Supporting Information
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Valuable Versatile Reactivity of Thiaisatoic Anhydrides:
Expedient Thieno[1,4]diazepine-2,5-diones Solid-Phase
Synthesis

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Supporting Information

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General Experimental Section. Starting materials and solvents were obtained commercially and used as received. Melting points were determined in open capillaries and are uncorrected. Optical rotations were measured on a Perkin Elmer polarimeter 341 using a 100mm path length cell at \( \lambda = 589 \) nm (Sodium D line). Infrared spectra were taken on a Perkin Elmer Spectrum One apparatus. Mass spectral data, HRMS/LRMS were obtained by (FAB/ESI) analyses. \(^1\)H NMR (300 MHz) and \(^{13}\)C NMR (75 MHz) spectra were recorded in DMSO-\(d_6\) at room temperature. Chemical shifts are reported in parts per million (δ units) downfield/upfield from residual DMSO (δ 2.50 and 39.5); coupling constants (\(J\)) are reported in hertz (Hz). The quaternary carbon of the thiophene ring emits a very weak signal on the \(^{13}\)C NMR spectrum in comparison to all other signals of the molecule. HPLC analyses were performed on Merck Chromolith Flash RP18e (5µm, 225 × 4.6 mm) analytical reversed-phase column using a flow rate of 3.0 mL/min, and gradients of 100/0 to 0/100 eluents A/B over 5 min (method A), in which eluents A = H$_2$O-0.1% TFA and B = CH$_3$CN-0.1% TFA. Retention times (\(R_t\)) are reported as follows: \(R_t\) (min) and elution conditions. HPLC preparative purification was performed on Chromolith SemiPrep RP-18 (5µm, 100 × 10 mm) semi preparative column, using a flow rate of 20 mL/min and gradient of 100/0 to 0/100 eluents A/B over 20 min (method B). Analytical thin-layer chromatography (TLC) was performed using aluminum-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Retention factors (\(R_f\)) are reported as follows: \(R_f\) (fraction) and elution conditions. Flash column chromatography was performed with a 230-400 mesh silica gel.

1-Methylthieno[3,2-\(d\)][1,3]oxazine-2,4-dione (5) \(N\)-methylation of thiaisatoic anhydride with methyl iodide (MeI) was performed using literature procedures (mp 186-188°C, lit.\(^2\) mp 189°C).

1-(4-Methoxybenzyl)[3,2-\(d\)][1,3]oxazine-2,4-dione (6) A stirring solution of thiaisatoic anhydride 1 (5.00 g, 29.6 mmol) in DMF (25 mL) was treated with K$_2$CO$_3$ (4.91 g, 35.5 mmol) and \(p\)-methoxybenzyl chloride (4.43 mL, 32.5 mmol) at rt for 1 h. A 5% HCl solution (100 mL) is gently poured into the resulting mixture, stirred 5 min and left to stand 5 min. The formed precipitate was filtered over a frit, washed with water (2 × 100 mL) and Et$_2$O (2 × 100 mL), and dried in a dessicator to
afford N-PMB-thiaisatoic 6 in 81% yield. Beige solid; mp 181-182°C; ¹H NMR (DMSO-d₆): δ 8.27 (d, 1H, J = 5.3), 7.34 (d, 2H, J = 8.6), 7.28 (d, 1H, J = 5.3), 6.90 (d, 2H, J = 8.6), 5.13 (s, 2H), 3.71 (s, 3H); ¹³C NMR (DMSO-d₆): δ 158.9, 154.3, 149.6, 149.4, 139.9, 128.8, 127.3, 117.9, 114.0, 107.5, 55.1, 49.1; HRMS: calcd for [M + H⁺] C₁₄H₁₂N₁O₄S 290.0487, found 290.0481; Rₜ: 2.30 (method A).

Typical Experimental Procedure for Ring Opening of Thiaisatoic Anhydride 5-6. A stirring suspension of N-p-methoxybenzylthieno[3,2-d][1,3]oxazine-2,4-dione 6 (7.00 g, 24.22 mmol) and the corresponding α-amino acid (26.64 mmol) in 100 mL of water was treated with Et₃N (7.43 mL, 53.29 mmol) at rt for 30 min. Drops of DMF can be added to favour complete solubility. The resulting solution was partitioned with EtOAc. The aqueous phase was extracted with EtOAc (40 mL × 3) and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to afford the corresponding product 8.

{(3-(4-Methoxy-benzylamino)-thiophene-2-carbonyl)-amino}acetic acid (8a) Orange solid, hygroscopic, mp 30°C; ¹H NMR (DMSO-d₆): δ 7.76 (t, 1H, J = 5.7), 7.66 (t, 1H, J = 5.9), 7.48 (d, 1H, J = 5.3), 7.24 (d, 2H, J = 8.3), 6.88 (d, 2H, J = 8.2), 6.78 (d, 1H, J = 5.4), 4.35 (d, 2H, J = 5.7), 3.79 (d, 2H, J = 6.1), 3.72 (s, 3H); ¹³C NMR (DMSO-d₆): δ 171.6, 164.9, 158.3, 154.5, 131.9, 128.9, 128.4, 117.8, 113.9, 100.6, 55.0, 47.5, 40.8; HRMS: calcd for [M + H⁺] C₁₅H₁₇N₂O₄S 321.0909, found 321.0881; Rₜ: 2.27 (method A).

(S)-2-[(3-(4-Methoxy-benzylamino)-thiophene-2-carbonyl)-amino]propionic acid (8b) Yellow solid, mp 140°C (decomp.); [α]°D −24.1 (c 0.3, DMSO); ¹H NMR (DMSO-d₆): δ 7.68 (t, 1H, J = 5.6), 7.61 (d, 1H, J = 7.1), 7.48 (d, 1H, J = 5.3), 7.24 (d, 2H, J = 8.4), 6.88 (d, 2H, J = 8.4), 6.78 (d, 1H, J = 5.4), 4.35 (d, 2H, J = 6.6), 4.34 (quad, 1H, J = 7.2), 3.70 (s, 3H), 1.35 (d, 3H, J = 7.3); ¹³C NMR (DMSO-d₆): δ 174.5, 164.6, 158.3, 154.7, 131.9, 128.9, 128.4, 117.7, 113.9, 100.7, 55.1, 47.7, 47.6, 17.0; MS (ESI, m/z) for [M+H⁺] C₁₆H₁₉N₂O₄S 335.0; Rₜ: 2.41 (method A).
(S)-2-[[3-(4-Methoxy-benzylamino)-thiophene-2-carbonyl-amino]-3-phenylpropionic acid (8e) White solid, mp 68-70°C; $[^{20}D]_2 -18.7$ (c 0.3, DMSO); $^1$H NMR (DMSO-$d_6$): $\delta$ 7.57 (m, 2H), 7.46 (d, 1H, $J = 5.4$), 7.26 (m, 5H), 7.22 (d, 2H, $J = 7.3$), 6.87 (d, 2H, $J = 7.1$), 6.74 (d, 1H, $J = 5.4$), 4.52 (quad, 1H, $J = 8.0$), 4.31 (d, 2H, $J = 5.5$), 3.71 (s, 3H), 3.10 (d, 2H, $J = 8.0$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 173.4, 164.6, 158.3, 154.5, 138.3, 131.8, 129.1, 129.0, 128.4, 128.1, 126.3, 117.6, 113.9, 100.6, 55.0, 53.6, 47.5, 36.1; HRMS: calcd for [M + H$^+$] $C_{22}H_{23}N_2O_4S$ 411.1379, found 411.1360; $R$: 2.84 (method A).

Typical Experimental Procedure for thieno[3,2-e][1,4]diazepinediones (9-10) synthesis. A solution of acid 8 in AcOH was magnetically stirred at reflux from 1 to 6 h. The resulting solution was concentrated under reduce pressure and triturated with Et$_2$O to afford the corresponding thienodiazepine 10. This procedure can be directly applied to the acids 7-8 crude mixture, after evaporation of volatile material, to attain a one flask protocol directly to thienodiazepines 9-10. The work-up remains the same. Traces of PMB cleavage from diazepines 10 after prolonged heating (>18 h) in AcOH can be observed by LC-MS. Alternative route: A stirring solution of acids 7-8 in dry DCM was treated with SOCl$_2$ (5000 mol%) at reflux for 1 h. Volatile material was evaporated and column chromatography purification was done when necessary.

3,4-Dihydro-1-methyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (9a): yield 55 % (partially hydrophilic), beige solid, mp 155°C (decomp); $^1$H NMR (DMSO-$d_6$): $\delta$ 8.40 (br s, 1H), 7.88 (d, 1H, $J = 5.3$), 7.22 (d, 1H, $J = 5.3$), 3.75 (d, 2H, $J = 5.1$), 3.30 (s, 3H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.4, 164.2, 142.4, 131.3, 122.9, 46.1, 34.5; HRMS: calcd for [M + H$^+$] $C_{12}H_{19}N_2O_2S$ 197.0385, found 197.0388; $R$: 1.15 (method A); IR (cm$^{-1}$): 3368 (NH), 1668 and 1638 (C=O).

(S)-3,4-Dihydro-1,3-dimethyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (9b): yield 61 %, beige solid, mp 211-214°C; $[^{20}D]_2 +251.0$ (c 0.2, DMSO); $^1$H NMR (DMSO-$d_6$): $\delta$ 8.28 (d, 1H, $J = 3.5$), 7.88 (d, 1H, $J = 5.4$), 7.22 (d, 1H, $J = 5.4$), 3.93 (m, 1H), 3.32 (s, 3H), 1.29 (d, 3H, $J = 6.8$); $^{13}$C NMR
(DMSO-$d_6$): $\delta$ 169.5, 163.1, 141.6, 130.7, 123.6, 122.4, 48.6, 34.4, 14.8; HRMS: calcd for [M + H$^+$] $C_9H_{11}N_2O_2S$ 211.0541, found 211.0556; $R$: 1.21 (method A).

**3,4-Dihydro-1,4-dimethyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (9c):** yield 79%, beige solid, mp 170-173$^\circ$C; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.87 (d, 1H, $J$ = 5.4), 7.21 (d, 1H, $J$ = 5.4), 4.00 (s, 2H), 3.30 (s, 3H), 3.06 (s, 3H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 166.7, 162.1, 141.7, 130.6, 123.3, 122.1, 53.4, 35.5, 33.8; HRMS: calcd for [M + H$^+$] $C_9H_{11}N_2O_2S$ 211.0541, found 211.0548; $R$: 1.19 (method A).

**(S)-4-Methyl-5a,6,7,8-tetrahydro-5H-pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine-5,10(4H)-dione (9d):** yield 74%, beige solid, mp 48-50$^\circ$C; $[\alpha]_{D}^{20}$ +310.1 (c 1.0, DMSO); $^1$H NMR (DMSO-$d_6$): $\delta$ 7.86 (d, 1H, $J$ = 5.4), 7.23 (d, 1H, $J$ = 5.4), 4.20 (d, 1H, $J$ = 7.3), 3.50 (m, 1H), 3.43 (m, 1H), 3.33 (s, 3H), 2.53 (m, 1H), 2.00 (m, 1H), 1.86 (m, 2H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.0, 160.3, 141.1, 130.2, 124.4, 122.6, 57.8, 46.3, 34.7, 26.5, 23.5; HRMS: calcd for [M + H$^+$] $C_{11}H_{13}N_2O_2S$ 237.0698, found 237.0702; $R$: 1.45 (method A).

**(S)-3-Benzyl-3,4-dihydro-1-methyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (9e):** yield 77%, brown solid, mp 78-80$^\circ$C; $[\alpha]_{D}^{20}$ +72.4 (c 0.1, DMSO); $^1$H NMR (DMSO-$d_6$): $\delta$ 8.4 (d, 1H, $J$ = 5.1), 7.88 (d, 1H, $J$ = 5.4), 7.32 (d, 2H, $J$ = 7.2), 7.24 (m, 4H), 4.05 (m, 1H), 3.22 (s, 3H), 3.19 (dd, 1H, $J$ = 14.1, 5.8), 2.92 (dd, 1H, $J$ = 14.1, 8.6); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.6, 162.9, 141.8, 137.8, 130.8, 129.4, 129.0, 128.2, 126.4, 122.5, 55.0, 34.5, 34.2; HRMS: calcd for [M + H$^+$] $C_{15}H_{15}N_2O_2S$ 287.0854, found 287.0856; $R$: 2.03 (method A).

1-(4-Methoxybenzyl)-3,4-dihydro-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (10a): yield 64%, beige solid, mp 162-165$^\circ$C; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.48 (t, 1H, $J$ = 5.0), 7.80 (d, 1H, $J$ = 5.4), 7.21 (d, 1H, $J$ = 5.4), 7.09 (d, 2H, $J$ = 8.5), 6.84 (d, 2H, $J$ = 8.5), 5.05 (s, 2H), 3.85 (d, 2H, $J$ = 5.2), 3.69 (s, 3H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 167.8, 163.6, 158.4, 140.6, 130.7, 128.8, 128.1, 124.2, 122.6, 114.0, 55.0, 48.2, 45.7; HRMS: calcd for [M + H$^+$] $C_{15}H_{15}N_2O_2S$ 303.0803, found 303.0810; $R$: 1.94 (method A), $R_f$: 0.4, CHCl$_3$-MeOH (19:1).

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(S)-1-(4-Methoxybenzyl)-3,4-dihydro-3-methyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (10b): yield 95 %, beige solid, mp 75°C; [α]D 20 +239.8 (c 1.0, DMSO); 1H NMR (DMSO-d6): δ 8.35 (d, 1H, J = 4.0), 7.80 (d, 1H, J = 5.4), 7.24 (d, 1H, J = 5.4), 7.07 (d, 2H, J = 8.4), 6.83 (d, 2H, J = 8.4), 5.21 (d, 1H, J = 15.5), 4.92 (d, 1H, J = 15.5), 4.07 (m, 1H), 3.69 (s, 3H), 1.34 (d, 3H, J = 6.7); 13C NMR (DMSO-d6): δ 169.4, 163.0, 158.4, 140.2, 130.6, 128.9, 128.2, 124.8, 122.5, 113.9, 55.0, 48.6, 48.6, 14.8; HRMS: calcd for [M + H]+ C16H17N2O3S 317.0960, found 317.0965; Rf: 0.5, CHCl3-MeOH (19:1).

1-(4-Methoxybenzyl)-3,4-dihydro-4-methyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (10c): yield 98 %, beige solid, mp 148-150°C; 1H NMR (DMSO-d6): δ 7.79 (d, 1H, J = 5.4), 7.17 (d, 1H, J = 5.4), 7.07 (d, 2H, J = 8.4), 6.84 (d, 2H, J = 8.6), 5.04 (s, 2H), 4.10 (s, 2H), 3.69 (s, 3H), 3.10 (s, 3H); 13C NMR (DMSO-d6): δ 166.6, 162.0, 158.4, 140.4, 130.5, 128.7, 128.1, 124.4, 122.1, 114.0, 55.0, 53.4, 48.1, 35.5; HRMS: calcd for [M + H]+ C16H17N2O3S 317.0960, found 317.0952; Rf: 0.6, AcOEt.

(S)-4-(4-Methoxybenzyl)-5a,6,7,8-tetrahydro-5H-pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine-5,10(4H)-dione (10d): yield 92 %, beige solid, mp 188-191°C; [α]D 20 313.8 (c 0.3, DMSO); 1H NMR (DMSO-d6): δ 7.78 (d, 1H, J = 5.4), 7.19 (d, 1H, J = 5.4), 7.06 (d, 2H, J = 8.3), 6.84 (d, 2H, J = 8.4), 5.17 (d, 1H, J = 15.6), 4.98 (d, 1H, J = 15.6), 4.33 (dd, 1H, J = 8.0, 2.9), 3.70 (s, 3H), 3.50 (m, 2H), 2.56 (m, 1H), 2.04 (m, 1H), 1.95 (m, 2H); 13C NMR (DMSO-d6): δ 167.9, 160.3, 158.4, 139.8, 130.1, 128.8, 128.1, 125.5, 122.6, 114.0, 57.8, 55.0, 49.0, 46.4, 26.6, 23.6; HRMS: calcd for [M + H]+ C18H19N2O3S 343.1116, found 343.1121; Rf: 2.21 (method A), Rf: 0.6, CHCl3-AcOEt (1:4).

(S)-1-(4-Methoxybenzyl)-3-benzyl-3,4-dihydro-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (10e): yield 75 %, orange solid, mp 66-68°C; [α]D 20 27.5 (c 0.1, DMSO); 1H NMR (DMSO-d6): δ 8.50 (d, 1H, J = 3.5), 7.81 (d, 1H, J = 5.3), 7.37-7.20 (m, 6H), 7.03 (d, 2H, J = 8.5), 6.81 (d, 2H, J = 8.6), 5.23 (d, 1H, J = 15.5), 4.89 (d, 1H, J = 15.5), 4.17 (m, 1H), 3.68 (s, 3H), 3.24 (dd, 1H, J = 13.8, 5.3), 3.58 (s, 3H).
2.98 (dd, 1H, J = 13.5, 9.0); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 168.6, 162.8, 158.4, 140.4, 137.8, 130.8, 129.5, 128.9, 128.4, 128.2, 126.5, 124.9, 122.7, 113.9, 55.0, 55.0, 48.6, 34.3; HRMS: calcd for [M + H$^+$]

C$_{22}$H$_{21}$N$_2$O$_3$S 393.1273, found 393.1298; $R_t$: 2.64 (method A), $R_f$: 0.4, CHCl$_3$-AcOEt (4:1).

**Thiaisatoic anhydride resin (11):** Wang bromide resin (5.0 g, 1.6 mmol/g), purchased from Novabiochem® or prepared from Wang resin, was swollen in a 200 mL glass SPOS fritted tube using 40 mL of dry DMF, washed with 40 mL of dry DMF (×2) and treated with a solution of anhydride 1 (2.03 g, 12.0 mmol) and K$_2$CO$_3$ (2.21 g, 16.0 mmol) in 50 mL of DMF for 1 h at rt. The filtered resin was washed sequentially with 40 mL solutions of H$_2$O (×2), DMF (×2), H$_2$O (×2), DMF (×2) and DCM (×3). The beige resin was dried *in vacuo* and usually stored in a dessicator under vacuum or under argon in the fridge; IR (cm$^{-1}$): 1774 and 1721(C=O).

**Typical Experimental Procedure for 3,4-dihydrothieno[3,2-e][1,4]diazepine-2,5-dione resins (13) Synthesis.** Resin 11 (0.400 g, 0.56 mmol) was loaded in a 20 mL polypropylene tube equipped with a polyethylene frit, swollen in 10 mL of DMF, filtered, washed with 10 mL of DMF (×2) and swollen in 10 mL of DMF-H$_2$O (4:1). The resin suspension was treated with the respective $\alpha$-amino acid (500 mol%) and Et$_3$N (1000 mol%). The resulting mixture was stirred for 5 h at 50 °C in an Argonaut Quest parallel synthesizer apparatus, cooled, filtered and washed sequentially with 10 mL volumes of DMF (×2), H$_2$O (×2), DMF (×2), H$_2$O (×2), DMF (×2), H$_2$O (×2), DMF (×2), DCM (×3). The beige resin was dried *in vacuo* and stored in the fridge under argon.

**Typical Experimental Procedure for 3,4-dihydrothieno[3,2-e][1,4]diazepine-2,5-diones (14) Synthesis.** Diazepine resin 13 (0.400 g, ~0.52 mmol), in the same polypropylene tube, was swollen in 8 mL of dry DCM, filtered, washed with 8 mL of dry DCM (×2), treated with a 50% v/v solution of TFA in DCM (8mL) and shaken for 30 min. The resin was filtered, washed with DCM (×2), and treated again with TFA-DCM (1:1) for an additional 30 min. The resin was filtered and washed with DCM (×2). The combined filtrates and washings were evaporated under reduced pressure and triturated with a pentane-Et$_2$O solution (1:1) to afford thienodiazepines 14.
3,4-Dihydro-4-methyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (14a): yield 95%, beige solid, mp >210°C; \( ^1\)H NMR (DMSO-\( d_6 \)): \( \delta \) 10.89 (s, 1H), 7.78 (d, 1H, \( J = 5.2 \)), 6.80 (d, 1H, \( J = 5.2 \)), 3.94 (s, 2H), 3.05 (s, 3H); \( ^13\)C NMR (DMSO-\( d_6 \)): \( \delta \) 168.0, 162.6, 138.7, 131.3, 121.6, 121.1, 53.6, 35.9; HRMS: calcd for [M + H\(^+\)] \( C_8H_9N_2O_2S \) 197.0385, found 197.0388; \( R_t \): 1.01 (method A).

\((S)\)-3,4-Dihydro-3,4-dimethyl-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (14b): yield 90%, beige solid, mp 191-194°C; \([\alpha]^{20}_D +51.6 \) (c 0.1, DMSO); \( ^1\)H NMR (DMSO-\( d_6 \)): \( \delta \) 10.91 (s, 1H), 7.78 (d, 1H, \( J = 5.1 \)), 6.80 (d, 1H, \( J = 5.1 \)), 4.20 (quad, 1H, \( J = 6.9 \)), 2.93 (s, 3H), 1.34 (d, 3H, \( J = 7.0 \)); \( ^13\)C NMR (DMSO-\( d_6 \)): \( \delta \) 169.2, 162.5, 138.1, 131.4, 128.5, 121.3, 54.7, 30.8, 12.6; HRMS: calcd for [M + H\(^+\)] \( C_8H_{11}N_2O_2S \) 211.0541, found 211.0575; \( R_t \): 1.24 (method A).

\((S)\)-6,7-Dihydroazeto[1,2-a]thieno[3,2-e][1,4]diazepine-5,9(4H,5aH)-dione (14c): yield 80%, white solid, mp 215°C (decomp.); \([\alpha]^{20}_D +305.9 \) (c 0.1, DMSO); \( ^1\)H NMR (DMSO-\( d_6 \)): \( \delta \) 10.90 (s, 1H), 7.78 (d, 1H, \( J = 5.3 \)), 6.85 (d, 1H, \( J = 5.2 \)), 4.90 (t, 1H, \( J = 7.6 \)), 4.07 (quad, 1H, \( J = 8.5 \)), 3.79 (td, 1H, \( J = 8.8, 3.6 \)), 2.60 (m, 1H), 2.35 (m, 1H); \( ^13\)C NMR (DMSO-\( d_6 \)): \( \delta \) 170.3, 162.4, 138.3, 131.1, 122.9, 119.6, 59.6, 45.5, 18.2; HRMS: calcd for [M + H\(^+\)] \( C_{9}H_{11}N_2O_2S \) 209.0385, found 209.0386; \( R_t \): 1.05 (method A).

4-Benzyl-3,4-dihydro-1H-thieno[3,2-e][1,4]diazepine-2,5-dione (14d): yield 95%, beige solid, mp 51-54°C; \( ^1\)H NMR (DMSO-\( d_6 \)): \( \delta \) 10.91 (s, 1H), 7.82 (d, 1H, \( J = 5.3 \)), 7.36-7.27 (m, 5H), 6.82 (d, 1H, \( J = 5.3 \)), 4.71 (s, 2H), 3.95 (s, 2H); \( ^13\)C NMR (DMSO-\( d_6 \)): \( \delta \) 168.0, 162.6, 139.1, 137.1, 131.8, 128.5, 127.6, 127.3, 121.7, 115.1, 52.2, 51.3; HRMS: calcd for [M + H\(^+\)] \( C_{14}H_{13}N_2O_2S \) 273.0698, found 273.0708; \( R_t \): 1.80 (method A).

\((S)\)-5a,6,7,8-Tetrahydro-5H-pyrrolo[1,2-a]thieno[3,2-e][1,4]diazepine-5,10(4H)-dione (14e): yield 86%, white solid, mp >210°C, lit. \(^4\) mp 248°C; HRMS: calcd for [M + H\(^+\)] \( C_{10}H_{11}N_2O_2S \) 223.0541, found 223.0533; \( R_t \): 1.25 (method A).
(5aS,7R)-7-Hydroxy-5a,6,7,8-tetrahydro-5H-pyrrolo[1,2-α]thieno[3,2-e][1,4]diazepine-5,10(4H)-dione (14f): yield 79%, pink solid, mp 210°C (decomp.); [α]D +187.1 (c 0.2, DMSO); 1H NMR (DMSO-d6): δ 10.96 (s, 1H), 7.79 (d, 1H, J = 5.2), 6.82 (d, 1H, J = 5.3), 5.12 (d, 1H, J = 3.5), 4.27 (m, 2H) 3.76 (d, 1H, J = 12.0), 2.58 (m, 1H), 2.54 (s, 1H), 1.99 (m, 1H); 13C NMR (DMSO-d6): δ 169.0, 162.0, 138.4, 131.6, 122.5, 121.5, 67.9, 57.2, 54.2, 35.3; HRMS: calcd for [M + H]+ C10H11N2O3S 239.0490, found 239.0484; Rf: 0.93 (method A).

(5aS,6S)-6-Hydroxy-5a,6,7,8-tetrahydro-5H-pyrrolo[1,2-α]thieno[3,2-e][1,4]diazepine-5,10(4H)-dione (14g): yield 88%, white solid, mp >225°C; [α]D +330.3 (c 0.1, DMSO); 1H NMR (DMSO-d6): δ 10.96 (s, 1H), 7.79 (d, 1H, J = 5.3), 6.82 (d, 1H, J = 5.3), 4.80 (s, 1H), 3.88 (s, 1H), 3.66 (m, 1H), 3.52 (m, 1H), 2.54 (s, 1H), 1.89 (m, 2H); 13C NMR (DMSO-d6): δ 168.1, 160.9, 138.1, 131.1, 122.1, 121.7, 70.5, 65.9, 44.8, 31.8; HRMS: calcd for [M + H]+ C10H11N2O3S 239.0490, found 239.0502; Rf: 0.85 (method A).

6,7,8,9-Tetrahydropyrido[1,2-α]thieno[3,2-e][1,4]diazepine-5,11(4H,5aH)-dione (14h): yield 71% (from a racemic mixture of piperidine-2-carboxylic acid); white solid, mp >225°C; 1H NMR (DMSO-d6): δ 10.85 (s, 1H), 7.79 (d, 1H, J = 5.3), 6.79 (d, 1H, J = 5.3), 4.15 (m, 2H), 2.89 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H), 1.71-1.57 (m, 4H); 13C NMR (DMSO-d6): δ 169.4, 162.9, 138.9, 131.4, 121.7, 121.3, 52.5, 38.7, 22.3, 21.9, 18.0; HRMS: calcd for [M + H]+ C11H13N2O2S 237.0698, found 237.0699; Rf: 1.45 (method A).
AMX300, in DMSO-d6, 303K
AMX300, in DMSO-d6, 303K
AXX396 in DMSO-d6, 303K
AMX300, in DMSO-δ6, 303K
References