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February 20, 2015

The Controller of Patents
The Patent Office
Intellectual Property Office Building,
CP-2, Sector V, Salt Lake City,
Kolkata-700091
Phone: 033-23679101

Sub: Representation u/s 25(1) of the Patents Act-in Indian Patent Application No. **3658/KOLNP/2009** filed on 20th October, 2009. National Phase of PCT Application No. PCT/US2008/058183 claiming priority from the US Patent Application No. 60/982,309 dated 24th March 2007, US Patent Applications No. 12/053,015 dated 21st March 2008.
Applicant: Pharmasset, Inc
Representation filed by: **OPTIMUS Pharma LTD**
Our Ref: **OPP0090**

Dear Sirs,

We submit herewith a Representation u/s 25(1) of the Patents Act, 2005 in Form 7A along with statement and evidence in support of the representation.

We crave leave of the Learned Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

The Learned Controller is requested to take the documents or record and proceed further in the matter and keep the Opponent advised of each and every step taken in the matter.

Lastly, we request the Learned Controller to grant us an opportunity of being heard before the above representation is finally decided.

Thanking you,

Yours Sincerely

CHITRA ARVIND
FOR RAJESHWARI & ASSOCIATES
AGENT FOR THE OPPONENT

Encl: Form 7A in triplicate
Opposition in triplicate
List of documents and documents in triplicate
Affidavit with annexures in triplicate

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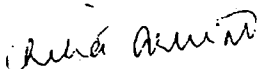
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**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,
KOLKATA**

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** 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:

OPTIMUS PHARMA LTD.

...PETITIONER/OPPONENT

VS.

PHARMASSET, INC.

...RESPONDENTS/APPLICANTS

PRE-GRANT OPPOSITION BY NATCO PHARMA LIMITED

Volume-I of VI

MASTER INDEX

Sl. No.	PARTICULARS	Page Nos.
	<u>Volume-I</u> <u>(Page Nos. 1 to 160)</u>	
1.	Representation u/s 25(1) by the Petitioner/Opponent	1-34
2.	List of Annexures	35-36

3.	Annexure A: WO 2005/012327	37-160
	<u>Volume-II</u> <u>(Page Nos. 161 to 496)</u>	
4.	Annexure B: WO 2001/92282	161-464
5.	Annexure C: Raffaele De Francesco and Charles Rice, New therapies on the horizon for Hepatitis C: Are we close? Clin Liver Dis, February Vol. 7, 211-243 (2003).	465-496
	<u>Volume-III</u> <u>(Page Nos. 497 to 731)</u>	
6.	Annexure D: 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.	497-501
7.	Annexure E: WO 2005/003147	502-731
	<u>Volume-IV</u> <u>(Page Nos. 732 to 1024)</u>	
8.	Annexure F: Jones et Al "Minireview: nucleotide prodrugs" Antiviral Research 27 (1995) 1-17.	732-748
9.	Annexure G: Van Rompay, "Phosphorylation of nucleosides and nucleoside analogs by mammalian nucleoside monophosphate kinases", Pharmacol Ther, 2000. 87(2-3): p. 189-98.	749-758
10.	Annexure H: Christopher McGuigan, et al in "Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully by-pass thymidine kinase", FEBS Letters 351 (1994) II-14.	759-762
11.	Annexure I: Christopher McGuigan et al, "Aryl Phosphoramidates of d4T have improved anti-HN efficacy in tissue culture and may act by the general of novel intracellular metabolite", Journal of Medicinal Chemistry, 1996, 39, 1748-1753	763-768

12.	Annexure J: Christopher P. Landowski et al, "Targeted delivery to PEPT1 over expressing cells: Acidic, basic, and secondary floxuridine amino acid ester prodrugs", Mol Cancer Ther 2005;4(4), April 2005.	769-778
13.	Annexure K: Jisook Kim <i>et al</i> , "Direct Measurement of Nucleoside Monophosphate Delivery from a Phosphoramidate Pronucleotide by stable isotope labelling and LC-ESI-MS/MS", MOLECULAR PHARMACEUTICS VOL. 1, NO. 2, 102-111	779-788
14.	Annexure L: Dider Saboulard et al, "Characterization of the activation pathway of phosphoramidates trimer prodrugs of stavudine and zidovudine" MOLECULAR PHARMACOLOGY, 56:693-704 (1999).	789-800
15.	Annexure M: J. Balzarini et al, "Mechanism of anti-HIV action of masked alaninyl d4TMP derivatives", Proc Natl Acad Sci USA Vol. 93, pp. 7295-7299, July 1996.	801-805
16.	Annexure N: Vidhya V. Iyer, et al "Synthesis, in vito anti-breast cancer activity, and intracellular decomposition of amino acid methyl ester and alkyl amide phosphoramidate monoesters of 3'-azido-3'-deoxythymidine (AZT)", J. Med. Chem, 2000, 43, 2266-2274.	806-814
17.	Annexure O: Dominique Cahard et al, "Aryloxy Phosphoramidates Tricesters as ProTides", Mini-Reviews in Medicinal Chemistry, 2004, 4, 371-381.	815-826
18.	Annexure P: 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	827-836
19.	Annexure Q: US 2003/0109697	837-894
20.	Annexure R: US 6589941	895-921
21.	Annexure S: WO1999/037753	922-1034

	<u>Volume-V</u> <u>(Page Nos. 1035 to 1240)</u>	
22.	Annexure T: WO 1996/29336	1035-1106
23.	Annexure U: WO 1999/43691	1107-1215
24.	Annexure V: WO 2003/000713	1216-1240
	<u>Volume-VI</u> <u>(Page Nos. 1241to -1585)</u>	
25.	Affidavit of Dr. Dnyandev R Rane with Annexures	1241-1585
30.	Power of Attorney in our favour (Form-26)	(To Follow)

Dated this 20th day of February, 2015.

Chitra Arvind

CHITRA ARVIND
FOR RAJESHWARI & ASSOCIATES
AGENT FOR THE OPPONENT

To,
The Controller of Patents
The Patent Office, Kolkata

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AND

IN THE MATTER OF:

OPTIMUS PHARMA LTD
Corporate office:#1-2-11/1,
Above SBI bank,
Street No:2, Kakatiya Nagar,
Habsiguda, Hyderabad – 500007
India.

...PETITIONER/OPPONENT

VS.

PHARMASSET, INC.
303A, College Road East,
Princeton New Jersey 08540,
United States of America.

...RESPONDENTS/APPLICANTS

STATEMENT OF CASE OF OPPONENT

I. DESCRIPTION OF THE OPPONENT

- A. Opponent is a pharmaceutical company having its corporate office at #1-2-11/1, above SBI Bank, Street no.2, Kakatiya nagar, Habsiguda, Hyderabad-500007, India.

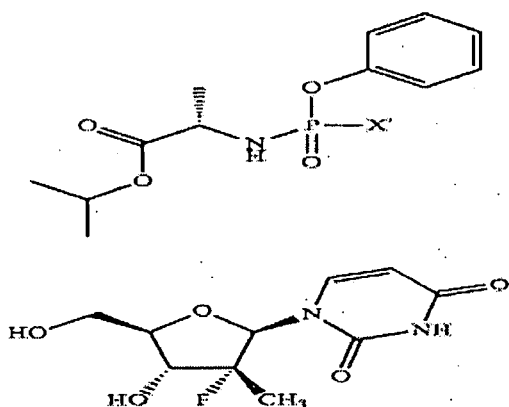
II. BACKGROUND OF THE ALLEGED INVENTION

A. The impugned application 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. Thus, any document published prior to 30 March 2007 falls under prior art of the present application.

B. 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. It appears that the examination report is yet to be issued by the Indian Patent Office. The claims on record are stated below:

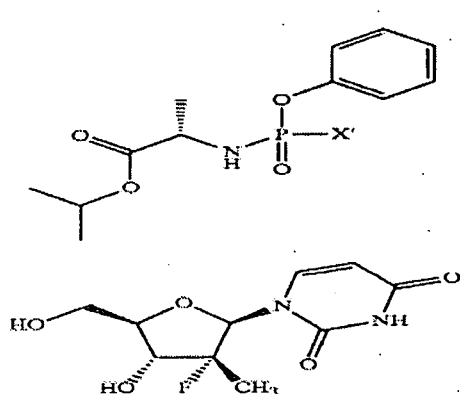
1. (S)-2-([(2R, 3R, 4R, 5R)-5-(2, 4-Dioxo-3, 4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester or a stereoisomer thereof.
2. A composition comprising the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium.
3. A composition for treating a hepatitis C virus, which comprises an effective amount of the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium.
4. A method of treating a subject infected by a virus, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1; wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhoea virus, and a Japanese encephalitis virus.
5. A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1.

6. 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.

7. A product comprising the compound or a stereoisomer thereof as claimed in claim 1 obtained by a process comprising: reacting a compound 4" with a nucleoside analog 5'



Wherein X' is a leaving group.

8. (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

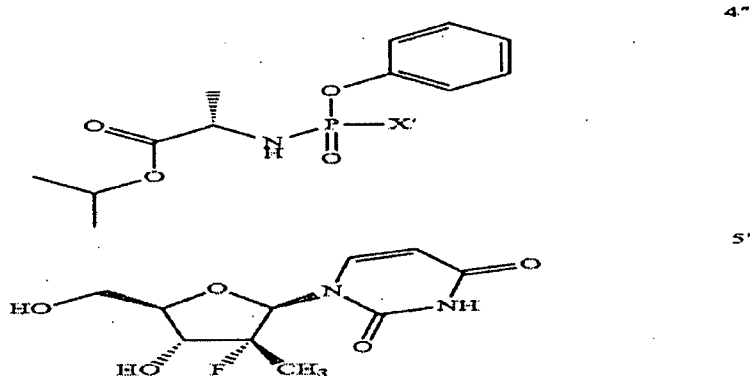
9. A composition comprising the compound as claimed in claim 8 and a pharmaceutically acceptable medium.

10. A composition for treating a hepatitis C virus, which comprises an effective amount of the compound as claimed in claim 8 and a pharmaceutically acceptable medium.

11. A method of treating a subject infected by a virus, which comprises: administering to the subject an effective amount of the compound as claimed in claim 8; wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

12. A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound as claimed in claim 8.

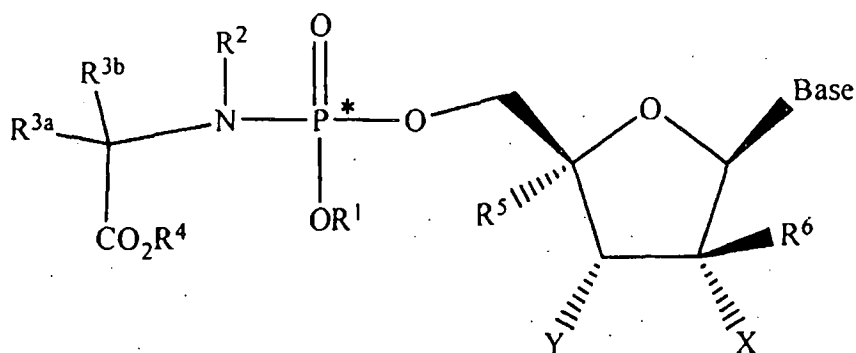
13. A process for preparing the compound as claimed in claim 8, said process comprising: reacting a compound 4" with a nucleoside analog 5'



- C. The impugned application related to nucleoside phosphoramidates for the treatment of viral diseases, particularly Hepatitis C. These compounds are known to be inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of the virus. The function of Hepatitis C virus is dependant on nonstructural protein 5B(NS5B), which is a viral protein found in the hepatitis C virus. It has a key function of replicating the HCV's viral RNA by using the viral positive RNA strand as its template and catalyzes the polymerization of ribonucleoside triphosphates (rNTP) during RNA replication.
- D. The nucleoside analog inhibitors mimic the natural substrates of the polymerase and are incorporated into the growing RNA chain, thus causing direct chain termination by tackling the active site of NS5B. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted *in vivo* to a triphosphate to compete for the polymerase nucleotide binding site. As of priority date, nucleoside phosphoramidates and their prodrugs were known substances.
- E. The impugned application claims allegedly novel phosphoramidate prodrugs of nucleoside derivatives for the treatment of viral infections mainly HCV.
- F. The Applicant admits that inhibitors of HCV NS5B as potential therapies for HCV infection were known before the date of priority. [see page 6, para 4 of the Complete Specification]
- G. The fact that nucleoside inhibitors of NS5B can act either as a non-natural substrate that results in chain terminator or as a competitive inhibitor which competes with the nucleotide binding to the polymerase was known and has been admitted in the impugned specification. It was also known that to function as a chain terminator the nucleoside analog must be taken up by the cell and converted *in vivo* to tri phosphate.
- H. It is known and admitted by the Applicant that the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphates form. Formation of the monophosphate by nucleoside kinase is generally viewed as the rate limiting step of the three phosphorylation events. To circumvent the need for the initial phosphorylation step in metabolism of a nucleoside to the active

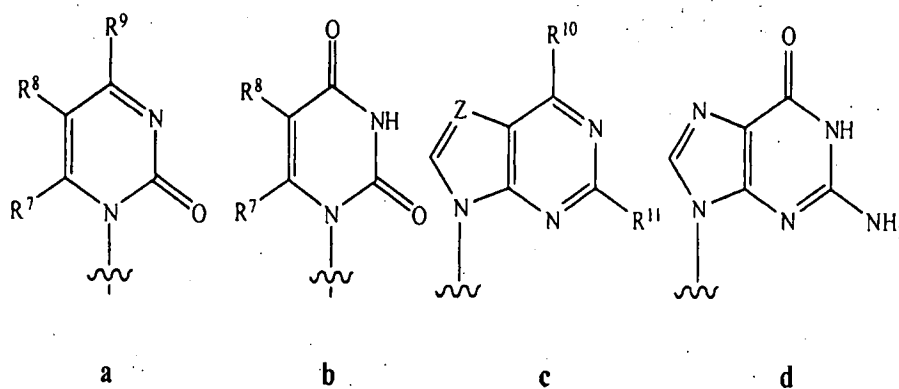
triphosphate analogue, the preparation of stable phosphate pro-drug has been known. Thus the specification admits that though there were several inhibitor of NS5B, these drugs had problems relating to physicochemical and pharmacokinetic properties.

- I. The specification admits that nucleoside phosphoramidate prodrugs have been shown to be precursors of the active nucleoside triphosphate and to inhibit viral replication when administered to viral infected whole cells. [see page 7, para 2 of the Complete Specification]. Hence, the prior art provides a solution that when such compounds were faced with problems of pharmacokinetic, they were converted to their pro-drugs. The present specification is also directed towards prodrugs of already known nucleoside derivatives.
- J. The impugned specification provides a general formula encompassing many compounds and claims such compounds. The general Markush structure is represented here below as Figure 1:



I

- K. The impugned specification provides a range of substitutions to the substituents namely R¹, R², R³ᵃ, R³ᵇ, R⁴, R⁵, R⁶, X and Y. The general formula represented at Figure 1, the nitrogenous base may be any of a to d as depicted in the Figure 2.



- L. It appears from the impugned specification that the substitution for a,b,c and d may comprise as its nitrogenous base of any substituted thymine base(a), substituted uracil base (b), substituted adenine base (c) and substituted guanine (d). It is pertinent to note that the impugned specification discloses several possible compounds with the broad substitutions described. However, the specification only provides only few examples of the compounds. The substitutions provided by the impugned specification are only mere mathematical probability that may be obtained from any computer software and it is not depicted after a thorough experimentation. It is only a possibility of compounds that could be formed as a result of the synthesis.
- M. The impugned application provides broad disclosures relating dosage administrations using the said compounds and also discloses possible compositions where the said compounds could be co-administered with other pharmaceutical active ingredients which are also anti-viral agents. However, the pharmaceutical composition and its *in vivo* use are not illustrated in the impugned specification. [see page 662-664 of the Complete Specification]
- N. Though the impugned specification enlists the possibilities of millions of compounds, only general disclosure for preparation of these compounds is provided. [see page 672-673 of the Complete Specification]
- O. The example 1 and 2 appears to be drawn towards a general procedure for the preparation of phosphorodichloridates. Examples 3 purportedly discloses a general procedure for preparation of phosphoramidate derivatives being represented as a general scheme depicted by way of Markush. Example 4 appears to be drawn to the synthesis of 2'-dexo-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 being the markush structure and various substitutions for the said markush structure. Examples 13 to 65 have been listed as various possible substitution of the said markush structure. 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 a similar manner example 67 to 74 are represented as the general chemical structure and by a mere general statement stating that these examples may be prepared as per the 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 the *in vitro* result for testing certain illustrated compound of the 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.

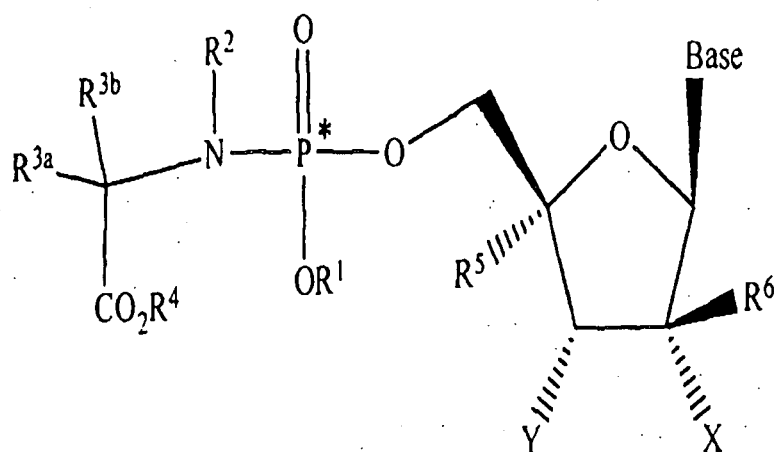
- P. The opponent submits that the claims as amended and as currently on record are not patentable as per the provisions of this Act.

III. GROUNDS OF OPPOSITION

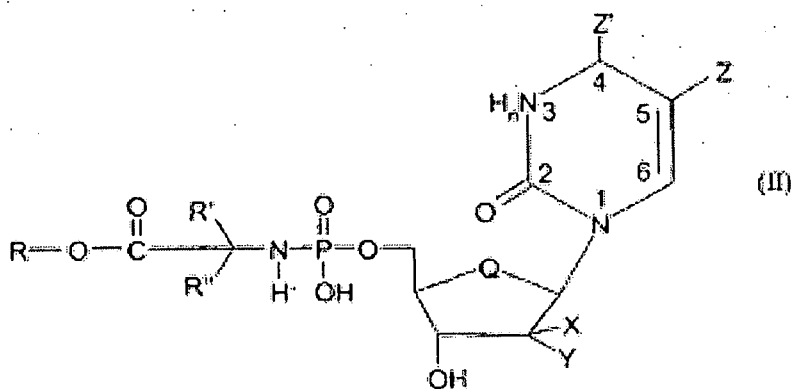
- A. Subject matter of claims 1-3 and 8-10 are not new and lack novelty, are anticipated by prior publication and hence ought to be rejected under Section 25 (1)(b) read with Section 2(1)(j) of the Patents Act, 1970:

- a. Section 2(1) (j) defines an "invention" as " a *new* product or process involving an inventive step and capable of industrial application." (emphasis added). Therefore, all inventions, in order to be patentable must satisfy the criteria of novelty.

- b. Section 25(1) (b) provides a ground of opposition where the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim... (ii) in India or elsewhere, in any other document.
- c. It is well established that novelty is determined by comparing the claims of the impugned specification and the disclosures in the prior art read in the light of general knowledge available to a person skilled in the art.
- d. The Opponent submits that the compounds of the alleged invention covered under claims 1 to 14 fail for lack of novelty and are anticipated in the light of disclosure of 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 A".
- e. The general formula of the alleged invention as disclosed in the impugned specification is reproduced below:



- f. The WO'327 discloses a chemical compound having formula 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 -CH₂;

X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃);

Ar is a monocyclic aromatic ring moiety or a fused bicycle 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 -NH₂ 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 (-CH₃), one of R' and R'' is H and one of R' and R'' is methyl (-CH₃), then Ar is not phenyl (-C₆H₅). [see page 3 of the complete specification of WO '327]

The opponents submit that the Sofosbuvir, as claimed in the impugned specification is covered by WO '327. The impugned specification discloses and claims (S)-2-([2R,3R,4R,5R]-5-((-2,4-dioxo-3,4-dihydro-2H-prrimidin-1-yl)-4-fluro-3-hydroxy-4-methyltetrahydrofuran-2-yl-methoxy]-phenoxy-phosphorylamino)-propionic acid isopropyl ester. Accordingly, compound Sofosbuvir claimed under claim 1 is directly disclosed in WO '327, where the substitutions of R, R', R'', Q, X, Y, Ar and Z given in therein are as below:

R is selected from a group comprising **alkyl**;

R' and R'' are independently selected from the group comprising H, alkyl;

Q is selected from the group comprising -O-;

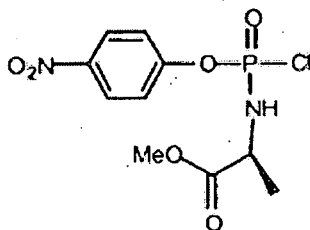
X and Y are independently selected from the group comprising F and methyl(-CH₃);

Ar is a monocyclic aromatic ring moiety;

Z is selected from when n is 1, Z' is =O;

When the scaffold disclosed in WO '327 is substituted with above groups or substituents, (S)-2-{[2R, 3R, 4R, 5R)-5-(-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl-methoxy]-phenoxy-phosphorylamino}-propionic acid isopropyl ester is obtained. Hence, the compound disclosed in claim 1 is anticipated by WO '327. Hence claims 1 and its diastereomer claim in claim 8 are not novel and are anticipated in the light of disclosures in WO'327.

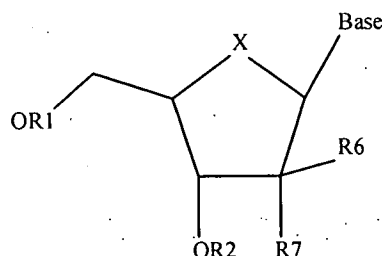
- g. The WO'327 exemplifies the process involving synthesis of phosphoramidate esters containing alanine as the amino acid, and unsubstituted phenyl is clearly exemplified by the preparation and use of the following prodrug moiety into the base compound:



- h. Therefore in the light of disclosures made in the WO'327 which matches all substituents in the structure of the impugned application showing that the compound claimed in claim 1 & 8 are not novel.
- i. Without prejudice to the above averments, the claims 1 to 14 of the impugned specification are anticipated in the light of the disclosures in WO 2001/92282 published on 06 December 2001 (hereinafter referred to as WO '282), filed by Novirio Pharmaceuticals, a copy of which is hereto annexed and marked as

“Annexure B”. This application is drawn to substituted nucleotide compounds for the treatment of HIV, HCV infections and the like. The WO '282 is drawn to a basic chemical moiety comprising of a sugar molecule which is substituted at 1'-position with a nitrogenous base and 5'-position with a phosphate prodrug chain as illustrated in Formula I to XVIII. The Formula XI of WO '282 is drawn to a sugar moiety, which is substituted with 2'-position with a nitrogenous base and other positions are substituted with several substituents, same are provided in the application. It is submitted that compounds claimed in Claim 1 and Claim 8 are known and encompassed within the basic chemical structure of the WO '282. It is submitted that the compound disclosed in Claim 1, allegedly known as Sofosbuvir, comprises of a nitrogenous base which is attached to a sugar molecule. The sugar molecule is substituted by a halo and alkyl substitution and one of the hydroxyl groups of the sugar is substituted by a phosphoramidate group. The NH group of phosphoramidate group is further substituted by an alkaryl and the oxygen atom is substituted by a phenyl ring.

- j. The general chemical formula in WO'282 [see structure XI, Page- 9, Page-26] is disclosed herein below:



- k. The basic structure as disclosed has an attachment at 2'-position with a nitrogenous base and hence is a substituted nucleoside compound. The other positions are further substituted with various other substituents. On substituting fluoro and methyl group at 3'-position, hydrogen at 4'-position and phosphate prodrug at 5'-position; the compound arrived at is similar to the compound of the impugned patent application. These compounds are found to be used for the treatment of HIV infections, HCV infections and the like.

1. The following assumptions can be made, based on the general Markush structure.

Base is **Uracil**

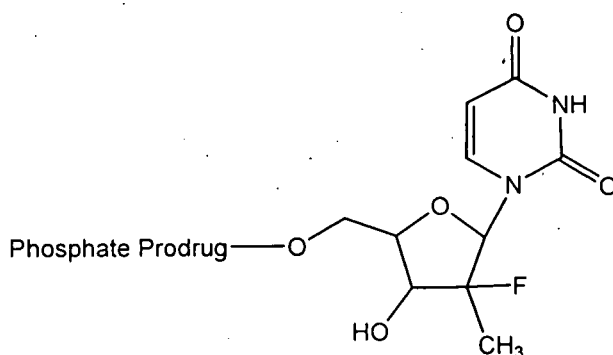
R₁ is **Phosphate Prodrug**

R₂ is **Hydrogen (H)**

R₆ is **Fluorine (F)**

R₇ is **Methyl (CH₃)**

Substituting the above groups in the general Markush Structure, the following compound is obtained which is structurally very similar to the compound of the impugned patent application.



- m. In the above structure when the phosphate prodrug is a phosphoramidate, then the resultant compound is Sofosbuvir and the structure similar to that of the compound claimed in claim 1 may be obtained.
- n. It is well known that phosphate prodrug by definition encompasses phosphoramidate compounds. These prodrugs also includes base such as uracil, thymidine etc, which may be found whether as their substituted/ unsubstituted form. The opponents submit that the compounds of impugned specification may be arrived at by the substitutions provided in WO'282. The compounds of the alleged invention would fall within the illustrations provided in WO'282. Thus the compounds of claims 1 and 8 are just isomers of each other and there it may be considered that both the compound of claim 1 and that of claim 8 are anticipated by the disclosures in WO '282.

- o. Thus all claims 1 to 14 are not novel as being anticipated by the disclosures in prior art as discussed above and ought to be rejected.

B. Section 25(1) (e): Section 25 (1)(e) read with section 2(1)(ja) of the Patents Act, 1970:

- a. Section 25(1)(e) of the Act provides a ground of opposition on the ground that the alleged invention is obvious and does not involve an inventive step.
- b. Section 2(1)(ja) of the Act defines an inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art".
- c. The requirement of inventive step, as defined in section 2(1)(ja), encompasses a two fold requirement—firstly the feature involved in the alleged invention ought to involve a technical advance as compared to the existing knowledge and secondly, the feature should not be obvious to the person skilled in art.
- d. According to the impugned specification, the alleged invention relates to a nucleoside phosphoramidate prodrugs. These compounds have been intended to use in the treatment of HCV.

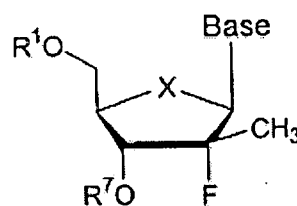
Basic compounds to arrive at the claimed compounds were known in art

- e. It is submitted that compound claimed in the impugned specification is a nucleoside derivative. Nucleoside analogue drugs which are long known for their antiviral effect and have been used in the treatment of cancers and HIV. It is well known that nucleosides such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC), and 2',3'-dideoxy-2',3'-didehydrothymidine (d4T), were reported to be active against human immunodeficiency virus.
- f. Raffaele De Francesco and Charles Rice, New therapies on the horizon for Hepatitis C: Are we close?, Clin Liver Dis, February Vol. 7, 211-

243 (2003) a copy of which is marked as **Annexure C** discusses various strategies for treating HCV that have been and are being pursued including the use of nucleoside analogues to inhibit NS5B enzymatic activity. These strategies include the use of nucleoside analogues to inhibit NS5B enzymatic activity. This article confirms that early 2003, NS5B had been identified as a target for the development of anti HCV therapies. It suggests that inhibition of this pivotal enzyme would lead to the suppression of HCV replication in infected cells.

- g. 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 D** discloses pyrimidine nucleoside beta-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine as a potential inhibitor for hepatitis C virus RNA-dependant RNA polymerase. It discloses that 2'-deoxy-2'-fluorocytidine (2'-FdCyd)² and 2'-C-methyl nucleosides. It also describes the synthesis and biological activity of 2'-deoxy-2'-fluoro-2'-C-methyl cytidine.
- h. Consequently before the date of priority of the impugned application, nucleoside analogues with 2'-fluoro-2'-methyl substitution were known. It was also known such nucleosides derivatives with fluoro substitution could be potential starting materials for enhanced bioactivity.
- i. The opponents submit that WO 2005/003147 hereinafter the WO '147 published on 13 January 2005 a copy of which hereto annexed and marked as **Annexure E**. This WO '147 discloses (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) or its pharmaceutically acceptable salt or prodrug thereof, and the use of such compounds for the treatment of Hepatitis C etc. It is further stated that 2' substitutions on the β -D or β -L nucleosides impart greater specificity for hepatitis C virus as well as exhibiting lower toxicity. The reason for this specificity is the presence of a 2'-fluoro substitution on the ribose ring.
[see lines 16-28, page 16]

- j. Further, claim 6 of the WO '147 discloses a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) or its pharmaceutically acceptable salt or prodrug thereof of structure:



wherein the base is a purine and pyrimidine base;

X can be O,

R¹ and R⁷ can be H, phosphate, including monophosphate, diphosphate, triphosphate or a stabilized phosphate prodrug.

The term "pharmaceutically acceptable salt or prodrug" has been described any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a compound which, upon administration to a patient, provides the active compound. Some of the examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. The prodrugs include that can be oxidized, reduced, animated, deanimated, hydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, Acylated, phosphorylated, dephosphorylated to produce the active compound.

- k. The prodrugs can include the 5'-triphosphate, tri phosphoric acid ester derivatives of a nucleoside compound and pharmaceutically acceptable salts of 5' diphosphate and 5' monophosphate ester derivatives of the compounds claimed. [see pages 42-43 of WO '147]

- l. The WO '147 discloses that any of the nucleosides described herein, or any other nucleoside that has anti-hepatitis activity, can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the

nucleoside. A number of nucleotide prodrug ligands are known. A nucleotide prodrug, as described herein, refers to a nucleoside that has a phosphate derivative on the 5'-position that is more stable in vivo than the parent phosphate, and which does not materially adversely affect the anti hepatitis C activity of nucleoside. Further,'147 Application also teaches pharmaceutical compositions based on β -D or β -L compound or its pharmaceutically acceptable salt of prodrug can be prepared in a therapeutically effective amount for treating a flaviviridae infection including HCV. Thus the WO '147, therefore teaches 2' substitution on the nucleoside tetrahydrofuran ring, biologically labile protecting moieties and its delivery through a stabilised phosphate pro-drug and compositions involving the same.

- m. Furthermore compounds such as Emtricitabine (FTC) and Lamivudine (3TC) have been known to have anti-viral activity. These compounds comprise a nucleoside that is, a nitrogenous base attached to a sugar molecule. Thus nucleosides as anti-viral agents were well established by various scholarly articles.
- n. The opponents submit that in the light of the disclosures in WO '327, the subject matter of the impugned specification is obvious to a person skilled in art.

C. Phosphate prodrugs including phosphoramidates are well-known in the art

- a. Due to poor oral bioavailability and low intestinal permeability, nucleoside analogue prodrugs were used to facilitate drug delivery. A class of prodrugs is aryl phosphoramidate which have been used as derivatives of zidovudine phosphomonoester amide and were known for their effective treatment for HIV as early as 1990.
- b. It is well known that nucleoside analogue is delivered inside the cell to its active triphosphate form. However, the triphosphate form of a nucleoside is not considered to a viable drug candidate because of its

chemical stability along with high polarity that hinders them from transporting across cell membranes. The nucleoside analogue phosphate activation process occurs in three steps, the first phosphorylation is often considered to be rate-limiting. This led the chemists to prepare stable monophosphate prodrugs of nucleoside analogues which could be delivered intracellularly. Such nucleoside monophosphate prodrugs cross the biological barriers and reach the target cells or tissues. Once inside the cell, the labile protecting groups are degraded enzymatically or chemically, thereby releasing the free nucleoside analogue in the monophosphate form. Within the nucleoside analogue phosphate activation process, the first phosphorylation has often been identified as a rate limiting step, which led medicinal chemists to prepare stable "protected" monophosphate nucleosides (prodrugs) capable of delivering nucleoside monophosphates intracellularly. Hence, most of the nucleoside analogues are converted to its monophosphate which will thereby convert intercellularly to its corresponding nucleoside triphosphate.

- c. Substitutions on aryl phosphoramidate prodrugs of nucleosides have been a subject of experimentation among scientists for both HIV and HCV. Hence it was very much within the prior art and more common among pharmaceutical scientists while conducting experiments on HCV drugs to apply nucleoside prodrugs to resolve oral bioavailability problems.
- d. The uses of prodrugs for modifying the physicochemical and pharmacokinetic properties of chemical molecules were already known in the art. Several scholars have also written about such modifications. For instance, Jones et al "Minireview: nucleotide prodrugs" Antiviral Research 27 (1995) 1-17, a copy of which is marked as **Annexure F** discusses such modification of pharmaceutical compounds using the phosphate prodrugs to improve the pharmacokinetic properties.
- e. Van Rompay, "Phosphorylation of nucleosides and nucleoside analogs by mammalian nucleoside monophosphate kinases", Pharmacol Ther, 2000. 87(2-3): p. 189-98 , a copy of which is marked as **Annexure G**

discloses that nucleoside monophosphate kinases catalyze the reversible phosphotransferase reaction between nucleoside triphosphates and monophosphates, i.e., monophosphates are converted to their corresponding diphosphate form. It gives an overview on the substrate specificity, tissue distribution, and subcellular location of the mammalian monophosphate kinases and their role in the activation of nucleoside and nucleotide analogs.

- f. Christopher McGuigan, *et al* "Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully by-pass thymidine kinase", FEBS Letter 351, published on 29 August 1994, a copy of which is marked as **Annexure H** discloses that the prodrug derivatives to mask the ionized phosphate group of nucleosides have been used. It discusses that using the ProTide prodrug strategy to activate the triphosphates of an inactive HIV compound. It also states that such aryloxy phosphoramidate could be more active than the parent nucleoside.
- g. Christopher McGuigan *et al*, "Aryl Phosphoramidates of d4T have improved anti-HN efficacy in tissue culture and may act by the general of novel intracellular metabolite", Journal of Medicinal Chemistry, published on 12 April 1996, a copy of which is marked as **Annexure I** discloses that in order to overcome the dependence on nucleoside kinase activation, it would be suitable to develop a nucleotide with (aryloxy) phosphoramidates derived from AZT. It emphasizes that better activity of aryloxy phosphoramidates in thymidine kinase deficient cell in comparison to thymidine dependent cells.
- h. Christopher P. Landowski *et al*, "Targeted delivery to PEPT1 over expressing cells: Acidic, basic, and secondary floxuridine amino acid ester prodrugs" Molecular Cancer Therapeutics, published in or about April 2005, a copy of which is marked as **Annexure J** teaches that prodrug strategies are generally adopted to improve undesirable properties of therapeutic drugs to overcome barriers such as poor bioavailability, chemical stability and toxicity.

- i. Jisook Kim *et al*, "Direct Measurement of Nucleoside Monophosphate Delivery from a Phosphoramidate Pronucleotide by stable isotope labelling and LC-ESI-MS/MS", Molecular Pharmaceutics, published in or about March 2004, a copy of which is marked as **Annexure K**, discusses that amino acid phosphoramidates of nucleosides have been shown to be potent antiviral and anticancer agents with the potential to act as nucleoside monophosphate prodrugs.

Specific amino acids used in preparing the prodrugs were also known

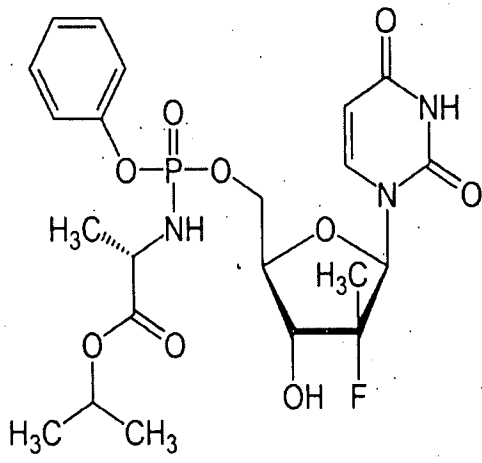
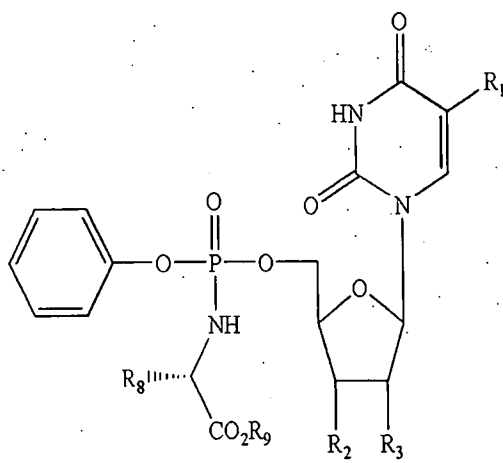
- j. Dider Saboulard *et al*, "Characterization of the activation pathway of phosphoramidates trimer prodrugs of stavudine and zidovudine" Molecular Pharmacology, 1999, a copy of which is marked as **Annexure L**, discloses that while selecting phosphoramidate trimer derivatives, it would be a good strategy to prefer L-alanine moiety over other stereoisomeric forms.
- k. J. Balzarini *et al*, "Mechanism of anti-HIV action of masked alaninyl d4TMP derivatives", Proc Natl Acad Sci USA, published on in July 1996, a copy of which is marked as **Annexure M**, discloses that discloses that alaninyl d4T-MP reached about 13-fold higher levels in So324-exposed cells than d4T-MP which means that the presence of alanine increased the activity of the monophosphate.
- l. Vidhya V. Iyer, *et al*, "Synthesis, *in vivo* anti-breast cancer activity, and intracellular decomposition of amino acid methyl ester and alkyl amide phosphoramidate monoesters of 3'-azido-3'-deoxythymidine (AZT)", Journal of Medicinal Chemistry, a copy of which is marked as **Annexure N**, suggests that various phosphoramidate mono esters containing amino acid methyl and N-alkyl amide moieties were found to be more cytotoxic. It showed a marked preference towards L-alanine stereoisomeric form in the phosphoramidate mono esters.
- m. Dominique Cahard *et al*, "Aryloxy Phosphoramidates Triesters as ProTides", Mini-Reviews in Medicinal Chemistry, published in or about May 2004 a copy of which is marked as **Annexure O**, discloses that aryloxy phosphoramidates are highly active antivirals. There is a

preference for alanine, wherein a preference for L-alanine over D-alanine.

- n. 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, which was published on 17 March 2007, a copy of which is marked as **Annexure P**, suggests aryloxy phosphoramidate ProTide approach which allows the bypass of the initial kinase dependence of intracellular delivery of the monophosphorylated nucleoside analogue as a membrane permeable "ProTide" form leads to improved activity over the parent compound.

Phosphoramidate compounds are well known in art

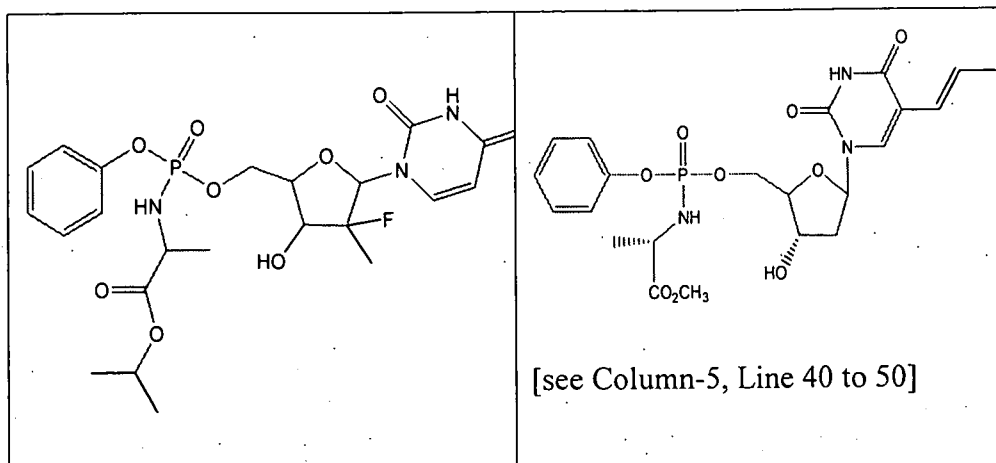
- o. US 2003/0109697 published 9 April 2002 (hereinafter referred to as '697 Application) titled as "Anticancer agents, infection therapy, autoimmune disease, anti-inflammatory agents" is hereto annexed and marked as **Annexure Q**, discloses phosphoramidate compounds. The '697 Application discloses a basic scaffold and the substitutions provided to the basic formula encompasses the compound claimed in the alleged invention. This has further illustrated in the table below:

3658/KOLNP/2009	US2003/0109697
	 <p>R1H, alkyl, alkenyl, alkynyl, vinyl, propargyl and substituted derivative</p>

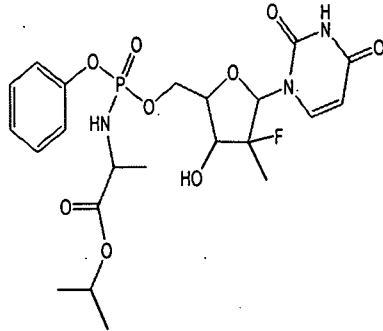
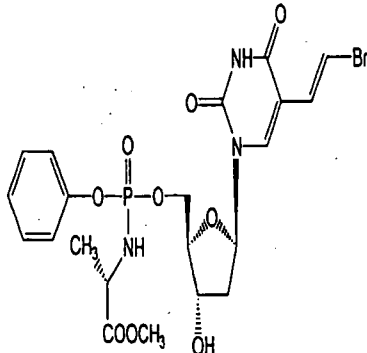
	<p>thereof;</p> <p>R² and R³Br, Cl,F,I,H,OH,OC(=O)CH₃,O,O-R_g; wherein R_ghydroxyl protecting group other than acetyl;</p> <p>R⁸ side chain of any naturally occurring amino acid, its analogue or its isomer;</p> <p>R⁹H,aliphatic group,alicyclic group,an aromatic group,etc.</p> <p>And any enantiomeric, diastereomeric or stereoisomeric form including D-form, L-for, etc.</p> <p>.....</p> <p>[see claim 1 and page 16, top left compound]</p>
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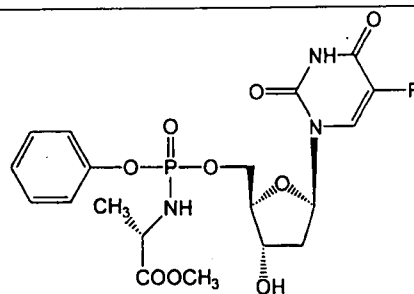
- p. Hence '697 Application discloses compounds that are substantially similar to the compounds disclosed in the impugned specification, in claim 1, 8 and 14.
- q. WO1996/23506 is the publication number of the PCT application filed 31 January, 1996 and has been published in German. Its corresponding US application US 6589941 was granted on 8 July 2003 (hereinafter referred to as '941 patent) is hereto annexed and marked as **Annexure R**.
- r. The opponents submit that '941 patent discloses compounds which have analogous structures to the compounds disclosed in the impugned specification in claims 1 and 8. A comparison table provides further details:

3658/KOLNP/2009	US589941
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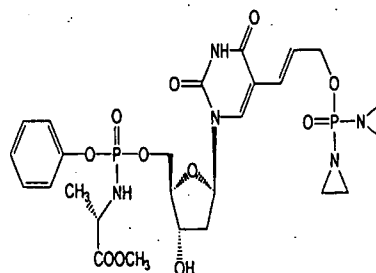


s. Further, WO1999/037753 published on 29 July 1999 (hereinafter referred to as WO'753) titled "Enzyme Catalyzed Therapeutic Agents" is hereto annexed and marked as **Annexure S**.

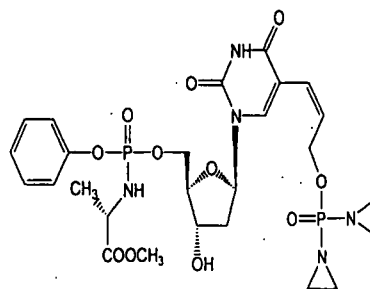
3658/KOLNP/2009	WO1999/037753
	<p>Compound disclosed in claim 35:</p>  <p>Compound disclosed in claim 36:</p>



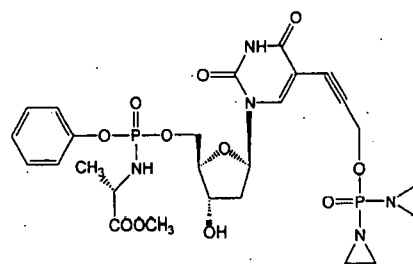
Compound disclosed in claim 37:



Compound disclosed in claim 38:



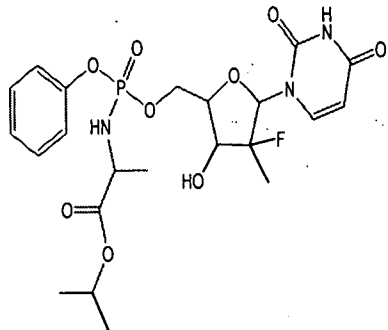
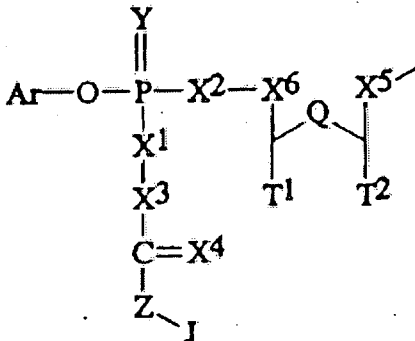
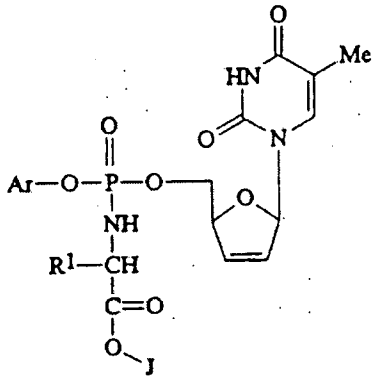
Compound disclosed in claim 39:



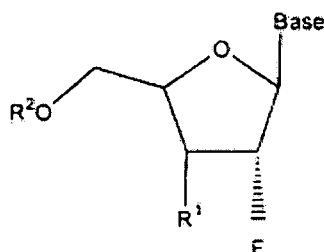
- t. Hence from above examples it very evident that phosphoramidate compounds analogous to the compounds as claimed in claim 1 are known and well established in prior art.

Structurally analogous compounds already known in art

- u. WO 1996/29336 published on 26 September 1996 (hereinafter referred to as WO'336) titled as "Chemical Compounds", is hereto annexed and marked as **Annexure T**. The '336 Application discloses masked monophosphate nucleoside analogues for the treatment of HIV and anti-viral infection. The general scaffold disclosed in the '336 Application and the suggested substitution appears to encompass the compounds disclosed and claimed in the impugned specification. Below is an illustration of the same:

3658/KOLNP/2009	WO1996/29336
	 <p data-bbox="962 1183 1412 1249">[see page 3, line 1 to page 4 line 21 of the '336 Application]</p>  <p data-bbox="970 1725 1420 1791">[see page 10. Line 7 to 25 of the '336 Application]</p>

- v. The compounds disclosed in WO '336 are nucleotides which consist of a nitrogenous base with a sugar and having a phosphoramidate group attached to it. These compounds have anti-viral activity.
- w. By following the changes recommended in the prior art an alternation could be brought to the sugar molecule by inserting a halo group in the sugar molecule. There are several examples of such modification to such molecules. For instance, WO 1999/43691 published 02.09.1999 (hereinafter referred to as WO '691) titled "2'-fluoronucleosides" is hereto annexed and marked as **Annexure U** discloses sugar with halo substitutes. [see page 14, lines 1-15, claims 1,6,9, 10, 12 , 13 of the '691 Application]

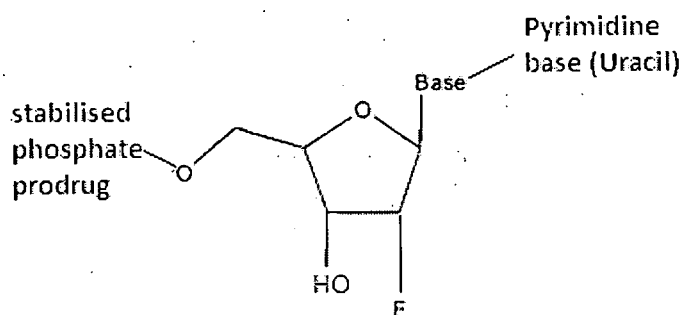
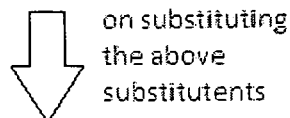


Wherein:

Base is Purine or Pyrimidine;

R1 is OH,H,OR3, N3, CN, Halogen etc;

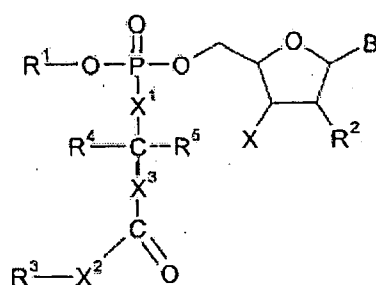
R2 is H, Phosphate (including monophosphate, diphosphate, triphosphate or a stabilized phosphate prodrug)



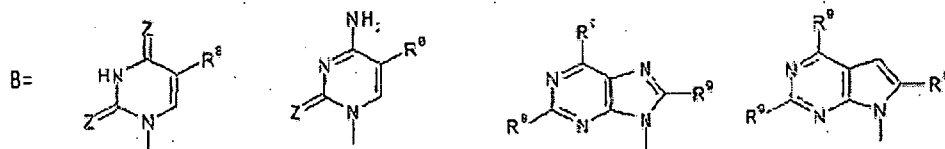
- x. The WO'691 is directed towards 2'-fluoronucleoside compound which are useful in the treatment of hepatitis B infection, Hepatitis C

infection, HIV infection and any abnormal cellular proliferation including tumors and cancer.

- y. The introduction of an alkyl group in the sugar molecule appears to be known and obvious for analogous molecules as disclosed in the prior art which are used in treatment of Hepatitis C infection. For instance, WO 2003/000713 published on 3 January 2003 (hereinafter referred to as WO '713), "Nucleoside compounds in HCV" is hereto annexed and marked as **Annexure V**.
- z. The WO '713 discloses protide derivatives of therapeutically active nucleoside derivatives, processes for their manufacture. These compounds are particularly used for the treatment or prophylaxis of certain viral infections especially Hepatitis C virus infection.



Wherein:



Z=O or S;	R ¹ = H, optionally substituted C ₁₋₆ alkyl, optionally substituted aryl, optionally substituted heteroaryl
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R⁸ = H, Halo, Hydroxy, etc

X=H,F,N₃,NH₂,CN,OMe

X¹= O, NR⁷;

R⁷ = H

X² = O,NH, NR⁶, S

X³=Absent

R² =OH, OCOR⁶, OCOR⁶

R³ = H, optionally substituted C₁₋₆ alkyl, aryl etc.

R⁴ and R⁵=H

aa. Thus it is quite obvious to arrive at the compounds disclosed in the impugned specification and claims therein. Further, while following the substitutions provided in the prior art, it appears that the compounds disclosed in the impugned application are also disclosed.

bb. Hence in the light of prior art following are well-established:

- i. Basic compounds to arrive at the claimed compounds were known in art
- ii. Phosphate prodrugs including phosphoramidates are well-known in the art
- iii. Specific amino acids used in preparing the prodrugs were also known
- iv. Phosphoramidate compounds are well known in art
- v. Structurally analogous compounds already known in art
- vi. Thus, all claim 1-14 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.

D. Section 25(1) (f): Subject matter of claims 1-14 is not an invention within the meaning of this Act

i. The subject matter of claims 1-14 do not constitute an invention as under section 25(1)(f) read with section 3(d) of the Act

1. Section 25(1) (f) of the Act provides a ground for opposition where the subject of any claim of the complete specification is not an invention within the meaning of the Act. Section 3 enumerates what are not inventions within the meaning of this Act. Thus, claims that fall within the ambit of section 3 are liable to be rejected.
2. Under section 3(d) of the Patents Act, a new form of a known substance is not an invention unless it results in enhancement of the known efficacy of the known substance. Section 3(d) was amended in 2005 to prevent patents on modifications of known substances, such as combinations and salts, esters, ethers and other derivatives of known substances. Under the law, each product claim that relates to a new form of a known substance has to satisfy section 3(d) of the Patents Act.

3. In the alternative to and without prejudice to the other grounds raised herein, Claims 1-14 fail under section 3(d) of the Act.
4. It is established law that section 3(d) has to be satisfied independently of sections 2(1)(j) and 2(1)(ja) [See *Novartis AG v Union of India and others*, (2013) 6 SCC 1]. This burden is always on the Patent Applicant. [see *Novartis AG and another v Union of India and others*, (2007) 4MLJ 1153, para 13]
5. In *Novartis AG v Union of India and others*, the Hon'ble Supreme Court of India held that the expression "efficacy" in the section 3(d), in case of pharmaceutical substances, is to be understood as therapeutic efficacy. Further, it is also an established position that the data relating to efficacy ought to be provided in the Complete Specification.
6. Claims 1, 7, 8 and 14 are directed towards a product. The impugned application appears to be derivatives of phosphoramidate. In order to discharge the burden of section 3(d), the Applicant ought to have compared therapeutic efficacy with the closest compounds. The applicant has failed to discharge this burden.
7. The claims 6 and 13 are drawn towards a process for synthesis of the compounds as claimed in claim 1, 7, 8, and 14. However no new reactants or resultant products are involved in the process. Hence, these claims ought to be rejected for not satisfying section 3(d).
8. Without prejudice to the above, the alleged invention claimed in the present application amounts to a new use of a known substance described in WO '327 marked as **Annexure A** which discloses the use of various phosphoramidate derivatives of nucleotides for use in the treatment of cancer.
9. Further, the WO '147 discloses (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) and prodrugs thereof. The compounds disclosed in WO '147 are structurally analogous to the compounds in the impugned application. The '147

Application discloses certain data regarding the activity of the compounds disclosed therein. It is to be noted that both WO '147 and the impugned application were filed by the Applicant. Hence, the Applicant should have provided the data regarding enhanced efficacy of the compounds disclosed in the impugned application. The Applicant has failed to disclose the same. The Applicant has not compared the efficacy of the claimed compounds with the compounds claimed in the WO '147.

10. In view of the above, the subject matter claimed in the impugned application does not satisfy the requirement laid down by section 3(d) and ought to be rejected in toto.

ii. The subject matter of claims 2,3,9 and 10 are not patentable under section 3(e) of the Act:

These claims are drawn towards to a composition. The composition claimed is mere admixture which results in mere aggregation of properties with no synergistic effect. Therefore these claims ought to be rejected on this ground.

iii. The subject matter of claims 4,5,11 and 12 are not patentable under Section 3(i) of the Act:

The claims relating to method of treatment are not allowable under section 3(i) of the Act.

D. 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.

i. The impugned specification does not disclose the best mode of preparation of said compounds

1. The impugned specification does not sufficiently and clearly describe the invention and the method in which the alleged invention is to be performed.

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

1. The claims 2 and 9 are relating to pharmaceutical composition of the compound which is claimed in claims 1 and 8. However, claims 2 and 9 are 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 or 8. Further, claims 2 and 9 lacks sufficient disclosure for obtaining the composition of compounds claimed in claims 1 and 8. Further, the specification does not disclose the best form of administration of the drug. Further, specific excipient for the preparation of best mode of administration is not disclosed. Therefore, a person skilled in the art will not be able to make the specific composition of compounds in claims 1 and 8 from the disclosure in the impugned specification.
2. The impugned application claims the diastomeric forms in claims 1 and 8, however this is not disclosed in the description.
3. The process as claimed in claims 6 and 13 and the product claimed in claims 7 and 14 seems to be the result of the process claimed in claims 6 and 13 are not disclosed in and supported by the impugned specification. The specific process conditions and parameters are not disclosed in the specification. These claims have been incorporated as amended claims filed on 26 December 2011, appears to be a new matter which draws no support from the specification. In the absence of appropriate support in the impugned specification such claims ought not to be granted.

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

- i. 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.
- ii. 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.
- iii. 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.
- iv. 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.

IV. HEARING REQUESTED

The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as "the Patents Act") and Rule 55 of the Patents Rules (hereinafter referred to as "the Rules").

PRAYER

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

- (i) For an order rejecting Claims 1-14 for lack of novelty under section 25(1)(b)(ii) of the Patents Act, 1970;
- (ii) For an order rejecting Claims 1-14 for lack of inventive step under section 2(1)(ja) read with section 25(1)(e) of the Patents Act, 1970;
- (iii) For an order rejecting Claims 1, 6, 7, 8, 13 and 14 as they are not inventions within the meaning of the Patents Act under section 3(d) read with section 25(1)(f) of the Patents Act, 1970;
- (iv) For an order rejecting Claims 2, 3, 9 and 10 as they are not inventions within the meaning of the Patents Act under section 3(e) read with section 25(1)(f) of the Patents Act, 1970;
- (v) For an order rejecting Claim 4, 5, 11 and 12 as not an invention within the meaning of the Patents Act under section 3(i) read with section 25(1)(f) of the Patents Act, 1970;
- (vi) For an order rejecting Claim^{1-2, 6-9 and 13+14} as it is insufficiently described and therefore not patentable under section 25(1)(g) of the Patents Act, 1970;
- (vii) For an order rejecting the Application for not providing details as required under Section 8 read with Section 25(1)(h) of the Patents Act, 1970;
- (viii) For an order rejecting any request by the Applicant for leave to amend its Application;
- (ix) For a copy of any reply statement and evidence and / or amended specifications that may be filed by the Applicant and a further opportunity to file a rejoinder and rebut the same;
- (x) For leave to amend the opposition, as and when required;

- (xi) For a hearing under section 25(1) of the Patents Act read with rule 55(1) of the Patents Rules;
- (xii) For costs;
- (xiii) For such further and other orders as may become necessary in the circumstances of the case.

Dated this 19 day of February, 2015

Chitra Arvind

CHITRA ARVIND
FOR RAJESHWARI & ASSOCIATES
AGENT FOR THE OPPONENT

To,

The Controller of Patents

The Patent Office, Kolkata.

List of Annexures

1. **Annexure A**—WO 2005/012327
2. **Annexure B**—WO 2001/92282
3. **Annexure C**—Raffaele De Francesco and Charles Rice, New therapies on the horizon for Hepatitis C: Are we close? Clin Liver Dis, February Vol. 7, 211-243 (2003).
4. **Annexure D**—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.
5. **Annexure E**—WO 2005/003147
6. **Annexure F**—Jones et Al "Minireview: nucleotide prodrugs" Antiviral Research 27 (1995) 1-17.
7. **Annexure G**—Van Rompay, "Phosphorylation of nucleosides and nucleoside analogs by mammalian nucleoside monophosphate kinases", Pharmacol Ther, 2000. 87(2-3): p. 189-98.
8. **Annexure H**—Christopher McGuigan, et al in "Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully by-pass thymidine kinase", FEBS Letters 351 (1994) 11-14.
9. **Annexure I**—Christopher McGuigan et al, "Aryl Phosphoramidates of d4T have improved anti-HN efficacy in tissue culture and may act by the general of novel intracellular metabolite", Journal of Medicinal Chemistry, 1996, 39, 1748-1753
10. **Annexure J**—Christopher P. Landowski et al, "Targeted delivery to PEPT1 over expressing cells: Acidic, basic, and secondary floxuridine amino acid ester prodrugs", Mol Cancer Ther 2005;4(4), April 2005.
11. **Annexure K**—Jisook Kim *et al*, "Direct Measurement of Nucleoside Monophosphate Delivery from a Phosphoramidate Pronucleotide by stable isotope labelling and LC-ESI-MS/MS", MOLECULAR PHARMACEUTICS VOL. 1, NO. 2, 102-111

12. **Annexure L**—Dider Saboulard et al, "Characterization of the activation pathway of phosphoramidates trimeric prodrugs of stavudine and zidovudine" *MOLECULAR PHARMACOLOGY*, **56**:693-704 (1999).
13. **Annexure M**—J. Balzarini et al, "Mechanism of anti-HIV action of masked alaninyl d4TMP derivatives", *Proc Natl Acad Sci USA* Vol. 93, pp. 7295-7299, July 1996.
14. **Annexure N**—Vidhya V. Iyer, et al "Synthesis, in vitro anti-breast cancer activity, and intracellular decomposition of amino acid methyl ester and alkyl amide phosphoramidate monoesters of 3'-azido-3'-deoxythymidine (AZT)", *J. Med. Chem.*, 2000, 43, 2266-2274.
15. **Annexure O**—Dominique Cahard et al, "Aryloxy Phosphoramidates Triesters as ProTides", *Mini-Reviews in Medicinal Chemistry*, 2004, 4, 371-381.
16. **Annexure P**—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
17. **Annexure Q**—US 2003/0109697
18. **Annexure R**—US 6589941
19. **Annexure S**—WO1999/037753
20. **Annexure T**—WO 1996/29336
21. **Annexure U**—WO 1999/43691
22. **Annexure V**—WO 2003/000713

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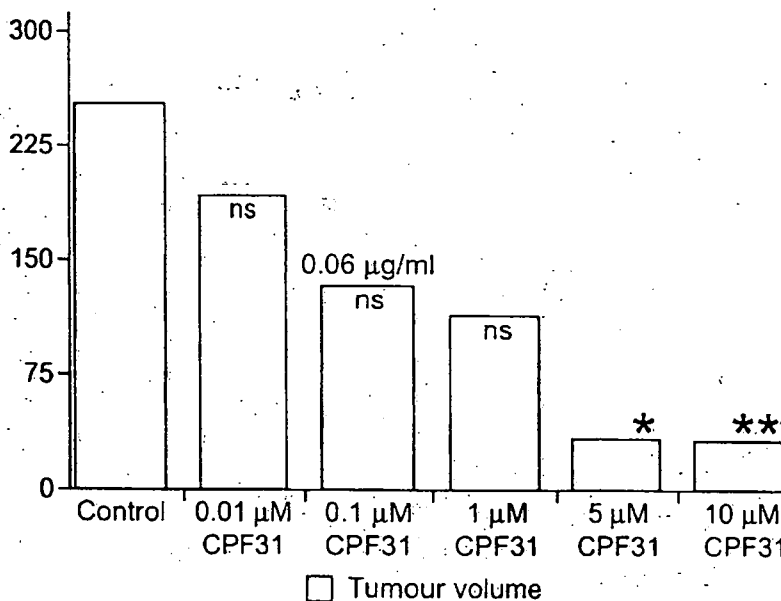
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[Continued on next page]

(54) Title: CHEMICAL COMPOUNDS



* p=0.096 vs control; ** p=0.094 vs control

(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 citidine 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.

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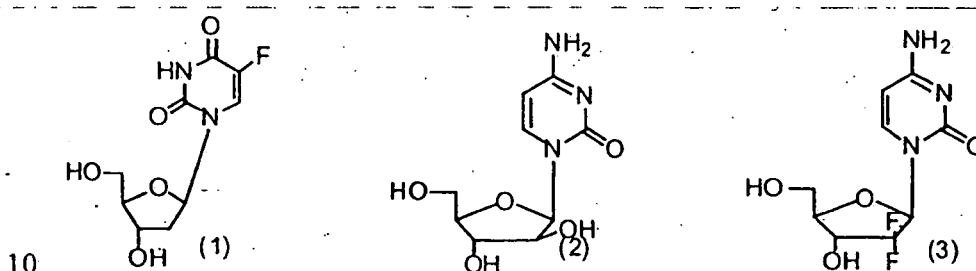
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Chemical Compounds

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

5

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:



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].

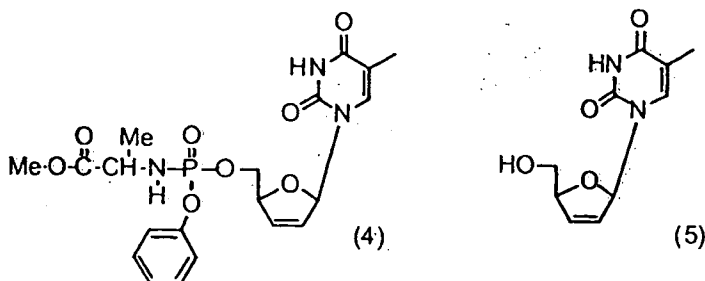
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In general the phosphate prodrugs have biological properties and therapeutic activities that are similar to, or somewhat lower than, the parent nucleoside analogue.

25 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.

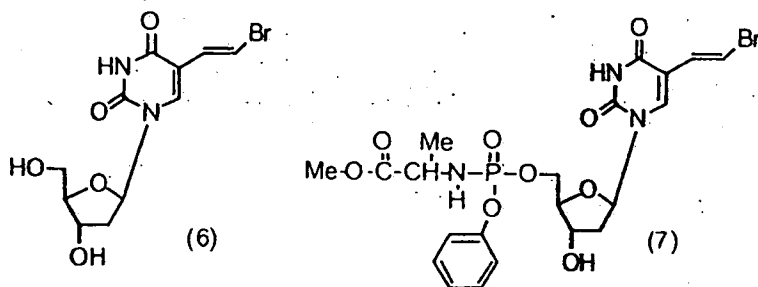
An example is the phosphoramidate (4) derived from anti-HIV d4T (5).



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].

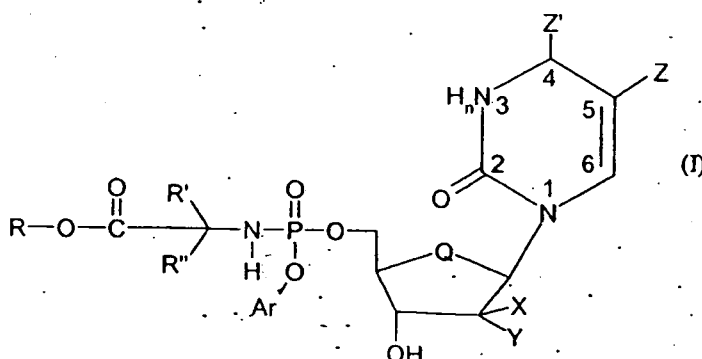
Lackey et al [Biochem Pharmacol., 2001, 61, 179-89] have reported the application of our phosphoramidate pro-drug method for antiviral nucleosides to the anti-herpetic agent bromovinyl-2'-deoxyuridine (BVDU) (6). In particular, they have found that the phenyl methoxyalaninyl phosphoramidate (7) has significant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



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:



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 -CH₂-;

X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃);

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 -NH₂ and a double bond exists between position 3 and position 4,

and

5 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 (-CH₃), one of R' and

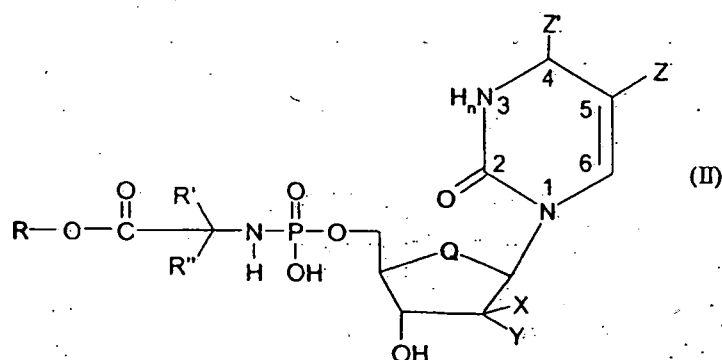
10 R'' is H and one of R' and R'' is methyl (-CH₃), then Ar is not phenyl (-C₆H₅).

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).

15

Suitably, except where R is 2-Bu (-CH₂-CH(CH₃)₂) and one of R' and R'' is H and one of R' and R'' is methyl (-CH₃), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl (-C₆H₅).

20 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

25 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 ($-\text{CH}_3$), one of R' and R'' is H and one of R' and R'' is methyl ($-\text{CH}_3$), then Z is not $-\text{CH}=\text{CHBr}$.

Suitably, with respect to compounds of formula II, when n is 1 and Z either is or is not $-\text{CH}=\text{CHBr}$, the moiety $\text{ROCOCR}'\text{R}''\text{NH}-$ corresponds neither to alanine (ie as above, R is not methyl ($-\text{CH}_3$), one of R' and R'' is not H and one of R' and R'' is not methyl ($-\text{CH}_3$)) 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 $-\text{CH}=\text{CHBr}$, the moiety $\text{ROCOR}'\text{R}''\text{NH}$ is neither derived from nor corresponds to any naturally occurring amino acid.

Even more suitably, with respect to compounds of formula II, when n is 1 or 0, the moiety $\text{ROCOCR}'\text{R}''\text{NH}-$ does not correspond to alanine (ie R is not methyl ($-\text{CH}_3$), one of R' and R'' is not H and one of R' and R'' is not methyl ($-\text{CH}_3$)), does not preferably correspond to tryptophan, and even more preferably the said moiety does not correspond to any naturally occurring amino acid.

Most preferably the moiety $\text{ROCOCR}'\text{R}''\text{NH}-$ 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.

44

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 CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyC₁₋₁₆alkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, C₁₋₆alkylamino, diC₁₋₆alkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, C₁₋₆alkylthiol, sulphonyl and sulfoxide; heterocyclic groups which may themselves be substituted; alkyl groups as defined above,

10 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, 15 alkyl-O- (for example where alkyl is C₁ to C₁₆, preferably C₁ to C₆) 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).

20 Reference in the present specification to alkoyl and aryloyl groups means, respectively, alkyl-CO- (for example where alkyl is C₁ to C₁₆, preferably C₁ to C₆) 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).

25

Reference in the present specification to alkoyloxy and aryloyloxy means, respectively, alkyl-CO-O (for example where alkyl is C₁ to C₁₆, preferably C₁ to C₆) 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, 30 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, imidazoliny, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indoliny, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, 5 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

10 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.

15

Suitably, R is a C₁₋₁₆ primary or secondary alkyl group, a C₅₋₇ carbocyclic aryl group or a C₁₋₆alkylC₅₋₁₁aryl group. More suitably, R is a C₁₋₁₀ alkyl group, a phenyl group or C₁₋₃ alkylC₅₋₇ aryl group. Preferably R is unsubstituted.

20 Preferably, R is methyl (-CH₃), ethyl (-C₂H₅), *n*- or *i*- propyl (-C₃H₇), *n*- or *i*- butyl (-C₄H₉) or benzyl (-CH₂C₆H₅). 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 (-CH₃); especially when Ar is unsubstituted phenyl, n is 0 and each of X and Y is F.

25 Suitably, R' and R'' are each independently selected from the group comprising H, C₁₋₆ primary, secondary or tertiary alkyl, C₁₋₃alkylC₅₋₇aryl, or, when together they form an alkylene chain, they provide, together the C atom to which they are attached, a C₃₋₈ carbocyclic aliphatic ring.

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

Alternatively, preferably, R' and R'' are, independently, H, methyl (-CH₃), secondary butyl (-CH₂-CH-(CH₃)₂), benzyl (-CH₂C₆H₅), or, together with the C atom to which they are attached, provide a C₅₋₆ ring.

- 5 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
10 compounds can be L or D or a mixture of stereoisomers. 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.

15

For example, when one of R' and R'' is H and one of R' and R'' is Me or PhCH₂, the moiety corresponds to alanine or phenylalanine, respectively.

- Preferably, the stereochemistry at the asymmetric centre -CR'R'' corresponds to an L-
20 amino acid. The stereochemistry at the asymmetric centre -CR'R'' can, however, correspond to a D-amino acid. Alternatively, mixtures 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,
25 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
30 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 tryptophan, 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.

5

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.

-
- 10 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 and Z is H, corresponding to phosphoramidated cytidine.

Suitably, Ar is a 5 to 14 membered aromatic ring moiety. The one or two rings may

- 15 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 C₆ monocyclic aromatic ring moiety, ie is optionally substituted phenyl.

- 20 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; -NO₂; -NH₂; optionally substituted -C₁₋₃alkyl; optionally substituted -C₁₋₃alkoxy, preferably methoxy (-OCH₃); optionally substituted -SC₁₋₃alkyl; -CN; optionally substituted -COC₁₋₃alkyl; and optionally substituted -CO₂C₁₋₃alkyl. The optional substituents are one or
- 25 more up to six, preferably three, members selected from the group comprising halogen which may be F, Cl, Br and I and NO₂. Preferred substituents on Ar include F, Cl, CF₃, and NO₂.

- The substituents may be at any position on the ring moiety. Where the ring moiety is C₆ ie
- 30 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 from the group comprising: Ph-, $p\text{CF}_3\text{C}_6\text{H}_4$ -, $p\text{FC}_6\text{H}_4$ -, $p\text{NO}_2\text{C}_6\text{H}_4$ -, $p\text{ClC}_6\text{H}_4$ - and $o\text{ClC}_6\text{H}_4$ -.

- 5 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 $-\text{CO}_2\text{Me}$. One, two or three substituents may be present. The alkenyl and alkynyl groups may contain one or more sites
- 10 of unsaturation.

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

- 15 Preferably Z is selected from the group comprising H, F, optionally substituted C_{1-6} alkyl particularly Me ($-\text{CH}_3$), optionally substituted C_{1-6} alkenyl and optionally substituted C_{1-6} alkynyl, the optional substituents being as recited immediately above.

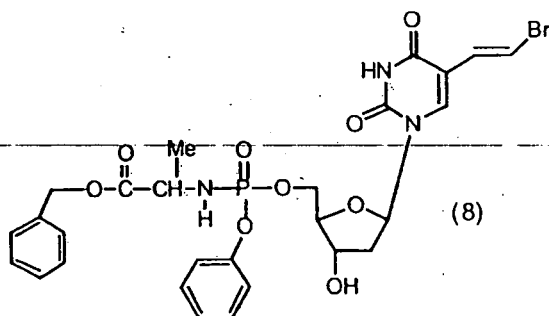
- When n is 1, Z' is O, Q is O and X and Y are each H, preferably Z is a substituted C_2
- 20 alkenyl (i.e. ethenyl or vinyl) moiety ($-\text{CH}=\text{CH}-$); more preferably, Z is bromovinyl ($-\text{CH}=\text{CHBr}$) or methylpropenoate ($-\text{CH}=\text{CHCO}_2\text{Me}$); and most preferably, Z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

- With respect to compounds of formula II, preferably when n is 1 and X and Y are both H,
- 25 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.

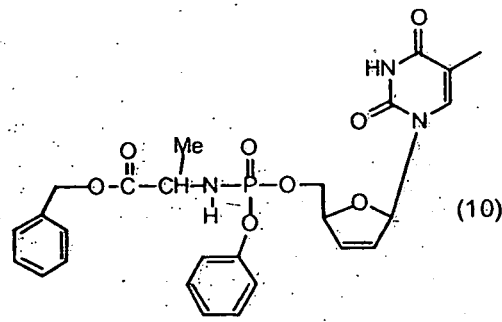
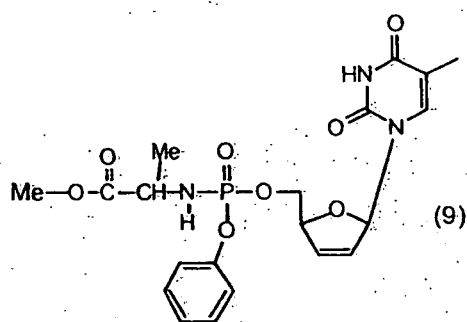
- 30 With respect to compounds of formula II, when n is 0, X is OH and Y is H, preferably neither R' nor R'' is phenylmethyl (ie benzyl) or 3-methylindolyl (ie 3- CH_2 indolyl).

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):



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]:

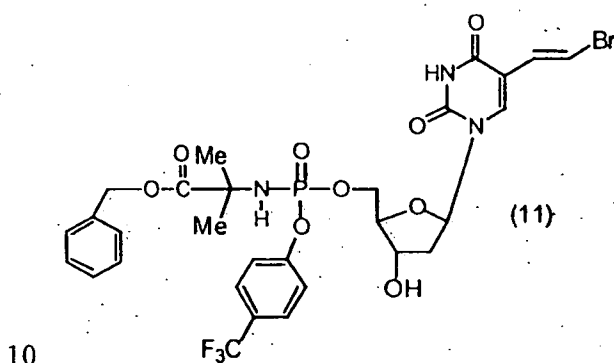


This would imply that the benzyl phosphoramidate motif in (10) is ca 4-fold more efficient at the intracellular delivery of the bio-active free phosphate forms of d4T than is the methyl ester (9). A person skilled in the art would anticipate a similar degree of

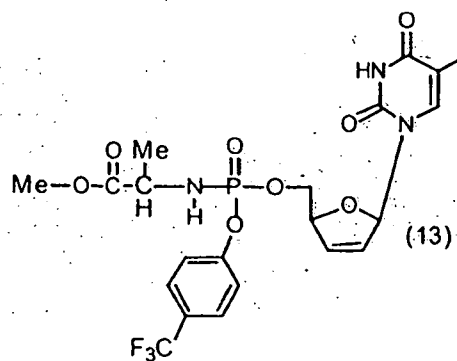
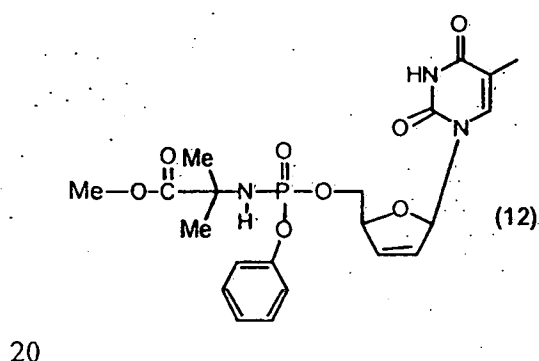
enhancement for the benzyl phosphoramidate of BVDU (8) over the methyl ester (7) whilst we observed an almost 200-fold enhancement for colon cancer as noted above.

Surprising efficacy of modifications in the amino acid and aryl moieties of the BVDU phosphoramidate 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 -dimethylglycyl] phosphoramidate.



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 (1.3 μ M vs 79 μ M), and for prostate cancer (11) is 254-fold more potent (0.61 μ M vs. 155 μ M). Against colon cancer, (11) is 35-fold more potent (7 μ M vs 244 μ M). 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-CF₃phenyl modification] to (9) shows no significant difference in potency.



Thus 50% effective doses vs HIV-1 for (9), (12) and (13) are: 0.075, 0.29, and 0.01 μ M 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.

5

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.

10

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.

15 According to a further aspect of the present invention there is provided a method of prophylaxis 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.

20 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 prophylaxis of cancer.

According to a further aspect of the present invention there is provided a pharmaceutical
25 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
30 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.

- 5 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

- 10 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
15 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,
20 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
25 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
30 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.

54

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.

5

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

10 may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone 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.

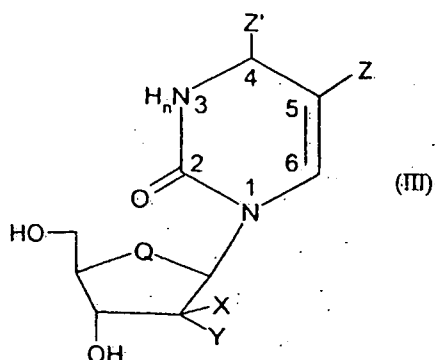
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In general a suitable dose will be in the range of 0.1 to 300 mg per kilogram body weight of the recipient per day. A preferred lower dose is 0.5 mg per kilogram body weight of recipient per day, a more preferred lower dose is 6 mg per kilogram body 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

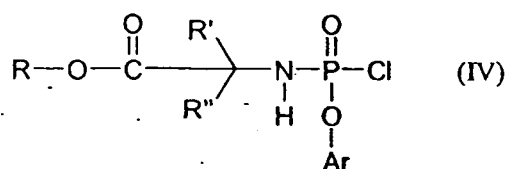
20 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

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

30 comprising reacting of a compound of formula (III):



with a compound of formula (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.

- 10 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

15

General methods

The following anhydrous solvents and reagents were bought from Aldrich with sure stopper: dichloromethane (DCM), diethyl ether (Et₂O), tetrahydrofuran (THF), N-methylimidazole (NMI), methanol (MeOH), dimethylformamide (DMF), 1,4-dioxane.

- 20 triethylamine was dried on molecular sieves of 4 Angstrom.

Thin Layer Chromatography

Thin layer chromatography (TLC) was performed on commercially available Merck Kieselgel 60 F₂₅₄ plates and separated components were visualized using ultraviolet light (254 nm and 366 nm).

5

Column Chromatography

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

10

NMR Spectroscopy

¹H, ¹³C and ³¹P-NMR were recorded on a Bruker Avance DPX300 spectrometer with operating frequencies of 300MHz, 75MHz and 121MHz respectively. ³¹P-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 are splitted due to stereoisomeric mixtures.

20 *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 (25 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.

30 *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, Et₂O was added and the

5 mixture was left in ice bath for 1hr then filtrated and washed with Et₂O. The solid was dissolved in DCM and washed with 10% K₂CO₃ and water. The organic layer was dried over MgSO₄, filtered and the solvent removed under reduced pressure to give an oil. This was solubilized in acetone and neutralized with 1 M HCl. Et₂O was added and the solid was filtered and washed with Et₂O 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
10 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.

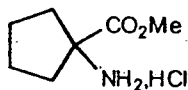
15 Phosphodichloridate (1.0 mol eq.) and the appropriate amino ester hydrochloric salt (1.0 mol eq.) were suspended in anhydrous DCM. Anhydrous triethylamine was added dropwise at -80 °C and after 1hr the reaction was left to rise to room temperature. The formation of phosphochloridate was monitored by ³¹P-NMR. After 2-5 hrs the solvent was removed under reduced pressure and the solid obtained washed with anhydrous ether (2x20-
20 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
25 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 MgSO₄, filtered, reduced to dryness and
30 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.



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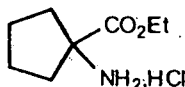
This was synthesised according to *Standard Procedure 1*, using 1-amino-1-cyclopentanecarboxylic acid (3.876 g, 30 mmol) with thionyl chloride (4.44 mL, 45 mmol,) and anhydrous methanol (15.5 mL). The product was isolated as a white solid (4.81 g, yield 89%).

- 10 1H -NMR ($CDCl_3$; 300 MHz): δ 9.1 (3H, bs, $NH_3^+Cl^-$), 3.85 (3H, s, OCH_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 (2CH₂ cyclopent), 38.1 (2CH₂ cyclopent), 54.8 (CH_3O), 66.6 (C_q cyclopentane), 174.1 ($COOMe$).

15

Synthesis of Ethyl-1-amino-1-cyclopentanoate hydrochloride salt.

$C_8H_{16}ClNO_2$, MW=193.71.

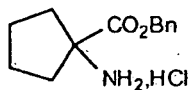


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This was synthesised according to *Standard Procedure 1*, using 1-amino-1-cyclopentanecarboxylic acid (5.0 g, 38.6 mmol) with thionyl chloride (5.72 mL, 58 mmol) and anhydrous ethanol (29 mL). The product was isolated as a white solid (6.98 g, yield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

- 25 1H -NMR ($CDCl_3$; 300 MHz): δ 9.0 (3H, bs, $NH_3^+Cl^-$), 4.3 (2H, q, $^3J=8$, OCH_2CH_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_2CH_3).
 ^{13}C -NMR ($CDCl_3$; 75 MHz): δ 14.5 (CH_3CH_2), 25.8 (2CH₂ cyclopent), 37.4 (2CH₂ cyclopent), 63.0 (CH_3CH_2), 66.2 (C_q cyclopentane), 172.1 ($COOEt$).

30

Synthesis of Benzyl-1-amino-1-cyclopentanoate hydrochloride salt.**C₁₄H₁₈ClNO₂, MW=255.78.**

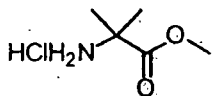
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This was synthesised according to *Standard Procedure 2*, using 1-amino-1-cyclopentanecarboxylic acid (3.682 g, 28.5 mmol) with *p*-toluene sulfonic acid monohydrate (5.625 g, 29.55 mmol) and anhydrous benzylic alcohol (12 mL, 116 mmol), in Toluene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

- 10 **Hydrochloride salt.** ¹H-NMR (CDCl₃; 300 MHz): δ 9.05 (3H, bs, NH₃⁺Cl⁻), 7.4-7.25 (5H, m, Ph), 5.15 (2H, s, CH₂Ph), 2.3 (4H, m, 4H cyclopentane), 2.15 (2H, 2H cyclopentane), 1.95 (2H, m, 2H cyclopentane).
- ¹³C-NMR (CDCl₃; 75 MHz): δ 25.9 (2CH₂ cyclopent), 37.3 (2CH₂ cyclopent), 66.3 (C_q cyclopentane), 68.3 (CH₂Ph), 129.2, 129.0, 128.8 ('*o*', '*m*', CH₂Ph), 135.5 ('*p*', CH₂Ph), 172.1 (COOBn).

Synthesis of methyl-2-amino-2-methylpropanoate hydrochloride salt**C₅H₁₂ClNO₃, MW 153.61.**

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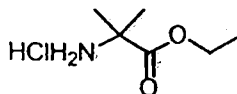


This was synthesised according to *Standard Procedure 1*, using 2-amino-isobutyric acid (5.102 g, 48.49 mmol) with thionyl chloride (11.538 g, 96.98 mmol, 7.04 mL) and anhydrous methanol (19.6 mL). The product was isolated as a white solid (6.636 g, yield 89.2%).

- 25 ¹H-NMR (CDCl₃; 300 MHz): δ 8.81 (3H, bs, NH₃Cl), 3.83 (3H, s, OCH₃), 1.74 (6H, s, [CH₃]₂C).
- ¹³C-NMR (CDCl₃; 75 MHz): δ 24.1, 24.3 ([CH₃]₂C), 57.9 (C[CH₃]₂), 172.4 (COOCH₃).

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

$C_6H_{14}ClNO_2$, MW 167.63.



- 5 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%).

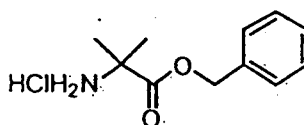
1H -NMR ($CDCl_3$; 300 MHz): δ 8.93 (3H, bs, NH_3Cl), 4.3 (2H, q, $^3J=7.1$ Hz, OCH_2CH_3),

- 10 1.75 (6H, s, $[CH_3]_2C$), 1.33 (3H, t, $^3J=7.1$ Hz, OCH_2CH_3).

^{13}C -NMR ($CDCl_3$; 75 MHz): δ 14.4 (CH_3CH_2O), 24.3 ($[CH_3]_2C$), 57.9 ($C[CH_3]_2$), 63.1 (OCH_2CH_3), 171.6 ($COOCH_2CH_3$).

15 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: 1H -NMR ($CDCl_3$, 300 MHz): δ 8.40 (3H, bs, NH_3Cl), 7.79 (2H, d, $^3J=8.0$ Hz, '*m*' *p*-TSA), 7.34 (5H, m, CH_2Ph), 7.14 (2H, d, $^3J=8.0$ Hz, '*o*' *p*-TSA), 5.16 (2H, s, CH_2Ph), 2.38 (3H, s, CH_3 *p*-TSA), 1.57 (6H, s, $[CH_3]_2C$)

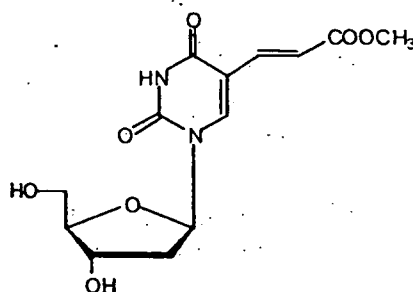
^{13}C -NMR (CDCl_3 ; 75 MHz): δ 21.8 ($\underline{\text{CH}_3}$, p -TSA), 23.9 ($[\underline{\text{CH}_3}]_2\text{C}$), 57.8 ($\underline{\text{C}}[\text{CH}_3]_2$), 68.3 ($\underline{\text{CH}_2\text{Ph}}$), 126.55, 128.5, 128.8, 129.0, 129.3 ($\text{CH}_2\text{Ph}+p$ -TSA), 135.4 ('*ipso*', CH_2Ph), 140.8 ('*p*', p -TSA), 141.9 ('*ipso*', p -TSA), 171.9 ($\underline{\text{COOCH}_2\text{Ph}}$).

Hydrochloride salt: ^1H -NMR (CDCl_3 ; 300 MHz): δ 9.10 (3H, bs, NH_2Cl), 7.41-7.31 (5H, m, CH_2Ph), 5.27 (2H, s, CH_2Ph), 1.77 ($[\underline{\text{CH}_3}]_2\text{C}$).

^{13}C -NMR (CDCl_3 ; 75 MHz): δ 24.2 ($[\underline{\text{CH}_3}]_2\text{C}$), 58.0 ($\underline{\text{C}}[\text{CH}_3]_2$), 68.5 ($\underline{\text{CH}_2\text{Ph}}$), 128.62, 129.0, 129.1 ('*o*', '*m*', '*p*', CH_2Ph), 135.2 ('*ipso*', CH_2Ph), 171.8 ($\underline{\text{COOCH}_2\text{Ph}}$).

10 Synthesis of (E)-5-(2-bromovinyl)-2'-deoxyuridine

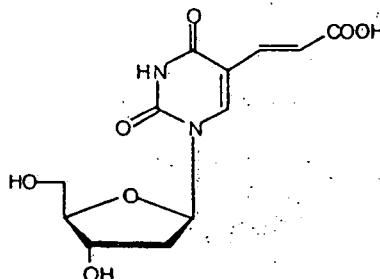
(E)-5-(2-Carbomethoxyvinyl)-2'-deoxyuridine



- 15 A mixture of $\text{Pd}(\text{OAc})_2$ (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 methylacrylate (4.862 g, 56.48 mmol, 5.1 mL) in 1,4-dioxane (20 mL) were added and the mixture stirred at reflux for 30 mins. The reaction was filtered while still hot and the
- 20 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%).

^1H -NMR ($\text{DMSO}-d_6$; 300 MHz): δ 11.64 (1H, bs, NH -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, CH_3), 3.60 (2H, m, H-5'), 2.18 (2H, m, H-2').

^{13}C -NMR ($\text{DMSO}-d_6$; 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

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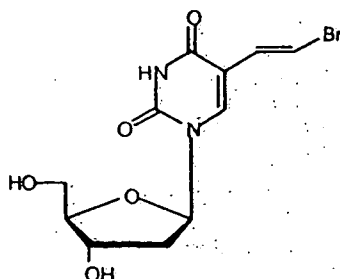
(E)-5-(2-carbomethoxyvinyl)-2'-deoxyuridine (6.0 g, 19.33 mmol) was dissolved in 300 mL of 1 M NaOH and the mixture stirred at room temperature for 3 hrs, filtered and the filtrate adjusted to pH 2 with 1M HCl. On cooling at 4°C a white precipitate formed. This was filtered off and washed with cold water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

¹H-NMR (DMSO-*d*₆; 300 MHz): δ 12.18 (1H, bs, CO₂H), 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').

¹³C-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

20



To a solution of (E)-5-(2-carboxyvinyl)-2'-deoxyuridine (5.777 g, 19.37 mmol) in dimethylformamide (29 mL) was added K₂CO₃ (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.

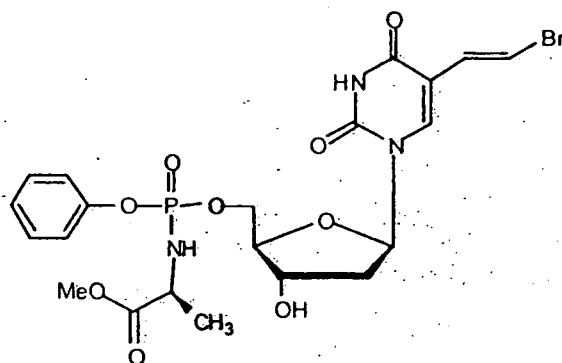
¹H-NMR (DMSO-*d*₆; 300 MHz) δ 11.59 (1H, bs, NH-3), 8.08 (1H, s, H-6), 7.25 (1H, d, ³J=13.6 Hz, H-5b), 6.85 (1H, d, ³J=13.6 Hz, H-5a), 6.13 (1H, t, ³J=6.5 Hz, H-1'), 5.29 (1H, bs, OH-3'), 5.13 (1H, bs, OH-5'), 4.24 (1H, m, H-3'), 3.79 (1H, m, H-4'), 3.66 (2H,

10 m, H-5'), 2.51 (1H, m, H-2'), 2.14 (1H, m, H-2'). -

¹³C-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).

15 **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.



20

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 CH₂Cl₂/Methanol 97:3 to give the pure product as a white

25 foamy solid (356 mg, yield 69%).

³¹P-NMR (CDCl₃, 121 MHz): δ 4.72, 4.40.

¹H-NMR (CDCl₃; 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, *OPh*), 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, CH₃O), 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, CH₃ala).

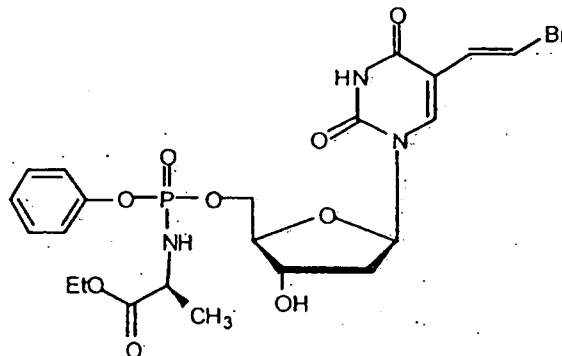
¹³C-NMR (DMSO; 75 MHz): δ 22.4 (CH₃ala), 41.9, 41.8 (C-2'), 51.9 (CH[CH₃]), 54.3 (CH₃O), 67.5 (C-5'), 72.3, 71.9 (C-3'), 87.3, 87.2, 86.9, 86.8 (C-1', C-4'), 110.6 (C-5b), 113.1 (C-5), 121.7 ('o', *OPh*), 127.0 ('p', *OPh*), 130.1 (C-5a), 131.5 ('m', *OPh*), 139.2 (C-6), 150.9 ('ipso', *OPh*) 151.9 (C-4), 163.2 (C-2), 175.7 (COOCH₃).

10

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

C₂₂H₂₇BrN₃O₉P, MW=588.34.

15



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 CH₂Cl₂/Methanol 97:3 to give the pure product as a white foamy solid (145 mg; yield 55%).

³¹P-NMR (CDCl₃, 121 MHz): δ 4.48, 4.86.

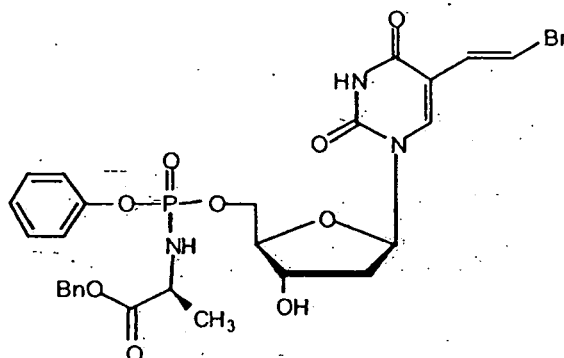
¹H-NMR (CDCl₃, 300 MHz): δ 7.65 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, ³J=13 Hz, H-5b), 7.35-7.10 (5H, m, *OPh*), 6.78-6.65 (1H, 2d, ³J=13 Hz, H-5a), 6.35-6.25 (1H, 2t, ³J=6 Hz, H1'), 4.62-3.95 (8H, m, H-5', H-3', H-4', CHala, NH, CH₃CH₂O), 2.49-2.40 (1H, m, one

of H-2'), 2.10-2.00 (1H, m, one of H-2'), 1.40 (3H, d, $^3J=7$ Hz, CH₃ala), 1.25 (3H, t, $^3J=7$ Hz, CH₂CH₂O).

¹³C-NMR (CDCl₃, 75 MHz): δ 14.5 (CH₃CH₂O) 21.2, 21.1 (CH₃ala), 40.9, 40.7 (C-2'), 50.8, 50.7 (CHala), 62.2, 62.1 (CH₃CH₂O), 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', OPh), 125.0 ('p', OPh), 129.0 (C-5a), 130.2 ('m', OPh), 138.2 (C-6), 149.9 (C-4), 150.7 ('ipso', OPh), 162.3 (C-2), 174.2, 174.1 (COOCH₂CH₃).

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

C₂₇H₂₉BrN₃O₉P, MW=649.08.



15

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 CH₂Cl₂/Methanol 97:3 to give the pure product as a white foamy solid (228 mg, yield 78%).

³¹P-NMR (CDCl₃, 121 MHz): δ 4.74, 4.44.

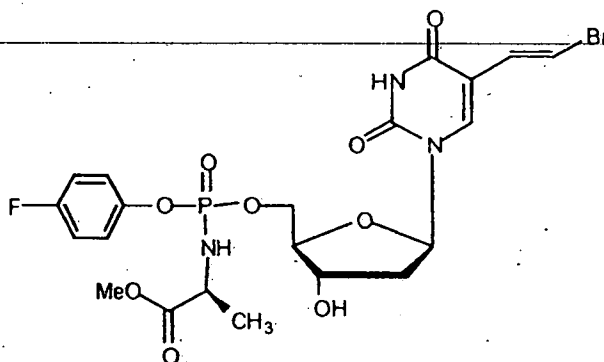
¹H-NMR (CDCl₃, 300 MHz): δ 10.31 (1H, bs, H-3), 7.63 (1H, 2xs, H-6), 7.45-7.14 (11H, m, OPh+CH₂Ph, H-5b), 6.75-6.66 (1H, 2d, $^3J=14$ Hz, H-5a), 6.30-6.25 (1H, m, H-1'), 5.18-5.09 (1H, s, CH₂Ph), 4.70-4.04 (6H, m, H-3', H-5', H-4', NH, CHala), 2.42 (1H, m, one of H-2'), 2.02 (1H, m, one of H-2'), 1.40 (3H, d, $^3J=7$ Hz, CH₃ala).

¹³C-NMR (CDCl₃, 75 MHz): δ 20.7, 20.8 (CH₃ala), 40.4 (C-2'), 50.4 (CHala), 66.0 (C-5'), 67.4 (CH₂Ph), 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' O_{Ph}, Bn, C-5a), 135.1 ('ipso', CH₂Ph) 137.8 (C-6), 149.8 (C-4) 150.2 ('ipso', O_{Ph}), 161.8 (C-2), 173.6 (COOBn).

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

C₂₁H₂₄BrFN₃O₉P, MW=592.31.



10

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 μ L) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH₂Cl₂/Methanol 97:3 to give the pure product as a

15 white foamy solid. (177 mg, yield 50%).

³¹P-NMR (CDCl₃, 121 MHz): δ 5.10, 4.81.

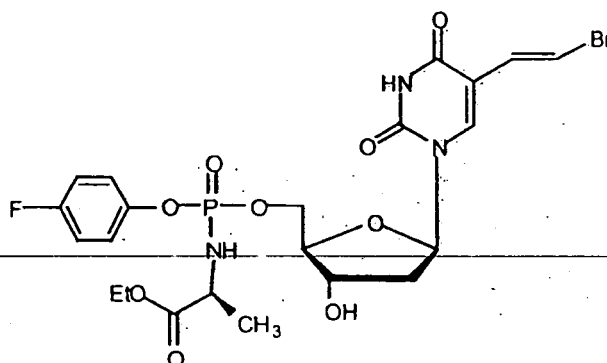
¹H-NMR (CDCl₃; 300 MHz): δ 10.1 (1H, bs, H-3), 7.60 (1H, 2xs, H-6), 7.39-7.32 (1H, 2d, ³J=14 Hz, H-5b), 7.20-6.95 (4H, m, O_{Ph}), 6.70-6.60 (1H, 2d, ³J=14 Hz, H-5a), 6.30-6.15 (1H, 2t, ³J=6 Hz, H1'), 4.55-4.29 (3H, m, H-5'+H-3'), 4.15 (1H, NH), 4.05-3.85 (2H, H-4', CHala), 3.72 (3H, 2s, CH₃O), 2.49-2.32 (1H, m, one of H-2'), 2.15-2.05 (1H, m, one of H-2'), 1.35 (3H, 2d, ³J=6 Hz, CH₃ ala).

¹³C-NMR (DMSO; 75 MHz): δ 21.2 (CH₃ ala), 40.8 (C-2'), 50.8, 50.6 (CH[CH₃]), 53.2 (CH₃O), 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

25 ('ipso', O_{Ph}) 149.9 (C-4), 158.5 ('p', O_{Ph}), 163.2(C-2), 175.1 (COOCH₃).

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.



5

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 μ L) 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%).

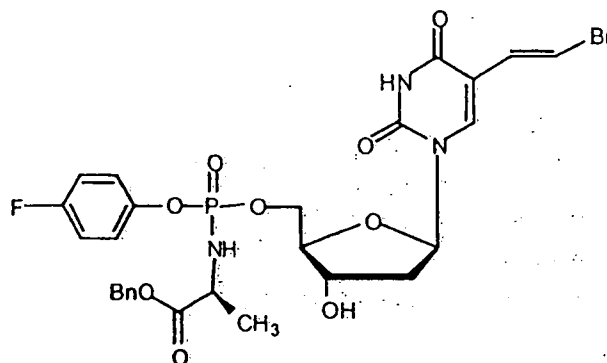
^{31}P -NMR ($CDCl_3$, 121 MHz): δ 5.14, 4.88.

1H -NMR ($CDCl_3$, 300 MHz): δ 10.25 (1H, bs, H-3), 7.85 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, $^3J=14$ Hz, H-5b), 7.3-7.0 (4H, m, *OPh*), 6.8-6.65 (1H, 2d, $^3J=14$ Hz, H-5a), 6.35-6.25 (1H, 2t, $^3J=6$ Hz, H1'), 4.6-4.1 (6H, m, H-5', H-3', CHala, NH, CH_3CH_2O), 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, $^3J=8$ Hz, CH_3 ala), 1.25 (3H, 2t, $^3J=7$ Hz, CH_3CH_2O).

^{13}C -NMR ($CDCl_3$, 75 MHz): δ 14.5 (CH_3CH_2O) 21.3 (CH_3 ala), 40.8, 40.7 (C-2'), 50.8, 50.7 (CHala), 62.3 (CH_3CH_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', *OPh*), 122.2 ('m', *OPh*), 128.9 (C-5a), 138.2 (C-6), 146.4 ('ipso', *OPh*), 149.9 (C-4), 158.5 ('p', *OPh*), 162.2, 161.8 (C-2), 174.2 ($COOCH_2CH_3$).

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 μ L) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH₂Cl₂/Methanol 97:3 to give the pure product as a white foamy solid (256 mg, yield 64%).

³¹P-NMR (CDCl₃, 121 MHz): δ 4.74, 4.44.

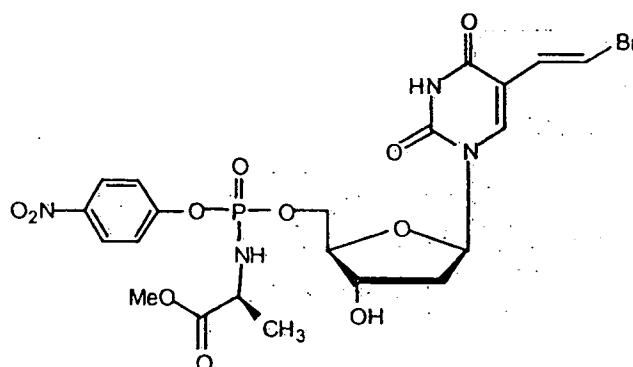
¹H-NMR (CDCl₃, 300 MHz): δ 7.69 (1H, 2xs, H-6), 7.45-7.39 (1H, 2d, ³J=14 Hz, H-5b), 7.37-7.00 (9H, m, OPh+CH₂Ph), 6.75-6.65 (1H, 2d, ³J=14 Hz, H-5a), 6.30-6.2 (1H, 2t, ³J=6Hz, H-1'), 5.2 (1H, 2s, CH₂Ph), 4.85-4.00 (6H, m, H-3', H-5', H-4', NH, CHala), 2.47 (1H, m, one of H-2'), 2.0-2.15 (1H, m, one of H-2'), 1.38 (3H, d, ³J=7 Hz, CH₃ala).

¹³C-NMR (CDCl₃, 75 MHz): δ 21.2, 21.1 (CH₃ala), 40.7 (C-2'), 50.4 (CHala), 66.7, 66.4 (C-5'), 67.8 (CH₂Ph), 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', OPh), 122.0 ('m', OPh), 128.7, 128.6 (Bn, C-5a), 135.4 ('ipso', CH₂Ph), 138.2 (C-6), 146.5 ('ipso', OPh), 149.9 (C-4), 158.5 ('p' OPh), 162.2 (C-2), 173.9 (COOBn).

20

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

C₂₁H₂₄BrN₄O₁₁P, 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),
 5 NMI (4.98 mmol, 332 μ L) 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%).

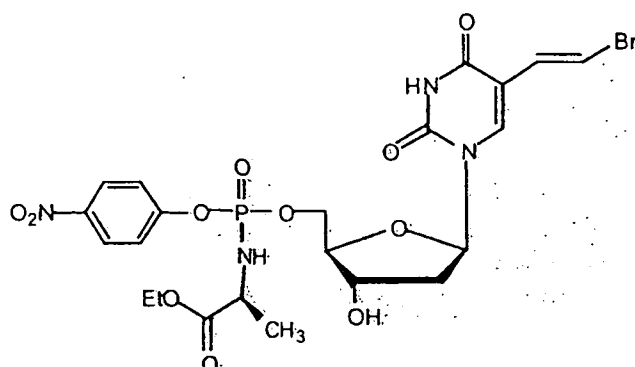
^{31}P -NMR (CDCl_3 , 121 MHz): δ 4.95.

^1H -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,
 10 7.55-7.4 (2H, m, *O_{Ph}*), 7.35-7.30 (1H, 2d, $^3J=14$ Hz, H-5b), 6.80-6.70 (1H, 2d, $^3J=14$ Hz, H-5a), 6.30-6.2 (1H, 2t, $^3J=6$ 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, $^3J=7$ Hz, 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]),
 15 53.4 (CH_3O), 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 (COOCH_3).

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

20 $\text{C}_{22}\text{H}_{26}\text{BrN}_4\text{O}_{11}\text{P}$, 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),
 5 NMI (4.98 mmol, 332 μ L) 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.

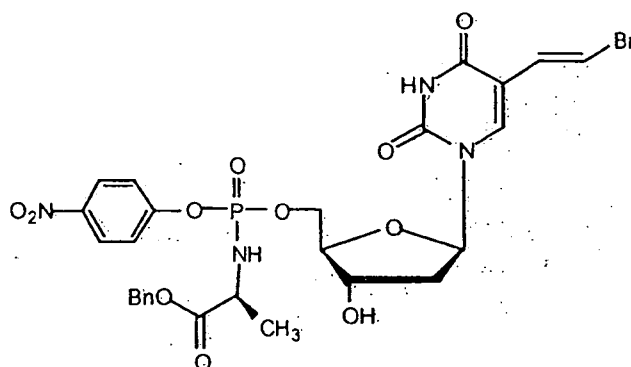
^1H -NMR (CDCl_3 , 300 MHz): δ 10.25 (1H, bs, H-3), 8.25-8.2 (2H, 2d, $^3J=9\text{ Hz}$ *OPh*), 7.7
 10 (1H, 2xs, H-6), 7.5-7.45 (2H, 2d, $^3J=9\text{ Hz}$ *OPh*), 7.4-7.35 (1H, 2d, $^3J=14\text{ Hz}$, H-5b), 6.7-
 6.65 (1H, 2d, $^3J=14\text{ Hz}$, H-5a), 6.3-6.2 (1H, 2t, $^3J=6\text{ Hz}$, H1'), 4.8-4.1 (7H, m, H-5', H-4',
 H-3', CHala, NH, $\text{CH}_3\text{CH}_2\text{O}$), 2.45-2.4 (1H, m, one of H-2'), 2.20-2.10 (1H, m, one of H-
 2'), 1.40 (3H, d, $^3J=8\text{ Hz}$, CH_3ala), 1.3 (3H, 2t, $^3J=7\text{ Hz}$, $\text{CH}_2\text{CH}_2\text{O}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$) 21.1 (CH_3ala), 40.6 (C-2'), 50.8, 50.7
 15 (CHala), 62.5 ($\text{CH}_3\text{CH}_2\text{O}$), 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', *OPh*), 126.1 ('m', *OPh*), 128.8 (C-5a),
 138.4 (C-6), 145.1 ('ipso', *OPh*), 149.9 (C-4), 155.5 ('p', *OPh*), 162.3 (C-2), 174.0, 173.9
 ($\text{COOCH}_2\text{CH}_3$).

20

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

$\text{C}_{27}\text{H}_{28}\text{BrN}_4\text{O}_{11}\text{P}$, 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),
 5 NMI (4.98 mmol, 332 μ L) 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.

^1H -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, $^3J=14$ Hz, H-5b), 7.37-7.00 (7H, m, *O**Ph*+*CH*₂*Ph*), 6.75-6.65 (1H, 2d, $^3J=14$ Hz, H-5a), 6.25-6.15 (1H, 2t, $^3J=6$ Hz, H-1'), 5.2 (1H, d, *CH*₂*Ph*), 4.87 (1H, m, H-3'), 4.6-4.2 (3H, m, H-5', *CH*ala) 4.2-4.00 (2H, m, H-4', *NH*), 2.55-2.45 (1H, m, one of H-2'), 2.2-2.05 (1H, m, one of H-2'), 1.38 (3H, d, $^3J=7$ Hz, *CH*₃ala).

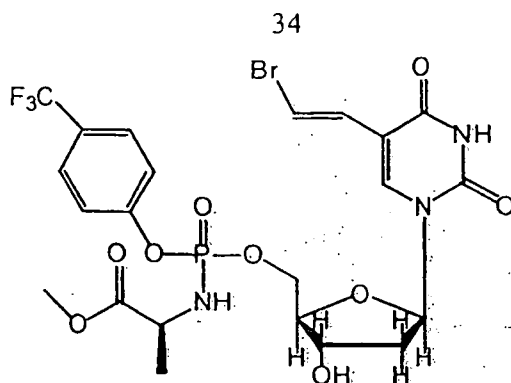
^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.2, 21.1 (*CH*₃ala), 40.6 (C-2'), 50.9 (*CH*ala), 67.1, 67.0 (C-5'), 68.0 (*CH*₂*Ph*), 71.3, 70.9 (C-3'), 86.3, 86.0, 85.3, 85.2 (C-1', C-4'), 110.4 (C-5b), 111.9, 111.8 (C-5), 121.3 ('o', *O**Ph*), 126.2-126.1 ('m', *O**Ph*), 129.1, 128.7, 128.6 (Bn, C-5a), 135.4 ('ipso',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

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

$\text{C}_{22}\text{H}_{24}\text{BrF}_3\text{N}_3\text{O}_9$, MW=642.31.

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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 μ L) 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.

^1H -NMR (MeOD, 300 MHz): δ 7.80 (1H, s, H-6), 7.70 (2H, d, $^3J=8.7$ Hz, *OPh*), 7.47-7.42 (2H, m, *OPh*), 7.37 (1H, d, $^3J=13.6$ Hz, H-5b), 6.82-6.78 (1H, d, $^3J=13.6$ 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, *CHCH*₃), 3.67 (3H, s, *OCH*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, $^3J=7.1$ Hz, *CHCH*₃).

^{13}C -NMR (MeOD; 75 MHz): δ 20.6, 20.7, 20.8, 20.9 (*CHCH*₃), 41.5, 41.7 (C-2'), 51.9, 52.0 (*CHCH*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', *OPh*), 125.8 (*CF*₃, $J=269$ Hz), 128.7 ('m', *OPh*), 128.8 ('p', $J=33$ Hz, *OPh*), 130.9 (C-5a), 140.3 (C-6), 151.4, 151.5 ('ipso', *OPh*), 155.1, 155.2 (C-4), 164.0 (C-2), 175.6, 175.9; (*COOCH*₃).

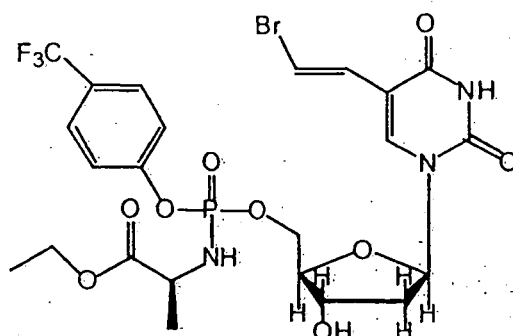
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Synthesis of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[*para*-(trifluoromethyl)-phenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 25):

$\text{C}_{23}\text{H}_{26}\text{BrF}_3\text{N}_3\text{O}_9\text{P}$, MW=656.34

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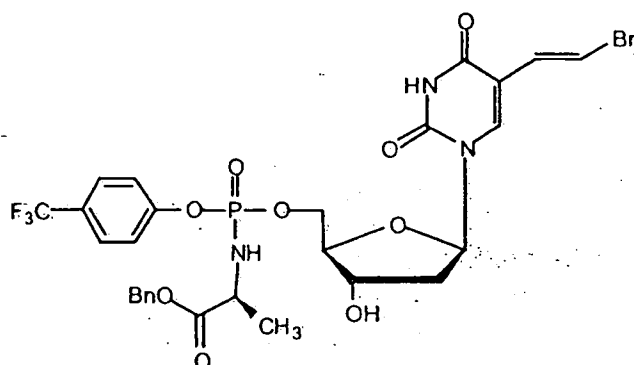
This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), phenyl-(ethoxy-L-alaninyl)-phosphorochloridate (539.5 mg, 1.5 mmol), NMI (246.3 mg, 3.0 mmol, 239 μ L) in THF (5 mL) for 20 hrs. The crude product was purified by column chromatography, eluting with dichloromethane/methanol 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.

^1H -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, $^3J=13.6$ Hz, H-5a), 6.34-6.25 (1H, m, H-1'), 4.57-4.35 (4H, m, H-3'+H-5'+*NH*), 4.27-4.13 (4H, m, H-4'+*OCH*₂*CH*₃+OH-3'), 4.12-3.98 (1H, m, *CHCH*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, $^3J=7.0$ Hz, *CHCH*₃), 1.28, 1.27 (3H, 2t, $^3J=7.0$ Hz, *OCH*₂*CH*₃).
 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 (*CH*₃*CH*₂*O*), 21.2, 21.3 (*CHCH*₃), 40.7 (C-2'), 50.8, 50.9 (*CHCH*₃), 62.4 (*CH*₃*CH*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 (*CF*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 (*COOCH*₂*CH*₃).

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

$\text{C}_{28}\text{H}_{28}\text{BrF}_3\text{N}_3\text{O}_9\text{P}$, 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 μ L) in THF (6 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH₂Cl₂/Methanol 97:3 to give the pure product as a white foamy solid (308 mg, yield 71%).

³¹P-NMR (CDCl₃, 121 MHz): δ 5.31, 4.87.

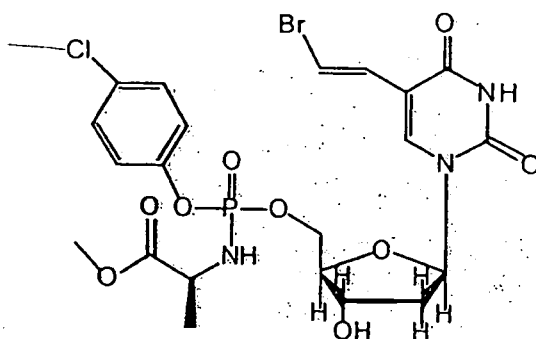
¹H-NMR (CDCl₃, 300 MHz): δ 10.05 (1H, bs, H-3), 7.7, 7.25 (1H, m, H-5b, H-6 OPh+CH₂Ph), 6.75-6.65 (1H, 2d, ³J=14 Hz, H-5a), 6.35-6.2 (1H, 2t, ³J=6Hz, H-1'), 5.15 (1H, 2s, CH₂Ph), 4.6-4.25 (4H, m, H-5', H-3', CHala) 4.2-4.00 (2H, m, H-4', NH), 2.55-2.4 (1H, m, one of H-2'), 2.2-2.05 (1H, m, one of H-2'), 1.38 (3H, d, ³J=7 Hz, CH₃ala).

¹³C-NMR (CDCl₃, 75 MHz): δ 21.2, 21.1 (CH₃ala), 40.7 (C-2'), 50.9, 50.8 (CHala), 67.1, 67.0 (C-5'), 68.0 (CH₂Ph), 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', OPh), 125.1 (d, J=270Hz, CF₃), 127.6 ('m', OPh), 129.1, 128.7, 128.6 (Bn, C-5a), 130.1 ('p', q, J=32Hz, OPh) 135.4 ('ipso', CH₂Ph) 138.2 (C-6), 150.2, 150.1 (C-4), 153.6 ('ipso' OPh), 162.7 (C-2), 173.9, 173.6 (COOBn).

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

C₂₁H₂₄BrClN₃O₉P, 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),
 5 NMI (246.3 mg, 3.0 mmol, 239 μ L) 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.

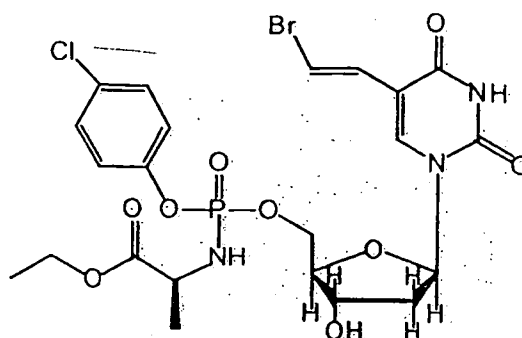
^1H -NMR (CDCl_3 , 300 MHz): δ 10.11 (1H, bs, H-3), 7.68 (1H, s, H-6), 7.46-7.40 (1H, d, $^3J=13.6$ Hz, H-5b), 7.35-7.20 (4H, m, *OPh*), 6.76-6.67 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.34-6.24 (1H, m, H-1'), 4.58-4.40 (5H, m, H-3'+H-5'+NH), 4.36-4.19 (1H, m, H-4'), 4.07-3.99 (1H, m, *CHCH*₃), 3.75 (3H, s, *OCH*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, $^3J=7.0$ Hz, *CHCH*₃).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.2 (*CHCH*₃), 40.7, 40.8 (C-2'), 50.6, 50.8 (*CHCH*₃),
 15 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', *OPh*), 128.9 (C-5a), 130.3 ('m', *OPh*), 131.1 ('p', *OPh*), 138.2 (C-6), 149.1, 149.2 ('ipso', *OPh*), 149.8 (C-4), 162.1, 162.2 (C-2), 174.5, 174.6 (*COOCH*₃).

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

25 $\text{C}_{22}\text{H}_{26}\text{BrN}_3\text{O}_9\text{P}$, 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),
 5 NMI (221.7 mg, 2.7 mmol, 215 μ L) 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.

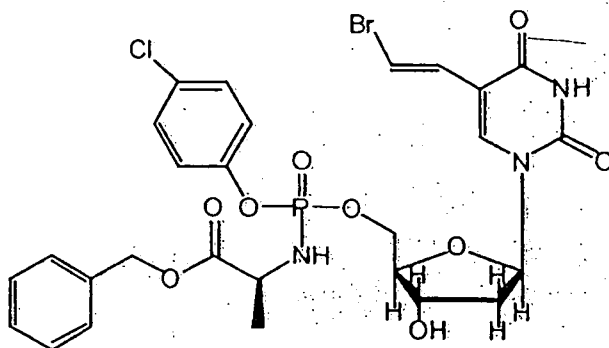
^1H -NMR (CDCl_3 , 300 MHz): δ 9.51 (1H, bs, H-3), 7.69-7.68 (1H, 2s, H-6), 7.49-7.43 (1H, 2d, $^3J=13.6$ Hz, H-5b), 7.37-7.22 (4H, m, *OPh*), 6.79-6.71 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.33-6.24 (1H, m, H-1'), 4.62-4.34 (3H, m, H-3'+H-5'), 4.28-3.89 (5H, m, H-4'+ OCH_2CH_3 + CHCH_3 +NH), 2.59-2.45 (1H, m, one of H-2'), 2.22-2.14 (1H, m, one of H-2'), 1.43-1.41 (3H, d, $^3J=7.0$ Hz, CHCH_3), 1.33-1.28 (3H, t, $^3J=7.2$ Hz, OCH_2CH_3)

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 21.2, 21.3 (CHCH_3), 40.7 (C-2'), 50.7, 50.8 (CHCH_3), 62.4 ($\text{CH}_2\text{CH}_2\text{O}$), 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', *OPh*), 128.9 (C-5a), 130.3 ('m', *OPh*), 131.1 ('p', *OPh*), 138.2 (C-6), 149.2 ('ipso', *OPh*), 150.0 (C-4), 162.2 (C-2), 174.1, 174.2 ($\text{COOCH}_2\text{CH}_3$).

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

25 $\text{C}_{22}\text{H}_{26}\text{BrN}_3\text{O}_9\text{P}$, 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),
 5 NMI (369.5 mg, 4.5 mmol, 358.7 μ L) 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.

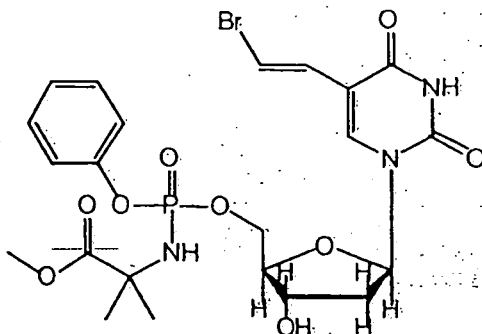
^1H -NMR (CDCl_3 , 300 MHz): δ 10.10 (1H, bs, H-3), 7.65-7.63 (1H, 2s, H-6), 7.69-7.68
 10 (1H, 2s, H-6), 7.46, 7.41 (1H, 2d, $^3J=13.6$ Hz, H-5b), 7.40-7.17 (9H, m, OPh), 6.75-6.66 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.33-6.23 (1H, 2t, $^3J=6.0$ Hz, H-1'), 5.17 (2H, s, CH_2Ph), 4.60-4.23 (4H, m, H-3'+H-5'+NH), 4.20-3.97 (2H, m, H-4'+ CHCH_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, $^3J=7.0$ Hz, CHCH_3).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.2 (CHCH_3), 40.7 (C-2'), 50.8, 50.9 (CHCH_3), 66.6 (C-
 15 5'), 67.9 (CH_2Ph), 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', OPh), 128.7, 129.0, 129.1, 130.3 ('m', $\text{OPh}+\text{C-5a}$), 131.1 ('ipso', CH_2Ph), 135.4 ('p', OPh), 138.2 (C-6), 149.1 ('ipso', OPh), 150.0 (C-4), 162.1 (C-2), 173.9, 174.0 (COOCH_2Ph).

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

$\text{C}_{22}\text{H}_{27}\text{BrN}_3\text{O}_9\text{P}$, 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 μ L) 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

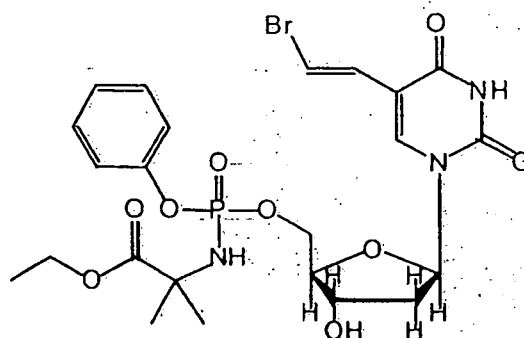
^1H -NMR (CDCl_3 , 300 MHz): δ 9.91 (1H, bs, H-3), 7.73, 7.65 (1H, 2s, H-6), 7.50-7.43 (1H, 2d, $^3J=13.6$ Hz, H-5b), 7.41-7.02 (5H, m, OPh), 6.81-6.71 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.34-6.28 (1H, m, H1'), 4.55-4.17 (6H, m, H-5'+H-4'+H-3', NH, OH-3'), 3.78 (3H, s, CH_3O), 2.53-2.39 (1H, m, one of H-2'), 2.25-1.99 (1H, m, one of H-2'), 1.60 (6H, s, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.5, 27.4, 27.2 ($[\text{CH}_3]_2\text{C}$), 40.7, 40.6 (C-2'), 53.5 (CH_3O), 57.6 ($[\text{CH}_3]_2\text{C}$), 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', OPh), 125.7 ('p', OPh), 128.9 (C-5a), 130.3 ('m', OPh), 138.0, 138.3 (C-6), 149.8 ('ipso', OPh), 150.9, 150.8 (C-4), 162.0, 162.1 (C-2), 176.4, 176.2 (COOCH_3).

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

25 $\text{C}_{23}\text{H}_{29}\text{BrN}_3\text{O}_9\text{P}$, 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 μ L) 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

^1H -NMR (MeOD, 300 MHz): δ 7.84, 7.81 (1H, 2s, H-6), 7.44-7.20 (6H, m, *OPh*+H-5b), 6.88-6.81 (1H, 2d, $^3J=13.6$ 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'+CH₃CH₂O), 2.38-2.28 (1H, m, one of H-2'), 2.22-2.09 (1H, m, one of H-2'), 1.51 (6H, s, [CH₃]₂C), 1.29 (3H, t, $^3J=7$ Hz, CH₃CH₂O)

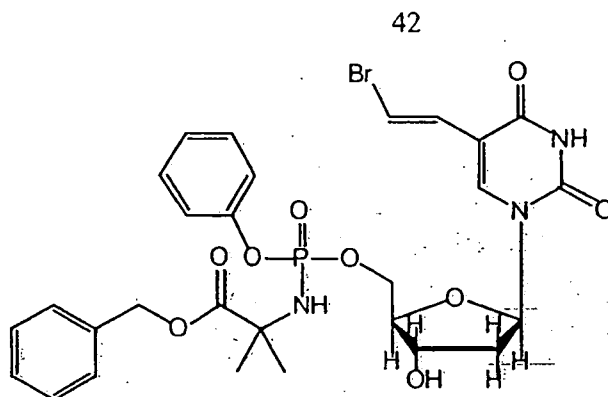
^{13}C -NMR (MeOD, 75 MHz): δ 14.9 (CH₃CH₂O) 27.9, 28.3 ([CH₃]₂C), 41.5 (C-2'), 58.51 (C[CH₃]₂), 63.1 (CH₃CH₂O), 68.2 (C-5'), 72.6 (C-3'), 87.1, 87.4 (C-1', C-4'), 109.6 (C-5b), 112.7 (C-5b), 122.0, 122.1, 122.2, ('o', *OPh*), 126.7 ('p', *OPh*), 131.0, 131.2 (C-5a, 'm' *OPh*), 140.4 (C-6), 151.4 ('ipso', *OPh*) 152.5 (C-4), 164.0 (C-2), 177.2 (COOCH₂CH₃).

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

C₂₈H₃₁BrN₃O₉P, MW=664.44.

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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 μ L) in THF (5 mL) for 4 hrs. The crude product was purified by column chromatography, eluting with chloroform/methanol 97:3 to give

5 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.

^1H -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, $^3J=13.6$ Hz, H-5b), 7.40-7.16 (10H, m, $\text{OPh}+\text{CH}_2\text{Ph}$), 6.78-6.67 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.31-6.25 (1H, m, H-1'), 5.18 (1H, s, CH_2Ph), 4.50-4.09 (6H, m, H-3'+H-5'+H-4',

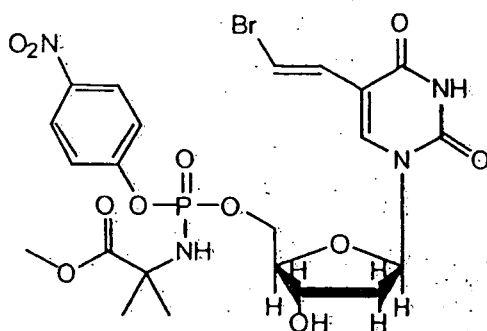
10 NH , OH-3'), 2.48-2.25 (1H, m, one of H-2'), 2.16-1.82 (1H, m, one of H-2'), 1.60 (6H, s, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.3, 27.4, 28.5 ($[\text{CH}_3]_2\text{C}$), 40.6, 40.7 (C-2'), 57.6, 57.6 ($\text{C}[\text{CH}_3]_2$), 66.2, 66.5 (C-5'), 68.1 (CH_2Ph), 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,

15 130.3 (OPh , C-5a), 135.7 ('ipso', CH_2Ph), 138.1, 138.3 (C-6), 149.8, 150.8, 150.9 ('ipso' OPh , C-4), 162.1 (C-2), 177.5, 175.7 (COOCH_2Ph).

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

$\text{C}_{22}\text{H}_{26}\text{BrN}_4\text{O}_{11}\text{P}$, 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 μ L) 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.

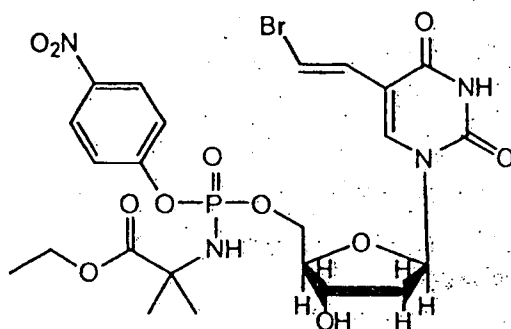
10 ^1H -NMR (MeOD, 300 MHz): δ 8.30-8.25 (2H, 2d, $^3J=9.0$ Hz, *OPh*), 7.79-7.78 (1H, 2s, H-6), 7.49-7.46 (2H, d, $^3J=9.0$ Hz, *OPh*), 7.37-7.32 (1H, 2d, $^3J=13.6$ Hz, H-5b), 6.79-6.72 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.32-6.25 (1H, m, H-1'), 4.48-4.35 (3H, m, H-3'+H-5'), 4.15-4.14 (1H, m, H-4'), 3.71 (3H, s, CH_3O), 2.41-2.17 (2H, m, H-2'), 1.51 (6H, s, $[\text{CH}_3]_2\text{C}$).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 28.0, 28.1, 28.2, 28.3 ($[\text{CH}_3]_2\text{C}$), 41.4, 41.5 (C-2'), 53.6 (CH_3O), 58.7 ($\text{C}[\text{CH}_3]_2$), 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', *OPh*), 127.0 ('m', *OPh*), 130.9 (C-5a), 140.5 (C-6), 146.5 ('p', *OPh*), 151.5 ('ipso', *OPh*), 157.3 (C-4), 164.0 (C-2), 177.5 (COOCH_3).

20

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

25 $\text{C}_{23}\text{H}_{28}\text{BrN}_4\text{O}_{11}\text{P}$, 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 μ L) 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 %).

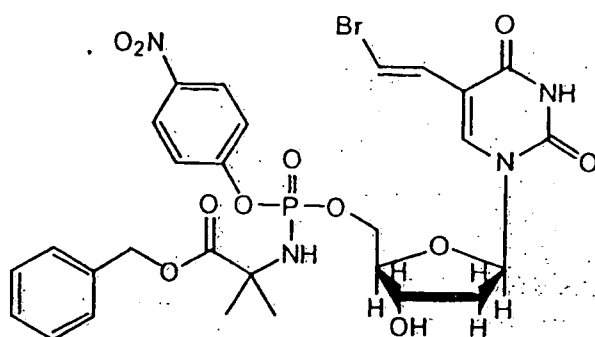
^{31}P -NMR (CDCl_3 , 121 MHz): δ 3.00, 2.96.

^1H -NMR (CDCl_3 , 300 MHz): δ 10.28 (1H, bs, H-3), 8.25-8.12 (2H, 2d, $^3J=9.0$ Hz, OPh), 7.68-7.67 (1H, 2s, H-6), 7.46-7.32 (3H, m, OPh +H-5b), 6.69-6.67 (1H, 2d, $^3J=13.5$ Hz, H-5a), 6.32-6.26 (1H, m, H-1'), 4.75-4.36 (5H, m, H-3'+H-5'+OH-3'+NH), 4.25-4.17 (3H, m, OCH_2CH_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, $[\text{CH}_3]_2\text{C}$), 1.30-1.28 (3H, 2t, $^3J=7.1$ Hz, OCH_2CH_3).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 27.1, 27.2, 27.3, 27.4 ($[\text{CH}_3]_2\text{C}$), 40.6 (C-2'), 57.7 ($\text{C}[\text{CH}_3]_2$), 62.7 ($\text{CH}_3\text{CH}_2\text{O}$), 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', OPh), 126.2 ('m', OPh), 128.8 (C-5a), 138.4 (C-6), 145.0 ('p', OPh), 150.0 (C-4), 155.7-155.9 ('ipso', OPh), 162.2 (C-2), 175.0-175.1 ($\text{COOCH}_2\text{CH}_3$).

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

$\text{C}_{28}\text{H}_{30}\text{BrN}_4\text{O}_{11}\text{P}$, 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 μ L) 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 %).

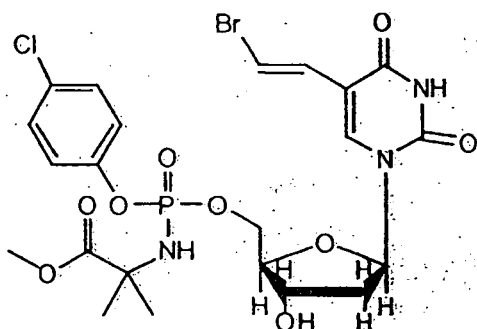
^{31}P -NMR (CDCl_3 , 121 MHz): δ 2.95, 2.89.

^1H -NMR (CDCl_3 , 300 MHz): δ 10.16 (1H, bs, H-3), 8.26-8.24 (2H, 2d, $^3J=9.1$ Hz, OPh), 7.71-7.69 (1H, 2s, H-6), 7.48-7.37 (8H, m, $\text{OPh}+\text{CH}_2\text{Ph}$, H-5b), 6.75-6.72 (1H, 2d, $^3J=13.5$ Hz, H-5a), 6.36-6.29 (1H, m, H-1'), 5.24 (2H, s, CH_2Ph), 4.81-4.40 (5H, m, H-3'+H-5'+OH-3', NH), 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, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.4 ($[\text{CH}_3]_2\text{C}$), 40.6 (C-2'), 57.8 ($\text{C}[\text{CH}_3]_2$), 67.0 (C-5'), 68.2 (CH_2Ph), 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', $\text{CH}_2\text{Ph}+\text{OPh}+\text{C-5a}$), 135.5 ('ipso', CH_2Ph), (C-5a), 138.4 (C-6), 145.0 ('p', OPh), 150.0 (C-4), 155.7 ('ipso', OPh), 162.2 (C-2), 175.4-175.5 (COOCH_2Ph).

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

$\text{C}_{22}\text{H}_{26}\text{BrClN}_3\text{O}_9\text{P}$, 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 μ L) 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).

10 ^1H -NMR (MeOD, 300 MHz): δ , 7.71-7.69 (1H, 2s, H-6); 7.31-7.13 (5H, m, *OPh*+H-5b), 6.73-6.66 (1H, 2d, $^3J=13.6$ 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, CH_3O), 2.29-2.19 (1H, m, one of H-2'), 2.15-2.05 (1H, m, one of H-2'), 1.38 (6H, s, $[\text{CH}_3]_2\text{C}$).

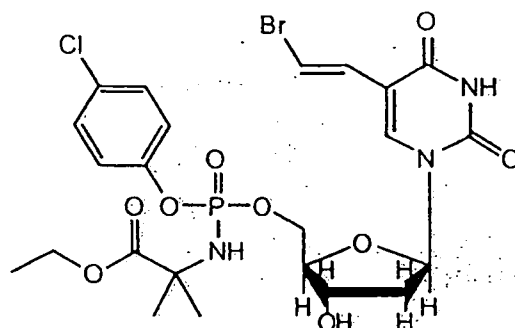
15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 28.0, 28.2, 28.3, 28.4 ($[\text{CH}_3]_2\text{C}$), 41.5, 41.6 (C-2'), 53.5, 53.6 (CH_3O), 58.6 ($\text{C}[\text{CH}_3]_2$), 68.2 (C-5'), 72.4, 72.5 (C-3'), 87.1, 87.2, 87.3, 87.4 (C-1', C-4'), 109.7 (C-5b), 112.7 (C-5), 123.7, 123.8 ('o', *OPh*), 130.9, 131.1 ('m', *OPh*+C-5a), 131.9 ('p', *OPh*), 140.4 (C-6), 151.1, 151.2, 151.4 ('ipso', *OPh*+C-4), 164.0 (C-2), 177.6, 177.7 (COOCH_3).

20

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

$\text{C}_{23}\text{H}_{28}\text{BrClN}_3\text{O}_9\text{P}$, MW=636.81.

25



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 μ L) 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 %).

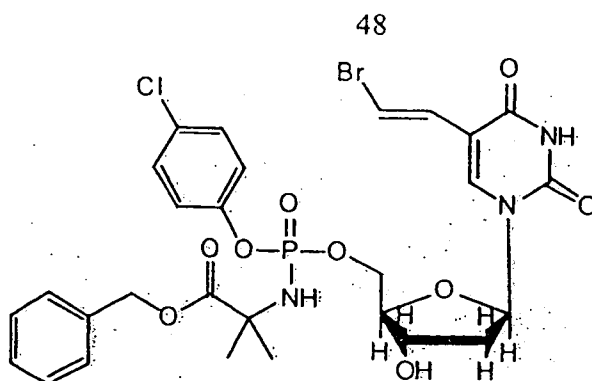
^{31}P -NMR (CDCl_3 , 121 MHz): δ 3.47, 3.33.

^1H -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, $^3J=13.6$ Hz, H-5b), 7.35-7.20 (4H, m, *OPh*), 6.77-6.68 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.33-6.27 (1H, m, H-1'), 4.55-4.29 (5H, m, H-3'+H-5'+OH-3'+NH), 4.22-4.17 (2H, q, $^3J=7.1$ Hz, OCH_2CH_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, $[\text{CH}_3]_2\text{C}$), 1.31-1.30 (3H, 2t, $^3J=7.1$ Hz, OCH_2CH_3).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 27.2, 27.3, 27.4 ($[\text{CH}_3]_2\text{C}$), 40.7 (C-2'), 57.6 ($\text{C}[\text{CH}_3]_2$), 62.6 ($\text{CH}_3\text{CH}_2\text{O}$), 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', *OPh*), 128.9, 130.2 ('m', *OPh*+C-5a), 130.9 ('p', *OPh*), 138.3 (C-6), 149.4 ('ipso', *OPh*), 149.9 (C-4), 162.1, 162.2 (C-2), 175.7-175.9 ($\text{COOCH}_2\text{CH}_3$).

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

$\text{C}_{28}\text{H}_{30}\text{BrClN}_3\text{O}_9\text{P}$, MW=698.88.



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 μ L) 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%).

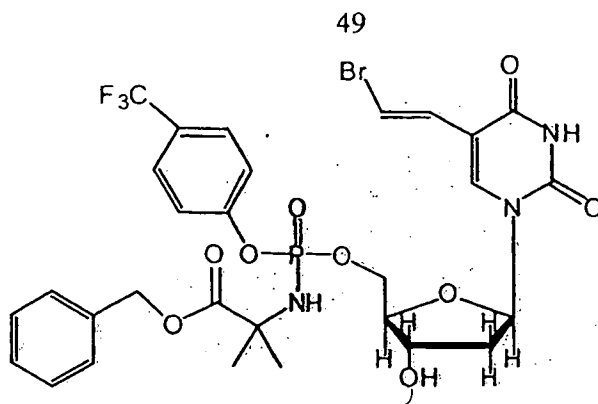
^{31}P -NMR (CDCl_3 , 121 MHz): δ 3.44, 3.26.

^1H -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, $^3J=13.5$, H-5b), 7.39-7.18 (9H, m, $\text{OPh}+\text{CH}_2\text{Ph}$), 6.74-6.69 (1H, 2d, $^3J=13.5$ Hz, H-5a), 6.31-6.25 (1H, m, H-1'), 5.19 (2H, CH_2Ph), 4.51-4.29 (4H, m, H-3'+H-5'+NH), 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, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.1, 27.5 ($[\text{CH}_3]_2\text{C}$), 40.7 (C-2'), 57.7 ($\text{C}[\text{CH}_3]_2$), 66.4, 66.6 (C-5'), 68.2 (CH_2Ph), 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', $\text{CH}_2\text{Ph}+\text{OPh}+\text{C-5a}$), 131.0 ('ipso', CH_2Ph), 135.6 ('p', OPh), 138.1 (C-6), 149.3 ('ipso', OPh), 149.8 (C-4), 162.1 (C-2), 175.6 (COOCH_2Ph).

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

$\text{C}_{29}\text{H}_{30}\text{BrF}_3\text{N}_3\text{O}_9\text{P}$, MW=732.44.



This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), 4-(trifluoromethyl)-phenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate (529.45 mg, 1.22 mmol), NMI (184.7 mg, 2.25 mmol, 179.4 μ L) 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%).

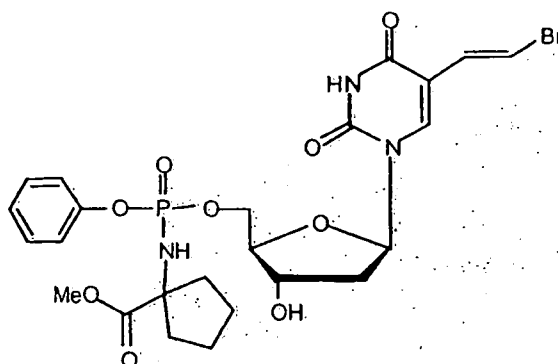
^{31}P -NMR (CDCl_3 , 121 MHz): δ 3.16, 3.01.

^1H -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, $^3J=8.8$ Hz, OPh), 7.46-7.32 (8H, m, $\text{OPh} + \text{CH}_2\text{Ph} + \text{H-5b}$), 6.77-6.68 (1H, 2d, $^3J=13.6$ Hz, H-5a), 6.31-6.26 (1H, m, H-1'), 5.18 (2H, s, CH_2Ph), 4.61-4.32 (4H, m, H-3' + H-5' + NH), 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, $\text{C}[\text{CH}_3]_2$)

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.0, 27.4, 27.5 ($\text{C}[\text{CH}_3]_2$), 40.6 (C-2'), 57.7, 57.8 ($\text{C}[\text{CH}_3]_2$), 66.8, 66.5 (C-5'), 68.2 (CH_2Ph), 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', $\text{OPh} + \text{CH}_2\text{Ph} + \text{C-5a}$), 124.2 (CF_3 , $J=267$ Hz), 135.6 ('ipso', CH_2Ph), 138.2 (C-6), 149.9 (C-4), 153.3 ('ipso', OPh), 162.1 (C-2), 175.4 (COOCH_2Ph).

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

$\text{C}_{24}\text{H}_{29}\text{BrN}_3\text{O}_9\text{P}$, MW=614.38.



This was synthesised according to *Standard procedure 5*, using BVdU (250 mg, 0.75 mmol), Phenyl-(methoxy- α,α -cycloleucynyl)-phosphorochloridate (589 mg, 1.87 mmol), NMI (6.2 mmol, 415 μ L) 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.

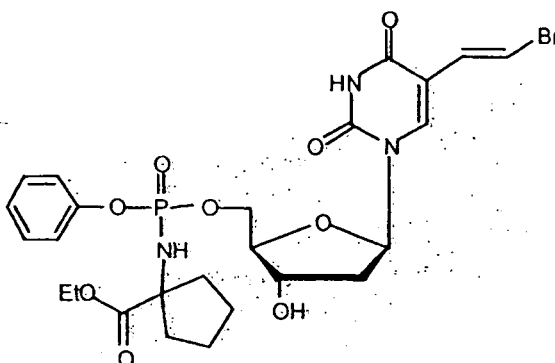
^1H -NMR (CDCl_3 , 300 MHz): δ 10.35-10.2 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.44-7.39 (1H, 2d, $^3J=13$ Hz, H-5b), 7.37-7.15 (5H, m, *OPh*), 6.8 (1H, 2d, $^3J=13$ Hz, H-5a), 6.30 (1H, 2t, $^3J=6$ Hz, H1'), 4.4-4.2 (4H, m, H-5', H-3', NH), 4.1 (1H, H-4'), 3.72 (3H, 2s, CH_3O), 2.49-2.40 (1H, m, one 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 (CH_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', *OPh*), 125.7 ('p', *OPh*), 129.0 (C-5a), 130.2 ('m', *OPh*), 138.5 (C-6), 149.9 (C-4), 150.9, 150.8 ('ipso', *OPh*), 162.3 (C-2), 176.3, 176.2 (COOCH_3).

20

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

$\text{C}_{25}\text{H}_{31}\text{BrN}_3\text{O}_9\text{P}$, 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 μ L) 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.

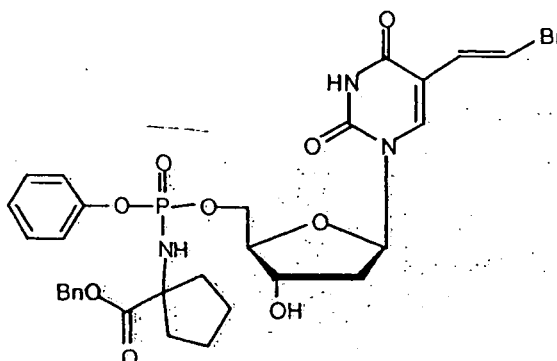
10 ^1H -NMR (CDCl_3 , 300 MHz): δ 10.3-10.1 (1H, bs, H-3), 7.8-7.75 (1H, 2xs, H-6), 7.51 (1H, 2d, $^3J=14$ Hz, H-5b), 7.45-7.10 (5H, m, *OPh*), 6.8 (1H, 2d, $^3J=14$ Hz, H-5a), 6.22 (1H, 2t, $^3J=4$ Hz, H1'), 4.55-4.05 (7H, m, H-5', H-3', H-4', NH, $\text{CH}_3\text{CH}_2\text{O}$), 2.50-2.40 (1H, m, 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, $\text{CH}_3\text{CH}_2\text{O}$).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 24.5, 24.4 (2 CH_2 cyclopent), 39.2, 38.9, 38.8, 38.4 (2 CH_2 cyclopent), 40.6 (C-2'), 62.2, 62.1 ($\text{CH}_3\text{CH}_2\text{O}$), 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', *OPh*), 125.6 ('p', *OPh*), 129.7 (C-5a), 130.2 ('m', *OPh*), 138.5, 138.3 (C-6), 149.7 (C-4), 150.9, 150.8 ('ipso', *OPh*), 162.3 (C-2), 176.3 ($\text{COOCH}_2\text{CH}_3$).

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

25 $\text{C}_{30}\text{H}_{33}\text{BrN}_3\text{O}_9\text{P}$, MW=690.48.



This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.6 mmol), Phenyl-(benzyloxy- α,α -cycloleucynyl)-phosphorochloridate (589 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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%).

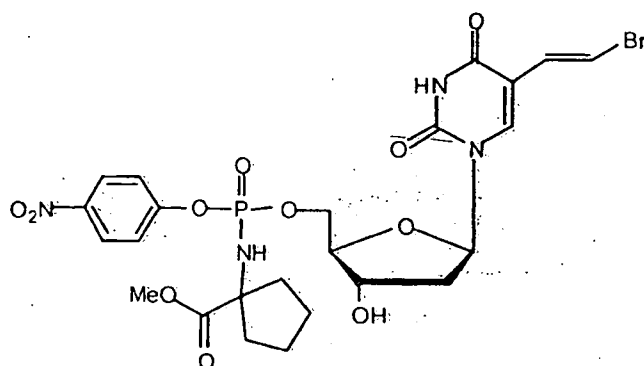
^{31}P -NMR (CDCl_3 , 121 MHz): δ 4.11, 4.01.

^1H -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, $\text{OPh}+\text{CH}_2\text{Ph}$), 6.85 (1H, 2d, $^3J=14$ Hz, H-5a), 6.20 (1H, m, H-1'), 5.15 (1H, s, CH_2Ph), 4.4-4.2 (3H, m, H-3', H-4', NH), 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 (C_q cyclopentane), 66.5 (C-5'), 67.8 (CH_2Ph), 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', OPh), 125.7 ('p', OPh), 130.2, 129.0, 128.8, 128.7, 128.5 ('m' OPh , Bn, C-5a), 135.8 ('ipso', CH_2Ph), 138.4, 138.2 (C-6), 149.8 (C-4), 150.9, 150.8 ('ipso', OPh), 162.2 (C-2), 175.7, 175.5 (COOBn).

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

$\text{C}_{24}\text{H}_{28}\text{BrN}_4\text{O}_{11}\text{P}$, MW=659.38.



This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol); para-nitrophenyl-(methoxy- α,α -cycloleucynyl)-phosphorochloridate (543 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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.

10 ^1H -NMR (CDCl_3 ; 300 MHz): δ 10.5-10.2 (1H, bs, H-3), 8.35-8.25 (2H, 2d, $^3J=6$ Hz *OPh*), 7.8-7.75 (1H, 2xs, H-6), 7.47 (2H, 2d, $^3J=6$ Hz, *OPh*), 7.45-7.35 (1H, 2d, $^3J=14$ Hz, H-5b), 6.75-6.67 (1H, 2d, $^3J=14$ Hz, H-5a), 6.30 (1H, 2t, $^3J=6$ Hz, H-1'), 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).

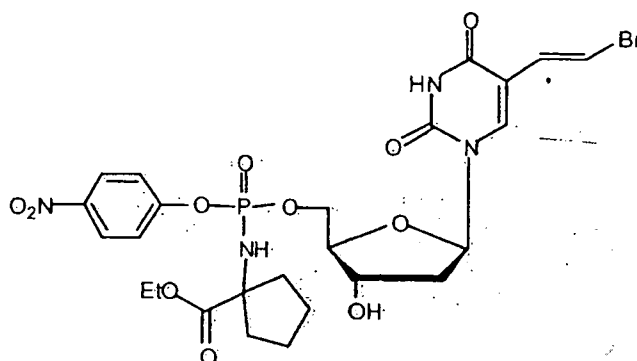
15 ^{13}C -NMR (CDCl_3 ; 75 MHz): δ 24.4, 24.3, 24.2 (2 CH_2 cyclopent), 39.2, 39.1 (2 CH_2 cyclopent), 40.5 (C-2'), 53.4, 53.3 (CH_3O), 66.8 (*Cq* cyclopentane), 67.1 (C-5'), 70.9 (C-3'), 86.1, 86.0, 85.5, 85.4 (C-1', C-4'), 110.2 (C-5b), 111.8 (C-5), 121.3, 121.2 ('o', *OPh*), 126.2 ('m', *OPh*), 128.9 (C-5a), 138.6 (C-6), 144.9 ('ipso', *OPh*), 149.9 (C-4), 155.9, 155.8 ('p', *OPh*), 162.3 (C-2), 176.3 (COOCH_3).

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

$\text{C}_{25}\text{H}_{30}\text{BrN}_3\text{O}_{11}\text{P}$, MW=673.4:

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This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(ethoxy- α,α -cycloleucynyl)-phosphorochloridate (563 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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.

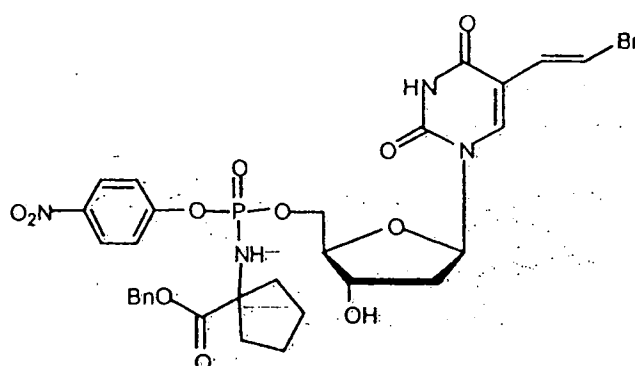
10 ^1H -NMR (CDCl_3 , 300 MHz): δ 8.25-8.2 (2H, 2d, $^3J=9\text{ Hz}$ *O*Ph), 7.66 (1H, s, H-6), 7.4 (2H, 2d, $^3J=9\text{ Hz}$, *O*Ph), 7.3 (1H, 2d, $^3J=14\text{ Hz}$, H-5b), 6.85 (1H, 2d, $^3J=14\text{ Hz}$, H-5a), 6.3-6.2 (1H, m, H1'), 4.7-4.45 (4H, m, H-5', H-3', NH), 4.2-4.05 (3H, m, H-4', $\text{CH}_3\text{CH}_2\text{O}$), 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, $^3J=8\text{ Hz}$, $\text{CH}_3\text{CH}_2\text{O}$).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.9 ($\text{CH}_3\text{CH}_2\text{O}$), 24.5, 24.4 (2 CH_2 cyclopent), 39.1, 39.0, 38.8 (2 CH_2 cyclopent), 40.7 (C-2'), 62.4 ($\text{CH}_3\text{CH}_2\text{O}$), 66.5 (*C*q 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 ($\text{COOCH}_2\text{CH}_3$).

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

25 $\text{C}_{30}\text{H}_{32}\text{BrN}_4\text{O}_{11}\text{P}$, MW=735.47.



This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), para-nitrophenyl-(benzyloxy- α,α -cycloleuciny)-phosphorochloridate (656 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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.

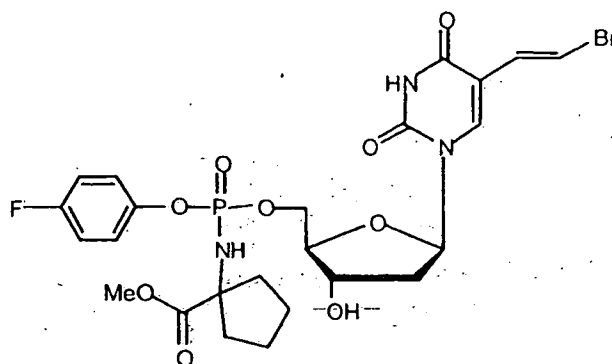
10 ^1H -NMR (CDCl_3 , 300 MHz): δ 10.3 (1H, bs, H-3), 8.22-8.12 (2H, 2d, $^3J=7$ Hz, *OPh*), 7.65 (1H, 2xs, H-6), 7.45-7.30 (8H, m, H-5b+*OPh*+ CH_2Ph), 6.72-6.65 (1H, 2d, $^3J=14$ Hz, H-5a), 6.28 (1H, 2t, $^3J=6$ Hz, H-1'), 5.15 (1H, d, CH_2Ph), 4.6-4.35 (4H, m, H-3', H-5', H-4', *NH*), 2.55-2.4 (1H, 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).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.4, 24.3, 24.2 (2 CH_2 cyclopent), 39.1, 38.9, 38.7 (2 CH_2 cyclopent), 40.5 (C-2'), 66.9 (*Cq* cyclopentane), 67.1 (C-5'), 68.0 (CH_2Ph), 70.9 (C-3'), 85.3, 85.0 (C-1', C-4'), 110.3 (C-5b), 111.8 (C-5), 121.2 ('o', *OPh*), 126.1 ('m', *OPh*), 129.0, 128.8 (Bn, C-5a), 135.7 ('ipso', CH_2Ph), 138.5 (C-6), 144.9 ('ipso', *OPh*), 149.9 (C-4), 155.8 ('p' *OPh*), 162.3 (C-2), 175.6 (COOBn).

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

25 $\text{C}_{24}\text{H}_{28}\text{BrFN}_3\text{O}_9\text{P}$, MW=632.37.



This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(methoxy- α,α -cycloleucynyl)-phosphorochloridate (503 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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.

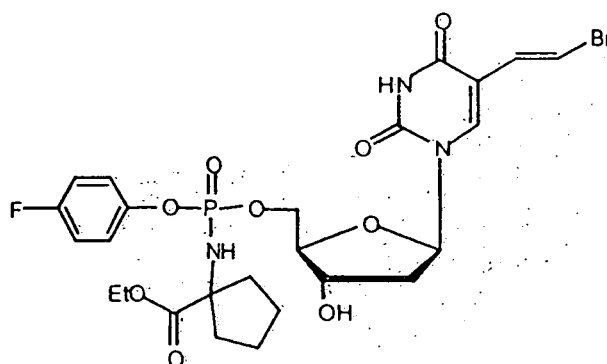
10 ^1H -NMR (CDCl_3 , 300 MHz): δ 10.3 (1H, bs, H-3); 7.70 (1H, 2xs, H-6), 7.4 (1H, 2d, $^3J=14$ Hz, H-5b), 7.25-7.15 (2H, m, *OPh*), 7.1-6.95 (2H, m, *OPh*), 6.70 (1H, 2d, $^3J=14$ Hz, H-5a), 6.30-6.15 (1H, 2t, $^3J=5$ Hz, H1'), 4.55-4.05 (5H, m, H-5'+H-3', NH, H-4'), 3.72 (3H, 2s, CH_3O), 2.55-2.35 (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).

15 ^{13}C -NMR (DMSO, 75 MHz): δ 24.4, 24.3, 24.2 (2 CH_2 cyclopent), 39.3, 39.2, 38.9, 38.5 (2 CH_2 cyclopent), 40.6 (C-2'), 53.3, 53.2 (CH_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', *OPh*), 122.2, 122.0 ('m', *OPh*), 128.5 (C-5a), 138.5 (C-6), 146.7 ('ipso', *OPh*) 149.9 (C-4), 158.5 ('p', *OPh*), 162.3 (C-2), 176.4, 176.3 (COOCH_3).

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

25 $\text{C}_{25}\text{H}_{30}\text{BrFN}_3\text{O}_9\text{P}$, MW=646.4.



This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(ethoxy- α,α -cycloleucynyl)-phosphorochloridate (524 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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.

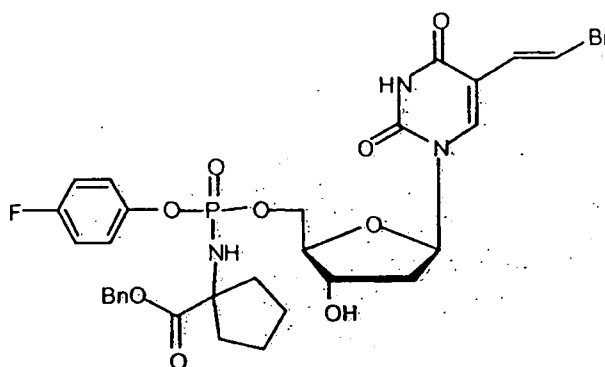
10 ^1H -NMR (CDCl_3 , 300 MHz): δ 10.35 (1H, bs, H-3), 7.7 (1H, 2xs, H-6), 7.44 (1H, 2d, $^3J=14$ Hz, H-5b), 7.25-7.15 (2H, m, *OPh*), 7.1-6.95 (2H, m, *OPh*), 6.7 (1H, 2d, $^3J=14$ Hz, H-5a), 6.30 (1H, 2t, $^3J=6$ Hz, H-1'), 4.55, 4.3 (3H, m, H-5', H-3'), 4.2-4.1 (4H, m, NH, H-4', $\text{CH}_3\text{CH}_2\text{O}$), 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, $\text{CH}_3\text{CH}_2\text{O}$).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 24.6, 24.4, 24.3 (2 CH_2 cyclopent); 39.3, 39.2, 38.9, 38.6 (2 CH_2 cyclopent), 40.6 (C-2'), 62.2 ($\text{CH}_3\text{CH}_2\text{O}$), 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', *OPh*), 122.2, 122.1 ('m', *OPh*), 129.0 (C-5a), 138.5 (C-6), 146.8, 146.7 ('ipso', *OPh*), 149.9 (C-4), 158.5 ('p', *OPh*), 162.3 (C-2), 175.9, 175.8 ($\text{COOCH}_2\text{CH}_3$).

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

25 $\text{C}_{30}\text{H}_{32}\text{BrN}_3\text{O}_9\text{P}$, MW=708.47.



This was synthesised according to *Standard procedure 5*, using BVdU (200 mg, 0.60 mmol), para-fluorophenyl-(benzyloxy- α,α -cycloleucynyl)-phosphorochloridate (616 mg, 1.5 mmol), NMI (4.98 mmol, 332 μ L) 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%).

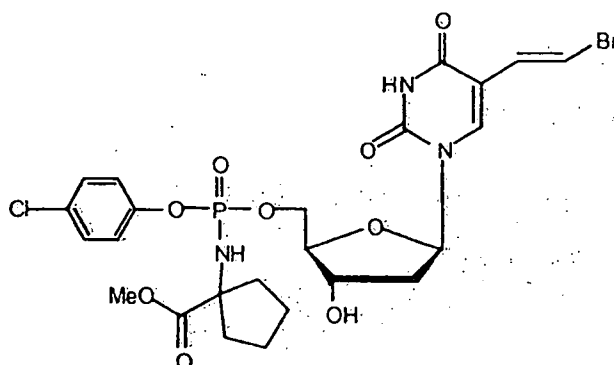
^{31}P -NMR (CDCl_3 , 121 MHz): δ 4.27.

10 ^1H -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, $^3J=14$ Hz, H-5b), 7.40-7.30 (5H, m, CH_2Ph), 7.25-7.15 (2H, m, OPh), 7.05-6.95 (2H, m, OPh), 6.71 (1H, 2d, $^3J=14$ Hz, H-5a), 6.27 (1H, 2t, $^3J=6$ Hz, H-1'), 5.15 (1H, s, CH_2Ph), 4.45 (1H, m, H-3'), 4.40-4.30 (2H, m, H-5') 4.20-4.05 (2H, m, H-4', NH), 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).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.5, 24.3, 24.2 (2CH_2 cyclopent), 39.7, 39.6, 39.3, 39.2 (2CH_2 cyclopent), 40.5, 40.0 (C-2'), 66.6 (Cq cyclopentane), 67.2, 66.7 (C-5'), 67.9 (CH_2Ph), 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', OPh), 122.2, 122.1 ('m', OPh), 129.0, 128.9, 128.6, 128.5 (Bn, C-5a), 135.8 ('ipso', CH_2Ph) 138.5 (C-6), 146.8, 146.7 ('ipso', OPh), 149.9 (C-4), 158.5 ('p' OPh), 162.2 (C-2), 175.7, 175.0 (COOBn).

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

25 $\text{C}_{24}\text{H}_{28}\text{BrClN}_3\text{O}_9\text{P}$, MW=648.82.



This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(methoxy- α,α -cycloleucynyl)-phosphorochloridate (475 mg, 1.35 mmol), NMI (4.5 mmol, 300 μ L) 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.

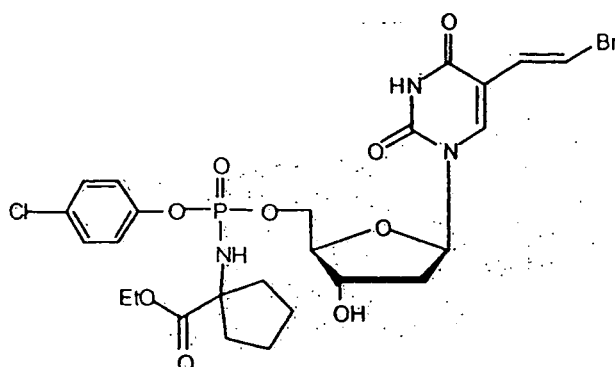
^1H -NMR (MeOD; 300 MHz): δ 7.75 (1H, 2xs, H-6), 7.32 (1H, 2d, $^3J=14$ Hz, H-5b), 7.32-7.27 (2H, m, *OPh*), 7.20-7.11 (2H, m, *OPh*), 6.72 (1H, 2d, $^3J=14$ Hz, H-5a), 6.27-6.20 (1H, 2t, $^3J=6$ Hz, H-1'), 4.35 (1H, m, H-3'), 4.30 (2H, m, H-5'), 4.1 (2H, m, H-4'), 3.72 (3H, 2s, CH_3O), 2.32-2.20 (1H, 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 (2 CH_2 cyclopent), 41.7, 41.6, 41.4, 41.3 (2 CH_2 cyclopent), 42.7 (C-2'), 54.1, 53.9 (CH_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', *OPh*), 128.9 (C-5a), 130.6 ('m', *OPh*), 130.8 ('p', *OPh*), 138.5 (C-6), 149.5, 149.4 ('ipso', *OPh*), 149.9 (C-4), 162.2 (C-2), 175.6 (COOCH_3).

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

$\text{C}_{25}\text{H}_{30}\text{BrClN}_3\text{O}_9\text{P}$, MW=662.85.



This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(ethoxy- α,α -cycloleucynyl)-phosphorochloridate (495 mg, 1.35 mmol), NMI (4.5 mmol, 300 μ L) 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.

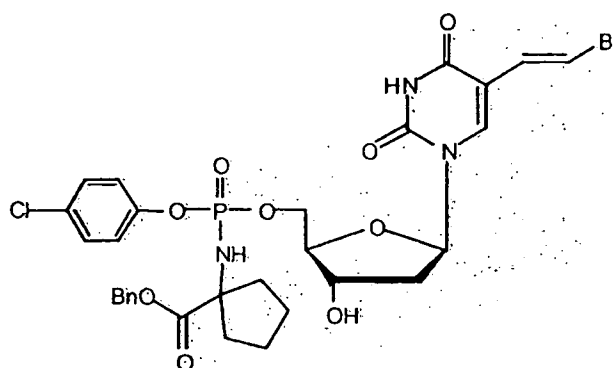
^1H -NMR (CDCl_3 , 300 MHz): δ 10.25-10.1 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.4-7.3 (1H, 2d, $^3J=14$ Hz, H-5b), 7.25-7.20 (2H, m, *OPh*), 7.20-7.10 (2H, m, *OPh*), 6.75 (1H, 2d, $^3J=14$ Hz, H-5a), 6.20 (1H, m, H1'), 4.35 (3H, m, H-3', H-5'), 4.2-4.0 (4H, m, H-4', NH, $\text{CH}_3\text{CH}_2\text{O}$), 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, $^3J=7$ Hz, $\text{CH}_3\text{CH}_2\text{O}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 24.5, 24.4 (2 CH_2 cyclopent), 39.3, 39.2, 38.8, 38.6 (2 CH_2 cyclopent), 40.5 (C-2'), 62.3 ($\text{CH}_3\text{CH}_2\text{O}$), 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', *OPh*), 129.0 (C-5a), 130.2 ('m', *OPh*), 130.8 ('p', *OPh*), 138.5 (C-6), 149.5, 149.4 ('ipso', *OPh*), 149.9 (C-4), 162.3 (C-2), 175.9 ($\text{COOCH}_2\text{CH}_3$).

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

$\text{C}_{30}\text{H}_{32}\text{BrClN}_3\text{O}_9\text{P}$, MW=724.92.



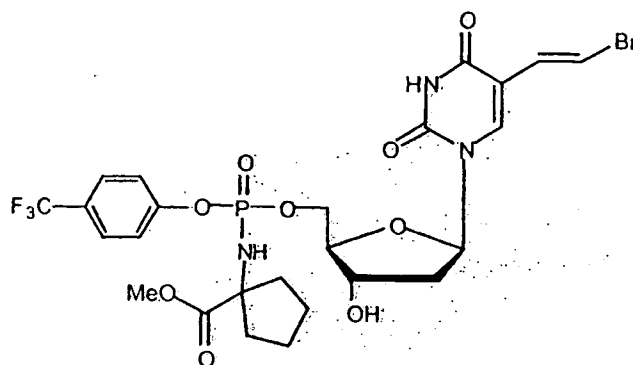
This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(benzyloxy- α,α -cycloleucynyl)-phosphorochloridate (578 mg, 1.35 mmol), NMI (4.5 mmol, 300 μ L) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH_2Cl_2 /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.

- 10 ^1H -NMR (CDCl_3 , 300 MHz): δ 7.65 (1H, 2xs, H-6), 7.45-7.29 (10H, m, H-5b, 2H $\text{OPh} + \text{CH}_2\text{Ph}$), 7.20-7.15 (2H, m, OPh), 6.75-6.67 (1H, 2d, $^3J=14$ Hz, H-5a), 6.28 (1H, 2t, $^3J=6$ Hz, H-1'), 5.15 (1H, 2s, CH_2Ph), 4.5 (1H, m, H-3'), 4.35 (2H, m, H-5') 4.1 (H, m, H-4'), 4.00 (1H, m, NH), 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).
- 15 ^{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 (C_α cyclopentane), 67.9 (CH_2Ph), 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', OPh), 129.1, 128.3, 128.2 (Bn, 'm', OPh), 130.2 (C-5a), 135.8 ('ipso', CH_2Ph), 136.3 ('p', OPh), 138.2 (C-6), 149.5, 149.3 ('ipso', OPh), 149.9 (C-4), 162.2 (C-2), 175.7, 175.5 (COOBn).
- 20 (COOBn):

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

- 25 $\text{C}_{25}\text{H}_{28}\text{BrF}_3\text{N}_3\text{O}_9\text{P}$, 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 μ L) 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.

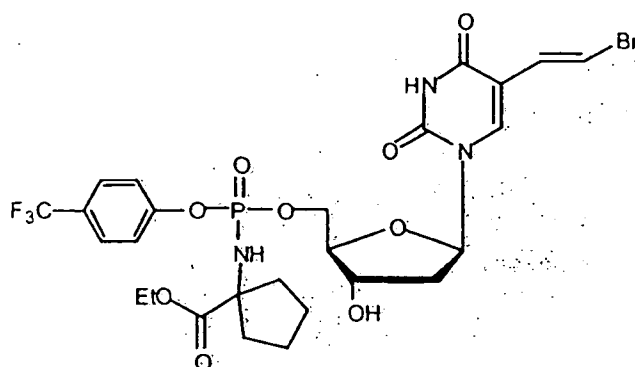
10 ^1H -NMR (CDCl_3 , 300 MHz): δ 7.70 (1H, 2s, H-6), 7.55 (1H, 2d, $^3J=14$ Hz, H-5b), 7.45-7.32 (4H, m, *OPh*), 6.72 (1H, 2d, $^3J=14$ Hz, H-5a), 6.28 (1H, 2t, $^3J=6$ Hz, H-1'), 4.55 (1H, m, H-3'), 4.45 (2H, m, H-5'), 4.25 (1H, H-4'), 4.15 (1H, NH), 3.71 (3H, 2s, CH_3O), 2.6-2.4 (1H, m, one of H-2'), 2.3-1.9 (5H, m, one of H-2' + 4H cyclopentane), 1.85-1.6 (4H, m, 4H cyclopentane).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.4, 24.3, 24.2 (2 CH_2 cyclopent), 39.2, 39.1, 38.8, 38.6 (2 CH_2 cyclopent), 40.5 (C-2'), 53.9 (CH_3O), 66.3 (C α 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, $J=270$ Hz, CF_3), 127.1, 127.0 ('o', *OPh*), 127.8 ('m', *OPh*), 128.9 (C-5a), 129.0 ('p', q, $J=32$ Hz, *OPh*), 138.5 (C-6), 149.9 (C-4), 153.5 ('ipso', *OPh*), 162.2 (C-2), 176.3, 176.2 (COOCH_3).

20

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

25 $\text{C}_{26}\text{H}_{30}\text{BrF}_3\text{N}_3\text{O}_9\text{P}$, MW=696.40.



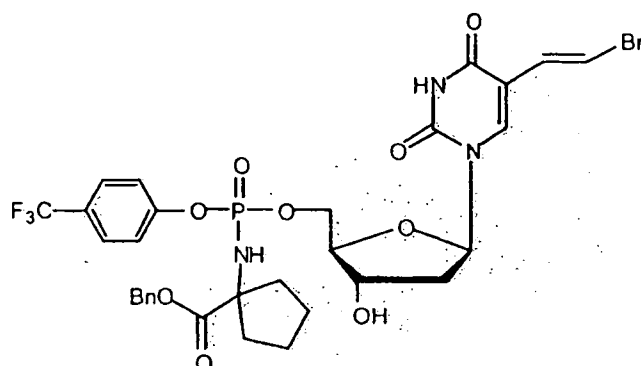
This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), para-trifluorophenyl-(ethoxy- α,α -cycloleucynyl)-phosphorochloridate (540 mg, 1.35 mmol), NMI (4.50 mmol, 300 μ L) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with 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.

10. ^1H -NMR (CDCl_3 , 300 MHz): δ 10.35 (1H, bs, H-3), 7.70 (1H, 2xs, H-6), 7.40 (1H, 2d, $^3J=14$ Hz, H-5b), 7.28-7.14 (2H, m, *OPh*), 7.05-6.95 (2H, m, *OPh*), 6.70 (1H, 2d, $^3J=14$ 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', $\text{CH}_3\text{CH}_2\text{O}$), 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, t, $^3J=7$ Hz, $\text{CH}_3\text{CH}_2\text{O}$).
15. ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 24.5, 24.4 (2 CH_2 cyclopent), 39.3, 39.2, 38.9, 38.5 (2 CH_2 cyclopent), 40.6 (C-2'), 62.2 ($\text{CH}_3\text{CH}_2\text{O}$), 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', *OPh*), 122.2, 122.1 ('m', *OPh*), 125.1 (d, $J=270$ Hz, CF_3), 129.0 (C-5a), 131.1 ('p', q, $J=32$ Hz, *OPh*), 138.5 (C-6), 146.8, 146.7 ('ipso', *OPh*), 149.9 (C-4), 162.3 (C-2), 175.9, 175.8 ($\text{COOCH}_2\text{CH}_3$).

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

25 $\text{C}_{31}\text{H}_{32}\text{BrF}_3\text{N}_3\text{O}_9\text{P}$, 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 μ L) 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%).

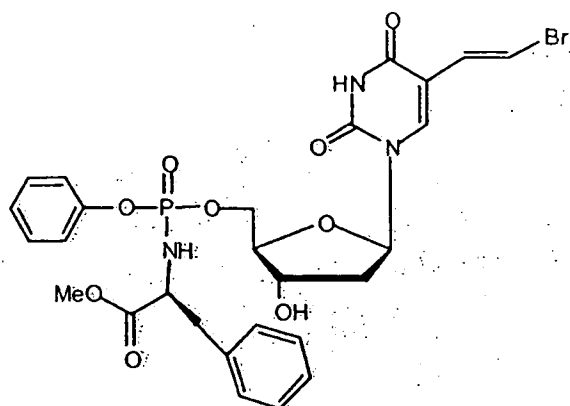
^{31}P -NMR (CDCl_3 , 121 MHz): δ 4.30.

^1H -NMR (CDCl_3 , 300 MHz): δ 10.35 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.55 (2H, m, 2H *OPh*), 7.45-7.25 (8H, m, 2H *OPh*+ CH_2Ph + H-5b), 6.7 (1H, 2d, $^3J=14\text{ Hz}$, H-5a), 6.30 (1H, 2t, $^3J=6\text{ Hz}$, H-1'), 5.15 (1H, 2s, CH_2Ph), 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 (2 CH_2 cyclopent), 39.2, 39.1, 38.7, 38.6 (2 CH_2 cyclopent), 40.5, 40.0 (C-2'), 66.4 (C α cyclopentane), 66.8 (C-5'), 68.0 (CH_2Ph), 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', *OPh*), 125.2 (d, $J=270\text{ Hz}$, CF_3), 128.5, 127.7, 127.5 (Bn, C-5a), 129.2 ('p', q, $J=32\text{ Hz}$, *OPh*), 135.4 ('ipso', CH_2Ph), 138.5 (C-6), 149.9 (C-4), 153.5 ('ipso' *OPh*), 162.2 (C-2), 175.6, 175.5 (COOBn).

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

$\text{C}_{27}\text{H}_{29}\text{BrN}_3\text{O}_9\text{P}$, 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 μ L) 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.

10 ^1H -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, $\text{CH}_2\text{Ph} + \text{OPh}$), 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').

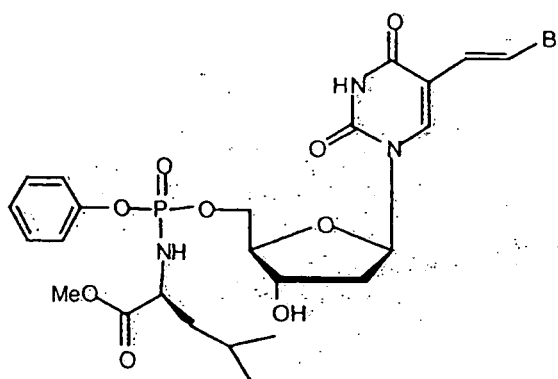
15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 36.3 ($\text{CH}_2\text{phenylalanine}$), 41.9, 41.8 (C-2'), 53.0 (CH_3O), 56.6, 56.1 (CHphenylala), 67.1 (C-5'), 71.3, 70.7 (C-3'), 85.7, 85.6, 85.5, 85.4 (C-1' , C-4'), 110.4 (C-5b), 111.9 (C-5), 120.6, 120.5 ('o' , OPh), 127.8 ('p' , OPh), 130.1, 129.9, 129.8, 129.1 (CH_2Ph , C-5a , 'm' OPh), 138.0, 137.9 (C-6), 149.8 (C-4), 150.7, 150.6 ('ipso' , OPh), 162.1, 162.0 (C-2), 173.5 (COOCH_3).

20

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

$\text{C}_{24}\text{H}_{31}\text{BrN}_3\text{O}_9\text{P}$, MW=616.40.

25



This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), Phenyl-(methoxy-L-leucynyl)-phosphorochloridate (432 mg, 1.35 mmol), NMI (4.42 mmol, 190 μ L) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH₂Cl₂/Methanol 97:3 to give the pure product as a white foamy solid (167 mg, yield 60%).

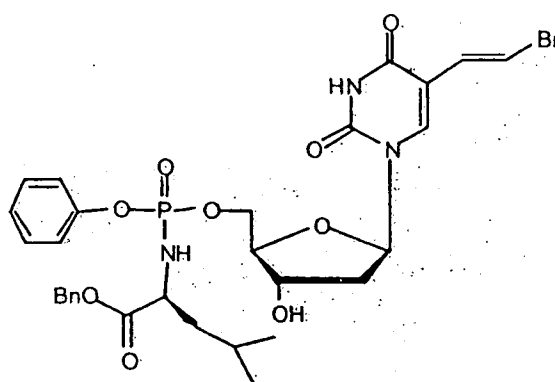
³¹P-NMR (CDCl₃, 121 MHz): δ 5.14, 4.60.

10 ¹H-NMR (CDCl₃; 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, CHCH₂CH(CH₃)₂), 3.70 (3H, 2s, CH₃O), 2.40-2.20 (1H, m, one of H-2'), 2.05-1.95 (1H, m, one of H-2'), 1.8 (1H, m, CHCH₂CH(CH₃)₂), 1.8-1.5 (2H, m, CHCH₂CH(CH₃)₂), 1.0-0.9 (6H, m, CHCH₂CH(CH₃)₂).

15 ¹³C-NMR (CDCl₃; 75 MHz): δ 23.2, 23.1, 22.0, 21.9 (2C, CHCH₂CH(CH₃)₂), 24.9, 24.7 (CHCH₂CH(CH₃)₂), 40.6 (C-2'), 43.7, 43.6 (CHCH₂CH(CH₃)₂), 53.0 (CH₃O), 53.7, 53.6 (CHCH₂CH(CH₃)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 (COOCH₃).

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

C₃₀H₃₅BrN₃O₉P, MW=692.49.



This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol); Phenyl-(benzoxy-L-leucynyl)-phosphorochloridate (534 mg, 1.35 mmol), NMI (4.42 mmol, 190 μ L) 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%).

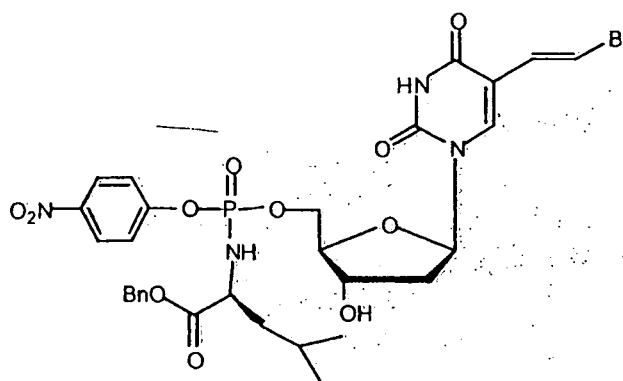
^{31}P -NMR (CDCl_3 , 121 MHz): δ 5.18, 4.54.

10 ^1H -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, $\text{CH}_2\text{Ph} + \text{OPh}$), 6.65 (1H, 2d, $^3J=14$ Hz, H-5a), 6.26-6.14 (1H, 2t, $^3J=6$ Hz, H-1'), 5.1 (2H, 2s, CH_2Ph), 4.4-3.8 (6H, m, H-5', H-3', NH, H-4', $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 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, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 0.8 (6H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$).

15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 23.2, 23.1, 22.0, 21.9 (2C, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 24.9, 24.7 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 40.7 (C-2'), 43.9, 43.8 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 53.9, 53.7 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 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', OPh), 125.8, 125.7 ('p', OPh), 130.2, 129.1, 128.9 (C-5a, CH_2Ph , 'm' OPh), 135.4 ('ipso', CH_2Ph), 138.1 (C-6), 149.8 (C-4), 150.2 ('ipso', OPh), 162.1 (C-2), 175.7, 174.6 (COOBn).

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

$\text{C}_{30}\text{H}_{34}\text{BrN}_4\text{O}_{11}\text{P}$, MW=737.49.



This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), para-nitrophenyl-(benzoxyl-L-leucynyl)-phosphorochloridate (595 mg, 1.35 mmol), NMI (4.42 mmol, 190 μ L) 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%).

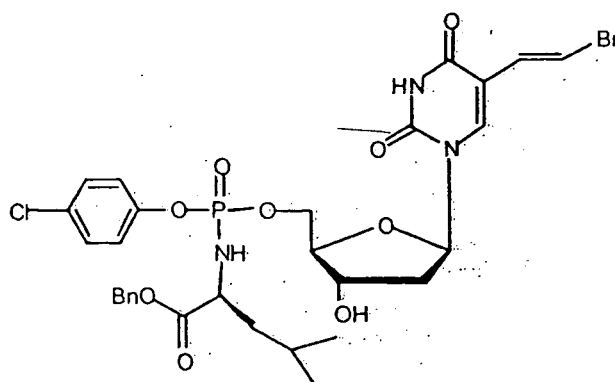
^{31}P -NMR (CDCl_3 , 121 MHz): δ 5.72, 4.35.

10: ^1H -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_2Ph + 2H *O*Ph), 6.65 (1H, 2d, $^3J=14$ Hz, H-5a), 6.35-6.2 (1H, 2t, $^3J=6$ Hz, H-1'), 5.15 (2H, 2s, CH_2Ph), 4.7-3.9 (6H, m, H-5', H-3', NH, H-4', $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 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, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 0.95-0.8 (6H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$).

15: ^{13}C -NMR (CDCl_3 , 75 MHz): δ 23.2, 23.1, 22.0, 21.9 (2C, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 24.9, 24.8 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 40.6 (C-2'), 43.7, 43.6 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 53.9, 53.7 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 66.9 (C-5'), 67.9 (CH_2Ph), 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_2Ph , 'm' *O*Ph), 135.4, 135.3 ('ipso', CH_2Ph), 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 (COOBn).

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

$\text{C}_{30}\text{H}_{34}\text{BrClN}_3\text{O}_9\text{P}$, MW=726.94.



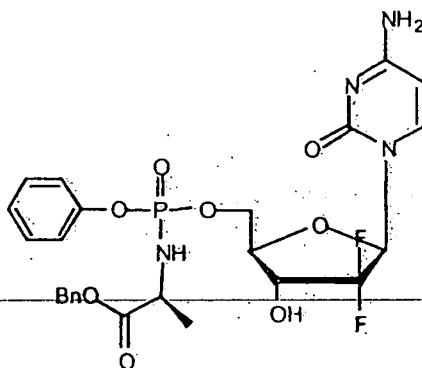
This was synthesised according to *Standard procedure 5*, using BVdU (150 mg, 0.45 mmol), para-chlorophenyl-(benzoxy-L-leucynyl)-phosphorochloridate (581 mg, 1.35 mmol), NMI (4.42 mmol, 190 μ L) in THF (5 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH_2Cl_2 /Methanol 97:3 to give the pure product as a white foamy solid (221 mg, yield 68%).

^{31}P -NMR (CDCl_3 , 121 MHz): δ 5.27, 4.76.

- 10 ^1H -NMR (CDCl_3 , 300 MHz): δ 10.25-10.15 (1H, bs, H-3), 7.65 (1H, 2xs, H-6), 7.45 (1H, 2d, $^3J=14$ Hz, H-5b), 7.4-7.15 (9H, m, $\text{CH}_2\text{Ph} + \text{OPh}$), 6.7 (1H, 2d, $^3J=14$ Hz, H-5a), 6.35-6.2 (1H, 2t, $^3J=6$ Hz, H1'), 5.15 (2H, 2s, CH_2Ph) 4.55-3.9 (6H, m, H-5', H-3', NH, H-4', $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 2.5-2.4 (1H, m, one of H-2'), 2.15-2.0 (1H, m, one of H-2'), 1.7-1.45 (3H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 0.94-0.82 (6H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$).
- 15 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 23.1, 23.0, 22.2, 22.0 (2C, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$); 24.9, 24.7 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$); 40.7 (C-2'), 43.9, 43.8 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 53.9, 53.7 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 66.7, 66.3 (C-5'), 67.8 (CH_2Ph), 71.1, 70.7 (C-3'), 85.8, 85.7, 85.4 (C-1', C-4'), 110.5 (C-5b), 111.9 (C-5), 122.1, 122.0 ('o', OPh), 130.2, 129.1, 129.0 (C-5a, CH_2Ph , 'm' OPh), 131.1, 130.9 ('p', OPh), 135.5, 135.4 ('ipso', CH_2Ph), 138.2 (C-6), 149.2, 149.1 ('ipso', OPh), 149.2, 149.1 (C-4), 162.2 (C-2), 174.2, 174.2 (COOBn).
- 20

Synthesis of Gemcitabine-[phenyl-(benzoxy-L-alaninyl)]-phosphate.

$C_{25}H_{27}F_2N_4O_8P$, MW=580.47 (CPF 31).



5

This was synthesised according to *Standard procedure 5*, using gemcitabine (131 mg, 0.5 mmol), Phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (529 mg, 1.5 mmol), NMI (4.42 mmol, 300 μ L) in THF/pyridine (4/2 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH_2Cl_2 /Methanol 95:5 to give the pure product as a

10 white foamy solid (46 mg, yield 16%).

^{31}P -NMR (MeOD, 121 MHz): δ 5.05, 4.94.

1H -NMR (MeOD, 300 MHz): δ 7.6-7.5 (1H, 2d, $^3J=7$ Hz, H-6), 7.4-7.2 (10H, m, $O\text{Ph}+CH_2Ph$), 6.25 (1H, m, H-1'), 5.95 (1H, 2d, $^3J=7$ Hz, H-5), 5.19 (1H, 2s, CH_2Ph), 4.55-4.1 (3H, m, H-3', H-4', CHala), 4.05 (2H, m, H-5'), 1.20 (3H, 2t, $^3J=6$ Hz, CH_3ala).

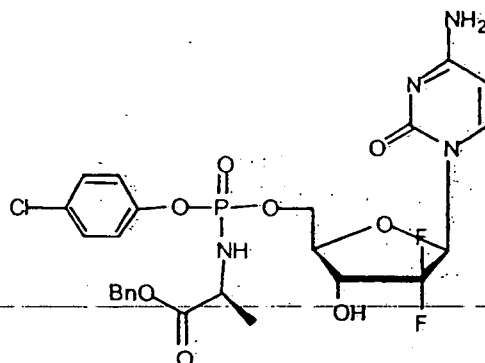
15 ^{13}C -NMR (MeOD, 75 MHz): δ 20.8, 20.7 (CH_3ala), 52.2, 52.0 ($CHala$), 66.1 (C-5'), 68.4 (CH_2Ph), 71.9, 71.3 (C-3'), 80.6 (C-4'), 85.9 (C-1'), 97.1 (C-5), 121.8, 121.6 ('o', $O\text{Ph}$), 123 (C-2'), 126.2 ('p', $O\text{Ph}$), 131.8, 130.0, 129.7 ('m' $O\text{Ph}$, Bn), 137.9 ('ipso', CH_2Ph), 142.7, 142.6 (C-6), 152.5, 152.4 ('ipso', $O\text{Ph}$), 158.2 (C-2), 168.0 (C-4), 175.3, 174.9 ($COOBn$).

20

25

Synthesis of Gemcitabine-[para-chlorophenyl-(benzoxy-L-alaninyl)]-phosphate.

$C_{25}H_{26}ClF_2N_4O_8P$, MW=614.92 (CPF 40).



5

This was synthesised according to *Standard procedure 5*, using gemcitabine (131 mg, 0.5 mmol), para-chlorophenyl-(benzoxy-L-alaninyl)-phosphorochloridate (582 mg, 1.5 mmol), NMI (4.42 mmol, 300 μ L) in THF/pyridine (4/2 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH_2Cl_2 /Methanol 95:5 to give the pure product as a white foamy solid (76 mg, yield 25%).

10

^{31}P -NMR (MeOD, 121 MHz): δ 5.08.

1H -NMR (MeOD, 300 MHz): δ 7.65 (1H, 2d, $^3J=7$ Hz H-6), 7.5-7.2 (9H, m, $O\text{Ph}+CH_2Ph$), 6.2 (1H, m, H-1'), 5.9 (1H, 2d, $^3J=7$ Hz, H-5), 5.12 (1H, 2s, CH_2Ph), 4.6-4.1 (3H, m, H-3', H-4', CHala), 4.05 (2H, m, H-5'), 1.45-1.35 (3H, 2t, $^3J=6$ Hz, CH_3ala).

15

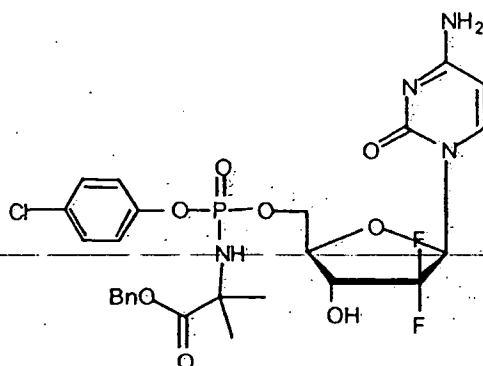
^{13}C -NMR (MeOD, 75 MHz): δ 20.9, 20.7 (CH_3ala), 52.2, 52.0 ($CHala$), 66.4, 66.2 (C-5'), 68.5 (CH_2Ph), 71.5 (C-3'), 80.7 (C-4'), 86.4 (C-1'), 97.2 (C-5), 123.5 ('o', $O\text{Ph}$), 126.9 (C-2'), 131.2, 130.6, 130.3 ('m' $O\text{Ph}$; Bn), 131.9 ('p', $O\text{Ph}$), 137.5 ('ipso', CH_2Ph), 142.8, 142.7 (C-6), 151.4, 151.0 ('ipso', $O\text{Ph}$), 158.2 (C-2), 166.9 (C-4), 175.1, 174.9 ($COOBn$).

20

25

Synthesis of Gemcitabine-[para-chlorophenyl-(benzoxy- α,α -dimethylglycyl)]-phosphate (CPF 41).

$C_{26}H_{28}ClF_2N_4O_8P$, MW=628.95.



5

This was synthesised according to *Standard procedure 5*, using gemcitabine (131 mg, 0.5 mmol), para-chlorophenyl-(benzoxy- α,α -dimethylglycyl)-phosphorochloridate (603 mg, 1.5 mmol), NMI (4.42 mmol, 300 μ L) in THF/pyridine (4/3 mL) for 2 hrs. The crude product was purified by column chromatography, eluting with CH_2Cl_2 /Methanol 95:5 to give the pure product as a white foamy solid (163 mg, yield 52%).

^{31}P -NMR (MeOD, 121 MHz): δ 3.56, 3.52.

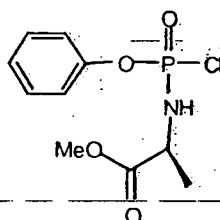
1H -NMR (MeOD, 300 MHz): δ 7.55 (1H, d, $^3J=7$ Hz, H-6), 7.4-7.15 (9H, m, *OPh*+*CH₂Ph*), 6.25 (1H, m, H-1'), 5.85 (1H, d, $^3J=7$ Hz, H-5), 5.15 (1H, 2s, *CH₂Ph*), 4.55-4.1 (3H, m, H-3', H-4'), 4.05 (2H, m, H-5'), 1.50 (6H, m, $^3J=6$ Hz, 2CH₃dimethygly).

^{13}C -NMR (MeOD, 75 MHz): δ 28.2, 28.0 (CH₃dimethygly), 58.6 (C_qdimethygly), 66.2, 66.1 (C-5'), 66.7 (C-2'), 71.5 (C-3'), 80.6 (C-4'), 86.4 (C-1'), 97.0 (C-5), 123.9, 123.6 ('o', *OPh*), 127.3 (C-2'), 130.0, 129.7 ('m' *OPh*, Bn), 131.8 ('p', *OPh*), 137.6 ('ipso', *CH₂Ph*), 142.8, 142.7 (C-6), 151.2, 151.1 ('ipso', *OPh*), 158.1 (C-2), 167.9 (C-4), 176.8, 176.7 (COOBn).

Synthesis of Phenyl-(methoxy-L-alaninyl)-phosphorochloridate:

$C_{10}H_{13}ClNO_4P$, MW=277.64.

5



This is synthesised according to *Standard procedure 4*, using L-alanine methyl ester hydrochloride (2 g, 14.3 mmol), phenyldichlorophosphate (3.02 g, 2.14 ml, 14.3 mmol),
 10 and TEA (2.9 g, 4.0 ml, 28.7 mmol) in DCM (60 mL), to yield 3.91 g (98%) of crude product used without further purification:

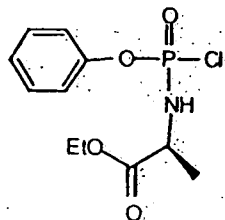
^{31}P -NMR ($CDCl_3$, 121 MHz): δ 9.28, 8.97.

1H -NMR ($CDCl_3$; 300 MHz): δ 7.39-7.34 (2H, m, 'o' OPh), 7.29-7.20 (2H, m, 'm+p' OPh), 4.98 (1H, bs, NH), 4.27-4.09 (1H, m, CH_{ala}), 3.78 (3H, s, OCH₃), 1.52-1.49 (3H,
 15 2xd, $^3J=7$ Hz, CH₃ala).

^{13}C -NMR ($CDCl_3$; 75 MHz): δ 20.9 (CH₃ala), 51.0 (CH_{ala}), 53.6 (OCH₃), 120.9 ('o' OPh), 126.4 ('p', OPh), 130.2 ('m', OPh), 150.1 ('ipso', OPh), 173.6 (COOCH₃).

20 Synthesis of Phenyl-(ethoxy-L-alaninyl)-phosphorochloridate:

$C_{11}H_{15}ClNO_4P$, MW=291.67.



25 This is synthesised according to *Standard procedure 4*, using L-alanine ethyl ester hydrochloride (770 mg, 5.01 mmol), phenyldichlorophosphate (1.12g, 5.01 mmol, 749

μL), and TEA (1.4 mL, 10.02 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 7:3) affording 1.02 (69%) of oil.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.49, 9.07.

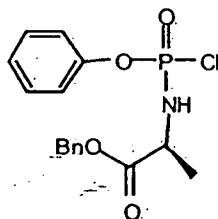
^1H -NMR (CDCl_3 , 300 MHz): δ 7.39-7.34 (2H, m, 'o' OPh), 7.29-7.20 (2H, m, 'm+p' OPh), 4.95 (1H, bs, NH), 4.3-4.1 (3H, m, OCH_2CH_3 , CHala), 1.50 (3H, 2xd, $^3J=7\text{Hz}$, CH_3ala), 1.30 (3H, t, $^3J=7.1\text{Hz}$, OCH_2CH_3).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 (CH_3CH_2), 20.9 (CH_3ala), 51.0 (CHala), 62.6 (CH_3CH_2), 120.9 ('o' OPh), 126.5 ('p', OPh), 130.1 ('m', OPh), 150.1 ('ipso', OPh), 175.1 ($\text{COOCH}_2\text{CH}_3$).

10

Synthesis of Phenyl-(benzoxo-L-alaninyl)-phosphorochloridate.

$\text{C}_{16}\text{H}_{17}\text{ClNO}_4\text{P}$, MW= 353.74.



15

This is synthesised according to *Standard procedure 4*, using L-alanine benzyl ester hydrochloride (1.0 g, 4.64 mmol), phenyl-dichlorophosphate (980 mg, 0.69 ml, 4.64 mmol), and TEA (0.94 g, 1290 μL, 9.27 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 6:4) affording 1.61 (98%) of oil.

20 ^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.41, 9.23.

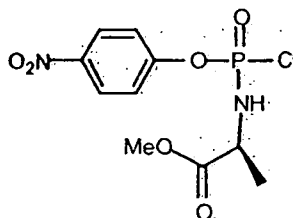
^1H -NMR (CDCl_3 , 300 MHz): δ 7.41-7.21 (10H, m, $\text{OPh}+\text{CH}_2\text{Ph}$), 5.24 (2H, s, CH_2Ph), 4.95-4.88 (1H, bs, NH), 4.36-4.15 (1H, m, CHala), 1.52-1.49 (3H, 2xd, $^3J=7\text{Hz}$, CH_3ala).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 20.8 (CH_3ala), 51.1 (CHala), 68.0 (CH_2Ph), 121.0 ('o' OPh), 126.4 ('p', OPh), 130.3, 129.0, 128.7 ('m' OPh , CH_2Ph), 135.5 ('ipso', CH_2Ph),

25 150.2 ('ipso', OPh), 172.9 (COOCH_2Ph).

Synthesis of p-nitrophenyl-(methoxy-L-alaninyl)-phosphorochloridate.

$\text{C}_{10}\text{H}_{12}\text{ClN}_2\text{O}_6\text{P}$, MW=322.64.



This is synthesised according to *Standard procedure 4*, using L-alanine methyl ester hydrochloride (0.70 g, 5.01 mmol), p-nitrophenyldichlorophosphate (1.362 g, 5.01 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL), to yield 1.60 g (99%) of crude product used without further purification.

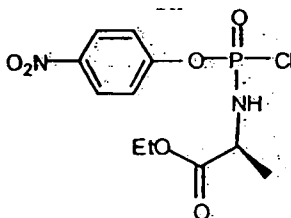
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.13, 9.03.

^1H -NMR (CDCl_3 , 300 MHz): δ 8.1 (2H, 2d, $^3J=8\text{Hz}$, OPh), 7.3 (2H, 2d, $^3J=8\text{Hz}$, OPh), 5.0 (1H, bs, NH), 4.1 (1H, m, CHala), 3.75 (3H, s, OCH₃), 1.5-1.45 (3H, m, CH₃ala).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 20.8, 20.7 (CH₃ala), 51.1, 50.9 (CHala), 53.2, 53.2 (OCH₃), 121.8, 121.6 ('o', OPh), 126.5 ('m', OPh), 145.7 ('ipso', OPh), 154.7, 154.6 ('p', OPh), 173.4, 173.2 (COOCH₃).

Synthesis of p-nitrophenyl-(ethoxy-L-alanyl)-phosphorochloridate.

$\text{C}_{11}\text{H}_{14}\text{ClN}_2\text{O}_6\text{P}$; MW=336.67.



This is synthesised according to *Standard procedure 4*, using L-alanine ethyl ester hydrochloride (770 mg, 5.01 mmol), p-nitrophenyldichlorophosphate (1.362g, 5.01 mmol), and TEA (1.4 mL, 10.02 mmol) in DCM (40 mL), to yield 1.64 g (98%) of crude product used without further purification.

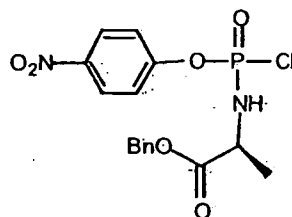
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.06, 8.81.

$^1\text{H-NMR}$ (CDCl_3 ; 300 MHz): δ 8.1 (2H, m, OPh), 7.4 (2H, m, OPh), 4.9-4.7 (1H, bs, NH), 4.3-4.1 (3H, m, OCH_2CH_3 , CHala), 1.55-1.45 (3H, 2xd, $^3J=7\text{Hz}$, CH_3ala), 1.40 (3H, t, $^3J=7\text{Hz}$, OCH_2CH_3).

$^{13}\text{C-NMR}$ (CDCl_3 ; 75 MHz): δ 14.5 (CH_3CH_2), 21.1, 20.9 (CH_3ala), 51.2, 51.0 (CHala), 62.6 (CH_3CH_2), 121.7, 121.3 ('o', OPh), 126.2, 126.0 ('m', OPh), 145.7 ('ipso', OPh), 154.5 ('p', OPh), 173.4, 173.3 ($\text{COOCH}_2\text{CH}_3$).

Synthesis of p-nitrophenyl-(benzoxy-L-alaninyl)-phosphorochloridate.

10 $\text{C}_{16}\text{H}_{16}\text{ClN}_2\text{O}_6\text{P}$, MW= 398.04.



This is synthesised according to *Standard procedure 4*, using L-alanine benzyl ester hydrochloride (1.08 g; 5.01 mmol), para-nitrophenyl-dichloro phosphate (1.362 g; 5.01 mmol), and TEA (1.4 mL, 1.4 mmol) in DCM (40 mL), to yield 1.85 g (93%) of crude product used without further purification.

$^{31}\text{P-NMR}$ (CDCl_3 ; 121 MHz): δ 9.15, 9.06.

$^1\text{H-NMR}$ (CDCl_3 ; 300 MHz): δ 8.15 (2H, m, OPh), 7.45 (2H, m, OPh), 7.35-7.25 (5H, m, CH_2Ph), 5.2 (2H, 2s, CH_2Ph), 5.00 (1H, bs, NH), 4.2 (1H, m, CHala), 1.64 (3H, 2xd, $^3J=7\text{Hz}$, CH_3ala).

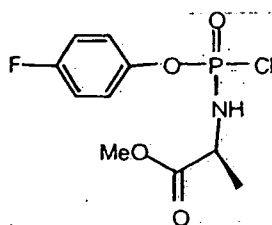
$^{13}\text{C-NMR}$ (CDCl_3 ; 75 MHz): δ 20.8 (CH_3ala), 51.1 (CHala), 68.0 (CH_2Ph), 121.4 ('o', OPh), 126.1 ('m', OPh), 130.3, 129.0 (CH_2Ph), 145.7 ('ipso', CH_2Ph), 150.2 ('ipso', OPh), 154.6 ('p', OPh), 172.9 (COOCH_2Ph).

25

Synthesis of p-fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate.

$\text{C}_{10}\text{H}_{12}\text{ClFNO}_4\text{P}$, MW=295.63.

77



This is synthesised according to *Standard procedure 4*, using L-alanine methyl ester hydrochloride (0.70 g, 5.01 mmol), p-fluorophenyldichlorophosphate (1.210 g, 5.01 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 7:3) affording 1.11 g (75%) of oil.

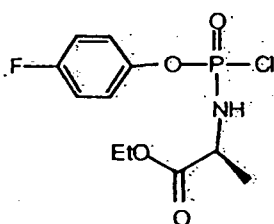
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.98, 9.96.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.1 (2H, m, OPh), 6.95 (2H, m, OPh), 5.0 (1H, bs, NH), 4.25-4.1 (1H, m, CHala), 3.78 (3H, 2s, OCH_3), 1.55 (3H, m, CH_3ala).

10. ^{13}C -NMR (CDCl_3 , 75 MHz): δ 20.8 (CH_3ala), 51.1, 50.9 (CHala), 53.3 (OCH_3), 117.1, 117.0 (o , OPh), 122.6, 122.5 (m , OPh), 146.0 (ipso , OPh), 159.1, 159.0 (p , OPh), 173.4, 173.2 (COOCH_3).

15 Synthesis of p-fluorophenyl-(ethoxy-L-alaninyl)-phosphorochloridate.

$\text{C}_{11}\text{H}_{14}\text{ClFNO}_4\text{P}$, MW=309.66.



20 This is synthesised according to *Standard procedure 4*, using L-alanine ethyl ester hydrochloride (770 mg, 5.01 mmol), p-fluorophenyldichlorophosphate (1.210g, 5.01 mmol), and TEA (1.4 mL, 10.02 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 7:3) affording 1.07 (69%) of oil.

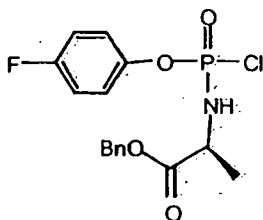
^{31}P -NMR (CDCl_3 , 121 MHz): δ 10.04, 9.95.

¹H-NMR (CDCl₃; 300 MHz): δ 7.1 (2H, m, *O*Ph), 6.95 (2H, m, *O*Ph), 5.0 (1H, bs, *NH*), 4.25-4.1 (3H, m, *OCH*₂CH₃, *CH*ala), 1.55 (3H, m, *CH*₃ala), 1.40 (3H, t, ³J=7Hz, *OCH*₂CH₃).

¹³C-NMR (CDCl₃; 75 MHz): δ 14.5 (*CH*₃CH₂), 21.1, 21.0 (*CH*₃ala), 51.2, 51.1 (*CH*ala), 62.6 (*CH*₃CH₂), 117.3 ('*o*' *O*Ph), 122.2, 122.0 ('*m*', *O*Ph), 145.9, 145.8 ('*ipso*', *O*Ph), 159.0 ('*p*', *O*Ph), 173.6, 173.5 (*COOCH*₂CH₃).

Synthesis of p-fluorophenyl-(benzoxy-L-alaninyl)-phosphorochloridate.

10 C₁₆H₁₆ClFNO₄P, MW= 371.73.



This is synthesised according to *Standard procedure 4*, using L-alanine benzyl ester hydrochloride (1.08 g, 5.01 mmol), para-fluorophenyl-dichloro phosphate (1.210 mg, 5.01 mmol), and TEA (1.4mL, 1.4 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 7:3) affording 1.599 (86%) of oil.

³¹P-NMR (CDCl₃, 121 MHz): δ 9.15, 9.06.

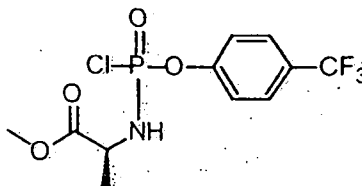
¹H-NMR (CDCl₃; 300 MHz): δ 7.35-7.25 (5H, m, *CH*₂Ph), 7.1 (2H, m, *O*Ph), 6.95 (2H, m, *O*Ph), 5.2 (2H, 2s, *CH*₂Ph), 5.00 (1H, bs, *NH*), 4.25-4.1 (1H, m, *CH*ala), 1.55 (3H, m, *CH*₃ala).

¹³C-NMR (CDCl₃; 75 MHz): δ 20.8 (*CH*₃ala), 51.1, 51.0 (*CH*ala), 68.1 (*CH*₂Ph), 117.0, 116.9 ('*o*' *O*Ph), 122.6 ('*m*' *O*Ph), 130.3, 129.0 (*CH*₂Ph), 135.7 ('*ipso*', *CH*₂Ph), 146.1, 146.0 ('*ipso*', *O*Ph), 158.9 ('*p*', *O*Ph), 173.1 (*COOCH*₂Ph).

25

Synthesis of 4-(trifluoromethyl)-phenyl-(methoxy-L-alaninyl)-phosphorochloridate.

C₁₁H₁₂ClF₃NO₄P, MW=345.64.



This is synthesised according to *Standard procedure 4*, using L-alanine methyl ester hydrochloride (1.0 g, 7.16 mmol), 4-(trifluoromethyl)-phenyl-phosphodichloridate (1.998 g, 7.16 mmol), and TEA (1.449 g, 14.32 mmol, 1916 μ L) in DCM (30 mL), to yield 2.202 g (89.0%) of crude product used without further purification.

5 ^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.36, 9.22.

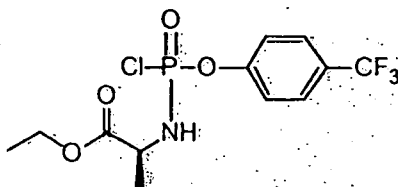
^1H -NMR (CDCl_3 , 300 MHz): δ 7.66 (2H, d, $^3J=8.1$ Hz, *OPh*), 7.44-7.33 (2H, m, *OPh*), 5.10 (1H, bs, *NH*), 3.81-3.78 (3H, 2s, *CH₃O*), 3.77-3.68 (1H, m, *CH₃CH*), 1.56-1.52 (3H, m, *CHCH₃*).

10 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 20.6, 20.7 (*CH₃CH*), 50.9, 51.1 (*CHCH₃*), 53.2 (*CH₃O*), 121.4 ('o', *OPh*), 124.1 (*CF₃*, $J=270$ Hz), 128.0 ('m', *OPh*), 128.6 ('p', $J=34$ Hz), 152.4, 152.6 ('ipso', *OPh*), 173.4, 173.5 (*COOCH₃*).

Synthesis of 4-(trifluoromethyl)-phenyl-(ethoxy-L-alaninyl)-phosphorochloridate.

$\text{C}_{12}\text{H}_{14}\text{ClF}_3\text{NO}_4$, MW=359.67.

15



This is synthesised according to *Standard procedure 4*, using L-alanine ethyl ester hydrochloride (1.0 g, 6.50 mmol), 4-(trifluoromethyl)-phenyl-phosphodichloridate (1.813 g, 6.50 mmol), and TEA (1.316 g, 13.00 mmol, 1740 μ L) in DCM (30 mL), to yield 2.150 g (92.2%) of crude product used without further purification.

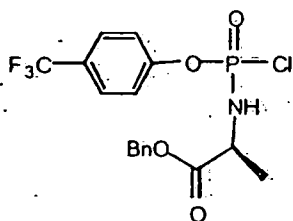
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.33, 9.28.

$^1\text{H-NMR}$ (CDCl_3 ; 300 MHz): δ 7.70 (2H, d, $^3J=8.2$ Hz, OPh), 7.46-7.39 (2H, m, OPh), 4.78 (1H, bs, NH), 4.33-4.17 (3H, m, $\text{CH}_3\text{CH}_2\text{O} + \text{CHCH}_3$), 1.59-1.55 (1H, m, CHCH_3), 1.56-1.52 (3H, m, CH_2CH_3).

$^{13}\text{C-NMR}$ (CDCl_3 ; 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 20.8, 20.9 (CH_3CH), 50.3, 50.9 (CHCH_3), 62.3, 62.5 ($\text{CH}_3\text{CH}_2\text{O}$), 121.4 ('o', OPh), 124.1 (CF_3 , $J=270$ Hz), 127.7 ('m', OPh), 128.7 ('p', $J=33$ Hz), 152.4 ('ipso', OPh), 172.9 ($\text{COOCH}_2\text{CH}_3$).

Synthesis of p-trifluorophenyl-(benzoxyl-L-alaninyl)-phosphorochloridate.

10. $\text{C}_{17}\text{H}_{16}\text{ClF}_3\text{NO}_4\text{P}$, MW=421.73.



This is synthesised according to *Standard procedure 4*, using L-alanine benzyl ester hydrochloride (1.08 g, 5.01 mmol), para-trifluorophenyl-dichloro phosphate (1.490 mg, 5.01 mmol), and TEA (1.4 mL, 1.4 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 6:4) affording 1.80 (85%) of oil.

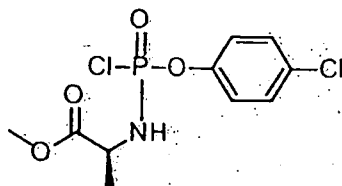
$^{31}\text{P-NMR}$ (CDCl_3 , 121 MHz): δ 9.11, 8.84.

$^1\text{H-NMR}$ (CDCl_3 ; 300 MHz): δ 7.65 (2H, m, OPh), 7.4-7.2 (7H, m, $\text{CH}_2\text{Ph} + 2\text{H OPh}$), 5.25 (2H, 2s, CH_2Ph), 4.75-4.55 (1H, bs, NH), 4.25-4.1 (1H, m, CHala), 1.60-1.55 (3H, 2d, $^3J=7\text{Hz}$, CH_3ala).

$^{13}\text{C-NMR}$ (CDCl_3 ; 75 MHz): δ 20.9 (CH_3ala), 51.3, 51.0 (CHala), 68.2, 68.1 (CH_2Ph), 121.4, 120.9 ('o', OPh), 125.2 (d, $J=270\text{Hz}$, CF_3), 126.6 ('m', OPh), 129.1, 128.8, 127.8 (Bn), 130.0 ('p', q, $J=32\text{Hz}$, OPh), 135.4 ('ipso', CH_2Ph), 153.0 ('ipso', OPh), 172.8 (COOCH_2Ph).

Synthesis of 4-chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate.

$\text{C}_{10}\text{H}_{12}\text{Cl}_2\text{NO}_4\text{P}$, MW=312.09.



This is synthesised according to *Standard procedure 4*, using L-alanine methyl ester hydrochloride (1.0 g, 7.16 mmol), 4-chlorophenylphosphorodichloridate (1.757 g, 7.16 mmol), and TEA (1.449 g, 14.32 mmol, 1995 μ L) in DCM (30 mL), to yield 1.621 g (72.5%) of crude product used without further purification.

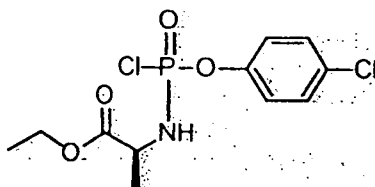
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.36, 9.07.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.35-7.15 (4H, m, *O*Ph), 4.48-4.36 (1H, bs, *N*H), 4.22-4.04 (1H, m, *CH*CH₃), 3.76-3.74 (3H, 2s, *CH*3*O*), 1.49-1.46 (3H, m, *CH*CH₃).

10 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.0 (*CH*3*CH*), 50.8, 51.1 (*CH*CH₃), 53.4 (*CH*3*O*), 121.9, 122.1, 122.3, 122.4 ('*o*', *O*Ph), 130.6, 130.4, 130.2 ('*m*', *O*Ph), 132.0 ('*p*', *O*Ph), 148.6 ('*ipso*', *O*Ph), 173.5 (*COOCH*₃).

15 Synthesis of 4-chlorophenyl-(ethoxy-L-alaninyl)-phosphorochloridate.

$\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{NO}_4\text{P}$, MW=326.11.



This is synthesised according to *Standard procedure 4*, using L-alanine ethyl ester hydrochloride (1.000 g, 6.50 mmol), 4-chlorophenylphosphorodichloride (1.595 g, 6.50 mmol), and TEA (1.315 g, 13.00 mmol, 1810 μ L) in DCM (20 mL), to yield 1.794 mg (yield 84.7%) of product.

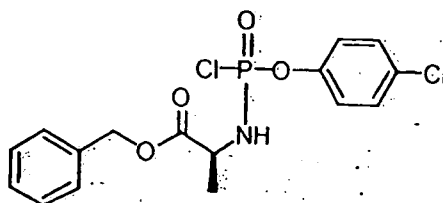
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.54, 9.25.

0 ^1H -NMR (CDCl_3 , 300 MHz): δ 7.44-7.21 (4H, m, *O*Ph), 4.59 (1H, bs, *N*H), 4.33-4.13 (3H, m, *OCH*2*CH*₃+*CH*CH₃), 1.57-1.56 (3H, m, *CH*2*CH*), 1.43-1.21 (3H, m, *OCH*2*CH*₃).

¹³C-NMR (CDCl₃; 75. MHz): δ 14.5, 14.6 (OCH₂CH₃), 21.0, 21.5 (CH₃CH), 50.9, 51.2 (CHCH₃), 62.4, 62.5 (OCH₂CH₃), 122.04, 122.3, 122.4 ('o', OPh), 130.4 ('m', OPh), 131.9 ('p', OPh), 148.5, 148.6 ('ipso', OPh), 173.0, 173.1 (COOCH₂CH₃).

5 **Synthesis of 4-nitrophenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate.**

C₁₆H₁₆Cl₂NO₄P, MW=388.18.



10

This is synthesised according to *Standard procedure 4*, using L-alanine benzyl ester hydrochloride (1.000 g, 4.63 mmol), 4-chlorophenylphosphodichloride (1.136 g, 4.63 mmol), and TEA (937.0 mg, 9.26 mmol, 1290 μL) in DCM (40 mL), to yield 1534 mg (yield 86.5%) of crude product used without further purification.

15 ³¹P-NMR (CDCl₃, 121 MHz): δ 9.43, 9.16.

¹H-NMR (CDCl₃; 300 MHz): δ 7.42-7.08 (9H, m, OPh+ CH₂Ph), 5.19 (2H, s, CH₂Ph), 4.61-4.54 (1H, bs, NH), 4.26-4.10 (1H, m, CHCH₃), 1.42-1.38 (3H, m, CH₃CH).

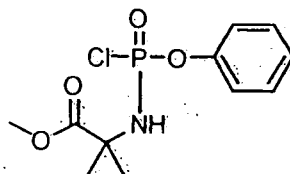
¹³C-NMR (CDCl₃; 75 MHz): δ 20.9, 21.0 (CH₃CH), 51.0, 51.2 (CHCH₃), 68.1, 68.2 (OCH₂Ph), 122.3, 122.4 ('o', OPh), 128.8, 129.1, 130.4 ('o', 'm', 'p', CH₂Ph+OPh), 131.9

20 ('ipso', CH₂Ph), 135.3 ('p', OPh), 148.5 ('ipso', OPh), 172.7, 172.8 (COOCH₂Ph).

Synthesis of phenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate.

C₁₁H₁₅ClNO₄P, MW=291.67.

25



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate methyl ester hydrochloride (583.5 mg, 3.75 mmol), phenyl dichlorophosphate (791.1 mg, 3.75, 560 μ L), and TEA (758.9 mg, 7.5 mmol, 1045 μ L) in DCM (20 mL), to yield 1.041 g (95.2%) of crude product used without further purification.

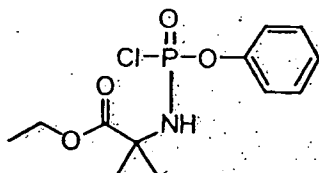
^{31}P -NMR (CDCl_3 , 121 MHz): δ 6.99 (s).

^1H -NMR (CDCl_3 , 300 MHz): δ 7.41-7.17 (5H, m, OPh), 4.98 (1H, bs, NH), 3.80 (3H, s, OCH_3), 1.71-1.69 (6H, 2s, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.3, 27.2, 27.0 ($[\text{CH}_3]_2\text{C}$), 53.6 (OCH_3), 58.8 ($\text{C}[\text{CH}_3]_2$), 120.0, 121.1 ('o' OPh), 126.2 ('p', OPh), 130.3 ('m', OPh), 145.7 ('p', OPh), 150.2, 150.3 ('ipso', OPh), 175.6, 175.7 (COOCH_3).

Synthesis of phenyl-(ethyl-2-amino-2-methylpropanoate)-phosphorochloridate.

$\text{C}_{12}\text{H}_{17}\text{ClNO}_4\text{P}$, MW=305.69.



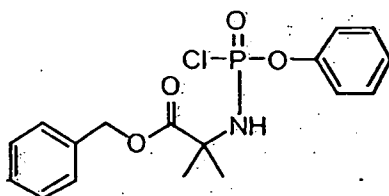
This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate ethyl ester hydrochloride (628.6 mg, 3.75 mmol), phenyl dichlorophosphate (791.1 mg, 3.75, 560 μ L), and TEA (758.9 mg, 7.5 mmol, 1045 μ L) in DCM (20 mL), to yield 1.018 g (88.8%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 7.02 (s).

^1H -NMR (CDCl_3 , 300 MHz): δ 7.23-7.37 (5H, m, OPh), 4.98 (1H, bs, NH), 4.24 (2H, q, $^3J=7.1$ Hz, OCH_2CH_3), 1.70, 1.68 (6H, 2s, $[\text{CH}_3]_2\text{C}$), 1.30 (3H, t, $^3J=7.1$ Hz, OCH_2CH_3).

^{13}C -NMR (CDCl_3 ; 75 MHz): δ 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 27.3, 26.9 ($[\text{CH}_3]_2\text{C}$), 58.7 ($\text{C}[\text{CH}_3]_2$), 62.7 (OCH_2CH_3), 121.1, 121.0 (o' , OPh), 127.6 (p' , OPh), 130.7 (m' , OPh), 150.4 ($ipso'$, OPh), 175.2, 175.1 ($\text{COOCH}_2\text{CH}_3$).

5 **Synthesis of phenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate.**
 $\text{C}_{17}\text{H}_{19}\text{ClNO}_4\text{P}$, MW=367.76.



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate benzyl ester hydrochloride (861.4 mg, 3.75 mmol), phenyl dichlorophosphate (791.1 mg, 3.75, 560 μL), and TEA (758.9 mg, 7.5 mmol, 1045 μL) in DCM (30 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 6:4) affording 580 mg (42.2%) of oil.

^{31}P -NMR (CDCl_3 ; 121 MHz): δ 6.79 (s).

15 ^1H -NMR (CDCl_3 ; 300 MHz): δ 7.45-7.27 (10H, m, OPh+CH₂Ph), 5.28 (2H, s, CH₂Ph), 4.81, 4.78 (1H, 2bs, NH), 1.78, 1.75 (6H, 2s, [CH₃]₂C).

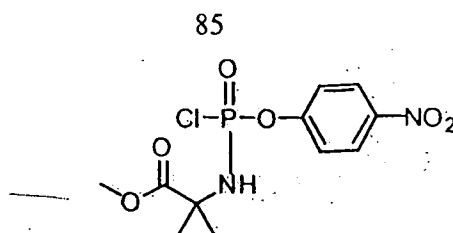
^{13}C -NMR (CDCl_3 ; 75 MHz): δ 27.3, 26.9 ($[\text{CH}_3]_2\text{C}$), 53.9 ($\text{C}[\text{CH}_3]_2$), 60.9 (CH_2Ph), 121.0, 126.3, 128.6, 129.0, 129.1, 130.3, 135.5 (OPh, CH₂Ph), 135.5 ($ipso'$, CH₂Ph), 150.3, 150.2 ($ipso'$, OPh), 175.0, 175.2 (COOCH_2Ph).

20

Synthesis of 4-nitrophenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate.

$\text{C}_{11}\text{H}_{14}\text{ClN}_2\text{O}_6\text{P}$, MW=336.67.

25



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate methyl ester hydrochloride (290.0mg, 1.89 mmol), 4-nitrophenylphosphodichloride (483.3 mg, 1.89 mmol), and TEA (382.5 mg, 3.78 mmol, 526.9 μ L) in DCM (15 mL), to yield 486 mg

5 (yield 76.4%) of crude product used without further purification.

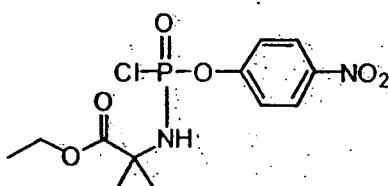
^{31}P -NMR (CDCl_3 , 121 MHz): δ 6.61 (s)

^1H -NMR (CDCl_3 , 300 MHz): δ 8.25 (2H, d, $^3J=9.0$ Hz, OPh), 7.43 (2H, d, $^3J=9.0$ Hz, OPh), 4.91-4.87 (1H, 2bs, NH), 3.79 (3H, s, OCH_3), 1.69-1.66 (6H, 2s, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.0, 27.1, 27.3 ($[\text{CH}_3]_2\text{C}$), 53.8 (OCH_3), 59.2 ($\text{C}[\text{CH}_3]_2$),
 10 121.7, 121.8 ('o' OPh), 126.2 ('m', OPh), 145.7 ('p', OPh), 154.8, 154.7 ('ipso', OPh),
 175.4, 175.6 (COOCH_3).

Synthesis of 4-nitrophenyl-(ethyl-2-amino-2-methylpropanoate)-phosphorochloridate.

15 $\text{C}_{12}\text{H}_{16}\text{ClN}_2\text{O}_6\text{P}$, MW=350.69:



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate ethyl ester hydrochloride (270.0 mg, 1.61 mmol), 4-nitrophenylphosphodichloride (412.3 mg, 1.61 mmol), and TEA (325.8 mg, 3.22 mmol, 448.8 μ L) in DCM (15 mL), to yield 500 mg

20 (yield 88.5%) of crude product used without further purification.

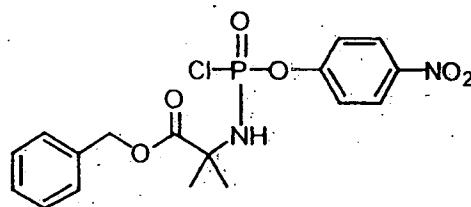
^{31}P -NMR (CDCl_3 , 121 MHz): δ 6.64 (s)

¹H-NMR (CDCl₃; 300 MHz): δ 8.35 (2H, d, ³J=9.0 Hz, OPh), 7.53 (2H, d, ³J=9.0 Hz, OPh), 4.99-4.96 (1H, 2bs, NH), 4.34 (2H, q, ³J=7.1 Hz, OCH₂CH₃), 1.79-1.76 (6H, 2s, [CH₃]₂C), 1.40 (3H, t, ³J=7.1 Hz, OCH₂CH₃).

¹³C-NMR (CDCl₃; 75 MHz): δ 14.5 (OCH₂CH₃), 27.0, 27.3 ([CH₃]₂C), 59.1, 59.2 (C[CH₃]₂), 62.9, 63.0 (OCH₂CH₃), 121.7, 121.8 ('o', OPh), 126.2 ('m', OPh), 145.7 ('p', OPh), 154.7, 154.8 ('ipso', OPh), 175.4, 175.6 (COOCH₂CH₃).

Synthesis of 4-nitrophenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate.

C₁₇H₁₈ClN₂O₆P, MW=412.76.



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate benzyl ester hydrochloride (578 mg, 2.52 mmol), 4-nitrophenylphosphodichloride (645 mg, 2.52 mmol), and TEA (510 mg, 5.04 mmol, 702.5 μL) in DCM (20 mL), to yield 936 mg (yield 90.0%) of crude product used without further purification.

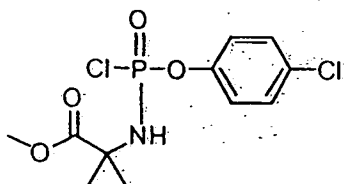
³¹P-NMR (CDCl₃, 121 MHz): δ 6.56 (s).

¹H-NMR (CDCl₃; 300 MHz): δ 8.29 (2H, d, ³J=9.0 Hz, OPh), 7.47 (2H, d, ³J=9.0 Hz, OPh), 7.40-7.37 (5H, m, CH₂Ph), 5.27 (2H, s, CH₂Ph), 5.04-5.01 (1H, 2bs, NH), 1.77-1.74 (6H, 2s, [CH₃]₂C).

¹³C-NMR (CDCl₃; 75 MHz): δ 27.0, 27.3, ([CH₃]₂C), 59.2 (C[CH₃]₂), 68.5 (OCH₂Ph), 121.6, 121.7, 126.2, 128.6, 129.1, ('o', 'm', 'p', CH₂Ph+ OPh), 135.7 ('ipso', CH₂Ph), 145.7 ('p', OPh), 154.7, 154.8 ('ipso', OPh), 175.8, 175.9 (COOCH₂Ph).

Synthesis of 4-chlorophenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate.

C₁₁H₁₄Cl₂NO₄P, MW=326.11



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate methyl ester hydrochloride (280.0 mg, 1.82 mmol), 4-chlorophenylphosphodichloride (447.4 mg, 1.82 mmol), and TEA (368.3 mg, 3.64 mmol, 507.3 μ L) in DCM (20 mL), to yield 554 mg (yield 91.1%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 7.05 (s)

^1H -NMR (CDCl_3 ; 300 MHz): δ 7.38 (2H, d, $^3J=9.0$ Hz, OPh), 7.28-7.24 (2H, 2d, $^3J=9.0$ Hz, OPh), 4.87-4.83 (1H, 2bs, NH), 3.84 (3H, s, OCH_3), 1.73-1.71 (6H, 2s, $[\text{CH}_3]_2\text{C}$).

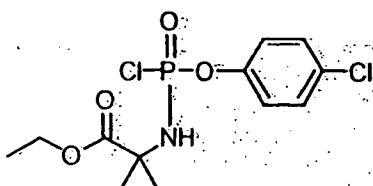
^{13}C -NMR (CDCl_3 ; 75 MHz): δ 27.0, 27.3, ($[\text{CH}_3]_2\text{C}$), 53.7 (OCH_3), 58.9 ($\text{C}[\text{CH}_3]_2$), 122.5 ('o', OPh), 129.7 ('m', OPh), 131.8 ('p', OPh), 148.7, 148.9 ('ipso', OPh), 175.5, 175.7 (COOCH_3).

15

Synthesis of 4-chlorophenyl-(ethyl-2-amino-2-methylpropanoate)-phosphorochloridate.

$\text{C}_{12}\text{H}_{16}\text{Cl}_2\text{NO}_4\text{P}$, MW=340.14.

20



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate ethyl ester hydrochloride (293.4 mg, 1.75 mmol), 4-chlorophenylphosphodichloride (430.0 mg,

1.75 mmol), and TEA (354.2 mg, 3.50 mmol, 488.0 μ L) in DCM (15 mL), to yield 571.7 mg (yield 96.1%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 7.09 (s).

^1H -NMR (CDCl_3 , 300 MHz): δ 7.38 (2H, d, $^3J=9.1$ Hz, OPh), 7.26 (2H, d, $^3J=9.1$ Hz, OPh), 4.88-4.84 (1H, 2bs, NH), 4.29 (2H, q, $^3J=7.1$ Hz, OCH_2CH_3), 1.74-1.70 (6H, 2s, $[\text{CH}_3]_2\text{C}$), 1.35 (3H, t, $^3J=7.1$ Hz, OCH_2CH_3).

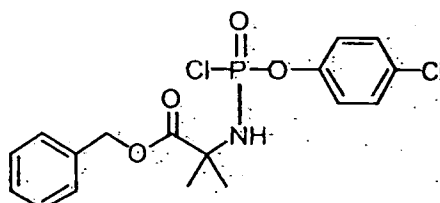
^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 (OCH_2CH_3), 27.0, 27.3 ($[\text{CH}_3]_2\text{C}$), 58.9 ($\text{C}[\text{CH}_3]_2$), 62.8 (OCH_2CH_3), 122.5 ('o', OPh), 130.4 ('m', OPh), 131.8 ('p', OPh), 148.7, 148.8 ('ipso', OPh), 175.1, 175.3 ($\text{COOCH}_2\text{CH}_3$).

10

Synthesis of 4-chlorophenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate.

$\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{NO}_4\text{P}$, MW=402.21.

15



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate benzyl ester hydrochloride (402.0 mg, 1.75 mmol), 4-chlorophenylphosphodichloride (430 mg, 1.75 mmol), and TEA (354.2 mg, 3.50 mmol, 488.0 μ L) in DCM (15 mL), to yield 657.9 mg (yield 93.5%) of crude product used without further purification.

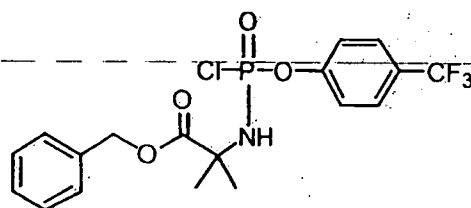
^{31}P -NMR (CDCl_3 , 121 MHz): δ 7.00 (s).

^1H -NMR (CDCl_3 , 300 MHz): δ 7.39-7.12 (9H, m, $\text{CH}_2\text{Ph} + \text{OPh}$), 5.18 (2H, s, CH_2Ph), 4.75-4.72 (1H, 2bs, NH), 1.68-1.65 (6H, 2s, $[\text{CH}_3]_2\text{C}$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 27.0, 27.3 ($[\text{CH}_3]_2\text{C}$), 59.0 ($\text{C}[\text{CH}_3]_2$), 68.4 (OCH_2Ph), 122.5, 128.6, 129.1, 130.7 ('o', 'm', 'p', $\text{CH}_2\text{Ph} + \text{OPh}$), 131.8 ('p', CH_2Ph), 135.4 ('p', OPh), 148.6, 148.7 ('ipso', OPh), 174.9, 175.1 (COOCH_2Ph).

Synthesis of 4-(trifluoromethyl)-phenyl-(benzyl-2-amino-2-methylpropanoate)-phosphorochloridate.

5 $C_{18}H_{18}ClF_3NO_4P$, MW=435.76.



This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate benzyl ester hydrochloride (341.0 mg, 1.49 mmol), 4-(trifluoromethyl)-phenyl-phosphodichloridate (414.3 mg, 1.49 mmol), and TEA (300.5 mg, 2.97 mmol, 413.9 μ L) in DCM (15 mL), to yield 623.9 mg (96.4%) of crude product used without further purification.

^{31}P -NMR ($CDCl_3$, 121 MHz): δ 6.74 (s).

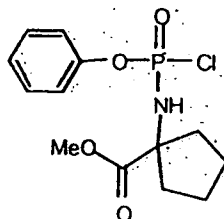
15 1H -NMR ($CDCl_3$, 300 MHz): δ 7.66 (2H, d, $^3J=8.8$ Hz, $O\text{Ph}$), 7.42-7.30 (7H, m, $O\text{Ph}+CH_2Ph$), 5.25 (2H, s, CH_2Ph), 4.95-4.91 (1H, 2bs, NH), 1.75-1.72 (6H, 2s, $[CH_3]_2C$).

^{13}C -NMR ($CDCl_3$, 75 MHz): δ 26.9, 27.0, 27.3 ($[CH_3]_2C$), 59.1 ($C[CH_3]_2$), 68.4 (CH_2Ph), 121.1, 121.4, 127.7, 128.4, 128.5, 128.6, 128.9 ('o', 'm', 'p', $O\text{Ph}+CH_2Ph$), 124.2 (CF_3 , $J=265$ Hz), 135.4 ('ipso', CH_2Ph), 152.6, 152.7 ('ipso', $O\text{Ph}$), 174.9, 175.0 ($COOCH_2Ph$).

20

Synthesis of Phenyl-(methoxy- α,α -cycloleucinyl)-phosphorochloridate.

$C_{13}H_{17}ClNO_4P$, MW=317.70.



This is synthesised according to *Standard procedure 4*, using methyl-1-amino-1-cyclopentanoate hydrochloride salt (0.885 g, 5.01 mmol), phenyldichlorophosphate (1.12 g, 0.749 ml, 5.01 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL), to yield 1.266 g (81%) of crude product used without further purification.

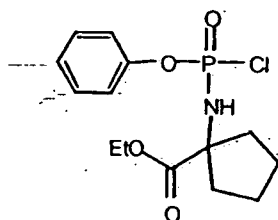
^{31}P -NMR (CDCl_3 , 121 MHz): δ 7.90.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.4-7.2 (5H, m, *O*Ph), 4.3 (1H, bs, *NH*), 3.75 (3H, 2s, *OCH*₃), 2.15 (4H, m, 4H cyclopentane), 1.9-1.7 (4H, m, 4H cyclopentane)...

^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.4 (2CH₂ cyclopent), 38.8, 38.7, 38.6 (2CH₂ cyclopent), 53.3, 53.2 (CH₃O), 66.6 (*Cq*-cyclopentane), 121.1, 121.0 ('*o*' OPh), 126.3 ('*p*', OPh), 130.3, 130.2 ('*m*', OPh), 150.2 ('*ipso*', OPh), 174.8 (COOCH₃).

Synthesis of Phenyl-(ethoxy- α,α -cycloleuciny)-phosphorochloridate.

$\text{C}_{14}\text{H}_{19}\text{ClNO}_4\text{P}$, MW=331.73.



This is synthesised according to *Standard procedure 4*, using ethyl-1-amino-1-cyclopentanoate hydrochloride salt (955 mg, 5.01 mmol), phenyldichlorophosphate (1.12 g, 5.01 mmol, 749 μL), and TEA (1.4 mL, 10.02 mmol) in DCM (40 mL). The crude was purified by flash chromatography (ethyl acetate/petroleum ether 7:3) affording 1.457 g (89%) of oil.

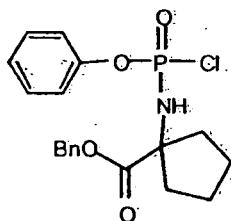
^{31}P -NMR (CDCl_3 , 121 MHz): δ 8.04, 7.97.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.4-7.1 (5H, m, *O*Ph), 4.7 (1H, bs, *NH*), 4.2 (2H, 2q, $^3J=7.1$ Hz, *OCH*₂CH₃), 2.15 (4H, m, 4H cyclopentane), 1.9-1.7 (4H, m, 4H cyclopentane), 1.30 (3H, t, $^3J=7.1$ Hz, *OCH*₂CH₃).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5 (CH₃CH₂), 24.5 (2CH₂ cyclopent), 38.8, 38.7, 38.6, 38.5 (2CH₂ cyclopent), 62.0 (CH₃CH₂), 68.3 (*Cq*-cyclopentane), 120.9 ('*o*' OPh), 126.3 ('*p*', OPh), 130.3 ('*m*', OPh), 150.3-150.2 ('*ipso*', OPh), 174.9-174.8 (COOCH₂CH₃).

Synthesis of Phenyl-(benzoxy- α,α -cycloleuciny)-phosphorochloridate.

$C_{19}H_{21}ClNO_4P$; MW=393.80.



5

This is synthesised according to *Standard procedure 4*, using benzyl-1-amino-1-cyclopentanoate hydrochloride salt (0.984 g, 3.84 mmol), phenyl-dichlorophosphate (0.577 ml, 3.84 mmol), and TEA (1.08 mL, 7.69 mmol) in DCM (30 mL), to yield 1.485 g (98%) of crude product used without further purification.

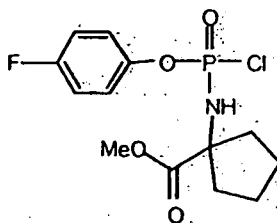
^{31}P -NMR ($CDCl_3$, 121 MHz): δ 7.85.

1H -NMR ($CDCl_3$, 300 MHz): δ 7.3-7.0 (10H, m, $O\text{Ph} + CH_2Ph$), 5.2 (2H, s, CH_2Ph), 4.95-4.65 (1H, bs, NH), 2.25-2.1 (4H, m, 4H-cyclopentane), 1.9-1.7 (4H, m, 4H-cyclopentane).

^{13}C -NMR ($CDCl_3$, 75 MHz): δ 24.4, 24.3 (2 CH_2 cyclopent), 38.8, 38.7, 38.5 (2 CH_2 cyclopent), 67.3 (C_q cyclopentane), 68.0 (CH_2Ph), 121.0 (o' OPh), 126.4 (p' OPh), 130.1, 129.0, 128.8 (m' OPh, CH_2Ph), 135.4 ($ipso'$, CH_2Ph), 150.1 ($ipso'$, OPh), 173.4 ($COOCH_2Ph$).

Synthesis of p-fluorophenyl-(methoxy- α,α -cycloleuciny)-phosphorochloridate.

$C_{13}H_{16}ClNO_4P$; MW=335.70.



This is synthesised according to *Standard procedure 4*, using methyl-1-amino-1-cyclopentanoate hydrochloride salt (0.885 g, 5.01 mmol), para-

fluorophenyldichlorophosphate (1.21 g, 5.01 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL), to yield 1.65 g (99%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 8.61.

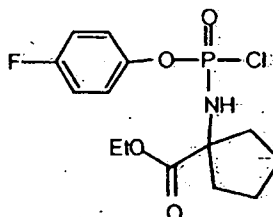
^1H -NMR (CDCl_3 , 300 MHz): δ 7.3-7.2 (2H, m, OPh), 7.1-7.0 (2H, m, OPh), 4.7 (1H, bs, NH), 3.78 (3H, 2s, OCH_3), 2.25-2.15 (4H, m, 4H cyclopentane), 2.0-1.8 (4H, m, 4H cyclopentane).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.4 (2CH_2 cyclopent), 38.7, 38.6, 38.5 (2CH_2 cyclopent), 53.3 (CH_3O), 66.3-66.2 (Cq cyclopentane), 117.1-116.8 ($'o'$ OPh), 122.6-122.5 ($'m'$ OPh), 146.1-145.9 ($'ipso'$ OPh), 159.0 ($'p'$ OPh), 175.3-175.2 (COOCH_3).

10

Synthesis of p-fluorophenyl-(ethoxy- α,α -cycloleuciny)-phosphorochloridate.

$\text{C}_{14}\text{H}_{18}\text{ClFNO}_4\text{P}$, MW=349.72.



15

This is synthesised according to *Standard procedure 4*, using ethyl-1-amino-1-cyclopentanoate hydrochloride salt (955 mg, 5.01 mmol), para-fluorophenyldichlorophosphate (1.21g, 5.01 mmol), and TEA (1.4 mL, 10.02 mmol) in DCM (40 mL), to yield 1.64 g (94%) of crude product used without further purification.

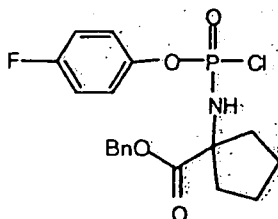
20 ^{31}P -NMR (CDCl_3 , 121 MHz): δ 8.70.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.3-7.2 (2H, m, OPh), 7.1-7.0 (2H, m, OPh), 4.8 (1H, bs, NH), 4.2 (2H, 2q, $^3J=7.1$ Hz, OCH_2CH_3), 2.25-2.1 (4H, m, 4H cyclopentane), 2.0-1.8 (4H, m, 4H cyclopentane), 1.4 (3H, t, $^3J=7.1$ Hz, OCH_2CH_3).

25 ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.4 (CH_3CH_2), 24.4 (2CH_2 cyclopent), 38.8, 38.7, 38.6, 38.5 (2CH_2 cyclopent), 62.3 (CH_3CH_2), 68.3 (Cq cyclopentane), 117.4, 117.0 ($'o'$ OPh), 122.7, 122.6 ($'m'$ OPh), 146.1, 146.0 ($'ipso'$ OPh), 159.0 ($'p'$ OPh), 174.9 ($\text{COOCH}_2\text{CH}_3$).

Synthesis of p-fluorophenyl-(benzoxy- α,α -cycloleuciny)-phosphorochloridate.

$C_{19}H_{20}ClFNO_4P$, MW= 411.79.



5

This is synthesised according to *Standard procedure 4*, using benzyl-1-amino-1-cyclopentanoate hydrochloride salt (1.281 g, 5.01 mmol), para-fluorophenyl-dichlorophosphate (1.21 g, 5.01 mmol), and TEA (1.4 mL, 10 mmol) in DCM (40 mL), to yield 1.85 g (90%) of crude product used without further purification.

10 ^{31}P -NMR ($CDCl_3$, 121 MHz): δ 7.85.

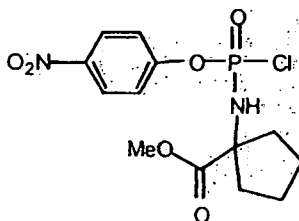
1H -NMR ($CDCl_3$, 300 MHz): δ 7.65-7.4 (5H, m, CH_2Ph), 7.3-7.2 (2H, m, OPh), 7.1-7.0 (2H, m, OPh), 5.2 (2H, s, CH_2Ph), 4.6 (1H, bs, NH), 2.2-2.1 (4H, m, 4H cyclopentane), 2.0-1.8 (4H, m, 4H cyclopentane).

^{13}C -NMR ($CDCl_3$, 75 MHz): δ 24.5 (2 CH_2 cyclopent), 38.9, 38.8, 38.6, 38.5 (2 CH_2 cyclopent), 68.1 (Cq cyclopentane), 68.4 (CH_2Ph), 117.0, 116.8 ($'o'$ OPh), 122.6, 122.5 ($'m'$ OPh), 129.1, 129.0, 128.8, 128.7 (CH_2Ph), 135.7 ($'ipso'$, CH_2Ph), 146.1, 145.9 ($'ipso'$, OPh), 159.0 ($'p'$, OPh), 174.6 ($COOCH_2Ph$).

15

20 Synthesis of p-nitrophenyl-(methoxy- α,α -cycloleuciny)-phosphorochloridate:

$C_{13}H_{16}ClN_2O_6P$, MW=362.70:



25 This is synthesised according to *Standard procedure 4*, using methyl-1-amino-1-cyclopentanoate hydrochloride salt (0.885 g, 5.01 mmol), para-

nitrophenyldichlorophosphate (1.632 g, 5.01 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL), to yield 1.601 g (90%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 8.02.

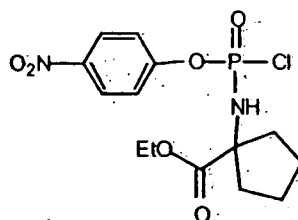
^1H -NMR (CDCl_3 , 300 MHz): δ 8.2 (2H, 2d, $^3J=8$ Hz, *OPh*), 7.32 (2H, 2d, $^3J=8$ Hz *OPh*),
5 4.9 (1H, bs, *NH*), 3.71 (3H, s, *OCH*₃), 2.25-2.00 (4H, m, 4H cyclopentane), 1.95-1.7 (4H, m, 4H cyclopentane)..

^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.3 (2CH₂ cyclopent), 38.7, 38.6 (2CH₂ cyclopent), 53.3 (*CH*₃O), 68.6 (*Cq* cyclopentane), 121.8, 121.7 ('*o*' *OPh*), 126.0 ('*m*', *OPh*), 145.6 ('*ipso*', *OPh*), 154.8, 154.7 ('*p*', *OPh*), 175.1-175.0 (*COOCH*₃).

10

Synthesis of p-nitrophenyl-(ethoxy- α,α -cycloleucynyl)-phosphorochloridate.

$\text{C}_{14}\text{H}_{18}\text{ClN}_2\text{O}_6\text{P}$, MW=376.73.



15

This is synthesised according to *Standard procedure 4*, using ethyl-1-amino-1-cyclopentanoate hydrochloride salt (955 mg, 5.01 mmol), para-nitrophenyldichlorophosphate (1.362 g, 5.01 mmol), and TEA (1.4 mL, 10.02 mmol) in DCM (40 mL), to yield 1.669 g (90%) of crude product used without further purification.

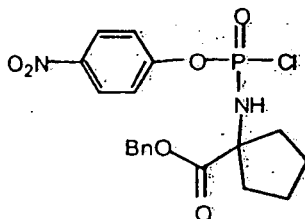
20: ^{31}P -NMR (CDCl_3 , 121 MHz): δ 7.95.

^1H -NMR (CDCl_3 , 300 MHz): δ 8.1 (2H, 2d, $^3J=8$ Hz, *OPh*), 7.28 (2H, 2d, $^3J=8$ Hz *OPh*),
4.8 (1H, bs, *NH*), 4.2 (2H, 2q, $^3J=7.1$ Hz, *OCH*₂CH₃), 2.2-2.0 (4H, m, 4H cyclopentane),
1.95-1.7 (4H, m, 4H cyclopentane), 1.27 (3H, t, $^3J=7.1$ Hz, *OCH*₂CH₃).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.4 (*CH*₃CH₂), 24.4 (2CH₂ cyclopent), 38.8, 38.7 (2CH₂
25 cyclopent), 62.4 (*CH*₃CH₂), 68.5 (*Cq* cyclopentane), 121.8, 121.1 ('*o*' *OPh*), 126.1, 125.9 ('*m*', *OPh*), 145.6 ('*ipso*', *OPh*), 154.8 ('*p*', *OPh*), 174.9 (*COOCH*₂CH₃).

Synthesis of p-nitrophenyl-(benzoxy- α,α -cycloleuciny)-phosphorochloridate.

$C_{19}H_{20}ClN_2O_6P$, MW= 438.80.



5

This is synthesised according to *Standard procedure 4*, using benzyl-1-amino-1-cyclopentanoate hydrochloride salt (0.835 g, 3.25 mmol), para-nitrophenyl-dichlorophosphate (0.85 g, 3.25 mmol), and TEA (0.91 mL, 6.7 mmol) in DCM (30 mL), to yield 1.215 g (85%) of crude product used without further purification.

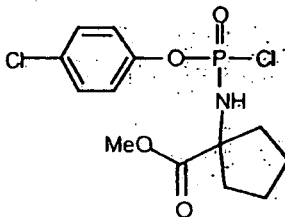
10 ^{31}P -NMR ($CDCl_3$, 121 MHz): δ 7.99, 7.90.

1H -NMR ($CDCl_3$, 300 MHz): δ 8.1 (2H, d, $^3J=8$ Hz, $O\text{Ph}$), 7.4-7.2 (7H, m, $O\text{Ph} + CH_2Ph$), 5.18 (2H, s, CH_2Ph), 5.0 (1H, bs, NH), 2.2-2.0 (4H, m, 4H cyclopentane), 1.95-1.75 (4H, m, 4H cyclopentane).

^{13}C -NMR ($CDCl_3$, 75 MHz): δ 24.4 (2 CH_2 cyclopent), 38.8, 38.7, 38.6, 38.5 (2 CH_2 cyclopent), 68.0 (CH_2Ph), 68.6 (Cq cyclopentane), 121.8, 121.7 ($'o'$ $O\text{Ph}$), 126.1, 125.9 ($'m'$ $O\text{Ph}$), 129.1, 129.0, 128.8, 128.6 (CH_2Ph), 135.7 ($'ipso'$, CH_2Ph), 145.6 ($'ipso'$, $O\text{Ph}$), 154.8, 154.7 ($'p'$, $O\text{Ph}$), 174.5, 174.4 ($COOCH_2Ph$).

20 Synthesis of p-chlorophenyl-(methoxy- α,α -cycloleuciny)-phosphorochloridate.

$C_{13}H_{16}Cl_2NO_4P$, MW=352.15.



25 This is synthesised according to *Standard procedure 4*, using methyl-1-amino-1-cyclopentanoate hydrochloride salt (0.443 g, 2.5 mmol), para-

chlorophenyldichlorophosphate (0.613 g, 2.5 mmol), and TEA (0.7 ml, 5 mmol) in DCM (20 mL), to yield 0.852 g (98%) of crude product used without further purification.

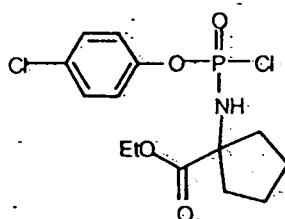
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.55, 9.5.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.35-7.15 (4H, m, OPh), 4.95 (1H, bs, NH), 3.78 (3H, s, OCH_3), 2.2-2.00 (4H, m, 4H cyclopentane), 1.95-1.7 (4H, m, 4H cyclopentane).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.3 (2CH_2 cyclopent), 38.7 (2CH_2 cyclopent), 53.3 (CH_3O), 68.6 (C_q cyclopentane), 122.0 ('o' OPh), 130.1 ('m', OPh), 133.2 ('p', OPh), 149.9 ('ipso', OPh), 175.1-175.0 (COOCH_3).

10 Synthesis of p-chlorophenyl-(ethoxy- α,α -cycloleuciny)-phosphorochloridate.

$\text{C}_{14}\text{H}_{18}\text{Cl}_2\text{NO}_4\text{P}$, MW=366.18.



15 This is synthesised according to *Standard procedure 4*, using ethyl-1-amino-1-cyclopentanoate hydrochloride salt (0.477 g, 2.5 mmol), para-chlorophenyldichlorophosphate (0.613 g, 2.5 mmol), and TEA (0.7 mL, 5 mmol) in DCM (20 mL), to yield 0.880 g (97%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.85, 9.70.

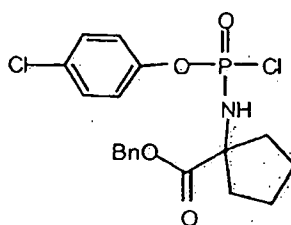
20 ^1H -NMR (CDCl_3 , 300 MHz): δ 7.35-7.15 (4H, m, OPh), 4.9 (1H, bs, NH), 4.22 (2H, 2q, $^3J=7.1$ Hz, OCH_2CH_3), 2.2-2.0 (4H, m, 4H cyclopentane), 1.95-1.7 (4H, m, 4H cyclopentane), 1.27 (3H, t, $^3J=7$ Hz, OCH_2CH_3).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.4 (CH_3CH_2), 24.4 (2CH_2 cyclopent), 38.8, 38.7 (2CH_2 cyclopent), 62.5, 62.4 (CH_3CH_2), 68.1 (C_q cyclopentane), 122.2, 122.1 ('o' OPh), 130.1 ('m', OPh), 133.2 ('p', OPh), 149.8 ('ipso', OPh), 174.8 ($\text{COOCH}_2\text{CH}_3$).

Synthesis of p-chlorophenyl-(benzoxy- α,α -cycloleuciny)-phosphorochloridate:

$\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{NO}_4\text{P}$, MW= 428.25.

97



This is synthesised according to *Standard procedure 4*, using benzyl-1-amino-1-cyclopentanoate hydrochloride salt (0.640 g, 2.5 mmol), para-chlorophenyl-dichlorophosphate (0.613 g, 2.5 mmol), and TEA (0.7 mL, 5 mmol) in DCM (20 mL), to yield 1.041 g (97%) of crude product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.39, 8.95.

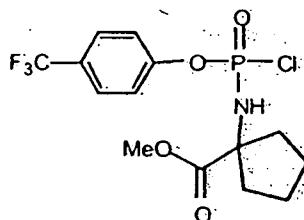
^1H -NMR (CDCl_3 , 300 MHz): δ 7.4-7.15 (9H, m, $\text{OPh} + \text{CH}_2\text{Ph}$), 5.20 (2H, s, CH_2Ph), 5.0 (1H, bs, NH), 2.2-2.0 (4H, m, 4H cyclopentane), 1.95-1.75 (4H, m, 4H cyclopentane).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.4 (2 CH_2 cyclopent), 38.8, 38.7, 38.6 (2 CH_2 cyclopent), 68.1, 68.0 (CH_2Ph), 68.2 (C_q cyclopentane), 121.9, 121.8 ('o' OPh), 130.5, 130.4, 129.3, 129.2 ('m' OPh , CH_2Ph), 133.2 ('p' , OPh), 135.7 ('ipso' , CH_2Ph), 149.9 ('ipso' , OPh), 174.3, 174.2 (COOCH_2Ph).

15

Synthesis of p-trifluorophenyl-(methoxy- α,α -cycloleuciny)-phosphorochloridate.

$\text{C}_{14}\text{H}_{16}\text{ClF}_3\text{NO}_4\text{P}$, MW=385.70.



20

This is synthesised according to *Standard procedure 4*, using methyl-1-amino-1-cyclopentanoate hydrochloride salt (0.443 g, 2.5 mmol), para-trifluorophenyldichlorophosphate (0.700 g, 2.5 mmol), and TEA (0.7 mL, 5 mmol) in DCM (20 mL), to yield 0.931 g (97%) of crude product used without further purification.

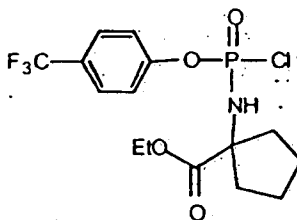
^{31}P -NMR (CDCl_3 , 121 MHz): δ 8.80, 8.62.

¹H-NMR (CDCl₃; 300 MHz): δ 7.65 (2H, 2d, ³J=8 Hz, *O**Ph*), 7.35 (2H, 2d, ³J=8 Hz *O**Ph*), 5.02 (1H, bs, *NH*), 3.78 (3H, s, *OCH**3*), 2.25-2.05 (4H, m, 4H cyclopentane), 1.95-1.7 (4H, m, 4H cyclopentane)..

¹³C-NMR (CDCl₃; 75 MHz): δ 22.8 (2CH₂ cyclopent), 37.5, 37.2 (2CH₂ cyclopent), 51.5 (CH₃O), 68.4 (C*q* cyclopentane), 120.0 ('o', *O**Ph*), 124.8 (d, J=270Hz, CF₃), 126.6 ('m', *O**Ph*), 129.5 ('p',q, J=32Hz, *O**Ph*), 152.8 ('ipso', *O**Ph*), 175.2 (COOCH₃).

Synthesis of p-trifluorophenyl-(ethoxy-α,α-cycloleuciny)-phosphorochloridate.

10 C₁₅H₁₈ClF₃NO₄P, MW=399.73.



This is synthesised according to *Standard procedure 4*, using ethyl-1-amino-1-cyclopentanoate hydrochloride salt (0.477 g, 2.5 mmol); para-trifluorophenyldichlorophosphate (0.700 g, 2.5 mmol), and TEA (0.7 mL, 5 mmol) in DCM (20 mL), to yield 0.950 g (89%) of crude product used without further purification.

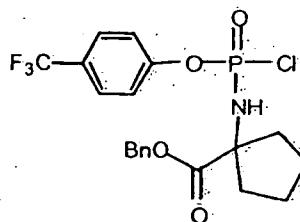
³¹P-NMR (CDCl₃; 121 MHz): δ 8.49.

¹H-NMR (CDCl₃; 300 MHz): δ 7.45 (2H, m, *O**Ph*), 7.2 (2H, m, *O**Ph*), 5.12 (1H, bs, *NH*), 4.05 (2H, m, *OCH**2*CH₃), 2.15-2.0 (4H, m, 4H cyclopentane), 1.9-1.65 (4H, m, 4H cyclopentane), 1.2 (3H, 2t, ³J=7 Hz, *OCH**2*CH₃).

¹³C-NMR (CDCl₃; 75 MHz): δ 14.3 (CH₃CH₂), 24.2, 24.1 (2CH₂ cyclopent), 38.6, 38.5, 38.4 (2CH₂ cyclopent), 62.0 CH₃CH₂, 68.4 (C*q* cyclopentane), 121.5 ('o', *O**Ph*), 125.0 (d, J=270Hz, CF₃), 127.5 ('m', *O**Ph*), 129.9 ('p',q, J=32Hz, *O**Ph*), 152.8, 152.7 ('ipso', *O**Ph*), 174.9, 174.6 (COOCH₂CH₃).

Synthesis of p-trifluorophenyl-(benzoxy-α,α-cycloleuciny)-phosphorochloridate.

C₂₀H₂₀ClF₃NO₄P; MW= 461.80.



This is synthesised according to *Standard procedure 4*, using benzyl-L-amino-L-cyclopentanoate hydrochloride salt (0.700 g, 2.73 mmol), para-trifluorophenyl-dichlorophosphate (0.75 g, 2.73 mmol), and TEA (0.75 mL, 5.47 mmol) in DCM (25 mL), to yield 1.089 g (86%) of crude product used without further purification.

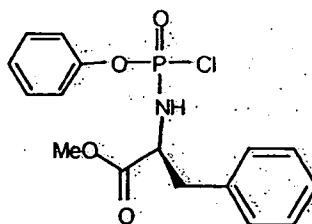
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.39, 8.95.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.50 (2H, m, *OPh*), 7.4-7.15 (7H, m, *OPh* + CH_2Ph), 5.20 (2H, s, CH_2Ph), 4.95 (1H, bs, *NH*), 2.2-2.0 (4H, m, 4H cyclopentane), 1.95-1.75 (4H, m, 4H cyclopentane).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 24.3 (2 CH_2 cyclopent), 38.8, 38.7, 38.6 (2 CH_2 cyclopent), 68.1, 68.0 (CH_2Ph), 68.2 (*Cq* cyclopentane), 121.4, 121.3 ('*o*', *OPh*), 125.1 (d, $J=270\text{Hz}$, CF_3), 126.6 ('*m*', *OPh*), 129.2, 128.8, 127.8 (Bn), 129.8 ('*p*', $J=32\text{Hz}$, *OPh*), 135.7 ('*ipso*', CH_2Ph), 153.5 ('*ipso*', *OPh*), 174.5, 174.4 (C=O OCH_2Ph).

Synthesis of Phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate.

$\text{C}_{16}\text{H}_{17}\text{ClNO}_4\text{P}$, MW=353.74.



20

This is synthesised according to *Standard procedure 4*, using L-phenylalanine methyl ester hydrochloride (1.08 g, 5 mmol), phenyldichlorophosphate (1.12 g, 0.75 ml, 5 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL), to yield 1.626 g (92%) of crude product used without further purification.

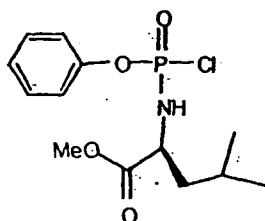
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.1, 8.95.

$^1\text{H-NMR}$ (CDCl_3 ; 300 MHz): δ 7.3-7.1 (10H, m, $\text{CH}_2\text{Ph} + \text{OPh}$), 5.00 (1H, bs, NH), 4.35 (1H, m, CHphenylala), 3.79 (3H, 2s, CH_3O), 3.00 (2H, m, CH_2Ph)

$^{13}\text{C-NMR}$ (CDCl_3 ; 75 MHz): δ 36.3 ($\text{CH}_2\text{phenylalanine}$), 53.0 (CH_3O), 56.6, 56.5 (CHphenylala), 121.0 ('o' OPh), 126.4 ('p', OPh), 130.2 ('m', OPh), 150.2 ('ipso', OPh), 174.1 (COOCH_3).

Synthesis of Phenyl-(methoxy-L-leuciny)-phosphorochloridate

$\text{C}_{13}\text{H}_{19}\text{ClNO}_4\text{P}$, MW=319.72.



10

This is synthesised according to *Standard procedure 4*, using L-leucine methyl ester hydrochloride (0.91 g, 5 mmol), phenyldichlorophosphate (1.12 g, 0.75 ml, 5 mmol), and TEA (1.4 ml, 10 mmol) in DCM (40 mL), to yield 1.58 g (99%) of crude product used without further purification.

$^{31}\text{P-NMR}$ (CDCl_3 ; 121 MHz): δ 9.45, 9.35.

$^1\text{H-NMR}$ (CDCl_3 ; 300 MHz): δ 7.4-7.2 (5H, m, OPh), 4.90 (1H, bs, NH), 3.95 (1H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 3.78 (3H, s, OCH_3), 1.8 (1H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 1.8-1.5 (2H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 1.0-0.9 (6H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$).

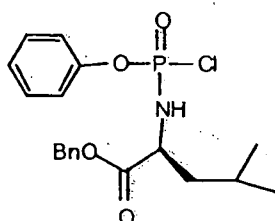
$^{13}\text{C-NMR}$ (CDCl_3 ; 75 MHz): δ 23.2, 23.1, 22.4, 22.3 (2C, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 24.9, 24.8 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 43.6 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 53.2 (CH_3O), 53.7, 53.6 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 120.9 ('o' OPh), 126.4 ('p', OPh), 130.2 ('m', OPh), 150.1 ('ipso', OPh), 173.6 (COOCH_3).

25

Synthesis of Phenyl-(benzoxy-L-leuciny)-phosphorochloridate.

$\text{C}_{19}\text{H}_{23}\text{ClNO}_4\text{P}$, MW= 395.82.

101



This is synthesised according to *Standard procedure 4*, using L-leucine benzyl ester hydrochloride (1.29 g, 5.0 mmol), phenyl-dichlorophosphate (1.12 g, 0.75 ml, 5.0 mmol),
 5 and TEA (1.4 mL, 10.0 mmol) in DCM (40 mL), to yield 1.88 g (95%) of crude product used without further purification.

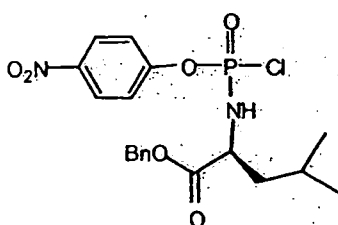
^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.93, 9.57.

^1H -NMR (CDCl_3 , 300 MHz): δ 7.5-7.2 (10H, m, $\text{OPh} + \text{CH}_2\text{Ph}$), 5.2 (2H, 2s, CH_2Ph), 4.95 (1H, bs, NH), 4.2-4.1 (1H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 1.95-1.80 (1H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$),
 10 1.7 (2H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 1.0-0.9 (6H, m, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 23.2, 23.1, 22.4, 22.3 (2C, $\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 24.9 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 43.5 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 53.8, 53.3 ($\text{CHCH}_2\text{CH}(\text{CH}_3)_2$), 67.8, 67.7 (CH_2Ph), 120.7 ('o' OPh), 126.4 ('p', OPh), 130.2, 129.1, 128.8, 128.7 ('m' OPh, CH_2Ph),
 15 135.8 ('ipso', CH_2Ph), 150.2 ('ipso', OPh), 174.1 (COOCH_2Ph).

Synthesis of p-nitrophenyl-(benzyloxy-L-leucyl)-phosphorochloridate.

$\text{C}_{19}\text{H}_{22}\text{ClN}_2\text{O}_6\text{P}$, MW= 440.81.



20

This is synthesised according to *Standard procedure 4*, using L-leucine benzyl ester hydrochloride (1.08 g, 5.01 mmol), para-nitrophenyl-dichloro phosphate (1.362 g, 5.01 mmol), and TEA (1.4 mL, 1.4 mmol) in DCM (40 mL), to yield 2.08g (95%) of crude
 25 product used without further purification.

^{31}P -NMR (CDCl_3 , 121 MHz): δ 9.87, 9.38.

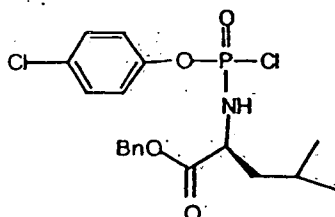
¹H-NMR (CDCl₃; 300 MHz): δ 8.25-8.10 (2H, m, *O*Ph), 7.35-7.25 (7H, m, *O*Ph + *CH*₂Ph), 5.15 (2H, s, *CH*₂Ph), 4.95 (1H, bs, NH), 4.15 (1H, m, CHCH₂CH(CH₃)₂), 1.95 (1H, m, CHCH₂CH(CH₃)₂), 1.7 (2H, m, CHCH₂CH(CH₃)₂), 1.0-0.9 (6H, m, CHCH₂CH(CH₃)₂).

- 5 ¹³C-NMR (CDCl₃; 75 MHz): δ 23.2, 23.1, 22.1, 22.0 (2C, CHCH₂CH(CH₃)₂), 24.8 (CHCH₂CH(CH₃)₂), 43.4, 43.3 (CHCH₂CH(CH₃)₂), 54.2, 53.9 (CHCH₂CH(CH₃)₂), 68.0, 67.9 (*CH*₂Ph), 121.6 ('*o*' OPh), 126.2, 126.1 ('*m*' OPh), 129.2, 129.0 (*CH*₂Ph), 135.4, 135.3 ('*ipso*', *CH*₂Ph), 145.8, 145.7 ('*ipso*', OPh), 154.7, 154.5 ('*p*', OPh), 173.0, 172.8 (COOCH₂Ph).

10

Synthesis of p-chlorophenyl-(benzoxy-L-leucinyl)-phosphorochloridate.

C₁₉H₂₂Cl₂NO₄P, MW= 430.26.



15

This is synthesised according to *Standard procedure 4*, using L-leucine benzyl ester hydrochloride (0.644 g, 2.5 mmol), para-chlorophenyl-dichlorophosphate (0.613 g, 2.5 mmol), and TEA (0.7 mL, 5 mmol) in DCM (20 mL), to yield 0.968 g (90%) of crude product used without further purification.

- 20 ³¹P-NMR (CDCl₃; 121 MHz): δ 9.71, 9.55.

¹H-NMR (CDCl₃; 300 MHz): δ 7.4-7.0 (9H, m, *O*Ph + *CH*₂Ph), 5.15 (2H, s, *CH*₂Ph), 4.5 (1H, d, ³J=7Hz, NH), 4.0 (1H, m, CHCH₂CH(CH₃)₂), 1.9-1.8 (1H, m, CHCH₂CH(CH₃)₂), 1.7 (2H, m, CHCH₂CH(CH₃)₂), 0.85 (6H, m, CHCH₂CH(CH₃)₂).

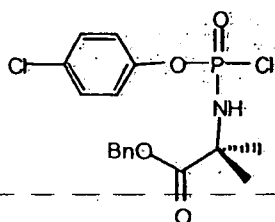
- ¹³C-NMR (CDCl₃; 75 MHz): δ 23.4, 23.3, 22.5, 22.4 (2C, CHCH₂CH(CH₃)₂), 25.0 (CHCH₂CH(CH₃)₂), 43.8, 43.7 (CHCH₂CH(CH₃)₂), 54.0, 53.8 (CHCH₂CH(CH₃)₂), 68.2 (*CH*₂Ph), 122.5 ('*o*' OPh), 130.5, 130.4, 129.3, 129.2 ('*m*' OPh, *CH*₂Ph), 133.2 ('*p*', OPh), 135.7 ('*ipso*', *CH*₂Ph), 149.9, 149.8 ('*ipso*', OPh), 173.4, 173.2 (COOCH₂Ph).

25

Synthesis of 4-chlorophenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate:

$C_{11}H_{14}Cl_2NO_4P$, MW=326.11.

5

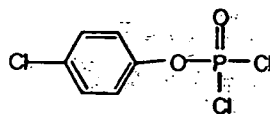


This is synthesised according to *Standard procedure 4*, using 2-aminoisobutyrate methyl ester hydrochloride (280.0mg, 1.82 mmol), 4-chlorophenylphosphodichloride (447.4 mg, 1.82 mmol), and TEA (368.3 mg, 3.64 mmol, 507.3 μ L) in DCM (20 mL), to yield 554 mg (yield 91.1%) of crude product used without further purification.

^{31}P -NMR ($CDCl_3$, 121 MHz): δ 7.05 (s)
 1H -NMR ($CDCl_3$, 300 MHz): δ 7.38 (2H, d, $^3J=9.0$ Hz, $O\text{Ph}$), 7.29-7.24 (2H, 2d, $^3J=9.0$ Hz, $O\text{Ph}$), 4.87-4.83 (1H, 2bs, NH), 3.84 (3H, s, OCH_3), 1.73-1.71 (6H, 2s, $[CH_3]_2C$).
 ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 27.0, 27.3, ($[CH_3]_2C$), 53.7 (OCH_3), 58.9 ($C[CH_3]_2$), 122.5 ('o', $O\text{Ph}$), 129.7 ('m', $O\text{Ph}$), 131.8 ('p', $O\text{Ph}$), 148.7, 148.9 ('ipso', $O\text{Ph}$), 175.5, 175.7 ($COOCH_3$).

20 Synthesis of 4-chlorophenyl-phosphodichloridate.

$C_6H_4Cl_2O_2P$, MW=245.43.



25

This was synthesised according to *Standard procedure 3*, using phosphorus-oxychloride (1533 mg, 10.00 mmol, 932 μ L), 4-chlorophenol (1.285 g, 10.00 mmol) and TEA (1.011 g, 10.00 mmol, 1394 μ L) in ethylether (100 mL) to give an oil (1.897 g, 77.3 % yield).

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

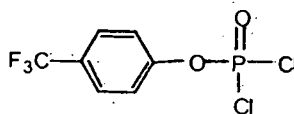
^1H -NMR (CDCl_3 ; 300 MHz): δ 7.45 (2H, d, $^3J=9.0$ Hz, *OPh*), 7.30 (2H, d, $^3J=9.0$ Hz, *OPh*).

^{13}C -NMR (CDCl_3 ; 75 MHz): δ 122.5 ('o', *OPh*), 130.6 ('m', *OPh*), 133.2 ('p', *OPh*), 148.5 ('ipso', *OPh*).

Synthesis of 4-(trifluoromethyl)-phenyl-phosphodichloridate.

$\text{C}_7\text{H}_4\text{ClF}_3\text{O}_3\text{P}$, MW=278.98.

10



This was synthesised according to *Standard procedure 3*, using phosphorus-oxychloride (1.570 mg, 10.24 mmol, 954.5 μL), 4-trifluoromethylphenol (1660 g, 10.24 mmol) and TEA (1.036 g, 10.24 mmol, 1427 μL) in ethylether (100 mL) to give an oil (2.521 g, 88.2% yield).

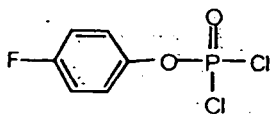
^{31}P -NMR (CDCl_3 , 121 MHz): δ 4.75.

^1H -NMR (CDCl_3 ; 300 MHz): δ 7.77 (2H, d, $^3J=8.4$ Hz, *OPh*), 7.49 (2H, d, $^3J=8.4$ Hz, *OPh*).

^{13}C -NMR (CDCl_3 ; 75 MHz): δ 121.6 ('o', *OPh*), 123.6 (CF_3 , $J=271$ Hz, *OPh*), 128.2 ('m', *OPh*), 129.7 ('p', $J=33$ Hz), 152.7 ('ipso', *OPh*).

Synthesis of 4-fluorophenyl-phosphodichloridate.

$\text{C}_6\text{H}_4\text{Cl}_2\text{FO}_2\text{P}$, MW=228.97.



143
This was synthesised according to *Standard procedure 3*, using phosphorus-oxychloride (1.395 mL, 15.00 mmol), 4-chlorophenol (1.68 g, 15.00 mmol) and TEA (2.1 mL, 15.00 mmol) in ethylether (140 mL) to give an oil (3.96 g, 96 % yield).

^{31}P -NMR (CDCl_3 , 121 MHz): δ 5.52.

5 ^1H -NMR (CDCl_3 , 300 MHz): δ 7.15 (2H, d, $^3J=8.0$ Hz, *OPh*), 7.05 (2H, d, $^3J=8.0$ Hz, *OPh*).

^{13}C -NMR (CDCl_3 , 75 MHz): δ 116.8 ('o', *OPh*), 122.1 ('m', *OPh*), 146.7 ('p', *OPh*), 158.7 ('ipso', *OPh*).

10

Experimental data are given in Table I illustrating the activity of compounds embodying the present invention, and of some comparative compounds, with respect to human breast cancer cell line MDA MB231, human colon cancer cell line HT115 and human prostate cancer cell line PC-3. The compounds include those whose preparations are described
15 above and compounds made by preparative methods corresponding to the methods described above.

The experimental procedures used human colon cancer cell line (HT115), human prostate cancer cell line (PC-3), human breast cancer cell line (MDA MB 231) and normal human
20 umbilical vein endothelial cell (HUVEC). Compounds were diluted over a range of concentrations and added to cells over 1 to 3 days. The cytotoxicity was determined using a MTT assay at the end of each experiment.

In the Table:

25

ArO refers to Ar as defined above with respect to formula I;

J refers to the moiety of the present compounds represented by, respectively, $\text{ROCOCR}'\text{R}''\text{NH}$ -, as defined above with respect to formula I; or, with respect to
30 Examples 51, 52 and 53, $\text{HOCO R}'\text{R}''\text{NH}$ -, as defined above with respect to formula II; and

B refers to the base moiety of the present compounds as defined above with respect to formula I or formula II.

BVU stands for 2-bromovinyluridine.

5

5-(C=CC[O]O)MeU stands for methyl propenoate-2'-deoxyuridine.

GemCyt stands for Gemcitabine.

10 Examples A, I, 67 and G are comparative Examples.

Example A is 5-(2-Bromovinyl)-2'-deoxyuridine.

Example 1 is Example 1 above corresponding to compound (7) above.

15

Example 67 is propenoate-2'-deoxyuridine.

Example G is gemcitabine.

20 Examples 51, 52 and 53 are compounds embodying formula II above.

TABLE

25

Ex	ArO	J	B	EC50/ μ M	EC50/ μ M	EC50/ μ M
				Breast	Colon	Prostate
				MDA-MB231	HT115	PC-3
A	-	-	BVU	125	78.7	120
1	PhO	MeAlaNH	BVU	79	244.5	155
2	PhO	BnAlaNH	BVU	34	1.4	19
3	PhO	EtAlaNH	BVU	56	52	36
4	p-CF ₃ PhO	BnAlaNH	BVU	31	7.4	9.3

5	p-FPhO	MeAlaNH	BVU	159	17	58
6	p-FPhO	EtAlaNH	BVU	46	11	42
7	p-FPhO	BnAlaNH	BVU	17	3.5	16
8	p-NO ₂ PhO	BnAlaNH	BVU	28	-	9
9	p-NO ₂ PhO	EtAlaNH	BVU	177	118.7	365
10	p-NO ₂ PhO	MeAlaNH	BVU	105	96.7	10.4
11	p-CIPhO	EtAlaNH	BVU	28.7	14.9	3.4
12	p-CIPhO	BnAlaNH	BVU	6.2	3.4	2.4
13	p-CIPhO	MeAlaNH	BVU	61	70.2	13
14	PhO	Bn(Me ₂ Gly)NH	BVU	19	14.5	5.1
15	p-CF ₃ PhO	MeAlaNH	BVU	47	79.2	15
16	PhO	Me(cPntGly)NH	BVU	79	77	16
17	PhO	Et(cPntGly)NH	BVU	44	81.3	41
18	PhO	Bn(cPntGly)NH	BVU	78	9.7	33
19	p-NO ₂ PhO	Me[cPntGly]NH	BVU	56	38.2	88
20	p-NO ₂ PhO	Et[cPntGly]NH	BVU	13	57.3	15
21	p-NO ₂ PhO	Bn[cPntGly]NH	BVU	8.4	17.2	2.2
22	PFPhO	Me[cPntGly]NH	BVU	57	59.7	51
23	PFPhO	Et[cPntGly]NH	BVU	9.9	18.1	2.7
24	PFPhO	Bn[cPntGly]NH	BVU	9.4	17	3.7
25	p-CF ₃ PhO	EtAlaNH	BVU	33.8		4.6
26	PhO	Me(Me ₂ Gly)NH	BVU	41.1	77.9	1.5
27	PhO	Et(Me ₂ Gly)NH	BVU	217.9	39.7	76.1
28	p-CF ₃ PhO	Me(cPntGly)NH	BVU	28.8	21.2	-
29	p-CF ₃ PhO	Et(cPntGly)NH	BVU	45.6	15.1	4.3
30	p-CF ₃ PhO	Bn(cPntGly)NH	BVU	6.9	6.4	-
32	p-CIPhO	Me[cPntGly]NH	BVU	2.6	99.3	52.2
33	p-CIPhO	Et[cPntGly]NH	BVU	12	97.9	83.2
34	p-CIPhO	Bn[cPntGly]NH	BVU	3.9	8.9	6.3
35	PhO	MeLeuNH	BVU	18.5	7.7	75.7
36	PhO	Me[Phe]NH	BVU	19.8	32.1	86.9
37	PhO	BnLeuNH	BVU	2.8	7	7.16
38	p-NO ₂ PhO	BnLeuNH	BVU	6.3	10.7	7.2
39	p-CIPhO	BnLeuNH	BVU	4.3	288.5	193.1
42	p-CIPhO	Me(Me ₂ Gly)NH	BVU	8.7	183.4	441.6
43	p-CIPhO	Et(Me ₂ Gly)NH	BVU	5.9	174.3	1.15
44	p-CIPhO	Bn(Me ₂ Gly)NH	BVU	2.3	4.5	9.12
45	p-NO ₂ PhO	Me(Me ₂ Gly)NH	BVU	9.4	24.7	222.8

46	p-NO ₂ PhO	Et(Me ₂ Gly)NH	BVU	2	224	82.4
47	p-NO ₂ PhO	Bn(Me ₂ Gly)NH	BVU	4.5	16.7	27.2
48	p-CF ₃ PhO	Bn(Me ₂ Gly)NH	BVU	1.3	7	0.61
49	o-ClPhO	BnAlaNH	BVU	5.4	16.2	5.4
50	o-ClPhO	Bn(Me ₂ Gly)NH	BVU	5.7	3.9	6.59
51	-	L-AlaNH	BVU		295.4	
52	--	LeuNH	BVU		438.1	
53	-	PhAlaNH	BVU		66	
54	PhO	Bn[PhAla]NH	BVU		5.1	
55	PhO	Me[D-Ala]NH	BVU		392.7	
56	PhO	Bn[D-Ala]NH	BVU		20.8	
57	p-NO ₂ PhO	Bn[D-Ala]NH	BVU		20.2	
58	p-CF ₃	Me[Me ₂ Gly]NH	BVU		83.6	
59	p-CF ₃	Et[Me ₂ Gly]NH	BVU		24.7	
60	p-FPhO	Et[Me ₂ Gly]NH	BVU		86.8	
61	p-CF ₃ PhO	Bn[L-PhAla]NH	BVU		6.3	
62	p-CF ₃ PhO	Bn[L-Leu]NH	BVU		1.9	
63	PhO	tBu[L-Ala]NH	BVU		31.5	
64	p-NO ₂ PhO	Bn[L-PhAla]NH	BVU		16.6	
65	p-FPhO	Me(Me ₂ Gly)NH	BVU			
66	p-NO ₂ PhO	Me(Me ₂ Gly)NH	5-(C=CC[O]O Me)U		20.7	
67	-	-	5-(C=CC[O]O Me)U		93.7	
69	PhO	MeMetNH	BVU	-	-	6.3
70	PhO	MeTrpNH	BVU	-	-	16
71	PhO	BnMetNH	BVU	-	-	6.3
72	PhO	BnIleNH	BVU	-	-	1.6
73	PhO	EdIleNH	BVU	-	-	30.6
74	PhO	MeGlyNH	BVU	-	-	31
75	PhO	BnGlyNH	BVU	-	-	29
77	p-ClPhO	BnGlyNH	BVU	-	-	150
78	p-CF ₃ PhO	BnValNH	BVU	-	-	1.6
80	PhO	Me ₂ AspNH	BVU	-	-	158
81	PhO	Et ₂ GluNH	BVU	-	-	31
82	m-ClPhO	BnAlaNH	BVU	-	-	21
83	m-ClPhO	BnMe ₂ GlyNH	BVU	-	-	6.3
84	p-FphO	BnMe ₂ GlyNH	BVU	-	-	4.5

85	PhO	BnValNH	BVU	-	-	31.2
86	p-ClPhO	BnValNH	BVU	-	-	0.9
87	p-FphO	BnValNH	BVU	-	-	1.6
88	PhO	BnPhGlyNH	BVU	-	-	0.75
89	p-ClPhO	BnPhGlyNH	BVU	-	-	6.5
91	p-CF ₃ PhO	BnPhGlyNH	BVU	-	-	0.7
94	PhO	i-BuAlaNH	BVU	-	-	51
95	PhO	2-BuAlaNH	BVU	-	-	6.8
G	-	-	GemCyt	2.8	606.1	3.12
31	PhO	BnAlaNH	GemCyt	42.6	5.7	0.22
40	p-ClPhO	BnAlaNH	GemCyt	9.2	16.1	15.4
41	p-ClPhO	Bn[Me ₂ Gly]NH	GemCyt	3.1	317.1	68.8

Gemcitabine (Example G in the Table) and compound CPF31 (Example 31 in the Table; gemcitabine-[phenyl-(benzoxo-L-alaninyl)]-phosphate) were compared in a mouse model with xenografts of human cancer (colon HT115 and prostate PC3).

Mice were dosed daily at a range of concentrations (0.01-10 μ M) and tumour volume assessed versus control.

10 Kaplan-Meier statistics were computed regarding incident-free survival.

In the attached drawings:

Figure 1 shows for the mouse xenograft the tumour volume for prostate data at day 13 using GemzarTM (gemcitabine available ex. Lilly);

Figure 2 shows for the mouse xenograft the tumour volume for prostate data at day 13 using CPF31;

20 Figure 3 shows the incident free survival functions v. day for each of CPF31 and gemcitabine; and

148

Figure 4 shows for the mouse xenograft the tumour volume for colon data at day 24 using, respectively, Gemzar and compound CPF31.

Referring to the drawings, CPF31 can be seen to be significantly less toxic than
5 gemcitabine.

CPF31 was significantly effective at reducing prostate and colon tumour volume relative to control at daily dosing of 5 and 10 μ M (3 and 6 μ g/ml). Gemcitabine was not effective at the highest non-toxic concentration.

10

Gemzar is seen from Figure 1 to be toxic above 1 μ M. In contrast, CPF31 is seen from Figure 2 to have substantially lower toxicity.

Figure 3 shows that CPF31 has significantly lower side effects on a comparable basis: 3
15 animals show serious toxicity (10% body mass loss) in GMZ and in CPF31 on day 10, collectively 4 in GMZ and 1 in CPF31 on day 11 and 5 in GMZ and 1 in CPE on day 13. Using Chi square analysis by combining 5 and 10 μ M groups, the significance is $p=0.193$, 0.078 and 0.0289 on day 10, 11 and 13. It is clear that by day 13, CPF31 displayed significantly less side effects, and the anti-cancer effects continue to exceed that of Gemzar.

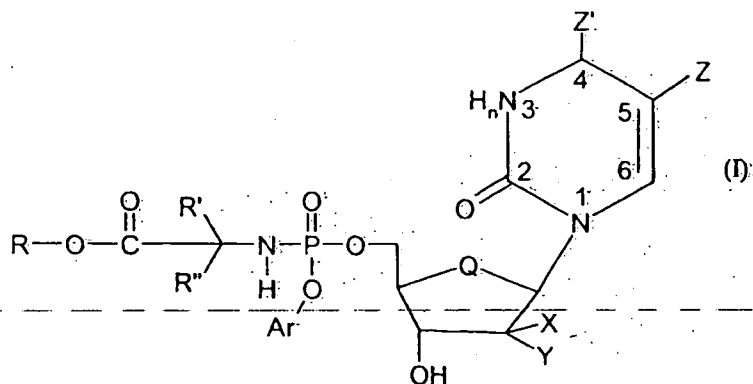
20

Figure 3 shows the Kaplan-Meier survival curve, incidence free survival: based on the loss according to weight loss. A Cox proportion analysis shows that CPF31 is far less toxic than GMZ based on the weight-loss calculated loss ($p=0.043$).

25 CPF31 was found to be active at 5 μ M *in vitro*, whereas Gemzar was found to be active at 600 μ M, with respect to the same colon cell line. Figure 4 shows the results of testing both *in vivo* at 5 μ M. The greater activity of CPF31 in reducing tumour volume is shown in Figure 4.

CLAIMS.

1. A chemical compound having formula I:



5 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;

10 Q is selected from the group comprising -O- and -CH₂-;

X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃);

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

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

n is 0 or 1,

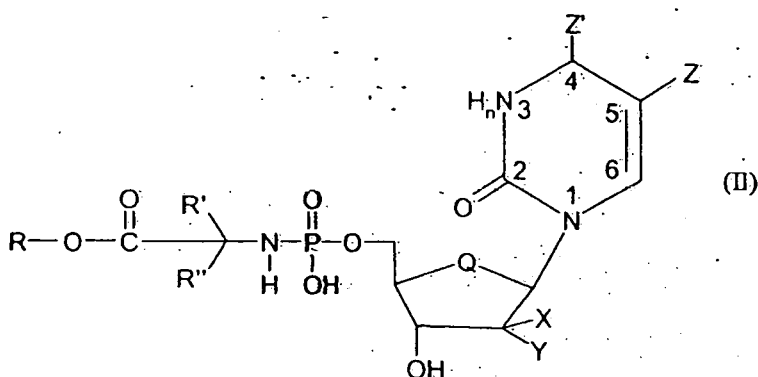
wherein when n is 0, Z' is -NH₂ and a double bond exists between position 3 and position 4, and

when n is 1, Z' is =O;

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

with the proviso that, except where R is 2-Bu (-CH₂-CH(CH₃)₂) and one of R' and R'' is H and one of R' and R'' is methyl (-CH₃), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl (-C₆H₅).

2. A compound according to claim 1 wherein R is selected from the group comprising a C₁₋₁₆ primary or secondary alkyl group, a C₅₋₇ carbocyclic aryl group or a C₁₋₆alkylC₅₋₁₁ aryl group.
3. A compound according to claim 2 wherein R is selected from the group comprising methyl (-CH₃), ethyl (-C₂H₅) and benzyl (-CH₂C₆H₅).
4. A compound according to claim 3 wherein R is benzyl.
5. A compound according to any one of the preceding claims wherein Ar is an optionally substituted C₆ monocyclic aromatic ring moiety, ie is optionally substituted phenyl.
6. A compound according to claim 5 wherein Ar is selected from the group comprising -C₆H₅, pCF₃C₆H₄-, pFC₆H₄-, pNO₂C₆H₄-, pClC₆H₄- and oClC₆H₄-.
7. A chemical compound having formula II:



- wherein n, Q, R, R', R'', X, Y, Z and Z' have the meanings described in claim 1, and additionally R can be H, with provisos that:
- when n is 1, X and Y are both H, R is methyl (-CH₃), one of R' and R'' is H and one of R' and R'' is methyl (-CH₃), then Z is not -CH=CHBr;
- when n is 1, X and Y are both H, R is methyl (-CH₃), one of R' and R'' is H and one of R' and R'' is phenylethyl, phenylmethyl, indol-3-ylmethyl or indol-3-ylethyl, then Z is not F;
- and
- when n is 0, X is not H.

8. A compound according to any one of the preceding claims wherein R' and R'' are, independently, selected from the group comprising H, C₁₋₆ primary, secondary and tertiary alkyl, C₁₋₃alkylC₅₋₇ aryl, or, when together they form an alkylene chain, they provide, together with the C atom to which they are attached, a C₃₋₈ carbocyclic aliphatic ring.

9. A compound according to claim 8 wherein R' and R'' are, independently, selected from the group comprising H, methyl, benzyl and -CH₂CH(CH₃)₂, or, R' and R'' together with the C atom to which they are attached, provide a C₅₋₆ ring.

10. A compound according to claim 9 wherein R' and R'' are each methyl.

11. A compound according to claim 9 wherein one of R' and R'' is H and one of R' and R'' is methyl.

12. A compound according to claim 9 wherein the carbocyclic ring is a pentyl ring.

13. A compound according to any one of the preceding claims wherein R' and R'' correspond to the side chains of a naturally occurring amino acid.

14. A compound according to any one of the preceding claims wherein Z is selected from the group comprising H, C₁₋₆alkyl, substituted C₁₋₆alkyl, C₁₋₆alkenyl, substituted C₁₋₆alkenyl, C₁₋₆alkynyl, and halogen.

15. A compound according to any one of the preceding claims wherein Q is O.

16. A compound according to any one of the preceding claims wherein when n is 1, each of X and Y is H.

17. A compound according to any one of claims 1 to 15 wherein when n is 0, each of X and Y is F.

18. A compound according to any one of claims 1 to 15 wherein when n is 0, X is OH and Y is H.
19. A compound according to any one of claims 1 to 15 wherein when n is 0, X is H and Y is OH.
20. A compound selected from the group comprising:
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 3)
- 10 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxo-L-alaninyl)]-phosphate (CPF 2)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(methoxy-L-alaninyl)]-phosphate (CPF 5)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 6)
- 15 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(benzoxo-L-alaninyl)]-phosphate (CPF 7)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(methoxy-L-alaninyl)]-phosphate (CPF 10)
- 20 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 9)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(benzoxo-L-alaninyl)]-phosphate (CPF 8)
- (E)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[para-(trifluoromethyl)-phenyl-(methoxy-L-alaninyl)]-phosphate (CPF 15)
- 25 (E)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[para-(trifluoromethyl)-phenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 25)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(benzoxo-L-alaninyl)]-phosphate (CPF 4)
- 30 (E)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(methoxy-L-alaninyl)]-phosphate (CPF 13)
- (E)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(ethoxy-L-alaninyl)]-phosphate (CPF 11)

- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 12)
- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy- α,α -dimethylglycinyl)]-phosphate (CPF 26)
- 5 (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[phenyl-(ethoxy- α,α -dimethylglycinyl)]-phosphate (CPF 27)
- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy- α,α -dimethylglycinyl)]-phosphate (CPF 14)
- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-nitrophenyl-(methoxy- α,α -dimethylglycinyl)]-phosphate (CPF 45)
- 10 (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-nitrophenyl-(ethoxy- α,α -dimethylglycinyl)]-phosphate (CPF 46)
- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-nitrophenyl-(benzoxy- α,α -dimethylglycinyl)]-phosphate (CPF 47)
- 15 (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(methoxy- α,α -dimethylglycinyl)]-phosphate (CPF 42)
- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(ethoxy- α,α -dimethylglycinyl)]-phosphate (CPF 43)
- (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[4-chlorophenyl-(benzoxy- α,α -dimethylglycinyl)]-phosphate (CPF 44)
- 20 (*E*)-5-(2-bromovinyl)-2'-deoxyuridine-5'-[*para*-(trifluoromethyl)-phenyl-(benzoxy- α,α -dimethylglycinyl)]-phosphate (CPF 48)
- (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy- α,α -cycloleucinyl)]-phosphate (CPF 16)
- 25 (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(ethoxy- α,α -cycloleucinyl)]-phosphate (CPF 17)
- (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy- α,α -cycloleucinyl)]-phosphate (CPF 18)
- (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[*para*-nitrophenyl-(methoxy- α,α -cycloleucinyl)]-phosphate (CPF 19)
- 30 (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[*para*-nitrophenyl-(ethoxy- α,α -cycloleucinyl)]-phosphate (CPF 20)

- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(benzoxy- α,α -cycloleucynyl)]-phosphate (CPF 21)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(methoxy- α,α -cycloleucynyl)]-phosphate (CPF 22)
- 5 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(ethoxy- α,α -cycloleucynyl)]-phosphate (CPF 23)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-fluorophenyl-(benzoxy- α,α -cycloleucynyl)]-phosphate (CPF 24)
- 10 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(methoxy- α,α -cycloleucynyl)]-phosphate (CPF 32)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(ethoxy- α,α -cycloleucynyl)]-phosphate (CPF 33)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-L-phenylalaninyl)]-phosphate (CPF 36)
- 15 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(benzoxy- α,α -cycloleucynyl)]-phosphate (CPF 34)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(methoxy- α,α -cycloleucynyl)]-phosphate (CPF 28)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(ethoxy- α,α -cycloleucynyl)]-phosphate (CPF 29)
- 20 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-trifluorophenyl-(benzoxy- α,α -cycloleucynyl)]-phosphate (CPF 30)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-L-phenylalaninyl)]-phosphate (CPF 36)
- 25 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(methoxy-L-leucinyl)]-phosphate (CPF 35)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(benzoxy-L-leucinyl)]-phosphate (CPF 37)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-nitrophenyl-(benzoxy-L-leucinyl)]-phosphate (CPF 38)
- 30 (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[para-chlorophenyl-(benzoxy-L-leucinyl)]-phosphate (CPF 39)
- (E)-5-(2-Bromovinyl)-2'-deoxyuridine-5'-[phenyl-(2-butyl-L-alaninyl)]-phosphate

Gemcitabine-[phenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 31)

Gemcitabine-[para-chlorophenyl-(benzoxy-L-alaninyl)]-phosphate (CPF 40) and

Gemcitabine-[para-chlorophenyl-(benzoxy- α,α -dimethylglycinyl)]-phosphate (CPF 41).

- 5 21. A compound according to any one of claims 1 to 6, claim 20, or to any one of claims 8 to 19 as dependent on any one of claims 1 to 6, for use in a method of treatment, preferably in the prophylaxis or treatment of cancer, with the proviso that when n is 1, X and Y are both H, one of R' and R'' is H and one of R' and R'' is methyl (CH_3), R is 2-Bu ($-\text{CH}_2-\text{CH}(\text{CH}_3)_2$) or R is benzyl ($-\text{CH}_2\text{C}_6\text{H}_5$), then Ar can be unsubstituted phenyl ($-\text{C}_6\text{H}_5$).

22. Use of a compound according to any one of claims 1 to 6, claim 20, or to any one of claims 8 to 19 as dependent on any one of claims 1 to 6, in the manufacture of a medicament for the prophylaxis or treatment of cancer, with the proviso set out in claim 21.

23. A method of prophylaxis or treatment of cancer comprising administration to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 6, claim 20, or to any one of claims 8 to 19 as dependent on any one of claims 1 to 6, with the proviso set out in claim 21.

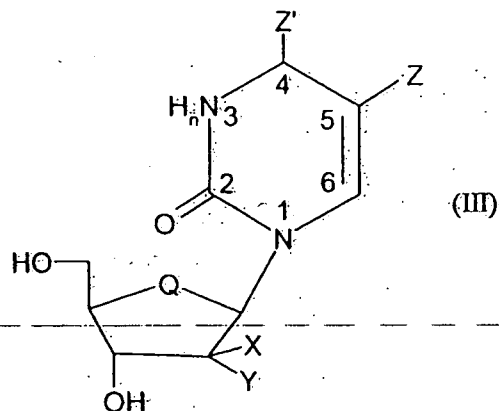
24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6, claim 20, or to any one of claims 8 to 19 as dependent on any one of claims 1 to 6, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

25. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to any one of claims 1 to 6, claim 20 or any one of claims 8 to 19 as dependent on any one of claims 1 to 6, with a pharmaceutically acceptable excipient, carrier or diluent.

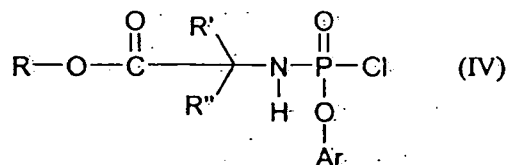
156

118

26. A process for the preparation of a compound of formula I according to claim 1, the process comprising reacting of a compound of formula (III):



5. with a compound of formula (IV)



wherein Ar, n, Q, R, R', R'', X, Y, Z' and Z'' have the meanings described in claim 1.

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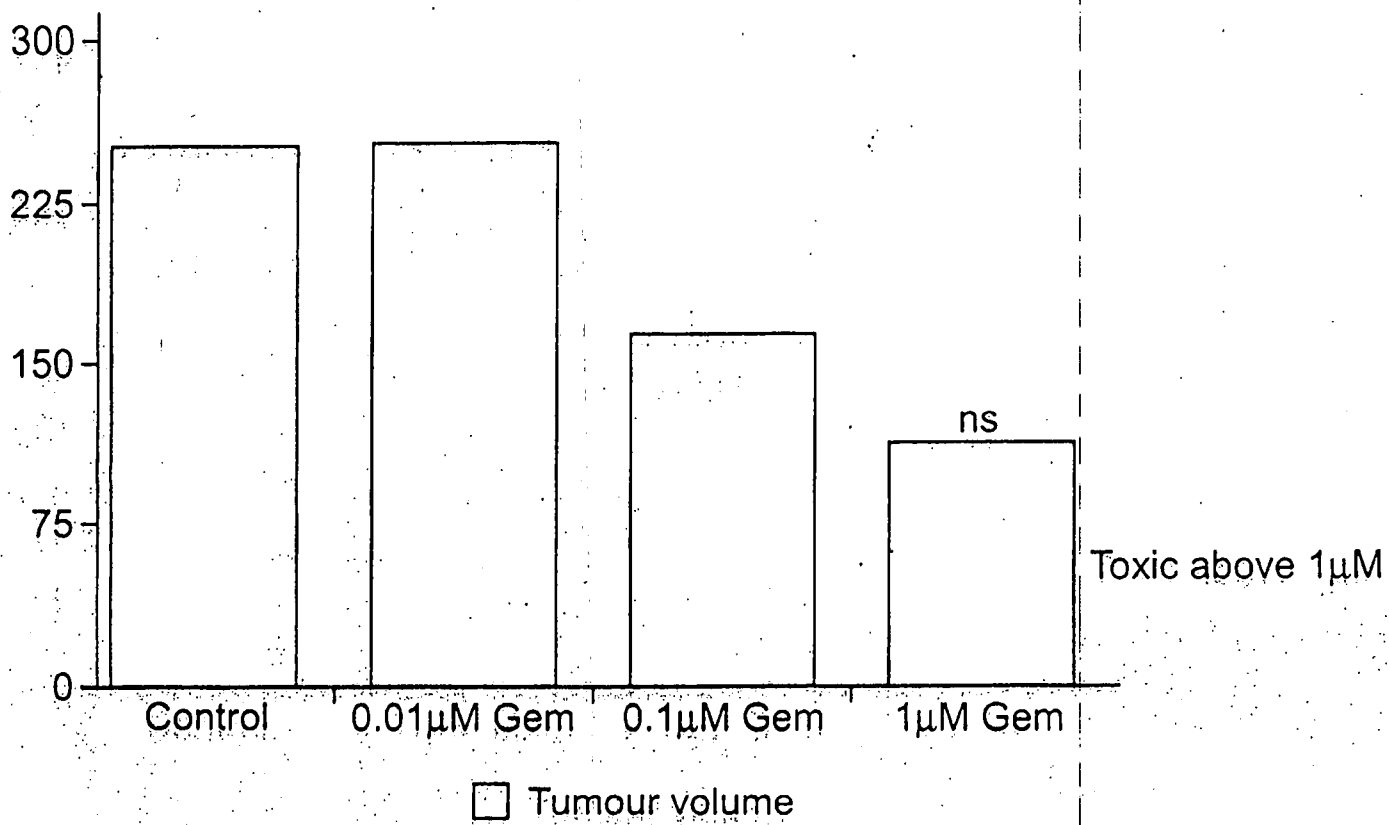


FIG. 1

1/4

157

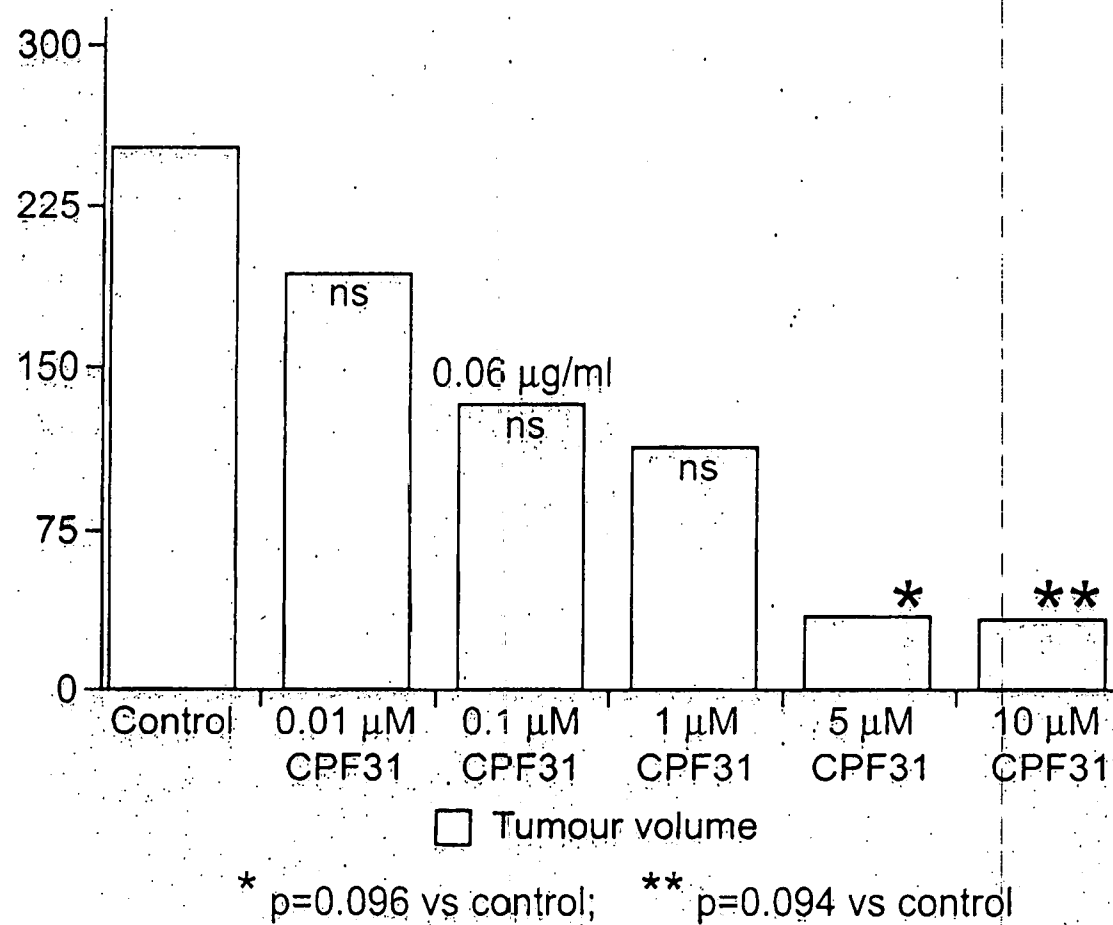


FIG. 2

3/4

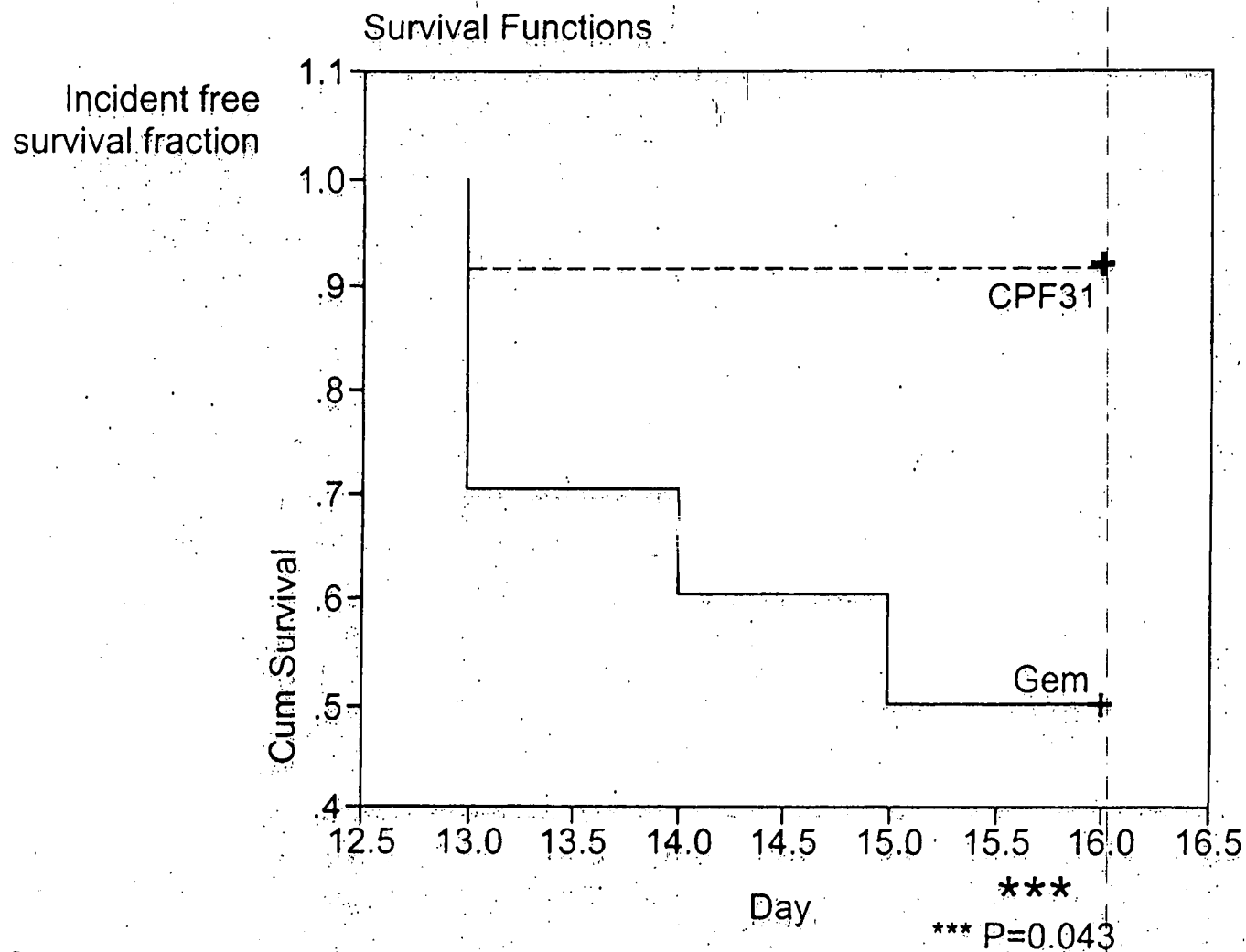
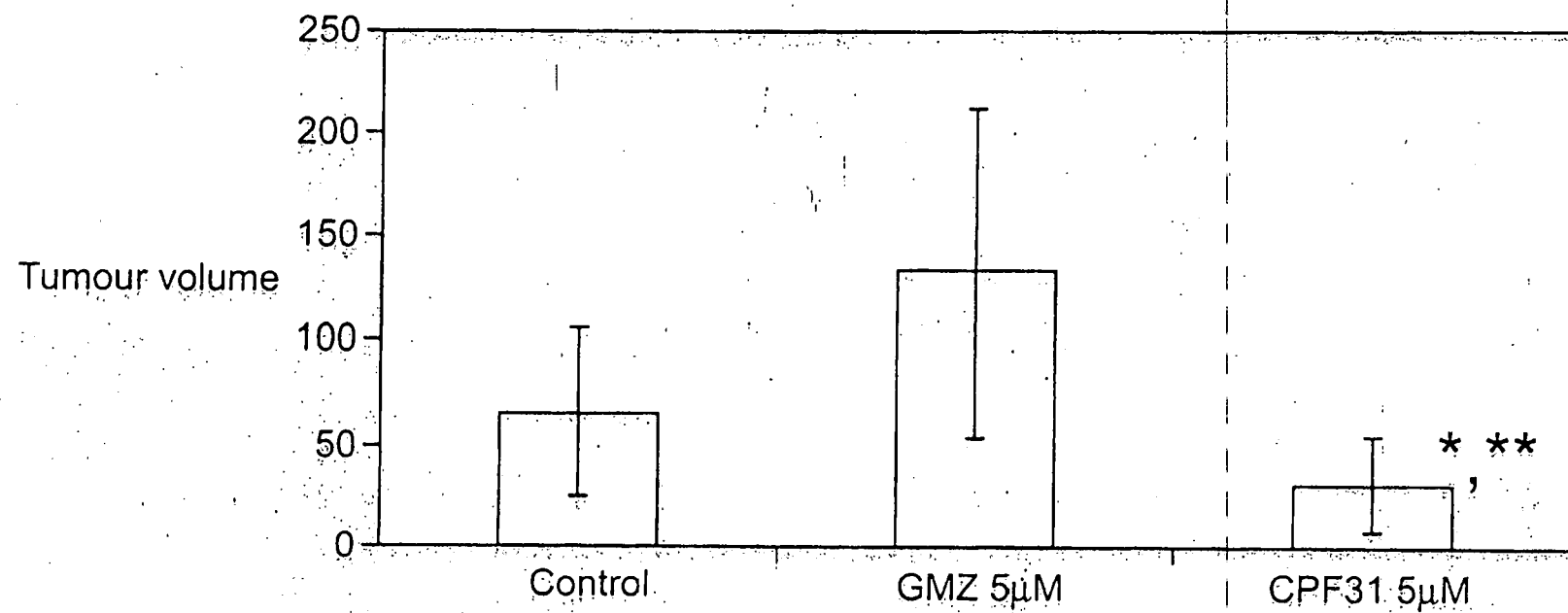


FIG. 3

159



Colon data @ 24 days

* significant vs control; ** significant vs GMZ

FIG. 4

4/4

160