Synthesis and Bio-Activity of Alkyl/Aryl [2-(1,2,4,5-Tetrahydro-3-Sulfanylene/Selenylene Naphtha[1,8][1,5,3]diazaphosphocin-3-yl)methyl Amino Acid Esters]

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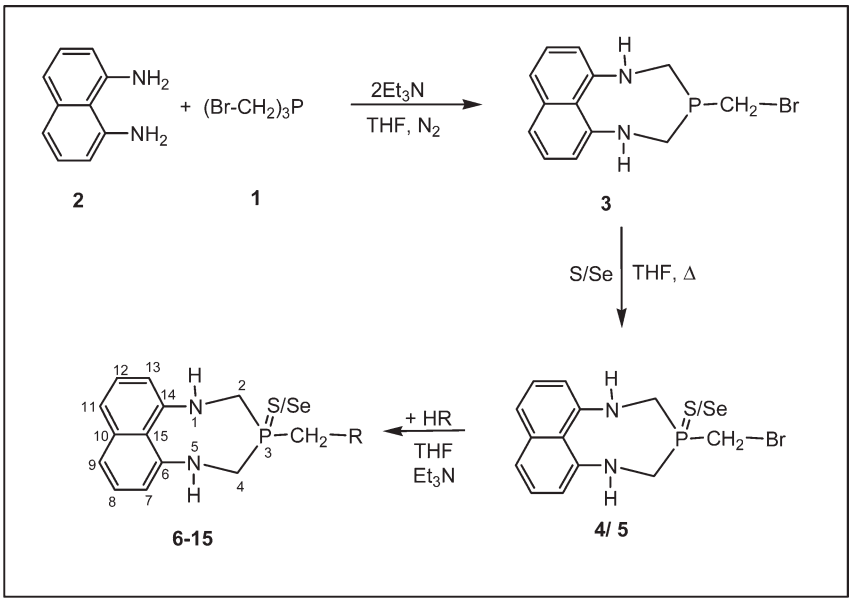

Synthesis of alkyl/aryl [2-(1,2,4,5-tetrahydro-3-sulfanylene/selenylene naphtha[1,8-*f*,*g*][1,5,3]diazaphosphocin-3-yl) methyl amino acid esters] (**6–15**) was accomplished in three steps. 1, 8-diamino naphthalene (**2**) was reacted with tris (bromomethyl) phosphine (**1**) in the presence of triethylamine in dry tetrahydrofuran (THF) under N_2 atmosphere to form a P_{III} intermediate (**3**). It was converted to the corresponding sulfide (**4**) and selenide (**5**) by reacting with sulfur and selenium, respectively. The intermediates **4** and **5** were further reacted with amino acid esters to obtain the title compounds (**6–15**). The structures of the title compounds were established by elemental analysis and spectral data (IR, ^{1}H, ^{13}C, ^{31}P NMR, and FAB mass). The antimicrobial activity of these compounds was evaluated and they exhibited significant activity.

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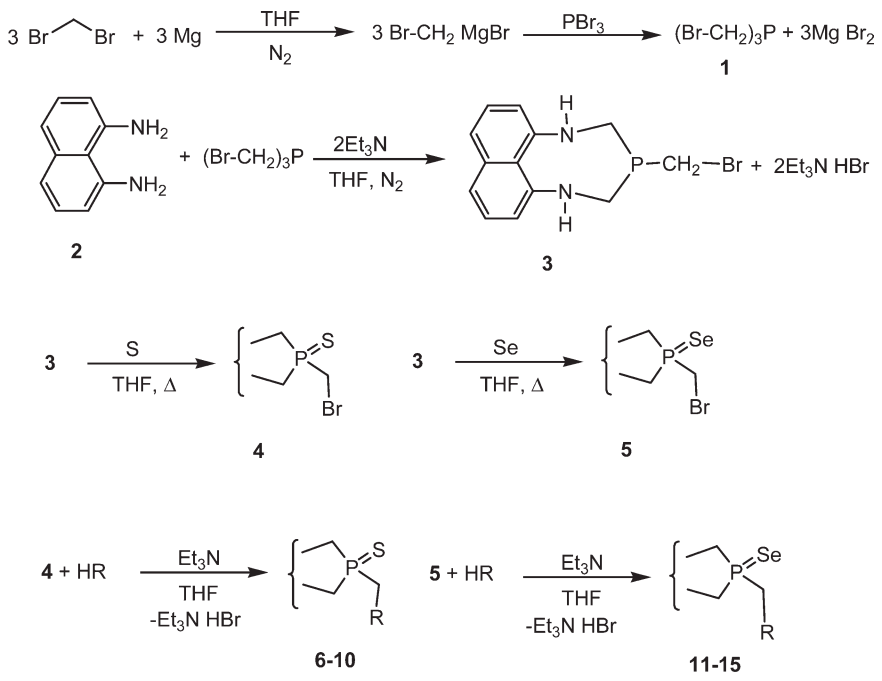
INTRODUCTION

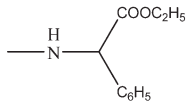
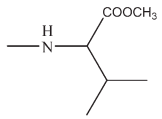
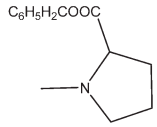
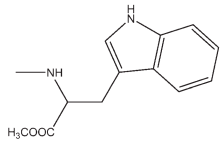
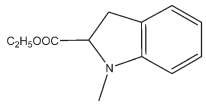
Organophosphate moiety is an important pharmacophore in agricultural and pharmaceutical chemistry [1]. Phosphocin/phosphepin and their related derivatives containing this group represent an important class of pesticides, antibiotics, herbicides, and antiviral agents [2]. Some of them are well known for their insecticidal activities [3] and are known to degrade hydrolytically and enzymatically to nontoxic residues. Discovery of their fungicidal properties also promotes interest in this research area. New chiral phosphorus ligands play vital role in asymmetric synthesis [4–8]. Synthesis of eight-membered phosphorus heterocyclic compounds, phosphocins have currently gained considerable interest in the polymer and oil industry because of their potential use as antioxidants and stabilizers, considerable research work is going on in the chemistry of the phosphocins [9,10]. Keeping in view the importance of eight-membered organophosphorus heterocyclic compounds, we herein report the synthesis, spectral characterization, and antimicrobial activity of the title compounds.

RESULTS AND DISCUSSION

Preparation of a few eight-membered phosphorus heterocyclic compounds such as alkyl/aryl [2-(1,2,4,5-tetrahydro-3-sulfanylene/selenylene naphtha[1,8-*f*,*g*][1,5,3]diazaphosphocin-3-yl) methyl amino acid esters] (**6–15**) was accomplished in three steps. The synthetic

Scheme 1



Compound	R
6 & 11	
7 & 12	
8 & 13	
9 & 14	
10 & 15	

route (Scheme 1) involves the cyclization of equimolar quantities of 1,8-diamino naphthalene (**2**) with tris (bromomethyl) phosphine (**1**) in the presence of triethylamine in dry tetrahydrofuran (THF) under N_2 atmosphere to form the corresponding P_{III} intermediate, 3-(bromomethyl)-1,2,4,5,-tetrahydro-1*H*-naphtho[1,8-

Table 1

Physical, IR, and ^{31}P NMR spectral data of the compounds **6–15**.

Compd.	Molecular formula	MP (°C)	Yield %	Elemental analysis % Found (Calcd.)			IR cm^{-1}			^{31}P NMR
				C	H	N	NH	P=S/Se	P—C_{alip}	
6	$C_{23}H_{26}N_3O_2PS$	182–184	72	62.75 (62.84)	5.90 (5.96)	9.53 (9.56)	3425	759	738	41.10
7	$C_{19}H_{26}N_3O_2PS$	187–189	69	58.20 (58.28)	6.65 (6.69)	10.69 (10.74)	3402	776	735	41.07
8	$C_{25}H_{28}N_3O_2PS$	193–195	73	64.44 (64.49)	6.04 (6.06)	8.97 (9.03)	3409	764	737	41.13
9	$C_{25}H_{27}N_4O_2PS$	186–188	71	62.71 (62.75)	5.67 (5.69)	11.68 (11.71)	3429	769	743	41.17
10	$C_{24}H_{26}N_3O_2PS$	177–179	72	63.75 (63.83)	5.75 (5.80)	9.28 (9.31)	3417	772	717	42.18
11	$C_{23}H_{26}N_3O_2PSe$	192–194	64	56.60 (56.66)	5.34 (5.37)	8.58 (8.62)	3410	625	719	83.19
12	$C_{19}H_{26}N_3O_2PSe$	189–191	61	51.84 (51.92)	5.92 (5.96)	9.51 (9.56)	3412	637	729	83.17
13	$C_{25}H_{28}N_3O_2PSe$	187–189	69	58.40 (58.46)	5.44 (5.49)	8.13 (8.18)	3404	629	752	82.45
14	$C_{25}H_{27}N_4O_2PSe$	182–185	65	57.11 (57.15)	5.15 (5.18)	10.62 (10.66)	3395	634	758	86.17
15	$C_{24}H_{26}N_3O_2PSe$	179–181	66	57.63 (57.70)	5.27 (5.25)	8.35 (8.41)	3405	627	753	86.14

f,*g*][1,5,3]diazaphosphocine (**3**). It was converted to the corresponding sulfide (**4**) and selenide (**5**) by reacting with sulfur and selenium, respectively. The compounds **4** and **5** were further reacted with amino acid esters in the presence of triethylamine in dry THF to obtain the title compounds (**6–15**) (Scheme 1) and mass fragments of compound **7** are given (Scheme 2).

The physical, elemental analyses, IR, and ^{31}P NMR data of the compounds **6–15** are given in the Table 1. Compounds **6–15** exhibited characteristic P=S/Se stretching frequencies in the region 759–776 (P=S) and 625-637 (P=Se) cm^{-1} [11]. Characteristic absorption bands for P—C $_{(aliphatic)}$ and N—H stretching vibrations were observed in the regions 717–758 and 3395–3429 cm^{-1}, respectively [12]. In the ^{1}H NMR spectra, aromatic protons of the naphthyl ring of the **6–15** gave complex multiplets [13] in the region 6.53–7.17 ppm. The N—H proton resonated as a broad singlet at δ 4.02–4.18. The other aliphatic protons of **6–15** were observed in the expected region (Table 2). ^{13}C NMR chemical shifts for aromatic carbons were observed in the expected region (Table 3). C-2 and C-4 which are directly linked to phosphorus experienced coupling with it and appeared as doublet in the region δ 54.21–55.26 (J = 126–132 Hz). The carbons of amino acid esters resonated in the expected region [13].

The ^{31}P NMR chemical shifts of 3-sulfides (**6–10**) appeared in the region 41.07–42.18 and the corresponding 3-selenides (**11–15**) were observed in the region

Table 2

^{1}H NMR spectral data[a] of the compounds **6–15**.

Compd.	Ar—H	NH	P—CH_2—R
6	6.54–7.17 (m, 11H)	4.07 (br s)	2.60–3.10 (m, 6H, CH_2-P(S)), 4.74 (d, 1H, *CH* Ar) (J = 8.1 Hz), 4.12 (q, 2H, O—*CH_2*—CH_3), 1.30(t, 3H, O—CH_2—*CH_3*)(J = 6.2 Hz)
7	6.54–7.10 (m, 6H)	4.04 (br s)	2.68–3.12 (m, 6H, CH_2—P(S)), 3.44 (t, 1H NH—*CH*), (J = 6.1 Hz), 2.70 (m, 1H, —*CH*— $(CH_3)_2$), 1.01(d, 6H, CH—*CH_3*) (J = 8.1Hz), 3.67(s, 3H, COO—*CH_3*)
8	6.56–7.12 (m, 11H)	4.09 (br s)	2.61–3.15 (m, 6H, CH_2-P(S)), 2.60 (t, 2H, N—*CH_2*—CH_2) (J = 6.2 Hz), 2.60 (t, 2H N-CH_2—*CH_2*) (J = 6.1 Hz), 3.28 (t, 1H, N—*CH*—CO— 2.60 (t, 2H N—CH—*CH_2*) (J = 6.3 Hz). 3.67(s, 2H, Ar-*CH_2*)
9	6.55–7.14 (m, 11H)	4.02 (br s)	2.65-3.40 (m, 6H, CH_2-P(S)), 3.45 (d, 2H *CH_2*-CH) (J = 8.0 Hz) 3.26 (d, 1H CH_2—*CH*) (J = 8.2 Hz), 4.12 (s, 3H COO*CH_3*).
10	6.54–7.13 (m, 10H)	4.12 (br s)	3.10–3.40 (m, 6H, CH_2—P(S)), 3.26 (t, 1H *CH*—CO) (J = 6.2 Hz), 3.84 (d, 2H, CH—*CH_2*) (J = 8.1 Hz), 4.12(q, 2H, *CH_2*—CH_3), 1.30(t, 3H, CH_2—*CH_3*) (J = 6.1 Hz).
11	6.54–7.14 (m, 11H)	4.11 (br s)	2.61–3.12 (m, 6H, CH_2-P(S)), 4.76 (d, 1H *CH*Ar) (J = 8.2 Hz), 4.14 (q, 2H, O-*CH_2*—CH_3), 1.31(t, 3H, O—CH_2—*CH_3*) (J = 6.3 Hz)
12	6.53–7.10 (m, 6H))	4.05 (br s)	2.60–3.10 (m, 6H, CH_2—P(S)), 3.46 (t, 1H, NH—*CH*) (J = 6.1 Hz), 2.72 (m, 1H, O—*CH*— $(CH_3)_2$). 1.03 (d, 6H, CH—*CH_3*) (J = 8.3 Hz), 3.68(s, 3H, COO—*CH_3*)
13	6.56–7.10 (m, 11H)	4.18 (br s)	2.64–3.14 (m, 6H, CH_2—P(S)), 2.62 (t, 2H, N—*CH_2*—CH_2) (J = 6.2Hz), 2.61 (t, 2H N—CH_2—*CH_2*) (J = 6.1 Hz), 3.25 (t, 1H, N—*CH*—CO— 2.62 (t, 2H N—CH—*CH_2*) (J = 6.2 Hz), 3.69 (s, 2H, Ar—*CH_2*)
14	6.52–7.14 (m, 11H)	4.02 (br s)	2.64–3.42 (m, 6H, CH_2—P(S)), 3.46(d, 2H, *CH_2*—CH) (J = 8.1 Hz), 3.24 (d, 1H CH_2—*CH*) (J = 8.2 Hz), 4.13 (s, 3H COO*CH_3*)
15	6.55–7.13 (m, 10H)	4.07 (br s)	3.12–3.42 (m, 6H, CH_2—P(S)), 3.25 (t, 1H, *CH*—CO) (J = 6.1 Hz), 3.83 (d, 2H, CH—*CH_2*) (J = 8.2 Hz), 4.14(q, 2H, *CH_2*—CH_3), 1.32 (t, 3H, CH_2—*CH_3*) (J = 6.2 Hz)

[a] Recorded in DMSO d_6, and J (Hz) given in parentheses.

Table 3

^{13}C NMR spectral data[a] of compounds **6, 7, 13**, and **14.**

	6	**7**	**13**	**14**
C_7 and C_{13}	110.3	111.3	111.2	111.3
C_8 and C_{12}	128.9	124.9	131.5	130.8
C_9 and C_{11}	115.9	115.8	130.6	130.3
C-10	132.8	132.8	129.9	129.8
C-15	111.9	112.1	106.2	106.2
C-6 and C-14	144.2	144.2	142.9	142.9
C_2 and C_4	46.4 (J = 128 Hz)	47.1 (J = 126 Hz)	46.8 (J = 132 Hz)	46.7 (J = 130 Hz)
(S)P—*C*H$_2$—NH	54.9 (J = 120 Hz)	54.6 (J = 122 Hz)	54.3 (J = 121 Hz)	54.3 (J = 124 Hz)
O—*C*H$_2$CH$_3$/O—*C*H$_3$/O—*C*H$_2$-Ph	62.9	56.9	65.8	54.1
O—CH$_2$*C*H$_3$	14.6	–	–	–
C_1^1	135.8	–	139.5	140.3
C_2^1 and C_6^1	128.8	–	127.7	122.8
C_3^1 and C_5^1	129.8	–	129.1	149.7
C_4^1	127.5	–	127.5	120.7
NH—*C*H—CO	70.2	70.9	–	62.2
*C*H(CH$_3$)$_2$	30.7	–	–	–
CH(*C*H$_3$)$_2$	17.8	–	–	–
*C*OOCH$_3$	171.6	–	–	–
COO*C*H$_3$	51.9	–	–	–
N—*C*H$_2$—CH$_2$	–	–	56.5	–
N—CH$_2$—*C*H$_2$	–	–	22.8	–
N—CH—*C*H$_2$	–	–	29.1	–
N—*C*H—CH$_2$	–	–	65.8	–
NH—CH—*C*O	–	–	171.6	172.8
NH—*C*H—CO	–	–	–	63.1
O—*C*H$_2$—Ar	–	–	68.5	–
—NH—*C*H—C	–	–	–	122.9
—NH—CH—*C*	–	–	–	112.1

[a] Recorded in DMSO d_6, and J (Hz) given in parentheses

82.45–86.17 ppm as expected [14]. Mass spectral data of compounds **7** and **11** are given (Table 4).

ANTIMICROIBIAL ACTIVITY

The compounds **6–15** were screened by disc diffusion method [15,16] for their antimicrobial activity against the fungi, *Aspergillus niger* and *Helminthosporium oryzae* and bacteria, *Escherichia coli* and *Staphylococcus aureus* by comparing with standard fungicide Griseofulvin and standard bactericide Penicillin at three different concentrations (100, 75, 50 ppm). The results are presented in Table 5.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Microanalysis was performed at the Indian Institute of Science, Bangalore and Central Drug Research Institute, Lucknow. IR Spectra were recorded in Environmental Engineering Lab, S.V.University, Tirupati as KBr discs on a Nicolet 380 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded 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 compounds were dissolved in DMSO-d_6. The ^{1}H and ^{13}C NMR chemical shifts were referenced to tetramethylsilane and ^{31}P chemical shifts to 85% H_3PO_4. Mass spectra were recorded on a Jeol SX 102 DA/600 mass spectrometer using Argon/Xenon (6 keV, 10 mA) as the FAB gas.

Preparation of tris (bromomethyl) phosphine (1). Because of the sensitivity of the reagents and products to moisture and oxygen, all manipulations were performed in an anhydrous inert nitrogen atmosphere. In a dry 100 mL three-necked round bottomed flask fitted with dropping funnel, a reflux condenser attached to a calcium chloride tube, an inlet for dry nitrogen and a thermometer reaching close to the bottom in the flask were placed magnesium turnings (0.12 g, 0.005 mole) and dry THF (5.0 mL). The reaction mixture was kept under stirring and dibromo methane (0.78 g, 0.005 moles) in 10 mL of dry THF was added drop wise at 10–15°C. When the reaction started the temperature increased to 40–50°C. The mixture was cooled to room temperature and stirring was

Table 4

Mass spectral data of compounds **7** and **11**.

Compd.	m/z (% relative abundance)
7	391[$M^{+\bullet}$, 20], 277 (53), 261 (100), 219 (35), 184 (09), 155 (25), 126 (45), 73 (36)
11	487[$M^{+\bullet}$, 19], 327 (26), 311 (56), 269 (100), 184 (13), 155 (29), 126 (81), 79 (19)

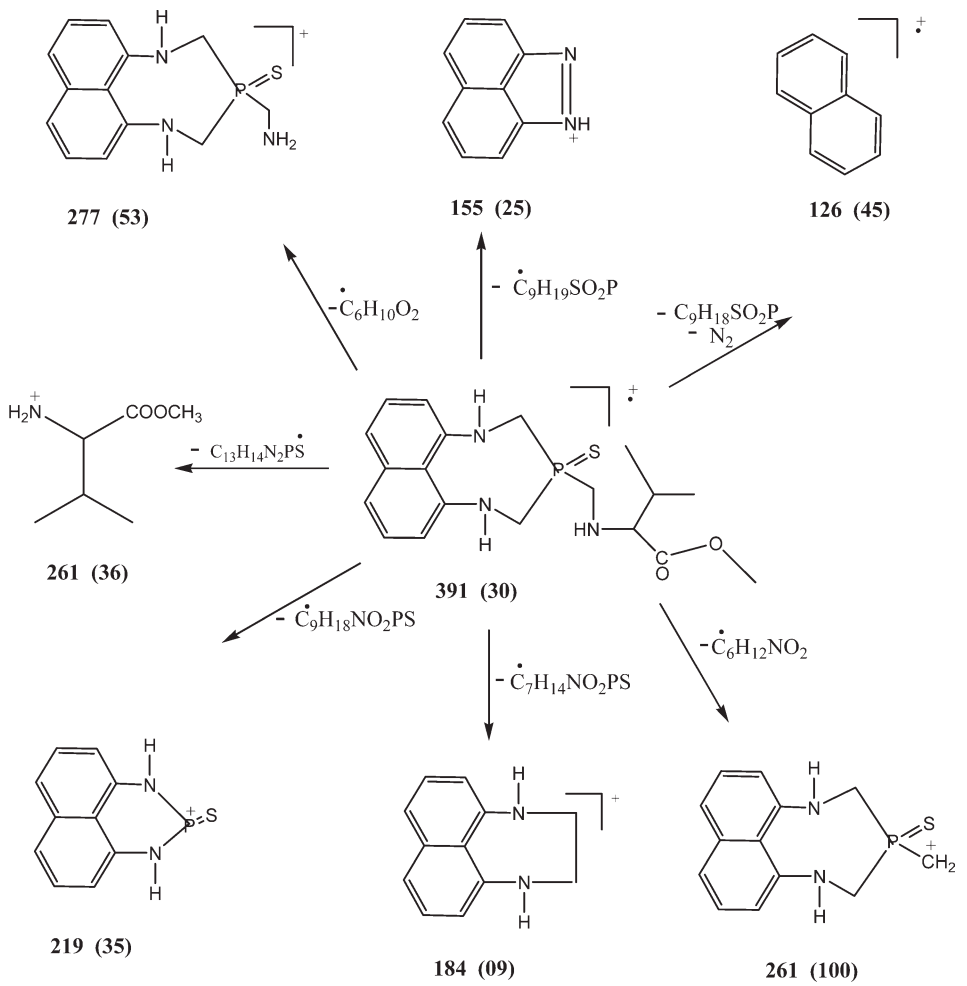
Table 5

Antimicrobial activity of the compounds **6–15.**

	Zone of inhibition (%)											
	Escherichia coli			*Staphylococcus aureus*			*Aspergillus niger*			*Helminthosporium oryzae*		
Compound	100	75	50	100	75	50	100	75	50	100	75	50
6	23	11	6	24	11	7	15	10	7	14	9	5
7	23	10	4	23	11	6	19	9	6	15	7	3
8	23	12	5	21	10	6	19	10	5	14	6	6
9	22	10	5	22	9	5	20	12	4	14	9	5
10	22	11	6	21	12	6	18	11	6	13	7	4
11	21	13	7	21	10	5	21	11	6	19	10	7
12	23	10	5	20	10	6	20	10	5	20	11	6
13	20	12	6	22	12	7	19	9	4	18	10	5
14	21	10	5	23	13	6	20	11	7	13	8	4
15	23	11	6	22	10	5	18	12	6	19	12	8
Penicillin	20	12	8	20	12	8						
Griseofulvin							20	10	5	20	10	5

continued until the magnesium metal was dissolved to form bromo methyl magnesium bromide. It is further reacted with PBr_3 to form tris (bromo methyl) phosphine and magnesium bromide salt. The magnesium bromide salt was separated by filtration under nitrogen atmosphere and the solvent was distilled off to get tris (bromo methyl) phosphine (**1**).

Scheme 2



3-(Bromomethyl)-2,3,4,5-tetrahydro-1*H*-naphtho [1, 8-*f*, *g*][1,5,3]diazaphosphocine (3). To a cooled (10°C) and stirred solution of 1,8-diaminonaphthalene (**2**, 0.69 g, 0.005 mole) and triethyl amine (1.01g, 0.01 mole) in 10 mL of dry THF under nitrogen gas, a solution of tris (bromo methyl) phosphine(**1**, 1.35 g, 0.005 mole) in 10 mL of dry THF was added 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 the intermediate (**3**).The progress of the reaction was judged by the TLC analysis. After completion of the reaction, it was filtered under nitrogen atmosphere and removed triethylamine hydrobromide.

3-(Bromomethyl)-1,2,4,5-tetrahydro-3-sulfanylene/selenylene-1*H*-naphtho[1,8- *f*,*g*][1,5,3]diazaphosphocine (4/5). The intermediate (3) in dry THF was cooled to 5°C, sulfur powder/ selenium metal was added to it and heated slowly up to gentle reflux with stirring and continued for 2 h for the completion of the reaction as indicated by TLC analysis. The solvent was removed in a rota-evaporator and the residue was extracted with ethyl acetate. The extract after drying over anhydrous $MgSO_4$ was removed in a rota- evaporator. The obtained crude products (4 and 5) were purified by column chromatography (hexane-ethylacetate 2:1) to yield 1.20 and 1.30 g (59, 70%) of 4 and 5, m.p. 180–182°C, 156–158°C, respectively.

General procedure for the preparation of 6–15. To the intermediate (**4**) in dry THF, phenyl glycine ethyl ester in dry THF (10 mL) was added in the presence of tri ethylamine 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. After completion of the reaction, Et3N.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 **6**. The same procedure was adopted for the preparation of other compounds **7–15**.

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