Supporting Information

Efficient Synthesis of Polyfunctionalized Pyrimidine Derivatives

Synthesis of $N$-(substituted-carbamothioyl)benzimidamides 3; General Procedure A mixture of benzimidamide hydrochloride 1 (2 mmol), isothiocyanate derivative 2 (2 mmol), and NEt$_3$ (4 mmol) in CH$_3$CN (2 mL) was stirred at room temperature for 3 h. After completion of reaction (checked by TLC), the solvent was evaporated under vacuum and the residue was extracted using ethyl acetate. The organic phase was dried over Na$_2$SO$_4$, the solvent was removed under reduced pressure, and the resulting residue was recrystallized from ethyl acetate and petroleum ether.

Synthesis of pyrimidine derivatives 5; General Procedure A mixture of $N$-(substituted-carbamothioyl)benzimidamides 3 (2 mmol), malononitrile 4 (2 mmol), CuBr (2 mmol), and NEt$_3$ (8 mmol) in DMF (2 mL) was stirred at 80 °C for 2 h. After completion of reaction (checked by TLC), the reaction mixture was filtered through a bed of celite and washed with 30 mL ethyl acetate. Then, water (30 mL) was added to the filtrate, they organic layer was extracted, dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/petroleum ether = 1/4 as eluent and silica gel as stationary phase. Then, it was recrystallized from ethyl acetate and petroleum ether to give pure product 5.

4-Amino-2-phenyl-6-(phenylamino)pyrimidine-5-carbonitrile (5a)

Yield: 0.24 g (85%); white solid; mp 218-220 °C. IR (KBr): 3451, 3371, 3251, 2204, 1645, 1605 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 7.12 (t, $J$ = 8.0 Hz, 1H, Ph), 7.38 (t, $J$ = 8.0 Hz, 2H, Ph), 7.45-7.51 (m, 5H, NH$_2$, Ph), 7.65 (d, $J$ = 8.0 Hz, 2H, Ph), 8.21 (dd, $J$ = 7.0, 1.5 Hz, 2H, Ph), 9.29 (s, 1H, NH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 68.0, 115.7, 122.6, 123.6, 128.2, 128.3, 128.4, 131.2, 137.0, 138.9, 161.4, 163.8, 165.2. MS (m/z) (%) = 287 (M$^+$, 90), 279 (10), 184 (87), 167 (34), 149 (95), 119 (17), 104 (52), 93 (26), 77 (50), 57 (100). Anal. Calcd for C$_{17}$H$_{13}$N$_5$: C, 71.06; H, 4.56; N, 24.37. Found: C, 71.24; H, 4.38; N, 24.51.

4-Amino-2-phenyl-6-(o-tolylamino)pyrimidine-5-carbonitrile (5b)

Yield: 0.21 g (72%); white solid; mp 216-217°C. IR (KBr): 3505, 3401, 3318, 2198, 1598, 1550 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.20 (s, 3H, Me), 7.12-7.45 (m, 9H, NH$_2$, Ph, H$_3$, H$_4$, H$_5$, H$_6$), 8.07 (d, $J$ = 7.0 Hz, 2H, Ph), 8.92 (s, 1H, NH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 18.0, 68.2, 115.7, 122.6, 123.6, 128.2, 128.3, 128.4, 131.2, 137.0, 162.2, 163.7, 165.1. Anal. Calcd for C$_{18}$H$_{15}$N$_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.79; H, 5.19; N, 23.31.

4-Amino-2-phenyl-6-(p-tolylamino)pyrimidine-5-carbonitrile (5c)

Yield: 0.22 g (74%); white solid; mp 223-235°C. IR (KBr): 3477, 3309, 3126, 2203, 1645, 1612 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.31 (s, 3H, OMe), 7.17 (d, $J$ = 8.0 Hz, 2H, H$_3$, H$_5$), 7.45-7.53 (m, 7H, NH$_2$, Ph, H$_2$, H$_6$), 8.21 (d, $J$ = 7.0 Hz, 2H, Ph), 9.19 (s, 1H, NH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 20.5, 67.7, 115.7, 122.7, 128.2, 128.3, 128.7, 131.1, 132.6, 136.3, 137.1, 161.4, 163.8, 165.2. Anal. Calcd for C$_{18}$H$_{15}$N$_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.62; H, 4.91; N, 23.12.

4-Amino-6-((4-methoxyphenyl)amino)-2-phenylpyrimidine-5-carbonitrile (5d)

Yield: 0.24 g (76%); yellow solid; mp 227-228°C. IR (KBr): 3477, 3309, 3126, 2203, 1648, 1612 cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.77 (s, 3H, OMe), 6.95 (d, $J$ = 9.0 Hz, 2H, H$_3$, H$_5$), 7.40 (bs, 2H, NH$_2$), 7.44-7.53 (m, 5H, Ph, H$_2$, H$_6$), 8.21 (dd, $J$ = 7.5, 1.0 Hz, 2H, Ph), 9.15 (s, 1H, NH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 53.7, 67.7, 115.7, 122.7, 128.2, 128.3, 131.1, 132.6, 136.3, 137.1, 161.4, 163.8, 165.2. MS (m/z) (%) = 305 (M$^+$, 90), 297 (10), 184 (87), 167 (34), 149 (95), 119 (17), 104 (52), 93 (26), 77 (50), 57 (100). Anal. Calcd for C$_{19}$H$_{15}$N$_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.62; H, 4.91; N, 23.12.
MHz, DMSO-d$_6$): δ = 55.2, 67.3, 113.4, 115.8, 124.6, 128.1, 128.2, 131.0, 131.7, 137.1, 155.8, 161.5, 163.8, 165.2. Anal. Caled for C$_{18}$H$_{15}$N$_5$O: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.24; H, 4.62; N, 22.18.

4-Amino-6-((2-fluorophenyl)amino)-2-phenylpyrimidine-5-carbonitrile (5e)

Yield: 0.19 g (63%); white solid; mp 235-236°C. IR (KBr): 3466, 3293, 3159, 2215, 1650, 1614 cm$^{-1}$. 1H NMR (500 MHz, DMSO-d$_6$): δ = 7.24-7.32 (m, 2H, H$_3$, H$_4$), 7.40-7.54 (m, 7H, NH$_2$, Ph, H$_5$, H$_6$), 8.08 (d, $J = 7.5$ Hz, 2H, Ph), 9.24 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 67.7, 115.6, 115.7, 124.2, 126.2 (d, $J_{C,F} = 12.5$ Hz), 127.1 (d, $J_{C,F} = 7.0$ Hz), 127.9, 128.1, 128.3, 131.2, 136.9, 156.7 (d, $J_{C,F} = 245.0$ Hz), 162.1, 163.8, 165.0. Anal. Caled for C$_{17}$H$_{12}$FN$_5$: C, 66.88; H, 3.96; N, 22.94. Found: C, 66.93; H, 4.15; N, 23.11.

4-Amino-6-((4-fluorophenyl)amino)-2-phenylpyrimidine-5-carbonitrile (5f)

Yield: 0.20 g (64%); white solid; mp > 250°C. IR (KBr): 3476, 3426, 3327, 3041, 2204, 1650, 1619, 1556 cm$^{-1}$. 1H NMR (500 MHz, DMSO-d$_6$): δ = 7.21 (t, $J = 9.0$ Hz, 2H, H$_3$, H$_5$), 7.45-7.52 (m, 5H, Ph, NH$_2$), 7.65 (dd, $J = 9.0$, 5.0 Hz, 2H, H$_2$, H$_6$), 8.20 (dd, $J = 7.2$, 1.5 Hz, 2H, Ph), 9.34 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 69.9, 114.9 (d, $J_{C,F} = 22.5$ Hz), 115.7, 124.8 (d, $J_{C,F} = 7.5$ Hz), 128.2 (d, $J_{C,F} = 15.0$ Hz), 131.2, 135.2, 137.0, 158.5 (d, $J_{C,F} = 238.7$ Hz), 161.5, 163.8, 165.2. Anal. Caled for C$_{17}$H$_{12}$FN$_5$: C, 66.88; H, 3.96; N, 22.94. Found: C, 66.96; H, 3.84; N, 23.11.

4-Amino-6-((2-chlorophenyl)amino)-2-phenylpyrimidine-5-carbonitrile (5g)

Yield: 0.21 g (67%); white solid; mp 203-204°C. IR (KBr): 3473, 3349, 3217, 3043, 2207, 1634, 1570 cm$^{-1}$. 1H NMR (500 MHz, DMSO-d$_6$): δ = 7.30 (t, $J = 8.0$ Hz, 1H, H$_4$), 7.39-7.48 (m, 4H, Ph, H$_5$), 7.51 (bs, 2H, NH$_2$), 7.57 (d, $J = 8.0$ Hz, 1H, H$_6$), 7.67 (d, $J = 8.0$ Hz, 1H, H$_3$), 8.08 (d, $J = 7.5$ Hz, 2H, Ph), 9.13 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 67.4, 115.5, 127.2, 127.5, 128.1, 128.3, 128.4, 129.5, 129.9, 131.2, 135.7, 137.0, 162.1, 163.8, 165.0. Anal. Caled for C$_{17}$H$_{12}$ClN$_5$: C, 63.46; H, 3.76; N, 21.77. Found: C, 63.57; H, 3.63; N, 21.63.

4-Amino-6-((3-bromophenyl)amino)-2-phenylpyrimidine-5-carbonitrile (5h)

Yield: 0.25 g (70%); white solid; mp > 250°C. IR (KBr): 3473, 3310, 3210, 3131, 2204, 1648, 1614 cm$^{-1}$. 1H NMR (500 MHz, DMSO-d$_6$): δ = 7.30 (t, $J = 8.0$ Hz, 1H, H$_4$), 7.39-7.48 (m, 4H, Ph, H$_5$), 7.51 (bs, 2H, NH$_2$), 7.57 (d, $J = 8.0$ Hz, 1H, H$_6$), 7.67 (d, $J = 8.0$ Hz, 1H, H$_3$), 8.08 (d, $J = 7.5$ Hz, 2H, Ph), 9.13 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 67.4, 115.5, 120.9, 120.9, 120.9, 120.9, 120.9, 120.9, 12.98, 12.98 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 67.5, 115.4, 115.7, 116.1, 120.9, 128.2, 128.4, 130.2, 131.3, 131.5, 131.7, 137.2, 162.5, 162.5, 166.7, 166.7. Anal. Caled for C$_{17}$H$_{12}$BrN$_5$: C, 55.75; H, 3.30; N, 19.12. Found: C, 55.90; H, 3.54; N, 19.26.

4-Amino-6-((2-chlorophenyl)amino)-2-phenylpyrimidine-5-carbonitrile (5j)

Yield: 0.21 g (67%); white solid; mp 203-204°C. IR (KBr): 3473, 3349, 3217, 3043, 2207, 1634, 1570 cm$^{-1}$. 1H NMR (500 MHz, DMSO-d$_6$): δ = 7.30 (t, $J = 8.0$ Hz, 1H, H$_4$), 7.39-7.48 (m, 4H, Ph, H$_5$), 7.51 (bs, 2H, NH$_2$), 7.57 (d, $J = 8.0$ Hz, 1H, H$_6$), 7.67 (d, $J = 8.0$ Hz, 1H, H$_3$), 8.08 (d, $J = 7.5$ Hz, 2H, Ph), 9.13 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 67.4, 115.5, 120.9, 120.9, 120.9, 120.9, 120.9, 120.9, 12.98, 12.98 (s, 1H, NH). 13C NMR (125 MHz, DMSO-d$_6$): δ = 67.5, 115.4, 115.7, 116.1, 120.9, 128.2, 128.4, 130.2, 131.3, 131.5, 131.7, 137.2, 162.5, 162.5, 166.7, 166.7. Anal. Caled for C$_{17}$H$_{12}$BrN$_5$: C, 55.75; H, 3.30; N, 19.12. Found: C, 55.90; H, 3.54; N, 19.26.

N-(Benzo[d]thiazol-2-yl)benzimidamide (11)
Yield: 0.19 g (75%); white solid; mp 189-190. IR (KBr): 3228, 3187, 3137, 3087, 1604, 1564 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 7.10 (t, J = 7.5 Hz, 1H, Ph), 7.44 (t, J = 7.5 Hz, 2H, Ph), 7.48-7.54 (m, 3H, benzo-thiazole, NH), 7.65 (d, J = 7.5 Hz, 2H, Ph), 8.18-8.20 (m, 2H, benzo-thiazole), 11.0 (s, 1H, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 117.6, 122.8, 126.8, 127.5, 128.6, 129.3, 130.0, 132.7, 139.8, 157.5, 168.5, 179.1. MS (m/z) (%) = 253 (M⁺, 100), 150 (64), 135 (88), 103 (35), 77 (48), 51 (31). Anal. Calcd for C₁₄H₁₁N₃S: C, 66.38; H, 4.38; N, 16.59. Found: C, 66.45; H, 4.21; N, 16.70.
Compound 5a
Compound 5b
Compound 5c
Compound 5d
Compound 5e
Compound 5f
Compound 5g
Compound 5h
Compound 5i
Compound 5j
Compound 11