Supporting Information

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

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\textbf{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). \(^1\)H NMR (200 MHz, CDCl\textsubscript{3}), \(\delta\) ppm: 1.24 (s, 9H), 2.59 (s, 3H), 4.05 (s, 1H), 7.39 (s, 1H), 8.10 (s, 1H). \(^13\)C NMR (100 MHz, CDCl\textsubscript{3}), \(\delta\) ppm: 19.5, 30.1, 55.2, 130.2, 130.8, 133.8, 136.4, 140.8. MS \(m/z\) 294 [M-H]\(^-\).

\textbf{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). \(^1\)H NMR (200 MHz, CDCl\textsubscript{3}), \(\delta\) 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). \textit{Anal.} calcd for C\textsubscript{11}H\textsubscript{15}Cl\textsubscript{2}NO\textsubscript{2}S: C, 44.60; H, 5.10; N, 4.73. Found: C, 44.56; H, 5.20; N, 4.57.

\textbf{2-(tert-Butyl)-5,6-dichlorobenzo[d]isothiazol-3(2H)-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: Rf=0.37 (Hex:EtOAc, 4:1). 1H NMR (200 MHz, CDCl3), δ ppm: 1.75 (s, 9H), 7.92 (s, 1H), 8.05 (s, 1H). 13C NMR (100 MHz, CDCl3), δ ppm: 27.7, 62.0, 122.2, 126.5, 126.8, 136.7, 139.5, 158.0. MS m/z 250 [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: Rf=0.33 (Hex:EtOAc, 20:1). 1H NMR (200 MHz, CDCl3), δ ppm: 1.76 (s, 9H), 7.72 (d, J = 1.6 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H); 13C NMR (100 MHz, CDCl3), δ ppm: 27.7, 62.2, 123.2, 128.9, 130.8, 133.5, 134.8, 141.4, 157.5. MS m/z 250 [M-57]- (tert-Bu).

Anal. calcd for C11H11Cl2NO3S: 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: Rf=0.12 (EtOAc:AcOH, 1:0.01). 1H NMR (200 MHz, DMSO-d6), δ ppm: 4.48 (s, 1H) 8.09 (s, 1H), 8.52 (s, 1H); 13C NMR (100 MHz, acetone-d6), δ ppm: 125.3, 128.8, 129.7, 140.7, 141.0, 141.4, 160.0. MS m/z 250 [M-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: Rf=0.01 (EtOAc:AcOH, 1:0.01). 1H NMR (200 MHz, DMSO-d6), δ ppm: 7.78 (d, J = 1.6 Hz, 1H), 7.91 (d, J = 1.6 Hz, 1H); 13C NMR (100 MHz, acetone-d6), δ ppm: 122.7, 127.1, 133.2, 134.6, 137.6, 139.2, 161.1. MS m/z 250 [M-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: Rf=0.28 (Hex:EtOAc, 4:1). 1H NMR (200 MHz, CDCl3), 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). 13C NMR (100 MHz, CDCl3), 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 [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: Rf=0.43 (petroleum ether: EtOAc, 4:1). 1H NMR (200 MHz, CDCl3), 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$_3$), $\delta$ 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 [M-121]$^\text{+}$ (p-MeOBn). Anal. calcd for C$_{15}$H$_{11}$Cl$_2$NO$_4$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). $^1$H KMR (200 MHz, CDCl$_3$), $\delta$ 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$_6$), $\delta$ 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 [M-H]$^-$. Anal. calcd for C$_{15}$H$_{15}$Cl$_2$NO$_4$S: C, 47.88; H, 4.02; N, 3.72. Found: C, 47.88; H, 4.07; N, 3.56.

**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). $^1$H NMR (200 MHz, CDCl$_3$), $\delta$ 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, $J = 2.0$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$), $\delta$ 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 [M-H]$^-$. Anal. calcd for C$_{15}$H$_{15}$Cl$_2$NO$_4$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). $^1$H NMR (200 MHz, CDCl$_3$), $\delta$ 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 [M-H]$^-$. Anal. calcd for C$_{13}$H$_{15}$Cl$_2$NO$_4$S: C, 47.88; H, 4.02; N, 3.72. Found: C, 47.88; H, 4.07; N, 3.56.

**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). $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ 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$_3$), $\delta$ 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 C₁₆H₁₂BrCl₃NO₄S: 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). $^{13}$C NMR (100 MHz, CDCl$_3$), 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). $^1$H NMR (200 MHz, CDCl$_3$), 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). $^{13}$C NMR (100 MHz, CDCl$_3$), 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). $^1$H NMR (400 MHz, CDCl$_3$), 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), 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). $^{13}$C NMR (125 MHz, CDCl$_3$), 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). $^1$H NMR (400 MHz, CDCl$_3$), 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 C$_{18}$H$_{17}$Cl$_2$NO$_4$S: 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 (100 mg, 0.35 mmol) and 4-chlorobenzyl chloride to give the product 17c (60 mg, 42%) as a white solid; mp 94-97 °C. TLC: R$_f$=0.25 (Hex:EtOAc, 4:1). $^1$H NMR (400 MHz, CDCl$_3$), 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 C$_{18}$H$_{17}$Cl$_2$NO$_4$S: C, 52.18; H, 4.14; N, 3.38. Found: C, 51.99; H, 4.20; N, 3.24.
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: Rf = 0.25 (Hex:EtOAc, 4:1). \(^1\)H 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 (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 [M+H]; low ionization. Anal. calcd for C\(_{18}\)H\(_{17}\)Cl\(_2\)NO\(_4\)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: Rf = 0.50 (Hex:EtOAc, 4:1). \(^1\)H 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 [M+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: Rf = 0.25 (Hex:EtOAc, 6:1). \(^1\)H 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 [M+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\(_3\)N and 2-chloromethyl pyridine to give the product 17f (20 mg, 6%) as a white solid; mp > 55 °C (decomp.). TLC: Rf = 0.16 (Hex:EtOAc, 2:1). \(^1\)H 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: Rf =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: Rf=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: Rf=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 = 7.4 Hz, 2H), 2.45 (m, 2H), 3.17 (dd, J = 16.4, 8.4 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 391 [M+H]+.
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: Rf=0.36 (Hex:EtOAc, 6:1). 1H NMR (400 MHz, CDCl3), 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: Rf=0.33 (Hex:EtOAc, 4:1). 1H NMR (400 MHz, CDCl3), 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), 3.25 – 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-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, CDCl3), 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: Rf=0.33 (Hex:EtOAc, 4:1). 1H NMR (400 MHz, CDCl3), δ ppm: 1.35 (t, J = 7.2 Hz, 3H), 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]+.
oil. TLC: Rf=0.28 (Hex:EtOAc, 4:1). \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 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 [M+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) un 2-bromo-1-(2-methoxyphenyl)-ethanone to give the product 17o (120 mg, 70%) as a colorless oil. TLC: Rf=0.34 (Hex:EtOAc, 2:1). \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 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 [M+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: Rf=0.22 (Hex:EtOAc, 4:1). \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 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 [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 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 [M+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, CDCl₃), 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 [M-H]. Anal. calcd for C₁₈H₁₆Cl₃N₂O₄S: 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, CDCl₃), 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 [M-H]; low ionization. Anal. calcd for C₁₉H₁₉Cl₂N₂O₄S: 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 LiOH•H₂O or NaOH (1 mmol) in H₂O (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 CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was triturated with Et₂O or hexane and washed with small amount of Et₂O, CH₂Cl₂ or CHCl₃. Dried in vacuo over P₂O₅ (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 LiOH•H₂O to give the product 18a (50 mg, 62%) as a white solid; mp 179-181 °C. ¹H NMR (400 MHz, CDCl₃), 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 [M-H]; purity (HPLC, 254 nm, Method I, t_R = 8.74 min) 99%. Anal. calcd for C₁₉H₁₆ClNO₅S: 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, tᵣ = 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, tᵣ = 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), 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, tᵣ = 6.72 min) 98%. Anal. calcd for C₁₆H₁₃Cl₂NO₅S: 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), 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•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•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 H, 1H). MS m/z 254 [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.
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 C\(_{17}\)H\(_{16}\)ClNO\(_4\)S: 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 159-162 °C. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)), \( \delta \) ppm: 2.69 – 2.83 (m, 2H), 3.17 – 3.26 (m, 2H), 3.30 (m, overlapped by H\(_2\)O), 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 C\(_{18}\)H\(_{18}\)ClNO\(_5\)S: 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. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)), \( \delta \) ppm: 2.73 – 2.79 (m, 2H), 3.18 – 3.23 (m, 2H), 3.28-3.33 (m, overlapped by H\(_2\)O), 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) 99%. *Anal. calcd for C\(_{18}\)H\(_{18}\)ClNO\(_5\)S: 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \( \delta \) 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 17n (40 mg, 0.09 mmol) and NaOH to give the product 18n (20 mg, 55%) as a white solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \( \delta \) 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%.
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, CDCl$_3$), 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 C$_{17}$H$_{15}$Cl$_2$NO$_4$S: 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 H$_2$O), 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 C$_{18}$H$_{16}$ClNO$_6$S: 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•H$_2$O to give the product 18o (70 mg, 71%) as a white solid; mp > 130 °C (decomp.). 1H NMR (400 MHz, CDCl$_3$), 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 C$_{18}$H$_{16}$ClNO$_6$S: C, 52.64; H, 3.79; N, 3.23. Found: C, 52.75; H, 3.93; N, 3.42.

6-Chloro-2-[2-(2-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•H$_2$O to give the product 18p (30 mg, 72%) as a white solid; mp 132-135 °C. 1H NMR (400 MHz, CDCl$_3$), 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) 97%. Anal. calcd for C$_{18}$H$_{15}$ClNO$_5$S: C, 52.34; H, 3.79; N, 3.23. Found: C, 52.75; H, 3.93; N, 3.42.
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•H₂O to give the product 18q (70 mg, 66%) as a white solid; mp 201-204 °C. ¹H NMR (400 MHz, DMSO-d₆), δ ppm: 3.26 (m, overlapped by H₂O), 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 C₁₇H₁₃ClFNO₅S×0.8CH₂Cl₂: C, 45.90; H, 3.16; N, 3.06. Found: C, 45.55; H, 3.29; N, 2.92.

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•H₂O to give the product 18r (7 mg, 42%) as a white solid; mp > 193 °C (decomp.). ¹H NMR (400 MHz, CDCl₃), 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 = 16.8, 9.2 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-d₆), 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•H₂O to give the product 18t (10 mg, 79%) as a white solid; mp 193-197 °C. ¹H NMR (400 MHz, CDCl₃), 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 C\(_{14}\)H\(_{13}\)ClN\(_2\)O\(_4\)S\(_2\): 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. \(^1\)H NMR (200 MHz, CDCl\(_3\)), \( \delta \) 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 C\(_{15}\)H\(_{18}\)ClNO\(_6\)S: C, 47.94; H, 4.83; N, 3.73. Found: C, 47.89; H, 4.65; N, 3.71.