Supporting Information

Organic Letters

One Step Three-Component Synthesis of Pyridines and 1,4-Dihydropyridines with Manifold Medicinal Utility

Nikolai M. Evdokimov, Igor V. Magedov,^{*} Artem S. Kireev, and Alexander Kornienko^{*}

*Department of Organic Chemistry, Timiryazev Agriculture Academy, Moscow 127550, Russia,
Intelbioscan Ltd., Timiryazevsky Proezd 2, Moscow 127550, Russia, and
Department of Chemistry, New Mexico Institute of Mining and Technology, Socorro, New Mexico
87801, USA*

intelbioscan@mtu-net.ru, akornien@nmt.edu

Table of contents

1. General Methods.	S2
2. General procedure for the preparation of compounds A and G .	S2
3. Characterization data for compounds A ₁₋₁₇ , G ₁₈₋₂₄ and J ₄ .	S3 – S12
4. Complete references 2a and 18.	S12
5. Copies of ¹ H and ¹³ C NMR spectra for compound J ₄ .	S13, S14

General Methods. All aldehydes, mercaptans, 1,4-diazabicyclo[2.2.2]octane (DABCO), and malononitrile were purchased from commercial sources and used without purification. Triethylamine (Et_3N) was distilled from CaH_2 . All reactions were performed in a reaction vessel open to the atmosphere and monitored by thin layer chromatography (TLC) on pre-coated (250 μm) silica gel 60F₂₅₄ glass-backed plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain followed by charring on a hot-plate. Flash column chromatography was performed on silica gel (32-63 μm , 60 Å pore size). ^1H and ^{13}C NMR spectra were recorded on either a JEOL 300 MHz or Bruker WM-250 250 MHz spectrometer. MS analyses were performed at the Mass Spectrometry Facility, University of New Mexico. Fourier transform infrared (FT-IR) spectra were obtained using KBr technique. Elemental analyses were performed at the microanalytical laboratory, Institute of Organoelement Compounds, Russian Academy of Sciences.

General procedure for 2-amino-4-(alkyl or aryl or heteroaryl)-6-(alkyl or aryl or heteroarylsulfanyl)-3,5-pyridinedicarbonitriles (A) and 2-amino-4-(aryl or heteroaryl)-6-(aryl or heteroarylsulfanyl)-1,4-dihydro-3,5-pyridinedicarbonitriles (G).

To a solution of a selected aldehyde (1.5 mmol) and malononitrile (3.1 mmol) in 5 mL of anhydrous ethanol was added Et_3N or DABCO (0.1 mmol) dropwise at room temperature. The resulting mixture was heated to 50 °C and a desired thiol (1.6 mmol) was added. The reaction mixture was refluxed for 2.5-3 hours and then allowed to cool to room temperature. The formed precipitate was isolated by filtration and the filtrate was concentrated under reduced pressure. To the dark residue was added methanol (2 mL), which resulted in the crystallization of additional 5-10% of the product. The solids were combined and recrystallized from acetonitrile to yield a corresponding pure pyridine **A** or 1,4-dihydropyridine **G**.

2-Amino-4-methyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₁). White solid, yield 80 mg (20%); mp 225-226 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 2.46 (s, 3H), 7.47 (m, 3H), 7.50 (bs, 2H), 7.57 (m, 2H); IR (KBr) 3416, 3324, 3224, 3080, 2216, 1642, 1564, 1548, 1472, 1440, 1420, 1272, 804, 750, 716, 542 cm⁻¹. Anal. Calcd for C₁₄H₁₀N₄S (266.328): C, 63.13; H, 3.79; N, 21.04; S, 12.04. Found: C, 63.00; H, 3.86; N, 20.96; S 11.98.

2-Amino-4-(3-pyridinyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₂). Light-yellow solid, yield 198 mg (40%); mp 305-306 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 7.51 (m, 3H), 7.60 (m, 2H), 7.62 (dd, *J* = 4.88 Hz, *J* = 7.93 Hz, 1H), 7.80 (bs, 2H), 8.03 (dd, *J* = 1.53 Hz, *J* = 7.93 Hz, 1H), 8.76 (dd, *J* = 1.53 Hz, *J* = 4.88 Hz, 1H), 8.77 (dd, *J* = 1.83 Hz, *J* = 4.78 Hz, 1H); IR (KBr) 3376, 3248, 3152, 2218, 2212, 1708, 1656, 1646, 1582, 1550, 1520, 1420, 1268, 1072, 1054, 1028, 810, 756, 728 cm⁻¹. Anal. Calcd for C₁₈H₁₁N₅S (329.387): C, 65.63; H, 3.37; N, 21.27; S, 9.73. Found: C, 65.80; H, 3.35; N, 21.20; S 9.62.

2-Amino-4-(4-nitrophenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₃). Yellow solid, yield 179 mg (32%); mp 286-287 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 7.47 (m, 3H), 7.57 (m, 2H), 7.76 (bs, 2H), 7.83 (d, *J* = 8.85 Hz, 2H), 8.37 (d, *J* = 8.85 Hz, 2H); IR (KBr) 3422, 3328, 3226, 3086, 2214, 2210, 1634, 1602, 1549, 1532, 1514, 1460, 1420, 1348, 1348, 1318, 1262, 1238, 1178, 1109, 1024, 1000, 898, 868, 850, 802, 798, 758, 710, 553 cm⁻¹. Anal. Calcd for C₁₉H₁₁N₅O₂S (373.398): C, 61.11; H, 2.98; N, 18.76; S, 8.59. Found: C, 60.88; H, 2.73; N, 18.95; S, 8.67.

2-Amino-4-phenyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₄). White solid, yield 175 mg (35%); mp 215-216 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 7.51 (m, 3H), 7.58 (m, 7H), 7.80 (bs, 2H); IR (KBr) 3360, 3058, 2212, 2208, 1620, 1544, 1516, 1460, 1264, 760, 746, 704, 688 cm⁻¹. Anal. Calcd for C₁₉H₁₂N₄S (328.399): C, 69.49; H, 3.69; N, 17.06; S: 9.76. Found: C, 69.38; H 3.61; N, 16.92; S, 9.90.

2-Amino-4-(4-hydroxyphenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₅). White solid, 217 mg yield (42%); mp 314 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 6.93 (d, *J* = 8.54 Hz, 2H), 7.39 (d, *J* = 8.54 Hz, 2H), 7.50 (m, 3H), 7.60 (m, 2H), 7.69 (bs, 2H), 10.04 (bs, 1H); IR (KBr) 3648, 3496, 3367, 3236, 2222, 2216, 1631, 1609, 1590, 1552, 1512, 1472, 1430, 1354, 1328, 1266, 1213, 1171, 1109, 1012, 846, 782, 758, 672, 570, 506 cm⁻¹. Anal. Calcd for C₁₉H₁₂N₄OS (344.399): C, 66.26; H, 3.52; N, 16.27; S, 9.31. Found: C, 66.09; H, 3.61; N, 16.22; S, 9.39.

2-Amino-4-[4-(diethylamino)phenyl]-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₆). Yellow solid, yield 270 mg (45%); mp 220-221 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 1.15 (t, *J* = 7.02 Hz, 6H), 3.42 (dd, *J* = 7.02 Hz, 4H), 6.79 (d, *J* = 8.85 Hz, 2H), 7.39 (d, *J* = 8.84 Hz, 2H), 7.44 (bs, 2H), 7.50 (m, 3H), 7.60 (m, 2H); IR (KBr) 3446, 3358, 3000, 2208, 1658, 1606, 1574, 1512, 1416, 1356, 1274, 1200, 1154, 1078, 1020, 806, 776, 752, 708, 696 cm⁻¹. Anal. Calcd for C₂₃H₂₁N₅S (399.522): C, 69.14; H, 5.31; N, 17.53; S: 8.02. Found: C, 69.05; H, 5.38; N 17.66; S, 7.93.

2-Amino-4-(3,4-dimethoxyphenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile

(**A₇**). White solid, yield 268 mg (46%); mp 263-264 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 3.81 (s, 3H), 3.85 (s, 3H), 7.11 (dd, *J* = 1.52 Hz, *J* = 8.24 Hz, 1H), 7.14 (d, *J* = 8.24 Hz, 1H), 7.19 (d, *J* = 1.52 Hz, 1H), 7.50-7.60 (m, 5H), 7.60 (bs, 2H); IR (KBr) 3420, 3332, 3226, 3008, 2972, 2936, 2836, 2216, 1684, 1652, 1648, 1640, 1600, 1548, 1528, 1520, 1510, 1462, 1450, 1424, 1334, 1308, 1260, 1230, 1144, 1024, 758, 708, 692, 586 cm⁻¹. Anal. Calcd for C₂₁H₁₆N₄O₂S (388.453): C, 64.93; H, 4.16; N, 14.43; S, 8.25. Found: C, 64.71; H, 3.99; N, 14.59; S, 8.38.

2-Amino-6-(phenylsulfanyl)-4-(3,4,5-trimethoxyphenyl)-3,5-pyridinedicarbonitrile

(**A₈**). White solid, yield 270 mg (43%); mp 238-239 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 3.78 (s, 3H), 3.83 (s, 6H), 6.92 (s, 2H), 7.50 (m, 3H), 7.60 (m, 2H), 7.65 (bs, 2H); IR (KBr) 3420, 3328, 3224, 2963, 2212, 1635, 1628, 1589, 1548, 1500, 1467, 1414, 1338, 1258, 1129, 990, 846, 779, 750, 710 cm⁻¹. Anal. Calcd for C₂₂H₁₈N₄O₂S (418.480): C, 63.14; H, 4.34; N, 13.39; S, 7.66. Found: C, 63.31; H, 4.35; N, 13.43; S, 7.52.

4-[2-amino-3,5-dicyano-6-(phenylsulfanyl)-4-pyridinyl]-benzenecarboxylic acid (A₉**).**

Light-yellow solid, 156 mg (28%); mp 340 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 7.50 (m,

3H), 7.60 (m, 2H), 7.68 (d, $J = 8.54$ Hz, 2H), 7.80 (bs, 2H), 8.12 (d, $J = 8.54$ Hz, 2H), 13.00 (bs, 1H); IR (KBr) 3448, 3316, 3224, 2212, 1738, 1720, 1640, 1554, 1528, 1504, 1408, 1260, 1206, 1178, 1030, 780, 760, 712, 656 cm^{-1} . Anal. Calcd for $\text{C}_{20}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$ (372.410): C, 64.50; H, 3.25; N, 15.05; S, 8.61. Found: C, 64.61; H, 3.33; N, 14.97; S, 8.59.

2-Amino-6-(phenylsulfanyl)-4-(3-thienyl)-3,5-pyridinedicarbonitrile (A₁₀). White solid, yield 241 mg (48%); mp 235-236 °C (CH_3CN); ^1H NMR ($\text{DMSO}-d_6$) δ 7.39 (dd, $J = 1.22$ Hz, $J = 4.89$ Hz, 1H), 7.50 (m, 3H), 7.60 (m, 2H), 7.65 (bs, 2H), 7.77 (dd, $J = 1.22$ Hz, $J = 3.05$ Hz, 1H), 8.04 (dd, $J = 1.22$ Hz, $J = 3.05$ Hz, 1H); IR (KBr) 3472, 3352, 3216, 2216, 1624, 1550, 1512, 1476, 1440, 1366, 1306, 1262, 1024, 830, 790, 772, 756, 708, 692 cm^{-1} . Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{N}_4\text{S}_2$ (334.427): C, 61.05; H, 3.02; N, 16.76; S, 19.17. Found: C, 60.90; H, 2.98; N, 16.83; S, 19.31.

2-Amino-4-[2-(1,3-benzodioxol-5-yl)-1-methylethyl]-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (A₁₁). White solid, yield 180 mg (29%); mp 203-204 °C (CH_3CN); ^1H NMR ($\text{DMSO}-d_6$) δ 1.42 (d, $J = 7.02$ Hz, 3H), 3.00 (dd, $J = 8.24$ Hz, $J = 14.34$ Hz, 1H), 3.13 (dd, $J = 8.24$ Hz, $J = 14.34$ Hz, 1H), 3.43 (dd, $J = 7.02$ Hz, $J = 8.24$ Hz, 1H), 5.94 (d, 1H), 5.96 (d, 1H), 6.56 (dd, $J = 1.53$ Hz, $J = 7.94$ Hz, 1H), 6.70 (d, $J = 1.53$ Hz, 1H), 6.78 (d, $J = 7.94$ Hz, 1H), 7.50 (bs, 2H), 7.45-7.55 (m, 5H); IR (KBr) 3460, 3348, 3238, 2982, 2924, 2208, 1630, 1556, 1534, 1508, 1442, 1250, 1044, 936, 820, 762, 696, 540 cm^{-1} . Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ (414.491): C, 66.64; H, 4.39; N, 13.52; S, 7.73. Found: C, 66.51; H, 4.34; N, 13.61; S, 7.88.

2-Amino-4-(4-chlorophenyl)-6-[(2-hydroxyethyl)sulfanyl]-3,5-pyridinedicarbonitrile (A₁₂). White solid, yield 105 mg (21%); mp 165-166 °C(CH₃CN); ¹H NMR (DMSO-*d*₆) δ 3.34 (t, *J* = 5.94 Hz, 2H), 3.66 (dt, *J* = 5.50 Hz, *J* = 5.95 Hz, 2H), 4.95 (t, *J* = 5.50 Hz, 1H), 7.56 (d, *J* = 8.80 Hz, 2H), 7.64 (d, *J* = 8.80 Hz, 2H), 7.98 (bs, 2H); IR (KBr) 3477, 3338, 3228, 2928, 2214, 2210, 1635, 1595, 1570, 1544, 1490, 1428, 1318, 1264, 1160, 1090, 1018, 839, 809, 781 cm⁻¹. Anal. Calcd for C₁₅H₁₁N₄OSCl (330.800): C, 54.46; H, 3.36; N, 16.94; S, 9.69. Found: C, 54.57; H, 3.29; N, 16.81; S, 9.53.

2-Amino-4-(4-chlorophenyl)-6-(cyclohexylsulfanyl)-3,5-pyridinedicarbonitrile (A₁₃). Light-yellow solid, yield 172 mg (31%); mp 230-231 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 1.40-1.60 (m, 6H), 1.70 (m, 2H), 2.00 (m, 2H), 3.98 (m, 1H), 7.55 (d, *J* = 8.54 Hz, 2H), 7.63 (d, *J* = 8.54 Hz, 2H), 7.90 (bs, 2H); IR (KBr) 3496, 3392, 3090, 2928, 2872, 2852, 2216, 1988, 1652, 1604, 1572, 1544, 1532, 1528, 1494, 1448, 1436, 1424, 1416, 1316, 1258, 1092, 998, 890, 834, 804, 780, 672 cm⁻¹. Anal. Calcd for C₁₉H₁₇N₄SCl (368.892): C, 61.86; H, 4.65; N, 15.19; S, 8.69. Found: C, 61.69; H, 4.72; N, 15.27; S, 8.78.

2-Amino-4-(4-chlorophenyl)-6-(mesitylsulfanyl)-3,5-pyridinedicarbonitrile (A₁₄). White solid, yield 286 mg (47%); mp 288-289 °C(CH₃CN); ¹H NMR (DMSO-*d*₆) δ 2.30

(s, 3H), 2.34 (s, 6H), 7.07 (s, 2H), 7.50 (bs, 2H), 7.60 (d, $J = 8.54$ Hz, 2H), 7.64 (d, $J = 8.54$ Hz, 2H); IR (KBr) 3484, 3396, 3344, 3212, 2968, 2216, 2212, 1652, 1624, 1546, 1528, 1492, 1450, 1390, 1262, 1092, 1016, 858, 802, 780, 674, 516 cm^{-1} . Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_4\text{SCl}$ (404.925): C, 65.25; H, 4.24; N, 13.84; S: 7.92. Found: C, 65.42; H, 4.23; N, 13.97; S, 7.84.

2-Amino-6-(benzylsulfanyl)-4-(4-fluorophenyl)-3,5-pyridinedicarbonitrile (A₁₅). Light-yellow solid, yield 200 mg (37%); mp 197-198 °C (CH_3CN); ^1H NMR ($\text{DMSO}-d_6$) δ 4.52 (s, 2H), 7.29 (m, 3H), 7.38 (dd, $J = 8.85$ Hz, 2H), 7.50 (dd, $J = 1.53$ Hz, $J = 8.24$ Hz, 2H), 7.58 (dd, $J = 5.49$ Hz, $J = 8.85$ Hz, 2H), 8.00 (bs, 2H); IR (KBr) 3444, 3340, 3212, 2212, 1624, 1606, 1546, 1520, 1510, 1460, 1262, 1236, 1166, 1028, 848, 824, 780, 696, 672, 560, 524 cm^{-1} . Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{FN}_4\text{S}$ (360.409): C, 66.65; H, 3.64; N, 15.55; S: 8.90. Found: C, 66.46; H, 3.70; N, 15.67; S, 8.84.

2-Amino-6-(benzylsulfanyl)-4-(2,5-dimethoxyphenyl)-3,5-pyridinedicarbonitrile (A₁₆). Light-yellow solid, yield 266 mg (44%); mp 214-215 °C (CH_3CN); ^1H NMR ($\text{DMSO}-d_6$) δ 3.73 (t, 6H), 4.51 (s, 2H), 6.92 (d, $J = 2.74$ Hz, 1H), 7.07 (dd, $J = 2.74$ Hz, $J = 8.85$ Hz, 1H), 7.13 (d, $J = 8.85$ Hz, 1H), 7.32 (m, 3H), 7.51 (dd, $J = 1.53$ Hz, $J = 7.94$ Hz, 2H), 7.93 (bs, 2H); IR (KBr) 3416, 3328, 3224, 3004, 2936, 2832, 2224, 2216, 1652, 1632, 1540, 1520, 1516, 1504, 1470, 1430, 1398, 1324, 1298, 1260, 1228, 1188, 1122, 1038, 844, 820, 736, 692, 564 cm^{-1} . Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ (402.480): C, 65.65; H, 4.52; N, 13.92; S, 7.97. Found: C, 65.52; H, 4.58; N, 13.99; S, 7.85.

2-Amino-6-[(2-furylmethyl)sulfanyl]-4-[4-(methylsulfanyl)phenyl]-3,5-pyridinedicarbonitrile (A₁₇). Yellow solid, yield 244 mg (43%); mp 182-183 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 2.55 (s, 3H), 4.60 (s, 2H), 6.40 (dd, *J* = 1.83 Hz, *J* = 3.35 Hz, 1H), 6.52 (d, *J* = 3.35 Hz, 1H), 7.41 (d, *J* = 8.55 Hz, 2H), 7.48 (d, *J* = 8.55 Hz, 2H), 7.58 (d, *J* = 1.83 Hz, 1H), 8.00 (bs, 2H); IR (KBr) 3460, 3338, 3228, 2920, 2204, 1624, 1584, 1552, 1528, 1404, 1264, 1080, 988, 800, 728, 524 cm⁻¹. Anal. Calcd for C₁₉H₁₄N₄OS₂ (378.481): C, 60.29; H, 3.74; N, 14.81; S, 16.94. Found: C, 60.05; H, 3.71; N, 14.90; S, 16.79.

2-Amino-4-(2,6-dichlorophenyl)-6-(phenylsulfanyl)-1,4-dihydro-3,5-pyridinedicarbonitrile (G₁₈). Light-yellow solid, yield 540 mg (90%); mp 317-318 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 5.63 (s, 1H), 5.85 (bs, 2H), 7.37 (q, *J* = 6.72 Hz, *J* = 7.02 Hz, 1H), 7.49 (d, *J* = 8.50 Hz, 2H), 7.50-7.60 (m, 5H), 9.07 (bs, 1H); IR (KBr) 3476, 3356, 3084, 2986, 2208, 2196, 2172, 1700, 1652, 1586, 1568, 1528, 1512, 1492, 1440, 1396, 1258, 788, 740, 686, 630, 548 cm⁻¹. Anal. Calcd for C₁₉H₁₂N₄SCl₂ (399.305): C, 57.15; H, 3.04; N, 14.04; S, 8.03. Found: C, 57.02; H, 3.10; N, 14.17; S, 7.86.

2-Amino-4-(2,6-dichlorophenyl)-6-(mesitylsulfanyl)-1,4-dihydro-3,5-pyridinedicarbonitrile (G₁₉). Light-yellow solid, yield 636 mg (96%); mp 325 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 2.30 (s, 3H), 2.43 (s, 6H), 5.51 (s, 1H), 6.10 (bs, 2H), 7.10 (s, 2H), 7.36 (q, *J* = 8.24 Hz, 1H), 7.51 (d, *J* = 8.24 Hz, 2H), 7.64 (bs, 1H); IR (KBr) 3328, 3248, 3216,

3078, 2976, 2926, 2196, 2184, 1684, 1658, 1648, 1584, 1560, 1492, 1472, 1468, 1432, 1392, 1296, 1250, 1192, 1148, 1088, 1036, 876, 850, 820, 784, 740, 728, 672, 630, 556 cm^{-1} . Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{SCl}_2$ (441.386): C, 59.86; H, 4.12; N, 12.70; S, 7.26. Found: C, 59.71; H, 4.17; N, 12.82; S, 7.39.

2-Amino-4-(2,6-dichlorophenyl)-6-[(2-furylmethyl)sulfanyl]-1,4-dihydro-3,5-pyridinedicarbonitrile (G_{20}). Yellow solid, yield 466 mg (77%); mp 260-261 $^{\circ}\text{C}$ (CH_3CN); ^1H NMR ($\text{DMSO}-d_6$) δ 4.32 (s, 2H), 5.45 (s, 1H), 5.90 (bs, 2H), 6.36 (dd, $J = 1.83$ Hz, $J = 3.36$ Hz, 1H), 6.43 (d, $J = 3.36$ Hz, 1H), 7.35 (q, $J = 8.54$ Hz, 1H), 7.48 (d, $J = 8.54$ Hz, 2H), 7.63 (d, $J = 1.83$ Hz, 1H), 9.26 (bs, 1H); IR (KBr) 3452, 3360, 3188, 3084, 2980, 2884, 2200, 2180, 1656, 1646, 1612, 1576, 1556, 1500, 1456, 1436, 1424, 1256, 1244, 1212, 1152, 1014, 936, 816, 794, 776, 748, 694, 646, 596, 540 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_4\text{OSCl}_2$ (403.294): C, 53.60; H, 3.01; N, 13.90; S, 7.95. Found: C, 53.82; H, 2.94; N, 13.81; S, 7.84.

2-Amino-4-(2-chloro-6-fluorophenyl)-6-(phenylsulfanyl)-1,4-dihydro-3,5-pyridine-dicarbonitrile (G_{21}). White solid, yield 356 mg (62%); mp 300-301 $^{\circ}\text{C}$ (CH_3CN); ^1H NMR ($\text{DMSO}-d_6$) δ 5.23 (d, $J = 1.80$ Hz, 1H), 5.87 (bs, 2H), 7.26 (dt, $J = 2.14$ Hz, $J = 7.93$ Hz, $J = 10.07$ Hz, 1H), 7.35-7.47 (m, 7H), 9.12 (bs, 1H); IR (KBr) 3452, 3412, 3356, 3108, 3084, 2248, 2208, 2196, 2168, 1684, 1656, 1648, 1616, 1602, 1584, 1574, 1516, 1492, 1452, 1440, 1244, 896, 780, 744, 700, 552 cm^{-1} . Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{N}_4\text{FSCl}$ (382.850): C, 59.60; H, 3.17; N, 14.64; S, 8.37. Found: C, 59.77; H, 3.18; N, 14.53; S, 8.49.

2-Amino-4-(2-chloro-6-fluorophenyl)-6-(mesitylsulfanyl)-1,4-dihydro-3,5-pyridine-dicarbonitrile (G₂₂). Light-yellow solid, yield 535 mg (84%); mp 293-294 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 2.28 (d, 3H), 2.41 (d, 6H), 5.12 (d, *J* = 1.83 Hz, 1H), 6.09 (bs, 2H), 7.08 (s, 2H), 7.25 (dt, *J* = 2.13 Hz, *J* = 7.93 Hz, *J* = 10.09 Hz, 1H), 7.35-7.40 (m, *J* = 7.94 Hz, 2H), 7.76 (bs, 1H); IR (KBr) 3332, 3216, 2972, 2920, 2192, 1658, 1646, 1602, 1572, 1540, 1484, 1452, 1392, 1298, 1240, 1040, 896, 850, 784, 554 cm⁻¹. Anal. Calcd for C₂₂H₁₈N₄FSCl (424.931): C, 62.18; H, 4.28; N, 13.19; S, 7.54. Found: C, 62.09; H, 4.36; N, 13.31; S, 7.47.

2-Amino-4-[6-chloro-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-3-yl]-6-(phenylsulfanyl)-1,4-dihydro-3,5-pyridine-dicarbonitrile (G₂₃). Light-yellow solid, yield 659 mg (86%); mp 308-309 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 3.83 (s, 3H), 5.50 (s, 1H), 6.10 (bs, 2H), 7.05 (d, *J* = 8.85 Hz, 2H), 7.43-7.47 (m, 7H), 7.61 (d, *J* = 8.85 Hz), 7.74 (d, *J* = 9.36 Hz, 1H), 9.40 (bs, 1H); IR (KBr) 3384, 3212, 2924, 2856, 2200, 2188, 1684, 1656, 1646, 1628, 1616, 1492, 1386, 1340, 1254, 1176, 1024, 836, 804, 750, 524 cm⁻¹. Anal. Calcd for C₂₇H₁₉N₆OSCl (511.01): C, 63.46; H, 3.76; N, 16.45; S, 6.27. Found: C, 63.63; H, 3.69; N, 16.34; S, 6.18.

2-Amino-4-(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)-6-(phenylsulfanyl)-1,4-dihydro-3,5-pyridine-dicarbonitrile (G₂₄). Yellow solid, yield 398 mg (68%); mp 280-281 °C (CH₃CN); ¹H NMR (DMSO-*d*₆) δ 2.20 (s, 3H), 5.10 (s, 1H), 5.94 (bs, 2H), 7.24 (d, *J* = 4.58, 1H), 7.41-7.46 (m, 6H), 9.25 (bs, 1H); IR (KBr) 3376, 3292, 3190, 3100, 2940,

2196, 2180, 1658, 1646, 1596, 1572, 1540, 1520, 1496, 1456, 1442, 1404, 1360, 1314, 1268, 1188, 902, 880, 832, 790, 776, 730, 716, 704, 678, 660, 582, 560 cm^{-1} . Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_6\text{S}_2$ (390.495): C, 58.44; H, 3.62; N, 21.53; S, 16.42. Found: C, 58.21; H, 3.55; N, 21.39; S, 16.56.

(E+Z)-3-Amino-2-benzyl-3-(phenylsulfanyl)acrylonitrile (J₄**)**. After pyridine **A₄** was removed by filtration the filtrate was concentrated under reduced pressure. The brown residue was dissolved in chloroform (20 mL), presorbed on silica gel, and enamionitrile **J₄** was isolated by column chromatography (16% - 40% EtOAc/hexane) as inseparable *E,Z*-isomeric mixture. Colorless liquid, yield 125 mg (34%); R_f 0.3 (25% EtOAc/hexane); ^1H NMR (CDCl_3) δ 7.52 - 7.26 (m, 20H), 4.46 (bs, 2H), 4.20 (bs, 2H), 3.65 (s, 2H), 3.52 (s, 2H); ^{13}C NMR (CDCl_3) δ 154.8, 152.5, 139.2, 137.4, 134.6, 134.0, 130.0, 129.8, 129.6, 129.2, 129.0, 128.7, 128.3, 128.0, 127.1, 126.7, 121.5, 120.0, 81.7, 79.0, 35.02, 34.8; HRMS m/z (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ 267.0956, found 267.0921.

Ref 2a:

Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R.M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. J. *Med. Chem.* **1988**, *31*, 2235–2246.

Ref 18:

Duncia, J. V.; Santella III, J. B.; Higley, C. A.; Pitts, W. J.; Wityak, J.; Fietze, W. E.; Rankin, F. W.; Sun, J.-H. Earl, R. A.; Tabaka, C.; Teleha, C. A.; Blom, K. F.; Favata, M. F.; Manos, E. J.; Daulerio, A. J.; Stradley, D. A.; Horiuchi, K.; Copeland, R. A.; Scherle, P. A.; Trzaskos, J. M.; Magolda, R. L.; Trainor, G. L.; Wexler, R. R.; Hobbs, F. W.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2839–2844.