Synthesis and antimicrobial activity of bisphosphonates

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Dimethyl [(substitutedphenyl)(6-oxo6λ^{5}dibenzo[*d,f*][1,3,2]dioxaphophepin-6-yl)methyl]phosphonates (**5a–j**) were synthesised through a three step process involving preparation of dimethyl hydroxy(substitutedphenyl)methyl-phosphonates (**4a–j**) and their reaction with 6-bromodibenzo[*d,f*][1,3,2]dioxaphosphepine (**2**) in dry toluene in the presence of triethylamine at 50–60 °C. Tetramethylguanidine (TMG) as a catalyst was found to increase the yields and purity of the products. These compounds were characterised by IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data found to possess higher antimicrobial activity then the standards.

Keywords: bisphosphonates, 2,2'-dihydroxybiphenyl, α-hydroxy phosphonates, anti microbial activity

Bisphosphonates (BPS) are carbon analogues of naturally occurring pyrophosphate (PP) and are a major class of drugs for the bone disease.[1] Besides their bone antiresorptive properties, several of them are also potent growth inhibitors of some pathogenic trypanosomatids.[2] Most of the antiviral compounds that are currently used for the treatment of the Herpes simplex virus (HSV), Human-Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Varicella Zoster Virus (VZV) and Cytomegalovirus (CMV) infections their acyclic nucleotide analogues.[3-6] Recent studies have shown that anti-tumour properties of BPS included inhibition of tumour cell proliferation and invasion, adhesion to bone, and angiogenesis.[7] These classes of chemical substances are presently undergoing intensive research for cancer therapy and viral diseases management.[8,9] Result on the compounds studied so for revealed that the absolute configuration significantly influences their biological potency.[10] A few of the derivates of BPS also activate the γ^{δ} T cell population which shows potential cytotoxic activity towards a broad spectrum of tumours.[11]

In view of this, dimethyl [substitutedphenyl-6-oxo-6λ^5-dibenzo[*d,f*][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonates (**5a–j**) were synthesised expecting them to possess broad spectrum of bioactivity.

Results and discussion

The synthesis of title compounds (**5a–j**) involves cyclisation of 2,2'-dihydroxy biphenyl (**1**) with phosphorus tribromide at 0 °C under inert and dry conditions in the presence of triethylamine in toluene to afford the corresponding 6-bromodibenzo[*d,f*][1,3,2]dioxaphosphepine (**2**). Various aromatic aldehydes, (**3a–j**), react with dimethyl phosphite at 0–25 °C in 1 h under inert and dry conditions in the presence of 10 mole% of tetramethyl guanidine (TMG) in dry toluene to afford the corresponding dimethyl hydroxy substituted phenyl methyl phosphonates (**4a–j**).[12] The reaction between (**2**) and dimethyl hydroxy (substitutedphenyl)methylphosphonates (**4a–j**) in dry toluene in the presence of triethylamine at 50–60 °C for 5 h afforded (**5a–j**)[13] in good yields. The progress of the reaction was monitored by TLC. TMG acts as an effective catalyst in this reaction and it can be easily recycled. The chemical structures of (**5a–j**) were confirmed by elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectra. Compounds (**5a–j**) exhibited characteristic IR stretching frequencies in the regions 1250–1289, 1298–1228, 746–770 cm^{-1} for P = O (phosphonates), P = O (phosphepine) and P–C$_{(aliphatic)}$ respectively.[14]

The aromatic protons (**5a–j**) showed a complex multiplet at δ 6.76–8.10. The P–C–H proton signal appeared as a doublet of doublet[15] at δ 5.50–6.12 (d, J = 9.8–10.4 Hz) due to its coupling with phosphorus. The methoxy group protons of the dimethylphosphonate moiety resonated as two distinct doublets in the range of δ 3.61–3.91 (d, J = 9.3 Hz) and 3.15–3.59 (d, J = 9.8 Hz) indicating their non equivalence.[16]

The P–C–H carbon chemical shift signal appeared as a doublet in the range 52.85–54.37 ppm (d, $^1J_{P-C}$ = 163.0–167.42 Hz).The methoxy carbon of dimethylphosphite group resonated as a doublet at 53.16–57.39 ppm (d, J = 6.0–6.6 Hz).[15] Two distinct ^{31}P signals[17] appeared one at δ 20.15–29.10 (P = O phosphonates), and other at δ3.00–9.26 (P = O dioxaphosphepine) for them. The mass spectra of compounds **4a, 4e, 4f** and **4j** showed their respective molecular ion peaks in the expected *m/z* mass values.

Experimental

All melting points were determined in open capillary tubes on melt-temp apparatus and are uncorrected. Micro-analyses were performed at the Central Drug Research Institute, Lucknow, India. IR spectra (γ_{max} in cm^{-1}) were recorded as KBr pellets on a Perkin-Elmer 283 double beam spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on AMX 400 MHz spectrophotometer operating at 400 MHz for ^{1}H 100 MHz for ^{13}C and 161.9 MHz for ^{31}P using DMSO-d_6 as solvent. The ^{1}H and ^{13}C NMR chemical shifts were referenced to TMS, and ^{31}P chemical shifts to 85% H_3PO_4. FAB mass spectra were recorded on a Jeol AX 10^2 DA/600 mass spectrometer using argon/xenon (6 keV, 10 mA) as the LCMS.

Preparation of dimethyl [(6-oxo-6λ^5-dibenzo[d,f][1,3,2] dioxaphosphepin-6-yl)(phenyl) methyl]phosphonate **5a***; general procedure*

A solution of slight excess of phosphorus tribromide (1.35 g, 0.005 mole) in dry toluene (25 mL) was added dropwise to a well stirred solution of 2,2'-dihydroxybiphenyl (**1)** (0.930 g, 0.005 mole) and triethylamine (1.4 g 0.01 mole) in dry toluene (20 mL) at 0 °C. After the addition, the temperature of the reaction mixture was slowly raised and kept at 25–30 °C for 2 hours. The reaction progress was monitored by TLC analysis. The mixture was filtered to remove triethylamine hydrobromide and the filtrate was rotaevaporately. The residue (**2**) was used for the next step without further purification. To a stirred solution of benzaldehyde (**3a**) (0.502 g, 0.005 mole). dimethhyl phosphite (0.458 g, 0.005 mole) in anhydrous toluene (20 mL) was added dropwise and then TMG (10 mol%) was added and the reaction was continued at 0–25 °C for 1 h. The progress of the reaction was monitored by TLC analysis. The filtrate was rotaevaporated. The residue (**4a**)[12] in toluene (20 mL) and triethylamine (0.005 mole) at 0 °C was added to the cold solution of **2** in dry toluene,(20 mL) dropwise with effective stirring. After the addition, the temperature of the reaction mixture was slowly raised and kept at 50–60 °C for 5 h. The progress reaction was monitored by TLC analysis. After cooling to room temperature, it was filtered to remove triethylamine hydrobromide. The filtrate was rotaevaporated. The residue was purified by column chromatography on silicagel (80–120 mesh) using petroleum ether–ethylacetate (7:3) as eluent. It was recrystallised from 2-propanol to afford pure (**5a**) with (70%) yield, m.p. 146–148 °C. All the other compounds (**5b–j**) were prepared by adopting the same procedure.

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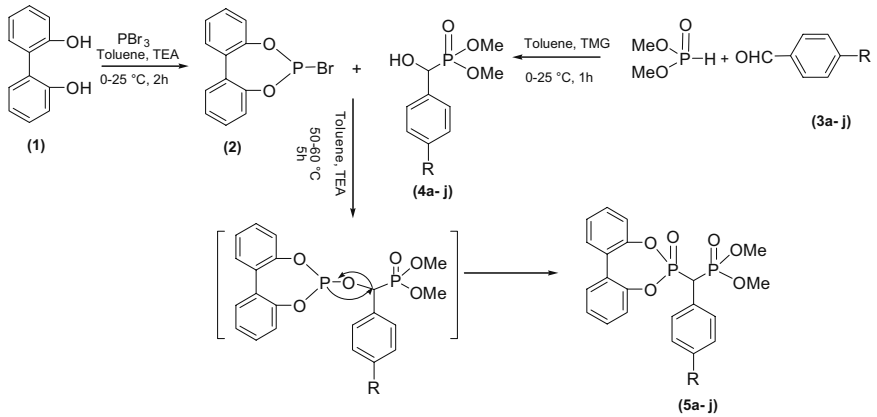

Entry	R	Entry	R	Entry	R
5a	H	5e	4-F-C_6H_4	5i	2-NO_2-C_6H_4
5b	4-Br-C_6H_4	5f	4-N$(CH_3)_2$-C_6H_4	5j	4-NO_2-C_6H_4
5c	4-Cl-C_6H_4	5g	4-OMe-C_6H_4		
5d	2-Cl,4-Cl-C_6H_3	5h	2-OMe-C_6H_4		

Scheme 1

Dimethyl [(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)(phenyl) methyl] phosphonate (**5a**): Yield 70%, m.p. 146–148 °C. IR (KBr) cm^{-1}: 1289 (P = O, phosphonate), 1238 (P = O, dioxaphosphepine), 745 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.95–7.98 (13H, m,), 5.89–5.95 (1H, dd, $^2J_{P\text{-}H}$ = 17.3 Hz, $^3J_{P\text{-}H}$ = 11.4 Hz), 3.61 (3H, d, $^3J_{P\text{-}H}$ = 9.2 Hz, P–O–CH_3), 3.21 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz, P–OCH_3); ^{13}C NMR data: 129.9 (C-1, C-11), 122.4 (C2-C10), 131.0 (C-3,C-9), 114.9 (C-4, C8), 130.7 (C-12, C-13), 152.8 (C-14, C-15), 142.5 (C-1'), 135.2 (C-2', C6'), 135.4 (C-3', C5'), 122.1 (C-4'), 57.4 (d, J = 6.4 Hz, P–OCH_3), 53.66 (d, 1JP–C = 163.0 P–CH-P); ^{31}P NMR data: δ 24.65 (P = O phosphonates), 3.00 (P = O dioxaphosphepine); LC-MS *m/z*: 453 [M + Na^+] (100%) 354.9 (100), 312 (22), 271 (40), 266.9 (12), 170 (20). Anal. Calcd for $C_{21}H_{20}O_6P_2$: C, 58.61; H, 4.68. Found C, 58.54; H, 4.60%

Dimethyl [(4-bromophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)ethyl]phosphonate (**5b**): Yield 68%, m.p. 158–160 °C. IR (KBr) cm^{-1}: 1280 (P = O, phosphonate), 1215 (P = O, dioxaphosphepine), 756 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.81–7.80 (12H, m, ArH), 5.80–5.91 (1H, dd, $^2J_{P\text{-}H}$ = 17.1 Hz, $^3J_{P\text{-}H}$ = 11.0 Hz, P–CH), 3.63 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz, P–OCH_3), 3.15 (3H, d, $^3J_{P\text{-}H}$ = 9.6 Hz, P–OCH_3); ^{31}P NMR data: δ 26.15 (P = O, phosphonate), 9.18 (P = Odioxaphosphepine); Anal. Calcd for $C_{21}H_{19}BrO_6P_2$: C, 49.53; H, 3.76. Found C, 49.43; H, 3.68%

Dimethyl [(4-chlorophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonate (**5c**): Yield 68%, m.p. 136–138 °C. IR (KBr) cm^{-1}: 1260 (P = O, phosphonate), 1212 (P = O, dioxaphosphepine), 749 (P–Calpha); ^{1}H NMR (DMSO-d_6): δ 6.85–7.50 (12H, m, ArH), 5.91–6.08 (1H, dd, $^2J_{P\text{-}H}$ = 16.9 Hz, $^3J_{P\text{-}H}$ = 10.9 Hz, P–CH), 3.85 (3H, d, $^3J_{P\text{-}H}$ = 9.3 Hz, P–OCH_3), 3.42 (3H, d, $^3J_{P\text{-}H}$ = 9.2 Hz, P–OCH_3); ^{31}P NMR data: δ 23.10 (P = O, phosphonate), 7.26 (P = O, phosphepine); Anal. Calcd for $C_{21}H_{19}ClO_6P_2$: C, 54.27; H, 4.12. Found C, 54.20; H, 4.06%

Dimethyl [(4,2-dichlorophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl) methyl]phosphonate (**5d**): Yield 71%, m.p. 149–151 °C. IR (KBr) cm^{-1} 1250 (P = O phosphonate), 1195 (P = O dioxaphosphepine), 780 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.81–7.59 (11H, m, ArH), 5.91–5.98 (1H, dd, $^2J_{P\text{-}H}$ = 16.9 Hz, $^3J_{P\text{-}H}$ = 10.9 Hz, P–CH), 3.61 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz, P–OCH_3), 3.25 (3H, d, $^3J_{P\text{-}H}$ = 9.3 Hz, P–OCH3); ^{31}P NMR data: δ 22.02 (P = O phosphonate), 5.25 (P = O dioxaphosphepin). Anal. Calcd for $C_{21}H_{18}Cl_2O_6P_2$: C, 50.52; H, 3.63. Found C, 50.50; H, 3.57%

Dimethyl [(4-fluorophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl] phosphonate (**5e**): Yield 69%, m.p .144–146 °C. IR (KBr) cm^{-1} 1280 (P = O, phosphonate), 1225 (P = O, dioxaphosphepine), 765 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.81–7.76 (12H, m, ArH), 5.50–5.65 (1H, dd, $^2J_{P\text{-}H}$ = 17.9 Hz, $^3J_{P\text{-}H}$ = 11.5 Hz, P–CH), 3.65 (3H, d, $^3J_{P\text{-}H}$ = 9.3 Hz, P–OCH_3), 3.45 (3H, d, $^3J_{P\text{-}H}$ = 9.7 Hz); ^{13}C NMR: data: 128.3 (C-1, C-11), 120.9 (C-2, C-10), 131.0 (C-3, C9), 115.4 (C-4, C-8), 129.2 (C-12, C-13), 148.2 (C-14, C-15), 132.1 (C-1'), 130.3 (C-2', C-6'), 115.2 (C-3', C-5'), 156.3 (C-4'), 54.2 (d, $^2J_{P\text{-}C}$ = 6.6 Hz, P–OCH_3), 52.5 (d, $^1J_{P\text{-}C}$ = 167.5 P–C–P); ^{31}P NMR data: δ 23.10 (P = O, phosphonates), 9.25 (P = O, dioxaphosphepine); LCMS *m/z*: 451 [M + 3] (100%) 424.2 (35), 420 (80), 378.2 (35), 350.2 (40), 238.2 (10). Anal. Calcd for $C_{21}H_{19}FO_6P_2$: C, 56.26; H, 4.27. Found C, 56.16; H, 4.20%

Dimethyl [(4-dimethylamino)phenyl(6-oxo-6dibenzo[d,f][1,3,2] dioxaphosphepin-6-yl)methyl]phosphonate (**5f**): Yield 72%, m.p. 161–162 °C. IR (KBr) cm^{-1} 1265 (P = O, phosphonate), 1228 (P = O, dioxaphosphepine), 775 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.81–7.56 (12H, m, ArH), 5.50–5.71 (1H, dd, $^2J_{P\text{-}H}$ = 17.2 Hz, $^3J_{P\text{-}H}$ = 11.2 Hz, P–CH, 3.75 (3H, d, $^3J_{P\text{-}H}$ = 9.3 Hz, P–OCH_3), 3.32 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz, P–OCH_3), 2.25 (6H, s, $ArCH_3$); ^{13}C NMR data: 129.9 (C-1, C-11), 122.4 (C2-C10), 131.0 (C-3, C-9), 114.6 (C-4, C8), 130.5 (C-12, C-13), 152.8 (C-14, C-15), 142.7 (C-1'), 135.2 (C-2', C6'), 135.4 (C-3', C5'), 122.1 (C-4'), 57.3 (d, J = 6.6 Hz, P–OCH_3), 53.66 (d, 1JP–C = 163.2P–CH-P); ^{31}P NMR data: δ 26.10 (P = O phosphonate), 3.15 (P = O dioxaphosphepine); (LC-MS *m/z*: 491 [M + H_2O (15%) 440(15), 398 (20), 352(45), 311 (65), 266 (80), 257 (30), 245 (55),196 (100),144 (48),130 (30). Anal. Calcd for $C_{23}H_{25}NO_6P_2$: C, 58.36; H, 5.32; N, 2.96. Found C, 58.28; H, 5.28; N, 2.91%

Dimethyl [(2-methoxyphenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonate (**5g**): Yield 72%, m.p. 152–154 °C. IR (KBr) cm^{-1} 1265 (P = O, phosphonate); 1215 (P = O, dioxaphosphepine), 756 (P–C) ^{1}H NMR (DMSO-d_6): δ 6.76–7.56 (12H, m, ArH), 5.89–5.93 (1H, dd, $^2J_{P\text{-}H}$ = 17.2 Hz, $^3J_{P\text{-}H}$ = 11.4 Hz, P–CH), 3.73 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz, P–OCH_3), 3.35 (3H, d, $^3J_{P\text{-}H}$ = 9.7 Hz, P–OCH_3), 3.95 (3H, s, OCH_3); ^{31}P NMR data: δ 26.10 (P = O, phosphonate), 4.26 (P = O, dioxaphosphepine); Anal. Calcd for $C_{22}H_{22}O_7P_2$: C, 57.40; H, 4.82. Found C, 57.32; H, 4.76%

Dimethyl [(4-methoxyphenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonate (**5h**): Yield 65%, m.p. 141–143 °C. IR (KBr) cm^{-1} 1285 (P = O, phosphonate), 1210 (P = O, dioxaphosphepin), 771 (P–C); ^{1}H- NMR (DMSO-d_6): δ 6.76–7.49 (12H, m, ArH), 5.73–5.93 (1H, dd, $^2J_{P\text{-}H}$ = 16.9 Hz, $^3J_{P\text{-}H}$ = 10.9 Hz, P–CH), 3.65 (3H, d, $^3J_{P\text{-}H}$ = 9.7 Hz, P–OCH_3), 3.22 (1H, d, $^3J_{P\text{-}H}$ = 9.2 Hz, P–OCH_3), 3.89 (3H, s, OCH_3); ^{31}P NMR data: δ 23.10 (P = O, phosphonate), 5.25 (P = O, dioxaphosphepine); Anal. Calcd for $C_{22}H_{22}O_7P_2$: C, 57.40; H, 4.82. Found: C, 57.33; H, 4.76%

Dimethyl [(2-nitrophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonate (**5i**): Yield 67%, m.p. 146–148 °C. IR (KBr) cm^{-1} 1257 (P = O, phosphonate), 1213 (P = O dioxaphosphepine), 771 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.81–7.73 (12H, m, ArH), 5.81-5.93 (1H, dd, $^2J_{P\text{-}H}$ = 17.3 Hz, $^3J_{P\text{-}H}$ = 11.6 Hz, P–CH), 3.63 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz), 3.20 (3H, d, $^3J_{P\text{-}H}$ = 9.7 Hz, P–OCH_3); ^{31}P NMR data: δ 20.15 (P = O, phosphonate), 3.90 (P = O, dioxaphosphepine); Anald. Calcd for $C_{21}H_{19}NO_8P_2$: C, 53.06; H, 4.03; N, 2.94. Found C, 52.98; H, 3.97; N, 2.89%

Table 1 Antibacterial activity of compounds **5a–j** (μg mL^{-1})

Compound	Zone of inhibition (%)					
	Escherichia coli			*Staphylococcus aureus*		
	100	50	25	100	50	25
5a	10	7	6	9	6	4
5b	14	10	8	11	8	6
5c	15	9	7	12	7	7
5d	8	6	3	7	6	5
5e	9	7	6	8	4	6
5f	12	7	6	9	7	6
5g	9	7	5	8	7	5
5h	9	8	6	2	4	–
5i	10	7	6	8	4	6
5j	12	8	7	9	8	5
Penicillin	12	8	–	10	7	–

Table 2 Antifungal activity of compounds **5a–j** (μg mL^{-1})

Compound	Zone of inhibition (%)					
	Aspergillus niger			*Helminthosporium oryzae*		
	100	50	25	100	50	25
5a	10	7	6	11	7	4
5b	15	8	7	15	8	5
5c	9	8	8	13	9	6
5d	11	9	6	12	8	5
5e	10	5	4	12	9	6
5f	14	9	8	11	9	7
5g	12	5	3	9	12	8
5h	10	8	9	10	9	7
5i	9	8	6	11	9	5
5j	9	7	7	10	7	8
Griseofulvin	12	7	–	12	9	–

Dimethyl [(4-nitrophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonate (**5j**): Yield 73%, m.p. 155–157 °C. IR (KBr) cm^{-1} 1268 (P = O, phosphonate), 1219 (P = O, dioxaphosphepine), 770 (P–C); ^{1}H NMR (DMSO-d_6): δ 6.81–8.10 (12H, m, ArH), 5.91–6.12 (1H, dd, $^2J_{P\text{-}H}$ = 16.9 Hz, $^3J_{P\text{-}H}$ = 10.9 Hz, P–CH), 3.71 (3H, d, $^3J_{P\text{-}H}$ = 9.2 Hz, P–OCH$_3$), 3.51 (3H, d, $^3J_{P\text{-}H}$ = 9.8 Hz, P–OCH$_3$). ^{13}C NMR data: 128.9 (C-1, C-11), 122.2 (C-2, C-10), 131.2 (C-3, C-9), 118.2 (C-4, C-8), 131.4 (C-12, C-13), 148.1 (C-14, C-15), 112.0 (C-1'), 110.6 (C-2',C-6'), 111.0 (C-3', C-5'), 149.9 (C-4'), 53.20(d, $^2J_{P\text{-}C}$ = 6.7 Hz, P–OCH$_3$), 51.5 (d, $^1J_{P\text{-}C}$ = 164.0P–C–P); ^{31}P NMR data: δ 29.01 (P = O, phosphonate), 9.10 (P = O, dioxaphosphepine); LCMS-*m/z*: 473 [M$^+$] (15), 474.8 [M + 1] (55%) 462.8 (25), 364.8 (50), 349.9 (45), 355.8 (20), 245.0 (45),237.9 (100), 266 (60), 142.9 (25). Anal. Calcd for $C_{21}H_{19}NO_8P_2$: C, 53.06; H, 4.03; N, 2.95. Found C, 53.01; H, 3.98; N, 2.92%

Antimicrobial activity

Antimicrobial activity of (**5a–j**) was tested against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve) by disc diffusion method at various concentrations (250, 500 ppm)[18] Table 1. All the compounds showed moderate activity against both the bacteria. The highlight is that the two compounds, dimethyl [(4-bromophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl) methyl]phosphonate (**5b**) and dimethyl [(4-chlorophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)(methyl]phosphonate (**5c**) were more effective than even the standard penicillin.

They were also screened for antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* species along with the standard fungicide Griseofulvin Table 2 by the disc diffusion method[17] at three different concentrations (100, 50, 25 ppm). It is gratifying to observe that most of the compounds (**5a–j**) exhibited higher antifungal activity when compared with that of Griseofulvin. Significant result is that dimethyl [(4-bromophenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2] dioxaphosphepin-6-yl)methyl]phosphonate **(5b),** and dimethyl [(4-dimethyl amino) phenyl)(6-oxo-6λ^5-dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)methyl]phosphonate (**5f**) exhibited higher activity than the standard Griseofulvin against both the fungi. Thus new group of compounds with very high antimicrobial/fungicidal activity than the presently used commercial bactericides/fungicides have been discovered.

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