# A Convenient Synthesis of Novel 3-(Heterocyclylsulfonyl)propanoic Acids and their Amide Derivatives

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**Abstract:** A large number of novel 3-(heterocyclylsulfonyl)propanoic acids and their amide derivatives were prepared in good yields and excellent purity starting from the corresponding heterocyclic compounds. At first, chlorosulfonates were generated by reaction of initial heterocycles with various sulfonating and chlorinating agents followed by their conversion into sodium sulfinates. Treatment of sulfinates with acrylic acid smoothly afforded a series of sulfonylpropionates, which were used as convenient reagents for the preparation of a large number of the corresponding carboxamide derivatives.

Key words: 3-(heterocyclylsulfonyl)propanoic acid, chlorosulfonates, heterocycles, parallel synthesis, libraries

Synthetic arylsulfonylalkylcarboxylic acids and their derivatives are present in a wide variety of physiologically active compounds. In particular, variously substituted derivatives of 3-(phenylsulfonyl)propanoic acid were described as antiinfective,<sup>1</sup> oncolytic,<sup>2</sup> antiarthritic<sup>3</sup> and gastrointestinal<sup>4</sup> agents. According to these examples and due to evident structural and bioisosteric similarity to the mentioned physiologically active agents, the heterocyclic analogs of 3-(phenylsulfonyl)propanoic acid represent promising synthetic targets. Development of effective strategies for their synthesis will provide a valuable source of novel pharmaceutical agents.

To the best of our knowledge, no physiologically active derivatives of 3-(heterocyclylsulfonyl)propanoic acids were reported to date. These observations prompted us to explore the synthetic pathways to 3-sulfonylpropanamide derivatives of several different heterocycles, such as indo-line **1a**–**d**, 2,1,3-benzoxadiazole **1e**, 2,1,3-benzothiadiazole **1f**, quinoline **1g**, and 1,4-dihydroquinoxaline-2,3-dione **1h** (Scheme 1). In this work, we report a convenient and versatile synthetic approach to these novel heterocyclic structures and discuss the scope and limitations of the chemistry involved.

Recently, we reported a convenient synthetic method for preparation 3-(2-thienylsulfonyl)propanoic and 3-(5-bromo-2-thienylsulfonyl)propanoic acids and the corresponding carboxamide derivatives.<sup>5</sup> The synthetic scheme included sulfochlorination of thiophene or 2-bromothiophene, treatment of 2-thienylchlorosulfonates with sodium sulfite and the reaction of the resulting sodium sulfinates with acrylic acid. The desired sulfonylpropionates were obtained in high yields (generally, in the range of 50-70% from the initial heterocycles) and excellent purity using easy purification procedures, such as precipitation from the reaction mixtures and recrystallization. We used these acids as starting reagents for the preparation of a large library of carboxamides via the corresponding acid chlorides.<sup>5</sup>

We found this general scheme suitable for preparation of other 3-(heterocyclylsulfonyl)propanoic acids and their amide derivatives (Scheme 1). At the first step, chlorosulfonates **2a–h** were obtained in good yields (39–88%) by reacting the heterocyclic compounds **1a–h** with a mixture of chlorosulfonic acid and PCl<sub>5</sub> (Method A) or with chlorosulfonic acid (Method B) at elevated temperature. In the case of quinoline **1g**, both methods led to mixtures of regioisomers, which were extremely difficult to separate using standard laboratory techniques. Therefore, we used a modified procedure (Method C). Quinoline **1g** was treated with fuming sulfuric acid (30% SO<sub>3</sub>) at 90 °C. The resulting quinoline-8-sulfate was then reacted with PCl<sub>5</sub> to afford chlorosulfonate **2g** (Table 1).

The principal concern in the reaction of heterocyclic compounds with chlorosulfonic acid is the regioselectivity of sulfochlorination. The structures of compounds **2a–h** were established by a combination of elemental analyses, MS and <sup>1</sup>H NMR spectroscopy, and by a series of NOE difference experiments which provided full information about the substitution pattern. Based on the <sup>1</sup>H NMR measurements, only one major sulfochlorination product has been formed in all the studied reactions under the described conditions (Table 1). For example, for compound **2a**, the key experiment enabled us to assign all three aromatic protons of the indoline ring by a single NOE difference spectrum. In this experiment, we observed the positive NOEs between the H-7 and H-6 protons, which is consistent with the suggested molecular structure.

Chlorosulfonates **2a–h** were then converted into sodium sulfinates **3a–h** by treatment with an aqueous solution of sodium sulfite and sodium bicarbonate (yield: 75–97%). Sulfinates **3a–h** were reacted with acetic acid in water to give sulfinic acids **4a–h**. Reaction of **4a–h** in situ with acrylic acid then furnished the corresponding 3-sulfonylpropanoic acids **5a–h** in 50–75% yields. Acids **5a–h** were converted into the corresponding chlorides **6a–h** by heat-

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**Scheme 1** *Reagents and conditions*: (a) Method A: i. HSO<sub>3</sub>Cl, 30–40 °C; ii. PCl<sub>5</sub>, 80 °C (39–53%); Method B: HSO<sub>3</sub>Cl, 65–135 °C (63–80%); Method C: i,  $H_2SO_4/SO_3$ , 65–70 °C; ii. PCl<sub>5</sub>, 145 °C (58%); (b)  $Na_2SO_3$ ,  $NaHCO_3$ ,  $H_2O$ , 85–90 °C, pH 9–10 (75–97%); (c) AcOH,  $H_2O$ , 20 °C; (d)  $H_2C$ =CHCO<sub>2</sub>H, 20 °C (50–75%); (e) PCl<sub>5</sub>, toluene, reflux (50–75%); (f) HNR<sup>1</sup>R<sup>2</sup>, Py, DMF, 55 °C (30–95%).

ing with PCl<sub>5</sub> in toluene (yield 50–75%). Finally, several amide libraries **7a–h** were smoothly obtained using the reaction of acid chlorides **6a–h** with primary and secondary amines in DMF in the presence of pyridine. The yields of amides were in the range of 30–95%. The developed approach to the amide libraries is compatible with the high-throughput parallel synthesis format, and a wide variety of different amino components can be used for this reaction. The representative examples of amines used for coupling

with acids **5a–h** are shown in Figure 1. The protocols are straightforward and can easily be reproduced on a 10–50 g scale.

All final amides within the studied heterocyclic series 7ah are stable crystalline compounds, which were characterized by LCMS and <sup>1</sup>H NMR spectroscopy. Several examples of compounds from these libraries are shown in Figure 2. All analytical data gave satisfactory results consistent with the suggested molecular structures.



Figure 1 Representative examples of amines used as building blocks in the reaction with acids 5a-h.

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Entry	Product	Structure	Reaction Conditions	Yield (%)	Mp (°C)
1	2a		Method A i. CISO <sub>3</sub> H, 0–40 °C, 1 h ii. PCl <sub>5</sub> , 80 °C, 1 h	53	171–172
2	2b		Method A i. ClSO <sub>3</sub> H, 30–40 °C, 1 h ii. PCl <sub>5</sub> , 80 °C, 1 h	39	143–144
3	2c		Method B i. ClSO <sub>3</sub> H, 65–70 °C, 3 h	63	212–214
4	2d	$H_{3}C$ Br $CH_{3}$ $SO_{2}CI = 0$	Method B i. ClSO <sub>3</sub> H, 65–70 °C, 3 h	80	175–177
5	2e		Method B i. CISO <sub>3</sub> H, 120–130 °C, 6 h	65	78–80
6	2f		Method B 130–135 °C, 6 h	70	163–165
7	2g		Method C i. H <sub>2</sub> SO <sub>4</sub> /SO <sub>3</sub> , 65–70 °C, 40 h ii. PCl <sub>5</sub> , 145 °C, 1 h	58	124–126
8	2h		Method B i. ClSO <sub>3</sub> H, 65–90 °C, 3 h	75	250–252

Table I         Heterocyclylsulfonyl Chlorides 2a-	erocyclylsulfonyl Chlorides <b>2a–h</b>
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The methylene protons of the sulfonylpropionate fragment of acids **5a–h** are usually clearly observed as triplets in the range of 2.24–2.86 ( $\alpha$ -protons) and 3.03–4.05 ( $\beta$ protons). The formation of carboxamides from the corresponding acids usually causes a definite downfield shift of 0.05–0.30 ppm for  $\alpha$ -protons and does not substantially influence the signals from  $\beta$ -protons. These characteristic signals can be used for identification of the obtained structures.

In summary, an efficient synthetic route has been developed for the preparation of a variety of 3-(heterocyclylsulfonyl)propanoic acids and their amide derivatives. In all the heterocyclic series investigated, the corresponding acids and amides were generated with low levels of impurities using easy purification procedures. Product yields varied according to the reactant structures, but in most cases, the desired products were obtained in high yields. The results provide further confirmation of the scope and generality of the applied approach to different 3-sulfonyl-propionate derivatives of heterocyclic compounds: >1000 analogues of these molecules have been made in our laboratories in the past two years by parallel synthesis methods.<sup>5</sup>

Melting points were measured with a Koeffler melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were recorded on a Bruker AMX-400 spectrometer in DMSO- $d_6$  using TMS as an internal standard (chemical shifts in ppm). LCMS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector ( $\lambda_{max}$  215 and 254 nm) and using a C<sub>18</sub> column (100 × 4 mm). Elution started with H<sub>2</sub>O and ended with

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Figure 2 Examples of 3-(heterocyclylsulfonyl)propanamides from libraries 7a-h synthesized in this work.

MeCN–H<sub>2</sub>O (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. All reagents and solvents were purchased from Acros Organics, Aldrich or ChemDiv and were used without further purification.

### Heterocyclylsulfonyl Chlorides 2a-h; General and Typical Procedures

Method A: Heterocyclic compound **1a** or **1b** (0.1 mol) was added portionwise to chlorosulfonic acid (20 mL, 0.3 mol) at 30–40 °C over 1–2 h. The reaction mixture was stirred at 40 °C for 15 min, and then PCl<sub>5</sub> (25.0 g, 0.12 mol) was added. The mixture was stirred at 80 °C for 1 h, then cooled to r.t. and poured onto ice (500 g). The formed precipitate was collected by filtration, washed with H<sub>2</sub>O and dried in vacuo. The product was recrystallized from benzene–petroleum ether (bp 40–60 °C) to give the corresponding chlorosulfonate **2a** or **2b** as a white solid; yield: 39–53%.

*Method B*: The appropriate heterocyclic compound **1c–f**, **1h** (0.1 mol) was added portionwise to  $CISO_3H$  (20 mL, 0.3 mol) at 65–135 °C over 0.5–6 h (see Table 1 for the exact reaction conditions for individual compounds). The reaction mixture was cooled to r.t. and poured onto ice (500 g). The formed precipitate was collected by filtration, washed with H<sub>2</sub>O and dried in vacuo. The product was recrystallized from benzene–petroleum ether (bp 40–60 °C) to give the corresponding chlorosulfonate **2c–f**, **2h** as a white solid; yield: 63–80%.

*Method C*: Anhyd quinoline **1g** (60 g, 0.46 mol) was added dropwise to fuming H<sub>2</sub>SO<sub>4</sub> (30% SO<sub>3</sub>, 120 mL) in an ice-cooled flask. During the addition, the temperature of the reaction mixture was kept below 90 °C. The resulting dark solution was heated at 90 °C for 40 h, then allowed to cool to r.t. and poured cautiously into icecold H<sub>2</sub>O (500 mL). The formed colorless prisms were collected by filtration, washed with H<sub>2</sub>O and dried to afford pure 8-quinolinesulfonic acid; yield: 67 g (54%); mp >300 °C (dec.). A portion of 8quinolinesulfonic acid (20 g, 0.088 mol) was added to PCl<sub>5</sub> (20 g, 0.096 mol). The resulting mixture was refluxed at 145 °C for 1 h, then cooled to r.t. and extracted with  $CHCl_3$  (3 × 30 mL). The combined organic fractions were evaporated in vacuo and the crude residue was recrystallized from benzene–petroleum ether (bp 40–60 °C) to afford pure **2g**; yield: 12.6 g (58%); mp 124–126 °C.

#### Sodium Heterocyclylsulfinates 3a-h; General Procedure

The chlorosulfonate **2a–h** (0.5 mol) was added at 85–90 °C and pH 9–10 over 1 h to a stirred solution of Na<sub>2</sub>SO<sub>3</sub> (63 g, 0.5 mol) and NaHCO<sub>3</sub> (4.2 g, 0.05 mol) in H<sub>2</sub>O (330 mL). The reaction mixture was stirred at 90 °C for 30 min and then was kept at 5 °C overnight. The formed precipitate was collected by filtration and dried to afford the corresponding sodium sulfinate **3a–h** in 75–97% yield. The product was used in the next step without further purification.

## 3-(Heterocyclylsulfonyl)propanoic Acids 5a-h; General Procedure

AcOH (30 mL, 0.5 mol) was added at r.t. to a stirred solution of the appropriate sodium sulfinate **3a–h** (0.5 mol) in  $H_2O$  (500 mL). Acrylic acid (36 mL, 0.5 mol) was then added to the in situ formed solution of sulfinic acid **4a–h** over 30 min. The formed precipitate was collected by filtration and dried to afford acid **5a–h** in 50–75% yield.

#### 3-[(1-Acetyl-2,3-dihydro-1*H*-indol-5-yl)sulfonyl]propanoic Acid (5a)

Yield: 67%; white solid; mp 201-202 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 2.23 (s, 3 H, CH<sub>3</sub>CO), 2.77 (t, 2 H, *J* = 7.5 Hz, CH<sub>2</sub>CO, 3.03 (t, 2 H, *J* = 7.5 Hz, SO<sub>2</sub>CH<sub>2</sub>), 3.98 (m, 1 H, NCH<sub>2</sub>), 4.08 (m, 1 H, NCH<sub>2</sub>), 3.15 (m, 1 H, ArCH<sub>2</sub>), 3.22 (m, 1 H, ArCH<sub>2</sub>), 6.93 (s, 1 H<sub>arom</sub>, H-4), 6.99 (d, 1 H<sub>arom</sub>, *J* = 8.2 Hz, H-7), 7.37 (d, 1 H<sub>arom</sub>, *J* = 8.2 Hz, H-6), 11.45 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 298 (M + H^+)$ .

Anal. Calcd for  $C_{13}H_{15}NO_5S$ : C, 52.52; H, 5.09; N, 4.71; S, 10.78. Found: C, 52.55; H, 5.11; N, 4.76; S, 10.83.

## 3-[(1-Acetyl-2-methyl-2,3-dihydro-1*H*-indol-5-yl)sulfonyl]propanoic Acid (5b)

Yield: 67%; white solid; mp 191–192 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.33 (d, 3 H, *J* = 5.7 Hz, NCHC*H*<sub>3</sub>), 2.29 (s, 3 H, CH<sub>3</sub>CO), 2.54 (t, 2 H, *J* = 7.7 Hz, CH<sub>2</sub>CO), 2.79 (m, 1 H, ArC*H*<sub>2</sub>), 3.49 (m, 1 H, ArC*H*<sub>2</sub>), 3.34 (t, 2 H, *J* = 7.7 Hz, SO<sub>2</sub>CH<sub>2</sub>), 4.69 (m, 1 H, NCH), 7.69 (dd, 1 H<sub>arom</sub>, *J*<sub>6,4</sub> = 1.9 Hz, *J*<sub>6,7</sub> = 8.9 Hz, H-6), 7.72 (d, 1 H<sub>arom</sub>, *J*<sub>4,6</sub> = 1.9 Hz, H-4), 8.20 (d, 1 H<sub>arom</sub>, *J*<sub>7,6</sub> = 8.9 Hz, H-7), 12.00 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 312 (M + H^+)$ .

Anal. Calcd for  $C_{14}H_{17}NO_5S$ : C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 54.06; H, 5.52; N, 4.54; S, 10.34.

#### 3-[(1-Acetyl-5-bromo-2,3-dihydro-1*H*-indol-7-yl)sulfonyl]propanoic Acid (5c)

Yield: 70%; white solid; mp 189-191 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 2.20 (s, 3 H, CH<sub>3</sub>CO), 2.55 (t, 2 H, *J* = 7.5 Hz, CH<sub>2</sub>CO), 3.30 (t, 2 H, *J* = 8.3 Hz, ArCH<sub>2</sub>), 3.65 (t, 2 H, *J* = 7.5 Hz, SO<sub>2</sub>CH<sub>2</sub>), 4.15 (t, 2 H, *J* = 7.8 Hz, NCH<sub>2</sub>C), 7.60 (s, 1 H<sub>arom</sub>, H-4), 8.80 (s, 1 H<sub>arom</sub>, H-6), 12.00 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 377 (M + H^+)$ .

Anal. Calcd for  $C_{13}H_{14}BrNO_5S$ : C, 41.50; H, 3.75; Br, 21.24; N, 3.72; S, 8.52. Found: C, 41.55; H, 3.80; Br, 21.26; N, 3.76; S, 8.56.

## 3-[(1-Acetyl-5-bromo-2-methyl-2,3-dihydro-1*H*-indol-7-yl)sulfonyl]propanoic Acid (5d)

Yield: 75%; white solid; mp 130-132 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.26 (d, 3 H, *J* = 5.7 Hz, CCH<sub>3</sub>), 2.00 (s, 3 H, CH<sub>3</sub>CO), 2.24 (t, 2 H, *J* = 7.7 Hz, CH<sub>2</sub>CO), 2.75 (m, 1 H, ArCH<sub>2</sub>), 3.45 (m, 1 H, ArCH<sub>2</sub>), 3.03 (t, 2 H, *J* = 7.7 Hz, SO<sub>2</sub>CH<sub>2</sub>), 4.40 (m, 1 H, NCH), 6.81 (s, 1 H<sub>arom</sub>, H-4), 6.90 (s, 1 H<sub>arom</sub>, H-6), 11.45 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 391 (M + H^+)$ .

Anal. Calcd for  $C_{14}H_{16}BrNO_5S$ : C, 43.09; H, 4.13; Br, 20.47; N, 3.59; S, 8.22. Found: C, 43.12; H, 4.16; Br, 20.49; N, 3.63; S, 8.27.

#### **3-(2,1,3-Benzoxadiazol-4-ylsulfonyl)propanoic Acid (5e)** Yield: 54%; white solid; mp 175–176 °C.

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 2.65$  (t, 2 H, J = 7.6 Hz, CH<sub>2</sub>CO), 3.75 (t, 2 H, J = 7.6 Hz, SO<sub>2</sub>CH<sub>2</sub>), 7.80 (t, 1 H<sub>arom</sub>, J = 7.4 Hz, H-6), 8.15 (d, J = 7.6 Hz, 1 H<sub>arom</sub>, H-7), 8.35 (d, 1 H<sub>arom</sub>, J = 7.2 Hz, H-5), 12.25 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 257 (M + H^{+})$ .

Anal. Calcd for  $C_9H_8N_2O_5S$ : C, 42.19; H, 3.15; N, 10.93; S, 12.51. Found: C, 42.22; H, 3.19; N, 10.95; S, 12.52.

### 3-(2,1,3-Benzothiadiazol-4-ylsulfonyl)propanoic Acid (5f)

Yield: 54%; white solid; mp 175–176 °C.

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 2.86$  (t, 2 H, J = 7.7 Hz, CH<sub>2</sub>CO), 3.03 (t, 2 H, J = 7.7 Hz, SO<sub>2</sub>CH<sub>2</sub>), 7.88 (t, 1 H<sub>arom</sub>, J = 7.4 Hz, H-6), 8.07 (d, 1 H<sub>arom</sub>, J = 7.5 Hz, H-5), 8.17 (d, 1 H<sub>arom</sub>, J = 7.2 Hz, H-7), 11.45 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 273 (M + H^{+})$ .

Anal. Calcd for  $C_9H_8N_2O_4S_2$ : C, 39.70; H, 2.96; N, 10.29; S, 23.55. Found: C, 39.72; H, 2.99; N, 10.33; S, 23.57.

### 3-(Quinolin-8-ylsulfonyl)propanoic Acid (5g)

Yield: 68%; white solid; mp 198-200 °C.

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 2.55$  (t, 2 H, J = 7.8 Hz, CH<sub>2</sub>CO), 4.05 (t, 2 H, J = 7.8 Hz, SO<sub>2</sub>CH<sub>2</sub>), 7.65 (dd, 1 H<sub>arom</sub>, J = 8.5 Hz, H-3), 7.70 (t, 1 H<sub>arom</sub>, J = 7.9 Hz, H-6), 8.30 (d, 1 H<sub>arom</sub>,

J = 7.5 Hz, H-7), 8.40 (d, 1 H<sub>arom</sub>, J = 8.1 Hz, H-4), 8.50 (d, 1 H<sub>arom</sub>, J = 7.8 Hz, H-5), 9.10 (d, 1 H<sub>arom</sub>, J = 6.5 Hz, H-2), 12.25 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 266 (M + H^{+})$ .

Anal. Calcd for  $C_{12}H_{11}NO_4S;\,C,\,54.33;\,H,\,4.18;\,N,\,5.28;\,S,\,12.09.$  Found: C, 54.35; H, 4.22; N, 5.28; S, 12.10.

### 3-[(1,4-Dimethyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6yl)sulfonyl]propanoic Acid (5h)

Yield: 60%; white solid; mp 273–275 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 2.55 (t, 2 H, *J* = 7.1 Hz, CH<sub>2</sub>CO), 3.55 (t, 2 H, *J* = 7.1 Hz, SO<sub>2</sub>CH<sub>2</sub>), 3.65 (s, 3 H, NCH<sub>3</sub>), 3.68 (s, 3 H, NCH<sub>3</sub>), 7.60 (dd, 1 H<sub>arom</sub>, *J*<sub>7,8</sub> = 8.3 Hz, *J*<sub>7,5</sub> = 1.0 Hz, H-7), 7.76 (d, 1 H<sub>arom</sub>, *J*<sub>8,7</sub> = 8.3 Hz, H-8), 7.77 (d, 1 H<sub>arom</sub>, *J*<sub>5,7</sub> = 1.0 Hz, H-5), 12.25 (s, 1 H, CO<sub>2</sub>H).

LCMS:  $m/z = 327 (M + H^{+})$ .

Anal. Calcd for  $C_{12}H_{11}NO_4S$ : C, 47.85; H, 4.32; N, 8.58; S, 9.83. Found: C, 47.88; H, 4.35; N, 8.64; S, 9.87.

## 3-(Heterocyclylsulfonyl)propanoic Acid Chlorides 6a-h; General Procedure

Acid **5a–h** (0.1 mol) was added at r.t. over 40 min to a solution of  $PCl_5$  (31.7 g, 0.15 mol) in toluene (300 mL). The mixture was heated at reflux until complete dissolution of the components. The mixture was cooled and the solvent was evaporated in vacuo. The residue was recrystallized from benzene to afford pure chlorides **6a–h** as white solids; yield: 50–75%.

# 3-(Heterocyclylsulfonyl)propanoic Acid Amides 7a-h; General Procedure

Parallel solution-phase reactions were performed using a laboratory synthesizer 'CombiSyn-012-3000'.<sup>6</sup> In each of twelve individual reaction units, amine HNR<sup>1</sup>R<sup>2</sup> (1.5 mmol), pyridine (1.45 mL, 1.8 mmol) and DMF (3 mL) were loaded. Appropriate chloride **6a–h** (1.5 mmol) was added at 10 °C with stirring. The reaction mixtures were stirred at 55 °C for 1 h, then cooled to r.t. H<sub>2</sub>O (50 mL) was added to each reaction unit, the formed precipitates were collected by filtration and recrystallized from MeOH to yield the corresponding members of amide libraries **7a–h**. The products were >96% pure (as measured by LCMS), and the reaction yields varied between 30 and 95%.

### Selected Data

### 3-[(1-Acetyl-2,3-dihydro-1*H*-indol-5-yl)sulfonyl]-*N*-[2-(3,4-diethoxyphenyl)ethyl]propanamide (7a{*I*})

Yield: 68%; white solid; mp 127–130 °C.

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 1.40$  (t, 6 H, J = 7.5 Hz, 2 CH<sub>3</sub>), 2.20 (s, 3 H, CH<sub>3</sub>CO), 2.40 (t, 2 H, J = 7.0 Hz, ArCH<sub>2</sub>), 2.60 (t, 2 H, J = 7.7 Hz, CH<sub>2</sub>CO), 3.20 (q, 2 H, J = 7.0 Hz, CH<sub>2</sub>NH), 3.25 (t, 2 H, J = 8.0 Hz, ArCH<sub>2</sub>), 3.30 (t, 2 H, J = 7.7 Hz, SO<sub>2</sub>CH<sub>2</sub>), 4.00 (m, 4 H, 2 OCH<sub>2</sub>), 4.20 (t, 2 H, J = 7.8 Hz, NCH<sub>2</sub>), 6.60 (d, 1 H<sub>arom</sub>, J = 7.4 Hz,), 6.70 (d, 1 H<sub>arom</sub>, J = 7.4 Hz, ), 6.65 (s, 1 H<sub>arom</sub>, H-2'), 7.80 (d, 1 H, J = 6.5 Hz, CONH), 7.60 (d, J = 7.9 Hz, 1 H<sub>arom</sub>, H-7), 7.65 (s, 1 H<sub>arom</sub>, H-4), 8.20 (d, 1 H<sub>arom</sub>, J = 7.9 Hz, H-6).

LCMS:  $m/z = 489 (M + H^+)$ .

### 1-Acetyl-5-({3-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-oxopropyl}sulfonyl)-2-methylindoline (7b{1})

Yield: 50%; white solid; mp 195–198 °C.

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 1.33$  (d, 3 H, NCHC $H_3$ ), 2.20 (s, 6 H, 2 ArC $H_3$ ), 2.25 (s, 3 H, CH<sub>3</sub>CO), 2.70 (t, 2 H, J = 7.5 Hz, CH<sub>2</sub>O), 2.80 [m, 4 H, NCH<sub>2</sub>CH<sub>2</sub>), 3.60 (m, 4 H, NCH<sub>2</sub>CH<sub>2</sub>), 3.30 (t, 2 H, J = 6.8 Hz, ArC $H_2$ ), 3.35 (t, 2 H, J = 7.7 Hz, SO<sub>2</sub>CH<sub>2</sub>), 4.20 (t, 1 H, J = 7.6 Hz, NCH), 6.70 (d, 1 H<sub>arom</sub>, J = 7.4 Hz, H-3'), 6.75 (s,

1 H<sub>arom</sub>, H-6'), 6.95 (d, 1 H<sub>arom</sub>, J = 7.4 Hz, H-4'), 7.60 (d, 1 H<sub>arom</sub>, J = 8.0 Hz, H-7), 7.65 (s, 1 H<sub>arom</sub>, H-4), 8.20 (d, 1 H<sub>arom</sub>, J = 8.0 Hz, H-6).

LCMS:  $m/z = 484 (M + H^+)$ .

# Ethyl 4-({3-[(1-Acetyl-5-bromo-2-methyl-2,3-dihydro-1*H*-in-dol-7-yl)sulfonyl]propanoyl}amino)piperidine-1-carboxylate (7d{*1*})

Yield: 45%; white solid; mp 184–187 °C.

<sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 1.25$  (t, 3 H, J = 6.7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.25 (d, 3 H, NCHCH<sub>3</sub>), 1.70 (m, 2 H, CH<sub>2</sub>), 2.90 (m, 2 H, CH<sub>2</sub>), 3.60 (m, 2 H, CH<sub>2</sub>), 2.20 (s, 3 H, CH<sub>3</sub>CO), 2.50 (t, 2 H, J = 7.7 Hz, CH<sub>2</sub>CO), 2.80 (m, 1 H, NCHCH<sub>3</sub>), 3.25 (t, 2 H, J = 7.7 Hz, SO<sub>2</sub>CH<sub>2</sub>), 3.80 (m, 2 H, CH<sub>2</sub>), 4.20 (t, 2 H, J = 6.5 Hz, CH<sub>2</sub>), 4.05 (q, 2 H, J = 7.0 Hz, OCH<sub>2</sub>), 7.60 (s, 1 H<sub>arom</sub>, H-4), 7.80 (d, 1 H, J = 6.5 Hz, CONH), 8.70 (s, 1 H<sub>arom</sub>, H-6).

LCMS:  $m/z = 545 (M + H^{+})$ .

#### **3-(2,1,3-Benzothiadiazol-4-ylsulfonyl)**-*N*-cycloheptylpropanamide (7f{1})

Yield: 65%; white solid; mp 191-194 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 1.35 (m, 4 H), 1.55 (m, 6 H), 1.70 (m, 2 H), 3.55 (m, 1 H), 2.50 (t, 2 H, *J* = 7.3 Hz, CH<sub>2</sub>CO), 3.80 (t, 2 H, *J* = 7.3 Hz, SO<sub>2</sub>CH<sub>2</sub>), 7.60 (d, 1 H, *J* = 6.6 Hz, CONH), 7.90 (t, 1 H<sub>arom</sub>, *J* = 7.2 Hz, H-6), 8.30 (d, 1 H<sub>arom</sub>, *J* = 7.2 Hz, H-7), 8.35 (d, 1 H<sub>arom</sub>, *J* = 1.3 Hz, H-5).

LCMS:  $m/z = 368 (M + H^+)$ .

### *N*-(3,4-Dimethoxyphenyl)-3-(quinolin-8-ylsulfonyl)propanamide (7g{*1*})

Yield: 55%; white solid; mp 103-106 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 2.70$  (t, 2 H, J = 7.4 Hz, CH<sub>2</sub>CO), 3.70 (s, 6 H, 2 OCH<sub>3</sub>), 4.10 (t, 2 H, J = 7.4 Hz, SO<sub>2</sub>CH<sub>2</sub>), 6.65 (d, 1 H<sub>arom</sub>, J = 7.4 Hz, H-6'), 6.85 (d, 1 H<sub>arom</sub>, J = 7.2 Hz, H-5'), 7.20 (s, 1 H<sub>arom</sub>, H-2'), 7.65 (dd, 1 H<sub>arom</sub>, J = 8.5 Hz, J = 1.2 Hz, H-5), 7.70 (t, 1 H<sub>arom</sub>, J = 7.7 Hz, H-6), 8.25 (d, 1 H<sub>arom</sub>, J = 7.7 Hz, H-7), 8.45 (d, 1 H<sub>arom</sub>, J = 1.0 Hz, H-4), 8.50 (d, 1 H<sub>arom</sub>, J = 1.0 Hz, H-5), 9.15 (d, 1 H<sub>arom</sub>, J = 7.5 Hz, H-2), 9.7 (s, 1 H, CONH).

LCMS:  $m/z = 401 (M + H^+)$ .

# *N*-(1,3-Benzodioxol-5-ylmethyl)-3-[(1,4-dimethyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)sulfonyl]propanamide (7h{1})

Yield: 58%; white solid; mp 197-199 °C.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 2.55$  (t, 2 H, J = 7.1 Hz, CH<sub>2</sub>CO), 3.55 (t, 2 H, J = 7.1 Hz, SO<sub>2</sub>CH<sub>2</sub>), 3.65 (s, 3 H, NCH<sub>3</sub>), 3.68 (s, 3 H, NCH<sub>3</sub>), 4.13 (d, 2 H, J = 5.9 Hz, NCH<sub>2</sub>), 5.95 (s, 2 H, OCH<sub>2</sub>), 6.70 (m, 3 H<sub>arom</sub>), 7.60 (dd, 1 H<sub>arom</sub>,  $J_{7.8} = 8.3$  Hz,  $J_{7.5} = 1.0$  Hz, H-7), 7.76 (d, 1 H<sub>arom</sub>,  $J_{8.7} = 8.3$  Hz, H-8), 7.77 (d, 1 H,  $J_{5.7} = 1.0$  Hz, H-5), 8.29 (t, 1 H, J = 5.9 Hz, CONH).

LCMS:  $m/z = 460 (M + H^{+})$ .

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