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Synthesis and antimicrobial activity of 2-(substituted)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxaza-phosphinin-2-ones, thiones and selones

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ABSTRACT

2-(substituted)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxaza-phosphinin-2-ones **(5a-d)** were synthesized by reaction of 2-{[(6-methyl-2-pyridyl) amino]methyl} phenol **(1)** with various aryl phosphorodichloridates **(4)** in the presence of triethylamine at 45-50°C. The title compounds **(5e-h)** were synthesized *via* an intermediate monochloride route. The compounds **(8a-f)** have been synthesized in two steps by the condensation of **(1)** with dichlorophenyl phosphine/ethyldichlro phosphite followed by reaction with hydrogen peroxide, sulfur and selenium respectively.

KEYWORDS

1,3,2-benzoxazaphosphinin-2-ones;
Thiones;
Selones;
Phosphorodichloridates.

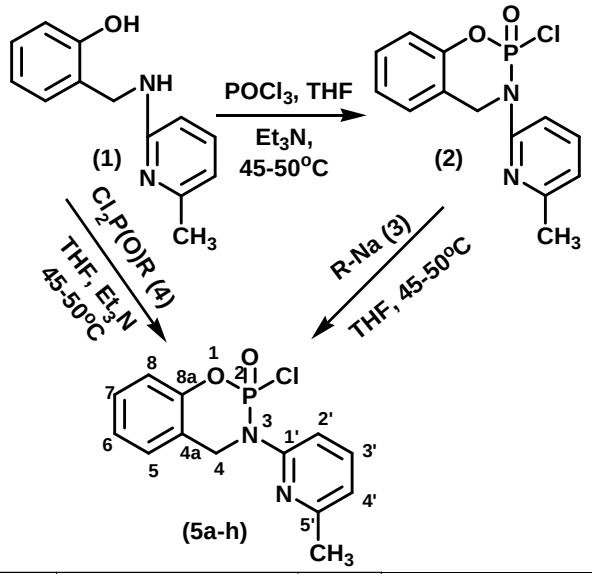
INTRODUCTION

Organophosphorus compounds[1] have been drawing widespread attention due to their ubiquity in biological systems[2], particularly their use as potential pharmaceuticals[3], agrochemicals[4] and chemical synthetic agents[5]. 1,3,2-O,N,P heterocycles are of great interest in their respect[6]. The 1,3,2-oxazaphosphinane ring system is found in alkylating anticancer agents such as cyclophosphamide ifosfamide and in numerous other derivatives. They have been prepared to determine structure-activity relationships[7]. Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory[8], pesticidal[9] and antimicrobial[10] activities. Simple phenolic compounds are well-known bactericides and fungicides, but their use is restricted only to soil due to phytotoxicity[11]. Phosphorylation of phenols and amines with appropriate phosphorus reagent has reduced their toxicity and enhanced their bio-activity.

In view of the importance and various applications of phosphorus heterocycles, a new class of benzoxazaphosphinins has been successfully synthesized and their biological activity was evaluated.

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on AMX 400 MHz NMR spectrometers operating at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR. NMR data recorded in $CDCl_3$



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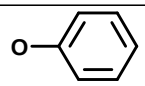
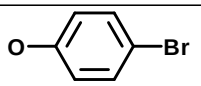
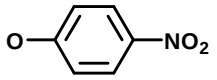
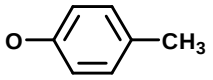
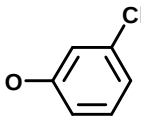
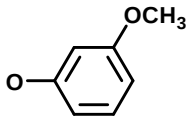
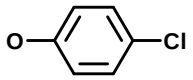
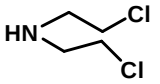
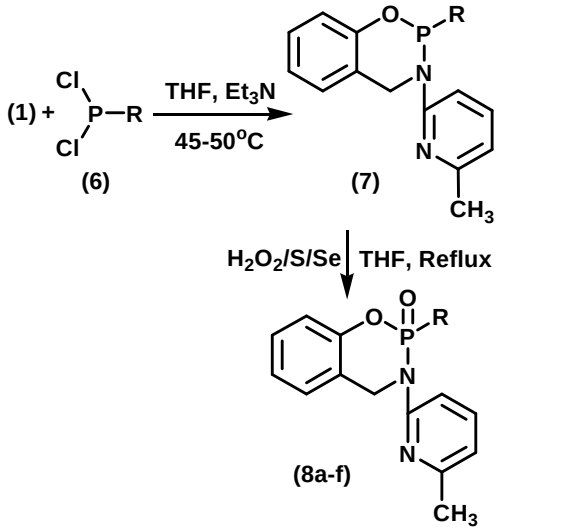
5a		5e	
5b		5f	
5c		5g	
5d		5h	

Scheme 1

and were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectra were recorded on a Micro-Mass Q-Tof micro AMPS MAX 10/6A, Hz 60/50 system fitted with a built-in inlet system. Dichlorophenyl phosphine, Ethyldichloro phosphite, Phosphorus oxychloride, phenols, salicylaldehyde, 6-methyl 2-amino pyridine were procured from Sigma-Aldrich chemicals company Inc, USA.

Synthesis of title compounds (5a-d)

A solution of phosphorodichloridate **(4)** (0.002 mole) in 25 mL of dry THF was added dropwise over a period of twenty minutes to a stirred solution of 2-{[(6-methyl-2-pyridyl)amino]methyl}phenol (1, 0.002 mole) and triethylamine (0.004 mole) in 30 mL of dry tetrahydrofuran at 0°C. After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 30 min. Later the reaction mixture was heated to 45-50°C and maintained at that temperature for three hours with stirring. Completion of the reaction was monitored by TLC analysis. Triethylamine hydrochloride was separated from the reaction mixture by filtration and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (100-200 mesh) as adsorbent and ethyl acetate:hexane as eluent to afford pure product.



Comp.	R	X	Comp.	R	X
8a	C_6H_5	O	8d	C_2H_5O	O
8b	C_6H_5	S	8e	C_2H_5O	S
8c	C_6H_5	Se	8f	C_2H_5O	Se

Scheme 2

Synthesis of the compounds (5e-h) through an intermediate (2)

A solution of phosphorus oxychloride (0.002 mole) in 10 mL of dry THF was added dropwise to a stirred solution of 1 (0.002 mole) and triethylamine (0.004 mole) in 20 mL of dry THF at 0°C over a period of 30 min. After stirring for 3 h at 45-50°C, formation of the intermediate **(2)** was ascertained by TLC analysis. The reaction mixture was filtered to remove triethylamine hydrochloride. The intermediate monochloride taken in a dropping funnel was added to a strried solution of sodium phenoxides **(3)** (0.002 mole) in 20 mL of dry THF at 0-5°C. The reaction mixture was stirred for 30 min at room temperature and then for 4 h at 45-50 °C. Progress of the reaction was monitored by TLC. The reaction mixture was filtered and the solvent was removed from the filtrate in a rota-evaporator. The crude product was purified by column chromatography on

silica gel (100-200 mesh, ethyl acetate:hexane) to afford pure product.

Synthesis of (8a-f)

The compounds **(8a-f)** were prepared through two-step synthetic route. Dichlorophenyl phosphine/ dichloroethyl phosphite (0.002 mole) in dry THF (10 mL) was added dropwise to a stirred solution of **(1)** (0.002 mole) and triethylamine (0.004 mole) in 20 mL of dry THF at 0°C during 20 min under N_2 atmosphere. After completion of the addition, the reaction temperature was slowly raised to 45-50°C and was maintained at this temperature for 4 h with stirring. The completion of the reaction was monitored by TLC. After completion of the reaction, the solid triethylamine hydrochloride was removed by filtration. The filtrate containing trivalent phosphorus intermediate **(7)** was further converted to the corresponding oxide, sulfide and selenide without isolation by adding hydrogen peroxide, sulfur and selenium respectively at 0-5°C. After completion of the addition, the temperature was raised to 45-50°C and maintained for 3 h with stirring. After completion of the reaction, it was filtered and solvent was removed under reduced pressure to obtain crude product. It was purified by column chromatography as described above.

SPECTRAL DATA

3-(6-methyl-2-pyridyl)-2-phenoxy-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphosphinin-2-one (5a)

Yield: 83 %; m.p: 65-67°C; IR (KBr): 1228 (P=O), 945, 1183 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.50-7.09 (m, 11H, Ar-H), 6.82 (d, J=7.6 Hz, 1H, Ar-H), 5.40 (t, J=15.2 Hz, 1H, -CH_2-), 4.93 (dd, J=8.0, 15.6 Hz, 1H, -CH_2-), 2.47 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$): δ 156.8 (C-5′), 152.6 (d, ^{2}Jp-c=10 Hz, C-1′), 150.5 (d, ^{2}Jp-c=7 Hz, C-1″), 150.2 (d, ^{2}Jp-c=9 Hz, C-8a), 138.1 (C-3′), 129.7 (C-3″& C-5″), 129.0 (C-5), 127.3 (C-7), 125.3 (C-4″), 124.7 (C-6), 124.1 (d, ^{3}Jp-c=7 Hz, C-4a), 120.4 (d, ^{2}Jp-c=4 Hz, C-2″&6″), 118.5 (d, ^{3}Jp-c=8 Hz, C-8), 117.9 (C-4′), 111.2 (C- 2′), 46.8 (-CH_2-), 24.3 (Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ -7.94; HRMS Calcd. for $C_{19}H_{18}N_2O_3P$: 353.1055; Found: 353.1052 (M+H).

3-(6-methyl-2-pyridyl)-2-(4-nitrophenoxy)-3,4-dihydro-2H-1,3,2λ^5-benzoxaza- phosphinin-2-one (5b)

Yield: 68 %; m.p: 131-135°C; IR (KBr): 1270 (P=O), 966, 1169 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.65-6.56 (m, 11H, Ar-H), 5.40 (t, J=15.1 Hz, 1H, -CH_2-), 4.99 (dd, J=8.3, 15.8 Hz, 1H, -CH_2-), 2.48 (s, 3H, Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ-4.05; Anal. Calcd. for $C_{19}H_{16}N_3O_5P$: C, 57.44; H, 4.06; N, 10.58; Found : C, 57.49; H, 4.09; N, 10.62.

2-(2-chlorophenoxy)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxaza- phosphinin-2-one (5c)

Yield: 82 %; m.p: 145-147°C; IR (KBr): 1259 (P=O), 963, 1168 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.47-6.83 (m, 11H, Ar-H), 5.45 (t, J=15.2 Hz, 1H, -CH_2-), 5.03 (dd, J=8.0, 15.6 Hz, 1H, -CH_2-), 2.46 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$): δ 156.4 (C-5′), 152.4 (d, ^{2}Jp-c=10 Hz, C-1′), 150.1 (d, ^{2}Jp-c=8 Hz, C-8a), 146.7 (d, ^{2}Jp-c=7 Hz, C-1″), 138.1 (C-3′), 130.5 (C-3″), 129.0 (C-5), 127.9 (C-5″), 127.6 (C-7), 126.0 (C-6″), 125.6 (d, ^{2}Jp-c=8 Hz, C-2″), 124.7 (C-6), 123.8 (d, ^{3}Jp-c=7Hz, C-4a), 122.1 (C-4″), 118.5 (d, ^{3}Jp-c=8 Hz, C-8), 118.1 (C-4′), 111.4 (C-2′), 47.0 (-CH_2-), 24.2 (Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ -8.03; Anal. Calcd. for $C_{19}H_{16}ClN_2O_3P$: C, 59.00; H, 4.17; N, 7.24; Found : C, 59.08; H, 4.14; N, 7.20.

2-(4-chlorophenoxy)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxaza- phosphinin-2-one (5d)

Yield: 81 %; m.p: 124-126°C; IR (KBr): 1265 (P=O), 980, 1159 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.65-6.56 (m, 11H, Ar-H), 5.40 (t, J=15.0 Hz, 1H, -CH_2-), 4.95 (dd, J=8.0, 15.2 Hz, 1H, -CH_2-), 2.43 (s, 3H, Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ -7.03; Anal. Calcd. for $C_{19}H_{16}ClN_2O_3P$: C, 59.00; H, 4.17; N, 7.24; Found: C, 59.06; H, 4.19; N, 7.23.

2-(4-bromophenoxy)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxaza- phosphinin-2-one (5e)

Yield: 80 %; m.p: 83-85°C; IR (KBr): 1266 (P=O), 979, 1173 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR

($CDCl_3$): δ 7.31-6.67 (m, 11H, Ar-H), 5.36 (t, J=14.8 Hz, 1H, -CH_2-), 4.92 (dd, J=8.8, 15.2 Hz, 1H, -CH_2-), 2.46 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$): δ 157.0 (C-5′), 152.4 (d, ^{2}Jp-c=10 Hz, C-1′), 150.0 (d, ^{2}Jp-c=8 Hz, C-1′′), 149.6 (d, ^{2}Jp-c=8 Hz, C-8a), 138.3 (C-3′), 132.9 (C-3′′ & C-5′′), 129.2 (C-5), 127.3 (C-7), 124.9 (C-6), 123.9 (d, ^{2}Jp-c=8 Hz, C-4a), 122.2 (d, J=5 Hz, C-2′′&6′), 118.4 (d, J=9 Hz, C-8), 117.3 (C-4′), 111.9 (C-4′′), 111.0 (C-2′), 47.1 (-CH_2-), 24.2 (Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ -10.21; HRMS Calcd for $C_{19}H_{17}BrN_2O_3P$: 431.0160; Found: 431.0166 (M+H) and 433.0114 (M+H+2).

2-(4-methylphenoxy)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxaza- phosphinin-2-one (5f)

Yield: 79 %; m.p: 70-73°C; IR (KBr): 1275 (P=O), 975, 1161 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.65-6.56 (m, 11H, Ar-H), 5.32 (t, J=14.6 Hz, 1H, -CH_2-), 4.98 (dd, J=8.2, 14.8 Hz, 1H, -CH_2-), 2.45 (s, 3H, CH_3), 2.20 (s, 3H, OArCH_3); ^{31}P NMR ($CDCl_3$): δ -9.05; Anal. Calcd. for $C_{20}H_{19}N_2O_3P$: C, 65.57; H, 5.23; N, 7.65; Found : C, 65.51; H, 5.21; N, 7.69.

2-(3-methoxyphenoxy)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxaza- phosphinin-2-one (5g)

Yield: 80 %; m.p: 92-94°C; IR (KBr): 1273(P=O), 980, 1168 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.61-6.53 (m, 11H, Ar-H), 5.45 (t, J=15.1 Hz, 1H, -CH_2-), 4.91 (dd, J=6.7, 15.8 Hz, 1H, -CH_2-), 3.72 (s, 3H, OCH_3), 2.48 (s, 3H, Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ -8.31; Anal. Calcd. for $C_{20}H_{19}N_2O_4P$: C, 62.83; H, 5.01; N, 7.33; Found : C, 62.86; H, 5.03; N, 7.38.

2-[di(2-chloroethyl)amino]-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-one (5h)

Yield: 78 %; m.p: 78-81°C; IR (KBr): 1259(P=O), 965, 1175 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.25-6.63 (m, 7H, Ar-H), 5.36 (t, J=14.8 Hz, 1H, -CH_2-), 4.82 (dd, J=8.2, 15.2 Hz, 1H, -CH_2-), 2.45 (s, 3H, Ar-CH_3), 4.04-3.92 (m, 4H, $N(CH_2)_2$), 3.14-3.02 (m, 4H, $(CH_2Cl)_2$); ^{31}P NMR ($CDCl_3$): δ -7.12; Anal. Calcd. for $C_{17}H_{20}Cl_2N_3O_2P$: C, 51.01; H, 5.04; N, 10.50; Found : C, 51.09; H, 5.07; N, 10.55.

3-(6-methyl-2-pyridyl)-2-phenyl-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-one (8a)

Yield: 84 %; m.p: 150-152°C; IR (KBr): 1230 (P=O), 915, 1125 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): δ 7.78-7.08 (m, 11H, Ar-H), 6.69 (d, J=7.6 Hz, 1H, Ar-H), 5.20 (dd, J=11.6, 15.2 Hz, 1H, -CH_2-), 5.07 (dd, J=10.0, 15.2 Hz, 1H, -CH_2-), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$): δ 156.8 (C-5′), 153.3 (d, ^{2}Jp-c=10 Hz, C-1′), 150.0 (d, ^{2}Jp-c=9 Hz, C-8a), 137.9 (C-3′), 132.5 (d, ^{2}Jp-c=3 Hz, C-2′′& C-6′′), 131.7 (C-4′′), 129.3 (C-3′′& C-5′′), 129.7 (d, ^{1}Jp-c=177 Hz, C-1′′), 128.6 (C-5), 127.3 (C-7), 125.8 (d, ^{3}Jp-c=7 Hz, C-4a), 124.5 (C-6), 118.8 (d, ^{3}Jp-c=5 Hz, C-8), 117.1 (C-4′), 109.7 (C-2′), 45.9 (-CH_2-), 24.2 (Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ 14.2 ppm; HRMS Calcd for $C_{19}H_{17}N_2O_2PNa$: 359.0925; Found: 359.0929 (M+Na).

3-(6-methyl-2-pyridyl)-2-phenyl-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-thione (8b)

Yield: 80 %; m.p: 115-117°C; IR (KBr): 775(P=S), 913, 1179 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): 7.90-6.66 (m, 12H, Ar-H), 5.28 (t, J=14.4 Hz, 1H, -CH_2-), 5.05 (dd, J=9.6, 14.8 Hz, 1H, -CH_2-), 2.37 (s, 3H, Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ 75.67; HRMS Calcd for $C_{19}H_{18}N_2OPS$: 353.0877; Found: 353.0875 (M+H).

3-(6-methyl-2-pyridyl)-2-phenyl-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-selone (8c)

Yield: 78 %; m.p: 110-113°C; IR(KBr): 630 (P=Se), 950, 1180cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): 7.54-6.73 (m, 12H, Ar-H), 5.23 (t, J=15.2 Hz, 1H, -CH_2-), 4.94 (dd, J=8.4, 14.8 Hz, 1H, -CH_2-), 2.51(s, 3H, Ar-CH_3); ^{31}P NMR ($CDCl_3$): δ 79.79; HRMS Calcd for $C_{19}H_{18}N_2OPSe$: 401.0322; Found: 401.0322 (M+H).

2-ethoxy-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-one (8d)

Yield: 78 %; Viscous liquid; IR (KBr): 1259(P=O), 968, 1164 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): 7.42-6.75 (m, 7H, Ar-H), 5.27 (t, J=15.2 Hz, 1H, -CH_2-), 4.97 (dd, J=8.4, 14.8 Hz, 1H, -CH_2-), 4.56-4.49 (m, 2H, -OCH_2), 2.39 (s, 3H, Ar-CH_3), 1.39 (t,

J=6.2 Hz, 3H, -CH_3); ^{31}P NMR ($CDCl_3$): δ 10.12; Anal. Calcd. for $C_{15}H_{17}N_2O_3P$: C, 59.21; H, 5.63; N, 9.21; Found : C, 59.29; H, 5.67; N, 9.25.

2-ethoxy-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-thione (8e)

Yield: 76 %; Viscous liquid; IR (KBr): 793 (P=S), 946, 1172 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): 7.49-6.74 (m, 7H, Ar-H), 5.22 (t, J=15.2 Hz, 1H, -CH_2), 4.87 (dd, J=8.4, 14.8 Hz, 1H, -CH_2-), 4.46-4.37 (m, 2H, -OCH_2), 2.43 (s, 3H, Ar-CH_3), 1.37 (t, J=6.4 Hz, 3H, -CH_3); ^{31}P NMR ($CDCl_3$): δ 56.29; HRMS Calcd for $C_{15}H_{18}N_2O_2PS$: 321.0826; Found: 321.0825 (M+H).

2-ethoxy-3-(6-methyl-2-pyridyl)-3,4-dihydro-2H-1,3,2λ^5-benzoxazaphosphinin-2-selone (8f)

Yield: 73 %; Viscous liquid; IR (KBr): 647 (P=Se), 958, 1182 cm^{-1} (P-O-$C_{aromatic}$); ^{1}H NMR ($CDCl_3$): 7.52-6.83 (m, 7H, Ar-H), 5.17 (t, J=15.2 Hz, 1H, -CH_2-), 4.90 (dd, J=8.4, 14.8 Hz, 1H, -CH_2-), 4.36-4.29 (m, 2H, -OCH_2), 2.49 (s, 3H, Ar-CH_3), 1.34 (t, J=6.0 Hz, 3H, -CH_3); ^{31}P NMR ($CDCl_3$): δ 63.51; HRMS Calcd for $C_{15}H_{17}N_2O_2PSeNa$: 391.0091; Found: 391.0091(M+Na).

RESULTS AND DISCUSSION

2-(substituted)-3-(6-methyl-2-pyridyl)-3,4-dihydro-2*H*-1,3,2λ^5-benzoxazaphos phinin-2-ones **(5a-d)** were synthesized by reaction of equimolar quantities of 2-{[(6-methyl-2-pyridyl)amino]methyl}phenol **(1)** with various aryl phosphorodichloridates **(4)** in dry tetrahydrofuran in the presence of dry triethylamine at 45-50°C (Scheme 1).

Cyclisation of amino phenol **(1)** with various aryl phosphorodichloridates **(4)** takes place smoothly in dry tetrahydrofuran (THF) in the presence of triethylamine in 4-5 hours. Reaction of **(1)** with phosphorodichloridates is a nucleophilic substitution reaction where the nitrogen/oxygen atom of the amino/hydroxyl group of the phenolic moiety of the **(1)** attacks the electrophilic phosphorus atom of the phosphorodichloridates **(4)**.

Alternatively, some of the title compounds **(5e-h)** were synthesized through the intermediate monochloride **(2)** which is prepared by condensation of **(1)** with phosphorus oxychloride in the presence of dry triethylamine in dry THF at 45-50°C. On subsequent reaction of the intermediate monochloride with sodium phenoxides **(3)** under similar conditions gave **(5e-h)** (Scheme 1). For these condensations dry THF was found to be an ideal solvent since the reactants readily dissolved in it and reacted without thermal decomposition.

TABLE 1 : Antifungal activity of compounds (5a-h) and (8a-f)

Compd.	Zone of inhibition (mm)			
	Colletotrichum gloeosporioides		Sclerotium rolfsii	
	250 ppm	500 ppm	250 ppm	500 ppm
5a	0.0	2.5	0.0	8.8
5b	2.0	0.8	1.5	0.0
5c	0.0	2.5	7.0	0.0
5d	0.5	1.0	0.0	1.0
5e	2.3	0.0	4.5	7.0
5f	0.5	1.0	0.0	0.5
5g	0.0	0.5	0.0	0.8
5h	4.3	5.3	3.3	8.8
8a	7.5	10.5	1.3	0.0
8b	0.0	0.3	7.0	8.0
8c	12.0	13.8	5.0	3.3
8d	0.5	1.5	0.0	1.0
8e	1.0	1.8	0.0	0.0
8f	2.5	3.0	2.0	3.3
Carbendazim	19.0	19.5	19.0	19.3

A few of the title compounds such as oxide, sulfide, selenides **(8a-f)** were prepared through a two step synthetic route involving condensation of **(1)** with dichlorophenyl phosphine/ethyldichlro phosphite in the presence of triethylamine in dry THF to form the corresponding trivalent phosphorus intermediate **(7)**, it was further converted to the corresponding oxide, sulfide, and selenide by reaction with hydrogen peroxide, sulfur and selenium respectively, under reflux conditions in THF. (Scheme 2).

The crude products were purified by column chromatography on silica gel. The synthetic and analytical data of **(5a-h)** and **(8a-f)** are given in the experimental part.

The IR spectra showed characteristic bands[12,13] for P=O, P=S, P=Se and P-O-C_{arom} at 1275-1228, 775-793, 630-647 and 1183-1125 cm^{-1} respectively. The C-4 methylene protons of **(5a-h)**, **(8a-f)** resonated as triplet and doublet of doublet in the region

TABLE 2 : Antibacterial activity of compounds (5a-h) and (8a-f)

Compd.	Staphylococcus aureus			Bacillus subtilis			Escherichia coli			Klebsiella pneumoniae		
	100 ppm	200 ppm	300 ppm	100 ppm	200 ppm	300 ppm	100 ppm	200 ppm	300 ppm	100 ppm	200 ppm	300 ppm
5a	3.0	4.1	6.0	-	2.1	4.0	-	-	2.0	2.2	3.1	5.0
5b	10.0	11.2	13.1	8.0	10.2	11.1	3.0	5.2	6.0	10.1	11.2	13.0
5c	8.0	9.2	11.0	10.1	12.4	15.0	6.1	8.2	9.0	11.0	13.2	18.1
5d	7.0	8.3	10.0	8.2	10.0	13.0	4.8	6.0	8.0	10.0	12.2	15.0
5e	9.0	10.1	12.2	8.2	12.3	16.2	3.2	4.4	6.0	13.1	16.0	19.2
5f	-	3.2	5.2	-	-	-	-	2.0	3.1	-	2.8	4.1
5g	2.2	4.1	5.1	-	-	1.2	-	3.0	5.2	-	-	1.5
5h	10.0	11.1	13.2	8.2	10.2	11.2	5.0	6.2	8.1	7.4	8.2	10.0
8a	4.0	5.1	7.0	10.1	12.0	13.2	2.1	4.2	7.0	2.0	2.5	5.3
8b	12.1	15.2	19.0	9.3	13.0	15.8	8.2	12.3	14.0	5.2	6.0	7.2
8c	13.2	14.2	16.0	9.0	12.1	14.0	7.0	12.0	15.1	6.1	9.0	10.0
8d	-	2.0	3.0	-	-	-	-	-	-	-	-	2.2
8e	-	3.2	5.1	8.0	11.2	13.0	5.2	6	7.8	12.2	15.1	18.0
8f	7.0	8.1	10.2	8.2	12.1	14.1	6.2	8.0	9.2	13.2	14.0	14.0
Gentamycin	19.0			19.0			20.0			18.0		

'-' indicates no activity

5.47-4.87 ppm indicating their non-equivalence and coupling with phosphorus in the six membered chair conformation of benzoxazaphosphinine ring system[14]. The ^{13}C NMR chemical shifts of the compounds **(5a)**, **(5c)**, **(5e)** and **(8a)** were observed in the expected range[15]. The ^{31}P NMR chemical shifts of compounds **(5a-h)**, **(8a)** and **(8d)** appeared in the region -10.21 to 14.2 ppm. Other compounds **(8b)**, **(8c)**, **(8e)** and **(8f)**, gave signals at δ 75.67, 79.79, 56.29 and 63.51 respectively depending on the nature of atoms present at phosphorus[16].

Bioactivity

Susceptibility of test organisms to the title compounds was determined by employing the standard disc diffusion technique[17]. All the compounds **(5a-h)** and **(8a-f)** were tested for their antifungal activity against the growth of *Colletotrichum gloeosporioides* and *Sclerotium rolfsii* at concentrations 250 and 500 ppm. Carbendazim is used as reference (TABLE 1). All the compounds **(5a-h)** and **(8a-f)** were screened for their antibacterial activity against the growth of *Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Klebsiella pneumoniae* at concentrations 100, 200 and 300 ppm. Gentamycin is used as reference (TABLE 2).

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