Synthesis Y. Chen et al. Paper

# A Convenient Synthetic Approach to Saccharin Derivatives Containing a Sulfonylamidine Scaffold

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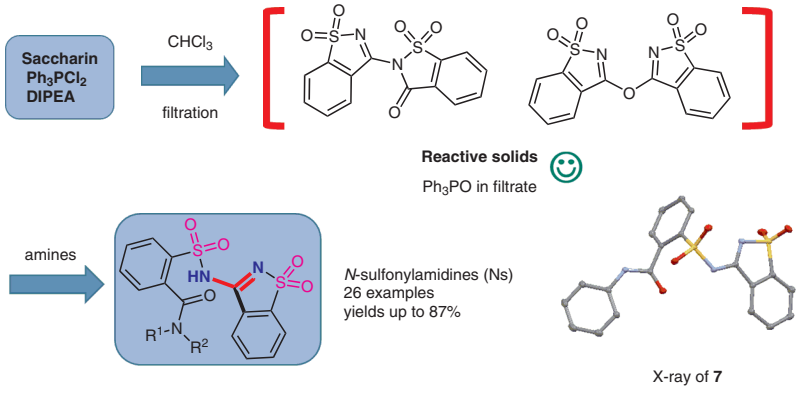



Received: 10.11.2017
Accepted after revision: 04.12.2017
Published online: 11.01.2018
DOI: 10.1055/s-0036-1591882; Art ID: ss-2017-t0727-op

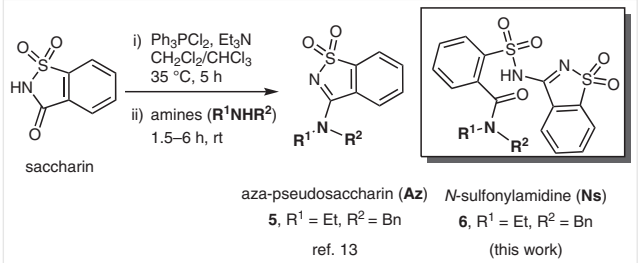
**Abstract** A key intermediate was obtained as solid through filtration of the reaction mixture of saccharin, chloro(triphenyl)phosphonium chloride, and *N*,*N*-diisopropylethylamine (DIPEA) in chloroform. The soluble triphenylphosphine oxide went to filtrate as waste, while the solid was reacted with amines to afford *N*-sulfonylamidines. In total, 26 *N*-sulfonylamidine products were obtained in moderate to good overall yields.

**Key words** amidine, *N*-sulfonylamidines, saccharin, chloro(triphenyl)phosphonium chloride, triphenylphosphine oxide, nucleophilic reaction, aza-pseudosaccharins, medicinal chemistry

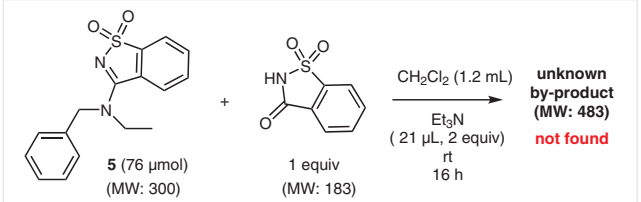
Amidines are commonly employed in medicinal chemistry[1] and organic chemistry.[2] Among functionalized amidines, *N*-sulfonylamidines (**Ns**) have been rarely studied after the first report by Schwenker and Bösl in 1970.[3] Since the late 1980s, the **Ns** moiety has been proposed as a prodrug form for the sulfonamide group.[4] Recently disclosed clinical examples of **Ns**-containing drugs include, but are not limited to, CCR4 chemokine antagonists **1**[5] and endothelin antagonist **2**[6] (Figure 1).

**Ns**-containing products have also been exploited for other drug discovery programs, such as antitumor studies,[7] neonicotinoid analogues,[8] antiresorptive agents for osteoporosis,[9] and antagonists of galectin-9.[10] However, the utility of **Ns** has been underexploited probably due to the limitations of synthetic scope and generality.[11] In 2013, Visser et al. at Novartis studied the role of the acidic nature of the N-heteroaryl sulfonamide **3** (Figure 1). By studying derivative **3** when co-crystallized with Bcl-2 family of proteins it was found that the isostere **4** appears to have similar binding mode as **3**. This was due to the additional vector from the S=O fragment in the saccharin core scaffold.[12]

In our previous work, chloro(triphenyl)phosphonium chloride ($Ph_3PCl_2$) was used as the chlorinating agent to prepare aza-pseudosaccharins (**Az**) from saccharin. However, the overall yields of the aza-pseudosaccharin deriva-




**Scheme 1** A general chemistry protocol for the synthesis of aza-pseudosaccharin and unexpected *N*-sulfonylamidine




**Scheme 2** A negative test for by-product formation

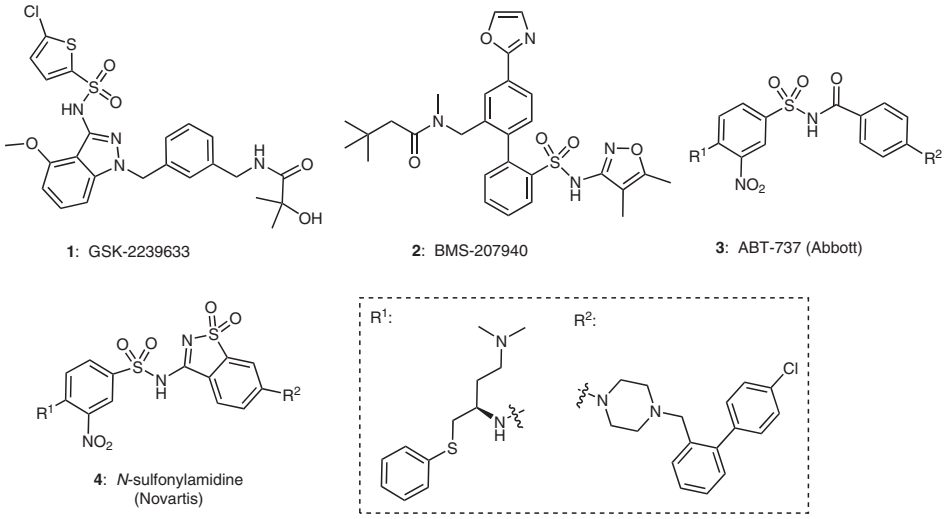
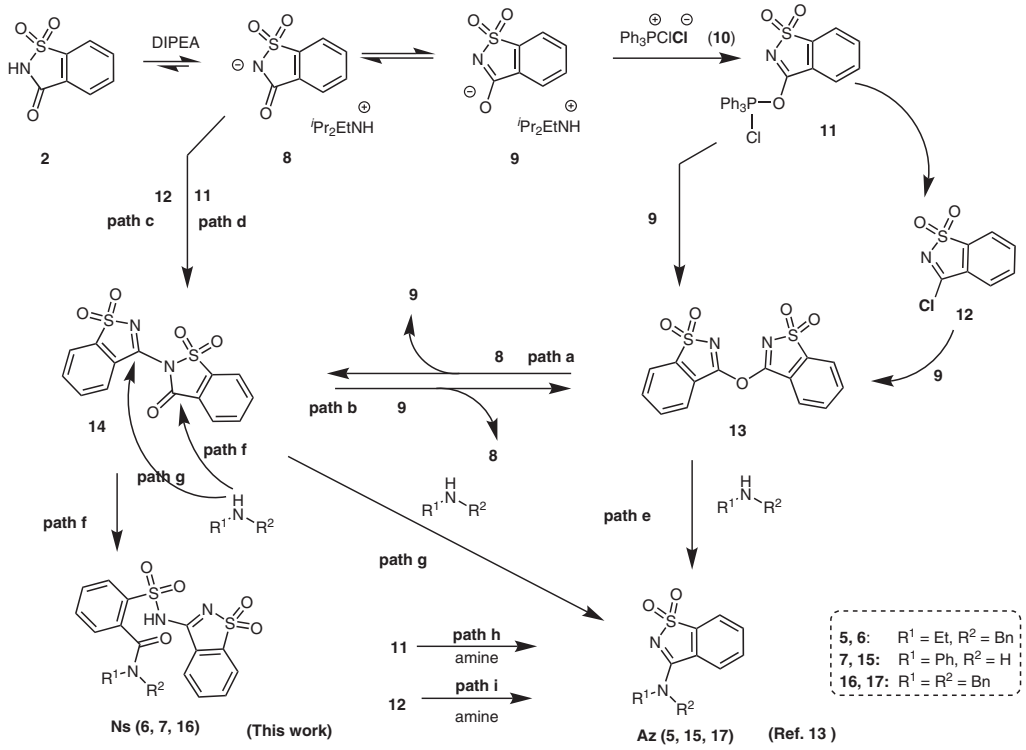



**Figure 1** Representatives of *N*-sulfonylamidines **1**, **2**, **4**, and linear acylsulfonamides **3**

tives were low (22–66%).[13] Under the reaction conditions, besides the expected **Az** product, we were surprised to find an additional product with a novel **Ns** scaffold (Scheme 1). This finding motivated us to optimize chemistry conditions to synthesize **Ns** products more selectively. Finally, through a one-pot approach, 26 saccharin derivatives containing **Ns** scaffolds were prepared in parallel in moderate to good overall yields. Structural features of the **Ns** scaffold, such as acidity and H-bonding potential, provide new opportunities in medicinal chemistry.

In the initial study, a by-product **6** was identified during the synthesis of the desired product **5** (Scheme 1). LCMS analysis of the reaction mixture revealed that the molecular weight of the by-product was 183 Da higher than **5**. Since




**Scheme 3** A possible mechanism of the formation of **Az** and **Ns** products

the unsubstituted saccharin has a molecular weight of 183 Da, we assumed that this by-product might be formed between **5** and unreacted saccharin. However, a quick test illustrated in Scheme 2 indicated that this assumption was incorrect because no reaction occurred when **5** was mixed with saccharin under the reaction conditions.

We tried to grow a crystalline solid of this by-product, but failed. Fortunately, when aniline was used as the amine, we isolated the analogous by-product **7**. Its structure was confirmed by X-ray results (Figure 2) (see Supporting information).[14]

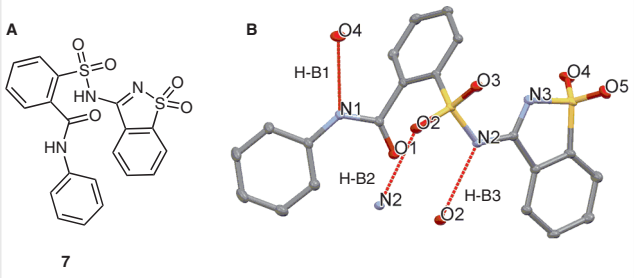



**Figure 2** Structure of **7**. **A**: 2D structure; **B**: X-ray crystal structure (CCDC 1522311). Three intermolecular H-bonds are displayed (only one full molecule is visualized for clarity).

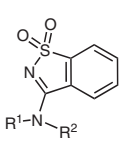
Based on the crystal structure result, we propose two key intermediates, namely **13** and **14**, for the formation of **5**, **6**, and related analogues (Scheme 3).

Under the conditions, saccharin (**2**) was deprotonated to form **8**. There is an equilibrium between **8** and **9**, and the latter reacts with $Ph_3PCl_2$ (**10**) to form **11** as the precursor to **12**. Compound **13** can be formed either directly from **11** or via the chloro species **12**. The reaction between **13** and **8** gives **14** (path a). Not surprisingly, **14** can react with **9** to give **13** back (path b). Additionally, **14** could be formed through the direct nucleophilic substitution between **8** and **12** (or **11**) (path c, d). Both **13** and **14** are reactive intermediates. The reaction between **13** and *N*-benzylethanamine (path e) afforded **5**, while the reaction between **14** and *N*-benzylethanamine may undergo two different nucleophilic reactions. The nucleophilic addition of **14** with the amine, followed by ring-opening affords *N*-sulfonylamidine **6** (path f), while the nucleophilic substitution of **14** with the amine led to the formation of **5** (path g). Another two possible pathways for the formation of **5** are through the nucleophilic substitution of **11** or **12** with the amine (path h, i). Triphenylphosphine oxide ($Ph_3PO$) was formed as the by-product from **10**.

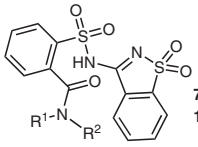
According to the proposed mechanism, we reasoned that if an excess amount of saccharin was used, the formation of **14** should be favored through three possible pathways (a, b, and c), thus **Ns** would be the major products. However, if an excess of $Ph_3PCl_2$ was used, **13** would be preferentially formed, leading to the formation of **Az** products.

Next, aniline and dibenzylamine were selected as the representatives of the nucleophiles for optimization. To study the chemoselectivity between **Az** and **Ns**, parallel experiments with different ratios of $Ph_3PCl_2$:saccharin:DIPEA:amine ([P]:[Sa]:[Di]:[Am]) were conducted, and the results are summarized in Table 1.

**Table 1** Selectivity between Azapseudosaccharins and *N*-Sulfonylamidines[a]



**15**, $R^1$ = Ph, $R^2$ = H
**17**, $R^1$ = $R^2$ = Bn



**7**, $R^1$ = Ph, $R^2$ = H
**16**, $R^1$ = $R^2$ = Bn

| Entry | Ratio [P]:[Sa]:[Di]:[Am] | $Ph_3PCl_2$ (mmol) | Amine | Ratio **Az**/**Ns**[b] |
|---|---|---|---|---|
| 1 | 1:3:5:5 | 0.1 | $PhNH_2$ | 2.0:1 |
| 2 | 1:1.4:3.4:5 | 0.1 | $PhNH_2$ | 2.8:1 |
| 3 | 1: 1:3:5 | 0.1 | $PhNH_2$ | 7.7:1 |
| 4 | 1.4:1:3.4:7 | 0.1 | $PhNH_2$ | 11:1 |
| 5 | 3: 1:5:15 | 0.3 | $PhNH_2$ | 15:1 |
| 6 | 1: 5:8:2[c] | 0.3 | $Bn_2NH$ | 0.5:1 |
| **7** | **1: 3.5:6.5:2[d]** | **0.3** | **$Bn_2NH$** | **0.48:1[e]** |
| 8 | 1: 4:7:2[d] | 0.3 | $Bn_2NH$ | 0.5:1 |

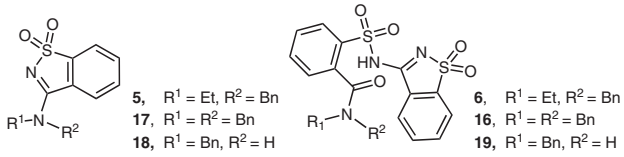
[a] General procedure: A mixture of $Ph_3PCl_2$, saccharin and DIPEA in $CHCl_3$ was stirred at 35 °C for 5 h, then the appropriate amine was added. The resulting mixture was stirred at r.t. for 6 h.
[b] Ratio of area integration of LCMS peaks of **Az** and **Ns**. Entries 1–5, the ratios of **15**:**7**; entries 6–8, the ratios of **17**:**16**. Detector: TIC (total ion current).
[c] The reaction mixture was stirred at r.t. for 23 h before the addition of amine.
[d] The reaction mixture was stirred at 60 °C for 6 h before the addition of amine.
[e] The ratio based on the NMR of the crude mixture was 0.47:1, which indicated that the LCMS analysis results were reliable in this work.

In this work, we focus on the preparation of **Ns** products. The results in Table 1 indicate that: 1) more equivalents of saccharin favored **Ns** formation; 2) results of entries 6 and 7 revealed that the reaction between saccharin and $Ph_3PCl_2$ went to completion after 23 hours stirring at room temperature or 6 hours stirring at 60 °C; and 3) NMR result was consistent with the result by LCMS analysis. Hence, LCMS peak area ratios were used to present the conversions of **Ns**. In the same manner, LCMS analysis was used in the following optimization experiments.

From the above tests, we noticed that a suspension was formed when saccharin, $Ph_3PCl_2$ and DIPEA were mixed in $CHCl_3$. We were curious about the components of the solids in the reaction mixture. Thus during a repetition of entry 7 (Table 1), the suspension was filtered before addition of the amine. To the filtrate was added benzylamine (Table 2,

entry 1). The solid was first mixed with DIPEA, and then EtNHBn and $Bn_2NH$ were added, respectively (entries 2, 3). The ratios of **Az**/**Ns** from each entry are given in Table 2.

**Table 2** Further Study on the Selectivity between **Az** and **Ns**




| Entry | Amine | **Ns**[a] | $Ph_3PO$[a] | Ratio **Az**/**Ns** |
|---|---|---|---|---|
| 1 | $BnNH_2$ | no product | 72 | – |
| 2 | EtNHBn | 57 | <3 | 0.47:1 |
| 3 | $Bn_2NH$ | 46 | <3 | 0.91:1 |

[a] LCMS peak area percentage.

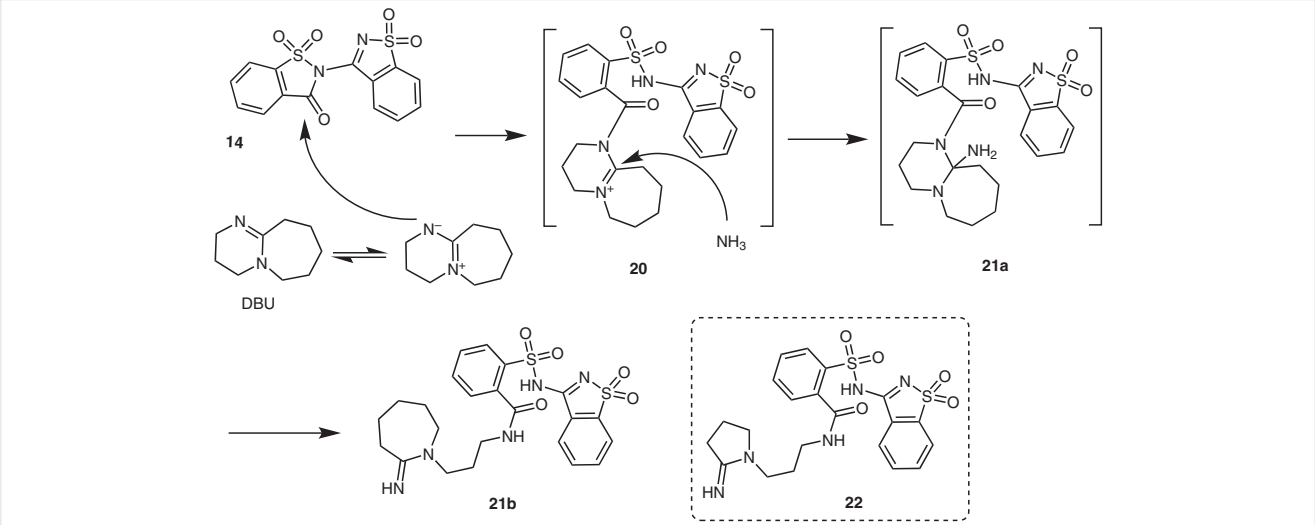
LCMS results of entry 1 (Table 2) show that there is no active intermediate **13** or **14**, but $Ph_3PO$ remains in the filtrate. $^1H$, $^{13}C$, and $^{31}P$ NMR results of the filtrate using $CDCl_3$ as the reaction solvent indicate that $Ph_3PO$ and the salt of saccharin with DIPEA are the main components in the filtrate (for comparison with commercial $Ph_3PO$, see Supporting Information, page S8–S11).

Entry 2 (Table 2) shows an exciting result from a purification perspective. $Ph_3PO$ is well known as a side product in reactions involving triphenylphosphine, or other analogues such as $Ph_3PCl_2$ in this work. The separation of $Ph_3PO$ can be accomplished by means of chromatography when the reaction scale is small, but it can become difficult on a large scale. In order to achieve the process scalability, Lukin et al. reported the remarkable development of a nonchromatographic method for the removal of $Ph_3PO$ through the precipitation of the $Ph_3PO/MgCl_2$ complex from the Mitsunobu reaction mixture.[15] Recently, Weix et al. disclosed a new method of removal of $Ph_3PO$ by precipitation with $ZnCl_2$ in polar solvents.[16] In the current work, the purification issue was simply solved by filtration of the reaction mixture: $Ph_3PO$ remained in $CHCl_3$ solution, while the 'active' solid was isolated, and used directly for further synthesis.

Entries 2 and 3 (Table 2) showed only trace of $Ph_3PO$. We can conclude that **11** is not one of the components in the solid. Since 3.5 equivalents of saccharin and 6.5 equivalents of DIPEA were used, we reason that the unreacted saccharin salts **8** and **9** are also present in the solid. The formation of both **Az** and **Ns** products in entries 2 and 3 (Table 2) reveals that both **13** and **14** existed in the solid. NMR analysis (using DMSO-$d_6$ as the solvent) of the solid was performed, but the spectra were too complex to interpret (see Supporting Information, page S12).

Other organic bases, such as 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) were also tried. Interestingly, after the addition of $Bn_2NH$, only approximately 15% conversion of **16** was achieved. To study the chemistry, the LCMS results prior the addition of the amine were checked. Surprisingly, we found that DBU itself participated as a nucleophile and reacted with **14** to form the unexpected product. A proposed mechanism is illustrated in Scheme 4.

DBU has been reported as a nucleophilic base by several research groups.[17] It was also reported as a nucleophilic catalyst for the esterification of carboxylic acids with dimethyl carbonate.[18] In 2003, Page et al. reported an unexpected nucleophilic participation of DBU and proposed a rearrangement of DBU in reactions with saccharin derivatives.[19] Similarly, we propose that **21b** was formed through rearrangement of **21a**, which was formed through the nucleophilic reaction of the DBU-derived intermediate **20** with the




**Scheme 4** Suggested mechanism of nucleophilic DBU participation in the formation of **21b**

ammonia present in the LCMS buffer. Not surprisingly, **22**, the analogue of **21b**, was also formed when 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) was used.

Taking all the above results into account, we suggest the key conditions for the synthesis of **Ns** products as follows: a $Ph_3PCl_2$:saccharin:DIPEA:amine ratio of 1:3.5:6.5:2 (Table 1, entry 7); the reaction mixture of saccharin and $Ph_3PCl_2$ should be stirred at 60 °C for 6 hours; the resulting suspension mixture should be filtered to remove $Ph_3PO$, and the resulting solid should be handled under $N_2$ environment.

Having the key conditions in hand, we prepared the 'active' solids on a large scale, then the solids were even divided into vials, in which a mixture of DIPEA and an amine was pre-added. When reactions were complete, solvents were evaporated in vacuo. A solution of each resulting residue in DMSO was subjected for a plate-based purification, which was performed at the Separation Science Laboratory (SSL) at AstraZeneca R & D, Gothenburg. Figure 3 demonstrates the process of an AstraZeneca workflow, from crude submission by chemists to analytical data collections.

Results in Scheme 5 show that the isolated yields were overall higher when secondary amines were used. Primary amines usually afforded poor yields. Under the optimized conditions, $BnNH_2$ mainly afforded the **Az** product **18** with >90% conversion by LCMS analysis; we attempted to isolate the **Ns** product **19**, but it was discarded due to low yield (<7%) and poor purity (<88%). Primary heteroaromatic amines generally afforded moderate yields of **24**, **26**, and **27**, while 2-aminopyridine gave very low yield of **23**. Under the reaction conditions, several functional groups were tolerated, such as amides, alcohols, esters, ethers, tertiary amines, allyl group, and some heterocycles.

In summary, *N*-sulfonylamidine derivatives **Ns** of saccharin were prepared by a convenient synthetic approach from saccharin, chloro(triphenyl)phosphonium chloride, and *N*,*N*-diisopropylethylamine in chloroform. The key intermediate formed could be purified by separation of $Ph_3PO$ through filtration to afford the active solid, which simplified the purification of the reaction mixture. Under the optimized conditions, the active solid was reacted with amines to afford the novel **Ns** products. Although the yields were low in some cases, the parallel chemistry provided a simple approach to access this novel scaffold from saccharin. The acidity and H-bonding potential of the saccharin-based sulfonylamidines can be applied in the field of medicinal chemistry. This novel **Ns** scaffold can be potentially used as ligands for metallic catalysis in organic and inorganic chemistry.

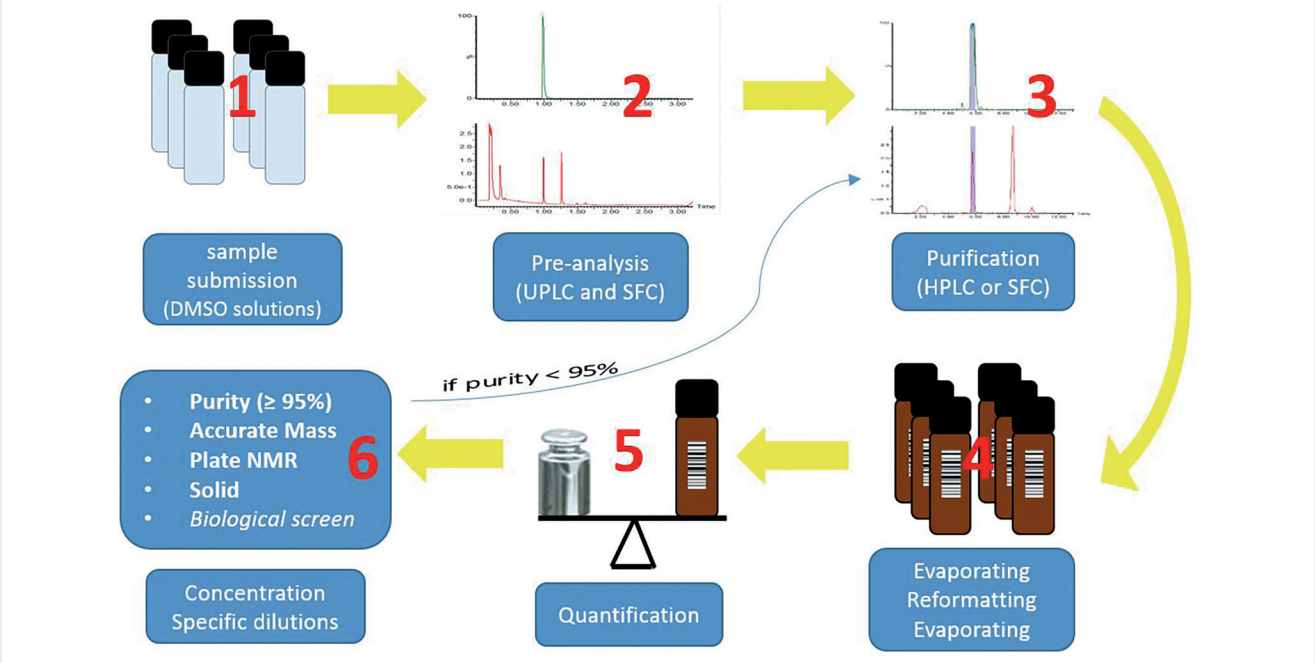
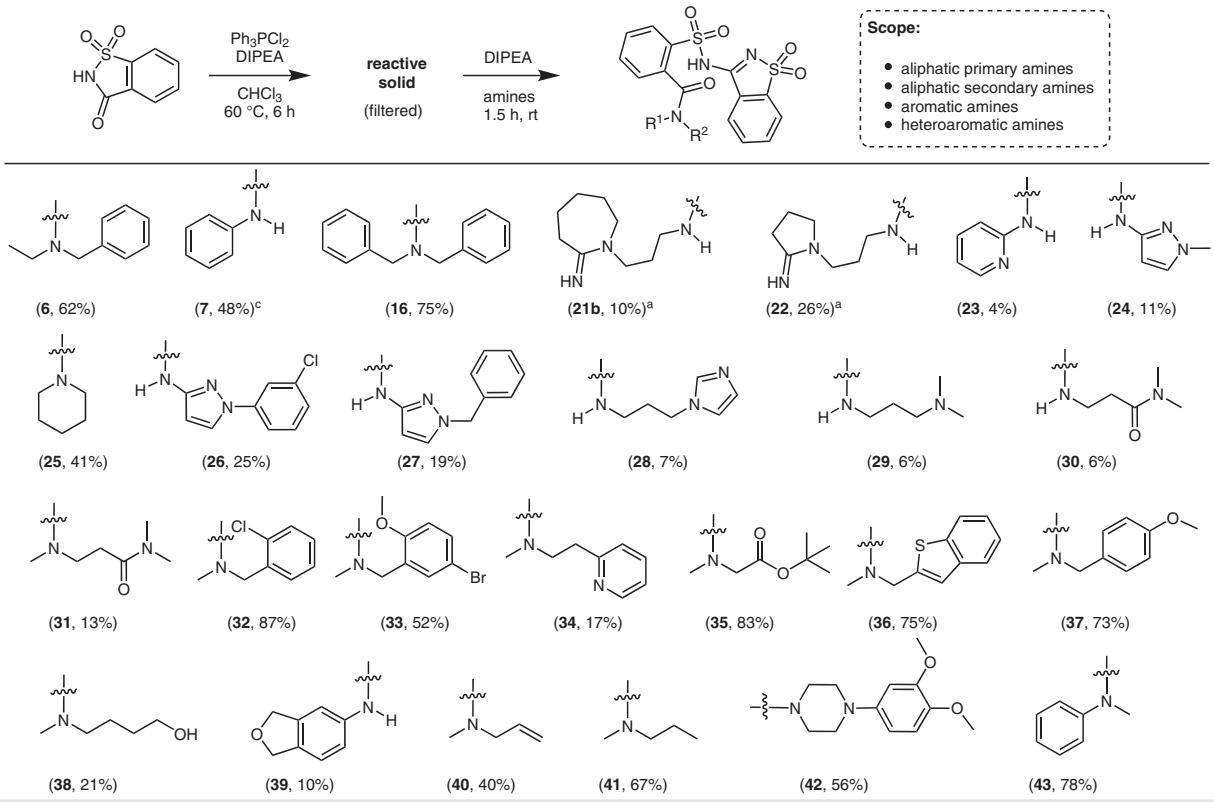



**Figure 3** Six stages of a standard purification workflow that is applied in AstraZeneca R & D, Gothenburg: 1) sample submission by synthetic chemists; 2) sample pre-analysis by both Ultra-Performance Liquid Chromatography (UPLC) and Supercritical Fluid Chromatography (SFC) to find the best separation condition; 3) sample purification by either HPLC or SFC; a combination of UV and MS is used to trigger the fraction collection, making sure that only the target compound is collected and that close-eluting impurities are removed; 4) the fractions are evaporated, reformatted into auto-vials, and evaporated a second time to afford dry products; 5) sample quantification by weight; and 6) a concentration specific dilution is performed to create plates for purity (at 210 nm) and accurate mass analysis, NMR and biological screen. The majority of the final products are pure after first purification attempt, while if purity <95%, the sample goes back to stage 3 for re-purification. Finally, the parallel chemistry was performed under the optimized conditions to afford the **Ns** products (Scheme 5).




**Scheme 5** Final product formation using parallel chemistry. Scale: 0.5 mmol $Ph_3PCl_2$, which was used to determine the isolated yields. The product code and the isolated yield are given in parentheses. All products having <95% purity were re-purified, and their yields are shown in italics. [a] Products **21b** and **22** were obtained when DMSO as solvent and aqueous ammonia as the nucleophile were applied.

Unless otherwise noted all materials and reagents were obtained from commercial sources and used without further purification. All solvents used in moisture sensitive reactions were of commercial anhydrous grade, and they were dried over MS (3 Å) before use. Melting points were measured on a Mettler Toledo DSC823e apparatus.The sample was heated at a rate of 3 °C/min. The onset value was used as mp result. NMR spectra were recorded on a Bruker Avance III spectrometer at 25 °C at a $^1$H frequency of 600.13 MHz and $^{13}$C NMR at 150.90 MHz. The chemical shifts (δ) are reported in ppm and referenced indirectly to TMS via the solvent signals ($^1$H: DMSO-$d_6$ at 2.50 ppm, and $^{13}$C: DMSO-$d_6$ at 39.50 ppm). Multiplicities are reported using the standard abbreviations. In the following NMR assignment for **7**, **16**, **23**–**28**, **30**, **35**–**41**, the sulfonamide NH signal is not detectable due to $H_2O$ exchange.

### Pre-Analysis and Preparative Chromatography; General Methods

Pre-analysis using LC was conducted on Waters Acquity SQD MS with two different columns: Waters Acquity HSS C18 1.8 µm, 2.1 × 50 mm, and Waters Acquity BEH C18 1.7 µm, 2.1 × 50 mm. A gradient of 2–94% MeCN (10 mM formic acid or 0.2% ammonia) was used with a flow of 1 mL/min in 2.5 min at 45 °C.

Pre-analysis using SFC was conducted on Waters Acquity UPC$^2$ 3100 MS. A gradient of 5–50% MeOH/ammonia 20 mM was used with a flow of 4 mL/min in 4 min at 40 °C and 120 bar on three different columns: 1) Phenomenex Luna Hilic 3.5 µm, 3 × 100 mm; 2) Waters Acquity UPC$^2$ BEH 2-EP 3.5 µm, 3 × 100 mm; and 3) Waters Acquity UPC$^2$ BEH 3.5 µm, 3 × 100 mm. A gradient of 5–50% MeOH/$H_2O$/ammonia 95:5:50 mM was also used with the same gradient and conditions on the column of Waters Acquity UPC2 BEH 3.5 µm, 3 × 100 mm.

The compound purity and accurate mass were determined on a Waters Acquity UPLC Xevo Q-TOF using two different columns: 1) Waters Acquity CSH C18 1.7 µm, 2.1 × 50 mm, and 2) Waters Acquity BEH C18 1.7 µm, 2.1 × 50 mm. A gradient of 5–90% MeCN (10 mM formic acid and 1 mM ammonium formate or 40 mM ammonia and 6.5 mM ammonia carbonate) was used with a flow of 1 mL/min in 2.5 min at 45 °C.

Preparative LC was performed on Waters Fraction Lynx system using one of two different columns: Waters Sunfire C18 ODB 5 µm, 30 × 150 mm, and Waters Xbridge C18 5 µm ODB, 30 × 150 mm. A focused 50% MeCN gradient (0.1 M formic acid or 0.2% ammonia) was used with a flow of 60 mL/min in 8.3 min at ambient temperature.

Preparative SFC was done on Waters Prep 100 SFC MS using one of two different columns: Waters BEH 5 µm, 30 × 250 mm, and Waters BEH 2-EP 5 µm, 30 × 250 mm. A focused 5% gradient (MeOH/20 mM ammonia) was used with the flow of 100 g/min in 6 min at 40 °C and 120 bar.

### 3-[(1,1-Dioxo-1,2-benzothiazol-3-yl)oxy]-1,2-benzothiazole 1,1-Dioxide (13) and 2-(1,1-Dioxo-1,2-benzothiazol-3-yl)-1,1-dioxo-1,2-benzothiazol-3-one (14)

A mixture of $Ph_3P$ (3148 mg, 12 mmol, 1 equiv) and hexachloroethane (2982 mg, 12.6 mmol, 1.05 equiv) in $CHCl_3$ (total volume 40 mL) was stirred at 65 °C for 8 h. After cooling to r.t., under $N_2$, to the mixture was added saccharin (7690 mg, 42.0 mmol, 3.5 equiv) in one portion, followed by the addition of the stock solution of DIPEA in $CHCl_3$ (1.32 M, 59 mL, 78 mmol, 6.5 equiv). The resulting mixture was heated under $N_2$ at 60 °C for 6 h. The mixture was cooled to r.t. and filtered under $N_2$. The solid crude was washed with $CHCl_3$ (3 × 5 mL) and dried under vacuum. The dry solid (5410 mg) was kept under $N_2$. No further separation was attempted, and the resulting solid was used directly in the parallel chemistry. The total yield from $Ph_3P$ to the solid was assumed to be 100%, thus the theoretical amount of the 'active' mixture of **13** and **14** was 451 mg/mol.

### Parallel Chemistry; General Procedure (Scheme 5)

Under $N_2$, to a mixture of the dry solid **13**/**14** (226 mg, 0.5 mmol) was added a stock solution of DIPEA (1.5 M, 2.17 mL, 3.25 mmol, 6.5 equiv) in $CHCl_3$ at r.t. The mixture was stirred at r.t. for 5 min before a solution of the appropriate amine (1.0 mmol, 2 equiv) in $CHCl_3$ (2 mL) was added. If the amine was in the form of HCl salt, 1 equiv extra of DIPEA was added to the reaction mixture. The resulting mixture was stirred at r.t. for 20 h, and then heated at 60 °C for 15 min. The solvents were evaporated, and the dry residue was dissolved in DMSO (4 mL). The DMSO solution was submitted to purification group for isolation.

### 2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-[3-(2-iminoazepan-1-yl)propyl]benzamide (21b) and 2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-[3-(2-iminopyrrolidin-1-yl)propyl]benzamide (22)

Under $N_2$, to a mixture of the dry solid **13**/**14** (226 mg, 0.5 mmol) in $CHCl_3$ (4 mL) was added DBU (152 mg, 1.0 mmol, 2 equiv) or DBN (124 mg, 1.0 mmol, 2 equiv) at r.t. The resulting mixture was stirred at 55 °C for 1.5 h. After cooling to r.t., to the mixture was added aq ammonia solution (25%, 5 mL, 71 equiv), and the reaction mixture was stirred at r.t. for 1 h. The solvents were evaporated in vacuo, and the residue was dissolved in DMSO (4 mL), which was submitted to purification group for isolation.

For spectral data, see below.

### *N*-Benzyl-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-ethylbenzamide (6)

Yield: 150.1 mg (62%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.03* (dd, *J* = 8.0, 1.1 Hz, 0.5 H), 7.98–7.94* (m, 0.5 H), 7.83–7.78* (m, 0.5 H), 7.77–7.74* (m, 0.5 H), 7.73–7.66* (m, 1.5 H), 7.63–7.47* (m, 4 H), 7.46–4.43* (m, 1 H), 7.36–7.26* (m, 3.5 H), 7.25–7.18* (m, 1 H), 7.14–7.10* (m, 1 H), 4.90* (d, *J* = 15.0 Hz, 0.5 H), 4.48–4.38* (m, 1 H), 4.09* (d, *J* = 17.2 Hz, 0.5 H), 3.83–3.75* (m, 0.5 H), 3.19–3.09* (m, 0.5 H), 2.87–2.74* (m, 1 H), 1.07* (t, *J* = 7.02 Hz, 1.4 H), 0.83* (t, *J* = 7.02 Hz, 1.6 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.7*, 160.4*, 160.2*, 141.53*, 141.46*, 139.8*, 139.4*, 137.8*, 137.5*, 135.6*, 135.4*, 134.22*, 134.18* (C) , 132.5*, 132.2*, 132.1*, 131.9*, 131.1*, 131.0*, 129.1, 128.9, 128.5, 128.20, 128.16, 128.1*, 128.0*, 127.12*, 127.07*, 127.0*, 126.9*, 126.8*, 123.3*, 123.2*, 120.0, 119.9* (CH), 51.4* ($CH_2$), 45.7* ($CH_2$), 42.3* ($CH_2$), 38.3* ($CH_2$), 12.8* ($CH_3$), 11.4* ($CH_3$).

* Separate signals due to the presence of rotamers (47:53).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_3O_5S_2$: 484.1001; found: 484.1022.

### 2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-phenylbenzamide (7)

Yield: 105 mg (48%); white solid; mp 180.5 °C (decompose).

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 10.4 (br s, 1 H), 7.93–7.89 (m, 1 H), 7.82–7.76 (m, 2 H), 7.73 (d, *J* = 7.4 Hz, 2 H), 7.72–7.64 (m, 2 H), 7.62 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.59–7.52 (m, 2 H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.05 (tt, *J* = 7.4, 1.1, 1 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 166.6, 160.2, 140.8, 139.7, 139.5, 136.3, 133.7 (C), 132.7, 132.5, 131.5, 129.4, 128.9, 128.6, 128.5, 123.5, 123.3, 120.1, 119.7 (CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_3O_5S_2$: 442.0531; found: 442.051.

### *N*,*N*-Dibenzyl-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]benzamide (16)

Yield: 203.4 mg (75%); off-white solid; mp 100.7 °C .

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.05–7.99 (m, 1 H), 7.71 (d, *J* = 7.5 Hz, 1 H), 7.61 (td, *J* = 7.4, 1.0 Hz, 1 H), 7.53–7.47 (m, 3 H), 7.45–7.36 (m, 4 H), 7.34–7.29 (m, 2 H), 7.27–7.18 (m, 4 H), 7.91 (d, *J* = 7.3 Hz, 2 H), 5.25 (d, *J* = 15.1 Hz, 1 H), 4.36 (d, *J* = 16.6 Hz, 1 H), 3.91–3.82 (m, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 169.3, 160.3, 141.5, 139.4, 136.6, 136.4, 135.1, 134.1 (C), 132.2, 132.0, 131.2, 129.2, 128.6, 128.5, 128.2, 128.1, 127.4, 127.2, 127.0, 126.9, 123.2, 119.9 (CH), 51.1 ($CH_2$), 46.1 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{23}N_3O_5S_2$: 546.1157; found: 546.1162.

### 2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-[3-(2-iminoazepan-1-yl)propyl]benzamide (21b)

Yield: 25.6 mg (10%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 9.08 (br s, 1 H), 8.36 (t, *J* = 5.6 Hz, 1 H), 8.28 (br s, 1 H), 7.93 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.81–7.78 (m, 1 H), 7.77–7.74 (m, 1 H), 7.72–7.66 (m, 2 H), 7.60–7.51 (m, 2 H), 7.41 (dd, *J* = 7.5, 1.4 Hz, 1 H), 3.76–3.60 (m, 2 H), 3.59–3.52 (m, 2 H), 3.29 (q, *J* = 6.0 Hz, 2 H), 2.69–2.63 (m, 2 H), 1.84–1.77 (m, 2 H), 1.67–1.47 (m, 6 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 169.0, 168.0, 160.3, 141.0, 139.5, 136.5, 133.7 (C), 132.7, 132.4, 131.5, 128.94, 128.90, 128.7, 123.4, 120.2 (CH), 52.3, 49.6, 36.6, 31.9, 28.2, 26.5, 25.6, 23.1 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_5O_5S_2$: 518.1532; found: 518.1525.

### 2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-[3-(2-iminopyrrolidin-1-yl)propyl]benzamide (22)

Yield: 63.5 mg (26%); off-white solid; mp 263 °C.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 9.15 (br s, 1 H), 8.53 (br s, 1 H), 8.38 (t, *J* = 5.8 Hz, 1 H), 7.93 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.81–7.75 (m, 2 H), 7.72–7.65 (m, 2 H), 7.60–7.52 (m, 2 H), 7.42 (dd, *J* = 7.5, 1.4 Hz, 1 H), 3.62 (t, *J* = 7.2 Hz, 2 H), 3.52 (t, *J* = 7.7 Hz, 2 H), 3.25 (q, *J* = 6.1 Hz, 2 H), 2.81 (t, *J* = 8.0 Hz, 2 H), 2.00 (pent, *J* = 7.8 Hz, 2 H), 1.83–1.74 (m, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.1, 167.6, 160.3, 141.0, 139.6, 136.4 (C), 133.7, 132.8, 132.4, 131.5, 129.0, 128.9, 128.6, 123.4, 120.2 (CH), 53.0, 43.0, 36.6, 31.3, 25.4, 18.4 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}N_5O_5S_2$: 490.1219; found: 490.1208.

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-(2-pyridyl)-benzamide (23)**

Yield: 8.1 mg (4%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 10.83 (br s, 1 H), 8.37–8.32 (m, 1 H), 8.14 (d, *J* = 8.3 Hz, 1 H), 8.09–8.05 (m, 1 H), 8.03–7.98 (m, 1 H), 7.86 (t, *J* = 7.8 Hz, 1 H), 7.78–7.72 (m, 1 H), 7.69–7.61 (m, 5 H), 7.19–7.15 (m, 1 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 166.8, 160.6, 151.5 (C), 147.3 (CH), 141.1 (C), 139.9 (C), 138.8 (CH), 134.8 (C), 133.7 (C), 132.5, 132.2, 131.6, 129.8, 129.7, 128.7, 123.97, 119.9, 119.7, 113.9 (CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}N_4O_5S_2$: 443.0484; found: 443.0475.

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-(1-methyl-pyrazol-3-yl)benzamide (24)**

Yield: 23.7 mg (11%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 10.81 (br s, 1 H), 8.10–8.02 (m, 2 H), 7.78–7.74 (m, 1 H), 7.70–7.65 (m, 2 H), 7.64–7.59 (m, 3 H), 7.56 (d, *J* = 2.2 Hz, 1 H), 6.53 (d, *J* = 2.2 Hz, 1 H), 3.77 (s, 3 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 164.7, 160.5, 146.9, 141.1, 139.9, 135.0, 133.7 (C), 132.5, 132.3, 131.5, 130.8, 130.2, 129.5, 128.7, 124.0, 120.0, 96.7 (CH), 38.4 ($CH_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_5O_5S_2$: 446.0593; found: 446.0605.

***N*-(1,1-Dioxo-1,2-benzothiazol-3-yl)-2-(piperidine-1-carbonyl)-benzenesulfonamide (25)**

Yield: 89.1 mg (41%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 7.99 (dd, *J* = 7.8, 0.8 Hz, 1 H), 7.79–7.71 (m, 2 H), 7.69–7.63 (m, 2 H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.20 (dd, *J* = 7.6, 1.4 Hz, 1 H), 3.83–3.75 (m, 1 H), 3.25–3.17 (m, 1 H), 3.08–2.95 (m, 2 H), 1.65–1.36 (m, 5 H), 1.30–1.17 (m, 1 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 166.9, 160.2, 141.5, 139.8, 135.6, 134.3 (C), 132.4, 132.0, 131.1, 128.9, 128.0, 126.7, 123.3, 119.9 (CH), 47.7, 41.7, 25.2, 25.0, 24.2 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_3O_5S_2$: 434.0844; found: 434.0841.

***N*-[1-(3-Chlorophenyl)pyrazol-3-yl]-2-[(1,1-dioxo-1,2-benzo-thiazol-3-yl)sulfamoyl]benzamide (26)**

Yield: 66.4 mg (25%); off-white solid; mp 82.5 °C .

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 11.25 (br s, 1 H), 8.53 (d, *J* = 2.5 Hz, 1 H), 8.09–8.04 (m, 2 H), 7.88–7.81 (m, 2 H), 7.75–7.63 (m, 6 H), 7.48 (t, *J* = 8.1 Hz, 1 H), 7.33–7.28 (m, 1 H), 6.95 (d, *J* = 2.5 Hz, 1 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 165.4, 160.5, 149.2, 141.2, 140.5, 139.9, 134.8, 134.0, 133.6 (C), 132.5, 132.4, 131.7, 131.2, 130.1, 129.9, 128.8, 128.4, 125.3, 123.7, 120.2, 117.1, 115.8, 100.6 (CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{16}ClN_5O_5S_2$: 542.0359; found: 542.0332.

***N*-(1-Benzylpyrazol-3-yl)-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)-sulfamoyl]benzamide (27)**

Yield: 50.4 mg (19%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 10.9 (br s, 1 H), 8.09–8.05 (m, 1 H), 8.01 (d, *J* = 7.7 Hz, 1 H), 7.77–7.73 (m, 2 H), 7.66–7.59 (m, 4 H), 7.46 (td, *J* = 7.7, 0.9 Hz, 1 H), 7.36–7.32 (m, 2 H), 7.31–7.27 (m, 1 H), 7.26–7.22 (m, 2 H), 6.61 (d, *J* = 2.1 Hz, 1 H), 5.24 (s, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 164.7, 160.5, 147.4, 141.2, 139.9, 137.6, 134.9, 133.6 (C), 132.4, 132.2, 131.6, 130.7, 128.5, 127.63, 127.61, 123.9, 112.0, 97.1 (CH), 54.7 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{19}N_5O_5S_2$: 522.0906; found: 522.0912.

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-(3-imidazol-1-ylpropyl)benzamide (28)**

Yield: 15.4 mg (7%); off-white solid; mp 256 °C.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.98 (t, *J* = 1.4 Hz, 1 H), 8.42 (t, *J* = 5.8 Hz, 1 H), 7.97 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.80–7.77 (m, 1 H), 7.76–7.74 (m, 2 H), 7.71–7.64 (m, 2 H), 7.63 (t, *J* = 1.6 Hz, 1 H), 7.58 (td, *J* = 7.5, 1.7 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.7 Hz, 1 H), 7.41 (dd, *J* = 7.5, 1.7 Hz, 1 H), 4.41 (t, *J* = 7.0 Hz, 2 H), 3.19 (q, *J* = 6.1 Hz, 2 H), 2.06–2.00 (m, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.2, 160.3, 141.0, 139.7, 136.5 (C), 135.6 (CH), 133.8 (C), 132.7, 132.4, 131.4, 128.9, 128.7, 123.4, 121.9, 120.4, 120.1 (CH), 45.8, 35.5, 29.5($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_5O_5S_2$: 474.0906; found: 474.0909.

***N*-[3-(Dimethylamino)propyl]-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]benzamide (29)**

Yield: 13.7 mg (6%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.52 (t, *J* = 5.90 Hz, 1 H), 7.93 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.82–7.76 (m, 2 H), 7.73–7.66 (m, 2 H), 7.57 (td, *J* = 7.4, 1.5 Hz, 1 H), 7.54 (td, *J* = 7.4, 1.5 Hz, 1 H), 7.41 (dd, *J* = 7.3, 1.6 Hz, 1 H), 3.28 (q, *J* = 6.1 Hz, 2 H), 3.23 (t, *J* = 7.9 Hz, 2 H), 2.75 (s, 6 H), 1.91–1.83 (m, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.6, 160.2, 140.9, 139.8, 136.2, 133.8 (C), 132.8, 132.4, 131.4, 129.1, 128.83, 128.81, 123.4, 120.2 (CH), 54.8 ($CH_2$), 42.5 ($CH_3$), 36.2 ($CH_2$), 23.9 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}N_4O_5S_2$: 451.111; found: 451.111.

***N*-[3-(Dimethylamino)-3-oxopropyl]-2-[(1,1-dioxo-1,2-benzo-thiazol-3-yl)sulfamoyl]benzamide (30)**

Yield: 14.9 mg (6%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.26 (t, *J* = 5.7 Hz, 1 H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.84–7.80 (m, 1 H), 7.79–7.76 (m, 1 H), 7.71–7.66 (m, 2 H), 7.56 (td, *J* = 7.3, 1.5 Hz, 1 H), 7.52 (td, *J* = 7.3, 1.5 Hz, 1 H), 7.44 (dd, *J* = 7.3, 1.5 Hz, 1 H), 3.40–3.36 (m, 2 H), 2.84 (s, 3 H), 2.75 (s, 3 H), 2.55–2.52 (m, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 170.4, 168.0, 160.1, 141.0, 140.0, 136.1, 133.8 (C), 132.7, 132.3, 131.3, 129.1, 129.0, 128.4, 123.5, 120.1 (CH), 36.4 ($CH_2$), 36.1 ($CH_3$), 34.6 ($CH_3$), 31.8 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_4O_6S_2$: 465.0902; found: 465.0903.

***N*-[3-(Dimethylamino)-3-oxopropyl]-2-[(1,1-dioxo-1,2-benzo-thiazol-3-yl)sulfamoyl]-*N*-methyl-benzamide (31)**

Yield: 31.1 mg (13%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.02* (dd, $J$ = 7.9, 1.1 Hz, 0.5 H), 7.99* (dd, $J$ = 7.9, 1.1 Hz, 0.5 H), 7.78–7.70 (m, 2 H), 7.69–7.62 (m, 2 H), 7.54 (td, $J$ = 7.5, 1.3 Hz, 1 H), 7.51–7.47 (m, 1 H), 7.30 (br s, 0.5 H), 7.24–7.19 (m, 1 H), 6.68 (br s, 0.5 H), 3.70–3.58* (m, 0.5 H), 3.52–3.30* (m, 1 H), 3.14–3.04* (m, 0.5 H), 2.96* (m, 1.5 H), 2.90* (s, 1.5 H), 2.81* (s, 1.5 H), 2.69–2.61* (m, 4.5 H), 2.60–2.52* (m, 1.5 H), 2.44–2.35* (m, 0.5 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 171.6*, 170.7*, 169.8*, 168.5*, 168.4*, 160.2*, 160.1*, 141.5*, 139.7*, 135.6*, 135.3*, 134.2* (C), 132.44*, 132.38*, 132.03*, 131.97*, 131.8*, 131.2*, 131.0*, 130.0*, 129.1*, 129.0*, 128.9*, 128.8*, 128.11*, 128.06*, 127.1*, 126.9*, 123.4*, 123.3*, 120.0*, 119.9* (CH), 47.0* ($CH_2$), 42.9* ($CH_2$), 36.8* ($CH_3$), 36.7* ($CH_3$), 36.5* ($CH_3$), 34.7* ($CH_3$), 34.6* ($CH_3$), 31.9* ($CH_3$), 31.4* ($CH_2$), 30.0* ($CH_2$).

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for $C_{20}H_{22}N_4O_6S_2$: 479.1059; found: 479.1026.

* Due to the presence of rotamers (40:60).

### *N*-[(2-Chlorophenyl)methyl]-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methylbenzamide (32)

Yield: 218.3 mg (87%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.10–8.02* (m, 1.1 H), 7.83–7.79* (m, 0.3 H), 7.76–7.69 (m, 1.8 H), 7.68–7.57* (m, 3.6 H), 7.54* (td, $J$ = 7.7, 1.4 Hz, 0.8 H), 7.50–7.40* (m, 1.5 H), 7.39–7.27* (m, 3.3 H), 7.26–7.22* (m, 0.6 H), 4.73* (d, $J$ = 16 Hz, 0.6 H), 4.65* (d, $J$ = 16 Hz, 0.6 H), 4.37–4.23* (m, 0.8 H), 2.89* (s, 1.3 H), 2.66* (s, 1.7 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 169.2*, 169.1*, 160.38*, 160.36*, 141.52*, 141.46*, 139.6*, 139.5*, 135.3*, 134.8*, 134.4*, 134.3*, 134.24*, 134.16* (C), 132.39*, 132.37*, 132.2*, 132.0*, 131.9*, 131.4*, 131.1*, 129.4*, 129.3*, 129.11*, 129.07*, 128.8*, 128.6*, 128.32*, 128.28*, 128.2*, 127.52*, 127.47*, 127.1*, 126.7*, 123.5*, 123.2*, 120.0*, 119.9* (CH), 52.0* ($CH_2$), 47.5* ($CH_2$), 36.7* ($CH_3$), 32.7* ($CH_3$).

* Due to the presence of rotamers (30:70).

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for $C_{22}H_{18}N_3O_5S_2$: 504.0454; found: 504.0471.

### *N*-[(5-Bromo-2-methoxyphenyl)methyl]-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methylbenzamide (33)

Yield: 150.1 mg (52%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.08–8.02* (m, 1 H), 7.82–7.75* (m, 1 H), 7.74–7.65* (m, 2.6 H), 7.63* (td, $J$ = 7.4, 1.2 Hz, 0.6 H), 7.61–7.55* (m, 1.2 H), 7.52* (td, $J$ = 7.6, 1.4 Hz, 0.6 H), 7.50–7.46* (m, 1 H), 7.44* (dd, $J$ = 8.7, 2.6 Hz, 0.6 H), 7.38* (dd, $J$ = 8.7, 2.6 Hz, 0.4 H), 7.21* (dd, $J$ = 7.5, 1.2 Hz, 0.6 H), 7.17–7.14* (m, 1.4 H), 6.98* (d, $J$ = 8.8 Hz, 0.6 H), 6.85* (d, $J$ = 8.8 Hz, 0.4 Hz), 4.60–4.48* (m, 1.2 H), 4.27* (d, $J$ = 17.3 Hz, 0.35 H), 4.11* (d, $J$ = 17.3 Hz, 0.35 H), 3.81* (s, 1.8 H), 3.55* (s, 1.2 H), 2.85* (s, 1.2 H), 2.60* (s, 1.8 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 169.2*, 169.1*, 160.34*, 160.28*, 156.3*, 156.1*, 141.54*, 141.45*, 139.52*, 139.49*, 135.5*, 135.0*, 134.29*, 134.25* (C), 132.4* (CH), 132.3* (CH), 131.99* (CH), 131.98* (CH), 131.3* (CH), 131.0* (CH), 130.68* (CH), 130.66* (CH), 130.0* (CH), 129.4* (CH), 129.1* (CH), 128.3* (CH), 128.1* (CH), 127.6* (C), 127.4* (C), 126.9* (CH), 126.8*, 123.4*, 123.3*, 119.9*, 113.0*, 112.8*, 112.4*, 111.8* (CH), 55.8* ($CH_3$), 55.3* ($CH_3$), 49.4* ($CH_3$), 44.5* ($CH_3$).

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for $C_{23}H_{20}BrN_3O_6S_2$: 578.0055; found: 578.007.

* Due to the presence of rotamers (40:60).

### 2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methyl-*N*-[2-(2-pyridyl)ethyl]benzamide (34)

Yield: 42 mg (17%); off-white solid; mp 233.5 °C.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.63* (br s, 0.6 H), 8.44* (br s, 0.4 H), 8.01–7.96* (m, 1.5 H), 7.80–7.70* (m, 2 H), 7.69–7.57* (m, 3 H), 7.55–7.43* (m, 2.3 H), 7.40* (td, $J$ = 7.5, 1.3 Hz, 0.4 H), 7.36–7.26* (m, 0.4 H), 7.16–7.11* (m, 1 H), 6.73* (d, $J$ = 7.5 Hz, 0.4 H), 3.80–3.69* (m, 1.6 H), 3.59–3.08* (m, 2.5 H), 2.98–2.91* (m, 1.5 H), 2.90–2.81* (m, 0.4 H), 2.65* (s, 2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.62*, 168.55*, 160.3*, 160.1*, 157.9* (C), 147.5* (CH), 146.2* (CH), 141.5* (C), 139.6*, 139.5*, 135.5*, 135.1*, 134.21*, 134.16* (C), 132.5* (CH), 132.4*, 132.1*, 132.0*, 131.2*, 130.9*, 128.9*, 128.8*, 128.2*, 128.1*, 126.9*, 126.8*, 125.1*, 124.0*, 123.31*, 123.29*, 122.8*, 122.3*, 120.0*, 119.9* (CH), 50.6* ($CH_2$), 46.2* ($CH_2$), 36.9* ($CH_3$), 35.0* ($CH_2$), 33.2* ($CH_2$), 32.1* ($CH_3$).

* Due to the presence of rotamers (40:60).

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for $C_{22}H_{20}N_4O_5S_2$: 485.0953; found: 485.0948.

### *tert*-Butyl 2-({2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-benzoyl}methylamino)acetate (35)

Yield: 204.6 mg (83%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.00* (dd, $J$ = 8.0, 1.2 Hz, 0.5 H), 7.96–7.92* (m, 0.5 H), 7.79–7.71* (m, 2 H), 7.69–7.63* (m, 2 H), 7.59* (td, $J$ = 7.5, 1.3 Hz, 0.5 H), 7.55–7.45* (m, 1.5 H), 7.19* (dd, $J$ = 7.5, 1.2 Hz, 0.5 H), 7.13–7.09* (m, 0.5 H), 4.50* (d, $J$ = 17.0 Hz, 0.5 H), 4.07* (d, $J$ = 18.6 Hz, 0.5 H), 3.61* (d, $J$ = 18.6 Hz, 0.5 H), 3.53* (d, $J$ = 3.5 Hz, 0.5 H), 2.91* (s, 1.5 H), 2.71* (s, 1.5 H), 1.45* (s, 4.5 H), 1.30* (s, 4.5 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 169.0*, 168.9*, 168.7*, 168.3*, 160.41*, 160.37*, 141.6*, 141.5*, 139.7*, 139.5*, 134.9*, 134.6*, 134.2*, 134.1* (C), 132.5* (CH), 132.4*, 132.0*, 131.2*, 130.8*, 128.8*, 128.6*, 128.4*, 128.3*, 127.0*, 126.7*, 123.34*, 123.30*, 120.0* (CH), 81.1* (C), 81.0* (C), 53.1* ($CH_2$), 49.2* ($CH_2$), 37.8* ($CH_2$), 33.7* ($CH_2$), 27.8* [$(CH_3)_3$], 27.6* [$(CH_3)_3$].

* Due to the presence of rotamers (47:53).

HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{21}H_{23}N_3O_7S_2$: 494.1056; found: 494.1065.

### *N*-(Benzothiophen-2-ylmethyl)-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methylbenzamide (36)

Yield: 196.9 mg (75%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.04* (dd, $J$ = 7.9, 0.9 Hz, 0.6 H), 7.98–7.95* (m, 0.4 H), 7.94–7.88* (m, 1 H), 7.85–7.81* (m, 0.4 H), 7.81–7.78* (m, 0.6 H), 7.77–7.72* (m, 1.5 H), 7.71–7.67* (m, 1.5 H), 7.63* (td, $J$ = 7.5, 1.1 Hz, 0.6 H), 7.60–7.55* (m, 1.4 H), 7.54–7.46* (m, 2 H), 7.39–7.27* (m, 3 H), 7.25–7.20* (m, 1 H), 5.17* (d, $J$ = 15.2 Hz, 0.6 H), 4.79* (d, $J$ = 16.8 Hz, 0.4 H), 4.55* (d, $J$ = 15.2 Hz, 0.6 H), 4.34* (d, $J$ = 16.8 Hz, 0.4 H), 2.93* (s, 1.3 H), 2.69* (s, 1.7 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.9*, 168.6*, 160.6*, 160.4*, 141.7*, 141.51*, 141.46*, 141.2*, 139.9*, 139.7*, 139.5*, 139.3*, 138.9*, 135.1*, 134.7*, 134.2*, 134.1* (C), 132.5*, 132.4*, 132.2*, 132.0*, 131.3*, 131.1*, 129.0*, 128.7*, 128.6*, 128.3*, 127.0*, 126.8*, 124.5*, 124.4*, 124.3*, 124.1*, 123.43*, 123.39*, 123.35*, 123.3*, 123.2*, 122.5*, 122.4*, 120.0*, 119.9* (CH), 50.7* ($CH_2$), 45.4* ($CH_2$), 36.2* ($CH_3$), 32.3* ($CH_3$).

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for $C_{24}H_{19}N_3O_5S_2$: 526.0565; found: 526.0577.

* Due to the presence of rotamers (40:60).

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-[(4-methoxyphenyl)methyl]-*N*-methylbenzamide (37)**

Yield: 182.6 mg (73%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.02* (dd, *J* = 7.90, 1.1 Hz, 0.6 H), 7.99–7.96* (m, 0.4 H), 7.81–7.77* (m, 0.4 H), 7.67–7.74* (m, 0.4 H), 7.73–7.71* (m, 0.6 H), 7.69–7.65* (m, 0.8 H), 7.64–7.59* (m, 1.2 H), 7.58–7.54* (m, 1.2 H), 7.51* (td, *J* = 7.7, 1.4 Hz, 0.6 H), 7.49–7.45* (m, 0.8 H), 7.34* (d, *J* = 8.7 Hz, 1.1 H), 7.31–7.27* (m, 0.5 H), 7.23* (dd, *J* = 7.5, 1.3 Hz, 0.5 H), 7.05* (d, *J* = 8.6 Hz, 0.9 H), 6.89* (d, *J* = 8.6 Hz, 1.2 H), 6.87* (d, *J* = 8.6 Hz, 0.8 H), 4.54* (q, *J* = 15.5 Hz, 1.2 H), 4.42* (d, *J* = 15.5 Hz, 0.4 H), 3.94* (d, *J* = 15.5 Hz, 0.4 H), 3.73* (s, 1.8 H), 3.70* (s, 1.2 H), 2.78* (s, 1.2 H), 2.52* (s, 1.8 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.9*, 168.6*, 160.4*, 160.2*, 158.39*, 158.36*, 141.52*, 141.47*, 139.8*, 139.6*, 135.6*, 135.2*, 134.23* (C), 134.18*, 132.5*, 132.3*, 132.1*, 131.9*, 131.2*, 131.0*, 129.3* (CH), 129.2* (C), 129.0* (CH), 128.8* (CH), 128.3* (CH), 128.2* (CH), 128.1* (C), 127.0*, 123.4*, 123.3*, 112.0*, 119.9*, 113.9*, 113.8* (CH), 55.0* ($CH_3$), 53.8* ($CH_2$), 48.6* ($CH_2$), 35.8* ($CH_3$), 31.9* ($CH_3$).

* Due to the presence of rotamers (40:60).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_3O_6S_2$: 500.095; found: 500.0937.

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-(4-hydroxybutyl)-*N*-methylbenzamide (38)**

Yield: 47.4 mg (21%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.01–7.98* (m, 1 H), 7.78–7.70* (m, 1 H), 7.68–7.63* (m, 2 H), 7.56–7.45* (m, 2 H), 7.21–7.13* (m, 1 H), 3.45–3.37* (m, 2.3 H), 3.32–3.22* (m, 0.7 H), 3.17* (t, *J* = 6.5 Hz, 1 H), 3.14–3.06* (m, 0.5 H), 2.86* (s, 1.2 H), 2.78–2.70* (m, 0.5 H), 2.63* (s, 1.8 H), 1.65–1.39* (m, 2.9 H), 1.34–0.99* (m, 1.1 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.4*, 168.3*, 160.3*, 160.2*, 141.52*, 141.49*, 139.58*, 139.56*, 135.9*, 135.5*, 134.3* (C), 132.41*, 132.38*, 132.0*, 131.2*, 131.0*, 129.0*, 128.9*, 128.0*, 127.9*, 127.0*, 126.9*, 123.3*, 123.3*, 119.9* (CH), 60.6*, 60.2*, 50.5*, 46.0*, 36.4*, 31.8*, 29.9*, 29.5*, 24.0*, 23.0*, 22.5* ($CH_2$).

* Due to the presence of rotamers (40:60).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_3O_6S_2$: 452.095; found: 452.0957.

***N*-(1,3-Dihydroisobenzofuran-5-yl)-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]benzamide (39)**

Yield: 23.5 mg (10%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 10.41 (s, 1 H), 7.91 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.80–7.76 (m, 2 H), 7.73 (d, *J* = 1.6 Hz, 1 H), 7.71–7.64 (m, 2 H), 7.62 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.59–7.52 (m, 3 H), 7.20 (d, *J* = 8.1 Hz, 1 H), 4.96 (s, 4 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 166.5, 160.3, 140.8, 139.8, 139.3, 138.7, 136.3, 133.7, 133.6 (C), 132.7, 132.4, 131.5, 129.4, 128.9, 128.6, 123.5, 121.0, 120.1 (CH), 119.0 (CH), 112.4 (CH), 72.6 ($CH_2$), 72.4 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_3O_6S_2$: 484.0637; found: 484.0642.

***N*-Allyl-2-[(1,1-dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methylbenzamide (40)**

Yield: 84.3 mg (40%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.03–7.96* (m, 1 H), 7.81–7.71* (m, 2 H), 7.70–7.62* (m, 2 H), 7.55* (td, *J* = 7.5, 1.4 Hz, 0.5 H), 7.52–7.47* (m, 1.5 H), 7.23–7.18* (m, 1 H), 5.87–5.77* (m, 0.52 H), 5.72–5.62* (m, 0.48 H), 5.30* (dq, *J* = 17.3, 1.6 Hz, 0.54 H), 5.16* (dq, *J* = 10.3, 1.4 Hz, 0.52 H), 5.07* (dq, *J* = 10.3, 1.4 Hz, 0.48 H), 5.03* (dq, *J* = 17.3, 1.6 Hz, 0.46 H), 4.08–4.02* (m, 0.5 H), 3.95* (br dd, *J* = 15.2, 6.1 Hz, 0.5 H), 3.86–3.80* (m, 0.44 H), 3.41–3.35* (m, 0.56 H), 2.84* (s, 1.4 H), 2.60 (s, 1.6 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.6*, 168.4*, 160.4*, 160.3*, 141.50*, 141.47*, 139.7*, 135.5*, 135.2*, 134.21*, 134.19*, 134.0* (C), 133.6*, 132.44*, 132.41*, 132.1*, 132.0*, 131.2*, 130.9*, 129.0*, 128.7*, 128.3*, 128.1*, 126.93* 126.86*, 123.4*, 123.3*, 120.0*, 119.9* (CH), 117.0*, 116.9*, 53.3*, 48.5* ($CH_2$), 36.0* ($CH_3$), 31.9* ($CH_3$).

* Due to the presence of rotamers (52:48).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_3O_5S_2$: 420.0688; found: 420.0703.

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methyl-*N*-propylbenzamide (41)**

Yield: 141.5 mg (67%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.03–7.97* (m, 1 H), 7.77–7.71* (m, 2 H), 7.68–7.63* (m, 2 H), 7.56–7.45* (m, 2 H), 7.20–7.14* (m, 1 H), 3.37–3.31* (m, 0.46 H), 3.29–3.23* (m, 0.54 H), 3.11–3.04* (m, 0.48 H), 2.87* (s, 1.4 H), 2.76–2.67* (m, 0.52 H), 2.64* (s, 1.6 H), 1.62–1.40* (m, 1.5 H), 1.32–1.20* (m, 0.5 H), 0.90* (t, *J* = 7.4, 1.6 Hz, 1.6 H), 0.55* (t, *J* = 7.4 Hz, 1.4 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.43*, 168.35*, 160.21*, 160.20*, 141.54*, 141.49*, 139.6*, 139.5*, 136.0*, 135.6*, 134.27*, 134.26* (C), 132.38*, 132.35*, 132.0*, 131.2*, 130.9*, 129.0*, 128.9*, 128.0*, 127.9*, 127.1*, 126.9*, 123.30*, 123.26*, 119.92*, 119.90* (CH), 52.2* ($CH_2$), 47.8* ($CH_2$), 36.5* ($CH_3$), 31.8* ($CH_3$), 20.5* ($CH_2$), 19.6* ($CH_2$), 11.3* ($CH_3$), 10.9* ($CH_3$).

* Due to the presence of rotamers (54:46).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_3O_5S_2$: 422.0844; found: 422.0828.

**2-[4-(3,4-Dimethoxyphenyl)piperazine-1-carbonyl]-*N*-(1,1-dioxo-1,2-benzothiazol-3-yl)benzenesulfonamide (42)**

Yield: 158.8 mg (56%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 7.93 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.80–7.74 (m, 2 H), 7.69–7.65 (m, 2 H), 7.55 (td, *J* = 7.5, 1.3 Hz, 2 H), 7.49 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.26 (dd, *J* = 7.5, 1.3 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.39 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.84–3.73 (m, 1 H), 3.71–3.64 (m, 6 H), 3.43–3.36 (m, 1 H), 3.24–3.05 (m, 4 H), 2.92–2.82 (m, 1 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 167.2, 160.5, 149.3, 145.6, 143.1, 141.5, 140.1, 135.1, 134.2 (C), 132.5, 132.1, 131.1, 128.6, 128.4, 126.9, 123.3, 120.0, 112.8, 107.8, 103.0 (CH), 56.0 ($CH_3$), 55.5 ($CH_3$), 50.0 ($CH_2$), 49.4 ($CH_2$), 46.3($CH_2$), 41.0 ($CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{26}N_4O_7S_2$: 571.1321; found: 571.132.

**2-[(1,1-Dioxo-1,2-benzothiazol-3-yl)sulfamoyl]-*N*-methyl-*N*-phenylbenzamide (43)**

Yield: 176.7 mg (78%); yellowish viscous oil.

$^1$H NMR (600 MHz, DMSO-$d_6$): δ = 8.06* (dd, *J* = 7.9, 1.3 Hz, 0.4 H), 7.86* (dd, *J* = 7.9, 1.3 Hz, 0.6 H), 7.82–7.76* (m, 1.2 H), 7.75–7.71* (m, 0.8 H), 7.70–7.67* (m, 11 H), 7.66–7.58* (m, 11 H), 7.57–7.51* (m, 1.6

H), 7.50–7.46* (m, 0.8 H), 7.43–7.38* (m, 1.2 H), 7.25* (td, *J* = 7.7, 1.3 Hz, 1 H), 7.22–7.15* (m, 2 H), 7.04* (t, *J* = 7.4 Hz, 0.6 H), 6.92* (dd, *J* = 7.6, 1.2 Hz, 0.6 H), 3.37* (s, 1.8 H), 3.03* (s, 1.2 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 168.4*, 167.6*, 160.41*, 160.35*, 144.0*, 143.4*, 141.54*, 141.47*, 140.9*, 139.5*, 135.5*, 135.4*, 134.3*, 134.1* (C), 132.43*, 132.41*, 132.0*, 131.3*, 123.0*, 129.1*, 128.8*, 128.7*, 128.6*, 128.3*, 127.8*, 127.7*, 127.0*, 126.7*, 126.1*, 126.0*, 123.34*, 123.27*, 119.99*, 119.97* (CH), 41.9* ($CH_3$), 36.7* ($CH_3$).

* Due to the presence of rotamers (40:60).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_3O_5S_2$: 456.0688; found: 456.0707.

## Acknowledgment

The authors thank Mark E. Light at the University of Southampton for the support of crystal structure examination and elucidation. The authors thank Anette Welinder, Richard J. Lewis, and Gunnar Grönberg for NMR assistance, Linda Thunberg for the chromatography study on the product **6**, and Richard J. Lewis for the proof-reading.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591882. Crystal data and experimental information of product **7**, $^1$H NMR and $^{13}$C NMR spectra of the key intermediate mixture (**13**, **14**) and final products are included.

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(14) CCDC 1522311 (**7**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
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