5 min linear gradient to 98% A + 2% B; 5 min equilibration at 98% A + 2% B.

[0135] Gradient B: 2 min 98% A + 2% B; 6 min linear gradient to 80% A + 20% B; 2 min linear gradient to 75% A + 25% B; 2 min linear gradient to 65% A + 35% B; 8 min linear gradient to 50% A + 50% B; 10 min 50% A + 50% B; 10 min linear gradient to 20% A + 80% B; 5 min 20% A + 80% B; 15 min linear gradient to 98% A + 2% B; 5 min 98% A + 2% B.

Table 2. Conversion of Compound **7** to Compound **5** and Compound **1** *in vitro*

	Formation of hydrolysis products (%)			
	Time (hr)	Compound **7**	Compound **5**	Compound **1**
CD26	0	100	0	0
	2	0	50.6	49.4
	6	0	37.1	62.9
	20	0	24.5	75.5
Bovine serum 10%	0	100	0	0
	1	59.8	19.9	20.3
	4	20.4	34.7	44.8
	20	3.3	21	74.4
Human serum 10%	0	100	0	0
	1	31	11.4	57.6
	4	5.0	21.5	73.4
	20	1.8	9.7	88.5

Rapid conversion of Compound **7** to Compound **5** occurs in the presence of purified CD26 (1.5 mU in PBS), bovine serum (10%) and human serum (10%) in PBS.
Compound **7** is fully stable in PBS for 6 hrs at 37°C (not shown).
Compound **5** is unstable. It spontaneously degrades to Compound **1** in buffer.
Compound **5** is stabilized as a salt derivative.

Example 14

[0136] **Anti-VZV activity of Compounds 7 and 9 and Compounds 5 and 3 in comparison with Compound 1**

[0137] The objective of this study was to compare the antiviral activity of Compounds **1, 3, 5, 7** and **9** in HEL cells inoculated with VZV strains. Antiviral activity was assessed as the ability of Compounds **1, 3, 5, 7** and **9** to reduce viral plaque formation after incubation periods of 5 days as compared to untreated control cultures. The results of the antiviral efficacy studies showing comparable efficacy between the three compounds are shown in Tables 3a and 3b below.

[0138] VZV-drug susceptibility assays were performed on confluent HEL cells in 96-well microtiter plates. Monolayers were infected with 20 PFU of cell-associated virus per well. For each assay, virus controls (infected-untreated cells) were included. After a 2-hour incubation period, the virus inoculum was removed and the media replaced by the different dilutions (in duplicate) of the tested molecules. Serial dilutions of test compounds were incubated with the infected monolayers for 5 days. After the 5-day incubation period, the cells were fixed and stained with Giemsa, and the level of virus-induced cytopathic effect was determined by counting the number of plaques for each dilution. Activity was expressed as EC_{50} (effective compound concentration required to reduce virus-plaque formation by 50%) compared to the untreated control.

Table 3

	EC_{50}[a] (μM)				
Cmpd	**VZV TK$^+$**		**VZV TK$^-$**	**MCC (μM)**	**CC_{50}(μM)**
	YS	OKA	07/1		
5	0.03	0.014	> 1	> 1	> 0.5
7	0.01	0.012	> 1	> 1	> 0.5
1	0.02	0.008	> 1	> 1	> 5.0

[a] 50% effective concentration

Table 3b

	EC_{50}[a] (μM)				
Cmpd	**VZV TK+**		**VZV TK-**	**MCC (μM)**	**CC_{50}(μM)**
	YS	OKA	07/1		
3	0.004	0.007	> 5	20	> 5
9	0.016	0.017	> 5	20	> 5
1	0.003	0.003	> 20	> 20	> 5

[a] 50% effective concentration

[0139] Compounds **7** and **9** and **5** and **3** are active in VZV-infected HEL cell cultures. They lose antiviral activity against VZV/TK-. Neither of them is cytotoxic or cytostatic at concentrations that largely exceed the antiviral concentrations.

Example 15

[0140] **Water-solubility studies**

The water-solubility of Compound **7** was determined by HPLC analysis and compared with that of Compound **5** and parent Compound **1**. HPLC was carried out on a Waters 484 System using Novapack C18 reverse phase column. Flow rate: 1 mL/min. Detection: UV 254 nm. Gradient solvent system A/B (acetonitrile/water): initial 15 % A + 85 % B; 5 min linear gradient to 25 % A + 75 % B; 5 min linear gradient to 35% A + 65% B; 10 min linear gradient to 45% A + 55% B; 5 min linear gradient to 60% A + 40% B and 5 min linear gradient to 100% A.

[0141] Excess amount of the prodrug or the parent drug was suspended in deionised water, sonicated for 10 min at room temperature, and then equilibrated overnight at room temperature. The samples were centrifuged at 14.000 rpm in an Eppendorf micro-centrifuge for 1.5 min at room temperature. An aliquot of the clear supernatant was removed and diluted to a concentration within the range of a five-point standard curve. Water-solubility was calculated from each peak area of the above solution by HPLC compared with the sample dissolved in acetonitrile, the concentration of which is already known.

[0142] The values of solubility and partition coefficients of the prodrugs and parent compound are provided in **Table 4** below. Predicted partition coefficient values suggest that lipophilicity can be significantly reduced from 3.24 to 1.60 or 0.70 upon introduction of the valyl or tripeptidyl moiety. The prodrugs exhibited higher water-solubility than the parent drug as shown in FIG. 2. Compound 7 prodrug improved the water-solubility (1.27 mg/mL) more than 57-fold in comparison with the parent Compound 1 (0.022 mg/mL). This result suggests that the CD26 prodrug approach could be useful for increasing the water-solubility of hydrophobic drugs.

Table 4. Physicochemical properties of Compounds **1, 5** and **7**

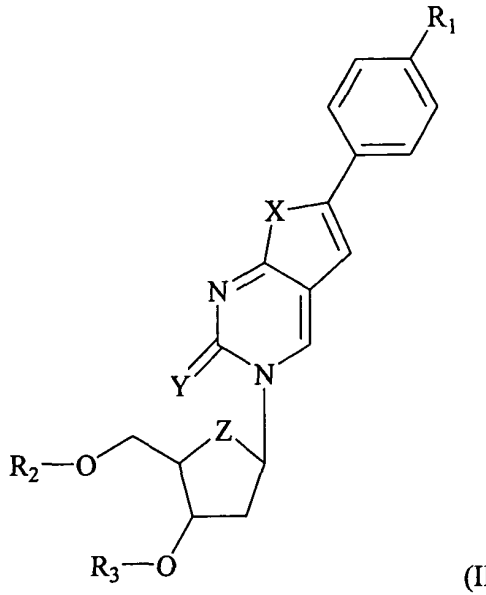
Test Compound	Predicted logP^a	Predicted logW^a	Solubility in water (mg/ml)[b]
1	3.24	-1.97	0.022 ± 0.007
5	1.60	-4.49	0.211 ± 0.044
7	0.70	-7.83	1.27 ± 0.05

[a]Predicted value of logP and logW (water solubility) was obtained using the website http://www.logp.com

[b]Data are means of three determinations

Claims

1. A compound a compound of the general formula (III):



(III)

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_{1-8} alkyl, especially C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl;

at least one of R_2 and R_3 is H-$[R_4$-$R_5]_n$-R_6-, in which:

H-$[R_4$-$R_5]_n$- comprises an oligopeptide, R_4 being an amino acid and R_5 being an amino acid selected from proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine;

R_6 is a neutral, non-polar amino acid moiety that is bonded to R_5 by a peptide bond, and

n is 1, 2, 3, 4 or 5; and

the other of R_3 and R_2 is H-$[R_4$-$R_5]_n$-R_6- or H; or

a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein one of R_2 and R_3 is H-$[R_4$-$R_5]_n$-R_6 and the other is H.

3. A compound as claimed in claim 1, wherein both of R_2 and R_3 are H-$[R_4$-$R_5]_n$-R_6.

4. A compound as claimed in claim 3, wherein R_2 and R_3 are the same as one another.

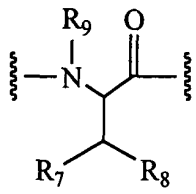
5. A compound as claimed in any preceding claim, wherein n=1.

6. A compound as claimed in any preceding claim, wherein R_4 is selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, preferably valine.

7. A compound as claimed in any preceding, wherein R_5 is selected from proline, alanine, glycine, serine, valine and leucine, preferably proline or alanine.

8. A compound as claimed in any preceding claim, wherein the oligopeptide -$[R_4$-$R_5]$- is selected from Val-Pro, Asp-Pro, Ser-Pro, Lys-Pro, Arg-Pro, His-Pro, Phe-Pro, Ile-Pro, Leu-Pro, Val-Ala, Asp-Ala, Ser-Ala, Lys-Ala, Arg-Ala, His-Ala, Phe-Ala, Ile-Ala and Leu-Ala, preferably Val-Pro.

9. A compound as claimed in any preceding claim, wherein said neutral, non-polar amino acid moiety R_6 is:



in which R_7, R_8 and R_9 are each independently H or C_{1-3} alkyl, especially C_{1-2} alkyl.

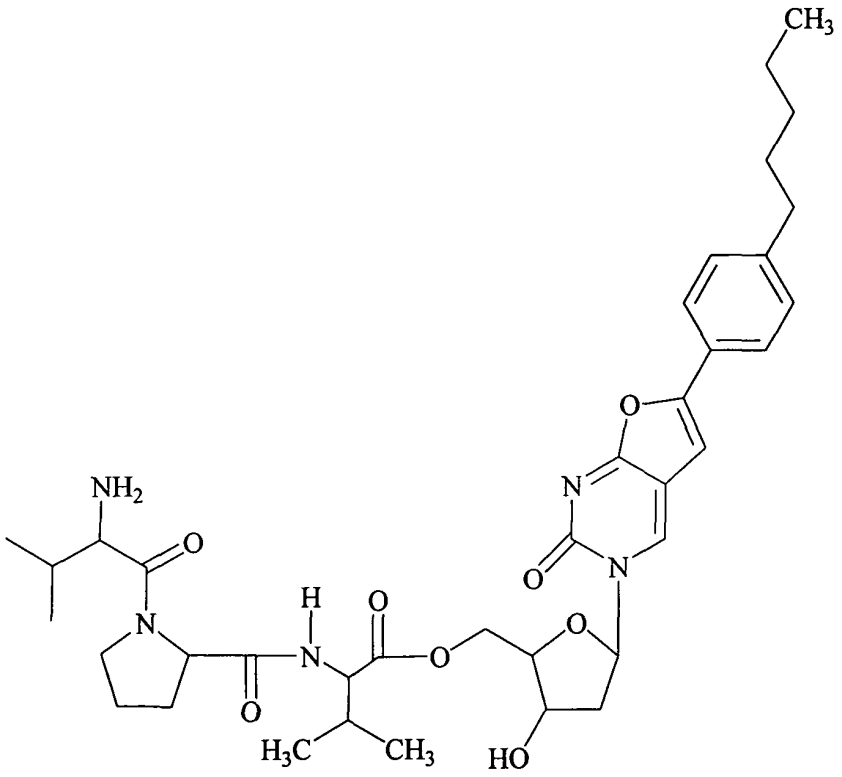
10. A compound as claimed in claim 9, wherein R_9 is H.

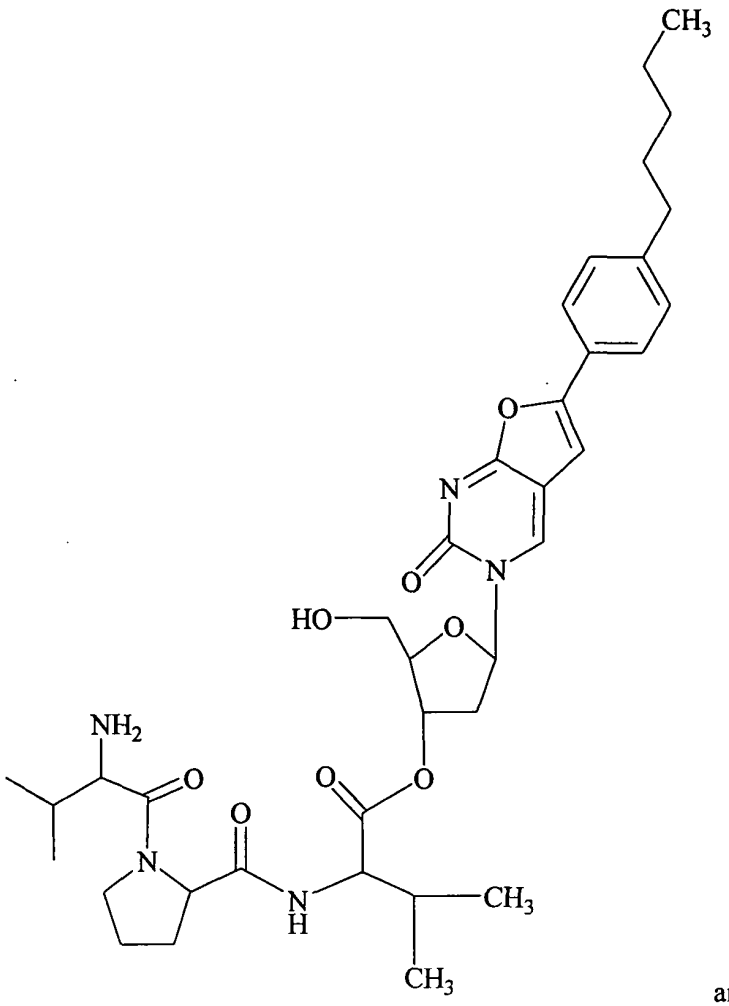
11. A compound as claimed in any preceding claim, wherein R_6 is valine, leucine, isoleucine or alanine, preferably valine.

12. A compound has claimed any preceding claim, wherein R_2 and R_3 are both H-Val-Pro-Val-.

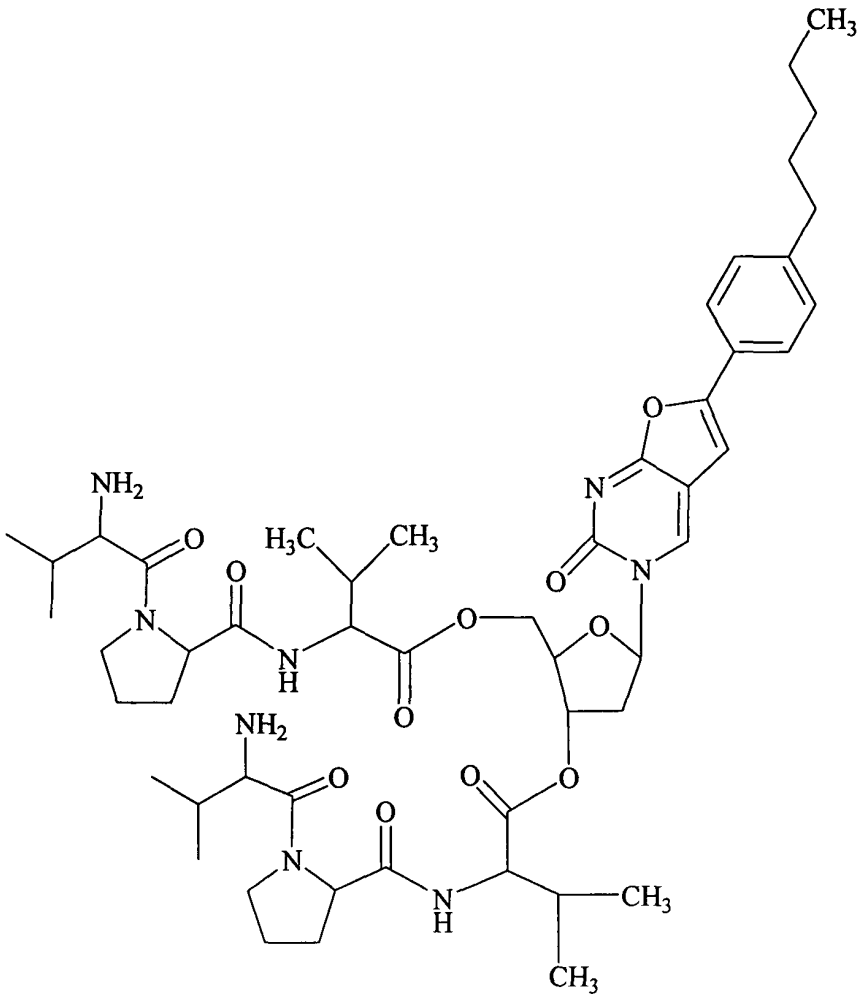
13. A compound as claimed in any preceding claim, wherein X, Y and Z are all O.

14. A compound as claimed in any preceding claim having a structural formula selected from:

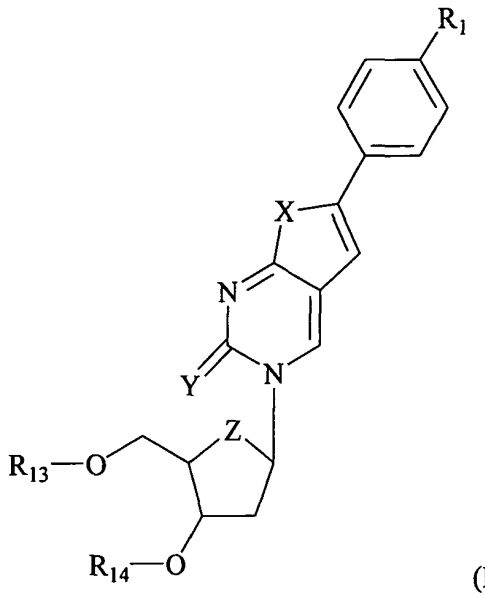




and



15. A method of synthesising the compound of the invention, said method comprising conjugating a compound of 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;

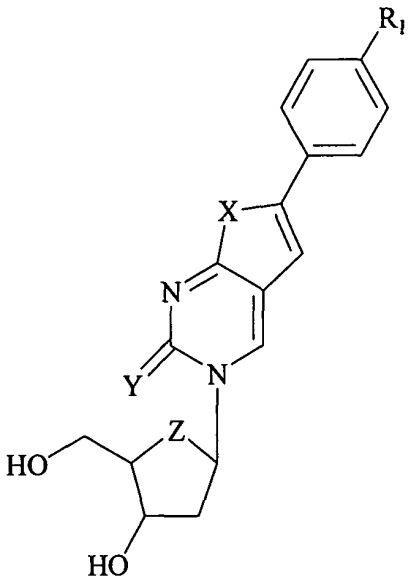
R_1 is C_{1-6} alkyl, preferably *n*-alkyl, e.g., *n*-pentyl or *n*-hexyl;

at least one of R_{13} and R_{14} is a neutral, non-polar amino acid moiety having a free amino terminus; and

the other of R_{14} and R_{13} is H, the resulting hydroxyl group being optionally protected, or a neutral, non-polar amino acid moiety;

with a protected oligopeptide of formula Z'-$[R_4$-$R_5]_n$-OH to form a peptide bond between R_5 and at least one of R_{13} or R_{14}, wherein R_4 and R_5 are as defined above and Z' is an amino-protecting group to protect the free amino terminus, and thereafter removing said protecting group.

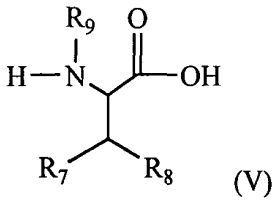
16. A method as claimed in claim 15, wherein said compound of formula (II) is synthesised by esterifying a compound of formula (IV):



(IV)

with a protected neutral, non-polar amino acid, wherein R_1, X, Y and Z are as defined above to obtain the 3- or 5' ester or 3', 5'- diester.

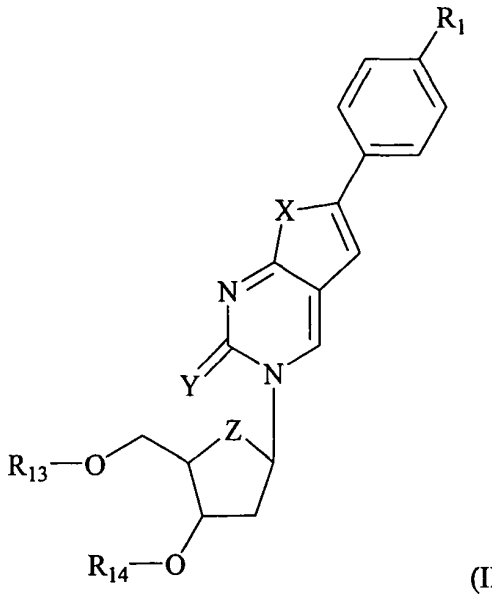
17. A method as claimed in claim 16, wherein said amino acid has the formula (V):



(V)

wherein R_7, R_8 and R_9 are as defined above.

18. A compound of formula (II):



(II)

wherein X is O, S, NH or CH_2;

Y is O, S or NH;

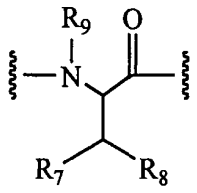
Z is O, S or CH_2;

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

R_{13} and R_{14} are both a neutral, non-polar amino acid moiety having a free amino terminus, or

a pharmaceutically acceptable salt thereof.

19. A compound as claimed in claim 18, wherein said neutral, non-polar amino acid moiety is:



in which R_7, R_8 and R_9 are each independently H or C_{1-3} alkyl, especially C_{1-2} alkyl.

20. A compound as claimed in claim 19, wherein R_9 is H.

21. A compound as claimed in claim 18, claim 19 or claim 20, wherein said neutral, non-polar amino acid moiety is valine, leucine, isoleucine or alanine, preferably valine.

22. The compound has claimed in any of claims 18-21, wherein R_{13} and R_{14} are the same as one another, preferably valine.

23. A compound as claimed in any of claims 18-22, wherein X, Y and Z are all O.

24. A compound according as defined in any of claims 1-14 or 18-22 for use in a method of treatment of the human or animal body by therapy, particularly the prophylaxis or treatment of a viral infection, especially an infection with the Varicella Zoster virus.

25. Use of a compound as defined in any of claims 1-14 or 18-22 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.

26. 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 amount of a compound as defined in any of claims 1-14 or 18-22.

27. A method as claimed in claim 26, wherein 100-500 mg of said compound is administered once daily (s.i.d.)

28. A pharmaceutical composition comprising a compound as claimed in any of claims 1-14 or 18-22 in combination with a pharmaceutically acceptable excipient.

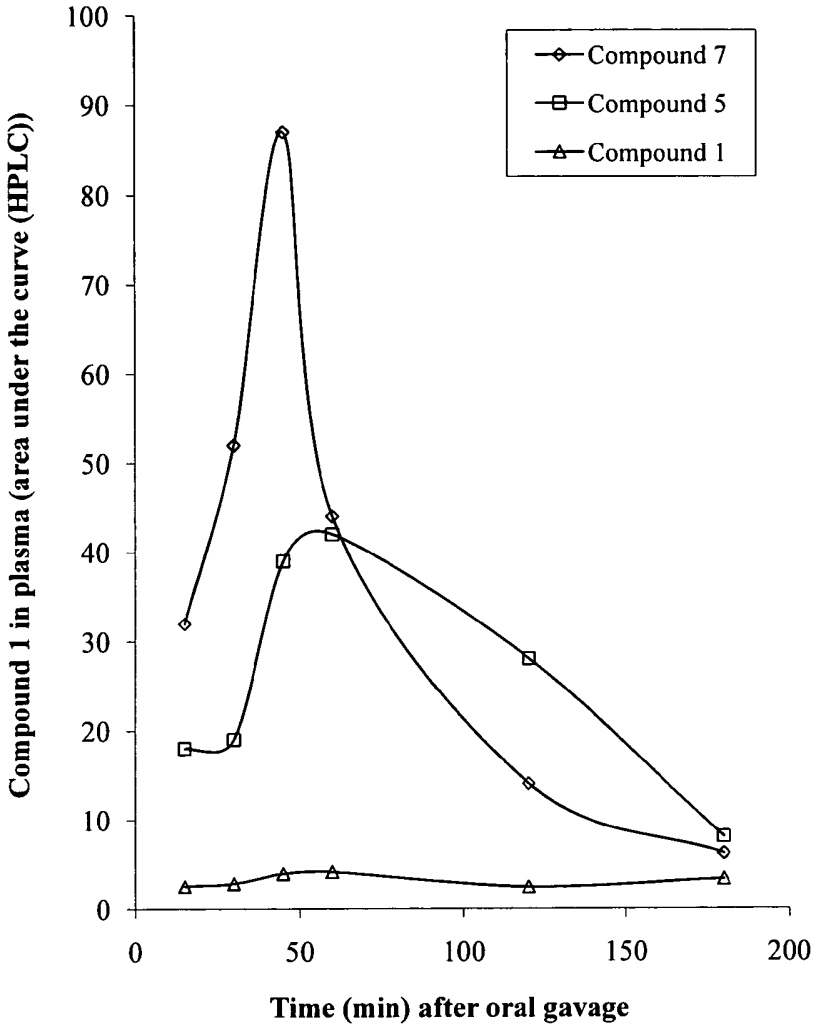

Compound 7
Compound 5
Compound 1
Compound 1 in plasma (area under the curve (HPLC))
Time (min) after oral gavage
0
10
20
30
40
50
60
70
80
90
100
0
50
100
150
200

FIG. 1

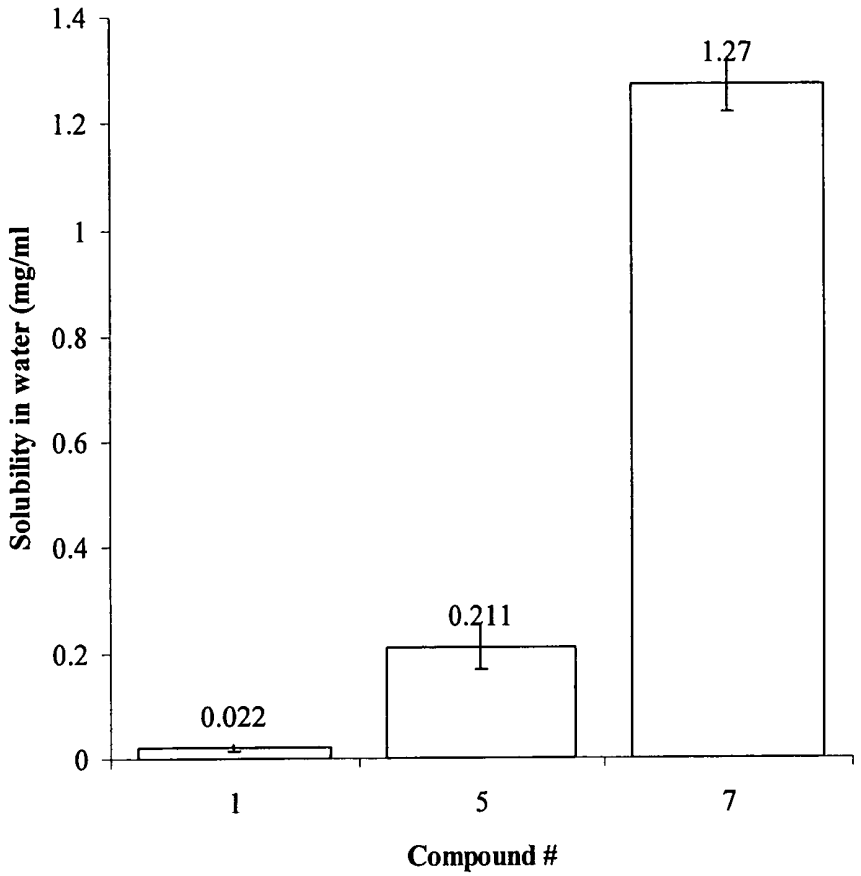

1.4
1.2
1
0.8
0.6
0.4
0.2
0
Solubility in water (mg/ml
0.022
0.211
1.27
1
5
7
Compound #

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/007009

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/02 C07K7/02 A61K31/198 C07H19/24 A61K31/7068

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)
C07K C07H A61K

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/83501 A (UNIV CARDIFF [GB]; REGA FOUNDATION [BE]; MCGUIGAN CHRISTOPHER [GB]; BA) 8 November 2001 (2001-11-08) cited in the application the whole document	1-28
P,X	WO 2007/129083 A (UNIV CARDIFF [GB]; UNIV LEUVEN KATH [BE]; MCGUIGAN CHRISTOPHER [GB]; B) 15 November 2007 (2007-11-15) the whole document	1-28
P,X	MCGUIGAN, CHRISTOPHER ET AL: "Preclinical development of bicyclic nucleoside analogues as potent and selective inhibitors of varicella zoster virus" JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY , 60(6), 1316-1330 CODEN: JACHDX; ISSN: 0305-7453, 2007, XP002505855 page 1321; compound 10	1-28

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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 when the document is taken alone

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2008	10/12/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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		PT 1274713 T	31-08-2004
		TR 200400785 T4	21-07-2004
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WO 2007129083 A	15-11-2007	NONE	