Full Paper

Synthesis and Antioxidant Activity of Bis and Tris Heterocycles

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A variety of bis heterocycles, oxazolyl/thiazolyl/imidazolyl oxadiazoles having a styryl sulfonylmethyl group at the 5-position of oxadiazole and tris heterocycles having a pyrrolyl/pyrazolyl sulfonylmethyl group at the 5-position of oxadiazole were prepared adopting simple and versatile synthetic methodologies. All the compounds were screened for their antioxidant activities. Compound **5b** displayed radical scavenging activity in all the three methods greater than the standard ascorbic acid, whereas compounds **8b** and **14b** showed activities equal to the standard ascorbic acid.

Keywords: Antioxidant activity / 1,3,4-Oxadiazoles / Pyrazole / Pyrrole

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Introduction

The widespread applications of heteroarenes in medicinal chemistry and in materials science have driven the development of a new class of heterocyclic cores. Pyrrole and its derivatives play a major role in drug discovery exhibiting various biological activities such as antibacterial [1], antifungal [2], anti-tubercular [1], antidiabetic [3], anti-inflammatory [4], antiviral [5], and anticancer [6]. Pyrazoles are significant in the agrochemical and pharmaceutical industry. They are known for their antitumor [7], antimicrobial [8], anti-inflammatory [9], antiviral [10], anti-convulsant, and antidepressant activities [11]. Celecoxib, a pyrazole derivative, is used successfully as an analgesic in arthritis [12]. Oxazoles are considered as an important class of heterocyclic compounds since they are structural subunits of various biologically active natural products and are valuable synthetic precursors and pharmaceuticals [13]. Oxazoles are associated with antibacterial, antifungal, anti-inflammatory, and antitumor activities and can be used as peptide mimetics or enzyme inhibitors [14]. Thiazole derivatives are well known common motifs in medicinal chemistry due to their broad application in drug development as antiviral, anticancer, antibacterial, antifungal, and anti-inflammatory agents [10, 15–18]. Among fused heterocycles, imidazole based compounds exhibit antibacterial [19, 20], anti-tubercular [21], antiparasitic [22], and anticancer [23, 24] activities. On the other hand, five membered heterocycles having three heteroatoms, *viz*., 1,3,4-oxadiazole, possess anticancer [25], antibacterial [26, 27], antifungal [27], anti-inflammatory [28–30], and antiviral [31] activities. In our earlier studies, we have identified the compounds having 1,3,4-oxadiazole unit as excellent antioxidant agents when compared with those having 1,3,4-thiadiazole and 1,2,4-triazole moieties [32, 33]. Very recently we have synthesized acetamidomethylsulfonyl linked bis heterocycles-oxazolyl/thiazolyl/imidazolyl 1,3,4-oxadiazoles having aryl moiety at 5-position of the oxadiazoles and studied their antioxidant activity. The oxadiazolylmethylsulfonyloxazolyl-acetamide displayed noticeable antioxidant activity [34]. The compounds with good antioxidant activity are expected to possess anti-inflammatory activity [35]. Encouraged by the results and our continued interest in the development of molecules having potential pharmacophoric units the present work is taken up.

Results and discussion

Chemistry

The reaction sequence to achieve the molecules in the present study is depicted in Scheme 1. The synthetic intermediates 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**1**), 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**2**), and 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)-

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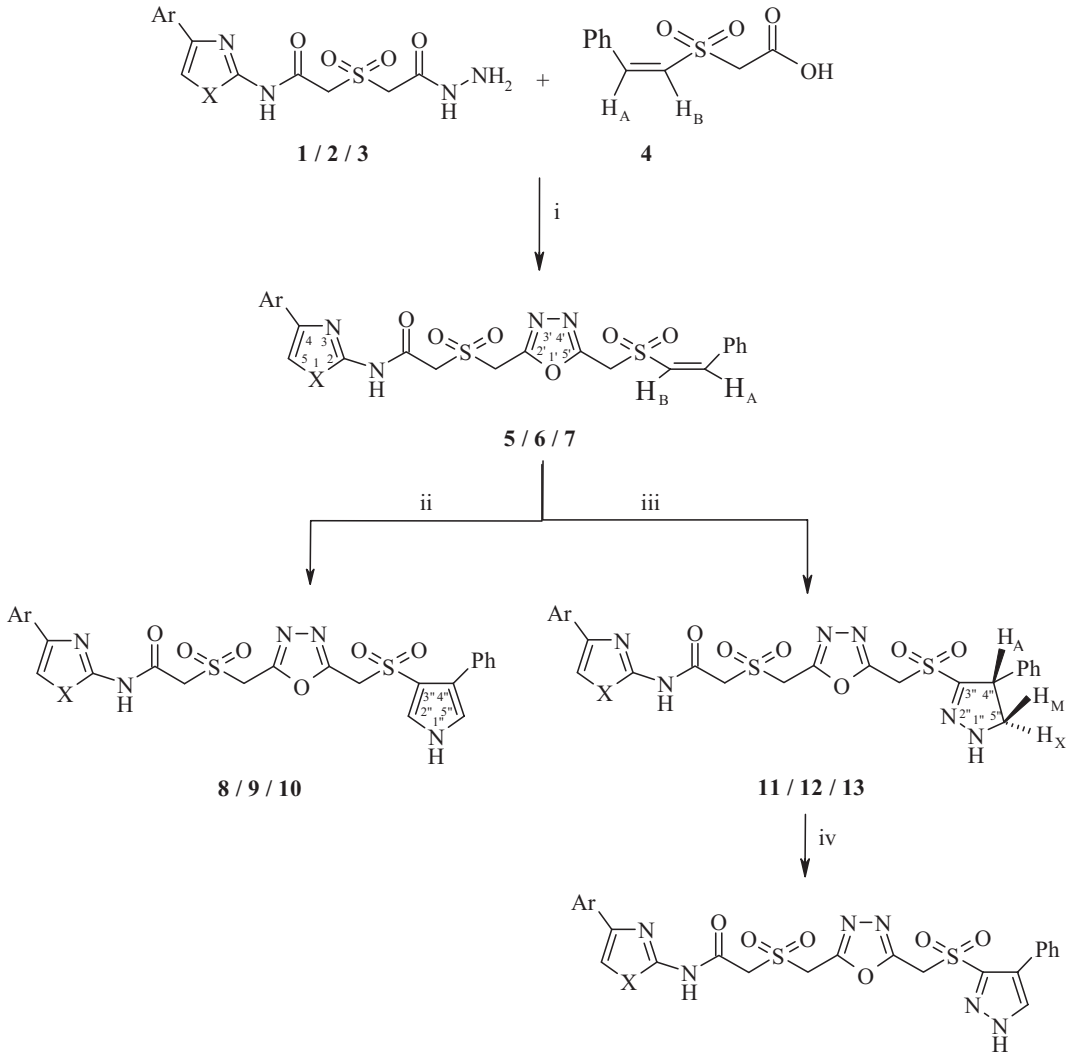

Scheme 1. Synthesis of bis and tris heterocycles.

methylsulfonyl)acetohydrazide (**3**) were prepared as per the literature procedure [34]. The reaction of **1** with styrylsulfonylacetic acid (**4**) gave 2-((5′-((styrylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (**5**). Similarly the cyclocondensation of **2** and **3** with **4** furnished 2-((5′-((styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (**6**), and 2-((5′-((styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**7**). The ^{1}H NMR spectra of **5a**, **6a**, and **7a** produced three singlet signals at δ 4.37, 4.32, 4.44; 4.69, 4.62, 4.64; and 4.95, 4.92, 4.94 ppm due to methylene protons attached to C-2′, C-5′, and those present between carbonyl and sulfonyl groups. The olefin proton, H_B, displayed a doublet at δ 6.71 in **5a**, at 6.59 in **6a**, and at 6.75 ppm in **7a**, while the other proton, H_A, exhibited signals in a more downfield region and merged with aromatic protons. The coupling constant value $J \approx 9.7$ Hz indicated that they are in *cis* geometry.

The 1,3 dipolar cycloaddition of tosylmethyl isocyanide in the presence of NaH and in a solvent mixture of Et_2O and DMSO to compound **5** gave 2-((5′-((4′-phenyl-1″*H*-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (**8**). Adopting similar methodology, 2-((5′-((4″-phenyl-1″*H*-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (**9**) and 2-((5′-((4″-phenyl-1″*H*-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**10**) were prepared from **6** and **7**, respectively. In the ^{1}H NMR spectra of **8a**, **9a**, and **10a**, the presence of a singlet at δ 6.51, 6.48, and 6.49 corresponding to C5″-H of pyrrole ring confirmed their formation. The other proton $C_{2''}$-H displayed signal in slightly downfield region and merged with aromatic protons. On the other hand, the cycloaddition of diazomethane to **5**, **6**, and **7** at −15 to −20°C for 42–46 h yielded 2-((5′-((4″,5″-dihydro-4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryloxazol-2-yl)-acetamide (**11**), 2-((5′-((4″,5″-dihydro-4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (**12**), and 2-((5′-((4″,5″-dihydro-4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**13**). The pyrazoline ring protons in **11a**, **12a**, and **13a** displayed an AMX splitting pattern. The double doublets observed at δ 4.54, 4.10, 3.63 in **11a**, at 4.61, 4.25, 3.55 in **12a**, and at 4.56, 4.19, 3.60 ppm in **13a** were assigned to H_A, H_M, and H_X, respectively. The coupling constant values $J_{AM} \approx 12.2$, $J_{MX} \approx 10.5$, and $J_{AX} \approx 6.4$ Hz indicated that H_A, H_M, are *cis*, H_A, H_X are *trans* and H_M, H_X are *geminal*. Aromatization of the compounds **11**, **12**, and **13** with chloranil gave the aromatized products 2-((5′-((4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (**14**), 2-((5′-((4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-arylthiazol-2-yl)-acetamide (**15**), and 2-((5′-((4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**16**). The absence of an AMX splitting pattern due to pyrazoline ring protons in **14**, **15**, and **16** indicated that aromatization took place. The multiplets observed in the regions δ 7.31–8.18 in **14a**, and 7.28–8.04 ppm in **16a** were accounted for C_5-H, C5″-H, and aromatic protons. However, in **15a**, the multiplet present in the region δ 7.33–8.10 was attributed to C5″-H and Ar–H and the singlet at 6.58 ppm was assigned to C_5-H. The structures of all the compounds were further established by IR and ^{13}C NMR spectral data.

Biological results

Antioxidant activity

The compounds **5**–**16** were tested for antioxidant activity by 2,2,-diphenyl-1-picrylhydrazyl (DPPH) [36, 37], nitric oxide (NO) [38, 39], and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) [40] methods. The results are presented in Tables 1–3 and Figs. 1–3. The bis heterocyclic systems having styryl sulfonyl moiety **5**, **6**, and **7** exhibited more activity than the respective tris heterocyclic compounds **8**–**16**. This may be due to the presence of more electron withdrawing styrylsulfonyl group at 5-position of 1,3,4-oxadiazole. In fact, 2-((5′-((styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-*p*-tolyloxazol-2-yl)-acetamide (**5b**) showed excellent antioxidant activity greater than the standard ascorbic acid. Among tris heterocyclic systems, 2-((5′-((4″-phenyl-1″*H*-pyrrol-3″-

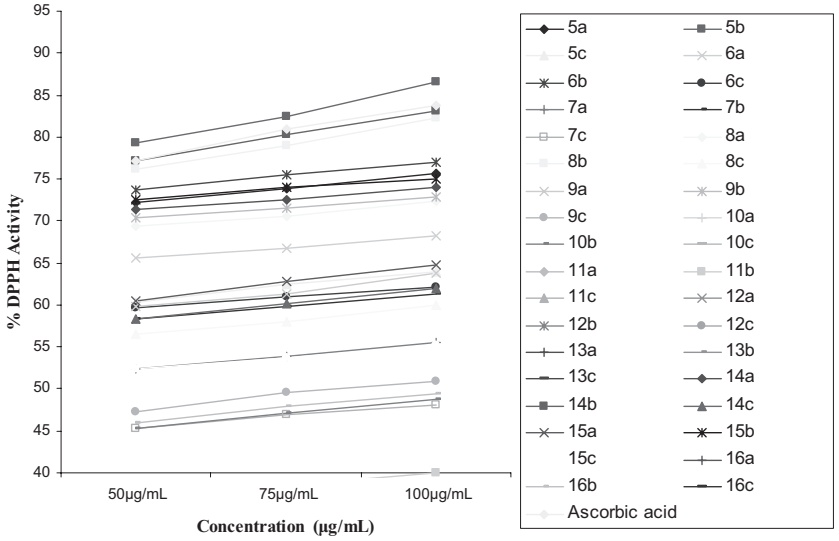

Figure 1. The *in vitro* antioxidant activity of **5**–**16** in DPPH method.

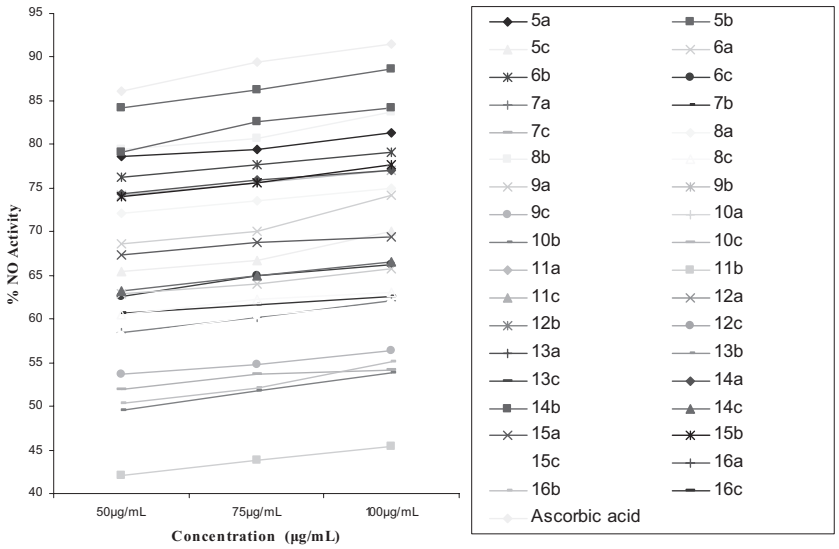

Figure 2. The *in vitro* antioxidant activity of **5–16** in NO method.

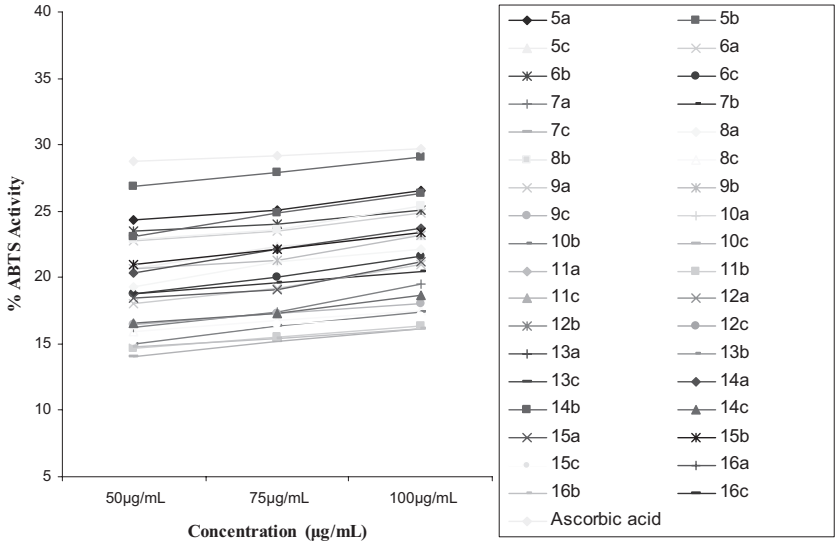

Figure 3. The *in vitro* antioxidant activity of **5–16** in ABTS method.

ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-*p*-tolyloxazol-2-yl)acetamide (**8b**) and 2-((5′-((4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-*p*-tolyloxazol-2-yl)acetamide (**14b**) displayed radical scavenging activity almost equal to the standard ascorbic acid. The compounds 2-((5′-((4″-phenyl-1″*H*-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-*p*-tolylthiazol-2-yl)acetamide (**9b**) and 2-((5′-((4″-phenyl-1″*H*-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-*p*-tolyloxazol-2-yl)acetamide (**15b**) exhibited good activity. On the other hand, the compounds **7**, **10**, **11**, and **16** displayed least activity whereas the compounds **12** and **13** showed no activity. Thus the results exemplified that aromatized heterocycles showed greater activity than non-aromatized compounds. It was also observed that there was no marked difference in activity between the compounds having pyrrole and pyrazole moieties. The presence of methyl substituent on the aromatic ring enhanced the activity, which may be due to +I effect of methyl group. Furthermore the compounds having more oxygen atoms displayed more activity. This was evidenced by the fact that oxazolyl oxadiazoles **5**, **8**, and **14** showed activity greater than the

Table 1. The *in vitro* antioxidant activity of **5–16** in DPPH method.

	Concentration			
Compound	**50 μg/mL**	**75 μg/mL**	**100 μg/mL**	**IC_{50} μmol/mL**
5a	72.25 ± 0.54	73.79 ± 1.12	75.64 ± 0.62	0.065 ± 0.36
5b	79.36 ± 1.02	82.44 ± 0.33	86.57 ± 0.45	0.058 ± 0.18
5c	60.35 ± 1.34	62.47 ± 1.09	63.98 ± 0.14	0.073 ± 0.72
6a	65.54 ± 0.98	66.79 ± 1.23	68.32 ± 0.52	0.070 ± 0.64
6b	73.64 ± 1.32	75.58 ± 0.88	76.95 ± 1.17	0.060 ± 1.02
6c	59.71 ± 0.84	60.96 ± 0.62	62.07 ± 1.44	0.072 ± 0.28
7a	52.37 ± 0.67	53.84 ± 1.13	55.52 ± 0.94	0.090 ± 0.44
7b	58.34 ± 1.11	59.79 ± 1.56	61.36 ± 0.36	0.079 ± 1.16
7c	45.33 ± 1.46	46.91 ± 1.05	48.04 ± 0.84	0.098 ± 0.82
8a	69.35 ± 0.85	70.58 ± 0.55	72.37 ± 1.62	0.063 ± 0.52
8b	76.12 ± 1.57	78.98 ± 0.43	82.34 ± 1.06	0.056 ± 0.48
8c	56.45 ± 1.72	58.04 ± 0.18	59.94 ± 1.14	0.073 ± 1.37
9a	59.76 ± 0.33	61.35 ± 1.67	63.74 ± 1.32	0.071 ± 1.24
9b	70.31 ± 0.42	71.47 ± 1.71	72.89 ± 0.98	0.059 ± 0.98
9c	47.33 ± 0.65	49.54 ± 1.44	50.98 ± 0.72	0.085 ± 0.25
10a	–	–	–	–
10b	45.32 ± 1.28	47.04 ± 0.90	48.79 ± 1.41	0.094 ± 1.12
10c	–	–	–	–
11a	–	–	–	–
11b	37.45 ± 1.02	38.59 ± 0.65	40.05 ± 1.52	0.114 ± 0.86
11c	–	–	–	–
12a	–	–	–	–
12b	–	–	–	–
12c	–	–	–	–
13a	–	–	–	–
13b	–	–	–	–
13c	–	–	–	–
14a	71.35 ± 0.66	72.58 ± 1.03	73.96 ± 0.66	0.061 ± 0.56
14b	77.09 ± 1.15	80.34 ± 0.92	83.05 ± 1.11	0.055 ± 0.37
14c	58.37 ± 1.55	60.15 ± 0.29	61.94 ± 0.48	0.071 ± 0.48
15a	60.49 ± 0.97	62.73 ± 0.18	64.85 ± 1.34	0.070 ± 1.33
15b	72.62 ± 0.51	73.95 ± 0.94	75.04 ± 1.66	0.057 ± 1.45
15c	52.45 ± 0.14	53.79 ± 1.16	55.24 ± 0.87	0.076 ± 0.49
16a	–	–	–	–
16b	45.97 ± 0.67	47.85 ± 1.32	49.34 ± 0.39	0.093 ± 0.72
16c	–	–	–	–
Ascorbic acid	77.15 ± 0.32	80.98 ± 1.44	83.82 ± 0.92	0.183 ± 0.56
Blank	–	–	–	–

(–) Showed no scavenging activity.
Values were the means of three replicates ± SD.

respective thiazolyl oxadiazoles **6**, **9**, and **15** and imidazolyl oxadiazoles **7**, **10**, and **16**. In our communication, we have reported that oxazolyloxadiazole having 2-chlorophenyl group at 5-position of oxadiazole displayed good antioxidant activity [34]. The replacement of 2-chlorophenyl moiety with styrylsulfonylmethyl, pyrrolylsulfonylmethyl and pyrazolylsulfonylmethyl units increases the antioxidant activity. The free radical scavenging activity of the compounds **5a**, **5b**, **6b**, **8b**, **9b**, **14a**, **14b**, and **15b** was measured at different concentrations and monitored the change in absorbance at 10, 20, and 30 min in DPPH method as shown in Table 4. At these 10 min intervals, the values are very close and the results indicated that the antioxidant activity is independent of time.

Conclusion

A variety of bis heterocycles, oxazolyl/thiazolyl/imidazolyl oxadiazoles having styryl sulfonylmethyl group at 5-position of oxadiazole and tris heterocycles having pyrrolyl/pyrazolyl sulfonylmethyl group at 5-position of oxadiazole were prepared adopting simple and versatile synthetic methodologies. All the compounds were screened for their antioxidant activity. The compound **5b** displayed radical scavenging

Table 2. The *in vitro* antioxidant activity of **5–16** in NO method.

	Concentration		
Compound	**50 μg/mL**	**75 μg/mL**	**100 μg/mL**
5a	78.56 ± 0.76	79.43 ± 1.52	81.34 ± 0.17
5b	84.12 ± 0.28	86.28 ± 1.08	88.64 ± 0.42
5c	65.42 ± 0.16	66.74 ± 1.24	70.08 ± 0.95
6a	68.57 ± 1.32	70.03 ± 1.16	74.15 ± 0.39
6b	76.32 ± 0.84	77.68 ± 0.28	79.04 ± 0.67
6c	62.61 ± 0.18	64.94 ± 1.33	66.28 ± 1.12
7a	58.43 ± 1.62	60.26 ± 1.02	62.09 ± 0.33
7b	60.72 ± 1.12	61.58 ± 1.64	62.64 ± 0.69
7c	51.92 ± 0.76	53.72 ± 1.45	54.22 ± 0.28
8a	72.16 ± 0.58	73.52 ± 0.81	75.04 ± 1.66
8b	79.43 ± 0.23	82.76 ± 0.38	84.69 ± 1.54
8c	60.48 ± 1.18	62.27 ± 0.73	63.12 ± 1.18
9a	62.93 ± 0.66	64.02 ± 1.11	65.71 ± 1.68
9b	74.19 ± 1.34	75.56 ± 1.06	77.01 ± 0.24
9c	53.68 ± 0.98	54.82 ± 0.66	56.33 ± 1.45
10a	–	–	–
10b	49.53 ± 1.22	51.75 ± 0.24	53.84 ± 1.03
10c	–	–	–
11a	–	–	–
11b	42.11 ± 0.78	43.82 ± 0.38	45.48 ± 0.86
11c	–	–	–
12a	–	–	–
12b	–	–	–
12c	–	–	–
13a	–	–	–
13b	–	–	–
13c	–	–	–
14a	74.37 ± 1.04	75.92 ± 0.92	77.06 ± 0.19
14b	79.18 ± 1.38	82.64 ± 0.74	84.25 ± 0.44
14c	63.27 ± 1.78	65.02 ± 1.16	66.53 ± 0.56
15a	67.42 ± 0.86	68.71 ± 1.04	69.44 ± 0.22
15b	73.94 ± 1.02	75.62 ± 0.63	77.68 ± 1.06
15c	58.19 ± 0.72	60.29 ± 0.32	61.82 ± 1.62
16a	–	–	–
16b	50.34 ± 0.55	52.13 ± 1.34	55.07 ± 0.94
16c	–	–	–
Ascorbic acid	79.02 ± 0.48	82.46 ± 0.88	84.53 ± 0.52
Blank	–	–	–

(–) Showed no scavenging activity.
Values were the means of three replicates ± SD.

activity in all the three methods greater than the standard ascorbic acid, whereas the compounds **8b** and **14b** showed activity equal to the standard ascorbic acid.

Experimental

Chemistry

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 spectra were recorded in DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat 1210 B at 70 eV with an emission current of 100 μA. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The antioxidant property was assessed by using Shimadzu UV-2450 spectrophotometer. The synthetic intermediates 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**1**), 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**2**), and 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylsulfonyl) acetohydrazide (**3**) were prepared as per the literature procedure [29].

Table 3. The *in vitro* antioxidant activity of **5–16** in ABTS method.

	Concentration		
Compound	**50 μg/mL**	**75 μg/mL**	**100 μg/mL**
5a	24.35 ± 0.44	25.03 ± 0.92	26.54 ± 1.32
5b	26.83 ± 0.97	27.91 ± 1.53	29.10 ± 0.41
5c	20.65 ± 1.04	22.38 ± 0.68	23.18 ± 0.35
6a	22.73 ± 0.53	23.46 ± 0.82	24.82 ± 1.15
6b	24.51 ± 0.28	25.05 ± 0.67	26.11 ± 1.02
6c	18.77 ± 1.36	20.02 ± 0.46	21.63 ± 0.76
7a	16.24 ± 0.48	17.38 ± 1.04	19.47 ± 0.26
7b	18.82 ± 0.22	19.65 ± 1.77	20.40 ± 0.92
7c	14.06 ± 0.56	15.23 ± 0.91	16.15 ± 0.17
8a	19.33 ± 1.39	21.17 ± 0.55	22.09 ± 0.68
8b	23.86 ± 0.87	24.64 ± 0.24	25.42 ± 1.04
8c	15.91 ± 0.45	16.75 ± 0.86	17.49 ± 1.44
9a	18.04 ± 0.68	19.14 ± 1.18	21.00 ± 0.16
9b	20.66 ± 1.23	21.32 ± 0.23	23.14 ± 0.98
9c	16.41 ± 1.08	17.28 ± 0.63	18.05 ± 0.33
10a	–	–	–
10b	15.02 ± 0.78	16.37 ± 1.47	17.41 ± 0.15
10c	–	–	–
11a	–	–	–
11b	14.69 ± 0.92	15.53 ± 0.26	16.31 ± 1.27
11c	–	–	–
12a	–	–	–
12b	–	–	–
12c	–	–	–
13a	–	–	–
13b	–	–	–
13c	–	–	–
14a	20.34 ± 0.63	22.18 ± 1.18	23.76 ± 0.27
14b	23.12 ± 0.29	24.82 ± 1.47	25.38 ± 0.92
14c	16.52 ± 1.12	17.25 ± 0.22	18.63 ± 0.83
15a	18.45 ± 0.84	19.04 ± 0.16	21.15 ± 0.75
15b	21.02 ± 0.71	22.14 ± 0.86	23.43 ± 1.08
15c	15.23 ± 0.32	16.48 ± 0.57	17.06 ± 1.21
16a	–	–	–
16b	14.78 ± 0.96	15.42 ± 0.33	16.12 ± 1.36
16c	–	–	–
Ascorbic acid	23.80 ± 0.38	24.20 ± 0.46	25.70 ± 0.28
Blank	–	–	–

(–) Showed no scavenging activity.
Values were the means of three replicates ± SD.

*General procedure for the synthesis of 2-((5′-((styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-aryloxazol-2-yl)acetamide (**5a–c**)/2-((5′-((styrylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-arylthiazol-2-yl)acetamide (**6a–c**)/2-((5′-((styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-aryl-1H-imidazol-2-yl)acetamide (**7a–c**)*
A mixture of **1**/**2**/**3** (10 mmol), *Z*-styrylsulfonylacetic acid (**4**) (10 mmol), and $POCl_3$ (7 mL) was heated under reflux for 7–9 h. The excess $POCl_3$ was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried, and recrystallized from 2-propanol.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-phenyloxazol-2-yl)acetamide (**5a**):*
White solid in 68%; m.p.: 135–137°C; IR (KBr) ν_{max} (cm^{-1}): 1122, 1322 (SO_2), 1565 (C=N), 1616 (C=C), 1668 (NH*CO*), 3246 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.37 (s, 2H, CH_2-(C-2′)), 4.69 (s, 2H, CH_2-(C-5′)), 4.95 (s, 2H, CO–CH_2), 6.71 (d, 1H, H_B, $J = 9.7$ Hz), 7.28–7.53 (m, 12H, Ar–H, C_5-H, and H_A), 11.22 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.9 (*C*H_2-(C-2′)), 50.2 (*C*H_2-(C-5′)), 54.1 (CO–*C*H_2), 111.6 (C-H_B), 127.2 (C-H_A), 137.4 (C-5), 140.8 (C-4), 148.0 (*C*-2), 158.7 (C-2′), 165.7 (C-5′), 168.7 (*C*O), 125.9, 127.0,

Table 4. Antioxidant activity of the compounds **5a**, **5b**, **6b**, **8b**, **9b**, **14a**, **14b**, and **15b** at 10 min.

Compound	10 min	20 min	30 min
5a	72.17	72.35	72.94
5b	79.34	79.65	79.88
6b	73.42	73.57	73.88
8b	76.05	76.34	76.59
9b	70.14	70.25	70.46
14a	70.98	71.16	71.32
14b	77.07	77.45	77.82
15b	72.05	72.34	72.58

Time intervals by DPPH scavenging method.

128.2, 130.5, 131.7, 132.6, 134.2, 136.7 (aromatic carbons); MS (*m/z*): 528.57 [M^+]. Anal. calcd. for $C_{23}H_{20}N_4O_7S_2$: C 52.26, H 3.81, N 10.60; Found: C 52.38, H 3.84, N 10.76%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-p-tolyloxazol-2-yl)acetamide (**5b**):* White solid in 66%; m.p.: 126–128°C; IR (KBr) ν_{max} (cm^{-1}): 1120, 1316 (SO_2), 1562 (C=N), 1610 (C=C), 1664 (NH*CO*), 3242 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.37 (s, 3H, Ar–CH_3), 4.33 (s, 2H, CH_2-(C-2′)), 4.64 (s, 2H, CH_2-(C-5′)), 4.92 (s, 2H, CO–CH_2), 6.69 (d, 1H, H_B, $J = 9.1$ Hz), 7.20–7.35 (m, 11H, Ar–H, C_5-H, and H_A), 10.82 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.6 (Ar–CH_3), 46.7 (*C*H_2-(C-2′)), 49.4 (*C*H_2-(C-5′)), 53.8 (CO–*C*H_2), 109.5 (C-H_B), 126.6 (C-H_A), 136.8 (C-5), 139.4 (C-4), 147.5 (C-2), 157.2 (C-2′), 164.8 (C-5′), 168.4 (CO), 128.3, 129.1, 129.8, 131.5, 132.2, 134.8, 135.6, 137.3 (aromatic carbons); MS (*m/z*): 542.59 [M^+]. Anal. calcd. for $C_{24}H_{22}N_4O_7S_2$: C 53.13, H 4.09, N 10.33; Found: C 53.21, H 4.08, N 10.46%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-(4-chloro-phenyl)oxazol-2-yl)acetamide (**5c**):* White solid in 72%; m.p.: 152–154°C; IR (KBr) ν_{max} (cm^{-1}): 1127, 1324 (SO_2), 1575 (C=N), 1622 (C=C), 1672 (NH*CO*), 3257 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.39 (s, 2H, CH_2-(C-2′)), 4.72 (s, 2H, CH_2-(C-5′)), 4.98 (s, 2H, CO–CH_2), 6.76 (d, 1H, H_B, $J = 9.8$ Hz), 7.23–7.62 (m, 11H, Ar–H, C_5-H, and H_A), 11.27 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.5 (*C*H_2-(C-2′)), 50.8 (*C*H_2-(C-5′)), 54.7 (CO–*C*H_2), 111.8 (C-H_B), 127.8 (C-H_A), 137.6 (C-5), 141.6 (C-4), 148.3 (C-2), 158.2 (C-2′), 166.7 (C-5′), 169.8 (CO), 127.5, 128.4, 129.5, 131.4, 132.6, 133.8, 135.2, 137.8 (aromatic carbons); MS (*m/z*): 563.01 [M^+]. Anal. calcd. for $C_{23}H_{19}ClN_4O_7S_2$: C 49.07, H 3.04, N 9.95; Found: C 49.17, H 3.44, N 10.09%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-phenylthiazol-2-yl)acetamide (**6a**):* White solid in 65%; m.p.: 147–149°C; IR (KBr) ν_{max} (cm^{-1}): 1126, 1318 (SO_2), 1578 (C=N), 1624 (C=C), 1667 (NH*CO*), 3248 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.32 (s, 2H, CH_2-(C-2′)), 4.62 (s, 2H, CH_2-(C-5′)), 4.92 (s, 2H, CO–CH_2), 6.56 (s, 1H, C_5-H), 6.59 (d, 1H, H_B, $J = 9.7$ Hz), 7.23–7.54 (m, 11H, Ar–H, and H_A), 10.92 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.6 (*C*H_2-(C-2′)), 50.4 (*C*H_2-(C-5′)), 53.6 (CO–*C*H_2), 103.4 (C-5), 111.4 (C-H_B), 126.4 (C-H_A), 147.3 (C-4), 156.4 (C-2′), 162.9 (C-2), 164.7 (C-5′), 168.9 (CO), 127.6, 128.1, 130.3, 132.7, 134.5, 136.0, 137.9, 139.5 (aromatic carbons); MS (*m/z*): 544.64 [M^+]. Anal. calcd. for $C_{23}H_{20}N_4O_6S_3$: C 50.72, H 3.70, N 10.29; Found: C 50.67, H 3.69, N 10.41%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-p-tolylthiazol-2-yl)acetamide (**6b**):* White solid in 67%; m.p.: 154–156°C; IR (KBr) ν_{max} (cm^{-1}): 1123, 1315 (SO_2), 1572 (C=N), 1618 (C=C), 1674 (NH*CO*), 3245 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.34 (s, 3H, Ar–CH_3), 4.30 (s, 2H, CH_2-(C-2′)), 4.60 (s, 2H, CH_2-(C-5′)), 4.90 (s, 2H, CO–CH_2), 6.44 (d, 1H, H_B, $J = 9.6$ Hz), 6.54 (s, 1H, C_5-H), 7.19–7.42 (m, 10H, Ar–H, and H_A), 10.84 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.4 (Ar–CH_3), 46.2 (*C*H_2-(C-2′)), 49.7 (*C*H_2-(C-5′)), 53.2 (CO–*C*H_2), 102.5 (C-5), 109.8 (C-H_B), 126.2 (C-H_A), 146.5 (C-4), 154.2 (C-2′), 162.5 (C-2), 166.5 (C-5′), 168.5 (CO), 128.4, 130.0, 131.3, 132.8, 134.7, 135.3, 137.1, 138.3 (aromatic carbons); MS (*m/z*): 558.66 [M^+]. Anal. calcd. for $C_{24}H_{22}N_4O_6S_3$: C 51.60, H 3.97, N 10.03; Found: C 51.67, H 4.00, N 10.13%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-(4-chloro-phenyl)thiazol-2-yl)acetamide (**6c**):* White solid in 70%; m.p.: 173–175°C; IR (KBr) ν_{max} (cm^{-1}): 1132, 1323 (SO_2), 1587 (C=N), 1615 (C=C), 1679 (NH*CO*), 3262 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.35 (s, 2H, CH_2-(C-2′)), 4.66 (s, 2H, CH_2-(C-5′)), 4.95 (s, 2H, CO–CH_2), 6.57 (s, 1H, C_5-H), 6.85 (d, 1H, H_B, $J = 9.9$ Hz), 7.28–7.47 (m, 10H, Ar–H, and H_A), 10.95 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.8 (*C*H_2-(C-2′)), 50.3 (*C*H_2-(C-5′)), 53.8 (CO-*C*H_2), 104.4 (C-5), 111.2 (C-H_B), 127.5 (C-H_A), 147.2 (C-4), 155.6 (C-2′), 163.0 (C-2), 164.8 (C-5′), 169.2 (CO), 127.6, 128.2, 129.6, 130.4, 131.3, 132.2, 132.3, 135.4 (aromatic carbons); MS (*m/z*): 579.08 [M^+]. Anal. calcd. for $C_{23}H_{19}ClN_4O_6S_3$: C 47.70, H 3.31, N 9.68; Found: C 47.79, H 3.36, N 9.84%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-phenyl-1H-imidazol-2-yl)acetamide (**7a**):* White solid in 69%; m.p.: 140–142°C; IR (KBr) ν_{max} (cm^{-1}): 1128, 1320 (SO_2), 1570 (C=N), 1626 (C=C), 1657 (NH*CO*), 3249 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.44 (s, 2H, CH_2-(C-2′)), 4.64 (s, 2H, CH_2-(C-5′)), 4.94 (s, 2H, CO–CH_2), 6.75 (d, 1H, H_B, $J = 9.3$ Hz), 7.22–7.51 (m, 12H, Ar–H, C_5-H, and H_A), 10.98 (bs, 1H, NH–CO), 12.47 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.5 (*C*H_2-(C-2′)), 50.1 (*C*H_2-(C-5′)), 54.5 (CO–*C*H_2), 111.0 (C-H_B), 119.5 (C-5), 126.8 (C-H_A), 136.3 (C-2), 143.4 (C-4), 154.8 (C-2′), 165.5 (C-5′), 169.9 (CO), 126.5, 128.1, 129.6, 130.0, 132.5, 134.9, 136.3, 137.6 (aromatic carbons); MS

(*m*/*z*): 527.58 [M^+]. Anal. calcd. for $C_{23}H_{21}N_5O_6S_2$: C 52.36, H 4.01, N 13.27; Found: C 52.41, H 4.02, N 13.42%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-p-tolyl-1H-imidazol-2-yl)acetamide (**7b**):*

White solid in 72%; m.p.: 135–137°C; IR (KBr) ν_{max} (cm^{-1}): 1125, 1317 (SO_2), 1566 (C=N), 1630 (C=C), 1656 (NH*CO*), 3244 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.36 (s, 3H, Ar–CH_3), 4.42 (s, 2H, CH_2-(C-2′)), 4.62 (s, 2H, CH_2-(C-5′)), 4.91 (s, 2H, CO–CH_2), 6.66 (d, 1H, H_B, J = 9.1 Hz), 7.23–7.46 (m, 11H, Ar–H, C_5-H, and H_A), 10.96 (bs, 1H, NH–CO), 12.45 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm) 24.8 (Ar–CH_3), 46.3 (*C*H_2-(C-2′)), 49.8 (*C*H_2-(C-5′)), 53.6 (CO–*C*H_2), 109.8 (C-H_B), 119.0 (C-5), 126.4 (C-H_A), 136.1 (C-2), 142.2 (C-4), 153.7 (C-2′), 165.3 (C-5′), 168.3 (CO), 125.4, 128.5, 129.0, 130.4, 131.5, 134.1, 135.2, 138.5 (aromatic carbons); MS (*m*/*z*): 541.60 [M^+]. Anal. calcd. for $C_{24}H_{23}N_5O_6S_2$: C 53.22, H 4.28, N 12.93; Found: C 53.16, H 4.32, N 13.04%.

*2-((5′-((Styrylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-(4-chloro-phenyl)-1H-imidazol-2-yl)-acetamide (**7c**):*

White solid in 68%; m.p.: 163–165°C; IR (KBr) ν_{max} (cm^{-1}): 1134, 1328 (SO_2), 1579 (C=N), 1622 (C=C), 1667 (NH*CO*), 3257 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.48 (s, 2H, CH_2-(C-2′)), 4.69 (s, 2H, CH_2-(C-5′)), 4.96 (s, 2H, CO–CH_2), 6.79 (d, 1H, H_B, J = 9.7 Hz), 7.24–7.58 (m, 11H, Ar–H, C_5-H, and H_A), 11.06 (bs, 1H, NH–CO), 12.52 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.8 (*C*H_2-(C-2′)), 50.6 (*C*H_2-(C-5′)), 54.2 (CO–*C*H_2), 111.5 (C-H_B), 119.8 (C-5), 127.2 (C-H_A), 137.6 (C-2), 143.8 (C-4), 155.4 (C-2′), 166.7 (C-5′), 170.2 (CO), 125.3, 127.3, 128.2, 128.8, 129.5, 130.2, 133.4, 134.6 (aromatic carbons); MS (*m*/*z*): 562.02 [M^+]. Anal. calcd. for $C_{23}H_{20}ClN_5O_6S_2$: C 49.15, H 3.59, N 12.46; Found: C 49.25, H 3.57, N 12.39%.

*General procedure for the synthesis of 2-((5′-((4″-phenyl-1″H-pyrrol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-aryloxazol-2-yl)acetamide (**8a–c**)/2-((5′-((4″-phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-arylthiazol-2-yl)-acetamide (**9a–c**)/2-((5′-((4″-phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′ -oxadiazol-2′-yl)methylsulfonyl)-N-(4-aryl-1H-imidazol-2-yl)acetamide (**10a–c**)*

To a suspension of NaH (0.05 g) in Et_2O (20 mL), **5**/**6**/**7** (1 mmol) and TosMIC (2 mmol) in Et_2O/DMSO (2:1) was added while stirring at room temperature and continued for 6–8 h. Then, water was added and the reaction mass was extracted with Et_2O. The ethereal layer was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude product, which was purified by passing through a column of silica gel using ethyl acetate and hexane (1:4) as eluent.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenyloxazol-2-yl)acetamide (**8a**):*

White solid in 69%; m.p.: 146–148°C; IR (KBr) ν_{max} (cm^{-1}): 1140, 1330 (SO_2), 1562 (C=N), 1620 (C=C), 1677 (NH*CO*), 3240 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.36 (s, 2H, CH_2-(C-2′)), 4.64 (s, 2H, CH_2-(C-5′)), 4.78 (s, 2H, CO–CH_2), 6.51 (s, 1H, C5″-H), 6.95–7.72 (m, 12H, Ar–H, C_5-H, and C2″-H), 8.62 (bs, 1H, NH-C2″), 11.24 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.4 (*C*H_2-(C-2′)), 50.2 (*C*H_2-(*C*-5′)), 53.8 (CO–*C*H_2), 106.5 (C-3″), 110.8 (C-5″), 118.0 (C-2″), 127.0 (C-4″), 137.4 (C-5), 140.8 (C-4), 150.2 (C-2), 158.7 (C-2′), 165.7 (C-5′), 170.4 (CO), 127.3, 128.1, 128.9, 129.2, 131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m*/*z*): 567.61 [M^+]. Anal. calcd. for $C_{25}H_{21}N_5O_7S_2$: C 52.90, H 3.73, N 12.34; Found: C 52.94, H 3.75, N 12.43%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolyloxazol-2-yl)acetamide (**8b**):*

White solid in 71%; m.p.: 152–154°C; IR (KBr) ν_{max} (cm^{-1}): 1138, 1326 (SO_2), 1564 (C=N), 1611 (C=C), 1671 (NH*CO*), 3235 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, Ar–CH_3), 4.30 (s, 2H, CH_2-(C-2′)), 4.62 (s, 2H, CH_2-(C-5′)), 4.69 (s, 2H, CO–CH_2), 6.48 (s, 1H, C5″-H), 6.92–7.52 (m, 11H, Ar–H, C_5-H, and C2″-H), 8.61 (bs, 1H, NH-C2″), 11.12 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.6 (Ar–CH_3), 47.1 (*C*H_2-(C-2′)), 50.1 (*C*H_2-(C-5′)), 53.8 (CO–*C*H_2), 105.7 (C-3″), 110.6 (C-5″), 118.2 (C-2″), 126.8 (C-4″), 138.0 (C-5), 140.4 (C-4), 150.5 (C-2), 157.2 (C-2′), 164.8 (C-5′), 169.8 (CO), 127.6, 128.3, 128.6, 129.3, 129.7, 130.5, 131.8, 134.3 (aromatic carbons); MS (*m*/*z*): 581.63 [M^+]. Anal. calcd. for $C_{26}H_{23}N_5O_7S_2$: C 53.69, H 3.99, N 12.04; Found: C 53.81, H 4.03, N 12.16%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chloro-phenyl)oxazol-2-yl)acetamide (**8c**):*

White solid in 68%; m.p.: 165–167°C; IR (KBr) ν_{max} (cm^{-1}): 1144, 1334 (SO_2), 1574 (C=N), 1628 (C=C), 1685 (NH*CO*), 3252 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.37 (s, 2H, CH_2-(C-2′)), 4.68 (s, 2H, CH_2-(C-5′)), 4.85 (s, 2H, CO–CH_2), 6.55 (s, 1H, C5″-H), 6.94–7.56 (m, 11H, Ar–H, C_5-H, and C2″-H), 8.65 (bs, 1H, NH-C2″), 11.20 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.6 (*C*H_2-(C-2′)), 50.4 (*C*H_2-(C-5′)), 54.7 (CO–*C*H_2), 106.9 (C-3″), 111.3 (C-5″), 119.1 (C-2″), 127.2 (C-4″), 138.3 (C-5), 140.7 (C-4), 151.3 (C-2), 158.2 (C-2′), 166.7 (C-5′), 171.8 (CO), 124.3, 125.6, 126.8, 128.5, 129.7, 130.4, 132.3, 134.5 (aromatic carbons); MS (*m*/*z*): 602.05 [M^+]. Anal. calcd. for $C_{25}H_{20}ClN_5O_7S_2$: C 49.88, H 3.35, N 11.63; Found: C 50.02, H 3.41, N 11.81%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenylthiazol-2-yl)acetamide (**9a**):*

White solid in 70%; m.p.: 153–155°C; IR (KBr) ν_{max} (cm^{-1}): 1131, 1333 (SO_2), 1586 (C=N), 1626 (C=C), 1670 (NH*CO*), 3245 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.42 (s, 2H, CH_2-(C-2′)), 4.57 (s, 2H, CH_2-(C-5′)), 4.64 (s, 2H, CO–CH_2), 6.48 (s, 1H, C5″-H), 6.58 (s, 1H, C_5-H), 6.83–7.66 (m, 11H, Ar–H, and C2″-H), 8.32 (bs, 1H, NH-C2″), 11.05 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.2 (*C*H_2-(C-2′)), 49.4 (*C*H_2-(C-5′)), 54.6 (CO–*C*H_2), 104.4 (C-5), 107.6 (C-3″), 110.5 (C-5″), 117.7 (C-2″), 126.9 (C-4″), 148.3 (C-4), 156.4 (C-2′), 163.9 (C-2), 164.7 (C-5′), 168.0 (CO), 129.1, 130.2, 130.9, 131.2, 132.7, 133.5, 135.4, 138.2 (aromatic carbons); MS (*m*/*z*): 583.68 [M^+]. Anal. calcd. for $C_{25}H_{21}N_5O_6S_3$: C 51.45, H 3.63, N 12.00; Found: C 51.51, H 3.60, N 12.12%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolylthiazol-2-yl)acetamide (**9b**):*

White solid in 72%; m.p.: 158–160°C; IR (KBr) ν_{max} (cm^{-1}): 1129, 1330 (SO_2), 1582 (C=N), 1613 (C=C), 1674 (NH*CO*), 3236 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.32 (s, 3H, Ar–CH_3), 4.37 (s, 2H, CH_2-(C-2′)), 4.54 (s, 2H, CH_2-(C-5′)), 4.62 (s, 2H, CO–CH_2), 6.44 (s, 1H, C5″-H), 6.55 (s, 1H, C_5-H), 6.81–7.55 (m, 10H, Ar–H, and C2″-H), 8.26 (bs, 1H, NH-C2″), 10.98 (bs, 1H, NH–CO);

^{13}C NMR (DMSO-d_6) δ (ppm): 23.6 (Ar–CH_3), 46.0 (CH_2-(C-2′)), 49.2 (CH_2-(C-5′)), 53.2 (CO–CH_2), 105.5 (C-5), 107.0 (C-3″), 110.2 (C-5″), 117.2 (C-2″), 126.3 (C-4″), 147.5 (C-4), 154.2 (C-2′), 163.5 (C-2), 166.5 (C-5′), 167.8 (CO), 128.5, 130.7, 131.2, 131.9, 132.5, 133.7, 134.1, 134.5 (aromatic carbons); MS (*m*/*z*): 597.67 [M^+]. Anal. calcd. for $C_{26}H_{23}N_5O_6S_3$: C 52.25, H 3.88, N 11.72; Found: C 52.21, H 3.90, N 11.79%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (**9c**):* White solid in 65%; m.p.: 184–186°C; IR (KBr) ν_{max} (cm^{-1}): 1138, 1340 (SO_2), 1590 (C=N), 1611 (C=C), 1682 (NH*CO*), 3254 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.45 (s, 2H, CH_2-(C-2′)), 4.60 (s, 2H, CH_2-(C-5′)), 4.77 (s, 2H, CO–CH_2), 6.53 (s, 1H, C5″-H), 6.60 (s, 1H, C_5-H), 6.88–7.48 (m, 10H, Ar–H, and C2″-H), 8.34 (bs, 1H, NH-C2″), 11.11 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.8 (CH_2-(C-2′)), 50.2 (CH_2-(C-5′)), 54.8 (CO–CH_2), 106.0 (C-5), 108.2 (C-3″), 110.9 (C-5″), 118.7 (C-2″), 127.2 (C-4″), 148.6 (C-4), 155.5 (C-2′), 164.3 (C-2), 165.8 (C-5′), 168.2 (CO), 124.7, 125.6, 126.4, 128.5, 128.9, 129.4, 130.2, 131.1 (aromatic carbons); MS (*m*/*z*): 618.12 [M^+]. Anal. calcd. for $C_{25}H_{20}ClN_5O_6S_3$: C 48.58, H 3.26, N 11.33; Found: C 48.65, H 3.31, N 11.46%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenyl-1H-imidazol-2-yl)acetamide (**10a**):* White solid in 66%; m.p.: 145–147°C; IR (KBr) ν_{max} (cm^{-1}): 1134, 1332 (SO_2), 1566 (C=N), 1627 (C=C), 1674 (NH*CO*), 3246 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.36 (s, 2H, CH_2-(C-2′)), 4.62 (s, 2H, CH_2-(C-5′)), 4.71 (s, 2H, CO–CH_2), 6.49 (s, 1H, C5″-H), 6.86–7.64 (m, 12H, Ar–H, C_5-H, and C2″-H), 8.57 (bs, 1H, NH-C2″), 11.09 (bs, 1H, NH–CO), 12.48 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.1 (CH_2-(C-2′)), 50.1 (CH_2-(C-5′)), 53.7 (CO–CH_2), 107.4 (C-3″), 111.7 (C-5″), 118.9 (C-2″), 123.5 (C-5), 127.5 (C-4″), 137.3 (C-2), 140.4 (C-4), 154.8 (C-2′), 165.5 (C-5′), 169.9 (CO), 124.4, 129.5, 131.2, 131.8, 132.9, 133.3, 134.1, 134.9 (aromatic carbons); MS (*m*/*z*): 566.62 [M^+]. Anal. calcd. for $C_{25}H_{22}N_6O_6S_2$: C 52.99, H 3.91, N 14.83; Found: C 53.08, H 3.94, N, 14.98%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolyl-1H-imidazol-2-yl)acetamide (**10b**):* White solid in 68%; m.p.: 152–154°C; IR (KBr) ν_{max} (cm^{-1}): 1130, 1325 (SO_2), 1564 (C=N), 1625 (C=C), 1672 (NH*CO*), 3241 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.42 (s, 3H, Ar–CH_3), 4.33 (s, 2H, CH_2-(C-2′)), 4.59 (s, 2H, CH_2-(C-5′)), 4.66 (s, 2H, CO–CH_2), 6.40 (s, 1H, C5″-H), 6.85–7.52 (m, 11H, Ar–H, C_5-H, and C2″-H), 8.48 (bs, 1H, NH-C2″), 11.06 (bs, 1H, NH–CO), 12.46 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.2 (Ar–CH_3), 46.8 (CH_2-(C-2′)), 49.7 (CH_2-(C-5′)), 53.4 (CO–CH_2), 107.1 (C-3″), 110.8 (C-5″), 118.5 (C-2″), 123.0 (C-5), 127.0 (C-4″), 137.1 (C-2), 140.2 (C-4), 153.7 (C-2′), 165.3 (C-5′), 168.3 (CO), 128.7, 130.4, 131.5, 131.9, 132.2, 133.7, 134.5, 135.7 (aromatic carbons); MS (*m*/*z*): 580.65 [M^+]. Anal. calcd. for $C_{26}H_{24}N_6O_6S_2$: C 53.78, H 4.17, N 14.47; Found: C 53.83, H 4.18, N 14.56%.

*2-((5′-((4″-Phenyl-1″H-pyrrol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)-1H-imidazol-2-yl)acetamide (**10c**):* White solid in 67%; m.p.: 175–177°C; IR (KBr) ν_{max} (cm^{-1}): 1136, 1336 (SO_2), 1569 (C=N), 1629 (C=C), 1677 (NH*CO*), 3250 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.38 (s, 2H, CH_2-(C-2′)), 4.63 (s, 2H, CH_2-(C-5′)), 4.80 (s, 2H, CO–CH_2), 6.51 (s, 1H, C5″-H), 6.91–7.56 (m, 11H, Ar–H, C_5-H, and C2″-H), 8.60 (bs, 1H, NH-C2″), 11.18 (bs, 1H, NH–CO), 12.50 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.3 (CH_2-(C-2′)), 50.5 (CH_2-(C-5′)), 54.0 (CO–CH_2), 107.8 (C-3″), 112.0 (C-5″), 119.2 (C-2″), 123.6 (C-5), 127.8 (C-4″), 138.0 (C-2), 141.2 (C-4), 155.4 (C-2′), 166.7 (C-5′), 171.2 (CO), 126.7, 129.5, 130.5, 131.2, 132.8, 133.5, 134.0, 135.1 (aromatic carbons); MS (*m*/*z*): 601.07 [M^+]. Anal. calcd. for $C_{25}H_{21}ClN_6O_6S_2$: C 49.96, H 3.52, N 13.98; Found: C 50.06, H 3.50, N 13.90%.

*General procedure for the synthesis of 2-((5′-((4″,5″-dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-aryloxazol-2-yl)acetamide (**11a–c**)/2-((5′-((4″,5″-dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-arylthiazol-2-yl)acetamide (**12a–c**)/2-((5′-((4″,5″-dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-aryl-1H-imidazol-2-yl)acetamide (**13a–c**)*

An ethereal solution of diazomethane (40 mL, 0.4 M) and triethylamine (0.12 g) were added to a cooled solution of **5**/**6**/**7** (5 mmol) in dichloromethane (20 mL). The reaction mixture was kept at −20 to −15°C for 42–46 h. The solvent was removed under reduced pressure. The resultant solid was purified by passing through a column of silica gel using ethyl acetate and hexane (1:3) as eluent.

*2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenyloxazol-2-yl)acetamide (**11a**):* White solid in 78%; m.p.: 155–157°C; IR (KBr) ν_{max} (cm^{-1}): 1145, 1331 (SO_2), 1570 (C=N), 1617 (C=C), 1666 (NH*CO*), 3248 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.63 (dd, 1H, H_X, $J_{AX} = 6.4$ Hz, $J_{MX} = 10.5$ Hz), 4.10 (dd, 1H, H_M, $J_{AM} = 12.2$ Hz), 4.36 (s, 2H, CH_2-(C-2′)), 4.54 (dd, 1H, H_A), 4.58 (s, 2H, CH_2-(C-5′)), 4.62 (s, 2H, CO–CH_2), 6.65 (bs, 1H, N–NH), 7.20–7.52 (m, 11H, Ar–H, and C_5-H), 11.23 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 40.4 (C-4″), 46.8 (CH_2-(C-2′)), 49.2 (CH_2-(C-5′)), 52.2 (C-5″), 54.1 (CO–CH_2), 138.3 (C-5), 140.8 (C-4), 150.2 (C-2), 158.7 (C-2′), 158.8 (C-3″), 165.7 (C-5′), 170.4 (CO), 125.6, 126.1, 127.4, 128.5, 129.7, 130.1, 130.4, 132.3 (aromatic carbons); MS (*m*/*z*): 570.60 [M^+]. Anal. calcd. for $C_{24}H_{22}N_6O_7S_2$: C 50.52, H 3.89, N 14.73; Found: C 50.40, H 3.93, N 14.77%.

*2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolyloxazol-2-yl)acetamide (**11b**):* White solid in 75%; m.p.: 164–166°C; IR (KBr) ν_{max} (cm^{-1}): 1138, 1326 (SO_2), 1577 (C=N), 1615 (C=C), 1663 (NH*CO*), 3234 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.35 (s, 3H, Ar–CH_3), 3.54 (dd, 1H, H_X, $J_{AX} = 6.2$ Hz, $J_{MX} = 10.2$ Hz), 4.04 (dd, 1H, H_M, $J_{AM} = 12.0$ Hz), 4.32 (s, 2H, CH_2-(C-2′)), 4.57 (dd, 1H, H_A), 4.52 (s, 2H, CH_2-(C-5′)), 4.59 (s, 2H, CO–CH_2), 6.60 (bs, 1H, N–NH), 7.24–7.46 (m, 10H, Ar–H, and C_5-H), 11.20 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.9 (Ar–CH_3), 39.8 (C-4″), 46.2 (CH_2-(C-2′)), 48.9 (CH_2-(C-5′)), 51.9 (C-5″), 53.8 (CO–CH_2), 137.8 (C-5), 140.2 (C-4), 149.5 (C-2), 157.2 (C-2′), 158.4 (C-3″), 164.8

(C-5′), 169.8 (CO), 127.2, 128.7, 129.5, 130.7, 131.6, 132.5, 133.1, 133.9 (aromatic carbons); MS (*m/z*): 584.64 [M^+]. Anal. calcd. for $C_{25}H_{24}N_6O_7S_2$: C, 51.36, H 4.14, N 14.38; Found: C 51.56, H 4.22, N 14.69%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)oxazol-2-yl)acetamide (11c): White solid in 77%; m.p.: 178–180°C; IR (KBr) ν_{max} (cm^{-1}): 1150, 1338 (SO_2), 1585 (C=N), 1620 (C=C), 1676 (NH*CO*), 3253 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.67 (dd, 1H, H_X, $J_{AX} = 6.7$ Hz, $J_{MX} = 10.8$ Hz), 4.20 (dd, 1H, H_M, $J_{AM} = 12.6$ Hz), 4.39 (s, 2H, CH_2-(C-2′)), 4.58 (dd, 1H, H_A), 4.60 (s, 2H, CH_2-(C-5′)), 4.71 (s, 2H, CO–CH_2), 6.67 (bs, 1H, N–NH), 7.29–7.59 (m, 10H, Ar–H, and C_5-H), 11.24 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 40.6 (C-4″), 47.2 (*C*H_2-(C-2′)), 50.1 (*C*H_2-(C-5′)), 52.6 (C-5″), 54.7 (CO–*C*H_2), 138.3 (C-5), 140.2 (C-4), 151.3 (C-2), 158.2 (C-2′), 159.0 (C-3″), 166.7 (C-5′), 171.8 (CO), 126.4, 127.2, 128.3, 129.1, 130.4, 131.4, 132.0, 137.4 (aromatic carbons); MS (*m/z*): 605.05 [M^+]. Anal. calcd. for $C_{24}H_{21}ClN_6O_7S_2$: C 47.64, H 3.50, N 13.89; Found: C 47.75, H 3.55, N 14.05%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenylthiazol-2-yl)acetamide (12a): White solid in 76%; m.p.: 159–161°C; IR (KBr) ν_{max} (cm^{-1}): 1132, 1332 (SO_2), 1574 (C=N), 1624 (C=C), 1677 (NH*CO*), 3256 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.55 (dd, 1H, H_X, $J_{AX} = 5.9$ Hz, $J_{MX} = 9.8$ Hz), 4.25 (dd, 1H, H_M, $J_{AM} = 11.8$ Hz), 4.33 (s, 2H, CH_2-(C-2′)), 4.54 (s, 2H, CH_2-(C-5′)), 4.61 (dd, 1H, H_A), 4.68 (s, 2H, CO–CH_2), 6.46 (bs, 1H, N–NH), 6.54 (s, 1H, C_5-H), 7.21–7.50 (m, 10H, Ar–H), 11.18 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 38.6 (C-4″), 46.5 (*C*H_2-(C-2′)), 49.3 (*C*H_2-(C-5′)), 52.8 (C-5″), 53.6 (CO–*C*H_2), 105.4 (C-5), 148.3 (C-4), 155.4 (C-2′), 157.4 (C-3″), 163.9 (C-2), 165.7 (C-5′), 167.5 (CO), 127.7, 128.4, 129.7, 130.6, 131.2, 132.0, 132.9, 135.1 (aromatic carbons); MS (*m/z*): 586.67 [M^+]. Anal. calcd. for $C_{24}H_{22}N_6O_6S_3$: C 49.13, H 3.78, N 14.32; Found: C 49.07, H 3.80, N 14.42%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolylthiazol-2-yl)acetamide (12b): White solid in 78%; m.p.: 166–168°C; IR (KBr) ν_{max} (cm^{-1}): 1130, 1329 (SO_2), 1568 (C=N), 1628 (C=C), 1669 (NH*CO*), 3248 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.30 (s, 3H, Ar–CH_3), 3.47 (dd, 1H, H_X, $J_{AX} = 5.7$ Hz, $J_{MX} = 9.5$ Hz), 4.14 (dd, 1H, H_M, $J_{AM} = 11.6$ Hz), 4.29 (s, 2H, CH_2-(C-2′)), 4.52 (dd, 1H, H_A), 4.56 (s, 2H, CH_2-(C-5′)), 4.62 (s, 2H, CO–CH_2), 6.41 (bs, 1H, N–NH), 6.52 (s, 1H, C_5-H), 7.18–7.58 (m, 9H, Ar–H), 11.15 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.5 (Ar–CH_3), 38.4 (C-4″), 46.0 (*C*H_2-(C-2′)), 48.9 (*C*H_2-(C-5′)), 52.4 (C-5″), 53.2 (CO–*C*H_2), 105.5 (C-5), 148.0 (C-4), 154.6 (C-2′), 156.8 (C-3″), 163.5 (C-2), 164.9 (C-5′), 166.8 (CO), 126.3, 127.5, 128.3, 128.6, 129.5, 131.6, 132.3, 135.0 (aromatic carbons); MS (*m/z*): 600.71 [M^+]. Anal. calcd. for $C_{25}H_{24}N_6O_6S_3$: C 49.99, H 4.03, N 13.99; Found: C 50.08, H 4.07, N 14.12%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (12c): White solid in 79%; m.p.: 193–195°C; IR (KBr) ν_{max} (cm^{-1}): 1138, 1341 (SO_2), 1585 (C=N), 1620 (C=C), 1682 (NH*CO*), 3257 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.59 (dd, 1H, H_X, $J_{AX} = 6.0$ Hz, $J_{MX} = 10.1$ Hz), 4.28 (dd, 1H, H_M, $J_{AM} = 12.0$ Hz), 4.33 (s, 2H, CH_2-(C-2′)), 4.58 (s, 2H, CH_2-(C-5′)), 4.64 (dd, 1H, H_A), 4.73 (s, 2H, CO–CH_2), 6.45 (bs, 1H, N–NH), 6.58 (s, 1H, C_5-H), 7.25–7.42 (m, 9H, Ar–H), 11.21 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 39.2 (C-4″), 46.9 (*C*H_2-(C-2′)), 50.2 (*C*H_2-(C-5′)), 53.5 (C-5″), 53.8 (CO–*C*H_2), 106.0 (C-5), 148.6 (C-4), 155.2 (C-2′), 158.3 (C-3″), 164.2 (C-2), 165.7 (C-5′), 168.2 (CO), 125.6, 126.3, 127.7, 128.3, 129.4, 130.3, 132.5, 134.8 (aromatic carbons); MS (*m/z*): 621.12 [M^+]. Anal. calcd. for $C_{24}H_{21}ClN_6O_6S_3$: C 46.41, H 3.41, N 13.53; Found: C 46.51, H 3.44, N 13.68%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenyl-1H-imidazol-2-yl)acetamide (13a): White solid in 78%; m.p.: 157–159°C; IR (KBr) ν_{max} (cm^{-1}): 1134, 1332 (SO_2), 1572 (C=N), 1624 (C=C), 1680 (NH*CO*), 3252 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.60 (dd, 1H, H_X, $J_{AX} = 6.4$ Hz, $J_{MX} = 10.4$ Hz), 4.19 (dd, 1H, H_M, $J_{AM} = 12.2$ Hz), 4.34 (s, 2H, CH_2-(C-2′)), 4.56 (dd, 1H, H_A), 4.59 (s, 2H, CH_2-(C-5′)), 4.70 (s, 2H, CO–CH_2), 6.61 (bs, 1H, N–NH), 7.18–7.56 (m, 11H, Ar–H, and C_5-H), 11.23 (bs, 1H, NH–CO), 12.46 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 40.2 (C-4″), 47.5 (*C*H_2-(C-2′)), 49.4 (*C*H_2-(C-5′)), 52.3 (C-5″), 53.7 (CO–*C*H_2), 123.5 (C-5), 137.3 (C-2), 140.4 (C-4), 154.8 (C-2′), 157.7 (C-3″), 165.5 (C-5′), 169.9 (CO), 127.3, 128.1, 128.9, 129.2, 131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m/z*): 569.62 [M^+]. Anal. calcd. for $C_{24}H_{23}N_7O_6S_2$: C 50.61, H 4.07, N 17.21; Found: C 50.68, H 4.06, N 17.33%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolyl-1H-imidazol-2-yl)acetamide (13b): White solid in 80%; m.p.: 166–168°C; IR (KBr) ν_{max} (cm^{-1}): 1132, 1326 (SO_2), 1565 (C=N), 1612 (C=C), 1678 (NH*CO*), 3245 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.32 (s, 3H, Ar–CH_3), 3.52 (dd, 1H, H_X, $J_{AX} = 6.0$ Hz, $J_{MX} = 10.1$ Hz), 4.13 (dd, 1H, H_M, $J_{AM} = 12.1$ Hz), 4.30 (s, 2H, CH_2-(C-2′)), 4.48 (dd, 1H, H_A), 4.55 (s, 2H, CH_2-(C-5′)), 4.63 (s, 2H, CO–CH_2), 6.57 (bs, 1H, N–NH), 7.28–7.53 (m, 10H, Ar–H, and C_5-H), 11.16 (bs, 1H, NH–CO), 12.39 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.4 (Ar–CH_3), 39.4 (C-4″), 46.8 (*C*H_2-(C-2′)), 49.2 (*C*H_2-(C-5′)), 51.7 (C-5″), 53.4 (CO–*C*H_2), 123.0 (C-5), 137.1 (C-2), 140.2 (C-4), 153.7 (C-2′), 156.1 (C-3″), 165.3 (C-5′), 168.3 (CO), 128.7, 129.2, 130.6, 131.2 132.6, 133.1, 133.9, 134.7 (aromatic carbons); MS (*m/z*): 583.66 [M^+]. Anal. calcd. for $C_{25}H_{25}N_7O_6S_2$: C 51.45, H 4.32, N 16.80; Found: C 51.50, H 4.34, N 16.89%.

2-((5′-((4″,5″-Dihydro-4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)-methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)-1H-imidazol-2-yl)acetamide (13c): White solid in 79%; m.p.: 188–190°C; IR (KBr) ν_{max} (cm^{-1}): 1138, 1336 (SO_2), 1581 (C=N), 1628 (C=C), 1682 (NH*CO*), 3253 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.65 (dd, 1H, H_X, $J_{AX} = 6.6$ Hz, $J_{MX} = 10.4$ Hz), 4.22 (dd, 1H, H_M, $J_{AM} = 12.6$ Hz), 4.37 (s, 2H, CH_2-(C-2′)), 4.58 (s, 2H, CH_2-(C-5′)), 4.60 (dd, 1H, H_A), 4.68 (s, 2H, CO–CH_2), 6.63 (bs, 1H, N–NH), 7.25–7.62 (m, 10H, Ar–H, and C_5-H), 11.24 (bs, 1H, NH–CO), 12.48 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 40.6 (C-4″), 47.8 (*C*H_2-(C-2′)), 49.6 (*C*H_2-(C-5′)), 52.8 (C-5″), 54.0 (CO–*C*H_2), 123.6 (C-5), 138.0 (C-2), 141.2 (C-4), 155.4 (C-2′), 157.8 (C-3″), 166.7 (C-5′), 171.2 (CO), 125.3, 126.2, 127.0, 127.8, 128.6, 129.3, 131.5, 132.0 (aromatic carbons); MS (*m/z*): 604.06 [M^+]. Anal. calcd. for $C_{24}H_{22}ClN_7O_6S_2$: C 47.72, H 3.67, N 16.23; Found: C 47.80, H 3.70, N 16.34%.

*General procedure for the synthesis of 2-((5′-((4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-aryloxazol-2-yl)acetamide (**14a–c**)/2-((5′-((4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-arylthiazol-2-yl)-acetamide (**15a–c**)/2-((5′-((4″-phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-aryl-1H-imidazol-2-yl)acetamide (**16a–c**)*

A solution of **11**/**12**/**13** (1 mmol) and chloranil (1.4 mmol) in xylene (10 mL) was refluxed for 21–24 h. Then, the reaction mixture was treated with a 5% NaOH solution. The organic layer was separated and repeatedly washed with water. It was then dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The resultant solid was recrystallized from 2-propanol.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenyloxazol-2-yl)acetamide (**14a**):* White solid in 69%; m.p.: 193–195°C; IR (KBr) ν_{max} (cm^{-1}): 1134, 1334 (SO_2), 1573 (C=N), 1616 (C=C), 1675 (NH*CO*), 3254 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.36 (s, 2H, CH_2-(C-2′)), 4.83 (s, 2H, CH_2-(C-5′)), 4.92 (s, 2H, CO–CH_2), 7.31–8.18 (m, 12H, Ar–H, C_5-H, and C5″-H), 9.85 (bs, 1H, N–NH), 11.32 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.2 (*C*H_2-(C-2′)), 50.4 (*C*H_2-(C-5′)), 54.1 (CO–*C*H_2), 122.9 (C-4″), 131.1 (C-3″), 135.5 (C-5″), 137.4 (C-5), 140.8 (C-4), 150.2 (C-2), 158.7 (C-2′), 165.7 (C-5′), 170.4 (CO), 125.8, 126.7, 127.5, 128.9, 129.2, 130.3, 131.4, 132.5 (aromatic carbons); 568.59 [M^+]. Anal. calcd. for $C_{24}H_{20}N_6O_7S_2$: C 50.70, H 3.55, N 14.78; Found: C 50.60, H 3.60, N 14.96%.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolyloxazol-2-yl)acetamide (**14b**):* White solid in 68%; m.p.: 187–189°C; IR (KBr) ν_{max} (cm^{-1}): 1131, 1328 (SO_2), 1565 (C=N), 1622 (C=C), 1667 (NH*CO*), 3249 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.43 (s, 3H, Ar–CH_3), 4.35 (s, 2H, CH_2-(C-2′)), 4.84 (s, 2H, CH_2-(C-5′)), 4.89 (s, 2H, CO–CH_2), 7.40–8.11 (m, 11H, Ar–H, C_5-H, and C5″-H), 9.82 (bs, 1H, N–NH), 11.26 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.6 (Ar–CH_3), 46.9 (*C*H_2-(C-2′)), 50.0 (*C*H_2-(C-5′)), 53.8 (CO–*C*H_2), 122.4 (C-4″), 130.8 (C-3″), 135.0 (C-5″), 138.0 (C-5), 140.4 (C-4), 150.5 (C-2), 157.2 (C-2′), 164.8 (C-5′), 169.8 (CO), 128.5, 129.8, 130.7, 131.2, 132.8, 133.1, 134.2, 135.8 (aromatic carbons); MS (*m*/*z*): 582.62 [M^+]. Anal. calcd. for $C_{25}H_{22}N_6O_7S_2$: C 51.54, H 3.81, N 14.42; Found: C 51.84, H 3.71, N 14.74%.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)oxazol-2-yl)acetamide (**14c**):* White solid in 71%; m.p.: 200–202°C; IR (KBr) ν_{max} (cm^{-1}): 1137, 1336 (SO_2), 1582 (C=N), 1628 (C=C), 1684 (NH*CO*), 3256 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.38 (s, 2H, CH_2-(C-2′)), 4.90 (s, 2H, CH_2-(C-5′)), 4.97 (s, 2H, CO–CH_2), 7.48–8.19 (m, 11H, Ar–H, C_5-H, and C5″-H), 9.91 (bs, 1H, N–NH), 11.34 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.6 (*C*H_2-(C-2′)), 50.9 (*C*H_2-(C-5′)), 54.7 (CO–*C*H_2), 123.0 (C-4″), 131.7 (C-3″), 135.9 (C-5″), 138.3 (C-5), 140.2 (C-4), 151.3 (C-2), 158.2 (C-2′), 166.7 (C-5′), 171.8 (CO), 127.1, 128.4, 129.6, 130.2, 130.8, 132.2, 133.8, 136.2 (aromatic carbons); MS (*m*/*z*): 603.03 [M^+]. Anal. calcd. for $C_{24}H_{19}ClN_6O_7S_2$: C 47.80, H 3.18, N 13.94; Found: C 47.89, H 3.14, N 14.10%.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenylthiazol-2-yl)acetamide (**15a**):* White solid in 66%; m.p.: 210–212°C; IR (KBr) ν_{max} (cm^{-1}): 1143, 1330 (SO_2), 1577 (C=N), 1625 (C=C), 1671 (NH*CO*), 3250 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.34 (s, 2H, CH_2-(C-2′)), 4.81 (s, 2H, CH_2-(C-5′)), 4.88 (s, 2H, CO–CH_2), 6.58 (s, 1H, C_5-H), 7.33–8.10 (m, 11H, Ar–H, and C5″-H), 9.80 (bs, 1H, N–NH), 11.06 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.2 (*C*H_2-(C-2′)), 49.6 (*C*H_2-(C-5′)), 53.6 (CO–*C*H_2), 103.4 (C-5), 122.3 (C-4″), 129.5 (C-3″), 134.7 (C-5″), 148.3 (C-4), 156.4 (C-2′), 163.9 (C-2), 164.7 (C-5′), 168.9 (CO), 127.3, 128.1, 128.9, 129.2, 131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m*/*z*): 584.66 [M^+]. Anal. calcd. for $C_{24}H_{20}N_6O_6S_3$: C 49.30, H 3.45, N 14.37; Found: C 49.45, H 3.51, N 14.17%.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolylthiazol-2-yl)acetamide (**15b**):* White solid in 69%; m.p.: 205–207°C; IR (KBr) ν_{max} (cm^{-1}): 1140, 1324 (SO_2), 1575 (C=N), 1620 (C=C), 1668 (NH*CO*), 3235 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.88 (s, 3H, Ar–CH_3), 4.32 (s, 2H, CH_2-(C-2′)), 4.74 (s, 2H, CH_2-(C-5′)), 4.79 (s, 2H, CO–CH_2), 6.51 (s, 1H, C_5-H), 7.27–8.06 (m, 10H, Ar–H, and C5″-H), 9.73 (bs, 1H, N–NH), 10.98 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.5 (Ar–CH_3), 46.7 (*C*H_2-(C-2′)), 49.4 (*C*H_2-(C-5′)), 53.2 (CO–*C*H_2), 102.5 (C-5), 121.9 (C-4″), 129.4 (C-3″), 134.0 (C-5″), 148.0 (C-4), 154.2 (C-2′), 163.5 (C-2), 166.5 (C-5′), 168.0 (CO), 126.8, 128.5, 130.3, 132.9, 133.5, 134.9, 135.7, 137.2 (aromatic carbons); MS (*m*/*z*): 598.69 [M^+]. Anal. calcd. for $C_{25}H_{22}N_6O_6S_3$: C 50.16, H 3.70, N 14.04; Found: C 50.27, H 3.74, N 14.18%.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)thiazol-2-yl)acetamide (**15c**):* White solid in 73%; m.p.: 223–225°C; IR (KBr) ν_{max} (cm^{-1}): 1144, 1332 (SO_2), 1576 (C=N), 1622 (C=C), 1674 (NH*CO*), 3258 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.36 (s, 2H, CH_2-(C-2′)), 4.82 (s, 2H, CH_2-(C-5′)), 4.91 (s, 2H, CO–CH_2), 6.61 (s, 1H, C_5-H), 7.26–8.15 (m, 10H, Ar–H, and C5″-H), 9.84 (bs, 1H, N–NH), 11.15 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.8 (*C*H_2-(C-2′)), 50.2 (*C*H_2-(C-5′)), 53.8 (CO–*C*H_2), 104.0 (C-5), 122.8 (C-4″), 129.7 (C-3″), 135.4 (C-5″), 148.6 (C-4), 155.6 (C-2′), 164.3 (C-2), 164.8 (C-5′), 168.2 (CO), 125.7, 126.9, 127.4, 128.8, 130.2, 131.5, 133.6, 134.2 (aromatic carbons); MS (*m*/*z*): 619.10 [M^+]. Anal. calcd. for $C_{24}H_{19}ClN_6O_6S_3$: C 46.56, H 3.09, N 13.57; Found: C 46.63, H 3.06, N 13.73%.

*2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-phenyl-1H-imidazol-2-yl)acetamide (**16a**):* White solid in 68%; m.p.: 198–200°C; IR (KBr) ν_{max} (cm^{-1}): 1141, 1330 (SO_2), 1574 (C=N), 1616 (C=C), 1678 (NH*CO*), 3254 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.35 (s, 2H, CH_2-(C-2′)), 4.83 (s, 2H, CH_2-(C-5′)), 4.90 (s, 2H, CO–CH_2), 7.28–8.04 (m, 12H, Ar–H, C_5-H, and C5″-H), 9.78 (bs, 1H, N–NH), 11.30 (bs, 1H, NH–CO), 12.50 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.5 (*C*H_2-(C-2′)), 50.1 (*C*H_2-(C-5′)), 54.5 (CO–*C*H_2), 122.9 (C-4″), 123.5 (C-5), 130.1 (C-3″), 135.0 (C-5″), 137.3 (C-2), 140.4 (C-4), 154.8 (C-2′), 165.5 (C-5′), 169.7 (CO), 127.3, 128.1, 128.9, 129.2,

131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m/z*): 567.61 [M^+]. Anal. calcd. for $C_{24}H_{21}N_7O_6S_2$: C 50.78, H 3.73, N 17.27; Found: C 50.90, H 3.76, N 17.44%.

2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-p-tolyl-1H-imidazol-2-yl)acetamide (16b): White solid in 72%; m.p.: 209–211°C; IR (KBr) ν_{max} (cm^{-1}): 1139, 1325 (SO_2), 1572 (C=N), 1613 (C=C), 1676 (NH*CO*), 3242 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.38 (s, 3H, Ar–CH_3), 4.33 (s, 2H, CH_2-(C-2′)), 4.80 (s, 2H, CH_2-(C-5′)), 4.87 (s, 2H, CO–CH_2), 7.22–8.01 (m, 11H, Ar–H, C_5-H, and C5″-H), 9.75 (bs, 1H, N–NH), 11.24 (bs, 1H, NH–CO), 12.48 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.8 (Ar–CH_3), 46.9 (CH_2-(C-2′)), 49.8 (CH_2-(C-5′)), 53.7 (CO–CH_2), 122.4 (C-4″), 123.0 (C-5), 129.6 (C-3″), 134.8 (C-5″), 137.1 (C-2), 139.6 (C-4), 153.7 (C-2′), 164.8 (C-5′), 168.3 (CO), 129.7, 131.6, 132.5, 132.8, 133.5, 133.8, 134.6, 135.7 (aromatic carbons); MS (*m/z*): 581.64 [M^+]. Anal. calcd. for $C_{25}H_{23}N_7O_6S_2$: C 51.63, H 3.99, N 16.86; Found: C 51.54, H 4.00, N 16.98%.

2-((5′-((4″-Phenyl-1″H-pyrazol-3″-ylsulfonyl)methyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-(4-chlorophenyl)-1H-imidazol-2-yl)acetamide (16c): White solid in 74%; m.p.: 227–229°C; IR (KBr) ν_{max} (cm^{-1}): 1142, 1334 (SO_2), 1578 (C=N), 1625 (C=C), 1682 (NH*CO*), 3256 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.37 (s, 2H, CH_2-(C-2′)), 4.85 (s, 2H, CH_2-(C-5′)), 4.94 (s, 2H, CO–CH_2), 7.31–8.06 (m, 11H, Ar–H, C_5-H, and C5″-H), 9.87 (bs, 1H, N–NH), 11.32 (bs, 1H, NH–CO), 12.54 (bs, 1H, NH-(C-5)); ^{13}C NMR (DMSO-d_6) δ (ppm): 47.8 (CH_2-(C-2′)), 50.4 (CH_2-(C-5′)), 54.8 (CO–CH_2), 123.7 (C-4″), 124.2 (C-5), 130.5 (C-3″), 135.5 (C-5″), 138.0 (C-2), 141.2 (C-4), 155.4 (C-2′), 166.1 (C-5′), 170.2 (CO), 128.6, 130.4, 129.8, 130.2, 131.6, 132.0, 132.3, 135.3 (aromatic carbons); MS (*m/z*): 602.05 [M^+]. Anal. calcd. for $C_{24}H_{20}ClN_7O_6S_2$: C 47.88, H 3.35, N 16.29; Found: C 47.94, H 3.40, N 16.39%.

Biological assays

Antioxidant activity

The compounds **5–16** were tested for antioxidant property by DPPH, NO, and ABTS 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 radical (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. To 4 mL of 0.004% w/v methanol solution of DPPH, 1 mL of various concentrations of the test compounds (50, 75, and 100 μg/mL) in methanol were added. After a 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. Ascorbic acid was used as the standard. The percent of inhibition (*I*%) of free radical production from DPPH was calculated by the following equation

$$I\% = \left[\frac{A_{control} - A_{sample}}{A_{blank}}\right] \times 100$$

where $A_{control}$ is the absorbance of the control reaction (containing methanolic DPPH and ascorbic acid), A_{sample} is the absorbance of the test compound (containing methanolic DPPH and test compound), and A_{blank} is 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. [38] and Marcocci et al. [39]. Nitric oxide (NO) radicals were generated from sodium nitroprusside. One milliliter of sodium nitroprusside (10 mM) and 1.5 mL of phosphate buffer 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 chromatophore was measured at 546 nm. Ascorbic acid was used as standard. Nitric oxide scavenging activity was calculated by the following equation

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

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

ABTS radical scavenging activity

The antioxidant activity of the test compounds and standard (ascorbic acid) were assessed on the basis of the radical scavenging effect of the stable ABTS free radical. The $ABTS^{\bullet+}$ solution was prepared by mixing 0.02 mol of ABTS salt with 0.01 mol of potassium persulfate in 25 mL of distilled water. The solution was kept at room temperature in the dark for 16 h before use. Then the $ABTS^{\bullet+}$ solution was diluted with methanol in order to obtain an absorbance between 0.7 and 0.9 at 734 nm using the spectrophotometer. Fresh $ABTS^{\bullet+}$ solutions were prepared for each assay. To 50, 75, and 100 μg/mL of each test compound and standard, 1 mL of $ABTS^{\bullet+}$ solution was added and allowed to react for 2 h in dark condition. Then the absorbance was taken at 734 nm using the spectrophotometer. The corresponding blank reading was also taken and the results in percentage were expressed as the ratio of absorbance decrease at 734 nm and the absorbance of $ABTS^{\bullet+}$ solution in the absence of test compounds.

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