Combinatorial Synthesis of Substituted Thieno[3,2-*b*]pyridines and Other Annulated Heterocycles via New S_N2 → Thorpe-Ziegler → Thorpe-Guareschi Domino Reactions

Anatoliy M. Shestopalov, Lyudmila A. Rodinovskaya, Alexander A. Shestopalov.*

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation

Fax: : +7(499)1355328
E-mail: shchem@dol.ru.

Supporting Information

Experimental Details

All reagents were purchased from Sigma-Aldrich and Acroc and used without further purification. The IR spectra were recorded on Perkin-Elmer-457 and Specord M80 spectrometers in KBr pellets at a 0.01 M concentration. The ^{1}H NMR spectra were recorded on a Bruker AM-300 (300.13 MHz) spectrometer in DMSO-d_6. The ^{13}C NMR spectra were recorded on a Bruker AC-200 (75.47 MHz) instrument in DMSO-d_6. The mass spectra were obtained on a Varian MAT-CH-6 spectrometer with direct sample injection at an ionization voltage of 70 eV.

The high-resolution mass spectra were recorded on a MicrOTOF II instrument (Bruker Daltonics) using electrospray ionization (ESI).

The reaction progresses and the purity of products were monitored by TLC on Silufol UV-254 plates using hexane-acetone (5 : 3) as an eluant and iodine vapor as a visualization reagent.

7-Hydroxy-2-(amino)-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridine-3-carbonitrile (5a-h).

Malononitrile (**2a)** (0.66 g, 0.01 mol) was added at room temperature to a solution of KOH (0.56 g, 0.01 mol) in EtOH (20 ml), followed by the addition of corresponding isothiocyanate **1 (**0.01 mol). The reaction mixture was stirred at 23 ^{o}C for 30 min and chloroacetoacetic ester (**4**) (1.37 ml, 0.01 mol) was added, followed by the addition of a KOH solution (0.56 g, 0.01 mol) in EtOH (20 ml). The reaction mixture was refluxed for 30 min and allowed to cool down to 23 ^{o}C over 4 h, after which it was diluted with 15 ml of water and acidified with a 10% aq. HCl to pH 7. The precipitate was filtered out and washed on the filter with water (2 x 15 ml), ethanol (2 x 10 ml), and hexane (2 x 15 ml) to give compounds **5**, which were recrystallized from ethanol or nitromethane.

5a. Yield: 1.9 g (86%). Mp.: >300^{o}C. IR (cm^{-1}): 2208 (CN), 1637 (δ NH, CONH), 3050-3428 (br. NH, OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 2.87 (s, 3H, CH_3); 5.15 (s, 1H, C^{6}H); 8.07 (br. s, 1H, NH); 4.51 (br. s, NH and OH protons are associated with water and overlaped CONH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 32.79, 74.04, 91.20, 101.81, 115.17, 143.58, 165.60, 167.20, 168.29. MS (EI, 70 eV) m/z: 221 $[M]^+$ (100%).

5b. Yield: 1.92 g (82%). Mp.: >300°C. IR (cm^{-1}): 2216 (CN), 1584, 1624 (br. δ NH, CONH), 3232 (br. NH), 3995 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 1.21 (t, 3H, CH_3 *J* = 7.34); 3.29 (m, 2H, CH_2); 5.67 (s, 1H, C^6H); 8.35 (s, 1H, NH); 10.89 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 14.02, 41.62, 75.95, 90.02, 98.37, 115.16, 150.39, 160.55, 164.73, 166.30. MS (EI, 70 eV) m/z: 235 $[M]^+$ (100%).

5c. Yield: 1.87 g (75%). Mp.: >300°C. IR (cm^{-1}): 2204 (CN), 1616 (br. δ NH, CONH), 3280-3412 (br. NH), 3400 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 1.22 (m, 6H, $2CH_3$); 3.58 (m, 1H, CH); 5.62 (s, 1H, C^6H); 8.06 (s, 1H, NH); 11.03 (br. s, 1H, NH), 15.77 (br. s, 1H, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 21.90, 49.41, 75.24, 96.03, 103.21, 114.54, 150.93, 164.80, 165.18, 168.43. MS (EI, 70 eV) m/z: 249 $[M]^+$ (24), 207 (100), 92 (25), 66 (53%).

5d. Yield: 2.2 g (89%). Mp.: >300°C. IR (cm^{-1}): 2204 (CN), 1612 (br. δ NH, CONH), 3125-3440 (br. NH, OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 3.87 (d, 2H, CH_2, *J* = 5.14); 4.78 (br. s, NH and OH protons are associated with water and overlaped CONH, OH) 5.16 (s, 1H, C^6H); 5.22 (d, 1H, CH_2, *J* = 8.8); 5.31 (d, 1H, CH_2, *J* = 11.74); 5.86 (m, 1H, CH); 8.46 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 48.58, 75.42, 91.13, 101.02, 115.02, 117.18, 132.48, 133.51, 165.37, 166.20, 166.29. MS (EI, 70 eV) m/z: 247 $[M]^+$ (100%).

5e. Yield: 2.63 g (93%). Mp.: 278-280°C. IR (cm^{-1}): 2216 (CN), 1610, 1640 (br. δ NH, CONH), 3026-3412 (br. NH, OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 5.60 (s, 1H, C^6H); 5.70 (br. s, NH and OH protons are associated with water and overlaped CONH, OH); 7.13 (m, 1H, C_6H_5); 7.38 (m, 4H, C_6H_5); 8.82 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 82.74, 91.84, 102.26, 114.38, 120.46, 124.31, 129.53, 140.95, 147.29, 161.57, 164.36, 165.35. MS (EI, 70 eV) m/z: 283 $[M]^+$ (100%).

5f. Yield: 2.5 g (83%). Mp.: >300°C. IR (cm^{-1}): 2216 (CN), 1588, 1628 (δ NH, CONH), 3044-3260 (br. NH), 3395 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 5.81 (s, 1H, C^6H); 7.25 (m, 2H, C_6H_4); 7.43 (m, 2H, C_6H_4); 10.23 (br. s, 1H, NH); 11.32 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6, *J*/Hz): 82.28, 91.01, 100.44, 114.29, 116.27 (d, *J* = 22.11), 123.81 (d, *J* = 7.74), 136.80 (d, *J* = 2.22), 150.31, 159.34 (d, J = 242.16 Hz), 160.53, 163.03, 164.85.

5g. Yield: 2.44 g (81%). Mp.: 297-298°C. IR (cm^{-1}): 2216 (CN), 1612, 1644 (δ NH, CONH), 3136-3248 (br. NH), 3396 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 5.88 (s, 1H, C^6H); 6.94 (m, 1H, C_6H_4); 7.22 (m, 2H, C_6H_4); 7.40 (m, 1H, C_6H_4); 10.43 (br. s, 1H, NH); 11.38 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6, *J*/Hz): 84.93, 91.72, 101.60, 107.05 (d, *J*=25.43), 110.77 (d, *J* = 21.01), 114.11, 115.85 (d, *J* = 3.31), 131.27 (d, *J* = 8.85), 142.48 (d, *J* = 11.00), 149.67, 160.92, 161.03, 162.55 (d, *J* = 258.75), 165.10. MS (EI, 70 eV) m/z: 301 $[M]^+$ (100%).

5h. Yield: 2.8 g (88%). Mp.: >300°C. IR (cm^{-1}): 2212 (CN), 1592, 1632 (δ NH, CONH), 3330-3425 (br. NH, OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 5.58 (br. s, NH and OH protons are associated with water and overlaped CONH, OH); 6.06 (s, 1H, C^6H); 7.17 (d, 1H, C_6H_4, *J* = 8.5); 7.31-7.51 (m, 3H, C_6H_4); 10.52 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 84.27, 91.60, 113.76, 118.71, 120.02, 124.14, 131.18, 133.81, 142.01, 148.72, 161.43, 164.64, 167.23.

7-Hydroxy-5-oxo-2-(R-methylenthio)-4,5-dihydrothieno[3,2-*b*]pyridine-3-carbonitrile (12a-t) and 7-hydroxy-5-oxo-2-(R-methylenthio)-4,5-dihydrothieno[3,2-*b*]pyridine-3-carboxamide (13a-i).

Method A. Malononitrile (**2a**) (3.3 g, 0.05 mol) or cyanoacetamide (**2b**) (4.2 g, 0.05 mol) was added to a KOH solution (2.8 g, 0.05 mol in EtOH 100 ml) at 23 °C, followed by the addition of carbon disulfide (3.0 ml, 0.05 mol). Subsequently, another portion of the KOH solution (2.8 g, 0.05 mol in EtOH 100 ml) was added. The reaction mixture was stirred at 23 °C for 1 h and diluted with water (50 ml). Chloroacetoacetic ester (**4**) (6.7 ml, 0.05 mol) was added dropwise to the reaction mixture at 10-12 °C over 45 min, the reaction mixture was diluted again with water (20 ml) and filtered. The solution of KOH (2.8 g, 0.05 mol) in EtOH (100 ml) was then added to the filtrate. The reaction mixture was refluxed for 2 h, cooled down to 23 °C, and treated with hydrobromic acid (47%, 5.8 ml, 0.05 mol, d=1.49 g/ml). The reaction mixture was filtered and diluted with a 40% aqueous ethanol solution to obtain 350 ml of the reaction mixture.

The resulting solution of compound **10** was used to perform ten syntheses with 35-ml portions placed in individual flasks. Corresponding alkyl halide **11** or **16** (0.05 mol) were added to each portion at 20 °C, and the reaction mixtures were brought to the boiling point (formation of precipitate was observed). Subsequently, the mixtures were kept in a refrigerator (5°C) overnight. The resulting precipitates were filtered and washed with water (2 x 10 ml), ethanol (2 x 5 ml), and hexane (2 x 10 ml) to give compounds **12, 13** in 98-100% purity.

Method B. (Compounds **12c,e-i).** A solution of KOH (0.06 g, 0.001 mol) in 5 ml of EtOH was added to a suspension of corresponding ester **18a-d,f,g** (0.001 mol) in 12 ml of EtOH, after which the reaction mixture was refluxed for 1 h. The solution was cooled to 23 °C and acidified with a 10% aq. HCl to pH 7. The formed precipitate was filtered out and washed with water (2 x 5 ml), ethanol (2 x 3 ml), and hexane (2 x 5 ml). Compounds **12c, e-i** were then purified by recrystallization from nitromethane.

12a. Yield: 1.06 g (89%). Mp.: >300°C. IR (cm^{-1}): 2228 (CN), 1611-1656 (br. δ CONH), 3200-3235 (br. NH), 3504 (br. OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 2.76 (s, 3H, CH_3); 5.95 (s, 1H, C^6H); 11.93 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 17.48, 92.63, 101.19, 112.08, 113.17, 150.45, 157.44, 160.32, 165.36.

12b. Yield: 1.54 g (77%). Mp.: 198-199°C. IR (cm^{-1}): 2224 (CN), 1616 (br. δ CONH), 1692 (CO), 3030-3458 (br. NH, OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 1.69 (m, 6H, Ad); 1.85 (m, 6H, Ad); 2.01 (m, 3H, Ad); 4.62 (s, 2H, SCH_2); 5.99 (s, 1H, C^6H); 10.61 (s, 1H, OH); 11.79 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 27.44, 35.90, 37.55, 42.79, 46.08, 93.19, 104.01, 113.15, 113.32, 149.72, 153.84, 160.40, 165.24, 207.20. HRMS (ESI), m/z: 399 $[M-H]^-$, 401 $[M+H]^+$, 423 $[M+Na]^+$, 439 $[M+K]^+$.

12c. Yield: 1.46 g (85%) *method A*; 1.27 g (74%) *method B*. Mp.: 246-247°C. IR (cm^{-1}): 2224 (CN), 1604 (br. δ CONH), 1684 (CO), 3288 (br. NH), 3380 (br. OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 5.04 (s, 2H, CH_2); 5.99 (s, 1H, C^6H); 7.55 (m, 2H, C_6H_5); 7.69 (m, 1H, C_6H_5); 8.03 (m, 2H, C_6H_5); 11.79 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 43.66, 93.32, 104.94, 113.09, 113.77, 128.63, 128.92, 134.08, 134.86, 149.86, 152.89, 160.34, 165.42, 192.98. MS (EI, 70 eV) m/z: 342 $[M]^+$ (38), 301 (37), 76 (81), 105 (100%).

12d. Yield: 1.4 g (84%). Mp.: 282-284°C. IR (cm^{-1}): 2228 (CN), 1640 (br. δ CONH), 3240 (br. NH), 3425 (br. OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 4.47 (s, 2H, SCH_2); 5.99 (s, 1H, C^6H); 7.08-7.40 (m, 4H, C_6H_4); 11.85 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz,

DMSO-d_6, *J*/Hz): 39.30 (d, *J* = 2.21), 93.40, 106.23, 112.95, 114.31, 114.69 (d, *J* = 21), 115.75 (d, *J* = 22), 125.14 (d, *J* = 2.21), 130.58 (d, *J* = 7.74), 139.02 (d, *J* = 7.74), 149.89, 151.69, 162.07 (d, *J* = 243.27), 163.69, 165.37.

12e. Yield: 1.65 g (84%) *method A*; 1.41 g (72%) *method B*. Mp.: 296-297°C. IR (cm^{-1}): 2224 (CN), 1636 (br. δ CONH), 3232 (br. NH), 3404 (br. OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 4.40 (s, 2H, SCH_2); 4.50 (br. s, 2H, NH, OH, NH and OH protons are associated with water and overlaped); 5.92 (s, 1H, C^6H); 7.33 (d, 2H, C_6H_4, *J* = 8.07), 7.52 (d, 2H, C_6H_4, *J* = 8.07). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 39.27, 93.53, 105.78, 112.98, 115.01, 120.99, 131.15, 131.51, 135.70, 149.19, 151.32, 161.44, 165.47.

12f. Yield: 1.19 g (68%) *method A*; 1.08 g (62%) *method B*. Mp.: >300°C. IR (cm^{-1}): 2228 (CN), 1640 (br. δ CONH), 3240 (br. NH), 3450 (br. OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6): 4.43 (s, 2H, SCH_2); 6.00 (s, 1H, C^6H); 7.37 (m, 4H, C_6H_4); 11.81 (br. s, 2H, NH, OH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 39.21, 93.48, 105.95, 112.96, 114.23, 128.60, 130.83, 132.51, 135.20, 149.76, 151.80, 160.32, 165.39.

12g. Yield: 1.2 g (73%) *method A*; 1.12 g (68%) *method B*. Mp.: 285-286°C. IR (cm^{-1}): 2232 (CN), 1640 (br. δ CONH), 3228 (br. NH), 3408 (br. OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 2.24 (s, 3H, CH_3); 4.40 (s, 2H, SCH_2); 6.00 (s, 1H, C^6H); 7.10 (d, 2H, C_6H_4, *J* = 7.34); 7.26 (d, 2H, C_6H_4, *J* = 7.34); 11.59 (br. s, 2H, NH, OH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 20.74, 39.55, 93.32, 104.86, 113.06, 113.82, 128.91, 129.20, 132.70, 137.15, 149.72, 152.87, 160.43, 165.39.

12h. Yield: 1.3 g (79%) *method A*; 1.23 g (75%) *method B*. Mp.: 248-250°C. IR (cm^{-1}): 2232 (CN), 1612, 1624, 1636 (br. δ CONH), 3236 (br. NH), 3402 (br. OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 2.26 (s, 3H, CH_3); 4.38 (s, 2H, SCH_2); 5.27 (br. s, 2H, NH, OH, NH and OH protons are associated with water and overlaped); 5.72 (s, 1H, C^6H); 7.08 (d, 1H, C_6H_4, *J* = 7.34); 7.17 (m, 3H, C_6H_4). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 20.93, 40.03, 93.42, 104.79, 113.17, 116.89, 126.08, 128.46, 128.47, 129.56, 135.82, 137.83, 147.72, 150.86, 164.37, 165.75.

12i. Yield: 1.28 g (67%) *method A*; 1.19 g (62%) *method B*. Mp.: 256-257°C. IR (cm^{-1}): 2224 (CN), 1616, 1636 (br. δ CONH), 3240 (br. NH), 3400 (br. OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 4.50 (s, 2H, SCH_2); 5.80 (s, 1H, C^6H); 6.29 (br. s, 2H, NH, OH, NH and OH protons are associated with water and overlaped); 7.51 (dd, 1H, C_6H_4, *J* = 7.34, *J* = 8.07); 7.61 (m, 2H, C_6H_4); 7.70 (s, 1H, C_6H_4). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6, *J*/Hz): 39.76, 93.79, 106.45, 112.94, 117.23, 120.49 and 127.71 (dd, both on *J* = 272.02, CF_3); 124.45 (dd, *J* = 4.42, *J* = 3.32); 125.64 (dd, *J* = 4.42, *J* = 3.32); 129.40 (dd, both on *J* = 32.08); 129.67, 133.08, 137.95, 147.67, 149.47, 163.84, 165.79.

12j. Yield: 1.46 g (85%). Mp.: 272-274°C. IR (cm^{-1}): 2232 (CN), 1584, 1608, 1632 (br. δ CONH), 3228 (br. NH), 3420 (br. OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 3.70 (s, 3H, OCH_3); 4.42 (s, 2H, SCH_2); 5.99 (s, 1H, C^6H); 6.84 (d, 1H, C_6H_4, *J* = 7.33); 6.94(d, 1H, C_6H_4, *J* = 7.33); 6.95 (s, 1H, C_6H_4); 7.23 (t, 1H, C_6H_4, *J* = 8.80); 11.79 (br. s, 2H, NH, OH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 39.82, 55.03, 93.33, 105.45, 113.04, 113.40, 113.98, 114.51, 121.20, 129.71, 137.38, 149.87, 152.53, 159.34, 160.30, 165.36. MS (EI, 70 eV) m/z: 344 $[M]^+$ (37), 121 (100%).

12k. Yield: 1.23 g (78%). Mp.: >300°C. IR (cm^{-1}): 2228 (CN), 1590-1630 (br. δ CONH), 3235-3459 (br. NH, OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 4.48 (s, 2H, SCH_2); 6.00 (s,

1H, C^6H); 7.42 (d, 2H, C_5H_4N, J = 5.87); 8.54 (d, 2H, C_5H_4N, J = 5.14); 11.86 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 93.51, 106.71, 112.89, 114.52, 124.12, 146.21, 149.32, 149.92, 150.99, 160.29, 165.39. HRMS (ESI), m/z: 316 $[M+H]^+$, 338 $[M+Na]^+$.

12l. Yield: 0.74 g (42%). Mp.: >300°C. IR (cm^{-1}): 2228 (CN), 1640 (br. δ CONH), 3260-3400 (br. NH, OH). ^1H NMR, δ, (300 MHz, DMSO-d_6): 4.67 (s, 2H, SCH_2); 6.00 (s, 1H, C^6H); 7.19 (m, 2H, $C_7H_5N_2$); 7.53 (m, 2H, $C_7H_5N_2$); 11.49 (br. s, 1H, NH); 11.94 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 33.46, 93.42, 104.61, 112.92, 114.99 m, 122.12, 138.47 m, 143.19, 149.27, 151.26, 160.27, 165.35.

12m. Yield: 0.76 g (46%). Mp.: 276-278°C. IR (cm^{-1}): 2232 (CN), 1648 (br. δ CONH), 3076, 3268 (br. NH), 3472 (br. OH). ^1H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 1.04 (d, 6H, $(CH_3)_2$, J = 5.87); 3.81 (m, 1H, NCH); 3.87 (s, 2H, SCH_2); 5.99 (s, 1H, C^6H); 8.12 (d, 1H, NH, J = 6.6); 11.66 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 22.15, 39.35, 41.16, 93.29, 104.29, 113.08, 113.87, 149.85, 153.20, 160.37, 165.07, 165.38. MS (EI, 70 eV) m/z: 323 $[M]^+$ (81), 238 (96), 100 (100), 85 (76%).

12n. Yield: 1.48 g (92%). Mp.: 255-256°C. IR (cm^{-1}): 2232 (CN), 1648 (br. δ CONH), 3076, 3268 (br. NH), 3472 (br. OH). ^1H NMR, δ, (300 MHz, DMSO-d_6): 0.41 (m, 2H, CH_2), 0.65 (m, 2H, CH_2), 2.64 (m, 1H, CH), 3.86 (s, 2H, SCH_2), 6.01 (s, 1H, C^6H); 8.28 (br s, 1H, NH); 11.28 (br. s, 1H, OH); 11.79 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 5.74, 22.76, 39.22, 93.41, 104.83, 113.11, 113.89, 149.70, 153.17, 160.44, 165.44, 167.33.

12o. Yield: 0.96 g (46%). Mp.: >300°C. IR (cm^{-1}): 2216 (CN), 1625, 1648 (br. δ CONH), 3456 (br. NH, OH). ^1H NMR, δ, (300 MHz, DMSO-d_6): 1.61 (m, 6H, Ad); 1.91 (m, 6H, Ad); 2.00 (m, 3H, Ad); 3.78 (s, 2H, SCH_2); 5.99 (s, 1H, C^6H); 7.69 (s, 1H, NH); 10.30 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 28.79, 36.93, 40.10, 40.80, 51.35, 93.18, 104.50, 113.12, 113.77, 149.86, 153.59, 160.41, 165.05, 165.35.

12p. Yield: 0.81 g (43%). Mp.: 268-271°C. IR (cm^{-1}): 2240 (CN), 1612, 1636, 1656 (br. δ CONH), 3224 (br. NH), 3384 (br. OH). ^1H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 4.16 (s, 2H, SCH_2); 6.00 (s, 1H, C^6H); 6.89 (t, 1H, C_6H_4, J = 8.07); 7.25-7.39 (m, 2H, C_6H_4); 7.54 (d, 1H, C_6H_4, J = 11.74); 10.54 (s, 1H, NH); 11.80 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6, J/Hz): 40.33, 93.41, 105.58, 106.16 (d, J = 26.54), 110.30 (d, J = 21.01), 113.06, 114.14, 115.07 (d, J =3.32), 130.57 (d, J = 8.84), 140.28 (d, J = 11.23), 149.98, 152.44, 160.35, 161.96 (d, J = 242.16), 165.43, 165.51.

12q. Yield: 1.19 g (56%). Mp.: >300°C. IR (cm^{-1}): 2232 (CN), 1592, 1636 (br. δ CONH), 3240 (br. NH), 3425 (br. OH). ^1H NMR, δ, (300 MHz, DMSO-d_6): 4.22 (s, 2H, SCH_2); 6.02 (s, 1H, C^6H); 7.43-7.54 (m, 2H, C_6H_4); 7.66-7.74 (m, 2H, C_6H_4); 9.98 (s, 1H, NH); 11.79 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6, J/Hz): 39.37; 93.35; 105.36; 113.09; 114.10; 119.88 and 127.13 (dd, both on J = 273.12, CF_3); 124.53 (dd, both on J =29.86); 126.39 (dd, both on J=5.53); 127.06; 129.70; 133.16; 134.74 (d, J = 2.21); 150.01; 152.61; 160.38; 165.43; 166.41. MS (EI, 70 eV) m/z: 425 $[M]^+$ (43), 161 (45), 154 (55), 141 (100%).

12r. Yield: 0.81g (38%). Mp.: >300°C. IR (cm^{-1}): 2228 (CN), 1608 (br. δ CONH), 3080, 3220, 3328 (br. NH), 3450 (br. OH). ^1H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 4.16 (s, 2H, SCH_2); 6.01 (s, 1H, C^6H); 7.69 (d, 2H, C_6H_4, J = 8.80); 7.76 (d, 2H, C_6H_4, J = 8.80); 10.69 (s, 1H, NH); 11.87 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6, J/Hz): 40.44; 93.48; 105.73; 113.05; 114.23; 119.28; 120.75 and 127.65 (dd, both on J = 270.90 Hz, CF_3); 123.69

(dd, both on J = 32.06 Hz); 126.25 (dd, J=4.43, J = 3.31); 142.15; 149.89; 152.30; 160.39; 165.45; 165.85. HRMS (ESI), m/z: 424 $[M-H]^-$, 448 $[M+Na]^+$.

12s. Yield: 1.32 g (67%). Mp.: 273-274°C. IR (cm^{-1}): 2240 (CN), 1628, 1664 (br. δ CONH), 3212, 3252 (br. NH), 3372 (br. OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 4.23 (s, 2H, SCH_2); 6.01 (s, 1H, C^6H); 6.79 (m, 1H, C_6H_3); 7.30 (m, 1H, C_6H_3); 7.86 (m, 1H, C_6H_3); 10.32 (s, 1H, NH); 11.53 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6, J/Hz): 40.06, 93.52, 105.98, 109.57 (d, J = 28.75), 111.18 (dd, J = 24.33, J = 8.84), 113.05, 114.38, 116.52 (dd, J = 22.12, J = 9.95), 127.01 (dd, J = 15.03, J = 10.01), 149.19 (d, J = 238.85), 149.86, 152.12, 157.70 (d, J = 238.85 Hz), 160.42, 165.45, 166.30.

12t. Yield: 1.5 g (85%). Mp.: >300°C. IR (cm^{-1}): 2232 (CN), 1608, 1644 (br. δ CONH), 1684 (COOEt), 3058, 3216 (br. NH), 3552 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 1.23 (t, 3H, CH_3, J = 7.34); 4.14 (dd, 2H, CH_2, J = 7.34); 4.32 (s, 2H, SCH_2); 6.01 (s, 1H, C^6H); 10.94 (s, 1H, NH); 11.82 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 14.15, 40.91, 61.55, 93.40, 105.36, 113.02, 114.01, 149.97, 151.81, 152.37, 160.38, 165.45, 167.61. MS (EI, 70 eV) m/z: 353 $[M]^+$ (7), 309 (7), 263 (19), 57 (53), 237 (100%).

13a. Yield: 0.99 g (77%). Mp.: >300°C. IR (cm^{-1}): 1616 (δ CONH), 1652 (δ $CONH_2$), 3316, 3200 (br. NH, NH_2), 3448 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 2.58 (s, 3H, CH_3); 6.04 (s, 1H, C^6H); 7.55 (br. s 1H, NH_2); 9.21 (br. s 1H, NH_2); 11.66 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 16.72, 90.29, 112.15 120.48, 151.73, 156.02, 160.34, 163.84, 164.25. MS (EI, 70 eV) m/z: 256 $[M]^+$ (61), 239 (100%).

13b. Yield: 1.43 g (86%). Mp.: 289-291°C. IR (cm^{-1}): 1636 (δ CONH), 1660 (δ $CONH_2$), 3312-3195, 3324 (br. NH, NH_2), 3436 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 4.34 (s, 2H, SCH_2); 6.03 (s, 1H, C^6H); 7.37 – 7.47 (m, 5H, C_6H_5); 7.62 (br. s 1H, NH_2); 9.21 (br. s 1H, NH_2); 10.78 (br. s, 1H, OH); 11.67 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 37.84, 90.76, 112.23, 120.92, 127.56, 128.60, 129.21, 136.07, 160.36, 163.85, 164.20. MS (EI, 70 eV) m/z: 332 $[M]^+$ (19), 91 (100), 84 (63), 65 (50), 59 (30%).

13c. Yield: 1.49 g (86%). Mp.: 298-299°C. IR (cm^{-1}): 1580, 1648 (δ CONH), 1651 (δ $CONH_2$), 3162, 3360 (br. NH, NH_2), 3448 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 2.30 (s, 3H, CH_3); 4.29 (s, 2H, SCH_2); 6.02 (s, 1H, C^6H); 7.17 (d, 2H, C_6H_4, J = 7.34); 7.35 (d, 2H, C_6H_4, J = 7.34); 7.48 (br. s 1H, NH_2); 9.02 (br. s 1H, NH_2); 11.47 (br. s, 2H, NH, OH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 20.73, 90.72, 112.23, 120.86, 129.10, 129.15, 132.90, 136.80, 150.90, 153.02, 160.37, 163.82, 164.18.

13d. Yield: 1.44 g (83%). Mp.: 295-296°C. IR (cm^{-1}): 1620 (δ CONH), 1660 (δ $CONH_2$), 3108-3140 (br. NH, NH_2), 3153 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 2.31 (s, 3H, CH_3); 4.29 (s, 2H, SCH_2); 6.03 (s, 1H, C^6H); 7.13 (d, 1H, C_6H_4, J = 2.93); 7.20-7.33 (m, 3H, C_6H_4); 7.55 (br. s 1H, NH_2); 9.18 (br. s 1H, NH_2); 10.69 (br. s, 1H, OH); 11.61 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 20.94, 37.81, 90.69, 112.21, 120.83, 126.30, 128.23, 128.48, 129.71, 135.86, 137.81, 150.81, 153.58, 160.35, 163.85, 164.21.

13e. Yield: 1.35 g (78%). Mp.: 294-295°C. IR (cm^{-1}): 1636 (δ CONH), 1652 (δ $CONH_2$), 3110-3200 (br. NH, NH_2), 3328 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, J/Hz): 2.40 (s, 3H, CH_3); 4.32 (s, 2H, SCH_2); 6.04 (s, 1H, C^6H); 7.13-7.28 (m, 3H, C_6H_4); 7.41 (d, 1H, C_6H_4, J = 4.40); 7.55 (br. s 1H, NH_2); 9.18 (br. s 1H, NH_2); 10.69 (br. s, 1H, OH); 11.61 (br. s, 1H, NH).

^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 18.73, 36.30, 90.89, 112.41, 121.08, 126.25, 128.02, 130.04, 130.48, 133.56, 136.93, 150.90, 153.05, 160.47, 163.93, 164.28.

13f. Yield: 1.87 g (93%). Mp.: 296-297^{o}C. IR (cm^{-1}): 1612 (δ CONH), 1640 (δ $CONH_2$), 3153 (br. NH, NH_2), 3352 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 4.41 (s, 2H, SCH_2); 6.03 (s, 1H, C^6H); 7.44 (d, 1H, C_6H_3, J = 8.70); 7.51-7.72 (m, 2H, C_6H_3); 7.70 (br. s 1H, NH_2, the signal is overlapped with the signal of the aromatic protons); 9.16 (br. s 1H, NH_2); 10.73 (br. s, 1H, OH); 11.63 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 35.23, 90.94, 112.44, 121.59, 127.71, 129.07, 132.53, 132.77, 133.31, 134.48, 150.62, 155.05, 160.38, 163.91, 164.11. HRMS (ESI), m/z: 401 $[M+H]^+$, 423 $[M+Na]^+$, 439 $[M+K]^+$.

13g. Yield: 1.3 g (75%). Mp.: >300^{o}C. IR (cm^{-1}): 1624 (δ CONH), 1652 (δ $CONH_2$), 3184-3328 (br. NH, NH_2), 3448 (br. OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 3.06 (t, 2H, CH_2, J = 7.34); 3.33 (t, 2H, CH_2, J = 7.34); 6.02 (s, 1H, C^6H); 7.18-7.36 (m, 5H, C_6H_5); 7.53 (br. s 1H, NH_2); 9.17 (br. s 1H, NH_2); 10.62 (br. s, 1H, OH); 11.55 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 34.47, 34.94, 90.77, 112.13, 121.15, 136.54, 128.51, 139.66, 151.07, 153.66, 160.42, 163.87, 164.21. MS (EI, 70 eV) m/z: 346 $[M]^+$ (83), 242 (56), 225 (98), 105 (100), 91 (73), 79 (80%).

13h. Yield: 1.45 g (92%). Mp.: 279-280^{o}C. IR (cm^{-1}): 1660-1636 (br. δ CONH, $CONH_2$), 1740 ($COOCH_3$), 3095, 3200 (br. NH, NH_2), 3320 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 3.71 (s, 3H, OCH_3); 4.07 (s, 2H, SCH_2); 6.04 (s, 1H, C^6H); 7.65 (br. s 1H, NH_2); 9.20 (br. s 1H, NH_2); 10.80 (br. s, 1H, OH); 11.68 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 13.62, 35.79, 90.82, 112.33, 121.52, 151.12, 152.52, 160.39, 163.98, 164.18, 169.08. HRMS (ESI), m/z: 313 $[M-H]^-$, 337 $[M+Na]^+$, 353 $[M+K]^+$, 651 $[2\ M+Na]^+$.

13i. Yield: 1.8 g (86%). Mp.: >300^{o}C. IR (cm^{-1}): 1616 (δ CONH), 1660 ($CONH_2$), 1696 (CO), 3150-3225 (br. NH), 3328 (NH_2), 3448 (br. OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 1.70 (m, 6H, Ad); 1.88 (m, 6H, Ad); 2.02 (m, 3H, Ad); 4.41 (s, 2H, SCH_2); 6.02 (s, 1H, C^6H); 7.63 (br. s 1H, NH_2); 9.22 (br. s 1H, NH_2); 10.73 (br. s, 1H, OH); 11.65 (br. s, 1H, NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 27.42, 35.90. 37.62, 40.81, 46.16, 90.62, 112.08, 121.19, 150.87, 152.81, 160.29, 163.83, 164.26, 208.23. HRMS (ESI), m/z: 417 $[M-H]^-$, 419 $[M+H]^+$, 441 $[M+Na]^+$, 457 $[M+K]^+$.

3-Amino-7-hydroxythieno[3',2':4,5]thieno[3,2-*b*]pyridine-5(4*H*)-ones (**14a,b**).

Method A. Malononitrile (**2a**) (0.66 g, 0.01 mol) was added at room temperature to a KOH solution (0.56 g, 0.01 mol) in EtOH (20 ml). Carbon disulfide (0.6 ml, 0.01 mol) was added to the reaction mixture, followed by the addition of the KOH solution (0.56 g, 0.01 mol in EtOH 20 ml). The reaction mixture was stirred at 23 ^{o}C for 1 h and diluted with 10 ml of water. Chloroacetoacetic ester (**4**) (1.34 ml, 0.01 mol) was added dropwise to the mixture at 10-12 ^{o}C over 10 min. The resulting solution was diluted with 5 ml of water and filtered. A KOH solution (0.56 g, 0.01 mol, in EtOH 10 ml) was added to the filtrate. The reaction mixture was refluxed for 1.5 h, then cooled to 23 ^{o}C and filtered. A 40% aqueous ethanol solution was added to the filtrate to obtain 80 ml of the reaction mixture.

The resulting solution of salt **9a** was divided into two 40-ml portions. Bromoacetyladamantane **11b** (1.29 g, 0.005 mol) or phenacyl bromide **11c** (1.0 g, 0.005 mol)

was added to an individual portion at 23 °C. The reaction mixture was stirred at 60-70 °C for 10 min and then cooled and kept in a refrigerator (5°C) overnight. Subsequently, the reaction mixture was acidified with a 10% aq. HCl to pH 7, the formed precipitate was filtered out and washed with water (2 x 10 ml), ethanol (2 x 5 ml), and hexane (2 x 10 ml). Compounds **14a,b** were recrystallized from nitromethane.

Method B. To a suspension of ester **18g** (0.39 g, 0.001 mol) in EtOH (15 ml), a solution of KOH (0.06 g, 0.001 mol) in EtOH (5 ml) was added and the reaction mixture was refluxed for 20 min. Subsequently, the solution was cooled down to 23 °C and acidified with a 10% aq. HCl to pH 7. The precipitate was filtered out and washed with water (2 x 5 ml), ethanol (2 x 3 ml), and hexane (2 x 5 ml). Pure compound **14b** was obtained after recrystallization from nitromethane.

14a. Yield: 1.52 g (76%). Mp.: >300°C. IR (cm^{-1}): 1584, 1624 br. (δ NH, δ NH_2, CONH, CO), 2904 br. (CH-, Ad); 3190-3475 (br. NH, NH_2, OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6): 1.73 (m, 6H, Ad); 2.04 (m, 9H, Ad); 4.62 (s, 2H, SCH_2); 5.95 (s, 1H, C^6H); 7.98 (br. s, 2H, NH_2); 8.45 (br. s, 1H, OH); 11.62 (br. s, 1H, NH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 27.92, 36.28, 38.85, 45.18, 92.68, 106.80, 115.49, 127.78, 138.92, 145.60, 150.12, 161.13, 164.54, 197.79. MS (EI, 70 eV) m/z: 400 $[M]^+$ (81), 265 (100%), 135 (81%).

14b. Yield: 1.33 g (78%) *method A*; 0.24 g (70%) *method B*. Mp.: >300°C. IR (cm^{-1}): 1592, 1636 br. (δ NH, δ NH_2, CONH, CO), 3196 (NH), 3268 (br. NH), 3364 (OH). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6): 6.01 (s, 1H, C^6H); 7.51-7.59 (m, 3H, C_6H_5); 7.75 (m, 2H, C_6H_5); 8.11 (br. s, 2H, NH_2); 8.58 (br. s, 1H, OH); 11.74 (s, 1H, NH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 93.23, 109.92, 115.12, 127.26, 127.94, 128.16, 128.45, 130.91, 140.63, 148.39, 149.59, 161.23, 164.59, 187.05. MS (EI, 70 eV) m/z: 342 $[M]^+$ (100%).

4,7-Dihydroxypyrido[2'',3'':4',5']thieno[3',2':4,5]thieno[3,2-*b*]pyridine-2,9(1*H*,10*H*)-dione (15), 7-hydroxypyrido[2'',3'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-2,4,9(1*H*,3*H*,10*H*)-trione (17).

Method A. Analogously to *Method A* for compounds **14**, 80 ml of a solution of salt **9a** was prepared. This solution was separated into two 40-ml portions, and chloroacetoacetic ester (**4**) (0.7 ml, 0.005 mol) or chloroacetyl urethane (**16**) (0.82 g, 0.005 mol) were added at room temperature to the individual portions, which contained 0.005 mol of salt **9a**. The reaction mixtures were refluxed for 1.5 h, cooled down to 23 °C and acidified with a 10% aq. solution of HCl to pH 7. Precipitates were filtered off. Compounds **15** and **17** were purified by reprecipitation: crude materials were dissolved in a mixture of EtOH (30 ml) and a 10% aqueous KOH solution (30 ml), the resulting solution was filtered and the filtrate was acidified with a 10% aq. solution of HCl to pH 7. The precipitates were filtered out and washed with water (2 x 10 ml), ethanol (2 x 5 ml), and hexane (2 x 10 ml)).

Compound **17** (*Method B*). To a suspension of thieno[3,2-*b*]pyridine-5-one **12t** (0.34 g, 0.001 mol) in EtOH (15 ml), a solution of KOH (0.06 g, 0.001 mol) in EtOH (10 ml) was added. The reaction mixture was refluxed for 1.5 h, cooled down to 23°C and acidified with a 10% aq. HCl to pH 7. Compound **17** was purified in accordance with *Method A*.

(15): Yield: 1.1 g (72%). Mp.: >300°C. IR (cm^{-1}): 1636, 1648, 1660, 1668 (δ NH, CONH, CO), 3020 (br. NH), 33375 (br. NH), 3364 (OH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 3.73 (br. s, 4H, NH, OH, NH and OH protons are associated with water and overlapped), 5.90 (s, 2H, C^3H, C^8H). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 93.66, 106.57, 114.64, 134.94, 143.13, 162.22, 164.15.

(17): Yield: 1.04 g (68%) *method A*; 0.18 g (59%) *method B*. Mp.: >300°C. IR (cm^{-1}): 1632 (br. CONH), 3404 (br. OH, NH). ^{1}H NMR, δ, (300 MHz, DMSO-d_6): 5.86 (s, 1H, C^8H), 7.17 br. s, 1H, OH), 11.45-12.03 (m, 3H, 3 NH). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 93.52, 95.15, 113.57, 114.54, 123.66, 134.63, 137.96, 151.50, 158.85, 161.89, 164.14.

Ethyl 3-{3-amino-5-[R-methylenthio]-4-cyanothien-2-yl}-3-oxopropanoates (18 a-h).

Malononitrile (**2a)** (3.3 g, 0.05 mol) was added to a solution of KOH (2.8 g, 0.05 mol) in EtOH (50 ml). Carbon disulfide (3.0 ml, 0.05 mol) was then quickly added dropwise to the formed suspension at 10 - 11°C. The solution of KOH (2.8 g, 0.05 mol) in EtOH (50 ml) was added to the reaction mixture dropwise over a period of 10 min. The resulting suspension was stirred for 30 min at room temperature. Water (20 ml) was added to the reaction mixture, followed by the dropwise addition of chloroacetoacetic ester (**4**) (6.7 ml, 0.05 mol) at 10 - 11°C over a 40 min period. The reaction mixture was filtered and 50 ml of EtOH and 2.8 ml of a 10% aqueous solution of KOH were added to the solution. The mixture was refluxed for 30 min, cooled down to 23°C, and diluted with EtOH to a total volume of 200 ml.

The resulting solution of salt **8a** was separated into 20-ml portions, which were placed in individual flasks, to perform ten syntheses. Corresponding alkyl halides **11** (0.005 mol) were added to each portion at 20 °C with stirring, and the resulting mixtures were stirred at room temperature for 5 – 6 h. Subsequently, the mixture were kept in a refrigerator (5°C) overnight. The formed precipitates were filtered out and washed with water (2 x 10 ml), ethanol (2 x 5 ml), and hexane (2 x 10 ml). Compounds **18** were recrystallized from EtOH, CH_3CN, or CH_3NO_2.

18a: Yield: 2.04 g (93%). Mp.: 135-137°C. IR (cm^{-1}): 2212 (CN), 1620 (δ NH_2), 1720 (COOEt), 3308, 3408 (NH_2). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 1.17 (t, 3H, CH_3, J = 7.34); 3.67 (s, 2H, CH_2); 4.09 (dd, 2H, CH_2, J = 7.34); 4.45 (s, 2H, SCH_2); 7.39 (d, 2H, C_6H_4, J = 8.80); 7.55 (d, 2H, C_6H_4, J = 8.80); 7.65 (br. s, 2H, NH_2). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 13.97, 38.04, 47.14, 60.77, 99.95, 108.32, 112.16, 121.17, 131.22, 131.56, 134.90, 154.72, 156.70, 166.89, 183.03. MS (EI, 70 eV) m/z: 171 (100), 89 (55), 440 $[M]^+$ (9%).

18b: Yield: 1.7 g (86%). Mp.: 136-138°C. IR (cm^{-1}): 2212 (CN), 1620 (δ NH_2), 1720 (COOEt), 3308, 3412 (NH_2). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 1.17 (t, 3H, CH_3, J = 7.34); 3.67 (s, 2H, CH_2); 4.09 (dd, 2H, CH_2, J = 7.34); 4.46 (s, 2H, SCH_2); 7.40 (d, 2H, C_6H_4, J = 8.08); 7.46 (d, 2H, C_6H_4, J = 8.08); 7.55 (br. s, 2H, NH_2). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 13.97, 38.02, 47.14, 60.78, 100.01, 108.34, 112.17, 128.64, 132.46, 134.46, 135.19, 154.73, 156.68, 166.89, 183.04. MS (EI, 70 eV) m/z: 125 (100), 89 (70), 494 $[M]^+$ (18%).

18c: Yield: 1.37 g (73%). Mp.: 99-101°C. IR (cm^{-1}): 2224 (CN), 1604 (δ NH_2), 1740 (COOEt), 3184, 3284, 3380 (NH_2). ^{1}H NMR, δ, (300 MHz, DMSO-d_6, *J*/Hz): 1.18 (t, 3H, CH_3, J = 7.34); 2.29 (s, 3H, CH_3); 3.68 (s, 2H, CH_2); 4.09 (dd, 2H, CH_2, J = 7.34); 4.43 (s, 2H, SCH_2); 7.12 (m, 1H, C_6H_4); 7.23 (s, 1H, C_6H_4); 7.25 (m, 2H, C_6H_4); 7.65 (s, 2H, NH_2). ^{13}C NMR, δ,

(75.47 MHz, DMSO-d_6): 13.96, 20.85, 38.72, 47.12, 60.75, 99.31, 108.04, 112.21, 126.16, 128.54, 128.64, 129.64, 134.90, 137.93, 154.79, 157.54, 166.90, 182.93. MS (EI, 70 eV) m/z: 105 (100), 57 (52), 374 $[M]^+$ (34%).

18d: Yield: 1.51 g (82%). Mp.: 117-118°C. IR (cm^{-1}): 2228 (CN), 1608 (δ NH_2), 1724 (COOEt), 3308, 3412 (NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.18 (t, 3H, CH_3, *J* = 7.34); 2.28 (s, 3H, CH_3); 3.67 (s, 2H, CH_2); 4.10 (dd, 2H, CH_2, *J* = 7.34); 4.42 (s, 2H, SCH_2); 7.16 (d, 2H, C_6H_4, *J* = 8.08); 7.32 (d, 2H, C_6H_4, *J* = 8.08); 7.61 (br. s, 2H, NH_2).. ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 14.06, 20.78, 38.72, 47.25, 60.68, 99.57, 108.25, 112.30, 129.08, 129.32, 132.10, 137.44, 154.90, 157.57, 166.97, 183.03. HRMS (ESI), m/z: 375 $[M+H]^+$, 397 $[M+Na]^+$, 413 $[M+K]^+$, 749 $[2\ M+H]^+$, 771 $[2\ M+Na]^+$, 787 $[2M+K]^+$, 1145 $[3\ M+Na]^+$, 1161 $[3\ M+K]^+$.

18e: Yield: 1.59 g (74%). Mp.: 112-114°C. IR (cm^{-1}): 2212 (CN), 1632 (δ NH_2), 1732 (COOEt), 3308, 3424 (NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.20 (t, 3H, CH_3, *J* = 7.34); 3.50 (s, 2H, CH_2); 4.11 (dd, 2H, CH_2, *J* = 7.34); 4.45 (s, 2H, SCH_2); 7.17 (m, 2H, C_6H_4); 7.31 (br. s, 2H, NH_2); 7.45 (m, 2H, C_6H_4). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6, *J*/Hz): 14.00, 38.06, 47.17, 60.81, 99.94, 108.33, 112.21, 115.52 (d, *J* = 21.01), 131.06, 131.38 (d, *J* =7.74), 154.76, 156.89, 161.80 (dd, *J* = 244.37, *J* = 5.53), 166.93, 183.07.

18f: Yield: 1.56 g (73%). Mp.: 117-118°C. IR (cm^{-1}): 2224 (CN), 1620 (δ NH_2), 1716 (COOEt), 3292, 3376 (NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.16 (t, 3H, CH_3, *J* = 7.34); 3.65 (s, 2H, CH_2); 4.08 (dd, 2H, CH_2, *J* = 7.34); 4.56 (s, 2H, SCH_2); 7.57-7.75 (m, 4H, C_6H_4); 7.80 (s, 2H, NH_2). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6, *J*/Hz): 14.53; 38.89; 47.69; 61.34; 94.01; 109.24; 112.67; 121.15 and 131.24(dd, both on *J* = 230.34, CF_3); 125.25; 126.32; 130.35; 133.72; 137.69; 151.79; 155.25; 156.53; 167.39; 183.66.

18g: Yield: 1.65 g (85%). Mp.: 182-184°C. IR (cm^{-1}): 2215 (CN), 1662, 1629 (CO, δ NH_2), 1710 (COOEt), 3312, 3395 (br. NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.17 (t, 3H, CH_3, *J* = 7.36); 3.66 (s, 2H, CH_2); 4.09 (dd, 2H, CH_2, *J* = 7.36); 5.10 (s, 2H, SCH_2); 7.59 (m, 3H, C_6H_5); 8.04 (m, 2H, C_6H_5); 8.07 (s, 2H, NH_2).

18h: Yield: 1.55 g (78%). Mp.: 119-120°C. IR (cm^{-1}): 2224 (CN), 1616 (δ NH_2), 1716 (COOEt), 3288, 3376 (NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.17 (t, 3H, CH_3, *J* = 7.34); 3.68 (s, 2H, CH_2); 4.10 (dd, 2H, CH_2, *J* = 7.34); 4.45 (s, 2H, SCH_2); 7.25-7.57 (m, 3H, C_6H_3); 7.65 (s, 2H, NH_2). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6, *J*/Hz): 13.94, 37.79, 47.15, 60.76, 100.46, 108.55, 112.13, 117.67 (d, *J* = 17.69), 118.19 (d, *J* = 17.69), 126.09 (m), 133.30 (m), 147.53 (m), 150.79 (m), 154.68, 156.13, 166.90, 183.14. MS (EI, 70 eV) m/z: 127 (100), 396 $[M]^+$ (43%).

8-Amino-5-oxo-6-aryl-4,6-dihydro-5*H*-pyrano[2,3-*d*]thieno[3,2-*b*]pyridine-3,7-dicarbonitrile (23a-f).

To a mixture of compounds **5a,d**, (0.002 mol), aldehydes **19a-d** (0.002 mol) and malononitrile **2a** (14 g, 0.002 mol) in 15 ml of DMF, triethylamine (0.5 ml) was added. The reaction mixture was heated at 70 - 80 °C for 30 min and then filtered hot. Filtrate was cooled down and kept in a refrigerator (5°C) overnight. The formed precipitate was filtered out and

washed with hot water (2 x 10 ml), ethanol (2 x 5 ml), and hexane (2 x 15 ml). Compounds **23** were recrystallized from 1,4-dioxane or CH_3NO_2.

23a. Yield: 0.7 g (83%). Mp.: 297-298°C. IR (cm^{-1}): 2208 (br. CN, CN), 1592, 1628 br (δ NH, δ NH_2, CONH), 3300, 3376 (br. NH, NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.24 (t, 3H, CH_3 *J* = 7.34); 3.21 (m, 2H, CH_2); 4.43 (s, 1H, C^6H); 7.17 (s, 2H, NH_2); 7.18 (d, 2H, *J* = 7.33); 8.12 (d, 2H, *J* = 7.33); 8.67 (s, 1H, NH); 11.79 (br. s, 1H, CONH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 13.82, 36.08, 41.86, 57.93, 75.10, 99.68, 114.29, 119.63, 128.20, 129.25, 131.07, 134.70, 143.85, 147.47, 150.63, 158.54, 161.18, 166.55. MS (EI, 70 eV) m/z: 53 (32), 66 (20), 101 (20), 311 (28), 356 (100), 423 $[M]^+$ (5%).

23b. Yield: 0.66 g (85%). Mp.: 293-294°C. IR (cm^{-1}): 2188, 2216 (CN), 1596, 1636 br., 1668 br. (δ NH, δ NH_2, CONH), 3096, 3256, 3356, 3636 (br. NH, NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.25 (t, 3H, CH_3 *J* = 7.34); 3.32 (m, 2H, CH_2); 4.48 (s, 1H, C^6H); 7.17 (s, 2H, NH_2); 7.31 (m, 1H, C_5H_4N); 7.31 (d, 1H, C_5H_4N, *J* = 8.70); 8.41 (d, 1H, C_5H_4N, *J* = 4.40); 8.44 (s, 1H, C_5H_4N); 8.63 (m, 1H, NH); 11.80 (br. s, 1H, CONH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 13.82, 34.36, 41.88, 57.40, 75.07, 99.21, 114.23, 119.58, 123.66, 134.63, 134.96, 140.13, 147.79, 147.41, 148.83, 150.71, 158.67, 161.13, 166.63. MS (EI, 70 eV) m/z: 66 (62), 92 (70), 104 (33), 155 (100), 219 (30), 234 (23), 323 (95), 390 $[M]^+$ (4%).

23c. Yield: 0.67 g (86%). Mp.: >300°C. IR (cm^{-1}): 2200 (br. CN, CN), 1600, 1656 br. (δ NH, δ NH_2, CONH), 3136, 3300, 3436 (br. NH, NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 1.25 (t, 3H, CH_3 *J* = 7.34); 3.45 (m, 2H, CH_2); 4.44 (s, 1H, C^6H); 7.16 (d, 2H, C_5H_4N, *J* = 5.13); 7.20 (s, 2H, NH_2); 8.46 (d, 2H, C_5H_4N, *J* = 4.41); 8.66 (1H, NH); 11.77 (br. s, 1H, CONH). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 13.80, 36.07, 41.87, 56.81, 74.88, 98.66, 114.21, 119.43, 122.63, 137.60, 145.58, 149.62, 150.87, 153.12, 158.70, 161.14, 166.64. MS (EI, 70 eV) m/z: 66 (96), 92 (37), 235 (62), 248 (25), 295 (30), 312 (29), 223 (100), 390 $[M]^+$ (11%).

23d. Yield: 0.64 g (74%). Mp.: 292-293°C. IR (cm^{-1}): 2198, 2204 (CN), 1592, 1620, 1664 br. (δ NH, δ NH_2, CONH), 3180, 3274 (br NH, NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 3.68 (s, 3H, CH_3); 3.96 (m, 2H, CH_2); 4.72 (s, 1H, C^6H); 5.24 (d, 1H, =CH_2, *J* = 11.01); 5.30 (d, 1H, =CH_2, *J* = 19.81); 5.88 (m, 1H, =CH); 6.82 (dd , 1H, C_6H_4, *J* =7.34); 6.93 (m, 2H, C_6H_4); 6.95 (s, 2H, NH_2); 7.15 (dd , 1H, C_6H_4, *J* =7.34); 8.84 (m, 1H, NH); 11.61 (br. s, 1H, NHCO). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 31.73, 48.71, 55.77, 57.56, 76.24, 99.77, 111.74, 114.50, 117.39, 120.00, 120.47, 127.92, 128.91, 132.57, 133.05, 151.52, 157.08, 159.23, 161.24, 166.61.

23e. Yield: 0.72 g (89%). Mp.: 296-298°C. IR (cm^{-1}): 2200 (br. CN, CN), 1604, 1652 br. (δ NH, δ NH_2, CONH), 3200, 3392, 3468 (br NH, NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz): 3.96 (m, 2H, CH_2); 4.48 (s, 1H, C^6H); 5.22 (d, 1H, =CH_2, *J* = 12.47); 5.33 (d, 1H, =CH_2, *J* = 19.08); 5.88 (m, 1H, =CH); 7.17 (s, 2H, NH_2); 7.30 (dd, 1H, C_5H_4N, *J* = 8.07, *J* = 5.14); 7.54 (d, 1H, C_5H_4N, *J* = 8.07); 8.40 (d, 1H, C_5H_4N, *J* = 5.14 Hz), 8.44 (s, 1H, C_5H_4N); 8.86 (m, 1H, NH); 11.83 (br. s, 1H, NHCO). ^{13}C NMR, *δ*, (75.47 MHz, DMSO-d_6): 34.48, 48.75, 57.59, 75.47, 99.49, 114.13, 117.43, 119.63, 123.70, 132.98, 134.31, 135.00, 140.17, 147.88, 148.45, 148.94, 150.81, 158.77, 161.21, 166.91. HRMS (ESI), m/z: 401 $[M-H]^-$, 403 $[M+H]^+$, 425 $[M+Na]^+$, 827 $[2\ M+Na]^+$, 1229 $[3\ M+Na]^+$.

23f. Yield: 0.63 g (78%). Mp.: >300°C. IR (cm^{-1}): 2200 (br. CN, CN), 1600, 1652 br. (δ NH, δ NH_2, CONH), 3148, 3300, 3444 (br. NH, NH_2). ^{1}H NMR, *δ*, (300 MHz, DMSO-d_6, *J*/Hz):

3.96 (m, 2H, CH_2); 4.44 (s, 1H, C^6H); 5.25 (d, 1H, =CH_2, J = 11.01); 5.30 (d, 1H, =CH_2, J = 18,34); 5.88 (m, 1H, =CH); 7.17 (d, 2H, C_5H_4N, J = 5.14); 7.20 (s, 2H, NH_2); 8.46 (d, 2H, C_5H_4N, J = 4.41); 8.87 (m, 1H, NH); 11.85 (br. s, 1H, NHCO). ^{13}C NMR, δ, (75.47 MHz, DMSO-d_6): 36.21, 48.74, 56.96, 77.96, 99.87, 114.21, 117.42, 119.46, 122.74, 132.96, 137.94, 149.67, 151.03, 153.25, 158.25, 161.25, 166.96.