Experimental Details

General

^{1}H NMR spectra were recorded in $CDCl_3$, CD_3OD, d_6-DMSO on a Bruker Avance DPX-400, DRX-500 or DRX-600 spectrometer with residual $CHCl_3$, CD_2HOD or DMSO as the internal reference (δ_H = 7.26, 3.31 or 2.50 ppm respectively). COSY, HMQC and HMBC were used to aid in the assignment of signals in the ^{1}H NMR spectra. ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD or d_6-DMSO on the same spectrometers with the central peak of $CDCl_3$, CD_3OD or d_6-DMSO as the internal reference (δ_C = 77.0, 49.0 or 39.5 ppm respectively). DEPT 135 was 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 reported to the nearest 0.1 Hz. ^{1}H NMR assignments were made according to the numbering applied to the compound figure.

Infrared spectra were recorded as a neat 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 compared to the most intense peak: w – weak, less than 40%; m – medium, 40-75%; s – strong, greater than 75%.

Melting points were obtained using an OptiMelt automated melting point system available from Stanford Research Systems calibrated against vanillin (mp 83 °C), phenacetin (mp 136 °C) and caffeine (mp 237 °C).

Microanalysis was performed by Alan Dickerson at the Department of Chemistry, University of Cambridge. All reported values are within ±0.4% of the calculated value.

High resolution mass spectrometry (HRMS) was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive and negative electrospray ionisation. All reported values are within ±5 ppm of the calculated value.

LC-MS analysis was performed with 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 MeCN and H_2O containing 0.1% formic acid. The gradient run is

described in the following table. Rt is the retention time in minutes and the $^{m}/_{z}$ value is reported.

LC-MS solvent gradient:

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

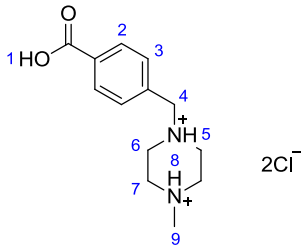
Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. The conc. $NH_{3(aq)}$ used was 18 M concentration. The PE used refers to the fraction boiling in the range 40-60 °C. Laboratory reagent grade solvents CH_2Cl_2, EtOAc, *n*-hexane, and PE were obtained from Fischer Scientific and distilled before use. Dry CH_2Cl_2 was obtained by distillation over CaH_2. THF was obtained from Fischer Scientific and distilled over $LiAlH_4$ and CaH_2 with triphenylmethane as an indicator. Microwave heating was carried out by using a Biotage AB Initiator.[1] The removal of solvent under reduced pressure was carried out on a Biotage AB V-10 evaporator[1] or rotary evaporator. TLC was performed on Merck 60 F254 silica gel plates and were visualised using short-wave ultra-violet light. Flash column chromatography was performed using silica gel (0.040 – 0.063 mm), purchased from Breckland Scientific Supplies. Preparative TLC was conducted using 20 × 20 cm Merck 60 F254 silica gel plates. Unless otherwise stated, the quoted purity is based on ^{1}H NMR.

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

Sources of equipment: Vapourtec R2+/R4 flow system: Vapourtec Ltd. (website: http://www.vapourtec.com). Gilson equipment and Unipoint (version 5.11) software: Gilson Inc. (website: http://www.gilson.com). Knauer K100 pump: Wissenschaftliche Gerätebau Dr. Ing. Herbert Knauer GmbH (website: http://www.knauer.net). Omnifit columns: Diba Industries Ltd. (website: http://www.omnifit.com).

Experimental Procedures

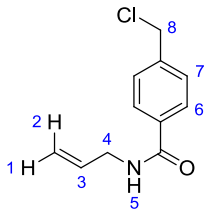
4-(4-Methylpiperazinomethyl)benzoic acid dihydrochloride 6.[2]



A solution of *N*-methylpiperazine (44 mL, 400 mmol) in EtOH (50 mL) was added portionwise to a solution of 4-(chloromethyl)benzoic acid (17.1 g, 100 mmol) in EtOH (200 mL) whilst stirring (rt). The mixture was heated under reflux (19 h), allowed to cool (rt) then the solvent removed *in vacuo*. The residue was partitioned between Et_2O (100 mL) and $NaOH_{(aq)}$ (1 M, 100 mL). The aqueous layer was separated, washed with Et_2O (3 × 100 mL) then acidified (pH 3) with $HCl_{(aq)}$ (10 M). The mixture was filtered under suction, washed with *i*-PrOH (250 mL), Et_2O (250 mL) and the solid dried *in vacuo* to yield the title compound hemihydrate (25.1 g, 79%, >95% purity) as an off-white powder.

mp 298 °C dec. (lit.[2] 310-312 °C). Rt 0.38, $[M + H]^+$ $^m/_z$ = 235.1. ^{1}H NMR (400 MHz, D_2O): δ/ppm = 8.04 (2 H, d, *J* = 8.2 Hz, H-2), 7.58 (2 H, d, *J* = 8.2 Hz, H-3), 4.46 (2 H, s, H-4), 3.59 (8 H, br s, H-6 and H-7), 2.95 (3 H, s, H-9). ^{13}C NMR (100 MHz, D_2O): δ/ppm = 169.91 (C), 132.84 (C), 131.93 (C), 131.65 (CH), 130.65 (CH), 59.68 (CH_2), 50.35 (CH_2), 48.51 (CH_2), 40.91 (CH_3). IR: ν_{max} = 2978 (w), 2359 (m), 1713 (s), 1615 (w), 1579 (w), 1466 (m), 1456 (m), 1420 (s), 1394 (m), 1311 (m), 1273 (m), 1229 (s), 1184 (m), 1175 (m), 1111 (s), 1078 (m), 1070 (m), 1056 (m), 1024 (s), 962 (m), 951 (s), 915 (m), 866 (m), 834 (m), 790 (m), 767 (m), 748 (s), 699 (s) cm^{-1}. HRMS calculated for $C_{13}H_{19}N_2O_2$, $[M + H]^+$, 235.1447; found 235.1438, Δ = -3.8 ppm.

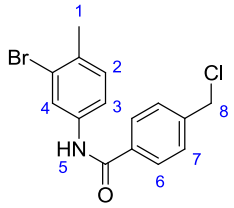
_N_-allyl-4-(chloromethyl)benzamide 7.



A solution (5 mL) of 4-(chloromethyl)benzoic acid (71.6 mg, 0.420 mmol), PyBrOP (206 mg, 0.440 mmol) and DIPEA (0.146 mL, 0.840 mmol) in dry DMF was left to stand (20 min, rt) then loaded into a 5 mL sample loop using a Vapourtec R2+. The sample loop was then switched in-line with a stream of dry DMF (0.1 mL/min) and directed into a 6.6 mm diameter Omnifit column packed with PS-HOBt (150 mg, 0.210 mmol) followed by a 100 psi BPR. After 1 h, the flow rate was increased to 0.8 mL/min for 15 min, then the column was then flushed with dry THF (0.8 mL/min, 15 min). A solution of allylamine (7.9 µL, 0.105 mmol) in dry THF (1 mL) was loaded into a 1 mL sample loop, switched in-line with a stream of dry THF (0.05 mL/min) flowing through the same column and the output collected. After 2 h, the flow rate was increased to 0.8 mL/min for 15 min. The solvent was removed *in vacuo* to give the title compound (12 mg, 55%, >90% purity) as a white solid.

Rt 3.99, $[M(^{35}Cl) + H]^+$ $^m/_z$ = 210.0. R_f 0.47 (1:1 PE/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 7.81 (2 H, d, *J* = 8.2 Hz, H-6), 7.49 (2 H, d, *J* = 8.2 Hz, H-7), 6.28 (1 H, s, H-5), 5.97 (1 H, ddt, *J* = 17.1, 10.2 and 5.7 Hz, H-3), 5.30 (1 H, dd, *J* = 17.1 and 1.3 Hz, H-2), 5.23 (1 H, dd, *J* = 10.2 and 1.3 Hz, H-1), 4.64 (2 H, s, H-8), 4.13 (2 H, t, *J* = 5.7 Hz, H-4). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 166.73 (C), 140.86 (C), 134.46 (C), 134.04 (CH), 128.74 (CH), 127.39 (CH), 116.84 (CH_2), 45.38 (CH_2), 42.48 (CH_2). IR: ν_{max} = 3279 (w), 3070 (w), 1635 (s), 1615 (m), 1573 (m), 1547 (s), 1507 (m), 1442 (w), 1418 (m), 1346 (w), 1327 (m), 1308 (s), 1265 (s), 1192 (w), 1154 (w), 1110 (w), 1036 (w), 1019 (w), 997 (m), 966 (m), 923 (m), 916 (m), 857 (m), 844 (m), 795 (m), 771 (m), 674 (s) cm^{-1}. HRMS calculated for $C_{11}H_{13}{}^{35}ClNO$, $[M + H]^+$, 210.0686; found 210.0689, Δ = 1.4 ppm.

***N*-(3-bromo-4-methylphenyl)-4-(chloromethyl)benzamide 9**.



Batch synthesis: To a solution of 4-(chloromethyl)benzoyl chloride (5.08 g, 26.9 mmol) in dry CH_2Cl_2 (70 mL) was added NEt_3 (4.12 mL, 29.5 mmol). A solution of 3-bromo-4-methylaniline (5.00 g, 26.9 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise over 15 min and the reaction mixture stirred overnight (rt). Water (100 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), the organic fractions combined and washed with water (2 × 100 mL), brine (100 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the title compound (7.76 g, 85%, >95% purity) as an off-white powder.

Solution phase flow synthesis: Using a Vapourtec R2+, a solution of 3-bromo-4-methylaniline (186 mg, 1.00 mmol) in dry CH_2Cl_2 (5 mL) was loaded into a 5 mL injection loop. A solution of 4-(chloromethyl)benzoyl chloride (189 mg, 1.00 mmol) and DIPEA (192 µL, 1.10 mmol) in dry CH_2Cl_2 (5 mL) was loaded into a second sample loop. The sample loops were switched in-line with streams of dry CH_2Cl_2 (0.2 mL/min each) simultaneously and injected into a T-piece followed by a 5 mL coil of tubing held at rt. The output was then directed into a 6.6 mm Omnifit column filled with a mixture of QP-DMA (1.5 g, 4.5 mmol) and QP-SA (1.5 g, 4.5 mmol) followed by a Gilson 170 UV DAD (340 nm monitor, 550 nm reference) and a 100 psi BPR. The output was collected whilst the UV absorption was positive and the solvent removed *in vacuo* to yield the title compound (226 mg, 67%, >95% purity) as an off-white powder.

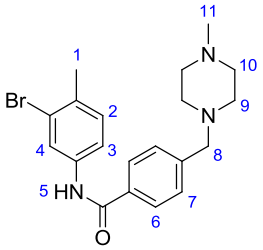
PS-DMAP supported flow synthesis: Using a Vapourtec R2+ a solution of 4-(chloromethyl)benzoyl chloride (57 mg, 0.30 mmol) in dry CH_2Cl_2 (1 mL) was loaded into a 1 mL sample loop. The sample loop was switched in-line with a stream of dry CH_2Cl_2 flowing at 0.1 mL/min into a 6.6 mm diameter Omnifit column filled with PS-DMAP (200 mg, 0.60 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 (37 mg, 0.20 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 loaded PS-DMAP column. The

output was directed through a Gilson 170 DAD (340 nm monitor, 550 nm reference) then a 100 psi BPR. The output was collected whilst the UV absorption was positive and the solvent removed *in vacuo* to yield the title compound (49 mg, 72%, >95% purity) as an off-white powder.

PS-DMAP supported flow synthesis with automated collection: The reaction was repeated as above, however the output was directed into a Gilson 233XL injector/fraction collector. The UV detector and fraction collector were controlled by Gilson Unipoint software. 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, otherwise direct the output to waste. 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% of the total output, was in the first fraction.

mp 155-158 °C. Calcd. for $C_{15}H_{13}BrClNO$: C 53.2 H 3.9 N 4.1, found: C 52.9 H 3.9 N 4.1. Rt 4.89, $[M(^{35}Cl/^{81}Br, ^{37}Cl/^{79}Br) + H]^+$ $^m/_z$ = 339.8. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 7.90 (1 H, d, *J* = 2.0 Hz, H-4), 7.85 (2 H, d, *J* = 8.1 Hz, H-6), 7.70 (1 H, s, H-5), 7.52 (2 H, d, *J* = 8.1 Hz, H-7), 7.48 (1 H, dd, *J* = 8.2 and 2.0 Hz, H-3), 7.23 (1 H, d, *J* = 8.2 Hz, H-2), 4.64 (2 H, s, H-8), 2.39 (3 H, s, H-1). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 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). IR: ν_{max} = 3275 (w), 1639 (s), 1612 (w), 1604 (w), 1579 (m), 1519 (m), 1499 (m), 1490 (m), 1441 (m), 1390 (m), 1376 (m), 1320 (m), 1308 (m), 1296 (m), 1280 (m), 1261 (m), 1205 (w), 1186 (w), 1147 (w), 1118 (w), 1108 (w), 1038 (m), 1019 (w), 995 (w), 973 (w), 921 (m), 876 (w), 861 (w), 854 (m), 842 (m), 804 (m), 763 (m), 711 (m), 668 (s) cm^{-1}. HRMS calculated for $C_{15}H_{14}{}^{79}Br^{35}ClNO$, $[M + H]^+$, 337.9947; found 337.9947, Δ = 0.0 ppm.

_N_-(3-bromo-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 4.[3]



Batch synthesis: To a solution of **9** (1.18 g, 3.47 mmol) and *N*-methylpiperazine (0.577 mL, 5.20 mmol) in DMF (30 mL) was added potassium carbonate (0.959 g, 6.94 mmol) and the reaction mixture stirred overnight (rt). The reaction mixture was poured into water (500 mL), stirred (5 min) and the slurry filtered under suction. The solid was washed with water (2 × 50 mL), diethyl ether (50 mL) and dried *in vacuo* to give the title compound (1.12 g, 80%, >95% purity) as a white powder.

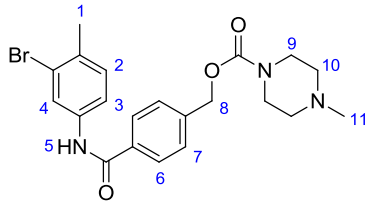
Flow synthesis, single step: A solution (5 mL) of **9** (53 mg, 0.16 mmol) and *N*-methylpiperazine (35 µL, 0.31 mmol) in 1:1 CH_2Cl_2/DMF was loaded into a 5 mL sample loop. The sample loop was switched in-line with a stream of 1:1 CH_2Cl_2/DMF, pumped at 0.05 mL/min using a Gilson 307 pump, by using a switching valve. The flow stream was then directed into a 6.6 mm diameter Omnifit column containing PS-TBD (324 mg, 0.94 mmol) heated to 80 °C using a Vapourtec R4 heating unit. The stream was then directed into a 6.6 mm diameter Omnifit column containing PS-NCO (307 mg, 0.47 mmol) followed by a 6.6 mm diameter Omnifit column packed with QP-SA (313 mg, 0.94 mmol) and a BPR (100 psi). Using a Vapourtec R2+, MeOH was then pumped through the QP-SA column followed by a 100 psi BPR at 0.5 mL/min for 30 min. A sample loop (5 mL) was then filled with 2 M NH_3 in MeOH and switched in-line with the MeOH stream (0.5 mL/min). The output was collected for 30 min and the solvent removed *in vacuo* to give the title compound (35 mg, 55%, >95% purity) as a white solid.

Two-step flow synthesis: The first fraction (4 mL) of the solution of **9** (40 mg, 0.118 mmol) in CH_2Cl_2 formed in the previously flow step was set to collect into a tapered 20 mL vial with a screw-top septum containing a solution (4 mL) of *N*-methylpiperazine (26 µL, 0.236 mmol) in DMF. A PTFE 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 through the solution for a further 30 min. Using Gilson Unipoint software, the injector was set to aspirate air (100 µL), followed by the reaction solution (5 mL) into a sample loop (20 mL) using a Gilson 402 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, 35 mmol) and a layer of SiO_2 (300 mg) and then a further 6.6 mm diameter Omnifit column packed with PS-NCO (270 mg, 0.35 mmol). The output of this column was then directed through a 3.0 mm diameter Omnifit column packed with SS-SA (250 mg, 0.2 mmol) and then a 100 psi BPR before directing the output to waste. After 1.5 h, a stream of MeOH, pumped at 0.4 mL/min using a Knauer K100 pump was directed through the column followed by a 100 psi BPR for 10 min. A sample loop (1 mL) filled with NH_3 in MeOH (2.0 M) was then switched in-line into the stream of MeOH (0.1 mL/min) flowing through the column to release the product. This was repeated with further NH_3 in MeOH (2.0 M, 1 mL), then the solvent of the reactor output was removed *in vacuo* to yield the title compound (38 mg, 47% over 2 steps, >95% purity) as a white solid.

mp 138-141 °C. Rt 4.04, $[M(^{81}Br) + H]^+$ $^m/_z$ = 404.0. ^{1}H NMR (600 MHz, d_6-DMSO): δ/ppm = 10.24 (1 H, s, H-5), 8.10 (1 H, d, J = 1.7 Hz, H-4), 7.88 (2 H, d, J = 8.1 Hz, H-6), 7.64 (1 H, dd, J = 8.3 and 1.7 Hz, H-3), 7.42 (2 H, d, J = 8.1 Hz, H-7), 7.30 (1 H, d, J = 8.3 Hz, H-2), 3.51 (2 H, s, H-8), 2.31 (8 H, br s, H-9 and H-10), 2.30 (3 H, s, H-1), 2.13 (3 H, s, H-11). ^{13}C NMR (150 MHz, d_6-DMSO): δ/ppm = 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). IR: ν_{max} = 3287 (w), 2936 (w), 2877 (w), 2798 (m), 2160 (w), 1647 (m), 1589 (m), 1524 (m), 1493 (s), 1456 (m), 1415 (w), 1375 (m), 1350 (m), 1303 (s), 1281 (m), 1256 (m), 1205 (w), 1162 (m), 1139 (m), 1105 (m), 1088 (m), 1079 (m), 1036 (m), 1011 (s), 923 (m), 856 (m), 813 (s), 784 (m), 766 (m), 748 (s), 691 (m), 677 (s) cm^{-1}. HRMS calculated for $C_{20}H_{25}{}^{79}BrN_3O$, $[M + H]^+$, 402.1181; found 402.1169, Δ = -3.0 ppm.

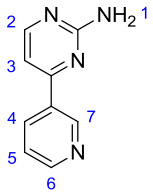
4-((3-Bromo-4-methylphenyl)carbamoyl)benzyl-4-methylpiperazine-1-carboxylate 10.



A solution of **9** (40 mg, 0.118 mmol) and *N*-methylpiperazine (26 µL, 0.236 mmol) in DMF (4 mL) was loaded into a sample loop (10 mL) and switched in-line into a stream of DMF, pumped at 0.1 mL/min with a Gilson 307 pump. The stream was directed through a 6.6 mm Omnifit column filled with K_2CO_3 (5.2 g, 37.6 mmol) and heated to 80 °C using a Vapourtec R4 column heater, followed by a 100 psi BPR. The output was then collected and passed through a 6 mL Biotage Isolute SCX-2 column[4] which was then washed with MeOH (20 mL). A solution of NH_3 in MeOH (2.0 M, 3 mL) was then passed through the column, the output collected and the solvent removed *in vacuo*. The residue was then purified by column chromatography using a Varian silica column (10 g) and eluting with MeOH to give the title compound (5 mg, 9%, >95% purity) as a pale yellow oil.

Rt 3.79, $[M(^{81}Br) + H]^+$ $^m/_z$ = 448.2. R_f 0.49 (MeOH). ^1H NMR (600 MHz, $CDCl_3$): δ/ppm = 7.89 (1 H, d, *J* = 1.9 Hz, H-4), 7.84 (2 H, d, *J* = 8.1 Hz, H-6), 7.81 (1 H, s, H-5), 7.48 (1 H, dd, *J* = 8.2 and 1.9 Hz, H-3), 7.45 (2 H, d, *J* = 8.2 Hz, H-7), 7.21 (1 H, d, *J* = 8.2 Hz, H-2), 5.19 (2 H, s, H-8), 3.54 (4 H, s, H-9), 2.38 (7 H, s, H-10 and H-11), 2.31 (3 H, s, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm = 165.19 (C), 154.94 (C), 140.93 (C), 136.65 (C), 134.22 (C), 134.04 (C), 130.85 (CH), 127.91 (CH), 127.25 (CH), 124.83 (C), 123.85 (CH), 119.10 (CH), 66.29 (CH_2), 54.66 (CH_2), 46.13 (CH_3), 43.76 (CH_2), 22.30 (CH_3). IR: ν_{max} = 3302 (w), 2940 (w), 2795 (w), 1673 (m), 1589 (m), 1525 (m), 1504 (m), 1493 (m), 1459 (m), 1436 (m), 1376 (m), 1360 (w), 1292 (s), 1258 (m), 1234 (s), 1176 (w), 1148 (m), 1104 (m), 1072 (m), 1052 (w), 1035 (m), 1018 (m), 1003 (m), 910 (w), 872 (m), 817 (m), 763 (m), 729 (s), 692 (m), 677 (m) cm^{-1}. HRMS calculated for $C_{21}H_{25}{}^{79}BrN_3O_3$, $[M + H]^+$, 446.1079; found 446.1095, Δ = 3.6 ppm.

4-(Pyridin-3-yl)pyrimidin-2-amine 5.[5]



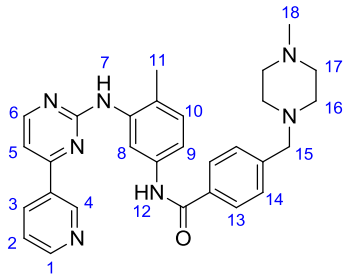
Based on a literature procedure.[6]

To a solution of 3-acetylpyridine (13.8 mL, 125 mmol) in xylene (35 mL) was added DMF-DMA (20.0 mL, 151 mmol) and the solution heated under reflux (16 h). The solution was concentrated *in vacuo* and *n*-hexane (20 mL) added. The mixture was filtered under suction, the residue washed with further *n*-hexane (4 × 20 mL) and dried *in vacuo*. Recrystallisation of the residue from CH_2Cl_2/*n*-hexane gave (*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (19.2 g, 87%) as orange/yellow crystals.

To a mixture of (*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (5.00 g, 28.4 mmol) and guanidine nitrate (3.81 g, 31.2 mmol) in *n*-butanol (40 mL) was added sodium hydroxide (1.25 g, 31.2 mmol) and the mixture heated under reflux (24 h). The slurry was cooled to room temperature, concentrated *in vacuo* and filtered under suction. The residue was washed with water (100 mL) and dried *in vacuo* to give the title compound (4.49 g, 92%, >95% purity) as cream crystals.

mp 188-189 °C (lit.[6] 189-191 °C). Calcd. for $C_9H_9N_4$: C 62.8 H 4.7 N 32.5, found: C 62.5 H 4.6 N 32.5. Rt 0.40, $[M + H]^+$ $^m/_z$ = 173.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 9.22 (1 H, d, *J* = 1.9 Hz, H-7), 8.63 (1 H, dd, *J* = 5.1 and 1.7 Hz, H-6), 8.48 (1 H, ddd, *J* = 8.1, 1.9 and 1.7 Hz, H-4), 8.33 (1 H, d, *J* = 5.3 Hz, H-2), 7.55 (1 H, dd, *J* = 8.1 and 5.1 Hz, H-5), 7.19 (1 H, d, *J* = 5.3 Hz, H-3), 3.30 (2 H, s, H-1). ^{13}C NMR (100 MHz, d_6-DMSO): δ/ppm = 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). IR: ν_{max} = 1576 (m), 1552 (s), 1472 (s), 1434 (m), 1411 (m), 1344 (m), 1294 (m), 1192 (m), 1021 (m), 907 (w), 829 (w), 797 (s), 752 (m), 714 (s), 655 (s) cm^{-1}. HRMS calculated for $C_9H_9N_4$, $[M + H]^+$, 173.0822; found 173.0828, Δ = 3.5 ppm.

***N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 1**.[7]



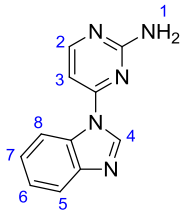
Batch synthesis: To a mixture of **4** (40 mg, 0.10 mmol), **5** (19 mg, 0.11 mmol) and NaO*t*-Bu (13 mg, 0.14 mmol) in 2:1 1,4-dioxane/*t*-BuOH (2:1, 1 mL) was added XantPhos (6 mg, 10 µmol) and $Pd_2(dba)_3$ (5 mg, 5 µmol). The mixture was heated (MW, 150 °C, 30 min) and then the solvent removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and water (10 mL) and extracted with further CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by column chromatography using a 5 g Varian silica column and MeOH as the eluent. The product fractions were combined, the solvent removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL). The mixture was filtered and the solvent removed *in vacuo* to give the title compound (28 mg, 57%, >95% purity) as a pale yellow solid.

Flow synthesis: Using a Knauer K100 pump, the column of SS-SA containing sequestered **4** (38 mg, 0.094 mmol) from the flow synthesis of **4** was washed with 1,4-dioxane/*t*-BuOH (2:1, 0.4 mL/min, 15 min). A solution (2.5 mL) of DBU (28 µL, 0.189 mmol) in 1,4-dioxane/*t*-BuOH (2:1) was loaded into a 5 mL sample loop and injected into the stream of 1,4-dioxane/*t*-BuOH (2:1) flowing through the column of SS-SA at 0.15 mL/min. A second solution (5 mL) of **5** (65 mg, 0.378 mmol), NaO*t*-Bu (36 mg, 0.378 mmol) and **11** (7.5 mg, 9.4 µmol) in 1,4-dioxane/*t*-BuOH (2:1) was sonicated (10 min) and loaded into a 5 mL sample loop. This was injected into a stream of 1,4-dioxane/*t*-BuOH (2:1, pumped at 0.15 mL/min by a second Knauer K100 pump) 10 min after the injection of the DBU solution. The two streams were combined in a T-piece after the column of SS-SA and directed into a flow coil (10 mL) heated to 150 °C using a Vapourtec R4 heater. 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[4] (25 g SNAP cartridge) 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 the title compound (32 mg, 69%, >95% purity) as an off-white powder.

mp 206-207 °C (lit.[6] 207-210 °C). Rt 3.48, $[M + H]^+$ $^m/_z$ = 494.2. R_f 0.09 (MeOH). ^{1}H NMR (600 MHz, d_6-DMSO): δ/ppm = 10.14 (1 H, s, H-12), 9.26 (1 H, d, *J* = 1.5 Hz, H-4), 8.95 (1 H, s, H-7), 8.66 (1 H, dd, *J* = 4.8 and 1.2 Hz, H-1), 8.49 (1 H, d, *J* = 5.1 Hz, H-6), 8.46 (1 H, ddd, *J* = 7.9, 1.5 and 1.2 Hz, H-3), 8.06 (1 H, d, *J* = 1.5 Hz, H-8), 7.89 (2 H, d, *J* = 8.1 Hz, H-13), 7.50 (1 H, dd, *J* = 7.9 and 4.8 Hz, H-2), 7.46 (1 H, dd, *J* = 8.3 and 1.5 Hz, H-9), 7.42-7.40 (3 H, m, H-5 and H-14), 7.18 (1 H, d, *J* = 8.3 Hz, H-10), 3.51 (2 H, s, H-15), 2.30 (8 H, br s, H-16 and H-17), 2.20 (3 H, s, H-11), 2.13 (3 H, s, H-18). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 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). IR: ν_{max} = 3275 (w), 2929 (w), 2797 (w), 1646 (m), 1586 (m), 1575 (s), 1554 (m), 1532 (s), 1510 (m), 1478 (m), 1449 (s), 1417 (m), 1378 (m), 1352 (m), 1335 (m), 1326 (m), 1309 (m), 1290 (s), 1261 (m), 1204 (m), 1164 (m), 1142 (m), 1125 (w), 1103 (m), 1089 (w), 1052 (w), 1024 (w), 1010 (m), 993 (w), 968 (w), 925 (w), 886 (w), 858 (w), 850 (w), 808 (m), 796 (s), 748 (m), 703 (m), 690 (m), 671 (m) cm^{-1}. HRMS calculated for $C_{29}H_{31}N_7ONa$, $[M + Na]^+$, 516.2488; found 516.2491, Δ = 0.8 ppm.

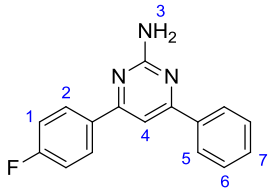
4-(1*H*-benzo[*d*]imidazol-1-yl)pyrimidin-2-amine 23.



To a solution of NH_3 in *i*-PrOH (2.0 M, 15 mL) was added 1-(2-chloropyrimidin-4-yl)-1*H*-benzo[*d*]imidazole (1.04 g, 4.50 mmol) and the mixture heated (MW, 140 °C, 2 h). The solvent was removed *in vacuo*, the residue washed with water (100 mL), Et_2O (30 mL), PE (30 mL) and dried *in vacuo* to give the title compound (0.81 g, 85%, >95% purity) as a colourless powder.

mp 188-190 °C. Calcd. for $C_{11}H_9N_5$: C 62.6 H 4.3 N 33.2, found: C 62.2 H 4.3 N 32.9. Rt 2.92, $[M + H]^+$ $^m/_z$ = 213.0. ^{1}H NMR (600 MHz, d_6-DMSO): δ/ppm = 9.04 (1 H, s, H-4), 8.64 (1 H, d, *J* = 7.9 Hz, H-8), 8.36 (1 H, d, *J* = 5.4 Hz, H-2), 7.76 (1 H, d, *J* = 7.6 Hz, H-5), 7.40-7.33 (2 H, m, H-6 and H-7), 7.14 (1 H, d, *J* = 5.4 Hz, H-3), 7.06 (2 H, s, H-1). ^{13}C NMR (150 MHz, d_6-DMSO): δ/ppm = 163.42 (C), 160.24 (CH), 156.80 (C), 144.21 (C), 141.86 (CH), 131.47 (C), 124.06 (CH), 123.39 (CH), 119.72 (CH), 115.96 (CH), 97.65 (CH). IR: ν_{max} = 3427 (w), 3301 (w), 3134 (m), 1675 (m), 1647 (m), 1597 (m), 1579 (m), 1559 (s), 1492 (m), 1466 (m), 1445 (s), 1372 (m), 1359 (m), 1337 (m), 1324 (m), 1305 (m), 1287 (m), 1236 (s), 1207 (s), 1158 (m), 1132 (m), 1108 (m), 1081 (m), 1028 (m), 1010 (m), 987 (m), 974 (w), 939 (w), 902 (m), 890 (m), 857 (w), 844 (w), 793 (m), 783 (m), 766 (m), 760 (m), 746 (m), 733 (s), 714 (s) cm^{-1}. HRMS calculated for $C_{11}H_{10}N_5$, $[M + H]^+$, 212.0936; found 212.0939, Δ = 1.4 ppm.

4-(4-Fluorophenyl)-6-phenylpyrimidin-2-amine 24.[8]



Based on a literature procedure.[9]

To a mixture of 4-fluorobenzylideneacetophenone[10] (1.48 g, 6.54 mmol), guanidine hydrochloride (0.94 g, 9.81 mmol) and NaOH (1.18 g, 29.4 mmol) was added water (200 µL) and the mixture heated (MW, 180 °C, 15 min). Water (15 mL) was added, the mixture filtered under suction and the residue washed with water (50 mL). The solid was purified by chromatography (1:4 EtOAc/PE) to give the title compound (0.69 g, 40%) as a pale yellow powder.

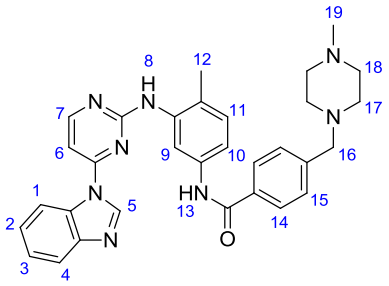
mp 132-133 °C (lit.[9] 132-133 °C). Rt 4.60, $[M + H]^+$ $^m/_z$ = 266.1. R_f 0.23 (1:4 EtOAc/PE). ^{1}H NMR (600 MHz, d_6-DMSO): δ/ppm = 8.29 (2 H, dd, *J* = 8.8 and 5.7 Hz, H-2), 8.23-8.21 (2 H, m, H-5), 7.72 (1 H, s, H-4), 7.53-7.51 (3 H, m, H-6 and H-7), 7.35 (2 H, app t, *J* = 8.8 Hz, H-1), 6.76 (2 H, s, H-3). ^{13}C NMR (150 MHz, d_6-DMSO): δ/ppm = 164.85 (C), 163.85 (C), 163.63 (C), 163.52 (C, d, *J* = 247.6 Hz), 137.19 (C), 133.70 (C, d, *J* = 2.8 Hz), 130.35 (CH), 129.22 (CH, d, *J* = 8.5 Hz), 128.48 (CH), 126.88 (CH), 115.38 (CH, d, *J* = 21.5 Hz), 101.52 (CH). IR: ν_{max} = 3496 (w), 3326 (w), 3207 (w), 3049 (w), 1635 (s), 1604 (m), 1587 (m), 1568 (s), 1542 (s), 1509 (s), 1497 (s), 1459 (m), 1450 (m), 1432 (m), 1406 (w), 1358 (s), 1297 (w), 1220 (s), 1184 (w), 1157 (m), 1128 (w), 1097 (m), 1073 (w), 1030 (w), 1016 (m), 1002 (w), 992 (w), 966 (w), 944 (w), 924 (w), 869 (w), 844 (m), 817 (s), 793 (m), 761 (s), 727 (m), 694 (s), 679 (s) cm^{-1}. HRMS calculated for $C_{16}H_{13}FN_3$, $[M + H]^+$, 266.1094; found 266.1093, Δ = -0.4 ppm.

General Procedure: Synthesis of imatinib analogues

Using a Vapourtec R2+, a solution of an aniline (0.20 mmol) in dry CH_2Cl_2 (1 mL) was loaded into a 1 mL injection loop. A solution of 4-(chloromethyl)benzoyl chloride (0.20 mmol) and DIPEA (38 µL, 0.22 mmol) in dry CH_2Cl_2 (1 mL) was loaded into a second sample loop. The sample loops were switched in-line with streams of dry CH_2Cl_2 (0.2 mL/min each) simultaneously, mixed in a T-piece and the mixed stream flowed into a 10 mL coil of tubing held at rt. The output was then directed into a 6.6 mm Omnifit column filled with sequential layers of QP-DMA (200 mg, 0.6 mmol), QP-SA (200 mg, 0.6 mmol) and SiO_2 (350 mg). The stream was then directed through a Gilson 170 UV DAD (340 nm monitor, 550 nm reference), a 100 psi BPR then into a Gilson 233XL fraction collector/autosampler. The UV detector and fraction collector were controlled by Gilson Unipoint software. The fraction collector was set to collect the output of the reaction when the UV absorption was over 7.5% of the full scale into a tapered 20 mL vial with a screw-top septum containing a solution (4 mL) of an amine (0.32 mmol) in DMF. A PTFE 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 with nitrogen bubbling through the solution for a further 30 min (50 °C). Using Gilson Unipoint software, the injector was set to aspirate air (100 µL), followed by the reaction solution (5 mL) into a sample loop (20 mL) using a Gilson 402 syringe pump. This was 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, 35 mmol) and a layer of SiO_2 (300 mg) and a further 6.6 mm diameter Omnifit column packed with PS-NCO (369 mg, 0.48 mmol). The output of this column was directed through a 3.0 mm diameter Omnifit column packed with SS-SA (250 mg, 0.20 mmol) and then a 100 psi BPR before directing the output to waste. After 1.5 h, the column was washed with 1,4-dioxane/*t*-BuOH (2:1, 0.4 mL/min, 15 min) using a Knauer K100 pump. A solution (2.5 mL) of DBU (30 µL, 0.20 mmol) in 1,4-dioxane/*t*-BuOH (2:1) was loaded into a 5 mL sample loop and injected into the stream of 1,4-dioxane/*t*-BuOH (2:1) flowing through the column of SS-SA at 0.15 mL/min. A second solution (5 mL) of an aryl amine (0.40 mmol), NaO*t*-Bu (38 mg, 0.40 mmol) and **11** (8 mg, 10 µmol) in 1,4-dioxane/*t*-BuOH (2:1) was sonicated (10 min) and loaded into a 5 mL sample

loop. This was injected into a stream of 1,4-dioxane/*t*-BuOH (2:1, pumped at 0.15 mL/min by a second Knauer K100 pump) 10 min after the injection of the DBU solution. The two streams were combined in a T-piece after the column of SS-SA and directed into a flow coil (10 mL) heated to 150 °C using a Vapourtec R4 heater. 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 solution was then concentrated *in vacuo* and the residue partitioned between CH_2Cl_2 (25 mL) and water (25 mL). The aqueous layer was extracted with further CH_2Cl_2 (3 × 10 mL), the organic layers combined and washed with water (30 mL), brine (30 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by chromatography with the specified solvent system.

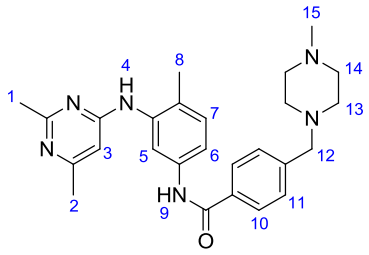
***N*-(3-((4-(1*H*-benzo[*d*]imidazol-1-yl)pyrimidin-2-yl)amino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 14**.



Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), *N*-methylpiperazine (35 µL, 0.32 mmol) and **23** (84 mg, 0.40 mmol). Purified by column chromatography (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$) to give the title compound (29 mg, 27%, >95% purity) as an off-white powder.

mp 204-207 °C. Rt 3.62, $[M + H]^+$ $^m/_z$ = 533.3. R_f 0.28 (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 8.65 (1 H, s, H-5), 8.47 (1 H, d, *J* = 5.2 Hz, H-7), 8.32 (1 H, s, H-9), 8.10 (1 H, s, H-13), 8.05 (1 H, m, H-1), 7.79-7.75 (3 H, m, H-4 and H-14), 7.49 (1 H, d, *J* = 8.0 Hz, H-10), 7.37 (2 H, d, *J* = 7.9 Hz, H-15), 7.27-7.25 (2 H, m, H-2 and H-3), 7.23 (1 H, d, *J* = 8.0 Hz, H-11), 7.19 (1 H, s, H-8), 6.91 (1 H, d, *J* = 5.2 Hz, H-6), 3.53 (2 H, s, H-16), 2.51 (8 H, br s, H-17 and H-18), 2.33 (3 H, s, H-19), 2.32 (3 H, s, H-12). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.55 (C), 160.65 (C), 160.32 (CH), 156.65 (C), 144.88 (C), 142.62 (C), 140.98 (CH), 137.04 (C), 136.72 (C), 133.62 (C), 131.60 (C), 130.97 (CH), 129.93 (CH), 127.04 (CH), 125.62 (C), 124.65 (CH), 123.89 (CH), 120.78 (CH), 116.39 (CH), 114.57 (CH), 114.26 (CH), 100.13 (CH), 62.48 (CH_2), 55.09 (CH_2), 53.12 (CH_2), 46.02 (CH_3), 17.60 (CH_3). IR: ν_{max} = 3203 (w), 2931 (w), 2794 (w), 1664 (w), 1593 (m), 1568 (m), 1528 (m), 1493 (m), 1440 (s), 1416 (s), 1363 (m), 1332 (w), 1307 (m), 1277 (m), 1254 (m), 1238 (m), 1223 (m), 1203 (m), 1182 (m), 1162 (m), 1139 (m), 1105 (m), 1052 (w), 1011 (m), 986 (w), 919 (w), 893 (w), 857 (w), 806 (m), 780 (m), 764 (m), 738 (s), 707 (m) cm^{-1}. HRMS calculated for $C_{31}H_{33}N_8O$, $[M + H]^+$, 533.2777; found 533.2792, Δ = 2.8 ppm.

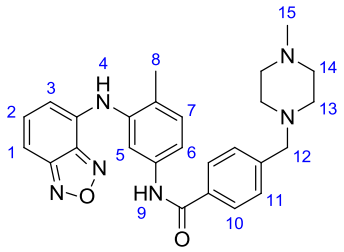
_N_-(3-((2,6-dimethylpyrimidin-4-yl)amino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 15.



Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), *N*-methylpiperazine (35 µL, 0.32 mmol) and 2,6-dimethylpyrimidin-4-amine (49 mg, 0.40 mmol). Purified by column chromatography (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$) to give the title compound (29 mg, 33%, >95% purity) as an off-white powder.

mp 170-174 °C dec. Rt 3.08, $[M + H]^+$ $^m/_z$ = 445.3. R_f 0.22 (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 8.13 (1 H, s, H-9), 7.80 (2 H, d, *J* = 8.0 Hz, H-10), 7.68 (1 H, d, *J* = 1.5 Hz, H-5), 7.41 (3 H, m, H-6 and H-11), 7.23 (1 H, d, *J* = 8.2 Hz, H-7), 6.79 (1 H, s, H-4), 6.18 (1 H, s, H-3), 3.54 (2 H, s, H-12), 2.47 (3 H, s, H-1), 2.46 (8 H, br s, H-13 and H-14), 2.29 (3 H, s, H-15), 2.27 (3 H, s, H-2), 2.21 (3 H, s, H-8). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm = 167.40 (C), 166.49 (C), 165.49 (C), 161.63 (C), 142.51 (C), 136.72 (C), 136.66 (C), 133.61 (C), 131.52 (CH), 129.36 (CH), 128.96 (C), 127.03 (CH), 117.86 (CH), 116.86 (CH), 99.22 (CH), 62.26 (CH_2), 54.83 (CH_2), 52.45 (CH_2), 45.56 (CH_3), 25.80 (CH_3), 24.20 (CH_3), 17.47 (CH_3). IR: ν_{max} = 3196 (w), 2939 (w), 2798 (w), 1649 (w), 1586 (s), 1527 (m), 1505 (m), 1443 (m), 1412 (m), 1369 (m), 1350 (w), 1307 (m), 1282 (m), 1268 (m), 1190 (w), 1163 (m), 1137 (m), 1108 (w), 1034 (w), 1011 (m), 985 (m), 908 (m), 814 (m), 766 (w), 727 (s) cm^{-1}. HRMS calculated for $C_{26}H_{33}N_6O$, $[M + H]^+$, 445.2716; found 445.2729, Δ = 2.9 ppm.

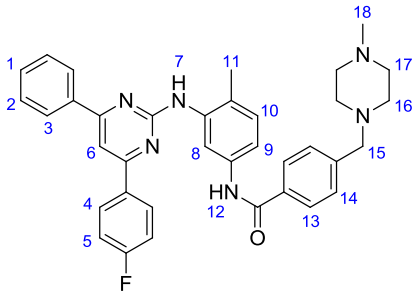
_N_-(3-(benzo[_c_][1,2,5]oxadiazol-4-ylamino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 16.



Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), *N*-methylpiperazine (35 µL, 0.32 mmol) and 2,1,3-benzoxadiazol-4-amine (54 mg, 0.40 mmol). Purified by column chromatography (85:15 CH_2Cl_2/MeOH) to give the title compound (28 mg, 31%, >95% purity) as a bright orange solid.

mp 113-117 °C. Rt 4.00, $[M + H]^+$ $^m/_z$ = 457.3. R_f 0.31 (85:15 CH_2Cl_2/MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 7.94 (1 H, s, H-5), 7.91 (1 H, s, H-9), 7.80 (2 H, d, *J* = 8.1 Hz, H-10), 7.43 (2 H, d, *J* = 8.1 Hz, H-11), 7.26-7.23 (3 H, m, H-2, H-6 and H-7), 7.15 (1 H, d, *J* = 8.9 Hz, H-1), 6.59 (1 H, d, *J* = 7.2 Hz, H-3), 6.53 (1 H, s, H-4), 3.55 (2 H, s, H-12), 2.47 (8 H, br s, H-13 and H-14), 2.29 (6 H, s, H-8 and H-15). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.63 (C), 150.06 (C), 145.27 (C), 142.84 (C), 138.07 (C), 136.85 (C), 133.82 (CH), 133.49 (C), 133.02 (C), 131.57 (CH), 129.35 (CH), 127.47 (C), 126.98 (CH), 116.65 (CH), 114.94 (CH), 104.84 (CH), 104.36 (CH), 62.46 (CH_2), 55.07 (CH_2), 53.08 (CH_2), 45.99 (CH_3), 17.32 (CH_3). IR: ν_{max} = 3295 (w), 2935 (w), 2801 (w), 1650 (m), 1599 (m), 1561 (s), 1528 (s), 1508 (m), 1436 (s), 1405 (m), 1349 (m), 1302 (m), 1288 (m), 1191 (w), 1163 (m), 1136 (m), 1051 (w), 1009 (s), 924 (w), 889 (m), 870 (m), 814 (m), 786 (m), 731 (s), 697 (m) cm^{-1}. HRMS calculated for $C_{26}H_{29}N_6O_2$, $[M + H]^+$, 457.2352; found 457.2363, Δ = 2.4 ppm.

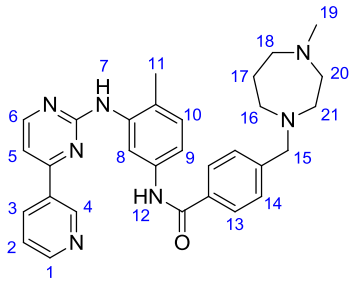
***N*-(3-((4-(4-fluorophenyl)-6-phenylpyrimidin-2-yl)amino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 17**.



Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), *N*-methylpiperazine (35 µL, 0.32 mmol) and **24** (106 mg, 0.40 mmol). Purified by column chromatography (9:1 CH_2Cl_2/MeOH) to give the title compound (30 mg, 26%, >95% purity) as a pale yellow powder.

mp 228-231 °C dec. Rt 4.35, $[M + H]^+$ $^m/_z$ = 587.3. R_f 0.28 (9:1 CH_2Cl_2/MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 8.87 (1 H, d, *J* = 1.5 Hz, H-8), 8.21 (2 H, dd, *J* = 8.6 and 5.4 Hz, H-4), 8.17-8.16 (2 H, m, H-3), 7.85 (1 H, s, H-12), 7.84 (2 H, d, *J* = 8.0 Hz, H-13), 7.54 (1 H, s, H-6), 7.51-7.50 (3 H, m, H-1 and H-2), 7.45 (2 H, d, *J* = 8.0 Hz, H-14), 7.25 (1 H, dd, *J* = 8.2 and 1.5 Hz, H-9), 7.19-7.15 (3 H, m, H-5 and H-10), 7.09 (1 H, s, H-7), 3.58 (2 H, s, H-15), 2.53 (8 H, br s, H-16 and H-17), 2.37 (3 H, s, H-11), 2.33 (3 H, s, H-18). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.96 (C), 165.14 (C), 164.69 (C), 164.46 (C, d, *J* = 250.6 Hz), 160.52 (C), 142.42 (C), 138.40 (C), 137.48 (C), 136.51 (C), 133.98 (C), 133.65 (C, d, *J* = 3.2 Hz), 130.67 (CH), 130.58 (CH), 129.41 (CH, d, *J* = 8.5 Hz), 129.31 (CH), 128.79 (CH), 127.27 (CH), 126.95 (CH), 123.26 (C), 115.75 (CH, d, *J* = 22 Hz), 114.41 (CH), 112.52 (CH), 104.36 (CH), 62.43 (CH_2), 54.99 (CH_2), 52.86 (CH_2), 45.81 (CH_3), 17.72 (CH_3). IR: ν_{max} = 3454 (w), 3437 (w), 3299 (w), 2933 (w), 2794 (w), 1645 (m), 1600 (m), 1588 (m), 1575 (m), 1531 (s), 1511 (m), 1486 (m), 1445 (s), 1426 (m), 1409 (m), 1364 (m), 1349 (s), 1308 (m), 1291 (m), 1254 (m), 1227 (m), 1180 (w), 1166 (m), 1155 (m), 1128 (w), 1102 (w), 1077 (w), 1054 (w), 1031 (w), 1012 (m), 990 (w), 948 (w), 924 (w), 901 (w), 869 (w), 847 (m), 823 (m), 800 (m), 787 (w), 766 (s), 750 (m), 725 (w), 714 (w), 686 (m) cm^{-1}. HRMS calculated for $C_{36}H_{36}FN_6O$, $[M + H]^+$, 587.2935; found 587.2937, Δ = 0.3 ppm.

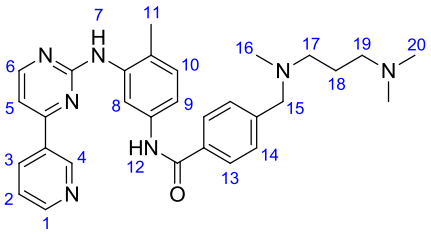
4-((4-Methyl-1,4-diazepan-1-yl)methyl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)benzamide 18.[11]



Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), *N*-methylhomopiperazine (40 µL, 0.32 mmol) and **5** (69 mg, 0.40 mmol). Purified by preparative TLC (89:10:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$) to give the title compound (25 mg, 25%, >95% purity) as an off-white solid.

mp 155-160 °C dec. Rt 3.43, $[M + H]^+$ $^m/_z$ = 508.3. R_f 0.17 (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.23 (1 H, d, *J* = 1.8 Hz, H-4), 8.70 (1 H, dd, *J* = 4.8 and 1.5 Hz, H-1), 8.58 (1 H, d, *J* = 1.5 Hz, H-8), 8.52-8.50 (2 H, m, H-3 and H-6), 7.93 (1 H, s, H-12), 7.83 (2 H, d, *J* = 8.0 Hz, H-13), 7.46 (2 H, d, *J* = 8.0 Hz, H-14), 7.41 (1 H, dd, *J* = 7.8 and 4.8 Hz, H-2), 7.31 (1 H, dd, *J* = 8.2 and 1.5 Hz, H-9), 7.20 (1 H, d, *J* = 8.2 Hz, H-10), 7.17 (1 H, d, *J* = 5.2 Hz, H-5), 7.04 (1 H, s, H-7), 3.69 (2 H, s, H-15), 2.73-2.69 (4 H, m, H-16 and H-21), 2.68 (2 H, t, *J* = 5.8 Hz, H-18), 2.62 (2 H, m, H-20), 2.37 (3 H, s, H-19), 2.34 (3 H, s, H-11), 1.82 (2 H, app quintet, *J* = 5.8 Hz, H-17). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.45 (C), 162.73 (C), 160.58 (C), 159.01 (CH), 151.47 (CH), 148.50 (CH), 143.97 (C), 137.78 (C), 136.62 (C), 134.92 (CH), 133.71 (C), 132.67 (C), 130.76 (CH), 128.97 (CH), 126.97 (CH), 124.17 (C), 123.71 (CH), 115.30 (CH), 113.13 (CH), 108.33 (CH), 62.45 (CH_2), 58.17 (CH_2), 56.76 (CH_2), 54.72 (CH_2), 54.34 (CH_2), 47.04 (CH_3), 27.54 (CH_2), 17.65 (CH_3). IR: ν_{max} = 3235 (w), 3032 (w), 2929 (w), 2800 (w), 1652 (m), 1575 (s), 1553 (s), 1526 (s), 1504 (s), 1478 (m), 1447 (s), 1415 (s), 1288 (s), 1253 (m), 1204 (m), 1127 (m), 1041 (m), 1020 (m), 1005 (m), 989 (m), 851 (m), 798 (s), 726 (s), 706 (s), 690 (s) cm^{-1}. HRMS calculated for $C_{30}H_{34}N_7O$, $[M + H]^+$, 508.2825; found 508.2837, Δ = 2.4 ppm.

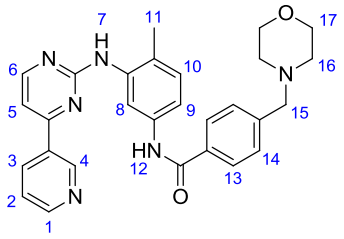
4-(((3-(Dimethylamino)propyl)(methyl)amino)methyl)-*N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)benzamide 19.



Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), *N*,*N*,*N*′-trimethyl-1,3-propanediamine (47 µL, 0.32 mmol) and **5** (69 mg, 0.40 mmol). Purified by preparative TLC (89:10:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$) to give the title compound (24 mg, 24%, >95% purity) as an off-white solid.

mp 152-155 °C dec. Rt 3.46, $[M + H]^+$ $^m/_z$ = 510.3. R_f 0.16 (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.24 (1 H, d, *J* = 1.8 Hz, H-4), 8.70 (1 H, dd, *J* = 4.8 and 1.5 Hz, H-1), 8.58 (1 H, d, *J* = 1.5 Hz, H-8), 8.53-8.50 (2 H, m, H-3 and H-6), 7.92 (1 H, s, H-12), 7.83 (2 H, d, *J* = 8.0 Hz, H-13), 7.44-7.40 (3 H, m, H-2 and H-14), 7.31 (1 H, dd, *J* = 8.2 and 1.5 Hz, H-9), 7.20 (1 H, d, *J* = 8.2 Hz, H-10), 7.18 (1 H, d, *J* = 5.1 Hz, H-5), 7.04 (1 H, s, H-7), 3.54 (2 H, s, H-15), 2.41 (2 H, t, *J* = 7.4 Hz, H-17), 2.34 (3 H, s, H-11), 2.31 (2 H, t, *J* = 7.4 Hz, H-19), 2.23 (6 H, s, H-20), 2.20 (3 H, s, H-16), 1.70 (2 H, app quintet, *J* = 7.4 Hz, H-18). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.43 (C), 162.75 (C), 160.58 (C), 159.01 (CH), 151.47 (CH), 148.49 (CH), 143.59 (C), 137.78 (C), 136.61 (C), 134.94 (CH), 133.75 (C), 132.68 (C), 130.76 (CH), 129.15 (CH), 126.97 (CH), 124.18 (C), 123.72 (CH), 115.30 (CH), 113.13 (CH), 108.34 (CH), 61.98 (CH_2), 57.78 (CH_2), 55.63 (CH_2), 45.49 (CH_3), 42.26 (CH_3), 25.67 (CH_2), 17.65 (CH_3). IR: ν_{max} = 3215 (w), 2940 (w), 2767 (w), 1655 (w), 1575 (s), 1526 (s), 1504 (s), 1478 (m), 1447 (s), 1415 (s), 1287 (m), 1252 (m), 1203 (m), 1097 (m), 1024 (m), 1005 (m), 797 (s), 745 (m), 705 (s) cm^{-1}. HRMS calculated for $C_{30}H_{36}N_7O$, $[M + H]^+$, 510.2981; found 510.2998, Δ = 3.3 ppm.

***N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-(morpholinomethyl)benzamide 20**.[12]

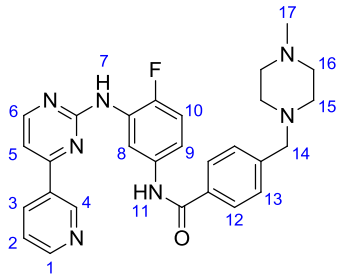


Prepared according to the general procedure using 3-bromo-4-methylaniline (37 mg, 0.20 mmol), morpholine (28 µL, 0.32 mmol) and **5** (69 mg, 0.40 mmol). Purified by column chromatography (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$) to give the title compound (23 mg, 24%, >95% purity) as an off-white solid.

mp 213-216 °C (lit.[6] 210-212 °C). Rt 3.61, $[M + H]^+$ $^m/_z$ = 481.2. R_f 0.29 (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 9.24 (1 H, d, *J* = 1.8 Hz, H-4), 8.70 (1 H, dd, *J* = 4.8 and 1.5 Hz, H-1), 8.59 (1 H, d, *J* = 1.6 Hz, H-8), 8.52-8.50 (2 H, m, H-3 and H-6), 7.90 (1 H, s, H-12), 7.84 (2 H, d, *J* = 8.0 Hz, H-13), 7.45 (2 H, d, *J* = 8.0 Hz, H-14), 7.42 (1 H, dd, *J* = 7.9 and 4.8 Hz, H-2), 7.31 (1 H, dd, *J* = 8.2 and 1.6 Hz, H-9), 7.21 (1 H, d, *J* = 8.2 Hz, H-10), 7.18 (1 H, d, *J* = 5.2 Hz, H-5), 7.04 (1 H, s, H-7), 3.72 (4 H, t, *J* = 4.3 Hz, H-17), 3.56 (2 H, s, H-15), 2.46 (4 H, app br s, H-16), 2.35 (3 H, s, H-11). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.31 (C), 162.76 (C), 160.57 (C), 159.01 (CH), 151.49 (CH), 148.52 (CH), 141.90 (C),* 137.81 (C), 136.57 (C), 134.91 (CH), 134.05 (C), 132.66 (C), 130.78 (CH), 129.34 (CH), 127.04 (CH), 124.20 (C), 123.70 (CH), 115.26 (CH), 113.07 (CH), 108.36 (CH), 66.94 (CH_2), 62.91 (CH_2), 53.62 (CH_2), 17.65 (CH_3). IR: ν_{max} = 3230 (w), 2932 (w), 2810 (w), 1663 (m), 1606 (m), 1580 (s), 1561 (s), 1526 (s), 1494 (m), 1481 (m), 1450 (m), 1423 (s), 1405 (s), 1354 (w), 1319 (s), 1286 (m), 1263 (m), 1202 (w), 1184 (w), 1116 (s), 1073 (w), 1027 (w), 1007 (m), 982 (w), 968 (w), 917 (w), 894 (w), 865 (s), 843 (m), 800 (s), 789 (m), 768 (w), 749 (m), 704 (s), 690 (m) cm^{-1}. HRMS calculated for $C_{28}H_{29}N_6O_2$, $[M + H]^+$, 481.2352; found 481.2371, Δ = 3.9 ppm.

*Carbon did not appear in ^{13}C spectrum, but was found by HMBC.

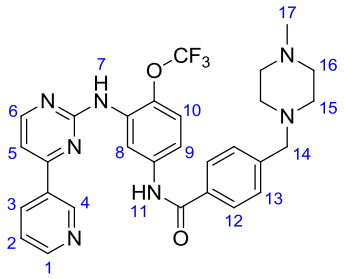
_N_-(4-fluoro-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide 21.[11]



Prepared according to the general procedure using 3-bromo-4-fluoroaniline (38 mg, 0.20 mmol), *N*-methylpiperazine (35 µL, 0.32 mmol), **5** (69 mg, 0.40 mmol) and purified by column chromatography (MeOH). The fractions corresponding to the product were combined and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL), filtered and the solvent removed *in vacuo* to give the title compound (35 mg, 35%, >95% purity) as an off-white solid.

mp 186-189 °C. Rt 3.40, $[M + H]^+$ $^m/_z$ = 498.3. R_f 0.11 (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 9.24 (1 H, d, *J* = 1.8 Hz, H-4), 8.96 (1 H, dd, *J* = 7.1 and 2.1 Hz, H-8), 8.70 (1 H, dd, *J* = 4.8 and 1.6 Hz, H-1), 8.60-8.58 (1 H, m, H-3), 8.54 (1 H, d, *J* = 5.2 Hz, H-6), 7.88 (1 H, s, H-11), 7.83 (2 H, d, *J* = 8.2 Hz, H-12), 7.47-7.42 (4 H, m, H-2, H-7 and H-13), 7.29-7.26 (2 H, m, H-5 and H-9), 7.09 (1 H, dd, *J* = 10.7 and 8.8 Hz, H-10), 3.57 (2 H, s, H-14), 2.53 (8 H, br s, H-15 and H-16), 2.34 (3 H, s, H-17). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm = 165.37 (C), 162.82 (C), 159.83 (C), 158.94 (CH), 151.64 (CH), 149.07 (C, d, *J* = 241.2 Hz), 148.49 (CH), 142.49 (C), 135.04 (CH), 134.20 (C, *d*, *J* = 2.7 Hz), 133.75 (C), 132.45 (C), 129.35 (CH), 128.27 (C, d, *J* = 10.7 Hz), 127.03 (CH), 123.80 (CH), 114.88 (CH, d, *J* = 20.6 Hz), 113.94 (CH, d, *J* = 7.2 Hz), 112.41 (CH), 109.03 (CH), 62.34 (CH_2), 54.90 (CH_2), 52.64 (CH_2), 45.67 (CH_3). IR: ν_{max} = 3395 (w), 3298 (w), 2933 (w), 2795 (w), 1642 (m), 1627 (m), 1581 (s), 1553 (m), 1533 (s), 1506 (m), 1475 (m), 1441 (s), 1398 (s), 1348 (m), 1335 (m), 1281 (m), 1247 (m), 1199 (m), 1163 (m), 1140 (m), 1104 (m), 1053 (w), 1012 (m), 991 (m), 925 (w), 897 (w), 870 (m), 841 (m), 802 (s), 788 (s), 751 (m), 703 (m), 685 (m) cm^{-1}. HRMS calculated for $C_{28}H_{29}FN_7O$, $[M + H]^+$, 498.2418; found 498.2419, Δ = 0.2 ppm.

4-((4-Methylpiperazin-1-yl)methyl)-*N*-(3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)-4-(trifluoromethoxy)phenyl)benzamide 22.

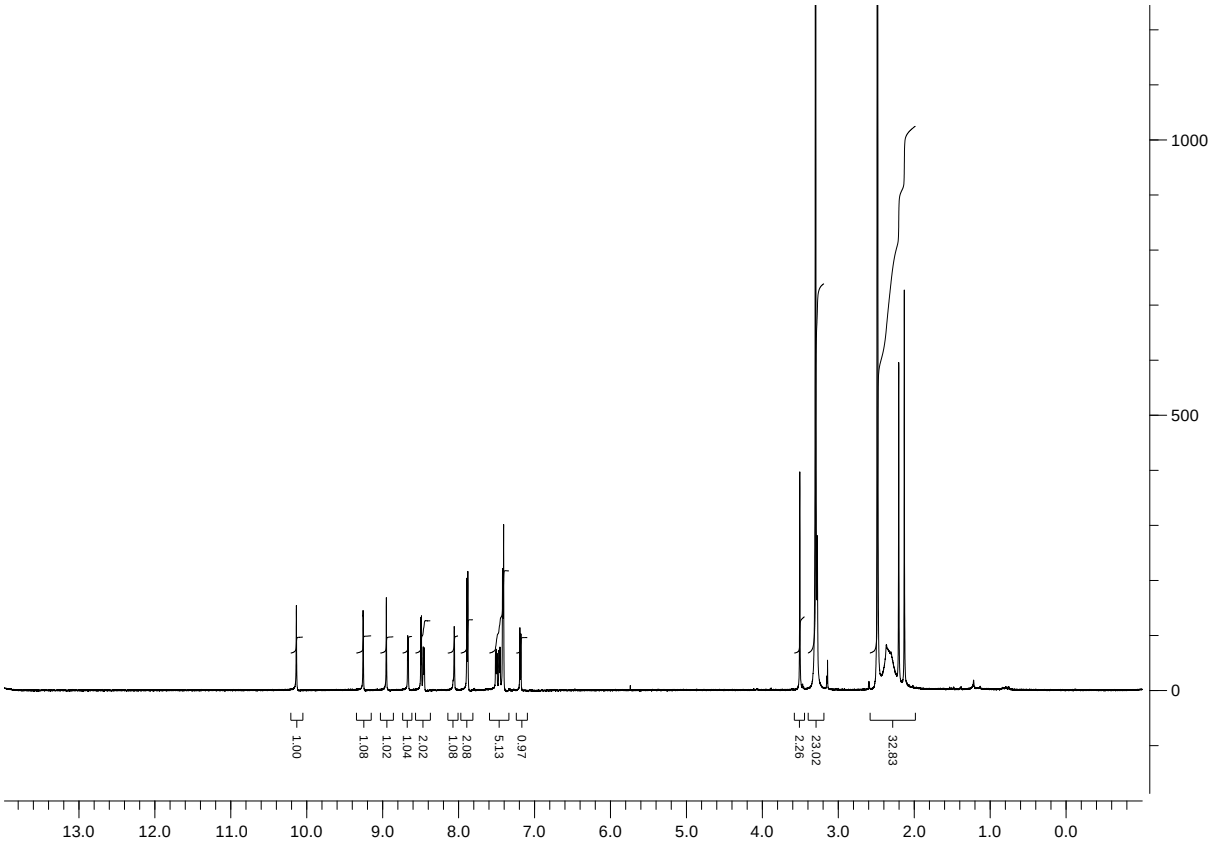


Prepared according to the general procedure using 3-bromo-4-(trifluoromethoxy)aniline (51 mg, 0.20 mmol), *N*-methylpiperazine (35 µL, 0.32 mmol) and **5** (69 mg, 0.40 mmol). Purified by column chromatography (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$) to give the title compound (31 mg, 28%, >95% purity) as an off-white solid.

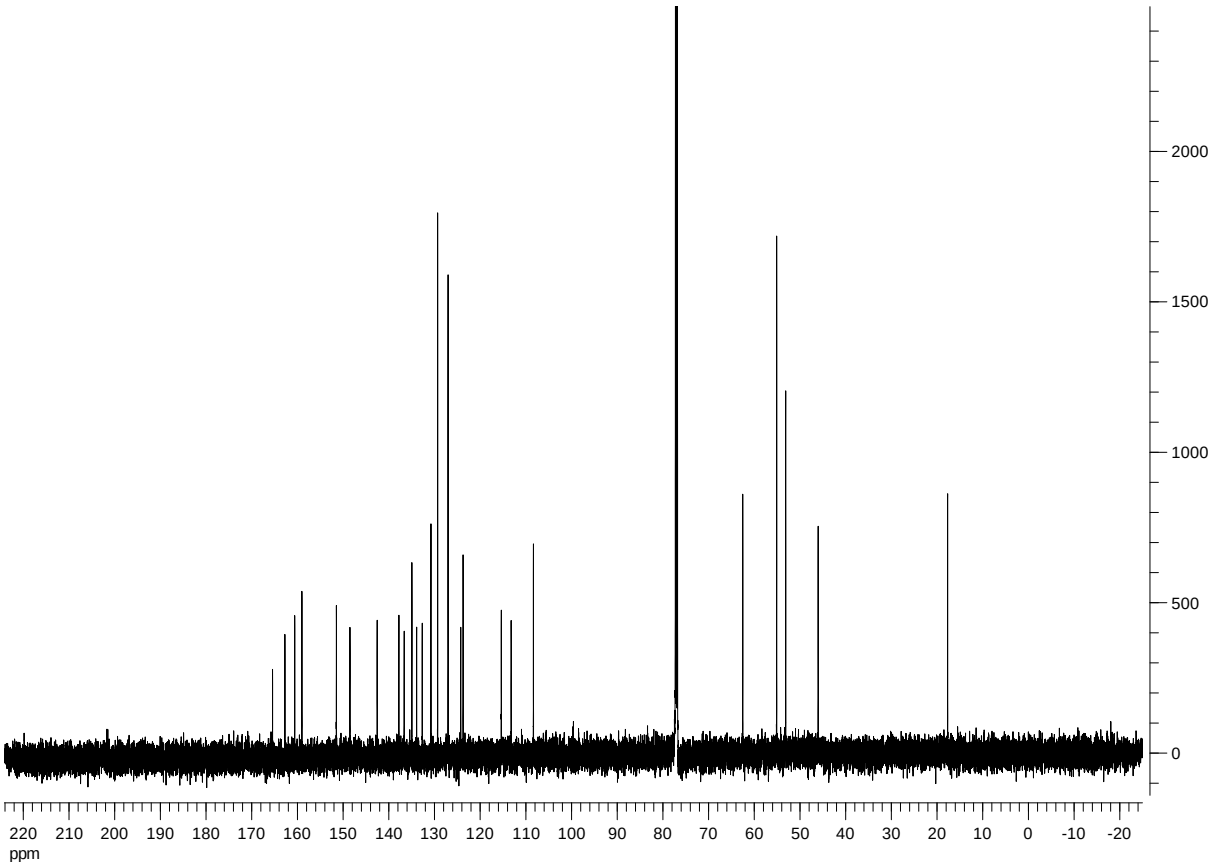
mp 198-201 °C. Rt 4.01, $[M + H]^+$ $^m/_z$ = 564.2. R_f 0.21 (94:5:1 CH_2Cl_2/MeOH/conc. $NH_{3(aq)}$). ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 9.25 (1 H, d, *J* = 1.8 Hz, H-4), 9.13 (1 H, d, *J* = 2.1 Hz, H-8), 8.70 (1 H, dd, *J* = 4.7 and 1.5 Hz, H-1), 8.61-8.58 (1 H, m, H-3), 8.56 (1 H, d, *J* = 5.1 Hz, H-6), 8.05 (1 H, s, H-11), 7.85 (2 H, d, *J* = 8.2 Hz, H-12), 7.56 (1 H, s, H-7), 7.45 (2 H, d, *J* = 8.2 Hz, H-13), 7.44 (1 H, dd, *J* = 7.9 and 4.7 Hz, H-2), 7.33 (1 H, dd, *J* = 8.8 and 2.1 Hz, H-9), 7.28-7.25 (2 H, m, H-5 and H-10), 3.57 (2 H, s, H-14), 2.49 (8 H, br s, H-15 and H-16), 2.30 (3 H, s, H-17). ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 165.51 (C), 162.86 (C), 159.71 (C), 158.93 (CH), 151.65 (CH), 148.51 (CH), 142.90 (C), 137.06 (C), 135.12 (CH), 133.99 (C), 133.51 (C), 132.80 (C), 132.40 (C), 129.35 (CH), 127.04 (CH), 123.80 (CH), 121.15 (CH), 120.74 (C, q, *J* = 259.1 Hz), 113.53 (CH), 111.85 (CH), 109.29 (CH), 62.46 (CH_2), 55.07 (CH_2), 53.07 (CH_2), 45.97 (CH_3). IR: ν_{max} = 3439 (w), 3411 (w), 2939 (w), 2805 (w), 1665 (w), 1647 (w), 1607 (m), 1580 (m), 1556 (m), 1524 (s), 1491 (m), 1475 (m), 1437 (m), 1402 (s), 1351 (w), 1337 (w), 1321 (w), 1297 (m), 1280 (m), 1245 (s), 1217 (s), 1196 (s), 1164 (s), 1148 (s), 1054 (w), 1013 (m), 990 (m), 923 (m), 899 (m), 859 (m), 840 (m), 800 (m), 787 (m), 754 (m), 728 (s), 703 (m), 687 (m) cm^{-1}. HRMS calculated for $C_{29}H_{29}F_3N_7O_2$, $[M + H]^+$, 564.2335; found 564.2331, Δ = -0.7 ppm.

NMR Spectra of Final Compounds

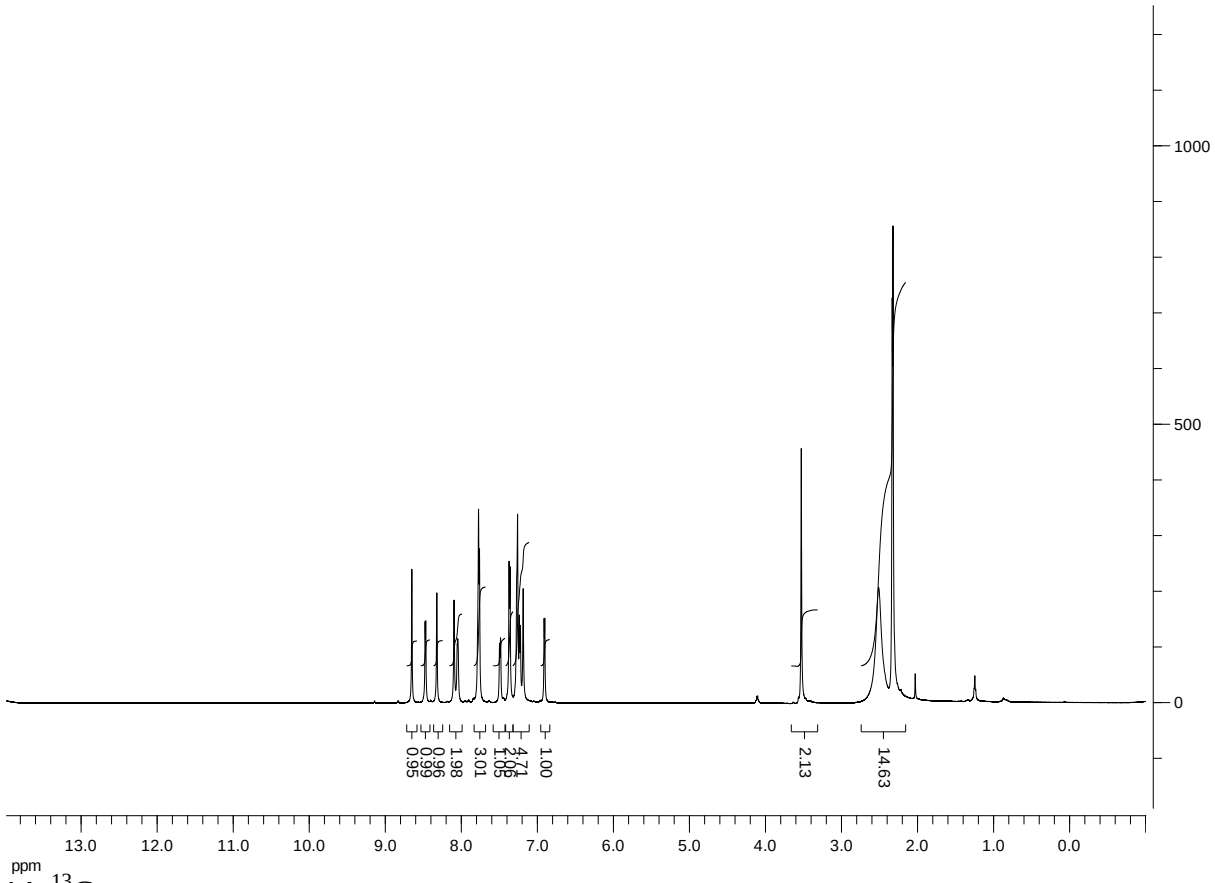
1: ^{1}H



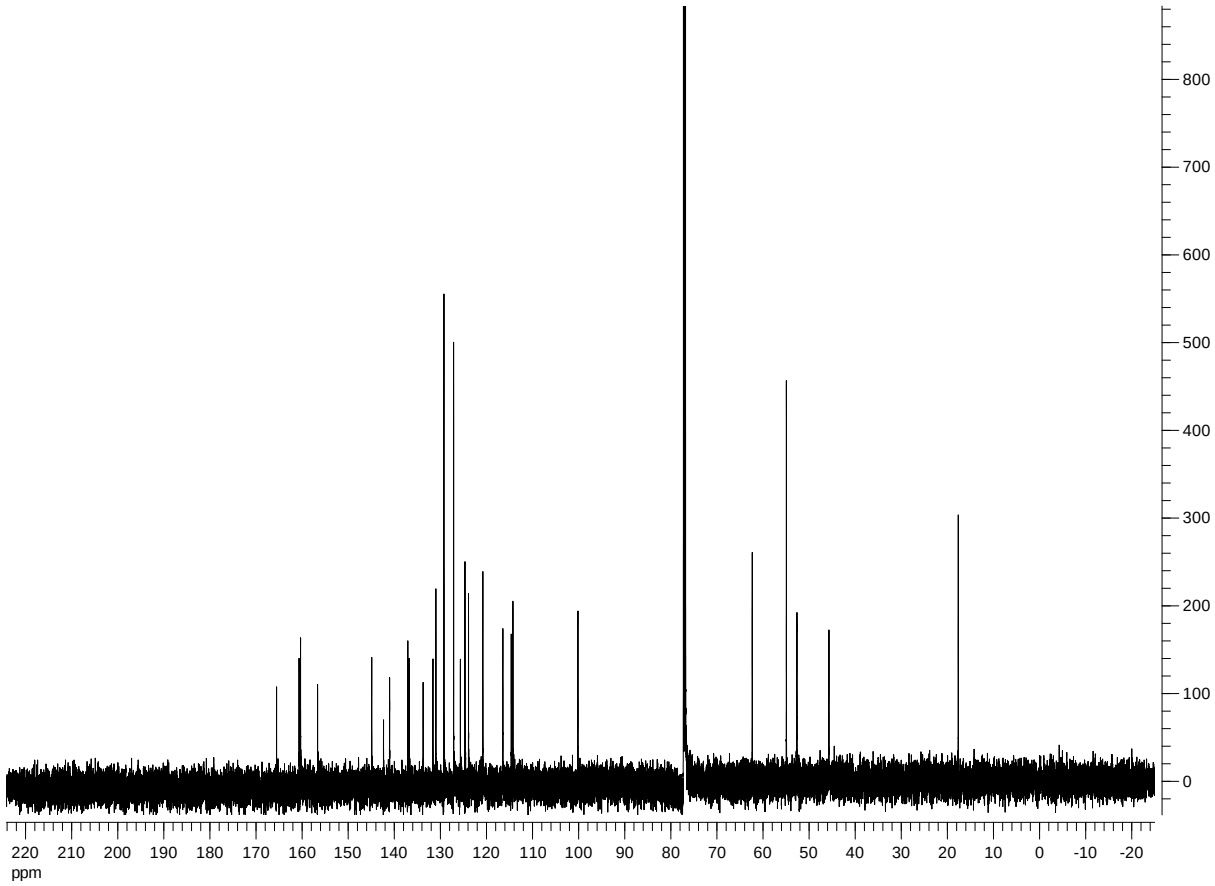
1: ^{13}C



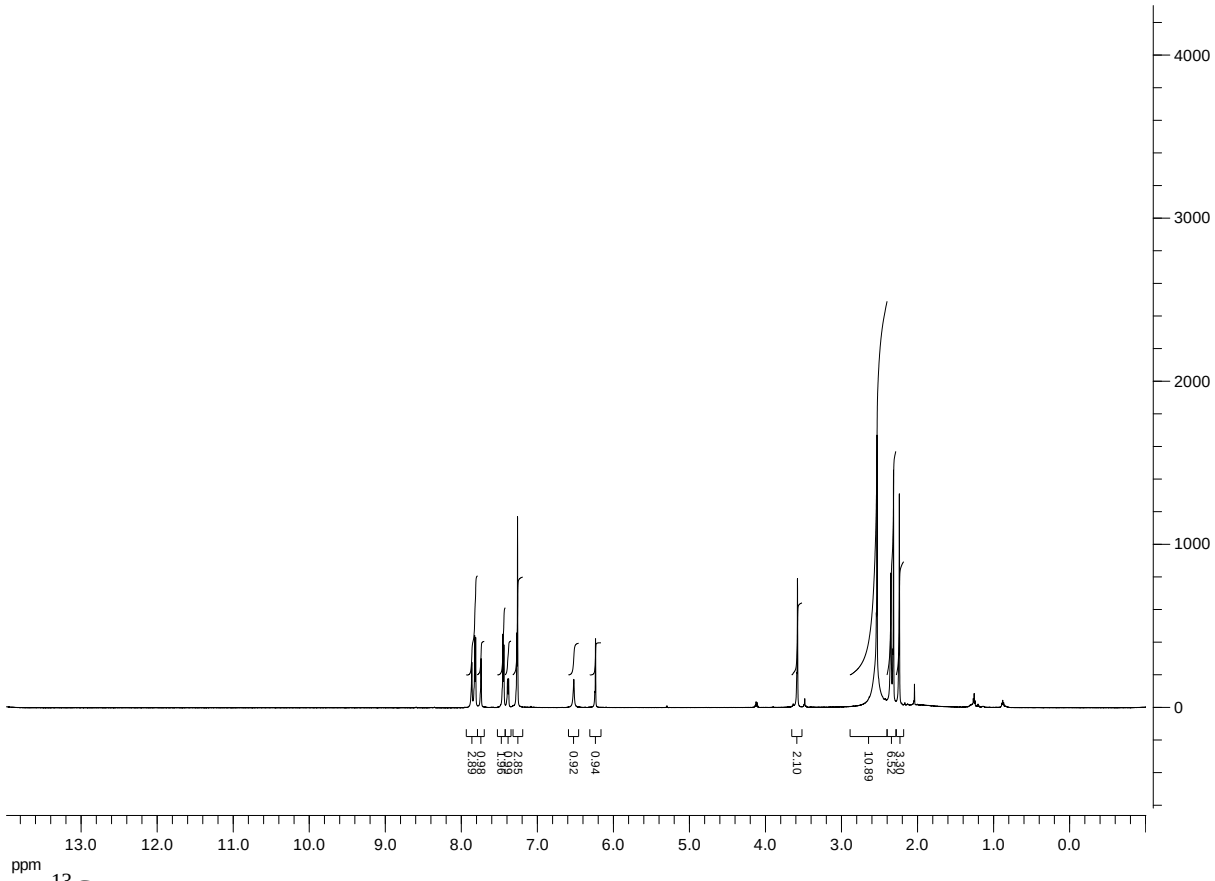
14: ^{1}H



14: ^{13}C



15: ^{1}H



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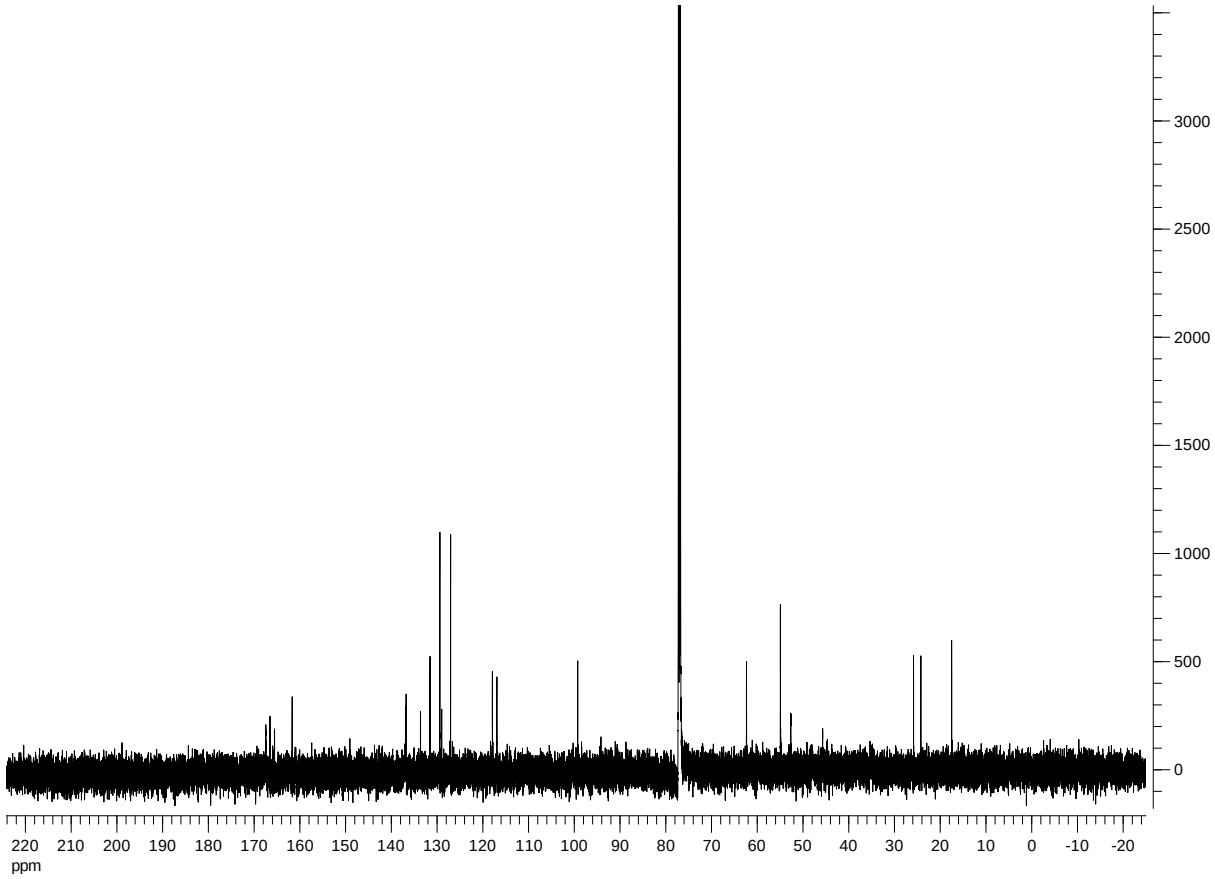

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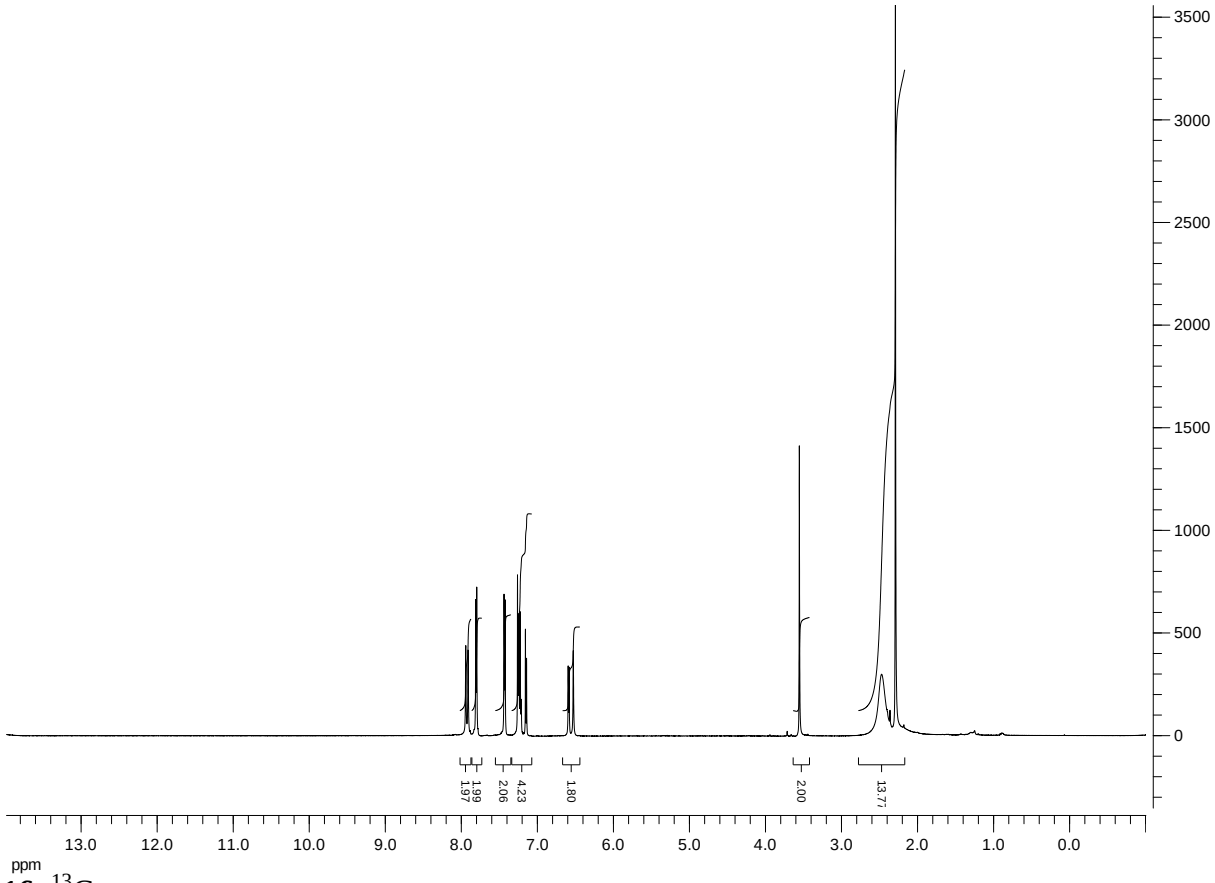

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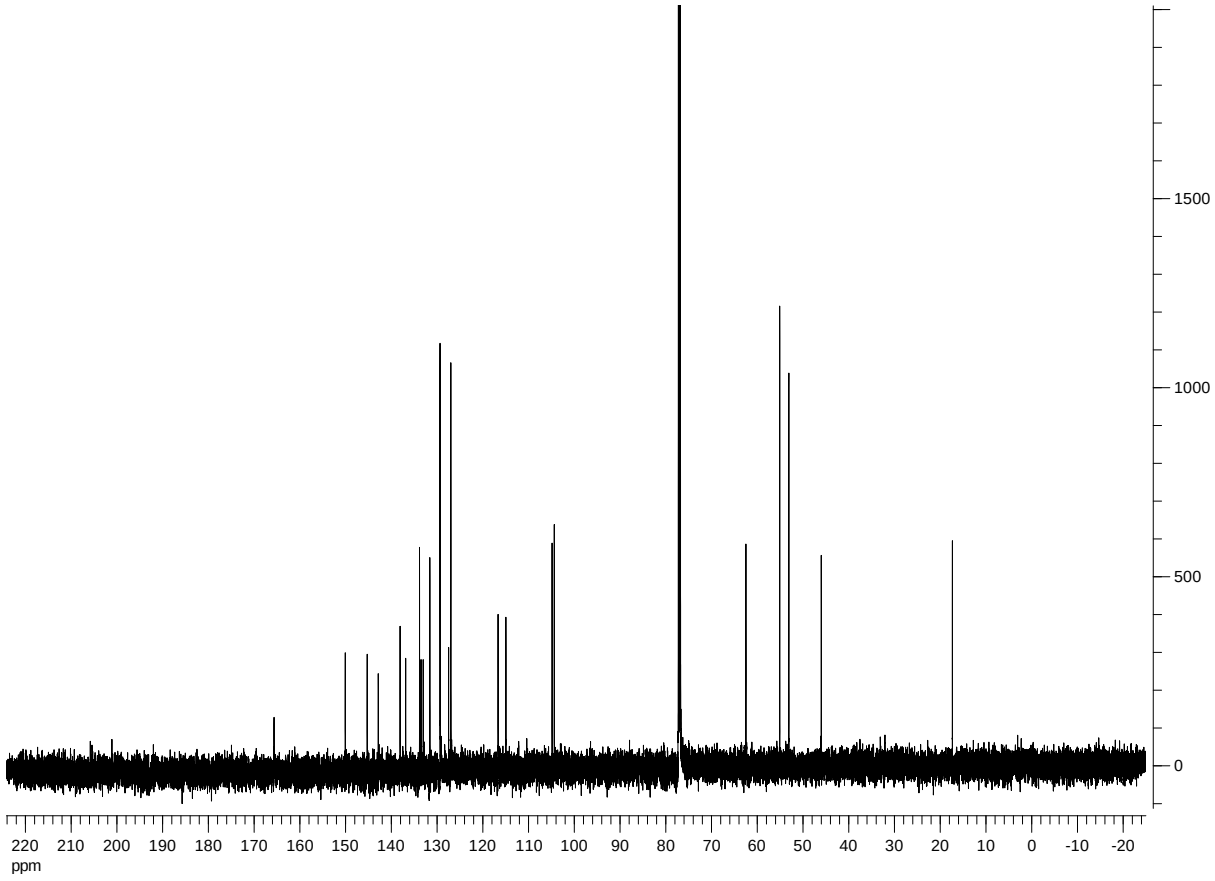

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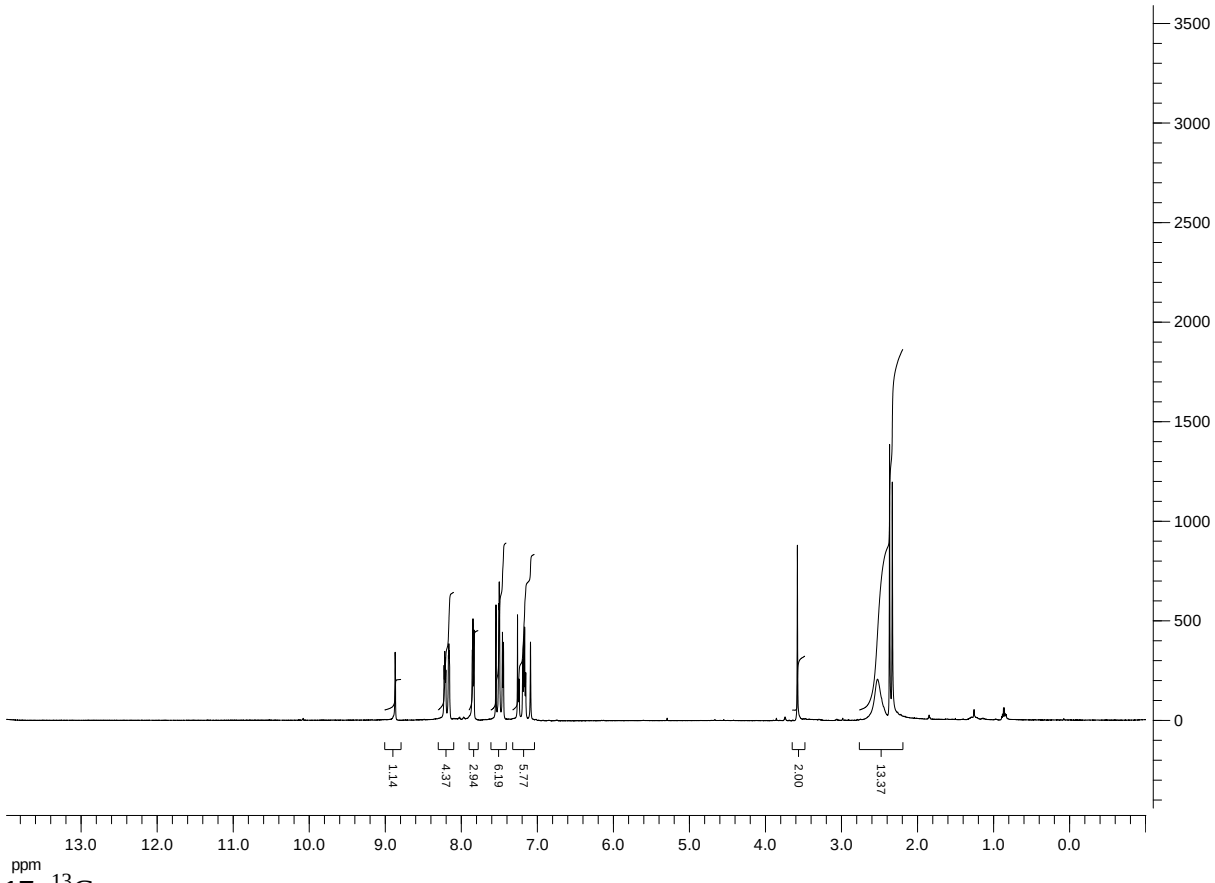

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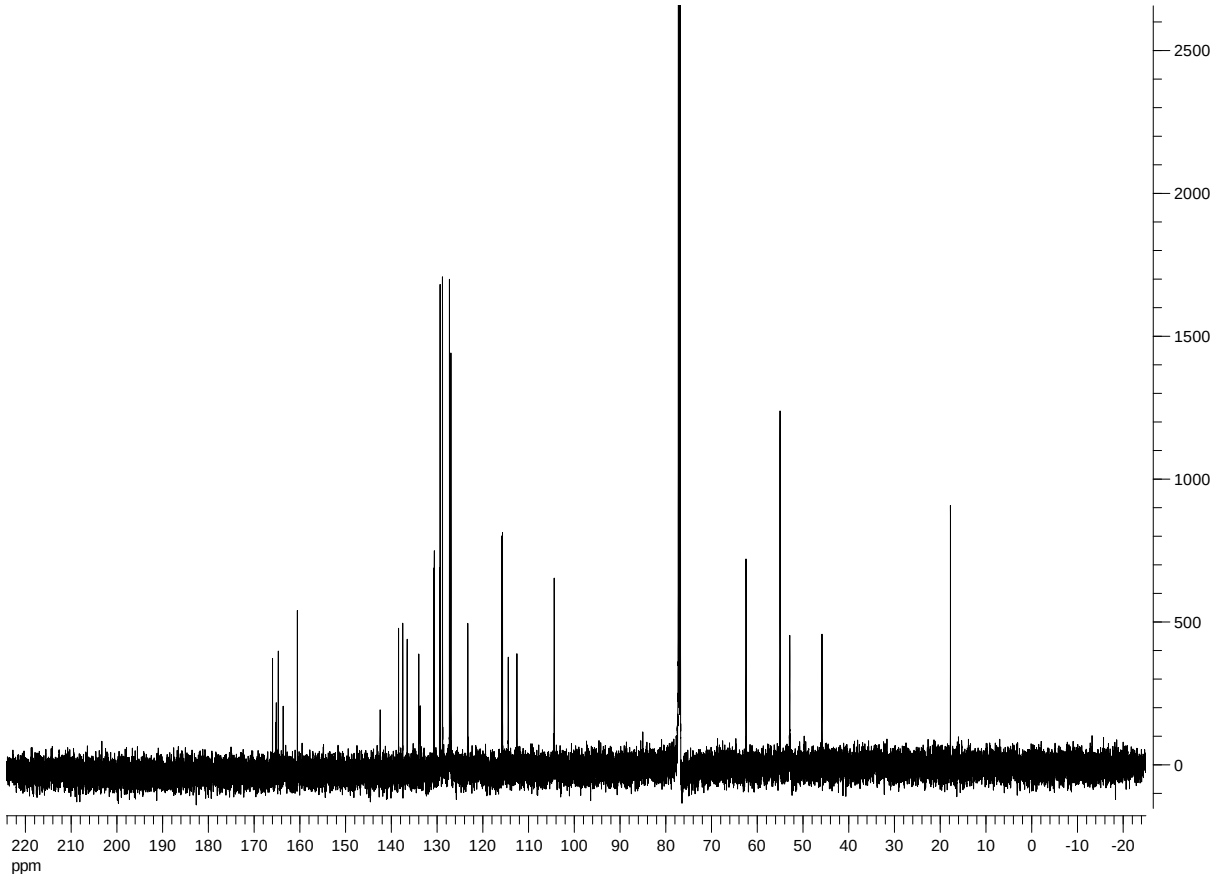

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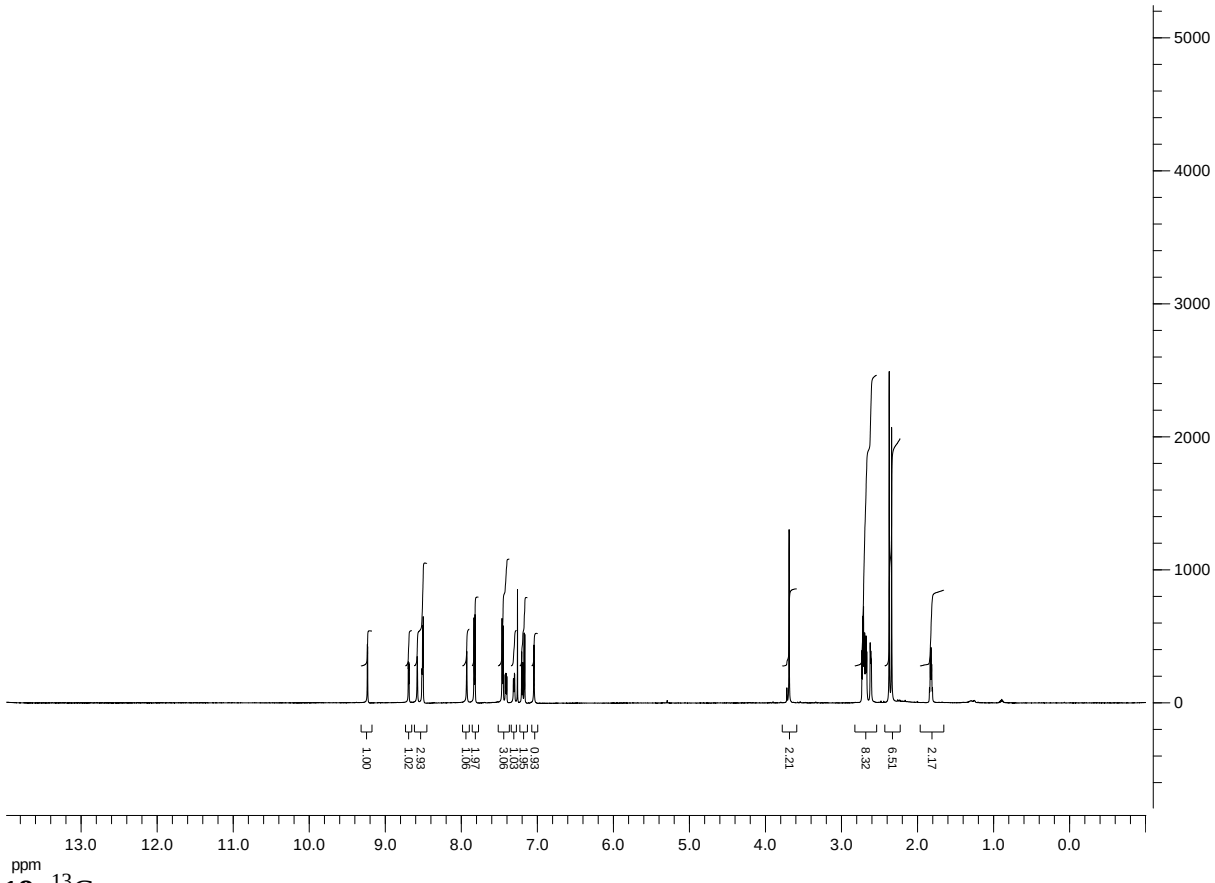

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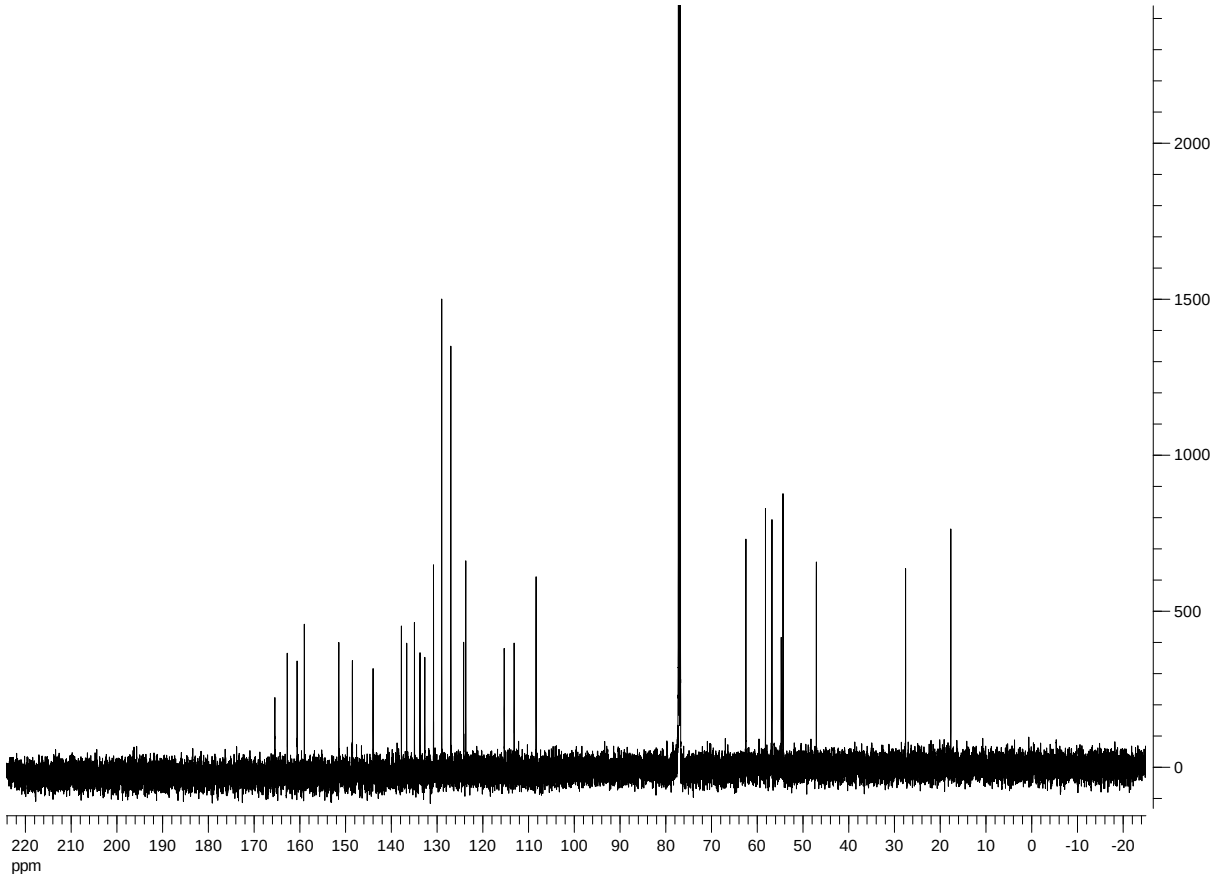

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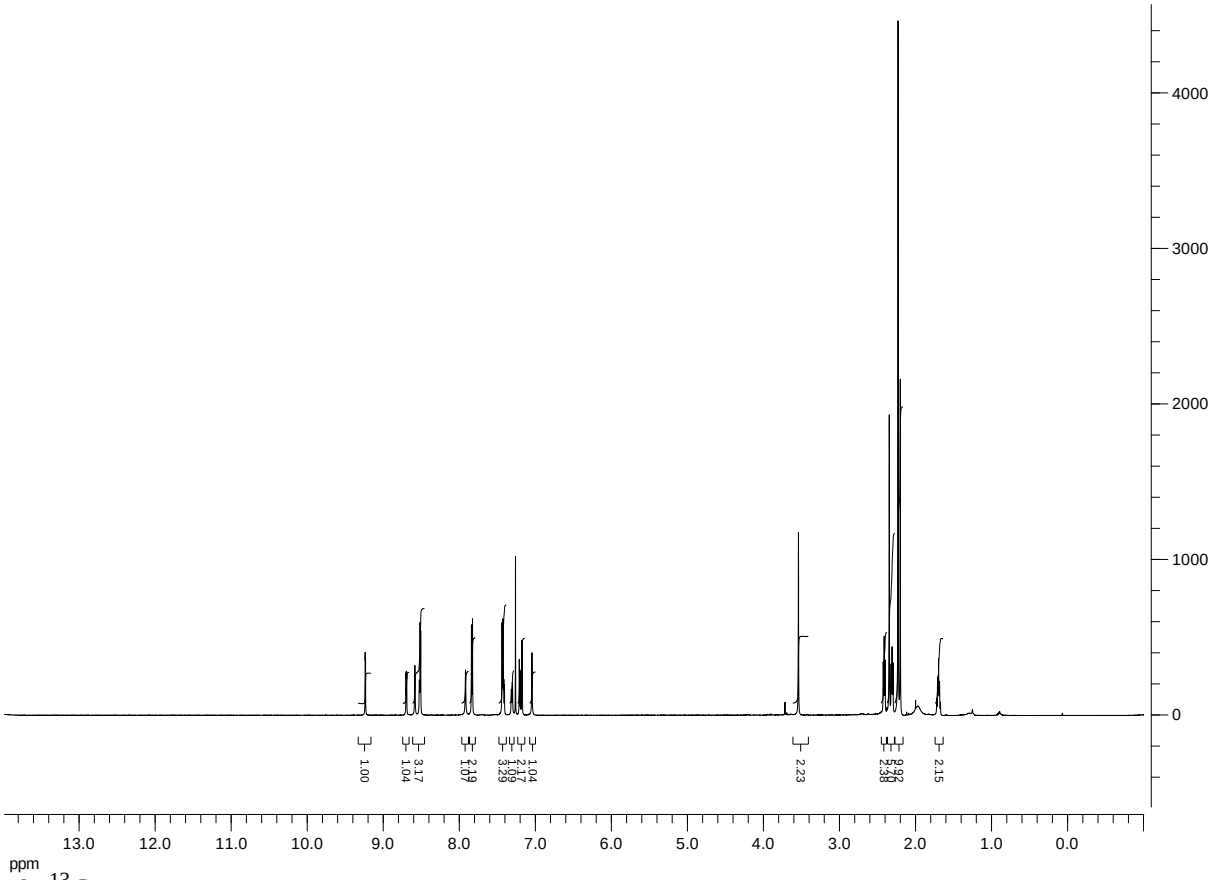

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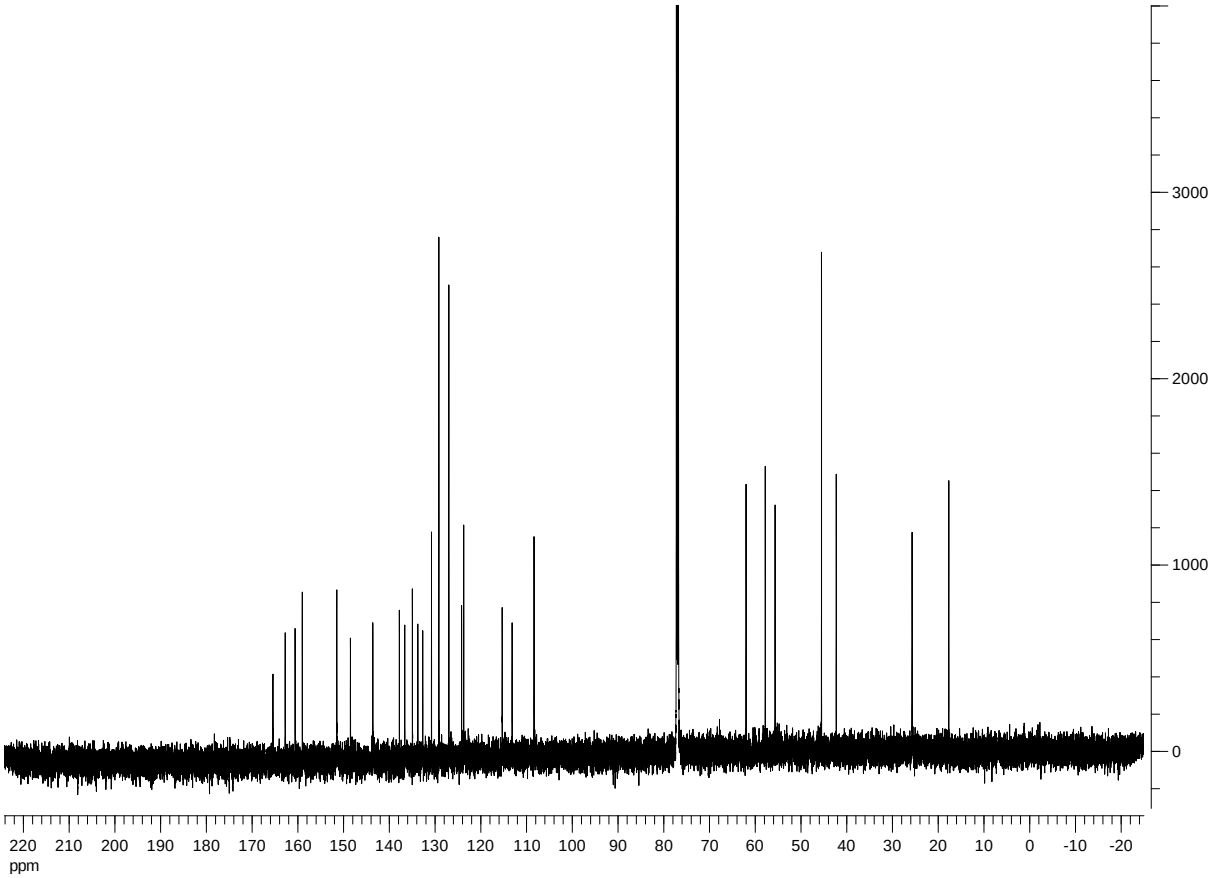

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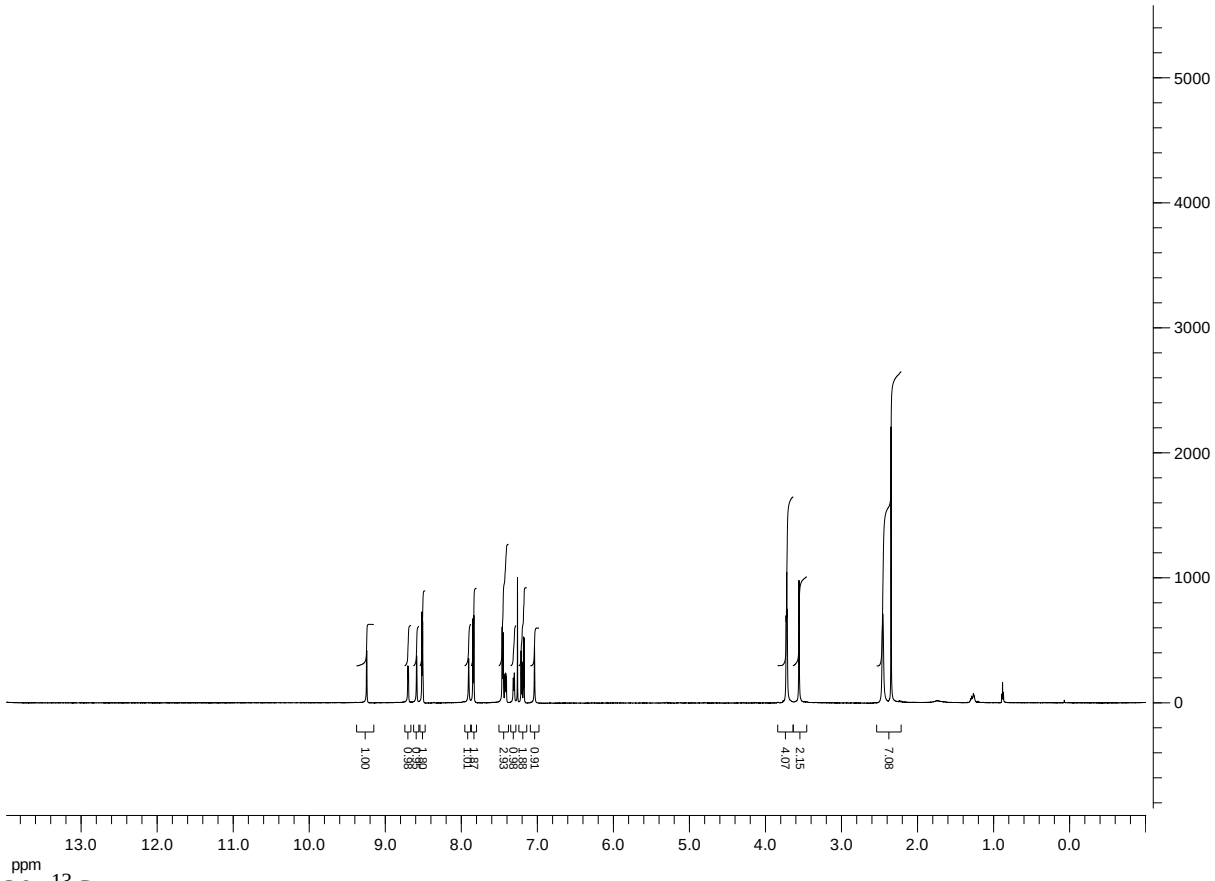

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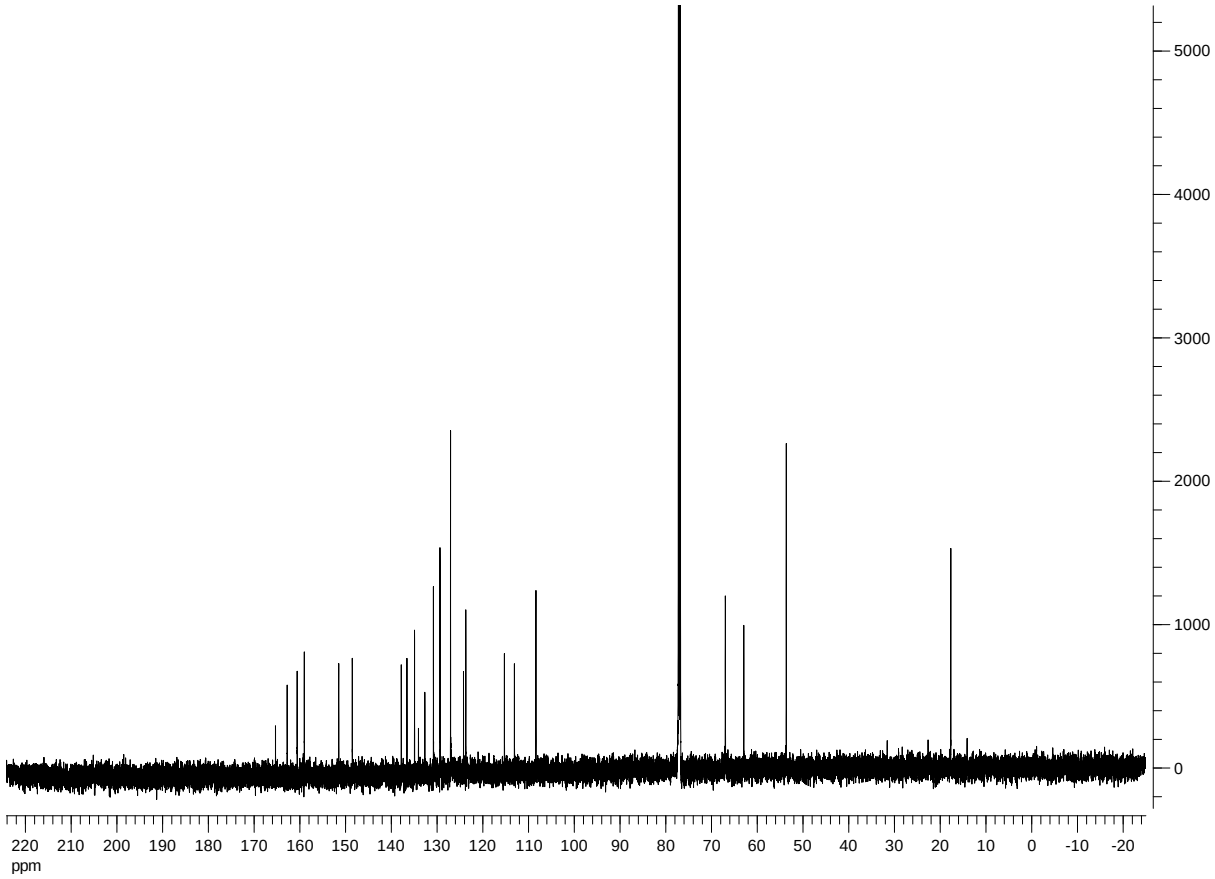

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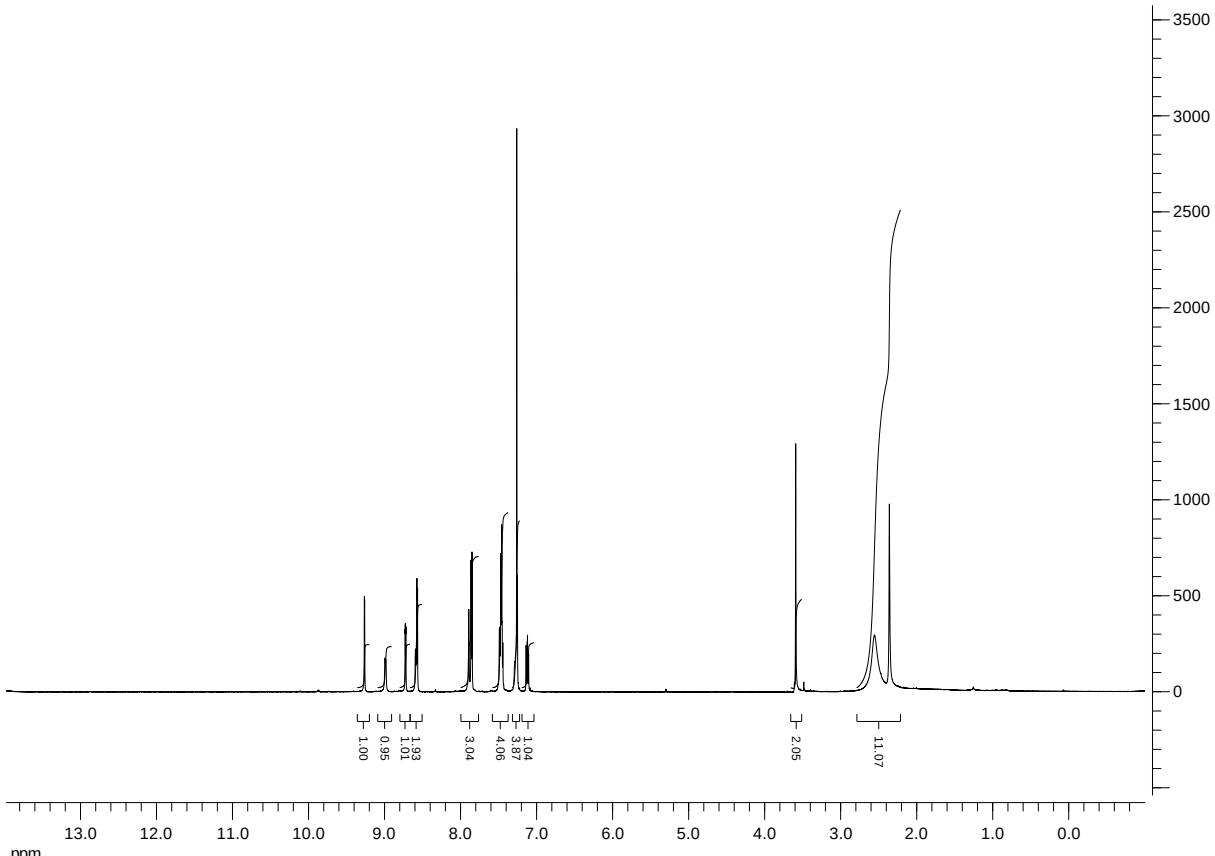

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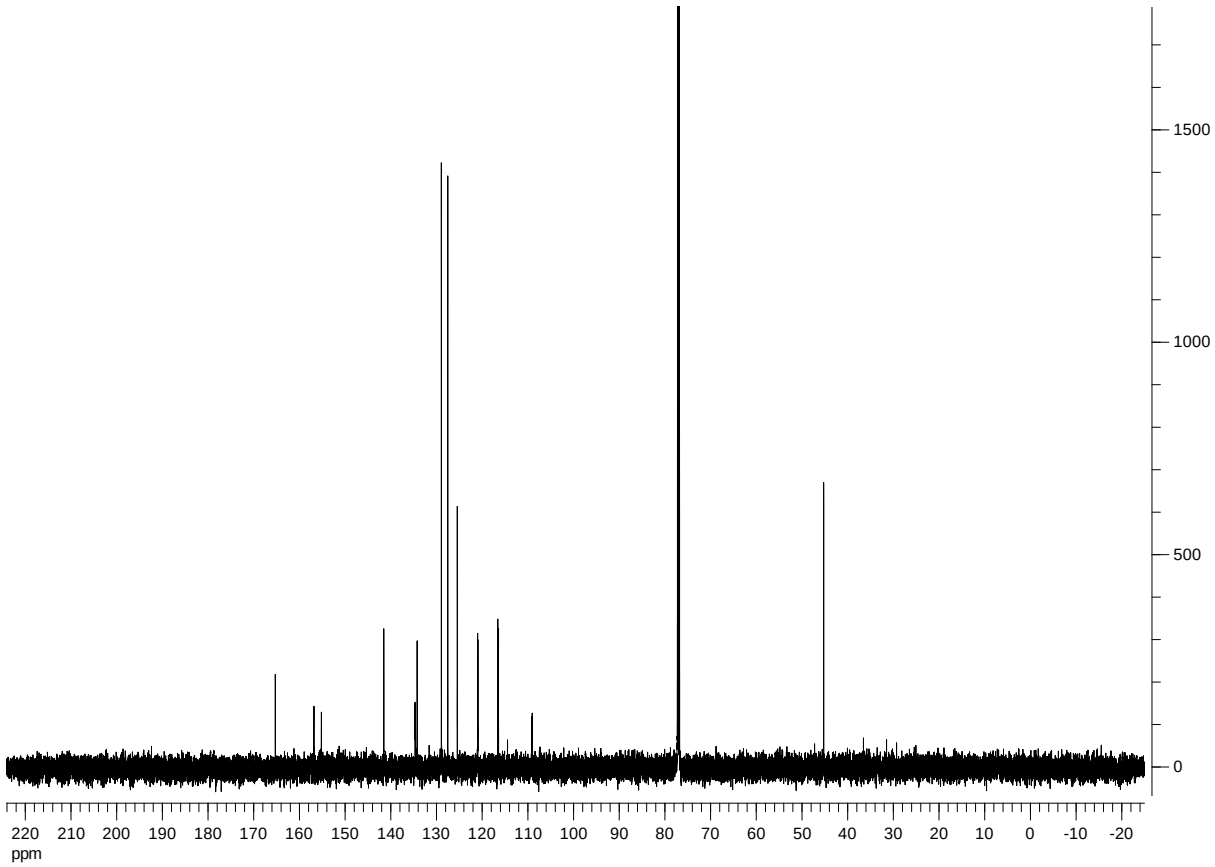

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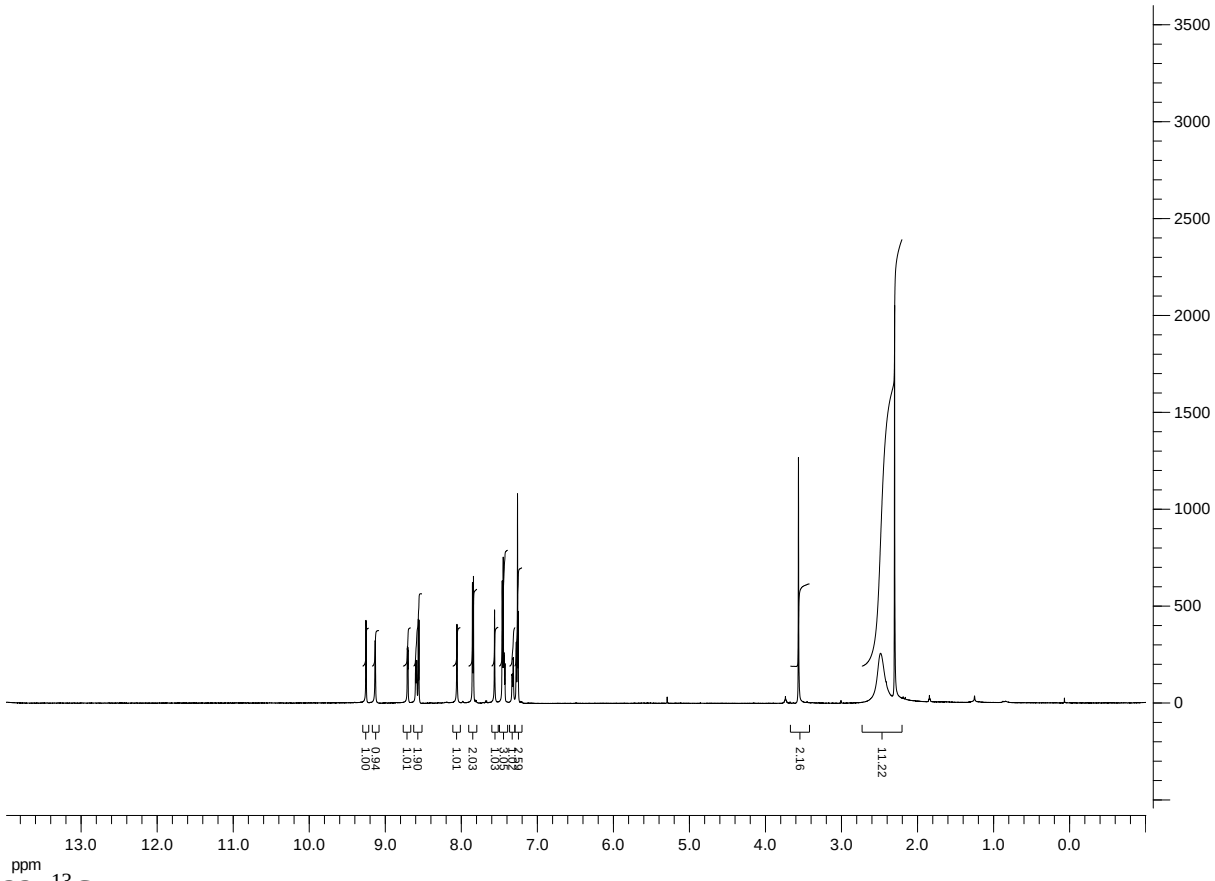

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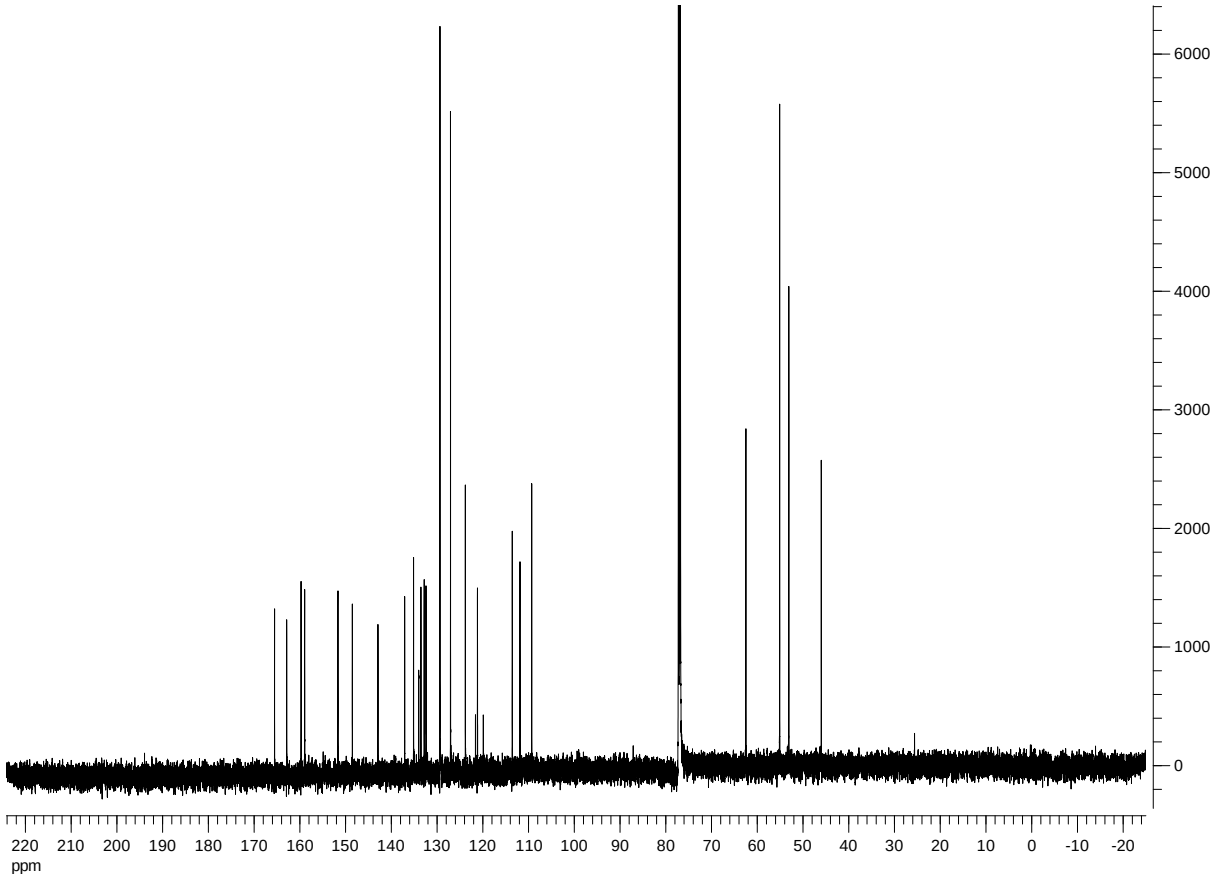

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