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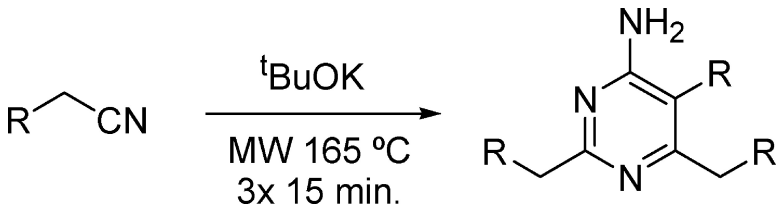

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Formation of 4-Aminopyrimidines via the Trimerization of Nitriles Using Focused Microwave Heating

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A series of substituted aliphatic nitriles have been trimerized to their corresponding pyrimidine structures under solvent-free conditions in the presence of catalytic quantities of potassium *tert*-butoxide using a focused microwave reactor. Multigram quantities of the corresponding 4-aminopyrimidines have been prepared in high yields and purity following a simple and scaleable protocol.

Introduction

The 4-aminopyrimidine structure **1** is an important chemical motif because of its close chemical association with biologically prevalent compounds, such as thiamine diphosphate (ThDP, the vitamin B_1 coenzyme) **2** and the cytosine unit in nucleic acids (Figure 1). It is also present in many natural product architectures, as exemplified by bleomycin **3** and its related complex phleomycin, which exhibit wide ranging biological cytotoxicity and have been shown to be effective chemotherapy treatments for certain types of cancers.[1] The 4-aminopyrimidine is also the key heterocyclic component in many commercial antiseptics, for example, Acsulfiso **4**, Aristoplo (Aristoplomb) **5**, Agsulfiso **6**, Sulfiona (Aristamid) **7**, Sulfisomi **8**, and Forsulfis **9** (traded under Aristamid, Belfarosan, Cibazol, Dimedon, and Domian), which not only show high activity against vulneraris *Chlamydia trachomatis*, *Actinomyces*, and *Chlostridium perfringens* but also function as dihydrofolate reductase inhibitors (Figure 1).[2]

In a recent study[3] directed toward the development of new mimics and artificial coenzymes,[4] we required access to a range of alkyl-substituted 4-aminopyrimidines **1** in multigram quantities. A search of the literature showed only a limited selection of existing protocols, all of which involved the trimerization of a nitrile component under extreme conditions of pressure and temperature.[5,6] Although alternative milder procedures involving the activation of nitriles possessing α-hydrogens by metal catalysts[7,8] showed more synthetic scope, they seemed limited for scale-up applications. We therefore thought to establish a generic method for the trimerization of nitriles under simple basic catalyzed coupling conditions.[9] We deduced from previous experience of condensation reactions carried out in our laboratories[10] that we could expedite the process through the use of flash microwave heating. This technique utilizes microwave dielectric heating to achieve rapid thermal transitions in a sample contained in a sealed reaction vessel. In such processes, it is possible to reach relatively high internal pressures (18 bar) as a result of the elevated reaction temperatures employed, which are usually significantly higher than the standard boiling point of the solvent or substrates contained within. Indeed, it was shown that the treatment of a neat sample of acetonitrile in the presence of a catalytic quantity (3 mol %) of potassium *tert*-butoxide at 140 °C for 20 min leads to the isolation of pure 2,6-dimethylpyrimidin-4-ylamine in 48% yield, requiring only filtration of the product from the reaction mixture. We therefore screened a small sample of 10 commercially available nitriles to devise an optimized set of conditions for the formation of a small collection of 4-aminopyrimidine derivatives. This process was achieved using two automated microwave synthesizers[11] in a parallel fashion to determine the most effective reaction parameters in terms of temperature, time, the effect of single or repeated heating cycles, the concentration and identity of the base used, and the result of added cosolvents. From this study, the best reaction conditions were found to involve the reaction of the neat nitrile with 5 mol % of potassium *tert*-butoxide using three heating cycles (from ambient to the reaction temperature of 165 °C) of 15 min. Using these conditions, all the reactions showed >90% conversion by LC/MS, with the majority showing the presence of no starting material and the desired product being the only material present. However, it should be noted that this procedure was only effective for liquid nitriles or those with melting points below 110 °C. Nitriles outside this range gave an incomplete reaction or failed to give any identifiable products (at present, no additional work has been conducted to extend the scope of the reaction). Under the optimized reaction conditions, both solid and liquid products were obtained, which required different workup protocols. The solid reaction mixtures could be easily purified and isolated as free-flowing solids when triturated with diethyl ether, filtered, and subjected to additional washing. The liquid products were alternatively diluted with an equal portion of diethyl ether and filtered through a short plug of neutral alumina before evaporation of the solvent. In this way, a collection of 23 different nitriles were subsequently reacted on 1-, 5-, and 20-g scales (Figure 2; n.b. for the 20-g reaction scale a three-times-25-min heating cycle was required). At all scales and for all reactions, the isolated products were obtained in high overall yield and in excellent purity, as indicated by both LC/MS and ^{1}H NMR (Figure 3).

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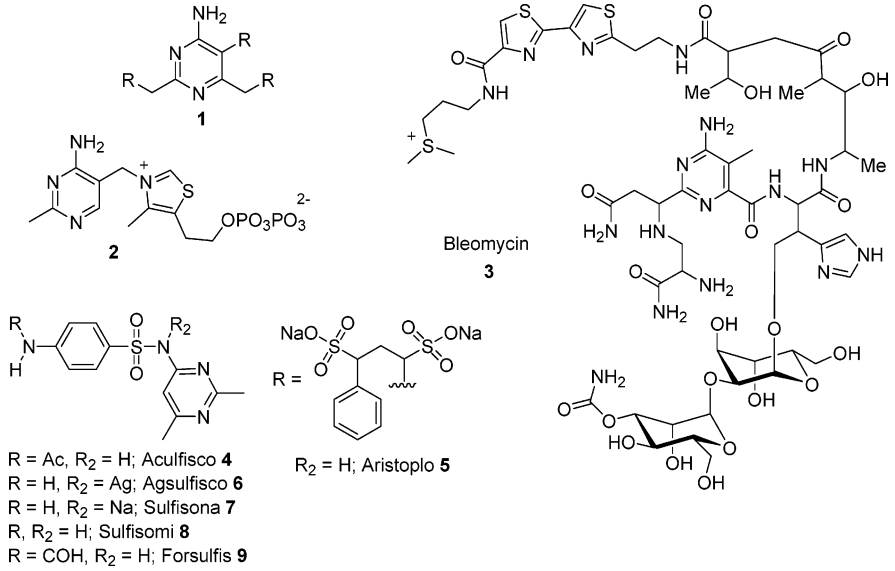

Figure 1. Generic structures of 4-aminopyrimidine **1**, thiamine diphosphate **2**, bleomycin **3**, and commercial antiseptics **4**−**9**.

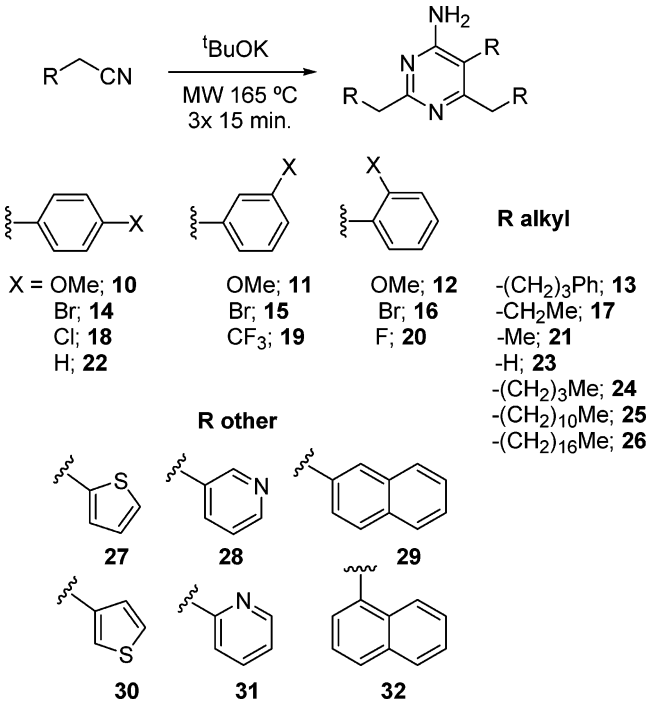

Figure 2. Compounds produced by the base-catalyzed trimerization of nitriles using flash microwave heating.

Conclusion

We have developed a simple and scaleable route for the preparation of 4-aminopyrimidines. Our current research is directed at investigating the potential for preparing products of *mixed* nitrile condensations as well as devising conditions to extend the range of nitrile components that can be coupled.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 or DPX-500 spectrometer with residual dimethyl sulfoxide as the internal reference (δ_H = 2.50 ppm). ^{13}C NMR spectra were recorded in DMSO-d_6 on the same spectrometers with the central peak of dimethyl sulfoxide as the internal reference (δ_C = 39.5 ppm). DEPT 135 was used to aid in the assignment of signal in the ^{13}C NMR spectra. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer neat. Letters in the parentheses refer to relative absorbency of the peak: w, weak, <40% of the main peak; m, medium, ~41−74% of the main peak; s, strong, >74% of the most intense peak. LC/MS analysis was performed on an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an HP LC/MSD mass spectrometer. Elution was carried out using a reversed-phase gradient of acetonitrile/water with both solvents containing 0.1% trifluoroacetic acid. The gradient run is as described in Table 1.

Table 1

t, min	acetonitrile, %	flow rate, mL/min
0.00	5	1
3.00	5	1
5.00	95	1
5.50	5	1
8.00	5	1

2,6-*Bis*-(4-methoxybenzyl)-5-(4-methoxyphenyl)pyrimidin-4-ylamine 10. Prepared from 4-methoxyphenylacetonitrile in 78%. Rt = 3.130, M + H *m*/*z* = 442.2; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.20 (2H, d, J = 5.1 Hz), 7.07 (2H, d, J = 5.1 Hz), 7.04 (2H, d, J = 5.1 Hz), 6.95 (2H, d, J = 5.1 Hz), 6.90 (2H, d, J = 5.1 Hz), 6.84 (2H, d, J = 5.1 Hz), 3.76 (2H, s, CH_2), 3.71 (3H, s, OMe), 3.64 (3H, s, OMe), 3.61 (3H, s, OMe), 3.48 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.45 (C), 163.97 (C), 162.91 (C), 159.27 (C), 158.18 (C), 157.99 (C), 131.58 (CH), 131.56 (C), 131.49 (C), 130.35 (CH), 129.98 (CH), 126.73 (C), 115.05 (CH), 114.18 (C), 114.02 (CH), 113.90 (CH), 55.55 (CH_3), 55.45 (CH_3), 55.40 (CH_3), 44.64 (CH_2), 40.23 (CH_2). IR (neat) ν 3747.8 (w), 3442.7 (w), 3294.4 (w), 3139.9 (w), 2921.0 (w), 2833.5 (w), 1633.9 (m), 1550.5 (s), 1510.3 (s), 1460.3 (m), 1427.6 (w), 1400.8 (m), 1287.8 (w), 1244.2 (s), 1179.8 (m), 1103.1 (w), 1027.1 (m), 995.7 (m), 847.4 (m), 807.4 (m), 769.4 (m), 731.6 (m), 688.7 (m) cm^{-1}. HRMS calculated for $C_{27}H_{28}N_3O_3$ 442.2131; found 442.2123.

2,6-*Bis*-(3-methoxybenyl)-5-(3-methoxyphenyl)pyrimidin-4-ylamine 11. Prepared from 3-methoxyphenylaceto-

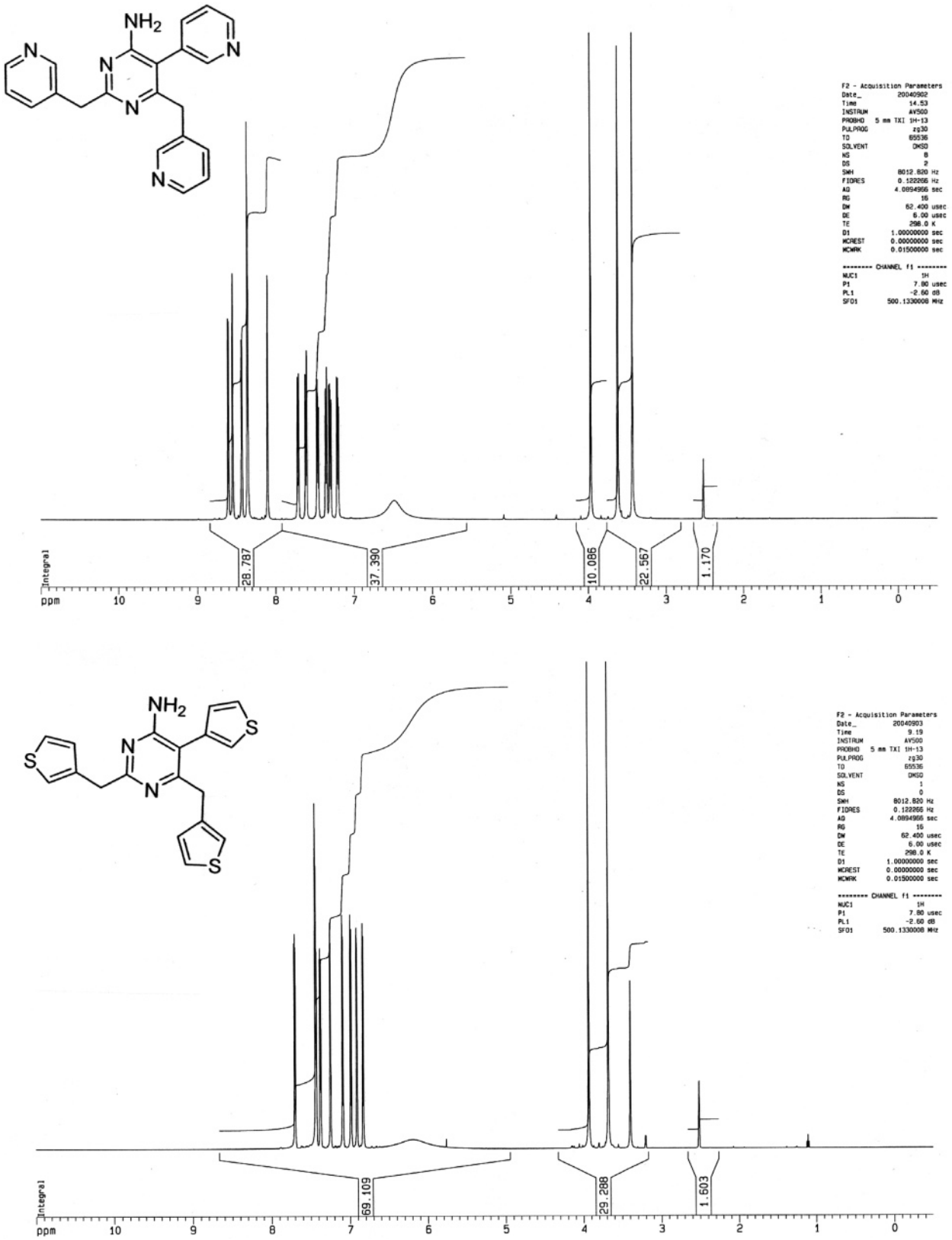

Figure 3. ^{1}H NMR spectra of isolated 4-aminopyrimidines.

nitrile in 85%. Rt = 3.013, M + H *m*/*z* = 442.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.29 (1H, dd, J = 8.1 and 7.9 Hz), 7.10 (1H, dd, J = 8.1 and 7.9 Hz), 7.01 (1H, m), 6.87 (1H, m), 6.82 (2H, m), 6.69 (1H, m), 6.63 (2H, m), 6.56 (1H, m), 6.46 (2H, m), 6.05 (2H, br s, NH_2), 3.80 (2H, s, CH_2), 3.62 (3H, s, OMe), 3.61 (3H, s, OMe), 3.55 (3H, s, OMe), 3.52 (2H, m, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.22 (C), 163.11 (C), 162.50 (C), 160.10 (C), 159.62 (C), 159.47 (C), 141.04 (C), 141.03 (C), 136.10 (C), 130.65 (CH), 129.56 (CH), 129.41 (CH), 122.39 (CH), 121.70 (CH), 121.29 (CH), 115.64 (CH), 115.64 (CH), 115.03 (CH), 114.74 (CH), 114.50 (CH), 114.31 (C), 112.03 (CH), 111.96 (CH), 55.39 (CH_3), 55.33 (CH_3), 55.20 (CH_3), 45.37 (CH_2), 40.23 (CH_2). IR (neat) ν 3429.5 (w), 3305.8

(w), 3147.0 (w), 2937.1 (w), 2832.8 (w), 2183.6 (w), 1639.0 (m), 1597.7 (m), 1555.0 (s), 1488.4 (m), 1463.3 (s), 1429.1 (m), 1401.6 (m), 1372.6 (m), 1316.3 (m), 1287.0 (m), 1256.5 (s), 1215.8 (s), 1183.7 (m), 1146.4 (m), 1080.7 (w), 1037.2 (s), 1016.9 (m), 993.9 (m), 863.3 (m), 850.9 (m), 820.4 (w), 791.5 (m), 767.4 (s), 747.2 (s), 728.4 (m), 705.3 (s), 689.0 (s) cm^{-1}. HRMS calculated for $C_{27}H_{28}N_3O_3$ 442.2131; found 442.2115.

2,6-*Bis*-(2-methoxybenzyl)-5-(2-methoxyphenyl)pyrimidin-4-ylamine 12. Prepared from 2-methoxyphenylacetonitrile in 95%. Rt = 3.317, M + H *m*/*z* = 442.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.26 (1H, m), 7.11 (1H, m), 7.08−7.00 (2H, m), 6.99 (1H, m), 6.92−6.81 (3H, m), 6.80−6.63 (4H, m), 5.78 (2H, br s, NH_2), 3.80 (2H, s, CH_2), 3.66 (3H, s, OMe), 3.62 (3H, s, OMe), 3.48 (3H, s, OMe), 3.40 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.04 (C), 163.93 (C), 162.51 (C), 157.43 (C), 157.42 (C), 157.00 (C), 131.55 (CH), 130.60 (CH), 129.98 (CH), 129.94 (CH), 127.71 (CH), 127.64 (C), 127.35 (CH), 123.19 (C), 121.13 (CH), 120.49 (CH), 120.22 (CH), 112.03 (C), 111.84 (CH), 111.19 (CH), 110.57 (CH), 55.86 (CH_3), 55.59 (CH_3), 55.50 (CH_3), 38.74 (CH_2), 34.28 (CH_2). IR (neat) ν 3479.8 (w), 3295.5 (w), 3122.0 (w), 2938.9 (w), 2836.9 (w), 1637.2 (m), 1598.6 (w), 1586.9 (w), 1555.3 (m), 1493.4 (m), 1462.7 (m), 1434.8 (w), 1411.2 (m), 1378.6 (w), 1330.8 (w), 1291.5 (w), 1240.4 (s), 1181.3 (w), 1165.7 (w), 1110.5 (m), 1049.9 (w), 1029.8 (m), 1021.4 (m), 997.1 (m), 897.7 (w), 854.3 (w), 842.0 (w), 820.1 (w), 801.9 (w), 762.3 (s), 750.6 (s), 713.5 (m), 689.1 (w) cm^{-1}. HRMS calculated for $C_{27}H_{28}N_3O_3$ 442.2131; found 442.2133.

5-Benzyl-2,6-diphenethyl-pyrimidin-4-ylamine 13. Prepared from 4-phenylbutyronitrile in 84%. Rt = 3.602, M + H *m*/*z* = 436.2; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.19−7.05 (15H, m), 6.39 (2H, br s, NH_2), 2.50 (6H, m), 2.31 (2H, dd, *J* = 7.0 and 6.9 Hz), 1.88 (2H, ap. q, *J* = 7.9 Hz), 1.75 (2H, ap. q, *J* = 7.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 166.62 (C), 165.00 (C), 162.65 (C), 142.70 (C), 142.45 (C), 141.86 (C), 128.98 (CH), 128.83 (CH), 128.80 (CH), 128.68 (CH), 128.65 (CH), 128.56 (CH), 126.26 (CH), 126.12 (CH), 126.06 (CH), 110.57 (C), 49.76 (CH_2), 37.67 (CH_2), 35.03 (CH_2), 34.84 (CH_2), 33.74 (CH_2), 32.56 (CH_2), 29.92 (CH_2), 27.09 (CH_2). IR (neat) ν 3350.2 (w), 3061.4 (w), 3025.4 (w), 2928.5 (w), 2858.9 (w), 1625.0 (m), 1563.5 (m), 1495.7 (m), 1452.6 (m), 1348.8 (w), 1128.2 (w), 1078.0 (w), 1029.0 (m), 908.1 (w), 743.5 (m), 697.7 (s) cm^{-1}. HRMS calculated for $C_{30}H_{34}N_3$ 436.2753; found 436.2742.

2,6-*Bis*-(4-bromobenzyl)-5-(4-bromophenyl)pyrimidin-4-ylamine 14. Prepared from 4-bromophenylacetonitrile in 82%. Rt = 3.367, M + H *m*/*z* = 587.9; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.64 (2H, d, *J* = 8.3 Hz), 7.46 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 7.26 (2H, d, *J* = 8.3 Hz), 7.10 (2H, d, *J* = 8.3 Hz), 6.92 (2H, d, *J* = 8.3 Hz), 6.29 (2H, br s, NH_2), 3.88 (2H, s, CH_2), 3.56 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.19 (C), 162.83 (C), 162.54 (C), 138.80 (C), 138.67 (C), 134.00 (C), 132.67 (CH), 132.60 (CH), 131.72 (CH), 131.44 (CH), 131.36 (CH), 131.29 (CH), 121.91 (C), 119.75 (C), 119.63 (C), 113.73 (C), 44.69 (CH_2), 40.00 (CH_2). IR (neat) ν 3441.3 (m), 3299.5 (w), 3139.2 (w), 1630.8 (m), 1553.3 (s), 1484.9 (s), 1454.7 (m), 1434.6 (m), 1400.6 (m), 1369.3 (m), 1180.1 (w), 1069.6 (s), 1012.5 (s), 999.6 (s), 819.5 (m), 790.4 (s), 765.3 (m), 723.4 (m) cm^{-1}. HRMS calculated for $C_{24}H_{19}Br_3N_3$ 585.9129; found 585.9119.

2,6-*Bis*-(3-bromobenzyl)-5-(3-bromophenyl)pyrimidin-4-ylamine 15. Prepared from 3-bromophenylacetonitrile in 76%. Rt = 3.311, M + H *m*/*z* = 589.8; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.60 (1H, m), 7.53 (1H, m), 7.40 (2H, m), 7.34 (2H, m), 7.26 (2H, m), 7.16 (2H, m), 7.10 (1H, m), 6.94 (1H, m), 6.35 (2H, br s, NH_2), 3.94 (2H, s, CH_2), 3.57 (2H, m, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.18 (C), 162.90 (C), 162.51 (C), 142.10 (C), 141.85 (C), 137.00 (C), 133.13 (CH), 132.11 (CH), 131.77 (CH), 131.63 (CH), 131.38 (CH), 130.80 (CH), 130.63 (CH), 129.55 (CH), 129.52 (CH), 129.43 (CH), 128.57 (CH), 128.03 (CH), 122.74 (C), 121.97 (C), 121.87 (C), 113.69 (C), 44.93 (CH_2), 40.37 (CH_2). IR (neat) ν 3463.6 (w), 3298.9 (w), 3160.0 (w), 1622.6 (m), 1592.9 (m), 1548.4 (s), 1472.2 (m), 1425.8 (m), 1406.4 (m), 1369.3 (w), 1297.6 (w), 1263.3 (w), 1089.8 (w), 1070.7 (m), 1013.8 (w), 996.2 (w), 884.1 (w), 849.9 (w), 782.2 (s), 762.7 (s), 736.2 (s), 698.6 (s), 678.0 (m) cm^{-1}. HRMS calculated for $C_{24}H_{19}N_3Br_3$ 585.9129; found 585.9131

2,6-*Bis*-(2-bromobenzyl)-5-(2-bromophenyl)pyrimidin-4-ylamine 16. Prepared from 2-bromophenylacetonitrile in 84%. Rt = 3.384, M + H *m*/*z* = 587.90; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.64 (1H, dd, *J* = 7.9 and 1.3 Hz), 7.48 (1H, dd, *J* = 7.9 and 1.3 Hz), 7.36 (1H, dd, *J* = 7.9 and 1.3 Hz), 7.29 (1H, m), 7.25−7.17 (3H, m), 7.12−7.02 (4H, m), 6.99 (1H, m), 6.17 (2H, br s, NH_2), 3.99 (2H, s, CH_2), 3.58 (1H, d, *J* = 15.8 Hz, CH_{2-A}), 3.53 (1H, d, *J* = 15.8 Hz, CH_{2-B}); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 166.74 (C), 162.39 (C), 162.05 (C), 138.72 (C), 138.15 (C), 135.34 (C), 132.70 (CH), 132.47 (CH), 132.46 (CH), 132.09 (CH), 131.56 (CH), 130.68 (CH), 128.90 (CH), 128.64 (CH), 128.48 (CH), 128.14 (CH), 127.86 (CH), 127.67 (CH), 125.09 (C), 124.94 (C), 124.62 (C), 114.58 (C), 45.22 (CH_2), 40.17 (CH_2). IR (neat) ν 3457.4 (w), 3298.8 (w), 3140.9 (w), 1634.4 (m), 1550.9 (m), 1470.6 (m), 1435.6 (w), 1421.1 (w), 1399.3 (m), 1376.1 (w), 1307.1 (w), 1158.5 (w), 116.2 (w), 1063.2 (w), 1046.6 (w), 1023.0 (m), 996.0 (m), 940.0 (w), 906.6 (w), 859.2 (w), 796.2 (w), 761.1 (m), 736.6 (s), 657.7 (m) cm^{-1}. HRMS calculated for $C_{24}H_{19}Br_3N_3$ 585.9129; found 585.9149.

2,6-Diisobutyl-5-isopropyl-pyrimidin-4-ylamine 17.[8,12] Prepared from isovaleronitrile in 91%. Rt = 5.892, M + H *m*/*z* = 250.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 2.60 (5H, m), 1.15 (6H, m, 2 × Me), 1.05 (6H, m, 2 × Me), 0.86 (6H, d, *J* = 7.8 Hz, 2 × Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.15 (C), 164.40 (C), 164.29 (C), 106.34 (C), 32.01 (CH_2), 26.59 (CH), 25.83 (CH), 25.77 (CH), 13.35 (CH_3), 13.29 (CH_3), 11.55 (CH_3). IR (neat) ν 3349.7 (m), 3173.7 (m), 2955.6 (m), 2870.1 (m), 2168.2 (w), 2063.7 (w), 1661.0 (m), 1627.0 (s), 1413.5 (s), 1383.7 (m), 1367.2 (m), 1268.3 (m), 1225.4 (m), 1148.2 (m), 956.3 (m), 880.3 (m) cm^{-1}. HRMS calculated for $C_{15}H_{28}N_3$ 250.2283; found 250.2261.

2,6-*Bis*-(4-chlorobenzyl)-5-(4-chlorophenyl)pyrimidin-4-ylamine 18. Prepared from 4-chlorophenylacetonitrile in 81%. Rt = 3.513, M + H *m/z* = 454.0; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.50 (2H, d, J = 8.6 Hz), 7.33 (4H, m), 7.24 (2H, d, J = 8.6 Hz), 7.16 (2H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 6.30 (2H, br s, NH_2), 3.91 (2H, s, CH_2), 3.59 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.25 (C), 162.99 (C), 162.63 (C), 138.38 (C), 133.59 (C), 133.22 (C), 132.35 (CH), 131.30 (C), 131.16 (CH), 131.08 (C), 130.86 (CH), 129.43 (CH), 128.44 (CH), 128.32 (CH), 113.71 (C), 44.64 (CH_2), 39.67 (CH_2). IR (neat) ν 3393.6 (w), 3188.4 (w), 2953.7 (w), 2914.6 (s), 2847.4 (s), 2167.0 (w), 1643.8 (m), 1570.7 (m), 1468.9 (m), 1412.0 (m), 1121.3 (w), 887.9 (w), 800.2 (w), 720.0 (m) cm^{-1}. HRMS calculated for $C_{24}H_{19}Cl_3N_3$ 454.0789; found 454.0793.

2,6-*Bis*-(3-trifluoromethylbenzyl)-5-(3-trifluoromethylphenyl)-pyrimidin-4-ylamine 19. Prepared from 3-(trifluoromethyl)phenylacetonitrile in 93%. Rt = 2.316, M + H *m/z* = 556.10; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 8.66 (1H, m), 8.46 (1H, m), 8.37 (1H, m), 7.82 (1H, m), 7.67 (1H, m), 7.59 (1H, m), 7.49 (1H, m), 7.35 (1H, m), 7.28 (1H, m), 7.21 (1H, m), 7.15 (1H, m), 7.11 (1H, m), 6.56 (2H, br s, NH_2), 4.10 (2H, s, CH_2), 3.93 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 166.72 (C), 162.94 (C), 162.49 (C), 159.30 (C), 159.21 (C), 154.61 (C), 150.22 (CH), 149.24 (CH), 149.16 (CH), 137.51 (CH), 136.67 (CH), 136.83 (CH), 136.57 (CH), 126.16 (CH), 123.97 (CH), 123.10 (CH), 121.92 (CH), 121.76 (CH), 114.39 (C), 48.08 (CH_2), 43.37 (CH_2). HRMS calculated for $C_{25}H_{19}N_3F_9$ 556.1436; found 556.1481.

2,6-*Bis*-(2-fluorobenzyl)-5-(2-fluorophenyl)pyrimidin-4-ylamine 20. Prepared from 2-fluorophenylacetonitrile in 89%. Rt = 2.920, M + H *m/z* = 406.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.45 (1H, m), 7.34−7.24 (4H, m), 7.21−7.06 (4H, m), 7.05−6.94 (3H, m), 6.30 (2H, br s, NH_2), 3.97 (2H, s, CH_2), 3.63 (1H, d, J = 14.7 Hz, CH_{2-A}), 3.57 (1H, d, J = 14.7 Hz, CH_{2-B}); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.07 (C), 163.36 (C), 162.66 (C), 161.23 (C, d, J = 243 Hz), 161.19 (C, d, J = 243 Hz), 161.17 (C, d, J = 243 Hz), 132.56 (CH, d, J = 2.7 Hz), 132.04 (CH, d, J = 4.6 Hz), 131.40 (CH, d, J = 4.6 Hz), 131.05 (CH, d, J = 8.2 Hz), 128.66 (CH, d, J = 8.2 Hz), 128.49 (CH, d, J = 8.2 Hz), 125.51 (CH, d, J = 2.7 Hz), 124.51 (CH, d, J = 3.7 Hz), 124.32 (CH, d, J = 3.7 Hz), 116.51 (CH, d, J = 22.0 Hz), 115.46 (CH, d, J = 22.0 Hz), 115.16 (CH, d, J = 22.0 Hz), 125.65 (C, d, J = 15.8 Hz), 126.00 (C, d, J = 15.8 Hz), 121.73 (C, d, J = 15.8 Hz). IR (neat) ν 3451.1 (w), 3301.1 (w), 3164.0 (w), 2176.9 (w), 1633.5 (m), 1585.9 (w), 1552.9 (m), 1491.3 (m), 1454.2 (m), 1400.7 (m), 1251.1 (w), 1232.5 (m), 1215.9 (w), 1097.5 (w), 1051.7 (w), 1034.2 (w), 1000.9 (w), 977.9 (w), 912.4 (w), 864.1 (w), 822.2 (m), 757.4 (s), 746.6 (s), 699.7 (m), 686.2 (m) cm^{-1}. HRMS calculated for $C_{24}H_{19}F_3N_3$ 406.1531; found 406.1541.

2,6-Diethyl-5-methyl-pyrimidin-4-ylamine 21.[12−18] Prepared from propionitrile in 82%. Rt = 1.724 *m/z* = 166.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 6.30 (2H, br s, NH2), 2.51 (4H, m), 1.94 (3H, s, Me), 1.15 (3H, t, J = 7.9 Hz, Me), 1.05 (3H, t, J = 7.8 Hz, Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.29 (C), 165.71 (C), 162.97 (C), 106.20 (C), 31.83 (CH_2), 27.64 (CH_2), 13.12 (CH_3), 13.02 (CH_3), 11.17 (CH_3). IR (neat) ν 332.6 (m), 3155.7 (m), 2977.0 (m), 2938.1 (w), 2876.7 (w), 2168.0 (w), 1655.2 (s), 1554.6 (s), 1465.6 (m), 1452.4 (m), 1412.7 (s), 1367.8 (m), 1298.2 (m), 1271.8 (m), 1233.5 (m), 1181.8 (m), 1131.8 (m), 1078.9 (m), 1034.5 (m), 1004.8 (m), 969.8 (w), 949.1 (m), 893.0 (m), 806.0 (m), 741.3 (m), 709.6 (m) cm^{-1}. HRMS calculated for $C_9H_{16}N_3$ 166.1344; found 166.1338.

2,6-Dibenzyl-5-phenyl-pyrimidin-4-ylamine 22.[6,7,18−21] Prepared from phenylacetonitrile in 89%. Rt = 3.762, M + H *m/z* = 352.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.46 (2H, m), 7.41 (1H, m), 7.36 (2H, m), 7.28 (2H, m), 7.22−7.12 (5H, m), 6.99 (2H, m), 6.07 (2H, br s, NH_2), 3.95 (2H, s, CH_2), 3.65 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.38 (C), 163.37 (C), 162.61 (C), 139.56 (C), 139.48 (C), 134.83 (C), 130.39 (CH), 129.58 (CH), 129.45 (CH), 129.05 (CH), 128.60 (CH), 128.46 (CH), 128.38 (CH), 126.52 (CH), 126.37 (CH), 114.81 (C). IR (neat) ν 3457.8 (w), 3296.5 (w), 3142.0 (w), 1632.9 (m), 1599.8 (w), 1546.6 (s), 1494.8 (w), 1450.6 (w), 1404.0 (m), 1380.0 (m), 1252.4 (w), 1178.9 (w), 1074.3 (w), 1031.7 (w), 1005.8 (w), 989.6 (w), 828.6 (w), 787.0 (w), 759.3 (w), 731.0 (m), 719.5 (s), 695.3 (s) cm^{-1}. HRMS calculated for $C_{24}H_{22}N_3$ 352.1814; found 352.1815.

2,6-Dimethyl-pyrimidin-4-ylamine 23.[5a,6−8,15,22−24] Prepared from acetonitrile in 80%. Rt = 1.696, M + H *m/z* = 124.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 6.55 (2H, s, NH_2), 5.99 (1H, s), 2.18 (3H, s, Me), 2.05 (3H, s, Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 166.61 (C), 164.41 (C), 164.36 (C), 100.76 (CH), 25.69 (CH_3), 23.69 (CH_3); N^{15} NMR (700 MHz, DMSO-d_6): δ/ppm = 259, 241, 81 ppm. IR (neat) ν 3312.5 (w), 3130.1 (m), 1660.0 (s), 1596.4 (s), 1552.2 (m), 1485.3 (m), 1442.5 (m), 1416.6 (s), 1395.9 (s), 1367.9 (s), 1251.1 (w), 1186.5 (m), 1034.8 (w), 982.1 (s), 961.2 (w), 943.7 (w), 835.0 (s), 778.1 (w) cm^{-1}. HRMS calculated for $C_6H_{10}N_3$ 124.0875; found 124.0902.

5-Butyl-2,6-dipentylpyrimidin-4-ylamine 24. Prepared from hexanenitrile in 95%. Rt = 3.224, M + H *m/z* = 292.2; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 6.30 (2H, br s, NH_2), 2.53−2.35 (6H, m), 1.70−1.52 (4H, m), 1.40−1.20 (12H, m), 0.85 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 168.04 (C), 166.80 (C), 162.02 (C), 111.89 (C), 39.67 (CH2), 34.85 (CH_2), 32.35 (CH_2), 32.21 (CH_2), 30.80 (CH_2), 29.14 (CH_2), 26.10 (CH_2), 23.38 (CH_2), 22.96 (CH_2), 14.41 (CH_3), 14.37 (CH_3), 14.24 (CH_3). IR (neat) ν 3307.1 (w), 3169.3 (w), 2955.5 (m), 2926.8 (m), 2858.8 (m), 2104.8 (w), 1635.8 (m), 1562.4 (s), 1419.2 (m), 1378.2 (m), 1105.1 (w), 958.2 (w), 729.2 (m) cm^{-1}. HRMS calculated for $C_{18}H_{34}N_3$ 292.2674; found 292.2753.

5-Decyl-2,6-diundecylpyrimidin-4-ylamine 25. Prepared from dodecanonitrile in 98%. Rt = 5.013, M + H *m/z* = 544.5; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 2.41(4H, m), 1.54 (6H, m), 1.37 (6H, m), 1.3−1.1 (42H, m), 0.82 (9H, m); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.43 (C), 166.44 (C), 162.60 (C), 111.34 (C), 33.82 (CH2), 31.84 (CH_2), 31.81 (CH_2), 29.56 (CH_2), 29.48 (CH_2), 29.45 (CH_2), 29.30 (CH_2), 29.22 (CH_2), 29.11 (CH_2), 28.72 (CH_2), 28.59 (CH_2), 25.32 (CH_2), 22.60 (CH_2), 16.77 (CH_2), 14.32 (CH_3). IR (neat) ν 3394.7 (w), 2954.5 (m), 2914.9 (s), 2847.3 (s),

2169.6 (w), 1639.6 (m), 1561.2 (m), 1466.1 (m), 1410.8 (m), 1120.8 (w), 720.9 (m) cm^{-1}. HRMS calculated for $C_{36}H_{70}N_3$ 544.5570; found 544.5558.

2,6-Diheptadecyl-5-hexadecylpyrimidin-4-ylamine 26. Prepared from stearonitrile (90% purity $C_{18}H_{35}N$) in 88%. ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 2.53 (4H, m), 2.06 (2H, m), 1.55 (4H, m), 1.46 (2H, m), 1.36 (4H, m), 1.27 (78H, m), 0.85 (9H, br t, 3 × Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm = 167.70 (C), 166.48 (C), 161.52 (C), 111.52 (C), 39.40 (CH_2), 35.93 (CH_2), 34.57 (CH_2), 31.91 (CH_2), 29.94 (CH_2), 29.79 (CH_2), 29.70 (CH_2), 29.65 (CH_2), 29.62 (CH_2), 29.59 (CH_2), 29.55 (CH_2), 29.54 (CH_2), 29.47 (CH_2), 29.48 (CH_2), 29.47 (CH_2), 29.33 (CH_2), 29.35 (CH_2), 29.29 (CH_2), 29.23 (CH_2), 29.16 (CH_2), 28.75 (CH_2), 28.26 (CH_2), 26.02 (CH_2), 25.53 (CH_2), 25.36 (CH_2), 22.68 (CH_2), 17.11 (CH_2), 14.10 (CH_3). IR (neat) ν 3393.4 (w), 3188.5 (w), 2954.0 (w), 2914.7 (s), 2847.5 (s), 2166.7 (w), 1643.6 (m), 1570.9 (m), 1468.9 (m), 1412.2 (m), 1121.3 (w), 882.2 (w), 801.9 (w), 720.0 (m) cm^{-1}. HRMS calculated for $C_{54}H_{106}N_3$ 796.8386; found 796.8401.

5-Thiophen-2-yl-2,6-*bis*-thiophen-2-ylmethylpyrimidin-4-ylamine 27. Prepared from 2-thiopheneacetonitrile in 92%. Rt = 2.833, M + H m/z = 370.0; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.72 (1H, dd, J = 5.1 and 1.2 Hz), 7.34 (1H, dd, J = 5.0 and 1.3 Hz), 7.29 (1H, J = 5.1 and 1.2 Hz), 7.19 (1H, dd, J = 5.1 and 3.4 Hz), 7.01 (1H, dd, J = 3.4 and 1.1 Hz), 6.96 (2H, m), 6.88 (1H, dd, J = 5.1 and 3.4 Hz), 6.67 (1H, m), 4.13 (2H, s, CH_2), 3,90 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.46 (C), 164.73 (C), 163.60 (C), 141.01 (C), 140.99 (C), 134.07 (C), 129.52 (CH), 128.53 (CH), 128.46 (CH), 127.04 (CH), 126.93 (CH), 126.18 (CH), 125.91 (CH), 125.11 (CH), 125.06 (CH), 106.90 (C), 39.94 (CH_2), 35.42 (CH_2). IR (neat) ν 3437.2 (w), 3301.3 (w), 3173.0 (w), 1629.8 (s), 1572.7 (m), 1547.9 (m), 1521.7 (m), 1461.4 (w), 1438.1 (w), 14212.6 (w), 1394.9 (m), 1355.8 (w), 1285.8 (w), 1258.4 (w), 1228.0 (w), 1198.6 (w), 1147.2 (w), 1077.6 (w), 1051.0 (w), 1040.6 (w), 990.7 (w), 943.3 (m), 921.7 (w), 850.8 (w), 833.0 (m), 809.9 (w), 763.2 (w), 701.9 (s) cm^{-1}. HRMS calculated for $C_{18}H_{16}N_3S_3$ 370.0828; found 370.0886.

5-Pyridin-3-yl-2,6-*bis*-pyridin-3-ylmethylpyrimidin-4-ylamine 28. Prepared from 3-pyridylacetonitrile in 86%. Rt = 0.312, M + H m/z = 355.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 8.60 (1H, dd, J = 4.8 and 1.6 Hz), 8.54 (1H, d, J = 1.9 Hz), 8.43 (1H, dd, J = 4.8 and 1.6 Hz), 8.35 (2H, m), 8.10 (1H, d, J = 1.9 Hz), 7.71 (1H, m), 7.61 (1H, m), 7.46 (1H, ddd, J = 7.8, 4.8 and 0.7 Hz), 7.35 (1H, m), 7.30 (1H, ddd, J = 7.8, 4.8 and 0.7 Hz), 7.21 (1H, ddd, J = 7.8, 4.8 and 0.7 Hz), 6.50 (2H, br s, NH_2), 3.97 (2H, CH_2), 3.62 (2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.38 (C), 163.36 (C), 162.93 (C), 150.84 (CH), 150.51 (CH), 149.98 (CH), 149.52 (CH), 147.90 (CH), 147.79 (CH), 138.35 (CH), 137.02 (CH), 136.51 (CH), 134.81 (C), 134.61 (C), 130.65 (C), 124.59 (CH), 123.78 (CH), 123.70 (CH), 111.64 (C), 42.47 (CH_2), 37.96 (CH_2). IR (neat) ν 3141.6 (w), 1649.9 (m), 1558.2 (m), 1547.1 (s), 1478.8 (w), 1411.6 (m), 1368.5 (m), 1189.9 (m), 1151.1 (w), 1044.9 (w), 1029.1 (m), 995.9 (m), 800.6 (w), 752.8 (m), 708.5 (s) cm^{-1}. HRMS calculated for $C_{21}H_{19}N_6$ 355.1671; found 355.1669.

5-Naphthalen-1-yl-2,6-*bis*-naphthalen-1-ylmethylpyrimidin-4-ylamine 29. Prepared from 1-naphthylacetonitrile in 87%. Rt = 3.498, M + H m/z = 502.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.89 (2H, m), 7.79−7.68 (4H, m), 7.64 (2H, m), 7.60 (1H, d, J = 8.2 Hz), 7.46 (4H, m), 7.40−7.30 (3H, m), 7.28 (1H, s), 7.21 (1H, dd, J = 8.5 and 1.5 Hz), 7.09 (1H, dd, J = 8.5 and 1.6 Hz), 6.14 (2H, br s, NH_2), 4.05 (2H, s, CH_2), 3.35 (2H, m, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.47 (C), 163.48 (C), 162.83 (C), 137.27 (C), 137.15 (C), 133.80 (C), 133.54 (C), 133.36 (C), 132.96 (C), 132.44 (C), 132.19 (C), 132.04 (C), 129.70 (C), 129.17 (CH), 128.69 (CH), 127.90 (CH), 127.84 (CH), 127.64 (CH), 127.48 (CH), 127.45 (CH), 127.40 (CH), 127.35 (CH), 127.33 (CH), 127.31 (CH), 127.28 (CH), 126.99 (CH), 126.72 (CH), 126.27 (CH), 126.22 (CH), 125.90 (CH), 125.83 (CH), 125.33 (CH), 125.29 (CH), 114.77 (C), 45.69 (CH_2), 40.81 (CH_2). IR (neat) ν 3448.1 (w), 3297.0 (w), 3148.4 (w), 3052.0 (w), 1736.4 (w), 1630.0 (s), 1597.6 (w), 1549.6 (s), 1505.8 (w), 1470.9 (w), 1449.0 (w), 1427.5 (w), 1403.9 (m), 1362.9 (w), 1340.5 (w), 1241.0 (w), 1207.5 (w), 1154.1 (w), 1124.0 (w), 1062.2 (w), 1020.6 (w), 988.7 (w), 964.8 (w), 951.6 (w), 942.7 (m), 919.0 (w), 896.2 (w), 865.5 (m), 849.9 (m), 824.9 (s), 812.0 (m), 781.1 (s), 757.4 (s), 732.9 (s), 689.5 (m), 666.2 (m) cm^{-1}. HRMS calculated for $C_{36}H_{28}N_3$ 502.2283; found 502.2264.

5-Thiophen-3-yl-2,6-*bis*-thiophen-3-ylmethylpyrimidin-4-ylamine 30. Prepared from 3-thiopheneacetonitrile in 85%. Rt = 2.927, M + H m/z = 370.0; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 7.70 (1H, dd, J = 4.9 and 2.9 Hz), 7.43 (2H, m), 7.37 (1H, dd, J = 5.0 and 3.05 Hz), 7.25 (1H, m), 7.09 (1H, dd, J = 4.9 and 1.1 Hz), 6.96 (1H, dd, J = 4.9 and 1.1 Hz), 6.91 (1H, m), 6.83 (1H, dd, J = 5.0 and 1.1 Hz), 6.24 (2H, br s, NH_2), 3.93 (2H, CH_2), 3.68 (2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.04 (C), 163.89 (C), 163.00 (C), 140.00 (C), 139.31 (C), 134.23 (C), 129.26 (CH), 129.24 (CH), 127.70 (CH), 125.93 (CH), 125.90 (CH), 122.07 (CH), 121.79 (CH), 109.62 (C), 40.21 (CH_2), 35.82 (CH_2). IR (neat) ν 3440.3 (m), 3302.6 (w), 3169.1 (w), 1626.2 (m), 1548.3 (s), 1519.4 (m), 1454.6 (m), 1409.3 (m), 1378.8 (m), 1354.8 (m), 1301.8 (w), 1252.8 (w), 1201.3 (w), 1081.2 (w), 1027.6 (w), 984.7 (w), 936.8 (w), 890.8 (w), 858.2 (m), 788.0 (s), 764.2 (s), 742.3 (s), 685.2 (s), 659.5 (s) cm^{-1}. HRMS calculated for $C_{18}H_{16}N_3S_3$ 370.0506; found 370.0513.

5-Pyridin-2-yl-2,6-*bis*-pyridin-2-ylmethylpyrimidin-4-ylamine 31. Prepared from 2-pyridylacetonitrile in 81%. Rt = 0.299, M + H m/z = 355.1. ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 8.65 (1H, d, J = 4.1 Hz), 8.45 (1H, d, J = 4.1 Hz), 8.37 (1H, d, J = 4.1 Hz), 7.81 (1H, dt, J = 7.7 and 1.4 Hz), 7.67 (1H, dt, J = 7.7 and 1.4 Hz), 7.59 (1H, dt, J = 7.7 and 1.4 Hz), 7.48 (1H, d, J = 7.7 Hz), 7.34 (1H, m), 7.27 (1H, d, J = 7.7 Hz), 7.20 (1H, m), 7.15 (1H, m), 7.10 (1H, d, J = 7.7 Hz), 6.50 (2H, br s, NH_2), 4.12 (2H, s, CH_2), 3.91 (2H, s, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 166.55 (C), 162.80 (C), 162.35 (C), 159.17 (C), 159.09 (C), 154.49 (C), 150.08 (CH), 149.10 (CH), 149.02 (CH), 137.38 (CH), 136.52 (CH), 136.42 (CH), 126.03 (CH), 123.83 (CH), 123.82 (C), 122.97 (CH), 121.78 (CH), 121.62 (CH), 114.25 (C), 47.96 (CH_2), 43.26 (CH_2); IR (neat) ν

3302.6 (m), 3170.3 (m), 1620.7 (m), 1587.6 (s), 1587.6 (s), 1546.4 (s), 1472.8 (m), 1432.6 (s), 1407.1 (s), 1372.7 (w), 1280.9 (w), 1215.4 (w), 1148.5 (w), 1050.1 (m), 1019.7 (m), 995.7 (m), 749.3 (s), 731.3 (s) cm^{-1}. HRMS calculated for $C_{21}H_{19}N_6$ 355.1671; found 355.1660.

5-Naphthalen-2-yl-2,6-*bis*-naphthalen-2-ylmethylpyrimidin-4-ylamine 32. Prepared from 2-naphthylacetonitrile in 89%. Rt = 3.428, M + H *m*/*z* = 502.1; ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm = 8.27 (1H, d, J = 8.6 Hz), 7.93 (3H, m), 7.79 (3H, m), 7.61 (1H, d, J = 8.3 Hz), 7.48 (4H, m), 7.42−7.33 (3H, m), 7.21 (1H, m), 7.09 (1H, m), 6.67 (1H, d, J = 7.2 Hz), 4.43 (2H, CH_2), 4.05 (1H, d, J = 15.0 Hz, CH_{2-A}), 3.88 (1H, d, J = 15.0 Hz, CH_{2-B}); ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm = 167.94 (C), 164.22 (C), 163.05 (C), 135.87 (C), 135.08 (C), 134.13 (C), 133.91 (C), 133.60 (C), 132.53 (C), 132.10 (C), 132.05 (C), 131.72 (C), 128.98 (CH), 128.97 (CH), 128.78 (CH), 128.72 (CH), 128.66 (CH), 128.17 (CH), 127.40 (CH), 127.25 (CH), 126.85 (CH), 126.76 (CH), 126.46 (CH), 126.45 (CH), 126.27 (CH), 126.05 (CH), 125.96 (CH), 125.95 (CH), 125.72 (CH), 125.44 (CH), 125.22 (CH), 124.78 (CH), 124.66 (CH), 112.73 (C), 43.58 (CH_2), 38.87 (CH_2). IR (neat) ν 3852.4 (w), 3438.3 (w), 3306.7 (w), 3201.4 (w), 3040.7 (w), 1624.5 (m), 1592.7 (w), 1543.3 (m), 1509.4 (w), 1450.2 (m), 1421.6 (w), 1384.8 (m), 1247.2 (w), 1214.1 (w), 1165.8 (w), 1140.6 (w), 1079.1 (w), 1051.0 (w), 1016.0 (w), 955.9 (w), 858.4 (w), 827.1 (w), 791.3 (m), 772.1 (s), 749.2 (m), 732.7 (m), 665.1 (m) cm^{-1}. HRMS calculated for $C_{36}H_{28}N_3$ 502.2468; found 502.2450.

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