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Synthesis and antimicrobial activity evaluation of new dialkyl heteroarylphosphonates

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ABSTRACT

*Synthesis of new dialkyl heteroaryl phosphonates (**4a-f and 5a-f**) is accomplished with high yields via Michaelis-Arbuzov rearrangement by the reaction of various heteroaryl halides with triethyl /triisopropyl phosphite at 50-55 °C in dry tetrahydrofuran (THF) in the presence of $BF_3.Et_2O$ as a catalyst. The structures of the title compounds were established by elemental analysis and spectral data (IR, ^1H, ^{13}C and ^{31}P NMR and LC- mass) and their antimicrobial activity was evaluated. The title compounds exhibited moderate antimicrobial activity.*

Key words: dialkyl heteroaryl phosphonates, triethyl/triisopropyl phosphite, $BF_3.Et_2O$, Anti-microbial activity, MIC.

INTRODUCTION

Michaelis-Arbuzov reaction is one of the most versatile routes to synthesize phosphonates, phosphinates and phosphine oxides, containing a phosphorus-carbon bond by the reaction of trialkyl phosphite and alkyl halides which are particularly scarce in nature [1-2]. Their diverse biological activity has attracted considerable synthetic and pharmacological interest [3]. Microwave assisted solid surface Michaelis-Arbuzov synthesis accomplishes the phosphonylation of aromatic compounds under catalytical conditions of organophosphorus compounds [4-5]. The catalytic Arbuzov rearrangement involves iodine [6], alkali metal iodide [7] and Ni [II] chloride [8] as catalysts. So far reported synthetic procedures for phosphonates require very high temperature long time and pressure [9]. Renard et al. used $BF_3.Et_2O$ and TMSOTf as Lewis acid catalysts these in the Arbuzov rearrangement of phosphinates to phosphine oxides [10] and found that these catalysts are very effective at 60 °C and the yields were 87 and 91 respectively. We herein report the synthesis of new dialkylheteroaryl

phosphonates **4a-f** and **5a-f** using $BF_3.Et_2O$ as a Lewis acid catalyst under mild reaction conditions (50-55°C) with high yields their structures were characterized by elemental analysis, IR, NMR (^1H, ^{13}C, ^{31}P NMR) and mass spectral data evaluated their antimicrobial activity

MATERIALS AND METHODS

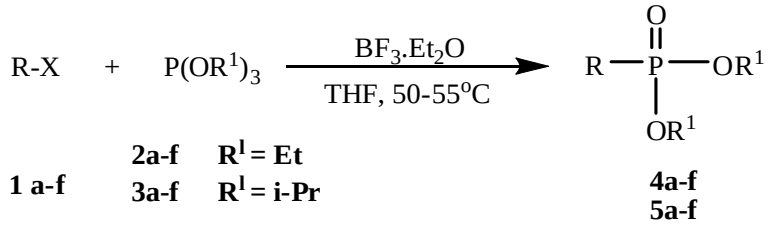
Experimental

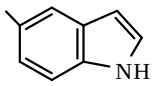
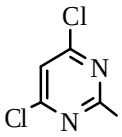
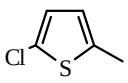
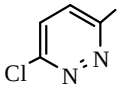
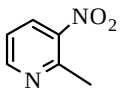
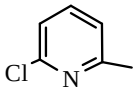
Chemistry

Chemicals were purchased from Sigma – Aldrich, Merck and Lancaster, and were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods (14). IR spectra were recorded as KBr pellets on a Perkin Elmer 283 unit. ^1H, ^{13}C, ^{31}P NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C, 161.9 MHz for ^{31}P NMR were recorded in DMSO and referenced to TMS (H^1 & ^{13}C) and 85% H_3PO_4 (^{31}P). LC-MS spectra were recorded on a Joel SX 102 DA/600 Mass spectrometer. Elemental analyses were performed on a Thermo Finnigan Instrument at University of Hyderabad, Hyderabad, India.

RESULTS AND DISCUSSION

The heteroaryl phosphonates (**4a-f/5a-f**) were synthesized by using $BF_3.Et_2O$ as a catalyst within 4-6 hrs with high yields (69-78%) through Michaelies-Arbuzov rearrangement. The chemical structures of all the title compounds (**4a-f/5a-f)** were characterized by IR, ^1H, ^{13}C, ^{31}P NMR and mass spectral data. The characteristic IR stretching absorptions were observed in the regions 1224-1256 (P=O), 1081-1012 (P-O-Caliphatic), 1420-1470 (P-Caromaic).In ^1H NMR, the methyleneoxy protons appeared as multiplets at δ 4.21 - 4.01 [13].



Compound	R	Compound	R
4a, 5a		4d, 5d	
4b, 5b		4e, 5e	
4c, 5c		4f, 5f	

Scheme 1

The methineoxy protons appeared as two distinct doublets in the region of δ 4.58 - 4.76 (d, *J* = 6.2-6.6 Hz). In ^{13}C NMR, methyleneoxy carbons resonated as a doublet at δ 62.3 - 61.4 (d, *J* = 5.4-5.8 Hz) [13]. ^{31}P NMR chemical shifts were observed in the region -11.2 to 9.32 ppm [13].

The antibacterial activity of the title compounds **4a** and **5a** showed pronounced activity against both G^{+ve} and G^{-ve} microorganisms, and **4b** and **5b** exhibitd good activity against G^{-ve} organisms only. This mode of action might be due to change of side chain at P of the title compounds. In addition to this remaining title compounds showed moderate to high antimicrobial activity.

Pharmacology

Antimicrobial activity

The antimicrobial activity of the title compounds was evaluated by the standard methods and the results were presented in the results and discussion section.

Antibacterial activity

The antibacterial activity of the title compounds was evaluated by Mueller-Hinton agar disc diffusion method [11, 12] against Gram positive bacteria *Bacillus subtilis* and *Enterococcus faecalis* and Gram negative bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The bacterial suspension was prepared with $1.3x10^9$ cells/mL concentrations approximately for the bioassay. The activity was measured at two different concentrations for all the title compounds at 25 µg/mL and 50 µg/mL. Then the title compounds were introduced on to the disc. Thus the disc was completely saturated with the test compound. Then the disc was introduced on to the upper layer of the medium with the bacteria. The bio-activity of compounds was determined by measuring diameter of the inhibition zone (**DIZ**) in millimeters and minimum inhibitory concentration (**MIC**) in mg/ mL by taking Ampicillin as standard reference in order to control the sensitivity of the bacteria. Each test was done in triplicate and the average values were taken as a final result.

Table 1: Antibacterial activity (DIZ) of the title compounds (4a-f/ 5a-f)

Compound	Diameter of Inhibition Zone in (mm)							
	Bacillus subtilis		*Enterococcus faecalis*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*	
	25	**50**	**25**	**50**	**25**	**50**	**25**	**50**
4a	4.1	11.4	3.8	10.7	4.4	12.3	3.6	13.7
4b	5.3	14.1	4.8	14.6	3.3	8.9	3.7	11.3
4c	3.7	8.1	1.5	5.0	2.2	5.2	3.4	7.9
4d	1.8	4.3	1.5	3.9	2.4	7.6	2.6	7.1
4e	1.5	3.7	1.5	2.8	1.7	5.4	1.8	5.2
4f	1.3	2.9	1.4	2.5	1.6	4.0	1.8	4.6
5a	3.9	13.6	2.5	7.8	5.7	14.2	3.7	11.3
5b	3.2	9.4	3.5	9.0	4.1	10.9	1.7	3.8
5c	2.4	7.5	2.8	7.2	1.9	4.5	1.8	4.2
5d	3.0	5.7	2.7	6.2	3.4	5.9	1.7	3.8
5e	2.4	5.0	2.1	4.4	1.9	4.6	2.7	5.0
5f	2.4	6.7	2.1	6.1	1.3	2.6	1.2	1.5
Ampicillin (20 µg/disc)	21	21	20	20	19	19	18	18

The concentration expressed in µg/disc and the diameter of the disc is in mm, solvent DMSO.

Antifungal activity

The antifungal activity of the title compounds was evaluated by agar-well diffusion method using Sabouraud Dextrose Agar. The Petri plates were incubated at 37°C for 24 h for bacteria and 48-72 h at 24°C for fungi. The bio-activity of compounds was determined by measuring

diameter of the inhibition zone (**DIZ**) in milli meters. Concentrations of the title compounds were taken as 25 µg/mL and 50 µg/mL were evaluated for antifungal activity by using Nystatine as standard reference in order to control the sensitivity of the fungi. Each test was done in triplicate and the average values were taken as a final result.

Evaluation of minimum inhibitory concentration [MIC]

Minimum inhibitory concentration [MIC] was determined for the title compounds. The lowest concentration of antimicrobial compounds that inhibit the visible growth of an organism after overnight incubation period is considered as MIC. The title compounds in concentrations of 1 to 6.3 mg/mL in steps of 100 µg/mLwere evaluated; 0.1 mL of bacterial inoculums ($1.4x10^6$ CFU/mL) was added to each tube. The tubes were incubated aerobically and anerobically at 37 ^oC for 24 hrs. Two control tubes were maintained for each test, for positive control ampicillin (Hi-media) and negative control nutrient broth having an organism.

Table 2: Antibacterial activity (MIC) of the title compounds (4a-f/ 5a-f)

Compound [a]	Minimum Inhibitory Concentration (mg/ mL)			
	Bacillus subtilis	*Enterococcus faecalis*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
4a	2.6	3.1	3.5	3.8
4b	3.1	2.9	2.4	3.5
4c	4.2	4.6	4.8	4.0
4d	3.9	4.2	4.7	5.1
4e	3.8	5.4	4.8	4.2
4f	4.2	4.6	4.8	4.0
5a	3.4	3.8	4.5	4.7
5b	3.3	3.8	4.2	3.9
5c	3.3	3.7	3.9	4.5
5d	4.1	4.4	5.2	5.5
5e	3.6	3.9	4.7	5.1
5f	3.4	4.0	4.4	4.9
Ampicillin (20 µg/disc)	0.1	0.2	0.2	0.3

[a] *Solvent DMSO.*

Preparation of diethyl/ diisoproyl hetero aryl phosphonates (4a-f & 5a-f)

A mixture of heteroaryl halide (**1a-f**) (0.002 mole), triethyl phosphite / triisopropyl phosphite (**2a-f**/ **3a-f**) (0.002 mole), $BF_3.Et_2O$ (catalytic amount) were placed in a 50 mL round-bottomed flask in THF (20 mL) and the mixture was stirred at 50-55^oC for 4-6 h (**Scheme 1**) to obtain the products (**4a-f**/ **5a-f**). The reaction progress was monitored by TLC (ethyl acetate and n-Hexane, 7:3). The solvent was removed in a rotaevaporator. The product was purified by column chromatography on silica gel using petroleum ether –ethyl acetate (4:1) as eluent.

Synthesis of diethyl 1*H*-indol-5-yl-phosphonate (4a):

Yield: 76%; Semi solid; IR (KBr): 1224 (P=O), 1065 (P-O-$C_{aliphatic}$), 1424 (P-$C_{Aromatic}$), cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (t, 6H, J = 7.6 Hz, CH_2-$\underline{CH_3}$), 3.94-4.03 (m, 4H -O$\underline{CH_2}$-CH_3), 6.84-7.01 (m, 2H), 7.21 (d, 1H, J = 8.6 Hz, H-2), 7.32 (d, 1H, J = 7.6 Hz, H-3), 8.24 (s,1H, H-4), 7.42 (d, 1H, J = 6.6 Hz, H-6), 10.14 (s, 1H, -NH); ^{13}C-NMR (DMSO-d_6) δ: 140.6, 126.6, 124.7, 123.4, 121.2, 120.4, 113.2, 104.6, 61.0, 16.8; ^{31}P-NMR (DMSO-d_6) δ: 2.3; LCMS

(m/z): 253 ($M^{+\bullet}$, 100), 224 (72), 208 (46), 163 (35); Anal. Calcd (%) for $C_{12}H_{16}NO_3P$: C, 56.92; H, 6.37; N, 5.53; Found: C, 56.85; H, 6.33; N, 5.58.

Table 3: Antifungal activity of the title compounds (4a-f/ 5a-f)

Compound	Inhibition zone in (mm)			
	Candida albicans		*Aspergillus niger*	
	25	**50**	**25**	**50**
4a	4.8	15.6	4.6	15.2
4b	4.3	16.8	4.6	15.5
4c	3.7	10.1	3.5	8.8
4d	2.8	6.1	2.0	4.9
4e	2.3	6.5	2.0	5.3
4f	2.3	4.7	2.5	4.2
5a	3.9	14.4	5.2	14.5
5b	1.6	3.9	1.4	5.9
5c	3.5	8.7	2.9	7.3
5d	2.4	5.1	2.7	5.6
5e	3.1	8.3	1.9	3.7
5f	1.5	4.8	1.5	4.2
Nystatine (30 µg/disc)	19	19	20	20

[a] *The concentration expressed in µg/disc solvent-DMSO.*

Synthesis of diisopropyl-1*H*-indol-5-yl-phosphonate (5a):

IR (KBr): 1210 (P=O), 1077 (P-O-$C_{aliphatic}$), 1466 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.28 (d, 12H, J = 5.2, CH-$\underline{CH}_3$), 4.11-4.16 (m, 2H, -O$\underline{CH}$-CH_3), 7.32 (d, 1H, J = 7.6 Hz, H-2), 6.41 (d, 1H, J = 6.6 Hz, H-3), 7.48 (d, 1H, J = 8.6 Hz, H-4), 7.12 (d, 1H, J = 7.6 Hz, H-6), 8.24 (s, 1H, H-7), 10.22 (s, 1H, -NH); ^{13}C-NMR (DMSO-d_6) δ: 144.6, 128.6, 127.6, 124.2, 122.8, 121.5, 119.2, 104.6, 71.6, 19.8; ^{31}P-NMR (DMSO-d_6) δ: -2.65; LCMS (m/z): 281($M^{+\bullet}$, 100), 238 (24), 224 (72), 161 (52), 116 (36); Anal. Calcd (%) for $C_{14}H_{20}NO_3P$: C, 59.78; H, 7.17; N, 4.98; Found: C, 59.88; H, 7.15; N, 4.91.

Synthesis of diethyl 5-chlorothiophen-2-yl-phosphonate (4b):

Yield: 68%, Semi solid; IR (KBr): 1214 (P=O) , 1052 (P-O-$C_{aliphatic}$), 1434 (P-$C_{Aromatic}$) cm^{-1} ; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (t, 6H, J = 6.6 Hz, CH_2-$\underline{CH}_3$), 4.16-4.22 (m, 4H -O$\underline{CH}_2$-CH_3,) 7.18 (d, 1H, J = 7.4Hz, H-3), 7.32 (d, 1H, J = 7.6 Hz, H-4); ^{13}C-NMR (DMSO-d_6) δ: 132.8, 128.2, 126.4, 122.6, 62.1, 16.4; ^{31}P-NMR (DMSO-d_6) δ: 3.5; LCMS (m/z): 254 ($M^{+\bullet}$, 100), 225 (65) ,209 (42), 164 (31); Anal. Calcd (%) for $C_8H_{12}ClO_3PS$: C, 37.73; H, 4.75; Found: C, 37.65; H, 4.75.

Synthesis of diisopropyl-5-chlorothiophen-2-yl-phosphonate (5b):

Yield: 69 %, Semi solid; IR (KBr): 1238 (P=O) , 1062 (P-O-$C_{aliphatic}$), 1448 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.58 (d, 12H, J = 5.4 Hz, CH-$\underline{CH}_3$), 4.82-4.68 (m, 2H, -O$\underline{CH}$-CH_3), 7.32 (d, 1H, J = 7.8, H-3), 7.51 (d, 1H, J = 7.8 Hz, H-4); ^{13}C-NMR (DMSO-d_6) δ: 128.2, 127.4, 126.8, 125.2, 72.4, 19.4; ^{31}P-NMR (DMSO-d_6) δ: -10.2; LCMS (m/z): 282 ($M^{+\bullet}$, 100), 225 (45), 209 (34),164 (72), 117 (56); Anal.Calcd (%) for $C_{1O}H_{16}ClO_3PS$: C, 42.48; H, 5.70; Found: C, 42.35; H, 5.73 .

Synthesis of diethyl 3-nitropyridin-2-yl-phosphonate (4c):
Yield: 78%, Semi solid; IR (KBr): 1236 (P=O) , 1068 (P-O-$C_{aliphatic}$), 1424 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (t, 6H, J = 6.42 Hz, CH_2-$\underline{CH_3}$), 4.62–4.54 (m, 4H, -O$\underline{CH_2}$-CH_3), 7.52-7.71 (m, 3H, H-4, H-5&H-6); ^{13}C-NMR (DMSO-d_6): 156.2, 148.4, 147.6, 132.8, 124.62, 62.24, 18.2; ^{31}P-NMR (DMSO-d_6) δ: 6.11; LCMS (m/z): 260 ($M^{+\bullet}$, 100), 231 (37), 215 (52),170 (64),124 (21); Anal. Calcd (%) for $C_9H_{13}N_2O_5P$: C, 41.55; H, 5.04; N, 10.77; Found: C, 41.52; H, 5.02; N, 10.72 .

Synthesis of diisopropyl-5-chlorothiophen-2-yl-phosphonate (5c):
Yield: 69 %, Semi solid; IR (KBr): 1238 (P=O) , 1032 (P-O-$C_{aliphatic}$), 1454(P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.42 (d, 12H, J = 4.2 Hz, CH-$\underline{CH_3}$),), 4.82-4.68 (m, 2H, -O$\underline{CH}$-CH_3), 7.32 (d, 1H, J = 7.8, H-3), 7.51 (d, 1H, J = 7.8 Hz, H-4). ^{13}C-NMR (DMSO-d_6) δ: 128.2, 127.4, 126.8, 125.2, 72.4, 19.4; ^{31}P-NMR (DMSO-d_6) δ: 6.11; LCMS (m/z): 282 ($M^{+\bullet}$, 100), 239 (35),161 (67),117 (48); Anal.Calcd (%) for $C_{1O}H_{16}ClO_3PS$: C, 42.48; H, 5.70; Found: C, 42.44; H, 5.68 .

Synthesis of diethyl 4,6-dichloropyrimidin-2-yl-phosphonate (4d):
Yield: 78%, Semi solid; IR (KBr): 1243 (P=O) , 1066 (P-O-$C_{aliphatic}$), 1458 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.36 (t, 6H, J = 6.3 Hz, CH_2-$\underline{CH_3}$), 4.48 – 4.52 (m, 4H -O$\underline{CH_2}$-CH_3,) 8.34 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6) δ: 166.4, 165.8, 161.6, 128.2, 61.2, 19.2; ^{31}P-NMR (DMSO-d_6) δ: -1.76; LCMS (m/z): 285 ($M^{+\bullet}$, 100), 256 (36), 240 (47), 185 (67),148 (23);Anal. Calcd (%) for $C_8H_{11}Cl_2N2O_3P$: C, 33.71; H, 3.89; N, 9.83; Found: C, 33.68; H, 3.84; N, 9.80.

Synthesis of diisopropyl-4,6-dichloropyrimidin-2-yl-phosphonate (5d):
Yield: 70 %, Semi solid; IR (KBr): 1252 (P=O) , 1052 (P-O-$C_{aliphatic}$), 1472 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.48 (d, 12H, J = 4.6 Hz, CH-$\underline{CH_3}$), 4.65- 472 (m, 2H, -O$\underline{CH}$-CH_3) 9.32 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6) δ: 166.3, 162.4, 160.2, 126.4, 65.6, 19.6; ^{31}P-NMR (DMSO-d_6) δ: -2.0; LCMS (m/z): 313 ($M^{+\bullet}$, 100), 260 (56), 193(68), 148 (36); Anal. Calcd(%) for $C_{10}H_{15}Cl_2N_2O_3P$: C, 38.36; H, 4.83; N, 8.95; Found: C, 38.32; H, 4.78; N, 8.90.

Synthesis of diethyl 6-chloropyridazin-3-yl-phosphonate (4e):
Yield: 73%, Semi solid; IR (KBr): 1223 (P=O) , 1062 (P-O-$C_{aliphatic}$), 1438 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.34 (t, 6H, J = 5.3 Hz, CH_2-$\underline{CH_3}$), 4.32-4.46 (m, 4H, -O$\underline{CH_2}$-CH_3), 8.12 (d, 1H, J = 6.2Hz, H-4), 7.78 (d, 1H, J = 5.4Hz, H-5); ^{13}C-NMR (DMSO-d_6) δ: 160.8, 152.8, 134.6, 126.4, 62.8, 19.7; ^{31}P-NMR (DMSO-d_6) δ: 9.3; LCMS (m/z): 250 ($M^{+\bullet}$, 100), 225 (45), 209 (26), 164 (63), 115 (21); Anal. Calcd (%) for $C_8H_{12}ClN_2O_3P$: C, 38.34; H, 4.83; N, 11.18; Found: C, 38.31; H, 4.78; N, 11.12.

Synthesis of diisopropyl-6-chloropyridazin-3-yl-phosphonate (5e):
Yield: 71%, Semi solid; IR (KBr): 1232 (P=O) , 1066 (P-O-$C_{aliphatic}$), 1474 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.52 (d, 12H, J = 4.8 Hz, CH-$\underline{CH_3}$), 4.54 - 4.62 (m, 2H -O$\underline{CH}$-CH_3), 7.62 (d, 1H, J = 5.6 Hz, H-4) , 7.89 (d, 1H, J= 6.2Hz, H-5); ^{13}C-NMR (DMSO-d_6) δ:162.6,158.4,152.1,132,4, 68.4, 19.6; ^{31}P-NMR (DMSO-d_6) δ: 9.1; LCMS (m/z): 278 ($M^{+\bullet}$, 100), 241(65),158 (67), 113 (27); Anal. Calcd (%) for $C_8H_{12}ClN_2O_3P$: C, 43.10; H, 5.79; N, 10.05; Found: C, 43.06; H, 5.76; N, 10.02.

Synthesis of diethyl-6-chloropyridin-2-yl-phosphonate (4f):
Yield: 78%, Semi solid; IR (KBr): 1228 (P=O) , 1046 (P-O-$C_{aliphatic}$), 1462 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (t, 6H, J =6.82 Hz, CH_2-$\underline{CH_3}$), 4.34 - 4.42 (m, 4H - O$\underline{CH_2}$-CH_3), 8.12 - 8.24 (m, 3H, H-3, H-4 & H-5); ^{13}C-NMR (DMSO-d_6) δ: 154.6, 152.8, 148.2, 140.4, 126.8, 61.2, 16.8; ^{31}P-NMR (DMSO-d_6) δ: 5.11; LCMS (m/z): 249 ($M^{+\bullet}$, 100), 220 (38), 204 (56), 159 (67), 112 (25); Anal. Calcd (%) for $C_9H_{13}ClNO_3P$: C, 43.26; H, 5.22; N, 5.61; Found: C, 43.21; H, 5.18; N, 5.56.

Synthesis of diisopropyl-6-chloropyridin-2–yl-phosphonate (5f):
Yield: 72%, Semi solid; IR (KBr): 1244 (P=O) , 1048 (P-O-$C_{aliphatic}$), 1472 (P-$C_{Aromatic}$) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.38 (d, 12H, J = 4.2 Hz, CH-$\underline{CH_3}$),), 4.62-4.72 (m, 2H, - O$\underline{CH}$-CH_3), 8.28 - 8.36 (m, 3H, H-3, H-4 & H-5); (^{13}C-NMR) (DMSO-d_6) δ: 154.4, 148.4, 141.4, 134.6, 128.2 72.8, 19.8; ^{31}P-NMR (DMSO-d_6) δ: -11.21. LCMS (m/z): 277 ($M^{+\bullet}$, 100), 234 (46), 157 (58), 136 (38), 112 (26); Anal. Calcd (%) for $C_{11}H_{17}ClNO_3P$: C, 47.58; H, 6.17; N, 5.04; Found: C, 47.54; H, 6.12; N, 4.98.

CONCLUSION

In conclusion, the synthesis of the novel dialkyl heteroaryl phosphonates with high yieds is accomplished in high yields by one-pot two-coponent reaction between heteroaryl halides and trialkyl phosphites in the presence of $BF_3.Et_2O$ as a catalyst in THF at 50-55°C Their structures were estabhished by elemental analysis, IR, NMR (^{1}H,^{13}Cand ^{31}P) and LC mas spectra. All the title compounds exhibited moderate antimicrobial activity. Their minimum inhibition concentrations were also evaluated.

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