

Efficient one-pot, three-component procedure to prepare new α -aminophosphonate and phosphonic acid acyclic nucleosides

Laila Baddi, Driss Ouzebla, Az-Eddine El Mansouri, Michael Smietana,

Jean-Jacques Vasseur, Hassan Lazrek

▶ To cite this version:

Laila Baddi, Driss Ouzebla, Az-Eddine El Mansouri, Michael Smietana, Jean-Jacques Vasseur, et al.. Efficient one-pot, three-component procedure to prepare new α -aminophosphonate and phosphonic acid acyclic nucleosides. Nucleosides, Nucleotides and Nucleic Acids, In press, pp.1-25. 10.1080/15257770.2020.1826516. hal-02989697

HAL Id: hal-02989697 https://hal.science/hal-02989697v1

Submitted on 6 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Efficient one-pot, three components procedure to prepare new αamino phosphonate and phosphonic acid acyclic nucleosides

Laila Baddi^a, DrissOuzebla^a, Azeddine El Mansouri^a, Michael Smietana^b, Jean-Jacques Vasseur^b and Hassan B. Lazrek^a

^a Unité de Chimie Biomoléculaire et Médicinale, Laboratoire de Chimie Biomoléculaire Faculty of Science SemLalia, Marrakech, Morocco. ^bInstitut des Biomolécules Max Mousseron UMR 5247 CNRS-UMI-UMII, Université Montpellier II, CC008, Place E. Bataillon 34095, Montpellier Cedex 5 France

E-mail for the *corresponding author:

Efficient one-pot, three components procedure to prepare new α amino phosphonate and phosphonic acid acyclic nucleosides

An efficient one-pot three-component Kabachnick-Fields reaction of aldehydes (acyclic nucleosides), amines (or amino acid), and triethylphosphite proceeded for the synthesis of amino phosphonates using natural phosphate coated with iodine ($I_2@NP$) as a catalyst. The novel α -aminophosphonate and phosphonic acid acyclic nucleosides were tested for their anti-HCV and anti-HIV activities. The molecular docking showed that the non-activity of these compounds may be is due to the absence of hydrophobic pharmacophores.

Keywords: acyclic nucleosides; α-Aminophosphonates; Kabachnik-Fields reaction; catalysis; Natural phosphate

Introduction

The viral disease is a major health problem worldwide. Indeed, there is still a need to discover new potent, safe, and selective antiviral drugs. Among these, α -aminophosphonates have attracted the attention of medicinal chemists due to their potential antiviral activity [1]. The α -aminophosphonates are structurally similar to α -amino acids, known to have good cell permeability[2], and physiological stability as the phosphorus-carbon bond, which is not susceptible to enzymatic degradation by phosphatases [3-5]. Moreover, acyclic nucleoside phosphonates, such as adefovir and tenofovir, are now in clinical use for the treatment of viral infections (HIV, HBV, CMV). These drugs possess a phosphonomethyl ether moiety allowing them to bypass the first phosphorylation step [6, 7]. The after-mentioned properties prompted many research groups including ours to synthesize acyclic nucleoside phosphonates varying notably the length and substitution pattern of the phosphonate link [8-12].

The synthesis of α -aminophosphonates has gained more attention due to their broad spectrum of biological activity like anticancer, antiviral, herbicides, fungicides, bactericides, peptide mimetic, and enzyme inhibitor [13-18]. Three-component one-pot Kabachnik-Fields condensation of carbonyl compounds with amines and phosphites is perhaps the most exploited reaction for the preparation of structurally diverse α -aminophosphonates [19, 20]. While early procedures were limited to simple starting

materials and newer wide-scope syntheses catalysed by Lewis acids, have been reported [21-27]. Recently, several solids catalysts have been used in the preparation of α aminophosphonates such as SbCl₃/Al₂O₃ (28), Mg(ClO₄)₂[29], Na₂CaP₂O₇[30], KF doped natural phosphate (NP) [31], and PEG-SO₃H [32]. In general, these threecomponent reactions may take place via an imine or an α -hydroxy-phosphonate intermediate [33]. During the formation of imine, water is formed which could either deactivate or decompose the Lewis acid catalyst thereby limiting the scope of carrying out this reaction in one-pot [34]. Among supports reported in the literature, natural phosphate was found [31] to be an efficient Lewis acid to catalyse the synthesis of α aminophosphonates in one-pot due to its ability to tolerate the water generated during the course of the reaction. Moreover, it was used widely as support because of its ionic substitution ability, structural stability, and high adsorption capacity, making it an attractive cost-effective catalyst for several chemical transformations [35-37]. Meanwhile, iodine has emerged as a very efficient Lewis acid catalyst for various organic transformations and is relatively inexpensive compared to other Lewis acids, including rare earth metal triflates, and is more tolerant in comparison to typical Lewis acids/bases [38-40]. Furthermore, Zahouily et al. showed that iodine supported on natural phosphate could be effectively employed for the protection of carbonyl compounds as their thioacetals in good yield at ambient temperature and mild conditions [41].

In the light of these successes, here we report a one-pot three-component reaction of α aminophosphonates using a catalytic amount of I₂@NP as a catalyst. A simple protocol was followed in the preparation of novel α -amino phosphonate and phosphonic acid acyclic nucleosides with both pyrimidine and purine nucleobases. Finally, all newly synthesized compounds were evaluated for their anti-HCV and anti-HIV activities.

Results and discussion

In the aim to synthesis a novel conjugated acyclic nucleoside- α -amino acid phosphonate **5-9** and their phosphonic analogs**10-14**.Our study started with the synthesis of various acyclic nucleoside N-acetaldehydes, which were obtained by treatment of the unprotected nucleobases with bromoacetaldehyde diethyl acetal in the presence of potassium carbonate. Then, aldehydes **4a-d** were obtained by hydrolysis of the acetal group**3a-d** using NP/HCl as an acidic medium (Table 1) [42].

BH + Br OAc 1a-d 2	$\frac{K_2CO_3}{DMF/110°C}$	OAc B OAc	NP/HCl B H 4a-d
B= NH N S			$B = \bigvee_{\substack{N \\ N \\ N \\ S}}^{N + N} N$
1a, 3a, 4a	1b, 3b, 4b	1c, 3c, 4c	1d, 3d, 4d

Table 1: Synthesis of nucleoside N-acetaldehydes 4a-d

To evaluate the influence of the catalyst, we prepared natural phosphates coated with different Lewis acids using aldehyde **4a**, aniline, and triethyl phosphite as a model experiment (Table 2). The best results were obtained with $I_2@NP$ in refluxing acetonitrile which yielded α -aminophosphonate **5a** in 77 % yields (Table 2, entry 4).

Table 2: Optimal condit	ions for the preparation	of amino phosphonates 5a
-------------------------	--------------------------	--------------------------

EtO _{、P} OEt Catalyst OEt CH ₃ CN, 80°C	$\rightarrow EtO = NH$ $to NH$ $to NH$ $to NH$ $5a$
Catalyst	Yield (%) ^a
	20
NP	0
I_2	30
$I_2@NP$	77
ZnCl ₂ @NP	65
ZnBr ₂ @NP	40
CF ₃ SO ₃ H@NP	25
Zn(OTf) ₂ @NP	51
SnCl ₄ @NP	38
	$ \begin{array}{c} EtO_{P} \\ OEt \end{array} \\ \hline Catalyst \\ \hline CH_3CN, 80^{\circ}C \end{array} \\ \hline CH_3CN, 80^{\circ}C \end{array} \\ \hline Catalyst \\ \hline \\ I_2 \\ I_2 \\ I_2 \\ I_2 \\ MP \\ I_3 \\ I_2 \\ MP \\ ZnCl_2 \\ MP \\ ZnCl_2 \\ MP \\ ZnBr_2 \\ MP \\ Zn(OTf)_2 \\ MP \\ SnCl_4 \\ MP \\ MP \\ SnCl_4 \\ MP \end{array} $

^a Isolated yield after gel chromatography purification.

As presented in table 3, the optimized conditions were generalized using acyclic nucleoside acetaldehydes **4a-d**, triethyl phosphite, and various amines, including amino acids. The acyclic nucleoside diethyl α -amino phosphonates obtained **5-9(a-d)** were further treated with TMSBr in DMF to yield the corresponding α -amino phosphonic acids **10-14(a-d)**. The reaction tolerates aromatic and aliphatic amines as well as amino acids. The results provide the first examples of conjugated nucleoside- α -amino acids phosphonates and pave the way for the design of new potential bioactive compounds through a simple and eco-friendly transformation.

	NH ₂ Et R +	$O_{P} OEt $ NP/I_2 $OEt $ $CH_3CN, 80^{\circ}C$	EtO H EtO H R NH	TMSBr DMF, RT HO ^U HO ^U HO ^V HO ^V R [−] NH
Entry	В	R	Phosphonate, Yield (% ^a)	Phosphonic, Yield (% ^a)
1	U	Ph	5 a, 77	10a , 60
2	Т	Ph	5b , 45	10b , 60
3	6-AzaU	Ph	5c , 40	10c , 50
4	А	Ph	5d , 40	10d , 70
5	U	Ph-CH ₂	6a , 50	11a , 60
6	Т	Ph-CH ₂	6b , 60	11b , 35
7	6-AzaU	Ph-CH ₂	6c , 60	11c , 35
8	А	Ph-CH ₂	6d , 62	11d , 25
9	U	CH ₃ -CH-CH ₂ -CH ₃	7a , 66	12a , 25
10	Т	CH ₃ -CH-CH ₂ -CH ₃	7b , 60	b
11	6-AzaU	CH ₃ -CH-CH ₂ -CH ₃	7c , 50	12c , 20
12	А	CH ₃ -CH-CH ₂ -CH ₃	7d , 50	b
13	U	CH ₂ -CO ₂ Et	8 a, 55	13a , 40
14	Т	CH ₂ -CO ₂ Et	8b , 60	13b , 20
15	6-AzaU	CH ₂ -CO ₂ Et	8c , 50	13c , 20
16	А	CH ₂ -CO ₂ Et	8d , 55	13d , 20
17	U	CH ₃ -CH-CO ₂ Me	9a , 40	14a , 35
18	Т	CH ₃ -CH-CO ₂ Me	9b , 40	14b , 25

Table 3: Results of the preparation of novel conjugated nucleoside- α -amino acid phosphonates **5-9(a-d)** and their phosphonic analogs**10-14 (a-d)**

19	6-AzaU	CH ₃ -CH-CO ₂ Me	9c , 41	14c , 30
20	А	CH ₃ -CH-CO ₂ Me	9d , 42	14d , 15

^a Isolated yield after gel chromatography purification. ^b A mixture undefined compounds

Next, we evaluated the antiviral activity of these new phosphonic acids in an HCV subgenomic RNA replicon using Huh 5.2 cells. Unfortunately, none of the compounds exhibited any significant antiviral activity. On the other hand, these new phosphonic acids were subjected to a standard in vitro antiviral screening using HIV-1 and HIV-2. None of the compounds exhibited any significant antiviral activity.

In the aim to understand the lack of activity of synthesized compounds and suggests some modifications to improve the antiviral activity, molecular docking was carried out. The HCV NS3 protease plays a pivotal role in the replication of the HCV virus. Its inhibition has proven effective in reducing viral loads in humans [43]. Furthermore, several phosphonate derivatives were reported as potential inhibitors of HCV NS3 protease [44-47]. Meanwhile, HIV reverse transcriptase (RT) is an interesting target for the treatment of HIV disease. Over the past years, various nucleoside phosphonates were described to inhibit RT [48-50]. Considering these facts, the compound **14a** was docked into the active sites of HCV NS3 protease (PDB: 1W3C) [51] and HIV reverse transcriptase (PDB: 2RF2) [52]. Before, to determine the validity of the docking protocol, first, the self-docking experiments were carried out. The root-mean-square deviations (RMSD) between the predicted and the native poses found to be 2.37Å (1W3C; DN1) and 0.27Å (2RF2; MRX). These results indicated that the adopted docking protocol is good for the reproduction of the native poses.

The docking results are summarized in Table 5 and figures 1-4. Regarding HCV NS3 protease, the compound **14a** showed a low affinity with an estimated binding energy of -3.55Kcal/mol. It has reported that the hydrophobic interactions with amino acid residues Val132, Cys159, and Val158 enhanced the inhibitory effect of HCV NS3 protease inhibitors [53]. As shown in figure 2, the hydrophile phosphonic acid group of ligand**14a** is located in the hydrophobic cavity (brown region) of protease protein, leading to a decrease in the inhibitory effect (absence of hydrophobic interactions). Thus, the introduction of aromatic hydrophobic pharmacophore (such as biphenyl) [53] will increase the hydrophobic interactions, especially with CYS159, which improve the

antiviral activity against HCV. On the other hand, HIV RT showed also low affinity for compound **14a** with the estimated free energy of binding -6.63 kcal/mol. This can be explained by the lack of hydrophobic and aromatic interactions. Also, the hydroxyl group (phosphonate) is located in the hydrophobic region, leading to repulsion between the protein and the ligand.

Protein	Ligand	Energy of binding	ΡΜΩΟ (Å)
	Liganu	(Kcal/mol)	RIVISU (A)
1W3C	DN1	-8.79	2.37
	14a	-3.55	
2RF2	MRX	-10.55	0.27
	14a	-6.63	

Table 5: Detail of binding interactions



Figure 1: 2D interactions of compound 14a in the binding sites of HCV NS3 protease



Figure 2: The position of ligand 14a in the hydrophobic cavity of HCV NS3 protease



Figure 3: 2D interactions of compound 14a in the binding sites of HIV-1 RT



Figure 4: The position of ligand 14a in the hydrophobic cavity of HIV-1 RT

Conclusion

In conclusion, $I_2@NP$ was found to be an efficient catalyst for the one-pot threecomponent reaction of acyclic nucleoside acetaldehydes, amines, and triethyl phosphites. New α -aminophosphonates and α -aminophosphonic acids were obtained in good yields with an eco-friendly, inexpensive, and efficient catalyst. This work opens a way to explore the chemical diversity offered by this methodology.

Experimental

Chemistry

Melting points were measured using a Büchi B-545 digital capillary melting point apparatus and used without correction. Reactions were checked with TLC using aluminium sheets with silica gel 60 F254 from Merck. The spectra of 1H NMR and 13C NMR were recorded in solution in DMSO-d6 or CDCl₃ on a Bruker Advance 300 spectrometer at 300 and 75 MHz, respectively. The chemical shifts are expressed in parts per million (ppm) by using DMSO-d6 as internal reference. The multiplicities of the signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quadruplet; and m, multiplet, and coupling constants are expressed in Hertz. FAB mass spectra were recorded on a Varian MAT 311A spectrometer. Mass spectra were

collected using an API 3200 LC/MS/MS system, equipped with an ESI source. The chemical reagents used in synthesis were purchased from Fluka, Sigma and Aldrich. Column chromatography was performed on silica gel (30–60 mm). All solvents were distilled and dried before using.

General Procedure for the preparation of aldehydes 1-4

To a solution of the base (0.80 mmol) and K_2CO_3 (0.5 eq) in DMF (15 mL) was added 1.5 eq. of bromo acetaldehyde diethylacetal and the resulting mixture was refluxed for a time ranging from 3 to 4 hours. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with acetic acid in water (10 % v/v) and filtered. Evaporation of the solvent followed by purification (chromatography column on silica gel, CH₂Cl₂/MeOH) afforded the corresponding aldehydes.

1,1-diethoxy-2-(thymin-1-yl) acetaldehyde 3a

Yield: 56 %;¹H NMR (300 MHz, CDCl₃) δ (ppm) 1.10 (t, *J*=7.03 Hz, 6H), 1.85 (s, 3H, CH₃), 3.50 (q,*J*=7.03Hz, 2H), 3.65 (q,*J*=7.04Hz, 2H), 3.65 (d, *J*=5.23Hz, 2H), 4.55 (t,*J*=5.25 Hz, 1H), 7.05 (s, 1H), 9.55 (sb, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 12.17, 15.27, 50.83, 64.27, 100.35, 109.89, 142.07, 151.30, 164.62. MS (FAB+), *m*/*z* = 243 [M+H]⁺.HMRS calcd for C11H18N2O4 [M+H]⁺: 243.2716 found 243.2722

1,1-diethoxy-2-(uracil-1-yl) acetaldehyde 3b

Yield: 60%; ¹H NMR(300 MHz, CDCl₃) δ (ppm) 1.10 (t, 6H, *J*=7.02Hz, 2CH₃), 3.50 (q, 2H, *J*=7.03Hz, OCH₂), 3.65 (q, 2H, *J*=7.03Hz, OCH₂), 3.70 (d, 2H, *J*=5.23Hz, N-CH₂), 4.55 (t,1H, *J*=5.25Hz, CH-CH₂), 5.50 (d, 1H, *J*=7.93Hz, H-5), 7.20 (d, 1H, *J*=7.9Hz, H-6), 9.55 (sl, 1H, N3-H). ¹³C NMR(100 MHz, CDCl₃) δ (ppm) 14.07-14.27(2<u>C</u>H₃), 50.09(<u>C</u>H₂-CH), 63.22(2<u>C</u>H₂-CH₃), 99.30 (<u>C</u>H-CH₂), 100.59(C5), 145.09(C6), 150.33(C4), 163.06 (C2). MS (FAB+), *m*/*z* = 229 [M+H]⁺. HMRS calcd for C10H16N2O4 [M+H]⁺: 229.2450 found 229.2458

1,1-diethoxy-2-(azauracil-1-yl) acetaldehyde 3c

Yield: 60%.¹H NMR(300 MHz, CDCl₃) δ (ppm) 1.10(t, 6H, *J*=7.02Hz, 2CH₃), 3.50(q, 2H, *J*=7.02Hz, OCH₂), 3.65(q, 2H, *J*=7.02Hz, OCH₂), 4.00(d, 2H, *J*=5.78Hz, N-CH₂), 4.85(t, 1H, *J*=5.80Hz, CH-CH₂), 7.35(s, 1H, H-5), 9.70 (sl, 1H, N-3H).¹³C NMR(100 MHz, CDCl₃) δ(ppm) 15.17(2<u>C</u>H₃), 41.36(<u>C</u>H₂-CH), 62.00(2<u>C</u>H₂-CH₃), 97.80(<u>C</u>H-

CH₂), 135.36(C5), 149.26(C4), 155.93(C2). MS (FAB+), $m/z = 230 \text{ [M+H]}^+$.HMRS calcd for C9H15N3O4 [M+H]⁺: 230.2331 found 230.2325

1, 1-diethoxy-2-(adenin-9-yl) acetaldehyde 3d

Yield: 60%. ¹H NMR(300 MHz, CDCl₃) δ (ppm) 1.10 (t, 6H, 7.02Hz, 2CH₃), 3.48 (q, 2H, *J*=7.03Hz, OCH₂-CH₃), 3.70 (q, 2H, *J*=7.03Hz, OCH₂-CH₃), 4.20 (d, 2H, *J*=5.22Hz, N-CH₂), 4.65 (t, 1H, J=5.23Hz, CH₂-CH-O), 5.50 (s, 2H, NH₂), 7.80 (s, 1H, H-2), 8.30 (s, 1H, H-8). ¹³C NMR(100 MHz, CDCl₃) δ (ppm) 15.22 (2<u>C</u>H₃), 46.28 (<u>C</u>H₂-CH), 63.96 (2<u>C</u>H₂-CH₃), 100.37 (<u>C</u>H-CH₂), 119.26 (C5), 141.77 (C6), 150.28 (C4), 153.02 (C2), 155.29 (C8). MS (FAB+), *m*/*z* = 252 [M+H]⁺.HMRS calcd for C11H17N5O2 [M+H]⁺: 252.2849 found 252.2858

Catalyst preparation:

Natural phosphate coated with iodine (I₂@NP):

To a solution of iodine (759 mg) in CH_2Cl_2 (5 mL) was added natural phosphate (3 g) and stirred for 15 min and evaporated to dryness.

Natural phosphate coated with ZnBr₂

To a solution of $ZnBr_2$ (25 mg) in water (5 mL) was added natural phosphate (175 mg). The mixture was stirred for 15 min and evaporated to dryness.

Natural phosphate coated with ZnCl₂

To a solution of $ZnCl_2$ (25 mg) in water (5 mL) was added natural phosphate (175 mg). The mixture was stirred for 15 min and evaporated to dryness.

Natural phosphate coated with CF₃SO₃H

To a solution of CF_3SO_3H (1 mL) in methylene chloride (5 mL) was added natural phosphate (3 g). The mixture was stirred for 15 min and evaporated to dryness.

Natural phosphate coated with SnCl₄

A mixture of 1g of $SnCl_4$ (0.45 mL) in 5 mL water was stirred for 5 minutes, and then 1g of natural phosphate was added. The mixture was stirred for 15 min and evaporated to dryness.

General Procedure for the Synthesis of α -amino, aminoacid phosphonate acyclonucleosides

To a suspension of the desired acetal (0.41 mmol) in acetonitrile (8 mL), was added 400mg of NP/HCl and water (2 mL) and the mixture was heated (80°C) for 2h. After filtration, the solid residue was washed by CH₃CN and the filtrate was evaporated to yield the corresponding aldehyde **4(a-d)** quantitatively. To the crude aldehyde was added acetonitrile (5 mL), 1 equivalent of the amine/aminoacid, triethylphosphite (0.9 eq, 0.06 mL), and 0.2 equivalent of natural doped phosphate (I₂@NP, 104 mg; (ZnCl₂@NP, 92mg; ZnBr₂@NP, 160 mg; CF₃SO₃H @NP, 40 mg; Zn(OTf)₂@NP, 280mg; SnCl₄@NP,44 mg). The mixture was refluxed for 3 h and the resulting suspension was filtered and washed with acetonitrile. The filtrate was then evaporated and the residue was dissolved in CH₂Cl₂, washed with a solution of Na₂S₂O₃ (1M) and the organic phase was dried over Na₂SO₄. After filtration and evaporation, the crude product was purified by silica gel chromatography (eluent: CH₂Cl₂/MeOH).

N¹ (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) uracil 5a

Yield: 77%. ¹H NMR(400MHz, CDCl₃) δ (ppm) 1.10 (t, 3H, *J*=7.02Hz, CH₃), 1.20 (t, 3H, *J*=7.02Hz, CH₃), 3.80-4,10 (m, 4H, 2 OCH₂-CH₃), 4.18 (m, 2H, N1-CH₂-CH), 4.40 (m, 1H, CH-CH₂); 4.60 (s, 1H, NH-Ph), 5.50 (d, 1H, *J* = 7.87Hz, H5), 6.50-7.00 (m, 5H, Ph), 7.05 (d, 1H, *J* = 7.87Hz ,H6), 10.10 (s, 1H, N3-H).¹³CNMR(100MHz, CDCl₃) δ (ppm) 15(2CH₃), 48.91(CH₂-CH), 61.80-63.12(2CH₂-CH₃), 100.69 (CH-CH₂), 112.28 (C5), 128.41-144(Ph), 145.23 (C6), 150.39(C4) 163.24(C2). MS (FAB+), *m/z* = 368 [M+H]⁺. HMRS calcd for C16H22N3O5P [M+H]⁺: 368.3367 found 368.3375

N¹ (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) thymine 5b

Yield: 45% ¹H NMR(400 MHz, CDCl₃) δ (ppm) 1.10 (t, 3H, CH₃), 1.20 (t, 3H, *J*=7.03 Hz, CH₃), 1.70 (s, 3H, CH₃), 3.80-4,10 (m, 4H, 2 OCH₂-CH₃), 4.20 (m, 2H, N1-CH₂-CH), 4.40 (m, 1H, CH-CH₂); 4.60 (s, 1H,NH- Ph), 6.50-7.00 (m, 5H, Ph), 7.05 (s, 1H, H6), 9.80 (s, 1H, N3-H). ¹³CNMR(100MHz, CDCl₃) δ (ppm) 12.11 (CH₃); 16.35 (2CH₃), 48.91 (CH₂-CH), 62.74(CH₂-CH₃), 63.99(CH₂-CH₃), 100.01(CH-CH₂), 113.35 (C5),129.32-141(Ph), 146.43 (C6), 151.46 (C4), 164.56(C2).MS (FAB+), *m*/*z* = 382 [M+H]⁺.HMRS calcd for C17H24N3O5P [M+H]⁺: 382.3633 found 382.3640

General Procedure for the Synthesis of α -amino, aminoacid phosphonate acyclonucleosides

To a suspension of the desired acetal (0.41 mmol) in acetonitrile (8 mL), was added 400mg of NP/HCl and water (2 mL) and the mixture was heated (80°C) for 2h. After

filtration, the solid residue was washed by CH₃CN and the filtrate was evaporated to yield the corresponding aldehyde quantitatively. To the crude aldehyde was added acetonitrile (5 mL), 1 equivalent of the amine/aminoacid, triethylphosphite (0.9 eq, 0.06 mL), and 0.2 equivalent of natural doped phosphate(NP/I₂, 104 mg)The mixture was refluxed for 3h and the resulting suspension was filtered and washed with acetonitrile. The filtrate was then evaporated and the residue was dissolved in CH₂Cl₂, washed with a solution of Na₂S₂O₃ (1M) and the organic phase was dried over Na₂SO₄. After filtration and evaporation, the crude product was purified by silica gel chromatography (eluent: CH₂Cl₂/MeOH).

N¹ (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) uracil 5a

Yield: 77%. ¹H NMR(400MHz, CDCl₃) δ (ppm) 1.10 (t, 3H, *J*=7.02Hz, CH₃), 1.20 (t, 3H, *J*=7.02Hz, CH₃), 3.80-4,10 (m, 4H, 2 OCH₂-CH₃), 4.18 (m, 2H, N1-CH₂-CH), 4.40 (m, 1H, CH-CH₂); 4.60 (s, 1H, NH-Ph), 5.50 (d, 1H, *J* = 7.87Hz, H5), 6.50-7.00 (m, 5H, Ph), 7.05 (d, 1H, *J* = 7.87Hz ,H6), 10.10 (s, 1H, N3-H).¹³CNMR(100MHz, CDCl₃) δ (ppm) 15(2CH₃), 48.91(CH₂-CH), 61.80-63.12(2CH₂-CH₃), 100.69 (CH-CH₂), 112.28 (C5), 128.41-144(Ph), 145.23 (C6), 150.39(C4) 163.24(C2). MS (FAB+), *m/z* = 368 [M+H]⁺.HMRS calcd for C16H22N3O5P [M+H]⁺: 368.3367 found 368.3375

N¹ (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) thymine 5b

Yield: 45% ¹H NMR(400 MHz, CDCl₃) δ (ppm) 1.10 (t, 3H, CH₃), 1.20 (t, 3H, *J*=7.03 Hz, CH₃), 1.70 (s, 3H, CH₃), 3.80-4,10 (m, 4H, 2 OCH₂-CH₃), 4.20 (m, 2H, N1-CH₂-CH), 4.40 (m, 1H, CH-CH₂); 4.60 (s, 1H,NH- Ph), 6.50-7.00 (m, 5H, Ph), 7.05 (s, 1H, H6), 9.80 (s, 1H, N3-H). ¹³CNMR(100MHz, CDCl₃) δ (ppm) 12.11 (CH₃); 16.35 (2CH₃), 48.91 (CH₂-CH), 62.74(CH₂-CH₃), 63.99(CH₂-CH₃), 100.01(CH-CH₂), 113.35 (C5),129.32-141(Ph), 146.43 (C6), 151.46 (C4), 164.56(C2).MS (FAB+), *m/z* = 382 [M+H]⁺.HMRS calcd for C17H24N3O5P [M+H]⁺: 382.3633 found 382.3640

N¹ (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) azauracil 5c

Yield: 40%.¹H NMR(400MHz, CDCl₃) δ (ppm) 1.10 (t,3H, CH₃), 1.22(t, 3H, *J*=7.02Hz, CH₃), 3.90-4.10 (m, 4H, 2 OCH₂-CH₃), 4.15 (m, 2H, N1-CH₂-CH), 4.40 (m, 1H, CH-CH₂), 4.50 (s, 1H, NH-Ph), 7.20 (s, 1H, H5), 6.50-7,10 (m, 5H, Ph), 10.60 (s, 1H,N3-H).¹³CNMR(100MHz, CDCl₃) δ (ppm) 14.38(2CH₃), 38.22(CH₂-CH), 60.83(CH₂-CH₃), 62.00 (CH₂-CH₃);111.45(CH-CH₂), 113.37 (C5), 127.27-144.53 (Ph), 147.59 (C4),

154.57(C2). MS (FAB+), $m/z = 369 [M+H]^+$.HMRS calcd for C15H21N4O5P $[M+H]^+$: 369.3248 found 369.3239

N⁹ (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) adenine 5d

Yield: $40\%^{1}$ H NMR(400 MHz, CDCl₃) δ (ppm) 1.10 (t,3H, *J*=7.06Hz, CH₃); 1.20 (t, 3H, CH₃), 3.90-4.10 (m, 4H, 2 OCH₂-CH₃), 4.30 (m, 2H, N9-CH₂-CH), 4.40 (m, 1H, CH-CH₂), 4.60 (s, 1H, NH-Ph), 5.60 (s, 2H, NH₂), 6.40-7.05 (m, 5H, Ph), 7.75 (s,1H,H2), 8.35 (s,1H,H8).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 16.34 (2CH₃), 44.66(CH₂-CH), 62.83-63.96 (2CH₂-CH₃), 113.52 (CH-CH₂), 119.52(C5),129.22-140 (Ph),141.34 (C6), 150.28 (C4), 153.02 (C2), 155.35(C8). MS (FAB+), *m*/*z* = 391 [M+H]⁺.HMRS calcd for C17H23N6O3P [M+H]⁺: 391.3766 found 391.3773

N¹ (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) uracil 6a

Yield: 50%. ¹H NMR(400 MHz, CDCl₃) δ (ppm) 1.20 (t, 3H, *J*=7.02Hz, CH₃), 1.30 (t, 3H, CH₃), 3.20 (m,1H,Ha),3.5 (m, 1H, Hb), 3.80-3.90 (m, 2H, N1-CH₂-CH), 4.20 (m, 4H, 2 OCH₂-CH₃), 4.25 (m, 1H, CH-CH₂), 4.30 (s, 1H, N-H-CH₂-Ph), 5.60 (d, 1H, *J* = 7.87 Hz, H5), 6.50-7.00 (m, 5H, ph), 7.20 (d, 1H, *J* = 7.87, H6), 9.20 (s, 1H, N3-H).¹³CNMR(100 MHz, CDCl₃) δ (ppm): 16.6(2CH₃), 49.72(CH₂-CH), 52.55(CH₂-Ph), 62.61-62.77(2CH₂-CH₃), 101.11 (CH-CH₂), 127.52 (C5),128-139 (Ph), 145.25 (C6), 150.83 (C4), 163.96(C2). MS(ES+), *m*/*z* = 382 [M+H]⁺.HMRS calcd for C17H24N3O5P [M+H]⁺: 382.3633 found 382.3640

N¹ (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) thymine6b

Yield: 60%. ¹H NMR(400 MHz, CDCl₃) δ (ppm) 1.20 (t, 3H, *J*=7.03 Hz, CH₃), 1.30 (t, 3H, *J*=7.03 Hz, CH₃), 1.80 (s, 3H, CH₃), 3.10 (m, 1H, Ha), 3.50 (m, 1H, Hb), 3.80-3.90 (m, 2H, N1-CH₂-CH), 4.00- 4.10 (m, 4 H, 2 OCH₂-CH₃), 4.10 (m, 1H, CH-CH₂), 4.25 (s, 1H, NH-Ph), 7.05 (s, 1H, H6), 7.20 (m, 5H, Ph), 9.80 (s, 1H,N3-H).¹³CNMR(100 MHz, CDCl₃) δ (ppm): 12.19 (CH₃); 16.44(2CH₃), 48.02(CH₂-CH), 52.31(CH₂-Ph), 62.57(CH₂-CH₃), 62.77 (CH₂-CH₃), 109 (CH-CH₂), 127 (C5), 141.9 (C6), 128-139 (Ph), 151.1 (C4), 164.64(C2).MS(ES+), *m*/*z* = 396 [M+H]⁺.HMRS calcd for C18H26N3O5P [M+H]⁺: 396.3899 found 396.3906

N^1 (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) azauracil 6c

Yield: 60%.¹H NMR(400 MHz, CDCl₃) δ (ppm) 1.30 (t,3H, *J*=7.02Hz, CH₃), 1.40 (t, 3H, *J*=7.02Hz, CH₃), 3.40 (m, 1H, Ha), 3.80 (m, 1H, Hb), 3.90-4,10 (m, 2H, N1-CH₂-

CH), 4.30 (m, 4H, 2 OCH₂-CH₃), 4.50 (m, 1H, CH-CH₂), 4.55 (s, 1H,NH-CH₂- Ph), 7.20 (s, 1H, H5), 7.40 (m, 5H, Ph), 10.60 (s, 1H,N3-H).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 16.60 (2CH₃), 39.80(CH₂-CH), 51.77(CH₂-Ph),62.51(CH₂-CH₃), 62.72(CH₂-CH₃), 127.23(CH-CH₂), 135.14 (C5), 128-135 (Ph), 149.48(C4), 156.26 (C2). MS(ES+), m/z = 383 [M+H]⁺.HMRS calcd for C16H23N4O5P [M+H]⁺: 383.3513 found 383.3506

N⁹ (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) adenine 6d

Yield: 62%.¹H NMR(400 MHz, CDCl₃) δ (ppm) 1.20 (t,3H, *J*=7.06Hz, CH₃), 1.30 (t, 3H, *J*=7.06Hz, CH₃), 3.30 (m, 1H, Ha), 3.90 (m,1H, Hb), 3.70- 3,90 (m, 2H, N9-CH₂-CH), 4.00 (m, 1H, CH-CH₂), 4.20 (m, 4H, 2 OCH₂-CH₃), 4.25 (s,1H,NH-CH₂-Ph), 5.90 (s, 2H, NH₂), 7.30 (m, 5H, Ph), 7.90 (s,1H,H2), 8.35 (s,1H, H8).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 16.44 (2CH₃), 44.11(CH₂-CH), 62.74-62.83(2CH₂-CH₃), 119.26 (CH-CH₂), 52.18(CH₂-Ph), 127.19 (C5), 128-138 (Ph), 141.86 (C6), 150.16(C4), 152.75 (C2), 155.28 (C8). MS(ES+), *m*/*z* = 405 [M+H]⁺.HMRS calcd for C18H25N6O3P [M+H]⁺: 405.4032 found 405.4040

N¹ (2-butylamino-2-diethoxyphosphinyl-éthan-1-yl) uracil 7a

Yield: 66%. ¹H NMR(400 MHz, CDCl₃) δ (ppm) 0.80 (t,3H,CH₃-CH₂), 1.20 (m, 6H, 2CH₃-CH₂), 1.30 (q,2H,CH₂-CH₃), 1.40 (m,2H,CH₂-CH₂-CH₃), 2.60-2,80 (m, 2H, NH-CH₂), 3.00 -3,60 (m, 2H, Ha and Hb), 4.10 (m, 1H, CH-CH₂), 4.25 (m, 4H, 2 OCH₂-CH₃), 4.30 (m, 1H, N-H), 5.60 (d, 1H, *J*= 7,87Hz, H5), 7.30 (d, 1H, *J*= 7,87Hz , H6), 9.00 (s, 1H,N3-H).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 13.87 (CH₃-CH₂), 16.45(CH₃), 16.50(CH₃), 20.08 (CH₂-CH₃), 28.92(CH₂-CH₂-CH₃), 48.82 (CH₂-CH₂-CH₂-CH₃), 49.84(CH₂-CH), 62.47-62,88(2CH₂-CH₃), 100.92 (CH-CH₂), 128.81 (C5), 146.48 (C6), 150.92 (C4), 163.91 (C2). MS(ES+), m/z = 348 [M+H]⁺.HMRS calcd for C14H26N3O5P [M+H]⁺: 348.3471 found 348.3480

N¹ (2-butylamino-2-diethoxyphosphinyl-ethan-1-yl) thymine 7b

Yield: 60%. ¹H NMR(400 MHz, CDCl₃) δ (ppm) 0.80 (t,3H, CH₃-CH₂), 1.30 (t, 6H,2 CH₃-CH₂), 1.80 (s, 3H, CH₃), 1.35 (m, 2H,CH₂-CH₃), 1.40 (m,2H,CH₂-CH₂-CH₃), 2.90 (m,2H,NH-CH₂), 3.10 (m, 2H, Ha and Hb), 3.90-4.10 (m, 6H, 2 OCH₂-CH₃,CH-CH₂ and N-H), 7.20 (s, 1H, H6), 8.70 (s, 1H,N3-H).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 12,19 (CH₃), 13.87 (CH₃-CH₂),16.45(CH₃), 16.50(CH₃), 20.08 (CH₂-CH₃),

28.92(CH₂-CH₂-CH₃), 48.82 (CH₂CH₂-CH₂-CH₃), 49.84(CH₂-CH), 62.47-62.88(2CH₂-CH₃), 100.92(CH-CH₂), 128.81 (C5), 146.48 (C6), 150.92 (C4), 163.91 (C2). MS(ES+), m/z = 362 [M+H]⁺.HMRS calcd for C15H28N3O5P [M+H]⁺: 362.3736 found 362.3742

N¹ (2-butylamino-2-diethoxyphosphinyl-ethan-1-yl) azauracil 7c

Yield: 47%.¹H NMR(400 MHz, CDCl₃) δ (ppm): 0.80 (t,3H,CH₃), 1.20 (m,6H, 2CH₃-CH₂), 1.30 (q, 2H,CH₂-CH₃), 1.40 (m,2H,CH₂-CH₂-CH₃), 2.50-2.80 (m,2H,NH-CH₂), 3.40 (m, 2H, Ha and Hb), 4.00-4.30 (m, 6H, 2 OCH₂, CH-CH₂, N-H), 7.30 (s, 1H, H5), 10.60 (s, 1H,N3-H).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 13.87(CH₃-CH₂), 16.49-16,54 (2CH₃), 48(CH₂-CH), 20.01 (CH₂-CH₃), 32.35 (CH₂-CH₂-CH₃), 39.69(CH₂-CH₂-CH₂-CH₂-CH₃), 62.22(CH₂-CH₃), 62.67(CH₂-CH₃), 100(CH-CH₂), 135,06 (C5), 149.51 (C4), 156.42 (C2) . MS(ES+), m/z = 349 [M+H]⁺.HMRS calcd for C13H25N4O5P [M+H]⁺: 349.3351 found 349.3360

N⁹ (2-butylamino-2-diethoxyphosphinyl-ethan-1-yl) adenine 7d

Yield: 50%. ¹H NMR(400 MHz, CDCl₃) δ (ppm) 0.80 (t,3H,CH₃), 1.20 (m,6H, 2 CH₃-CH₂), 1.20-1,40 (q, 2H,CH₂-CH₃), 1.40-1,50 (m,2H,CH₂-CH₂-CH₃), 2.50-2.70 (m,2H,NH-CH₂), 3.10 (m, 2H, Ha and Hb), 4.10 (m,4H, 2OCH₂-CH₃), 4.25 (m, 1H, N-H), 4.30 (m,1H,CH-CH₂), 6.10 (s,2H, NH₂), 8.10 (s, 1H, H2), 8.30 (s,1H, H8).¹³CNMR(100 MHz, CDCl₃) δ (ppm) 13.53 (CH₃-CH₂), 16.44 (2CH₃),20.04 (CH₂-CH₃), 29.35 (CH₂-CH₂-CH₃), 40.02 (CH₂-CH₂-CH₂-CH₃)44.17(CH₂-CH), 63.02(2CH₂-CH₃), 118.99 (CH-CH₂), 120 (C5), 142.31 (C6), 150.08 (C4), 152.7 (C2), 155.2 (C8). MS(ES+), m/z = 371 [M+H]⁺.HMRS calcd for C15H27N6O3P [M+H]⁺: 371.3870 found 371.3865

N¹(2-glycinoethylester-2 diethoxyphosphinyl-ethan-1-yl) uracil 8a

Yield: 60%. ¹H NMR(400 MHz,CDCl₃) δ (ppm) 1.13 (t, 3H,*J*=7.13Hz,CH₃), 1.30(t,6H,*J*=7.06Hz,2CH₃), 3.25(t,1H,*J*=4.6Hz,CH), 3.50-3.60(m,2H,CH₂), 3.70(d, 2H,*J*=4.6Hz,CH₂), 4.10(m,7H,3CH₂, NH), 5.60(d,1H,*J*=7.9Hz,H-5), 7.20 (d, 1H, *J*= 7.9 Hz, H-6), 9.55 (sd, 1H, NH).¹³C NMR(100 MHz,CDCl₃) δ (ppm) 14.15(CH₃), 16.45 (CH₃), 16.49 (CH₃), 49.40 (CH), 52.98 (CH₂), 54.45 (CH₂), 60.90 (CH₂), 62.77 (CH₂), 62.73 (CH₂), 101.39(C5), 146.06(C6),151.35 (C4), 164.11 (C2), 173.63 (CO, ester). MS(ES+), m/z =378 [M+H]⁺.HMRS calcd for C14H24N3O7P [M+H]⁺: 378.3300 found 378.3310

N¹(2-glycinoethylester-2-diethoxyphosphinyl-ethan-1-yl)thymine 8b

Yield: 50%. ¹H NMR(400 MHz,CDCl₃) δ (ppm) 1.15 (t, 3H,*J*=7.15Hz,CH₃), 1.30(t, 6H,*J*=7.05Hz,2CH₃), 1.80 (s, 3H,CH₃), 3.25(t, 1H,*J*=4.5Hz,CH), 3.50-3.60(m,2H,CH₂), 3.70(d, 2H,*J*=4.5Hz, CH₂), 4.10(m,7H,3CH₂, NH), 7.10(s,1H,H-6), 9.20 (sd, 1H, NH).¹³C NMR(100 MHz,CDCl₃) δ (ppm) 14.15(CH₃), 16.45 (CH₃), 16.67 (CH₃), 44.70 (CH₂), 44.80 (CH₂), 54.46 (CH₂), 56.48 (CH₂), 61.81 (CH₂), 64.27 (CH), 119.82(C5), 143.71(C6),151.28(C4), 153.63(C2), 157.11(C8), 173.19(CO, ester). MS(ES+), *m/z* =392 [M+H]⁺. HMRS calcd for C15H26N3O7P [M+H]⁺: 392.3566 found 392.3574

N¹(2-glycinoethylester-2-diethoxyphosphinyl-ethan-1-yl)6-Azauracil 8c

Yield: 50%. ¹H NMR(400 MHz,CDCl₃) δ (ppm) 1.15 (t, 3H,*J*=7.13Hz,CH₃), 1.30(t, 6H,*J*=7.06Hz,2CH₃), 3.25(t, 1H,*J*=3.6Hz,CH), 3.50-3.60(dd,2H,*J*=3.6Hz,CH₂), 4.00-4.20(m,9H,4CH₂, NH), 7.20(s,1H,H-5), 10.50 (sd, 1H, NH). ¹³C NMR(100 MHz,CDCl₃) δ (ppm) 14.15(CH₃), 16.53 (CH₃), 16.48 (CH₃), 39.50 (CH), 49.01 (CH₂), 52.02 (CH₂), 54.07 (CH₂), 60.72 (CH₂), 62.70 (CH₂), 135.00(C5), 150.09(C4),156.97(C2), 172.65 (CO, ester). MS(ES+), *m*/*z* =379 [M+H]⁺.HMRS calcd for C13H23N4O7P [M+H]⁺: 379.3181 found 379.3175

N⁹(2-glycinoethylester-2-diethoxyphosphinyl-ethan-1-yl)adenine 8d

Yield: 55%. ¹H NMR(400 MHz,CD₃OD) δ (ppm) 1.20 (t, 3H, *J*=7.15Hz, CH₃), 1.30(t, 6H, *J*=7.05Hz, 2CH₃), 3.20(t,1H,*J*=4.5Hz,CH), 3.30(d,2H,*J*=4.5Hz,CH₂), 3.70(m,2H,CH₂), 4.00 (q, 2H,*J*=7.15Hz, CH₂), 4.35(q,4H,*J*=7.05Hz,2CH₂), 8.20 (s, 2H, H-2, H-8).¹³C NMR(100 MHz,CD₃OD) δ (ppm): 9.31(CH₃), 14.46 (CH₃), 16.67 (CH₃), 44.70 (CH₂), 44.80 (CH₂), 54.46 (CH₂), 56.48 (CH₂), 61.81 (CH₂), 64.27 (CH), 119.82(C5), 143.71(C6),151.28(C4), 153.63(C2), 157.11(C8),173.19 (CO, ester). MS(ES+), *m*/*z* =401 [M+H]⁺.HMRS calcd for C15H25N6O5P [M+H]⁺: 401.3700 found 401.3710

N¹(2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) uracil 9a

Yield: 50%. ¹H NMR(400 MHz,CDCl₃) δ (ppm) 1.11 (d, 3H,*J*=7.13Hz,CH₃), 1.16(m, 9H,3CH₃), 3.25 (t, 1H,*J*=4.6Hz,CH), 3.50-3.60(q,1H,*J*=7.13Hz,CH), 3.70(d, 2H,*J*=4.6Hz, CH₂), 4.01(m,5H,2CH₂, NH),5.60(d,1H,*J*=7.9Hz, H-5), 7.20(d,1H,*J*=7.9Hz, H-6), 9.55(sd, 1H, NH). ¹³C NMR(100 MHz,CDCl₃) δ (ppm) 16.42 (CH₃), 18.71 (CH₃), 19.06 (CH₃), 46.41 (CH₂), 49.30 (CH), 50.70 (CH₃), 51.90 (CH), 62.60 (CH₂), 62.70 (CH₂), 101.30(C5), 146.10(C6),151.10(C4), 164.40(C2), 174.70

(CO, ester). MS(ES+), $m/z = 392[M+H]^+$.HMRS calcd for C15H26N3O7P $[M+H]^+$ 392.3566 found 392.3572

N¹ (2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) Thymine 9b

Yield: 55%. ¹H NMR(400 MHz,CDCl₃) δ (ppm) 1,00 (d, 3H,*J*=7.10Hz,CH₃), 1.30(m, 12H,4CH₃) 3.25(t, 1H,*J*=4.60 Hz,CH), 3.50-3.60(q,1H,*J*=7.10Hz,CH), 3.70(d, 2H,*J*=4.6Hz, CH₂), 4.01(m,5H, 2CH₂, NH), 7.10(s,1H,H-6), 9.60 (sd, 1H, NH). ¹³C NMR(100 MHz,CDCl₃) δ (ppm)11.00 (CH₃), 16.60 (CH₃), 18.80 (CH₃), 19.20 (CH₃), 49.10 (CH₂), 49.60 (CH), 50.90 (CH₃), 52.09 (CH), 55.30 (CH₂), 62.70 (CH₂), 109.20(C5), 141.90(C6), 151.30(C4), 164.90(C2), 174.80 (CO, ester). MS(ES+), *m/z* = 406[M+H]⁺.HMRS calcd for C16H28N3O7P [M+H]⁺: 406.3832 found 406.3842

N¹ (2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) 6azauracil 9c

Yield: 52%. ¹H NMR(400 MHz,CDCl₃) δ (ppm) 1,00 (d, 3H,*J*=7,10Hz,CH₃), 1,30(m, 9H,3CH₃) 3,25(t, 1H,*J*=4,6Hz,CH), 3,50-3,60(q,1H,*J*=7,10Hz,CH), 3,70(d, 2H,*J*=4,60Hz, CH₂), 4,01 (m,5H, 2CH₂, NH),7,20(s,H-5), 9,60 (sd, 1H, NH).¹³C NMR(100 MHz,CDCl₃) δ (ppm)16,42 (CH₃), 19,06 (CH₃), 19,32 (CH₃), 46,00 (CH₂), 50,50 (CH),51,80 (CH₃), 54,13 (CH), 62,60 (CH₂), 63,70 (CH₂), 135,00(C5), 150,20(C4), 157,10(C2), 176,50 (CO, ester). MS(ES+), *m*/*z* = 393[M+H]⁺. HMRS calcd for C14H25N4O7P [M+H]⁺: 393.3447 found 393.3440

N⁹ (2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) adenine 9d

Yield: 55%. ¹H NMR(400 MHz,CD₃OD) δ (ppm) 1.00 (d, 3H,*J*=7.13Hz, CH₃), 1.40-1.60 (m, 9H, 3CH₃), 3.10 (t, 1H, *J*=4.5Hz,CH), 3.50-3.70 (q, 1H,*J*=7.13Hz, CH), 4.01(d, 2H,*J*=4.50 Hz, CH₂), 4.35 (m, 5H, 2CH₂, NH), 8.20 (s, 2H, H-2, H-8). ¹³C NMR(100 MHz,CD₃OD) δ (ppm)10.00 (CH₃), 16.74 (CH₃), 19.18 (CH₃), 45.01 (CH₂), 48.00 (CH₂), 52.23 (CH₃), 53.07 (CH), 56.17(CH) 119.82 (C5), 143.75 (C6), 151.08 (C4), 153.70 (C2), 157.17 (C8), 176.24 (CO, ester). MS(ES+), *m/z* = 415[M+H]⁺.HMRS calcd for C16H27N6O5P [M+H]⁺. 415.3965 found 415.3975

Deprotection of α -amino, and α -aminoacids phosphonates acyclonucleosides

General Procedure

To a suspension of α -aminophosphonate acyclonucleosides **5-9** (0.15 mmol) in acetonitrile (5 mL) was added TMSBr (10 eq), and the resulting mixture was stirred overnight at room temperature. After evaporation of the solvent, water (5 mL) was

added and the resulting suspension was neutralized with an 28% ammonia solution. The water was then removed in vaccuo and the residue was purified with on preparative plate (eluent: isopropanol/NH₄OH/H₂O) and reverse phase HPLC (C18). The final product was obtained after a cation exchange chromatographie on a Na⁺ DOWEX50WX2. The residue obtained is dried, the purity of products was controlled by HPLC (eluent: CH₃CN/H₂O, 50/50 v / v).

N¹ (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) uracil 10a

Yield: 64%. ¹H NMR (400 MHz, D₂O) δ (ppm) 3.60 (m, 1H, Ha), 3.85 (m, 1H, Hb), 4.35 (m, 1H, CH- CH₂), 5.50 (d, 1H, *J*= 7.87 Hz, H5), 6.50-7.00 (m, 5H, Ph), 7.45 (d, 1H, *J*=7,87 Hz,H6). ¹³C NMR (100 MHz, D₂O) δ (ppm) 51.6(CH₂-CH), 100.69(CH-CH₂), 112.48 (C5), 129-144 (Ph), 148.23(C6), 152.73 (C4), 167.24(C2). MS(ES+), *m/z* = 312 [M+H]⁺.HMRS calcd for C12H14N3O5P [M+H]⁺: 312.2304 found 312.2312

N¹ (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) thymine 10b

Yield: 60%. ¹H NMR (400MHz, D₂O) δ (ppm) 1.50 (s, 3H, CH₃), 3.70 (m, 1H, Ha), 4.20 (m, 1H, Hb), 4.35 (m, 1H, CH-CH₂), 6.50-7.00 (m, 5H, Ph), 7.30 (s, 1H, H6). ¹³C NMR (100MHz, D₂O) δ (ppm) 12.11 (CH₃), 51.53 (CH₂-CH), 110.01 (CH-CH₂), 113.42 (C5), 129.32-141.00 (Ph), 143.95 (C6), 152 (C4), 164.56 (C2). MS (ES+), *m/z* = 326 [M+H]⁺. HMRS calcd for C13H16N3O5P [M+H]⁺: 326.2570 found 326.2580

N¹ (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) azauracil 10c

Yield: 50%. ¹H NMR (400 MHz, D₂O) δ (ppm) 4.05 (m, 1H, CH-CH₂), 4.20 (m, 1H, Ha), 4.40 (m, 1H, Hb), 7.15 (s, 1H, H5), 6.50-7.00 (m, 5H, Ph).¹³C NMR (100 MHz, D₂O) δ (ppm) 42.24(CH₂-CH), 113.17(CH-CH₂), 129.39-141 (Ph), 135.05 (C5), 150.42 (C4), 158.24 (C2). MS(ES+), m/z = 313 [M+H]⁺.HMRS calcd for C11H13N4O5P [M+H]⁺: 313.2184 found 313.2178

N⁹ (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) adenine 10d

Yield: 70%. ¹H NMR (400MHz, D₂O) δ (ppm) 4.35 (m, 1H, Ha), 4.50 (m, 1H, Hb), 4.90 (m, 1H, CH-CH₂), 6.30-7,10 (m, 5H, Ph), 7.75 (s, 1H, H2), 8.35 (s, 1H, H8). ¹³C NMR (100 MHz, D₂O) δ (ppm) 46.48 (CH₂-CH), 112.49 (CH-CH₂), 117.30 (C5), 128.40-144 (Ph), 142.88 (C6), 149.06 (C4), 151.79 (C2), 154.92 (C8). MS (ES+), *m/z* = 363 [M+H]⁺. HMRS calcd for C13H15N8O3P [M+H]⁺. 363.2837 found 363.2845

N¹ (2-benzylamino-2- dihydroxyphosphinyl -ethan-1-yl) uracil 11a

Yield: 60%.¹H NMR(400 MHz, D₂O), δ (ppm) 3.20 (m, 1H, Ha), 3.90 (m, 1H, Hb), 4.00 (m, 2H, N1-CH₂-CH), 4.30 (m, 1H, CH-CH₂), 5.60 (d, 1H, *J*=7,87, H5), 7.30 (m, 5H, Ph), 7.45 (d, 1H, *J*=7.87, H6). ¹³C NMR (100MHz, D₂O) δ (ppm) 48.81(CH₂-CH), 51.60(CH₂-Ph), 102.12(CH-CH₂), 129.29 (C5), 129 -131.11 (Ph), 146.84 (C6), 153 (C4), 166.45(C2). MS(ES+), *m*/*z* =326 [M+H]⁺.HMRS calcd for C13H16N3O5P [M+H]⁺: 326.25.70 found 326.2564

N¹ (2-benzylamino-2-dihydroxyphosphinyl-ethan-1-yl) thymine 11b

Yield: 35%. ¹H NMR (400 MHz, D₂O) δ (ppm) 1.70 (s, 3H, CH₃), 3.30 (m, 1H, Ha), 3.90 (m, 1H, Hb), 4.10- 4,30 (m, 2H, N1-CH₂-CH), 4.50 (m, 1H, CH-CH₂), 7.40 (m, 5H, Ph), 7.20 (s, 1H, H6). ¹³C NMR (100 MHz, D₂O) δ (ppm) 11.19 (CH₃), 48.50 (CH₂-CH), 111.39 (CH-CH₂), 127 (C5), 129-130 (Ph), 142.22 (C6), 153.14 (C4), 166.64 (C2). MS (ES+), m/z = 340 [M+H]⁺. HMRS calcd for C14H18N3O5P [M+H]⁺: 340.2835 found 340.2841

N¹ (2-benzylamino-2- dihydroxyphosphinyl -ethan-1-yl) azauracil 11c

Yield: 35%. ¹H NMR (400MHz, D₂O) δ (ppm) 3.40 (m,1H,Ha), 4.10 (m, 1H, Hb), 4.20 (m, 2H, N1-CH₂-CH), 4.50 (m, 1H, CH-CH₂), 7.30 (s, 1H, H5), 7.40 (m, 5H, Ph). ¹³C NMR (100MHz, D₂O) δ (ppm) 39.63 (CH₂-CH), 50.13 (CH₂-Ph), 128.21 (CH-CH₂), 129-131 (Ph), 135.51 (C5), 150.59 (C4), 157.93 (C2). MS(ES+), *m*/*z* =327 [M+H]⁺.HMRS calcd for C12H15N4O5P [M+H]⁺. 327.2450 found 327.2457

N⁹ (2-benzylamino-2- dihydroxyphosphinyl -éthan-1-yl) adenine 11d

Yield: 24%. ¹H NMR (400 MHz, D₂O) δ (ppm): 3.30 (m, 1H, Ha), 3.90 (m, 1H, Hb), 4.00-4.30 (m, 2H, N9-CH₂-CH), 4.60 (m, 1H, CH-CH₂), 7.00 (m, 5H, Ph), 7.90 (s, 1H, H2), 7.95 (s, 1H, H8). ¹³C NMR (100MHz, D₂O) δ (ppm) 44.11 (CH₂-CH), 52.18 (CH₂-Ph), 119.26 (CH-CH₂), 127.15 (C5), 128-130 (Ph), 141.86 (C6), 150.16 (C4), 152.75 (C2), 155.28 (C8). MS(ES+), m/z = 349 [M+H]⁺.HMRS calcd for C14H17N6O3P [M+H]⁺: 349.2969 found 349.2977

N¹ (2-butylamino-2-dihydroxyphosphinyl-éthan-1-yl) uracil 12a

Yield: 25%. ¹H NMR (400MHz, D₂O), δ (ppm) 0.80 (t, 3H, CH₃-CH₂), 1.20 (q, 2H, CH₂-CH₃), 1.50 (m, 2H, CH₂-CH₂-CH₃), 3.10 (m, 2H, CH₂-(CH₂)₂-CH₃), 3.40-4,10 (m, 2H, N1-CH₂), 4.30 (m, 1H, CH-CH₂), 5.60 (d, 1H, J = 7.87Hz, H5), 7.30 (d, 1H, J = 7.87Hz, H6). ¹³C NMR (100MHz, D₂O) δ (ppm) 12.74 (CH₃-CH₂), 19.04 (CH₂-CH₃),

28.03 (CH₂-CH₂-CH₃), 46.42 (CH₂-CH₂-CH₂-CH₃), 47.90 (CH₂-CH), 102.05 (CH-CH₂), 128.81 (C5), 147.21 (C6), 153,21 (C4), 166.72 (C2) .MS (ES+), m/z = 292 [M+H]⁺. HMRS calcd for C10H18N3O5P [M+H]⁺: 292.2407 found 292.2415

N¹ (2-butylamino-2-dihydroxyphosphinyl-éthan-1-yl) azauracil 12c

Yield: 20%. ¹H NMR (400MHz, D₂O) δ (ppm) 0.80 (t, 3H, CH₃), 1.20 (q, 2H, CH₂-CH₃), 1.50 (m, 2H, CH₂-CH₃-CH₃), 3.10 (m, 2H, CH₂-(CH₂)₂-CH₃), 3.70 (m, 1H, CH-CH₂), 4.30 (m, 2H, N1-CH₂), 7.50 (s, 1H, H5). ¹³C NMR (100MHz, D₂O) δ (ppm) 12.75 (CH₃-CH₂), 19.04 (CH₂-CH₃), 28.03 (CH₂-CH₂-CH₃), 46.42 (CH₂-CH₂-CH₂-CH₂-CH₃), 47.90 (CH₂-CH), 100 (CHCH₂), 135.06 (C5), 147.21 (C4); 153.21 (C2). MS (ES+), m/z = 293 [M+H]⁺. HMRS calcd for C9H17N4O5P [M+H]⁺ 293.2288 found 293.2295

N¹(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) uracil 13a

Yield: 40%. ¹H NMR(400MHz, D₂O) δ (ppm) 1.15 (t, 3H, *J*=7.10Hz, CH₃),3.25 (t, 1H, *J*=3.50Hz, CH),3.70 (m, 2H, CH₂), 3.80 (d, 2H, *J*=3.5Hz, CH₂), 4.10 (q, 4H, *J*=7.10Hz, 2CH₂), 5.70 (d, 2H, *J*=7.9Hz,1H, H-5), 7.60 (d, 2H , *J*=7.90Hz, 1H, H-6). ¹³CNMR (100MHz, D₂O) δ (ppm) 16.45 (CH₃),49.40 (CH), 54.79 (CH₂), 56.50 (CH₂), 57.39 (CH₂), 101.37 (C5), 147.18 (C6), 152.20 (C4), 166.67 (C2), 171.42 (CO, ester). MS (ES+), *m*/*z* = 322 [M+H]⁺.HMRS calcd for C10H16N3O7P [M+H]⁺: 322.2237 found 322.2246

N¹(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) Thymine 13b

Yield: 20%. ¹HNMR (400MHz, D₂O) δ (ppm) 1.15 (t, 3H, *J*=7.10Hz, CH₃), 1.70 (s, 3H, CH₃), 3.25(t, 1H, *J*=3.50Hz, CH),3.70 (m, 2H, CH₂), 3.80(d, 1H,*J*=3.25Hz,CH₂), 4.10(q, 4H, *J*=7.10Hz,2CH₂), 7.60(s,1H,H-6).¹³CNMR(100 MHz,D₂O) δ (ppm) 13.20 (CH₃), 16.45 (CH₃), 49.40 (CH), 54.79 (CH₂), 56.50 (CH₂), 57.39 (CH₂), 101.37(C5), 147.18 (C6),152.20(C4), 166.67(C2), 171.42 (CO,ester). MS(ES+), *m*/*z* =336 [M+H]⁺.HMRS calcd for C11H18N3O7P [M+H]⁺: 336.2502 found 336.2512

N¹(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) azauracil 13c

Yield: 20%. ¹H NMR(400MHz, D₂O) δ(ppm) 1.15 (t, 3H, *J*=7.10Hz, CH₃),3.25 (t, 1H, *J*=3.5Hz, CH), 3.70 (m, 2H, CH₂), 3.80 (d, 2H, *J*=3.5Hz, CH₂), 4.10 (q, 4H, *J*=7.10Hz, 2CH₂), 7.50 (s, 1H, H-5). ¹³CNMR (100MHz, D₂O) δ (ppm) 13.16 (CH₃), 39.50 (CH), 49.01 (CH₂), 52.02 (CH₂), 62.57 (CH₂), 135.55 (C5), 150.77 (C4), 158.23 (C2), 172.65

(CO, ester). MS(ES+), $m/z = 323[M+H]^+$.HMRS calcd for C9H15N4O7P $[M+H]^+$: 323.2117 found 323.212.

N⁹(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) adenine 13d

Yield: 20%. ¹H NMR(400 MHz, D₂O) δ (ppm) 1.00 (t, 3H,*J*=7.13Hz,CH₃), 3.20(t, 1H,*J*=3.6Hz,CH), 3.40(m,2H,CH₂), 3.70(d, 2H, *J*=3.6Hz,CH₂), 4.20(q,2H,*J*=7.13Hz,CH₂), 8.10 (s, 2H, H-2, H-8). ¹³C NMR (100MHz D₂O) δ (ppm) 12.99 (CH₃), 44.80 (CH₂), 54.46 (CH₂), 56.48 (CH₂), 62.71 (CH), 119.82 (C5), 143.71 (C6),152.28(C4), 153.63 (C2), 157.11 (C8), 173.19 (CO, ester). MS(ES+), *m*/*z* = 345 [M+H]⁺.HMRS calcd for C11H17N6O5P [M+H]⁺: 345.2636 found 345.2628

N¹(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) uracil 14a

Yield: 35%. ¹H NMR(400 MHz, D₂O) δ (ppm) 1.15 (d, 3H,*J*=7.10Hz,CH₃), 2.75(t, 1H,*J*=4.6Hz,CH), 3.40(q,1H,*J*=7.10Hz,CH),3.60(s,3H,CH₃), 4.00(d,2H,*J*=4.6Hz,CH₂), 5.65(d,*J*=7.90 Hz,1H,H-5), 7.50(d,*J*=7.90 Hz,1H,H-6).¹³CNMR (100MHz, D₂O) δ (ppm) 17.84 (CH₃), 48.84 (CH), 52.7 (CH), 55.03 (CH₃), 58.49 (CH₂), 101(C5), 147.07(C6), 158.50(C4), 174.64 (C2), 181.70 (CO, ester). MS(ES+), *m*/z = 326[M+H]⁺. ³¹PNMR (75 MHz, D₂O) δ (ppm) 14.93, 16.22. HMRS calcd for C11H18N3O7P [M+H]⁺: 326.2502 found 326.2509

N¹(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) thymine 14b

Yield: 25%. ¹HNMR(400 MHz, D₂O) δ (ppm) 1.15 (d, 3H,*J*=7.10Hz,CH₃), 1.80(s,3H,CH₃) 2.75(t, 1H,*J*=4.60 Hz,CH), 3.40(q,1H,*J*=7.10Hz,CH), 3.60(s,3H,CH₃), 4.00(d,2H,*J*=4.6Hz,CH₂), 7.44(s,1H,H-6).¹³C NMR (100MHz, D₂O) δ (ppm)13.20 (CH₃), 17.83 (CH₃), 48.84 (CH), 52.62 (CH), 53.54 (CH₃), 58.54 (CH₂), 101.55 (C5), 147.06 (C6),158.50(C4), 174.60(C2), 181.65 (CO, ester). MS(ES+), *m*/*z* = 350 (M+H+). ³¹PNMR (75 MHz, D₂O) δ (ppm): 14.09, 16.06. HMRS calcd for C12H20N3O7P [M+H]⁺: 350.2768 found 350.2774

N¹(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) azauracil 14c

Yield: 30%. ¹H NMR (400 MHz, D₂O) δ (ppm) 1.19(d, 3H,*J*=7.13Hz,CH₃), 3.30(t,1H,*J*=4.4Hz,CH), 3.40(q,1H,*J*=7.13Hz,CH), 3.60(s,3H,CH₃), 4.00(d,2H,*J*=4.40 Hz,CH₂), 7.50(s,1H,H-5).¹³CNMR (100MHz, D₂O) δ (ppm) 13.20 (CH₃), 39.85 (CH), 47.30 (CH), 53.79 (CH₃), 62.63 (CH₂), 135.59(C5), 150.78(C4), 158.31(C2), 181.60

(CO,ester). MS(ES+), m/z = 337 (M+H+). ³¹PNMR (75 MHz, D₂O) δ (ppm) 14.34, 16.25. HMRS calcd for C10H17N4O7P [M+H]⁺: 337.2383 found 337.2376

N⁹(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) adenine 14d

Yield: 15%. ¹H NMR (400 MHz, D₂O) δ (ppm) 1.19(d, 3H,*J*=7.10Hz,CH₃), 3.30(t,1H,*J*=4.5Hz,CH), 3.40(q,1H,*J*=7.10Hz,CH), 3.60(s,3H,CH₃), 4.00(d,2H,*J*=4.50 Hz,CH₂), 8,00 (s, 2H, H-8, H-2). ¹³CNMR (100MHz, D₂O) δ (ppm) 13.20 (CH₃), 39.85 (CH), 47.30 (CH), 53.79 (CH₃), 62.63 (CH₂), 119.82 (C5), 143.71 (C6), 152.28 (C4), 153.63 (C2), 157.11 (C8), 173.19 (CO, ester). MS(ES+), m/z = 359 (M+H+). ³¹PNMR (75 Mhz, D₂O) δ (ppm) 15.06, 15.90. HMRS calcd for C12H19N6O5P [M+H]⁺: 359.2902 found 359.2912

Molecular docking

In silico computational docking studies were performed using AutoDock4.2 [54]. TheX-ray crystallographic structures of HCV NS3 protease and HIV reverse transcriptase weredownloaded from the RCSB Protein Data Bank (PDB) 1W3C [51] and 2RF2 [52], respectively. The proteins were prepared separately by removing water and co-crystallized ligands bound with the proteins to make receptor free of any ligand before docking. Then, Polar hydrogens and Gastieger charges were added using the MGL Tools and proteins saved in PDBQT format [55]. Ligand 14a was created separately using ChemDraw Ultra 12.0, energy minimized in Chem3D, torsional bonds of ligand were set flexible and saved in PDBQT format. Next, the receptor was kept rigid, the gridcovering all the amino acid residues present inside the active site of proteins was built for 1W3C(grid box size of 40Å X46Å X 52Å with a spacing of 0.375Å between the grid points and centered at 66.685 (x), 18.626 (y), and 0.736 (z)) and for 2RF2(grid box size of 50Å X 40Å X56Å with a spacing of 0.375Å between the grid points and centered at 7.845 (x), 13.204 (y), and 15.671 (z)). The best conformers were searched by theLamarckian genetic algorithm (LGA), the population size was set to 150and maximum number of energy evaluation was set to 250,000,00. Finally,the results were analyzed and visualized by the discovery studio.

Acknowledgements

This project was supported by the comité mixte inter-universitaire Franco-Marocain programme (A.I. $N^{\circ} = Ma/06/143$) and by Centre National de Recherche Scientifique et

Technique project RS/2011/01 (Rabat, Morocco). The authors would like to thank Professor J. Balzarini (Rega Institute for Medical Research, Katholieke University Leuven, Leuven, Belgium) for his scientific contribution and help on the realization of this work. Also, we would like to acknowledge the technical staff of the CAC (Centre of Analysis and Characterization) University Cadi Ayyad Marrakech for running the spectroscopic analysis.

References

[1] G. Zhang, G. Hao, J. Pan, J. Zhang, D. Hu, B.J.J.o.a. Song, f. chemistry, Asymmetric synthesis and bioselective activities of α -amino-phosphonates based on the dufulin motif, 64 (2016) 4207-4213

[2] N. Azizi, F. Rajabi, M.R. Saidi, A mild and highly efficient protocol for the one-pot synthesis of primary α -amino phosphonates under solvent-free conditions, Tetrahedron Letters, 45 (2004) 9233-9236

[3] J. Oleksyszyn, J.C. Powers, Amino acid and peptide phosphonate derivatives as specific inhibitors of serine peptidases, in: Methods in Enzymology, Academic Press, 1994, pp. 423-441.

[4] J.-L. Chen, W. Tang, J.-Y. Che, K. Chen, G. Yan, Y.-C. Gu, D.-Q. Shi, Synthesis and Biological Activity Evaluation of Novel α -Amino Phosphonate Derivatives Containing a Pyrimidinyl Moiety as Potential Herbicidal Agents, Journal of Agricultural and Food Chemistry, 63 (2015) 7219-7229

[5] J.-y. Che, X.-y. Xu, Z.-l. Tang, Y.-c. Gu, D.-q. Shi, Synthesis and herbicidal activity evaluation of novel α -amino phosphonate derivatives containing a uracil moiety, Bioorganic & Medicinal Chemistry Letters, 26 (2016) 1310-1313

[6] E. De Clercq, Antiviral agents active against influenza A viruses, Nature Reviews Drug Discovery, 5 (2006) 1015-1025

[7] E. De Clercq, A 40-Year Journey in Search of Selective Antiviral Chemotherapy*, Annual Review of Pharmacology and Toxicology, 51 (2011) 1-24

[8] W.A. Lee, J.C. Martin, Perspectives on the development of acyclic nucleotide analogs as antiviral drugs, Antiviral Res, 71 (2006) 254-259

[9] A. Holy, Antiviral acyclic nucleoside phosphonates structure activity studies, Antiviral Res, 71 (2006) 248-253

[10] Y. Kabbaj, H.B. Lazrek, J.L. Barascut, J.L. Imbach, Synthesis and biological activity of some unsaturated 6-azauracil acyclonucleosides, Nucleos. Nucleot. Nucl, 24 (2005) 161-172

[11] N. Redwane, H.B. Lazrek, J.L. Barascut, J.L. Imbach, J. Balzarini, M. Witvrouw,E. De Clerq, Synthesis and biological activities of (Z) and (E) alpha-ethenyl acyclonucleosides, Nucleos. Nucleot. Nucl, 20 (2001) 1439-1447

[12] H. Elayadi, M. Smietana, C. Pannecouque, P. Leyssen, J. Neyts, J.J. Vasseur, H.B. Lazrek, Straightforward synthesis of triazoloacyclonucleotide phosphonates as potential HCV inhibitors, Bioorg. Med. Chem. Lett, 20 (2010) 7365-7368

[13] R. Grzywa, A.M. Sokol, M. Sienczyk, M. Radziszewicz, B. Kosciolek, M.P. Carty, J. Oleksyszyn, New aromatic monoesters of alpha-aminoaralkylphosphonic acids as inhibitors of aminopeptidase N/CD13, Bioorg. Med. Chem, 18 (2010) 2930-2936

[14] M. Sienczyk, J. Oleksyszyn, Irreversible Inhibition of Serine Proteases - Design and In Vivo Activity of Diaryl alpha-Aminophosphonate Derivatives, Curr. Med. Chem, 16 (2009) 1673-1687

[15] P.P. Giannousis, P.A. Bartlett, Phosphorus Amino-Acid-Analogs as Inhibitors of Leucine Aminopeptidase, J. Med. Chem, 30 (1987) 1603-1609

[16] F.R. Atherton, C.H. Hassall, R.W. Lambert, Synthesis and Structure-Activity-Relationships of Antibacterial Phosphonopeptides Incorporating (1-Aminoethyl)Phosphonic Acid and (Aminomethyl)Phosphonic Acid, J. Med. Chem, 29 (1986) 29-40

[17] M.C. Allen, W. Fuhrer, B. Tuck, R. Wade, J.M. Wood, Renin Inhibitors -Synthesis of Transition-State Analog Inhibitors Containing Phosphorus-Acid Derivatives at the Scissile Bond, J. Med. Chem, 32 (1989) 1652-1661

[18] W.W. Smith, P.A. Bartlett, Macrocyclic inhibitors of penicillopepsin. 3. Design, synthesis, and evaluation of an inhibitor bridged between P2 and P1 ', J. Am. Chem. Soc, 120 (1998) 4622-4628

[19]P. Kafarski, M. G. vel Górniak, I. Andrasiak, Kabachnik-Fields Reaction UnderGreen Conditions – A Critical Overview, Current Green Chemistry, 2 (2015) 218-222

[20]R. A. Cherkasov, V. I. Galkin, The Kabachnik–Fields reaction: synthetic potential and the problem of the mechanism Russian, Chemical Reviews 67 (1998) 857 - 882

[21] A. Heydari, A. Javidan, M. Schaffie, Lithium perchlorate/diethyl ether catalyzed one-pot synthesis of alpha-hydrazinophosphonates from aldehydes by a three-component reaction, Tetrahedron Lett, 42 (2001) 8071-8073

[22] M.R. Saidi, N. Azizi, A new protocol for a one-pot synthesis of alpha-amino phosphonates by reaction of imines prepared in situ with trialkylphosphites, Synlett, (2002) 1347-1349

[23] C.T. Qian, T.S. Huang, One-pot synthesis of alpha-amino phosphonates from aldehydes using lanthanide triflate as a catalyst, J. Org. Chem, 63 (1998) 4125-4128

[24] K. Manabe, S. Kobayashi, Facile synthesis of alpha-amino phosphonates in water using a Lewis acid-surfactant-combined catalyst, Chem. Commun,8 (2000) 669-670

[25] S. Chandrasekhar, S.J. Prakash, V. Jagadeshwar, C. Narsihmulu, Three component coupling catalyzed by TaCl5-SiO2: synthesis of alpha-amino phosphonates, Tetrahedron Lett, 42 (2001) 5561-5563

[26] R. Ghosh, S. Maiti, A. Chakraborty, D.K. Maiti, In(OTf)(3) catalysed simple onepot synthesis of alpha-amino phosphonates, J. Mol. Catal. A-Chem, 210 (2004) 53-57

[27] N. Azizi, F. Rajabi, M.R. Saidi, A mild and highly efficient protocol for the onepot synthesis of primary alpha-amino phosphonates under solvent-free conditions, Tetrahedron Lett, 45 (2004) 9233-9236

[28] Ambica, S. Kumar, S.C. Taneja, M.S. Hundal, K.K. Kapoor, One-pot synthesis of alpha-aminophosphonates catalyzed by antimony trichloride adsorbed on alumina, Tetrahedron Lett, 49 (2008) 2208-2212

[29] J. Wu, W. Sun, H.G. Xia, X.Y. Sun, A facile and highly efficient route to alphaamino phosphonates via three-component reactions catalyzed by Mg(ClO4)(2) or molecular iodine, Org. Biomol. Chem, 4 (2006) 1663-1666

[30] A. Elmakssoudi, M. Zahouily, A. Mezdar, A. Rayadh, S. Sebti, Na2CaP2O7 a new catalyst for the synthesis of alpha-amino phosphonates under solvent-free conditions at room temperature, CR Chim, 8 (2005) 1954-1959

[31] M.Zahouily, A.Elmakssoudi, A.Mezdar, A.Rayadh, S.Sebti, Natural phosphate and potassium fluoride doped natural phosphate catalysed simple one-pot synthesis of - amino phosphonates under solvent-free conditions at room temperature, Catal. Commun, 8(2007), 225-230

[32] C.B. Reddy, K.S. Kumar, M.A. Kumar, M.V.N. Reddy, B.S. Krishna, M. Naveen, M.K. Arunasree, C.S. Reddy, C.N. Raju, C.D. Reddy, PEG-SO3H catalyzed synthesis and cytotoxicity of alpha-aminophosphonates, Eur. J. Med. Chem, 47 (2011) 553-559

[33] G. Keglevich, E. Bálint, The Kabachnik–Fields Reaction: Mechanism and Synthetic Use, Molecules, 17(2012) 12821–12835

[34] J.P. Genet, J. Uziel, M. Port, A.M. Touzin, S. Roland, S. Thorimbert, S. Tanier, Apractical synthesis of α -aminophosphonic acids. Tetrahedron Lett. 33 (1992) 77-80

[35] Y. Essamlali, M. Larzek, B. Essaid, M. Zahouily, Natural Phosphate Supported Titania as a Novel Solid Acid Catalyst for Oleic Acid Esterification, Industrial & Engineering Chemistry Research, 56 (2017) 5821-5832

[36] F. Bazi, H. El Badaoui, S. Tamani, S. Sokori, L. Oubella, M. Hamza, S. Boulaajaj,
S. Sebti, Catalysis by phosphates: A simple and efficient procedure for transesterification reaction, Journal of Molecular Catalysis A: Chemical, 256 (2006) 43-47

[37] S. Sebti, M. Zahouily, Ha. B. Lazrek, J. A. Mayoral, D. J. Macquarrie, Phosphates: New Generation of Liquid-Phase Heterogeneous, Catalysts in Organic ChemistryCurrent Organic Chemistry, 3 (2008)203-232

[38]B. Liu and S. J. Ji, Facile Synthesis of 2-Amino-1,4-naphthoquinones catalyzed by Molecular Iodine under Ultrasonic Irradiation,Synth. Commun, 38 (2008) 1201-1211

[39]. Y. M. Ren, C. Cai, A green procedure for the protection of carbonyl compounds catalyzed by iodine in ionic liquidTetrahedron Lett, 49(2008) 7110-7112

[40] H. S. Wang, J. E. Zeng, Iodine Catalyzed One-pot Synthesis of 3,4Dihydroquinazolin-4-ones from Anthranilic Acids, Ortho Esters and Amines under Solvent-free ConditionsChin. J. Chem, 26(2008) 175-178

[41]M. Zahouily, A. Mezdar, J. Rakik, A. Elmakssoudi, A. Rayadh, S.Sebti, Amild and efficient method for the protection of carbonyl compounds asithioacetals, dithiolanes and dithianes catalysed by iodinesupported on naturalphosphate, Journal of Molecular Catalysis A: Chemical 233 (2005) 43–47
[42] M. Quibell, W. G.Tumell, T. d. Johnson, Synthesis of azapeptidesby the Fmoc/tert-

butyl/polyamide technique, Chem. SocPerkin Trans. 1 (1993) 2843-2849

[43]F. Velázquez, S. Venkatraman, W. Wu, M. Blackman, A. Prongay, V. Girijavallabhan, N.-Y. Shih, F.G. Njoroge, Application of Ring-Closing Metathesis for the Synthesis of Macrocyclic Peptidomimetics as Inhibitors of HCV NS3 Protease, Organic Letters, 9 (2007) 3061-3064

[44] M. Skoreński, M. Pachota, K. Pyrć, M. Sieńczyk, J. Oleksyszyn, Novel peptidyl αaminoalkylphosphonates as inhibitors of hepatitis C virus NS3/4A protease, Antiviral Research, 144 (2017) 286-298

[45] X.C. Sheng, H.-J. Pyun, K. Chaudhary, J. Wang, E. Doerffler, M. Fleury, D. McMurtrie, X. Chen, W.E. Delaney, C.U. Kim, Discovery of novel phosphonate derivatives as hepatitis C virus NS3 protease inhibitors, Bioorganic & Medicinal Chemistry Letters, 19 (2009) 3453-3457

[46] H.-J. Pyun, K. Chaudhary, J.R. Somoza, X.C. Sheng, C.U. Kim, Synthesis and resolution of diethyl (1S,2S)-1-amino-2-vinylcyclopropane-1-phosphonate for HCV NS3 protease inhibitors, Tetrahedron Letters, 50 (2009) 3833-3835

[47] N.J. Liverton, Evolution of HCV NS3/4a Protease Inhibitors, in: M.J. Sofia (Ed.) HCV: The Journey from Discovery to a Cure: Volume I, Springer International Publishing, Cham, 31 (2019) 231-259

(48)Y. Yang, D. Kang, L.A. Nguyen, Z.B. Smithline, C. Pannecouque, P. Zhan, X. Liu, T.A. Steitz, Structural basis for potent and broad inhibition of HIV-1 RT by thiophene[3,2-d]pyrimidine non-nucleoside inhibitors, eLife, 7 (2018) e36340

[49]C.C.P. Costa, N. Boechat, M.M. Bastos, F.d.C. da Silva, A. Marttorelli, T.M.L. Souza, M.S. Baptista, L.V.B. Hoelz, E.R. Cafffarena, New Efavirenz Derivatives and 1,2,3-Triazolyl-phosphonates as Inhibitors of Reverse Transcriptase of HIV-1, Current Topics in Medicinal Chemistry, 18 (2018) 1494-1505

[50]R.L. Mackman, A.S. Ray, H.C. Hui, L. Zhang, G. Birkus, C.G. Boojamra, M.C. Desai, J.L. Douglas, Y. Gao, D. Grant, G. Laflamme, K.-Y. Lin, D.Y. Markevitch, R. Mishra, M. McDermott, R. Pakdaman, O.V. Petrakovsky, J.E. Vela, T. Cihlar, Discovery of GS-9131: Design, synthesis and optimization of amidate prodrugs of the novel nucleoside phosphonate HIV reverse transcriptase (RT) inhibitor GS-9148, Bioorganic & Medicinal Chemistry, 18 (2010) 3606-3617

[51] J.M.Ontoria, S.Di Marco, I.Conte, M.E.Di Francesco, C.Gardelli, U.Koch, V.G.Matassa, M.Poma, C.Steinkuhler, C.Volpari, S.Harper, The Design and Enzyme-Bound Crystal Structure of Indoline Based Peptidomimetic Inhibitors of Hepatitis C Virus Ns3 Protease, J Med Chem 47(2004) 6443

[52] Z.Zhao, S.E. Wolkenberg, M. Lu, V. Munshi, G. Moyer, M. Feng, A.V. Carella, L.T. Ecto, L.J. Gabryelski, M.T. Lai, S.G. Prasad, Y. Yan, G.B. McGaughey, M.D. Miller, C.W. Lindsley, G.D. Hartman, J.P. Vacca, T.M. Williams, Novel indole-3sulfonamides as potent HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) Bioorg Med Chem Lett 18 (2008)554-559

[53] H.-Y. Wei, C.-S. Lu, T.-H. Lin, Exploring the P2 and P3 ligand binding features for Hepatitis C virus NS3 protease using some 3D QSAR techniques, Journal of Molecular Graphics and Modelling, 26 (2008) 1131-1144

[54] G. M.Morris, R.Huey, W.Lindstrom, M. F.Sanner, R. K.Belew, D. S.Goodsell, A. J.Olson, AutoDock4 and AutoDockTools4: Automated Docking withSelective Receptor Flexibility. J. Comput. Chem, 30 (2009) 2785–2791.

[55]A.-E. El Mansouri, M. Maatallah, H. Ait Benhassou, A. Moumen, A. Mehdi, R. Snoeck, G. Andrei, M. Zahouily, H.B. Lazrek, Design, synthesis, chemical characterization, biological evaluation, and docking study of new 1,3,4-oxadiazole homonucleoside analogs, Nucleosides, Nucleotides & Nucleic Acids, (2020) 1-20