Synthesis and Bioactivity of 6-Bromo-2-(Substituted)-3-(1-Phenyl-ethyl)- 3,4-Dihydro-1*H*- Isophosphinoline 2-Chalcogenides

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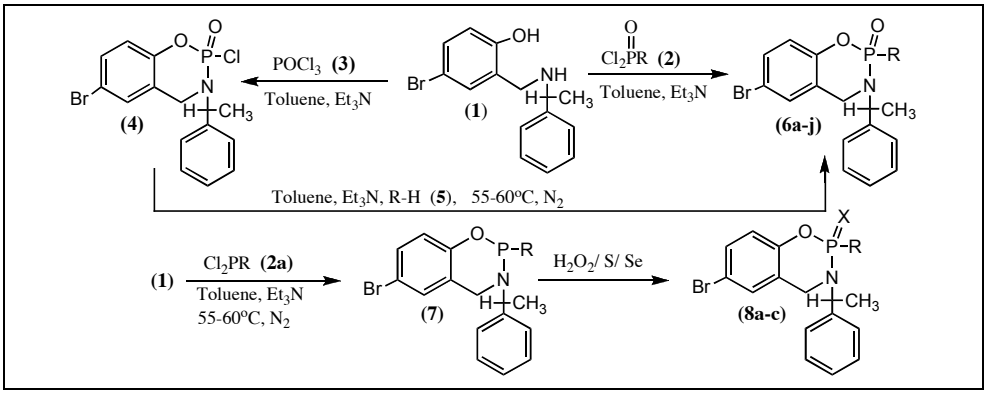

Synthesis of 6-bromo-2-(substituted)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-chalcogenides derivatives **(6)** were synthesized from 2-[(1-phenylethylamino)methyl]-4-bromophenol (**1**) by reaction with aryl/alkyl phosphoro dichloridates (**2**) in the presence of triethylamine at 55°C to 60°C to obtained the title compounds (**6a-g**). The title compounds (**6h-j**), were prepared *via* intermediate route. Few other title compounds (**8a-c**) were accomplished through a two step synthetic route involving **1** with dichlorophenyl phosphine (**2a**) and dichloroethyl phosphine (**2a,b**) in the presence of triethylamine in dry toluene under N_2 atmosphere to form the corresponding trivalent phosphorus intermediate **(7)**. In the second step they were further converted to the corresponding chalcogenides **8a-c** by reaction with hydrogen peroxide, sulfur and selenium respectively. They exhibited significant antibacterial, fungal and insecticidal activity.

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INTRODUCTION

Discovery of an effective, target specific and eco-friendly pesticides is an ever-persuing endeavor since quality pesticides are required for crop protection, food production and preservation. Pesticides currently in use not only strike the targeted pest species but also affect the non-target species and the environment. Polyhalogenated hydrocarbon pesticides are banned due to their non-biodegradability and toxic residues [1]. The phenolic compounds are well-known bactericides and fungicides, their use is restricted only to soil due to phytotoxicity [2]. Phosphorylation of phenols and amines with appropriate phosphorus reagent has reduced their toxicity and enhanced their bio-activity. Scientists were successful in developing some organophosphorus systemic [3] insecticides (*e.g.* Schradan), antibiotics [4] (*e.g.* Phosfomycin, Phosfadecin), antiviral (Foscarnet) and anticancer agents (Cyclophosphamide).

RESULTS AND DISCUSSION

Condensation of 2-[(1-phenylethylamino)methyl]-4-bromophenol (**1**) with phenylphosphorodichloridates [5] (**2**) in equimolar quantities in the presence of triethylamine in dry toluene at 55-60°C produced the title compounds (**6a-g**) (Scheme 1). The title compounds **6h-j** were prepared through intermediate (**4**). The reaction of (**1**) with phosphorus oxychloride (**3**) in the presence of triethylamine which was further treated with 4-bromophenol, 1-phenylethylamine and indole to get **6h-j**. A few of the title compounds such as oxide, sulfide, selenide (**8a-c**) were prepared through a two step synthetic route involving (**1**) with dichlorophenyl phosphine in the presence of triethylamine in dry toluene to form the corresponding trivalent phosphorus intermediate (**7**), it was further converted to the corresponding chalcogenides by reaction with hydrogen peroxide, sulfur and selenium respectively, under reflux conditions in the same vessel (Scheme 2). In all the reactions, the title compounds separated by removing the solvent from the filtrate. The crude products were purified by recrystallization from methanol, and characterized by elemental analysis, IR, ^{1}H, ^{13}C and ^{31}P NMR and mass spectral data. [5-6] Reaction yields, melting points, IR, ^{31}P NMR data of (**6a-j**), (**8a-c**), elemental analysis for (**6a-j**), (**8a-c**), ^{1}H NMR data for

(**6a-j**), (**8a-c**) and ^{13}C NMR for (**6a-h**), (**8a-c**) and MS data for (**6a**), (**6b**), (**6g**), (**6i**), (**6j**), (**8b**) and (**8c**) are recorded.

The compounds (**6a-j**), (**8a-c**) showed absorption bands in the region 3251, 1297-1202, 994-937, 1186-1167, 776, 632 cm^{-1} for P-NH, P=O, P-O and O-C of P-O-C_{arom} and P=S, P=Se respectively. [6]

The aromatic protons of (**6a-j**), (**8a-c**) resonated as multiplets in the region δ 8.26-6.51. The proton attached to the exocyclic chiral methine carbon exhibited a quartet at δ 5.41-5.01 due to its coupling with the methyl group attached to the same carbon. The C-4 methylene protons resonated as multiplet at δ 4.37-4.04 indicating their non-equivalence and coupling with phosphorus in the six membered chair conformation of the isophosphinoline 2-oxide system.

The ^{13}C NMR spectra were recorded for **6a-h,** and **8a-c**. ^{13}C NMR chemical shifts were interpreted based on the additivity rules, coupling with phosphorus and intensity of signals [7,9]. The endocyclic oxygen bonded to C-9, gave signals as a doublet at δc 153.01-151.14 (J = 8-9 Hz). The chiral carbon resonated as a doublet due to coupling with phosphorus in the region δc 41.6-45.9 (d, J= 7.0-7.7 Hz). The methylene carbon (C-4) gave signal in the region δc 48.5-54.4. The methyl carbon which is linked to the chiral carbon resonated in the region δc 16.5-18.2.

The ^{13}C NMR chemical shifts for C-5 to C-10, C-1' to C6' and C-1" to C-6" were observed in the expected range [7]. The ^{31}P NMR chemical shifts of compounds **6a-j** were observed in the region δp -3.65 to -4.63 other compounds **8a-c**, gave signals at 12.08, 78.04 and 89.19 respectively depending on the atoms present near phosphorus. The observed chemical shifts are in agreement with the literature values. [8]

The compound **6** exhibited $M^{+\bullet}$ ion at m/z 489 with 71 per cent intensity. Appearance of isotopic peak as $M^{+\bullet}$ +2 ion in the expected ratio agreed well with the presence of one bromine atom in the compound. [9]

Expulsion of $C_{15}H_{13}BrNO_3$ radical from $M^{+\bullet}$ formed the ion at m/z 154 (100) as a base peak. The ions at m/z 383 (13), 289 (28), 105 (20) and 91 (11) were also observed in the mass spectrum of **6a**. The mass spectral data of the representative compounds exhibited $[M+2]^+$, $M^{+\cdot}$ and ions with substituted isophosphinoline moieties at appropriate m/z values. Their mass spectral behavior is well in agreement with that of similar organophosphorus (OP) compounds [10-11].

Thus, the combined analytical, IR, NMR and mass spectral data conclusively agreed with the proposed structures for the title compounds (**6a-j**), (**8a-c**)

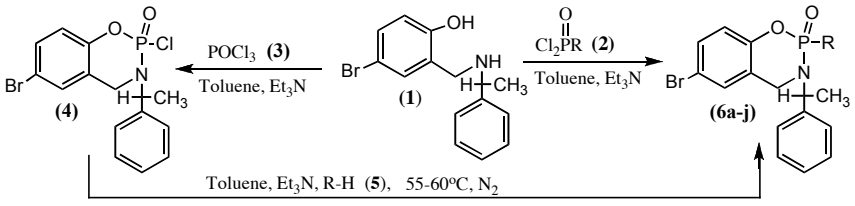
CONCLUSION

In conclusion, we have evolved an effective and simple route for the synthesis of novel Phenyl phos–phoro–dichloridates linked Isophosphinoline 2-chalcogenides, whose structures were supported by elemental and spectral analyses. The reaction can be performed smoothly in dry toluene in the presence of a base and the products are relatively easy to isolate and purify. The possible advantages of these new phosphorus heterocycles are that they may be used as potential antibacterial fungal and insecticides.

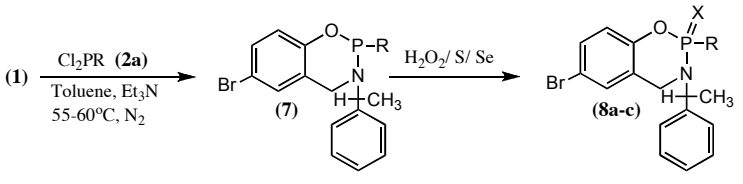
EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-temp apparatus and are uncorrected. Microanalysis was performed at Central Drug Research Institute, Lucknow, India and Environmental Engineering Lab, S. V. University, Tirupati. IR spectra were recorded as KBr pellets on a Perkin - Elmer 283 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX- 400 MHz spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P using

Scheme 1



Scheme 2



Compd.	R	Compd.	R	Compd.	R	Compd.	X
6a	4"-$NO_2C_6H_4O$	**6d**	4"-ClC_6H_4O	**6g**	4"-CH_3CH_2O	**8a**	O
6b	C_6H_5O	**6e**	2"-ClC_6H_4O	**6h**	4"-BrC_6H_4O	**8b**	S
6c	$(ClCH_2CH_2)_2N$	**6f**	4"-$CH_3C_6H_4O$	**6i**	$C_6H_5(CH)CH_3NH$	**8c**	Se
				6j	C_8H_8N		

deuterochloroform. The ^{1}H and ^{13}C chemical shifts were referenced to TMS and ^{31}P chemical shifts to 85% H_3PO_4 (*ortho*-phosphoric acid). FAB-Mass spectra were recorded on a Jeol SX 102 DA / 600 Mass spectrometer using Argon / Xenon (6 kV, 10 mA) as the FAB gas.

Synthesis of 6-bromo-2-(Nitrophenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6a). 4-Nitrophenyl phosphorodichloridate (**2**) 0.51 g (2.0 mmole) in dry toluene (10 mL) was added dropwise to a stirred solution of (**1**) 0.61 g (2.0 mmole) and triethylamine 0.40 g (4.0 mmole) in 20 mL of dry toluene at 0°C during 20 min. After the completion of the addition, the reaction temperature was slowly raised to 55-60°C and was maintained at this temperature for 5 h. Progress of the reaction was monitored by TLC using hexne-ethyl acetate (3:1) as mobile phase on silica gel (adsorbent). On separation of the triethylamine hydrochloride by filtration, and evaporation of the filtrate under reduced pressure, a solid residue was obtained. It was washed with water and recrystallised from methanol to obtain yield the compound **6a** yield 0.66g (67.4%). mp. 148-150 °C.

Compounds **6b-g** were prepared by adopting the above procedure.

Synthesis of the compounds 6h, through an intermediate (4), 6-bromo-2-(chloro)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide. A solution of phosphorus oxy-chloride (**3**) 0.30 g (2.0 mmole) in 10 mL of dry toluene was added drop wise to a stirred solution of (**1**) 0.61 g (2.0 mmole) and triethylamine 0.40 g (4.0 mmole) in 20 mL of dry toluene at 0°C over a period of 30 min. After stirring for 4 h at 50-55°C, formation of the intermediate 6-bromo-2-(chloro)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (**4**) was ascertained by TLC analysis. To the cooled (0-5°C) solution of (**4**) in the same vessel additional quantity of triethylamine (2.0 mmole) in 20 mL of dry toluene followed by 4-bromophenol/1-phenyl-ethylamine/ indole (**5**) (2.0 mmole) in 20 mL of dry toluene were added. The reaction mixture was stirred for 1 h at room temperature and then for 4 h at 50-60°C. Progress of the reaction was monitored by TLC. Triethylamine hydrochloride was separated by filtration and the solvent was removed from the filtrate in a rota-evaporator. The residue after washing with water and recrystallisation from methanol afforded the compounds, **6h** respectively.

Compounds **6i-j** were prepared by adopting the above procedure.

Synthesis of compound 8a. The compounds **8a** were prepared through a two step synthetic route. dichlorophenyl phosphine (**2a**) 0.35 g (2.0 mmole) in dry toluene (10 mL) was added drop wise to a stirred solution of (**1**) 0.61 g (2.0 mmole) and triethylamine 0.40 g (4.0 mmole) in 20 mL of dry toluene at 0°C during 20 min under N_2 atmosphere. After completion of the addition, the reaction temperature was slowly raised to 55-60°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 contains trivalent phosphorus intermediate (**7**), it was further converted to the corresponding chalcogenides without isolation by reacting it with hydrogen peroxide at 5 °C. After completion of the addition, the temperature was raised to 50-60 °C and maintained for 3 h with stirring. After completion of the reaction and on evaporation of the filtrate using a rota-evaporator, a solid residue was obtained. It was washed with water and recrystallised from methanol to yield the title compounds **8a.**

Compounds **8b-c** were prepared by adopting the above procedure.

Physical, Analytical and Spectral Data for the test Compounds (6a-j), (8a-c).

Characterization of 6-bromo-2-(4-nitrophenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6a) yield 0.66g (66.8%). mp 148-150 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1277, P-O 941, O-C 1180. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.45. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.26-6.84 (m, 12H, Ar-H), 4.01-3.81 (m, 2H, -CH_2-), 5.32-5.15 (m, 1H, CH), 1.65 (d, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 53.8 (C-4), 132.2(C-5), 116.2 (C-6), 132.2 (C-7), 139.5 (C-8), 150.9 (d, $^{2}J_{(P\text{-}O\text{-}C\ endo)}$= 8.2 Hz, C-9), 124.0 (C-10), 121.3 (C-1'), 128.7 (C-2'& C-6'), 128.3 (C-3'&C-5'), 127.1 (C-4'), 156.1 (C-1''), 120.2 (C-2''), 124.1 (C-3''), 141.2 (C-4''), 124.1 (C-5''), 141.2 (C-6''), 42.9 ($^{2}J_{pc}$= 7.4 Hz, *C*-CH_3), 16.7 (C-*C*H_3). FAB-MS m/z (%) : 491 [(77), $M^{+\bullet}$ +2], 489 [(71), $M^{+\bullet}$], 383 (13), 307 (46), 289 (28), 204 (8), 154 (100), 136 (52), 105 (20), 91(11). *Anal.* Calcd for $C_{21}H_{18}BrN_2O_5P$: C 51.53, H 3.71, N 5.72; Found: C 51.61, H 3.65, N 5.70%.

Characterization of 6-bromo-2-(phenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6b) yield 0.69g (77.7%). mp 68-70 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1284, P-O 942 ,O-C 1183. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.18. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-6.83 (m, 13H, Ar-H), 4.31-4.14 (m, 2H, -CH_2-), 5.29-5.12 (m, 1H, CH), 1.61 (d, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 51.3 (C-4), 132.6 (C-5), 117.1 (C-6), 133.2 (C-7), 138.1 (C-8), 151.1 (d, $^{2}J_{(P\text{-}O\text{-}C\ endo)}$= 8.1 Hz, C-9), 124.2 (C-10), 120.2 (C-1'), 128.4 (C-2'& C-6'), 128.1 (C-3'&C-5'), 126.1 (C-4'), 148.1 (C-1''), 129.1 (C-2''&C-6''), 128.9 (C-3''&C-5''), 125.0 (C-4''), 43.2 ($^{2}J_{pc}$= 7.0 Hz, *C*-CH_3), 17.1 (C-*C*H_3). FAB-MS m/z(%): 446 [(80), $M^{+\bullet}$ +2], 444 [(88), $M^{+\bullet}$], 340 (91), 306 (22), 202 (5), 154 (13), 105 (100), 102 (83). *Anal.* Calcd for $C_{21}H_{19}BrNO_3P$: C 56.77, H 4.03, N 3.15; Found: C 56.83, H 4.09, N 3.21%.

Characterization of 6-bromo-2-(Bis-(2''-chloroethylam-ine)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6c) yield 0.68g (69.5%). mp 97-99 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1273, P-O 982, O-C 1179. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.88. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87-6.51 (m, 8H, Ar-H), 4.62-4.42 (m, 2H, -CH_2-), 5.32-5.10 (m, 1H, CH), 1.71 (d, J = *6.5,* 3H, CH_3), 4.37-4.11(m, 4H, NCH_2), 3.30-3.27 (m, 4H, CH_2 Cl). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 52.9 (C-4), 129.0 (C-5), 122.2 (C-6), 127.4 (C-7), 117.5 (C-8), 156.0 (d, $^{2}J_{(P\text{-}O\text{-}C\ endo)}$= 8.3 Hz, C-9), 122.6 (C-10), 123.2 (C-1'), 128.5 (C-2'& C-6'), 128.2 (C-3'&C-5'), 129.1 (C-4'), 65.2 (s, 2C, C-1''), 43.2 (s, 2C, C-2''), 44.3 ($^{2}J_{pc}$= 7.2 Hz, *C*-CH_3), 17.8 (C-*C*H_3). *Anal.* Calcd for $C_{19}H_{22}BrCl_2N_2O_2P$: C 46.36, H 4.50, N 5.69; Found: C 46.41, H 4.56, N 5.75%.

Characterization of 6-bromo-2-(4-chlorophenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6d) yield 0.75g (78.4%). mp 95-97 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1297, P-O 973, O-C 1186. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.19. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-6.84 (m, 12H, Ar-H), 4.29-4.16 (m, 2H, -CH_2-), 5.30-5.17 (m, 1H, CH), 1.64 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 53.1 (C-4), 128.1 (C-5), 123.2 (C-6), 127.0 (C-7), 116.1 (C-8), 152.9 (d, $^{2}J_{(P\text{-}O\text{-}C\ endo)}$= 8.7 Hz, C-9), 123.2 (C-10), 119.3 (C-1'), 128.1 (C-2'& C-6'), 128.1 (C-3'&C-5'), 126.0 (C-4'), 146.1 (C-1''), 118.3 (C-2''), 130.1 (C-3''), 120.0 (C-4''), 131.1 (C-5''), 116.1 (C-6''), 41.6 ($^{2}J_{pc}$= 7.7 Hz, *C*-CH_3), 16.9 (C-*C*H_3). *Anal.* Calcd for

$C_{21}H_{18}BrClNO_3P$: C 52.69, H 3.78, N 2.63; Found: C 52.75, H, 3.73, N 2.70%.

Characterization of 6-bromo-2-(2-chlorophenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6e) yield 0.73g (76.3%). mp 78-81 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1287, P-O 959, O-C 1185; ^{31}P NMR ($CDCL_3$, 161.9 MHz) δ: 1.82. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.41-6.74 (m, 12H, Ar-H), 4.20-4.04 (m, 2H, -CH_2-), 5.32-5.02 (m, 1H, -CH), 1.60 (d, *J* = 5.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCL_3$ 100 MHz) δ: 52.1 (C-4), 128.0 (C-5), 124.3 (C-6), 127.1 (C-7), 117.2 (C-8), 156.0 (d, $^2J_{(P\text{-}O\text{-}C\ endo)}$= *9* Hz, C-9), 125.0 (C-10), 121.2 (C-1'), 128.1 (C-2'& C-6'), 128.1 (C-3'&C-5'), 122.1 (C-4'), 153.0 (C-1''), 125.2 (C-2''), 132.0 (C-3''), 121.3 (C-4''), 135.2 (C-5''), 117.3 (C-6''), 45.9 ($^2J_{pc}$= 7.5 Hz, *C*-CH_3), 20.5 (C-*C*H_3). *Anal.* Calcd for $C_{21}H_{18}BrClNO_3P$: C 52.69, H 3.78, N 2.63; Found: C 52.76, H 3.74, N 2.69%.

Characterization of 6-bromo-2-(4-methylphenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6f) yield 0.65g (70.9%). mp 98-100 °C. $IR_{(KBr)}$: ν_{max} (Cm^{-1}), P=O 1293, P-O 956, O-C 1169. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.19. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.70-7.20 (m, 12H, Ar-H), 4.23-4.10 (m, 2H, -CH_2-), 5.25-5.12 (m, 1H, CH), 1.71 (d, *J* = 6.2 Hz, 3H, CH_3), 2.12-2.20 (s, 3H, 4''-CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 48.5 (C-4), 129.0 (C-5), 121.2 (C-6), 127.7 (C-7), 115.7 (C-8), 150.4 (d, $^2J_{(P\text{-}O\text{-}C\ endo)}$= 8.5 Hz, C-9), 125.0 (C-10), 121.3 (C-1'), 128.8 (C-2'& C-6'), 128.3 (C-3'&C-5'), 122.0 (C-4'), 153.2 (C-1''), 116.3 (C-2''), 130.2 (C-3''), 132.1 (C-4''), 132.1 (C-5''), 116.3 (C-6''), 22.9 (Ar-CH3), 41.6 (*C*-CH3), 20.0 (C-*C*H3). *Anal.* Calcd for $C_{22}H_{21}BrNO_3P$: C 57.66, H 4.61, N 3.06; Found: C 57.71, H 4.58, N 3.12%.

Characterization of 6-bromo-2-(ethoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6g) yield 0.54g (68.1%). mp 87-89 °C. $IR_{(KBr)}$: (cm^{-1}), P=O 1252, P-O 994, O-C 1167. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.63. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.84-6.79 (m, 8H, Ar-H), 4.37-4.24 (m, 2H, CH_2), 5.30-5.10 (m, 1H, CH), 1.48 (d, *J* = 6.6 Hz, 3H, CH_3), 3.57-3.40 (m, 2H, -CH_2-), 1.90-1.50 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 52.8 (C-4), 129.4 (C-5), 120.3 (C-6), 128.4 (C-7), 11.9 (C-8), 156.0 (d, $^2J_{(P\text{-}O\text{-}C\ endo)}$= 8.1 Hz, C-9), 124.7 C-10), 125.1 (C-1'), 128.6 (C-2'& C-6'), 128.3 (C-3'&C-5'), 127.0 (C-4'), 65.2 (d, $^1J_{pc}$= 8.6 Hz 1C, C-1''), 14.5 (d, $^2J_{pc}$= 6.3 Hz 1C, C-2''), 42.8 ($^2J_{pc}$= 7.6 Hz, *C*-CH3), 16.5 (C-*C*H3). FAB-MS m/z 398 [(8), $M^{+\bullet}$ +2], 396 [(11), $M^{+\bullet}$], 380 (2), 306 (100), 289 (13), 279 (2), 202 (11), 154 (91), 136 (58), 120 (11), 105 (77), 91 (13). *Anal.* Calcd for $C_{17}H_{19}BrNO_3P$: C 51.53, H 4.82, N 3.53; Found: C 51.60, H 4.86, N 3.60%.

Characterization of 6-bromo-2-(4-bromophenoxy)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6h) yield 0.67g (67%) mp 110-112 °C $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1262, P-O 982, O-C 1167. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -4.45. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.50-6.80 (m, 12H, Ar-H), 4.52-4.23 (m, 2H, -CH_2-), 5.42-5.25 (m, 1H, CH), 1.60 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 49.1 (C-4), 128.3 (C-5), 123.7 (C-6), 127.5 (C-7), 116.1 (C-8), 150.8 (C-9), 124.9 (C-10), 121.3 (C-1'), 128.4 (C-2'& C-6'), 128.1 (C-3'&C-5'), 128.6 (C-4'), 155.3 (C-1''), 118.2 (C-2''), 132.2 (C-3''), 116.1 (C-4''), 132.1 (C-5''), 118.2 (C-6''), 40.6 (*C*-CH_3), 16.1 (C-*C*H_3). *Anal.* Calcd for $C_{21}H_{18}Br_2NO_3P$: C 48.21, H 3.46, N 2.67; Found: C 48.15, H 3.40, N 2.72%.

Characterization of 6-bromo-2-(1-phenylethylamine)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6i) yield 0.66g (70%). mp 123-124 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1243, P-O 937, O-C 1181, P-NH 3251. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -3.65. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.60-6.72 (m,13H, Ar-H), 4.25-4.15 (m, 2H, -CH_2-), 5.34-5.12 (m, 1H, CH), 1.55 (d, *J* = 7.0 Hz, 3H, CH_3), 3.65 (d, *J* = 8.0 Hz, 1H, -NH-), 4.56-4.46 (m1H, CH), 1.68 (d, *J* = 6.0 Hz 3H, CH_3). FAB-MS m/z (%):473 [(83), $M^{+\bullet}$ +2], 471 [(86), $M^{+\bullet}$], 408 (27), 365 (16), 306 (61), 210 (30), 202 (8), 148 (30), 136 (13), 105 (100), 91 (11). *Anal.* Calcd for $C_{23}H_{24}BrN_2O_2P$: C, 58.64, H 5.13, N 5.94; Found: C 58.70, H 5.19, N 5.87%.

Characterization of 6-bromo-2-(4-indole)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (6j) yield 0.67g (71.7%). mp 135-137 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1243, P-O 956, O-C 1180. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: -3.77. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.64-6.87 (m, 14H, Ar-H), 4.29-4.13 (m, 2H, -CH_2-), 5.21-5.02 (m, 1H, CH), 1.68 (d, *J* = 6.9 Hz, 3H, CH_3). FAB-MS m/z (%): 469 [(30), $M^{+\bullet}$ +2], 467 [(33), $M^{+\bullet}$], 386 (75), 325 (11), 307 (19), 282 (13), 154 (58), 136 (41), 105 (100) *Anal.* Calcd for $C_{23}H_{20}BrNO_2P$: C 59.11, H 4.31, N 5.99; Found: C 59.20, H 4.25, N 5.92%.

Characterization of 6-bromo-2-(phenyl)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-oxide (8a) yield 0.54g (63%). mp 140-142 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=O 1202. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 12.08. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.82-6.86 (m, 13H, Ar-H), 4.27-4.15 (m, 2H, -CH_2-), 5.30-5.12 (m, 1H, CH), 1.42 (d, *J* = 6.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 54.4 (C-4), 132.3 (C-5), 120.1 (C-6), 132.3 (C-7), 133.8 (C-8), 156.6 (C-9), 125.0 (C-10), 122.3 (C-1'), 128.6 (C-2'& C-6'), 128.1 (C-3'&C-5'), 126.1 (C-4'), 140.1 (C-1''), 130.2 (C-2''&C-6''), 128.3 (C-3''& C-5''), 132.0 (C-4''), 42.4 (*C*-CH_3), 16.9 (C-*C*H_3). *Anal.* Calcd for $C_{21}H_{19}BrNO_2P$: C 58.89, H 4.46, N 3.27; Found: C 58.96, H 4.41, N 3.33%.

Characterization of 6-bromo-2-(phenyl)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-sulfide (8b) yield 0.6g (67.5%). mp 130-132 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=S 776. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 78.04. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.80-6.69 (m, 13H, Ar-H), 4.30-4.18 (m, 2H, -CH_2-), 5.21-5.10 (m, 1H, CH), 1.52 (d, *J* = 6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 54.4 (C-4), 132.3 (C-5), 120.1 (C-6), 132.3 (C-7), 133.8 (C-8), 156.6 (d, $^2J_{(P\text{-}O\text{-}C\ endo)}$= 8.8 Hz, C-9), 125.0 (C-10), 122.29 (C-1'), 128.4 (C-2'& C-6'), 128.2 (C-3'&C-5'), 127.5 (C-4'), 140.1 (C-1''), 132.2 (C-2''&C-6''), 128.3 (C-3''& C-5''), 132.0 (C-4''), 42.4 (*C*-CH3), 16.9 (C-*C*H3). FAB-MS m/z(%):446 [(94), $M^{+\bullet}$ +2], 444 [(100), $M^{+\bullet}$], 430 (11), 412 (19), 368 (8), 340 (83), 307 (16), 289 (13), 258 (38), 154 (50), 105 (75), 120 (8), 91 (11). *Anal.* Calcd for $C_{21}H_{19}BrNOPS$: C 56.76, H 4.30, N 3.15; Found: C 56.81, H 4.34, N 3.23%.

Characterization of 6-bromo-2-(phenyl)-3-(1-phenyl-ethyl)-3,4-dihydro-1*H*-isophosphinoline 2-Selenide (8c) yield 0.68g (69.2%). mp 100-102 °C; $IR_{(KBr)}$: ν_{max} (cm^{-1}), P=Se 632. ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 89.19. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.81-6.97 (m, 12H, Ar-H), 4.30-4.20 (m, 2H, -CH_2-), 5.48-5.39 (m, 1H, CH), 1.57 (d, *J* = 6.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 100 MHz) δ: 52.6 (C-4), 129.3 (C-5), 127.3 (C-6), 132.5 (C-7), 133.6 (C-8), 156.2 (d, $^2J_{(P\text{-}O\text{-}C\ endo)}$= 8.0 Hz, C-9), 125.2 (C-10), 118.2 (C-1'), 128.5 (C-2'& C-6'), 128.1 (C-3'&C-5'), 125.6 (C-4'), 138.1 (C-1''), 130.1 (C-2''&C-6''), 129.5 (C-3''& C-5''), 127.4 (C-4''), 43.4 (*C*-CH3), 19.1 (C-*C*H3). GC-MS m/z (%):493 [(5), $M^{+\bullet}$ +2], 491 [(12), $M^{+\bullet}$], 414 (9), 307 (13), 301 (100), 158 (8), 146 (58), 128 (5), 105 (6). *Anal.* Calcd for $C_{21}H_{19}BrNOPSe$: C, 51.34, H, 3.89, N 2.85; Found: C, 51.39, H, 3.94, N 2.90%.

Bioassays. The experiments were carried out on the laboratory cultures of *Bombyx mori* L (eggs, mulberrysilkworm); *epilachna vigintioctopun- ctata* F (adults,

brinjal epilachna beetle); *Bacillus subtilis, Escherichia coli, Aspergillus niger* and *Alternaria alternata*.

Effect on Hatchability of Eggs. Eggs of *Bombyx mori* were collected from local grainage and were stored at laboratory conditions. Solutions of the respective treatments **(6a-j)** and **(8a-c)**, were prepared in 0.2% ethanol in distilled water to get a concentration of 40 mgL^{-1} and thiodicarb was used as reference compound at 500 mgL^{-1}. Three sets of eggs (20 eggs/set) of the test insect were soaked in respective treatments for 30 min. The treated eggs were air dried and maintained at temperature 30 (±2) °C under laboratory conditions in glass tubes for hatching. The unhatched eggs were counted on 2nd and 3rd days to determine cumulative reduction in hatching in the respective treatments. Distilled water without the test compound was used as a control (Table 1).

Mortality of Brinjal Epilachna Beetles. From the laboratory culture, 2-day-old adult beetles were collected and starved for 12 h before their exposure to the respective treatments. Brinjal leaf discs (4 cm diameter) were soaked in respective treatments with concentration given in 2.3.1 for 10 min and were then air dried. The treated leaf discs of respective treatments were placed in individual petri plates. Ten adult test insects were introduced onto treated leaf materials. Three replications were maintained for each treatment. Average mortality of beetles in each treatment was recorded after 24 hrs of feeding with respective treatments. The treated leaf discs were replaced with untreated fresh material and mortality of beetles were recorded on 2nd, 3rd and 4th days after treatment.

The data on egg hatching and natural control of beetles, which corrected values and reference to the check were computed and statistical inference [12-13] was drawn (Table 1).

Antimicrobial Properties. The antibacterial and antifungal properties of the test compounds were evaluated by the agar diffusion method [14] their effect was compared to antibiotics like gentamycin and nystatin. Methanolic solutions of the test compounds were used for testing microbial activity. The bacterial cultures were grown overnight in agar nutrient broth at 37°C and the fungal cultures were grown in potato dextrose broth for one week. The bacterial lawns were prepared by spread plating and fungal lawns were prepared by pour plating. The samples were loaded in the wells, the test plates were incubated and the zone of inhibition was measured. Bacterial strains used: *Bacillus subtilis* (Gram positive), *Escherichia coli* (Gram negative). Fungal cultures used: *Aspergillus niger, Alternaria alternata* (Table 3).

Antimicrobial Activity. The antimicrobial activity of the compounds was comparable to the commercial antibiotics like gentamycin and nystatin. Test compounds were found to inhibit the growth of bacteria *Bacillus subtilis* and *Escherichia coli* and fungi of species *Aspergillus niger, Alternaria alternata* respectively. The compounds **(6a), (6f)** and **(8a)** were more effective in inhibiting the growth of Gram-positive *Bacillus* as compared to Gram-negative *E. coli*. Compound **8c** exhibited moderate antifungal activity whereas compound **6f** showed equal activity when compared to that of Nystatin against *A. niger*.

Antibacterial Activity. Compounds **(6a-j)**, **(8a-c)** were screened for their antibacterial activity by the method of Vincent and Vincent [15] employing *Pseudomonas solanacearum, Xanthomonas campestris* and *Agrobacterium tumefaciens*. The stock solutions of the test compounds were prepared by dissolving 1 mg of the compound in 0.6 mL of ethanol and the final volume was made up to 1 mL with sterile water, 0.1 mL of the test solution consists of 100 μg of test compound. Sterile Whatman No.1 filter paper discs of 3 mm diameter were impregnated with definite amount of test compound by adding desired volume of test solution on to the disc drop by drop with a time lag to facilitate solvent evaporation. Control filter paper discs were impregnated with solvent only. Using disc diffusion method the sensitivity of test organisms grown on media in the title and reference compound Aeromycin was determined by measuring the diameter of the zone of inhibition after 24 h. The results are given in (Table 4).

Insecticidal Activity. The egg hatching of *Bombyx mori* was treated with different concentrations of test compounds and their effect on egg hatching had statistically significance. Egg hatching of *Bombyx mori* was greatly affected in compounds **(6a), (6j)** and **(8a)** which were on par with thiodicarb and the effect of the carbamate was comparable with Helicoverpa armigera on cotton. The compound **(6g), (6f), (6e), (6i), (6b),** and **(8a)** even at 11.5 times lesser concentration (30 mg/L) exhibited significant insecticidal activity on Epilachna beetle as compared to thiodicarb at 40 mg/L. These insecticidal efficacies of the new test compounds would be attributed to their novel chemical structural features. Another example to prove the insecticidal activity of the test compound by using the *Scirpophaga incertulas*.

To prepare test solution of the compounds (**6a-j**), (**8a-c**) 5 mg of test compound was dissolved in 1 mL of ethanol and the volume was made up to 10 mL with sterile water. 1 mL of this test solution was spread over the surface of artificial diet of 4 g taken in a polyethylene cup for rearing rise stem borer *Scirpophaga incertulas*. Twenty, 15 day-old larvae of *S.incertulas* were released on to the diet. Observations were made to evaluate the effect of test compounds on survival of the larvae. The live and the dead larvae of *Scirpophaga incertulas* were counted after 10 days. In order to record the insecticidal effect of the test compounds on the hatchability of the eggs of *Scirpophaga incertulas,* 25 eggs of *S. incertulas* were placed on the diet. The

Table 1

Effect of **(6a-j), (8a-c)** at 40 mgL^{-1} on Egg Hatching and Adult Mortality

Compd	Unhatched eggs of *Bombyxmori* (%) @	Corrected adult mortality of *Henosepilachna vigintioctopunctata* (%)#
6a	65.00 (52.00)	13.33 (17.68)
6b	23.38 (27.80)	06.76 (08.16)
6c	75.00 (58.92)	36.00 (34.85)
6d	23.38 (27.80)	12.38 (14.40)
6e	45.07 (42.08)	24.03 (21.04)
6f	23.08 (27.92)	11.06 (15.86)
6g	24.76 (28.97)	13.33 (17.68)
6h	36.07 (36.93)	18.98 (12.42)
6i	23.38 (27.80)	12.38 (14.40)
6j	53.30 (46.92)	27.15 (25.86)
8a	10.00 (14.17)	11.22 (18.68)
8b	36.76 (36.83)	18.30 (21.02)
8c	36.76 (36.83)	18.30 (21.02)
Thidocarb	84.01 (70.66)	96.82 (73.33)
Generalmean	40.00 (38.26)	22.86 (22.60)
Fest	**	**
CD(P=005)	1556	2391

Figures in parenthesis are angular transformed values; @ With reference to treated eggs in water soaking; # Corrected with reference to natural mortality in untreated leaf bite regions; ** 'F' test significance at 1% level; CD-Critical difference

number of larvae hatched in the diet after 10 days were recorded. [16-17] The results are shown in (Table-2) and compared with untreated control. In each test three replications were maintained.

Table 2

Antimicrobial activity of compounds **(6a-j), (8a-c)** at 150 μg/L Zone of inhibition (mm)

Compd	*Bacteria*		*Fungi*	
	B. subtilis	*E. coli*	*A. Niger*	*A. alternata*
6a	9	6	-	-
6b	3	2	-	2
6c	4	3	2	2
6d	6	4	2	-
6e	5	3	2	2
6f	10	5	8	-
6g	3	2	2	-
6h	6	3	-	2
6i	2	1	1	-
6j	3	1	-	-
8a	3	-	3	3
8b	2	-	1	1
8c	8	3	5	6
Gentamcin	9	14	-	-
Nystatin	-	-	8	11

(-) No activity

Table 3

Insecticidal Activity of **(6a-j), (8a-c)**

Compd	**+**	**#**
6a	43.8	21.5
6b	13.6	62.9
6c	44.2	23.6
6d	18.6	38.5
6e	36.6	34.4
6f	14.5	53.5
6g	21.4	44.6
6h	23.6	46.8
6i	16.6	56.8
6j	40.1	20.2
8a	12.2	61.8
8b	25.2	42.2
8c	34.2	32.1
Control	00.0	94.0

+ % of mortality on 10 days adult larvae of *Scirpophaga incertulas*. # % of hatched eggs of *Scirpophaga incertulas*

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REFERENCES

[1] Srivastava, R. P.; Saxena, R. C.; *Text book of insect toxicology,* Himachal Publications, Udaipur, India, pp. 165 1989.

[2] Perry, A. S.; Yamamoto, I.; Ishaye, I.; Perry, R.; *Insecticides in agriculture and environment retrospect and prospects,* Narosa Publishing House, New Delhi, p. 261, 1998.

[3] White-Stevens Robert, Pesticides in the Environment, Part I, Vol. I, Marcel Dekker Inc., New York, pp. 4, 1971.

[4] Hendlin, D.; Stapley, E. O.; Jackson, M.; Wallick, H.; Miller, A. K.; Wolf, F. J.; Miller, T. W.; Chaiet, L.; Kahan, F. M.; Foltz, E. L.; Woodruff, H. B.; Mata, J. M.; Hernandez, S.; Mochales, S.; Phosphonomycin, a New Antibiotic Produced by Strains of Streptomyces, *Science,* **1969**, *166*, 122.

[5] White, D. W.; Gibbs, D. E.; Verkade, J. G.; Solution Stereochemistry of Cyclophosphamide and Rigid Model Analogues, *J. Am. Chem. Soc*. **1979**, *101*, 1937.

[6] The Interpretation of the Infrared Spectra of Organophosphorus Compounds, Heydon and Sons Ltd, London 1974.

[7] (a) Silverstein, R. M.; Webster, F. X.; Spectrometric Identification of Organic Compounds, 6th ed., John Wiley, New York, 1998. (b) Hari Babu, Y.; Srinivasulu, K.; Suresh Reddy, C.; Devendranath Reddy, C.; *Arkivoc*, **2007**, *15*, 97. (c) Vasu Govardhana Reddy, P.; Kiran, Y. B.; Suresh Reddy, C.; Devendranath Reddy, C .; *Chem Pharm Bull* **2004**, *52(3)*, 307.

[8] Quin, L. D.; Verkade, J. G.; *Phosphorus 31 NMR Spectral Properties in Composund Characterization and Structural Analysis*, VCH Publishers, New York, 1994.

[9] Vasugovardhana Reddy, P.; Suresh Reddy, C.; and Venugopal, M.; *Heteroatom Chem*. **2003**, *14(6),* 509.

[10] Hari Babu, Y.; Vasugovardhana Reddy, P.; Suresh Reddy, C., Devendranath Reddy C.; and Umamaheswari Devi, P.; *J. Heterocycl. Chem*. **2002**, *39* 1039.

[11] Devendranath Reddy, C.; and Rao, C. V. N.; *Org Mass Spectrom*, **1982**, *17*, 598.

[12] Busvine, J. R.; *A Critical Review on the Techniques for Testing Insecticides*, 6th ed., CAB, Slough, England, pp. 345, 1971.

[13] Snedecor, G. W.; Cochran, W.G.; *Statistical Methods,* Iowa State University Press, Iowa, pp. 533, 1968.

Table 4

Antibacterial Activity of Compound **(6a-j), (8a-c)**

Compd	Diameter of zone of inhibition in millimeters								
	Pseudomonas solanacearum			*Xanthomonas campestris*			*Agrobacterium tumefaciens*		
	50 μg/disc	100 μg/disc	150 μg/disc	50 μg/disc	100 μg/disc	150 μg/disc	50 μg/disc	100 μg/disc	150 μg/disc
6a	16	16	20	19	19	22	20	21	23
6b	5	5	6	8	9	11	10	11	13
6c	17	19	21	19	22	26	21	24	27
6d	10	12	13	11	14	16	13	16	18
6e	14	16	17	13	16	18	15	17	19
6f	9	11	12	12	14	15	14	16	17
6g	11	12	14	13	15	17	15	17	19
6h	11	14	16	14	16	18	16	18	20
6i	10	10	12	12	13	15	14	15	17
6j	15	18	19	18	19	22	20	21	24
8a	5	5	7	8	10	12	10	12	14
8b	11	13	16	14	15	18	16	17	19
8c	12	14	17	15	16	19	17	18	20
Aeromycin	19	21	23	22	24	26	26	28	30

[14] Deans, S.; G.; Richie, G.; Antibacterial Properties of Plant Essential oils, *International J Food Microbiol,* **1987**, *5*, 165.

[15] Amanlou, M.; Fazeli, M. R.; Arvin, A.; Amin, H. G.; and Farsan, H.; *Fitoterapia* **2004**, *75*, 768.

[16] Manne, P. N.; Deshmukh, S. D.; Rao, N. G. V.; Dodale, H. G.; Tikar, S. N.; Nimbalkar, S. A.; Efficacy of some Insecticide against *Helicoverpa armigera* (Hub), *Pestology,* **2000**, *34*, 65.

[17] Tsushima Kazunori, Yano Toshihiko, Umeda Kimitoshi, Nortiadamatsuo, Hisano Masachika & Nobuoohno, *Pest Sci,* **1989**, *25*, 17.