Supporting Information

General

^{1}H-NMR spectra were recorded on a Bruker Avance DRX-600 or DPX-400 spectrometer with residual DMSO, $CHCl_3$ or MeOH as the internal reference (DMSO δ_H = 2.50 ppm, $CHCl_3$ δ_H = 7.26 and MeOH δ_H = 3.31 ppm). COSY and HMQC experiments were used to aid in the assignment of signals in the ^{1}H and ^{13}C-NMR spectra. ^{13}C-NMR spectra were recorded on the same spectrometers with the central peak of d_6-DMSO, $CDCl_3$ or d_3-MeOD as the internal reference (d_6-DMSO δ_C = 39.5 ppm, $CDCl_3$ δ_C = 77.2 ppm and d_3-MeOD = 49.0). DEPT 135 experiments were used to aid in the assignment of signals in the ^{13}C-NMR spectra. The multiplicity of a signal is indicated as: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, br – broad, dd – doublet of doublets, *etc*. Coupling constants (*J*) are quoted in Hz and recorded to the nearest 0.1 Hz.

Infrared spectra were recorded neat as a thin film on a Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in the parentheses refer to the relative absorbency of the peak; w-weak less than 40% of the main peak, m-medium ca. 41-74% of the main peak, s-strong greater than 75% of the most intense peak.

High resolution mass spectrometry (HRMS) within ±5 ppm was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive and negative electrospray ionisation. HPLC-MS analysis was performed on an Agilent HP 1100 series chromatograph (Mercury Luna 3µ C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of acetonitrile and water containing 0.1% formic acid. The gradient run is described in the table below:

HPLC-MS solvent gradient

Time (min)	Acetonitrile (%)
0.0	5
1.0	5
4.0	95
5.0	95
7.0	5
8.0	5

t_R is the retention time in minutes and the *m*/*z* value is reported. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. Laboratory reagent grade CH_2Cl_2 was obtained from Fischer Scientific and distilled over CaH_2 before use. The removal of solvent under reduced pressure was carried out on a Biotage V-10 evaporator or a standard rotary evaporator. TLC was performed on Merck 60 F254 silica gel plates and were visualised using short-wave ultra-violet light. Melting points were performed using an OptiMelt automated melting point system available from Stanford Research Systems and are calibrated against vanillin (mp 83 °C), phenacetin (mp 136 °C) and caffeine (mp 237 °C).

All columns of polymer-supported reagents were pre-conditioned with the reaction solvent before use and the plunger inserted to the resultant height of the reagent.

Sources of compounds

Quadrapure Dimethylamine (QP-DMA) and Quadrapure Sulfonic Acid (QP-SA) are high-loading polystyrene-supported scavengers commercially available from Reaxa. Quadrasil-SA (SS-SA), a silica-supported sulfonic acid is also available. Website: http://www.reaxa.com.

TBD-methyl polystyrene (PS-TBD) available from Novabiochem. Website: http://www.merck-chemicals.co.uk/.

MP-Isocyanate (PS-NCO) is available from Biotage. Website: http://www.biotage.com.

Dimethylaminopyridine on polystyrene (PS-DMAP) is commercially available from Sigma-Aldrich. Website http://www.sigmaaldrich.com.

4-(pyridin-3-yl)pyrimidin-2-amine (**7**) is commercially available, however was synthesised from guanidine nitrate and 3-(dimethylamino)-1-(3-pyridinyl)-2-propen-1-one as described below

Equipment

Biotage SP1 auto-purification system and V-10 solvent evaporator are available from Biotage. Website: http://www.biotage.com.

Vapourtec R2/R4 flow system is available from Vapourtec: Website: http://www.vapourtec.com.

Experimental

N-(3-bromo-4-methylphenyl)-4-(chloromethyl)benzamide (**4**)

A solution of 4-(chloromethyl)benzoyl chloride (**2**) (57 mg, 0.3 mmol) in dry CH_2Cl_2 (1 mL) was loaded into a 1 mL sample loop. The sample loop was switched in-line with a switching valve into a stream of dry CH_2Cl_2 flowing at 0.1 mL/min into a 6.6 mm diameter Omnifit column filled with PS-DMAP (200 mg, 0.6 mmol). After 25 min, the flow rate was increased to 0.4 mL/min for a further 15 min to wash the column. A second solution of 3-bromo-4-methylaniline (**3**) (37 mg, 0.2 mmol) in dry CH_2Cl_2 (1 mL) was loaded into the same 1 mL sample loop and this switched in-line with the stream of dry CH_2Cl_2 flowing at 0.4 mL/min into the PS-DMAP column. The output was directed through a Gilson 170 DAD equipped with an Agilent G1315-60016 flow cell with 3 mm path length then a 100 psi BPR followed by a Gilson 233XL injector/fraction collector. The UV detector and fraction collector were controlled by Gilson Unipoint software with the UV detector monitor wavelength set to 346 nm and a reference of 550 nm. The switching and injection valves of the injector/fraction collector were connected as in the scheme below. The fraction collector was set to collect the output of the reaction when the UV absorption was over 7.5% of the full scale, in fractions of 10 min (4 mL) each. The output was collected over 3 fractions, the solvent removed *in vacuo* to yield the product as a cream solid (53 mg, 78%, >95% purity) of which 40 mg, 75% was in the first fraction. Mp 150-156 °C dec; IR ν_{max}/cm^{-1} 3274.6(w), 1639.3(s), 1612.1(w), 1604.1(w), 1578.9(m), 1519.4(m), 1498.7(m), 1489.6(m), 1441.2(m), 1389.7(m), 1376.1(m), 1320.3(m), 1307.8(m), 1296.0(m), 1280.0(m), 1260.8(m), 1204.5(w), 1185.9(w), 1147.4(w), 1118.1(w), 1108.4(w), 1038.1(m), 1019.2(w), 995.1(w), 973.4(w), 921.0(m), 875.5(w), 861.3(w), 853.6(m), 841.5(m), 804.4(m), 763.4(m), 711.1(m), 668.0(s); δ_H ($CDCl_3$, 600 MHz) = 7.90 (1 H, d, *J* = 2.0 Hz, 2H-bromophenyl), 7.85 (2 H, d, *J* = 8.1 Hz, 2H-benzamide), 7.70 (1 H, s, NH), 7.52 (2 H, d, *J* = 8.1 Hz, 3H-benzamide), 7.48 (1 H, dd, *J* = 8.2 and 2.0 Hz, 4H-bromophenyl), 7.23 (1 H, d, *J* = 8.2 Hz, 5H-bromophenyl), 4.64 (2 H, s, C*H*$_2$), 2.39 (3 H, s, C*H*$_3$); δ_C ($CDCl_3$, 150 MHz) = 165.08(C), 141.31(C), 136.53(C), 134.51(C), 134.15(C), 130.83(CH), 128.88(CH), 127.47(CH), 124.80(C), 124.01(CH), 119.25(CH), 45.26(CH_2), 22.28(CH_3); Rt 5.00, M+H m/z = 339.8; HRMS calculated for $C_{15}H_{14}BrClNO$ $[M + H]^+$, 337.9947; found 337.9947.

N-(3-bromo-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**6**)

The first fraction (10 mL) of the solution of **4** (40 mg, 0.118 mmol) in CH_2Cl_2 formed in the previously described step was set to collect into a tapered 20 mL vial with a screw-top septum containing a solution (4 mL) of *N*-methylpiperazine (24 mg, 26 µL, 0.236 mmol) in DMF. A polymer tube connected to a nitrogen gas supply (0.5 bar) bubbled nitrogen through the solution during collection, with a second polymer tube placed at the top of the vial to allow solvent vapours to vent to an exhaust. The vial was placed on a hotplate set to 65 °C to provide a solution temperature of approximately 50 °C. When the collection was complete, the solution was allowed to stand (50 °C) with nitrogen bubbling for a further 30 min. The injector was set to aspirate air (100 µL), followed by the reaction solution (5 mL) into a sample loop using a syringe pump. This was then injected into a sample loop (10 mL) and switched in-line with a switching valve into a stream of DMF flowing at 0.1 mL/min. The flow stream was then directed into a 10 mm diameter Omnifit column packed with $CaCO_3$ (3.5 g) and then a further 6.6 mm diameter Omnifit column packed with PS-NCO (273 mg, 0.354 mmol). The output of this column was then directed through a 3.0 mm diameter Omnifit column packed with silica-supported sulfonic acid (250 mg, 0.2 mmol) and then a 100 psi BPR before directing the output to waste. When no further product was observed to be caught on the supported acid as determined by the change in appearance of the silica from translucent to opaque (approx 1.5 h), a stream of MeOH (0.4 mL/min) was directed through the column for 10 min. A sample loop (1 mL) filled with NH_3 in MeOH (2.0 M) was then switched in-line into a stream of MeOH (0.1 mL/min) flowing through the column to release the product. This was repeated a further time then the solvent of the output of the reactor removed *in vacuo* to yield a white solid (38 mg, 80%, >95% purity). Mp 138 – 141 °C; IR ν_{max}/cm^{-1} 3286.7(w), 2936.3(w), 2876.8(w), 2798.0(m), 2160.0(w), 1647.2(m), 1589.4(m), 1523.8(m), 1493.3(s), 1455.5(m), 1414.6(w), 1375.4(m), 1349.9(m), 1303.2(s), 1281.2(m), 1255.6(m), 1204.8(w), 1162.4(m), 1139.3(m), 1105.4(m), 1087.5(m), 1079.0(m), 1035.7(m), 1010.6(s), 922.9(m), 856.1(m), 813.1(s), 783.8(m), 765.6(m), 748.2(s), 691.4(m), 676.7(s); δ_H (CD_3OD, 600 MHz) = 8.01 (1 H, d, *J* = 1.8 Hz, 2H-bromophenyl), 7.87 (2 H, d, *J* = 8.1 Hz, 2H-benzamide), 7.54 (1 H, dd, *J* = 8.3 and 1.8 Hz, 4H-bromophenyl), 7.47 (2 H, d, *J* = 8.1 Hz, 3H-benzamide), 7.25 (1 H, d, *J* = 8.3 Hz, 5H-bromophenyl), 3.59 (2 H, s, CH_2), 2.60 - 2.40 (8 H, m, piperazine CH_2), 2.36 (3 H, s, CCH_3), 2.28 (3 H, s, NCH_3); δ_C (d_6-DMSO, 150 MHz) = 165.85(C), 142.90(C), 138.85(C), 133.69(C), 132.44(C), 131.29(CH), 129.10(CH), 128.05(CH), 124.03(C), 123.71(CH), 119.83(CH), 62.03(CH_2), 55.15(CH_2), 53.03(CH_2), 46.19(CH_3), 22.17(CH_3); Rt 4.04, M+H m/z = 404.1; HRMS calculated for $C_{20}H_{25}BrN_3O$ $[M + H]^+$, 402.1181; found 402.1169.

4-(pyridin-3-yl)pyrimidin-2-amine (**7**)[1]

To a mixture of guanidine nitrate (1.65 g, 13.5 mmol) and 3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (2.38 g, 13.5 mmol) in n-butanol (20 mL) was added sodium hydroxide (0.54 g, 13.5 mmol). The mixture was heated under reflux (16 h), the mixture cooled (ambient temperature) and filtered under suction. The precipitate was washed with water (100 mL) and dried *in vacuo* (80 °C) to yield the title compound (1.56 g, 67%) as off-white crystals Mp 188 – 189 °C (lit.:[1] 189 – 191 °C); Found: C, 62.5; H, 4.6; N, 32.5. Calc. for $C_9H_8N_4$: C, 62.8; H, 4.7; N, 32.5%; IR ν_{max}/cm^{-1} 1576.0(m), 1551.6(s), 1472.3(s), 1433.8(m), 1411.4(m), 1344.0(m), 1293.5(m), 1191.7(m), 1020.9(m), 906.7(w), 829.1(w), 796.6(s), 752.3(m), 714.1(s), 654.5(s); δ_H ($CDCl_3$, 400 MHz) = 9.22 (1 H, d, *J* = 1.9 Hz, 2H-pyridin-3-yl), 8.63 (1 H, dd, *J* = 5.1 and 1.7 Hz, 4H-pyridin-3-yl), 8.48 (1 H, ddd, *J* = 8.1, 1.9 and 1.7 Hz, 6H-pyridin-3-yl), 8.33 (1 H, d, *J* = 5.3 Hz, 6H-pyridin-2-amine), 7.55 (1 H, dd, *J* = 8.1 and 5.1 Hz, 5H-pyridin-3-yl), 7.19 (1 H, d, *J* = 5.3 Hz, 5H-pyridin-2-amine), 3.30 (2 H, s, N*H*$_2$); δ_C (d_6-DMSO, 100 MHz) = 164.50(C), 162.25(C), 160.06(CH), 151.82(CH), 148.65(CH), 134.81(CH), 133.17(C), 124.42(CH), 106.70(CH); HRMS calculated for $C_9H_9N_4$ $[M + H]^+$, 173.0822; found 173.0828.

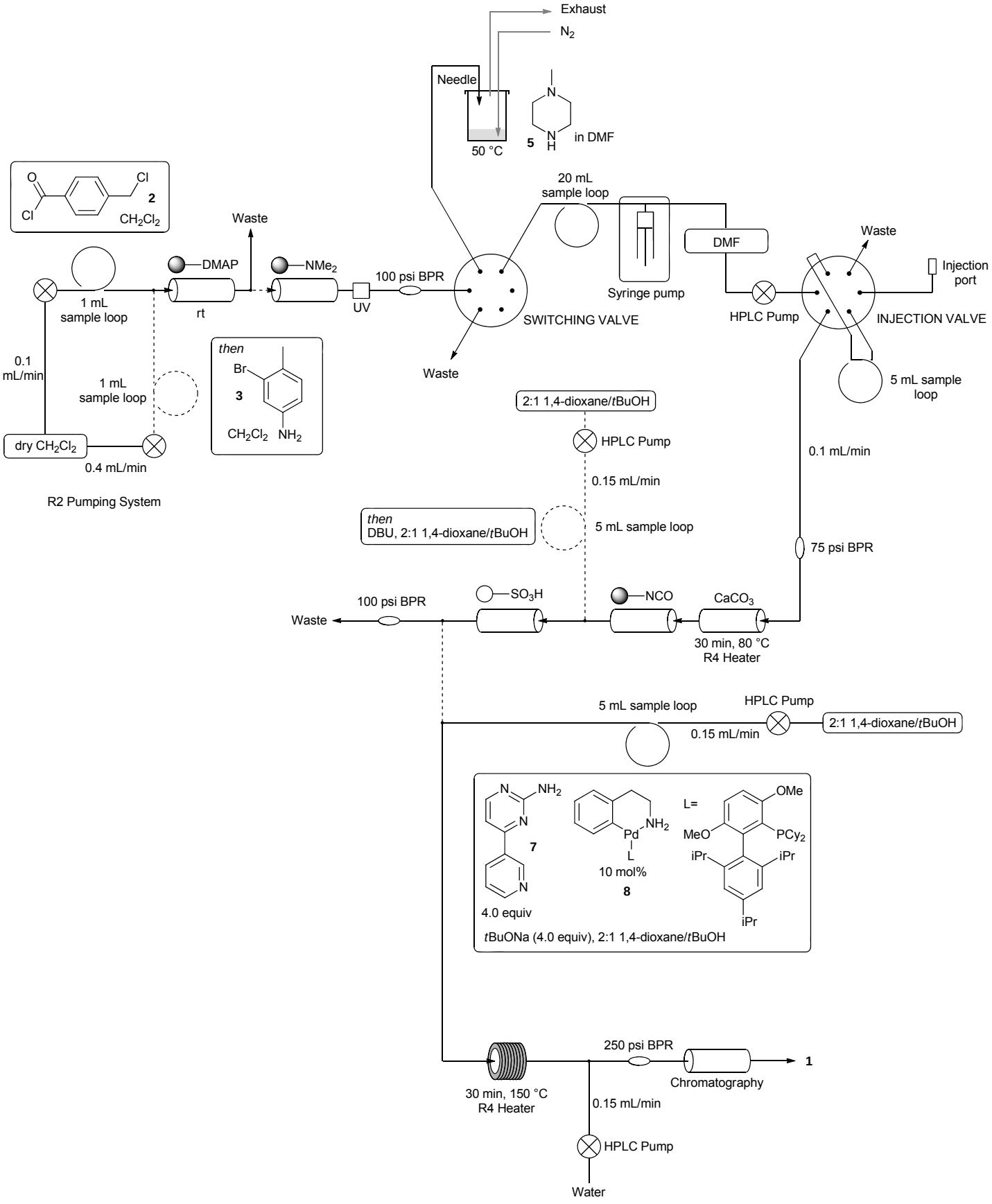
3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one[1]

A mixture of 3-acetylpyridine (15.2 g, 125 mmol) and dimethylformamidedimethylacetal (17.9 g, 20 mL, 151 mmol) in xylenes (35 mL) was heated under reflux (16 h). The solution was concentrated *in vacuo* and n-hexane (20 mL) added to the residue. The mixture was filtered under suction, the precipitate washed with further n-hexane (4 x 20 mL) and dried *in vacuo*. The product was recrystallised from CH_2Cl_2/n-hexane to give the title compound (19.2 g, 87%) as orange/yellow crystals Mp 77 – 80 °C (lit.:[1] 81 – 82 °C from xylene) IR ν_{max}/cm^{-1} 3091.2(w), 2921.6(w), 2806.1(w), 1677.5(m), 1635.4(s), 1574.7(s), 1533.7(s), 1439.6(m), 1411.9(s), 1363.2(s), 1327.9(m), 1275.2(s), 1247.6(s), 1184.8(s), 1123.4(s), 1082.3(m), 1064.8(s), 1035.1(m), 1022.9(m), 999.3(m), 964.1(m), 900.6(s), 828.3(m), 812.3(m), 800.1(m), 764.0(s), 719.6(s), 701.0(s), 675.9(s); δ_H (CD_3OD, 600 MHz) = 9.07 (1 H, d, *J* = 1.8 Hz, 2H-pyridin-3-yl), 8.66 (1 H, dd, *J* = 4.8 and 1.8 Hz, 6H-pyridin-3-yl), 8.18 (1 H, dt, *J* = 7.8 and 1.8 Hz, 4H-pyridin-3-yl), 7.83 (1 H, d, *J* = 12.3 Hz, $(CH_3)_2NCH$), 7.34 (1 H, dd, *J* = 7.8 and 4.8 Hz, 5H-pyridin-3-yl), 5.68 (1 H, d, *J* = 12.3 Hz, COC*H*), 3.17 (3 H, s, NCH_3), 2.95 (1 H, s, NCH_3); δ_C (d_6-DMSO, 150 MHz) = 186.26(C), 154.62(CH), 151.32(CH), 148.79(CH), 135.65(C), 135.08(CH), 123.24(CH), 91.82(CH), 45.13(CH_3), 37.33(CH_3); Rt 0.40, M+H m/z = 177.2; HRMS calculated for $C_{10}H_{13}N_2O$ $[M + H]^+$, 177.1028; found 177.1029.

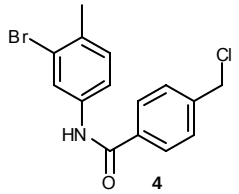
N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**1**)[1]

The column of silica-supported sulfonic acid containing caught **6** (38 mg, 0.094 mmol) from the previous step was washed with a 2:1 1,4-dioxane/*t*BuOH solvent mixture (0.4 mL/min, 15 min). A 2.5 mL solution of DBU (28 µL, 0.189 mmol) in 2:1 1,4-dioxane/*t*BuOH was loaded into a 5 mL sample loop and injected into a stream of 2:1 1,4-dioxane/*t*BuOH through the column of silica-supported sulfonic acid at 0.15 mL/min. A second solution (5 mL) of **7** (65 mg, 0.378 mmol), NaO*t*Bu (36 mg, 0.378 mmol) and **8** (7.5 mg, 9.4 µmol) in 2:1 1,4-dioxane/*t*BuOH was sonicated (10 min) and loaded into a 5 mL sample loop. This was injected into a stream of 2:1 1,4-dioxane/*t*BuOH (0.15 mL/min) 10 min after the injection of the DBU solution. The two streams were combined in a t-piece after the column of silica-supported sulfonic acid and directed into a flow coil (10 mL) heated to 150 °C. A stream of water (0.15 mL/min) was introduced to the output of the flow coil *via* a t-piece, the resultant stream passed through a 250 psi BPR and the output collected. The solvent was removed *in vacuo* , the residue loaded onto a Biotage silica samplet with MeOH (5 mL) and purified using a Biotage SP1 chromatographic purification system eluting with MeOH. The desired fractions were combined and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), filtered and the solvent removed *in vacuo* to give **1** (32 mg, 69%) as an off-white powder Mp 206 – 207 °C (lit.:[1] 207 – 210 °C); IR ν_{max}/cm^{-1} 3275.0(w), 2928.5(w), 2796.5(w), 1645.9(m), 1586.0(m), 1575.1(s), 1554.0(m), 1531.5(s), 1510.3(m), 1478.1(m), 1448.9(s), 1416.7(m), 1377.7(m), 1352.2(m), 1334.8(m), 1325.6(m), 1308.8(m), 1290.3(s), 1261.1(m), 1204.3(m), 1164.1(m), 1141.7(m), 1124.6(w), 1102.6(m), 1089.2(w), 1052.0(w), 1024.4(w), 1010.0(m), 992.5(w), 968.3(w), 924.5(w), 886.2(w), 857.9(w), 850.3(w), 807.8(m), 795.7(s), 748.1(m), 703.2(m), 690.1(m), 670.7(m); δ_H (d_6-DMSO, 600 MHz) = 10.14 (1 H, s, N*H*), 9.26 (1 H, d, *J* = 1.5 Hz, 2H-pyridin-3-yl), 8.95 (1 H, s, N*H*), 8.66 (1 H, dd, *J* = 4.8 and 1.2 Hz, 6H-pyridin-3-yl), 8.49 (1 H, d, *J* = 5.1 Hz, 6H-pyridin-2-amine), 8.46 (1 H, ddd, *J* = 7.9, 1.5 and 1.2 Hz, 4H-pyridin-3-yl), 8.06 (1 H, d, *J* = 1.5 Hz, 3H-2-aminotoluene), 7.89 (2 H, d, *J* = 8.1 Hz, 2H-benzamide), 7.50 (1 H, dd, *J* = 7.9 and 4.8 Hz, 5H-pyridin-3-yl), 7.46 (1 H, dd, *J* = 8.3 and 1.5 Hz, 5H-2-aminotoluene), 7.42 – 7.40 (3 H, m, 3H-benzamide and 5H-pyridin-2-amine), 7.18 (1 H, d, *J* = 8.3 Hz, 6H-2-aminotoluene), 3.51 (2 H, s, CH_2), 2.50 - 2.20 (8 H, m, piperazine CH_2), 2.20 (3 H, s, CCH_3), 2.13 (3 H, s, NCH_3); δ_C ($CDCl_3$, 150 MHz) = 165.42(C), 162.72(C), 160.57(C), 158.99(CH), 151.44(CH), 148.48(CH), 142.52(C), 137.77(C), 136.60(C), 134.92(CH), 133.88(C), 132.66(C), 130.75(CH), 129.28(CH), 127.00(CH), 124.23(C), 123.71(CH), 115.35(CH), 113.19(CH), 108.32(CH), 62.49(CH_2), 55.07(CH_2), 53.10(CH_2), 45.98(CH_3), 17.65(CH_3); R_f (MeOH) = 0.09; Rt 3.48, M+H m/z = 494.2; HRMS calculated for $C_{29}H_{31}N_7ONa$ $[M + Na]^+$, 516.2488; found 516.2491.

Flow Diagram



^{1}H NMR Spectra



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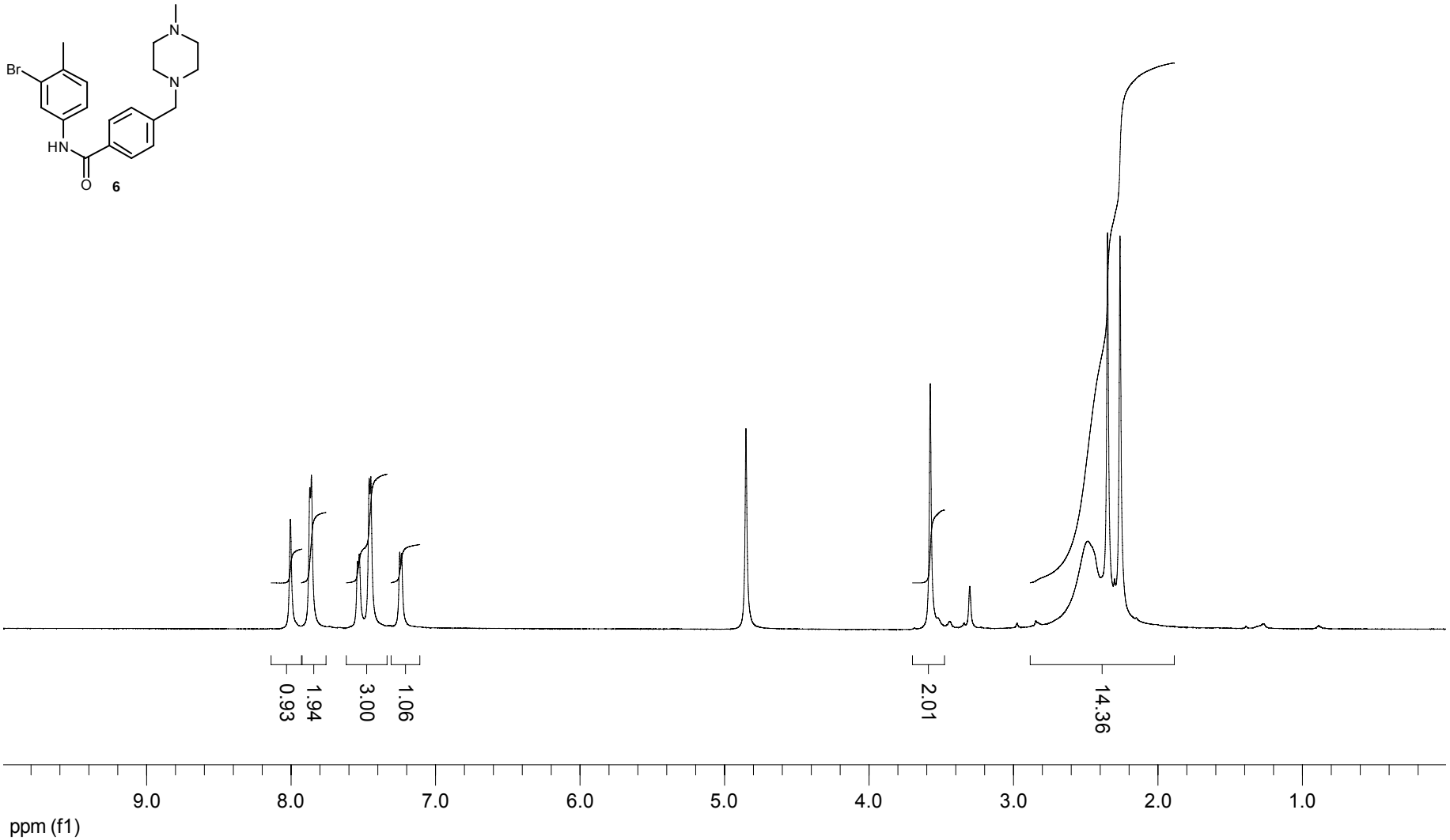
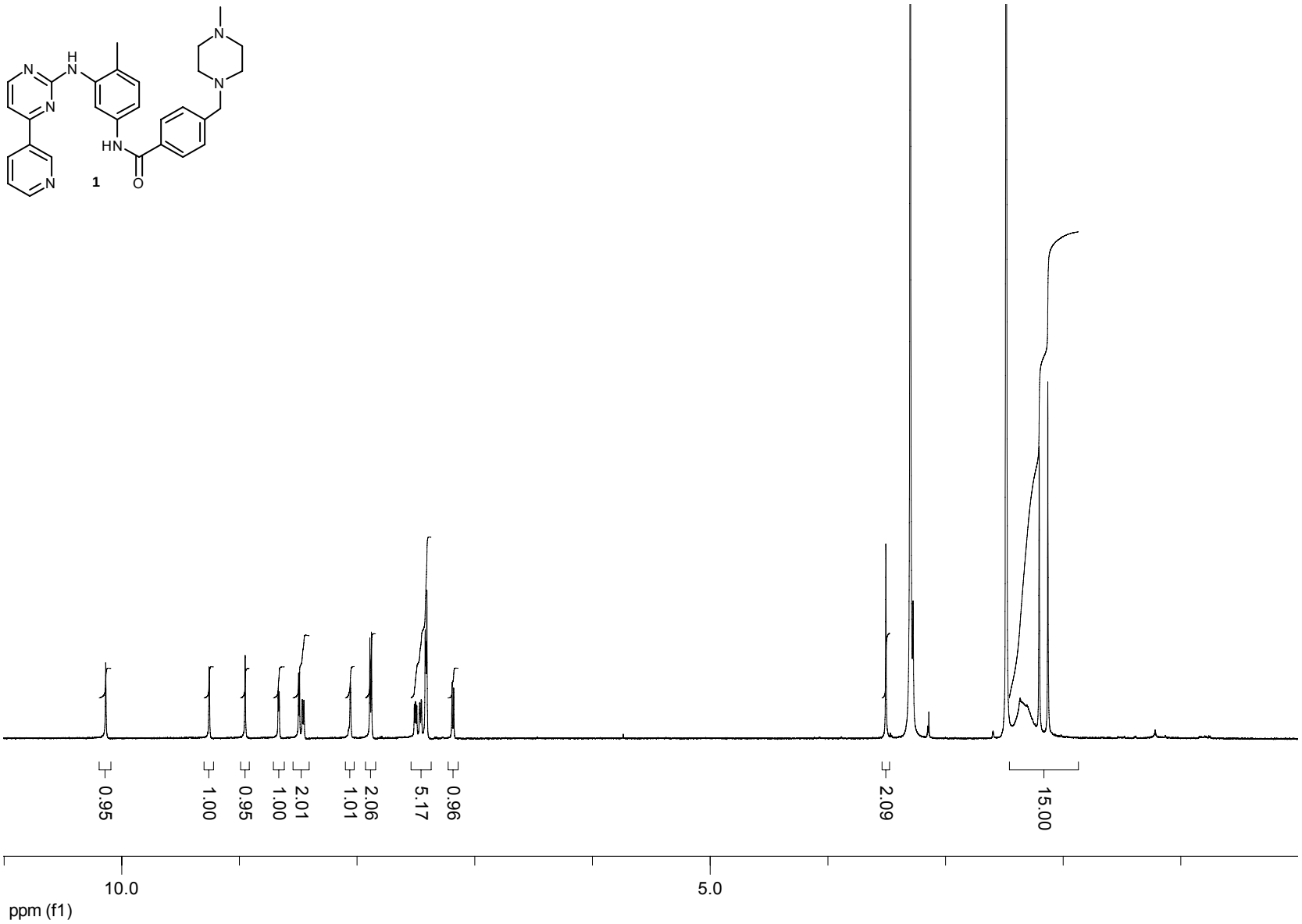
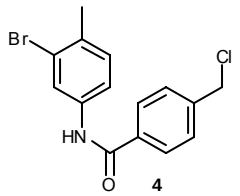




^{13}C NMR Spectra



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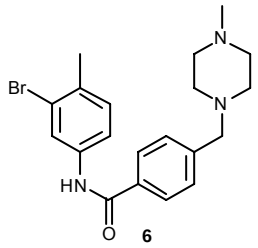

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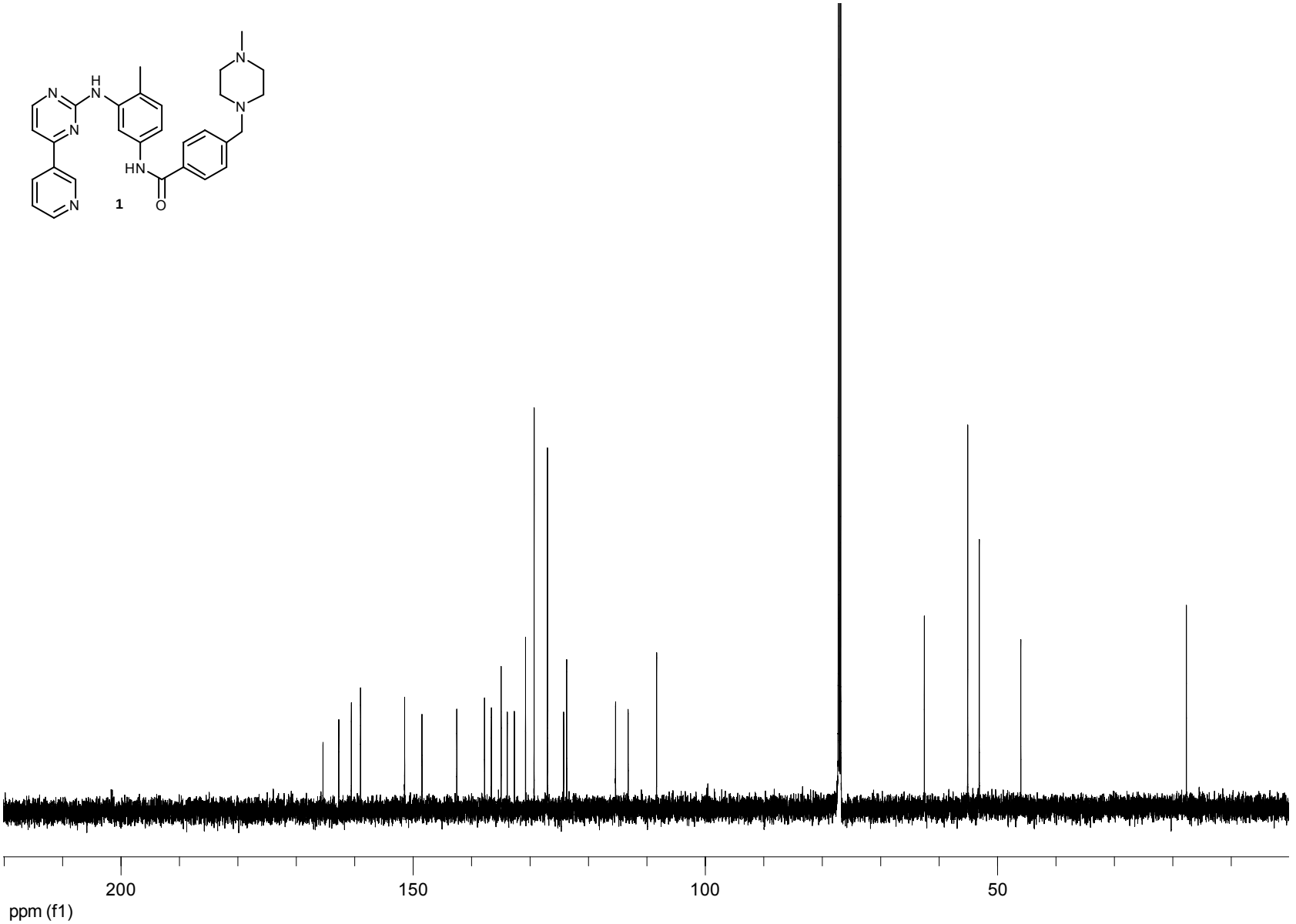

References

1 Y.-F. Liu, C.-L. Wang, Y.-J. Bai, N. Han, J.-P. Jiao and X.-L. Qi, *Org. Process Res. Dev.*, 2008, **12**, 490.