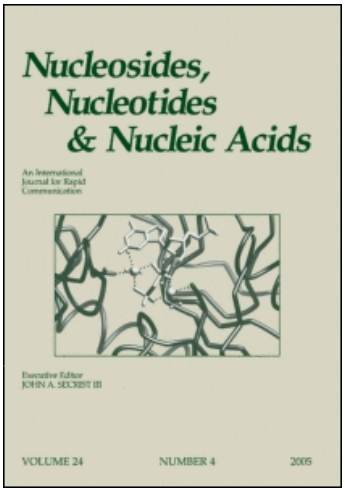

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 19 July 2010

To cite this Article Zhang, Xinying , Qu, Yingying , Fan, Xuesen , Bores, C. , Feng, Dong , Andrei, Graciela , Snoeck, Robert , De Clercq, Erik and Loiseau, Philippe M.(2010) 'Solvent-Free Synthesis of Pyrimidine Nucleoside-Aminophosphonate Hybrids and Their Biological Activity Evaluation', Nucleosides, Nucleotides and Nucleic Acids, 29: 8, 616 — 627
To link to this Article: DOI: 10.1080/15257770.2010.496281
URL: http://dx.doi.org/10.1080/15257770.2010.496281

Nucleosides, Nucleotides and Nucleic Acids, 29:616–627, 2010

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770.2010.496281

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SOLVENT-FREE SYNTHESIS OF PYRIMIDINE NUCLEOSIDE-AMINOPHOSPHONATE HYBRIDS AND THEIR BIOLOGICAL ACTIVITY EVALUATION

Xinying Zhang,[1] Yingying Qu,[1] Xuesen Fan,[1] C. Bores,[2] Dong Feng,[1] Graciela Andrei,[3] Robert Snoeck,[3] Erik De Clercq,[3] and Philippe M. Loiseau[2]

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□ *A novel and highly efficient one-pot three-component synthesis of α-aminophosphonates under neat condition was developed. By employing this method, hybrid compounds of aminophosphonate with pyrimidine nucleosides were synthesized in good to excellent yields starting from 5-formyl-2′-deoxyuridine, aniline and dimethyl phosphite. The antiviral and antileishmanial activities of these novel hybrid compounds were also studied but none were found to be active.*

Keywords Pyrimidine nucleoside; α-aminophosphonate; hybrid; solvent-free reaction; biological activities

INTRODUCTION

As bioisosteric analogue of α-amino acids, the α-aminophosphonate moiety, is a versatile and novel pharmacophore due to the broad spectrum of biological activity exhibited by compounds bearing this structural unit. They have revealed diverse and interesting biological and biochemical properties by acting as antibacterial agents,[1] enzyme inhibitors[2] (including HIV protease),[3] antiviral agents,[4] as well as their role for antibody

Received 26 January 2010; accepted 21 May 2010.

This work was financially supported by the National Natural Science Foundation of China (Nos. 20772025 and 20972042), Program for Science & Technology Innovation Talents in Universities of Henan Province (No. 2008HASTIT006), Innovation Scientists and Technicians Troop Construction Projects of Henan Province (No. 104100510019), and the Natural Science Foundation of Henan Province (Nos. 092300410192 and 094300510054). The authors sincerely thank Prof. Dr. Paul F Torrence, Department of Chemistry, Northern Arizona University, USA, for his kind help and excellent instructions.

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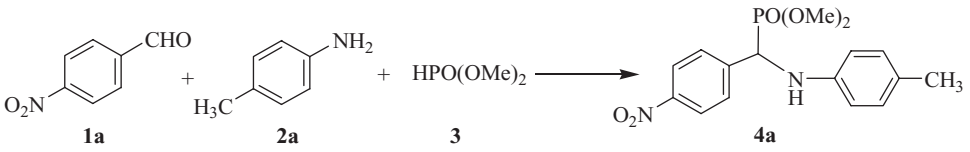
generation. Therefore, α-aminophosphonates have been the subject of considerable current interest among medicinal and organic chemists. To date, various methodologies have been developed for the synthesis of α-aminophosphonate. First, nucleophilic addition of phosphite to imine is established as a useful method to construct such scaffold.[5] However, this method has limitations as many imines are hygroscopic and are not sufficiently stable for isolation. As an improvement, the one-pot synthesis of α-aminophosphonates directly from aldehyde, amine, and phosphite was first achieved under the catalysis of lanthanide triflates.[6] Subsequently, one-pot variations in organic solvents were improved.[7] Furthermore, it was reported that solvent-free transformations of phosphites to α-aminophosphonates could be accomplished in the presence of acidic catalysts.[8] More recently, microwave-assisted and ultrasonic-assisted reactions proved to be promising for such three-component reaction.[9] However, most of the existing methods still displayed such drawbacks as environmental pollution caused by utilization of volatile solvents and costly and moisture-sensitive catalysts, harsh reaction conditions, and unsatisfactory yields. Therefore, it is currently a challenging task to develop more efficient and convenient methods for the preparation of α-aminophosphonates.

On the other hand, the "privileged" structure of nucleosides has led to a variety of efficacious antiviral agents. Many pyrimidine nucleoside analogues with potent biological properties have arisen by substitution at the 5-position of the uracil base, particularly in the 2′-deoxyuridine series.[10] In this regard, we have an ongoing program on the design and preparation of novel 5-substituted pyrimidine nucleoside derivatives with potential biological activities.[11] Our approaches to new lead compounds have been guided by the following considerations. First, the nucleoside scaffold is an excellent point of departure in the search for new compounds with potential biological activities; second, other privileged molecular scaffolds, taking α-aminophosphonate as an example, has also spawned a significant number of drugs and biologically active agents. Therefore, we were interested in the preparation of novel hybrids of 5-substituted pyrimidine nucleoside and aminophosphonate to get new entities with potentially synergic biological activities. To obtain these new hybrid compounds, we envisioned a route by employing 5-formyl-2′-deoxyuridine as the aldehyde component in the three-component condensation process leading to α-aminophosphonates as described previously.

RESULTS AND DISCUSSION

First, the reaction of 4-nitrobenzaldehyde (**1a**), 4-methylaniline (**2a**) and dimethyl phosphite (**3**) was considered as a model reaction to optimize the reaction (Scheme 1). The results are summarized in Table 1.



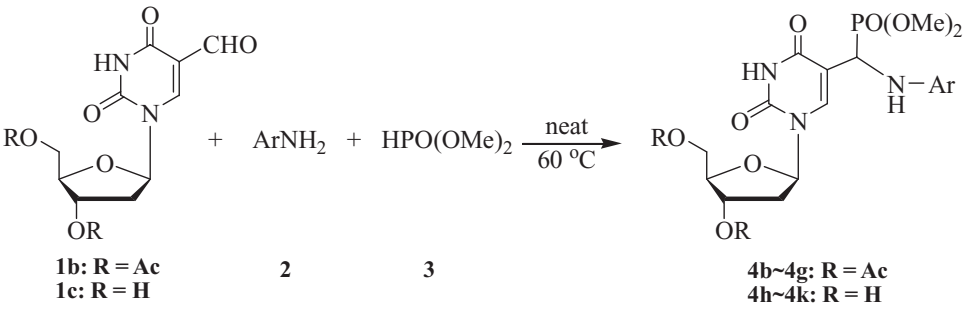
SCHEME 1 Optimization of the reaction conditions.

The mixture of **1a**, **2a**, and **3** was firstly stirred at 60°C in 10 mL of THF for 3 hours and the corresponding product (**4a**) was obtained in low yield (Table 1, entry 1). Similar results were also observed with CH_2Cl_2, CH_3CN or toluene as the reaction medium (Table 1, entry 2–4). Next, the reaction was tried in two readily available ionic liquids, [bmim]BF_4 and [bmim]PF_6, and to our delight, **4a** was obtained in much improved yield (Table 1, entries 5 and 6). As a further aspect, considering the fact that there has been increasing interest in solvent-free organic reactions since they are generally faster, give higher selectivity and yields, and require easier work-up procedures and simpler equipment, we continued our study by running this reaction under neat condition. Quite encouragingly, the reaction of **1a**, **2a**, and **3** could be realized in neat condition and **4a** was obtained in a yield of 91% when the three-component reaction was run at 60°C for 1 hour (Table 1, entry 9). No significant improvement in terms of yield was observed when the reaction temperature was increased to 80°C (Table 1, entry 10). It should be noted that upon completion of the reaction, **4a** was in solid state and could be obtained with high purity through filtration and washing with cold ethanol. It was observed that for **4a**, the carbon connecting to the P(O)$(OMe)_2$ moiety is a newly formed chiral center. Since all the starting materials for the synthesis of **4a** are achiral, the product is formed as a racemic mixture of two enantiomers.

TABLE 1 Optimization of the reaction conditions[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[d]
1	THF[b]	60	3	21
2	CH_2Cl_2[b]	reflux	3	25
3	CH_3CN[b]	60	3	28
4	Toluene[b]	60	3	26
5	[bmim]BF_4[c]	80	3	82
6	[bmim]PF_6[c]	80	3	85
7	neat	r t	1	40
8	neat	40	1	65
9	neat	60	1	91
10	neat	80	1	93

[a]**1a**: 1 mmol, **2a**: 1 mmol, **3**: 1.2 mmol.
[b]10 mL of solvent was used.
[c]1 mL of solvent was used.
[d]Isolated yields.

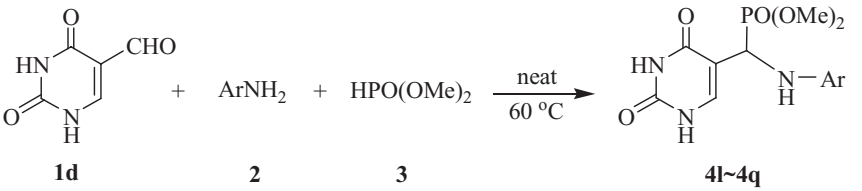


SCHEME 2 Preparation of pyrimidine nucleoside-aminophosphonate hybrids.

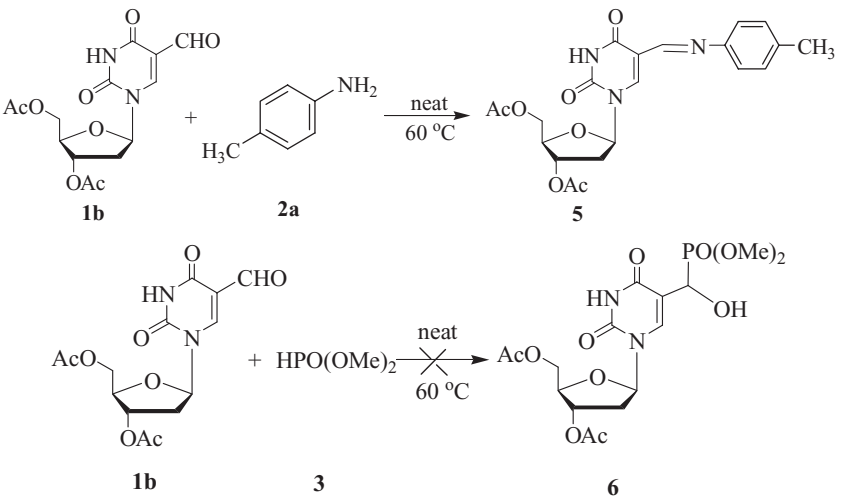
Having established such a simple and efficient procedure, we then applied the optimized reaction conditions in the preparation of pyrimidine nucleoside-aminophosphonate hybrids by using 5-formyl-2′-deoxyuridine as the aldehyde component (**1b** or **1c**, Scheme 2). By treating **1b** or **1c**, **2** and **3** under neat condition, good to excellent results were obtained and the reaction was compatible with various functional groups such as OMe, Cl, Br, and F. Excellent chemoselectivity was also observed for substrates containing a halogen atom. We did not experience any competitive aromatic nucleophilic substitution of the halogen atom. In addition, based on NMR data, it was concluded that compound **4b–4k** were obtained as a 1:1 diastereomeric mixture arising from the generation of a chiral carbon connecting to the $P(O)(OMe)_2$ moiety.

Then, the reaction was extended to 5-formyluracil (**1d**, Scheme 3), used as another kind of aldehyde substrate. It also gave the corresponding product with excellent yields through a very simple and convenient procedure (Table 3). Compared with their nucleoside counterparts, they are devoid of the sugar moiety and were expected to serve as control compounds in the QSAR study.

The formation of α-aminophosphonate was reported to follow two distinct pathways: (a) imine formation from aldehyde and amine followed by nucleophilic attack by the phosphite and (b) nucleophilic displacement of the hydroxyl group of the initially formed α-hydroxyphosphonate. Thus, in separate experiments we treated (a) **1b** with **2a** at 60°C under neat condition; (b) **1b** with **3** at 60°C under neat condition (Scheme 4). As a result,



SCHEME 3 Preparation of uracil-aminophosphonate hybrids.



SCHEME 4 Mechanism study for the formation of hybrid compounds.

imine (**5**) was formed in the former procedure but no corresponding α-hydroxyphosphonate (**6**) was observed in the latter case. This means that the formation of the hybrid compounds followed the first pathway.

As many 5-substituted pyrimidine nucleosides are known to exhibit remarkable antiviral and antileishmania activities,[10–12] the hybrid compounds (**4b–4q**) were evaluated against varicella-zoster virus (VZV) and cytomegalovirus (CMV) in human embryonic lung (HEL) cells and Leishmania donovani promastigotes. Unfortunately, none of these hybrid compounds showed any significant antiviral activity or toxicity up to 250 μM. They are also inactive against Leishmanial donovani promastigotes according to previously described protocol.

EXPERIMENTAL

Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. ^{1}H, ^{13}C, and ^{31}P NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts were expressed in parts per million (δ) downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets) and coupling constants J were given in Hz. The high-resolution mass spectra (HRMS) were performed on a JEOL HX 110A spectrometer.

TABLE 2 Preparation of hybrid compounds from 5-formyl-2′-deoxyuridine[a]

Entry	R	Ar	Time (h)	Temperature (°C)	Product	Yield (%)[b]
1	Ac	*p*-$CH_3C_6H_4$	2	60	**4b**	90
2	Ac	*p*-$CH_3OC_6H_4$	2	60	**4c**	88
3	Ac	*p*-BrC_6H_4	2	60	**4d**	85
4	Ac	*p*-ClC_6H_4	2	60	**4e**	84
5	Ac	*p*-FC_6H_4	2	60	**4f**	84
6	Ac	C_6H_5	2	60	**4g**	86
7	H	*p*-$CH_3C_6H_4$	3	80	**4h**	80
8	H	*p*-$CH_3OC_6H_4$	3	80	**4i**	78
9	H	*p*-BrC_6H_4	3	80	**4j**	75
10	H	C_6H_5	3	80	**4k**	75

[a]**1b** or **1c**: 1 mmol, **2**: 1 mmol, **3**: 1.2 mmol.
[b]Isolated yield.

General Experimental Procedure for the Preparation of Compounds 4a–4g

Carbonyl compound (**1a** or **1b**, 1 mmol), amine (**2**, 1 mmol) and dimethylphosphite (**3**, 1.2 mmol) were taken into a 50 mL flask. The mixture was stirred at 60°C for a certain period of time (shown in Tables 1 and 2) to complete the reaction (monitored by thin layer chromatography; TLC). Upon completion, the solid product was collected and washed with cold ethanol. All the products were characterized from their spectral data.

4a m.p.: 210–212°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.20 (s, 3H, CH_3), 3.64 (d, $^2J_{PH}$ = 10.8 Hz, OCH_3), 3.81 (d, $^2J_{PH}$ = 10.8 Hz, OCH_3), 4.90 (d, $^1J_{PH}$ = 25.2 Hz, CH), 6.47 (d, 2H, J = 8.0 Hz, ArH), 6.94 (d, 2H, J = 8.0 Hz, ArH), 7.67 (dd, 2H, J1 = 8.4 Hz, J2 = 2.0 Hz, ArH), 8.22 (d, 2H, J = 8.4Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3, 53.8 (d, J = 7.0 Hz), 54.2 (d, J = 7.0 Hz), 55.1, 56.5, 113.1, 123.8, 128.6, 129.8, 143.1, 143.8, 147.6. ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.20; HRMS (FAB) Calcd for $C_{16}H_{20}N_2O_5P$: 351.1111 (MH^+), Found 351.1115.

TABLE 3 Preparation of hybrid compounds[a] from 5-formyluracil

Entry	Ar	Time (h)	Temperature (°C)	Product	Yield (%)[b]
1	*p*-$CH_3C_6H_4$	2	60	**4l**	96
2	*p*-$CH_3OC_6H_4$	2	60	**4m**	95
3	*p*-BrC_6H_4	2	60	**4n**	93
4	*p*-ClC_6H_4	2	60	**4o**	90
5	*p*-FC_6H_4	2	60	**4p**	90
6	C_6H_5	2	60	**4q**	92

[a]**1d**: 1 mmol, **2**: 1 mmol, **3**: 1.2 mmol.
[b]Isolated yield.

4b ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.02 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.34–2.37 (m, 2H, CH_2), 3.63 (d, 3H, $^{2}J_{PH}$ = 10.8 Hz, OCH_3), 3.68 (d, 3H, $^{2}J_{PH}$ = 10.8 Hz, OCH_3), 4.17–4.24 (m, 3H, CH, CH_2), 4.85 (dd, 1H, $^{1}J_{PH}$ = 23.2 Hz, $J2$ = 10.8 Hz, 1H, CH), 5.18–5.21 (m, 1H, CH), 5.75 (dd, 1H, $^{2}J_{PH}$ = 10.0 Hz, $J2$ = 4.8 Hz 1H, NH), 6.11–6.15 (m, 1H, CH), 6.50 (d, 2H, J = 8.0 Hz, ArH), 6.90 (d, 2H, J = 8.0 Hz, ArH), 7.85 (s, 1H, CH), 11.67 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 20.9, 21.2, 35.9, 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 64.2, 74.4, 81.7, 85.3, 110.8, 113.9, 126.7, 129.9, 139.5, 144.7, 150.2, 162.7, 170.5, 170.7; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.13; HRMS (FAB) Calcd for $C_{23}H_{31}N_3O_{10}P$: 540.1748 (MH^+), Found 540.1756.

4c ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.02 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.34–2.37 (m, 2H, CH_2), 3.61–3.67 (m, 9H, 3 × OCH_3), 4.17–4.26 (m, 3H, CH, CH_2), 4.83 (dd, $^{1}J_{PH}$ = 23.2 Hz, $J2$ = 10.8 Hz, 1H, CH), 5.18–5.20 (m, 1H, CH), 5.63 (dd, $^{2}J_{PH}$ = 10.0 Hz, $J2$ = 4.8 Hz 1H, NH), 6.11–6.15 (m, 1H, CH), 6.65 (d, 2H, J = 8.0 Hz), 6.72 (d, 2H, J = 8.0 Hz), 7.85 (s, 1H, CH), 11.67 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 21.2, 35.8, 53.5 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 55.6, 64.2, 74.4, 81.6, 85.2, 110.9, 115.0, 115.2, 139.5, 140.9, 150.2, 152.4, 162.7, 170.5, 170.7; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.02; HRMS (FAB) Calcd for $C_{23}H_{31}N_3O_{11}P$: 556.1697 (MH^+), Found 556.1706.

4d ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.33–2.50 (m, 2H, CH_2), 3.63 (d, 3H, $^{2}J_{PH}$ = 10.4 Hz, OCH_3), 3.68 (d, 3H, $^{2}J_{PH}$ = 10.8 Hz, OCH_3), 4.17–4.25 (m, 3H, CH, CH_2), 4.85 (dd, 1H, $^{1}J_{PH}$ = 22.4 Hz, $J2$ = 10.4 Hz, CH), 5.18–5.20 (m, 1H, CH), 6.11–6.14 (m, 1H, CH), 6.28 (dd, 1H, $^{2}J_{PH}$ = 9.6 Hz, $J2$ = 4.4 Hz, NH), 6.66 (d, 2H, J = 8.8 Hz, ArH), 7.23–7.25 (d, 2H, J = 8.8 Hz, ArH), 7.86 (s, 1H, CH), 11.72 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9, 21.2, 36.1, 53.6 (d, J = 7.0 Hz), 54.1 (d, J = 7.0 Hz), 64.1, 74.4, 81.8, 85.4, 108.9, 110.3, 115.6, 132.0, 146.5, 150.1, 162.6, 170.5, 170.7; ^{31}P NMR (162 MHz, DMSO-d_6): δ 24.88; HRMS (FAB) Calcd for $C_{22}H_{28}BrN_3O_{10}P$: 604.0696 (MH^+), Found 604. 0680.

4e ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.35–2.66 (m, 2H, CH_2), 3.63 (d, 3H, $^{2}J_{PH}$ = 10.4 Hz, OCH_3), 3.68 (d, 3H, $^{2}J_{PH}$ = 10.4 Hz, OCH_3), 4.17–4.25 (m, 3H, CH, CH_2), 4.88 (dd, $^{1}J_{PH}$ = 22.4 Hz, $J2$ = 10.0 Hz, 1H, CH), 5.18–5.20 (m, 1H, CH), 6.12 (t, J = 6.4 Hz, 1H, CH), 6.26 (dd, $^{2}J_{PH}$ = 9.6 Hz, $J2$ = 4.0 Hz, 1H, NH), 6.70 (d, 2H, J = 8.4 Hz, ArH), 7.12 (d, 2H, J = 8.4 Hz, ArH), 7.86 (s, 1H, CH), 11.71 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9, 21.2, 36.1, 53.6 (d, J = 7.0 Hz), 54.1 (d, J = 7.0 Hz), 64.1, 74.4, 81.8, 85.4, 110.3, 115.1, 121.4, 129.1, 139.6, 146.1, 150.1, 162.7, 170.5, 170.7; ^{31}P NMR (162 MHz, DMSO-d_6): δ 24.62; HRMS (FAB) Calcd for $C_{22}H_{28}ClN_3O_{10}P$: 560.1202 (MH^+), Found 560. 1207.

4f ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.00 (s, 3H, CH_3), 2.06 (s, 3H,CH_3), 2.22–2.42 (m, 2H, CH_2), 3.63 (d, 3H, $^2J_{PH}$ = 10.4 Hz, OCH_3), 3.68 (d, 3H, $^2J_{PH}$ = 10.4 Hz, OCH_3), 4.19–4.23 (m, 3H, CH, CH_2), 4.86 (dd, $^1J_{PH}$ = 22.4 Hz, $J2$ = 10.4 Hz, 1H, CH), 5.18–5.20 (m, 1H, CH), 5.99 (dd, $^2J_{PH}$ = 9.6 Hz, $J2$ = 4.0 Hz 1H, NH), 6.10–6.14 (m, 1H, CH), 6.69–6.71 (m, 2H, ArH), 6.92–9.96 (m, 2H, ArH), 7.85 (s, 1H, CH), 11.69 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9, 21.2, 36.0, 53.6 (d, J = 7.0 Hz), 54.1 (d, J = 7.0 Hz), 64.1, 74.4, 81.7, 85.3, 110.5, 114.8 (d, J = 7.0 Hz), 115.8, 139.5, 143.7, 150.1, 154.0, 156.8, 162.7, 170.5, 170.7; ^{31}P NMR (162 MHz, DMSO-d_6): δ 24.90; HRMS (FAB) Calcd for $C_{22}H_{28}FN_3O_{10}P$: 544.1497 (MH^+), Found 544.1493.

4g ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.02–2.05 (m, 6H, 2×CH_3), 2.32–2.38 (m, 2H, CH_2), 3.61–3.71 (m, 6H, 2×OCH_3), 4.10–4.25 (m, 3H, CH, CH_2), 4.87–4.96 (m, 1H, CH), 5.16–5.19 (m, 1H, CH), 5.92–6.13 (m, 2H, CH, NH), 6.60–6.69 (m, 3H, ArH), 7.05–7.10 (m, 2H, ArH), 7.81–7.86 (m, 1H, CH), 11.66 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.7, 20.9, 37.5, 46.9, 53.6, 54.5, 63.7, 74.2, 82.7, 85.9, 110.6, 113.8, 119.0, 129.4, 138.6, 145.5, 149.8, 162.4, 170.3, 170.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 24.92; HRMS (FAB) Calcd for $C_{22}H_{29}N_3O_{10}P$: 526.1591 (MH^+), Found 526.1590.

General Experimental Procedure for the Preparation of Compounds 4h–4k

Carbonyl compound (**1c**, 1 mmol), amine (**2**, 1 mmol), dimethylphosphite (**3**, 1.2 mmol) were taken in a 50 mL flask. The mixture was stirred at 80°C for 3 hours. Upon completion, the syrupy product was purified by silica gel column chromatography eluting with methanol-methylene chloride (1–5%) to give pure product. All the products were characterized from their spectral data.

4h ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.98–2.18 (m, 5H, CH_3, CH_2), 3.54–3.79 (m, 9H, 2 × OCH_3, CH, CH_2), 4.21–4.26 (m, 1H, CH), 4.84–4.92 (m, 1H, CH), 5.02 (s, 1H, OH), 5.26 (s, 1H, OH), 5.68–5.70 (m, 1H, NH), 6.08–6.16 (m, 1H, CH), 6.59 (d, 2H, J = 8.0 Hz, ArH), 6.90 (d, 2H, J = 8.0 Hz, ArH), 8.03–8.04 (m, 1H, CH), 11.54 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 53.7 (d, J = 7.0 Hz), 54.1 (d, J = 7.0 Hz), 62.1, 71.0, 84.9, 88.0, 109.9, 110.3, 113.9, 126.6, 129.8, 139.6, 139.7, 144.5, 144.7, 150.3, 162.8; ^{31}P NMR (162 MHz, DMSO): δ 25.22; HRMS (FAB) Calcd for $C_{19}H_{27}N_3O_8P$: 456.1537 (MH^+), Found 456.1540.

4i ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12–2.33 (m, 2H, CH_2), 3.70–3.96 (m, 12H, CH, CH_2, 3 × OCH_3), 4.45–4.47 (m, 1H, CH), 5.05 (d, $^1J_{PH}$ = 23.2 Hz, 1H, CH), 6.29 (t, J = 6.4 Hz, 1H, CH), 6.69 (d, 2H, J = 9.2 Hz, ArH), 6.74 (d, 2H, J = 9.2 Hz, ArH), 8.28 (s, 1H, CH), 10.03 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.5, 53.9, 54.7, 55.6, 61.7, 71.1, 85.5, 87.6,

109.9, 114.9, 115.5, 139.2, 150.2, 153.1, 162.8; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.27; HRMS (FAB) Calcd for $C_{19}H_{27}N_3O_9P$: 472.1486 (MH^+), Found 472.1480.

4j ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.88–2.20 (m, 2H, CH_2), 3.49–3.80 (m, 9H, CH, CH_2, 2 × OCH_3), 4.19–4.26 (m, 1H, CH), 4.82–4.92 (m, 1H, CH), 4.96 (s, 1H, OH), 5.28 (s, 1H, OH), 6.08–6.20 (m, 2H, CH, NH), 6.65 (d, 2H, J = 8.0 Hz, ArH), 7.24 (d, 2H, J = 8.0 Hz, ArH), 8.00–8.02 (m, 1H, CH), 11.54 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 36.0, 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 54.1, 64.1, 74.4, 81.7, 85.3, 110.5, 114.7 (d, J = 7.0 Hz), 115.7, 115.9, 139.5, 143.6, 143.8, 150.1, 162.7; ^{31}P NMR (162 MHz, DMSO-d_6): δ 24.7; HRMS (FAB) Calcd for $C_{18}H_{24}BrN_3O_8P$: 520.0485 (MH^+), Found 520.0488.

4k ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.90–2.18 (m, 2H, CH_2), 3.51–3.69 (m, 8H, CH_2, 2 × OCH_3), 3.76–3.78 (m, 1H, CH), 4.18–4.24 (m, 1H, CH), 4.87–4.95 (m, 1H, CH), 4.96 (s, 1H, OH), 5.28 (s, 1H, OH), 5.91–6.15 (m, 2H, NH, CH), 6.59–6.67 (m, 3H, ArH), 7.06–7.10 (m, 2H, ArH), 8.00–8.03 (m, 1H, CH), 11.57 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 53.6 (d, J = 7.0 Hz), 53.7 (d, J = 7.0 Hz), 54.0, 54.1, 62.0, 71.0, 84.8, 88.0, 109.8, 110.2, 113.6, 113.7, 118.0, 129.4, 147.0, 150.2, 150.2, 162.8; ^{31}P NMR (162 MHz, DMSO-d_6): δ 24.89; HRMS (FAB) Calcd for $C_{18}H_{25}N_3O_8P$: 442.1380 (MH^+), Found 442.1366.

General Experimental Procedure for the Preparation of Compounds 4l–4q

Carbonyl compound (**1d**, 1 mmol), amine (**2**, 1 mmol), dimethylphosphite (**3**, 1.2 mmol) were taken in a 50 mL flask. The mixture was stirred at 60°C for 2 hours. Upon completion, the solid product was collected and washed with cold ethanol. All the products were characterized from their spectral data.

4l m.p.: 184–185°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.13 (s, 3H, CH_3), 3.61 (d, $^2J_{PH}$ = 10.8 Hz, 3H, OCH_3), 3.69 (d, $^2J_{PH}$ = 10.8 Hz, 3H, OCH_3), 4.83 (dd, $^1J_{PH}$ = 23.2 Hz, $J2$ = 10.8 Hz, 1H, CH), 5.63 (dd, $^2J_{PH}$ = 10.8 Hz, $J2$ = 4.8 Hz, 1H, NH), 6.56 (d, 2H, J = 8.4 Hz, ArH), 6.89 (d, 2H, J = 8.4 Hz, ArH), 7.57–7.59 (m, 1H, CH), 11.05 (d, 1H, J = 5.2 Hz, NH), 11.29 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.5, 52.2, 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 108.7, 113.9, 126.4, 129.8, 141.1, 144.7, 151.2, 163.8, 163.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.09; HRMS (FAB) Calcd for $C_{14}H_{19}N_3O_5P$: 340.1063 (MH^+), Found 340.1058.

4m m.p.: 188–189°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.62 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.69 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 4.79 (dd, $^1J_{PH}$ = 23.6 Hz, $J2$ = 11.2 Hz, 1H, CH), 5.63 (dd, $^2J_{PH}$ = 11.2 Hz, $J2$ = 4.8 Hz, 1H, NH), 6.60 (d, 2H, J = 8.0 Hz, ArH), 6.71

(d, 2H, J = 8.0 Hz, ArH), 7.57–7.59 (m, 1H, CH), 11.05 (d, 1H, J = 5.2 Hz, NH), 11.28 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 55.6, 108.7, 114.9, 115.0, 140.8, 141.0, 151.2, 152.2, 163.8, 163.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.10; HRMS (FAB) Calcd for $C_{14}H_{19}N_3O_6P$: 356.1012 (MH^+), Found 356.1008.

4n m.p.: 221–223°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.62 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 3.69 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 4.82 (dd, $^1J_{PH}$ = 22.8 Hz, $J2$ = 10.4 Hz, 1H, CH), 6.39 (dd, $^2J_{PH}$ = 10.4 Hz, $J2$ = 4.8 Hz, 1H, NH), 6.62 (d, 2H, J = 8.0Hz, ArH), 7.23 (d, 2H, J = 8.0Hz, ArH), 7.56–7.58 (m, 1H, CH), 11.08 (d, 1H, J = 4.8 Hz, NH), 11.34 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 108.2, 108.7, 115.6, 131.9, 141.2, 146.5, 151.1, 163.8, 163.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.12; HRMS (FAB) Calcd for $C_{13}H_{16}BrN_3O_5P$: 404.0012 (MH^+), Found 404.0005.

4o m.p.: 210–212°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.62 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 3.68 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 4.83 (dd, $^1J_{PH}$ = 22.8 Hz, $J2$ = 10.4 Hz, 1H, CH), 6.39 (dd, $^2J_{PH}$ = 10.4 Hz, $J2$ = 4.8 Hz 1H, NH), 6.66 (d, 2H, J = 8.8 Hz, ArH), 7.12 (d, 2H, J = 8.8 Hz, ArH), 7.55–7.58 (m, 1H, CH), 11.08 (d, 1H, J = 5.2 Hz, NH), 11.34 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 53.7 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 108.3, 115.1, 121.2, 129.1, 141.2, 146.1, 151.1, 163.8, 163.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.22; HRMS (FAB) Calcd for $C_{13}H_{16}ClN_3O_5P$: 360.0517 (MH^+), Found 360.0515.

4p m.p.: 207–209°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.62 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 3.69 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 4.81 (dd, $^1J_{PH}$ = 23.2 Hz, $J2$ = 10.8 Hz, 1H, CH), 6.39 (dd, $^2J_{PH}$ = 10.8 Hz, $J2$ = 4.8 Hz, 1H, NH), 6.63–6.96 (m, 4H, ArH), 7.56–7.59 (m, 1H, CH), 11.07 (d, 1H, J = 4.8 Hz, NH), 11.32 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 52.2, 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 108.4, 114.7 (d, J = 7.0 Hz), 115.7, 115.9, 141.2, 143.6, 151.2, 163.8, 163.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.34; HRMS (FAB) Calcd for $C_{13}H_{16}FN_3O_5P$: 344.0812 (MH^+), Found 344.0811.

4q m.p.: 195°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.61 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 3.67 (d, $^2J_{PH}$ = 10.4 Hz, 3H, OCH_3), 4.85 (dd, $^1J_{PH}$ = 23.2 Hz, $J2$ = 10.8 Hz, 1H, CH), 6.13 (dd, $^2J_{PH}$ = 10.8 Hz, $J2$ = 4.8 Hz, 1H, NH), 6.62–6.65 (m, 3H, ArH), 7.07 (t, J = 7.6 Hz, 2H, ArH), 7.57–7.59 (m, 1H, CH), 11.06 (d, 1H, J = 5.2 Hz, NH), 11.30 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 52.2 53.6 (d, J = 7.0 Hz), 54.0 (d, J = 7.0 Hz), 108.6, 113.6, 117.9, 129.4, 141.2, 147.0, 151.2, 163.8, 163.9; ^{31}P NMR (162 MHz, DMSO-d_6): δ 25.18; HRMS (FAB) Calcd for $C_{13}H_{17}N_3O_5P$: 326.0907 (MH^+), Found 326.0901.

5 ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.42–2.46 (m, 2H, CH_2), 4.25–4.33 (m, 3H, CH, CH_2), 5.23–5.25 (m, 1H, CH), 6.20–6.23 (m, 1H, CH), 7.06 (d, 2H, J = 8.0 Hz, ArH), 7.19 (d, 2H, J = 8.0 Hz, ArH), 8.40 (s, 1H, CH), 8.43 (s, 1H, CH),

11.83 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0, 21.2, 37.6, 53.6, 64.1, 74.7, 82.4, 86.0, 110.6, 121.2, 130.2, 135.7, 139.7, 149.2, 150.1, 152.3, 162.7, 170.5, 170.6.

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