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SYNTHESIS, SPECTRAL CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF 1,3,2-DIOXAPHOSPHINANE DERIVATIVES

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ABSTRACT

Synthesis of a series of new 1, 3, 2- dioxaphosphinane derivatives (3a-j) was accomplished. The key step in the synthesis of 3a-j involves the cyclization reaction of tris (hydroxy methyl) nitromethane (1) with $P(X)Cl_3$ (X=S,O) in presence of TEA in THF at 40-45 °C to afford the phosphoryl mono chloride intermediate (2). The intermediate (2) when treated with different substituted aromatic amines and with a few substituted phenols *in situ* in the presence of TEA at 0-15 °C afforded 3a-j. The structures of 3a-j were established by IR, NMR (1H, ^{13}C and ^{31}P) and Mass spectral data and elemental analysis. All these compounds exhibited good antimicrobial activity.

KEY WORDS: **Aromatic amines, Phenols, Tris(hydroxymethyl)nitromethane, antimicrobial activity, 1,3,2-dioxaphosphinane.**

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INTRODUCTION

1,3,2-Dioxaphosphinane derivatives are an important class of organophosphorus heterocycles, having potential biological importance[1-3] due to their unique features. They have multifaceted applications as important pharmacophores in agriculture,[4] pharmaceuticals,[5] chemical synthesis[6] and in diverse other potential biological areas.[7] The thiophosphoryl group is the fundamental structural unit in many important molecules that control molecular replication, cell biochemistry and metabolic processes in all living species.[8] They are eco-friendly, hydrolytically and enzymatically degradable to non-toxic residues and represent as an important class of insecticides, pesticides, antitumour and antiviral agents.[9] The nucleoside cyclic phosphoramidates are precursors to inhibitors of RNA-dependent RNA viral polymerase and hepatitis C virus (HCV) NS5B polymerase and also act as precursors to inhibit HCV replication. There are only a few [3,3]-Sigmatropic rearrangements available for selective carbon-nitrogen bond formation despite their enormous potential for the synthesis of molecules containing nitrogen-bearing stereocenters.[10,11] This important back ground of these heterocyclic systems of biological interest and the clinical success of cyclophosphamide as an anti-cancer drug [12,13] prompted the author for the synthesis of novel potential bio-active six membered phosphorus heterocycles.

EXPERIMENTAL:

GENERAL:

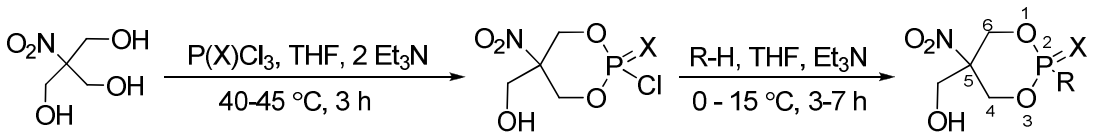
Chemicals were procured from Sigma-Aldrich and used as without further purification. All solvents used for the spectroscopic and other physical studies were reagent grade and further purified by literature methods.[14] All solvents were freshly distilled prior to use. The melting points (mp) were determined in open capillary tubes on a Mel-Temp apparatus, expressed in degrees centigrade (°C) and were uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr pellets on Perkin Elmer 1000 unit. Samples were analyzed as potassium bromide (KBr) disks. Absorptions were reported in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ on a Bruker AMX 500 MHz spectrometer by operating at 500 MHz for ^{1}H, 125 MHz for ^{13}C and 200 MHz for ^{31}P respectively. The chemical shift values were expressed in ppm and were referenced to TMS (^{1}H & ^{13}C) and 85% H_3PO_4 (^{31}P) as an external standard. LCMS mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer. Micro analytical data were obtained from Central Drug Research Institute, Lucknow, India.

CHEMISTRY:

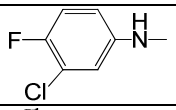
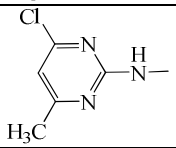
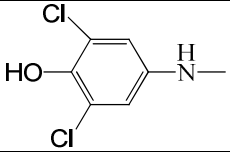
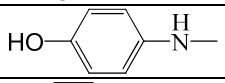
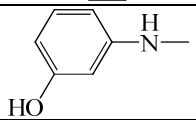
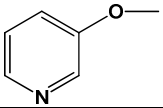
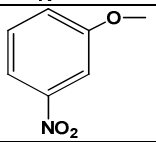
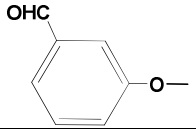
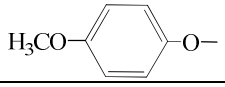
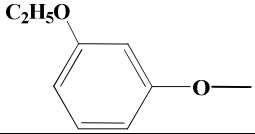
General procedure for the synthesis of a series of new 1, 3, 2-dioxaphosphinane derivatives (3a-j):

A solution of 3-chloro, 4-fluoro aniline (0.436 g, 0.003 mole) in dry THF (20 mL) was added drop wise to a solution of the intermediate, phosphoryl mono chloride intermediate (**2**) (0.003 mole), and triethyl amine (0.9 mL, 0.003 mole), in dry THF *in situ* at 0 to 15 °C. After completion of the addition, the temperature of the reaction mixture was raised to 55 °C and the reaction mixture was kept stirred for 3h. The completion of the reaction was indicated by TLC conducted in 3:7 mixtures of ethyl acetate and hexane, with an average R_f value of 0.60. The reaction mixture was filtered to remove solid triethylamine hydrochloride salt and the solvent was removed in a rota evaporator to get the crude product. It was purified by column chromatography on silica gel (100-200 mesh) using ethylacetate: hexane (1:9) as eluent to afford the pure compound.

Scheme 1
Synthesis of *1, 3, 2-dioxaphosphinane derivatives (3a-j)*



(1) **(2)** **(3a-j)**

Compound	R	X	Yield (%)	mp (°C)
3a		S	75	147-149
3b		O	70	135-137
3c		S	65	143-145
3d		O	69	138-140
3e		S	60	149-151
3f		O	67	139-141
3g		S	60	135-137
3h		O	65	119-121
3i		S	58	131-132
3j		O	60	116-118

Here the intermediate 2, phosphoryl mono chloride was prepared by adding a solution of $PSCl_3$ (0.30 mL, 0.003 mole) in 20 mL of dry THF in drop wise to a stirred solution of tris (hydroxy methyl) nitro methane and triethyl amine (0.9 mL, 0.003 mole) (**1**) (0.453 g, 0.003 mole) and triethyl amine (1.8 mL, 0.006 mole) in dry THF (20 mL) at 0 °C over a period of 20 min. After stirring for 3h at 40-45 °C, formation of the intermediate, (**2**) was ascertained by TLC analysis which was run in a 3:7 mixture of ethylacetate and hexane and

the average of R_f value observed was 0.75. Then the formed triethyl ammoniumhydrochloride salt was removed by filtration and the filtrate containing 2 was used for the next reaction without further purification. All the synthesized compounds thus obtained were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR, mass spectral and elemental analysis.

{2-[(3-chloro-4-fluorophenyl)amino]-5-nitro-2-sulfido-1,3,2-dioxaphosphinan-5-l}methanol (3a):

Yield: 75%. Solid. mp: 147-149 °C. IR (KBr) υ_{max}: 790 (P=S), 1038 (P-O-$C_{aliphatic}$), 1560 (NO_2), 3320 (P-NH), 3380 (-OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.80 (2H, s, -CH_2-OH), 4.10-4.42 (m, 4H, 4 & 6 –CH_2), 4.20 (1H, s, -CH_2-OH), 6.80-7.25 (3H, m, Ar-H), 5.85 (1H, d, *J* =10 Hz, P(S)-NH-C). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 46.0 (C-7), 64.5 (C-4 & C-6), 96.0 (C-5), 115.1 (C-5^1), 116.2 (C-6^1), 119.0 (C-2^1), 121.8 (C-3^1), 137.0 (C-1^1), 150.2 (C-4^1). ^{31}P NMR (200 MHz, DMSO) δ: 78.10. LCMS (*m/z*): 356 (M^+). Anal. Calc. for $C_{10}H_{11}ClFN_2O_5PS$: C, 33.67; H, 3.11; N, 7. 85%. found: C, 33.58; H, 3.08; N, 7.82%.

{2-[(4-chloro-6-methylpyrimidin-2-yl)amino]-5-nitro-2-oxido-1,3,2-dioxaphosphinan-5-yl}methanol (3b):

Yield: 70%. solid. mp: 135-137 °C. IR (KBr) υ_{max}: 1033 (P-O-$C_{aliphatic}$), 1255 (P=O), 1565 (NO_2), 3336 (P-NH), 3365 (-OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.43 (3H, s, Ar-CH_3), 3.90-4.34 (m, 4H, 4 & 6 –CH_2), 3.72 (2H, s, -CH_2-OH), 4.50 (1H, s, -OH), 6.94 (1H, s, Ar-H), 6.45 (1H, d, *J* =8 Hz, P(O)-NH-C). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (Ar-CH_2), 50.5 (C-7), 67.8 (C-4 & C-6), 97.2 (C-5), 105.2 (C-4^1), 161.1 (C-5^1), 170.1 (C-1^1), 171.8 (C-3^1). ^{31}P NMR (200 MHz, DMSO) δ: -21.12. LCMS (*m/z*): 338 (M^+). Anal.Calc. for $C_9H_{12}ClN_4O_6P$: C, 31.92; H, 3.57; N, 16.54%; found: C, 31.84; H, 3.52; N, 16.51%.

3,5-dichloro-4-{[5-(hydroxymethyl)-5-nitro-2-sulfido-1,3,2-dioxaphosphinan-2-l]amino}phenol (3c):

Yield: 65%. Solid. mp: 143-145 °C. IR (KBr) υ_{max}: 778 (P=S), 1043 (P-O-$C_{aliphatic}$), 1542 (NO_2), 3340 (P-NH), 3390 (OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.54 (1H,s, CH_2-OH), 3.82 (2H, s, -CH_2-OH), 4.12-4.26 (m, 4H, 4 & 6 –CH_2), 5.89 (1H, s, Ar-OH), 7.26-7.38 (2H, s, Ar-H), 6.15 (1H, d, *J* =8 Hz, P(S)-NH-C). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 47.2 (C-7), 64.5 (C-4 & C-6), 95.3 (C-5), 116.0 (2^1 & 6^1), 127.1 (3^1 &5^1), 136.1 (1^1), 139.1 (4^1). ^{31}P NMR (200 MHz, DMSO) δ: 72.02. LCMS (*m/z*): 388 (M^+). Anal.Calc. for $C_{10}H_{11}Cl_2N_2O_6PS$: C, 30.86; H, 2.85; N, 7.20%; found: C, 30.79; H, 2.80; N, 7.18%.

4-{[5-(hydroxymethyl)-5-nitro-2-oxido-1,3,2-dioxaphosphinan-2-yl]amino}phenol (3d):

Yield: 69%. Solid. mp: 138-140 °C. IR (KBr) υ_{max}: 1042 (P-O-$C_{aliphatic}$), 1274 (P=O), 1563 (NO_2), 3335 (P-NH), 3378 (-OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.69 (2H, s, -CH_2-OH), 4.15-4.30 (m, 4H, 4 & 6 -CH_2), 3.91 (1H, s, -OH), 7.06-7.38 (4H, m, Ar-H), 5.96 (1H, d, *J* =8 Hz, P(O)-NH-C), 9.44 (1H, s, Ar-OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 59.6 (C-7), 68.8 (C-4 & C-6), 95.9 (C-5), 116.1 (3^1 &5^1), 117.9 (2^1& 6^1), 135.9 (1^1), 148.5 (4^1). ^{31}P NMR (200 MHz, DMSO) δ: -14.54. LCMS (*m/z*): 304 (M^+). Anal. Calc. for $C_{10}H_{13}N_2O_7P$: C, 39.48; H, 4.31; N, 9.21%; found: C, 39.37; H, 4.27; N, 9.18%.

3-{[5-(hydroxymethyl)-5-nitro-2-sulfido-1,3,2-dioxaphosphinan-2-yl]amino}phenol (3e):

Yield: 60%. Solid. mp: 149-151 °C. IR (KBr) υ_{max}: 890 (P=S), 1056 (P-O-$C_{aliphatic}$), 1539 (NO_2), 3325 (P-NH), 3388 (-OH). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.78 (2H, s, -CH_2-OH), 3.99-4.18 (m, 4H, 4 & 6 –CH_2), 4.34 (1H, s, -OH), 7.26-7.41 (4H, m, Ar-H), 6.27 (1H, d, *J* =8 Hz, P(S)-NH-C), 6.74 (1H, s, Ar-OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 51.2 (C-7), 69.7 (C-4 & C-6), 88.9 (C-5), 101.1 (2^1), 111.1 (6^1), 130.3 (5^1), 140.1 (1^1), 160.3 (3^1), 190.1 (4^1). ^{31}P NMR (200 MHz, DMSO) δ: 65.65. LCMS (*m/z*): 320 (M^+). Anal. Calc. for $C_{10}H_{13}N_2O_6PS$: C, 37.50; H, 4.09; N, 8.75%; found: C, 37.43; H, 4.03; N, 8.72%.

[5-nitro-2-oxido-2-(pyridin-3-yloxy)-1,3,2-dioxaphosphinan-5-yl]methanol (3f):

Yield: 67 %. Solid. mp: 139-141 °C. IR (KBr) υ_{max}: 961 (P-O-($C_{aromatic}$)), 1015 (P-O-$C_{aliphatic}$), 1238 ((P)-O-$C_{aromatic}$), 1282 (P=O), 1540 (NO_2), 3375(-OH). ^{1}H NMR (500 MHz, DMSO-

d$_6$) *δ*: 3.66 (2H, s, -CH_2-OH), 3.71-3.88 (m, 4H, 4 & 6 –CH_2), 4.82 (1H, s, -OH), 7.86-8.24 (4H, m, Ar-H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) *δ*: 55.8 (C-7), 68.1 (C-4 & C-6), 91.0 (C-5), 120.3 (6^1), 125.5 (5^1), 140.3 (2^1), 142.8 (4^1), 156.3 (1^1). ^{31}P NMR (200 MHz, DMSO) *δ*: -11.20. LCMS (*m/z*): 290 (M^+). Anal. Calc. for $C_9H_{11}N_2O_7P$: C, 37.25; H, 3.82; N, 9.65%; found: C, 37.16; H, 3.77; N, 9. 63%.

[5-nitro-2-(4-nitrophenoxy)-2-sulfido-1,3,2-dioxaphosphinan-5-yl]methanol (3g):

Yield 60 %. Solid. mp: 135-137 °C. IR (KBr) υ_{max}: 786 (P=S), 965 (P-O-($C_{aromatic}$)), 1028 (P-O-$C_{aliphatic}$), 1230 ((P)-O-$C_{aromatic}$), 1542 (NO_2), 3392 (-OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ*: 3.95 (2H, s, -CH_2-OH), 4.31-4.72 (m, 4H, 4 & 6 –CH_2), 4.86 (1H, s, -OH), 7.22-7.34 (4H, m, Ar-H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) *δ*: 55.8 (C-7), 69.7 (C-4 & C-6), 91.7 (C-5), 121.1 (2^1 & 6^1), 125.3 (3^1 & 5^1), 146.1 (4^1), 156.1 (1^1). ^{31}P NMR (200 MHz, DMSO) *δ*: 62.21. LCMS (*m/z*): 350 (M^+). Anal. Calc. for $C_{10}H_{11}N_2O_8PS$: C, 34.29; H,3.17; N, 8.00%; found: C, 34.18; H, 3.12; N, 7.96%.

4-{[5-(hydroxymethyl)-5-nitro-2-oxido-1,3,2-dioxaphosphinan-2-yl]oxy}benzaldehyde (3h):

Yield: 65 %. Solid. mp: 119-121 °C. IR (KBr) υ_{max}: 963 (P-O-($C_{aromatic}$)), 1015 (P-O-$C_{aliphatic}$), 1239 ((P)-O-$C_{aromatic}$), 1293 (P=O), 1544 (NO_2), 3386 (-OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ*: 3.78 (2H, s, -CH_2-OH), 4.11-4.17 (m, 4H, 4 & 6 –CH_2), 4.63 (1H, s, -OH), 7.68-7.75 (4H, m, Ar-H), 9.92 (Ar-CHO). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) *δ*: 54.9 (C-7), 66.7 (C-4 & C-6), 87.8 (C-5), 115.9 (2^1 & 6^1), 130.5 (4^1), 132.3 (3^1 & 5^1), 155.1 (1^1), 190.2 (Ar-CHO). ^{31}P NMR (200 MHz, DMSO) *δ*: -15.82. LCMS (*m/z*): 317 (M^+). Anal. Calc. for $C_{11}H_{12}NO_8P$: C, 41.65; H, 3.81; N, 4.42%; found: C, 41.54; H, 3.76; N, 4.38%.

[2-(4-methoxyphenoxy)-5-nitro-2-sulfido-1,3,2-dioxaphosphinan-5-yl]methanol (3i):

Yield: 58 %. Solid. mp: 131-132 °C. IR (KBr) υ_{max}: 890 (P=S), 936 (P-O-($C_{aromatic}$)), 1027 (P-O-$C_{aliphatic}$), 1235 ((P)-O-$C_{aromatic}$), 1541 (NO_2), 3389 (-OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ*: 3.81 (3H, s, Ar-OCH_3), 3.95 (2H, s, -CH_2-OH), 4.08-4.16 (m, 4H, 4 & 6 –CH_2), 5.18 (1H, s, -OH), 6.68-7.21 (4H, m, Ar-H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) *δ*: 55.9 (C-7), 56.1 (-OCH_3), 68.2 (C-4 & C-6), 89.4 (C-5), 115.1 (3^1 & 5^1), 117.3 (2^1 & 6^1), 141.1 (1^1), 153.1 (4^1). ^{31}P NMR (200 MHz, DMSO) *δ*: 74.20. LCMS (*m/z*): 335 (M^+). Anal. Calc. for $C_{11}H_{14}NO_7PS$: C, 39.41; H, 4.21; N, 4.18%; found: C, 39.30; H, 4.17; N, 4.15%.

[2-(3-ethoxyphenoxy)-5-nitro-2-oxido-1,3,2-dioxaphosphinan-5-yl]methanol (3j):

Yield: 60 %. Solid. mp: 116-118 °C. IR (KBr) υ_{max}: 962 (P-O-($C_{aromatic}$)), 1075 (P-O-$C_{aliphatic}$), 1186 ((P)-O-$C_{aromatic}$), 1302 (P=O), 1533 (NO_2), 3358 (-OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ*: 1.32-1.38 (3H, t, Ar-O-CH_2-CH_3), 3.88 (2H, s, -CH_2-OH), 3.99-4.09 (m, 4H, 4 & 6 –CH_2), 4.12-4.18 (2H, q, Ar-O-CH_2-), 4.78 (1H, s, -OH), 7.61-7.77 (4H, m, Ar-H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) *δ*: 15.1 (Ar-O-CH_2-CH_3), 54.7 (C-7), 65.1 (Ar-O-CH_2-CH_3), 68.5 (C-4 & C-6), 91.7 (C-5), 102.1 (2^1), 106.1 (4^1), 119.1 (6^1), 130.2 (5^1), 150.1 (1^1), 161.3 (3^1). ^{31}P NMR (200 MHz, DMSO) *δ*: -19.21. LCMS (*m/z*): 333 (M^+). Anal. Calc. for $C_{12}H_{16}NO_8P$: C, 43.25, H, 4.84, N, 4.20%; found: C, 43.13; H, 4.77; N, 4.17%.

PHARMACOLOGY:

Antimicrobial activity:

In view of the report given by Schrader-Clark that all the organophosphorus compounds containing P=O(S) are inherently good phosphorylating agents of enzymes and possesses significant biological activity,[15] we had studied the antimicrobial activity of the compounds **3a-j** by screening with various bacteria like Staphylococcus aureus, Escherichia coli and fungi like Curvularia lunata, Fusarium oxysporium and the results were presented in **Table 1**.

Table 1
Antimicrobial activity of 3a-j.

Compound	Zone of inhibition/mm[a] ((µg/disc)							
	Bacteria (µg/disc)				Fungi (µg/disc)			
	Staphylococcus aureus[a]		*Escherichia coli*[a]		*Curvularia lunata*[a]		*Fusarium oxysporium*[a]	
	250	**500**	**250**	**500**	**250**	**500**	**250**	**500**
3a	17.2	18.9	16.6	17.6	15.5	19.1	17.3	17.9
3b	19.6	17.9	17.9	19.4	18.8	18.0	18.9	17.0
3c	18.5	18.1	18.1	18.3	17.9	17.1	18.3	18.0
3d	14.8	18.8	17.8	17.9	18.4	16.9	14.9	18.7
3e	17.1	18.0	18.5	16.0	18.1	17.0	18.1	18.5
3f	16.7	17.5	17.8	17.6	17.7	18.2	17.8	19.0
3g	18.5	15.9	16.9	18.8	19.1	14.7	15.6	17.5
3h	16.1	19.4	18.6	17.7	17.1	16.9	16.7	18.1
3i	13.2	18.4	17.7	18.8	16.3	17.0	18.1	18.3
3j	17.8	18.3	18.9	18.0	17.9	18.0	17.8	16.7
Penicillin[b]	20.0		19.0					
Griseofulvin[b]					18.5		18.5	

[a] ***Concentrations expressed in ppm***
[b]***Reference compounds***

Antibacterial activity:
Compounds **3a-j** were screened for their antibacterial activity (**Table 1**) against Staphylococcus aureus (gram positive) and Escherichia coli (gram negative) by the disc-diffusion method in Mueller- Hinton agar medium, at various concentrations (250, 500 mg/disc) in dimethyl formamide (DMF). These solutions were added to each filter disc and DMF was used as control. The plates were incubated at 35°C and examined for zone of inhibition around each disc after 12 h. The results were compared with the activity of the standard antibiotic Penicillin (250 mg/disc). The results were tabulated in Table 1 and they are graphically represented in Figure 1 and Figure 2 respectively below.

Figure 1
Antibacterial activity against Staphylococcus aureus

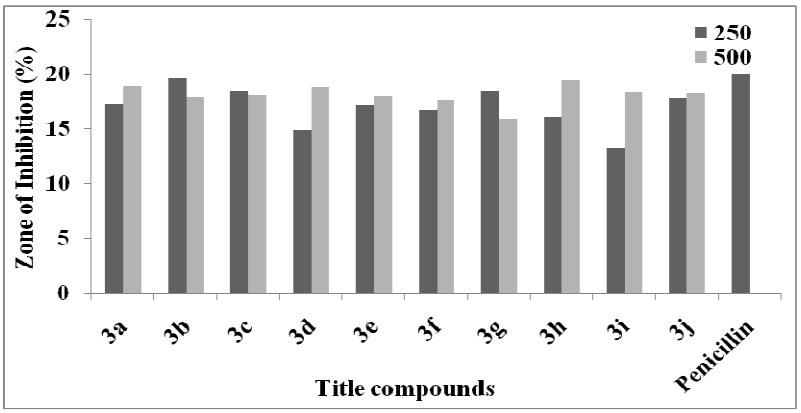
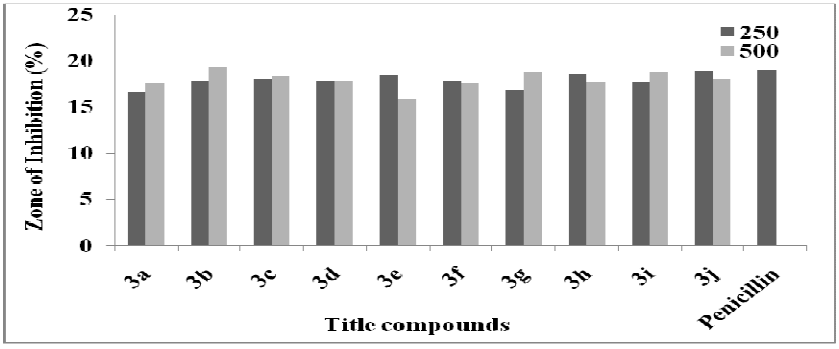


Figure 2
Antibacterial activity against Escherichia coli



Antifungal activity:

Then their antifungal activity1[16] were evaluated against Curvularia lunata and Fusarium oxysporium at different concentrations (250 & 500 mg/disc). Griseofulvin was used as the reference compound. Fungal cultures were grown on potato dextrose broth at 25°C and finally spore suspension was adjusted to10^5 spore/mL. Most of the compounds showed moderate activity against both bacteria and fungi. The results were summarized in Table 1 and they are graphically represented in Figure 3 and Figure 4 respectively below.

Figure 3
Antifungal activity against Curvularia lunata

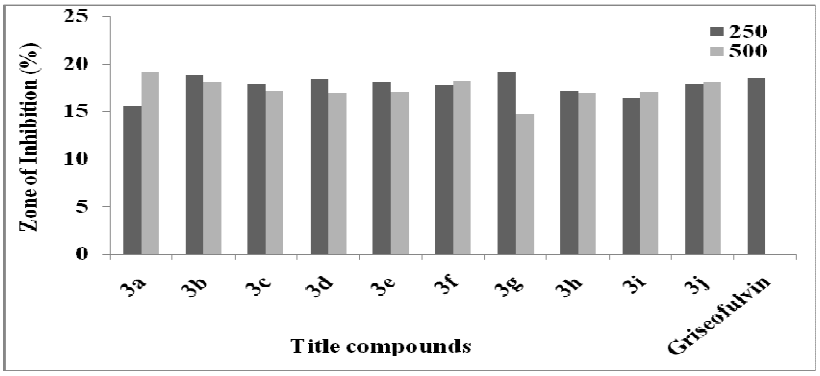
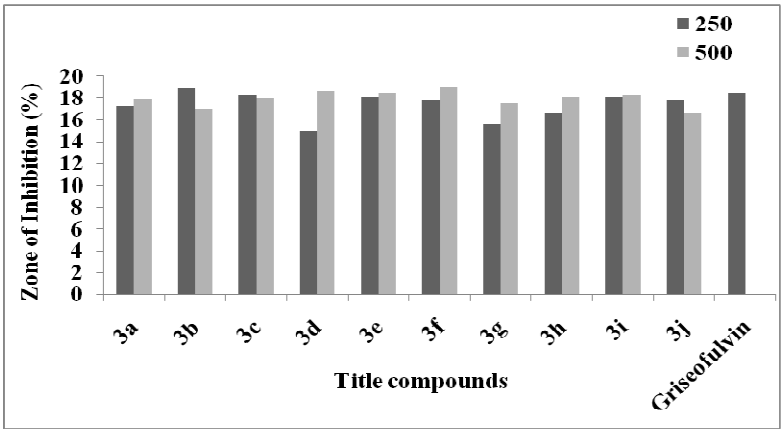


Figure 4
Antifungal activity against Fusarium oxysporium



RESULTS AND DISCUSSION

The synthesis of new 1,3,2-dioxaphosphinane derivatives **3a-j** is accomplished in a two-steps. The first step involves the cyclisation reaction of tris (hydroxy methyl) nitromethane (**3**) with $PXCl_3$ (X=S, O) in dry THF in the presence of TEA at 40-45 °C to afford the corresponding phosphoryl monochloride intermediates (**2**). In the second step the intermediate **2** was reacted with different substituted aromatic amines and with a few substituted phenols in *situ* in dry THF in the presence of TEA to afford the title compounds (**3a-j**) in good yields. The second step of the reaction was completed in 3 hours at 0-15°C with stirring. The progress of the reaction was monitored by TLC analysis at different time intervals and the crude products obtained after removing the solvent were purified by column chromatography on silica gel using ethylacetate and hexane (1:4) as a step grade mixture eluent. The compounds thus obtained were characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR and Mass spectral and elemental analysis.

The Infrared spectral data of all the compounds are given in the experimental part. All the compounds (**3a-j**) exhibited absorption bands for -OH, P-NH, P=O, P=S, NO_2, and P-O-C $_{aliphatic}$ in the regions 3358-3392, 3320-3340, 1255-1302, 778-890, 1533-1565, and 1015-1075 cm^{-1} respectively.[17,18] P-O-$C_{aromatic}$ for a few compounds (**3g-j**) gave two absorptions in the regions 935-960 and 1196-1236 cm^{-1} for P-O and O-C respectively. Analysis of ^{1}H, ^{13}C and ^{31}P NMR spectra of compounds confirmed the proposed structures of (**3a-j**) and their NMR spectral data are given in experimental part. The ^{1}H NMR spectra (500 MHz) of **3a-j** exhibited multiplets in the range of δ 3.69-4.72 accounting for the 4 and 6 methylene protons of the dioxaphosphinane.[19] The aromatic protons of **3a-j** resonated as multiplets at δ 6.68-7.99. The –NH proton signal was observed at δ 8.11-8.98 as a doublet (*J*=8-10 Hz). The –CH_2-OH protons of **3a-j** resonated at δ 4.50-5.89 as a singlet. The –CH_2-OH protons of **3a-j** resonated at δ 3.66-3.95 as a singlet. The remaining protons gave signals in the expected regions. The ^{13}C NMR spectral data of all the compounds were recorded and the data was given in the experimental part. The C-4 and C-6 resonated at δ 64.5-70.5, C-5 chemical shift appeared at δ 87.8-97.2 and C-7 signals were observed at δ 46.0-59.6. The CHO carbon gave a signal at δ 190.2. Other carbons gave chemical shifts in the expected regions.[20]

Compounds **3a-j** exhibited phosphorus-31 resonance signals in the range of 62.21-78.1 (P=S) and -21.12 to -11.2 (P=O) ppm.[21] The LC-MS of all the compounds were recorded and the presence of $M^{+\cdot}$ and characteristic daughter ions at their respective m/z values confirmed the proposed structures for **3a-j**. The C, H, N analysis data of all the compounds concurred with their structures.

The antimicrobial activity of the synthesized compounds specifically compounds 3b, 3c & 3j was good enough to inhibit the growth of various bacteria like Staphylococcus aureus, Escherichia coli and fungi like Curvularia lunata, Fusarium oxysporium at both the concentrations (250, 500 mg/disc) in dimethyl formamide (DMF).

CONCLUSION

In conclusion here we are reported the synthesis of new 1,3,2-dioxaphosphinane derivatives of tris (hydroxy methyl) nitromethane through phosphorylation with phosphorus oxy chloride/ thiophosphoryl chloride and with various phenolic compounds.

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