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Synthesis, spectral characterization and anti-microbial activity of 6- Substituted [(2-aminoethyl)amino]-6λ^5-dibenzo [d, h] [1, 3,6,2]oxathiaza- phosphonin-6-ones

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Abstract: Synthesis of a series of a new class of phosphorus macrocycles was accomplished in two steps by condensation of (Z)-2-((2-mercaptophenylimino) methyl) phenol (**1**) with phosphorus oxychloride (**2**) in dry THF in the presence of triethylamine at 0-5 °C. In the second step ethylene diols/ amino alcohols/ diamine/ aminothiols/ phenols were reacted at room temperature in THF to afford the title compounds (**5a-l**). The chemical structures of the title products were characterized by IR, ^{1}H, ^{13}C, ^{31}P-NMR, mass spectral studies and elemental analysis. All the title compounds were evaluated for antimicrobial activity to determine their efficacy and they were found role effective in suppressing the growth of bacteria and fungi.

Keywords: Phosphorus macrocycles; antimicrobial activity; anti-bacterial activity; anti-fungal activity.

1. Introduction

Study of organophosphorus macrocyclic compounds can be regarded, by full right, as a priority line of development of synthetic and structural organic chemistry in the past decades. By varying the components of macrocyclic systems, by introducing functional groups and heteroatoms

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into their ensemblies, one can prepare cavity structures with different levels of preorganization and different lability, size and properties.

Phosphorus, nitrogen, oxygen and sulfur mixed donors containing macrocyclic systems have attracted increasing attention in recent years because of their interesting complexing abilities to form stable complexes with alkali and transition metal ions. Recent reports illustrated characterization of palladium and silver complexes from the thiophosphonate moiety of these macrocyclic ligands.[1] Some of them are able to transport metals, Fe^{3+}, Cu^{2+}, Co^{2+} or Ni^{2+}, through liquid membrane.[2,3] They find potential application in homogenous and phase-transfer catalysis,[4,5] and as drug-carriers to the designated site in the human body.

As phosphorus analogues of crown ethers, they have important potential catalytic activity and ion-carrier properties in supra molecular and synthetic organic chemistry.[6] Therefore, mixed donor macrocycles have received much attention as receptors for a range of metal ions and other cations.[7] Phosphorus containing macrocyclic compounds are expected to function as good 'hosts' in the 'host-guest' chemistry. This particular property enables them to carry the drug molecules to the required site in the living system, thus foreseeing great future for them in pharmaceutical industry.

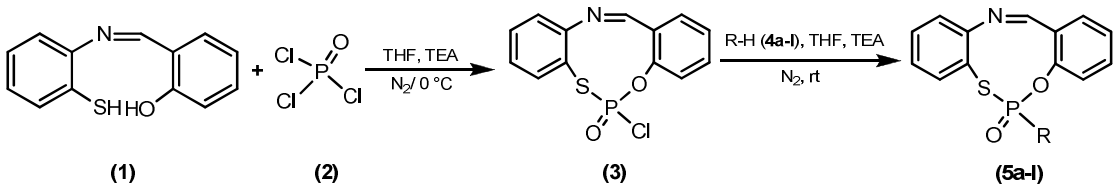
Phosphorus containing nine-membered heterocycle was reported recently.[8] Some of our past and present research work has led to the construction of large preorganised macrocyclic cavities (**3**, **4**) bearing concave functionalities.[9-11] They also constitute a family of promising flame retardants due to their unique combustion inhibition properties.[11]

Keeping in mind these numerous applications of the phosphorus containing macrocycles with nitrogen and oxygen as donor atoms and novelty in 'host-guest chemistry', we have successfully synthesized a series of new macrocyclic phosphorus compounds, characterized their structures and evaluated their antimicrobial activity.

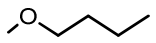
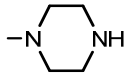
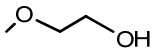
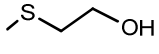
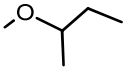
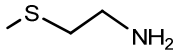
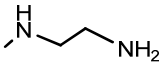
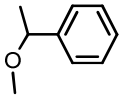
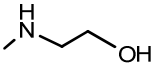
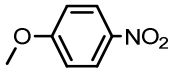
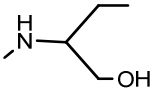
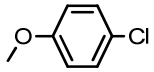
2. Results and discussion

Phosphorus, nitrogen, sulfur and oxygen containing 9-membered heterocyclic title compounds (**5a-l**) were synthesized (**Scheme-1**) by reaction of oxathiazaphosphonine-2-oxide monochloridate (**3**) with various alcohols, amines and thiols (**4a-l**) in THF in the presence of triethylamine (TEA) at rt. The monochloride (**3**) was previously prepared from (Z)-2-((2-mercaptophenylimino) methyl) phenol (**1**) by reacting with phosphorus oxychloride (**2**).

The title compounds **5a-l**, exhibited characteristic bands in their IR spectra, in the regions 3525-3450, 3484-3070, 1564, 1671-1656, 1245-1231 and 658-635 $cm^{-1}$for O-H, N-H, N=O, C=N, P=O, and (P-S) respectively. In proton NMR spectral data of the title compounds **5a-l**, proton of imine gave singlet at δ 8.90-8.78. The entire aromatic protons resonated as multiplet at δ 7.53-7.10 and the remaining all alkyl protons resonated at the expected regions. The ^{13}C-NMR spectral data of **5a**, **5b**, **5c**, **5i**, **5k**, **5g** and **5l** showed characteristic chemical shifts for aromatic carbons. The carbon chemical shift of imine carbon observed at 166.3-164.2 ppm. ^{31}P-NMR resonance signals appeared within the region 6.87-6.35 ppm for the title compounds. The compounds **5a**, **5b**, **5e**, **5g** and **5j** gave $M^{+\bullet}$ ion peaks in their LC-MS at m/z 347, 335, 334, 359 and 395 respectively.



(1) (2) (3) (5a-l)

Comp.	R	Comp.	R
5a		**5g**	
5b		**5h**	
5c		**5i**	
5d		**5j**	
5e		**5k**	
5f		**5l**	

Scheme 1. Synthesis of macrocyclic organophosphorus compounds (**5a-l**)

3. Conclusion

In conclusion, we reported an efficient and easy protocol for the synthesis of biologically active organophosphorus macrocyclic compounds. All the titled compounds exhibited significant antimicrobial activity.

4. Experimental

Chemicals were obtained from Sigma-Aldrich and used as such without further purification. All solvents (AR or extra pure grade) were used for spectroscopic and other physical studies were further purified by literature methods. All operations were performed under nitrogen atmosphere using standard glasswares. Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. Elemental analyses were performed at University of Hyderabad, Hyderabad, India. IR Spectra were recorded in Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati as KBr discs on a Nicolet 380 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. The ^{1}H and ^{13}C chemical shifts were

referenced to tetramethylsilane (TMS) and ^{31}P chemical shifts to 85% H_3PO_4. LC-MS spectra were recorded on a Jeol SX 102 DA/ 600 Mass Spectrometer.

Synthesis of (Z)-2-((2-mercaptophenylimino) methyl) phenol (1)

To a stirred solution of 2-amino thiophenol (6.25 g, 0.05 mol) in absolute ethanol (20 mL) was added dropwise ethanolic (20 mL) solution of salicylaldehyde (6.1 g, 0.05 mol). The resulting mixture was then refluxed for 1 h. After cooling to rt, water (5 mL) was added and the mixture stirred for 30 min. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 2:8) analysis. The yellow precipitate formed was filtered, washed with water and dried. It was recrystallized from chloroform to afford yellow needles of **1,** yield 9.07 g (79.2 %), m.p 137-139 ºC.[13]

Synthesis of 6- substituted [(2-aminoethyl)amino]-6λ^5-dibenzo [*d*, *h*][1, 3,6,2]oxathiaza-phosphonin-6-one (5a)

To a cooled (0-5 ºC) and stirred solution of 2-[(2-[(*Z*)-1-(2-hydroxyphenyl) methylidene] aminophenyl) imino] methylphenol (**1**, 0.687 g, 0.003 mol) and triethyl amine (1.01 g, 0.006 mol) in 10 mL of dry THF, phosphorus oxychloride (**2**, 1.11 g, 0.003 mol) in 10 mL of dry THF was added over a period of 20 min. After completion of the addition, the temperature of the reaction mixture was raised to rt and stirred for one hour to form the intermediate monocholoride (**3**). The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 2:6) analysis. After completion of the reaction, it was filtered under nitrogen atmosphere to remove triethylamine hydrochloride.
To the intermediate monochloride (**3**) in dry THF (20 mL), *n*-butanol (**4a**, 0.222 g, 0.003 mol) was added at 10 °C in the presence of TEA (0.003 mol). After completion of the addition, the temperature of the reaction mixture was raised to rt and stirred for one hour. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 2:8) analysis. After completion of the reaction, it was filtered to remove triethylamine hydrochloride. The solvent was removed in a rota-evaporator to obtain crude product (**5a**). It was recrystallized from 2-propanol to get pure product **5a** (0.78 g, 75 %).
The same experimental procedure was adopted for the preparation of the remaining title compounds **5b-l**.

(12*Z*)-6-butoxydibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonine-6-oxide (5a). M.p. 165 - 167 °C; IR (KBr) υ_{max} (cm^{-1}): 1656 (C=N), 1242 (P=O), 1195 (C-O), 1027 (P-O), 690 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.83 (1H, *s*, C-H$_{olefin}$), 7.43-7.14 (8H, *m*, Ar-H), 3.76 (2H, *m*, OCH_2), 1.93 (2H, *m*, CH_2), 1.38 (2H, *m*, CH_2), 0.91 (3H, *t*, $^3J_{HH}$ = 6.5 Hz, CH_3); ^{13}C-NMR (DMSO-d_6) δ: 129.8 (C-2′), 131.7 (C-3), 130.3 (C-4), 139.2 (C-5), 120.3 (C-6), 160.3 (C-6′), 165.8 (C-8), 120.7 (C-8′), 133.4 (C-9), 124.7 (C-10), 135.4 (C-11), 119.7 (C-12), 160.4 (C-12′), 63.8 (C-15), 33.4 (C-16), 20.3 (C-17), 15.2 (C-18); ^{31}P-NMR δ: 6.35; LC-MS (*m/e*, %): 347 ($M^{+\bullet}$, 23), 318 (20), 304 (100), 291 (85), 274 (80), 258 (48), 211 (37), 195 (66), 182 (56), 102 (45). *Anal*. Calcd. for $C_{17}H_{18}NO_3PS$: C, 58.78; H, 5.22; N, 4.03. Found: C, 58.64; H, 5.13; N, 3.98.

2-{[(12*Z*)-6-oxidodibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonin-6-yl]oxy}ethanol (5b).Yield 70 %; m.p. 181 - 183 °C; IR (KBr) υ_{max} (cm^{-1}): 3525 (O-H), 1658 (C=N), 1237 (P=O), 1210 (C-O), 1010 (P-O), 645 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.85 (1H, *s*, C-H$_{olefin}$), 7.45 -7.18 (8H, *m*, Ar-H), 3.96 (2H, *m*, -O$\underline{CH_2}CH_2OH$), 3.23 (2H, *m*, -$OCH_2\underline{CH_2}OH$); ^{13}C-NMR (DMSO-d_6) δ: 130.1 (C-2′), 131.8 (C-3), 130.1 (C-4), 139.6 (C-5), 120.7 (C-6), 160.8 (C-6′), 166.3 (C-8), 120.5 (C-8′), 133.1 (C-9), 125.3 (C-10), 135.7 (C-11), 120.1 (C-12), 160.8 (C-12′), 68.8 (C-15), 63.4 C-16); ^{31}P-NMR δ: 6.42; LC-MS *m/e*: 335 ($M^{+\bullet}$,15), 318 (20), 308 (45), 291 (30), 274 (100), 264 (35), 226 (50), 211 (32), 182 (28), 171 (30), 102 (20). *Anal*. Calcd. for $C_{15}H_{14}NO_4PS$: C, 53.73; H, 4.21; N, 4.18. Found: C, 53.61; H, 4.13; N, 4.11.

(12*Z*)-6-(butan-2-yloxy)dibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonine-6-oxide (5c). Yield 71 %; m.p. 196 - 198 °C; IR (KBr) υ_{max} (cm^{-1}): 1657 (C=N), 1235 (P=O), 1211 (C-O), 1014 (P-O), 638 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.81 (1H, *s*, C-H$_{olefin}$), 7.40-7.12 (8H, *m*, Ar-H), 3.82 (1H, *m*, OCH), 1.82 (2H, *m*,

CH_2), 1.23 (6H, *m*, CH_3); ^{31}P-NMR δ: 6.49. *Anal*. Calcd. for $C_{17}H_{18}NO_3PS$: C, 58.78; H, 5.22; N, 4.03; Found: C, 58.66; H, 5.14; N, 3.97.

***N*-[(12*Z*)-6-oxidodibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonin-6-yl]ethane-1,2-diamine (5d).**Yield 69 %; m.p. 201 - 203 °C; IR (KBr) υ_{max} (cm^{-1}): 3486 (N-H), 3070 (N-H), 1664 (C=N), 1238 (P=O), 1209 (C-O), 1021 (P-O), 644 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.78 (1H, *s*, C-H_{olefin}), 7.45-7.18 (8H, *m*, Ar-H), 3.32 (2H, *m*, $NHCH_2$), 3.13 (2H, *m*, CH_2NH_2); ^{31}P-NMR δ: 6.41. *Anal*. Calcd. for $C_{15}H_{16}N_3O_2PS$: C, 54.05; H, 4.84; N, 12.61. Found: C, 53.95; H, 4.75; N, 12.53.

2-{[(12*Z*)-6-oxidodibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonin-6-yl]amino}ethanol (5e).Yield 68 %; m.p. 157 - 159 °C; IR (KBr) υ_{max} (cm^{-1}): 3510 (O-H), 3055 (N-H), 1670 (C=N), 1241 (P=O), 1216 (C-O), 1020 (P-O), 646 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.88 (1H, *s*, C-H_{olefin}), 7.41-7.10 (8H, *m*, Ar-H), 3.38 (2H, *m*, $NHCH_2$), 3.94 (2H, *m*, CH_2OH); ^{13}C-NMR (DMSO-d_6) δ: 129.4 (C-2′), 131.2 (C-3), 130.1 (C-4), 138.7 (C-5), 120.1 (C-6), 160.4 (C-6′), 165.4 (C-8), 120.2 (C-8′), 133.1 (C-9), 124.2 (C-10), 135.1 (C-11), 118.5 (C-12), 160.1 (C-12′), 56.2 (C-15), 64.7 (C-16); ^{31}P-NMR δ: 6.78; LC-MS (*m/e*, %): 334 ($M^{+\bullet}$, 12), 317 (20), 303 (82), 290 (35), 274 (100), 241 (25), 225 (67), 212 (48), 195 (38), 135 (20), 102 (71). *Anal*. Calcd. for $C_{15}H_{15}N_2O_3PS$: C, 53.89; H, 4.52; N, 8.38; N, 4.03. Found: C, 53.78; H, 4.41; N, 8.31

2-{[(12*Z*)-6-oxidodibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonin-6-yl]amino}butan-1-ol (5f).Yield 73 %; m.p. 186 - 188 °C; IR (KBr) υ_{max} (cm^{-1}): 3450 (O-H), 3080 (N-H), 1659 (C=N), 1231 (P=O), 1212 (C-O), 1015 (P-O), 647 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.85 (1H, *s*, C-H_{olefin}), 7.42-7.17 (8H, *m*, Ar-H), 5.12 (1H, *brs*, OH), 3.41 (1H, *m*, NHCH), 3.78 (2H, *m*, CH_2OH), 1.98 (2H, *m*, CH_2), 1.12 (3H, *m*, CH_3); ^{31}P-NMR δ: 6.58. *Anal*. Calcd. for $C_{17}H_{19}N_2O_3PS$: C, 56.34; H, 5.28; N, 7.73. Found: C, 56.21; H, 5.19; N, 7.63.

(12*Z*)-6-(piperazin-1-yl)dibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonine 6-oxide (5g).Yield 65 %; m.p. 142 - 144 °C; IR (KBr) υ_{max} (cm^{-1}): 3100 (N-H), 1661 (C=N), 1237 (P=O), 1218 (C-O), 1019 (P-O), 651 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.90 (1H, *s*, C-H_{olefin}), 7.40-7.12 (8H, *m*, Ar-H), 3.12 (4H, *m*, $N(CH_2)_2$), 3.15 (4H, *m*, $(CH_2)_2N$); ^{13}C-NMR (DMSO-d_6) δ: 128.9 (C-2′), 131.1 (C-3), 129.7 (C-4), 139.5 (C-5), 119.8 (C-6), 160.1 (C-6′), 165.2 (C-8), 120.1(C-8′), 133.6 (C-9), 124.2 (C-10), 134.8 (C-11), 118.9 (C-12), 159.7 (C-12′), 51.3 (C-15 & 19), 48.6 (C-16 & 18),; ^{31}P-NMR δ: 6.87; LC-MS (*m/e*, %): 359 ($M^{+\bullet}$, 20), 316 (35), 302 (65), 274 (100), 250 (41), 211 (25), 195 (35), 179 (43), 132 (68), 102 (52). *Anal*. Calcd. for $C_{17}H_{18}N_3O_2PS$: C, 56.81; H, 5.05; N, 11.69. Found: C, 56.69; H, 4.93; N, 11.61.

2-{[(12*Z*)-6-oxidodibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonin-6-yl]sulfanyl}ethanol (5h).Yield 65 %; m.p. 148 - 150 °C; IR (KBr) υ_{max} (cm^{-1}): 3471 (O-H), 1668 (C=N), 1235 (P=O), 1215 (C-O), 1019 (P-O), 643 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.78 (1H, *s*, C-H_{olefin}), 7.40-7.11 (8H, *m*, Ar-H), 5.26 (1H, *m*, OH), 2.69 (2H, *m*, SCH_2), 3.23 (2H, *m*, CH_2OH); ^{31}P-NMR δ: 6.75. *Anal*. Calcd. for $C_{15}H_{14}NO_3PS_2$: C, 51.27; H, 4.02; N, 3.99. Found: C, 51.15; H, 3.95; N, 3.91.

2-{[(12*Z*)-6-oxidodibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonin-6-yl]sulfanyl} ethanamine (5i).Yield 62 %; m.p. 132 - 134 °C; IR (KBr) υ_{max} (cm^{-1}): 3482 (N-H), 1671 (C=N), 1237 (P=O), 1218 (C-O), 1021 (P-O), 644 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.79 (1H, *s*, C-H_{olefin}), 7.37-7.10 (8H, *m*, Ar-H), 2.69 (2H, *m*, SCH_2), 3.21 (1H, *m*, NH_2), 3.01 (2H, *m*, CH_2NH); ^{31}P-NMR δ: 6.65. *Anal*. Calcd. for $C_{15}H_{15}N_2O_2PS_2$: C, 51.42; H, 4.31; N, 7.99. Found: C, 51.30; H, 4.22; N, 7.91.

(12*Z*)-6-(1-phenylethoxy)dibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonine 6-oxide (5j).Yield 78 %; m.p. 182 - 184 °C; IR (KBr) υ_{max} (cm^{-1}): 1670 (C=N), 1235 (P=O), 1214 (C-O), 1017 (P-O), 654 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.88 (1H, *s*, C-H_{olefin}), 7.50-7.19 (13H, *m*, Ar-H), 4.87 (1H, *m*, OCH), 1.98 (3H, *m*, CH_3); ^{13}C-NMR (DMSO-d_6) δ: 129.7 (C-2′), 131.4 (C-3), 129.2 (C-4), 139.1 (C-5), 120.1 (C-6), 159.7 (C-6′), 165.3 (C-8), 120.9 (C-8′), 132.8 (C-9), 124.4 (C-10), 134.6 (C-11), 119.2 (C-12), 160.1 (C-12′),

82.4 (C-15), 142.5 (C-16), 128.8 (C-17 & 21), 131.5 (C-18 & 20), 129.3 (C-19); ^{31}P-NMR δ: 6.42; LC-MS (*m/e*, %): 395 ($M^{+\bullet}$, 24), 380 (40), 368 (20), 318 (250, 292 (37), 286 962), 274 (100), 264 (32), 211 (31), 195 (38), 102 (65). *Anal*. Calcd. for $C_{21}H_{18}NO_3PS$: C, 63.79; H, 4.59; N, 3.54. Found: C, 63.68; H, 4.50; N, 3.45.

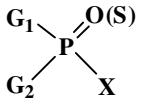
(12*Z*)-6-(4-nitrophenoxy)dibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonine 6-oxide (5k).Yield 67 %; m.p. 168 - 170 °C; IR (KBr) υ_{max} (cm^{-1}): 1662 (C=N), 1564 (N=O), 1245 (P=O), 1218 (C-O), 1021 (P-O), 652 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.83 (1H, *s*, C-H_{olefin}), 7.53-7.18 (12H, *m*, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 127.9 (C-2′), 131.7 (C-3), 129.4 (C-4), 139.2 (C-5), 120.5 (C-6), 159.4 (C-6′), 164.8 (C-8), 120.7 (C-8′), 133.2 (C-9), 124.5 (C-10), 134.8 (C-11), 119.5 (C-12), 160.3 (C-12′), 160.2 (C-15), 122.3 (C-16 & 20), 132.5 (C-17 & 19), 172.6 (C-18); ^{31}P-NMR δ: 6.48. *Anal*. Calcd. for $C_{19}H_{13}N_2O_5PS$: C, 55.34; H, 3.18; N, 6.79. Found: C, 55.21; H, 3.07; N, 6.71.

(12*Z*)-6-(4-chlorophenoxy)dibenzo[*d*,*h*][1,3,6,2]oxathiazaphosphonine 6-oxide (5l).Yield 73 %; m.p. 165 - 167 °C; IR (KBr) υ_{max} (cm^{-1}): 1669 (C=N), 1232 (P=O), 1215 (C-O), 1015 (P-O), 654 (P-S); ^{1}H-NMR (DMSO-d_6) δ: 8.84 (1H, *s*, C-H_{olefin}), 7.52 -7.20 (12H, *m*, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 127.7 (C-2′), 131.5 (C-3), 129.6 (C-4), 139.7 (C-5), 120.9 (C-6), 159.8 (C-6′), 164.2 (C-8), 120.1 (C-8′), 133.5 (C-9), 124.7 (C-10), 134.3 (C-11), 119.5 (C-12), 160.6 (C-12′), 155.3 (C-15), 123.1 (C-16 & 20), 134.8 (C-17 & 19), 134.8 (C-18); ^{31}P-NMR δ: 6.40. *Anal*. Calcd. for $C_{19}H_{13}ClNO_3PS$: C, 56.79; H, 3.26; N, 3.49. Found: C, 56.65; H, 3.15; N, 3.42.

4.1.Biological Activity

4.1.1. Structure–activity relationships of organophosphorus compounds (OPCs)

Schrader[14] proposed that OPCs containing the main pharmacophoric structural unit (I) may posses significant biological activity.



G_1 and G_2 = Groups which are difficult to displace from phosphorus

X = Fairly good leaving group

(I)

Slight variation in structure **I** can have very drastic effects on the bioactive efficacy of OPCs due to the fact that the interaction of an enzyme/ virus/ bacteria/ fungi is very sensitive to the size, shape and polarity of the organophosphorus substrate molecules.

4.1.2. Anti-bacterial Activity

All the title compounds (**5a-l**) were tested for their anti-bacterial activity[15,16] (**Table 1**) against *Staphylococcus aureus,* ATCC-25923, (Gram positive) and *Escherichia coli,* ATCC-25922, (Gram negative) by the Kirby-Bauer's disc diffusion method in Mueller-Hinton agar medium, which are spread by bacteria of 0.1 mL (10^5 CFU/mL) at two different concentrations (250 and 500 µg/disc) in dimethyl formamide (DMF). These solutions were added to each filter disc and DMF was used as control. Solvent control was included although no antibacterial activity has been noted in the solvent employed. The plates of 8 mm were punched into the agar medium and filled with the title compound solutions to each filter paper disc and DMF was used as control. The plates were incubated at 35 °C and examined for zone of inhibition around each disc after 24 h. The results were compared with the activity of the standard antibiotic *Penicillin-G* (250 µg/disc). All samples were tested in triplicate and average results were recorded for each observation. Majority of the compounds exhibited high activity.

4.1.3. Anti-fungal Activity

The compounds **5a-l** were screened for their anti-fungal activity[16,17] (**Table 2**) against *Aspergillus niger* and *Helminthosporium oryzae* species along with standard fungicide Griseofulvin at three different concentrations (100 and 250 ppm) in DMF. Fungal cultures were grown on potato dextrose plates for 72 h at 25 °C and finally spore suspension was adjusted to 105 spores/ mL. Each test was done in triplicate and the mean of the diameter of the inhibition zones was calculated. All the compounds **5a-l** exhibited moderate to high antifungal activity when compared to that of the reference compound.

Table 1. Anti-bacterial activity of title compounds (5a-l)

Compd.	Zone of Inhibition (mm)			
	Staphylococcus aureus		*Escherichia coli*	
	250 (µg/disc)	**500 (µg/disc)**	**250 (µg/disc)**	**500 (µg/disc)**
5a	17.2	20.1	16.5	20.0
5b	16.8	19.8	17.2	20.1
5c	18.1	22.0	18.4	21.5
5d	17.1	19.4	17.6	20.0
5e	16.4	18.5	15.7	18.6
5f	18.0	19.2	18.2	20.4
5g	15.4	18.6	16.1	18.7
5h	17.9	20.1	18.1	21.2
5i	18.6	22.3	18.4	21.5
5j	17.4	18.8	17.2	18.5
5k	18.0	19.2	18.4	19.3
5l	17.6	18.5	17.8	18.6
Penicillin-G[a]	24.0	-	20.0	-

[a]Reference Compound.

Table 2. Anti-fungal activity[a] of title compounds (**5a-l**)

Compd.	Zone of inhibition (mm)			
	Aspergillus niger		*Helminthosporium oryzae*	
	100 ppm	**250 ppm**	**100 ppm**	**250 ppm**
5a	6	9	5	9
5b	5	7	5	8
5c	7	10	6	11
5d	7	9	7	10
5e	5	6	5	5
5f	7	10	6	11
5g	4	7	5	7
5h	7	9	8	9
5i	7	10	5	10
5j	5	8	6	9
5k	6	10	8	11
5l	5	7	6	8
[b]*Griseofulvin*	8	16	8	16

[a]Concentration in ppm, [b]Reference Compound

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