Synthesis, spectral characterisation and anti-microbial activity of novel 3-substituted-2, 4-dihydro-12*H*-3λ^5- tribenzo [*f, j, n*] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selones

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Tris(bromomethyl)phosphineoxide and 2-[(2-[(*Z*)-1-(2-hydroxyphenyl)methylidene]aminophenyl)imino]methylphenol have been utilised as precursors in the synthesis of novel pentaco-ordinate dioxadiazaphosphacyclopentadecines [e.g. 3-[(2-hydroxyethoxy)methyl]-2,4-dihydro-12*H*-3λ^5-tribenzo[*f, j, n*][1,5,9,12,3]dioxadiazaphosphacyclopenta-decine-3-selone] in moderate (overall) yields. The synthesised compounds were characterised by elemental and spectral (IR, ^{1}H, ^{13}C, ^{31}P NMR and MS) studies and their anti-microbial activity was evaluated.

Keywords: tris (bromomethyl)phosphineoxide, 2-[(2-[(*Z*)-1-(2-hydroxyphenyl)methylidene] aminophenyl) imino] methylphenol, dioxadiazaphosphacyclopentadecine, anti-microbial activity

Phosphorus containing macrocycles are interesting molecules with potential applications in supra-molecular and synthetic organic chemistry.[1,2] They have been synthesised as phosphineoxides, phosphines, phosphates, phosphonates and phosphoranes.[3] Crown ether analogues of this class have been examined for their potential catalytic activity and ion carrying properties. The design of host molecules capable of binding neutral organic molecules and cations of metals as guests is an area of rapidly expanding interest. This particular property enables them to carry certain metal ion species and drug molecules in the living system to their respective target sites. Diederich and others have made significant advances in this field of host–guest complexation.[3-6] Increasing interest has been paid to the chemistry of heterocyclic rings containing phosphorus due to their unique properties, specific chemical reactivity and their remarkable potential biological activity.[7-12] In view of the various possible applications of phosphorus heterocycles, macro-heterocycles containing phosphorus, oxygen and nitrogen have been synthesised.

Our present research has led to the synthesis of various 3-substituted-2,4-dihydro-12*H*-3λ^5-tribenzo [*f,j,n*] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selones **5(a–j)**.

Results and discussion

The synthesis of various 3-substituted-2, 4-dihydro-12*H*-3λ^5 -tribenzo [*f, j, n*] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selones **5a–j** was accomplished in three steps. Schiff's base **(2)** was prepared by reacting benzene-1,2-diamine with two moles of salicylaldehyde in ethanol. It was further reacted with tris(2-bromomethyl) phosphineoxide **(1)** in the presence of triethylamine (TEA) in dry THF to give 3-[(2-bromomethyl-2, 4-dihydro-12*H*-3λ^5 tribenzo[*f, j, n*][1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-oxide **(3).** This was then treated with ethylene glycol to form 3-[(2-hydroxyethoxy]methyl-2,4,-dihydro-12*H*-14λ^5-tribenzo[*f,j,n*] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-oxide **4(a).** The compound **4(a)** was converted to the corresponding 3-selone **5(a)** by reacting with selenium (Se) in THF at 60–65 °C for about 5 h.[13] The same procedure was employed to synthesise other members of the series **5b–j.**

The characteristic IR, ^{1}H, ^{13}C, ^{31}P NMR, physical and elemental analysis data of the compounds **5a–j** are given in the experimental. Compounds **5a–j** exhibited P=Se stretching frequencies[13] in the region 593–610 cm^{-1}. Characteristic absorption bands for P–$C_{(aliphatic)}$, N–H and O–H stretching vibrations were observed in the regions 739–757 cm^{-1}, 3380–3390 cm^{-1} and 3410–3471 cm^{-1} respectively.[14,15] A strong absorption band in the region 1620–1628 cm^{-1} was attributed to C=N stretching vibration. In ^{1}H NMR spectra of **5a–j** the chemical shifts of the aromatic hydrogens of the phenyl rings were observed as multiplets[16] in the region δ 6.39–7.90. The N–H hydrogen resonated as a multiplet at δ 4.72–5.13. The imine carbons (C-8, C-13) resonated as singlets at δ 163.5–165.1. Endocyclic methylene carbons (C-2, C-4) which are directly linked to phosphorus gave doublets at δ 61.5–62.5 (d, $^1J_{P\text{-}C}$ = ~130 Hz).[17] The Exocyclic methylene carbon (C-16) resonated as a doublet at δ 48.9 to 59.4 (d, $^1J_{P\text{-}C}$ = ~128 Hz). ^{13}C NMR chemical shifts of the carbons of compounds **5a–j** were observed in the expected region. ^{31}P NMR resonances for the compounds **5a–j** were observed as singlets in the region δ 69.92–75.79.[18]

Experimental

Chemicals were obtained from Sigma-Aldrich, Merck and Lancaster, and used as such without further purification. All solvents (AR or extra pure grade) used for spectroscopic and other physical studies were further purified by literature methods.[17] All operations were performed under a nitrogen atmosphere using standard glasswares. 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. ^{1}H and ^{13}C 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 chemical shifts were referenced to tetramethylsilane and ^{31}P chemical shifts to 85% H_3PO_4. LC mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer.

Tris(bromomethyl)phosphine oxide (**1**) was prepared following the literature procedure.[20]

Synthesis of 2-[(2-[(Z)-1-(2-hydroxyphenyl) methylidene] amino-phenyl) imino]methylphenol (**2**): An ethanolic (25 mL) solution of salicylaldehyde (11.0 g, 0.1 mole) was added dropwise to a cooled (10 °C) and stirred solution of benzene-1, 2-diamine (5.3 g, 0.05 mole) in absolute ethanol (25 mL). The resulting mixture was refluxed for 2 h. After cooling to room temperature, water (5 mL) was added and the mixture was stirred for 1 h. The yellow precipitate which formed was filtered, washed with water and dried. The progress of the reaction was monitored by the TLC (ethyl acetate: hexane, 2 : 8) analysis. The product was recrystallised from chloroform to afford yellow needles[21] of **(2)**, yield 10.68 g (73.2%), m.p. 151–152 °C.

Synthesis of 3-(2-bromomethyl)-2, 4-tetrahydro-12H-3λ^5-tribenzo [f, j, n] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-oxide (**3**): A solution of tris (bromo methyl) phosphine oxide (**1**, 1.11 g, 0.003 mole) in 10 mL of dry THF was added over a period of 20 minutes to a cooled (10 °C) and stirred solution of 2-[(2-[(Z)-1-(2-hydroxyphenyl)methylidene] aminophenyl) imino] methylphenol (**2**, 1.0 g, 0.003 mole) and triethyl amine (0.60 g, 0.006 mole) in 10 mL of dry THF under nitrogen gas. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for 1 h to form the intermediate (**3**).

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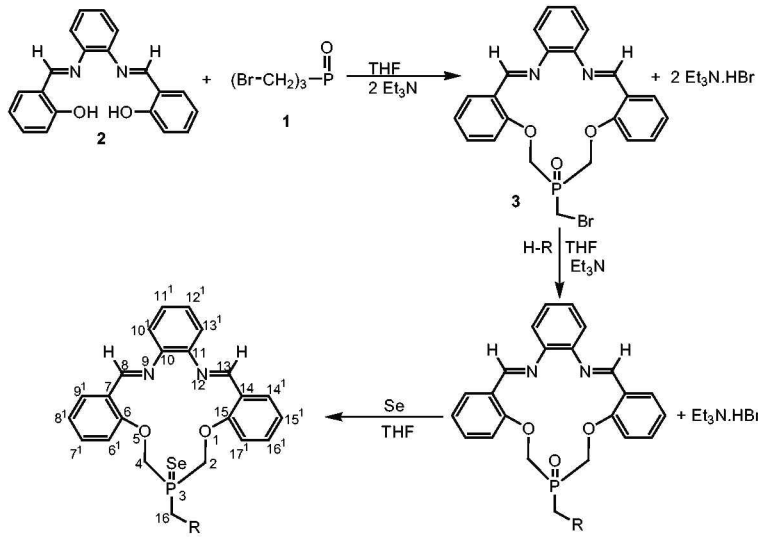
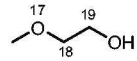
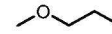
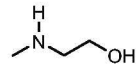
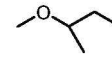
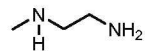
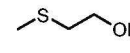
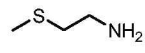
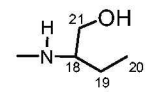
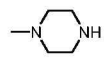
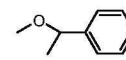


Compound	R	Compound	R
5a		**5f**	
5b		**5g**	
5c		**5h**	
5d		**5i**	
5e		**5j**	

Scheme 1

The progress of the reaction was monitored by the TLC (ethyl acetate: hexane, 2:6) analysis. After completion of the reaction, the solution was filtered to remove triethylamine hydrobromide. The filtrate was used for the next step of the reaction.

Synthesis of 3-[(2-hydroxyethoxy) methyl]-2, 4-dihydro-12H-3λ^5-tribenzo [f, j, n] [1, 5, 9, 12, 3]dioxadiazaphosphacyclopentadecine-3-selone (**5a**): Ethylene glycol (0.18 g, 0.003 mole) was added at 10 °C in the presence of TEA under nitrogen atmosphere to the intermediate **(3)** in dry THF (20 mL). After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for 1 h to form the 3-(2-hydroxyethoxy)-2, 4-dihydro-12*H*-3λ^5-tribenzo[*f*, *j*, *n*] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-oxide **(4a)**. The progress of the reaction was monitored by the TLC (ethyl acetate: hexane, 2 : 8) analysis. After completion of the reaction, the solution was filtered under a nitrogen atmosphere to remove triethylamine hydrobromide. The filtrate was reacted with selenium[15] in THF at 60–65 °C for 4 h to afford the corresponding 13-selone **(5a).** The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 2:8) analysis. After completion of the reaction, solvent was removed in a rota-evaporator to obtain crude product. It was recrystallised from 2-propanol to get pure compound **5(a).** The same experimental procedure was adopted for the preparation of the remaining title compounds **5b–j.**

3-[(2-hydroxyethoxy)methyl]-2,4-dihydro-12H-3λ^5-tribenzo[f,j,n] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5a**): Yield: 60%; m.p. 152–153 °C; IR (KBr) cm^{-1} 3428 (O-H), 1625 (C=N), 596 (P=Se), 742 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.42 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–C<u>H</u>$_2$–O_{arom}), 4.35 (m, 2H, P–C<u>H</u>$_2$–O_{aliph}), 3.61 (t, *J* = 7.4 Hz, 2H, –O–C<u>H</u>$_2$–CH$_2$), 3.82 (t, *J* = 7.4 Hz, 2H, –CH$_2$–C<u>H</u>$_2$–OH), 4.27 (s, 1H, –CH$_2$–O<u>H</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.5 (d, $^1J_{P\text{-}C}$ = 126 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.7 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (s, C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 59.4 (d, $^1J_{P\text{-}C}$ = 131 Hz, C-16), 72.5 (C-18), 61.4 (C-19); ^{31}P NMR (DMSO-d_6) δ 70.82; LCMS *m/z* (%) 527[28, M$^{+\cdot}$], 482(19), 452(100), 326 (37), 138(15). Anal. Calcd for $C_{25}H_{25}N_2O_4PSe$: C, 56.93; H, 4.78; N, 5.31. Found: C, 56.89; H, 4.76; N, 5.30%.

3-[(2-hydroxyamino)methyl]-2,4-dihydro-12H-3λ^5-tribenzo[f, j, n] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5b**): Yield: 59%; m.p. 172–173 °C; IR (KBr) cm^{-1} 3471 (OH), 3390 (NH), 1627 (C=N), 603 (P=Se), 739 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–C<u>H</u>$_2$–O_{arom}), 3.35 (m, 2H, P–C<u>H</u>$_2$–NH), 5.13 (m, H, P–CH$_2$–<u>NH</u>), 3.64 (t, *J* = 7.2 Hz, 2H, –NH–C<u>H</u>$_2$–CH$_2$), 3.84 (t, *J* = 7.2 Hz, 2H, –CH$_2$–C<u>H</u>$_2$–OH), 4.30 (s, 1H, –CH$_2$–O<u>H</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.8 (d, $^1J_{P\text{-}C}$ = 133 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.5 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C-6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 55.4 (d, $^1J_{P\text{-}C}$ = 130 Hz, C-16), 74.5 (C-18), 41.4 (C-19); ^{31}P NMR (DMSO-d_6) δ 72.38; LCMS *m/z* (%) 526[47, M$^{+\cdot}$],480(46), 452(100), 326 (18), 138(15),104(37). Anal. Calcd $C_{25}H_{26}N_3O_3PSe$: C, 57.04; H, 4.98; N, 7.98. Found: C, 57.01; H, 4.95; N, 7.95%.

3-[(2-aminoethyl)amino]methyl-2,4-dihydro-12H-3λ^5-tribenzo[f, j, n][1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5c**): Yield: 60%; m.p. 154–156°C; IR (KBr) cm^{-1} 3385 (NH), 1626 (C=N), 596 (P=Se), 750 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.50 (m, 4H, P–<u>CH_2</u>–O_{arom}), 4.72 (m, 1H, P–CH_2–<u>NH</u>) 3.20 (m, 2H, P–<u>CH_2</u>–NH), 3.24 (t, *J* = 7.6 Hz, 2H, –NH–<u>CH_2</u>–CH_2), 3.14 (t, *J* = 7.6 Hz, 2H, –CH_2– <u>CH_2</u>–NH_2), 3.12 (t, *J* = 7.9 Hz 2H, –CH_2–<u>NH_2</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.5 (d, $^1J_{P\text{-}C}$ = 130 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.4 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 36.9 (d, $^1J_{P\text{-}C}$ = 126 Hz, C-16), 55.6 (C-18), 41.2 (C-19); ^{31}P NMR (DMSO-d_6) δ 70.43; LCMS *m/z* (%) 525[23, M$^{+\cdot}$], 480(24), 452(100), 326(37), 138(15), 104(19). Anal. Calcd $C_{25}H_{27}N_4O_2PSe$: C, 57.15; H, 5.18; N, 10.66. Found: C, 57.13; H, 5.16; N, 10.64%.

3-[(2-aminoethyl)sulfanyl]methyl-2,4-dihydro-12H-3λ^5-tribenzo [f, j, n][1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5d**): Yield:58%; m.p. 167–168°C; IR (KBr) cm^{-1} 3380 (NH), 1628(C=N), 593 (P=Se), 749 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 2.80 (m, 2H, P–<u>CH_2</u>–S–), 2.40 (t, *J* = 7.4 Hz, 2H, –S–<u>CH_2</u>–CH_2), 2.60 (t, *J* = 7.4 Hz, 2H, –CH_2– <u>CH_2</u>–NH_2), 3.80 (t, *J* = 7.8 Hz 2H, –CH_2–<u>NH_2</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.5 (d, $^1J_{P\text{-}C}$ = 128 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.5 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 48.9 (d, $^1J_{P\text{-}C}$ = 130 Hz, C-16), 36.2 (C-18), 38.4 (C-19); ^{31}P NMR (DMSO-d_6) δ 69.92; LCMS *m/z* (%) 542[33, M$^{+\cdot}$], 498(100), 452(17), 326 (37), 138(15), 104(62). Anal. Calcd $C_{25}H_{26}N_3O_2PSSe$: C, 55.35; H, 4.83; N, 7.75. Found: C, 55.33; H, 4.82; N, 7.73%.

3-(piperazinomethyl)-2,4-dihydro-12H-3λ^5-tribenzo[f, j, n][1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5e**): Yield: 62%; m.p. 158–160°C; IR (KBr) cm^{-1} 3389 (NH) 1628 (C=N), 610 (P=Se), 753(P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 3.40 (m, 2H, P–<u>CH_2</u>–N), 2.53 (t, *J* = 6.7 Hz, 4H, –N–<u>CH_2</u>–CH_2), 2.30 (m, 4H, –CH_2– <u>CH_2</u>–NH), 3.70 (m, 1H, –CH_2–<u>NH</u>–CH_2), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.5 (d, $^1J_{P\text{-}C}$ = 129 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.6 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C-6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 59.4 (d, $^1J_{P\text{-}C}$ = 131 Hz, C-16), 72.5 (C-18, C-22), 61.4 (C-19, C-21); ^{31}P NMR (DMSO-d_6) δ 71.92; Anal. Calcd $C_{27}H_{29}N_4O_2PSe$: C, 58.80; H, 5.30; N, 10.16. Found: C, 58.76; H, 5.27; N, 10.14%.

3-(propoxymethyl)-2,4-dihydro-12H-3λ^{5}tribenzo[f,j,n][1,5,9,12,3] dioxadiazaphosphacyclopentadecine-3-selone (**5f**): Yield: 63%; m.p. 156–158°C; IR (KBr) cm^{-1} 1625 (C=N), 598 (P=Se), 752 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 4.34 (m, 2H, P–<u>CH_2</u>–O–), 2.18 (t, *J* = 7.4 Hz, 2H, –O–<u>CH_2</u>–CH_2), 1.61 (m, 2H, –CH_2–<u>CH_2</u>–CH_2), 1.10 (t, *J* = 6.2 Hz, 3H, –CH_2–<u>CH_3</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.6 (d, $^1J_{P\text{-}C}$ = 128 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.7 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 59.4 (d, $^1J_{P\text{-}C}$ = 131 Hz, C-16), 72.5 (C-18), 35.4 (C-19) 19.4 (C-20), 14.6 (C-21); ^{31}P NMR (DMSO-d_6) δ 73.72; Anal. Calcd $C_{27}H_{29}N_2O_3PSe$: C, 60.11; H, 5.42; N, 5.19. Found: C, 60.08; H, 5.40; N, 5.16%.

3-(sec-butoxymethyl)-2,4-dihydro-12H-3λ^5-tribenzo[f, j, n] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5g**): Yield: 58%; m.p. 165–167°C; IR (KBr) cm^{-1} 1625 (C=N), 609 (P=Se), 739 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 4.31 (m, 2H, P–<u>CH_2</u>–O–), 2.30 (m, 1H, –O–<u>CH</u>–CH_2), 1.41 (m, 2H, –CH– <u>CH_2</u>–CH_3), 0.97 (t, *J* = 6.4 Hz, 3H, –CH_2–<u>CH_3</u>), 1.2 (d, *J* = 7.1 Hz, 3H, –CH–<u>CH_3</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.5 (d, $^1J_{P\text{-}C}$ = 130 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.6 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 59.2 (d, $^1J_{P\text{-}C}$ = 127 Hz, C-16), 76.5 (C-18), 21.4 (C-19), 40.9 (C-20), 17.1 (C-21), 15.4 (C-22); ^{31}P NMR (DMSO-d_6) δ 71.25; Anal. Calcd $C_{27}H_{29}N_2O_3PSe$: C, 60.11; H, 5.42; N, 5.19. Found: C, 60.08; H, 5.40; N, 5.16%.

3-[(2-hydroxyethyl)sulfanyl]methyl-2,4-dihydro-12H-3λ^5-tribenzo [f, j, n] [1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5h**): Yield: 57%; m.p. 147–149°C; IR (KBr) cm^{-1} 3428 (OH), 1620 (C=N), 594(P=Se), 755 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 2.80 (m, 2H, P–<u>CH_2</u>–S–), 2.40 (t, J = 7.4 Hz, 2H, –S–<u>CH_2</u>–CH_2), 2.60 (t, J = 7.4 Hz, 2H, –CH_2– <u>CH_2</u>–OH), 4.28 (s, 1H, –CH_2–<u>OH</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 62.5 (d, $^1J_{P\text{-}C}$ = 126 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.4 (C-8, C-13), 165.0 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 58.1 (d, $^1J_{P\text{-}C}$ = 129 Hz, C-16), 61.3 (C-18), 70.6 (C-19); ^{31}P NMR (DMSO-d_6) δ 65.25; Anal. Calcd $C_{25}H_{25}N_2O_3PSSe$: C, 55.25; H, 4.64; N, 5.15. Found: C, 55.21; H, 4.61; N, 5.12%.

3-[(1-ethyl-2-hydroxyamino)methyl]-2,4-dihydro-12H-3λ^5-tribenzo[f, j, n][1, 5, 9, 12, 3] dioxadiazaphosphacyclopentadecine-3-selone (**5i**): Yield: 58%; m.p. 152–154°C; IR (KBr) cm^{-1} 3410 (OH), 3390 (NH), 1625 (C=N), 595 (P=Se), 757 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.40–7.82 (m, 12H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 3.35 (m, 2H, P–<u>CH_2</u>–NH), 3.13 (m, 1H, –NH–<u>CH</u>–$(CH_2)_2$), 1.54 (m, 2H, –CH–<u>CH_2</u>–CH_3), 1.10 (t, 3H, J = 6.8 Hz, –CH_2–<u>CH_3</u>), 2.71 (d, J = 7.2 Hz, 2H, –CH–<u>CH_2</u>–OH), 4.30 (s, 1H, –CH_2–<u>OH</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 62.5 (d, $^1J_{P\text{-}C}$ = 131 Hz, C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 163.5 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 48.9 (d, J = 128 Hz,C-16), 61.5 (C-18), 26.7 (C-19), 11.4 (C-20), 67.4 (C-21); Anal. Calcd $C_{27}H_{30}N_3O_3PSe$: C, 58.49; H, 5.45; N, 7.58. Found: C, 58.45; H, 5.43; N, 7.56%.

3-[(1-phenylethoxy)methyl]-2,4-dihydro-12H-3λ^5-tribenzo[f,j,n] [1,5,9,12,3]dioxadiazaphosphacyclopentadecine-3-selone(**5j**):Yield: 64%; m.p. 138–140°C; IR (KBr) cm^{-1} 3420 (OH), 1625 (C=N), 596 (P=Se), 753 (P–C_{alip}); ^{1}H NMR (DMSO–d_6): δ (ppm) 8.72 (s, 2H, –N=C<u>H</u>–), 6.39–7.82 (m, 17H, ArH), 5.45 (m, 4H, P–<u>CH_2</u>–O_{arom}), 4.34 (m, 2H, P–<u>CH_2</u>–O_{aliph}), 4.14 (t, *J* = 7.4 Hz, 1H, –O–<u>CH</u>–C_{arom}), 1.98 (d, *J* = 6.8 Hz, 3H, –CH–<u>CH_3</u>), ^{13}C NMR (DMSO-d_6) δ (ppm) 61.5 (d, $^1J_{P\text{-}C}$ = 132 Hz,C-2, C-4), 153.8 (C-6, C-15), 118.2 (C-7, C-14), 164.4 (C-8, C-13), 162.7 (C-10, C-11), 114.2 (C- 6^1, C-17^1), 131.5 (C-7^1, C-16^1), 121.2 (C-8^1, C-15^1), 130.5 (C-9^1, C-14^1), 122.6 (C-10^1, C-13^1), 128.9 (C-11^1, C-12^1), 59.4 (d, $^1J_{P\text{-}C}$ = 130 Hz, C-16), 72.5 (C-18),

Table 1 Antibacterial activity of the title compounds **5a–j**

Compd	Zone of inhibition/mm					
	Staphylococcus aureus			*Escherichia coli*		
	100 ppm[a]	50 ppm[a]	25 ppm[a]	100 ppm[a]	50 ppm[a]	25 ppm[a]
5a	11	8	6	12	8	4
5b	8	6	–	10	7	5
5c	10	8	6	12	8	4
5d	6	5	4	12	6	6
5e	14	9	5	14	12	8
5f	13	11	8	13	11	7
5g	7	4	–	9	8	4
5h	10	8	5	10	6	5
5i	12	10	8	10	6	4
5j	11	8	5	12	8	6
Penicillin[b]	9	6	–	12	8	–

[a]In DMF.
[b]Reference compound.

Table 2 Antifungal activity[a] of the title compounds **5a–j**

Compd.	Zone of inhibition/mm					
	Aspergillus niger			*Helminthosporium oryzae*		
	100 ppm[a]	50 ppm[a]	25 ppm[a]	100 ppm[a]	50 ppm[a]	25 ppm[a]
5a	10	7	5	11	6	5
5b	11	8	4	11	9	5
5c	12	9	6	12	10	7
5d	13	10	8	14	10	4
5e	10	7	5	12	8	7
5f	9	5	3	12	10	9
5g	10	6	4	9	8	4
5h	9	8	6	11	9	5
5i	14	11	9	13	12	8
5j	8	9	6	9	7	4
Griseofulvnb	12	10	5	12	10	5

[a]In DMF.
[b]Reference compound.

21.3 (C-19), 81.3 (C-20), 127.1 (C-21,C-25), 128.9 (C-22, C-24), 128.4 (C-23); ^{31}P NMR (DMSO-d_6) δ 75.79; Anal. Calcd $C_{31}H_{29}N_2O_3PSe$: C, 63.38; H, 4.98; N, 4.77. Found: C, 63.35; H, 4.96; N, 4.75%.

Antibacterial activity

Antibacterial activity of all the compounds **5a–j** was assayed[22] against *Staphylococcus aureus* ATCC-25923 (Gram positive) and *Escherichia coli* ATCC-25922 (Gram-negative) at three different concentrations (100, 50 and 25 ppm) in DMF (Table 1). The compounds were diluted in DMF for bioassay. Solvent control was included although no antibacterial activity has been noted in the solvent employed. Penicillin G (Hi-media) controls (20 μg mL^{-1}) were included to compare with compounds **5a–j**. All samples were tested in triplicate and average results were recorded.

Disc diffusion bioassay

For the bioassay a suspension of approximately 1.5×10^8 bacterial cells per mL was used. The bacterial suspension 1.5 mL was uniformly spread on nutrient agar (Hi-media) in 12 × 1.2 cm glass Petri dishes, left aside for 15 min and excess of suspension was then drained and discarded. For the agar disc diffusion method, the test compound was introduced onto the disc and then allowed to dry. The disc was completely saturated with the test compound. Then the disc was introduced onto the upper layer of the medium seeded with bacteria. The Petri dishes were incubated at 35 °C for 24 h. Bioactivity was determined by measuring the diameters of the inhibition zones in mm. The compounds **5a–j** were made up at 25, 50 and 100 μg mL^{-1} concentrations for bio-activity screening by the disc diffusion method. Each test was done in triplicate and the mean diameter of the inhibition zones was calculated. Controls included the use of solvent without test compounds although antibacterial activity was not noted for the solvent employed in the test. The minimum inhibitory concentration (MIC) was determined for the compounds **5a–j** used at concentrations of 0.1–5.6 mg mL^{-1}. Specifically 0.1 mL of standardised inoculum (1–2 × 107CFU mL^{-1}) was added to each tube. The tubes were incubated aerobically at 35 °C for 24 h. Two control tubes were maintained for each test batch. These included antibiotic control (tube containing the growth medium without inoculum) and organism control (tube containing the growth medium, physiological saline and the inoculum). The lowest concentration (highest dilution) of the compounds **5a–j** that produced no visible bacterial growth (no turbidity) when compared with the control tubes was considered as MIC. The highlight is that majority of the compounds exhibited high activity against both bacteria and two compounds (**5e** and **5f**) were more effective than the standard compound. Penicillin was tested as a standard reference to compare the activities of these compounds.

Antifungal activity

The compounds **5a–j** were screened for their antifungal activity (Table 2) against *Aspergillus niger* and *Helminthosporium oryzae* along with standard fungicide griseofulvin at three different concentrations (100, 50 and 25 ppm) in DMF[23]. All the compounds **5a–j** exhibited moderate to high antifungal activity when compared with that of the reference compound. The majority of the compounds exhibited high activity against fungi. The compounds **5d** and **5i** showed higher activity against *H. oryzae* and *A. niger* respectively, when compared with that of the standard and warrants further testing to determine their minimum inhibitory concentrations as well as their cytotoxicity.

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