A New and Simple Synthesis of Sulfonyl Ureas from Sulfonamides and *N*-Alkyl-1,2,4-dithiazolidine-3,5-diones

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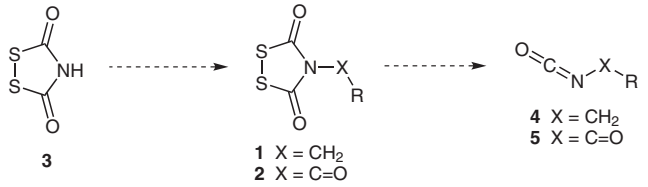
Abstract: A new, short, and simple synthetic approach to sulfonyl ureas is reported. The method involves the transformation of readily synthesized *N*-alkyl-1,2,4-dithiazolidine-3,5-diones by reaction with primary sulfonamides. Sulfonyl ureas were obtained in moderate to high yields.

Key words: sulfonyl ureas, isocyanates, sulfonamides, heterocycles, protecting group

Isocyanates and acyl isocyanates are important and useful agents for the preparation of *N*-acyl ureas and *N*-acyl carbamates, as well as, for the synthesis of a variety of heterocycles.[1–4]

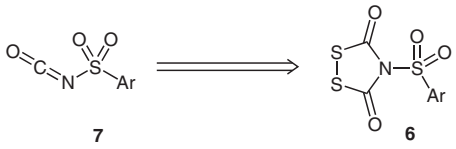
Recent studies have shown that *N*-alkyl-1,2,4-dithiazolidine-3,5-diones[5,6] **1** and *N*-aroyl-1,2,4-dithiazolidine-3,5-diones[7] **2** can be prepared relatively easily by the reaction of alkyl halides and acid chlorides with the heterocyclic scaffold **3**.[8–10] These compounds are regarded as protected isocyanates, as upon treatment with triphenylphosphine under anhydrous conditions, the respective isocyanate **4** is formed in situ. In the case of protected acyl isocyanates **5**, it has recently been demonstrated that the reaction with the desired amine and alcohol nucleophiles proceeds in the absence of triphenylphosphine (Scheme 1).[7]



Scheme 1 *N*-Alkyl- and *N*-aroyl-1,2,4-dithiazolidine-3,5-diones as isocyanate and acyl isocyanate equivalents

As part of a medicinal chemistry program, we have been investigating new synthetic methods for accessing sulfonyl ureas. In this regard the use of *N*-alkyl- and/or *N*-aroyl-1,2,4-dithiazolidine-3,5-diones appealed to us. We had originally envisaged proceeding via *N*-arylsulfonyl-1,2,4-dithiazolidine-3,5-diones **6** which would generate sulfonyl isocyanates **7** in situ via treatment with triphenylphosphine (Scheme 2).

As previously described in the literature,[5,7] the predicted approach to the *N*-acyl imides **2** was to react the NH imide with an acid chloride in the presence of a base (pyridine was chosen as the base and solvent for this type of reaction) following studies of the reaction of phthalimide with benzoyl chloride.[11] Following this protocol as well as using other bases such as Hünig's base, cesium carbonate, and potassium *tert*-butoxide, the various efforts were unsuccessful. Eventually success was achieved by performing the reaction in dichloromethane and using poly(4-vinylpyridine) as an insoluble base.[7]



Scheme 2 *N*-Arylsulfonyl-1,2,4-dithiazolidine-3,5-dione as a hypothetical protected isothiocyanate

Our initial attempts to generate the equivalent *N*-sulfonyl imide followed a similar strategy. Various weak bases, including pyridine, *N*,*N*-dimethylaminopyridine, sodium bicarbonate, potassium carbonate, cesium carbonate, as well as solvent systems, including *N*,*N*-dimethylformamide (DMF), dichloromethane, and pyridine were attempted but to no avail. Our lack of success was attributed to the possible high instability of the desired *N*-sulfonyl imide product. Several other observations already recorded in the literature may help explain the failure of these attempts. Decomposition of 1,2,4-dithiazolidine-2,5-dione in reactions with alkyl halides using DMF and dimethylsulfoxide as solvent, as well as at elevated temperatures (>40 °C) had been documented.[5] The reactivity and decomposition of 1,2,4-dithiazolidine-2,5-diones in the presence of amines (and amine bases), respectively, is also well described in the literature.[10]

In view of the failure of our initial approach, an alternative route to access the desired target compounds was considered. The reaction of 1,2,4-dithiazolidine-2,5-dione **3** with alkyl halides is well documented (Scheme 3, Table 1).[5] The resulting *N*-alkyl-1,2,4-dithiazolidine-2,5-diones **1**, in the presence of triphenylphosphine, were converted into isocyanates and reacted with amines to give

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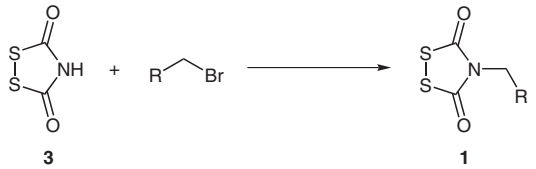
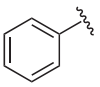
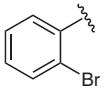
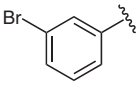
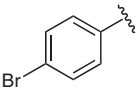
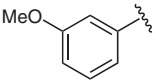
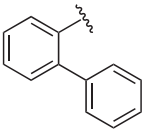
the corresponding ureas. Based on this, we proposed that reaction of protected isocyanates **1** with primary sulfonamides in the presence of triphenylphosphine and a weak base would give the desired corresponding sulfonyl ureas.

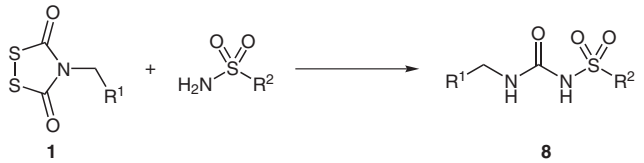
Thus, following the optimized protocol[5] using acetonitrile as the solvent and sodium bicarbonate as the base, a range of *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **1** were synthesized by the coupling of 1,2,4-dithiazolidine-3,5-dione **3** with various alkyl bromides.



Scheme 3 Alkylation of 1,2,4-dithiazolidine-3,5-dione. *Reagents and conditions*: $NaHCO_3$ (2 equiv), MeCN, 20 °C, 16 h.

Table 1 Synthesis of *N*-Alkyl-1,2,4-dithiazolidine-3,5-diones

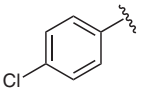
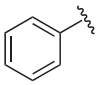
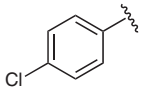
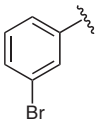
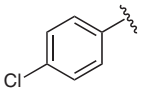
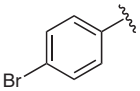
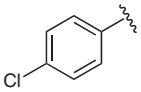
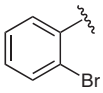
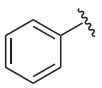
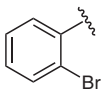
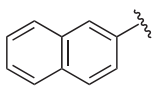
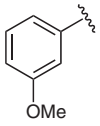
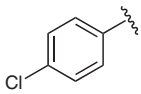
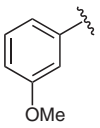
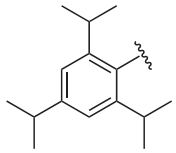
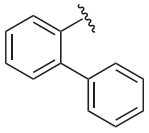
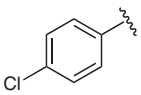
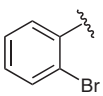
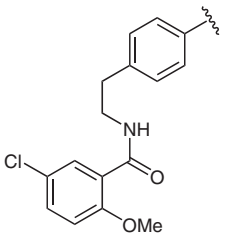
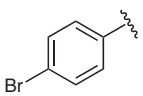
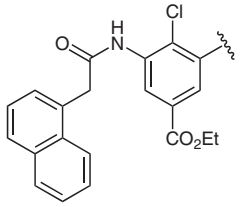
Entry	R	Product	Yield (%)
1	CO_2Et	**1a**	65
2		**1b**	74
3		**1c**	94
4		**1d**	79
5		**1e**	92
6		**1f**	68
7		**1g**	76
8		**1h**	78



Scheme 4 Reaction of *N*-alkyl-1,2,4-dithiazolidine-3,5-diones with sulfonamides *Reagents and conditions*: Ph_3P (1 equiv), K_2CO_3 (1 equiv), PhMe, reflux, 24 h.

A number of the *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **1** were chosen and successfully reacted with 4-chlorobenzene sulfonamide in the presence of triphenylphosphine

Table 2 Synthesis of Sulfonyl Ureas from *N*-Alkyl-1,2,4-dithiazolidine-3,5-diones

Entry	R^1	R^2	Product	Yield (%)
1	CO_2Et		**8a**	48
2			**8b**	65
3			**8c**	52
4			**8d**	58
5			**8e**	79
6			**8f**	67
7			**8g**	67
8			**8h**	32
9			**8i**	71
10			**8j**	80
11			**8k**	47

and potassium carbonate in toluene. As a result of the success of this reaction, a number of structurally diverse sulfonamides were then used to emphasize the broad scope of the reaction. Yields for target sulfonyl ureas **8** ranged from moderate to good (30–80%; Scheme 4, Table 2).

In summary, all attempts to develop a method to produce sulfonyl ureas via a *N*-arylsulfonyl-1,2,4-dithiazolidine-3,5-dione intermediate (protected sulfonyl isocyanate) were unsuccessful. However, a new method using readily available, diverse alkyl halides and sulfonamides (via the relatively easily accessible intermediate *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **1**) has been demonstrated. This method clearly provides a simple approach to new and novel classes of sulfonyl ureas. It is clear that this methodology has its limitations as, to date, only *N*-alkyl-1,2,4-dithiazolidine-3,5-diones **1** have been used. Further work to extend this methodology via the generation of possible *N*-aryl-1,2,4-dithiazolidine-3,5-dione intermediates would be important in order to extend this methodology to include the vast number of commercially available aryl halides.

All commercially available chemicals were purchased from either Sigma-Aldrich or Merck. All solvents were dried by appropriate techniques. Unless otherwise stated, all solvents used were anhydrous. Reactions were monitored by TLC using Merck silica gel plates (60 F-254), and were visualized by the ultraviolet light. Silica gel chromatography was performed using Merck kieselgel 60: 70–230 mesh for gravity columns. Melting points were determined on a Reichert-Jung Thermovar hotstage microscope and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet FTIR instrument in the 4000–500 cm^{-1} range using KBr discs. Microanalyses were determined using a Fisons EA 1108 CHNO-S instrument. Mass spectra were recorded at the School of Chemistry, University of the Witwatersrand. NMR spectra were recorded on either a Varian Mercury-300 (^{1}H NMR: 300.13 MHz; ^{13}C NMR: 75.5 MHz) or a Varian Unity-400 (^{1}H NMR: 400.13; ^{13}C NMR: 100.6 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from TMS as the internal standard.

General Procedure for the Synthesis of Alkyl/Aryl-[1,2,4]dithiazolidine-3,5-diones (1a–h)[5]

1,2,4-Dithiazolidine-3,5-dione **3** (100 mg, 0.74 mmol) was dissolved in MeCN (1.5 mL). $NaHCO_3$ (120 mg, 1.43 mmol) was added with stirring to the solution at r.t. (19 °C). The alkyl bromide (0.87 mmol) was added, and the mixture was left to stir for 16 h. The solvent was removed under reduced pressure with adsorption of the residue onto silica gel for purification by flash chromatography (EtOAc–hexane, 1:9).

Ethyl {3,5-Dioxo-[1,2,4]dithiazolidin-4-yl}acetate (1a)

Yield 65% (106 mg); yellow oil; R_f = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.46 (s, 2 H, CH_2), 4.25 (q, 2 H, *J* = 7.1 Hz, CH_2), 1.29 (t, 3 H, *J* = 7.2 Hz, CH_3).

4-Benzyl[1,2,4]dithiazolidine-3,5-dione (1b)

Yield 74% (124 mg); white crystals; mp 87–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2 H, 2 × ArH), 7.43 (m, 3 H, 3 × ArH), 4.91 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 167.47 (2 C), 136.18, 129.06 (2 C), 128.82 (2 C), 128.71, 49.38.

HRMS (EI): *m/z* = 224.99127 [M^+]. Anal. Calcd for $C_9H_7NO_2S_2$: C, 48.0; H, 3.13; N, 6.22; S, 28.5. Found: C, 47.8; H, 3.14; N, 6.10; S, 28.0.

4-(2-Bromobenzyl)[1,2,4]dithiazolidine-3,5-dione (1c)

Yield 94% (211 mg); white needlelike crystals; R_f = 0.21; mp 80–81 °C. IR (film): 3060 (w), 1655 (s), 1603 (m), 1477 (m), 1312 (s), 749 (s), 555 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, 1 H, *J* = 7.8, 1.3 Hz, ArH), 7.29 (td, 1 H, *J* = 7.6, 1.3 Hz, ArH), 7.18 (td, 1 H, *J* = 7.8, 1.7 Hz, ArH), 7.07 (dd, 1 H, *J* = 7.7, 1.7 Hz, ArH), 5.05 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.77 (2 C), 133.25, 132.78, 129.62, 127.86, 127.72, 122.85, 49.21. HRMS (EI): *m/z* = 302.90180 [M^+].

Anal. Calcd for $C_9H_6BrNO_2S_2$: C, 35.5; H, 1.99; N, 4.60; S, 21.1. Found: C, 34.9; H, 1.86; N, 4.18; S, 20.0.

4-(3-Bromobenzyl)[1,2,4]dithiazolidine-3,5-dione (1d)

Yield 79% (178 mg); white needlelike crystals; R_f = 0.30; mp 95–97 °C. IR (film): 3000 (w), 1652 (s), 1572 (m), 1474 (m), 1303 (s), 708 (s), 544 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 1 H, ArH), 7.47 (d, 1 H, *J* = 7.8 Hz, ArH), 7.34 (d, 1 H, *J* = 7.7 Hz, ArH), 7.21 (t, 1 H, *J* = 7.8 Hz, ArH), 4.86 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 167.34 (2 C), 136.17, 132.03, 131.96, 130.38, 127.73, 122.81, 48.57. HRMS (EI): *m/z* = 302.90191 [M^+]. Anal. Calcd for $C_9H_6BrNO_2S_2$: C, 35.5; H, 1.99; N, 4.60; S, 21.1. Found: C, 35.0; H, 1.84; N, 3.98; S, 19.8.

4-(4-Bromobenzyl)[1,2,4]dithiazolidine-3,5-dione (1e)

Yield 92% (207 mg); white crystals; R_f = 0.21; mp 93–97 °C. IR (film): 2995 (w), 1645 (s), 1486 (m), 1301 (s), 724 (s), 525 (w) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, 2 H, *J* = 8.4 Hz, 2 × ArH), 7.29 (d, 2 H, *J* = 8.30 Hz, 2 × Ar^2), 4.85 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 167.38 (2 C), 133.08, 132.03 (2 C), 130.86 (2 C), 123.02, 48.65. HRMS (EI): *m/z* = 302.90176 [M^+]. Anal. Calcd for $C_9H_6BrNO_2S_2$: C, 35.5; H, 1.99; N, 4.60; S, 21.1. Found: C, 35.1; H, 1.96; N, 4.09; S, 19.7.

4-Allyl[1,2,4]dithiazolidine-3,5-dione (1f)

Yield 68% (88 mg); clear, yellow oil; R_f = 0.31 (EtOAc–hexane, 1:19). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (m, 1 H, CH), 5.28 (m, 2 H, CH_2), 4.33 (dt, 2 H, *J* = 6.0, 1.4 Hz, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.35 (2 C), 129.18, 120.20, 47.96. HRMS (EI): *m/z* = 174.97561 [M^+].

4-(4-Methoxybenzyl)[1,2,4]dithiazolidine-3,5-dione (1g)

Yield 76% (143 mg); white, crystalline solid; R_f = 0.23 (EtOAc–hexane, 1:19); mp 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, 1 H, *J* = 8.3 Hz, ArH), 6.97 (m, 2 H, 2 × ArH), 6.87 (d, 1 H, *J* = 8.3 Hz, ArH), 4.87 (s, 2 H, CH_2), 3.80 (s, 3 H, OCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 167.42 (2 C), 159.85, 135.53, 129.85, 121.20, 114.51, 114.28, 55.27, 49.27. HRMS (EI): *m/z* = 255.00182 [M^+]. Anal. Calcd for $C_{10}H_9NO_3S_2$: C, 47.0; H, 3.55; N, 5.49; S, 25.1. Found: C, 46.9; H, 3.60; N, 5.31; S, 24.9.

4-(Biphenyl-2-ylmethyl)[1,2,4]dithiazolidine-3,5-dione (1h)

Yield 78% (174 mg); white, crystalline solid; R_f = 0.38 (EtOAc–hexane, 1:19); mp 92–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.14 (m, 9 H, 9 × ArH), 4.88 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 167.12 (2 C), 141.87, 140.20, 131.27, 130.41, 129.13 (2 C), 128.40 (2 C), 127.88, 127.85, 127.49, 126.49, 47.28. HRMS (EI): *m/z* = 301.02259 [M^+]. Anal. Calcd for $C_{15}H_{11}NO_2S_2$: C, 59.8; H, 3.68; N, 4.65; S, 21.3. Found: C, 59.9; H, 3.61; N, 4.58; S, 21.1.

General Procedure for the Synthesis of Sulfonyl Ureas 8a–k

One equiv of 4-chlorobenzene sulfonamide was added to a solution of alkylated 1,2,4-dithiazolidine-3,5-dione (50 mg for **8a–d** and 60 mg for **8e–k**) and Ph_3P (1 equiv) dissolved in toluene (2.0 mL). K_2CO_3 (1 equiv) was added, and the reaction was stirred under reflux for 24 h. The reaction mixture was allowed to cool to r.t. The

suspended material was filtered off and washed with deionised H_2O and toluene.

Ethyl 2-[3-(4-Chlorophenylsulfonyl)ureido]acetate (8a)
Purified by column chromatography (EtOAc–hexane, 1:9; adjusting to EtOAc–hexane, 2:3). Yield 48% (30.6 mg); yellow oil; R_f = 0.05 (EtOAc–hexane, 2:3). ^{1}H (400 MHz, DMSO): δ = 8.17 (s, 1 H, NH), 7.58 (m, 4 H, 4 × ArH), 4.12 (q and s overlapping, 3 H, J = 7.1 Hz, CH_2 and NH), 4.00 (s, 2 H, CH_2), 1.18 (t, 3 H, J = 7.1 Hz, CH_3). ^{13}C NMR (100.6 MHz, DMSO): δ = 171.43, 167.37, 131.45 (2 C), 128.97, 128.72 (2 C), 127.53, 45.99, 38.90, 13.90. MS (EI): m/z = 320.0 [M$^+$].

***N*-(Benzylcarbamoyl)-4-chlorobenzenesulfonamide (8b)**
Yield 65% (46.1 mg); white powder; mp 248–252 °C. IR (film): 3378 (s), 3028 (w), 1603 (s), 1476 (w), 1458 (s), 1344 (s), 1220 (s), 1134 (s), 728 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 7.72 (d, 2 H, J = 8.3 Hz, 2 × ArH), 7.37 (d, 2 H, J = 8.4 Hz, 2 × ArH), 7.22 (t, 2 H, J = 7.9 Hz, 2 × ArH), 7.14 (m, 3 H, 3 × ArH), 4.05 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, DMSO): δ = 160.50, 146.73, 133.53, 128.35 (2 C), 127.79 (2 C), 127.33 (2 C), 126.83 (2 C), 125.95, 123.46, 43.06. MS (EI): m/z = 324.0 [M$^+$]. Anal. Calcd for $C_{14}H_{13}N_2O_3SCl$: C, 51.8; H, 4.03; N, 8.63; S, 9.87. Found: C, 51.3; H, 3.73; N, 8.08; S, 9.24.

***N*-(3-Bromobenzylcarbamoyl)-4-chlorobenzenesulfonamide (8c)**
Yield 52% (46.1 mg); white powder; mp 240–244 °C. IR (film): 3386 (s), 3022 (w), 2933 (w), 1599 (s), 1458 (s), 1334 (s), 1214 (s), 1130 (s), 783 (s), 520 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 7.71 (d, 2 H, J = 8.2 Hz, 2 × ArH), 7.36 (m, 4 H, 4 × ArH), 7.16 (m, 2 H, 2 × ArH), 4.03 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, DMSO): δ = 160.65, 145.08, 133.54, 130.28, 129.94, 129.48, 128.74, 128.30 (2 C), 127.35 (2 C), 125.83, 121.35, 42.32. MS (EI): m/z = 400.9 [M$^+$]. Anal. Calcd for $C_{14}H_{12}BrN_2O_3SCl$: C, 41.7; H, 3.00; N, 6.94; S, 7.94. Found: C, 41.2; H, 2.69; N, 6.32; S, 7.18.

***N*-(4-Bromobenzylcarbamoyl)-4-chlorobenzenesulfonamide (8d)**
Yield 58% (51.5 mg); white powder; mp 243–247 °C. IR (film): 3378 (s), 3039 (w), 2882 (w), 1603 (s), 1574 (m), 1462 (s), 1343 (s), 1218 (s), 1133 (s), 755 (s), 521 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 7.70 (d, 2 H, J = 8.3 Hz, 2 × ArH), 7.38 (m, 4 H, 4 × ArH), 7.10 (d, 2 H, J = 8.0 Hz, 2 × ArH), 4.00 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, DMSO): δ = 160.75, 141.27, 133.70, 130.94, 130.62 (2 C), 129.10 (2 C), 128.34 (2 C), 127.39 (2 C), 118.90, 42.29. MS (EI): m/z = 400.9 [M$^+$]. Anal. Calcd for $C_{14}H_{12}BrN_2O_3SCl$: C, 41.7; H, 3.00; N, 6.94; S, 7.94. Found: C, 41.2; H, 2.44; N, 6.18; S, 7.57.

***N*-(2-Bromobenzylcarbamoyl)benzenesulfonamide (8e)**
Yield 79% (58.6 mg); white powder; mp 214–216 °C. IR (film): 3334 (s), 3054 (w), 2905 (w), 1623 (s), 1588 (m), 1532 (s), 1443 (s), 1366 (s), 1293 (m), 1133 (s), 753 (s), 579 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 7.71 (m, 2 H, 2 × ArH), 7.49 (d, 1 H, J = 7.5 Hz, ArH), 7.32 (m, 3 H, 3 × ArH), 7.23 (m, 2 H, 2 × ArH), 7.10 (t, 1 H, J = 7.6 Hz, ArH), 4.07 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, DMSO): δ = 166.42, 141.04, 132.90, 132.50, 129.70, 129.17, 128.71, 128.11 (2 C), 127.96, 126.98 (2 C), 122.57, 44.10. MS (EI): m/z = 368.0 [M$^+$]. Anal. Calcd for $C_{14}H_{13}BrN_2O_3S$: C, 45.5; H, 3.55; N, 7.59; S, 8.68. Found: C, 45.0; H, 2.96; N, 7.66; S, 8.04.

***N*-(2-Bromobenzylcarbamoyl)naphthalene-2-sulfonamide (8f)**
Yield 67% (56.5 mg); white powder; mp 166–170 °C. IR (film): 3371 (s), 1624 (s), 1590 (s), 1453 (s), 1337 (s), 1260 (m), 1182 (s), 744 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 8.24 (s, 1 H, ArH), 7.92 (m, 2 H, 2 × ArH), 7.84 (m, 2 H, 2 × ArH), 7.54 (m, 2 H, 2 × ArH), 7.47 (d, 1 H, J = 8.1 Hz, ArH), 7.18 (m, 2 H, 2 × ArH), 7.08 (t, 1 H, J = 8.0 Hz, ArH), 4.05 (s, 2 H, CH_2). ^{13}C NMR (100.6 MHz, DMSO): δ = 145.74, 133.75, 132.89, 132.62, 132.48, 129.25, 129.13, 128.68, 128.12, 127.90, 127.71, 127.42, 126.99, 126.17, 124.98, 122.55, 44.10. MS (EI): m/z = 418.0 [M$^+$]. Anal. Calcd for $C_{18}H_{15}BrN_2O_3S$: C, 51.6; H, 3.61; N, 6.68; S, 7.65. Found: C, 51.1; H, 3.28; N, 6.72; S, 6.30.

4-Chloro-*N*-(3-methoxybenzylcarbamoyl)benzenesulfonamide (8g)
Yield 67% (47.6 mg); white solid; mp 232–234 °C. ^{1}H NMR (400 MHz, DMSO): δ = 7.75 (d, 2 H, J = 8.4 Hz, 2 × ArH), 7.35 (d, 2 H, J = 8.5 Hz, 2 × ArH), 7.13 (t, 1 H, J = 7.8 Hz, ArH), 6.76 (m, 3 H, 3 × ArH), 4.07 (d, 2 H, J = 6.5 Hz, CH_2), 3.70 (s, 3 H, OCH_3). ^{13}C NMR (100.6 MHz, DMSO): δ = 160.58, 159.07, 146.76, 143.57, 133.45, 128.75, 128.34 (2 C), 127.28 (2 C), 119.02, 112.31, 111.52, 54.74, 42.82. MS (EI): m/z = 354.0 [M$^+$]. Anal. Calcd for $C_{15}H_{15}ClN_2O_4S$: C, 50.8; H, 4.26; N, 7.90; S, 9.04. Found: C, 50.2; H, 3.87; N, 6.76; S, 8.17.

2,4,6-Triisopropyl-*N*-(3-methoxybenzylcarbamoyl)benzenesulfonamide (8h)
Purified by column chromatography (EtOAc–hexane, 1:4); yield 32% (28.4 mg); white solid; R_f = 0.17); mp 135–137 °C. ^{1}H NMR (300 MHz, acetone): δ = 7.29 (s, 2 H, 2 × ArH), 7.13 (t, 1 H, J = 7.8, ArH), 6.79 (m, 3 H, 3 × ArH), 4.36 (sept, 2H, J = 6.8 Hz, 2 × CH), 4.29 (s, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 2.96 (sept, 1 H, J = 6.9 Hz, C*H*), 2.06 (m, 3 H, 3 × CH), 1.25 (m, 18 H, 6 × CH_3). ^{13}C NMR (75.5 MHz, acetone): δ = 160.17, 159.54, 153.19, 150.98 (2 C), 141.07, 133.78, 129.56, 123.91 (2 C), 119.43, 112.89, 112.74, 54.74, 43.15 (2 C), 34.15, 29.28, 24.29 (4 C), 23.15 (2 C). HRMS (EI): m/z = 446.22338 [M$^+$]. Anal. Calcd for $C_{24}H_{34}N_2O_4S$: C, 64.5; H, 7.67; N, 6.27; S, 7.18. Found: C, 63.9; H, 6.87; N, 6.76; S, 8.17.

***N*-(Biphenyl-2-ylmethylcarbamoyl)-4-chlorobenzenesulfonamide (8i)**
Yield 71% (56.9 mg); white solid; mp 192–195 °C. ^{1}H NMR (400 MHz, DMSO): δ = 7.70 (d, 2 H, J = 8.4 Hz, 2 × ArH), 7.48–7.11 (m, 11 H, 11 × ArH), 6.49 (t, 1 H, J = 5.8 Hz, CH_2NH), 4.05 (d, 2 H, J = 5.7 Hz, CH_2), 3.70 (s, 3 H, OCH_3). ^{13}C NMR (100.6 MHz, DMSO): δ = 160.58, 146.72, 140.41, 140.07, 137.65, 133.48, 129.13, 128.89 (2 C), 128.41, 128.30 (2 C), 128.07 (2 C), 127.31 (2 C), 127.03, 126.83, 125.99, 40.83. MS (EI): m/z = 400.0 [M$^+$]. Anal. Calcd for $C_{20}H_{17}ClN_2O_3S$: C, 59.9; H, 4.27; N, 6.99; S, 8.00. Found: C, 59.2; H, 3.99; N, 6.76; S, 7.17.

***N*-{4-[*N*-(2-Bromobenzylcarbamoyl)sulfamoyl]-phenethyl}-5-chloro-2-methoxybenzamide (8j)**
Yield 80% (92.6 mg); white powder; mp 206–210 °C. IR (film): 3363 (s), 3285 (s), 2902 (w), 1638 (s), 1615 (s), 1535 (s), 1508 (s), 1462 (s), 1342 (s), 1295 (s), 1227 (s), 1163 (s), 743 (s), 572 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 8.20 (t, 1 H, J = 5.5 Hz, NH-CO), 7.65 (m, 3 H, 3 × ArH), 7.48 (m, 2 H, 2 × ArH), 7.23 (m, 2 H, 2 × ArH), 7.21 (d, 2 H, J = 8.1 Hz, 2 × ArH), 7.12 (m, 2 H, 2 × ArH), 4.07 (s, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 3.51 (m, 2 H, CH_2), 2.82 (t, 2 H, J = 7.0 Hz, CH_2). ^{13}C NMR (75.5 MHz, DMSO): δ = 163.36, 160.44, 155.70, 145.84, 140.35, 132.15, 131.71, 131.43, 129.52, 128.93, 128.47, 127.91, 127.61, 127.16, 126.41, 125.56, 124.28, 122.14, 121.83, 114.11, 56.22, 43.34, 40.45, 34.52. MS (EI): m/z = 579.0 [M$^+$]. Anal. Calcd for $C_{24}H_{23}BrN_3O_5SCl$: C, 49.6; H, 3.99; N, 7.23; S, 5.52. Found: C, 49.0; H, 3.54; N, 6.25; S, 5.22.

Ethyl 3-[*N*-(4-Bromobenzylcarbamoyl)sulfamoyl]-4-chloro-5-[2-(naphthalene-1-yl)acetamido]benzoate (8k)
Yield 47% (50.7 mg); white powder; mp 213–217 °C. IR (film): 3366 (s), 3262 (s), 2978 (w), 1706 (s), 1673 (s), 1599 (s), 1512 (s), 1443 (s), 1315 (s), 1285 (s), 1243 (s), 1160 (s), 778 (s), 573 (s) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 8.30 (d, 1 H, J = 2.1 Hz, ArH),

8.27 (d, 1 H, *J* = 2.1 Hz, ArH), 8.16 (d, 1 H, *J* = 8.3 Hz, ArH), 7.94 (d, 1 H, *J* = 7.7 Hz, ArH), 7.85 (d, 1 H, *J* = 8.1 Hz, ArH), 7.53 (m, 3 H, 3 × ArH), 7.48 (d, 2 H, *J* = 8.5 Hz, 2 × ArH), 7.38 (d, 1 H, *J* = 8.3 Hz, ArH), 7.18 (d, 2 H, *J* = 8.5 Hz, 2 × ArH), 4.29 (m, 4 H, CH_2 and OCH_2), 3.97 (s, 2 H, CH_2), 1.28 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3). ^{13}C NMR (100.6 MHz, DMSO): δ = 170.68, 170.37, 165.51, 147.25, 141.17, 134.10, 132.81, 132.65, 131.70 (2 C), 131.33 (2 C), 129.88, 129.80, 129.13, 128.79, 128.09, 127.93, 127.60, 126.85, 126.44, 126.24, 124.86, 120.14, 119.57, 62.29, 61.78, 43.06, 14.83. MS (EI): *m/z* = 657.0 [M^+]. Anal. Calcd for $C_{29}H_{25}BrN_3O_6SCl$: C, 52.9; H, 3.82; N, 6.38; S, 4.87. Found: C, 51.5; H, 3.47; N, 5.76; S, 4.17.

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