Full Paper

Synthesis and Anti-Oxidant Activity of (5*E*,9*E*)-16-(Substituted)-7,8-dihydro-16λ^5-dibenzo[*d*,*l*][1,3,7,10,2]-dioxadiazaphosphacyclotridecine-16-ones

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A new class of biologically active 13-membered phosphorus-macroheterocycles (**6a–l**) were conveniently synthesized from 1,2-*bis*(salicylidene amino)-phenylene (**1**), by treating with phosporusoxychloride (**3**) and followed by reacting with various aromatic thiols and amines (**5f–l**) in one path, and in another path **1** was directly treated with various phosphorodichloridates (**2a–e**) in the presence of triethylamine at 0–10°C under N_2 atmosphere in THF. All the title compounds were confirmed by analytical and spectral data (IR, ^{1}H-, ^{13}C-, ^{31}P-NMR, and mass spectra) and screened for anti-oxidant activity. Among these compounds, **6k**, **6e**, and **6l** containing nitro, fluoro, and chloro groups as substituents on the phenyl ring exhibited high anti-oxidant activity with effective inhibitory concentration (IC_{50}) values.

Keywords: Anti-oxidant activity / Phosphorus macrocycles / Radical scavenging activity

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Introduction

An increasing interest has been paid for several years to the chemistry of heterocyclic rings containing phosphorus due to their unique physical properties, specific chemical reactivity, and their remarkable potential biological activity [1–6]. Phosphorus containing macrocycles are interesting molecules with potential applications in supra-molecular and synthetic organic chemistry [7]. They have been synthesized as phosphineoxides, phosphines, phosphates, phosphonates, and phosphoranes [8]. By varying the components of macrocyclic systems by introducing functional groups and heteroatoms into their ensembles, one can prepare cavity structures with different levels of pre-organization and different lability, size, and properties.

The importance of these molecules as phosphorus analogues of crown ethers is derived from the potential catalytic activity and ion carrying properties. The design of host molecules capable of binding neutral organic molecules as guests is an area of rapidly expanding interest [9]. Cram and co-workers [10], Lehn and co-workers [11], Vogtle and co-workers [12], Diederich and co-workers [13], and others have made significant advances in this field of host–guest complexation [14]. They are expected to function as good hosts in the host–guest chemistry. This particular property enables them to carry certain metal ion species and drug molecules in the living system. The versatile behavior of phosphorus compounds in addition to the complexity and low yield of multistage macrocyclic synthesis presumably explains the slow development of the corresponding phosphorus macrocyclic chemistry. Most of the studies were concerned with the incorporation of phosphorus (III) or (V) in crown ether links or with the substitution of some oxygen atoms of crown ethers by phosphorus leading to species possessing one or more P–C, P–O, P–S, or, much more scarcely, P–N bonds [15].

Macrocyclic phosphates were also well known for their insecticidal activities [16] and are known to degrade hydrolytically and enzymatically to non-toxic residues. Discovery of their fungicidal properties became an important development [17]. Antioxidants are widely studied for their capacity

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to protect organisms and cells from damage induced by oxidative stress during metabolism.

Recently much effort has been devoted to macrocyclic organophosphorus compounds as asymmetric catalysts due to their active heterogeneous catalytic property, having practical advantages in terms of product separation and recycling in enantioselective synthesis [18, 19].

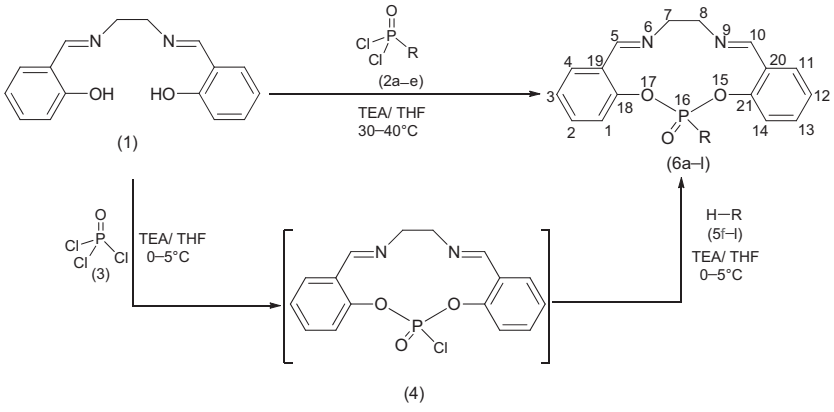
In view of the various possible applications of phosphorus macro-heterocycles containing phosphorus, oxygen, and nitrogen, we synthesized 13-membered phosphorus macro-heterocycles (PMHCs).

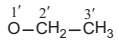
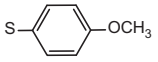
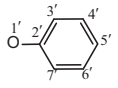
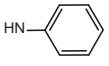
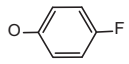
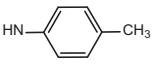
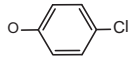
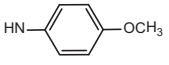
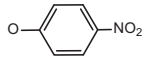
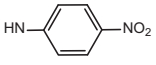
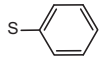
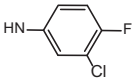
Results and discussion

Chemistry

The synthesis of a few of the title compounds, (5*E*,9*E*)-16-(substituted)-7,8-dihydro-16λ^5-dibenzo[*d*,*l*][1,3,7,10,2]dioxadiazaphosphacyclotridecine-16-ones (**6f–l**) was accomplished in two steps (Scheme 1). In the first step, 1,2-*bis*(salicylidene amino)-phenylene (**1**), which is previously prepared [20] by the condensation reaction of ethylenediamine with salicylaldehyde in ethanol at room temperature, was reacted with phosporusoxychloride (**3**) in the presence of triethylamine (TEA) in dry tetrahydrofuran (THF) to give the monochloride (5*E*,9*E*)-16-chloro-7,8-dihydrodibenzo[*d*,*l*][1,3,7,10,2]dioxadiazaphosphacyclotridecine-16-oxide (**4**) [21, 22]. Later it was treated with various aromatic thiols and amines (**5f–l**) in the presence of TEA in THF to get the compounds **6f–l**. The remaining compounds (**6a–e**) were synthesized in a single step by reacting **1** with various phosphorodichloridates (**2a–e**) in the presence of TEA in THF in good yields. The chemical structures of the newly synthesized compounds **6a–l** were confirmed by IR, ^{1}H-, ^{13}C-, ^{31}P-NMR, mass spectral, and elemental analytical data.

The title compounds **6a–l** exhibited characteristic IR bands [21–24] in the regions of 3335–3370, 1595–1632, 1230–1265, and 960–974 cm^{-1} for N–H, C=N, P=O, and =C–H$_{trans}$, respectively. Two absorption bands at 1196–1128 and 954–964 cm^{-1} correspond to symmetric absorption bands of P–O–C (Ar).



Compound	R	Compound	R
6a		**6g**	
6b		**6h**	
6c		**6i**	
6d		**6j**	
6e		**6k**	
6f		**6l**	

Scheme 1. Synthesis of (5*E*,9*E*)-16-(substituted)-7,8-dihydro-16λ^5-dibenzo[*d*,*l*][1,3,7,10,2]-dioxadiazaphosphacyclotridecine-16-ones (**6a–l**).

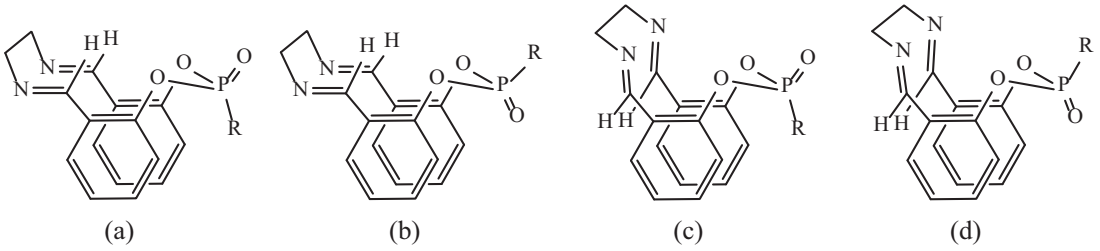


Figure 1. Conformational isomers of compounds **6a–l**.

The nitrogen attached protons in compounds **6h–l** are observed at δ 5.96–6.07 as broad peak, showing the broad nature of the hydrogen in binding with other nitrogen atoms in their boat form (Fig. 2a and b). All the aromatic protons and imine protons are observed at δ 7.37–7.98 and δ 8.71–8.95, respectively. The higher resonance values for imine protons are due to the anisotropic effect of aromatic ring current which is extended to imine conjugation and the imine protons as extra-annular hydrogens have come into the paramagnetic region of anisotropic effect. This phenomenon was also observed for carbons of imine and they resonated with higher frequency at δ 162.9–165.3 and all the aromatic and aliphatic carbons resonated in expected region.

All the title compounds showed a significant molecular ionic fragment at their respective mass and they shown a common base peak at 250 *m/z*.

Pharmacology/evaluation of anti-oxidant activity

The title PMHCs containing oxygen and nitrogen are stable in boat form isomer (Fig. 1) and are expected to be more active due to the presence of heteroatoms containing non-bonded electron pairs that serve as binding sites in the bio-matrix (Fig. 2c and d). The compounds **6k**, **6e**, and **6l** which are containing nitro, fluoro, and chloro groups as substituents on the phenyl ring exhibited high anti-oxidant activity with effective inhibitory concentration (IC_{50}) values. The remaining compounds also showed moderate to good anti-oxidant activity.

All the synthesized compounds were evaluated for their anti-oxidant activity by calculating the IC_{50} (Eq. 1) by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) method, reducing power and hydroxyl radical scavenging activity methods. Vitamin-C was measured as standard for anti-oxidant activity, the IC_{50} values varied based on the substituent on the phenyl rings.

$$\text{Scavenged}(\%) = \frac{(A_{\text{cont}} - A_{\text{test}})}{A_{\text{cont}}} \times 100 \quad (1)$$

where A_{cont} is the absorbance of the control reaction (containing all reagents except the test compound and blank sample) and A_{test} is the absorbance of the test compound.

DPPH radical scavenging activity

The scavenging activity of PMHCs, **6a–l**, against DPPH radical was performed in accordance with Choi et al. [25]. The DPPH free radical is a stable free radical, which has been widely accepted as a tool for estimating the free radical scavenging activity of anti-oxidants. This spectrophotometric assay uses the stable radical DPPH as a reagent. 85 μM of DPPH was

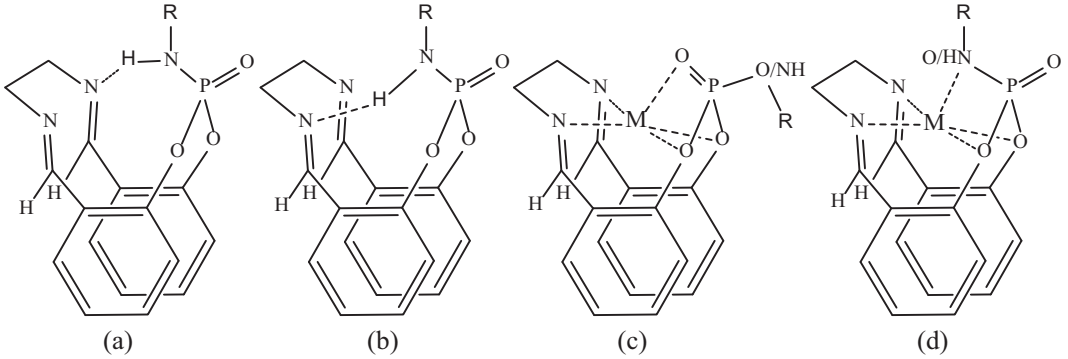


Figure 2. Possible binding nature of the titled compounds, **6a–l**, with drug molecules, hydroxyl radicals, and metal ions, etc.

added to a medium containing different PMHCs concentrations. The medium was incubated for 30 min at room temperature. The decrease in absorbance was measured at 518 nm. Ascorbic acid was used as standard reference to record maximal decrease in DPPH radical absorbance. The values are expressed in percentage of inhibition of DPPH radical absorbance with those of the standard control values without the title compounds (Fig. 3; ascorbic acid maximal inhibition was considered 100% of inhibition).

The anti-oxidant activity of these compounds was expressed as IC_{50} (inhibitory concentration, 50%). DPPH forms a stable molecule on accepting an electron or hydrogen and thus found application in the determination of radical scavenging and antioxidant activity. In the case of PMHs **6a–l**, fluoro and nitro substituted compounds **6k**, **6e**, and **6l** showed the highest DPPH radical scavenging activity with IC_{50} at 31.3, 31.8, and 32.6 μg/mL, respectively, when compared with other compounds. The remaining compounds exhibited DPPH radical scavenging activity in the following order: **6c** (IC_{50} 33.6 μg/mL), **6g** (IC_{50} 37.3 μg/mL), **6d** (IC_{50} 39.7 μg/mL), **6i** (IC_{50} 43.1 μg/mL), **6j** (IC_{50} 45.3 μg/mL), **6f** (IC_{50} 47.6 μg/mL), **6h** (IC_{50} 48.2 μg/mL), **6b** (IC_{50} 51.3 μg/mL), and **6a** (IC_{50} 61.7 μg/mL) when compared with ascorbic acid (IC_{50} 32.5 μg/mL; Fig. 3).

Reducing power assay

The reducing power was determined according to the method of Oyaizu [26]. Different concentrations of the compound (25, 50, 75, and 100 μg/mL) prepared in methanol were mixed with phosphate buffer (2.5 mL, 0.2 M, pH 6.6) and potassium ferricyanide [$K_3Fe(CN)_6$] (2.5 mL, 1%). The mixture was incubated at 50°C for 20 min and 2.5 mL of trichloroaceticacid (TCA, 10%) was added to the mixture, which was then centrifuged at 3000 rpm for 20 min. The upper layer of the solution (2.5 mL) was mixed with deionized water (2.5 mL) and ferric chloride ($FeCl_3$, 0.5 mL, 0.1%) and the UV absorbance was measured at 700 nm using a spectrophotometer. Increase in absorbance of the reaction mixture indicated increased reducing power (Fig. 4). Mean values from three independent samples were calculated for each compound and standard deviations were less than 5%.

In the case of PMHCs **6a–l**, derivatives **6k**, **6e**, and **6l** exhibited the highest reducing power with IC_{50} of 2.34, 2.42, and 2.51 μg/mL, respectively, when compared with other compounds. The remaining compounds exhibited reducing power activity in the following order: **6c** (IC_{50} 2.65 μg/mL), **6g** (IC_{50} 2.72 μg/mL), **6d** (IC_{50} 2.86 μg/mL), **6i** (IC_{50} 2.97 μg/mL), **6j** (IC_{50} 3.08 μg/mL), **6f** (IC_{50} 3.15 μg/mL), **6h** (IC_{50} 3.19 μg/mL), **6b** (IC_{50} 3.22 μg/mL), and **6a** (IC_{50} 3.46 μg/mL) when compared with ascorbic acid (IC_{50} 2.54 μg/mL).

Hydroxyl radical scavenging activity

The hydroxyl radical is the most reactive oxygen species (ROS) that attacks almost every molecule in the body. It initiates the peroxidation of cell membrane lipids [27, 28] yielding malondialdehyde, which is mutagenic and carcinogenic [29]. It was carried out by measuring the competition between deoxyribose and the compounds that generate hydroxyl radicals were measured by the method of Okhawa et al. [30]. The absorbance value of the reaction mixture was recorded at 230 nm by spectrophotometer.

Even though the PMHCs are known to scavenge the hydroxyl radical, the compounds **5k**, **5e**, and **5l** showed significant hydroxyl radical scavenging activity with IC_{50} of 1.09, 1.13, and 1.18 μg/mL, respectively, when compared with other compounds. The remaining compounds exhibited hydroxyl radical scavenging activity in the following order, respectively: **5c** (IC_{50} 1.23 μg/mL), **5g** (IC_{50} 1.25 μg/mL), **5d**

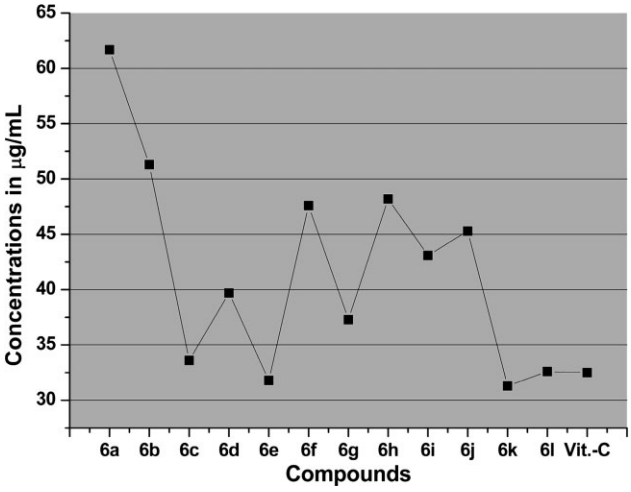


Figure 3. DPPH scavenging activity of **6a–l**.

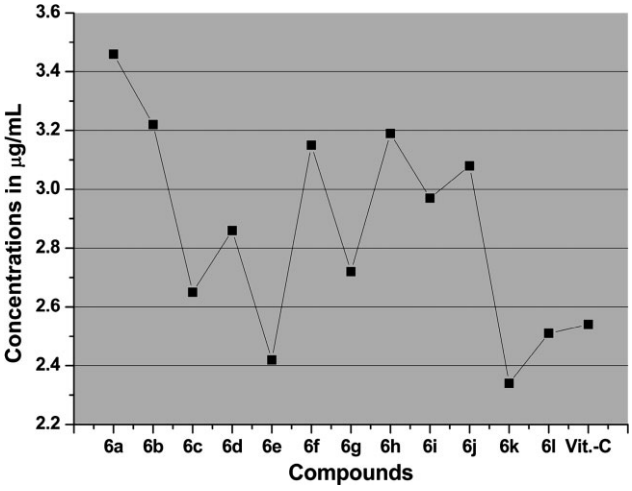


Figure 4. Reducing power activity of **6a–l**.

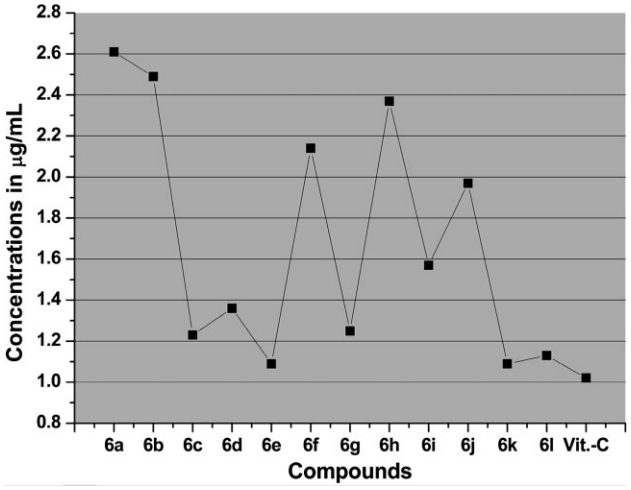


Figure 5. Hydroxyl radical scavenging activity of **6a–l**.

(IC_{50} 1.36 μg/mL), **5i** (IC_{50} 1.57 μg/mL), **5j** (IC_{50} 1. 97 μg/mL), **5f** (IC_{50} 2.14 μg/mL), **5h** (IC_{50} 2.37 μg/mL), **5b** (IC_{50} 2.49 μg/mL), and **5a** (IC_{50} 2.61 μg/mL). The IC_{50} values indicate that the title compounds can be considered as promising anti-oxidants when compared to ascorbic acid (IC_{50} 1.02 μg/mL; Fig. 5).

Conclusion

A simple and an efficient method for the synthesis of novel biologically active PMHCs in three/two steps is reported. According to our predicted results, they have ability as anti-oxidants to scavenge the free-radicals generated in the cell membrane, and after thorough investigation of their activity, they may be used as anti-oxidant drugs in medicine and drug carriers to the site.

Experimental

Chemicals were obtained from Sigma–Aldrich, Merck, and Lancaster, and used without further purification. All operations were performed under nitrogen atmosphere using standard glassware. Melting points were determined using a calibrated thermometer using a Guna Digital Melting Point apparatus. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. IR spectra were recorded in Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati as KBr discs on a Nicolet 380 FT-IR spectrophotometer. NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P. The ^{1}H and ^{13}C-NMR chemical shifts were referenced to tetramethylsilane (TMS) and ^{31}P-NMR chemical shifts to 85% H_3PO_4. LC-mass spectra were recorded on a Jeol SX 102 DA/600 mass spectrometer. The bio-assay was measured on a Elico SL-160 UV–Visible double beam spectrophotometer, Vitamin-C was used as reference.

*General procedure for the synthesis of phosphorus macroheterocycles (PMHCs; **6a–l**)*

Literature procedure was employed for the synthesis of 2,2′-((1*E*,1′*E*)-(ethane-1,2-diyl*bis*(azanylylidene))*bis*(methanylylidene))-diphenol (**1**) [21, 22]. The title compounds were synthesized in two ways (Scheme 1). Some of the compounds (**6a–e**) were prepared indirectly by addition of various substituted phosphorodichloridates (**2a–e**) to **1** and the remaining compounds (**6f–l**) were synthesized through the formation of an intermediate (**4**) followed by the addition of various aromatic amines and thiols (**5f–l**).

Method 1

In this method, a solution of ethylphosphorodichloride (**2a**, 0.64 mL, 0.006 mol) in 25 mL of dry THF was added dropwise over a period of 15 min to a stirred mixture of 2,2′-((1*E*,1′*E*)-(ethane-1,2-diyl*bis*(azanylylidene))*bis*(methanylylidene))diphenol (**1**, 1.608 g, 0.006 mol) and TEA (1.22 g, 0.006 mol) in 20 mL of dry THF at 10°C. After the addition, the temperature of the reaction mixture was raised to 40–45°C and stirred for another 3 h. The progress of the reaction was monitored by TLC analysis (ethyl acetate/hexane, 1:2) on silica gel as adsorbent. The precipitated TEA hydrochloride was separated by filtration and the filtrate was evaporated in a rotary evaporator to get crude product. The crude product was washed with water, followed by hexane, and recrystallized from 2-propanol to obtain pure compound **6a**, yield 1.59 g (74%), m.p. 168°C.

Compounds **6b–e** were also prepared by adopting the same procedure. These compounds (**6b–e**) were also recrystallized from 2-propanol.

Method 2

In this method, the title compound **6f** was synthesized by the reaction of 2,2′-((1*E*,1′*E*)-(ethane-1,2-diyl*bis*(azanylylidene))-*bis*(methanylylidene))diphenol (**1**, 1.608 g, 0.006 mol) with phosphorus oxychloride (**2**, 0.559 mL, 0.006 mol) at 0–5°C, in the presence of TEA (1.22 g, 0.006 mol) in dry THF [21, 22]. After completion of reaction (TLC), precipitated TEA hydrochloride was separated by filtration to get the intermediate **4** solution and to the cold solution of filtrate, **4**, in THF, and TEA (1.22 g, 0.006 mol), a solution of thiopenol (**5f**, 0.616 mL, 0.006 mol) in 10 mL of dry THF was added dropwise with stirring in the course of 30 min. After completion of the addition, the temperature of the reaction mixture was slowly raised to 35–40°C and stirring was continued for another 3 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the solvent was removed in a rota-evaporator. The residue was washed with water, followed by hexane, and recrystallized from 2-propanol to afford pure compound **6f** with high yield, 2.03 g (80%), m.p. 175°C.

The same procedure was successfully adopted to synthesize remaining compounds (**6g–l**). These compounds (**6g–l**) were also recrystallized from 2-propanol.

*(5E,9E)-16-Ethoxy-7,8-dihydro-16λ^5-dibenzo[d,l]-[1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6a**)*

Yield: 1.59 g (74%), Color: pale yellow, m.p. 168°C, IR (KBr): $\nu_{max} = 1615$, 1245, and 960 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.90 (s, 2H, =CH), 7.45–7.62 (m, 8H, Ar–H), 5.02 (m, 2H, OCH_2),

3.91 (s, 4H, N–CH_2), 1.45 (t, 3H, J = 6.2 Hz, CH_3); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.2 (C-5 and C-10), 163.1 (C-18 and C-21), 132.4 (C-2 and C-13), 132.2 (C-4 and C-11), 121.2 (C-19 and C-20), 119.1 (C-3 and C-12), 118.0 (C-1 and C-14), 62.8 (C-2′), 55.7 (C-7 and C-8), 15 (C-3′); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm) 18.84. Mass: m/z, 358.319 ($M^{+\bullet}$, 15), 330 (28), 313 (32), 251 (37), 250 (100), 210 (45), 102 (64), 91 (15). Anal. Calcd. $C_{18}H_{19}N_2O_4P$: C, 60.33; H, 5.34; N, 7.82; P, 8.64. Found: C, 60.26; H, 5.27; N, 7.76; P, 8.61%.

*(5E,9E)-16-Phenoxy-7,8-dihydro-16λ^5-dibenzo[d,l]-[1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6b**)*

Yield: 1.95 g (80%), Color: pale yellow, m.p. 170°C, IR (KBr): ν_{max} = 1609, 1240, and 962 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.95 (s, 2H, =CH), 7.45–7.91 (m, 13H, Ar–H), 3.91 (s, 4H, N–CH_2); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.8 (C-5 and C-10), 162.5 (C-18 and C-21), 140.6 (C-2′), 133.7 (C-5′), 133.1 (C-2 and C-13), 131.3 (C-4 and C-11), 130.8 (C-4′ and C-6′), 127.4 (C-3′ and C-7′), 122.1 (C-19 and C-20), 119.1 (C-3 and C-12), 118.6 (C-1 and C-14), 55.9 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 21.43. Mass: m/z, 406.365 ($M^{+\bullet}$, 11), 330 (28), 313 (34), 215 (37), 250 (100), 210 (45), 196 (34), 102 (68), 91 (20). Anal. Calcd. $C_{22}H_{19}N_2O_4P$: C, 65.02; H, 4.71; N, 6.89; P, 7.62. Found: C, 64.94; H, 4.65; N, 6.83; P, 7.59%.

*(5E,9E)-16-(4-Fluorophenoxy)-7,8-dihydro-16λ^5-dibenzo-[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6c**)*

Yield: 2.00 g (79%), Color: pale yellow, m.p. 210°C, IR (KBr): ν_{max} = 1600, 1262, and 970 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.94 (s, 2H, =CH), 7.44–7.85 (m, 12H, Ar–H), 3.98 (s, 4H, N–CH_2); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.8 (C-5 and C-10), 163.4 (C-18 and C-21), 141.6 (C-2′), 134.4 (C-5′), 133.1 (C-2 and C-13), 131.4 (C-4 and C-11), 130.8 (C-4′ and C-6′), 128.9 (C-3′ and C-7′), 121.3 (C-19 and C-20), 119.2 (C-3 and C-12), 118.5 (C-1 and C-14), 55.8 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 21.24. Mass: m/z, 424.358 ($M^{+\bullet}$, 19), 405 (34), 397 (25), 329 (48), 313 (65), 304 (53), 276 (58), 250 (100), 196 (47), 119 (31), 111 (23), 102 (26), 91 (17). Anal. Calcd. $C_{22}H_{18}FN_2O_4P$: C, 62.27; H, 4.28; N, 6.60; P, 7.30. Found: C, 62.21; H, 4.23; N, 6.56; P, 7.28%.

*(5E,9E)-16-(4-Chlorophenoxy)-7,8-dihydro-16λ^5-dibenzo-[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6d**)*

Yield: 2.05 g (78%), Color: pale yellow, m.p. 234°C, IR (KBr): ν_{max} = 1595, 1255, and 965 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.74 (s, 2H, =CH), 7.54–7.98 (m, 12H, Ar–H), 3.90 (s, 4H, N–CH_2); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.1 (C-5 and C-10), 162.3 (C-18 and C-21), 140.2 (C-2′), 134.1 (C-5′), 133.6 (C-2 and C-13), 131.8 (C-4 and C-11), 131.3 (C-4′ and C-6′), 127.7 (C-3′ and C-7′), 122.5 (C-19 and C-20), 119.8 (C-3 and C-12), 118.3 (C-1 and C-14), 56.4 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 20.57. Mass: m/z, 440.811 ($M^{+\bullet}$, 17), 313 (53), 250 (100), 196 (29), 102 (31), 91 (12). Anal. Calcd. $C_{22}H_{18}ClN_2O_4P$: C, 59.94; H, 4.12; N, 6.35; P, 7.03. Found: C, 59.88; H, 4.05; N, 6.28; P, 7.00%.

*(5E,9E)-16-(4-Nitrophenoxy)-7,8-dihydro-16λ^5-dibenzo-[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6e**)*

Yield: 2.30 g (85%), Color: dark yellow, m.p. 242°C, IR (KBr): ν_{max} = 1627, 1265, and 972 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.87 (s, 2H, =CH), 7.45–7.94 (m, 12H, Ar–H), 3.95 (s, 4H, N–CH_2); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.3 (C-5 and C-10), 161.4 (C-18 and C-21), 142.3 (C-5′), 140.6 (C-2′), 131.2 (C-2 and C-13), 131.1 (C-4 and C-11), 128.0 (C-4′ and C-6′), 128.4 (C-3′ and C-7′), 120.1 (C-3 and C-12), 119.9 (C-19 and C-20), 118.8 (C-1 and C-14), 56.0 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 22.21. Mass: m/z, 451.362 ($M^{+\bullet}$, 10), 313 (51), 250 (100), 91 (10). Anal. Calcd. $C_{22}H_{18}N_3O_6P$: C, 58.54; H, 4.02; N, 9.31; P, 6.86. Found: C, 58.48; H, 3.87; N, 9.26; P, 6.83%.

*(5E,9E)-16-(Phenylsulfanyl)-7,8-dihydro-16λ^5-dibenzo-[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6f**)*

Yield: 2.03 g (80%), Color: yellow, m.p. 175°C, IR (KBr): ν_{max} = 1630, 1264, and 971 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.71 (s, 2H, =CH), 7.37–7.83 (m, 13H, Ar–H), 3.89 (s, 4H, N–CH_2); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 163.3 (C-5 and C-10), 161.7 (C-18 and C-21), 135.8 (C-2′), 131.1 (C-4 and C-11), 129.2 (C-2 and C-13), 128.9 (C-4′ and C-6′), 127.6 (C-3′ and C-7′), 126.7 (C-5′), 121.1 (C-3 and C-12), 120.9 (C-19 and C-20), 118.0 (C-1 and C-14), 56.4 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 23.12. Mass: m/z, 422.432 ($M^{+\bullet}$, 25), 313 (43), 250 (100), 91 (13). Anal. Calcd. $C_{22}H_{19}N_2O_3PS$: C, 62.55; H, 4.53; N, 6.63; P, 7.59. Found: C, 62.47; H, 4.48; N, 6.57; P, 7.57%.

*(5E,9E)-16-[(4-Methoxyphenyl)sulfanyl]-7,8-dihydro-16λ^5-dibenzo[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6g**)*

Yield: 2.22 g (82%), Color: yellow, m.p. 205°C, IR (KBr): ν_{max} = 1632, 1254, and 968 cm^{-1} for C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.78 (s, 2H, =CH), 7.55–7.93 (m, 12H, Ar–H), 3.85 (s, 4H, N–CH_2), 3.31 (s, 3H, OCH_3); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 163.1 (C-5 and C-10), 161.0 (C-18 and C-21), 135.1 (C-2′), 131.8 (C-4 and C-11), 130.2 (C-2 and C-13), 128.0 (C-4′ and C-6′), 121.9 (C-19 and C-20), 121.0 (C-3 and C-12), 126.9 (C-3′ and C-7′), 120.7 (C-5′), 117.0 (C-1 and C-14), 57.3 (C-7 and C-8), 55.0 (C-22); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm) 22.39. Mass: m/z, 452.458 ($M^{+\bullet}$, 22), 313 (68), 250 (100), 91 (15). Anal. Calcd. $C_{23}H_{21}N_2O_4PS$: C, 61.05; H, 4.68; N, 6.19; P, 6.85. Found: C, 60.98; H, 4.62; N, 6.13; P, 6.83%.

*(5E,9E)-16-Anilino-7,8-dihydro-16λ^5-dibenzo[d,l]-[1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6h**)*

Yield: 1.90 g (78%), Color: pale yellow, m.p. 180°C, IR (KBr): ν_{max} = 3366, 1625, 1250, and 969 cm^{-1} for N–H, C=N, P=O, and =C–H_{trans}, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.74 (s, 2H, =CH), 7.41–7.87 (m, 13H, Ar–H), 5.97 (m, 1H, NH), 3.89 (s, 4H, N–CH_2); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 162.9 (C-5 and C-10), 160.0 (C-18 and C-21), 137.0 (C-2′), 132.8 (C-4 and C-11), 131.2 (C-2 and C-13), 128.8 (C-4′ and C-6′), 123.9 (C-19 and C-20), 121.7 (C-5′), 121.1 (C-3 and C-12), 120.5 (C-3′

and C-7′), 117.1 (C-1 and C-14), 57.3 (C-7 and C-8), 55.1 (C-22); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 20.78. Mass: *m/z*, 405.384 ($M^{+\bullet}$, 26), 313 (70), 250 (100), 91 (23). Anal. Calcd. $C_{22}H_{20}N_3O_3P$: C, 65.18; H, 4.97; N, 10.37; P, 7.64. Found: C, 65.12; H, 4.90; N, 10.33; P, 7.61%.

*(5E,9E)-16-(4-Toluidino)-7,8-dihydro-16λ^5-dibenzo[d,l]-[1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6i**)*

Yield: 1.98 g (79%), Color: yellow, m.p. 230°C, IR (KBr): ν_{max} = 3370, 1625, 1245, and 974 cm^{-1} for N–H, C=N, P=O, and =C–H$_{trans}$, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.78 (s, 2H, =CH), 7.47–7.87 (m, 12H, Ar–H), 5.99 (m, 1H, NH), 3.73 (s, 4H, N-CH$_2$), 3.28 (s, 3H, CH$_3$); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 163.2 (C-5 and C-10), 159.0 (C-18 and C-21), 137.2 (C-2′), 132.9 (C-4 and C-11), 131.9 (C-2 and C-13), 128.9 (C-4′ and C-6′), 124.7 (C-5′), 124.0 (C-19 and C-20), 121.0 (C-3 and C-12), 120.7 (C-3′ and C-7′), 118.1 (C-1 and C-14) 57.5 (C-7 and C-8), 22.1 (C-22); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 24.17. Mass: *m/z*, 419.410 ($M^{+\bullet}$, 12), 313 (68), 250 (100), 91 (9). Anal. Calcd. $C_{23}H_{22}N_3O_3P$: C, 65.86; H, 5.29; N, 10.02; P, 7.39. Found: C, 65.79; H, 5.23; N, 9.96; P, 7.35%.

*(5E,9E)-16-(4-Methoxyanilino)-7,8-dihydro-16λ^5-dibenzo-[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6j**)*

Yield: 2.32 (89%), Color: pale yellow, m.p. 210°C, IR (KBr): ν_{max} = 3355, 1615, 1255, and 971 cm^{-1} for N–H, C=N, P=O, and =C–H$_{trans}$, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.83 (s, 2H, =CH), 7.54–7.97 (m, 12H, Ar–H), 5.98 (m, 1H, NH), 3.88 (s, 4H, N–CH$_2$), 3.29 (s, 3H, OCH$_3$); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.5 (C-5 and C-10), 162.2 (C-18 and C-21), 158.8 (C-5′), 140.1 (C-2′), 132.3 (C-2 and C-13), 131.6 (C-4 and C-11), 131.2 (C-4′ and C-6′), 127.8 (C-3′ and C-7′), 122.3 (C-19 and C-20), 118.6 (C-3 and C-12), 118.1 (C-1 and C-14), 54.7 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm) 22.39. Mass: *m/z*, 435.408 ($M^{+\bullet}$, 27), 313 (60), 250 (100), 91 (12). Anal. Calcd. $C_{23}H_{22}N_3O_4P$: C, 63.44; H, 5.09; N, 9.65; P, 7.11. Found: C, 63.36; H, 5.03; N, 9.60; P, 7.08%.

*(5E,9E)-16-(4-Nitroanilino)-7,8-dihydro-16λ^5-dibenzo[d,l]-[1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6k**)*

Yield: 2.35 g (87%), Color: dark yellow, m.p. 250°C, IR (KBr): ν_{max} = 3335, 1620, 1258, and 968 cm^{-1} for N–H, C=N, P=O, and =C–H$_{trans}$, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.95 (s, 2H, =CH), 7.58–7.98 (m, 12H, Ar–H), 6.07 (m, 1H, NH), 3.83 (s, 4H, N–CH$_2$); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.8 (C-5 and C-10), 162.5 (C-18 and C-21), 161.7 (C-5′), 140.8 (C-2′), 132.5 (C-2 and C-13), 131.4 (C-4 and C-11), 131.6 (C-4′ and C-6′), 127.6 (C-3′ and C-7′), 122.1 (C-19 and C-20), 118.8 (C-3 and C-12), 118.4 (C-1 and C-14), 54.2 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 22.94. Mass: *m/z*, 450.380 ($M^{+\bullet}$, 22), 404 (33), 395 (52), 345 (47), 328 (36), 313 (63), 302 (35), 250 (100), 137 (25), 122 (26), 102 (23), 91 (18). Anal. Calcd. $C_{22}H_{19}N_4O_5P$: C, 58.67; H, 4.25; N, 12.44; P, 6.88. Found: C, 58.60; H, 4.18; N, 12.39; P, 6.86%.

*(5E,9E)-16-(3-Chloro-4-fluoroanilino)-7,8-dihydro-16λ^5-dibenzo[d,l][1,3,7,10,2]dioxadiazaphosphacyclotridecin-16-one (**6l**)*

Yield: 2.30 g (84%), Color: yellow, m.p. 230°C, IR (KBr): ν_{max} = 3370, 1630, 1263, and 969 cm^{-1} for N–H, C=N, P=O, and =C–H$_{trans}$, respectively; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.87 (s, 2H, =CH), 7.51–7.92 (m, 11H, Ar–H), 5.96 (m, 1H, NH), 3.85 (s, 4H, N–CH$_2$); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) 165.3 (C-5 and C-10), 163.4 (C-5′), 162.6 (C-18 and C-21), 142.3 (C-2′), 132.4 (C-2 and C-13), 130.9 (C-4′), 130.6 (C-4 and C-11), 128.3 (C-6′), 126.7 (C-3′), 125.5 (C-7′), 122.6 (C-19 and C-20), 119.2 (C-3 and C-12), 118.1 (C-1 and C-14), 53.7 (C-7 and C-8); ^{31}P-NMR (DMSO-d_6, 161.9 MHz): δ (ppm): 23.41. Mass: *m/z*, 457.818 ($M^{+\bullet}$, 10), 438 (25), 422 (20), 402 (35), 364 (20), 328 (35), 313 (62), 309 (55), 250 (100), 144 (38), 119 (32), 102 (26). Anal. Calcd. $C_{22}H_{18}ClFN_3O_3P$: C, 57.72; H, 3.96; N, 7.74; P, 6.77. Found: C, 57.64; H, 3.90; N, 7.69; P, 6.75%.

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