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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antioxidant activity of pyrazolyl-oxazolines/thiazolines and isoxazolyl-oxazolines/thiazolines

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Abstract A new class of pyrazolyl/isoxazolyl-oxazolines and thiazolines were synthesized from *E*-arylsulfonylethenesulfonylacetic acid methyl ester and tested for antioxidant activity. Among the tested compounds, **14b** exhibited excellent antioxidant activity when compared with the standard ascorbic acid.

Keywords Pyrazolyl-oxazoline/thiazoline · Isoxazolyl-oxazoline/thiazoline · Nitrile imine · Nitrile oxide · Antioxidant activity

Introduction

Azoles are one of the most prevalent heterocyclic compounds that are frequently found in a variety of natural products and pharmaceuticals. Pyrazoles and isoxazoles have attracted much attention since they play vital role in synthetic organic chemistry over the years and are important bioactive compounds as anticancer (Shin *et al.*, 2005; Amer *et al.*, 2007; Abdolhamid *et al.*, 2008), antiviral (Sechi *et al.*, 2005), anti-inflammatory (Rapposelli *et al.*, 2004), antidiabetic (Cottineau *et al.*, 2002), antibacterial and antifungal agents (Cali *et al.*, 2004; Shinde *et al.*, 2004; Al-Omran and El-Khair, 2004). Several pharmaceutical drugs including celecoxib (Penning *et al.*, 1997), rimonabant (Deng and Mani, 2008) and valdecoxib (Dannhardt *et al.*, 2000) contain the pyrazole and isoxazole as their core molecular entity (Katritzky *et al.*, 2001; Elguero *et al.*, 1996; Deng and Mani, 2006). Besides, the marketed drugs of isoxazole such as acetylsulfisoxazole, cycloserine, drazoxol, sulfisoxazole, and zonisamide show antimicrobial (Vyas *et al.*, 2007; Clark and McElligott, 1969), tuberculostatic (Folkers and co-workers, 1955), anticonvulsant (Ozdemir *et al.*, 2007), neurotoxic (Kamei *et al.*, 1978), and antiepileptic activities (Sackellares *et al.*, 1985). Oxazoline and thiazoline rings are important constituents of bioactive natural products and pharmaceuticals (Wang and Dervan, 2001; Sharma *et al.*, 2001; Dyatkina *et al.*, 2002). The oxazole ring is a useful structural moiety found in numerous biologically active molecules (Padmaja *et al.*, 2011). Natural product hennoxazole A, first isolated from the marine sponge, exhibit predominant antiviral activity against herpes simplex type I (Ichiba *et al.*, 1991). The thiazole ring is an interesting building block in a variety of natural products and bioactive compounds useful as pharmaceuticals or agrochemical agents (Rivkin *et al.*, 2004; Ganesh *et al.*, 2003; Plazzi *et al.*, 1995; Bai *et al.*, 2008; Hu *et al.*, 2009). In fact, compounds with good antioxidant activity are supposed to have good anti-inflammatory activity. In view of the importance of different five-membered heterocycles we have synthesized a variety of bioactive heterocycles and studied their biological activity (Padmaja *et al.*, 2011; Muralikrishna *et al.*, 2012; Mallikarjuna *et al.*, 2013). In continuation of our efforts in this direction the present work, synthesis and antioxidant activity of sulfonylmethane-linked pyrazolyl-oxazolines/thiazolines and isoxazolyl-oxazolines/thiazolines is taken up Figs. 1, 2, 3.

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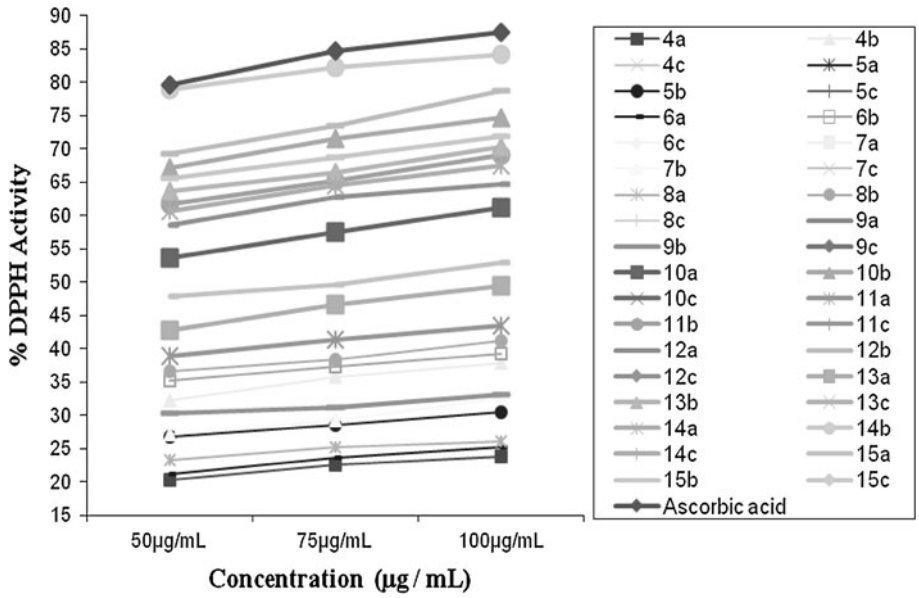


Fig. 1 The in vitro antioxidant activity of **4**–**15** in DPPH method

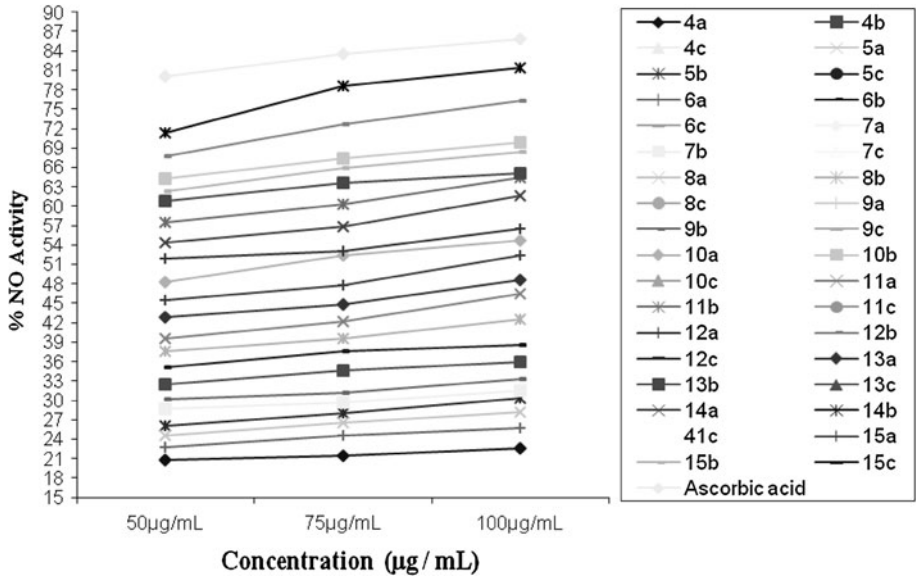


Fig. 2 The in vitro antioxidant activity of **4**–**15** in nitric oxide method

Results and discussion

Chemistry

The cyclocondensation of *E*-arylsulfonylethenesulfonylacetic acid methyl ester (**1**) with 2-aminoethanol/2-aminoethanethiol in the presence of samarium (III) chloride and *n*-BuLi produced 2-(*E*-arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole (**2**) and 2-(*E*-arylsulfonyl-ethenesulfonylmethyl)-4,5-dihydrothiazole (**3**) (Scheme 1). The ^{1}H NMR spectra of **2a** and **3a** exhibited a singlet at δ 4.24 and 4.27 for SO_2CH_2, two triplets at δ 3.62, 3.76 and δ 4.65, 3.37 ppm for C_4-H and C_5-H and a doublet at δ 7.28, 7.37 for olefin proton, H_B. However, the signal corresponding to another olefin proton H_A appeared at much downfield region and merged with aromatic protons. The coupling constant values $J_{AB} \approx 14.1$ and 14.3 Hz indicated that they possess *trans* geometry. The 1,3-dipolar cycloaddition of diazomethane to **2** and **3** in the presence of triethylamine in ether at -20 to -15 °C gave 2-(4′,5′-dihydro-3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole (**4**) and 2-(4′,5′-dihydro-3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**5**). In fact, the addition of diazomethane to **2** and **3** may produce regioisomers. However, only one pure regioisomer was isolated under the applied reaction conditions. This may be due to electron withdrawing effect of

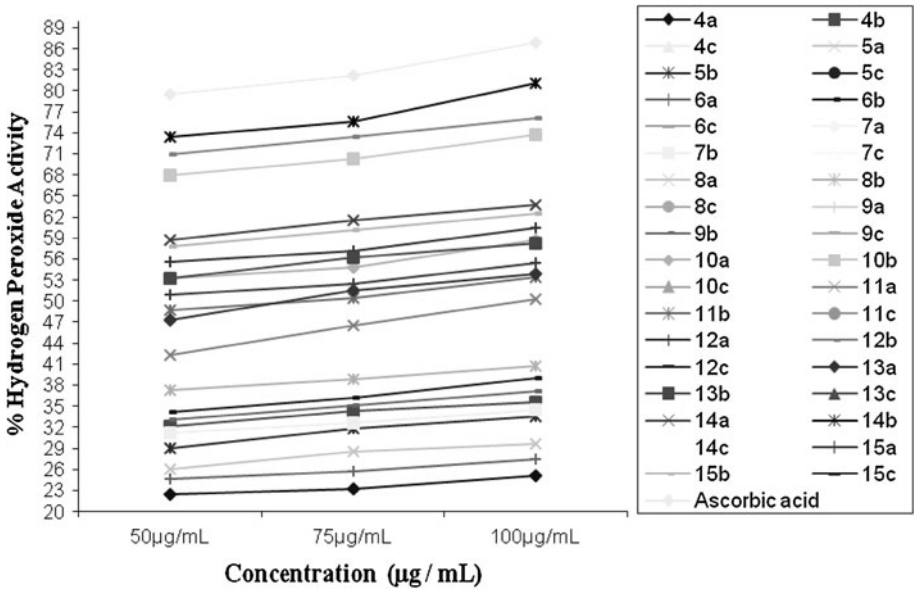


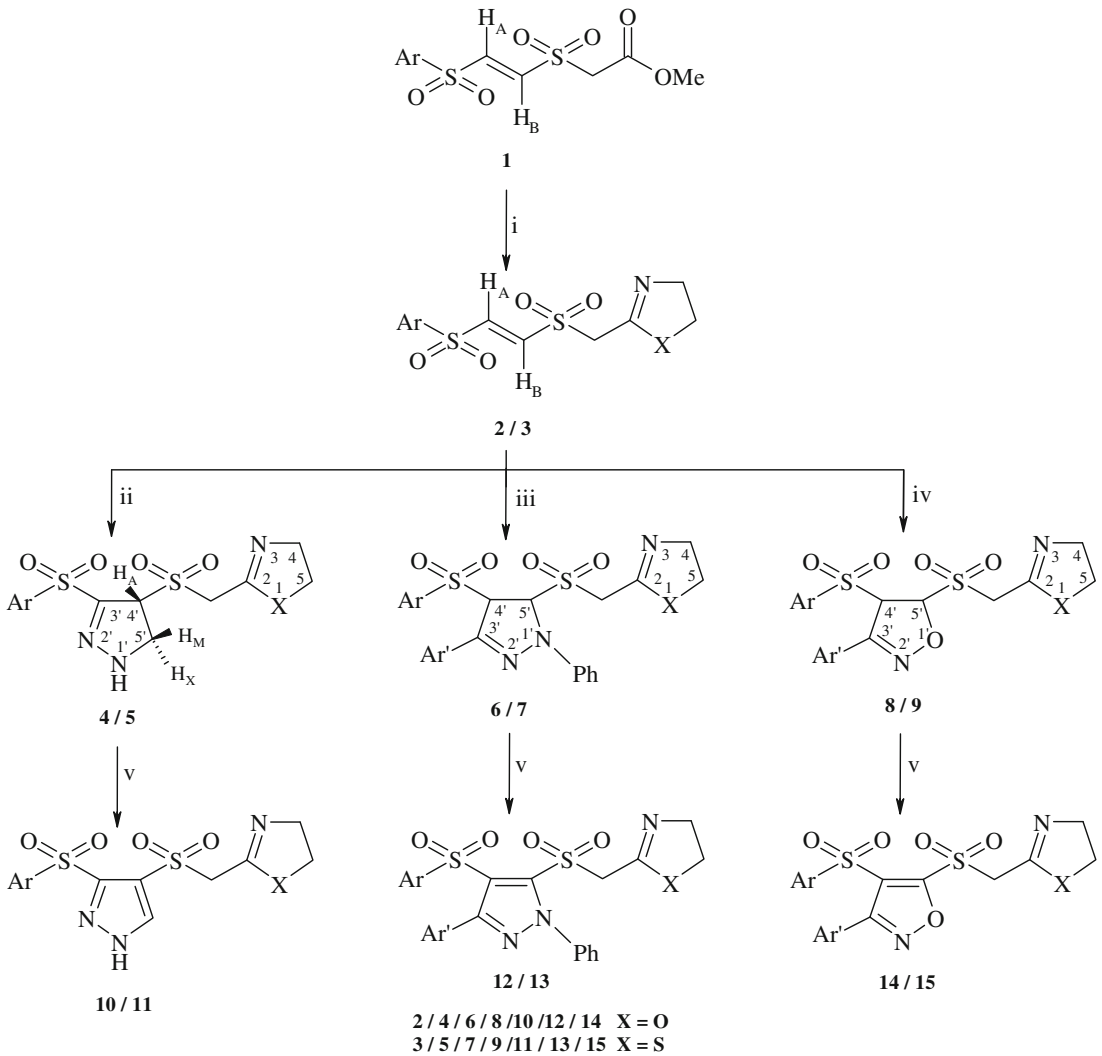
Fig. 3 The in vitro antioxidant activity of **4–15** in hydrogen peroxide method

sulfonyl group (Padmavathi *et al.*, 2002; Padmaja *et al.*, 2011). A small amount of the other isomer if any, formed could not be detected by this process (Padmavathi *et al.*, 2003). The ^{1}H NMR spectra of **4a** and **5a** showed three double doublets at δ 4.63, 4.59; 4.36, 4.23 and δ 3.95, 3.83 which were assigned to pyrazoline ring protons, H_A, H_M and H_X, respectively. The coupling constant values $J_{AM} =$ 12.4 Hz, $J_{AX} = 6.3$ Hz, and $J_{MX} = 11.5$ Hz in **4a** and $J_{AM} = 12.0$ Hz, $J_{AX} = 6.0$ Hz, $J_{MX} = 10.8$ Hz in **5a** indicated that H_A, H_M are *cis*, H_A, H_X are *trans* and H_M, H_X are *geminal*. On the other hand, the cycloaddition of nitrile imines and nitrile oxides generated from araldehyde phenylhydrazones and araldoximes in the presence of chloramine-T to **2** and **3** resulted in 2-(4′,5′-dihydro-1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl) -4,5-dihydrooxazole (**6**), 2-(4′,5′-dihydro-1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl)-4, 5-dihydrothiazole (**7**), 2-(4′,5′-dihydro-3′-aryl-4′-aryl sulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole (**8**), and 2-(4′,5′-dihydro-3′-aryl-4′-arylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**9**), respectively. In the ^{1}H NMR spectra of **6a**, **7a**, **8a**, and **9a** two doublets were observed at δ 5.28, 5.26, 5.25, 5.22 and at δ 5.65, 5.63, 5.68, 5.71 due to for $C_{4'}$-H and $C_{5'}$-H, respectively, in addition to signals due to other protons. The reaction of compounds **4–9** with chloranil in xylene afforded 2-(3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydro-oxazole (**10**), 2-(3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**11**), 2-(1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole (**12**), 2-(1′-phenyl-3′-aryl-4′-aryl-sulfonylpyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**13**), 2-(3′-aryl-4′-arylsulfonyl-isoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole (**14**) and 2-(3′-aryl-4′-arylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**15**). The absence of doublets due to at $C_{4'}$-H and $C_{5'}$-H in the ^{1}H NMR spectra of compounds **10–15** confirmed that oxidation took place. The structures of all the new compounds were further established by IR, ^{13}C NMR spectra and elemental analyses.

Biological evaluation

Antioxidant activity

The results of antioxidant activity of the test compounds and control drug are presented in Tables 1, 2, 3. The aim of this study is to identify the potential heterocyclic compound for antioxidant activity. In general, bis heterocycles having pyrazole/isoxazole with oxazoline and thiazoline moieties (**10–15**) exhibited greater activity than the compounds containing pyrazoline/isoxazoline with oxazoline and thiazoline (**4–9**). It was also observed that compounds having pyrazole/isoxazole unit in combination with oxazoline (**10**, **12**, **14**) displayed considerable antioxidant activity than the corresponding thiazolines (**11**, **13**, **15**). Moreover, the presence of electron-donating methyl substituent on aromatic ring enhanced the activity when compared with unsubstituted and chloro-substituted compounds. The compounds oxazolyl pyrazoles and isoxazoles having methyl substituent **10b**, **12b**, and **14b** showed high antioxidant activity than other compounds. In fact, the compound **14b** exhibited excellent radical scavenging activity in all the three methods when



Scheme 1 Synthesis of pyrazolyl-oxazolines/thiazolines and isoxazolyl-oxazolines/thiazolines

compared with the standard ascorbic acid. The activity of **14b** may be due to the presence of more oxygen atoms. On the other hand, the compounds **5a**, **7a**, **9a**, and **4c–15c** were inactive. Apart from this, the results also indicated that radical scavenging activity in all the three methods increases with increase in concentration.

Conclusion

A new class of sulfonylmethane-linked pyrazolyl-oxazolines/thiazolines and isoxazolyl-oxazolines/thiazolines were synthesized by functionalization of ester and olefin moieties in *E*-arylsulfonylethenesulfonylacetic acid methyl ester utilizing samarium chemistry and 1,3-diploar cycloaddition methodology. All the new compounds were tested for their antioxidant activity. Amongst all the compounds, **14b** exhibited promising antioxidant activity.

Experimental protocols

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). 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 ^1H NMR

Table 1 The in vitro antioxidant activity of **4–15** in DPPH method

Compounds	Concentration			
	50 (μg/ml)	75 (μg/ml)	100 (μg/ml)	IC_{50} (μmol/ml)
4a	20.37 ± 1.09	22.54 ± 1.62	23.82 ± 1.35	0.587 ± 1.52
4b	32.22 ± 1.60	35.65 ± 1.52	37.82 ± 1.41	0.355 ± 1.31
4c	–	–	–	–
5a	–	–	–	–
5b	26.71 ± 1.65	28.54 ± 1.54	30.43 ± 1.32	0.424 ± 1.12
5c	–	–	–	–
6a	21.16 ± 1.21	23.53 ± 1.32	25.16 ± 1.54	0.389 ± 1.28
6b	35.26 ± 0.95	37.31 ± 0.54	39.28 ± 1.08	0.229 ± 0.85
6c	–	–	–	–
7a	–	–	–	–
7b	27.16 ± 0.54	29.23 ± 0.82	32.54 ± 1.09	0.269 ± 0.98
7c	–	–	–	–
8a	23.27 ± 1.08	25.18 ± 1.26	26.07 ± 1.43	0.455 ± 1.23
8b	36.54 ± 1.32	38.27 ± 1.45	41.13 ± 1.62	0.254 ± 1.54
8c	–	–	–	–
9a	–	–	–	–
9b	30.23 ± 1.44	31.21 ± 1.32	33.02 ± 1.48	0.306 ± 1.58
9c	–	–	–	–
10a	53.61 ± 1.28	57.43 ± 1.03	61.22 ± 0.87	0.229 ± 1.15
10b	67.10 ± 1.55	71.54 ± 0.85	74.62 ± 0.38	0.181 ± 0.76
10c	–	–	–	–
11a	38.86 ± 1.52	41.31 ± 1.10	43.53 ± 1.09	0.309 ± 0.93
11b	61.65 ± 1.34	65.21 ± 1.09	69.13 ± 0.33	0.187 ± 0.98
11c	–	–	–	–
12a	58.50 ± 1.26	62.82 ± 1.13	64.61 ± 1.42	0.152 ± 0.86
12b	69.31 ± 1.20	73.42 ± 0.73	78.68 ± 0.85	0.115 ± 0.72
12c	–	–	–	–
13a	42.81 ± 1.43	46.67 ± 1.30	49.36 ± 1.22	0.193 ± 1.30
13b	63.62 ± 0.56	66.51 ± 1.32	70.32 ± 1.22	0.125 ± 0.35
13c	–	–	–	–
14a	60.72 ± 0.75	64.43 ± 0.45	67.57 ± 0.64	0.171 ± 0.56
14b	78.83 ± 0.12	82.26 ± 0.87	84.21 ± 0.23	0.124 ± 0.21
14c	–	–	–	–
15a	47.80 ± 1.23	49.54 ± 1.12	52.86 ± 0.53	0.210 ± 1.23
15b	65.48 ± 0.62	68.73 ± 0.43	71.86 ± 0.75	0.141 ± 0.84
15c	–	–	–	–
Ascorbic acid	79.54 ± 0.45	84.63 ± 0.57	87.43 ± 0.63	0.079 ± 0.11
Blank	–	–	–	

(–) Showed no scavenging activity. Values are the mean of three replicates ±SD

spectra were recorded in $CDCl_3$ on a Bruker spectrospin operating at 400 MHz. The ^{13}C NMR spectra were run in $CDCl_3$ on Bruker spectrospin operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compound *E*-arylsulfonylethenesulfonylacetic acid methyl ester (**1**) was prepared as per the literature procedure (Padmavathi *et al.*, 2010).

General procedure for the synthesis of 2-(*E*-arylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole (**2a–c**)/2-(*E*-arylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole (**3a–c**)

To a flask charged with anhydrous samarium (III) chloride (1 mmol), dry toluene (10 ml) and aminoalcohol/aminoethanethiol (2 mmol) were added followed by *n*-butyllithium (2.2 mmol) at 0 °C and stirred for 20 min at the same

Table 2 The in vitro antioxidant activity of **4–15** in nitric oxide method

Compounds	Concentration		
	50 (μg/ml)	75 (μg/ml)	100 (μg/ml)
4a	20.72 ± 1.27	21.44 ± 1.47	22.63 ± 1.38
4b	32.54 ± 1.32	34.62 ± 1.54	35.89 ± 1.62
4c	–	–	–
5a	–	–	–
5b	26.12 ± 1.12	28.08 ± 1.28	30.32 ± 1.33
5c	–	–	–
6a	22.72 ± 1.72	24.55 ± 1.65	25.72 ± 1.56
6b	35.08 ± 1.18	37.63 ± 1.54	38.54 ± 1.27
6c	–	–	–
7a	–	–	–
7b	28.72 ± 1.65	29.67 ± 1.54	31.54 ± 1.44
7c	–	–	–
8a	24.63 ± 0.98	26.54 ± 1.12	28.27 ± 1.28
8b	37.62 ± 1.26	39.54 ± 1.32	42.46 ± 1.43
8c	–	–	–
9a	–	–	–
9b	30.12 ± 1.02	31.23 ± 1.24	33.31 ± 1.38
9c	–	–	–
10a	48.26 ± 0.79	52.41 ± 0.92	54.78 ± 0.57
10b	64.27 ± 1.43	67.38 ± 1.29	69.89 ± 1.34
10c	–	–	–
11a	39.53 ± 1.48	42.24 ± 1.37	46.46 ± 1.12
11b	57.53 ± 1.54	60.28 ± 1.39	64.37 ± 1.45
11c	–	–	–
12a	51.89 ± 0.65	53.12 ± 0.59	56.59 ± 0.48
12b	67.78 ± 1.43	72.64 ± 1.62	76.30 ± 1.29
12c	–	–	–
13a	42.91 ± 1.56	44.86 ± 1.48	48.65 ± 1.39
13b	60.83 ± 1.25	63.62 ± 1.11	65.15 ± 1.32
13c	–	–	–
14a	54.35 ± 1.64	56.84 ± 1.25	61.63 ± 1.42
14b	71.42 ± 0.47	78.52 ± 0.35	81.34 ± 0.23
14c	–	–	–
15a	45.53 ± 0.98	47.82 ± 0.87	52.34 ± 1.08
15b	62.26 ± 0.65	65.86 ± 0.78	68.42 ± 0.85
15c	–	–	–
Ascorbic acid	80.12 ± 0.57	83.56 ± 0.45	85.83 ± 0.32
Blank	–	–	–

(–) Showed no scavenging activity. Values are the mean of three replicates ±SD

Table 3 The in vitro antioxidant activity of **4–15** in hydrogen peroxide method

Compounds	Concentration		
	50 (μg/ml)	75 (μg/ml)	100 (μg/ml)
4a	22.37 ± 1.51	23.28 ± 1.35	25.08 ± 1.82
4b	32.16 ± 1.41	34.26 ± 1.54	35.62 ± 1.39
4c	–	–	–
5a	–	–	–
5b	29.07 ± 1.65	31.87 ± 1.58	33.62 ± 1.44
5c	–	–	–
6a	24.61 ± 1.87	25.65 ± 1.79	27.38 ± 1.63
6b	34.18 ± 1.08	36.23 ± 1.16	39.08 ± 1.72
6c	–	–	–
7a	–	–	–
7b	31.21 ± 1.62	32.63 ± 1.44	34.56 ± 1.29
7c	–	–	
8a	26.09 ± 1.18	28.53 ± 1.27	29.63 ± 1.32
8b	37.25 ± 1.23	38.94 ± 1.37	40.72 ± 1.44
8c	–	–	–
9a	–	–	–
9b	33.07 ± 0.98	35.13 ± 1.02	37.18 ± 1.28
9c	–	–	–
10a	53.23 ± 1.59	54.85 ± 1.43	58.74 ± 1.27
10b	68.02 ± 1.45	70.34 ± 1.33	73.76 ± 1.29
10c	–	–	–
11a	42.36 ± 1.12	46.53 ± 0.98	50.22 ± 1.32
11b	48.65 ± 1.26	50.43 ± 1.35	53.37 ± 1.22
11c	–	–	–
12a	55.61 ± 1.58	57.23 ± 1.49	60.45 ± 1.37
12b	70.86 ± 0.97	73.38 ± 0.85	76.03 ± 0.54
12c	–	–	–
13a	47.25 ± 1.62	51.46 ± 1.34	53.84 ± 1.11
13b	53.33 ± 1.08	56.16 ± 1.35	58.29 ± 1.46
13c	–	–	–
14a	58.73 ± 1.23	61.54 ± 1.54	63.68 ± 1.36
14b	73.47 ± 0.56	75.62 ± 0.44	81.13 ± 0.28
14c	–	–	–
15a	50.86 ± 1.42	52.43 ± 1.38	55.37 ± 1.23
15b	57.79 ± 1.12	60.08 ± 1.34	62.44 ± 1.23
15c	–	–	–
Ascorbic acid	79.56 ± 0.36	82.26 ± 0.25	86.84 ± 0.13
Blank	–	–	–

(–) Showed no scavenging activity. Values are the mean of three replicates ±SD

temperature. The reaction mixture was heated to reflux at 100 °C. Then, compound **1** (1 mmol) was added to the contents and refluxion was continued further for 8–10 h. The suspension was cooled to ambient temperature and filtered. The filtrate was extracted with chloroform and washed with water. Removal of the solvent under vacuum gave a residue which was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate–hexane (1:3) as eluent.

2-(Phenylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole ***2a***

m. p. 125–126 °C, yield 71 %; IR (KBr) (cm^{-1}): 1628 (C=C), 1581 (C=N), 1334, 1128 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.83 (m, 6H, H_A & Ar–H), 7.28 (*d*, $J = 14.1$ Hz, 1H, H_B), 4.65 (*t*, 2H, C_5-H, $J = 5.5$ Hz), 4.24 (*s*, 2H, SO_2CH_2), 3.62 (*t*, 2H, C_4-H, $J = 5.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (C-2), 143.9 ($CHSO_2$), 137.4 (SO_2CH), 59.4 (C-5), 57.6 (SO_2CH_2), 51.4 (C-4), 131.5, 130.7, 129.4, 127.4 (aromatic carbons); MS (*m/z*): 315.37 [$M^{+\cdot}$]. Anal. Calcd. for $C_{12}H_{13}NO_5S_2$: C, 45.70; H, 4.15; N, 4.44 %; Found: C, 45.79; H, 4.19; N, 4.50 %.

2-(p-Methylphenylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole ***2b***

m. p. 152–154 °C, yield 66 %; IR (KBr) (cm^{-1}): 1642 (C=C), 1595 (C=N), 1336, 1138 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.74 (*m*, 5H, H_A & Ar–H), 7.32 (*d*, $J = 14.3$ Hz, 1H, H_B), 4.71 (*t*, 2H, C_5-H, $J = 5.7$ Hz), 4.28 (*s*, 2H, SO_2CH_2), 3.71 (*t*, 2H, C_4-H, $J = 5.7$ Hz), 2.23 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (C-2), 142.6 ($CHSO_2$), 138.7 (SO_2CH), 60.2 (C-5), 58.2 (SO_2CH_2), 51.9 (C-4), 22.1 (Ar–CH_3), 132.4, 130.2, 129.9, 128.6 (aromatic carbons); MS (*m/z*): 329.39 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{15}NO_5S_2$: C, 47.40; H, 4.59; N, 4.25 %; Found: C, 47.32; H, 4.64; N, 4.29 %.

2-(p-Chlorophenylsulfonylethenesulfonylmethyl)-4,5-dihydrooxazole ***2c***

m. p. 166–168 °C, yield 69 %; IR (KBr) (cm^{-1}): 1637 (C=C), 1587 (C=N), 1332, 1134 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.79 (*m*, 5H, H_A & Ar–H), 7.41 (*d*, $J = 14.6$ Hz, 1H, H_B), 4.62 (*t*, 2H, C_5-H, $J = 5.2$ Hz), 4.31 (*s*, 2H, SO_2CH_2), 3.65 (*t*, 2H, C_4-H, $J = 5.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (C-2), 143.1 ($CHSO_2$), 138.1 (SO_2CH), 59.7 (C-5), 58.9 (SO_2CH_2), 52.2 (C-4), 132.6, 131.8, 130.4, 129.2 (aromatic carbons); MS (*m/z*): 349.81 [$M^{+\cdot}$]. Anal. Calcd. for $C_{12}H_{12}ClNO_5S_2$: C, 41.20; H, 3.46; N, 4.00 %; Found: C 41.26, H 3.49, N 4.06 %.

2-(Phenylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole ***3a***

m. p. 114–116 °C, yield 76 %; IR (KBr) (cm^{-1}): 1640 (C=C), 1594 (C=N), 1339, 1130 (SO_2),; ^1H (400 MHz, $CDCl_3$): δ 7.39–7.73 (*m*, 6H, H_A & Ar–H), 7.37 (*d*, $J = 14.3$ Hz, 1H, H_B), 4.27 (*s*, 2H, SO_2CH_2), 3.76 (*t*, 2H, C_4-H, $J = 7.3$ Hz), 3.37 (*t*, 2H, C_5-H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7 (C-2), 143.6 ($CHSO_2$), 136.9 (SO_2CH), 58.0 (SO_2CH_2), 51.7 (C-4), 36.9 (C-5), 131.9, 130.2, 129.7, 128.2 (aromatic carbons); MS (*m/z*): 331.43 [$M^{+\cdot}$]. Anal. Calcd. for $C_{12}H_{13}NO_4S_3$: C, 43.49; H, 3.95; N, 4.23 %; Found: C, 43.54; H, 3.91; N, 4.28 %.

2-(p-Methylphenylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole ***3b***

m. p. 125 °C, yield 78 %; IR (KBr) (cm^{-1}): 1635 (C=C), 1583 (C=N), 1343, 1136 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.76 (*m*, 5H, H_A & Ar–H), 7.35 (*d*, $J = 14.4$ Hz, 1H, H_B), 4.34 (*s*, 2H, SO_2CH_2), 3.69 (*t*, 2H, C_4-H, $J = 7.0$ Hz), 3.33 (*t*, 2H, C_5-H, $J = 7.0$ Hz), 2.21 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C-2), 142.9 ($CHSO_2$), 136.2 (SO_2CH), 59.9 (SO_2CH_2), 52.5 (C-4), 37.3 (C-5), 21.6 (Ar–CH_3), 131.2, 130.6, 129.9, 128.6; (aromatic carbons); MS (*m/z*): 345.46 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{15}NO_4S_3$: C, 45.2; H, 4.38; N, 4.05 %; Found: C, 45.14; H, 4.35; N, 4.08 %.

2-(p-Chlorophenylsulfonylethenesulfonylmethyl)-4,5-dihydrothiazole ***3c***

m. p. 133–135 °C, yield 70 %; IR (KBr) (cm^{-1}): 1632 (C=C), 1588 (C=N), 1345, 1129 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.79 (*m*, 5H, H_A & Ar–H), 7.47 (*d*, $J = 14.2$ Hz, 1H, H_B), 4.32 (*s*, 2H, SO_2CH_2), 3.73 (*t*, 2H, C_4-H, $J = 7.5$ Hz), 3.39 (*t*, 2H, C_5-H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7 (C-2), 143.2 ($CHSO_2$), 137.7 (SO_2CH), 59.2 (SO_2CH_2), 51.9 (C-4), 36.8 (C-5), 131.6, 130.4, 129.7, 128.1; (aromatic carbons); MS (*m/z*): 365.88 [$M^{+\cdot}$]. Anal. Calcd. for $C_{12}H_{12}ClNO_4S_3$: C, 39.39; H, 3.31; N, 3.83 %; Found: C, 39.43; H, 3.28; N, 3.87 %.

General procedure for the synthesis of 2-(4′,5′-dihydro-3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole (**4a–c**)/2-(4′,5′-dihydro-3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**5a–c**)

To a well-cooled solution of **2/3** (2.5 mmol) in dichloromethane (20 ml), an ethereal solution of diazomethane (40 ml, 0.4 M) and triethylamine (0.1 ml) were added. The reaction mixture was kept at −20 to −15 °C for 40–48 h. Evaporation of the solvent in vacuo yielded a solid which was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate–hexane (1:2.5) as eluent.

2-(4′,5′-Dihydro-3′-phenylsulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole ***4a***

m. p. 174–176 °C, yield 82 %; IR (KBr) (cm^{-1}): 3338 (NH), 1585 (C=N), 1336, 1131 (SO_2); ^1H NMR (400 MHz,

$CDCl_3$): δ 7.38–7.52 (*m*, 5H, Ar–H), 8.89 (*brs,* 1H, NH), 4.77 (*t*, 2H, C_5-H, $J = 5.8$ Hz), 4.63 (*dd*, 1H, H_A, $J_{AM} = 12.4$ Hz, $J_{AX} = 6.3$ Hz), 4.36 (*dd*, 1H, H_M, $J_{AM} = 12.4$ Hz, $J_{MX} = 11.5$ Hz), 4.13 (*s*, 2H, SO_2CH_2), 3.95 (*dd*, 1H, H_X, $J_{AX} = 6.3$ Hz, $J_{MX} = 11.5$ Hz), 3.82 (*t*, 2H, C_4-H, $J = 5.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7 (C-2), 152.3 (C-3′), 60.4 (C-5′), 56.2 (C-5), 54.7 (SO_2CH_2), 53.3 (C-4), 51.6 (C-4′), 135.4, 132.6, 129.7, 128.5; (aromatic carbons); MS (*m/z*): 357.41 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{15}N_3O_5S_2$: C, 43.69; H, 4.23; N, 11.76 %; Found: C, 43.74; H, 4.25; N, 11.84 %.

2-(4′,5′-Dihydro-3′-(p-methylphenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole ***4b***

m. p. 158–160 °C, yield 80 %; IR (KBr) (cm^{-1}): 3348 (NH), 1570 (C=N), 1323, 1125 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (*brs*, 1H, NH), 7.32–7.48 (*m*, 4H, Ar–H), 4.73 (*t*, 2H, C_5-H, $J = 5.5$ Hz), 4.58 (*dd*, 1H, H_A, $J_{AM} = 12.2$ Hz, $J_{AX} = 6.0$ Hz), 4.28 (*dd*, 1H, H_M, $J_{AM} = 12.2$ Hz, $J_{MX} = 10.8$ Hz), 4.11 (*s*, 2H, SO_2CH_2), 3.91 (*dd*, 1H, H_X, $J_{AX} = 6.0$ Hz, $J_{MX} = 10.8$ Hz), 3.76 (*t*, 2H, C_4-H, $J = 5.5$ Hz), 2.38 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (C-2), 151.6 (C-3′), 59.8 (C-5′), 55.8 (C-5), 54.3 (SO_2CH_2), 52.6 (C-4), 51.9 (C-4′), 23.1 (Ar–CH_3), 134.9, 131.8, 129.6, 128.2; (aromatic carbons); MS (*m/z*): 371.43 [$M^{+\cdot}$]. Anal. Calcd. for $C_{14}H_{17}N_3O_5S_2$: C, 45.27; H, 4.61; N, 11.31 %; Found: C, 45.35; H, 4.60; N, 11.41 %.

2-(4′,5′-Dihydro-3′-(p-chlorophenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole ***4c***

m. p. 185–187 °C, yield 78 %; IR (KBr) (cm^{-1}): 3341 (NH), 1573 (C=N), 1342, 1142 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (*brs*, 1H, NH), 7.41–7.65 (*m*, 4H, Ar–H), 4.79 (*t*, 2H, C_5-H, $J = 5.9$ Hz), 4.65 (*dd*, 1H, H_A, $J_{AM} = 12.6$ Hz, $J_{AX} = 6.5$ Hz), 4.39 (*dd*, 1H, H_M, $J_{AM} = 12.6$ Hz, $J_{MX} = 11.8$ Hz), 4.17 (*s*, 2H, SO_2CH_2), 3.97 (*dd*, 1H, H_X, $J_{AX} = 6.5$ Hz, $J_{MX} = 11.8$ Hz), 3.85 (*t*, 2H, C_4-H, $J = 5.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C-2), 153.2 (C-3′), 60.9 (C-5′), 56.5 (C-5), 55.2 (SO_2CH_2), 53.9 (C-4), 52.1 (C-4′), 135.9, 132.5, 128.9, 127.6; (aromatic carbons); MS (*m/z*): 391.85 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{14}ClN_3O_5S_2$: C, 39.85; H, 3.60; N, 10.72 %; Found: C, 39.80; H, 3.63; N, 10.79 %.

2-(4′,5′-Dihydro-3′-phenylsulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole ***5a***

m. p. 178–180 °C, yield 73 %; IR (KBr) (cm^{-1}): 3335 (NH), 1594 (C=N), 1322, 1134 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.37 (*m*, 5H, Ar–H), 8.75 (*brs*, 1H, NH), 4.59 (*dd*, 1H, H_A, $J_{AM} = 12.0$ Hz, $J_{AX} = 6.0$ Hz), 4.23 (*dd*, 1H, H_M, $J_{AM} = 12.0$ Hz, $J_{MX} = 10.8$ Hz), 4.12 (*s*, 2H, SO_2CH_2), 3.83 (*dd*, 1H, H_X, $J_{AX} = 6.0$ Hz, $J_{MX} = 10.8$ Hz), 3.72 (*t*, 2H, C_4-H, $J = 7.5$ Hz), 3.43 (*t*, 2H, C_5-H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4 (C-2), 149.5 (C-3′), 59.6 (C-5′), 54.1 (SO_2CH_2), 49.4 (C-4′), 52.7 (C-4), 36.7 (C-5), 135.3, 134.8, 128.8, 127.6; (aromatic carbons); MS (*m/z*): 373.47 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{15}N_3O_4S_3$: C, 41.81; H, 4.05; N, 11.25 %; Found: C, 41.87; H, 4.07; N, 11.21 %.

2-(4′,5′-Dihydro-3′-(p-methylphenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole ***5b***

m. p. 173–175 °C, yield 75 %; IR (KBr) (cm^{-1}): 3331 (NH), 1587 (C=N), 1330, 1128 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (*brs*, 1H, NH), 7.13-7.37 (*m*, 4H, Ar–H), 4.54 (*dd*, 1H, H_A, $J_{AM} = 11.8$ Hz, $J_{AX} = 5.6$ Hz), 4.20 (*dd*,1H, H_M, $J_{AM} = 11.8$ Hz, $J_{MX} = 10.5$ Hz), 4.08 (*s*, 2H, SO_2CH_2), 3.79 (*dd*, 1H, H_X, $J_{AX} = 5.6$ Hz, $J_{MX} = 10.5$ Hz), 3.66 (*t*, 2H, C_4-H, $J = 7.2$ Hz), 3.40 (*t*, 2H, C_5-H, $J = 7.2$ Hz), 2.36 (*s*, 3H, Ar–CH_3),; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (C-2), 149.6 (C-3′), 59.1 (C-5′), 53.7 (SO_2CH_2), 52.4 (C-4), 48.9 (C-4′), 35.5 (C-5), 22.9 (Ar–CH_3), 135.7, 132.8, 129.6, 128.5 (aromatic carbons); MS (*m/z*): 387.50 [$M^{+\cdot}$]. Anal. Calcd. for $C_{14}H_{17}N_3O_4S_3$: C, 43.39; H, 4.42; N, 10.84 %; Found: C, 43.46; H, 4.44; N, 10.93 %.

2-(4′,5′-Dihydro-3′-(p-chlorophenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole ***5c***

m. p. 192–194 °C, yield 77 %; IR (KBr) (cm^{-1}): 3343 (NH), 1572 (C=N), 1343, 1142 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (*brs*, 1H, NH), 7.26–7.48 (*m*, 4H, Ar–H), 4.61 (*dd*, 1H, H_A, $J_{AM} = 12.2$ Hz, $J_{AX} = 6.1$ Hz), 4.25 (*dd*, 1H, H_M, $J_{AM} = 12.2$ Hz, $J_{MX} = 11.0$ Hz), 4.16 (*s*, 2H, SO_2CH_2), 3.84 (*dd*, 1H, H_X, $J_{AX} = 6.1$ Hz, $J_{MX} = 11.0$ Hz), 3.77 (*t*, 2H, C_4-H, $J = 7.7$ Hz), 3.47 (*t*, 2H, C_5-H, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (C-2), 150.4 (C-3′), 60.2 (C-5′), 54.5 (SO_2CH_2), 53.2 (C-4), 49.7 (C-4′), 37.1 (C-5), 136.9, 134.6, 131.6, 129.2 (aromatic carbons); MS (*m/z*): 407.92 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{14}ClN_3O_4S_3$: C, 38.28; H, 3.46; N, 10.30 %; Found: C, 38.24; H, 3.50; N, 10.37 %.

General procedure for the synthesis of 2-(4′,5′-dihydro-1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole (**6a–c**)/2-(4′,5′-dihydro-1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**7a–c**)

The compound **2/3** (1 mmol), araldehyde phenylhydrazone (1.2 mmol), chloramine-T (1.2 mmol) and methanol

(20 ml) were refluxed for 18–20 h using a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, brine, and dried (an. Na_2SO_4). The solvent was removed under reduced pressure and the resultant solid was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate–hexane (1:2.5) as eluent.

2-(4′,5′-Dihydro-1′,3′-diphenyl-4′-(phenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***6a***

m. p. 186–188 °C, IR yield 74 %; (KBr) (cm^{-1}): 1582 (C=N), 1330, 1128 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.92 (15H, Ar & Ar'–H), 5.65 (*d*, 1H, $C_{5'}$-H, $J = 7.9$ Hz), 5.28 (*d*, 1H, $C_{4'}$-H, $J = 7.9$ Hz), 4.71 (*t*, 2H, C_5-H, $J = 5.4$ Hz), 4.27 (*s*, 2H, SO_2CH_2), 3.63 (*t*, 2H, C_4-H, $J = 5.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (C-2), 157.8 (C-3′), 88.5 (C-5′), 65.3 (C-4′), 59.8 (C-5), 57.9 (SO_2CH_2), 51.8 (C-4), 135.8, 135.2, 134.8, 133.5, 132.3, 131.8, 131.3, 129.5, 128.8, 128.1, 127.4, 126.2 (aromatic carbons); MS (*m/z*): 509.60 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{23}N_3O_5S_2$: C, 58.92; H, 4.55; N, 8.25 %; Found: C, 59.00; H, 4.52; N, 8.20 %.

2-(4′,5′-Dihydro-1′-phenyl-3′-(p-methoxyphenyl)-4′-(p-methylphenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***6b***

m. p. 177–179 °C, yield 76 %; IR (KBr) (cm^{-1}): 1579 (C=N), 1332, 1120 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.87 (13H, Ar & Ar'–H), 5.68 (*d*, 1H, $C_{5'}$-H, $J = 7.6$ Hz), 5.23 (*d*, 1H, $C_{4'}$-H, $J = 7.6$ Hz), 4.71 (*t*, 2H, C_5-H, $J = 5.6$ Hz), 4.25 (*s*, 2H, SO_2CH_2), 3.84 (*s*, 3H,Ar–OCH_3), 3.65 (*t*, 2H, C_4-H, $J = 5.6$ Hz), 2.28 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (C-2), 157.6 (C-3′), 88.4 (C-5′), 65.0 (C-4′), 59.5 (C-5), 58.3 (SO_2CH_2), 55.8 (Ar–OCH_3), 52.1 (C-4), 22.3 (Ar–CH_3), 135.6, 134.2, 133.4, 132.6, 131.7, 129.7, 128.9, 128.2, 127.3, 126.3, 125.7, 125.5 (aromatic carbons); MS (*m/z*): 553.65 [$M^{+\cdot}$]. Anal. Calcd. for $C_{27}H_{27}N_3O_6S_2$: C, 58.57; H, 4.92; N, 7.59 %; Found: C, 58.50; H, 4.95; N, 7.65 %.

2-(4′,5′-Dihydro-1′-phenyl-3′-(p-chlorophenyl)-4′-(p-chlorophenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***6c***

m. p. 190–191 °C, yield 78 %; IR (KBr) (cm^{-1}): 1587 (C=N), 1338, 1133 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.95 (13H, Ar & Ar'–H), 5.69 (*d*, 1H, $C_{5'}$-H, $J = 8.0$ Hz), 5.30 (*d*, 1H, $C_{4'}$-H, $J = 8.0$ Hz), 4.72 (*t*, 2H, C_5-H, $J = 5.8$ Hz), 4.31 (*s*, 2H, SO_2CH_2), 3.68 (*t*, 2H, C_4-H, $J = 5.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C-2), 158.1 (C-3′), 88.9 (C-5′), 65.8 (C-4′), 60.1 (C-5), 58.7 (SO_2CH_2), 52.3 (C-4), 134.3, 133.7, 132.8, 131.6, 130.7, 130.1, 129.8, 128.3, 127.6, 125.8, 124.2, 123.5 (aromatic carbons); MS (*m/z*): 578.49 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{21}Cl_2N_3O_5S_2$: C, 51.91; H, 3.66; N, 7.26 %; Found: C, 51.96; H, 3.65; N, 7.34 %.

2-(4′,5′-Dihydro-1′,3′-diphenyl-4′-(phenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***7a***

m. p. 195–197 °C, yield 71 %; IR (KBr) (cm^{-1}): 1595 (C=N), 1333, 1124 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.74 (15H, Ar & Ar'–H), 5.63 (*d*, 1H, $C_{5'}$-H, $J = 8.1$ Hz), 5.26 (*d*, 1H, $C_{4'}$-H, $J = 8.1$ Hz), 4.31 (*s*, 2H, SO_2CH_2), 3.72 (*t*, 2H, C_4-H, $J = 7.3$ Hz), 3.35 (*t*, 2H, C_5-H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (C-2), 155.4 (C-3′), 87.9 (C-5′), 63.8 (C-4′), 58.9 (SO_2CH_2), 51.6 (C-4), 38.2 (C-5), 135.8, 133.4, 132.9, 132.0, 131.8, 130.1, 129.8, 129.2, 128.3, 127.9, 126.3, 125.8 (aromatic carbons); MS (*m/z*): 525.66 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{23}N_3O_4S_3$: C, 57.12; H, 4.41; N, 7.99 %; Found: C, 57.19; H, 4.43; N, 7.95 %.

2-(4′,5′-Dihydro-1′-phenyl-3′-(p-methoxyphenyl)-4′-(p-methylphenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***7b***

m. p. 192–194 °C, yield 72 %; IR (KBr) (cm^{-1}): 1586 (C=N), 1334, 1126 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.83 (13H, Ar & Ar'–H), 5.58 (*d*, 1H, $C_{5'}$-H, $J = 7.4$ Hz), 5.23 (*d*, 1H, $C_{4'}$-H, $J = 7.4$ Hz), 4.28 (*s*, 2H, SO_2CH_2), 3.87 (*s*, 3H, Ar–OCH_3), 3.69 (*t*, 2H, C_4-H, $J = 7.0$ Hz), 3.32 (*t*, 2H, C_5-H, $J = 7.0$ Hz), 2.31 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C-2), 154.8 (C-3′), 86.8 (C-5′), 63.5 (C-4′), 58.2 (SO_2CH_2), 56.1 (Ar–OCH_3), 51.2 (C-4), 37.8 (C-5), 22.5 (Ar–CH_3), 135.7, 134.3, 133.8, 132.6, 131.2, 130.3, 129.4, 128.5, 127.8, 126.4, 125.2, 124.5 (aromatic carbons); MS (*m/z*): 569.72 [$M^{+\cdot}$]. Anal. Calcd. for $C_{27}H_{27}N_3O_5S_3$: C, 56.92; H, 4.78; N, 7.38 %; Found: C, 56.97; H, 4.81; N, 7.44 %.

2-(4′,5′-Dihydro-1′-phenyl-3′-(p-chlorophenyl)-4′-(p-chlorophenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***7c***

m. p. 205–207 °C, yield 75 %; IR (KBr) (cm^{-1}): 1597 (C=N), 1331, 1135 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.81 (13H, Ar & Ar'–H), 5.68 (*d*, 1H, $C_{5'}$-H, $J = 8.3$ Hz), 5.29 (*d*, 1H, $C_{4'}$-H, $J = 8.3$ Hz), 4.35 (*s*, 2H, SO_2CH_2), 3.74 (*t*, 2H, C_4-H, $J = 7.5$ Hz), 3.38 (*t,* 2H, C_5-H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (C-2), 155.9 (C-3′), 88.3 (C-5′), 63.9 (C-4′), 59.2 (SO_2CH_2), 51.9 (C-4), 38.7 (C-5), 135.9, 135.1, 134.9, 133.7, 132.5,

131.6, 130.2, 129.5, 128.3, 127.6, 126.4, 125.7 (aromatic carbons); MS (*m/z*): 594.55 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{21}Cl_2N_3O_4S_3$: C, 50.50; H, 3.56; N, 7.07 %; Found: C, 50.58; H, 3.55; N, 7.15 %.

General procedure for the synthesis of 2-(4′,5′-dihydro-3′-aryl-4′-arylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole (**8a–c**)/2-(4′,5′-dihydro-3′-aryl-4′-arylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**9a–c**)

A mixture of **2/3** (1 mmol), araldoxime (1.2 mmol), chloramine-T (1.2 mmol) and methanol (20 ml) was refluxed for 15–17 h on a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, brine, and dried (an. Na_2SO_4). Evaporation of the solvent under vacuum afforded a solid which was purified by passing through a column of silica gel (60–120 mesh) using ethyl acetate–hexane (1:3) as eluent.

2-(4′,5′-Dihydro-3′-phenyl-4′-phenylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***8a***

m. p. 172–174 °C, yield 77 %; IR (KBr) (cm^{-1}): 1573 (C=N), 1338, 1148 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.69 (10H, Ar & Ar'–H), 5.68 (*d*, 1H, $C_{5'}$-H, $J = 8.0$ Hz), 5.25 (*d*, 1H, $C_{4'}$-H, $J = 8.0$ Hz), 4.63 (*t*, 2H, C_5-H, $J = 5.3$ Hz), 4.25 (*s*, 2H, SO_2CH_2), 3.65 (*t*, 2H, C_4-H, $J = 5.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (C-2), 155.2 (C-3′), 85.8 (C-5′), 66.3 (C-4′), 60.5 (C-5), 59.3 (SO_2CH_2), 53.8 (C-4), 134.5, 133.7, 132.6, 131.4, 130.3, 129.8, 129.2, 127.1 (aromatic carbons); MS (*m/z*): 434.49 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{18}N_2O_6S_2$: C, 52.52; H, 4.18; N, 6.45 %; Found: C, 52.46; H, 4.20; N, 6.53 %.

2-(4′,5′-Dihydro-3′-(p-methoxyphenyl)-4′-(p-methylphenylsulfonyl)isoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***8b***

m. p. 165–167 °C, yield 74 %; IR (KBr) (cm^{-1}): 1571 (C=N), 1342, 1132 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.65 (8H, Ar & Ar'–H), 5.67 (*d*, 1H, $C_{5'}$-H, $J = 7.7$ Hz), 5.18 (*d*, 1H, $C_{4'}$-H, $J = 7.7$ Hz), 4.64 (*t*, 2H, C_5-H, $J = 5.5$ Hz), 4.26 (*s*, 2H, SO_2CH_2), 3.82 (*s*, 3H, Ar–OCH_3), 3.68 (*t*, 2H, C_4-H, $J = 5.5$ Hz), 2.25 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9 (Ar–CH_3), 52.7 (C-4), 57.2 (Ar–OCH_3), 58.9 (SO_2CH_2), 162.7 (C-2), 154.8 (C-3′), 85.5 (C-5′), 65.9 (C-4′), 60.1 (C-5), 135.1, 134.2, 132.0, 131.6, 130.8, 129.7, 129.1, 128.3 (aromatic carbons); MS (*m/z*): 478.54 [$M^{+\cdot}$]. Anal. Calcd. for $C_{21}H_{22}N_2O_7S_2$: C, 52.71; H, 4.63; N, 5.85 %;Found: C, 52.78; H, 4.66; N, 5.91 %.

2-(4′,5′-Dihydro-3′-(p-chlorophenyl)-4′-(p-chlorophenylsulfonyl)isoxazol-5′-ylsulfonyl-methyl)-4,5-dihydrooxazole ***8c***

m. p. 185–187 °C, yield 76 %; IR (KBr) (cm^{-1}): 1578 (C=N), 1347, 1140 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.82 (8H, Ar & Ar'–H), 5.74 (*d*, 1H, $C_{5'}$-H, $J = 8.1$ Hz), 5.31 (*d*, 1H, $C_{4'}$-H, $J = 8.1$ Hz), 4.67 (*t*, 2H, C_5-H, $J = 5.7$ Hz), 4.34 (*s*, 2H, SO_2CH_2), 3.71 (*t*, 2H, C_4-H, $J = 5.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (C-2), 155.8 (C-3′), 86.2 (C-5′), 66.4 (C-4′), 60.7 (C-5), 59.8 (SO_2CH_2), 54.1 (C-4), 135.5, 134.9, 134.3, 133.4, 132.3, 130.5, 128.9, 128.0 (aromatic carbons); MS (*m/z*): 503.38 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_6S_2$: C, 45.33; H, 3.20; N, 5.57 %; Found: C, 45.29; H, 3.18; N, 5.52 %.

2-(4′,5′-Dihydro-3′-phenyl-4′-phenylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydro-thiazole ***9a***

m. p. 177–179 °C, yield 78 %; IR (KBr) (cm^{-1}): 1580 (C=N), 1331, 1130 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.69 (10H, Ar & Ar'–H), 5.71 (*d*, 1H, $C_{5'}$-H, $J = 8.2$ Hz), 5.22 (*d*, 1H, $C_{4'}$-H, $J = 8.2$ Hz), 4.32 (*s*, 2H, SO_2CH_2), 3.73 (*t*, 2H, C_4-H, $J = 7.4$ Hz), 3.36 (*t*, 2H, C_5-H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (C-2), 155.3 (C-3′), 84.8 (C-5′), 65.2 (C-4′), 59.1 (SO_2CH_2), 52.9 (C-4), 38.4 (C-5), 135.8, 135.3, 134.1, 133.5, 132.8, 131.6 130.8, 128.4 (aromatic carbons); MS (*m/z*): 450.55 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{18}N_2O_5S_3$: C, 50.65; H, 4.03; N, 6.22 %; Found: C, 50.71; H, 4.04; N 6.18 %.

2-(4′,5′-Dihydro-3′-(p-methoxyphenyl)-4′-(p-methylphenylsulfonyl)isoxazol-5′-yl-sulfonylmethyl)-4,5-dihydrothiazole ***9b***

m. p. 181–183 °C, yield 71 %; IR (KBr) (cm^{-1}): 1576 (C=N), 1334, 1136 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14–7.59 (8H, Ar & Ar'–H), 5.64 (*d*, 1H, $C_{5'}$-H, $J = 7.9$ Hz), 5.21 (*d*, 1H, $C_{4'}$-H, $J = 7.9$ Hz), 4.28 (*s*, 2H, SO_2CH_2), 3.89 (*s*, 3H, Ar–OCH_3), 3.65 (*t*, 2H, C_4-H, $J = 7.2$ Hz), 3.34 (*t*, 2H, C_5-H, $J = 7.2$ Hz), 2.32 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (C-2), 154.8 (C-3′), 84.7 (C-5′), 65.1 (C-4′), 58.6 (SO_2CH_2), 56.5 (Ar–OCH_3), 52.6 (C-4), 38.2 (C-5), 22.7 (Ar–CH_3), 135.2, 134.2, 133.6, 131.3, 130.7, 129.8, 129.2, 128.5 (aromatic carbons); MS (*m/z*): 494.60 [$M^{+\cdot}$]. Anal. Calcd. for $C_{21}H_{22}N_2O_6S_3$: C, 51.00; H, 4.48; N, 5.66 %; Found: C, 51.08; H, 4.50; N, 5.73 %.

2-(4′,5′-Dihydro-3′-(p-chlorophenyl)-4′-(p-chlorophenylsulfonyl)isoxazol-5′-ylsulfonyl-methyl)-4,5-dihydrothiazole ***9c***

m. p. 196–198 °C, yield 80 %; IR (KBr) (cm^{-1}): 1585 (C=N), 1342, 1129 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.73 (8H, Ar & Ar'–H), 5.72 (*d*, 1H, $C_{5'}$-H, $J = 8.3$ Hz), 5.26 (*d*, 1H, $C_{4'}$-H, $J = 8.3$ Hz), 4.33 (*s*, 2H, SO_2CH_2), 3.76 (*t*, 2H, C_4-H, $J = 7.6$ Hz), 3.39 (*t*, 2H, C_5-H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1 (C-2), 155.8 (C-3′), 65.7 (C-4′), 85.1 (C-5′), 59.4 (SO_2CH_2), 53.3 (C-4), 38.8 (C-5), 135.4, 134.3, 133.9, 133.1, 132.9, 132.6, 131.2, 129.6; (aromatic carbons); MS (*m/z*): 519.44 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_5S_3$: C, 43.93; H, 3.10; N, 5.39 %; Found: C, 44.00; H, 3.09; N, 5.44 %.

General procedure for the synthesis of 2-(3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonyl-methyl)-4,5-dihydrooxazole (**10a–c**)/2-(3′-arylsulfonyl-1′*H*-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**11a–c**)/2-(1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole (**12a–c**)/2-(1′-phenyl-3′-aryl-4′-arylsulfonylpyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**13a–c**)/2-(3′-aryl-4′-arylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydro-oxazole (**14a–c**)/2-(3′-aryl-4′-arylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole (**15a–c**)

A solution of **4/5/6/7/8/9** (1 mmol) in xylene (10 ml) and chloranil (1.2 mmol) was refluxed for 24–28 h. The reaction mixture was treated with a 5 % sodium hydroxide solution. The organic extract was separated, repeatedly washed with water and dried (an. Na_2SO_4). Removal of the solvent in vacuo yielded a solid which was purified by recrystallization from 2-propanol.

2-(3′-Phenylsulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole ***10a***

m. p. 189–192 °C, yield 82 %; IR (KBr) (cm^{-1}): 3336 (NH), 1565 (C=N), 1327, 1131 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (*brs*, 1H, NH), 7.29–7.95 (*m*, 6H, $C_{5'}$-H & Ar–H), 4.81 (*t*, 2H, C_5-H, $J = 5.6$ Hz), 4.08 (*s*, 2H, SO_2CH_2), 3.81 (*t*, 2H, C_4-H, $J = 5.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C-2), 151.2 (C-3′), 140.6 (C-5′), 136.1 (C-4′), 56.2 (SO_2CH_2), 55.0 (C-5), 53.6 (C-4), 134.6, 132.8, 129.9, 128.5 (aromatic carbons); MS (*m/z*): 355.39 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{13}N_3O_5S_2$: C, 43.93; H, 3.69; N, 11.82 %; Found: C, 43.90; H, 3.72; N, 11.94 %.

2-(3′-(p-Methylphenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole ***10b***

m. p. 180–182 °C, yield 79 %; IR (KBr) (cm^{-1}): 1578 (C=N), 1338, 1127 (SO_2), 3329 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (*brs*, 1H, NH), 7.19–7.92 (*m*, 5H, $C_{5'}$-H & Ar–H), 4.78 (*t*, 2H, C_5-H, $J = 5.4$ Hz), 4.05 (*s*, 2H, SO_2CH_2), 3.73 (*t*, 2H, C_4-H, $J = 5.4$ Hz), 2.36 (*s*, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C-2), 139.5 (C-5′), 151.1 (C-3′), 135.8 (C-4′), 56.1 (SO_2CH_2), 54.7 (C-5), 53.0 (C-4), 23.8 (Ar-CH_3), 133.5, 131.2, 129.7, 128.6 (aromatic carbons); MS (*m/z*): 369.42 [$M^{+\cdot}$]. Anal. Calcd. for $C_{14}H_{15}N_3O_5S_2$: C, 45.52; H, 4.09; N, 11.37 %; Found: C, 45.58; H, 4.07; N, 11.47 %.

2-(3′-(p-Chlorophenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole ***10c***

m. p. 200–202 °C, yield 81 %; IR (KBr) (cm^{-1}): 3344 (NH), 1583 (C=N), 1343, 1139 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (*brs*, 1H, NH), 7.31–8.05 (*m*, 5H, $C_{5'}$-H & Ar–H), 4.82 (*t*, 2H, C_5-H, $J = 5.8$ Hz), 4.12 (*s*, 2H, SO_2CH_2), 3.83 (*t*, 2H, C_4-H, $J = 5.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (C-2), 151.5 (C-3′), 141.2 (C-5′), 136.5 (C-4′), 56.5 (SO_2CH_2), 55.2 (C-5), 53.8 (C-4), 134.7, 132.0, 131.3, 129.2 (aromatic carbons); MS (*m/z*): 389.83 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{12}ClN_3O_5S_2$: C, 40.05; H, 3.10; N, 10.78 %; Found: C, 40.10; H, 3.13; N, 10.86 %.

2-(3′-Phenylsulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole ***11a***

m. p. 197–199 °C, yield 73 %; IR (KBr) (cm^{-1}): 3327 (NH), 1560 (C=N), 1323, 1130 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (*brs*, 1H, NH), 7.29–8.05 (*m*, 6H, $C_{5'}$-H & Ar–H), 4.10 (*s*, 2H, SO_2CH_2), 3.74 (*t*, 2H, C_4-H, $J = 7.8$ Hz), 3.51 (*t*, 2H, C_5-H, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6 (C-2), 149.9 (C-3′), 139.1 (C-5′), 135.7 (C-4′), 55.1 (SO_2CH_2), 52.8 (C-4), 36.2 (C-5), 133.8, 132.7, 129.3, 127.8 (aromatic carbons); MS (*m/z*): 371.46 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{13}N_3O_4S_3$: C, 42.03; H, 3.53; N, 11.31 %; Found: C, 42.10; H, 3.54; N, 11.40 %.

2-(3′-(p-Methylphenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole ***11b***

m. p. 186–188 °C, yield 70 %; IR (KBr) (cm^{-1}): 3335 (NH), 1574 (C=N), 1331, 1125 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (*brs*, 1H, NH), 7.27–8.21 (*m*, 5H, $C_{5'}$-H & Ar–H), 4.09 (*s*, 2H, SO_2CH_2), 3.73 (*t*, 2H, C_4-H, $J = 7.6$ Hz), 3.47 (*t*, 2H, C_5-H, $J = 7.6$ Hz), 2.30 (*s*, 3H,

Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (C-2), 149.6 (C-3′), 139.0 (C-5′), 135.3 (C-4′), 54.7 (SO_2CH_2), 52.1 (C-4), 35.9 (C-5), 22.1 (Ar-CH_3), 133.6, 130.7, 128.5, 127.6 (aromatic carbons); MS (*m/z*): 385.48 [$M^{+\cdot}$]. Anal. Calcd. for $C_{14}H_{15}N_3O_4S_3$: C, 43.62; H, 3.92; N, 10.90 %; Found: C, 43.69; H, 3.95; N, 10.85 %.

2-(3′-(p-Chlorophenyl)sulfonyl-1′H-pyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole ***11c***

m. p. 211–213 °C, yield 78 %; IR (KBr) (cm^{-1}): 3348 (NH), 1582 (C=N), 1338, 1148 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.91 (*brs*, 1H, NH), 7.31–8.15 (*m*, 5H, $C_{5'}$-H & Ar–H), 4.11 (*s*, 2H, SO_2CH_2), 3.85 (*t*, 2H, C_4-H, $J = 8.0$ Hz), 3.55 (*t,* 2H, C_5-H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1 (C-2), 150.7 (C-3′), 139.6 (C-5′), 135.9 (C-4′), 55.3 (SO_2CH_2), 53.1 (C-4), 36.5 (C-5), 132.9, 132.1, 129.7, 128.1 (aromatic carbons); MS (*m/z*): 405.90 [$M^{+\cdot}$]. Anal. Calcd. for $C_{13}H_{12}ClN_3O_4S_3$: C, 38.47; H, 2.98; N, 10.35 %; Found: C, 38.43; H, 2.96; N, 10.42 %.

2-(1′,3′-Diphenyl-4′-(phenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***12a***

m. p. 190–192 °C, yield 67 %; IR (KBr) (cm^{-1}): 1635 (C=C), 1573 (C=N), 1337, 1135 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.18–7.79 (15H, Ar & Ar'-H), 4.67 (*t*, 2H, C_5-H, $J = 5.5$ Hz), 4.28 (*s*, 2H, SO_2CH_2), 3.72 (*t*, 2H, C_4-H, $J = 5.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C-2), 158.1 (C-3′), 148.9 (C-4′), 136.0 (C-5′), 60.6 (C-5), 59.3 (SO_2CH_2), 52.8 (C-4), 134.3, 133.9, 133.1, 132.5, 131.6, 130.7, 129.5, 128.7, 127.2, 126.3, 125.8, 125.0 (aromatic carbons); MS (*m/z*): 507.58 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{21}N_3O_5S_2$: C, 59.16; H, 4.17; N, 8.28 %; Found: C, 59.23; H, 4.18; N, 8.33 %.

2-(1′-Phenyl-3′-(p-methoxyphenyl)-4′-(p-methylphenylsulfonyl)pyrazol-5′-yl-sulfonyl-methyl)-4,5-dihydrooxazole ***12b***

m. p. 203–205 °C, yield 65 %; IR (KBr) (cm^{-1}): 1628 (C=C), 1575 (C=N), 1332, 1142 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.15–7.69 (13H, Ar & Ar'-H), 4.66 (*t*, 2H, C_5-H, $J = 5.2$ Hz), 4.24 (*s*, 2H, SO_2CH_2), 3.81 (*s*, 3H,Ar-OCH_3), 3.70 (*t*, 2H, C_4-H, $J = 5.2$ Hz), 2.29 (*s*, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (C-2), 157.8 (C-3′), 148.6 (C-4′), 135.7 (C-5′), 60.2 (C-5), 59.1 (SO_2CH_2), 56.5 (Ar–OCH_3), 52.5 (C-4), 22.8 (Ar–CH_3), 134.1, 133.5, 133.1, 132.6, 132.0, 131.5, 129.3, 128.6, 127.8, 127.0, 126.2, 125.3 (aromatic carbons); MS (*m/z*): 551.63 [$M^{+\cdot}$]. Anal. Calcd. for $C_{27}H_{25}N_3O_6S_2$: C, 58.79; H, 4.57; N, 7.62 %; Found: C, 58.84; H, 4.55; N, 7.58 %.

2-(1′-Phenyl-3′-(p-chlorophenyl)-4′-(p-chlorophenylsulfonyl)pyrazol-5′-yl-sulfonyl-methyl)-4,5-dihydrooxazole ***12c***

m. p. 208–210 °C, yield 69 %; IR (KBr) (cm^{-1}): 1637 (C=C), 1581 (C=N), 1339, 1147 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–7.83 (13H, Ar & Ar'-H), 4.69 (*t*, 2H, C_5-H, $J = 5.6$ Hz), 4.31 (*s*, 2H, SO_2CH_2), 3.78 (*t*, 2H, C_4-H, $J = 5.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6 (C-2), 158.7 (C-3′), 149.9 (C-4′), 137.1 (C-5′), 61.3 (C-5), 59.4 (SO_2CH_2), 53.2 (C-4), 135.6, 134.2, 133.7, 133.0, 132.3, 130.4, 130.1, 129.7, 128.5, 127.4, 126.1, 125.6 (aromatic carbons). MS (*m/z*): 576.47 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{19}Cl_2N_3O_5S_2$: C, 52.09; H, 3.32; N, 7.29 %; Found: C, 52.03; H, 3.34; N, 7.36 %.

2-(1′,3′-Diphenyl-4′-(phenylsulfonyl)pyrazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***13a***

m. p. 199–202 °C, yield 66 %; IR (KBr) (cm^{-1}): 1628 (C=C), 1572 (C=N), 1341, 1133 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.83 (15H, Ar & Ar'-H), 4.32 (*s*, 2H, SO_2CH_2), 3.76 (*t*, 2H, C_4-H, $J = 7.5$ Hz), 3.52 (*t*, 2H, C_5-H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (C-2), 157.2 (C-3′), 148.2 (C-4′), 135.1 (C-5′), 58.7 (SO_2CH_2), 51.9 (C-4), 38.4 (C-5), 134.5, 133.5, 132.4, 131.8, 130.7, 130.3, 129.8, 128.5, 127.3, 126.7, 125.9, 125.2 (aromatic carbons); MS (*m/z*): 523.65 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{21}N_3O_4S_3$: C, 57.34; H, 4.04; N, 8.02 %; Found: C, 57.40; H, 4.03; N, 8.09 %.

2-(1′-Phenyl-3′-(p-methoxyphenyl)-4′-(p-methylphenylsulfonyl)pyrazol-5′-ylsulfonyl-methyl)-4,5-dihydrothiazole ***13b***

m. p. 185–187 °C, yield 68 %; IR (KBr) (cm^{-1}): 1631 (C=C), 1576 (C=N), 1337, 1141 (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.78 (13H, Ar & Ar'-H), 4.29 (*s*, 2H, SO_2CH_2), 3.85 (*s*, 3H, Ar–OCH_3), 3.73 (*t*, 2H, C_4-H, $J = 7.2$ Hz), 3.47 (*t*, 2H, C_5-H, $J = 7.2$ Hz), 2.35 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C-2), 156.9 (C-3′), 148.3 (C-4′), 134.8 (C-5′), 58.5 (SO_2CH_2), 56.1 (Ar–OCH_3), 51.3 (C-4), 37.8 (C-5), 22.7 (Ar–CH_3), 134.0, 133.2, 132.8, 132.3, 131.7, 130.5, 129.6 129.0, 128.8, 127.2, 126.6, 125.8 (aromatic carbons); MS (*m/z*): 567.70 [$M^{+\cdot}$]. Anal. Calcd. for $C_{27}H_{25}N_3O_5S_3$: C, 57.12; H, 4.44; N, 7.40 %; Found: C, 57.90; H, 4.46; N, 7.34 %.

2-(1′-Phenyl-3′-(p-chlorophenyl)-4′-(p-chlorophenylsulfonyl)pyrazol-5′-ylsulfonyl-methyl)-4,5-dihydrothiazole ***13c***

m. p. 216–218 °C, yield 70 %; IR (KBr) (cm^{-1}): 1634 (C=C), 1583 (C=N), 1343, 1147 (SO_2); ^1H NMR

(400 MHz, $CDCl_3$): δ 7.31–7.87 (13H, Ar & Ar'–H), 4.37 (*s*, 2H, SO_2CH_2), 3.82 (*t*, 2H, C_4-H, $J = 7.7$ Hz), 3.55 (*t*, 2H, C_5-H, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (C-2), 158.4 (C-3′), 149.2 (C-4′), 136.2 (C-5′), 59.1 (SO_2CH_2), 52.1 (C-4), 38.5 (C-5), 135.3, 134.3, 133.7, 132.6, 131.5, 130.2, 129.7, 128.6, 127.4, 126.9, 126.2, 125.3 (aromatic carbons); MS (*m/z*): 592.54 [$M^{+\cdot}$]. Anal. Calcd. for $C_{25}H_{19}Cl_2N_3O_4S_3$: C, 50.67; H, 3.23; N, 7.09 %; Found: C, 50.62; H, 3.20; N, 7.18 %.

2-(3′-Phenyl-4′-phenylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***14a***

m. p. 211–213 °C, yield 62 %; IR (KBr) (cm^{-1}): 1626 (C=C), 1589 (C=N), 1336, 1127 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.82 (10H, Ar & Ar'–H), 4.64 (*t*, 2H, C_5-H, $J = 5.7$ Hz), 4.31 (*s*, 2H, SO_2CH_2), 3.76 (*t*, 2H, C_4-H, $J = 5.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2 (C-2), 157.8 (C-3′), 148.8 (C-4′), 135.8 (C-5′), 61.8 (C-5), 59.4 (SO_2CH_2), 52.7 (C-4), 133.4, 132.6, 131.2, 130.7, 129.4, 128.7, 127.6, 126.3 (aromatic carbons); MS (*m/z*): 432.47 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{16}N_2O_6S_2$: C, 52.77; H, 3.73; N, 6.48 %; Found: C, 52.86; H, 3.71; N, 6.58 %.

2-(3′-(p-Methoxyphenyl)-4′-(p-methylphenylsulfonyl)isoxazol-5′-ylsulfonyl-methyl)-4,5-dihydrooxazole ***14b***

m. p. 194–196 °C, yield 60 %; IR (KBr) (cm^{-1}): 1622 (C=C), 1585 (C = N), 1329, 1138 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.79 (8H, Ar & Ar'-H), 4.61 (*t*, 2H, C_5-H, $J = 5.5$ Hz), 4.27 (*s*, 2H, SO_2CH_2), 3.91 (*s*, 3H, Ar–OCH_3), 3.69 (*t*, 2H, C_4-H, $J = 5.5$ Hz), 2.32 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (C-2), 157.1 (C-3′), 147.9 (C-4′), 135.4 (C-5′), 61.5 (C-5), 59.8 (SO_2CH_2), 57.2 (Ar–OCH_3), 52.6 (C-4), 23.1 (Ar–CH_3), 134.2, 133.6, 132.4, 131.3, 130.5, 129.3, 128.8, 127.5 (aromatic carbons); MS (*m/z*): 476.52 [$M^{+\cdot}$]. Anal. Calcd. for $C_{21}H_{20}N_2O_7S_2$: C, 52.93; H, 4.23; N, 5.88 %; Found: C, 53.00; H, 4.26; N, 5.96 %.

2-(3′-(p-Chlorophenyl)-4′-(p-chlorophenylsulfonyl)isoxazol-5′-ylsulfonylmethyl)-4,5-dihydrooxazole ***14c***

m. p. 207–209 °C, yield 65 %; IR (KBr) (cm^{-1}): 1629 (C=C), 1592 (C=N), 1341, 1135 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.85 (8H, Ar & Ar'-H), 4.68 (*t*, 2H, C_5-H, $J = 5.9$ Hz), 4.32 (*s*, 2H, SO_2CH_2), 3.78 (*t*, 2H, C_4-H, $J = 5.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (C-2), 157.9 (C-3′), 149.7 (C-4′), 136.8 (C-5′), 62.1 (C-5), 59.9 (SO_2CH_2), 52.9 (C-4), 133.7, 133.1, 132.3, 131.4, 130.7, 129.8, 128.1, 127.8 (aromatic carbons); MS (*m/z*): 501.36 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O_6S_2$: C, 45.52; H, 2.81; N, 5.59 %; Found: C, 45.57; H, 2.80; N, 5.55 %.

2-(3′-Phenyl-4′-phenylsulfonylisoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***15a***

m. p. 201–203 °C, yield 63 %; IR (KBr) (cm^{-1}): 1627 (C=C), 1587 (C=N), 1345, 1124 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.78 (10H, Ar & Ar'–H), 4.24 (*s*, 2H, SO_2CH_2), 3.73 (*t*, 2H, C_4-H, $J = 7.2$ Hz), 3.38 (*t*, 2H, C_5-H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2 (C-2), 157.4 (C-3′), 148.2 (C-4′), 135.3 (C-5′), 59.1 (SO_2CH_2), 52.5 (C-4), 38.3 (C-5), 134.7, 134.1, 133.8, 132.3, 131.4, 130.8, 129.4, 128.2 (aromatic carbons); MS (*m/z*): 448.54 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{16}N_2O_5S_3$: C, 50.88; H, 3.60; N, 6.25 %; Found: C, 50.84; H, 3.63; N, 6.32 %.

2-(3′-(p-Methoxyphenyl)-4′-(p-methylphenylsulfonyl)isoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***15b***

m. p. 215–217 °C, yield 61 %; IR (KBr) cm^{-1}): 1633 (C=C), 1581 (C=N), 1342, 1127 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.83 (8H, Ar & Ar'-H), 4.21 (*s*, 2H, SO_2CH_2), 3.88 (*s*, 3H, Ar–OCH_3), 3.72 (*t*, 2H, C_4-H, $J = 7.0$ Hz), 3.32 (*t*, 2H, C_5-H, $J = 7.0$ Hz), 2.34 (*s*, 3H, Ar–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (C-2), 156.4 (C-3′), 147.9 (C-4′), 135.4 (C-5′), 59.5 (SO_2CH_2), 56.7 (Ar–OCH_3), 52.3 (C-4), 38.0 (C-5), 22.5 (Ar–CH_3), 134.7, 133.3, 132.6, 131.9, 131.3, 130.4, 129.8, 129.3 (aromatic carbons); MS (*m/z*): 492.59 [$M^{+\cdot}$]. Anal. Calcd. for $C_{21}H_{20}N_2O_6S_3$: C, 51.20; H, 4.09; N, 5.69 %; Found: C, 51.28; H, 4.10; N, 5.76 %.

2-(3′-(p-Chlorophenyl)-4′-(p-chlorophenylsulfonyl)isoxazol-5′-ylsulfonylmethyl)-4,5-dihydrothiazole ***15c***

m. p. 234–236 °C, yield 67 %; IR (KBr) (cm^{-1}): 1628 (C=C), 1594 (C=N), 1346, 1123 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.85 (8H, Ar & Ar'-H), 4.35 (*s*, 2H, SO_2CH_2), 3.86 (*t*, 2H, C_4-H, $J = 7.4$ Hz), 3.45 (*t*, 2H, C_5-H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (C-2), 157.8 (C-3′), 148.5 (C-4′), 135.6 (C-5′), 59.8 (SO_2CH_2), 52.7 (C-4), 38.6 (C-5), 134.3, 133.4, 132.5, 131.6, 130.6, 129.7, 126.3, 125.8 (aromatic carbons); MS (*m/z*): 517.43 [$M^{+\cdot}$]. Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O_5S_3$; C, 44.10; H, 2.73; N 5.41 %; Found: C, 44.16; H, 2.75; N, 5.45 %.

Antioxidant activity

The compounds **4–15** were evaluated for antioxidant property by DPPH (Burits and Bucar, 2000; Cuendet *et al.*, 1997), nitric oxide (Green *et al.*, 1982; Marcocci *et al.*, 1994), and H_2O_2 (Ruch *et al.*, 1989) methods.

DPPH radical scavenging activity

The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of 2,2,-diphenyl-1-picrylhydrazyl (DPPH). This property makes it suitable for spectrophotometric studies. 1 ml of various concentrations of the test compounds (50, 75, and 100 μg/ml) in methanol were added to 4 ml of 0.004 % (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation

$$I\,\% = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{blank}}\right] \times 100$$

where A_{control} was the absorbance of the control reaction (containing methanolic DPPH and ascorbic acid), A_{sample} was the absorbance of the test compound (containing methanolic DPPH and test compound) and A_{blank} was the absorbance of the blank (containing only methanolic DPPH). Tests were carried out in triplicate.

Nitric oxide (NO) scavenging activity

Nitric oxide scavenging activity was measured by slightly modified methods of Green *et al.* and Marcocci *et al.* Nitric oxide radicals (NO) were generated from sodium nitroprusside. One millilitre of sodium nitroprusside (10 mm) and 1.5 ml of phosphate-buffered saline (0.2 M, pH 7.4) were added to different concentrations (50, 75, and 100 μg/ml) of the test compounds and incubated for 150 min at 25 °C. After incubation 1 ml of the reaction mixture was treated with 1 ml of Griess reagent (1 % sulfanilamide, 2 % H_3PO_4, and 0.1 % naphthylethylenediamine dihydrochloride). The absorbance of the chromophore was measured at 546 nm. Ascorbic acid was used as standard. Nitric oxide scavenging activity was calculated by the following equation

$$\%\,\text{of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{blank}}\right] \times 100$$

where A_{control} was the absorbance of the control reaction (containing all reagents and ascorbic acid), A_{sample} was the absorbance of the test compound (containing all reagents and test compound) and A_{blank} was the absorbance of the blank (containing only reagents). Tests were carried out in triplicate.

Hydrogen peroxide (H_2O_2) scavenging activity

The H_2O_2 scavenging ability of the test compound was determined according to the method of Ruch et al. A solution of H_2O_2 (40 mm) was prepared in phosphate buffer (pH 7.4). 50, 75, and 100 μg/ml concentrations of the test compounds in 3.4 ml-phosphate buffer were added to H_2O_2 solution (0.6 ml, 40 mm). The absorbance value of the reaction mixture was recorded at 230 nm. The per cent of scavenging of H_2O_2 was calculated by the following equation

$$\%\,\text{of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{blank}}\right] \times 100$$

where A_{control} was the absorbance of the control reaction (containing all reagents and ascorbic acid), A_{sample} was the absorbance of the test compound (containing all reagents and test compound), and A_{blank} was the absorbance of the blank (containing only reagents). Tests were carried out in triplicate.

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