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A Facile Catalyst-free Pudovik Reaction for the Synthesis of α-Amino Phosphonates

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ABSTRACT

Some imines were synthesized by the reaction of 5-amino 1-naphthol with substituted aromatic aldehydes in ethanol under reflux conditions. Dialkyl phosphites underwent addition with aromatic imines to give novel α-amino phosphonates. All the title compounds were characterized by elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data. All the newly-synthesized compounds (4a–j) exhibited moderate antibacterial and antifungal activity.

KEYWORDS

5-Amino-1-naphthol, imines, dialkyl phosphite, α-amino phosphonates, antimicrobial activity.

1. Introduction

α-Amino phosphonates are an important class of compounds since they are structural analogues of naturally-occurring aminoacids as building blocks of peptides in biological systems. In addition to this the structural similarity with naturally-occurring α-aminoacids gave momentum to the synthesis of α-amino phosphonic acids and their derivatives for applications in biological systems. α-Amino phosphonates possess an array of potential binding sites for both ammonium (phosphoryl group, nitrogen lone pair) and carboxylate (N-H bond) moieties.[1] The α-amino phosphonate derivatives are gaining much importance in medicinal chemistry[2] and their applications as enzyme inhibitors,[3] pharmacological agents,[4] herbicides,[5] antibiotics[6] and inhibitors of excitatory post-synaptic potential (EPSP) synthase[7] and HIV protease.[8] α-Amino phosphonic acids seem to be even closer analogues of their α-amino phosphonic counterparts due to their monobasic/acidic character and higher stability of the P-C bond of phosphonic acids compared with the P-O bond.[9] There are now numerous reviews to guide the reader into this fascinating aspect of phosphorus chemistry. Moreover, extensive coverage of the role of phosphonates in living systems has been provided in books by Hildebrand and Henderson[10]. The Pudovik reaction is one of the most convenient methods for the formation of P-C bonds and involves the addition of compounds containing a labile P-H bond with imines.[11,12] The reaction usually needs a Lewis acid catalyst such as indium (III) chloride,[13] rare earth triflates,[14] SmI_2,[15] or $LiClO_4$.[16] However, many of these catalysts are expensive and have to be used in stoichiometric amounts. Reports on catalyst-free synthesis of α-amino phosphonates are rather limited.[17] Keeping this in view, we have developed a new protocol of catalyst-free synthesis of α-amino phosphonates and evaluated their antimicrobial activity.

2. Results and Discussion

A series of new α-amino phosphonates was synthesized in a two-step process. The synthetic route involves the condensation of 5-amino-1-naphthol (**1**) with different substituted aromatic aldehydes (**2a–j**) in dry ethanol under reflux conditions to form different substituted imines (**3a–j**) (Scheme 1). In the second step, the imines were reacted with the respective dialkyl phosphites in dry ethanol at reflux temperature to obtain the α-amino phosphonates (**4a–j**) in high yields (75–84 %). The second step of the reaction was completed at reflux temperature of ethanol with stirring for 3–4 h. The progress of the reaction was monitored by TLC analysis using ethyl acetate:n-hexane(4:6) as mobile phase. The crude products were obtained after removing the solvent under reduced pressure. The crude products were purified by column chromatography on silica gel using ethyl acetate:n-hexane (2:8) solvent mixture as eluent. The synthetic and analytical data of α-amino phosphonates (**4a–j**) are given in the experimental part.

The IR spectra of the title compounds (**4a–j**) show absorption bands at 3520–3340 cm^{-1} for O-H stretching vibrations. The N-H and P=O stretching vibrations[18] are observed in the regions 3310–3100 cm^{-1} and 1290–1210 cm^{-1}, respectively. The aromatic O-H proton signal appears as a singlet in the range of δ 10.31–9.69 ppm. The aromatic protons of **4a–j** resonate as multiplets in the region δ 7.89–6.51 ppm. The N-H proton signal appeared as a triplet in the range of δ 6.3–5.68 ppm (t, J 7.6–12 Hz) due to its coupling with neighbouring proton and phosphorus. The P-C-H protons resonated as a pair of doublets in the region δ 5.47–5.02 ppm (dd, J 8–12 Hz, 10–18 Hz), due to its coupling with phosphorus and a neighbouring N-H proton.[19] The methylene oxy protons resonate as a multiplet in the region δ 4.28–3.89 ppm. The P-O-CH_2-CH_2-CH_2-CH_3 proton signal appears as a multiplet in the region δ 1.71–1.25 ppm. The methyl protons appear as a triplet in the region δ 1.27–0.75 ppm (t, J 6–11 Hz). The ^{13}C NMR spectral data for **4a, b, c, d** and **e** are given in the experimental part. The ^{31}P NMR signals appeared as singlets in the range δ 23.16–18.59 ppm. The LCMS data of **4a**, **c**, **d**, **f**, h and **j** are given in the experimental section.

2.1. Biological Activity

The antibacterial and antifungal activities of the test compounds were evaluated by the disc diffusion method[20] and their effect was compared with the standard antibiotic *Ampicillin* and antifungal agent *Nystatin*. The antibacterial rôle of all the title compounds (**4a–j**) was assayed against the growth of *Escherichia*

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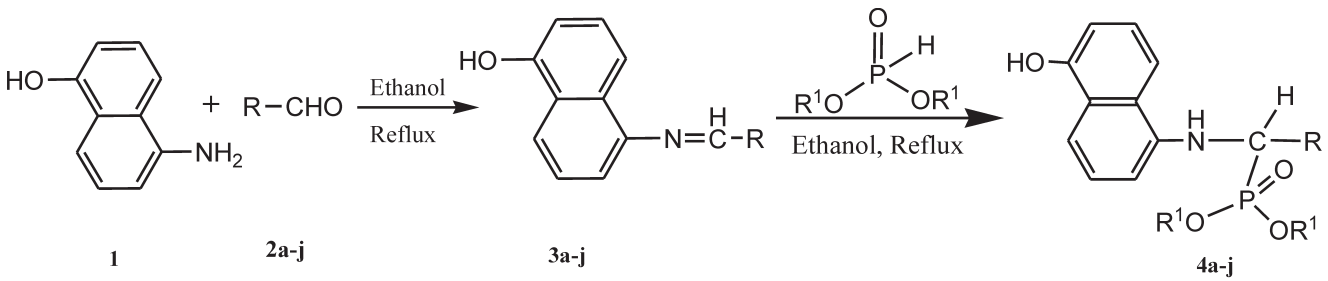
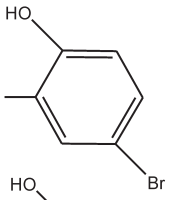
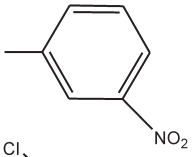
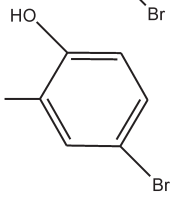
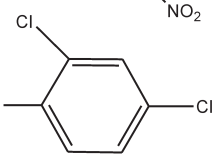
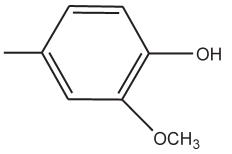
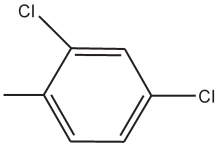
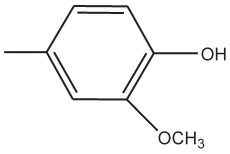
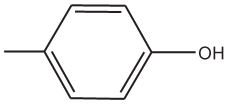
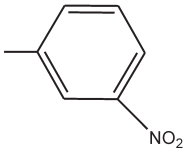
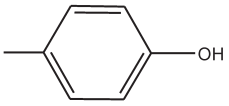


1 **2a-j** **3a-j** **4a-j**

Compound	R	R^1	Compound	R	R^1
4a		Et	**4f**		But
4b		But	**4g**		Et
4c		Et	**4h**		But
4d		But	**4i**		Et
4e		Et	**4j**		But

Scheme 1

coli and *Pseudomonas aeuroinosa* at two different concentrations, 100 μg disc^{-1} and 250 μg disc^{-1} (Table 1). The majority of the compounds exhibited moderate activity against both bacteria. *Ampicillin* was used as a standard reference compound to compare the activities of these compounds. The compounds (**4a–j**) (Table 1) were screened for their antifungal activities against *Aspergillus niger* and *Fusarium moniliforme* along with the standard fungicide *Nystatin*. It is gratifying to observe that all the compounds (**4a–j**) exhibited moderate antifungal activity compared with that of the reference compound.

3. Experimental

Melting points were determined in open capillary tubes on a Mel-temp apparatus (Tempo Instruments and Equip (Pvt.) Ltd., Mumbai, India) and were uncorrected. IR spectra were recorded in KBr pellets using a Perkin-Elmer 240-c FT-IR spectrometer (Waltham, MA, USA). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer (Ettlingen, Germany) operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. Some compounds were recorded in DMSO-d_6 and a few compounds were recorded in $CDCl_3$ and the chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85 % H_3PO_4 (^{31}P). Microanalytical data were obtained from the University of Hyderbad, Hyderbad, India.

3.1. Synthesis of Different Substituted Imines (3)

To a stirred solution of 5-amino 1-naphthol (0.002 mol) in 30 mL of dry ethanol, different substituted aromatic aldehydes (0.002 mol) in 10 mL of dry ethanol were added at 20 °C. After stirring for 2 h at reflux temperature, formation of the intermediates, substituted imines **3a–j** was ascertained by TLC analysis, using ethyl acetate:n-hexane (4:6) as eluent. The imines **3a–j** were used for the next reaction step without further purification and isolation.

3.2. Typical Procedure for the Synthesis of 4a–j

A solution of diethyl/dibutyl phosphite in 15 mL of dry ethanol was added dropwise to a stirred solution of substituted imines **3a–j** at 20 °C. After completion of the addition the temperature of the reaction was raised to reflux and the reaction mixture was stirred for 3–4 h. Completion of the reaction was ascertained by TLC analysis using ethyl acetate:n-hexane (4:6) mixture. The solvent was removed in a rotary evaporator to isolate the crude product. It was purified by column chromatography on silica gel

Table 1 Antimicrobial activity of compounds **4a–j**.

Compound	Zone of inhibition/mm			
	Antibacterial activity		Antifungal activity	
	Escherichia coli 100 μg disc^{-1}	*Pseudomonas aeuroinosa* 100 μg disc^{-1}	*Aspergillus niger* 100 μg disc^{-1}	*Fusarium moniliforme* 100 μg disc^{-1}
4a	8	11	11	12
4b	9	10	12	13
4c	11	7	13	13
4d	9	9	14	13
4e	9	9	19	20
4f	8	5	14	16
4g	7	7	18	19
4h	8	7	21	15
4i	7	6	11	12
4j	8	8	10	12
Ampicillin	20	21	–	–
Nystatin	–	–	25	23

100–200 mesh using ethyl acetate:n-hexane (2:8) mixture as eluent to obtain the pure compounds. The compounds were characterized by ^{1}H, ^{13}C, ^{31}P NMR, IR and mass spectral data.

3.3. Spectral Data

3.3.1. *Diethyl (5-bromo-2-hydroxyphenyl)(5-hydroxynaphthalen-1-ylamino) methylphosphonate* (**4a)**

Yield 82 %; solid, m.p. 129–130 °C. R_f 0.5. δ_H (400 MHz, DMSO-d_6): 10.31 (1H, s, -OH), 9.92 (1H, s, -OH), 7.55–6.57 (9H, m, Ar-H), 6.01 (1H, t, *J* 7.8 Hz, -NH), 5.30 (1H, dd, *J* 12,16 Hz, -P-CH), 4.05–3.98 (4H, m, -OCH_2), and 1.11 ppm (6H, t, *J* 10 Hz, -CH_3); δ_C (100 MHz, DMSO-d_6): 154.7 (C-1), 153.4 (C-2^1), 141.8 (C-5), 131.3 (C-6^1), 130.9 (C-4^1), 125.6 (C-3), 125.4 (C-1^1), 125.2 (C-9), 125.1 (C-7), 124.9 (C-10), 117.2 (C-3^1), 112.15 (C-5^1), 111.9 (C-2), 110.5 (C-6), 108.4 (C-4), 105.6 (C-8), 62.8 (d, *J* 10.8 Hz, P-O-*CH*$_2$-CH_3), 50.6 (-P-CH) and 16.2 ppm (d, *J* 6 Hz, P-O-CH_2-*CH*$_3$); δ_P (DMSO-d_6): 22.37 ppm; ν_{max} (KBr): 3450 (-OH), 3395 (-OH), 3275 (-NH), 1223 (P=O) and 768 cm^{-1} (P-$C_{aliphatic}$); Calc. for $C_{21}H_{23}NPO_5Br$: C, 52.47; H, 4.78; N, 2.91 %; found: C, 52.51; H, 4.69; N, 2.95 %.

3.3.2. *Dibutyl (5-bromo-2-hydroxyphenyl)(5-hydroxynaphthalen-1-ylaminomethyl phosphonate* (**4b)**

Yield 84 %; solid, m.p. 135–137 °C. R_f 0.55. δ_H (400 MHz, DMSO-d_6): 10.27 (1H, s, -OH), 9.88 (1H, s, -OH), 7.73–6.51 (9H, m, Ar-H), 5.99 (1H, t, *J* 10.2 Hz, -NH), 5.32 (1H, dd, *J* 9.6,15.6 Hz, -P-CH), 4.08–3.89 (4H, m, -O-CH_2), 1.55–1.43 (8H, m, -CH_2-) and 0.78 ppm (6H, t, *J* 8.8 Hz, -CH_3); δ_C (100 MHz, DMSO-d_6): 154.7 (C-1), 153.7 (C-2^1), 141.0 (C-5), 131.5 (C-6^1), 130.6 (C-4^1), 125.6 (C-7), 125.5 (C-9), 125.2 (C-10), 124.8 (C-3), 117.8 (C-1^1), 112.9 (C-3^1), 111.7 (C-5^1), 110.9 (C-4), 108.7 (C-6), 106.3 (C-2), 66.9 (d, *J* 8.49 Hz, P-O-*CH*$_2$-CH_2-), 51.1 (-P-CH), 32.4 (d, *J* 12.2 Hz, P-O-CH_2-*CH*$_2$-CH_2-CH_3), 18.5 (d, *J* 9.7 Hz, P-O-CH_2-CH_2-*CH*$_2$-CH_3) and 13.7 ppm (d, *J* 7.5 Hz, P-O-CH_2-CH_2-CH_2-*CH*$_3$); δ_P (DMSO-d_6): 22.93 ppm; ν_{max} (KBr): 3495 (-OH), 3345 (-OH), 3185 (-NH), 1250 (P=O) and 725 cm^{-1} (P-$C_{aliphatic}$); m/z (LCMS): 535 (M^+, 100 %), 537 (M+2, 98 %); Calc. for $C_{25}H_{31}NPO_5Br$: C, 56.03; H, 5.79; N, 2.61 %; found: C, 56.08; H, 5.81; N, 2.69 %.

3.3.3. *Diethyl (4-hydroxy-3-methoxyphenyl)(5-hydroxynaphthalen-1-ylamino) methylphosphonate* (**4c)**

Yield 79 %; solid, m.p. 138–140 °C. R_f 0.45. δ_H (400 MHz, DMSO-d_6): 9.91 (1H, s, -OH), 9.72 (1H, s, -OH), 7.56–6.51 (9H, m, Ar-H), 5.74 (1H, t, *J* 7.6 Hz, -NH), 5.01 (1H, dd, *J* 12,16 Hz, -P-CH), 4.08–3.94 (4H, m, -OCH_2), 3.73 (3H, s, -OCH_3), and 1.12 ppm (6H, t, *J* 8 Hz, -CH_3); δ_C (100 MHz, DMSO-d_6): 153.6 (C-1), 147.4 (C-3^1), 146.2 (C-4^1), 141.6 (C-5), 126.9 (C-1^1), 125.3 (C-9), 125.1 (C-7), 124.9 (C-10), 124.6 (C-3), 120.5 (C-6^1), 115.2 (C-5^1), 112.6 (C-4), 111.8 (C-8), 111.2 (C-2^1), 108.2 (C-2), 108.2 (C-6), 62.5 (d, *J* 9.4 Hz, P-O-*CH*$_2$$CH_3$), 59.7 (Ar-$OCH_3$), 53.6 (-P-CH) and 16.2 ppm (d, *J* 6.5 Hz, P-O-CH_2-*CH*$_3$); δ_P (DMSO-d_6): 21.17 ppm; ν_{max} (KBr): 3510 (-OH), 3340 (-OH), 3125 (-NH), 1270 (P=O), and 750 cm^{-1} (P-$C_{aliphatic}$); Calc. for $C_{22}H_{26}NPO_6$: C, 61.21; H, 6.02; N, 3.24 %; found: C, 61.15; H, 5.98; N, 3.29 %.

3.3.4. *Dibutyl (4-hydroxy-3-methoxyphenyl)(5-hydroxynaphthalen-1-ylamino) methylphosphonate* (**4d**)

Yield 81 %; solid, m.p. 142–144 °C. R_f 0.6. δ_H (400 MHz, DMSO-d_6): 9.88 (1H, s, -OH), 9.69 (1H, s, -OH), 7.52–6.61 (9H, m, Ar-H), 5.70 (1H, t, *J* 8 Hz, -NH), 5.02 (1H, dd, *J* 12.5,18.0 Hz, -P-CH), 4.09–3.95 (4H, m, -OCH_2), 3.72 (3H, s, -OCH_3), 1.54–1.28 (8H, m, -CH_2-) and 0.83 ppm (6H, t, *J* 9.6 Hz, -CH_3); δ_C (100 MHz, DMSO-d_6): 154.6 (C-1), 153.7 (C-3^1), 147.7 (C-5), 147.4 (C-4^1), 146.6 (C-1^1), 132.9 (C-9), 132.7 (C-7), 127.2 (C-10), 126.1 (C-3), 122.9 (C-6^1), 122.6 (C-5^1), 115.5 (C-4), 115.3 (C-2^1), 114.8 (C-6), 114.6 (C-2), 60.41 (d, *J* 8.5 Hz, P-O-*CH*$_2$-CH_2-CH_2-CH_3), 57.7 (-P-CH), 54.7 (Ar-OCH_3) 30.2 (d, *J* 14 Hz, P-O-CH_2-*CH*$_2$-CH_2-CH_3), 18.6 (d, *J* 10.6 Hz, P-O-CH_2-CH_2-*CH*$_2$-CH_3) and 13.5 ppm (d, *J* 8 Hz, P-O-CH_2-CH_2-CH_2-*CH*$_3$); δ_P (DMSO-d_6): 23.10 ppm; ν_{max} (KBr): 3503 (-OH), 3364 (-OH), 3100 (-NH), 1235 (P=O) and 727 cm^{-1} (P-$C_{aliphatic}$); m/z (LCMS): 487 (M^+); Calc. for $C_{26}H_{34}NPO_6$: C, 64.01; H, 6.97; N, 2.87 %; found: C, 64.08; H, 6.89; N, 2.91 %.

3.3.5. *Diethyl (5-hydroxynaphthalen-1-ylamino) (3-nitrophenyl) methylphosphonate* (**4e**)

Yield 80 %; solid, m.p. 129–130 °C. R_f 0.57. δ_H (400 MHz, $CDCl_3$): 10.25 (1H, s, -OH), 7.68–6.92 (10H, m, Ar-H), 5.91 (1H, t, *J* 12 Hz, N-H), 5.04 (1H, dd, *J* 10.8,12 Hz, -P-CH), 4.25–4.09 (4H, m, -OCH_2), and 1.21 ppm (6H, t, *J* 8 Hz, -CH_3); δ_C (100 MHz, $CDCl_3$): 152.8 (C-1), 148.5 (C-5), 148.7 (C-3^1), 133.6 (C-1^1), 129.7 (C-6^1), 125.6 (C-5^1), 125.3 (C-7), 125.1(C-9), 123.1 (C-3), 122.8 (C-10), 113.1 (C-2^1), 112.1 (C-4^1), 109.2 (C-4), 109.7 (C-6), 107.0 (C-2), 63.8 (d, *J* 7 Hz, P-O-*CH*$_2$-CH_3), 58.5 (-P-CH) and 16.5 ppm (d, *J* 5 Hz, P-O-CH_2-CH_3); δ_p ($CDCl_3$): 19.35 ppm; ν_{max} (KBr): 3386 (-OH), 3235 (-NH), 1261 (P=O) and 727 cm^{-1} (P-$C_{aliphatic}$). m/z (LCMS): 431 (M+H); Calc. for $C_{21}H_{23}N_2PO_6$: C, 58.55; H, 5.34; N, 6.50 %; found: C, 58.46; H, 5.31; N, 6.57 %.

3.3.6. *Dibutyl (5-hydroxynaphthalen-1-ylamino)(3-nitrophenyl) methylphosphonate* (**4f**)

Yield 79 %; solid, m.p. 140–142 °C. R_f 0.43. δ_H (400 MHz, $CDCl_3$): 10.10 (1H, s, -OH), 7.89–6.90 (10H, m, Ar-H), 6.07 (1H, t, *J* 8 Hz, -NH), 5.11 (1H, dd, *J* 8,12 Hz, -P-CH), 4.15–4.05 (4H, m, $-OCH_2$), 1.71–1.39 (8H, m, $-CH_2$-) and 0.87 ppm (6H, t, *J* 7.5 Hz, $-CH_3$); δ_P ($CDCl_3$): 21.10 ppm; ν_{max} (KBr): 3380 (-OH), 3155 (-NH), 1274 (P=O) and 769 cm^{-1} (P-$C_{aliphatic}$); m/z (LCMS): 487(M+H); Calc. for $C_{25}H_{31}N_2PO_6$: C, 61.72; H, 6.37; N, 5.76 %; found: C, 61.60; H, 6.30; N, 5.80 %.

3.3.7. *Diethyl (2,4-dichlorophenyl)(5-hydroxynaphthalen-1-ylamino) methylphosphonate* (**4g**)

Yield 75 %; solid, m.p. 110-112 °C. R_f 0.63. δ_H (400 MHz, $CDCl_3$): 9.93 (1H, s, -OH), 7.68–6.73 (9H, m, Ar-H), 5.89 (1H, t, *J* 10 Hz, -NH), 5.47 (1H, dd, *J* 8.0, 10.0 Hz, -P-CH), 4.28–4.09 (4H, m, $-OCH_2$) and 1.20 ppm (6H, t, *J* 6 Hz, $-CH_3$); δ_P ($CDCl_3$): 18.59 ppm; ν_{max} (KBr): 3400 (O-H), 3230 (N-H), 1272 (P=O) and 797 cm^{-1} (P-$C_{aliphatic}$); Calc. for $C_{21}H_{22}NPO_4Cl_2$: C, 55.50; H, 4.84; N, 3.08 %; found: C, 55.45; H, 4.79; N, 3.12 %.

3.3.8. *Dibutyl (2,4-dichlorophenyl)(5-hydroxynaphthalen-1-ylamino)methylphosphonate* (**4h**)

Yield 77 %; solid, m.p. 135–138 °C. R_f 0.65. δ_H (400 MHz, $CDCl_3$): 9.89 (1H, s, -OH), 7.71–7.09 (9H, m, Ar-H), 5.68 (1H, t, *J* 7.6 Hz, -NH), 5.42 (1H, dd, *J* 8,12 Hz, -P-CH), 4.11–3.93 (4H, m, O-CH_2),1.69–1.41 (8H, m, -ch_2-) and 0.91 ppm (6H, t, J 8 Hz, $-CH_3$); δ_P (DMSO-d_6): 19.12 ppm; ν_{max} (KBr): 3433 (O-H), 3162 (N-H), 1261 (P=O) and 760 cm^{-1} (P-$C_{aliphatic}$); Calc. for $C_{25}H_{30}NPO_4Cl_2$: C, 58.79; H, 5.87; N, 2.74 %; found: C, 58.65; H, 5.78; N, 2.80 %.

3.3.9. *Diethyl (5-hydroxynaphthalen-1-ylamino)(4-hydroxyphenyl) methylphosphonate* (**4i**)

Yield 76 %; solid, m.p. 150–151 °C. R_f 0.52. δ_H (400 MHz, DMSO-d_6): 10.31 (1H, s, -OH), 9.79 (1H, s, -OH), 7.77–6.92 (10H, m, Ar-H), 6.10 (1H, t, *J* 10 Hz, -NH), 5.08 (1H, dd, *J* 8.5,13.0 Hz, -P-CH), 4.01–3.89 (4H, m, $-OCH_2$) and 1.19 ppm (6H, t, *J* 11 Hz, $-CH_3$); δ_P (DMSO-d_6): 19.95 ppm; ν_{max} (KBr): 3366 (-OH), 3355 (-OH), 3310 (-NH), 1216 (P=O) and 732 cm^{-1} (P-$C_{aliphatic}$); Calc. for $C_{21}H_{24}NPO_5$: C, 62.80; H, 5.98; N, 3.48 %; found: C, 62.79; H, 5.94; N, 3.49 %.

3.3.10. *Dibutyl (5-hydroxynaphthalen-1-ylamino)(4-hydroxyphenyl)methylphosphonate* (**4j**)

Yield 78 %; solid, m.p. 148–150 °C. R_f 0.47. δ_H (400 MHz, DMSO-d_6): 10.21 (1H, s, -OH), 9.79 (1H, s, -OH), 7.76–6.64 (10H, m, Ar-H), 6.21 (1H, t, *J* 8 Hz, -NH), 5.16 (1H, dd, *J* 12, 14 Hz, -P-CH), 4.19–4.01 (4H, m, $-OCH_2$), 1.58–1.41 (8H, m, $-CH_2$-) and 0.90 ppm (6H, t, *J* 10.5 Hz, $-CH_3$); δ_P (DMSO-d_6): 19.75 ppm; ν_{max} (KBr): 3335 (-OH), 3261 (-OH), 3200 (-NH), 1214 (P=O) and 768 cm^{-1} (P-$C_{aliphatic}$); Calc. for $C_{25}H_{32}NPO_5$: C, 65.59; H, 6.99; N, 3.06 %; found: C, 65.51; H, 6.95; N, 3.12 %.

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