**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, KOLKATA**

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES, 2003.

In the Matter of a pre-grant representation under Section 25(1)

And

In the Matter of Indian Patent Application **3658/KOLNP/2009**

400054052

And

IN THE MATTER OF:

India Cares ... PETITIONER/OPPONENT

VS.

Pharmasset, Inc. ... RESPONDENTS/APPLICANTS

**MASTER INDEX**

**(VOLUME I)**



Dated this 23rd day of October, 2015.

chitra arvind

CHITRA ARVIND
FOR RAJESHWARI & ASSOCIATES
AGENT FOR THE OPPONENT

IPO KOLKATA 12112015 10:40

To,
The Controller of Patents
The Patent Office, Kolkata

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,**

**KOLKATA**

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

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**AND**

IN THE MATTER OF:

Indian Patent Application **3658/KOLNP/2009** filed on 20th October, 2009 claiming priority from the US Patent Application No. 60/909,315 dated 30th March 2007, US Patent Application No. 60/982,309 dated 24th March 2007, US Patent Applications No. 12/053,015 dated 21st March 2008 by Pharmasset, Inc. National Phase of PCT Application No.PCT/US2008/058183 (Published as WO 2008/121634).

AND

IN THE MATTER OF:

INDIA CARES
India Cares, 2nd Floor,
A1 Sarvodaya Enclave,
Opposite Mothers International School,
New Delhi – 110017 ... PETITIONER/OPPONENT

VS.

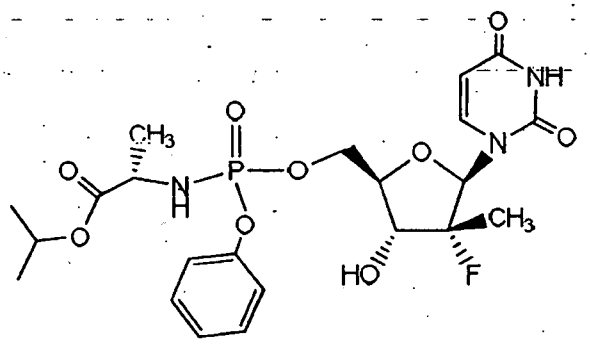
PHARMASSET, INC.
A Corporation organized and
existing under and by virtue of the
laws of the state of Delaware.
303A, College Road East,
Princeton New Jersey 08540,
United States of America. ... RESPONDENTS/APPLICANTS

# STATEMENT OF CASE OF OPPONENT

1. Opponent is aware that the Indian Application No. 3658/KOLNP/2009 titled 'Nucleoside Phosphoramidate Prodrugs' filed in India on 20 October 2009 pursuant to international application, bearing No. PCT/US2008/058183 by Pharmasset, INC. PCT/US2008/058183 claims priority from three US provisional applications—US 60/909,315 dated 30 March 2007, US 60/982,309 dated 24 October 2007 and US 12/053,015 dated 21 March 2008.

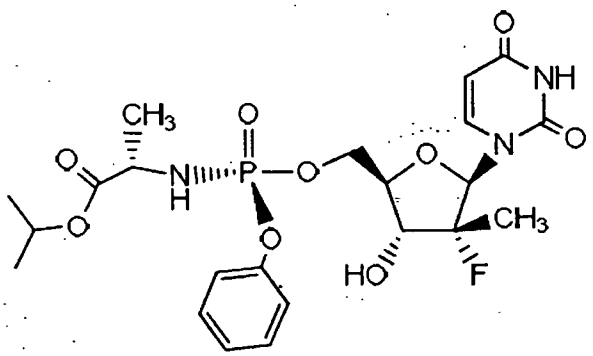
2. The impugned application was published on 19/03/2010 under section 11A. A request for examination vide Form 18 has been filed on 21.03.2011. The Opponent understands that this application is under examination before this Patent Office. The examination report was issued on 29.01.2015 by the Indian Patent Office. The claims on record are stated below:

1. (S)-2{[2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro02H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester having the following structure:

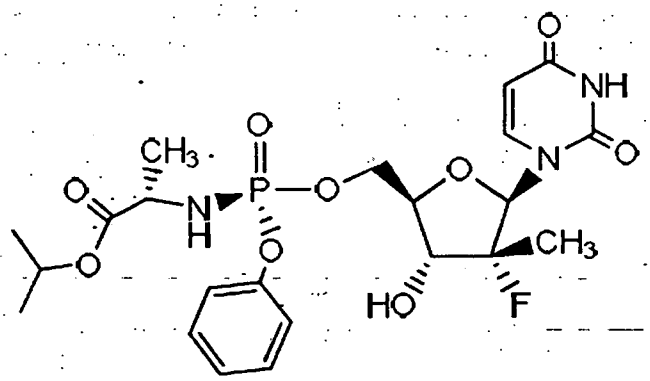



or a stereoisomer thereof.

2. The compound as claimed in claim 1 wherein the stereoisomer is (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methoxy) (phenoxy)phosphoryl)amino) propanoate having following structure:



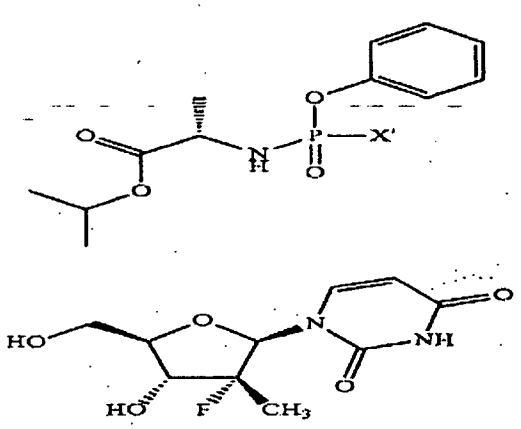
3. The compound as claimed in claim 1 wherein the stereoisomer is (S)-isopropyl2-(((R)-(((2R,3R,4R;5R)-5-(2,4-dioxo 3,4dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)(phenoxy)phosphoryl)amino) propanoate having following structure:



4. A composition comprising the compound as claimed in claim 1 to 3, and a pharmaceutically acceptable medium.

5. A process for preparing the compound or a stereoisomer thereof as claimed in claim 1, said process comprising:

reacting a compound 4" with a nucleoside analog 5'



Wherein X' is a leaving group.

3. The claims presently on record, could be summarized as below:

The Compound of Claim 1 is composed by the nucleoside "β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine and by the moiety "(2S)-isopropyl 2-(((phenoxy) phosphoryl) amino) propanoate" hereinafter referred to also as "phosphoramidate" moiety or "L-alanine-phenyl phosphoramidate isopropyl ester" moiety. The compound of Claim 1 is known by its generic name as Sofosbuvir. However, despite the necessity of disclosing the generic name or the International Non-Proprietary Names (INN) before the Indian Patent Office, the Applicant has failed to disclose the same. The compound of Claim 1, also referred to as PSI-7851 in the art, comprises two stereoisomers from the phosphate group and he isomers are respectively claimed in Claim 2 and Claim 3. The stereochemistry at the phosphorus atom in the compound of Claim 1 is not specified and Claim 2 and Claim 3 are not specifically enabled in the impugned application. Claim 2 is drawn $S_p$-diastereoisomer of the compound of claim, which has the INN sofosbuvir and compound of claim 3 is the corresponding $R_p$-diastereomer. Sofosbuvir is the active ingredient of Solvadi®, a drug indicated for

the treatment of HCV infection. Claim 4 is drawn towards a composition comprising the compound of claim1 and a pharmaceutically acceptable medium. There is no clarification in the impugned application with respect to the word "medium". Claim 5, is drawn to process for preparing the compound as claimed in Claim 1, however, such process is not supported by disclosure in the specification. Without admitting to validity of the application both technically and on procedural aspects, the Opponent proceeds to submit the grounds of Opposition pertaining to the said claims on record.

4. Before traversing the various grounds of the opposition, the Opponent proceeds to analyze the disclosure in the impugned application. The impugned patent application is drawn to nucleoside phosphoramidates that are alleged to be inhibitors of RNA dependent viral replication. The impugned specification, discloses that Hepatitis C virus (HCV) infection generally causes deaths among humans infected with the virus, belonging to the Flaviviridae family. The specification discloses that there are several inhibitors of HCV NS5B that are already known and their problems pertaining to pharmacokinetics and physiochemical properties were also known. The impugned specification discloses that nucleoside inhibitors of NS5B can act either as a non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. The impugned specification admits that the said properties of these nucleoside inhibitors have merely been improved by converting the same into their pro-drugs and pro-drug formation is well known in the art.

5. The impugned specification claims compounds, depicted by a general chemical structure which is represented here below at Figure 1.

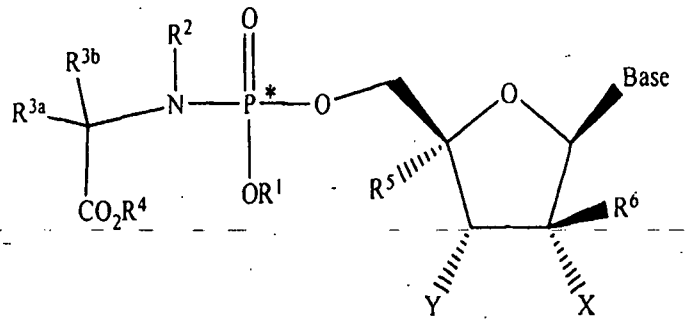



**Figure 1: Chemical structure of the impugned specification**

6. The specification then discloses certain substitutions to the substituents namely $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^4$, $R^5$, $R^6$, X and Y. In the general chemical structure represented at figure 1, the nitrogenous base may be any of a to d as depicted in the Figure 2.

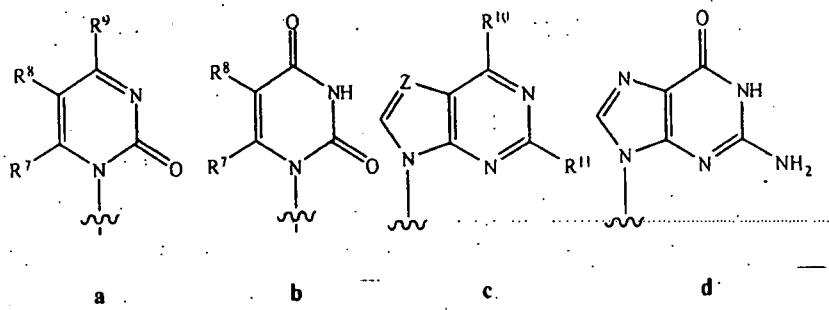



**Figure 2: Structure of Base**

7. From the above figure, as disclosed by the impugned specification, the compounds may contain any of the above nitrogenous bases consisting of substituted thymine base (a), substituted uracil base (b), substituted adenine base (c) and substituted guanine base (d). Further, the impugned specification also provides various possible substituents for Z as provided in the base structures and substituents for $R^7$ to $R^{12}$.

8. Additionally, the impugned specification discloses a set of chemical compounds which fall within the scope and sweep of the chemical structure of formula I (as shown in figure 1) by substitution of various bases (a) to (d). The impugned

specification provides chemical structures from I-1 to I-10. These sub-structures from I-1 to I-10 may be further substituted with various substituents. The impugned specification further proceeds to list these structures as a different series of chemical compounds namely II to XXXII. Each chemical compound structure is provided with different options of substitutions from table II-1 to II-50. Similarly these chemical structures are listed as mere possible substituents that are theoretically possible and depicted in 50 tablets. These tables list the various substitution of $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^4$, $R^5$, $R^6$, X and Y, $R^7$ and $R^8$. It is pertinent to note that these substituents as listed in these 50 tables are same and are comparable between the various chemical structure between II to XXXII and tablets, differing only by the Markush structure in which it is substituents. Moreover, the substituents listed in the impugned specification in the 50 tables, are only a mathematical probability that could be obtained from any computed software and does not provide any confirmation as to synthetic possibility of obtaining the said compounds. The application also provides various general disclosures pertaining to dosage, administrations and use of the said compounds of this impugned specification and that these compounds may be co-administered with other compounds that are also as anti-viral compounds, which are text book materials and not supported by any exemplification. General processes for preparation of these compounds is disclosed in the impugned specification and it is also disclosed that these compounds could be prepared by processes known in prior art. It is pertinent to note that only a general process is disclosed in the impugned specification for preparing all compounds falling within the formulas of structure I to XXXII without any disclosure as to the changes that could be required for each substructure. Hence, the impugned specification professes that all the compounds could be arrived at, by a single procedure. The only logical conclusion for such a procedure is that all

compounds differ from each other in a few substituents or there is no change in the basic structure and all compounds are mere derivates of the compound of Formula I.

Examples 1 and 2 are drawn to a general procedure for preparation of phosphorodichloridates. Example 3 purportedly discloses a general procedure for preparation of nucleoside phosphoramidate derivatives being represented as a general scheme. Example 4 appears to be drawn to the synthesis of 2'-dexoy-2'-fluoro-2'-C-methyluridine. Examples 5 to 12 appear to be drawn to processes for synthesis of specific compounds not being the compound as claimed in claim 1. The impugned specification then proceeds to disclose a general chemical structure which is a basic scaffold and various substitutions for the said structure. Examples 13 to 65 have been listed as various possible substitution of the said basic scaffold. The impugned specification provides certain analytical data against example 13 to 65 but does not provide any experimental conditions for the process of performing the experiments. It may be noted that in the context of the analytical softwares available during the time of filing the said application, it is possible to obtain the analytical data *in silico*. In similar manner examples 67 to 74 are represented by a general chemical structure along with a mere statement that these examples could be prepared as per example 66. Examples 75 to 80 are also illustrated as a table without any actual, "on-bench" experimental details. Example 81 discloses a method for separation of diastereomers specifically for the compounds disclosed at Example 15, 39 and 49. Example 82 discloses certain *in vitro* results for testing a mere handful of compounds of impugned specification from the Table at Example 82, it appears that the most active compound is the compound of example 49 followed by the compound of example 27 both of which are not covered in the claims. It is submitted that all compounds that are not claimed ought to be considered as disclaimed. The opponent further submit the

claims as amended and currently on record are not patentable under this act on various grounds as below:

## GROUND I

**I) Section 25(1)(b)/(c): Lack of Novelty**

The invention as claimed in Claims 1 to 3, 6 to 10, 13 and 14 lacks novelty and are not patentable under Section 25(1)(b)-(c) of the Patents Act, 1970 (as amended in 2005; hereinafter referred to as "the Act"). It is submitted that none of the claims of **3658/KOLNP/2009** are novel and they are all liable to be rejected on this ground alone.

It is submitted that all Claims 1 to 5 of the impugned patent applications anticipated by disclosure in WO 2005/012327 published on 10 February 2005 (hereinafter referred to as WO '327), a copy of which is hereto annexed and marked as **ANNEXURE-1.** The basic structure of WO '327 is drawn to a sugar attached to a nitrogenous base and is represented at Figure 3:

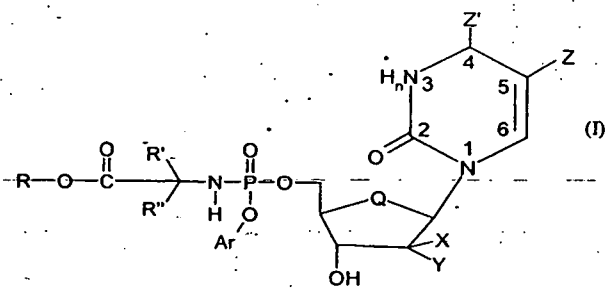



**Figure 3: Structure of general chemical structure disclosed in WO'327**

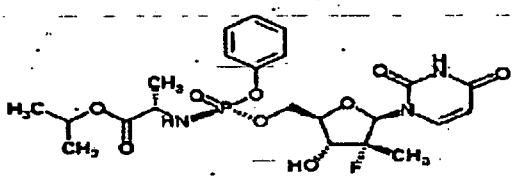
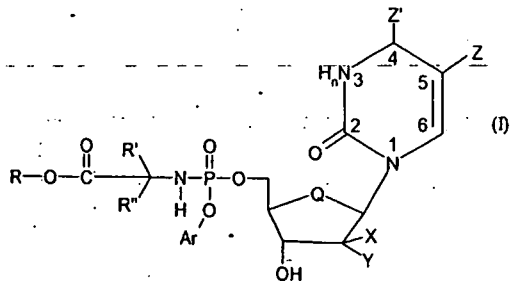
WO '327 is drawn to compounds wherein a sugar is attached to a nitrogenous base and provides for various options for substitutions in the general structure. Further WO '327 sets out that the nitrogenous base may be pyrimidine based including uracil,

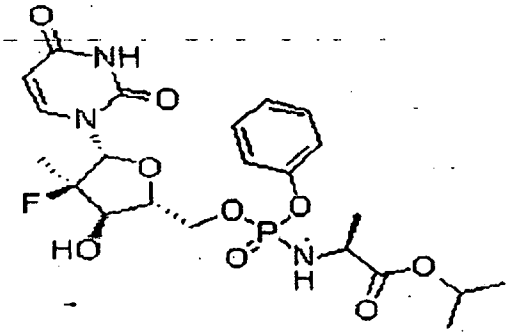
thymine. WO '327 also sets out the various options for the substituents such as R, R', R", Q, X Y, Ar, Z and Z'. From these substitutions it is evident that WO'327 envisages and encompasses compounds that are akin to those disclosed by the impugned specification. WO '327 discloses that it is advantageous to have substituted sugars which have substitutions including Fluorine, Chlorine, Bromine, Iodine and methyl ($CH_3$).

Further, as evident from Figure 3, it may be seen that WO '327 is drawn to phosphoramidate prodrugs, from the disclosure in WO '327, it may be seen that the compounds of the impugned application fall within the scope and sweep of the general structure of WO '327. The same may be discerned by way of illustration.

For instance, it may be noted that the compound claimed at Claim 1 of the impugned application falls within the scope and sweep of WO '327.

**Table: Illustration that compounds of impugned patent application fall within the scope of WO '327**

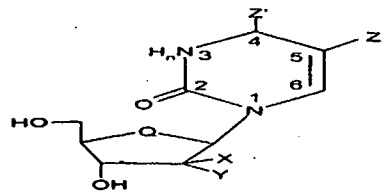
| **Impugned Patent Application (3658/KOLNP/2009)** | **WO 2005/012327** |
|---|---|
|  |  (I) |
| Compound claimed in claim 1- (S)-2-{[2R,3R,4R,5R)-5 -(2,4-Dioxo- 3,4-dihydro-2H-pyrimidin-l-yl)-4-fl-uoro-3-hydroxy-4-methyl-tetrahydro- furan- 2-ylmethoxy ]- | R =**alkyl**, aryl and alkylaryl;<br><br>R' and R" are, independently, selected from the group comprising **H, alkyl** and |

| | |
|---|---|
| phenoxy-phosphorylamino}-propionic acid isopropyl ester<br>  <br>Compound claimed in claim 8-(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4,-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-flu-oro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate. | alkylaryl,<br><br>Q is selected from a group comprising -**O**- and -eH2<br><br>X &Y are independently selected from the group comprising H, **F**, CI, Br, I, OH and **CH3**:<br><br>Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted;<br><br>Z is selected from the group comprising H, alkyl and halogen; and n is 0 or 1, wherein when n is 0, Z' is NH2 and a double bond exists between position 3 and position 4 and **when n is 1, Z' is =O**<br>... |

T

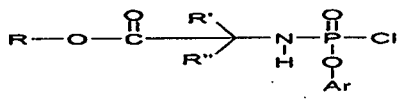
The impugned specification discloses the preparation of nucleoside phosphoramidate prodrugs by reacting an appropriately substituted phosphochloridate with a nucleoside containing a free 5'-hydroxyl moiety. Claims 5 is purportedly drawn such a synthesis.

WO '327 exemplifies the process involving synthesis of phosphoramidate esters containing alanine as the amino acid, and unsubstituted phenyl, using a leaving group (see Figure 4). Thus, the process as disclosed in the impugned application is anticipated by disclosure in the impugned application.



(III)

with a compound of formula (IV):



(IV)

**Figure 4: Process involving synthesis of phosphoramidate esters in WO'327**

WO '327 discloses the above process for the preparation and use of the following prodrug moiety into the base compound:

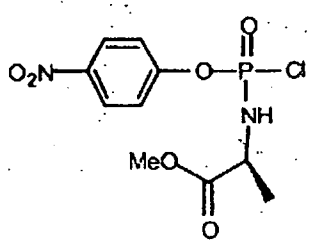


**Figure 5: Prodrug moiety disclosed in WO'327**

Therefore, the process as claimed in Claim 5 is anticipated in light of above disclosures in WO '327 and hence, such process is not novel.

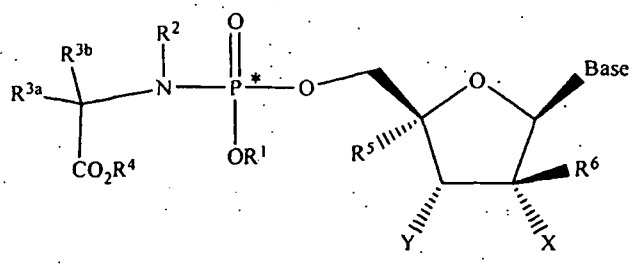
A pharmaceutical composition comprising the compounds disclosed in WO '327 and a pharmaceutically acceptable excipients, carrier or diluent is also disclosed in WO '327 (see page 14, lines 24 to 26). Thus, the composition claimed in Claim 4 lacks novelty over WO '327. Thus, given the disclosures in WO '327 the impugned application stands anticipated. Hence, all claims 1 to 5 are anticipated by disclosure in WO '327 and ought to be rejected on this ground alone.

## GROUND II

### I) Section 25(1)(e): Lack of Inventive Step

The invention so far claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regards to the matter published as mentioned in clause (b) or having regard to what was used in India before the date of priority.

The impugned specification claims compounds, depicted by a chemical structure, which is represented by figure as disclosed below:




I

**Figure 6: General Chemical Structure disclosed in the Impugned Application**

The alleged invention disclosed in the impugned application, relates to phosphoramidate derivatives of modified nucleoside and their use in treating hepatitis C infection. The impugned specification discloses phosphoramidate prodrugs of 2'-deoxy-2'-C-methyl nucleoside compounds. The nucleoside was known before the priority date and the concept of developing a phosphoramidate prodrug form of such a nucleoside in order to effectively deliver such a nucleoside for its intended anti-viral effect was well known before the priority date. Furthermore, the alleged invention pertaining to a phosphoramidate derivative of a modified nucleoside is a routine modification obtained by well established techniques. The impugned specification

also professes that the alleged invention relates to compounds which are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV. The compound has a deoxyribose sugar ring, which is substituted at the 2'-position with a methyl group is present above the plane and is referred to as methyl ("up") and a fluoro radical is present below the plane and is referred to as fluoro ("down"). The deoxyribose sugar is substituted with a base at the conventional position via a glycosidic bond. The base is uracil. It is well-known that the combined sugar and base is termed a "nucleoside". The nucleoside is linked to a monophosphate group to form a nucleotide. The phosphate group is so called "masked" phosphate, in that it is masked with two substituents, the isopropyl ester of L-alanine to form a "phosphoramidate" at one position on the phosphorous atom and a phenyl group at another position on the phosphorous atom.

**i. Nucleoside analogues were known to be used for the treatment of HCV**

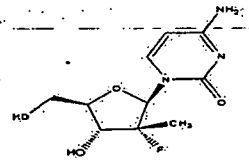
Since 1994, it was known that nucleoside and nucleotide analogues have great potential for the treatment of viral diseases such as HCMV, HSV, HIV, HBV and HCV and for the treatment of cancer. For example, AZT is a nucleoside that is used in the treatment of HIV and gemcitabine is a nucleoside approved for the treatment of various cancers. AZT and gemcitabine are reported to interfere with the replication process and thereby hinder replication. Such nucleoside(s)/nucleotide(s) compound preventing replication of HCV in the cell is recognised by HCV polymerase, so that it is incorporated into new viral RNA strands instead of the nucleotides that occur naturally in the cells resulting in prevention of replication.

*ii. 2'-deoxy-2'-fluoro-2'-C-methyluridine was known*

Several inhibitors of HCV NS5B are already known and these drugs are known to have problems pertaining to pharmacokinetics and physiochemical properties. The prior art sets out examples wherein the properties of nucleoside analogues have been improved by converting the same into their pro-drugs.

For instance, 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside is such an example.

Nucleosides having antiviral activity, in particular anti HCV activity, are well known and well established in literature. For instance, Clark *et al*, ("Design, Synthesis and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication", Journal of Medicinal Chemistry, 2005, 48, 5504-5508, a copy of which is marked as **ANNEXURE-2)**, discloses the design, synthesis and antiviral activity of 2'-deoxy-2'-fluoro-2'-C-methylcytidine(compound 1), and to 2'-deoxy-2'-fluoro-2'-C-methyl uridine (compound 9) in the treatment of hepatitis C virus (HCV).



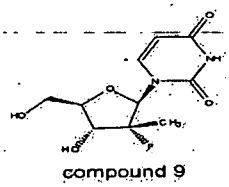



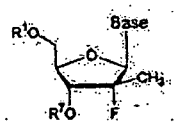

**Figure 7: 2'-deoxy-2'-fluoro-2'-C-methyl nucleosides**

Clark *et al* describes compound 1 (of Figure 7) as a potent inhibitor of hepatitis C virus (see section 'Results and Discussion' and Table 2 on page

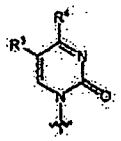
5506 of Clark *et al*). Clark *et al,* discloses that 2'-deoxy-2'-fluoro-2'-C-methyluridine was synthesized to "facilitate future *in vivo* studies (see page 5506, left column, para1 of Clark *et al*).

WO 2005/003147, titled "Modified fluorinated nucleoside analogues" published on January 13, 2005, a copy of which is marked as **ANNEXURE-3,** with uracil and cytosine bases. WO'147 discloses on page 39, 12 embodiments—the 2' deoxy-2'-fluoro-2'C-methyl nucleoside and in particular the cytidine and the enol uracil derivatives. WO '147 disclosed that prodrug is a viable option for increasing the pharmacokinetic and physicochemical properties of these molecules.

It may be noted that the configuration of the molecule in WO '147 is 2'methyl-up-fluoro-down configuration.




wherein Base is:



and wherein $R^1$ is H; $R^2$ is H, $R^3$ is $NH_2$ or OH, and $R^7$ is H.

**Figure 7: 2'methyl-up-fluoro-down configuration disclosed in WO'147**

WO '147 discloses enol form of the nucleoside in chemistry, it is a well known fact that Uracil can exist in both keto and enolic forms and that at a physiological pH the keto form prevails. Hence, WO '147, clearly sets out the stereochemistry and various possible configurations for nucleoside bases.

Furthermore, WO '147 sets out the advantages of administering the molecule in a prodrug form. "*Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise after the properties of the nucleoside. A number of nucleotide prodrug ligands are known*" [see page 45, line 23 *et* seq; page 46, lines 16-17 of WO'147]. This renders it plausible that the claimed nucleotide prodrugs have a useful activity; bioavailability and/or stability [see page 57, lines 15-17 of WO'147]. Prodrugs containing a phosphate group are also set out in WO '147 [see page 57, line 25 and page 59, line 16-23]. Thus, WO'147 teaches that administering nucleoside prodrug will increase the activity and modification of the mono-, di- or triphosphate of nucleoside reduces polarity and allows passage into cells.

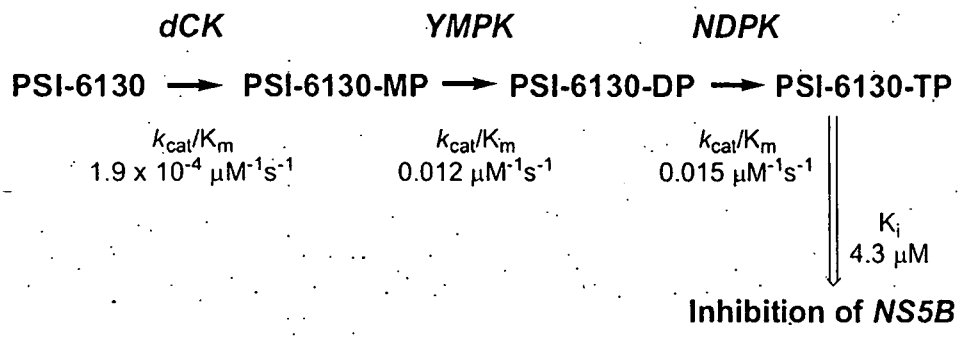
iii. **Prodrug of β-D-2'-Deoxy-2'-Fluoro-2'-C-Methyl nucleosides were known**

Several nucleoside analogues were known for the treatment of anti-viral diseases such as HIV, HCMV, HSV, HBV and HCV. However, many of these nucleosides had problems relating pharmacokinetics properties. These problems were generally known as "first kinase bypass" or "first phosphorylation bypass" and "the cell permeability (entry of the drug into the cell)". With respect to first kinase bypass relates to the known problem where some nucleosides fail to undergo the necessary phosphorylation to the active triphosphate nucleotides either because they are poor substrates for the first phosphorylation to the monophosphate nucleoside or due to the absence of the phosphorylating enzyme (kinase). However, the problem of the first kinase bypass was overcome by the corresponding monophosphate nucleosides.

Monophosphate nucleosides however have some disadvantages over nucleosides. Because of their negative charge on the oxygen atoms of the phosphate group at a physiological pH, their ability to enter into the cell was shown to be very poor. As a consequence monophosphate nucleosides showed generally low or no activity in vitro leading to the second mentioned problem: the cell permeability problem. To overcome the first kinase bypass and the cell permeability problems, the ProTide approach was developed which led to the development of the "phosphoramidate" prodrug moiety [See page 4, para 1 and 2 of Jones *et al* "Minireview: nucleotide prodrugs" Antiviral Research 27 (1995) 1-17]. By using this prodrug strategy, the first and inefficient rate-limiting phosphorylation step of nucleostides could be circumvented and the cellular penetration of nucleotides could be improved. The ProTide of a nucleoside phosphate is a phosphoramidate prodrug consisting of an amino acid promoiety linked via P—N bond to a nucleoside aryl phosphate. Such prodrugs have increased lipophilicity and thus are capable of altering cell and tissue distribution. The ProTide technology was successfully and extensively applied to a wide variety of nucleoside phosphates, endowed with antiviral and anticancer activity.

For instance, Eisuke Murakami *et al,* 'Mechanism of Activation of D-2'-Deoxy-2'-Fluoro-2'-c-Methy1cytidine and Inhibition of Hepatitis C virus NS5B RNA polymerase' Antimicrobial Agents and Chemotherapy, Feb. 2007, p. 503–509 a copy of which is marked as **ANNEXURE-4**, highlights a similar pharmacokinetic problem incurred by β-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine (PSI-6130). Murakami *et al*, discloses that β-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine (PSI-6130) is a potent specific inhibitor of

hepatitis C virus (HCV) RNA synthesis in Huh-7 replicon cells. It discloses that to inhibit the HCV NS5B RNA polymerase, PSI-6130 must be phosphorylated to the 5'-triphosphate form. In order for a nucleoside analogue to inhibit the viral polymerase, it must to be activated to the 5-triphosphate form by host cell kinases. It discloses that PSI 6130 is not very efficiently phosphorylated to PSI 6130MP (mono-phospahte) within the cell. Typically, phosphorylation of a nucleoside to its monophosphate is a rate-limiting step for the activation of many cytidine analogues. However, PSI-6130 monophosphate (PSI-6130-MP) was efficiently phosphorylated to the diphosphate and subsequently to the triphosphate by recombinant human UMP-CMP kinase and nucleoside diphosphate kinase, respectively.




Thus, Murakami *et al*, points towards the need for converting β-D-2'-Deoxy-2'-Fluoro-2'-C-Methyl nucleosides into phosphate prodrugs such as phosphoramidate prodrugs for improving the pharmacokinetic properties and to render the compound more active as an anti-HCV agent.

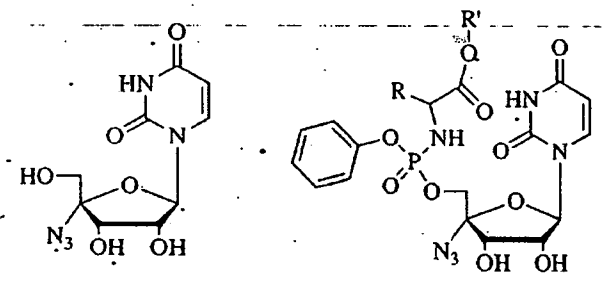
**II) Phosphoramidate prodrugs of compounds analogous to β-D-2'-Deoxy-2'-Fluoro-2'-C-Methyl nucleosides were known**

The Pro-Tide approach was adopted in prior art in order to overcome the pharmacokinetic problems associated with nucleosides analogues used as anti-HIV

and anti-HCV agents. For instance, using the phosphoramidate prodrug, was discussed in Plinio Perrone, "Application of the phosphoramidate Protide approach to 4'- Azidouridine confers sub-micromolar potency versus Hepatitis C virus on an inactive nucleoside", Journal of Medicinal Chemistry, 2007, 50, 1840-1849 a copy of which is marked as **ANNEXURE-5,** provides a discussion of protected nucleotide prodrugs and the "Pro-Tide Approach". Perrone *et al*, attempts to improve the activity of nucleotide pro-drugs against HCV. Perrone *et al* discloses that unmodified nucleoside compounds are likely to be poor substrate for phosphorylation enzymes and proposes the ProTide approach as a suitable solution. Perrone *et al* opines that Pro Tide technology greatly increases the lipophilicity of the nucleoside monophosphate analogue with a consequent increase of membrane permeation and intracellular availability.

Perrone *et al* discloses the application of the phosphoramidate pronucleotide (Pro Tide) technology to the ribonucleoside analogue 4'-azidouridine (AZU) to generate novel antiviral agents for the inhibition of hepatitis C virus (HCV).

Structure of AZU and its corresponding phenyl-phosphoramidate ProTide is disclosed below [see page 1841 of Perrone *et al*]:




AZU (1) 2

**Figure 8: Structure of AZU and its corresponding phenyl-phosphoramidate ProTide**

The AZU (1) and the phenyl-phosphoramidate (2) indicates that the delivery of the molecule into the cell can be altered by Protide technology. The penultimate sentence on the first page also confirms that "*Aryloxy-phosphoramidates are considered to be efficient lipophilic prodrugs of the corresponding 5'-monophosphate species...*" [see page 1841 of Perrone *et al*].

Perrone *et al* reports that L-alanine phosphoramidate of 4'azidouridine with different substituents were prepared to explore the structure activity relationship in the ester position. The biological activity of the L-alanine phosphoramidates in the HCV replicon assay are presented in Table 1 of Perrone *et al* (see page 1843, left-hand column) and concludes that *"the isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared."* Perrone *et al* disclose the preparation of "L-alanine-phenyl-phosphoramidate isopropyl ester" prodrug of a uridine nucleoside in order to deliver the nucleoside monophosphate into cell.

Further Perrone *et al* also discusses that the (R) - and (S) –Configuration at the phosphate and the difference in their biological activities.

Thus, the skilled person attempting to prepare a nucleoside prodrug formulation for treating HCV infection, will be aware that β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine is disclosed in WO '147 and Clark *et al.* Further, Murakami *et al*, suggests that β-D-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides having problems relating to phosphorylation and cell permeation. It was pointed out that conversion to its monophosphate is a rate-limiting step for the activation of many cytidine analogues. Furthermore, the skilled person in the art in light of the disclosures in

Perrone *et al*, will be aware that WO '147 and Murakami *et al* discussed that in order to overcome the problems of first phosphorylation bypass and cell permeation, phosphoramidate prodrugs strategy could be adopted. Furthermore, it is a well established concept that pentavalent phosphorous atom with a double bond to oxygen generally has a centre of asymmetry at the phosphorus atom and may give rise to a pair of stereoisomers and one of the latter could have a greater activity than the other stereoisomer. It is very routine to identify the physiologically active stereoisomer and separate the stereoisomers. It is an established principle that when stereoisomers/diastereomers of a compound and the process of preparing them are disclosed and claimed in the prior art, then mere use of known process of separation or isolation of such stereoisomers/diastereomers cannot be regarded to involve inventive step.

Thus, before the priority date:

1. Nucleoside analogue were known to be used for the treatment of HCV

2. 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside in particular the cytidine and the uracil derivatives were known to be active against Flaviviradae virus and in particular against the HCV virus.

3. The metabolism of β-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine (PSI-6130) results in the formation of the 5'-triphosphate of the uridine derivative—β-D-2'-Deoxy-2'-Fluoro-2'-C-Methyluridine was already known and disclosed.

4. The ProTide approach was a well-known strategy to be used to overcome the problems relating to the first kinase bypass and the cell permeability.

5. Application of ProTide technology in compounds such as 4'- Azidouridine resulted in better activity was known and disclosed.

6. It is known that "L-alanine-phenyl-phosphoramidate isopropyl ester" prodrug of a uridine nucleoside in order to deliver the nucleoside monophosphate into cell.

In the light of the above disclosures, the alleged invention claimed in the impugned application is rendered obvious does not provide for any technical advance over the existing knowledge and is obvious to a person skilled in the art.

**III) Process for synthesising phosphoramidate prodrug were known**

Claims 5 of the current pending set of claims relates to a process for preparing the compound claimed in Claim 1. The process, as set out in claim 5 involves reacting a phosphoramidate compound and a substituted or modified nucleoside.

It is submitted that the process claimed in Claims 5 is well-known in art and is commonly practiced by skilled person while attempting to prepare a nucleoside phosphoramidate prodrug. For instance, WO 2006/121820 (hereinafter WO '820) "Phosphoramidate prodrugs for treatment of viral infection" published on 16 November 2006, a copy of which is marked as **ANNEXURE-6,** discloses 2'-methyl ribonucleotide phosphoramidates prodrugs which are converted in vivo to 2'-methyl ribonucleotide triphosphates. WO '820 discloses a basic scaffold as below:

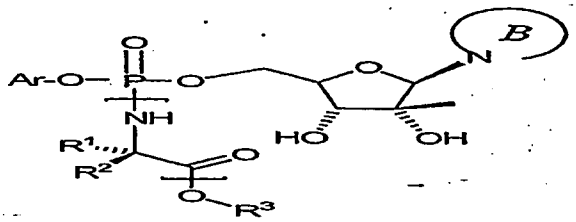



**Figure 9: Phosphoramidate prodrug disclosed in WO'820**

The compounds as disclosed in WO'820 are nucleotides, i.e., comprising a nitrogenous base with that of a sugar having a phosphoramidate group attached to it. These compounds are also considered to be active against HCV. WO '820 discloses that modified nucleotides and nucleosides are widely used. Though the active drug is nucleotide triphosphate that the native nucleotide is never administered to the patient because it is unstable in plasma and, being charged, does not penetrate the cell membrane. The effectiveness of modified nucleotides as anti-viral thus depends not only on the selectivity and affinity of the active drug for the viral polymerase, but also on the efficiency of the in vivo phosphorylation of the form that is administered. Therefore the compound administered to the patient is a prodrug; the active drug results from intracellular phosphorylation to yield the triphosphate.

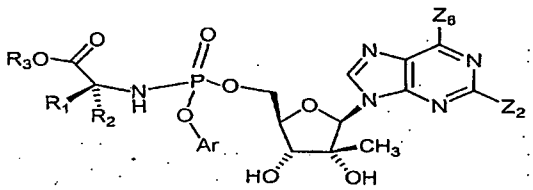


**Figure 10: Compound disclosed in WO'820**

Further, WO '820 discloses a general method of synthesising the phosphoramidate prodrug as below:

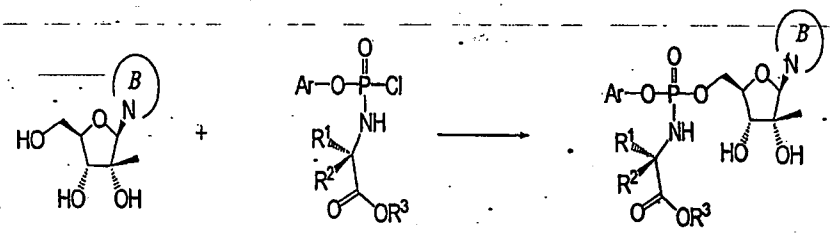


**Figure 11: Synthesis of Phosphoramidate Prodrug**

The above process involves the reacting the modified or substituted nucleoside and a phosphoramidate compound. WO '820 also discloses that due to the chirality of the

phosphorous atom, all nucleoside phosphoramidates are obtained and tested as mixtures of enantiomers and diastereomers. A skilled person in light of the disclosure in WO'820 would be motivated to use the analogous process as claimed in Claim 5 for preparing the compound claimed in Claims 1. Therefore claim 5 is rendered obvious in light of the disclosures in WO'890. Further, Claim 1 relating to a compound and Claims 2 and 3 relating to stereoisomers prepared through known processes are also rendered obvious in light of the disclosures in WO '890. Claim 5 will thereby be rendered obvious in the light of the disclosures in the prior art disclosed above.

WO '820 discloses a pharmaceutical composition comprising one of more of the compounds of the invention, in combination with pharmaceutically acceptable carriers, excipients, and other additives, as are well known in the art. The pharmaceutical compositions may be adapted for oral or parenteral administration. Thus WO '820 teaches that pharmaceutical compositions of phosphoramidate prodrugs could be prepared. Thus, the in light of the disclosure in WO'820, the composition Claim 4 is rendered obvious.

Thus, all claim 1-5 are obvious by a combined reading of the above detailed prior art documents. Hence all claims ought to be rejected and the impugned application ought to be refused.

**GROUND III**

I) **Section 25 (1)(f): Subject of claims 1 to 5 is not an invention within the meaning of this Act or is not patentable under this Act**

a) The Subject matter of the claims 1-5 do not constitute an invention as understood under Section 2(1)(j) of the Act:

It is submitted that since the Claims 1-4 are not inventive and lack industrial application, they do not constitute an 'invention' under the Act. All averments made herein above are reiterated in this ground and not repeated for the sake of brevity.

b) The subject matter of Claims 1, 2 and 3 are not an invention under Section 3(d) of the Act:

The compounds of the impugned specification are nothing but derivatives of compounds known in prior art. The compounds claimed in the impugned application are derivatives of phosphoramidate. This is an admitted position by the Applicants. The derivatives as disclosed in the impugned application do not possess enhanced therapeutic efficacy over the closest compounds. Activities of compounds of Claim 2 and 3 are not specifically disclosed. In order to discharge the burden of section 3(d), the Applicant ought to have compared and disclosed the therapeutic efficacy of the claimed compounds with the closest compounds disclosed in prior art. The applicant has failed to discharge this burden.

c) The subject matter of Claim 4 is not patentable under Section 3(e) of the Act:

These claims are drawn towards to a composition. The composition reflects only the qualities of the individual components and does the functions only of its individual components and has no enhanced effect or does a new function different from that of its constituents. Therefore the composition as a whole results only in the aggregation of the properties of its components without any synergistic/enhanced effect and hence is not patentable under section 3(e) of the Act. Therefore, these claims ought to be rejected on this ground.

In regard, the Opponent craves leave to refer and rely on submission made in Grounds I-III above and the same are not being reiterated for the sake of brevity.

## GROUND IV

**I) Section 25 (1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.**

**A. Best mode not disclosed**

a. Examples 5-8 discloses a process for the preparation of methyl ester analog of sofosbuvir. The impugned specification provided in examples 13-54 and 56-66 in a table form and it is evident that the examples are only theoretical and have not been carried out on the bench.

b. Claims 2 and 3 are drawn to diastereomers. The separation of a mixture of diastereoisomers at the phosphorous atom into the individual Sp and Rp-diastereoisomers is set out at Example 81 on page 43. However, example 81 only provides the conditions of chromatographic resolution of the diastereoisomers of compounds 125, 39 and 49 but not of Example 25 which corresponds to the compound of Claim 1. Example 25 does not specify the chromatographic conditions to separate the diastereoisomer mixture of Example 25 into two diastereoisomers of claims 2 and 3. Hence, there is no exemplification of the compounds claimed in Claim 2 and 3.

c. Example 82 is drawn to in vitro assay of the compounds of the impugned patent application. The most active compound appears to be the compound disclosed at Example 49 followed by Example 55, then examples 27, 69 and 70. Since, the amended claims are not drawn to any these compounds such compound should be considered as disclaimed.

**B. The claims of the alleged invention are not appropriately supported by the impugned specification**

1. Claim 4 is relates to a pharmaceutical composition of the compound which is claimed in Claims 1 to 3. However, Claim 4 is not supported by the description in the specification. The specification gives definition of pharmaceutically acceptable medium which broadly covers excipients, carrier and diluent. However, there is no suggestion in the impugned application regarding the manner in which the specific excipients, carrier and diluent are to be used for the specific compounds of claimed in Claims 1 to 3. Further, Claim 4 lacks sufficient disclosure for obtaining the composition of compounds claimed in claims 1 to 3. The specification does not disclose the best form of administration of the drug and specific excipients for the preparation of best mode of administration are not disclosed. Therefore, a person skilled in the art will not be able to make the specific composition of compounds in Claims 1 to 3 from the disclosure in the impugned specification. The impugned application

claims the diasteromeric forms in Claims 1 to 3; however this is not disclosed in the description.

2. The process as claimed in Claims is not disclosed in and supported by the impugned specification. The specific process conditions and parameters are not disclosed in the specification.

3. These claims have been incorporated as amended claims filed in 2015, appears to be a new matter which draws no support from the specification. For instance, Claims 2 and 3 are completely a new matter and is not supported in the specification. In the absence of appropriate support in the impugned specification such claims ought not to be granted.

In view of the above, the complete specification of the impugned application is insufficient and does not describe the best of mode of performing the invention.

**GROUND V**

I) **Section 25 (1) (h): The Applicant has failed to disclose to the Controller the information required under Section 8.**

The Applicant is required to provide all the information regarding the prosecution of the corresponding applications until the grant of the Indian Application to the Controller in writing from time to time and also within the prescribed time, which applicant failed to comply with.

Under section 8(1) of the Act the applicant was under obligation to furnish to the Patent Office details of corresponding foreign applications and also to furnish an undertaking under section 8(1) (b) and subsequently furnished further details with respect to corresponding foreign applications including their status from time to time. The opponent thereby states that the applicant is required to provide all the information regarding the prosecution of his equivalent applications till the grant of his Indian Application to the Controller in writing from time to time and also within the prescribed time, which the applicant has failed to do. The applicant has failed to furnish statement and undertaking under section 8, therefore the applicant has the opponent demands rejection on this ground also.

Accordingly the applicant is under the obligation to submit the application in respect of the same or substantially the same invention or to file along with his application a statement setting out his knowledge for such an application being prosecuted by some person through whom he claims or by some person deriving title from him. However, the applicant has failed to furnish statement and undertaking under section 8, and the opponent therefore demands rejection on this ground also.

It is submitted that the Applicant/Respondent has failed to disclose the details of corresponding foreign applications filed, and on this ground alone the patent application should be rejected.

**PRAYER**

In the fact and circumstances of the case, the Opponent prays as follows:

a. that the Indian Patent Application No. 3658/KOLNP/2009 made by PHARMASSET, INC., a corporation organized and existing under and by

virtue of the laws of the state of Delaware. 303A, College Road East, Princeton New Jersey 08540, United States of America. be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

b. the Opponent may be allowed to file further documents as evidence if necessary to support their averments;

c. the Opponent may be allowed to amend the opposition, add additional grounds and documents if required;

d. the Opponent may be granted leave to adduce evidence in support of the opposition;

e. the Opponent may be granted an opportunity of being heard in the matter before any intention final orders are passed;

f. the Opponent may be allowed to make further submissions and file rejoinder or other appropriate evidence in case the applicant makes any amendments in the claims;

g. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 23rd day of October, 2015

chitra arvind

CHITRA ARVIND
FOR RAJESHWARI & ASSOCIATES
AGENT FOR THE OPPONENT

ANNEXURE-1

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(71) Applicant *(for all designated States except US)*: UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED [GB/GB]; P.O. Box 497, 30-36 Newport Road, Cardiff CF24 0DE (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: MCGUIGAN, Christopher [GB/GB]; 2 Alfreda Road, Whitchurch, Cardiff CF4 2EH (GB).

(74) Agents: HOWARD, Paul, Nicholas et al.; Carpmaels & Ransford, 43-45 Bloomsbury Square, London WC1A 2RA (GB).

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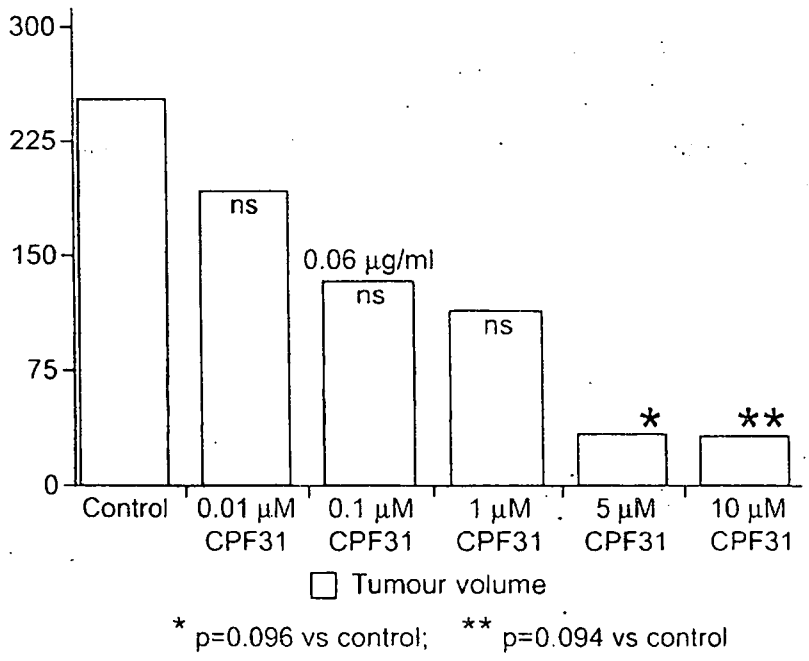
*[Continued on next page]*

(54) Title: CHEMICAL COMPOUNDS




(57) Abstract: Phosphoramidate derivatives of nucleotides and their use in the treatment of cancer are described. The base moieties of, for example, each of deoxyuridine, cytarabine, gemcitabine and cytidine may be substituted at the 5-position. The phosphoramidate moiety has attached to the P atom an aryl-O moiety and an α-amino acid moiety. The α-amino acid moiety may correspond to or be derived from either a naturally occurring or a non-naturally occurring amino acid.

WO 2005/012327 A2

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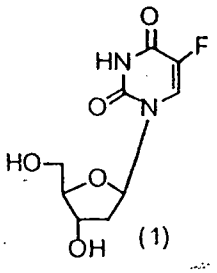
*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## Chemical Compounds

The present invention relates to nucleotide derivatives and their use in the treatment of cancer.

Nucleoside analogues such as fluorodeoxyuridine (1), cytarabine (2) and gemcitabine (3) are well established as anticancer agents. They function as inhibitors of DNA synthesis after activation to their 5'-phosphate form.



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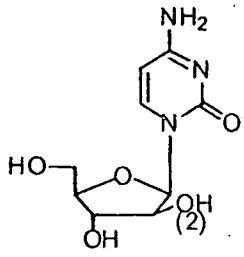

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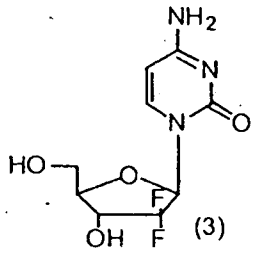


(3)

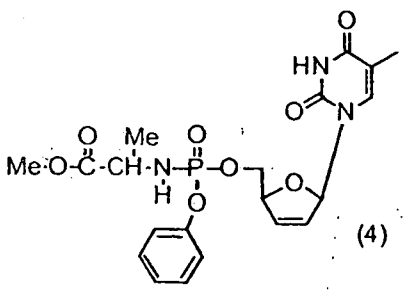
The free bioactive phosphate forms do not in general represent useful drugs due to their poor membrane permeation. In an effort to circumvent this a number of phosphate pro-drug approaches have been reported [Rosowsky et al, J. Med. Chem., 1982, 25, 171-8; Hong et al, J. Med. Chem., 1985, 28, 171-8; Kodama et al, Jpn. J. Cancer Res., 1989, 80, 679-85; Hong et al, 1979, 22, 1428-32; Ji et al, J. Med. Chem., 1990, 33, 2264-70; Jones et al, Nucleic Acids Res., 1989, 17, 7195-7201; Hunston et al, J. Med. Chem., 1984, 27, 440-4; Lorey et al, Nucleosides Nucleotides, 1997, 16, 1307-10; Farquhar et al, J. Med. Chem., 1983, 26, 1153-8; Shuto et al, Nucleosides Nucleotides, 1992, 11, 437-46; Le Bec et al, Tet. Letts., 1991, 32, 6553-6; Phelps et al, J. Med. Chem., 1980, 23, 1229-32].

In general the phosphate prodrugs have biological properties and therapeutic activities that are similar to, or somewhat lower than, the parent nucleoside analogue.

We have carried out extensive work in this area from an antiviral perspective, largely on dideoxy nucleosides, and have reported a phosphoramidate approach which has been widely adopted for the delivery of bio-active phosphates of antiviral nucleosides.



An example is the phosphoramidate (4) derived from anti-HIV d4T (5).



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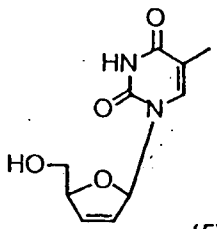
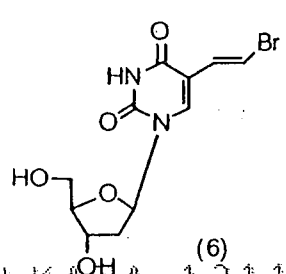


(5)

We observed the effect of variations in the ester [McGuigan et al, AVCC, 1998, 9, 473-9], amino acid [McGuigan et al, Antiviral Res., 1997, 35, 195-204; AVCC, 2000, 11, 111-6], and aryl [Siddiqui et al, J. Med. Chem., 1999, 42, 393-9] regions of the phosphoramidate, as well as the effect of amino acid stereochemistry [McGuigan et al, AVCC, 1996, 7, 184-8]; phosphate stereochemistry [Allender et al, Analytica Chim. Acta, 2001, 435, 107-13] and nucleoside [Balzarini et al, BBRC, 1996, 225, 363-9; McGuigan et al, BioOrg. Med, Chem. Lett., 1996, 6, 2369-62; McGuigan et al, Bioorg. Med. Chem. Lett., 2000, 10, 645-7].

This work has lead to the optimal description of phenyl methoxyalaninyl phosphoramidate as the prototype pro-moiety for the intracellular delivery of bioactive nucleotides [Balzarini et al, PNAS, 1996, 93, 7295-9; McGuigan et al, J. Med. Chem., 1996, 39, 1748-53].

Lackey et al [Biochem Pharmacol., 2001, 61, 179-89] have reported the application of our phosphoramidate pro-drug method for antiviral nucleosides to the anti-herpetic agent bromovinyl-2'-deoxyuridine (BVDU) (6). In particular, they have found that the phenyl methoxyalaninyl phosphoramidate (7) has significant anti-cancer activity. This is in marked contrast to the parent (antiviral) nucleoside (6).



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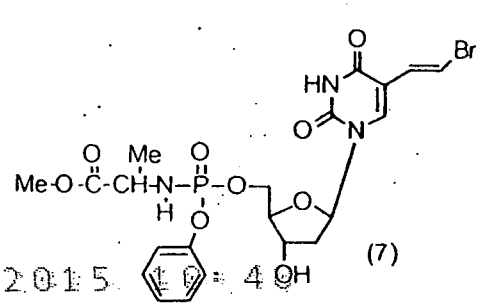
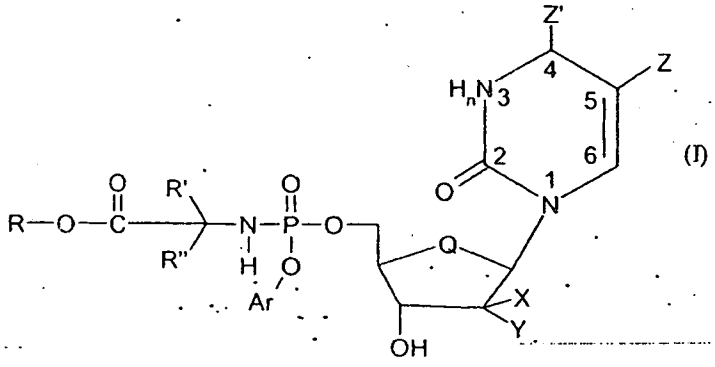


(7)

Limited SAR has been presented by this group, although in their patent applications [WO0239952, EP1200455, CA2317505, US6339151, EP116797, AU2451601] they claim a series of general variations in the base, and phosphate regions. However, based on our prior art, the phenyl methoxyalaninyl phosphoramidate (7) would be anticipated to be amongst the most optimal of structures.

Surprisingly, it has now been found that other derivatives of oxyamino acid-phosphoramidate nucleoside analogues are significantly more potent in the treatment of cancer than the phenyl methoxyalaninyl phosphoramidate (7).

According to a first aspect of the present invention there is provided a compound of formula I:




(I)

wherein:

R is selected from the group comprising alkyl, aryl and alkylaryl;

R' and R" are, independently, selected from the group comprising H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;

Q is selected from the group comprising –O- and $-CH_2-$;

X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl ($-CH_3$);

Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted;

Z is selected from the group comprising H, alkyl and halogen; and

n is 0 or 1,

wherein

when n is 0, Z' is $-NH_2$ and a double bond exists between position 3 and position 4, and

when n is 1, Z' is =O;

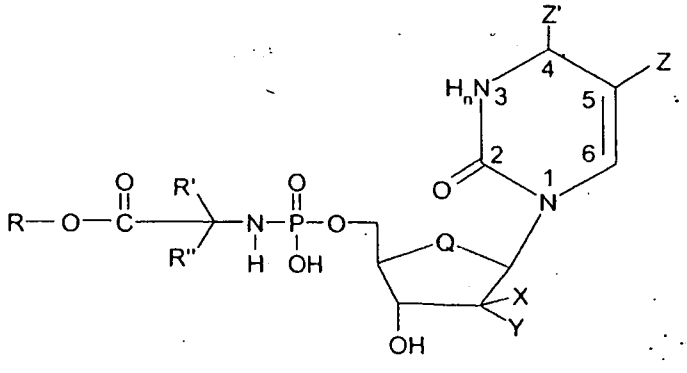
or a pharmaceutically acceptable derivative or metabolite of a compound of formula I;

with the proviso that when n is 1, X and Y are both H, R is methyl ($-CH_3$), one of R' and R" is H and one of R' and R" is methyl ($-CH_3$), then Ar is not phenyl ($-C_6H_5$).

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of formula (I).

Suitably, except where R is 2-Bu ($-CH_2-CH(CH_3)_2$) and one of R' and R" is H and one of R' and R" is methyl ($-CH_3$), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl ($-C_6H_5$).

By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a




compound of formula (I) which gives rise in use to a compound of formula (II):

wherein n, Q, R, R', R", X, Y, Z and Z' have the meanings described above and below for formula I, and additionally R can be H, with the proviso that when n is 1, X and Y are both

H, R is methyl (–$CH_3$), one of R' and R" is H and one of R' and R" is methyl (-$CH_3$), then Z is not –CH=CHBr.

Suitably, with respect to compounds of formula II, when n is 1 and Z either is or is not –CH=CHBr, the moiety ROCOCR'R"NH- corresponds neither to alanine (ie as above, R is not methyl (-$CH_3$), one of R' and R" is not H and one of R' and R" is not methyl (-$CH_3$)) nor to tryptophan (ie α-amino-β-indolylpropionic acid).

More suitably with respect to compounds of formula II, when n is 1 and Z either is or is not –CH=CHBr, the moiety ROCOR'R"NH is neither derived from nor corresponds to any naturally ocurring amino acid.

Even more suitably, with respect to compounds of formula II, when n is 1 or 0, the moiety ROCOCR'R"NH- does not correspond to alanine (ie R is not methyl (-$CH_3$), one of R' and R" is is not H and one of R' and R" is not methyl (-$CH_3$)), does not preferably correspond to tryptophan, and even more preferably the said moiety does not correspond to any naturally ocurring amino acid.

Most preferably the moiety ROCOCR'R"NH- in compounds of formula II corresponds to a non-naturally occurring amino acid.

Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkylene group is preferably $C_3$ to $C_{12}$, more preferably $C_5$ to $C_{10}$, more preferably $C_5$ to $C_7$. Where acyclic, the alkyl group is preferably $C_1$ to $C_{16}$, more preferably $C_1$ to $C_6$.

Reference in the present specification to an aryl group means an aromatic group containing 5 to 14 ring atoms, for example phenyl or naphthyl. The aromatic group may be a heteroaromatic group containing one, two, three or four, preferably one, heteroatoms selected, independently, from the group consisting of O, N and S. Examples of such heteroaromatic groups include pyridyl, pyrrolyl, furanyl and thiophenyl. Preferably, the aryl group comprises phenyl or substituted phenyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be one to three substituents present, preferably one substituent. Substituents may include halogen atoms, by which is meant F, Cl, Br and I atoms, and halomethyl groups such as $CF_3$ and $CCl_3$; oxygen containing groups such as oxo, hydroxy, carboxy, carboxy$C_{1-16}$alkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, $C_{1-6}$alkylamino, di$C_{1-6}$alkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, $C_{1-6}$alkylthiol, sulphonyl and sulphoxide; heterocyclic groups which may themselves be substituted; alkyl groups as defined above, which may themselves be substituted; and aryl groups as defined above, which may themselves be substituted, such as phenyl and substituted phenyl. Substituents on said heterocyclic, alkyl and aryl groups are as defined immediately above.

Reference in the present specification to alkoxy and aryloxy groups means, respectively, alkyl-O- (for example where alkyl is $C_1$ to $C_{16}$, preferably $C_1$ to $C_6$) and aryl-O- (for example where aryl is a 5 to 14 membered aromatic mono- or bifused ring moiety, optionally containing 1, 2, 3 or 4 heteroatoms selected, independently, from O, S and N, preferably aryl is phenyl).

Reference in the present specification to alkoyl and aryloyl groups means, respectively, alkyl-CO- (for example where alkyl is $C_1$ to $C_{16}$, preferably $C_1$ to $C_6$) and aryl-CO- (for example where aryl is a 5 to 14 membered aromatic mono or bifused ring moiety, optionally containing 1, 2, 3 or 4 heteroatoms selected, independently, from O, S and N, preferably aryl is phenyl).

Reference in the present specification to alkoyloxy and aryloyloxy means, respectively, alkyl-CO-O (for example where alkyl is $C_1$ to $C_{16}$, preferably $C_1$ to $C_6$) and aryl-CO-O (for example where aryl is a 5 to 14 membered mono- or bifused aromatic ring system, optionally containing 1, 2, 3 or 4 heteroatoms selected, independently, from O, S and N, preferably aryl is phenyl).

Reference in the present specification to heterocyclic groups means groups containing one or more pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl,

pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronly, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

The group Ar comprises a substituted or unsubstituted aryl group, wherein the term "aryl group" and the possible substitution of said group is as defined herein. Preferably, Ar is a substituted or unsubstituted phenyl group. Particularly preferred substituents are electron withdrawing groups such as halogen (preferably chlorine or fluorine), trihalomethyl (preferably trifluoromethyl), cyano and nitro groups. For example, Ar can be phenyl, 3,5-dichloro-phenyl, p-trifluoromethyl-phenyl, p-cyano-phenyl, or p-nitro-phenyl. When Ar is a heteroaromatic group, preferably it is optionally substituted pyridyl.

Suitably, R is a $C_{1-16}$ primary or secondary alkyl group, a $C_{5-7}$ carbocyclic aryl group or a $C_{1-6}$alkyl$C_{5-11}$aryl group. More suitably, R is a $C_{1-10}$ alkyl group, a phenyl group or $C_{1-3}$ alkyl$C_{5-7}$ aryl group. Preferably R is unsubstituted.

Preferably, R is methyl (-$CH_3$), ethyl (-$C_2H_5$), *n*- or *i*- propyl (-$C_3H_7$), *n*- or *i*- butyl (-$C_4H_9$) or benzyl (-$CH_2C_6H_5$). Most preferably, R is benzyl. Particularly, R is preferably benzyl when one of R' and R" is H and one of R' and R" is methyl (-$CH_3$), especially when Ar is unsubstituted phenyl, n is 0 and each of X and Y is F.

Suitably, R' and R" are each independently selected from the group comprising H, $C_{1-6}$ primary, secondary or tertiary alkyl, $C_{1-3}$alkyl$C_{5-7}$aryl, or, when together they form an alkylene chain, they provide, together the C atom to which they are attached, a $C_{3-8}$ carbocyclic aliphatic ring.

Preferably, R' and R'' are the same and are alkyl, more prefearbly they are both methyl, ethyl or *n*- or *i*- propyl.

Alternatively, preferably, R' and R" are, independently, H, methyl ($-CH_3$), secondary butyl ($-CH_2-CH-(CH_3)_2$), benzyl ($-CH_2C_6H_5$), or, together with the C atom to which they are attached, provide a $C_{5-6}$ ring.

Preferred compounds include those where R' and R" are both methyl, one of R' and R" is H and one of R' and R" is methyl, and R' and R", together with the C atom to which they are attached, provide a pentyl ring.

When R' and R" are different, the C atom to which they are attached is chiral. The present compounds can be L or D or a mixture of stereoiosomers. Preferably they are L.

It will be appreciated that the moiety $-O-C(O)-CR'R"-NH-$ corresponds to a carboxy-protected α-amino acid. R' and R" can thus correspond to the side chains of a naturally occurring amino acid.

For example, when one of R' and R" is H and one of R' and R" is Me or $PhCH_2$, the moiety corresponds to alanine or phenylalanine, respectively.

Preferably, the stereochemistry at the asymmetric centre $-CR'R"$ corresponds to an L-amino acid. The stereochemistry at the asymmetric centre $-CR'R"$ can, however, correspond to a D-amino acid. Alternatively, mixtures of of compounds can be employed having asymmetric centres corresponding to L and D amino acids.

In the present specification by "naturally occurring amino acid" we mean Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Cystine, Glycine, Glutamic Acid, Glutamine, Histidine, Hydroxylysine, Hydroxyproline, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine and Valine.

The present invention is not, however, limited to compounds having a moiety corresponding to a naturally occurring amino acid. The present invention specifically includes compounds having a moiety which corresponds to a non-naturally occurring amino acid, such as, for example, those where R'=R"=alkyl, or, where together with the C atom to which they are attached, R' and R" provide a cyclic moiety. Preferably with

respect to the compound of formula I, the moiety ROCOCR'R"NH- corresponds to or is derived from a non-naturally occurring amino acid.

With respect to compounds of formula I when n is 1, the moiety ROCOCR'R"NH- preferably neither corresponds to nor is derived from alanine, more preferably neither corresponds to nor is derived from either of alanine or tryptophan, even more preferably neither corresponds to nor is derived from any naturally occurring amino acid.

With respect to compounds of formula I when n is 0, the moiety ROCOCR'R"NH- preferably neither corresponds to nor is derived from alanine, more preferably neither corresponds to nor is derived from either of alanine or trytophan, even more preferably neither corresponds to nor is derived from any naturally occurring amino acid.

Preferably Q is O.

Preferably, X and Y are, independently, selected from the group comprising F, H and OH.

When n is 1, preferably each of X and Y is H.

When n is 0, preferably each of X and Y is F, or X is OH and Y is H, or X is H and Y is OH.

When Z is F, Q is O, n is 1 and X and Y are each H, the base moiety of the compound of formula I corresponds to that of fluorodeoxyuridine i.e. compound (1) above.

When Z is H, Q is O, n is 0 and X is OH and Y is H, the base moiety of the compound of formula I corresponds to that of cytarabine i.e. compound (2) above.

When Z is H, Q is O, n is 0 and X and Y are each F, the base moiety of the compound of formula I corresponds to that of gemcitabine i.e. compound (3) above.

When Z is H, Q is O, n is 0 and X is H and Y is OH, the base moiety of the compound of formula I corresponds to that of cytidine.

Compounds of formula I wherein n is 0 and X and Y are F are preferred. Particularly preferred are compounds of formula I wherein n is 0, X and Y are F, Q is O and Z is H, corresponding to phosphoramidated gemcitabine.

Also preferred are compounds of formula I wherein n is 0 and X is OH and Y is H. Particularly preferred are compounds of formula I wherein n is 0, X is OH, Y is H, Q is O and Z is H, corresponding to phosphoramidated cytarabine.

Also preferred are compounds of formula I wherein n is 0 and X is H and Y is OH. Particularly preferred are compounds of formula I wherein n is 0, X is H, Y is OH, Q is O andZ is H, corresponding to phosphoramidated cytidine.

Suitably, Ar is a 5 to 14 membered aromatic ring moiety. The one or two rings may include 1, 2, 3 or 4 heteroatoms, preferably 1, selected, independently, from O, S and N.

Preferably, Ar is a carbomonocyclic aromatic ring moiety. More preferably, Ar is a $C_6$ monocyclic aromatic ring moiety, ie is optionally substituted phenyl.

One, two, three or four substituents, which may be the same or different, may be present on Ar and are selected from the group comprising halogen, which may -F, -Cl, -Br or -I; -$NO_2$; -$NH_2$; optionally substituted -$C_{1-3}$alkyl; optionally substituted -$C_{1-3}$alkoxy, preferably methoxy (-$OCH_3$); optionally substituted –$SC_{1-3}$alkyl; -CN; optionally substituted -$COC_{1-3}$alkyl; and optionally substituted -$CO_2C_{1-3}$alkyl. The optional substitutents are one or more up to six, preferably three, members selected from the group comprising halogen which may be F, Cl, Br and I and $NO_2$. Preferred substituents on Ar include F, Cl, $CF_3$, and $NO_2$.

The substituents may be at any position on the ring moiety. Where the ring moiety is $C_6$ ie phenyl, a single substituent at the 2 (*ortho*) or 4 (*para*) position is preferred. Where Ar is phenyl, a single substituent at the 4 position is more preferred.

Preferably, Ar is an optionally substituted phenyl moiety. More preferably, Ar is selected form the group comprising: Ph-, $p$CF$_3$C$_6$H$_4$-, $p$FC$_6$H$_4$-, $p$NO$_2$C$_6$H$_4$-, $p$ClC$_6$H$_4$- and $o$ClC$_6$H$_4$-.

Suitably, Z is selected from the group comprising H, $C_{1-6}$ alkyl, substituted $C_{1-6}$ alkyl, $C_{1-6}$ alkenyl, substituted $C_{1-6}$ alkenyl, $C_{1-6}$ alkynyl, substituted $C_{1-6}$ alkynyl and halogen, where halogen is F, Cl, Br or I. Substituents that may be present on the alkenyl or alkynyl moiety are selected from the group comprising F, Cl, Br, I, and $-CO_2Me$. One, two or three substituents may be present. The alkenyl and alkynyl groups may contain one or more sites of unsaturation.

Where Z is substituted alkenyl or alkynyl, the substituent is preferably on the terminal C atom.

Preferably Z is selected from the group comprising H, F, optionally substituted $C_{1-6}$alkyl particularly Me ($-CH_3$), optionally substituted $C_{1-6}$alkenyl and optionally substituted $C_{1-6}$alkynyl, the optional substituents being as recited immediately above.

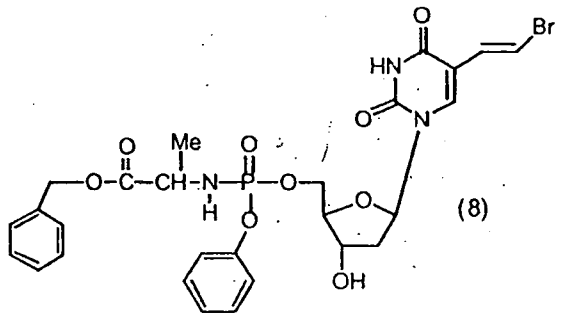
When n is 1, Z' is O, Q is O and X and Y are each H, preferably Z is a substituted $C_2$ alkenyl (i.e. ethenyl or vinyl) moiety (-CH=CH-); more preferably, Z is bromovinyl (–CH=CHBr) or methylpropenoate (–CH=CHCO$_2$Me); and most preferably, Z is –CH=CHBr.

With respect to compounds of formula II, preferably when n is 1 and X and Y are both H, then Z is not F.

With respect to compounds of formula II, when n is 0, preferably X is not H and Y is not OH, more preferably X is OH and Y is H or X and Y are both F.

With respect to compounds of formula II, when n is 0, X is OH and Y is H, preferably neither R' nor R" is phenylmethyl (ie benzyl) or 3-methylindolyl (ie 3-$CH_2$indolyl).

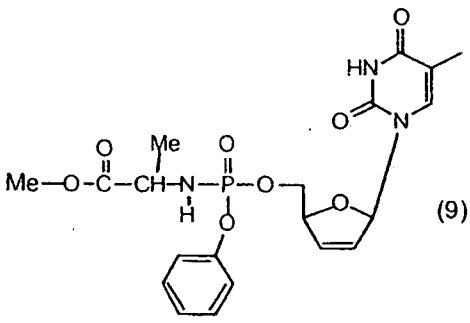
Surprisingly, modifying the ester moiety in compound (7) has been found to show a marked increase in potency with respect to cancer cell lines. A preferred compound embodying the present invention is the benzyl ester (8). It has surprisingly been found that the benzyl ester (8) is very significantly more potent against several cancer cell lines than the methyl ester (7):



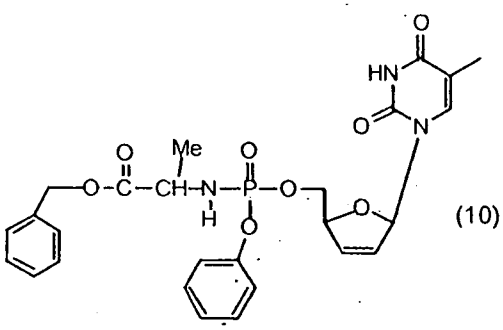
(8)

Compound (8) inhibits the growth of colon cancer cell line HT115 by 50% at 1.4 μM, whilst (7) requires a concentration of 244 μM; (8) is thus 174 times more potent. Compound (8) is also 8 times more potent than (7) versus prostate cancer cell line PC-3 (19 μM vs. 155 μM).

The degree of potency enhancement for (8) vs. (7) is surprising based on the prior art. Thus, comparing the equivalent phosphoramidates of d4T reveals a ca 4-fold potency boost of (10) over (9) [McGuigan et al, AVCC, 1998, 9, 473-9].



(9)



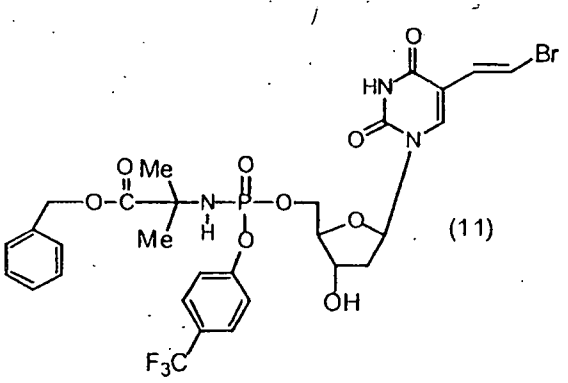
(10)

This would imply that the benzyl phosphoramidate motif in (10) is ca 4-fold more efficient at the intracellular delivery of the bio-active free phosphate forms of d4T than is the methyl ester (9). A person skilled in the art would anticipate a similar degree of

enhancement for the benzyl phosphoramidate of BVDU (8) over the methyl ester (7) whilst we observed an almost 200-fold enhancement for colon cancer as noted above.

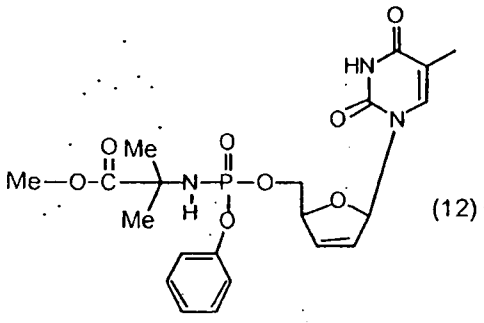
Surprising efficacy of modifications in the amino acid and aryl moieties of the BVDU phosporamidate has also been found in compounds embodying the present invention.

Thus, compound (11) has simultaneous modification in these two regions, being the p-trifluoromethylphenyl benzyl [α,α-dimethylglycinyl ]phosphoramidate.

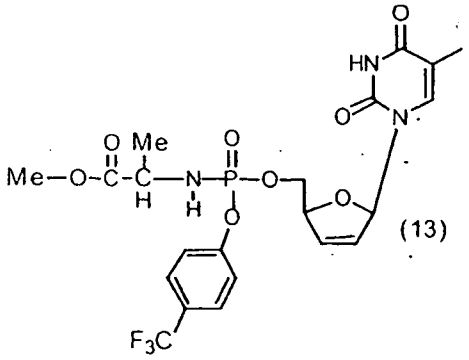



(11)

Compound 11 shows high potency against a range of cancer cell types and is significantly and surprisingly more potent than (7). Thus, for breast cancer (11) is 60-fold more active (1.3μM vs 79 μM), and for prostate cancer (11) is 254-fold more potent (0.61 μM vs. 155 μM). Against colon cancer, (11) is 35-fold more potent (7 μM vs 244 μM). Again, the degree of enhancement of the analogue (11) vs. (7) is surprising based on prior art. Thus, comparing (12) [dimethyl glycine modification] and (13) [p-$CF_3$phenyl modification] to (9) shows no significant difference in potency.




(12)




(13)

Thus 50% effective doses vs HIV-1 for (9), (12) and (13) are: 0.075, 0.29, and 0.01 μM respectively; within experimental error, (12) and (13) are identical in potency to (9). Thus a person skilled in the art would have predicted that (11) would show little enhancement over (7) as opposed to the 35 to 254-fold enhancements noted above.

Thus, compounds embodying the present invention and having variations in one or more of the ester (R), amino acid (R', R") and aryl (Ar) region of the phosphoramidate structure compared to phenyl methoxyalaninyl phosphoramidate can give surprising and substantial potency boosts of pro-tides derived from BVDU against a range of cancer cell types.

According to a further aspect of the present invention there is provided a compound having formula I according to the present invention for use in a method of treatment, preferably in the prophylaxis or treatment of cancer.

According to a further aspect of the present invention there is provided a method of phrophylaxis or treatment of cancer comprising administration to a patient in need of such treatment an effective dose of a compound having formula I according to the present invention.

According to a further aspect of the present invention there is provided use of a compound having formula I of the present invention in the manufacture of a medicament for use in the treatment or prophlylaxis of cancer.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound having formula I of the present invention in combination with a pharmaceutically acceptable excipient, carrier or diluent.

According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of combining a compound having formula I of the present invention with a pharmaceutically acceptable excipient, carrier or diluent.

The present invention is particularly applicable for the treatment of a patient having breast cancer, colon cancer or prostate cancer. Examples of such cancers include breast MDA MB231, colon HT115 and prostate PC-3.

The compound having formula I or pharmaceutical composition according to the present invention can be administered to a patient, which may be human or animal, by any suitable means.

The medicaments employed in the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

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

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 cornstarch 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.

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.

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

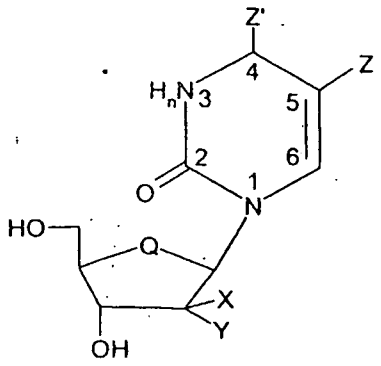
Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the 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 according to 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.

The compounds of the invention may also be presented as liposome formulations.

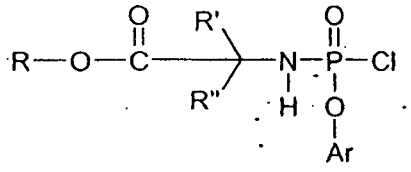
In general a suitable dose will be in the range of 0.1 to 300 mg per kilogram body weight of the recipient per day. A preferred lower dose is 0.5 mg per kilogrm body weight of recpient per day, a more preferred lower dose is 6 mg per kilogram body weight of recipient per day, an even more preferred lower dose is 10 mg per kilogram body weight per recipient per day. A suitable dose is preferably in the range of 6 to 150 mg per kilogram body weight per day, and most preferably in the range of 15 to 100 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 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

According to a further aspect of the present invention there is provided a process for the preparation of a compound having formula I according to the present invention, the process comprising reacting of a compound of formula (III):




(III)

with a compound of formula (IV):




(IV)

wherein Ar,n Q, R, R', R", X, Y, Z' and Z have the meanings described above with respect to formula (I).

Embodiments of the present invention will now be described, by way of example only, with reference to the following examples, experimental procedures and experimental data.

Data are presented for a range of structures against tumour cell types representing a range of common cancers in man with un-met clinical need: breast MDA MB231, colon HT115, prostate PC-3. Data from these assays are presented as Table I.

## Experimental Procedure

***General methods***

The following anhydrous solvents and reagents were bought from Aldrich with sure stopper: dichloromethane (DCM), diethyl ether ($Et_2O$), tetrahydrofuran THF), N-methylimidazole (NMI), methanol (MeOH), dimethylformamide (DMF), 1,4-dioxane. triethylamine was dried on molecular sieves of 4 Angstrom.

*Thin Layer Chromatography*

Thin layer chromatography (TLC) was performed on commercially available Merck Kieselgel 60 $F_{254}$ plates and separated components were visualized using ultraviolet light (254 nm and 366 nm).

*Column Chromatography*

Columns were performed using (Kieselgel 60, 35-70μm, Fluka) as the stationary phase. Samples were applied as a concentrated solution in the same eluent, or pre-adsorbed onto silica gel.

*NMR Spectroscopy*

$^{1}H$, $^{13}C$ and $^{31}P$-NMR were recorded on a Bruker Avance DPX300 spectrometer with operating frequencies of 300MHz, 75MHz and 121MHz respectively. $^{31}P$-NMR spectra are reported in units of δ relative to 85% phosphoric acid as external standard, positive shifts are downfield. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal), dd (doublet of doublet), dt (doublet of triplet). Starred signal signal are splitted due to stereoisomeric mixtures.

*Standard procedures*

For practical purposes, standard procedures are given where applicable.

*Standard procedure 1: Synthesis of Amino ester hydrochloride salts.*

To a stirring solution of anhydrous alcohol ( 10 mol eq.) was added thionyl chloride (2 mol eq.) at 0° C, and the resulting solution stirred for 1 hr. After warming to room temperature, the appropriate amino acid (1 mol eq) was added and the reaction heated at reflux for 6-16 hrs. Removal of solvent and recrystallisation from methanol/ether gave the amino ester hydrochloride salts.

*Standard procedure 2: Synthesis of Amino benzyl ester hydrochloride salts.*

The appropriate amino acid (1.0 mol eq.), *p*-toluene sulfonic acid (1.0 mol eq.) and anhydrous benzyl alcohol (4.1 mol eq.) were heated at reflux in toluene (10 mol eq.) with Dean-Stark trap for 24 hrs. On cooling to room temperature, $Et_2O$ was added and the

mixture was left in ice bath for 1hr then filtrated and washed with $Et_2O$. The solid was dissolved in DCM and washed with 10% $K_2CO_3$ and water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give an oil. This was solubilized in acetone and neutralized with 1 M HCl. $Et_2O$ was added and the solid was filtered and washed with $Et_2O$ to give a white solid.

***Standard procedure 3: Synthesis of Phosphorodichloridate species.***

Phosphorus oxychloride (1.0 mol eq.) and the appropriate substituted phenol (1.0 mol) were stirred with anhydrous diethylether (31 mol eq.). To this was added anhydrous triethylamine (1.0 mol eq) at –80 °C and left to rise to room temperature over 16 hrs. the triethylamine hydrochloride salt was filtered off, and the filtrate reduced to dryness to give the crude product as a clear liquid.

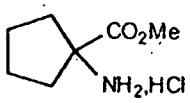
***Standard procedure 4: Synthesis of Phosphochloridate species.***

Phosphodichloridate (1.0 mol eq.) and the appropriate amino ester hydrochloric salt (1.0 mol eq.) were suspended in anhydrous DCM. Anhydrous triethylamine was added dropwise at –80 °C and after 1hr the reaction was left to rise to room temperature. The formation of phosphochloridate was monitored by $^{31}$P-NMR. After 2-5 hrs the solvent was removed under reduced pressure and the solid obtained washed with anhydrous ether (2x20 ml), filtered, and the filtrate reduced to dryness to give the products as crude oil. These oils were usually used without further purification.

***Standard procedure 5: Synthesis of Phosphoroamidate derivatives.***

To a stirring solution of (E)-5-(2-bromovinyl)-2'-deoxyuridine (1.0 mol eq.) and the appropriate phosphochloridate (2.0- 3.0 mol eq) in anhydrous THF at –80°C was added dropwise over 1 min NMI (5.0 mol eq.). After 15 mins the reaction was left to rise to room temperature and stirred at room temperature for 2-19 hrs. The solvent was removed under reduced pressure and the yellow oil obtained was dissolved in DCM, washed with 0.5 M HCl, and water. The organic layer is dried over $MgSO_4$, filtered, reduced to dryness and purified by flash chromatography (Chloroform/Methanol 97/3, Dichloromethane/Methanol 97/3).

**Synthesis of Methyl-1-amino-1-cyclopentanoate hydrochloride salt.**
**$C_6H_{14}ClNO_3$, MW=179.68.**

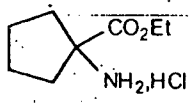



This was synthesised according to ***Standard Procedure 1***, using 1-amino-1-cyclopentanecarboxylic acid (3.876 g, 30 mmol) with thionyl chloride (4.44 mL, 45 mmol,) and anhydrous methanol (15.5 mL). The product was isolated as a white solid (4.81 g, yield 89%).

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.1 (3H, bs, $N\underline{H_3}^+Cl^-$), 3.85 (3H, s, $OC\underline{H_3}$), 2.3-2.2 (4H, m, 4H cyclopentane), 2.15 (2H, 2H cyclopentane), 1.95 (2H, m, 2H cyclopentane).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 26.6 ($2CH_2$ cyclopent), 38.1 ($2CH_2$ cyclopent), 54.8 ($\underline{C}H_3O$), 66.6 ($\underline{Cq}$ cyclopentane), 174.1 ($\underline{C}OOMe$).

**Synthesis of Ethyl-1-amino-1-cyclopentanoate hydrochloride salt.**
**$C_8H_{16}ClNO_2$, MW=193.71.**



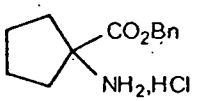

This was synthesised according to ***Standard Procedure 1***, using 1-amino-1-cyclopentanecarboxylic acid (5.0 g, 38.6 mmol) with thionyl chloride (5.72 mL, 58 mmol) and anhydrous ethanol (29 mL). The product was isolated as a white solid (6.98 g, yield 93%).

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.0 (3H, bs, $N\underline{H_3}^+Cl^-$), 4.3 (2H, q, $^3J$=8, $OC\underline{H_2}CH_3$), 2.3-2.2 (4H, m, 4H cyclopentane), 2.15 (2H, 2H cyclopentane), 1.95 (2H, m, 2H cyclopentane), 1.4 (3H, t, $^3J$=8, $OCH_2C\underline{H_3}$).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 14.5 ($\underline{C}H_3CH_2$), 25.8 ($2CH_2$ cyclopent), 37.4 ($2CH_2$ cyclopent), 63.0 ($CH_3\underline{C}H_2$), 66.2 ($\underline{Cq}$ cyclopentane), 172.1 ($\underline{C}OOEt$).

**Synthesis of Benzyl-1-amino-1-cyclopentanoate hydrochloride salt.**

**$C_{14}H_{18}ClNO_2$, MW=255.78.**



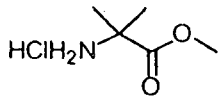

This was synthesised according to ***Standard Procedure 2***, using 1-amino-1-cyclopentanecarboxylic acid (3.682 g, 28.5 mmol) with *p*-toluene sulfonic acid monohydrate (5.625 g, 29.55 mmol) and anhydrous benzylic alcohol (12 mL, 116 mmol), in Toluene (20 mL). The product was isolated as a white solid (6.441 g, yield 88.5%)

**Hydrochloride salt.** $^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.05 (3H, bs, $NH_3^+Cl^-$), 7.4-7.25 (5H, m, Ph), 5.15 (2H, s, $CH_2Ph$), 2.3 (4H, m, 4H cyclopentane), 2.15 (2H, 2H cyclopentane), 1.95 (2H, m, 2H cyclopentane).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 25.9 ($2CH_2$ cyclopent), 37.3 ($2CH_2$ cyclopent), 66.3 (*Cq* cyclopentane), 68.3 ($CH_2$Ph), 129.2, 129.0, 128.8 (*'o'*, *'m'*, $CH_2Ph$), 135.5 (*'p'*, $CH_2Ph$), 172.1 (COOBn).

**Synthesis of methyl-2-amino-2-methylpropanoate hydrochloride salt**

**$C_5H_{12}ClNO_2$, MW 153.61.**



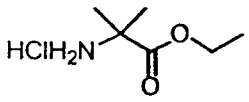

This was synthesised according to ***Standard Procedure 1***, using 2-amino-isobutyric acid (5.102 g, 48.49 mmol) with thionyl chloride (11.538 g, 96.98 mmol, 7.04 mL) and anhydrous methanol (19.6 mL). The product was isolated as a white solid (6.636 g, yield 89.2%).

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 8.81 (3H, bs, $NH_3Cl$), 3.83 (3H, s, $OCH_3$), 1.74 (6H, s, $[CH_3]_2C$).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 24.1, 24.3 ($[CH_3]_2C$), 57.9 ($C[CH_3]_2$), 172.4 ($COOCH_3$).

**Synthesis of ethyl-2-amino-2-methylpropanoate hydrochloride salt.**

**$C_6H_{14}ClNO_2$, MW 167.63.**



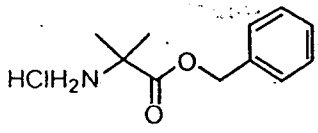
This was synthesised according to ***Standard Procedure 1***, using 2-amino-isobutyric acid (5.102 g, 48.49 mmol) with thionyl chloride (11.772 g, 98.95 mmol, 7.2 mL) and anhydrous ethanol (29 mL). The product was isolated as a white solid (7.159 g, yield 86.3%).

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 8.93 (3H, bs, N$\underline{H_3}$Cl), 4.3 (2H, q, $^3J$=7.1 Hz, OC$\underline{H_2}$CH$_3$), 1.75 (6H, s, [C$\underline{H_3}$]$_2$C), 1.33 (3H, t, $^3J$=7.1 Hz, OCH$_2$C$\underline{H_3}$).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 14.4 ($\underline{C}$H$_3$CH$_2$O), 24.3 ([$\underline{C}$H$_3$]$_2$C), 57.9 ($\underline{C}$[CH$_3$]$_2$), 63.1 (O$\underline{C}$H$_2$CH$_3$), 171.6 ($\underline{C}$OOCH$_2$CH$_3$).

**Synthesis of benzyl-2-amino-2-methylpropanoate hydrochloride salt.**

**$C_{11}H_{16}ClNO_2$, MW 229.70.**



This was synthesised according to ***Standard Procedure 2***, using 2-amino-isobutyric acid (1.960 g, 19.00 mmol) with *p*-toluene sulfonic acid monohydrate (3.750g, 19.7 mmol) and benzylic alcohol (8.360 g, 77.30 mmol, 8 mL), in toluene (20 mL). The product was isolated as a white solid (2.556 g, yield 87.4%)

***p*-toluenesulfonate salt**: $^1$H-NMR ($CDCl_3$, 300 MHz): δ 8.40 (3H, bs, N$\underline{H_3}$Cl), 7.79 (2H, d, $^3J$=8.0 Hz, *'m' p*-TSA), 7.34 (5H, m, CH$_2$$\underline{Ph}$), 7.14 (2H, d, $^3J$=8.0 Hz, *'o'* p-TSA), 5.16 (2H, s, C$\underline{H_2}$Ph), 2.38 (3H, s, C$\underline{H_3}$ *p*-TSA), 1.57 (6H, s, [C$\underline{H_3}$]$_2$C)

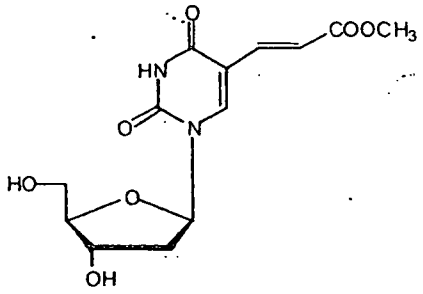
$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 21.8 (*C*H$_3$, *p*-TSA), 23.9 ([*C*H$_3$]$_2$C), 57.8 (*C*[CH$_3$]$_2$), 68.3 (*C*H$_2$Ph), 126.55, 128.5, 128.8, 129.0, 129.3 (CH$_2$*Ph*+*p*-TSA), 135.4 (*'ipso'*, CH$_2$*Ph*), 140.8 (*'p'*, *p*-TSA), 141.9 (*'ipso'*, *p*-TSA), 171.9 (*C*OOCH$_2$Ph).

**Hydrochloride salt**: $^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.10 (3H, bs, N*H*$_3$Cl), 7.41-7.31 (5H, m, CH$_2$*Ph*), 5.27 (2H, s, CH$_2$*Ph*), 1.77 ([C*H*$_3$]$_2$C).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 24.2 ([*C*H$_3$]$_2$C), 58.0 (*C*[CH$_3$]$_2$), 68.5 (*C*H$_2$Ph), 128.62, 129.0, 129.1 (*'o'*, *'m'*, *'p'*, CH$_2$*Ph*), 135.2 (*'ipso'*, CH$_2$*Ph*), 171.8 (*C*OOCH$_2$Ph).

## *Synthesis of (E)-5-(2-bromovinyl)-2'-deoxyuridine*

**(E)-5-(2-Carbomethoxyvinyl)-2'-deoxyuridine**

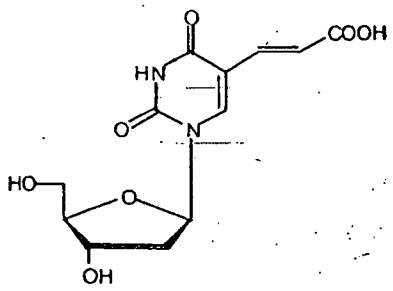



A mixture of $Pd(OAc)_2$ (0.316 g, 1.41 mmol), $PPh_3$ (0.741 g, 2.82 mmol), and triethylamine (4.9 mL) in 1,4-dioxane (50 mL) was stirred at 70°C until an intense red colour had developed. To this 5-iodo-2'-deoxyuridine (10 g, 28.24 mmol) and methylacrilate (4.862 g, 56.48 mmol, 5.1 mL) in 1,4-dioxane (20 mL) were added and the mixture stirred at refluxed for 30 mins. The reaction was filtered while still hot and the filtrate cooled over night at 4°C. The resulting pale yellow precipitate was filtered, washed with DCM and dried *in vacuo* to give the product as white solid (6.2 g, yield 70.7%).

$^1$H-NMR (DMSO-$d_6$; 300 MHz) δ 11.64 (1H, bs, N*H*-3), 8.42 (1H, s, H-6), 7.37 (1H, d, $^3J$=15.8 Hz, H vinylic), 6.86 (1H, d, $^3J$=15.8 Hz, H vinylic), 6.13 (1H, t, $^3J$=6.5 Hz, H-1'), 5.27-5.20 (2H, 2bs, OH-3', OH-5'), 4.27 (1H, m, H-3'), 3.81 (1H, m, H-4'), 3.68 (3H, s, C*H*$_3$), 3.60 (2H, m, H-5'), 2.18 (2H, m, H-2').

$^{13}$C-NMR (DMSO-$d_6$; 75 MHz): δ 40.4 (C-2'), 51.6 ($CH_3$), 66.7 (C-5'), 70.0 (C-3'), 85.2 (C-4'), 88.0 (C-1'), 108.5 (C-5), 116.5 (C-5b), 138.5 (C-5a), 144.4 (C-6), 149.6, 162.1 (C-2, C-4), 167.6 (COO).

**(E)-5-(2-Carboxyvinyl)-2'-deoxyuridine**

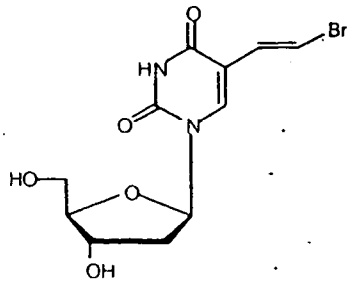


(E)-5-(2-carbomethoxyvinyl)-2'-deoxyuridine (6.0 g, 19.33 mmol) was dissolved in 300 mL of 1 M NaOH and the mixture stirred at room temperature for 3 hrs, filtered and the filtrate adjusted to pH 2 with 1M HCl. On cooling at 4°C a white precipitate formed. This was filtered off and washed with cold water (2x 20 ml) and acetone (2x20 mL) and dred to give a white solid (4.441 g, yield 77.1%).

$^1$H-NMR (DMSO-$d_6$; 300 MHz): δ 12.18 (1H, bs, $CO_2H$), 11.64 (1H, s, NH-3), 8.40 (1H, s, H-6), 7.30 (1H, d, $^3J$=15.6 Hz, H vinylic), 6.78 (1H, d, $^3J$=15.8 Hz, H vinylic), 6.14 (1H, t, $^3J$=6.4 Hz, H-1'), 5.38 -5.08 (2H, bs, OH-3', OH-5'), 4.26 (1H, m, H-3'), 3.80 (1H, m, H-4'), 3.64 (2H, m, H-5'), 2.18 (2H, m, H-2').

$^{13}$C-NMR (DMSO-$d_6$; 75 MHz): δ 40.1 (C-2'), 61.2 (C-5'), 70.1 (C-3'), 85.1 (C-4'), 88.0 (C-1'), 108.7 (C-5), 118.0 (C-5b), 137.9 (C-5a), 143.9 (C-6), 149.6, 162.1 (C-2, C-4), 168.4 (COOH).

**(E)-5-(2-bromovinyl)-2'-deoxyuridine**



To a solution of (E)-5-(2-carboxyvinyl)-2'-deoxyuridine (5.777 g, 19.37 mmol) in dimethylforamide (29 mL) was added $K_2CO_3$ (5.890 g, 42.61 mmol) and the suspension stirred at room temperature for 15 mins. A solution of N-bromosuccinimide (3.655 g,

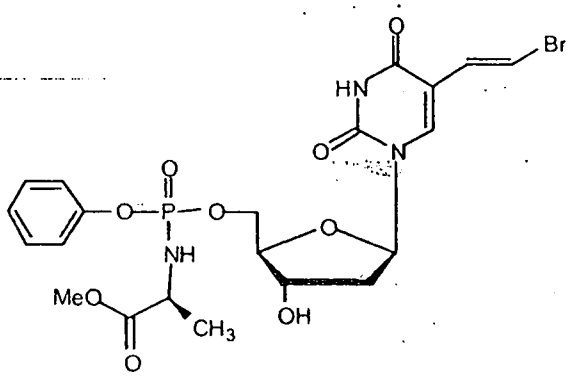
20.53 mmol) was added dropwise over 30 mins at 20°C. The resulting suspension was filtered and the solid washed with DMF. The combined filtrate and washings were evaporated to dryness *in vacuo* and the residue dissolved in MeOH. To this silica gel was added and the suspension evaporated to dryness and the solid applied to the top of chromatographic column. The column was eluted with chloroform/methanol 92/8 to give a white solid (5787g, 71.9%). Crystallisation from water gave a white powder.

$^1$H-NMR (DMSO-$d_6$; 300 MHz) δ 11.59 (1H, bs, NH-3), 8.08 (1H, s, H-6), 7.25 (1H, d, $^3J$=13.6 Hz, H-5b), 6.85 (1H, d, $^3J$=13.6 Hz, H-5a), 6.13 (1H, t, $^3J$=6.5 Hz, H-1'), 5.29 (1H, bs, OH-3'), 5.13 (1H, bs, OH-5'), 4.24 (1H, m, H-3'), 3.79 (1H, m, H-4'), 3.66 (2H, m, H-5'), 2.51 (1H, m, H-2'), 2.14 (1H, m, H-2').

$^{13}$C-NMR (DMSO-$d_6$; 75 MHz): δ 40.2 (C-2'), 61.3 (C-5), 70.3 (C-4'), 84.8 (C-3'), 87.8 (C-1'), 108.9 (C-5b), 110.0 (C-5), 130.3 (C-5a), 149.6, 162.1 (C-2, C4).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-L-alaninyl)]-phosphate (CPF 1).**

**$C_{21}H_{25}BrN_3O_9P$, MW 574.32.**




This was synthesised according to ***Standard procedure 5***, using BVdU (300 mg, 0.90 mmol), Phenyl-(methoxy-L-alaninyl)-phosphorochloridate (472 mg, 1.7 mmol), NMI (4.5 mmol, 378 µL) in THF (9 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (356 mg, yield 69%).

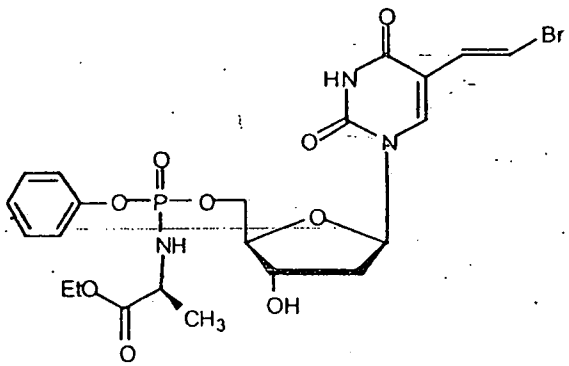
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.72, 4.40.

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.9 (1H, bs, H-3), 7.64 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, $^3J$=14 Hz, H-5b), 7.37-7.15 (5H, m, O*Ph*), 6.75-6.67 (1H, 2d, $^3J$=14 Hz, H-5a), 6.30-6.21 (1H, 2t, $^3J$=6 Hz, H1'), 4.57-4.29 (3H, m, H-5'+H-3'), 4.2-3.96 (3H, H-4', NH, CHala), 3.72 (3H, s, $CH_3O$), 2.49-2.40 (1H, m, one of H-2'), 2.12-2.01 (1H, m, one of H-2'), 1.38 (3H, d, $^3J$=7 Hz, $CH_{3\ ala}$).

$^{13}$C-NMR (DMSO; 75 MHz): δ 22.4 ($CH_{3\ ala}$), 41.9, 41.8 (C-2'), 51.9 (*CH*[$CH_3$]), 54.3 ($CH_3O$), 67.5 (C-5'), 72.3, 71.9 (C-3'), 87.3, 87.2, 86.9, 86.8 (C-1', C-4'), 110.6 (C-5b), 113.1 (C-5), 121.7 ('*o*', O*Ph*), 127.0 ('*p*', O*Ph*), 130.1 (C-5a), 131.5 ('*m*', O*Ph*), 139.2 (C-6), 150.9 ('*ipso*', O*Ph*) 151.9 (C-4), 163.2(C-2), 175.7 ($COOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(ethoxy-L-alaninyl)]-phosphate(CPF 3).**

**$C_{22}H_{27}BrN_3O_9P$, MW=588.34.**




This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), Phenyl-(ethoxy-L-alaninyl)-phosphorochloridate (249 mg, 0.9 mmol), NMI (2.8 mmol, 190 μL) in THF (4 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (145 mg, yield 55%).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.48, 4.86.

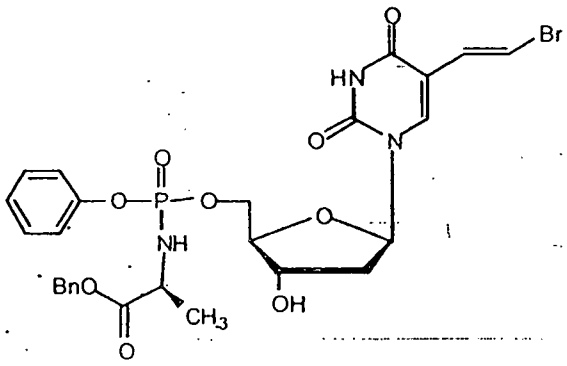
$^1$H-NMR ($CDCl_3$, 300 MHz): δ 7.65 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, $^3J$=13 Hz, H-5b), 7.35-7.10 (5H, m, O*Ph*), 6.78-6.65 (1H, 2d, $^3J$=13 Hz, H-5a), 6.35-6.25 (1H, 2t, $^3J$=6 Hz, H1'), 4.62-3.95 (8H, m, H-5', H-3', H-4', CHala, NH, $CH_3CH_2O$), 2.49-2.40 (1H, m, one

of H-2'), 2.10-2.00 (1H, m, one of H-2'), 1.40 (3H, d, $^3J$=7 Hz, $CH_{3\ ala}$), 1.25 (3H, 2t, $^3J$=7 Hz, $C\underline{H_3}CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($\underline{C}H_3CH_2O$) 21.2, 21.1 ($CH_3$ala), 40.9,40.7 (C-2'), 50.8, 50.7 (CHala), 62.2, 62.1 ($CH_3\underline{C}H_2O$), 66.5, 66.3 (C-5'), 70.9, 70.6 (C-3'), 86.0, 85.6 (C-1', C-4'), 110.1 (C-5b), 111.8 (C-5), 120.6 ('o', O*Ph*), 125.0 ('*p*', O*Ph*), 129.0 (C-5a), 130.2 ('*m*', O*Ph*), 138.2 (C-6), 149.9 (C-4), 150.7 ('*ipso*', O*Ph*), 162.3 (C-2), 174.2,174.1 ($\underline{C}OOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 2).**

**$C_{27}H_{29}BrN_3O_9P$, MW=649.08.**




This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), Phenyl-(benzyloxy-L-alaninyl)-phosphorochloridate (249 mg, 0.9 mmol), NMI (2.8 mmol, 190 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (228 mg, yield 78%).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.74, 4.44.

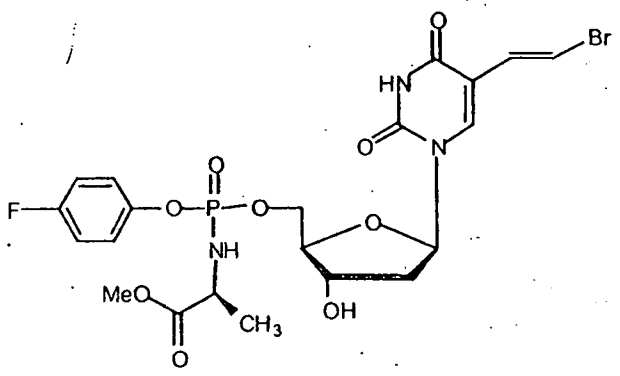
$^1$H-NMR ($CDCl_3$, 300 MHz): δ 10.31 (1H, bs, H-3), 7.63 (1H, 2xs, H-6), 7.45-7.14 (11H. m, O*Ph*+$CH_2$*Ph*, H-5b), 6.75-6.66 (1H, 2d, $^3J$=14 Hz, H-5a), 6.30-6.25 (1H, m, H-1'), 5.18-50.9 (1H, s, $C\underline{H_2}$Ph), 4.70-4.04 (6H, m, H-3', H-5',H-4', N*H*, CHala), 2.42 (1H, m, one of H-2'), 2.02 (1H, m, one of H-2'), 1.40 (3H, d, $^3J$=7 Hz, $CH_3$ala).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 20.7, 20.8 ($CH_3$ala), 40.4 (C-2'), 50.4 ($\underline{C}$Hala), 66.0 (C-5'), 67.4 ($\underline{C}H_2$Ph), 70.6 (C-3'), 85.4, 85.5, 85.6, 85.8 (C-1', C-4'), 109.9 (C-5b), 111.5 (C-5b),

120.2 ('o', O*Ph*), 125.4 ('*p*', O*Ph*), 128.5, 128.6, 129.9 ('*m*' OPh, Bn, C-5a), 135.1('*ipso*', $CH_2$*Ph*) 137.8 (C-6), 149.8 (C-4) 150.2 ('*ipso*', O*Ph*), 161.8 (C-2), 173.6 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(methoxy-L-alaninyl)]-phosphate** (CPF 5).

**$C_{21}H_{24}BrFN_3O_9P$, MW=592.31.**




This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (442 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (177 mg, yield 50%).

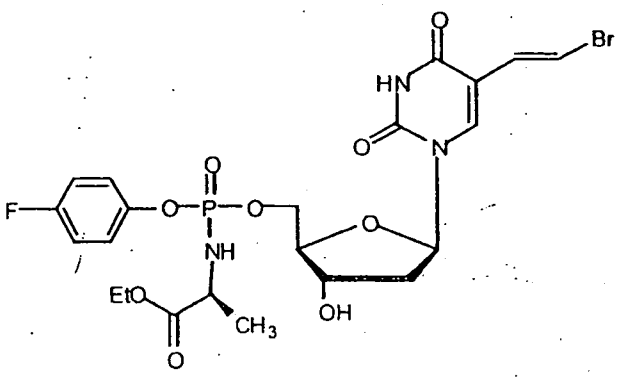
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.10, 4.81.

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 10.1 (1H, bs, H-3), 7.60 (1H, 2xs, H-6), 7.39-7.32 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.20-6.95 (4H, m, O*Ph*), 6.70-6.60 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.30-6.15 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.55-4.29 (3H, m, H-5'+H-3'), 4.15 (1H, NH), 4.05-3.85 (2H, H-4', CHala), 3.72 (3H, 2s, $CH_3O$), 2.49-2.32 (1H, m, one of H-2'), 2.15-2.05 (1H, m, one of H-2'), 1.35 (3H, 2d, $^{3}J$=6 Hz, $CH_{3\ ala}$).

$^{13}$C-NMR (DMSO; 75 MHz): δ 21.2 ($CH_{3\ ala}$), 40.8 (C-2'), 50.8, 50.6 (*CH*[$CH_3$]), 53.2 (*C*$H_3O$), 66.7, 66.3 (C-5'), 71.9, 71.8 (C-3'), 86.1, 85.7, 85.8 (C-1', C-4'), 110.3 (C-5b), 111.9 (C-5), 117.0, 116.7 ('*o*', O*Ph*), 122.0 ('*m*', O*Ph*), 128.2 (C-5a), 138.2 (C-6), 149.0 ('*ipso*', O*Ph*) 149.9 (C-4), 158.5 ('*p*', O*Ph*), 163.2(C-2), 175.1 (*C*O$OCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 6).**

**$C_{22}H_{26}BrFN_3O_9P$, MW=606.33.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(ethoxy-L-alaninyl)-phosphorochloridate (464 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (240 mg, yield 66%).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.14, 4.88.

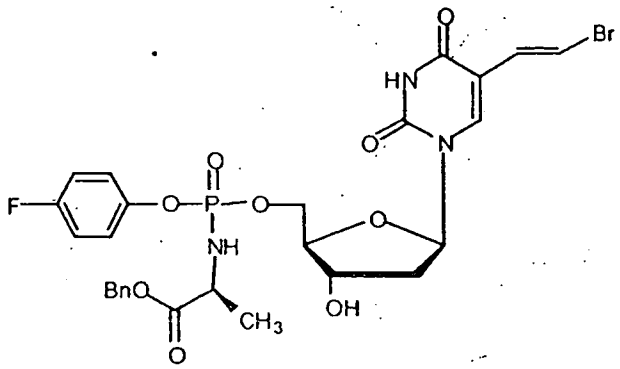
$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.25 (1H, bs, H-3), 7.85 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.3-7.0 (4H, m, O*Ph*), 6.8-6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.35-6.25 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.6-4.1 (6H, m, H-5', H-3', CHala, NH, $CH_3C\underline{H_2}O$), 4.02 (1H, m, H-4'), 2.55-2.45 (1H, m, one of H-2'), 2.20-2.10 (1H, m, one of H-2'), 1.40 (3H, d, $^{3}J$=8 Hz, $CH_{3\ ala}$), 1.25 (3H, 2t, $^{3}J$=7 Hz, $C\underline{H_3}CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($\underline{C}H_3CH_2O$) 21.3 ($CH_3$ala), 40.8,40.7 (C-2'), 50.8, 50.7 (CHala), 62.3 ($CH_3\underline{C}H_2O$), 66.7, 66.3 (C-5'), 71.1, 70.7 (C-3'), 86.1, 85.8, 85.6, 85.4 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 117.0 ('o', O*Ph*), 122.2 ('*m*', O*Ph*), 128.9 (C-5a), 138.2 (C-6), 146.4 ('*ipso*', O*Ph*), 149.9 (C-4), 158.5 ('*p*', O*Ph*), 162.2, 161.8 (C-2), 174.2 ($\underline{C}OOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 7).**



**$C_{27}H_{28}BrFN_3O_9P$, MW=668.40.**




This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(benzyloxy-L-alaninyl)-phosphorochloridate (556 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (256 mg, yield 64%).

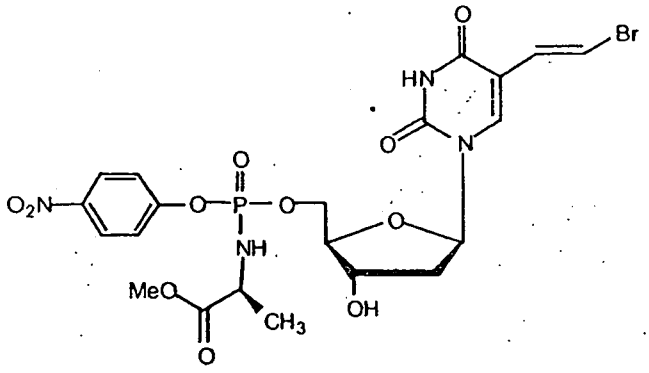
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.74, 4.44.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 7.69 (1H, 2xs, H-6), 7.45-7.39 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.37-7.00 (9H. m, O*Ph*+$CH_2$*Ph*), 6.75-6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.30-6.2 (1H, 2t, $^{3}J$=6Hz, H-1'), 5.2 (1H, 2s, C*H*$_2$Ph), 4.85-4.00 (6H, m, H-3',H-5',H-4', N*H*, CHala), 2.47 (1H, m, one of H-2'), 2.0-2.15 (1H, m, one of H-2'), 1.38 (3H, d, $^{3}J$=7 Hz, $CH_3$ala).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 21.2, 21.1 ($CH_3$ala), 40.7 (C-2'), 50.4 (*C*Hala), 66.7, 66.4 (C-5'), 67.8 (*C*$H_2$Ph), 71.1, 70.7 (C-3'), 86.0, 85.7, 85.4, 85.3 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 117.0 ('o', O*Ph*), 122.0 ('*m*', O*Ph*), 128.7, 128.6 (Bn, C-5a), 135.4(*'ipso'*, $CH_2$*Ph*) 138.2 (C-6), 146.5 (*'ipso'*, O*Ph*), 149.9 (C-4), 158.5 (*'p'* OPh), 162.2 (C-2), 173.9 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(methoxy-L-alaninyl)]-phosphate (CPF 10).**

**$C_{21}H_{24}BrN_4O_{11}P$, MW=619.31.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(methoxy-L-alaninyl)-phosphorochloridate (483 mg, 1.5 mmol), NMI (4.98 mmol, 332 μL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (211 mg, yield 57%).

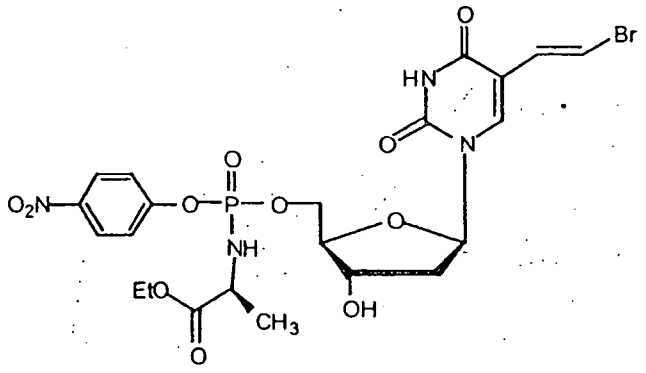
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.95.

$^{1}$H-NMR (MeOD; 300 MHz): δ 8.3-8.2 (2H, m, O*Ph*) 7.8-7.75 (1H, 2xs, H-6), 7.35-7.30, 7.55-7.4 (2H, m, O*Ph*), 7.35-7.30 (1H, 2d, $^{3}J$=14 Hz, H-5b), 6.80-6.70 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.30-6.2 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.5-4.3 (3H, m, H-5',H-3'), 4.2-4.0 (2H, m, H-4', CHala), 3.72 (3H, 2s, $CH_3O$), 2.35-2.15 (2H, m, 2 H-2'), 1.35 (3H, 2d, $^{3}J$=7Hz, $CH_{3\ ala}$).

$^{13}$C-NMR (DMSO; 75 MHz): δ 20.9 ($CH_{3\ ala}$), 41.6, 41.5 (C-2'), 52.0, 51.9 (*CH*[$CH_3$]), 53.4 (*C*$H_3$O), 68.5 (C-5'), 72.4, 72.3 (C-3'), 87.7, 87.4, 87.0, 86.9 (C-1', C-4'), 109.8 (C-5b), 112.8 (C-5), 122.6 (*'o'*, O*Ph*), 127.1 (*'m'*, O*Ph*), 130.8 (C-5a), 140.3 (C-6), 146.5 (*'ipso'*, O*Ph*), 151.4 (C-4), 157.2 (*'p'*, O*Ph*), 163.9 (C-2), 175.8,175.5 (*C*$OOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 9).**

**$C_{22}H_{26}BrN_4O_{11}P$, MW=633.34.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(ethoxy-L-alaninyl)-phosphorochloridate (504 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 1 hr. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (232 mg, yield: 61%).

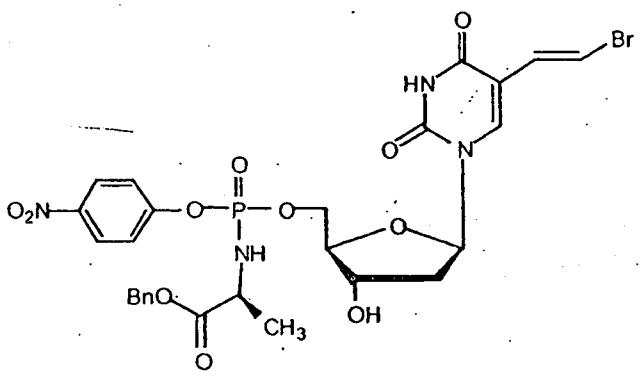
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.28.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.25 (1H, bs, H-3), 8.25-8.2 (2H, 2d, $^{3}J$=9Hz O*Ph*), 7.7 (1H, 2xs, H-6), 7.5-7.45 (2H, 2d , $^{3}J$=9Hz, O*Ph*), 7.4-7.35 (1H, 2d, $^{3}J$=14 Hz, H-5b), 6.7-6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.3-6.2 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.8-4.1 (7H, m, H-5', H-4' H-3', CHala, NH, $CH_3CH_2O$), 2.45-2.4 (1H, m, one of H-2'), 2.20-2.10 (1H, m, one of H-2'), 1.40 (3H, d, $^{3}J$=8 Hz, $CH_{3\ ala}$), 1.3 (3H, 2t, $^{3}J$=7 Hz, $CH_3CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($CH_3CH_2O$) 21.1 ($CH_3$ala), 40.6 (C-2'), 50.8, 50.7 (CHala), 62.5 ($CH_3CH_2O$), 66.9, 66.8 (C-5'), 71.2, 70.9 (C-3'), 86.3, 85.9, 85.4, 85.3 (C-1', C-4'), 110.3 (C-5b), 111.8 (C-5), 121.3 ('*o*', O*Ph*), 126.1 ('*m*', O*Ph*), 128.8 (C-5a), 138.4 (C-6), 145.1 ('*ipso*', O*Ph*), 149.9 (C-4), 155.5 ('*p*', O*Ph*), 162.3 (C-2), 174.0, 173.9 ($COOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(benzoxy-L-alaninyl)]-phosphate** (CPF 8).

**$C_{27}H_{28}BrN_4O_{11}P$, MW=695.41.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(benzyloxy-L-alaninyl)-phosphorochloridate (597 mg, 1.5 mmol), NMI (4.98 mmol, 332 μL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (228 mg, yield 55%).

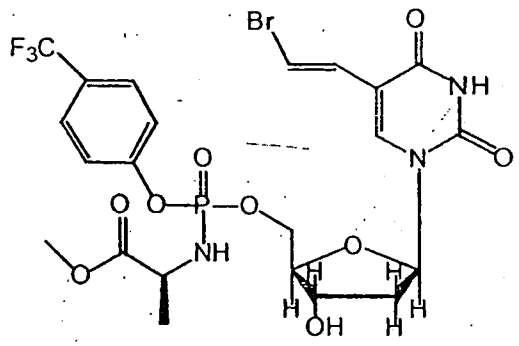
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.74, 4.44.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.4-10.3 (1H, bs, H-3), 8.2-8.1 (2H, m, O*Ph*), 7.69 (1H, 2xs, H-6), 7.4-7.2 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.37-7.00 (7H. m, O*Ph*+$CH_2$*Ph*), 6.75-6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.25-6.15 (1H, 2t, $^{3}J$=6Hz, H-1'), 5.2 (1H, d, C*H*$_2$Ph), 4.87 (1H, m, H-3'), 4.6-4.2 (3H, m, H-5', CHala) 4.2-4.00 (2H, m, H-4', N*H*$_2$), 2.55-2.45 (1H, m, one of H-2'), 2.2-2.05 (1H, m, one of H-2'), 1.38 (3H, d, $^{3}J$=7 Hz, $CH_3$ala).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 21.2, 21.1 ($CH_3$ala), 40.6 (C-2'), 50.9 (*C*Hala), 67.1, 67.0 (C-5'), 68.0 (*C*$H_2$Ph), 71.3, 70.9 (C-3'), 86.3, 86.0, 85.3, 85.2 (C-1', C-4'), 110.4 (C-5b), 111.9, 111.8 (C-5), 121.3 ('o', O*Ph*), 126.2-126.1 ('*m*', O*Ph*), 129.1, 128.7, 128.6 (Bn, C-5a), 135.4 ('*ipso*', $CH_2$*Ph*), 138.3 (C-6), 145.1 ('*ipso*', O*Ph*), 149.9 (C-4), 155.6 ('*p*' OPh), 162.2 (C-2), 173.8,173.7 (*C*OOBn).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[*para*-(trifluoromethyl)-phenyl-(methoxy-L-alaninyl)]-phosphate (CPF 15).**

**$C_{22}H_{24}BrF_3N_3O_9$, MW=642.31.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), phenyl-(methoxy-L-alaninyl)-phosphorochloridate (518.8 mg, 1.5 mmol), NMI (246.3 mg, 3.0 mmol, 239 μL) in THF (5 mL) for 4 hrs. The crude product was purified by column chromatography, eluting with chloroform/methanol 97:3 to give the pure product as a white foamy solid (211.1 mg, yield 54.7%).

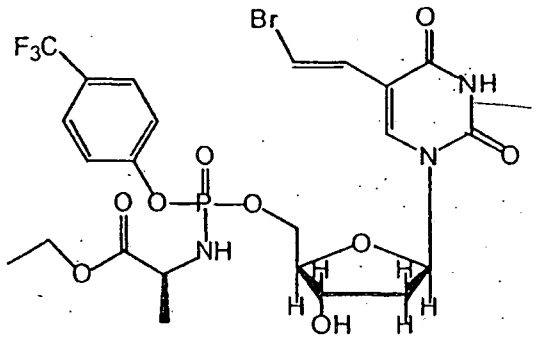
$^{31}$P-NMR (MeOD, 121 MHz): δ 5.23, 5.07.

$^{1}$H-NMR (MeOD, 300 MHz): δ 7.80 (1H, s, H-6), 7.70 (2H, d, $^{3}J$=8.7 Hz, O*Ph*), 7.47-7.42 (2H, m, O*Ph*), 7.37 (1H, d, $^{3}J$=13.6 Hz, H-5b), 6.82-6.78 (1H, d, $^{3}J$=13.6 Hz, H-5a), 6.30-6.23 (1H, m, H-1'), 4.52-4.29 (3H, m, H-3'+H-5'), 4.17-4.13 (1H, m, H-4'), 4.05-3.91 (1H, m, C*H*CH$_3$), 3.67 (3H, s, OC*H*$_3$), 2.35-2.32 (1H, m, one of H-2'), 2.23-2.16 (1H, m, one of H-2'), 1.37-1.34 (3H, d, $^{3}J$=7.1 Hz, CH*CH*$_3$).

$^{13}$C-NMR (MeOD, 75 MHz): δ 20.6, 20.7, 20.8, 20.9 (CH*C*H$_3$), 41.5, 41.7 (C-2'), 51.9, 52.0 (*C*HCH$_3$), 68.2, 68.3 (C-5'), 72.4, 72.5 (C-3'), 87.1, 87.2, 87.4, 87.6 (C-1', C-4'), 109.7 (C-5b), 112.6 (C-5), 122.5, 122.7 (*'o'*, O*Ph*), 125.8 (*C*F$_3$, *J*=269 Hz), 128.7 (*'m'*, O*Ph*), 128.8 (*'p'*, *J*=33 Hz, O*Ph*), 130.9 (C-5a), 140.3 (C-6), 151.4, 151.5 (*'ipso'*, O*Ph*), 155.1, 155.2 (C-4), 164.0 (C-2), 175.6, 175.9, (*C*OOCH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[*para*-(trifluoromethyl)-phenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 25).**

**$C_{23}H_{26}BrF_3N_3O_9P$, MW=656.34**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), phenyl-(ethoxy-L-alaninyl)-phosphorochloridate (539.5 mg, 1.5 mmol), NMI (246.3 mg, 3.0 mmol, 239 µL) in THF (5 mL) for 20 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 95:5 to give the pure product as a white foamy solid (172.6 mg, yield 43.8%).

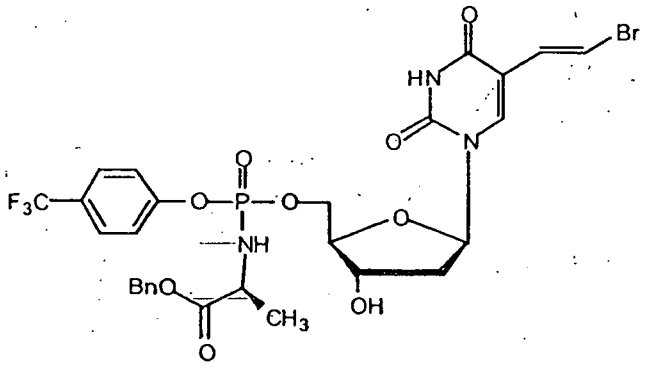
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.65, 4.35.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.05 (1H, s, H-3), 7.69-7.64 (3H, m, H-6+O*Ph*), 7.46-7.39 (3H, m, O*Ph*+ H-5b), 6.76-6.68 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.34-6.25 (1H, m, H-1'), 4.57-4.35 (4H, m, H-3'+H-5'+N*H*), 4.27-4.13 (4H, m, H-4'+OC*H*$_2$CH$_3$+OH-3'), 4.12-3.98 (1H, m, C*H*CH$_3$), 2.53-2.47 (1H, m, one of H-2'), 2.21-2.12 (1H, m, one of H-2'), 1.43-1.40 (3H, d, $^{3}J$=7.0 Hz, CH*CH*$_3$), 1.28, 1.27 (3H, 2t, $^{3}J$=7.0 Hz, OCH$_2$C*H*$_3$)

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 (*C*H$_3$CH$_2$O), 21.2, 21.3 (CH*C*H$_3$), 40.7 (C-2'), 50.8, 50.9 (*C*HCH$_3$), 62.4 (CH$_3$*C*H$_2$O), 66.3, 66.7 (C-5'), 70.7, 71.1 (C-3'), 85.3, 85.4, 85.8, 86.1 (C-1', C-4'), 110.5 (C-5b), 112.0 (C-5), 122.0 (*'o'*, O*Ph*), 124.2 (*C*F$_3$, $J$=271 Hz), 127.7, 127.8, 128.7 (*'m'*, *'p'*, O*Ph*), 128.8 (C-5a), 138.0 (C6), 149.7 (*'ipso'*, O*Ph*), 153.2 (C-4), 161.9 (C-2), 174.0, 174.1 (*C*OOCH$_2$CH$_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 4).**

**$C_{28}H_{28}BrF_3N_3O_9P$, MW=718.41.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-trifluorophenyl-(benzyloxy-L-alaninyl)-phosphorochloridate (632 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (6 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (308 mg, yield 71%).

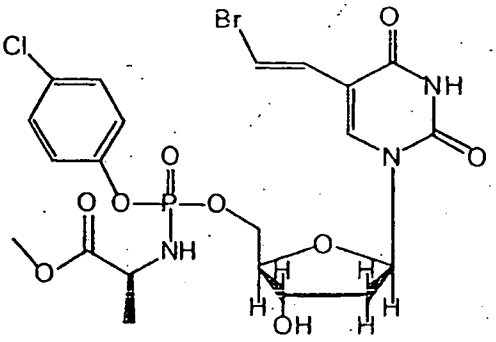
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.31, 4.87.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.05 (1H, bs, H-3), 7.7, 7.25 (11H. m, H-5b, H-6 O*Ph*+$CH_2$*Ph*), 6.75-6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.35-6.2 (1H, 2t, $^{3}J$=6Hz, H-1'), 5.15 (1H, 2s, C*H*$_2$Ph), 4.6-4.25 (4H, m, H-5', H-3', CHala) 4.2-4.00 (2H, m, H-4', N*H*$_2$), 2.55-2.4 (1H, m, one of H-2'), 2.2-2.05 (1H, m, one of H-2'), 1.38 (3H, d, $^{3}J$=7 Hz, $CH_3$ala).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 21.2, 21.1 ($CH_3$ala), 40.7 (C-2'), 50.9, 50.8 (*C*Hala), 67.1, 67.0 (C-5'), 68.0 (*C*$H_2$Ph), 71.2, 70.9 (C-3'), 86.1, 85.8, 85.5, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.9, 111.8 (C-5), 121.1 ('*o*', O*Ph*), 125.1 (d, J=270Hz, $CF_3$), 127.6 ('*m*', O*Ph*), 129.1, 128.7, 128.6 (Bn, C-5a), 130.1 ('*p*',q , J=32Hz, O*Ph*) 135.4 ('*ipso*', $CH_2$*Ph*) 138.2 (C-6), 150.2, 150.1 (C-4), 153.6 ('*ipso*' OPh), 162.7 (C-2), 173.9, 173.6 (*C*OOBn).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(methoxy-L-alaninyl)]-phosphate (CPF 13).**

**$C_{21}H_{24}BrClN_3O_9P$, MW=608.76.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), 4-chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (374.5 mg, 1.2 mmol), NMI (246.3 mg, 3.0 mmol, 239 µL) in THF (8 mL) for 5 hrs. The crude product was purified by column chromatography, eluting with Chloroform/Methanol 97:3 to give the pure product as a white foamy solid (139.0 mg, yield 38.0%).

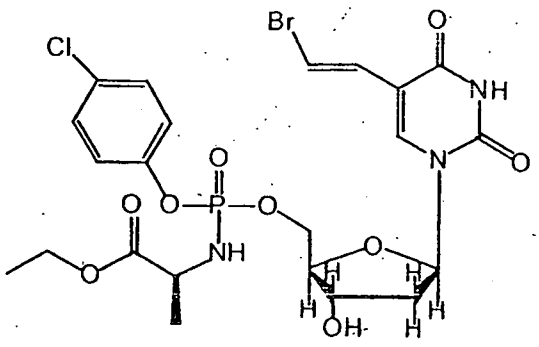
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.81, 4.54.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.11 (1H, bs, H-3), 7.68 (1H, s, H-6), 7.46-7.40 (1H, d, $^{3}J$=13.6 Hz, H-5b), 7.35-7.20 (4H, m, O*Ph*), 6.76-6.67 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.34-6.24 (1H, m, H-1'), 4.58-4.40 (5H, m, H-3'+H-5'+N*H*), 4.36-4.19 (1H, m, H-4'), 4.07-3.99 (1H, m, C*H*CH$_3$), 3.75 (3H, s, OC*H*$_3$), 2.49-2.48 (1H, m, one of H-2'), 2.17-2.15 (1H, m, one of H-2'), 1.42-1.39 (3H, d, $^{3}J$=7.0 Hz, CHC*H*$_3$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 21.2 (CH*C*H$_3$), 40.7, 40.8 (C-2'), 50.6, 50.8 (*C*HCH$_3$), 53.2, 53.3 ($OCH_3$), 66.4, 66.7 (C-5'), 70.8, 71.2 (C-3'), 85.4, 85.5, 85.8, 86.2 (C-1', C-4'), 110.5 (C-5b), 111.9, 112.0 (C-5), 122.0 (*'o'*, O*Ph*), 128.9 (C-5a), 130.3 (*'m'*, O*Ph*), 131.1 (*'p'*, O*Ph*), 138.2 (C-6), 149.1, 149.2 (*'ipso'*, O*Ph*), 149.8 (C-4), 162.1, 162.2 (C-2), 174.5, 174.6 (*C*OOCH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 11).**

$C_{22}H_{26}BrN_3O_9P$, MW=622.79.



This was synthesised according to ***Standard procedure 5***, using BVdU (300 mg, 0.90 mmol), 4-chlorophenyl-(ethoxy-L-alaninyl)-phosphorochloridate (557.7 mg, 1.71 mmol), NMI (221.7 mg, 2.7 mmol, 215 µL) in THF (10 mL) for 16 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (168.4 mg, yield 30.0%).

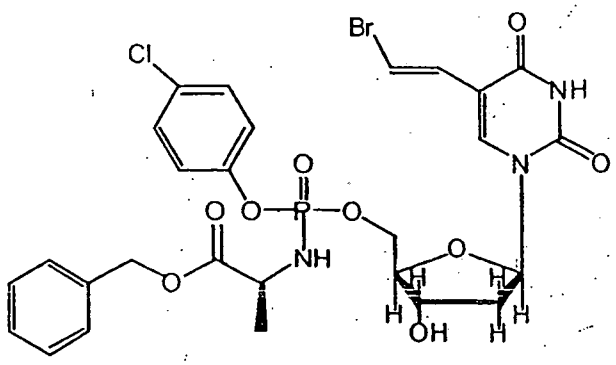
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.88, 4.65.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 9.51 (1H, bs, H-3), 7.69-7.68 (1H, 2s, H-6), 7.49-7.43 (1H, 2d, $^{3}J$=13.6 Hz, H-5b), 7.37-7.22 (4H, m, O*Ph*), 6.79-6.71 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.33-6.24 (1H, m, H-1'), 4.62-4.34 (3H, m, H-3'+H-5'), 4.28-3.89 (5H, m, H-4'+OC*H*$_2$CH$_3$+C*H*CH$_3$+N*H*), 2.59-2.45 (1H, m, one of H-2'), 2.22-2.14 (1H, m, one of H-2'), 1.43-1.41 (3H, d, $^{3}J$=7.0 Hz, CH*CH*$_3$), 1.33-1.28 (3H, 2t, $^{3}J$=7.2 Hz, OCH$_2$C*H*$_3$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 (*C*H$_3$CH$_2$O), 21.2, 21.3 (CH*C*H$_3$), 40.7 (C-2'), 50.7, 50.8 (*C*HCH$_3$), 62.4 (CH$_3$*C*H$_2$O), 66.7 (C-5'), 70.8, 71.2 (C-3'), 85.4, 85.8, 86.1 (C-1', C-4'), 110.4 (C-5b), 112.0 (C-5), 122.0, 122.1 (*'o'*, O*Ph*), 128.9 (C-5a), 130.3 (*'m'*, O*Ph*), 131.1 (*'p'*, O*Ph*), 138.2 (C-6), 149.2 (*'ipso'*, O*Ph*), 150.0 (C-4), 162.2 (C-2), 174.1, 174.2 (*C*OOCH$_2$CH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 12).**

**$C_{22}H_{26}BrN_3O_9P$, MW=622.79.**



This was synthesised according to ***Standard procedure 5***, using BVdU (300 mg, 0.90 mmol), 4-chlorophenyl-(benzoxy-L-alaninyl)-phosphorochloridate (698.7 mg, 1.80 mmol), NMI (369.5 mg, 4.5 mmol, 358.7 µL) in THF (10 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 95:5 to give the pure product as a white foamy solid (310.0 mg, yield 50.3%).

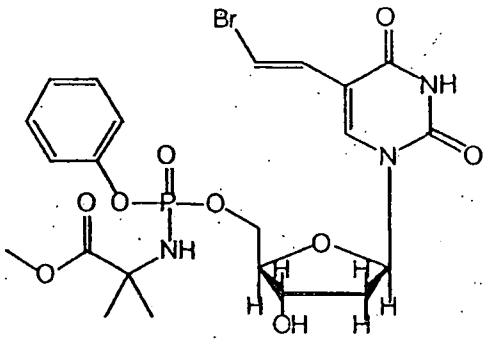
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.81, 4.53.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.10 (1H, bs, H-3), 7.65-7.63 (1H, 2s, H-6), 7.69-7.68 (1H, 2s, H-6), 7.46, 7.41 (1H, 2d, $^{3}J$=13.6 Hz, H-5b), 7.40-7.17 (9H, m, O*Ph*), 6.75-6.66 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.33-6.23 (1H, 2t, $^{3}J$=6.0 Hz, H-1'), 5.17 (2H, s, C*H*$_2$Ph), 4.60-4.23 (4H, m, H-3'+H-5'+N*H*), 4.20-3.97 (2H, m, H-4'+ C*H*CH$_3$), 2.48-2.44 (1H, m, one of H-2'), 2.15-2.05 (1H, m, one of H-2'), 1.43-1.40 (3H, d, $^{3}J$=7.0 Hz, CH*CH*$_3$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 21.2 (CH*C*H$_3$), 40.7 (C-2'), 50.8, 50.9 (*C*HCH$_3$), 66.6 (C-5'), 67.9 (*C*H$_2$Ph), 70.7, 71.1 (C-3'), 85.4, 85.5, 85.8, 86.1 (C-1', C-4'), 110.5 (C-5b), 111.9, 112.0 (C-5), 122.0, (*'o'*, O*Ph*), 128.7, 129.0, 129.1, 130.3 (*'m'*, O*Ph*+C-5a), 131.1 (*'ipso'*, CH$_2$*Ph*), 135.4 (*'p'*, O*Ph*), 138.2 (C-6), 149.1 (*'ipso'*, O*Ph*), 150.0 (C-4), 162.1 (C-2), 173.9, 174.0 (*C*OOCH$_2$Ph).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-α,α-dimethylglycinyl)]-phosphate (CPF 26).**

**$C_{22}H_{27}BrN_3O_9P$, MW 588.34**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), phenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate (437.5 mg, 1.5 mmol), NMI (246.3 mg, 3.0 mmol, 239.1 µL) in THF (5 mL) for 4 hrs. The crude product was purified by column chromatography, eluting with chloroform/methanol 97:3 to give the pure product as a white foamy solid (117 mg, yield 33.1%).

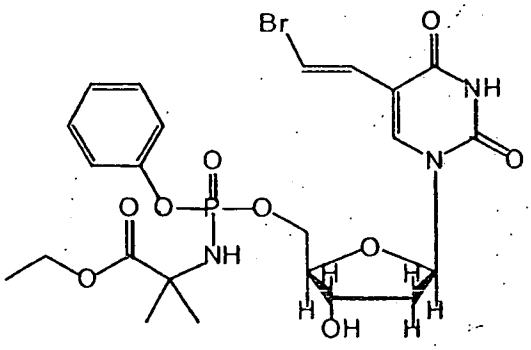
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.36, 3.14

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 9.91 (1H, bs, H-3), 7.73,7.65 (1H, 2s, H-6), 7.50-7.43 (1H, 2d, $^{3}J$=13.6 Hz, H-5b), 7.41-7.02 (5H, m, O*Ph*), 6.81-6.71 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.34-6.28 (1H, m, H1'), 4.55-4.17 (6H, m, H-5'+H-4'+H-3', NH, OH-3'), 3.78 (3H, s, C*H*$_3$O), 2.53-2.39 (1H, m, one of H-2'), 2.25-1.99 (1H, m, one of H-2'), 1.60 (6H, s, [C*H*$_3$]$_2$C).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 27.5, 27.4, 27.2 ([*C*H$_3$]$_2$C), 40.7, 40.6 (C-2'), 53.5 (*C*H$_3$O), 57.6 (*C*[CH$_3$]$_2$), 66.5, 66.2 (C-5'), 70.7, 71.1 (C-3'), 85.4, 85.6, 85.5, 85.9 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 120.5, 120.6 (*'o'*, O*Ph*), 125.7 (*'p'*, O*Ph*), 128.9 (C-5a), 130.3 (*'m'*, O*Ph*), 138.0, 138.3 (C-6), 149.8 (*'ipso'*, O*Ph*) 150.9, 150.8 (C-4), 162.0, 162.1 (C-2), 176.4, 176.2 (*C*OOCH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[phenyl-(ethoxy-α,α-dimethylglycinyl)]-phosphate (CPF 27).**

**$C_{23}H_{29}BrN_3O_9P$, MW=602.37**




This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), phenyl-(ethyl-2-amino-2-methylpropanoate)-phosphorochloridate (458.0 mg, 1.5 mmol), NMI (246.3 mg, 3.0 mmol, 239.1 μL) in THF (5 mL) for 5 hrs. The crude product was purified by column chromatography, eluting with chloroform/methanol 97:3 to give the pure product as a white foamy solid (106 mg, yield 29.3%).

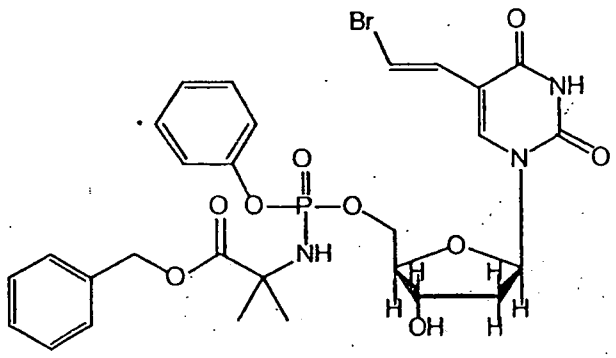
$^{31}$P-NMR (MeOD, 121 MHz): δ 3.91, 3.85

$^{1}$H-NMR (MeOD, 300 MHz): δ 7.84, 7.81 (1H, 2s, H-6), 7.44-7.20 (6H, m, O*Ph*+H-5b), 6.88-6.81 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.34-6.28 (1H, m, H-1'), 4.50-4.34 (3H, m, H-5'+H-3'), 4.23-4.15 (3H, m, H-4'+$CH_3CH_2O$), 2.38-2.28 (1H, m, one of H-2'), 2.22-2.09 (1H, m, one of H-2'), 1.51 (6H, s, $[CH_3]_2C$), 1.29 (3H, t, $^{3}J$=7 Hz, $CH_3CH_2O$)

$^{13}$C-NMR (MeOD, 75 MHz): δ 14.9 ($CH_3CH_2O$) 27.9, 28.3 ($[CH_3]_2C$), 41.5 (C-2'), 58.51 ($C[CH_3]_2$), 63.1 ($CH_3CH_2O$), 68.2 (C-5'), 72.6 (C-3'), 87.1, 87.4 (C-1', C-4'), 109.6 (C-5b), 112.7 (C-5b), 122.0, 122.1, 122.2, ('o', O*Ph*), 126.7 ('*p*', O*Ph*), 131.0, 131.2 (C-5a, *'m'* O*Ph*), 140.4 (C-6), 151.4 (*'ipso'*, O*Ph*) 152.5 (C-4), 164.0 (C-2), 177.2 ($COOCH_2CH_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy-α,α-dimethylglycinyl)]-phosphate (CPF 14).**

**$C_{28}H_{31}BrN_3O_9P$, MW=664.44.**



This was synthesised according to ***Standard procedure 5***, using BVdU (242 mg, 0.73 mmol), phenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate (533.0 mg, 2.0 mmol), NMI (298.0 mg, 3.63 mmol, 289 µL) in THF (5 mL) for 4 hrs. The crude product was purified by column chromatography, eluting with chloroform/methanol 97:3 to give the pure product as a white foamy solid (129.0 mg, yield 26.7%).

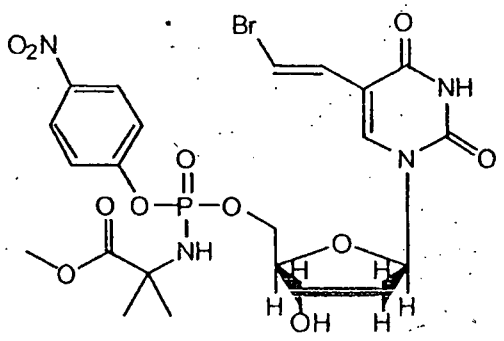
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.39, 3.12.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 9.92 (1H, bs, H-3), 7.67-7.60 (1H, 2s, H-6), 7.48-7.41 (1H, 2d, $^{3}J$=13.6 Hz, H-5b), 7.40-7.16 (10H. m, O*Ph*+$CH_2$*Ph*), 6.78-6.67 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.31-6.25 (1H, m, H-1'), 5.18 (1H, s, C*H*$_2$Ph), 4.50-4.09 (6H, m, H-3'+H-5'+H-4', N*H*, OH-3'), 2.48-2.25 (1H, m, one of H-2'), 2.16-1.82 (1H, m, one of H-2'), 1.60 (6H, s, [C*H*$_3$]$_2$C).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 27.3, 27.4, 28.5 ([*C*H$_3$]$_2$C), 40.6, 40.7 (C-2'), 57.6, 57.6 (*C*[$CH_3$]$_2$), 66.2, 66.5 (C-5'), 68.1 (*C*H$_2$Ph), 70.6, 71.1 (C-3'), 85.4, 85.5, 85.6, 85.8 (C-1', C-4'), 110.4 (C-5b), 112.0 (C-5), 120.4, 120.5, 120.6, 125.7, 128.4, 128.5, 128.8, 128.9, 130.3 (O*Ph*, C-5a), 135.7(*'ipso'*, $CH_2$*Ph*) 138.1, 138.3 (C-6), 149.8, 150.8, 150.9 (*'ipso'* O*Ph*, C-4), 162.1 (C-2), 177.5, 175.7 (*C*OOCH$_2$Ph).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-nitrophenyl-(methoxy-α,α-dimethylglycinyl)]-phosphate (CPF 45).**

**$C_{22}H_{26}BrN_4O_{11}P$, MW=633.34.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), 4-nitrophenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate (378.8 mg, 1.13 mmol), NMI (184.7 mg, 2.25 mmol, 179.4 µL) in THF (5 mL) for 3 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (145.7 mg, yield 50.9 %).

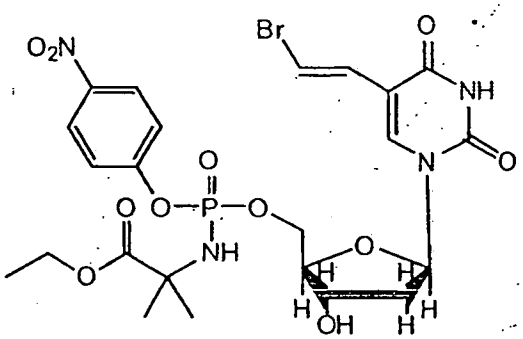
$^{31}$P-NMR (MeOD, 121 MHz): δ 3.61, 3.56.

$^{1}$H-NMR (MeOD, 300 MHz): δ 8.30-8.25 (2H, 2d, $^{3}J$=9.0 Hz, O*Ph*), 7.79-7.78 (1H, 2s, H-6), 7.49-7.46 (2H, d, $^{3}J$=9.0 Hz, O*Ph*), 7.37-7.32 (1H, 2d, $^{3}J$=13.6 Hz, H-5b), 6.79-6.72 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.32-6.25 (1H, m, H-1'), 4.48-4.35 (3H, m, H-3'+H-5'), 4.15-4.14 (1H, m, H-4'), 3.71 (3H, s, C*H*$_3$O), 2.41-2.17 (2H, m, H-2'), 1.51 (6H, s, [C*H*$_3$]$_2$C).

$^{3}$C-NMR ($CDCl_3$, 75 MHz): δ 28.0, 28.1, 28.2, 28.3 ([*C*H$_3$]$_2$C), 41.4, 41.5 (C-2'), 53.6 (*C*H$_3$O), 58.7 (*C*[CH$_3$]$_2$), 68.5 (C-5'), 72.3, 72.4 (C-3'), 86.9, 87.0, 87.4, 87.5 (C-1', C-4'), 109.7 (C-5b), 112.6 (C-5), 122.8, 122.9 ('*o*', O*Ph*), 127.0 ('*m*', O*Ph*), 130.9 (C-5a), 140.5 (C-6), 146.5 ('*p*', O*Ph*), 151.5 ('*ipso*', O*Ph*), 157.3 (C-4), 164.0 (C-2), 177.5 (*C*OOCH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-nitrophenyl-(ethoxy-α,α-dimethylglycinyl)]-phosphate (CPF 46).**

**$C_{23}H_{28}BrN_4O_{11}P$, MW=647.3.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), 4-nitrophenyl-(ethyl-2-amino-2-methylpropanoate)-phosphorochloridate (442.1 mg, 1.26 mmol), NMI (184.7 mg, 2.25 mmol, 179.4 µL) in THF (5 mL) for 4 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (152.9 mg, yield 52.5 %).

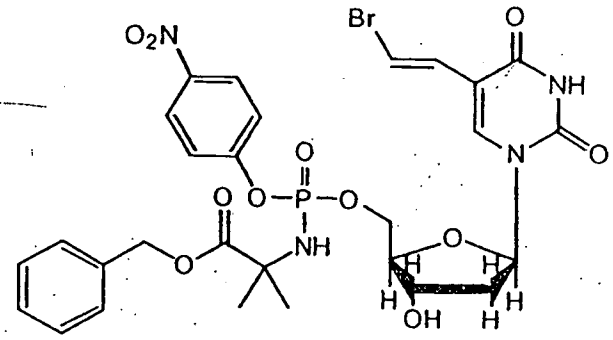
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.00, 2.96.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.28 (1H, bs, H-3), 8.25.-8.12 (2H, 2d, $^{3}J$=9.0 Hz, O*Ph*), 7.68-7.67 (1H, 2s, H-6), 7.46-7.32 (3H, m, O*Ph*+H-5b), 6.69-6.67 (1H, 2d, $^{3}J$=13.5 Hz, H-5a), 6.32-6.26 (1H, m, H-1'), 4.75-4.36 (5H, m, H-3'+H-5'+OH-3'+N*H*), 4.25-4.17 (3H, m, OC*H*$_2$CH$_3$, H-4'), 2.60-2.98 (1H, m, one of H-2'), 2.31-2.10 (1H, m, one of H-2'), 1.58 (6H, s, [C*H*$_3$]$_2$C), 1.30-1.28 (3H, 2t, $^{3}J$=7.1 Hz, OCH$_2$C*H*$_3$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 (*C*H$_3$CH$_2$O), 27.1, 27.2, 27.3, 27.4 ([*C*H$_3$]$_2$C), 40.6 (C-2'), 57.7 (*C*[CH$_3$]$_2$), 62.7 (CH$_3$*C*H$_2$O), 67.0 (C-5'), 71.0, 71.2 (C-3'), 85.4, 85.9, 86.1 (C-1', C-4'), 110.3 (C-5b), 111.9 (C-5), 121.2, 121.3 (*'o'*, O*Ph*), 126.2 (*'m'*, O*Ph*), 128.8 (C-5a), 138.4 (C-6), 145.0 (*'p'*, O*Ph*), 150.0 (C-4), 155.7-155.9 (*'ipso'*, O*Ph*), 162.2 (C-2), 175.0-175.1 (*C*OOCH$_2$CH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-nitrophenyl-(benzoxy-α,α-dimethylglycinyl)]-phosphate (CPF 47).**

**$C_{28}H_{30}BrN_4O_{11}P$, MW=709.44**



This was synthesised according to ***Standard procedure 5***, using BVdU (100 mg, 0.30 mmol), 4-nitrophenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate (309.6 mg, 1.07 mmol), NMI (123.7 mg, 1.5 mmol, 120.1 μL) in THF (5 mL) for 5 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (160.2 mg, yield 50.2 %).

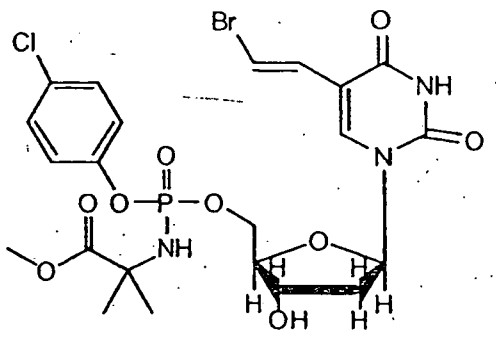
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 2.95, 2.89.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.16 (1H, bs, H-3), 8.26-8.24 (2H, 2d, $^{3}J$=9.1 Hz, O*Ph*), 7.71-7.69 (1H, 2s, H-6), 7.48-7.37 (8H, m, O*Ph*+$CH_2$*Ph*, H-5b), 6.75-6.72 (1H, 2d, $^{3}J$=13.5 Hz, H-5a), 6.36-6.29 (1H, m, H-1'), 5.24 (2H, s, C*H*$_2$Ph), 4.81-4.40 (5H, m, H-3'+H-5'+OH-3', N*H*), 4.22-4.21 (1H, m, H-4'), 2.57-2.36 (1H, m, one of H-2'), 2.27-2.22 (1H, m, one of H-2'), 1.64 (6H, s, [C*H*$_3$]$_2$C).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 27.4 ([*C*H$_3$]$_2$C), 40.6 (C-2'), 57.8 (*C*[CH$_3$]$_2$), 67.0 (C-5'), 68.2 (*CH*$_2$Ph), 71.1, 71.2 (C-3'), 85.3, 86.2 (C-1', C-4'), 110.5 (C-5b), 111.9 (C-5), 121.2, 126.2, 128.5, 128.8, 129.0, 129.1 (*'o'*, *'m'*, *'p'*, $CH_2$*Ph*+O*Ph*+C-5a), 135.5 (*'ipso'*, $CH_2$*Ph*), (C-5a), 138.4 (C-6), 145.0 (*'p'*, O*Ph*), 150.0 (C-4), 155.7 (*'ipso'*, O*Ph*), 162.2 (C-2), 175.4-175.5 (*C*OOCH$_2$Ph).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(methoxy-α,α-dimethylglycinyl)]-phosphate (CPF 42).**

**$C_{22}H_{26}BrClN_3O_9P$, MW=622.79.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), 4-chlorophenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate (440.2 mg, 1.35 mmol), NMI (184.7 mg, 2.25 mmol, 179.4 µL) in THF (5 mL) for 6 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (146.7 mg, yield 56.5 %).

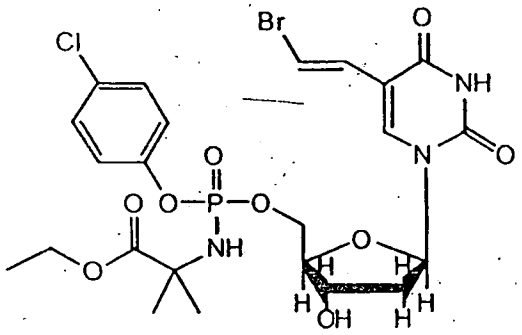
$^{31}$P-NMR (MeOD, 121 MHz): δ 3.98 (s).

$^{1}$H-NMR (MeOD, 300 MHz): δ), 7.71-7.69 (1H, 2s, H-6), 7.31-7.13 (5H, m, O*Ph*+H-5b), 6.73-6.66 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.23-6.16 (1H, m, H-1'), 4.39-4.22 (3H, m, H-3'+H-5'), 4.05-4.03 (1H, m, H-4'), 3.61 (3H, s, C*H*$_3$O), 2.29-2.19 (1H, m, one of H-2'), 2.15-2.05 (1H, m, one of H-2'), 1.38 (6H, s, [C*H*$_3$]$_2$C).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 28.0, 28.2, 28.3, 28.4 ([*C*H$_3$]$_2$C), 41.5, 41.6 (C-2'), 53.5, 53.6 (*C*H$_3$O), 58.6 (*C*[CH$_3$]$_2$), 68.2 (C-5'), 72.4, 72.5 (C-3'), 87.1, 87.2, 87.3, 87.4 (C-1', C-4'), 109.7 (C-5b), 112.7 (C-5), 123.7, 123.8 (*'o'*, O*Ph*), 130.9, 131.1 (*'m'*, O*Ph*+C-5a), 131.9 (*'p'*, O*Ph*), 140.4 (C-6), 151.1, 151.2, 151.4 (*'ipso'*, O*Ph*+C-4), 164.0 (C-2), 177.6, 177.7 (*C*OOCH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(ethoxy-α,α-dimethylglycinyl)]-phosphate (CPF 43).**

**$C_{23}H_{28}BrClN_3O_9P$, MW=636.81.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), 4-chlorophenyl-(ethyl-2-amino-2-methylpropanoate)-phosphorochloridate (413.3 mg, 1.22 mmol), NMI (184.7 mg, 2.25 mmol, 179.3 µL) in THF (5 mL) for 16 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (74 mg, yield 25.8 %).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.47, 3.33.

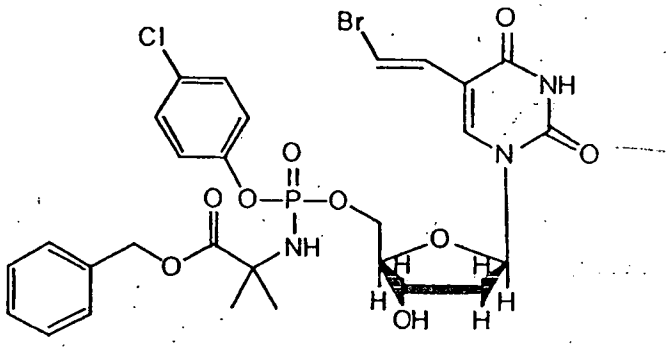
$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.03-9.99 (1H, 2bs, H-3), 7.70-7.67 (1H, 2s, H-6), 7.47-7.43 (1H, 2d, $^{3}J$=13.6 Hz, H-5b), 7.35-7.20 (4H, m, O*Ph*), 6.77-6.68 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.33-6.27 (1H, m, H-1'), 4.55-4.29 (5H, m, H-3'+H-5'+ OH-3'+N*H*), 4.22-4.17 (2H, q, $^{3}J$=7.1 Hz, OC*H*$_2$CH$_3$+H-4'), 2.53-2.42 (1H, m, one of H-2'), 2.22-2.08 (1H, m, one of H-2'), 1.57-1.54 (6H, 2s, [C*H*$_3$]$_2$C), 1.31-1.30 (3H, 2t, $^{3}J$=7.1 Hz, OCH$_2$C*H*$_3$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 (*C*H$_3$CH$_2$O), 27.2, 27.3, 27.4 ([*C*H$_3$]$_2$C), 40.7 (C-2'), 57.6 (*C*[CH$_3$]$_2$), 62.6 (CH$_3$*C*H$_2$O), 66.5, 66.6 (C-5'), 70.8, 71.1 (C-3'), 85.5, 85.74, 86.0 (C-1', C-4'), 110.4 (C-5b), 112.0 (C-5), 121.9, 122.0, 122.1 (*'o'*, O*Ph*), 128.9, 130.2 (*'m'*, O*Ph*+ C-5a), 130.9 (*'p'*, O*Ph*), 138.3 (C-6), 149.4 (*'ipso'*, O*Ph*), 149.9 (C-4), 162.1, 162.2 (C-2), 175.7-175.9 (*C*OOCH$_2$CH$_3$).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(benzoxy-α,α-dimethylglycinyl)]-phosphate (CPF 44).**

**$C_{28}H_{30}BrClN_3O_9P$, MW=698.88.**

48



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), 4-chlorophenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate (505.0 mg, 1.25 mmol), NMI (184.7 mg, 2.25 mmol, 179.3 µL) in THF (5 mL) for 16 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (134.8 mg, yield 42.9%).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.44, 3.26.

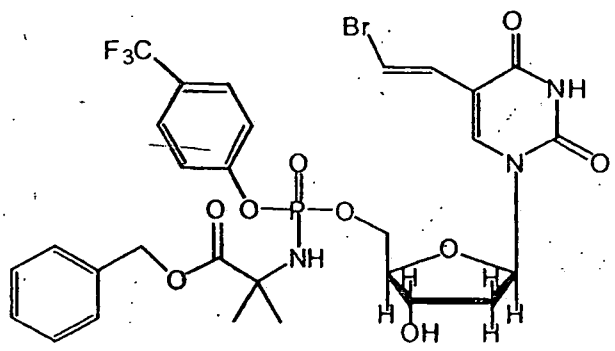
$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 9.96-9.93 (1H, 2bs, H-3), 7.66-7.65 (1H, 2s, H-6), 7.47-7.41 (1H, 2d, $^{3}J$=13.5, H-5b), 7.39-7.18 (9H, m, O*Ph*+$CH_2$*Ph*) 6.74-6.69 (1H, 2d, $^{3}J$=13.5 Hz, H-5a), 6.31-6.25 (1H, m, H-1'), 5.19 (2H, C$H_2$Ph), 4.51-4.29 (4H, m, H-3'+H-5'+N*H*), 4.15-4.12 (2H, m, H-4'+OH-3'), 2.48-2.40 (1H, m, one of H-2'), 2.18-2.05 (1H, m, one of H-2'), 1.60-1.59 (6H, 2s, [C$H_3$]$_2$C).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 27.1, 27.5 ([*C*$H_3$]$_2$C), 40.7 (C-2'), 57.7 (*C*[$CH_3$]$_2$), 66.4, 66.6 (C-5'), 68.2 (*C*$H_2$Ph), 70.7, 71.1 (C-3'), 85.4, 85.5, 85.7, 86.0 (C-1', C-4'), 110.5 (C-5b), 112.0 (C-5), 121.9, 122.0, 128.4, 128.5, 128.9, 129.1 (*'o'*, *'m'*, *'p'*, $CH_2$*Ph*+O*Ph*+C-5a), 131.0 (*'ipso'*, $CH_2$*Ph*), 135.6 (*'p'*, O*Ph*), 138.1 (C-6), 149.3 (*'ipso'*, O*Ph*), 149.8 (C-4), 162.1 (C-2), 175.6 (*C*$OOCH_2$Ph).

**Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[*para*-(trifluoromethyl)-phenyl-(benzoxy-α,α-dimethylglycinyl)]-phosphate (CPF 48).**

**$C_{29}H_{30}BrF_3N_3O_9P$, MW=732.44.**

49



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), 4-(trifluoromethyl)-phenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate (529.4.5 mg, 1.22 mmol), NMI (184.7 mg, 2.25 mmol, 179.4 µL) in THF (5 mL) for 4 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 97:3 to give the pure product as a white foamy solid (142.1 mg, yield 43.1%).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.16, 3.01.

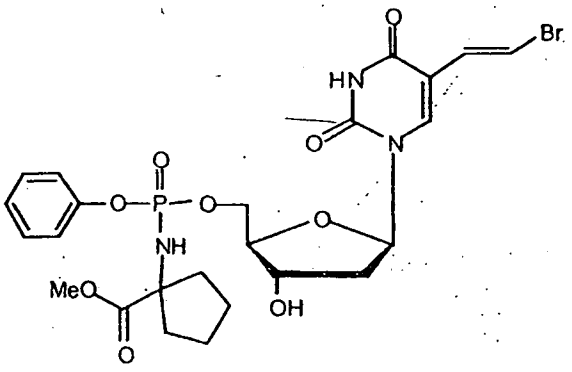
$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.06-10.02 (1H, 2bs, H-3), 7.67-7.66 (1H, s, H-6), 7.64-7.60 (2H, 2d, $^{3}J$=8.8 Hz, O*Ph*), 7.46-7.32 (8H, m, O*Ph*+ $CH_2$*Ph* +H-5b), 6.77-6.68 (1H, 2d, $^{3}J$=13.6 Hz, H-5a), 6.31-6.26 (1H, m, H-1'), 5.18 (2H, s, C*H*$_2$Ph), 4.61-4.32 (4H, m, H-3'+H-5'+N*H*), 4.16-4.15 (2H, m, H-4'+OH-3'), 2.48-2.41 (1H, m, one of H-2'), 2.23-2.09 (1H, m, one of H-2'), 1.60-1.58 (6H, 2s, C[C*H*$_3$]$_2$)

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 27.0, 27.4, 27.5 (C[*C*H$_3$]$_2$), 40.6 (C-2'), 57.7, 57.8 (*C*[CH$_3$]$_2$), 66.8, 66.5 (C-5'), 68.2 (*C*H$_2$Ph), 70.8, 71.1 (C-3'), 85.4, 85.7, 86.0 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 120.8, 120.9, 121.0, 127.6, 127.7, 128.0, 128.5, 128.8, 129.0 (*'o'*, *'m'*, *'p'*, O*Ph*+ $CH_2$*Ph*+ C-5a), 124.2 (*C*F$_3$, *J*=267 Hz), 135.6 (*'ipso'*, $CH_2$*Ph*), 138.2 (C-6), 149.9 (C-4), 153.3 (*'ipso'*, O*Ph*), 162.1 (C-2), 175.4 (*C*OOCH$_2$Ph).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-α,α-cycloleucinyl)]-phosphate (CPF 16).**

**$C_{24}H_{29}BrN_3O_9P$, MW=614.38.**

50




This was synthesised according to ***Standard procedure 5***, using BVdU (250 mg, 0.75 mmol), Phenyl-(methoxy-α,α-cycloleucinyl)-phosphorochloridate (589 mg, 1.87 mmol), NMI (6.2 mmol, 415 µL) in THF (7 mL) for 3 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (234 mg, yield 51%).

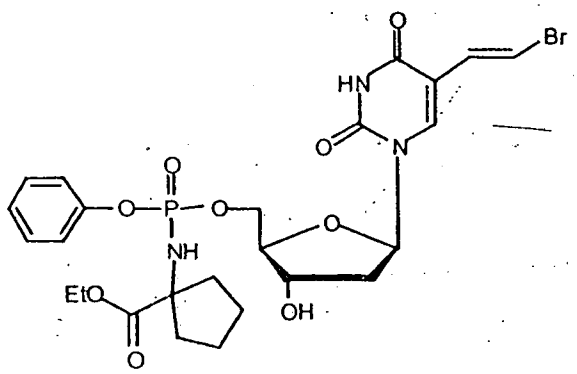
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.87, 3.82.

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 10.35-10.2 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, $^{3}J$=13 Hz, H-5b), 7.37-7.15 (5H, m, O*Ph*), 6.8 (1H, 2d, $^{3}J$=13 Hz, H-5a), 6.30 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.4-4.2 (4H, m, H-5', H-3', NH), 4.1 (1H, H-4'), 3.72 (3H, 2s, $CH_3O$), 2.49-2.40 (1H, m, one of H-2'), 2.35-2.01 (5H, m, one of H-2'+4H cyclopentane), 1.8-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR (DMSO; 75 MHz): δ 24.4, 24,3, 24.2 ($2CH_2$ cyclopent), 39.2, 38.6, 38.5 ($2CH_2$ cyclopent), 40.0 (C-2'), 53.2 (*C*$H_3O$), 66.4 (*Cq* cyclopentane), 66.6 (C-5'), 70.9 (C-3'), 85.8, 85.6, 85.4, 85.3 (C-1', C-4'), 110.2 (C-5b), 111.9 (C-5), 120.7-120.6 (*'o'*, O*Ph*), 125.7 (*'p'*, O*Ph*), 129.0 (C-5a), 130.2 (*'m'*, O*Ph*), 138.5 (C-6), 149.9 (C-4), 150.9, 150.8 (*'ipso'*, O*Ph*), 162.3(C-2), 176.3, 176.2 (*C*$OOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(ethoxy-α,α-cycloleucinyl)]-phosphate(CPF 17).**

**$C_{25}H_{31}BrN_3O_9P$; MW=628.41**



This was synthesised according to ***Standard procedure 5***, using BVdU (250 mg, 0.75 mmol), Phenyl-(ethoxy-α,α-cycloleucinyl)-phosphorochloridate (642 mg, 1.87 mmol), NMI (6.2 mmol, 415 μL) in THF (7 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (258 mg, yield 55%).

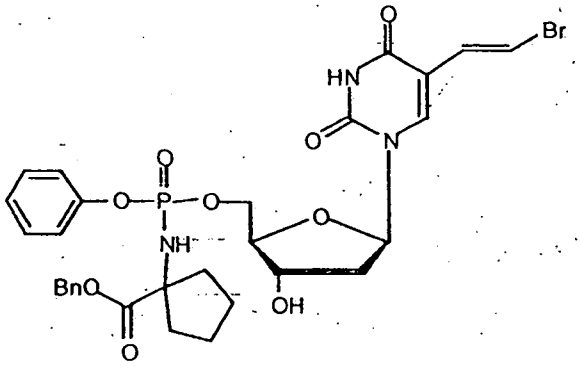
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.23, 4.1.

$^1$H-NMR ($CDCl_3$, 300 MHz): δ 10.3-10.1 (1H, bs, H-3), 7.8-7.75 (1H, 2xs, H-6), 7.51 (1H, 2d, $^3J$=14 Hz, H-5b), 7.45-7.10 (5H, m, O*Ph*), 6.8 (1H, 2d, $^3J$=14 Hz, H-5a), 6.22 (1H, 2t, $^3J$=4 Hz, H1'), 4.55-4.05 (7H, m, H-5', H-3', H-4', NH, $CH_3CH_2O$), 2.50-2.40 (1H, m, one of H-2'), 2.35-1.95 (5H, m, one of H-2'+4H cyclopentane), 1.95-1.75 (4H, m, 4H cyclopentane), 1.25 (3H, 2t, $^3J$=7 Hz, $CH_3CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($CH_3CH_2O$), 24.5, 24,4 ($2CH_2$ cyclopent), 39.2, 38.9 38.8, 38.4 ($2CH_2$ cyclopent), 40.6 (C-2'), 62.2, 62.1 ($CH_3CH_2O$), 66.2 (*Cq* cyclopentane), 66.6 (C-5'), 70.8 (C-3'), 85.7, 85.5 (C-1', C-4'), 110.2 (C-5b), 111.5 (C-5), 120.7, 120.6 ('*o*', O*Ph*), 125.6 ('*p*', O*Ph*), 129.7 (C-5a), 130.2 ('*m*', O*Ph*), 138.5, 138.3 (C-6), 149.7 (C-4), 150.9, 150.8 ('*ipso*', O*Ph*), 162.3 (C-2), 176.3 ($COOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy-α,α-cycloleucinyl)]-phosphate (CPF 18).**

**$C_{30}H_{33}BrN_3O_9P$, MW=690.48.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.6 mmol), Phenyl-(benzyloxy-α,α-cycloleucinyl)-phosphorochloridate (589 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 10 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (127 mg, yield 31%).

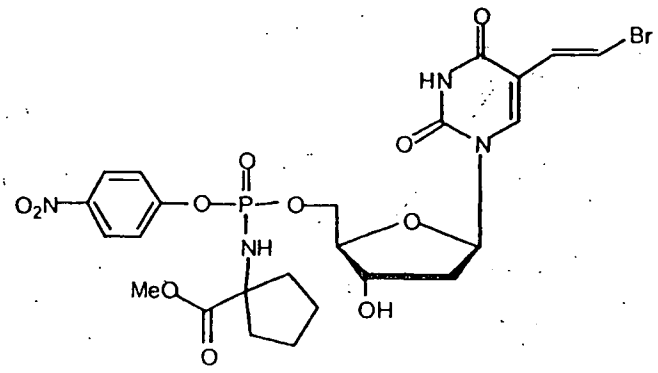
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.11, 4.01.

$^1$H-NMR ($CDCl_3$, 300 MHz): δ 10.2 (1H, bs, H-3), 7.8-7.6 (1H, 2xs, H-6), 7.45-7.4 (1H, 2d, $^3J$=14 Hz, H-5b), 7.40-7.10 (10H. m, O*Ph*+$CH_2$*Ph*), 6.85 (1H, 2d, $^3J$=14 Hz, H-5a), 6.20 (1H, m, H-1'), 5.15 (1H, s, C*H*$_2$Ph), 4.4-4.2 (3H, m, H-3',H-4', N*H*), 4.1 (2H, m, H-5'), 2.45-2.35 (1H, m, one of H-2'), 2.35-1.95 (5H, m, one of H-2'+4H cyclopentane), 1.95-1.75 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 24.4, 24,3, 24.2 (2$CH_2$ cyclopent), 39.9, 39.7 38.6, 38.5 (2$CH_2$ cyclopent), 40.5 (C-2'), 66.2 (*Cq* cyclopentane), 66.5 (C-5'), 67.8 (*C*$H_2$Ph), 70.8, 70.7 (C-3'), 85.7, 85.6, 85.5, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.8, 118.7 (C-5b), 120.7, 120.5 ('o', O*Ph*), 125.7 ('*p*', O*Ph*), 130.2, 129.0, 128.8, 128.7, 128.5 ('*m*' OPh, Bn, C-5a), 135.8('*ipso*', $CH_2$*Ph*) 138.4, 138.2 (C-6), 149.8 (C-4), 150.9, 150.8 ('*ipso*', O*Ph*), 162.2 (C-2), 175.7, 175.5 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(methoxy-α,α-cycloleucinyl)]-phosphate (CPF 19).**

$C_{24}H_{28}BrN_4O_{11}P$, MW=659.38.



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(methoxy-α,α-cycloleucinyl)-phosphorochloridate (543 mg, 1.5 mmol), NMI (4.98 mmol, 332 μL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (239 mg, yield 60%).

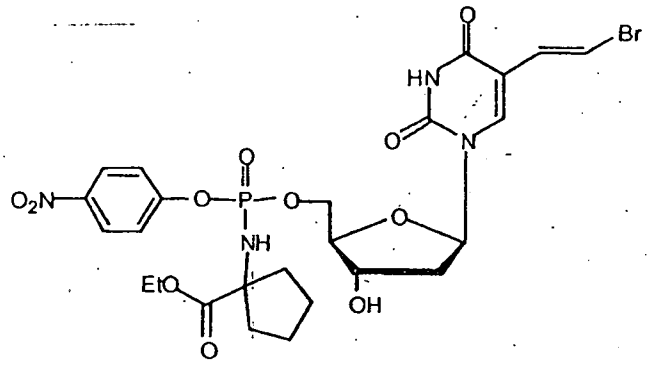
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.73.

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 10.5-10.2 (1H, bs, H-3), 8.35-8.25 (2H, 2d, $^{3}J$=6 Hz O*Ph*) 7.8-7.75 (1H, 2xs, H-6), 7.47 (2H ,2d; $^{3}J$=6 Hz , O*Ph*), 7.45-7.35 (1H, 2d, $^{3}J$=14 Hz, H-5b), 6.75-6.67 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.30 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.65-4.4 (3H, m, H-5',H-3'), 4.25-4.20 (1H, m, H-4'), 3.79 (3H, s, $CH_3O$), 2.6-2.4 (1H, m, one of H-2'), 2.3-1.98 (5H, m, one of H-2'+4H cyclopentane), 1.9-1.76 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 24.4, 24,3, 24.2 ($2CH_2$ cyclopent), 39.2, 39.1 ($2CH_2$ cyclopent), 40.5 (C-2'), 53.4, 53.3 ($\underline{C}H_3O$), 66.8 (*Cq* cyclopentane), 67.1 (C-5'), 70.9 (C-3'), 86.1, 86.0, 85.5, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.8 (C-5), 121.3, 121.2 (*'o'*, O*Ph*), 126.2 (*'m'*, O*Ph*), 128.9 (C-5a), 138.6 (C-6), 144.9 (*'ipso'*, O*Ph*) 149.9 (C-4), 155.9, 155.8 (*'p'*, O*Ph*), 162.3 (C-2), 176.3 ($\underline{C}OOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(ethoxy-α,α-cycloleucinyl)]-phosphate** (CPF 20).

**$C_{25}H_{30}BrN_3O_{11}P$, MW=673.4.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(ethoxy-α,α-cycloleucinyl)-phosphorochloridate (563 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 1 hr. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (240 mg, yield: 59%).

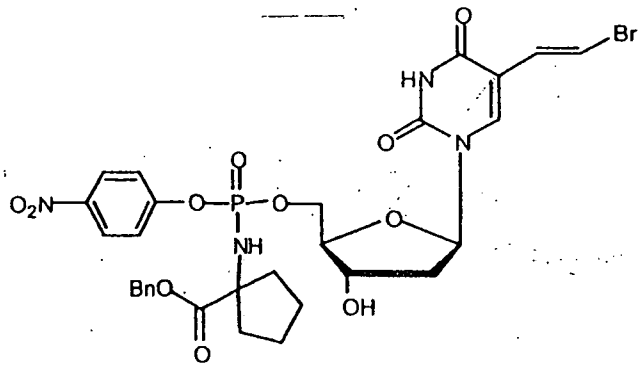
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.83, 3.79.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 8.25-8.2 (2H, 2d, $^{3}J$=9Hz O*Ph*), 7.66 (1H, s, H-6), 7.4 (2H ,2d , $^{3}J$=9Hz, O*Ph*), 7.3 (1H, 2d, $^{3}J$=14 Hz, H-5b), 6.85 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.3-6.2 (1H, m, H1'), 4.7-4.45 (4H, m, H-5', H-3', NH), 4.2-4.05 (3H, m, H-4', $CH_3CH_2O$), 2.55-2.4 (1H, m, one of H-2'), 2.2-1.95 (5H, m, one of H-2'+4H cyclopentane), 1.95-1.8 (4H, m, 4H cyclopentane), 1.2 (3H, 2t, $^{3}J$=8 Hz, $CH_3CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.9 ($CH_3CH_2O$), 24.5, 24,4 ($2CH_2$ cyclopent), 39.1, 39.0, 38.8 ($2CH_2$ cyclopent), 40.7 (C-2'), 62.4 ($CH_3CH_2O$), 66.5 (*Cq* cyclopentane), 67.0 (C-5'), 70.9 (C-3'), 85.9, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.8 (C-5), 121.3 ('o', O*Ph*), 126.2 ('*m*', O*Ph*), 128.8 (C-5a), 138.5 (C-6), 144.9 ('*ipso*', O*Ph*), 149.9 (C-4), 155.5 ('*p*', O*Ph*), 162.3 (C-2), 175.8, 175.7 ($COOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(benzoxy-α,α-cycloleucinyl)]-phosphate (CPF 21).**

$C_{30}H_{32}BrN_4O_{11}P$, MW=735.47.



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(benzyloxy-α,α-cycloleucinyl)-phosphorochloridate (656 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 3 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (269 mg, yield 61%).

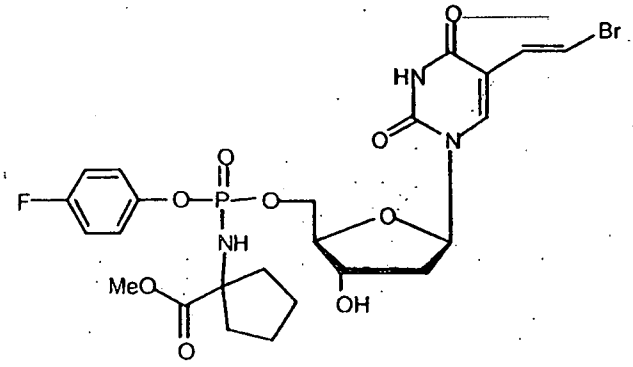
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.72.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.3 (1H, bs, H-3), 8.22-8.12 (2H, 2d, $^{3}J$=7 Hz, O*Ph*), 7.65 (1H, 2xs, H-6), 7.45-7.30 (8H, m, H-5b+O*Ph*+$CH_2$*Ph*), 6.72-6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.28 (1H, 2t, $^{3}J$=6Hz, H-1'), 5.15 (1H, d, C*H*$_2$Ph), 4.6-4.35 (4H, m, H-3', H-5', H-4', N*H*,), 2.55-2.4 (1H, m, one of H-2'), 2.3-1.92 (5H, m, one of H-2'+4H cyclopentane), 1.85-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 24.4, 24,3, 24.2 ($2CH_2$ cyclopent), 39.1, 38.9, 38.7 ($2CH_2$ cyclopent), 40.5 (C-2'), 66.9 (*Cq* cyclopentane), 67.1 (C-5'), 68.0 (*C*$H_2$Ph), 70.9 (C-3'), 85.3, 85.0 (C-1', C-4'), 110.3 (C-5b), 111.8 (C-5), 121.2 ('o', O*Ph*), 126.1 ('*m*', O*Ph*), 129.0, 128.8 (Bn, C-5a), 135.7 ('*ipso*', $CH_2$*Ph*), 138.5 (C-6), 144.9 ('*ipso*', O*Ph*), 149.9 (C-4), 155.8 ('*p*' OPh), 162.3 (C-2), 175.6 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(methoxy-α,α-cycloleucinyl)]-phosphate (CPF 22).**

**$C_{24}H_{28}BrFN_3O_9P$, MW=632.37.**




This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(methoxy-α,α-cycloleucinyl)-phosphorochloridate (503 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (251 mg, yield 66%).

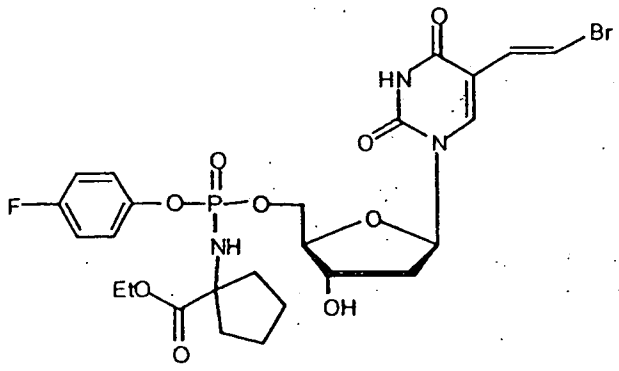
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.22.

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 10.3 (1H, bs, H-3), 7.70 (1H, 2xs, H-6), 7.4 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.25-7.15 (2H, m, O*Ph*), 7.1-6.95 (2H, m, O*Ph*), 6.70 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.30-6.15 (1H, 2t, $^{3}J$=5 Hz, H1'), 4.55-4.05 (5H, m, H-5'+H-3', NH, H-4'), 3.72 (3H, 2s, $CH_3O$), 2.55-2.35 (1H, m, one of H-2'), 2.25-1.92 (5H, m, one of H-2'+4H cyclopentane), 1.85-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR (DMSO; 75 MHz): δ 24.4, 24,3, 24.2 ($2CH_2$ cyclopent), 39.3, 39.2, 38.9, 38.5 ($2CH_2$ cyclopent), 40.6 (C-2'), 53.3, 53.2 ($\underline{C}H_3O$), 66.5 (*Cq* cyclopentane), 66.7 (C-5'), 70.9 (C-3'), 85.8, 85.7, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.9 (C-5), 116.9, 116.6 (*'o'*, O*Ph*), 122,2, 122.0 (*'m'*, O*Ph*), 128.5 (C-5a), 138.5 (C-6), 146.7 (*'ipso'*, O*Ph*) 149.9 (C-4), 158.5 (*'p'*, O*Ph*), 162.3(C-2), 176.4, 176.3 ($\underline{C}OOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(ethoxy-α,α-cycloleucinyl)]-phosphate (CPF 23).**

**$C_{25}H_{30}BrFN_3O_9P$, MW=646.4.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(ethoxy-α,α-cycloleucinyl)-phosphorochloridate (524 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (274 mg, yield 71%).

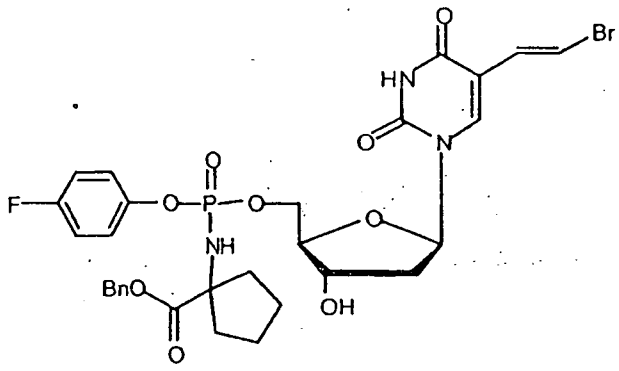
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.30.

$^1$H-NMR ($CDCl_3$, 300 MHz): δ 10.35 (1H, bs, H-3), 7.7 (1H, 2xs, H-6), 7.44 (1H, 2d, $^3J$=14 Hz, H-5b), 7.25-7.15 (2H, m, O*Ph*), 7.1-6.95 (2H, m, O*Ph*), 6.7 (1H, 2d, $^3J$=14 Hz, H-5a), 6.30 (1H, 2t, $^3J$=6 Hz, H1'), 4.55-4.3 (3H, m, H-5', H-3'), 4.2-4.1 (4H, m, NH, H-4', $CH_3CH_2O$), 2.55-2.4 (1H, m, one of H-2'), 2.22-1.90 (5H, m, one of H-2'+4H cyclopentane), 1.8-1.6 (4H, m, 4H cyclopentane), 1.3-1.2 (3H, 2t, $^3J$=7 Hz, $CH_3CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($CH_3CH_2O$), 24.6, 24,4, 24.3 ($2CH_2$ cyclopent), 39.3, 39.2, 38.9, 38.6 ($2CH_2$ cyclopent), 40.6 (C-2'), 62.2 ($CH_3CH_2O$), 66.5 (*Cq* cyclopentane), 66.7 (C-5'), 71.0 (C-3'), 85.8, 85.7, 85.5, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.9 (C-5), 116.9, 116.5 ('o', O*Ph*), 122.2, 122.1 ('*m*', O*Ph*), 129.0 (C-5a), 138.5 (C-6), 146.8,146.7 ('*ipso*', O*Ph*), 149.9 (C-4), 158.5 ('*p*', O*Ph*), 162.3 (C-2), 175.9, 175.8 ($COOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(benzoxy-α,α-cycloleucinyl)]-phosphate (CPF 24).**

**$C_{30}H_{32}BrN_3O_9P$, MW=708.47.**



This was synthesised according to ***Standard procedure 5***, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(benzyloxy-α,α-cycloleucinyl)-phosphorochloridate (616 mg, 1.5 mmol), NMI (4.98 mmol, 332 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography; eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (283 mg, yield 67%).

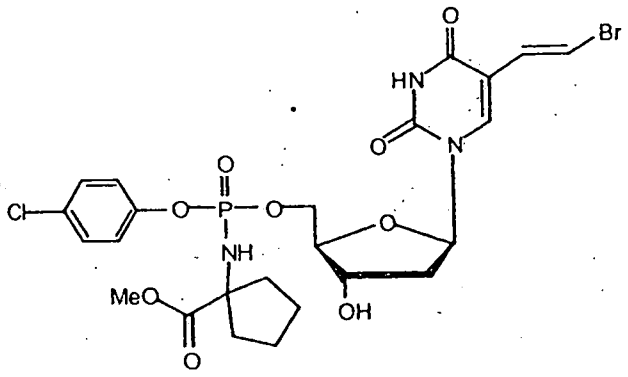
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.27.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.3-9.85 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.45-7.35 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.40-7.30 (5H. m, $CH_2$*Ph*), 7.25-7.15 (2H, m, O*Ph*), 7.05-6.95 (2H, m, O*Ph*), 6.71 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.27 (1H, 2t, $^{3}J$=6Hz, H-1'), 5.15 (1H, s, C*H*$_2$Ph), 4.45 (1H, m, H-3'), 4.40-4.30 (2H, m, H-5') 4.20-4.05 (2H, m, H-4', N*H*), 2.5-2.4 (1H, m, one of H-2'), 2.25-1.9 (5H, m, one of H-2'+4H cyclopentane), 1.8-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 24.5, 24.3, 24.2 (2$CH_2$ cyclopent), 39.7, 39.6, 39.3, 39.2 (2$CH_2$ cyclopent), 40.5, 40.0 (C-2'), 66.6 (*Cq* cyclopentane), 67.2, 66.7 (C-5'), 67.9 (*C*$H_2$Ph), 70.8, 70.7 (C-3'), 85.8, 85.7, 85.4, 85.3 (C-1', C-4'), 110.3 (C-5b), 111.8 (C-5), 116.9, 116.6 ('o', O*Ph*), 122.2, 122.1 ('*m*', O*Ph*), 129.0, 128.9, 128.6, 128.5 (Bn, C-5a), 135.8(*'ipso'*, $CH_2$*Ph*) 138.5 (C-6), 146.8, 146.7 (*'ipso'*, O*Ph*), 149.9 (C-4), 158.5 (*'p'* OPh), 162.2 (C-2), 175.7, 175.0 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(methoxy-α,α-cycloleucinyl)]-phosphate (CPF 32).**

**$C_{24}H_{28}BrClN_3O_9P$, MW=648.82.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(methoxy-α,α-cycloleucinyl)-phosphorochloridate (475 mg, 1.35 mmol), NMI (4.5 mmol, 300 μL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (187 mg, yield 64%).

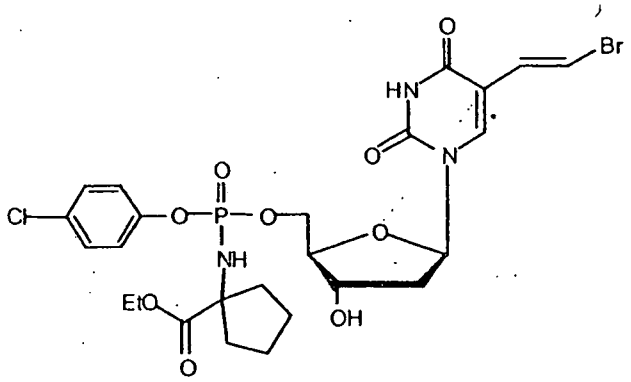
$^{31}$P-NMR (MeOD, 121 MHz): δ 4.64.

$^{1}$H-NMR (MeOD; 300 MHz): δ 7.75 (1H, 2xs, H-6), 7.32 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.32-7.27 (2H, m, O*Ph*), 7.20-7.11 (2H, m, O*Ph*), 6.72 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.27-6.20 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.35 (1H, m, H-3'), 4.30 (2H, m, H-5') 4.1 (2H, m, H-4'), 3.72 (3H, 2s, $CH_3O$), 2.32-2.20 (1H, m, one of H-2'), 2.20-1.92 (5H, m, one of H-2'+4H cyclopentane), 1.8-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR (MeOD; 75 MHz): δ 25.7, 25.6 ($2CH_2$ cyclopent), 41.7, 41.6, 41.4, 41.3 ($2CH_2$ cyclopent), 42.7 (C-2'), 54.1, 53.9 (*C*$H_3O$), 67.8 (*Cq* cyclopentane), 69.1, 69.0 (C-5'), 73.8 (C-3'), 88.4, 88.3, 88.2 (C-1', C-4'), 110.2 (C-5b), 111.8 (C-5), 122.1, 121.9 (*'o'*, O*Ph*), 128.9 (C-5a), 130.6 (*'m'*, O*Ph*), 130.8 (*'p'*, O*Ph*), 138.5 (C-6), 149.5, 149.4 (*'ipso'*, O*Ph*), 149.9 (C-4), 162.2(C-2), 175.6 (*C*O$OCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(ethoxy-α,α-cycloleucinyl)]-phosphate (CPF 33).**

**$C_{25}H_{30}BrClN_3O_9P$, MW=662.85.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(ethoxy-α,α-cycloleucinyl)-phosphorochloridate (495 mg, 1.35 mmol), NMI (4.5 mmol, 300 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (240 mg, yield 66%).

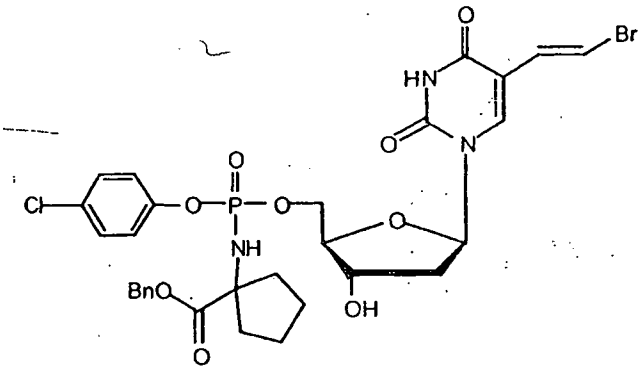
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.15.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.25-10.1 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.4-7.3 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.25-7.20 (2H, m, O*Ph*), 7.20-7.10 (2H, m, O*Ph*), 6.75 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.20 (1H, m, H1'), 4.35 (3H, m, H-3', H-5'), 4.2-4.0 (4H, m, H-4', NH, $CH_3C\underline{H_2}O$), 2.45-2.25 (1H, m, one of H-2'), 2.25-1.85 (5H, m, one of H-2'+4H cyclopentane), 1.75-1.55 (4H, m, 4H cyclopentane), 1.2 (3H, 2t, $^{3}J$=7 Hz, $C\underline{H_3}CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($\underline{C}H_3CH_2O$), 24.5, 24,4 ($2CH_2$ cyclopent), 39.3, 39.2, 38.8, 38.6 ($2CH_2$ cyclopent), 40.5 (C-2'), 62.3 ($CH_3\underline{C}H_2O$), 66.1 (*Cq* cyclopentane), 66.7 (C-5'), 70.8 (C-3'), 85.8, 85.4 (C-1', C-4'), 110.3 (C-5b), 111.9 (C-5), 122.1, 121.9 ('o', O*Ph*), 129.0 (C-5a), 130.2 ('*m*', O*Ph*), 130.8 ('*p*', O*Ph*), 138.5 (C-6), 149.5, 149.4 ('*ipso*', O*Ph*), 149.9 (C-4), 162.3 (C-2), 175.9 ($\underline{C}OOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(benzoxy-α,α-cycloleucinyl)]-phosphate (CPF 34).**

**$C_{30}H_{32}BrClN_3O_9P$, MW=724.92.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(benzyloxy-α,α-cycloleucinyl)-phosphorochloridate (578 mg, 1.35 mmol), NMI (4.5 mmol, 300 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (222 mg, yield 68%).

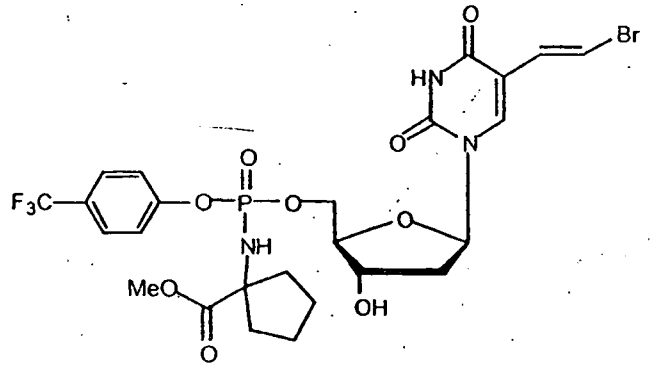
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.11, 4.05.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 7.65 (1H, 2xs, H-6), 7.45-7.29 (10H, m, H-5b, 2H O*Ph*+$CH_2$*Ph*), 7.20-7.15 (2H, m, O*Ph*), 6.75-6.67 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.28 (1H, 2t, $^{3}J$=6Hz, H-1'), 5.15 (1H, 2s, C*H*$_2$Ph), 4.5 (1H, m, H-3'), 4.35 (2H, m, H-5') 4.1 (H, m, H-4'), 4.00 (1H, m, N*H*), 2.48-2.35 (1H, m, one of H-2'), 2.3-1.92 (5H, m, one of H-2'+4H cyclopentane), 1.8-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 24.5, 24.4, 24,3, 24.2 (2$CH_2$ cyclopent), 39.3, 38.8, 38.6 (2$CH_2$ cyclopent), 40.5 (C-2'), 66.7 (*Cq* cyclopentane), 67.9 (*C*H$_2$Ph), 68.4 (C-5'), 70.7 (C-3'), 85.7 , 85.7, 85.4, 85.3 (C-1', C-4'), 110.3 (C-5b), 111.8 (C-5), 122.0, 121.9 ('o', O*Ph*), 129.1, 128.3, 128.2 (Bn, '*m*', O*Ph*) , 130.2 (C-5a), 135.8 (*'ipso'*, $CH_2$*Ph*), 136.3 (*'p'* OPh), 138.2 (C-6), 149.5, 149.3 (*'ipso'*, O*Ph*), 149.9 (C-4), 162.2 (C-2), 175.7, 175.5 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(methoxy-α,α-cycloleucinyl)]-phosphate (CPF 28).**

**$C_{25}H_{28}BrF_3N_3O_9P$, MW=682.38.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-trifluorophenyl-(methoxy-α,α-cycloleucinyl)-phosphorochloridate (521 mg, 1.35 mmol), NMI (4.5 mmol, 300 μL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (199 mg, yield 65%).

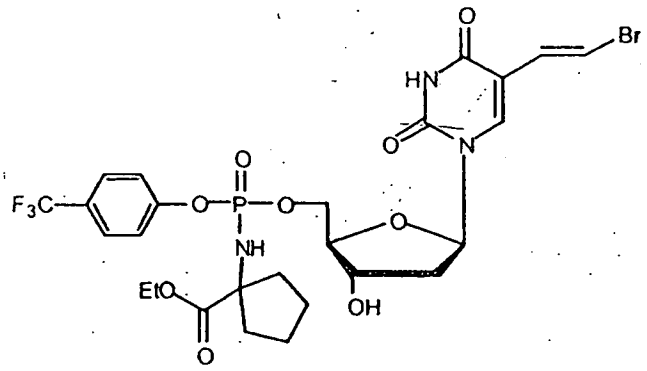
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 3.80.

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 7.70 (1H, 2s, H-6), 7.55 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.45-7.32 (4H, m, O*Ph*), 6.72 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.28 (1H, 2t, $^{3}J$=6 Hz, H1'), 4.55 (1H, m, H-3'), 4.45 (2H, m, H-5'), 4.25 (1H, H-4'), 4.15 (1H, NH), 3.71 (3H, 2s, $CH_3O$), 2.6-2.4 (1H, m, one of H-2'), 2.3-1.9 (5H, m, one of H-2'+4H cyclopentane), 1.85-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 24.4, 24,3, 24.2 ($2CH_2$ cyclopent), 39.2, 39.1, 38.8, 38.6 ($2CH_2$ cyclopent), 40.5 (C-2'), 53.9 (*C*$H_3$O), 66.3 (*Cq* cyclopentane), 66.8 (C-5'), 70.9 (C-3'), 85.8, 85.4 (C-1', C-4'), 110.3 (C-5b), 111.9 (C-5), 125.1 (d, J=270Hz, $CF_3$), 127.1, 127.0 (*'o'*, O*Ph*), 127.8 (*'m'*, O*Ph*), 128.9 (C-5a), 129.0 (*'p'*, q, J=32Hz, O*Ph*), 138.5 (C-6), 149.9 (C-4), 153.5 (*'ipso'*, O*Ph*), 162.2 (C-2), 176.3, 176.2 (*C*$OOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(ethoxy-α,α-cycloleucinyl)]-phosphate (CPF 29).**

**$C_{26}H_{30}BrF_3N_3O_9P$, MW=696.40.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-trifluorophenyl-(ethoxy-α,α-cycloleucinyl)-phosphorochloridate (540 mg, 1.35 mmol), NMI (4.50 mmol, 300 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (185 mg, yield 59%).

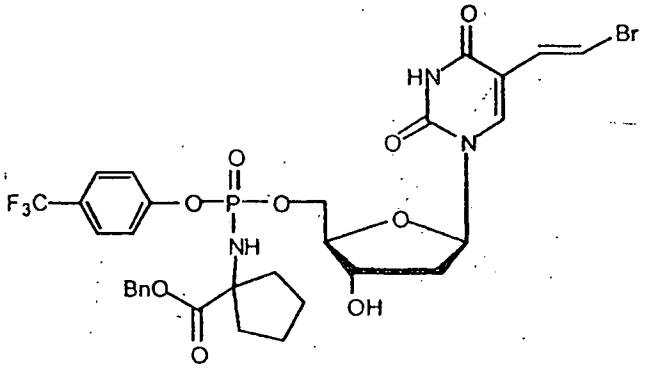
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.30.

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ 10.35 (1H, bs, H-3), 7.70 (1H, 2xs, H-6), 7.40 (1H, 2d, $^{3}J$=14 Hz, H-5b), 7.28-7.14 (2H, m, O*Ph*), 7.05-6.95 (2H, m, O*Ph*), 6.70 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.3 (1H, m, H1'), 4.55-4.3 (3H, m, H-5', H-3'), 4.2-4.1 (3H, m, H-4', $CH_3C\underline{H}_2O$), 2.5-2.35 (1H, m, one of H-2'), 2.20-1.9 (5H, m, one of H-2'+4H cyclopentane), 1.85-1.6 (4H, m, 4H cyclopentane), 1.25 (3H, 2t, $^{3}J$=7 Hz, $C\underline{H}_3CH_2O$).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 14.5 ($\underline{C}H_3CH_2O$), 24.5, 24,4 ($2CH_2$ cyclopent), 39.3, 39.2, 38.9, 38.5 ($2CH_2$ cyclopent), 40.6 (C-2'), 62.2 ($CH_3\underline{C}H_2O$), 66.7 (*Cq* cyclopentane), 67.4, 67.3 (C-5'), 70.9 (C-3'), 85.8, 85.7 (C-1', C-4'), 110.2 (C-5b), 111.9 (C-5), 116.8, 116.5 ('o', O*Ph*), 122.2, 122.1 (*'m'*, O*Ph*), 125.1 (d, J=270Hz, $CF_3$), 129.0 (C-5a), 131.1 (*'p'*, q, J=32Hz, O*Ph*), 138.5 (C-6), 146.8, 146.7 (*'ipso'*, O*Ph*), 149.9 (C-4), 162.3 (C-2), 175.9,175.8 ($\underline{C}OOCH_2CH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(benzoxy-α,α-cycloleucinyl)]-phosphate (CPF 30).**

**$C_{31}H_{32}BrF_3N_3O_9P$, MW=758.47.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-trifluorophenyl-(benzyloxy-α,α-cycloleucinyl)-phosphorochloridate (623 mg, 1.35 mmol), NMI (4.5 mmol, 300 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (218 mg, yield 64%).

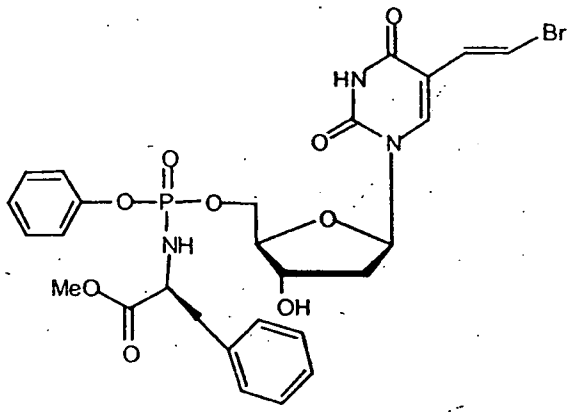
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.30.

$^1$H-NMR ($CDCl_3$, 300 MHz): δ 10.35 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.55 (2H, m, 2H O*Ph*), 7.45-7.25 (8H. m, 2H O*Ph*+$CH_2$*Ph*+ H-5b), 6.7 (1H, 2d, $^3J$=14 Hz, H-5a), 6.30 (1H, 2t, $^3J$=6Hz, H-1'), 5.15 (1H, 2s, C*H*$_2$Ph), 4.55-4.35 (3H, m, H-3'+ H-5'), 4.25 (1H, H-4'), 4.10 (1H, NH), 2.55-2.35 (1H, m, one of H-2'), 2.30-1.92 (5H, m, one of H-2'+4H cyclopentane), 1.8-1.6 (4H, m, 4H cyclopentane).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ 25.5, 24.4, 24,3, 24.2 ($2CH_2$ cyclopent), 39.2,39.1, 38.7, 38.6 ($2CH_2$ cyclopent), 40.5, 40.0 (C-2'), 66.4 (*Cq* cyclopentane), 66.8 (C-5'), 68.0 (*C*$H_2$Ph), 70.9 (C-3'), 86.0, 85.8, 85.4, 85.3 (C-1', C-4'), 110.3 (C-5b), 111.9 (C-5), 121.8, 120.8 ('o, *m*', O*Ph*), 125.2 (d, J=270Hz, $CF_3$), 128.5, 127.7, 127.5 (Bn, C-5a), 129,2 ('*p*',q , J=32Hz, O*Ph*), 135.4 ('*ipso*', $CH_2$*Ph*), 138.5 (C-6), 149.9 (C-4), 153.5 ('*ipso*' OPh), 162.2 (C-2), 175.6,175.5 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-L-phenylalaninyl)]-phosphate (CPF 36).**

**$C_{27}H_{29}BrN_3O_9P$, MW=650.41.**




This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), Phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate (477 mg, 1.35 mmol), NMI (4.42 mmol, 190 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (169 mg, yield 58%).

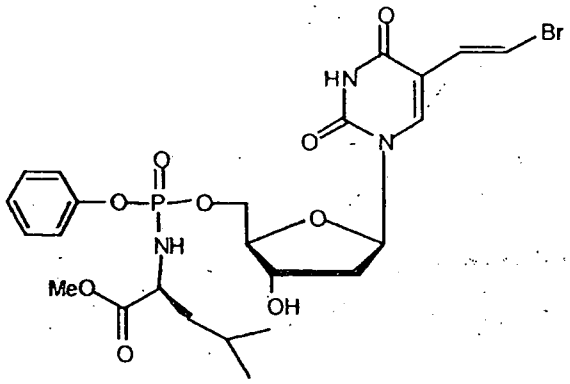
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 4.79, 4.71.

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.95 (1H, bs, H-3), 7.60-7.55 (1H, 2xs, H-6), 7.48-7.4 (1H, 2d, $^3J$=14 Hz, H-5b), 7.3-7.1 (10H, m, $CH_2Ph$+ O*Ph*), 6.75-6.65 (1H, 2d, $^3J$=14 Hz, H-5a), 6.27-6.18 (1H, m, H1'), 4.57-4.29 (6H, m, H-5',H-3',H-4', NH, CHphenylala), 3.70 (3H, 2s, $CH_3O$), 3.01 (2H, m, $CH_2Ph$), 2.35-2.20 (1H, m, one of H-2'), 2.07-1.95 (1H, m, one of H-2').

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 36.3 ($CH_2$phenylalanine), 41.9, 41.8 (C-2'), 53.0 ($\underline{C}H_3O$), 56.6, 56.1 (CHphenylala), 67.1 (C-5'), 71.3, 70.7 (C-3'), 85.7, 85.6, 85.5, 85.4 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 120.6,120.5 (*'o'*, O*Ph*), 127.8 (*'p'*, O*Ph*), 130.1, 129.9, 129.8, 129.1 ($CH_2Ph$, C-5a; *'m'* O*Ph*), 138.0, 137.9 (C-6), 149.8 (C-4), 150.7,150.6 (*'ipso'*, O*Ph*), 162.1, 162.0 (C-2), 173.5 ($\underline{C}OOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-L-leucinyl)]-phosphate (CPF 35).**

**$C_{24}H_{31}BrN_3O_9P$, MW=616.40.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), Phenyl-(methoxy-L-leucinyl)-phosphorochloridate (432 mg, 1.35 mmol), NMI (4.42 mmol, 190 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (167 mg, yield 60%).

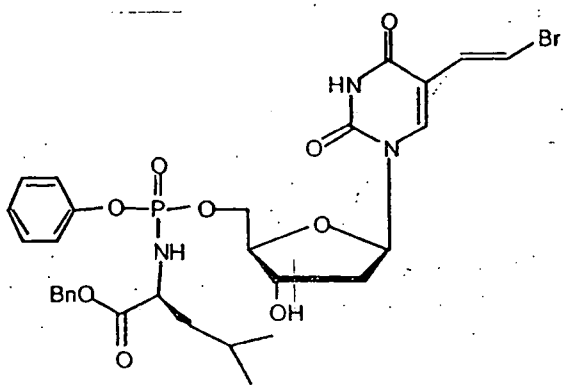
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.14, 4.60.

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 10.1 (1H, bs, H-3), 7.75 (1H, 2xs, H-6), 7.45 (1H, 2d, $^3J$=14 Hz, H-5b), 7.4-7.2 (5H, m, O*Ph*), 6.85 (1H, 2d, $^3J$=14 Hz, H-5a), 6.27-6.18 (1H, 2t, $^3J$=6 Hz, H1'), 4.5-4.2 (4H, m, H-5',H-3', NH), 4.1 (1H, m,H-4'), 3.95 (1H, m, C*H*$CH_2CH(CH_3)_2$), 3.70 (3H, 2s, $CH_3O$), 2.40-2.20 (1H, m, one of H-2'), 2.05-1.95 (1H, m, one of H-2'), 1.8 (1H, m, $CHCH_2CH(CH_3)_2$), 1.8-1.5 (2H, m, $CHCH_2CH(CH_3)_2$), 1.0-0.9 (6H, m, $CHCH_2CH(CH_3)_2$).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 23.2, 23.1, 22.0, 21.9 (2C, $CHCH_2CH(CH_3)_2$), 24.9, 24.7 ($CHCH_2CH(CH_3)_2$), 40.6 (C-2'), 43.7, 43.6 ($CHCH_2CH(CH_3)_2$), 53.0 ($CH_3O$), 53.7, 53.6 ($CHCH_2CH(CH_3)_2$), 66.6, 66.3 (C-5'), 71.1, 70.8 (C-3'), 86.0, 85.7, 85.6, 85.5 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 120.6, 120.5, 120.4 (*'o'*, O*Ph*), 125.8, 125.7 (*'p'*, O*Ph*), 128.9 (C-5a), 130.2 (*'m'* O*Ph*), 138.1 (C-6), 149.9 (C-4), 150.8, 150.7 (*'ipso'*, O*Ph*), 162.2 (C-2), 175.1, 174.9 ($COOCH_3$).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy-L-leucinyl)]-phosphate (CPF 37).**

**$C_{30}H_{35}BrN_3O_9P$, MW=692.49.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), Phenyl-(benzoxy-L-leucinyl)-phosphorochloridate (534 mg, 1.35 mmol), NMI (4.42 mmol, 190 µL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (199 mg, yield 64%).

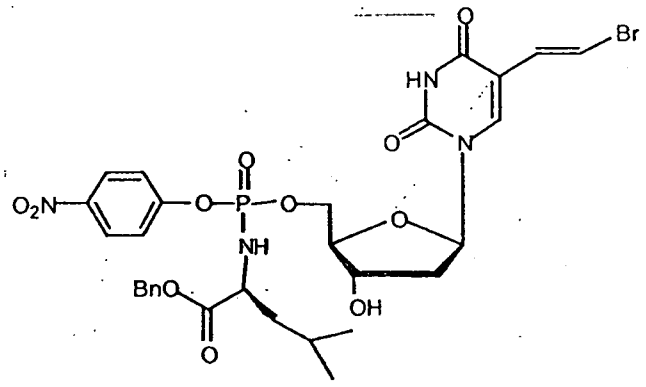
$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.18, 4.54.

$^1$H-NMR ($CDCl_3$; 300 MHz): δ 9.95-9.85 (1H, bs, H-3), 7.55 (1H, 2xs, H-6), 7.38 (1H, 2d, $^3J$=14 Hz, H-5b), 7.3-7.1 (5H, m, $CH_2Ph$+ O*Ph*), 6.65 (1H, 2d, $^3J$=14 Hz, H-5a), 6.26-6.14 (1H, 2t, $^3J$=6 Hz, H1'), 5.1 (2H, 2s, $CH_2Ph$) 4.4-3.8 (6H, m, H-5',H-3', NH, H-4', $CHCH_2CH(CH_3)_2$), 2.35-2.25 (1H, m, one of H-2'), 1.95-1.85 (1H, m, one of H-2'), 1.6-1.4 (3H, m, $CHCH_2CH(CH_3)_2$), 0.8 (6H, m, $CHCH_2CH(CH_3)_2$).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 23.2, 23.1, 22.0, 21.9 (2C, $CHCH_2CH(CH_3)_2$), 24.9, 24.7 ($CHCH_2CH(CH_3)_2$), 40.7 (C-2'), 43.9, 43.8 ($CHCH_2CH(CH_3)_2$), 53.9, 53.7 ($CHCH_2CH(CH_3)_2$), 66.4, 66.2 (C-5'), 67.8 ,67.7 ($CH_2Ph$), 71.1, 70.7 (C-3'), 85.9, 85.6, 85.4, 85.3 (C-1', C-4'), 110.4 (C-5b), 111.9 (C-5), 120.6, 120.5 (*'o'*, O*Ph*), 125.8, 125.7 (*'p'*, O*Ph*), 130.2, 129.1, 128.9 (C-5a, $CH_2Ph$, *'m'* O*Ph*), 135.4 (*'ipso'*, $CH_2$*Ph*), 138.1 (C-6), 149.8 (C-4), 150.2 (*'ipso'*, O*Ph*), 162.1 (C-2), 175.7, 174.6 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(benzoxy-L-leucinyl)]-phosphate (CPF 38).**

**$C_{30}H_{34}BrN_4O_{11}P$, MW=737.49.**



This was synthesised according to ***Standard procedure 5***, using BVdU (150 mg, 0.45 mmol), para-nitrophenyl-(benzoxy-L-leucinyl)-phosphorochloridate (595 mg, 1.35 mmol), NMI (4.42 mmol, 190 μL) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with $CH_2Cl_2$/Methanol 97:3 to give the pure product as a white foamy solid (176 mg, yield 53%).

$^{31}$P-NMR ($CDCl_3$, 121 MHz): δ 5.72, 4.35.

$^{1}$H-NMR ($CDCl_3$; 300 MHz): δ 10.2 (1H, bs, H-3), 8.1(2H, m, 2H O*Ph*), 7.65 (1H, 2xs, H-6), 7.45-7.2 (8H, m, H-5b, $CH_2$Ph+ 2H O*Ph*), 6.65 (1H, 2d, $^{3}J$=14 Hz, H-5a), 6.35-6.2 (1H, 2t, $^{3}J$=6 Hz, H1'), 5.15 (2H, 2s, $CH_2$Ph) 4.7-3.9 (6H, m, H-5',H-3', NH, H-4', C*H*$CH_2$CH($CH_3$)$_2$), 2.55-2.4 (1H, m, one of H-2'), 2.15-2.05 (1H, m, one of H-2'), 1.7-1.5 (3H, m, CHC$H_2$C*H*($CH_3$)$_2$), 0.95-0.8 (6H, m, CHC$H_2$CH(*$CH_3$*)$_2$).

$^{13}$C-NMR ($CDCl_3$; 75 MHz): δ 23.2, 23.1, 22.0, 21.9 (2C, CHC$H_2$CH(*$CH_3$*)$_2$), 24.9, 24.8 (CHC$H_2$*CH*($CH_3$)$_2$), 40.6 (C-2'), 43.7, 43.6 (CH*$CH_2$*CH($CH_3$)$_2$), 53.9, 53.7 (*CH*$CH_2$CH($CH_3$)$_2$), 66.9 (C-5'), 67.9 (*$CH_2$*Ph), 71.2, 70.8 (C-3'), 85.8, 85.3, 85.2 (C-1', C-4'), 110.6 (C-5b), 111.9 (C-5), 121.3 (*'o'*, O*Ph*), 129.2, 129.1, 128.8, 126.2 (C-5a, *$CH_2$*Ph, *'m'* O*Ph*), 135.4, 135.3 (*'ipso'*, $CH_2$*Ph*), 138.2 (C-6), 145.2, 145.1 (*'ipso'*, O*Ph*), 149.9 (C-4), 155.5 (*'p'*, O*Ph*), 162.1 (C-2), 174.2 (*C*OOBn).

**Synthesis of (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(benzoxy-L-leucinyl)]-phosphate (CPF 39).**

**$C_{30}H_{34}BrClN_3O_9P$, MW=726.94.**