

Supporting information for

Synthesis of 2,5-asymmetrically substituted 3,4-diaminothieno[2,3-*b*]thiophenes by domino reaction.

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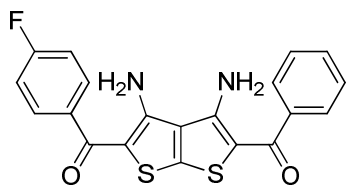
Experimental Details

The ^1H NMR spectra were recorded on a “Bruker AM300” (300.13 MHz) using DMSO d_6 as the solvent, a chemical shifts were reported in ppm (δ) and coupling constants (J) values were given in Hertz (Hz). The ^{13}C NMR spectra were recorded on a “Bruker AM300” (75.47 MHz) and “Bruker AV 600” (151 MHz) using DMSO- d_6 as the solvent. The IR spectra recorded on a “Bruker Alpha” in KBr pellets. Melting points measured on Kofler bench.

Synthesis of thienothiophenes **8**. *General Procedure.*

To solution of 1.4 g (25 mmol) KOH in 50 mL EtOH at 10 ^0C the malononitrile (**1**) 1.65 g (25 mmol) was added and stirred until dissolution. To the obtained solution CS_2 1.5 mL (25 mmol) and then solution KOH 1.4 g (25 mmol) in 50 mL EtOH were added and stirred for 20 min. To the reaction mixture 20 mL of H_2O was added to dissolve the precipitate. To the resulting solution (total volume 120 mL) 25 mmol of appropriate alkylating agent **3**{1-5} in 70 mL of EtOH was added drop-wise over 5 h, then solution KOH 1.4 g (25 mmol) in 10 mL of H_2O was added and heated up to reflux. To the cooled solution 35 mL of H_2O and 2.8 mL (25 mmol) of concentrated HBr were added and stirred for 30 min before the precipitate was filtered off. The obtained solution was divided into 5 equal portions and to each portion an appropriate alkylhalogenide **6**{1-20} (4.7 mmol) was added, stirred for 10 min before 1.25 mL of 20% KOH in water was added and heated to reflux, then cooled down and the precipitate was filtered off. The thienothiophenes **8** were obtained as pure products, without additional purification, in 50-85% yields.

(3,4-Diamino-5-(4-fluorobenzoyl)thieno[2,3-*b*]thiophen-2-yl)(phenyl)methanone (8{1, 6}).



Yield: 1.39 g (70 %), mp > 300 °C.

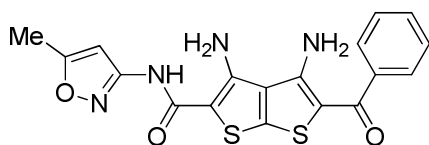
IR (KBr): 3417, 3376, 3291, 3249, 1638, 1600, 1588 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.34 (m, 2H, 4-FC₆H₄, H(3,5)), 7.53 (m, 3H, Ph, H(3,4,5)), 7.69 (d, *J* = 7.0, 2H, Ph, H(2,6)), 7.77 (m, 2H, 4-FC₆H₄, H(2,6)), 8.45 (s, 4H, 2 NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 108.9, 109.2, 115.28 (d, *J* = 21, 4-F-C₆H₄, C(3)H, C(5)H), 121.2, 123.2, 126.9, 128.3, 129.6 (d, *J* = 9, 4-F-C₆H₄, C(2)H, C(6)H), 130.7, 136.9, 140.5, 150.9, 151.1, 164.8 (d, *J* = 247, C(4)F), 185.5, 186.9.

Anal. Calcd for C₂₀H₁₃FN₂O₂S₂: C, 60.59, H, 3.31, N, 7.07. Found: C, 60.38, H, 3.26, N, 6.98.

3,4-Diamino-5-benzoyl-N-(5-methylisoxazol-3-yl)thieno[2,3-*b*]thiophene-2-carboxamide (8{1, 7}).



Yield: 1.18 g (59 %), mp = 274 – 276 °C.

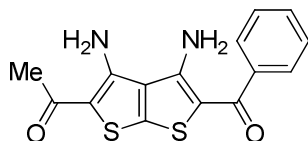
IR (KBr): 3443, 3377, 3314, 3229 (NH₂, NH), 1656 (CO), 1625, 1598 (CO, δ NH₂), 1572 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.39 (s, 3H, Me), 6.64 (s, 1H, Het, C(4)H), 7.50-7.60 (m, 5H, Ph, H(3,4,5), C(4)NH₂), 7.71 (d, *J* = 7.0, 2H, Ph, H(2,6)), 8.33 (s, 2H, C(3)NH₂), 10.45 (s, 1H, CONH).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 11.9, 97.1, 100.7, 109.2, 126.9, 127.7, 128.2, 130.6, 140.6, 148.7, 149.2, 150.7, 158.4, 162.6, 168.6, 186.8.

Anal. Calcd for C₁₈H₁₄N₄O₃S₂: C, 54.26, H, 3.54, N, 14.06. Found: C, 53.95, H, 3.44, N, 13.83.

1-(3,4-Diamino-5-benzoylthieno[2,3-*b*]thiophen-2-yl)ethanone (8{1, 8}).



Yield: 0.94 g (59 %), mp = 290 – 292 °C.

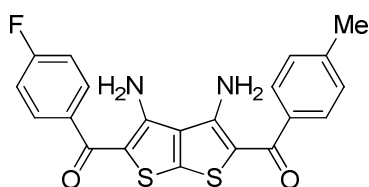
IR (KBr): 3435, 3379, 3297, 3238 (NH₂), 1635, 1594 (CO, δ NH₂), 1566 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.25 (s, 3H, Me), 7.49-7.59 (m, 3H, Ph, H(3,4,5)), 7.70 (d, J = 7.1, 2H, Ph, H(2,6)), 8.04 (s, 2H, C(4)NH₂), 8.37 (s, 2H, C(3)NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 27.8, 109.2, 110.3, 126.9, 127.3, 128.2, 130.6, 140.6, 148.7, 150.3, 150.9, 186.7, 188.9.

Anal. Calcd for C₁₅H₁₂N₂O₂S₂: C, 56.94, H, 3.82, N, 8.85. Found: C, 56.68, H, 3.87, N, 8.96.

(3,4-Diamino-5-(4-fluorobenzoyl)thieno[2,3-*b*]thiophen-2-yl)(*p*-tolyl)methanone (8{2, 6}).



Yield: 1.58 g (77 %), mp = 288 – 290 °C.

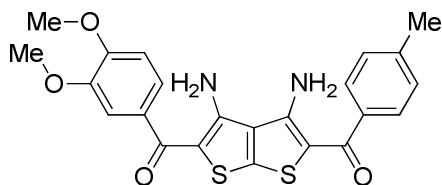
IR (KBr): 3418, 3292, 3247, 3187 (NH₂), 1636, 1599 (CO, δ NH₂), 1587 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.36 (s, 3H, Me), 7.28-7.35 (m, 4H, Ar), 7.58 (d, J = 7.9, 2H, Ar), 7.74-7.78 (m, 2H, Ar), 8.39-8.42 (m, 4H, 2 NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 20.8, 108.8, 109.2, 109.4, 115.2 (d, J = 21, 4-F-C₆H₄, C(3)H, C(5)H), 127.1, 128.7, 129.6 (d, J = 8, 4-F-C₆H₄, C(2)H, C(6)H), 137.0, 137.8, 140.6, 150.8, 151.1, 152.5, 163.3 (d, J = 249, C(4)F), 185.4, 186.7.

Anal. Calcd for C₂₁H₁₅FN₂O₂S₂: C, 61.45, H, 3.68, N, 6.82. Found: C, 61.63, H, 3.76, N, 6.97.

(3,4-Diamino-5-(3,4-dimethoxybenzoyl)thieno[2,3-*b*]thiophen-2-yl)(*p*-tolyl)methanone (8{2, 9}).



Yield: 1.91 g (84 %), mp = 165 – 168 °C.

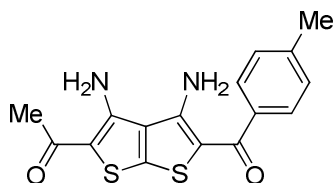
IR (KBr): 3426 br (NH₂), 1630, 1597 (CO, δ NH₂), 1566 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.34 (s, 3H, Me), 3.79-3.81 (m, 6H, 2 MeO), 7.02 (d, J = 8.3, 1H, (MeO)₂C₆H₃, H(5)), 7.25-7.30 (m, 3H, (MeO)₂C₆H₃, H(2), 4-MeC₆H₄, H(3,5)), 7.35 (d, J = 8.3, 1H, (MeO)₂C₆H₃, H(6)), 7.58 (d, J = 7.9, 2H, 4-MeC₆H₄, H(2,6)), 8.4 (br s, 4H, 2 NH₂).

^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ = 23.0, 57.7, 57.8, 111.2, 111.3, 113.2, 113.3, 122.8, 129.2, 129.4, 130.9, 135.3, 140.0, 142.8, 150.7, 153.0, 153.1, 153.4, 154.3, 188.1, 188.9.

Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4\text{S}_2$: C, 61.04, H, 4.45, N, 6.19. Found: C, 60.74, H, 4.31, N, 6.06.

1-(3,4-Diamino-5-(4-methylbenzoyl)thieno[2,3-b]thiophen-2-yl)ethanone (8{2, 8}).



Yield: 1.21 g (73 %), mp = 295 – 297 °C.

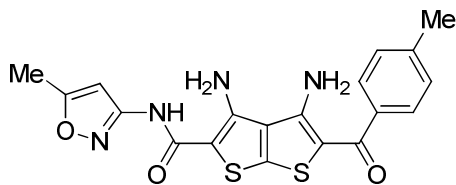
IR (KBr): 3443, 3372, 3299, 3244, 3189 (NH_2), 1644 (CO), 1594 (CO, δ NH_2) cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 2.26 (s, 3H, COMe), 2.39 (s, 3H, Me), 7.32 (d, J = 7.7, 2H, 4-MeC₆H₄, H(3,5)), 7.61 (d, J = 7.7, 2H, 4-MeC₆H₄, H(2,6)), 8.03 (s, 2H, C(4)NH₂), 8.33 (s, 2H, C(3)NH₂).

^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ = 20.8, 27.8, 109.1, 110.3, 127.1, 127.3, 128.7, 137.8, 140.6, 148.7, 150.0, 150.8, 186.7, 188.9.

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$: C, 58.16, H, 4.27, N, 8.48. Found: C, 57.92, H, 4.22, N, 8.41.

3,4-Diamino-5-(4-methylbenzoyl)-N-(5-methylisoxazol-3-yl)thieno[2,3-b]thiophene-2-carboxamide (8{2, 7}).



Yield: 1.22 g (59 %), mp = 297 – 300 °C.

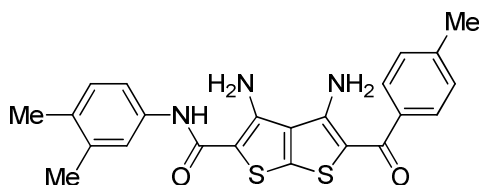
IR (KBr): 3441, 3365, 3315, 3286, 3223 (NH_2 , NH), 1655 (CO), 1623, 1598 (CO, δ NH_2) cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 2.39 (s, 6H, 2 Me), 6.64 (s, 1H, Het, C(4)H), 7.32 (d, J = 7.7, 2H, 4-MeC₆H₄, H(3,5)), 7.55 (s, 2H, C(4)NH₂), 7.63 (d, J = 7.7, 2H, 4-MeC₆H₄, H(2,6)), 8.31 (s, 2H, C(3)NH₂), 10.44 (s, 1H, CONH).

^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ = 11.9, 20.8, 97.1, 100.7, 109.2, 127.1, 127.8, 128.7, 137.9, 140.6, 148.5, 149.2, 150.6, 158.4, 162.6, 168.5, 186.7.

Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}_2$: C, 55.32, H, 3.91, N, 13.58. Found: C, 55.58, H, 4.02, N, 13.75.

3,4-Diamino-N-(3,4-dimethylphenyl)-5-(4-methylbenzoyl)thieno[2,3-b]thiophene-2-carboxamide (8{2, 10}).



Yield: 1.65 g (76 %), mp = 225 – 228 °C.

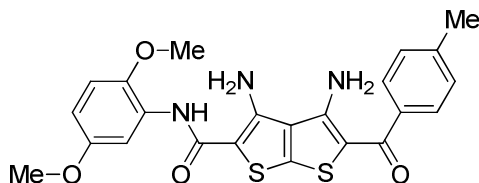
IR (KBr): 3454, 3397, 3303, 3263 (NH₂, NH), 1643, 1588 (CO, δ NH₂) cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.18-2.20 (m, 6H, 2 Me) 2.39 (s, 3H, Me), 7.05 (d, *J* = 8.1, 1H, Me₂C₆H₃, H(5)), 7.24-7.37 (m, 5H, Ar, C(4)NH₂), 7.43 (s, 1H, Me₂C₆H₃, H(2)), 7.63 (d, *J* = 7.8, 2H, 4-MeC₆H₄, H(2,6)), 8.26 (s, 2H, C(3)NH₂), 9.18 (s, 1H, CONH).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 18.5, 19.3, 20.8, 109.2, 118.6, 122.3, 127.1, 128.3, 128.7, 128.9, 129.1, 130.8, 135.7, 136.5, 138.0, 140.5, 147.0, 147.9, 150.7, 163.0, 186.7.

Anal. Calcd for C₂₃H₂₁N₃O₂S₂: C, 63.42, H, 4.86, N, 9.65. Found: C, 63.12, H, 4.69, N, 9.52.

3,4-Diamino-N-(2,5-dimethoxyphenyl)-5-(4-methylbenzoyl)thieno[2,3-b]thiophene-2-carboxamide (8{2, 11}).



Yield: 1.38 g (59 %), mp = 235 – 238 °C.

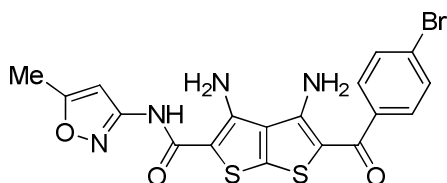
IR (KBr): 3443, 3403, 3384, 3328, 3286 (NH₂, NH), 1619, 1610, 1598 (CO, δ NH₂), 1565 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.39 (s, 3H, Me), 3.72 (s, 3H, MeO), 3.82 (s, 3H, MeO), 6.66 (m, 1H, (MeO)₂C₆H₃, H(4)), 6.99 (d, *J* = 8.9, 1H, (MeO)₂C₆H₃, H(3)), 7.30-7.35 (m, 4H, Ar, C(4)NH₂), 7.61-7.67 (m, 3H, Ar), 8.24 (s, 1H, CONH), 8.27 (s, 2H, C(3)NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 20.8, 55.3, 56.4, 102.2, 107.8, 108.2, 109.5, 111.7, 127.1, 128.0, 128.5, 128.7, 137.9, 140.6, 143.5, 146.8, 147.6, 150.6, 153.0, 162.2, 186.8.

Anal. Calcd for C₂₃H₂₁N₃O₄S₂: C, 59.08, H, 4.53, N, 8.99. Found: C, 58.79, H, 4.38, N, 8.77.

3,4-Diamino-5-(4-bromobenzoyl)-N-(5-methylisoxazol-3-yl)thieno[2,3-b]thiophene-2-carboxamide (8{3, 7}).



Yield: 1.27 g (53 %), mp = 294 – 297 °C.

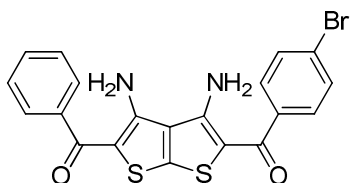
IR (KBr): 3437, 3365, 3314, 3281, 3224 (NH₂, NH), 1655 (CO), 1623, 1599 (CO, δ NH₂), 1587 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.38 (s, 3H, Me), 6.62 (s, 1H, Het C(4)H), 7.54 (s, 2H, C(4)NH₂), 7.64-7.73 (m, 4H, Ar), 8.34 (s, 2H, C(3)NH₂), 10.45 (s, 1H, CONH).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 12.1, 97.3, 100.6, 108.9, 124.4, 127.6, 129.3, 131.4, 139.7, 149.2, 149.4, 151.2, 158.6, 162.7, 168.8, 185.5.

Anal. Calcd for C₁₈H₁₃BrN₄O₃S₂: C, 45.29, H, 2.74, N, 11.74. Found: C, 45.62, H, 2.93, N, 11.89.

(4-Bromophenyl)(3,4-diamino-5-benzoylthieno[2,3-b]thiophen-2-yl)methanone (8{3, 1}).



Yield: 1.75 g (77 %), mp = 280 – 282 °C.

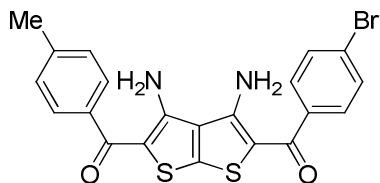
IR (KBr): 3418 br, 3295, 3249 (NH₂), 1636 (CO, δ NH₂), 1590 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.50-7.75 (m, 9H, 2 Ar), 8.45-8.48 (m, 4H, 2 NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 108.8, 109.2, 119.1, 124.3, 126.9, 128.2, 129.0, 130.6, 131.3, 139.5, 140.5, 150.9, 151.2, 152.9, 185.4, 186.8.

Anal. Calcd for C₂₀H₁₃BrN₂O₂S₂: C, 52.52, H, 2.86, N, 6.12. Found: : C, 52.84, H, 2.99, N, 6.31.

(4-Bromophenyl)(3,4-diamino-5-(4-methylbenzoyl)thieno[2,3-b]thiophen-2-yl)methanone (8{3, 2}).



Yield: 1.78 g (76 %), mp = 289 – 291 °C.

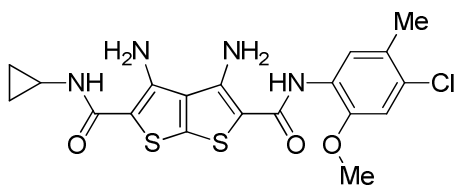
IR (KBr): 3437 br, 3288 (NH₂), 1630 (CO, δ NH₂), 1587 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.36 (s, 3H, Me), 7.30 (d, *J* = 7.9, 2H, 4-MeC₆H₄, H(3,5)), 7.58-7.72 (m, 6H, Ar), 8.39-8.45 (m, 4H, 2 NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 20.8, 108.8, 109.2, 124.2, 126.9, 127.1, 129.1, 131.3, 131.6, 137.8, 139.5, 140.6, 150.8, 151.2, 152.6, 185.4, 186.7.

Anal. Calcd for C₂₁H₁₅BrN₂O₂S₂: C, 53.51, H, 3.21, N, 5.94. Found: C, 53.26, H, 3.12, N, 5.74.

3,4-Diamino-N²-(4-chloro-2-methoxy-5-methylphenyl)-N⁵-cyclopropylthieno[2,3-b]thiophene-2,5-dicarboxamide (8{4, 12}).



Yield: 1.10 g (49 %), mp = 249 – 251 °C.

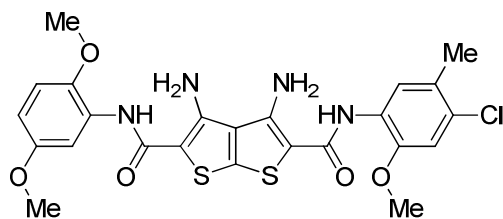
IR (KBr): 3438, 3361, 3328, 3282 (NH₂, NH), 1601 (CO, δ NH₂), 1523 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 0.5-0.65 (m, 4H, (CH₂)₂CH), 2.26 (s, 3H, Me), 2.72 (m, 1H, (CH₂)₂CH), 3.84 (s, 3H, MeO), 7.1 (m, 5H, 2 NH₂, Ar), 7.57 (s, 1H, Ar), 7.85 (s, 1H, CONH), 8.23 (s, 1H, CONH).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 5.6, 18.7, 22.6, 56.3, 102.0, 102.5, 111.8, 123.8, 126.1, 126.6, 127.6, 129.9, 140.5, 146.5, 147.5, 148.6, 162.4, 165.7.

Anal. Calcd for C₁₉H₁₉ClN₄O₃S₂: C, 50.60, H, 4.25, N, 12.42. Found: C, 50.41, H, 4.09, N, 12.23.

3,4-Diamino-N²-(4-chloro-2-methoxy-5-methylphenyl)-N⁵-(2,5-dimethoxyphenyl)thieno[2,3-b]thiophene-2,5-dicarboxamide (8{4, 11}).



Yield: 1.73 g (63 %), mp = 262 – 264 °C.

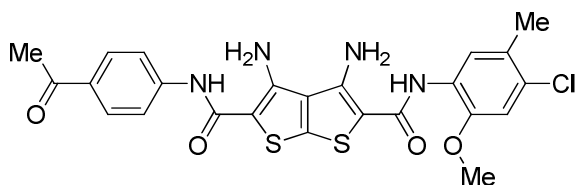
IR (KBr): 3397, 3314 (NH₂, NH), 1622, 1599 (CO, δ NH₂), 1529 cm⁻¹.

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 2.27 (s, 3H, Me), 3.72 (s, 3H, MeO), 3.83-3.86 (m, 6H, 2 MeO), 6.66 (m, 1H, $(\text{MeO})_2\text{C}_6\text{H}_3$, H(4)), 6.99 (d, J = 8.9, 1H, $(\text{MeO})_2\text{C}_6\text{H}_3$, H(3)), 7.13-7.20 (m, 5H, Ar, 2 NH_2), 7.68 (s, 1H, Ar), 7.82 (s, 1H, Ar), 8.25 (s, 1H, CONH), 8.37 (s, 1H, CONH).

^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ = 18.7, 55.3, 56.3, 56.4, 102.5, 102.7, 107.7, 108.0, 111.7, 111.8, 124.1, 126.1, 126.6, 127.8, 128.1, 130.1, 141.1, 143.4, 147.4, 147.5, 148.9, 153.1, 162.3, 162.4.

Anal. Calcd for $\text{C}_{24}\text{H}_{23}\text{ClN}_4\text{O}_5\text{S}_2$: C, 52.69, H, 4.24, N, 10.24. Found: C, 53.02, H, 4.41, N, 10.46.

N^2 -(4-Acetylphenyl)-3,4-diamino- N^5 -(4-chloro-2-methoxy-5-methylphenyl)thieno[2,3-b]thiophene-2,5-dicarboxamide (8{4, 13}).



Yield: 2.11 g (80 %), mp = 262 – 265 °C.

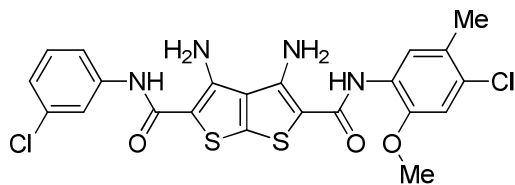
IR (KBr): 3441, 3425, 3397, 3324 (NH_2 , NH), 1669 (CO), 1620 (CO, δ NH_2), 1588 cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 2.27 (s, 3H, Me), 2.54 (s, 3H, COMe), 3.86 (s, 3H, MeO), 7.13 (s, 1H, Ar), 7.23 (s, 2H, NH_2), 7.39 (s, 2H, NH_2), 7.82-7.94 (m, 5H, Ar, 4-MeCOC C_6H_4), 8.30 (s, 1H, CONH), 9.62 (s, 1H, CONH).

^{13}C NMR (151 MHz, $\text{DMSO}-d_6$): δ = 18.72, 26.11, 56.35, 101.75, 102.14, 111.78, 113.2, 119.61, 123.79, 126.12, 126.62, 127.73, 128.81, 129.54, 131.38, 142.16, 143.69, 147.55, 148.52, 162.37, 163.30, 196.24.

Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}_2$: C, 54.49, H, 4.00, N, 10.59. Found: C, 54.82, H, 3.86, N, 10.39.

3,4-Diamino- N^2 -(4-chloro-2-methoxy-5-methylphenyl)- N^5 -(3-chlorophenyl)thieno[2,3-b]thiophene-2,5-dicarboxamide (8{4, 14}).



Yield: 1.90 g (73 %), mp = 264 – 266 °C.

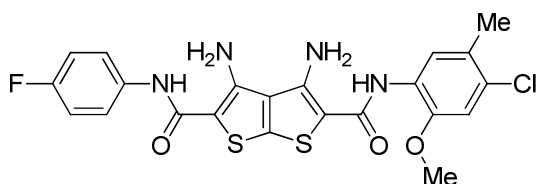
IR (KBr): 3397 br, 3328 br (NH_2 , NH), 1615 (CO, δ NH_2), 1589 cm^{-1} .

^1H NMR (300 MHz, DMSO- d_6): δ = 2.28 (s, 3H, Me), 3.86 (s, 3H, MeO), 7.10-7.40 (m, 7H, 2 Ar, NH₂), 7.60 (d, J = 8.2, 1H, Ar), 7.86 (s, 2H, NH₂), 8.35 (br s, 1H, CONH), 9.43 (br s, 1H, CONH).

^{13}C NMR (151 MHz, DMSO- d_6): δ = 18.73, 56.35, 101.82, 102.07, 111.81, 113.3, 119.04, 120.18, 122.40, 123.88, 126.19, 126.62, 127.69, 129.69, 132.58, 140.80, 141.89, 147.58, 148.23, 148.74, 162.40, 163.32.

Anal. Calcd for C₂₂H₁₈Cl₂N₄O₃S₂: C, 50.67, H, 3.48, N, 10.74. Found: C, 50.42, H, 3.41, N, 10.62.

3,4-Diamino-N²-(4-chloro-2-methoxy-5-methylphenyl)-N⁵-(4-fluorophenyl)thieno[2,3-b]thiophene-2,5-dicarboxamide (8{4, 15}).



Yield: 1.88 g (74 %), mp = 260 – 263 °C.

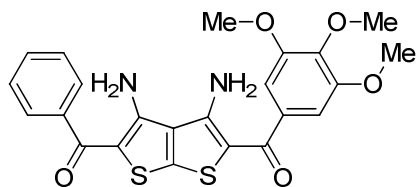
IR (KBr): 3432, 3408, 3374, 3332 (NH₂, NH), 1610 (CO, δ NH₂), 1521 cm⁻¹.

^1H NMR (300 MHz, DMSO- d_6): δ = 2.28 (s, 3H, Me), 3.86 (s, 3H, MeO), 7.10-7.30 (m, 7H, 2 Ar, NH₂), 7.65 (s, 2H, NH₂), 7.86 (s, 1H, Ar), 8.31 (s, 1H, CONH), 9.39 (s, 1H, CONH).

^{13}C NMR (151 MHz, DMSO- d_6): δ = 18.7, 56.4, 92.71, 109.4, 111.8, 114.6 (d, J = 22 Hz, Ar, C(3)H, C(5)H), 114.8, 122.90, 123.93, 126.14, 126.64, 127.75, 132.1, 135.2, 141.6, 142.6, 147.9, 158.3 (d, J = 239 Hz, Ar, C(4)F), 162.4, 163.2.

Anal. Calcd for C₂₂H₁₈ClFN₄O₃S₂: C, 52.33, H, 3.59, N, 11.09. Found: C, 51.98, H, 3.38, N, 10.77.

(3,4-Diamino-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophen-2-yl)(phenyl)methanone (8{5, 1}).



Yield: 1.84 g (79 %), mp = 232 – 235 °C.

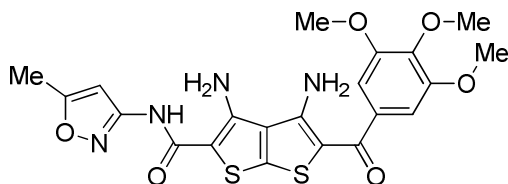
IR (KBr): 3432, 3387, 3290 (NH₂), 1630, 1596 (CO, δ NH₂), 1573 cm⁻¹.

^1H NMR (300 MHz, DMSO- d_6): δ = 3.73 (s, 3H, 4-MeO), 3.83 (s, 6H, 3-MeO, 5-MeO), 7.01 (s, 2H, (MeO) $_3$ C $_6$ H $_2$), 7.47-7.57 (m, 3H, Ph, H(3,4,5)), 7.69 (d, J = 6.5, 2H, Ph, H(2,6)), 8.42 (s, 4H, 2 NH $_2$).

^{13}C NMR (75 MHz, DMSO- d_6): δ = 56.1, 60.1, 105.0, 109.1, 113.6, 127.0, 127.2, 128.4, 130.8, 135.9, 139.7, 140.7, 151.1, 151.2, 152.7, 153.1, 186.1, 187.0.

Anal. Calcd for C $_{23}$ H $_{20}$ N $_2$ O $_5$ S $_2$: C, 58.96, H, 4.30, N, 5.98. Found: C, 59.32, H, 4.17, N, 5.76.

3,4-Diamino-N-(5-methylisoxazol-3-yl)-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophene-2-carboxamide (8{5, 7}).



Yield: 1.44 g (59 %), mp = 302 – 305 °C.

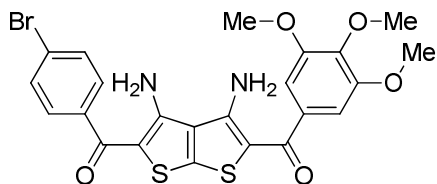
IR (KBr): 3441, 3367, 3314, 3268, 3187 (NH $_2$, NH), 1654 (CO), 1624, 1595 (CO, δ NH $_2$), 1568 cm $^{-1}$.

^1H NMR (300 MHz, DMSO- d_6): δ = 2.38 (s, 3H, Me), 3.73 (s, 3H, 4-MeO), 3.84 (s, 6H, 3-MeO, 5-MeO), 6.63 (s, 1H, Het C(4)H), 7.03 (s, 2H, (MeO) $_3$ C $_6$ H $_2$), 7.53 (s, 2H, C(4)NH $_2$), 8.30 (s, 2H, C(3)NH $_2$), 10.44 (s, 1H, CONH).

^{13}C NMR (151 MHz, DMSO- d_6): δ = 12.1, 56.1, 60.1, 97.3, 100.5, 104.9, 109.1, 113.6, 127.7, 135.9, 149.1, 149.4, 151.0, 152.6, 158.5, 162.7, 168.8, 186.0.

Anal. Calcd for C $_{21}$ H $_{20}$ N $_4$ O $_6$ S $_2$: C, 51.63, H, 4.13, N, 11.47. Found: C, 51.49, H, 4.08, N, 11.42.

(4-Bromophenyl)(3,4-diamino-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophen-2-yl)methanone (8{5, 3}).



Yield: 2.21 g (81 %), mp = 270 – 272 °C.

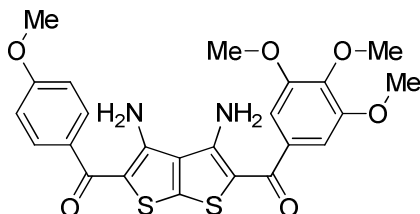
IR (KBr): 3417 br (NH $_2$), 1630 (CO, δ NH $_2$), 1584 cm $^{-1}$.

^1H NMR (300 MHz, DMSO- d_6): δ = 3.72 (s, 3H, 4-MeO), 3.82 (s, 6H, 3-MeO, 5-MeO), 7.00 (s, 2H, (MeO) $_3$ C $_6$ H $_2$), 7.56-7.72 (m, 4H, 4-BrC $_6$ H $_4$), 8.43-8.46 (m, 4H, 2 NH $_2$).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 56.1, 60.1, 105.0, 108.8, 109.1, 113.7, 124.4, 126.9, 129.3, 131.4, 135.9, 139.6, 151.1, 151.4, 152.6, 153.2, 185.5, 186.1.

Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{BrN}_2\text{O}_5\text{S}_2$: C, 50.46, H, 3.50, N, 5.12. Found C, 50.68, H, 3.59, N, 5.23.

(3,4-Diamino-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophen-2-yl)(4-methoxyphenyl)methanone (8{5, 16}).



Yield: 1.85 g (74 %), mp = 149 – 152 °C.

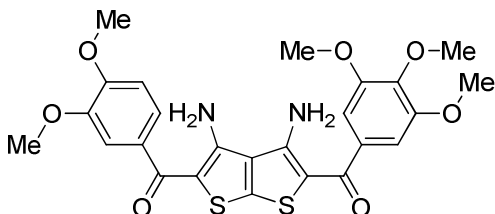
IR (KBr): 3437 br, 3297 br (NH_2) 1630, 1598 (CO , δ NH_2), 1572 cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 3.74 (s, 3H, 4-MeO), 3.84 (m, 9H, 3-MeO, 5-MeO, 4-(MeO) C_6H_4), 7.03-7.06 (m, 4H, (MeO) $_3\text{C}_6\text{H}_2$, 4-MeOC $_6\text{H}_4$, H(3,5)), 7.71 (d, J = 8.1, 2H, 4-MeOC $_6\text{H}_4$, H(2,6)), 8.37-8.42 (m, 4H, 2 NH_2).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 55.3, 56.0, 60.1, 105.0, 109.0, 109.1, 113.6, 127.1, 129.3, 133.0, 135.9, 139.6, 150.9, 151.2, 152.4, 152.7, 161.3, 186.0, 186.1.

Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_6\text{S}_2$: C, 57.82, H, 4.45, N, 5.62. Found: C, 57.47, H, 4.29, N, 5.44.

(3,4-Diamino-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophen-2-yl)(3,4-dimethoxyphenyl)methanone (8{5, 9}).



Yield: 1.88 g (71 %), mp = 149 – 152 °C.

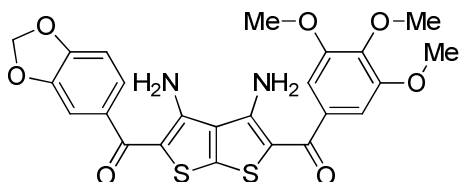
IR (KBr): 3441 br, 3297 br (NH_2), 1630, 1597 (CO , δ NH_2), 1576 cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 3.73 (s, 3H, MeO), 3.80-3.85 (m, 12H, 4 MeO), 7.01-7.05 (m, 3H, (MeO) $_3\text{C}_6\text{H}_2$, (MeO) $_2\text{C}_6\text{H}_3$, H(5)), 7.28 (s, 1H, (MeO) $_2\text{C}_6\text{H}_3$, H(2)), 7.35 (d, J = 8.4, 1H, (MeO) $_2\text{C}_6\text{H}_3$, H(6)), 8.38-8.42 (m, 4H, 2 NH_2).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 55.5, 55.6, 56.0, 60.1, 104.7, 105.0, 105.8, 109.0, 110.8, 110.9, 120.7, 127.1, 133.0, 135.9, 139.6, 148.4, 150.9, 151.2, 152.5, 152.6, 186.0. The signals of CO groups are overlapped.

Anal. Calcd for C₂₅H₂₄N₂O₇S₂: C, 56.80, H, 4.58, N, 5.30. Found: C, 57.02, H, 4.68, N, 5.43.

Benzo[d][1,3]dioxol-5-yl(3,4-diamino-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophen-2-yl)methanone (8{5, 17}).



Yield: 2.00 g (78 %), mp = 152 – 154 °C.

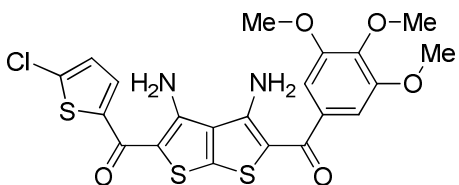
IR (KBr): 3440 br (NH₂), 1629 (CO, δ NH₂), 1579 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.74 (s, 3H, MeO), 3.84 (s, 6H, 2 MeO), 6.13 (s, 2H, OCH₂O), 7.02 (m, 3H, (MeO)₃C₆H₂, Ar, H(5)), 7.23 (s, 1H, Ar, H(2)), 7.31 (d, *J* = 8.0, 1H, Ar, H(6)), 8.37, 8.42 (both s, 2H, 2H, 2 NH₂).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 56.0, 60.1, 101.7, 104.9, 107.6, 107.8, 108.8, 109.0, 113.5, 122.3, 127.0, 134.7, 135.9, 139.1, 147.4, 149.5, 150.9, 151.1, 152.6, 185.6, 186.0.

Anal. Calcd for C₂₄H₂₀N₂O₇S₂: C, 56.24, H, 3.93, N, 5.47. Found: C, 56.42, H, 3.88, N, 5.40.

(5-Chlorothiophen-2-yl)(3,4-diamino-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophen-2-yl)methanone (8{5, 18}).



Yield: 2.06 g (81 %), mp = 263 – 266 °C.

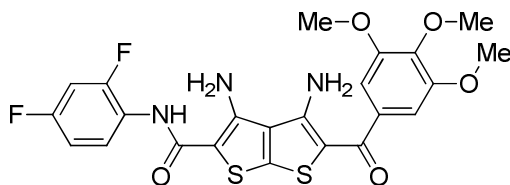
IR (KBr): 3439 br, 3289 br (NH₂), 1629 (CO, δ NH₂), 1578 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.75 (s, 3H, MeO), 3.85 (s, 6H, 2 MeO), 7.03 (s, 2H, (MeO)₃C₆H₂), 7.25, 7.66 (both d, *J* = 3.9, 1H, 1H, thienyl), 8.43, 8.54 (both s, 2H, 2H, 2 NH₂).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 56.0, 60.1, 105.0, 106.6, 109.3, 113.6, 126.6, 128.2, 129.2, 134.9, 135.8, 139.2, 144.3, 150.9, 152.4, 152.7, 175.2, 185.9.

Anal. Calcd for C₂₁H₁₇ClN₂O₅S₃: C, 49.55, H, 3.37, N, 5.50. Found: C, 49.28, H, 3.29, N, 5.41.

3,4-Diamino-N-(2,4-difluorophenyl)-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophene-2-carboxamide (8{5, 19}).



Yield: 1.76 g (68 %), mp = 283 – 285 °C.

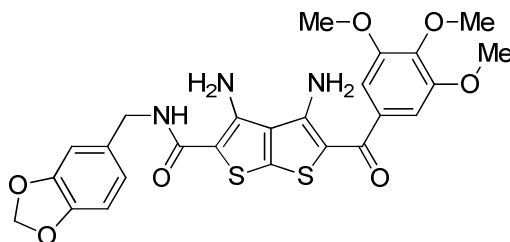
IR (KBr): 3456, 3417, 3368, 3298 (NH₂, NH), 1664 (CONH), 1620 (CO, δ NH₂), 1567 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.74 (s, 3H, MeO), 3.85 (s, 6H, 2 MeO), 7.03-7.09 (m, 3H, (MeO)₃C₆H₂, Ar), 7.25-7.40, (m, 3H, Ar, NH₂), 7.49 (m, 1H, Ar), 8.26 (s, 2H, NH₂), 9.20 (br. s, 1H, NH).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 56.1, 60.1, 100.9, 104.2 (dd, J = 24.9 Hz, J = 26.2 Hz, Ar, C(3)H), 104.9, 109.2, 111.0 (d, J = 21.9 Hz, Ar, C(5)H), 122.2, 122.3, 128.1, 128.9 (d, J = 11.9 Hz, Ar, C(6)H), 136.0, 148.1, 148.3, 151.0, 152.7, 156.6 (dd, J = 249 Hz, J = 12.7 Hz, Ar, C(2)F), 159.5 (dd, J = 244 Hz, J = 11.0 Hz, Ar, C(4)F), 163.3, 186.1.

Anal. Calcd for C₂₃H₁₉F₂N₃O₅S₂: C, 53.17, H, 3.69, N, 8.09. Found: C, 53.42, H, 3.81, N, 8.26.

3,4-Diamino-N-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophene-2-carboxamide (8{5, 20}).



Yield: 2.08 g (77 %), mp = 172 – 175 °C.

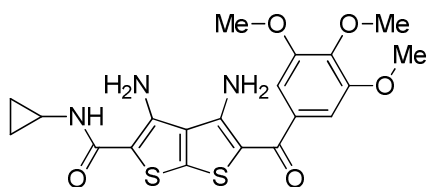
IR (KBr): 3419, 3319 (NH₂, NH), 1606 (CO, δ NH₂), 1572 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.73 (s, 3H, MeO), 3.84 (s, 6H, 2 MeO), 4.27 (d, J = 5.8, 2H, CH₂NH), 5.96 (s, 2H, OCH₂O), 6.75 (d, J = 7.3, 1H, Ar), 6.86 (s, 1H, Ar, H(2)), 7.02 (s, 2H, (MeO)₃C₆H₂), 7.23 (d, J = 7.3, 1H, Ar), 8.09 (t, J = 5.8, 1H, NH), 8.21 (m, 4H, 2 NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 41.9, 56.1, 60.0, 100.6, 100.7, 102.0, 105.1, 107.7, 107.8, 109.1, 120.3, 128.5, 133.9, 135.9, 139.8, 145.8, 146.9, 147.0, 150.9, 152.6, 164.2, 185.9.

Anal. Calcd for C₂₅H₂₃N₃O₇S₂: C, 55.44, H, 4.28, N, 7.76. Found: C, 55.17, H, 4.21, N, 7.65.

3,4-Diamino-N-cyclopropyl-5-(3,4,5-trimethoxybenzoyl)thieno[2,3-b]thiophene-2-carboxamide (8{5, 12}).



Yield: 1.15 g (51 %), mp = 158 – 161 °C.

IR (KBr): 3407, 3316 (NH₂, NH), 1607 (CO, δ NH₂), 1569 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 0.53-0.64 (m, 4H, (CH₂)₂CH), 2.71 (m, 1H, (CH₂)₂CH), 3.73 (s, 3H, MeO), 3.83 (s, 6H, 2 MeO), 7.01 (s, 2H, (MeO)₃C₆H₂), 7.25 (s, 2H, NH₂), 7.61 (d, *J* = 3.0, 1H, NH), 8.22 (s, 2H, NH₂).

¹³C NMR (151 MHz, DMSO-*d*₆): δ = 5.7, 22.6, 56.1, 60.0, 102.1, 105.1, 109.1, 112.1, 128.4, 135.9, 146.6, 146.7, 150.9, 152.6, 165.6, 185.8.

Anal. Calcd for C₂₀H₂₁N₃O₅S₂: C, 53.68, H, 4.73, N, 9.39. Found: C, 53.91, H, 4.64, N, 9.26.

