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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL 5-[(SUBSTITUTED) METHYL]-5-OXO-1, 3, 2λ^4, 5λ^5–DIOXASELENA PHOSPHINAN-2-ONES

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Abstract – A series of novel 5-[(substituted) methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxa selenaphosphinan-2-ones (**4-17**) were successfully synthesized from tris(bromomethyl)phosphine oxide (**1**) and sodium selenite (**2**) to form the intermediate(**3**) which on further treatment with various alcohols/ thiols/ phenols/ aminoacid esters afforded the title compounds (**4-17**) and their structures were established by multinuclear NMR (^{1}H-, ^{13}C- and ^{31}P-) and mass spectral data. Their antimicrobial activity was evaluated and they exhibited promising antibacterial activity.

INTRODUCTION

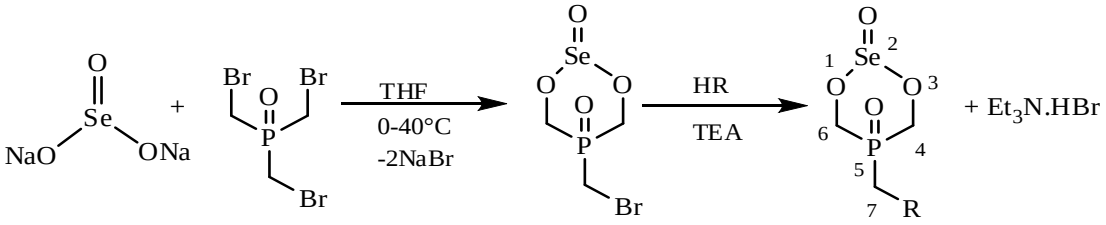
Six-membered phosphorus heterocycles containing O, N as hetero atoms and P as P=O (S) have been the subject of research ever since cyclophosphamide [2-bis-2-(2-chloroethyl)amino]-2*H*-[1,3,2]-oxazaphosphorinane-2-oxide was discovered as an anti-cancer drug.[1,2] Success of cyclophosphamide as an anti-cancer drug led to the synthesis of several [1,3,2]-oxazaphosphorinane derivatives. Schmidt *et al*[3] synthesized two new compounds 2-[bis(2-chloroethyl)amino]-2,3-dioxo-7-thia-1-aza-2-phosphobicyclic[4.4.0]-decane and [4.3.0] nonane in their search for less toxic potential antitumor agents. 4-Carbonyl and 4-aryl cyclophosphamides were synthesized by Takamizawa[4] and Shin[5] respectively. 3-Cyclohexyl-6-(1,1-dimethyl)-3,4-dihydro-2-substituted-2*H*-[1,3,2]benzoxazaphosphorin-2-oxides were found to possess high antitumor activity.[6] Their 4-bromophenyl and naphthyl substituted analogues also exhibited significant bioactivity.[7] Even though several compounds related to six membered phosphorus heterocycles have been synthesized, none of them was found to possess satisfactory pharmacological properties. Hence the search continued for the development of potential bioactive molecule from six membered phosphorus

heterocycles. In the present investigation, we have made an attempt and synthesized first time successfully novel six-membered heterocyclic compounds containing Se and P. A series of novel 5-[(substituted)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxa selena phosphinan-2-ones were successfully synthesized and their structures were established by elemental analyses, multinuclear NMR (^{1}H, ^{13}C and ^{31}P) and mass spectral data and their antimicrobial activity was evaluated.

RESULTS AND DISCUSSION

CHEMISTRY

To a cooled (10 °C) and stirred solution of sodium selenite **2** in 20 mL of dry THF, a solution of tris(bromomethyl)phosphine oxide **1** in 10 mL of dry THF was added over a period of twenty minutes. After completion of addition, the temperature of the reaction mixture was raised to room temperature and stirred for one hour to form the intermediate **3** and sodium bromide salt was removed. The filtrate was further treated with various alcohols/ thiols/ phenols/ amino acid esters in the presence of triethylamine to obtain the title compounds **4-17** as shown in Scheme 1 and Table 1.

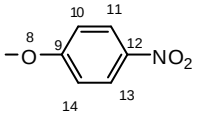
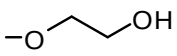
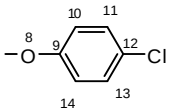
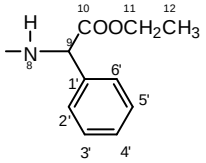
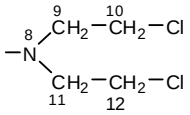
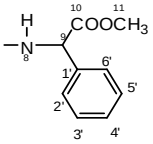
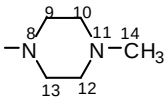
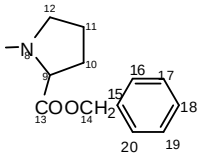
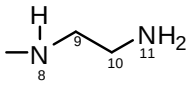
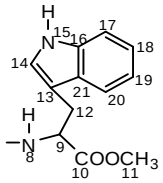
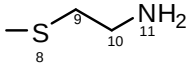
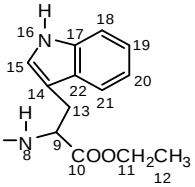
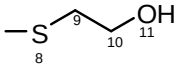
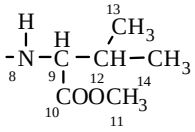


2 **1** **3** **4-17**

Scheme 1

The title compounds exhibited P=O, Se=O and P-C stretching frequencies in the region(s) 1234-1254, 1201-1220 and 742-756 cm^{-1} respectively.[8-11] In ^{1}H NMR spectra of **4-17** the chemical shifts of the aromatic protons showed complex multiplets[9] in the region(s) 6.94-8.02 ppm. The methylene protons appeared as multiplets in the region(s) δ 2.54-5.02. The amino acid esters were observed in the expected region(s).[8, 11] The ^{13}C NMR chemical shifts for aromatic skeleton were observed in the range of 115.1-164.4 ppm. The methylene carbons which are directly linked to phosphorus experienced coupling with it and resonated as doublets in the region(s) 54.10-54.30 (d, J = 126-132 Hz).[12] The ^{31}P NMR chemical shifts of title compounds were appeared in the region(s) 19.23-24.39 ppm as singlets.[13,14]

Table 1. Synthesis of title compounds 4-17

Entry	R	Entry	R
4		**11**	
5		**12**	
6		**13**	
7		**14**	
8		**15**	
9		**16**	
10		**17**	

BIOLOGICAL ACTIVITY

Antibacterial Activity

All the compounds **4-17** were screened for their antibacterial activity against the growth of *Staphylococcus aureus* and *Escherichia coli* at three concentrations[15,16] of 100 μg / disc, 50 μg / disc and 25 μg / disc. All the compounds **4-17** showed moderate to high antibacterial activity against both the bacteria when compared with that of the standard. These results are presented in Table 2. The title compounds exhibited very significant antibacterial activity when compared to similar six-membered phosphorus heterocycles.[17]

Table 2. Antibacterial Activity[a] of compounds 4-17 in terms of zone inhibition (mm)

Entry	Zone of inhibition (mm)					
	***Escherichia coli* (µg / disc)**			***Staphylococus aureus* (µg / disc)**		
	100[a]	**50[a]**	**25[a]**	**100[a]**	**50[a]**	**25[a]**
4	23	11	6	24	11	7
5	23	10	4	25	11	6
6	23	12	5	24	10	6
7	22	10	6	24	10	5
8	22	11	5	22	9	6
9	21	13	4	19	11	5
10	20	11	5	20	11	5
11	19	10	5	18	10	5
12	21	10	6	20	9	6
13	20	12	6	19	8	8
14	19	10	5	18	10	7
15	20	10	7	18	9	6
16	19	10	6	18	10	7
17	19	12	5	16	10	7
Penicillin	20	12	6	20	10	8

[a] Concentrations expressed in ppm

Antifungal Activity

All the compounds **4-17** were tested for their anti fungal activity against the growth of *Aspergillus niger* and *Helminthosporium oryzae* at three concentrations 100 µg / disc 50, 25 µg/disc.[18] When compared with the reference compound Griseofulvin, the title compounds exhibited moderate to high activity against the growth of both the fungi at three different concentrations. The results are furnished in Table 3. Compounds **4-17** showed very promising antifungal activities when compared to similar six-membered phosphorus heterocycles.[17,19]

Table 3. Antifungal Activity[a] of compounds 4-17 in terms of zone inhibition (mm)

Entry	Zone of inhibition (mm)					
	***Aspergillus niger* (µg / disc)**			***Helminthosporium oryzae* (µg / disc)**		
	100[a]	**50[a]**	**25[a]**	**100[a]**	**50[a]**	**25[a]**
4	15	10	7	14	9	5
5	19	9	6	15	7	3
6	19	10	5	14	6	6
7	20	12	4	14	9	5
8	18	11	6	13	7	4
9	21	11	6	19	10	7
10	20	10	5	20	11	6
11	19	9	4	18	10	5
12	20	11	7	13	8	4
13	18	12	6	19	12	8
14	19	10	6	14	10	7
15	18	11	5	15	9	7
16	18	10	5	14	10	5
17	18	10	6	16	11	7
Griseofulvin	20	10	5	20	10	5

[a]Concentrations expressed in ppm

EXPERIMENTAL

Chemicals were obtained from Sigma-Aldrich, 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. All operations were performed under nitrogen atmosphere using standard glasswares. Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. Elemental analyses were performed by Thermo Finnigan Flash EA 1112 at University of Hyderabad, Hyderabad. IR Spectra were recorded with 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, 161.9 MHz for ^{31}P and 76.2 MHz for ^{77}Se. The ^{1}H and ^{13}C chemical shifts were referenced to tetramethylsilane, ^{31}P chemical shifts to 85% H_3PO_4 and ^{77}Se Chemical shifts were referenced to dimethylselenium in $CFCl_3$. LC mass spectra were recorded on a Jeol SX 102 DA / 600 Mass Spectrometer.

Tris(bromomethyl)phosphine oxide (1):

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

5-[(1-Bromo)methyl]-5-oxo-1, 3, 2λ^4, 5λ^5-dioxaselenaphosphinan-2-one (3).

To a cooled (10 °C) and stirred solution of sodium selenite (**2**, 0.86 g, 0.005 mole) in 50 mL of dry THF, a solution of tris(bromomethyl) phosphineoxide (**1**, 1.43 g, 0.005 mole) in 15 mL of dry THF was added dropwise over a period of 20 min. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for 1 h to form 5-[(1-bromo)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one **3**. After completion of the reaction, sodium bromide was separated by filtration and the solvent was removed from the filtrate in a rota-evaporator. Then the resulted crude product was recrystallized from 2-propanol to obtain the compound-3. The progress of the reaction was judged by the TLC analysis. Yield: 69% (1.01 g), ^{1}H NMR (DMSO-d_6) δ: 3.68 (m, 4H, P-C<u>H$_2$</u>-O-), 3.34 (m, 2H, P-C<u>H$_2$</u>-Br). LCMS (%): 295 [$M^{+\bullet}$] (100), 297 [M+2] (97).

5-[(4-Nitrophenoxy)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (4).

To the intermediate **3** (1.01 g, 0.003 mole), *p*-nitrophenol (0.42 g, 0.003 mole) in dry THF (10 mL) was added in the presence of triethylamine at 10-15 °C over a period of 30 min. After the addition, temperature of the reaction mixture was slowly raised to 30-35 °C and continued stirring. The progress of the reaction was monitored by the TLC analysis (EtOAc: hexane 1:2). After completion of the reaction, Et_3N:HBr was separated by filtration and the solvent was removed from the filtrate in a rota-evaporator. The resulting crude product was recrystallized from 2-propanol to obtain pure compound of **4**. Yield 1.18 g, 67%: mp 161-163 °C. The same procedure was adopted for the preparation of other compounds **5-17**.

Physical, Analytical and Spectral data for the compounds 4-17.

5-[(4-Nitrophenoxy)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (4).

Yield 67%, mp 161-163 °C, IR (KBr): ν_{max} 1243 (P=O), 1201 (Se=O), 742 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1289. ^{31}P NMR (85%, H_3PO_4) δ: 21.62. ^{1}H NMR (DMSO-d_6) δ: 7.01-7.85 (m, 4H, Ar–H), 5.01 (m, 2H, P-<u>CH$_2$</u>-O-Ar), 3.69 (m, 4H, P-<u>CH$_2$</u>-O). ^{13}C NMR δ: 54.3 (d, J = 127 Hz) C_4 and C_6, 55.7 (d, J = 127 Hz) C_7, 164.4 C_9, 115.1 C_{10} and C_{14}, 126.7 C_{11} and C_{13}, 142.2 C_{12}. Anal. Calcd for $C_9H_{10}NO_7PSe$: C

30.53, H 2.85, N 3.96. Found: C 30.49, H 2.82, N 3.95%. LCMS(%): 354 [$M^{+\bullet}$, 50], 341 (100), 327 (67), 314 (17), 226 (39), 134 (7).

5-[(4-Chlorophenoxy)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (5).

Yield 69%, mp 168-169 °C, IR (KBr): ν $_{max}$ 1240 (P=O), 1213 (Se=O), 745 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) *δ*: 1295. ^{31}P NMR (85%, H_3PO_4) δ: 19.27. ^{1}H NMR(DMSO-d_6) δ: 7.02-7.46 (m, 4H, Ar–H), 5.02 (m, 2H, P-$\underline{CH_2}$-O-Ar), 3.82 (m, 4H, P-$\underline{CH_2}$-O). ^{13}C NMR δ: 54.1 (d, *J* = 126 Hz) C_4 and C_6, 55.2 (d, *J* = 129 Hz) C_7, 159 C_9, 116 C_{10} and C_{14}, 131 C_{11} & C_{13}, 128 $C_{12.}$ Anal. Calcd: for $C_9H_{10}ClO_5PSe$. C 31.46, H 2.93. Found: C 31.42, H 2.89 %. LCMS(%): 343 [$M^{+\bullet}$, 28], 297 (45), 260 (31), 223 (100), 187 (23), 150 (45), 125 (66), 98 (39).

5-[(Bis(2-chloroethyl)amino)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (6).

Yield 68%, mp 168-170 °C. IR (KBr): ν_{max} 1234 (P=O), 1209 (Se=O), 747 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) *δ*: 1288. ^{31}P NMR (85%, H_3PO_4) δ: 22.19. ^{1}H NMR (DMSO-d_6) δ: 4.05 (m, 4H, P-$\underline{CH_2}$-O-), 3.65 (m, 2H, P-$\underline{CH_2}$-N), 2.84 (t, *J*= 8.2 Hz, 4H, N$\underline{CH_2}$-CH_2), 2.54 (t, *J* = 7.8 Hz, 4H, NCH_2-$\underline{CH_2}$-Cl). ^{13}C NMR δ: 54.1 (d, *J* = 126 Hz) C_4 and C_6, 55.3 (d, *J* = 129 Hz) C_7, 59.2 C_9 and $C_{11,}$ 43.5 C_{10} and C_{12} . Anal. Calcd: for $C_7H_{14}NO_4Cl_2PSe$; C 23.55, H 3.95, N 3.92. Found: C 23.50, H 3.88%, N 3.90. LCMS (%): 360 [M+4], 358[M+2], 356[$M^{+\bullet}$, 37], 301 (51), 282 (22), 251 (65), 164 (100), 151 (33), 136 (41), 86 (19).

5-[(*N*-Methylpiperazino)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (7). Yield 71%, mp 160-161 °C. IR (KBr): ν $_{max}$ 1245 (P=O), 1219 (Se=O), 744 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) *δ*: 1299. ^{31}P NMR (85%, H_3PO_4): δ 23.19. ^{1}H NMR (DMSO-d_6): δ 4.05 (m, 4H, P-$\underline{CH_2}$-O-), 3.65 (m, 2H, P-$\underline{CH_2}$-N), 2.62 (t, *J*= 7.5 Hz, 4H, N$\underline{CH_2}$-CH_2), 2.54 (t, *J*= 8.2 Hz, 4H, NCH_2-$\underline{CH_2}$), 2.32 (s, 3H, N-CH_3). ^{13}C NMR: δ 54.1 (d, *J* = 127 Hz) C_4 and C_6, 55.2 (d, *J* = 128 Hz) C_7, 52 C_9 and $C_{13,}$ 57 C_{10} and $C_{12,}$ 44 $C_{14.}$ Anal. Calcd: for $C_8H_{17}N_2O_4PSe$: C 30.49, H 5.44, N 8.89. Found: C 30.45, H 5.41, N 8.86%. LCMS (%): 315 [$M^{+\bullet}$, 31], 287 (100), 263 (52), 224 (25), 152 (74), 138 (33), 114 (41), 75 (16).

5-[(2-Aminoethylamino)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (8).

Yield 68%, mp 151-153 °C. IR (KBr): ν_{max} 3409 (N-H), 1239 (P=O), 1211 (Se=O), 746 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) *δ*: 1305. ^{31}P NMR (85% H_3PO_4): δ 24.33. ^{1}H NMR (DMSO-d_6): δ 5.4 (m, 1H, NH), 4.81 (t, 2H, *J* = 7.8 Hz, NH_2), 4.05 (m, 4H, P-$\underline{CH_2}$-O-), 3.65 (m, 2H, P-$\underline{CH_2}$-N), 2.83 (m, 2H, -NH$\underline{CH_2}$-CH_2), 2.79 (m, 2H, -$\underline{CH_2}NH_2$).^{13}C NMR: δ 54.2 (d, *J* = 128 Hz) C_4 and C_6, 55.1 (d, *J* = 126 Hz) C_7, 52 C_9 , 41 $C_{10.}$ Anal. Calcd: for $C_5H_{13}N_2O_4PSe$: C 21.83, H 4.76, N 10.18. Found: C 21.78, H 4.72, N 10.17%. LCMS (%): 275 [$M^{+\bullet}$, 28], 234 (64), 207 (32), 169 (100), 137 (47), 103 (58), 74 (81).

5-[(2-Aminoethylsulfanyl)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (9).

Yield 73%, mp 163-165 °C. IR (KBr): ν_{max} 3417 (N-H), 1235 (P=O), 1215 (Se=O), 749 cm^{-1}(P-C_{alip}). ^{77}Se

NMR ($CDCl_3$) δ: 1302. ^{31}P NMR (85%, H_3PO_4) δ: 21.45, ^{1}H NMR (DMSO-d_6) δ: 4.82 (t, 2H, J = 7.6 Hz, NH_2), 4.06 (m, 4H, P-$\underline{CH_2}$-O-), 3.64 (m, 2H, P-$\underline{CH_2}$-S), 2.83 (t, J = 7.6 Hz, 2H, -S$\underline{CH_2}$-CH_2), 2.76 (m, 2H, -$\underline{CH_2}NH_2$). 13C NMR δ: 54.1 (J = 126 Hz) C_4 & C_6, 55.2 (J = 128 Hz) C_7, 53 C_9 , 42 C_{10}. Anal. Calcd: for $C_5H_{12}NO_4PSSe$; C 20.56, H 4.14, N 4.79. Found: C 20.52, H 4.13, N 4.78%. LCMS (%): 292 [$M^{+\bullet}$].

5-[(2-Hydroxyethylsulfanyl)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (10).

Yield 71%, mp 173-175 °C. IR (KBr): ν_{max} 3417 (O-H), 1254 (P=O), 1208 (Se=O), 747 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1288. ^{31}P NMR (85%, H_3PO_4) δ: 23.43. ^{1}H NMR (DMSO-d_6) δ: 4.82 (t, 1H, J = 7.8 Hz, OH), 4.06 (m, 4H, P-$\underline{CH_2}$-O-), 3.64 (m, 2H, P-$\underline{CH_2}$-S), 2.83 (t, J = 7.4 Hz, 2H, -S-$\underline{CH_2}$-CH_2), 2.76 (t, J = 7.4 Hz, 2H, -S-CH_2-$\underline{CH_2}$). ^{13}C NMR δ: 54.2 (J = 127 Hz) C_4 and C_6, 55.2 (J = 128 Hz) C_7, 52 C_9 , 41 C_{10}, Anal. Calcd: for $C_5H_{11}O_5PSSe$: C 20.49, H 3.78. Found: C 20.44, H 3.76%. LCMS (%): 293 [$M^{+\bullet}$].

5-[(2-Hydroxyethoxy)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (11).

Yield 67%, mp 167-168 °C. IR (KBr): ν_{max} 3432 (O-H), 1244 (P=O), 1212 (Se=O), 745 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1298. ^{31}P NMR (85% H_3PO_4) δ: 22.22. ^{1}H NMR (DMSO-d_6) δ: 4.80 (t, 1H, J = 7.8 Hz, OH), 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.62 (m, 2H, P-$\underline{CH_2}$-O), 3.84 (t, J = 8.4 Hz, 2H, -$\underline{CH_2}$-OH), 3.56 (t, J = 8.2 Hz, 2H, O-$\underline{CH_2}$-CH_2) 2.76 (t, J = 7.4 Hz, 2H, -O-CH_2-$\underline{CH_2}$). ^{13}C NMR δ: 54.2 (d, J = 128 Hz) C_4 and C_6, 55.1 (d, J = 126 Hz) C_7, 52.4 C_9, 41.7 $C_{10.}$ Anal. Calcd: for $C_5H_{11}O_6PSe$: C 21.68, H 4.00. Found: C 21.62, H 3.98%. LCMS (%): 277 [$M^{+\bullet}$].

5-[(Phenyl glycine ethyl ester)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (12).

Yield 71%, mp 179-181 °C. $[\alpha]_D^{25}$ -120.8^o; IR (KBr): ν_{max} 3392 (NH), 1678 (C=O), 1238 (P=O), 1217 (Se=O), 747 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1310. ^{31}P NMR (85%, H_3PO_4) δ: 19.23. ^{1}H NMR (DMSO-d_6) δ: 7.09-7.49 (m, 5H, Ar-H), 4.69 (q, 1H, NH), 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.62 (m, 2H, P-$\underline{CH_2}$-NH), 3.68 (q, 2H, O-$\underline{CH_2}$-CH_3), 1.14 (t, (J = 10.2 Hz, 3H, O-CH_2-$\underline{CH_3}$). ^{13}C NMR δ: 54.2 (d, J = 128 Hz) C_4 and C_6, 55.2 (d, J = 132 Hz) C_7, 67.7 C_9, 172.1 C_{10}, 62.2 C_{11}, 17.6 $C_{12,}$ 135.8 C_1^1, 129.8 C_2^1 and C_6^1, 129.1 C_3^1 and C_5^1, 127.6 C_4^1. Anal. Calcd: for $C_{13}H_{18}NO_6PSe$; C 39.61, H 4.60, N 3.55. Found: C 39.57, H 4.59, N 3.52%. LCMS (%): 394 [$M^{+\bullet}$].

5-[(Phenyl glycine methyl ester)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (13).

Yield 70%, mp 174-176 °C. $[\alpha]_D^{25}$ -122.5^o; IR (KBr): ν_{max} 3404 (NH), 1687 (C=O), 1252 (P=O), 1210 (Se=O), 749 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1307. ^{31}P NMR (85%, H_3PO_4) δ: 19.48. ^{1}H NMR (DMSO-d_6) δ: 7.09-7.49 (m, 5H, Ar-H), 4.69 (q, 1H, NH), 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.62 (m, 2H, P-$\underline{CH_2}$-NH), 3.68 (s, 3H, O-$\underline{CH_3}$), 2.29 (d, J = 10.2 Hz, 1H, $\underline{CH}$-CO). ^{13}C NMR: δ 54.2 (d, J = 126 Hz) C_4 and C_6, 55.1 (d, J = 130 Hz) C_7, 67.6 C_9, 172.5 $C_{10,}$ 62.1$C_{11,}$ 135.7 C_1^1, 129.9 C_2^1 and C_6^1, 129.0 C_3^1 and C_5^1,

127.8 C_4^1 Anal. Calcd: for $C_{12}H_{16}NO_6PSe$: C 37.91, H 4.24, N 3.68. Found: C 37.85, H 4.23, N 3.64%. LCMS (%): 380 [$M^{+\bullet}$].

5-[(Proline ethyl ester)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (14).

Yield 68%, mp 168-170 °C. $[\alpha]_D^{25}$ -119.3^o; IR (KBr): ν_{max} 1687 (C=O), 1237 (P=O), 1214 (Se=O), 756 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1312. ^{31}P NMR (85%, H_3PO_4) δ: 24.39. ^{1}H NMR (DMSO-d_6) δ: 7.07-7.48 (m, 5H, Ar-H), 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.62 (m, 2H, P-$\underline{CH_2}$-NH), 3.69 (s, 2H, O-$\underline{CH_2}$-Ar), 2.29 (d, J = 10.2 Hz, 1H, $\underline{CH}$-CO), 1.91-2.02 (m, 2H, CH_2), 1.64-1.79 (m, 2H, CH_2), 2.02-2.21 (t, 2H, CH_2).^{13}C NMR δ: 54.2 (d, J = 128 Hz) C_4 and C_6, 55.2 (d, J = 132 Hz) C_7, 66.8 C_9, 29.8 C_{10} 22.7 C_{11}, 57.6 C_{12}, 171.6 C_{13}, 63.1 C_{14}, 135.8 C_1^1, 129.8 C_2^1 and C_6^1, 129.1 C_3^1 and C_5^1, 127.6 C_4^1. Anal. Calcd: for $C_{15}H_{20}NO_6PSe$: C 42.87, H 4.80, N 3.33 Found: C 42.82, H 4.77, N 3.30 %. LCMS (%): 420 [$M^{+\bullet}$].

5-[(Tryptophan methyl ester)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (15). Yield 69%, mp 178-180 °C. $[\alpha]_D^{25}$ -116.4^o; IR (KBr): ν_{max} 3396 (NH), 1677 (C=O), 1248 (P=O), 1217 (Se=O), 747 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1318. ^{31}P NMR (85%, H_3PO_4) δ: 24.27. ^{1}H NMR (DMSO-d_6) δ: 10.21 (br s, 1H, Ar-$\underline{NH}$), 6.94-7.67 (m, 5H, Ar-H), 4.72 (q, 1H, NH), 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.69 (t, 2H, $\underline{CH_2}$-Ar), 3.62 (m, 2H, P-$\underline{CH_2}$-NH), 3.68 (s, 3H, O-$\underline{CH_3}$), 2.29 (d, J = 10.2 Hz, 1H, $\underline{CH}$-CO). M.F: $C_{15}H_{19}N_2O_6PSe$: Anal. Calcd: C 41.58, H 4.42, N 6.47. Found: C 41.54, H 4.40, N 6.43%. LCMS (%): 433 [$M^{+\bullet}$].

5-[(Tryptophan ethyl ester)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (16).

Yield 71%, mp 169-171 °C. $[\alpha]_D^{25}$ -123.5^o; IR (KBr): ν_{max} 3392 (NH), 1678 (C=O), 1244 (P=O), 1220 (Se=O), 749 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1310. ^{31}P NMR (85%, H_3PO_4) δ: 24.27. ^{1}H NMR (DMSO-d_6) δ:10.11 (br s, 1H, Ar-$\underline{NH}$), 6.94-7.67 (m, 5H, Ar-H), 4.72 (q, 1H, NH), 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.69 (t, 2H, $\underline{CH_2}$-Ar), 3.62 (m, 2H, P-$\underline{CH_2}$-NH), 2.29 (d, J = 10.2 Hz, 1H, $\underline{CH}$-CO), 3.68 (q, 2H, O-$\underline{CH_2}$-CH_3), 1.14 (t, J = 10.2 Hz, 3H, O-CH_2-$\underline{CH_3}$). Anal. Calcd: for $C_{16}H_{21}N_2O_6PSe$: C 42.97, N 4.73, H 6.26. Found: C 42.94, N 4.70, H 6.25%. LCMS (%): 447 [$M^{+\bullet}$].

5-[(Valine methyl ester)methyl]-5-oxo-1,3,2λ^4,5λ^5-dioxaselenaphosphinan-2-one (17).

Yield 70%, mp 177-178 °C. $[\alpha]_D^{25}$ -124.9^o; IR (KBr): ν_{max} 3399 (NH), 1678 (C=O), 1251 (P=O), 1210 (Se=O), 745 cm^{-1}(P-C_{alip}). ^{77}Se NMR ($CDCl_3$) δ: 1315. ^{31}P NMR (85%, H_3PO_4) δ: 24.29. ^{1}H NMR (DMSO-d_6) δ: 4.07 (m, 4H, P-$\underline{CH_2}$-O-), 3.62 (m, 2H, P-$\underline{CH_2}$-NH), 4.72 (q, 1H, NH), 2.29 (d, J = 10.2 Hz, 1H, $\underline{CH}$-CO), 3.68 (q, 2H, O-CH_3), 2.10 (m, 1H, $\underline{CH}(CH_3)_2$), 1.17 (t, J = 7.2 Hz, 6H, CH($\underline{CH_3}$)$_2$). Anal. Calcd for $C_9H_{18}NO_6PSe$: C 31.23, H 5.24, N 4.05. Found: C 31.18, N 5.21, H 4.04%. LCMS (%): 346 [$M^{+\bullet}$].

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