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Synthesis, spectral characterization and antimicrobial evaluation of novel α-aminophosphonates

Sampath Chinnam, Chandrakala Potturi[1], Suresh Maddila[2], Vijaya Bhaskara Reddy Muttana, Anjaneyulu Ediga[3] and Venkateswarlu Chinnam[4]*

Department of Chemistry, Sri Venkateswara Univeristy, Tirupati, India
[1]Department of Environmental Sciences, Sri Rama Engineering College, Tirupati,India
[2]School of Chemistry, University of KwaZulu-Natal, West Ville Campus, Chilten Hills, Durban-4000, South Africa
[3]Department of Biochemistry, Sri Venkateswara University, Tirupati, India
[4]Department of Chemistry, KVR College, Nandigama, India

ABSTRACT

*A facile method has been developed for the synthesis of novel α-aminophosphonates **5a-j** by the one-pot three component reaction of equimolar quantities of 4-amino-N-2-thiazolyl-benzenesulfonamide (Sulfathiazole) (**1**), dimethyl phosphite (**2**) and various aldehydes (**4a-j**) in dry toluene at reflux conditions via Kabachinik-Fields reaction in high yields (70-80%) without use of any 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 and antifungal activities.*

Key words: Sulfathiazole, dimethyl/diethyl phosphites, Kabachinik-Fields reaction, antibacterial activity, antifungal activity.

INTRODUCTION

α-Amino phosphonates are an important class of compounds since they are considered as structural analogues of the corresponding a-amino acids, and their utilities as enzyme inhibitors, antibiotics and pharmacological agents [1]. Phosphonates are widely used as imaging agents and as antitumor, antihypertensive and antibacterial agents [2]. α-amino phosphonates applications are significant in agriculture as plant regulators, herbicides [3], pesticides and in medicine as anticancer 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.

Depending on the importance of α-aminophosphonates, we wish to report the synthesis of α-aminophosphonates by using Sulfathiazole **(1)** as an amine, dimethyl phosphite **(2)**, various aldehydes **(4a-j)** without any catalyst.

MATERIALS AND METHODS

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.

General procedure for the synthesis of α-aminophosphonates (5a-j):
Synthesis of dimethyl (3-nitrophenyl) (4-(*N*-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate (5a):
To a stirred solution of Sulfathiazole **(1)** (0.001 mole), 3-Nitro benzaldehyde **4a** (0.001 mole) in anhydrous toluene (20 mL) was added drop wise and stirring continued at room temperature (RT) for 1 hour. Then dimethyl phosphite (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 **5a**. Similarly, the compounds **5b** to **5j** were prepared by adopting the above procedure.

Analytical data
Dimethyl (3-nitrophenyl) (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5a**
Yield: 71 %, M.P:188-190 ^{o}C. FT-IR (KBr): 3367 (N-H), 1213 (P=O), 767 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.74-7.82 (m, 10H), 5.84 (dd, 1H, *J*=22.4 Hz, *J*=21.0 Hz), 5.43 (t, 1H), 4.12 (d, 3H), 4.32 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 171.4, 150.2, 138.2, 137.5, 134.2, 128.5, 113.8, 108.4, 60.3, 53.4, 43.2, 20.7. ^{31}P NMR ($CDCl_3$): δ 18.78. LC-MS (*m/z*): 499 (M+H) +. *Anal*. Calcd for $C_{18}H_{19}N_4O_7PS_2$: C, 43.37; H, 3.84; N, 11.24. Found: C, 43.26; H, 3.88; N, 11.20.

Dimethyl (3-cyanophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5b**
Yield: 70 %, M.P:178-180 ^{o}C. FT-IR (KBr): 3343 (N-H), 1212 (P=O), 764 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.67-7.12 (m, 10H), 5.63 (dd, 1H, *J*=21.4 Hz, *J*=20.0 Hz), 5.33 (t, 1H), 4.21 (d, 3H), 4.22 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 169.8, 151.2, 137.2, 136.5, 133.2, 128.5, 114.1, 108.4, 61.3, 52.4, 42.2, 19.7. ^{31}P NMR ($CDCl_3$): δ 20.70. LC-MS (*m/z*): 479 (M+H) +. *Anal*. Calcd for $C_{19}H_{19}N_4O_5PS_2$: C, 47.69; H, 4.00; N, 11.71. Found: C, 47.56; H, 3.96; N, 11.60.

Dimethyl (4-nitrophenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5c**
Yield: 75 %, M.P:182-184 ^{o}C. FT-IR (KBr): 3354 (N-H), 1218 (P=O), 743 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.54-7.42 (m, 10H), 5.43 (dd, 1H, *J*=20.1 Hz, *J*=22.0 Hz), 5.23 (t, 1H), 4.11 (d, 3H), 4.32 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 168.2, 150.2, 136.1, 135.5, 133.2, 128.3, 113.1, 108.3, 60.6, 51.4, 41.2, 20.3. ^{31}P NMR ($CDCl_3$): δ 21.14. LC-MS (*m/z*): 499 (M+H) +. *Anal*. Calcd for $C_{18}H_{19}N_4O_7PS_2$: C, 43.37; H, 3.84; N, 11.24. Found: C, 43.56; H, 3.96; N, 11.45.

Dimethyl (3-methoxyphenyl)(4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5d**
Yield: 74 %, M.P:190-192 ^{o}C. FT-IR (KBr): 3322 (N-H), 1219 (P=O), 749 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.44-7.23 (m, 10H), 5.34 (dd, 1H, *J*=19.4 Hz, *J*=20.0 Hz), 5.13 (t, 1H), 4.20 (d, 3H), 4.12 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 169.1, 150.0, 137.1, 138.1, 134.2, 128.0, 112.1, 108.3, 62.6, 50.1, 40.2, 23.1. ^{31}P NMR ($CDCl_3$): δ 23.24. LC-MS (*m/z*): 484 (M+H) +. *Anal*. Calcd for $C_{19}H_{22}N_3O_6PS_2$: C, 47.20; H, 4.59; N, 8.69. Found: C, 47.16; H, 4.36; N, 8.45.

Dimethyl(3-trifluoromethyll)phenyl)(4-(N-thiazol-2ylsulfamoyl)phenylamino)methylphosphonate **5e**
Yield: 77 %, M.P:177-179 ^{o}C. FT-IR (KBr): 3312 (N-H), 1221 (P=O), 751 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.32-7.43 (m, 10H), 5.44 (dd, 1H, *J*=20.4 Hz, *J*=23.0 Hz), 5.27 (t, 1H), 4.10 (d, 3H), 4.19 (d, 3H). ^{31}P NMR ($CDCl_3$): δ 22.40. *Anal*. Calcd for $C_{19}H_{19}N_3F_3O_5PS_2$: C, 43.76; H, 3.67; N, 8.06. Found: C, 43.46; H, 3.36; N, 8.15.

Dimethyl (3-chlorophenyl) (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5f**
Yield: 78 %, M.P:185-187 ^{o}C. FT-IR (KBr): 3334 (N-H), 1223 (P=O), 747 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.22-7.31 (m, 10H), 5.40 (dd, 1H, *J*=19.2 Hz, *J*=23.0 Hz), 5.37 (t, 1H), 4.20 (d, 3H), 4.17 (d, 3H). ^{31}P NMR ($CDCl_3$): δ 23.10. *Anal*. Calcd for $C_{18}H_{19}ClN_3O_5PS_2$: C, 44.31; H, 3.93; N, 8.61. Found: C, 44.46; H, 3.66; N, 8.75.

Dimethyl (4-chlorophenyl) (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5g**
Yield: 72 %, M.P:193-195 ^{o}C. FT-IR (KBr): 3319 (N-H), 1220 (P=O), 753 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.34-7.31 (m, 10H), 5.30 (dd, 1H, *J*=18.2 Hz, *J*=21.0 Hz), 5.17 (t, 1H), 4.19 (d, 3H), 4.12 (d, 3H). ^{31}P NMR ($CDCl_3$): δ 25.14. *Anal*. Calcd for $C_{18}H_{19}ClN_3O_5PS_2$: C, 44.31; H, 3.93; N, 8.61. Found: C, 44.56; H, 3.76; N, 8.85.

Dimethyl (3-fluorophenyl) (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5h**
Yield: 73 %, M.P:197-199 ^{o}C. FT-IR (KBr): 3321 (N-H), 1225 (P=O), 755 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.24-7.41 (m, 10H), 5.34 (dd, 1H, *J*=19.2 Hz, *J*=21.4 Hz), 5.19 (t, 1H), 4.24 (d, 3H), 4.10 (d, 3H). ^{31}P NMR ($CDCl_3$): δ 24.23. *Anal*. Calcd for $C_{18}H_{19}FN_3O_5PS_2$: C, 45.86; H, 4.06; N, 8.91. Found: C, 45.67; H, 4.76; N, 8.85.

Dimethyl (2-chlorophenyl) (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5i**
Yield: 80 %, M.P:186-188 ^{o}C. FT-IR (KBr): 3326 (N-H), 1222 (P=O), 756 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.36-7.31 (m, 10H), 5.44 (dd, 1H, *J*=19.2 Hz, *J*=21.4 Hz), 5.29 (t, 1H), 4.26 (d, 3H), 4.20 (d, 3H). ^{31}P NMR ($CDCl_3$): δ 23.13. *Anal*. Calcd for $C_{18}H_{19}ClN_3O_5PS_2$: C, 44.31; H, 3.93; N, 8.61. Found: C, 44.23; H, 3.76; N, 8.85.

Dimethyl (2-nitrophenyl) (4-(N-thiazol-2-ylsulfamoyl)phenylamino)methylphosphonate **5j**
Yield: 79 %, M.P:176-178 ^{o}C. FT-IR (KBr): 3320 (N-H), 1227 (P=O), 752 (P-Caliphatic).^{1}H NMR ($CDCl_3$): δ 6.30-7.42 (m, 10H), 5.40 (dd, 1H, *J*=19.8 Hz, *J*=22.4 Hz), 5.31 (t, 1H), 4.29 (d, 3H), 4.12 (d, 3H). ^{31}P NMR ($CDCl_3$): δ 21.14. *Anal*. Calcd for $C_{18}H_{19}N_4O_7PS_2$: C, 43.37; H, 3.84; N, 11.24. Found: C, 43.23; H, 3.76; N, 11.10.

Biological assay
Antibacterial activity
A standard inoculum (1-2 × 10^7 c.f.u/cm^3 0.5 McFarland standards) was introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 6.25 mm in diameter were prepared from Whatmann no.1 filter paper and sterilized by dry heat at 140 ˚C for 1 h. The sterile disc previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. The plates were inverted and incubated for 24 h at 37 ˚C. The inhibition zones were measured and compared with the controls. Minimum inhibitory concentration (MIC) was determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 5 × 10^5 c.f.u of actively dividing bacteria cells. The cultures were incubated for 24 h at 37 ˚C and the growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentrations (*MIC*). Streptomycin was used as a standard drug. The diameter of the zone of inhibition and minimum inhibitory concentration (MIC) values are given in Table 1.

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli, Bacillus subtilis and Streptococcus bovis* (recultured) bacterial strains by disc diffusion method. The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. The compounds **5a-j** showed very good activity against all the bacterial strains.

Antifungal activity
Sabourauds agar media was prepared by dissolving 1 g peptone, 4 g D-glucose, and 2 g agar in 100 cm^3 distilled water, and adjusting pH to 5.7 using buffer. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 cm^3 saline to get a suspension of corresponding species. 20 cm^3 of agar media was poured in to each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 ˚C for 1 h. Using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37 ˚C for 3-4 d. The inhibition zones in diameter were measured and compared with the controls. The Nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 1.6 × 10^4-6 × 10^4 c.f.u cm^{-3}. The cultures were incubated for 48 h at 35 ˚C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory

concentrations (*MIC*). Bovastin was used as the standard drug. The diameter of zone of inhibition and minimum inhibitory concentration values are given in Table 2.

Newly prepared compounds were screened for their antifungal activity against *Fusarium oxyporum, Aspergillus flavus, Aspergillus niger* (recultured) in DMSO by serial plate dilution method. The antifungal screening data showed moderate to good activity. Compounds **5a-j** emerged as very active against all the fungal strains.

RESULTS AND DISCUSSION

α-Aminophosphonates **5a-j** were synthesized by one-pot, three-component reaction of equimolar quantities of Sulfathiazole **(1)**, dimethyl phosphite **(2)** and various aldehydes **(4a-j)** in dry toluene at reflux conditions for 5-6 hours in 70-80% yields. 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 reaction proceeds smoothly without any catalyst.

The structures of the title compounds **5a-j** were established by their spectroscopical data. All the compounds **5a-j** exhibited infrared absorption bands for P=O, P-C (aliphatic) and N-H in the regions 1252-1202, 769-745 and 3446–3343 cm^{-1} respectively [13]. Chemical shifts for aromatic protons of the title compounds **5a-j** appeared as a complex multiplet in the region 6.34-8.44 ppm [14]. The proton of methyne (P-C-H) chemical shift appeared as a doublet of doublet [14] 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 [14] at δ 4.30-5.44 indicating its coupling with neighbouring proton and phosphorus. The ^{13}C NMR spectral data of **5a, 5b, 5c** and **5d** 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-O-C = 7.5 Hz) and singlet at δ 56.1-62.9 respectively [15]. The ^{31}P NMR chemical shifts appeared as singlets in the region δ 18.59-35.01 for all the compounds [16] **5a-j.** The LC mass spectra of **5a, 5b, 5c** and **5d** agreed with the proposed structures.

Biological activity

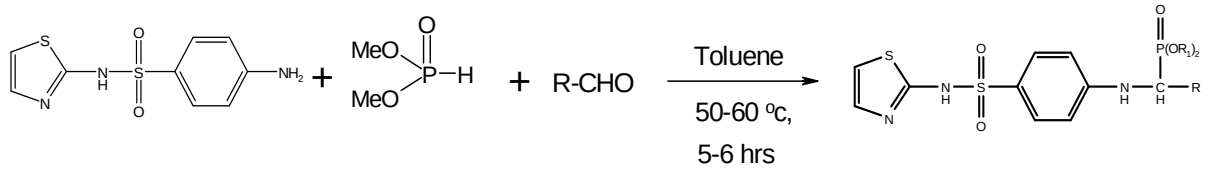
Antibacterial activity

All the synthesized compounds were screened against Gram positive bacteria and Gram negative bacteria by the disc diffusion method and the results were compared with the standard drug (Streptomycin). The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the compounds **5c** and **5e** were more effective towards *Eschrichia coli,* **5d** and **5i** were more effective towards *Streptococcus bovis* and the compounds **5f,** and **5i** were more effective towards *Bacillus subtilis.*

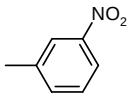
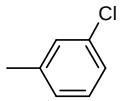
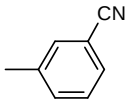
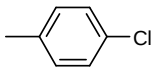
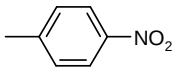
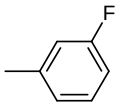
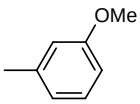
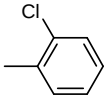
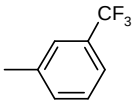
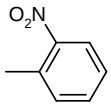
Minimum inhibitory concentration (MIC) was determined for the compounds **5a-j** by broth dilution technique. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentrations (MIC). Streptomycin was used as a standard drug. The diameter of the zone of inhibition and minimum inhibitory concentration values are given in Table 1.

Antifungal activity

All the titled compounds **5a-j** were tested for antifungal activity and the results were compared with the standard drug, Bovastin. Among them, the compounds **5e** and **5f** were more effective towards *Aspergillus flavus*, **5d** and **5f** compounds were more effective towards *Aspergillus niger* and the compounds **5e** were more effective towards *Fusarium oxysporum.* 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 concentration (MIC). Bovastin was used as the standard drug. The diameter of zone of inhibition and minimum inhibitory concentration (MIC) values are given in Table 2.



1 **2** **4a-j** **5a-j**

Compound	R	Compound	R
5a		**5f**	
5b		**5g**	
5c		**5h**	
5d		**5i**	
5e		**5j**	

Scheme 1. Synthesis of of α-aminophosphonates 5a-j.

Table 1. Antibacterial activity of α-aminophosphonates 5a-j against Gram positive and Gram negative bacteria

Compound	Zone of inhibition (mm)								
	Escherichia coli			*Bacillus subtilis*			*Streptococcus bovis*		
	150 µg	250 µg	350 µg	150 µg	250 µg	350 µg	150 µg	250 µg	350 µg
5a	9	12	16	--	--	8	--	12	15
MIC	63 µg			180 µg			160 µg		
5b	6	11	15	6	12	17	8	11	16
MIC	70 µg			80 µg			55 µg		
5c	8	15	18	--	10	14	--	11	15
MIC	51 µg			165 µg			175 µg		
5d	5	11	17	7	13	16	9	15	18
MIC	55 µg			75 µg			52 µg		
5e	10	16	20	7	14	17	--	8	15
MIC	35 µg			68 µg			175 µg		
5f	7	13	16	10	14	19	8	12	15
MIC	62 µg			30 µg			80 µg		
5g	--	5	11	4	11	16	--	8	13
MIC	180 µg			95 µg			175 µg		
5h	7	13	17	6	13	17	--	6	11
MIC	95 µg			65 µg			180 µg		
5i	4	9	13	8	13	15	6	13	16
MIC	180 µg			60 µg			90 µg		
5j	--	--	7	--	6	13	--	--	8
MIC	190 µg			170 µg			200 µg		
Streptomycin (Standard)	22			23			21		

MIC=Minimum inhibitory concentration

Table 2. Antifungal activity of α-aminophosphonates 5a-j

Compound	Zone of inhibition (mm)								
	Fusarium oxysporum			*Aspergillus flavus*			*Aspergillus niger*		
	150 µg	250 µg	350 µg	150 µg	250 µg	350 µg	150 µg	250 µg	350 µg
5a	7	11	14	--	7	13	--	--	11
MIC	75 µg			190 µg			200 µg		
5b	8	13	16	5	11	14	7	12	16
MIC	60 µg			120 µg			95 µg		
5c	7	13	17	3	9	16	6	14	17
MIC	65 µg			170 µg			110 µg		
5d	6	12	18	4	8	14	--	--	12
MIC	80 µg			130 µg			170 µg		
5e	9	16	20	7	15	18	6	13	18
MIC	50 µg			70 µg			115 µg		
5f	6	12	15	9	11	17	7	14	19
MIC	85 µg			55 µg			95 µg		
5g	3	13	15	6	12	16	4	12	18
MIC	140 µg			95 µg			125 µg		
5h	8	13	18	6	13	16	--	--	8
MIC	65 µg			105 µg			170 µg		
5i	--	6	13	6	11	16	6	9	14
MIC	140 µg			120 µg			120 µg		
5j	--	--	--	2	8	12	--	7	11
MIC	------			135 µg			180 µg		
Bovastin (Standard)	24			23			24		

MIC=Minimum inhibitory concentration

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CONCLUSION

We have successfully synthesized novel α-aminophosphonates **5a-j** in one-pot, three-component reaction of amines **1**, dimethyl phosphite **2**, various aldehydes **4a-j** via Kabachinik-Fields reaction. The major feature of the synthesis was the reaction proceeds without any catalyst. All the title compounds exhibited promising antibacterial and antifungal activities.

REFERENCES

[1] M. R. Saidi, N. Azizi, *Synlett*, **2002**, 1347.
[2] X. J.Mu, M. Y.Lei, L.P. Zou, W. Zhang, *Tetrahedron Lett*, **2006**, 47, 1125.
[3] P. Kafarski, B. Lejczak, P. Mastalerz, *Beitr. Wirk. Forsh*, H25, *Chem. Abstr*., **1985**, 103, 174532.
[4] P. Kafarski, B. Lejczak, *Curr. Med. Chem. Anticancer Agents*, **2001**, 1(3), 301.
[5] M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem*., **1989**, 32, 1652.
[6] P. Kafarski, B. Lejczak, *Phosphorus, Sulfur, Silicon, Relat. Elem*., **1991**, 115, 63193.
[7] F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem*., **1986**, 29, 29.
[8] a) M. I. Kabachinik, T. I. Medve, *Dokl. Akad. Nauk SSSR*, **1952**, 83, 689, *Chem. Abstr.* **1953**, 47, 2724b.
b) E. K. Fields, *J. Am. Chem. Soc.*, **1952**, 74, 1528.
[9] F. Texier-Boullet, M. Lequitte, *Tetrahedron Lett.*, **1986**, 27, 3515.
[10] V. J. Blazis, K. J. Koeller, C. D. Spilling, *J. Org. Chem.*, **1995**, 60, 931.
[11] O. Pamies, J. E. Backvall, *J. Org. Chem.*, **2003**, 68, 4815.
[12] A. R. Sardarian, B. Kaboudin, *Synth. Commun.*, **1997**, 27543.
[13] L. C. Thomas, *Interpretation of the Infrared Spectra of Organophosphorus Compounds*(London: Heyden), **1974**.
[14] L. H. Jin, B. A. Song, G. P. Zhang, R. Xu, S. M. Zhang, X. W. Gao, D. W. Hu, S. Yang, *Bioorganic.Med. Chem. Lett.*, **2006**, 16, 1537.

[15] J. C. Cochart, M. B. Mc. Donell, P. D. Tyson, *J. Chem. Soc., Perkin. Trans*., **1953**, 1, 2153.
[16] D. Petersen, M. Marcolini, L. Bernadi, F. Fini, P. R. Herrera, V. Sgarzani, A. Ricci, *J. Org. Chem.,* **2006**, 71, 6296.