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Research Article

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A facile and efficient One-pot Three Component Reaction (Kabachinik-Fields Reaction) for the Synthesis of Novel α-Aminophosphonates by 1, 4-Dimethylpiperazine as a new catalyst

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ABSTRACT

*A facile and an efficient method has been developed for the synthesis of novel α-aminophosphonates **4a-n** by the one-pot three component reaction of equimolar quantities of 4-amino-N-2-thiazolyl-benzenesulfonamide (Sulfathiazole) (**1**), diethyl/dibutyl phosphites (**2**) and various aldehydes (**3a-n**) in dry toluene at reflux conditions via Kabachinik-Fields reaction in high yields (70-80%) in the presence of 1, 4-dimethylpiperazine as a new catalyst. Their chemical structures were established by IR, ^{1}H, ^{13}C, ^{31}P-NMR, mass spectral studies and elemental analyses. All the title compounds exhibited promising antibacterial, antifungal and antioxidant activities.*

Keywords: α-aminophosphonates, Kabachinik-Fields reaction, antibacterial activity, antifungal activity, antioxidant activity.

INTRODUCTION

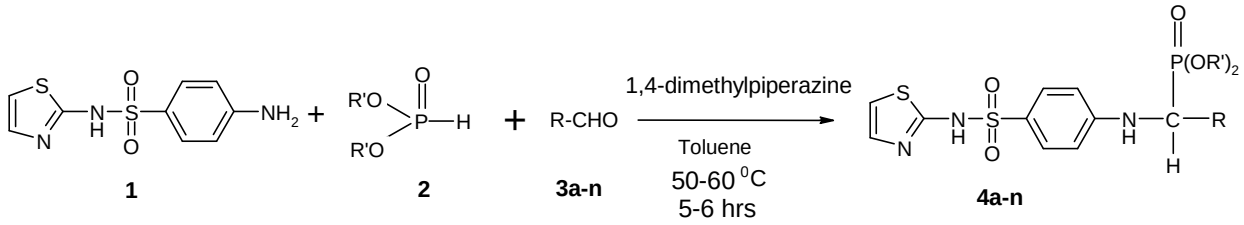
The α-aminophosphonate moiety is a versatile and novel pharmacaphore due to broad spectrum of biological activity exhibited by compounds bearing this structural unit. Thus, the development of new synthetic methodologies for α-aminophosphonates has attracted the attention of medical/organic chemists. α-aminophosphonates are the important class of compounds, since they are considered to be structural analogs of the corresponding α-amino acids, as well as heterocyclic phosphonates [1] and the ω-aminophosphonates [2], with several biological activities. Their applications are significant in agriculture as plant regulators, herbicides [3], pesticides and in medicine as anti-cancer agents [4], enzyme inhibitors [5], peptide mimics [6], antibiotics and pharmacological agents [7]. A great variety of synthetic methods have been developed for the synthesis of α-aminophosphonates. Of them, Kabachinik-Fields [8] reaction is one of the most versatile pathways for the formation of carbon-phosphorus bonds. These synthetic methods are generally carried out in the presence of various bases such as potassium fluoride on alumina [9], lithium diisopropylamine (LDA) [10], 1, 8-diazabicycloundec-7-ene (DBU) [11] magnesium oxide (MgO) [12]. A few Lewis acids such as zirconium tetrachloride ($ZrCl_4$), indium trichloride ($InCl_3$), tantalum pentachloride ($TaCl_5$), ferric chloride ($FeCl_3$) and Lanthanide-triflates were also used as catalysts. In addition, antimicrobial and antioxidant activity of α-aminophosphonates have been extensively studied and well established in the literature [13-18].

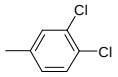
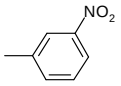
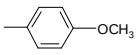
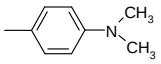
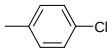
Based on the importance of α-aminophosphonates, we herein report the synthesis of novel α-aminophosphonates using 4-amino-*N*-2-thiazolyl-benzenesulfonamide (Sulfathiazole) **1** as an amine, diethyl/dibutyl phosphites **2**, various aldehydes **3a-n** and 1, 4-dimethylpiperazine as a new catalyst.

EXPERIMENTAL SECTION

Sigma-Aldrich, Merck and Lancaster Chemicals were used as such. Solvents used for spectroscopic and other physical studies were reagent grade and were further purified by standard procedures and techniques. The IR spectra

(KBr pellets) were recorded on a Perkin-Elmer FT-IR 1000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Burker ACF NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) with TMS as an internal standard. ^{31}P NMR spectra were measured using 85% H_3PO_4 as external reference. Mass spectra were recorded on LCMS-2010A, SHIMADZU spectrometer. Melting points were determined in an open capillary tube on Mel-temp apparatus, Tempo instruments, India and were uncorrected.



Compound	R	Compound	R	R'
4a & 4h		**4e & 4l**		**4a-4g =** Ethyl
4b & 4i		**4f & 4m**		**4h-4n**= n-Butyl
4c & 4j		**4g & 4n**		
4d & 4k				

Scheme 1. Synthesis of of α-aminophosphonates 4a-n.

General procedure for the synthesis of α-aminophosphonates (4a-n):

Synthesis of diethylpyridin-3-yl (4-(N-thiazol-2-ylsulfamoyl)phenylamino) methyl phosphonate (4a) :

To a stirred solution of 4-amino-*N*-2-thiazolylbenzenesulfonamide (Sulfathiazole) **1** (0.255 g, 0.001 mole), pyridine-3-aldehyde **3a** (0.093 mL, 0.001 mole) in anhydrous toluene (20 mL) was added drop wise, and the 1, 4-dimethylpiperazine (1 mL) was added and stirring continued at room temperature (RT) for 1 hour. Then diethyl phosphite (0.128 mL, 0.001 mole) in dry toluene (20 mL) was added drop wise. Stirring was continued at room temperature (RT) for half-an-hour, and then the mixture was heated at gentle for 5-6 hours. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, as indicated by TLC (silica gel) using hexane and ethyl acetate (3:1) as a mobile phase, the solvent was removed in a rota-evaporator and the crude product obtained was purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate (3:1) as an eluent to afford the analytically pure **4a**. Similarly, the compounds **4b** to **4n** were prepared by adopting the above procedure.

Diethylpyridin-3-yl (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate(4a):

Brown solid. Yield 78%; m. p. 200-202 ^{o}C; IR (KBr): υ 3369 (-NH), 1213 (-P=O), 769 (-P-C $_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.74-7.82 (m, 10H), 5.84 (dd, 1H, *J*=22.4 Hz, *J*=21.0 Hz), 5.43 (t, 1H), 3.43- 3.79 (m, 4H), 1.48 (t, 6H, *J*=10.0 Hz); ^{31}P -NMR (DMSO-d_6): 20.45; LC-MS (*m/z*): 483 $(M+H)^{+}$; *Anal*. Calcd. for $C_{19}H_{23}N_4O_5PS_2$: C, 47.29; H, 4.80; N, 11.61. Found: C, 47.42; H, 4.85; N, 11.51.

Diethyl(2-chloro-6-fluorophenyl)(4-(N-thiazol-2- ylsulfamoyl)phenylamino) methyl phosphonate (4b):

Brown solid. Yield 76%; m. p. 180-182 ^{o}C; IR (KBr): υ) 3395 (-NH), 1219 (-P=O), 771 (-P-C $_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.57-7.53 (m, 9H), 5.67 (dd, 1H, *J*=22.5 Hz, *J*=20.1 Hz), 5.44 (t, 1H), 3.71-4.09 (m, 4H, *J*=9.8 Hz), 1.09 (t, 6H); ^{13}C-NMR (DMSO-d_6): δ 128.0, 130.14, 111.69, 149.46, 111.69, 130.14, 112.69, 139.68, 169.60, 130.33, 133.46, 124.36, 130.32, 112.46, 162.28, 57.1, 68.2, 16.3; ^{31}P-NMR (DMSO-d_6): 25.39; LC-MS (*m/z*): 534 $(M+H)^{+}$; *Anal*. Calcd. for $C_{20}H_{22}ClFN_3O_5PS_2$: C, 44.99; H, 4.15; N, 7.87. Found: C, 44.85; H, 4.19; N, 7.91.

Table 1. Antibacterial activity of α-aminophosphonates 4a-n against Gram positive and Gram negative bacteria

Compound	*S. aureus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
4a	20 (6.25)	25 (6.25)	29 (6.25)	18 (6.25)
4b	23 (6.25)	28 (6.25)	30 (6.25)	18 (6.25)
4c	10 (12.5)	--	--	17 (6.25)
4d	14 (25.0)	23 (6.25)	19 (25.0)	--
4e	22 (6.25)	27 (6.25)	28 (6.25)	20 (6.25)
4f	21 (6.25)	29 (6.25)	30 (6.25)	20 (6.25)
4g	16 (12.5)	24 (25.0)	--	16 (6.25)
4h	14 (12.5)	--	21 (6.25)	--
4i	21 (6.25)	24 (6.25)	29 (6.25)	19 (6.25)
4j	21 (6.25)	26 (6.25)	32 (6.25)	21 (6.25)
4k	--	18 (6.25)	--	16 (6.25)
4l	11 (25.0)	16 (25.0)	18 (25.0)	14 (6.25)
4m	13 (6.25)	18 (6.25)	22 (6.25)	18 (6.25)
4n	14 (6.25)	--	24 (6.25)	--
Ciprofloxacin	24 (6.25)	30 (6.25)	33 (6.25)	23 (6.25)

Zone of inhibition in mm at 100 µg/mL concentration.

Table 2. Antifungal activity of α-aminophosphonates 4a-n

Compound	*A. fumigatus*	*A. flavus*	*T. mentagrophytes*
4a	22 (6.25)	22 (6.25)	25 (6.25)
4b	12 (25.0)	10 (6.25)	12 (12.5)
4c	16 (6.25)	14 (6.25)	17 (6.25)
4d	15 (6.25)	--	16 (25.0)
4e	11 (25.0)	18 (6.25)	--
4f	24 (6.25)	21 (6.25)	21 (6.25)
4g	17 (12.5)	12 (25.0)	--
4h	19 (25.0)	--	12 (12.5)
4i	22 (6.25)	19 (6.25)	20 (6.25)
4j	21 (6.25)	20 (6.25)	20 (6.25)
4k	10 (6.25)	14 (6.25)	10 (6.25)
4l	19 (6.25)	17 (6.25)	20 (6.25)
4m	20 (6.25)	--	18 (6.25)
4n	--	15 (6.25)	--
Amphotericin B	25 (6.25)	21 (6.25)	23 (6.25)

Zone of inhibition in mm at 100 µg/mL concentration.

Table 3. Antioxidant activity of α-aminophosphonates 4a-n by Nitric Oxide and DPPH methods

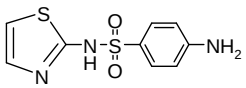
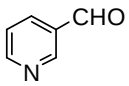
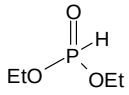
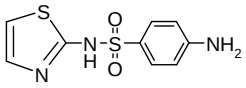
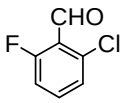
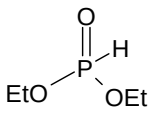
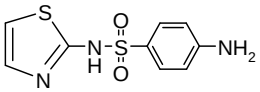
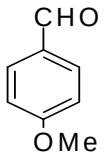
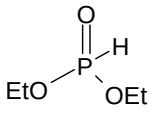
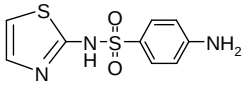
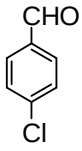
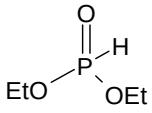
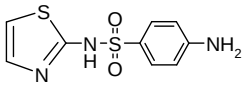
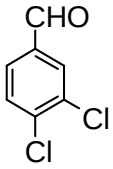
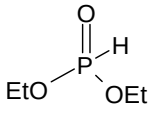
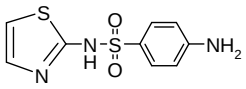
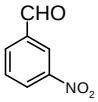
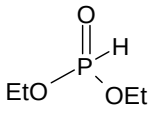
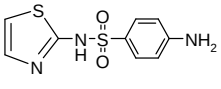
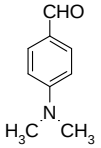
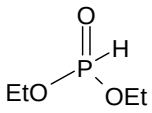
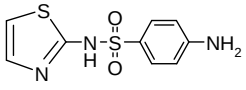
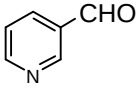
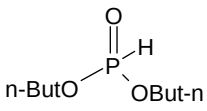
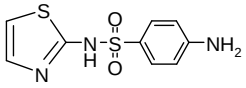
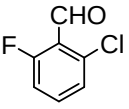
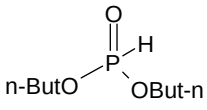
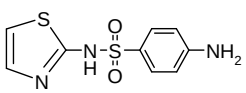
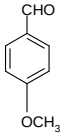
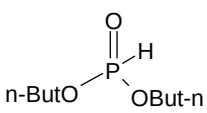
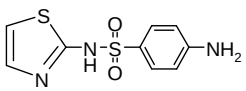
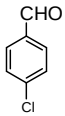
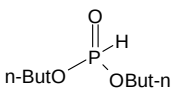
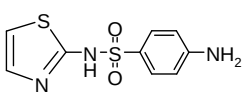
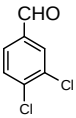
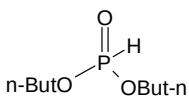
Compound	% Inhibition at 100 μM	
	Nitric oxide method	DPPH method
4a	47.55	50.45
4b	82.25	84.24
4c	91.18	93.65
4d	59.21	61.75
4e	70.23	72.25
4f	79.10	75.85
4g	45.16	48.22
4h	78.84	76.15
4i	72.14	74.15
4j	95.18	94.11
4k	35.35	39.25
4l	68.25	71.15
4m	58.45	66.12
4n	65.10	29.25
BHT	89.95	86.27

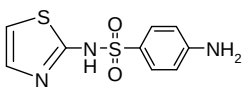
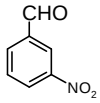
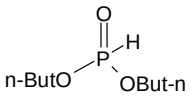
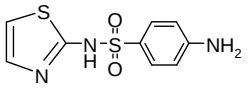
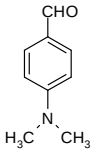
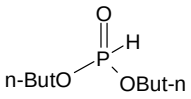
Diethyl(4-methoxyphenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate (4c):
Brown solid. Yield 81%; m. p. 192-194 ^{o}C; IR (KBr): υ 3395 (-NH), 1253 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.57-7.88 (m, 10H), 5.76 (dd, 1H, *J*=23.2 Hz, *J*=21.5 Hz), 5.43 (t, 1H), 3.74-3.86(m, 4H), 1.11 (t, 6H, *J*=10.6 Hz); ^{31}P-NMR (DMSO-d_6): 23.43; *Anal*. Calcd. for $C_{21}H_{26}N_3O_6PS_2$: C, 49.31; H, 5.12; N, 8.21. Found: C, 49.27; H, 5.07; N, 8.15.

Diethyl(4-chlorophenyl(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate(4d):
Brown solid. Yield 85%; m. p. 185-187 ^{o}C; IR (KBr): υ 3416 (-NH), 1219 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.56-7.44 (m, 10H), 5.85 (dd, 1H, *J*=24.3 Hz, *J*=22.0 Hz), 4.93 (t, 1H), 3.43-3.79 (m, 4H), 1.17 (t, 6H, *J*=10.6 Hz); ^{13}C-NMR (DMSO-d_6) *δ*: 128.68, 131.08, 112.69, 149.25, 112.29, 131.08, 112.45, 139.28,

168.07, 132.42, 128.90, 128.68, 132.42, 128.68, 128.90, 56.2, 62.3, 16.1; ^{31}P-NMR (DMSO-d_6): 23.83; LC-MS (*m/z*): 516 $(M+H)^+$; *Anal*. Calcd. for $C_{20}H_{23}ClN_3O_5PS_2$: C, 46.56, H, 4.49, N, 8.14. Found: C, 46.68; H, 4.42; N, 8.23.

Table 4. One-pot three component synthesis of α-aminophosphonates 4a-n

Compound	Amine	Aldehyde	Phosphite	Yield (%)
4a				78
4b				76
4c				81
4d				85
4e				80
4f				77
4g				82
4h				78
4i				76
4j				80
4k				77
4l				79

4m				76
4n				80

Diethyl(3,4-dichlorophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino) methyl phosphonate (4e):
Yellow solid. Yield 80%; m. p. 186-188 ^{o}C; IR (KBr): υ 3366 (-NH), 1220 (-P=O), 775 (-P-$C_{aliphatic}$);. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.55-7.55 (m, 9H), 5.85 (dd, 1H, *J*=23.7 Hz, *J*=21.3 Hz), 5.04 (t, 1H), 3.42-3.73 (m, 4H), 1.04 (t, 6H, *J*=10.9 Hz); ^{13}C-NMR (DMSO-d_6) *δ*: 128.89, 130.16, 112.36, 149.63, 112.36,130.16, 112.45, 141.47, 168.10, 131.36, 128.89, 131.36, 131.42, 130.42, 125.33, 60.8, 68.5, 16.4; ^{31}P-NMR(DMSO-d_6) : 20.56; *Anal*. Calcd. for $C_{20}H_{22}Cl_2N_3O_5PS_2$**:** C, 43.64, H, 4.03, N, 7.63. Found: C,43.50, H, 4.0, N, 7.50.

Diethyl(3-nitrophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate(4f):
Yellow solid. Yield 77%; m. p. 190-192 ^{o}C; IR (KBr): υ 3409 (-NH), 1217 (-P=O), 771 (-P-C $_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.08-7.91 (m, 10H), 5.85 (dd, 1H, *J*=24.4 Hz, *J*=20.5 Hz), 5.34 (t, 1H), 3.43-4.01 (m, 4H), 1.03 (t, 6H, *J*=10.6 Hz); ^{13}C-NMR (DMSO-d_6) *δ*: 127.93, 130.26, 112.44, 149.64, 112.44, 130.26, 112.44, 141.16, 168.10, 141.16, 122.90, 148.10, 121.77, 129.28, 133.74, 61.3, 67.5, 15.2; ^{31}P-NMR (DMSO-d_6) : 19.74; LC-MS (*m/z*)*:* 527 (M+H) $^{+}$; *Anal*. Calcd. for $C_{20}H_{23}N_4O_7PS_2$: C, 45.62, H, 4.40, N, 10.64. Found: C, 45.53, H, 4.46, N, 10.71.

Diethyl(4-(dimethylaminophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino) methyl phosphonate (4g):
Black solid. Yield 82%; m. p. 184-186 ^{o}C; IR (KBr): υ 3409 (-NH), 1216 (-P=O), 771 (-P-$C_{aliphatic}$); ^{1}H-NMR 400 MHz, (DMSO-d_6): δ 6.55-7.69 (m, 10H), 5.72 (dd, 1H, *J*=22.1 Hz, *J*=20.8 Hz), 4.87 (t, 1H), 3.03-3.80 (m, 4H), 1.16 (t, 6H, *J*=9.9 Hz); ^{31}P-NMR (DMSO-d_6): 22.54; *Anal*. Calcd. for $C_{22}H_{29}N_4O_5PS_2$: C, 50.37; H, 5.57; N, 10.68.Found C, 50.20; H, 5.50; N, 10.64.

Dibutylpyridin-3-yl(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate (4h):
Black soild. Yield 78%; m. p. 190-192 ^{o}C; IR (KBr): υ 3400 (-NH), 1219 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.55-7.69 (m, 10H), 5.64 (dd, 1H, *J*=23.6 Hz, *J*=21.0 Hz), 4.06 (t, 1H), 3.88-3.98 (m, 4H), 1.46-1.53 (m, 4H), 1.14-1.53 (m, 4H), 0.81 (t, 6H, *J*=7.0 Hz); ^{31}P-NMR (DMSO-d_6) : 20.04; *Anal*. Calcd for $C_{22}H_{31}N_4O_5PS_2$: C, 52.86, H, 5.98, N, 10.72. Found C, 52.70, H, 5.80, N, 10.59.

Dibutyl(2-chloro-6-fluorophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino) methyl phosphonate (4i):
Brown solid. Yield 76%; m. p. 170-172 ^{o}C; IR (KBr): υ 3411 (-NH), 1219 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.55-7.51 (m, 9H), 5.85 (dd, 1H, *J*=24.8 Hz, *J*=21.0 Hz), 4.31 (t, 1H), 3.64-3.99 (m, 4H), 1.32-1.55 (m, 4H), 1.14-1.23 (m, 4H), 0.81 (t, 6H, *J*=6.5 Hz); ^{13}C-NMR (DMSO-d_6) *δ*: 127.96, 130.30, 111.68, 152.18, 111.68, 130.30, 112.43, 141.32, 168.11, 128.0, 130.40, 124.19, 128.02, 112.43, 152.18, 59.6, 67.3, 32.4, 18.6, 13.4; ^{31}P-NMR (DMSO-d_6): 23.71; *Anal*. Calcd. for $C_{24}H_{30}ClFN_3O_5PS_2$: C, 50.21, H, 5.27, N, 6.18. Found C, 50.35; H, 5.22; N, 7.26.

Dibutyl(4-methoxyphenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate (4j):
Black solid. Yield 80%; m. p. 195-197 ^{o}C; IR (KBr): υ 3359 (-NH), 1220 (-P=O), 769 (-P-$C_{aliphatic}$); 1H-NMR 400 MHz, (DMSO-d_6) δ 6.54-7.88 (m, 10H), 5.67 (dd, 1H, *J*=23.5 Hz, *J*=21.0 Hz), 4.02(t, 1H), 3.63-3.91 (m, 4H), 1.45-1.99 (m, 4H), 1.17-1.45(m, 4H), 0.85 (t, 6H, *J*=7.5 Hz); ^{31}P-NMR (DMSO-d_6): 19.21; LC-MS (*m/z*): 568 (M+H)$^{+}$; *Anal*. Calcd. for $C_{25}H_{34}N_3O_6PS_2$: C, 54.43; H, 6.21; N,7.62. Found: C, 54.38; H, 6.17; N, 7.71.

Dibutyl(4-chlorophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate (4k):
Brown solid. Yield 77%; m. P. 182-184 ^{o}C; IR (KBr): υ 3357 (-NH), 1220 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.56-7.95 (m, 10H), 5.86 (dd, 1H, *J*=21.8 Hz, *J*=20.0 Hz), 4.02 (t, 1H), 3.39-3.92 (m, 4H), 1.46-1.99 (m, 4H), 1.15-1.28 (m, 4H), 0.85 (t, 6H, *J*=7.0 Hz); ^{31}P-NMR *δ*: 26.45; *Anal*. Calcd. for $C_{24}H_{31}ClN_3O_5PS_2$: C, 51.84; H, 5.62; N, 7.56. Found C, 51.72; H, 5.68; N, 7.45.

Dibutyl(3,4-dichlorophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino) methyl phosphonate (4l):
Brown solid. Yield 79%; m. p. 178-180 ^{o}C; IR (KBr): υ 3413 (-NH), 1219 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.54-7.89 (m, 10H), 5.58 (dd, 1H, *J*=23.9 Hz, *J*=21.6 Hz), 4.30 (t, 1H), 3.47-3.61 (m, 4H), 1.40-

1.99 (m, 4H), 1.16-1.23 (m, 4H), 0.81 (t, 6H, *J*=6.5 Hz); ^{31}P-NMR (DMSO-d_6): 25.32; *Anal*. Calcd. for $C_{24}H_{30}Cl_2N_3O_5PS_2$: C, 48.81; H, 5.12; N, 7.12. Found C, 48.73; H, 5.0; N, 7.0.

Dibutyl(3-nitrophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methyl phosphonate(4m):
Brown solid. Yield 76%; m. p. 201-203 ^{o}C; IR (KBr): υ 3413 (-NH), 1218 (-P=O), 771 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.56-7.89 (m, 10H), 5.72 (dd, 1H, *J*=24.5 Hz, *J*=22.0 Hz), 4.20 (t, 1H), 3.63-3.94 (m, 4H), 1.49-1.98(m, 4H), 1.17-1.26 (m, 4H), 0.82 (t, 6H, *J*=7.4 Hz); ^{13}C-NMR (DMSO-d_6) *δ*: 127.67, 130.23, 112.44, 148.10, 112.44, 130.23, 112.44, 141.24, 168.11, 133.73, 124.50, 147.45, 121.66, 129.26, 133.42, 60.3, 68.1, 32.2, 18.2, 13.7; ^{31}P-NMR (DMSO-d_6): 24.46; LC-MS (*m/z*): 583 (M+H) $^{+}$; *Anal*. Calcd. for $C_{24}H_{31}N_4O_7PS_2$: C, 50.87; H, 5.51, N, 9.89. Found C, 50.79; H, 5.57; N, 9.81.

Dibutyl(4-(dimethylamino)phenyl)(4-(N-thiazol-2-ylsulfamoyl) phenylamino) methyl phosphonate (4n):
Black solid. Yield 80%; m. P. 170-172 ^{o}C; IR (KBr): υ 3413 (-NH), 1219 (-P=O), 772 (-P-$C_{aliphatic}$); ^{1}H-NMR (400 MHz, DMSO-d_6): *δ* 6.54-7.70 (m, 10H), 5.85 (dd, 1H, *J*=23.6 Hz, *J*=21.4 Hz), 4.10 (t, 1H), 3.17-3.99 (m, 4H), 1.46-1.99 (m, 4H), 1.17-1.35 (m, 4H), 0.86 (t, 6H, *J*=7.8 Hz); ^{31}P-NMR (DMSO-d_6): 23.42; *Anal*. Calcd. for $C_{26}H_{37}N_4O_5PS_2$: C, 55.30; H, 6.60; N, 9.92. Found C, 55.15; H, 6.60; N, 9.80.

RESULTS AND DISCUSSION

α-Aminophosphonates **4a-n** were synthesized by one-pot, three-component reaction of equimolar quantities of 4-amino-*N*-2-thiazolyl-benzenesulfonamide (Sulfathiazole) **1**, diethyl/dibutyl phosphites **2** and various aldehydes **3a-n** in the presence of 1, 4-dimethylpiperazine in dry toluene at reflux conditions for 5-6 hours in 76-85% yields (Table 4).The progress of the reaction was monitored by thin layer chromatography (TLC) analysis and the products were purified by column chromatography using hexane: ethyl acetate(3:1) as eluent. We found that the 1, 4-dimethylpiperazine is proved to be an efficient catalyst in the Kabachinik-Fields reaction.

The structures of the title compounds **4a-n** were established by their spectroscopical data. All the compounds **4a-n** exhibited infrared absorption bands for P=O, P-C $_{(aliphatic)}$ and N-H in the regions 1249-1202, 769-745 and 3446–3343 cm^{-1} respectively [19]. Chemical shifts for aromatic protons of the title compounds **4a-n** appeared as a complex multiplet in the region 6.34-8.44 ppm [20]. The proton of methyne (P-C-H) chemical shift appeared as a doublet of doublet [20] at δ 5.20-5.85 and 5.67-5.82 due to its coupling with phosphorus and the neighbouring N-H proton. The N-H proton exhibited a triplet [20] at δ 4.30-5.44 indicating its coupling with neighbouring proton and phosphorus.

The ^{13}C NMR spectral data of **4a-n** showed characteristic chemical shifts for aromatic carbons. The carbon chemical shifts of P-O-CH_2 and P-CH-N appeared as a doublet at δ 66.9-69.4 (d, $^{2}J_{P\text{-}O\text{-}C}$ = 6.5 Hz) and singlet at δ 56.1-62.9 respectively [21]. The ^{31}P NMR chemical shifts appeared as singlets in the region δ 18.59-35.01 for all the compounds [22] **4a-n.** The LC mass spectra of **4a-n** agreed with the proposed structures.

Biological assay
Antibacterial activity
Preliminary antimicrobial activities of **4a-n** were tested by Agar disc-diffusion method [23]. The results of the final compounds of preliminary antibacterial testing are shown in Table 1. All the synthesized compounds were screened against Gram positive bacteria *Staphylococcus aureus* and Gram negative bacteria *Eschrichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* by the disc diffusion method and the results were compared with the standard drug (Ciprofloxacin). The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the compounds **4a**, **4b**, **4e**, **4f** and **4j** showed higher activity against Gram positive bacteria and Gram negative bacteria whereas the rest of the compounds showed moderate activity.

Minimum inhibitory concentration (MIC) was determined for the compounds **4a-n** by broth dilution technique. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentrations (MIC). Ciprofloxacin was used as a standard drug. The diameter of the zone of inhibition and minimum inhibitory concentration values are given in Table 1.

Antifungal activity
All the titled compounds **4a-n** was tested for antifungal activity and the results were compared with the standard drug, Amphotericin B. Among them, the compounds **4a**, **4f**, **4i**, **4j** and **4m** emerged as the most effective against *Aspergillus fumigatus*, *Aspergillus flavus* and *Trichophyton mentagrophytes* (recultured) whereas the rest of the compounds showed moderate activity (Table 2). The inhibition zones in diameter were measured and compared with

the controls. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentrations (MIC). Amphotericin B was used as the standard drug. The diameter of zone of inhibition and minimum inhibitory concentration values are given in Table 2.

Antioxidant activity

The antioxidant activity of α-aminophosphonates **4a-n** was determined by Nitric Oxide (NO) [24-25] and 1, 1-diphenyl-2-picrylhydrazyl (DPPH) [26] methods. The results of the final compounds of preliminary antioxidant testing are shown in Table 3. All the synthesized compounds **4a-n** exhibited higher to moderate antioxidant activity. In general, the compounds **4b**, **4c**, **4f**, **4h**, and **4j** exhibited higher antioxidant activity in both NO and DPPH methods at a concentration of 100 μM and the rest of the compounds showed moderate activity. The highlight of this activity is that the compounds **4c** and **4j** showed highest activity than that of the standard, butyrated hydroxytoluene (BHT) in both NO and DPPH methods.

CONCLUSION

A convenient high-yielding one-pot, three-component reaction of amines **1**, diethyl/dibutylphosphites **2**, various aldehydes **3a-n** and 1, 4-dimethylpiperazine as a new catalyst for the synthesis of novel α-aminophosphonates **4a-n** was accomplished by Kabachinik-Fields reaction. 1, 4-dimethylpiperazine was found to be an efficient catalyst in the Kabachinik-Fields reaction. The compounds **4a**, **4b**, **4e**, **4f**, **4i** and **4j** showed highest antibacterial activity against Gram positive bacteria and Gram negative bacteria when compared to that of the standard. The compounds **4a**, **4f**, **4i**, **4j** and **4m** showed promising antifungal activity and the compounds **4b**, **4c**, **4f**, **4h**, and **4j** exhibited significant antioxidant activity.

Acknowledgements

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