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SYNTHESIS OF A LIBRARY OF 1,5,2-DITHIAZEPINE 1,1-DIOXIDES. PART 2: ROUTES TO BICYCLIC SULTAMS

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Abstract – The synthesis of a library of bicyclic sultams incorporating the 1,5,2-dithiazepine 1,1-dioxide moiety is reported. Following scaffold synthesis via a one-pot sulfonylation/intramolecular thia-Michael protocol, several additional cyclization strategies have been realized enabling access to new bicyclic sultams.

Sultams have attracted attention recently due to their potent biological activity.[1,2] In particular, a number of 7-membered thiazepane 1,1-dioxide-containing compounds have shown interesting bioactivities. Some representative examples include mitogen-activated protein (MAP) kinases inhibitor **A**,[3] CCR2, CCR5, and/or CCR3 antagonist **B**,[4] PKC-theta inhibitor **C** for the treatment of inflammatory diseases,[5] thiadiazepinoindole **D**, an inhibitor of BACE-1 for treatment of Alzheimer's disease;[6] platelet aggregation inhibitor **E**,[7] derivatives of avermectin monosaccharide **F** and **G** with pesticidal properties,[8] and HIV integrase inhibitor **H** (Figure 1).[9]

Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

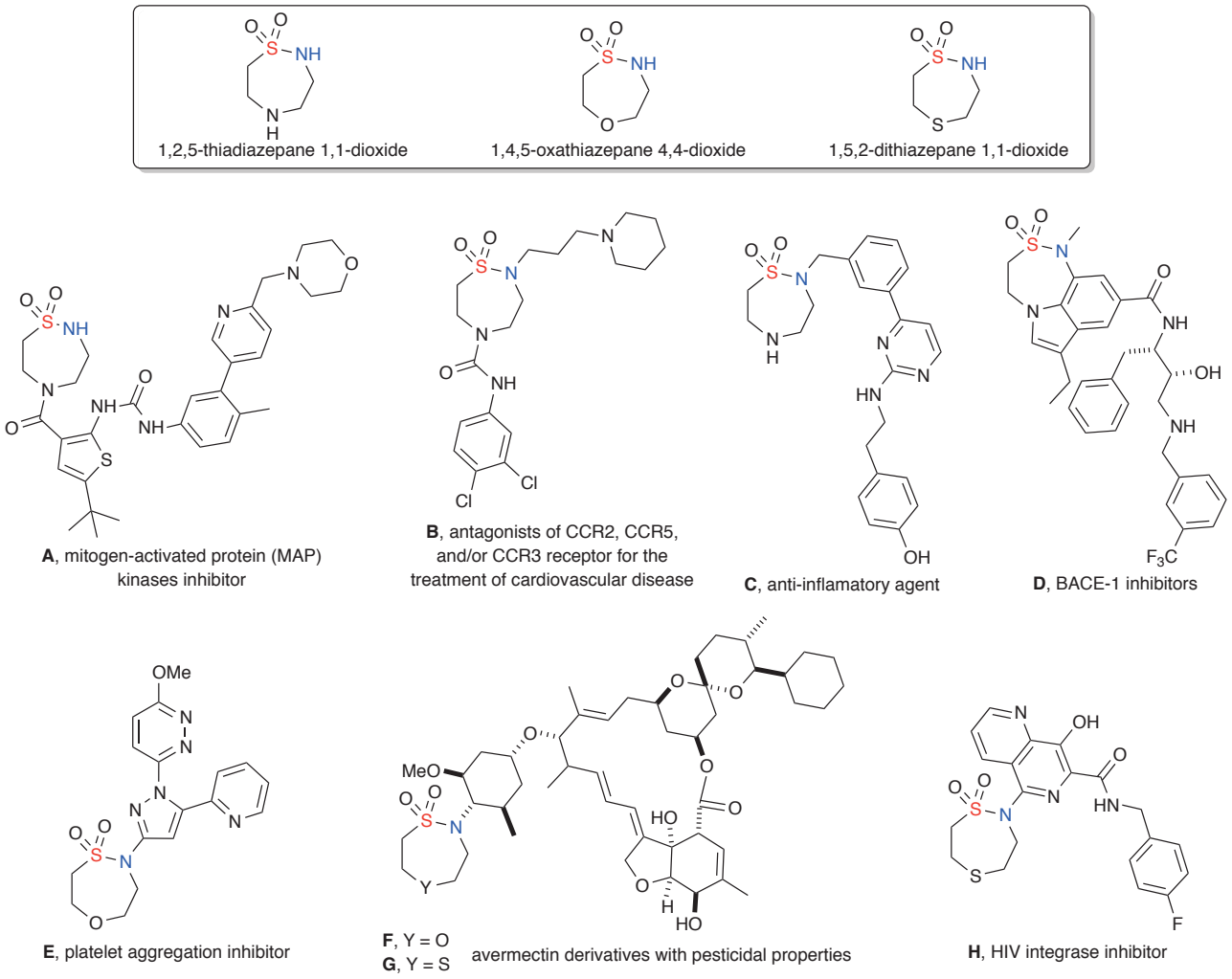
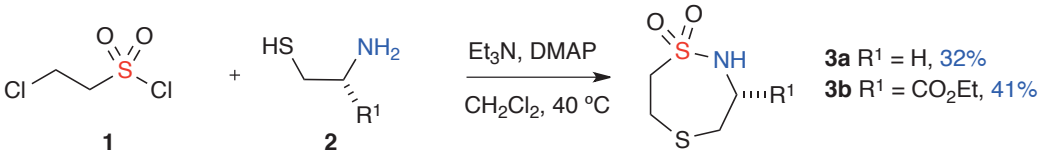


Figure 1. Bioactive thiazepanes

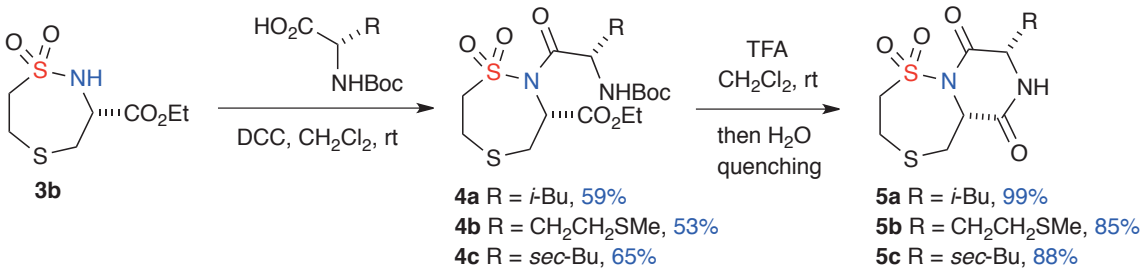
Despite the diverse biological activity of thiazepane 1,1-dioxides shown in Figure 1, the synthesis of bicyclic sultams incorporating this type of moiety is limited.[10,11] The reported methodologies for other non-benzofused bicyclic sultams include Diels-Alder reaction,[12] 1,3-dipolar cycloaddition,[13] Pauson Khand cyclization,[14] RCM,[15] Heck-type cyclization,[16] oxa-Michael and Baylis-Hillman reaction,[17] as well as oxidation from isothiazole.[18] In this regard, we sought simple installation of an additional ring to the previously reported 1,5,2-dithiazepine 1,1-dioxide scaffolds in order to enrich our collection of sultam chemotypes.

In previous work, we reported a one-pot sulfonylation/intramolecular thia-Michael protocol for the synthesis of 1,5,2-dithiazepine 1,1-dioxide scaffolds (Scheme 1). The reaction was carried out up to 40-gram scale (cysteine ethyl ester), and about 20 grams of the desired product **3b** was obtained after recrystallization ($CHCl_3$) in a single reaction step. With the large quantity of scaffold **3b** in hand, we set out to utilize the free sulfonamide N-H and a nearby ester group for initial functional group manipulations, followed by additional cyclization.



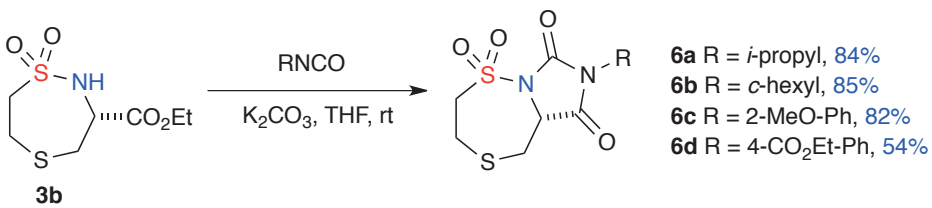
Scheme 1. The synthesis of core scaffolds **3**

Initial coupling of sultam **3b** and Boc-protected amino acids started investigations of secondary cyclization pathways to form fused sultams (Scheme 2). Subsequently, Boc removal from coupling product **4** with TFA and quenching with water enabled *in situ* cyclization to **5**. Three amino acids, leucine, methionine, and isoleucine were used to generate the three corresponding (*R*)-hexahydropyrazino[1,2-*b*][1,5,2]dithiazepine-6,9-dione 1,1-dioxides (**5a–c**) (Scheme 2).



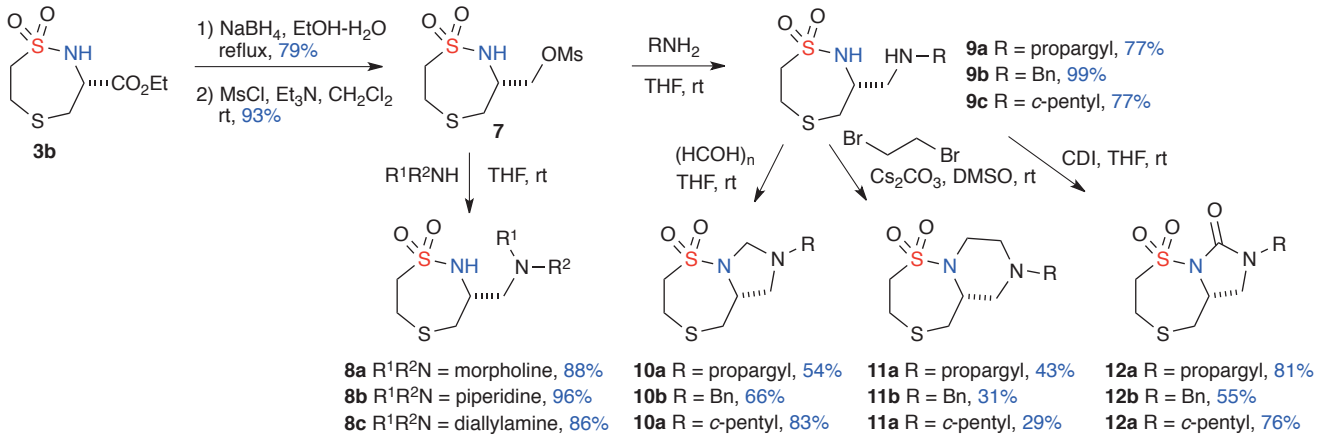
Scheme 2. Secondary cyclization strategies toward (*R*)-hexahydropyrazino[1,2-*b*][1,5,2]dithiazepine-6,9-dione 1,1-dioxides (**5a–c**)

A number of *N*-substituted (*R*)-dihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxides (**6a–d**) were synthesized by treatment of **3b** with isocyanates under basic condition (K_2CO_3) in THF (Scheme 3). In this reaction, nucleophilic addition of sulfonamide to the isocyanate formed urea intermediates, which were shown to rapidly undergo *in situ* cyclization at room temperature with the neighboring ester group to afford the bicyclic product in good to excellent yields.



Scheme 3. Secondary cyclization strategies toward (*R*)-dihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxides (**6a–d**)

Alternatively, the ester group in **3b** was reduced and mesylated to generate **7**, which could be further reacted with secondary amines in simple nucleophilic substitutions to form **8**, while reaction with primary amines afforded **9**, and thus providing additional cyclization manifolds to explore. To this end, sultams **9a–c** were reacted with 1,1'-carbonyldiimidazole (CDI), 1,2-dibromoethane, and paraformaldehyde to provide bicyclic products **10**, **11**, and **12**, respectively (Scheme 4). It should be mentioned that the yield for compounds **11a–c** were generally low. We envisioned it is because the difficulty in the alkylation of the sulfonamide due to its low nucleophilicity.



Scheme 4. Secondary cyclization strategies toward diverse bicyclic sultams

In conclusion, we have successfully developed five different strategies for the production of different bicyclic sultams, namely (*R*)-hexahydropyrazino[1,2-*b*][1,5,2]dithiazepine-6,9-dione 1,1-dioxides (**5**), (*R*)-dihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxides (**6**), (*R*)-hexahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine 1,1-dioxides (**10**), (*R*)-octahydropyrazino[1,2-*b*][1,5,2]dithiazepine 1,1-dioxides (**11**), and (*R*)-tetrahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepin-8(3*H*)-one 1,1-dioxides (**12**). To the best of our knowledge, these bicyclic systems containing the 1,5,2-dithiazepine 1,1-dioxide motif have not been previously reported. The compounds produced are under screening within the NIH Molecular Library Screening Network (NIH-MLSCN) and with other biological collaborators.

EXPERIMENTAL

All reactions were carried out under argon atmosphere. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, toluene, THF and CH_2Cl_2 were either purchased through Sigma-Aldrich or purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics*, 1996, **15**, 1518–1520). Et_3N was purified by passage over basic alumina or distilled over CaH and stored over KOH. Flash column chromatography was performed with

Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H, ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz, 100 MHz respectively as well as a Bruker DRX-500 spectrometer operating at 500 MHz, 125 MHz respectively and a Avance AV-III 500 with a dual carbon/proton (CPDUL) cryoprobe operating at 500 MHz, 125 MHz respectively. Observed rotations at 589 nm were measured using AUTOPOL IV Model automatic polarimeter. Weights were taken on a Flexiweigh Automatic Weigher; weight tolerance +/- 0.3mg. Samples were concentrated on a GeneVac EZ personal evaporator and placed under high vacuum for ≥ 2 hours before final weights were taken.

General procedure for the synthesis of 4 from scaffolds 3b.

To a solution of **3b** (0.5 mmol, 1 equiv.), Boc-protected amino acid (0.55 mmol, 1.1 equiv.) and DMAP (0.25 mmol, 0.5 equiv.) in CH_2Cl_2 (5 mL) was added DCC (0.55 mmol, 1.1 equiv.). After the reaction was stirred at rt for 14 h, the reaction was quenched with the addition of H_2O. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried (Na_2SO_4). The crude product was purified via flash chromatography.

(*R*)-Ethyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-methylpentanoyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4a).

White solid, yield 59%. mp 63–64 °C. $[\alpha]_D^{20}$ -43.0 (c 1.05, CH_2Cl_2). FTIR: 3377, 2959, 2934, 1742, 1697, 1506, 1367, 1161 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (dd, *J* = 10.1, 8.1 Hz, 1H), 5.22 (td, *J* = 11.0, 2.8 Hz, 1H), 5.03 (d, *J* = 9.8 Hz, 1H), 4.59 (ddd, *J* = 15.1, 11.3, 5.2 Hz, 1H), 4.26 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.18 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.67 (dt, *J* = 14.8, 2.9 Hz, 1H), 3.49–3.36 (m, 2H), 3.02–2.88 (m, 2H), 1.90–1.82 (m, 1H), 1.81–1.75 (m, 1H), 1.57–1.50 (m, 1H), 1.43 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 169.1, 156.1, 80.3, 62.0, 56.5, 54.3, 52.9, 41.1, 35.6, 28.3, 28.2, 24.9, 23.5, 20.8, 14.0. HRMS (ESI) *m/z* calculated for $C_{18}H_{32}N_2O_7S_2Na$ 475.1549 $(M+Na)^+$, found 475.1542.

(*R*)-Ethyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-(methylthio)butanoyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4b).

Colorless oil, yield 53%. $[\alpha]_D^{20}$ -45.6 (c 1.15, CH_2Cl_2). FTIR: 3385, 2967, 2932, 1742, 1703, 1504, 1366, 1163 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (dd, *J* = 10.0, 8.1 Hz, 1H), 5.20 (ddd, *J* = 30.4, 18.4, 6.6 Hz, 2H), 4.59–4.47 (m, 1H), 4.23 (ddq, *J* = 46.8, 10.7, 7.1 Hz, 2H), 3.68 (dt, *J* = 14.8, 2.8 Hz, 1H), 3.43 (qd, *J* = 15.6, 9.1 Hz, 2H), 3.03–2.89 (m, 2H), 2.74–2.56 (m, 2H), 2.37–2.24 (m, 1H), 2.13 (s,

3H), 1.89–1.78 (m, 1H), 1.43 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 168.9, 156.1, 80.6, 62.0, 56.6, 54.4, 53.7, 35.5, 32.7, 30.2, 28.3, 28.2, 15.3, 14.0. HRMS (ESI) *m/z* calculated for $C_{17}H_{30}N_2O_7S_3Na$ 493.1113 $(M+Na)^+$, found 493.1101.

(*R*)-Ethyl 2-((2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylpentanoyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4c).

Colorless oil, yield 65%. $[\alpha]_D^{20}$ -46.3 (c 0.95, CH_2Cl_2). FTIR: 3364, 2970, 2935, 1742, 1697, 1504, 1367, 1163 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (dd, *J* = 10.1, 8.1 Hz, 1H), 5.13 (dd, *J* = 10.2, 6.8 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.63–4.53 (m, 1H), 4.25 (ddd, *J* = 14.3, 8.9, 5.4 Hz, 1H), 4.18 (ddd, *J* = 14.3, 8.9, 5.4 Hz, 1H), 3.67 (dt, *J* = 15.0, 2.9 Hz, 1H), 3.43 (qd, *J* = 15.6, 9.1 Hz, 2H), 3.00–2.89 (m, 2H), 1.93–1.86 (m, 1H), 1.64 (ddd, *J* = 13.3, 7.6, 2.9 Hz, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20 (ddd, *J* = 13.4, 9.7, 7.3 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 169.2, 156.1, 80.3, 62.0, 57.5, 56.8, 54.0, 38.6, 35.7, 28.4, 28.2, 24.0, 15.5, 14.0, 11.2. HRMS (ESI) *m/z* calculated for $C_{18}H_{32}N_2O_7S_2Na$ 475.1549 $(M+Na)^+$, found 475.1547.

General procedure for the synthesis of 5 from 4.

To a solution of **4** (0.2 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) was added TFA (0.4 mL) at rt and kept stirring for 30 min, then added with H_2O (4 mL). The reaction was stirred at rt for 48 h and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with sat. aq. $NaHCO_3$, brine and dried (Na_2SO_4). The crude product was purified via flash chromatography.

(5a*R*,8*S*)-8-Isobutylhexahydropyrazino[1,2-*b*][1,5,2]dithiazepine-6,9-dione 1,1-dioxide (5a).

White solid, yield 99%. mp 187–188 °C. $[\alpha]_D^{20}$ -58.1 (c 1.20, CH_2Cl_2). FTIR: 3354, 2959, 2934, 1688, 1369, 1167, 731 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.89 (dd, *J* = 8.8, 1.8 Hz, 1H), 4.23–4.13 (m, 2H), 3.65–3.57 (m, 2H), 3.48 (dd, *J* = 15.9, 1.3 Hz, 1H), 3.03 (dt, *J* = 15.5, 3.5 Hz, 1H), 2.88 (ddd, *J* = 15.7, 12.9, 3.1 Hz, 1H), 1.97 (ddd, *J* = 15.0, 11.1, 3.9 Hz, 1H), 1.83–1.75 (m, 2H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 166.4, 56.3, 54.4, 52.4, 45.6, 41.0, 29.4, 24.0, 23.1, 20.8. HRMS (ESI) *m/z* calculated for $C_{11}H_{19}N_2O_4S_2$ 307.0786 $(M+H)^+$, found 307.0775.

(5a*R*,8*S*)-8-(2-(Methylthio)ethyl)hexahydropyrazino[1,2-*b*][1,5,2]dithiazepine-6,9-dione 1,1-dioxide (5b).

White solid, yield 85%. mp 192–193 °C. $[\alpha]_D^{20}$ -73.6 (c 0.85, CH_2Cl_2). FTIR: 3329, 2920, 1688, 1369, 1167, 731 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.89 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.44

(ddd, *J* = 9.0, 4.0, 2.5 Hz, 1H), 4.18 (ddd, *J* = 15.0, 12.9, 4.1 Hz, 1H), 3.66–3.58 (m, 2H), 3.51 (dd, *J* = 15.9, 1.4 Hz, 1H), 3.04 (dt, *J* = 15.5, 3.5 Hz, 1H), 2.89 (ddd, *J* = 15.7, 12.9, 3.1 Hz, 1H), 2.78 (ddd, *J* = 12.9, 6.7, 6.0 Hz, 1H), 2.71–2.64 (m, 1H), 2.51–2.43 (m, 1H), 2.18–2.12 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 166.0, 56.4, 54.9, 52.4, 41.1, 34.7, 30.0, 29.4, 15.0. HRMS (ESI) *m/z* calculated for $C_{10}H_{17}N_2O_4S_3$ 325.0350 $(M+H)^+$, found 325.0347.

(5a*R*,8*S*)-8-((*R*)-*sec*-Butyl)hexahydropyrazino[1,2-*b*][1,5,2]dithiazepine-6,9-dione 1,1-dioxide (5c). White solid, yield 88%. mp 195–196 °C. $[\alpha]_D^{20}$ -53.2 (c 0.75, CH_2Cl_2). FTIR: 3341, 2964, 2932, 1682, 1369, 1167, 733 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1H), 4.91–4.85 (m, 1H), 4.22–4.11 (m, 2H), 3.67 (dt, *J* = 15.0, 3.1 Hz, 1H), 3.62–3.59 (m, 2H), 3.01 (dt, *J* = 15.5, 3.7 Hz, 1H), 2.90 (ddd, *J* = 15.6, 12.7, 3.0 Hz, 1H), 2.25 (ddd, *J* = 13.9, 7.1, 3.5 Hz, 1H), 1.76–1.67 (m, 1H), 1.19 (ddd, *J* = 13.5, 10.2, 7.3 Hz, 1H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 166.2, 61.3, 56.5, 53.9, 40.9, 38.0, 29.1, 24.4, 15.5, 11.6. HRMS (ESI) *m/z* calculated for $C_{11}H_{19}N_2O_4S_2$ 307.0786 $(M+H)^+$, found 307.0779.

General procedure for the synthesis of 6 from 3b.

To a solution of **3b** (0.2 mmol, 1 equiv.) in THF (2 mL) was added K_2CO_3 (0.22 mmol, 1.1 equiv.), isocynate (0.22 mmol, 1.1 equiv.) at rt and kept stirring for 14 h. The reaction was quenched with the addition of H_2O. The mixture was extracted with EtOAc and combined organic layers were washed with brine and dried (Na_2SO_4). The crude product was purified via flash chromatography.

(*R*)-7-Isopropyldihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxide (6a). White solid, yield 84%. mp 157–158 °C. $[\alpha]_D^{20}$ -79.4 (c 0.85, CH_2Cl_2). FTIR: 2972, 2931, 1790, 1722, 1410, 1389, 1367, 1167, 756, 546 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 5.7, 1.2 Hz, 1H), 4.39 (hept, *J* = 6.9 Hz, 1H), 3.81–3.67 (m, 2H), 3.52 (dd, *J* = 15.4, 5.7 Hz, 1H), 3.48–3.44 (m, 1H), 3.02–2.90 (m, 2H), 1.45 (d, *J* = 5.1 Hz, 3H), 1.44 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 153.5, 58.2, 54.3, 45.4, 38.0, 28.1, 19.6, 19.2. HRMS (ESI) *m/z* calculated for $C_9H_{14}N_2O_4S_2Na$ 301.0293 $(M+Na)^+$, found 301.0290.

(*R*)-7-Cyclohexyldihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxide (6b). White solid, yield 85%. mp 169–170 °C. $[\alpha]_D^{20}$ -92.7 (c 0.10, CH_2Cl_2). FTIR: 2931, 1720, 1408, 1371, 1167, 1148, 754, 548 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 5.8, 1.1 Hz, 1H), 3.97 (tt, *J* = 12.4, 3.9 Hz, 1H), 3.80–3.67 (m, 2H), 3.52 (dd, *J* = 15.4, 5.8 Hz, 1H), 3.48–3.43 (m, 1H), 3.00–2.89 (m, 2H), 2.18–2.04 (m, 2H), 1.90–1.81 (m, 2H), 1.77–1.63 (m, 3H), 1.38–1.15 (m, 3H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 169.3, 153.6, 58.1, 54.3, 53.0, 38.0, 29.3, 28.8, 28.1, 25.7, 25.6, 24.9. HRMS (ESI) *m/z* calculated for $C_{12}H_{19}N_2O_4S_2$ 319.0786 $(M+H)^+$, found 319.0782.

(*R*)-7-(2-Methoxyphenyl)dihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine-6,8(3*H*,7*H*)-dione 1,1-dioxide (6c).

White solid, yield 82%. mp 216–217 °C. $[\alpha]_D^{20}$ -73.8 (c 0.85, CH_2Cl_2). FTIR: 2970, 2932, 1736, 1506, 1404, 1369, 1167, 750, 731, 548 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (td, *J* = 8.2, 1.7 Hz, 1H), 7.22 (td, *J* = 7.9, 1.6 Hz, 1H), 7.09–7.01 (m, 2H), 4.75 (ddd, *J* = 19.6, 5.5, 1.5 Hz, 1H), 3.88–3.71 (m, 5H), 3.67–3.55 (m, 2H), 3.06–2.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.2, 155.0, 152.6, 131.60, 129.4, 120.9, 112.2, 59.0, 55.9, 54.3, 38.1, 28.2. HRMS (ESI) *m/z* calculated for $C_{13}H_{14}N_2O_5S_2Na$ 365.0242 $(M+Na)^+$, found 365.0239.

(*R*)-Ethyl 4-(1,1-dioxido-6,8-dioxodihydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepin-7(3*H*,5*H*,8*H*)yl)-benzoate (6d).

White solid, yield 54%. mp 203–204 °C. $[\alpha]_D^{20}$ -12.8 (c 0.75, CH_2Cl_2). FTIR: 2982, 2930, 1738, 1398, 1369, 1279, 1167, 768, 748, 731, 721, 548 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.21–8.16 (m, 2H), 7.55–7.49 (m, 2H), 4.77 (dd, *J* = 5.5, 1.4 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.89–3.75 (m, 2H), 3.63 (qd, *J* = 15.5, 3.4 Hz, 2H), 3.08–2.98 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 165.4, 152.3, 134.0, 131.1, 130.6, 125.9, 61.4, 58.8, 54.4, 38.1, 28.3, 14.3. HRMS (ESI) *m/z* calculated for $C_{15}H_{16}N_2O_6S_2Na$ 407.0347 $(M+Na)^+$, found 407.0344.

General procedure for the synthesis of 7 from scaffolds 3b.

A solution of $NaBH_4$ (24 mmol, 4 equiv.) in 50% EtOH/H_2O (10 mL) was added to a suspension of **3b** (6 mmol, 1 equiv.) in 50% EtOH/H_2O (10 mL). After the reaction was stirred at 80 ºC for 4 h, solvent was evaporated to afford the crude alcohol, which was purified via flash chromatography. Mesyl chloride (4.8 mmol, 1.2 equiv.) and Et_3N (4.8 mmol, 1.2 equiv.) was added to a solution of the resulted alcohol (4 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) at 0 ºC. The reaction was warmed to rt and stirred for 2 h, and solvent was removed under reduced pressure. The crude product was purified via flash chromatography.

(*R*)-(1,1-Dioxido-1,5,2-dithiazepan-3-yl)methyl methanesulfonate (7).

White solid, yield 73% (over two steps). mp 97–98 °C. $[\alpha]_D^{20}$ +16.0 (c 1.00, CH_2Cl_2). FTIR: 2982, 2930, 1738, 1398, 1369, 1279, 1167, 768, 748, 731, 721, 548 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 4.26 (dd, *J* = 10.2, 7.4 Hz, 1H), 4.19 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.63–3.57 (m, 1H), 3.55–3.46 (m, 1H), 3.40 (ddd, *J* = 14.3, 8.3, 5.9 Hz, 1H), 3.16 (dd, *J* = 15.2, 5.3 Hz, 1H), 3.13 (s, 3H), 3.01 (dd, *J* = 15.2, 10.3 Hz,

1H), 2.95–2.90 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 72.6, 60.4, 54.7, 37.5, 37.0, 29.0. HRMS (ESI) *m/z* calculated for $C_6H_{13}NO_5S_3Na$ 297.9854 $(M+Na)^+$, found 297.9857.

General procedure for the synthesis of 8 and 9 from 7.

A solution of **7** (0.2 mmol, 1 equiv.) in MeCN (0.4 mL) was added amine (2 mmol, 10 equiv. for primary amine; 0.8 mmol, 4 equiv. for secondary amine). After the reaction was stirred at rt for 14 h, solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with H_2O and brine, and dried over Na_2SO_4. The crude product was purified via flash chromatography.

(*R*)-3-(Morpholinomethyl)-1,5,2-dithiazepane 1,1-dioxide (8a).

White solid, yield 88%. mp 148–150 °C. $[\alpha]_D^{20}$ -2.6 (c 0.80, CH_2Cl_2). FTIR: 3306, 2918, 2960, 2799, 1331, 1294, 1148, 1126, 1111 cm^{-1}. 1H NMR (500 MHz, CDCl3) δ 5.59 (s, 1H), 3.70–3.58 (m, 5H), 3.55 (dt, *J* = 14.0, 3.3 Hz, 1H), 3.30 (dd, *J* = 15.7, 5.4 Hz, 1H), 3.18 (ddd, *J* = 14.0, 10.4, 5.5 Hz, 1H), 2.86–2.81 (m, 2H), 2.64 (dd, *J* = 15.7, 1.3 Hz, 1H), 2.54 (dd, *J* = 10.7, 5.0 Hz, 2H), 2.47 (t, *J* = 11.7 Hz, 1H), 2.31 (d, *J* = 5.8 Hz, 2H), 2.12 (dd, *J* = 12.0, 4.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.8, 61.4, 58.7, 53.3, 46.6, 37.7, 28.5. HRMS (ESI) *m/z* calculated for $C_9H_{19}N_2O_3S_2$ 267.0837 $(M+H)^+$, found 267.0837.

(*R*)-3-(Piperidin-1-ylmethyl)-1,5,2-dithiazepane 1,1-dioxide (8b).

White solid, yield 96%. mp 151–152 °C. $[\alpha]_D^{20}$ -3.5 (c 0.95, CH_2Cl_2). FTIR: 3321, 2931, 1329, 1294, 1148, 1128 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.71–3.64 (m, 1H), 3.63–3.56 (m, 1H), 3.35 (dd, *J* = 15.6, 5.4 Hz, 1H), 3.24 (ddd, *J* = 14.0, 10.9, 5.0 Hz, 1H), 2.97–2.84 (m, 2H), 2.69 (dd, *J* = 15.6, 1.2 Hz, 1H), 2.54 (s, 2H), 2.46 (t, *J* = 11.7 Hz, 1H), 2.28 (s, 2H), 2.11 (dd, *J* = 12.0, 4.1 Hz, 1H), 1.57 (dq, *J* = 11.0, 5.6 Hz, 4H), 1.43 (dd, *J* = 11.0, 5.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 61.5, 58.6, 54.3, 46.9, 37.8, 28.5, 25.9, 24.2. HRMS (ESI) *m/z* calculated for $C_{10}H_{21}N_2O_2S_2$ 265.1044 $(M+H)^+$, found 265.1044.

(*R*)-3-((Diallylamino)methyl)-1,5,2-dithiazepane 1,1-dioxide (8c).

Pale yellow viscous oil, yield 86%. $[\alpha]_D^{20}$ -21.1 (c 0.95, CH_2Cl_2). FTIR: 3080, 2931, 1643, 1329, 1294, 1144, 1130 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89–5.76 (m, 2H), 5.65 (s, 1H), 5.20 (s, 2H), 5.19–5.16 (m, 2H), 3.61 (dddd, *J* = 11.9, 9.8, 4.6, 2.5 Hz, 2H), 3.32 (dd, *J* = 15.6, 5.3 Hz, 1H), 3.28–3.21 (m, 3H), 3.02 (dd, *J* = 14.1, 7.4 Hz, 2H), 2.92–2.88 (m, 2H), 2.71 (dd, *J* = 15.6, 1.8 Hz, 1H), 2.62 (dd, *J* = 12.4, 11.0 Hz, 1H), 2.30 (dd, *J* = 12.4, 4.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3, 118.5, 58.7, 56.6, 56.0, 47.8, 37.6, 28.5. HRMS (ESI) *m/z* calculated for $C_{11}H_{21}N_2O_2S_2$ 277.1044 $(M+H)^+$, found

277.1039.

(*R*)-3-((Prop-2-yn-1-ylamino)methyl)-1,5,2-dithiazepane 1,1-dioxide (9a).

Pale yellow oil, yield 77%. $[\alpha]_D^{20}$ -3.0 (c 1.00, CH_2Cl_2). FTIR: 3279, 2920, 2851, 1325, 1294, 1144, 1128, 717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.62–3.49 (m, 2H), 3.45–3.41 (m, 2H), 3.36–3.25 (m, 2H), 2.92–2.82 (m, 4H), 2.72 (dd, *J* = 12.0, 10.1 Hz, 1H), 2.25 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.3, 72.0, 58.7, 51.3, 50.5, 37.6, 37.5, 28.3. HRMS (ESI) *m/z* calculated for $C_8H_{16}N_2O_2S_2$ 235.0575 $(M+H)^+$, found 235.0580.

(*R*)-3-((Benzylamino)methyl)-1,5,2-dithiazepane 1,1-dioxide (9b).

Colorless oil, yield 99%. $[\alpha]_D^{20}$ -4.3 (c 0.60, CH_2Cl_2). FTIR: 3298, 2918, 2843, 1325, 1294, 1147, 1128, 737, 717, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.29 (dd, *J* = 7.8, 2.1 Hz, 3H), 3.79 (q, *J* = 13.3 Hz, 2H), 3.56 (ddt, *J* = 9.5, 5.2, 3.7 Hz, 2H), 3.35–3.26 (m, 2H), 2.93–2.87 (m, 2H), 2.81 (dd, *J* = 15.6, 3.3 Hz, 1H), 2.70 (qd, *J* = 12.0, 7.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 128.6, 128.1, 127.3, 58.7, 53.3, 52.0, 50.4, 37.7, 28.4. HRMS (ESI) *m/z* calculated for $C_{12}H_{19}N_2O_2S_2$ 287.0888 $(M+H)^+$, found 287.0883.

(*R*)-3-((Cyclopentylamino)methyl)-1,5,2-dithiazepane 1,1-dioxide (9c).

Colorless oil, yield 77%. $[\alpha]_D^{20}$ -4.3 (c 1.00, CH_2Cl_2). FTIR: 3294, 2953, 1329, 1294, 1148, 1126, 719 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.62–3.53 (m, 1H), 3.49 (qd, *J* = 5.3, 3.6 Hz, 1H), 3.34–3.25 (m, 2H), 3.22–2.96 (m, 2H), 2.93–2.86 (m, 2H), 2.81 (dd, *J* = 15.5, 3.5 Hz, 1H), 2.66 (dd, *J* = 7.2, 4.7 Hz, 1H), 1.88–1.78 (m, 2H), 1.74–1.63 (m, 2H), 1.59–1.50 (m, 2H), 1.34–1.23 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.5, 58.7, 51.5, 50.9, 37.7, 33.4, 32.9, 28.4, 23.9, 23.7. HRMS (ESI) *m/z* calculated for $C_{10}H_{21}N_2O_2S_2$ 265.1044 $(M+H)^+$, found 265.1049.

General procedure for the synthesis of 10.

A solution of **9** (0.2 mmol, 1 equiv.) in DCM (1 mL) was added Na_2SO_4 (0.6 mmol, 3 equiv.) followed by paraformaldhyde (0.6 mmol, 3 equiv.) at rt. After the reaction was warmed to 40 ºC and stirred for 14 h, the solid was removed by filtration. The solution was concentrated to get the crude product, which was purified via flash chromatography.

(*R*)-7-(Prop-2-yn-1-yl)hexahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine 1,1-dioxide (10a).

White solid, yield 54%. mp 129–130 °C. $[\alpha]_D^{20}$ -2.7 (c 0.90, CH_2Cl_2). FTIR: 3275, 2920, 2824, 1335, 1298, 1165, 1148, 1126, 1072, 868, 717, 669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.44 (d, *J* = 5.7 Hz,

1H), 4.21 (d, *J* = 5.8 Hz, 1H), 4.15–4.09 (m, 1H), 3.59 (dt, *J* = 14.5, 3.1 Hz, 1H), 3.48 (dd, *J* = 4.3, 2.4 Hz, 2H), 3.42 (dd, *J* = 15.8, 4.7 Hz, 1H), 3.33–3.25 (m, 2H), 2.99 (dd, *J* = 10.9, 9.3 Hz, 1H), 2.93 (ddd, *J* = 15.0, 12.5, 2.6 Hz, 1H), 2.88–2.81 (m, 2H), 2.31 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.5, 73.5, 70.9, 57.5, 55.2, 54.0, 42.4, 38.3, 28.0. HRMS (ESI) *m/z* calculated for $C_{13}H_{16}N_2O_3S_2Na$ 335.0500 $(M+Na)^+$, found 335.0506.

(*R*)-7-Benzylhexahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine 1,1-dioxide (10b).

White solid, yield 66%. mp 112–113 °C. $[\alpha]_D^{20}$ +4.0 (c 1.00, CH_2Cl_2). FTIR: 2920, 2812, 1337, 1163, 1148, 1126, 1070, 984, 868, 741, 717, 548 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.38 (d, *J* = 6.0 Hz, 1H), 4.17–4.09 (m, 2H), 3.76 (dd, *J* = 32.0, 12.8 Hz, 2H), 3.58 (dt, *J* = 14.5, 2.8 Hz, 1H), 3.43 (dd, *J* = 15.6, 4.1 Hz, 1H), 3.26 (ddd, *J* = 14.7, 12.6, 3.9 Hz, 1H), 3.19 (dd, *J* = 11.0, 6.4 Hz, 1H), 2.96–2.90 (m, 1H), 2.90–2.82 (m, 2H), 2.80 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 128.8, 128.5, 127.6, 71.9, 58.5, 58.4, 55.2, 53.7, 38.4, 28.1. HRMS (ESI) *m/z* calculated for $C_{13}H_{19}N_2O_2S_2$ 299.0888 $(M+H)^+$, found 299.0875.

(*R*)-7-Cyclopentylhexahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepine 1,1-dioxide (10c).

White solid, yield 83%. mp 77–78 °C. $[\alpha]_D^{20}$ -8.5 (c 1.00, CH_2Cl_2). FTIR: 2955, 2868, 2804, 1337, 1177, 1148, 1072, 868, 717 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (d, *J* = 4.8 Hz, 1H), 4.15–4.07 (m, 1H), 3.94 (d, *J* = 4.9 Hz, 1H), 3.60–3.53 (m, 1H), 3.40 (dd, *J* = 15.7, 4.7 Hz, 1H), 3.33–3.23 (m, 2H), 2.92 (ddd, *J* = 15.1, 12.4, 2.5 Hz, 1H), 2.87–2.74 (m, 3H), 2.70 (t, *J* = 9.8 Hz, 1H), 1.89–1.69 (m, 4H), 1.61–1.53 (m, 2H), 1.51–1.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.1, 63.5, 58.0, 55.1, 54.7, 38.4, 31.9, 31.7, 28.1, 24.1, 23.9. HRMS (ESI) *m/z* calculated for $C_{11}H_{21}N_2O_2S_2$ 277.1044 $(M+H)^+$, found 277.1034.

General procedure for the synthesis of 11.

A solution of **9** (0.3 mmol, 1 equiv.) in DMSO (1.5 mL) was added 1,2-dibromoethane (0.36 mmol, 1.2 equiv.) and stirred at rt for 14 h. The reaction was quenched with addition of H_2O and the mixture was extracted with EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). The crude product was purified via flash chromatography.

(*R*)-7-(Prop-2-yn-1-yl)octahydropyrazino[1,2-*b*][1,5,2]dithiazepine 1,1-dioxide (11a).

Brown solid, yield 43%. mp 103–105 °C. $[\alpha]_D^{20}$ -14.4 (c 0.80, CH_2Cl_2). FTIR: 3273, 2922, 2822, 1329, 1296, 1150, 1134, 1055, 959, 729 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75–3.57 (m, 3H), 3.43–3.26 (m, 4H), 3.24–3.13 (m, 1H), 2.99–2.81 (m, 3H), 2.74–2.54 (m, 4H), 2.28 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 78.0, 73.8, 59.0, 55.3, 51.7, 46.8, 35.1. HRMS (ESI) *m/z* calculated for $C_{10}H_{17}N_2O_2S_2$ 261.0731 $(M+H)^+$, found 261.0721.

(*R*)-7-Benzyloctahydropyrazino[1,2-*b*][1,5,2]dithiazepine 1,1-dioxide (11b).

Colorless oil, yield 31%. $[\alpha]_D^{20}$ -16.2 (c 0.50, CH_2Cl_2). FTIR: 2922, 2812, 1344, 1331, 1296, 1150, 1138, 960, 729 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 4.00 (s, 1H), 3.68–3.60 (m, 3H), 3.53 (dd, *J* = 44.1, 13.1 Hz, 2H), 3.38 (dd, *J* = 14.3, 9.1 Hz, 2H), 3.10 (dd, *J* = 14.4, 6.1 Hz, 1H), 2.94 (ddd, *J* = 15.9, 10.5, 2.1 Hz, 1H), 2.84 (ddd, *J* = 16.0, 6.0, 2.8 Hz, 1H), 2.69 (d, *J* = 10.4 Hz, 1H), 2.59–2.52 (m, 1H), 2.44 (dd, *J* = 11.4, 3.0 Hz, 1H), 2.41 (d, *J* = 11.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 128.9, 128.4, 127.3, 62.5, 58.9, 56.2, 53.0, 35.0, 24.8. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}N_2O_2S_2$ 313.1044 $(M+H)^+$, found 313.1040.

(*R*)-7-Cyclopentyloctahydropyrazino[1,2-*b*][1,5,2]dithiazepine 1,1-dioxide (11c).

White solid, yield 29%. mp 198–100 °C. $[\alpha]_D^{20}$ -18.0 (c 0.55, CH_2Cl_2). FTIR: 2955, 2868, 2808, 1331, 1294, 1277, 1150, 959, 729 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 1H), 3.75–3.51 (m, 3H), 3.42–3.27 (m, 2H), 3.17 (dd, *J* = 14.6, 6.0 Hz, 1H), 2.93 (tt, *J* = 16.4, 4.2 Hz, 1H), 2.87–2.80 (m, 1H), 2.88–2.42 (m, 5H), 1.84–1.78 (m, 2H), 1.72–1.64 (m, 2H), 1.59–1.52 (m, 2H), 1.44–1.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.7, 59.0, 55.7, 51.9, 35.5, 30.3, 24.0, 24.0. HRMS (ESI) *m/z* calculated for $C_{12}H_{23}N_2O_2S_2$ 291.1201 $(M+H)^+$, found 291.1206.

General procedure for the synthesis of 12.

A solution of **9** (0.2 mmol, 1 equiv.) in THF (2 mL) was added carbonyldiimidazole (0.3 mmol, 1.5 equiv.) at 0 ºC. After the reaction was warmed to 40 ºC and stirred for 14 h, the reaction was quenched with addition of H_2O. The mixture was extracted with EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). The crude product was purified via flash chromatography.

(*R*)-7-(Prop-2-yn-1-yl)tetrahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepin-8(3*H*)-one 1,1-dioxide (12a).

White solid, yield 81%. Decomposed above 150 ºC. $[\alpha]_D^{20}$ -91.1 (c 0.75, CH_2Cl_2). FTIR: 2978, 2922, 1726, 1358, 1161, 1126, 746, 554 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50–4.41 (m, 1H), 4.12 (t, *J* = 2.4 Hz, 2H), 3.89–3.78 (m, 2H), 3.62 (dt, *J* = 14.9, 2.9 Hz, 1H), 3.54 (dd, *J* = 15.6, 5.1 Hz, 1H), 3.21 (dd, *J* = 9.2, 3.4 Hz, 1H), 2.98–2.83 (m, 3H), 2.31 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 76.3, 73.6, 54.0, 50.5, 47.6, 42.7, 33.0, 28.2. HRMS (ESI) *m/z* calculated for $C_9H_{12}N_2O_3S_2Na$ 283.0187 $(M+Na)^+$, found 283.0183.

(*R*)-7-Benzyltetrahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepin-8(3*H*)-one 1,1-dioxide (12b).

White solid, yield 55%. decomposed above 160 °C. $[\alpha]_D^{20}$ -34.1 (c 0.75, CH_2Cl_2). FTIR: 2905, 1726, 1356, 1161, 1126, 746, 554 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 4.53 (d, *J* = 15.0 Hz, 1H), 4.43–4.35 (m, 2H), 3.93 (ddd, *J* = 14.9, 12.6, 4.3 Hz, 1H), 3.65 (dt, *J* = 14.9, 2.9 Hz, 1H), 3.57 (t, *J* = 9.5 Hz, 1H), 3.52 (dd, *J* = 15.6, 5.1 Hz, 1H), 3.00–2.86 (m, 3H), 2.80 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 135.1, 128.8, 128.3, 128.0, 54.0, 50.3, 48.0, 47.6, 42.8, 28.3. HRMS (ESI) *m/z* calculated for $C_9H_{15}N_2O_2S_2$ 247.0575 $(M+H)^+$, found 247.0572.

(*R*)-7-Cyclopentyltetrahydro-2*H*-imidazo[1,5-*b*][1,5,2]dithiazepin-8(3*H*)-one 1,1-dioxide (12c).

White solid, yield 76%. mp 193–194 °C. $[\alpha]_D^{20}$ -36.9 (c 1.15, CH_2Cl_2). FTIR: 2957, 2870, 1720, 1356, 1161, 746, 554 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.41–4.38 (m, 1H), 4.35 (dd, *J* = 16.1, 8.1 Hz, 1H), 3.91 (ddd, *J* = 14.9, 12.1, 4.8 Hz, 1H), 3.71 (t, *J* = 9.4 Hz, 1H), 3.60 (dt, *J* = 14.9, 2.9 Hz, 1H), 3.54 (dd, *J* = 15.6, 5.0 Hz, 1H), 3.06 (dd, *J* = 9.3, 3.0 Hz, 1H), 2.96–2.84 (m, 3H), 1.96–1.81 (m, 2H), 1.74–1.59 (m, 4H), 1.56–1.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 53.8, 53.6, 50.2, 44.9, 43.2, 28.6, 28.3, 28.2, 24.1, 24.1. HRMS (ESI) *m/z* calculated for $C_{11}H_{18}N_2O_3S_2Na$ 313.0657 $(M+Na)^+$, found 313.0651.

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