

Supporting Information

Synthesis and Biological Evaluation of 1,2,4-Triazinylphenylalkylthiazolecarboxylic Acid Esters as Cytokine Inhibiting Antedrugs with Strong Bronchodilating Effects in Animal Model of Asthma

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Contents

S2: NMR and elemental analysis data of compounds 3-6 and 10-18

S3: NMR and elemental analysis data of compounds 19-30

S4: NMR and elemental analysis data of compounds 31-33

Compound 3:

¹H NMR (300MHz, CDCl₃) δ 1.37 (t, 3H), 4.38 (q, 2H), 5.72 (s, 1H), 8.32 (s, 2H).

Compound 4:

¹H NMR (360 MHz, DMSO-d₆) δ 4.31 (s, 2 H), 8.41 (s, 2 H).

Anal. Calcd for (C₈H₄Cl₂N₂O₂) C, 41.59; H, 1.75; N, 12.13. Found C, 41.54; H, 1.66; N, 12.26.

Compound 5:

¹H NMR (400 MHz, CDCl₃) δ 2.13 (s, 6 H), 8.22 (s, 2 H).

Compound 6:

¹H NMR (300MHz, DMSO-d₆) δ 1.92 (s, 6H), 5.82 (s, 2H) 6.68 (s, 2H).

Compound 10:

¹H NMR (360 MHz, DMSO-d₆) δ 2.05 (s, 6 H), 7.76 (s, 2 H), 12.74 (br s, 1 H). ¹³C NMR (91 MHz) δ 28.4, 38.1, 123.5, 127.8, 132.9, 133.5, 136.8, 139.6, 147.5, 154.2, 161.5.

Compound 11:

¹H NMR (400 MHz, DMSO-d₆) δ 2.04 (s, 6 H), 7.72 (s, 1 H), 7.76 (s, 2 H), 12.52 (br.s, 1 H). ¹³C NMR (101 MHz) δ 28.5, 38.0, 123.4, 127.0, 132.1, 133.4, 137.1, 139.9, 147.3, 156.6.

Compound 12:

¹H NMR (360 MHz, DMSO-d₆) δ 1.83 (s, 6 H), 7.58 (s, 2 H), 7.69 (s, 1 H), 8.80 (s, 1 H), 9.60 (s, 1 H), 12.44 (s, 1 H).

¹³C NMR (101 MHz) δ 30.5, 56.0, 126.7, 134.8, 136.8, 138.5, 139.6, 147.4, 156.7, 214.2.

Compound 13:

¹H NMR (360 MHz, CDCl₃) δ 1.27 (t, J=7.1 Hz, 3 H), 2.11 (s, 6 H), 4.26 (q, J=7.1 Hz, 2 H), 7.36 (m, 3 H), 7.52 (s, 1 H), 7.63 (s, 2 H), 7.69 (m, 2 H), 9.96 (br.s, 1 H).

Anal. Calcd for (C₂₄H₂₀Cl₂N₄O₄S) C, 54.24; H, 3.79; N, 10.54. Found C, 54.22; H, 3.67; N, 10.31.

Compound 14:

¹H NMR (360 MHz, CDCl₃) δ 1.26 (d, J=6.2 Hz, 6 H), 2.11 (s, 6 H), 5.11 (m, 1 H), 7.36 (m, 3 H), 7.53 (s, 1 H), 7.64 (s, 2 H), 7.68 (m, 2 H), 9.60 (br.s, 1 H).

Anal. Calcd for (C₂₅H₂₂Cl₂N₄O₄S) C, 55.05; H, 4.07; N, 10.27. Found C, 55.19; H, 4.25; N, 9.99.

Compound 15:

¹H NMR (360 MHz) δ 1.72 (m, 2 H), 2.05 (s, 6 H), 3.40 (q, J=5.2 Hz, 2 H), 4.23 (t, J=6.4 Hz, 2 H), 4.53 (m, 1 H), 7.41 (m, 3 H), 7.62 (m, 2 H), 7.69 (s, 2 H), 7.71 (s, 1 H), 12.48 (s, 1 H).

¹³C NMR (101 MHz, CDCl₃) δ 31.1, 31.5, 49.2, 59.1, 62.3, 121.8, 126.1, 127.7, 129.0, 129.9, 134.1, 136.0, 136.4, 138.5, 139.4, 146.4, 155.3, 159.4, 161.9, 184.6.

Anal. Calcd for (C₂₅H₂₂Cl₂N₄O₅S): C, 53.48; H, 3.95; N, 9.98; S, 5.71. Found C, 53.12; H, 4.05; N, 9.65; S, 5.77.

Compound 16:

¹H NMR (360 MHz, DMSO-d₆) δ 1.40 (s, 9 H), 2.05 (s, 6 H), 7.36 (m, 3 H), 7.53 (m, 2 H), 7.70 (m, 3 H), 12.48 (br.s, NH).

Anal. Calcd for (C₂₆H₂₄Cl₂N₄O₄S) C, 55.82; H, 4.32; N, 10.01. Found C, 55.83; H, 4.23; N, 10.05.

Compound 17:

¹H NMR (360 MHz, CDCl₃) δ 2.03 (s, 6H), 7.37 (m, 3H), 7.67 (m, 4H), 7.70 (s, 1H).

Anal. Calcd for (C₂₂H₁₆Cl₂N₄O₄S) C, 52.50; H 3.20; N, 11.13; S, 6.37. Found C, 52.60; H, 3.13; N, 11.42; S, 6.27.

Compound 18:

¹H NMR (360 MHz, CDCl₃) δ 2.11 (s, 6 H), 3.80 (s, 3 H), 7.39 (m, 3 H), 7.55 (s, 1 H), 7.64 (s, 2 H), 7.70 (m, 2 H), 9.45 (br.s, 1 H).

Anal. Calcd for (C₂₃H₁₈Cl₂N₄O₄S) C, 53.39; H, 3.51; N, 10.83. Found C, 52.39; H, 3.38 N, 10.38.

Compound 19:

¹H NMR (360 MHz, CDCl₃) δ 0.90 (t, *J*=7.4 Hz, 3 H), 1.66 (m, 2 H), 2.11 (s, 6 H), 4.16 (t, *J*=6.6 Hz, 2 H), 7.37 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.68 (m, 2 H), 9.56 (br.s, 1 H).

Anal. Calcd for (C₂₅H₂₂Cl₂N₄O₄S) C, 55.05; H, 4.07; N, 10.27. Found C, 55.20; H, 3.85; N, 10.02.

Compound 20:

¹H NMR (360 MHz, CDCl₃) δ 0.90 (t, *J*=7.4 Hz, 3 H), 1.32 (m, 2 H), 1.61 (m, 2 H), 2.11 (s, 6 H), 4.20 (t, *J*=6.6 Hz, 2 H), 7.37 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.68 (m, 2 H), 9.54 (br.s, 1 H).

Anal. Calcd for (C₂₆H₂₄Cl₂N₄O₄S) C, 55.82; H, 4.32; N, 10.01. Found C, 55.64; H, 4.19; N, 9.97.

Compound 21:

¹H NMR (360 MHz, CDCl₃) δ 0.88 (t, *J*=7.0 Hz, 3 H), 1.27 (m, 4 H), 1.62 (m, 2 H), 2.11 (s, 6 H), 4.19 (t, *J*=6.7 Hz, 2 H), 7.37 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.68 (m, 2 H), 9.54 (br.s, 1 H).

Anal. Calcd for (C₂₇H₂₆Cl₂N₄O₄S) C, 56.55; H, 4.57; N, 9.77. Found C, 56.35; H, 4.53; N, 9.77.

Compound 22:

¹H NMR (360 MHz, CDCl₃) δ 0.28 (dt, *J*=5.9, 4.7 Hz, 2 H), 0.56 (m, 2 H), 1.13 (m, 1 H), 2.11 (s, 6 H), 4.03 (d, *J*=7.3 Hz, 2 H), 7.36 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.70 (m, 2 H), 9.51 (br.s, 1 H).

Anal. Calcd for (C₂₆H₂₂Cl₂N₄O₄S) C, 56.02; H, 3.98; N, 10.05. Found C, 56.13; H, 3.92; N, 9.67.

Compound 23:

¹H NMR (360 MHz, CDCl₃) δ 0.89 (d, *J*=6.8 Hz, 6 H), 1.93 (m, 1 H), 2.11 (s, 6 H), 3.98 (d, *J*=6.7 Hz, 2 H), 7.37 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.68 (m, 2 H), 9.51 (br.s, 1 H).

Anal. Calcd for (C₂₆H₂₀Cl₂N₄O₄S) C, 55.82; H, 4.32; N, 10.01. Found C, 55.63; H, 4.09; N, 9.93.

Compound 24:

¹H NMR (360 MHz, CDCl₃) δ 2.11 (s, 6 H), 4.70 (dt, *J*=5.7, 1.3 Hz, 2 H), 5.24 (dq, *J*=10.4, 1.3 Hz, 1 H), 5.29 (dq, *J*=17.2, 1.5 Hz, 1 H), 5.92 (m, *J*=17.2, 10.4, 6.0, 5.4 Hz, 1 H), 7.37 (m, 3 H), 7.55 (s, 1 H), 7.64 (s, 2 H), 7.70 (m, 2 H), 9.41 (br.s, 1 H).

Anal. Calcd for (C₂₅H₂₀Cl₂N₄O₄S) C, 55.26; H, 3.71; N, 10.31. Found C, 55.26; H, 3.50; N, 10.40.

Compound 25:

¹H NMR (360 MHz, CDCl₃) δ 1.69 (s, 3 H), 1.75 (s, 3 H), 2.10 (s, 6 H), 4.70 (d, *J*=7.1 Hz, 2 H), 5.35 (m, 1 H), 7.37 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.70 (m, 2 H), 9.46 (br.s, 1 H).

Anal. Calcd for (C₂₇H₂₄Cl₂N₄O₄S) C, 56.75; H, 4.23; N, 9.80. Found C, 56.56; H, 4.33; N, 9.36.

Compound 26:

¹H NMR (360 MHz, CDCl₃) δ 2.11 (s, 6 H), 2.50 (t, *J*=2.5 Hz, 1 H), 4.80 (d, *J*=2.5 Hz, 2 H), 7.39 (m, 3 H), 7.56 (s, 1 H), 7.65 (s, 2 H), 7.72 (m, 2 H), 9.38 (br.s, 1 H).

Anal. Calcd for (C₂₅H₁₈Cl₂N₄O₄S) C, 55.46; H, 3.35; N, 10.35. Found C, 55.51; H, 3.28; N, 10.27.

Compound 27:

¹H NMR (360 MHz, CDCl₃) δ 2.11 (s, 6 H), 2.95 (t, *J*=7.1 Hz, 2 H), 4.40 (t, *J*=7.1 Hz, 2 H), 7.15 (m, 2 H), 7.26 (m, 3 H), 7.36 (m, 3 H), 7.55 (s, 1 H), 7.66 (m, 4 H), 9.39 (br.s, 1 H).

Anal. Calcd for (C₃₀H₂₄Cl₂N₄O₄S) C, 59.31; H, 3.98; N, 9.22. Found C, 58.86; H, 3.88; N, 9.19.

Compound 28:

¹H NMR (360 MHz, CDCl₃) δ 2.12 (s, 6 H), 4.83 (s, 2 H), 7.42 (m, 3 H), 7.59 (s, 1 H), 7.67 (s, 2 H), 7.70 (m, 2 H), 8.80 (br.s, 1 H).

Anal. Calcd for (C₂₄H₁₇Cl₂N₅O₄S) C, 53.15; H, 3.16; N, 12.91. Found C, 53.33; H, 2.97; N, 12.32.

Compound 29:

¹H NMR (360 MHz, CDCl₃) δ 2.12 (s, 6 H), 4.57 (q, *J*=8.4 Hz, 2 H), 7.40 (m, 3 H), 7.57 (s, 1 H), 7.66 (s, 2 H), 7.68 (m, 2 H), 9.30 (br.s, 1 H).

Anal. Calcd for (C₂₄H₁₇Cl₂F₃N₄O₄S) C, 49.24; H, 2.93; N, 9.57. Found C, 48.62; H, 2.97; N, 9.37.

Compound 30:

¹H NMR (360 MHz, CDCl₃) δ 1.86 (t, *J*=2.3 Hz, 3 H), 2.11 (s, 6 H), 4.77 (q, *J*=2.3 Hz, 2 H), 7.38 (m, 3 H), 7.55 (s, 1 H), 7.64 (s, 2 H), 7.72 (m, 2 H), 9.42 (br.s, 1 H).

Anal. Calcd for (C₂₆H₂₀Cl₂N₄O₄S) C, 56.22; H, 3.63; N, 10.09. Found C, 56.48; H, 3.29; N, 9.93.

Compound 31:

^1H NMR (360 MHz, CDCl_3) δ 2.11 (s, 6 H), 3.76 (m, 2 H), 4.29 (m, 2 H), 7.40 (m, 3 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.66 (m, 2 H), 9.51 (br.s, 1 H).

Anal. Calcd for $(\text{C}_{24}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_5\text{S})$ C, 52.66; H, 3.68; N, 10.23; S, 5.86. Found C, 52.86; H, 3.65; N 10.38; S, 5.78.

Compound 32:

^1H NMR (360 MHz, CDCl_3) δ 2.10 (s, 6 H), 4.16 (t, $J=4.7$ Hz, 2 H), 4.54 (t, $J=4.7$ Hz, 2 H), 6.90 (d, $J=7.7$ Hz, 2 H), 6.97 (t, $J=7.4$ Hz, 1 H), 7.30 (m, 5 H), 7.54 (s, 1 H), 7.64 (s, 2 H), 7.68 (m, 2 H), 9.37 (br.s, 1 H)

Anal. Calcd for $(\text{C}_{30}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_5\text{S})$ C, 57.79; H, 3.88; N, 8.99. Found C, 57.61; H, 4.08; N, 8.62.

Compound 33:

^1H NMR (360 MHz, CDCl_3) δ 2.12 (s, 6 H), 2.15 (s, 3 H), 4.75 (s, 2 H), 7.38 (m, 3 H), 7.56 (s, 1 H), 7.65 (s, 2 H), 7.72 (m, 2 H), 9.15 (br.s, 1 H).

Anal. Calcd for $(\text{C}_{25}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_5\text{S})$ C, 53.68; H, 3.60; N, 10.02. Found C, 53.77; H, 3.47; N, 10.04.