Synthesis and Bioassay of Oxazolyl/Thiazolyl Selenadiazoles, Thiadiazoles and Diazaphospholes

Venkatapuram Padmavathi,* Konda Mahesh, Annaji Venkata Nagendra Mohan, and Adivireddy Padmaja

Department of Chemistry, Sri Venkateswara University; Tirupati–517 502, India.
Received October 9, 2008; accepted February 27, 2009; published online March 10, 2009

A new class of bis heterocycles, oxazolyl/thiazolyl selenadiazoles, thiadiazoles and diazaphospholes were prepared from phenacylsulfonylacetic acid methyl ester and tested for their antimicrobial and antioxidant properties.

Key words oxazolyl/thiazolyl selenadiazole; thiadiazole; antioxidant property; diazaphosphole antimicrobial activity

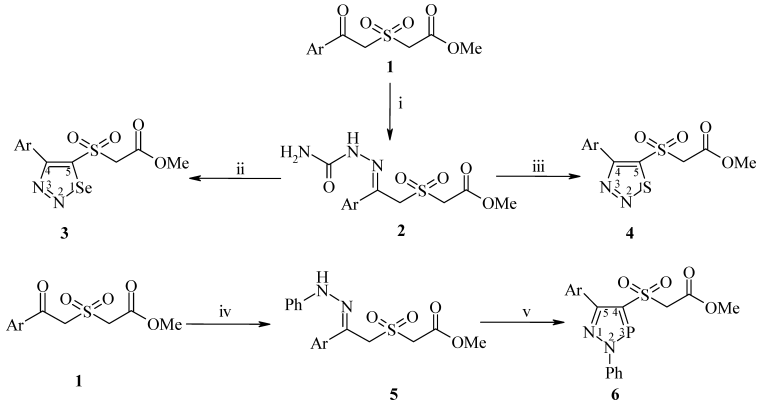
Heterocycles, the largest classical division of organic chemistry are of immense importance biologically, industrially and indeed to the functioning of any developed human society. The development of simple, facile and efficient synthetic methods for the synthesis of five-membered heterocycles is one of the major challenges in organic synthesis. In fact, we have reported the synthetic utility of multifunctional synthetic intermediate phenacylsulfonylacetic acid methyl ester for the synthesis of different heterocyclic systems.[1—4] In continuation of our studies in this direction we wish to report a new class of bis heterocycles *viz.*, selenadiazoles, thiadiazoles and 2*H*-diazaphospholes in combination with oxazolines and thiazolines.

Chemistry

In our earlier communication we have reported the synthesis of 1,2,3-selenadiazoles, thiadiazoles and 2*H*-diazaphospholes by exploiting α-ketomethylene group in phenacylsulfonylacetic acid methyl ester[3] (Chart 1). In fact, the preparation of oxazolines and thiazolines was reported by the traditional four step three intermediate route.[5] However, a one-pot methodology was developed for the preparation of oxazolines and thiazolines from the sulfonylacetic acid methyl esters exploiting lanthanide chemistry.[1,6] Indeed this method provides a simple and elegant route to develop oxazolines and thiazolines directly from carboxylic esters. In continuation of our efforts to develop bis heterocycles the ester functionality in (4-aryl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (**3**), (4-aryl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (**4**) and (2-phenyl-5-aryl-2*H*-[1,2,3]diazaphosphole-4-sulfonyl)acetic acid methyl ester (**6**) was used for oxazolines and thiazolines.

To achieve the desired bis heterocycles, (4-aryl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (**3**) was treated with 2-aminoethanol in the presence of *n*-butyllithium complexed with a suspension of 5—10% molar equivalents of anhydrous $SmCl_3$ in toluene. The compound obtained was identified as 5-(4′,5′-dihydrooxazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-selenadiazole (**7**). On the other hand, when the reaction of **3** was carried out with 2-aminoethanethiol in the presence of $SmCl_3$, 5-(4′,5′-dihydrothiazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-selenadiazole (**9**) was obtained (Chart 2). The ^{1}H-NMR spectra of **7a** and **9a** displayed three signals at 3.68, 3.71 (C_4′-H), 4.97, 3.32 (C_5′-H) and at 4.28, 4.25 ppm for (SO_2–CH_2). The ^{13}C-NMR spectrum of **7a** exhibited signals at 160.4 (C-2′), 52.4 (C-4′), 59.2 (C-5′), 159.1 (C-4), 157.7 (C-5), 55.2 ppm (SO_2–CH_2), whereas **9a** at 160.9 (C-2′), 52.8 (C-4′), 37.4 (C-5′), 158.7 (C-4), 157.8 (C-5), 55.4 ppm (SO_2–CH_2) besides signals due to aromatic carbons.

In a much similar way, 5-(4′,5′-dihydrooxazol-2′-yl-

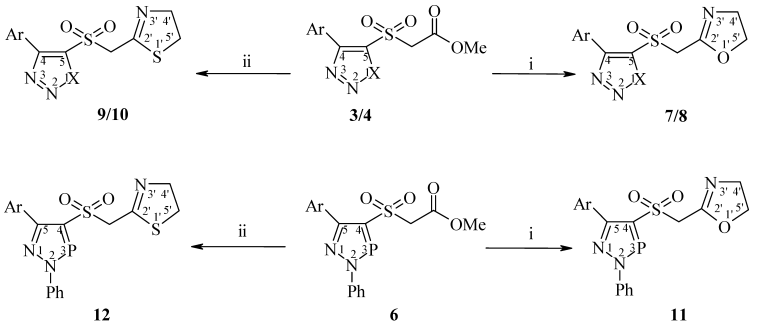


a: Ar = C_6H_5; **b**: Ar = *p*-$CH_3C_6H_4$; **c**: Ar = *p*-ClC_6H_4

(i) $NH_2NHCONH_2$ / AcONa/MeOH (ii) SeO_2/AcOH (iii) $SOCl_2/CH_2Cl_2$
(iv) $PhNHNH_2$/MeOH (v) $PCl_3/Et_3N/Et_2O$

Chart 1

* To whom correspondence should be addressed. e-mail: vkpuram2001@yahoo.com



7, **9** X = Se; **8**, **10** X =S

a: Ar = C_6H_5 ; **b**: Ar = *p*-$CH_3C_6H_4$; **c**: Ar = *p*-ClC_6H_4

i) $NH_2CH_2CH_2OH$, Sm(III)Cl_3, n-BuLi, Toluene

ii) $SHCH_2CH_2NH_2$, Sm(III)Cl_3, n-BuLi, Toluene

Chart 2

methylsulfonyl)-4-aryl-1,2,3-thiadiazole (**8**) and 5-(4′,5′-dihydrothiazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-thiadiazole (**10**) were prepared by the reaction of (4-aryl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (**4**) with 2-aminoethanol/2-aminoethanethiol in the presence of *n*-butyllithium complexed with 5—10% molar equivalents of anhydrous $SmCl_3$ (Chart 2). The ^{1}H-NMR spectra of **8a** and **10a** showed signals at 3.72, 3.74 (C_4'-H), 4.92, 3.36 (C_5'-H) and at 4.20, 4.23 ppm for (SO_2–CH_2). The ^{13}C-NMR spectrum of **8a** exhibited signals at 160.3 (C-2′), 52.3 (C-4′), 59.7 (C-5′), 158.6 (C-4), 157.7 (C-5), 55.8 ppm (SO_2–CH_2) whereas **10a** at 160.6 (C-2′), 52.0 (C-4′), 37.1 (C-5′), 159.2 (C-4), 158.6 (C-5), 55.1 ppm (SO_2–CH_2).

The ester functionality in (2-phenyl-5-aryl-2*H*-[1,2,3]diazaphosphole-4-sulfonyl)-acetic acid methyl ester (**6**) was also exploited to synthesize 4-(4′,5′-dihydrooxazol-2′-yl-methylsulfonyl)-2-phenyl-5-aryl-2*H*-1,2,3-diazaphosphole (**11**) and 4-(4′,5′-dihydrothiazol-2′-yl-methylsulfonyl)-2-phenyl-5-aryl-2*H*-1,2,3-diazaphosphole (**12**). Thus, the treatment of **6** with 2-aminoethanol/2-aminoethanethiol in the presence of *n*-butyllithium and 5—10% molar equivalents of $SmCl_3$ produced **11** and **12**, respectively (Chart 2). The ^{1}H-NMR spectra of **11a** and **12a** showed two triplets and a singlet at 3.66, 4.96, 4.24 and 3.78, 3.33, 4.22 ppm for C_4'-H, C_5'-H and SO_2CH_2. The ^{13}C-NMR spectrum of **11a** displayed signals at 161.2 (C-2′), 52.8 (C-4′), 59.7 (C-5′), 158.1 (C-4), 147.7 (C-5), 55.6 (SO_2–CH_2) whereas **12a** at 161.8 (C-2′), 52.3 (C-4′), 37.5 (C-5′), 157.2 (C-4), 148.2 (C-5), 55.1 ppm for (SO_2–CH_2).

Antimicrobial Testing The compounds **7**—**12** were tested for antimicrobial activity at two different concentrations 100 and 200 μg/ml. The antibacterial activity was screened against *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive bacteria) and *Escherichia coli*, *Klebsiella pneumoniae* (Gram-negative bacteria) on nutrient agar plates at 37 °C for 24 h using chloramphenicol (25 μg per disc) as reference drug. The compounds were also evaluated for their antifungal activity against *Fusarium solani*, *Curvularia lunata* and *Aspergillus niger* using ketoconazole (25 μg per disc) as standard drug. Fungi cultures were grown on potato dextrose agar medium (PDA) at 25 °C for 3 d. The spore suspension was adjusted to 10^6 pores/ml at a mg/ml concentration by the Vincent and Vincent method.[7)]

Table 1. Antibacterial Activity of **7**—**12**

Compound	Concentration (μg/ml)	Zone of inhibition (mm)			
		Gram (+)ve		Gram (−)ve	
		S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
7a	100	11	10	8	—
	200	14	12	9	9
7b	100	9	8	—	—
	200	11	11	—	—
7c	100	12	9	8	—
	200	15	13	10	—
8a	100	22	23	16	16
	200	26	26	20	19
8b	100	18	18	13	14
	200	22	23	16	17
8c	100	23	22	19	20
	200	27	25	21	23
9a	100	15	17	11	9
	200	18	21	14	11
9b	100	11	11	9	10
	200	13	14	12	12
9c	100	18	19	16	14
	200	24	23	18	11
10a	100	27	25	20	21
	200	31	28	24	23
10b	100	22	20	17	16
	200	25	24	20	19
10c	100	32	29	22	23
	200	34	33	26	25
11a	100	10	9	—	—
	200	12	12	—	—
11b	100	9	9	—	—
	200	11	10	—	—
11c	100	12	10	9	8
	200	15	14	11	9
12a	100	25	23	19	18
	200	28	27	22	22
12b	100	19	19	15	14
	200	23	24	18	17
12c	100	27	26	20	22
	200	29	29	23	24
Chloramphenicol	100	35	38	40	42
	200	39	41	44	45

The results of the compounds of preliminary antibacterial testing are shown in Table 1. The results revealed that, in general, the inhibitory activity against the Gram-positive bacteria was higher than that of the Gram-negative bacteria. The compounds having thiadiazole moiety showed greater activity than the compounds having selenadiazole unit. Similarly, compounds with thiazoline unit showed greater activity than compounds with oxazoline unit. In fact, the compounds **10a**, **10c**, **12a** and **12c** showed excellent activity against Gram-positive bacteria (inhibitory zone >27 mm) and good activity against Gram-negative bacteria (inhibitory zone >22 mm). The compounds **7** and **11** displayed less activity against both bacteria. All the test compounds exhibited moderate (**7a**—**c**, **8a**—**c**, **9a**—**c**, **11a**—**c**) to high (**10a**—**c**, **12a**—**c**) inhibitory effect towards tested fungi (Table 2).

Table 2. Antifungal Activity of **7**—**12**

Compound	Concentration (μg/ml)	Zone of inhibition (mm)		
		F. solani	*C. lunata*	*A. niger*
7a	100	15	16	16
	200	18	19	20
7b	100	14	15	17
	200	18	18	21
7c	100	17	17	15
	200	20	21	19
8a	100	25	26	25
	200	27	28	29
8b	100	22	23	22
	200	26	25	24
8c	100	28	28	26
	200	32	30	29
9a	100	22	23	20
	200	25	25	24
9b	100	19	20	18
	200	21	23	20
9c	100	23	23	21
	200	25	26	24
10a	100	33	33	30
	200	36	35	34
10b	100	28	27	28
	200	32	33	32
10c	100	34	34	33
	200	37	38	37
11a	100	17	16	17
	200	20	18	21
11b	100	16	15	16
	200	19	18	20
11c	100	17	17	18
	200	21	20	21
12a	100	29	26	25
	200	32	32	28
12b	100	26	25	26
	200	30	28	31
12c	100	33	32	30
	200	35	36	34
Ketoconazole	100	38	41	36
	200	42	44	39

The minimal inhibitory concentration (MIC) values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (Table 3). The structure–antimicrobial activity relationship of the synthesized compounds revealed that the compounds having selenadiazole and diazaphosphole rings in combination with oxazoline moiety exhibited less activity when compared with compounds having thiadiazole with thiazoline moiety. Among the substituents on the aryl group, 4-chlorophenyl derivatives were the most active. The maximum activity was observed with compounds **10a**, **10c** and **12c**.

Antioxidant Testing The compounds **7**—**12** were tested for antioxidant property by nitric oxide[8,9] and 1,1-diphenyl-2-picrylhydrazyl (DPPH)[10] methods. The compounds **7a**, **7c**, **9a** and **9c** exhibited high antioxidant property in both nitric oxide and DPPH methods at 100 μM concentration (Table 4).

Conclusion

A new class of bis heterocycles-oxazolyl/thiazolyl selenadiazoles, thiadiazoles and diazaphospholes were developed by appropriate functionalization of α-ketomethylene and ester functionalities in phenacylsulfonylacetic acid methyl ester. The compounds thiazolyl thiadiazoles and thiazolyl diazaphospholes exhibited good antimicrobial activity. However, oxazoyl/thiazolyl selenadiazoles showed good antioxi-

Table 4. Antioxidant Property of **7**—**12**

Compound	% Inhibition at 100 μM	
	Nitric oxide method	DPPH method
7a	81.17	83.52
7b	41.44	43.68
7c	88.14	86.48
8a	32.27	33.74
8b	40.74	39.57
8c	34.69	36.74
9a	89.64	91.21
9b	41.52	42.29
9c	91.42	92.31
10a	34.71	34.79
10b	38.16	39.14
10c	24.11	25.65
11a	32.62	34.71
11b	24.32	26.21
11c	36.44	34.52
12a	29.58	28.65
12b	22.43	21.28
12c	39.42	38.69

Table 3. Minimal Inhibitory Concentrations (MIC, μg/ml) of Compounds **10a**, **10c** and **12c**

Compound	Minimal inhibitory concentration (MIC, μg/ml)						
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*F. solani*	*C. lunata*	*A. niger*
10a	12.5	50	12.5	50	50	12.5	25
10c	25	100	50	50	100	50	100
12c	100	200	50	100	100	100	100
Chloramphenicol	6.25	6.25	6.25	12.5	—	—	—
Ketoconazole	—	—	—	—	12.5	6.25	6.25

dant property.

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and were uncorrected. The purity of the compounds was checked by TLC (silica gel H, British Drug House (BDH), ethyl acetate–hexane, 0.5 : 2). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts were reported in δ (ppm) using tetramethylsilane (TMS) as an internal standard. The microanalyses were performed on Perkin-Elmer 240C elemental analyzer. The antioxidant property was carried out by using Shimadzu UV-2450 spectrophotometer. The starting compounds (4-aryl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (**3**), (4-aryl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (**4**) and (2-phenyl-5-aryl-2*H*-[1,2,3]diazaphosphole-4-sulfonyl)acetic acid methyl ester (**6**) were prepared by the literature procedure.[3)]

General Procedure of Synthesis of 5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-selenadiazole (7a—c) To a flask charged with anhydrous samarium chloride (0.1 mmol), dry toluene (10 ml) and 2-aminoethanol (2 mmol) followed by *n*-butyllithium (2.2 mmol) were added at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. Then the contents were refluxed to 100—120 °C and (4-aryl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (**3**) (1 mmol) was added and continued the refluxion for an additional period of 12—14 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with chloroform, washed with water followed by brine solution. The solvent was removed *in vacuo*. The product was purified by column chromatography (hexane–ethyl acetate, 1.5 : 1).

5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-phenyl-1,2,3-selenadiazole (**7a**): Red solid, yield 65%, mp 136—138 °C; IR (KBr) cm^{-1}: 1579 (C=N), 1444 (N=N), 1336, 1137 (SO_2), 731 (C–Se); ^{1}H-NMR (DMSO-d_6) δ: 3.68 (t, 2H, C-4′ J=5.1 Hz), 4.28 (s, 2H, SO_2–CH_2), 4.97 (t, 2H, C-5′, J=5.1 Hz), 7.30—7.60 (m, 5H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 52.4 (C-4′), 55.2 (SO_2–CH_2), 59.2 (C-5′), 157.7 (C-5), 159.1 (C-4), 160.4 (C-2′), 127.2, 130.7, 135.3, 135.9 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{11}N_3O_3SSe$: C, 40.46; H, 3.11; N, 11.79; Found: C, 40.58; H, 3.18; N, 11.90.

5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-*p*-methylphenyl-1,2,3-selenadiazole (**7b**): Red solid, yield 62%, mp 125—127 °C; IR (KBr) cm^{-1}: 1584 (C=N), 1431 (N=N), 1332, 1131 (SO_2), 729 (C–Se); ^{1}H-NMR (DMSO-d_6) δ: 2.22 (s, 3H, Ar-CH_3), 3.65 (t, 2H, C-4′, J=5.5 Hz), 4.22 (s, 2H, SO_2–CH_2), 4.93 (t, 2H, C-5′, J=5.5 Hz), 7.32—7.61 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.4 (Ar-CH_3), 51.8 (C-4′), 55.8 (SO_2–CH_2), 58.6 (C-5′), 157.5 (C-5), 158.1 (C-4), 160.1 (C-2′), 126.2, 130.4, 132.8, 135.6 (aromatic carbons): *Anal.* Calcd for $C_{13}H_{13}N_3O_3SSe$: C, 42.17; H, 3.54; N, 11.35; Found: C, 42.25; H, 3.58; N, 11.30.

5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-*p*-chlorophenyl-1,2,3-selenadiazole (**7c**): Red solid, yield 67%, mp 140—142 °C; IR (KBr) cm^{-1}: 1581 (C=N), 1452 (N=N), 1340, 1140 (SO_2), 724 (C–Se); ^{1}H-NMR (DMSO-d_6) δ: 3.70 (t, 2H, C-4′, J=5.3 Hz), 4.25 (s, 2H, SO_2–CH_2), 5.02 (t, 2H, C-5′, J=5.3 Hz), 7.34—7.66 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 51.6 (C-4′), 55.6 (SO_2–CH_2), 60.2 (C-5′), 158.1 (C-5), 159.3 (C-4), 161.0 (C-2′), 128.7, 128.8, 129.4, 133.4 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{10}ClN_3O_3SSe$: C, 36.89; H, 2.58; N, 10.75; Found: C, 36.80; H, 2.55; N, 10.85.

General Procedure of Synthesis of 5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-thiadiazole (8a—c) To a mixture of anhydrous samarium chloride, (0.1 mmol), dry toluene (10 ml) and 2-aminoethanol, (2 mmol), *n*-butyllithium (2.2 mmol) was added at 0 °C and stirred for 15 min. Then the contents were allowed to attain room temperature. To this (4-aryl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (**4**) (1 mmol) was added and the reaction mixture was refluxed for a period of 13—15 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with chloroform, washed with water and the solvent was removed under reduced pressure. The solid obtained was purified by column chromatography (hexane–ethyl acetate, 1.3 : 1).

5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-phenyl-1,2,3-thiadiazole (**8a**): White solid, yield 64%, mp 180—182 °C; IR (KBr) cm^{-1}: 1586 (C=N), 1449 (N=N), 1331, 1133 (SO_2), 719 (C–S); ^{1}H-NMR (DMSO-d_6) δ: 3.72 (t, 2H, C-4′, J=5.2 Hz), 4.20 (s, 2H, SO_2–CH_2), 4.92 (t, 2H, C-5′, J=5.2 Hz), 7.28—7.63 (m, 5H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 52.3 (C-4′), 55.8 (SO_2–CH_2), 59.7 (C-5′), 157.7 (C-5), 158.6 (C-4), 160.3 (C-2′), 128.4, 129.4, 131.2, 132.1 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{11}N_3O_3S_2$: C, 46.59 ; H, 3.58; N, 13.58 ; Found: C, 46.68; H, 3.63; N, 13.66.

5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-*p*-methylphenyl-1,2,3-thiadiazole (**8b**): White solid, yield 68%, mp 187—188 °C; IR (KBr) cm^{-1}: 1582 (C=N), 1447 (N=N), 1342, 1137 (SO_2), 721 (C–S); ^{1}H-NMR (DMSO-d_6) δ: 2.25 (s, 3H, Ar-CH_3), 3.63 (t, 2H, C-4′, J=5.5 Hz), 4.26 (s, 2H, SO_2–CH_2), 4.90 (t, 2H, C-5′, J=5.5 Hz), 7.25—7.60 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 21.8 (Ar-CH_3), 51.2 (C-4′), 55.3 (SO_2–CH_2), 58.9 (C-5′), 157.3 (C-5), 158.2 (C-4), 160.8 (C-2′), 126.0, 128.4, 129.6, 131.7 (aromatic carbons): *Anal.* Calcd for $C_{13}H_{13}N_3O_3S_2$: C, 48.28; H, 4.05; N, 12.99; Found: C, 48.22; H, 4.08; N, 13.06.

5-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-4-*p*-chlorophenyl-1,2,3-thiadiazole (**8c**): White solid, yield 70%, mp 195—196 °C; IR (KBr) cm^{-1}: 1589 (C=N), 1452 (N=N), 1338, 1141 (SO_2), 726 (C–S); ^{1}H-NMR (DMSO-d_6) δ: 3.67 (t, 2H, C-4′, J=5.3 Hz), 4.24 (s, 2H, SO_2–CH_2), 5.00 (t, 2H, C-5′, J=5.3 Hz), 7.34—7.67 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 50.8 (C-4′), 55.1 (SO_2–CH_2), 59.3 (C-5′), 158.7 (C-5), 158.9 (C-4), 161.8 (C-2′), 128.2, 129.5, 130.6, 132.6 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{10}ClN_3O_3S_2$: C, 41.92; H, 2.93; N, 12.22; Found: C, 41.97; H, 3.00; N, 12.28.

General Procedure of Synthesis of 5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-selenadiazole (9a—c) Dry toluene (10 ml) and 2-aminoethnethiol (2 mmol) were added to a flask charged with anhydrous samarium chloride (0.1 mmol). Then *n*-buyllithium (2.2 mmol) was added at 0 °C portion-wise while stirring and the flask was allowed to attain room temperature. To this, (4-aryl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (**3**) was added and refluxed for 9—12 h. The suspension was cooled to room temperature, filtered and washed with chloroform. The filtrate was extracted with chloroform and washed with water. The solvent was removed *in vacuo*. The solid obtained was purified by column chromatography (hexane–ethyl acetate, 2 : 1.4).

5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-phenyl-1,2,3-selenadiazole (**9a**): Red solid, yield 62%, mp 145—147 °C; IR (KBr) cm^{-1}: 1591 (C=N), 1451 (N=N), 1334, 1139 (SO_2), 722 (C–Se); ^{1}H-NMR (DMSO-d_6) δ: 3.32 (t, 2H, C-5′, J=7.3 Hz), 3.71 (t, 2H, C-4′, J=7.3 Hz), 4.25 (s, 2H, SO_2–CH_2), 7.31—7.64 (m, 5H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 37.4 (C-5′), 52.8 (C-4′), 55.4 (SO_2–CH_2), 157.8 (C-5), 158.7 (C-4), 160.9 (C-2′), 127.9, 129.4, 130.4, 132.4 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{11}N_3O_2S_2Se$: C, 38.71; H, 2.98; N, 11.29; Found: C, 38.79; H, 2.92; N, 11.21.

5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-*p*-methylphenyl-1,2,3-selenadiazole (**9b**): Red solid, yield 70%, mp 152—154 °C; IR (KBr) cm^{-1}: 1588 (C=N), 1455 (N=N), 1345, 1140 (SO_2), 727 (C–Se); ^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H, Ar-CH_3), 3.35 (t, 2H, C-5′, J=7.1 Hz), 3.76 (t, 2H, C-4′, J=7.1 Hz), 4.21 (s, 2H, SO_2–CH_2), 7.34—7.69 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.6 (Ar-CH_3), 38.1 (C-5′), 51.7 (C-4′), 55.0 (SO_2–CH_2), 157.3 (C-5), 158.2 (C-4), 161.3 (C-2′), 126.5, 128.3, 129.8, 131.4 (aromatic carbons): *Anal.* Calcd for $C_{13}H_{13}N_3O_2S_2Se$: C, 40.41; H, 3.39; N, 10.88; Found: C, 40.50; H, 3.43; N, 10.95.

5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-*p*-chlorophenyl-1,2,3-selenadiazole (**9c**): Red solid, yield 65%, mp 159—161 °C; IR (KBr) cm^{-1}: 1594 (C=N), 1459 (N=N), 1339, 1146 (SO_2), 734 (C–Se); ^{1}H-NMR (DMSO-d_6) δ: 3.39 (t, 2H, C-5′, J=7.6 Hz), 3.79 (t, 2H, C-4′, J=7.6 Hz), 4.27 (s, 2H, SO_2–CH_2), 7.35—7.71 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 37.8 (C-5′), 52.3 (C-4′), 55.6 (SO_2–CH_2), 158.0 (C-5), 158.9 (C-4), 161.7 (C-2′), 128.7, 128.8, 129.4, 135.4 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{10}ClN_3O_2S_2Se$: C, 35.43; H, 2.48; N, 10.33; Found: C, 35.39; H, 2.54; N, 10.38.

General Procedure of Synthesis of 5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-aryl-1,2,3-thiadiazole (10a—c) Dry toluene (10 ml) and 2-aminoethanethiol (2 mmol) were added to the flask charged with anhydrous samarium chloride (0.1 mmol). To this, *n*-butyllithium (2.2 mmol) was added at 0 °C and stirred at the same temperature for 15 min. Then (4-aryl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (**4**) (1 mmol) was added and the reaction mixture was refluxed for 8—10 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with chloroform and washed with water. The solvent was removed under reduced pressure. The resultant solid was purified by column chromatography (hexane–ethyl acetate, 2 : 1.5).

5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-phenyl-1,2,3-thiadiazole (**10a**): White solid, yield 72%, mp 178—180 °C; IR (KBr) cm^{-1}: 1596 (C=N), 1453 (N=N), 1331, 1132 (SO_2), 720 (C–S); ^{1}H-NMR (DMSO-d_6) δ: 3.36 (t, 2H, C-5′, J=7.0 Hz), 3.74 (t, 2H, C-4′, J=7.0 Hz), 4.23 (s, 2H, SO_2–CH_2), 7.36—7.71 (m, 5H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 37.1 (C-5′), 52.0 (C-4′), 55.1 (SO_2–CH_2), 158.6 (C-5), 159.2 (C-4), 160.6 (C-2′), 127.0,

128.4, 130.4, 131.6 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{11}N_3O_2S_3$: C, 44.29; H, 3.41; N, 12.91; Found: C, 44.25; H, 3.37; N, 12.95.

5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-*p*-methylphenyl-1,2,3-thiadiazole (**10b**): White solid, yield 70%, mp 171—173 °C; IR (KBr) cm^{-1}: 1582 (C=N), 1459 (N=N), 1340, 1146 (SO_2), 729 (C–S); ^{1}H-NMR (DMSO-d_6) δ: 2.23 (s, 3H, Ar-CH_3), 3.38 (t, 2H, C-5′, J=7.4 Hz), 3.70 (t, 2H, C-4′, J=7.4 Hz), 4.26 (s, 2H, SO_2–CH_2), 7.31—7.62 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.2 (Ar-CH_3), 37.9 (C-5′), 52.2 (C-4′), 55.3 (SO_2–CH_2), 157.9 (C-5), 159.6 (C-4), 160.1 (C-2′), 127.8, 128.1, 129.2, 130.6 (aromatic carbons): *Anal.* Calcd for $C_{13}H_{13}N_3O_2S_3$: C, 46.00; H, 3.86; N, 12.38; Found: C, 46.10; H, 3.91; N, 12.31.

5-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-4-*p*-chlorophenyl-1,2,3-thiadiazole (**10c**): White solid, yield 74%, mp 185—186 °C; IR (KBr) cm^{-1}: 1599 (C=N), 1452 (N=N), 1332, 1141 (SO_2), 737 (C–S); ^{1}H-NMR (DMSO-d_6) δ: 3.42 (t, 2H, C-5′, J=7.7 Hz), 3.76 (t, 2H, C-4′, J=7.4 Hz), 4.21 (s, 2H, SO_2–CH_2), 7.34—7.69 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 37.6 (C-5′), 52.7 (C-4′), 55.9 (SO_2–CH_2), 158.7 (C-5), 159.2 (C-4), 160.6 (C-2′), 128.2, 129.6, 130.4, 131.4 (aromatic carbons): *Anal.* Calcd for $C_{12}H_{10}ClN_3O_2S_3$: C, 40.05; H, 2.80; N, 11.68; Found: C, 40.11; H, 2.83; N, 11.74.

General Procedure of Synthesis of 4-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-2-phenyl-5-aryl-2*H*-1,2,3-diazaphospholes (11a—c) To a flask charged with anhydrous samarium chloride (0.1 mmol), dry toluene (10 ml) and 2-aminoethanol (2 mmol) were added followed by *n*-butyllithium (2.2 mmol) at 0 °C. the reaction mixture was stirred at 0 °C for 30—40 min. Then the contents were refluxed to 100—120 °C and (2-phenyl-5-aryl-2*H*-[1,2,3]diazaphosphole-4-sulfonyl)acetic acid methyl ester (**6**) (1 mmol) was added and continued the refluxion for an additional period of 14—18 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with dichloromethane, washed with water followed by brine solution. the solvent was removed *in vacuo*. The product was purified by column chromatography (hexane–ethyl acetate, 2 : 1).

4-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-2,5-diphenyl-2*H*-1,2,3-diazaphosphole (**11a**): Yellow solid, yield 62%, mp 160—162 °C; IR (KBr) cm^{-1}: 1581 (C=N), 1331, 1132 (SO_2); ^{1}H-NMR (DMSO-d_6) δ: 3.66 (t, 2H, C-4′, J=5.5 Hz), 4.24 (s, 2H, SO_2–CH_2), 4.96 (t, 2H, C-5′, J=5.5 Hz), 7.64—7.72 (m, 10H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 52.8 (C-4′), 55.6 (SO_2–CH_2), 59.7 (C-5′), 147.7 (C-5), 158.1 (C-4), 161.2 (C-2′), 128.2, 129.7, 130.8, 131.2, 132.2, 133.8, 134.2, 134.4 (aromatic carbons): *Anal.* Calcd for $C_{18}H_{16}N_3O_3PS$: C, 56.10; H, 4.18; N, 10.90; Found: C, 56.16; H, 4.22; N, 10.96.

4-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-5-*p*-methylphenyl-2-phenyl-2*H*-1,2,3-diazaphosphole (**11b**): Yellow solid, yield 66%, mp 155—157 °C; IR (KBr) cm^{-1}: 1576 (C=N), 1340, 1146 (SO_2); ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, Ar-CH_3), 3.63 (t, 2H, C-4′, J=5.1 Hz), 4.34 (s, 2H, SO_2–CH_2), 4.89 (t, 2H, C-5′, J=5.1 Hz), 7.30—7.68 (m, 9H, Ar-H) ^{13}C-NMR (DMSO-d_6) δ: 22.3 (Ar-CH_3), 51.2 (C-4′), 55.4 (SO_2–CH_2), 58.9 (C-5′), 148.4 (C-5), 159.0 (C-4), 161.6 (C-2′), 127.3, 128.7, 129.3, 130.6, 131.1, 131.9, 132.7, 133.9 (aromatic carbons): *Anal.* Calcd for $C_{19}H_{18}N_3O_3PS$: C, 57.14; H, 4.54; N, 10.52; Found: C, 57.10; H, 4.51; N, 10.55.

4-(4′,5′-Dihydrooxazol-2′-yl-methylsulfonyl)-5-*p*-chlorophenyl-2-phenyl-2*H*-1,2,3-diazaphosphole (**11c**): Yellow solid, yield 65%, mp 168—170 °C; IR (KBr) cm^{-1}: 1584 (C=N), 1334, 1149 (SO_2); ^{1}H-NMR (DMSO-d_6) δ: 3.69 (t, 2H, C-4′, J=5.4 Hz), 4.29 (s, 2H, SO_2–CH_2), 4.99 (t, 2H, C-5′, J=5.4 Hz), 7.38—7.82 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 51.8 (C-4′), 55.9 (SO_2–CH_2), 59.5 (C-5′), 148.9 (C-5), 157.9 (C-4), 161.4 (C-2′), 128.3, 128.9, 129.6, 131.5, 132.6, 133.4, 133.9, 134.8 (aromatic carbons): *Anal.* Calcd for $C_{18}H_{15}ClN_3O_3PS$: C, 51.50; H, 3.60; N, 10.01; Found: C, 51.56; H, 3.65; N, 10.08.

General Procedure of Synthesis of 4-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-2-phenyl-5-aryl-2*H*-1,2,3-diazaphospholes (12a—c) Anhydrous samarium chloride (0.1 mmol), dry toluene (10 ml) and 2-aminoethanethiol (2 mmol) were taken into a flask, and to this, *n*-butyllithium (2.2 mmol) was added at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min, the flask was heated to reflux. Then (2-phenyl-5-aryl-2*H*-[1,2,3]diazaphosphole-4-sulfonyl)acetic acid methyl ester (**6**) (1 mmol) was added and refluxed for an additional period of 10—12 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with chloroform, washed with water, and the solvent was removed under vacuum. The product was purified by column chromatography (hexane–ethyl acetate, 2 : 0.8).

4-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-2,5-diphenyl-2*H*-1,2,3-diazaphosphole (**12a**): Yellow solid, yield 67%, mp 176—178 °C: IR (KBr) cm^{-1}: 1586 (C=N), 1330, 1137 (SO_2); ^{1}H-NMR (DMSO-d_6) δ: 3.33 (t, 2H, C-5′, J=7.2 Hz), 3.78 (t, 2H, C-4′, J=7.2 Hz), 4.22 (s, 2H, SO_2–CH_2), 7.61—7.70 (m, 10H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 37.5 (C-5′), 52.3 (C-4′), 55.1 (SO_2–CH_2), 148.2 (C-5), 157.2 (C-4), 161.8 (C-2′), 128.7, 129.4, 130.2, 131.6, 132.1, 132.8, 133.7, 134.0 (aromatic carbons): *Anal.* Calcd for $C_{18}H_{16}N_3O_2PS_2$: C, 53.85; H, 4.02; N, 10.47; Found: C, 53.92; H, 4.00; N, 10.40.

4-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-5-*p*-methylphenyl-2-phenyl-2*H*-1,2,3-diazaphosphole (**12b**): Yellow solid, yield 69%, mp 149—151 °C; IR (KBr) cm^{-1}: 1588 (C=N), 1342, 1145 (SO_2); ^{1}H-NMR (DMSO-d_6) δ: 2.26 (s, 3H, Ar-CH_3), 3.37 (t, 2H, C-5′, J=7.5 Hz), 3.72 (t, 2H, C-4′, J=7.5 Hz), 4.30 (s, 2H, SO_2–CH_2), 7.64—7.71 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 22.7 (Ar-CH_3), 37.9 (C-5′), 53.1 (C-4′), 54.2 (SO_2–CH_2), 148.9 (C-5), 156.9 (C-4), 161.1 (C-2′), 128.1, 129.8, 130.7, 131.3, 132.5, 133.2, 133.9, 134.2 (aromatic carbons): *Anal.* Calcd for $C_{19}H_{18}N_3O_2PS_2$: C, 54.93; H, 4.37; N, 10.11; Found: C, 54.88; H, 4.40; N, 10.15.

4-(4′,5′-Dihydrothiazol-2′-yl-methylsulfonyl)-5-*p*-chlorophenyl-2-phenyl-2*H*-1,2,3-diazaphosphole (**12c**): Yellow solid, yield 63%, mp 162—164 °C; IR (KBr) cm^{-1}: 1592 (C=N), 1333, 1141 (SO_2); ^{1}H-NMR (DMSO-d_6) δ: 3.40 (t, 2H, C-5′, J=7.8 Hz), 3.76 (t, 2H, C-4′, J=7.8 Hz), 4.23 (s, 2H, SO_2–CH_2), 7.62—7.79 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ: 37.1 (C-5′), 52.6 (C-4′), 55.4 (SO_2–CH_2), 148.0 (C-5), 157.6 (C-4), 160.5 (C-2′), 128.5, 129.1, 130.4, 131.9, 132.7, 133.1 133.9, 134.8 (aromatic carbons): *Anal.* Calcd for $C_{18}H_{15}ClN_3O_2PS_2$: C, 49.60; H, 3.47; N, 9.64; Found: C, 49.67; H, 3.49; N, 9.70.

Antimicrobial Testing The compounds **7**—**12** were dissolved in dimethyl sulfoxide (DMSO) at different concentrations of 100, 200 and 800 μg/ml.

Antibacterial and Antifungal Assays Preliminary antimicrobial activity of compounds **7**—**12** was tested by agar disc-diffusion method. Sterile filter paper discs (6 mm diameter) moistened with the test compound solution in DMSO of specific concentration 100 μg and 200 μg/disc were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 °C and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and after 48 h in case of fungi.

The MICs of the compound assays were determined using microdilution susceptibility method. Chloramphenicol was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The test compounds, chloramphenicol and ketoconazole were dissolved in DMSO at concentration of 800 μg/ml. The two-fold dilution of the solution was prepared (400, 200, 100, …, 6.25 μg/ml). The microorganism suspensions were incubated at 36 °C for 24 and 48 h for bacteria and fungi, respectively. The minimum inhibitory concentrations of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no turbidity (*i.e.* no growth) of inoculated bacteria/fungi.

Antioxidant Testing The compounds **7**—**12** are tested for antioxidant property by nitric oxide and DPPH methods.

Assay for Nitric Oxide (NO) Scavenging Activity Sodium nitroprusside (5 μM) in phosphate buffer pH 7.4 was incubated with 100 μM concentration of test compounds dissolved in a suitable solvent (dioxane/methanol) and tubes were incubated at 25 °C for 120 min. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 ml of incubation solution was taken and diluted with 0.5 ml of griess reagent (1% sulfanilamide, 0.1% *N*-naphthylethylenediamine dihydrochloride and 2% *O*-phosphoric acid dissolved in distilled water). The absorbance of the chordophone formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthylethylenediamine dihydrochloride was read at λ 546 nm. The experiment was repeated in triplicate.

Reduction of 1,1-Diphenyl-2-picrylhydrazyl (DPPH) Free Radical (DPPH Method) The nitrogen centered stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at λ 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties.

The solutions of test compounds (100 μM) were added to DPPH (100 μM) in dioxane/ethanol. The tubes were kept at an ambient temperature for 20 min and the absorbance was measured at λ 517 nm. The difference between the test and the control experiments was taken and expressed as the

per cent scavenging of the DPPH radical.

Acknowledgements The authors are thankful to UGC, New Delhi, India for financial assistance under major research project. One of the authors K. Mahesh is thankful to CSIR, New Delhi, India for the sanction of Senior Research Fellowship.

References

1) Padmavathi V., Obula Reddy B. C., Thriveni P., Nagendra Mohan A. V., *Synth. Commun.*, **37**, 3127—3142 (2007).
2) Padmavathi V., Thriveni P., Obula Reddy B. C., Mahesh K., *J. Heterocycl. Chem.*, **44**, 93—98 (2007).
3) Padmavathi V., Mahesh K., Thriveni P., Ramana Reddy T. V., *J. Heterocycl. Chem.*, **44**, 1165—1169 (2007).
4) Padmavathi V., Nagendra Mohan A. V., Mahesh K., *J. Heterocycl. Chem.*, **45**, 1131— 1138 (2008).
5) Padmavathi V., Obula Reddy B. C., Venkata Subbaiah D. R. C., Padmaja A., *Indian J. Chem.*, **43B**, 2456—2458 (2004).
6) Padmavathi V., Obula Reddy B. C., Nagendra Mohan A. V., Padmaja A., *J. Heterocycl. Chem.*, **44**, 459—462 (2007).
7) Vincent J. C., Vincent H. W., *Proc. Soc. Exp. Biol. Merd.*, **55**, 162—164 (1944).
8) Shirwaiker A., Rajendran K., Dinesh Kumar C., *Indian J. Expl. Biol.*, **42**, 803—807 (2004).
9) Babu B. H., Shailesh B. S., Paddikala J., *Fitotherapia*, **72**, 272—279 (2001).
10) Kato K., Terao S., Shimamoto N., Hirata M., *J. Med. Chem.*, **31**, 793—798 (1988).