Reactions of *o*-Aminothiophenol and *o*-Aminophenyl Disulfide with Itaconic Anhydride and (–)-Dimenthyl Itaconate: Access to Enantiomerically Pure 1,5-Benzothiazepines and Benzothiazolyl-2-methylacrylic Acid[1]

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Abstract: A facile chemo- and regioselective reactions of *o*-aminothiophenol (*o*-ATP) with itaconic anhydride is described. 1,5-Benzothiazepinyl-3-acetic acid is obtained in 81% yield via the exclusive Michael type addition of the thiol unit from *o*-ATP to the carbon–carbon double bond in itaconic anhydride followed by an intramolecular anhydride ring opening with an amine unit. The moderately stereoselective Michael type addition of the thiol unit from *o*-ATP to (–)-dimenthyl itaconate to obtain a mixture of diastereomers in a 7:3 ratio in 82% yield has been demonstrated. The reductive sulfur–sulfur bond cleavage in the dicarboxylic acid, 2-({2-[2-(3-carboxybut-3-enoylamino)phenyldisulfanyl]phenylcarbamoyl}methyl)acrylic acid, to the corresponding benzothiazolyl-2-methylacrylic acid in 84% yield, instead of the desired benzothioazocine is also reported.

Key words: *o*-aminothiophenol, itaconic anhydride, dimenthyl itaconate, chemo-, regio- and stereoselective reactions, benzothiazepines, benzothiazoles, synthesis

Heterocycles play a pivotal role in pharmaceutical and agrochemical industries.[2] The 1,5-benzothiazepines are known to have antimitochondrial sodium–calcium exchanger (mNCE),[3a] angiotensin converting enzyme inhibitor,[3b] anti-inflammatory,[3c] anticancer,[3d] vasodilating,[3e] antihypertensive,[3f] platelet aggregation inhibitory,[3g] antipsychotic,[3h] antidiabetic,[3i] cardioprotective,[3j] antifungal,[3k] antibacterial[3l] and anti-HIV[3m] activities. Development of new facile routes to these seven-membered 1,5-benzothiazepines is a challenging task of current interest.[4] To date, the nucleophilic reactions of a variety of cyclic anhydrides/imides with *ortho*-aminothiophenol (*o*-ATP) have been used to design structurally interesting and biologically important five and six-membered thioaza-heterocyclic systems via the intramolecular Michael addition, condensation and dehydration pathway[5] (Figure 1). In continuation of our studies[6] on cyclic anhydride chemistry to design bioactive natural and unnatural heterocyclic compounds, we felt that, with a proper combination of reactivity and selectivity, the itaconic anhydride (**2**) and *o*-ATP (**1**) could be used as potential building blocks to synthesize higher-membered heterocycles. We now report an easy access to enantiomerically pure 1,5-benzothiazepines and benzothiazolylmethylacrylic acid starting from anhydride **2** and *o*-ATP (**1**) (Schemes 1– 3).

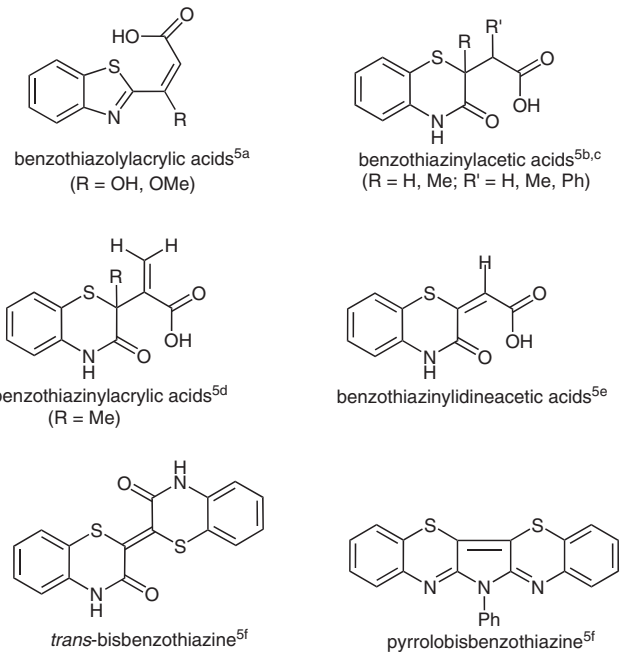

Figure 1 Benzothiazoles and benzothiazines designed from *o*-aminothiophenol and maleic anhydrides/maleimide

The Michael-type additions of aromatic thiols to activated carbon–carbon double bonds and nucleophilic ring opening of cyclic anhydrides with primary aromatic amines are well known in the litrature.[7,8] We envisaged that in the reaction of itaconic anhydride (**2**) with *o*-ATP (**1**), the Michael type addition of thiol to a highly activated carbon–carbon double bond in itaconic anhydride (**2**) followed by an intramolecular nucleophilic ring opening of an adjacent anhydride carbonyl with an amine moiety would provide benzothiazepinylacetic acid **4a**. However, the first nucleophilic regioselective ring opening of anhydride **2** with *o*-ATP (**1**) at the unconjugated carbonyl with primary amine moiety followed by intramolecular dehydrative condensation/Michael type addition of thiol unit could also provide an easy access to the benzothiazole/benzothioazocine system. Hence, we performed the reaction of anhydride **2** with *o*-ATP (**1**) in tetrahydrofuran at room temperature to test this reaction and obtained a sin-

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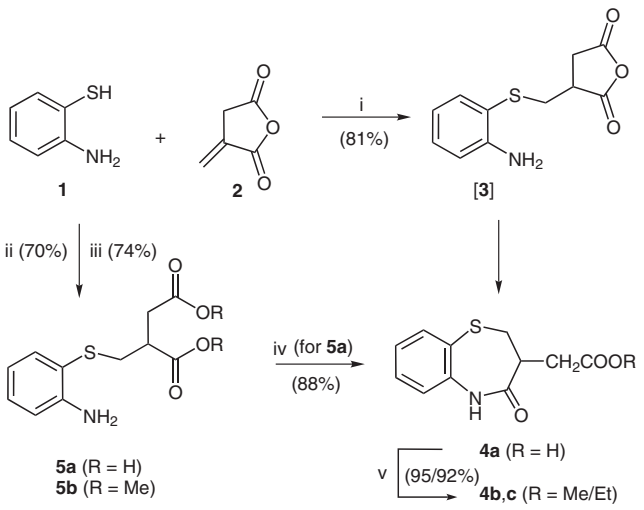
gle product in 81% yield (Scheme 1). The ^{1}H and ^{13}C NMR data of the product revealed a very clean formation of Michael type addition–condensation/condensation–Michael-type addition products **4a/16**, ruling out the formation of thiazole **15** (Scheme 3). It was difficult to conclusively assign the structure **4a** or **16** to the formed product on the basis of NMR data and hence we carried out the reaction of itaconic acid with *o*-ATP (**1**) at room temperature and obtained the Michael adduct **5a** in 70% yield. Similarly the reaction of dimethyl itaconate with *o*-ATP (**1**) also furnished the desired adduct **5b** in 74% yield. The water soluble carbodimide, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), induced regioselective intramolecular dehydrative cyclization of diacid **5a** to give the same product in 88% yield, which was earlier obtained from the reaction of **1** and **2** (see above). Since the formation of seven-membered rings are preferred over the formation of 8-membered rings,[9] we propose here the formation of benzothiazepinylacetic acid **4a**. The benzothiazepinylacetic acid **4a** was further characterized as its methyl and ethyl esters **4b** and **4c**. Finally, we confirmed the formation of seven-membered benzothiazepine **4a** by X-ray crystallographic data (Figure 2) ruling out the possibility of formation of the eight-membered compound benzothioazocine **16**. From these observations we propose that in the reaction of itaconic anhydride (**2**) with *o*-ATP (**1**), chemoselective Michael type addition of thiol takes place first to form the unisolable intermediate **3**, the amine moiety of which condenses in an intramolecular fashion with the adjacent anhydride carbonyl to furnish the benzothiazepine **4a**. Herein, an addition of thiol to the carbon–carbon double bond on an anhydride system before the anhydride ring opening with an amine moiety is shown as an example of delicately balanced selectivity.

Next, we planned to study the stereoselective addition of thiol from *o*-ATP (**1**) to the itaconate system and prepared



Scheme 1 *Reagents and conditions*: (i) THF, r.t., 12 h (81%); (ii) itaconic acid, THF, r.t., 36 h (70%); (iii) dimethyl itaconate, THF, r.t., 24 h (74%); (iv) EDCI, DMAP (cat.), THF, r.t., 4 h (88%); (v) MeOH/EtOH, H^{+}/H_2SO_4, 50 °C, 2 h (95/92%).

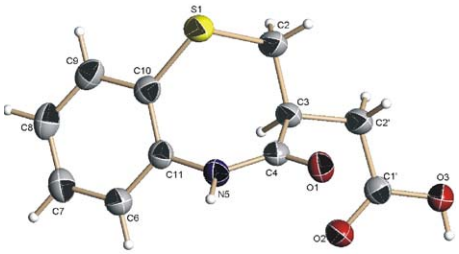
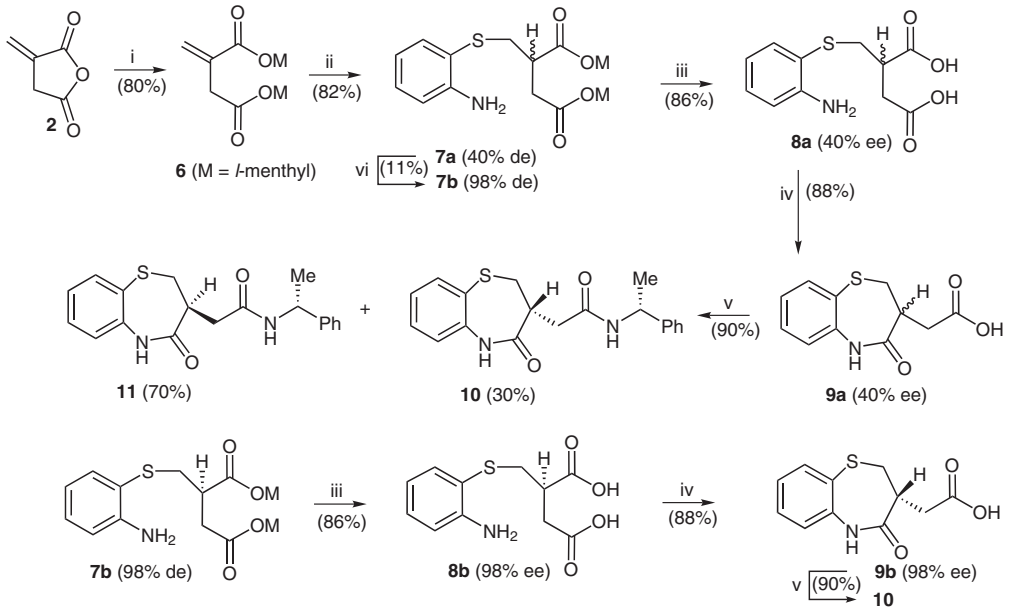


Figure 2 ORTEP diagram of **4a**[10]

the (–)-dimenthyl itaconate (**6**) from the reaction of itaconic anhydride (**2**) with natural (–)-menthol in 80% yield (Scheme 2). In our hands the reaction of *o*-ATP (**1**) with dimenthyl ester **6** in THF at room temperature and also under reflux condition was not successful and the TLC of the reaction mixture indicated the clear presence of both the starting materials along with slight formation of the corresponding disulfide **12** (Scheme 3). The stereoselective reaction of *o*-ATP (**1**) with the chiral diester **6** in glacial acetic acid at room temperature furnished the desired adduct **7a** in 82% yield in 36 hours. The ^{1}H NMR data of product **7a** revealed that the reaction was moderately stereoselective and the mixture of two diastereomers had formed in nearly 7:3 ratio (from the comparison of the relative integrations of one of the α-methyl protons). The TLC of the mixture of diastereomers in **7a** did not show any resolution and separation of these two diastereomers by flash column chromatography was also not successful in our hands. The adduct **7a** on acid-catalyzed hydrolysis gave the diacid **8a** in 86% yield. As expected, the carbodiimide EDCI induced regioselective ring closure of **8a** yielded the 1,5-benzothiazepinyl-1,3-acetic acid (**9a**) in 88% yield. Finally, for the separation of the two enantiomers of **9a** and their stereochemical assignments, we transformed **9a** into two diastereomers **10** and **11** in 90% yield, by reacting **9a** with (+)-(*R*)-phenylethylamine. The mixture of diastereomers **10** and **11** was easily separated by flash column chromatography to obtain pure **10** and **11** with quantitative recovery (**10**:**11** = 30:70).

The mixture of diastereomers in **7a** was semi-solid and after three successive recrystallizations from petroleum ether, gave the minor diastereomer **7b** as a fine powder with only 11% recovery, but with 98% de. This observation indicates that the major isomer has higher solubility in petroleum ether. Due to the powder nature of **7b**, we were unable to get the X-ray crystallographic data to fix the stereochemistry of the newly generated chiral centre. The single isomer **7b** on hydrolysis followed by ring closure gave the desired enantiomerically pure 1,5-benzothiazepinylacetic acid **9b** in 76% yield. The reaction of **9b** with (+)-(*R*)-phenylethylamine gave compound **10** in 90% yield. On the basis of X-ray crystallographic data of diastereomer **10** (Figure 3), we could assign the *R*-configuration to the newly generated chiral centre in **7b** and **10** and consequently, the *S*-configuration to the chiral center in **11**.



Scheme 2 *Reagents and conditions*: (i) *l*-menthol, *p*-TSA, toluene, reflux, 36 h (80%); (ii) *o*-aminothiophenol, anhyd AcOH, r.t., 36 h (82%); (iii) (a) AcOH–HCl (3:1), reflux, 12 h, (b) 10% aq $NaHCO_3$, (c) AcOH (86%); (iv) EDCI, DMAP (cat.), THF, r.t., 4 h (88%); (v) (*R*)-(+)-1-phenylethylamine, EDCI, DMAP (cat.), THF, r.t., 4 h (**10**/**11** = 3:7, 90%); (vi) three recrystallizations from petroleum ether (11%).

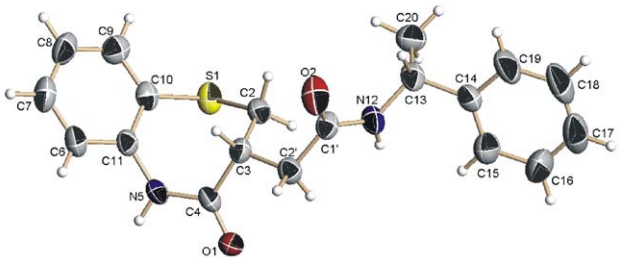
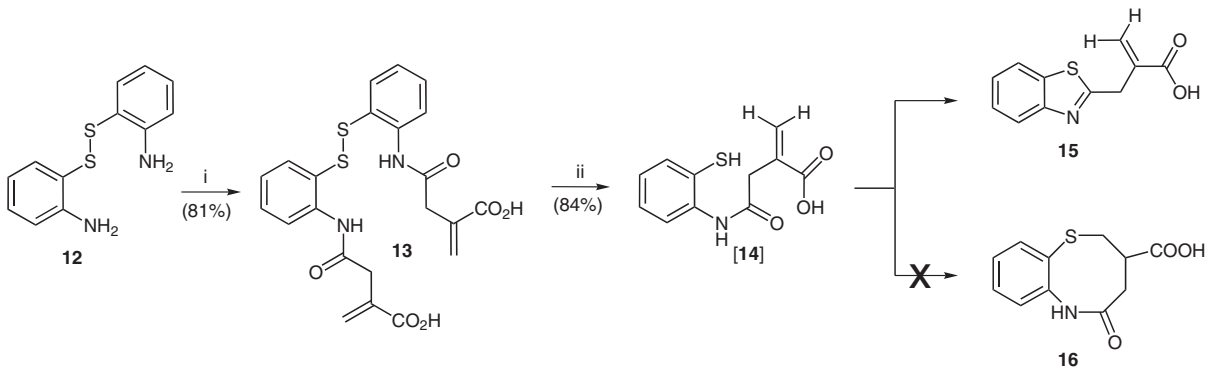


Figure 3 ORTEP diagram of **10**[10]

As the activation of α,β-unsaturated double bond by the carboxylic acid unit in itaconic acid is sufficient for Michael type addition of the thiol unit from *o*-ATP (Scheme 1, **1** → **5a**), we felt that the *o*-mercapto-α-methylenesuccinanilic acid **14** would be a potential precursor for the synthesis of benzothioazocine **16**. Hence to obtain the acid **14**, we performed the reaction of 2-aminophenyl disulfide (**12**) with 2.2 equivalents of itaconic anhydride (**2**) in tetrahydrofuran at room temperature and obtained the dicarboxylic acid **13** in 81% yield (Scheme 3). The triphenylphosphine-induced reductive cleavage of the sulfur–sulfur bond in diacid **13** formed the expected but unisolable intermediate acid **14**, which by an in situ intramolecular dehydrative cyclization furnished the 2-benzothiazo-2-ylmethylacrylic acid **15** in 84% yield. The expected benzothioazocine **16** was not obtained, indicating the reluctance for the intramolecular Michael type addition of thiol in **14** to form the eight-membered heterocycle.

In summary, we have demonstrated chemo-, regio- and stereoselective reactions of *o*-ATP (**1**) with itaconic anhydride (**2**) and (–)-dimenthyl itaconate (**6**) to obtain the corresponding racemic and enantiomerically pure 1,5-benzothiazepines in very good yields. The remarkably selective addition of the thiol unit from *o*-ATP (**1**) to the activated carbon–carbon double bond in itaconic anhydride



Scheme 3 *Reagents and conditions*: (i) itaconic anhydride, THF, r.t., 8 h (81%); (ii) TPP, 1,4-dioxane–water (4:1), H^+/HCl, r.t., 2 h (84%).

(**2**) in the presence of an internal amine unit is noteworthy. We also feel that our present simple approach to 1,5-benzothiazepines is general in nature and will be useful to design large number of its congeners for biological screening. All our attempts to obtain the benzothioazocine met with failure and instead we obtained the corresponding benzothiazole.

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available itaconic anhydride, itaconic acid, dimethyl itaconate, *o*-aminothiophenol (**1**), 2-aminophenyldisulfide, *l*-menthol, (*R*)-(+)-1-phenylethylamine, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and Ph_3P were used. Petroleum ether used had bp 60–80 °C.

(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)acetic Acid (4a)

Method A: To a solution of itaconic anhydride (**2**; 1.00 g, 8.92 mmol) in THF (25 mL) was added *o*-aminothiophenol (**1**; 1.05 mL, 10.70 mmol) and the mixture was stirred under argon for 8 h at r.t. A white precipitate was obtained, which was then filtered, washed with Et_2O and dried in vacuo to give **4a** as a white solid; yield: 1.71 g (81%). Analytically pure **4a** was obtained by recrystallization from MeOH.

Method B: To a solution of **5a** (300 mg, 1.18 mmol) and DMAP (5 mg) in THF (10 mL) was added EDCI (248 mg, 1.29 mmol) in THF (5 mL) and the mixture was stirred under argon for 4 h at r.t. The mixture was concentrated in vacuo and acidified with aq 2 N HCl (10 mL). The precipitate was filtered, washed with H_2O and dried in vacuo to give **4a** as a white solid; yield: 245 mg (88%); mp 234–235 °C (MeOH).

IR (Nujol): 3171, 2725–2500, 1703, 1639, 1630, 1462, 1454 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ = 2.29 (dd, *J* = 20, 5 Hz, 1 H), 2.68 (dd, *J* = 18, 10 Hz, 1 H), 2.82–2.92 (m, 1 H), 2.96 (dd, *J* = 10, 8 Hz, 1 H), 3.47 (dd, *J* = 10, 5 Hz, 1 H), 7.12 (d, *J* = 10 Hz, 1 H), 7.17 (dt, *J* = 10, 2 Hz, 1 H), 7.41 (dt, *J* = 10, 2 Hz, 1 H), 7.56 (d, *J* = 10 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 34.9, 38.1, 38.8, 123.6, 125.8, 126.2, 130.0, 134.8, 142.4, 172.7, 173.4.

Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.55; H, 4.49; N, 6.02; S, 13.47.

2-(2-Aminophenylsulfanylmethyl)succinic Acid (5a)

To a solution of itaconic acid (500 mg, 3.84 mmol) in THF (15 mL) was added *o*-aminothiophenol (**1**; 0.50 mL, 4.61 mmol) and the mixture was stirred under argon for 36 h at r.t. The mixture was concentrated in vacuo and the residue was dissolved in 10% aq $NaHCO_3$ solution. The resulting solution was washed with EtOAc (3 × 10 mL), acidified with glacial AcOH and extracted with EtOAc containing 5% MeOH (4 × 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo to give **5a**. Analytically pure **5a** was obtained by recrystallization from MeOH; yield: 686 mg (70%); yellow solid; mp 146 °C (MeOH).

IR (Nujol): 3356, 3285, 2725, 1697, 1462, 1377 cm^{-1}.

^1H NMR (CD_3OD, 500 MHz): δ = 2.69 (t, *J* = 5 Hz, 2 H), 2.87 (q, *J* = 5 Hz, 2 H), 3.14 (q, *J* = 5 Hz, 1 H), 6.61 (t, *J* = 10 Hz, 1 H), 6.76 (d, *J* = 10 Hz, 1 H), 7.07 (t, *J* = 10 Hz, 1 H), 7.33 (d, *J* = 10 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 35.0, 35.6, 41.4, 114.8, 115.5, 116.9, 129.8, 135.3, 149.6, 173.0, 174.6.

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.88; H, 5.26; N, 5.37; S, 12.66.

2-(2-Aminophenylsulfanylmethyl)succinic Acid Dimethyl Ester (5b)

To a solution of dimethyl itaconate (500 mg, 3.16 mmol) in THF (15 mL) was added *o*-aminothiophenol (0.40 mL, 3.79 mmol) and the mixture was stirred under argon for 24 h at r.t. The mixture was concentrated in vacuo and the crude residue was purified by silica gel column chromatography using petroleum ether–EtOAc (8:2) to furnish **5b** as a yellow thick oil; yield: 662 mg (74%).

IR (neat): 3460, 3364, 2847, 1740, 1726, 1611, 1479, 1439 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 2.71 (dd, *J* = 15, 5 Hz, 1 H), 2.83 (dd, *J* = 15, 5 Hz, 1 H), 2.95 (dd, *J* = 10, 5 Hz, 1 H), 3.02 (quintet, *J* = 5 Hz, 1 H), 3.13 (dd, *J* = 10, 5 Hz, 1 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 4.04 (br s, 2 H), 6.69 (t, *J* = 10 Hz, 1 H), 6.73 (d, *J* = 10 Hz, 1 H), 7.13 (t, *J* = 10 Hz, 1 H), 7.37 (d, *J* = 10 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 34.5, 35.6, 41.2, 51.7, 51.9, 114.9, 116.1, 118.3, 130.0, 135.9, 148.3, 171.7, 173.3.

Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.32. Found: C, 54.99; H, 6.11; N, 5.07; S, 11.17.

(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)acetic Acid Methyl Ester (4b)

To a solution of **4a** (500 mg, 2.10 mmol) in MeOH (15 mL), were added conc. H_2SO_4 (two drops) and the mixture was heated at 50 °C for 2 h. The mixture was concentrated in vacuo and the residue was dissolved in EtOAc (25 mL). The resulting solution was washed successively with 5% aq $NaHCO_3$ solution (10 mL), brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using petroleum ether–EtOAc (7:3) to furnish **4b** as a white solid; yield: 503 mg (95%); mp 168 °C (EtOAc).

IR (Nujol): 3179, 1734, 1666, 1462, 1439 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.35 (dd, *J* = 18, 6 Hz, 1 H), 2.93–3.06 (m, 2 H), 3.10–3.23 (m, 1 H), 3.52 (dd, *J* = 10, 5 Hz, 1 H), 3.63 (s, 3 H), 7.16 (d, *J* = 6 Hz, 1 H), 7.19 (t, *J* = 9 Hz, 1 H), 7.38 (t, *J* = 9 Hz, 1 H), 7.60 (d, *J* = 6 Hz, 1 H), 7.80–8.20 (br s, 1 H).

^1H NMR (DMSO-d_6, 300 MHz): δ = 2.38 (dd, *J* = 18, 6 Hz, 1 H), 2.74 (dd, *J* = 15, 9 Hz, 1 H), 2.58–3.05 (m, 2 H), 3.44–3.51 (m, 1 H), 3.52 (s, 3 H), 7.05–7.20 (m, 2 H), 7.42 (t, *J* = 9 Hz, 1 H), 7.57 (d, *J* = 9 Hz, 1 H), 9.93 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 34.7, 38.1, 39.1, 51.7, 123.6, 126.4, 126.8, 129.9, 135.0, 141.0, 171.8, 174.4.

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 34.4, 38.1, 38.6, 51.6, 123.6, 125.9, 126.1, 130.1, 134.9, 142.3, 171.9, 173.2.

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.58; S, 12.76. Found: C, 57.22; H, 5.29; N, 5.43; S, 12.63.

(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)acetic Acid Ethyl Ester (4c)

Repetition of the procedure similar to that used for the synthesis of **4b** in EtOH furnished the corresponding ethyl ester as a white solid; yield: 514 mg (92%); mp 146 °C (EtOAc).

IR (Nujol): 3296, 1713, 1688, 1587, 1468 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.20 (t, *J* = 8 Hz, 3 H), 2.33 (dd, *J* = 16, 4 Hz, 1 H), 2.85–3.25 (m, 3 H), 3.51 (dd, *J* = 10, 6 Hz, 1 H), 4.08 (q, *J* = 8 Hz, 2 H), 7.10–7.45 (m, 3 H), 7.60 (d, *J* = 6 Hz, 1 H), 8.05–8.30 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.0, 34.9, 38.1, 39.0, 60.6, 123.5, 126.3, 126.8, 129.9, 135.0, 141.1, 171.3, 174.5.

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.10. Found: C, 59.02; H, 5.84; N, 5.13; S, 12.25.

2-Methylenesuccinic Acid Bis(2-isopropyl-5-methylcyclohexyl)ester (6)

To a solution of itaconic anhydride (**2**; 5.20 g, 40 mmol) in toluene (70 mL) was added L-menthol (12.48 g, 80 mmol) and *p*-TSA (100 mg, 40 mmol) and the mixture was refluxed under argon for 36 h using a Dean–Stark apparatus. The mixture was allowed to cool to r.t., concentrated in vacuo, and the residue was dissolved in EtOAc (150 mL). The EtOAc layer was washed successively with 5% aq $NaHCO_3$ solution (25 mL), brine (25 mL) and dried (Na_2SO_4) and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using petroleum ether–EtOAc (9:1) to give **6** as a thick oil; yield: 13.12 g (80%); $[\alpha]_D^{25}$ – 85.12 (*c* = 1.77, $CHCl_3$).

IR (neat): 1734, 1719, 1641, 1456, 1200 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.77 (d, *J* = 8 Hz, 6 H), 0.90 (d, *J* = 6 Hz, 12 H), 0.75–1.25 (m, 6 H), 1.30-1.55 (m, 4 H), 1.55–1.75 (m, 4 H), 1.80–2.10 (m, 4 H), 3.31 (s, 2 H), 4.60–4.85 (m, 2 H), 5.65 (s, 1 H), 6.29 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 16.2, 20.6, 21.9, 23.3, 23.4, 26.0, 26.1, 31.2, 34.1, 37.9, 40.5, 40.6, 46.8, 46.9, 74.4, 74.6, 127.5, 134.4, 165.4, 170.0 (three carbon atoms from the two menthol units did not show splitting).

Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 74.01; H, 10.33.

2-(2-Aminophenylsulfanylmethyl)succinic Acid Bis(2-isopropyl-5-methylcyclohexyl)ester (7a)

To a solution of diester **6** (6.57 g, 15 mmol) in glacial AcOH (25 mL) was added *o*-aminothiophenol (1.63 mL, 15 mmol) and the mixture was stirred under argon for 36 h at r.t. The mixture was concentrated in vacuo and the residue was dissolved in EtOAc (70 mL). The EtOAc solution was washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using petroleum ether–EtOAc (8:2) to give **7a** as a thick oil/semi solid; yield: 6.92 g (82%). The compound **7a** (1.00 g, 40% de) on three recrystallizations from petroleum ether furnished compound **7b** (white solid, minor isomer, 110 mg, 98% de); mp 104 °C (petroleum ether); $[\alpha]_D^{25}$ –85.71 (*c* = 0.50, $CHCl_3$).

IR (Nujol): 3468, 3371, 1724, 1607, 1215 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.74 (d, *J* = 4 Hz, 3 H), 0.77 (d, *J* = 4 Hz, 3 H), 0.80–0.95 (m, 12 H), 0.95–1.10 (m, 6 H), 1.25–1.53 (m, 4 H), 1.62–1.72 (m, 4 H), 1.77–1.87 (m, 1 H), 1.90–2.05 (m, 3 H), 2.63 (dd, *J* = 16, 8 Hz, 1 H), 2.76 (dd, *J* = 16, 8 Hz, 1 H), 2.89 (dd, *J* = 12, 8 Hz, 1 H), 2.98 (q, *J* = 8 Hz, 1 H), 3.11 (dd, *J* = 12, 8 Hz, 1 H), 4.38 (br s, 2 H), 4.67 (dt, *J* = 8, 4 Hz, 1 H), 4.71 (dt, *J* = 8, 4 Hz, 1 H), 6.69 (t, *J* = 8 Hz, 1 H), 6.72 (d, *J* = 8 Hz, 1 H), 7.13 (t, *J* = 8 Hz, 1 H), 7.38 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.0, 16.3, 20.8, 22.0, 23.1, 23.4, 26.0, 26.2, 31.3, 34.2, 34.3, 35.6, 36.1, 40.6, 40.7, 42.0, 46.8, 46.9, 74.6, 75.0, 115.0, 116.8, 118.5, 130.1, 136.1, 148.4, 170.7, 172.6 (one of the carbon atom from the two menthol units did not show splitting).

Anal. Calcd for $C_{31}H_{49}NO_4S$: C, 70.01; H, 9.29; N, 2.63; S, 6.03. Found: C, 69.93; H, 9.27; N, 2.55; S, 6.12.

2-(2-Aminophenylsulfanylmethyl)succinic Acid (8a)

A solution of **7a** (5.63 g, 10 mmol) in AcOH–HCl (3:1, 30 mL) was refluxed for 12 h. The mixture was allowed to cool to r.t. and concentrated in vacuo, and the residue was dissolved in 10% aq $NaHCO_3$ solution. The resulting solution was washed with EtOAc (3 × 10 mL), acidified with glacial AcOH and extracted with EtOAc containing 5% MeOH (4 × 25 mL). The combined organic layer was washed with brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo to give **8a** as a yellow solid; yield: 2.19 g (86%). Similarly compound **7b** furnished compound **8b**; yellow solid; mp 146 °C (MeOH); $[\alpha]_D^{25}$ +20.83 (*c* = 0.24, MeOH). Analytical and spectral data obtained for **8a/b** were identical with (±)-**5a**.

(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)acetic Acid (9a)

To a solution of **8a** (1.28 g, 5 mmol) and DMAP (20 mg) in THF (20 mL) was added EDCI (1.06 g, 5.50 mmol) in THF (5 mL) and the mixture was stirred under argon for 4 h at r.t. The mixture was concentrated in vacuo, dried and acidified with aq 2 N HCl (20 mL). The precipitate was filtered, washed with H_2O and dried in vacuo to give **9a** as a white solid; yield: 1.04 g (88%). Similarly compound **8b** furnished compound **9b**; white solid; mp 234–235 °C (MeOH); $[\alpha]_D^{25}$ +178.30 (*c* = 0.19, MeOH). Analytical and spectral data obtained for **9a/b** were identical with (±)-**4a**.

2-(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)-*N*-(1-phenylethyl)acetamides (10 and 11)

To a solution of **9a** (474 mg, 2 mmol), (*R*)-(+)-1-phenylethylamine (290 mg, 2.40 mmol) and DMAP (10 mg) in THF (10 mL), was added a solution of EDCI (422 mg, 2.20 mmol) in THF (5 mL) and the mixture was stirred under argon for 4 h at r.t. The mixture was concentrated in vacuo, the residue was dissolved in EtOAc (50 mL). The EtOAc solution was washed with H_2O (15 mL), brine (20 mL) and dried (Na_2SO_4) and concentrated in vacuo. The residue obtained was purified by silica gel column chromatography using petroleum ether–EtOAc (8:2) to give a mixture of diastereomers 612 mg (90% yield). The diastereoisomeric mixture was separated by flash column chromatography using petroleum ether–EtOAc (9:1) to give the major isomer **11**; white solid; yield: 428 mg (70%) and the minor isomer **10**; white solid; yield: 183 mg (30%). Analytically pure **10** was obtained by recrystallization from petroleum ether–EtOAc (7:3).

(3*R*)-2-(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)-*N*-(1*R*-phenylethyl)acetamide (10, Minor Isomer)

Mp 198 °C; $[\alpha]_D^{25}$ +45.45 (*c* = 0.08, $CHCl_3$).

IR (Nujol): 3287, 3190, 1665, 1632, 1551, 1466, 1377 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.44 (d, *J* = 6 Hz, 3 H), 2.24 (dd, *J* = 14, 4 Hz, 1 H), 2.80 (dd, *J* = 24, 14 Hz, 1 H), 2.99 (d, *J* = 10 Hz, 1 H), 3.05–3.30 (m, 1 H), 3.53 (dd, *J* = 10, 6 Hz, 1 H), 5.01 (q, *J* = 8 Hz, 1 H), 6.49 (br s, 1 H), 7.00 (d, *J* = 8 Hz, 1 H), 7.14 (d, *J* = 8 Hz, 1 H), 7.20–7.40 (m, 6 H), 7.57 (dd, *J* = 8, 2 Hz, 1 H), 8.15 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.0, 37.2, 39.1, 39.7, 48.8, 123.7, 126.0, 126.7, 127.0, 127.1, 128.5, 130.0, 135.2, 140.6, 143.2, 169.5, 175.0.

Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.02; H, 5.92; N, 8.22; S, 9.42. Found: C, 67.20; H, 6.04; N, 8.13; S, 9.36.

(3*S*)-2-(4-Oxo-2,3,4,5-tetrahydrobenzo[*b*][1,5]thiazepin-3-yl)-*N*-(1*R*-phenylethyl)acetamide (11, Major Isomer)

Mp 104 °C; $[\alpha]_D^{25}$ +172.83 (*c* = 0.08, $CHCl_3$).

IR (Nujol): 3296, 3192, 1663, 1635, 1535, 1475 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 1.40 (d, *J* = 8 Hz, 3 H), 2.21 (dd, *J* = 14, 2 Hz, 1 H), 2.77 (dd, *J* = 24, 12 Hz, 1 H), 2.94 (d, *J* = 12 Hz, 1 H), 3.10–3.30 (m, 1 H), 3.45 (dd, *J* = 12, 6 Hz, 1 H), 4.99 (q, *J* = 8 Hz, 1 H), 6.68 (br s, 1 H), 7.00–7.40 (m, 8 H), 7.56 (d, *J* = 6 Hz, 1 H), 8.74 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.8, 36.8, 38.7, 39.5, 48.8, 123.7, 126.0, 126.6, 126.8, 127.1, 128.4, 129.9, 135.1, 140.7, 143.3, 169.6, 175.5.

Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.02; H, 5.92; N, 8.22; S, 9.42. Found: C, 66.97; H, 5.85; N, 8.30; S, 9.50.

2-({2-[2-(3-Carboxybut-3-enoylamino)phenyldisulfanyl]phenylcarbamoyl}methyl)acrylic Acid (13)

To a solution of itaconic anhydride (**2**; 695 mg, 6.20 mmol) in THF (15 mL) was added a solution of 2-aminophenyl disulfide (**12**; 700 mg, 2.81 mmol) in anhyd THF (15 mL) and the mixture was stirred under argon for 8 h at r.t. The mixture was concentrated in vacuo and the residue was stirred with Et_2O (30 mL) for 1 h. The precipitate was filtered and washed with Et_2O. Analytically pure **13** was obtained by recrystallization from MeOH as a yellow solid; yield: 1.08 g (81%); mp 192–193 °C (MeOH).

IR (Nujol): 3242, 2725, 2633, 1697, 1659, 1634, 1578, 1535 cm^{-1}.

^{1}H NMR (CD_3OD, 200 MHz): δ = 3.38 (br s, 4 H), 5.88 (br s, 2 H), 6.35 (s, 2 H), 7.11 (t, *J* = 8 Hz, 2 H), 7.31 (t, *J* = 8 Hz, 2 H), 7.47 (d, *J* = 8 Hz, 2 H), 7.68 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (DMSO-d_6, 50 MHz): δ = 39.3, 126.3, 127.0, 128.2, 128.5, 129.2, 131.8, 136.0, 136.3, 168.0, 169.5.

Anal. Calcd for $C_{22}H_{20}N_2O_6S_2$: C, 55.92; H, 4.27; N, 5.93; S, 13.57. Found: C, 56.09; H, 4.13; N, 6.02; S, 13.72.

2-Benzothiazol-2-ylmethylacrylic Acid (15)

To a solution of **13** (500 mg, 1.06 mmol) in dioxane–H_2O (4:1, 15 mL), was added Ph_3P (278 mg, 1.06 mmol) and conc. HCl (two drops) and the mixture was stirred at r.t. for 2 h. The mixture was concentrated in vacuo and extracted with EtOAc (4 × 25 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), concentrated in vacuo and the residue was purified by silica gel column chromatography using petroleum ether–EtOAc (7:3) to furnish **15** as a white solid; yield: 390 mg (84%); mp 139–142 °C (EtOAc).

IR (Nujol): 2700–2500, 1701, 1690, 1630, 1462, 1456 cm^{-1}.

^{1}H NMR (CD_3OD, 200 MHz): δ = 4.12 (s, 2 H), 5.92 (s, 1 H), 6.41 (s, 1 H), 7.30–7.55 (m, 2 H), 7.80–8.00 (m, 2 H).

^{13}C NMR (CD_3OD, 50 MHz): δ = 37.4, 122.8, 123.0, 126.2, 127.3, 129.7, 136.3, 138.3, 153.8, 169.0, 172.0.

Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39; S, 14.63. Found: C, 60.28; H, 4.09; N, 6.51; S, 14.54.

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