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Synthesis and Biological Evaluation of Substituted phenoxy Derivatives of Phosphorylated and Thiophosphorylatedbenzazoles.

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ABSTRACT

A series of biologically active phenoxy derivatives of 2-substituted benzazoles organophosphates have been synthesized by the reaction of S,S-(benzoxazolyl-2)phosphorochloridothioate / phosphorochloridodithioate and NH,NH-bis (phenyl benzothiazolyl-4)methyl phosphorochloridoamidate / phosphorochloridoamidothioate with phenol/4-chlorophenol/4-nitrophenol in 1:1 molar ratio. These compounds have been characterized by elemental analysis, IR, ^{1}H NMR and ^{31}P NMR spectral studies. The antibacterial activity of these 2-substituted benzazolephenoxyderivatives has been evaluated against pathogenic bacteria *staphylococcus aureus* (+ve) and *Escherichia Coli* (–ve). All the compounds were found to have significant antibacterial and antifungal activity.

Keywords : Benzoxazole, Benzothiazole, Phenoxy derivatives, Antibacterial activity, Antifungal activity.

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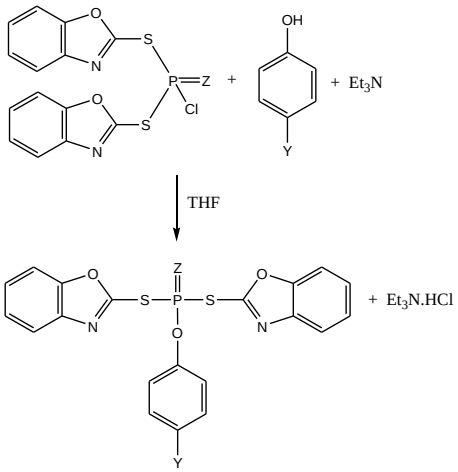
INTRODUCTION

Organophosphates are biodegradable, short lived chemical compounds, and their mode of action involves inhibition of acetylcholinesterase (AChE) [1]. Organophosphorus compounds are well known for their broad spectrum biocidal activities [2-5]. These compounds have found numerous applications in insectides, fungicides, herbicides and pesticides [6-9]. These compounds find considerable use as asymmetric hydrogenating catalysts, medicines and flame retardants [10, 11]. Heterocyclic compounds are an important group of ligands in organophosphorus chemistry and find a critical role in various fields. Organophosphorus compounds containing a heterocyclic moiety increase the protonation at the site of pesticides and enhance their biological activity [12]. Being a heterocyclic compounds, benzoxazole and benzothiazole are structurally releated to biologically important bases and are used in research as a starting material for the synthesis of bioactive compounds. The reported biological activity of benzoxazoles [13-17] and benzothiazoles [18-21] and organophosphorus compounds stimulated our interest to synthesize several organophosphate derivatives. In continuation of our research work on organophosphates [22-25], we report here the synthesis, characterization and biological activity of organophosphate phenoxy derivatives derived from 2-substitutedbenzoxazole and benzothiazole.

RESULTS AND DISCUSSION

Thereaction of S, S-bis(benzoxazolyl-2) phosphorochloridothioate / phosphorochloridodithioate and NH,NH-bis (phenyl benzothiazolyl-4)methyl-phosphorochloridoamidate/phosphorochlorido-amidothioatewith molar ratio(1:1) of phenol / 4-chlorophenol / 4-nitrophenol in stoichiometric amounts of triethylamine in dry tetrahydrofurane (THF) has offered a series of the corresponding organophosphate phenoxy derivatives (1-12). A schematic presentation of these reactions is given in Scheme-1 and Scheme-2. The physical and analytical data of the compound are given in Table-1.



	1	2	3	4	5	6
Z	O	S	O	S	O	S
Y	H	H	Cl	Cl	NO_2	NO_2

Scheme-I :Schematic presentation of organophosphate phenoxy derivatives derived from 2-substituted benzoxazole (1-6)

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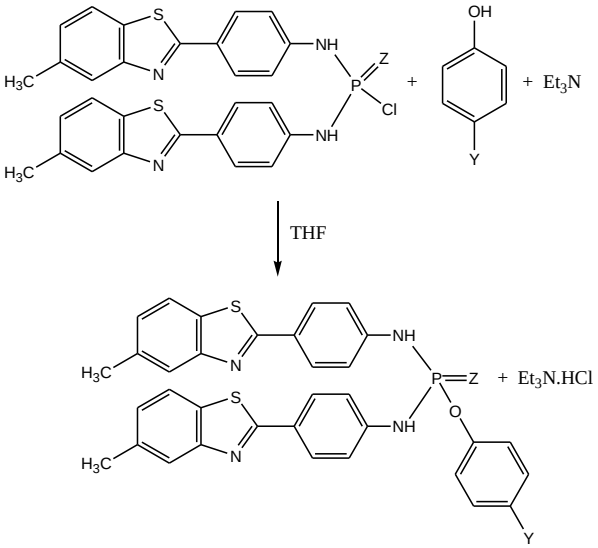

	7	8	9	10	11	12
Z	O	S	O	S	O	S
Y	H	H	Cl	Cl	NO_2	NO_2

Scheme-2 :Schematic presentation of organophosphate phenoxy derivatives derived from 2-substituted benzothiazole (7-12).

Table-1 Physical properties and Analytical data of organophosphate phenoxy derivatives (1-12) derived from substituted benzoxazole and benzothiazole.

Compound	Yield (%)	Analysis (%) Found (Calcd.)						Mol. Wt. Found (Calcd)
		C	H	N	S	P	Cl	
1. $(C_7H_4NOS)_2(C_6H_5O)P(O)$	30	54.54 (54.55)	2.95 (2.97)	6.36 (6.38)	14.54 (14.56)	7.04 (7.06)	-	440.00 (440.43)
2. $(C_7H_4NOS)_2(C_6H_5O)P(S)$	42	52.63 (52.64)	2.85 (2.87)	6.14 (6.15)	21.05 (21.07)	6.78 (6.79)	-	456.00 (456.50)
3. $(C_7H_4NOS)_2(ClC_6H_4O)P(O)$	35	50.57 (50.58)	2.52 (2.54)	5.90 (5.92)	13.48 (13.50)	6.53 (6.54)	7.48 (7.49)	474.5 (474.88)
4. $(C_7H_4NOS)_2(ClC_6H_4O)P(S)$	25	48.90 (48.92)	2.44 (2.46)	5.70 (5.72)	19.57 (19.59)	6.32 (6.35)	7.23 (7.24)	490.50 (490.94)
5. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(O)$	32	49.45 (49.48)	2.47 (2.49)	8.65 (8.68)	13.19 (13.21)	6.39 (6.40)	-	485.00 (485.43)
6. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(S)$	50	47.90 (47.92)	2.39 (2.41)	8.38 (8.39)	19.16 (19.18)	6.18 (6.19)	-	501.00 (501.49)
7. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(O)$	42	66.01 (66.05)	4.36 (4.39)	9.06 (9.07)	10.35 (10.38)	5.01 (5.04)	-	618.00 (618.71)
8. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(S)$	38	64.35 (64.38)	4.25 (4.28)	8.83 (8.85)	15.14 (15.16)	4.88 (4.87)	-	634.00 (634.77)
9. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(O)$	46	62.52 (62.54)	3.98 (4.01)	8.58 (8.57)	9.80 (9.81)	4.75 (4.77)	5.44 (5.46)	632.50 (635.15)
10. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(S)$	28	61.03 (61.05)	3.88 (3 91)	8.37 (8.38)	14.36 (14.37)	4.63 (4.65)	5.31 (5.35)	668.50 (669.22)
11. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(O)$	30	61.53 (61.55)	3.92 (3.94)	10.55 (10.57)	9.65 (9.66)	4.67 (4.69)	-	663.00 (663.70)
12. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(S)$	33	60.05 (60.07)	3.82 (3.85)	10.30 (10.32)	14.13 (14.15)	4.56 (4.58)	-	679.00 (679.77)

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IR SPECTRA

The assignments of some important bands are summarized in Table-2. The absorption band due to *v*(P-Cl) of 2-substituted benzoxazole and benzothiazole, disappearin the spectra of organophosphate phenoxy derivatives(1-12) due to the dechlorination of the P-Cl group. New band appears in the region 930-1190 cm^{-1} due to the *v* (P-O-C) (aryl). The *v*(P=O) band is observed at 1180-1245 cm^{-1}. The *v* (P=S) (I) and *v* (P=S) (II) bands are observed at 820-900 cm^{-1} and 665-715 cm^{-1} respectively [26]. The ν P-NH and ν P-N-C bands are observed at 2935-2950 cm^{-1} along with 2850-2860 cm^{-1} and 1020-1050 cm^{-1} along with 620-655 cm^{-1} respectively. The absorption band at 1520-1530cm^{-1} and 1320-1330 cm^{-1} are due to *v* (NO_2).

Table-2 IR Spectral data (cm^{-1}) of organophosphate phenoxy derivatives (1-12)

Compound	*v*(P–O–C)	*v*(P-N-C)	*v*(P=O)	*v*(P=S)	*v*(P–NH)	*v*(NO_2)
1. $(C_7H_4NOS)_2(C_6H_5O)P(O)$	1160-940	-	1180	-	-	-
2. $(C_7H_4NOS)_2(C_6H_5O)P(S)$	1140-950	-	-	780 (I) 690 (II)	-	-
3. $(C_7H_4NOS)_2(ClC_6H_4O)P(O)$	1130-940	-	1245	-	-	-
4. $(C_7H_4NOS)_2(ClC_6H_4O)P(S)$	1125-945	-	-	800 (I) 705 (II)	-	-
5. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(O)$	1160-975	-	1205	-	-	1530, 1335
6. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(S)$	1150-965	-	-	810 (I) 715 (II)	-	1535, 1330
7. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(O)$	1170-935	1035, 640	1235	-	2945, 2855	-
8. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(S)$	1160-930	1050, 650	-	820 (I) 680 (II)	2950, 2860	-
9. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(O)$	1180-945	1020 620	1225	-	2940, 2850	-
10. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(S)$	1180-935	1040 650	-	820 (I) 665 (II)	2940, 2855	-
11. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(O)$	1195-960	1025 635	1220	-	2935, 2850	1520, 1325
12. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(S)$	1190-955	1050 655	-	820 (I) 680 (II)	2940, 2855	1520, 1320

^{1}H NMR and ^{31}P NMR SPECTRA

The characteristic signals in ^{1}H NMR and ^{31}P NMR spectra of organophosphate phenoxy derivatives (1-12) are summarized in Table-3. All the organophosphate phenoxy derivatives show multiplets in the region of δ 6.8-8.5 ppm attributable to the aromatic protons of a phenyl ring along with benzoxazolyl and benzothiazolyl ring. In the ^{1}H NMR spectra of organophosphate phenoxy derivatives derived from 2-substituted benzothiazole the –NH proton signal was observed at δ 5.4-6.0 ppm The ^{31}P NMR spectra of these organophosphate phenoxy derivatives have been observed at somewhat downfield at δ 55.5-70.8 ppm [27].

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Table-3 ^{1}H NMR and ^{31}P NMR spectral data (δ, ppm) of organophosphate phenoxyderivatives (1-12)

Compound	^{1}H NMR		^{31}P NMR
	P-NH	Ar-H (m)	
1. $(C_7H_4NOS)_2(C_6H_5O)P(O)$	-	6.8-7.2	60.1
2. $(C_7H_4NOS)_2(C_6H_5O)P(S)$	-	7.4-8.0	70.4
3. $(C_7H_4NOS)_2(ClC_6H_4O)P(O)$	-	7.8-8.2	72.1
4. $(C_7H_4NOS)_2(ClC_6H_4O)P(S)$	-	7.2-7.9	73.5
5. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(O)$	-	8.1-8.5	70.8
6. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(S)$	-	7.9-8.3	72.9
7. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(O)$	5.4	7.3-8.1	59.5
8. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(S)$	5.7	6.9-7.7	62.7
9. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(O)$	5.5	7.0-7.9	56.8
10. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(S)$	5.7	7.5-8.2	59.2
11. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(O)$	5.6	6.9-7.4	55.7
12. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(S)$	5.9	7.5-8.3	56.5

ANTIBACTERIAL ACTIVITY

The results of the antibacterial activity of organophosphate phenoxy derivatives (1-12) have been compared with standard streptomycin and are summarized in Table-4. The organisms selected for the studies are *staphylococcus aureus* (+ve) and *Escherichia Coli* (– ve). The antibacterial activity was evaluated by a paper disk plate method. The results reveal that 4-chlorophenoxy derivatives show highest bactericidal activity among all derivatives but they show less activity than standard streptomycin.

EXPERIMENTAL

All the commercial reagents and solvents were dried and distilled by common methods before use. Phosphorus oxychloride / Phosphorus thiochloride were purchased from fluka.All operations involving phosphorus compounds were carried out in dry equipment under nitrogen atmosphere. The IR spectra of the compounds were recorded as KBr disks on a SHIMADZU 8400 S FT IR spectrophometer. The ^{1}H NMR spectra were recorded on a JEOL Al 300 MHz FT-NMR spectrometer in $CDCl_3$ using TMS as an internal reference. The ^{31}PNMR spectra were recorded on a JEOL AL 300 MHz FT-NMR spectrometer at 121.49 MHz in $CDCl_3$ using TMS and 85% H_3PO_4 as internal and external reference respectively. Nitrogen was estimated by the Kjeldahl's method and sulfur was estimated volumetrically by the volhard method. Phsophorus was estimated as ammonium phosphomolybdate. The molecular weights were determined by the Rast camphor method.

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Table-4 Antibacterial Screening Data of organophosphate phenoxy Derivatives (1-12)

Compound	Diameter of inhibition zone after 24 hours (conc. in ppm)			
	Staphylococcus Aureus		*Escherichia Coli*	
	500	1000	500	1000
1. $(C_7H_4NOS)_2(C_6H_5O)P(O)$	13	17	15	25
2. $(C_7H_4NOS)_2(C_6H_5O)P(S)$	21	23	20	27
3. $(C_7H_4NOS)_2(ClC_6H_4O)P(O)$	21	30	28	40
4. $(C_7H_4NOS)_2(ClC_6H_4O)P(S)$	25	42	30	45
5. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(O)$	20	25	23	35
6. $(C_7H_4NOS)_2(O_2NC_6H_4O)P(S)$	24	37	25	38
7. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(O)$	22	35	24	36
8. $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(S)$	25	36	27	38
9. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(O)$	25	38	22	42
10. $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(S)$	28	40	25	47
11. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(O)$	23	30	25	37
12. $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(S)$	27	38	28	40
Streptomycin (standard)	45	60	52	64

Synthesis of $(C_7H_4NOS)_2(C_6H_5O)P(O)$ [1] / $(C_7H_4NOS)_2(C_6H_5O)P(S)$ [2]

To an ice cold solution of S, S- bis-(benzoxazolyl-2) phosphorochloridothioate/ phosphorochloridodithioate (0.001 mol) in dry THF (30 ml) and Et_3N (0.001 mol) in dry THF (20 ml), a solution of phenol (0.001 mol) in dry THF (30 ml) was added dropwise in a nitrogen flushed round bottom flask equipped with a mechanical stirrer.After mixing the reactants, stirring was continued for 4 hours at 0°C. Further the reaction mixture was removed from the ice bath and then refluxed further under nitrogen atmosphere for 14-16 hours with continuous stirring. Then it was cooled and the adduct ($Et_3N.HCl$) that formed was filtered off with closed sintered funnel. Then the filterate was concentrated and recrystallized.

Synthesis of $(C_7H_4NOS)_2(ClC_6H_4O)P(O)$ [3] / $(C_7H_4NOS)_2(Cl_6H_4O)P(S)$ [4]

In the fast stirring solution of S,S-bis-(benzoxazolyl-2)phosphorochloridothioate/ phosphorochloridodithioate (0.001 mol) in dry THF (30 ml) and Et_3N (0.001 mol) in dry THF (20 ml), a solution of 4-chlorophenol(0.001 mol) in dryl THF (30 ml) was added dropwise by

dropping funnel. The mixture was refluxed for 14-16 hours. Then the reaction was carried out in a manner similar as described above.

Synthesis of $(C_7H_4NOS)_2(O_2NC_6H_4O)P(O)$ [5] / $(C_7H_4NOS)_2(O_2NC_6H_4O)P(S)$ [6]

In the fast stirring solution of S,S-bis-(benzoxazolyl-2)phosphorochloridothioate/ phosphorochloridodithioate (0.001 mol) in dry THF (30 ml) and Et_3N (0.001 mol) in dry THF (20 ml), a solution of 4-nitrophenol (0.001 mol) in dry THF (30 ml) was added dropwise by dropping funnel. Then the reaction was carried out in a manner similar as described above.

Synthesis of $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(O)$ [7] / $(C_{14}H_{11}N_2S)_2(C_6H_5O)P(S)$ [8]

In the fast stirring solution of NH,NH-bis-(phenybenzothiazolyl-4)methyl phosphorochloridoamidate/ phosphorochloridoamidothioate (0.001 mol) in dry THF (30 ml) and Et_3N (0.001 mol) in dry THF (20 ml), a solution of phenol (0.001 mol) in dry THF (30 ml) was added dropwise by dropping funnel. Then the reaction was carried out in a manner similar as described above.

Synthesis of $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(O)$ [9] / $(C_{14}H_{11}N_2S)_2(ClC_6H_4O)P(S)$ [10]

In the fast stirring solution ofNH,NH-bis-(phenyl benzothiazolyl-4)methyl phosphorochloridoamidate/phosphorochloridoamidothioate (0.001 mol) in dry THF (30ml) and Et_3N (0.001 mol) in dry THF (20 ml), a solution of 4-chlorophenol (0.001 mol) in dry THF (30 ml) was added dropwise by dropping funnel. Then the reaction was carried out in a manner similar as described above.

Synthesis of $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(O)$ [11] / $(C_{14}H_{11}N_2S)_2(O_2NC_6H_4O)P(S)$ [12]

In the fast stirring solution ofNH,NH-bis-(phenyl benzothiazolyl-4)methyl phosphorochloridoamidate/phosphorochloridoamidothioate (0.001 mol) in dry THF (30ml) and Et_3N (0.001 mol) in dry THF (20 ml), a solution of 4-nitrophenol (0.001 mol) in dry THF (30 ml) was added dropwise by dropping funnel. Then the reaction was carried out in a manner similar as described above.

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