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Synthesis and antimicrobial activity of 4-substituted phenyl (11*H*,16*H*-5,6-dioxa-11a, 15b-diaza-5aλ^5-phosphabenzo[*b*]naphtha-[2, 3-*l*] fluoren-5-yl) ether

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Abstract

Synthesis of 4-substituted phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*] naphtha-[2, 3-*l*] fluoren-5-yl) ether (**4a-j**) were accomplished via two step process. It involves the prior preparation of monochloride intermediate (**2**) and its subsequent reaction with various phenols in dry tetrahydrofuran in the presence of TEA under reflux condition. These compounds were characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR and were found to exhibit potent antimicrobial activity.

Key words: Tri cyclic phosphoranes, PCl_5, Antimicrobial activity.

Introduction

An increasing interest has been paid for several years to the chemistry of phosphorus heterocycles due to their unique physical properties, specific chemical reactivity [1].Current literature status of organophosphorus heterocycles is poignant with the possibility of several applications not only in the life-processes but also in the several industrial sectors [2,3]**.** Organophosphorus heterocycles are being used as drugs in medicine[4], pesticides in agriculture[5]**,** chemical warfare agents in defense, flame retardant oil and polymer additives in the industry is well established, still vast scope exists for further discovery and development in this area. In view of the various applications of organophosphorus hetero cycles compounds, series of 4-substituted phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[b]naphtha-

[2,3-l]fluoren-5-yl ether(**4a-j**) have been successfully accomplished and their bio activity studies have been evaluated.

Material and Methods

Experimental

Phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho-[2,3-*l*]-fluoren-5-yl) ether

Synthesis of Phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho-[2,3-*l*]-fluoren-5-yl) ether was conveniently accomplished in a two step process. In the first step, a solution of phosphorus pent chloride (1.04 g, 0.005 mole) in dry tetrahydrofuran was added to a mixture of 2,2'-(1,2-phenyl bis (azanediyl)bis(methane) diphenol (1.6 g, 0.005 mole) and TEA (triethylamine) in THF (25 mL) at 0°C over a period of 30 minutes. After addition, the temperature of the reaction mixture was slowly raised to room temperature and continued for 1h and then refluxed at 60°C for3h. The solid triethylamine hydrochloride was filtered and the solvent was concentrated in a rotaevaporator. To the concentrated solution in THF a solution of phenol (0.47 g, 0.005 mole) in THF was added at room temperature in the presence of TEA and then refluxed at 60°C for 2h. Progress of the reaction was monitored by TLC analysis. After the removal of solid triethylamine hydrochloride was removed and solvent was evaporated in a rotaevaporator under reduced pressure. The obtained crude product was purified by column chromatography on 60-120 silica gel mesh using ethyl acetate : hexane (1:2) as eluent to obtain 1.35 g (65%), mp 190-192°C of pure compound **4a**.

Phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho-[2,3-*l*]-fluoren-5-yl) ether (4a): Yield 62 %, Colour less solid, mp 190-192 ^{0}C, IR (KBr) cm^{-1}: 930 (O-C), 1230 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.42-7.45 (17H, m, Ar-H), 5.09- 4.91 (4H, m, -CH_2-); ^{13}C-NMR data: 52.5 (C-4 and C-14), 129.7 (C-4a and C-13a), 130.6 (C-5 and C-13), 123.3 (C-6 and C-12), 130.6 (C-7 and C-11), 119.9 (C-8 and C-10), 149.6 (C-8a and C-9a), 129.5 (C-16 and C-21), 113.0 (C-17 and C-20), 119.1 (C-18 and C-19), 153.0 (C-1'), 123.6 (C-2' and C-6'), 132.0 (C-3' and C-5'), 132.1(C-4'); ^{31}P NMR data: δ 42.13; FAB-MS m/z: 440 (M+H); Anal. Calcd for $C_{26}H_{21}N_2O_3P$: C, 70.90.; H, 4.81; N, 6.36. Found C, 70.85; H, 4.77; N, 6.30.

4-fluoro phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho-[2,3-*l*] fluoren-5-yl) ether(4b): Yield 60 %, Colour less solid,mp 197-199 ^{0}C IR (KBr) cm^{-1}: 940 (O-C), 1235 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.45-7.55 (16H, m, Ar-H), 4.25- 4.60 (4H, m, -CH_2-); ^{31}P NMR data: δ 37.25; Anal. Calcd for $C_{26}H_{20}FN_2O_3P$: C, 68.12.; H, 4.40; N, 6.11. Found C, 68.08; H, 4.36; N, 6.06.

4-methoxyphenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho-[2,3-*l*] fluoren-5-yl) ether (4c): Yield 65 %, Colour less solid, mp 189-191 ^{0}C IR (KBr) cm^{-1}: 930 (O-C), 1230 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.35-7.69 (16H, m, Ar-H), 4.50-4.95 (4H, m, -CH_2-), 365 (3H, s, OCH_3); ^{13}C-NMR data: 50.5 (C-4 and C-14), 128.0 (C-4a and C-13a), 132.6 (C-5 and C-13), 121.9 (C-6 and C-12), 129.6 (C-7 and C-11), 121.0 (C-8 and C-10), 149.5 (C-8a and C-9a), 128.3 (C-16 and C-21), 112.0 (C-17 and C-20), 117.1 (C-18 and C-19), 143.2 (C-1'), 115.2 (C-2' and C-6'), 118.0 (C-3' and C-5'), 153.1(C-4'), 54.9 (OCH_3); ^{31}P NMR data: δ 42.13;

FAB-MS m/z: 470 (M+H); Anal. Calcd for $C_{27}H_{23}N_2O_4P$: C, 68.90; H, 4.93; N, 5.95. Found C, 68.85; H, 4.89; N, 5.90.

4-methyl phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo-[*b*]naphtho-[2,3-*l*] fluoren-5-yl) ether (4d): Yield 62 %, Colour less solid, mp 206-208 ^{0}C IR (KBr) cm^{-1}: 890 (O-C), 1245 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.25-7.25 (16H, m, Ar-H), 4.15- 4.50 (4H, m, -CH_2-), 2.53 (3H, s, ar-CH_3); ^{13}C-NMR data: 50.3 (C-4 and C-14), 128.9 (C-4a and C-13a), 130.2 (C-5 and C-13), 123.1 (C-6 and C-12), 129.2 (C-7 and C-11), 120.1 (C-8 and C-10), 151.6 (C-8a and C-9a), 129.7 (C-16 and C-21), 113.2 (C-17 and C-20), 118.4 (C-18 and C-19), 153.1 (s, 1C,C-1'), 116.2 (C-2' and C-6'), 132.5 (C-3' and C-5'), 133.1 (C-4'), 20.8 (C-CH_3(4'); ^{31}P NMR data: δ 40.15; FAB-MS m/z: 454 (M+H); Anal. Calcd for $C_{27}H_{23}N_2O_3P$: C, 71.36; H, 5.10; N, 6.16. Found C, 71.30; H, 5.05; N, 6.10.

4-chlorophenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho-[2,3-*l*]fluo -ren-5-yl) ether (4e): Yield 64 %, Colour less solid, mp 234-236 ^{0}C IR (KBr) cm^{-1}: 910 (O-C),1210 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.60-7.85 (16H, m, Ar-H), 4.25- 4.60 (4H, m, -CH_2-); ^{31}P NMR data: δ 46.50; Anal. Calcd for $C_{26}H_{20}N_2O_3PCl$: C, 65.76; H, 4.25; N, 5.90. Found C, 65.71; H, 4.20; N, 5.85.

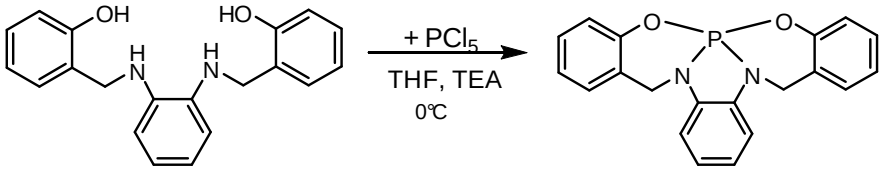
4-bromophenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtha-[2,3-*l*]flu -oren-5-yl) ether (4f): Yield 65 %, Colour less solid, mp 241-244^{0}C IR (KBr) cm^{-1}: 1216 (O-C), 913 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.35-7.60 (16H, m, Ar-H), 4.15- 4.50 (4H, m, -CH_2-); ^{31}P NMR data: δ 41.23; Anal. Calcd for $C_{26}H_{20}N_2O_3PBr$: C, 60.13; H, 3.88; N, 5.39. Found C, 60.09; H, 3.82; N, 5.33.

4-nitrophenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo[*b*]naphtho[2,3-*l*]fluo - ren-5-yl) ether (4g): Yield 67 %, Colour less solid, mp 226-228 ^{0}C IR (KBr) cm^{-1}: 1214 (O-C), 918 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.30-8.20 (16H, m, Ar-H), 4.75-5.25 (4H, m, -CH_2-); ^{13}C-NMR data: 51.3 (C-4 and C-14), 127.9 (C-4a and C-13a), 130.0 (C-5 and C-13), 122.1 (C-6 and C-12), 129.9 (C-7 and C-11), 120.9 (C-8 and C-10), 150.6 (C-8a and C-9a), 128.7 (C-16 and C-21), 115.2 (C-17 and C-20), 119.4 (C-18 and C-19), 158.1 (C-1'), 126.2 (C-2' and C-6'), 116.5 (C-3' and C-5'), 141.2 (C-4'); ^{31}P NMR data: δ 39.12; FAB-MS m/z: 485 (M+H); Anal. Calcd for $C_{26}H_{20}N_3O_5P$: C, 64.33; H, 4.15; N, 8.66. Found C, 64.29; H, 4.10; N, 8.60.

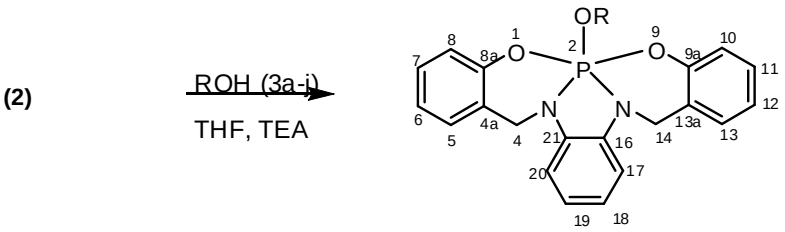
2,4-dichlorophenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo-[*b*]naphtho[2,3-*l*] fluoren-5-yl) ether (4h): Yield 60 %, Colour less solid, mp 214-216 ^{0}C IR (KBr) cm^{-1}: 920 (O-C),1220 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.80-7.79 (15H, m, Ar-H), 4.35-4.80 (4H, m, -CH_2-); ^{31}P NMR data: δ 40.15; Anal. Calcd for $C_{26}H_{19}N_2O_3PCl_2$: C, 61.31; H, 3.76; N, 5.50. Found C, 61.25; H, 3.72; N, 5.45.

2,4-dimethylphenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo-[*b*]naphtho[2,3-*l*]fluoren-5-yl) ether (4i): Yield 67 %, Colour less solid,mp 245-247 ^{0}C IR (KBr) cm^{-1}: 915 (O-C), 1215 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.40-7.40 (16H, m, Ar-H), 4.35-4.80 (4H, m, -CH_2-), 2.52 (6H, s, Ar-CH_3); ^{31}P NMR data: δ 36.15; Anal. Calcd for $C_{28}H_{25}N_2O_3P$: C, 71.78; H, 5.38; N, 5.98. Found C, 71.73; H, 5.32; N, 5.93.

3-chloro-4-methylphenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phosphabenzo-[*b*]naphtho [2,3-*l*]fluoren-5-yl) ether (4j) Yield 67 %, Colour less solid, mp 229-231^{0}C IR (KBr) cm^{-1}: 920 (O-C), 1230 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.60-7.89 (15H, m, Ar-H), 4.35-4.80 (4H, m, -CH_2-), 2.50 (3H, s, Ar-CH_3); ^{31}P NMR data: δ 37.15; Anal. Calcd for $C_{27}H_{22}N_2O_3PCl$: C, 66.33; H, 4.54; N, 5.73. Found C, 66.28; H, 4.50; N, 5.69.



(1) **(2)**



(4a-j)

Compd.	R	Compd.	R
3a & 4a	-C_6H_5	**3f & 4f**	-$C_6H_4Br(4)$
3b & 4b	-$C_6H_4F(4)$	**3g & 4g**	-$C_6H_4NO_2(4)$
3c & 4c	-$C_6H_4OCH_3(4)$	**3h & 4h**	-$C_6H_3Cl_2(2,4)$
3d & 4d	-$C_6H_4CH_3(4)$	**3i & 4i**	-$C_6H_4(CH_3)_2$ (2)(4)
3e & 4e	-$C_6H_4Cl(4)$	**3j & 4j**	-$C_6H_3Cl(3)(CH_3)(4)$

Scheme -1

Results and Discussion

A new class of novel 4-substituted phenyl (11*H*, 16H-5, 6-dioxa-11a, 15b-diaza-5aλ^5-phosphabenzo[*b*]naphtha-[2, 3-*l*] fluoren-5-yl) ether (**4a-j**) have been synthesized in a two step process. In the first step the intermediate monochloride (**2**) was prepared by the cyclocondensation of 2, 2'-(1, 2-phenylene bis (azenedily) bis methane) (**1**) with phosphorus pentachloride in presence of triethylamine in anhydrous tetrahydrofuran (THF) at 60 ^{0}C for 3h.

In the second step the intermediate monochloride was further reacted with various phenols in presence of triethylamine in anhydrous tetrahydrofuran at at 60 ^{0}C for 2h. Progress of the reaction was monitored by TLC analysis.

IR absorption bands for (P-O-$C_{aromatic}$) C-O and P-O in the region 1210-1238, 935-911 cm^{-1} respectively were observed for **4a-j** [6]. The aromatic hydrogens of compounds **4a-j** gave multiplets in the region δ 6.25-8.25. The bridged methylene protons signals appeared as multiplets in the region δ 4.15-5.09 indicating their non-equivalence [7] and coupling with phosphorus.

The ^{13}C NMR spectral data for **4a, 4c, 4d** & **4g** are given in the experimental section. The methylene C-4&C-14 resonated as singlets in the region of 50.3-52.5 ppm [8]. The remaining carbon signals were observed in their expected regions.

The compounds **4a-j** were exhibited a singlet in their ^{31}P NMR spectra in the region 36.15-46.50 ppm [9]. FAB Mass of **4a, 4c, 4d** & **4g** gave molecular ions and diagnostic daughter ions at their expected m/z values.

Table 1: Antibacterial activity of compounds (4a-j)

Compd.	**Zone of inhibition**			
	Staphylococcus aureus		***Escherichia* coli**	
	100 [a] μg/disc	**50 [a] μg/disc**	**100[a] μg/disc**	**50 [a] μg/disc**
4a	8	5	7	5
4b	6	4	7	4
4c	7	4	6	4
4d	5	3	8	6
4e	5	-	5	-
4f	6	4	6	5
4g	6	4	5	-
4h	7	5	6	5
4i	5	3	8	7
4j	7	5	7	4
Penicillin	12	8	11	8

[a]Concentration in ppm

Antibacterial Activity

Antibacterial activity of all the title compounds (**4a-j)** was evaluated against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve) at different concentrations [10] (100, 50 ppm) **Table 1**. All the compounds are less active against both the bacteria when compared to the reference compound Penicillin.

Antifungal Activity

The antifungal activity [10] of compounds (**4a-j**) was tested against the growth of *Aspergillus Niger* and *Curvularia lunata* at various concentration (100, 50 ppm) and the results were presented in **Table 2** and Griseofulvin was used as the standard reference compound. Majority of the title compounds showed low antifungal activity against both the fungi.

Table 2: Antifungal activity of compounds (4a-j)

Compd.	**Zone of inhibition**			
	Asperigillus niger		***Curvularia lunatai***	
	100 [a] µg/disc	**50 [a] µg/disc**	**100[a] µg/disc**	**50 [a] µg/disc**
4a	8	5	7	4
4b	7	4	6	4
4c	5	4	6	5
4d	6	4	5	3
4e	7	5	4	4
4f	4	3	6	4
4g	5	4	5	3
4h	6	5	5	-
4i	4	-	6	3
4j	4	-	4	-
Griseofulvin	13	9	14	11

[a]*Concentration in ppm*

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