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Mitsunobu C-alkylation of β-alkoxycarbonyl 2-nitrobenzenesulfones and its use for the rapid synthesis of novel benzothiazine derivatives

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ABSTRACT

Herein, we report the first examples of the Mitsunobu alkylation of β-alkoxycarbonyl 2-nitrobenzenesulfones. Wang resin was acylated with α-halocarboxylic acids followed by the reaction with 2-nitrothiophenols. After oxidation with *m*-chloroperbenzoic acid, the immobilized β-alkoxycarbonyl 2-nitrobenzensulfones were subjected to alkylation with various alcohols. The reaction outcome strongly depended on the selection of the alkylating species. After the reduction of the nitro group, acid-mediated cleavage and subsequent cyclization, the C^2-(di)substituted benzothiazin-3(4*H*)-one 1,1-dioxides were obtained in high crude purities and good overall yields.

1. Introduction

The reaction of primary or secondary alcohols with nucleophiles mediated by phosphines and azodicarboxylates is well known as the Mitsunobu reaction.[1,2] This synthetic methodology has been extensively utilized in both traditional solution-phase[3] and solid-phase[4] synthesis to generate C–O, C–N or C–S bonds using various heteronucleophiles.[2] C–H protonucleophiles, such as malonate esters, β-diketones or β-ketoesters, have been applied to form C–C bonds considerably less frequently. In this regard, β-acyl- and β-alkoxycarbonyl heterocyclic sulfones derived from benzothiazole (BT) and tetrazole (Tet) have received considerable attention recently.[5–8] Their Mitsunobu alkylation was followed by the cleavage of the arylsulfonyl moiety, and further conversion of the desulfonylated intermediates yielded branched fluoroalkenes.[5] Inspired by this work, we decided to study the C-alkylation of 2-nitrobenzenesulfonyl (Nos) analogues, which has yet to be reported. In contrast to the chemistry of BT or Tet sulfones, we did not intend to cleave the Nos group but instead intended to use it to construct a heterocyclic scaffold. In this study, we targeted pharmacologically attractive benzothiazines[9] with focus on benzothiazin-3(4*H*)-one 1,1-dioxides. Such compounds have medicinal and agricultural interest as antiviral,[10] fungicidal[11] or anxiolytic[12] agents. Regardless of the type of substrate, a common feature of each Mitsunobu reaction is the formation of phosphine oxide and hydrazide derivatives originating from the coupling reagents. In this regard, the use of polymer-supported reagents or immobilized starting substrates is significantly beneficial. This allows for fast elimination of by-products by simple filtration, which can yield the desired product in high crude purity. For this reason, we decided to apply a solid-phase synthesis concept[13] with a commonly used Wang resin[14] as the polymer-support.

2. Results and discussion

The key intermediates **5** and **6** were obtained in three steps according to Scheme 1. Acylation of the Wang resin with iodoacetic acid or 2-bromopropionyl bromide was followed by the reaction with thiophenols **2a**–**c**, which were readily accessible from the commercially available disulfides after slightly modified synthetic procedures.[15,16] Intermediates **3** and **4** were subsequently converted to key sulfones **5** and **6**, respectively by oxidation with *m*-chloroperbenzoic acid (*m*CPBA).

Reagents and conditions: i) mercaptoethanol, PPh_3, THF, 50 °C (90%, **2a**); PBu_3, THF/10% aq. AcOH 4:1, 65 °C (72%, **2b**); PBu_3, THF, r.t. (88%, **2c**); ii) iodoacetic acid, diisopropylethylamine (DIPEA),

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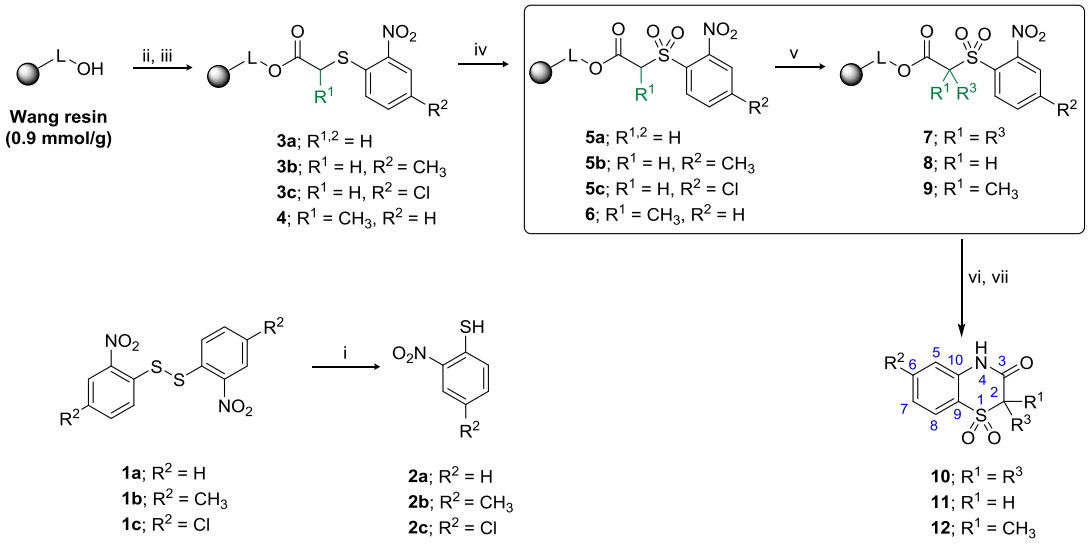


Scheme 1. General synthetic route.

CH_2Cl_2, rt (for **3a**–**c**); 2-bromopropionyl bromide, 2,6-lutidine, CH_2Cl_2, r.t. (for **4**); iii) 2-nitrobenzothiols **2a**–**c**, DIPEA, CH_2Cl_2, r.t.; iv) *m*CPBA, CH_2Cl_2, r.t.; v) alcohol, PPh_3, diisopropylazodicarboxylate (DIAD), THF, −20 °C to r.t.; vi) $Na_2S_2O_4$, K_2CO_3, TBAHS, CH_2Cl_2/H_2O 2:1, r.t.; vii) trifluoroacetic acid (TFA), 80 °C.

Immobilized compound **5a** was then subjected to alkylation with diverse alcohols under Mitsunobu reaction conditions (Scheme 2). In contrast to previously reported BT sulfones,[5] the reaction did not require use of azodicarbonyldipiperidide (ADDP). Rather, conventional diisopropylazodicarboxylate (DIAD) was a sufficient reagent to deprotonate the protonucleophile after the formation of the DIAD-PPh_3 adduct. From the results, we concluded that the reaction outcome strongly depended on the type of alcohol. It should be noted that the use of polymer-supported starting materials requires an excess of solution-phase reagents to force reactions to completion. Due to this fact, we observed quantitative formation of dialkylated products **7a**–**d** using excess benzyl alcohol, methanol, allyl alcohol and propargyl alcohol, respectively. The use of butane-1,4-diol led to an intramolecular dialkylation, and the spirocyclic product **7e** was obtained. Similarly, the reaction with 2-chloroethanol yielded the spirocyclic derivative **8f,** which was formed after monoalkylation of intermediate **5a** followed by a spontaneous intramolecular S_N2 reaction. Surprisingly, the alkylation of intermediate **5a** with ethanol, cyclopentanol, isopropanol, 2-phenylethanol and 2-methoxyethanol afforded only monoalkylated products **8a**–**e**, respectively. Even repeating the reaction steps, again with excess solution-phase reagents, or use of ADDP instead of DIAD did not lead to the formation of the dialkylated analogues. In cases where alcohols possessed other acidic protons (e.g. methylglycolate and trifluoroethanol) we observed only the starting material after alkylation. Interestingly, the reaction with 3-(pyridin-4-yl)propan-1-ol yielded a mixture of mono- and dialkylated products in the ratio of 3:1 (the ratio was calculated from LC-UV traces; monoalkylated **11g** was separated and fully characterized, the dialkylated analogue was not isolated). After alkylation, the reaction sequence was followed by the reduction of the nitro group with sodium dithionate. An acid-mediated cleavage from the resin with simultaneous cyclization using trifluoroacetic acid (TFA) at elevated temperature yielded the final benzothiazines **10** and **11** (Scheme 2).

Reagents and conditions: i) R^3OH, DIAD, PPh_3, THF, r.t.; ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, CH_2Cl_2/H_2O 2:1, r.t.; iii) trifluoroacetic acid (TFA), 80 °C (overall yields after 4 steps: 25%, **10a**; 50%, **10b**; 50%, **10c**; 28%, **10d**; 79% **10e**; 37%, **11a**; 60%, **11b**; 43%, **11c**; 46%, **11d**; 18%, **11e**; 38%, **11f**; 45%, **11g**).

In the case of but-3-yne-1-ol, the monoalkylation was observed but the target benzothiazine product was not obtained due to unsuccessful cyclization of the corresponding reduced intermediate **8h**. Alkylation with Fmoc-aminoethanol yielded the desired monoalkylated intermediate **8i**. However, during the reduction step, the Fmoc-protecting group was cleaved due to presence of sodium carbonate and the subsequent cyclization yielded more favorable product **13** (Scheme 3).

Reagents and conditions: i) $Na_2S_2O_4$, K_2CO_3, TBAHS, CH_2Cl_2/H_2O 2:1, r.t.; ii) trifluoroacetic acid (TFA), 80 °C.

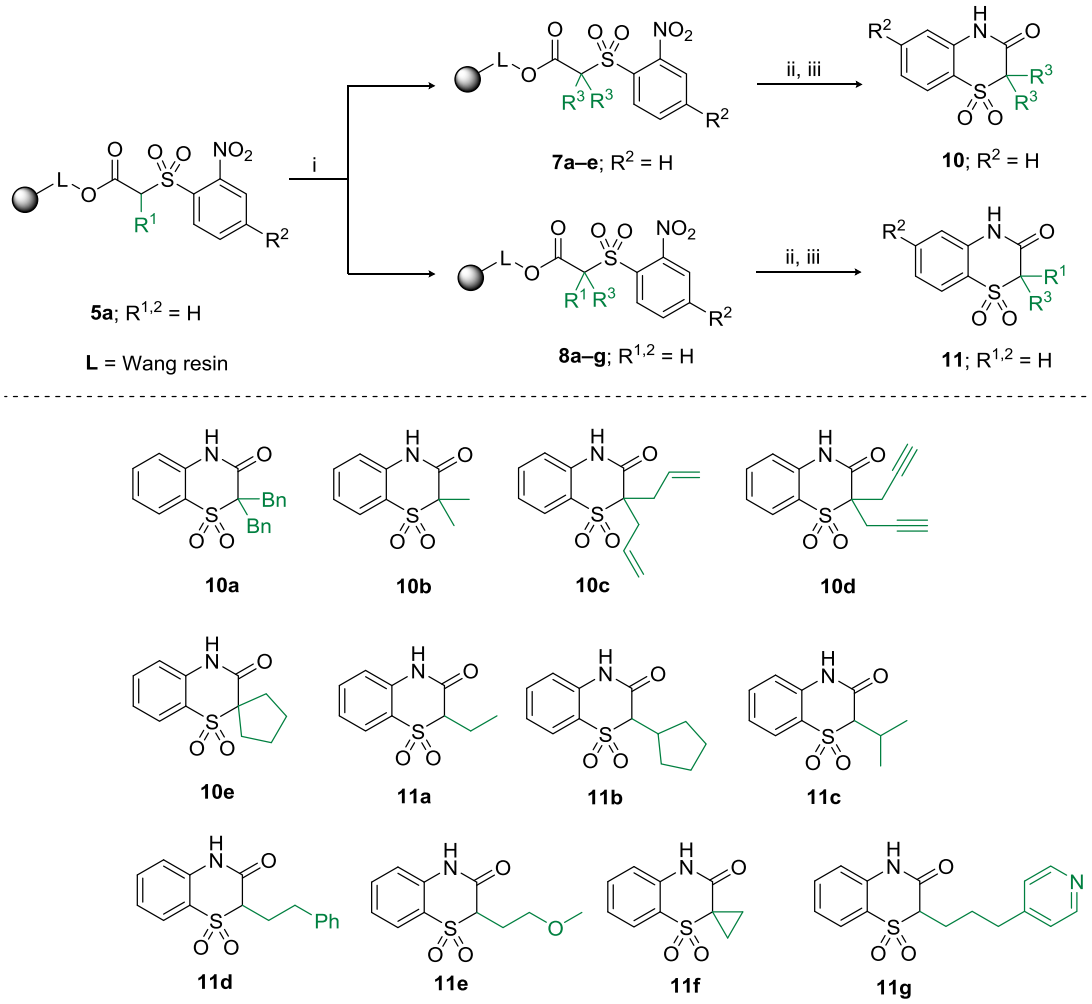
Next, the preparation of nonsymmetric C^2-disubstituted benzothiazines was tested using intermediate **6** (Scheme 4). The alkylation with five representative alcohols (benzyl alcohol, 3-(pyridin-4-yl)propan-1-ol, ethanol, cyclopentanol and 2-methoxyethanol) proceeded smoothly and afforded all the target benzothiazines **12a**–**e** in good overall yields.

Reagents and conditions: i) R^3OH, DIAD, PPh_3, THF, r.t.; ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, CH_2Cl_2/H_2O 2:1, r.t.; iii) trifluoroacetic acid (TFA), 80 °C (overall yields after 4 steps: 50%, **12a**; 27%, **12b**; 62%, **12c**; 55%, **12d**; 33% **12e**).

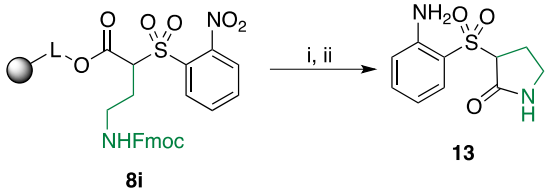
Finally, we also tested the effect of substitution on the 2-nitrophenyl moiety (Scheme 5). Gratifyingly, the use of intermediates **5b** or **5c** with either electron-donating (CH_3) or electron-withdrawing (Cl) substituents did not affect the outcome compared to the unsubstituted analogues.

Reagents and conditions: i) R^3OH, DIAD, PPh_3, THF, r.t.; ii) $Na_2S_2O_4$, K_2CO_3, TBAHS, CH_2Cl_2/H_2O 2:1, r.t.; iii) trifluoroacetic acid (TFA), 80 °C (overall yields after 4 steps: 25%, **10ba**; 18%, **10ca**; 30%, **11ba**; 30%, **11ca**).

The overall results revealed a strong structure-reactivity relationship, which can be clearly seen from the comparison of the structurally related alcohols. For instance, the reaction with benzyl alcohol and methanol yielded the dialkylated intermediates **7a** and **7b**, whereas the use of ethanol and 2-phenylethanol led to formation of only monoalkylated intermediates **8a** and **8d**, respectively. The same dependence was observed for propargyl alcohol (dialkylation) and but-3-yne-1-ol (monoalkylation). This shows

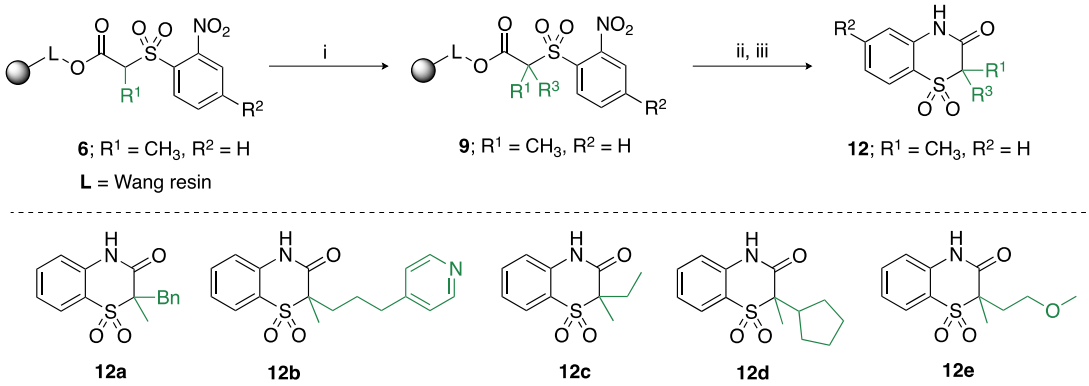


Scheme 2. Reaction sequence using intermediate **5a**.

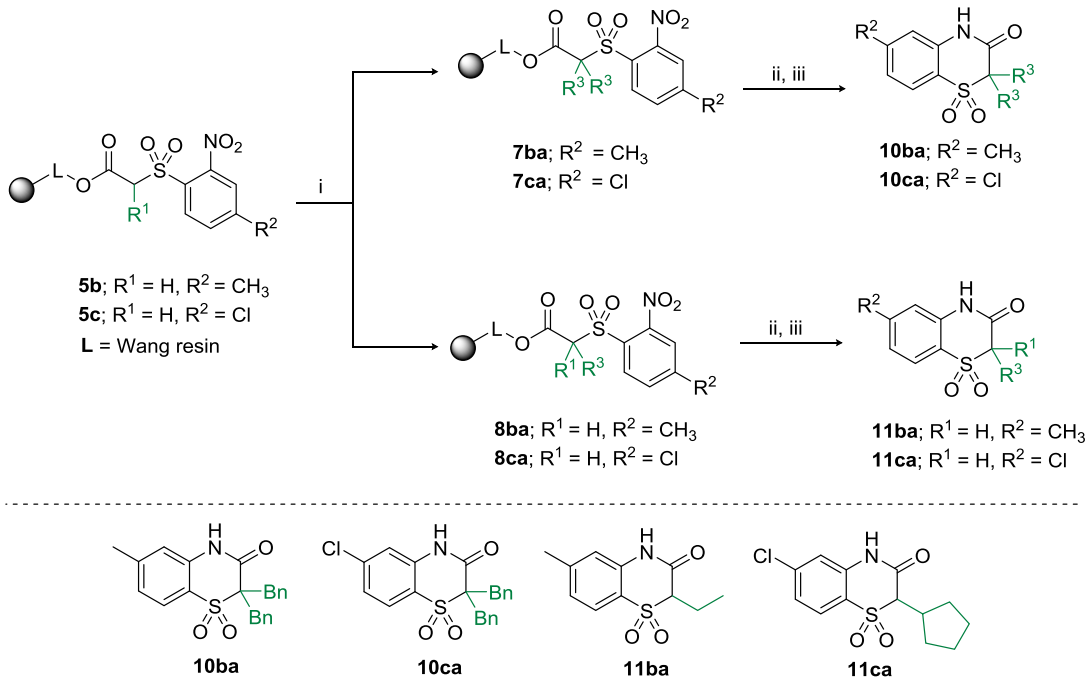


Scheme 3. Reaction sequence using intermediate **8i**.

that the insertion of an additional sp^3 carbon (even a methylene group) dramatically changes the reaction outcome. From a reactivity point of view, allyl alcohol and propargyl alcohol are considered as structurally analogous scaffolds to benzyl alcohol, which is in accordance with the obtained experimental results (dialkylated intermediates **7c** and **7d**, respectively). The alkylation with more sterically demanding alcohols, such as cyclopentanol, isopropanol, or 2-Fmoc-aminoethanol, yielded the monoalkylated intermediates **8b**, **8c** and **8i**. Furthermore, the steric influences of both the substrate and the alcohol were clearly visible from a comparison of ethanol, 2-methoxyethanol, 2-chloroethanol and butane-1,4-diol. The first two reagents afforded only monoalkylated intermediates **8a** and **8e**, whereas the use of butane-1,4-diol and 2-chloroethanol led to second alkylation. Although the second alkylation was performed by two different approaches in the last two cases, both times the reaction proceeded by an intramolecular mechanism and was enforced by the formation of the energetically favorable spirocyclic intermediates **7e** and **8f**. The mixture of mono- and dialkylated products obtained after the reaction with 3-(pyridin-4-yl)propan-1-ol indicates, that the alkyl chain with three sp^3-hybridized carbons likely does not impose steric strain on the α-methylene position. From a practical point of view, one can generally presume that alcohols consisting of a single sp^3-hybridized carbon next to a hydroxyl group (followed by sp/sp^2-hybridized carbons) are less sterically hindered, and due to their flat nature and possible π-π stacking, they afford dialkylated products. On the other hand (except for the intramolecular second alkylation), alcohols with more than one sp^3-hybridized carbon next to a hydroxy group afford exclusively monoalkylated products due to lower kinetic acidity of the second α-methylene proton. Increasing the number of sp^3-hybridized carbons leads to the formation of mixtures of both products. Consequently, the reaction outcome can be efficiently controlled. Furthermore, compared to alternative methodologies, mono-/dialkylated products can be obtained without the use of transition metal catalysis or strong base, which is typically required for the synthesis of C^2-substituted 1,3-dioxo compounds.[17–21] For clarity, the Mitsunobu reaction outcomes, including the crude purities of the corresponding intermediates, are summarized in Table 1. It is worth mentioning that a more detailed relationship could be developed using a high-



Scheme 4. Reaction sequence using intermediate **6**.



Scheme 5. Preparation of benzothiazines with C^6-substitution.

throughput approach, which would be capable of producing a substantial number of diverse products in a short time.

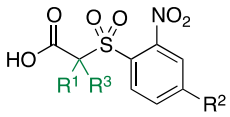
3. Conclusion

In conclusion, we report the first C-alkylation of β-alkoxycarbonyl 2-nitrobenzensulfones based on the Mitsunobu reaction. The results indicated that, depending on the structure of the alcohol, the reaction is sterically controlled and it can selectively yield either dialkylated or monoalkylated products, even when using an excess of reagents or other azodicarboxylates. Furthermore, we have reported the first practical application of alkylated β-alkoxycarbonyl 2-nitrobenzensulfones. The reduction of the nitro group was followed by cleavage from the polymer support, which provided benzothiazin-3(4*H*)-one 1,1-dioxides in a traceless manner. These heterocycles have been previously synthesized using a solid-phase technique,[22–25] but the significantly limited availability of α-halocarboxylic acids did not allow for C^2 diversification of the scaffold. The reported Mitsunobu C-alkylation overcomes this problem using a wide variety of alcohols, including functionalized reagents suitable for the further modification of intermediates/products. Importantly, this method is not limited to solid-phase synthesis; it can be applied using traditional solution-phase chemistry with methyl esters of α-halocarboxylic acids. The further application of the Mitsunobu-alkylated β-alkoxycarbonyl 2-nitrobenzensulfones to synthesize diverse molecules is in progress in our laboratory.

4. Experimental section

All reagents were of reagent grade and were used without further purification. Solvents and chemicals were purchased from Sigma-Aldrich (Milwaukee, IL, www.sigmaaldrich.com) and Acros Organics (Geel, Belgium, www.across.cz). The dry solvents were dried over 4 A molecular sieves or stored as received from commercial suppliers. Wang resin (100–200 mesh, 1% DVB, 0.9 mmol/g) was obtained from AAPPTec (Louisville, KY, www.aapptec.com). The reactions were carried out in plastic reaction vessels (syringes,

Table 1
Crude purities of intermediates **7**, **8** and **9**.



7; $R^1 = R^3$
8; $R^1 = H$
9; $R^1 = CH_3$

Cmpd	R^3OH	R^1	R^2	Purity %[a]	Cmpd	R^3OH	R^1	R^2	Purity %[a]
7a	benzyl alcohol	–	H	90	**8d**	2-phenylethanol	H	H	90
7b	methanol	–	H	90	**8e**	methoxyethanol	H	H	90
7ba	benzyl alcohol	–	CH_3	85	**8f**	2-chloroethanol	H	H	90
7c	allyl alcohol	–	H	90	**8g**	3-(pyridin-4-yl)propan-1-ol	H	H	70
7ca	benzyl alcohol	–	Cl	90	**8h**	but-3-yn1-ol	H	H	85
7d	propargyl alcohol	–	H	90	**8i**	Fmoc-2-aminoethanol	H	H	85
7e	1,4-butanediol	–	H	90	**9a**	benzyl alcohol	CH_3	H	90
8a	ethanol	H	H	90	**9b**	3-(pyridin-4-yl)propan-1-ol	CH_3	H	90
8b	cyclopentanol	H	H	90	**9c**	ethanol	CH_3	H	85
8ba	ethanol	H	CH_3	90	**9d**	cyclopentanol	CH_3	H	90
8c	isopropanol	H	H	90	**9e**	methoxyethanol	CH_3	H	85
8ca	cyclopentanol	H	Cl	90					

[a] Calculated from HPLC-UV traces (205–400 nm) after TFA-mediated cleavage from the polymer support.

each equipped with a porous disk) using a manually operated synthesizer (Torviq, Niles, MI, www.torviq.com) or in dried glassware, unless stated otherwise. The volume of wash solvent was 10 mL per 1 g of resin. For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. Resin-bound intermediates were dried under a stream of nitrogen for prolonged storage and/or quantitative analysis. For the LC/MS analysis a sample of resin (~5 mg) was treated with TFA in CH_2Cl_2, the cleavage cocktail was evaporated under a stream of nitrogen, and cleaved compounds extracted into CH_3CN/H_2O (1:1, 1 mL).

The LC/MS analyses were carried out on a UHPLC-MS system consisting of a UHPLC chromatograph Acquity with photodiode array detector and single quadrupole mass spectrometer (Waters), using X-Select C18 column at 30 °C and flow rate of 600 μl/min. The mobile phase was (A) 0.01 M ammonium acetate in H_2O, and (B) CH_3CN, linearly programmed from 20% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with 20% of solution B for 1 min. The ESI I source operated at a discharge current of 5 μA, vaporizer temperature of 350 °C and capillary temperature of 200 °C.

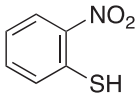
Purification was carried out on a C18 reverse phase column (YMC Pack ODS-A, 20 × 100 mm, 5 μm particles), the gradient was formed from 10 mM aqueous ammonium acetate and CH_3CN, flow rate 15 mL/min. Flash chromatography was carried out on silica gel (230–400 mesh). TLC plates were visualized under UV and/or with CAM. For lyophilization of residual solvents at −110 °C the ScanVac Coolsafe 110–4 was used.

NMR spectra were recorded on a JEOL ECX500 spectrometer at magnetic field strengths of 11.75 T (with operating frequencies 500.16 MHz for ^1H and 125.77 MHz for ^{13}C) and a JEOL ECA400II spectrometer at magnetic field strengths of 9.39 T (with operating frequencies 399.78 MHz for ^1H and 100.53 MHz for ^{13}C) at ambient temperature (20 °C). Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are reported in Hertz (Hz). The ^1H and ^{13}C NMR chemical shifts (δ in ppm) were referenced to the residual signals of solvents: $CDCl_3$ [7.26 (^1H) and 77.23 (^{13}C)], CD_3OD [3.31 (^1H)] and DMSO-d_6 [2.50 (^1H) and 39.51 (^{13}C)]. Structural assignment of resonances have been performed with the help of 2D NMR gradients experiments (COSY, $^1H-^{13}C$ HMQC, NOESY). Acetate salt (residual agent from the semipreparative HPLC purification) exhibited a singlet at 1.89–1.90 ppm in the ^1H NMR spectrum and two resonances at 21.1–21.3 ppm and 172.0–172.1 ppm in the ^{13}C NMR spectrum. Abbreviations in NMR spectra: appt – apparent triplet, brs – broad singlet, d – doublet, dd -– doublet of doublets, m – multiplet, s – singlet, t – triplet, q -– quartet.

IR spectra (4000–400 cm^{-1}) were collected on Nicolet Avatar 370 FTIR spectrometer. Solid samples were measured neat and oily samples as films. Abbreviations in IR spectra: s – strong, m – medium, w – weak.

HRMS analysis was performed using LC-MS on an Orbitrap Elite high-resolution mass spectrometer (Dionex Ultimate 3000, Thermo Exactive plus, MA, USA) operating at positive full scan mode (120,000 FWMH) in the range of 100–1000 m/z. The settings for electrospray ionization were as follows: oven temperature of 150 °C and source voltage of 3.6 kV. The acquired data were internally calibrated with diisooctyl phthalate as a contaminant in CH_3OH (m/z 391.2843). Samples were diluted to a final concentration of 0.1 mg/mL in H_2O and CH_3OH (50:50, v/v). Before HPLC separation (column Phenomenex Gemini, 50 × 2.00 mm, 3 μm particles, C18), the samples were injected by direct infusion into the mass spectrometer using an autosampler. The mobile phase was isocratic CH_3CN/IPA/0.01 M ammonium acetate (40:5:55) and flow 0.3 mL/min.

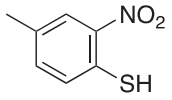
4.1. 2-Nitrobenzenethiol ***2a***



To a suspension of 1,2-bis(2-nitrophenyl)disulfane **1a** (500 mg, 1.62 mmol) in degassed THF (15 mL) was added PPh_3 (638 mg, 2.43 mmol), mercaptoethanol (115 μL, 1.62 mmol) and water (300 μL) and the reaction mixture was stirred at 50 °C for 21 h under a nitrogen atmosphere. The crude mixture was cooled to

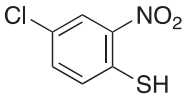
ambient temperature, concentrated, diluted with brine (100 mL) and extracted with CH_2Cl_2 (3 × 90 mL). The organic extracts were dried over Na_2SO_4, evaporated and the crude product was purified by flash chromatography (EtOAc/hexane = 3:1; R_f = 0.23). The compound **2a** was yielded as a bright yellow crystalline solid (450 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (dd, J = 8.3, 1.3 Hz, 1H), 7.86–7.84 (m, 1H), 7.60–7.56 (m, 1H), 7.42–7.38 (m, 1H) ppm. Other spectral data were consistent with commercially available compound.

4.2. 4-Methyl-2-nitrobenzenethiol **2b**



To a suspension of 1,2-bis(4-methyl-2-nitrophenyl)disulfane **1b** (300 mg, 0.9 mmol) in a degassed mixture of THF/10% aquenous AcOH (4:1, 20 mL) was added PPh_3 (353 mg, 1.35 mmol), mercaptoethanol (95 μL, 1.35 mmol) and the reaction mixture was stirred at 65 °C under a nitrogen atmosphere. The reaction was monitored by TLC (hexane/EtOAc = 3:1), which indicated completition after 24 h. The reaction mixture was diluted with 10% aquenous AcOH (100 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were dried over Na_2SO_4, evaporated and the crude product was purified by flash chromatography (hexane/EtOAc = 3:1 to 2:1; R_f = 0.35). The compound **2b** was yielded as a bright yellow crystalline solid (215 mg, 72% yield). ^{1}H NMR (500 MHz, CD_3OD): δ 8.17 (s, 1H), 7.74–7.72 (m, 1H), 7.51–7.48 (m, 1H), 2.42 (s, 3H) ppm. Other spectral data were consistent with commercially available compound.

4.3. 4-Chloro-2-nitrobenzenethiol **2c**



To a suspension of 1,2-bis(4-chloro-2-nitrophenyl)disulfane **1c** (300 mg, 0.8 mmol) in degassed THF (12 mL) was added dropwise PBu_3 (218 μL, 0.88 mmol) and water (500 μL) at 0 °C. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere. The reaction was monitored by TLC (EtOAc/CH_2Cl_2 = 1:1) which indicated completition after 4 h. The reaction mixture was diluted with 10% aquenous AcOH (100 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were dried over Na_2SO_4, evaporated and the crude product was purified by flash chromatography (EtOAc/CH_2Cl_2 = 1:1, R_f = 0.35). The compound **2c** was prepared as a bright yellow crystalline solid (271 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 4.06 (s, 1H) ppm. Other spectral data were consistent with commercially available compound.

4.4. General procedures for acylation of Wang resin

a) **Procedure A:** Wang resin (500 mg, loading 0.9 mmol/g) was swollen in CH_2Cl_2 (5 mL) for 20 min. Iodoacetic acid (418 mg, 2.25 mmol) was dissolved in CH_2Cl_2 (5 mL) and DIC (156 μL, 1.0 mmol) was added. The reaction mixture was stirred for 30 min at ambient temperature, followed by precipitation of diisopropylurea. The resulting solution was added to a polypropylene fritted syringe with Wang resin. The reaction mixture was shaken at ambient temperature for 16 h, followed by washes with DMF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL).

b) **Procedure B:** Wang resin (500 mg, loading 0.9 mmol/g) was swollen in CH_2Cl_2 (5 mL) for 20 min and then washed with CH_2Cl_2 (2 × 5 mL). To solution of 2-brompropionyl bromide (236 μL, 2.25 mmol) in CH_2Cl_2 (5 mL) was added DIPEA (392 μL, 2.25 mmol). The resulting solution was added to a polypropylene fritted syringe with Wang resin. The reaction mixture was shaken at ambient temperature for 16 h, followed by washes with DMF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL).

c) **Determination of loading**: 100 mg of each resin was cleaved using TFA/CH_2Cl_2 (1:1) at r.t. for 30 min. After removal of resin and evaporation of the cleavage cocktail, the residual material was dissolved in DMSO-d_6. The quantity of iodoacetic was calculated using ^{1}H NMR analysis from the ratio of the diagnostic signal area compared to the integrated DMSO-d_6 multiplet. A defined concentration of iodoacetic acid or 2-brompropionyl bromide in DMSO-d_6 was used as the external standard. Calculated loading: 0.4 mmol/g (iodoacetic acid), 0.27 mmol/g (2-brompropionyl bromide).

4.5. General procedure for substitution with thiols

The starting resin (500 mg) was washed with CH_2Cl_2 (3 × 5 mL). A solution of thiol (1.5 mmol), and 2,6-lutidine (52 μL, 0.45 mmol) in CH_2Cl_2 (5 mL) was added to the polypropylene fritted syringe with the resin. The reaction mixture was shaken at ambient temperature for 16 h, followed by washes with CH_2Cl_2 (5 × 5 mL).

4.6. General procedure for oxidation of sulfide

The starting resin (500 mg) was washed with CH_2Cl_2 (3 × 5 mL). A solution of *m*CPBA (431 mg, 2.5 mmol) in CH_2Cl_2 (5 mL) was added to the polypropylene fritted syringe with the resin. The reaction mixture was shaken at ambient temperature for 16 h, followed by washes with CH_2Cl_2 (5 × 5 mL).

4.7. General procedure for Mitsunobu alkylation

The starting resin (250 mg) was swollen in CH_2Cl_2 (5 mL) for 20 min and then washed with dry DMF (3 × 5 mL) and dry THF (3 × 5 mL). A solution of alcohol (1.13 mmol) and PPh_3 (295 mg, 1.13 mmol) in dry degassed THF (2 mL) was added to the resin. A solution of DIAD (222 μL, 1.13 mmol) in dry degassed THF (2 mL) was added to the syringe and was connected with the polypropylene fritted syringe through a joint. The syringes were put into the freezer (−20 °C) for 30 min. Then a solution of DIAD in THF was slowly added to the polypropylene fritted syringe with the resin. The reaction mixture was allowed to warm to ambient temperature and was shaken for 16 h, followed by washes with THF (3 × 5 mL), DMF (3 × 5 mL) and CH_2Cl_2 (5 × 5 mL).

4.8. General procedure for reduction of nitro group

The starting resin (250 mg) was washed with CH_2Cl_2 (3 × 5 mL). A solution of $Na_2S_2O_4$ (1.25 g, 7.2 mmol), K_2CO_3 (1.41 g, 10.2 mmol) and TBAHS (244 mg, 0.72 mmol) in CH_2Cl_2/water (2:1, 6 mL) was added to the polypropylene fritted syringe with the resin. The reaction mixture was shaken at ambient temperature for 16 h, followed by washes with water (3 × 10 mL), water/DMF (1:1, 3 × 10 mL), DMF (3 × 10 mL) and CH_2Cl_2 (5 × 10 mL).

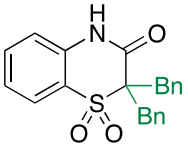
4.9. General procedure for final cyclization

The starting resin (250 mg) was washed with CH_2Cl_2 (3 × 5 mL) and transferred into the glass microreactor vial with neat TFA (8 mL). The reaction mixture was shaken at reflux for 3–16 h, cooled down to ambient temperature and residual acid was slowly evaporated under a stream of nitrogen. The crude final product was dissolved in CH_3CN (2 mL) and purified by UHPLC. CH_3CN from the combined fractions was removed using a rotavapor and residual water was freeze-dried.

4.10. Analytical data of final compounds

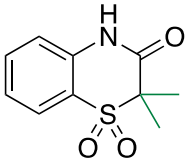
Note: Overall yields are calculated after the entire reaction sequence and HPLC purification starting from loadings of iodoacetic acid or 2-bromopropionyl bromide, respectively.

4.11. 2,2-Dibenzyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***10a***



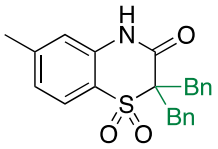
Bright yellow solid (10 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (brs, 1H), 7.70–7.66 (m, 1H), 7.29–7.23 (m, 5H, *overlap with solvent*), 7.14–7.09 (m, 7H), 6.44–6.42 (m, 1H), 3.58 (d, J = 14.6 Hz, 2H), 3.52 (d, J = 14.6 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 134.5, 133.5, 133.5, 131.4, 128.0, 127.7, 125.9, 124.5, 124.3, 117.2, 71.1, 37.9 ppm. IR ($\tilde{\nu}_{max}$) = 3258 (m), 2919 (m), 2580 (w), 1685 (s), 1596 (m), 1483 (m), 1285 (s), 1135 (s), 1128 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{22}H_{19}NO_3S$ $[M+H]^+$ = 378.1164, found $[M+H]^+$ = 378.1158.

4.12. 2,2-Dimethyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***10b***



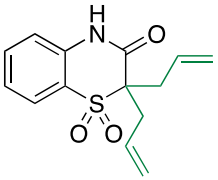
Yellow solid (12 mg, 50% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.08 (brs, 1H), 7.80 (dd, J = 7.8, 1.4 Hz, 1H), 7.69–7.65 (m, 1H), 7.31–7.28 (m, 1H), 7.18 (dd, J = 8.1, 0.7 Hz, 1H), 1.41 (s, 6H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.0, 135.2, 124.4, 124.1, 123.9, 122.1, 118.0, 61.7, 16.6 ppm. IR ($\tilde{\nu}_{max}$) = 3066 (w), 2988 (w), 2932 (w), 1678 (s), 1597 (s), 1483–1303 (s), 1118 (s), 844 (m) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{10}H_{11}NO_3S$ $[M-H]^-$ = 224. 0387, found $[M-H]^-$ = 224.0372.

4.13. 2,2-Dibenzyl-6-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***10ba***



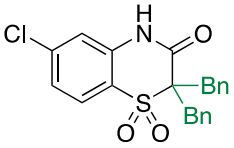
Colorless oil (10 mg, 25% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.17 (brs, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.21–7.16 (m, 10H), 7.01–6.99 (m, 1H), 6.59–6.58 (m, 1H), δ 3.42 (d, J = 14.5 Hz, 2H), 3.29 (d, J = 14.5 Hz, 2H, *overlap with solvent*), 2.23 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.7, 145.3, 134.5, 133.7, 130.9, 127.6, 126.9, 124.3, 123.5, 121.6, 117.5, 69.9, 36.2, 21.1 ppm. IR ($\tilde{\nu}_{max}$) = 3087–2973 (w), 1670 (s), 1588 (m), 1316 (s), 1140 (s), 815–780 (m) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{23}H_{21}NO_3S$ $[M-H]^-$ = 390.1169, found $[M-H]^-$ = 390.1162.

4.14. 2,2-Diallyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***10c***



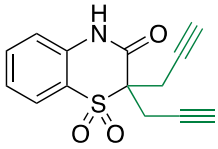
Yellow solid (15 mg, 50% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.70 (brs, 1H), 7.80 (dd, J = 7.9, 1.4 Hz, 1H), 7.72–7.69 (m, 1H), 7.34–7.31 (m, 1H), 7.20 (dd, J = 8.2, 0.7 Hz, 1H), 5.84–5.76 (m, 2H), 5.18–5.17 (m, 1H), 5.15–5.13 (m, 3H), 2.76 (dd, J = 14.8, 7.9 Hz, 2H), 2.64 (dd, J = 15.0, 6.5 Hz, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.8, 135.4, 135.0, 130.7, 124.2, 124.0, 122.6, 120.2, 117.9, 67.5, 32.3 ppm. IR ($\tilde{\nu}_{max}$) = 3196 (w), 3130 (w), 3064 (w), 2982 (w), 2918 (w), 2851 (w), 1675 (s), 1596 (m), 1480 (m), 1440 (w), 1304 (s), 1155 (s), 1121 (m), 993 (m), 927 (m), 757 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{14}H_{15}NO_3S$ $[M-H]^-$ = 276.0700, found $[M-H]^-$ = 276.0687.

4.15. 2,2-Dibenzyl-6-chloro-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***10ca***



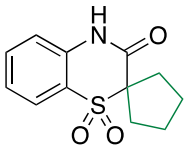
Bright yellow solid (8 mg, 18% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.37 (brs, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.23–7.15 (m, 11H), 6.72 (d, J = 1.8 Hz, 1H), 3.47 (d, J = 14.5 Hz, 2H), 3.35 (d, J = 14.5 Hz, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.8, 138.8, 135.7, 133.3, 130.9, 127.6, 127.0, 125.4, 123.4, 123.4, 116.9, 70.1, 36.8 ppm. IR ($\tilde{\nu}_{max}$) = 3068–2922 (w), 1675 (s), 1590 (s), 1472 (m), 1455 (w), 1315 (s), 1158 (w), 1139 (m), 993 (m), 1092 (m), 811 (w), 757 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{22}H_{18}^{35}ClNO_3S$ $[M-H]^-$ = 410.0696, found $[M-H]^-$ = 410.0690.

4.16. 2,2-di(prop-2-yn-1-yl)-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***10d***



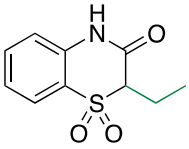
White solid (8 mg, 28% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.51 (brs, 1H), 7.81 (dd, J = 7.9, 1.3 Hz, 1H), 7.75–7.71 (m, 1H), 7.36–7.33 (m, 1H), 7.21 (dd, J = 7.4, 0.8 Hz, 1H), 3.08 (t, J = 2.7 Hz, 2H), 3.05 (d, J = 2.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 164.0, 135.8, 134.8, 124.5, 124.4, 122.2, 118.2, 76.5, 75.6, 65.5, 18.9 ppm. IR ($\tilde{\nu}_{max}$) = 3355 (w), 3271 (m), 3204–3083 (w), 2920 (m), 2850 (w), 1676 (s), 1596 (m), 1482 (m), 1425 (m), 1358 (m), 1315 (s), 1297 (s), 1168 (s), 1153 (s), 1133 (s), 993 (m), 927 (m), 804 (m), 757 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}NO_3S$ [M − H]$^-$ = 272.0387, found [M − H]$^-$ = 272.0390.

4.17. Spiro[benzo[b][1,4]thiazine-2,1′-cyclopentan]-3(4H)-one 1,1-dioxide ***10e***



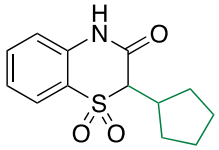
Bright yellow solid (21 mg, 79% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.21 (brs, 1H), 7.83 (dd, J = 7.8, 1.5 Hz, 1H), 7.72–7.68 (m, 1H), 7.33–7.30 (m, 1H), 7.22 (dd, J = 7.4, 0.8 Hz, 1H), 2.16–2.11 (m, 4H), 1.76–1.70 (m, 4H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.0, 135.5, 135.3, 124.3, 123.8, 123.4, 118.2, 71.2, 29.9, 26.2 ppm. IR ($\tilde{\nu}_{max}$) = 3207 (w), 3064 (w), 2923 (w), 2852 (w), 1676 (s), 1595 (m), 1482 (m), 1425 (m), 1350 (m), 1315 (s), 1297 (s), 1168 (s), 1123 (s), 1027–840 (m), 733 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{12}H_{13}NO_3S$ [M − H]$^-$ = 250.0543, found [M − H]$^-$ = 250.0550.

4.18. 2-Ethyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11a***



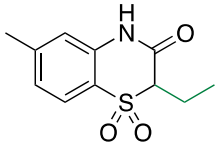
Bright yellow solid (9 mg, 37% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.88 (brs, 1H), 7.81 (dd, J = 7.8, 1.4 Hz, 1H), 7.70–7.66 (m, 1H), 7.32–7.29 (m, 1H), 7.21 (dd, J = 8.1, 0.8 Hz, 1H), 4.53 (dd, J = 7.7, 5.4 Hz, 1H), 2.00–1.86 (m, 2H), 1.09 (appt, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.9, 136.3, 135.6, 125.3, 124.1, 124.1, 118.8, 65.3, 16.9, 12.3 ppm. IR ($\tilde{\nu}_{max}$) = 3188 (w), 3131 (w), 3056 (w), 2978 (w), 2971 (w), 1673 (s), 1595 (m), 1478 (m), 1425 (m), 1361 (m), 1314 (s), 1210 (m), 1168 (s), 1124 (s), 1026–821 (m), 725 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{10}H_{11}NO_3S$ [M − H]$^-$ = 224.0387, found [M − H]$^-$ = 224.0372.

4.19. 2-Cyclopentyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11b***



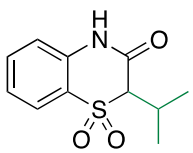
Bright yellow solid (17 mg, 60% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.19 (brs, 1H), 7.81 (dd, J = 7.8, 1.4 Hz, 1H), 7.70–7.66 (m, 1H), 7.32–7.29 (m, 1H), 7.21–7.19 (d, J = 8.2, 0.7 Hz, 1H), 4.43 (d, J = 9.0 Hz, 1H), 2.17–2.08 (m, 1H), 2.05–1.71 (m, 2H), 1.61–1.57 (m, 3H), 1.47–1.36 (m, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.4, 135.8, 135.1, 124.2, 123.8, 123.7, 118.2, 68.4, 36.6, 30.4, 23.8 ppm. IR ($\tilde{\nu}_{max}$) = 3353 (w), 3228 (w), 3154 (w), 2921 (w), 2852 (w), 1673 (s), 1595 (m), 1479 (m), 1357 (m), 1318 (s), 1205 (m), 1169 (m), 1114 (m), 760 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{13}H_{15}NO_3S$ [M − H]$^-$ = 264.0700, found [M − H]$^-$ = 264.0702.

4.20. 2-Ethyl-6-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11ba***



Bright yellow solid (7 mg, 30% yield). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 11.14 (brs, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.13–7.11 (m, 1H), 6.99 (s, 1H), 4.46 (dd, J = 7.8, 5.4 Hz, 1H), 2.37 (s, 3H), 2.01–1.94 (m, 1H), 1.90–1.83 (m, 1H), 1.08 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.6, 145.6, 135.7, 124.3, 123.5, 122.1, 118.2, 64.9, 21.2, 16.5, 11.7 ppm. IR ($\tilde{\nu}_{max}$) = 3050 (w), 3013 (w), 2972 (w), 2937 (w), 1681 (s), 1604 (m), 1586 (m), 1470 (m), 1382 (m), 1334 (s), 1290 (m), 1214 (m), 1126 (s), 822 (s), 759 (m) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NO_3S$ [M − H]$^-$ = 238.0543, found [M − H]$^-$ = 238.0536.

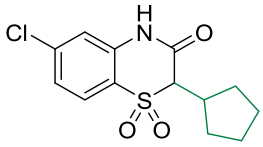
4.21. 2-Isopropyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11c***



Bright yellow solid (11 mg, 43% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.22 (brs, 1H), 7.80 (dd, J = 7.8, 1.4 Hz, 1H), 7.69–7.66 (m, 1H), 7.32–7.28 (m, 1H), 7.20 (dd, J = 8.2, 0.8 Hz, 1H), 4.38 (d, J = 5.3 Hz, 1H), 2.38–2.30 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.0, 135.9, 135.1, 125.0, 123.7, 123.3, 118.2, 69.2, 26.6, 20.9, 19.2 ppm. IR ($\tilde{\nu}_{max}$) = 3352 (w), 3192–3054 (w), 2962 (w), 2919 (m), 2851 (w), 1681 (s), 1677 (m), 1594 (m), 1478 (m), 1392 (m), 1359 (m), 1252 (m), 1224 (m), 1126 (s), 1072 (m), 869 (s), 760 (m) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NO_3S$ [M − H]$^-$ = 238.0543, found

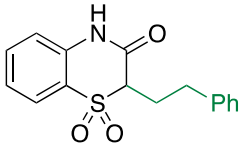
$[M - H]^-$ = 238.0534.

4.22. 6-Chloro-2-ethyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11ca***



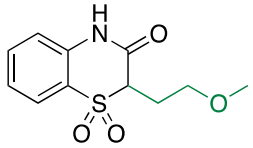
Brown oil (10 mg, 30% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.29 (brs, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 8.3, 1.9 Hz, 1H), 7.23 (d, J = 1.9 Hz, 1H), 4.53 (d, J = 8.2 Hz, 1H), 2.18–2.12 (m, 1H), 1.93–1.92 (m, 1H), 1.61–1.57 (m, 4H), 1.43–1.35 (m, 4H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.4, 139.2, 137.3, 125.9, 123.6, 123.1, 117.6, 68.4, 36.4, 30.3, 24.0 ppm. HRMS (ESI): *m/z* calcd for $C_{13}H_{14}^{35}ClNO_3S$ $[M - H]^-$ = 298.0310, found $[M - H]^-$ = 298.0380.

4.23. 2-Phenethyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11d***



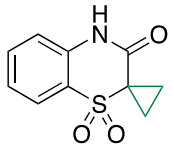
Pale yellow solid (15 mg, 46% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.20 (brs, 1H), 7.82 (dd, J = 7.8, 1.4 Hz, 1H), 7.72–7.67 (m, 1H), 7.33–7.28 (m, 3H), 7.24–7.19 (m, 4H), 4.56 (appt, J = 6.2 Hz, 1H), 2.87–2.83 (m, 2H), 2.22–2.17 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.3, 140.6, 135.8, 135.2, 128.5, 128.2, 126.2, 124.7, 123.7, 123.6, 118.4, 63.0, 32.6, 24.1 ppm. IR ($\tilde{\nu}_{max}$) = 3140 (w), 3064 (w), 2992 (w), 2922 (w), 1692 (s), 1595 (m), 1478 (m), 1361 (m), 1311 (s), 1267 (m), 1134 (m), 1072 (m), 809 (w), 760 (m), 726 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{22}H_{18}ClNO_3S$ $[M - H]^-$ = 300.0700, found $[M - H]^-$ = 300.0695.

4.24. 2-(2-methoxyethyl)-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11e***



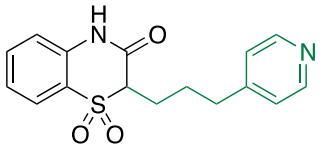
Brown oil (5 mg, 18% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.06 (brs, 1H), 7.81 (dd, J = 7.9, 1.0 Hz, 1H), 7.71–7.67 (m, 1H), 7.31–7.29 (m, 1H), 7.22–7.21 (m, 1H), 4.57 (appt, J = 6.2 Hz, 1H), 3.56–3.47 (m, 2H), 3.23 (s, 3H), 2.17–2.16 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.2, 135.8, 135.1, 124.7, 123.6, 123.5, 118.4, 68.6, 60.7, 57.8, 22.1 ppm. IR ($\tilde{\nu}_{max}$) = 3206 (w), 3065 (w), 2994 (w), 2936 (w), 2903 (w), 1676 (s), 1595 (m), 1481 (m), 1429 (m), 1369 (m), 1319 (s), 1292 (m), 1267 (s), 1134 (s), 1083 (m), 801 (w), 762 (m), 724 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NO_4S$ $[M - H]^-$ = 254.0493, found $[M - H]^-$ = 254.0480.

4.25. Spiro[benzo[b][1,4]thiazine-2,1′-cyclopropan]-3(4H)-one 1,1-dioxide ***11f***



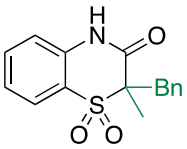
Brown oil (9 mg, 38% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.37 (brs, 1H), 7.79 (dd, J = 7.8, 1.3 Hz, 1H), 7.73–7.69 (m, 1H), 7.35–7.29 (m, 2H), 1.73–1.70 (m, 2H), 1.68–1.64 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.8, 135.5, 135.1, 124.5, 123.9, 122.7, 118.5, 41.1, 13.3 ppm. IR ($\tilde{\nu}_{max}$) = 3270 (w), 3107 (w), 2921 (w), 1680 (s), 1599 (m), 1478 (m), 1339 (m), 1319 (s), 1231 (m), 1196 (m), 1155 (s), 1100 (s), 1070 (m), 942 (m), 800 (w), 762 (m), 734 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{10}H_9NO_3S$ $[M - H]^-$ = 222.0230, found $[M - H]^-$ = 222.0221.

4.26. 2-(3-(pyridin-4-yl)propyl)-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***11g***



Brown oil (15 mg, 45% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.24 (brs, 1H), 8.52 (dd, J = 4.6, 1.6 Hz, 2H), 7.81 (dd, J = 7.9, 1.4 Hz, 1H), 7.71–7.67 (m, 1H), 7.38–7.36 (m, 2H), 7.32–7.29 (m, 1H), 7.23–7.20 (m, 1H), 4.71 (dd, J = 6.9, 5.7 Hz, 1H), 2.74–2.71 (m, 2H), 1.96–1.93 (m, 2H), 1.90–1.84 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.4, 147.8, 135.7, 135.1, 124.8, 124.5, 123.7, 118.3, 67.8, 63.0, 33.7, 27.4, 21.9, 21.4 ppm. IR ($\tilde{\nu}_{max}$) = 3500–3000 (w), 2923 (w), 2852 (w), 1681 (s), 1598 (m), 1478 (m), 1346 (m), 1302 (s), 1242 (m), 1153 (m), 1125 (s), 1030 (s), 808 (w), 762 (m), 734 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{16}H_{16}N_2O_3S$ $[M - H]^-$ = 315.0809, found $[M - H]^-$ = 315.0807.

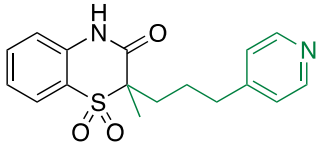
4.27. 2-Benzyl-2-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***12a***



White solid (10 mg, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (brs, 1H), 7.94–7.92 (m, 1H), 7.54–7.51 (m, 1H), 7.30–7.27 (m, 1H), 7.18–7.13 (m, 3H), 7.06–7.04 (m, 2H), 6.88–6.86 (m, 1H), 3.18 (d, J = 14.0 Hz, 1H), 3.13 (d, J = 14.0 Hz, 1H), 1.68 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.2, 134.9, 134.2, 133.1, 130.2, 130.2, 130.2, 128.3, 127.7, 125.4, 124.8, 123.8, 117.8, 67.3, 39.5, 12.0 ppm. IR ($\tilde{\nu}_{max}$) = 3278 (w), 3155 (w), 2919 (w), 1703 (s), 1665 (s), 1596 (s), 1480 (s), 1348 (m), 1319 (s), 1298 (s), 1155 (s), 1097 (s), 1070 (m), 797 (w), 762 (m), 734 (s), 711 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for

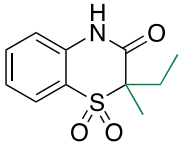
$C_{16}H_{15}NO_3S$ $[M-H]^-$ = 300.0700, found $[M-H]^-$ = 300.0689.

4.28. 2-Methyl-2-(3-(pyridin-4-yl)propyl)-2H-benzo[b][1,4] thiazin-3(4H)-one 1,1-dioxide ***12b***



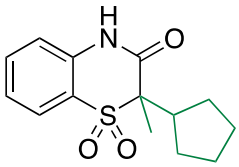
Brown solid (6 mg, 27% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.23 (brs, 1H), 8.46–8.43 (m, 2H), 7.79 (dd, J = 7.8, 1.3 Hz, 1H), 7.70–7.66 (m, 1H), 7.32–7.29 (m, 1H), 7.22–7.21 (m, 2H), 7.16–7.14 (m, 1H), 2.60–2.55 (m, 2H), 1.74–1.66 (m, 2H), 1.49 (s, 3H), 1.23–1.15 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.9, 148.4, 135.2, 135.0, 124.4, 124.0, 123.9, 123.5, 122.1, 117.9, 65.1, 33.6, 30.7, 24.1, 11.2 ppm. IR ($\tilde{\nu}_{max}$) = 2954–2848 (s), 1692 (s), 1599 (m), 1481 (s), 1378 (m), 1304 (m), 1155–1024 (m), 800 (m), 763 (m), 729 (s), 719 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{17}H_{18}N_2O_3S$ $[M-H]^-$ = 329.0965, found $[M-H]^-$ = 329.0954.

4.29. 2-Ethyl-2-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***12c***



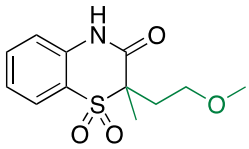
Brown solid (10 mg, 62% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.24 (brs, 1H), 7.82 (dd, J = 7.8, 1.5 Hz, 1H), 7.71–7.68 (m, 1H), 7.33–7.30 (m, 1H), 7.19 (dd, J = 8.2, 0.8 Hz, 1H), 1.79–1.64 (m, 2H), 1.48 (s, 3H), 0.88 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 166.9, 135.2, 135.2, 124.4, 124.0, 122.2, 117.9, 65.7, 25.3, 10.4, 8.4 ppm. IR ($\tilde{\nu}_{max}$) = 3223 (w), 2981–2923 (w), 1682 (s), 1596 (s), 1481 (s), 1375 (m), 1304 (s), 1151 (m), 1110 (m), 1070 (m), 763 (s), 722 (s) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{11}H_{13}NO_3S$ $[M-H]^-$ = 238.0543, found $[M-H]^-$ = 238.0550.

4.30. 2-Cyclopentyl-2-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***12d***



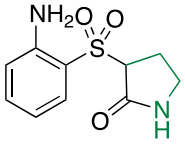
Brown solid (11 mg, 55% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.98 (brs, 1H), 7.81 (dd, J = 7.8, 1.4 Hz, 1H), 7.71–7.67 (m, 1H), 7.33–7.30 (m, 1H), 7.18 (dd, J = 8.1, 0.7 Hz, 1H), 2.18–2.11 (m, 1H), 1.73–1.68 (m, 1H), 1.52–1.49 (m, 2H), 1.48 (s, 3H), 1.45–1.26 (m, 5H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 167.3, 135.4, 135.2, 124.3, 123.9, 122.7, 117.8, 67.9, 41.0, 28.1, 26.6, 24.4, 24.0 ppm. IR ($\tilde{\nu}_{max}$) = 3231 (w), 3157 (w), 2922 (w), 2871 (w), 1682 (s), 1595 (m), 1480 (m), 1342 (m), 1316 (s), 1159 (m), 1113 (m), 1065 (m), 867 (m), 758 (s), 730 (m) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{14}H_{17}NO_3S$ $[M-H]^-$ = 278.0856, found $[M-H]^-$ = 278.0867.

4.31. 2-(2-methoxyethyl)-2-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 1,1-dioxide ***12e***



Brown solid (6 mg, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (brs, 1H), 7.93–7.91 (m, 1H), 7.62–7.58 (m, 1H), 7.32–7.28 (m, 1H), 7.02–7.00 (m, 1H), 3.54–3.45 (m, 2H), 3.22 (s, 3H), 2.16–2.11 (m, 2H), 1.73 (s, 3H) ppm.^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 135.1, 134.4, 125.6, 124.6, 123.3, 117.7, 67.5, 65.1, 58.7, 32.6, 12.3 ppm. IR ($\tilde{\nu}_{max}$) = 3234 (w), 2917 (m), 2849 (w), 3157 (w), 1707 (s), 1600 (m), 1503 (m), 1480 (m), 1342 (s), 1270 (m), 1168 (m), 1098 (s), 972 (m), 758 (s), 731 (m), 718 (m) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{12}H_{15}NO_4S$ $[M-H]^-$ = 268.0649, found $[M-H]^-$ = 268.0637.

4.32. 3-((2-aminophenyl)sulfonyl)pyrrolidin-2-one ***13***



^{1}H NMR (500 MHz, DMSO-d_6): δ 7.88–7.87 (m, 1H), 7.67–7.65 (m, 1H), 7.41–7.38 (m, 1H), 7.35–7.28 (m, 2H), 7.24–7.22 (m, 1H), 4.63–4.61 (m, 1H), 4.30–4.29 (m, 1H), 4.22–4.20 (m, 1H), 4.10–4.07 (m, 1H) ppm.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.09.017.

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