Supporting Information to:

Microwave-Assisted Synthesis of 1,3-Benzothiazol-2(3*H*)-one Derivatives and Analysis of Their Antinociceptive Activity

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Materials and Methods

Chemistry

All chemicals and solvents used in this study were purchased locally from Merck AG, Aldrich Chemical. The microwave reaction was carried out in a MicroSYNTH Microwave Lab station (Milestone S.r.l.). Fourier transform infrared attenuated total reflectance (FTIR-ATR) spectra were recorded on Perkin Elmer Spectrum 400 FT-IR and FT-NIR spectrometers with a Universal ATR sampler. The ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker 400 MHz NMR spectrometer. Chemical shifts are reported in parts per million relative to the internal standard tetramethylsilane. ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Varian Mercury 400, 400 MHz High Performance Digital FT-NMR spectrometer with tetramethylsilane as the internal standard at the NMR facility of the Faculty of Pharmacy, Ankara University. All chemical shifts were recorded as δ (ppm). Microanalyses were performed by TÜBITAK Analytical Laboratory. The elemental data for all derivatives are within ±0.4% of the theoretical value.

Synthesis of 1,3-benzothiazol-2(3*H*)-one (1a)

Conventional condition [13, 14]

A mixture of 2-aminothiophenol (0.1 mol) and urea (0.2 mol) was heated to 180°C and stirred for 24 h in an oil bath. The reaction mixture was poured into crushed ice. The precipitated solid product was collected by suction filtration, washed with water, dried and crystallized from water with a yield of 71%.

Microwave irradiation condition [12]

The mixture of 2-aminothiophenol (0.1 mol) and urea (0.2 mol) was heated to 140°C and stirred for 10 min under MWI. The reaction mixture was poured into crushed ice. The precipitated solid product was collected by suction filtration, washed with water, dried and crystallized from water with a yield of 85%.

Synthesis of 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives (1b, 1c, 1d)

Conventional methods for synthesis of 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives have already been published [19-22].

Microwave irradiation condition

A mixture of 1,3-benzothiazol-2(3*H*)-one (**1a**) (0.1 mol) and the appropriate benzoic acid derivatives (0.15 mol) in polyphosphoric acid was heated to 120°C and stirred for 45 min under MWI. The reaction mixture was poured into crushed ice. After stirring for 1 h, the precipitated solid product was collected by suction filtration, washed with 5% $NaHCO_3$ and water, dried, and crystallized from the appropriate solvent.

6-(4-Fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (1b)

Crystallized from 2-propanol with a yield of 54%. m.p.: 238-239°C. FTIR-ATR, cm^{-1}: 1749, 1669 and 1641. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.75 (1H, s, NH), 8.04 (1H, d, *J*: 1.7 Hz, benzothiazolone H^{7}), 7.80 (2H, dd, *J*: 5.5 Hz, 8.7 Hz, phenyl H^{2,6}), 7.69 (1H, dd, *J*: 1.7 Hz, 8.3 Hz, benzothiazolone H^{5}), 7.38 (2H, t, *J*: 8.8 Hz, phenyl H^{3,5}), 7.25 (1H, d, *J:* 8.3 Hz, benzothiazolone H^{4}). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.9, 170.4, 164.4 (d, *J*: 250 Hz, phenyl C^{4}), 140.2, 133.8 (d, phenyl C^{1}), 132.3 (d, *J*: 9.1 Hz, phenyl C^{2,6}), 131.1, 128.8, 124.8, 123.7, 115.5 (d, *J*: 22.1 Hz, phenyl C^{3,5}), 111.1. Anal. Calc. for $C_{14}H_8FNO_2S$.

6-(4-Methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (1c)

Crystallized from methanol with a yield of 65%. m.p.: 223°C. FTIR-ATR, cm^{-1}: 1687, 1641. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.81 (1H, s, NH), 8.01 (1H, d, *J*: 1.6 Hz, benzothiazolone

H^7), 7.66 (1H, dd, *J*: 1.6 Hz, 8.3 Hz, benzothiazolone H^5), 7.63 (2H, d, *J*: 8.1 Hz, phenyl $H^{2,6}$), 7.35 (2H, d, *J*: 8.1 Hz, phenyl $H^{3,5}$), 7.24 (1H, d, *J:* 8.3 Hz, benzothiazolone H^4), 2.40 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.9, 170.4, 142.6, 139.9, 134.5, 131.5, 129.6, 128.9, 128.7, 124.6, 123.6, 111.0, 21.0. Anal. Calc. for $C_{15}H_{11}NO_2S$.

6-(4-Methoxybenzoyl)-1,3-benzothiazol-2(3*H*)-one (1d)
Crystallized from 2-propanol with a yield of 66%. m.p.: 216°C. FTIR-ATR, cm^{-1}: 1682, 1641. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.34 (1H, s, NH), 8.00 (1H, d, *J*: 1.6 Hz, benzothiazolone H^7), 7.74 (2H, d, *J*: 8.8 Hz, phenyl $H^{2,6}$), 7.64 (1H, dd, *J*: 1.6 Hz, 8.3 Hz, benzothiazolone H^5), 7.24 (1H, d, *J:* 8.3 Hz, benzothiazolone H^4), 7.09 (2H, d, *J*: 8.8 Hz, phenyl $H^{3,5}$), 3.86 (3H, s, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.9, 170.4, 162.6, 139.7, 131.9, 131.7, 129.5, 128.5, 124.4, 123.6, 113.8, 110.9, 55.4. Anal. Calc. for $C_{15}H_{11}NO_3S$.

Synthesis of 5-chloro-1,3-benzothiazol-2(3*H*)-one (1e)
The conventional and microwave-assisted methods for synthesis of 5-chloro-1,3-benzothiazol-2(3*H*)-one have been reported before [8, 15, 24]. In this study, we used the microwave-assisted method for synthesis of compound **1e**.

Synthesis of 5-chloro-6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives (1f, 1g)
Microwave irradiation condition
A mixture of 5-chloro-1,3-benzothiazol-2(3*H*)-one (**1e**) (0.1 mol) and the appropriate benzoic acid derivatives (0.3 mol) in polyphosphoric acid was heated to 140°C and stirred for 2 h under MWI. The reaction mixture was poured into crushed ice. After stirring for 1 h, the precipitated solid product was collected by suction filtration, washed with 5% $NaHCO_3$ and water, dried, and crystallized from the appropriate solvent.

5-Chloro-6-(4-fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (1f)
The crude product was purified by column chromatography using dichloromethane (DCM). The collected product **1f** was crystallized from ethanol/water with a yield of 64%. m.p.: 213-214°C. FTIR-ATR, cm^{-1}: 1659. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.85-7.81 (3H, m, benzothiazolone H^7, phenyl $H^{2,6}$), 7.39 (2H, t, *J*: 8.8 Hz, phenyl $H^{3,5}$), 7.24 (1H, benzothiazolone H^4). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.1, 170.1, 165.3 (d, *J*: 254 Hz, phenyl C^4), 138.9, 132.8 (d, phenyl C^1), 132.6 (d, *J*: 9.9 Hz, phenyl $C^{2,6}$), 131.5, 128.0, 123.6, 122.7, 116.0 (d, *J*: 22.12 Hz, phenyl $C^{3,5}$), 112.1. Anal. Calc. for $C_{14}H_7ClFNO_2S$: C, 54.64; H, 2.29; N, 4.55. Found: C, 54.77; H, 2.45; N, 4.93%.

5-Chloro-6-(4-methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (1g)
The crude product was purified by column chromatography using DCM. The collected product **1g** was crystallized from 2-propanol/water with a yield of 72%. m.p.: 208-209°C. FTIR-ATR, cm^{-1}: 1662, 1656. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.77 (1H, s, benzothiazolone H^7), 7.64 (2H, d, *J*: 8 Hz, phenyl $H^{2,6}$), 7.36 (2H, d, *J*: 8 Hz, phenyl $H^{3,5}$), 7.23 (1H, s, benzothiazolone H^4), 2.39 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.1, 170.1, 144.6, 138.7, 133.6, 132.0, 129.7, 129.4, 127.9, 123.4, 122.7, 112.0, 21.1. Anal. Calc. for $C_{15}H_{10}ClNO_2S$: C, 59.31; H, 3.32; N, 4.61. Found: C, 59.29; H, 3.44; N, 4.87%.

Synthesis of ester derivatives (2a-2g)
A mixture of the appropriate core compound (**1a-1g**) (0.05 mol), potassium carbonate (0.08 mol) and ethyl bromoacetate (0.08 mol) in 100 mL acetone was heated under reflux and stirred for 20 min under MWI. 100 g ice water was added to the cooled (0–10°C) reaction

mixture and stirred. The precipitate was collected on a suction filter, washed with water, dried, and crystallized from the appropriate solvent.

Ethyl (2-oxo-1,3-benzothiazol-3(2*H*)-yl)acetate (2a) [23]
Crystallized from ethanol/water with a yield of 94.5%. m.p.: 96°C.

Ethyl (6-(4-fluorobenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetate (2b)
Crystallized from 2-propanol with a yield of 93%. m.p.: 130°C. FTIR-ATR, cm^{-1}: 1729, 1692 and 1657. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.18 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.84 (2H, dd, *J*: 5.5 Hz, 8.8 Hz, phenyl $H^{2,6}$), 7.75 (1H, dd, *J*: 1.7 Hz, 8.5 Hz, benzothiazolone H^5), 7.51 (1H, d, *J:* 8.5 Hz, benzothiazolone H^4), 7.40 (2H, d, *J*: 8.8 Hz, phenyl $H^{3,5}$), 4.94 (2H, s, CH_2), 4.19 (2H, q, CH_2), 1.23 (3H, t, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.6, 170.4, 167.9, 165.2 (d, *J*: 249.1 Hz, phenyl C^4), 140.9, 134.4 (d, phenyl C^1), 133.2 (d, *J*: 9.9 Hz, phenyl $C^{2,6}$), 132.8, 129.5, 125.8, 122.3, 116.3 (d, *J*: 21.3 Hz, phenyl $C^{3,5}$), 111.8, 62.2, 44.3, 14.7. Anal. Calc. for $C_{18}H_{14}FNO_4S$: C, 60.16; H, 3.93; N, 3.90. Found: C, 59.83; H, 3.94; N, 3.90%.

Ethyl (6-(4-methylbenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetate (2c)
Crystallized from 2-propanol with a yield of 92%. m.p.: 104°C. FTIR-ATR, cm^{-1}: 1736, 1688 and 1646. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.16 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.73 (1H, dd, *J*: 1.7 Hz, 8.4 Hz, benzothiazolone H^5), 7.66 (2H, d, *J*: 8.1 Hz, phenyl $H^{2,6}$), 7.50 (1H, d, *J:* 8.4 Hz, benzothiazolone H^4), 7.38 (2H, d, *J*: 8.1 Hz, phenyl $H^{3,5}$), 4.93 (2H, s, CH_2), 4.20 (2H, q, CH_2), 2.42 (3H, s, CH_3), 1.23 (3H, t, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 194.6, 170.4, 167.9, 143.6, 140.7, 135.1, 133.2, 130.5, 129.8, 129.4, 125.7, 122.2, 111.8, 62.2, 44.3, 21.8, 14.7. Anal. Calc. for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 63.83; H, 4.67; N, 3.92%.

Ethyl (6-(4-methoxybenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetate (2d)
Crystallized from methanol with a yield of 95%. m.p.: 127-128°C. FTIR-ATR, cm^{-1}: 1754, 1667 and 1638. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.13 (1H, d, *J*: 1.6 Hz, benzothiazolone H^7), 7.76 (2H, d, *J*: 8.8 Hz, phenyl $H^{2,6}$), 7.72 (1H, dd, *J*: 1.7 Hz, 8.4 Hz, benzothiazolone H^5), 7.49 (1H, d, *J:* 8.4 Hz, benzothiazolone H^4), 7.10 (2H, d, *J*: 8.8 Hz, phenyl $H^{3,5}$), 4.93 (2H, s, CH_2), 4.19 (2H, q, CH_2), 3.87 (3H, s, OCH_3), 1.23 (3H, t, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.8, 169.5, 167.1, 162.8, 139.7, 132.8, 132.0, 129.4, 128.4, 124.7, 121.3, 113.8, 110.9, 61.4, 55.5, 43.5, 13.9. Anal. Calc. for $C_{19}H_{17}NO_5S$: C, 61.44; H, 4.61; N, 3.77. Found: C, 61.09; H, 4.45; N, 3.68%.

Ethyl (5-chloro-2-oxo-1,3-benzothiazol-3(2*H*)-yl)acetate (2e) [24]
Crystallized from ethanol/water with a yield of 87%. m.p.: 108°C

Ethyl [5-chloro-6-(4-fluorobenzoyl)-2-oxo-1,3-benzothiazol-3(2*H*)-yl]acetate (2f)
Crystallized from 2-propanol with a yield of 96%. m.p.: 173-74°C. FTIR-ATR, cm^{-1}: 1742, 1676 and 1655. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.95 (1H, s, benzothiazolone H^7), 7.84 (2H, dd, *J*: 5.5 Hz, 8.8 Hz, phenyl $H^{2,6}$), 7.79 (1H, s, benzothiazolone H^4), 7.40 (2H, t, *J*: 8.8 Hz, phenyl $H^{3,5}$), 4.93 (2H, s, CH_2), 4.20 (2H, q, CH_2), 1.24 (3H, t, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.5, 169.9, 166.5, 166.4 (d, *J*: 256 Hz, phenyl C^4), 139.0, 133.6 (phenyl C^1), 133.0 (d, *J*: 13.1 Hz, phenyl $C^{2,6}$), 130.4, 123.7, 121.5, 116.2 (d, *J*: 22.23 Hz, phenyl $C^{3,5}$), 111.9, 62.7, 43.9, 14.3. Anal. Calc. for $C_{18}H_{13}ClFNO_4S$: C, 54.90; H, 3.33; N, 3.56. Found: C, 54.52; H, 3.33; N, 3.47%.

Ethyl [5-chloro-6-(4-methylbenzoyl)-2-oxo-1,3-benzothiazol-3(2*H*)-yl]acetate (2g)
Crystallized from cyclohexane with a yield of 79%. m.p.: 145°C. FTIR-ATR, cm^{-1}: 1741, 1674 and 1651. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.91(1H, s, benzothiazolone H^7), 7.77 (1H, s, benzothiazolone H^4), 7.65 (2H, d, *J*: 8 Hz, phenyl $H^{2,6}$), 7.37 (2H, d, *J*: 8 Hz, phenyl $H^{3,5}$), 4.93 (2H, s, CH_2), 4.20 (2H, q, CH_2), 2.40 (3H, s, CH_3), 1.22 (3H, t, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.0, 169.3, 167.0, 144.7, 138.8, 133.4, 132.9, 129.7, 129.5, 128.5, 123.6, 120.3, 112.5, 61.4, 43.7, 26.2, 21.9, 13.8. Anal. Calc. for $C_{19}H_{16}ClNO_4S$: C, 58.54; H, 4.14; N, 3.59. Found: C, 58.71; H, 4.33; N, 3.45%.

Synthesis of acid derivatives (3a-g)
Ester derivatives (**2a-g**) (0.022 mol) and potassium hydroxide (0.025 mol) in 150 mL ethanol/water were refluxed for 15 min under MWI. After cooling to room temperature, the mixture was acidified with acetic acid to give a precipitate. The product was collected by suction filtration, washed with water, dried, and crystallized from the appropriate solvent.

(2-Oxo-1,3-benzothiazol-3(2*H*)-yl)acetic acid (3a) [23]
Crystallized from water with a yield of 87.6%. m.p.: 177°C.

(6-(4-Fluorobenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetic acid (3b)
Crystallized from ethanol, the yield was 66%. m.p.: 222°C decomp. FTIR-ATR, cm^{-1}: 1736, 1685. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.67 (1H, s, OH), 8.17 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.83 (2H, dd, *J*: 5.5 Hz, 8.8 Hz, phenyl $H^{2,6}$), 7.75 (1H, dd, *J*: 1.7 Hz, 8.5 Hz, benzothiazolone H^5), 7.49 (1H, d, *J:* 8.5 Hz, benzothiazolone H^4), 7.39 (2H, d, *J*: 8.8 Hz, phenyl $H^{3,5}$), 4.82 (2H, s, CH_2). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.7, 170.3, 169.2, 165.2 (d, *J*: 250 Hz, phenyl C^4), 141.1, 134.5 (d, phenyl C^1), 133.2 (d, *J*: 9.1 Hz, phenyl $C^{2,6}$), 132.6, 129.5, 125.7, 122.3, 116.3 (d, *J*: 21.3 Hz, phenyl $C^{3,5}$), 111.9, 44.4. Anal. Calc. for $C_{16}H_{10}FNO_4S$: C, 58.00; H, 3.04; N, 4.23. Found: C, 58.05; H, 2.95; N, 4.19%.

(6-(4-Methylbenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetic acid (3c) [19]
Crystallized from methanol, the yield was 88%. m.p.: 195°C. FTIR-ATR, cm^{-1}: 1735, 1692. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.99 (1H, s, OH), 8.14 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.73 (1H, dd, *J*: 1.7 Hz, 8.5 Hz, benzothiazolone H^5), 7.66 (2H, d, *J*: 8.1 Hz, phenyl $H^{2,6}$), 7.48 (1H, d, *J:* 8.5 Hz, benzothiazolone H^4), 7.37 (2H, d, *J*: 8 Hz, phenyl $H^{3,5}$), 4.81 (2H, s, CH_2), 2.42 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 194.6, 170.3, 169.2, 143.6, 140.9, 135.2, 133.1, 130.5, 129.8, 129.4, 125.6, 122.2, 111.8, 44.4, 21.8. Anal. Calc. for $C_{17}H_{13}NO_4S$.

(6-(4-Methoxybenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetic acid (3d)
Crystallized from 2-propanol with a yield of 60%. m.p.: 239°C. FTIR-ATR, cm^{-1}: 1734, 1690. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.21 (1H, s, OH), 8.12 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.76 (2H, d, *J*: 8.8 Hz, phenyl $H^{2,6}$), 7.72 (1H, dd, *J*: 1.7 Hz, 8.4 Hz, benzothiazolone H^5), 7.47 (1H, d, *J:* 8.4 Hz, benzothiazolone H^4), 7.10 (2H, d, *J*: 8.8 Hz, phenyl $H^{3,5}$), 4.81 (2H, s, CH_2), 3.86 (3H, s, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.6, 170.3, 169.2, 163.5, 140.7, 133.5, 132.8, 130.2, 129.2, 125.4, 122.1, 114.6, 111.7, 56.2, 44.4. Anal. Calc. for $C_{17}H_{13}NO_5S$: C, 59.47; H, 3.82; N, 4.08. Found: C, 59.07; H, 3.81; N, 4.03%.

(5-Chloro-2-oxo-1,3-benzothiazol-3(2*H*)-yl)acetic acid (3e) [24]
Crystallized from ethanol/water with a yield of 74%. m.p.: 246°C.

[5-Chloro-6-(4-fluorobenzoyl)-2-oxo-1,3-benzothiazol-3(2*H*)-yl]acetic acid (3f)

Crystallized from ethanol with a yield of 96%. m.p.: 268°C. FTIR-ATR, cm^{-1}: 1744, 1663 and 1646. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.23 (1H, s, OH), 7.94 (1H, s, benzothiazolone H^{7}), 7.85 (2H, dd, *J*: 5.5 Hz, 8.8 Hz, phenyl H2,6), 7.77 (1H, s, benzothiazolone H^{4}), 7.39 (2H, t, *J*: 8.8 Hz, phenyl $H^{3,5}$), 4.83 (2H, s, CH_2). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.8, 170.1, 169.1, 166.2 (d, *J*: 250 Hz, phenyl C^{4}), 140.0, 133.5, 133.4 (d, *J*: 10.0 Hz, phenyl $C^{2,6}$), 133.0 (phenyl C^{1}), 129.4, 124.5, 121.1, 116.29 (d, *J*: 22.23 Hz, phenyl $C^{3,5}$), 113.3, 44.6. Anal. Calc. for $C_{16}H_9ClFNO_4S$: C, 52.54; H, 2.48; N, 3.83. Found: C, 52.62; H, 2.64; N, 3.60%.

[5-Chloro-6-(4-methylbenzoyl)-2-oxo-1,3-benzothiazol-3(2*H*)-yl]acetic acid (3g)
Crystallized from ethanol with a yield of 73%. m.p.: 203°C decomp. FTIR-ATR, cm^{-1}: 1747, 1690 and 1643. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.88 (1H, s, benzothiazolone H^{7}), 7.73 (1H, s, benzothiazolone H^{4}), 7.64 (2H, d, *J*: 8 Hz, phenyl $H^{2,6}$), 7.36 (2H, d, *J*: 8 Hz, phenyl $H^{3,5}$), 4.80 (2H, s, CH_2), 2.39 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.8, 170.1, 169.2, 145.5, 140.0, 134.2, 133.5, 130.5, 130.3, 129.2, 124.3, 121.1, 113.2, 44.6, 21.9. Anal. Calc. for $C_{17}H_{12}ClNO_4S$: C, 56.44; H, 3.34; N, 3.87. Found: C, 56.51; H, 3.25; N, 3.83%.

Synthesis of amide derivatives
Acid derivatives (0.002 mol) and $SOCl_2$ (0.06 mol) in 15 mL toluene were refluxed for 1 h under MWI. The final mixture was evaporated to dryness and 20 mL tetrahydrofurane was added. The solutions of the acid chloride derivatives were mixed with potassium carbonate (0.004 mol) and the appropriate piperazine derivatives (0.004 mol) THF. The mixture was refluxed for 20 min under MWI and poured into ice water. Then, the precipitated solid material was filtered and crystallized from the appropriate solvent.

3-[2-(4-Methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5a)
Crystallized from cyclohexane with a yield of 46.4%. m.p.: 145-146°C. FTIR-ATR, cm^{-1}: 1671, 1660. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.66 (1H, d, *J*: 7.4 Hz, benzothiazolone H^{7}), 7.34 (1H, t, *J*: 7.4 Hz, benzothiazolone H^{5}), 7.21-7.17 (2H, m, benzothiazolone $H^{4,6}$), 4.91 (2H, s, CH_2), 3.57 (2H, t, piperazine), 3.43 (2H, t, piperazine), 2.40 (2H, t, piperazine), 2.28 (2H, t, piperazine), 2.21(3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.63, 164.21, 137.96, 126.90, 123.55, 123.20, 121.55, 112.05, 55.04, 54.64, 46.14, 44.55, 44.00, 42.01. Anal. Calc. for $C_{14}H_{17}N_3O_2S$: C, 57.71; H, 5.88; N, 14.42. Found: C, 57.74; H, 5.52; N, 14.50%.

3-[2-(4-Ethylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (6a)
Crystallized from ethyl acetate/petroleum ether with a yield of 30%. m.p.: 169-170°C. FTIR-ATR, cm^{-1}: 1678, 1646. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.66 (1H), 7.34 (1H), 7.21-7.17 (2H), 4.91 (2H), 3.57 (2H), 3.44 (2H), 2.45 (2H), 2.39 (2H), 2.33 (2H), 1.02 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.13, 163.64, 137.47, 126.40, 123.04, 122.70, 121.04, 111.56, 52.39, 51.87, 51.47, 44.19, 43.49, 41.62, 11.85. Anal. Calc. for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76. Found: C, 58.65; H, 6.05; N, 13.64%.

3-{2-Oxo-2-[4-(propan-2-yl)piperazin-1-yl]ethyl}-1,3-benzothiazol-2(3*H*)-one (7a)
Crystallized from tetrahydrofurane/water with a yield of 45.3%. m.p.: 130°C. FTIR-ATR, cm^{-1}: 1676, 1666. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.65 (1H), 7.34 (1H), 7.21-7.17 (2H), 4.91 (2H), 3.55 (2H), 3.42 (2H), 2.72-2.67 (1H), 2.55-2.5 (2H), 2.40 (2H), 1.02 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.13, 163.54, 137.48, 126.40, 123.04, 122.69, 121.03, 111.57, 53.70, 48.20, 47.67, 44.60, 43.50, 42.00, 18.01. Anal. Calc. for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 59.77; H, 6.23; N, 12.79%.

3-[2-(4-Butylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (8a)
Crystallized from tetrahydrofurane/water with a yield of 75.7%. m.p.: 132°C. FTIR-ATR, cm^{-1}: 1671, 1660. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.65 (1H), 7.33 (1H), 7.21-7.18 (2H), 4.91 (2H), 3.67-3.50 (2H), 3.50-3.39 (2H), 2.48-2.39 (2H), 2.32-2.29 (4H), 1.45-1.41 (2H), 1.33-1.28 (2H), 0.9 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.13, 163.63, 137.47, 126.40, 123.05, 122.69, 121.04, 111.56, 57.38, 52.83, 52.33, 43.49, 41.65, 28.34, 20.04, 13.89. Anal. Calc. for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60. Found: C, 60.91; H, 6.56; N, 12.20%.

6-(4-Fluorobenzoyl)-3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5b)
Crystallized from tetrahydrofurane/water with a yield of 33%. m.p.: 130°C. FTIR-ATR, cm^{-1}: 1672, 1662 and 1641. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.15 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.84 (2H, dd, *J*: 5.5 Hz, 8.8 Hz, phenyl $H^{2,6}$), 7.74 (1H, dd, *J*: 1.7 Hz, 8.4 Hz, benzothiazolone H^5), 7.42-7.36 (3H, m, benzothiazolone H^4, phenyl $H^{3,5}$), 5.01 (2H, s, CH_2), 3.57 (2H, t, piperazine), 3.45 (2H, t, piperazine), 2.42 (2H, t, piperazine), 2.29 (2H, t, piperazine), 2.22 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.56, 170.30, 165.02 (d, *J*: 251 Hz, phenyl C^4), 164.07, 141.48, 134.21 (d, *J*: 2.6 Hz, phenyl C^1), 132.95 (d, *J*: 9.4 Hz, phenyl $C^{2,6}$), 132.23, 129.16, 125.35, 122.05, 116.10 (d, *J*: 22.22 Hz, phenyl $C^{3,5}$), 111.80, 54.59, 54.24, 45.55, 44.25, 44.12, 41.59. Anal. Calc. for $C_{21}H_{20}FN_3O_3S$: C, 61.00; H, 4.88; N, 10.16. Found: C, 61.26; H, 4.70; N, 10.05%.

3-[2-(4-Ethylpiperazin-1-yl)-2-oxoethyl]-6-(4-fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (6b)
Crystallized from tetrahydrofurane/water with a yield of 37%. m.p.: 130°C. FTIR-ATR, cm^{-1}: 1673, 1659 and 1648. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.15 (1H), 7.84 (2H), 7.74 (1H), 7.42-7.36 (3H), 5.01 (2H), 3.58 (2H), 3.45 (2H), 2.47 (2H), 2.38-2.33 (4H), 1.03 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.61, 170.38, 165.05 (d, *J*: 255 Hz, phenyl C^4), 163.94, 141.51, 134.20, (d, *J*: 2.5 Hz, phenyl C^1), 132.99 (d, *J*: 9.6 Hz, phenyl $C^{2,6}$), 132.29, 129.20, 125.28, 122.09, 116.13 (d, *J*: 24.6 Hz, phenyl $C^{3,5}$), 111.79, 52.74, 52.26, 51.91, 44.62, 44.27, 42.08, 12.23. Anal. Calc. for $C_{22}H_{22}FN_3O_3S$: C, 61.81; H, 5.19; N, 9.83. Found: C, 61.49; H, 4.82; N, 10.17%.

6-(4-Fluorobenzoyl)-3-{2-oxo-2-[4-(propan-2-yl)piperazin-1-yl]ethyl}-1,3-benzothiazol-2(3*H*)-one (7b)
Crystallized from acetone/cyclohexane with a yield of 31%. m.p.: 129°C. FTIR-ATR, cm^{-1}: 1671, 1658 and 1646. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.15 (1H), 7.84 (2H), 7.74 (1H), 7.42-7.37 (3H), 5.00 (2H), 3.55 (2H), 3.43 (2H), 2.79-2.63 (1H), 2.54 (2H), 2.41 (2H), 0.99 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.00, 170.00, 163.94, 163.60, 141.00, 132.00, 131.50, 129.00, 125.00, 121.9, 115.13, 111.50, 105.02, 54.74, 48.2, 47.80, 44.90, 44.00, 42.25, 18.00. Anal. Calc. for $C_{23}H_{24}FN_3O_3S$: C, 62.57; H, 5.48; N, 9.52. Found: C, 62.73; H, 5.50; N, 9.27%.

3-[2-(4-Butylpiperazin-1-yl)-2-oxoethyl]-6-(4-fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (8b)
Crystallized from acetone/cyclohexane with a yield of 54%. m.p.: 152-153°C. FTIR-ATR, cm^{-1}: 1673, 1659 and 1649. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.15 (1H), 7.84 (2H), 7.74 (1H), 7.42-7.36 (3H), 5.00 (2H), 3.57 (2H), 3.43 (2H), 2.46 (2H), 2.33-2.29 (4H), 1.45-1.40 (2H), 1.33-1.29 (2H), 0.89 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.96, 170.12, 169.72, 165.95, 141.06, 133.80, 132.41, 131.72, 128.64, 124.88, 121.52, 115.60, 111.35 57.35, 52.78,

52.28, 44.21, 43.80, 41.68, 28.31, 20.03, 13.88. Anal. Calc. for $C_{24}H_{26}FN_3O_3S$: C, 63.28; H, 5.75; N, 9.22. Found: C, 62.92; H, 5.62; N, 9.34%.

6-(4-Methylbenzoyl)-3-[2-(methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5c)

Crystallized from acetone/cyclohexane with a yield of 49%. m.p.: 160°C. FTIR-ATR, cm^{-1}: 1672, 1649. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.13 (1H, d, *J*: 1.6 Hz, benzothiazolone H^7), 7.72 (1H, dd, *J*: 1.6 Hz, 8.4 Hz, benzothiazolone H^5), 7.66 (2H, d, *J*: 8 Hz, phenyl $H^{2,6}$), 7.39-7.35 (3H, m, phenyl $H^{3,5}$ and benzothiazolone H^4), 5.01 (2H, s, CH_2), 3.57 (2H, t, piperazine), 3.45 (2H, t, piperazine), 2.47-2.37 (5H, m, piperazine and CH_3), 2.29 (2H, t, piperazine), 2.22 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.95, 169.71, 163.52, 142.86, 140.86, 134.49, 132.15, 129.78, 129.09, 128.55, 124.74, 121.47, 111.25, 54.49, 54.11, 45.62, 43.80, 41.54, 21.12. Anal. Calc. for $C_{22}H_{23}N_3O_3S$: C, 64.53; H, 5.66; N, 10.26. Found: C, 64.56; H, 5.32; N, 10.27%.

3-[2-(Ethylpiperazin-1-yl)-2-oxoethyl]-6-(4-methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (6c)

Crystallized from cyclohexane with a yield of 56.6%. m.p.: 126-127°C. FTIR-ATR, cm^{-1}: 1685, 1664 and 1642. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.12 (1H), 7.72 (1H), 7.66 (2H), 7.39-7.35 (3H), 5.00 (2H), 3.58 (2H), 3.45 (2H), 2.47 (2H), 2.42-2.33 (7H), 1.03 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.93, 169.70, 163.44, 142.85, 141.72, 134.49, 132.14, 129.77, 129.08, 128.54, 125.51, 121.47, 111.25, 52.33, 51.83, 51.46, 44.19, 43.79, 41.64, 21.12, 11.83. Anal. Calc. for $C_{23}H_{25}N_3O_3S$: C, 65.23; H, 5.95; N, 9.92. Found: C, 65.17; H, 5.73; N, 9.62%.

6-(4-Methylbenzoyl)-3-[2-oxo-2-[4-(propan-2-yl)piperazin-1-yl]ethyl]-1,3-benzothiazol-2(3*H*)-one (7c)

Crystallized from cyclohexane with a yield of 63%. m.p.: 100°C. FTIR-ATR, cm^{-1}: 1670, 1645. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.12 (1H), 7.72 (1H), 7.66 (2H), 7.39-7.35 (3H), 4.99 (2H), 3.54 (2H), 3.45 (2H), 2.82-2.63 (1H), 2.53 (2H), 2.48-2.22 (5H), 1.00 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.93, 169.70, 163.34, 142.85, 140.87, 134.49, 132.13, 129.77, 129.08, 128.54, 124.73, 121.47, 111.27, 53.73, 48.16, 47.64, 44.60, 43.79, 42.03, 21.12, 17.99. Anal. Calc. for $C_{24}H_{27}N_3O_3S$: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.76; H, 6.06; N, 9.22%.

3-[2-(Butylpiperazin-1-yl)-2-oxoethyl]-6-(4-methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (8c)

Crystallized from tetrahydrofurane /water with a yield of 80%. m.p.: 117°C. FTIR-ATR, cm^{-1}: 1673, 1660. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.12 (1H), 7.73 (1H), 7.66 (2H), 7.39-7.35 (3H), 5.00 (2H), 3.57 (2H), 3.44 (2H), 2.46 (2H), 2.42 (3H), 2.34-2.29 (4H), 1.45-1.40 (2H), 1.36-1.28 (2H), 0.90 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 194.67, 170.29, 163.86, 143.39, 142.35, 134.98, 132.67, 130.25, 129.58, 129.07, 125.19, 121.98, 111.68, 57.89, 53.28, 52.79, 44.68, 44.24, 42.10, 25.55, 21.61, 20.56, 14.37. Anal. Calc. for $C_{25}H_{29}N_3O_3S$: C, 66.49; H, 6.47; N, 9.31. Found: C, 66.67; H, 6.17; N, 9.20%.

6-(4-Methoxybenzoyl)-3-[2-(methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5d)

Crystallized from acetone/cyclohexane with a yield of 53%. m.p.: 115-116°C. FTIR-ATR, cm^{-1}: 1671, 1659 and 1638. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.10 (1H, d, *J*: 1.7 Hz, benzothiazolone H^7), 7.76 (2H, d, *J*: 8.8 Hz, phenyl $H^{2,6}$), 7.70 (1H, dd, *J*: 1.7 Hz, 8.4 Hz,

benzothiazolone H^5), 7.36 (1H, d, *J:* 8.4 Hz, benzothiazolone H^4), 7.10 (2H, d, *J*: 8.8 Hz, phenyl $H^{3,5}$), 5.00 (2H, s, CH_2), 3.87 (3H, s, OCH_3), 3.58 (2H, t, piperazine), 3.45 (2H, t, piperazine), 2.42 (2H, t, piperazine), 2.29 (2H, t, piperazine), 2.22 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.83, 170.39, 163.44, 163.26, 140.15, 133.58, 132.40, 130.02, 128.92, 124.59, 122.33, 113.68, 110.49, 55.54, 54.86, 54.44, 45.95, 45.04, 43.87, 42.25. Anal. Calc. for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.45; N, 9.88. Found: C, 62.34; H, 5.33; N, 9.48%.

3-[2-(Ethylpiperazin-1-yl)-2-oxoethyl]-6-(4-methoxybenzoyl)-1,3-benzothiazol-2(3*H*)-one (6d)

Crystallized from acetone/cyclohexane with a yield of 65%. m.p.: 198-199°C. FTIR-ATR, cm^{-1}: 1673, 1655 and 1638. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.09 (1H), 7.76 (2H), 7.70 (1H), 7.36 (1H), 7.10 (2H), 5.00 (2H), 3.87 (3H), 3.58 (2H), 3.45 (2H), 2.47 (2H), 2.40-2.35 (4H), 1.02 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.61, 170.30, 164.05, 163.33, 141.08, 133.05, 132.60, 129.97, 128.91, 124.97, 121.94, 114.42, 111.64, 56.04, 52.55, 52.09, 51.89, 44.34, 44.22, 41.85, 11.91. Anal. Calc. for $C_{23}H_{25}N_3O_4S$: C, 62.85; H, 5.73; N, 9.56. Found: C, 63.01; H, 5.42; N, 9.66%.

6-(4-Methoxybenzoyl)-3-[2-oxo-2-[4-(propan-2-yl)piperazin-1-yl]ethyl]-1,3-benzothiazol-2(3*H*)-one (7d)

Crystallized from cyclohexane with a yield of 34%. m.p.: 199-200°C. FTIR-ATR, cm^{-1}: 1670, 1656 and 1638. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.10 (1H), 7.76 (2H), 7.70 (1H), 7.36 (1H), 7.10 (2H), 4.99 (2H), 3.87 (3H), 3.56 (2H), 3.42 (2H), 2.73-2.70 (1H), 2.54 (2H), 2.43 (2H), 0.99 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.84, 170.40, 163.29, 163.24, 140.19, 133.57, 132.41, 130.05, 128.93, 124.58, 122.34, 113.67, 110.52, 55.54, 54.58, 48.72, 48.13, 45.57, 43.90, 42.72, 18.32. Anal. Calc. for $C_{24}H_{27}N_3O_4S$: C, 63.56; H, 6.00; N, 9.26. Found: C, 63.34; H, 5.96; N, 8.86%.

3-[2-(Butylpiperazin-1-yl)-2-oxoethyl]-6-(4-methoxybenzoyl)-1,3-benzothiazol-2(3*H*)-one (8d)

Crystallized from cyclohexane with a yield of 44%. m.p.: 106-107°C. FTIR-ATR, cm^{-1}: 1673, 1660. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.10 (1H), 7.76 (2H), 7.70 (1H), 7.35 (1H), 7.10 (2H), 5.00 (2H), 3.87 (3H), 3.57 (2H), 3.45 (2H), 2.47 (2H), 2.34-2.32 (4H), 1.55-1.37 (2H), 1.37-1.18 (2H), 0.90 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.84, 170.40, 163.38, 163.25, 140.16, 133.60, 132.41, 130.05, 128.93, 124.59, 122.35, 113.67, 110.51, 58.17, 55.54, 53.14, 52.63, 43.90, 42.34, 28.79, 26.91, 20.60, 13.99. Anal. Calc. for $C_{25}H_{29}N_3O_4S$: C, 64.22; H, 6.25; N, 8.99. Found: C, 64.38; H, 6.26; N, 8.77%.

5-Chloro-3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5e) [25-27]

Crystallized from acetone/cyclohexane with a yield of 46%. m.p.: 172°C. FTIR-ATR, cm^{-1}: 1684, 1648. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.70 (1H, d, *J*: 8.4 Hz, benzothiazolone H^7), 7.45 (1H, d, *J*: 2 Hz, benzothiazolone H^4), 7.25 (1H, dd, *J*: 2 Hz, 8.4 Hz, benzothiazolone H^6), 4.93 (2H, s, CH_2), 3.54 (2H, t, piperazine), 3.44 (2H, t, piperazine), 2.41 (2H, t, piperazine), 2.28 (2H, t, piperazine), 2.20 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.81, 164.11, 139.24, 131.73, 124.68, 123.35, 120.39, 112.18, 54.97, 54.62, 46.13, 44.54, 44.26, 42.01. Anal. Calc. for $C_{14}H_{16}ClN_3O_2S$.

5-Chloro-3-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (6e)

Crystallized from cyclohexane with a yield of 43%. m.p.: 153-154°C. FTIR-ATR, cm^{-1}: 1694, 1646. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.70 (1H), 7.45 (1H), 7.25 (1 H), 4.93 (2H), 3.54

(2H), 3.44 (2H), 2.47 (2H), 2.38-2.34 (4H), 1.03 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.98, 164.10, 139.19, 131.73, 124.64, 123.43, 120.35, 112.14, 52.69, 52.21, 51.93, 44.51, 44.18, 41.99, 12.10. Anal. Calc. for $C_{15}H_{18}ClN_3O_2S$: C, 53.01; H, 5.34; N, 12.36. Found: C, 52.99; H, 5.05; N, 12.33%.

5-Chloro-3-{2-oxo-2-[4-(propan-2-yl)piperazin-1-yl]ethyl}-1,3-benzothiazol-2(3*H*)-one (7e)

Crystallized from tetrahydrofurane /water with a yield of 57%. m.p.: 169°C. FTIR-ATR, cm^{-1}: 1685, 1648. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.70 (1H), 7.46 (1H), 7.25 (1H), 4.93 (2H), 3.52 (2H), 3.43 (2H), 2.73-2.68 (1H), 2.55 (2H), 2.41 (2H), 0.98 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.77, 164.01, 139.31, 131.79, 124.76, 123.49, 120.46, 112.17, 54.22, 48.64, 48.16, 45.09, 44.24, 42.52, 18.49. Anal. Calc. for $C_{16}H_{20}ClN_3O_2S$: C, 54.31; H, 5.70; N, 11.87. Found: C, 54.06; H, 5.54; N, 11.71%.

3-[2-(4-Butylpiperazin-1-yl)-2-oxoethyl]-5-chloro-1,3-benzothiazol-2(3*H*)-one (8e)

Crystallized from tetrahydrofurane/water with a yield of 79%. m.p.: 98-99°C. FTIR-ATR, cm^{-1}: 1689, 1650. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.70 (1H), 7.46 (1H), 7.25 (1H), 4.93 (2H), 3.54 (2H), 3.43 (2H), 2.45 (2H), 2.34-2.29 (4H), 1.45-1.40 (2H), 1.36-1.28 (2H), 0.90 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.80, 164.05, 139.31, 131.79, 124.72, 123.41, 120.43, 112.20, 57.92, 53.28, 52.82, 44.73, 44.27, 42.21, 28.85, 20.60, 14.39. Anal. Calc. for $C_{17}H_{22}ClN_3O_2S$: C, 55.50; H, 6.03; N, 11.42. Found: C, 55.46; H, 5.66; N, 11.20%.

5-Chloro-6-(4-fluorobenzoyl)-3-[2-(methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5f)

Crystallized from acetone/cyclohexane with a yield of 47%. m.p.: 145-146°C. FTIR-ATR, cm^{-1}: 1669, 1660. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.92 (1H, s, benzothiazolone H^7), 7.84 (2H, dd, *J*: 5.5 Hz, 8.8 Hz, phenyl H^{2,6}), 7.65 (1H, s, benzothiazolone H^4), 7.40 (2H, t, *J*: 8.8 Hz, phenyl H^{3,5}), 5.01 (2H, s, CH_2), 3.56 (2H, t, piperazine), 3.46 (2H, t, piperazine), 2.42 (2H, t, piperazine), 2.30 (2H, t, piperazine), 2.22 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.17, 169.43, 165.00 (d, *J*: 253 Hz, phenyl C^4), 163.51, 140.02, 132.87 (phenyl C^1), 132.73 (d, *J*: 9.7 Hz, phenyl C^{2,6}), 132.09, 128.54, 123.71, 120.47, 116.18 (d, *J*: 22.03 Hz, phenyl C^{3,5}), 112.75, 54.45, 54.12, 45.64, 44.03, 44.02, 41.55. Anal. Calc. for $C_{21}H_{19}ClFN_3O_3S$: C, 56.31; H, 4.28; N, 9.38. Found: C, 55.96; H, 4.11; N, 9.09%.

5-Chloro-3-[2-(ethylpiperazin-1-yl)-2-oxoethyl]-6-(4-fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (6f)

Crystallized from acetone/cyclohexane with a yield of 63%. m.p.: 191°C. FTIR-ATR, cm^{-1}: 1673, 1660. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.92 (1H), 7.84 (2H), 7.65 (1H), 7.40 (2H), 5.01 (2H), 3.56 (2H), 3.46 (2H), 2.47 (2H), 2.39-2.35 (4H), 1.03 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.00, 169.92, 165.94 (d, *J*: 253 Hz, phenyl C^4), 163.93, 140.52, 133.38 (phenyl C^1), 133.22 (d, *J*: 9.9 Hz, phenyl C^{2,6}), 132.58, 129.03, 124.19, 120.96, 116.67 (d, *J*: 22.2 Hz, phenyl C^{3,5}), 113.24, 52.80, 52.32, 51.97, 44.69, 44.49, 42.18, 12.33. Anal. Calc. for $C_{22}H_{21}ClFN_3O_3S$: C, 57.20; H, 4.58; N, 9.10. Found: C, 57.13; H, 4.61; N, 8.70%.

5-Chloro-6-(4-fluorobenzoyl)-3-[2-oxo-2-(4-(propan-2-yl)piperazin-1-yl)ethyl]-1,3-benzothiazol-2(3*H*)-one (7f)

Crystallized from acetone/cyclohexane with a yield of 49.5%. m.p.: 181°C. FTIR-ATR, cm^{-1}: 1677, 1659. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.92 (1H), 7.84 (2H), 7.65 (1H), 7.40 (2H), 5.00 (2H), 3.54 (2H), 3.45 (2H), 2.73-2.70 (1H), 2.54 (2H), 2.43 (2H), 1.00 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.65, 169.93, 163.86, 163.45 (d, *J*: 250 Hz, phenyl C^4), 140.56,

133.41 (phenyl C^1), 133.23 (d, *J*: 10 Hz, phenyl $C^{2,6}$), 132.62, 129.06, 124.25, 120.98, 116.67 (d, *J*: 22.2 Hz, phenyl $C^{3,5}$), 113.29, 54.21, 48.64, 48.16, 45.11, 44.49, 42.56, 18.51. Anal. Calc. for $C_{23}H_{23}ClFN_3O_3S$: C, 58.04; H, 4.87; N, 8.83. Found: C, 57.72; H, 4.76; N, 8.57%.

3-[2-(Butylpiperazin-1-yl)-2-oxoethyl]-5-chloro-6-(4-fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (8f)

Crystallized from acetone/cyclohexane with a yield of 73%. m.p.: 169°C. FTIR-ATR, cm^{-1}: 1678, 1669 and 1654. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.92 (1H), 7.84 (2H), 7.65 (1H), 7.40 (2H), 5.00 (2H), 3.55 (2H), 3.46 (2H), 2.47 (2H), 2.36-2.30 (4H), 1.44-1.40 (2H), 1.38-1.17 (2H), 0.90 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 192.67, 169.94, 165.95 (d, *J*: 253 Hz, phenyl C^4), 163.96, 140.49, 133.38 (d, *J*: 2.6 Hz, phenyl C^1), 133.22 (d, *J*: 10.7 Hz, phenyl $C^{2,6}$), 132.59, 129.03, 124.18, 120.96, 116.67 (d, *J*: 22.4 Hz, phenyl $C^{3,5}$), 113.23, 57.77, 53.13, 52.68, 44.55, 44.48, 42.05, 28.66, 20.49, 14.34. Anal. Calc. for $C_{24}H_{25}ClFN_3O_3S$: C, 58.83; H, 5.14; N, 8.58. Found: C, 59.11; H, 4.88; N, 8.50%.

5-Chloro-6-(4-methylbenzoyl)-3-[2-(methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (5g)

Crystallized from acetone/cyclohexane with a yield of 53.4%. m.p.: 178-179°C. FTIR-ATR, cm^{-1}: 1656. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.88 (1H, s, benzothiazolone H^7), 7.65 (2H, d, *J*: 8 Hz, phenyl $H^{2,6}$), 7.63 (1H, s, benzothiazolone H^4), 7.37 (2H, d, *J*: 8 Hz, phenyl $H^{3,5}$), 5.00 (2H, s, CH_2), 3.56 (2H, t, piperazine), 3.46 (2H, t, piperazine), 2.43-2.40 (5H, m, piperazine and CH_3), 2.30 (2H, t, piperazine), 2.22 (3H, s, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.70, 170.00, 164.07, 145.33, 140.34, 134.15, 133.22, 130.37, 130.08, 129.00, 124.01, 120.94, 113.21, 54.96, 54.61, 46.13, 44.54, 44.49, 42.04, 21.77. Anal. Calc. for $C_{22}H_{22}ClN_3O_3S$: C, 59.52; H, 4.99; N, 9.47. Found: C, 59.13; H, 5.01; N, 9.12%.

5-Chloro-3-[2-(ethylpiperazin-1-yl)-2-oxoethyl]-6-(4-methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (6g)

Crystallized from cyclohexane with a yield of 68%. m.p.: 171°C. FTIR-ATR, cm^{-1}: 1676, 1655. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.88 (1H), 7.65 (2H), 7.63 (1H), 7.37 (2H), 5.00 (2H), 3.56 (2H), 3.46 (2H), 2.47 (2H), 2.40-2.35 (7H), 1.03 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.15, 169.43, 163.47, 144.77, 139.79, 133.60, 132.65, 129.82, 129.58, 128.44, 123.50, 120.39, 112.65, 52.30, 51.84, 51.48, 44.19, 43.97, 41.67, 26.31, 21.24, 11.85. Anal. Calc. for $C_{23}H_{24}ClN_3O_3S$: C, 60.32; H, 5.28; N, 9.18. Found: C, 60.69; H, 5.00; N, 8.78%.

5-Chloro-6-(4-methylbenzoyl)-3-[2-oxo-2-(4-(propan-2-yl)piperazin-1-yl)ethyl]-1,3-benzothiazol-2(3*H*)-one (7g)

Crystallized from cyclohexane with a yield of 75.5%. m.p.: 199-200°C. FTIR-ATR, cm^{-1}: 1697, 1674 and 1656. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.88 (1H), 7.65 (2H), 7.63 (1H), 7.37 (2H), 5.00 (2H), 3.54 (2H), 3.45 (2H), 2.72 (1H), 2.55 (2H), 2.43 (2H), 2.40 (3H), 1.00 (6H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.63, 169.93, 163.87, 145.26, 140.30, 134.11, 133.15, 130.31, 130.07, 128.94, 123.99, 120.88, 113.16, 54.23, 48.62, 48.15, 45.10, 44.48, 42.55, 21.74, 18.50. Anal. Calc. for $C_{24}H_{26}ClN_3O_3S$: C, 61.07; H, 5.55; N, 8.90. Found: C, 61.02; H, 5.57; N, 8.64%.

3-[2-(Butylpiperazin-1-yl)-2-oxoethyl]-5-chloro-6-(4-methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (8g).

Crystallized from acetone/cyclohexane with a yield of 36%. m.p.: 133-134°C. FTIR-ATR, cm^{-1}: 1666, 1656. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.88 (1H), 7.65 (2H), 7.63 (1H), 7.37

(2H), 5.00 (2H), 3.55 (2H), 3.46 (2H), 2.47 (2H), 2.40 (3H), 2.35-2.30 (4H), 1.46-1.42 (2H), 1.34-1.28 (2H), 0.90 (3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 193.66, 169.94, 163.97, 145.28, 140.27, 134.09, 133.15, 130.31, 130.08, 128.93, 124.76, 120.88, 113.85, 57.86, 53.22, 52.76, 44.67, 44.47, 42.15, 28.79, 21.74, 20.53, 14.38. Anal. Calc. for $C_{25}H_{28}ClN_3O_3S$: C, 61.78; H, 5.81; N, 8.65. Found: C, 61.41; H, 5.87; N, 8.25%.

Pharmacology

Albino mice weighing 30-35 g were used in the present study. The laboratory temperature was maintained at 20±1^{0}C with a 12h/12h light-dark schedule. Prior to the experiment, the mice were allowed 1 week of adaptation. They were used only once. The study was approved by the Ethics Committee of the Osmangazi University Medical School. The animals were divided into 15 groups. Each group included eight animals. All compounds were dissolved in DMSO/water (1:4) and administered to the animals intraperitoneally (i.p.) at 100 mg/kg. Control animals received 0.1 mL DMSO/water (1:4) i.p. The tail clip and tail flick tests to radiant heat as well as the hot plate and writhing tests induced by acetic acid were performed sequentially 60 min following administration of the compounds or vehicle (DMSO for control group).

Mouse tail clip test: This analgesic test was based on a method described by Bianchi and Franceshini [28] and Dajani EZ. et al [29]. A pressure-standardized artery clip was placed approximately 2 cm from the base of the tail and only those mice responding to the clip placement by turning or biting at the clip within 15 s were used.

Tail flick test to radiant heat: This test described by D'Amour and Smith [30] was performed with a beam of high-intensity light (MAY Commat) focused on the dorsal surface of the tail. The response latency between onset of the radiant heat stimulus and movement of the tail away from the light beam was determined. The light intensity was set such as to provide a predrug response time of 2-4 s. A cut-off at 15 s was used in order to prevent damage to the tail.

Hot plate test: The test was based on a protocol described by Eddy and Leimbach [31] and Noble et al [32]. A glass cylinder (16 mm in height 16 mm in diameter) was used to keep the mouse on the heated surface of the plate kept at a temperature of 55.0±0.5^{0}C with a thermoregulated water-circulating pump. The latency period until the mouse licked a foot or jumped was registered with a stopwatch (cut–off time was 45 s).

The results are expressed as percentage of the maximal possible effect (%MPE±SD)

$$\%MPE = \frac{\text{Postdrug latency-Predrug latency}}{\text{Cutoff time-Predrug latency}} \times 100$$

Writhing test: The abdominal constrictor test [33] was performed following i.p. administration of 0.6% acetic acid (60 mg/kg). Stretching movements (arching of the back, development of tension in the abdominal muscles, elongation of the body and extension of forelimbs) were counted over a period of 10 min starting 5 min after the i.p. administration of acetic acid.

All tests were conducted between 9 and 12 a.m. All results are expressed as the mean± SD. Statistical comparison was performed with the Student's t test.