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Ring Contraction of 2,5-Dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-Dioxides: Access to 4*H*-Benzo[*b*][1,4]thiazine 1,1-Dioxides

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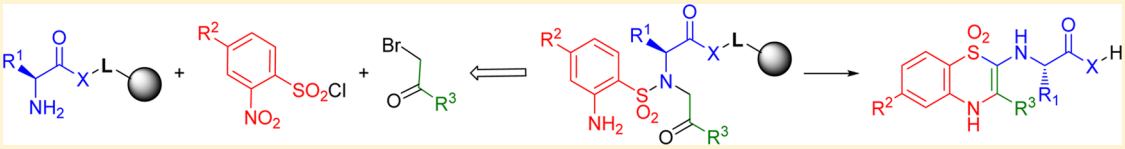
Supporting Information



ABSTRACT: We report an efficient synthesis of 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides via unprecedented ring contraction of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides under mild conditions involving carbon−sulfur bond formation. 2,5-Dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides are easily accessible from commercially available building blocks, including Fmoc-protected amino acids, 2-nitrobenzenesulfonyl chlorides, and bromo ketones. Benzothiazine 1,1-dioxides represent pharmacologically relevant derivatives with biological, medicinal, and industrial applications.

INTRODUCTION

The structural similarity of 1,4-benzothiazines **I** (Figure 1) to pharmacologically important 10*H*-phenothiazines **II** has

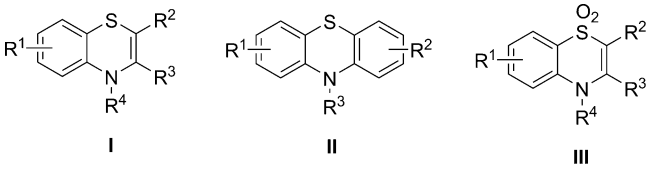


Figure 1. General structures of thiazines.

triggered considerable interest in synthetic and biological studies of this class of compounds.[1−3] 1,4-Benzothiazines **I** and their analogues are well documented to exhibit pharmacologically relevant activities, including sedative, anthelmintic, antiulcer, anticancer, antibacterial, and antifungal effects.[4−6] They also inhibit acetylcholinesterase (AchE), which is responsible for several neurological disorders, such as Parkinson's and Alzheimer's diseases.[7] In addition, numerous benzothiazines are in clinical development as antipsychotics, analgesics, diuretics, antitussives, and antihistamines.[3,8] The corresponding S-oxidized 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxide analogues **III**[9−11] were first described in 1968. Since then, they have assumed a prominent role in organic synthesis, medicinal chemistry, and the chemical industry.[12,13] Several analogues of **III** have been isolated from a bryozoan.[14] Benzothiazine 1,1-dioxides are being widely investigated for inhibition of hepatitis C virus (HCV NS5B) and activation of ATP-sensitive potassium channels.[15−20] Structure−activity analyses have revealed that the biological properties of benzothiazine 1,1-dioxides are strongly dependent on substitution, which makes **III** pharmacologically relevant and highly attractive.

The benzothiazine 1,1-dioxide scaffold **III** has been prepared by several procedures. The first method is based on intramolecular ring closure of S-oxidized precursors. The authors of the original 1968 article[12] employed ozonolysis of *o*-nitrophenyl allyl sulfone followed by catalytic hydrogenation, which led to unsubstituted **III**. Tsui and co-workers[21] used efficient intramolecular nucleophilic aromatic substitution of novel (*Z*)-*β*-(2-fluorobenzenesulfonyl)vinylamines to afford benzothiazine 1,1-dioxides. The use of Boc-protected 2-(methylsulfanyl)-aniline has also been reported.[22] After N-acylation and S-oxidation, the sulfonyl intermediate underwent acyl migration from the nitrogen to the methylsulfonyl group. Treatment with trifluoroacetic acid (TFA) gave **III** by simultaneous deprotection−cyclization. The second route to construct 1,4-benzothiazine 1,1-dioxides used condensation and oxidative cyclization of various substituted benzenehiols with *β*-diketones/*β*-keto esters. The key 1,1-dioxides **III** were obtained after S-oxidation with 30% hydrogen peroxide in glacial acetic acid.[23,24] This last method is based on opening of the thiazole ring under basic conditions followed by double alkylation with ethyl 4-chloroacetoacetate. The benzothiazine underwent selective sulfur oxidation and subsequent hydrolysis, providing **III**.[17]

Our ongoing research is focused on the polymer-supported synthesis of pharmacologically relevant heterocyclic compounds. We have already reported nitrobenzenesulfonamide (Nos) chemistry and Fukuyama alkylation,[25] giving key building

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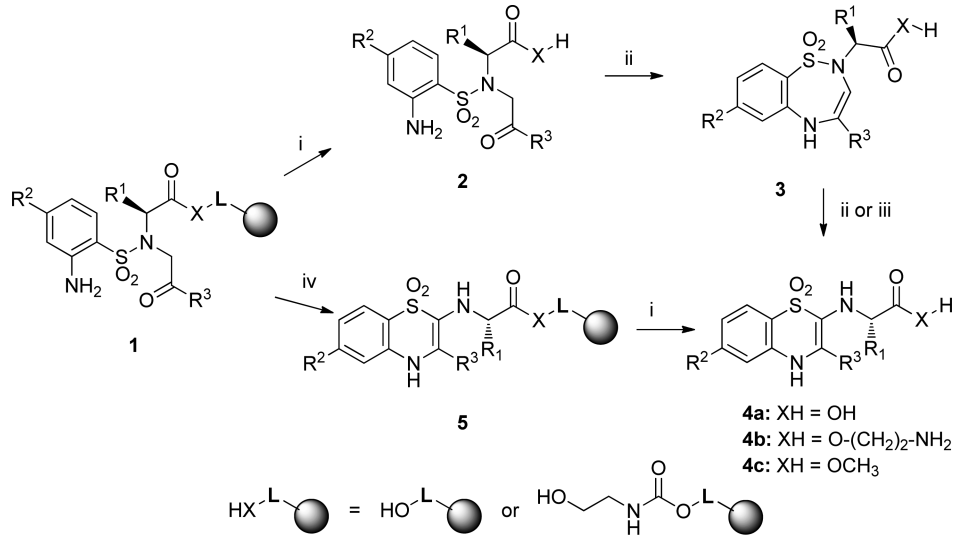
Scheme 1. Synthesis of Benzothiazine 1,1-Dioxides 4[a]



[a]Reagents: (i) 50% TFA in DCM; (ii) DMSO-d_6, room temperature (see the Supporting Information for the reaction time); (iii) DMSO, 70 °C (see the Supporting Information for the reaction time); (iv) 5% AcOH, DMSO, 80 °C, overnight.

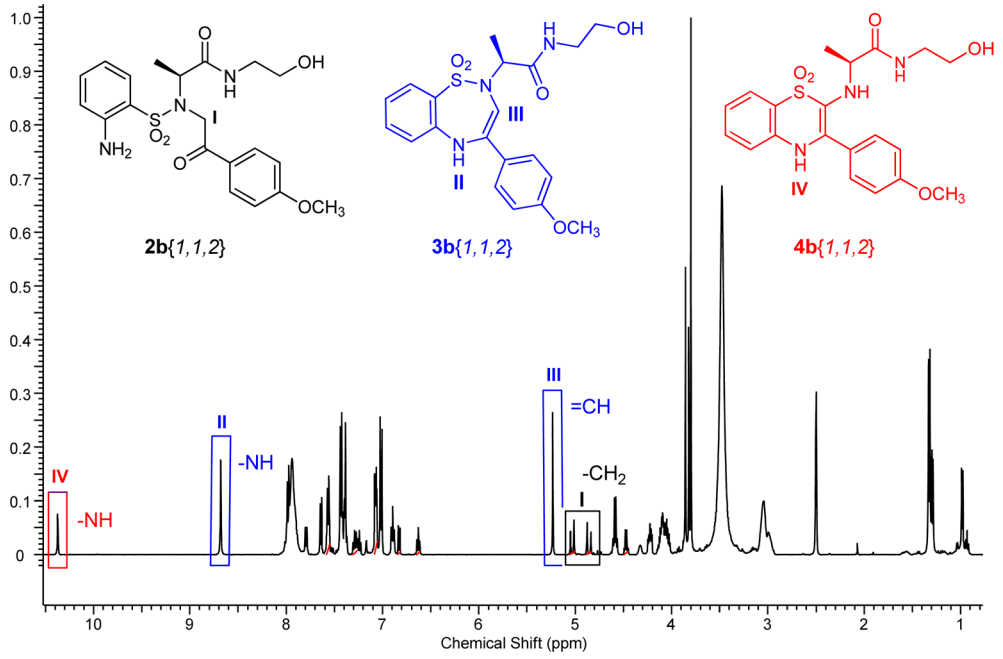


Figure 2. ^{1}H NMR spectrum of a mixture of **2b**{*1,1,2*}, **3b**{*1,1,2*}, and **4b**{*1,1,2*}.

blocks[26−32] and activating/protecting groups[33−35] in syntheses of diverse heterocycles. Here, we extend Nos chemistry into an unprecedented and efficient method for the preparation of pharmacologically relevant 4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides **III** via unanticipated ring contraction of dihydrobenzo[*f*]-[1,2,5]thiadiazepine 1,1-dioxides.

RESULTS AND DISCUSSION

Synthesis. We have recently reported an efficient synthetic route to 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides **3** (Scheme 1) using three commercially available building blocks: Fmoc-protected amino acids, 2-Nos-Cl, and bromo ketones.[36] Although the synthetic sequence can be carried out in solution, we took advantage of specific features of solid-phase synthesis: in particular, expeditious preparation due to isolation of resin-bound intermediates by simple filtration and washing of the resin. Accordingly, any high-boiling solvent can be used and then removed by simple filtration in a separate step.

Briefly, resin-bound amines were reacted with 2-Nos-Cl. The polymer-supported sulfonamides were then alkylated with bromo ketones. Compounds were cleaved from the resin with TFA in dichloromethane (DCM) and purified by reverse-phase HPLC. We evaluated the stability of target compounds at room temperature and at −20 °C in DMSO, which is typically used for high-throughput screening. Whereas no significant instability was observed at the lower temperature, a new compound formed at room temperature. This transformed product exhibited an MS ionization pattern identical with that of benzothiadiazepine dioxide and was eluted with a shorter

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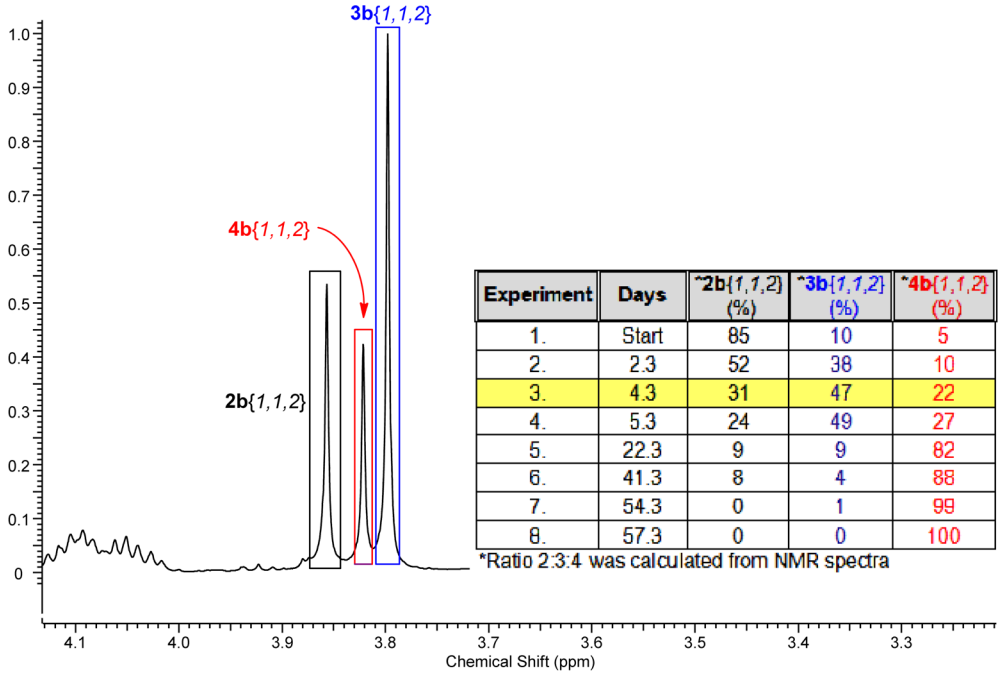

Experiment	Days	*2b{1,1,2} (%)	*3b{1,1,2} (%)	*4b{1,1,2} (%)
1.	Start	85	10	5
2.	2.3	52	38	10
3.	4.3	31	47	22
4.	5.3	24	49	27
5.	22.3	9	9	82
6.	41.3	8	4	88
7.	54.3	0	1	99
8.	57.3	0	0	100

Figure 3. Expansion of the ^{1}H NMR aliphatic region: methoxy protons of a mixture of **2b**{*1,1,2*}, **3b**{*1,1,2*}, and **4b**{*1,1,2*}.

retention time during LC/MS analysis. To obtain a preparative quantity of the new compound for structure determination, the DMSO solution was exposed to elevated temperature (70 °C) to accelerate the transformation. Almost quantitative conversion was observed.

The new compound was isolated and purified. Its structure was determined as benzothiazine 1,1-dioxide **4**. Because of the pharmacological relevance of benzothiazine 1,1-dioxides **4** and the unprecedented and clean rearrangement of benzothiadiazepine 1,1-dioxides **3** to **4**, we prepared a set of model compounds **1** and focused on the scope and limitations of this interesting and synthetically useful ring contraction. Model compounds **1** were prepared using six amino acids (Ala, Phe, Glu, Val, Leu, Gly) attached to Wang resin either directly or via an ethanolamine linker. We also used several types of Nos-Cl and bromo ketones with R^2 and R^3 groups containing neutral (H), electron-donating (OCH_3), and electron-withdrawing (CF_3) substituents.

Scope and Limitations. We assessed the effects of R groups and linkers on the ring contraction rate. Diagnostic peaks in the ^{1}H NMR spectra of compounds **2**–**4** allowed straightforward monitoring of the reaction (Figures 2 and 3). The type of amino acid, linker, and R^2 substituent did not significantly affect the rate of rearrangement (Table 1). In contrast, we observed a significant effect of the R^3 substituent. Whereas an electron-donating methoxy group at R^3 accelerated the reaction, a strongly electron withdrawing CF_3 group gave no product **4**{*1,1,3*}. The time course of rearrangement at room temperature for selected compounds is tabulated in the Supporting Information.

The experiments in solution provided important information concerning the rate and mechanism of the ring contraction. Nevertheless, from a preparative point of view, we wished to carry out the contraction on resin as the last step of the synthesis, thereby allowing isolation of the final compounds by cleavage from the polymer support. We evaluated several different reaction conditions and observed that 5% AcOH in DMSO at 80 °C overnight cleanly provided the expected products (Table 2). Synthesized compounds are given in Table 3.

Table 1. Effect of Substituents on the Formation of 4

entry	compound	amino acid	R^2	R^3	yield of **4** (%)[a]
1	**4a**{*1,1,1*}	Ala	H	H	10
2	**4a**{*1,1,2*}	Ala	H	OCH_3	56
3	**4a**{*1,1,3*}	Ala	H	CF_3	0
4	**4a**{*1,2,1*}	Ala	OCH_3	H	9
5	**4a**{*1,3,1*}	Ala	CF_3	H	20
6	**4a**{*2,1,1*}	Phe	H	H	42
7	**4b**{*1,1,1*}	Ala	H	H	54
8	**4b**{*1,1,2*}	Ala	H	OCH_3	82

[a]Calculated from ^{1}H NMR spectra after 23 days at room temperature.

Table 2. Reaction Conditions for Ring Contraction of Compound 1{*1,1,1*} on Resin

				yield (%)[a]	
entry	solvent	additive	*T* (°C)	SM	thiazine[a]
1	DMSO	5% H_2O	80	50	50
2	DMSO	5% AcOH	80	3	97
3	DMF	5% H_2O	80	99	<1
4	DMF	5% AcOH	80	90	10
5	DMSO	5% AcOH	70	92	8
6	DMSO	none	70	99	<1

[a]Relative ratio calculated from LC traces at 205–450 nm.

Structure Determination. The structure of **4** was unambiguously determined by analysis of 2D homonuclear (DQFCOSY and TOCSY) and heteronuclear (^{13}C/^{15}N HSQC and HMBC) NMR spectra. Proton connectivities were established from the DQFCOSY and TOCSY spectra. Resonances of carbon and nitrogen atoms with attached protons were assigned using ^{13}C and ^{15}N HSQC spectra, respectively. The ^{13}C HMBC spectrum was then used to assign

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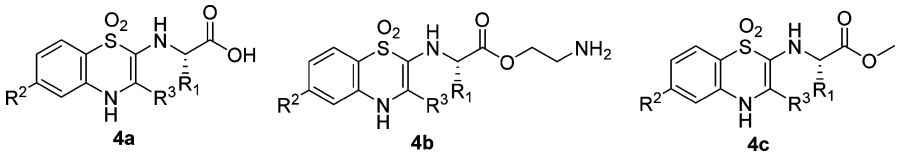
Table 3. Synthesized Benzothiadiazine 1,1-Dioxides



compound	R^1	R^2	R^3	method[a]	reaction time (h)	purity (%)[b]	yield (%)[c]
4a{*1,1,1*}	CH_3	H	Ph	B	16	65	41
4a{*1,1,4*}	CH_3	H	4-Cl-C_6H_4	B	16	40	25
4a{*1,1,5*}	CH_3	H	3,5-Cl_2-4-NH_2-C_6H_4	B	16	30	19
4b{*1,1,2*}	CH_3	H	4-CH_3O-C_6H_4	A	3.3	88	33
4b{*2,1,1*}	Bn	H	Ph	B	16	77	41
4b{*3,1,1*}	$(CH_2)_2CO_2H$	H	Ph	B	16	81	55
4b{*4,1,1*}	$CH(CH_3)_2$	H	Ph	B	16	65	35
4b{*5,1,1*}	$CH_2CH(CH_3)_2$	H	Ph	B	16	83	49
4b{*6,1,1*}	H	H	Ph	B	16	59	15
4c{*1,1,5*}	CH_3	H	3,5-Cl_2-4-NH_2-C_6H_4	B	16	21	12

[a]Methods: (A) ring contraction in DMSO at 70 °C; (B) ring contraction on resin at 80 °C. [b]Crude purity estimated from LC traces at 205−450 nm. [c]Yield of six-step synthesis calculated from the NMR spectra.

the signals of quaternary carbons and (together with the ^{15}N HMBC spectrum) to verify the connectivities inferred from the other spectra. In the ^{13}C-HMBC spectrum, the 7a proton signal (δ 10.37 ppm) exhibited cross peaks with the carbon signals at δ 114.72, 117.82, 123.06, 125.54, 136.82, and 141.03 ppm corresponding to C-5, CH-8, C-12, C-14, C-7, and C-6, respectively (Figure 4). The carbonyl C-3 signal (δ 172.75 ppm) exhibited cross peaks with the methyl CH_3-13, methylene CH_2-2, methine CH-4, and amide NH-5a proton signals. Additionally, the NH-5a proton signal displayed a cross peak with the C-6 carbon signal as well as the CH-15 and CH-19 proton signals. The ^{15}N HMBC spectrum revealed cross peaks between the NH_2-1a nitrogen signal and the methylene CH_2-2 proton signals, the NH-5a nitrogen and the CH_3-20 protons, and the NH-7a nitrogen and the CH-8 proton. The complete ^1H, ^{13}C, and ^{15}N resonance assignments for **4b**{*1,1,2*} are given in Table 1 in the Supporting Information.

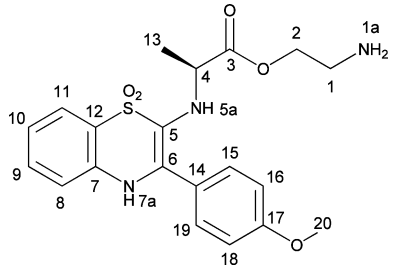
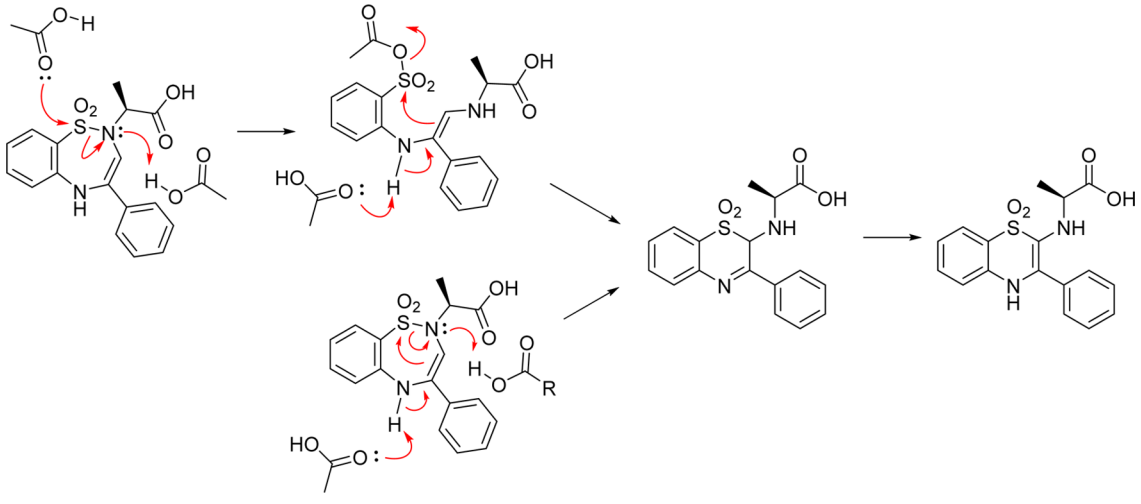


Figure 4. Numbering of atoms.

Unlike esters **4b**, ^1H NMR spectra of the free acids **4a** did not show the 5a proton resonance signal. To prove that this signal was absent due to a free acid, we esterified compound **4a**{*1,1,5*} and prepared the methyl ester **4c**. As expected, the ^1H NMR spectra of methyl ester **4c** exhibited this signal.

Mechanism of Rearrangement. Compounds **3** were purified by reverse phase HPLC using 0.1% aqueous TFA and MeCN. After purification the solution was lyophilized, and it contained residual traces of TFA. We initially observed spontaneous rearrangement of HPLC-purified benzothiadiazepine 1,1-dioxides **3** in DMSO-d_6 solution at room temperature. The on-resin cyclization experiments confirmed the effect of an acid (Table 2). On the basis of these results, we surmised that

Scheme 2. Proposed Mechanisms of 2-(Alkylamino)-3-aryl-4*H*-benzo[*b*][1,4]thiazine 1,1-Dioxide Formation



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the key step of the ring contraction is the attack of sulfur by the alkene electron pair, supported by the beneficial effect of electron-donating R groups (Scheme 2). There are two plausible pathways: ring opening followed by ring closure and direct ring contraction (suggested by one reviewer).

CONCLUSION

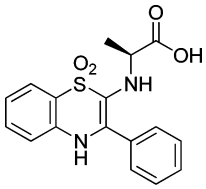
We report an unprecedented rearrangement of 2,5-dihydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxides to 2-(alkylamino)-3-aryl-4*H*-benzo[*b*][1,4]thiazine 1,1-dioxides via carbon−sulfur bond formation. The resin-bound acyclic substrates were readily accessible from commercially available building blocks in a short reaction sequence, and ring contraction occurred under mild conditions on a solid support. Structures were confirmed by 2D NMR. This solid-phase synthesis represents an efficient synthetic route to pharmacologically relevant heterocycles and is amenable to combinatorial synthesis.

EXPERIMENTAL SECTION

Solid-phase syntheses were performed in plastic reaction vessels (syringes, each equipped with a porous disk) using a manually operated synthesizer.[37] The volume of wash solvent was 10 mL/g of resin. For washing, the resin slurry was shaken with fresh solvent for at least 1 min before the solvent was changed. Commercially available Wang resin (100−200 mesh, 1.0 mmol/g) was used. Yields of crude products were calculated with respect to the loading of the first building block. The reaction conditions for the individual steps of the solid-phase synthesis of **1**, including cleavage and purification, have been reported previously.[36]

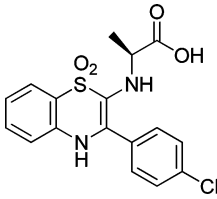
Benzothiazine 1,1-Dioxide (resin 5). Resin **1**[36] (250 mg) was washed (3 × DCM, 3 × DMSO). Five milliliters of 5% AcOH in DMSO was added, and the resin slurry was shaken in an incubator at 80 °C, overnight. The resin was subsequently washed (5 × DCM).

Analytical Data of Individual Compounds. *(S)-2-((1,1-Dioxido-3-phenyl-4H-benzo[b][1,4]thiazin-2-yl)amino)propanoic Acid (**4a**{1,1,1}).*



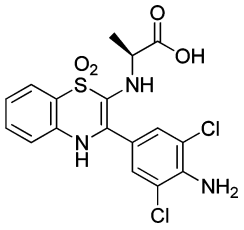
Yield: 34.6 mg (41%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (br. s., 1 H), 7.80 (dd, J = 8.2, 1.2 Hz, 1 H), 7.46−7.61 (m, 6 H), 7.41 (dd, J = 8.5, 0.5 Hz, 1 H), 7.22 (ddd, J = 8.1, 7.1, 1.0 Hz, 1 H), 3.34 (q, J = 6.9 Hz, 1 H), 0.85 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.4, 138.2, 137.2, 133.7, 131.9, 129.4, 129.3, 128.3, 122.4, 122.2, 121.9, 117.7, 116.1, 56.5, 18.5. HRMS (FAB): m/z calcd for $C_{17}H_{16}N_2O_4S$ [M + H]$^+$ 345.0904, found 345.0891.

*(S)-2-((3-(4-Chlorophenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino)propanoic Acid (**4a**{1,1,4}).*



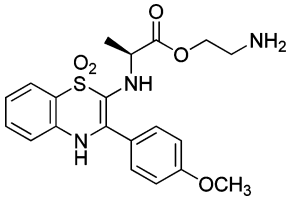
Yield: 22.3 mg (25%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.38 (s, 1 H), 7.81 (dd, J = 8.2, 1.5 Hz, 1 H), 7.62−7.67 (m, 2 H), 7.54−7.59 (m, 3 H), 7.38 (dd, J = 8.5, 0.6 Hz, 1 H), 7.25 (ddd, J = 8.1, 7.1, 1.1 Hz, 1 H), 3.56 (q, J = 6.9 Hz, 1 H), 0.95 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.8, 139.3, 136.9, 134.1, 132.2, 132.1, 131.5, 128.3, 123.0, 122.3, 122.2, 117.8, 115.5, 56.4, 18.4. HRMS (FAB): m/z calcd for $C_{17}H_{15}ClN_2O_4S$ [M + H]$^+$ 379.0514, found 379.0542.

*(S)-2-((3-(4-Amino-3,5-dichlorophenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino)propanoic Acid (**4a**{1,1,5}).*



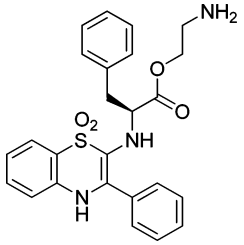
Yield: 19.8 mg (19%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (br. s., 1H), 7.77 (dd, J = 8.2, 1.2 Hz, 1 H), 7.51−7.57 (m, 3 H), 7.40 (dd, J = 8.5, 0.5 Hz, 1 H), 7.21 (ddd, J = 8.1, 7.1, 1.0 Hz, 1 H), 5.90 (s, 2 H), 3.45 (q, J = 6.9 Hz, 1 H), 0.94 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 175.1, 142.0, 137.0, 136.6, 131.8, 129.1, 122.6, 122.0, 121.9, 121.5, 117.8, 117.2, 115.8, 56.4, 18.5. HRMS (FAB): m/z calcd for $C_{17}H_{15}Cl_2N_3O_4S$ [M + H]$^+$ 428.0233, found 428.0218.

*(S)-2-Aminoethyl 2-((3-(4-Methoxyphenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino)propanoate (**4b**{1,1,2}).*



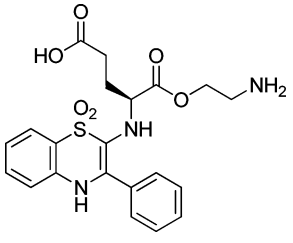
Yield: 6.9 mg (33%) of amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.36 (s, 1 H), 7.78 (dd, J = 8.1, 1.4 Hz, 1 H), 7.52−7.58 (m, 3 H), 7.41 (d, J = 7.9 Hz, 1 H), 7.23 (ddd, J = 8.1, 7.1, 1.0 Hz, 1 H), 7.03−7.08 (m, 2 H), 4.32 (d, J = 6.4 Hz, 1 H), 3.99−4.14 (m, 2 H), 3.81 (s, 3 H), 3.01−3.08 (m, 2 H), 0.97 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 172.7, 160.1, 141.0, 136.8, 132.0, 130.9, 125.4, 123.1, 122.3, 122.2, 117.8, 114.7, 113.6, 60.6, 57.5, 55.4, 37.9, 18.2. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{23}N_3O_5S$ [M + H]$^+$ 418.1431, found 418.1464.

*2-Aminoethyl (1,1-Dioxido-3-phenyl-4H-benzo[b][1,4]thiazin-2-yl)-L-phenylalaninate (**4b**{2,1,1}).*



Yield: 12.8 mg (41%) of amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.53 (s, 1 H), 7.81 (d, J = 8.2 Hz, 1 H), 7.63−7.60 (m, 2 H), 7.60−7.56 (m, 1 H), 7.55−7.51 (m, 3 H), 7.42 (d, J = 8.5 Hz, 1 H), 7.28−7.24 (m, 1 H), 7.18−7.11 (m, 3 H), 6.81 (d, J = 6.7 Hz, 2 H), 4.56 (d, J = 8.5 Hz, 1 H), 4.01 (td, J = 11.5, 5.5 Hz, 1 H), 3.92 (td, J = 11.5, 5.6 Hz, 1 H), 3.42−3.36 (m, 1 H), 2.98−2.92 (m, 2 H), 2.68−2.63 (m, 1 H), 2.62−2.57 (m, 1 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.0, 140.6, 136.9, 136.8, 133.3, 132.2, 129.6, 129.4, 128.9, 128.5, 128.2, 126.5, 123.0, 122.5, 122.3, 117.9, 115.8, 65.0, 60.3, 37.9. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{26}N_3O_4S$ [M + H]$^+$ 464.1639, found 464.1627.

*(S)-5-(2-Aminoethoxy)-4-((1,1-dioxido-3-phenyl-4H-benzo[b][1,4]thiazin-2-yl)amino)-5-oxopentanoic Acid (**4b**{3,1,1}).*



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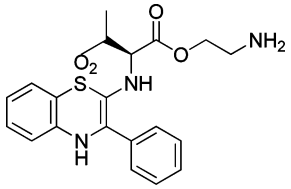
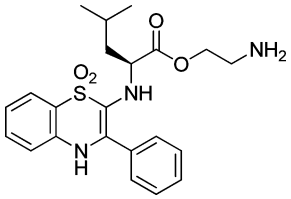
Yield: 19.6 mg (55%) of amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.48 (s, 1 H), 7.81 (d, J = 8.2 Hz, 1 H), 7.60−7.54 (m, 3 H), 7.53−7.48 (m, 3 H), 7.40 (d, J = 8.2 Hz, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 4.40 (d, J = 8.2 Hz, 1 H), 4.15−4.09 (m, 1 H), 4.05−3.99 (m, 1 H), 3.36−3.30 (m, 1 H), 3.06 (br. s., 2 H), 1.87−1.80 (m, 1 H), 1.73−1.66 (m, 1 H), 1.63−1.50 (m, 2 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 174.1, 172.1, 141.9, 136.8, 133.3, 132.3, 129.6, 129.5, 128.4, 123.3, 122.5, 122.3, 117.9, 115.3, 62.6, 60.7, 38.0, 29.2, 28.1. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{24}N_3O_6S$ $[M + H]^+$ 446.1380, found 446.1419.

*2-Aminoethyl (1,1-Dioxido-3-phenyl-4H-benzo[b][1,4]thiazin-2-yl)-L-valinate (**4b**{4,1,1}).*



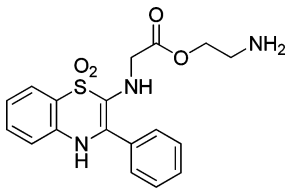
Yield: 11.5 mg (35%) of amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.46 (s, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 7.59−7.55 (m, 3 H), 7.54−7.48 (m, 3 H), 7.40 (d, J = 8.2 Hz, 1 H), 7.25 (t, J = 7.9 Hz, 1 H), 4.35 (d, J = 9.1 Hz, 1 H), 4.19−4.13 (m, 1 H), 4.09−4.02 (m, 1 H), 3.09 (br. s., 2 H), 2.98 (dd, J = 9.1, 6.5 Hz, 1 H), 1.64−1.56 (m, 1 H), 0.49 (d, J = 6.7 Hz, 3 H), 0.44 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (151 MHz, DMSO-*d6*): δ 171.8, 141.6, 136.8, 133.5, 132.2, 129.7, 129.5, 128.3, 123.2, 122.4, 122.2, 117.8, 116.0, 69.7, 60.3, 38.1, 31.3, 18.5, 18.2. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{26}N_3O_4S$ $[M + H]^+$ 416.1639, found 416.1620.

*2-Aminoethyl (1,1-Dioxido-3-phenyl-4H-benzo[b][1,4]thiazin-2-yl)-L-leucinate (**4b**{5,1,1}).*



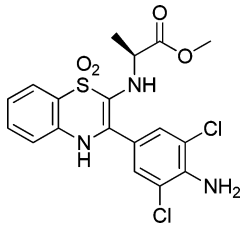
Yield: 13.5 mg (39%) of amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.46 (s, 1 H), 7.80 (d, J = 7.9 Hz, 1 H), 7.61−7.55 (m, 3 H), 7.54−7.49 (m, 3 H), 7.40 (d, J = 8.5 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 4.37 (d, J = 8.8 Hz, 1 H), 4.19−4.12 (m, 1 H), 4.10−4.02 (m, 1 H), 3.15−3.05 (m, 3 H), 1.31−1.24 (m, 1 H), 1.17−1.07 (m, 1 H), 0.66 (td, J = 14.4, 7.5 Hz, 1 H), 0.60−0.55 (m, 3 H), 0.48 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.5, 141.5, 136.8, 133.5, 132.1, 129.6, 129.4, 128.2, 123.2, 122.3, 122.2, 117.8, 116.0, 68.2, 60.3, 38.2, 38.0, 24.7, 14.9, 11.4. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{28}N_3O_4S$ $[M + H]^+$ 430.1795, found 430.1766.

*2-Aminoethyl (1,1-Dioxido-3-phenyl-4H-benzo[b][1,4]thiazin-2-yl)glycinate (**4b**{6,1,1}).*



Yield: 4.1 mg (15%) of amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.42 (s, 1 H), 7.82 (dd, J = 8.4, 1.1 Hz, 1 H), 7.63−7.59 (m, 2 H), 7.57 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H), 7.53−7.49 (m, 3 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.27−7.22 (m, 1 H), 4.16−4.12 (m, 2 H), 4.11 (t, J = 5.3 Hz, 1 H), 3.64 (d, J = 5.3 Hz, 2 H), 3.05 (br. s., 2 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.5, 140.7, 137.3, 133.6, 132.6, 130.0, 129.6, 128.8, 123.4, 122.7, 122.6, 118.2, 116.4, 61.1, 52.0, 38.4. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}N_3O_4S$ $[M + H]^+$ 374.1169, found 374.1160.

*(S)-Methyl 2-((3-(4-Amino-3,5-dichlorophenyl)-1,1-dioxido-4H-benzo[b][1,4]thiazin-2-yl)amino)propanoate (**4c**{1,1,5}).*



Yield: 13.4 mg (12%) of amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1 H), 7.78 (dd, J = 8.1, 1.3 Hz, 1 H), 7.53−7.58 (m, 3 H), 7.41 (dd, J = 8.5, 0.6 Hz, 1 H), 7.23 (ddd, J = 8.1, 7.1, 1.1 Hz, 1 H), 5.92 (s, 2 H), 4.28 (d, J = 6.1 Hz, 1 H), 3.53 (dq, J = 6.9, 6.1 Hz, 1 H), 3.44 (s, 3 H), 1.07 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 173.6, 142.1, 138.4, 136.8, 131.8, 129.2, 123.2, 122.2, 122.0, 121.1, 117.9, 117.1, 115.4, 57.0, 51.34, 18.4. HRMS (FAB): m/z calcd for $C_{18}H_{17}Cl_2N_3O_4S$ $[M + H]^+$ 442.0390, found 442.0380.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving details of experimental synthetic and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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