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Synthesis of new benzenesulfonylthiourea-containing compounds

Bongani S Tshifaro, Mpelegeng V. Bvumbi, Tiyisela N Mbhokazi, and Simon S. Mnyakeni Moleele*

Faculty of Science, Engineering and Agriculture, Department of Chemistry,
University of Venda, Private Bag X5050, Thohoyandou, Limpopo, 0950 South Africa
Email: Mnyakeni.moleele@univen.ac.za

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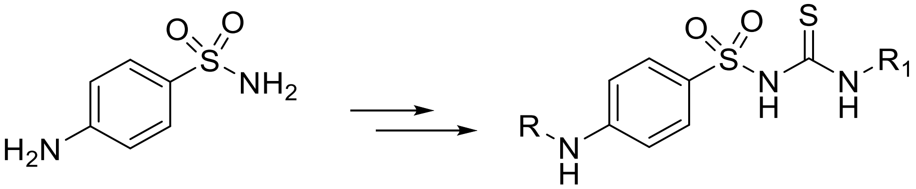
Abstract

Sulfur-containing compounds are considered as attractive pharmacophores for discovery of new drugs regarding their versatile properties to interact with various biological targets. In this project fifteen new benzenesulfonylthiourea containing compounds were synthesized over two or three reaction steps. The structures of synthesized compounds were characterized using Fourier-transform infrared spectroscopy (FT-IR), ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry.



Keywords: sulfanilamide, thiourea, benzenesulfonamide, sulfonamide)

Introduction

Thiourea derivatives bearing benzenesulfonamide moiety are well known for their different pharmacological activities. They are generally stable and are well-recognized for their synthetic feasibility. Moreover, benzenesulfonamide derivatives are well-known for their preferable bioavailability (i.e., good oral absorption) and safety (low side effects).[1] Ngah and co-workers synthesized several thiourea derivatives bearing benzenesulfonamide and screened them against different cancer cells. Compound **1** (Figure 1) exhibited broad selective cytotoxicity against cancer cells HepG2, MCF-7, Caco-2, and PC-3 with IC_{50} values of 19.3, 20.5, 15.08 and 15.6 μg/ml, respectively.[2] Compound **2** has been reported to have anti-inflammatory action through inhibition of lipoxygenase.[3] Liu *et. al*. synthesized novel thiourea benzenesulfonamides based 1,8-naphthalimide derivatives as carbonic anhydrase (CA) IX inhibitors that induced ferroptosis and inhibited triple-negative breast cancer metastasis. One of the representative compounds, **3**, effectively inhibited CA IX enzymatic activity and displayed high selective for CA IX over CA II.[4] Trang and co-workers synthesized benzenesulfonyl thiourea derivatives containing a 4,6-diarylpyrimidine moiety (e.g. compound **4**), which exhibited remarkable dual inhibitory activity against human carbonic anhydrase hCA I, II, IX and XII isoenzymes and cancer cell lines HepG2, HeLa, and A549.[5]

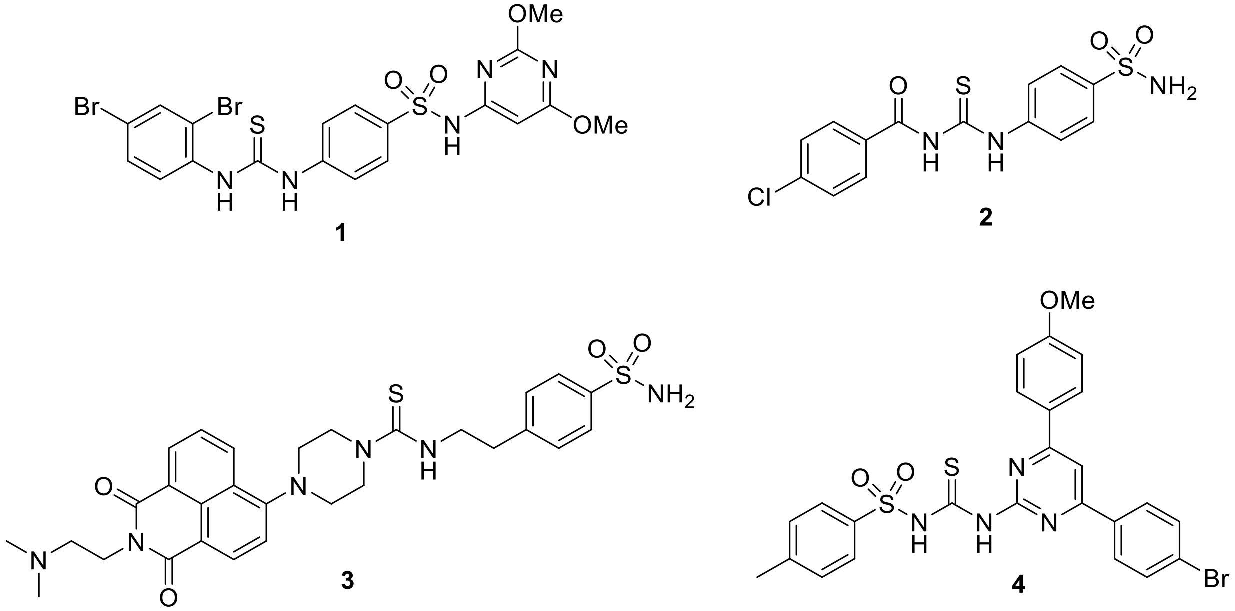
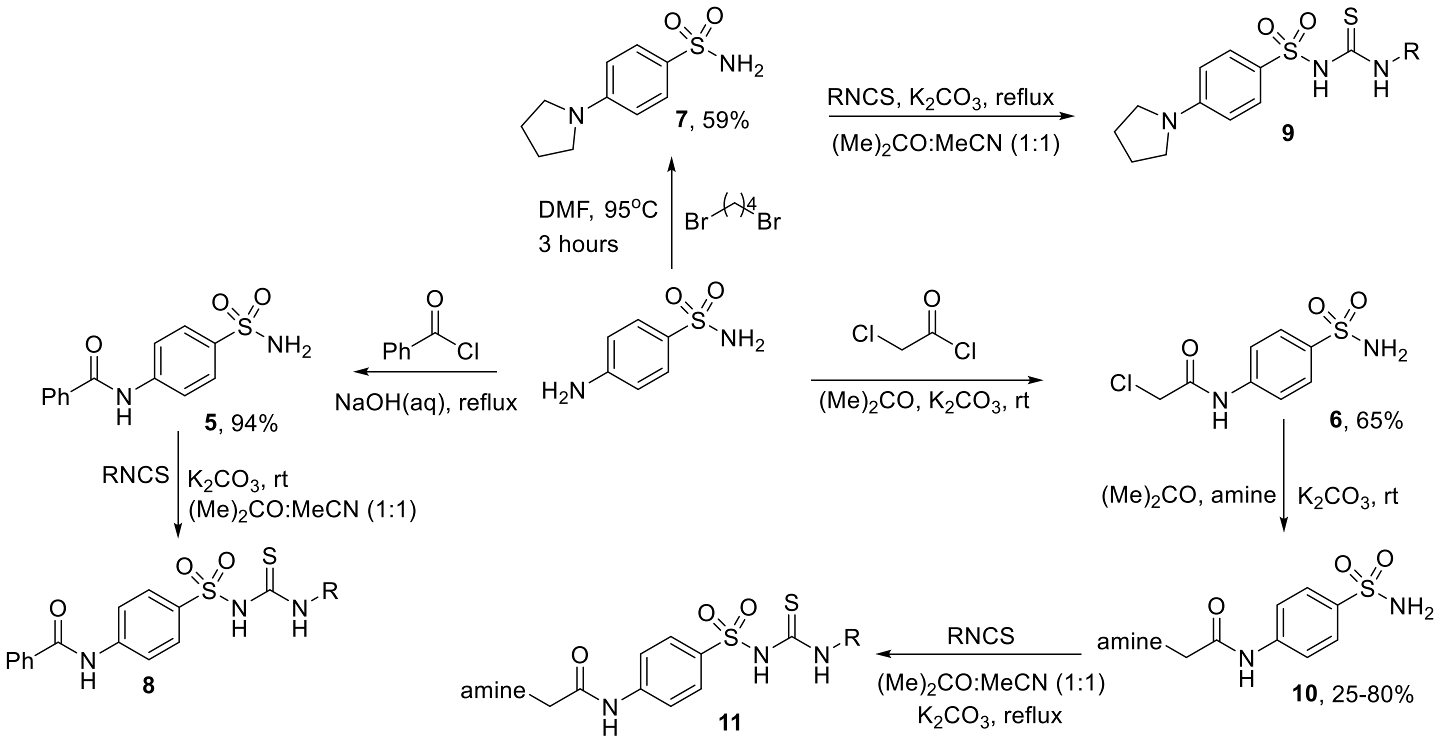


Figure 1. Biologically active compounds containing benzenesulfonyl thiourea moieties.

In continuation of our interest in the synthesis of biologically and chemically valuable compounds,[6,7] we herein report the synthesis new compounds containing the benzenesulfonylthiourea moiety.

Results and Discussion

Syntheses of the three series of benzenesulfonylthiourea **8**, **9** and **11** began with sulfanilamide as depicted in Scheme 1 below. In the synthesis of compounds **8**, sulfanilamide was reacted with benzoyl chloride in the presence of a solution of sodium hydroxide to obtain compound **5** in 94.1% yield as reported by Ozaki et al.[8] To obtain compounds **9**, a procedure described by Ahmed and co-workers was followed,[9] in which sulfanilamide was reacted with 1,4-dibromobutane in DMF at 95°C for 3 hours to get compound **7** in 59.4%. In turn, both compounds **5** and **7** were reacted with different isothiocyanates in the presence of potassium carbonate under a refluxing mixture of acetone and acetonitrile (1:1). Compounds **8** and **9** were obtained in acceptable to excellent yields as shown in Table 1 below. These compounds were characterized with ^{1}H and ^{13}C NMR spectroscopy. Proton NMR spectra of compounds **8** and **9** were characterized by the disappearance of a singlet peak accounting for two protons (NH_2) at 7.31 ppm in compound **5** and 6.95 ppm in compound **7**, confirming that the reaction has taken place. This is further evidenced by the appearance of two new NH peaks at ~11 and 8 ppm. A peak at ~8 ppm appears as a doublet in compounds **8b** and **9b** and as a triplet in compounds **8c**, **8d** and **9c**, confirming that it results from a hydrogen attached to the nitrogen of the isothiocyanate moiety. ^{13}C NMR spectra of compounds **8** and **9** were characterized by a new peak at ~177–182 ppm, confirming the thiocarbonyl carbon (C=S).



Scheme 1: Syntheses of benzenesulfonylthiourea compounds.

Table 1: Yields of final compounds **8** and **9**.

Entry	R	Yield (%)
8a	Phenyl	66
8b	Cyclohexyl	96
8c	Butyl	64
8d	Propyl	40
9a	Phenyl	50
9b	Cyclohexyl	73
9c	Butyl	69

On the other hand, to obtain the final compounds **11**, sulfanilamide was first reacted with chloroacetyl chloride to yield compound **6** in 84.7% yield as described by Altamimia et.al.[10] Compound **6** was then reacted with different amines in acetone in the presence of potassium carbonate to obtain compounds **10**, which were subsequently reacted with different isothiocyanates in the presence of potassium carbonate under a refluxing mixture of acetone and acetonitrile (1:1) to yield the desired compounds **11**. Compounds **11** were obtained in acceptable to good yields as shown in Table 2 below. These compounds were characterized with ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR spectra of compounds **11** were characterized by the disappearance of a singlet peak accounting for two protons (NH_2) at ~7.2 ppm in compounds **10**, confirming that the reaction has taken place. This is further evidenced by the appearance of two new NH peaks at ~11 and 9 ppm. A peak at ~9 ppm appears as a doublet in compounds **11b**, **11e** and **11g** and as a triplet in compounds **11c** and **11h**, confirming that it results from a hydrogen attached to the nitrogen of the isothiocyanate moiety. ^{13}C NMR spectra of compounds **11** were characterized by a new peak at ~177–183 ppm, confirming the thiocarbonyl carbon (C=S).

Table 2: Yields of final compounds **11**.

Entry	**Amine**	**R**	**Yield (%)**
11a	Diethylamine	Phenyl	56
11b	Piperidine	Cyclohexyl	81
11c		Propyl	80
11d		Phenyl	50
11e	Morpholine	Cyclohexyl	86
11f		Phenyl	52
11g	Pyrrolodine	Cyclohexyl	46
11h		Butyl	53

Conclusions

Fifteen new benzenesulfonylthiourea containing compounds **8, 9** and **11** were synthesized in this project. Compounds **8** and **9** were synthesized over two reactions steps whereas compounds **11** were synthesized over three reaction steps. Syntheses of all fifteen compounds starting from sulfanilamide. In the synthesis of compounds **8**, sulfanilamide was reacted with benzoyl chloride in the presence of a solution of sodium hydroxide to obtain benzamidobenzenesulfonamide (**5)** in 94% yield. To obtain compound **9**, sulfanilamide was reacted with 1,4-dibromobutane in DMF at 95°C for 3 hours, yielding 4-pyrrolidinobenzenesulfonamide (**7**) in 59% yield. Subsequently, both compounds **5** and **7** were reacted with different isothiocyanates in the presence of potassium carbonate under a refluxing mixture of acetone and acetonitrile (1:1). On the other hand, to obtain the final compounds **11**, sulfanilamide was first reacted with chloroacetyl chloride to yield 4-(2-chloroacetamido)benzenesulfonamide (**6)** in 85% yield. Compound **6** was then reacted with different amines in acetone in the presence of potassium carbonate to obtain compounds **10**, which were subsequently reacted with different isothiocyanates in the presence of potassium carbonate under a refluxing mixture of acetone and acetonitrile (1:1) to yield the desired compounds **11.** Final compounds **8**, **9** and **11** were obtained in acceptable to good yields varying from 33% to 96%.

Experimental Section

General. All reagents used were of analytical grade, sourced from Sigma-Aldrich and Marula Chemicals. Thin-layer chromatography (TLC) was performed using Macherey-Nagel Alugram Sil G/UV254 plates, which were pre-coated with 0.25mm silica gel 60. Detection was done under ultraviolet light at 254 nm. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and 19F NMR (376.5 MHz) spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 or DMF-d_7 as solvents, and TMS at 0.00 ppm as the internal standard. Values for the chemical shifts are expressed in parts per million (ppm). The following abbreviations are used: br.s for broad singlet, s for singlet, d for doublet, dd for doublet of doublets, q for quartet, quint for quintet and m for multiplet and (*J*) for coupling constants measured in hertz (Hz). All melting points were determined using a Buchi melting point apparatus (B-540) with capillary tubes. Infrared spectra were run on a Bruker Platinum 22 vector Fourier Transform spectrometer (FTIR). Mass spectra (High Resolution) were recorded on a Waters GCT using a Restek Rxi Wintegra Guard column (15 m, 0.25 mm ID, 0.25 µm film thickness) mass spectrometer. The samples were dissolved in acetonitrile and injected at a volume of 1 µl at a ratio of 10:1 and a temperature of 280 °C. The source temperature was 100 °C and the desolvation temperature was set at 300 °C. Helium gas was used as the carrier gas. The software used to control the hyphenated system and to do all data manipulation was MassLynx 4.1 (SCN 704).

General method for the synthesis of aminoacetamido benzenesulfonamides (10). A solution of 4-(2-chloroacetamido)benzenesulfonamide **6** (1 mmol) in dry acetone was cooled to 0°C before being treated with anhydrous potassium carbonate (1 mmol). The reaction mixture was treated with an amine (1 mmol) and then allowed to warm to room temperature before refluxing for 10 hours. After being allowed to cool to room temperature, the mixture was poured into ice water and a precipitate was formed, which was collected by filtration to give the desired products.

4-(2-isopropylaminoacetamido)benzenesulfonamide (10a).[11] [12] A mixture of compound **6** (34.8 mmol, 8.62 g), potassium carbonate (34.8 mmol, 4.81 g) and isopropylamine (34.8 mmol, 3 ml) in acetone (50 ml) afforded compound **10a** as a brown powder (7.52 g, 79.8%); **^{1}H NMR (400 MHz, DMSO-d_6), δ_H** (ppm), 10.79 (s, 1H, NH), 7.81 (d, 2H, *J* 8.4 Hz, 2 × ArH), 7.75 (d, 2H, *J* 8.7 Hz, 2 × ArH), 7.27 (br s, 2H, NH_2), 3.32 (s, 2H, CH_2), 2.78 (septet, 1H, *J* 6.1 Hz, CH, 1.01 (d, 6H, *J* 6.1 Hz, 2 × CH_3); **^{13}C NMR (100 MHz, DMSO-d_6) δ_C** (ppm), 171.7 (C=O), 141.9 (ArC), 138.8 (ArC), 127.2 (ArCH), 119.1 (ArCH), 51.0 (CH_2), 48.7 (CH), 23.1 (CH_3); HRMS (ESI-TOF): m/z $[M+H]^+$) calculated for $C_{11}H_{17}N_3O_3S$, 272.1069; found:272.1078.

4-(2-Pyrrolidinoacetamido)benzenesulfonamide (10b).[13]A mixture of compound **6** (34.7 mmol, 8.60 g), potassium carbonate (34.7 mmol, 4.79 g) and pyrrolidine (34.7 mmol, 3 ml) in acetone (50 ml) afforded compound **10b** as a light brown powder (7.76 g, 79.0%); **^{1}H NMR (400 MHz, DMSO-d_6), δ_H** (ppm), 10.11 (br s, 1H, NH), 7.83 (d, 2H, *J* 8.3 Hz, 2 × ArCH), 7.76 (d, 2H, *J* 8.6 Hz, 2 × ArCH), 7.24 (br s, 2H, NH_2), 3.27 (s, 2H, CH_2), 2.58 (m, 4H, 2 × CH_2), 1.74 (m, 4H, 2 × CH_2); **^{13}C NMR (100 MHz, DMSO-d_6) δ_C** (ppm), 169.9 (C=O), 142.1 (ArC), 138.9 (ArC), 127.0 (ArCH), 119.4 (ArCH), 59.9 (CH_2), 54.1 (CH_2), 23.9 (CH_2); HRMS (ESI-TOF): m/z $[M+H]^+$) calculated for $C_{12}H_{17}N_3O_3S$, 284.1069; found:284.1096.

4-(2-Piperidinodinoacetamido)benzenesulfonamide (10c).[14] A mixture of compound **6** (34.7 mmol, 8.61 g), potassium carbonate (34.7 mmol, 4.79 g) and piperidine (34.7 mmol, 3.5 ml) in acetone (50 ml) afforded compound **10c** as a brown powder (4.63 g, 47.1%). **^{1}H NMR (400 MHz, DMF-d_7), δ_H** (ppm), 9.98 (s, 1H, NH), 7.81 (d, 2H, *J* 8.8 Hz, 2 × ArCH), 7.75 (d, 2H, *J* 8.4 Hz, 2 × ArCH), 7.25 (s, 2H, NH_2), 3.10 (s, 2H, CH_2), 2.45–2.26 (m, 4H, 2 × CH_2), 1.58–1.54 (m, 4H, 2 × CH_2), 1.41–1.40 (m, 2H, CH_2); **^{13}C NMR (100 MHz, DMF-d_7) δ_C** (ppm), 169.7 (C=O), 141.9 (ArC), 138.9 (ArC), 127.1 (ArCH), 119.4 (ArCH), 61.1 (CH_2), 54.1 (CH_2), 25.9 (CH_2), 24.0 (CH_2); HRMS (ESI-TOF): m/z $[M+H]^+$) calculated for $C_{13}H_{19}N_3O_3S$, 298.1225; found:298.1218.

4-(2-Cyclopentylaminoacetamido)benzenesulfonamide (10d).[15] A mixture of compound **6** (34.7 mmol, 8.61 g), potassium carbonate (34.7 mmol, 4.79 g) and cyclopentylamine (34.7 mmol, 3.5 ml) in acetone (50 ml) afforded compound **10d** as a light brown powder (2.58 g, 25.4%); **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 10.66 (s, 1H, NH), 7.83 (d, 2H, *J* 8.4 Hz, 2 × ArCH), 7.79 (d, H, *J* 8.8 Hz, 2 × ArCH), 7.26 (br s, 2H, NH_2), 3.52 (s, 2H, CH_2), 3.33 (m, 1H, NH), 3.22–3.18 (m, 1H, CH), 1.76–174 (m, 2H, CH_2), 1.62–1.60 (m, 2H, CH_2), 1.48–1.47 (m, 2H, CH_2), 1.41–1.38 (m, 2H, CH_2); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 171.9 (C=O), 142.0 (ArC), 139.0 (ArC), 127.2 (ArCH), 119.2 (ArCH), 65.5 (CH), 58.3 (CH_2), 29.6 (CH_2), 23.6 (CH_2); HRMS (ESI-TOF): m/z $[M+H]^+$) calculated for $C_{13}H_{19}N_3O_3S$, 298.1225; found:298.1218.

4-(2-Morpholinoacetamido)benzenesulfonamide (10e).[16] A mixture of compound **6** (20.2 mmol, 5.00 g), potassium carbonate (20.2 mmol, 2.76 g) and morpholine (20.2 mmol, 2 ml) in acetone (30 ml) afforded compound **10e** as a white powder (3.64 g, 60.3%); **^{1}H NMR (400 MHz, DMF-d$_7$), δ**$_H$ (ppm), 10.26 (br s, 1H, NH), 7.83 (d, 2H, *J* 7.9 Hz, 2 × ArCH), 7.76 (d, 2H, *J* 8.3 Hz, 2 × ArCH), 7.31 (br s, 2H, NH_2), 3.64–3.62 (m, 4H, 2 × CH_2), 3.48–3.39 (m, 4H, 2 × CH_2), 3.18 (s, 2H, CH_2); **^{13}C NMR (100 MHz, DMF-d$_7$) δ**$_C$ (ppm), 169.2 (C=O), 142.0 (ArC), 138.9 (ArC), 127.0 (ArCH), 119.4 (ArCH), 66.5 (CH_2), 62.3 (CH_2), 53.5 (CH_2); HRMS (ESI-TOF): m/z $[M+H]^+$) calculated for $C_{12}H_{17}N_3O_4S$, 300.1018; found:300.1015.

4-(2-Diethylaminoacetamido)benzenesulfonamide (10f).[17] A mixture of compound **6** (34.7 mmol, 8.61 g), potassium carbonate (34.7 mmol, 4.79 g) and diethylamine (34.7 mmol, 3.5 ml) in acetone (50 ml) afforded compound **10f** as a white powder (5.89 g, 59.6%); **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 9.99 (s, 1H, NH), 7.84 (d, 2H, *J* 8.3 Hz, 2 × ArH), 7.77 (d, 2H, *J* 8.3 Hz, 2 × ArH), 7.25 (br s, 2H, NH_2), 3.19 (s, 2H, CH_2), 2.62 (q, 4H, *J* 7.0 Hz, 2 × CH_2), 1.03 (t, 6H, *J* 7.0 Hz, 2 × CH_3); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 171.0 (C=O), 141.7 (ArC), 139.0 (ArC), 127.0 (ArCH), 119.3 (ArCH), 57.8 (CH_2), 48.2 (CH_2), 12.3 (CH_3); HRMS (ESI-TOF): m/z $[M+H]^+$) calculated for $C_{12}H_{19}N_3O_3S$, 286.1225; found:286.1253.

General method for the synthesis of new benzenesulfonylthioureas (8, 9, 11). Solutions of compounds **5, 7** and **10** (1.0 mmol) in a solvent mixture of dry acetone and dry acetonitrile (1:1) was treated with anhydrous potassium carbonate (1.0 mmol). The reaction mixtures were heated under reflux for 1 to 2 hours to achieve the potassium salt and then appropriate isothiocyanates (1.0 mmol) were added and the reaction mixtures were further refluxed for 16 hours. After being allowed to cool to room temperature, the solvent mixtures were removed using rotatory evaporation and a slurry of crude products was obtained. These crude products were treated with acidic water until a precipitate was formed, filtered and washed with ice cold water. The products were recrystallized from ethanol where necessary.

4-Benzamido-*N*-(phenylcarbamothioyl)benzenesulfonamide (8a). A mixture of 4-benzenamidobenzenesulfonamide **5** (3.62 mmol, 1.00 g) and anhydrous potassium carbonate (3.62 mmol, 0.50 g) in a dry mixture of acetone and acetonitrile (20 ml) was reacted with phenyl isothiocyanate (3.62 mmol, 0.5 ml). The product was obtained as a white solid (0.99 g, 66.49 %); mp = 263.5–264.7 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.38 (br-s, 1H, NH), 10.42 (br-s, 1H, NH), 8.98 (br-s, 1H, NH), 7.98 (d, 2H, *J* 7.0 Hz, 2 × ArH), 7.81 (d, 2H, *J* 8.7 Hz, 2 × ArH), 7.74 (d, 2H, *J* 8.8 Hz, 2 × ArH), 7.71 (d, 2H, *J* 7.9 Hz, 2 × ArH) 7.60–7.58 (m, 1H, ArH), 7.55–7.52 (m, 2H, 2 × ArH), 7.18 (t, 2H, 2 × ArH), 6.88 (t, 1H, ArH); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 182.6 (C=S), 166.1 (C=O), 141.8 (ArC), 140.8 (ArC), 140.6 (ArC), 135.2 (ArC), 132.1 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 121.5 (ArCH), 120.4 (ArCH), 119.2 (ArCH): **IR** (KBr cm^{-1}): 3336 (N-H), 2945 (ArC-H), 1629 (C=O), 1571 (C=C), 1092 (C=S); HRMS (ESI-TOF): calculated for $C_{20}H_{17}N_3O_3S_2$ $[M+H]^+$) 412.0790; found: 412.0788.

4-Benzamido-*N*-(cyclohexylcarbamothiol)-benzenesulfonamide (8b). A mixture of 4-benzenamidobenzenesulfonamide **5** (3.62 mmol, 1.00 g) and potassium carbonate (3.62 mmol, 0.50 g) in a dry mixture of acetone and acetonitrile (20 ml) was reacted with cyclohexyl isothiocyanate (3.62 mmol, 0.5 ml). The product was obtained as a white solid (1.45 g, 95.96 %); mp = 201.9–203.9 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.44 (br-s, 1H, NH), 10.72 (s, 1H, NH), 8.54 (d, 1H, *J* 7.8 Hz, NH), 8.04 (d, 2H, *J* 8.8 Hz, 2 × ArH), 8.00 (d, 2H, *J* 7.2 Hz, 2 × ArH), 7.89 (d, 2H, *J* 8.8 Hz, 2 × ArH), 7.64–7.61 (m, 1H, ArH), 7.57–7.53 (m, 2H, 2 × ArH), 3.93 (m, 1H, CH), 1.79–1.77 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 1.52–1.50 (m, 1H, CH), 1.30–1.21 (m, 5H, CH & 2 × CH_2); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 177.3 (C=S), 166.6 (C=O), 144.1 (ArC) 134.8 (ArC), 133.7 (ArC), 132.4 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 128.3 (ArCH), 120.1 (ArCH), 53.1 (CH), 31.3 (CH_2), 25.3 (CH_2), 24.4 (CH_2) : **IR** (KBr cm^{-1}): 3344 (N-H), 2917 (ArC-H), 1601 (C=O), 1589 (C=C), 1138 (C=S); HRMS (ESI-TOF): calculated for $C_{20}H_{23}N_3O_3S_2$ [M+H]$^+$ 418.1259; found: 418.1261.

4-Benzamido-*N*-(butylcarbamothioyl)benzenesulfonamide (8c). A mixture of 4-benzenamidobenzenesulfonamide **5** (3.62 mmol, 1.00 g) and potassium carbonate (3.69 mmol, 0.51 g) in a dry mixture of acetone and acetonitrile (20 ml) was reacted with butyl-isothiocyanate (3.62 mmol, 0.5 ml). The product was obtained as a white solid (0.91 g, 64.27 %); mp = 175.6–176 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.50 (br-s, 1H, NH), 10.71 (s, 1H, NH), 8.56 (t, 1H, *J* 5.4 Hz, NH), 8.05 (d, 2H, *J* 8.8 Hz, 2 × ArH), 7.99 (d, 2H, *J* 7.1 Hz, 2 × ArH). 7.92 (d, 2H, *J* 8.8 Hz, 2 × ArH), 7.63–7.60 (m, 1H, ArH), 7.63–7.53 (m, 2H, 2 × ArH), 3.43 (q, 2H, *J* 6.3 Hz, CH_2), 1.47 (quintet, 2H, *J* 7.2 Hz, CH_2), 1.23 (sextet, 2H, *J* 7.4 Hz, CH_2), 0.84 (t, 3H, *J* 7.3 Hz, CH_3); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm),178.4 (C=S), 166.6 (C=O), 144.2 (ArC), 134.8 (ArC), 133.6 (ArC), 132.4 (ArCH), 128.9 (ArCH), 128.3 (ArCH), 120.1 (ArCH), 118.1 (ArCH), 44.6 (CH_2), 30.2 (CH_2), 19.8 (CH_2), 14.0 (CH_3) : **IR** (KBr cm^{-1}): 3330 (N-H), 2954 (ArC-H), 1676 (C=O), 1569 (C=C), 1102 (C=S); HRMS (ESI-TOF): calculated for $C_{18}H_{21}N_3O_3S_2$ [M+H]$^+$) 392.1103; found: 392.1111.

4-Benzamido-*N*-(propylcarbamothioyl)benzenesulfonamide (8d). A mixture of 4-benzenamidobenzenesulfonamide **5** (3.62 mmol, 1.01 g) and potassium carbonate (3.62 mmol, 0.5 g) in a dry mixture of acetone and acetonitrile (20 ml) was reacted with propyl-isothiocyanate (3.62 mmol, 0.50 ml). The product was obtained as a white solid (0.45 g, 32.94 %); mp = 162–162.9 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.44 (br-s, 1H, NH), 10.68 (s, 1H, NH), 8.54 (t, 1H, *J* 5.2 Hz, NH), 8.02 (d, 2H, *J* 8.4 Hz, 2 × ArH), 7.98 (d, 2H, *J* 7.6 Hz, 2 × ArH), 7.90 (d, 2H, *J* 8.4 Hz, 2 × ArH), 7.62 (d, 1H, *J* 7.2 Hz, ArH), 7.56 (d, 2H, *J* 7.2 Hz, 2 × ArH), 3.90 (t, 2H, *J* 6.4 Hz, CH_2), 1.48 (sextet, 2H, *J* 7.2 Hz, CH_2), 0.80 (t, 3H, *J* 7.2 Hz, CH_3) **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 178.5 (C=S), 166.6 (C=O), 144.2 (ArC), 134.8 (ArC), 133.6 (ArC), 132.4 (ArCH), 128.9 (ArCH), 128.3 (ArCH), 126.9 (ArCH), 120.2 (ArCH), 46.6 (CH_2), 21.4 (CH_2), 11.5 (CH_3) : **IR** (KBr cm^{-1}): 3327 (N-H), 2966 (ArC-H), 1667 (C=O), 1589 (C=C), 1163 (C=S); HRMS (ESI-TOF): calculated for $C_{17}H_{19}N_3O_3S_2$ [M+H]$^+$) 378.0946; found: 378. 0906.

4-Pyrrolidino-*N*-(phenylcarbamothioyl)-benzenesulfonamide (9a). A mixture of 4-(pyrrolidin-1-yl)benzenesulfonamide **7** (4.42 mmol, 1.00 g) and potassium carbonate (4.42 mmol, 3.20 g) in a dry mixture of acetonitrile and acetone (20 ml) was reacted with phenyl-isothiocyanate (4.42 mmol, 0.5 ml). The product was obtained as a brown solid (0.79 g, 49.5%); mp = 163.8–164.5 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.11 (s, 1H, NH), 8.79 (br s, 1H, NH), 7.68 (d, 2H, *J* 7.7 Hz, 2 × ArH), 7.58 (d, 2H, *J* 8.5 Hz, 2 × ArH), 7.15 (t, 2H, *J* 7.8 Hz, 2 × ArH), 6.85 (t, 1H, *J* 7.3 Hz, ArH), 6.46 (d, 2H, *J* 8.8 Hz, 2 × ArH), 3.26 (t, 4H, *J* 6.4 Hz, 2 × CH_2), 1.96 (t, 4H, *J* 6.4 Hz, 2 × CH_2); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 181.8 (C=S), 148.9 (ArC), 141.9 (ArC), 131.7 (ArC), 129.3 (ArCH), 128.3 (ArCH), 121.2 (ArCH), 120.2 (ArCH), 110.0 (ArCH), 47.7 (CH_2), 25.4 (CH_2): **IR** (KBr cm^{-1}): 3213 (N-H), 2956 (C-H), 1592 (C=C), 1108 (C=S); HRMS (ESI-TOF): calculated for $C_{17}H_{20}N_3O_2S_2$ [M+H]$^+$) 362.0997; found: 362.0996.

4-Pyrrolidino-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (9b). A mixture of 4-(pyrrolidin-1-yl)benzenesulfonamide **7** (4.42 mmol, 1.00 g) and potassium carbonate (4.42 mmol, 0.61 g) in a dry mixture of acetonitrile and acetone (20 ml) was reacted with cyclohexyl isothiocyanate (4.42 mmol, 0.6 ml). The product was obtained as a light brown solid (1.18 g, 72.6%); **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.15 (br s, 1H, NH), 8.18 (d, 1H, *J* 7.6 Hz, NH), 7.63 (d, 2H, *J* 8.4 Hz, 2 × ArH), 6.63 (d, 2H, *J* 8.4 Hz, 2 × ArH), 3.33–3.30 (m, 2 × CH$_2$ & CH), 1.96 (m, 4H, 2 × CH$_2$), 1.77 (m, 2H, CH$_2$), 1.96 (m, 2H, CH$_2$), 1.29–1.27 (m, 6H, 3 × CH$_2$); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 177.4 (C=S), 151.1 (ArC), 129.4 (ArCH), 123.3 (ArC), 111.2 (ArCH), 53.2 (CH), 47.8 (CH$_2$), 31.4 (CH$_2$), 25.4 (CH$_2$), 25.3 (CH$_2$), 24.5 (CH$_2$); **IR** (KBr cm^{-1}): 3271 (N-H), 2956 (ArC-H), 1576 (C=C), 1115 (C=S).HRMS (ESI-TOF): calculated for $C_{17}H_{26}N_3O_2S_2$ [M+H]$^+$) 368.1466; found: 368.1428.

4-Pyrrolidino-*N*-(butylcarbamothioyl)-benzenesulfonamide (9c). A mixture of 4-(pyrrolidin-1-yl)benzenesulfonamide **7** (4.42 mmol, 1.00 g) and potassium carbonate (4.42 mmol, 0.61 g) in a dry mixture of acetonitrile and acetone (20 ml) was reacted with butyl isothiocyanate (4.42 mmol, 0.5 ml). The product was obtained as a brown solid (1.04 g, 69.2%); **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.18 (s, 1H, NH), 8.36 (t, 1H, *J* 5.2 Hz, NH), 7.65 (d, 2H, *J* 8.4 Hz, 2 × ArH), 6.61 (d, 2H, *J* 8.4 Hz, 2 × ArH), 3.42–3.38 (m, 4H, H, 2 × CH$_2$), 3.36–3.30 (m, 2H, CH$_2$) 1.96 (m, 4H, Hz, 2 × CH$_2$), 1.45–1.42 (m, 2H, CH$_2$), 1.21-1.16 (m, 2H, CH$_2$), 0.83 (t, 3H, *J* 7.2 Hz, CH$_3$); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 178.6 (C=S), 151.0 (ArC), 129.5 (ArCH), 123.4 (ArC), 111.2 (ArCH), 47.8 (CH$_2$), 44.7 (CH$_2$), 30.4 (CH$_2$), 25.4 (CH$_2$), 19.9 (CH$_2$), 14.1 (CH$_3$): **IR** (KBr cm^{-1}): 3213.22 (N-H), 2956.50 (C-H), 1714.84 (C=O), 1592.41 (C=C); **IR** (KBr cm^{-1}): 3268 (N-H), 2936 (ArC-H), 1588 (C=C), 1125 (C=S).HRMS (ESI-TOF): calculated for $C_{15}H_{23}N_3O_2S_2$ [M+H]$^+$) 342.1310; found: 342.1338.

4-(2-Diethylaminoacetamido)-*N*-(phenylcarbamothioyl)-benzenesulfonamide (11a). A mixture of 4-(2-diethylaminoacetamido)benzenesulfonamide **10f** (3.50 mmol, 1.00 g) and potassium carbonate (3.50 mmol, 0.48 g) in a dry mixture of acetonitrile and acetone (30 ml) was reacted with phenyl-isothiocyanate (3.50 mmol, 0.5 ml). Product **11a** was obtained as yellowish granular crystals (0.82 g, 55.6 %); mp = 222.8–224.5 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.42 (s, 1H, NH), 9.82 (s, 1H, NH), 8.93 (s, 1H, NH), 7.69 (d, 2H, *J* 7.5 Hz, 2 × ArH), 7.65 (d, 2H, *J* 8.8 Hz, 2 × ArH), 7.65–7.62 (m, 2H, 2 × ArH), 7.17 (t, 2H, *J* 7.9 Hz, 2 × ArH), 6.87 (t, 1H, *J* 7.3 Hz, ArH), 3.16 (s, 2H, CH$_2$), 2.62 (q, 4H, *J* 7.1 Hz, 2 × CH$_2$), 1.03 (t, 6H, *J* 7.1 Hz, 2 × CH$_3$); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 182.6 (C=S), 170.6 (C=O), 141.8 (ArC), 140.4 (ArC), 139.9 (ArC), 128.6 (ArCH), 128.3 (ArCH), 121.5 (ArCH), 120.4 (ArCH), 118.1 (ArCH), 57.8 (CH$_2$), 48.2 (CH$_2$), 12.4 (CH$_3$) : **IR** (KBr cm^{-1}): 3250 (N-H), 2971 (ArC-H), 1656 (C=O), 1518 (C=C), 1176 (C=S).**HRMS** (ESI-TOF): calculated for $C_{19}H_{24}N_4O_3S_2$ [M+1]$^+$ 421.1368; found: 421.1334.

4-(2-Piperidinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (11b). A mixture of 4-(2-piperidinoacetamido)benzenesulfonamide **10c** (3.36 mmol, 1.00 g) and potassium carbonate (3.36 mmol, 0.46 g) in a dry mixture of acetonitrile and acetone (15 ml) was reacted with cyclohexyl isothiocyanate (3.36 mmol, 0.5 ml). Product **11b** was obtained as a white powder (1.19 g, 80.7%); mp = 184.8–187.6 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$) δ**$_H$ 10.94 (s, 1H, NH), 10.31 (s, 1H, NH), 8.62 (d, 1H, *J* 7.8 Hz, NH), 7.84 (m, 4H, 4 × ArH), 4.14 (quint, 1H, *J* 7.4 Hz, CH), 2.84 (t, 2H, *J* 5.0 Hz, CH$_2$), 2.47 (t, 2H, *J* 5.4 Hz, CH$_2$), 2.23 (t, 2H, *J* 5.4 Hz, CH$_2$), 1.69–1.63 (m, 4H, 2 × CH$_2$), 1.54–1.51 (m, 6H, 3 × CH$_2$), 1.38–1.32 (m, 2H, CH$_2$), 1.29–1.20 (m, 4H, 2 × CH$_2$); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ 177.30 (C=S), 169.23 (C=O), 143.75 (ArC), 133.52 (ArC), 129.32 (ArCH), 119.03 (ArCH), 52.97 (CH$_2$), 52.63 (CH$_2$), 51.91 (CH), 31.30 (CH$_2$), 25.39 (C CH$_2$), 24.46 (CH$_2$), 22.84 (CH$_2$), 21.72 (CH$_2$). **IR** (KBr cm^{-1}): 3286 (N-H), 2940 (ArC-H), 1654 (C=O), 1564 (C=C), 1098 (C=S). **HRMS** (ESI-TOF): calculated for $C_{20}H_{30}N_4O_3S_2$ [M$^+$] 438.1759; found: 438.1739.

4-(2-Piperidinoacetamido)-*N*-(propylcarbamothioyl)-benzenesulfonamide (11c). A mixture of 4-(2-piperidinoacetamido)benzenesulfonamide **10c** (3.36 mmol, 1.00 g) and potassium carbonate (3.36 mmol, 0.46 g) in a dry mixture of acetonitrile and acetone (15 ml) was reacted with propyl isothiocyanate (3.36 mmol, 0.3 ml). Product **11c** was obtained as a cream-white powder (1.07 g, 79.90%); mp = 186.1–188.4 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ_H** 10.93 (s, 1H, NH), 10.19 (s, 1H, NH), 8.70 (t, *J* 5.4 Hz, 1H, NH), 7.86 (d, 2H, *J* 9.2 Hz, 2 × ArH), 7.83 (d, 2H, *J* 9.2 Hz, 2 × ArH), 3.41 (d, *J* = 12.4 Hz, 2H, NHCH_2CH$_2$CH$_3$), 3.34 (dd, *J* = 12.5, 6.7 Hz, 4H, piperidine CH$_2$), 3.00 (t, *J* = 7.2 Hz, 2H, NCH$_2$), 1.78 (m, 4H, piperidine CH$_2$), 1.71 (quint, *J* = 8.0 Hz, 2H, piperidine CH$_2$), 1.47 (dt, *J* = 14.5, 7.3 Hz, 2H, NHCH$_2$CH_2CH$_3$), 0.79 (t, *J* = 7.4 Hz, 3H, NHCH$_2$CH$_2$CH_3); **^{13}C NMR (100 MHz, DMSO-d_6) δ_C** 178.51 (C=S), 169.23 (C=O), 143.78 (ArC), 133.49 (ArC), 129.22 (ArCH), 119.08 (ArCH), 52.66 (CH$_2$), 51.92 (CH$_2$), 46.45 (CH$_2$), 22.85 (CH$_2$), 21.70 (CH$_2$), 21.43 (CH$_2$), 11.61 (CH$_3$). **IR** (KBr cm^{-1}): 3216 (N-H), 2975 (ArC-H), 1624 (C=O), 1533 (C=C), 1094 (C=S). **HRMS** (ESI-TOF): calculated for $C_{17}H_{26}N_4O_3S_2$ [M$^+$] 398.1446; found: 398.1464.

4-(2-Piperidinoacetamido)-*N*-(phenylcarbamothioyl)-benzenesulfonamide (11d). A mixture of 4-(2-piperidinoacetamido)benzenesulfonamide **10c** (3.36 mmol, 1.00 g) and potassium carbonate (3.36 mmol, 0.46 g) in a dry mixture of acetonitrile and acetone (15 ml) was reacted with phenyl isothiocyanate (3.36 mmol, 0.5 ml). Product **11d** was obtained as a yellow powder (0.72 g, 49.5%); mp = 140.9–143.8 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ_H** 10.55 (s, 1H, NH), 9.94 (s, 1H, NH), 8.97 (s, 1H, NH), 7.91 (d, 2H, *J* 7.4 Hz, 2 × ArH), 7.72 (d, 2H, *J* 7.5 Hz, 2 × ArH), 7.37 (t, 2H, *J* 7.5 Hz, 2 × ArH), 7.28 (dd, 2H, *J* 7.5, 1.5 Hz, 2 × ArH), 7.18–7.14 (m, 1H, ArH), 3.23 (s, 2H, NCH$_2$), 2.57 (m, 4H, piperidine CH$_2$), 1.68–1.49 (m, 6H, piperidine CH$_2$); **^{13}C NMR (100 MHz, DMSO-d_6) δ_C** 178.36 (C=S), 167.76 (C=O), 144.27 (ArC), 139.18 (ArC), 136.86 (ArC), 129.18 (ArCH), 128.96 (ArCH), 124.47 (ArCH), 121.54 (ArCH), 119.07 (ArCH), 60.23 (CH$_2$), 54.34 (CH$_2$), 24.60 (CH$_2$), 23.42 (CH$_2$). **IR** (KBr cm^{-1}): 3327 (N-H), 2947 (ArC-H), 1689 (C=O), 1534 (C=C), 1126 (C=S). **HRMS** (ESI-TOF): calculated for $C_{20}H_{24}N_4O_3S_2$ [M$^+$] 432.1290; found: 432.1328.

4-(2-Morpholinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (11e). A mixture of 4-(2-mopholinoacetamido)benzenesulfonamide **10e** (3.34 mmol, 1.00 g) and potassium carbonate (3.34 mmol, 0.46 g) in a dry mixture of acetonitrile and acetone (15 ml) was reacted with cyclohexyl isothiocyanate (3.34 mmol, 0.5 ml). Product **11e** was obtained as a white powder (1.26 g, 85.6%); mp = 210.1–213.4 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ_H** 11.53 (s, 1H, NH), 8.75 (d, 1H, *J* 7.8 Hz, NH), 7.88 (d, 2H, *J* 9.0 Hz, 2 × ArH), 7.85 (d, 2H, *J* 9.1 Hz, 2 × ArH), 3.80 (m, 2H, CH$_2$), 3.54–3.47 (m, 4H, 2 × CH$_2$), 3.46–3.36 (m, 4H, 2 × CH$_2$), 3.12 (m, 1H, CH), 1.75 (m, 2H, CH$_2$), 1.61 (m, 2H, CH$_2$), 1.49 (d, 2H, *J* 8.5 Hz, CH$_2$), 1.22 (dd, 4H, *J* 17.8, 8.9 Hz, 2 × CH$_2$); **^{13}C NMR (100 MHz, DMSO-d_6) δ_C** 177.25 (C=S), 169.06 (C=O), 143.73 (ArC), 133.50 (ArC), 129.32 (ArCH), 119.07 (ArCH), 63.65 (CH$_2$), 53.00 (CH), 52.04 (CH$_2$), 51.66 (CH$_2$), 31.29 (CH$_2$), 25.37 (C CH$_2$), 24.45 (CH$_2$). **IR** (KBr cm^{-1}): 3243 (N-H), 2928 (ArC-H), 1627 (C=O), 1578 (C=C), 1120 (C=S). **HRMS** (ESI-TOF): calculated for $C_{19}H_{28}N_4O_4S_2$ [M$^+$] 440.1552; found: 440.1560.

4-(2-Morpholinoacetamido)-*N*-(phenylcarbamothioyl)-benzenesulfonamide (11f). A mixture of 4-(2-mopholinoacetamido)benzenesulfonamide **10e** (3.34 mmol, 1.00 g) and potassium carbonate (3.34 mmol, 0.46 g) in a dry mixture of acetonitrile and acetone (15 ml) was reacted with phenyl isothiocyanate (3.34 mmol, 0.5 ml). Product **11f** was obtained as a yellow powder (0.75 g, 51.7%); mp = 228.2–231.7 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ_H** 9.90 (s, 1H, NH), 8.94 (s, 1H, NH), 7.71–66 (m, 4H, 4 × ArH), 7.63 (d, 2H, *J* 8.7 Hz, 2 × ArH), 7.16 (t, 2H, *J* 7.8 Hz, 2 × ArH), 6.86 (t, 1H, *J* 7.3 Hz, ArH), 3.91–3.84 (m, 4H, 2 × CH$_2$), 3.36 (s, 2H, CH$_2$), 2.78–2.72 (m, 4H, 2 × CH$_2$); **^{13}C NMR (100 MHz, DMSO-d_6) δ_C** 183.68 (C=S), 169.13 (C=O), 142.50 (ArC), 141.38 (ArC), 140.67 (ArC), 128.60 (ArCH), 128.37 (ArCH), 121.50 (ArCH), 120.39 (ArCH), 118.31 (ArCH), 67.01 (CH$_2$), 63.08 (CH$_2$), 54.12 (CH$_2$). **IR** (KBr cm^{-1}): 3287 (N-H), 2945 (ArC-H), 1655 (C=O), 1532 (C=C), 1148 (C=S). **HRMS** (ESI-TOF): calculated for $C_{19}H_{22}N_4O_4S_2$ [M$^+$] 434.1180; found: 434.1217.

4-(2-Pyrrolidinoacetamido)-*N*-(cyclohexylcarbamothioyl)-benzenesulfonamide (11g). A mixture of 4-(2-pyrrolidinoacetamido)bezenesulfonamide **10b** (3.53 mmol, 1.00 g) and potassium carbonate (3.53 mmol, 0.49 g) in a dry mixture of acetonitrile and acetone (20 ml) was reacted with cyclohexyl-isothiocyanate (3.52 mmol, 0.5 ml). Product **11g** was obtained as cream-white leaf-like crystals (0.69 g, 46.3 %); mp = 223.8–225.2 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.37 (s, 1H, NH), 10.39 (br-s, 1H, NH), 8.64 (d, 1H, *J* 7.5 Hz, NH), 7.88 (d, 2H, *J* 8.8 Hz, 2 × ArH), 7.84 (d, 2H, *J* 8.7 Hz, 2 × ArH), 4.31 (s, 2H, CH_2), 3.90 (m, 1H, CH), 1.96 (m, 4H, 2 × CH_2), 1.61 (m, 4H, 2 × CH_2), 1.51 (m, 4H, 2 × CH_2), 1.23–1.21 (m, 6H, 3 × CH_2); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 177.2 (C=S), 164.8 (C=O), 142.8 (ArC), 134.3 (ArC), 129.4 (ArCH), 119.2 (ArCH), 56.2 (CH_2), 54.5 (CH_2), 52.8 (CH), 31.3 (CH_2), 25.4 (CH_2), 24.1 (CH_2), 23.2 (CH_2): **IR** (KBr cm^{-1}): 3278 (N-H), 2956 (ArC-H), 1691 (C=O), 1593 (C=C), 1172 (C=S); HRMS (ESI-TOF): calculated for $C_{19}H_{28}N_4O_3S_2$ $[M+2]^+$ 426.1759; found: 426.1816.

4-(2-Pyrrolidinoacetamido)-*N*-(butylcarbamothioyl)-benzenesulfonamide (11h). A mixture of 4-(2-pyrrolidinoacetamido)bezenesulfonamide **10b** (1.83 mmol, 0.52 g) and potassium carbonate (1.83 mmol, 0.25 g) in a dry mixture of acetonitrile and acetone (10 ml) was reacted with butyl-isothiocyanate (1.83 mmol, 0.2 ml). Product **11h** was obtained as cream-white crystals (0.38 g, 53.2 %); mp = 218.6–220.1 °C; **^{1}H NMR (400 MHz, DMSO-d$_6$), δ**$_H$ (ppm), 11.18 (s, 1H, NH), 10.28 (br-s, 1H, NH), 8.36 (t, 1H, *J* 5.2 Hz, NH), 7.65 (d, 2H, *J* 8.4 Hz, 2 × ArH), 6.61 (d, 2H, *J* 8.4 Hz, 2 × ArH), 3.41–3.89 (m, 4H, 2 × CH_2), 3.35–3.30 (m, 4H, 2 × CH_2), 1.96 (m, 4H, 2 × CH_2), 1.45–1.39 (m, 2H, CH_2), 1.18 (q, 2H, *J* 7.6 Hz, H-12), 0.83 (t, 2H, *J* 7.2 Hz CH_3); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ**$_C$ (ppm), 178.6 (C=S), 166.7 (C=O), 142.1 (ArC), 132.8 (ArC), 129.5 (ArCH), 117.5 (ArCH), 47.8 (CH_2), 44.7 (CH_2), 30.4 (CH_2), 25.4 (CH_2), 19.9 (CH_2), 14.1 (CH_2), 13.4 (CH_3): **IR** (KBr cm^{-1}): 3297 (N-H), 2937 (ArC-H), 1694 (C=O), 1595 (C=C), 1156 (C=S). HRMS (ESI-TOF): calculated for $C_{17}H_{26}N_4O_3S_2$ $[M]^+$ 398.1446; found: 398.1502

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of new compounds are available in the supplementary material file associated with this manuscript.

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