Research Article

Preparation of New α -Aminophosphonate Derivatives by Kabachnik-Fields Reaction Using a Recyclable Catalyst

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A convenient and efficient synthetic method for the preparation of some new α -aminophosphonate derivatives via a one-pot three-component system has been achieved using Amberlite IRC-748 as a recyclable catalyst. This method not only provides an excellent complement for the synthesis of α -aminophosphonates but also avoids the use of hazardous acids or expensive/toxic Lewis acids and harsh reaction conditions. Most of the synthesized compounds (**4a–o**) exhibited activity against bacteria/fungi strains and moderate DPPH radical scavenging activity.

1. Introduction

Organophosphorus compounds are ubiquitous in nature and find applications in the fields of agriculture, medicine, and industry [1–3]. Some organophosphorus compounds are important pesticides [4], bactericides [5–7], and antibiotics [5]. Phosphorus analogues of α -pyrones act as HIV protease inhibitors [8]. α -Aminophosphonic acids constitute important motifs among the organophosphorus compounds in medicinal chemistry due to their obvious structural similarities to α -amino acids [9, 10]. Many natural and synthetic aminophosphonic acids and their ester and peptide derivatives display a wide range of biological activities [11, 12], act as herbicides [13], enzyme inhibitors [14], and antibacterial [15, 16], antiviral [10], and antitumor [17] agents, and may even be peptide mimics [18].

The most common synthetic route to α -aminophosphonic acids is via chemical manipulation of the corresponding α -aminophosphonates [19–21]. The hydrophosphonylation of imines is a widely used method for the synthesis of α -aminophosphonates [19–27]. This is achieved by one of two pathways: (i) in a two-component fashion known as the Pudovik reaction [28, 29] or (ii) by the Kabachnik-Fields reaction [22, 23, 30, 31] which combines in situ formation of imine by condensation of amines with an aldehyde or ketone and an hydrophosphonylation step [32].

One-pot Kabachnik-Fields reaction can be promoted by acidic or basic catalysts, microwave irradiation, or by heating [33]. Several Lewis acid catalysts, such as InCl_3 [34], LiClO_4 [35, 36], $\text{Mg}(\text{ClO}_4)_2$ [37], $\text{ZrOCl}_2 \cdot 5\text{H}_2\text{O}$ [38], $\text{Al}(\text{H}_2\text{PO}_4)_3$ [39], BiCl_3 [40], FeCl_3 [41], YbCl_3 [42], $\text{In}(\text{OTf})_3$ [43], $\text{Ce}(\text{OTf})_4$ [44], $\text{Al}(\text{OTf})_3$ [45], CAN [46], $\text{TaCl}_5\text{-SiO}_2$ [47], and SmI_2 [48] solid acids (montmorillonite KSF, silica sulfuric acid, Amberlyst-15, and Amberlite-IR 120) [49], base catalysts such as CaCl_2 and PPh_3 and other catalysts such as ZnO , TiO_2 , tosyl chloride, and mesoporous aluminosilicate nanocage [50] have also been used to promote this reaction. Due to the above-mentioned factors, in this paper we reported the synthesis of α -aminophosphonates with high yield using a recyclable catalyst for applications in medicine and industry.

2. Results and Discussion

In the initial experiments, the one-pot, three-component reaction of aniline, benzaldehyde, and diethyl phosphite was chosen as the model reaction to optimize the reaction conditions. In the present work, the procedures followed for the synthesis of α -aminophosphonates are conventional reflux in toluene, in the presence of catalyst (Amberlite IRC-748) and microwave irradiation (solvent-free). The data obtained are

TABLE 1: Reaction time and percentage yield of 4 in different reaction conditions.

Entry	Catalyst used	Reaction condition	Reaction time	% yield	Reference
1	Al(H ₂ PO ₄) ₃	Solvent-free/100°C	90 min	93	[39]
2	InCl ₃	THF/RT	11 h	92	[34]
3	BiCl ₃	CH ₃ CN/reflux	6 h	92	[40]
4	FeCl ₃	THF/60°C	0.75 h	92	[41]
5	YbCl ₃	CH ₃ CN/RT	24 h	93	[42]
6	In(OTf) ₃	THF/reflux	21 h	79	[43]
7	Ce(OTf) ₄	Solvent-free/50°C	20 min	94	[44]
8	Mg(ClO ₄) ₂	Solvent-free/80°C	5 h	99	[37]
9	CAN	Solvent-free/reflux	30 min	96	[46]
10	TaCl ₅ -SiO ₂	CH ₂ Cl ₂ /RT	22 h	92	[47]
11	TiO ₂	Solvent-free/50°C	3.5 h	98	[50]
12	ZnO	Solvent-free/RT	9 h	90	[50]
13	NBS	Solvent-free/50°C	3 h	99	[50]
14	Silica sulfuric acid	CH ₃ CN/RT	5 h	87	[49]
15	3D mesoporous aluminosilicate nanocage	CH ₃ CN/80°C	4 h	86	[50]
16	Cu(3,4-tmtppa)(MeSO ₄) ₄	H ₂ O/80°C	0.5 h	96	[50]
17	B-CD	H ₂ O/reflux	24 h	61	[50]
18	CaCl ₂	Solvent-free/60°C	3 h	90	[48]
19	PPh ₃	Solvent-free/60°C	1 h	87	[48]
20	NbCl ₅	Solvent-free/50°C	30 min	95	[50]
21	—	Toluene/reflux	5 h	81	Present work
22	—	Solvent-free/mw	1 min	87	Present work
23	Amberlyst-IRC 748	Toluene/reflux	30 min	93	Present work

shown in Table 1, entries 21–23. A comparison of the catalysts used in the Kabachnik-Field reaction for the synthesis of 4 is listed in Table 1, serial numbers 1–20.

The products α -aminophosphonates were obtained by solvent-free microwave irradiation of aldehyde, amine, and diethyl phosphite for 1 min. In toluene, without any catalyst, the product formed was in a good yield, but the time taken was 4 to 5 h, which is considerably longer. Therefore, the reaction time has been reduced to 30 min by using Amberlite IRC-748 a recyclable catalyst. This catalyst is mildly acidic with iminodiacetic acid functional group. Amberlite IRC-748 acts as an efficient and recyclable acidic promoter which yields good results when compared to the catalysts reported earlier (Table 1). The reaction mechanism proceeds as in case of acid catalysts. In optimization of reaction time, the yield of the product did not increase, when more than 5 mg of catalyst was used. This suggested the use of 5 mg of Amberlite catalyst for 0.005 mol of reactants. Thin layer chromatography (TLC) was employed to monitor reaction progress and to determine the purity of the products.

New α -aminophosphonic acid esters (**4a–o**) were synthesized by a one-pot reaction using equimolar quantities of different substituted aromatic amines and aldehydes with diethylphosphite (Scheme 2). The reaction was carried out using catalytic amount of Amberlite IRC-748, in toluene for 30 min. All the title compounds are readily soluble in polar organic solvents.

The IR spectra of compounds (**4a–o**) showed the NH band in the range of 3338–3438 cm⁻¹. The sharp band observed

in the range 1240–1291 cm⁻¹ is due to the $\nu_{\text{P=O}}$, and a band for P–C stretching occurred in the range 740–770 cm⁻¹. All the stretching frequencies are compiled in Table 2. The ¹H NMR spectra of the compounds (**4a–o**) were recorded in the DMSO-d₆ solvent. The aromatic protons of α -aminophosphonic acid esters appeared as a multiplet in the region δ 6.15–8.69. The P–C–H group proton resonated as a multiplet in the range δ 3.77–4.86 due to coupling with phosphorus and N–H. The N–H proton signal appeared at δ 4.58–5.90 as a multiplet. The protons of P–O–CH₂–C that appeared as a quartet at δ 3.56–3.62 and P–O–C–CH₃ gave a triplet at δ 1.12–1.19. The compounds were analyzed by mass spectroscopy, the M + 1 peak confirmed product formation, and compounds containing one chlorine atom showed molecular ion peaks in a 3 : 1 ratio.

Antibacterial activity was carried out by the well diffusion method using nutrient agar medium, DMSO as control, and chloramphenicol as a standard bactericide. The antifungal activity was carried out by well diffusion method using potato dextrose agar (PDA) medium, DMSO as control, and fluconazole as a standard fungicide [51–54]. The antioxidant activity of the synthesized derivatives was evaluated using the DPPH (diphenyl picrylhydrazyl) radical scavenging assay by standard methods [55].

2.1. Antimicrobial Studies. The synthesized compounds (**4a–o**) were screened for the antimicrobial activity. Most of the synthesized compounds showed inhibited growth of the strains (Table 3). Among the samples tested, **4b**, **4d**, **4e**, **4i**,

TABLE 2: Elemental analysis and IR data of compounds (**4a–o**).

	Mol. formula	Elemental analysis found (Calc.)			IR spectral data in cm ⁻¹		
		C	H	N	–NH	P=O	P–C
4a	C ₁₉ H ₂₅ ClNO ₅ P	55.23 (55.14)	6.02 (6.09)	3.32 (3.38)	3390	1285	747
4b	C ₁₇ H ₂₀ ClN ₂ O ₇ P	47.38 (47.40)	4.59 (4.68)	6.47 (6.50)	3338	1241	739
4c	C ₁₈ H ₂₂ ClN ₂ O ₇ P	48.57 (48.60)	4.94 (4.99)	6.27 (6.30)	3135	1210	751
4d	C ₁₉ H ₂₅ ClNO ₅ P	55.18 (55.14)	6.13 (6.09)	3.32 (3.38)	3381	1268	745
4e	C ₁₇ H ₂₀ ClN ₂ O ₇ P	47.37 (47.40)	4.69 (4.68)	6.48 (6.50)	3340	1263	765
4f	C ₁₈ H ₂₂ ClN ₂ O ₇ P	48.58 (48.60)	4.94 (4.99)	6.27 (6.30)	3421	1266	756
4g	C ₂₀ H ₂₈ NO ₅ P	61.14 (61.06)	7.13 (7.17)	3.52 (3.56)	3405	1276	743
4h	C ₁₈ H ₂₃ N ₂ O ₇ P	52.72 (52.68)	5.68 (5.65)	6.80 (6.83)	3401	1271	741
4i	C ₁₉ H ₂₅ N ₂ O ₇ P	53.75 (53.77)	5.97 (5.94)	6.54 (6.60)	3375	1256	762
4j	C ₁₆ H ₂₈ NO ₅ P	55.61 (55.64)	8.19 (8.17)	3.99 (4.06)	3399	1235	748
4k	C ₁₄ H ₂₃ N ₂ O ₇ P	46.45 (46.41)	6.44 (6.40)	7.70 (7.73)	3410	1247	753
4l	C ₁₅ H ₂₅ N ₂ O ₇ P	47.84 (47.87)	6.73 (6.70)	7.39 (7.44)	3438	1278	769
4m	C ₁₉ H ₂₅ ClNO ₅ P	55.18 (55.14)	6.12 (6.09)	3.35 (3.38)	3385	1290	758
4n	C ₁₇ H ₂₀ ClN ₂ O ₇ P	47.46 (47.40)	4.63 (4.68)	6.47 (6.50)	3356	1274	749
4o	C ₁₈ H ₂₂ ClN ₂ O ₇ P	48.63 (48.60)	4.97 (4.99)	6.26 (6.30)	3391	1256	758

TABLE 3: Antimicrobial studies.

Entry	Comp.	Zone of inhibition in mm						
		Antibacterial					Antifungal	
		<i>S. aureus</i>	<i>B. subtilis</i>	<i>S. typhi</i>	<i>E. coli</i>	<i>S. cocus</i>	<i>C. albicans</i>	<i>A. niger</i>
1	4a	02	06	09	05	07	07	11
2	4b	08	07	06	12	11	08	10
3	4c	05	06	06	07	05	07	06
4	4d	05	09	06	11	10	09	09
5	4e	09	10	07	06	11	10	11
6	4f	09	10	08	12	08	09	11
7	4g	08	08	09	10	08	09	09
8	4h	05	06	06	07	05	07	06
9	4i	05	09	06	11	10	09	09
10	4j	09	10	07	06	11	10	11
11	4k	10	13	08	12	11	11	09
12	4l	08	11	09	10	08	10	12
13	4m	08	10	06	11	05	08	06
14	4n	07	05	07	08	07	05	06
15	4o	09	12	11	12	08	10	09
16	Std1.	08	07	10	10	09	—	—
17	Std2.	—	—	—	—	—	08	09
18	Cont.	—	—	—	—	—	—	—

Where Std1. is chloramphenicol, Std2. is fluconazole, and Cont. is DMSO.

and **4j** showed promising activity against most of the stains compared to the standard drug used. The presence of substitutions like –OH, –Cl, and –NO₂ enabled the compounds to show promising activity.

2.2. Antioxidant Activity. The novel compounds were checked for the free radical scavenging activity by the DPPH method, and the data are listed in Table 4. The graphical representation of the DPPH activity, indicated in Figure 1, showed that most of the compounds are good antioxidants with more than 50%

scavenging activity. Among them, the compounds **4c**, **4e**, **4h**, and **4j** showed higher activity than the standard used. This may be attributed to the presence of substitutions like –NO₂ and –OH groups in the compounds synthesized.

2.3. Experimental Procedure. All the reagents and solvents were used as received from commercial suppliers, unless otherwise stated. All chemicals used for the synthesis were of analytical grade or laboratory grade and purchased from HiMedia Laboratories Pvt. Ltd., Sigma Chemical Co., USA,

TABLE 4: Antioxidant activity.

Compounds	% Scavenging activity at different concentrations				
	25 $\mu\text{g/mL}$	50 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$	250 $\mu\text{g/mL}$	500 $\mu\text{g/mL}$
4a	12.32	24.15	54.87	72.03	84.26
4b	7.05	14.25	23.57	42.1	66.32
4c	24.15	40.25	60.58	87.51	98.35
4d	7.61	17.25	29.45	39.25	61.23
4e	20.15	32.45	63.25	88.71	95.26
4f	12.89	20.45	29.87	38.26	42.1
4g	12.32	24.15	54.87	72.03	84.26
4h	24.15	40.25	60.58	87.51	98.35
4i	7.61	17.25	29.45	39.25	61.23
4j	20.15	32.45	63.25	88.71	95.26
4k	12.86	21.56	32.79	42.13	56.52
4l	10.23	22.83	33.56	51.23	62.81
4m	6.32	12.52	21.83	34.54	49.42
4n	3.25	11.59	20.94	33.54	46.23
4o	6.23	11.25	20.38	32.45	48.24
BHT	12.35	25.72	58.51	86.25	94.32

BHT: butylated hydroxytoluene.

FIGURE 1: DPPH radical scavenging activity of the synthesized compounds.

E. Merck, Germany, and Sarabhai Merck Company, India, and specialty chemicals are procured as samples from the commercial suppliers in India. Mass spectra of the synthesized compounds were recorded on Agilent 6320 Ion Trap mass spectrometer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer (300 MHz).

2.4. General Procedure for the Synthesis (Scheme 1)

2.4.1. Synthetic Procedure-a. A mixture of benzaldehyde (0.005 mol), aniline (0.005 mol) and diethylphosphite (0.005 mol) in dry toluene was stirred for 10 min at room temperature. Then the temperature was raised to reflux for 5 h. The reaction was monitored by TLC. After completion of the reaction, toluene was removed by distillation and the residue

was purified using column chromatography (6 : 4, ethyl acetate: hexane).

2.4.2. Synthetic Procedure b. A mixture of benzaldehyde (0.005 mol), aniline (0.005 mol), diethylphosphite (0.005 mol), and 5 mg of Amberlite IRC-748 in dry toluene was stirred for 10 min at room temperature. Then it was refluxed for 30 min. The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered to separate the solid catalyst. The filtrate was distilled to remove toluene, and the residue obtained was purified using column chromatography (6 : 4, ethyl acetate: hexane).

2.4.3. Synthetic Procedure c. A mixture of benzaldehyde (0.005 mol), aniline (0.005 mol), and diethylphosphite (0.005 mol) was irradiated with microwaves twice, for 30 sec, to control the temperature. The reaction was monitored by TLC. After completion of the reaction, the crude product was purified using column chromatography (6 : 4, ethyl acetate: hexane).

2.4.4. Synthesis of Compounds (4a–o). The compounds (4a–o) (Scheme 2) were synthesized by following the aforementioned synthetic procedure b.

Diethyl(4-chlorophenylamino)(3-ethoxy-4-hydroxyphenyl)methylphosphonate (4a). Yield-92.1%, colour-dark yellow. ^1H -NMR (300 MHz, DMSO-d_6) δ 10.1 (s, 1H, -OH), 7.73–6.40 (m, 7H, Ar-H), 5.38 (m, 1H, N-H), 3.98 (m, 1H, P-CH), 3.71 (q, 6H, -OCH₂), 1.32 (t, 9H, O-CCH₃). ^{31}P -NMR (161.9 MHz, DMSO-d_6) δ 32.5. *M/z*: 413 and 415 with 3 : 1 ratio. M.P. 175–178°C.

Diethyl(4-chlorophenylamino)(3,4-dihydroxy-5-nitrophenyl)methylphosphonate (4b). Yield-79.4%, colour-brown,

a: conventional method: toluene-reflux, 4-5 h.

b: catalytic amount of Amberlite-IRC 748, toluene, 30 min.

c: microwave irradiation. 30 to 90 s.

SCHEME 1: Kabachnik-Fields reaction.

b: catalytic amount of Amberlyst-IRC 748, toluene, 30 min.

1	R	R ¹	R ²	4	R	R ¹	R ²	R ³
a	-OEt	-OH	-H	4a	-OEt	-OH	-H	4-ClC ₆ H ₄ -
b	-OH	-OH	-NO ₂	4b	-OH	-OH	-NO ₂	4-ClC ₆ H ₄ -
c	-OMe	-OH	-NO ₂	4c	-OMe	-OH	-NO ₂	4-ClC ₆ H ₄ -
				4d	-OEt	-OH	-H	3-ClC ₆ H ₄ -
				4e	-OH	-OH	-NO ₂	3-ClC ₆ H ₄ -
				4f	-OMe	-OH	-NO ₂	3-ClC ₆ H ₄ -
				4g	-OEt	-OH	-H	C ₆ H ₅ CH ₂ -
				4h	-OH	-OH	-NO ₂	C ₆ H ₅ CH ₂ -
				4i	-OMe	-OH	-NO ₂	C ₆ H ₅ CH ₂ -
				4j	-OEt	-OH	-H	<i>n</i> -C ₃ H ₇ -
				4k	-OH	-OH	-NO ₂	<i>n</i> -C ₃ H ₇ -
				4l	-OMe	-OH	-NO ₂	<i>n</i> -C ₃ H ₇ -
				4m	-OEt	-OH	-H	2-ClC ₆ H ₄ -
				4n	-OH	-OH	-NO ₂	2-ClC ₆ H ₄ -
				4o	-OMe	-OH	-NO ₂	2-ClC ₆ H ₄ -

2	R ³
a	4-ClC ₆ H ₄ -
b	3-ClC ₆ H ₄ -
c	C ₆ H ₅ CH ₂ -
d	<i>n</i> -C ₃ H ₇ -
e	2-ClC ₆ H ₄ -

SCHEME 2: Newly synthesized derivatives.

¹H-NMR (300 MHz, DMSO-*d*₆) δ 10.5 (br, 2H, -OH), 7.90–6.79 (m, 6H, Ar-H), 5.45 (m, 1H, N-H), 4.14 (m, 1H, P-CH₂), 3.68 (q, 4H, P-OCH₂), 1.25 (t, 6H, P-CCH₃). ³¹P-NMR (161.9 MHz, DMSO-*d*₆) δ 31.6. *M/z*: 430 and 432 with 3 : 1 ratio. M.P. 178–181 °C.

Diethyl(4-chlorophenylamino)(4-hydroxy-3-methoxy-5-nitrophenyl)methylphosphonate (4c). Yield-86.0%, colour-brown. ¹H-NMR (300 MHz, DMSO-*d*₆) δ 10.5 (s, 1H, -OH), δ

8.22–6.52 (m, 6H, Ar-H), 5.44 (m, 1H, N-H), 4.15 (m, 1H, P-CH), 3.64 (q, 4H, -OCH₂), 2.95 (s, 3H, -OCCH₃), 1.04 (t, 6H, -OCCH₃). ³¹P-NMR (161.9 MHz, DMSO-*d*₆) δ 31.5. *M/z*: 444 and 446 with 3 : 1 ratio. M.P. 162–164 °C.

Diethyl(3-chlorophenylamino)(3-ethoxy-4-hydroxyphenyl)methylphosphonate (4d). Yield-93.4%, colour-yellow. ¹H-NMR (300 MHz, DMSO-*d*₆) δ 10.3 (s, 1H, -OH), 8.21–6.89 (m, 7H, Ar-H), 5.68 (m, 1H, N-H), 4.20 (m, 1H, P-CH),

3.82 (q, 6H, $-\text{OCH}_2$), 1.18 (t, 9H, $-\text{CCH}_3$). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 32.6. M/z : 413 and 415 with 3 : 1 ratio. M.P. 167–169°C.

Diethyl(3-chlorophenylamino)(3,4-dihydroxy-5-nitrophenyl)methylphosphonate (4e). Yield-82.9%, colour-brown. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.4 (br, 2H, $-\text{OH}$), 8.11–6.68 (m, 6H, Ar-H), 5.55 (m, 1H, N-H), 3.92 (m, 1H, P-CH), 3.81 (q, 4H, P- OCH_2), 1.33 (t, 6H, $-\text{CCH}_3$). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 30.6. M/z : 430 and 432 with 3 : 1 ratio. M.P. 143–147°C.

Diethyl(3-chlorophenylamino)(4-hydroxy-3-methoxy-5-nitrophenyl)methylphosphonate (4f). Yield-76.5%, colour-dark brown, ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.2 (s, 1H, $-\text{OH}$), 8.10–6.59 (m, 6H, Ar-H), 5.03 (m, 1H, N-H), 4.06 (m, 1H, P-CH), 3.83 (q, 4H, P- OCH_2), 3.14 (s, 3H, $-\text{OCH}_3$), 1.13 (t, 6H, $-\text{OCCCH}_3$). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 31.6. M/z : 444 and 446 with 3 : 1 ratio. M.P. 178–180°C.

Diethyl(benzylamino)(3-ethoxy-4-hydroxyphenyl)methylphosphonate (4g). Yield-94.1%, colour-pale yellow. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.8 (s, 1H, $-\text{OH}$), 8.05–6.59 (m, 8H, Ar-H), 4.87 (m, 1H, N-H), 4.32 (d, 2H, N- CH_2), 4.13 (m, 1H, P-CH), 3.77 (q, 6H, $-\text{OCH}_2$), 1.23 (t, 9H, $-\text{CCH}_3$). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 32.6. M/z : 394. M.P. 134–136°C.

Diethyl(benzylamino)(3,4-dihydroxy-5-nitrophenyl)methylphosphonate (4h). Yield-85.4%, colour-reddish brown, ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.1 (br, 2H, $-\text{OH}$), 7.92–6.62 (m, 7H, Ar-H), 4.98 (m, 1H, N-H), 4.37 (d, 2H, N- CH_2), 4.29 (m, 1H, P-CH), 3.76 (q, 4H, P- OCH_2), 1.28 (t, 6H, P- CCH_3). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 29.4. M/z : 411. M.P. 123–125°C.

Diethyl(benzylamino)(4-hydroxy-3-methoxy-5-nitrophenyl)methylphosphonate (4i). Yield-82.5%, colour-dark brown ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.2 (s, 1H, $-\text{OH}$), 8.26–6.69 (m, 7H, Ar-H), 4.78 (m, 1H, N-H), 4.32 (d, 2H, N- CH_2), 4.18 (m, 1H, P-CH), 3.81 (q, 4H, P- OCH_2), 2.31 (s, 3H, $-\text{OCH}_3$), 1.31 (t, 6H, P- CCH_3). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 31.3. M/z : 425. M.P. 138–140°C.

Diethyl(3-ethoxy-4-hydroxyphenyl)(propylamino)methylphosphonate (4j). Yield-91.8%, colour-dark yellow. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.45 (s, 1H, $-\text{OH}$), 7.93–6.89 (m, 3H, Ar-H), 4.67 (m, 1H, N-H), 4.25 (m, 1H, P-CH), 3.71 (q, 6H, $-\text{OCH}_2$), 3.06 (q, 2H, NCH_2C), 1.56 (m, 2H, CCH_2C), 1.23 (t, 9H, $-\text{OCCCH}_3$), 0.96 (t, 3H, $-\text{CCCH}_3$). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 32.9. M/z : 346. M.P. 121–123°C.

Diethyl(3,4-dihydroxy-5-nitrophenyl)(propylamino)methylphosphonate (4k). Yield-87.5%, colour-reddish brown. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.25 (br, 2H, $-\text{OH}$), 7.32–6.64 (m, 2H, Ar-H), 4.58 (m, 1H, N-H), 4.28 (m, 1H, P-CH), 3.73 (q, 4H, P- OCH_2), 3.2 (q, 2H, NCH_2C), 1.83 (m, 2H, CCH_2C), 1.09 (t, 3H, CCCH_3), 1.02 (t, 6H, P- CCH_3). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 28.9. M/z : 363. M.P. 128–130°C.

Diethyl(4-hydroxy-3-methoxy-5-nitrophenyl)(propylamino)methylphosphonate (4l). Yield-82.4%, colour-brown. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.35 (s, 1H, $-\text{OH}$), 7.56–6.34 (m, 2H, Ar-H), 4.37 (m, 1H, N-H), 4.17 (m, 1H, P-CH), 3.77 (q, 4H, P- OCH_2), 3.12 (q, 2H, NCH_2C), 3.05 (s, 6H, $-\text{OCH}_3$), 1.69 (m, 2H, CCH_2C), 1.24 (t, 6H, P- CCH_3), 1.02 (t, 3H, CCCH_3). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 31.82. M/z : 377. M.P. 112–114°C.

Diethyl(2-chlorophenylamino)(3-ethoxy-4-hydroxyphenyl)methylphosphonate (4m). Yield-93.2%, colour-yellow. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.1 (s, 1H, $-\text{OH}$), 8.15–6.78 (m, 7H, Ar-H), 5.21 (m, 1H, N-H), 3.98 (m, 1H, P-CH), 3.72 (q, 6H, $-\text{OCH}_2$), 1.28 (t, 9H, $-\text{CCH}_3$). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 32.7. M/z : 413 and 415 with 3 : 1 ratio. M.P. 182–184°C.

Diethyl(2-chlorophenylamino)(3,4-dihydroxy-5-nitrophenyl)methylphosphonate (4n). Yield-84.6%, colour-brown. ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.2 (br, 2H, $-\text{OH}$), 8.29–6.56 (m, 6H, Ar-H), 5.45 (m, 1H, N-H), 3.95 (m, 1H, P-CH), 3.74 (q, 4H, P- OCH_2), 1.31 (t, 6H, P- CCH_3). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 31.6. M/z : 430 and 432 with 3 : 1 ratio. M.P. 175–178°C.

Diethyl(2-chlorophenylamino)(4-hydroxy-3-methoxy-5-nitrophenyl)methylphosphonate (4o). Yield-90.2%, colour-reddish brown, ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.4 (s, 1H, $-\text{OH}$), 8.09–6.78 (m, 6H, Ar-H), 5.38 (m, 1H, N-H), 4.12 (m, 1H, P-CH), 3.76 (q, 4H, P- OCH_2), 2.91 (s, 6H, $-\text{OCH}_3$), 1.17 (t, 6H, P- CCH_3). ^{31}P -NMR (161.9 MHz, $\text{DMSO}-d_6$) δ 30.5. M/z : 444 and 446 with 3 : 1 ratio. M.P. 173–175°C.

2.5. Experimental Procedure for Antioxidant Activity. The antioxidant activity of the synthesized derivatives was evaluated using the DPPH free radical scavenging assay. 200 μL of test sample solution (100 $\mu\text{g/mL}$) was added to 4 mL of 100 μM methanolic DPPH. The mixture was incubated for 20 minutes at room temperature, and the absorbance at 517 nm was measured. BHT was used as standard. A blank was prepared without adding standard or test compound. Lowering the absorbance of the reaction mixture indicates higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH scavenged (\%)} = \frac{\text{Abs control} - \text{Abs test}}{\text{Abs control}} \times 100, \quad (1)$$

where Abs control is the absorbance of the control reaction and Abs test is the absorbance in the presence of the test compounds. The antioxidant activities of the synthesized compounds are expressed comparing with standard BHT.

3. Conclusion

The synthesis of new α -aminophosphonic acid esters was achieved in high yields through a one-pot three-component reaction process, a Kabachnik-Fields reaction. It involves the reactions among substituted anilines, substituted aromatic

aldehydes, and dialkyl phosphites in dry toluene at reflux temperature, in the presence of Amberlite IRC-748 as catalyst. Their structures were established by elemental analysis IR, ^1H and ^{31}P -NMR, and mass spectral data. All the title compounds were screened for their antibacterial and antioxidant activity. Most of the compounds exhibited moderate antimicrobial activity, and for some the activity was fairly good.

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