Full Paper

Synthesis and Anticandidal Activity of Azole-Containing Sulfonamides

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Twenty five benzenesulfonamides containing one imidazole or triazole ring, or two imidazole or triazole rings have been synthesized and evaluated as anticandidal agents. The most active compounds were **5c, 6b, 6c, 6e**, and **17b**, which exhibited MIC values of 4.55 – 24.39 mM depending on the clinical isolate. Comparing imidazole to triazole derivatives did not show a clear effect on activity. Compounds containing a *N*-benzyl group also showed no clear evidence on activity given the fact that they have an extra aromatic ring. Secondary sulfonamides, **5l, 5m,** and **5n** showed activities that were proportional to their lipophilicity. The activities of *N*-aryl-substituted derivatives **5j, 5k**, **5l, 5m, 5n**, and **6j** were also proportional to their lipophilicity. Halogenation enhanced the activity as a result of improvement of lipophilicity. The presence of two imidazole or triazole rings in the same compound did not show a clear enhancement of activity.

Keywords: Anticandidal activity / Antifungal activity / Azoles / Benzenesulfonamides

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Introduction

The recent years have witnessed a dramatic increase in the frequency of systemic fungal infections [1 – 3], with *Candida albicans* being the major pathogen [4]. This is mainly due to the proliferation of AIDS, increased use of cancer chemotherapy, and immunosuppressive therapy for organ transplantation [1, 5 – 8]. The increase in fungal infections was accompanied by an increased number of therapeutic failures especially in candidal infections in large part due to an increase in drug-resistant strains. Consequently, it is urgent to develop new effective anticandidal agents [5, 6, 8 – 10]. Azole antifungal agents such as ketoconazole, voriconazole, and posaconazole, which inhibit fungal *CYP-450 14α-demethylase*, are among the most researched agents with respect to their pharmacology and chemistry [11, 12]. In our quest to develop a new scaffold of antifungal azoles, compound **1** (Fig. 1) was synthesized in our lab and was found to posses modest anticandidal activity with an of MIC = 32 μg/mL [13]. In this work, we report the synthesis and anticandidal evaluation of a series of analogs of compound **1** with the general formulae shown in Fig. 1.

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Results and discussion

Synthesis

The target compounds can be divided into three groups. Group 1 contains compounds **5a – n** and compounds **6b, 6c, 6h, 6e**, and **6j**, Group 2 contains compounds **11** and **12**, and group 3 contains compounds **16a – 17b**. The synthesis of the compounds in group 1 is depicted in Scheme 1. In general, 3-nitrobenzenesulfonyl chloride was treated with the appropriate amine in the presence of triethylamine as a base [14, 15]. When the amine was either aniline or benzylamine, pyridine, a milder base, was used to obtain the monosulfonated product. Monosulfonation of *m*-chloroaniline was only possible in a biphasic mixture of an ethyl acetate layer containing the

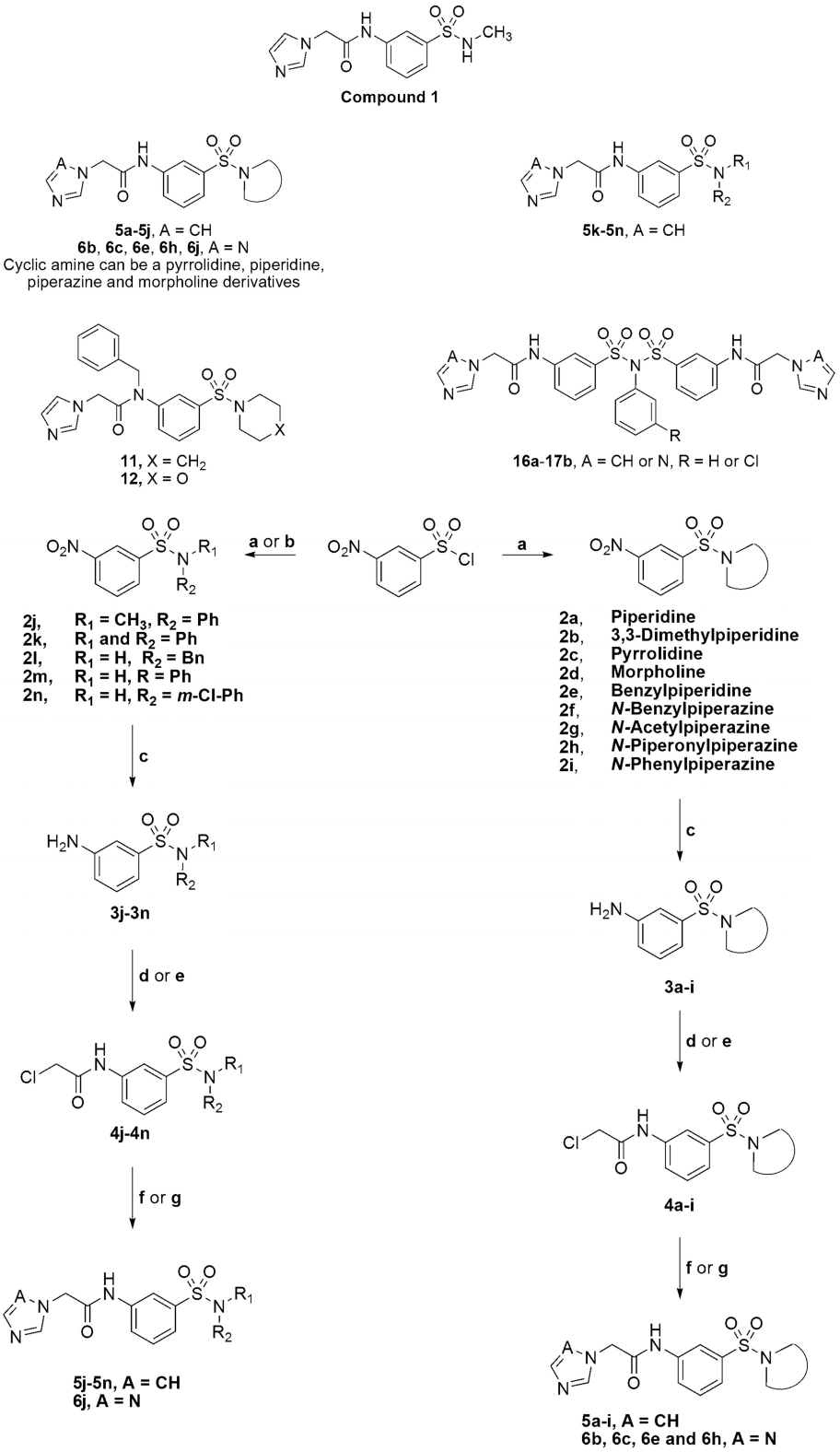
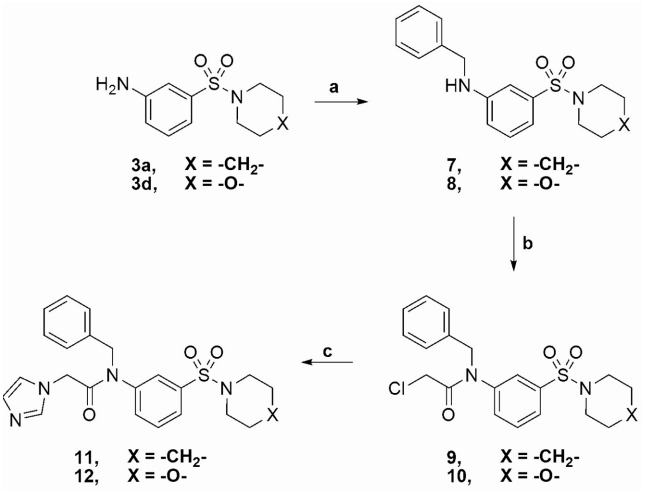


Figure 1. The structure of compound **1** and the chemical formula of proposed compounds.

Reagents and conditions: A HNR_1R_2, Et_3N or pyridine, CH_2Cl_2; (b) 3-Chloroaniline, $NaHCO_3$, H_2O/ethyl acetate; (c) Fe(0), $FeSO_4$, H_2O/EtOH or H_2O/MeOH, reflux; (d) Chloroacetyl chloride, Et_3N, CH_2Cl_2; (e) Chloroacetyl chloride, and K_2CO_3 or $NaHCO_3$, H_2O/ethyl acetate; (f) Imidazole or triazole, K_2CO_3, DMF; (g) Imidazole or triazole, K_2CO_3, NaI, acetone.

Scheme 1. Synthesis of target compounds **5a–n**, **6b**, **6c**, **6f**, **6i**, and **6j**.



Reagents and conditions: (a) Benzyl bromide, K_2CO_3, DMF; (b) Chloroacetyl chloride, Et_3N, CH_2Cl_2; (c) Imidazole, K_2CO_3, DMF.

Scheme 2. Synthesis of compounds **11** and **12**.

sulfonylchloride and excess *m*-chloroaniline and a water layer containing sodium bicarbonate. The resultant nitrobenzenesulfonamides **2a–n** were then reduced using metallic iron and ferrous sulfate in water/ethanol or water/methanol to afford the desired aromatic amines **3a–m** [13, 16–20]. These aminobenzenesulfonamides were then coupled with chloroacetyl chloride either in dichloromethane in the presence of triethylamine, or in a biphasic mixture of water/ethyl acetate in the presence of potassium carbonate to obtain the α-chloroacetamides **4a–m** or in the presence of sodium bicarbonate to obtain **4n** [21–24]. Finally, these α-chloroacetamides were treated with either imidazole or triazole in the presence of potassium carbonate in either dimethylformamide or acetone. When acetone was used, sodium iodide was added to the mixture to facilitate the reaction.

The synthesis of group 2, compounds **11** and **12**, is illustrated in Scheme 2. Alkylation of the amines **3a** and **3d** with benzyl bromide in the presence of potassium carbonate afforded *N*-benzylamines **7** and **8** in modest yields. Chloroacetylation followed by coupling with imidazole or triazole was done in a manner analogous to group 1 to afford compounds **11** and **12** in good yields.

The synthesis of group 3, compounds **16a–17b**, is shown in Scheme 3. Two equivalents of 3-nitrobenzensulfonyl chloride were treated with one equivalent of either aniline or *m*-chloroaniline in the presence of excess triethylamine which afforded the disulfonated intermediates **13a** and **13b** in good yields. In analogy to group 1, these nitrobenzenesulfonamides were reduced to amines **14a** and **14b**, and then treated with chloroacetyl chloride to afford chlorides **15a** and **15b** that were reacted with imidazole or triazole to give compounds **16a, 16b, 17a**, and **17b** in modest yields.

Anticandidal activity

The *in vitro* anticandidal activities of the synthesized compounds were evaluated against four clinical isolates of *Candida albicans* (C1–C4). Fluconazole was used as the reference antifungal agent. Susceptibility testing was performed according to the M27-A2 macrodilution standard method of the National Committee for Clinical Laboratory Standards (NCCLS) [25]. Because of the very low water solubility of the compounds under investigation, the NCCLS method was modified by increasing the concentration of DMSO and the use of Tween 80. The final concentration of DMSO was 4% and that of Tween 80 was 0.05%. Such modifications have been reported in the literature previously, in addition to the use of dilute hydrochloric acid or acetone as co-solvent [26]. Positive and negative controls as well as dilutions of the reference antifungal fluconazole were included in every run. The results were recorded after 24 h of incubation at 35°C.

The MIC values (in μg/mL and mM) for the synthesized compounds against *C. albicans* are summarized in Table 1. The most active compounds were **5c, 6b, 6c, 6e**, and **17b** which exhibited MIC values of 4.55–24.39 mM, which are comparable to the positive control; fluconazole had a MIC of 3.27-13.06 mM. On the other hand, compounds **5a, 5b, 5d, 5e, 5g, 5h, 5k, 5n, 6h, 11**, and **16b** were moderately active and some even showed MIC values as low as 4.13–10.63 mM against some of the isolates. At the same time, none of them had an MIC above 45.92 mM. Finally, compounds **5f, 5m, 12, 16a**, and **17a** showed MIC >50 mM against all strains and were considered to be inactive.

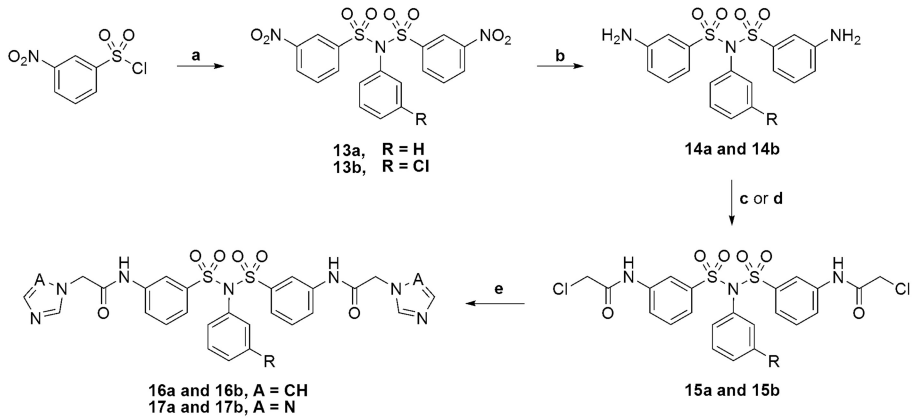
The triazole derivatives did not show a definitive trend of superior activity compared to their imidazole counterparts as can be seen by comparing the pairs **5b** and **6b, 5c** and **6c, 5e** and **6e, 5h** and **6h**, **16a** and **17a**, and 1**6b** and **17b**. The highest difference in MIC was for compound **5e** 36.48 mM (against isolate C-4) compared to that of **6e**, 4.55 mM (against the same isolate).

There was no clear evidence for the effect of *N*-benzylation of the amide on anticandidal activity. Actually, when comparing compound **5a** with its benzylated analog, compound **11**, it can be seen that there is 2–4 folds enhancement in activity for clinical isolates C-1 and C-2 after benzylation. On the contrary, there was a clear drop in activity upon benzylation of compound **5d**.

The secondary sulfonamides **5l, 5m**, and **5n** show activities that are proportional to their lipophilicity. The least lipophilic, **5m,** was evidently much less active than the two more lipophilic compounds **5l** and **5n**.

Table 1. The *in-vitro* anticandidal activity of the synthesized compounds against *Candida albicans* isolates C1-C4 (MIC in μg/mL and mM).

Compound	MIC for Candida albicans							
	C-1		C-2		C-3		C-4	
	(μg/mL)	(mM)	(μg/mL)	(mM)	(μg/mL)	(mM)	(μg/mL)	(mM)
1	32	108.72	32	108.72	32	108.72	32	108.72
2e	>32	>88.78	>32	>88.78	>32	>88.78	>32	>88.78
3e	>32	>96.84	>32	>96.84	>32	>96.84	>32	>96.84
5a	16	45.92	16	45.92	8	22.96	4	11.48
5b	8	21.25	16	42.50	8	21.25	4	10.63
5c	4	11.96	8	23.92	4	11.96	4	11.96
5d	8	22.83	4	11.42	8	22.83	8	22.83
5e	16	36.48	8	18.24	16	36.48	16	36.48
5f	>32	>72.81	32	72.81	>32	>72.81	>32	>72.81
5g	16	40.87	16	40.87	16	40.87	8	20.44
5h	8	16.54	8	16.54	4	8.27	8	16.54
5i	>32	>75.21	32	75.21	4	9.40	4	9.40
5j	>32	>86.39	4	10.80	4	10.80	32	86.39
5k	8	19.96	8	19.96	8	19.96	4	9.98
5l	8	21.60	16	43.19	16	43.19	16	43.19
5m	>32	>89.54	>32	>89.54	>32	>89.54	>32	>89.54
5n	4	10.23	4	10.23	16	40.94	8	20.47
6b	2	5.30	2	5.30	8	21.19	4	10.60
6c	2	5.96	2	5.96	8	23.85	4	11.93
6e	4	9.10	4	9.10	8	18.20	2	4.55
6h	8	16.51	8	16.51	8	16.51	2	4.13
6j	>32	>86.16	8	21.54	16	43.08	32	86.16
11	4	9.12	8	18.24	8	18.24	4	9.12
12	>32	>72.67	>32	>72.67	>32	>72.67	>32	>72.67
16a	>32	>51.64	>32	>51.64	>32	>51.64	>32	>51.64
16b	8	12.23	8	12.23	8	12.23	16	24.46
17a	>32	>51.58	>32	>51.58	>32	>51.58	>32	>51.58
17b	16	24.39	16	24.39	4	6.10	4	6.10
Fluconazole	4	13.06	2	6.53	1	3.27	2	6.53



Reagents and conditions: (a) Aniline or *m*-chloroaniline, Et_3N, CH_2Cl_2; (b) Fe(0), $FeSO_4$, H_2O/EtOH, reflux; (c) Chloroacetyl chloride, Et_3N, CH_2Cl_2; (d) Chloroacetyl chloride, $NaHCO_3$, H_2O/ethyl acetate; (e) Imidazole or triazole, K_2CO_3, NaI, acetone or DMF.

Scheme 3. Synthesis of compounds **16a**, **16b**, **17a**, and **17b**.

With regard to *N*-aryl-substituted sulfonamides, **5j, 5k, 5l, 5m, 5n**, and **6j**, it can be seen that enhancement of lipophilicity also leads to an improvement of activity.

Comparing the halogenated compounds **5n**, **16b**, and **17b** with their non-halogenated analogues **5m, 16a**, and **17a** give a clear indication that halogenation increases

anticandidal activity which can be also linked to an improvement in lipophilicity.

It was interesting to see the effect of the presence of two imidazole or triazole rings on the anticandidal activity. Unfortunately, the presence of two iron-chelating groups in the symmetrical scaffold presented in this work, did not improve activity, rather, it seems to have a negative effect as can be seen by comparing **5n** with **16b** or **17b**.

Finally, it can be concluded that a novel series of potential anticandidal agents has been synthesized. The anticandidal evaluation revealed that some of these compounds have potencies comparable to the reference anticandidal agent, fluconazole, and hence, represent good candidates for further developments. In general, further investigation is needed to reveal other structure-activity relationship aspects which may lead to an increase in the activity and selectivity.

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The authors have declared no conflict of interest.

Experimental

Material and chemicals

Bulk solvents were purchased through local vendors. Reagent grade and fine chemicals were obtained from Aldrich Chemical Company (St. Louis, MO, USA; www.sigmaaldrich.com), Acros Organics (Geel, Belgium; www.acros.com) and Scharlau Chemie (Barcelona, Spain; www.scharlau.com). Melting points were determined using a digital Stuart Scientific melting point apparatus, (Stuart Scientific, Stone, Staffordshire, UK). Atmospheric Pressure Chemical Ionization (APCI) mass spectra were obtained using Agilent 1100 series LC-MS, (Agilent, Palo Alto, CA, USA). IR spectra were recorded on Niclolet Avatar 360 FT-IR, (Nicolet, Madison, WI, USA), using KBr disks. Absorptions are reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Bruker Advance Ultrashield 400 MHz instrument, (Bruker, Switzerland) and are reported in ppm relative to automatic calibration to the residual proton peak of the solvents used namely $CDCl_3$ or DMSO-d_6.

*General procedures for the synthesis of compounds **2a–2n***

Methods A: To a solution of 3-nitrobenzenesulfonyl chloride (1 equiv.) in dichloromethane (150 mL), the amine (1 equiv.) and triethylamine (1 equiv.) were added and the reaction mixture was allowed to stir for two hours. The organic layer was washed with water, followed by 2 M HCl solution, dried over $MgSO_4$, and then the solvent was evaporated. The solid residue was crystallized from the appropriate solvent to afford the desired sulfonamide.

Methods B: Same as method A, but washing was done with saturated sodium bicarbonate solution instead of 2 M HCl.

Methods C: Same as method A, but pyridine was used instead of triethylamine.

*1-(3-Nitrophenylsulfonyl)piperidine **2a***

Method A: Yield was 56% from ethanol. Mp. 124–124°C; IR (KBr): 3099, 1604, 1533, 1351 cm^{-1}; LC-MS (APCI) m/z: 271 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.46 (m, 2H, piperidine *N*-C-C-CH_2); 1.67 (m, 4H, piperidine CH_2-C-N-C-CH_2); 3.07 (m, 4H, piperidine CH_2-N-CH_2); 7.78 (t, 1H, Ar-*H*, *J* = 8.0 Hz); 8.09 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.45 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.58 (s, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.4, 25.1, 47.0, 122.6, 127.1, 130.4, 133.1, 139.0, and 148.3.

*3,3-Dimethyl-1-(3-nitrophenylsulfonyl)piperidine **2b***

Methods A: Yield was 91% from ethanol. Mp. 93–94°C; IR (KBr): 1605, 1533, 1391 cm^{-1}; LC-MS (APCI) m/z: 299 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 6H, piperidine N-C-C(CH_3)$_2$); 1.26 (t, 2H, piperidine N-C-C(CH_3)$_2$-CH_2, *J* = 6.0 Hz); 1.70 (p, 2H, piperidine N-C-CH_2, *J* = 6.0 Hz); 2.71 (s, 2H, piperidine N-CH_2-C(CH_3)$_2$-C); 3.02 (t, 2H, piperidine N-CH_2-C, *J* = 6.0 Hz); 7.78 (t, 1H, Ar-*H*, *J* = 8.0 Hz); 8.08 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.45 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.58 (s, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6, 26.2, 30.8, 36.7, 46.7, 57.3, 122.5, 127.0, 130.4, 133.0, 139.2, and 148.3.

*1-(3-Nitrophenylsulfonyl)pyrrolidine **2c***

Methods A: Yield was 88.3% from ethanol. Mp. 99–100°C; IR (KBr): 1606, 1524, 1352 cm^{-1}; LC-MS (APCI) m/z: 257 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.83 (m, 4H, pyrrolidine *N*-C-CH_2-CH_2-C); 3.31 (m, 4H, pyrrolidine CH_2-N-CH_2); 7.78 (t, 1H, Ar-*H*, *J* = 8.0 Hz); 8.17 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.45 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.66 (s, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.4, 48.1, 122.4, 127.0, 130.5, 132.9, 139.6 and 148.4.

*1-(3-Nitrophenylsulfonyl)morpholine **2d***

Methods A: Yield was 88.3% from ethyl acetate. Mp. 173–174°C; IR (KBr): 1604, 1525, 1311, 1135 cm^{-1}; LC-MS (APCI) m/z: 273 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.08 (t, 4H, morpholine CH_2-N-CH_2, *J* = 4.7 Hz); 3.78 (t, 4H, morpholine CH_2-O-CH_2, *J* = 4.7 Hz); 7.81 (t, 1H, Ar-*H*, *J* = 8.0 Hz); 8.10 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.50 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.60 (s, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.0, 66.0, 122.8, 127.5, 130.7, 133.2, 137.8, and 148.4.

*1-(3-Nitrophenylsulfonyl)benzylpiperidine **2e***

Methods A: Yield was 43.5% from ethyl acetate/methanol. Mp. 150–151°C; IR (KBr): 1604, 1532, 1364 cm^{-1}; LC-MS (APCI) m/z: 360 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.37 (m, 2H, pyridine, *N*-CH_2-CH_2-CH); 1.50 (m, 1H, piperidine, *N*-CH_2-CH_2-*CH*); 1.73 (d, 2H, piperidine, *N*-CH_2-CH_2, *J* = 12.0 Hz); 2.30 (t, 2H, piperidine, *N*-CH_2-CH_2, *J* = 12.0 Hz); 2.54 (d, 2H, piperidine, *N*-CH_2-CH_2, *J* = 7.0 Hz); 3.85 (d, 2H, phenyl-CH_2-CH, *J* = 12.0 Hz); 7.09 (d, 2H, Ar-H, *J* = 7.0 Hz); 7.19 (m, 1H, Ar-H); 7.26 (m, 2H, Ar-H); 7.76 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.08 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.44 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.58 (s, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.2, 37.22, 42.5, 46.5, 122.6, 126.2, 127.1, 128.3, 129.0, 130.4, 133.1, 139.0, 139.5, and 148.3.

1-(3-Nitrophenylsulfonyl)benzylpiperazine ***2f***

Methods B: Yield was 70% from ethanol. Mp. 145–146°C; IR (KBr): 1592, 1531, 1340, 1175 cm^{-1}; LC-MS (APCI) m/z: 361 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.55 (m, 4H, piperazine CH_2-*N*-(CH_2)$_2$); 3.12 (m, 4H, piperazine S-*N*-(CH_2)$_2$); 3.45 (s, 2H, Ar-CH_2-N); 7.27 (m, 5H, Ar-H); 7.79 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.59 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.47 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.59 (s, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2, 51.9, 62.5, 122.8, 127.3, 127.4, 128.4, 129.4, 130.6, 133.3, 137.2, 138.0, and 148.4.

1-(3-Nitrobenzenesulfonyl)acetylpiperazine ***2g***

Methods A: Yield was 79% from ethanol. Mp. 154–155°C; IR (KBr): 3446, 1638, 1605, 1533, 1131 cm^{-1}; LC-MS (APCI) m/z: 313 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H, -*N*-CO-CH_3); 3.08 (m, 4H, acetyl-*N*-(CH_2)$_2$, *J* = 20.0 Hz); 3.59 (m, 2H, SO_2-*N*-CH_2); 3.73 (m, 2H, SO_2-*N*-CH_2); 7.81 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.08 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.49 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.57 (s,1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.3, 40.6, 45.6, 45.8, 46.1, 122.7, 127.7, 130.8, 133.1, 137.8, 148.4, and 168.9.

1-(3-Nitrophenylsulfonyl)-4-piperonylpiperazine ***2h***

Methods B: Yield was 82.5% from ethanol. Mp. 127–128°C; IR (KBr): 1604, 1503, 1397, 1143 cm^{-1}; LC-MS (APCI) m/z: 405 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.54 (m, 4H, piperazine, CH_2-*N*-(CH_2)$_2$); 3.10 (s, 4H, piperazine, SO_2-*N*-(CH_2)$_2$); 3.42 (s, 2H, Ar-CH_2-N); 5.93 (s, 2H, -O-CH_2-O-); 6.71 (m, 3H, Ar-H); 7.79 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.09 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.48 (d,1H, Ar-H, *J* = 8.0 Hz); 8.60 (s,1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2, 51.8, 62.2, 101.0, 108.0, 109.2, 122.2, 122.8, 127.3, 130.5, 131.2, 133.2, 138.0, 146.8, 147.7, and 148.4.

1-(3-Nitrophenylsulfonyl)phenylpiperazine ***2i***

Methods B: Yield was 92.4% from ethanol. Mp. 153–154°C; IR (KBr): 1600, 1533, 1392, 1171 cm^{-1}; LC-MS (APCI) m/z: 348 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.27 (m, 8H, piperazine CH_2-CH_2-N-CH_2-CH_2); 6.91 (m, 3H, Ar-H); 7.28 (m, 2H, Ar-H); 7.81 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.14 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.49 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.65 (m, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.1, 49.2, 117.0, 121.1, 122.8, 127.5, 129.3, 130.6, 133.2, 138.1, 148.4, and 150.5.

1-(3-Nitrophenylsulfonyl)-N-methylaniline ***2j***

Methods A: Yield was 80% from ethanol. Mp. 99–100°C; IR (KBr): 1608, 1533, 1160 cm^{-1}; LC-MS (APCI) m/z: 293 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.26 (s, 3H, *N*-CH_3); 7.10 (d, 2H, Ar-H, *J* = 6.0 Hz); 7.34 (m, 3H, Ar-H); 7.69 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.83 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.44 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 38.5, 122.8, 126.6, 127.3, 128.1, 129.3, 130.2, 133.3, 138.7, 140.6, and 148.1.

1-(3-Nitrophenylsulfonyl)diphenylamine ***2k***

Methods A: Yield was 21% from ethanol. Mp. 159–160°C; IR (KBr): 1605, 1490, 1358 cm^{-1}; LC-MS (APCI) m/z: 354 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 10H, Ar-H); 7.72 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.03 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.47 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.57 (m, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 122.9, 127.2, 128.2, 128.3, 129.6, 130.3, 133.2, 140.8, 142.5, and 148.2.

1-(3-Nitrophenylsulfonyl)benzylamine ***2l***

Methods C: Yield was 44% from ethanol. Mp. 91–92°C; IR (KBr): 1610, 1495, 1334 cm^{-1}; LC-MS (APCI) m/z: 292 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.26 (d, 2H, phenyl-CH_2-CH, *J* = 6.0 Hz); 5.35 (m, 1H, SO_2-*NH*); 7.25 (m, 5H, Ar-H); 7.68 (t, 1H, Ar-H, *J* = 8.00 Hz); 7.13 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.38 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.60 (m, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 47.4, 122.4, 127.0, 128.0, 128.1, 128.8, 130.4, 132.6, 135.4, 142.5, and 148.1.

1-(3-Nitrophenylsulfonyl)aniline ***2m***

Methods C: Yield was 68% from ethanol. Mp. 123–124°C; IR (KBr): 1606, 1495, 1084 cm^{-1}; LC-MS (APCI) m/z: 278 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.12 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.18 (m, 1H, Ar-H); 7.27 (m, 3H, Ar-H); 7.67 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.08 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.41 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.66 (m, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 122.2, 122.5, 126.4, 127.5, 129.7, 130.4, 132.8, 135.5, 141.1, and 148.2.

1-(3-Nitrophenylsulfonyl)-m-chloroaniline ***2n***

To a solution of 3-nitrobenzenesulfonyl chloride (6g, 27.07 mmol) in ethyl acetate (100 mL), 40 mL of water containing sodium bicarbonate (2.27 g, 27.07 mmol) was added with continuous stirring. Then, *m*-choroaniline (6.84 g, 5.7 mL, 53.61 mmol) in ethyl acetate (20 mL) was added dropwise, and the reaction was allowed to stir overnight. The organic layer was washed with water followed by 2 M HCl solution, and then dried over $MgSO_4$ and the solvent was evaporated. The solid residue was crystallized from methanol to obtain 6.08 g of fine off-white crystals (72%). Mp. 140–141°C; IR (KBr): 1596, 1526, 1162 cm^{-1}; LC-MS (APCI) m/z: 313 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 7.12 (m, 3H, Ar-H); 7.30 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.88 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.16 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.48 (m, 2H, Ar-H); 10.85 (s, 1H, SO_2-*NH*-). ^{13}C-NMR (100 MHz, DMSO): δ 119.3, 120.4, 121.9, 125.1, 128.3, 131.6, 132.0, 133.0, 134.0, 138.9, 141.0, and 148.4.

General procedure for the synthesis of compounds ***3a–3n***

The 3-nitrobenzenesulfonamide **2a–2n** (1 equiv.) was added to methanol/water or ethanol/water (3 : 1 ratio) with heating to dissolve the sulfonamide. Then, a mixture of iron powder (5 equiv.) and ferrous sulfate (1 equiv.) was added in portions and the reaction mixture was maintained at reflux overnight. The reaction mixture was then filtered while hot and the insoluble residue was re-heated with 200 mL methanol and filtered. The combined solvents were then evaporated and the solid residue was crystallized from the appropriate solvent to afford the desired 3-aminobenzenesulfonamide.

1-(3-Aminophenylsulfonyl)piperidine ***3a***

Yield was 60% from ethanol/water. Mp. 114–115°C; IR (KBr): 3474, 3377, 1625, 1600, 1356 cm^{-1}; LC-MS (APCI) m/z: 241 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 2H, piperidine N-C-C-CH_2); 1.63 (m, 4H, piperidine CH_2-C-N-C-CH_2); 2.98 (m, 4H, piperidine CH_2-N-CH_2); 4.00 (s, 2H, Ar-NH_2); 6.85 (dd, 1H, Ar-*H*, *J* = 1.7 and 7.8 Hz); 7.04 (s, 1H, Ar-*H*); 7.08 (d, 1H, Ar-*H*, *J* = 7.8 Hz); 7.27 (t, 1H, Ar-*H*, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.5, 25.2, 47.0, 113.3, 117.2, 118.8, 129.8, 136.9, and 147.2.

3,3-Dimethyl-1-(3-aminophenylsulfonyl)piperidine ***3b***

Yield was 97% from ethanol/water. Mp. 80–81°C; IR (KBr): 3476, 3426, 1629, 1355 cm^{-1}; LC-MS (APCI) m/z: 268 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 6H, piperidine N-C-C(CH_3)$_2$); 1.22 (t, 2H, piperidine N-C-C(CH_3)$_2$-CH_2, *J* = 6.0 Hz); 1.67 (p, 2H, piperidine N-C-CH_2-C, *J* = 6.0 Hz); 2.64 (s, 2H, piperidine N-CH_2-C(CH_3)$_2$-C); 2.94 (t, 2H, piperidine N-CH_2-C, *J* = 6.0 Hz); 3.90 (broad s, 2H, NH_2); 6.85 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 7.07 (m, 1H, Ar-*H*); 7.27 (m, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7, 26.3, 30.7, 36.8, 46.7, 57.4, 113.3, 117.1, 118.8, 129.8, 137.2, and 147.1.

1-(3-Aminophenylsulfonyl)pyrrolidine ***3c***

Yield was 84% from methanol/water. Mp. 155–156°C; IR (KBr): 3463, 3365, 1599, 1325 cm^{-1}; LC-MS (APCI) m/z: 227 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 4H, pyrrolidine *N*-C-CH_2-CH_2-C); 3.25 (s, 4H, pyrrolidine CH_2-N-CH_2); 3.99 (s, 2H, NH_2); 6.86 (ds, 1H, Ar-*H*, *J* = 7.6 Hz); 7.16 (m, 2H, Ar-*H*); 7.28 (m, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.2, 48.0, 113.3, 117.1, 118.8, 129.9, 137.5, and 147.2.

1-(3-Aminophenylsulfonyl)morpholine ***3d***

Yield was 90% from ethanol. Mp. 123–124°C; IR (KBr): 3453, 3367, 1623, 1320, 1106 cm^{-1}; LC-MS (APCI) m/z: 243 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.01 (t, 4H, morpholine CH_2-N-CH_2, *J* = 4.6 Hz); 3.73 (t, 4H, morpholine CH_2-O-CH_2, *J* = 4.6 Hz); 4.02 (s, 2H, Ar-NH_2); 6.88 (dd, 1H, Ar-*H*, *J* = 2.0, 8.0 Hz); 7.03 (t, 1H, Ar-H, *J* = 2.0 Hz); 7.08 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.29 (m, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.1, 66.1, 113.3, 117.3, 119.2, 130.0, 135.7, and 147.4.

1-(3-Aminophenylsulfonyl)benzylpiperidine ***3e***

Yield was 68% from ethanol. Mp. 129–130°C; IR (KBr): 3474, 3381, 1625, 1155 cm^{-1}; LC-MS (APCI) m/z: 331 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 3H, piperidine, *N*-CH_2-CH_2-CH); 1.68 (d, 2H, piperidine, *N*-CH_2-CH_2, *J* = 14.0 Hz); 2.25 (t, 2H, piperidine, *N*-CH_2-, *J* = 11.0 Hz); 2.52 (d, 2H, piperidine, *N*-CH_2, *J* = 7.0 Hz); 3.75 (d, 2H, phenyl-CH_2-*N*-, *J* = 11.0 Hz); 3.95 (s, 2H, Ar-NH_2); 6.84 (d, 1H, Ar-H, *J* = 7.0 Hz); 7.02 (s, 1H, Ar-H); 7.09 (m, 3H, Ar-H); 7.19 (m, 1H, Ar-H); 7.25 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.3, 37.3, 42.6, 46.5, 113.3, 117.2, 118.8, 126.1, 128.3, 129.0, 129.8, 136.8, 139.8, and 147.1.

1-(3-Aminophenylsulfonyl)benzylpiperazine ***3f***

Yield was 90% from ethanol. Mp. 155–156°C; IR (KBr): 3472, 3445, 1624, 1485, 1162 cm^{-1}; LC-MS (APCI) m/z: 332 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.53 (m, 4H, piperazine CH_2-*N*-(CH_2)$_2$); 3.05 (s, 4H, piperazine *S*-*N*-(CH_2)$_2$); 3.49 (s, 2H, Ar-CH_2-N); 3.97 (s, 2H, Ar-NH_2); 6.85 (dd, 1H, Ar-H, *J* = 2.0, 8.0 Hz); 7.02 (s, 1H, Ar-H); 7.09 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.28 (m, 6H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2, 52.1, 62.6, 113.4, 117.4, 119.0, 127.3, 128.3, 129.1, 129.9, 136.2, 137.5, and 147.2.

1-(3-Aminobenzenesulfonyl)acetylpiperazine ***3g***

Yield was 97% from ethanol/water. Mp. 253–254°C; IR (KBr): 3452, 1646, 1480, 1166 cm^{-1}; LC-MS (APCI) m/z: 287 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.92 (s, 3H, CO-CH_3); 2.82 (d, 4H, acetyl-*N*-(CH_2)$_2$, *J* = 19.0 Hz); 3.47 (m, 4H, SO_2-*N*-(CH_2)$_2$; 5.63 (s, 2H, Ar-NH_2); 6.79 (dd, 2H, Ar-H, *J* = 8.0 and 19.0 Hz); 6.87 (s, 1H, Ar-H); 7.22 (t, 1H, Ar-H, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, DMSO): δ 21.5, 45.36, 46.3, 46.5, 112.1, 114.5, 118.5, 129.1, 130.2, 135.5, and 168.9.

1-(3-Aminophenylsulfonyl)-4-piperonylpiperazine ***3h***

Yield was 85% from ethanol/water. Mp. 116–117°C; IR (KBr): 3475, 3384, 1628, 1367, 1398 cm^{-1}; LC-MS (APCI) m/z: 376 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 4H, piperazine, CH_2-*N*-(CH_2)$_2$); 3.03 (s, 4H, piperazine, SO_2-*N*-(CH_2)$_2$); 3.40 (s, 2H, Ar-CH_2-N); 3.97 (s, 2H, Ar-NH_2); 5.93 (s, 2H, -O-CH_2-O-); 6.72 (m, 3H, Ar-H); 6.86 (d, 1H, Ar-H, *J* = 7.6 Hz); 7.02 (s, 1H, Ar-H); 7.08 (d, 1H, Ar-H, *J* = 7.6 Hz); 7.28 (t,1H, Ar-H, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2, 52.0, 62.3, 101.0, 107.9, 109.3, 113.4, 117.4, 119.0, 122.2, 129.9, 131.4, 136.0, 146.8, 147.2, and 147.7.

1-(3-Aminophenylsulfonyl)phenylpiperazine ***3i***

Yield was 82% from ethanol. Mp. 162–163°C; IR (KBr): 3482, 3390, 1627, 1384, 1169 cm^{-1}; LC-MS (APCI) m/z: 317 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.23 (m, 8H, piperazine CH_2-CH_2-N-CH_2-CH_2); 3.97 (s, 2H, Ar-NH_2); 6.90 (m, 4H, Ar-H); 7.08 (m, 1H, Ar-H); 7.15 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.30 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2, 49.2, 113.4, 116.9, 117.4, 119.2, 120.8, 129.3, 130.0, 136.1, 147.2, and 150.7.

1-(3-Aminophenylsulfonyl)-N-methylaniline ***3j***

Yield was 80% from methanol / water. Mp. 110–111°C; IR (KBr): 3469, 3377, 1626, 1593, 1171 cm^{-1}; LC-MS (APCI) m/z: 262 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.19 (s, 3H, *N*-CH_3); 3.89 (s, 2H, Ar-NH_2) 6.87 (m, 3H, Ar-H); 7.23 (m, 6H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 38.2, 113.5, 117.5, 119.0, 126.7, 127.3, 128.8, 129.6, 137.2, 141.7, and 147.0.

1-(3-Aminophenylsulfonyl)diphenylamine ***3k***

Yield was 80% from methanol/water. Mp. 96–97°C; IR (KBr): 3482, 3390, 1618, 1349 cm^{-1}; LC-MS (APCI) m/z: 324 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.87 (broad s, 2H, Ar-NH_2); 6.85 (d, 1H, Ar-H, *J* = 8.0 Hz); 6.97 (s, 1H, Ar-H); 7.07 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.29 (m, 11H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 113.4, 117.4, 118.9, 127.4, 128.4, 129.2, 129.8, 141.4, 141.6, and 147.0.

1-(3-Aminophenylsulfonyl)benzylamine ***3l***

Yield was 79% from chloroform. Mp. 72–73°C; IR (KBr): 3442, 3405, 1632, 1150 cm^{-1}; LC-MS (APCI) m/z: 262 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.88 (broad s, 2H, Ar-NH_2); 4.13 (m, 2H, phenyl-CH_2-NH); 4.86 (s, 1H, SO_2-*NH*); 6.85 (d, 1H, Ar-H, *J* = 7.0 Hz); 7.24 (m, 8H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 47.3, 112.9, 116.7, 119.0, 127.9, 128.7, 130.1, 136.4, 140.5, and 147.3.

1-(3-Aminophenylsulfonyl)aniline ***3m***

Yield was 44% from ethanol. Mp. 126–127°C; IR (KBr): 3409, 3324, 1596, 1155 cm^{-1}; LC-MS (APCI) m/z: 248 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 5.57 (d, 2H, Ar-NH_2, *J* = 8.0 Hz); 6.71 (dd, 1H, Ar-H, *J* = 2.0 and 8.0 Hz); 6.86 (d, 1H, Ar-H, *J* = 8.0 Hz); 6.99 (m, 2H, Ar-H); 7.11 (m, 3H, Ar-H); 7.22 (m, 2H, Ar-H); 10.16 (s, 1H, SO_2-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 111.6, 113.8, 118.0, 120.0, 124.1, 129.5, 130.0, 138.4, 140.6, and 149.7.

1-(3-Aminophenylsulfonyl)-m-chloroaniline ***3n***

Yield was 82% from methanol/water. Mp. 106–107°C; IR (KBr): 3409, 3337, 1637, 1595, 1155 cm^{-1}; LC-MS (APCI) m/z: 282 [M^+]

(100); ^{1}H-NMR (400 MHz, DMSO): δ 5.60 (s, 2H, phenyl-NH_2); 6.72 (m, 1H, Ar-H); 6.87 (m, 1H, Ar-H); 6.98 (m, 8H, Ar-H); 7.11 (m, 6H, Ar-H); 10.44 (s, 1H, SO_2-NH-). ^{13}C-NMR (100 MHz, DMSO): δ 111.4, 113.7, 118.1, 118.3, 119.1, 123.8, 130.2, 131.3, 133.8, 140.1, 140.2, and 149.9.

General procedures for the synthesis of compounds ***4a–4n***

Methods A: To a solution of the amine (1 equiv.) in dichloromethane (40 mL), chloroacetyl chloride (1.5-2 equiv.) was added followed by triethylamine (1 equiv.) and the reaction mixture was allowed to stir overnight. The organic layer was washed with water followed by saturated sodium bicarbonate solution, and then dried over Na_2SO_4. The solvent was evaporated and the residue was crystallized from the appropriate solvent to afford the desired product.

Methods B: To a solution of the amine (1 equiv.) in ethyl acetate (40 mL), water (15 mL) containing potassium carbonate (1 equiv.) was added with continuous stirring. Then, chloroacetyl chloride (1.5 equiv.) in ethyl acetate (10 mL) was added to the reaction dropwise, and the reaction mixture was allowed to stir overnight. Then, the layers were separated and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated, and the solid product was crystallized from the appropriate solvent to afford the desired product.

2-Chloro-N-[3-(piperidinyl-1-sulfonyl)phenyl]acetamide ***4a***

Methods A: Yield was 84% from ethanol. Mp. 101–102°C; IR (KBr): 3337, 1701, 1600, 1335 cm^{-1}; LC-MS (APCI) m/z: 317 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43 (m, 2H, piperidine N-C-C-CH_2); 1.65 (m, 4H, piperidine CH_2-C-N-C-CH_2); 3.02 (m, 4H, piperidine CH_2-N-CH_2); 4.23 (s, 2H, Cl-CH_2-CO); 7.53 (m, 2H, Ar-H); 7.93 (m, 2H, Ar-H); 8.58 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.4, 25.1, 42.9, 47.0, 119.0, 123.9, 124.1, 129.9, 137.2, 137.7, and 164.5.

2-Chloro-N-[3-(3,3-dimethyl-piperidinyl-1-sulfonyl)phenyl]acetamide ***4b***

Methods A: Yield was 74% from ethyl acetate/hexane. Mp. 100–101°C; IR (KBr): 3354, 1682, 1589, 1368 cm^{-1}; LC-MS (APCI) m/z: 345 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 6H, piperidine N-C-C(CH_3)$_2$); 1.23 (t, 2H, piperidine N-C-C(CH_3)$_2$-CH_2, J = 6.0 Hz); 1.68 (p, 2H, piperidine N-C-CH_2-C, J = 6.0 Hz); 2.66 (s, 2H, piperidine N-CH_2-C(CH_3)$_2$-C); 2.97 (t, 2H, piperidine N-CH_2-C, J = 6.0 Hz); 4.22 (s, 2H, Cl-CH_2-CO); 7.52 (ds, 2H, Ar-H, J = 4.92 Hz); 7.86 (s, 1H, Ar-H); 7.60 (m, 1H, Ar-H); 8.60 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6, 26.3, 30.8, 36.7, 42.9, 46.8, 57.4, 118.9, 123.7, 124.1, 129.9, 137.4, 137.7, and 164.5.

2-Chloro-N-[3-(pyrrolidinyl-1-sulfonyl)phenyl]acetamide ***4c***

Method A: Yield was 55% from ethanol. Mp. 84–85°C; IR (KBr): 3322, 1712, 1663, 1196 cm^{-1}; LC-MS (APCI) m/z: 303 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.78 (m, 4H, pyrrolidine N-C-CH_2-CH_2-C); 3.30 (m, 4H, pyrrolidine CH_2-N-CH_2); 4.22 (s, 2H, Cl-CH_2-CO); 7.53 (t, 1H, Ar-H, J = 8.0 Hz); 7.62 (d, 1H, Ar-H, J = 8.0 Hz); 7.96 (m, 2H, Ar-H); 8.60 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.3, 42.9, 48.1, 118.9, 123.7, 124.1, 130.0, 137.6, 137.8, and 164.4.

2-Chloro-N-[3-(morpholinyl-1-sulfonyl)phenyl]acetamide ***4d***

Method B: Yield was 73% from ethanol. Mp. 161–162°C; IR (KBr): 3260, 1678, 1597, 1331, 1110 cm^{-1}; LC-MS (APCI) m/z: 318 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.05 (t, 4H, morpholine CH_2-N-CH_2, J = 4.7 Hz); 3.76 (t, 4H, morpholine CH_2-O-CH_2, J = 4.7 Hz); 4.24 (s, 2H, Cl-CH_2-CO); 7.56 (m, 2H, Ar-H); 7.89(m, 1H, Ar-H); 7.97 (s, 1H, Ar-H); 8.48 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 42.8, 46.0, 66.1, 119.1, 124.1, 124.4, 130.1, 136.2, 137.7, and 164.3.

2-Chloro-N-[3-(benzylpiperidinyl-1-sulfonyl)phenyl]acetamide ***4e***

Method A: Yield was 53% from ethanol. Mp. 109–110°C; IR (KBr): 3301, 1673, 1599, 1155 cm^{-1}; LC-MS (APCI) m/z: 407 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 31.41 (m, 3H, pyridine, N-CH_2-CH_2-CH); 1.70 (d, 2H, pyridine, N-CH_2-CH_2, J = 12.0 Hz); 2.27 (t, 2H, pyridine, N-CH_2-, J = 12.0 Hz); 2.52 (d, 2H, pyridine, N-CH_2, J = 7.0 Hz); 3.79 (d, 2H, phenyl-CH_2-N-, J = 12.0 Hz); 4.22 (s, 2H, Cl-CH_2-CO); 7.09 (d, 2H, Ar-H, J = 7.0 Hz); 7.19 (m, 1H, Ar-H); 7.26 (m, 2H, Ar-H); 7.53 (m, 2H, Ar-H); 7.90 (m, 2H, Ar-H); 8.48 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.3, 37.3, 42.6, 42.8, 46.5, 119.0, 124.0, 124.1, 126.1, 128.3, 129.0, 129.9, 137.1, 137.5, 139.7, and 164.3.

2-Chloro-N-[3-(benzylpiperazinyl-1-sulfonyl)phenyl]acetamide ***4f***

Method B: Yield was 71% from ethanol. Mp. 117–118°C; IR (KBr): 3292, 1671, 1593, 1320, 1161 cm^{-1}; LC-MS (APCI) m/z: 407 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.53 (m, 4H, piperazine CH_2-N-(CH_2)$_2$); 3.07 (s, 4H, piperazine S-N-(CH_2)$_2$); 3.49 (s, 2H, Ar-CH_2-N); 4.22 (s, 2H, Cl-CH_2-CO); 7.27 (m, 5H, Ar-H); 7.52 (m, 2H, Ar-H); 7.92 (m, 2H, Ar-H); 8.52 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 42.8, 46.2, 52.0, 62.6, 119.1, 124.1, 124.2, 127.3, 128.3, 129.1, 130.0, 136.5, 137.4, 147.7, and 164.3.

2-Chloro-N-[3-(acetylpiperazinyl-1-sulfonyl)phenyl]acetamide ***4g***

Method A: Yield was 78% from ethanol. Mp. 173–174°C; IR (KBr): 3262, 1701, 1635, 1380 cm^{-1}; LC-MS (APCI) m/z: 262 [M$^+$] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, -N-CO-CH_3); 3.04 (d, 4H, acetyl-N-(CH_2)$_2$, J = 20.0 Hz); 3.70 (m, 2H, SO_2-N-CH_2); 3.72 (m, 2H, SO_2-N-CH_2); 4.22 (s, 2H, Cl-CH_2-CO); 7.54 (m, 1H, Ar-H); 7.87 (m, 1H, Ar-H); 7.98 (m, 1H, Ar-H); 8.68 (s, 1H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.3, 40.7, 42.9, 45.7, 45.9, 46.2, 119.0, 123.9, 124.5, 130.1, 136.1, 137.9, 164.5, and 169.0.

2-Chloro-N-[3-(4-piperonylpiperazinyl-1-sulfonyl)phenyl]acetamide ***4h***

Method A: Yield was 68% from dichloromethane. Mp. 217–218°C; IR (KBr): 3451, 1690, 1612, 1166 cm^{-1}; LC-MS (APCI) m/z: 451 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 2.79 (m, 2H, piperazine, CH_2-N-CH_2); 3.12 (s, 2H, piperazine, CH_2-N-CH_2); 3.34 (m, 2H, piperazine, SO_2-N-CH_2); 3.74 (m, 2H, piperazine, SO2-N-CH_2); 4.23 (s, 2H, Ar-CH_2-N); 4.35 (s, 2H, Cl-CH_2-CO); 6.05 (s, 2H, -O-CH_2-O-); 6.97 (m, 2H, Ar-H); 7.17 (s, 1H, Ar-H); 7.45 (d, 1H, Ar-H, J = 8.0 Hz); 7.64 (t, 1H, Ar-H, J = 8.0 Hz); 7.90 (d,1H, Ar-H, J = 8.0 Hz); 8.17 (s, 1H, Ar-H); 11.10 (s, 1H, CO-NH). ^{13}C-NMR (100 MHz, DMSO): δ 43.3, 43.9, 49.9, 55.4, 58.7, 101.9, 108.8, 111.6, 118.1, 123.0, 124.3, 126.0, 130.8, 135.3, 140.0, 147.9, 148.7, and 165.8.

2-Chloro-N-[3-(phenylpiperazinyl-1-sulfonyl)phenyl]acetamide ***4i***

Method B: Yield was 37% from ethyl acetate/hexane. Mp. 115–116°C; IR (KBr): 3317, 1669, 1376, 1166 cm^{-1}; LC-MS (APCI) m/z: 394 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.23 (d,s, 8H, piperazine CH_2-CH_2-N-CH_2-CH_2, *J* = 3.6 Hz); 4.23 (s, 2H,Cl-CH_2-CO); 6.90 (m, 3H, Ar-H); 7.27 (m, 2H, Ar-H); 7.57 (m, 2H, Ar-H); 7.89 (d, 1H, Ar-H, *J* = 7.6 Hz); 8.02 (m, 1H, Ar-H); 8.57 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 42.9, 46.2, 49.1, 116.9, 119.1, 120.9, 124.0, 124.4, 129.3, 130.1, 136.3, 137.9, 150.6, and 164.5.

2-Chloro-N-[3-(N-methyanilinyl-1-sulfonyl)phenyl]acetamide ***4j***

Method A: Yield was 77% from methanol. Mp. 93–94°C; IR (KBr): 3286, 1663, 1595, 1170 cm^{-1}; LC-MS (APCI) m/z: 339 [M^+] (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 3H, *N*-CH_3); 4.19 (s, 2H, Cl-CH_2-CO); 7.10 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.28 (m, 4H, Ar-H); 7.43 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.73 (s, 1H, Ar-H); 7.98 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.61 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 38.4, 42.9, 119.1, 124.0, 124.3, 126.8, 127.7, 129.0, 129.7, 137.2, 137.6, 141.1, and 164.6.

2-Chloro-N-[3-(diphenylaminyl-1-sulfonyl)phenyl]acetamide ***4k***

Method B: Yield was 77% from ethyl acetate/hexane. Mp. 97–98°C; IR (KBr): 3318, 1678, 1593, 1076 cm^{-1}; LC-MS (APCI) m/z: 400 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.31 (s, 2H, Cl-CH_2-CO); 7.36 (m, 11H, Ar-H); 7.57 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.93 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.15 (s, 1H, Ar-H); 10.72 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 44.0, 118.1, 123.0, 124.0, 128.2, 128.8, 130.0, 130.6, 139.7, 140.8, 141.4, and 165.7.

2-Chloro-N-[3-(benzylaminyl-1-sulfonyl)phenyl]acetamide ***4l***

Method A: Yield was 56% from ethanol. Mp. 125–126°C; IR (KBr): 3330, 3262, 1711, 1593, 1147 cm^{-1}; LC-MS (APCI) m/z: 336 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 3.99 (m, 2H, phenyl-CH_2-N); 4.30 (s, 2H, Cl-CH_2-CO); 7.25 (m, 5H, Ar-H); 7.54 (m, 2H, Ar-H); 7.77 (d, 1H, Ar-H, *J* = 7.0 Hz); 8.15 (s, 1H, Ar-H); 8.24 (t, 1H, SO_2-*NH*, *J* = 7.0 Hz); 10.65 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 43.9, 46.5, 117.5, 122.1, 123.1, 127.6, 128.0, 128.7, 130.4, 138.0, 139.4, 141.7, and 165.5.

2-Chloro-N-[3-(anilinyl-1-sulfonyl)phenyl]acetamide ***4m***

Method A: Yield was 74% from ethanol. Mp. 132–133°C; IR (KBr): 3340, 1664, 1596, 1407 cm^{-1}; LC-MS (APCI) m/z: 325 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.27 (s, 2H, Cl-CH_2-CO); 7.02 (t, 1H, Ar-H, *J* = 14.0 Hz); 7.09 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.22 (m, 2H, Ar-H); 7.48 (m, 2H, Ar-H); 7.71(d, 1H, Ar-H, *J* = 8.0 Hz); 8.19 (s, 1H, Ar-H); 10.38 (s, 1H, SO_2-*NH*); 10.62 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 43.9, 117.5, 120.5, 122.3, 123.5, 124.6, 129.6, 130.4, 138.0, 139.5, 140.6, and 165.6.

2-Chloro-N-[3-(3-chloroanilinyl-1-sulfonyl)phenyl]acetamide ***4n***

To a solution of 1-(3-aminophenylsulfonyl)-3-chloroaniline (**3**) (2 g, 7.07 mmol) in ethyl acetate (30 mL), water (20 mL) containing sodium bicarbonate (0.59 g, 7.07 mmol) was added with continuous stirring. Then, chloroacetyl chloride (0.6 mL, 0.85 g, 7.54 mmol) in ethyl acetate (10 mL) was added to the reaction dropwise, and the reaction was allowed to stir for five hours. The layers were then separated and the organic layer was washed with 2 M HCl solution followed by water and dried over $MgSO_4$. Then the solvent was evaporated, and the waxy product was purified by chromatography (5% methanol/dichloromethane), to obtain 2.4 g of brown granules (94.5%). Mp. 103–104°C; IR (KBr): 3340, 1662, 1592, 1157 cm^{-1}; LC-MS (APCI) m/z: 358 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.27 (s, 2H, Cl-CH_2-CO); 7.10 (m, 3H, Ar-H); 7.26 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.52 (m, 2H, Ar-H); 7.73 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.23 (s, 1H, Ar-H); 10.66 (m, 1H, CO-*NH*-phenyl). ^{13}C-NMR (100 MHz, DMSO): δ 43.9, 117.5, 118.4, 119.5, 122.2, 123.9, 124.3, 130.5, 131.4, 133.9, 139.6, 139.7, 140.2, and 165.6.

General procedures for the synthesis of compounds ***5a–5n, 6b, 6c, 6h, 6i, and 6j***

Methods A: To a solution of the α-chloroacetamide (1 equiv.) in DMF (15 mL), imidazole or triazole (2–3 equiv.) and potassium carbonate (1 equiv.) were added and the reaction was allowed to stir overnight. Then, brine was added to the reaction mixture with vigorous shaking, and the mixture was placed in the refrigerator overnight to precipitate the product. The precipitate was filtered and the solid was crystallized from the appropriate solvent to give the desired products.

Methods B: To a solution of the a-chloroacetamide (1 equiv.) in acetone (15 mL), imidazole, or triazole (3–4 equiv.), potassium carbonate (1 equiv.) and sodium iodide (1 equiv.) were added consecutively and the reaction mixture was allowed to stir overnight. Then, the solvent was evaporated and the solid residue was dissolved in ethyl acetate and the resultant solution was washed with water. The organic layer was dried over Na_2SO_4 and the solvent was evaporated, the solid residue was crystallized from the appropriate solvent to afford the desired product

2-Imidazol-1-yl-N-[3-(piperidine-1-sulfonyl)phenyl]acetamide ***5a***

Method A: Yield was 46% from ethanol. Mp. 240–241°C; IR (KBr): 3237, 1709, 1596, 1596, 1333 cm^{-1}; LC-MS (APCI) m/z: 348 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.35 (m, 2H, piperidine N-C-C-CH_2); 1.53 (s, 4H, piperidine CH_2-C-N-C-CH_2); 2.87 (m, 4H, piperidine CH_2-N-CH_2); 4.95 (s, 2H, imidazole-CH_2-CO); 6.91 (s, 1H, Ar-*H*); 7.18 (s, 1H, Ar-*H*); 7.42 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 7.61 (m, 2H, Ar-*H*); 7.81 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.08 (s, 1H, Ar-*H*); 10.71 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 23.3, 25.1, 47.1, 49.6, 117.9, 118.0, 122.7, 123.4, 123.5, 130.5, 136.6, 139.7, 139.8, and 166.8.

2-Imidazol-1-yl-N-[3-(3,3-dimethylpiperidinyl-1-sulfonyl)phenyl]acetamide ***5b***

Method A: Yield was 37% from ethanol. Mp. 239–240°C; IR (KBr): 3250, 1702, 1593, 1181 cm^{-1}; LC-MS (APCI) m/z: 377 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 0.91 (s, 6H, piperidine N-C-C-$C(CH_3)_2$); 1.18 (t, 2H, piperidine N-C-C$(CH_3)_2$-CH_2, *J* = 5.8 Hz); 1.59 (m, 2H, piperidine N-C-CH_2-C); 2.54 (s, 2H, piperidine N-CH_2-C$(CH_3)_2$-C); 2.84 (m, 2H, piperidine N-CH_2-C-C); 4.94 (s, 2H, imidazole-CH_2-CO); 6.91 (s, 1H, Ar-*H*); 7.17(s, 1H, Ar-*H*); 7.40 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 7.59 (t, 1H, Ar-*H*, *J* = 8 Hz); 7.64 (s, 1H, Ar-*H*); 7.82 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.04 (s, 1H, Ar-*H*); 10.68 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 21.6, 26.4, 30.8, 36.4, 46.8, 49.6, 57.3, 117.8, 121.2, 122.5, 123.4, 128.4, 130.5, 136.8, 138.8, 139.7, and 166.9.

2-Imidazol-1-yl-N-[3-(pyrrolidinyl-1-sulfonyl)phenyl]acetamide ***5c***

Method A: Yield was 53% from ethanol. Mp. 229 – 230°C; IR (KBr): 3229, 1699, 1608, 1112 cm^{-1}; LC-MS (APCI) m/z: 335 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.65 (m, 4H, pyrrolidine *N*-C-CH_2-CH_2-C); 3.13 (m, 4H, pyrrolidine CH_2-N-CH_2); 4.94 (s, 2H, imidazole-CH_2-CO); 6.91 (s, 1H, Ar-*H*); 7.18 (s, 1H, Ar-*H*); 7.49 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 7.59 (t, 1H, Ar-*H*, *J* = 8.0 Hz); 7.64 (s, 1H, Ar-*H*); 7.81 (d, 1H, Ar-*H*, *J* = 8.0 Hz); 8.14 (s, 1H, Ar-*H*); 10.69 (s,1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 25.2, 48.3, 49.6, 117.9, 121.2, 122.5, 123.4, 128.4, 130.6, 137.1, 138.8, 139.7, and 166.8.

2-Imidazol-1-yl-N-[3-(morpholine-1-sulfonyl)phenyl]acetamide ***5d***

Method A: Yield was 40% from ethanol. Mp. 234 – 235°C; IR (KBr): 3239, 1708, 1607, 1319, 1116 cm^{-1}; LC-MS (APCI) m/z: 335 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 2.86 (t, 4H, morpholine CH_2-N-CH_2, *J* = 4.7 Hz); 3.63 (t, 4H, morpholine CH_2-O-CH_2, *J* = 4.7 Hz); 4.95 (s, 2H, imidazole-CH_2-CO); 6.91 (s, 1H, Ar-H); 7.18 (s, 1H, Ar-H); 7.43 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.63 (m, 2H, Ar-H); 7.83 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.11 (m, 1H,Ar-H); 10.72 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 46.4, 49.7, 65.9, 118.0, 121.1, 122.8, 123.8, 128.4, 130.7, 135.3, 138.8, 139.8, and 166.8.

2-Imidazol-1-yl-N-[3-(benzylpiperidinyl-1-sulfonyl)phenyl]acetamide ***5e***

Method A: Yield was 96% from methanol. Mp. 211 – 212°C; IR (KBr): 3235, 1706, 1595, 1082 cm^{-1}; LC-MS (APCI) m/z: 439 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.18 (m, 2H, piperidine, *N*-CH_2-CH_2-CH); 1.48 (broad s, 1H, piperidine, *N*-CH_2-CH_2-*CH*); 1.59 (d, 2H, piperidine, *N*-CH_2-CH_2, *J* = 12.0 Hz); 2.18 (t, 2H, piperidine, *N*-CH_2-, *J* = 12.0 Hz); 2.45 (d, 2H, piperidine, *N*-CH_2, *J* = 8.0 Hz); 3.59 (d, 2H, phenyl-CH_2-*N*-, *J* = 12.0 Hz); 4.93 (s, 2H, imidazole-CH_2-CO); 6.90 (s, 1H, Ar-H); 7.14 (m, 4H, Ar-H); 7.24 (m, 2H, Ar-H); 7.39 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.59 (m, 2H, Ar-H); 7.81 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.05 (s, 1H, Ar-H); 10.68 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 31.1, 36.6, 42.1, 46.5, 49.6, 118.0, 121.2, 122.7, 123.5, 126.3, 128.5, 128.6, 129.4, 130.5, 136.6, 138.8, 140.0, 140.2, and 167.0.

2-Imidazol-1-yl-N-[3-(benzylpiperazinyl-1-sulfonyl)phenyl]acetamide ***5f***

Method A: Yield was 64% from ethanol. Mp. 228 – 229°C; IR (KBr): 3233, 1701, 1609, 1368, 1161 cm^{-1}; LC-MS (APCI) m/z: 440 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 2.42 (s, 4H, piperazine CH_2-*N*-$(CH_2)_2$); 2.88 (s, 4H, piperazine S-*N*-$(CH_2)_2$); 3.45 (s, 2H, Ar-CH_2-N); 4.94 (s, 2H, imidazole-CH_2-CO); 6.90 (s, 1H, Ar-H); 7.17 (s, 1H, Ar-H); 7.22 (m, 3H, Ar-H); 7.28 (m, 2H, Ar-H); 7.41 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.62 (m, 2H, Ar-H); 7.83 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.08 (s,1H,Ar-H); 10.71 (s,1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 46.5, 49.6, 51.9, 61.8, 118.1, 121.2, 122.9, 123.7, 127.5, 128.4, 128.7, 129.2, 130.6, 135.7, 138.1, 138.8, 139.8, and 166.9.

2-Imidazol-1-yl-N-[3-(acetylpiperazinyl-1-sulfonyl)phenyl]acetamide ***5g***

Method A: Yield after column chromatography (5% methanol/dichloromethane followed by 10% methanol/dichloromethane) was 43%. Mp. 180 – 181°C; IR (KBr): 3405, 1707, 1654, 1154 cm^{-1}; LC-MS (APCI) m/z: 440 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.93 (s, 3H, CO-CH_3); 2.87 (m, 4H, piperazine, CO-*N*-$(CH_2)_2$); 3.50 (m, 4H, piperazine, SO_2-*N*-$(CH_2)_2$); 4.94 (s, 2H, imidazole-CH_2-CO); 6.91 (s, 1H, Ar-H); 7.17 (s, 1H, Ar-H); 7.43 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.63 (m, 2H, Ar-H); 7.81 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.10 (s, 1H, Ar-H); 10.71 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 21.5, 45.3, 46.2, 46.4, 49.6, 118.0, 121.3, 122.8, 123.9, 128.4, 130.7, 135.8, 138.8, 139.9, 166.9, and 168.9.

2-Imidazol-1-yl-N-[3-(4-piperonylpiperazinyl-1-sulfonyl)phenyl]acetamide ***5h***

Method A: Yield was 40% from ethanol. Mp. 222 – 223°C; IR (KBr): 1706, 1608, 1365, 1157 cm^{-1}; LC-MS (APCI) m/z: 483 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 2.39 (s, 4H, piperazine, CH_2-*N*-$(CH_2)_2$); 2.87 (s, 4H, piperazine, SO2-*N*-$(CH_2)_2$); 3.36 (m, 2H, Ar-CH_2-N); 4.95 (s, 2H, imidazole-CH_2-CO); 5.96 (s, 2H, -O-CH_2-O-); 6.80 (m, 4H, Ar-H); 7.18 (s, 1H, Ar-H); 7.41 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.62 (m, 2H, Ar-H); 7.82 (d,1H, Ar-H, *J* = 8.0 Hz); 8.08 (s, 1H, Ar-H); 10.72 (s, 1H, CO-*NH*-Ar). ^{13}C-NMR (100 MHz, DMSO): δ 46.5, 49.5, 51.7, 61.5, 101.2, 108.3, 109.4, 118.1, 121.3, 122.4, 122.8, 123.7, 128.4, 130.6, 131.9, 135.7, 138.9, 139.8, 146.7, 147.7, and 166.9.

2-Imidazol-1-yl-N-[3-(phenylpiperazinyl-1-sulfonyl)phenyl]acetamide ***5i***

Method A: Yield was 85% from methanol. Mp. 230 – 231°C; IR (KBr): 1698, 1618, 1270, 1158 cm^{-1}; LC-MS (APCI) m/z: 426 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 3.01 (s, 4H, piperazine, phenyl-N-$(CH_2)_2$); 3.19 (m, 4H, piperazine, S-N-$(CH_2)_2$); 4.95 (s, 2H, imidazole-CH_2-CO); 6.79 (t, 1H, Ar-H, *J* = 8.0 Hz); 6.89 (m, 3H, Ar-H); 7.19 (m, 3H, Ar-H); 7.47 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.63 (m, 2H, Ar-H); 7.82 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.16 (s, 1H, Ar-H); 10.72 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 46.3, 48.4, 49.6, 116.6, 118.0, 120.2, 121.2, 122.9, 123.8, 128.4, 129.5, 130.7, 135.7, 138.9, 139.9, 150.8, and 166.8.

2-Imidazol-1-yl-N-[3-(N-methylanilinyl-1-sulfonyl)phenyl]acetamide ***5j***

ethod B: Yield was 53% from ethanol/water. Mp. 216 – 217°C; IR (KBr): 3235, 1700, 1609, 1174 cm^{-1}; LC-MS (APCI) m/z: 371 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 3.15 (s, 3H, *N*-CH_3); 4.91 (s, 2H, imidazole-CH_2-CO); 6.89 (s, 1H, Ar-H); 7.12 (m, 4H, Ar-H); 7.30 (m, 3H, Ar-H); 7.51 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.63 (s, 1H, Ar-H); 7.89 (m, 2H, Ar-H); 10.68 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 38.5, 49.6, 118.0, 121.2, 122.6, 123.6, 126.7, 127.8, 128.4, 129.4, 130.4, 137.2, 138.8, 139.6, 141.4, and 166.8.

2-Imidazol-1-yl-N-[3-(diphenylaminyl-1-sulfonyl)phenyl]acetamide ***5k***

Method A: Yield was 71% from ethanol. Mp. 207 – 208°C; IR (KBr): 3437, 1702, 1594, 1109 cm^{-1}; LC-MS (APCI) m/z: 433 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.95 (s, 2H, imidazole-CH_2-CO); 6.92 (s, 1H, Ar-H); 7.18 (s, 1H, Ar-H); 7.35 (m, 11H, Ar-H); 7.56 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.66 (s, 1H, Ar-H); 7.92 (d, 1H, Ar-H, *J* = 8.0 Hz); 8.09 (s, 1H, Ar-H); 10.71 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 49.7, 117.9, 121.2, 122.7, 123.8, 128.3, 128.5, 128.8, 130.0, 130.6, 138.9, 139.9, 140.8, 141.4, and 166.8.

2-Imidazol-1-yl-N-[3-(benzylaminyl-1-sulfonyl)phenyl]acetamide ***5l***

Method A: Yield was 48% from ethanol. Mp. 216 – 217°C; IR (KBr): 1707, 1593, 1153 cm^{-1}; LC-MS (APCI) m/z: 371 [M^+] (100); ^{1}H-NMR

(400 MHz, DMSO): δ 3.97 (d, 2H, phenyl-CH_2-N, J = 7.0 Hz); 4.95 (s, 2H, imidazole-CH_2-CO); 6.93 (s, 1H, Ar-H); 7.25 (m, 7H, Ar-H); 7.53 (m, 2H, Ar-H); 7.69 (s, 1H, Ar-H); 7.75 (d, 1H, Ar-H, J = 7.0 Hz); 8.16 (s, 1H, Ar-H); 8.23 (t, 1H, SO_2-*NH*, J = 7.0 Hz); 10.66 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 46.6, 49.6, 117.4, 121.3, 121.8, 122.9, 127.6, 128.0, 128.2, 128.7, 130.4, 138.0, 138.8, 139.6, 141.8, and 166.7.

2-Imidazol-1-yl-N-[3-(anilinyl-1-sulfonyl)phenyl]acetamide ***5m***

Method B: Yield was 55% from ethanol. Mp. 233–234°C; IR (KBr): 3245, 1713, 1594, 1152 cm^{-1}; LC-MS (APCI) m/z: 356 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.92 (s, 2H, imidazole-CH_2-CO); 6.90 (s, 1H, Ar-H); 7.01 (t, 1H, Ar-H, J = 8.0 Hz); 7.08 (d, 2H, Ar-H, J = 8.0 Hz); 7.16 (s, 1H, Ar-H); 7.22 (m, 2H, Ar-H); 7.80 (m, 2H, Ar-H); 7.63 (s, 1H, Ar-H); 7.71 (d, 1H, Ar-H, J = 8.0 Hz); 8.17(s,1H, Ar-H); 10.60 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 49.6, 117.5, 120.5, 121.2, 122.0, 123.3, 124.5, 128.4, 129.6, 130.3, 138.1, 138.8, 139.6, 140.7, and 166.7.

2-Imidazol-1-yl-N-[3-(m-chloroanilinyl-1-sulfonyl)phenyl]acetamide ***5n***

Method B: Yield was 31% from methanol. Mp. 226–227°C; IR (KBr): 3177, 1714, 1543, 1154 cm^{-1}; LC-MS (APCI) m/z: 356 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.91 (s, 2H, imidazole-CH_2-CO); 6.89 (s, 1H, Ar-H); 7.06 (m, 3H, Ar-H); 7.15 (s, 1H, Ar-H); 7.24 (t, 1H, Ar-H, J = 8.0 Hz); 7.49 (m, 2H, Ar-H); 7.63 (s, 1H, Ar-H); 7.71 (d, 1H, Ar-H, J = 8.0 Hz); 8.19 (s, 1H, Ar-H); 10.63 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 54.3, 117.8, 119.0, 120.1, 121.8, 122.5, 124.1, 124.7, 128.9, 131.1, 132.0, 134.9, 139.8, 140.3, 140.4, 140.9, and 167.4.

2-Triazol-1-yl-N-[3-(3,3-dimethylpiperidinyl-1-sulfonyl)phenyl]acetamide ***6b***

Method A: Yield after column chromatography (5% methanol / dichloromethane) was 86%. Mp. 226–227°C; IR (KBr): 3267, 1708, 1618, 1392 cm^{-1}; LC-MS (APCI) m/z: 377 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 0.74 (s, 6H, piperidine N-C-C(CH_3)$_2$); 1.71 (m, 2H, piperidine N-C-C(CH_3)$_2$-CH_2); 1.58 (m, 2H, piperidine *N*-C-CH_2-C); 2.53 (s, 2H, piperidine *N*-CH_2-C(CH_3)$_2$-C); 2.83 (m, 2H, piperidine *N*-CH_2-C-C); 5.19 (s, 2H, triazole-CH_2-CO); 7.42 (d, 1H, Ar-*H*, J = 8.0 Hz); 7.60(t, 1H, Ar-*H*, J = 8.0 Hz); 7.82 (d, 1H, Ar-*H*, J = 8.0 Hz); 8.01 (s, 1H, Ar-*H*); 8.04 (s, 1H, Ar-H); 8.57 (s, 1H, Ar-H); 10.80 (broad s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 21.6, 26.4, 30.8, 36.4, 46.8, 52.2, 57.3, 117.9, 122.7, 123.5, 130.6, 136.8, 139.6, 146.1, 151.9, and 165.7.

2-Triazol-1-yl-N-[3-(pyrrolidinyl-1-sulfonyl)phenyl]acetamide ***6c***

Method A: Yield after column chromatography (10% methanol/ dichloromethane) was 53%. Mp. 175–176°C; IR (KBr): 3749, 3271, 1707, 1609, 1330 cm^{-1}; LC-MS (APCI) m/z: 335 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.64 (m, 4H, pyrrolidine C-CH_2-CH_2-C); 3.13 (m, 4H, pyrrolidine CH_2-N-CH_2); 5.19 (s, 2H, triazole-CH_2-CO); 7.51 (d, 1H, Ar-*H*, J = 8.0 Hz); 7.60 (t, 1H, Ar-*H*, J = 8.0 Hz); 7.81 (d, 1H, Ar-*H*, J = 8.0 Hz); 8.02 (s, 1H, Ar-*H*); 8.14 (s, 1H, Ar-*H*); 8.57 (s, 1H, Ar-*H*); 10.79 (broad s,1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): 25.2, 48.3, 52.2, 118.0, 122.7, 123.6, 130.6, 137.1, 139.6, 146.1, 151.9, and 165.7.

2-Triazol-1-yl-N-[3-(benzylpiperidinyl-1-sulfonyl)phenyl]acetamide ***6e***

Method B: Yield was 66% from ethanol. Mp. 190–191°C; IR (KBr): 3267, 1706, 1598, 1324 cm^{-1}; LC-MS (APCI) m/z: 439 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 1.17 (m, 2H, piperidine, *N*-CH_2-CH_2-CH); 1.47 (broad s, 1H, piperidine, *N*-CH_2-CH_2-*CH*); 1.58 (d, 2H, piperidine, *N*-CH_2-CH_2, J = 12.0 Hz); 2.15 (t, 2H, piperidine, *N*-CH_2-, J = 12.0 Hz); 2.44 (d, 2H, piperidine, *N*-CH_2, J = 8.0 Hz); 3.58 (d, 2H, phenyl-CH_2-*N*-, J = 12.0 Hz); 5.18 (s, 2H, triazole-CH_2-CO); 7.13 (m, 3H, Ar-H); 7.24 (m, 2H, Ar-H); 7.41 (d, 1H, Ar-H, J = 8.0 Hz); 7.59 (t, 1H, Ar-H, J = 8.0 Hz); 7.81 (d, 1H, Ar-H, J = 8.0 Hz); 8.03 (m, 2H, Ar-H); 8.57 (s, 1H, Ar-H); 10.80 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 31.1, 36.5, 42.1, 46.5, 52.2, 118.0, 122.9, 123.6, 126.3, 128.6, 129.4, 130.5, 136.5, 139.6, 140.2, 146.1, 151.9, and 165.7.

2-Triazol-1-yl-N-[3-(4-piperonylpiperazinyl-1-sulfonyl)phenyl]acetamide ***6h***

Method A: Yield was 50% from methanol. Mp. 200–201°C; IR (KBr): 3260, 1701, 1610, 1159 cm^{-1}; LC-MS (APCI) m/z: 356 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 2.39 (s, 4H, piperazine, CH_2-*N*-(CH_2)2); 2.87 (s, 4H, piperazine, SO_2-*N*-(CH_2)$_2$); 3.36 (m, 2H, Ar-CH_2-N); 5.18 (s, 2H, triazole-CH_2-CO); 5.96 (s, 2H, -O-CH_2-O-); 6.67 (d, 1H, Ar-H, J = 8.0 Hz); 6.79 (m, 2H, Ar-H); 7.43 (d, 1H, Ar-H, J = 8.0 Hz); 7.62 (t, 1H, Ar-H, J = 8.0 Hz); 7.82 (d, 1H, Ar-H, J = 8.0 Hz); 8.01 (s, 1H, Ar-H); 8.07 (s, 1H, Ar-H); 8.56 (s, 1H, Ar-H); 10.81 (s, 1H, CO-*NH*-Ar). ^{13}C-NMR (100 MHz, DMSO): δ 46.4, 51.69, 52.2, 61.5, 101.2, 108.3, 109.4, 118.1, 122.4, 123.1, 123.8, 130.6, 131.9, 135.8, 139.6, 146.1, 146.7, 147.7, 151.9, and 165.7.

2-Triazol-1-yl-N-[3-(N-methylanilinyl-1-sulfonyl)phenyl]acetamide ***6j***

Method A: Yield after chromatography (10% methanol/dichloromethane) was 55%. Mp. 213–214°C; IR (KBr): 3236, 1705, 1593, 1170 cm^{-1}; LC-MS (APCI) m/z: 370 [M$^+$] (100); ^{1}H-NMR (400 MHz, DMSO): δ 3.13 (s, 3H, *N*-CH_3); 5.15 (s, 2H, triazole-CH_2-CO); 7.09 (m, 2H, Ar-H); 7.15 (d, 1H, Ar-H, J = 8.0 Hz); 7.30 (m, 3H, Ar-H); 7.51 (t, 1H, Ar-H, J = 8.0 Hz); 7.85 (d, 1H, Ar-H, J = 8.0 Hz); 7.90 (m, 1H, Ar-H); 8.00 (s, 1H, Ar-H); 8.54 (s, 1H, Ar-H); 10.76 (s, 1H, CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 39.1, 52.8, 118.6, 123.4, 124.3, 127.3, 128.4, 130.0, 131.0, 137.8, 140.0, 142.0, 146.7, 152.5, and 166.1.

General procedure for the synthesis of compounds ***7*** *and* ***8***

To a solution of the amine **3a** or **3d** (1.25 equiv.) in DMF (15 mL), benzyl bromide (1 equiv.) was added, then potassium carbonate (1.25 equiv.) was added and the reaction mixture was allowed to stir overnight. Then, water was added and the reaction was placed in the refrigerator overnight and the formed precipitate was filtered and crystallized from ethanol to afford the desired products.

1-(3-Benzylaminophenylsulfonyl)piperidine ***7***

Yield was 66.2%. Mp. 129–130°C; IR (KBr): 3409, 1602, 1347 cm^{-1}; LC-MS (APCI) m/z: 330 ([M$^+$H]$^+$, 100%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.38 (m, 2H, piperidine N-C-C-CH_2); 1.59 (m, 4H, piperidine CH_2-C-*N*-C-CH_2); 2.84 (t, 4H, piperidine CH_2-N-CH_2, J = 5.3 Hz); 4.40 (ds, 2H, benzylic H, J = 5.3 Hz); 4.50 (m, 1H, *amine H*); 6.82 (dd, 1H, Ar-*H*, J = 2.0 and 8.0 Hz); 6.90 (s, 1H, Ar-*H*); 7.05 (d, 1H, Ar-*H*, J = 8.0 Hz); 7.32 (m, 6H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.5,

25.2, 46.8, 55.2, 110.9, 116.2, 117.1, 126.6, 127.3, 128.8, 129.6, 136.8, 138.5, and 148.2.

*Benzyl-[3-(morpholinyl-1-sulfonyl)phenyl]amine **8***

Yield was 55.6%. Mp. 148–149°C; IR (KBr): 3420, 1600, 1294, 1110 cm^{-1}; LC-MS (APCI) m/z: 330 $[M^+]$ (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.83 (t, 4H, morpholine CH_2-N-CH_2, *J* = 4.6 Hz); 3.68 (t, 4H, morpholine CH_2-O-CH_2, *J* = 4.6 Hz); 4.41 (s, 2H, benzylic H); 4.52 (s, 1H, *amine H*); 6.85 (m, 2H, Ar-H); 7.04 (d, 1H, Ar-H, *J* = 7.7 Hz); 7.34 (m, 6H, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 45.9, 47.8, 66.1, 110.9, 116.3, 117.6, 127.4, 127.5, 128.8, 129.8, 135.5, 138.3, and 148.2.

*General procedure for the synthesis of compounds **9** and **10***

To a solution of compound **7** or **8** (1 equiv.) in dichloromethane (20 mL), chloroacetyl chloride (1–1.5 equiv.) was added while stirring, then, triethylamine (1 equiv.) was added and the reaction mixture was allowed to stir overnight. The organic layer, which was washed with water followed by saturated sodium bicarbonate solution and dried over Na_2SO_4. The solvent was evaporated and the product was crystallized from ethyl acetate/hexane to afford the desired product.

*N-Benzyl-2-chloro-N-[3-(piperidinyl-1-sulfonyl)phenyl]acetamide **9***

Yield was 85.3%. Mp. 116–117°C; IR (KBr):3063, 1682, 1590, 1309 cm^{-1}; LC-MS (APCI) m/z: 406 $[M + H]^+$, (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42 (m, 2H, piperidine *N*-C-C-CH_2); 1.60 (m, 4H, piperidine CH_2-C-N-C-CH_2); 2.76 (s, 4H, piperidine CH_2-N-CH_2); 3.85 (s, 2H, benzylic H); 4.96 (s, 2H, Cl-CH_2-CO); 7.18 (m, 2H, Ar-*H*); 7.28 (m, 3H, Ar-*H*); 7.37 (d, 2H, Ar-*H*, *J* = 7.6 Hz); 7.58 (t, 1H, Ar-*H*, *J* = 7.6 Hz); 7.74 (d, 1H, Ar-*H*, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.4, 25.1, 41.6, 46.8, 53.6, 127.8, 127.9, 128.7, 129.0, 130.6, 132.4, 135.9, 138.2, 141.3, and 166.0. ^{13}C-NMR (100 MHz, DMSO): δ 28.0, 29.8, 51.7, 57.8, 60.3, 127.5, 127.8, 128.1, 128.4, 129.2, 129.4, 129.6, 131.7, 133.8, 137.3, and 165.2.

*N-Benzyl-2-chloro-N-[3-(morpholinyl-1-sulfonyl)phenyl]acetamide **10***

Yield was 63.4%. Mp. 81–82°C; IR (KBr): 1681, 1591, 1329, 1116 cm^{-1}; LC-MS (APCI) m/z: 408 $[M^+]$ (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 4H, morpholine CH_2-N-CH_2); 3.70 (m, 4H, morpholine CH_2-O-CH_2); 3.85 (s, 2H, benzylic H); 4.96 (s, 2H, Cl-CH_2-CO); 7.18 (m, 2H, Ar-H); 7.31 (m, 4H, Ar-H); 7.43 (d, 1H, Ar-H, *J* = 7.8 Hz); 7.62 (t, 1H, Ar-H, *J* = 7.8 Hz); 7.74 (d, 1H, Ar-H, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 41.6, 45.8, 53.6, 66.0, 128.0, 128.2, 128.8, 129.0, 130.8, 133.0, 135.9, 136.9, 141.5, and 165.9.

*General procedure for the synthesis of compounds **11** and **12***

The α-chloroacetamide (**9** or **10**) (1 equiv.) was dissolved in (15 mL) DMF, then, imidazole (3 equiv.) and potassium carbonate (1 equiv.) were added and the reaction mixture was allowed to stir overnight. After stirring, water was added, the mixture was placed in the refrigerator overnight and the precipitate was filtered and crystallized from ethanol to afford the desired product.

*2-Imidazol-1-yl-N-benzyl-N-[3-(piperidinyl-1-sulfonyl)phenyl]acetamide **11***

Yield was 72.3%. Mp. 162–163°C; IR (KBr): 3089, 1672, 1589, 1341 cm^{-1}; LC-MS (APCI) m/z: 439 $[M^+]$ (100); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 2H, piperidine N-C-C-CH_2); 1.59 (m, 4H, piperidine CH_2-C-N-C-CH_2); 2.72 (m, 4H, piperidine CH_2-N-CH_2); 4.46 (s, 2H, imidazole-CH_2-CO); 4.94 (s, 2H, benzylic CH_2); 6.88 (s, 1H, Ar-*H*); 7.04 (s, 1H, Ar-*H*); 7.14 (m, 2H, Ar-*H*); 7.28 (m, 6H, Ar-*H*); 7.60 (t, 1H, Ar-*H*, *J* = 7.9 Hz); 7.74 (d, 1H, Ar-*H*, *J* = 7.9 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.3, 25.1, 46.8, 48.7, 53.5, 119.9, 126.6, 127.9, 128.0, 128.6, 129.1, 129.5, 131.0, 132.2, 135.9, 137.9, 138.5, 140.7, and 165.9.

*2-Imidazol-1-yl-N-benzyl-N-[3-(morpholinyl-1-sulfonyl)phenyl]acetamide **12***

Yield was 66.6%. Mp. 195–196°C; IR (KBr): 3445, 1681, 1591, 1305, 1129 cm^{-1}; LC-MS (APCI) m/z: 440 $[M^+]$ (100); ^{1}H-NMR (400 MHz, DMSO): δ 2.66 (m, 4H, morpholine CH_2-N-CH_2); 3.57 (m, 4H, morpholine CH_2-O-CH_2); 4.73 (s, 2H, benzylic H); 4.96 (s, 2H, imidazole-CH_2-CO); 6.86 (s, 1H, Ar-H); 7.09 (s, 1H, Ar-H); 7.27 (m, 5H, Ar-H); 7.53 (s, 1H, Ar-H); 7.56 (s, 1H, Ar-H); 7.74 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, DMSO): δ 46.3, 48.6, 52.9, 65.7, 121.4, 127.1, 127.4, 127.9, 128.1, 128.8, 128.8, 131.5, 134.1, 135.9, 136.9, 138.8, 140.7, and 165.2.

*General procedure for the synthesis of compounds **13a** and **13b***

To a solution of 3-nitrobenzenesulfonyl chloride (2 equiv.) in dichloromethane (150 mL), aniline or 3-chloroaniline (1 equiv.) and triethylamine (2 equiv.) were added and the reaction mixture was allowed to stir overnight. The organic layer was washed with water, then with 2 M HCl solution, and finally with 0.5 M NaOH solution and dried over $MgSO_4$. The solvent was evaporated and solid residue was crystallized from the appropriate solvent to afford the desired products.

*N,N-[Di-(3-nitrophenylsulfonyl)]aniline **13a***

Yield was 74.7% from ethyl acetate. Mp. 193–194°C; IR (KBr): 1604, 1532, 1169 cm^{-1}; LC-MS (APCI) m/z: 464 $[M + H]^+$ (100); ^{1}H-NMR (400 MHz, DMSO): δ 7.18 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.50 (t, 2H, Ar-H, *J* = 8.0 Hz); 7.60 (t, 1H, Ar-H, *J* = 8.0 Hz); 8.01 (t, 2H, Ar-H, *J* = 8.0 Hz); 8.27(d, 2H, Ar-H, *J* = 8.0 Hz); 8.51 (m, 2H, Ar-H); 8.69 (dd, 2H, Ar-H, *J* = 1.5 and 8.0 Hz). ^{13}C-NMR (100 MHz, DMSO): δ 123.3, 130.0, 130.5, 131.7, 131.8, 132.4, 133.2, 134.4, 139.8, and 148.5.

*N,N-[Di-(3-nitrophenylsulfonyl)]-3-chloroaniline **13b***

Yield was 67.6% from methanol. Mp. 195–196°C; IR (KBr): 1604, 1533, 1312, 1179 cm^{-1}; LC-MS (APCI) m/z: 497 $[M^+]$ (100); ^{1}H-NMR (400 MHz, DMSO): δ 7.15 (dd, 1H, Ar-H, *J* = 2.0 and 8.04 Hz); 7.42 (t, 1H, Ar-H, *J* = 2.0 Hz); 7.52 (t, 1H, Ar-H, *J* = 8.1 Hz); 7.70 (dd, 1H, Ar-H, *J* = 2.0, 8.1 Hz); 8.01 (t, 2H, Ar-H, *J* = 8.1 Hz); 8.28 (m, d, 2H, Ar-H, *J* = 8.3 Hz); 8.52 (t, 2H, Ar-H, *J* = 2.0 Hz); 8.70 (dd, 2H, Ar-H, *J* = 2.20, 8.3 Hz). ^{13}C-NMR (100 MHz, DMSO): δ 123.5, 130.2, 130.9, 131.7, 131.9, 132.0, 132.4, 134.2, 134.5, 134.6, 139.4, and 148.6.

*N,N-[Di-(3-aminophenylsulfonyl)]aniline **14a***

N,N-[Di-(3-nitrophenylsulfonyl)]aniline **13a** (7.5 g, 16.18 mmol) was dissolved in ethanol : water (300 : 100 mL) and the mixture was heated to dissolve the sulfonamide. Then, a mixture of iron

powder (6.5 g, 116.38 mmol) and ferrous sulfate (4.5 g, 16.19 mmol) were added in portions and the reaction mixture was maintained at reflux overnight. The reaction mixture was filtered while hot and the residue was re-heated with in 150 mL ethanol and filtered. The combined solvents were evaporated and the solid product was crystallized from ethanol to afford 4.63 g of light-brown crystals (70.9%). Mp. 118–119°C; IR (KBr): 3463, 3376, 1621, 1163 cm^{-1}; LC-MS (APCI) m/z: 403 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): 5.75 (s, 4H, 2 × Ar-NH_2); 6.91 (d, 4H, Ar-H, *J* = 8.0 Hz); 7.05 (m, 4H, Ar-H); 7.27 (t, 2H, Ar-H, *J* = 8.0 Hz); 7.45 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, DMSO): δ 112.5, 114.9, 119.5, 129.7, 130.2, 130.7, 131.8, 134.4, 139.8, and 150.0.

N,N-[Di-(3-aminophenylsulfonyl)]-3-chloroaniline ***14b***

N,N-[Di-(3-nitrophenylsulfonyl)]-3-chloroaniline **13b** (10.28 g, 20.65 mmol) was dissolved in ethanol : water (400 : 100 mL) and the mixture was heated to dissolve sulfonamide. Then, a mixture of iron powder (5.8 g, 103.85 mmol) and ferrous sulfate (5.8 g, 20.86 mmol) were added in portions and the reaction mixture was maintained at reflux overnight. The reaction mixture was filtered while hot and the residue was re-heated with in 150 mL ethanol and filtered. The combined solvents were evaporated and the solid product was crystallized from ethanol/water to afford 6.47 g of fine off-white crystals (71.6%). Mp. 201–203°C; IR (KBr): 3484, 3386, 1626, 1330, 1169 cm^{-1}; LC-MS (APCI) m/z: 437 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 5.78 (d, 2H, 2 x Ar-NH_2, *J* = 6.4 Hz); 6.89 (m, 4H, Ar-H); 6.99 (m, 4H, Ar-H); 7.27 (t, 2H, Ar-H, *J* = 8.0 Hz); 7.47 (t, 1H, Ar-H, *J* = 8.0 Hz); 7.60 (d, 1H, Ar-H, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, DMSO): δ 112.3, 114.7, 119.6, 130.3, 130.7, 131.0, 131.3, 131.5, 133.6, 135.4, 139.3, and 150.1.

N,N-[Di-3-(2-chloroacetamidophenyl-1-sulfonyl)]aniline ***15a***

To a solution of *N,N*-[di-(3-aminophenylsulfonyl)]aniline **14a** (2 g, 4.96 mmol) in ethyl acetate (30 mL), water (20 mL) containing potassium carbonate (1.4 g, 10.13 mmol) was added with continuous stirring. Then, chloroacetyl chloride (1.6 mL, 2.27 g, 20.1 mmol) in ethyl acetate (10 mL) was added to the reaction dropwise, and the reaction mixture was allowed to stir for five hours. The layers were separated and the aqueous layer was extracted with 15 mL ethyl acetate, and the combined organic layers were washed with 2 M HCl solution followed by water, then dried by $MgSO_4$. The solvent was evaporated, and the solid product was crystallized from ethanol to afford 2.4 g of an orange powder (87%). Mp. 173–175°C; IR (KBr): 3316, 1666, 1593, 1162 cm^{-1}; LC-MS (APCI) m/z: 555 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): 4.30 (s, 4H, 2 × Cl-CH_2-CO); 7.09 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.48 (m, 5H, Ar-H); 7.64 (t, 2H, Ar-H, *J* = 8.0 Hz); 7.96 (d, 2H, Ar-H, *J* = 8.0 Hz); 8.21 (s, 2H, Ar-H); 10.77 (s, 2H, 2 × CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 43.9, 118.6, 123.4, 125.2, 130.1, 130.7, 131.1, 131.8, 133.7, 139.6, 139.8, and 165.7.

N,N-[Di-3-(2-chloroacetamidophenyl-1-sulfonyl)]-3-chloroaniline ***15b***

To a solution of *N,N*-[di-(3-aminophenylsulfonyl)]-3-chloroaniline **14b** (2 g, 4.57 mmol) in dichloromethane (40 mL), chloroacetyl chloride (1.5 mL, 2.13 g, 18.86 mmol) and triethylamine (1.3 mL, 0.94 g, 9.3 mmol) were added and the reaction mixture was allowed to stir overnight. The organic layer was washed with water followed by 2 M HCl and dried over $MgSO_4$. After evaporation of the solvent, the solid residue was crystallized from ethanol to afford 1.83 g of a tan powder (67.8%). Mp. 200–201°C; IR (KBr): 3374, 3345, 1689, 1319, 1165 cm^{-1}; LC-MS (APCI) m/z: 589 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 4.32 (s, 4H, 2 × Cl-CH_2-CO); 7.06 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.13 (m, 1H, Ar-H); 7.52 (m, 3H, Ar-H); 7.66 (m, 3H, Ar-H); 7.97 (d, 2H, Ar-H, *J* = 8.0 Hz); 8.22 (s, 2H, Ar-H); 10.79 (s, 2H, 2 × CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 43.9, 118.5, 123.5, 125.40, 130.7, 130.9, 131.4, 131.6, 134.0, 134.9, 139.1, 139.8, 139.9, and 165.8 ppm.

General procedure for the synthesis of compounds ***16a, 16b,*** *and* ***17a***

To a solution of the α-chloroacetamide **15a** or **15b** (1 equiv.) in acetone (15 mL), imidazole, or triazole (4–5 equiv.), potassium carbonate (2 equiv.) and sodium iodide (2 equiv.) were added consecutively and the reaction mixture was allowed to stir overnight. Then, the reaction mixture was filtered and the solvent was evaporated and the residue was subjected to column chromatograph (10% methanol/dichloromethane) to afford the desired products.

N,N-[Di-3-(2-imidazol-1-yl-acetamidophenyl-1-sulfonyl)]aniline ***16a***

Yield was 41.9%. Mp. 223–224°C; IR (KBr): 3411, 1702, 1596, 1161 cm^{-1}; LC-MS (APCI) m/z: 620 [M + H]$^+$ (100); ^{1}H-NMR (400 MHz, DMSO): 4.96 (s, 4H, 2 × imidazole-CH_2-CO); 6.91 (s, 2H, Ar-H); 7.05 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.19 (s, 2H, Ar-H); 7.47 (m, 5H, Ar-H); 7.63 (m, 4H, Ar-H); 7.96 (d, 2H, Ar-H, *J* = 8.0 Hz); 8.21 (m, 2H, Ar-H); 10.83 (s, 2H, 2 × CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 49.5, 118.4, 121.3, 123.1, 124.9, 128.4, 130.1, 130.8, 131.1, 131.7, 133.8, 138.9, 139.6, 139.9, and 166.9.

N,N-[Di-3-(2-imidazol-1-yl-acetamidophenyl-1-sulfonyl)]-3-chloroaniline ***16b***

Yield was 52.4%. Mp. 204–205°C; IR (KBr): 3447, 1704, 1597, 1317,1157 cm^{-1}; LC-MS (APCI) m/z: 654 [M + H]$^+$ (16); ^{1}H-NMR (400 MHz, DMSO): δ 4.98 (s, 4H, 2 x imidazole-CH_2-CO); 6.94 (s, 2H, Ar-H); 7.02 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.10 (s, 1H, Ar-H); 7.20 (s, 2H, Ar-H); 7.49 (d, 3H, Ar-H, *J* = 8.0 Hz); 7.66 (m, 5H, Ar-H); 7.96 (d, 2H, Ar-H, *J* = 8.0 Hz); 8.24 (s, 2H, Ar-H); 10.83 (s, 2H, 2 × CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 49.6, 118.4, 121.3, 123.2, 125.1, 128.2, 130.7, 130.9, 131.4, 131.6, 134.0, 134.9, 138.8, 139.2, 139.9, 140.0, and 166.9.

N,N-[Di-3-(2-triazol-1-yl-acetamidophenyl-1-sulfonyl)]aniline ***17a***

Yield was 75.8%. Mp. 266–267°C; IR (KBr): 3273, 1710, 1599, 1160 cm^{-1}; LC-MS (APCI) m/z: 621 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): 5.25 (s, 4H, triazole-CH_2-CO); 7.05 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.48 (m, 5H, Ar-H); 7.64 (t, 2H, Ar-H, *J* = 8.0 Hz); 7.95 (d, 2H, Ar-H, *J* = 8.0 Hz); 8.03 (s, 2H, Ar-H); 8.20 (s, 2H, Ar-H); 8.58 (s, 2H, Ar-H); 10.89 (s, 2H, 2 x CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 52.2, 118.4, 123.3, 125.0, 130.1, 130.8, 131.1, 131.7, 133.8, 139.6, 146.1, 151.9, and 165.7. ^{13}C-NMR (100 MHz, DMSO + D_2O): δ 53.2, 119.6, 124.6, 126.4, 131.2, 131.9, 132.4, 132.7, 134.8, 140.4, 140.5, 147.2, 152.9, and 165.7.

N,N-[Di-3-(2-triazol-1-yl-acetamidophenyl-1-sulfonyl)]-3-chloroaniline ***17b***

To a solution of *N,N*-[di-3-(2-chloroacetamidophenyl-1-sulfonyl)]-3-chloroaniline **15b** (1.1 g, 1.86 mmol) in DMF (15 mL), triazole (0.51 g, 7.40 mmol), potassium carbonate (0.51 g, 3.70 mmol) and sodium iodide (0.56 g, 3.70 mmol) were added consecutively and the reaction mixture was allowed to stir overnight. Water was then added to the reaction mixture was placed in the refrigerator for two hours. The precipitate was filtered, dried and then crystallized from ethyl acetate to afford 0.67 g of a white powder (54.9%). Mp. 262–263°C; IR (KBr): 1708, 1598, 1160 cm^{-1}; LC-MS (APCI) m/z: 655 [M^+] (100); ^{1}H-NMR (400 MHz, DMSO): δ 5.20 (s, 4H, 2 × triazole-CH_2-CO); 7.01 (d, 1H, Ar-H, *J* = 8.0 Hz); 7.12 (s, 1H, Ar-H); 7.49 (m, 3H, Ar-H); 7.65 (m, 3H, Ar-H); 7.95 (d, 2H, Ar-H, *J* = 8.0 Hz); 8.03 (s, 2H, Ar-H); 8.22 (s, 2H, Ar-H); 8.58 (s, 2H, Ar-H); 10.90 (s, 2H, 2 × CO-*NH*). ^{13}C-NMR (100 MHz, DMSO): δ 52.2, 118.4, 123.4, 125.2, 130.7, 130.9, 131.4, 131.6, 134.0, 134.9, 139.2, 139.7, 139.8, 146.1, 151.9, and 165.8.

Anticandidal macrodilution-susceptibility testing

Candida albicans strains C1-C4 were obtained from the diagnostic labs at the King Abdullah University Hospital (KAUH) at the Jordan University of Science and Technology, Irbid, Jordan. Sabouraud dextrose agar CM0041 (Oxoid LTD., Basingstoke, Hampshire, England), Sabouraud dextrose broth M 033 (Himedia Laboratories Pvt. Ltd. Mumbai-India) and disposable sterile petri dishes 15 × 90 mm (Arab Food and Medical Appliance Co. Ltd. Zarka-Jordan) were purchased through local vendors. Dimethylsulfoxide and Tween 80 were obtained from ACROS Chemicals, Geel, Belgium. Wet sterilization was done using Stainless-Steel Steam-Pressure Disinfecting Apparatus; model YX280A, Shanghai Sanshen Medical Instrument Co. Ltd, China. The fungi were incubated in a Binder-B28 incubator, (Binder, Tuttlingen, Germany.

The four clinical isolates of *Candida albicans* were cultured on sterile Sabouraud-dextrose agar for 24 hours at 35°C prior to inoculum preparation. From the stock solutions of the test compounds, dilutions in sterile Sabouraud-dextrose broth were made resulting in seven concentrations of each test compound having no more than 40% DMSO and 0.5% Tween 80. To 0.1 mL of the prepared diluted solutions, 0.9 mL of the fungal inoculum was added resulting in concentrations of 32, 16, 8, 4, 2, 1, and 0.5 μg/mL and a final concentration of DMSO and Tween 80 of no more than 4% and 0.05%, respectively. These dilutions were then incubated at 35°C for 24 hours. Always positive and negative controls as well as dilutions of the reference antifungal fluconazole were included in every run.

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