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**Efficient one-pot, three components procedure to prepare new  $\alpha$ -amino phosphonate and phosphonic acid acyclic nucleosides**

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## **Efficient one-pot, three components procedure to prepare new $\alpha$ -amino phosphonate and phosphonic acid acyclic nucleosides**

An efficient one-pot three-component Kabachnik-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  $\alpha$ -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;  $\alpha$ -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,  $\alpha$ -aminophosphonates have attracted the attention of medicinal chemists due to their potential antiviral activity [1]. The  $\alpha$ -aminophosphonates are structurally similar to  $\alpha$ -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  $\alpha$ -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  $\alpha$ -aminophosphonates [19, 20]. While early procedures were limited to simple starting

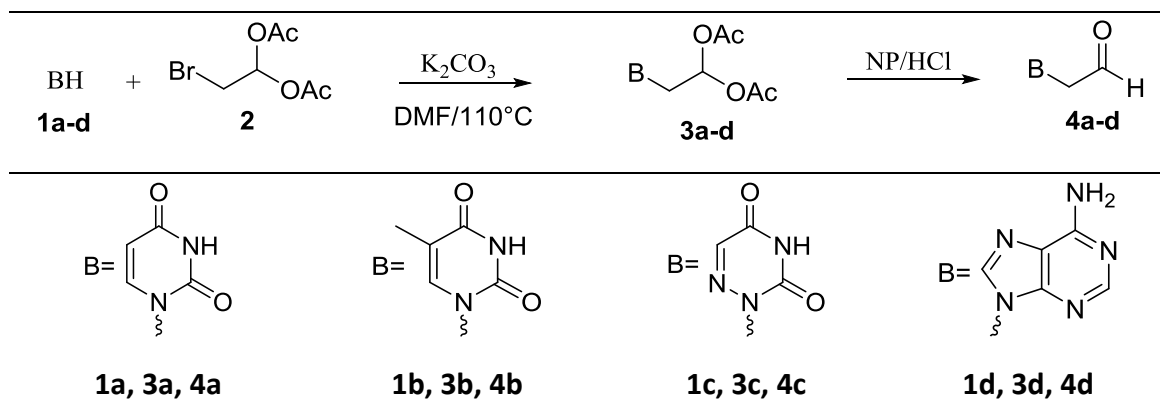
materials and newer wide-scope syntheses catalysed by Lewis acids, have been reported [21-27]. Recently, several solids catalysts have been used in the preparation of  $\alpha$ -aminophosphonates such as  $\text{SbCl}_3/\text{Al}_2\text{O}_3$  (28),  $\text{Mg}(\text{ClO}_4)_2$ [29],  $\text{Na}_2\text{CaP}_2\text{O}_7$ [30], KF doped natural phosphate (NP) [31], and PEG- $\text{SO}_3\text{H}$  [32]. In general, these three-component reactions may take place via an imine or an  $\alpha$ -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  $\alpha$ -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  $\alpha$ -aminophosphonates using a catalytic amount of  $\text{I}_2@\text{NP}$  as a catalyst. A simple protocol was followed in the preparation of novel  $\alpha$ -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- $\alpha$ -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].

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  $\text{I}_2$ @NP in refluxing acetonitrile which yielded  $\alpha$ -aminophosphonate **5a** in 77 % yields (Table 2, entry 4).

Table 2: Optimal conditions for the preparation of amino phosphonates **5a**

Entry	Catalyst	Yield (%) <sup>a</sup>
1	---	20
2	NP	0
3	$\text{I}_2$	30
4	$\text{I}_2$ @NP	77
5	$\text{ZnCl}_2$ @NP	65
6	$\text{ZnBr}_2$ @NP	40
7	$\text{CF}_3\text{SO}_3\text{H}$ @NP	25
8	$\text{Zn}(\text{OTf})_2$ @NP	51
9	$\text{SnCl}_4$ @NP	38

<sup>a</sup> 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  $\alpha$ -amino phosphonates obtained **5-9(a-d)** were further treated with TMSBr in DMF to yield the corresponding  $\alpha$ -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- $\alpha$ -amino acids phosphonates and pave the way for the design of new potential bioactive compounds through a simple and eco-friendly transformation.

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

Entry	B	R	Phosphonate, Yield (% <sup>a</sup> )	Phosphonic, Yield (% <sup>a</sup> )
1	U	Ph	<b>5a</b> , 77	<b>10a</b> , 60
2	T	Ph	<b>5b</b> , 45	<b>10b</b> , 60
3	6-AzaU	Ph	<b>5c</b> , 40	<b>10c</b> , 50
4	A	Ph	<b>5d</b> , 40	<b>10d</b> , 70
5	U	Ph-CH <sub>2</sub>	<b>6a</b> , 50	<b>11a</b> , 60
6	T	Ph-CH <sub>2</sub>	<b>6b</b> , 60	<b>11b</b> , 35
7	6-AzaU	Ph-CH <sub>2</sub>	<b>6c</b> , 60	<b>11c</b> , 35
8	A	Ph-CH <sub>2</sub>	<b>6d</b> , 62	<b>11d</b> , 25
9	U	CH <sub>3</sub> -CH-CH <sub>2</sub> -CH <sub>3</sub>	<b>7a</b> , 66	<b>12a</b> , 25
10	T	CH <sub>3</sub> -CH-CH <sub>2</sub> -CH <sub>3</sub>	<b>7b</b> , 60	--- <sup>b</sup>
11	6-AzaU	CH <sub>3</sub> -CH-CH <sub>2</sub> -CH <sub>3</sub>	<b>7c</b> , 50	<b>12c</b> , 20
12	A	CH <sub>3</sub> -CH-CH <sub>2</sub> -CH <sub>3</sub>	<b>7d</b> , 50	--- <sup>b</sup>
13	U	CH <sub>2</sub> -CO <sub>2</sub> Et	<b>8a</b> , 55	<b>13a</b> , 40
14	T	CH <sub>2</sub> -CO <sub>2</sub> Et	<b>8b</b> , 60	<b>13b</b> , 20
15	6-AzaU	CH <sub>2</sub> -CO <sub>2</sub> Et	<b>8c</b> , 50	<b>13c</b> , 20
16	A	CH <sub>2</sub> -CO <sub>2</sub> Et	<b>8d</b> , 55	<b>13d</b> , 20
17	U	CH <sub>3</sub> -CH-CO <sub>2</sub> Me	<b>9a</b> , 40	<b>14a</b> , 35
18	T	CH <sub>3</sub> -CH-CO <sub>2</sub> Me	<b>9b</b> , 40	<b>14b</b> , 25

19	6-AzaU	CH <sub>3</sub> -CH-CO <sub>2</sub> Me	<b>9c</b> , 41	<b>14c</b> , 30
20	A	CH <sub>3</sub> -CH-CO <sub>2</sub> Me	<b>9d</b> , 42	<b>14d</b> , 15

<sup>a</sup> Isolated yield after gel chromatography purification. <sup>b</sup> A mixture undefined compounds

Next, we evaluated the antiviral activity of these new phosphonic acids in an HCV sub-genomic 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.

Table 5: Detail of binding interactions

Protein	Ligand	Energy of binding (Kcal/mol)	RMSD (Å)
1W3C	DN1	-8.79	2.37
	<b>14a</b>	-3.55	----
2RF2	MRX	-10.55	0.27
	<b>14a</b>	-6.63	----

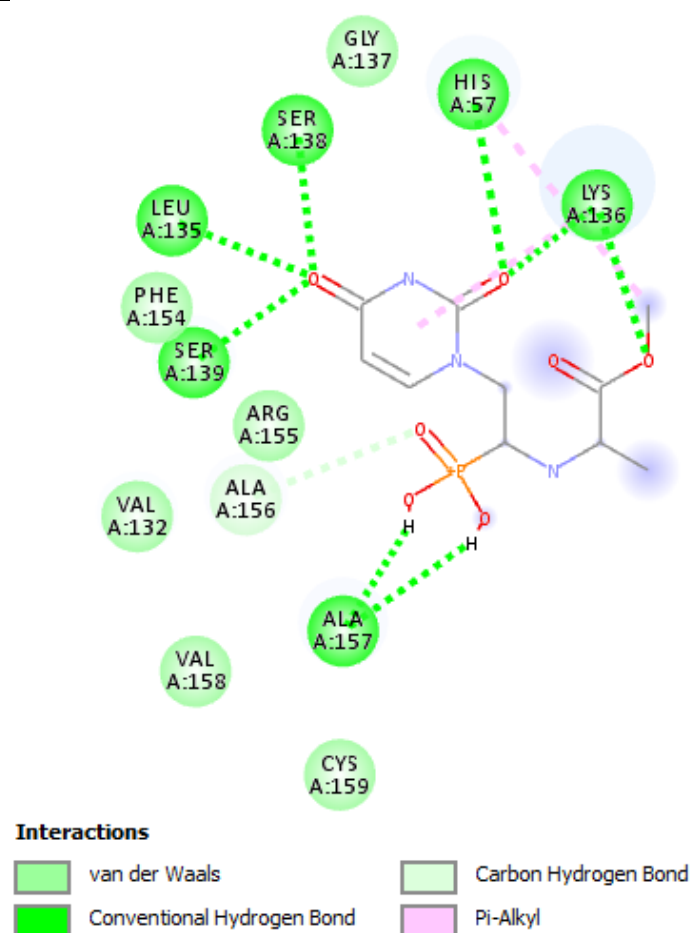


Figure 1: 2D interactions of compound **14a** in the binding sites of HCV NS3 protease



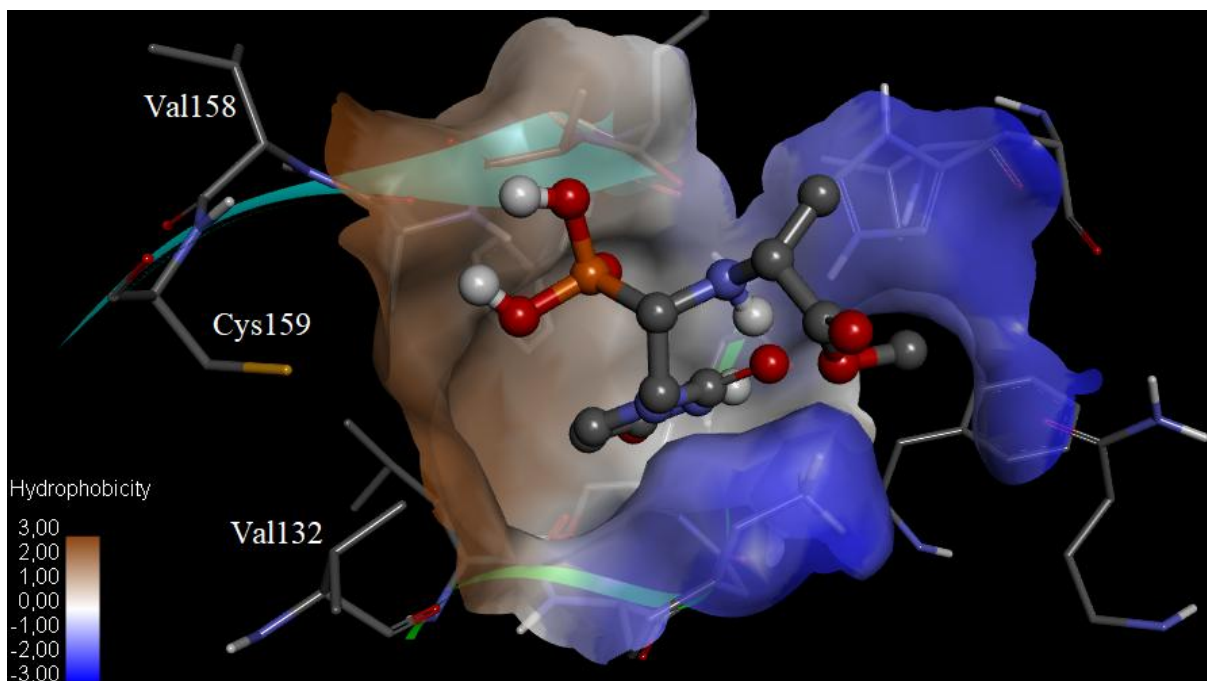


Figure 2: The position of ligand **14a** in the hydrophobic cavity of HCV NS3 protease

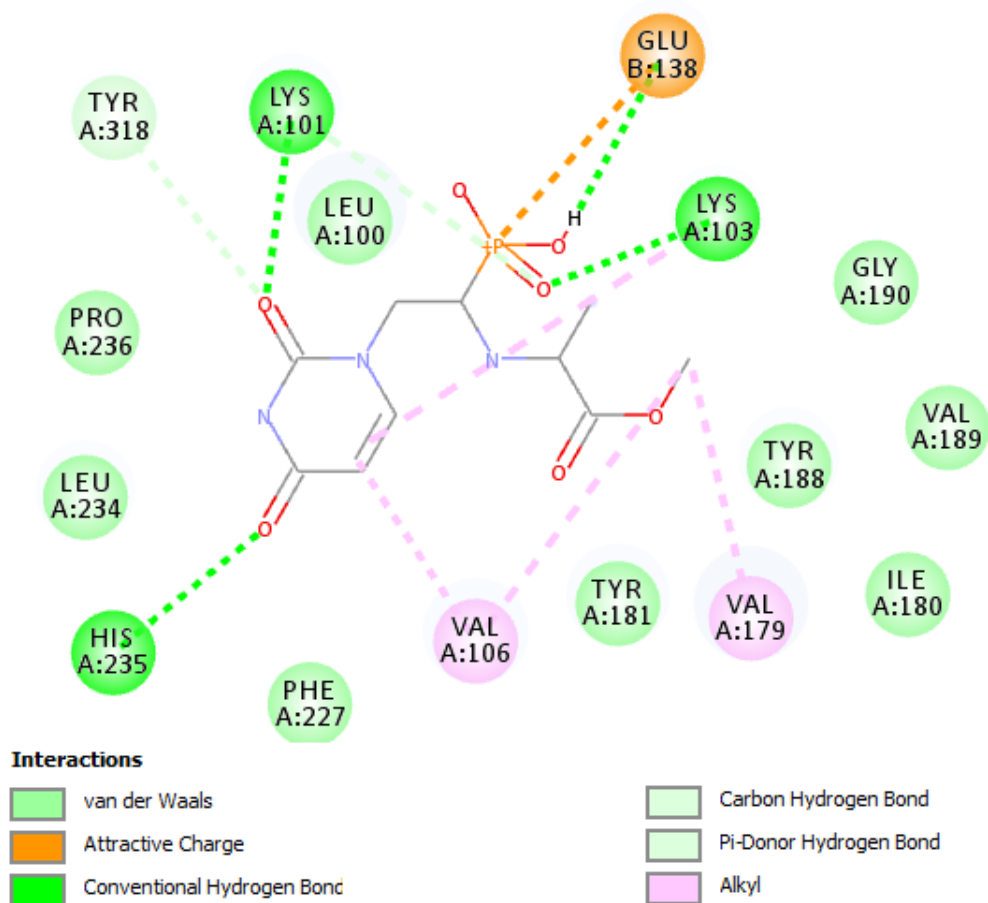


Figure 3: 2D interactions of compound **14a** in the binding sites of HIV-1 RT

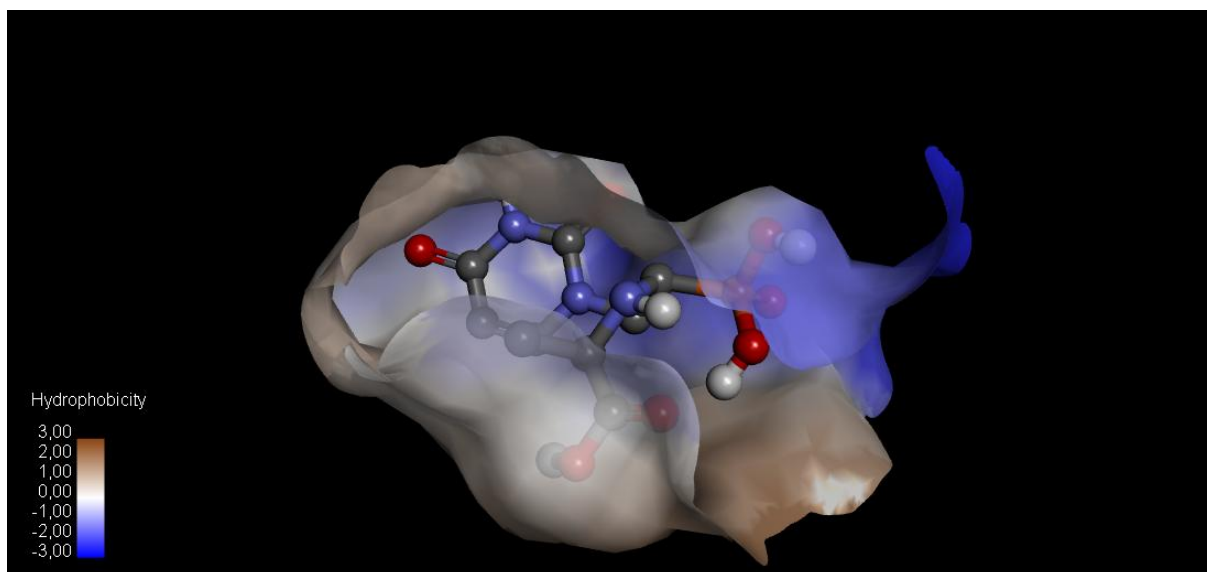


Figure 4: The position of ligand **14a** in the hydrophobic cavity of HIV-1 RT

## Conclusion

In conclusion,  $I_2@NP$  was found to be an efficient catalyst for the one-pot three-component reaction of acyclic nucleoside acetaldehydes, amines, and triethyl phosphites. New  $\alpha$ -aminophosphonates and  $\alpha$ -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  $^{13}C$  NMR were recorded in solution in DMSO- $d_6$  or  $CDCl_3$  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- $d_6$  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,  $CH_2Cl_2/MeOH$ ) afforded the corresponding aldehydes.

#### **1,1-diethoxy-2-(thymine-1-yl) acetaldehyde 3a**

Yield: 56 %;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 1.10 (t,  $J=7.03$  Hz, 6H), 1.85 (s, 3H,  $CH_3$ ), 3.50 (q,  $J=7.03$  Hz, 2H), 3.65 (q,  $J=7.04$  Hz, 2H), 3.65 (d,  $J=5.23$  Hz, 2H), 4.55 (t,  $J=5.25$  Hz, 1H), 7.05 (s, 1H), 9.55 (sb, 1H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (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  $C_{11}H_{18}N_2O_4$   $[M+H]^+$ : 243.2716 found 243.2722

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

Yield: 60%;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 1.10 (t, 6H,  $J=7.02$  Hz, 2 $CH_3$ ), 3.50 (q, 2H,  $J=7.03$  Hz,  $OCH_2$ ), 3.65 (q, 2H,  $J=7.03$  Hz,  $OCH_2$ ), 3.70 (d, 2H,  $J=5.23$  Hz,  $N-CH_2$ ), 4.55 (t, 1H,  $J=5.25$  Hz,  $CH-CH_2$ ), 5.50 (d, 1H,  $J=7.93$  Hz, H-5), 7.20 (d, 1H,  $J=7.9$  Hz, H-6), 9.55 (sl, 1H, N3-H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm) 14.07-14.27 (2 $CH_3$ ), 50.09 ( $CH_2-CH$ ), 63.22 (2 $CH_2-CH_3$ ), 99.30 ( $CH-CH_2$ ), 100.59 (C5), 145.09 (C6), 150.33 (C4), 163.06 (C2). MS (FAB+),  $m/z$  = 229  $[M+H]^+$ . HMRS calcd for  $C_{10}H_{16}N_2O_4$   $[M+H]^+$ : 229.2450 found 229.2458

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

Yield: 60%.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm) 1.10 (t, 6H,  $J=7.02$  Hz, 2 $CH_3$ ), 3.50 (q, 2H,  $J=7.02$  Hz,  $OCH_2$ ), 3.65 (q, 2H,  $J=7.02$  Hz,  $OCH_2$ ), 4.00 (d, 2H,  $J=5.78$  Hz,  $N-CH_2$ ), 4.85 (t, 1H,  $J=5.80$  Hz,  $CH-CH_2$ ), 7.35 (s, 1H, H-5), 9.70 (sl, 1H, N-3H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm) 15.17 (2 $CH_3$ ), 41.36 ( $CH_2-CH$ ), 62.00 (2 $CH_2-CH_3$ ), 97.80 ( $CH-$

CH<sub>2</sub>), 135.36(C5), 149.26(C4), 155.93(C2). MS (FAB+),  $m/z = 230$  [M+H]<sup>+</sup>.HMRS calcd for C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 230.2331 found 230.2325

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

Yield: 60%. <sup>1</sup>H NMR(300 MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t, 6H, 7.02Hz, 2CH<sub>3</sub>), 3.48 (q, 2H,  $J=7.03$ Hz, OCH<sub>2</sub>-CH<sub>3</sub>), 3.70 (q, 2H,  $J=7.03$ Hz, OCH<sub>2</sub>-CH<sub>3</sub>), 4.20 (d, 2H,  $J=5.22$ Hz, N-CH<sub>2</sub>), 4.65 (t, 1H,  $J=5.23$ Hz, CH<sub>2</sub>-CH-O), 5.50 (s, 2H, NH<sub>2</sub>), 7.80 (s, 1H, H-2), 8.30 (s, 1H, H-8). <sup>13</sup>C NMR(100 MHz, CDCl<sub>3</sub>) δ(ppm) 15.22 (2C<sub>H</sub><sub>3</sub>), 46.28 (C<sub>H</sub><sub>2</sub>-CH), 63.96 (2C<sub>H</sub><sub>2</sub>-CH<sub>3</sub>), 100.37 (C<sub>H</sub>-CH<sub>2</sub>), 119.26 (C5), 141.77 (C6), 150.28 (C4), 153.02 (C2), 155.29 (C8). MS (FAB+),  $m/z = 252$  [M+H]<sup>+</sup>.HMRS calcd for C<sub>11</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 252.2849 found 252.2858

### **Catalyst preparation:**

#### **Natural phosphate coated with iodine (I<sub>2</sub>@NP):**

To a solution of iodine (759 mg) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added natural phosphate (3 g) and stirred for 15 min and evaporated to dryness.

#### **Natural phosphate coated with ZnBr<sub>2</sub>**

To a solution of ZnBr<sub>2</sub> (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 ZnCl<sub>2</sub>**

To a solution of ZnCl<sub>2</sub> (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 CF<sub>3</sub>SO<sub>3</sub>H**

To a solution of CF<sub>3</sub>SO<sub>3</sub>H (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 SnCl<sub>4</sub>**

A mixture of 1g of SnCl<sub>4</sub> (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 CH<sub>3</sub>CN 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 (I<sub>2</sub>@NP, 104 mg; (ZnCl<sub>2</sub>@NP, 92mg; ZnBr<sub>2</sub>@NP, 160 mg; CF<sub>3</sub>SO<sub>3</sub>H @NP, 40 mg; Zn(OTf)<sub>2</sub>@NP, 280mg; SnCl<sub>4</sub>@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 CH<sub>2</sub>Cl<sub>2</sub>, washed with a solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1M) and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation, the crude product was purified by silica gel chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH).

#### **N<sup>1</sup> (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) uracil 5a**

Yield: 77%. <sup>1</sup>H NMR(400MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t, 3H, *J*=7.02Hz, CH<sub>3</sub>), 1.20 (t, 3H, *J*=7.02Hz, CH<sub>3</sub>), 3.80-4.10 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.18 (m, 2H, N1-CH<sub>2</sub>-CH), 4.40 (m, 1H, CH-CH<sub>2</sub>); 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). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>)δ (ppm) 15(2CH<sub>3</sub>), 48.91(CH<sub>2</sub>-CH), 61.80-63.12(2CH<sub>2</sub>-CH<sub>3</sub>), 100.69 (CH-CH<sub>2</sub>), 112.28 (C5), 128.41-144(Ph), 145.23 (C6), 150.39(C4) 163.24(C2). MS (FAB+), *m/z* =368 [M+H]<sup>+</sup>. HMRS calcd for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 368.3367 found 368.3375

#### **N<sup>1</sup> (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) thymine 5b**

Yield: 45% <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t, 3H, CH<sub>3</sub>), 1.20 (t, 3H, *J*=7.03 Hz, CH<sub>3</sub>), 1.70 (s, 3H, CH<sub>3</sub>), 3.80-4.10 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.20 (m, 2H, N1-CH<sub>2</sub>-CH), 4.40 (m, 1H, CH-CH<sub>2</sub>); 4.60 (s, 1H, NH- Ph), 6.50-7.00 (m, 5H, Ph), 7.05 (s, 1H, H6), 9.80 (s, 1H, N3-H). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>)δ (ppm) 12.11 (CH<sub>3</sub>); 16.35 (2CH<sub>3</sub>), 48.91 (CH<sub>2</sub>-CH), 62.74(CH<sub>2</sub>-CH<sub>3</sub>), 63.99(CH<sub>2</sub>-CH<sub>3</sub>), 100.01(CH-CH<sub>2</sub>), 113.35 (C5),129.32-141(Ph), 146.43 (C6), 151.46 (C4), 164.56(C2).MS (FAB+), *m/z* = 382 [M+H]<sup>+</sup>.HMRS calcd for C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 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 CH<sub>3</sub>CN 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/I<sub>2</sub>, 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 CH<sub>2</sub>Cl<sub>2</sub>, washed with a solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1M) and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation, the crude product was purified by silica gel chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH).

#### **N<sup>1</sup> (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) uracil 5a**

Yield: 77%. <sup>1</sup>H NMR(400MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t, 3H, *J*=7.02Hz, CH<sub>3</sub>), 1.20 (t, 3H, *J*=7.02Hz, CH<sub>3</sub>), 3.80-4.10 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.18 (m, 2H, N1-CH<sub>2</sub>-CH), 4.40 (m, 1H, CH-CH<sub>2</sub>); 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). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>)δ (ppm) 15(2CH<sub>3</sub>), 48.91(CH<sub>2</sub>-CH), 61.80-63.12(2CH<sub>2</sub>-CH<sub>3</sub>), 100.69 (CH-CH<sub>2</sub>), 112.28 (C5), 128.41-144(Ph), 145.23 (C6), 150.39(C4) 163.24(C2). MS (FAB+), *m/z* = 368 [M+H]<sup>+</sup>. HMRS calcd for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 368.3367 found 368.3375

#### **N<sup>1</sup> (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) thymine 5b**

Yield: 45% <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t, 3H, CH<sub>3</sub>), 1.20 (t, 3H, *J*=7.03 Hz, CH<sub>3</sub>), 1.70 (s, 3H, CH<sub>3</sub>), 3.80-4.10 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.20 (m, 2H, N1-CH<sub>2</sub>-CH), 4.40 (m, 1H, CH-CH<sub>2</sub>); 4.60 (s, 1H, NH-Ph), 6.50-7.00 (m, 5H, Ph), 7.05 (s, 1H, H6), 9.80 (s, 1H, N3-H). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>)δ (ppm) 12.11 (CH<sub>3</sub>); 16.35 (2CH<sub>3</sub>), 48.91 (CH<sub>2</sub>-CH), 62.74(CH<sub>2</sub>-CH<sub>3</sub>), 63.99(CH<sub>2</sub>-CH<sub>3</sub>), 100.01(CH-CH<sub>2</sub>), 113.35 (C5), 129.32-141(Ph), 146.43 (C6), 151.46 (C4), 164.56(C2). MS (FAB+), *m/z* = 382 [M+H]<sup>+</sup>. HMRS calcd for C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 382.3633 found 382.3640

#### **N<sup>1</sup> (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) azauracil 5c**

Yield: 40%. <sup>1</sup>H NMR(400MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t, 3H, CH<sub>3</sub>), 1.22(t, 3H, *J*=7.02Hz, CH<sub>3</sub>), 3.90-4.10 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.15 (m, 2H, N1-CH<sub>2</sub>-CH), 4.40 (m, 1H, CH-CH<sub>2</sub>), 4.50 (s, 1H, NH-Ph), 7.20 (s, 1H, H5), 6.50-7.10 (m, 5H, Ph), 10.60 (s, 1H, N3-H). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>)δ(ppm) 14.38(2CH<sub>3</sub>), 38.22(CH<sub>2</sub>-CH), 60.83(CH<sub>2</sub>-CH<sub>3</sub>), 62.00 (CH<sub>2</sub>-CH<sub>3</sub>); 111.45(CH-CH<sub>2</sub>), 113.37 (C5), 127.27-144.53 (Ph), 147.59 (C4),

154.57(C2). MS (FAB+),  $m/z = 369$   $[M+H]^+$ .HMRS calcd for C<sub>15</sub>H<sub>21</sub>N<sub>4</sub>O<sub>5</sub>P  $[M+H]^+$ : 369.3248 found 369.3239

**N<sup>9</sup> (2-anilino-2-diethoxyphosphinyl-ethan-1-yl) adenine 5d**

Yield: 40% <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.10 (t,3H,  $J=7.06$ Hz, CH<sub>3</sub>); 1.20 (t, 3H, CH<sub>3</sub>), 3.90-4.10 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.30 (m, 2H, N<sub>9</sub>-CH<sub>2</sub>-CH), 4.40 (m, 1H, CH-CH<sub>2</sub>), 4.60 (s, 1H, NH-Ph), 5.60 (s, 2H, NH<sub>2</sub>), 6.40-7.05 (m, 5H, Ph), 7.75 (s,1H,H<sub>2</sub>), 8.35 (s,1H,H<sub>8</sub>).<sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>)δ (ppm) 16.34 (2CH<sub>3</sub>), 44.66(CH<sub>2</sub>-CH), 62.83-63.96 (2CH<sub>2</sub>-CH<sub>3</sub>), 113.52 (CH-CH<sub>2</sub>), 119.52(C<sub>5</sub>),129.22-140 (Ph),141.34 (C<sub>6</sub>), 150.28 (C<sub>4</sub>), 153.02 (C<sub>2</sub>), 155.35(C<sub>8</sub>). MS (FAB+),  $m/z = 391$   $[M+H]^+$ .HMRS calcd for C<sub>17</sub>H<sub>23</sub>N<sub>6</sub>O<sub>3</sub>P  $[M+H]^+$ : 391.3766 found 391.3773

**N<sup>1</sup> (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) uracil 6a**

Yield: 50%. <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.20 (t, 3H,  $J=7.02$ Hz, CH<sub>3</sub>), 1.30 (t, 3H, CH<sub>3</sub>), 3.20 (m,1H,Ha),3.5 (m, 1H, Hb), 3.80-3.90 (m, 2H, N<sub>1</sub>-CH<sub>2</sub>-CH), 4.20 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.25 (m, 1H, CH-CH<sub>2</sub>), 4.30 (s, 1H, N-H-CH<sub>2</sub>-Ph), 5.60 (d, 1H,  $J = 7.87$  Hz, H<sub>5</sub>), 6.50-7.00 (m, 5H, ph), 7.20 (d, 1H,  $J = 7.87$ , H<sub>6</sub>), 9.20 (s, 1H, N<sub>3</sub>-H).<sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>)δ (ppm): 16.6(2CH<sub>3</sub>), 49.72(CH<sub>2</sub>-CH), 52.55(CH<sub>2</sub>-Ph), 62.61-62.77(2CH<sub>2</sub>-CH<sub>3</sub>), 101.11 (CH-CH<sub>2</sub>), 127.52 (C<sub>5</sub>),128-139 (Ph), 145.25 (C<sub>6</sub>), 150.83 (C<sub>4</sub>), 163.96(C<sub>2</sub>). MS(ES+),  $m/z = 382$   $[M+H]^+$ .HMRS calcd for C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub>P  $[M+H]^+$ : 382.3633 found 382.3640

**N<sup>1</sup> (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) thymine6b**

Yield: 60%. <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.20 (t, 3H,  $J=7.03$  Hz, CH<sub>3</sub>), 1.30 (t, 3H,  $J=7.03$  Hz, CH<sub>3</sub>), 1.80 (s, 3H, CH<sub>3</sub>), 3.10 (m, 1H, Ha), 3.50 (m, 1H, Hb), 3.80-3.90 (m, 2H, N<sub>1</sub>-CH<sub>2</sub>-CH), 4.00- 4.10 (m, 4 H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.10 (m, 1H, CH-CH<sub>2</sub>), 4.25 (s, 1H, NH-Ph), 7.05 (s, 1H, H<sub>6</sub>), 7.20 (m, 5H, Ph), 9.80 (s, 1H,N<sub>3</sub>-H).<sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>)δ (ppm): 12.19 (CH<sub>3</sub>); 16.44(2CH<sub>3</sub>), 48.02(CH<sub>2</sub>-CH), 52.31(CH<sub>2</sub>-Ph), 62.57(CH<sub>2</sub>-CH<sub>3</sub>), 62.77 (CH<sub>2</sub>-CH<sub>3</sub>), 109 (CH-CH<sub>2</sub>), 127 (C<sub>5</sub>), 141.9 (C<sub>6</sub>), 128-139 (Ph), 151.1 (C<sub>4</sub>), 164.64(C<sub>2</sub>).MS(ES+),  $m/z = 396$   $[M+H]^+$ .HMRS calcd for C<sub>18</sub>H<sub>26</sub>N<sub>3</sub>O<sub>5</sub>P  $[M+H]^+$ : 396.3899 found 396.3906

**N<sup>1</sup> (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) azauracil 6c**

Yield: 60%.<sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.30 (t,3H,  $J=7.02$ Hz, CH<sub>3</sub>), 1.40 (t, 3H,  $J=7.02$ Hz, CH<sub>3</sub>), 3.40 (m, 1H, Ha), 3.80 (m, 1H, Hb), 3.90-4,10 (m, 2H, N<sub>1</sub>-CH<sub>2</sub>-

CH), 4.30 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.50 (m, 1H, CH-CH<sub>2</sub>), 4.55 (s, 1H, NH-CH<sub>2</sub>-Ph), 7.20 (s, 1H, H5), 7.40 (m, 5H, Ph), 10.60 (s, 1H, N3-H). <sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>)δ (ppm) 16.60 (2CH<sub>3</sub>), 39.80(CH<sub>2</sub>-CH), 51.77(CH<sub>2</sub>-Ph), 62.51(CH<sub>2</sub>-CH<sub>3</sub>), 62.72(CH<sub>2</sub>-CH<sub>3</sub>), 127.23(CH-CH<sub>2</sub>), 135.14 (C5), 128-135 (Ph), 149.48(C4), 156.26 (C2). MS(ES+), *m/z* = 383 [M+H]<sup>+</sup>. HMRS calcd for C<sub>16</sub>H<sub>23</sub>N<sub>4</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 383.3513 found 383.3506

#### **N<sup>9</sup> (2-benzylamino-2-diethoxyphosphinyl-ethan-1-yl) adenine 6d**

Yield: 62%. <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.20 (t, 3H, *J*=7.06Hz, CH<sub>3</sub>), 1.30 (t, 3H, *J*=7.06Hz, CH<sub>3</sub>), 3.30 (m, 1H, Ha), 3.90 (m, 1H, Hb), 3.70- 3.90 (m, 2H, N9-CH<sub>2</sub>-CH), 4.00 (m, 1H, CH-CH<sub>2</sub>), 4.20 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 4.25 (s, 1H, NH-CH<sub>2</sub>-Ph), 5.90 (s, 2H, NH<sub>2</sub>), 7.30 (m, 5H, Ph), 7.90 (s, 1H, H2), 8.35 (s, 1H, H8). <sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>)δ (ppm) 16.44 (2CH<sub>3</sub>), 44.11(CH<sub>2</sub>-CH), 62.74-62.83(2CH<sub>2</sub>-CH<sub>3</sub>), 119.26 (CH-CH<sub>2</sub>), 52.18(CH<sub>2</sub>-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]<sup>+</sup>. HMRS calcd for C<sub>18</sub>H<sub>25</sub>N<sub>6</sub>O<sub>3</sub>P [M+H]<sup>+</sup>: 405.4032 found 405.4040

#### **N<sup>1</sup> (2-butylamino-2-diethoxyphosphinyl-éthan-1-yl) uracil 7a**

Yield: 66%. <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 0.80 (t, 3H, CH<sub>3</sub>-CH<sub>2</sub>), 1.20 (m, 6H, 2CH<sub>3</sub>-CH<sub>2</sub>), 1.30 (q, 2H, CH<sub>2</sub>-CH<sub>3</sub>), 1.40 (m, 2H, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 2.60-2.80 (m, 2H, NH-CH<sub>2</sub>), 3.00 -3.60 (m, 2H, Ha and Hb), 4.10 (m, 1H, CH-CH<sub>2</sub>), 4.25 (m, 4H, 2 OCH<sub>2</sub>-CH<sub>3</sub>), 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). <sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>)δ (ppm) 13.87 (CH<sub>3</sub>-CH<sub>2</sub>), 16.45(CH<sub>3</sub>), 16.50(CH<sub>3</sub>), 20.08 (CH<sub>2</sub>-CH<sub>3</sub>), 28.92(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 48.82 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 49.84(CH<sub>2</sub>-CH), 62.47-62.88(2CH<sub>2</sub>-CH<sub>3</sub>), 100.92 (CH-CH<sub>2</sub>), 128.81 (C5), 146.48 (C6), 150.92 (C4), 163.91 (C2). MS(ES+), *m/z* = 348 [M+H]<sup>+</sup>. HMRS calcd for C<sub>14</sub>H<sub>26</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 348.3471 found 348.3480

#### **N<sup>1</sup> (2-butylamino-2-diethoxyphosphinyl-ethan-1-yl) thymine 7b**

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



28.92(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 48.82 (CH<sub>2</sub>CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 49.84(CH<sub>2</sub>-CH), 62.47-62.88(2CH<sub>2</sub>-CH<sub>3</sub>), 100.92( CH-CH<sub>2</sub>), 128.81 (C5), 146.48 (C6), 150.92 ( C4), 163.91 (C2). MS(ES+),  $m/z$  = 362 [M+H]<sup>+</sup>.HMRS calcd for C<sub>15</sub>H<sub>28</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 362.3736 found 362.3742

#### **N<sup>1</sup> (2-butylamino-2-diethoxyphosphinyl-ethan-1-yl) azauracil 7c**

Yield: 47%. <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm): 0.80 (t,3H,CH<sub>3</sub>), 1.20 (m,6H , 2CH<sub>3</sub>-CH<sub>2</sub>), 1.30 (q, 2H,CH<sub>2</sub>-CH<sub>3</sub>), 1.40 (m,2H,CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 2.50-2.80 ( m,2H,NH-CH<sub>2</sub>), 3.40 (m, 2H, Ha and Hb), 4.00-4.30 (m, 6H, 2 OCH<sub>2</sub>, CH-CH<sub>2</sub>, N-H), 7.30 (s, 1H, H5), 10.60 (s, 1H,N3-H) . <sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>) δ (ppm) 13.87(CH<sub>3</sub>-CH<sub>2</sub>), 16.49-16,54 (2CH<sub>3</sub>), 48(CH<sub>2</sub>-CH), 20.01 (CH<sub>2</sub>-CH<sub>3</sub>), 32.35 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 39.69(CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 62.22(CH<sub>2</sub>-CH<sub>3</sub>), 62.67(CH<sub>2</sub>-CH<sub>3</sub>), 100(CH-CH<sub>2</sub>), 135,06 (C5), 149.51 (C4), 156.42 (C2) . MS(ES+),  $m/z$  = 349 [M+H]<sup>+</sup>.HMRS calcd for C<sub>13</sub>H<sub>25</sub>N<sub>4</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 349.3351 found 349.3360

#### **N<sup>9</sup> (2-butylamino-2-diethoxyphosphinyl-ethan-1-yl) adenine 7d**

Yield: 50%. <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ (ppm) 0.80 (t,3H,CH<sub>3</sub>), 1.20 (m,6H, 2 CH<sub>3</sub>-CH<sub>2</sub>), 1.20-1,40 (q, 2H,CH<sub>2</sub>-CH<sub>3</sub>), 1.40-1,50 (m,2H,CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 2.50-2.70 ( m,2H,NH-CH<sub>2</sub>), 3.10 (m, 2H, Ha and Hb), 4.10 (m,4H, 2OCH<sub>2</sub>-CH<sub>3</sub>), 4.25 (m, 1H, N-H), 4.30 (m,1H,CH-CH<sub>2</sub>), 6.10 (s,2H, NH<sub>2</sub>), 8.10 (s, 1H, H2), 8.30 (s,1H, H8). <sup>13</sup>CNMR(100 MHz, CDCl<sub>3</sub>) δ (ppm) 13.53 (CH<sub>3</sub>-CH<sub>2</sub>), 16.44 (2CH<sub>3</sub>),20.04 (CH<sub>2</sub>-CH<sub>3</sub>), 29.35 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 40.02 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>),44.17(CH<sub>2</sub>-CH), 63.02(2CH<sub>2</sub>-CH<sub>3</sub>), 118.99 (CH-CH<sub>2</sub>), 120 (C5), 142.31 (C6), 150.08 (C4), 152.7 (C2), 155.2 (C8). MS(ES+),  $m/z$  = 371 [M+H]<sup>+</sup>.HMRS calcd for C<sub>15</sub>H<sub>27</sub>N<sub>6</sub>O<sub>3</sub>P [M+H]<sup>+</sup>: 371.3870 found 371.3865

#### **N<sup>1</sup>(2-glycinoethylester-2 diethoxyphosphinyl-ethan-1-yl) uracil 8a**

Yield: 60%. <sup>1</sup>H NMR(400 MHz,CDCl<sub>3</sub>) δ(ppm) 1.13 (t, 3H, $J$ =7.13Hz,CH<sub>3</sub>), 1.30(t,6H, $J$ =7.06Hz,2CH<sub>3</sub>), 3.25(t,1H, $J$ =4.6Hz,CH), 3.50-3.60(m,2H,CH<sub>2</sub>), 3.70(d, 2H, $J$ =4.6Hz,CH<sub>2</sub>), 4.10(m,7H,3CH<sub>2</sub>, 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). <sup>13</sup>C NMR(100 MHz,CDCl<sub>3</sub>) δ(ppm) 14.15(CH<sub>3</sub>), 16.45 (CH<sub>3</sub>), 16.49 (CH<sub>3</sub>), 49.40 (CH), 52.98 (CH<sub>2</sub>), 54.45 (CH<sub>2</sub>), 60.90 (CH<sub>2</sub>), 62.77 (CH<sub>2</sub>), 62.73 (CH<sub>2</sub>), 101.39( C5), 146.06( C6),151.35 (C4), 164.11 (C2), 173.63 (CO, ester). MS(ES+),  $m/z$  =378 [M+H]<sup>+</sup>.HMRS calcd for C<sub>14</sub>H<sub>24</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 378.3300 found 378.3310

**N<sup>1</sup>(2-glycinoethylester-2-diethoxyphosphinyl-ethan-1-yl)thymine 8b**

Yield: 50%. <sup>1</sup>H NMR(400 MHz,CDCl<sub>3</sub>) δ(ppm) 1.15 (t, 3H,*J*=7.15Hz,CH<sub>3</sub>), 1.30(t, 6H,*J*=7.05Hz,2CH<sub>3</sub>), 1.80 (s, 3H,CH<sub>3</sub>), 3.25(t, 1H,*J*=4.5Hz,CH), 3.50-3.60(m,2H,CH<sub>2</sub>), 3.70(d, 2H,*J*=4.5Hz, CH<sub>2</sub>), 4.10(m,7H,3CH<sub>2</sub>, NH), 7.10(s,1H,H-6), 9.20 (sd, 1H, NH). <sup>13</sup>C NMR(100 MHz,CDCl<sub>3</sub>) δ(ppm) 14.15(CH<sub>3</sub>), 16.45 (CH<sub>3</sub>), 16.67 (CH<sub>3</sub>), 44.70 (CH<sub>2</sub>), 44.80 (CH<sub>2</sub>), 54.46 (CH<sub>2</sub>), 56.48 (CH<sub>2</sub>), 61.81 (CH<sub>2</sub>), 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]<sup>+</sup>. HMRS calcd for C<sub>15</sub>H<sub>26</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 392.3566 found 392.3574

**N<sup>1</sup>(2-glycinoethylester-2-diethoxyphosphinyl-ethan-1-yl)6-Azauracil 8c**

Yield: 50%. <sup>1</sup>H NMR(400 MHz,CDCl<sub>3</sub>) δ(ppm) 1.15 (t, 3H,*J*=7.13Hz,CH<sub>3</sub>), 1.30(t, 6H,*J*=7.06Hz,2CH<sub>3</sub>), 3.25(t, 1H,*J*=3.6Hz,CH), 3.50-3.60(dd,2H,*J*=3.6Hz,CH<sub>2</sub>), 4.00-4.20(m,9H,4CH<sub>2</sub>, NH), 7.20(s,1H,H-5), 10.50 (sd, 1H, NH). <sup>13</sup>C NMR(100 MHz,CDCl<sub>3</sub>) δ(ppm) 14.15(CH<sub>3</sub>), 16.53 (CH<sub>3</sub>), 16.48 (CH<sub>3</sub>), 39.50 (CH), 49.01 (CH<sub>2</sub>), 52.02 (CH<sub>2</sub>), 54.07 (CH<sub>2</sub>), 60.72 (CH<sub>2</sub>), 62.70 (CH<sub>2</sub>), 135.00(C5), 150.09(C4),156.97(C2), 172.65 (CO, ester). MS(ES+), *m/z* =379 [M+H]<sup>+</sup>.HMRS calcd for C<sub>13</sub>H<sub>23</sub>N<sub>4</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 379.3181 found 379.3175

**N<sup>9</sup>(2-glycinoethylester-2-diethoxyphosphinyl-ethan-1-yl)adenine 8d**

Yield: 55%. <sup>1</sup>H NMR(400 MHz,CD<sub>3</sub>OD) δ(ppm) 1.20 (t, 3H, *J*=7.15Hz, CH<sub>3</sub>), 1.30(t, 6H, *J*=7.05Hz, 2CH<sub>3</sub>), 3.20(t,1H,*J*=4.5Hz,CH), 3.30(d,2H,*J*=4.5Hz,CH<sub>2</sub>), 3.70(m,2H,CH<sub>2</sub>), 4.00 (q, 2H,*J*=7.15Hz, CH<sub>2</sub>), 4.35(q,4H,*J*=7.05Hz,2CH<sub>2</sub>), 8.20 (s, 2H, H-2, H-8). <sup>13</sup>C NMR(100 MHz,CD<sub>3</sub>OD) δ(ppm): 9.31( CH<sub>3</sub>), 14.46 (CH<sub>3</sub>), 16.67 (CH<sub>3</sub>), 44.70 (CH<sub>2</sub>), 44.80 (CH<sub>2</sub>), 54.46 (CH<sub>2</sub>), 56.48 (CH<sub>2</sub>), 61.81 (CH<sub>2</sub>), 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]<sup>+</sup>.HMRS calcd for C<sub>15</sub>H<sub>25</sub>N<sub>6</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 401.3700 found 401.3710

**N<sup>1</sup>(2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) uracil 9a**

Yield: 50%. <sup>1</sup>H NMR(400 MHz,CDCl<sub>3</sub>) δ(ppm) 1.11 (d, 3H,*J*=7.13Hz,CH<sub>3</sub>), 1.16(m, 9H,3CH<sub>3</sub>), 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, CH<sub>2</sub>), 4.01(m,5H,2CH<sub>2</sub>, NH),5.60(d,1H,*J*=7.9Hz, H-5), 7.20(d,1H,*J*=7.9Hz, H-6), 9.55(sd, 1H, NH). <sup>13</sup>C NMR(100 MHz,CDCl<sub>3</sub>) δ(ppm) 16.42 (CH<sub>3</sub>), 18.71 (CH<sub>3</sub>), 19.06 (CH<sub>3</sub>), 46.41 (CH<sub>2</sub>), 49.30 (CH), 50.70 (CH<sub>3</sub>), 51.90 (CH), 62.60 (CH<sub>2</sub>), 62.70 (CH<sub>2</sub>), 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 C<sub>15</sub>H<sub>26</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup> 392.3566 found 392.3572

#### **N<sup>1</sup> (2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) Thymine 9b**

Yield: 55%. <sup>1</sup>H NMR(400 MHz,CDCl<sub>3</sub>) δ(ppm) 1,00 (d, 3H,*J*=7.10Hz,CH<sub>3</sub>), 1.30(m, 12H,4CH<sub>3</sub>) 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, CH<sub>2</sub>), 4.01(m,5H, 2CH<sub>2</sub>, NH), 7.10(s,1H,H-6), 9.60 (sd, 1H, NH). <sup>13</sup>C NMR(100 MHz,CDCl<sub>3</sub>) δ(ppm)11.00 (CH<sub>3</sub>), 16.60 (CH<sub>3</sub>), 18.80 (CH<sub>3</sub>), 19.20 (CH<sub>3</sub>), 49.10 (CH<sub>2</sub>), 49.60 (CH), 50.90 (CH<sub>3</sub>), 52.09 (CH), 55.30 (CH<sub>2</sub>), 62.70 (CH<sub>2</sub>), 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 C<sub>16</sub>H<sub>28</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 406.3832 found 406.3842

#### **N<sup>1</sup> (2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) 6azauracil 9c**

Yield: 52%. <sup>1</sup>H NMR(400 MHz,CDCl<sub>3</sub>) δ(ppm) 1,00 (d, 3H,*J*=7,10Hz,CH<sub>3</sub>), 1,30(m, 9H,3CH<sub>3</sub>) 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, CH<sub>2</sub>), 4,01 (m,5H, 2CH<sub>2</sub>, NH),7,20(s,H-5), 9,60 (sd, 1H, NH).<sup>13</sup>C NMR(100 MHz,CDCl<sub>3</sub>) δ(ppm)16,42 (CH<sub>3</sub>), 19,06 (CH<sub>3</sub>), 19,32 (CH<sub>3</sub>), 46,00 (CH<sub>2</sub>), 50,50 (CH),51,80 (CH<sub>3</sub>), 54,13 (CH), 62,60 (CH<sub>2</sub>), 63,70 (CH<sub>2</sub>), 135,00(C5), 150,20(C4), 157,10(C2), 176,50 (CO, ester). MS(ES+),  $m/z = 393[M+H]^+$ . HMRS calcd for C<sub>14</sub>H<sub>25</sub>N<sub>4</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 393.3447 found 393.3440

#### **N<sup>9</sup> (2-alaninomethylester-2-diethoxyphosphinyl-ethan-1-yl) adenine 9d**

Yield: 55%. <sup>1</sup>H NMR(400 MHz,CD<sub>3</sub>OD) δ (ppm) 1.00 (d, 3H,*J*=7.13Hz, CH<sub>3</sub>), 1.40-1.60 (m, 9H, 3CH<sub>3</sub>), 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, CH<sub>2</sub>), 4.35 (m, 5H, 2CH<sub>2</sub>, NH), 8.20 (s, 2H, H-2, H-8). <sup>13</sup>C NMR(100 MHz,CD<sub>3</sub>OD) δ(ppm)10.00 (CH<sub>3</sub>), 16.74 (CH<sub>3</sub>), 19.18 (CH<sub>3</sub>), 45.01 (CH<sub>2</sub>), 48.00 (CH<sub>2</sub>), 52.23 (CH<sub>3</sub>), 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 C<sub>16</sub>H<sub>27</sub>N<sub>6</sub>O<sub>5</sub>P [M+H]<sup>+</sup>. 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 vacuo and the residue was purified with on preparative plate (eluent: isopropanol/NH<sub>4</sub>OH/H<sub>2</sub>O) and reverse phase HPLC (C18). The final product was obtained after a cation exchange chromatographie on a Na<sup>+</sup> DOWEX50WX2. The residue obtained is dried, the purity of products was controlled by HPLC (eluent: CH<sub>3</sub>CN/H<sub>2</sub>O, 50/50 v / v).

#### **N<sup>1</sup> (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) uracil 10a**

Yield: 64%. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ (ppm) 3.60 (m, 1H, Ha), 3.85 (m, 1H, Hb), 4.35 (m, 1H, CH-CH<sub>2</sub>), 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). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ (ppm) 51.6(CH<sub>2</sub>-CH), 100.69(CH-CH<sub>2</sub>), 112.48 (C5), 129-144 (Ph), 148.23(C6), 152.73 (C4), 167.24(C2). MS(ES+), *m/z* = 312 [M+H]<sup>+</sup>.HMRS calcd for C<sub>12</sub>H<sub>14</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 312.2304 found 312.2312

#### **N<sup>1</sup> (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) thymine 10b**

Yield: 60%. <sup>1</sup>H NMR (400MHz, D<sub>2</sub>O) δ (ppm) 1.50 (s, 3H, CH<sub>3</sub>), 3.70 (m, 1H, Ha), 4.20 (m, 1H, Hb), 4.35 (m, 1H, CH-CH<sub>2</sub>), 6.50-7.00 (m, 5H, Ph), 7.30 (s, 1H, H6). <sup>13</sup>C NMR (100MHz, D<sub>2</sub>O) δ (ppm) 12.11 (CH<sub>3</sub>), 51.53 (CH<sub>2</sub>-CH), 110.01 (CH-CH<sub>2</sub>), 113.42 (C5), 129.32-141.00 (Ph), 143.95 (C6), 152 (C4), 164.56 (C2). MS (ES+), *m/z* = 326 [M+H]<sup>+</sup>. HMRS calcd for C<sub>13</sub>H<sub>16</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 326.2570 found 326.2580

#### **N<sup>1</sup> (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) azauracil 10c**

Yield: 50%. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ (ppm) 4.05 (m, 1H, CH-CH<sub>2</sub>), 4.20 (m, 1H, Ha), 4.40 (m, 1H, Hb), 7.15 (s, 1H, H5), 6.50-7.00 (m, 5H, Ph).<sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O)δ (ppm) 42.24(CH<sub>2</sub>-CH), 113.17(CH-CH<sub>2</sub>), 129.39-141 (Ph), 135.05 (C5), 150.42 (C4), 158.24 (C2). MS(ES+), *m/z* = 313 [M+H]<sup>+</sup>.HMRS calcd for C<sub>11</sub>H<sub>13</sub>N<sub>4</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 313.2184 found 313.2178

#### **N<sup>9</sup> (2-anilino-2-dihydroxyphosphinyl-ethan-1-yl) adenine 10d**

Yield: 70%. <sup>1</sup>H NMR (400MHz, D<sub>2</sub>O) δ (ppm) 4.35 (m, 1H, Ha), 4.50 (m, 1H, Hb), 4.90 (m, 1H, CH-CH<sub>2</sub>), 6.30-7,10 (m, 5H, Ph), 7.75 (s, 1H, H2), 8.35 (s, 1H, H8). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O) δ (ppm) 46.48 (CH<sub>2</sub>-CH), 112.49 (CH-CH<sub>2</sub>), 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]<sup>+</sup>. HMRS calcd for C<sub>13</sub>H<sub>15</sub>N<sub>8</sub>O<sub>3</sub>P [M+H]<sup>+</sup>. 363.2837 found 363.2845

#### **N<sup>1</sup> (2-benzylamino-2- dihydroxyphosphinyl -ethan-1-yl) uracil 11a**

Yield: 60%.  $^1\text{H}$  NMR(400 MHz,  $\text{D}_2\text{O}$ ),  $\delta$  (ppm) 3.20 (m, 1H, Ha), 3.90 (m, 1H, Hb), 4.00 (m, 2H, N1- $\text{CH}_2$ -CH), 4.30 (m, 1H, CH- $\text{CH}_2$ ), 5.60 (d, 1H,  $J=7.87$ , H5), 7.30 (m, 5H, Ph), 7.45 (d, 1H,  $J=7.87$ , H6).  $^{13}\text{C}$  NMR (100MHz,  $\text{D}_2\text{O}$ ) $\delta$  (ppm) 48.81(CH $_2$ -CH), 51.60(CH $_2$ -Ph), 102.12(CH- $\text{CH}_2$ ), 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 C $_{13}$ H $_{16}$ N $_3$ O $_5$ P [M+H] $^+$ : 326.2570 found 326.2564

#### **N $^1$ (2-benzylamino-2-dihydroxyphosphinyl-ethan-1-yl) thymine 11b**

Yield: 35%.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm) 1.70 (s, 3H, CH $_3$ ), 3.30 (m, 1H, Ha), 3.90 (m, 1H, Hb), 4.10- 4,30 (m, 2H, N1- $\text{CH}_2$ -CH), 4.50 (m, 1H, CH- $\text{CH}_2$ ), 7.40 (m, 5H, Ph), 7.20 (s, 1H, H6).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm) 11.19 (CH $_3$ ), 48.50 (CH $_2$ -CH), 111.39 ( CH- $\text{CH}_2$ ), 127 ( C5), 129-130 (Ph), 142.22 (C6), 153.14 ( C4), 166.64 ( C2). MS (ES+),  $m/z = 340$  [M+H] $^+$ . HMRS calcd for C $_{14}$ H $_{18}$ N $_3$ O $_5$ P [M+H] $^+$ : 340.2835 found 340.2841

#### **N $^1$ (2-benzylamino-2- dihydroxyphosphinyl -ethan-1-yl) azauracil 11c**

Yield: 35%.  $^1\text{H}$  NMR (400MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm) 3.40 (m,1H,Ha), 4.10 (m, 1H, Hb), 4.20 (m, 2H, N1- $\text{CH}_2$ -CH), 4.50 (m, 1H, CH- $\text{CH}_2$ ), 7.30 (s, 1H, H5), 7.40 (m, 5H, Ph).  $^{13}\text{C}$  NMR (100MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm) 39.63 (CH $_2$ -CH), 50.13 (CH $_2$ -Ph), 128.21 (CH- $\text{CH}_2$ ), 129-131 (Ph), 135.51 (C5), 150.59 (C4), 157.93 ( C2). MS(ES+),  $m/z =327$  [M+H] $^+$ .HMRS calcd for C $_{12}$ H $_{15}$ N $_4$ O $_5$ P [M+H] $^+$ . 327.2450 found 327.2457

#### **N $^9$ (2-benzylamino-2- dihydroxyphosphinyl -éthan-1-yl) adenine 11d**

Yield: 24%.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm): 3.30 (m, 1H, Ha), 3.90 (m, 1H, Hb), 4.00-4.30 (m, 2H, N9- $\text{CH}_2$ -CH), 4.60 (m, 1H, CH- $\text{CH}_2$ ), 7.00 (m, 5H, Ph), 7.90 (s, 1H, H2), 7.95 (s, 1H, H8).  $^{13}\text{C}$  NMR (100MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm) 44.11 (CH $_2$ -CH), 52.18 (CH $_2$ -Ph), 119.26 (CH- $\text{CH}_2$ ), 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 C $_{14}$ H $_{17}$ N $_6$ O $_3$ P [M+H] $^+$ : 349.2969 found 349.2977

#### **N $^1$ (2-butylamino-2-dihydroxyphosphinyl-éthan-1-yl) uracil 12a**

Yield: 25%.  $^1\text{H}$  NMR (400MHz,  $\text{D}_2\text{O}$ ),  $\delta$  (ppm) 0.80 (t, 3H, CH $_3$ -CH $_2$ ), 1.20 (q, 2H, CH $_2$ -CH $_3$ ), 1.50 (m, 2H, CH $_2$ -CH $_2$ -CH $_3$ ), 3.10 (m, 2H, CH $_2$ -(CH $_2$ ) $_2$ -CH $_3$ ), 3.40-4,10 (m, 2H, N1- $\text{CH}_2$ ), 4.30 (m, 1H, CH- $\text{CH}_2$ ), 5.60 (d, 1H,  $J = 7.87\text{Hz}$ , H5), 7.30 (d, 1H,  $J = 7.87\text{Hz}$ , H6).  $^{13}\text{C}$  NMR (100MHz,  $\text{D}_2\text{O}$ )  $\delta$  (ppm) 12.74 (CH $_3$ -CH $_2$ ), 19.04 (CH $_2$ -CH $_3$ ),

28.03 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 46.42 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 47.90 (CH<sub>2</sub>-CH), 102.05 (CH-CH<sub>2</sub>), 128.81 (C5), 147.21 (C6), 153.21 (C4), 166.72 (C2) .MS (ES+), *m/z* = 292 [M+H]<sup>+</sup>. HMRS calcd for C<sub>10</sub>H<sub>18</sub>N<sub>3</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 292.2407 found 292.2415

### **N<sup>1</sup> (2-butylamino-2-dihydroxyphosphinyl-éthan-1-yl) azaauracil 12c**

Yield: 20%. <sup>1</sup>H NMR (400MHz, D<sub>2</sub>O) δ (ppm) 0.80 (t, 3H, CH<sub>3</sub>), 1.20 (q, 2H, CH<sub>2</sub>-CH<sub>3</sub>), 1.50 (m, 2H, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.10 (m, 2H, CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 3.70 (m, 1H, CH-CH<sub>2</sub>), 4.30 (m, 2H, N1-CH<sub>2</sub>), 7.50 (s, 1H, H5). <sup>13</sup>C NMR (100MHz, D<sub>2</sub>O) δ (ppm) 12.75 (CH<sub>3</sub>-CH<sub>2</sub>), 19.04 (CH<sub>2</sub>-CH<sub>3</sub>), 28.03 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 46.42 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 47.90 (CH<sub>2</sub>-CH), 100 (CHCH<sub>2</sub>), 135.06 (C5), 147.21 (C4); 153.21 (C2). MS (ES+), *m/z* = 293 [M+H]<sup>+</sup>. HMRS calcd for C<sub>9</sub>H<sub>17</sub>N<sub>4</sub>O<sub>5</sub>P [M+H]<sup>+</sup> 293.2288 found 293.2295

### **N<sup>1</sup>(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) uracil 13a**

Yield: 40%. <sup>1</sup>H NMR(400MHz, D<sub>2</sub>O) δ (ppm) 1.15 (t, 3H, *J*=7.10Hz, CH<sub>3</sub>), 3.25 (t, 1H, *J*=3.50Hz, CH), 3.70 (m, 2H, CH<sub>2</sub>), 3.80 (d, 2H, *J*=3.5Hz, CH<sub>2</sub>), 4.10 (q, 4H, *J*=7.10Hz, 2CH<sub>2</sub>), 5.70 (d, 2H, *J*=7.9Hz, 1H, H-5), 7.60 (d, 2H, *J*=7.90Hz, 1H, H-6). <sup>13</sup>CNMR (100MHz, D<sub>2</sub>O) δ(ppm) 16.45 (CH<sub>3</sub>), 49.40 (CH), 54.79 (CH<sub>2</sub>), 56.50 (CH<sub>2</sub>), 57.39 (CH<sub>2</sub>), 101.37 (C5), 147.18 (C6), 152.20 (C4), 166.67 (C2), 171.42 (CO, ester). MS (ES+), *m/z* = 322 [M+H]<sup>+</sup>.HMRS calcd for C<sub>10</sub>H<sub>16</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 322.2237 found 322.2246

### **N<sup>1</sup>(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) Thymine 13b**

Yield: 20%. <sup>1</sup>HNMR (400MHz, D<sub>2</sub>O) δ(ppm) 1.15 (t, 3H, *J*=7.10Hz, CH<sub>3</sub>), 1.70 (s, 3H, CH<sub>3</sub>), 3.25(t, 1H, *J*=3.50Hz, CH), 3.70 (m, 2H, CH<sub>2</sub>), 3.80(d, 1H, *J*=3.25Hz, CH<sub>2</sub>), 4.10(q, 4H, *J*=7.10Hz, 2CH<sub>2</sub>), 7.60(s, 1H, H-6). <sup>13</sup>CNMR(100 MHz, D<sub>2</sub>O) δ(ppm) 13.20 (CH<sub>3</sub>), 16.45 (CH<sub>3</sub>), 49.40 (CH), 54.79 (CH<sub>2</sub>), 56.50 (CH<sub>2</sub>), 57.39 (CH<sub>2</sub>), 101.37(C5), 147.18 (C6), 152.20(C4), 166.67(C2), 171.42 (CO, ester). MS(ES+), *m/z* = 336 [M+H]<sup>+</sup>.HMRS calcd for C<sub>11</sub>H<sub>18</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 336.2502 found 336.2512

### **N<sup>1</sup>(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) azaauracil 13c**

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

(CO, ester). MS(ES+),  $m/z = 323[M+H]^+$ .HMRS calcd for C<sub>9</sub>H<sub>15</sub>N<sub>4</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 323.2117 found 323.212.

#### **N<sup>9</sup>(2-glycinoethylester-2-dihydroxyphosphinyl-ethan-1-yl) adenine 13d**

Yield: 20%. <sup>1</sup>H NMR(400 MHz, D<sub>2</sub>O) δ(ppm) 1.00 (t, 3H, $J=7.13$ Hz,CH<sub>3</sub>), 3.20(t, 1H, $J=3.6$ Hz,CH), 3.40(m,2H,CH<sub>2</sub>), 3.70(d, 2H,  $J=3.6$ Hz,CH<sub>2</sub>), 4.20(q,2H, $J=7.13$ Hz,CH<sub>2</sub>), 8.10 (s, 2H, H-2, H-8). <sup>13</sup>C NMR (100MHz D<sub>2</sub>O) δ(ppm) 12.99 (CH<sub>3</sub>), 44.80 (CH<sub>2</sub>), 54.46 (CH<sub>2</sub>), 56.48 (CH<sub>2</sub>), 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]<sup>+</sup>.HMRS calcd for C<sub>11</sub>H<sub>17</sub>N<sub>6</sub>O<sub>5</sub>P [M+H]<sup>+</sup>: 345.2636 found 345.2628

#### **N<sup>1</sup>(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) uracil 14a**

Yield: 35%. <sup>1</sup>H NMR(400 MHz, D<sub>2</sub>O) δ(ppm) 1.15 (d, 3H, $J=7.10$ Hz,CH<sub>3</sub>), 2.75(t, 1H, $J=4.6$ Hz,CH), 3.40(q,1H, $J=7.10$ Hz,CH),3.60(s,3H,CH<sub>3</sub>), 4.00(d,2H, $J=4.6$ Hz,CH<sub>2</sub>), 5.65(d, $J=7.90$  Hz,1H,H-5), 7.50(d, $J=7.90$  Hz,1H,H-6).<sup>13</sup>CNMR (100MHz, D<sub>2</sub>O) δ(ppm) 17.84 (CH<sub>3</sub>), 48.84 (CH), 52.7 (CH), 55.03 (CH<sub>3</sub>), 58.49 (CH<sub>2</sub>), 101(C5), 147.07(C6), 158.50(C4), 174.64 (C2), 181.70 (CO, ester). MS(ES+),  $m/z = 326[M+H]^+$ . <sup>31</sup>PNMR (75 MHz, D<sub>2</sub>O) δ(ppm) 14.93, 16.22. HMRS calcd for C<sub>11</sub>H<sub>18</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 326.2502 found 326.2509

#### **N<sup>1</sup>(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) thymine 14b**

Yield: 25%. <sup>1</sup>HNMR(400 MHz, D<sub>2</sub>O) δ(ppm) 1.15 (d, 3H, $J=7.10$ Hz,CH<sub>3</sub>), 1.80(s,3H,CH<sub>3</sub>) 2.75(t, 1H, $J=4.60$  Hz,CH), 3.40(q,1H, $J=7.10$ Hz,CH),3.60(s,3H,CH<sub>3</sub>), 4.00(d,2H, $J=4.6$ Hz,CH<sub>2</sub>), 7.44(s,1H,H-6).<sup>13</sup>C NMR (100MHz, D<sub>2</sub>O) δ(ppm)13.20 (CH<sub>3</sub>), 17.83 (CH<sub>3</sub>), 48.84 (CH), 52.62 (CH), 53.54 (CH<sub>3</sub>), 58.54 (CH<sub>2</sub>), 101.55 (C5), 147.06 (C6),158.50(C4), 174.60(C2), 181.65 (CO, ester). MS(ES+),  $m/z = 350$  (M+H+). <sup>31</sup>PNMR (75 MHz, D<sub>2</sub>O) δ(ppm): 14.09, 16.06. HMRS calcd for C<sub>12</sub>H<sub>20</sub>N<sub>3</sub>O<sub>7</sub>P [M+H]<sup>+</sup>: 350.2768 found 350.2774

#### **N<sup>1</sup>(2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) azauracil 14c**

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

(CO,ester). MS(ES+),  $m/z = 337$  (M+H+).  $^{31}\text{P}$ NMR (75 MHz,  $\text{D}_2\text{O}$ )  $\delta(\text{ppm})$  14.34, 16.25. HMRS calcd for  $\text{C}_{10}\text{H}_{17}\text{N}_4\text{O}_7\text{P}$  [M+H] $^+$ : 337.2383 found 337.2376

### **$\text{N}^9$ (2-alaninometylester-2-dihydroxyphosphinyl-ethan-1-yl) adenine 14d**

Yield: 15%.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta(\text{ppm})$  1.19(d, 3H, $J=7.10\text{Hz}$ , $\text{CH}_3$ ), 3.30(t,1H, $J=4.5\text{Hz}$ ,CH), 3.40(q,1H, $J=7.10\text{Hz}$ ,CH), 3.60(s,3H, $\text{CH}_3$ ), 4.00(d,2H, $J=4.50\text{Hz}$ , $\text{CH}_2$ ), 8,00 (s, 2H, H-8, H-2).  $^{13}\text{C}$ NMR (100MHz,  $\text{D}_2\text{O}$ )  $\delta(\text{ppm})$  13.20 ( $\text{CH}_3$ ), 39.85 (CH), 47.30 (CH), 53.79 ( $\text{CH}_3$ ), 62.63 ( $\text{CH}_2$ ), 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+).  $^{31}\text{P}$ NMR (75 Mhz,  $\text{D}_2\text{O}$ )  $\delta(\text{ppm})$  15.06, 15.90. HMRS calcd for  $\text{C}_{12}\text{H}_{19}\text{N}_6\text{O}_5\text{P}$  [M+H] $^+$ : 359.2902 found 359.2912

### ***Molecular docking***

In silico computational docking studies were performed using AutoDock4.2 [54]. The X-ray crystallographic structures of HCV NS3 protease and HIV reverse transcriptase were downloaded 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 Gasteiger 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 grid covering all the amino acid residues present inside the active site of proteins was built for 1W3C (grid box size of  $40\text{\AA} \times 46\text{\AA} \times 52\text{\AA}$  with a spacing of  $0.375\text{\AA}$  between the grid points and centered at 66.685 (x), 18.626 (y), and 0.736 (z)) and for 2RF2 (grid box size of  $50\text{\AA} \times 40\text{\AA} \times 56\text{\AA}$  with a spacing of  $0.375\text{\AA}$  between the grid points and centered at 7.845 (x), 13.204 (y), and 15.671 (z)). The best conformers were searched by the Lamarckian genetic algorithm (LGA), the population size was set to 150 and maximum number of energy evaluation was set to 250,000,00. Finally, the results were analyzed and visualized by the discovery studio.

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