Synthesis, and antimicrobial activity of 2,10-dichloro–6- substituted aminobenzyl–12*H* –dibenzo [*d, g*][1,3,2]dioxaphosphocin– 6–oxides

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Abstract

Novel 2,10-dichloro-6-substituted aminobenzyl-12*H*-dibenzo[d,g][1,3,2] dioxaphosphocin-6-oxides (**5a-n**) have been synthesized in excellent yields from three component one-pot reaction of aldehydes, anilines and 2,10-dichloro-12*H*-dibenzo [d,g][1,3,2] dioxaphosphoro-bromodite(**3**)/corresponding cyclic hydrogen phosphite(**4**) in dry toluene. The title compounds were characterized by elemental analysis, IR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, and mass spectral studies and exhibited moderate antimicrobial activity.

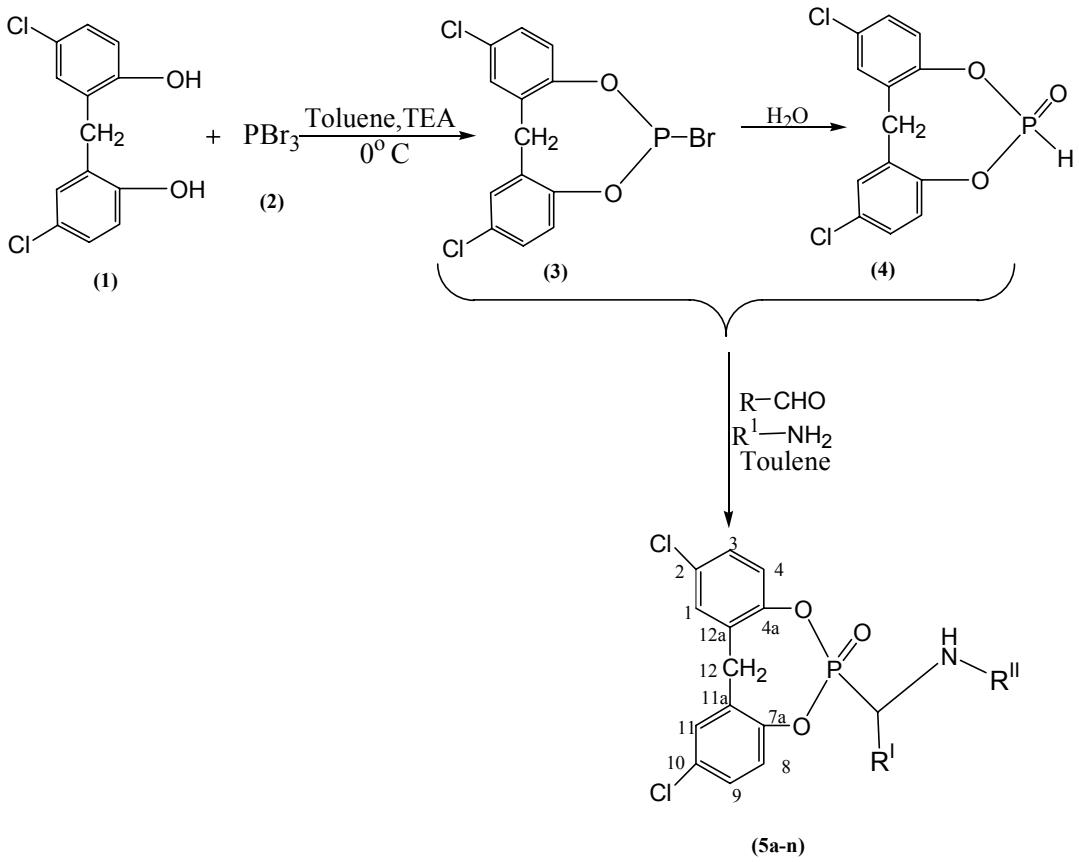
Keywords: 5,5'- Dichloro-2,2'- dihydroxy biphenylmethane, 2,10-dichloro-12*H*-dibenzo[*d,g*] [1,3,2] dioxaphosphorobromodite, dioxaphosphocin, antimicrobial activity

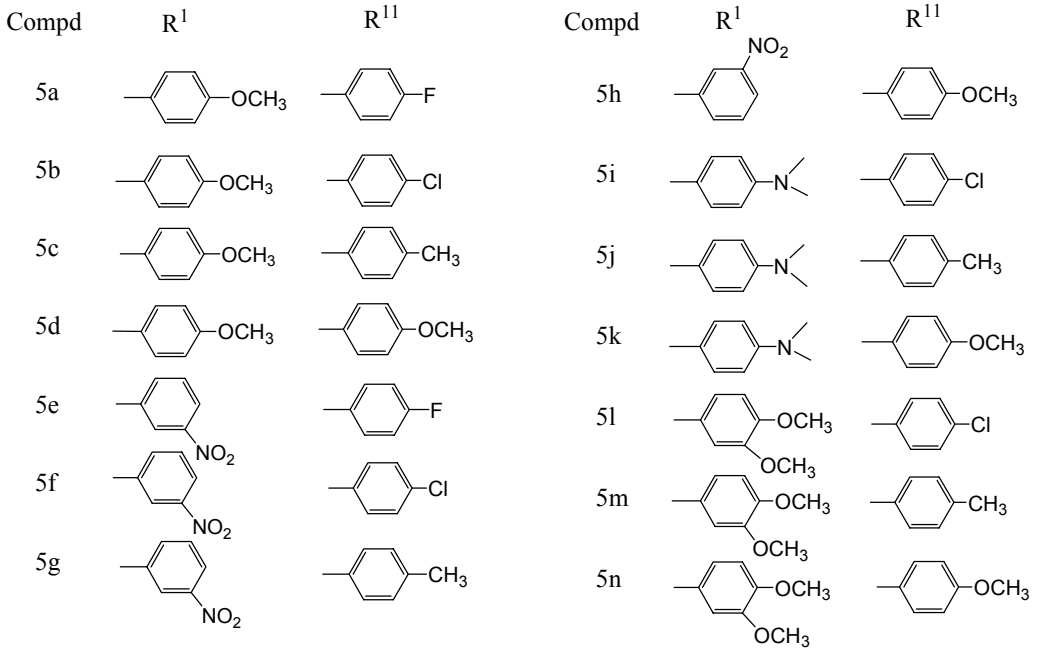
Introduction

A new class of α-aminophosphonates structurally resembling α-amino acids[1] has attracted much interest as enzyme inhibitors,[2] antibiotics, pharmacological agents,[3] and herbicides.[4] A large number of α-aminophosphonates have been synthesized by using acyclic hydrogen phosphites over the past few years under different reaction conditions.[5-10] However the preparation of α-aminophosphonates from cyclic hydrogen phosphites is rare. In view of this, preparation of α-aminophosphonates in a one-pot three component reaction containing a cyclic hydrogen phosphite, an aldehyde and amine has been accomplished and the products have been characterized by elemental analysis, IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and mass spectral studies. Their antimicrobial activity has also been evaluated.

Results and Discussion

The synthesis (Scheme 1) involves cyclisation of 5,5'-dichloro-2,2'-dihydroxybiphenyl-methane(**1**) with phosphorus tribromide(**2**) at 0°C under inert and dry conditions in toluene to afford the corresponding phosphorobromodite (**3**). Hydrolysis of **3** gave the corresponding cyclic hydrogen phosphite (**4**)[11]. The reaction of both phosphorobromodite (**3**)/ cyclic hydrogenphosphite (**4**) with various aldehydes and amines in dry toluene at 50-60°C afforded the title compounds in good yields. They were purified by column chromatography on 60-120 mesh silica gel using ethyl acetate-hexane (1:2) as an eluent. Out of the two routes carried out for the preparation of the title compounds (**5a-n**), that involving cyclic hydrogen phosphite (**4**) is found to be better than that of the phosphorobromodite (**3**). Further the intermediate (**3**) is highly hygroscopic and difficult to handle when compared to the cyclic hydrogen phosphite (**4**) which could obtained as a stable product in high yield.





Scheme 1

The IR spectra of **(5a-n)** showed absorption bands[12-14] at 3305-3396, 1226-1267 and 763-745cm^{-1} for NH, P=O and P-C respectively. Their ^{1}H NMR spectra showed complex multiplets at δ 6.54 – 8.52 for aromatic protons. The bridged methylene protons (12H) signals appeared as a doublet in the region 3.62-3.74 ppm (J = 13.2–14.8 Hz) and another doublet of doublet in the region 4.24-4.45 ppm (J = 3.7-4.5 Hz) indicating their non-equivalance.[15,16] The coupling constant J = 13.2 – 14.8 Hz is rationalized as geminal coupling ($^{2}J_{H\text{-}H}$) between bridged methylene protons. The small coupling (J = 3.7-4.5 Hz) is attributed to the long range coupling of one of the methylene protons ($^{5}J_{H\text{-}P}$) with phosphorus. The dioxaphosphocin ring system in all these compounds **(5a-n)** appeared to exist in a boat-like conformation (**Figure 2**) which facilitates the coupling between the phosphorus and one of the methylene protons[16]. The N-H proton resonated as a singlet at 5.24 -6.28 ppm.

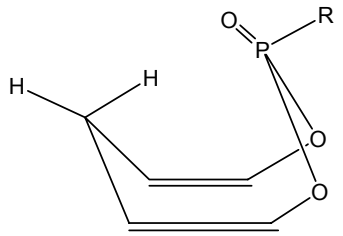
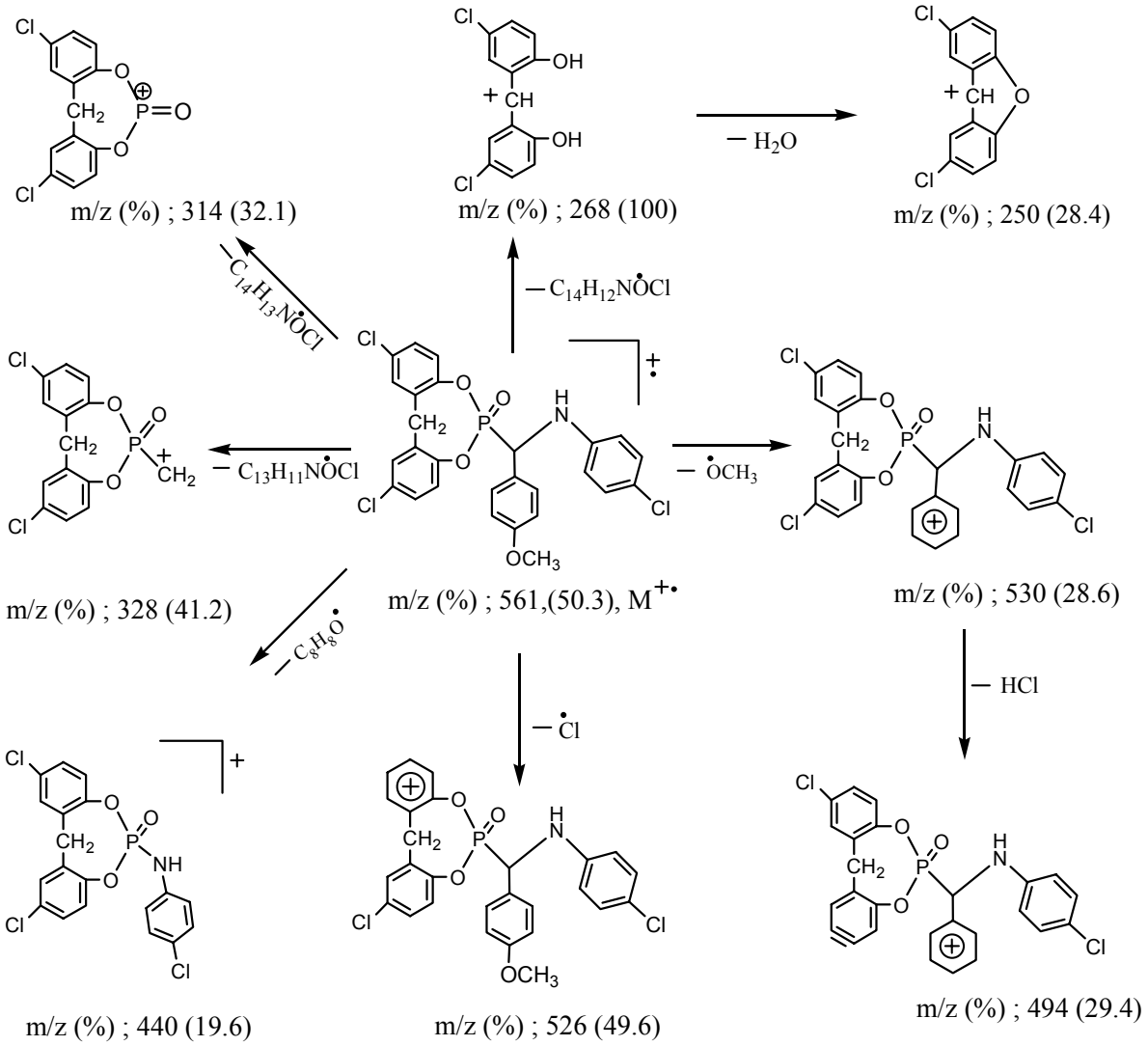


Figure 2

Their ^{13}C chemical shifts were interpreted based on comparison with those of basic structural units present in them. The oxygen-bearing C(4a) and C(7a) gave signals in the down field region

at 149.0-151.4 ppm. The doublet at δ121.0-123.0 was assigned to the C-11a & C-12a. The chemical shift in the region 130.1-132.3 ppm was assigned to chlorine-bearing C-2 & C-10. The α-carbon of the side chain directly attached to phosphorus exhibited a doublet at δ 58.2- 59.6 ($^{2}J_{C\text{-}P}$ = 131.4 -138.2 Hz) due to its coupling with phosphorus. The bridged C-12 gave a singlet at 33.2– 36.6 ppm. ^{31}P NMR chemical shifts appeared as singlets in the region 30.2 - 45.4 ppm[17].

All the compounds exhibited molecular ion peaks at their respective molecular weights in their mass spectra. The mass spectrum of **5b** is rationalized in **Scheme 2**.



Scheme 2

Antimicrobial activity

Compounds **5a-n** were screened for their antibacterial activity against *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram-ve) by the disc-fusion method in nutrient 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 24 h. The results were compared with the activity of the standard antibiotic Penicillin (250mg/disc). Their antifungal activities were evaluated against *Aspergillus niger* and *Fusarium oxysporium* at different concentrations (250,500 mg/disc) and Griseofulvin was used as the reference compound. Fungal cultures were grown on potato dextrose broth at 25°C and spore suspension was adjusted to 10^5 spore/mL. Most of the compounds showed moderate activity against bacteria and low activity on fungi.

Table 1. Antibacterial activity of **5a-n**

Compd	Zone of inhibition(mm)			
	Staphylococcus aureus		*Escherichia coli*	
	250[a]mg/disk	500[a]mg/disk	250[a]mg/disk	500[a]mg/disk
5a	8	12	12	17
5b	7	11	15	19
5c	8	13	13	19
5d	7	11	14	18
5e	7	10	16	26
5f	7	11	13	22
5g	5	12	13	21
5h	8	10	15	23
5i	6	09	14	22
5j	7	12	14	23
5k	7	11	16	25
5l	6	13	15	22
5m	7	12	13	21
5n	8	11	14	23
Penicillin[b]	12		24	

[a] Concentration in ppm, [b] standard reference.

Table 2. Antifungal activity of 5a-n

Compd	Zone of inhibition(mm)			
	Curvularia lunata		*Asperigillus niger*	
	250[a]mg/disk	500[a]mg/disk	250[a]mg/disk	500[a]mg/disk
5a	16	10	13	16
5b	14	08	14	20
5c	15	11	10	19
5d	13	09	14	19
5e	14	10	09	15
5f	18	12	12	17

5g	15	10	13	17
5h	15	09	14	18
5i	16	08	15	20
5j	17	11	11	19
5k	16	10	14	20
5l	16	09	15	19
5m	15	08	14	23
5n	14	09	16	24
Griseofulvin[b]	23		26	

[a] Concentration in ppm, [b] Standard reference.

Experimental Section

General Procedures. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and were uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr pellets on Perkin Elmer 1000 unit. The ^{1}H, ^{13}C & ^{31}P NMR spectra were recorded on Varian Gemini 300 and Varian AM X 400 MHz NMR spectrometers operating at 300 or 400 MHz for ^{1}H, 75.46 or 100.57 MHz for ^{13}C and 121.7 MHz for ^{31}P. All compounds were dissolved in DMSO-d_6 and chemical shifts were referenced to TMS (^{1}H &^{13}C) and 85% H_3PO_4 (^{31}P). Microanalytical data were obtained from Central Drug Research Institute, Lucknow, India.

Synthesis of 2,10-dichloro-12*H*-dibenzo [*d,g*] [1,3,2]dioxaphosphorobromodite (3)/ corresponding cyclic hydrogen phosphite(4). A solution of slight excess of phosphorus tribromide (1.35 g, 0.005 mole) in dry toluene(25 mL) was added dropwise to a well stirred solution of 5,5'-dichloro 2,2'-dihydroxy biphenyl methane (1.35 g, 0.005 mole) and triethylamine (1.01 g, 0.001 mole) in dry toluene (20 mL) at 0°C. After addition, the temperature of the reaction mixture was slowly raised and kept at 50-60°C for 2 hours. The reaction was monitored by TLC analysis. After cooling to room temperature, it was filtered to remove triethylamine hydrobromide. The filtrate was rotaevaporated. The residue (**3**), after washing with petroleum ether, was used for the next step without further purification.

To a cold solution of **3** in dry toluene, was added water (50 mL) dropwise with effective stirring. The first few drops of water were added very slowly at 5-10°C. After an additional one hour at room temperature the organic layer was separated, diluted with toluene and washed successively with 5% HCl solution (15 mL), 5% $NaHCO_3$ solution (30 mL) and water. The dried toluene layer was removed in *vacuo*. The oily compound obtained solidified when refrigerated overnight. It was recrystallised from petroleum ether (60-80°C). m.p.147-149°C. Yield 82%.

2,10-Dichloro- 6- (4-chlorophenyl) amino-4-methoxybenzyl -12*H*-dibenzo[*d,g*] [1,3,2] dioxaphosphocin-6-oxide(5b). General procedure

To a concentrated solution of phosphorobromodite **3**, 4-methoxybenzaldehyde (0.73 g, 0.005 mole) and 4-chloroaniline (0.64 g, 0.005 mole) were added and the solution was refluxed for one hour. The progress of the reaction was monitored by TLC analysis. After cooling to room temperature the solvent was removed in *vacuo* and the residue was washed with petroleum ether and column chromatographed on 60-120 mesh silica gel using ethyl acetate: hexane (1:2) as an eluent Yield 2.39 g.

Alternatively the same compound **5b** was synthesized by refluxing hydrogen phosphite (**4**) (1.58 g, 0.005 mole), 4-methoxybenzaldehyde (0.73 g, 0.005 mole) and 4-chloroaniline (0.64 g, 0.005 mole) in dry toluene for 30 minutes.

Yield 2.39 (85%), m.p. 159 – 162°C; IR (KBr): 3337 (CN-H), 1252 (P=O), 756 (P-C) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.55-7.96 (m, 14 H), 5.61 (s, 1H, N-H), 5.12 (d, *J*= 23.2Hz, 1H, P-CH), 4.36 (dd, *J* = 13.2, 3.9 Hz,1H, CH_2), 3.59 (d, *J* = 13.5 Hz,1H, CH_2), 3.42 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6); δ 129.52(s, 2C, C-1 & 11), 132.01 (s, 2C, C-2 & 10), 128.38 (s, 2C, C-3 & 9), 124.63 (s, 2C, C – 4 & 8), 149.92 (d, *J*=7.1 Hz, 2C, C-4a & 7a), 132.58 (s, 2C, C -11a & 12a), 33.05 (s, 1C, C -12), 126.63 (s, 1C, C- 1'), 129.59 (s, 2C, C- 2' & 6'), 114.49 (s, 2C, C – 3' & 5'), 155.70 (s, 1C, C-4'), 149.29 (s,1C, C-1"), 118.24 (s, 2C, C-2" & 6"), 130.65 (s, 2C, C - 3" & 5"), 125.42 (s, 1C, C- 4"), 55.08 (d, *J* = 131.4 Hz,1C,P-CH), 54.3 (s,1C,OCH_3). ^{31}P NMR (DMSO-d_6): δ 35.25 Mass data 561(50.3), 530 (28.6), 526(29.4), 494 (49.6), 440 (19.6), 328 (41.2), 314 (32.1), 268 (100), 250 (28.4). *Anal.* Calcd for $C_{27}H_{21}NO_4Cl_3P$: C, 57.83; H, 3.77; N, 2.50: Found: C, 57.94; H, 3.84; N, 2.56 %.

2,10-Dichloro-6-(4-fluorophenyl)amino-4-methoxybenzyl-12*H*-dibenzo[*d,g*]1,3,2] dioxaphosphocin 6-oxide (5a). Yield 2.26 (83%), m.p. 182 – 185°C; IR (KBr) : 3309 (CN-H), 1234 (P=O), 749 (P-C) cm^{-1}; ^{1}H NMR: δ 6.80-7.81 (m, 14 H), 5.52 (brs, 1H, N-H), 5.18 (d, *J*= 23.4, 1H, CH_2) 3.38 (s,3H, OCH_3); ^{13}C NMR: δ 129.49(s, 2C, C-1 & 11), 131.84 (s, 2C, C-2 & 10), 128.37 (s, 2C, C-3 & 9), 124.61 (s, 2C, C - 4 & 8), 149.04 (d, *J*= 6.9 Hz, 2C, C-4a & 7a), 133.58 (d, *J*= 4.3 Hz, 2C, C -11a & 12a), 33.08 (s, 1C, C -12), 126.84 (s, 1C, C- 1'), 129.72 (s, 2C, c- 2' & 6'), 114.2 (s, 2C, C – 3'& 5'), 156.56 (s, 1C, C-4'), 148.51 (s,1C, C-1"), 117.87 (s, 2C, C-2" & 6"), 115.66 (s, 2C, C - 3" & 5"), 154.23 (s, 1C, C- 4"), 55.27(d, *J* = 136.3 Hz, 1C,P-CH), 54.37(s,1C,OCH_3). ^{31}P NMR: δ 37.19 *Anal.* Calcd for $C_{27}H_{21}NO_4FCl_2P$: C, 60.01; H, 4.50; N, 2.50; Found: C, 60.63; H, 4.55; N, 2.57%

2,10-Dichloro-6-(4-methylphenyl)amino-4-methoxybenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5c). Yield 2.33 (86%), m.p. 174 – 176°C; IR (KBr) : ν 3342 (CN-H), 1258 (P=O), 761 (P-C) cm^{-1}; ^{1}H NMR: δ 8.12 - 6.72 (m, 14 H), 5.72 (s, 1H, N-H), 5.06 (d, *J*= 24.1 Hz, 1H, P-CH), 4.28 (dd, *J* = 13.2,3.8 Hz, 1H, CH_2), 3.67 (d, *J* = 13.7 Hz, 1H, CH_2), 3.36 (s, 3H, OCH_3), 1.92 (s, 3H, CH_3); ^{13}C NMR; δ 129.52 (s, 2C, C-1 & 11), 132.01 (s, 2C, C-2 & 10), 123.51 (s, 2C, C-3 & 9), 124.67 (s, 2C, C– 4 & 8), 148.11 (d, *J*= 7.3 Hz 2C, C-4a & 7a), 133.61 (d, *J*= 4.2 Hz 2C, C -11a & 12a), 33.18 (s, 1C, C -12), 127.68 (s, 1C, C- 1'), 129.78(s, 2C, C- 2' & 6'), 114.12 (s, 2C, C – 3' & 5'), 154.87 (s, 1C, C-4'), 149.01 (s,1C, C-1"), 118.52 (s, 2C,

C-2" & 6"), 130.56 (s, 2C, C - 3" & 5"), 128.09 (s, 1C, C- 4"), 55.58 (d, *J* = 137.5 Hz, 1C, P-CH), 54.31 (s, 1C, OCH_3), 20.80 (s,1C, C - 4" (CH_3)); ^{31}P NMR: δ 38.29 *Anal.* Calcd for $C_{28}H_{24}NO_4Cl_2P$: C, 62.24; H, 4.47; N, 2.59; Found: C, 62.29; H, 4.52; N, 2.68%

2,10-Dichloro-6-(4-methoxyphenyl)amino-4-methoxybenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5d). Yield 2.32 (83%), m.p. 203-206°C; IR (KBr) : 3355 (CN-H), 1248 (P=O), 756 (P-C) cm^{-1}; ^{1}H NMR: δ 7.82-6.54 (m, 14 H), 5.79 (s, 1H, N-H), 4.98 (d, *J*= 23.8 Hz, 1H, P-CH), 4.37 (dd, *J* = 13.2,3.4 Hz, 1H, CH_2), 3.69 (d, *J* = 13.8 Hz, 1H, CH_2), 3.42, 3.33 (s, 6H, $(OCH_3)_2$); ^{13}C NMR; δ 129.34(s, 2C, C-1 & 11), 131.97 (s, 2C, C-2 & 10), 128.81 (s, 2C, C-3 & 9), 124.13 (s, 2C, C – 4 & 8), 148.32 (d, *J*= 7.1 Hz, 2C, C-4a & 7a), 133.92 (d, *J*= 4.3 Hz, 2C, C -11a & 12a), 33.24 (s, 1C, C -12), 127.57 (s, 1C, C- 1'), 129.67 (s, 2C, C- 2' & 6'), 113.97 (s, 2C, C – 3' & 5'), 156.78 (s, 1C, C-4'), 145.09 (s,1C, C-1"), 117.92 (s, 2C, C-2" & 6"), 116.58 (s, 2C, C - 3" & 5"), 150.12 (s, 1C, C- 4"), 55.11 (d, *J* = 136.3 Hz, 1C, PCH), 54.9(s, 2C, $(OCH_3)_2$); ^{31}P NMR: δ 35.25 *Anal.* Calcd for $C_{28}H_{24}NO_5Cl_2P$: C, 60.45; H, 4.35; N, 2.52; Found: C, 60.53; H, 4.44; N, 2.58%

2,10-Dichloro-6-(4-fluorophenyl)amino-3-nitrobenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5e). Yield 2.19 (78%), m.p. 191-194°C; IR (KBr) : 3349 (CN-H), 1259 (P=O), 758 (P-C) cm^{-1}; ^{1}H NMR: δ 8.04 - 6.58 (m, 14 H), 5.56 (s, 1H, N-H), 4.98 (d, *J*= 24.4 Hz, 1H, P-CH), 4.32 (dd, *J* = 13.3,3.3 Hz, 1H, CH_2), 3.69 (d, *J* = 13.7 Hz, 1H, CH_2); ^{13}C NMR: δ 129.81 (s, 2C, C-1 & 11), 132.07 (s, 2C, C-2 & 10), 128.42 (s, 2C, C-3 & 9), 124.21 (s, 2C, C – 4 & 8), 150.64 (d, *J*= 7.1 Hz, 2C, C-4a & 7a), 133.68 (d, *J*= 4.0 Hz, 2C, C -11a & 12a), 33.21 (s, 1C, C -12), 135.12 (s, 1C, C- 1'), 124.92(s, 2C, C- 2'),148.2(s,1C,C-3') 124.3(s,1C,C-4'),129.3(s,1C,C-5'),132.1(s,1C,C-6'),150.34 (s,1C, C-1"), 118.32 (s, 2C, C-2" & 6"), 116.56 (s, 2C, C - 3"& 5"), 155.02 (s, 1C, C- 4"), 55.01(d, *J* = 135.7 Hz, 1C, P-CH); ^{31}P NMR: δ 28.18 *Anal.* Calcd for $C_{26}H_{18}N_2O_5FCl_2P$: C, 56.36; H, 3.85; N, 4.87; Found: C, 56.42; H, 3.94; N, 4.94%

2,10-Dichloro-6-(4-chlorophenyl)amino-3-nitrobenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5f). Yield 2.51 (87%), m.p. 174-177°C; IR (KBr) : 3327 (CN-H), 1262 (P=O), 761 (P-C) cm^{-1}; ^{1}H NMR: δ 7.82 - 6.41 (m, 14 H), 5.52 (s, 1H, N-H), 5.01 (d, *J*= 23.9 Hz, 1H, P-CH), 4.29 (dd, *J* = 13.4,3.5 Hz, 1H, CH_2), 3.67 (d, *J* = 13.8 Hz, 1H, CH_2); ^{13}C NMR: δ 129.88 (s, 2C, C-1 & 11), 132.08 (s, 2C, C-2 & 10), 123.44 (s, 2C, C-3 & 9), 124.55 (s, 2C, C – 4 & 8), 150.32 (d, *J*= 7.1 Hz, 2C, C-4a & 7a), 133.42 (d, *J*= 4.1 Hz, 2C, C -11a & 12a), 33.37 (s, 1C, C-12), 135.34 (s, 1C, C-1'), 123.94 (s, 1C, C-2'), 148.03 (s, 2C, C–3'), 124.83 (s, 1C, 4'), 130.12(s,1C, C-5')133.84 (s, 1C, C-6'), 148.69 (s,1C, C-1"), 117.49 (s, 2C, C-2" & 6"), 130.41 (s, 2C, C - 3" & 5"), 125.36 (s, 1C, C- 4"), 55.09(d, *J* = 136.5 Hz, 1C, P-CH); ^{31}P NMR: δ 39.72 *Anal.* Calcd for $C_{26}H_{18}N_2O_5Cl_3P$: C, 54.24; H, 3.15; N, 4.86; Found: C, 54.29; H, 3.23; N, 4.93%

2,10-Dichloro-6-(4-methylphenyl)amino-3-nitrobenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5g). Yield 2.20 (79%), m.p.168-171°C; IR (KBr): 3384 (CN-H), 1244 (P=O), 759 (P-C) cm^{-1}; ^{1}H NMR: δ 8.12 - 6.49 (m, 14 H), 5.61 (s, 1H, N-H), 5.12 (d, *J*= 23.6 Hz, 1H, P-CH), 4.31 (dd, *J* = 13.2,3.4 Hz, 1H, CH_2), 3.68 (d, *J* = 13.7 Hz, 1H, CH_2), 1.96

(s,3H, CH_3); ^{13}C NMR: δ 129.39 (s, 2C, C-1 & 11), 132.01 (s, 2C, C-2 & 10), 128.42 (s, 2C, C-3 & 9), 124.34 (s, 2C, C – 4 & 8), 148.91 (d, *J*= 7.2 Hz,, 2C, C-4a & 7a), 133.49 (d, *J*= 4.4 Hz, 2C, C -11a & 12a), 33.34 (s, 1C, C -12), 136.01 (s, 1C, C- 1'), 124.13(s,1C,C- 2'), 148.14 (s,1C,C- 3'),124.45(s,1C,C-4'),129.88(s,1C,C-5')132.79 (s,1C,C-6'), 149.79 (s,1C, C-1"), 116.71 (s, 2C, C-2" & 6"), 130.82 (s,2C,C - 3"& 5"), 128.89(s,1C,C- 4"), 55.02(d, *J* = 134.8 Hz, 1C, P-CH),23.03(s,1C,4'-CH_3); ^{31}PNMR: δ 42.3 *Anal.* Calcd for $C_{27}H_{21}N_2O_5Cl_2P$: C, 58.39; H, 3.81; N, 5.04; Found: C, 58.46; H, 3.85; N, 5.09%

2,10-Dichloro-6-(4-methoxyphenyl)amino-3-nitrobenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5h). Yield 2.52 (88%), m.p.159-162°C; IR (KBr) : 3318 (CN-H), 1242 (P=O), 759 (P-C) cm^{-1}; ^{1}H NMR: δ 8.04 - 6.72 (m, 14 H), 5.21 (s, 1H, N-H), 5.17 (d, *J*= 23.7 Hz, 1H, P-CH), 4.29 (dd, *J* = 13.1,3.3 Hz, 1H, CH_2), 3.61 (d, *J* = 13.8 Hz, 1H, CH_2), 3.41 (s, 3H, OCH_3); ^{13}C NMR: δ 130.04 (s, 2C, C-1 & 11), 132.04 (s, 2C, C-2 & 10), 128.11 (s, 2C, C-3 & 9), 124.41 (s, 2C, C – 4 & 8), 150.42 (d, *J*= 7.3 Hz, 2C, C-4a & 7a), 133.62 (d, *J*= 3.9 Hz, 2C, C -11a & 12a), 33.39 (s, 1C, C -12), 135.32 (s, 1C, C- 1'),), 124.53(s,1C,C- 2'), 148.21(s,1C, C- 3'), 125.78 (s,1C,C-4'),129.57 (s,1C,C-5'),132.62(s,1C,C-6'),146.12 (s,1C, C-1"), 117.61 (s, 2C, C-2" & 6"), 115.78 (s, 2C, C - 3" & 5"), 149.93 (s, 1C, C- 4"), 55.14(d, *J* = 135.8 Hz, 1C, P-CH), 54.90 (s, 1C, OCH_3); ^{31}PNMR: δ 33.12. Mass data: 571(13.4), 525(7.9), 489(31.6), 436(33.4), 328 (16.8), 315(19.3), 314(100), 268(14.5). *Anal.* Calcd for $C_{27}H_{21}N_2O_6Cl_2P$: C, 56.76; H, 3.70; N, 4.90; Found: C, 56.81; H, 3.75; N, 4.99%

2,10-Dichloro-6-(4-chlorophenyl)amino-4-*N,N*-dimethylaminobenzyl-12*H*-dibenzo[*d,g*] [1,3,2] dioxaphosphocin 6-oxide (5i). Yield 2.33 (81%), m.p. 147-149°C; IR (KBr) : 3391 (CN-H), 1258 (P=O), 755 (P-C) cm^{-1}; ^{1}H NMR: δ 7.89 - 6.62 (m, 14 H), 5.82 (s, 1H, N-H), 5.34 (d, *J*= 23.3 Hz, 1H, P-CH), 4.42 (dd, *J* = 12.9,3.4 Hz, 1H, CH_2), 3.69 (d, *J* = 13.6 Hz,1H,CH_2), 2.72 (s, 6H, $(CH_3)_2$); ^{13}C NMR: δ 129.59 (s, 2C, C-1 & 11), 131.84 (s, 2C, C-2 & 10), 128.22 (s, 2C, C-3 & 9), 124.41 (s, 2C, C – 4 & 8), 150.92 (d, *J*= 7.1 Hz, 2C, C-4a & 7a), 132.92 (d, *J*= 4.1 Hz, 2C, C -11a & 12a), 33.18 (s, 1C, C -12), 125.88 (s, 1C, C- 1'), 127.62(s, 2C, C- 2' & 6'), 115.11 (s, 2C, C – 3' & 5'), 146.92 (s, 1C, C-4'), 149.21 (s,1C, C-1"), 118.02 (s, 2C, C-2" & 6"), 130.62 (s, 2C, C- 3" & 5"),125.83 (s,1C, C- 4"), 55.12 (d, *J* = 136.5 Hz, 1C, P-CH), 39.03 (s, 2C, $N(CH_3)_2$); ^{31}P NMR: δ 41.04. *Anal.* Calcd for $C_{28}H_{24}N_2O_3Cl_3P$: C, 58.61; H, 4.22; N, 4.88; Found: C, 58.68; H, 4.27; N, 4.96%

2,10-Dichloro-6-(4-methylphenyl)amino-4-*N,N*-dimethylaminobenzyl-12*H*-dibenzo[*d,g*] [1,3,2] dioxaphosphocin 6-oxide (5j). Yield 2.34 (84%), m.p.158-161°C; IR (KBr): 3324 (CN-H), 1226 (P=O), 747 (P-C) cm^{-1}; ^{1}H NMR: δ 7.92 - 6.59 (m, 14 H), 5.63 (brs, 1H, N-H), 5.29 (d, *J*= 23.9Hz, 1H, P-CH), 4.41 (dd, *J* = 13.4,3.7 Hz,1H,CH_2),3.59 (d, *J* = 13.6 Hz,1H,CH_2), 2.81 (s, 6H, $(CH_3)_2$),1.92 (s,3H, CH_3); ^{13}C NMR: δ 130.02 (s, 2C, C-1 & 11), 131.61 (s, 2C, C-2 & 10), 128.10 (s, 2C, C-3 & 9), 124.21 (s, 2C, C – 4 & 8), 148.91 (d, *J*= 7.3 Hz, 2C, C-4a & 7a), 132.73 (d, *J*= 4.3 Hz, 2C, C -11a & 12a), 33.18 (s, 1C,C -12), 125.91 (s, 1C, C- 1'), 127.74(s, 2C, C- 2' & 6'), 115.17 (s, 2C, C – 3' & 5'), 146.76 (s, 1C, C-4'), 149.29 (s,1C, C-1"), 116.17 (s, 2C, C-2" & 6"), 131.12 (s, 2C, C - 3" &5"), 129.02 (s, 1C, C- 4"), 55.16(d, *J* = 138.2 Hz, 1C, P-

CH), 39.23 (s, 2C, N(CH_3)), 20.91 (s, 1C, CH_3); ^{31}P NMR: δ 36.02 *Anal.* Calcd for $C_{29}H_{27}N_2O_3Cl_2P$: C, 62.94; H, 4.92; N, 5.06; Found: C, 63.01; H, 4.99; N, 5.16%

2,10-Dichloro-6-(4-methoxyphenyl)amino-4-*N,N*-dimethylaminobenzyl-12*H*-dibenzo [*d,g*][1,3,2] dioxaphosphocin 6-oxide (5k). Yield 2.54 (89%), m.p.181-183°C; IR (KBr) : 3336 (CN-H), 1239 (P=O), 757 (P-C) cm^{-1}; ^{1}H NMR: δ 7.92 - 6.59 (m, 14 H), 5.63 (brs, 1H, N-H), 5.29 (d, *J*= 24.1 Hz, 1H, P-CH), 4.41 (dd, *J* = 13.2,3.4 Hz, 1H, CH_2); ^{13}C NMR: δ 130.13 (s, 2C, C-1 & 11), 131.48 (s, 2C, C-2 & 10), 128.30 (s, 2C, C-3 & 9), 124.63 (s, 2C, C – 4 & 8), 150.11 (d, *J*= 7.0 Hz, 2C, C-4a & 7a), 132.98 (d, *J*= 4.1 Hz, 2C, C -11a & 12a), 33.18 (s, 1C, C -12), 124.91 (s, 1C, C- 1'), 127.65(s, 2C, C- 2' & 6'), 115.13 (s, 2C, C – 3' & 5'), 147.19 (s, 1C, C-4'), 145.09 (s,1C, C-1"), 117.07 (s, 2C, C-2" & 6"), 115.69 (s, 2C, C - 3" &5"), 150.72 (s,1C, C-4"), 55.16 (d, *J* = 133.3 Hz, 1C, P-CH), 56.12 (s,1C,OCH_3), 39.18 (s,2C,N(CH_3)$_2$), 20.91 (s,1C,CH_3); ^{31}P NMR: δ 34.82 *Anal.* Calcd for $C_{29}H_{27}N_2O_4Cl_2P$: C, 61.17; H, 4.78; N, 4.92; Found: C, 61.22; H, 4.86; N, 4.97%

2,10-Dichloro-6-(4-chlorophenyl)amino-3,4-dimethoxybenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5l). Yield 2.55 (86%), m.p.175-177 °C; IR (KBr) : 3381 (CN-H), 1261 (P=O), 751 (P-C) cm^{-1}; ^{1}H NMR: δ 8.28 - 6.59 (m, 13 H), 5.61 (s, 1H, N-H), 5.19 (d, *J*= 23.8 Hz, 1H, P-CH), 4.24 (dd, *J* = 13.7,3.7 Hz,1H,CH_2), 3.69 (d, *J* = 12.9 Hz, 1H, CH_2), 3.58 (s, 6H, (OCH_3)$_2$), 3.46 (s,3H, OCH_3); ^{13}C NMR: δ 130.34 (s, 2C, C-1 & 11), 131.87 (s, 2C, C-2 & 10), 128.69 (s, 2C, C-3 & 9), 124.73 (s, 2C, C – 4 & 8), 149.37 (d, *J*= 6.9 Hz, 2C, C-4a&7a), 132.98 (d, *J*= 4.0 Hz, 2C, C-11a & 12a),33.29 (s,1C, C -12) ,131.63 (s, 1C, C- 1'), 116.81 (s, 2C, C-2'), 145.18(s, 2C, C-3'),142.82 (s,1C,C-4'),115.3 (s,1C,C-5'),123.32 (s,1C,C-6'),148.82 (s,1C, C-1"), 117.32 (s, 2C, C-2" & 6"), 131.88 (s, 2C, C - 3" & 5"), 125.76 (s, 1C, C- 4"), 55.29 (d, *J* = 134.7 Hz, 1C, P-CH), 55.93 (s, 3C, (OCH_3)$_2$); ^{31}P NMR: δ 37.98 *Anal.* Calcd for $C_{28}H_{23}NO_5Cl_3P$: C, 56.92; H, 3.92; N, 2.37; Found: C, 56.96; H, 3.99; N, 2.47%

2,10-Dichloro-6-(4-methylphenyl)amino-3,4-dimethoxybenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5m). Yield 2.34 (82%), m.p.204-207°C; IR (KBr) : 3372 (CN-H), 1242 (P=O), 762 (P-C) cm^{-1}; ^{1}H NMR: δ 8.18 - 6.78 (m, 13 H), 5.43(s, 1H, N-H), 5.21 (d, *J* = 23.1Hz, 1H, P-CH), 4.28(dd, *J* = 13.3,3.2 Hz, 1H, CH_2), 3.64 (d, *J* = 13.2 Hz,1H,CH_2), 3.55 (s, 6H, (OCH_3)$_2$), 3.44 (s,3H, OCH_3); ^{13}C NMR: δ 130.42 (s, 2C, C-1 & 11), 131.83 (s, 2C, C-2 & 10), 128.39 (s, 2C, C-3 & 9), 124.65 (s, 2C, C – 4 & 8), 148.39 (d, *J*= 7.3 Hz, 2C, C-4a & 7a), 133.22 (s, 2C, C -11a & 12a), 33.29 (s, 1C, C -12), 132.47 (s,1C,C- 1'), 116.54(s, 2C, C- 2'), 144.92 (s, 2C, C–3'),143.11(s,1C, C-4'),115.83(s,1C,C-5'),121.21 (s,1C,C-6'),148.83 (s,1C,C-1"), 116.10 (s, 2C, C-2"&6"), 132.02 (s, 2C, C-3"&5"), 128.63 (s, 1C, C-4"),55.29 (d, *J*=136.7 Hz,1C,P-CH), 55.96 (s,2C,(OCH_3)$_2$), 23.12 (s,1C, CH_3); ^{31}P NMR: δ 33.71. *Anal.* Calcd for $C_{29}H_{26}NO_5Cl_2P$: C, 61.07; H, 4.59; N, 2.46; Found: C, 61.14; H, 4.63; N, 2.49%

2,10-Dichloro-6-(4-methoxyphenyl)amino-3,4-dimethoxybenzyl-12*H*-dibenzo[*d,g*][1,3,2] dioxaphosphocin 6-oxide (5n). Yield 2.35 (80%), m.p.159-162°C; IR (KBr) : 3361 (CN-H), 1249 (P=O), 742 (P-C) cm^{-1}; ^{1}H NMR: δ 8.28 - 6.59 (m, 13 H), 5.61 (s, 1H, N-H), 5.19 (d, *J*= 24.1 Hz, 1H, P-CH), 4.24 (dd, *J* = 13.2,3.5 Hz, 1H, CH_2), 3.69 (d, *J* = 12.8 Hz,1H,CH_2), 3.58 (s, 6H, (OCH_3)$_2$), 3.46 (s,3H, OCH_3); ^{13}C NMR: δ 130.09 (s, 2C, C-1 & 11), 131.14 (s, 2C, C-2 &

10), 128.74 (s, 2C, C-3 & 9), 124.38 (s, 2C, C – 4 & 8), 150.37 (d, *J*= 7.3 Hz, 2C, C-4a & 7a), 133.68 (d, *J*= 4.2 Hz, 2C, C -11a & 12a), 33.29 (s, 1C, C -12), 131.81 (s, 1C, C- 1'), 114.42(s, 2C, C- 2'), 146.08 (s, 2C, C–3'),142.87 (s,1C,C-4'),115.61 (s,1C,C-5'),122.11 (s,1C,C-6'), 146.21 (s,1C, C-1"), 117.43 (s, 2C, C-2" & 6"), 115.97 (s,2C,C-3" &5"), 150.89 (s, 1C, C- 4"), 55.29 (d, *J* = 137.9 Hz, 1C, P-CH), 56.89 (s, 2C, $(OCH_3)_2$),55.36 (s, 1C, (OCH_3)); ^{31}P NMR: δ 44.32: *Anal.* Calcd for $C_{29}H_{26}NO_6Cl_2P$: C, 59.40; H, 4.47; N, 2.39; Found: C, 59.46; H, 4.53; N, 2.47%

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