Supporting Information

Synthesis of 3,4-dihydro-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxides and their evaluation as ligands for NMDA receptor glycine binding site

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***N*-tert-Butyl-4,5-dichloro-2-methylbenzenesulfonamide (3b)**

Prepared according to procedure for compound **3a** using 4,5-dichloro-2-methylbenzenesulfonyl chloride (**2b**). Yield 69%, white solid; mp 223-227 °C. TLC: R_f =0.45 (Hex:EtOAc, 6:1). ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.24 (s, 9H), 2.59 (s, 3H), 4.05 (s, 1H), 7.39 (s, 1H), 8.10 (s, 1H). ¹³C NMR (100 MHz, CDCl₃), δ ppm: 19.5, 30.1, 55.2, 130.2, 130.8, 133.8, 136.4, 140.8. MS m/z 294 [M-H]⁻.

***N*-tert-Butyl-2,4-dichloro-6-methylbenzenesulfonamide (3c)**

Prepared according to procedure for compound **3a** using 2,4-dichloro-6-methylbenzenesulfonyl chloride (**2c**). Yield 79%, white solid; mp 150-153 °C. TLC: R_f =0.41 (Hex:EtOAc, 6:1). ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.23 (s, 9H), 2.71 (s, 3H), 5.25 (s, 1H), 7.21 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H). MS m/z 240 [M-56]⁺ (elimination of *tert*-Bu). *Anal.* calcd for C₁₁H₁₅Cl₂NO₂S: C, 44.60; H, 5.10; N, 4.73. Found: C, 44.56; H, 5.20; N, 4.57.

***2*-(tert-Butyl)-5,6-dichlorobenzo[d]isothiazol-3(2*H*)-one 1,1-dioxide (4b)**

Prepared according to procedure for compound **4a** using *N*-*tert*-butyl 4,5-dichloro-2-methylbenzenesulfonamide (**3b**). Yield 83%, white solid; mp 182-185 °C. TLC: R_f =0.37 (Hex:EtOAc, 4:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 1.75 (s, 9H), 7.92 (s, 1H), 8.05 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 27.7, 62.0, 122.2, 126.5, 126.8, 136.7, 139.5, 158.0. MS m/z 250 $[\text{M}-57]^-$ (*tert*-Bu).

2-(*tert*-Butyl)-5,7-dichlorobenzo[d]isothiazol-3(2H)-one 1,1-dioxide (4c)

Prepared according to procedure for compound **4a** using *N*-*tert*-butyl-2,4-dichloro-6-methylbenzenesulfonamide (**3c**). Yield 88%, white solid; mp 94-97 °C. TLC: R_f =0.33 (Hex:EtOAc, 20:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 1.76 (s, 9H), 7.72 (d, J = 1.6 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 27.7, 62.2, 123.2, 128.9, 130.8, 133.5, 134.8, 141.4, 157.5. MS m/z 250 $[\text{M}-57]^-$ (*tert*-Bu). *Anal.* calcd for $\text{C}_{11}\text{H}_{11}\text{Cl}_2\text{NO}_3\text{S}$: C, 42.87; H, 3.60; N, 4.54. Found: C, 42.59; H, 3.61; N, 4.50.

5,6-Dichlorobenzo[d]isothiazol-3(2H)-one 1,1-dioxide (5b)

Prepared from compound **4b** according to procedure for compound **5a**. Recrystallised from MeCN, yield 88%, beige solid, mp > 191 °C (decomp.). TLC: R_f =0.12 (EtOAc:AcOH, 1:0.01). ^1H NMR (200 MHz, $\text{DMSO}-d_6$), δ ppm: 4.48 (s, 1H) 8.09 (s, 1H), 8.52 (s, 1H); ^{13}C NMR (100 MHz, acetone- d_6), δ ppm: 125.3, 128.8, 129.7, 140.7, 141.0, 141.4, 160.0. MS m/z 250 $[\text{M}-\text{H}]^-$.

5,7-Dichlorobenzo[d]isothiazol-3(2H)-one 1,1-dioxide (5c)

Prepared from compound **4c** according to procedure for compound **5a**. Recrystallised from MeCN, yield 98%, white solid; mp 226-229 °C. TLC: R_f =0.17 (EtOAc:AcOH, 1:0.01). ^1H NMR (200 MHz, DMSO), δ ppm: 7.78 (d, J = 1.6 Hz, 1H), 7.91 (d, J = 1.6 Hz, 1H); ^{13}C -NMR (100 MHz, CDCl_3), δ ppm: 122.7, 127.1, 133.2, 134.6, 137.6, 139.2, 161.1. MS m/z 250 $[\text{M}-\text{H}]^-$.

5,6-Dichloro-2-(4-methoxybenzyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (6b)

Prepared from compound **5b** according to procedure for compound **6a**. Yield 66%, white solid; mp 163-166 °C. TLC: R_f =0.28 (Hex:EtOAc, 4:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 3.78 (s, 3H), 4.83 (s, 2H), 6.87 (d, J = 8.8 Hz, 2H); 7.41 (d, J = 8.8 Hz, 2H), 7.99 (s, 1H), 8.09 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 42.8, 55.2, 114.0, 123.0, 125.9, 126.7, 126.9, 130.4, 136.5, 139.8, 140.1, 157.0, 159.7. MS m/z 250 $[\text{M}-121]^-$ (*p*-MeOBn).

5,7-Dichloro-2-(4-methoxybenzyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (6c)

Prepared from compound **5c** according to procedure for compound **6a**. Yield 64%, white solid; mp 157-160 °C. TLC: R_f =0.43 (petroleum ether: EtOAc, 4:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 3.79 (s, 3H), 4.85 (s, 2H), 6.87 (d, J = 8.0 Hz, 2H); 7.42 (d, J = 8.0 Hz, 2H);

7.75 (d, $J = 1.4$ Hz, 1H); 7.88 (d, $J = 2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 42.8, 55.3, 114.1, 123.7, 125.9, 129.7, 130.5, 133.7, 135.1, 141.9, 156.4, 159.7. MS m/z 250 $[\text{M}-121]^-$ (*p*-MeOBn). *Anal.* calcd for $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{NO}_4\text{S}$: C, 48.40; H, 2.98; N, 3.76. Found: C, 48.27; H, 3.05; N, 3.61

4,5-Dichloro-2-(hydroxymethyl)-N-(4-methoxybenzyl)-benzenesulfonamide (7b)

Prepared from compound **6b** according to procedure for compound **7a**. Yield 96%, white solid; mp 136-139 °C. TLC: $R_f=0.21$ (Hex:EtOAc, 2:1). ^1H -KMR (200 MHz, CDCl_3), δ ppm: 3.77 (s, 3H), 4.10 (s, 2H), 4.93 (s, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 7.06 (d, $J = 8.6$ Hz, 2H), 7.56 (s, 1H), 7.90 (s, 1H). ^{13}C NMR (100 MHz, acetone- d_6), δ ppm: 48.2, 55.5, 61.9, 114.4, 130.5, 131.2, 132.0, 132.5, 137.6, 140.0, 142.9, 161.0. MS m/z 374 $[\text{M}-\text{H}]^-$.

2,4-Dichloro-6-(hydroxymethyl)-N-(4-methoxybenzyl)-benzenesulfonamide (7c)

Prepared from compound **6c** according to procedure for compound **7a**. Yield 94%, white solid; mp > 136 °C (decomp.). TLC: $R_f=0.35$ (Hex:EtOAc, 2:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 3.77 (s, 3H), 4.11 (s, 2H), 4.93 (s, 2H), 6.75 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 8.0$ Hz, 2H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.54 (d, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 47.2, 55.3, 64.0, 114.0, 127.1, 129.3, 129.6, 131.0, 133.6, 134.4, 138.7, 145.3, 159.5. MS m/z 374 $[\text{M}-\text{H}]^-$. *Anal.* calcd for $\text{C}_{15}\text{H}_{15}\text{Cl}_2\text{NO}_4\text{S}$: C, 47.88; H, 4.02; N, 3.72. Found: C, 47.88; H, 4.07; N, 3.56.

Ethyl 2-(4,5-dichloro-2-(hydroxymethyl)-N-(4-methoxybenzyl)phenylsulfonamido)acetate (8b)

Prepared from compound **7b** according to procedure for compound **8a**. Yield 50%. Light yellow oil. TLC: $R_f=0.34$ (Hex:EtOAc, 2:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 1.18 (t, $J = 7.2$ Hz, 3H), 3.80 (s, 1H), 3.91 (s, 2H), 4.02 (q, $J = 7.2$ Hz, 2H), 4.52 (s, 2H), 4.90 (d, $J = 7.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 8.6$ Hz, 2H), 7.79 (s, 1H), 8.08 (s, 1H). MS m/z 460 $[\text{M}-\text{H}]^-$.

Ethyl 2-(2,4-dichloro-6-(hydroxymethyl)-N-(4-methoxybenzyl)phenylsulfonamido)acetate (8c)

Prepared from compound **7b** according to procedure for compound **8a**. Yield 59%. Colorless oil; TLC: $R_f=0.21$ (petroleum ether:EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.20 (t, $J = 7.0$ Hz, 3H), 3.06 (t, $J = 7.0$ Hz, 1H), 3.76 (s, 3H), 3.98 (s, 2H), 4.10 (q, $J = 7.0$ Hz, 2H), 4.48 (s, 2H), 4.93 (d, $J = 6.8$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 2.4$ Hz, 1H), 7.55 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 14.1, 47.3, 51.3, 55.3, 61.5, 64.4, 114.1, 125.9, 129.3, 129.5, 130.1, 131.5, 135.5, 139.0, 145.9, 159.6, 168.7. MS m/z low ionization.

2-(3-Bromobenzyl)-6,8-dichloro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (13b)

To a solution of compound **12b** (100 mg, 0.2 mmol, 1 equiv) in THF (2 mL) was added a solution of LiOH·H₂O (10 mg, 0.26 mmol, 1.28 equiv) in water (2 mL) and stirred at room temperature for 72 h. THF was removed under reduced pressure. The aqueous residue was acidified to pH~2 by addition of 1N HCl and extracted with CHCl₃ (3×10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was washed with Et₂O and CHCl₃ to give the title compound **13b** (90 mg, 92%) as a white solid, mp:>150 °C (decomp.). R_f=0.20 (CH₂Cl₂/MeOH 20:1). ¹H NMR (400 MHz, CDCl₃): δ ppm: 4.93 (s, 2H); 7.01 (d, *J*=7.6 Hz, 1H); 7.13 (t, *J*=7.6 Hz, 1H); 7.22 (s, 1H); 7.35 (d, *J*=8.0 Hz, 1H); 7.72 (s, 1H); 7.86 (s, 1H); 7.95 ppm (s, 1H). ¹³C NMR (100 MHz, DMSO-d₆): δ=52.4; 121.1; 123.4; 127.0; 128.7; 129.1; 130.1; 130.3; 130.6; 132.0; 133.3; 134.4; 137.1; 162.7. HPLC: (Method IV), t_R=6.95 min, purity 99%. MS: *m/z* 460 [M-H]⁻. Anal. calcd for C₁₆H₁₀BrCl₂NO₄S·H₂O: C 39.94, H 2.51, N 2.91, found: C 40.21, H 2.47, N 2.84.

6,8-Dichloro-2-(3-chlorobenzyl)-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (13c)

Prepared from compound **12c** according to procedure for compound **13a**. Yield 88%. White solid, mp:>175 °C (decomp.). ¹H NMR (200 MHz, CDCl₃), δ: 5.05 (s, 2H); 6.93 (d, *J*=7.0 Hz, 1H); 7.02-7.15 (m, 3H); 7.24 (d, *J*=2.0 Hz, 1H), 7.56 (s, 2H). HPLC: (Method I) t_R=7.38 min, purity 98%. MS: *m/z* 418 [M-H]⁻. Anal. calcd for C₁₆H₁₀Cl₃NO₄S: C 45.90, H 2.41, N 3.35, found: C 46.07, H 2.33, N 3.23.

Ethyl 2-(2-(bromomethyl)-4,5-dichloro-N-(4-methoxybenzyl)phenylsulfonamido)acetate (14b)

Prepared in 98% yield from compound **8b** according to procedure for compound **14a**. A light yellow oil. TLC: R_f=0.27 (Hex:EtOAc, 7:1). ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.22 (t, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 3.98 (s, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 4.50 (s, 2H), 4.85 (s, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.72 (s, 1H), 8.06 (s, 1H). ¹³C NMR (100 MHz, CDCl₃), δ ppm: 14.0, 27.7, 46.8, 51.3, 55.2, 61.6, 114.1, 125.7, 130.4, 131.4, 132.8, 134.7, 136.0, 137.4, 137.8, 159.7, 168.5;. MS *m/z* 548 [M+Na]⁺.

Ethyl 2-(2-(bromomethyl)-4,6-dichloro-N-(4-methoxybenzyl)phenylsulfonamido)acetate (14c)

Prepared in 98% yield from compound **8c** according to procedure for compound **14a**. A colorless oil;. TLC: R_f=0.29 (Hex:EtOAc, 6:1). ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.20 (t, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 4.06 (s, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 4.63 (s, 2H), 5.04 (s, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J* =

2.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃), δ ppm: 14.1, 30.9, 47.3, 51.7, 55.3, 61.4, 114.1, 126.4, 130.2, 132.1, 132.5, 134.8, 136.2, 138.5, 142.5, 159.6, 168.5.

Ethyl 6,7-dichloro-2-(4-methoxybenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (15b)

Prepared in 36% yield from compound **14b** according to procedure for compound **15a**. White solid; mp 104-108 °C. TLC: R_f=0.22 (Hex:EtOAc, 4:1). ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.23 (t, *J* = 7.2 Hz, 3H), 3.08 (dd, *J* = 16.5, 6.6 Hz, 1H), 3.39 (dd, *J* = 16.5, 9.4 Hz, 1H), 3.77 (s, 3H), 4.04 - 4.26 (m, 3H), 4.30 (d, *J* = 14.4 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 7.35 (s, 1H), 7.92 (s, 1H). ¹³C NMR (100 MHz, CDCl₃), δ ppm: 14.0, 27.0, 51.9, 55.3, 57.1, 62.1, 113.9, 125.6, 126.3, 130.3, 130.8, 132.0, 133.9, 136.6, 137.4, 159.2, 169.3. MS *m/z* 442 [M-H]⁻.

Ethyl 6,8-dichloro-2-(4-methoxybenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (15c)

Prepared in 25% yield from compound **14c** according to procedure for compound **15a**. White solid; mp 105-108 °C. TLC: R_f=0.22 (Hex:EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃), δ ppm: 1.21 (t, *J* = 7.4 Hz, 3H), 3.02 (dd, *J* = 17.4, 6.0 Hz, 1H), 3.41 (dd, *J* = 17.4, 9.6 Hz, 1H), 3.78 (s, 3H), 3.97 - 4.05 (m, 1H), 4.10 - 4.18 (m, 1H), 4.29 (d, *J* = 15.2 Hz, 1H), 4.53 (dd, *J* = 10, 6 Hz, 1H), 4.60 (d, *J* = 15.2 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 1.6 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃), δ ppm: 13.9, 27.5, 50.8, 55.3, 56.2, 62.3, 113.9, 127.1, 128.1, 130.0, 130.2, 132.7, 134.4, 137.9, 138.2, 159.5, 168.7. MS *m/z* 464 [M+Na]⁺.

Ethyl 6-chloro-2-(4-chlorobenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17b)

Prepared according to general procedure A using compound **16a** (100 mg, 0.35 mmol) and 4-chlorobenzyl chloride to give the product **17b** (60 mg, 42%) as a white solid; mp 94-97 °C. TLC: R_f=0.25 (Hex:EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃), δ ppm: 1.19 (t, *J* = 7.0 Hz, 3H), 3.15 (dd, *J* = 16.8, 6.4 Hz, 1H), 3.47 (dd, *J* = 16.8, 10.0 Hz, 1H), 4.01 - 4.18 (m, 2H), 4.31 (dd, *J* = 10.0, 6.4 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 4.39 (d, *J* = 15.2 Hz, 1H), 7.20 - 7.26 (m, 4H), 7.30 (d, *J* = 1.2 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H). MS *m/z* 437 [M+Na]⁺; low ionization. *Anal.* calcd for C₁₈H₁₇Cl₂NO₄S: C, 52.18; H, 4.14; N, 3.38. Found: C, 51.99; H, 4.20; N, 3.24.

Ethyl 6-chloro-2-(3-chlorobenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17c)

Prepared according to general procedure A using compound **16a** (150 mg, 0.52 mmol) and 3-chlorobenzyl chloride to give the product **17c** (180 mg, 82%) as a white solid; mp > 92 °C (decomp.). TLC: R_f =0.25 (Hex:EtOAc, 4:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 1.22 (t, J = 7.0 Hz, 3H), 3.15 (dd, J = 16.8, 6.6 Hz, 1H), 3.49 (dd, J = 16.8, 10.3 Hz, 1H), 3.98 – 4.21 (m, 2H), 4.32 (dd, J = 10.3, 6.6 Hz, 1H), 4.34 (d, J = 15 Hz, 1H), 4.38 (d, J = 15 Hz, 1H), 7.11 – 7.30 (m, 5H), 7.41 (dd, J = 8.0, 1.6 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H). MS m/z 414 $[\text{M}+\text{H}]^+$; low ionization. Anal. calcd for $\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{NO}_4\text{S}$: C, 52.18; H, 4.14; N, 3.38. Found: C, 52.01; H, 3.86; N, 3.08.

Ethyl 2-(3-bromobenzyl)-6-chloro-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17d)

Prepared according to general procedure A using compound **16a** (40 mg, 0.14 mmol) and 3-bromobenzyl bromide to give the product **17d** (30 mg, 47%) as a white solid; mp 103-106 °C. TLC: R_f =0.50 (Hex:EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.23 (t, J = 7.2 Hz, 3H), 3.15 (dd, J = 16.8, 6.8 Hz, 1H), 3.49 (dd, J = 16.8, 10.4 Hz, 1H), 4.04 - 4.20 (m, 2H), 4.30 (dd, J = 9.6, 6.4 Hz; 1H), 4.33 (d, J = 15.2 Hz, 1H), 4.40 (d, J = 15.2 Hz, 1H), 7.12 - 7.20 (m, 2H), 7.30 (s, 1H), 7.38 - 7.43 (m, 3H), 7.79 (d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3), δ ppm: 13.9, 27.4, 51.5, 57.9, 62.2, 122.6, 125.3, 127.1, 127.9, 129.2, 130.0, 131.1, 131.5, 135.8, 137.6, 138.6, 169.1. MS m/z 459 $[\text{M}+\text{H}]^+$.

Ethyl 2-benzyl-6-chloro-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17e)

Prepared according to general procedure A using compound **16a** (100 mg, 0.35 mmol) and benzyl bromide to give the product **17e** (60 mg, 42%) as a white solid; mp 80-83 °C. TLC: R_f =0.25 (Hex:EtOAc, 6:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.19 (t, J = 7.4 Hz, 3H), 3.13 (dd, J = 16.8, 6.6 Hz, 1H), 3.47 (dd, J = 16.8, 10.0 Hz, 1H), 3.99 – 4.16 (m, 2H), 4.27 (dd, J = 10.0, 6.6 Hz, 1H), 4.37 (d, J = 15.2 Hz, 1H), 4.48 (d, J = 15.2 Hz, 1H), 7.23 – 7.29 (m, 5H), 7.40 (dd, J = 8.4, 2.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H). MS m/z 380 $[\text{M}+\text{H}]^+$.

Ethyl 6-chloro-2-[(2-pyridinyl)-methyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17f)

Prepared according to general procedure A using compound **16a** (200 mg, 0.69 mmol), Et_3N and 2-chloromethyl pyridine to give the product **17f** (20 mg, 6%) as a white solid; mp > 55 °C (decomp.). TLC: R_f =0.16 (Hex:EtOAc, 2:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.20 (t, J = 7.2 Hz, 3H), 3.22 (dd, J = 16.8, 6.8 Hz, 1H), 3.50 (dd, J = 16.4, 11.6 Hz, 1H), 4.10 – 4.22 (m, 2H), 4.47 (d, J = 6.8 Hz, 1H), 4.52 (d, J = 6.8 Hz, 1H), 4.73 (dd, J = 10.8, 6.8 Hz, 1H), 7.11 – 7.14 (m, 1H), 7.27 (s, 1H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 7.47 (d, J = 7.6 Hz,

1H), 7.60 (td, $J = 7.6, 1.6$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 8.32 – 8.34 (m, 1H). MS m/z 381 $[M+H]^+$.

Ethyl 6-chloro-2-[(3-pyridinyl)-methyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17g)

Prepared according to general procedure A using compound **16a** (60 mg, 0.19 mmol), Et₃N and 3-bromomethylpyridine hydrogenbromide to give the product **17g** (30 mg, 34%) as a white solid; mp 91-94 °C. TLC: $R_f=0.35$ (Hex:EtOAc, 2:1). ¹H NMR (400 MHz, CDCl₃), δ ppm: 1.19 (t, $J = 7.2$ Hz, 3H), 3.17 (dd, $J = 16.8, 6.4$ Hz, 1H), 3.50 (dd, $J = 16.8, 10$ Hz, 1H), 4.02 – 4.18 (m, 2H), 4.37 (dd, $J = 10.4, 6.4$ Hz, 1H), 4.40 (s, 2H), 7.22 – 7.26 (m, 1H), 7.31 (d, $J = 1.3$ Hz, 1H), 7.41 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.74 (dt, $J = 8.4, 4$ Hz, 1H), 7.79 (d, $J = 8$ Hz, 1H), 8.47 (d, $J = 0.8$ Hz, 1H), 8.52 (d, $J = 3.6$ Hz, 1H). MS m/z 382 $[M+H]^+$.

Ethyl 6-chloro-2-[(2-methyl-1,3-thiazolyl-4)-methyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17h)

Prepared according to general procedure A using compound **16a** (100 mg, 0.35 mmol), Et₃N and 4-chloromethyl-2-methyl-1,3-thiazole hydrogenchloride to give the product **17h** (20 mg, 16%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃), δ ppm: 1.31 (t, $J = 7.2$, 3H), 2.45 (s, 3H), 3.19 (dd, $J = 16.4, 7.2$ Hz, 1H), 3.48 (dd, $J = 16.4, 10.4$ Hz, 1H), 4.24 – 4.30 (m, 2H), 4.36 (d, $J = 15.6$ Hz, 1H), 4.67 (d, $J = 15.6$ Hz, 1H), 4.78 (dd, $J = 10.4, 7.2$ Hz, 1H), 6.95 (s, 1H), 7.23 – 7.26 (m, 2H), 7.52 (d, $J = 8.4$ Hz, 1H). MS m/z 401 $[M+H]^+$.

Ethyl 2-(tert-butoxycarbonylmethyl)-6-chloro-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17i)

Prepared according to general procedure A using compound **16a** (120 mg, 0.41 mmol) and *tert*-butyl chloroacetate to give the product **17i** (120 mg, 74%) as a white solid; mp 104-107 °C. TLC: $R_f=0.35$ (Hex:EtOAc, 2:1). ¹H NMR (400 MHz, CDCl₃), δ ppm: 1.28 (s, 9H), 1.32 (t, $J = 7.2$ Hz, 3H), 3.29 (dd, $J = 15.8, 6.0$ Hz, 1H), 3.53 (dd, $J = 15.8, 11.2$ Hz, 1H), 3.79 (d, $J = 18.2$ Hz, 1H), 4.25 – 4.33 (m, 3H), 4.35 (d, $J = 18.2$ Hz, 1H), 7.34 – 7.37 (m, 2H), 7.65 (d, $J = 8.4$ Hz, 1H). ¹³C NMR (100 MHz, CDCl₃), δ ppm: 14.1, 27.8, 28.7, 49.7, 59.2, 62.2, 82.4, 123.7, 127.5, 128.8, 135.9, 137.6, 138.1, 167.4, 169.5. MS m/z 346 $[M-57]^-$ (elimination of *tert*-Bu).

Ethyl 6-chloro-2-(2-phenethyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17j)

Prepared according to general procedure A using compound **16a** (150 mg, 0.52 mmol) and 2-bromoethylbenzene to give the product **17j** (70 mg, 33%) as a light yellow oil. TLC: $R_f=0.32$ (Hex:EtOAc, 4:1). ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.34 (t, $J = 7.4$ Hz, 3H), 2.04 (t, $J =$

8.6 Hz, 2H), 3.15 (dd, J = 17.0, 6.2 Hz, 1H), 3.23 – 3.47 (m, 3H), 4.28 (q, J = 7.4 Hz, 2H), 4.49 (dd, J = 10.8, 5.6 Hz, 1H), 7.09 – 7.18 (m, 2H), 7.20 – 7.29 (m, 4H), 7.38 (dd, J = 8.8, 2.4 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H). MS m/z 394 $[M+H]^+$.

Ethyl 6-chloro-2-[2-(3-methoxyphenyl)-ethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17k)

Prepared according to general procedure A using compound **16a** (100 mg, 0.35 mmol) and 1-(2-bromoethyl)-3-methoxybenzene to give the product **17k** (50 mg, 36%) as a colorless oil. TLC: R_f =0.36 (Hex:EtOAc, 6:1). 1H NMR (400 MHz, $CDCl_3$), δ ppm: 1.34 (t, J = 7.2 Hz, 3H), 2.92 (t, J = 7.2 Hz, 2H), 3.14 (dd, J = 16.8, 6.4 Hz, 1H), 3.25 – 3.33 (m, 1H), 3.36 – 3.45 (m, 2H), 3.76 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 4.47 (dd, J = 10.8, 5.6 Hz, 1H), 6.64 (t, J = 2.0 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.72 (dd, J = 8.0, 2.4 Hz, 1H), 7.15 (t, J = 8.4 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.38 (dd, J = 8.8, 2.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H). MS m/z 424 $[M+H]^+$.

Ethyl 6-chloro-2-[2-(2-methoxyphenyl)-ethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17l)

Prepared according to general procedure A using compound **16a** (90 mg, 0.11 mmol) and 1-(2-bromoethyl)-2-methoxybenzene to give the product **17l** (70 mg, 60%) as a colorless oil. TLC: R_f =0.33 (Hex:EtOAc, 4:1). 1H NMR (400 MHz, $CDCl_3$), δ ppm: 1.32 (t, J = 7.0 Hz, 3H), 2.83 – 2.89 (m, 2H), 3.13 (dd, J = 17.6, 6.4 Hz, 1H), 3.27 – 3.47 (m, 3H), 3.78 (s, 3H), 4.22 – 4.34 (m, 2H), 4.47 (dd, J = 10.4, 6.2 Hz, 1H), 6.77 – 6.82 (m, 2H), 7.00 (dd, J = 7.2, 1.2 Hz, 1H), 7.16 (td, J = 7.6, 1.6 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H). MS m/z 424 $[M+H]^+$.

Ethyl 6-chloro-2-[2-(2-fluorophenyl)-ethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17m)

Prepared according to general procedure A using compound **16a** (90 mg, 0.31 mmol) and 1-(2-bromoethyl)-2-fluorobenzene to give the product **17m** (40 mg, 29%) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$), δ ppm: 1.35 (t, J = 7.2 Hz, 3H), 3.00 (t, J = 7.6 Hz, 2H), 3.17 (dd, J = 17.2, 6.4 Hz, 1H), 3.26 – 3.44 (m, 3H), 4.23 – 4.35 (m, 2H), 4.54 (dd, J = 11.2, 6.0 Hz, 1H), 6.93 – 7.03 (m, 2H), 7.12 – 7.20 (m, 2H), 7.29 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 8.4, 1.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H). MS m/z 412 $[M+H]^+$.

Ethyl 6-chloro-2-[2-(3-methoxyphenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17n)

Prepared according to general procedure A using compound **16a** (120 mg, 0.41 mmol) and 2-bromo-1-(3-methoxyphenyl)-ethanone to give the product **17n** (80 mg, 42%) as a colorless

oil. TLC: R_f =0.28 (Hex:EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.31 (t, J = 7.2 Hz, 3H), 3.35 (dd, J = 15.6, 9.0 Hz, 1H), 3.63 (dd, J = 15.6, 11.2 Hz, 1H), 3.81 (s, 3H), 4.23 – 4.30 (m, 3H), 4.68 (d, J = 18.6 Hz, 1H), 5.20 (d, J = 18.6 Hz, 1H), 7.12 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 – 7.34 (m, 2H), 7.39 – 7.44 (m, 3H), 7.65 (d, J = 7.6 Hz, 1H). MS m/z 438 $[\text{M}+\text{H}]^+$.

Ethyl 6-chloro-2-[2-(2-methoxyphenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17o)

Prepared according to general procedure A using compound **16a** (110 mg, 0.38 mmol) and 2-bromo-1-(2-methoxyphenyl)-ethanone to give the product **17o** (120 mg, 70%) as a colorless oil. TLC: R_f =0.34 (Hex:EtOAc, 2:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.32 (t, J = 7 Hz, 3H), 3.34 (dd, J = 15.6, 6.4 Hz, 1H), 3.62 (dd, J = 15.5, 11.2 Hz, 1H), 4.20 (dd, J = 12.2, 6.4 Hz, 1H), 4.24 – 4.34 (m, 2H), 4.63 (d, J = 19.2 Hz, 1H), 5.23 (d, J = 19.2 Hz, 1H), 6.96 (m, 2H), 7.39 (m, 2H), 7.48 (td, J = 8.0, 2.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H). MS m/z 438 $[\text{M}+\text{H}]^+$.

Ethyl 6-chloro-2-[2-(3-fluorophenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17p)

Prepared according to general procedure A using compound **16a** (100 mg, 0.35 mmol) and 2-bromo-1-(3-fluorophenyl)-ethanone to give the product **17p** (110 mg, 77%) as a light yellow oil. TLC: R_f =0.22 (Hex:EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.38 (t, J = 6.8 Hz, 3H), 3.36 (dd, J = 16.0, 6.0 Hz, 1H), 3.63 (dd, J = 16.0, 11.6 Hz, 1H), 4.22 – 4.33 (m, 3H), 4.67 (d, J = 18.8 Hz, 1H), 5.16 (d, J = 18.8 Hz, 1H), 7.27 – 7.31 (m, 1H), 7.40 – 7.47 (m, 3H), 7.51 – 7.54 (m, 1H), 7.63 – 7.66 (m, 2H). MS m/z 426 $[\text{M}+\text{H}]^+$.

Ethyl 6-chloro-2-[2-(4-chlorophenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17q)

Prepared according to general procedure A using compound **16a** (100 mg, 0.35 mmol) and 2-bromo-1-(4-chlorophenyl)-ethanone to give the product **17q** (120 mg, 75%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3), δ ppm: 1.29 (t, J = 7.2 Hz, 3H), 3.34 (dd, J = 15.8, 6.4 Hz, 1H), 3.61 (dd, J = 15.8, 11.4 Hz, 1H), 4.20 – 4.30 (m, 2H), 4.65 (d, J = 18.5 Hz, 1H), 5.12 (d, J = 18.5 Hz, 1H), 7.39 – 7.43 (m, 4H), 7.63 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H). MS m/z 442 $[\text{M}+\text{H}]^+$.

Ethyl 6,7-dichloro-2-(3-chlorobenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17r)

Prepared according to general procedure A using compound **16b** (120 mg, 0.37 mmol) and 3-chlorobenzyl chloride to give the product **17r** (160 mg, 96%) as a white solid; mp 120-123

°C. TLC: R_f =0.37 (Hex:EtOAc, 4:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 1.23 (t, J = 7.2 Hz, 3H), 3.17 (dd, J = 16.5, 6.4 Hz, 1H), 3.44 (dd, J = 16.5, 10.0 Hz, 1H), 4.03 – 4.21 (m, 2H), 4.31 (dd, J = 10.0, 6.4 Hz, 1H), 4.36 (s, 2H), 7.11 – 7.28 (m, 4H), 7.41 (s, 1H), 7.94 (s, 1H). MS m/z 448 $[\text{M-H}]^-$. *Anal.* calcd for $\text{C}_{18}\text{H}_{16}\text{Cl}_3\text{NO}_4\text{S}$: C, 48.18; H, 3.59; N, 3.12. Found: C, 48.47; H, 3.65; N, 2.90.

Ethyl 6,7-dichloro-2-(2-phenylethyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (17s)

Prepared according to general procedure A using compound **16b** (120 mg, 0.37 mmol) and 2-bromoethylbenzene to give the product **17s** (70 mg, 45%) as a white solid; mp > 97 °C (decomp.). TLC: R_f =0.35 (Hex:EtOAc, 4:1). ^1H NMR (200 MHz, CDCl_3), δ ppm: 1.35 (t, J = 7.2 Hz, 3H), 2.93 (t, J = 8.2 Hz, 2H), 3.13 (dd, J = 17.0, 6.0 Hz, 1H), 3.23 – 3.52 (m, 3H), 4.28 (q, J = 7.2 Hz, 2H), 4.47 (dd, J = 11.0, 6.4 Hz, 1H), 7.06 – 7.11 (m, 2H), 7.20 – 7.26 (m, 3H), 7.39 (s, 1H), 7.85 (s, 1H). MS m/z 428 $[\text{M-H}]^-$, low ionization. *Anal.* calcd for $\text{C}_{19}\text{H}_{19}\text{Cl}_2\text{NO}_4\text{S}$: C, 53.28; H, 4.47; N, 3.27. Found: C, 53.27; H, 4.50; N, 3.20.

Hydrolysis of ethyl 3,4-dihydro-2H-1,2-benzothiazine-3-carboxylates 15, 16 and 17 (General procedure B)

To a solution of ethyl 3,4-dihydro-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide (1 mmol) in THF (2 mL) was added a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ or NaOH (1 mmol) in H_2O (2 mL), then it was stirred at room temperature for 2 – 8 h (TLC control). The reaction mixture was acidified by 1N HCl (~ pH 2) and extracted with CH_2Cl_2 (3 $\times$ 15 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The residue was triturated with Et_2O or hexane and washed with small amount of Et_2O , CH_2Cl_2 or CHCl_3 . Dried *in vacuo* over P_2O_5 (room temperature).

6-Chloro-2-(4-methoxybenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18a)

Prepared according to general procedure B using compound **15a** (90 mg, 0.21 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ to give the product **18a** (50 mg, 62%) as a white solid; mp 179-181 °C. ^1H NMR (400 MHz, CDCl_3), δ ppm: 3.21 (dd, J = 16.2, 7.8 Hz, 1H), 3.43 (dd, J = 15.4, 9.6 Hz, 1H), 3.77 (s, 3H), 4.11 (dd, J = 9.4, 7.2 Hz, 1H), 4.21 (d, J = 14.6 Hz, 1H), 4.43 (d, J = 14.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 7.29 (s, 1H), 7.43 (dd, J = 7.8, 1.6 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H). MS m/z 380 $[\text{M-H}]^-$; purity (HPLC, 254 nm, Method I, t_R = 8.74 min) 99%. *Anal.* calcd for $\text{C}_{17}\text{H}_{16}\text{ClNO}_5\text{S}$: C, 53.48; H, 4.22; N, 3.67. Found: C, 53.56; H, 3.98; N, 3.67.

6,8-Dichloro-2-(4-methoxybenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18b)

Prepared according to general procedure B using compound **15b** (30 mg, 0.06 mmol) and NaOH to give the product **18b** (5 mg, 21%) as a white solid; mp 184-187 °C. ¹H NMR (200 MHz, CDCl₃), δ ppm: 3.12 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.39 (dd, *J* = 17.0, 11.0 Hz, 1H), 3.78 (s, 3H), 4.34 – 4.54 (m, 3H), 6.78 (d, *J* = 8.0 Hz, 2H), 7.14 – 7.26 (m, 3H), 7.42 (s, 1H). MS *m/z* 414 [M-H]⁻; purity (HPLC, 254 nm, Method I, *t_R* = 9.38) 99%.

6-Chloro-2-(3-methoxybenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18c)

Prepared according to general procedure B using compound **17a** (80 mg, 0.2 mmol) and LiOH•H₂O to give the product **18c** (40 mg, 46%) as a white solid; mp 142-145 °C. ¹H NMR (400 MHz, CDCl₃), δ ppm: 3.24 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.45 (dd, *J* = 16.0, 9.6 Hz, 1H), 3.71 (s, 3H), 4.12 (dd, *J* = 9.2, 7.6 Hz, 1H), 4.26 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 6.71 - 6.75 (m, 2H), 6.79 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.44 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H). MS *m/z* 380 [M-H]⁻; purity (HPLC, 254 nm, Method I, *t_R* = 7.16 min) 94%. *Anal.* calcd for C₁₇H₁₆ClNO₅S: C, 53.48; H, 4.22; N, 3.67. Found: C, 53.50; H, 3.88; N, 3.56.

6-Chloro-2-(4-chlorobenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18d)

Prepared according to general procedure B using compound **17b** (50 mg, 0.12 mmol) and LiOH•H₂O to give the product **18d** (20 mg, 50%) as a white solid; mp 209-211 °C. ¹H NMR (400 MHz, CDCl₃), δ ppm: 3.26 (dd, *J* = 16.4, 7.2 Hz, 1H), 3.46 (dd, *J* = 16.4, 9.6 Hz, 1H), 4.15 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.23 (d, *J* = 15.2 Hz, 1H), 4.45 (d, *J* = 15.2 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 1.6 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H). MS *m/z* 384 [M-H]⁻; purity (HPLC, 254 nm, Method II, *t_R* = 6.72 min) 98%. *Anal.* calcd for C₁₆H₁₃Cl₂NO₄S: C, 49.75; H, 3.39; N, 3.68. Found: C, 49.58; H, 3.38; N, 3.45.

6-Chloro-2-(3-chlorobenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18e)

Prepared according to general procedure B using compound **17c** (0.17 g, 0.41 mmol) and NaOH to give the product **18e** (0.13 g, 80%) as a white solid; mp 196-199 °C. ¹H NMR (200 MHz, CDCl₃), δ ppm: 3.24 (dd, *J* = 16.2, 7.4 Hz, 1H), 3.47 (dd, *J* = 16.2, 9.8 Hz, 1H), 4.16 (dd, *J* = 9.6, 7.4 Hz, 1H), 4.32 (d, *J* = 15.4 Hz, 1H), 4.42 (d, *J* = 15.4 Hz, 1H), 7.09 – 7.15 (m, 2H), 7.20 – 7.26 (m, 2H), 7.31 (s, 1H), 7.45 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.81 (d, *J* = 8.0

Hz, 1H). MS m/z 384 $[M-H]^-$; purity (HPLC, 254 nm, Method I, t_R = 9.41 min) 99%. *Anal.* calcd for $C_{16}H_{13}Cl_2NO_4S$: C, 49.75; H, 3.39; N, 3.68. Found: C, 49.35; H, 3.08; N, 3.58.

2-(3-Bromobenzyl)-6-chloro-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18f)

Prepared according to general procedure B using compound **17d** (0.1 g, 0.03 mmol) and $LiOH \cdot H_2O$ to give the product **18f** (0.07 g, 73%) as a white solid; mp > 155 °C (decomp.). 1H NMR (400 MHz, $CDCl_3$), δ ppm: 3.21 (dd, J = 16.2, 6.8 Hz, 1H), 3.45 (dd, J = 16.2, 10.0 Hz, 1H), 4.19 (dd, J = 9.6, 6.8 Hz, 1H), 4.37 (d, J = 15.4 Hz, 1H), 4.47 (d, J = 15.4 Hz, 1H), 7.10–7.19 (m, 2H), 7.29 (s, 1H), 7.33 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.42 (dd, J = 8.4, 1.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H). MS m/z 430 $[M-H]^-$, purity (HPLC, 254 nm, Method III, t_R = 6.93 min) 99%. *Anal.* calcd for $C_{16}H_{13}BrClNO_4S$: C, 44.62; H, 3.04; N, 3.25. Found: C, 44.99; H, 2.95; N, 2.98.

2-Benzyl-6-chloro-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18g)

Prepared according to general procedure B using compound **17e** (50 mg, 0.14 mmol) and $LiOH \cdot H_2O$ to give the product **18g** (20 mg, 52%) as a white solid; mp 185–188 °C. 1H NMR (400 MHz, $CDCl_3$), δ ppm: 3.24 (dd, J = 16.4, 7.6 Hz, 1H), 3.44 (dd, J = 16.4, 9.4 Hz, 1H), 4.12 (dd, J = 9.4, 7.6 Hz, 1H), 4.23 (d, J = 14.4 Hz, 1H), 4.51 (d, J = 14.4 Hz, 1H), 7.18 – 7.21 (m, 2H), 7.26 – 7.28 (m, 3H), 7.31 (s, 1H), 7.45 (dd, J = 8.4, 2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H). MS m/z 350 $[M-H]^-$; purity (HPLC, 254 nm, Method I, t_R = 8.60 min) 99%. *Anal.* calcd for $C_{16}H_{14}ClNO_4S$: C, 54.63; H, 4.01; N, 3.98. Found: C, 54.48; H, 3.86; N, 3.96.

6,7-Dichloro-2-(3-chlorobenzyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18h)

Prepared according to general procedure B using compound **17r** (0.15 g, 0.33 mmol) and NaOH to give the product **18h** (0.05 g, 38%) as a white solid; mp 164–167 °C. 1H NMR (200 MHz, $CDCl_3$), δ ppm: 3.21 (dd, J = 16.5, 7.4 Hz, 1H), 3.42 (dd, J = 16.5, 9.6 Hz, 1H), 4.18 (dd, J = 9.6, 7.4 Hz, 1H), 4.39 (s, 2H), 7.09 – 7.17 (m, 2H), 7.21 – 7.26 (m, 2H), 7.41 (s, 1H), 7.94 (s, 1H). MS m/z 420 $[M-H]^-$, purity (HPLC, 254 nm, Method I, t_R = 10.12 min) 97%. *Anal.* calcd for $C_{16}H_{12}Cl_3NO_4S$: C, 45.68; H, 2.88; N, 3.33. Found: C, 45.86; H, 2.72; N, 3.24.

6-Chloro-2-(2-phenylethyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18i)

Prepared according to general procedure B using compound **17j** (60 mg, 0.15 mmol) and NaOH to give the product **18i** (30 mg, 52%) as a white solid; mp 188–190 °C. 1H NMR (200 MHz, $CDCl_3$), δ ppm: 2.88 (t, J = 7.7 Hz, 2H), 3.20 – 3.48 (m, 4H), 4.29 (dd, J = 10.2, 7.4

Hz, 1H), 7.06 – 7.11 (m, 2H), 7.22 – 7.26 (m, 2H), 7.34 (s, 1H), 7.42 (dd, $J = 8.8, 1.4$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 1H). MS m/z 364 [M-H]⁻; purity (HPLC, 254 nm, Method I, $t_R = 9.31$ min) 96%. *Anal.* calcd for C₁₇H₁₆ClNO₄S: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.58; H, 4.18; N, 3.80.

6-Chloro-2-[2-(3-methoxyphenyl)-ethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18j)

Prepared according to general procedure B using compound **17k** (50 mg, 0.12 mmol) and NaOH to give the product **18j** (40 mg, 89%) as a white solid; mp 159-132 °C. ¹H NMR (400 MHz, DMSO-d₆), δ ppm: 2.69 – 2.83 (m, 2H), 3.17 – 3.26 (m, 2H), 3.33 (m, overlapped by H₂O), 3.69 (s, 1H), 4.65 (t, $J = 7.6$ Hz, 1H), 6.68 – 6.69 (m, 2H), 6.72 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.14 (t, $J = 8.0$ Hz, 1H), 7.52 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.65 (d, $J = 1.6$ Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H). MS m/z 394 [M-H]⁻, purity (HPLC, 254 nm, Method I, $t_R = 9.17$ min) 99%. *Anal.* calcd for C₁₈H₁₈ClNO₅S: C, 54.61; H, 4.58; N, 3.54. Found: C, 54.95; H, 4.69; N, 3.78.

6-Chloro-2-[2-(2-methoxyphenyl)-ethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18k)

Prepared according to general procedure B using compound **17l** (0.08 g, 0.186 mmol) and NaOH to give the product **18k** (0.05 g, 68%) as a white solid; mp 147-150 °C. ¹H NMR (400 MHz, DMSO-d₆), δ ppm: 2.73 – 2.79 (m, 2H), 3.18 – 3.23 (m, 2H), 3.28-3.33 (m, overlapped by H₂O), 3.73 (s, 1H), 4.61 (t, $J = 8.4$ Hz, 1H), 6.78 (td, $J = 7.2, 1.2$ Hz, 1H); 6.88 (d, $J = 8.0$ Hz, 1H), 7.00 (dd, $J = 7.2, 1.6$ Hz, 1H), 7.15 (td, $J = 8.0, 2.0$ Hz, 1H), 7.52 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.64 (d, $J = 1.6$ Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H). MS m/z 394 [M-H]⁻; purity (HPLC, 254 nm, Method I, $t_R = 9.34$ min) 98%. *Anal.* calcd for C₁₈H₁₈ClNO₅S: C, 54.61; H, 4.58; N, 3.54. Found: C, 55.31; H, 4.73; N, 3.37.

6-Chloro-2-[2-(2-fluorophenyl)-ethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18l)

Prepared according to general procedure B using compound **17m** (40 mg, 0.09 mmol) and NaOH to give the product **18l** (20 mg, 55%) as a white solid. ¹H NMR (400 MHz, CDCl₃), δ ppm: 2.91 (t, $J = 6.8$ Hz, 2H), 3.25 – 3.31 (m, 2H), 3.38 – 3.47 (m, 2H), 4.36 (dd, $J = 10.0, 7.2$ Hz, 1H), 6.92 (m, 2H), 7.08 – 7.12 (m, 1H), 7.14 – 7.20 (m, 1H), 7.33 (s, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.0$ Hz, 1H). MS m/z 382 [M-H]⁻; purity (HPLC, 254 nm, Method I, $t_R = 9.22$ min) 97%.

6,7-Dichloro-2-(2-phenylethyl)-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18m)

Prepared according to general procedure B using compound **17s** (60 mg, 0.15 mmol) and NaOH to give the product **18m** (50 mg, 76%) as a white solid; mp 196-200 °C. ¹H NMR (200 MHz, CDCl₃), δ ppm: 2.89 (t, *J* = 7.4 Hz, 2H), 3.18 – 3.32 (m, 2H), 3.38 – 3.47 (m, 2H), 4.32 (dd, *J* = 10.4, 7.6 Hz, 1H), 7.05 – 7.09 (m, 2H), 7.20 – 7.26 (m, 3H), 7.43 (s, 1H), 7.85 (s, 1H). MS *m/z* 398 [M-H]⁻; purity (HPLC, 254 nm, Method I, *t_R* = 10.07 min) 94%. *Anal.* calcd for C₁₇H₁₅Cl₂NO₄S: C, 51.01; H, 3.78; N, 3.50. Found: C, 51.28; H, 3.50; N, 3.45.

6-Chloro-2-[2-(3-methoxyphenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18n)

Prepared according to general procedure B using compound **17n** (70 mg, 0.17 mmol) and NaOH to give the product **18n** (40 mg, 58%) as a white solid; mp 185-188 °C. ¹H NMR (400 MHz, DMSO-*d*₆), δ ppm: 3.26 (m, overlapped by H₂O), 3.41 (dd, *J* = 16.2, 6.0 Hz, 1H), 3.75 (s, 3H), 4.36 (dd, *J* = 11.6, 6.0 Hz, 1H), 4.77 (d, *J* = 19.2 Hz, 1H), 5.00 (d, *J* = 19.2 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.37 (s, 1H), 7.40 (t, *J* = 8.4 Hz, 1H), 7.51 – 7.56 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H). MS *m/z* 408 [M-H]⁻; purity (HPLC, 254 nm, Method I, *t_R* = 8.94 min) 99%. *Anal.* calcd for C₁₈H₁₆ClNO₆S: C, 52.75; H, 3.93; N, 3.42. Found: C, 52.38; H, 3.95; N, 3.33.

6-Chloro-2-[2-(2-methoxyphenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18o)

Prepared according to general procedure B using compound **17o** (110 mg, 0.25 mmol) and LiOH•H₂O to give the product **18o** (70 mg, 71%) as a white solid; mp > 130 °C (decomp.). ¹H NMR (400 MHz, CDCl₃), δ ppm: 3.36 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.73 (dd, *J* = 16.5, 9.0 Hz, 1H), 3.85 (s, 3H), 3.99 (t, *J* = 8.8 Hz, 1H), 4.06 (d, *J* = 19.2 Hz, 1H), 5.02 (d, *J* = 19.2 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.58 (td, *J* = 8.8, 2.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.98 (dd, *J* = 8.0, 1.6 Hz, 1H). MS *m/z* 408 [M-H]⁻; purity (HPLC, 254 nm, Method III, *t_R* = 6.48 min) 99%. *Anal.* calcd for C₁₈H₁₆ClNO₆S: C, 52.64; H, 3.79; N, 3.23. Found: C, 52.75; H, 3.93; N, 3.42.

6-Chloro-2-[2-(3-fluorophenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18p)

Prepared according to general procedure B using compound **17p** (40 mg, 0.09 mmol) and LiOH•H₂O to give the product **18p** (30 mg, 72%) as a white solid; mp 132-135 °C. ¹H NMR (200 MHz, CDCl₃), δ ppm: 3.77 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.73 (dd, *J* = 16.5, 9.6 Hz, 1H), 4.04 (t, *J* = 9.6 Hz, 1H), 4.28 (d, *J* = 18.6 Hz, 1H), 5.01 (d, *J* = 18.6 Hz, 1H), 7.26 - 7.69 (m, 6H), 7.77 (d, *J* = 8 Hz, 1H). MS *m/z* 396 [M-H]⁻; purity (HPLC, 254 nm, Method I, *t_R* = 8.96

min) 99%. *Anal.* calcd for $C_{17}H_{13}ClFNO_5S \times 0.8CH_2Cl_2$: C, 45.90; H, 3.16; N, 3.06. Found: C, 45.55; H, 3.29; N, 2.92.

6-Chloro-2-[2-(4-chlorophenyl)-2-oxoethyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18q)

Prepared according to general procedure B using compound **17q** (110 mg, 0.25 mmol) and $LiOH \cdot H_2O$ to give the product **18q** (70 mg, 66%) as a white solid; mp 201-204 °C. 1H NMR (400 MHz, $DMSO-d_6$), δ ppm: 3.26 (m, overlapped by H_2O), 3.45 (dd, $J = 16.4, 6.2$ Hz, 1H), 4.42 (dd, $J = 11.6, 6.2$ Hz, 1H), 4.80 (d, $J = 19.2$ Hz, 1H), 5.00 (d, $J = 19.2$ Hz, 1H), 7.53 – 7.57 (m, 2H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.75 (s, 1H), 7.92 (d, $J = 8.8$ Hz, 2H). MS m/z 414 $[M+H]^+$; low ionization; purity (HPLC, 254 nm, Method I, $t_R = 9.56$ min) 99%. *Anal.* calcd for $C_{17}H_{13}Cl_2NO_5S$: C, 49.29; H, 3.16; N, 3.38. Found: C, 49.26; H, 3.21; N, 3.30.

6-Chloro-2-[(2-pyridinyl)-methyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18r)

Prepared according to general procedure B using compound **17f** (20 mg, 0.05 mmol) and $LiOH \cdot H_2O$ to give the product **18r** (7 mg, 42%) as a white solid; mp > 193 °C (decomp.). 1H NMR (400 MHz, $CDCl_3$), δ ppm: 3.41 (dd, $J = 16.8, 8.0$ Hz, 1H), 3.75 (dd, $J = 16.8, 9.2$ Hz, 1H), 3.92 (d, $J = 17.2$ Hz, 1H), 4.29 (dd, $J = 9.2, 8.0$ Hz, 1H), 4.83 (d, $J = 17.2$ Hz, 1H), 7.25 – 7.26 (m, 1H), 7.41 – 7.45 (m, 3H), 7.79 (d, $J = 8.4$ Hz, 1H), 7.85 (td, $J = 7.6, 1.6$ Hz, 1H), 8.61 (d, $J = 4.8$ Hz, 1H). MS m/z 351 $[M-H]^-$; purity (HPLC, 254 nm, Method I, $t_R = 5.44$ min) 99%.

6-Chloro-2-[(3-pyridinyl)-methyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18s)

Prepared according to general procedure B using compound **17g** (20 mg, 0.05 mmol) and NaOH to give the product **18s** (7 mg, 42%) as a white solid; mp > 195 °C (decomp.). 1H NMR (400 MHz, $DMSO-d_6$), δ ppm: 4.22 (d, $J = 15.8$ Hz, 1H), 4.36 (d, $J = 15.8$ Hz, 1H), 4.69 (t, $J = 8.2$ Hz, 1H), 7.31 (dd, $J = 7.2, 4.8$ Hz, 1H), 7.55 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.68 (s, 1H), 7.76 (d, $J = 8.4$ Hz, 2H), 8.43 (d, $J = 5.6$ Hz, 1H), 8.52 (s, 1H). MS m/z 351 $[M-H]^-$; purity (HPLC, 254 nm, Method I, $t_R = 4.28$ min) 94%.

6-Chloro-2-[(2-methyl-1,3-thiazolyl-4)-methyl]-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18t)

Prepared according to general procedure B using compound **17h** (20 mg, 0.05 mmol) and $LiOH \cdot H_2O$ to give the product **18t** (10 mg, 79%) as a white solid; mp 193-197 °C. 1H NMR (400 MHz, $CDCl_3$), δ ppm: 2.74 (s, 3H), 3.34 (dd, $J = 16.4, 8.0$ Hz, 1H), 3.69 (dd, $J = 16.4, 10.0$ Hz, 1H), 3.89 (d, $J = 16.8$ Hz, 1H), 4.34 (dd, $J = 9.4, 8.0$ Hz, 1H), 4.66 (d, $J = 16.8$ Hz,

1H), 6.94 (s, 1H), 7.40 – 7.42 (m, 2H), 7.76 (d, $J = 8.4$ Hz, 1H). MS m/z 371 [M-H]⁻; purity (HPLC, 254 nm, Method I, $t_R = 7.60$ min) 95%. *Anal.* calcd for C₁₄H₁₃ClN₂O₄S₂: C, 45.10; H, 3.51; N, 7.51. Found: C, 45.33; H, 3.34; N, 7.33.

2-(tert-Butoxycarbonylmethyl)-6-chloro-3,4-dihydro-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (18u)

Prepared according to general procedure B using compound **17i** (100 mg, 0.26 mmol) and NaOH to give the product **18u** (70 mg, 75%) as a white solid; mp 139-141 °C. ¹H NMR (200 MHz, CDCl₃), δ ppm: 1.45 (s, 9H), 3.29 (d, $J = 18.2$ Hz, 1H), 3.32 (dd, $J = 15.6, 8.4$ Hz, 1H), 3.69 (dd, $J = 15.6, 8.4$ Hz, 1H), 4.00 (t, $J = 8.4$ Hz, 1H), 4.23 (d, $J = 18.2$ Hz, 1H), 7.41 – 7.44 (m, 2H), 7.75 (d, $J = 8.4$, 1H). MS m/z 374 [M-H]⁻; purity (HPLC, 254 nm, Method I, $t_R = 8.70$ min) 98%. *Anal.* calcd for C₁₅H₁₈ClNO₆S: C, 47.94; H, 4.83; N, 3.73. Found: C, 47.89; H, 4.65; N, 3.71.