



# Benzosultam synthesis exploiting sequential palladium-catalysed intermolecular aminosulfonylation and intramolecular sulfamidation

Charlotte S. Richards-Taylor, and Michael C. Willis\*

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK.

This paper is dedicated to the memory of Professor Jonathan Williams, who was a truly inspiring colleague and friend.

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## ABSTRACT

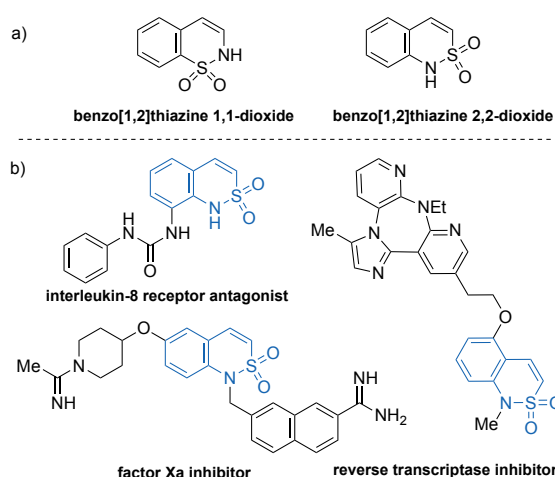
We report a route to benzosultams that exploits the palladium catalysed aminosulfonylation of alkenyl iodides as the initial step. An (*Z*)-configured alkenyl iodide substrate is combined with DABSO, a *N,N*-dialkylhydrazine nucleophile and a palladium(0) catalyst to achieve aminosulfonylation. A second palladium(0)-catalysed transformation, this time intramolecular, leads to benzosultam formation. Good variation of the starting alkenyl iodides is possible. A related  $S_NAr$  route was also explored, but was shown to be less efficient.

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## 1. Introduction

The sulfonamide functional group is often used as an amide replacement in biological settings due to its unique physicochemical properties.<sup>1</sup> Cyclic sulfonamides, named sultams, are an important subclass of these compounds, and benzosultams with an aryl- $N$ -SO<sub>2</sub> linkage (benzothiazine 2,2-dioxides) are far less explored in their biological relevance compared to the regioisomer with an aryl-SO<sub>2</sub>- $N$  linkage (Figure 1a). However, there is growing interest in this structure with reports of its use as a reverse transcriptase (RT) inhibitor,<sup>2</sup> an interleukin-8 receptor antagonist,<sup>3</sup> and a factor Xa inhibitor (Figure 1b).<sup>4</sup>

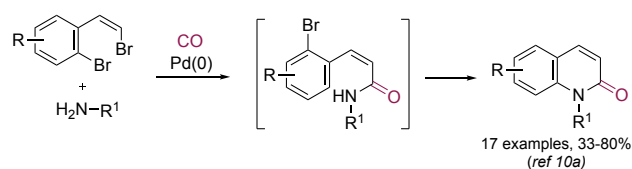
There are only a handful of methods towards the synthesis of benzothiazine 2,2-dioxides, most of which primarily feature multi-step sequences and lack functional group tolerance, consequently resulting in limited substrate scope. The first known synthesis of a benzothiazine 2,2-dioxide was reported in 1966 by two groups, Loev *et al.* and Rossi *et al.*, both describing a similar 7-step procedure from a sulfoacetic acid.<sup>5</sup> More recently, a report by Mindville and co-workers described the synthesis of benzothiazine 2,2-dioxides by implementing a ring-closing metathesis,<sup>6</sup> with the synthesis of the cyclisation substrate again requiring several synthetic steps. Literature examples for the synthesis of related derivatives, such as dibenzosultam,<sup>7</sup> dihydrosulfostyryl<sup>8</sup> and heteroarylsultams,<sup>9</sup> also predominately involve either multi-step procedures from a sulfonyl chloride or are restricted in the functionality of the scaffold due to the reagents employed.



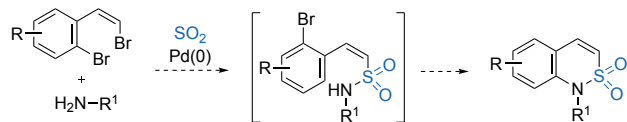
**Figure 1.** a) Benzosultams with aryl- $N$ -SO<sub>2</sub> and aryl-SO<sub>2</sub>- $N$  linkages; b) Biologically relevant examples of sultams with an aryl- $N$ -SO<sub>2</sub> arrangement.

Aiming to develop a more general route to the desired benzosultams, we drew inspiration from the report from our laboratory describing a tandem palladium catalysed aminocarbonylation/amidation sequence to obtain 2-quinolones (Scheme 1a).<sup>10</sup> We speculated that a similar approach, but employing sulfur dioxide in place of carbon monoxide, would lead to the desired benzosultams (Scheme 1b). Herein, we report the successful realisation of a variant of this approach.

a) Aminocarbonylation/amidation route to quinolones

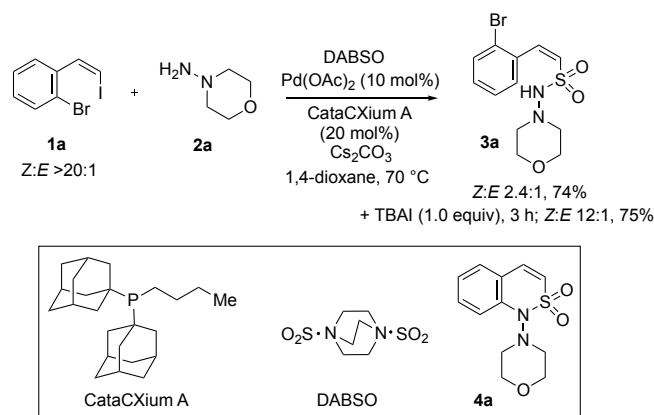


b) This work: aminosulfonylation/sulfamidation route to sultams

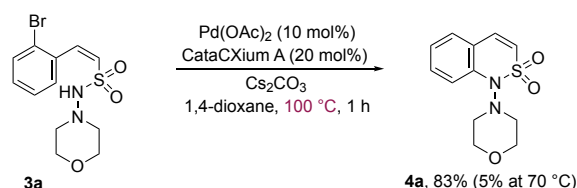
**Scheme 1.** a) Pd-catalysed aminocarbonylation route to 2-quinolones; b) Proposed route to benzosultams.

## 2. Results and discussion

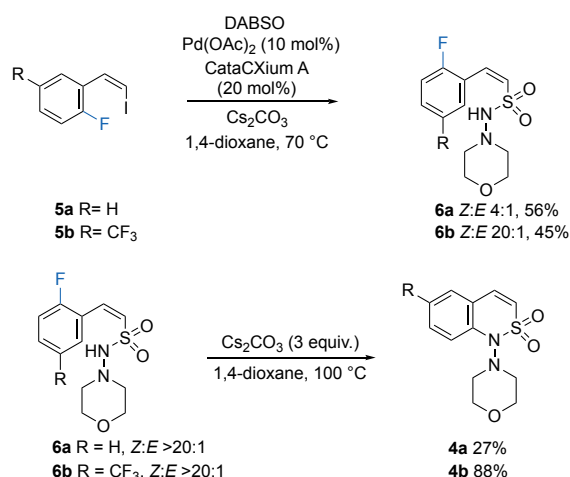
Our laboratory,<sup>11</sup> as well as others,<sup>12</sup> have developed a variety of palladium-catalysed sulfonylation processes, but examples that employ aryl or alkenyl halides as substrates, and proceed directly to sulfonamide products are limited to variants that use *N,N*-dialkylhydrazines as coupling partners.<sup>11a,b, 12b</sup> Using our earlier 2-quinolone methodology as a guide,<sup>10</sup> and with the knowledge that palladium-catalysed aminosulfonylation reactions perform better with aryl iodide substrates,<sup>11b</sup> we selected alkenyl iodide **1a** as our test substrate. Accordingly, we combined alkenyl iodide **1a** with *N*-aminomorpholine, DABSO (as an SO<sub>2</sub> surrogate),<sup>13</sup> Pd(OAc)<sub>2</sub> and CataCXium A as ligand, in dioxane at 70 °C, which are the optimised reaction conditions from our earlier studies.<sup>11b,c</sup> Unfortunately, none of the desired benzosultam product (**4a**) was isolated, but alkenyl sulfonamide **3a** was obtained in 74% yield (Scheme 2). The starting alkenyl iodide was used as a >20:1 mixture of *Z:E* isomers, and it was notable that alkenyl sulfonamide **3a** was obtained with *Z:E* of only 2.4:1. Disappointing as the failure to achieve cyclisation was, this erosion of *Z:E* ratio was also concerning, as our earlier 2-quinoline work had established that only the *Z*-isomers underwent efficient palladium-catalysed cyclisation.<sup>10</sup> A brief survey of reaction conditions established that prolonged reaction times were problematic. A solution to this issue was found with the use of TBAI (tetrabutylammonium iodide) as an additive; the use of one equivalent of TBAI allowed the reaction time to be reduced to 3 hours, and for *N*-aminosulfonamide **3a** to be isolated in 75% yield and with a *Z:E* ratio of 12:1.

**Scheme 2.** Initial reactions using alkenyl iodide **1a**, leading to *N*-aminosulfonamide **3a**.

With the efficient preparation of alkenyl sulfonamide **3a** in place, we tuned our attention to developing conditions for cyclisation. With the goal of achieving a single-step aminosulfonylation/cyclisation in mind, we focused on developing cyclisation conditions that were similar to the optimised aminosulfonylation process. Pleasingly, when alkenyl sulfonamide **3a** was reacted with Pd(OAc)<sub>2</sub> and CataCXium A, smooth conversion to benzosultam **4a** was achieved in 83% yield (Scheme 3). Importantly, a temperature of 100 °C was needed to achieve an efficient reaction, as performing the reaction at 70 °C delivered only a 5% yield of benzosultam **4a**. Returning to the desired single-step approach, we first attempted to pause the process only for a work-up and filtration of the intermediate alkenyl sulfonamide **3a**, with the crude material being subjected directly to the cyclisation conditions. Unfortunately, this approach was unsuccessful, with a maximum of 13% yield of benzosultam **4a** being achieved.

**Scheme 3.** Palladium-catalysed cyclisation of *N*-aminosulfonamide **3a**, to benzosultam **4a**.

As an alternative to a palladium-catalysed cyclisation, we considered that with an appropriate substrate an S<sub>N</sub>Ar cyclisation might be feasible. Accordingly, *ortho*-fluoro alkenylsulfonamide **6a** was prepared using the developed conditions, starting from the corresponding F-substituted starting material (**5a**) (Scheme 4). However, cyclisation of sulfonamide **6a** was not efficient, and only a poor yield (27%) of the desired sultam (**4a**) could be achieved. A more efficient cyclisation was possible if a strongly electron-withdrawing trifluoromethyl substituent was added to the substrate, allowing benzosultam **4b** to be isolated in 88% yield from the cyclisation of alkenylsulfonamide **6b**. As with our earlier approach, it was not possible to achieve sulfonylation and cyclisation in a single step using either substrate **5a** or **5b**.

**Scheme 4.** S<sub>N</sub>Ar cyclisation routes to benzosultams **4a** and **4b**.

Given the requirement for an activating electron-withdrawing group to achieve efficient S<sub>N</sub>Ar reactions, we reverted to a palladium-catalysed transformation to achieve cyclisation. With a one-step sulfonylation/cyclisation not possible, we then set about exploring the scope of the developed two-step route to

benzothiazine 2,2-dioxides (Table 1). The required alkenyl iodides (**1**) were prepared using Wittig chemistry, as previously

described,<sup>10a,14</sup> and were subjected to the optimized reaction conditions.

**Table 1.** Two-step route to benzosultams **4**, starting from alkenyl iodides **1** and proceeding via alkenylsulfonamides **3**.<sup>a</sup>

entry	alkenylsulfonamide	yield/ <i>E</i> : <i>Z</i>	sultam	yield	entry	alkenylsulfonamide	yield/ <i>E</i> : <i>Z</i>	sultam	yield
1		75% <i>Z</i> : <i>E</i> 12:1		83%	8		78% <i>Z</i> : <i>E</i> 15:1		71%
2		79% <i>Z</i> : <i>E</i> 15:1		75%	9		84% <i>Z</i> : <i>E</i> 15:1		85%
3		70% <i>Z</i> : <i>E</i> 20:1		69%	10		59% <i>Z</i> : <i>E</i> 10:1		0%
4		65% <i>Z</i> : <i>E</i> 15:1		78%	11		83% <i>Z</i> : <i>E</i> 20:1		77%
5		75% <i>Z</i> : <i>E</i> 15:1		68%	12		74% <i>Z</i> : <i>E</i> 11:1		82%
6		78% <i>Z</i> : <i>E</i> 20:1		80%	13		59% <i>Z</i> : <i>E</i> 20:1		75%
7		79% <i>Z</i> : <i>E</i> 8:1		79%	14		76% <i>Z</i> : <i>E</i> 10:1		42%

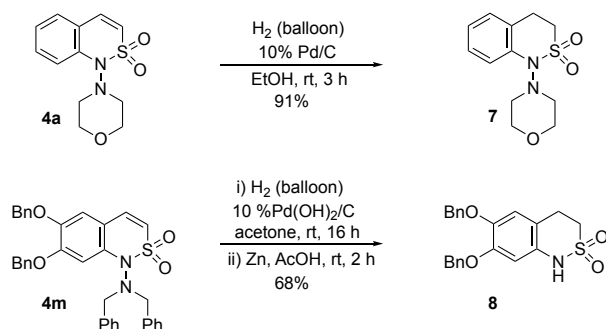
<sup>a</sup> Reaction conditions: (i) 2-(2-iodoalkenyl)aryl halide (1 equiv.), Pd(OAc)<sub>2</sub> (10 mol%), CataCXium A (20 mol%), DABSO (1.1 equiv.), TBAI (1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 3–4 h; (ii) Alkenyl *N*-aminosulfonamide (1 equiv.), Pd(OAc)<sub>2</sub> (10 mol%), CataCXium A (20 mol%), Cs<sub>2</sub>CO<sub>3</sub>, 100 °C, 1 h. Isolated yields.

As expected, a small drop in *Z*:*E* ratio was observed for most examples during the initial palladium-catalysed aminosulfonylation step, but the alkenyl *N*-aminosulfonamides were generally obtained in moderate to high yields, and with good *Z*:*E* selectivity. The lowest *Z*:*E* ratio was obtained with the benzyl

ether variant, but was still measured at 8:1 (entry 7). After purification of the alkenyl *N*-aminosulfonamides by column chromatography, they were subjected to the cyclisation reaction conditions. The key palladium-catalysed cyclisation step worked well, and was able to deliver sultams featuring a variety of aryl and

*N*-substituents. For example, trifluoromethyl and fluoro aryl substituents were well tolerated (entries 2-4). Substrates bearing electron-donating substituents on the aryl ring also performed well (entries 6-9). Pleasingly, two heteroaryl alkenyl iodides gave the corresponding aminosulfonylation products in good yields, however, only the pyridyl example was successfully cyclised, with the thiophenyl variant failing (entries 10 and 11). Three additional hydrazine nucleophiles were explored; all delivering the expected products (entries 12-14). However, a significant drop in yield was observed for the *N*-methyl-*N*-phenyl hydrazine example, presumably due to the increased steric hindrance of the hydrazine (entry 14).

With a range of *N*-amino benzosultams available we briefly explored derivatisation of these structures. Reduction of the C-C double bond in benzosultam **4a** was achieved with a balloon pressure of hydrogen over a Pd/C catalyst, to deliver the dihydro-derivative **7** in excellent yield (Scheme 5). Cleavage of the N-N bond, required to deliver the parent sultam scaffold, was achieved using our previously reported procedure;<sup>11b</sup> hydrogenolysis of the benzyl groups in *N*-amino benzosultam **4m** was followed by *in-situ* hydrazone formation, and finally Zn-mediated reduction. In this way N-H derivative **8** was obtained in 68% yield for the 2-step procedure. It should be noted that the deprotection/N-N bond cleavage process also resulted in reduction of the C-C double bond.



**Scheme 5.** C-C Double-bond reduction and the preparation of N-H sultam-derivative **8**.

### 3. Conclusions

Although a single-step amino-sulfonylation/cyclisation sequence was not possible, the use of two discrete palladium-catalysed processes, first an aminosulfonylation using *N,N*-dialkylhydrazines as the *N*-nucleophiles, and DABSO as the SO<sub>2</sub> source, and then a palladium-catalysed intramolecular sulfamidation, allowed a new entry into benzosultams to be achieved. Both steps use a catalyst generated from the combination of Pd(OAc)<sub>2</sub>/CataCXium A. The method tolerates good variation of the halide precursor, as well as variation of the hydrazine coupling partner. Access to the N-H benzosultam is possible if dibenzyl hydrazine is used as the coupling partner.

## 4. Experimental

### 4.1. General information

<sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Brüker AVIII400 (400 MHz) or AVII (500 MHz) spectrometer. Proton-decoupled spectra are denoted as {<sup>1</sup>H}. Chemical shifts (δ) were reported in parts per million (ppm) using the residual solvent signal as an internal standard (CDCl<sub>3</sub>: δ<sub>H</sub> = 7.26 ppm, δ<sub>C</sub> = 77.16 ppm). All coupling constants (*J* values) were reported in Hertz (Hz). Multiplicities were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet. High-resolution

mass spectrometry (HRMS) measurements were recorded on a Bruker Daltonics microTOF (ESI) spectrometer. Infrared spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Flash chromatography was carried out using matrix 60 silica. All alkynes were distilled prior to use. The alkenyl iodide substrates were prepared from the corresponding aldehydes using Wittig chemistry, as previously reported.

### 4.2. Synthesis of alkenylsulfonamides **3**

#### 4.2.1. General procedure A for the preparation of alkenylsulfonamides **3**.

An oven-dried tube was evacuated and backfilled with N<sub>2</sub>. It was then charged with the appropriate alkenyl iodide (1 equiv.), CataCXium A (20 mol%), palladium(II) acetate (10 mol%), TBAI (1 equiv.) and DABSO (1.1 equiv.). The solid reagents were weighed out in the air. The tube was then evacuated and backfilled with N<sub>2</sub>. The appropriate dialkyl hydrazine (1.5 equiv.) and 1,4-dioxane [0.15 M] were added *via* microsyringe through a sub-seal under N<sub>2</sub>. The reaction mixture was stirred at 70 °C for the specified length of time. After cooling to RT, the suspension was filtered through a short pad of Celite and the residue washed sequentially with CH<sub>2</sub>Cl<sub>2</sub> (20 mL mmol<sup>-1</sup>) and ether (20 mL mmol<sup>-1</sup>) before being concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding alkenyl *N*-aminosulfonamide.

#### 4.2.2. (Z)-2-(2-Bromophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide (**3a**)

Prepared according to the general procedure A using (Z)-1-bromo-2-(2-iodovinyl)benzene (74 mg, 0.24 mmol, *Z:E*, >20:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded alkenyl *N*-aminosulfonamide **3a** as an off-white crystalline solid (63 mg, 75%, *Z:E*, 12:1); mp 89-92 °C (CH<sub>2</sub>Cl<sub>2</sub>); ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3202, 3061, 2960, 2922, 2853, 1463, 1434, 1387, 1363, 1334, 1277, 1263, 1220, 1150, 1110, 1071, 1043, 1025; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.89 (1H, dd, *J* 7.5, 1.5, ArH), 7.61 (1H, dd, *J* 7.5, 1.5, ArH), 7.41-7.31 (1H, app td, *J* 7.5, 1.5, ArH), 7.31-7.21 (1H, m, ArH), 7.23 (1H, d, *J* 12.0, ArCH=CHS), 6.57 (1H, d, *J* 12.0, ArCH=CHS), 5.33 (1H, s, NH), 3.73 (4H, t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 2.81 (4H, t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 140.3 (CH), 133.1 (C), 132.3 (CH), 132.0 (CH), 131.0 (CH), 128.4 (CH), 126.9 (CH), 123.4 (C), 66.6 (2 × CH<sub>2</sub>), 57.2 (2 × CH<sub>2</sub>); *m/z* (ESI<sup>+</sup>) 719 ([2M + Na]<sup>+</sup>, 60%), 717 ([2M + Na]<sup>+</sup>, 100%), 715 ([2M + Na]<sup>+</sup>, 50%); *m/z* (ESI<sup>-</sup>) 383 ([M + Cl]<sup>-</sup>, 100%), 381 ([M + Cl]<sup>-</sup>, 77%); HRMS (ESI<sup>+</sup>) C<sub>12</sub>H<sub>15</sub>BrN<sub>2</sub>NaO<sub>3</sub>S<sup>+</sup> ([M + Na]<sup>+</sup>) requires 370.9859 and 368.9879, found 370.9855 and 368.9869.

#### 4.2.3. (Z)-2-(2-Bromo-5-(trifluoromethyl)phenyl)-*N*-morpholinoethenesulfonamide (**3b**)

Prepared according to the general procedure using A (Z)-1-bromo-2-(2-iodovinyl)-4-(trifluoromethyl)benzene (90 mg, 0.24 mmol, *Z:E*, >20:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded alkenyl *N*-aminosulfonamide **3b** as a white crystalline solid (79 mg, 79%, *Z:E*, 15:1); mp 212-215 °C (dec.); ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3206, 2962, 2926, 2856, 1603, 1459, 1414, 1327, 1262, 1206, 1155, 1128, 1112, 1081, 1029; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 8.15 (1H, d, *J* 1.5, ArH), 7.72 (1H, d, *J* 8.5, ArH), 7.49 (1H, dd, *J* 8.5, 1.5, ArH), 7.21 (1H, d, *J* 12.0, ArCH=CHS), 6.54 (1H, d, *J* 12.0, ArCH=CHS), 5.34 (1H, br. s, NH), 3.75 (4H, t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 2.87 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O); δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) 139.5 (CH), 134.0 (C), 132.8 (CH), 129.4(3) (C, q, *J*<sub>CF</sub> 32.5), 129.3(8) (CH),

129.2 (CH, q,  $J_{CF}$  3.5), 127.3 (CH, q,  $J_{CF}$  4.0), 127.0 (C, m), 123.8 (C, q,  $J_{CF}$  272.5), 66.6 ( $2 \times CH_2$ ), 57.6 ( $2 \times CH_2$ );  $\delta_F$  (377 MHz,  $CDCl_3$ ) -62.4 (s,  $ArCF_3$ )  $\{^1H\}$ ;  $m/z$  ( $ESI^+$ ) 439 ( $[M + Na]^+$ , 100%), 437 ( $[M + Na]^+$ , 95%); HRMS ( $ESI^+$ )  $C_{13}H_{14}BrF_3N_2NaO_3S^+$  ( $[M + Na]^+$ ) requires 438.9732 and 436.9753; found 438.9745 and 436.9761.

#### 4.2.4. (Z)-2-(2-Bromo-4-fluorophenyl)-N-morpholinoethanesulfonamide (3c)

Prepared according to the general procedure A using 2-bromo-4-fluoro-1-(2-iodovinyl)benzene (78 mg, 0.24 mmol, *Z:E*, 20:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **3c** as a white crystalline solid (61 mg, 70%, *Z:E*, 20:1); mp 116-118 °C ( $CH_2Cl_2$ );  $\nu_{max}$  (neat)/ $cm^{-1}$  3191, 3048, 2978, 2923, 2855, 1622, 1591, 1477, 1457, 1390, 1357, 1315, 1265, 1239, 1189, 1158, 1140, 1114, 1073, 1033;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.92 (1H, dd,  $J$  9.0, 6.0, *ArH*), 7.35 (1H, dd,  $J$  8.0, 3.0, *ArH*), 7.16 (1H, d,  $J$  12.0, *ArCH=CHS*), 7.07 (1H, app td,  $J$  8.5, 2.5, *ArH*), 6.53 (1H, d,  $J$  12.0, *ArCH=CHS*), 5.35 (1H, s, *NH*), 3.72 (4H, t,  $J$  4.5,  $N(CH_2CH_2)_2O$ ), 2.83 (4H, br t,  $J$  4.5,  $N(CH_2CH_2)_2O$ );  $\delta_C$  (126 MHz,  $CDCl_3$ ) 163.0 (C, d,  $J_{CF}$  255.0), 139.4 (CH), 133.6 (CH, d,  $J_{CF}$  9.0), 129.3 (C, d,  $J_{CF}$  4.0), 128.5 (CH), 124.0 (C, d,  $J_{CF}$  10.0), 119.8 (CH, d,  $J_{CF}$  24.5), 114.5 (CH, d,  $J_{CF}$  21.5), 66.6 ( $2 \times CH_2$ ), 57.4 ( $2 \times CH_2$ );  $\delta_F$  (377 MHz,  $CDCl_3$ ) -108.8 (s, *ArF*)  $\{^1H\}$ ;  $m/z$  ( $ESI^+$ ) 365 ( $[M - H]^+$ , 90%), 363 ( $[M - H]^+$ , 100%); HRMS ( $ESI^+$ )  $C_{12}H_{14}BrFN_2NaO_3S^+$  ( $[M + Na]^+$ ) requires 388.9764 and 386.9785, found 388.9771 and 386.9792.

#### 4.2.5. (Z)-2-(2-Bromo-5-fluorophenyl)-N-morpholinoethanesulfonamide (3d)

Prepared according to the general procedure A using (Z)-1-bromo-4-fluoro-2-(2-iodovinyl)benzene (78 mg, 0.24 mmol, *Z:E*, 18:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **3d** as a white crystalline solid (57 mg, 65%, *Z:E*, 15:1); mp 125-127 °C ( $CH_2Cl_2$ );  $\nu_{max}$  (neat)/ $cm^{-1}$  3135, 2867, 1575, 1460, 1340, 1267, 1200, 1156, 1104, 1069, 1033;  $\delta_H$  (500 MHz,  $CDCl_3$ ) 7.78 (1H, dd,  $J$  9.0, 3.0, *ArH*), 7.53 (1H, dd,  $J$  9.0, 5.0, *ArH*), 7.16 (1H, d,  $J$  12.0, *ArCH=CHS*), 7.00-6.95 (1H, m, *ArH*), 6.52 (1H, d,  $J$  12.0, *ArCH=CHS*), 5.36 (1H, s, *NH*), 3.75 (4H, t,  $J$  4.5,  $N(CH_2CH_2)_2O$ ), 2.86 (4H, br t,  $J$  4.5,  $N(CH_2CH_2)_2O$ );  $\delta_C$  (126 MHz,  $CDCl_3$ ) 161.2 (C, d,  $J_{CF}$  247.0), 139.6 (CH, d,  $J_{CF}$  2.0), 134.7 (C, d,  $J_{CF}$  9.0), 133.5 (CH, d,  $J_{CF}$  7.5), 129.0 (CH), 119.5 (CH, d,  $J_{CF}$  24.5), 118.3 (CH, d,  $J_{CF}$  23.0), 117.7 (C, d,  $J_{CF}$  3.5), 66.7 ( $2 \times CH_2$ ), 57.5 ( $2 \times CH_2$ );  $\delta_F$  (377 MHz,  $CDCl_3$ ) -114.5 (s, *ArF*)  $\{^1H\}$ ;  $m/z$  ( $ESI^+$ ) 365 ( $[M - H]^+$ , 95%), 363 ( $[M - H]^+$ , 100%); HRMS ( $ESI^+$ )  $C_{12}H_{13}BrFN_2O_3S^+$  ( $[M - H]^+$ ) requires 364.9801 and 362.9825, found 364.9799 and 362.9820.

#### 4.2.6. (Z)-2-(1-Bromonaphthalen-2-yl)-N-morpholinoethanesulfonamide (3e)

Prepared according to the general procedure A using (Z)-1-bromo-2-(2-iodovinyl)naphthalene (86 mg, 0.24 mmol, *Z:E*, >20:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **3e** as a white crystalline solid (72 mg, 75%, *Z:E*, 15:1); mp 152-156 °C ( $CH_2Cl_2$ );  $\nu_{max}$  (neat)/ $cm^{-1}$  3191, 3041, 2959, 2926, 2857, 1632, 1553, 1498, 1457, 1417, 1386, 1364, 1320, 1270, 1238, 1142, 1105, 1072, 1016;  $\delta_H$  (400 MHz,  $(CD_3)_2SO$ ) 8.88 (1H, s, *NH*), 8.23 (1H, d,  $J$  8.5, *ArH*), 8.03-7.90 (3H, m,  $3 \times ArH$ ), 7.71 (1H, app t,  $J$  7.0 *ArH*) overlapping 7.65

(1H, app t,  $J$  8.0, *ArH*), 7.43 (1H, d,  $J$  11.5, *ArCH=CHS*), 6.75 (1H, d,  $J$  11.5, *ArCH=CHS*), 3.64 (4H, br t,  $J$  4.0,  $N(CH_2CH_2)_2O$ ), 2.84-2.78 (4H, m,  $N(CH_2CH_2)_2O$ );  $\delta_C$  (126 MHz,  $CDCl_3$ ) 141.5 (CH), 134.6 (C), 131.8(9) (C), 131.7(7) (C), 128.4 (CH), 128.3(3) (CH), 128.2(6) (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 124.2 (C), 66.8 ( $2 \times CH_2$ ), 57.4 ( $2 \times CH_2$ );  $m/z$  ( $ESI^+$ ) 397 ( $[M - H]^+$ , 100%), 395 ( $[M - H]^+$ , 80%); HRMS ( $ESI^+$ )  $C_{16}H_{17}BrN_2NaO_3S^+$  ( $[M + Na]^+$ ) requires 421.0015 and 419.0035, found 421.0019 and 419.0042.

#### 4.2.7. (Z)-2-(6-Bromobenzo[d][1,3]dioxol-5-yl)-N-morpholinoethanesulfonamide (3f)

Prepared according to the general procedure A using (Z)-bromo-6-(2-iodovinyl)benzo[d][1,3]dioxole (85 mg, 0.24 mmol, *Z:E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **3f** as a white crystalline solid (73 mg, 78%, *Z:E*, 20:1); mp 128-131 °C ( $CH_2Cl_2$ );  $\nu_{max}$  (neat)/ $cm^{-1}$  3157, 3044, 2958, 2931, 2852, 1621, 1502, 1275, 1415, 1388, 1363, 1318, 1260, 1246, 1197, 1142, 1106, 1070, 1036;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.67 (1H, s, *ArH*), 7.15 (1H, d,  $J$  12.0, *ArCH=CHS*), 7.04 (1H, s, *ArH*), 6.40 (1H, d,  $J$  12.0, *ArCH=CHS*), 6.03 (2H, s,  $OCH_2O$ ), 5.58 (1H, s, *NH*), 3.74 (4H, t,  $J$  4.5,  $N(CH_2CH_2)_2O$ ), 2.86 (4H, br t,  $J$  4.5,  $N(CH_2CH_2)_2O$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 149.8 (C), 147.0 (C), 140.5 (CH), 126.9 (CH), 125.9 (C), 116.1 (C), 112.4 (CH), 112.0 (CH), 102.3 (CH), 66.7 ( $2 \times CH_2$ ), 57.3 ( $2 \times CH_2$ );  $m/z$  ( $ESI^+$ ) 391 ( $[M - H]^+$ , 100%), 389 ( $[M - H]^+$ , 98%); HRMS ( $ESI^+$ )  $C_{13}H_{14}BrN_2O_5S^+$  ( $[M - H]^+$ ) requires 390.9792 and 388.9812, found 390.9793 and 388.9819.

#### 4.2.8. (Z)-2-(5-(Benzyloxy)-2-bromophenyl)-N-morpholinoethanesulfonamide (3g)

Prepared according to the general procedure A using 4-(benzyloxy)-1-bromo-2-(2-iodovinyl)benzene (100 mg, 0.24 mmol, *Z:E*, 15:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **3g** as white needles (86 mg, 79%, 8:1); mp 178-180 °C ( $CH_2Cl_2$ );  $\nu_{max}$  (neat)/ $cm^{-1}$  3207, 3059, 2952, 2855, 2820, 1616, 1589, 1460, 1446, 1404, 1363, 1333, 1262, 1249, 1231, 1179, 1156, 1112, 1046, 1016;  $\delta_H$  (400 MHz,  $CDCl_3$ ) 7.61 (1H, d,  $J$  3.0, *ArH*), 7.46 (1H, d,  $J$  9.0, *ArH*), 7.44-7.32 (5H, m,  $5 \times OBnH$ ), 7.16 (1H, d,  $J$  12.0, *ArCH=CHS*), 6.90 (1H, dd,  $J$  9.0, 3.0, *ArH*), 6.54 (1H, d,  $J$  12.0, *ArCH=CHS*), 5.11 (2H, s,  $OCH_2Ph$ ), 4.99 (1H, s, *NH*), 3.67 (4H, t,  $J$  4.5,  $N(CH_2CH_2)_2O$ ), 2.68 (4H, br t,  $J$  4.5,  $N(CH_2CH_2)_2O$ );  $\delta_C$  (101 MHz,  $CDCl_3$ ) 157.5 (C), 140.1 (CH), 136.6 (CH), 133.6(4) (CH), 133.1 (CH), 129.0 (C), 128.8 ( $2 \times CH$ ), 128.2 (CH), 127.6(4) ( $2 \times CH$ ), 118.9 (CH), 118.1 (CH), 114.5 (C), 70.3 (CH), 66.6 ( $2 \times CH_2$ ), 57.2 ( $2 \times CH_2$ );  $m/z$  ( $ESI^+$ ) 477 ( $[M + Na]^+$ , 95%), 475 ( $[M + Na]^+$ , 100%); HRMS ( $ESI^+$ )  $C_{19}H_{21}BrN_2NaO_4S^+$  ( $[M + Na]^+$ ) requires 477.0278 and 475.0298, found 477.0287 and 475.0306; Anal. Calcd. (%) for  $C_{19}H_{21}BrN_2O_4S$ : C 50.34, H 4.67, N 6.18; found C 50.06, H 4.52, N 6.03.

#### 4.2.9. (Z)-2-(2-Bromo-4-methylphenyl)-N-morpholinoethanesulfonamide (3h)

Prepared according to the general procedure A using 2-bromo-1-(2-iodovinyl)-4-methylbenzene (78 mg, 0.24 mmol, *Z:E*, 18:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **3h** as a white crystalline solid (68 mg, 78%, *Z:E*, 15:1); mp 148-149 °C ( $CH_2Cl_2$ );  $\nu_{max}$  (neat)/ $cm^{-1}$  3245, 2852,

1619, 1600, 1446, 1360, 1330, 1283, 1267, 1152, 1106, 1071, 1042;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.81 (1H, d,  $J$  8.0, ArH), 7.43 (1H, d,  $J$  1.0, ArH), 7.20 (1H, d,  $J$  12.0, ArCH=CHS), 7.16-7.13 (1H, m, ArH), 6.51 (1H, d,  $J$  12.0, ArCH=CHS), 5.31 (1H, s, NH), 3.71 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.80 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.35 (3H, s, ArMe);  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 141.9 (CH), 140.4 (CH), 132.9 (CH), 131.9 (CH), 130.1 (C), 128.0 ( $2 \times \text{CH}$ ), 123.6 (C), 66.7 ( $2 \times \text{CH}_2$ ), 57.3 ( $2 \times \text{CH}_2$ ), 21.2 ( $\text{CH}_3$ );  $m/z$  (ESI<sup>+</sup>) 361 ([M - H]<sup>+</sup>, 95%), 359 ([M - H]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>)  $\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{NaO}_3\text{S}^+$  ([M + Na]<sup>+</sup>) requires 385.0015 and 383.0035, found 385.0026 and 383.0048; Anal. Calcd. (%) for  $\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{O}_3\text{S}$ : C 43.22, H 4.74, N 7.75; found C 43.01, H 4.81, N 7.66.

#### 4.2.10. (Z)-2-(2-Bromo-4,5-dimethoxyphenyl)-N-morpholinoethanesulfonamide (**3i**)

Prepared according to the general procedure A using 1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene (89 mg, 0.24 mmol,  $Z:E$ , >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide 3i* as a white crystalline solid (82 mg, 84%,  $Z:E$ , 15:1); mp 181-185 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3217, 3006, 2973, 2932, 2858, 1596, 1500, 1463, 1442, 1392, 1325, 1308, 1267, 1232, 1203, 1186, 1157, 1132, 1114, 1021;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.67 (1H, s, ArH), 7.17 (1H, d,  $J$  12.0, ArCH=CHS), 7.05 (1H, s, ArH), 6.51 (1H, d,  $J$  12.0, ArCH=CHS), 5.19 (1H, s, NH), 3.91 (3H, s, OMe) overlapping 3.90 (3H, s, OMe), 3.69 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.76 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 150.9 (C), 148.0 (C), 140.0 (CH), 127.7 (CH), 124.9 (C), 115.5 (C), 115.0 ( $2 \times \text{CH}$ ), 66.7 ( $2 \times \text{CH}_2$ ), 57.3 ( $2 \times \text{CH}_2$ ), 56.5 ( $\text{CH}_3$ ), 56.4 ( $\text{CH}_3$ );  $m/z$  (ESI<sup>+</sup>) 431 ([M + Na]<sup>+</sup>, 95%), 429 ([M + Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>)  $\text{C}_{14}\text{H}_{19}\text{BrN}_2\text{NaO}_5\text{S}^+$  ([M + Na]<sup>+</sup>) requires 431.0070 and 429.0090, found 431.0083 and 429.0104.

#### 4.2.11. (Z)-2-(2-Bromothiophen-3-yl)-N-morpholinoethanesulfonamide (**3j**)

Prepared according to the general procedure A using 2-bromo-3-(2-iodovinyl)thiophene (76 mg, 0.24 mmol,  $Z:E$ , 10:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide 3j* as a white crystalline solid (50 mg, 59%,  $Z:E$ , 10:1); mp 185-186 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3207, 3108, 2962, 2920, 2855, 1605, 1456, 1412, 1362, 1337, 1264, 1149, 1109;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.60 (1H, d,  $J$  5.5, CH=CHS), 7.31 (1H, dd,  $J$  12.0, 1.0, ArCH=CHS), 7.09 (1H, d,  $J$  5.5, CH=CHS), 6.32 (1H, d,  $J$  12.0, ArCH=CHS), 5.53 (1H, s, NH), 3.65 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.83 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 132.7 (CH), 132.0 (CH), 130.0 (CH), 128.9 (C), 123.2 (CH), 120.0 (C), 66.7 ( $2 \times \text{CH}_2$ ), 57.2 ( $2 \times \text{CH}_2$ );  $m/z$  (ESI<sup>+</sup>) 377 ([M + Na]<sup>+</sup>, 90%), 375 ([M + Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>)  $\text{C}_{10}\text{H}_{13}\text{BrN}_2\text{NaO}_3\text{S}_2^+$  ([M + Na]<sup>+</sup>) requires 376.9422 and 374.9443, found 376.9432 and 374.9455.

#### 4.2.12. (Z)-2-(2-Bromopyridin-3-yl)-N-morpholinoethanesulfonamide (**3k**)

Prepared according to the general procedure A using (Z)-2-bromo-3-(2-iodovinyl)pyridine (74 mg, 0.24 mmol,  $Z:E$ , >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide 3k* as a pale yellow crystalline solid (69 mg, 83%,  $Z:E$ , >20:1), mp 118-121 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3140,

3031, 2978, 2887, 1618, 1572, 1555, 1460, 1396, 1370, 1337, 1279, 1265, 1206, 1150, 1123, 1103, 1070, 1061, 1051, 1012;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.37 (1H, dd,  $J$  5.0, 1.5, ArH), 8.21-8.13 (1H, m, ArH), 7.32 (1H, dd,  $J$  7.5, 5.0, ArH), 7.16 (1H, d,  $J$  11.5, ArCH=CHS), 6.61 (1H, d,  $J$  11.5, ArCH=CHS), 5.36 (1H, s, NH), 3.72 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.85 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 138.3 (C), 138.1 (CH), 135.1 (CH), 134.3 (CH), 133.5 (CH), 127.9 (CH), 120.2 (C), 66.6 ( $2 \times \text{CH}_2$ ), 56.7 ( $2 \times \text{CH}_2$ );  $m/z$  (ESI<sup>+</sup>) 372 ([M + Na]<sup>+</sup>, 100%), 370 ([M + Na]<sup>+</sup>, 95%); HRMS (ESI<sup>+</sup>)  $\text{C}_{11}\text{H}_{14}\text{BrN}_3\text{NaO}_3\text{S}^+$  ([M + Na]<sup>+</sup>) requires 371.9811 and 369.9831, found 371.9826 and 369.9849.

#### 4.2.13. (Z)-2-(2-Bromo-4,5-dimethoxyphenyl)-N-(4-methylpiperazin-1-yl)ethanesulfonamide (**3l**)

Prepared according to the general procedure A using (Z)-1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene (89 mg, 0.24 mmol,  $Z:E$ , >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 4% MeOH in  $\text{CH}_2\text{Cl}_2$ ) yielded *alkenyl N-aminosulfonamide 3l* as a white crystalline solid (75 mg, 74%,  $Z:E$ , 11:1); mp 160 °C (dec) ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3227, 2926, 2851, 1597, 1502, 1463, 1439, 1389, 1326, 1271, 1209, 1181, 1150, 1027;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.63 (1H, s, ArH), 7.16 (1H, d,  $J$  12.0, ArCH=CHS), 7.04 (1H, s, ArH), 6.46 (1H, d,  $J$  12.0, ArCH=CHS), 6.15 (1H, br. s, NH), 3.91 (3H, s, OMe) overlapping 3.90 (3H, s, OMe), 3.12 (4H, br. s,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{NMe}$ ) overlapping 3.03 (4H, br. s,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{NMe}$ ), 2.64 (3H, s, NMe);  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ , Z isomer) 151.1 (C), 148.1 (C), 140.3 (CH), 127.6 (CH), 124.8 (C), 115.3 (C), 115.0(0) (CH), 114.9(7) (CH), 56.5 ( $\text{CH}_3$ ), 56.4 ( $\text{CH}_3$ ), 53.7 ( $2 \times \text{CH}_2$ ), 43.9 ( $2 \times \text{CH}_2$ ), 29.8 ( $\text{CH}_3$ ); HRMS (FI<sup>+</sup>)  $\text{C}_{15}\text{H}_{22}\text{BrN}_3\text{NaO}_4\text{S}^+$  ([M]<sup>+</sup>) requires 422.0523 and 421.0495, found 422.0348 and 421.0372.

#### 4.2.14. (Z)-N',N'-Dibenzyl-2-(2-bromo-4,5-dimethoxyphenyl)ethanesulfonohydrazide (**3m**)

Prepared according to the general procedure A using (Z)-1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene (89 mg, 0.24 mmol,  $Z:E$ , >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 70:29:1, ether:petrol:Et<sub>3</sub>N to ether) yielded *alkenyl N-aminosulfonamide 3m* as an off-white crystalline solid (73 mg, 59%,  $Z:E$ , 20:1); mp >300 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3225, 2935, 2849, 1599, 1502, 1455, 1440, 1389, 1323, 1268, 1211, 1143, 1028;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.53 (1H, s, Ar(OMe)H), 7.39-7.32 (6H, m,  $6 \times \text{PhH}$ ), 7.31-7.27 (4H, m,  $4 \times \text{PhH}$ ), 7.02 (1H, s, Ar(OMe)H), 6.86 (1H, d,  $J$  12.0, ArCH=CHS), 5.80 (1H, d,  $J$  12.0, ArCH=CHS), 5.34 (1H, s, NH), 3.89 (3H, s, OMe) overlapping 3.89 (3H, s, OMe), 3.87 (4H, s,  $2 \times \text{CH}_2\text{Ph}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 151.9 (C), 148.8 (C), 138.1 (CH), 137.9 (CH), 130.9 ( $4 \times \text{CH}$ ), 129.1 ( $4 \times \text{CH}$ ), 129.0 ( $2 \times \text{C}$ ), 128.5 ( $2 \times \text{CH}$ ), 126.0 (C), 116.7 (CH), 115.8 (CH), 115.5 (C), 61.6 ( $2 \times \text{CH}_2$ ), 56.4(4) ( $\text{CH}_3$ ), 56.4(2) ( $\text{CH}_3$ );  $m/z$  (ESI<sup>+</sup>) 541 ([M + Na]<sup>+</sup>, 95%), 539 ([M + Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>)  $\text{C}_{24}\text{H}_{26}\text{O}_4\text{N}_2\text{BrS}^+$  ([M + H]<sup>+</sup>) requires 519.0782 and 517.0802, found 519.0769 and 517.0788.

#### 4.2.15. (Z)-2-(2-Bromo-4,5-dimethoxyphenyl)-N'-methyl-N'-phenylethanesulfonohydrazide (**3n**)

Prepared according to the general procedure A using 1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene (89 mg, 0.24 mmol,  $Z:E$ , >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 70:29:1, ether:petrol:Et<sub>3</sub>N to ether) yielded *alkenyl N-aminosulfonamide 3n* as an off-white solid (78

mg, 76%, *Z:E*, 10:1); mp 91–94 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3226, 2928, 2852, 1599, 1502, 1464, 1439, 1390, 1337, 1275, 1210, 1182, 1152, 1029;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.61 (1H, s, Ar(OMe)*H*), 7.31–7.26 (2H, m, 2 × Ph*H*), 7.21 (1H, d, *J* 12.0, ArCH=CHS), 7.05–7.00 (3H, m, Ar(OMe)*H*, 2 × Ph*H*), 6.95 (1H, t, *J* 7.5, Ph*H*), 6.47 (1H, d, *J* 12.0, ArCH=CHS), 6.04 (1H, s, *NH*), 3.88 (3H, s, OMe), 3.76 (3H, s, OMe), 3.21 (3H, s, NMe);  $\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 151.0 (C), 149.8 (C), 147.9 (C), 140.5 (CH), 129.4 (2 × CH), 126.8 (CH), 124.6 (C), 121.5 (CH), 115.8 (C), 115.0 (CH), 114.7(3) (CH), 114.6(8) (2 × CH), 56.3 (CH<sub>3</sub>), 56.2 (CH<sub>3</sub>), 43.7 (CH<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 451 ([M + Na]<sup>+</sup>, 100%), 449 ([M + Na]<sup>+</sup>, 95%); HRMS (ESI<sup>+</sup>) C<sub>17</sub>H<sub>20</sub>O<sub>4</sub>N<sub>2</sub>BrS<sup>+</sup> ([M + H]<sup>+</sup>) requires 429.0312 and 427.0333, found 429.0312 and 427.0332.

### 4.3. Synthesis of benzosultams from alkenylsulfonamides.

#### 4.3.1. General procedure B for the preparation of benzosultams 4

An oven-dried tube was evacuated and backfilled with N<sub>2</sub>. It was then charged with CataCXium A (20 mol%), palladium(II) acetate (10 mol%), and Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv.). The solid reagents were weighed out in the air. The tube was then evacuated and backfilled with N<sub>2</sub>. 1,4-ioxane [0.05 M] was added *via* syringe through a suba-seal under N<sub>2</sub>. The reaction mixture was stirred for 10 minutes. A solution of the alkenyl *N*-aminosulfonamide (1 equiv.) in 1,4-dioxane [0.1 M] was added *via* microsyringe. The reaction mixture was stirred at 100 °C for 1 h. After cooling to RT, the suspension was filtered through a short pad of Celite and the residue washed sequentially with CH<sub>2</sub>Cl<sub>2</sub> (20 mL mmol<sup>-1</sup>) and ether (20 mL mmol<sup>-1</sup>) before being concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding alkenyl *N*-aminobenzosultam.

#### 4.3.2. 1-(Morpholin-4-yl)-1*H*-2,1-benzothiazine 2,2-dioxide (4a)

Prepared according to the general procedure B using (Z)-2-(2-bromophenyl)-*N*-(morpholin-4-yl)ethanesulfonamide **3a** (50 mg, 0.14 mmol, *Z:E*, 12:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4a* as a white crystalline solid (32 mg, 83%); mp 150–153 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2955, 2915, 2863, 1612, 1559, 1453, 1360, 1320, 1270, 1213, 1159, 1145, 1111, 1070, 1037;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 7.74 (1H, d, *J* 8.0, Ar*H*), 7.61–7.53 (2H, m, 2 × Ar*H*), 7.50 (1H, d, *J* 10.0, ArCH=CHS), 7.25–7.19 (1H, m, Ar*H*) overlapping 7.19 (1H, d, *J* 10.0, ArCH=CHS), 3.74 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.43 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 141.5 (C), 135.6 (CH), 131.5 (CH), 129.9 (CH), 125.8 (CH), 123.0 (CH), 120.5 (C), 116.9 (CH), 67.1 (2 × CH<sub>2</sub>), 53.5 (2 × CH<sub>2</sub>); *m/z* (ESI<sup>+</sup>) 289 ([M + Na]<sup>+</sup>, 100%), 267 ([M + H]<sup>+</sup>, 45%); HRMS (ESI<sup>+</sup>) C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>3</sub>S<sup>+</sup> ([M + Na]<sup>+</sup>) requires 289.0617, found 289.0617.

#### 4.3.3. 1-(Morpholin-4-yl)-6-(trifluoromethyl)-1*H*-2,1-benzothiazine 2,2-dioxide (4b)

Prepared according to the general procedure B using 2-(2-bromo-5-(trifluoromethyl)phenyl)-*N*-morpholinoethanesulfonamide **3b** (68 mg, 0.16 mmol, *Z:E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4b* as a white crystalline solid (41 mg, 75%); mp 120–122 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3082, 2869, 1620, 1359, 1320, 1299, 1277, 1202, 1162, 1133, 1104, 1075, 1029, 1012;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 8.06 (1H, s, Ar*H*), 7.96 (1H, d, *J* 9.0, Ar*H*), 7.86 (1H, d, *J* 9.0, Ar*H*), 7.68 (1H, d, *J* 10.5, ArCH=CHS), 7.41 (1H, d, *J* 10.5, ArCH=CHS), 3.78 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.47 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126

MHz, CDCl<sub>3</sub>) 144.5 (C), 134.6 (CH), 128.1 (CH, q, *J*<sub>CF</sub> 3.5), 127.1 (CH, q, *J*<sub>CF</sub> 3.5), 126.0 (CH), 125.2 (C, q, *J*<sub>CF</sub> 33.0), 123.6 (C, q, *J*<sub>CF</sub> 272.0), 119.7 (C), 117.1 (CH), 67.8 (2 × CH<sub>2</sub>), 53.9 (2 × CH<sub>2</sub>);  $\delta_{\text{F}}$  (377 MHz, CDCl<sub>3</sub>) –62.1 (s, ArCF<sub>3</sub>) {<sup>1</sup>H}; *m/z* (ESI<sup>+</sup>) 357 ([M + Na]<sup>+</sup>, 100%); 334 ([M + H]<sup>+</sup>, 30%); HRMS (ESI<sup>+</sup>) C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>3</sub>S<sup>+</sup> ([M + Na]<sup>+</sup>) requires 357.0491, found 357.0477.

#### 4.3.4. 7-Fluoro-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide (4c)

Prepared according to the general procedure B using 2-(2-bromo-4-fluorophenyl)-*N*-morpholinoethanesulfonamide **3c** (50 mg, 0.14 mmol, *Z:E*, 20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4c* as a white crystalline solid (27 mg, 69%); mp >250 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2918, 2853, 1617, 1567, 1493, 1457, 1315, 1268, 1214, 1164, 1107;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 7.67 (1H, dd, *J* 8.5, 6.5, Ar*H*), 7.52 (1H, d, *J* 10.0, ArCH=CHS) overlapping 7.52–7.49 (1H, m, Ar*H*), 7.18 (1H, d, *J* 10.0, ArCH=CHS), 7.04 (1H, td, *J* 8.5, 3.0, Ar*H*), 3.76 (3H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.45 (3H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) 163.4 (d, *J*<sub>CF</sub> 248.0), 143.4 (d, *J*<sub>CF</sub> 12.0), 134.4, 132.1 (d, *J*<sub>CF</sub> 10.0), 123.9 (d, *J*<sub>CF</sub> 3.0), 116.6 (d, *J*<sub>CF</sub> 3.0), 110.0 (d, *J*<sub>CF</sub> 23.0), 103.1 (d, *J*<sub>CF</sub> 28.0), 66.6 (2C), 53.1 (2C);  $\delta_{\text{F}}$  (377 MHz, CDCl<sub>3</sub>) –105.8 (s, ArF) {<sup>1</sup>H}; HRMS (FI<sup>+</sup>) C<sub>12</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 284.0631 and 284.0626.

#### 4.3.5. 6-Fluoro-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide (4d)

Prepared according to the general procedure B using 2-(2-bromo-5-fluorophenyl)-*N*-morpholinoethanesulfonamide **3d** (42 mg, 0.11 mmol, *Z:E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4d* as a white crystalline solid (25 mg, 78%); mp 145–148 °C;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3078, 2959, 2923, 2850, 1608, 1564, 1471, 1426, 1370, 1346, 1318, 1265, 1239, 1157, 1109, 1071, 1029, 1012;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 7.76 (1H, dd, *J* 9.0, 5.0, Ar*H*), 7.50 (1H, d, *J* 10.0, ArCH=CHS) overlapping 7.48 (1H, dd, *J* 9.0, 3.0, Ar*H*), 7.43–7.37 (1H, m, Ar*H*), 7.30 (1H, d, *J* 10.0, ArCH=CHS), 3.73 (4H, t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.42 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) 157.6 (C, d, *J*<sub>CF</sub> 241.5), 138.0 (C), 134.5 (CH, d, *J*<sub>CF</sub> 2.0), 127.5 (CH), 121.9 (C, d, *J*<sub>CF</sub> 9.0), 120.0 (CH, d, *J*<sub>CF</sub> 8.0), 118.6 (CH, d, *J*<sub>CF</sub> 23.0), 115.1 (CH, d, *J*<sub>CF</sub> 23.7), 67.1 (2 × CH<sub>2</sub>), 53.4 (2 × CH<sub>2</sub>);  $\delta_{\text{F}}$  (377 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) –120.2 (s, ArF) {<sup>1</sup>H}; HRMS (FI<sup>+</sup>) C<sub>12</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 284.0631 and 284.0630.

#### 4.3.6. 1-Morpholino-1*H*-naphtho[1,2-*c*][1,2]thiazine 2,2-dioxide (4e)

Prepared according to the general procedure B using 2-(1-bromonaphthalen-2-yl)-*N*-morpholinoethanesulfonamide **3e** (60 mg, 0.15 mmol, *Z:E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4e* as a white crystalline solid (32 mg, 68%); mp 204–207 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3058, 2916, 2851, 1593, 1504, 1459, 1371, 1335, 1305, 1261, 1205, 1162, 1130, 1102, 1019;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 8.24 (1H, d, *J* 8.0, Ar*H*), 7.98 (1H, d, *J* 8.0, Ar*H*), 7.91 (1H, d, *J* 8.5, Ar*H*), 7.70–7.59 (4H, m, ArCH=CHS, 3 × Ar*H*) 7.25 (1H, d, *J* 10.0, ArCH=CHS), 3.45 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.36 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) 137.0 (CH), 136.9 (C), 134.4 (C), 128.8 (C), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 125.3 (CH), 124.6 (CH),



122.8 (C), 67.0 (2 × CH<sub>2</sub>), 52.2 (2 × CH<sub>2</sub>); HRMS (FI<sup>+</sup>) C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 316.0882, found 316.0894.

#### 4.3.7. 1-Morpholino-1H-[1,3]dioxolo[4',5':4,5]benzo[1,2-c][1,2]thiazine 2,2-dioxide (**4f**)

Prepared according to the general procedure B using (Z)-2-(6-bromobenzo[d][1,3]dioxol-5-yl)-N-morpholinoethanesulfonamide **3f** (62 mg, 0.16 mmol, Z:E, 20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4f* as a white crystalline solid (39 mg, 80%); mp 188-189 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2912, 2852, 1625, 1574, 1499, 1475, 1432, 1383, 1311, 1260, 1241, 1221, 1180, 1156, 1124, 1103, 1073, 1037;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 7.36 (1H, d, *J* 10.0, ArCH=CHS), 7.28 (1H, s, ArH), 7.10 (1H, s, ArH), 7.00 (1H, d, *J* 10.0, ArCH=CHS), 6.10 (2H, s, OCH<sub>2</sub>O), 3.72 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.39 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) 150.2 (C), 143.7 (C), 138.1 (C), 135.3 (CH), 122.8 (CH), 114.6 (C), 107.6 (CH), 102.0 (CH<sub>2</sub>), 99.0 (CH), 67.0 (2 × CH<sub>2</sub>), 53.3 (2 × CH<sub>2</sub>); HRMS (FI<sup>+</sup>) C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 310.0623, found 310.0625.

#### 4.3.8. 6-(Benzyloxy)-1-morpholino-1H-benzo[c][1,2]thiazine 2,2-dioxide (**4g**)

Prepared according to the general procedure B using 2-(5-(benzyloxy)-2-bromophenyl)-N-morpholinoethanesulfonamide **3g** (75 mg, 0.17 mmol, Z:E, 8:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4g* as a white crystalline solid (49 mg, 79%); mp 195-198 °C (dec.);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2923, 2852, 1599, 1564, 1455, 1332, 1270, 1243, 1161, 1111, 1013;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.61 (1H, d, *J* 9.0, ArH), 7.44-7.34 (5H, m, 5 × OBnH), 7.14 (1H, d, *J* 10.0, ArCH=CHS) overlapping 7.16-7.12 (1H, m, ArH), 6.94 (1H, d, *J* 2.5, ArH), 6.78 (1H, d, *J* 10.0, ArCH=CHS), 5.08 (2H, s, OCH<sub>2</sub>Ph), 3.80 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.51 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 154.8 (C), 136.5 (C), 135.9 (C), 135.2 (CH), 128.8 (2 × CH), 128.3 (CH), 127.5 (2 × CH), 126.0 (CH), 121.8 (C), 119.9 (CH), 119.6 (CH), 113.8 (CH), 70.7 (CH<sub>2</sub>), 68.0 (2 × CH<sub>2</sub>), 53.8 (2 × CH<sub>2</sub>); HMRS (FI<sup>+</sup>) C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 372.1144, found 372.1140.

#### 4.3.9. 7-Methyl-1-morpholino-1H-benzo[c][1,2]thiazine 2,2-dioxide (**4h**)

Prepared according to the general procedure B using 2-(2-bromo-4-methylphenyl)-N-morpholinoethanesulfonamide **3h** (53 mg, 0.15 mmol, Z:E, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4h* as a white crystalline solid (29 mg, 71%); mp 115-118 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2957, 2920, 2854, 1613, 1550, 1488, 1452, 1362, 1319, 1268, 1213, 1159, 1146, 1110, 1071, 1039;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 7.53 (1H, s, ArH), 7.49-7.42 (2H, m, ArH, ArCH=CHS), 7.09 (1H, d, *J* 10.0, ArCH=CHS), 7.04 (1H, d, *J* 7.5, ArH), 3.74 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.42 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 2.43 (3H, s, ArMe);  $\delta_{\text{C}}$  (126 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) 141.9 (C), 141.5 (C), 135.5 (CH), 129.9 (CH), 124.7 (CH), 124.1 (CH), 118.1 (C), 117.0 (CH), 67.0 (2 × CH<sub>2</sub>), 53.4 (2 × CH<sub>2</sub>), 21.6 (CH<sub>3</sub>); HRMS (FI<sup>+</sup>) C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 280.0882, found 280.0887.

#### 4.3.10. 6,7-Dimethoxy-1-morpholino-1H-benzo[c][1,2]thiazine 2,2-dioxide (**4i**)

Prepared according to the general procedure B using 2-(2-bromo-4,5-dimethoxyphenyl)-N-morpholinoethanesulfonamide **3i** (70 mg, 0.17 mmol, Z:E, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4i* as a white crystalline solid (48 mg, 85%); mp 189-190 °C (CH<sub>2</sub>Cl<sub>2</sub>:petrol, 1:1);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3046, 2851, 1613, 1557, 1501, 1459, 1363, 1302, 1276, 1239, 1203, 1181, 1152, 1133, 1112, 1039, 1004;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 7.37 (1H, d, *J* 10.0, ArCH=CHS), 7.26 (1H, s, ArH), 7.15 (1H, s, ArH), 6.96 (1H, d, *J* 10.0, ArCH=CHS), 3.90 (3H, s, OMe), 3.80 (3H, s, OMe), 3.72 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.39 (4H, br. t, *J* 4.5, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 152.3 (C), 145.8 (C), 137.3 (C), 135.2 (CH), 122.3 (CH), 113.7 (C), 111.1 (CH), 101.2 (CH), 68.2 (2 × CH<sub>2</sub>), 56.5 (CH<sub>3</sub>), 56.2 (CH<sub>3</sub>), 53.9 (2 × CH<sub>2</sub>); HMRS (FI<sup>+</sup>) C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 326.0928, found 326.0937.

#### 4.3.11. 1-Morpholino-1H-pyrido[2,3-c][1,2]thiazine 2,2-dioxide (**4k**)

Prepared according to the general procedure B using 2-(2-bromopyridin-3-yl)-N-morpholinoethanesulfonamide **3k** (54 mg, 0.16 mmol, Z:E, >20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4k* as a yellow crystalline solid (32 mg, 77%); mp 240-243 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3054, 2923, 2866, 1622, 1588, 1560, 1458, 1420, 1363, 1304, 1271, 1250, 1171, 1154, 1127, 1104, 1013;  $\delta_{\text{H}}$  (500 MHz, (CD<sub>3</sub>)<sub>2</sub>SO, 363 K) 8.49 (1H, dd, *J* 5.0, 2.0, ArH), 8.03 (1H, dd, *J* 7.5, 2.0, ArH), 7.50 (1H, d, *J* 10.5, ArCH=CHS), 7.25 (1H, d, *J* 10.5, ArCH=CHS) overlapping 7.23 (1H, dd, *J* 7.5, 5.0, ArH), 3.79-3.73 (4H, m, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O), 3.57 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O);  $\delta_{\text{C}}$  (126 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) 151.9 (C), 149.2 (CH), 139.4 (CH), 131.8 (CH), 122.5 (CH), 118.3 (CH), 113.9 (C), 66.8 (2 × CH<sub>2</sub>), 52.8 (2 × CH<sub>2</sub>); HRMS (FI<sup>+</sup>) C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>S<sup>+</sup> ([M]<sup>+</sup>) requires 267.0677, found 267.0681.

#### 4.3.12. 6,7-Dimethoxy-1-(4-methylpiperazin-1-yl)-1H-benzo[c][1,2]thiazine 2,2-dioxide (**4l**)

Prepared according to the general procedure B using 2-(2-bromo-4,5-dimethoxyphenyl)-N-(4-methylpiperazin-1-yl)ethanesulfonamide **3l** (60 mg, 0.14 mmol, Z:E, 11:1). Column chromatography (eluent: 1% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) yielded *benzothiazine 2,2-dioxide 4l* as a yellow solid (40 mg, 82%); mp 218-220 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2940, 2739, 2603, 2495, 1510, 1475, 1398, 1245, 1206, 1171, 1073, 1036;  $\delta_{\text{H}}$  (200 MHz, CD<sub>3</sub>CN) 7.26 (1H, s, ArH) overlapping 7.25 (1H, d, *J* 10.0, ArCH=CHS), 7.00 (1H, s, ArH), 6.71 (1H, d, *J* 10.0, ArCH=CHS), 3.90 (3H, s, OMe), 3.81 (3H, s, OMe), 3.42 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NMe), 2.52 (4H, br. s, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NMe), 2.25 (3H, s, NMe);  $\delta_{\text{C}}$  (126 MHz, CD<sub>3</sub>CN) 153.2 (C), 146.5 (C), 138.1 (C), 136.3 (CH), 123.2 (CH), 114.5 (C), 112.3 (CH), 102.3 (CH), 56.7 (CH<sub>3</sub>), 53.6 (CH<sub>3</sub>), 46.0 (CH<sub>3</sub>), 37.3 (CH<sub>2</sub>), 37.2 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>); *m/z* (ESI<sup>+</sup>) 340 ([M + H]<sup>+</sup>, 100%); HMRS (ESI<sup>+</sup>) C<sub>15</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>S<sup>+</sup> ([M + H]<sup>+</sup>) requires 340.1326, found 340.1321.

#### 4.3.13. 1-(Dibenzylamino)-6,7-dimethoxy-1H-benzo[c][1,2]thiazine 2,2-dioxide (**4m**)

Prepared according to the general procedure B using *N,N*-dibenzyl-2-(2-bromo-4,5-dimethoxyphenyl)ethanesulfonohydrazide **3m** (55 mg, 0.11 mmol, Z:E, 20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4m* as a pale yellow crystalline solid (35 mg, 75%); mp 190 °C (dec.) (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2923, 2853, 1603, 1508, 1463, 1321, 1242, 1208, 1152, 1118,



1029, 1012;  $\delta_{\text{H}}$  (200 MHz,  $\text{CD}_3\text{CN}$ ) 7.39–7.22 (10H, m,  $10 \times \text{BnH}$ ), 7.06 (1H, d,  $J$  10.0,  $\text{ArCH=CHS}$ ), 6.75 (1H, s,  $\text{ArH}$ ), 6.67 (1H, d,  $J$  10.0,  $\text{ArCH=CHS}$ ), 6.62 (1H, s,  $\text{ArH}$ ), 4.54 (2H, d,  $J$  13.0,  $\text{NCH}_2\text{Ph}$ ), 4.30 (2H, d,  $J$  13.0,  $\text{NCH}_2\text{Ph}$ ), 3.71 (3H, s,  $\text{OMe}$ ), 3.64 (3H, s,  $\text{OMe}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 152.5 (C), 146.5 (C), 138.5 (C), 138.3 (C), 136.3 (CH), 130.8 ( $4 \times \text{CH}$ ), 129.2 ( $4 \times \text{CH}$ ), 128.7 ( $2 \times \text{CH}$ ), 126.4 (C), 122.9 (CH), 114.8 (C), 111.3 (CH), 104.0 (CH), 60.7 ( $2 \times \text{CH}_2$ ), 56.6 ( $\text{CH}_3$ ), 56.5 ( $\text{CH}_3$ );  $m/z$  ( $\text{ESI}^+$ ) 459 ( $[\text{M} + \text{Na}]^+$ , 100%); HMRS ( $\text{ESI}^+$ )  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{NaO}_4\text{S}^+$  ( $[\text{M} + \text{Na}]^+$ ) requires 459.1349, found 459.1356.

#### 4.3.14. 6,7-Dimethoxy-1-(methyl(phenyl)amino)-1H-benzo[c][1,2]thiazine 2,2-dioxide (**4n**)

Prepared according to the general procedure B using 2-(2-bromo-4,5-dimethoxyphenyl)-N-methyl-N-phenylethanesulfonohydrazide **3n** (65 mg, 0.15 mmol,  $Z:E$ , 10:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4n* (22 mg, 42%) as an off-white crystalline solid; mp 205–208 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2934, 2867, 1605, 1510, 1474, 1245, 1208, 1152, 1110;  $\delta_{\text{H}}$  (200 MHz,  $(\text{CD}_3)_2\text{CO}$ ) 7.46 (1H, d,  $J$  10.0,  $\text{ArCH=CHS}$ ), 7.19–6.55 (8H, m,  $\text{ArCH=CHS}$ ,  $7 \times \text{ArH}$ ), 3.83 (3H, s,  $\text{OMe}$ ), 3.63 (3H, s,  $\text{OMe}$ ), 2.83 (3H, s,  $\text{NMe}$ );  $\delta_{\text{C}}$  (126 MHz,  $(\text{CD}_3)_2\text{CO}$ ) 152.7 (C), 146.3 (C), 135.7 (CH), 131.5 ( $2 \times \text{CH}$ ), 129.6 (C), 126.0 ( $2 \times \text{CH}$ ), 121.4 (CH), 115.5 (C), 114.5 (C), 113.1 (CH), 112.6 (CH), 103.3 (CH), 56.5 ( $\text{CH}_3$ ), 56.1 ( $\text{CH}_3$ ), 35.0 ( $\text{CH}_3$ );  $m/z$  ( $\text{ESI}^+$ ) 369 ( $[\text{M} + \text{Na}]^+$ , 50%), 347 ( $[\text{M} + \text{H}]^+$ , 100%); HMRS ( $\text{ESI}^+$ )  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{NaO}_4\text{S}^+$  ( $[\text{M} + \text{Na}]^+$ ) requires 347.1060, found 347.1066.

#### 4.4. (Z) and (E)-2-(2-Fluorophenyl)-N-(morpholin-4-yl)ethanesulfonamide (Z)-**6a**, (E)-**6a**

Prepared according to the general procedure A using DABSO (63 mg, 0.28 mmol), CataCXium A (17 mg, 0.05 mmol), (Z)-1-fluoro-2-(2-iodovinyl)benzene (69 mg, 0.24 mmol,  $Z:E$ , >20:1), 4-aminomorpholine (35  $\mu\text{L}$ , 0.36 mmol) and 1,4-dioxane (1.6 mL). The reaction mixture was stirred at 70 °C for 8 h. Column chromatography (eluent: 0–50%, ether in hexane) yielded, in order of elution, *alkenyl N-aminosulfonamide (Z)-6a* (31 mg, 45%) and *alkenyl N-aminosulfonamide (E)-6a* (8 mg, 11%), as off-white crystalline solids. (Z)-**6a** mp 96–98 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3212, 2827, 2777, 1325, 1311, 1278, 1265, 1243, 1211, 1203, 1170, 1142, 1100, 1070, 1029, 1008;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.95 (1H, app t,  $J$  8.0,  $\text{ArH}$ ), 7.40 (1H, app q,  $J$  8.0,  $\text{ArH}$ ), 7.26–7.16 (2H, m,  $\text{ArH}$ ,  $\text{ArCH=CHS}$ ), 7.09 (1H, app t,  $J$  8.0,  $\text{ArH}$ ), 6.58 (1H, d,  $J$  12.0,  $\text{ArCH=CHS}$ ), 5.43 (1H, s,  $\text{NH}$ ), 3.72 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.83 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 160.5 (C, d,  $J_{\text{CF}}$  249.5), 134.0 (CH, d,  $J_{\text{CF}}$  5.0), 132.0 (CH, d,  $J_{\text{CF}}$  2.0), 131.9 (CH, d,  $J_{\text{CF}}$  8.5), 128.8 (CH), 123.9 (CH, d,  $J_{\text{CF}}$  3.0), 120.8 (C, d,  $J_{\text{CF}}$  13.0), 115.2 (CH, d,  $J_{\text{CF}}$  21.0), 66.6 ( $2 \times \text{CH}_2$ ), 57.1 ( $2 \times \text{CH}_2$ );  $\delta_{\text{F}}$  (377 MHz,  $\text{CDCl}_3$ ) –113.3 (s,  $\text{ArF}$ )  $\{^1\text{H}\}$ ;  $m/z$  ( $\text{ESI}^+$ ) 595 ( $[\text{2M} + \text{Na}]^+$ , 100%), 309 ( $[\text{M} + \text{Na}]^+$ , 42%);  $m/z$  ( $\text{ESI}^-$ ) 285 ( $[\text{M} - \text{H}]^-$ , 100%); HRMS ( $\text{ESI}^+$ )  $\text{C}_{12}\text{H}_{15}\text{FN}_2\text{NaO}_3\text{S}^+$  ( $[\text{M} + \text{Na}]^+$ ) requires 309.0680, found 309.0675; Anal. Calcd. (%) for  $\text{C}_{12}\text{H}_{15}\text{FN}_2\text{O}_3\text{S}$ : C 50.34, H 5.28, N 9.78; found C 50.45, H 5.18, N 9.75. (E)-**6a**: mp 137–140 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3280, 2917, 2850, 1368, 1333, 1318, 1293, 1264, 1238, 1221, 1138, 1106, 1032;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.66 (1H, d,  $J$  15.5,  $\text{ArCH=CHS}$ ), 7.49 (1H, app t,  $J$  7.5,  $\text{ArH}$ ), 7.46–7.38 (1H, m,  $\text{ArH}$ ), 7.22 (1H, app t,  $J$  7.5,  $\text{ArH}$ ), 7.19–7.11 (1H, m,  $\text{ArH}$ ), 6.99 (1H, d,  $J$  15.5,  $\text{ArCH=CHS}$ ), 5.45 (1H, s,  $\text{NH}$ ), 3.74 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.89 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ );  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 161.7 (C, d,  $J_{\text{CF}}$  261.5), 137.0 (CH), 132.7 (CH, d,  $J_{\text{CF}}$  9.0), 130.5 (CH, d,  $J_{\text{CF}}$  3.0), 126.8 (CH, d,  $J_{\text{CF}}$  9.5), 124.9 (CH,

d,  $J_{\text{CF}}$  5.0), 120.9 (C, d,  $J_{\text{CF}}$  11.0), 116.6 (CH, d,  $J_{\text{CF}}$  21.5), 66.7 ( $2 \times \text{CH}_2$ ), 57.5 ( $2 \times \text{CH}_2$ );  $m/z$  ( $\text{ESI}^+$ ) 595 ( $[\text{2M} + \text{Na}]^+$ , 100%), 309 ( $[\text{M} + \text{Na}]^+$ , 42%);  $m/z$  ( $\text{ESI}^-$ ) 285.1 ( $[\text{M} - \text{H}]^-$ , 100%);  $\delta_{\text{F}}$  (377 MHz,  $\text{CDCl}_3$ ) –112.6 (s,  $\text{ArF}$ )  $\{^1\text{H}\}$ ; HRMS ( $\text{ESI}^+$ )  $\text{C}_{12}\text{H}_{15}\text{FN}_2\text{NaO}_3\text{S}^+$  ( $[\text{M} + \text{Na}]^+$ ) requires 309.0680, found 309.0675.

#### 4.5 (Z)-2-[2-Fluoro-5-(trifluoromethyl)phenyl]-N-(morpholin-4-yl)ethanesulfonamide **6b**

Prepared according to the general procedure A using DABSO (126 mg, 0.53 mmol), CataCXium A (34 mg, 0.10 mmol), (Z)-1-fluoro-2-(2-iodovinyl)-4-(trifluoromethyl)benzene (152 mg, 0.24 mmol,  $Z:E$ , >20:1) and 4-aminomorpholine (69  $\mu\text{L}$ , 0.72 mmol). The reaction mixture was stirred at 70 °C for 6 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide 6b* as a pale yellow crystalline solid (38 mg, 45%,  $Z:E$ , >20:1); mp 87–89 °C ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3200, 2963, 1635, 1499, 1459, 1329, 1287, 1259, 1208, 1105, 1073, 1015;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 8.28 (1H, dd,  $J$  7.0, 2.0  $\text{ArH}$ ), 7.67–7.62 (1H, m,  $\text{ArH}$ ), 7.24–7.16 (2H, m,  $\text{ArH}$ ,  $\text{ArCH=CHS}$ ), 6.58 (1H, d,  $J$  12.0,  $\text{ArCH=CHS}$ ), 5.70 (1H, s,  $\text{NH}$ ), 3.73 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 2.88 (4H, br. t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 162.0 (C, d,  $J_{\text{CF}}$  255.5), 132.8 (CH, d,  $J_{\text{CF}}$  4.0), 130.1 (CH), 129.9 (CH, app quin,  $J_{\text{CF}}$  4.0), 128.8 (CH, dq,  $J_{\text{CF}}$  9.5, 4.0), 126.4 (CH, qd,  $J_{\text{CF}}$  30.0, 4.0), 123.7 (C, q,  $J_{\text{CF}}$  272.5), 121.3 (C, d,  $J_{\text{CF}}$  14.5), 115.9 (CH, d,  $J_{\text{CF}}$  23.0), 66.6 ( $2 \times \text{CH}_2$ ), 57.4 ( $2 \times \text{CH}_2$ );  $\delta_{\text{F}}$  (377 MHz,  $\text{CDCl}_3$ ) –61.8 (s,  $\text{ArCF}_3$ ), –107.9 (s,  $\text{ArF}$ )  $\{^1\text{H}\}$ ;  $m/z$  ( $\text{ESI}^+$ ) 731 ( $[\text{2M} + \text{Na}]$ , 98%), 377 ( $[\text{M} + \text{Na}]^+$ , 100%), 355 ( $[\text{M} + \text{H}]^+$ , 12%);  $m/z$  ( $\text{ESI}^-$ ) 353 ( $[\text{M} - \text{H}]^-$ , 100%); HRMS ( $\text{ESI}^+$ )  $\text{C}_{13}\text{H}_{14}\text{F}_4\text{N}_2\text{NaO}_3\text{S}^+$  ( $[\text{M} + \text{Na}]^+$ ) requires 377.0553, found 377.0544.

#### 4.6 1-(Morpholin-4-yl)-6-(trifluoromethyl)-1H-2,1-benzothiazine 2,2-dioxide (**4b**) using $S_{\text{N}}\text{Ar}$ chemistry

2-[2-Fluoro-5-(trifluoromethyl)phenyl]-N-(morpholin-4-yl)ethanesulfonamide **6b** (30 mg, 0.08 mmol,  $Z:E$ , >20:1) was added to a mixture of  $\text{Cs}_2\text{CO}_3$  (83 mg, 0.24 mmol) and 1,4-dioxane (0.5 mL). The reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to RT and filtered through a short pad of Celite with  $\text{CH}_2\text{Cl}_2$  (5 mL) and ether (5 mL). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide 4b* as a white crystalline solid (24 mg, 88%). Data as above.

#### 4.7 1-Morpholino-3,4-dihydro-1H-benzo[c][1,2]thiazine 2,2-dioxide **7**

To a solution of 1-(morpholin-4-yl)-1H-2,1-benzothiazine 2,2-dioxide **4a** (53 mg, 0.20 mmol) in degassed ethanol (5 mL) was added Pd/C 10 wt.% (5 mg) and the flask flushed with  $\text{H}_2$ . The reaction mixture was stirred at RT under a  $\text{H}_2$  balloon for 3 h. The flask was flushed with  $\text{N}_2$  and the suspension filtered through Celite and washed with ethanol. The filtrate was concentrated *in vacuo* to yield *sulfonamide 7* as a white crystalline solid (49 mg, 91%); mp 270 °C (dec) ( $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2924, 2857, 1434, 1452, 1337, 1294, 1269, 1160, 1134, 1110;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.52 (1H, dd,  $J$  8.5, 1.0,  $\text{ArH}$ ), 7.29–7.24 (1H, m,  $\text{ArH}$ ), 7.13 (1H, d,  $J$  7.5,  $\text{ArH}$ ), 7.04 (1H, app td,  $J$  7.5, 1.0,  $\text{ArH}$ ), 3.79 (4H, t,  $J$  4.5,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ), 3.47–3.41 (6H, m,  $\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ ,  $\text{ArCH}_2\text{CH}_2\text{S}$ ), 3.37–3.33 (2H, m,  $\text{ArCH}_2\text{CH}_2\text{S}$ );  $\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 141.3 (C), 129.5 (CH), 128.0 (CH), 123.7 (CH), 122.1 (C), 118.4 (CH), 68.1 ( $2 \times \text{CH}_2$ ), 53.2 ( $2 \times \text{CH}_2$ ), 47.9 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ );  $m/z$  ( $\text{ESI}^+$ ) 291 ( $[\text{M} + \text{Na}]^+$ , 100%), 269 ( $[\text{M} + \text{H}]^+$ , 20%);

HMRS (ESI<sup>+</sup>) C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup> ([M + H]<sup>+</sup>) requires 269.0954, found 269.0959.

#### 4.8 6,7-Dimethoxy-3,4-dihydro-1H-benzo[c][1,2]thiazine 2,2-dioxide **8**

To a solution of 1-(dibenzylamino)-6,7-dimethoxy-1H-benzo[c][1,2]thiazine 2,2-dioxide **4m** (45 mg, 0.10 mmol) in degassed acetone (0.3 mL) was added Pearlman's catalyst (9 mg, 20 wt.% 60% moisture, Pd(OH)<sub>2</sub>/C) and the reaction flask was flushed with H<sub>2</sub>. The reaction mixture was stirred at RT under a H<sub>2</sub> balloon for 16 h. The flask was then flushed with N<sub>2</sub> and the suspension filtered through Celite and washed with acetone. The filtrate was concentrated *in vacuo*. Acetic acid (1.1 mL) and zinc dust (17 mg, 2.60 mmol) was added and the reaction mixture stirred for 2 h at RT. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the suspension filtered through Celite. Water was added and the organic layer extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Column chromatography (eluent: ether) yielded *sulfonamide 8* as a white crystalline solid (16 mg, 68%); mp 145-148 °C (CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3225, 2925, 2850, 1605, 1503, 1463, 1325, 1270, 1152, 1121, 1111;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 6.64 (1H, s, ArH), 6.31 (1 H, s, ArH), 6.01 (1H, s, NH), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.43-3.37 (2H, m, CH<sub>2</sub>), 3.31-3.26 (2H, m, CH<sub>2</sub>);  $\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 149.9, 146.2, 129.9, 113.4, 112.2, 104.0, 56.4, 56.2, 45.9, 28.2; HMRS (ESI<sup>+</sup>) C<sub>10</sub>H<sub>12</sub>NO<sub>4</sub>S<sup>+</sup> ([M + H]<sup>+</sup>) requires 242.0493, found 242.0495.

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#### Appendix A. Supplementary data

Supplementary data relating to this article (NMR spectra) may be found at XXXXXXXX.

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