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Synthesis and Antioxidant Activities of Acetamidomethylsulfonyl Bis Heterocycles-Oxazolyl/Thiazolyl/ Imidazolyl-1,3,4-Oxadiazoles

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A new class of acetamidomethylsulfonyl bis heterocycles-oxazolyl-1,3,4-oxadiazoles, -thiazolyl-1,3,4-oxadiazoles, and -imidazolyl-1,3,4-oxadiazoles were synthesized from the synthetic intermediates, methyl 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetate, methyl 2-((4-arylthiazol-2-ylcarbamoyl)-methylsulfonyl)acetate, and methyl 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylsulfonyl)acetate. All the title compounds were tested for their antioxidant activity. The oxadiazolylmethylsulfonyloxazolylacetamide displayed excellent radical-scavenging activity when compared with the standard ascorbic acid.

Keywords: Antioxidant activity / Imidazole / 1,3,4-Oxadiazole / Oxazole / Thiazole

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Introduction

Azoles are the principal core structures present in a variety of natural products and have acquired significance due to a wide variety of medicinal and biological properties associated with them. Several oxazoles have been used as therapeutic agents. Because of their structural relationship to procaine, oxazole derivatives might be expected to have local anesthetic properties [1]. The thiazole ring is a main structural motif of many natural compounds such as vitamin B_1 (thiamine), penicillin, and carboxylase. Moreover, 2-aminothiazoles as important precursors have been employed in the preparation of different drugs required for the treatment of allergies, hypertension, inflammation, schizophrenia, and bacterial and HIV infections [2]. The imidazole nucleus forms the main structure of some well-known components of the human organism, viz. histidine, vitamin B_{12}, histamine, and biotin. Dacarbazine [3], zoledronic acid [4], tipifarnib [5, 6], and azathioprine [7] are some of the potent anticancer agents bearing an imidazole ring. Apart from these, the azole having three heteroatoms, 1,3,4-oxadiazole (a privileged structure), endows its derivatives with broad and potent biological functions such as anti-inflammatory [8], hypoglycemic [9], anti-anxiety [10], and antidepressant activities [11]. Motivated by the aforesaid findings and in continuation of our studies towards the synthesis and bioassay of different bis heterocyclic derivatives [12–16], the present work is formulated.

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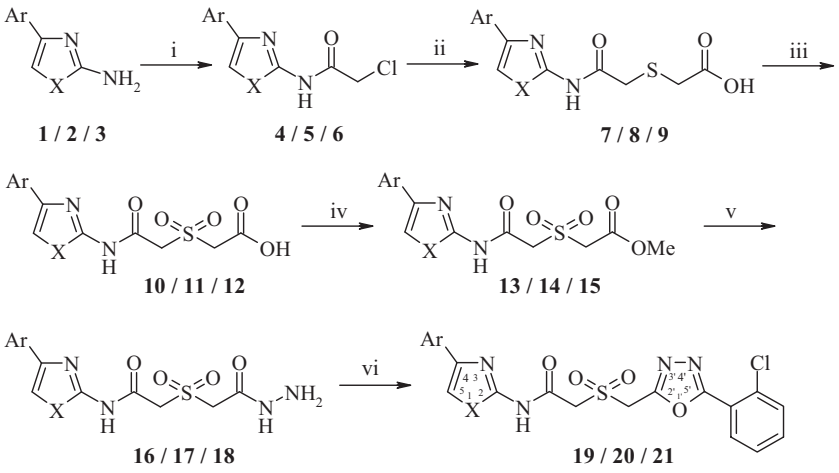
Results and discussion

Chemistry

In our earlier studies, we have identified compounds having the 1,3,4-oxadiazole unit as excellent antioxidant agents when compared with those having the 1,3,4-thiadiazole and 1,2,4-triazole units [16, 17]. Our continued interest in this direction induced us to report here the synthesis and antioxidant activities of acetamidomethylsulfonyl bis heterocycles-oxazolyl/thiazolyl/imidazolyl-1,3,4-oxadiazoles (Scheme 1). These compounds were obtained by functionalizing the amino group in 4-aryloxazol-2-amine (**1**), 4-arylthiazol-2-amine (**2**), and 4-aryl-1*H*-imidazol-2-amine (**3**). The reaction of **1**–**3** with chloroacetyl chloride produced 2-chloro-*N*-(4-aryloxazol-2-yl)acetamide (**4**), 2-chloro-*N*-(4-arylthiazol-2-yl)acetamide (**5**), and 2-chloro-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**6**). The reaction of **4**–**6** with thioglycolic acid afforded 2-((4-aryloxazol-2-ylcarbamoyl)methylthio)acetic acid (**7**), 2-((4-arylthiazol-2-ylcarbamoyl)methylthio)acetic acid (**8**), and 2-



Scheme 1. Synthesis of the bis heterocycles.

((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylthio)acetic acid (**9**). The latter compounds were subjected to oxidation with hydrogen peroxide in acetic acid to give 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetic acid (**10**), 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetic acid (**11**), and 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylsulfonyl)acetic acid (**12**). The ^{1}H NMR spectra of **10a**, **11a**, and **12a** displayed two singlet signals at δ 4.32, 4.29, 4.30 and 4.37, 4.34, 4.36 ppm due to methylene protons flanked between carbonyl and sulfonyl and sulfonyl and acid functionalities, respectively. Besides, two broad singlets were observed at δ 11.01, 10.08, 10.09 and 12.17, 12.13, 12.15 ppm due to NH and OH. Compound **12a** displayed another broad singlet at δ 12.61 ppm due to the NH of the imidazole ring. The signals of NH and OH disappeared when D_2O was added. Esterification of compounds **10**–**12** with methanol in the presence of sulfuric acid gave methyl 2-((4-aryloxazol-2-ylcarbamoyl)-methylsulfonyl)acetate (**13**), methyl 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetate (**14**), and methyl 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylsulfonyl)acetate (**15**). The ^{1}H NMR spectra of **13a**, **14a**, and **15a** displayed a singlet at δ 3.85, 3.82, and 3.84 ppm due to methoxy protons in addition to the signals of other protons. The acid hydrazides, 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**16**), 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**17**), and 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide (**18**) were prepared by the treatment of **13**–**15** with hydrazine hydrate in pyridine. In the ^{1}H NMR spectra of **16a**, **17a**, and **18a**, the absence of a singlet corresponding to methoxy protons and the presence of two broad singlets at δ 8.50, 8.45, 8.49 and 3.52, 3.49, 3.50 ppm due to NH and NH_2, which disappeared on deuteration, indicated their formation. The cyclocondensation of acid hydrazides **16**–**18** with 2-chlorobenzoic acid in $POCl_3$ resulted in acetamidomethylsulfonyl bis heterocycles-2-((5′-(2-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryloxazol-2-yl)acetamide (**19**), 2-((5′-(2-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-arylthiazol-2-yl)acetamide (**20**), and 2-((5′-(2-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**21**). The ^{1}H NMR spectra of **19a**, **20a**, and **21a** displayed two singlets at δ 4.34, 4.31, 4.32 and 4.69, 4.65, 4.67 ppm due to methylene protons present between carbonyl and sulfonyl and sulfonyl and the heterocyclic ring. Moreover, a broad singlet observed at δ 11.34, 11.03, and 11.26 ppm was assigned to NH. Besides, compound **21a** showed another broad singlet at δ 12.48 ppm due to the NH of the imidazole ring. The signals of NH disappeared when D_2O was added. The structures of all the compounds were further established by IR and ^{13}C NMR spectral data.

Biological results

Antioxidant activity

Compounds **19**–**21** were tested for antioxidant activity by the 2,2′-diphenyl-1-picrylhydrazyl (DPPH) [18, 19], nitric oxide (NO) [20, 21], and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) [22] methods. The results are shown in Tables 1–3. Among all the tested compounds, acetamidomethylsulfonyl oxazolyl oxadiazoles (**19**) displayed excellent

Table 1. The *in vitro* antioxidant activities of **19–21** determined by the DPPH method.

Compound	Concentration (μg/mL)		
	50	75	100
19a	65.63 ± 0.15	69.42 ± 1.42	72.24 ± 0.61
19b	75.06 ± 1.17	78.65 ± 1.23	82.94 ± 0.41
19c	60.54 ± 0.14	61.32 ± 1.02	65.24 ± 1.47
20a	59.36 ± 0.12	62.44 ± 0.76	66.35 ± 0.95
20b	72.05 ± 1.45	73.56 ± 1.04	79.46 ± 0.17
20c	54.35 ± 0.98	58.81 ± 1.55	60.37 ± 1.71
21a	–	–	–
21b	45.36 ± 1.33	49.62 ± 1.16	54.51 ± 0.86
21c	–	–	–
Ascorbic acid	77.15 ± 0.36	80.98 ± 1.32	83.82 ± 0.83
Blank	–	–	–

–, Showed no scavenging activity.
Values are the means of three replicates ± SD.

Table 2. The *in vitro* antioxidant activities of **19–21** determined by the nitric oxide method.

Compound	Concentration (μg/mL)		
	50	75	100
19a	70.34 ± 0.16	72.26 ± 0.63	75.37 ± 0.45
19b	84.58 ± 1.02	88.64 ± 0.86	91.25 ± 1.32
19c	66.24 ± 0.93	68.72 ± 1.43	70.37 ± 0.91
20a	64.45 ± 1.18	67.32 ± 0.64	69.06 ± 0.06
20b	80.72 ± 1.27	83.54 ± 0.97	87.71 ± 0.21
20c	59.35 ± 0.67	62.26 ± 1.01	64.30 ± 0.42
21a	–	–	–
21b	49.62 ± 1.32	52.34 ± 0.84	57.37 ± 1.14
21c	–	–	–
Ascorbic acid	86.02 ± 0.13	89.46 ± 0.87	91.53 ± 1.11
Blank	–	–	–

–, Showed no scavenging activity.
Values are the means of three replicates ± SD.

radical-scavenging activity in all three methods, when compared with the standard ascorbic acid. Recently, we have identified that isoxazolyl oxadiazoles displayed greater activity than pyrazolyl oxadiazoles [14]. Further, it was observed that there was no marked difference in activity between the compounds having isoxazolyl oxadiazoles [14] and oxazolyl oxadiazoles. The thiazolyl oxadiazole compounds (**20**) also showed good radical-scavenging activity. However, the imidazolyl oxadiazoles (**21**) exhibited the least activity. With reference to the nature of the substituents on the aromatic ring, the electron-donating 4-methyl group enhanced the activity when compared with the unsubstituted and chloro-substituted compounds. The free radical-scavenging activity of the compounds **19a**, **19b**, **19c**, and **20b** was measured at different concentrations, monitored by the change in absorbance at 10, 20, and 30 min in the DPPH method, as shown in Table 4. It was noticed that, at these 10-min intervals, the values are very close, and the results exemplify that the antioxidant activity is independent of time.

Table 3. The *in vitro* antioxidant activities of **19–21** determined by the ABTS method.

Compound	Concentration (μg/mL)		
	50	75	100
19a	23.31 ± 0.86	24.56 ± 1.05	25.96 ± 0.91
19b	25.51 ± 1.57	26.37 ± 1.24	28.35 ± 1.32
19c	20.15 ± 0.85	22.10 ± 1.41	23.97 ± 1.02
20a	17.32 ± 0.96	18.94 ± 0.19	20.07 ± 1.64
20b	20.05 ± 0.61	21.72 ± 1.13	24.32 ± 0.33
20c	15.98 ± 0.76	17.01 ± 0.66	18.87 ± 1.14
21a	–	–	–
21b	15.35 ± 1.04	16.71 ± 1.56	18.04 ± 0.11
21c	–	–	–
Ascorbic acid	28.80 ± 0.44	29.20 ± 1.31	29.70 ± 0.99
Blank	–	–	–

–, Showed no scavenging activity.
Values are the means of three replicates ± SD.

Conclusion

A new class of acetamidomethylsulfonyl bis heterocycles-oxazolyl-1,3,4-oxadiazoles, -thiazolyl-1,3,4-oxadiazoles, and -imidazolyl-1,3,4-oxadiazoles were synthesized from the synthetic intermediates, methyl 2-((4-aryloxazol-2-ylcarbamoyl)-methylsulfonyl)acetate, methyl 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetate, and methyl 2-((4-aryl-1*H*-imidazol-2-ylcarbamoyl)methylsulfonyl)acetate. All the title compounds were tested for their antioxidant activity. The oxadiazolylmethylsulfonyloxazolylacetamide displayed excellent radical-scavenging activity when compared with 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

Table 4. Antioxidant activities of compounds **19a–c** and **20b** at 10-min time intervals determined by the DPPH radical-scavenging method.

Compound	10 min	20 min	30 min
19a	72.01	72.18	72.24
19b	82.33	82.65	82.94
19c	64.98	64.15	65.24
20b	79.25	79.32	79.46

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 are 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 internal standard. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat 1210 B instruments at 70 eV, with an emission current of 100 μA. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The antioxidant activity measurement was carried out using a Shimadzu UV-2450 spectrophotometer. The compounds 4-aryloxazol-2-amine (**1**), 4-arylthiazol-2-amine (**2**), 4-aryl-1*H*-imidazol-2-amine (**3**), 2-chloro-*N*-(4-aryloxazol-2-yl)acetamide (**4**), 2-chloro-*N*-(4-arylthiazol-2-yl)acetamide (**5**), and 2-chloro-*N*-(4-aryl-1*H*-imidazol-2-yl)acetamide (**6**) were prepared as per literature procedures [23–25].

*General procedure for the synthesis of 2-((4-aryloxazol-2-ylcarbamoyl)methylthio)acetic acid (**7a–c**)/ 2-((4-arylthiazol-2-ylcarbamoyl)methylthio)acetic acid (**8a–c**)/2-((4-aryl-1H-imidazol-2-ylcarbamoyl)methylthio)-acetic acid (**9a–c**)*

To a solution of sodium hydroxide (0.40 g, 10 mmol) in methanol (6 mL), mercaptoacetic acid (0.46 g, 5 mmol) and compound **4**/**5**/**6** (5 mmol) were added and refluxed for 4–6 h. The reaction mixture was cooled and poured into crushed ice containing conc. HCl. The separated solid was filtered, dried, and recrystallized from water.

*2-((4-Phenyloxazol-2-ylcarbamoyl)methylthio)acetic acid **7a***

White solid in 65% (0.76 g) yield; m.p.: 145–147°C; IR (KBr) υ_{max} (cm^{-1}): 1578 (C=N), 1628 (C=C), 1690 (NH–*CO*), 1709 (*CO*OH), 3240 (NH), 3344 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 3.42 (s, 2H, CO–CH_2), 3.51 (s, 2H, S–CH_2), 7.34–7.72 (m, 6H, Ar–H, and C_5–H), 10.90 (bs, 1H, NH), 12.15 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 41.7 (CO–*C*H_2), 44.2 (S–CH_2), 137.9 (C-5), 140.4 (C-4), 151.3 (C-2), 169.1 (NH–CO), 174.3 (COOH), 127.6, 130.0, 132.1, 135.7 (aromatic carbons); MS (*m/z*): 292.31 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{12}N_2O_4S$: C 53.41, H 4.13, N 9.58; Found: C 53.52, H 4.19, N 9.74%.

*2-((4-p-Tolyloxazol-2-ylcarbamoyl)methylthio)acetic acid **7b***

White solid in 67% (0.83 g) yield; m.p.: 162–164°C; IR (KBr) υ_{max} (cm^{-1}): 1571 (C=N), 1621 (C=C), 1688 (NH–*CO*), 1704 (*CO*OH), 3235 (NH), 3342 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 2.39 (s, 3H, Ar–CH_3), 3.40 (s, 2H, CO–CH_2), 3.49 (s, 2H, S–CH_2), 7.31–7.69 (m, 5H, Ar–H and C_5–H), 10.82 (bs, 1H, NH), 12.12 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 25.3 (Ar–CH_3), 41.2 (CO–*C*H_2), 43.7 (S–CH_2), 137.2 (C-5), 140.1 (C-4), 150.9 (C-2), 168.6 (NH–CO), 174.1 (COOH), 127.1, 129.6, 131.5, 135.2 (aromatic carbons); MS (*m/z*): 306.34 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}N_2O_4S$: C 54.88, H 4.60, N 9.14; Found: C 54.96, H 4.65, N 9.26%.

*2-((4-(p-Chlorophenyl)oxazol-2-ylcarbamoyl)methylthio)-acetic acid **7c***

White solid in 64% (0.83 g) yield; m.p.: 169–171°C; IR (KBr) υ_{max} (cm^{-1}): 1585 (C=N), 1633 (C=C), 1693 (NH–*CO*), 1711 (*CO*OH), 3249 (NH), 3350 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 3.43 (s, 2H, CO–CH_2), 3.52 (s, 2H, S–CH_2), 7.43–7.86 (m, 5H, Ar–H and C_5–H), 10.97 (bs, 1H, NH), 12.20 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 42.0 (CO–*C*H_2), 44.8 (S–CH_2), 138.4 (C-5), 141.3 (C-4), 151.7 (C-2), 169.3 (NH–CO), 174.6 (COOH), 128.9, 130.5, 132.7, 135.9 (aromatic carbons); MS (*m/z*): 326.76 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{11}ClN_2O_4S$: C 47.78, H 3.39, N 8.57; Found: C 47.86, H 3.32, N 8.65%.

*2-((4-Phenylthiazol-2-ylcarbamoyl)methylthio)acetic acid **8a***

White solid in 65% (0.82 g) yield; m.p.: 149–151°C; IR (KBr) υ_{max} (cm^{-1}): 1576 (C=N), 1630 (C=C), 1689 (NH–*CO*), 1708 (*CO*OH), 3242 (NH), 3343 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 3.39 (s, 2H, CO–CH_2), 3.48 (s, 2H, S–CH_2), 6.61 (s, 1H, C_5–H), 7.32–7.69 (m, 5H, Ar–H), 10.08 (bs, 1H, NH), 12.15 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 41.8 (CO–*C*H_2), 43.6 (S–CH_2), 104.3 (C-5), 148.3 (C-4), 162.8 (C-2), 167.1 (NH–CO), 173.0 (COOH), 127.1, 129.7, 131.8, 135.0 (aromatic carbons); MS (*m/z*): 308.37 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{12}N_2O_3S_2$: C 50.63, H 3.92, N 9.08; Found: C 50.74, H 3.97, N 9.14%.

*2-((4-p-Tolylthiazol-2-ylcarbamoyl)methylthio)acetic acid **8b***

White solid in 63% (0.84 g) yield; m.p.: 173–175°C; IR (KBr) υ_{max} (cm^{-1}): 1569 (C=N), 1627 (C=C), 1685 (NH–*CO*), 1706 (*CO*OH), 3236 (NH), 3340 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 2.34 (s, 3H, Ar–CH_3), 3.38 (s, 2H, CO–CH_2), 3.47 (s, 2H, S–CH_2), 6.58 (s, 1H, C_5–H), 7.15–7.61 (m, 4H, Ar-H), 10.06 (bs, 1H, NH), 12.09 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.5 (Ar–CH_3), 41.8 (CO–*C*H_2), 43.2 (S–CH_2), 103.0 (C-5), 149.1 (C-4), 162.3 (C-2), 166.8 (NH–CO), 173.8 (COOH), 126.2, 128.1, 129.2, 131.8 (aromatic carbons); MS (*m/z*): 322.40 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}N_2O_3S_2$: C 52.15, H 4.38, N 8.69; Found: C 52.07, H 4.44, N 8.60%.

*2-((4-(p-Chlorophenyl)thiazol-2-ylcarbamoyl)methylthio)-acetic acid **8c***

White solid in 66% (0.94 g) yield; m.p.: 182–184°C; IR (KBr) υ_{max} (cm^{-1}): 1584 (C=N), 1632 (C=C), 1690 (NH–*CO*), 1712 (*CO*OH), 3254 (NH), 3349 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 3.41 (s, 2H, CO–CH_2), 3.50 (s, 2H, S–CH_2), 6.63 (s, 1H, C_5–H), 7.21–7.80 (m, 4H, Ar–H), 11.02 (bs, 1H, NH), 12.17 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 42.7 (CO–*C*H_2), 44.3 (S–CH_2), 104.7 (C-5), 149.4 (C-4), 163.7 (C-2), 168.1 (NH–CO), 173.3 (COOH), 128.4, 130.0, 132.2, 135.3 (aromatic carbons); MS (*m/z*): 342.82 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{11}ClN_2O_3S_2$: C 45.55, H 3.23, N 8.17; Found: C 45.67, H 3.28, N 8.27%.

*2-((4-Phenyl-1H-imidazol-2-ylcarbamoyl)methylthio)acetic acid **9a***

White solid in 64% (0.75 g) yield; m.p.: 157–159°C; IR (KBr) υ_{max} (cm^{-1}): 1572 (C=N), 1633 (C=C), 1689 (NH–*CO*), 1705 (*CO*OH), 3248 (NH), 3336 (OH); ^1H NMR (DMSO-d_6) δ (ppm): 3.40 (s, 2H, CO–CH_2), 3.49 (s, 2H, S–CH_2), 7.31–7.72 (m, 6H, Ar–H and C_5–H), 11.00 (bs, 1H, NH–CO), 12.15 (bs, 1H, COOH), 12.52 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 41.6 (CO–*C*H_2), 43.9 (S–CH_2), 122.9 (C-5), 137.1 (C-2), 141.4 (C-4), 168.6 (NH–CO), 173.7 (COOH), 128.3, 129.7, 131.7, 134.6 (aromatic carbons); MS (*m/z*): 291.33 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{13}N_3O_3S$: C 53.60, H 4.50, N 14.42; Found: C 53.69, H 4.56, N 14.51%.

2-((4-p-Tolyl-1H-imidazol-2-ylcarbamoyl)methylthio)acetic acid ***9b***

White solid in 66% (0.82 g) yield; m.p.: 189–191°C; IR (KBr) υ_{max} (cm^{-1}): 1567 (C=N), 1629 (C=C), 1687 (NH–*CO*), 1708 (*CO*OH), 3241 (NH), 3331 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.36 (s, 3H, Ar–CH_3), 3.39 (s, 2H, CO–CH_2), 3.48 (s, 2H, S–CH_2), 7.28–7.70 (m, 5H, Ar–H, and C_5–H), 10.95 (bs, 1H, NH–CO), 12.10 (bs, 1H, COOH), 12.50 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm) 24.9 (Ar–CH_3), 41.1 (CO–*C*H_2), 43.4 (S–CH_2), 122.2 (C-5), 137.6 (C-2), 141.0 (C-4), 168.1 (NH–CO), 173.1 (COOH), 127.6, 129.0, 131.1, 133.9 (aromatic carbons); MS (*m/z*): 305.36 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{15}N_3O_3S$: C 55.07, H 4.95, N 13.76; Found: C 55.16, H 4.90, N 13.85%.

2-((4-(p-Chlorophenyl)-1H-imidazol-2-ylcarbamoyl)-methylthio)acetic acid ***9c***

White solid in 67% (0.90 g) yield; m.p.: 201–203°C; IR (KBr) υ_{max} (cm^{-1}): 1581 (C=N), 1635 (C=C), 1694 (NH–*CO*), 1710 (*CO*OH), 3250 (NH), 3339 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.42 (s, 2H, CO–CH_2), 3.51 (s, 2H, S–CH_2), 7.35–7.76 (m, 5H, Ar–H, and C_5–H), 11.13 (bs, 1H, NH–CO), 12.18 (bs, 1H, COOH), 12.57 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 41.9 (CO–*C*H_2), 44.2 (S–CH_2), 123.3 (C-5), 138.8 (C-2), 141.9 (C-4), 168.8 (NH–CO), 174.0 (COOH), 128.6, 130.1, 132.1, 134.9 (aromatic carbons); MS (*m/z*): 325.77 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{12}ClN_3O_3S$: C 47.93, H 3.71, N 12.90; Found: C 48.86, H 3.62, N 13.02%.

*General procedure for the synthesis of 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetic acid (**10a–c**)/2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetic acid (**11a–c**)/2-((4-aryl-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetic acid (**12a–c**)*

An ice-cold solution of compound **7**/**8**/**9** (10 mmol) in glacial acetic acid (10 mL) was treated with 30% hydrogen peroxide (3 mL) in portions. The contents were allowed to attain laboratory temperature and then were refluxed for 2–3 h. The reaction mixture was cooled, and acetic acid was removed *in vacuo*. The residual portion was poured onto crushed ice, and the product obtained was filtered, dried, and recrystallized from water.

2-((4-Phenyloxazol-2-ylcarbamoyl)methylsulfonyl)acetic acid ***10a***

White solid in 82% (2.39 g) yield; m.p.: 162–164°C; IR (KBr) υ_{max} (cm^{-1}): 1121, 1320 (SO_2), 1587 (C=N), 1634 (C=C), 1686 (NH–*CO*), 1709 (*CO*OH), 3246 (NH), 3352 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.32 (s, 2H, CO–CH_2), 4.37 (s, 2H, SO_2–CH_2), 7.36–7.75 (m, 6H, Ar–H and C_5–H), 11.01 (bs, 1H, NH), 12.17 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.8 (CO–*C*H_2), 57.6 (SO_2–CH_2), 137.9 (C-5), 140.4 (C-4), 151.3 (C-2), 169.3 (NH–CO), 174.7 (COOH), 128.6, 130.0, 132.1, 135.7 (aromatic carbons); MS (*m/z*): 324.31 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{12}N_2O_6S$: C 48.14, H 3.37, N 8.64, Found: C 32.52, H 3.65, N 14.72%.

2-((4-p-Tolyloxazol-2-ylcarbamoyl)methylsulfonyl)acetic acid ***10b***

White solid in 80% (2.45 g) yield; m.p.: 175–177°C; IR (KBr) υ_{max} (cm^{-1}): 1120, 1316 (SO_2), 1582 (C=N), 1630 (C=C), 1690 (NH–*CO*), 1706 (*CO*OH), 3240 (NH), 3348 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.43 (s, 3H, Ar–CH_3), 4.29 (s, 2H, CO–CH_2), 4.36 (s, 2H, SO_2–CH_2), 7.30–7.71 (m, 5H, Ar–H, and C_5–H), 10.07 (bs, 1H, NH), 12.13 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 25.6 (Ar–CH_3), 53.3 (CO–*C*H_2), 57.2 (SO_2–CH_2), 137.4 (C-5), 140.0 (C-4), 150.8 (C-2), 169.1 (NH–CO), 174.2 (COOH), 128.0, 129.5, 131.5, 135.1 (aromatic carbons); MS (*m/z*): 338.34 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}N_2O_6S$: C 49.70, H 4.17, N 8.28; Found: C 49.80, H 4.22, N 8.17%.

2-((4-(p-Chlorophenyl)oxazol-2-ylcarbamoyl)-methylsulfonyl)acetic acid ***10c***

White solid in 82% (2.67 g) yield; m.p.: 183–185°C; IR (KBr) υ_{max} (cm^{-1}): 1130, 1324 (SO_2), 1591 (C=N), 1636 (C=C), 1692 (NH–*CO*), 1712 (*CO*OH), 3257 (NH), 3358 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.33 (s, 2H, CO–CH_2), 4.40 (s, 2H, SO_2–CH_2), 7.38–7.79 (m, 5H, Ar–H, and C_5–H), 11.03 (bs, 1H, NH), 12.21 (bs, 1H, OH); ^{13}C NMR (DMSO-d_6) δ (ppm): 54.7 (CO–*C*H_2), 58.1 (SO_2–CH_2), 138.4 (C-5), 140.9 (C-4), 151.6 (C-2), 169.5 (NH–CO), 174.9 (COOH), 128.9, 130.7, 132.8, 136.1 (aromatic carbons); MS (*m/z*): 358.76 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{11}ClN_2O_6S$: C 43.52, H 3.09, N 7.81; Found: C 43.63, H 3.02, N 7.92%.

2-((4-Phenylthiazol-2-ylcarbamoyl)methylsulfonyl)acetic acid ***11a***

White solid in 83% (2.55 g) yield; m.p.: 171–173°C; IR (KBr) υ_{max} (cm^{-1}): 1126, 1317 (SO_2), 1585 (C=N), 1635 (C=C), 1688 (NH–*CO*), 1708 (*CO*OH), 3248 (NH), 3350 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.29 (s, 2H, CO–CH_2), 4.34 (s, 2H, SO_2–CH_2), 6.65 (s, 1H, C_5–H), 7.34–7.73 (m, 5H, Ar–H), 10.08 (bs, 1H, NH), 12.13 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.3 (CO–*C*H_2), 57.0 (SO_2–CH_2), 104.6 (C-5), 146.9 (C-4), 163.0 (C-2), 167.8 (NH–CO), 174.1 (COOH), 128.3, 129.9, 131.9, 135.2 (aromatic carbons); MS (*m/z*): 340.37 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{12}N_2O_5S_2$: C 45.87, H 3.55, N 8.23, Found: C 45.80, H 3.53, N 8.33%.

2-((4-p-Tolylthiazol-2-ylcarbamoyl)methylsulfonyl)acetic acid ***11b***

White solid in 82% (2.64 g) yield; m.p.: 184–186°C; IR (KBr) υ_{max} (cm^{-1}): 1123, 1315 (SO_2), 1581 (C=N), 1631 (C=C), 1687 (NH–*CO*), 1704 (*CO*OH), 3241 (NH), 3347 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, Ar–CH_3), 4.28 (s, 2H, CO–CH_2), 4.33 (s, 2H, SO_2–CH_2), 6.63 (s, 1H, C_5–H), 7.30–7.67 (m, 4H, Ar–H), 11.00 (bs, 1H, NH), 12.10 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 25.1 (Ar–CH_3), 53.1 (CO–*C*H_2), 56.7 (SO_2–CH_2), 104.2 (C-5), 146.5 (C-4), 162.8 (C-2), 167.4 (NH–CO), 173.8 (COOH), 127.9, 129.6, 131.4, 134.6 (aromatic carbons); MS (*m/z*): 354.40 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}N_2O_5S_2$: C 47.45, H 3.98, N 7.90; Found: C 47.54, H 4.05, N 8.02%.

2-((4-(p-Chlorophenyl)thiazol-2-ylcarbamoyl)-methylsulfonyl)acetic acid ***11c***

White solid in 80% (2.74 g) yield; m.p.: 193–195°C; IR (KBr) υ_{max} (cm^{-1}): 1131, 1321 (SO_2), 1590 (C=N), 1638 (C=C), 1690 (NH–*CO*), 1710 (*CO*OH), 3261 (NH), 3355 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.32 (s, 2H, CO–CH_2), 4.38 (s, 2H, SO_2–CH_2), 6.69 (s, 1H, C_5–H), 7.37–7.81 (m, 4H, Ar–H), 11.02 (bs, 1H, NH), 12.18 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.9 (CO–*C*H_2), 56.2 (SO_2–CH_2), 105.1 (C-5), 147.3 (C-4), 163.7 (C-2), 168.2 (NH–CO), 174.4 (COOH), 128.5, 130.1, 132.2, 135.9 (aromatic carbons); MS (*m/z*): 374.82 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{11}ClN_2O_5S_2$: C 41.66, H 2.96, N 7.47; Found: C 41.75, H 3.01, N 7.56%.

2-((4-Phenyl-1H-imidazol-2-ylcarbamoyl)methylsulfonyl)-acetic acid ***12a***

White solid in 81% (2.35 g) yield; m.p.: 169–171°C; IR (KBr) υ_{max} (cm^{-1}): 1128, 1320 (SO_2), 1582 (C=N), 1687 (C=C), 1687 (NH–*CO*), 1705 (*CO*OH), 3249 (NH), 3340 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.30 (s, 2H, CO–CH_2), 4.36 (s, 2H, SO_2–CH_2), 7.24–7.62 (m, 6H, Ar–H, and C_5–H), 10.09 (bs, 1H, NH–CO), 12.15 (bs, 1H, COOH), 12.61 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 54.4 (CO–*C*H_2), 57.3 (SO_2–CH_2), 123.6 (C-5), 136.9 (C-2), 140.4 (C-4), 169.1 (NH–CO), 174.3 (COOH), 128.2, 129.6, 131.8, 135.4 (aromatic carbons); MS (*m/z*): 323.33 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{13}N_3O_5S$: C 48.29, H 4.05, N 13.00, Found: C 48.37, H 3.98, N, 13.14%.

2-((4-p-Tolyl-1H-imidazol-2-ylcarbamoyl)methylsulfonyl)-acetic acid ***12b***

White solid in 83% (2.53 g) yield; m.p.: 196–198°C; IR (KBr) υ_{max} (cm^{-1}): 1126, 1317 (SO_2), 1577 (C=N), 1632 (C=C), 1685 (NH–*CO*), 1708 (*CO*OH), 3244 (NH), 3338 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.38 (s,3H, Ar–CH_3), 4.28 (s, 2H, CO–CH_2), 4.37 (s, 2H, SO_2–CH_2), 7.30–7.70 (m, 5H, Ar–H, and C_5–H), 10.17 (bs, 1H, NH–CO), 12.12 (bs, 1H, COOH), 12.55 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 25.7 (Ar–CH_3), 54.1 (CO–*C*H_2), 57.0 (SO_2–CH_2), 123.1 (C-5), 136.0 (C-2), 140.6 (C-4), 168.7 (NH–CO), 174.0 (COOH), 127.8, 129.2, 131.3, 135.0 (aromatic carbons); MS (*m/z*): 337.36 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{15}N_3O_5S$: C 49.84, H 4.48, N 12.46; Found: C 49.72, H 4.52, N 12.56%.

2-((4-(p-Chlorophenyl)-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetic acid ***12c***

White solid in 80% (2.60 g) yield; m.p.: 214–216°C; IR (KBr) υ_{max} (cm^{-1}): 1132, 1322 (SO_2), 1588 (C=N), 1639 (C=C), 1691 (NH–*CO*), 1711 (*CO*OH), 3253 (NH), 3345 (OH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.31 (s, 2H, CO–CH_2), 4.39 (s, 2H, SO_2–CH_2), 7.36–7.74 (m, 5H, Ar–H, and C_5–H), 11.20 (bs, 1H, NH–CO), 12.19 (bs, 1H, COOH), 12.62 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 54.8 (CO–*C*H_2), 57.5 (SO_2–CH_2), 123.8 (C-5), 137.2 (C-2), 140.7 (C-4), 169.5 (NH–CO), 174.6 (COOH), 128.8, 130.0, 132.1, 135.9 (aromatic carbons); MS (*m/z*): 357.77 [$M^{+\bullet}$]. Anal. calcd. for $C_{13}H_{12}ClN_3O_5S$: C 43.64, H 3.38, N 11.74; Found: C 43.71, H 3.31, N 11.86%.

*General procedure for the synthesis of methyl 2-((4-aryloxazol-2-ylcarbamoyl)methyl-sulfonyl)acetate (**13a–c**)/ methyl 2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)-acetate (**14a–c**)/methyl 2-((4-aryl-1H-imidazol-2-ylcarbamoyl)methylsulfonyl)acetate (**15a–c**)*

A mixture of compound **10**/**11**/**12** (10 mmol), methanol (10 mL), and conc. H_2SO_4 (1 mL) was refluxed for 9–11 h. The contents were cooled and poured onto crushed ice. The solid separated was filtered, dried, and recrystallized from methanol.

Methyl 2-((4-phenyloxazol-2-ylcarbamoyl)methylsulfonyl)-acetate ***13a***

White solid in 82% (2.65 g) yield; m.p.: 155–157°C; IR (KBr) υ_{max} (cm^{-1}): 1146, 1331 (SO_2), 1579 (C=N), 1629 (C=C), 1690 (NH–*CO*), 1736 (*CO*O), 3248 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.85 (s, 3H, OCH_3), 4.33 (s, 2H, CO–CH_2), 4.41 (s, 2H, SO_2–CH_2), 7.17–7.55 (m, 6H, Ar–H, and C_5–H), 11.00 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 52.7 (OCH_3), 53.1 (SO_2–CH_2), 55.6 (CO–*C*H_2), 138.6 (C-5), 140.8 (C-4), 152.0 (C-2), 163.8 (CO_2Me), 169.6 (NH–CO), 124.3, 126.4, 128.5, 130.8 (aromatic carbons); MS (*m/z*): 338.34 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}N_2O_6S$: C 49.70, H 4.17, N 8.28; Found: C 49.81, H 4.22, N 8.31%.

Methyl 2-((4-p-tolyloxazol-2-ylcarbamoyl)methylsulfonyl)-acetate ***13b***

White solid in 84% (2.84 g) yield; m.p.: 170–172°C; IR (KBr) υ_{max} (cm^{-1}): 1138, 1327 (SO_2), 1575 (C=N), 1626 (C=C), 1689 (NH–*CO*), 1734 (*CO*O), 3234 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.32 (s, 3H, Ar–CH_3), 3.84 (s, 3H, OCH_3), 4.31 (s, 2H, CO–CH_2), 4.39 (s, 2H, SO_2–CH_2), 7.12–7.46 (m, 5H, Ar–H, and C_5–H), 10.08 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.5 (Ar–CH_3), 52.3 (OCH_3), 52.8 (SO_2–CH_2), 54.5 (CO–*C*H_2), 138.2 (C-5), 139.5 (C-4), 150.6 (C-2), 163.5 (CO_2Me), 169.3 (NH–CO), 122.6, 124.6, 128.7, 135.4 (aromatic carbons); MS (*m/z*): 352.38 [$M^{+\bullet}$]. Anal. calcd. for $C_{15}H_{16}N_2O_6S$: C, 51.13, H 4.58, N 7.95; Found: C 51.23, H 4.63, N 8.08%.

Methyl 2-((4-(p-chlorophenyl)oxazol-2-ylcarbamoyl)-methylsulfonyl)acetate ***13c***

White solid in 85% (3.04 g) yield; m.p.: 176–178°C; IR (KBr) υ_{max} (cm^{-1}): 1149, 1338 (SO_2), 1581 (C=N), 1638 (C=C), 1694 (NH–*CO*), 1738 (*CO*O), 3256 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.89 (s, 3H, OCH_3), 4.35 (s, 2H, CO–CH_2), 4.43 (s, 2H, SO_2–CH_2), 7.28–7.62 (m, 5H, Ar–H, and C_5–H), 11.01 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.0 (OCH_3), 53.9 (SO_2–CH_2), 55.9 (CO–*C*H_2), 139.0 (C-5), 140.2 (C-4), 151.3 (C-2), 163.7 (CO_2Me), 169.8 (NH–CO), 128.8, 130.2, 131.4, 133.8 (aromatic carbons); MS (*m/z*): 372.78 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{13}ClN_2O_6S$: C 45.11, H 3.51, N 7.51; Found: C 45.05, H 3.46, N 7.59%.

Methyl 2-((4-phenylthiazol-2-ylcarbamoyl)methylsulfonyl)-acetate ***14a***

White solid in 83% (2.82 g) yield; m.p.: 158–160°C; IR (KBr) υ_{max} (cm^{-1}): 1144, 1330 (SO_2), 1576 (C=N), 1632 (C=C), 1691 (NH–*CO*), 1734 (*CO*O), 3250 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.82 (s, 3H, OCH_3), 4.32 (s, 2H, CO–CH_2), 4.40 (s, 2H, SO_2–CH_2), 6.64 (s, 1H, C_5–H), 7.14–7.48 (m, 5H, Ar–H), 11.22 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 52.1 (OCH_3), 52.9 (SO_2–CH_2), 54.7 (CO–*C*H_2), 104.6 (C-5), 147.4 (C-4), 162.3 (NH–CO), 163.5 (C-2), 168.4 (CO_2Me), 122.8, 124.6, 128.0, 130.1 (aromatic carbons); MS (*m/z*): 354.40 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}N_2O_5S_2$: C 47.45, H 3.98, N 7.90; Found: C 47.53, H 4.03, N 8.01%.

Methyl 2-((4-p-tolylthiazol-2-ylcarbamoyl)methylsulfonyl)-acetate ***14b***

White solid in 84% (2.97 g) yield; m.p.: 173–175°C; IR (KBr) υ_{max} (cm^{-1}): 1140, 1324 (SO_2), 1574 (C=N), 1631 (C=C), 1687 (NH–*CO*), 1730 (*CO*O), 3235 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.31 (s, 3H, Ar–CH_3), 3.80 (s, 3H, OCH_3), 4.30 (s, 2H, CO–CH_2), 4.37 (s, 2H, SO_2–CH_2), 6.61 (s, 1H, C_5–H), 7.10–7.42 (m, 4H, Ar–H), 10.18 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.0 (Ar–CH_3), 51.8 (OCH_3), 52.6 (SO_2–CH_2), 54.4 (CO–*C*H_2), 104.1 (C-5), 147.1 (C-4), 161.7 (NH–CO), 164.1 (C-2), 168.2 (CO_2Me), 122.4, 125.6, 129.7, 130.0 (aromatic carbons); MS (*m/z*): 368.44 [$M^{+\bullet}$]. Anal. calcd. for $C_{15}H_{16}N_2O_5S_2$: C 48.90, H 4.38, N 7.60; Found: C 48.98, H 4.03, N 7.72%.

Methyl 2-((4-(p-chlorophenyl)thiazol-2-ylcarbamoyl)-methylsulfonyl)acetate ***14c***

White solid in 81% (3.03 g) yield; m.p.: 186–188°C; IR (KBr) υ_{max} (cm^{-1}): 1145, 1333 (SO_2), 1578 (C=N), 1641 (C=C), 1693 (NH–*CO*), 1735 (*CO*O), 3255 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.86 (s, 3H,

OCH_3), 4.33 (s, 2H, CO–CH_2), 4.41 (s, 2H, SO_2–CH_2), 6.66 (s, 1H, C_5–H), 7.22–7.63 (m, 4H, Ar–H), 11.33 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 52.5 (OCH_3), 53.2 (SO_2–CH_2), 55.2 (CO–*C*H_2), 105.9 (C-5), 148.5 (C-4), 162.9 (NH–CO), 164.3 (C-2), 168.9 (CO_2Me), 128.2, 129.1, 130.4, 132.8 (aromatic carbons); MS (*m/z*): 388.84 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{13}ClN_2O_5S_2$: C 43.24, H 3.37, N 7.20; Found: C 43.35, H 3.42, N 7.09%.

Methyl 2-((4-phenyl-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetate **15a**

White solid in 84% (2.71 g) yield; m.p.: 155–157°C; IR (KBr) υ_{max} (cm^{-1}): 1140, 1330 (SO_2), 1575 (C=N), 1634 (C=C), 1688 (NH–*CO*), 1733 (*CO*O), 3254 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.84 (s, 3H, OCH_3), 4.34 (s, 2H, CO–CH_2), 4.39 (s, 2H, SO_2–CH_2), 7.20–7.56 (m, 6H, Ar–H, and C_5–H), 10.87 (bs, 1H, NH–CO), 12.60 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 52.4 (OCH_3), 53.5 (SO_2–CH_2), 54.8 (CO–*C*H_2), 123.0 (C-5), 137.3 (C-2), 140.8 (C-4), 163.4 (CO_2Me), 169.3 (NH–CO), 124.2, 126.3, 128.2, 130.6 (aromatic carbons); MS (*m/z*): 337.36 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{15}N_3O_5S$: C 49.84, H 4.48, N 12.46; Found: C 49.96, H 4.55, N 12.60%.

Methyl 2-((4-p-tolyl-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetate **15b**

White solid in 82% (2.76 g) yield; m.p.: 176–178°C; IR (KBr) υ_{max} (cm^{-1}): 1139, 1325 (SO_2), 1573 (C=N), 1632 (C=C), 1686 (NH–*CO*), 1731 (*CO*O), 3242 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.34 (s, 3H, Ar–CH_3), 3.82 (s, 3H, OCH_3), 4.31 (s, 2H, CO–CH_2), 4.39 (s, 2H, SO_2–CH_2), 7.17–7.48 (m, 5H, Ar–H, and C_5–H), 10.69 (bs, 1H, NH–CO), 12.57 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.4 (Ar–CH_3), 52.1 (OCH_3), 53.0 (SO_2–CH_2), 54.5 (CO–*C*H_2), 122.6 (C-5), 136.7 (C-2), 141.1 (C-4), 163.1 (CO_2Me), 168.7 (NH–CO), 122.6, 125.3, 130.2, 134.6 (aromatic carbons); MS (*m/z*): 351.39 [$M^{+\bullet}$]. Anal. calcd. for $C_{15}H_{17}N_3O_5S$: C 51.27, H 4.87, N 11.96; Found: C 51.39, H 4.96, N 12.09%.

Methyl 2-((4-(p-chlorophenyl)-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetate **15c**

White solid in 81% (2.89 g) yield; m.p.: 192–194°C; IR (KBr) υ_{max} (cm^{-1}): 1144, 1334 (SO_2), 1576 (C=N), 1643 (C=C), 1691 (NH–*CO*), 1737 (*CO*O), 3257 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.88 (s, 3H, OCH_3), 4.33 (s, 2H, CO–CH_2), 4.42 (s, 2H, SO_2–CH_2), 7.30–7.66 (m, 5H, Ar–H, and C_5–H), 10.23 (bs, 1H, NH–CO), 12.61 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 52.8 (OCH_3), 53.7 (SO_2–CH_2), 55.3 (CO–*C*H_2), 123.2 (C-5), 137.5 (C-2), 141.3 (C-4), 163.9 (CO_2Me), 169.0 (NH–CO), 128.6, 129.8, 130.6, 134.8 (aromatic carbons); MS (*m/z*): 371.80 [$M^{+\bullet}$]. Anal. calcd. for $C_{14}H_{14}ClN_3O_5S$: C 45.23, H 3.79, N 11.30; Found: C 45.32, H 3.71, N 11.43%.

*General procedure for the synthesis of 2-((4-aryloxazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**16a–c**)/2-((4-arylthiazol-2-ylcarbamoyl)methylsulfonyl)acetohydrazide (**17a–c**)/2-((4-aryl-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetohydrazide (**18a–c**)*

Compound **13**/**14**/**15** (10 mmol), hydrazine hydrate (0.55 g, 11 mmol), pyridine (0.2 mL), and methanol (6 mL) were refluxed for 5–7 h. The reaction mixture was cooled and the solid separated was filtered, dried, and recrystallized from methanol.

2-((4-Phenyloxazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide **16a**

White solid in 78% (2.63 g) yield; m.p.: 171–173°C; IR (KBr) υ_{max} (cm^{-1}): 1131, 1333 (SO_2), 1572 (C=N), 1631 (C=C), 1674 (*CO*–NH), 1687 (NH*CO*), 3255 (NH), 3366, 3443 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.52 (bs, 2H, NH_2), 4.31 (s, 2H, CO–CH_2), 4.36 (s, 2H, SO_2–CH_2), 7.26–7.50 (m, 6H, Ar–H, and C_5–H), 8.50 (bs, 1H, CO–NH), 10.90 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 56.9 (CO–*C*H_2), 58.2 (SO_2–CH_2), 138.7 (C-5), 140.7 (C-4), 151.8 (C-2), 171.4 (NH–CO), 173.2 (CO–NH), 123.3, 124.2, 128.9, 134.8 (aromatic carbons); 338.35 [$M^{+\bullet}$], 187.34, 144.16, 103.17 (100%), 77.24; Anal. calcd. for $C_{13}H_{14}N_4O_5S$: C 46.15, H 4.17, N 16.56; Found: C 46.08, H 4.24, N 16.68%.

2-((4-p-Tolyloxazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide **16b**

White solid in 76% (2.67 g) yield; m.p.: 186–188°C; IR (KBr) υ_{max} (cm^{-1}): 1130, 1329 (SO_2), 1569 (C=N), 1629 (C=C), 1671 (*CO*–NH), 1685 (NH*CO*), 3248 (NH), 3360, 3435 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.41 (s, 3H, Ar–CH_3), 3.50 (bs, 2H, NH_2), 4.30 (s, 2H, CO–CH_2), 4.33 (s, 2H, SO_2–CH_2), 7.16–7.42 (m, 5H, Ar–H, and C_5–H), 8.49 (bs, 1H, CO–NH), 10.87 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.9 (Ar–CH_3), 56.6 (CO–*C*H_2), 57.8 (SO_2–CH_2), 138.1 (C-5), 140.2 (C-4), 151.4 (C-2), 171.0 (NH–CO), 172.9 (CO–NH), 122.4, 124.3, 128.5, 132.5 (aromatic carbons); MS (*m/z*): 352.38 [$M^{+\bullet}$], 201.08, 158.13, 117.19 (100%), 91.22; Anal. calcd. for $C_{14}H_{16}N_4O_5S$: C 47.72, H 4.58, N 15.90; Found: C 47.81, H 4.63, N 15.84%.

2-((4-(p-Chlorophenyl)oxazol-2-ylcarbamoyl)-methylsulfonyl)acetohydrazide **16c**

White solid in 75% (2.79 g) yield; m.p.: 195–197°C; IR (KBr) υ_{max} (cm^{-1}): 1138, 1340 (SO_2), 1587 (C=N), 1636 (C=C), 1675 (*CO*–NH), 1692 (NH*CO*), 3256 (NH), 3366, 3443 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.53 (bs, 2H, NH_2), 4.34 (s, 2H, CO–CH_2), 4.37 (s, 2H, SO_2–CH_2), 7.33–7.48 (m, 5H, Ar–H, and C_5–H), 8.52 (bs, 1H, CO–NH), 11.11 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 57.5 (CO–*C*H_2), 58.6 (SO_2–CH_2), 138.8 (C-5), 140.5 (C-4), 152.0 (C-2), 171.6 (NH–CO), 173.5 (CO–NH), 126.3, 128.2, 131.8, 135.2 (aromatic carbons); MS (*m/z*): 372.79 [$M^{+\bullet}$], 221.74, 178.59, 137.43, (100%), 111.27; Anal. calcd. for $C_{13}H_{13}ClN_4O_5S$: C 41.88, H 3.51, N 15.03; Found: C 41.97, H 3.56, N 15.15%.

2-((4-Phenylthiazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide **17a**

White solid in 77% (2.72 g) yield; m.p.: 183–185°C; IR (KBr) υ_{max} (cm^{-1}): 1134, 1332 (SO_2), 1570 (C=N), 1634 (C=C), 1677 (*CO*–NH), 1690 (NH*CO*), 3250 (NH), 3365, 3431 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.49 (bs, 2H, NH_2), 4.30 (s, 2H, CO–CH_2), 4.35 (s, 2H, SO_2–CH_2), 6.63 (s, 1H, C_5–H), 7.18–7.43 (m, 5H, Ar–H), 8.45 (bs, 1H, CO–NH), 10.86 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 56.4 (CO–*C*H_2), 57.5 (SO_2–CH_2), 104.7 (C-5), 147.1 (C-4), 163.8 (C-2), 170.1 (NH–CO), 171.2 (CO–NH), 125.3, 128.0, 129.9, 132.8 (aromatic carbons); MS (*m/z*): 354.41 [$M^{+\bullet}$], 203.09, 160.25 (100%), 103.22, 77.18; Anal. calcd. for $C_{13}H_{14}N_4O_4S_2$: C 44.06, H 3.98, N 15.81; Found: C 44.17, H 4.03, N 15.91%.

2-((4-p-Tolylthiazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide **17b**

White solid in 76% (2.80 g) yield; m.p.: 192–194°C; IR (KBr) υ_{max} (cm^{-1}): 1132, 1326 (SO_2), 1566 (C=N), 1630 (C=C), 1670 (*CO*–NH),

1688 (NH*CO*), 3243 (NH), 3358, 3426 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.38 (s, 3H, Ar–CH_3), 3.45 (bs, 2H, NH_2), 4.28 (s, 2H, CO–CH_2), 4.31 (s, 2H, SO_2–CH_2), 6.60 (s, 1H, C_5–H), 7.10–7.35 (m, 4H, Ar–H), 8.42 (bs, 1H, CO–NH), 10.22 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.6 (Ar–CH_3), 56.0 (CO–*C*H_2), 57.1 (SO_2–CH_2), 104.5 (C-5), 147.8 (C-4), 163.4 (C-2), 169.9 (NH–CO), 170.9 (CO–NH), 124.4, 126.3, 130.5, 134.5 (aromatic carbons); MS (*m/z*): 368.44 [$M^{+\bullet}$], 217.32, 174.17 (100%), 117.21, 91.36; Anal. calcd. for $C_{14}H_{16}N_4O_4S_2$: C 45.64, H 4.38, N 15.21; Found: C 45.75, H 4.41, N 15.30%.

2-((4-(p-Chlorophenyl)thiazol-2-ylcarbamoyl)-methylsulfonyl)acetohydrazide ***17c***

White solid in 74% (2.87 g) yield; m.p.: 201–203°C; IR (KBr) υ_{max} (cm^{-1}): 1139, 1336 (SO_2), 1582 (C=N), 1637 (C=C), 1772 (*CO*–NH), 1691 (NH*CO*), 3252 (NH), 3372, 3438 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.51 (bs, 2H, NH_2), 4.33 (s, 2H, CO–CH_2), 4.34 (s, 2H, SO_2–CH_2), 6.67 (s, 1H, C_5–H), 7.26–7.44 (m, 4H, Ar–H), 8.50 (bs, 1H, CO–NH), 11.07 (bs, 1H, NH–CO); ^{13}C NMR (DMSO-d_6) δ (ppm): 56.5 (CO–*C*H_2), 58.1 (SO_2–CH_2), 105.8 (C-5), 147.7 (C-4), 164.0 (C-2), 170.4 (NH–CO), 171.3 (CO–NH), 127.3, 130.2, 132.8, 134.6 (aromatic carbons); MS (*m/z*): 388.85 [$M^{+\bullet}$], 237.71, 194.73 (100%), 137.28, 111.15; Anal. calcd. for $C_{13}H_{13}ClN_4O_4S_2$: C 40.15, H 3.37, N 14.41; Found: C 40.09, H 3.42, N 14.52%.

2-((4-Phenyl-1H-imidazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide ***18a***

White solid in 72% (2.42 g) yield; m.p.: 177–179°C; IR (KBr) υ_{max} (cm^{-1}): 1134, 1333 (SO_2), 1571 (C=N), 1637 (C=C), 1673 (*CO*–NH), 1685 (NH*CO*), 3254 (NH), 3364, 3440 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.50 (bs, 2H, NH_2), 4.29 (s, 2H, CO–CH_2), 4.33 (s, 2H, SO_2–CH_2), 7.24–7.49 (m, 6H, Ar–H, and C_5–H), 8.49 (bs, 1H, CO–NH), 11.12 (bs, 1H, NH–CO), 12.42 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 56.8 (CO–*C*H_2), 57.9 (SO_2–CH_2), 123.2 (C-5), 137.8 (C-2), 141.8 (C-4), 170.7 (NH–CO), 171.4 (CO–NH), 126.4, 128.8, 130.9, 133.8 (aromatic carbons); MS (*m/z*): 337.36 [$M^{+\bullet}$], 186.22, 143.19, 103.24 (100%), 77.15; Anal. calcd. for $C_{13}H_{15}N_5O_4S$: C 46.28, H 4.48, N 20.76; Found: C 46.36, H 4.42, N 20.89%.

2-((4-p-Tolyl-1H-imidazol-2-ylcarbamoyl)methylsulfonyl)-acetohydrazide ***18b***

White solid in 76% (2.67 g) yield; m.p.: 213–215°C; IR (KBr) υ_{max} (cm^{-1}): 1131, 1328 (SO_2), 1564 (C=N), 1631 (C=C), 1671 (*CO*–NH), 1687 (NH*CO*), 3249 (NH), 3367, 3434 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.46 (s, 3H, Ar–CH_3), 3.49 (bs, 2H, NH_2), 4.31 (s, 2H, CO–CH_2), 4.36 (s, 2H, SO_2–CH_2), 7.21–7.43 (m, 5H, Ar–H, and C_5–H), 8.47 (bs, 1H, CO–NH), 10.74 (bs, 1H, NH–CO), 12.48 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.7 (Ar–CH_3), 56.2 (CO–*C*H_2), 58.6 (SO_2–CH_2), 122.0 (C-5), 136.4 (C-2), 140.8 (C-4), 170.2 (NH–CO), 171.2 (CO–NH), 122.4, 124.3, 127.5, 134.0 (aromatic carbons); MS (*m/z*): 351.38 [$M^{+\bullet}$], 200.31, 157.24, 117.23 (100%), 91.23; Anal. calcd. for $C_{14}H_{17}N_5O_4S$: C 47.85, H 4.88, N 19.93; Found: C 47.94, H 4.93, N 20.03%.

2-((4-(p-Chlorophenyl)-1H-imidazol-2-ylcarbamoyl)-methylsulfonyl)acetohydrazide ***18c***

White solid in 78% (2.90 g) yield; m.p.: 227–229°C; IR (KBr) υ_{max} (cm^{-1}): 1137, 1337 (SO_2), 1580 (C=N), 1639 (C=C), 1677 (*CO*–NH), 1694 (NH*CO*), 3255 (NH), 3378, 3447 (NH_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.52 (bs, 2H, NH_2), 4.32 (s, 2H, CO–CH_2), 4.35 (s, 2H, SO_2–CH_2), 7.36–7.53 (m, 5H, Ar–H, and C_5–H), 8.51 (bs, 1H, CO–NH), 10.92 (bs, 1H, NH–CO), 12.57 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 57.6 (CO–*C*H_2), 58.8 (SO_2–CH_2), 123.8 (C-5), 137.9 (C-2), 142.0 (C-4), 170.9 (NH–CO), 171.5 (CO–NH), 126.3, 130.4, 132.8, 135.8 (aromatic carbons); MS (*m/z*): 371.80 [$M^{+\bullet}$], 220.58, 177.59, 137.32 (100%), 111.14; Anal. calcd. for $C_{13}H_{14}ClN_5O_4S$: C 42.00, H 3.80, N 18.84; Found: C 42.09, H 3.86, N 18.72%.

*General procedure for the synthesis of 2-((5′-(o-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-aryloxazol-2-yl)acetamide (**19a–c**)/2-((5′-(o-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-arylthiazol-2-yl)acetamide (**20a–c**)/2-((5′-(o-chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)methylsulfonyl)-N-(4-aryl-1H-imidazol-2-yl)acetamide (**21a–c**)*

To an equimolar mixture of (10 mmol) acid hydrazide **16**/**17**/**18** and 2-chlorobenzoic acid (1.56 g, 10 mmol), $POCl_3$ (7 mL) was added and refluxed for 6–9 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. It was dried and recrystallized from ethanol.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-phenyloxazol-2-yl)acetamide ***19a***

White solid in 69% (2.33 g) yield; m.p.: 127–129°C; IR (KBr) υ_{max} (cm^{-1}): 1129, 1317 (SO_2), 1564 (C=N), 1620 (C=C), 1685 (C=O), 3249 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.34 (s, 2H, CO–CH_2), 4.69 (s, 2H, SO_2–CH_2), 7.46–7.72 (m, 10H, Ar–H, and C_5–H), 11.34 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.4 (SO_2–CH_2), 54.1 (CO–*C*H_2), 137.4 (C-5), 140.8 (C-4), 150.2 (C-2), 158.7 (C-2′), 165.7 (C-5′), 170.4 (CO), 126.1, 126.8, 127.3, 128.1, 128.9, 129.2, 131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m/z*): 458.89 [$M^{+\bullet}$], 192.54, 187.23, 179.43, 144.24, 111.24 (100%), 103.17; Anal. calcd. for $C_{20}H_{15}ClN_4O_5S$: C 52.34, H 3.29, N 12.20; Found: C 52.44, H 3.34, N 12.34%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-p-tolyloxazol-2-yl)acetamide ***19b***

White solid in 71% (2.50 g) yield; m.p.: 134–136°C; IR (KBr) υ_{max} (cm^{-1}): 1125, 1311 (SO_2), 1559 (C=N), 1618 (C=C), 1687 (C=O), 3243 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.47 (s, 3H, Ar–CH_3), 4.32 (s, 2H, CO–CH_2), 4.67 (s, 2H, SO_2–CH_2), 7.42–7.62 (m, 9H, Ar–H, and C_5–H), 10.98 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.6 (Ar–CH_3), 50.2 (SO_2–CH_2), 53.8 (CO–*C*H_2), 138.0 (C-5), 140.4 (C-4), 150.5 (C-2), 157.2 (C-2′), 164.8 (C-5′), 169.8 (CO), 126.3, 126.7, 127.2, 127.5, 128.3, 128.6, 129.5, 131.6, 132.3, 135.0 (aromatic carbons); MS (*m/z*): 472.91 [$M^{+\bullet}$], 201.33, 192.31, 179.45, 158.24, 117.24, 111.20 (100%); Anal. calcd. for $C_{21}H_{17}ClN_4O_5S$: C 53.33, H 3.62, N 11.84; Found: C 53.42, H 3.58, N 11.98%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-(p-chlorophenyl)-oxazol-2-yl)-acetamide ***19c***

White solid in 72% (2.68 g) yield; m.p.: 150–152°C; IR (KBr) υ_{max} (cm^{-1}): 1134, 1320 (SO_2), 1568 (C=N), 1629 (C=C), 1692 (C=O),

3262 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.35 (s, 2H, CO–CH_2), 4.70 (s, 2H, SO_2–CH_2), 7.47–7.80 (m, 9H, Ar–H, and C_5–H), 11.38 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.6 (SO_2–CH_2), 54.7 (CO–CH_2), 138.3 (C-5), 140.2 (C-4), 151.3 (C-2), 158.2 (C-2′), 166.7 (C-5′), 171.8 (CO), 127.8, 128.0, 128.6, 128.9, 129.8, 130.2, 131.6, 132.0, 132.3, 135.9 (aromatic carbons); MS (*m/z*): 493.34 [$M^{+\bullet}$], 221.54, 192.18, 179.24, 178.33, 137.26, 111.16 (100%); Anal. calcd. for $C_{20}H_{14}Cl_2N_4O_5S$: C 48.69, H 2.86, N 11.35; Found: C 48.60, H 2.82, N 11.23%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-phenylthiazol-2-yl)-acetamide **20a**

White solid in 70% (2.48 g) yield; m.p.: 141–143°C; IR (KBr) υ_{max} (cm^{-1}): 1132, 1312 (SO_2), 1563 (C=N), 1624 (C=C), 1688 (C=O), 3251 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.31 (s, 2H, CO–CH_2), 4.65 (s, 2H, SO_2–CH_2), 6.68 (s, 1H, C_5–H), 7.36–7.76 (m, 9H, Ar–H), 11.03 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 49.6 (SO_2–CH_2), 53.6 (CO–CH_2), 105.4 (C-5), 148.3 (C-4), 156.4 (C-2′), 163.9 (C-2), 164.7 (C-5′), 167.9 (CO), 126.1, 126.8, 127.3, 128.1, 128.9, 129.2, 131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m/z*): 474.95 [$M^{+\bullet}$], 203.20, 192.61, 179.24, 160.15, 111.05, 103.16 (100%), 77.19; Anal. calcd. for $C_{20}H_{15}ClN_4O_4S_2$: C 50.57, H 3.18, N 11.79; Found: C 50.66, H 3.12, N 11.91%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-p-tolylthiazol-2-yl)-acetamide **20b**

White solid in 68% (2.50 g) yield; m.p.: 148–150°C; IR (KBr) υ_{max} (cm^{-1}): 1130, 1310 (SO_2), 1557 (C=N), 1623 (C=C), 1685 (C=O), 3244 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.42 (s, 3H, Ar–CH_3), 4.30 (s, 2H, CO–CH_2), 4.64 (s, 2H, SO_2–CH_2), 6.66 (s, 1H, C_5–H), 7.33–7.71 (m, 8H, Ar–H), 11.30 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.5 (Ar–CH_3), 50.3 (SO_2–CH_2), 53.2 (CO–CH_2), 105.5 (C-5), 148.0 (C-4), 154.2 (C-2′), 163.5 (C-2), 166.5 (C-5′), 167.8 (CO), 126.3, 126.7, 127.2, 127.5, 128.3, 128.6, 129.5, 131.6, 132.3, 135.0 (aromatic carbons); MS (*m/z*): 488.97 [$M^{+\bullet}$], 217.34, 192.51, 179.23, 174.17, 117.24 (100%), 111.55, 91.00; Anal. calcd. for $C_{21}H_{17}ClN_4O_4S_2$: C 51.58, H 3.50, N 11.45; Found: C 51.69, H 3.57, N 11.58%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-(p-chlorophenyl)-thiazol-2-yl)-acetamide **20c**

White solid in 69% (2.68 g) yield; m.p.: 164–166°C; IR (KBr) υ_{max} (cm^{-1}): 1135, 1315 (SO_2), 1567 (C=N), 1633 (C=C), 1690 (C=O), 3264 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.33 (s, 2H, CO–CH_2), 4.68 (s, 2H, SO_2–CH_2), 7.02 (s, 1H, C_5–H), 7.41–7.78 (m, 8H, Ar–H), 11.37 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.8 (SO_2–CH_2), 53.8 (CO–CH_2), 106.0 (C-5), 148.6 (C-4), 155.6 (C-2′), 164.3 (C-2), 164.8 (C-5′), 168.2 (CO), 127.8, 128.0, 128.6, 128.9, 129.8, 130.2, 131.6, 132.0, 132.3, 135.9 (aromatic carbons); MS (*m/z*): 509.40 [$M^{+\bullet}$], 237.58, 194.34, 192.47, 179.31, 137.29 (100%), 111.05; Anal. calcd. for $C_{20}H_{14}Cl_2N_4O_4S_2$: C 47.15, H 2.76, N 10.99; Found: C 47.08, H 2.72, N 11.11%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-phenyl-1H-imidazol-2-yl)acetamide **21a**

White solid in 71% (2.39 g) yield; m.p.: 135–137°C; IR (KBr) υ_{max} (cm^{-1}): 1133, 1318 (SO_2), 1561 (C=N), 1628 (C=C), 1689 (C=O), 3253 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.32 (s, 2H, CO–CH_2), 4.67 (s, 2H, SO_2–CH_2), 7.42–7.83 (m, 10H, Ar–H, and C_5–H), 11.26 (bs, 1H, NH–CO), 12.48 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.7 (SO_2–CH_2), 54.7 (CO–CH_2), 123.5 (C-5), 137.3 (C-2), 140.4 (C-4), 154.8 (C-2′), 165.5 (C-5′), 169.9 (CO), 126.1, 126.8, 127.3, 128.1, 128.9, 129.2, 131.2, 132.4, 134.7, 135.6 (aromatic carbons); MS (*m/z*): 457.90 [$M^{+\bullet}$], 192.55, 186.17, 179.31, 143.54 (100%), 103.16, 111.55, 77.14; Anal. calcd. for $C_{20}H_{16}ClN_5O_4S$: C 52.46, H 3.52, N 15.29; Found: C 52.57, H 3.58, N 15.41%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-p-tolyl-1H-imidazol-2-yl)acetamide **21b**

White solid in 72% (2.52 g) yield; m.p.: 129–131°C; IR (KBr) υ_{max} (cm^{-1}): 1131, 1313 (SO_2), 1552 (C=N), 1624 (C=C), 1686 (C=O), 3244 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.49 (s, 3H, Ar–CH_3), 4.31 (s, 2H, CO–CH_2), 4.65 (s, 2H, SO_2–CH_2), 7.48–7.66 (m, 9H, Ar–H, and C_5–H), 11.18 (bs, 1H, NH–CO), 12.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.8 (Ar–CH_3), 49.7 (SO_2–CH_2), 54.4 (CO–CH_2), 123.0 (C-5), 137.1 (C-2), 140.2 (C-4), 153.7 (C-2′), 165.3 (C-5′), 168.3 (CO), 126.3, 126.7, 127.2, 127.5, 128.3, 128.6, 129.5, 131.6, 132.3, 135.0 (aromatic carbons); MS (*m/z*): 471.92 [$M^{+\bullet}$], 200.19, 192.61, 179.28, 157.24 (100%), 117.26, 111.36, 91.34; Anal. calcd. for $C_{21}H_{18}ClN_5O_4S$: C 53.44, H 3.84, N 14.83; Found: C 53.57, H 3.81, N 14.95%.

2-((5′-(o-Chlorophenyl)-1′,3′,4′-oxadiazol-2′-yl)-methylsulfonyl)-N-(4-(p-chlorophenyl)-1H-imidazol-2-yl)-acetamide **21c**

White solid in 70% (2.60 g) yield; m.p.: 159–161°C; IR (KBr) υ_{max} (cm^{-1}): 1134, 1321 (SO_2), 1566 (C=N), 1631 (C=C), 1693 (C=O), 3268 (NH); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.34 (s, 2H, CO–CH_2), 4.69 (s, 2H, SO_2–CH_2), 7.47–7.86 (m, 9H, Ar–H, and C_5–H), 11.34 (bs, 1H, NH–CO), 12.51 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.9 (SO_2–CH_2), 55.0 (CO–CH_2), 123.6 (C-5), 138.0 (C-2), 141.2 (C-4), 155.4 (C-2′), 166.7 (C-5′), 171.2 (CO), 127.8, 128.0, 128.6, 128.9, 129.8, 130.2, 131.6, 132.0, 132.3, 135.9 (aromatic carbons); MS (*m/z*): 492.35 [$M^{+\bullet}$], 220.58, 192.54, 179.23, 177.53, (100%), 137.28, 111.28; Anal. calcd. for $C_{20}H_{15}Cl_2N_5O_4S$: C 48.79, H 3.07, N 14.22; Found: C 48.87, H 3.12, N 14.37%.

Biological assays

Antioxidant activity

The compounds **19**–**21** were tested for antioxidant activity by the 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 DPPH radicals. The spectrophotometric assay uses the stable radical DPPH$^\bullet$ as 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 was added. After a 30-min incubation period at room temperature, the absorbance was read against the 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 the test compound), and A_{blank} is the absorbance of the blank (containing only methanolic DPPH). The tests were carried out in triplicate.

Nitric oxide-scavenging activity

The NO-scavenging activity was measured by the methods of Green et al. [20] and Marcocci et al. [21], with slight modifications. NO radicals were generated from sodium nitroprusside. Of sodium nitroprusside, 1 mL (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 Griess reagent (1% sulfanilamide, 2% H_3PO_4, 0.1% naphthylethylenediamine dihydrochloride). The absorbance of the chromatophore was measured at 546 nm. Ascorbic acid was used as standard. The 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 the test compound), and A_{blank} is the absorbance of the blank (containing only reagents). The tests were carried out in triplicate.

ABTS radical-scavenging activity

The antioxidant activities of the test compounds and the 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 ABTS salt with 0.01 mol potassium persulfate in 25 mL 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 or standard, 1 mL $ABTS^{\bullet+}$ solution was added and allowed to react for 2 h in the dark. Then the absorbance was read at 734 nm, using the spectrophotometer. The corresponding blank reading was also taken and the results as percentage were expressed as the ratio of the absorbance decrease at 734 nm to the absorbance of the $ABTS^{\bullet+}$ solution in the absence of test compounds.

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