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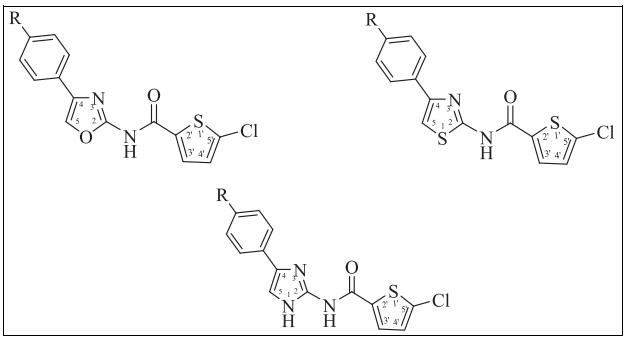

A new class of amido linked azolyl thiophenes was prepared from the synthetic intermediates azolyl amines and 5-chlorothiophene-2-carbonyl chloride adopting conventional and ultrasonication methodologies. It was observed that the reaction took place in shorter reaction times with higher yields under ultrasonication. The structures of the synthesized compounds were characterized by spectral parameters and also tested for antioxidant activity. Among all the tested compounds, methoxy substituted oxazolyl thiophene carboxamide (**8c**) displayed promising antioxidant activity. Besides, the electron donating groups on the phenyl ring enhanced the antioxidant activity when compared with the electron withdrawing groups.

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INTRODUCTION

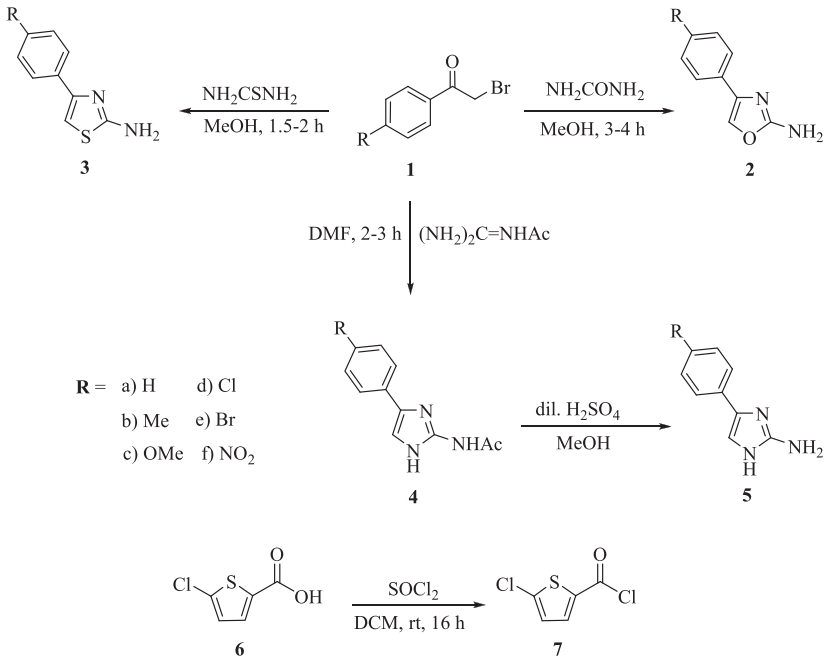
Among nitrogen and sulfur-containing five-membered heteroarenes-thiophenes, oxazoles, thiazoles, and imidazoles have gained prominence due to their unique biological and physical properties. Thiophenes are prevalent in many natural and synthetic products with a broad spectrum of biological activites. Besides, thiophenes are of particular interest for both medicinal and synthetic chemists because they are useful as versatile intermediates in organic synthesis [1]. Oxazoles occur as subunits in numerous natural products [2] such as Leucamide A and its analogues, function as anticancer reagents. Besides, oxazole is a precursor in many biochemical and synthetic transformations [3–6]. The pharmaceutical agents, namely, inthomycin C, oxaprozin, pemoline, and bengazole A, contain oxazole motif. In addition, thiazoles are useful in the treatment of allergies [7], hypertension [8], inflammation [9], schizophrenia [10], microbial [11,12], and HIV infections [13]. Sulfathiazole, bleomycin, and tiazofurin are some of the drugs having thiazole moiety. On the other hand, imidazole nucleus is a privileged scaffold in histidine, Vit-B_{12}, a component of DNA base structure, histamine, and biotin. Moreover, imidazole derivatives exhibit anti-inflammatory [14,15], antipyretic [16], antidepressant [17], anticonvulsant [18], antitumor [19–22], anticancer [23–25], antimicrobial [16,26,27], antimalarial [28], antiviral [29], and antioxidant [30–32] activities. On the other hand, amide bonds occur in many drugs and biomolecules [33,34]. They also find many applications due to their high polarity, stability, and conformational flexibility. It is well known that the combination of two or more types of heterocycles linked by amide moiety into one molecular frame work would afford a novel entity with enhanced pharmacological activities [35,36]. The exploration of new, efficient, and inexpensive synthetic methods based on green chemistry in organic synthesis is always in demand. Ultrasound activation is used successfully to promote reaction rates of a number of chemical transformations. Motivated by the previously mentioned findings and as part of a continuing effort towards the development of biologically active heterocycles [37–39], synthesis and antioxidant activity of a new class of amido linked azolyl thiophenes have been taken up.

RESULTS AND DISCUSSION

The amido linked oxazolyl thiophenes, thiazolyl thiophenes, and imidazolyl thiophenes were synthesized

from the synthetic intermediates 4-aryloxazol-2-amine (**2**), 4-arylthiazol-2-amine (**3**), 4-aryl-1*H*-imidazol-2-amine (**5**), and 5-chlorothiophene-2-carbonyl chloride (**7**). The compounds **2** and **3** were obtained by the reaction of phenacyl bromide (**1**) with urea and thiourea in methanol [40]. However, the reaction of compound **1** with acetyl guanidine gave *N*-(4-aryl-*1H*-imidazol-2-yl)acetamide (**4**) which on hydrolysis under acidic conditions [41] produced compound **5**. The chlorination of 5-chlorothiophene-2-carboxylic acid (**6**) with thionyl chloride in dichloromethane led to the formation of **7** [42] (Scheme 1). The 5-chloro-*N*-(4-aryloxazol-2-yl) thiophene-2-carboxamide (**8**) was synthesized by condensation of compound **2** with **7** in tetrahydrofuran in the presence of 10% NaOH. In a similar way, the reaction between compound **3** with **7** afforded 5-chloro-*N*-(4-arylthiazol-2-yl)thiophene-2-carboxamide (**9**). Furthermore, 5-chloro-*N*-(4-aryl-*1H*-imidazol-2-yl)-thiophene-2-carboxamide (**10**) was prepared by the condensation of compound **5** with **7** in tetrahydrofuran in the presence of 10% NaOH. The compounds **8**–**10** were also synthesized under ultrasonication (Scheme 2 and Table 1). It was observed that the target compounds were obtained in shorter reaction times and in high yield under ultrasonication. The ^{1}H NMR spectra of **8a** and **9a** showed two doublets at δ 6.88, 6.83 ppm (C_4'─H), 8.10, 8.06 ppm (C_3'─H), and a broad singlet at 9.25, 9.36 ppm (NHCO). In addition, a singlet due to C_5─H appeared at much downfield region

Scheme 1. Synthesis of azolyl amines and 5-chlorothiophene-2-carbonyl chloride.



Scheme 2. Synthesis of amido linked oxazolyl/thiazolyl/imidazolyl thiophenes.

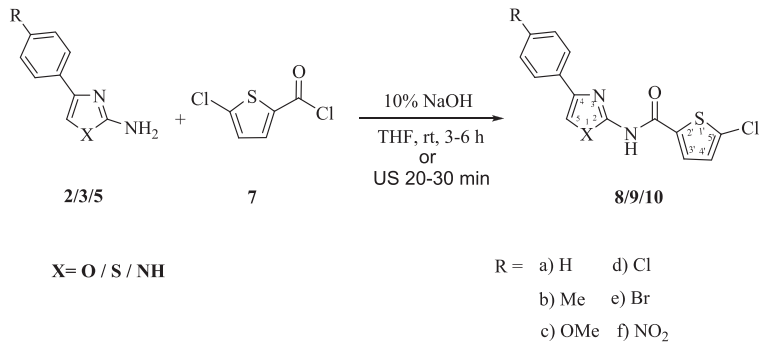


Table 1

The preparation of compounds **8–10** under conventional and ultrasound irradiation methods.

		Conventional		Ultrasound	
Entry	Product	Time (h)	Yield (%)	Time (min)	Yield (%)
1	**8a**	4.1	75	30	86
2	**8b**	4.0	68	28	88
3	**8c**	5.2	74	26	90
4	**8d**	5.4	69	25	89
5	**8e**	5.6	77	27	85
6	**8f**	6.0	71	24	87
7	**9a**	3.0	80	21	91
8	**9b**	3.5	82	26	95
9	**9c**	3.2	84	23	93
10	**9d**	3.3	87	27	92
11	**9e**	3.6	83	22	88
12	**9f**	3.8	74	24	89
13	**10a**	4.2	76	23	90
14	**10b**	4.4	72	25	93
15	**10c**	4.1	78	27	91
16	**10d**	4.3	75	29	88
17	**10e**	4.5	79	26	91
18	**10f**	4.6	77	28	92

and merged with aromatic protons. However, the ^{1}H NMR spectrum of **10a** displayed two doublets and two broad singlets at δ 6.78, 7.97, 9.80, and 11.50 ppm due to C_4'—H, C_3'—H, NHCO, and NH of imidazole, respectively. Besides, a singlet due to C_5—H observed at much downfield region and merged with aromatic protons. The signals due to NH protons disappeared when D_2O was added. The structures of all the new compounds were also established by infrared (IR), ^{13}C NMR, mass spectral data, and microanalyses.

ANTIOXIDANT ACTIVITY

The compounds **8**–**10** were evaluated for antioxidant activity by 2,2-diphenyl-1-picrylhydrazyl [43,44], nitric oxide [45,46], and hydrogen peroxide (H_2O_2) [47] methods at four concentrations (25, 50, 75, and 100 μg/mL). Ascorbic acid was used as the standard drug in all the three methods. The perusal of results (Tables 2–4 and Figs. 1–3) indicated that oxazolyl thiophene carboxamides (**8**) showed greater radical scavenging activity than the thiazolyl thiophene carboxamides (**9**) and imidazolyl thiophene carboxamides (**10**). However, the compounds **9** displayed slightly higher activity than the compounds **10**. It was observed that compounds **8a**–**c**, **9a**–**c**, and **10a**–**c** exhibited greater radical scavenging activity when compared with the other compounds. It was also noticed that with increasing electron donating effect the antioxidant activity increases. In fact, methoxy substituted compounds showed higher activity than methyl substituted ones. This may be due to inductive effect of methyl and mesomeric effect of methoxy substituents. The methoxy substituted oxazolyl

Table 2

% Scavenging activity of compounds **8**–**10** on 2,2-diphenyl-1-picrylhydrazyl radical.

	Concentration (μg/mL)				
Compd. No.	25	50	75	100	IC_{50}
8a	44.26 ± 0.21	50.69 ± 0.14	62.47 ± 0.44	69.23 ± 0.27	49.31 ± 0.19
8b	53.44 ± 0.10	57.95 ± 0.39	66.13 ± 0.13	74.31 ± 0.38	23.39 ± 0.66
8c	55.52 ± 0.45	59.64 ± 0.53	69.16 ± 0.54	79.52 ± 0.35	22.51 ± 0.32
8d	-	-	-	-	-
8e	23.22 ± 0.34	26.42 ± 0.83	35.55 ± 0.49	42.43 ± 0.27	117.84 ± 0.22
8f	-	-	-	-	-
9a	34.38 ± 0.55	40.32 ± 0.15	49.17 ± 0.79	59.52 ± 0.21	76.26 ± 0.14
9b	39.65 ± 0.44	46.42 ± 0.31	56.27 ± 0.71	66.42 ± 0.56	53.85 ± 0.26
9c	48.32 ± 0.59	56.17 ± 1.07	66.18 ± 0.63	72.13 ± 0.62	25.86 ± 0.20
9d	-	-	-	-	-
9e	11.12 ± 0.49	16.66 ± 0.28	28.37 ± 0.31	33.53 ± 0.67	149.12 ± 0.44
9f	-	-	-	-	-
10a	26.42 ± 0.98	34.73 ± 0.36	45.06 ± 0.58	55.20 ± 0.95	90.57 ± 0.68
10b	29.83 ± 0.63	34.39 ± 0.17	46.18 ± 0.61	57.12 ± 0.34	81.20 ± 0.78
10c	36.56 ± 0.42	41.42 ± 0.25	53.11 ± 0.82	62.68 ± 0.43	70.60 ± 0.36
10d	-	-	-	-	-
10e	7.13 ± 1.14	12.76 ± 0.48	20.16 ± 0.95	28.47 ± 0.64	175.62 ± 0.12
10f	-	-	-	-	-
Ascorbic acid	58.30 ± 0.98	64.29 ± 0.47	72.44 ± 0.36	81.20 ± 0.59	21.44 ± 0.42
Blank	-	-	-	-	-

-, no activity; ±, standard deviation.

Table 3

% Scavenging activity of compounds **8**–**10** on H_2O_2 radical.

	Concentration (μg/mL)				
Compd. No.	25	50	75	100	IC_{50}
8a	35.15 ± 0.16	42.67 ± 0.50	50.18 ± 0.63	62.32 ± 0.43	74.73 ± 0.19
8b	44.68 ± 0.19	50.27 ± 0.89	59.76 ± 0.25	68.24 ± 0.47	49.73 ± 0.48
8c	45.52 ± 0.45	54.64 ± 0.23	62.86 ± 0.34	71.52 ± 0.55	45.75 ± 0.42
8d	-	-	-	-	-
8e	15.74 ± 0.59	20.65 ± 0.28	31.21 ± 1.12	39.32 ± 0.40	127.16 ± 0.34
8f	-	-	-	-	-
9a	26.38 ± 0.68	36.25 ± 0.87	56.18 ± 0.62	56.22 ± 0.57	88.93 ± 0.25
9b	33.07 ± 0.95	40.58 ± 0.65	48.28 ± 0.71	62.42 ± 0.38	77.67 ± 0.33
9c	42.01 ± 0.59	48.54 ± 0.57	56.18 ± 0.63	66.83 ± 0.39	51.50 ± 0.79
9d	-	-	-	-	-
9e	8.15 ± 1.01	10.19 ± 0.28	21.76 ± 0.31	33.53 ± 0.98	149.12 ± 0.57
9f	-	-	-	-	-
10a	23.84 ± 1.17	27.68 ± 0.44	39.56 ± 0.65	51.36 ± 0.38	97.35 ± 0.74
10b	26.12 ± 0.68	32.33 ± 0.67	41.18 ± 0.61	53.14 ± 0.54	94.09 ± 0.42
10c	32.56 ± 0.42	39.01 ± 0.34	47.51 ± 0.89	60.89 ± 0.64	78.93 ± 1.02
10d	-	-	-	-	-
10e	5.41 ± 1.14	9.76 ± 0.68	14.62 ± 0.65	26.12 ± 0.74	191.42 ± 0.11
10f	-	-	-	-	-
Ascorbic acid	49.46 ± 0.60	59.21 ± 0.27	68.59 ± 0.35	75.38 ± 0.47	25.27 ± 0.32
Blank	-	-	-	-	-

-, no activity, ±, standard deviation.

Table 4

% Scavenging activity of compounds **8–10** on nitric oxide radical.

	Concentration (μg/mL)				
Compd. No.	25	50	75	100	IC_{50}
8a	18.06 ± 0.52	22.56 ± 0.21	30.84 ± 0.31	40.51 ± 0.20	123.42 ± 0.36
8b	22.88 ± 0.44	28.29 ± 0.11	33.02 ± 0.39	43.55 ± 0.61	114.81 ± 0.31
8c	24.31 ± 0.39	30.55 ± 0.13	35.22 ± 0.16	45.89 ± 0.54	185.94 ± 0.31
8d	-	-	-	-	-
8e	6.52 ± 0.84	10.12 ± 1.19	18.17 ± 0.26	28.19 ± 0.42	108.95 ± 0.71
8f	-	-	-	-	-
9a	11.74 ± 0.34	16.70 ± 0.24	26.35 ± 0.35	34.87 ± 0.89	177.36 ± 0.26
9b	14.14 ± 1.16	21.43 ± 0.56	29.75 ± 0.20	38.20 ± 0.14	143.38 ± 0.39
9c	20.13 ± 0.56	26.13 ± 1.06	30.14 ± 0.26	42.48 ± 0.43	130.89 ± 0.57
9d	-	-	-	-	-
9e	5.12 ± 1.13	8.18 ± 0.95	16.23 ± 0.29	23.82 ± 0.35	117.70 ± 0.48
9f	-	-	-	-	-
10a	8.25 ± 0.87	11.61 ± 0.33	20.43 ± 0.28	28.17 ± 0.12	209.90 ± 0.69
10b	12.73 ± 0.29	16.63 ± 0.53	26.32 ± 0.42	35.73 ± 0.35	177.49 ± 1.01
10c	15.61 ± 0.82	23.37 ± 0.52	30.83 ± 0.25	38.21 ± 0.33	139.93 ± 1.10
10d	-	-	-	-	-
10e	4.27 ± 0.76	7.12 ± 0.73	11.21 ± 1.25	36.17 ± 0.47	130.85 ± 1.03
10f	-	-	-	-	-
Ascorbic acid	28.64 ± 0.58	34.31 ± 0.31	39.22 ± 0.92	48.70 ± 0.26	138.23 ± 1.01
Blank	-	-	-	-	-

-, no activity; ±, standard deviation.

thiophene carboxamide (**8c**) displayed promising radical scavenging activity among all the tested compounds when compared with the standard drug. The bromo substituted compounds showed the least activity. On the other hand, the chloro and nitro substituted compounds **8d**, **8f**, **9d**, **9f**, **10d**, and **10f** exhibited no activity. The structure–activity relationship of the compounds revealed that amido linked oxazolyl thiophenes and

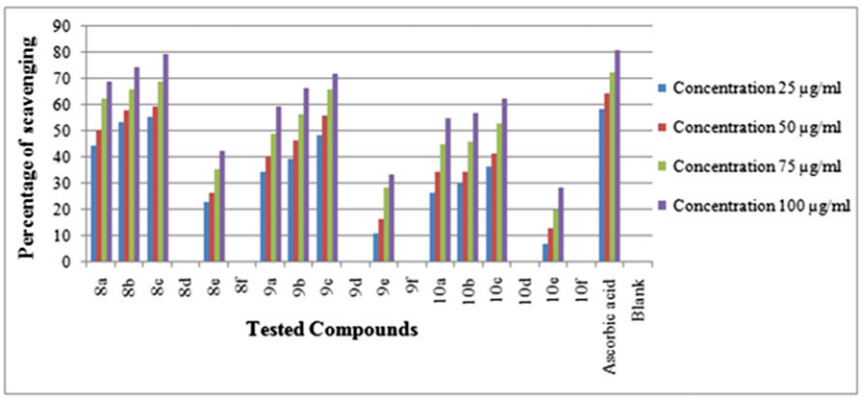


Figure 1. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity of the compounds **8**–**10.** [Color figure can be viewed at wileyonlinelibrary.com]

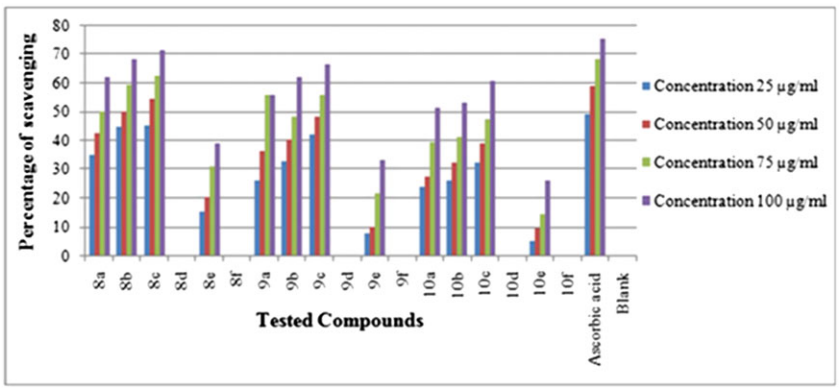


Figure 2. Hydrogen peroxide (H_2O_2) radical scavenging activity of the compounds **8**–**10.** [Color figure can be viewed at wileyonlinelibrary.com]

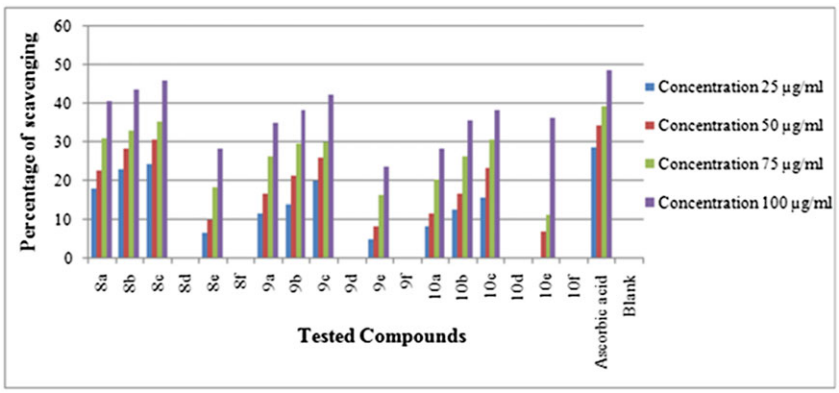


Figure 3. Nitric oxide (NO) radical scavenging activity of the compounds **8**–**10.** [Color figure can be viewed at wileyonlinelibrary.com]

thiazolyl thiophenes displayed higher radical scavenging activity than imidazolyl thiophenes. In general, it was observed that unsubstituted, methyl, and methoxy substituted compounds displayed higher radical scavenging than the chloro, bromo, and nitro substituted compounds.

CONCLUSIONS

A new class of heterocycles-oxazolyl thiophene carboxamides, thiazolyl thiophene carboxamides, and imidazolyl thiophene carboxamides were synthesized from the simple substrates 4-aryloxazol-2-amine, 4-arylthiazol-2-amine, 4-aryl-1*H*-imidazol-2-amine, and 5-chlorothiophene-2-carbonyl chloride adopting conventional and ultrasonication methodologies. Indeed, the reaction proceeded in shorter reaction times with higher yields under ultrasonication than conventional method. The structures of all compounds were characterized by IR, ^{1}HNMR, ^{13}C NMR, and mass spectral data and also evaluated for antioxidant activity. Among all the tested compounds, methoxy substituted oxazolyl thiophene carboxamide displayed promising antioxidant activity. Besides, amido linked thiazolyl thiophenes exhibited comparatively higher radical scavenging activity than the imidazolyl thiophenes. It was observed that compounds having electron donating groups showed greater antioxidant activity than the compounds having electron withdrawing groups.

EXPERIMENTAL

General. Melting points were determined in open capillaries on a Mel-Temp apparatus (Ft-IR spectrometer-Thermo Electron Scientific Instruments LLC, Madison, WI) and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (silica gel H, BDH, hexane/ethyl acetate, 3:1). The IR spectra were recorded on a Thermo Nicolet IR 200 FT–IR spectrometer (Darmstadt, Germany) as KBr pellets, and the wave numbers were given in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded in hexadeuterated dimethyl sulfoxide (DMSO-d_6) on a Bruker spectrometer (Germany) operating at 400 and 100 MHz. All chemical shifts are reported in δ (ppm) using tetramethylsilane as an internal standard. High-resolution mass spectra were recorded on Micromass Q-TOF spectrometer (Woburn, MA) using electrospray ionization. The antioxidant activity was carried out by measuring the absorbance of the test solutions using UV–Visible spectrophotometer, Shimadzu UV-2450 (Shimadzu, Tokyo, Japan). The microanalyses were determined using Perkin-Elmer 240C elemental analyzer (Waltham, MA). Ultrasonication was performed in a Bandelin (Berlin, Germany) sonorex RK 102 H ultrasonic bath operating at a frequency of 46 KHz.

General procedure for the synthesis of 5-chloro-*N*-(4-aryloxazol-2-yl)thiophene-2-carboxamide (8) / 5-chloro-*N*-(4-arylthiazol-2-yl) thiophene-2-carboxamide (9) / 5-chloro-*N*-(4-aryl-1*H*-imidazol-2-yl)thiophene-2-carboxamide (10). ***Conventional method.*** To a stirred solution of compound **2**/**3**/**5** (0.642 g, 1 mmol) in tetrahydrofuran (5 mL), 10% NaOH (10 mL) was added. To this, 5-chlorothiophene-2-carbonyl chloride (**7**) (0.513 g, 0.8 mmol) was added portion-wise while stirring at room temperature and continued the stirring for 3–6 h at the same temperature. Then, dil. HCl was slowly added to the reaction mixture until pH 2. The resultant gummy substance was purified by passing through a column of silica gel (60–120 mesh) using hexane-ethyl acetate (3:1) as eluent.

Ultrasound irradiation method. To a solution of compound **2**/**3**/**5** (0.642 g, 1 mmol) in tetrahydrofuran (3 mL), 10% NaOH (10 mL) was added. Then, 5-chlorothiophene-2-carbonyl chloride (**7**) (0.513 g, 0.8 mmol) was added to the contents of the flask and subjected to ultrasound irradiation at a frequency of 46 KHz for 20–30 min at room temperature. Then, dil. HCl was slowly added to the reaction mixture until pH 2. The resultant gummy substance was purified by column chromatography (silica gel, 60–120 mesh) using hexane-ethyl acetate (3:1) as eluent.

5-Chloro-N-(4-phenyloxazol-2-yl)thiophene-2-carboxamide (8a). Mp 147–149°C; IR (KBr cm^{-1}): 3,382 (NH), 1,674 (C═O), 1,626 (C═C), 1,575 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.88 (d, J = 4 Hz, 1H, C_4'─H), 7.53–7.86 (m, 6H, Ar─H, C_5─H), 8.10 (d, J = 4 Hz, 1H, C_3'─H), 9.25 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 126.7, 129.1, 131.2, 132.4, 133.7, 137.9, 140.3, 140.6, 141.5, 150.1, 151.8, 163.7 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 327.7370 [M + Na]. *Anal*. Calcd. for $C_{14}H_9ClN_2O_2S$: C 55.18; H 2.98; N 9.19. Found: C 55.29; H 3.00; N 9.39%.

5-Chloro-N-(4-(4-methylphenyl)oxazol-2-yl)thiophene-2-carboxamide (8b). Mp 155–157°C; IR (KBr cm^{-1}): 3,365 (NH), 1,654 (C═O), 1,638 (C═C), 1,563 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, Ar─CH_3), 6.81 (d, J = 3.6 Hz, 1H, C_4'─H), 7.23–7.69 (m, 5H, Ar─H, C_5─H), 8.05 (d, J = 3.6 Hz, 1H, C_3'─H), 9.32 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.2 (Ar─CH_3), 126.4, 128.7, 129.9, 131.1, 132.9, 137.5, 139.7, 140.5, 141.8, 143.5, 152.2, 164.9 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 341.7641 [M + Na]. *Anal*. Calcd. for $C_{15}H_{11}ClN_2O_2S$: C 56.52; H 3.48; N 8.79. Found: C 56.65; H 3.52; N 9.03%.

5-Chloro-N-(4-(4-methoxyphenyl)oxazol-2-yl)thiophene-2-carboxamide (8c). Mp 162–164°C; IR (KBr cm^{-1}): 3,389 (NH), 1,687 (C═O), 1,634 (C═C), 1,566 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81 (s, 3H, Ar─OCH_3), 6.79 (d, J = 3.8 Hz, 1H, C_4′─H), 7.01–7.67 (m, 5H, Ar─H, C_5─H), 8.03 (d, J = 3.8 Hz, 1H, C_3'─H), 9.29 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.6 (Ar─OCH_3), 139.2, 126.1, 127.4, 128.9, 129.4, 130.7, 136.1, 139.3, 140.5, 142.8, 151.7, 165.3 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 357.7645 [M + Na]. *Anal*. Calcd. for

$C_{15}H_{11}ClN_2O_3S$: C 53.82; H 3.31; N 8.37. Found: C 53.92; H 3.30; N 8.46%.

5-Chloro-N-(4-(4-chlorophenyl)oxazol-2-yl)thiophene-2-carboxamide (8d). Mp 167–169°C. IR (KBr cm^{-1}): 3,371 (NH), 1,648 (C═O), 1,639 (C═C), 1,553 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 7.10 (d, J = 3.7 Hz, 1H, C_4'─H), 7.57–7.98 (m, 5H, Ar─H, C_5─H), 8.02 (d, J = 3.7 Hz, 1H, C_3'─H), 9.42 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 128.3, 130.7, 131.9, 132.8, 133.6, 139.4, 142.1, 142.9, 143.2, 145.1, 154.3, 165.7 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 362.1786 [M + Na]. *Anal*. Calcd. for $C_{14}H_8Cl_2N_2O_2S$: C 49.58; H 2.38; N 8.26. Found: C 49.66; H 2.39; N 8.33%.

N-(4-(4-Bromophenyl)oxazol-2-yl)-5-chlorothiophene-2-carboxamide (8e). Mp 170–172°C. IR (KBr cm^{-1}): 3,385 (NH), 1,682 (C═O), 1,642 (C═C), 1,572 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 7.07 (d, J = 3.9 Hz, 1H, C_4'─H), 7.55–7.86 (m, 5H, Ar─H, C_5─H), 8.19 (d, J = 3.9 Hz, 1H, C_3'─H), 9.38 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.8, 130.6, 131.1, 131.9, 132.9, 138.5, 140.1, 141.9, 142.8, 144.3, 153.2, 164.9 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 404.6346 [M + Na]. *Anal*. Calcd. for $C_{14}H_8BrClN_2O_2S$: C 43.83; H 2.10; N 7.30. Found: C 43.75; H 2.12; N 7.45%.

5-Chloro-N-(4-(4-nitrophenyl)oxazol-2-yl)thiophene-2-carboxamide (8f). Mp 160–162°C; IR (KBr cm^{-1}): 3,392 (NH), 1,687 (C═O), 1,645 (C═C), 1,569 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 7.15 (d, J = 4 Hz, 1H, C_4'─H), 7.69–8.14 (m, 5H, Ar─H, C_5─H), 8.27 (d, J = 4 Hz, 1H, C_3'─H), 9.40 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 129.3, 132.4, 133.5, 134.7, 135.1, 139.6, 142.9, 143.7, 144.2, 145.4, 155.6, 166.2 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 372.7354 [M + Na]. *Anal*. Calcd. for $C_{14}H_8ClN_3O_4S$: C 48.08; H 2.31; N 12.01. Found: C 48.20; H 2.34; N 12.23%.

5-Chloro-N-(4-phenylthiazol-2-yl)thiophene-2-carboxamide (9a). Mp 158–160°C; IR (KBr cm^{-1}): 3,292 (NH), 1,676 (C═O), 1,633 (C═C), 1,569 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 6.83 (d, J = 4 Hz, 1H, C_4'─H), 7.39–7.83 (m, 6H, Ar─H, C_5─H), 8.06 (d, J = 4 Hz, 1H, C_3'─H), 9.36 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 125.2, 128.6, 129.4, 129.9, 130.3, 136.7, 139.1, 139.8, 140.7, 142.9, 151.5, 162.2 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 343.7976 [M + Na]. *Anal*. Calcd. for $C_{14}H_9ClN_2OS_2$: C 52.42; H 2.83; N 8.73. Found: C 52.51; H 2.84; N 8.91%.

5-Chloro-N-(4-(4-methylphenyl)thiazol-2-yl)thiophene-2-carboxamide (9b). Mp 164–166°C; IR (KBr cm^{-1}): 3,272 (NH), 1,686 (C═O), 1,643 (C═C), 1,577 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, Ar─CH_3), 6.76 (d, J = 3.6 Hz, 1H, C_4'─H), 7.26–7.61 (m, 5H, Ar─H, C_5─H), 7.93 (d, J = 3.6 Hz, 1H, C_3'-H), 9.47 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.4 (Ar─CH_3), 124.1, 127.4, 128.3, 129.2, 129.6, 129.8 136.5, 139.8, 140.3, 142.7, 151.4, 162.6 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: (*m/z*) 357.8267 [M + Na]. *Anal*. Calcd. for $C_{15}H_{11}ClN_2OS_2$: C 53.81; H 3.31; N 8.37. Found: C 53.81; H 3.31; N 8.37%.

5-Chloro-N-(4-(4-methoxyphenyl)thiazol-2-yl)thiophene-2-carboxamide (9c). Mp 173–175°C; IR (KBr cm^{-1}): 3,265 (NH), 1,684 (C═O), 1,639 (C═C), 1,567 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 3.79 (s, 3H, Ar─OCH_3), 6.74 (d, J = 3.8 Hz, 1H, C_4'─H), 7.03–7.59 (m, 5H, Ar─H, C_5─H), 7.91 (d, J = 3.8 Hz, 1H, C_3'─H), 9.39 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.8 (Ar─OCH_3), 123.5, 125.4, 127.8, 128.9, 129.3, 135.6, 138.3, 138.7, 139.1, 141.4, 149.8, 162.7 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 373.8235 [M + Na]. *Anal. Calcd*. for $C_{15}H_{11}ClN_2O_2S_2$: C 51.35; H 3.16; N 7.98. Found: C 51.45; H 3.14; N 8.19%.

5-Chloro-N-(4-(4-chlorophenyl)thiazol-2-yl)thiophene-2-carboxamide (9d). Mp 177–178°C; IR (KBr cm^{-1}): 3,254 (NH), 1,667 (C═O), 1,633 (C═C), 1,559 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 7.09 (d, J = 3.7 Hz, 1H, C_4'─H), 7.54–8.04 (m, 5H, Ar─H, C_5─H), 8.07 (d, J = 3.7 Hz, 1H, C_3'─H), 9.46 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.2, 129.6, 131.8, 132.4, 132.7, 137.9, 140.1, 141.6, 142.8, 144.6, 153.9, 164.5 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 378.2417 [M + Na]. *Anal. Calcd*. for $C_{14}H_8Cl_2N_2OS_2$: C 47.33; H 2.27; N 7.89. Found: C 47.41; H 2.28; N 8.06%.

N-(4-(4-Bromophenyl)thiazol-2-yl)-5-chlorothiophene-2-carboxamide (9e). Mp 184–186°C; IR (KBr cm^{-1}): 3,259 (NH), 1,675 (C═O), 1,638 (C═C), 1,561 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 7.02 (d, J = 4.2 Hz, 1H, C_4'─H), 7.55–7.86 (m, 5H, Ar─H, C_5─H), 8.17 (d, J = 4.2 Hz, 1H, C_3'─H), 9.42 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 126.7, 129.4, 130.3, 130.9, 131.1, 136.5, 139.1, 139.9, 140.8, 142.8, 151.4, 163.7 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 422.6957 [M + Na]. *Anal. Calcd*. for $C_{14}H_8BrClN_2OS_2$: C 42.07; H 2.02; N 7.01. Found: C 42.18; H 2.05; N 7.21%.

5-Chloro-N-(4-(4-nitrophenyl)thiazol-2-yl)thiophene-2-carboxamide (9f). Mp 180–181°C; IR (KBr) (cm^{-1}): 3,249 (NH), 1,665 (C═O), 1,640 (C═C), 1,551 (C═N); ^1H NMR (400 MHz, DMSO-d_6): δ 7.13 (d, J = 4 Hz, 1H, C_4'─H), 7.61–8.11 (m, 5H, Ar─H, C_5─H), 8.19 (d, J = 4 Hz, 1H, C_3'─H), 9.56 (bs, 1H, NHCO) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.5, 131.3, 131.5, 134.2, 135.6, 137.2, 142.3, 144.5, 145.8, 146.3, 158.7, 164.3 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: (*m/z*) 388.7946 [M + Na].

Anal. Calcd. for $C_{14}H_8ClN_3O_3S_2$: C, 45.97; H, 2.20; N, 11.67%. Found: C, 46.04; H, 2.21; N, 11.49%.

5-Chloro-N-(4-phenyl-1H-imidazol-2-yl)thiophene-2-carboxamide (10a). Mp 169–170°C; IR (KBr cm^{-1}): 3,255 (NH), 1,674 (C═O), 1,637 (C═C), 1,569 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.78 (d, J = 3.2 Hz, 1H, C_4'─H), 7.49–7.70 (m, 6H, Ar─H, C_5─H), 7.97 (d, J = 3.2 Hz, 1H, C_3'─H), 9.80 (bs, 1H, NHCO), 11.50 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 124.5, 127.6, 128.1, 129.9, 130.9, 135.7, 138.4, 138.9, 143.4, 144.2, 152.3, 165.8 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 326.7545 [M + Na]. *Anal. Calcd*. for $C_{14}H_{10}ClN_3OS$: C 55.36; H 3.32; N 13.83. Found: C 55.46; H 3.34; N 14.06%.

5-Chloro-N-(4-(4-methylphenyl)-1H-imidazol-2-yl) thiophene-2-carboxamide (10b). Mp 173–175°C; IR (KBr cm^{-1}): 3,264 (NH), 1,681 (C═O), 1,643 (C═C), 1,578 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, Ar─CH_3), 6.73 (d, J = 3.4 Hz, 1H, C_4'─H), 7.15–7.59 (m, 5H, Ar─H, C_5─H), 8.02 (d, J = 3.4 Hz, 1H, C_3'─H), 9.74 (bs, 1H, NHCO), 11.42 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6 (Ar─CH_3), 125.3, 129.6, 130.1, 130.5, 131.7, 133.5, 136.8, 141.4, 142.4, 143.8, 153.2, 164.8 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 340.7819 [M + Na]. *Anal. Calcd*. for $C_{15}H_{12}ClN_3OS$: C 56.69; H 3.81; N 13.22. Found: C 56.82; H 3.86; N 13.47%.

5-Chloro-N-(4-(4-methoxyphenyl)-1H-imidazol-2-yl) thiophene-2-carboxamide (10c). Mp 181–182°C; IR (KBr cm^{-1}): 3,260 (NH), 1,676 (C═O), 1,638 (C═C), 1,575 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (s, 3H, Ar─OCH_3), 6.67 (d, J = 3.9 Hz, 1H, C_4'─H), 7.01–7.89 (m, 5H, Ar─H, C_5─H), 7.92 (d, J = 3.9 Hz, 1H, C_3'─H), 9.78 (bs, 1H, NHCO), 11.68 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.2 (Ar─OCH_3), 125.6, 126.8, 127.9, 129.7, 130.6, 134.2, 137.3, 140.6, 142.8, 143.6, 154.2, 163.9 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 356.7791 [M + Na]. *Anal. Calcd*. for $C_{15}H_{12}ClN_3O_2S$: C 53.98; H 3.62; N 12.59. Found: C 54.07; H 3.64; N 12.81%.

5-Chloro-N-(4-(4-chlorophenyl)-1H-imidazol-2-yl) thiophene-2-carboxamide (10d). Mp 178–179°C; IR (KBr cm^{-1}): 3,248 (NH), 1,664 (C═O), 1,633 (C═C), 1,557 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.12 (d, J = 3.6 Hz, 1H, C_4'─H), 7.43–8.12 (m, 5H, Ar─H, C_5─H), 8.15 (d, J = 3.6 Hz, 1H, C_3'─H), 9.76 (bs, 1H, NHCO), 11.78 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 127.4, 130.9, 131.3, 131.9, 132.7, 137.9, 140.7, 141.4, 142.9, 143.2, 151.6, 162.4 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 361.1952 [M + Na]. *Anal. Calcd*. for $C_{14}H_9Cl_2N_3OS$: C 49.72; H 2.68; N 12.42. Found: C 49.84; H 2.72; N 12.46%.

N-(4-(4-Bromophenyl)-1H-imidazol-2-yl)-5-chlorothiophene-2-carboxamide (10e). Mp 188–190°C; IR (KBr cm^{-1}): 3,252 (NH), 1,673 (C═O), 1,637 (C═C), 1,565 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10 (d, J = 3.9 Hz, 1H, C_4'─H), 7.47–8.06 (m, 5H, Ar─H, C_5─H), 8.16 (d, J = 3.9 Hz, 1H, C_3'─H), 9.80 (bs, 1H, NHCO), 11.45 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 128.2, 130.4, 130.7, 132.6, 139.4, 139.9, 140.4, 141.1, 143.5, 144.5, 150.6, 163.6 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 405.6488 [M + Na]. *Anal. Calcd*. For $C_{14}H_9BrClN_3OS$: C 43.94; H 2.37; N 10.98. Found: C 43.88; H 2.36; N 11.13%.

5-Chloro-N-(4-(4-nitrophenyl)-1H-imidazol-2-yl)thiophene-2-carboxamide (10f). Mp 185–186°C; IR (KBr cm^{-1}): 3,263 (NH), 1,671 (C═O), 1,636 (C═C), 1,567 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.17 (d, J = 3.7 Hz, 1H, C_4'─H), 7.71–8.22 (m, 5H, Ar─H, C_5─H), 8.29 (d, J = 3.7 Hz, 1H, C_3'─H), 9.84 (bs, 1H, NHCO), 11.65 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 128.6, 130.8, 131.5, 134.2, 137.2, 138.6, 141.2, 141.9, 143.2, 145.8, 152.3, 165.4 ppm (C-2, C-4, C-5, C-5′, C-2′, C-3′, C-4′, C═O, aromatic carbons). HRMS: *m/z* 371.7508 [M + Na]. *Anal. Calcd*. For $C_{14}H_9ClN_4O_3S$: C 48.21; H 2.60; N 16.06. Found: C 48.29; H 2.62; N 16.25%.

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