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Synthesis Procedures and Spectra Details

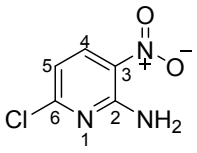
General Working Procedure 1 (GWP1)

In a microwave vessel, **5** (1 eq.) was suspended together with triethylamine (1.4 eq.) and the corresponding amine (1.2 eq.) in 2-propanol. The mixture heated in the microwave reactor for 15 min at 110 °C. Subsequently, addition of water precipitated the product, which was stored in the refrigerator to complete the precipitation. Finally, the resulting solid filtered off, washed with water and then dried.

General Working Procedure 2 (GWP2)

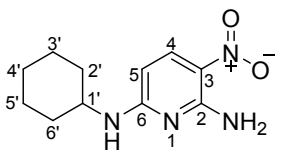
In a 3-necked flask, compound **i12** (1 mmol) together with palladium-activated carbon (0.10 g) were suspended in tetrahydrofuran (10 mL) and stirred at 40 °C under a hydrogen atmosphere. After TLC-controlled completion of the reduction (about 18 h), the catalyst was filtered through diatomaceous earth and the residue was washed with a suitable solvent. The filtrate sparged with nitrogen via a capillary, cooled to 0 °C, and triethylamine (1.4 eq., 194 μL) was added. A solution of the corresponding acylating reagent (1.2 eq.) In 5 mL of a suitable solvent added dropwise over 30 min. After completion of the reaction, purification carried out as described in the corresponding instructions.

2-Amino-6-chloro-3-nitropyridine (**5**)



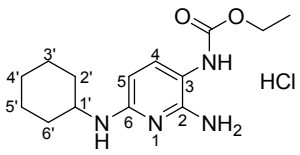
2,6-Dichloro-3-nitropyridine (40 mmol, 7.72 g) was dissolved in 2-propanol (300 mL). A relatively excess (20 mL, 25%) aqueous ammonia was added. The reaction mixture was warmed to 35 ˚C and stirred for 5 days. A light yellow precipitate was collected by filtration, which was washed with water (2 x 50 mL) and dried using desiccator; Yield: 77.0%, light yellow solid; Mp: 194-195 ˚C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, 1H, ^{3}J = 8.6 Hz, C(4)H), 8.26 (bs, 2H, $N^{2}H_2$), 6.78 (d, 1H, ^{3}J = 8.6 Hz, C(5)H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.0 (C6), 153.5 (C2), 138.4 (C4), 126.1 (C3), 112.0 (C5); IR (cm^{-1}): $\tilde{\nu}$ = 3442 (N-H), 3277 (N-H), 1556 (NO_2), 1495 (C=C), 762 (Ar-H).

N^{2}-Cyclohexyl-5-nitropyridine-2,6-diamine (**6a**)



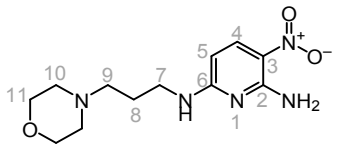
Compound **5** (2 mmol, 348 mg) was suspended in 2-propanol (10 mL). Triethylamine (4 mmol, 555 µL) and cyclohexylamine (3 mmol, 342 µL) sequentially added. The reaction mixture refluxed for overnight. Cooling of the mixture resulted in precipitation of the product. A yellow product collected by filtration, which was washed with distilled water; Yield: 72%, yellow solid; Mp: 175-176 °C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12 (bs & bs, 2H, N^2H_2), 7.92 (d, 1H, ^{3}J = 9.2 Hz, C(4)H), 7.83 (m, 1H, N^6H), 5.95 (d, 1H, ^{3}J = 9.2 Hz, C(5)H), 3.92 (m, 1H, C(1')H), 1.89 (m, 2H, C(2')H_a & C(6')H_a), 1.75 (m, 2H, C(3')H_a & C(5')H_a), 1.61 (m, 1H, C(4')H_a), 1.35 (m, 5H, C(2')H_b, C(6')H_b, C(3')H_b, C(5')H_b & C(4')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.7 (C6), 156.0 (C2), 134.0 (C4), 117.1 (C3), 102.8 (C5), 62.0 (C1'), 32.2 (C2' & C6'), 25.2 (C3' & C5'), 24.6 (C4'); IR (cm^{-1}): $\tilde{\nu}$ = 3297 (N-H), 1572 (NO_2).

Ethyl [2-amino-6-(cyclohexylamino)pyridin-3-yl]carbamate hydrochloride (**7a**)



Compound **6a** (4 mmol, 946 mg) and Pd/C (10%, 400 mg) were suspended in 2-propanol (20 mL). The suspension carefully set under hydrogen atmosphere and stirred for overnight. Ethyl chloroformate (5.2 mmol, 498 µL) added slowly and then stirred for 2 h. The suspension filtered and washed with ethanol (3 x 10 mL). The filtrate was concentrated and the product precipitated with the addition of water to the filtrate. A pure product collected by filtration; Yield: 25%, brown solid; Purity 100%; Mp: 212 - 213 °C (from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.85 (bs, 1H, HCl), 8.46 (bs, 1H, N^3H), 7.79 (m, 1H, N^6H), 7.44 (d, 1H, ^{3}J = 8.4 Hz, C(4)H & N^2H_2), 5.96 (d, 1H, ^{3}J = 8.8 Hz, C(5)H), 4.08 (q, 2H, ^{3}J = 6.9 Hz, -OCH_2), 3.74 (m, 1H, C(1')H), 1.90 (m, 2H, C(2')H_a & C(6')H_a), 1.71 (m, 2H, C(3')H_a & C(5')H_a), 1.60 (m, 1H, C(4')H_a), 1.45 (m, 5H, C(2')H_b, C(6')H_b, C(3')H_b, C(5')H_b & C(4')H_b) 1.07 (t, 3H, ^{3}J = 7.0 Hz, -$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.1 (C=O), 148.8 (C6), 148.6 (C2), 142.8 (C4), 105.4 (C3), 94.1 (C5), 60.4 (-OCH_2), 50.0 (C1'), 32.0 (C2' & C6'), 24.9 (C4'), 24.0 (C3' & C5'), 14.5 (-$OCH_2\underline{C}H_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3143 (N-H), 1690 (C=O), 780 (Ar-H); HRMS ((ESI) m/z) calculated for [$C_{14}H_{22}N_4O_2$ + H]$^{+}$: 279.1816.1063, found: 279.1814.

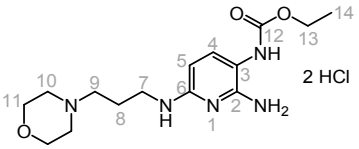
N^2-(3-Morpholinprop-1-yl)-2,6-diamino-5-nitropyridine (**6b**)



The synthesis carried out according to GWP1 with **5** (5 mmol, 0.87 g), 3-(morpholin-4-yl)-propyl-1-amine (6 mmol, 875 µL) and triethylamine (7 mmol, 966 µL) in 2-propanol (5 mL). Yield: 0.95 g (68 %)

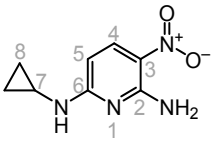
of orange-yellow, amorphous solid; Mp: 125–127 °C (solid from 2-propanol); R_f = 0.41 (cyclohexane/ethanol/triethylamine); ^{1}H-NMR: (DMSO-d_6): δ = 1.70 (q, ^3J = 7.0 Hz, 2H, C^8H_2), 2.33–2.34 (m, 6H, C^9H_2 & 2×$C^{10}H_2$), 3.34–3.37 (t, ^3J = 6.0 Hz, 2H, C^7H_2), 3.56–3.58 (m, 4H, 2×$C^{11}H_2$), 5.95 (d, ^3J = 9.3 Hz, 1H, C^5H), 7.71 & 8.14 (bs & bs, 2H, NH_2), 7.92 (d, ^3J = 9.4 Hz, 1H, C^4H), 7.95 (t, ^3J = 5.2 Hz, 1H, NH); ^{13}C-NMR: (DMSO-d_6): δ = 25.5 (C^8), 38.9 (C^7), 53.3 (C^{10}), 55.8 (C^9), 66.1 (C^{11}), 102.6 (C^5), 117.2 (C^3), 134.0 (C^4), 155.9 (C^2), 160.6 (C^6); IR: $\tilde{\nu}$ = 1529 (m, $\nu_{C\text{-}NO}$), 3284 & 3410 (m, $\nu_{N\text{-}H}$).

Ethyl-{2-amino-6-[(3-morpholinpropyl)amino]pyridin-3-yl}carbamate-Hydrochloride (**7b**)



Compound **6b** (1 mmol, 0.28 g) and 0.10 g of palladium-activated carbon (10%) were suspended in 2-propanol (20 mL). The suspension set under hydrogen atmosphere and stirred for 28.5 h. The reaction mixture then cooled to 0 °C and triethylamine (1.5 eq., 1.5 mmol, 0.2 mL) was added. After dropwise addition of ethyl chloroformate (1.2 eq., 1.2 mmol, 114 μL), the mixture was stirred at 0 °C for 2.5 h. The catalyst was then filtered and the pH of the filtrate was adjusted to 2 with 10% hydrochloric acid. A hydrochloride salt precipitated by addition of diethyl ether (20 mL) and the resulting in the solid filtered off and washed with diethyl ether and boiling tetrahydrofuran. Finally, the product recrystallized from methanol; yield: 0.13 g (34%); Purity 100%; Mp: 176–177 °C (solid from methanol); R_f = 0.43 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR: (DMSO-d_6): δ = 1.22 (bs, 3H, $C^{14}H_3$), 2.02 (q, ^3J = 7.3 Hz, 2H, C^8H_2), 3.06 (m, 2H, $C^{10}H_2$), 3.19 (m, 2H, C^9H_2), 3.41 (m, 2H, $C^{10}H_2$), 3.44 (m, 2H, C^7H_2), 3.90 (bs, 4H, 2×$C^{11}H_2$), 4.06 (q, ^3J = 6.9 Hz, 2H, $C^{13}H_2$), 6.01 (d, ^3J = 8.8 Hz, 1H, C^5H), 7.48 (d, ^3J = 8.0 Hz, 1H, C^4H), 7.48 (s, 2H, NH_2), 8.20 (s, 1H, N^6H), 8.55 (s, 1H, N^3H), 11.25 (s, 1H, HCl), 13.26 (s, 1H, HCl); ^{13}C-NMR:(DMSO-d_6): δ = 14.5 (C^{14}), 22.6 (C^8), 51.1 (2×C^{10}), 53.4 (C^9), 60.5 (C^{13}), 63.1 (2×C^{11}), 94.1 (C^5), 106.1 (C^3), 142.7 (C^4), 149.0 (C^2), 149.2 (C^6), 155.1 (C^{12}); IR: $\tilde{\nu}$ = 1702 (m, $\nu_{C=O}$), 2979 (w, $\nu_{Ar\text{-}H}$), 3163, 3262, 3458 (w, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{15}H_{25}N_5O_3 + H]^+$: 324.2030, found: 324.2015.

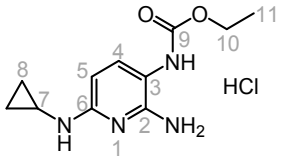
N^2-Cyclopropyl-2,6-diamino-5-nitropyridine (**6c**)



The synthesis was carried out according to GWP1 with **5** (4 mmol, 0.69 g), cyclopropylamine (4.8 mmol, 334 μL) and 5.6 mmol triethylamine (773 μL) in 5 mL of 2-propanol. Contrary to the instructions, the mixture was heated first to 130 °C for 30 min and then to 150 °C for 30 min. The product dried using a

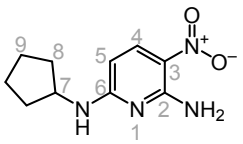
drying oven at 60 °C. Yield: 0.58 g (75%) of yellow, amorphous solid; Mp: 163–165 °C (solid form 2-Propanol); R_f = 0.70 (cyclohexane/ethanol/triethylamine 6:2:2). ^{1}H-NMR: (DMSO-d_6): δ = 0.50-0.54 und 0.72-0.77 (m & m, 4H, 2×C^{8}H$_2$), 2.94 (bs, 1H, C^{7}H), 5.90 & 6.25 (bs & bs, 1H, C^{5}H), 7.80-8.13 (m, 4H, C^{4}H, NH & NH$_2$); ^{13}C-NMR: (DMSO-d_6): δ = 6.3 (C^8), 23.9 (C^7), 102.4 (C^5), 117.6 (C^3), 134.0 (C^4), 155.9 (C^2), 161.7 (C^6); MIR: $\tilde{\nu}$ = 1524 (m, $\nu_{C\text{-}NO}$), 3083 (w, $\nu_{Ar\text{-}H}$), 3328 und 3403 (w, $\nu_{N\text{-}H}$).

Ethyl-[2-amino-6-(cyclopropylamin)pyridin-3-yl]carbamate-hydrochloride (**7c**)



1 mmol of **6c** (0.19 g) and 0.15 g of palladium activated carbon (10%) were suspended in 20 mL of 2-propanol and stirred under hydrogen atmosphere for 6 h. Subsequently, the reaction mixture was cooled to 0 °C and a solution of ethyl chloroformate (1.2 eq., 1.2 mmol, 114 μL) in 2-propanol (2 mL) was added dropwise over a period of 1 h. Two hours after the addition, the reaction was completed and the catalyst filtered through diatomaceous earth. Thereafter, the pH of the filtrate was adjusted to 2 with 10% hydrochloric acid and the solution was stored in the refrigerator. Since precipitation did not occurred, the solvent removed in a partial vacuum and the residue recrystallized from tetrahydrofuran. The drying takes place at 40 °C and 8 mbar. Yield: 0.12 g (44%); Purity 100%, Mp: 189–191 °C (solid from tetrahydrofuran); R_f = 0.80 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR: (DMSO-d_6): δ = 0.54–0.58 (m, 2H, C^{8}H$_2$), 0.85–0.90 (m, 2H, C^{8}H$_2$), 1.22 (bs, 3H, C^{11}H$_3$), 2.63 (bs, 1H, C^{7}H), 4.06 (q, ^3J = 6.8 Hz, 2H, C^{10}H$_2$), 6.00 (d, ^3J = 8.8 Hz, 1H, C^{5}H), 7.50 (d, ^3J = 8.0 Hz, 1H, C^{4}H), 7.57 (s, 2H, NH$_2$), 8.34 (s, 1H, N^{6}H), 8.57 (s, 1H, N^{3}H), 12.91 (bs, 1H, HCl); ^{13}C-NMR: (DMSO-d_6): δ = 7.3 (2×C^8), 14.5 (C^{11}), 23.6 (C^7), 60.5 (C^{10}), 94.0 (C^5), 106.8 (C^3), 142.6 (C^4), 149.0 (C^2), 150.4 (C^6), 155.0 (C^9); MIR: $\tilde{\nu}$ = 1701 (m, $\nu_{C=O}$), 2961 (w, $\nu_{Ar\text{-}H}$), 3169, 3258 & 3360 (w, $\nu_{N\text{-}H}$); HRMS: calculated for [C$_{11}$H$_{16}$N$_4$O$_2$ + H]$^+$: 237.1346, found: 237.1335.

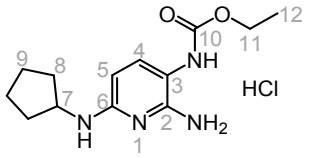
N^2-Cyclopentyl-2,6-diamino-5-nitropyridine (**6d**)



The synthesis carried out according to GWP1, with 5 (4 mmol, 0.69 g) and cyclopropylamine (4.8 mmol, 475 μL) in of 2-propanol (5 mL) were used and the reaction stirred at 120 °C. After filtration, the product washed with little 2-propanol. Yield: 0.68 g (76%) of yellow, amorphous solid; Mp: 151–154 °C (solid from 2-propanol); R_f = 0.85 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR: (DMSO-d_6): δ =

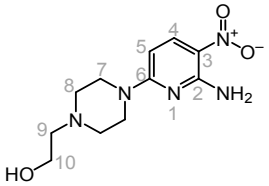
1.43-1.46 & 1.92-1.97 (m & m, 4H, 2×C^8H_2), 1.53-1.57 & 1.67-1.71 (m, 4H, C^9H_2), 4.29-4,35 (m, 1H, C^7H), 5.94 (d, ^3J = 9.2 Hz, 1H, C^5H), 7.72 & 8.13 (bs & bs, 2H, NH_2), 7.91 (d, ^3J = 9.2 Hz, 1H, C^4), 7.92 (s, 1H, NH); ^{13}C-NMR: (DMSO-d_6): δ = 23.4 (C^9), 25.4 (C^8), 51.9 (C^7), 102.7 (C^5), 117.1 (C^3), 133.9 (C^4), 155.9 (C^2), 160.1 (C^6); MIR: $\tilde{\nu}$ = 1513 (m, $\nu_{C\text{-}NO}$), 2939 (w, $\nu_{C\text{-}H}$), 3286 (w, $\nu_{N\text{-}H}$).

Ethyl-[2-amino-6-(cyclopentylamino)pyridin-3-yl]carbamate hydrochloride (**7d**)



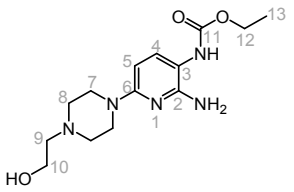
Intermediate **6d** (2 mmol, 0.44 g) together with 0.10 g of palladium activated carbon (10%) were suspended in 2-propanol (10 mL) and stirred under hydrogen atmosphere for 6 h. Since the TLC monitoring still detected the starting material, another 0.18 g of palladium-activated carbon (10%) added under counter current to hydrogen gas. After 18 h, the reduction was complete and the reaction was cooled to 0 °C. A solution of ethyl chloroformate (1.25 eq., 2.5 mmol, 238 µL) in 2-propanol (2 mL) was added dropwise over 25 min. Additional ethyl chloroformate (0.5 eq., 1 mmol, 57 µL) dissolved in 2-propanol (1 mL) was necessary to complete the reaction. Three hours after the last addition, the reaction was complete and the catalyst was filtered. The residue washed with 2-propanol and the pH of the filtrate was adjusted to 2 with 10% hydrochloric acid. Since precipitation did not occurred, the solution was concentrated in a partial vacuum and then recrystallized from ethanol. The product was dried at 45 °C and 8 mbar. Yield: 0.16 g (27%) of light blue coloured, shining plates; Purity 100%; Mp: 216-218 °C (solid from Ethanol); R_f = 0.80 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR: (DMSO-d_6): δ = 1.21 (t, ^3J = 6.8 Hz, 3H, $C^{12}H_3$), 1.41-1.43 (m, 2H, C^8H_2), 1.58-1.61 (m, 2H, C^9H_2), 1.64-1.70 (m, 2H, C^9H_2), 1.98-2.05 (m, 2H, C^8H_2), 4.06 (q, ^3J = 6.8 Hz, 2H, $C^{11}H_2$), 5.94 (d, ^3J = 8.8 Hz, 1H, C^5H), 7.44 (d, ^3J = 8.8 Hz, 1H, C^4H), 7.44 (s, 2H, NH_2), 8.00 (d, ^3J = 6.8 Hz, 1H, N^6H), 8.49 (s, 1H, N^3H), 12.87 (bs, 1H, HCl); ^{13}C-NMR: (DMSO-d_6): δ = 14.5 (C^{12}), 23.3 (2×C^9), 32.2 (2×C^8), 53.1 (C^7), 60.5 (C^{11}), 94.3 (C^5), 105.5 (C^3), 142.6 (C^4), 148.8 (C^2), 149.0 (C^6), 155.1 (C^{10}); MIR: $\tilde{\nu}$ = 1689 (m, $\nu_{C=O}$), 2952 (w, $\nu_{Ar\text{-}H}$), 3140 & 3320 (w, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{13}H_{20}N_4O_2 + H]^+$: 265.1659, found: 265,1658.

2-[4-(6-Amino-5-nitropyridin-2-yl)piperazin-1-yl)ethanl-1-ol (**6e**)



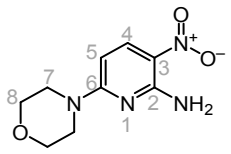
The synthesis carried out according to GWP1 with **5** (2 mmol, 0.35 g), 2-(piperazin-1-yl)ethanol (2.4 mmol, 294 μL) and triethylamine (2.8 mmol, 386 μL) in 2-propanol (2 mL). Yield: 0.5 g (93%) of yellow, amorphous solid; Mp: 212-214 °C (solid from 2-propanol); R_f = 0.26 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR (DMSO-d_6): δ = 2.42 (t, ^3J = 6.2 Hz, 2H, C^9H_2), 2.47 (t, ^3J = 5.1 Hz, 4H, 2×C^8H_2), 3.53 (q, ^3J = 5.9 Hz, 2H, $C^{10}H_2$), 3.70 (bs, 4H, 2×C^7H_2), 4.45 (t, ^3J = 5.4 Hz, 1H, OH), 6.33 (d, ^3J = 9.6 Hz, 1H, C^5H), 7.70 & 7.96 (bs & bs, 2H, NH_2), 8.05 (d, ^3J = 9.6 Hz, 1H, C^4H); ^{13}C-NMR (DMSO-d_6): δ = 44.2 (C^7), 52.89 (C^8), 58.5 (2×C^{10}), 60.0 (2×C^9), 98.7 (C^5), 117.7 (C^3), 135.6 (C^4), 154.6 (C^2), 159.1 (C^6); MIR: $\tilde{\nu}$ = 1560 (m, $\nu_{C\text{-}NO}$), 3102 (m, $\nu_{O\text{-}H}$), 3275 & 3425 (m, $\nu_{N\text{-}H}$).

Ethyl-{2-amino-6-[4-(2-hydroxyethyl)piperazin-1-yl]pyridin-3-yl}carbamate (**7e**)



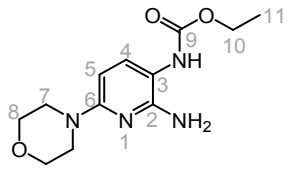
Intermediate **6e** (2 mmol, 0.53 g) together with 0.2 g of palladium-activated carbon (10%) were suspended in 2-propanol (40 mL) and stirred under hydrogen atmosphere for 2.5 h. The suspension then filtered through diatomaceous earth and cooled to 0 °C under an argon atmosphere. A solution of ethyl chloroformate (1.2 eq., 2.4 mmol, 228 μL) in 2-propanol (5 mL) was added dropwise over a period of 1 h and the reaction mixture was stirred for another 3 h at 0 °C. The pH of the solution was adjusted to 2 with 10% hydrochloric acid. Since precipitation did not occur, the hydrochloride precipitated by the addition of diethyl ether. The resulting solid was filtered off and purified by flash chromatography (column: Biotage® Snap silica 50 g, mobile phase: dichloromethane/methanol, gradient: 0-3 min 0% methanol, 3-13 min 0-40% methanol, 13- 25 min 40% methanol, flow rate: 40 mL/min). The fractions containing the product combined and concentrated in a partial vacuum. The pH of the solution adjusted to 11 with sodium hydroxide solution (1 mol/L) and then extracted with n-butanol (4 × 15 mL). The combined organic phases were concentrated under partial vacuum and recrystallized from dichloromethane. Yield: 0.04 g (7%) of orange, amorphous solid; Purity 100%; Mp: 141-143 °C (solid from dichloromethane); R_f = 0.31 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR (DMSO-d_6): δ = 1.20 (bs, 3H, $C^{13}H_3$), 2.45 (bs, 6H, 2×C^8H_2 & C^9H_2), 3.33 (bs, 4H, 2×C^7H_2), 3.52 (bs, 2H, $C^{10}H_2$), 5.35 (s, 2H, NH_2), 5.95 (bs, 1H, C^5H), 7.20 (bs, 1H, C^4H), 8.33 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 14.6 (C^{13}), 45.0 (2×C^7), 53.1 (2×C^8), 58.5 (C^{10}), 60.0 (C^{12}), 60.4 (C^9), 94.6 (C^5), 108.4 (C^3), 135.0 (C^4), 152.3 (C^2), 154.9 (C^{11}), 155.9 (C^6); MIR: $\tilde{\nu}$ = 1710 (m, $\nu_{C=O}$), 2820 (w, $\nu_{C\text{-}H}$), 3212, 3312 & 3397 (w, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{14}H_{23}N_5O_3 + H]^+$: 310,1874, found: 310,1870.

2-Amino-6-(morpholin-4-yl)-3-nitropyridine (**6f**)



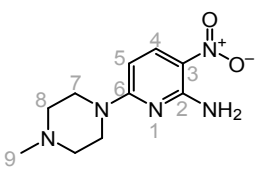
The synthesis carried out according to GWP1 with **5** (5 mmol, 0.87 g), morpholine (6 mmol, 522 µL) and triethylamine (7 mmol, 966 µL) in 2-propanol (5 mL). Yield: 0.96 g (86 %) of yellow crystalline solid; Mp: 182-184 °C (solid from 2-propanol); R_f = 0.61 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR (DMSO-d_6): δ = 3.66-3.69 (m, 8H, 2×C^{7}H$_2$ & 2×C^{8}H$_2$), 6.32 (d, ^3J = 9.5 Hz, 1H, C^{5}H), 7.72 & 7.97 (bs & bs, 2H, NH$_2$), 8.08 (d, ^3J = 9.5 Hz, 1H, C^{4}H); ^{13}C-NMR (DMSO-d_6): δ = 44.5 (2×C^7), 65.9 (2×C^8), 98.6 (C^5), 118.0 (C^3), 135.7 (C^4), 154.5 (C^2), 159.3 (C^6); MIR: $\tilde{\nu}$ = 1556 (m, $\nu_{C\text{-}NO}$), 3361 & 3451 (m, $\nu_{N\text{-}H}$).

Ethyl-[2-amino-6-(morpholin-1-yl)pyridin-3-yl]carbamate-Hydrochloride (**7f**)



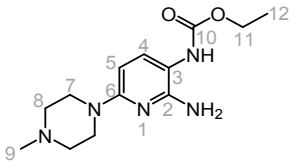
In a 3-necked flask, **6f** (1 mmol, 0.22 g) was suspended in 20 mL of 2-propanol and 0.10 g of palladium-charcoal (10%) was added. Under hydrogen atmosphere, the reaction mixture stirred for 4 h and triethylamine (1.5 eq., 1.5 mmol, 0.2 mL) was added. The mixture cooled to 0 °C and ethyl chloroformate (1.2 eq., 1.2 mmol, 114 µL) added dropwise. After 2.5 h of stirring at 0 °C, the reaction was complete and then filtered. With the aid of 10% hydrochloric acid, the pH of the solution was adjusted to 2, whereby the colour turned from green to red. By adding diethyl ether (20 mL), triethylammonium chloride precipitated first, which was filtered off. An additional diethyl ether (20 mL) added to the filtrate, whereby the product precipitated. After filtering off, the solid dried in a partially evacuated sulfuric acid desiccator. Yield: 0.08 g (28%) of green coloured needles; Purity 100%; Mp: 198-200 °C (solid form 2-propanol); R_f = 0,51 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 1.22 (t, ^3J = 6.7 Hz, 3H, C^{11}H$_3$), 3.54 (s, 4H, 2×C^{7}H$_2$), 3.71 (s, 4H, 2×C^{8}H$_2$), 4.08 (q, ^3J = 6.9 Hz, C^{10}H$_2$), 6.17 (d, ^3J = 8.8 Hz, 1H, C^{5}H), 7.63 (d, ^3J = 5.7 Hz, 1H, C^{4}H), 7.71 (bs, 2H, NH$_2$), 8.70 (s, 1H, NH), 13.48 (bs, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 14.4 (C^{11}), 46.7 (2×C^7), 60.6 (C^{10}), 65.3 (2×C^8), 94.6 (C^5), 109.3 (C^3), 141.3 (C^4), 149.5 (C^2), 150.0 (C^6), 154.8 (C^9); MIR: $\tilde{\nu}$ = 1707 (s, $\nu_{C=O}$), 3278 & 3329 (w, $\nu_{N\text{-}H}$); HRMS: calculated for [C$_{12}$H$_{18}$N$_4$O$_3$ + H]$^+$: 267.1452, found: 267,1450.

2-Amino-6-(4-methylpiperazin-1-yl)-3-nitropyridine (**6g**)



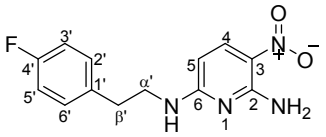
The synthesis carried out according to GWP1 with **5** (5 mmol, 0.87 g), N-methylpiperazine (6 mmol, 665 µL) and triethylamine (7 mmol, 966 µL) in 2-propanol (5 mL). Yield: 1.00 g (84%) of orange, amorphous solid; Mp: 173–174 °C (solid from 2-propanol); R_f = 0.30 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR (DMSO-d_6): δ = 2.21 (s, 3H, C^{9}H$_3$), 2.36 (t, ^3J = 5.2 Hz, 4H, 2×C^{8}H$_2$), 3.71 (t, ^3J = 4.6 Hz, 4H, 2×C^{7}H$_2$), 6.34 (d, ^3J = 9.6 Hz, 1H, C^{5}H), 7.70 & 7.97 (bs & bs, 2H, NH$_2$), 8.05 (d, ^3J = 9.6 Hz, 1H, C^{4}H); ^{13}C-NMR (DMSO-d_6): δ = 44.0 (2×C^7), 45.5 (C^9), 54.3 (2×C^8), 98.7 (C^5), 117.7 (C^3), 135.7 (C^4), 154.6 (C^2), 159.2 (C^6); MIR: $\tilde{\nu}$ = 1561 (m, ν_{C-NO}), 3247 & 3427 (m, ν_{N-H}).

Ethyl-[2-amino-6-(4-methylpiperazin-1-yl)pyridin-3-yl]carbamate (**7g**)



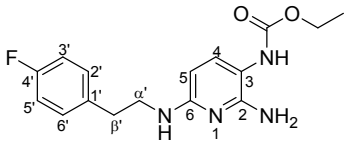
Intermediate **6g** (2 mmol, 0.47 g) and 0.30 g of palladium activated carbon (10%) were suspended in 2-propanol (40 mL), which was stirred under hydrogen atmosphere for 4 h. Under argon atmosphere, the catalyst filtered off through diatomaceous earth and the filtrate cooled to 0 °C. Ethyl chloroformate (1.2 eq., 2.4 mmol, 228 µL) was dissolved in 2-propanol (2 mL) and added dropwise to the filtrate. After 3 h, another 0.5 mmol of ethyl chloroformate (0.25 eq., 50 µL) dissolved in 1 mL of 2-propanol was added dropwise and the reaction mixture was stirred further for an hour at 0 °C. Subsequently, the pH of the solution was adjusted to 2 with 10% hydrochloric acid and the resulting suspension stored for 16 h in the refrigerator. The solid was then filtered off, dissolved in 30 ml of water and the pH was adjusted to 11 with 1 mol/L sodium hydroxide solution. The solution extracted with *n*-butanol (3 × 20 mL) and the combined organic phases were concentrated under partial vacuum. The residue was purified by flash chromatography (column: Biotage® Snap silica 50 g, mobile phase: dichloromethane/methanol, gradient: 0-3 min 10% methanol, 3-13 min 10-40% methanol, 13-15 min 40 % Methanol, flow rate: 50 mL/min). The product fractions were evaporated and the resulting green, oily residue was recrystallized from a mixture of diethyl ether (50 mL) and dichloromethane (8 mL). Eventually, the product was dried at 40 ° C and 8 mbar. Yield: 0.12 g (22%) of light pink, amorphous solid; Purity 100%; Mp: 152-153 °C (solid form diethyl ether/dichloromethane); R_f = 0.40 (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR (DMSO-d_6): δ = 1.21 (t, ^3J = 6.1 Hz, 3H, C^{12}H$_3$), 2.20 (s, 3H, C^{9}H$_3$), 2.35 (t, ^3J = 5.0 Hz, 4H, 2×C^{8}H$_2$), 3.33 (t, ^3J = 4.9 Hz, 4H, C^{7}H$_2$), 4.05 (q, ^3J = 7.1 Hz, 2H, C^{11}H$_2$), 5.34 (s, 2H, NH$_2$), 5.95 (d, ^3J = 8.5 Hz, 1H, C^{5}H), 7.20 (d, ^3J = 5.8 Hz, 1H; C^{4}H), 8.30 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 14.6 (C^{12}), 44.8 (2×C^8), 45.8 (C^9), 54.4 (2×C^7), 60.0 (C^{11}), 94.6 (C^5), 108.4 (C^3), 135.0 (C^4), 152.2 (C^2), 154.9 (C^{10}), 155.9 (C^6); MIR: $\tilde{\nu}$ = 1703 (m, $\nu_{C=O}$), 2942 (w, ν_{Ar-H}), 3372 (w, ν_{N-H}); HRMS: calculated for [$C_{13}H_{21}N_5O_2$ + H]$^+$: 280.1768, found: 280.1765.

N^2-(4-Fluorophenethyl)-5-nitropyridine-2,6-diamine (**6h**)



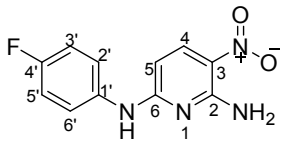
Intermediate **5** (5 mmol, 868 mg), 4-fluorophenethyl amine (7.5 mmol, 984 µL) and triethylamine (10 mmol, 1.4 mL) suspended in 2-propanol (10 mL). The suspension heated in microwave (120 ˚C, 20 min). Water then added to precipitate the product. A pure product collected using filtration; Yield: 90%, yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.14 (bs & bs, 2H, *N*^{2}H$_2$), 8.02 (bs, 1H, *N*^{6}H), 7.94 (d, 1H, ^3J = 9.2 Hz, C(4)H), 7.33 (m, 2H, C(2')H & C(6')H), 7.14 (m, 2H, C(3')H & C(5')H), 5.95 (d, 1H, ^3J = 9.2 Hz, C(5)H), 3.57 (m, 2H, C(α')H$_2$), 2.86 (m, 2H, C(β')H$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0 (d, $^1J_{C,F}$ = 240 Hz, C4'), 160.5 (C6), 155.8 (C2), 135.5 (d, $^4J_{C,F}$ = 3 Hz, C1'), 134.2 (C4), 130.5 (d, $^3J_{C,F}$ = 7 Hz, C2' & C6'), 117.3 (C3), 115.0 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 102.4 (C5), 42.2 (Cβ'), 33.8 (Cα').

Ethyl {2-amino-6-[(4-fluorophenethyl)amino]pyridin-3-yl}carbamate (**7h**)



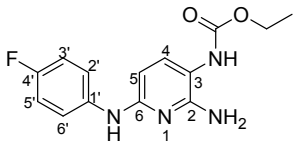
Intermediate **6h** (4 mmol, 1.105 g) and Pd/C (400 mg, 10% Pd) suspended in 2-propanol (15 mL). The suspension carefully set under hydrogen atmosphere and stirred for overnight. Triethylamine (6 mmol, 837 µL) and ethyl chloroformate (5 mmol, 476 µL) added respectively and the mixture stirred for 4 h. The mixture filtered and washed with ethanol (3 x 25 mL). The filtrate evaporated to dryness and then partitioned between dichloromethane and water. The dichloromethane phase evaporated to dryness and packed for flash chromatography (solvent: dichloromethane and ethanol); Yield: 24%, off-white solid; Purity 100%; Mp: 133-134 ˚C (solid from dichloromethane and ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17 (bs, 1H, *N*^{3}H), 7.30 (m, 2H, C(2')H & C(6')H), 7.12 (m, 2H, C(3')H & C(5')H), 7.03 (d, 1H, ^3J = 8 Hz, C(4)H), 5.99 (m, 1H, *N*^{6}H), 5.69 (d, 1H, ^3J= 8.4 Hz, C(5)H), 5.18 (s, 2H, *N*^{2}H$_2$), 4.06 (q, 2H, ^3J= 7.03 Hz, -OCH$_2$), 3.32 (m, 2H, C(α')H$_2$), 2.80 (m, 2H, C(β')H$_2$), 1.21 (bs, 3H, -OCH$_2$C<u>H$_3$</u>); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.9 (d, $^1J_{C,F}$ = 240 Hz, C4'), 155.8 (C6), 155.1 (C=O), 153.1 (C2), 136.3 (d, $^4J_{C,F}$ = 3 Hz, C1'), 135.6 (C4), 130.4 (d, $^3J_{C,F}$= 8 Hz, C2' & C6'), 115.0 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 106.3 (C3), 95.1 (C5), 59.9 (OCH$_2$), 43.0 (Cα'), 34.4 (Cβ'), 14.6 (OCH$_2$<u>C</u>H$_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3154 (N-H), 1698 (C=O), 1217 (C-F); HRMS ((ESI) m/z) calculated for [$C_{16}H_{19}FN_4O_2$ + H]$^+$: 319.1565, found: 319.1553.

N^2-(4-Fluorophenyl)-5-nitropyridine-2,6-diamine (**6i**)



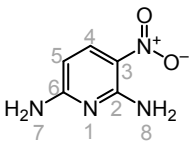
Intermediate **5** (5 mmol, 868 mg), triethylamine (10 mmol, 1.4 mL), 4-fluoroaniline (7.5 mmol, 720 µL) and 2-propanol (10 mL) were mixed. The mixture held at reflux for 3 days. Water added to precipitate the product that was collected by filtration; Yield: 84 %, yellow solid; Mp: 200-201 ˚C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.90 (s, 1H, *N*^{6}H), 8.12 (d, 3H, ^{3}J = 9.2 Hz, C(4)H & *N*^{2}H$_2$), 7.91 (m, 2H, C(2')H & C(6')H), 7.16 (m, 2H, C(3')H & C(5')H), 6.20 (d, 1H, ^{3}J = 9.2 Hz, C(5)H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (d, $^{1}J_{C,F}$ = 239 Hz, C4'), 158.0 (C6), 155.1 (C2), 136.2 (d, $^{4}J_{C,F}$ = 2 Hz, C1'), 135.0 (C4), 121.6 (d, $^{3}J_{C,F}$ = 7 Hz, C2' & C6'), 118.5 (C3), 115.3 (d, $^{2}J_{C,F}$ = 22 Hz, C3' & C5'), 102.9 (C5); IR (cm^{-1}): $\tilde{\nu}$ = 3482 (N-H), 1226 (C-F).

Ethyl {2-amino-6-[(4-fluorophenyl)amino]pyridine-3-yl}carbamate (**7i**)



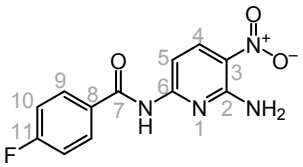
Compound **6i** (4 mmol, 993 g) and Pd/C (400 mg, 10% Pd) suspended in 2-propanol (20 mL) and then carefully set under hydrogen atmosphere and stirred for overnight. Triethylamine (6 mmol, 837 µL) and ethyl chloroformate (5 mmol, 476 µL) added respectively and the mixture stirred for additional 4 h. The mixture filtered and washed with ethanol (3 x 25 mL). The filtrate evaporated to dryness and a pure product collected by recrystallization from dichloromethane; Yield: 30%, ghost-white solid; Purity 100%; Mp: 184-185 ˚C (solid from dichloromethane); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61 (s, 1H, *N*^{6}H), 8.34 (bs, 1H, *N*^{3}H), 7.68 (m, 2H, C(2')H & C(6')H), 7.22 (d, 1H, ^{3}J = 5.24 Hz, C(4)H), 7.04 (m, 2H, C(3')H & C(5')H), 6.02 (d, 1H, ^{3}J= 8.28 Hz, C(5)H), 4.08 (q, 2H, ^{3}J= 7.03 Hz, -OCH_2), 1.23 (t, 3H, ^{3}J = 6.60 Hz, -$OCH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.2 (d, $^{1}J_{C,F}$ = 234 Hz, C4'), 155.0 (C=O), 152.4 (C6), 152.2 (C2), 138.9 (d, $^{4}J_{C,F}$ = 2 Hz, C1'), 135.2 (C4), 118.5 (d, $^{3}J_{C,F}$ = 7 Hz, C2' & C6'), 114.9 (d, $^{2}J_{C,F}$ = 21 Hz, C3' & C5'), 108.6 (C3), 97.7 (C5), 60.1 (OCH_2), 14.6 ($OCH_2\underline{C}H_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3309 (N-H), 1683 (C=O); HRMS ((ESI) m/z) calculated for $[C_{16}H_{15}FN_4O_2 + H]^+$: 292.1252, found: 292.1240.

2,6-Diamino-3-nitropyridine (**6ji**)



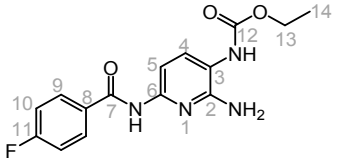
In a PTFE reaction vessel, **5** (30 mmol, 5.79 g) and 25% strength aqueous ammonia solution (48 mL) were suspended in ethanol (200 mL) and the resulting mixture stirred for 2 h at 140 °C. During cooling, a yellow precipitate formed and to complete the precipitation, the suspension was stored overnight in the refrigerator. The product then filtered off, washed with water and dried in a drying oven at 70 °C. To increase the yield, the filtrate can be concentrated under partial vacuum and then recrystallize from ethanol. Yield: 4.61 g (91%) of yellow needle-shaped crystals; Mp: 225-227 °C (solid from ethanol); R_f = 0.18 (*n*-hexane/ethyl acetate 6:4); ^{1}H-NMR (DMSO-d_6): δ = 5.92 (d, ^3J = 9.3 Hz, 1H, C^{5}H), 7.26 (bs, 2H, N^{7}H$_2$), 7.58 & 8.01 (bs, 2H, N^{8}H$_2$), 7.98 (d, ^3J = 9.2 Hz, 1H, C^{4}H); ^{13}C-NMR (DMSO-d_6): δ = 101.6 (C^5), 117.7 (C^3), 135.3 (C^4), 155.8 (C^2), 162.5 (C^6); MIR: $\tilde{\nu}$ = 1593 (s, $\nu_{C\text{-}NO}$), 3140 (m, $\nu_{Ar\text{-}H}$), 3338, 3393 & 3435 (m, $\nu_{N\text{-}H}$).

N-(6-Amino-5-nitropyridin-2-yl)-4-fluorobenzamide (**6j**)



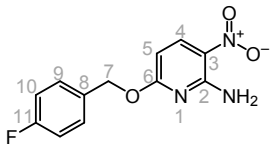
In a glass vial, **6ji** (5 mmol, 0.77 g) was dissolved in pyridine (15 mL) and then 4-fluorobenzoyl chloride (5.5 mol) was added. The reaction mixture heated in the microwave reactor (60 °C, 5 min) and precipitated by the addition of water. The precipitate filtered off, taken up in dichloromethane (200 mL) and washed with water (100 mL), and saturated brine (100 mL). The organic phase dried over Na_2SO_4 and adsorbed on diatomaceous earth using a partial vacuum. The product purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 7: 3, as soon as the by-product was eluted, switch to n-hexane/ethyl acetate 1:1). The product dried at 40 °C and 6 mbar. Yield: 0.74 g (54%) of pale yellow, amorphous solid. Mp: 195-198 °C (solid form *n*-hexane/ethyl acetate); R_f = 0.34 (dichloromethane); ^{1}H-NMR (DMSO-d_6): δ = 7.33-7.37 (m, 2H, 2×C^{10}H), 7.56 (d, ^3J = 9.2 Hz, 1H, C^{5}H), 7.74 (s, 2H, NH_2), 8.05-8.09 (m, 2H, 2×C^{9}H), 8.45 (d, ^3J = 9.2 Hz, 1H, C^{4}H), 10.98 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 104.1 (C^5), 115.3 (d, ^2J = 22 Hz, 2×C^{10}), 123.2 (C^3), 130.1 (d, ^4J = 3 Hz, C^8), 131.2 (d, ^3J = 9 Hz, 2×C^9), 137.5 (C^4), 153.4 (C^2), 156.4 (C^6), 163.3 & 165.7 (d, ^1J = 251 Hz, C^{11}), 165.9 (C^7); MIR: $\tilde{\nu}$ = 1569 (m, $\nu_{C\text{-}NO}$), 1692 (m, $\nu_{C\text{-}NO}$), 3332 & 3453 (m, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{12}H_9N_4O_3F + H]^+$: 277.0731, found: 277.0737.

Ethyl-[2-amino-6-(4-fluorbenzamido)pyridin-3-yl]carbamate (**7j**)



In a 3-necked flask, **6j** (1 mmol, 0.28 g) and 0.05 g of palladium-charcoal (10%) were suspended in 10 mL of pyridine, which was stirred under hydrogen atmosphere for 5.5 h. The suspension subsequently cooled to 0 °C and ethyl chloroformate (1.25 mmol, 120 μL) added dropwise. The mixture stirred for 2.5 h at 0 °C and then filtered through diatomaceous earth. The residue washed with a little pyridine and the product precipitated by addition of water to the filtrate. The suspension was stored overnight in the refrigerator, the product was then filtered off and finally recrystallized from methanol. The product was dried at 40 °C and 4 mbar. Yield: 0.08 g (27%) of pale yellow, amorphous solid; Purity 100%; Mp: degradation ca 160 °C; R_f = 0.29 (dichloromethane/methanol/acetic acid 96:3:1); ^{1}H-NMR (DMSO-d_6): δ = 1.24 (t, ^3J = 7.0 Hz, 3H, $C^{14}H_3$), 4.11 (q, ^3J = 7.1 Hz, 2H, $C^{13}H_2$), 7.29-7.33 (m, 2H, 2×C^{10}H), 7.35 (d, ^3J = 8.4 Hz, 1H, C^5H), 7.57 (d, ^3J = 8.0 Hz, 1H, C^4H), 8.04-8.07 (m, 2H, 2×C^9), 8.62 (s, 1H, N^3H), 10.24 (s, 1H, N^6H); ^{13}C-NMR (DMSO-d_6): δ = 14.5 (C^{14}), 60.3 (C^{13}), 102.9 (C^5), 114.8 (C^3), 115.2 (d, ^2J = 22 Hz, 2×C^{10}), 130.5 (d, ^3J = 9 Hz, 2×C^9), 130.9 (d, ^4J = 3 Hz, C^8), 133.0 (C^4), 146.6 (C^2), 151.9 (C^6), 154.5 (C^{12}), 162.8 & 165.3 (d, ^1J = 249 Hz, C^{11}), 164.2 (C^7); MIR: $\tilde{\nu}$ = 1661 & 1713 (s, $\nu_{C=O}$), 2984 (w, ν_{C-H}), 3176, 3291 & 3331 (m, ν_{N-H}); HRMS: calculated for $[C_{15}H_{15}N_4O_3F + H]^+$: 319.1201, found: 319.1200.

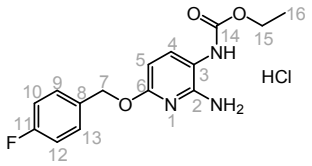
6-[(4-Fluorbenzyl)oxy]-3-nitropyridin-2-amine (**6k**)



Method A: In a 3-necked flask, potassium tert-butoxide (1.5 eq., 7.5 mmol, 0.84 g) and under argon atmosphere, a solution of 4-fluorobenzyl alcohol (1.02 eq., 5.1 mmol, 593 μL) in anhydrous 1,4-dioxane (20 mL) was introduced. The mixture heated for 1 h at 50 °C and then in an argon counter current, **5** (5 mmol, 0.87 g) added, wherein the suspension turns abruptly to red. Subsequently, the reaction mixture heated to 95 °C for 16 h. The reaction quenched by adding a spatula tip of NH_4Cl and the solvent removed in a partial vacuum. The residue mixed with water (30 mL) and sonicated for 5 minutes. The product finally filtered off and washed with water (20 mL). For structural analysis, 100 mg of the product recrystallized from a mixture of *n*-hexane (25 mL) and ethyl acetate (10 mL). The remaining amount used without further purification. Yield: 0.70 g (53%) of yellow, crystalline solid; Mp: 160-162 °C (solid from *n*-hexane/ethyl acetate); R_f = 0.66 (*n*-hexane/ethyl acetate 8:2); ^{1}H-NMR (DMSO-d_6): δ = 5.37 (s, 2H, C^7H_2), 6.18 (d, ^3J = 9.1 Hz, 1H, C^5H), 7.19-7.24 (m, 2H, 2×C^{10}H), 7.55-7.59 (m, 2H, 2×C^9H), 8.19 (bs, 2H, NH_2), 8.27 (d, ^3J = 9.1 Hz, 1H, C^4H); ^{13}C-NMR (DMSO-d_6): δ = 67.2 (C^7), 101.1 (C^5), 115.2 (d, ^2J = 21 Hz, 2×C^{10}), 121.1 (C^3), 131.0 (d, ^3J = 8 Hz, 2×C^9), 132.4 (d, ^4J = 3 Hz, C^8), 138.0 (C^4), 155.0 (C^2), 160.7 & 163.2 (d, ^1J = 244 Hz, C^{11}), 165.6 (C^6); MIR: $\tilde{\nu}$ = 1590 (m, ν_{C-NO}), 3364 & 3483 (w, ν_{N-H}).

Method B: Intermediate **5** (4.17 mmol, 0.72 g) and 4-fluorobenzyl alcohol (1.2 eq., 5 mmol, 537 µL) were dissolved in 50 mL anhydrous toluene and then cooled to 0 °C. Under an argon atmosphere, NaH (1.4 eq., 7 mmol, 0.25 g of a 65% mixture with petroleum ether) added in 4 portions, each with a 15-minute interval, and the mixture was stirred at rt after the last addition. After 16 and 20.5 h, further additions of NaH (7 mmol) were necessary, as the TLC monitoring detected the starting material. After a total of 41 h, the reaction terminated by addition of saturated sodium chloride solution (100 mL). The mixture diluted with another 50 mL of toluene and the resulting phases separated using a separating funnel. The organic phase washed with water (4 × 100 mL) and saturated brine (100 mL) and then dried over $MgSO_4$. Finally, the solvent removed in a partial vacuum. Yield: 0.49 g (45%) of yellow, amorphous solid; Mp: 157-160 °C (solid from toluene). A similar analytical data to method A found.

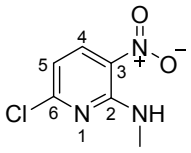
Ethyl-{2-amino-6-[(4-fluorbenzyl)oxy]pyridin-3-yl}carbamate hydrochloride (**7k**)



Intermediate **6k** (1 mmol, 0.26 g) was suspended in a mixture of water (6 mL) and 2-propanol (10 mL). Subsequently, iron powder (3.0 eq., 0.17 g) and NH_4Cl (4.5 eq., 0.24 g) were added and the reaction mixture was heated under reflux for 4 h. The resulting suspension filtered through diatomaceous earth and the filtrate was concentrated in a partial vacuum. The residue taken by 100 mL of water and extracted with ethyl acetate (3 × 40 mL). The organic phase washed with saturated brine and dried over $MgSO_4$. Triethylamine (1.5 eq., 1.5 mmol, 207 µL) added to the solution and cooled to 0 °C. A mixture of ethyl chloroformate (1.25 eq., 1.25 mmol, 119 µL) in 5 mL of ethyl acetate added dropwise over 15 min and the reaction stirred for 2 h at 0 °C. Since the TLC monitor detected a starting material, a further ethyl chloroformate (0.5 eq., 0.5 mmol, 57 µL) dissolved in 5 mL of ethyl acetate added dropwise. After a further 45 min, the reaction was completed and the solvent removed in a partial vacuum. The residue taken up in 30 ml of ethyl acetate and washed with water (2 × 30 mL) and 30 mL of saturated common salt solution. The organic phase was evaporated and then purified by flash chromatography (Büchi MPLC system, self-packed column, mobile phase: n-hexane/ethyl acetate, gradient: 0-3 min 30% ethyl acetate, 3-13 min 30-80% ethyl acetate , 13-15 min 80% ethyl acetate). The product was then dissolved in 2-propanol (3 mL), the pH of the solution was adjusted to 2 with 10% strength hydrochloric acid and the resulting hydrochloride salt was filtered off. Finally, the product was recrystallized from 2-propanol. Yield: 0.13 g (38%) of light brown, shiny platelets; Purity 100%; Mp: 153-156 °C (solid form 2-propanol); R_f = 0.83 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6):

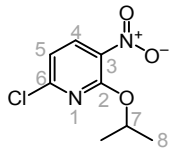
δ = 1.22 (t, ^{3}J = 6.9 Hz, 3H, $C^{14}H_3$), 4.09 (q, ^{3}J = 7.1 Hz, 2H, $C^{13}H_2$), 5.27 (s, 2H, $C^{7}H_2$), 6.27 (d, ^{3}J = 8.4 Hz, 1H, $C^{5}H$), 7.20-7.26 (m, 2H, 2×$C^{10}H$), 7.51-7.67 (m, 2H, 2×$C^{9}H$), 7.68 (d, ^{3}J = 7.5 Hz, 1H, $C^{4}H$), 8.78 (bs, 2H, NH & HCl); ^{13}C-NMR (DMSO-d_6): δ = 14.5 (C^{14}), 60.5 (C^{13}), 68.6 (C^{7}), 94.4 (C^{5}), 113.3 (C^{3}), 115.3 (d, ^{2}J = 21 Hz, 2×C^{10}), 130.5 (d, ^{3}J = 9 Hz, 2×C^{9}), 132.1 (C^{8}), 139.1 (C^{4}), 150.7 (C^{2}), 154.6 (C^{12}), 155.9 (C^{6}), 160.8 & 163.2 (d, ^{1}J = 244 Hz, C^{11}); MIR: $\tilde{\nu}$ = 1692 (s, $\nu_{C=O}$), 2608 (w, $\nu_{N\text{-}H,\ protonated\ amine}$), 3113 & 3240 (w, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{15}H_{16}N_3O_3F + H]^+$: 306.1248, found: 306.1263.

6-Chloro-N-methyl-3-nitropyridin-2-amine (**8a**)



2,6-Dichloro-3-nitropyridine (5 mmol, 1.0 g) was dissolved in acetonitrile (20 mL). After adding triethylamine (7.5 mmol, 1 mL), the mixture was cooled to about 0 ˚C. Methylamine (6 mmol, 613 µL) dissolved in acetonitrile (10 mL) and added slowly over a period of 30 min. After complete addition of methylamine, the mixture stirred for 10 min at about 0 ˚C and then allowed to rise to rt. The mixture was stirred at rt for 30 min. The product was purified using silica gel chromatography (solvent: toluene). Yield: 68%, yellow solid; Mp: 119 - 120 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.72 (d, 1H, ^{3}J = 3.1 Hz, N^{2}H), 8.43 (d, 1H, ^{3}J = 8.6 Hz, C(4)H), 6.78 (d, 1H, ^{3}J = 8.6 Hz, C(5)H), 3.01 (d, 3H, ^{3}J = 4.8 Hz, $N^{2}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.2 (C6), 152.1 (C2), 138.4 (C4), 126.9 (C3), 111.0 (C5), 28.5 ($N^{2}CH_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3397 (N-H), 1567 (NO_2), 758 (Ar-H).

6-Chloro-2-isopropoxy-3-nitropyridine (**8b**)



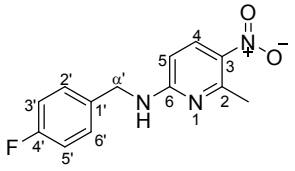
In a 3-necked flask, 2,6-dichloro-3-nitropyridine (5 mmol, 0.97 g) was dissolved in 50 mL of anhydrous toluene and then placed under argon atmosphere. The mixture cooled to 0 °C and 2-propanol (1.2 eq., 462 µL) and NaH (1.4 eq., 0.17 g) added over the side neck under counter current argon. The mixture was stirred overnight at rt. A further 2-propanol (6 mmol) and of NaH (7 mmol) added under counter current to argon. The reaction completed after 3 h and quenched by adding 50 mL of saturated saline. The phases separated in a separating funnel; the toluene phase was washed with water (3 × 50 mL) and saturated saline solution (50 mL) and then dried over Na_2SO_4. Removal of the solvent under partial vacuum gave a brown solid that was purified by flash chromatography (mobile phase: n-hexane/diethyl ether 9:1). Yield: 0.73 g (67%) of yellow, amorphous solid; Mp: 66-68 °C (solid form *n*-hexane/ethyl

acetate); R_f = 0.56 (*n*-hexane/diethyl ether 9:1); ^{1}H-NMR (DMSO-d_6): δ = 1.36 (d, ^3J = 6.2 Hz, 6 H, 2×C^{8}H$_3$), 5.37 (sep, ^3J = 6.2 Hz, 1H, C^{7}H), 7.30 (d, ^3J = 8.3 Hz, 1H, C^{5}H), 8.47 (d, ^3J = 8.3 Hz, 1H, C^{4}H); ^{13}C-NMR (DMSO-d_6): δ = 21.4 (2×C^8), 72.0 (C^7), 116,7 (C^5), 132.9 (C^3), 138.5 (C^4), 151.1 (C^6), 154.7 (C^2); MIR: $\tilde{\nu}$ = 1554 (m, $\nu_{c\text{-}NO}$), 2988 (w, $\nu_{C\text{-}H}$), 3177 (w, $\nu_{Ar\text{-}H}$).

6-Chloro-2-hydroxy-3-nitropyridine (**9a**)

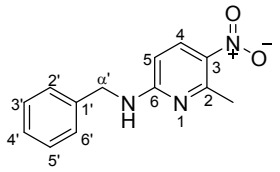
To a solution of **5** (5 mmol, 0.87 g) in concentrated sulfuric acid (15 mL), was added a dropwise solution of $NaNO_2$ (2 eq., 10 mmol, 0.69 g) in 6 mL water. The product precipitated by the addition of another water (30 mL), then filtered off and washed with cold water. Finally, the product was recrystallized from 2-propanol. The product dried in a partially evacuated desiccator. Yield; 0.52 g (60%) of yellow, powdery solid. Mp: 177-183 °C (solid from 2-propanol); R_f = 0.16 (*n*-hexane/ethyl acetate 7:3); ^{1}H-NMR (DMSO-d_6): δ = 7.08 (d, ^3J = 8.3 Hz, 1H, C^{5}H), 8.43 (d, ^3J = 8.4 Hz, 1H, C^{4}H), 13.74 (bs, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ = 114.1 (C^5), 132.2 (C^3), 139.0 (C^4), 150.4 (C^2), 156.6 (C^6); MIR: $\tilde{\nu}$ = 1582 (m, $\nu_{C\text{-}NO}$), 1650 (m, $\nu_{C=O}$), 2767 (w, $\nu_{C\text{-}H}$), 3104 (w, $\nu_{Ar\text{-}H}$).

N-(4-Fluorobenzyl)-6-methyl-5-nitropyridin-2-amine (**10a**)



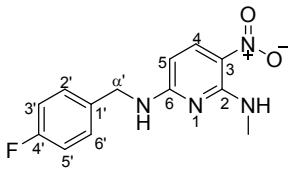
6-Bromo-2-methyl-3-nitropyridine (4 mmol, 868 mg), triethylamine (8 mmol, 1.2 mL), 4-fluorobenzylamine (6 mmol, 686 µL) and 2-propanol (10 mL) were mixed. The mixture stirred for 20 min at 120 °C using microwave. Water added to precipitate the product, which was washed with water (2 x 10 mL) and 2-propanol (5 mL); Yield: 77%, yellow solid; Mp: 155-156 ˚C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.39 (m, 1H, *N*^{6}H), 8.12 (d, 1H, ^3J = 9.2 Hz, C(4)H), 7.40 (m, 2H, C(2')H & C(6')H), 7.18 (m, 2H. C(3')H & C(5')H), 6.50 (d, 1H, ^3J = 8.4 Hz, C(5)H), 4.58 (bs, 2H. C(α')H$_2$), 2.65 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 162.4 (d, $^1J_{C,F}$ = 241 Hz, C4'), 159.2 (C6), 155.9 (C2), 135.3 (t, $^4J_{C,F}$ = 6 Hz, C1'), 134.6 (C4), 129.5 (d, $^3J_{C,F}$ = 6 Hz, C2' & C6'), 115.2 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 43.4 (Cα'), 25.5 (CH$_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3327 (N-H), 1221 (C-F).

N-Benzyl-6-methyl-5-nitropyridin-2-amine (**10b**)



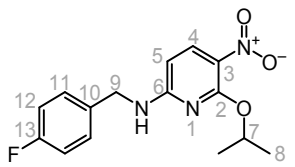
6-Bromo-2-methyl-3-nitropyridine (4 mmol, 868 mg), triethylamine (8 mmol, 1.2 mL), benzyl amine (6 mmol, 656 µL) and 2-propanol (10 mL) were mixed. The mixture stirred for 15 min at 120 °C using microwave. Water added to precipitate the product, and the precipitate washed with water (2 x 10 mL) and 2-propanol (5 mL). Yield: 68%, yellow solid; Mp: 156-157 °C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (bs, 1H, N^6H), 8.12 (d, 1H, ^{3}J = 9.2 Hz, C(4)H), 7.34 (m, 4H, C(2')H, C(6')H, C(3')H & C(5')H), 7.28 (m, 1H, C(4')H), 6.50 (d, 1H, ^{3}J = 5.6 Hz, C(5)H), 4.61 (bs, 2H, C(α')H_2), 2.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9 (C6), 134.6 (C4), 128.4 (C2' & C6'), 127.5 (C4'), 127.0 (C3' & C5'), 44.1 (Cα'), 25.5 (CH_3); IR (cm^{-1}): $\tilde{\nu}$ = 3332 &1590 (N-H).

N^6-(4-Fluorobenzyl)-N^2-methyl-3-nitropyridine-2,6-diamine (**10c**)



Compound **9a** (3.2 mmol, 601 mg), triethylamine (6.4 mmol, 893 mL), 4-fluorobenzyl amine (4.8 mmol, 550 µL) and 2-propanol (10 mL) were mixed and heated using microwave (120 °C, 30 min). Water added to precipitate the product, which was filtered and washed with water (2 x 10 mL) and 2-propanol (5 mL). Yield: 93%, yellow solid; Mp: 147-148 °C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.89 (m, 1H, N^2H), 8.58 (t, 1H, ^{3}J = 5.4 Hz, N^6H), 8.0 (d, 1H, ^{3}J = 9.2 Hz, C(4)H), 7.40 (m, 2H, C(2')H & C(6')H), 7.18 (m, 2H, C(3')H & C(5')H), 6.00 (d, 1H, ^{3}J = 9.3 Hz, C(5)H), 5.0 (d, 2H, ^{3}J = 5.7 Hz, C(α')H_2), 2.97 (d, 3H, ^{3}J = 4.8 Hz, N^2(CH_3)); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4 (d, $^{1}J_{C,F}$ = 241 Hz, C4'), 154.5 (C6), 135.4 (C1'), 134.8 (C4), 129.6 (d, $^{3}J_{C,F}$ = 8 Hz, C2' & C6'), 117.8 (C3), 115.2 (d, $^{2}J_{C,F}$ = 21 Hz, C3' & C5'), 43.4 (Cα'), 27.8 (N^2(CH_3)); IR (cm^{-1}): $\tilde{\nu}$ = 1599 (N-H), 1229 (C-F).

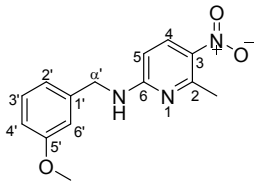
2-[(4-Fluorbenzyl)amino]-6-isopropoxy-5-nitropyridine (**10d**)



In a microwave vessel, compound **9b** (3.6 mmol, 0.79 g) was suspended in 2-propanol (15 mL), triethylamine (1.4 eq., 5.04 mmol, 696 µL) and 4-fluorobenzylamine (1.2 eq., 4.32 mmol, 493 µL). The suspension heated under microwave (1.5 h at 120 °C). Since the TLC monitoring detected the starting

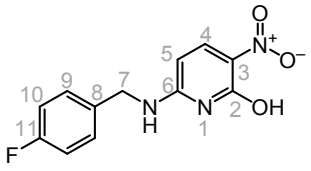
material, a further 4-fluorobenzylamine (0.6 eq., 2.16 mmol, 247 µL) added and the suspension was heated in the microwave reactor for a further 3 h at 120 °C. The resulting yellow solution poured onto water (100 mL), resulting in the precipitation of the product. The solid filtered off and dried at 60 °C in a drying oven. Yield: 1.07 g (97 %) of yellow, amorphous solid; Mp: 137-139 °C (solid from 2-propanol); R_f = 0.49 (*n*-hexane/ethyl acetate 7:3); ^{1}H-NMR (DMSO-d_6): δ = 1.23 (d, ^3J = 6.0 Hz, 6H, 2×C^{8}H$_3$), 4.55 (d, ^3J = 4.9 Hz, 2H, C^{9}H$_2$), 5.31 (sep, ^3J = 6.0 Hz, 1H, C^{7}H), 6.21 (d, ^3J = 8.9 Hz, 1H, C^{5}H), 7.14-7.19 (m, 2H, 2×C^{12}H), 7.34-7.37 (m, 2H, 2×C^{11}H), 8.10 (d, ^3J = 9.0 Hz, 1H, C^{4}H), 8.60 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 21.7 (2×C^8), 43.7 (C^9), 69.5 (C^7), 101.5 (C^5), 115.1 (d, ^2J = 21 Hz, 2×C^{12}), 121.3 (C^3), 129.0 (d, ^3J = 8 Hz, 2×C^{11}), 135.4 (C^{10}), 136.5 (C^4), 157.6 (C^2), 159.5 (C^6), 160.0 & 162.4 (d, ^1J = 242 Hz, C^{13}); MIR: $\tilde{\nu}$ = 1531 (m, $\nu_{C\text{-}NO}$), 2977 (w, $\nu_{C\text{-}H\ (alkyl)}$), 3174 (w, $\nu_{Ar\text{-}H'}$), 3307 & 3355 (m, $\nu_{N\text{-}H}$).

N-(3-Methoxybenzyl)-6-methyl-5-nitropyridin-2-amine (**10e**)



6-Bromo-2-methyl-3-nitropyridine (4 mmol, 868 mg), triethylamine (8 mmol, 1.2 mL), 3-methoxybenzyl amine (6 mmol, 768 µL) and isopropanol (10 mL) mixed and then held at reflux for overnight. Water added to precipitate the product, which was washed with water (2 x 10 mL) and 2-propanol (5 mL). Yield: 95%, yellow solid; Mp: 124-125 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.38 (bs, 1H, *N*^{6}H), 8.12 (d, 1H, ^3J = 9.2 Hz, C(4)H), 7.27 (m, 1H, C(3')H), 6.92 (m, 3H, C(2')H, C(6')H & C(4')H), 6.50 (d, 1H, ^3J = 4.8 Hz, C(5)H), 4.58 (bs, 2H, C(α')H$_2$), 3.73 (s, 3H, C(5')OCH$_3$), 2.65 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 159.3 (C5'), 155.9 (C6), 140.6 (C1'), 134.6 (C4), 129.4 (C3'), 119.6 (C6'), 113.2 (C4'), 112.3 (C2'), 55.0 (OCH$_3$), 44.1 (Cα'), 25.5 (CH$_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3340 & 1587 (N-H), 1530 (NO$_2$).

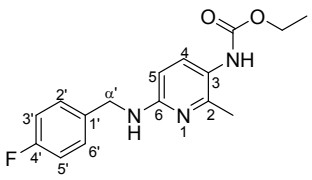
6-[(4-Fluorbenzyl)amino]-2-hydroxy-3-nitropyridine (**10f**)



Intermediate **9c** (3 mmol, 0.53 g), 4-fluorobenzylamine (4.5 mmol, 514 µL) and triethylamine (6 mmol, 840 µL) were dissolved in 2-propanol (45 mL) and heated under reflux for overnight. After cooling to rt, a yellow, voluminous precipitate was formed, which was filtered off and washed with water (2 × 30 mL) and 2-propanol (30 mL). Finally, the product recrystallized from 2-propanol/water (1:1). Yield: 0.32

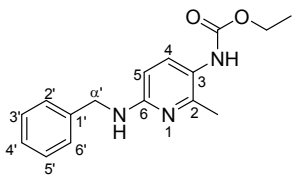
g (40%) of pale yellow, amorphous solid; Mp: 263-265 °C (solid from 2-propanol/water); R_f = 0.41 (*n*-hexane/ethyl acetate/acetic acid 5:5:0.5); ^{1}H-NMR (DMSO-d_6): δ = 4.55 (s, 2H, C^{7}H$_2$), 5.74 (bs, 1H, C^{5}H), 7.19-7.23 (m, 2H, 2×C^{10}H), 7.38-7.41 (m, 2H, 2×C^{9}H), 8.23 (d, ^3J = 8.0 Hz, 1H, C^{4}H), 9.00 (bs, 1H, NH), 11.48 (bs, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ = 44.2 (C^7), 89.1 (C^5), 115.4 (d, ^2J = 21 Hz, 2×C^{10}), 122.4 (C^3), 129.6 (d, ^3J = 6 Hz, 2×C^9), 133.3 (C^8), 140.3 (C^4), 156.3 (C^2 & C^6), 160.4 & 162.8 (d, ^1J = 243 Hz, C^{11}); MIR: $\tilde{\nu}$ = 1509 (m, $\nu_{C\text{-}NO}$), 1665 (m, $\nu_{C=O}$), 3190 & 3255 (w, $\nu_{N\text{-}H}$).

Ethyl {6-[(4-fluorobenzyl)amino]-2-methylpyridin-3-yl}carbamate (**11a**)



Compound **10a** (2.5 mmol, 656 mg) and Pd/C (10%, 250 mg) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred overnight. Triethylamine (3.75 mmol, 523 µL) and ethyl chloroformate (3.125 mmol, 300 µL) added respectively and the mixture stirred for 2 h. The mixture was filtered and washed with ethanol. The product precipitated with the addition of water, which was further purified by recrystallization from dichloromethane; Yield: 40 %, white solid; Purity 100%; Mp: 98-99 ˚C (solid from dichloromethane); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.55 (bs, 1H, *N*^{3}H), 7.38 (m, 2H, C(2')H & C(6')H), 7.18 (d, 1H, ^3J = 8 Hz, C(4)H), 7.14 (m, 2H, C(3')H & C(5')H), 6.90 (t, 1H, ^3J = 6.1 Hz, *N*^{6}H), 6.28 (d, 1H, ^3J = 8.4 Hz, C(5)H), 4.41 (d, 2H, ^3J = 6.0 Hz, C(α')H$_2$), 4.07 (q, 2H, ^3J = 7.0 Hz, -OCH$_2$), 2.16 (s, 3H, CH$_3$), 1.20 (bs, 3H, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 162.2 (d, $^1J_{C,F}$ = 240 Hz, C4'), 155.8 (C6), 156.0 (C2), 136.9 (d, $^4J_{C,F}$ = 3 Hz, C1'), 135.7 (C4), 129.2 (d, $^3J_{C,F}$ = 8 Hz, C2' & C6'), 121.3 (C3), 114.9 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 105.0 (C5), 60.0 (-OCH$_2$), 43.6 (Cα'), 20.6 (CH$_3$), 14.6 (-OCH$_2$C<u>H</u>$_3$); IR (cm^{-1}): $\tilde{\nu}$ = 1693 (C=O), 1223 (C-F); HRMS ((ESI) m/z) calculated for [C$_{16}$H$_{18}$FN$_3$O$_2$ + H]$^+$: 304.1456, found: 304.1454.

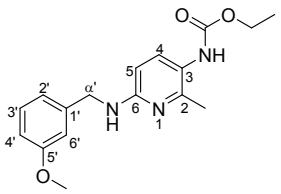
Ethyl [6-(benzylamino)-2-methylpyridin-3-yl]carbamate (**11b**)



Compound **10b** (2.5 mmol, 609 mg) and Pd/C (10%, 250 mg) were suspended in isopropanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for 5 h at rt. Triethylamine (25 mmol, 3.5 mL) and ethyl chloroformate (3.125 mmol, 300 µL) added respectively and the mixture was stirred for 4 h. The mixture was filtered and washed with ethanol. The product was separated using flash chromatography (solvent: dichloromethane and ethanol). The filtrates containing the

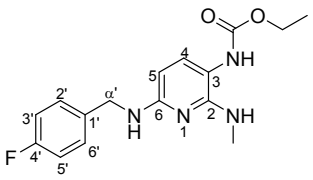
product were combined, evaporated to dryness and re-dissolved in ethanol. Eventually the product precipitated with the addition of water; Yield: 25%, white solid; Purity 100%; Mp: 125-126 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (bs, 1H, *N*^{3}H), 7.34 (m, 4H, C(2')H, C(6')H, C(3')H & C(5')H), 7.23 (m, 2H, C(4)H & C(4')H), 6.88 (t, 1H, ^{3}J = 6.0 Hz, *N*^{6}H), 6.28 (d, 1H, ^{3}J = 8.8 Hz, C(5)H), 4.43 (d, 1H, ^{3}J = 6.0 Hz, C(α')H_2), 4.07 (q, 2H, ^{3}J = 7.0 Hz, -OCH_2), 2.16 (s, 3H, CH_3), 1.22 (t, 3H, ^{3}J = 7.0 Hz, -OCH_2C$\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0 (C6), 155.0 (C=O), 140.7 (C1'), 135.6 (C4), 128.1 (C2' & C6'), 127.4 (C3' & C5'), 126.4 (C4'), 121.2 (C3), 104.9 (C5), 59.9 (-OCH_2), 44.4 (Cα'), 20.6 (CH_3), 14.6 (-O$CH_2\underline{C}H_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3261 (N-H), 1686 (C=O); HRMS ((ESI) m/z) calculated for [$C_{16}H_{19}N_3O_2$ + H]$^{+}$: 286.1550, found: 286.1549.

Ethyl {6-[(3-methoxybenzyl)amino]-2-methylpyridin-3-yl}carbamate (**11c**)



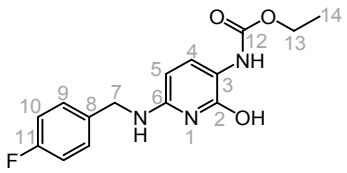
Compound **10e** (3.5 mmol, 954 mg) and Pd/C (10%, 350 mg) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for overnight. Triethylamine (5.25 mmol, 732 µL) and ethyl chloroformate (4.375 mmol, 420 µL) added respectively and the mixture was stirred for 5 h. The mixture was filtered and washed with ethanol (3 x 25 mL). The product was separated using flash chromatography (solvent: dichloromethane and ethanol). The filtrate containing the product were combined, evaporated to dryness and re-dissolved in ethanol. Eventually, water added to precipitate the product. Yield: 14%, white solid; Purity 100%; Mp: 85-86 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (bs, 1H, *N*^{3}H), 7.22 (m, 2H, C(4)H & C(3')H), 6.91 (m, 2H, C(2')H & C(6')H), 6.86 (t, 1H, ^{3}J = 6.1 Hz, *N*^{6}H), 6.78 (m, 1H, C(4')H), 6.28 (d, 1H, ^{3}J = 8.6 Hz, C(5)H), 4.40 (d, 2H, ^{3}J = 6.1 Hz, C(α')H_2), 4.07 (q, ^{3}J = 7.0 Hz, 2H, -OCH_2), 3.72 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3), 1.23 (t, 3H, ^{3}J = 6.1 Hz, -OCH_2C$\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2 (C5'), 156.0 (C6), 155.0 (C=O), 151.1 (C2), 142.4 (C1'), 129.2 (C3'), 121.3 (C3), 119.4 (C6'), 113.0 (C2'), 111.8 (C4'), 104.9 (C5), 59.9 (-OCH_2), 54.9 (OCH_3), 44.4 (Cα'), 20.6 (CH_3), 14.6 (-O$CH_2\underline{C}H_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3270 (N-H), 1687 (C=O); HRMS ((ESI) m/z) calculated for [$C_{17}H_{21}N_3O_3$ + H]$^{+}$: 316.1656, found: 316.1646.

Ethyl {6-[(4-fluorobenzyl)amino]-2-(methylamino)pyridine-3-yl}carbamate (**11d**)



Compound **10c** (2.8 mmol, 774 mg) and Pd/C (10%, 280 mg) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for 4 h. Triethylamine (4.2 mmol, 586 µL) and ethyl chloroformate (4 mmol, 380 µL) added respectively and the mixture was stirred for additional 5 h. The mixture was filtered and washed with ethanol (3 x 25 mL). The product separated using flash chromatography (solvent: dichloromethane and ethanol). The combined filtrate was evaporated to dryness, re-dissolved in ethanol and water added to precipitate the product. The product further purified by recrystallization from dichloromethane. Yield: 18%, off-white solid; Purity 100%; Mp: 196-197 °C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.16 (bs, 1H, N^3H), 7.34 (m, 2H, C2' & C6'), 7.04 (m, 2H, C3' & C5'), 6.84 (bs, 1H, C(4)H), 5.63 (d, 1H, ^{3}J = 4.4 Hz, N^2H), 5.38 (t, 1H, ^{3}J = 5.8 Hz, N^6H), 4.47 (t, 2H, ^{3}J = 6 Hz, C(α')H_2), 4.06 (q, 2H, ^{3}J = 6.8 Hz, -OCH_2), 2.73 (d, 3H, ^{3}J = 4.6 Hz, N^2(CH_3)), 1.20 (bs, 3H, -$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0 (d, $^{1}J_{C,F}$ = 240 Hz, C4'), 155.2 (C=O), 152.3 (C6), 152.1 (C2), 138.0 (d, $^{4}J_{C,F}$ = 2 Hz, C1'), 136.8 (C4), 129.2 (d, $^{3}J_{C,F}$ = 7 Hz, C2' & C6'), 114.6 (d, $^{2}J_{C,F}$ = 21 Hz, C3' & C5'), 107.5 (C3), 102.7 (C4), 60.0 (-OCH_2), 44.0 (Cα'), 27.9 (N^2(CH_3)), 14.6 (-$OCH_2\underline{C}H_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3223 (N-H), 1683 (C=O), 1059 (C-O); HRMS ((ESI) m/z) calculated for [$C_{16}H_{19}N_4O_2F$ + H]$^{+}$: 319.1565, found: 319.1564.

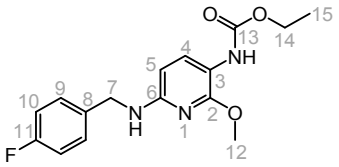
Ethyl-{6-[(4-fluorbenzyl)amino]-2-hydroxypyridin-3-yl}carbamate (**11e**)



In a 3-necked flask, compound **10f** (1 mmol, 0.26 g) and 0.05 g of palladium activated carbon (10%) were suspended in pyridine (10 mL), which then stirred under hydrogen atmosphere for 3.5 h. The reaction mixture cooled to 0 °C and ethyl chloroformate (1.25 eq., 1.25 mmol, 117 µL) added by pots. The suspension stirred for 3 h at 0 °C and then added another 1.25 mmol of ethyl chloroformate (1.25 eq., 117 µL). The reaction completed 45 min after the second addition and the catalyst filtered through diatomaceous earth. The residue washed with a little pyridine and the product precipitated by the addition of water to the filtrate. The solid filtered off, recrystallized from methanol (60 mL) and dried in a partially evacuated desiccator. Yield: 0.08 g (27%) of colourless, fine needles; Purity 100%; Mp: 227-230 °C (solid from pyridine); R_f = 0.66 (*n*-hexane/ethyl acetate/acetic acid 6:4:0.5); ^{1}H-NMR (DMSO-d_6): δ = 1.17 (t, ^{3}J = 7.1 Hz, 3H, $C^{14}H_3$), 4.02 (q, ^{3}J = 7.1 Hz, 2H, $C^{13}H_2$), 4.27 (d, ^{3}J = $C^{7}H_2$), 5.23 (bs, 1H, C^{5}H), 6.26 (bs, 1H, N^{6}H), 7.13-7.19 (m, 2H, 2×C^{10}H), 7.35-7.39 (m, 3H, C^{4}H & 2×C^{9}H), 7.69 (s, 1H, N^{3}H), 10.92 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ = 14.5 (C^{14}), 44.5 (C^{7}), 59.9 (C^{13}), 115.1 (d, ^{2}J = 21 Hz, 2×C^{10}), 129.1 (d, ^{3}J = 8 Hz, 2×C^{9}), 135.1 (C^{3}), 154.2 (C^{6}), 157.6 (C^{2}), 160.0 & 162.4 (d, ^{1}J = 243 Hz, C^{11});

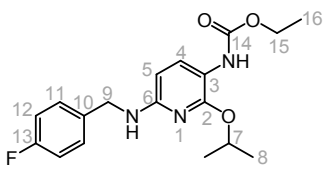
MIR: $\tilde{\nu}$ = 1691 (s, $\nu_{C=O}$), 3296, 3386 & 3413 (w, ν_{N-H}); HRMS: calculated for $[C_{15}H_{16}N_3O_3F + H]^+$: 306.1248, found: 306.1252

Ethyl-{6-[(4-fluorbenzyl)amino]-2-methoxypyridin-3-yl)carbamate (**11f**)



Compound **10g** (1 mmol, 0.28 g) and 0.05 g of palladium-carbon (10%) suspended in pyridine (20 mL) and stirred under hydrogen atmosphere for 22.5 h. The reaction mixture cooled to 0 °C and ethyl chloroformate (1.25 eq., 1.25 mmol, 117 μL) added dropwise. After 2.5 h of stirring, the reaction was complete and the catalyst filtered through diatomaceous earth. The residue washed with a little pyridine; the filtrate taken up by water (100 mL) and then extracted with dichloromethane (2 × 50 mL). The organic phase washed with water (3 × 100 mL) and 100 mL of saturated brine, and dried over Na_2SO_4. The solvent was removed in a partial vacuum, the oily residue was dissolved in little ethanol. A milky emulsion resulted from the addition of water, which was stored for a week in a refrigerator, forming a colourless precipitate with yellow inclusions. The water decanted off and the solid taken up in diethyl ether and again concentrated in a partial vacuum. The residue combined with *n*-hexane and heated to boiling. After cooling to 0 °C, a mixture of yellow and colourless solid formed that was recrystallized twice from *n*-hexane. Yield: 0.06 g (19%) of colourless needles; Purity 100%; Mp: 83-84 °C (solid from *n*-hexane); R_f = 0.90 (*n*-hexane/ethyl acetate/acetic acid 5:5:0.5); ^{1}H-NMR (DMSO-d_6): δ = 1.17 (t, ^3J = 6.3 Hz, 3H, $C^{15}H_3$), 3.72 (s, 3H, $C^{12}H_3$), 4.01 (q, ^3J = 7.1 Hz, 2H, $C^{14}H_2$), 4.40 (d, ^3J = 6.1 Hz, 2H, C^7H_2), 5.99 (d, ^3J = 8.3 Hz, 1H, C^5H), 7.02 (d, ^3J = 6.0 Hz, 1H, N^6H), 7.09-7.14 (m, 2H, 2×C^{10}H), 7.27 (d, ^3J = 5.4 Hz, 1H, C^4H), 7.35-7.38 (m, 2H, 2×C^9H), 8.15 (s, 1H, N^3H); ^{13}C-NMR (DMSO-d_6): δ = 14.6 (C^{15}), 43.9 (C^7), 52.5 (C^{12}), 59.8 (C^{14}), 98.4 (C^5), 108.5 (C^3), 114.8 (d, ^2J = 21 Hz, 2×C^{10}), 129.1 (d, ^3J = 8 Hz, 2×C^9), 136.5 (C^4), 137.1 (d, ^4J = 3 Hz, C^8), 154.7 (C^2), 154.9 (C^6), 159.8 & 162.2 (d, ^1J = 242 Hz, C^{11}); MIR: $\tilde{\nu}$ = 1500 (m, ν_{C-NO}), 1719 (s, $\nu_{C=O}$), 2955 (w, ν_{C-H}), 3281, 3310 & 3360 (w, ν_{N-H}); HRMS: calculated for $[C_{16}H_{18}N_3O_3F + H]^+$: 320.1405, found: 320,1406.

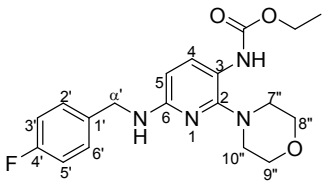
Ethyl-{6-[(4-fluorbenzyl)amino]-2-isopropoxypyridin-3-yl}carbamate (**11g**)



Compound **10d** (1 mmol, 0.30 g), iron powder (3.0 eq., 3 mmol, 0.17 g) and NH_4Cl (4.5 eq., 4.5 mmol, 0.24 g) were suspended in a mixture of 2-propanol (10 mL) and water (6 mL). The mixture heated under

reflux for 3 h and after subsequent cooling to rt, the solvent was removed in a partial vacuum. The residue mixed with 100 ml of water and extracted with ethyl acetate (3 × 50 mL). The combined organic phases washed with saturated brine, dried over Na_2SO_4 and cooled to 0 °C. Triethylamine (1.4 eq., 1.4 mmol, 193 µL) and a solution of ethyl chloroformate (1.2 eq., 1.2 mmol, 114 µL) in ethyl acetate (2 mL) added dropwise and the mixture stirred for 3 h at 0 °C. The solvent was evaporated and the residue purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 8:2). The purple residue was further purified by preparative HPLC (self-packed column, mobile phase: methanol/water, gradient: 0-70 min 60% methanol, 70 -95 min 80% methanol, flow rate: 15 mL/min). The fractions containing the product freed from methanol in a partial vacuum and the resulting emulsion finally lyophilized. Yield: 0.06 (17%) of pink, viscous oil; Purity 100%; Mp: not determined; R_f = 0.68 (*n*-hexane/ethyl acetate 7:3); ^{1}H-NMR (DMSO-d_6): δ = 1.16 (d, ^3J = 6.2 Hz, 6H, 2×C^{8}H$_3$), 1.18 (t, ^3J = 6.3 Hz, 3H, C^{16}H$_3$), 4.02 (q, ^3J = 7.0 Hz, 2H, C^{15}H$_2$), 4.37 (d, ^3J = 6.0 Hz, 2H, C^{9}H$_2$), 5.04 (sep, ^3J = 6.1 Hz, 1H, C^{7}H), 5.99 (d, ^3J = 8.3 Hz, 1H, C^{5}H), 6.97 (t, ^3J = 5.8 Hz, 1H, N^{6}H), 7.08-7.13 (m, 2H, 2×C^{12}H), 7.32-7.35 (m, 3H, C^{4}H & 2×C^{11}H), 7,96 (s, 1H, N^{3}H); ^{13}C-NMR (DMSO-d_6): δ = 14.6 (C^{16}), 22.0 (2×C^8), 43.9 (C^9), 59.8 (C^{15}), 67.2 (C^7), 98.2 (C^5), 109.0 (C^3), 114.8 (d, ^2J = 21 Hz, 2×C^{12}), 128.8 (d, ^3J = 8 Hz, 2×C^{12}), 135.5 (C^4), 137.2 (d, ^4J = 3 Hz, C^{10}), 154.3 (C^6), 154.7 (C^{14}), 155.1 (C^2), 159.7 & 162.1 (d, ^1J = 241 Hz, C^{13}); MIR: $\tilde{\nu}$ = 1714 (m, $\nu_{C=O}$), 2978 (w, ν_{Ar-H}), 3390 & 3435 (w, ν_{N-H}); HRMS: calculated for $[C_{19}H_{24}N_3O_2F + H]^+$:346.1925, found: 346.1917

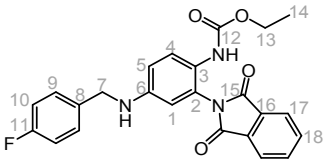
Ethyl {6-[(4-flurobenzyl)amino]-2-morpholinopyridin-3-yl}carbamate (**11h**)



Compound **24b** (2.5 mmol, 831 mg) and Pd/C (250 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred at 40 °C for overnight. Triethylamine (4.5 mmol, 630 µL) and ethyl chloroformate (4 mmol, 400 µL) added respectively and stirred at 40 °C for 1 h. The mixture filtered off and washed with ethanol (3 x 25 mL). The product separated using flash chromatography (solvent: *n*-hexane and ethyl acetate). The filtrate containing the product combined and evaporated to dryness. Yield: 43%, brown solid; Purity 99%; Mp: 70-71 ˚C (solid from *n*-hexane and ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.14 (bs, 1H, *N*^{3}H), 7.36 (m, 2H, C(2')H & C(6')H), 7.16 (m, 3H, C(4)H, C(3')H & C(5')H), 6.91 (t, 1H, ^3J = 6.06 Hz, *N*^{6}H), 6.05 (d, 1H, ^3J = 8.4 Hz, C(5)H), 4.39 (d, 2H, ^3J = 6.00 Hz, C(α')H$_2$), 4.06 (q, 2H, ^3J = 7.08 Hz, -OCH$_2$), 3.63 (m, 4H, C(8")H$_a$, C(9")H$_a$, C(8")H$_b$ & C(9")H$_b$), 3.07 (m, 4H, C(7")H$_a$, C(10")H$_a$, C(7")H$_b$ & C(10")H$_b$), 1.19 (t, 3H, ^3J = 6.92 Hz, -OCH$_2$C<u>H$_3$</u>); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 162.1 (d, $^1J_{C,F}$ = 240 Hz, C4'), 155.0 (C6), 154.9 (C=O), 154.6 (C2), 137.8 (C4), 137.3 (d, $^4J_{C,F}$ = 2 Hz, C1'), 129.1 (d, $^3J_{C,F}$ = 7 Hz, C2' & C6'), 114.8 (d, $^2J_{C,F}$ = 21 Hz,

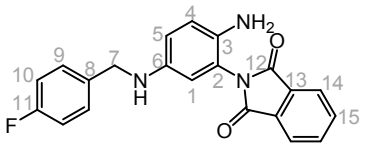
C3' & C5'), 112.2 (C3), 100.2 (C5), 66.1 (C8" & C9"), 59.9 (-OCH_2), 48.6 (C7" & C10"), 43.8 (Cα'), 14.7 (-$OCH_2\underline{C}H_3$); MIR (cm^{-1}): $\tilde{\nu}$ = 3326 (N-H), 1703 (C=O); HRMS ((ESI) m/z) calculated for $[C_{19}H_{23}FN_4O_3 + H]^+$: 375.1827, found: 375.1839.

Ethyl-{2-(1,3-dioxoisoindolin-2-yl)-4-[(4-fluorbenzyl)amino]phenyl}carbamate (**13**)



Compound **2** (10 mmol, 3.03 g) and phthalic anhydride (1.0 eq, 10 mmol, 1.48 g) dissolved in toluene (50 mL) and heated to reflux with the removal of water for 6 h. The solution stored overnight in a refrigerator, forming a brown precipitate. The product filtered off and dried at 60 °C in a drying oven. Yield: 3.97 g (92%) of brown, acicular solid; Mp: 176-178 °C (toluene); R_f = 0.75 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 1.07 (t, ^3J = 7.2 Hz, 3H, $C^{14}H_3$), 3.95 (q, ^3J = 7.2 Hz, 2H, $C^{13}H_2$), 4.22 (d, ^3J = 6.0 Hz, 2H, C^7H_2), 6.29 (t, ^3J = 6.0 Hz, 1H, N^6H), 6.54 (d, ^4J = 2.7 Hz, 1H, C^1H), 6.65 (dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz, 1H, C^5H), 7.11–7.16 (m, 2H, 2×$C^{10}H$), 7.38-7.41 (m, 3H, C^4H & 2×C^9H), 7.86-7.93 (m, 4H, 2×$C^{17}H$ & 2×$C^{18}H$), 8.88 (s, 1H, N^3H); ^{13}C-NMR (DMSO-d_6): δ = 14.4 (C^{14}), 45.9 (C^7), 59.8 (C^{13}), 112.6 (C^5), 113.0 (C^1), 114.9 (d, ^2J = 21 Hz, 2×C^{10}), 123.1 (2×C^{17}), 124.5 (C^4), 125.1 (C^3), 129.1 (d, ^3J = 8 Hz, 2×C^9), 132.4 (2×C^{16}), 134.2 (2×C^{18}), 136.1 (d, ^4J = 3 Hz, C^8), 145.4 (C^6), 154.2 (C^{12}), 159.9 & 162.3 (d, ^1J = 242 Hz, C^{11}), 166.8 (2×C^{15}); MIR: $\tilde{\nu}$ = 1712 & 1763 (s, $\nu_{C=O}$), 2977 (w, ν_{C-H}), 3311 & 3364 (w, ν_{N-H}); HRMS: calculated for $[C_{24}H_{20}N_3O_4F + H]^+$: 434.1511, found: 434.1512.

2-{2-Amino-5-[(4-fluorbenzyl)amino]phenyl}isoindolin-1,3-dione (**14**)

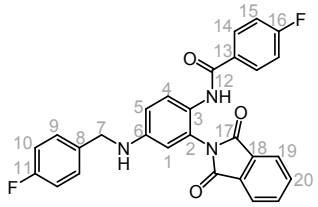


Method A: compound **13** (3.8 mmol, 1.64 g) dissolved in 20 mL of hydrobromic acid (32% in acetic acid) and stirred at rt. After 22 and 40 h, additional 20 mL of hydrobromic acid (32% in acetic acid) added. After 64 h, the reaction mixture was neutralized using 10% strength sodium hydroxide solution and extracted with ethyl acetate (100 mL). The organic phase washed with saturated $NaHCO_3$ solution (100 mL) and saturated common salt solution (100 mL), dried over Na_2SO_4 and adsorbed on diatomaceous earth using a partial vacuum. The product was purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 4:6) and dried at 40 °C and 6 mbar. Yield: 0.70 g (51%) of light brown, amorphous solid; Mp: 143-145 °C (solid from *n*-hexane/ethyl acetate); R_f = 0.63 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 4.12 (d, ^3J = 5.2 Hz, 2H, C^7H_2), 4.47 (s, 2H, NH_2), 5.51

(t, ^3J = 5.6 Hz, 1H, N^6H), 6.37 (d, ^4J = 2,5 Hz, 1H, C^1H), 6.53 (dd, ^3J = 8.6 Hz, ^4J = 2.6 Hz, 1H, C^5H), 6.60 (d, ^3J = 8,6 Hz, 1H, C^4H), 7.09-7.14 (m, 2H, 2×$C^{10}H$), 7.37-7.40 (m, 2H, 2×C^9H), 7.85-7.92 (m, 4H, 2×$C^{14}H$ & 2×$C^{15}H$); ^{13}C-NMR (DMSO-d_6): δ = 46.8 (C^7), 113.7 (C^5), 114.8 (d, ^2J = 21 Hz, 2×C^{10}), 115.4 (C^1), 117,0 (C^4); 117.3 (C^3), 123.0 (2×C^{14}), 129.2 (d, ^3J = 8 Hz, 2×C^9), 132.3 (2×C^{13}), 134.1 (2×C^{15}), 136.7 (d, ^4J = 3 Hz, C^8), 136.9 (C^6), 140.0 (C^2), 159.8 & 162.2 (d, ^1J = 242 Hz, C^{11}), 167.4 (2×C^{12}); MIR: $\tilde{\nu}$ = 1705 & 1773 (s, $\nu_{C=O}$), 2851 (w, ν_{C-H}), 3342 & 3418 (w, ν_{N-H}); HRMS: calculated for $[C_{21}H_{16}N_3O_2F + H]^+$: 362.1299, found: 362,1298.

Method B: In a 3-necked flask, compound **13** (1 mmol, 0.43 g) dissolved under argon atmosphere in 10 mL of anhydrous dichloromethane (if possible use alcohol without a stabilizer). Subsequently, a solution of trimethylsilyl iodide (1.2 eq., 1.2 mmol, 171 μL) in dichloromethane (2 mL) added dropwise and the reaction mixture heated to reflux. After 24 and 30.5 h, an additional trimethylsilyl iodide (1.2 eq., 1.2 mmol, 171 μL) dissolved in dichloromethane (2 mL) added dropwise. After a total of 48 h, the reaction mixture was cooled to rt and methanol (4.0 eq., 4 mmol 162 μL) was added. The suspension was concentrated in a partial vacuum, sodium methoxide (0.5 eq., 0.5 mmol, 0.03 g) was added and the solid dissolved in methanol. The solution again concentrated and then purified by flash chromatography (mobile phase: n-hexane/ethyl acetate/ triethylamine 50:49:1). The product dried at 40 °C and 4 mbar. Yield: 0.18 g (36%) of light brown, amorphous solid. The analytical data collected were similar to method A.

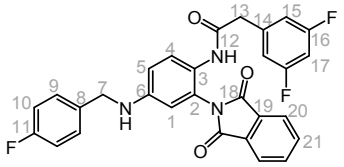
N-{2-(1,3-Dioxoisoindolin-2-yl)-4-[(4-fluorbenzyl)amino]phenyl}-4-fluorbenzamide (**15a**)



Compound **14** (0.89 mmol, 0.32 g), 4-fluorobenzoic acid (1.0 eq, 0.89 mmol, 0.13 g), O-(7-azabenzotriazol-1-yl)N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 2.0 eq, 1.78 mmol 0.68 g) and diisopropylethylamine (3.0 eq, 2.67 mmol, 453 μL) dissolved in dimethylformamide (10 mL). The reaction mixture heated at 40 °C for 18 h, then diluted with dichloromethane (100 mL) and washed with water (2 × 100 mL) and saturated brine (100 mL). The organic phase was concentrated under partial vacuum and the residue was purified by flash chromatography (EZ Prep system from Axel Semrau, column: 24 g silica, mobile phase: *n*-hexane/ethyl acetate, gradient: 0-12 min 0-60% ethyl acetate , 12-15 min 60% ethyl acetate, 15-17 min 60-100% ethyl acetate, 17-25 min 100% ethyl acetate, flow rate: 38 mL/min). For structural analysis, the product recrystallized from ethanol. Yield: 0.29 g (67%) of orange, amorphous solid; Mp: 240-242 °C (solid from ethanol); R_f = 0.60 (*n*-hexane/ethyl

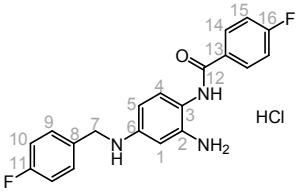
acetate 5:5); ^{1}H-NMR (DMSO-d_6): δ = 4.28 (d, ^{3}J = 6.0 Hz, 2H, C^{7}H$_2$), 6.48 (t, ^{3}J = 6.0 Hz, 1H, N^{6}H), 6.64 (d, ^{4}J = 2.6 Hz, 1H, C^{1}H), 6.69 (dd, ^{3}J = 8.7 Hz, ^{4}J = 2.6 Hz, 1H, C^{5}H), 7.15 (t, ^{3}J = 8.9 Hz, 2H, 2×C^{10}H), 7.20 (t, ^{3}J = 8.9 Hz, 2H, 2×C^{15}H), 7.37 (d, ^{3}J = 8.6 Hz, 1H, C^{4}H), 7.41-7.44 (m, 2H, 2×C^{9}H), 7.70–7.73 (m, 2H, 2×C^{14}H), 7.83–7.90 (m, 4H, 2×C^{19}H und 2×C^{20}H), 9.71 (s, 1H, N^{3}H); ^{13}C-NMR (DMSO-d_6): δ = 45.8 (C^{7}), 112.4 (C^{5}), 112.4 (C^{1}), 115.0 (d, ^{2}J = 21 Hz, 2×C^{10}), 115.0 (d, ^{2}J = 21 Hz, 2×C^{15}), 123.1 (2×C^{20}), 123.7 (C^{2}), 126.8 (C^{3}), 127.2 (C^{4}), 129.1 (d, ^{3}J = 8 Hz, 2×C^{9}), 130.0 (d, ^{3}J = 9 Hz, 2×C^{14}), 131.4 (d, ^{4}J = 3 Hz, C^{13}), 131.9 (2×C^{18}), 134.4 (2×C^{19}), 136.0 (d, ^{3}J = 3 Hz, C^{8}), 146.6 (C^{6}), 159.9 & 162.3 (d, ^{1}J = 242 Hz, C^{11}), 162.5 & 164.9 (d, ^{1}J = 248 Hz, C^{16}), 164.3 (C^{12}), 166.6 (2×C^{17}); MIR: $\tilde{\nu}$ = 1651, 1712 & 1782 (s, $\nu_{C=O}$), 2898 (w, ν_{C-H}), 3360 & 3397 (w, ν_{N-H}).

2-(3,5-Difluophenyl)-*N*-{2-(1,3-dioxoindolin-2-yl)-4-[(4-fluorbenzyl)amino]phenyl}acetamide (**15b**)



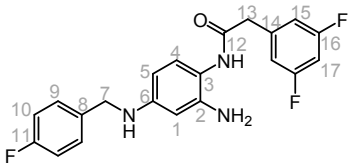
Compound **14** (1 mmol, 0.36 g), 3,5-difluoroacetic acid (1.0 eq., 1 mmol, 0.17 g), HATU (2.0 eq., 2 mmol, 0.76 g) and diisopropylethylamine (3.0 eq., 3 mmol, 510 µL) dissolved in of dimethylformamide (10 mL) and stirred for 6 h at rt. Diethyl ether (100 mL) and ethyl acetate (150 mL) added, and the organic phase was washed with water (200 mL), saturated $NaHCO_3$ solution (2 × 100 mL) and saturated common salt solution (100 mL). The organic phase dried over Na_2SO_4 and adsorbed on diatomaceous earth in a partial vacuum. The product was purified by flash chromatography (Puriflash system from Interchim, column: 40 g silica 15 µm spherical, mobile phase: n-hexane/ethyl acetate + 5% triethylamine, gradient: 1 CV 10% ethyl acetate, 10 CV 10-80% ethyl acetate, 5 CV 80% ethyl acetate, flow rate: 26 mL/min). The product was dried at 40 ° C and 4 mbar. Yield: 0.23 g (44%) of orange, amorphous solid; Mp: 236-238 °C (solid from *n*-hexane/ethyl acetate/triethylamine); R_f = 0.51 (*n*-hexane/ethyl acetate 5:5); ^{1}H-NMR (DMSO-d_6): δ = 3.45 (s, 2H, C^{13}H$_2$), 4.24 (d, ^{3}J = 5.4 Hz, 2H, C^{7}H$_2$), 6.41 (t, ^{3}J = 5.5 Hz, 1H, N^{6}H), 6.58 (d, ^{4}J = 1.7 Hz, 1H, C^{1}H), 6.65 (dd, ^{3}J = 8.8 Hz, ^{4}J = 1.7 Hz, 1H, C^{5}H), 6.79 (d, ^{3}J = 7.0 Hz, 2H, 2×C^{15}H), 6.97 (t, ^{3}J = 9.3 Hz, 1H, C^{17}H), 7.14 (t, ^{3}J = 8.7 Hz, 2H, 2×C^{10}H), 7.36-7.41 (m, 3H, C^{4}H & 2×C^{9}H), 7.86 (s, 4H, 2×C^{20}H & 2×C^{21}H), 9.40 (s, 1H, N^{3}H); ^{13}C NMR (DMSO-d_6): δ = 41.9 (C^{13}), 45.7 (C^{7}), 101.8 (t, ^{2}J = 26 Hz, C^{17}), 111.9 (dd, ^{2}J = 18 Hz, ^{4}J = 7 Hz, 2×C^{15}), 112.5 (C^{1}), 112,6 (C^{5}), 115.0 (d, ^{2}J = 21 Hz, 2×C^{10}), 123.1 (2×C^{21}H), 124.0 (C^{3}), 125.9 (C^{6}), 126.0 (C^{4}), 129.1 (d, ^{3}J = 8 Hz, 2×C^{9}), 131.9 (2×C^{19}), 134.3 (2×C^{20}), 136.0 (d, ^{4}J = 3 Hz, C^{8}), 140.3 (t, ^{3}J = 10 Hz, C^{13}), 146.3 (C^{2}), 159.9 & 162.3 (d, ^{1}J = 242 Hz, C^{11}), 160.8 & 163.2 (dd, ^{1}J = 245 Hz, ^{3}J = 13 Hz, 2×C^{16}), 166.6 (2×C^{18}), 167.6 (C^{12}); MIR: $\tilde{\nu}$ = 1633 (m, $\nu_{C=O}$), 1715 (s, $\nu_{C=O}$), 2927 (w, ν_{C-H}), 3244, 3354 & 3462 (w, ν_{N-H}).

N-{2-Amino-4-[(4-fluorbenzyl)amino]phenyl}-4-fluorbenzamide (**16a**)



Compound **15a** (0.6 mmol, 0.29 g) was dissolved in 40 mL methanol/2-propanol (1:1) and hydrazine hydrate (1.5 eq, 0.9 mmol, 59 mL of an 80% aqueous solution) added to the solution. The reaction mixture stirred for 17 h at rt, then treated with water (100 mL) and stored in a refrigerator. The resulting brown precipitate filtered off, dissolved in ethyl acetate/tetrahydrofuran (1:1) and precipitated by bubbling HCl gas as a hydrochloride salt. The product dried at 40 °C and 6 mbar. Yield: 0.11 g (47%) of orange, amorphous solid; Purity 100%; Mp: 232-235 °C (solid from ethyl acetate/tetrahydrofuran); Mp: it did not melt uniformly; R_f = 0.84 (*n*-hexane/ethyl acetate 5:5); ^{1}H-NMR (DMSO-d_6): d = 4.29 (s, 2H, C^7H_2), 6.61 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1H, C^5H), 6.67 (d, ^4J = 2.3 Hz, 1H, C^1H), 7.17 (t, ^3J = 8.9 Hz, 2H, 2×C^{10}H), 7.18 (d, ^3J = 8.7 Hz, 1H, C^4H), 7.35 (t, ^3J = 8.8 Hz, 2H, 2×C^{15}), 7.40-7.44 (m, 2H, 2×C^9H), 8.13-8.18 (m, 2H, 2×C^{14}H), 10.18 (s, 1H, N^3H); ^{13}C-NMR (DMSO-d_6): δ = 46.2 (C^7), 106.9 (C^5), 111.6 (C^1), 115.1 (d, ^2J = 21 Hz, 2×C^{10}), 115.2 (d, ^2J = 21 Hz, 2×C^{15}), 119.8 (C^3), 128.4 (C^4), 129.4 (d, ^3J = 8 Hz, 2×C^9), 130.4 (d, ^4J = 3 Hz, 2×C^8), 130.6 (d, ^3J = 9 Hz, C^{14}), 135.2 (d, ^4J = 3 Hz, C^{13}), 144.3 (C^2), 146.2 (C^6), 160.1 & 162.5 (d, ^1J = 242 Hz, C^{11}), 162.9 & 165.4 (d, ^1J = 249 Hz, C^{16}), 164.6 (C^{12}); MIR: $\tilde{\nu}$ = 1654 (s, $\nu_{C=O}$), 2865 (w, ν_{C-H}), 3038 (w, ν_{Ar-H}), 3296, 3327 & 3440 (w, ν_{N-H}); HRMS: calculated for $[C_{20}H_{17}N_3OF_2 + H]^+$: 354.1412, found: 354.1425.

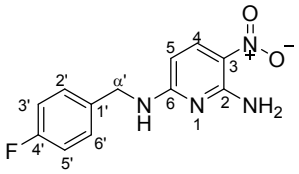
N-{2-Amino-4-[(4-fluorbenzyl)amino]phenyl}-2-(3,5-difluorphenyl)acetamide (**16b**)



Compound **15b** (0.44 mmol, 0.23 g) and hydrazine hydrate (1.5 eq., 0.66 mmol, 40.3 µL of 80% aqueous solution) dissolved in 100 mL of tetrahydrofuran/2-propanol/methanol (3: 1: 1). The reaction mixture stirred for 24 h at rt and then concentrated in a partial vacuum. The resulting grey solid dissolved in methanol/tetrahydrofuran (1:1), adsorbed on diatomaceous earth and purified by flash chromatography (Reveleris system from Büchi, column: 24 g silica, 20 µm spherical, mobile phase: *n*-hexane/ethyl acetate +5% triethylamine, gradient: 0-1 min 16% ethyl acetate, 1-12 min 16-100% ethyl acetate, 12-28 min 100% ethyl acetate, 28-30 min 0-20% methanol instead of *n*-hexane, 30-38 min 20% methanol, flow rate: 32 mL/min). The first fraction further purified by preparative HPLC (column: Lichrospher xy, mobile phase: water/acetonitrile, gradient: 0-2 min 50% acetonitrile, 2-12 min 50-90% acetonitrile, 12-18 min 90% acetonitrile, 18-22 min 50% acetonitrile, flow rate 39 mL/min). When the

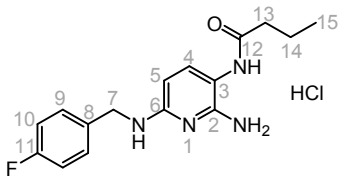
fractions containing the product were being concentrated, a colourless solid precipitated. This was filtered off and dried at 40 °C and 6 mbar. Yield: 0.07 g (41%) of colourless, amorphous solid; Purity 100%; Mp: 172-174 °C (solid from water/acetonitrile); R_f = 0.72 (ethyl acetate/triethylamine 100:1); ^{1}H-NMR (DMSO-d_6): δ = 3.63 (s, 2H, C^{13}H$_2$), 4.18 (d, ^3J = 6.1 Hz, 2H, C^{7}H$_2$), 4.56 (s, 2H, NH$_2$), 5.85 (dd, ^3J = 8,5 Hz, ^4J = 2,4 Hz, 1H, C^{5}H), 5.94 (t, ^3J = 6.5 Hz, 1H, N^{6}H), 5.95 (d, ^4J = 2.6 Hz, 1H, C^{1}H), 6.72 (d, ^3J = 8,4 Hz, 1H, C^{4}H), 7.05-7.08 (m, 3H, 2×C^{15}H & C^{17}H), 7.10-7.15 (m, 2H, 2×C^{9}H), 7.34-7.38 (m, 2H, 2×C^{9}H), 9.08 (s, 1H, N^{3}H); ^{13}C-NMR (DMSO-d_6): δ = 41.9 (C^{13}), 45.8 (C^7), 99.0 (C^1), 101.7 (C^5), 101.9 (t, ^2J = 26 Hz, C^{17}), 112.3 (dd, ^2J = 18 Hz, ^4J = 6 Hz, 2×C^{15}), 112.9 (C^3), 114.8 (d, ^2J = 21 Hz, 2×C^{10}), 126.8 (C^4), 128.8 (d, ^3J = 8 Hz, 2×C^9), 136.7 (d, ^4J = 3 Hz, C^8), 140.9 (t, ^3J = 10 Hz, C^{13}), 143.3 (C^2), 147.3 (C^6), 159.8 & 162.2 (d, ^1J = 242 Hz, C^{11}), 160.9 & 163.4 (dd, ^1J = 245 Hz, ^3J = 14 Hz, 2×C^{16}), 168,0 (C^{12}); MIR: $\tilde{\nu}$ = 1642 (s, $\nu_{C=O}$), 3027 (w, ν_{Ar-H}), 3254, 3370 & 3406 (w, ν_{N-H}); HRMS: calculated for [$C_{21}H_{18}N_3OF_3$ + H]$^+$: 386.1475, found: 386.1464.

N^2-(4-Fluorobenzyl)-5-nitropyridin-2,6-diamine (**i12**)



Compound **5** (5 mmol, 868 mg), triethylamine (10 mmol, 1.4 mL) and 4-fluorobenzylamine (7.5 mmol, 858 µL) were suspended in 2-propanol (15 mL). The suspension held at reflux for overnight. A yellow product precipitated with the addition of water, which was washed with *n*-hexane; Yield: 95%, yellow solid; Mp: 180 -181 ˚C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.38 (bs, 1H, *N*^{6}H), 8.12 (bs, bs, 2H, *N*^{2}H$_2$), 7.98 (d, 1H, ^3J = 9.2 Hz, C(4)H), 7.41 (m, 2H, C(2')H & C(6')H), 7.18 (m, 2H, C(3')H & C(5')H), 6.01 (d, 1H, ^3J = 9.2 Hz, C(5)H), 4.57 (d, 2H, C(α')H$_2$); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 162.5 (d, $^1J_{C,F}$ = 241 Hz, C4'), 160.4 (C6), 155.7 (C2), 135.2 (d, $^4J_{C,F}$ = 3 Hz, C1'), 134.5 (C4), 129.7 (d, $^3J_{C,F}$ = 8 Hz, C2' & C6'), 117.6 (C3), 115.2 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 102.3 (C5), 43.1 (Cα'), IR (cm^{-1}): $\tilde{\nu}$ = 749 (Ar-H).

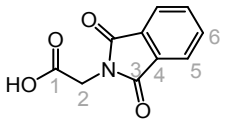
N-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}butyramide hydrochloride (**12a**)



In a 3-necked flask, compound **i12** (1 mmol, 0.26 g) together with 0.10 g of palladium-activated carbon (10%) were suspended in 2-propanol (20 mL) and stirred under hydrogen atmosphere for 3.5 h at rt, then for 19 h at 40 °C. The reaction mixture then cooled to 0 °C and treated with triethylamine (1.4

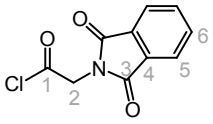
eq., 1.4 mmol, 0.2 mL). A solution of butyric acid chloride (1.2 eq, 1.2 mmol, 125 μL) in tetrahydrofuran (2 mL) added dropwise and the suspension stirred for 7 h at 0 °C. The suspension treated with water (50 mL) and then extracted with dichloromethane (50 mL). The organic phase washed with water (50 mL) and saturated brine (100 mL), dried over Na_2SO_4 and concentrated in a partial vacuum. The residue was purified by flash chromatography (Büchi MPLC, self-packed column, mobile phase: dichloromethane/methanol, gradient: 0-3 min 100% dichloromethane, 3-13 min 0-10% methanol, 13-16 min 10% methanol , flow rate: 40 mL/min). The product then dissolved in 2-propanol (100 mL) and precipitated by adjusting the pH to 2 using 10% hydrochloric acid. The product dried at 40 °C and 3 mbar. Yield: 0.07 g (22%) of bluish shimmering crystals; Purity 100%; Mp; 255-257 °C (solid from 2-propanol); R_f = 0.39 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 0.90 (t, ^3J = 7.4 Hz, 3H, $C^{15}H_3$), 1.57 (sep, ^3J = 7.3 Hz, 2H, $C^{14}H_2$), 2.27 (t, ^3J = 7.4 Hz, 2H, $C^{13}H_2$), 4.54 (d, ^3J = 3.8 Hz, 2H, C^7H_2), 5.94 (d, ^3J = 8.8 Hz, 1H, C^5H), 7.19 (t, ^3J = 8.8 Hz, 2H, 2×$C^{10}H$), 7.37 (bs, 2H, NH_2), 7.43−7.47 (m, 2H, 2×C^9H), 7.50 (d, ^3J = 8.8 Hz, 1H, C^4H), 8.22 (s, 1H, N^6H), 9.20 (s, 1H, N^3H), 13.25 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 13.6 (C^{15}), 18.3 (C^{14}), 37.2 (C^{13}), 44.5 (C^7), 93.6 (C^5), 107.1 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 129.5 (d, ^3J = 8 Hz, 2×C^9), 133.7 (d, ^4J = 3 Hz, C^8), 142.4 (C^4), 148.3 (C^2), 148.9 (C^6), 160.3 & 162.7 (d, ^1J = 243 Hz, C^{11}), 172.1 (C^{12}); MIR: $\tilde{\nu}$ = 1636 (s, $\nu_{C=O}$), 2872 & 2960 (w, ν_{C-H}), 3168, 3277 & 3355 (w, ν_{N-H}); HRMS: calculated for $[C_{16}H_{19}N_4OF + H]^+$: 303.1616, found: 303,1603.

2-(1,3-Dioxoisoindolin-2-yl)acetic acid (**i112b**)



In a glass vial, glycine (20 mmol, 1.50 g) mixed with phthalic anhydride (1.0 eq, 20 mmol, 2.96 g) and heated in the microwave reactor (210 °C for 30 min). Upon cooling to rt, a colourless solid crystallized, which was finally recrystallized from ethanol. The product was dried at 40 ° C and 4 mbar. Yield: 2.93 g (72%) of colourless plates; Mp; 194-196 °C (solid from ethanol); ^{1}H-NMR (DMSO-d_6): δ = 4.33 (s, 2H, C^2H_2), 7.90 (m, 2H, 2×C^6H), 7.94 (m, 2H, 2×C^5H), 13.26 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ = 38.9 (C^2), 123.4 (2×C^5), 131.4 (2×C^4), 134.8 (2×C^6), 167.2 (2×C^3), 168.9 (C^1); MIR: $\tilde{\nu}$ = 1742 (s, $\nu_{C=O}$), 1704 & 1771 (s, $\nu_{C=O}$), 3100 (w, ν_{Ar-H}), 3210 (w, ν_{O-H}).

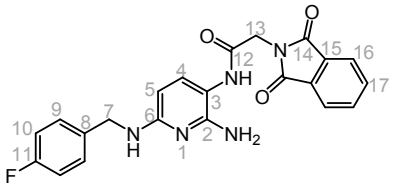
2-(1,3-Dioxoisoindolin-2-yl)acetyl chloride (**i212b**)



Compound **i112b** (5 mmol, 1.03 g) dissolved in anhydrous toluene (10 mL) and cooled to 0 °C. Under argon atmosphere, a solution of thionyl chloride (1.2 eq., 6 mmol, 435 μL) in anhydrous toluene (5 mL)

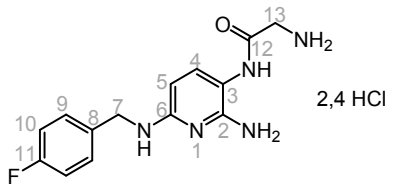
added dropwise and the reaction mixture heated to reflux. After 18 h, additional thionyl chloride (1.2 eq., 6 mmol, 435 μL) added and the reaction continued for another 6 h. Subsequently, the reaction mixture allowed to cool to rt and then concentrated using partial vacuum. Finally, the resulting solid dried in at 10 mbar for overnight. Yield: 1.01 g (99%) of brown, amorphous solid; Mp: 117–119 °C (solid from toluene); ^{1}H-NMR (DMSO-d_6): δ = 4.33 (s, 2H, C^{2}H$_2$), 7.90 (m, 2H, 2×C^{6}H), 7.94 (m, 2H, 2×C^{5}H); ^{13}C-NMR (DMSO-d_6): δ = 39.0 (C^{2}), 123.5 (2×C^{5}), 131.5 (2×C^{4}), 134.9 (2×C^{6}), 167.3 (2×C^{3}), 168.9 (C^{1}); MIR: $\tilde{\nu}$ = 1704, 1771 & 1801 (s, $\nu_{C=O}$), 2936 (w, ν_{C-H}).

N-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-2-(1,3-dioxoisoindolin-2-yl)acetamide (**i312b**)



The synthesis carried out according to the GWP2. The acylation carried out with **i212b** (1.2 eq., 1.2 mmol, 0.27 g) and completed 1 h after addition. The reaction mixture was then washed with water (5 × 20 mL), dried over Na_2SO_4 and adsorbed onto diatomaceous earth using a partial vacuum. Finally, the product purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 8:2). Yield: 0.19 g (46%) of yellow, amorphous solid; Mp: 209-211 °C (solid from *n*-hexane/ethyl acetate); R_f = 0.51 (*n*-hexane/ethyl acetate 8:2); ^{1}H-NMR (DMSO-d_6): δ = 4.36 (d, ^{3}J = 6.1 Hz, 2H, C^{7}H$_2$), 4.40 (s, 2H, C^{13}H$_2$), 5.28 (s, 2H, N^{2}H$_2$), 5.68 (d, ^{3}J = 8.3 Hz, 1H, C^{4}H), 6.58 (t, ^{3}J = 6.2 Hz, 1H, N^{6}H), 6.99 (d, ^{3}J = 8.3 Hz, 1H, C^{4}H), 7.10 (m, 2H, 2×C^{10}H), 7.34 (m, 2H, 2×C^{9}H), 7.88 (m, 2H, 2×C^{17}H), 7.92 (m, 2H, 2×C^{16}H), 9.19 (s, 1H, N^{3}H); ^{13}C NMR (DMSO-d_6): δ = 40.5 (C^{13}), 43.6 (C^{7}), 95.1 (C^{5}), 105.6 (C^{3}), 114.7 (d, ^{2}J = 21 Hz, 2×C^{10}), 123.2 (2×C^{16}), 129.0 (d, ^{3}J = 8 Hz, 2×C^{9}), 131.7 (2×C^{15}), 134.6 (2×C^{17}), 135.8 (C^{4}), 137.1 (d, ^{4}J = 3 Hz, C^{8}), 153.1 (C^{2}), 156.1 (C^{6}), 159.7 & 162.1 (d, ^{1}J = 242 Hz, C^{11}), 165.4 (C^{12}), 167.6 (2×C^{14}); MIR: $\tilde{\nu}$ = 1656, 1717 & 1775 (s, $\nu_{C=O}$), 3075 (w, ν_{Ar-H}), 3279, 3355, 3444 & 3483 (m, ν_{N-H}); HRMS: calculated for [$C_{22}H_{18}N_5O_3F$ + H]$^{+}$: 420.1466, found: 420.1474.

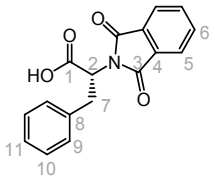
2-Amino-*N*-{2-amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}acetamide hydrochloride (**12b**)



In a 3-necked flask, compound **i312b** (0.81 mmol, 0.34 g) dissolved in methanol (50 mL) and treated with hydrazine hydrate (1.44 eq., 1.17 mmol, 71 μL of 80% aqueous solution). Under argon atmosphere, the reaction mixture heated to reflux for 8 h. Subsequently, another hydrazine hydrate

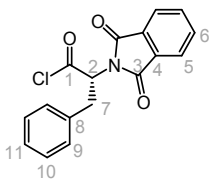
(0.77 eq., 0.62 mmol, 36 µL of 80% aqueous solution) added and the mixture heated to reflux for a further 3 h. After cooling to rt, the solution was concentrated in a partial vacuum, then dissolved in 60 ml of a mixture of ethyl acetate/tetrahydrofuran/ethanol (1:1:1) and the product precipitated as a hydrochloride salt by introducing HCl gas. The product was dried at 40 °C and 6 mbar. Yield: 0.16 g (62%) of light brown, amorphous solid; Purity 100%; Mp: 263-265 °C (solid form ethyl acetate/tetrahydrofuran/ethanol); R_f = 0.60 for the free base (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 3.75 (d, ^3J = 5.2 Hz, 2H, C^{13}H$_2$), 4.57 (d, ^3J = 3.6 Hz, C^{7}H$_2$), 5.97 (d, ^3J = 8.8 Hz, C^{5}H), 7.20 (m, 2H, 2×C^{10}H), 7.47 (m, 3H, C^{4}H & 2×C^{9}H), 7.66 (s, 2H, N^{2}H$_2$), 8.29 (s, 2H, N^{13}H$_2$), 8.40 (s, 1H, N^{6}H), 9.99 (s, 1H, N^{3}H), 13.47 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 40.6 (C^{13}), 44.5 (C^7), 93.8 (C^5), 105.3 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 133.7 (d, ^4J = 3 Hz, C^8), 142.2 (C^4), 148.7 (C^2), 149.5 (C^6), 160.3 & 162.7 (d, ^1J = 242, C^{11}), 166.1 (C^{12}); MIR: $\tilde{\nu}$ = 1639 (s, $\nu_{C=O}$), 3007 (w, ν_{Ar-H}), 2300–3600 (m, $\nu_{N-H\ protonated}$), 3144 (w, ν_{N-H}); HRMS: calculated for [$C_{14}H_{16}N_5OF$ + H]$^+$: 290.1412, found: 290.1417.

(*R*)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropionic acid (**i112c**)



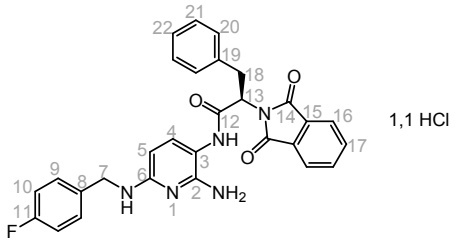
In a glass vial, D-phenylalanine (20 mmol, 3.30 g) and phthalic anhydride (1.0 eq, 20 mmol, 2.96 g) were mixed and heated in a microwave reactor at 210 °C for 30 min. On cooling to rt and storage at 10 mbar, a solid slowly crystallizes out of the brown, viscous substance. The solid dissolved in dichloromethane (20 mL) and washed with hydrochloric acid (2 × 20 mL, 0.1 mol/L). The organic phase dried over Na_2SO_4 and then concentrated in a partial vacuum. The residue recrystallized from dichloromethane and dried at 40 °C and 4 mbar. Yield; 2.89 g (49%) of beige, amorphous solid; Purity 100%; Mp: 170-172 °C (solid from dichloromethane); ^{1}H-NMR (DMSO-d_6): δ = 3.35 & 3.49 (m & m, 2H, C^{7}H$_2$), 5.13 (m, 1H, C^{2}H), 7.08-7.20 (m, 5H, 2×C^{9}H, 2×C^{10}H & C^{12}H), 7.84 (s, 4H, 2×C^{5}H & 2×C^{6}H), 13.36 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ = 33.9 (C^8), 52.9 (C^3), 123.4 (2×C^5), 126.5 (C^{11}), 128.3 (2×C^9), 128.7 (2×C^{10}), 130.7 (2×C^4), 134.9 (2×C^6), 137.3 (C^8), 167.1 (2×C^3), 170.0 (C^1); MIR: $\tilde{\nu}$ = 1697 & 1771 (s, $\nu_{C=O}$), 2934 (w, ν_{C-H}). 3029 (w, ν_{Ar-H}), 3250 (w, ν_{O-H}).

(*R*)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropanoylchloride (**i212c**)



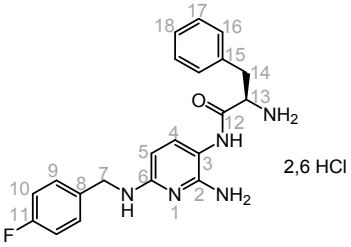
The synthesis is analogous to **i212b** except compound **i112c** (5 mmol, 1.48 g) and thionyl chloride (2.4 eq., 12 mmol, 870 μL) were used. Yield: 1.47 g (94%) of beige, amorphous solid; Mp: 119-121 °C (solid from toluene); ^{1}H-NMR (DMSO-d_6): δ = 3.41 (m, 2H, C^{7}H$_2$), 5.12 (m, 1H, C^{2}H), 7.10-7.19 (m, 5H, 2×C^{9}H, 2×C^{10}H & C^{12}H), 7.84 (s, 4H, 2×C^{5}H & 2×C^{6}H); ^{13}C-NMR (DMSO-d_6): δ = 33.9 (C^{8}), 52.9 (C^{3}), 123.4 (2×C^{5}), 126.6 (C^{11}), 128.3 (2×C^{9}), 128.7 (2×C^{10}), 130.7 (2×C^{4}), 134.9 (2×C^{6}), 137.3 (C^{8}), 167.1 (2×C^{3}), 170.0 (C^{1}); MIR: $\tilde{\nu}$ = 1697, 1774 & 1794 (s, $\nu_{C=O}$), 2924 (w, ν_{C-H}), 3030 (w, ν_{Ar-H}).

(*R*)-*N*-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide hydrochloride (**i312c**)



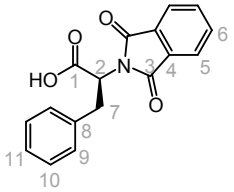
The synthesis carried out according to GWP2, while compound **i212c** (1.2 eq., 1 mmol, 0.38 g) used for the acylation. Following the completion of the reaction, the solution washed with water (5 × 20 mL), dried over Na_2SO_4 and adsorbed onto diatomaceous earth in a partial vacuum. The product was purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 1:1) and precipitated as hydrochloride salt by passing HCl gas. The product was dried at 40 °C and 6 mbar. Yield: 0.32 g (58%) of colourless, amorphous solid; Mp: 161-163 °C (solid from tetrahydrofuran/ethyl acetate); R_f = 0.81 for the free base (*n*-hexane/ethyl acetate 2:8); ^{1}H-NMR (DMSO-d_6): δ = 3.21 (dd, ^{3}J = 13.8 Hz, ^{3}J = 11.6 Hz, 1H, C^{13}H), 3.56 (dd, ^{2}J = 13.9 Hz, ^{3}J = 4.6 Hz, 1H, C^{18}H$_2$), 4.54 (d, ^{3}J = 6.8 Hz, 2H, C^{7}H$_2$), 5.26 (dd, ^{2}J = 11.4 Hz, ^{3}J = 4.6 Hz, 1H, C^{18}H$_2$), 5.97 (d, ^{3}J = 8.8 Hz, C^{5}H), 7.09-7.47 (bs, 2H, NH$_2$), 7.09-7.14 (m, 5H, 2×C^{20}H, 2×C^{21}H & C^{22}H), 7.20 (t, ^{3}J = 8.8 Hz, 2H, 2×C^{10}H), 7.30 (d, ^{3}J = 8.8 Hz, 1H, C^{4}H), 7.47-7.43 (m, 2H, 2×C^{9}H), 7.82 (s, 4H, 2×C^{16}H & 2× C^{17}H), 8.28 (s, 1H, N^{6}H), 9.46 (s, 1H, N^{3}H), 13.25 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 34.2 (C^{18}), 44.5 (C^{7}), 53.9 (C^{13}), 93.8 (C^{5}), 106.0 (C^{3}), 115.3 (d, ^{2}J = 21 Hz, 2×C^{10}), 123.1 (2×C^{17}), 126.5 (C^{22}), 128.2 (2×C^{20}),128.9 (2×C^{21}), 129.6 (d, ^{3}J = 8 Hz, 2×C^{9}), 131.3 (2×C^{15}), 133.6 (d, ^{4}J = 3 Hz, C^{8}), 134.5 (2×C^{16}), 137.4 (C^{19}), 143.2 (C^{4}), 149.1 (C^{6}), 149.6 (C^{2}), 160.3 & 162.7 (d, ^{1}J = 242 Hz, C^{11}), 167.4 (C^{12}), 168.0 (2×C^{14}); MIR: $\tilde{\nu}$ = 1650, 1703 & 1779 (s, $\nu_{C=O}$), 3066 (w, ν_{Ar-H}), 2600–3300 (w, $\nu_{N-H\ protonated}$), 3401 (m, ν_{N-H}); HRMS: calculated for $[C_{29}H_{24}N_5O_3F + H]^+$: 510.1936, found: 510.1945.

(*R*)-2-Amino-*N*-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-3-phenylpropanamide hydrochloride (**12c**)



In a 3-necked flask, compound **i312c** (0.48 mmol, 0.25 g) dissolved in methanol (50 mL) and treated with hydrazine hydrate (1.44 eq., 0.69 mmol, 42 µL of 80% aqueous solution). Under argon atmosphere, the reaction mixture heated under reflux for 18 h. Subsequently, additional hydrazine hydrate (1.44 eq., 0.69 mmol, 42 µL of 80% aqueous solution) added and heated to reflux for a further 6 h. After cooling to rt, the solution was concentrated under partial vacuum and the product was adsorbed onto diatomaceous earth. The product purified by flash chromatography (mobile phase: dichloromethane/methanol 9:1). Finally, the product taken up in ethyl acetate/tetrahydrofuran (1:1) and precipitated as hydrochloride salt by introducing HCl gas. The product was dried at 40 °C and 6 mbar. Yield: 0.12 g (62%) of light brown, amorphous solid; Purity 100%; Mp: 238-240 °C (solid from ethyl acetate/tetrahydrofuran); R_f = 0.69 for the free base (dichloromethane/methanol 9:1); ^{1}H-NMR (DMSO-d_6): δ = 3.12 (d, ^3J = 7.3 Hz, 2H, $C^{14}H_2$), 4.20 (d, ^3J = 4.8 Hz, 1H, $C^{13}H$), 4.56 (s, 2H, C^7H_2), 5.94 (d, ^3J = 8.8 Hz, 1H, C^5H), 7.08 (d, ^3J = 8.8 Hz, 1H, C^4H), 7.19 (t, ^3J = 9.0 Hz, 2H, 2×$C^{10}H$), 7.32 (m, 5H, 2×$C^{16}H$, 2×$C^{17}H$ & $C^{18}H$), 7.46 (m, 2H, 2×C^9H), 7.63 (s, 2H, N^2H_2), 8.37 (s, 1H, N^6H), 8.60 (s, 2H, $N^{13}H_2$), 10.04 (s, 1H, N^3H), 13,37 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 36.6 (C^{14}), 44.5 (C^7), 53.8 (C^{13}), 93.7 (C^5), 105.0 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 127.1 (C^{18}), 128.5 (2×C^{17}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 129.6 (2×C^{16}) 133.7 (d, ^4J = 3 Hz, C^8), 135.0 (C^{15}), 141.9 (C^4), 148.7 (C^2), 149.6 (C^6), 160.3 & 162.7 (d, ^1J = 242, C^{11}), 167.9 (C^{12}); MIR: $\tilde{\nu}$ = 1643 (s, $\nu_{C=0}$), 3144 (m, ν_{N-H}); HRMS: calculated for $[C_{21}H_{22}N_5OF + H]^+$: 380.1881, found: 380.1891.

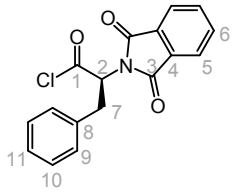
(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropionsäure (**i112d**)



The synthesis is analogous to **i112c**, while L-phenylalanine (20 mmol, 3.30 g) and phthalic anhydride (1.0 eq., 20 mmol, 2.96 g) were used. Yield; 3.26 g (55%) of colourless, amorphous solid; Mp: 171-173 °C (solid from dichloromethane); ^{1}H-NMR (DMSO-d_6): δ = 3.33 & 3.48 (m & m, 2H, C^7H_2), 5.12 (m, 1H, C^2H), 7.08-7.20 (m, 5H, 2×C^9H, 2×$C^{10}H$ & $C^{12}H$), 7.84 (s, 4H, 2×C^5H & 2×C^6H), 13.36 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ = 33.9 (C^8), 52.9 (C^3), 123.4 (2×C^5), 126.5 (C^{11}), 128.3 (2×C^9), 128.7 (2×C^{10}), 130.7

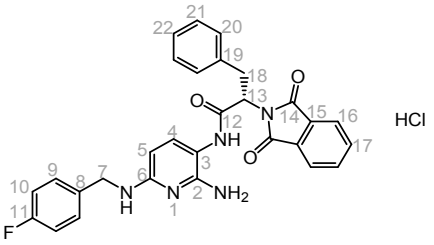
(2×C^4), 134.9 (2×C^6), 137.3 (C^8), 167.1 (2×C^3), 170.0 (C^1); MIR: $\tilde{\nu}$ = 1697, 1740 & 1772 (s, $\nu_{C=O}$), 2923 (w, ν_{C-H}). 3027 (w, ν_{Ar-H}), 3252 (w, ν_{O-H}).

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropanoyl chloride (**i212d**)



The synthesis is analogous to **i212b**; **i112d** (5 mmol, 1.48 g) and thionyl chloride (2.4 eq., 12 mmol, 870 µL) were used. Yield: 2.91 g (93%) of colourless, amorphous solid; Mp: 119-121 °C (solid from toluene); ^{1}H-NMR (DMSO-d_6): δ = 3.35 & 3.49 (m & m, 2H, C^7H_2), 5.13 (m, 1H, C^2H), 7.10-7.19 (m, 5H, 2×C^9H, 2×C^{10}H & C^{12}H), 7.84 (s, 4H, 2×C^5H & 2×C^6H); ^{13}C NMR (DMSO-d_6): δ = 34.0 (C^8), 52.9 (C^3), 123.4 (2×C^5), 126.6 (C^{11}), 128.3 (2×C^9), 128.7 (2×C^{10}), 130.7 (2×C^4), 135.0 (2×C^6), 137.3 (C^8), 167.1 (2×C^3), 170.0 (C^1); MIR: $\tilde{\nu}$ = 1698, 1775 & 1793 (s, $\nu_{C=O}$), 2899 (w, ν_{C-H}), 3030 (w, ν_{Ar-H}).

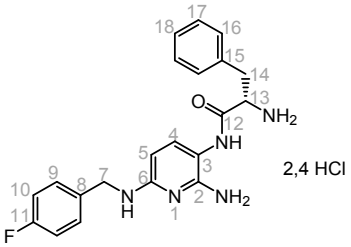
(S)-*N*-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropan hydrochloride (**i312d**)



The synthesis carried out according to GWP2, while it was acylated with **i212c** (1.2 eq., 1.2 mmol, 0.38 g). The reaction completed after 1 h of complete addition. The solution then washed with water (5 × 20 mL), dried over Na_2SO_4 and adsorbed onto diatomaceous earth using partial vacuum. The product purified by flash chromatography (n-hexane/ethyl acetate 4:6). The product precipitated as hydrochloride from ethyl acetate/tetrahydrofuran (1:1) by bubbling HCl gas. Yield: 0.23 g (43%) of colourless, amorphous solid; Mp: 168-170 °C (solid from tetrahydrofuran/ethyl acetate); R_f = 0.70 for the free base (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 3.20 (dd, ^3J = 13.8 Hz, ^3J = 11.6 Hz, 1H, C^{13}H), 3.56 (dd, ^2J = 13.9 Hz, ^3J = 4.6 Hz, 1H, $C^{18}H_2$), 4.53 (d, ^3J = 6.8 Hz, 2H, C^7H_2), 5.25 (dd, ^2J = 11.4 Hz, ^3J = 4.6 Hz, 1H, $C^{18}H_2$), 5.97 (d, ^3J = 8.8 Hz, C^5H), 7.11 (bs, 2H, NH_2), 7.09-7.14 (m, 5H, 2×C^{20}H, 2×C^{21}H & C^{22}H), 7.20 (t, ^3J = 8.8 Hz, 2H, 2×C^{10}H), 7.30 (d, ^3J = 8.8 Hz, 1H, C^4H), 7.47-7,43 (m, 2H, 2×C^9H), 7.82 (s, 4H, 2×C^{16}H & 2× C^{17}H), 8.25 (s, 1H, N^6H), 9.45 (s, 1H, N^3H), 13.20 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 34.2 (C^{18}), 44.5 (C^7), 53.9 (C^{13}), 93.8 (C^5), 106.0 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 123.1 (2×C^{17}), 126.5 (C^{22}), 128.2 (2×C^{20}),128.9 (2×C^{21}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 131.3 (2×C^{15}), 133.6 (d,

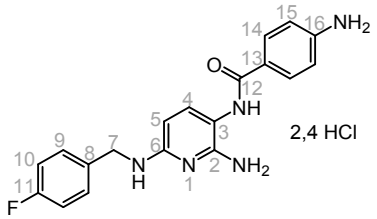
^4J = 3 Hz, C^8), 134.5 (2×C^{16}), 137.4 (C^{19}), 143.2 (C^4), 149.1 (C^6), 149.7 (C^2), 160.3 & 162.7 (d, ^1J = 242 Hz, C^{11}), 167.4 (C^{12}), 168.0 (2×C^{14}); MIR: $\tilde{\nu}$ = 1650, 1703 & 1779 (s, $\nu_{C=O}$), 3066 (w, ν_{Ar-H}), 2600–3300 (w, $\nu_{N-H\ protonated}$), 3401 (m, ν_{N-H}); HRMS: calculated for $[C_{29}H_{24}N_5O_3F + H]^+$: 510.1936, found: 510.1931.

(*S*)-2-Amino-*N*-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-3-phenylpropanamide hydrochloride (**12d**)



The synthesis was similar to **12c** except it started from compound **i312d**. Yield: 0.09 g (45%) of beige, amorphous solid; Purity 100%; Mp: 213-215 °C (solid from ethyl acetate/tetrahydrofuran); R_f = 0.67 for the free base (dichloromethane/methanol 9:1); ^{1}H-NMR (DMSO-d_6): δ = 3.11 (dd, ^2J = 7.2 Hz, ^3J = 3.2 Hz, 2H, $C^{14}H_2$), 4.19 (m, 1H, C^{13}H), 4.54 (s, 2H, C^7H_2), 5.93 (d, ^3J = 8.8 Hz, 1H, C^5H), 7.09 (d, ^3J = 8.8 Hz, 1H, C^4H), 7.17-7.22 (m, 2H, 2×C^{10}H), 7.29-7.37 (m, 5H, 2×C^{16}H, 2×C^{17}H & C^{18}H), 7.43-7.47 (m, 2H, 2×C^9H), 7.57 (s, 2H, N^2H_2), 8.37 (s, 1H, N^6H), 8.60 (s, 2H, $N^{13}H_2$), 10.01 (s, 1H, N^3H), 13.36 (s, 1H, HCl); ^{13}C NMR (DMSO-d_6): δ = 36.6 (C^{14}), 44.5 (C^7), 53.8 (C^{13}), 93.7 (C^5), 105.0 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 127.1 (C^{18}), 128.5 (2×C^{17}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 129.6 (2×C^{16}) 133.7 (d, ^4J = 3 Hz, C^8), 135.0 (C^{15}), 141.9 (C^4), 148.7 (C^2), 149.6 (C^6), 160.3 & 162.7 (d, ^1J = 242, C^{11}), 167.9 (C^{12}); MIR: $\tilde{\nu}$ = 1638 (s, $\nu_{C=0}$), 3167 (m, ν_{N-H}); HRMS: calculated for $[C_{21}H_{22}N_5OF + H]^+$: 380.1881, found: 380.1889.

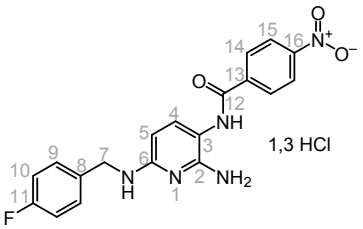
4-Amino-*N*-{2-amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}benzamide hydrochloride (**12e**)



The synthesis is analogously to **12f**, while compound **i12** (1 mmol, 0.26 g), 0.10 g of palladium-activated carbon (10%), triethylamine (1.4 eq., 1.4 mmol, 194 µL) and 4-nitrobenzoyl chloride (1.2 eq., 1.2 mmol, 0.22 g) were used. After purification by column chromatography, the product dissolved in tetrahydrofuran (10 mL) and treated with 0.10 g of palladium-activated carbon (10%). Under hydrogen atmosphere, the reaction mixture stirred for 3.5 h at 40 ° C. The catalyst then filtered off through diatomaceous earth and the residue washed with tetrahydrofuran (30 mL). The solution was concentrated using partial vacuum and by introducing HCl gas, the product finally precipitated as a

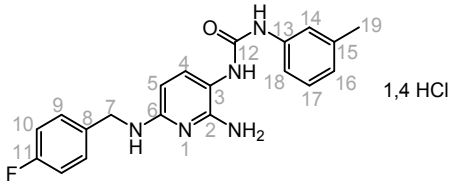
hydrochloride salt. The product was dried at 40 °C and 6 mbar. Yield: 0.11 g (28%) of brown, amorphous solid; 281-283 °C (solid from tetrahydrofuran); R_f = 0.28 for the free base (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 4.60 (s, 2H, C^{7}H$_2$), 6.01 (d, ^3J = 8.8 Hz, 1H, C^{5}H), 7.14 (d, ^3J = 7.9 Hz, 2H, 2×C^{15}H), 7.21 (t, ^3J = 8.6 Hz, 2H, 2×C^{10}H), 7.47-7.50 (m, 2H, 2×C^{9}H), 7.53 (d, ^3J = 8.8 Hz, 1H, C^{4}H), 7.95 (d, ^3J = 8.0 Hz, 2×C^{14}H), 8.40 (s, 1H, N^{6}H), 9.60 (s, 1H, N^{3}H), 13.36 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 46.1 (C^7), 95.7 (C^5), 107.1 (C^3), 117.1 (d, ^2J = 21 Hz, 2×C^{10}), 122.1 (2×C^{14}), 130.6 (d, ^3J = 8 Hz, 2×C^9), 131.1 (2×C^{14}), 134.1 (d, ^4J = 2 Hz, C^8), 140.7 (C^{13}), 145.9 (C^4), 146.0 (C^{16}), 150.2 (C^6), 151.1 (C^2), 162.1 & 164.5 (d, ^1J = 244 Hz, C^{11}), 169.7 (C^{12}); MIR: $\tilde{\nu}$ = 1634 (s, $\nu_{C=O}$), 2559-3127 (m, $\nu_{N\text{-}H,\ protonated}$), 3285 (m, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{19}H_{18}N_5OF + H]^+$: 352.1568, found: 352.1559.

N-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-4-nitrobenzaminde hydrochloride (**12f**)



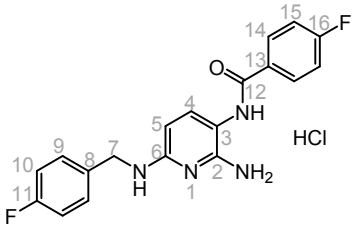
The synthesis carried out according to the GWP2. The residue washed with ethyl acetate (20 mL) and dichloromethane (10 mL). The acylation carried out by a solution of 4-nitrobenzoyl chloride (1.2 eq, 1.2 mmol, 0.22 g) in 5 mL of ethyl acetate. After complete addition, the reaction mixture stirred for 2 h. The solution then washed with water (5 × 20 mL), the organic phase dried over Na_2SO_4 and concentrated using partial vacuum. The residue adsorbed onto diatomaceous earth and purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 4: 6). The product then dissolved in tetrahydrofuran/ethyl acetate (1:1) and precipitated as hydrochloride salt by introducing HCl gas. The product was dried at 40 °C and 4 mbar. Yield: 0.17 g (40%) of bright green, amorphous solid; Purity 100%; Mp: 269-271 °C (solid from tetrahydrofuran/ethyl acetate); R_f = 0.52 for the free base (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 4.58 (s, 2H, C^{7}H$_2$), 6.00 (d, ^3J = 8.8 Hz, 1H, C^{5}H), 7.21 (t, ^3J = 8.8 Hz, 2H, 2×C^{10}H), 7.46-7.50 (m, 2H, 2×C^{9}H), 7.56 (d, ^3J = 8.8 Hz, 1H, C^{4}H), 8.22 (d, ^3J = 8.8 Hz, 2H, 2×C^{14}H), 8.33 (s, 1H, N^{6}H), 8.36 (d, ^3J = 8.8 Hz, 2×C^{15}H), 10.01 (s, 1H, N^{3}H), 13.32 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 44.5 (C^7), 93.7 (C^5), 106.0 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 123.3 (2×C^{14}), 129.5 (2×C^{15}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 133.7 (d, ^4J = 3 Hz, C^8), 139.6 (C^{13}), 143.8 (C^4), 149.2 (C^6), 149.3 (C^2), 149.8 (C^{16}) 160.3 & 162.7 (d, ^1J = 243 Hz, C^{11}), 160.3 & 162.7 (d, ^1J = 243 Hz, C^{11}), 164.7 (C^{12}); MIR: $\tilde{\nu}$ = 1582 (s. $\nu_{C\text{-}NO}$), 1636 (s, $\nu_{C=O}$), 2956 (w, $\nu_{C\text{-}H}$), 2700-3400 (m, $\nu_{N\text{-}H,\ protonated}$), 3303 (m, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{19}H_{16}N_5O_3F + H]^+$: 382.1310, found: 382.1324.

1-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-3-[*m*-tolyl)urea hydrochloride (**12g**)



In a 3-necked flask, compound **i12** (1 mmol, 0.26 g) together with 0.10 g of palladium activated carbon (10%) were suspended in dichloromethane (10 mL) and stirred under hydrogen atmosphere for 20 h at rt. The catalyst then filtered off through diatomaceous earth and the residue washed ethyl acetate (30 mL). The filtrate sprinkled with nitrogen via a capillary and cooled to 0 °C and triethylamine (1.4 eq., 1.4 mmol, 194 μL) added and then a solution of m-tolyl isocyanate (1.2 eq., 1.2 mmol, 142 μL) in ethyl acetate (5 mL) added dropwise. After complete addition, the reaction mixture stirred for 1 h at rt. By storing for 2 h at -15 °C, a solid crystallizes out, which filtered off and recrystallized from methanol. Finally, the solid dissolved in ethyl acetate/ tetrahydrofuran (1:1) and precipitated as hydrochloride by introducing HCl gas. The product dried at 40 °C and 6 mbar. Yield = 0.09 g (21%) of beige, amorphous solid; Purity 100%; Mp: 203–205 °C (solid from ethyl acetate/tetrahydrofuran); R_f = 0.35 for the free base (cyclohexane/ethanol/triethylamine 6:2:2); ^{1}H-NMR (DMSO-d_6): δ = 2.25 (s, 3H, C^{19}H$_3$), 4.53 (s, 2H, C^{7}H$_2$), 5.95 (d, ^3J = 8.0 Hz, 1H, C^{5}H), 6.75 (m, 1H, C^{16}H), 7.13 (m, 1H, C^{17}H), 7.23 (m, 4H, 2×C^{10}H, C^{14}H & C^{18}H), 7.39 (s, 2H, NH$_2$), 7.45 (s, 2H, 2×C^{9}H), 7.57 (d, ^3J = 8.0 Hz, C^{4}H), 8.03 (s, 1H, N^{3}H), 8.11 (s, 1H, N^{6}H), 8.93 (s, 1H, N^{12}H), 13.05 (s, 1H, HCl); ^{13}C-NMR (DMSO-d_6): δ = 21.2 (C^{19}), 44.5 (C^7), 93.6 (C^5), 107.7 (C^3), 115.2 (d, ^2J = 21 Hz, 2×C^{10}), 118.5 (C^{14}), 122.3 (C^{16}), 128.5 C^{17}), 129.5 (d, ^3J = 8 Hz, 2×C^9), 133.8 (d, ^4J = 3 Hz, C^8), 137.8 (C^{15}), 139.8 (C^{13}), 142.4 (C^4), 148.7 (C^6), 149.6 (C^2), 153.8 (C^{12}) 160.3 & 162.7 (d, ^1J = 242, C^{11}); MIR: $\tilde{\nu}$ = 1634 (s, $\nu_{C=0}$), 3052 (w, ν_{Ar-H}), 3177, 3245, 3354 & 3395 (m, ν_{N-H}); HRMS: calculated for [$C_{20}H_{20}N_5OF$ + H]$^+$: 366.1725, found: 366.1727.

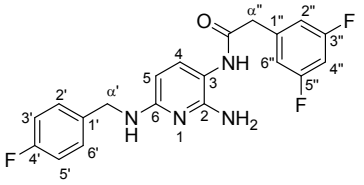
N-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-4-fluorbenzamide hydrochloride (**12h**)



In a 3-necked flask, compound **i12** (1 mmol, 0.26 g) together with 0.10 g of palladium activated carbon (10%) were suspended in dichloromethane (10 mL) and stirred under hydrogen atmosphere for 20 h at rt. Subsequently, triethylamine (1.4 eq., 1.4 mmol, 194 μL) added and the reaction mixture cooled to 0 °C. A solution of 4-fluorobenzoyl chloride (1.2 eq, 1.2 mmol, 142 μL) in dichloromethane (5 mL) added dropwise. After complete addition, the reaction continued for 30 min at rt and then the catalyst filtered through diatomaceous earth. The residue washed with ethyl acetate (30 mL) and the filtrate

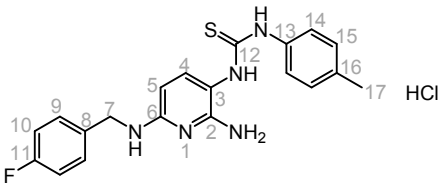
was concentrated under partial vacuum. The residue dissolved in a little methanol and precipitated by the addition of water. The resulting solid was filtered off, dissolved in a little 2-propanol and the solution was adjusted to pH 2 with 10% strength hydrochloric acid. The crystallized hydrochloride filtered off and finally recrystallized from methanol/ethanol (2:1). The product dried at 40 °C and 4 mbar. Yield: 0.10 g (26%) of colourless, crystalline solid; Purity 100%; Mp: 296-298 °C (solid from methanol/ethanol); R_f = 0.31 for the free base (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 4.58 (s, 2H, C^{7}H$_2$), 5.99 (d, ^3J = 8.6 Hz, 1H, C^{5}H), 7.21 (t, ^3J = 8.5 Hz, 2H, 2×C^{10}H), 7.35 (d, ^3J = 8.4 Hz, 2H, 2×C^{9}H), 7.48 (t, ^3J = 6.1 Hz, 2H, 2×C^{15}H), 7.53 (d, ^3J = 8.7 Hz, 1H, C^{4}H), 8.07 (t, ^3J = 6.2 Hz, 2H, 2×C^{14}H), 8.32 (s, 1H, N^{6}H), 9.70 (s, 1H, N^{3}H), 13.32 (s, 1H, HCl); ^{13}C NMR (DMSO-d_6): δ = 44.5 (C^7), 93.7 (C^5), 106.5 (C^3), 115.1 (d, ^2J = 22 Hz, 2×C^{10}), 115.3 (d, ^2J = 21 Hz, 2×C^{15}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 130.4 (d, ^4J = 3 Hz, C^8), 130.7 (d, ^3J = 9 Hz, 2×C^{14}), 133.7 (d, ^4J = 3 Hz, C^{13}), 143.8 (C^4), 149.3 (C^6), 149.5 (C^2), 160.3 & 162.7 (d, ^1J = 243 Hz, C^{11}), 162.9 & 165.4 (d, ^1J = 249 Hz, C^{16}), 165.1 (C^{12}); MIR: $\tilde{\nu}$ = 1634 (s, $\nu_{C=O}$), 2949 (w, ν_{C-H}), 3172, 3282 & 3345 (m, ν_{N-H}); HRMS: calculated for [$C_{19}H_{16}N_4OF_2$ + H]$^+$: 355.1365, found: 355.1351.

N-{2-Amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}-2-(3,5-difluorophenyl)acetamide (**12i**)



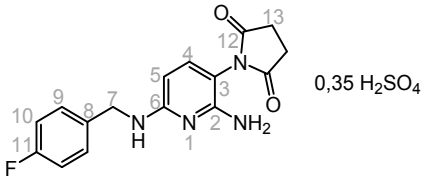
Compound **i12** (3 mmol, 787 mg) and Pd/C (300 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for 24 h at 40 ˚C. The reaction mixture filtered off and washed with ethyl acetate (3 x 15 mL). The filtrate cooled using ice-cooled water and then triethylamine (3.75 mmol, 523 µL) and 3,5-difluorobenzoyl chloride (3.3 mmol) added respectively. After complete addition, the mixture stirred for 2 h. The reaction mixture evaporated to dryness and dissolved in ethanol. Eventually, the product precipitated with the addition of water. Yield: 16%, off-white solid; Purity 100%; Mp: 172-173 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 9.04 (s, 1H, *N*^{3}H), 7.36 (m, 2H, C(2')H & C(6')H), 7.12 (m, 6H, C(4)H, C(3')H, C(5')H, C(2")H, C(6")H & C(4")H), 6.58 (m, 1H, *N*^{6}H), 5.69 (d, 1H, ^3J = 8.4 Hz, C(5)H), 5.25 (s, 2H, *N*^{2}H$_2$), 4.37 (m, 2H, C(α')H$_2$), 3.36 (s, 2H, C(α")H$_2$); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 168.2 (C=O), 163.4 (dd, $^1J_{C,F}$ = 244 Hz, $^3J_{C,F}$ = 13 Hz, C3" & C5") 162.1 (d, $^1J_{C,F}$= 239 Hz, C4'), 155.8 (C6), 152.9 (C2), 140.8 (d, $^3J_{C,F}$ = 10 Hz, C4"), 137.2 (d, $^4J_{C,F}$ = 3 Hz, C1'), 135.6 (C4), 129.1 (d, $^3J_{C,F}$ = 8 Hz, C2' & C6'), 114.8 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 112.5 ($^2J_{C,F}$ = 19 Hz, $^4J_{C,F}$ = 6 Hz, C2" & C6"), 106.4 (C3), 102.1 (t, $^2J_{C,F}$ = 51 Hz, C4"), 95.2 (C5), 43.6 (Cα'), 41.8 (Cα"); MIR (cm^{-1}): $\tilde{\nu}$ = 3421 & 3334 (N-H), 1644 (C=O), 1224 (C-F); HRMS ((ESI) m/z) calculated for [$C_{20}H_{17}F_3N_4O$ + H]$^+$: 387.1427, found: 387.1445.

1-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}-3-[*m*-tolyl)thiourea hydrochloride (**12j**)



The synthesis carried out in accordance with GWP2, except tolyl isothiocyanate (1.2 eq., 1.2 mmol, 0.18 g) instead of carboxylic acid chloride used and the addition of triethylamine omitted. After the completed addition of the isothiocyanate, the batch was stirred for 5 h at rt. The solution then washed with water (5 × 20 mL), dried over Na_2SO_4 and adsorbed on diatomaceous earth in a partial vacuum. The product purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 1:1). The solid taken up in ethyl acetate/tetrahydrofuran (1:1) and precipitated as hydrochloride by bubbling HCl gas. The product dried at 40 °C and 6 mbar. Yield: 0.18 g (44%) of light grey, amorphous solid; Purity 100%; Mp: 244-246 °C (solid from ethyl acetate/tetrahydrofuran); R_f = 0.21 for the free base (*n*-hexane/ethyl acetate 1:1); ^{1}H-NMR (DMSO-d_6): δ = 2.27 (s, 3H, $C^{17}H_3$), 4.56 (d, ^3J = 5.2 Hz, 2H, C^7H_2), 5.95 (d, ^3J = 8.8 Hz, 1H, C^5H), 7.13 (d, ^3J = 8.4 Hz, 2H, 2×C^{15}H), 7,21 (t, ^3J = 8.8 Hz, 2H, 2×C^{10}H), 7.39-7.49 (bs, 2H, NH_2), 7.41 (m, 2H, 2×C^{14}H), 7.45 (s, 1H, C^4H), 7.47 (m, 2H, 2×C^9H), 8.29 (s, 1H, N^6H), 8.96 (s, 1H, N^{12}H), 9.99 (s, 1H, N^3H), 13.13 (s, 1H, HCl); ^{13}C NMR (DMSO-d_6): δ = 20.5 (C^{17}), 44.5 (C^7), 93.7 (C^5), 108.3 (C^3), 115.3 (d, ^2J = 21 Hz, 2×C^{10}), 123.7 (2×C^{14}), 128.8 (2×C^{15}), 129.6 (d, ^3J = 8 Hz, 2×C^9), 133.7 (d, ^4J = 3 Hz, C^8), 133.7 (C^{13}), 136.8 (C^{16}), 145.1 (C^4), 149.5 (C^6), 149.9 (C^2), 160.3 & 162.7 (d, ^1J = 242, C^{11}), 181.5 (C^{14}); MIR: $\tilde{\nu}$ = 1634 (s, $\nu_{C=O}$), 3052 (w, ν_{Ar-H}), 3177, 3245, 3354 & 3395 (m, ν_{N-H}); HRMS: calculated for $[C_{20}H_{20}N_5FS + H]^+$: 382.1496, found: 382.1512.

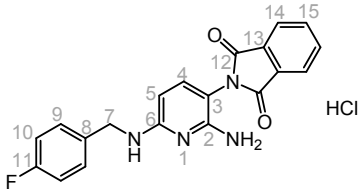
1-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}pyrrolidin-2,5-dione sulfate (**12k**)



The synthesis carried out in accordance with GWP2, while succinic anhydride (1.2 eq., 1.2 mmol, 0.12 g) used for the derivatization of the primary amine. After complete addition, the mixture first stirred for 2.5 h at rt (after amide formation), concentrated sulfuric acid (2.8 eq., 1.4 mmol, 75 µL) was added and the reaction mixture heated to reflux with water separation. After 2 h, the imide formation was complete and the solution washed with water (5 × 20 mL), dried over Na_2SO_4 and adsorbed onto diatomaceous earth in a partial vacuum. The product purified by flash chromatography (mobile phase: ethyl acetate). The resulting solid finally recrystallized from ethanol and dried at 40 °C and 6 mbar. Yield: 0.13 g (37%) of colourless, amorphous solid; Purity 100%; Mp: 187–189 °C (solid from ethyl acetate); R_f = 0.37 (ethyl acetate); ^{1}H-NMR (DMSO-d_6): δ = 2.62-2.74 (m, 4H, 2×$C^{13}H_2$), 4.46 (d,

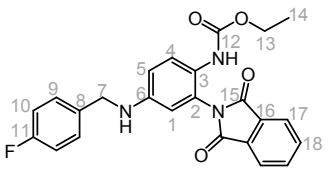
^3J = 4.2 Hz, 2H, C^7H_2), 5.81 (d, ^3J = 8.5 Hz, 1H, C^5H), 6.30 (bs, 2H, NH_2), 6.99 (d, ^3J = 7.9 Hz, 1H, C^4H), 7.15 (t, ^3J = 8.8 Hz, 2H, 2×$C^{10}H$), 7.38-7.42 (m, 3H, N^6H & 2×C^9H), 13.31 (s, 1H, H_2SO_4); ^{13}C-NMR (DMSO-d_6): δ = 28.7 (2×C^{13}), 43.8 (C^7), 94.7 (C^5), 100.4 (C^3), 115.0 (d, ^2J = 21 Hz, 2×C^{10}), 129.2 (d, ^3J = 8 Hz, 2×C^9), 135.8 (C^8), 140.3 (C^4), 153.0 (C^2), 155.6 (C^6), 160.0 & 162.4 (d, ^1J = 242 Hz, C^{11}), 177.5 (C^{14}); MIR: $\tilde{\nu}$ = 1701 (s, $\nu_{C=O}$), 2943 (w, ν_{C-H}), 3181, 3348 & 3378 (m, ν_{N-H}); HRMS: calculated for $[C_{16}H_{15}N_4OF + H]^+$: 315.1252, found: 315.1251.

2-{2-Amino-6-[(4-fluorbenzyl)amino]pyridin-3-yl}isoindolin-1,3-dione hydrochloride (**12l**)



The synthesis carried out in accordance with GWP2, while phthalic anhydride (1.2 eq., 1.2 mmol, 0.18 g) used. After complete addition of the anhydride, the reaction mixture stirred for 1 h at rt and then heated to reflux under water for 3.5 h. The solution then washed with of water (5 × 20 mL), dried over Na_2SO_4 and adsorbed on diatomaceous earth using a partial vacuum. The product purified by flash chromatography (mobile phase: n-hexane/ethyl acetate 6:4). The resulting solid dissolved in ethyl acetate/tetrahydrofuran (1:1) and precipitated as hydrochloride by bubbling HCl gas. The product was dried at 40 °C and 6 mbar. Yield: 0.15 g (38%) of pale yellow, amorphous solid; Purity 100%; Mp: 187-189 °C (solid from ethyl acetate/tetrahydrofuran); R_f = 0.57 for the free base (*n*-hexane/ethyl acetate 6:4); ^{1}H-NMR (DMSO-d_6): δ = 4.61 (s, 2H, C^7H_2), 6.07 (d, ^3J = 8.9 Hz, 1H, C^5H), 7.22 (t, ^3J = 8.9 Hz, 2H, 2×$C^{10}H$), 7.49-7.52 (m, 2H, 2×C^9H), 7.61 (d, ^3J = 8.9 Hz, 1H, C^4H), 7.81 (s, 2H, NH_2), 7.87-7.91 (m, 2H, 2×$C^{15}H$), 7.93-7.97 (m, 2H, 2×$C^{14}H$), 8.71 (s, 1H, NH), 13.58 (s, 1H, HCl); ^{13}C NMR (DMSO-d_6): δ = 44.6 (C^7), 94.3 (C^5), 99.3 (C^3), 115.4 (d, ^2J = 22 Hz, 2×C^{10}), 123.3 (2×C^{15}), 129.7 (d, ^3J = 8 Hz, 2×C^9), 132.4 (C^{14}), 133.5 (d, ^3J = 3 Hz, C^8), 134.4 (2×C^{13}), 145.3 (C^4), 150.5 (C^2), 151.3 (C^6), 160.3 & 162.8 (d, ^1J = 242 Hz, C^{11}), 167.3 (C^{14}); MIR: $\tilde{\nu}$ = 1704 & 1785 (s, $\nu_{C=O}$), 2977 (w, ν_{C-H}), 3166, 3249 & 3387 (m, ν_{N-H}); HRMS: calculated for $[C_{20}H_{15}N_4O_2F + H]^+$: 363.1252, found: 363.1245.

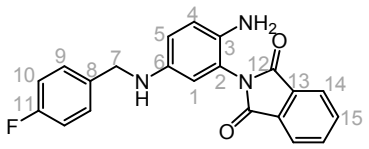
Ethyl-{2-(1,3-dioxoisoindolin-2-yl)-4-[(4-fluorbenzyl)amino]phenyl}carbamate (**13**)



Compound **2** (10 mmol, 3.03 g) and phthalic anhydride (1.0 eq, 10 mmol, 1.48 g) were dissolved in toluene (50 mL) and heated to reflux with the removal of water for 6 h. The solution was stored

overnight in a refrigerator, forming a brown precipitate. The product was filtered off and dried at 60 °C in a drying oven. Yield: 3.97 g (92%) of brown, acicular solid; Mp: 176-178 °C (toluene); R_f = 0.75 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 1.07 (t, ^3J = 7.2 Hz, 3H, $C^{14}H_3$), 3.95 (q, ^3J = 7.2 Hz, 2H, $C^{13}H_2$), 4.22 (d, ^3J = 6.0 Hz, 2H, C^7H_2), 6.29 (t, ^3J = 6.0 Hz, 1H, N^6H), 6.54 (d, ^4J = 2.7 Hz, 1H, C^1H), 6.65 (dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz, 1H, C^5H), 7.11–7.16 (m, 2H, 2×$C^{10}H$), 7.38-7.41 (m, 3H, C^4H & 2×C^9H), 7.86-7.93 (m, 4H, 2×$C^{17}H$ & 2×$C^{18}H$), 8.88 (s, 1H, N^3H); ^{13}C-NMR (DMSO-d_6): δ = 14.4 (C^{14}), 45.9 (C^7), 59.8 (C^{13}), 112.6 (C^5), 113.0 (C^1), 114.9 (d, ^2J = 21 Hz, 2×C^{10}), 123.1 (2×C^{17}), 124.5 (C^4), 125.1 (C^3), 129.1 (d, ^3J = 8 Hz, 2×C^9), 132.4 (2×C^{16}), 134.2 (2×C^{18}), 136.1 (d, ^4J = 3 Hz, C^8), 145.4 (C^6), 154.2 (C^{12}), 159.9 & 162.3 (d, ^1J = 242 Hz, C^{11}), 166.8 (2×C^{15}); MIR: $\tilde{\nu}$ = 1712 & 1763 (s, $\nu_{C=O}$), 2977 (w, ν_{C-H}), 3311 & 3364 (w, ν_{N-H}); HRMS: calculated for $[C_{24}H_{20}N_3O_4F + H]^+$: 434.1511, found: 434.1512.

2-{2-Amino-5-[(4-fluorbenzyl)amino]phenyl}isoindolin-1,3-dione (**14**)

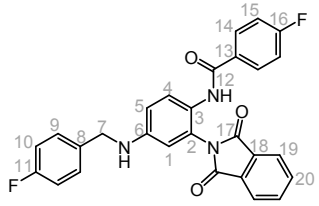


Method A: Compound **13** (3.8 mmol, 1.64 g) was dissolved in hydrobromic acid (20 mL, 32% in acetic acid) and stirred at rt. After 22 and 40 h, additional hydrobromic acid (20 mL, 32% in acetic acid) were added. After 64 h, the reaction mixture was neutralized using 10% strength sodium hydroxide solution and extracted with ethyl acetate (100 mL). The organic phase washed with of saturated $NaHCO_3$ solution (100 mL) and saturated common salt solution (100 mL), dried over Na_2SO_4 and adsorbed on diatomaceous earth using a partial vacuum. The product was purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate 4:6) and dried at 40 °C and 6 mbar. Yield: 0.70 g (51%) of light brown, amorphous solid; Mp: 143-145 °C (solid from *n*-hexane/ethyl acetate); R_f = 0.63 (*n*-hexane/ethyl acetate 4:6); ^{1}H-NMR (DMSO-d_6): δ = 4.12 (d, ^3J = 5.2 Hz, 2H, C^7H_2), 4.47 (s, 2H, NH_2), 5.51 (t, ^3J = 5.6 Hz, 1H, N^6H), 6.37 (d, ^4J = 2,5 Hz, 1H, C^1H), 6.53 (dd, ^3J = 8.6 Hz, ^4J = 2.6 Hz, 1H, C^5H), 6.60 (d, ^3J = 8,6 Hz, 1H, C^4H), 7.09-7.14 (m, 2H, 2×$C^{10}H$), 7.37-7.40 (m, 2H, 2×C^9H), 7.85-7.92 (m, 4H, 2×$C^{14}H$ & 2×$C^{15}H$); ^{13}C-NMR (DMSO-d_6): δ = 46.8 (C^7), 113.7 (C^5), 114.8 (d, ^2J = 21 Hz, 2×C^{10}), 115.4 (C^1), 117,0 (C^4); 117.3 (C^3), 123.0 (2×C^{14}), 129.2 (d, ^3J = 8 Hz, 2×C^9), 132.3 (2×C^{13}), 134.1 (2×C^{15}), 136.7 (d, ^4J = 3 Hz, C^8), 136.9 (C^6), 140.0 (C^2), 159.8 & 162.2 (d, ^1J = 242 Hz, C^{11}), 167.4 (2×C^{12}); MIR: $\tilde{\nu}$ = 1705 & 1773 (s, $\nu_{C=O}$), 2851 (w, ν_{C-H}), 3342 & 3418 (w, ν_{N-H}); HRMS: calculated for $[C_{21}H_{16}N_3O_2F + H]^+$: 362.1299, found: 362,1298.

Method B: In a 3-necked flask, compound **13** (1 mmol, 0.43 g) was dissolved under argon atmosphere in anhydrous dichloromethane (10 mL, if possible without alcohols used as stabilizer). Subsequently, a solution of trimethylsilyl iodide (1.2 eq., 1.2 mmol, 171 µL) in of dichloromethane (2 mL) was added

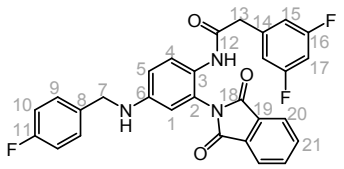
dropwise and the reaction mixture was heated to reflux. After 24 and 30.5 h, an additional trimethylsilyl iodide (1.2 eq., 1.2 mmol, 171 µL) dissolved in of dichloromethane (2 mL) were added dropwise. After a total of 48 h, the reaction mixture was cooled to rt and methanol (4.0 eq., 4 mmol 162 µL) was added. The suspension was concentrated in a partial vacuum, sodium methoxide (0.5 eq., 0.5 mmol, 0.03 g) was added and the solid was dissolved in methanol. The solution was concentrated again and then purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate/ triethylamine 50:49:1). The product was dried at 40 °C and 4 mbar. Yield: 0.18 g (36%) of light brown, amorphous solid. Analytical data similar to method A were obtained.

N-{2-(1,3-Dioxoisoindolin-2-yl)-4-[(4-fluorbenzyl)amino]phenyl}-4-fluorbenzamide (**15a**)



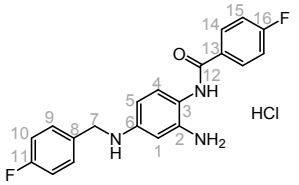
Compound **14** (0.89 mmol, 0.32 g), 4-fluorobenzoic acid (1.0 eq, 0.89 mmol, 0.13 g), O- (7-azabenzotriazol-1-yl) Dissolve N, N, N', N'-tetramethyluronium hexafluorophosphate (HATU, 2.0 eq, 1.78 mmol 0.68 g) and diisopropylethylamine (3.0 eq, 2.67 mmol, 453 µL) were dissolved in dimethylformamide (10 mL). The reaction mixture was heated at 40 °C for 18 h, then diluted with dichloromethane (100 mL) and washed with water (2 × 100 mL) and saturated brine (100 mL). The organic phase was concentrated under partial vacuum and the residue was purified by flash chromatography (EZ Prep system from Axel Semrau, column: 24 g silica, mobile phase: *n*-hexane/ethyl acetate, gradient: 0-12 min 0-60% ethyl acetate , 12-15 min 60% ethyl acetate, 15-17 min 60-100% ethyl acetate, 17-25 min 100% ethyl acetate, flow rate: 38 mL/min). For structural analysis, the product was recrystallized from ethanol. Yield: 0.29 g (67%) of orange, amorphous solid; Mp: 240-242 °C (solid from ethanol); R_f = 0.60 (*n*-hexane/ethyl acetate 5:5); ^{1}H-NMR (DMSO-d_6): δ = 4.28 (d, ^3J = 6.0 Hz, 2H, C^7H_2), 6.48 (t, ^3J = 6.0 Hz, 1H, N^6H), 6.64 (d, ^4J = 2.6 Hz, 1H, C^1H), 6.69 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1H, C^5H), 7.15 (t, ^3J = 8.9 Hz, 2H, 2×$C^{10}H$), 7.20 (t, ^3J = 8.9 Hz, 2H, 2×$C^{15}H$), 7.37 (d, ^3J = 8.6 Hz, 1H, C^4H), 7.41-7.44 (m, 2H, 2×C^9H), 7.70–7.73 (m, 2H, 2×$C^{14}H$), 7.83–7.90 (m, 4H, 2×$C^{19}H$ und 2×$C^{20}H$), 9,71 (s, 1H, N^3H); ^{13}C-NMR (DMSO-d_6): δ = 45.8 (C^7), 112.4 (C^5), 112.4 (C^1), 115.0 (d, ^2J = 21 Hz, 2×C^{10}), 115.0 (d, ^2J = 21 Hz, 2×C^{15}), 123.1 (2×C^{20}), 123.7 (C^2), 126.8 (C^3), 127.2 (C^4), 129.1 (d, ^3J = 8 Hz, 2×C^9), 130.0 (d, ^3J = 9 Hz, 2×C^{14}), 131.4 (d, ^4J = 3 Hz, C^{13}), 131.9 (2×C^{18}), 134.4 (2×C^{19}), 136.0 (d, ^3J = 3 Hz, C^8), 146.6 (C^6), 159.9 & 162.3 (d, ^1J = 242 Hz, C^{11}), 162.5 & 164.9 (d, ^1J = 248 Hz, C^{16}), 164.3 (C^{12}), 166.6 (2×C^{17}); MIR: $\tilde{\nu}$ = 1651, 1712 & 1782 (s, $\nu_{C=O}$), 2898 (w, ν_{C-H}), 3360 & 3397 (w, ν_{N-H}).

2-(3,5-Difluophenyl)-*N*-{2-(1,3-dioxoindolin-2-yl)-4-[(4-fluorbenzyl)amino]phenyl}acetamide (**15b**)



Compound **14** (1 mmol, 0.36 g), 3,5-difluoroacetic acid (1.0 eq., 1 mmol, 0.17 g), HATU (2.0 eq., 2 mmol, 0.76 g) and diisopropylethylamine (3.0 eq., 3 mmol, 510 µL) were dissolved in dimethylformamide (10 mL) and stirred for 6 h at rt. Diethyl ether (100 mL) and ethyl acetate (150 mL) added to the solution, and the organic phase washed with water (200 mL), saturated $NaHCO_3$ solution (2 × 100 mL) and of saturated common salt solution (100 mL). The organic phase dried over Na_2SO_4 and adsorbed on diatomaceous earth in a partial vacuum. The product was then purified by flash chromatography (Puriflash system from Interchim, column: 40 g silica 15 µm spherical, mobile phase: n-hexane/ethyl acetate + 5% triethylamine, gradient: 1 CV 10% ethyl acetate, 10 CV 10-80% ethyl acetate, 5 CV 80% ethyl acetate, flow rate: 26 mL/min). The product was dried at 40 ° C and 4 mbar. Yield: 0.23 g (44%) of orange, amorphous solid; Mp: 236-238 °C (solid from *n*-hexane/ethyl acetate/triethylamine); R_f = 0.51 (*n*-hexane/ethyl acetate 5:5); ^{1}H-NMR (DMSO-d_6): δ = 3.45 (s, 2H, $C^{13}H_2$), 4.24 (d, ^3J = 5.4 Hz, 2H, C^7H_2), 6.41 (t, ^3J = 5.5 Hz, 1H, N^6H), 6.58 (d, ^4J = 1.7 Hz, 1H, C^1H), 6.65 (dd, ^3J = 8.8 Hz, ^4J = 1.7 Hz, 1H, C^5H), 6.79 (d, ^3J = 7.0 Hz, 2H, 2×$C^{15}H$), 6.97 (t, ^3J = 9.3 Hz, 1H, $C^{17}H$), 7.14 (t, ^3J = 8.7 Hz, 2H, 2×$C^{10}H$), 7.36-7,41 (m, 3H, C^4H & 2×C^9H), 7.86 (s, 4H, 2×$C^{20}H$ & 2×$C^{21}H$), 9.40 (s, 1H, N^3H); ^{13}C NMR (DMSO-d_6): δ = 41.9 (C^{13}), 45.7 (C^7), 101.8 (t, ^2J = 26 Hz, C^{17}), 111.9 (dd, ^2J = 18 Hz, ^4J = 7 Hz, 2×C^{15}), 112.5 (C^1), 112,6 (C^5), 115.0 (d, ^2J = 21 Hz, 2×C^{10}), 123.1 (2×$C^{21}H$), 124.0 (C^3), 125.9 (C^6), 126.0 (C^4), 129.1 (d, ^3J = 8 Hz, 2×C^9), 131.9 (2×C^{19}), 134.3 (2×C^{20}), 136.0 (d, ^4J = 3 Hz, C^8), 140.3 (t, ^3J = 10 Hz, C^{13}), 146.3 (C^2), 159.9 & 162.3 (d, ^1J = 242 Hz, C^{11}), 160.8 & 163.2 (dd, ^1J = 245 Hz, ^3J = 13 Hz, 2×C^{16}), 166.6 (2×C^{18}), 167.6 (C^{12}); MIR: $\tilde{\nu}$ = 1633 (m, $\nu_{C=O}$), 1715 (s, $\nu_{C=O}$), 2927 (w, ν_{C-H}), 3244, 3354 & 3462 (w, ν_{N-H}).

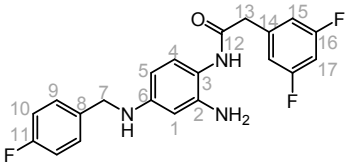
N-{2-Amino-4-[(4-fluorbenzyl)amino]phenyl}-4-fluorbenzamide (**16a**)



Compound **15a** (0.6 mmol, 0.29 g) was dissolved in methanol/2-propanol (40 mL, 1:1) and hydrazine hydrate (1.5 eq, 0.9 mmol, 59 mL, 80% aqueous solution) added was added to the solution. The reaction mixture was stirred for 17 h at rt, then treated with water (100 mL) and stored in a refrigerator. The resulting brown precipitate was filtered off, dissolved in ethyl acetate/tetrahydrofuran (1:1) and precipitated by bubbling HCl gas as a hydrochloride salt. The product was dried at 40 °C and 6 mbar. Yield: 0.11 g (47%) of orange, amorphous solid; Purity 100%;

Mp: 232-235 °C (solid from ethyl acetate/Tetrahydrofuran); Mp: it did not melt uniformly; R_f = 0.84 (*n*-Hexane/Ethyl acetate 5:5); ^{1}H-NMR (DMSO-d_6): d = 4.29 (s, 2H, C^{7}H$_2$), 6.61 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1H, C^{5}H), 6.67 (d, ^4J = 2.3 Hz, 1H, C^{1}H), 7.17 (t, ^3J = 8.9 Hz, 2H, 2×C^{10}H), 7.18 (d, ^3J = 8.7 Hz, 1H, C^{4}H), 7.35 (t, ^3J = 8.8 Hz, 2H, 2×C^{15}), 7.40-7.44 (m, 2H, 2×C^{9}H), 8.13-8.18 (m, 2H, 2×C^{14}H), 10.18 (s, 1H, N^{3}H); ^{13}C-NMR (DMSO-d_6): δ = 46.2 (C^7), 106.9 (C^5), 111.6 (C^1), 115.1 (d, ^2J = 21 Hz, 2×C^{10}), 115.2 (d, ^2J = 21 Hz, 2×C^{15}), 119.8 (C^3), 128.4 (C^4), 129.4 (d, ^3J = 8 Hz, 2×C^9), 130.4 (d, ^4J = 3 Hz, 2×C^8), 130.6 (d, ^3J = 9 Hz, C^{14}), 135.2 (d, ^4J = 3 Hz, C^{13}), 144.3 (C^2), 146.2 (C^6), 160.1 & 162.5 (d, ^1J = 242 Hz, C^{11}), 162.9 & 165.4 (d, ^1J = 249 Hz, C^{16}), 164.6 (C^{12}); MIR: $\tilde{\nu}$ = 1654 (s, $\nu_{C=O}$), 2865 (w, ν_{C-H}), 3038 (w, ν_{Ar-H}), 3296, 3327 und 3440 (w, ν_{N-H}); HRMS: calculated for [$C_{20}H_{17}N_3OF_2$ + H]$^+$: 354.1412, found: 354.1425.

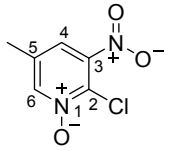
N-{2-Amino-4-[(4-fluorbenzyl)amino]phenyl}-2-(3,5-difluorphenyl)acetamide (**16b**)



Compound **15b** (0.44 mmol, 0.23 g) and hydrazine hydrate (1.5 eq., 0.66 mmol, 40.3 µL of 80% aqueous solution) were dissolved in 100 mL of tetrahydrofuran/2-propanol/methanol (3: 1: 1). The reaction mixture was stirred for 24 h at rt and then concentrated in a partial vacuum. The resulting gray solid was dissolved in methanol/tetrahydrofuran (1:1), adsorbed on diatomaceous earth and purified by flash chromatography (Reveleris system from Büchi, column: 24 g silica, 20 µm spherical, mobile phase: n-hexane/ethyl acetate +5% triethylamine, gradient: 0-1 min 16% ethyl acetate, 1-12 min 16-100% ethyl acetate, 12-28 min 100% ethyl acetate, 28-30 min 0-20% methanol instead of n-hexane, 30-38 min 20% methanol, flow rate: 32 mL/min). The first fraction was further worked up by preparative HPLC (column: Lichrospher xy, mobile phase: water/acetonitrile, gradient: 0-2 min 50% acetonitrile, 2-12 min 50-90% acetonitrile, 12-18 min 90% acetonitrile, 18-22 min 50% acetonitrile, flow rate 39 mL/min). During the subsequent concentration of the product containing fractions in a partial vacuum, a colorless solid precipitated. This was filtered off and dried at 40 °C and 6 mbar. Yield: 0.07 g (41%) of colorless, amorphous solid; Purity 100%; Mp: 172-174 °C (solid from water/acetonitrile); R_f = 0.72 (ethyl acetate/triethylamine 100:1); ^{1}H-NMR (DMSO-d_6): δ = 3.63 (s, 2H, C^{13}H$_2$), 4.18 (d, ^3J = 6.1 Hz, 2H, C^{7}H$_2$), 4.56 (s, 2H, NH$_2$), 5.85 (dd, ^3J = 8,5 Hz, ^4J = 2,4 Hz, 1H, C^{5}H), 5.94 (t, ^3J = 6.5 Hz, 1H, N^{6}H), 5.95 (d, ^4J = 2.6 Hz, 1H, C^{1}H), 6.72 (d, ^3J = 8,4 Hz, 1H, C^{4}H), 7.05-7.08 (m, 3H, 2×C^{15}H & C^{17}H), 7.10-7.15 (m, 2H, 2×C^{9}H), 7.34-7.38 (m, 2H, 2×C^{9}H), 9.08 (s, 1H, N^{3}H); ^{13}C-NMR (DMSO-d_6): δ = 41.9 (C^{13}), 45.8 (C^7), 99.0 (C^1), 101.7 (C^5), 101.9 (t, ^2J = 26 Hz, C^{17}), 112.3 (dd, ^2J = 18 Hz, ^4J = 6 Hz, 2×C^{15}), 112.9 (C^3), 114.8 (d, ^2J = 21 Hz, 2×C^{10}), 126.8 (C^4), 128.8 (d, ^3J = 8 Hz, 2×C^9), 136.7 (d, ^4J = 3 Hz, C^8), 140.9 (t, ^3J = 10 Hz, C^{13}), 143.3 (C^2), 147.3 (C^6), 159.8 & 162.2 (d, ^1J = 242 Hz, C^{11}), 160.9 & 163.4 (dd, ^1J = 245 Hz, ^3J = 14 Hz,

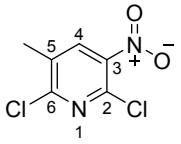
2×C^{16}), 168,0 (C^{12}); MIR: $\tilde{\nu}$ = 1642 (s, $\nu_{C=O}$), 3027 (w, ν_{Ar-H}), 3254, 3370 & 3406 (w, ν_{N-H}); HRMS: calculated for $[C_{21}H_{18}N_3OF_3 + H]^+$: 386.1475, found: 386.1464.

2-Chloro-5-methyl-3-nitropyridine 1-oxide (**17**)



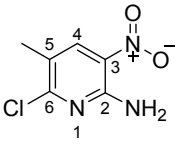
2-Chloro-5-methyl-3-nitropyridine (20 mmol, 3.452 g) and urea-hydrogen peroxide (42 mmol, 3.95 g) dissolved in dichloromethane (80 mL). The mixture cooled using ice-cold water. Trifluoroacetic anhydride (42 mmol, 6 mL) added slowly and the mixture stirred for 30 min. The temperature was raised to rt and stirred for 36 h. Following completion of the reaction, the mixture filtered and poured into water (50 mL). The product extracted using dichloromethane (2 x 25 mL) and then washed with brine. The product separated using flash chromatography (solvent *n*-hexane and ethyl acetate). Yield: 81.64%, yellow solid; Mp: 137-138 ˚C (solid from *n*-hexane and ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.71 (q, 1H, ^4J = 0.9 Hz, C(6)H), 8.00 (q, 1H, ^4J = 0.8 Hz, C(4)H), 2.33 (m, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.6 (C2), 142.8 (C6), 134.9 (C3), 132.9 (C5), 122.3 (C4), 17.2 (CH_3); IR (cm^{-1}): $\tilde{\nu}$ = 1338 & 1534 (NO_2).

2,6-Dichloro-3-methyl-5-nitropyridine (**18**)



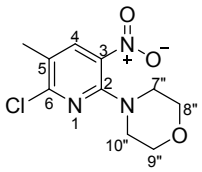
Compound **17** (32.3 mmol, 6.091 g) suspended in phosphorous oxychloride (30 mL) and the suspension was refluxed for 5 h. The mixture carefully added to pre-warmed water, then cooled and extracted with ethyl acetate (3 x 20 mL). The ethyl acetate phase washed with sodium bicarbonate solution (aq.) and packed for flash chromatography (*n*-hexane and ethyl acetate). Yield: 74%, off-white solid; Mp:68-69 ˚C (solid from *n*-hexane and ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.69 (d, 1H, ^4J = 0.6 Hz, C(4)H), 2.42 (d, 3H, ^4J = 0.6 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.0 (C2), 143.2 (C6), 138.3 (C3), 138.1 (C4), 134.1 (C5), 18.2 (CH_3); IR: (cm^{-1}): $\tilde{\nu}$ = 1512 & 1333 (NO_2).

6-Chloro-5-methyl-3-nitropyridin-2-amine (**19a**)



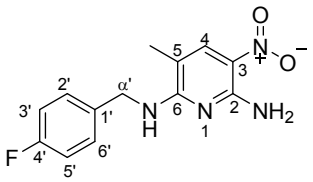
Compound **18** (11.85 mmol, 2.453 g) suspended in 2-propanol (100 mL) and followed by addition of a relatively excess aqueous ammonia (10 mL, 25%). The reaction mixture then warmed to 35 ˚C and stirred for 5 days. A yellow product collected by filtration, which was further purified using flash chromatography (*n*-hexane and ethyl acetate). Yield: 50.38%, yellow solid; Mp: 196-197 ˚C (*n*-hexane and ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.38 (d, 1H, ^{4}J= 0.4 Hz, C(4)H), 8.03 (bs, 2H, $N^{2}H_2$), 2.23 (d, 3H, ^{4}J= 0.4 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.4 (C6), 151.8 (C2), 137.6 (C4), 125.9 (C3), 119.5 (C5), 17.6 (CH_3); IR: (cm^{-1}): $\tilde{\nu}$ = 3461 (N-H), 1553 (NO_2).

4-(6-Chloro-5-methyl-3-nitropyridin-2-yl)morpholine (**19b**)



Compound **18** (5 mmol, 1.035 g) dissolved in acetonitrile (25 mL). After adding triethylamine (15 mmol, 2.1 mL), the mixture was cooled to about 0 ˚C. Morpholine (5.5 mmol, 480 µL) taken up in acetonitrile (10 mL) and added slowly over a period of 30 min. After complete addition, the mixture stirred for 30 min at about 0 ˚C and then allowed to rise to rt. The mixture was stirred at rt for 3 h. The mixture taken up by water (50 mL) and extracted using ethyl acetate (3 x 25 mL). The product purified using silica gel chromatography (solvent: *n*-hexane and ethyl acetate). Yield: 62%, yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (d, 1H, ^{4}J= 0.04 Hz, C(4)H), 3.68 (m, 4H, C(8")H_a, C(9")H_a, C(8")H_b & C(9")H_b), 3.33 (m, 4H, C(7")H_a, C(10")H_a, C(7")H_b & C(10")H_b), 1.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.4 (C6), 150.0 (C2), 138.9 (C4), 131.4 (C3), 121.6 (C5), 65.7 (C8" & C9"), 47.9 (C7" & C10"), 17.3 (CH_3).

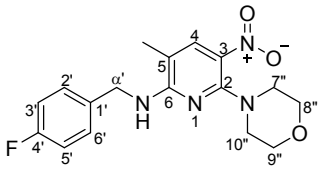
N^{2}-(4-Fluorobenzyl)-3-methyl-5-nitropyridine-2,6-diamine (**20a**)



Compound **19a** (1.5 mmol, 282 mg), 4-fluorobenzyl amine (2.7 mmol, 309 µL) and triethylamine (4.5 mmol, 628 µL) suspended in dimethyl sulfoxide (10 mL). The suspension heated in microwave (100 ˚C, 2.5 hours), poured into water (150 mL) and extracted with ethyl acetate (2 x 50 mL). A pure product collected by evaporated to dryness. Yield: 93%, yellow solid; Mp: 176-177 ˚C (solid from ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (t, 1H, ^{3}J = 5.98 Hz, N^{6}H), 7.83 (d, 1H, ^{4}J = 0.8 Hz, C(4)H), 7.44 (m, 2H, C(2')H & C(6')H), 7.15 (m, 2H, C(3')H & C(5')H), 4.62 (d, 2H, ^{3}J = 6.04 Hz, C(α')H_2), 2.03 (s, 3H,

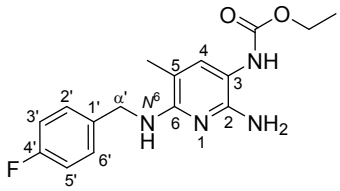
CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4 (d, $^1J_{C,F}$ = 242 Hz, C4'), 159.4 (C6), 154.5 (C2), 135.8 (d, $^4J_{C,F}$ = 3 Hz, C1'), 133.0 (C4), 129.7 (d, $^3J_{C,F}$ = 8 Hz, C2' & C6'), 117.3 (C3), 115.0 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 109.9 (C5), 43.3 (Cα'), 15.8 (CH_3); IR (cm^{-1}): $\tilde{\nu}$ = 3493 (N-H), 1231 (C-F).

N-(4-Fluorobenzyl)-3-methyl-6-morpholino-5-nitropyridin-2-amine (**20b**)



Compound **19b** (3.1 mmol, 800 mg), triethylamine (6.2 mmol, 865 µL) and 4-fluorobenzylamine (4.65 mmol, 530 µL) suspended in 2-propanol (15 mL) and the suspension held at reflux for 24 h. The mixture partitioned between dichloromethane and water. The dichloromethane phase packed for flash chromatography (solvent: *n*-hexane and ethyl acetate). The fractions containing the product combined and evaporated to dryness to yield a sticky yellow semi-solid. The product used for the next reaction without further purification.

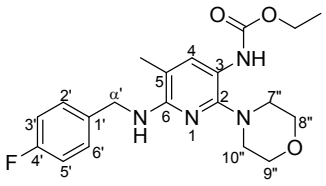
Ethyl {2-amino-6-[(4-fluorobenzyl)amino]-5-methylpyridin-3-yl}carbamate (**21a**)



Compound **20a** (2.5 mmol, 690 mg) and Pd/C (250 mg, 10% Pd) suspended in 2-propanol (15 mL). The suspension carefully set under hydrogen atmosphere and stirred for 24 h at 40 ˚C. The reaction mixture cooled using ice-cooled water and triethylamine (3.75 mmol, 523 µL) was added. Ethyl chloroformate (3.125 mmol, 297 µL) then added slowly. After complete addition, the mixture was stirred at rt until the reaction was completed. The reaction progress was monitored using thin layer chromatography (*n*-hexane and ethyl acetate). Water added to precipitate the product, which further purified by recrystallization from ethanol. Yield: 38.4%, pale yellow solid; Purity 100%; Mp: 156-157 ˚C (solid from ethanol); ^1H NMR (400 MHz, DMSO-d_6): δ = 8.17 (bs, 1H, N^3H), 7.38 (m, 2H, C(3')H & C(5')H), 7.11 (m, 2H, C(2')H & C(6')H), 6.92 (bs, 1H, C(4)H), 6.08 (t, 1H, ^3J = 6.12 Hz, N^6H), 4.93 (s, 2H, N^2H_2), 4.49 (d, 2H, ^3J = 6.04 Hz, C(α')H_2), 4.06 (q, 2H, ^3J = 7.06 Hz, -OCH_2), 1.93 (s, 3H, CH_3), 1.21 (t, 3H, ^3J = 6.34 Hz, -$OCH_2\underline{C}H_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0 (d, $^1J_{C,F}$ = 241 Hz, C4'), 155.1 (C=O), 153.0 (C6), 150.8 (C2), 138.0 (d, $^4J_{C,F}$ = 3 Hz, C1'), 136.1 (C4), 129.2 (d, $^3J_{C,F}$ = 8 Hz, C2' & C6'), 114.6 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 106.1 (C3), 103.6 (C5), 59.9 (OCH_2), 43.2 (Cα'), 15.8 (CH_3), 14.6 ($OCH_2\underline{C}H_3$); IR (cm^{-1}): $\tilde{\nu}$ = 3355 (N-

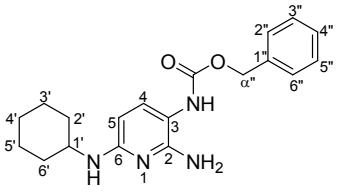
H), 1686 (C=O), 1255 (C-F); HRMS ((ESI) m/z) calculated for $[C_{16}H_{19}FN_4O_2 + H]^+$: 319.1565, found: 319.1555.

Ethyl {6-[(4-fluorobenzyl)amino]-5-methyl-2-morpholinopyridin-3-yl}carbamate (**21b**)



Compound **20b** (2 mmol, 680 mg) and Pd/C (200 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension carefully set under hydrogen atmosphere and stirred for overnight. Triethylamine (3 mmol, 368 µL) and ethyl chloroformate (2.2 mmol, 220 µL) added respectively and stirred for 1 h. The mixture filtered off and washed with ethanol (3 x 25 mL). The product was separated using flash chromatography (solvent: *n*-hexane and ethyl acetate). The filtrate containing the product combined, evaporated to dryness and dissolved in ethanol. Eventually, the product precipitated with the addition of water. Yield: 35%, off-white solid; Purity 100%; Mp: 193-194 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08 (bs, 1H, *N*^{3}H), 7.37 (m, 2H, C(2')H & C(6')H), 7.11 (m, 3H, C(4)H, C(3')H & C(5')H), 6.46 (t, 1H, ^3J = 5.84 Hz, *N*^{6}H), 4.49 (d, 2H, ^3J = 5.72 Hz, C(α')H_2), 4.06 (q, 2H, ^3J = 7.03 Hz, -OCH_2), 3.61 (m, 4H, C(8")H_a, C(9")H_a, C(8")H_b & C(9")H_b), 2.96 (m, 4H, C(7")H_a, C(10")H_a, C(7")H_b & C(10")H_b), 2.01 (s, 3H, CH_3), 1.23 (t, 3H, ^3J = 6.70 Hz, -OCH_2C$\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0 (d, $^1J_{C,F}$ = 240 Hz, C4'), 154.9 (C=O), 152.5 (C6), 138.0 (d, $^4J_{C,F}$ = 3 Hz, C1'), 128.9 (d, $^3J_{C,F}$ = 8 Hz, C2' & C6'), 114.6 (d, $^2J_{C,F}$ = 21 Hz, C3' & C5'), 112.4 (C3), 109.1 (C5), 66.1 (C8" & C9"), 59.9 (-OCH_2), 49.0 (C7" & C10"), 43.7 (Cα'), 15.7 (CH_3), 14.7 (-OCH_2C$\underline{H}_3$); MIR (cm^{-1}): $\tilde{\nu}$ = 3379 (N-H), 1703 (C=O), 1496 (C=C); HRMS ((ESI) m/z) calculated for $[C_{20}H_{25}FN_4O_3 + H]^+$: 389.1983, found: 389.1998.

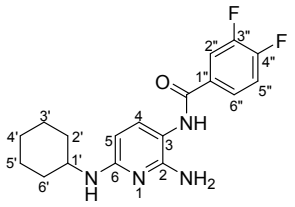
Benzyl [2-amino-6-(cyclohexylamino)pyridin-3-yl]carbamate (**22a**)



Compound **6a** (3.75 mmol, 887 mg) and Pd/C (375 mg, 10% Pd) were suspended in 2-propanol (20 mL). The suspension carefully set under hydrogen atmosphere and stirred for overnight. The reaction mixture filtered off and washed with 2-propanol (3 x 10 mL). Triethylamine (5.63 mmol, 785 µL) and benzyl chloroformate (4.7 mmol, 670 µL) added respectively and the mixture stirred for 30 min. The mixture packed for flash chromatography (*n*-hexane and ethyl acetate). The fractions containing the product combined, evaporated to dryness and re-dissolved in ethanol. Eventually, the product

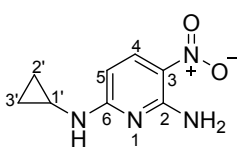
precipitated with the addition of water. Yield: 31%, pale lavender coloured solid; Purity 100%; Mp: 153-154 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.31 (bs, 1H, N^3H), 7.40 (m, 5H, C(2")H, C(6")H, C(3")H, C(5")H & C(4")H), 7.01 (d, 1H, ^{3}J = 8.0 Hz, C(4)H), 5.72 (d, 1H, ^{3}J= 8.00 Hz, C(5)H), 5.72 (m, 1H, N^6H), 5.12 (s, 2H, N^2H_2), 5.07 (s, 2H, -OCH_2), 3.54 (m, 1H, C(1')H), 1.87 (m, 5H, C(2')H_a, C(6')H_a, C(3')H_a, C(5')H_a & C(4')H_a), 1.29 (m, 5H, C(3')H_b, C(5')H_b, C(2')H_b, C(6')H_b & C(4')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.4 (C6), 155.0 (C=O), 137.0 (C1"), 135.6 (C4), 128.33 (C2", C3", C5" & C6"), 127.8 (C4"), 105.7 (C3), 95.5 (C5), 65.5 (OCH_2), 48.8 (C1'), 32.9 (C2' & C6'), 25.5 (C4'), 24.7 (C3' & C5'); IR (cm^{-1}): $\tilde{\nu}$ = 3378 (N-H), 1721 (C=O); HRMS ((ESI) m/z) calculated for [$C_{19}H_{24}N_4O_2$ + H]$^+$: 341.1972, found: 341.1982.

N-[2-Amino-6-(cyclohexylamino)pyridin-3-yl]-3,4-difluorobenzamide (**22b**)



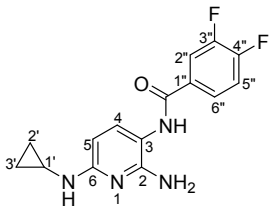
Compound **6a** (3.75 mmol, 887 mg) and Pd/C (375 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for overnight. The reaction mixture filtered off and washed with 2-propanol (3 x 10 mL). After adding triethylamine (5.63 mmol, 784 µL) to the filtrate, 3,4-difluorobenzoyl chloride (3.75 mmol, 470 µL) added over a period of 30 min. After complete addition, the mixture stirred at rt for 30 min. Water added to precipitate the product, which was further purified by recrystallization from ethanol. Yield: 33%, off-white solid; Purity 100%; Mp: 209-210 ˚C (solid from dichloromethane); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.40 (s, 1H, N^3H), 8.05 (m, 1H, C(2")H), 7.86 (m, 1H, C(5")H), 7.60 (m, 1H, C(6")H), 7.05 (d, 1H, ^{3}J = 8.4 Hz, C(4)H), 5.84 (d, 1H, N^6H), 5.72 (d, 1H, ^{3}J = 8.4 Hz, C(5)H), 5.25 (s, 2H, N^2H_2), 3.61 (m, 1H, C(1')H), 1.90 (m, 5H, C(2')H_a, C(6')H_a, C(3')H_a, C(5')H_a & C(4')H_a), 1.34 (m, 5H, C(3')H_b, C(5')H_b, C(2')H_b, C(6')H_b & C(4')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.4 (C=O), 155.9 (C6), 153.6 (C2), 152.5 (dd, $^{1}J_{C,F}$ = 242 Hz, $^{2}J_{C,F}$ = 12 Hz, C3"), 150.1 (dd, $^{1}J_{C,F}$ = 238 Hz, $^{2}J_{C,F}$ = 13 Hz, C4"), 136.5 (C4), 132.3 (q, $^{3}J_{C,F}$ = 8 Hz, C1"), 125.2 (dd, $^{2}J_{C,F}$ = 11 Hz, $^{3}J_{C,F}$ = 4 Hz, C5"), 117.4 (d, $^{2}J_{C,F}$ = 18 Hz, C2"), 117.0 (C6"), 105.3 (C3), 95.5 (C5), 48.8 (C1'), 33.0 (C2' & C6'), 25.5 (C4'), 24.8 (C3' & C5'); IR (cm^{-1}): $\tilde{\nu}$ = 3342 & 3305 (N-H), 766 (Ar-H); HRMS ((ESI) m/z) calculated for [$C_{18}H_{20}N_4O_2F$ + H]$^+$: 347.1678, found: 347.1673.

N^2-Cyclopropyl-5-nitropyridine-2,6-diamine (**i22c**)



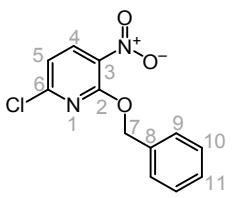
Compound **5** (6 mmol, 1.042 g), cyclopropyl amine (9 mmol, 627 µL) and triethylamine (12 mmol, 1.673 mL) were suspended in 2-propanol (10 mL). The suspension heated in microwave (120 ˚C, 30 min). The reaction mixture cooled to allow the precipitation of the product, which collected by filtration and washed with water (10 mL). The product further purified by recrystallization from dichloromethane. Yield: 75%, yellow solid; Mp:164-165 ˚C (solid from dichloromethane); ^{1}H NMR (400 MHz, DMSO-d_6): d = 8.13 (m, 4H, N^2H_2, C(4)H, N^6H), 5.90 (bs, 1H, C(5)H), 2.94 (bs, 1H, C(1')H), 0.77 (m, 2H, C(2')H_a & C(3')H_a), 0.54 (m, 2H, C(2')H_b & C(3')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): d = 161.7 (C6), 155.8 (C2), 134.0 (C4), 117.5 (C3), 102.4 (C5), 23.9 (C2' & C3'), 6.34 (C1'); IR (cm^{-1}): $\tilde{\nu}$ = 3332 (N-H), 1380 (NO_2).

N-[2-Amino-6-(cyclopropylamino)pyridin-3-yl]-3,4-difluorobenzamide (**22c**)



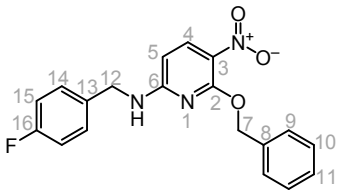
Compound **i22c** (4 mmol, 777 mg) and Pd/C (400 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for overnight. The reaction mixture filtered off and washed with 2-propanol (2 x 10 mL). The filtrate then cooled using ice-cooled water. Triethylamine (6 mmol, 837 µL) and 3,4-difluorobenzoyl chloride (4 mmol, 504 µL) added respectively and the mixture stirred for 1 h. After concentrating the mixture, water added to precipitate the product. The product further purified by recrystallization from ethanol. Yield: 15%, white solid; Purity 100%; Mp: 188-189 ˚C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.45 (s, 1H, N^3H), 8.06 (m, 1H, C(2")H), 7.87 (m, 1H, C(5")H), 7.61 (m, 1H, C(6")H), 7.17 (d, 1H, ^{3}J = 8.4 Hz, C(4)H), 6.20 (m, 1H, N^6H) 5.92 (d, 1H, ^{3}J = 8.0 Hz, C(5)H), 5.32 (s, 2H, N^2H_2), 2.24 (m, 1H, C(1')H), 0.67 (m, 2H, C(2')H_a & C(3')H_a), 0.42 (m, 2H, C(2')H_b & C(3')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.5 (C=O), 157.4 (C6), 153.8 (C2), 152.8 (dd, $^{1}J_{C,F}$ = 244 Hz, $^{2}J_{C,F}$ = 12 Hz, C3"), 150.1 (dd, $^{1}J_{C,F}$ = 242 Hz, $^{2}J_{C,F}$ = 12 Hz, C4"), 136.8 (C4), 132.2 (q, $^{3}J_{C,F}$ = 11 Hz, C1"), 125.3 (dd, $^{2}J_{C,F}$ = 10 Hz, $^{3}J_{C,F}$ = 2 Hz, C5"), 117.4 (C2"), 117.2 (d, $^{3}J_{C,F}$ = 19 Hz, C6"), 107.0 (C3), 93.9 (C5), 23.9 (C1'), 6.9 (C2' & C3'); IR (cm^{-1}): $\tilde{\nu}$ = 1623 (C=O), 752 (Ar-H); HRMS ((ESI) m/z) calculated for $[C_{15}H_{14}N_4OF_2 + H]^+$: 305.1208, found: 305.1211.

2-Benzoxy-6-chloro-3-nitropyridin (**i122d**)



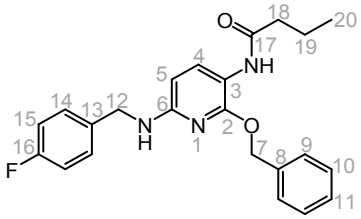
In a 3-necked flask, 2,6-dichloro-3-nitropyridine (5 mmol, 0.97 g) and benzyl alcohol (1.2 eq., 6 mmol, 623 µL) dissolved in anhydrous toluene (50 mL) and placed under argon atmosphere. The mixture then cooled to 0 °C and NaH (1.4 eq, 7 mmol, 0.17 g) added. The reaction stirred at rt overnight. Since the TLC monitoring still detected a starting material, the solution cooled to 0 °C and a further 3 mmol of benzyl alcohol and 3.5 mmol of NaH added under counter current to argon. After a further 3 h, the reaction was complete and saturated saline (50 mL) added to the solution. The phases separated using a separating funnel and the organic phase washed with water (3 × 50 mL) and saturated brine (50 mL). After the toluene phase dried over Na_2SO_4, the solvent removed in a partial vacuum. Yield: 0.98 g (74%) of yellow, amorphous solid; Mp: 74–76 °C (solid from toluene); R_f = 0.68 (*n*-hexane/diethyl ether 9:1); ^{1}H-NMR (DMSO-d_6): δ = 5.53 (s, 2H, C^7H_2), 7.34-7.44 (m, 3H, $C^{11}H$ & 2×$C^{10}H$), 7.38 (d, ^3J = 8.3 Hz, 1H, C^5H), 7.50-7.52 (m, 2H, 2×C^9H), 8.54 (d, ^3J = 8.3 Hz, 1H, C^4H); ^{13}C-NMR (DMSO-d_6): δ = 69.4 (C^7), 117.5 (C^5), 127.9 (2×C^{10}), 128.2 (C^{11}), 128.4 (2×C^9), 132.8 (C^3), 135.5 (C^8), 138.8 (C^4), 151.2 (C^6), 154.9 (C^2); MIR: $\tilde{\nu}$ = 1562 (m, $\nu_{C\text{-}NO}$), 2854 (w, $\nu_{C\text{-}H}$), 3087 (w, $\nu_{Ar\text{-}H}$).

6-Benzoxy-2-[(4-fluorbenzyl)amino]- 5-nitropyridine (**i222d**)



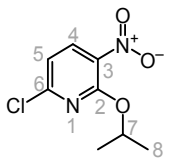
In a microwave vessel, **i122d** (3.7 mmol, 0.98 g) was suspended in 2-propanol (15 mL), triethylamine (1.4 eq., 3.9 mmol, 538 µL) and 4-fluorobenzylamine (1.2 Eq., 3.34 mmol, 381 µL). In the microwave reactor, the reaction mixture heated to 120 °C for 2 h. Subsequently, a further 4-fluorobenzylamine (0.6 eq., 1.67 mmol, 191 µL) added to the suspension and heated in the microwave to 120 ° C for 30 min. Since the TLC monitor still detected starting material, a further 1.11 mmol of 4-fluorobenzylamine added and again heated to 120 °C for 30 min. The resulting yellow solution was poured onto water (100 mL) and stored in the refrigerator to complete the precipitation. The product filtered off and dried at 60 °C in a drying oven. Yield: 1.27 g (97%) of yellow, amorphous solid; Mp: 159-162 °C (solid from 2-propanol); R_f = 0.52 (*n*-hexane/ethyl acetate 7:3); ^{1}H-NMR (DMSO-d_6): δ = 4.58 (d, ^3J = 4.5 Hz, 2H, $C^{12}H_2$), 6.24 (d, ^3J = 9.0 Hz, 1H, C^5H), 7.12-7.16 (m, 2H, 2×$C^{15}H$), 7.31-7.40 (m, 5H, 2×$C^{14}H$, 2×C^9H, 2×$C^{10}H$ & $C^{11}H$), 8.14 (d, ^3J = 9.0 Hz, 1H, C^4H), 8.65 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 43.7 (C^{12}), 67.4 (C^7), 102.1 (C^5), 115.1 (d, ^2J = 21 Hz, 2×C^{15}), 121.2 (C^3), 127.2 (C^9), 127.6 (C^{11}), 128.3 (C^{10}), 129.3 (d, ^3J = 8 Hz, 2×C^{14}), 135.2 (C^{13}), 136.6 (C^4), 136.7 (C^8), 157.6 (C^6), 159.5 (C^2), 160.0 & 162.4 (d, ^1J = 243 Hz); MIR: $\tilde{\nu}$ = 1537 (m, $\nu_{C\text{-}NO}$), 3034 (w, $\nu_{Ar\text{-}H}$), 3316 (m, $\nu_{N\text{-}H}$); HRMS: calculated for $[C_{19}H_{16}N_3O_3F + H]^+$: 354.1248, found: 354.1256.

N-{2-(benzyloxy)-6-[(4-fluorbenzyl)amino]pyridin-3-yl}butyramide (**22d**)



Intermediate **i222d** (1 mmol, 0.35 g) was suspended in a mixture of 2-propanol (10 mL), of water (6 mL), iron powder (3.0 eq., 3 mmol, 0.17 g) and NH_4Cl (4, 5 eq., 4.5 mmol, 0.24 g). The reaction mixture heated to reflux for 3 h, cooled to rt and the solvent removed in partial vacuum. The residue combined with water (100 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phase washed with saturated brine and dried over Na_2SO_4. To the filtrate were added triethylamine (1.4 eq., 1.4 mmol, 193 μL) followed by dropwise addition of a solution of butyric acid chloride (1.2 eq., 1.2 mmol, 124 μL) in ethyl acetate (10 mL) and the reaction mixture stirred for 3 h at rt. The solvent was then evaporated, the residue adsorbed on diatomaceous earth and purified by flash chromatography (puriFlash 450 system from Interchim, column: silica 37 g, mobile phase: n-hexane/ethyl acetate, gradient: 0-4 min 0% ethyl acetate, 4-34 min 0-30% ethyl acetate, 34-50 min 30% ethyl acetate, 50-60 min 50% ethyl acetate, flow rate: 26 mL / min). After concentrating the product fractions, an oily residue remained, which taken up in diethyl ether and the solvent evaporated over several days at 0 °C. Yield; 0.03 g (8%) of grey, amorphous solid; Purity 100%; Mp: 85-87 °C (solid from diethyl ether), R_f = 0.66 (*n*-hexane/ethyl acetate 6:4); ^{1}H-NMR (DMSO-d_6): δ = 0.88 (t, ^3J = 7.4 Hz, 3H, $C^{20}H_3$), 1.56 (se, ^3J = 9.2 Hz, 2H, $C^{19}H_2$), 2.22 (t, ^3J = 7.3 Hz, $C^{18}H_2$), 4.38 (d, ^3J = 6.0 Hz, 2H, $C^{12}H_2$), 5.27 (s, 2H, C^7H_2), 6.03 (d, ^3J = 8.3 Hz, 1H, C^5H), 7.00 (t, ^3J = 6.1 Hz, N^6H), 7.06-7.11 (m, 2H, 2×$C^{15}H$), 7.27-7.33 (m, 5H, 2×$C^{10}H$, $C^{11}H$, 2×$C^{14}H$), 7.36-7.38 (m, 2H, 2×C^9H), 7.49 (d, ^3J = 8.3 Hz, 1H, C^4H), 8.84 (s, 1H, N^3H); ^{13}C-NMR (DMSO-d_6): δ = 13.5 (C^{20}), 18.8 (C^{19}), 37.5 (C^{18}), 43.5 (C^{12}), 66.0 (C^7), 98.8 (C^5), 109.0 (C^3), 114.8 (d, ^2J = 21 Hz, 2×C^{15}), 127.3 (2×C^9), 127.3 (C^{11}), 128.1 (2×C^{10}), 129.0 (d, ^3J = 8 Hz, 2×C^{14}), 136.1 (C^4), 137.1 (d, ^4J = 3 Hz, C^{13}), 138.0 (C^8), 154.2 (C^6), 154.6 (C^2), 159.7 & 162.1 (d, ^1J = 241 Hz, C^{16}), 171.2 (C^{17}); MIR: $\tilde{\nu}$ = 1649 (m, $\nu_{C=O}$), 2870 & 2930 (w, ν_{C-H}), 2961 (w, ν_{Ar-H}), 3294 & 3423 (w, ν_{N-H}); HRMS: calculated for $[C_{23}H_{24}N_3O_2F + H]^+$: 394.1925, found: 394.1930.

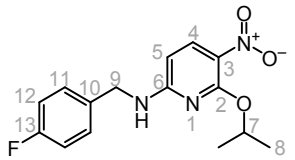
6-Chloro-2-isopropoxy-3-nitropyridine (**i122e**)



In a 3-necked flask, 2,6-dichloro-3-nitropyridine (5 mmol, 0.97 g) was dissolved in anhydrous toluene (50 mL) and placed under argon atmosphere. The mixture cooled to 0 °C and 2-propanol (1.2 eq., 6 mmol, 462 μL) and NaH (1.4 eq., 7 mmol, 0.17 g) added over the side neck under counter current to

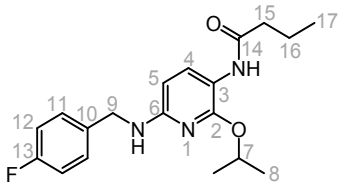
argon. The batch stirred overnight at rt. Since the starting material was detected, the suspension again cooled to 0 °C and a further 6 mmol of 2-propanol and 7 mmol of NaH added under counter current to argon. The reaction completed after 3 h and the reaction stopped by adding saturated saline (50 mL). The phases separated in a separating funnel, the toluene phase washed with water (3 × 50 mL) and saturated saline solution (50 mL) and finally dried over Na_2SO_4. Removal of the solvent under partial vacuum gave a brown solid that finally purified using flash chromatography (mobile phase: *n*-hexane/diethyl ether 9:1). Yield: 0.73 g (67%) of yellow, amorphous solid; Mp: 66–68 °C (solid from *n*-hexane/ethyl acetate); R_f = 0.56 (*n*-hexane/diethyl ether 9:1); ^{1}H-NMR (DMSO-d_6): δ = 1.36 (d, ^3J = 6.2 Hz, 6 H, 2×C^{8}H$_3$), 5.37 (sep, ^3J = 6.2 Hz, 1H, C^{7}H), 7.30 (d, ^3J = 8.3 Hz, 1H, C^{5}H), 8.47 (d, ^3J = 8.3 Hz, 1H, C^{4}H); ^{13}C NMR (DMSO-d_6): δ = 21.4 (2×C^8), 72.0 (C^7), 116.7 (C^5), 132.9 (C^3), 138.5 (C^4), 151.1 (C^6), 154.7 (C^2); MIR: $\tilde{\nu}$ = 1554 (m, $\nu_{c\text{-}NO}$), 2988 (w, $\nu_{C\text{-}H}$), 3177 (w, $\nu_{Ar\text{-}H}$).

2-[(4-Fluorbenzyl)amino]-6-isopropoxy-5-nitropyridine (**i222e**)



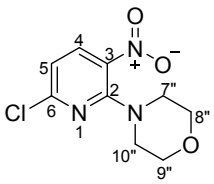
In a microwave vessel, **i122e** (3.6 mmol, 0.79 g) was suspended in a mixture of 2-propanol (15 mL), triethylamine (1.4 eq., 5.04 mmol, 696 μL) and 4-fluorobenzylamine (1.2 eq., 4.32 mmol, 493 μL). The batch heated in microwave for 1.5 h at 120 °C. Since the TLC monitoring detected the starting material, a further 4-fluorobenzylamine (0.6 eq., 2.16 mmol, 247 μL) added and the suspension heated in the microwave reactor for a further 3 h at 120 °C. The resulting yellow solution poured onto water (100 mL) to precipitate the product. The solid filtered off and dried at 60 °C in a drying oven. Yield: 1.07 g (97%) of yellow, amorphous solid; Mp: 137-139 °C (solid from 2-propanol); R_f = 0.49 (*n*-hexane/ethyl acetate 7:3); ^{1}H-NMR (DMSO-d_6): δ = 1.23 (d, ^3J = 6.0 Hz, 6H, 2×C^{8}H$_2$), 4.55 (d, ^3J = 4.9 Hz, 2H, C^{9}H$_2$), 5.31 (sep, ^3J = 6.0 Hz, 1H, C^{7}H), 6.21 (d, ^3J = 8.9 Hz, 1H, C^{5}H), 7.14-7.19 (m, 2H, 2×C^{12}H), 7.34-7.37 (m, 2H, 2×C^{11}H), 8.10 (d, ^3J = 9.0 Hz, 1H, C^{4}H), 8.60 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ = 21.7 (2×C^8), 43.7 (C^9), 69.5 (C^7), 101.5 (C^5), 115.1 (d, ^2J = 21 Hz, 2×C^{12}), 121.3 (C^3), 129.0 (d, ^3J = 8 Hz, 2×C^{11}), 135.4 (C^{10}), 136.5 (C^4), 157.6 (C^2), 159.5 (C^6), 160.0 & 162,4 (d, ^1J = 242 Hz, C^{13}); MIR: $\tilde{\nu}$ = 1531 (m, $\nu_{C\text{-}NO}$), 2977 (w, $\nu_{C\text{-}H\ (alkyl)}$), 3174 (w, $\nu_{Ar\text{-}H'}$), 3307 & 3355 (m, $\nu_{N\text{-}H}$); HRMS: calculated for [C$_{15}$H$_{16}$FN$_3$O$_3$ + H]$^+$: 306.1248, found: 306.1263.

N-{6-[(4-fluorbenzyl)amino]-2-isopropoxypyridin-3-yl}butyramide (**22e**)



Compound **i222e** (1.5 mmol, 0.45 g) along with iron powder (3.0 eq, 4.5 mmol, 0.25 g) and NH_4Cl (4.5 eq, 6.75 mmol, 0.36 g) suspended in a mixture of 2-propanol (15 mL) and water (9 mL). The reaction mixture was heated to reflux for 3.5 h and concentrated after subsequent cooling to rt in a partial vacuum. The residue combined with water (150 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phase washed with saturated brine (150 mL), dried over Na_2SO_4, cooled to 0 °C and triethylamine (1.4 eq., 2.1 mmol, 290 µL) was added. Butyric acid chloride (1.2 eq., 1.8 mmol, 186 µL, dissolved in 10 mL of ethyl acetate) added dropwise. After 3 h of stirring at 0 °C, the reaction was complete and the solvent evaporated. The residue purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate 7:3). Finally, the product recrystallized twice from *n*-hexane to give two different crystal forms, which, however, do not differ in their identity or purity. Yield: 0.22 g (43%) of fine, colourless, crystalline solid next to larger colourless needles; Purity 100%; Mp: 94–95 °C (solid from *n*-hexane); R_f = 0.37 (*n*-hexane/ethyl acetate 7:3); ^{1}H-NMR (DMSO-d_6): δ = 0.91 (t, ^3J = 7.4 Hz, 3H, $C^{17}H_2$), 1.18 (d, ^3J = 6.2 Hz, 3H, 2×C^8H_3), 1.57 (sep, ^3J = 7.3 Hz, 2H, $C^{16}H_2$), 2.22 (t, ^3J = 7.2 Hz, 2H, $C^{15}H_2$), 4.38 (d, ^3J = 5,9 Hz, 2H, C^9H_2), 5.06 (sep, ^3J = 6.2 Hz, 1H, C^7H), 5.99 (d, ^3J = 8.3 Hz, 1H, C^5H), 6.97 (t, ^3J = 5.9 Hz, 1H, N^6H), 7.09-7.14 (m, 2H, 2×C^{12}H), 7.33–7.36 (m, 2H, 2×C^{11}H), 7.51 (d, ^3J = 8.3 Hz, 1H, C^4H), 8.59 (s, 1H, N^3H); ^{13}C NMR (DMSO-d_6): δ = 13.5 (C^{17}), 18.8 (C^{16}), 22.0 (2×C^8), 37.5 (C^{15}), 43.8 (C^9), 67.2 (C^7), 98.1 (C^5), 109.4 (C^3), 114.8 (d, ^2J = 21 Hz, 2×C^{12}), 128.8 (d, ^3J = 8 Hz, 2×C^{11}), 135.4 (C^4), 137.2 (C^{10}), 154.1 (C^6), 154.4 (C^2), 159.7 & 162.1 (d, ^1J = 241 Hz, C^{13}), 171.0 (C^{14}); MIR: $\tilde{\nu}$ = 1631 (m, $\nu_{C=O}$), 2938 & 2971 (w, ν_{C-H}), 3310 & 3355 (m, ν_{N-H}); HRMS: calculated for $[C_{19}H_{24}N_3O_2F + H]^+$: 346.1925, found: 346.1917.

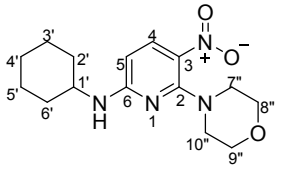
4-(6-Chloro-3-nitropyridin-2-yl)morpholine (**23a**)



2,6-Dichloro-3-nitropyridine (5 mmol, 1.0 g) dissolved in acetonitrile (25 mL). After adding triethylamine (15 mmol, 2.1 mL), the mixture cooled to about 0 ˚C. Morpholine (5.5 mmol, 480 µL) in acetonitrile (10 mL) added slowly over a period of 30 min. After complete addition, the mixture was stirred for 30 min at about 0 ˚C and then allowed to rise to rt. The mixture was stirred at rt for 3 h. The product was purified using silica gel chromatography (solvent: *n*-hexane and ethyl acetate). Yield: 72%, yellow solid; Mp: 118-119 ˚C (solid from *n*-hexane and ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ

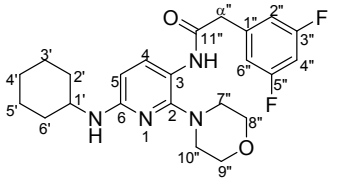
= 8.31 (d, 1H, ^3J = 8.4 Hz, C(4)H), 6.95 (d, 1H, ^3J = 8.4 Hz, C(5)H), 3.65 (m, 4H, C(8")H_a, C(9")H_a, C(8")H_b & C(9")H_b), 3.39 (m, 4H, C(7")H_a, C(10")H_a, C(7")H_b & C(10")H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.4 (C6), 151.3 (C2), 134.4 (C4), 131.1 (C3), 113.2 (C5), 65.7 (C8" & C9"), 47.9 (C7" & C10"); IR: (cm^{-1}): $\tilde{\nu}$ = 1549 & 1314 (NO_2).

N-Cyclohexyl-6-morpholino-5-nitropyridin-2-amine (**24a**)



Compound **23a** (3 mmol, 731 mg), triethylamine (6 mmol, 837 µL) and cyclohexylamine (4.5 mmol, 515 µL) suspended in 2-propanol (15 mL). The suspension held at reflux for overnight. The product precipitated with the addition of water, which was washed with *n*-hexane. Yield: 86%, yellow solid; Mp: 160-162 °C (solid from 2-propanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (d, 1H, ^3J = 8.8 Hz, C(4)H), 7.81 (bs, 1H, N^6H), 6.03 (d, 1H, ^3J = 8.8 Hz, C(5)H), 3.78 (m, 1H, C(1')H), 3.67 (m, 4H, C(8")H_a, C(9")H_a, C(8")H_b & C(9")H_b), 3.36 (m, 4H, C(7")H_a, C(10")H_a, C(7")H_b & C(10")H_b), 1.91 (m, 2H, C(2')H_a & C(6')H_a), 1.73 (m, 2H, C(3')H_a & C(5')H_a), 1.60 (m, 1H, C(4')H_a), 1.34 (m, 5H, C(2')H_b, C(6')H_b, C(3')H_b, C(5')H_b & C(4')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.9 (C6), 155.3 (C2), 136.7 (C4), 120.6 (C3), 101.9 (C5), 66.0 (C8" & C9"), 49.7 (C1'), 48.8 (C7" & C10"), 32.0 (C2' & C6'), 25.2 (C4'), 24.4 (C3' & C5'); IR (cm^{-1}): $\tilde{\nu}$ = 3323 & 1587 (N-H).

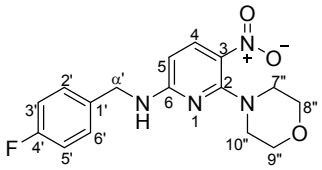
N-[6-(Cyclohexylamino)-2-morpholinopyridin-3-yl]-2-(3,5-difluorophenyl)acetamide (**25a**)



Compound **24a** (2.25 mmol, 690 mg) and Pd/C (225 mg, 10% Pd) suspended in ethyl acetate (15 mL). The suspension carefully set under hydrogen atmosphere and stirred for overnight. The reaction mixture filtered off and washed with ethyl acetate (3 x 15 mL). The filtrate cooled using ice-cooled water and triethylamine (3.375 mmol, 435 µL) was added. 3,5-difluorobenzoyl chloride (2.475 mmol) then added slowly. After complete addition, the mixture stirred for 30 min at rt. The reaction mixture evaporated to dryness and dissolved in ethanol. The product precipitated with the addition of water and further purified by preparative HPLC (methanol and water). Yield: 64%, white solid; Purity 100%; Mp: 145-146 °C (solid from methanol and water); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.04 (s, 1H, N^3H), 7.30 (d, 1H, ^3J = 8.4 Hz, C(4)H), 7.16 (m, 3H, C(2")H, C(6")H & C(4")H), 6.15 (d, 1H, ^3J = 8.4 Hz, N^6H), 6.04 (d, 1H, ^3J = 8.4 Hz, C(5)H), 3.64 (s, 2H, C(α")H_2), 3.59 (m, 5H, C(1')H), C(8")H_a, C(9")H_a, C(8")H_b & C(9")H_b),

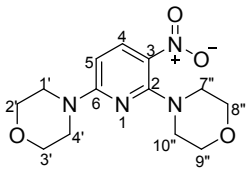
3.36 (m, 4H, C(7”)H_a, C(10”)H_a, C(7”)H_b & C(10”)H_b), 1.91 (m, 2H, C(2’)H_a & C(6’)H_a), 1.73 (m, 2H, C(3’)H_a & C(5’)H_a), 1.60 (m, 1H, C(4’)H_a), 1.34 (m, 5H, C(2’)H_b, C(6’)H_b, C(3’)H_b, C(5’)H_b & C(4’)H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.9 (C=O), 163.5 (dd, $^1J_{C,F}$ = 244 Hz, $^3J_{C,F}$ = 13 Hz, C3” & C5”), 154.7 (C6), 153.9 (C2), 140.5 (t, $^3J_{C,F}$ = 10 Hz, C1”), 136.6 (C4), 112.4 (dd, $^2J_{C,F}$ = 25 Hz, $^4J_{C,F}$ = 7 Hz, C2” & C6”), 111.8 (C3), 102.3 (t, $^2J_{C,F}$ = 51 Hz, C4”), 100.7 (C5), 66.0 (C8” & C9”), 49.3 (C1’), 48.9 (C7” & C10”), 42.2 (Cα”), 32.6 (C2’ & C6’), 25.6 (C4’), 24.7 (C3’ & C5’); IR (cm^{-1}): $\tilde{\nu}$ = 3352 (N-H), 1619 (C=O); HRMS ((ESI) m/z) calculated for $[C_{23}H_{28}F_2N_4O_2 + H]^+$: 431.2253, found: 431.2266.

N-(4-Fluorobenzyl)-6-morpholino-5-nitropyridin-2-amine (**24b**)



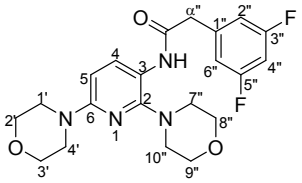
Compound **23a** (3 mmol, 731 mg), triethylamine (9 mmol, 1.25 mL) and 4-fluorobenzylamine (5.4 mmol, 670 µL) were suspended in dimethyl sulfoxide (10 mL). The suspension heated in a microwave (100 °C, 2 h). The reaction mixture poured onto water (150 mL) and extracted using ethyl acetate (3 x 50 mL). The ethyl acetate phase evaporated to dryness to yield a sticky yellow semi-solid. The product used for the next reaction without any further purification.

4,4’-(3-Nitropyridine-2,6-diyl)dimorpholine (**23b**)



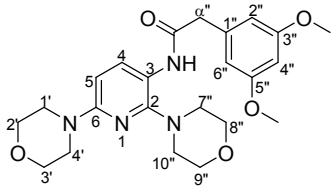
Compound **23b** is a side product in the synthesis of **23a**. Compound **23b** separated from the reaction mixture using flash chromatography (solvent: *n*-hexane and ethyl acetate). The product dried using a desiccator. Yield: 28%, yellow solid; Mp: 105-106 °C (solid from *n*-hexane and ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.16 (d, 1H, ^3J = 9.2 Hz, C(4)H), 6.40 (d, 1H, ^3J = 9.2 Hz, C(5)H), 3.70 (m, 12H, C(8”)H_a, C(9”)H_a, C(8”)H_b, C(9”)H_b , C(2’)H_a, C(3’)H_a, C(2’)H_b, C(3’)H_b, C(7”)H_a, C(10”)H_a, C(7”)H_b & C(10”)H_b), 3.36 (m, 4H, C(1’)H_a, C(4’)H_a, C(1’)H_b & C(4’)H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.8 (C6), 153.9 (C2), 138.1 (C4), 121.9 (C3), 98.5 (C5), 65.9 (C8” & C9”), 65.8 (C2’ & C3’), 48.7 (C1’ & C4’), 44.6 (C7” & C10”).

2-(3,5-Difluorophenyl)-*N*-(2,6-dimorpholinopyridin-3-yl)acetamide (**25b**)



Compound **23b** (3 mmol, 883 mg) and Pd/C (300 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for overnight. The reaction mixture filtered off and washed with ethyl acetate (3 x 25 mL). Triethylamine (4.5 mmol, 630 µL) and compound **AS-69** (4.5 mmol, 627 µL) added respectively and stirred for 2 h. The reaction mixture evaporated to dryness and re-dissolved in ethanol. The product precipitated with the addition of water. Yield: 82%, off-white solid; Purity 100%; Mp: 137-138 °C (solid from ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.18 (s, 1H, *N*^{3}H), 7.55 (d, 1H, ^{3}J = 8.4 Hz, C(4)H), 7.16 (m, 3H, C(2")H, C(6")H & C(4")H), 6.38 (d, 1H, ^{3}J = 8.4 Hz, C(5)H), 3.69 (m, 6H, C(8")H_a, C(9")H_a, C(8")H_b, C(9")H_b, C(α")H_2) 3.62 (m, 4H, C(2')H_a, C(3')H_a, C(2')H_b, C(3')H_b), 2.99 (m, 4H, C(7")H_a, C(10")H_a, C(7")H_b & C(10")H_b), 2.51 (m, 4H, C(1')H_a, C(4')H_a, C(1')H_b & C(4')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.0 (C=O), 163.5 (dd, $^{1}J_{C,F}$ = 244 Hz, $^{3}J_{C,F}$ = 13 Hz, C3" & C5"), 155.3 (C6), 153.4 (C2), 140.3 ($^{3}J_{C,F}$ = 20 Hz, C1"), 136.9 (C4), 114.3 (C3), 112.4 (dd, $^{2}J_{C,F}$ = 25 Hz, $^{4}J_{C,F}$ = 7 Hz, C2" & C6"), 102.4 (t, $^{2}J_{C,F}$ = 52 Hz, C4"), 99.5 (C5), 65.9 (C8", C9", C2' & C3'), 48.8 (C1' & C4'), 48.7 (C7" & C10"), 44.6 (Cα"); IR (cm^{-1}): $\tilde{\nu}$ = 3317 (N-H), 1592 (C=C); HRMS ((ESI) m/z) calculated for $[C_{21}H_{24}F_2N_4O_3 + H]^+$: 419.1889, found: 419.1816.

2-(3,5-Dimethoxyphenyl)-*N*-(2,6-dimorpholinopyridin-3-yl)acetamide (**25c**)



Compound **23b** (1 mmol, 295 mg) and Pd/C (100 mg, 10% Pd) were suspended in 2-propanol (15 mL). The suspension was carefully set under hydrogen atmosphere and stirred for overnight. The reaction mixture filtered off and washed with ethyl acetate (3 x 25 mL). Triethylamine (1.5 mmol, 210 µL) and compound **AS-118** (1.5 mmol) were added respectively and stirred for 2 h. The product separated using flash chromatography (solvent: *n*-hexane and ethyl acetate). The product further purified by recrystallization from methanol. Yield: 61%, white solid; Purity 100%; Mp: 157-158 °C (solid from methanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.92 (s, 1H, *N*^{3}H), 7.63 (d, 1H, ^{3}J = 8.4 Hz, C(4)H), 6.52 (m, 2H, C(2")H & C(6")H), 6.42 (m, 2H, C(4")H & C(5)H), 3.73 (m, 12H, C(8")H_a, C(9")H_a, C(8")H_b, C(9")H_b, C(3")OCH_3, C(5")OCH_3 & C(α")H_2), 3.54 (m, 4H, C(2')H_a, C(3')H_a, C(2')H_b, C(3')H_b), 3.36 (m, 4H, C(7")H_a, C(10")H_a, C(7")H_b & C(10")H_b), 2.94 (m, 4H, C(1')H_a, C(4')H_a, C(1')H_b & C(4')H_b); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.7 (C=O), 160.5 (C3" & C5"), 155.1 (C6), 152.9 (C2), 137.9 (C1"), 136.1 (C4), 114.8

(C3), 107.3 (C2" & C6"), 99.7 (C5), 98.3 (C4"), 65.9 (C8", C9", C2' & C3'), 55.1 (C(3")OCH_3 & C(5")OCH_3), 48.8 (C1' & C4'), 45.2 (C7" & C10"), 43.2 (Cα"); IR (cm^{-1}): $\tilde{\nu}$ = 3381 (N-H), 1671 (C=O); HRMS ((ESI) m/z) calculated for $[C_{23}H_{30}N_4O_5 + H]^+$:, 443.2289 found: 443.2269.

Determination of $LogD_{7.4}$

Thirteen solvents used as references: uracil (unretained solvent), pyridine, benzyl alcohol, acetanilide, picoline, acetophenone, methyl benzoate, ethyl benzoate, benzophenone, phenyl benzoate, diphenyl ether, dibenzyl and triphenylamine. Reference solutions were prepared by dissolving 4 mg or the equivalent reference solutions in methanol (2 mL). 2-propanol (2 mL), however, used to dissolve dibenzyl and triphenylamine. A reference mixture created by transferring a similar amount (50 µL) of each reference into an HPLC vial. As per the synthesized analogues, 1 mmol solution in methanol was prepared (2 mL).

Using the HPLC method given in the article, the retention time of each reference was determined (Figure 1). Once a capacity factor (k') calculated from references' retention times, a calibration curve computed (Figure 2). A capacity factor or retention factor used in order to determine the affinity of compounds to the stationary phase and calculate using a formula below;

$$k' = (t_R - t_0) / t_0$$

Where t_0 and t_R are retention times of uracil (the unretained reference) and references respectively.

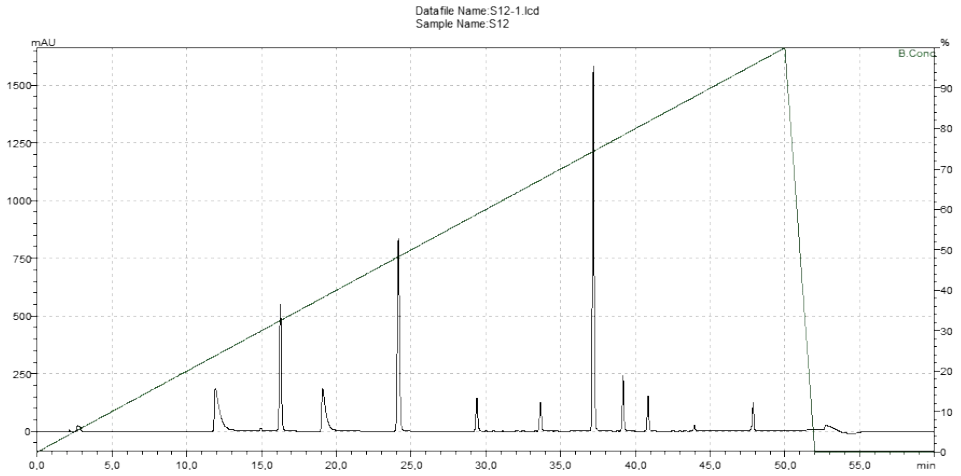


Figure 1: the chromatogram of the reference solvents

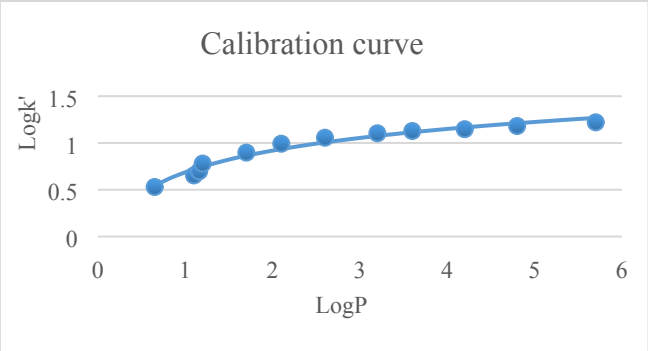


Figure 2: the calibration curve

Retention times of the synthesized analogues measured in duplicate and the mean value used to calculate their retention factor. The calibration equation (Figure 1) applied in order to determine the $logD_{7.4}$ of the synthesized analogues (Table 1).

Table 1; the logk' and $logD_{7.4}$ of synthesized analogues

Analogues	Logk'	$LogD_{7.4}$	Analogues	Logk'	LogD7.4
7a	1.067	3.12	**12c**	1.076	3.21
7b	0.859	1.68	**12d**	1.077	3.21
7c	0.922	2.02	**12e**	1.011	2.64
7d	1.030	2.80	**12f**	1.100	3.44
7e	0.754	1.22	**12g**	1.117	3.62
7f	0.872	1.74	**12h**	1.086	3.30
7g	0.801	1.41	**12i**	1.113	3.58
7h	1.079	3.23	**12j**	1.125	3.71
7i	1.031	2.80	**12k**	0.976	2.38
7j	1.007	2.62	**12l**	1.108	3.53
7k	1.082	3.26	**16a**	1.085	3.30
11a	1.077	3.21	**16b**	1.113	3.58
11b	n.d.	n.d.	**21a**	1.066	3.11
11c	1.075	3.19	**21b**	1.148	3.98
11d	1.206	4.73	**22a**	1.138	3.86
11e	1.062	3.08	**22b**	1.116	3.62
11f	1.130	3.76	**22c**	1.075	2.80
11g	1.248	5.36	**22d**	1.176	4.32
11h	0.895	3.74	**22e**	1.152	4.02
12a	0.818	2.49	**25a**	1.173	4.29
12b	0.887	1.82	**25b**	1.113	3.58

A different calibration curve (Figure 3) assembled using a different column, employed for the determination of **11h** and **12a**.

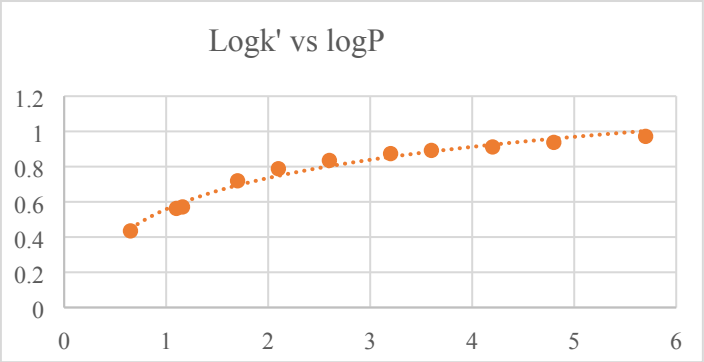


Figure 3: a calibration curve used for **11h** and **12a**.

Cyclic voltammetry

Oxidation potential of the synthesized analogues measured using Metrohm 797 VA computrace.

Working electrode: Glassy carbon electrode

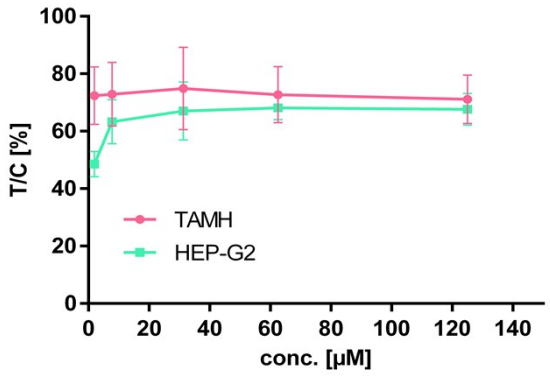
Reference electrode: Ag/AgCl electrode

Auxiliary electrode: Platinum wire

A compound (0.01 mmol) suspended in Tris-HCl buffer (0.1 M, pH 7.4, 10 mL) and sonicated for 3 min. After transferring the above mixture into the sample holder of the cyclic voltammetry, the mixture purged with nitrogen for 3 min. The cycles swept through -0.5 to 1.0 V in triplicate. A pre-treatment of working electrode using aluminum oxide powder was necessary between measurements.

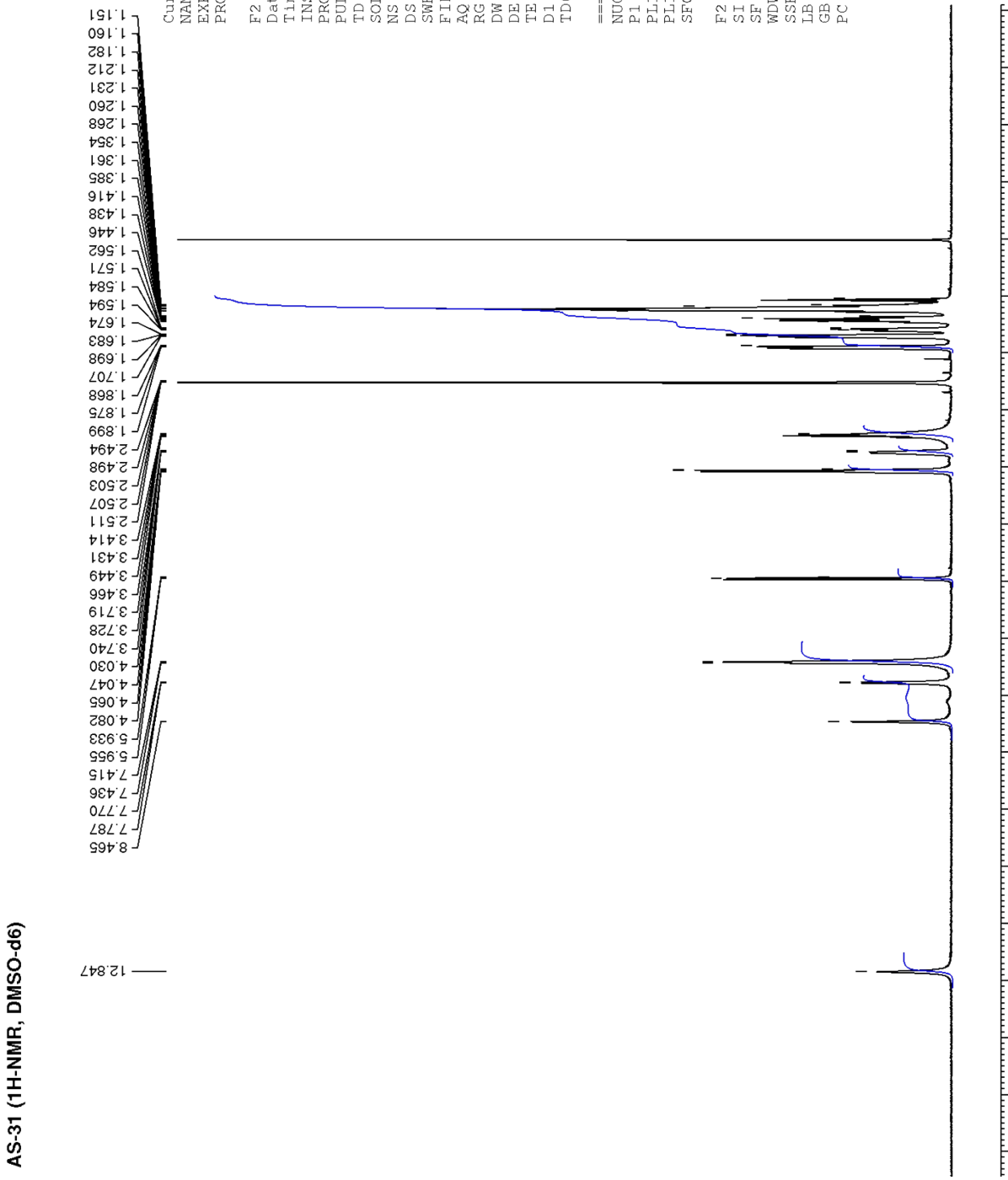
Hepatotoxicity profile of **11g**

The initial cells viability in TAMH and HEPG-2 cells was less than 80% and 60% respectively. As displayed in the curves below, the increase in the concentration of **11g** briefly increased cells viability followed by no change in cells viability.

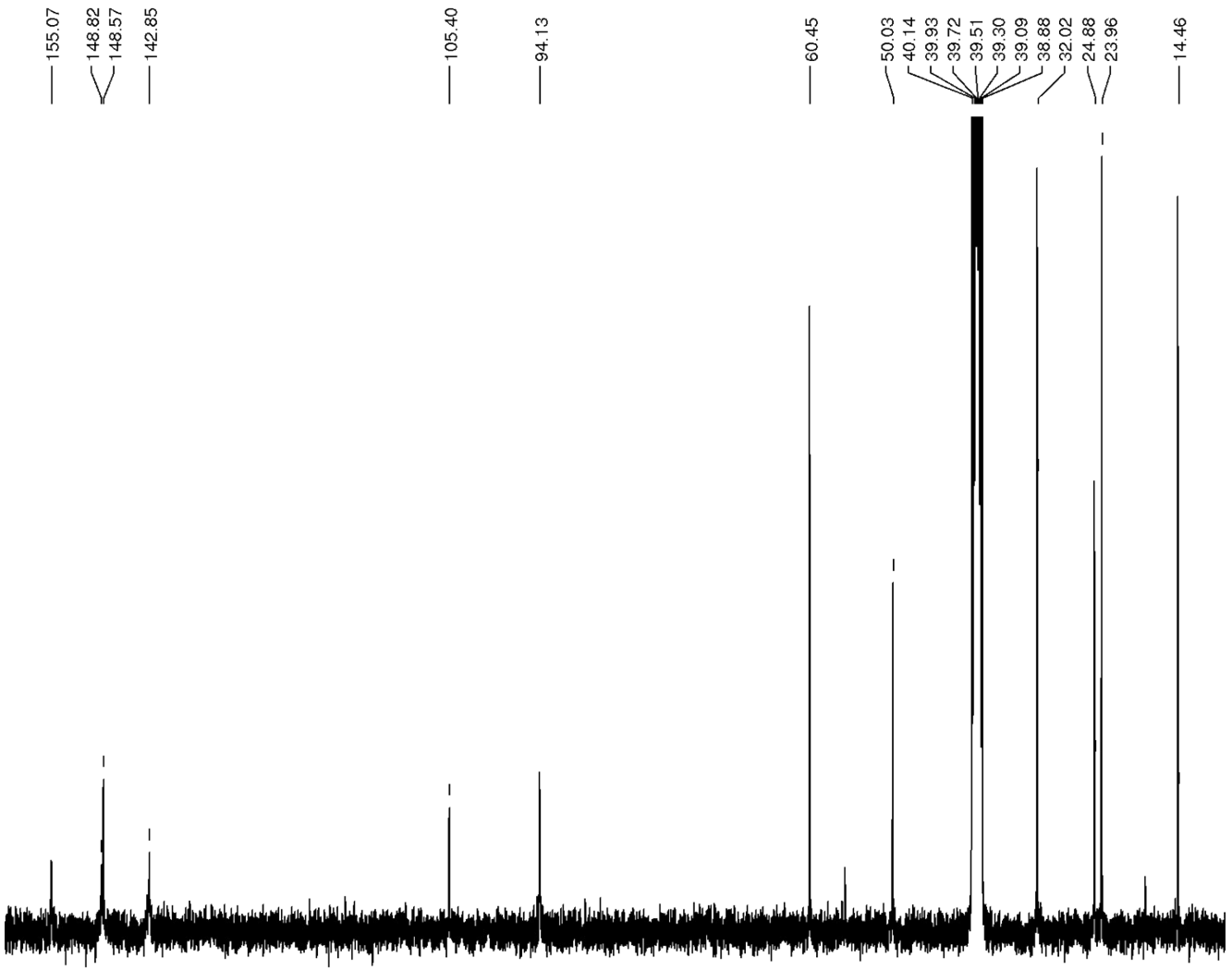


Appendix

Ethyl-[2-amino-[illegible]xylamino)pyridin-3-yl]carbamate hydrochloride (7a)



AS-31 (13C-NMR, DMSO-d6)

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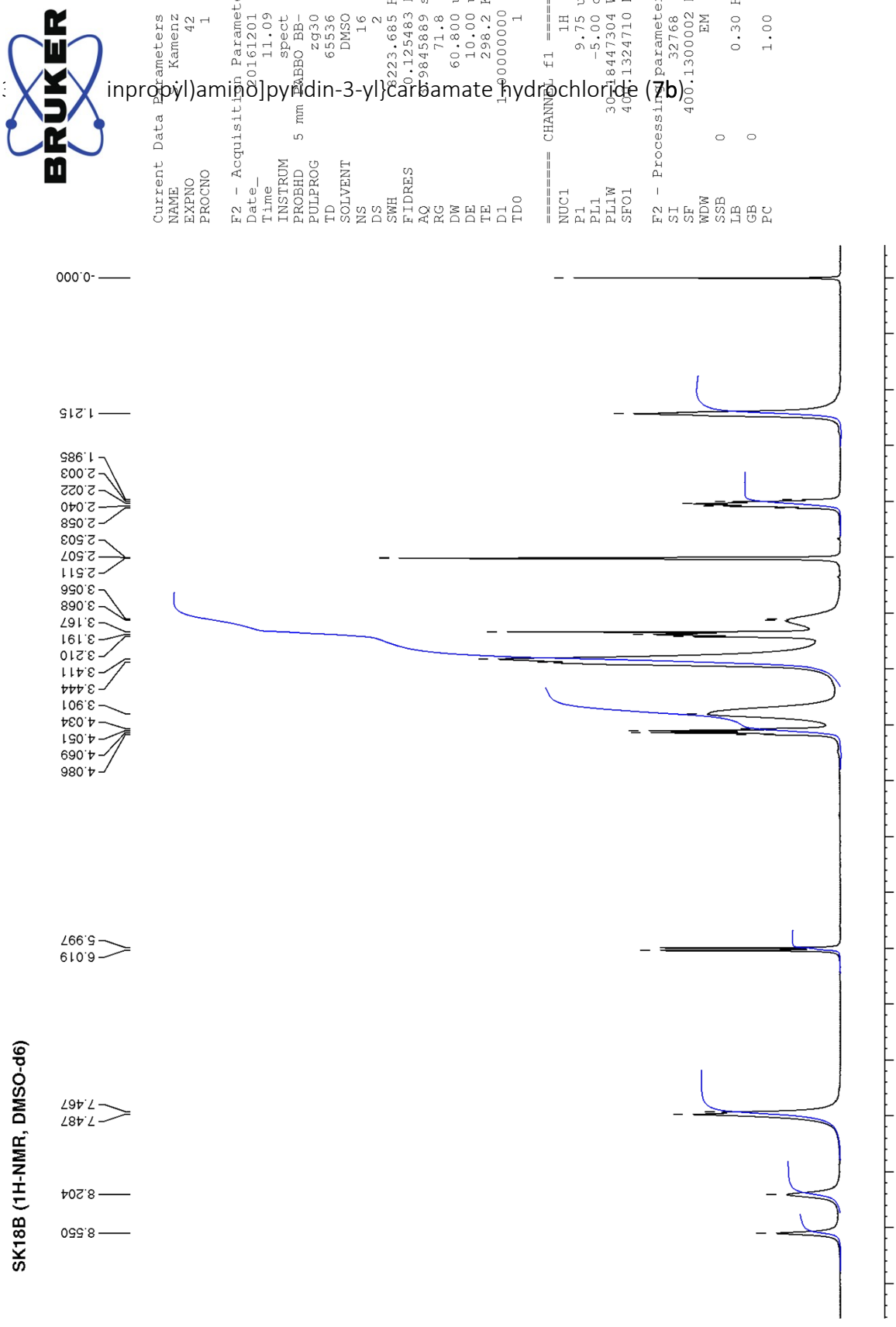
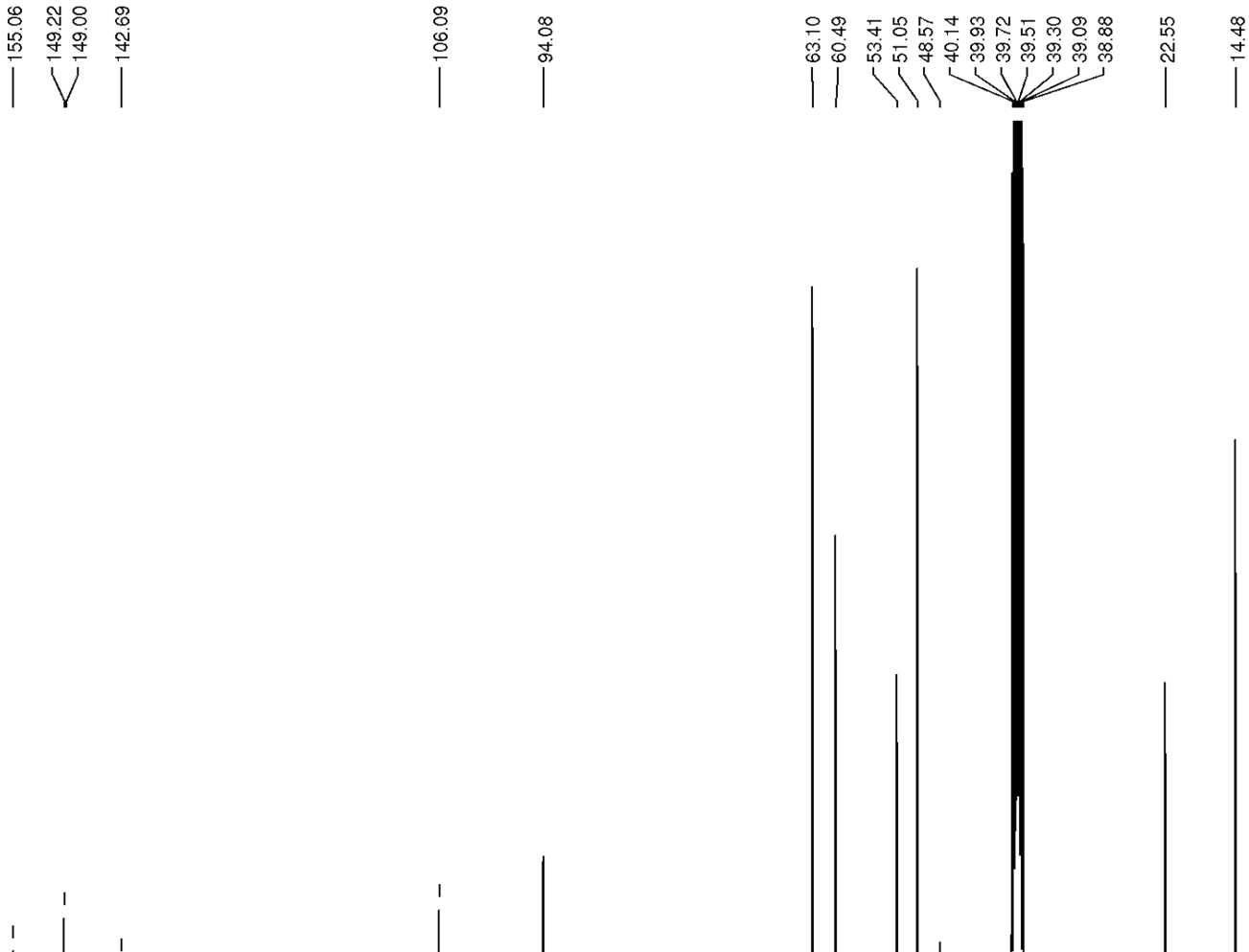
Ethyl-{2-amino-6-[(3 inprobyl)amino]pyridin-3-yl}carbamate hydrochloride (**7b**)



SK18B (13C-NMR, DMSO-d6)

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TD0

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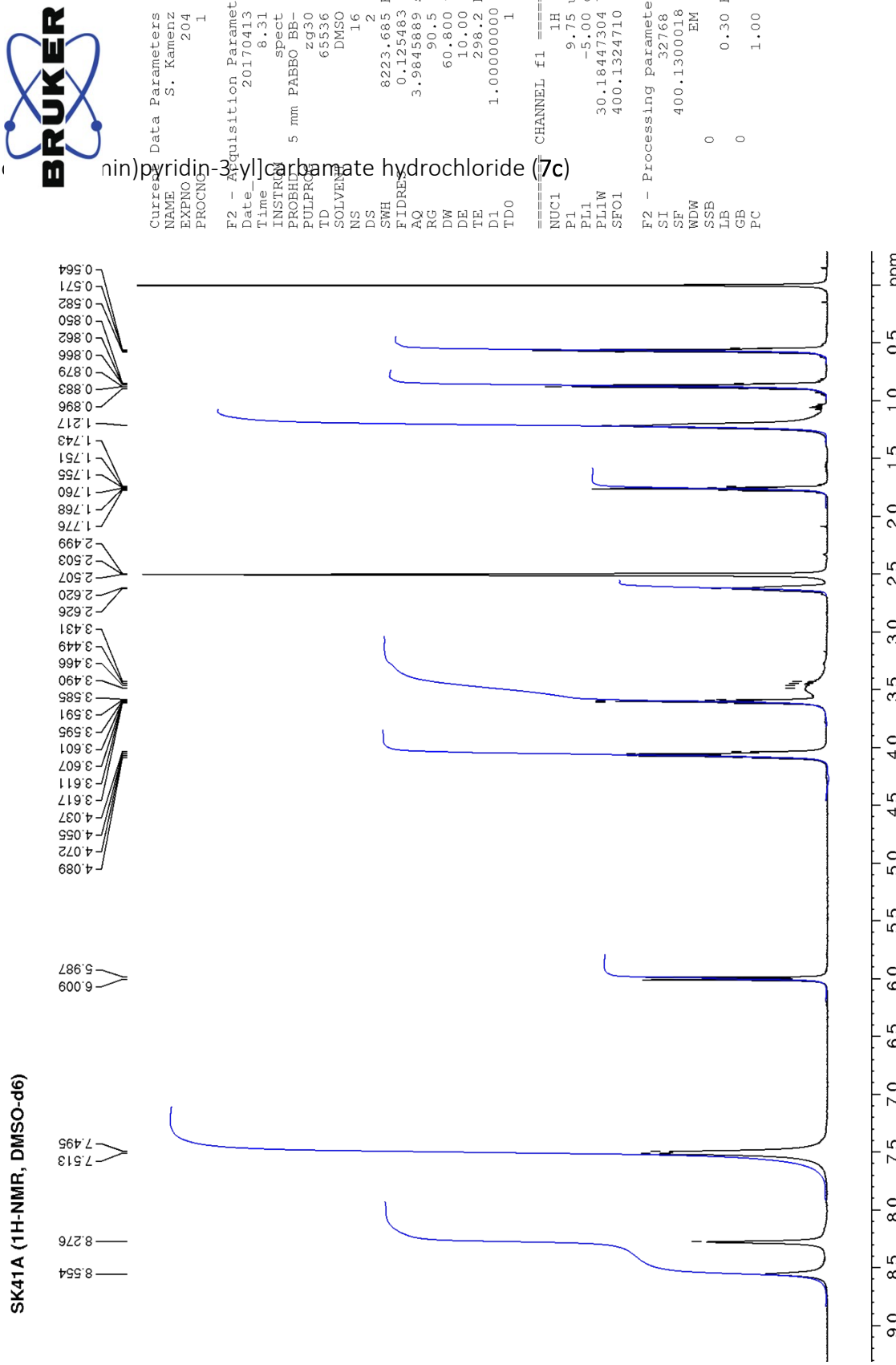
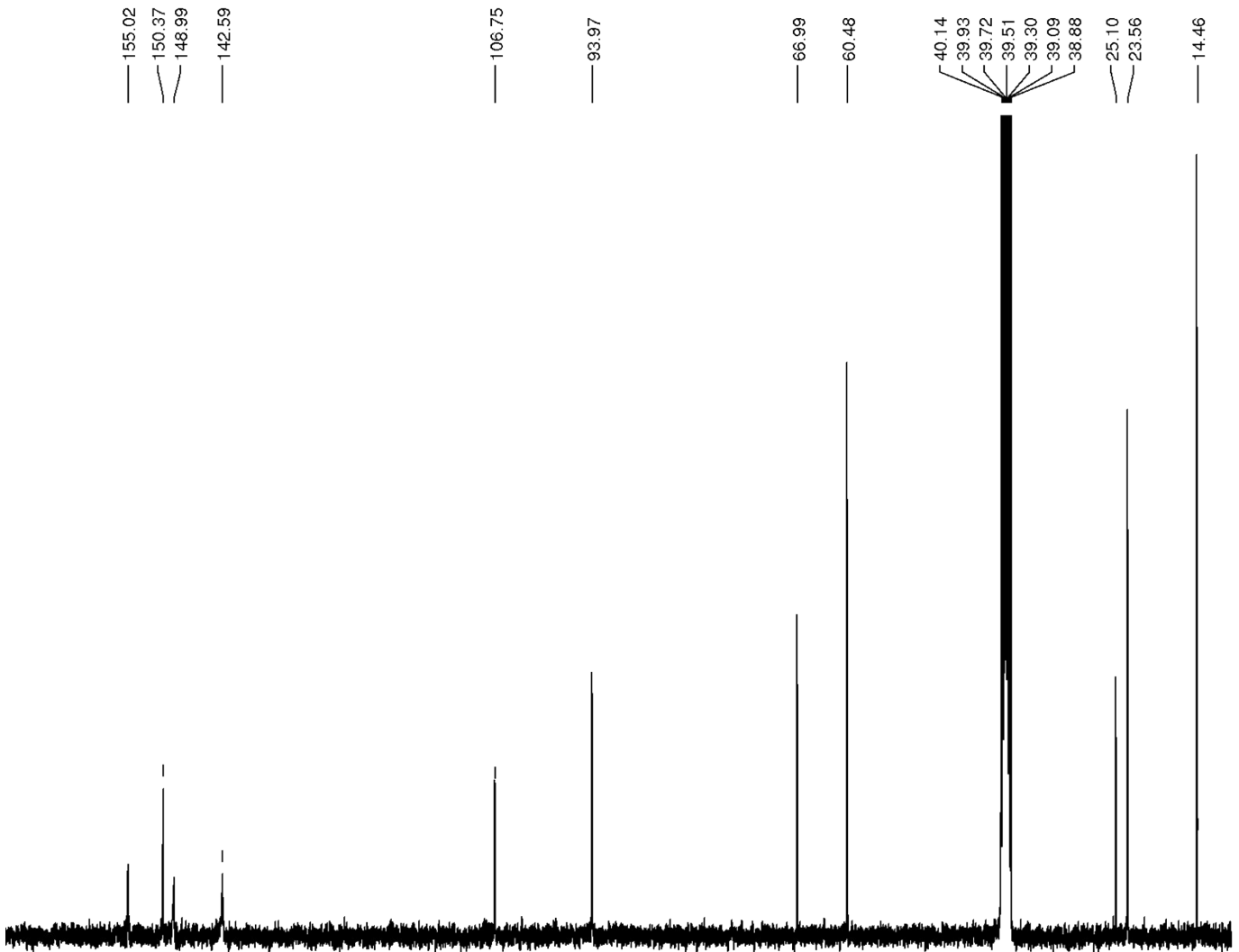
Ethyl-[2-amino-6-(cycl nin)pyridin-3-yl]carbamate hydrochloride (**7c**)

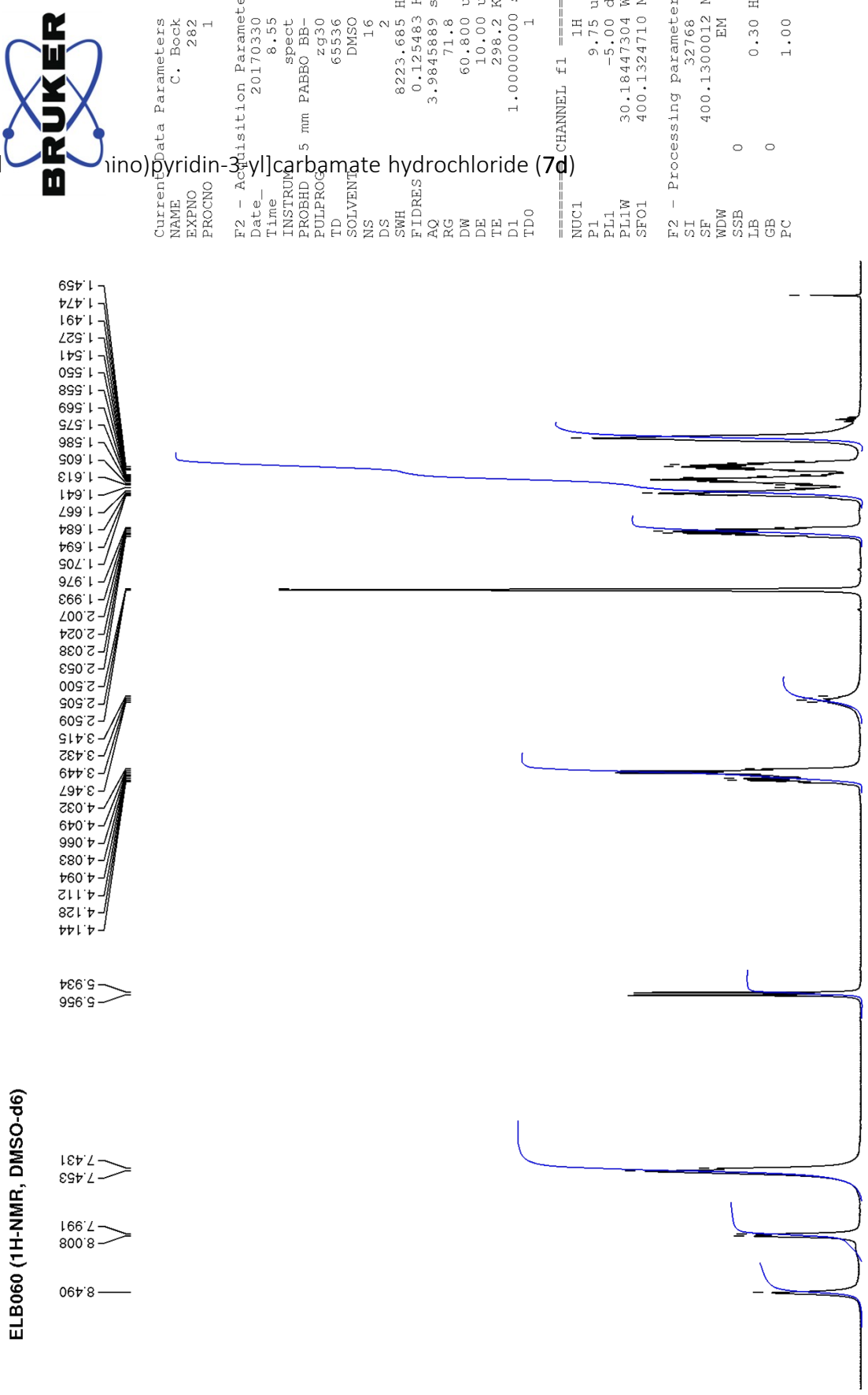


SK41A (13C-NMR, DMSO-d6)

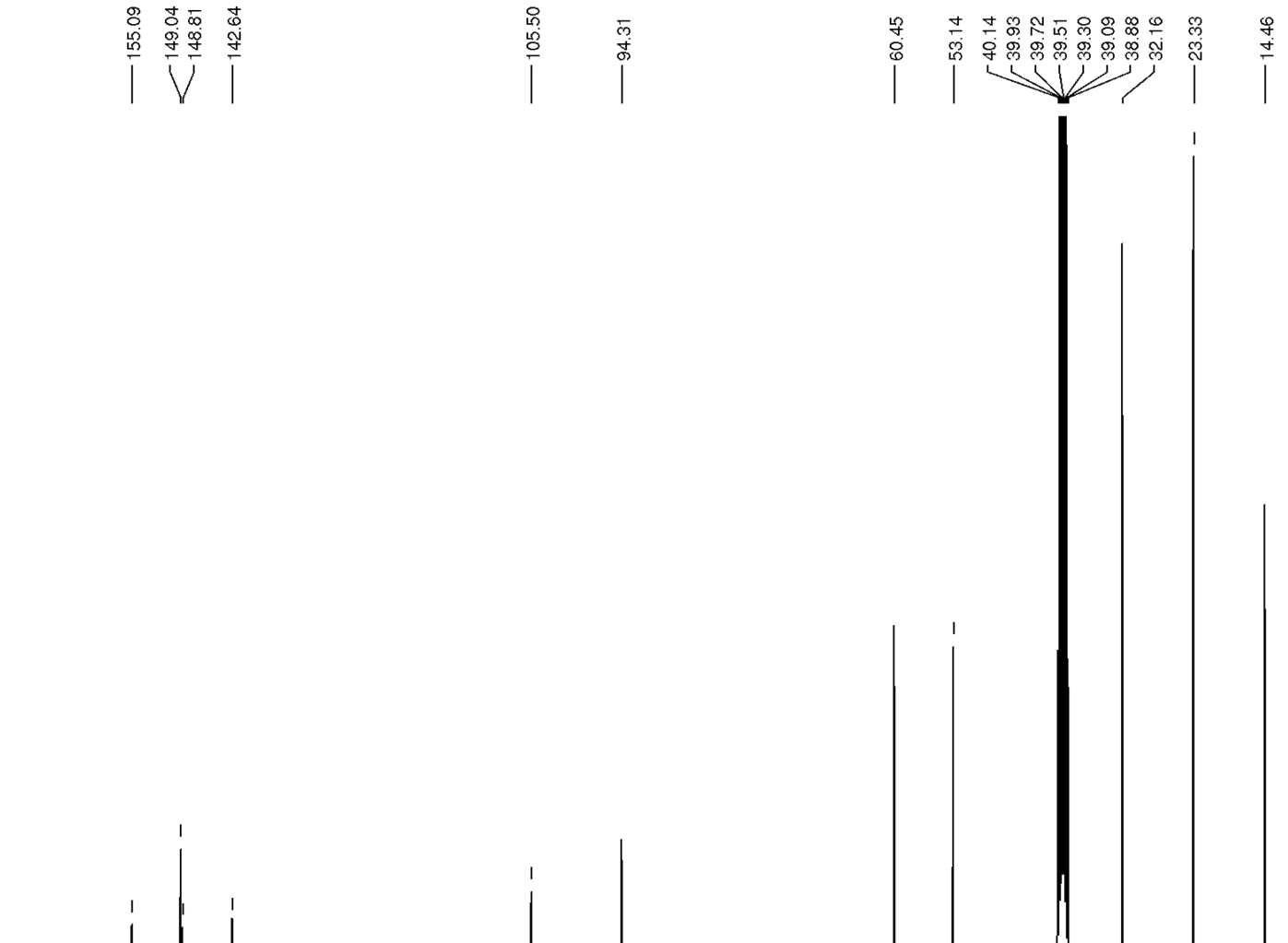



```
Current Data Parameters
NAME            S. Kamenz
EXPNO                 207
PROCNO                  1

F2 - Acquisition Paramete
Date_            20170418
Time                18.26
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  3000
DS                     4
SWH            24038.461
FIDRES          0.366798
AQ             1.3631488
RG                  2050
DW                20.800
DE                10.00
TE                299.2
D1           2.00000000
D11          0.03000000
TD0                    1

======== CHANNEL f1 =====
NUC1                13C
P1                10.00
PL1               -2.70
PL1W        62.67650986
SFO1       100.6228298

======== CHANNEL f2 =====
CPDPRG[2         waltz16
NUC2                1H
PCPD2              60.00
PL2                -5.00
PL12               10.78
PL13               15.00
PL2W        30.18447304
PL12W        0.79759723
PL13W        0.30184472
SFO2       400.1316005

F2 - Processing parameter
SI                 32768
SF          100.6128184
WDW                   EM
```

Ethyl-[2-amino-6-(cycl ino)pyridin-3-yl]carbamate hydrochloride (7d)



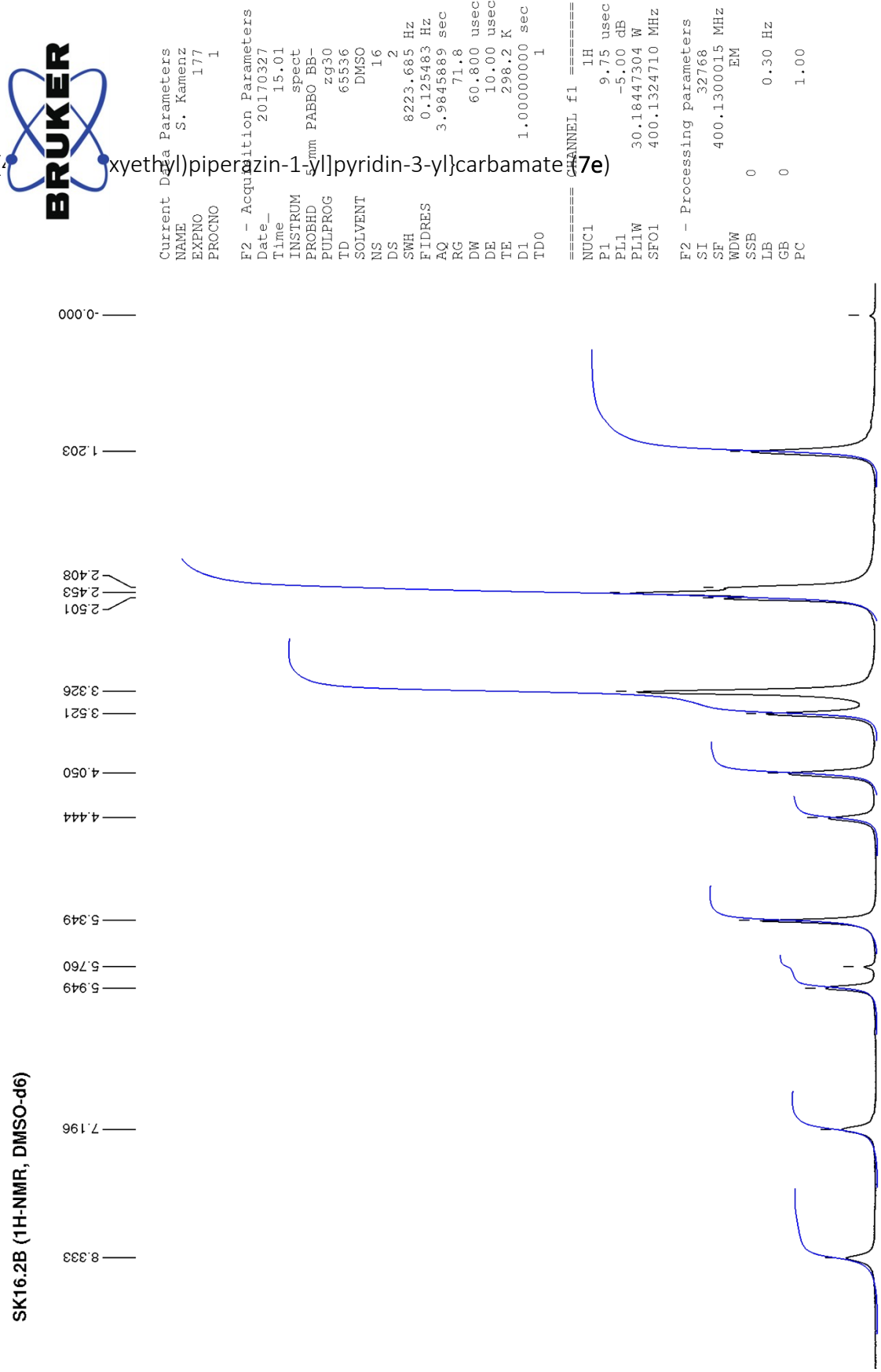
ELB060 (13C-NMR, DMSO-d6)



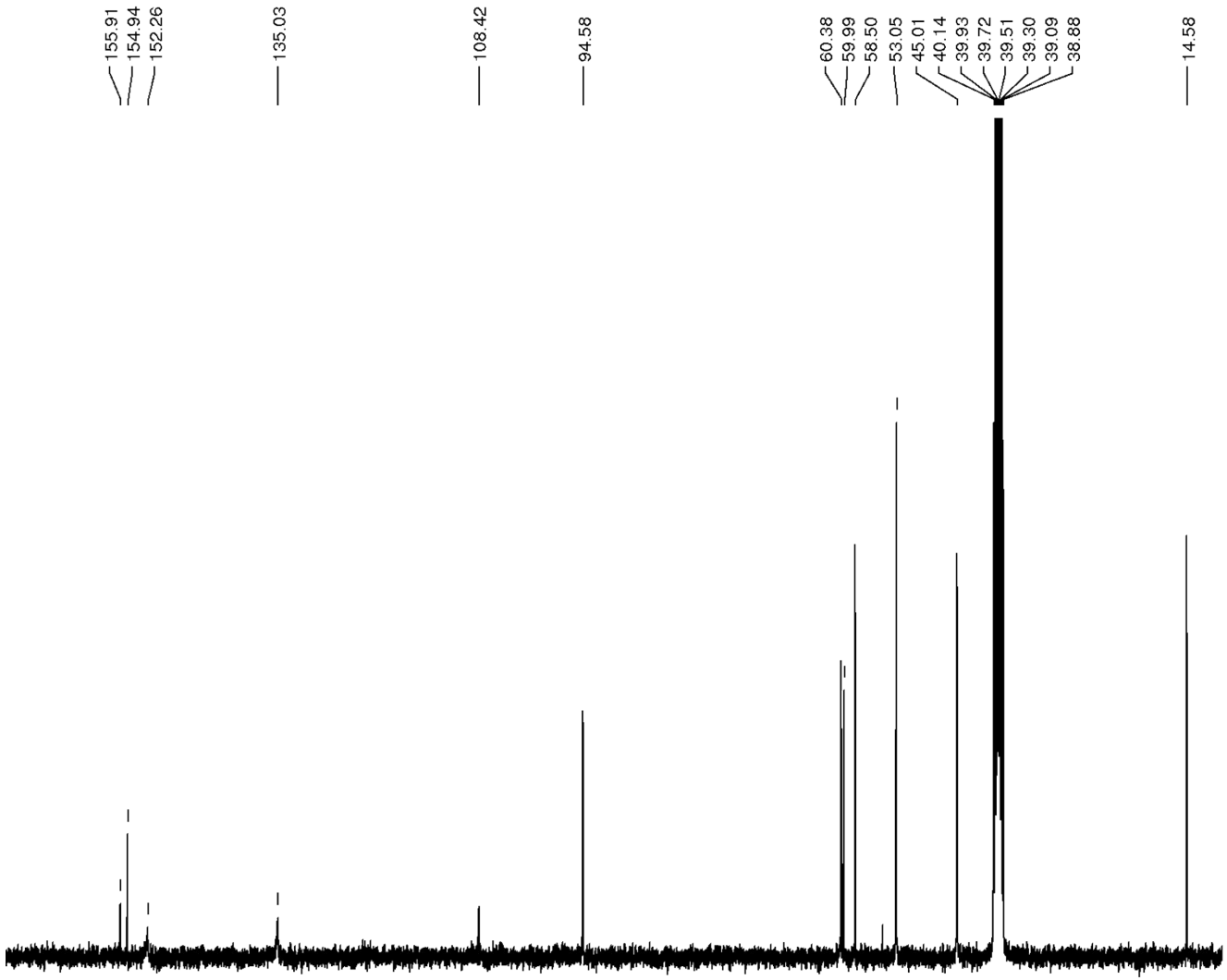
BRUKER

```
Current Data Parameter
NAME                 C. Boc
EXPNO                    28
PROCNO

F2 - Acquisition Param
Date_             2017033
Time                 12.2
INSTRUM              spec
PROBHD    5 mm PABBO BB
PULPROG             zgpg3
TD                    6553
SOLVENT                DMS
NS                      102
DS
SWH              24038.46
FIDRES           0.36679
AQ               1.363148
RG                     205
DW                   20.80
DE                   10.0
TE                   299.
D1               2.0000000
D11              0.0300000
TD0

======== CHANNEL f1 ==
NUC1                    13
P1                   10.0
PL1                  -2.7
PL1W          62.6765098
SFO1         100.622829

======== CHANNEL f2 ==
CPDPRG[2           waltz1
NUC2                    1
PCPD2                60.0
PL2                  -5.0
PL12                 10.7
PL13                 15.0
PL2W          30.1844730
PL12W          0.7975972
PL13W          0.3018447
SFO2         400.131600

F2 - Processing parame
SI                    3276
SF           100.612817
```

Ethyl-{2-amino-6-[4-(2-hydroxyethyl)piperazin-1-yl]pyridin-3-yl}carbamate (**7e**)

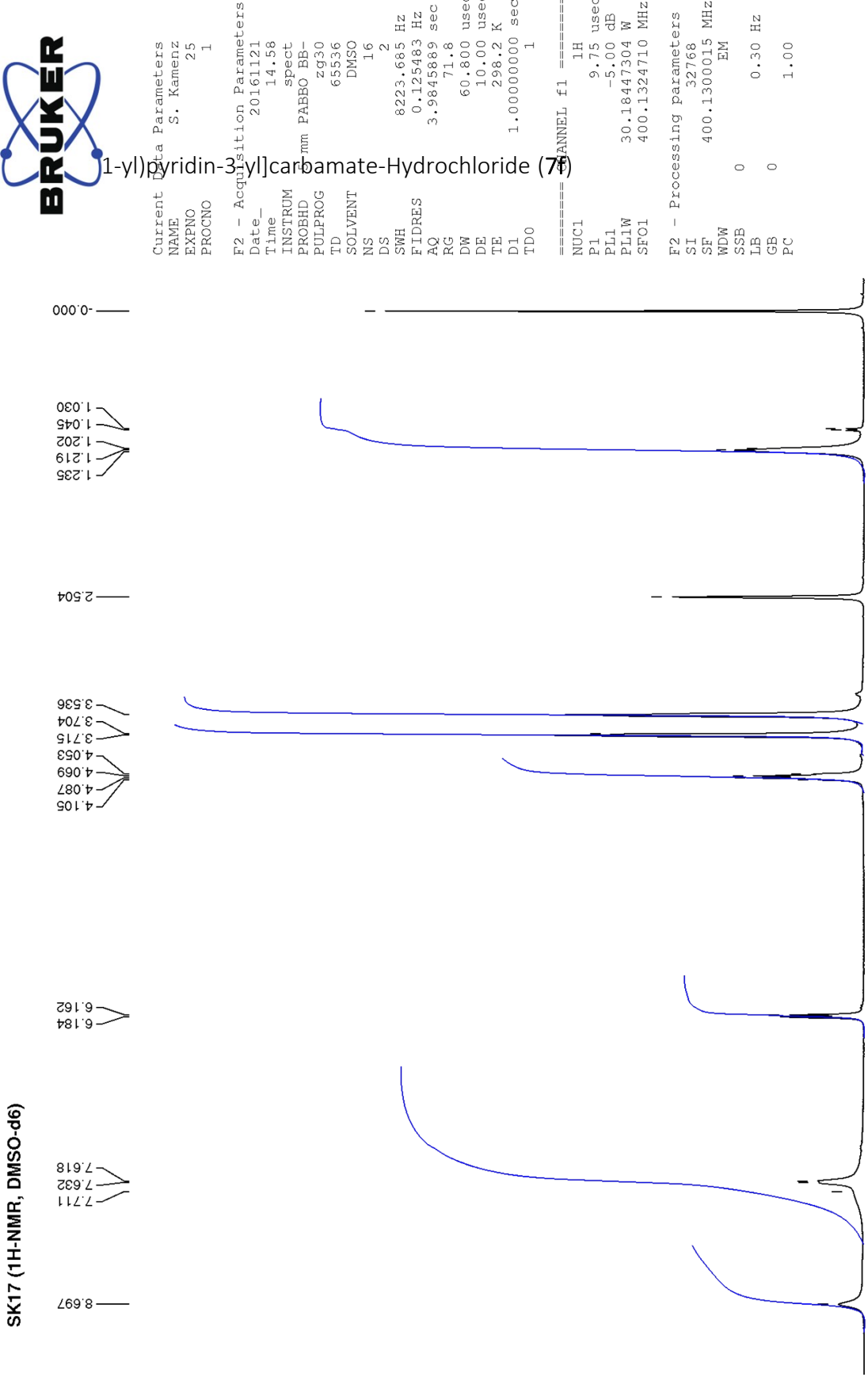


SK16.2B (13C-NMR, DMSO-d6)

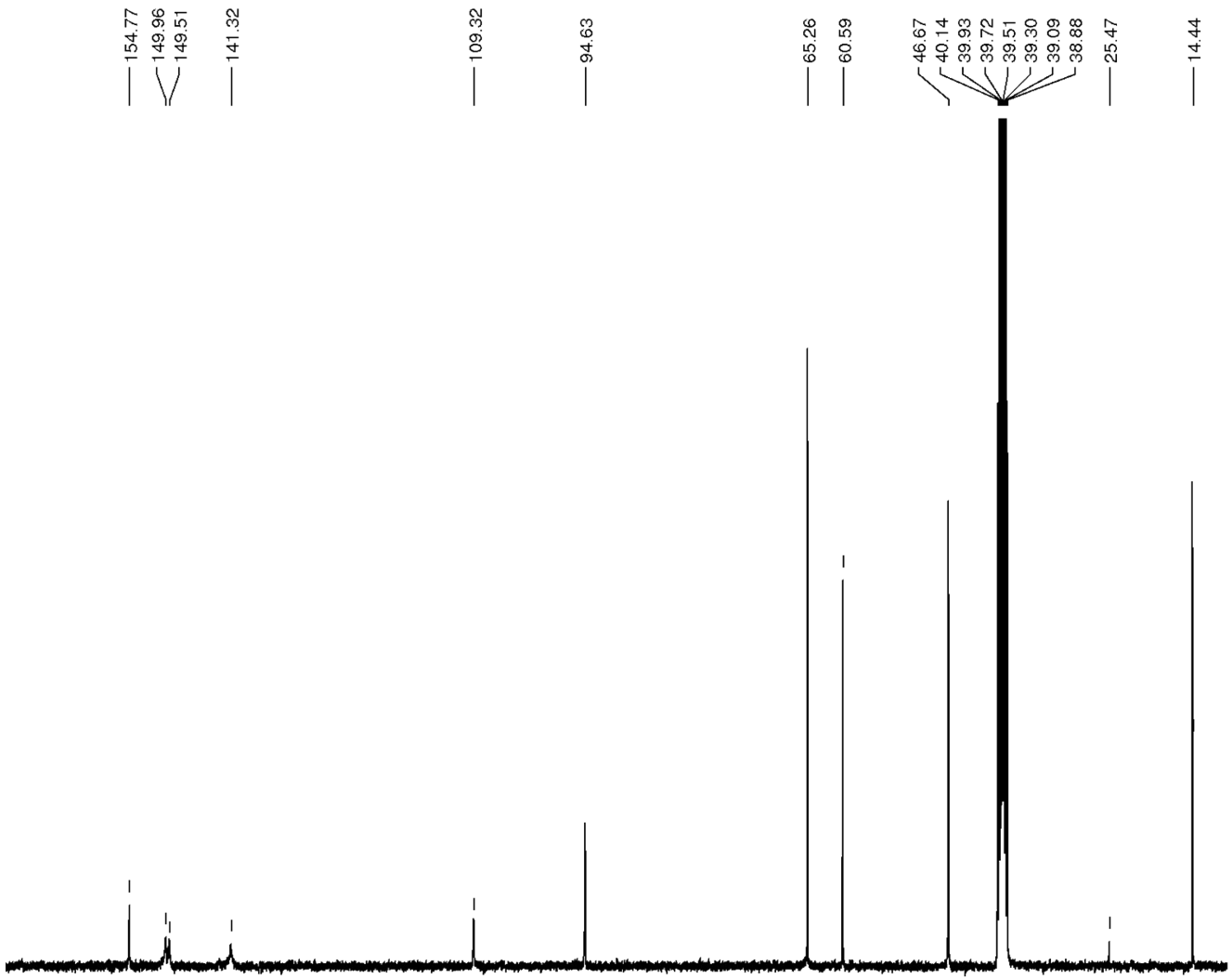



```
Current Data Parameters
NAME                 S. Kamenz
EXPNO                      178
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170328
Time                     10.45
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                       65536
SOLVENT                   DMSO
NS                        1024
DS                           4
SWH                  24038.461 Hz
FIDRES                0.366798 Hz
AQ                    1.3631488 sec
RG                       2050
DW                      20.800 use
DE                      10.00 use
TE                      299.2 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                          1

======== CHANNEL f1 =======
NUC1                       13C
P1                      10.00 use
PL1                     -2.70 dB
PL1W               62.67650986 W
SFO1              100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2                waltz16
NUC2                       1H
PCPD2                   60.00 use
PL2                     -5.00 dB
PL12                    10.78 dB
PL13                    15.00 dB
PL2W               30.18447304 W
PL12W               0.79759723 W
PL13W               0.30184472 W
SFO2              400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF                100.6128183 MHz
WDW                         EM
SSB          0
```

Ethyl-[2-amino-6-(m[illegible]1-yl)pyridin-3-yl]carbamate-Hydrochloride (74)



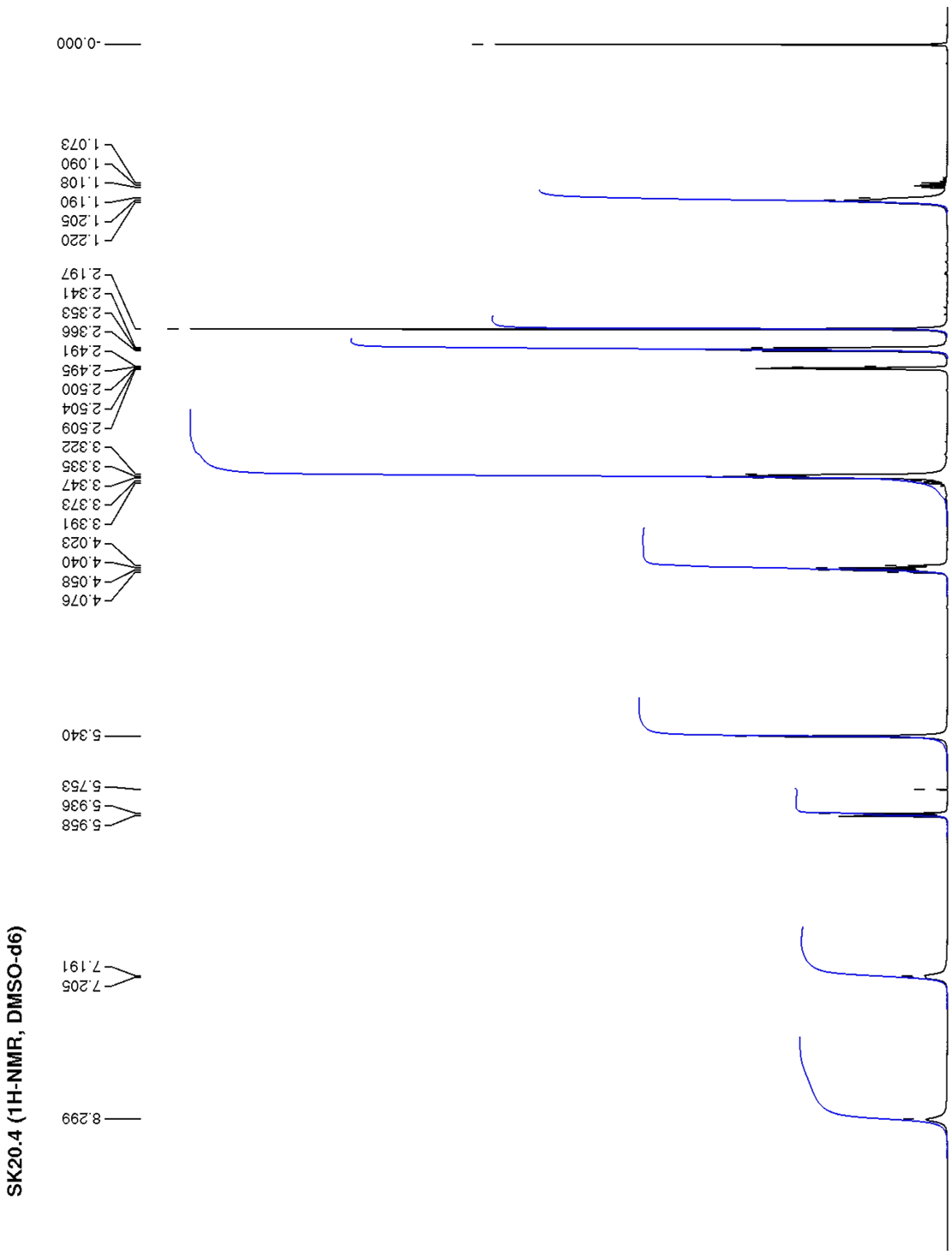
SK17 (13C-NMR, DMSO-d6)



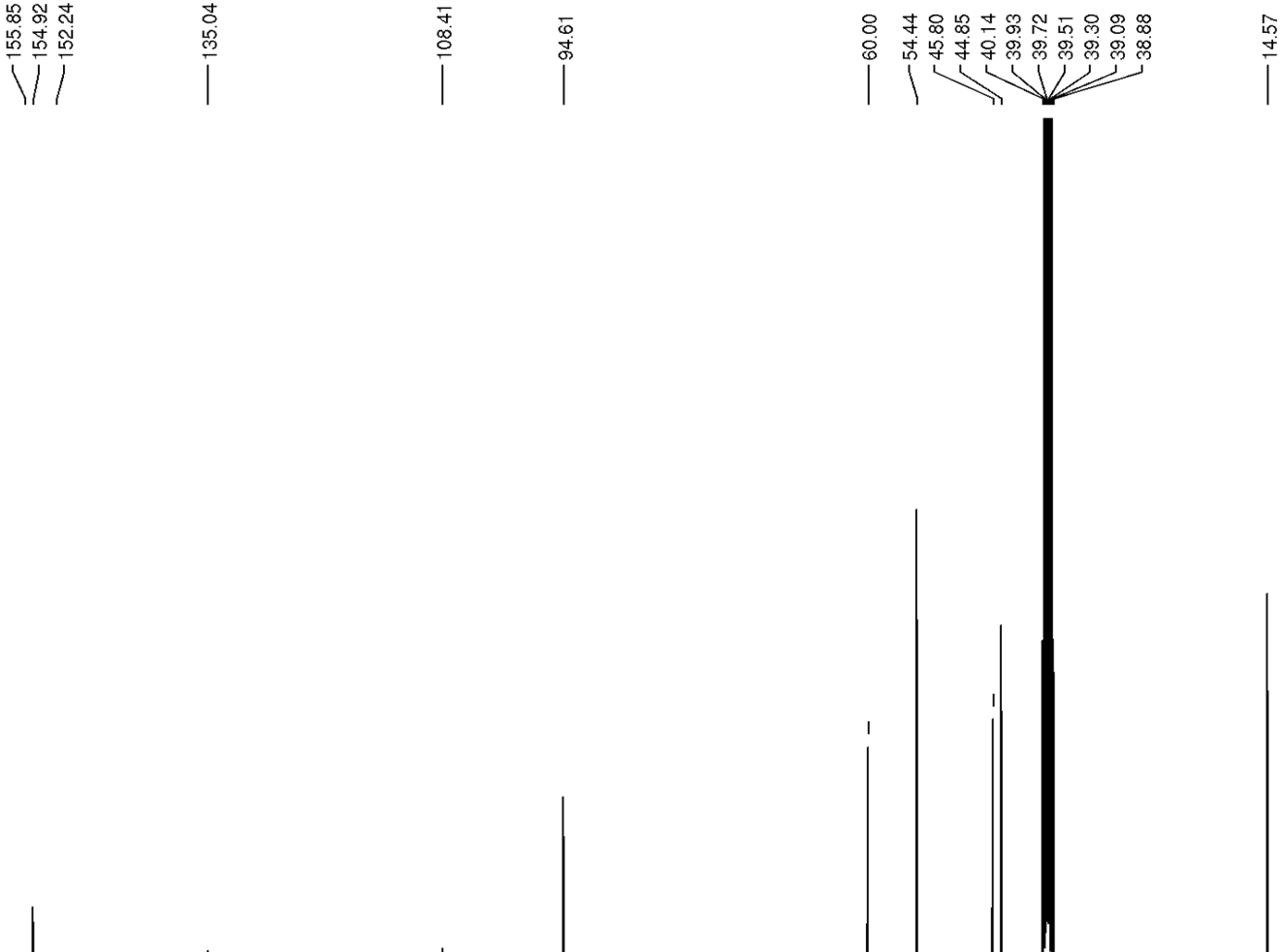
BRUKER

```
Current Data Parameters
NAME                 S. Kamenz
EXPNO                       26
PROCNO                       1

F2 - Acquisition Parameters
Date_               20161122
Time                    6.53
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                   DMSO
NS                        4000
DS                           4
SWH                 24038.461 Hz
FIDRES                0.366798 Hz
AQ                    1.3631488 sec
RG                         2050
DW                       20.800 use
DE                       10.00 use
TE                       298.2 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

======== CHANNEL f1 =======
NUC1                        13C
P1                       10.00 use
PL1                      -2.70 dB
PL1W               62.67650986 W
SFO1               100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                    60.00 use
PL2                      -5.00 dB
PL12                     10.78 dB
PL13                     15.00 dB
PL2W               30.18447304 W
PL12W               0.79759723 W
PL13W               0.30184472 W
SFO2               400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF                 100.6128181 MHz
WDW                         EM
SSB          0
LB                       1.00 Hz
```

Ethyl-[2-amino-6-(4-m azin-1-yl)pyridin-3-yl]carbamate (**7g**)



SK20.4 (13C-NMR, DMSO-d6)



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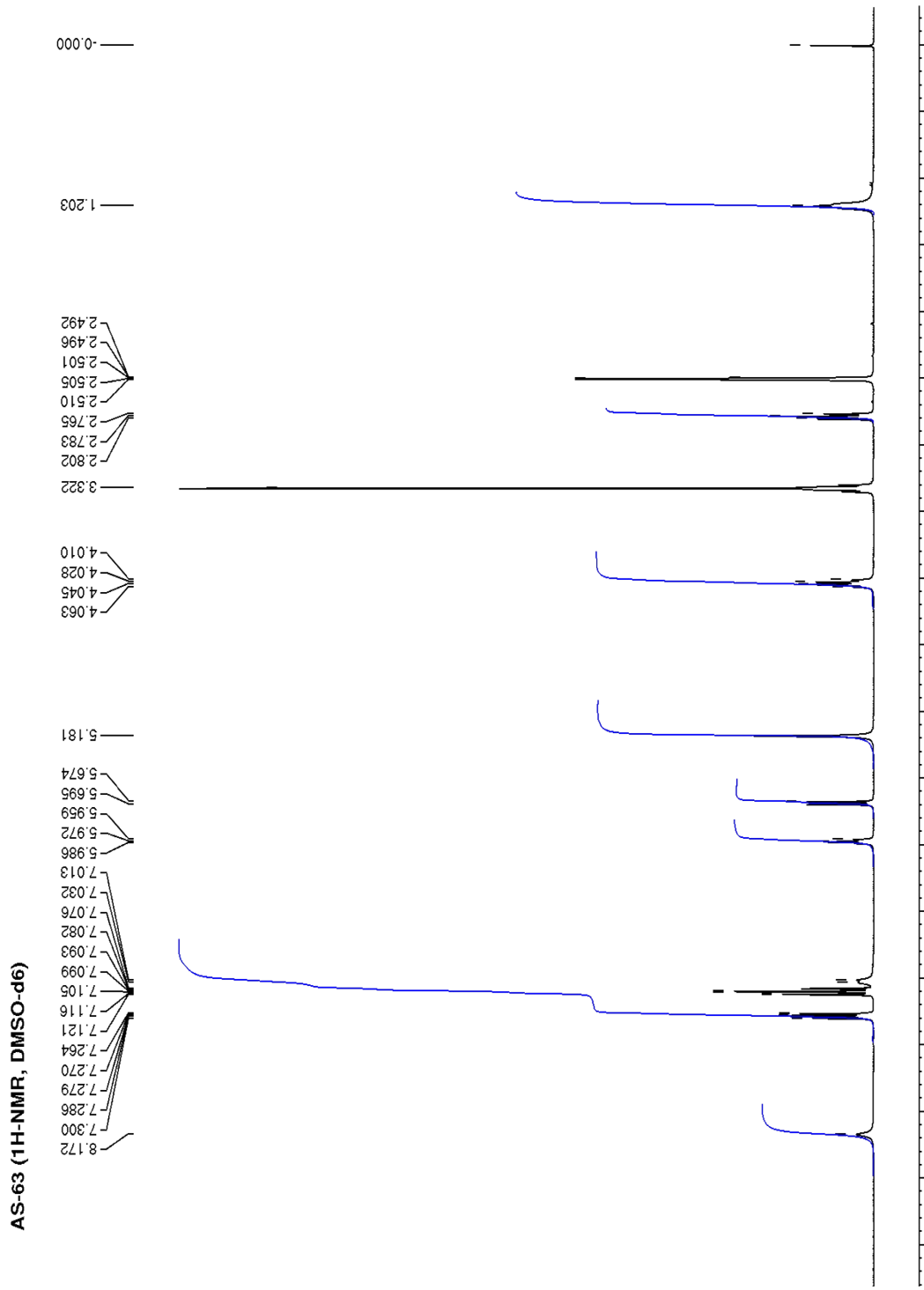
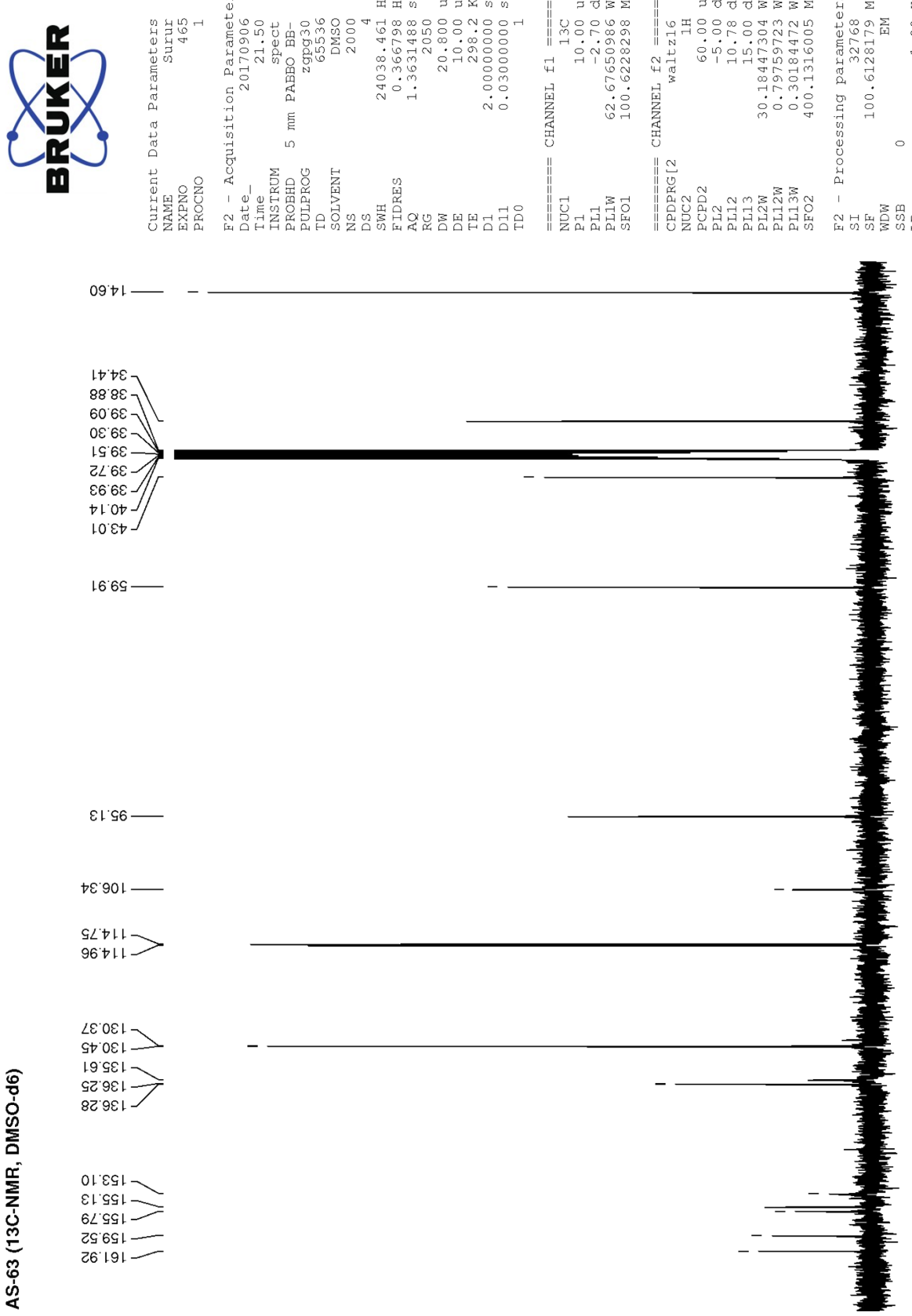
```
Current Data Parame
NAME              S. Ka
EXPNO
PROCNO

F2 - Acquisition Pa
Date_               2017
Time
INSTRUM               sp
PROBHD    5 mm PABBO
PULPROG             zgp
TD                     6
SOLVENT
NS
DS
SWH                24038
FIDRES              0.36
AQ                 1.363
RG
DW                    20
DE                     1
TE                     2
D1                2.0000
D11               0.0300
TD0

======== CHANNEL f1
NUC1
P1                     1
PL1                    -
PL1W           62.6765
SFO1           100.622

======== CHANNEL f2
CPDPRG[2            wal
NUC2
PCPD2                  6
PL2                    -
PL12                   1
PL13                   1
PL2W           30.1844
PL12W           0.7975
PL13W           0.3018
SFO2           400.131

F2 - Processing par
```

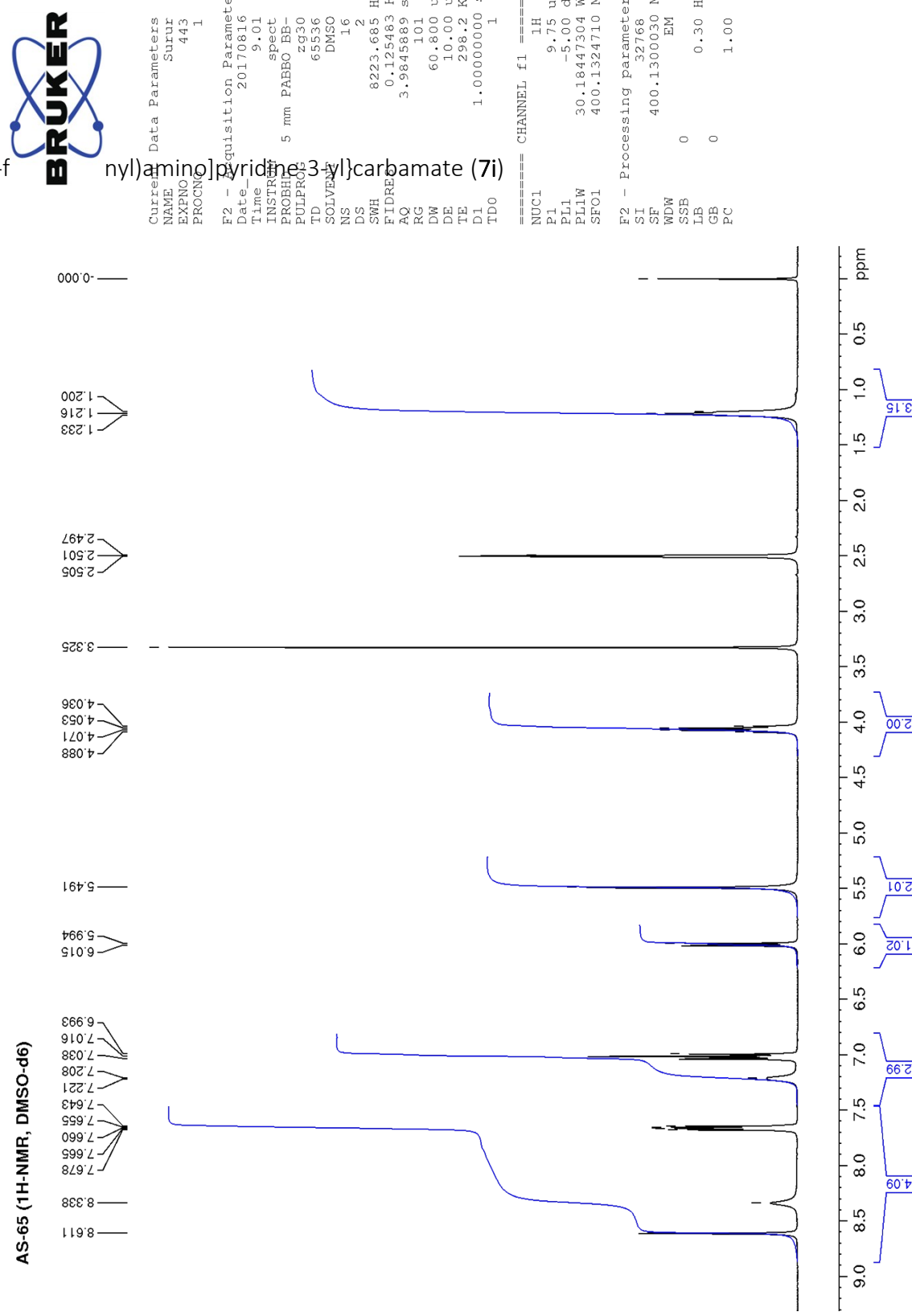
Ethyl {2-amino-6-[(4-fluorophenethyl)amino]pyridin-3-yl}carbamate (7h)



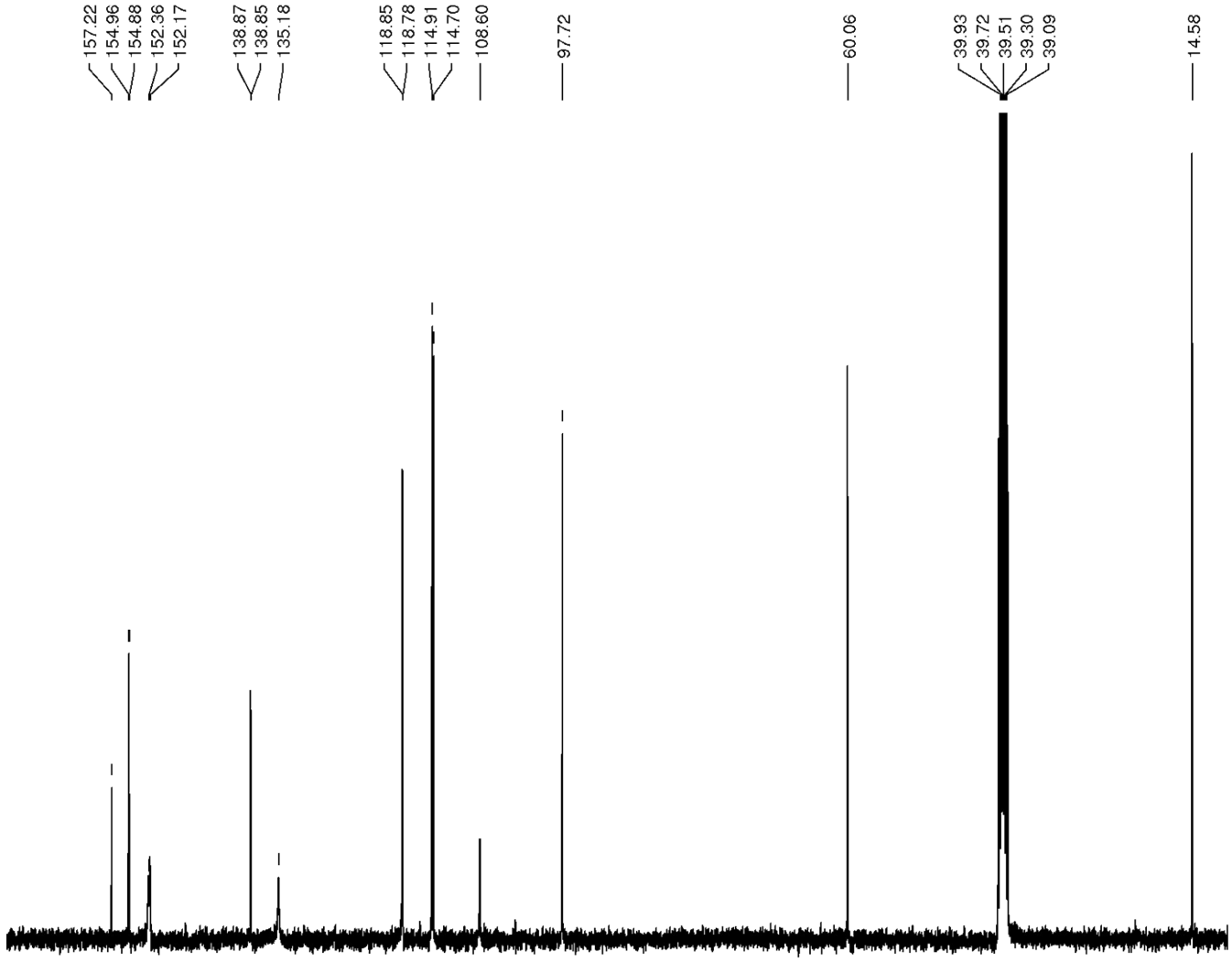


AS-63 (13C-NMR, DMSO-d6)

Ethyl {2-amino-6-[(4-f nyl)amino]pyridine-3-yl}carbamate (**7i**)

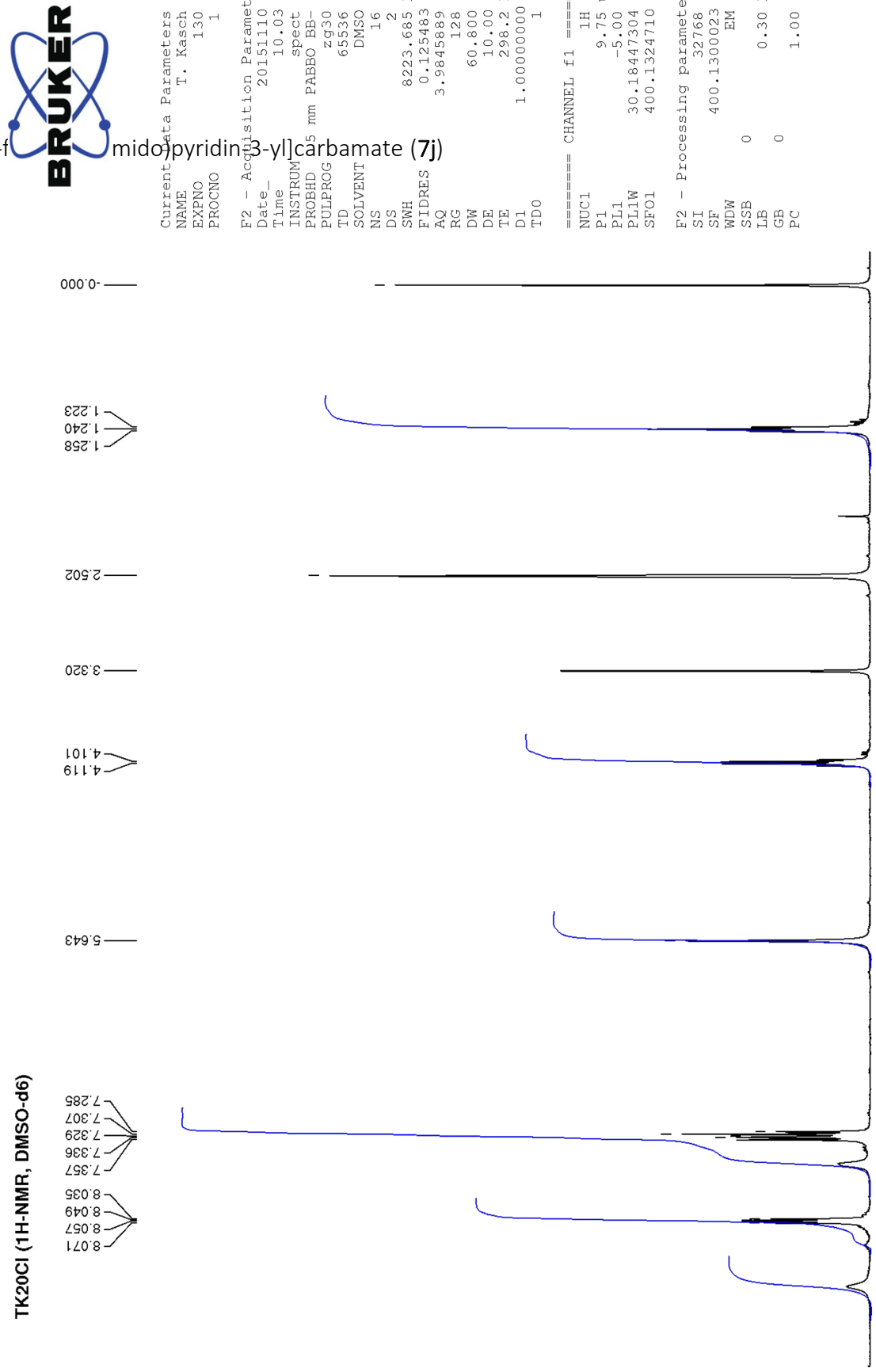


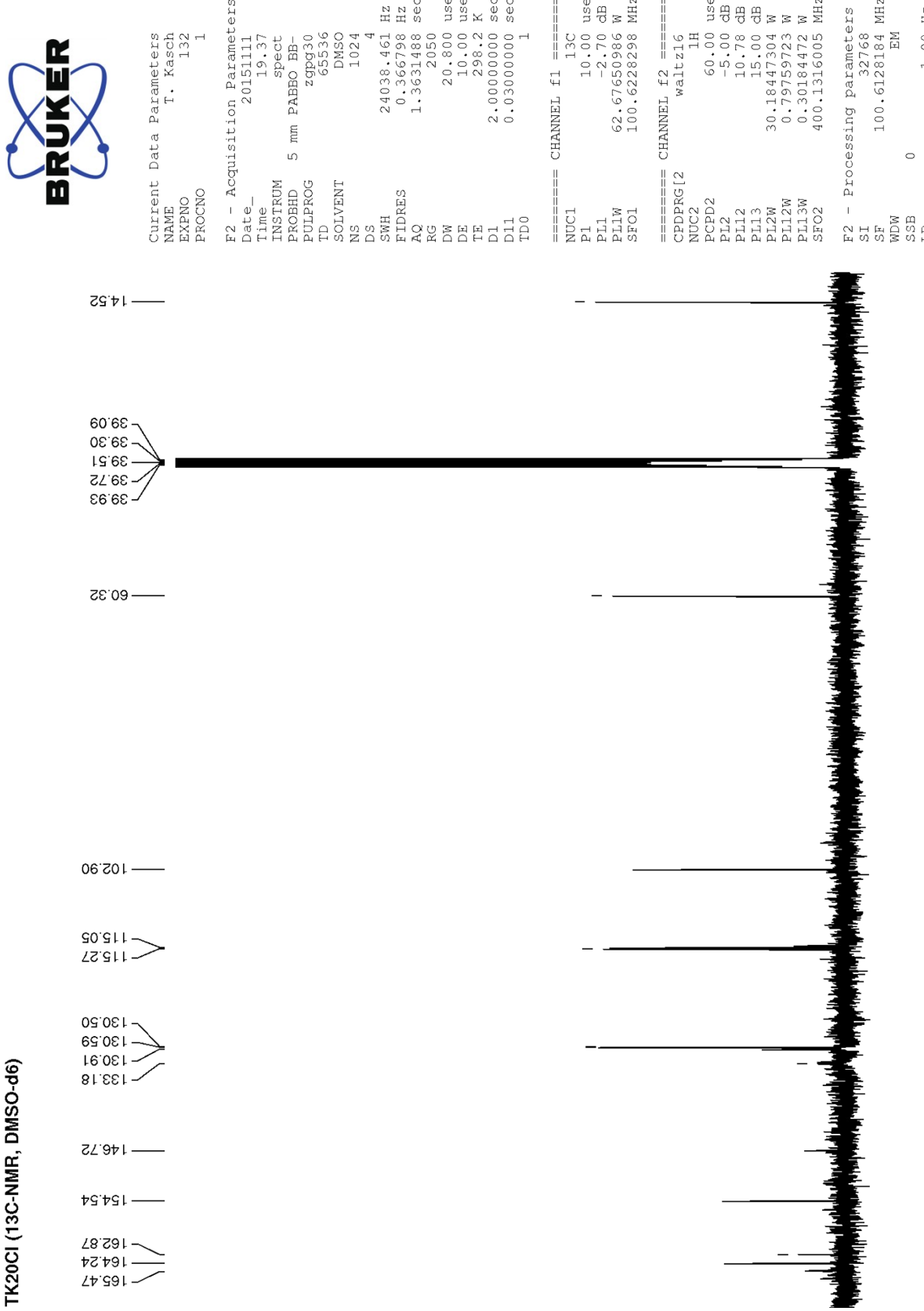
AS-65 (13C-NMR, DMSO-d6)



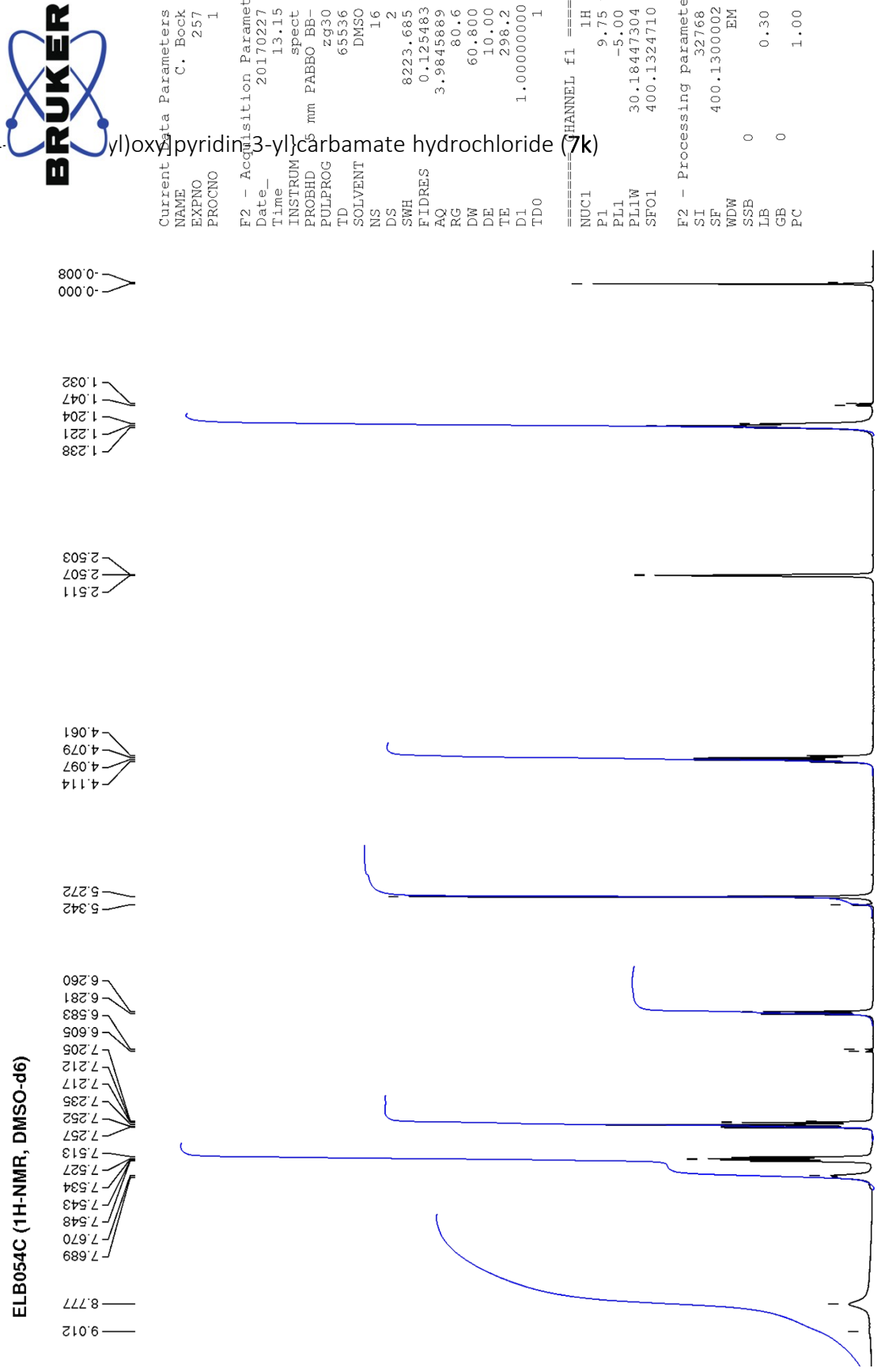

```
Current Data Parameters
NAME                  Surur
EXPNO                   445
PROCNO                    1

F2 - Acquisition Parameter
Date_              20170817
Time                  19.18
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH               24038.461 H
FIDRES             0.366798 H
AQ                 1.3631488 s
RG                      2050
DW                   20.800 u
DE                   10.00 u
TE                   299.2 K
D1                2.00000000 s
D11               0.03000000 s
TD0                       1

======== CHANNEL f1 =====
NUC1                    13C
P1                   10.00 u
PL1                  -2.70 d
PL1W           62.67650986 W
SFO1           100.6228298 M

======== CHANNEL f2 =====
CPDPRG[2           waltz16
NUC2                    1H
PCPD2                60.00 u
PL2                  -5.00 d
PL12                 10.78 d
PL13                 15.00 d
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2           400.1316005 M

F2 - Processing parameter
SI                    32768
SF               100.6128171 M
WDW                      EM
SSB          0
```

Ethyl-[2-amino-6-(4-f mido)pyridin-3-yl]carbamate (**7j**)

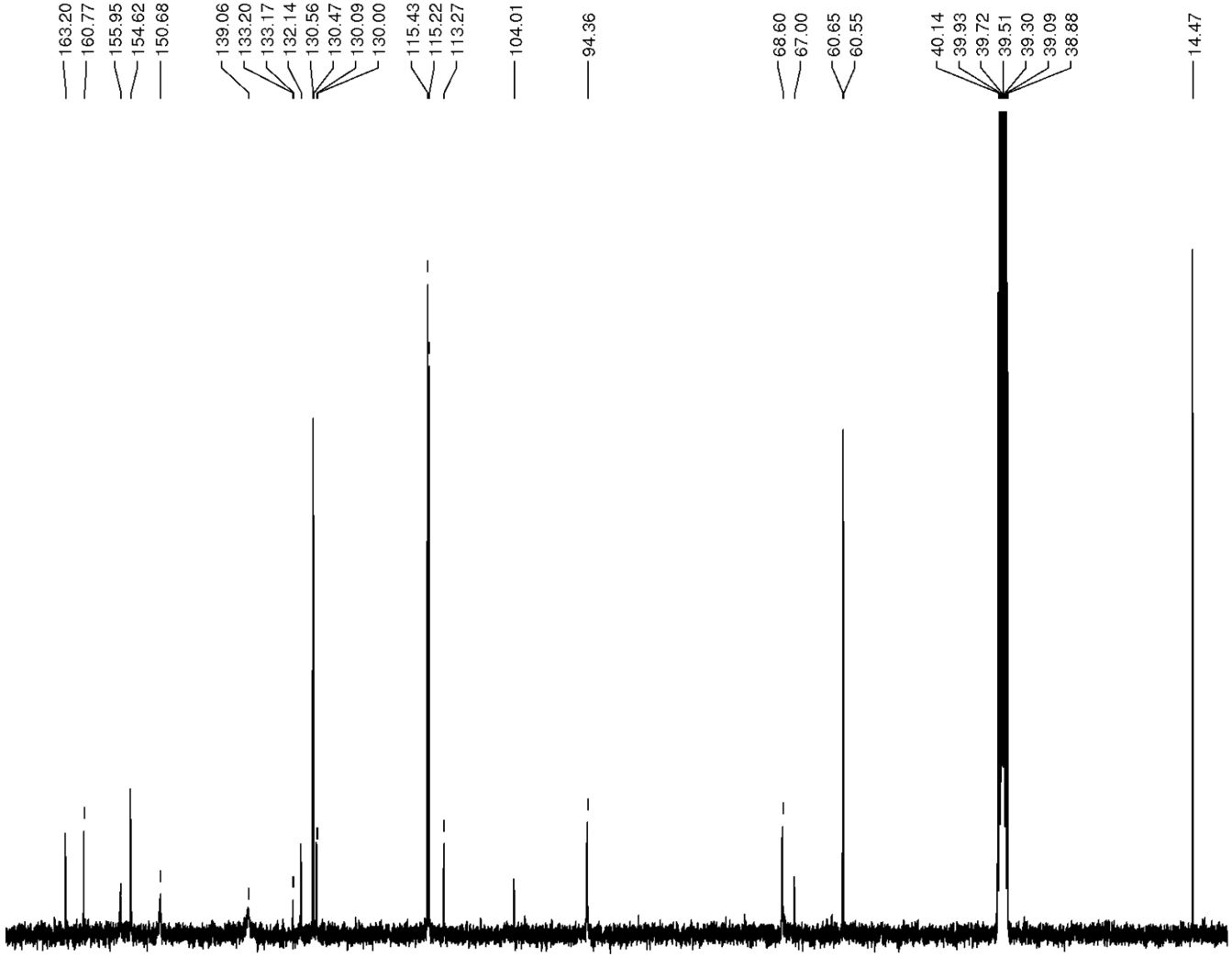



Current Data Parameters
NAME T. Kasch
EXPNO 132
PROCNO 1
F2 - Acquisition Parameters
Date_ 20151111
Time 19.37
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 2050
DW 20.800 use
DE 10.00 use
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 use
PL1 -2.70 dB
PL1W 62.67650986 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00 use
PL2 -5.00 dB
PL12 10.78 dB
PL13 15.00 dB
PL2W 30.18447304 W
PL12W 0.79759723 W
PL13W 0.30184472 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128184 MHz
WDW EM
SSB 0
14.52
39.09
39.30
39.51
39.72
39.93
60.32
102.90
115.05
115.27
130.50
130.59
130.91
133.18
146.72
154.54
162.87
164.24
165.47
TK20Cl (13C-NMR, DMSO-d6)

Ethyl-{2-amino-6-[(4-[illegible]yl)oxy]pyridin-3-yl}carbamate hydrochloride (7k)

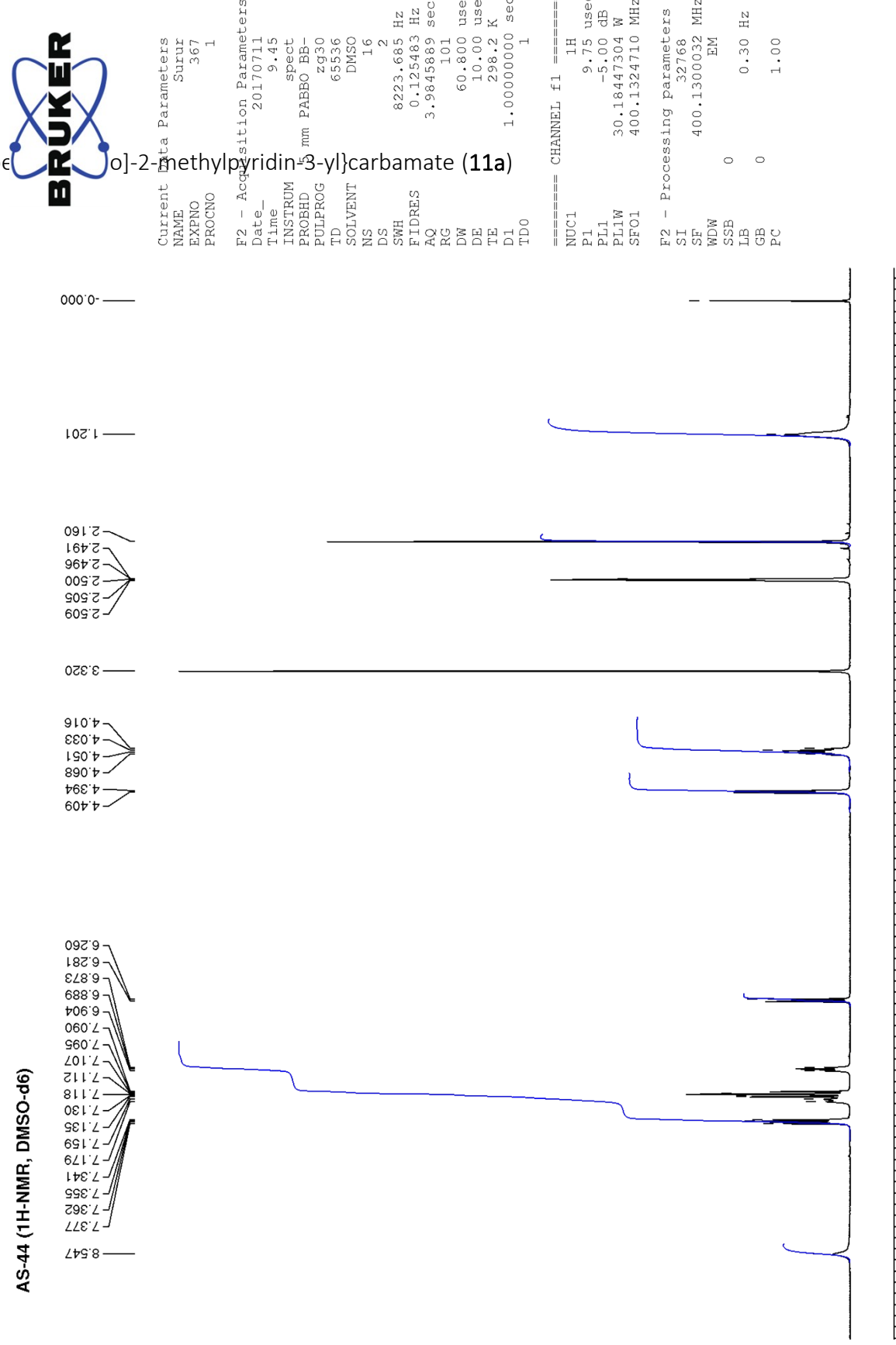


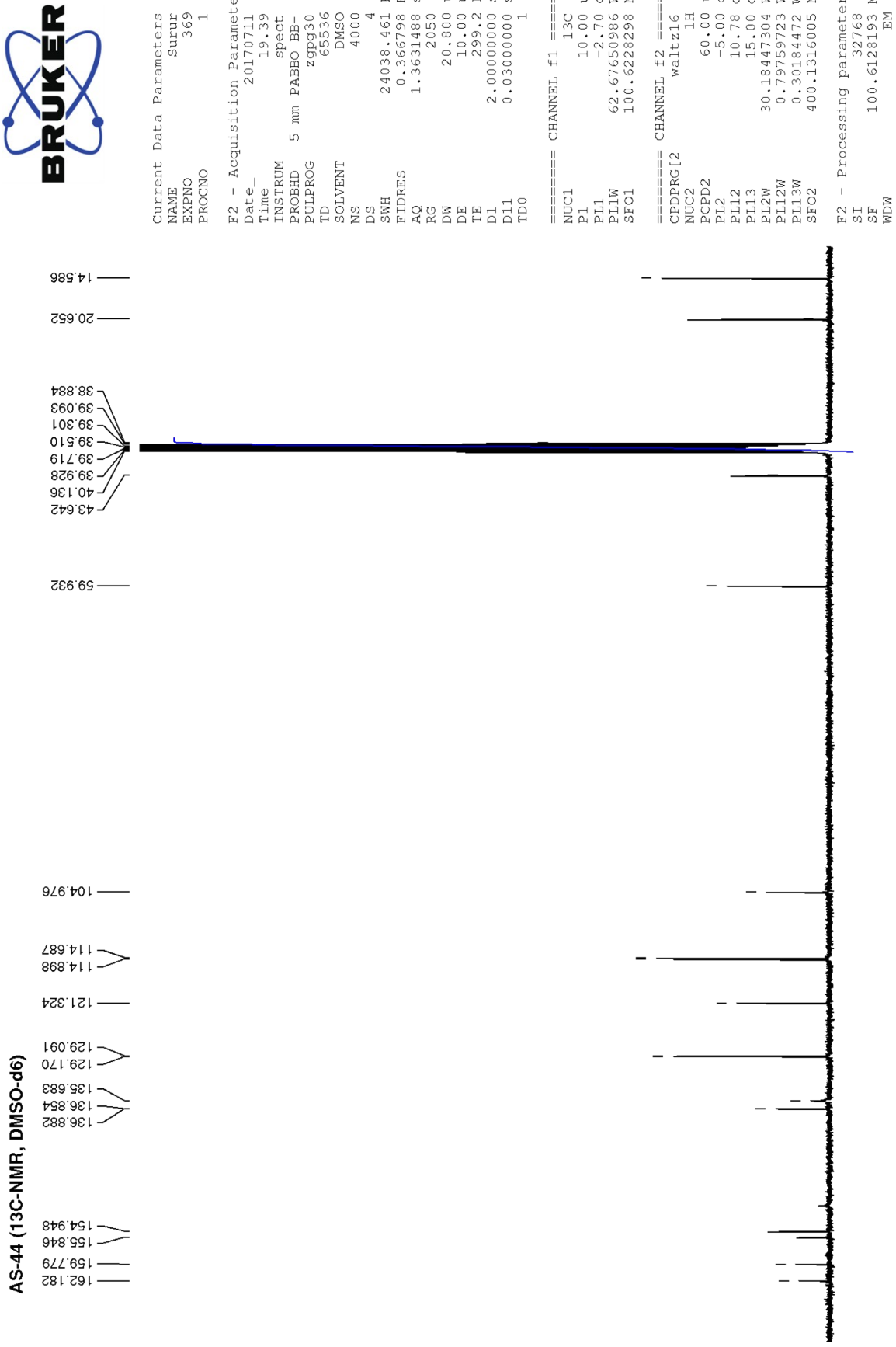
ELB054 (13C-NMR, DMSO-d6)



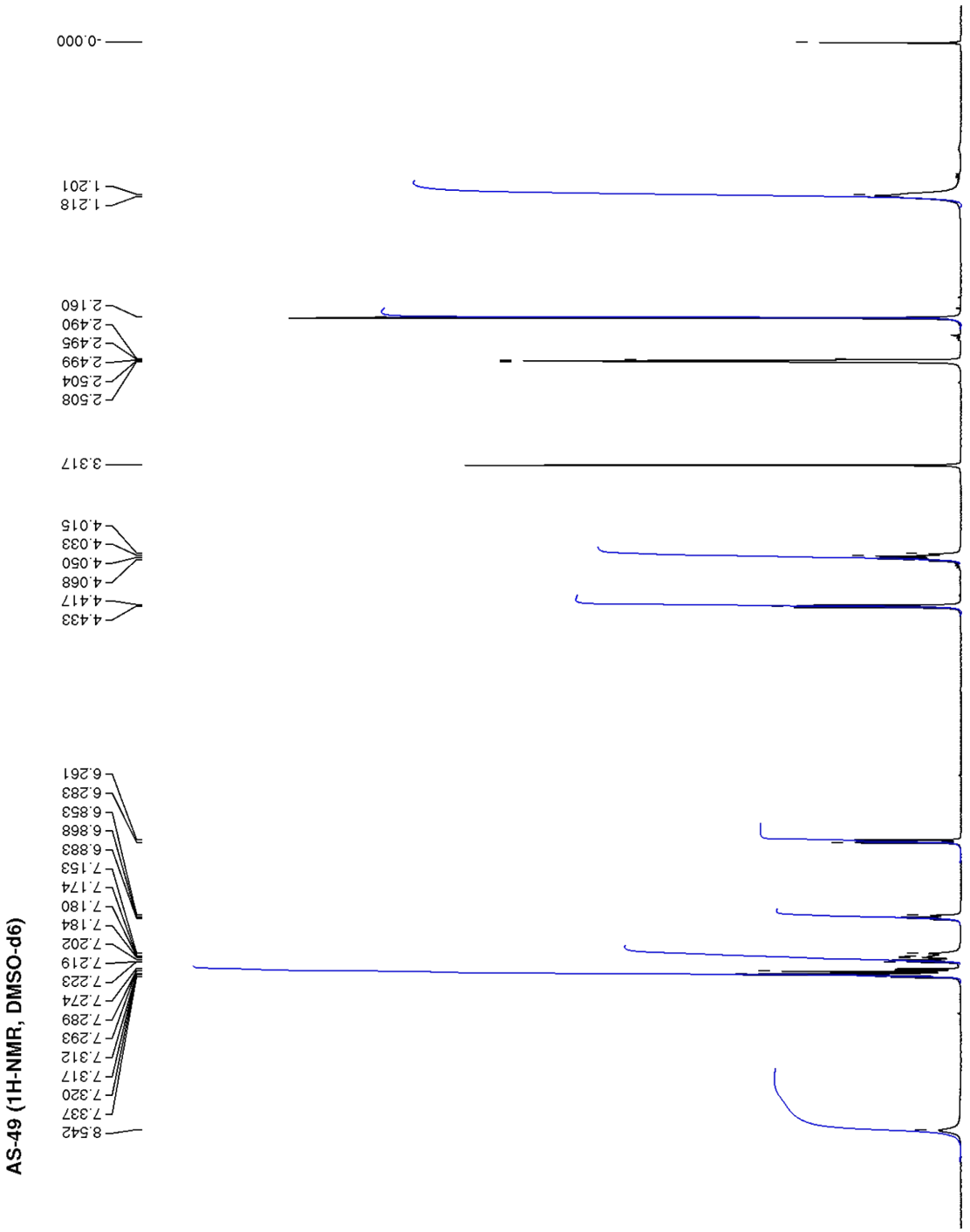

```
Current Data Parameters
NAME                 C. Bock
EXPNO                    267
PROCNO                     1

F2 - Acquisition Paramete
Date_                20170307
Time                    13.55
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       1024
DS                          4
SWH                24038.461 H
FIDRES              0.366798 H
AQ                  1.3631488 s
RG                       2050
DW                     20.800 u
DE                     10.00 u
TE                     298.2 K
D1                 2.00000000 s
D11                0.03000000 s
TD0                         1

======== CHANNEL f1 =====
NUC1                      13C
P1                     10.00 u
PL1                    -2.70 d
PL1W              62.67650986 W
SFO1              100.6228298 M

======== CHANNEL f2 =====
CPDPRG[2               waltz16
NUC2                       1H
PCPD2                  60.00 u
PL2                    -5.00 d
PL12                   10.78 d
PL13                   15.00 d
PL2W              30.18447304 W
PL12W              0.79759723 W
PL13W              0.30184472 W
SFO2              400.1316005 M

F2 - Processing parameters
SI                       32768
SF                100.6128164 M
WDW                         EM
SSB          0
```

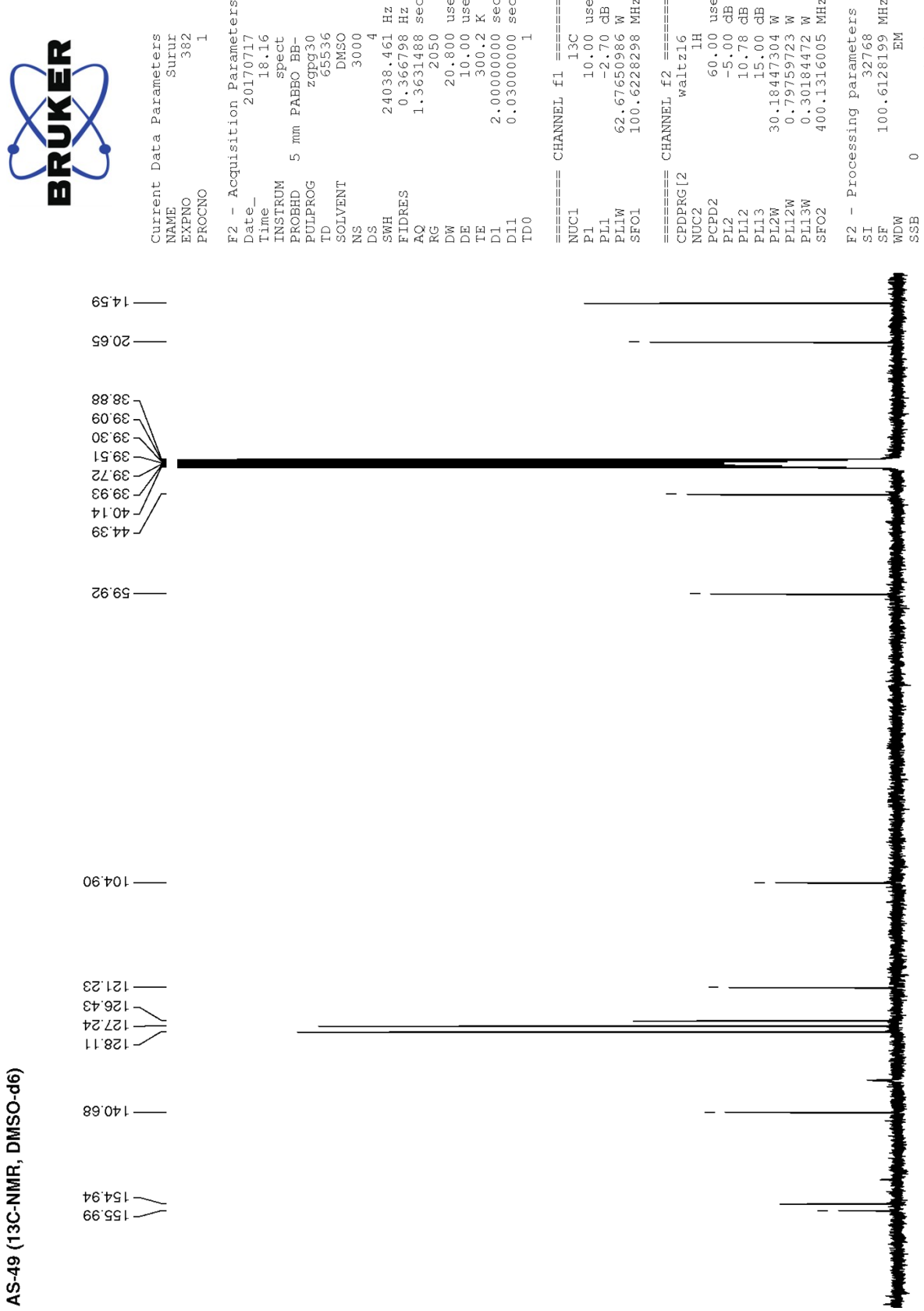
Ethyl {6-[(4-fluorobe o]-2-methylpyridin-3-yl}carbamate (**11a**)



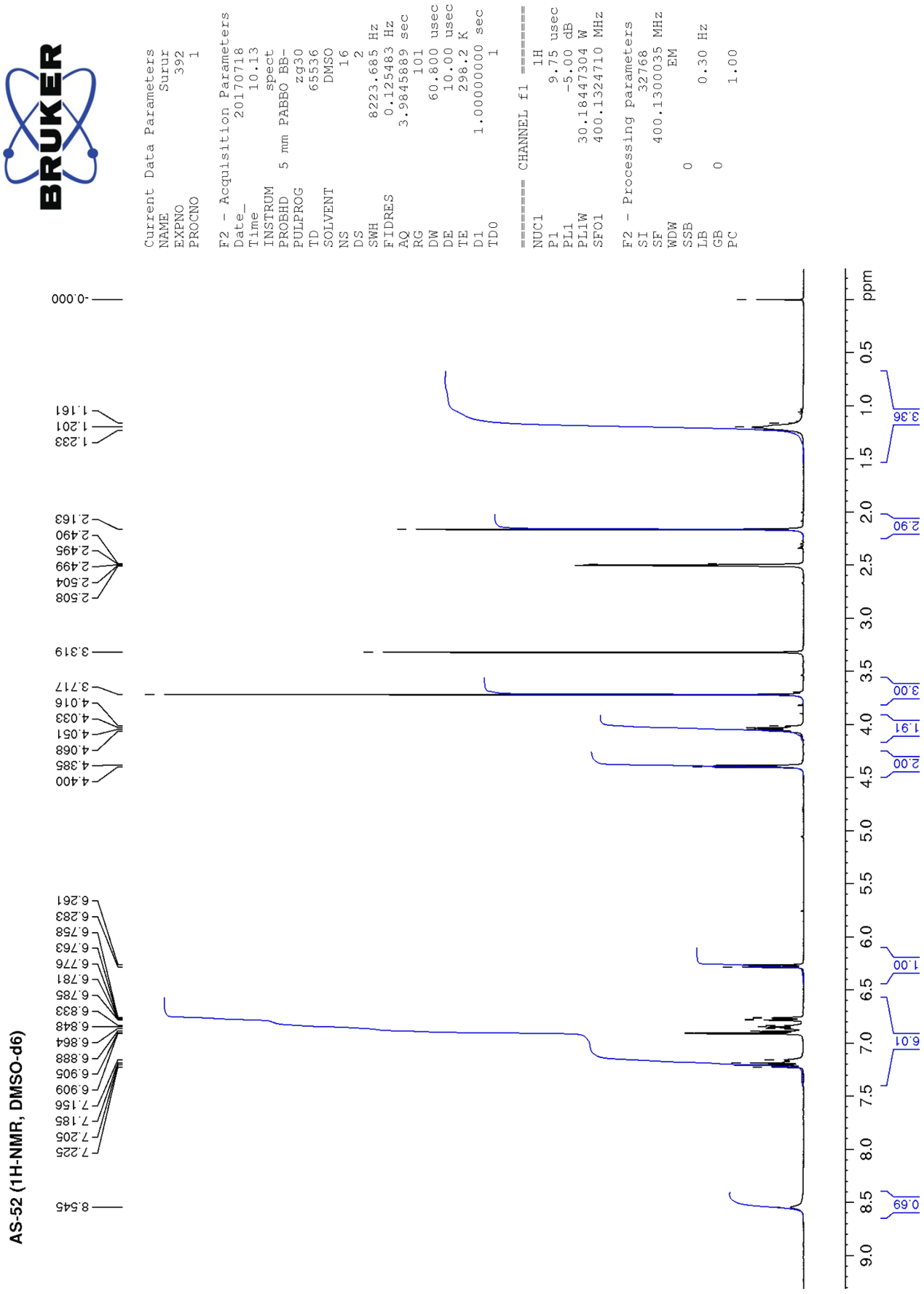

AS-44 (13C-NMR, DMSO-d6)
14.586
20.652
38.884
39.093
39.301
39.510
39.719
39.928
40.136
43.642
59.932
104.976
114.687
114.898
121.324
129.091
129.170
135.683
136.854
136.882
154.948
155.846
159.779
162.182
Current Data Parameters
NAME Surur
EXPNO 369
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170711
Time 19.39
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 4000
DS 4
SWH 24038.461
FIDRES 0.366798
AQ 1.3631488
RG 2050
DW 20.800
DE 10.00
TE 299.2
D1 2.00000000
D11 0.03000000
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00
PL1 -2.70
PL1W 62.67650986
SFO1 100.6228298
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00
PL2 -5.00
PL12 10.78
PL13 15.00
PL2W 30.18447304
PL12W 0.79759723
PL13W 0.30184472
SFO2 400.1316005
F2 - Processing parameters
SI 32768
SF 100.6128193
WDW EM

Ethyl [6-(benzylamir ıylpyridin-3-yl]carbamate (**11b**)

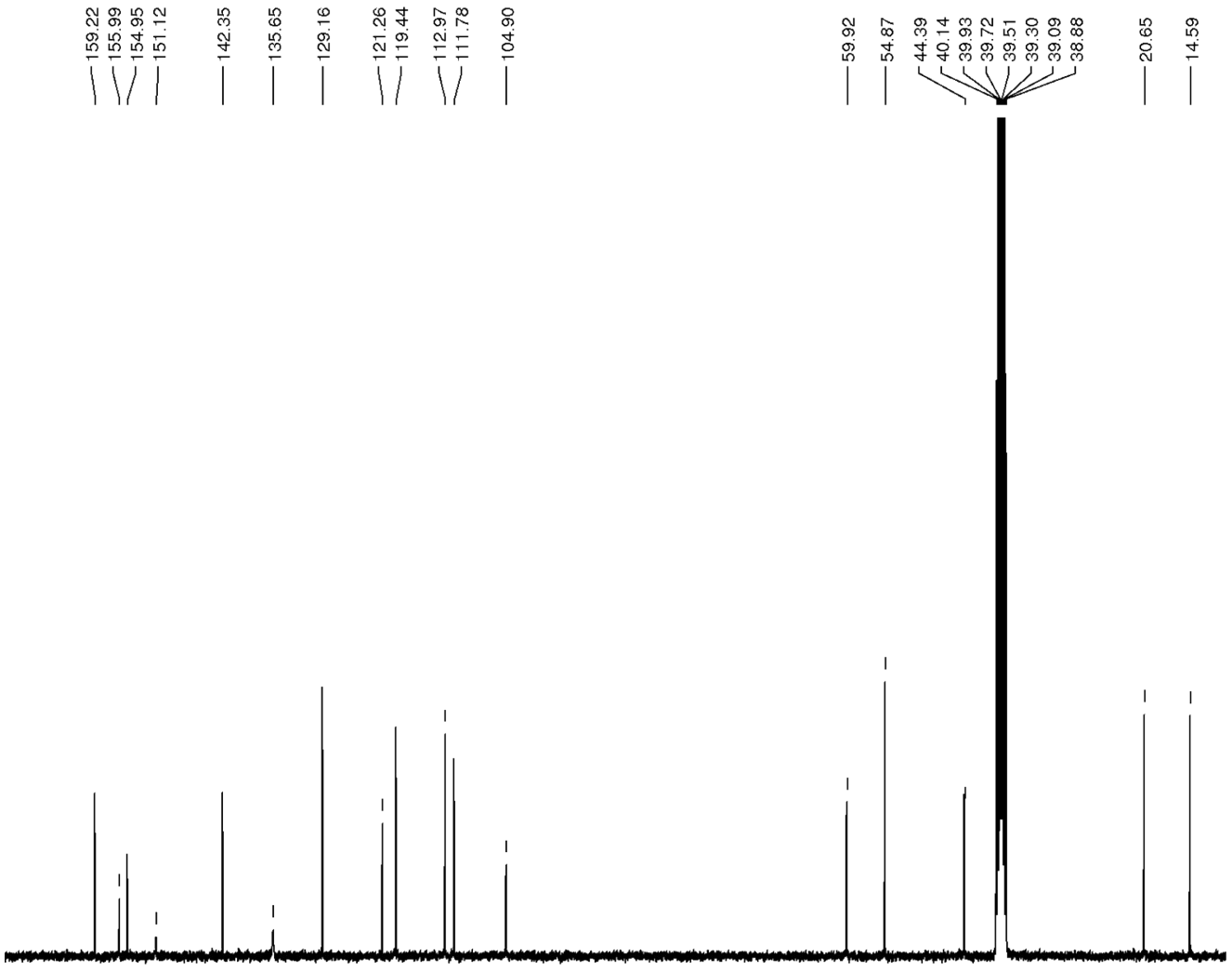



Current Data Parameters
NAME Surur
EXPNO 382
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170717
Time 18.16
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3000
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 2050
DW 20.800 use
DE 10.00 use
TE 300.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 use
PL1 -2.70 dB
PL1W 62.67650986 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00 use
PL2 -5.00 dB
PL12 10.78 dB
PL13 15.00 dB
PL2W 30.18447304 W
PL12W 0.79759723 W
PL13W 0.30184472 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128199 MHz
WDW EM
SSB 0
14.59
20.65
38.88
39.09
39.30
39.51
39.72
39.93
40.14
44.39
59.92
104.90
121.23
126.43
127.24
128.11
140.68
154.94
155.99
AS-49 (13C-NMR, DMSO-d6)

Ethyl {6-[(3-methoxybenzyl)amino]-2-methylpyridin-3-yl}carbamate (**11c**)



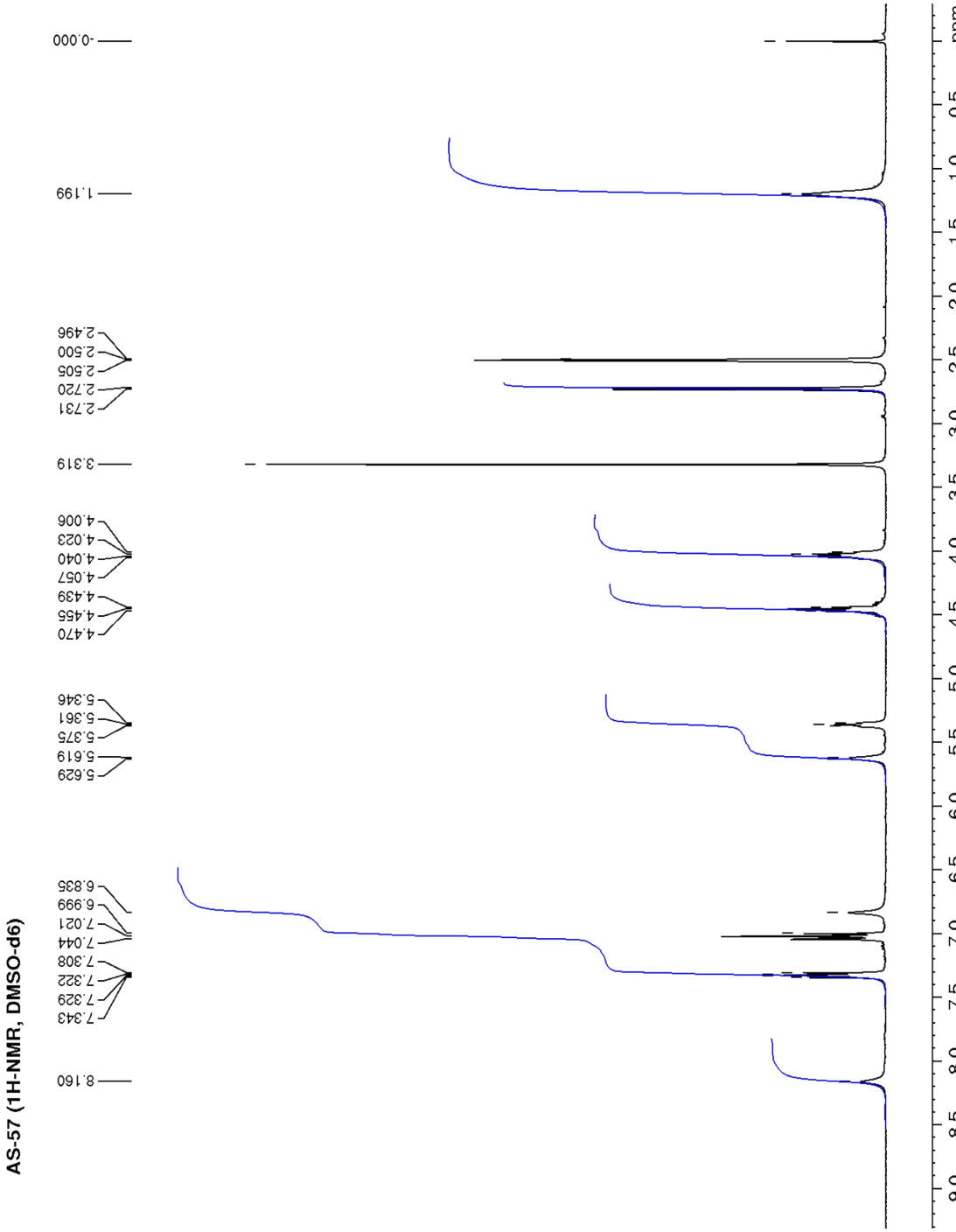
AS-52 (13C-NMR, DMSO-d6)



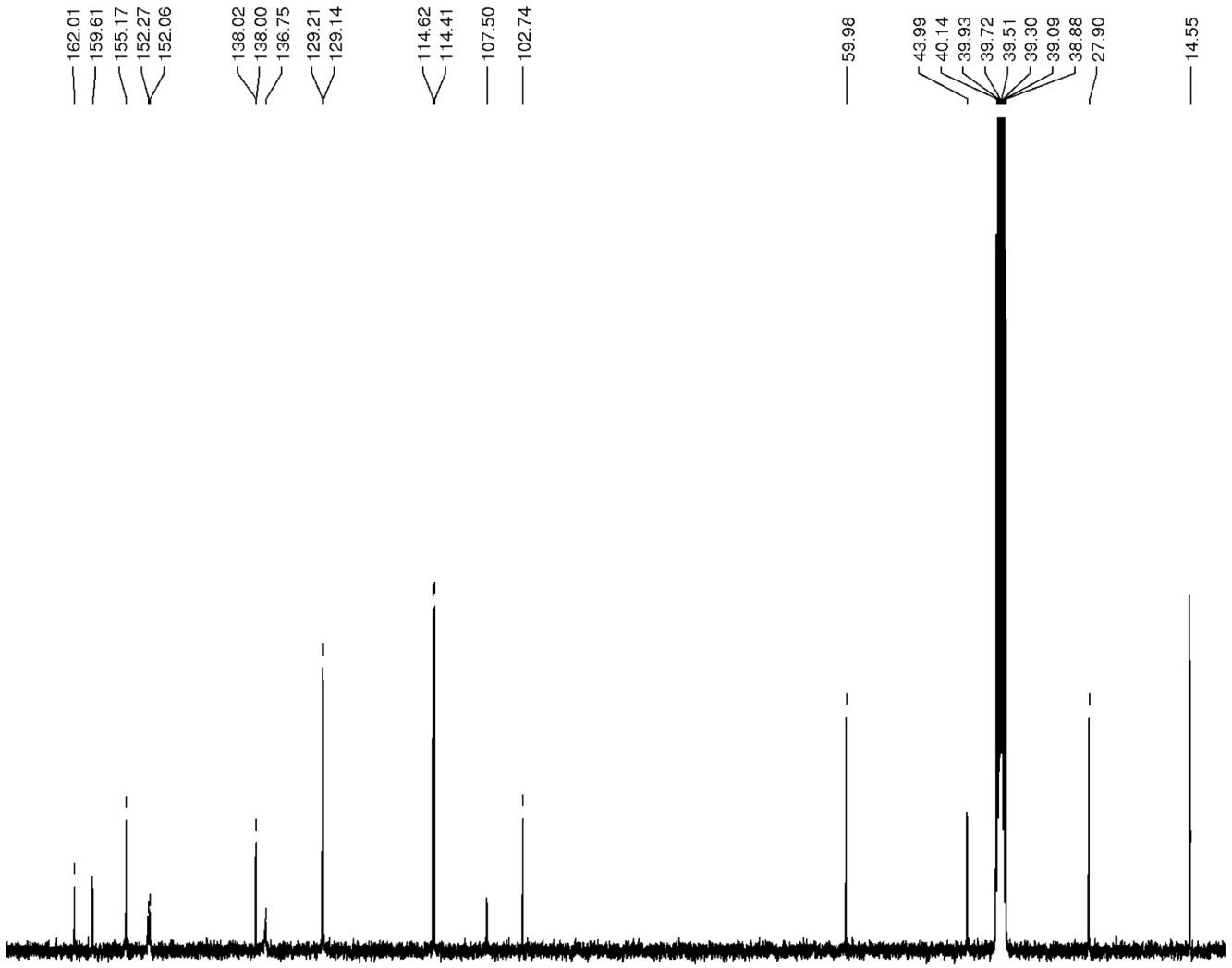
BRUKER

```
Current Data Parameters
NAME                 Surur
EXPNO                  394
PROCNO                   1

F2 - Acquisition Parameters
Date_             20170718
Time                 23.42
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                     4000
DS                        4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                     2050
DW                   20.800 use
DE                   10.00 use
TE                   299.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 =======
NUC1                    13C
P1                   10.00 use
PL1                  -2.70 dB
PL1W           62.67650986 W
SFO1           100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2            waltz16
NUC2                    1H
PCPD2                60.00 use
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF             100.6128194 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
```

Ethyl {6-[(4-fluorobenzyl)amino]-2-(methylamino)pyridine-3-yl}carbamate (**11d**)



AS-57 (13C-NMR, DMSO-d6)



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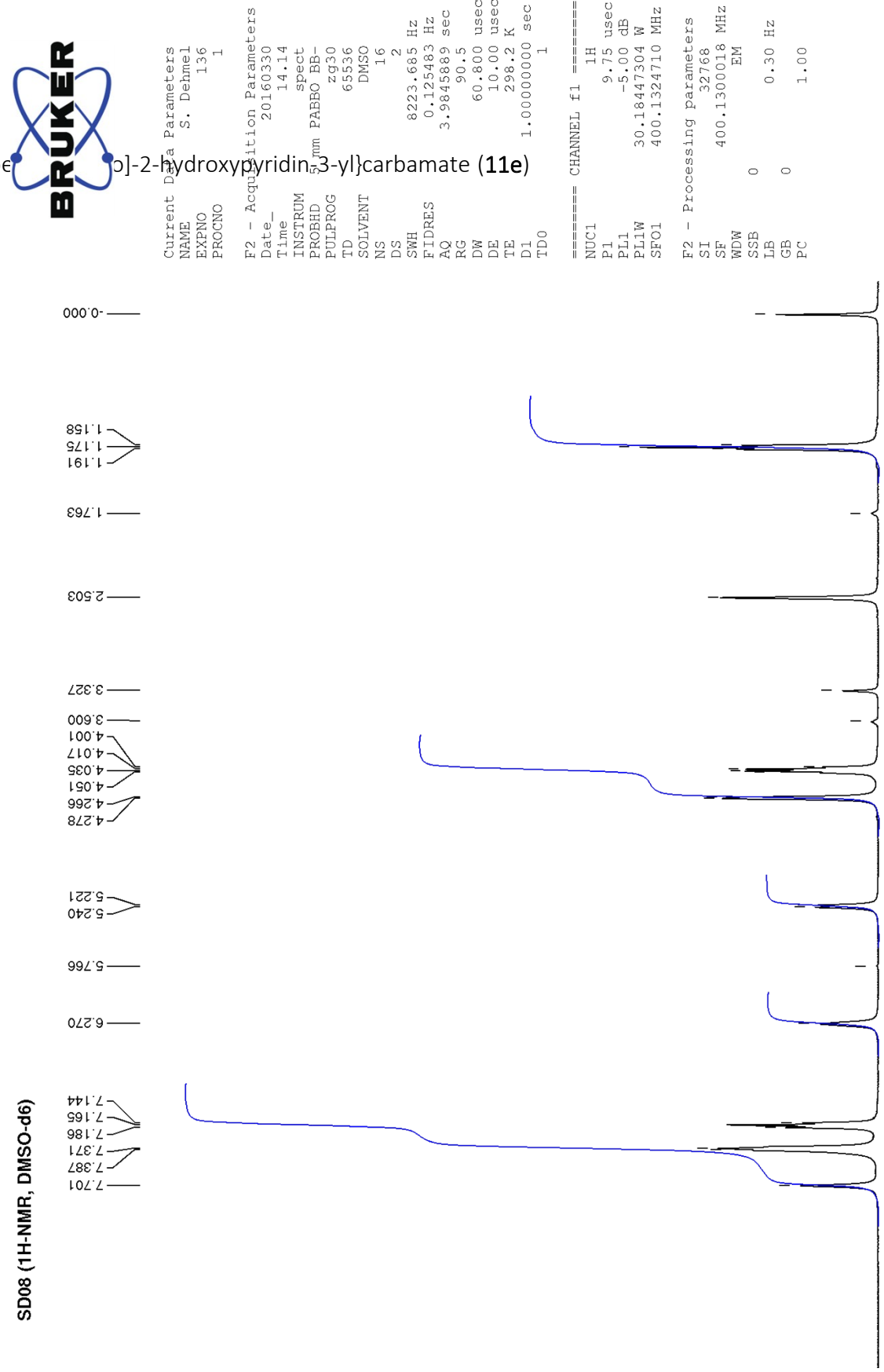
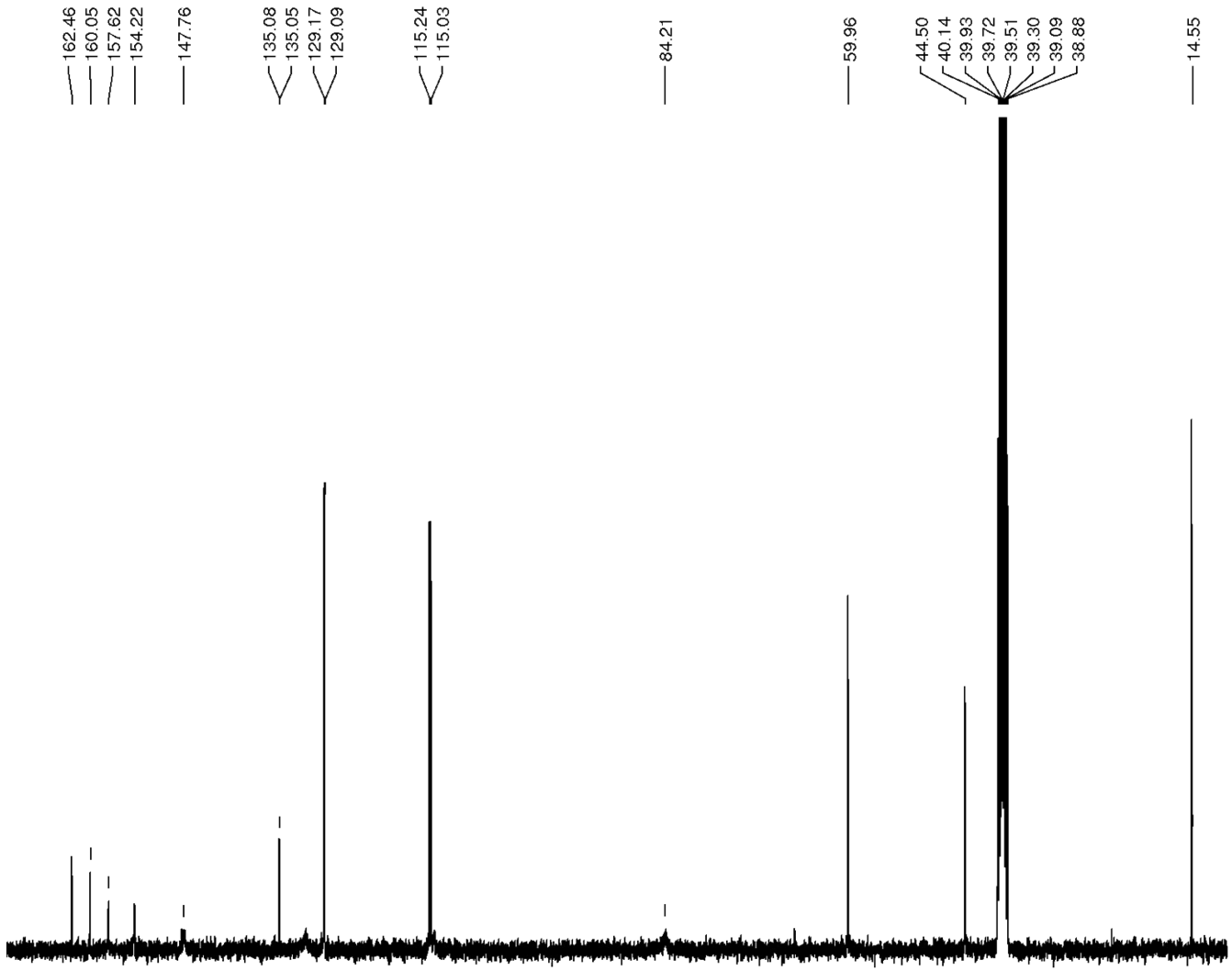
```
Current Data Parameters
NAME                  Surur
EXPNO                   460
PROCNO                    1

F2 - Acquisition Parameters
Date_              20170906
Time                 18.00
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                    3000
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                    2050
DW                  20.800 use
DE                  10.00 use
TE                  298.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 =======
NUC1                   13C
P1                  10.00 use
PL1                 -2.70 dB
PL1W           62.67650986 W
SFO1          100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2           waltz16
NUC2                   1H
PCPD2                60.00 use
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF            100.6128182 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
```

Ethyl-{6-[(4-fluorbe[illegible]c]-2-hydroxypyridin-3-yl}carbamate (**11e**)

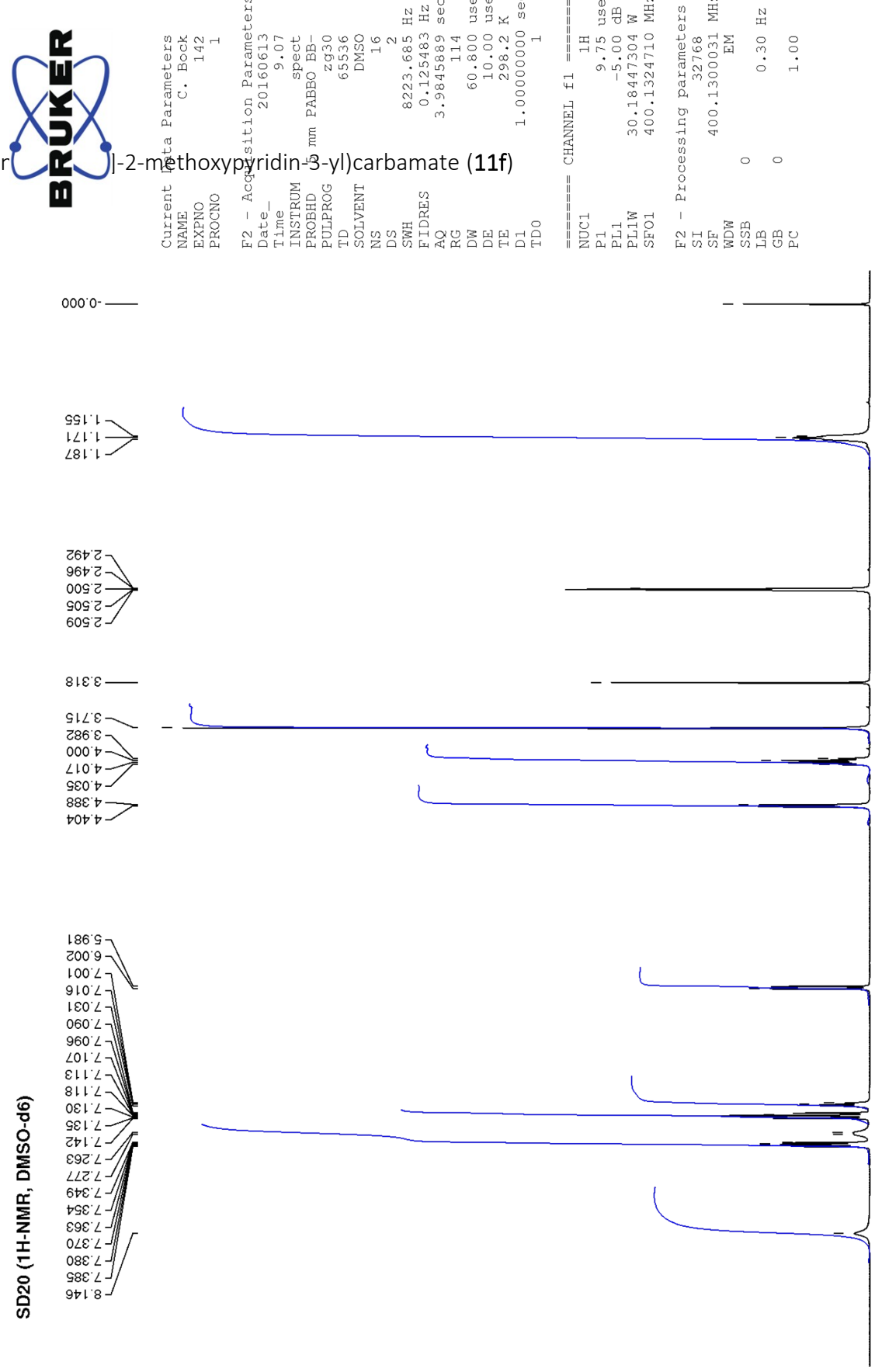


SD08 (13C-NMR, DMSO-d6)

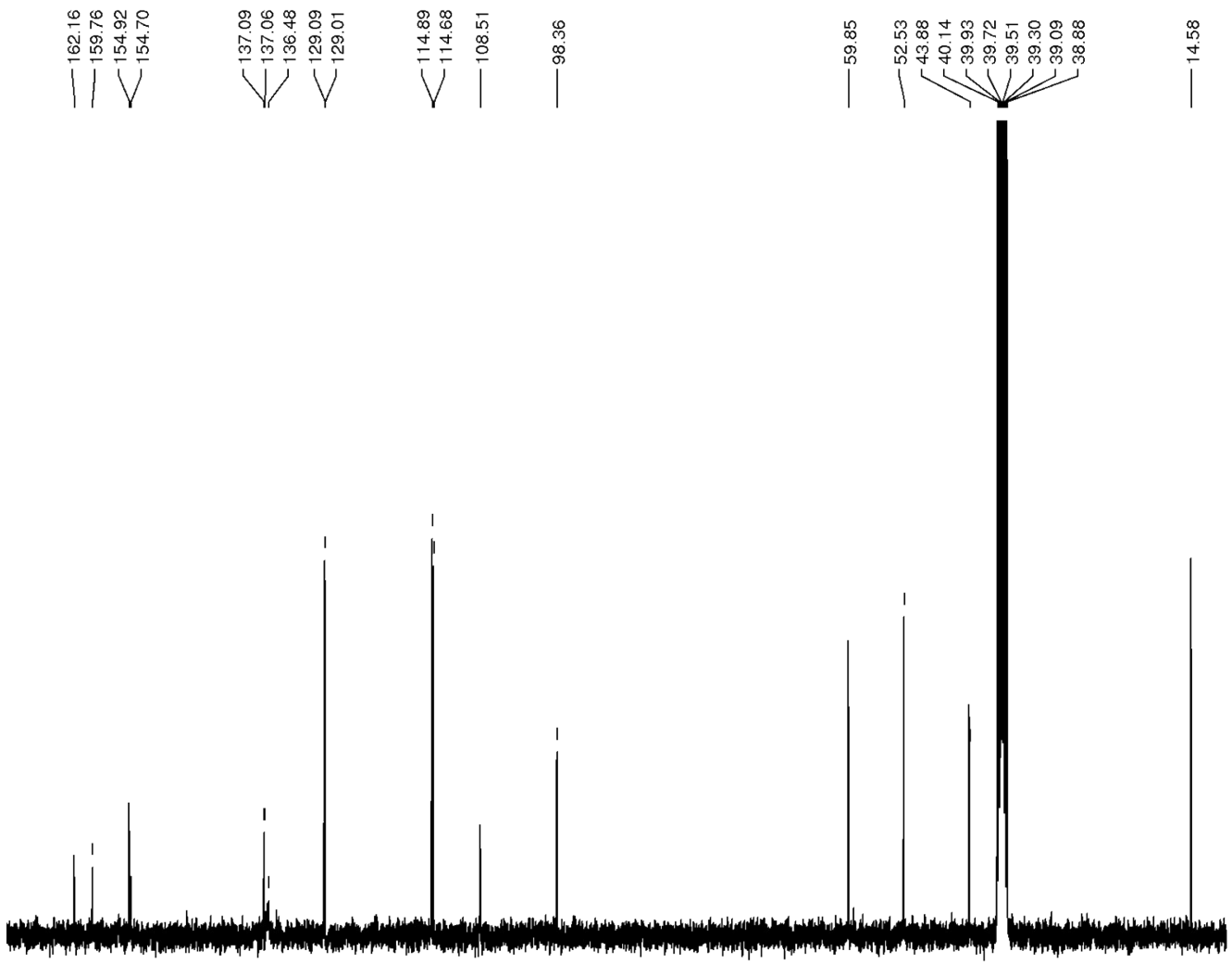



```
Current Data Parameters
NAME                 S. Dehmel
EXPNO                      137
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20160331
Time                      9.22
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                       65536
SOLVENT                    DMSO
NS                         1024
DS                            4
SWH                  24038.461 Hz
FIDRES                0.366798 Hz
AQ                    1.3631488 se
RG                         2050
DW                       20.800 us
DE                       10.00 us
TE                       298.2 K
D1                  2.00000000 se
D11                 0.03000000 se
TD0                          1

======== CHANNEL f1 ======
NUC1                       13C
P1                       10.00 us
PL1                      -2.70 dB
PL1W               62.67650986 W
SFO1              100.6228298 MH

======== CHANNEL f2 ======
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                    60.00 us
PL2                      -5.00 dB
PL12                     10.78 dB
PL13                     15.00 dB
PL2W               30.18447304 W
PL12W               0.79759723 W
PL13W               0.30184472 W
SFO2              400.1316005 MH

F2 - Processing parameters
SI                       32768
SF                100.6128168 MH
WDW                         EM
SSB          0
```

Ethyl-{6-[(4-fluorober]-2-methoxypyridin-3-yl)carbamate (**11f**)



SD20C (13C-NMR, DMSO-d6)



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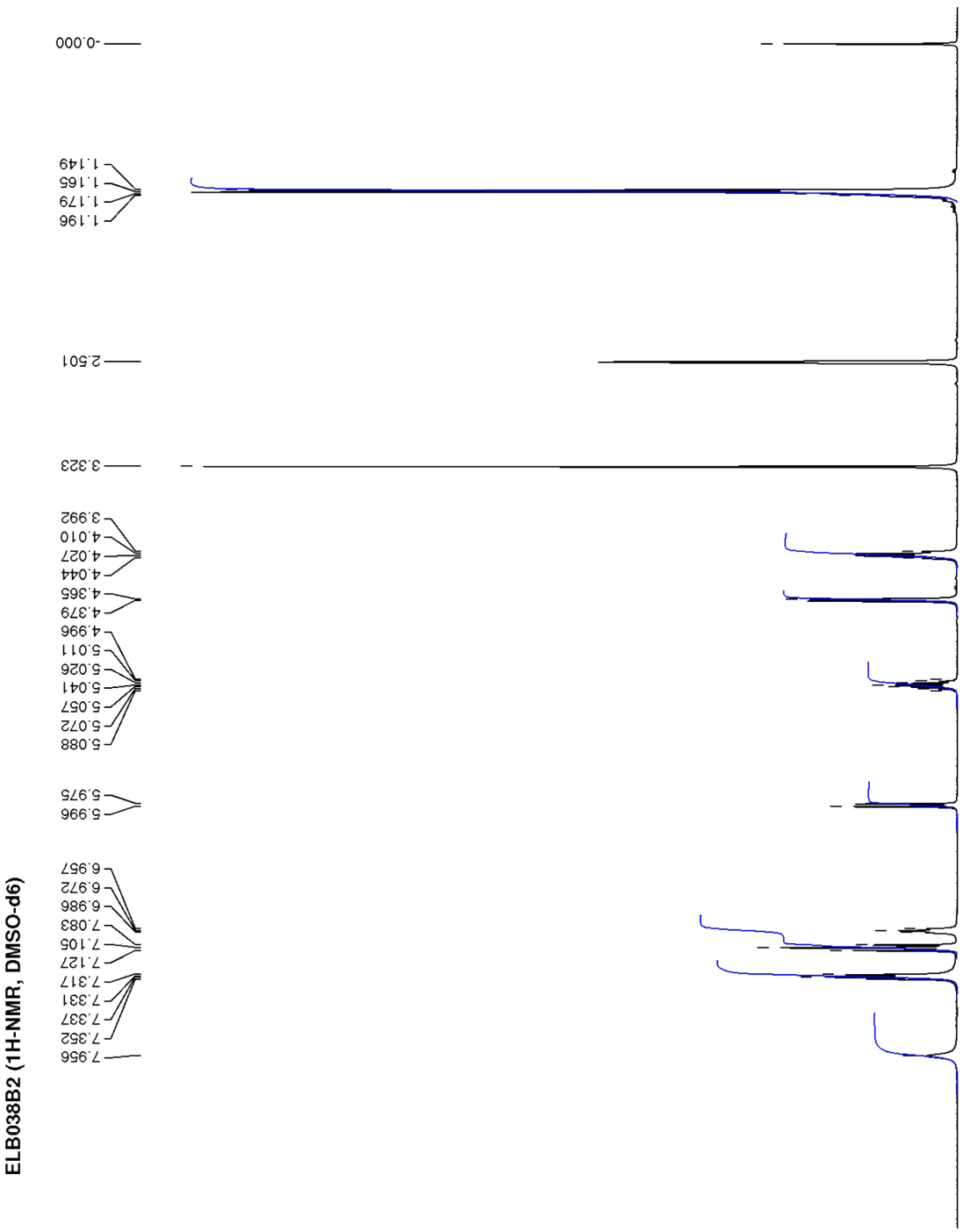
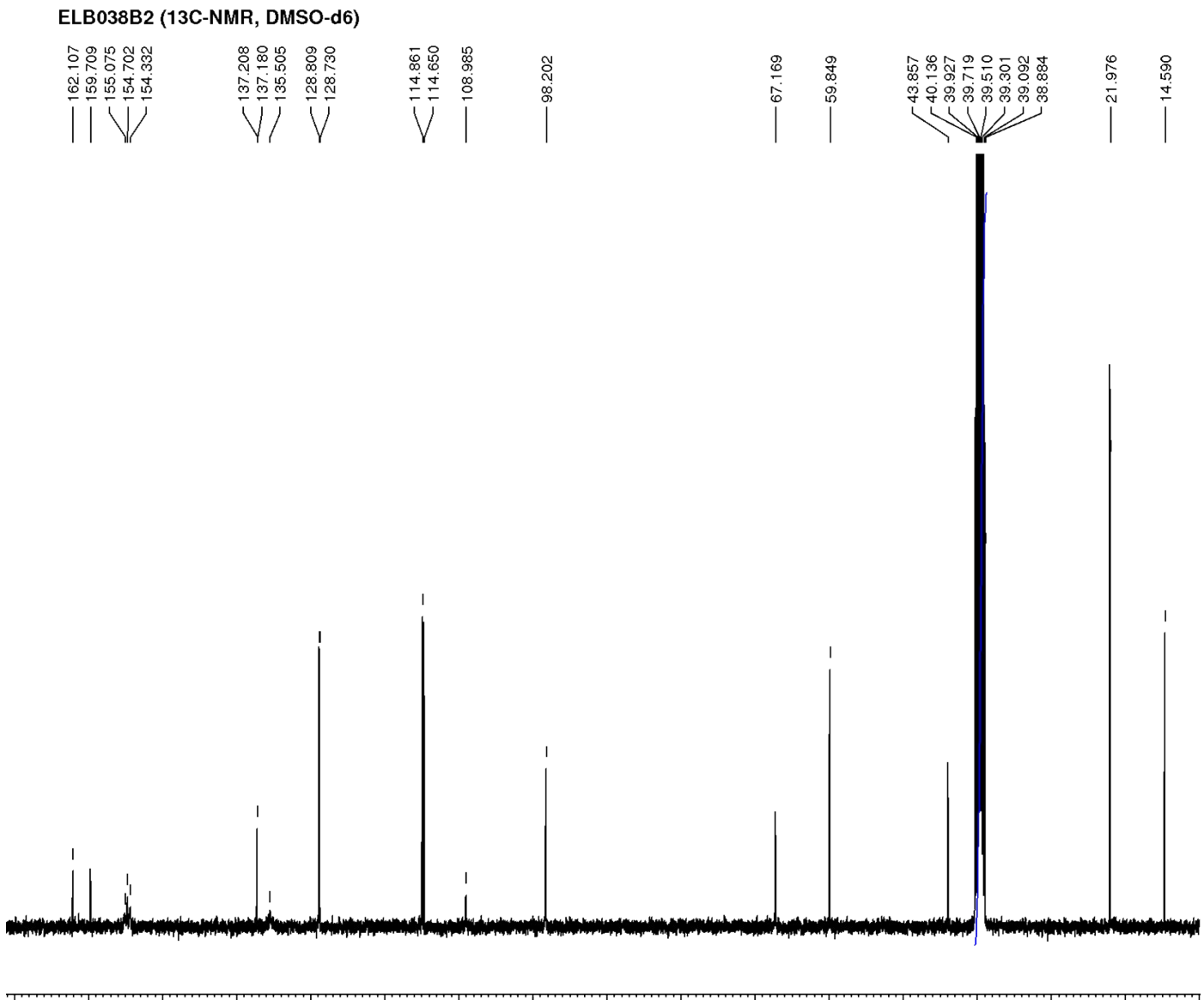
```
Current Data Parameters
NAME                  C. Bock
EXPNO                     144
PROCNO                      1

F2 - Acquisition Parameters
Date_              20160613
Time                   12.03
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                     65536
SOLVENT                DMSO
NS                      1024
DS                         4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                1.3631488 sec
RG                      2050
DW                    20.800 use
DE                    10.00 use
TE                    299.2 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                         1

======== CHANNEL f1 =======
NUC1                      13C
P1                    10.00 use
PL1                   -2.70 dB
PL1W            62.67650986 W
SFO1           100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2              waltz16
NUC2                      1H
PCPD2                 60.00 use
PL2                   -5.00 dB
PL12                  10.78 dB
PL13                  15.00 dB
PL2W            30.18447304 W
PL12W            0.79759723 W
PL13W            0.30184472 W
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF             100.6128190 MHz
WDW                          EM
SSB          0
LB                        1.00 Hz
```

Ethyl-{6-[(4-fluorber]-2-isopropoxypyridin-3-yl}carbamate (**11g**)

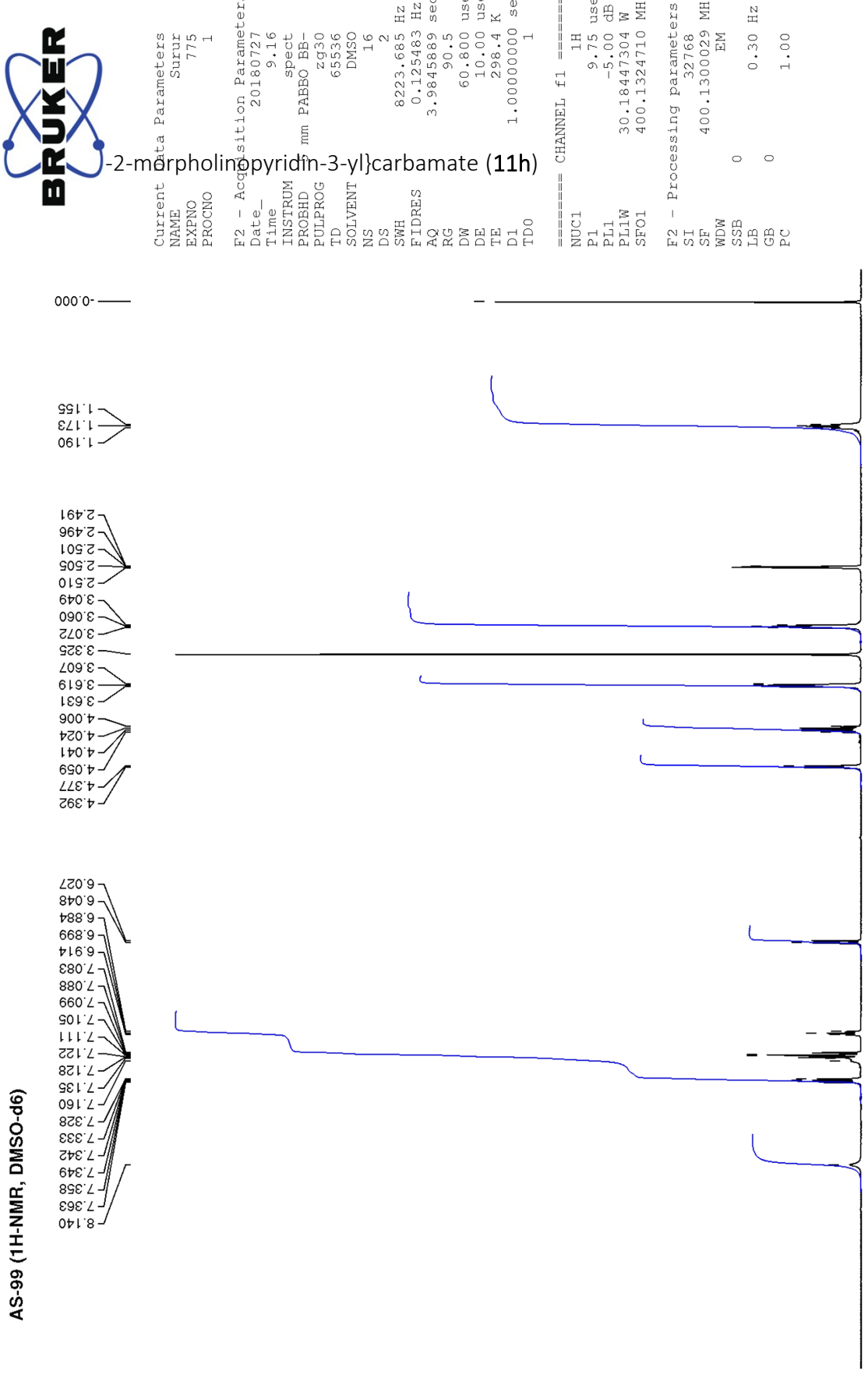


ELB038B2 (13C-NMR, DMSO-d6)

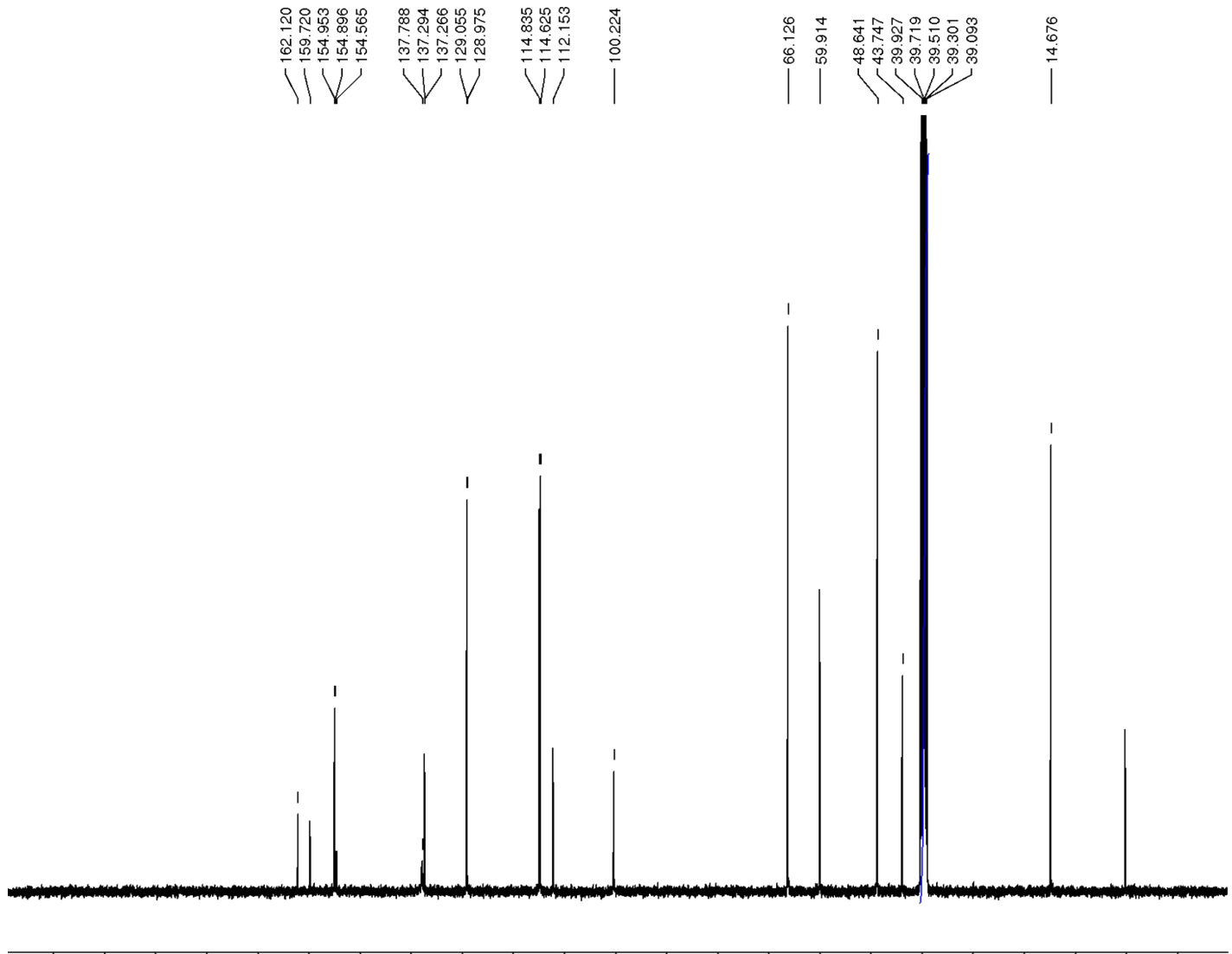



```
Current Data Parameters
NAME                 C. Bock
EXPNO                    621
PROCNO                     1

F2 - Acquisition Parameter
Date_             20180921
Time                 12.51
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                      1500
DS                         4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 se
RG                      2050
DW                   20.800 us
DE                   10.00 us
TE                   299.3 K
D1               2.00000000 se
D11              0.03000000 se
TD0                        1

======== CHANNEL f1 ======
NUC1                    13C
P1                   10.00 us
PL1                  -2.70 dB
PL1W           62.67650986 W
SFO1          100.6228298 MH

======== CHANNEL f2 ======
CPDPRG[2            waltz16
NUC2                    1H
PCPD2                60.00 us
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2          400.1316005 MH

F2 - Processing parameters
SI                      32768
SF            100.6128186 MH
WDW                      EM
```

Ethyl {6-[(4-fluroben -2-morpholinopyridin-3-yl}carbamate (**11h**)

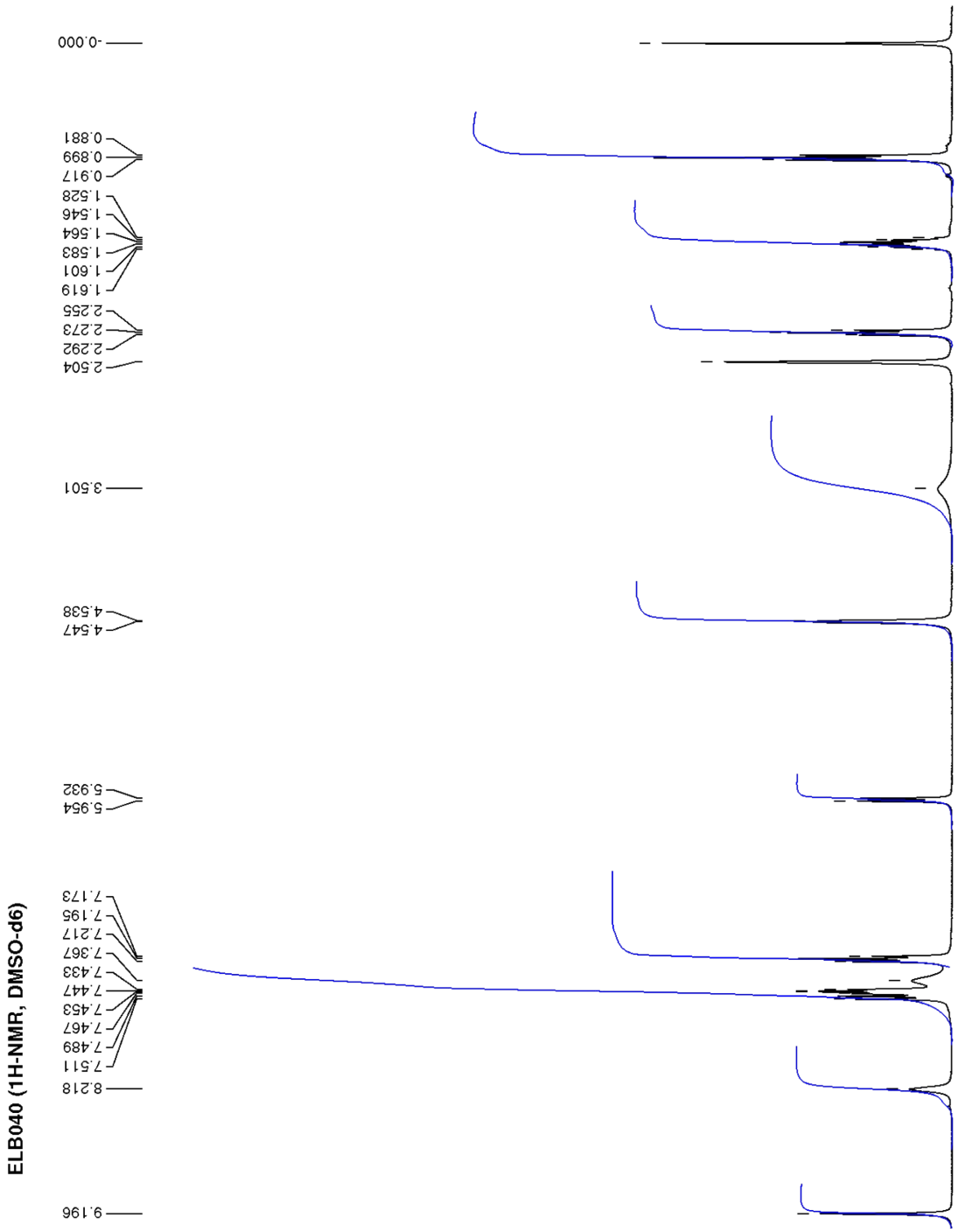


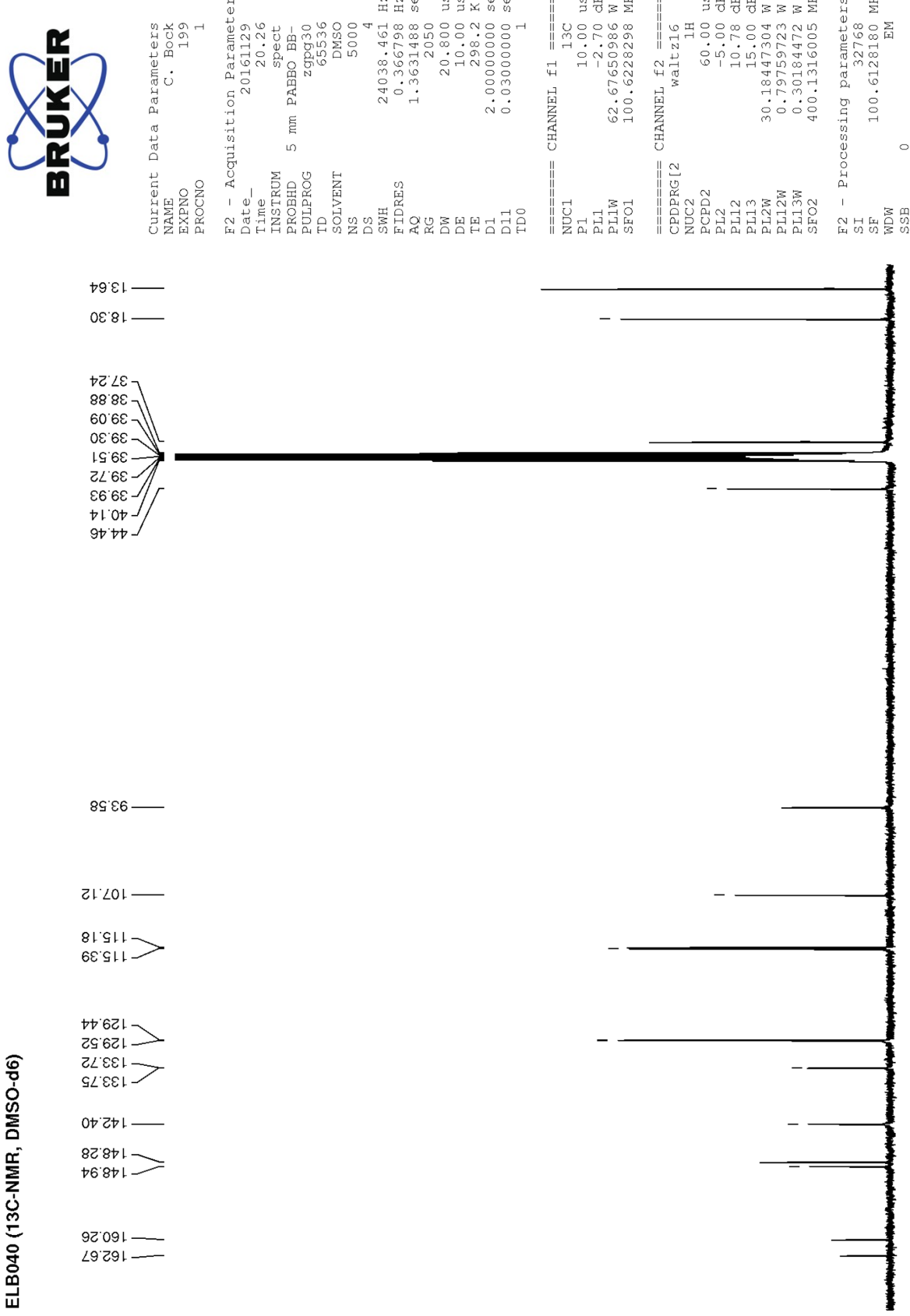
AS-99 (13C-NMR, DMSO-d6)



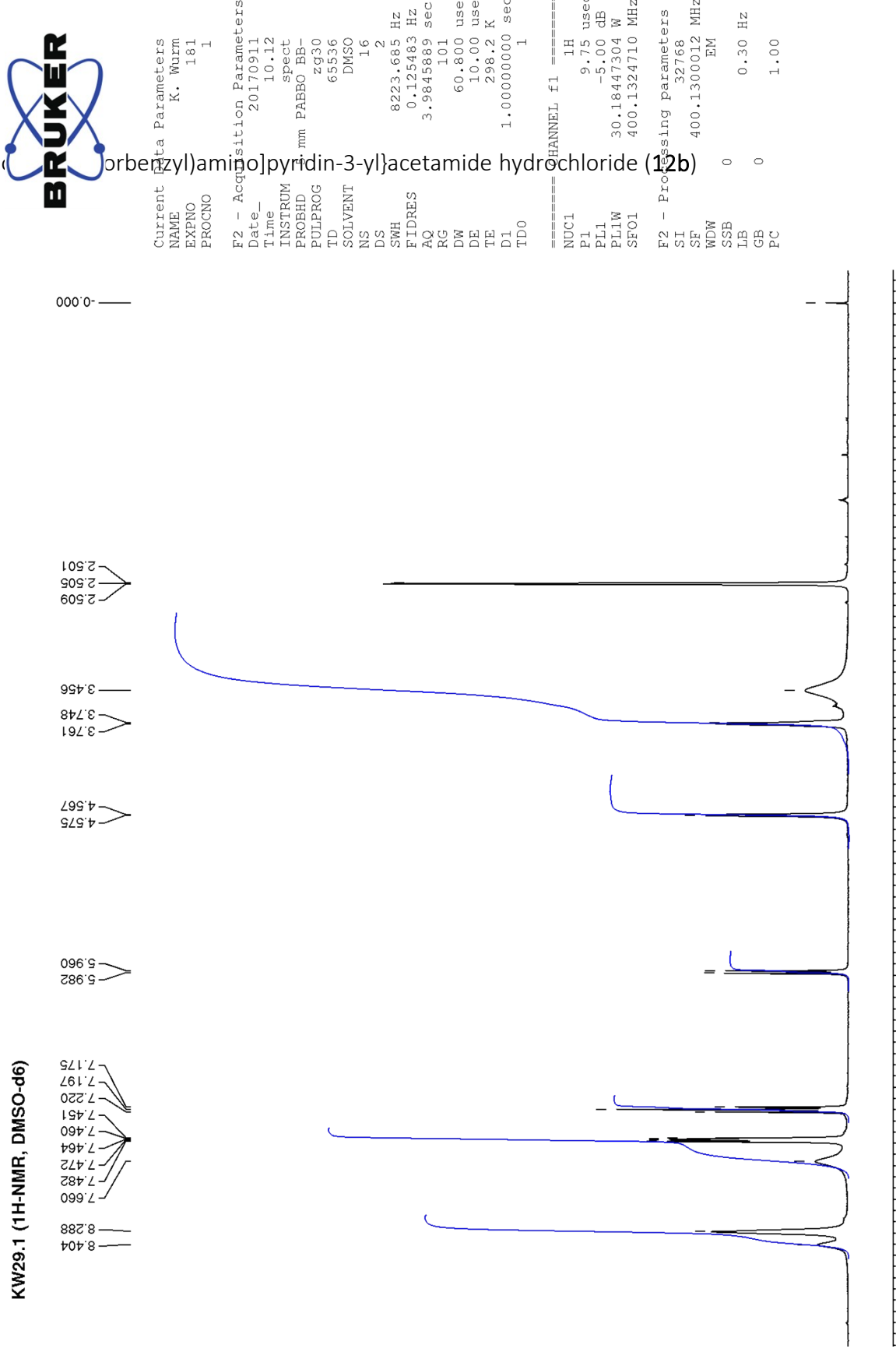

```
Current Data Parameters
NAME                  Surur
EXPNO                   776
PROCNO                    1

F2 - Acquisition Paramet
Date_              20180727
Time                  20.11
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     6000
DS                        4
SWH               24038.461
FIDRES             0.366798
AQ                 1.3631488
RG                      2050
DW                    20.800
DE                    10.00
TE                    299.3
D1              2.00000000
D11             0.03000000
TD0                       1

======== CHANNEL f1 ====
NUC1                    13C
P1                    10.00
PL1                   -2.70
PL1W          62.67650986
SFO1          100.6228298

======== CHANNEL f2 ====
CPDPRG[2           waltz16
NUC2                    1H
PCPD2                 60.00
PL2                   -5.00
PL12                  10.78
PL13                  15.00
PL2W          30.18447304
PL12W          0.79759723
PL13W          0.30184472
SFO2          400.1316005

F2 - Processing paramete
SI                    32768
SF            100.6128188
WDW                      EM
```

N-{2-Amino-6-[(4-flu amino]pyridin-3-yl}butyramide hydrochloride (**12a**)

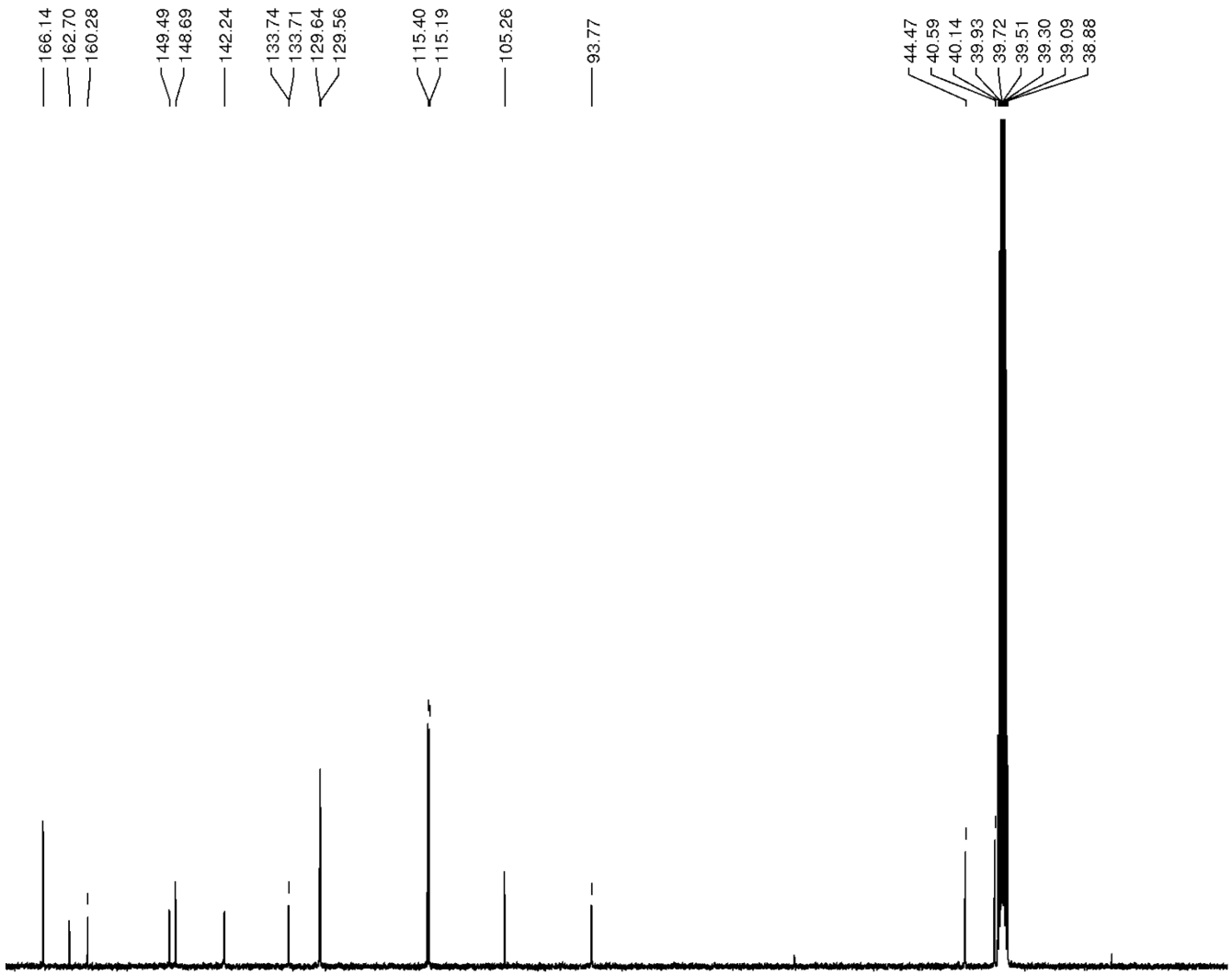



Current Data Parameters
NAME C. Bock
EXPNO 199
PROCNO 1
F2 - Acquisition Parameter
Date_ 20161129
Time_ 20.26
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 5000
DS 4
SWH 24038.461 H
FIDRES 0.366798 H
AQ 1.3631488 s
RG 2050
DW 20.800 u
DE 10.00 u
TE 298.2 K
D1 2.00000000 s
D11 0.03000000 s
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 u
PL1 -2.70 d
PL1W 62.67650986 W
SFO1 100.6228298 M
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00 u
PL2 -5.00 d
PL12 10.78 d
PL13 15.00 d
PL2W 30.18447304 W
PL12W 0.79759723 W
PL13W 0.30184472 W
SFO2 400.1316005 M
F2 - Processing parameters
SI 32768
SF 100.6128180 M
WDW EM
SSB 0
13.64
18.30
37.24
38.88
39.09
39.30
39.51
39.72
39.93
40.14
44.46
93.58
107.12
115.18
115.39
129.44
129.52
133.72
133.75
142.40
148.28
148.94
160.26
162.67
ELB040 (13C-NMR, DMSO-d6)

2-Amino-*N*-{2-amino[(4-chlorobenzyl)amino]pyridin-3-yl}acetamide hydrochloride (**12b**)

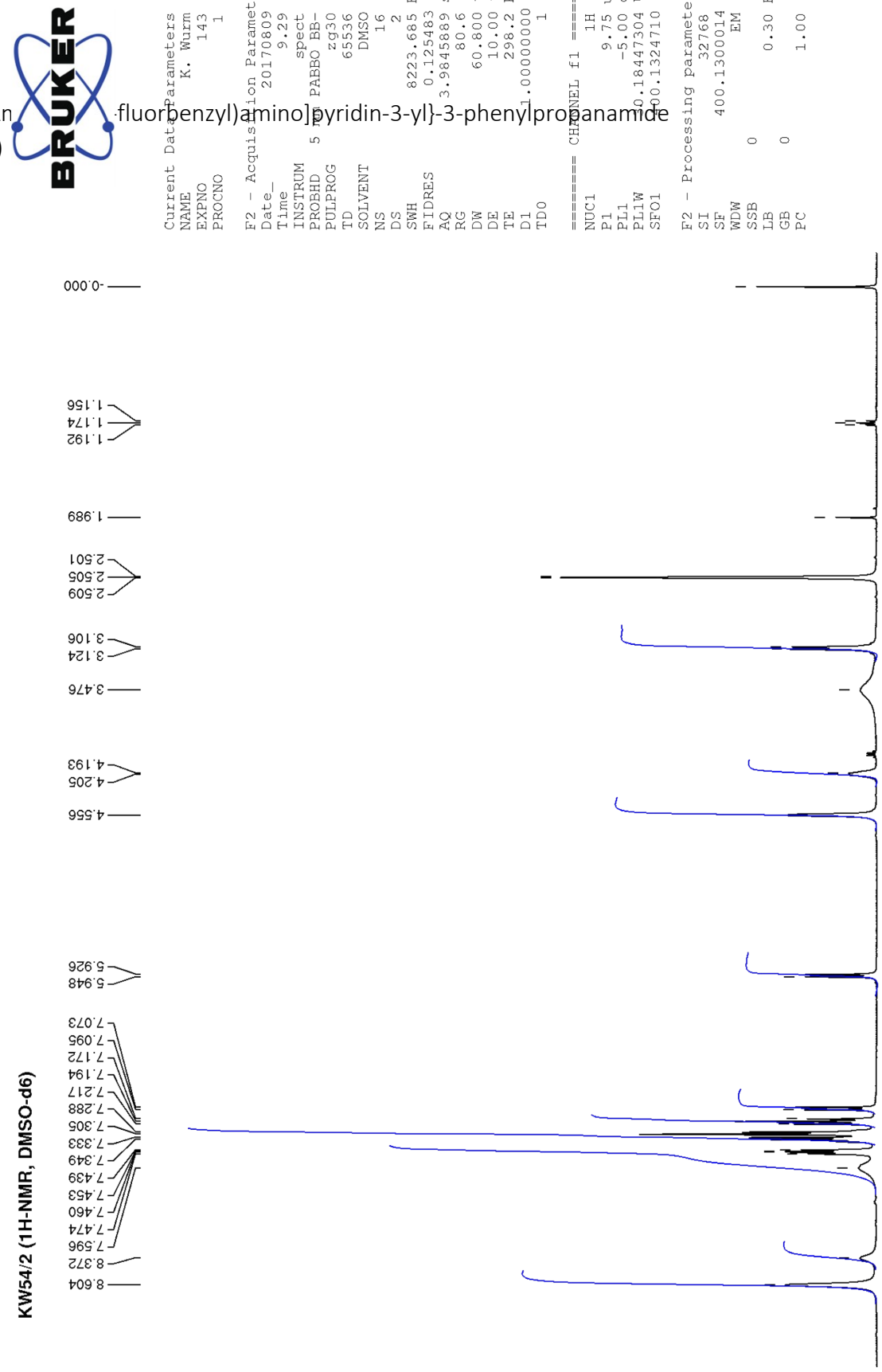


KW29.1 (13C-NMR, DMSO-d6)

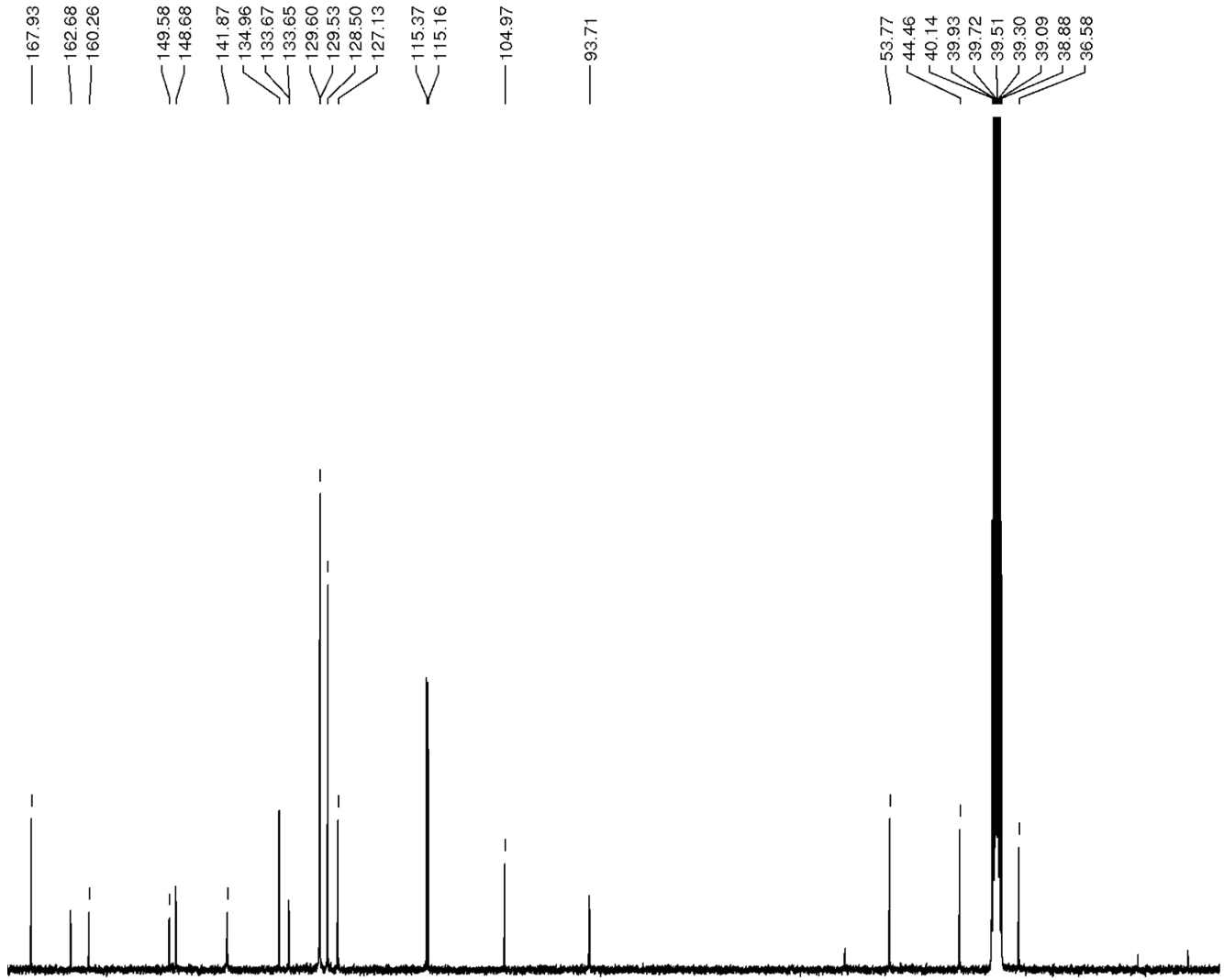



```
Current Data Parameters
NAME                 K. Wurm
EXPNO                    183
PROCNO                     1

F2 - Acquisition Parameters
Date_              20170911
Time                  22.16
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     2000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                1.3631488 sec
RG                     2050
DW                   20.800 use
DE                   10.00 use
TE                   298.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 =======
NUC1                    13C
P1                   10.00 use
PL1                  -2.70 dB
PL1W           62.67650986 W
SFO1          100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2           waltz16
NUC2                    1H
PCPD2                60.00 use
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF            100.6128156 MHz
WDW                      EM
SSB       0
```

(*R*)-2-Amino-*N*-{2-An[illegible]fluorbenzyl)amino]pyridin-3-yl}-3-phenylpropanamide hydrochloride (**12c**)

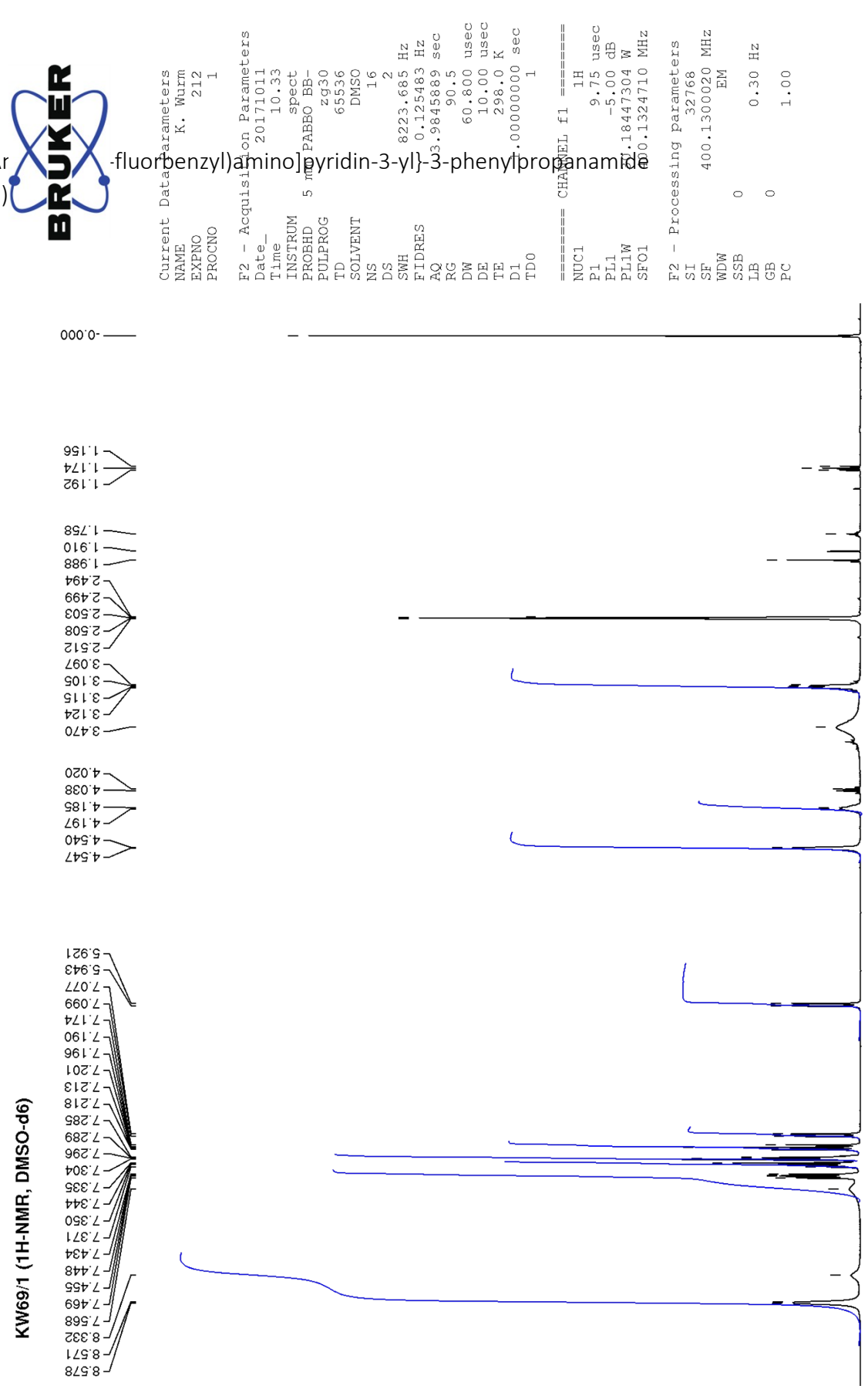


KW54/2 (DEPT 135, DMSO-d6)

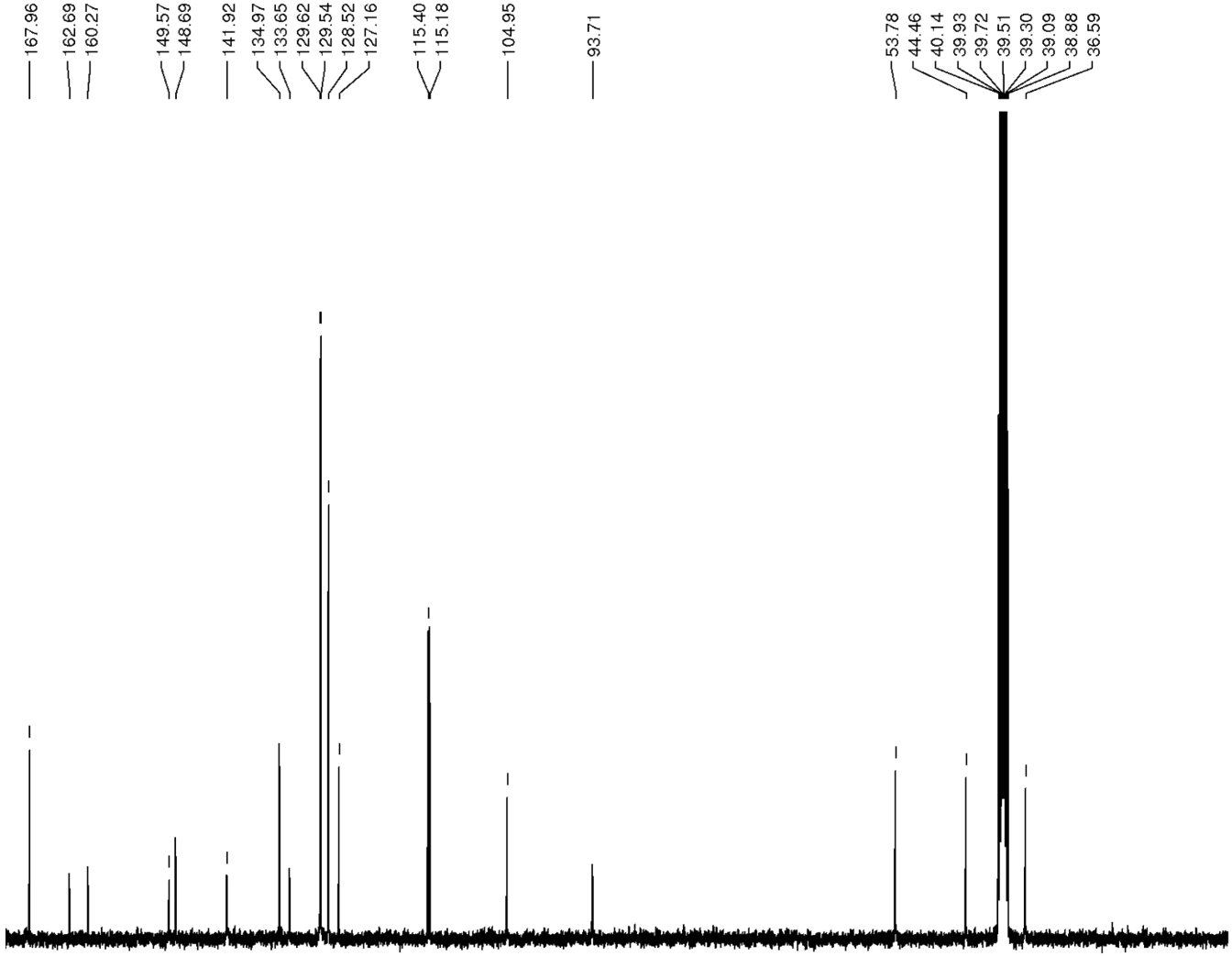



```
Current Data Parameters
NAME                  K. Wurm
EXPNO                     150
PROCNO                      1

F2 - Acquisition Parameters
Date_                20170809
Time                    20.56
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       3000
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       2050
DW                     20.800 use
DE                     10.00 use
TE                     300.2 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 use
PL1                    -2.70 dB
PL1W            62.67650986 W
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                      1H
PCPD2                  60.00 use
PL2                    -5.00 dB
PL12                   10.78 dB
PL13                   15.00 dB
PL2W            30.18447304 W
PL12W            0.79759723 W
PL13W            0.30184472 W
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                      32768
SF             100.6128186 MHz
WDW                        EM
SSB          0
```

(*S*)-2-Amino-*N*-{2-Ar -fluorbenzyl)amino]pyridin-3-yl}-3-phenylpropanamide hydrochloride (**12d**)



KW69 (13C-NMR, DMSO-d6)



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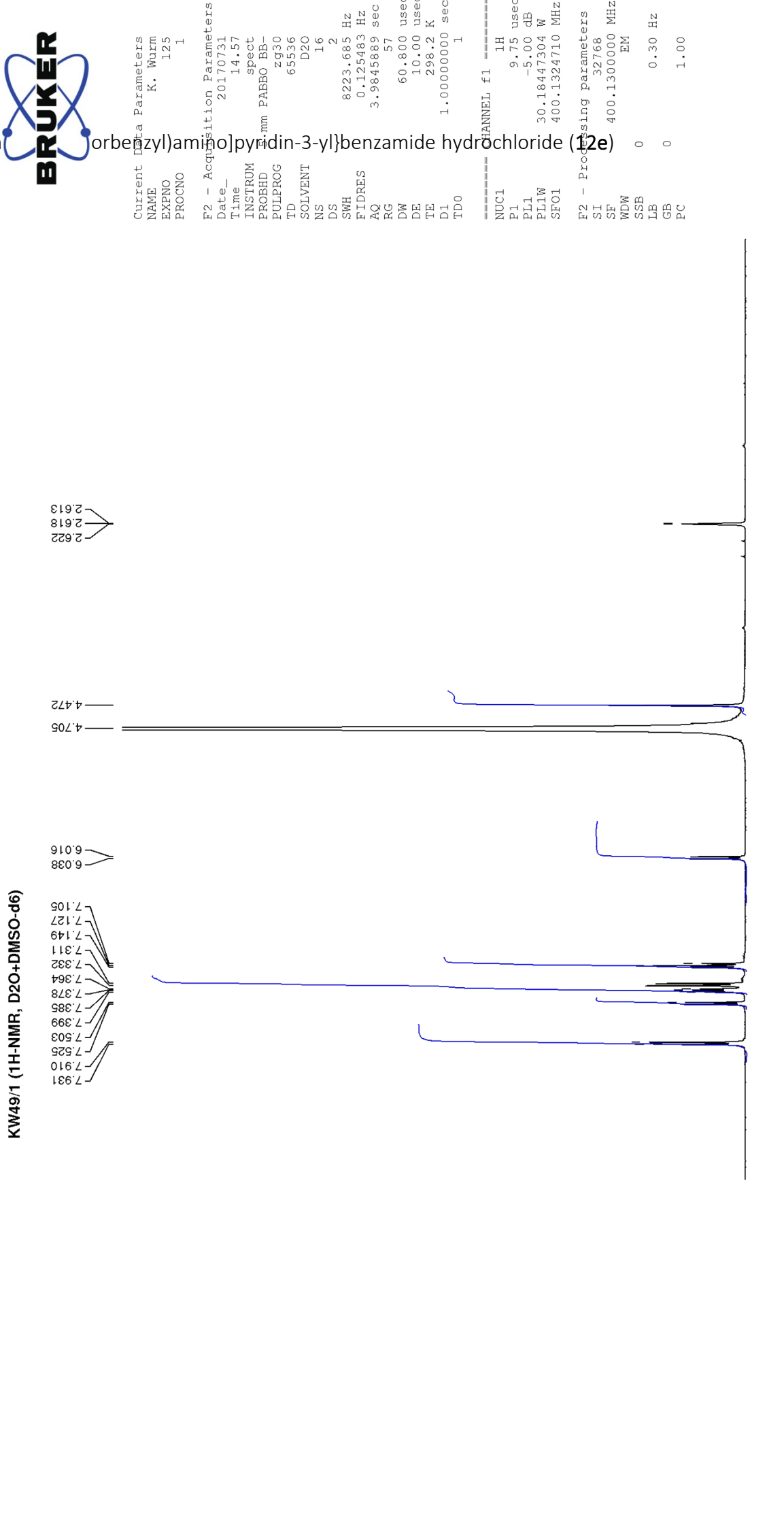
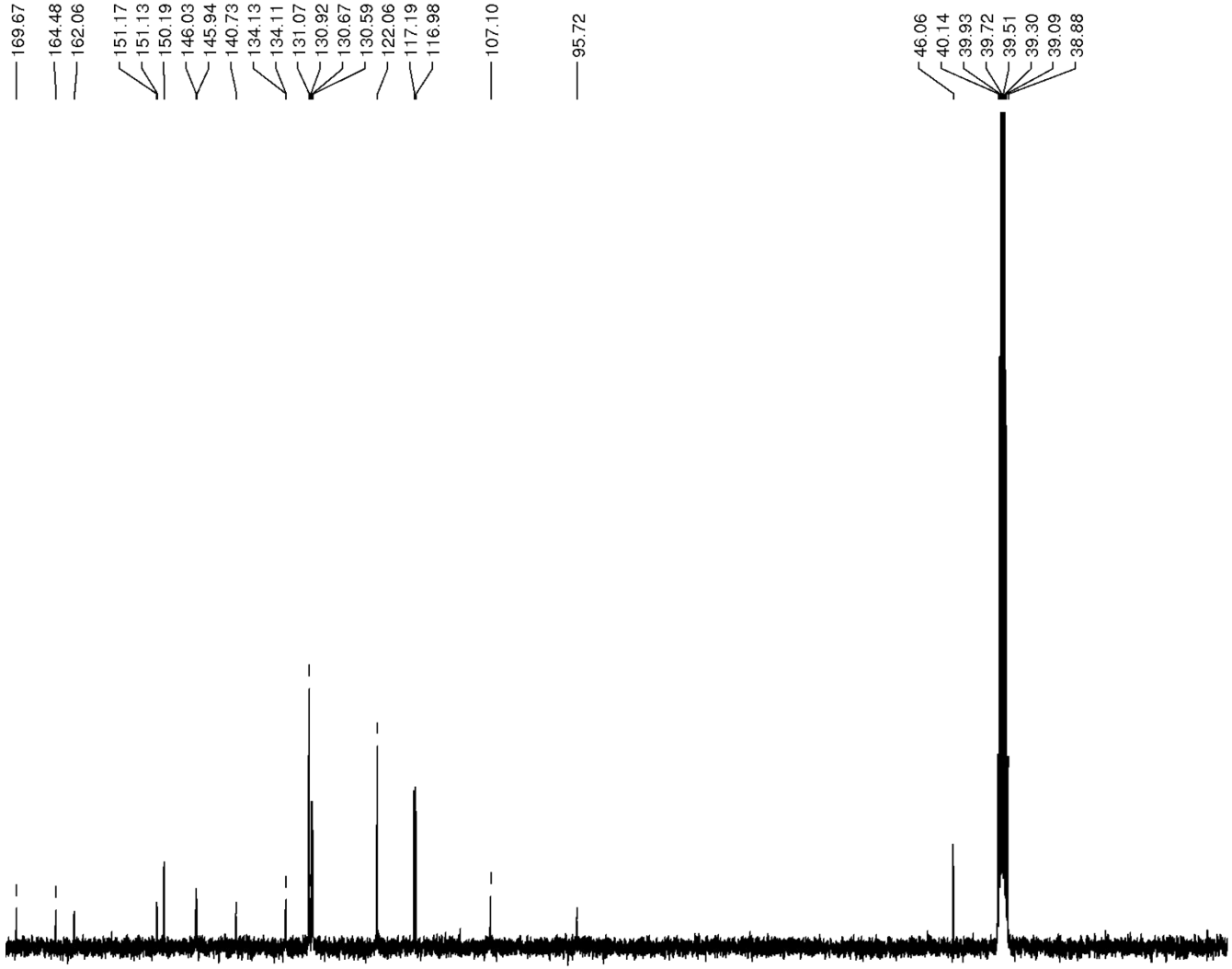
```
Current Data Parameters
NAME                  K. Wurm
EXPNO                     228
PROCNO                      1

F2 - Acquisition Parameter
Date_                20180105
Time                     9.20
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       1024
DS                          4
SWH                 24038.461 H
FIDRES               0.366798 H
AQ                   1.3631488 s
RG                        2050
DW                      20.800 u
DE                      10.00 u
TE                      298.2 K
D1                 2.00000000 s
D11                0.03000000 s
TD0                         1

======== CHANNEL f1 =====
NUC1                       13C
P1                      10.00 u
PL1                     -2.70 d
PL1W               62.67650986 W
SFO1               100.6228298 M

======== CHANNEL f2 =====
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                   60.00 u
PL2                     -5.00 d
PL12                    10.78 d
PL13                    15.00 d
PL2W               30.18447304 W
PL12W               0.79759723 W
PL13W               0.30184472 W
SFO2               400.1316005 M

F2 - Processing parameters
SI                        32768
SF                 100.6128170 M
WDW                          EM
SSB          0
```

4-Amino-*N*-{2-amin orbenzyl)amino]pyridin-3-yl}benzamide hydrochloride (**12e**)



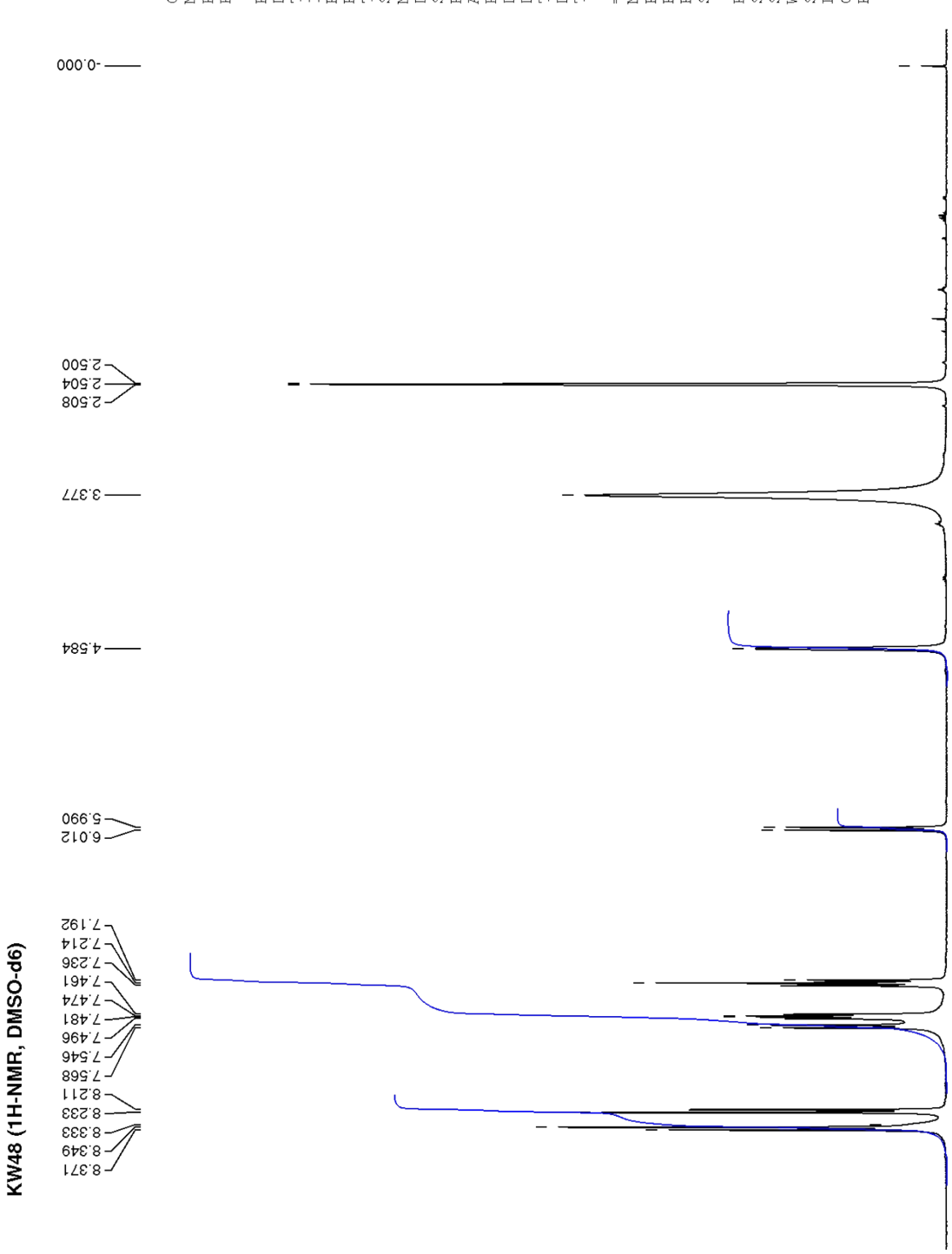
KW49/1 (13C-NMR, D2O+DMSO-d6)



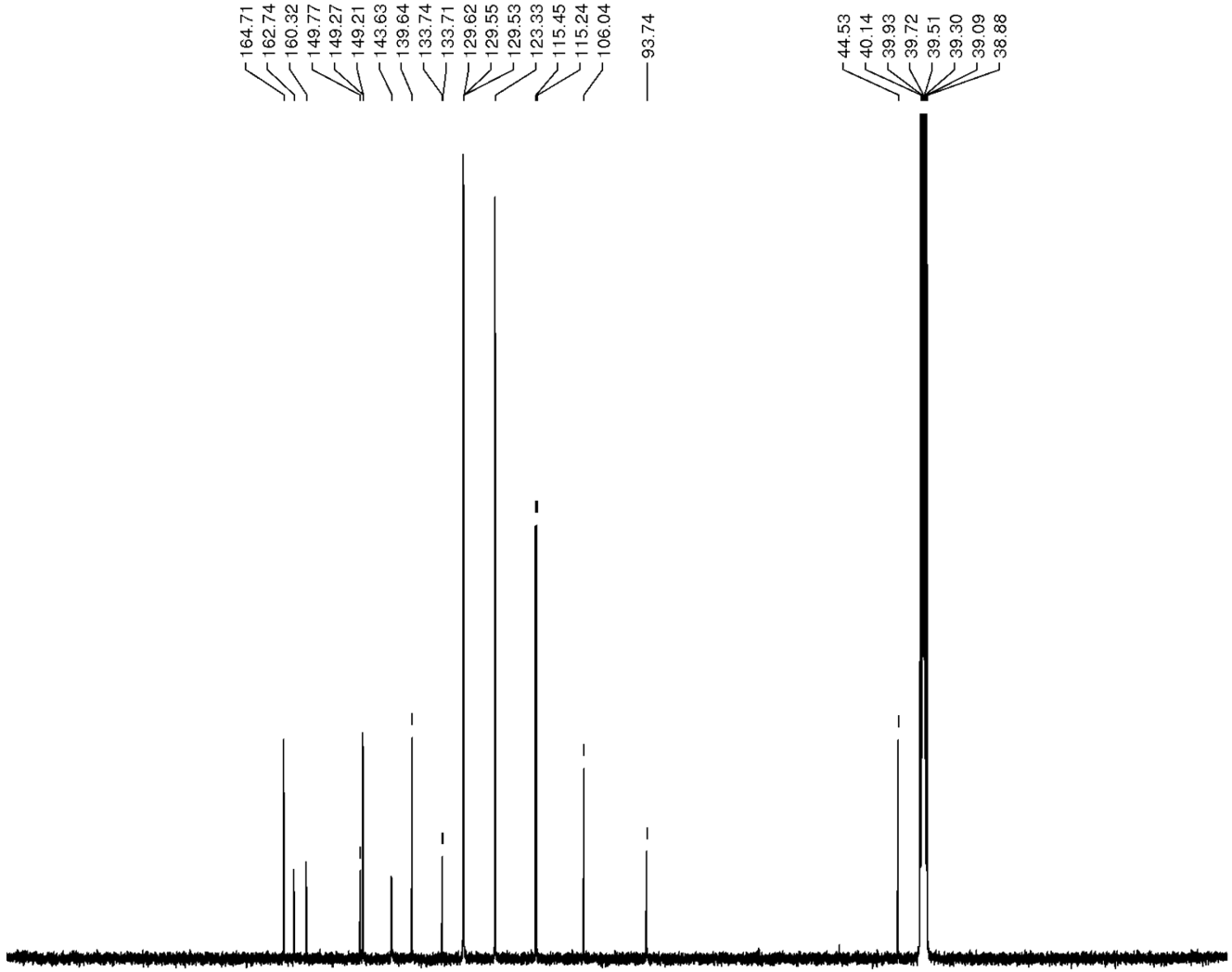
BRUKER

```
Current Data Parameters
NAME                 K. Wurm
EXPNO                    126
PROCNO                     1

F2 - Acquisition Parameter
Date_              20170802
Time                   9.13
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                 D2O
NS                     1024
DS                        4
SWH               24038.461 H
FIDRES             0.366798 H
AQ                 1.3631488 s
RG                      2050
DW                    20.800 u
DE                    10.00 u
TE                    299.2 K
D1                2.00000000 s
D11               0.03000000 s
TD0                        1

======== CHANNEL f1 =====
NUC1                    13C
P1                    10.00 u
PL1                   -2.70 d
PL1W             62.67650986 W
SFO1            100.6228298 M

======== CHANNEL f2 =====
CPDPRG[2             waltz16
NUC2                    1H
PCPD2                 60.00 u
PL2                   -5.00 d
PL12                  10.78 d
PL13                  15.00 d
PL2W             30.18447304 W
PL12W             0.79759723 W
PL13W             0.30184472 W
SFO2            400.1316005 M

F2 - Processing parameters
SI                     32768
SF               100.6126579 M
WDW                       EM
SSB       0
LB                     1.00 H
```

N-{2-Amino-6-[(4-fluorophenyl)amino]pyridin-3-yl}-4-nitrobenzaminde hydrochloride (**12f**)



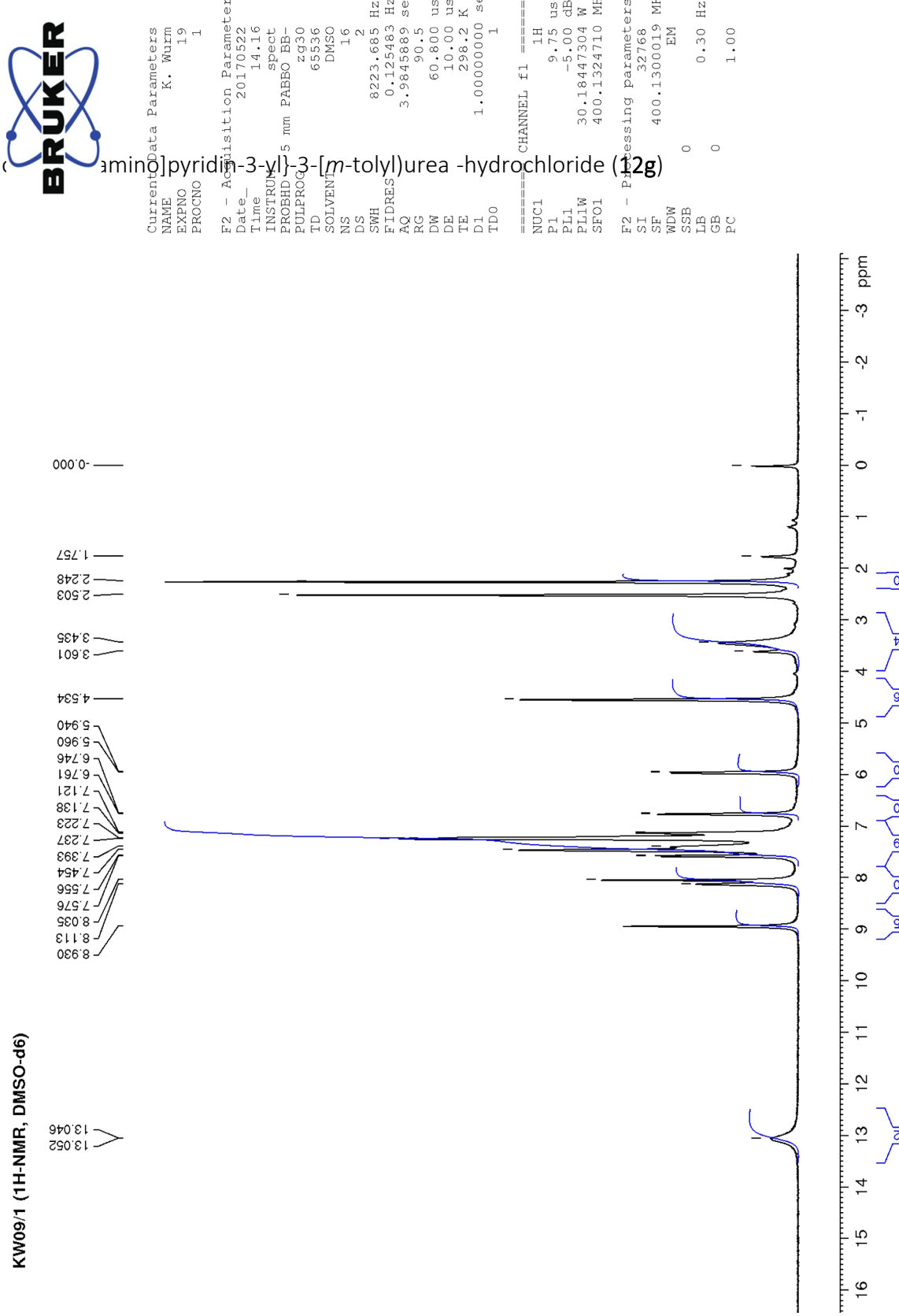
KW48 (13C-NMR, DMSO-d6)

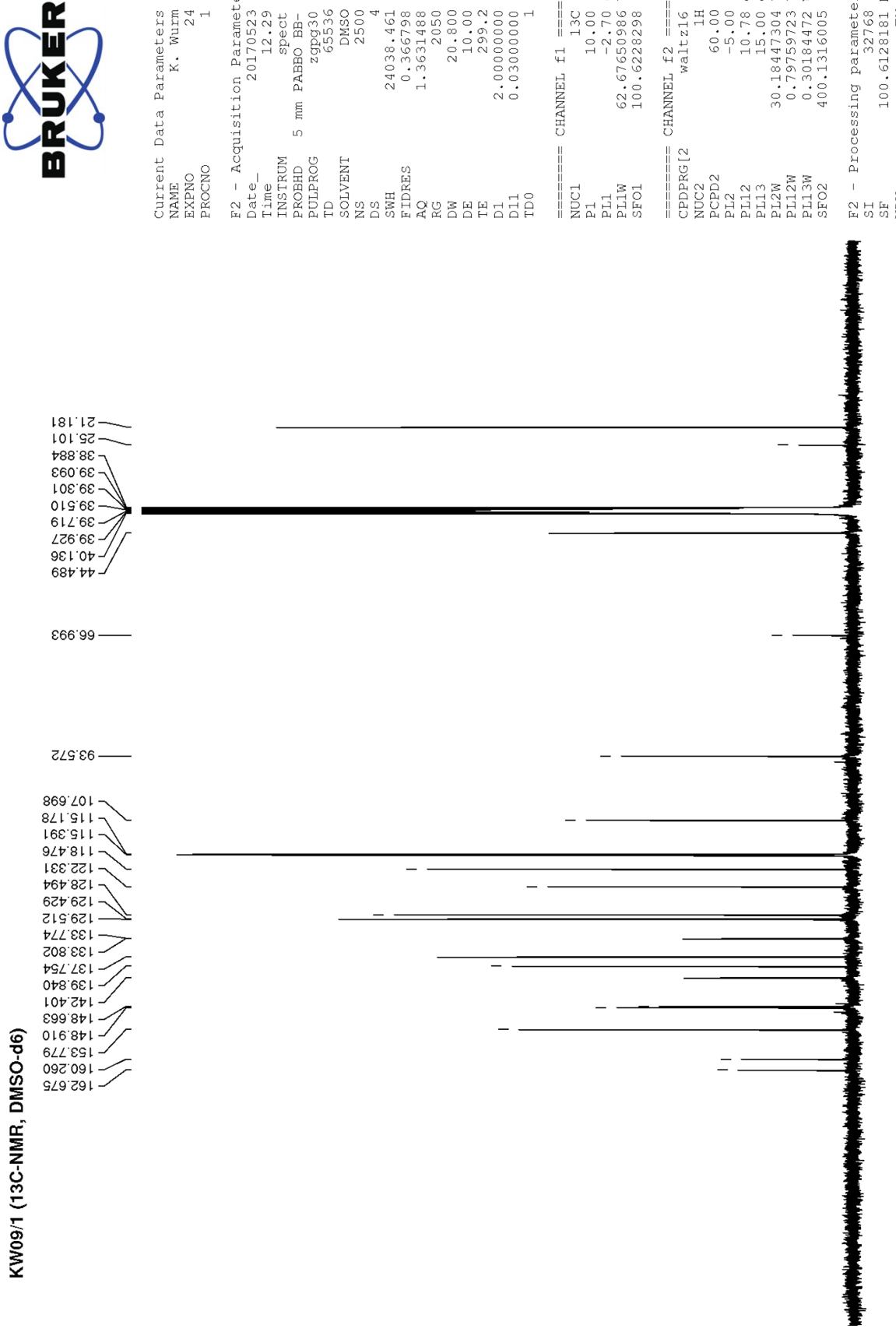


BRUKER

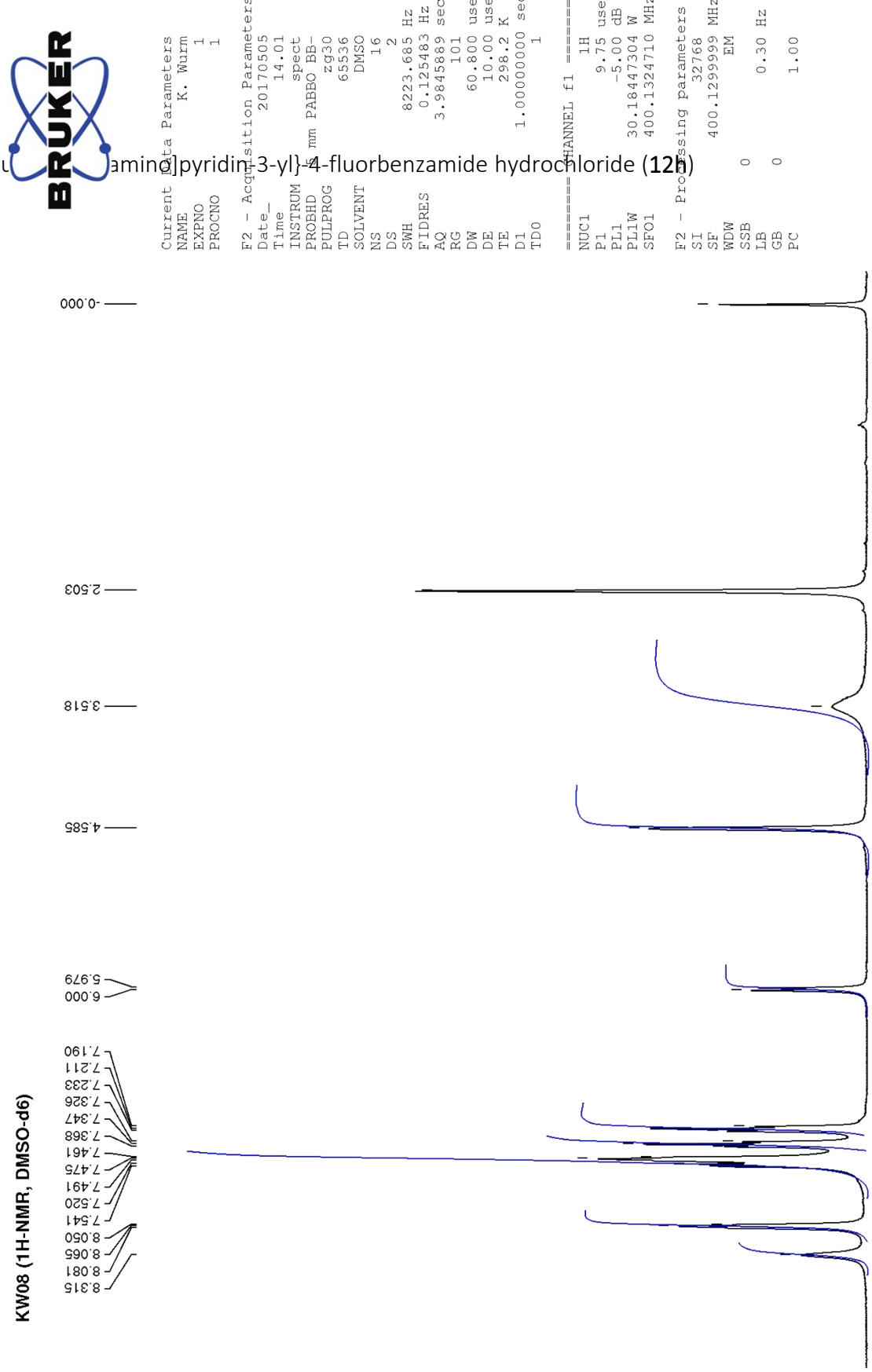
```
Current Data Parameters
NAME                  K. Wurm
EXPNO                     104
PROCNO                      1

F2 - Acquisition Parameter
Date_              20170718
Time                   3.50
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     3000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631488 se
RG                     2050
DW                   20.800 us
DE                   10.00 us
TE                   298.2 K
D1              2.00000000 se
D11             0.03000000 se
TD0                       1

======== CHANNEL f1 ======
NUC1                    13C
P1                   10.00 us
PL1                  -2.70 dB
PL1W           62.67650986 W
SFO1           100.6228298 MH

======== CHANNEL f2 ======
CPDPRG[2            waltz16
NUC2                    1H
PCPD2                60.00 us
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2           400.1316005 MH

F2 - Processing parameters
SI                    32768
SF               100.6128144 MH
WDW                     EM
SSB       0
LB                     1.00 Hz
```

1-{2-Amino-6-[(4-fluo amino]pyridin-3-yl}-3-[*m*-tolyl)urea -hydrochloride (**12g**)

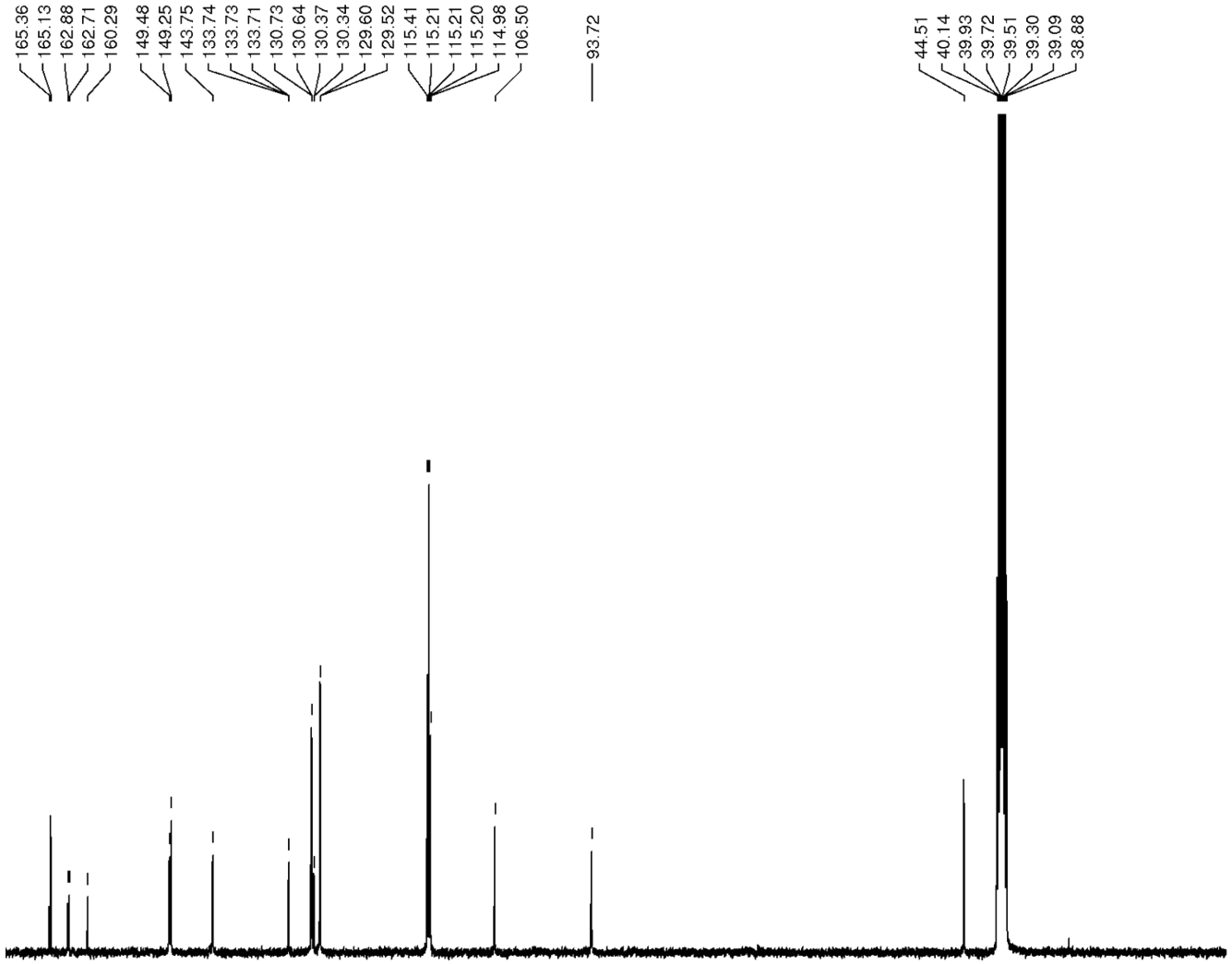



Current Data Parameters
NAME K. Wurm
EXPNO 24
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170523
Time 12.29
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2500
DS 4
SWH 24038.461
FIDRES 0.366798
AQ 1.3631488
RG 2050
DW 20.800
DE 10.00
TE 299.2
D1 2.00000000
D11 0.03000000
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00
PL1 -2.70
PL1W 62.67650986
SFO1 100.6228298
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00
PL2 -5.00
PL12 10.78
PL13 15.00
PL2W 30.18447304
PL12W 0.79759723
PL13W 0.30184472
SFO2 400.1316005
F2 - Processing parameters
SI 32768
SF 100.6128181
21.181
25.101
38.884
39.093
39.301
39.510
39.719
39.927
40.136
44.489
66.993
93.572
107.698
115.178
115.391
118.476
122.331
128.494
129.429
129.512
133.774
133.802
137.754
139.840
142.401
148.663
148.910
153.779
160.260
162.675
KW09/1 (13C-NMR, DMSO-d6)

N-{2-Amino-6-[(4-fluorophenyl)amino]pyridin-3-yl}-4-fluorbenzamide hydrochloride (**12h**)

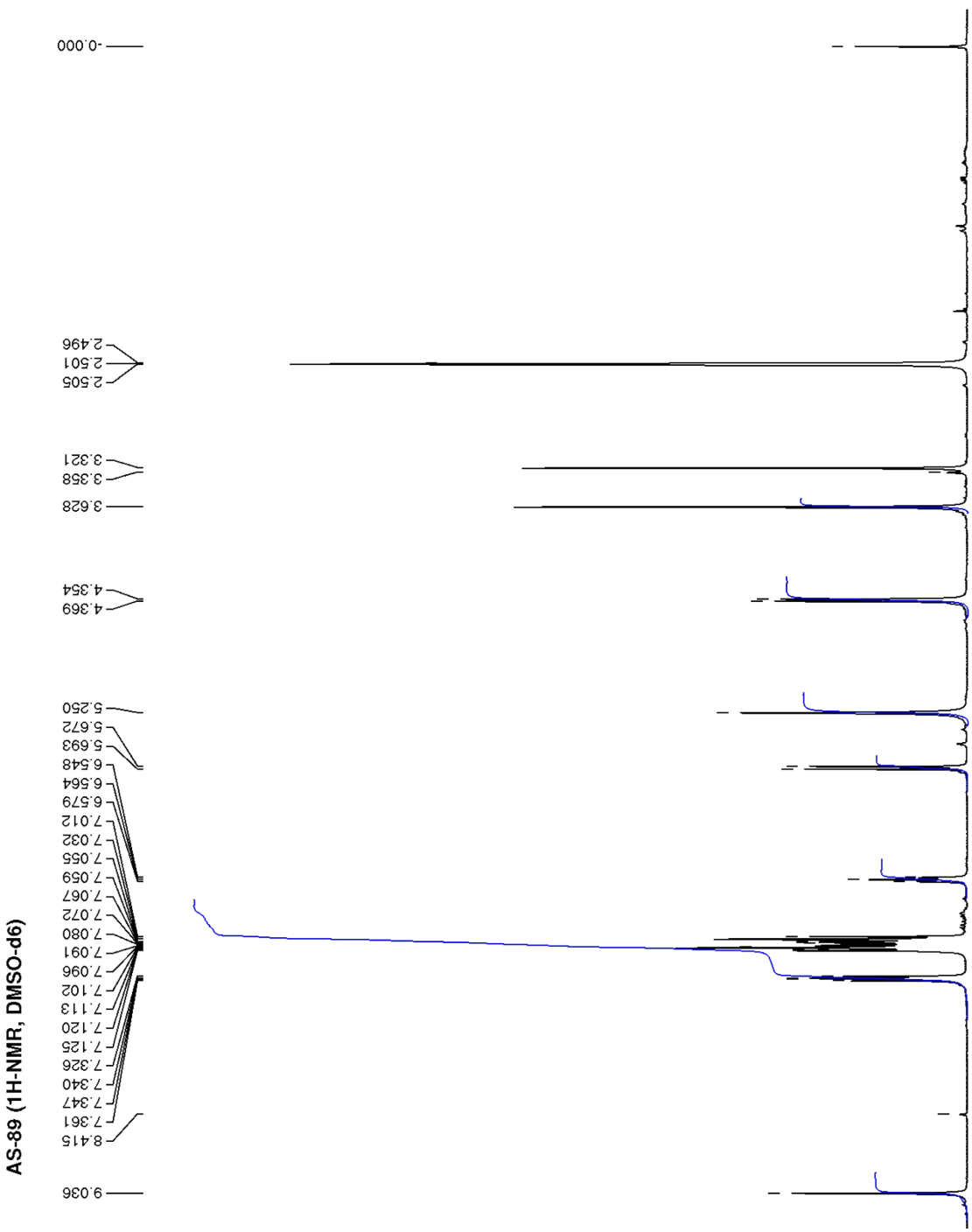


KW08 (13C-NMR, DMSO-d6)

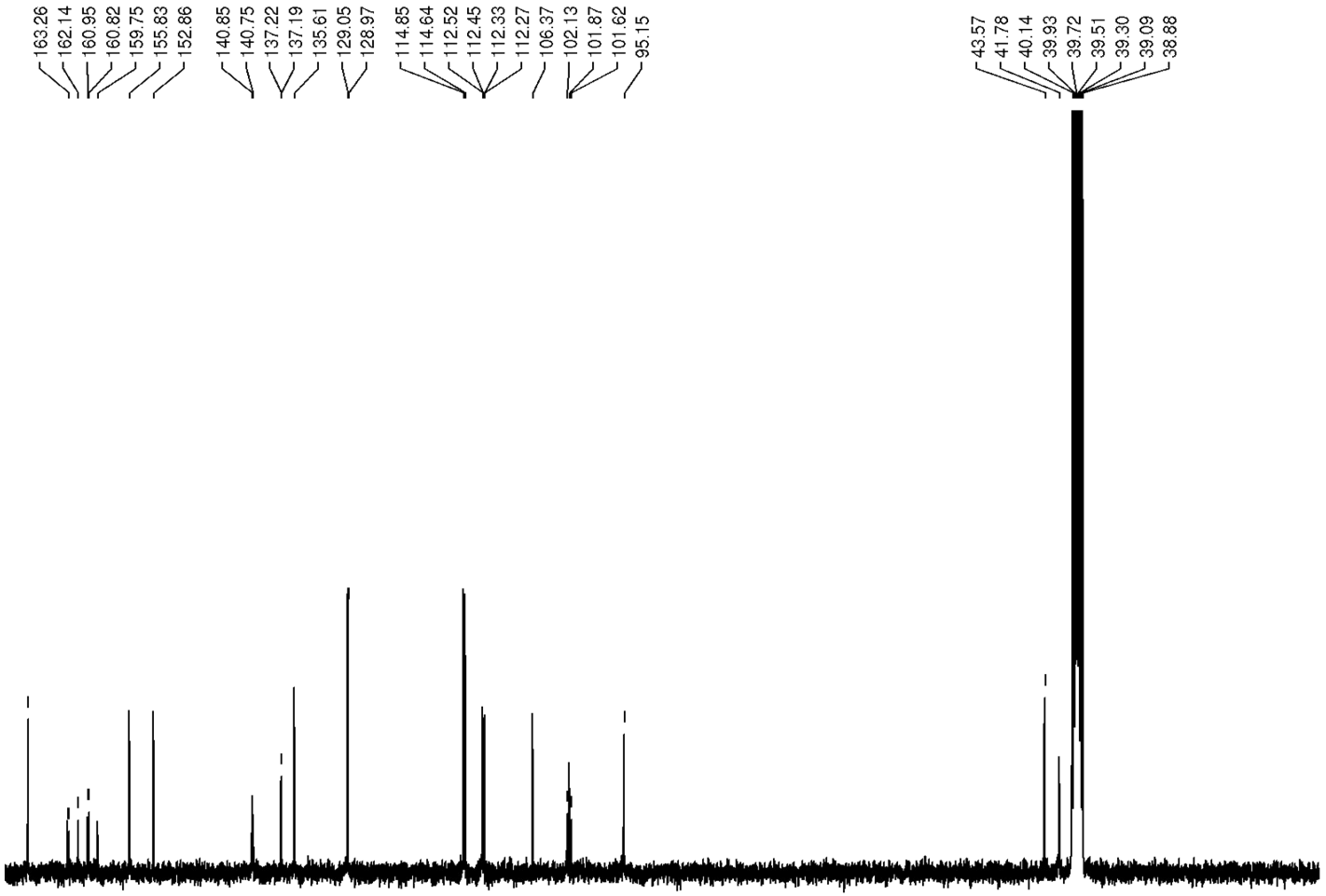



```
Current Data Parameters
NAME                 K. Wurm
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameter
Date_               20170508
Time                   12.32
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       3000
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 se
RG                       2050
DW                     20.800 us
DE                     10.00 us
TE                     299.2 K
D1                 2.00000000 se
D11                0.03000000 se
TD0                         1

======== CHANNEL f1 ======
NUC1                     13C
P1                     10.00 us
PL1                    -2.70 dB
PL1W              62.67650986 W
SFO1             100.6228298 MH

======== CHANNEL f2 ======
CPDPRG[2              waltz16
NUC2                      1H
PCPD2                  60.00 us
PL2                    -5.00 dB
PL12                   10.78 dB
PL13                   15.00 dB
PL2W              30.18447304 W
PL12W              0.79759723 W
PL13W              0.30184472 W
SFO2             400.1316005 MH

F2 - Processing parameters
SI                       32768
SF                100.6128174 MH
WDW                         EM
SSB       0
LB                      1.00 Hz
```

N-{2-Amino-6-[(4-fl[illegible]l)amino]pyridin-3-yl}-2-(3,5-difluorophenyl)acetamide (12i)



AS-89 (13C-NMR, DMSO-d6)



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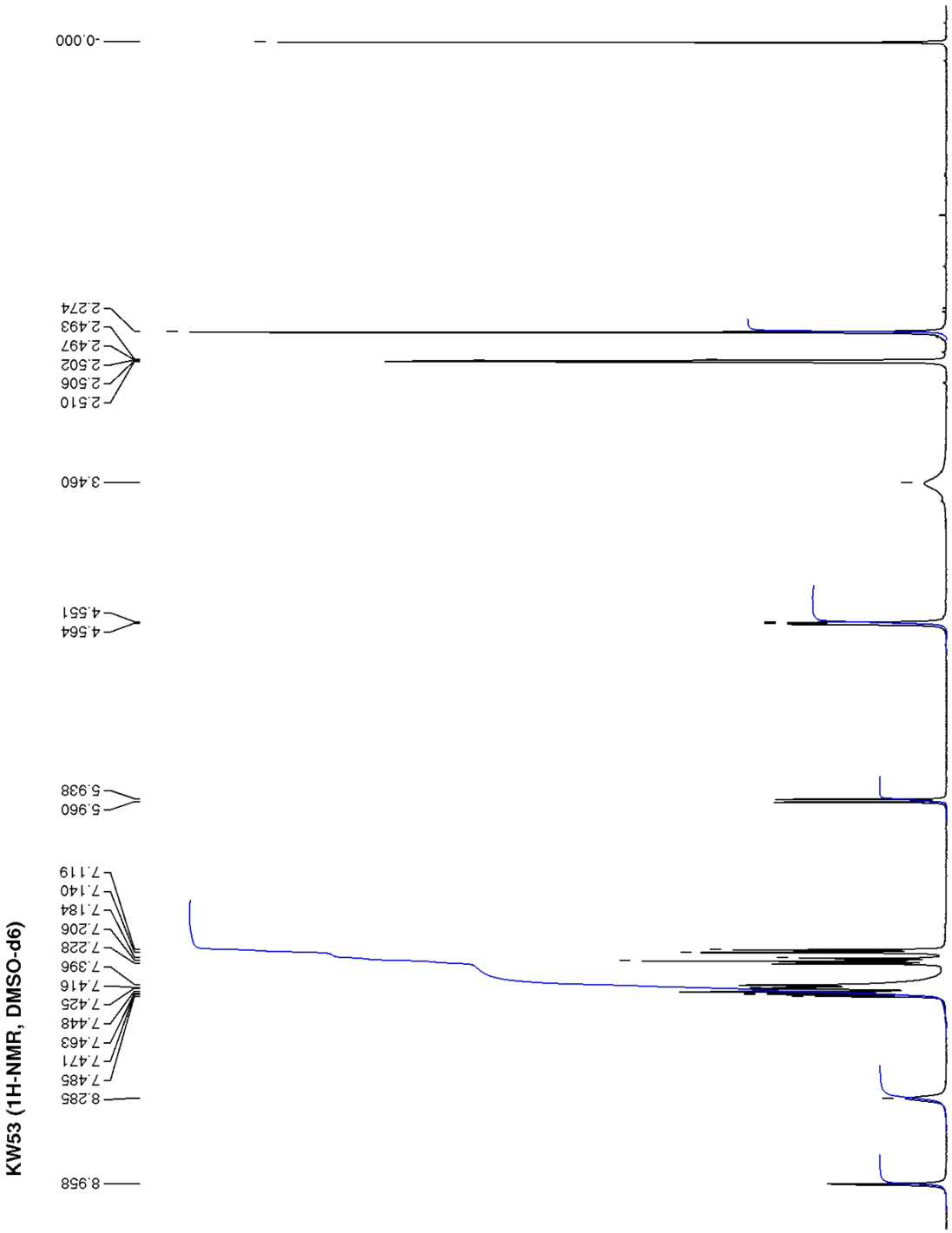
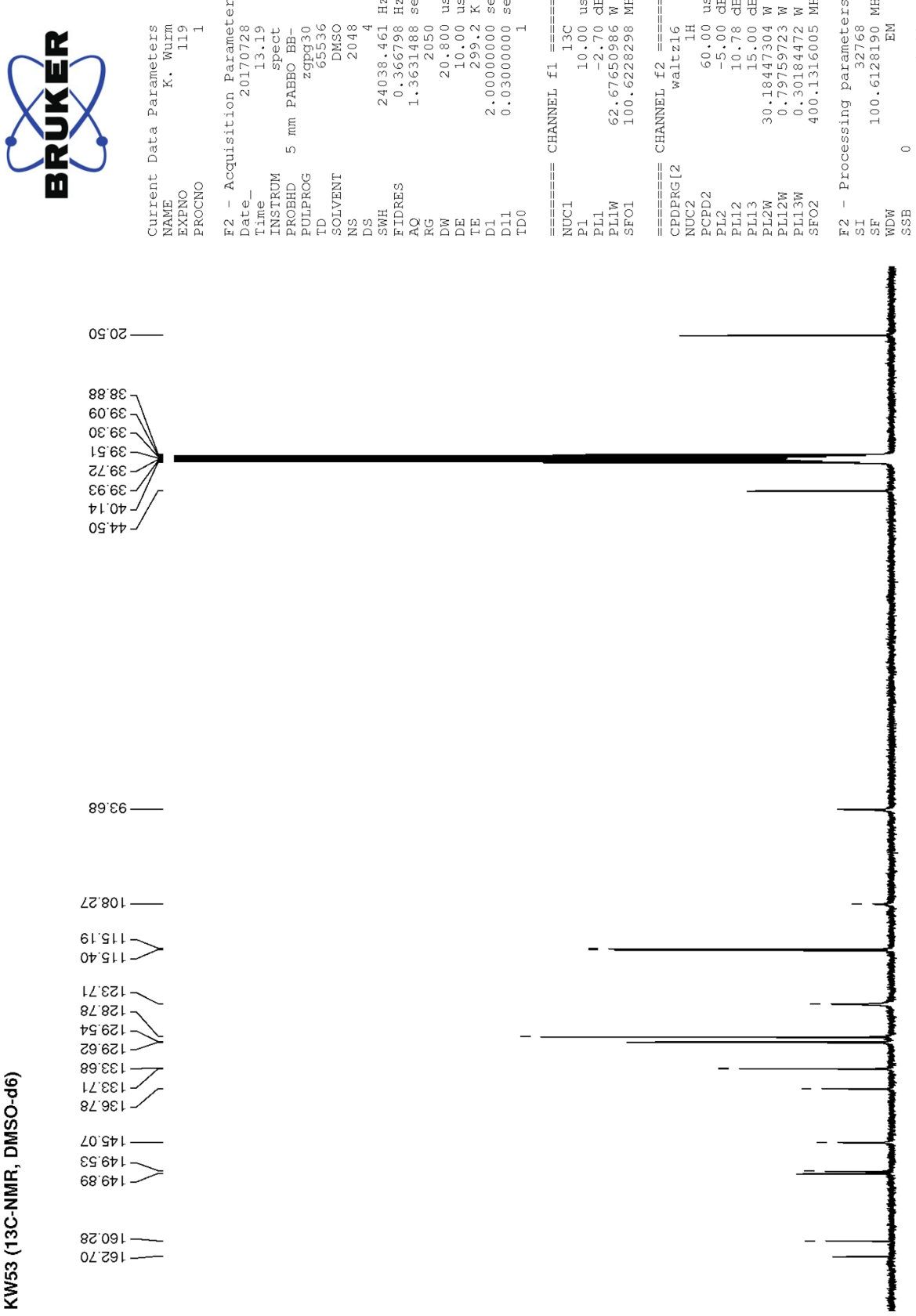
```
Current Data Parame
NAME                 S
EXPNO
PROCNO

F2 - Acquisition Pa
Date_             2017
Time                 1
INSTRUM              s
PROBHD    5 mm PABBO
PULPROG             zg
TD                   6
SOLVENT
NS
DS
SWH              24038
FIDRES            0.36
AQ               1.363
RG
DW                  20
DE                   1
TE                   2
D1               2.0000
D11              0.0300
TD0

======== CHANNEL f1
NUC1
P1                   1
PL1                  -
PL1W          62.6765
SFO1          100.622

======== CHANNEL f2
CPDPRG[2           wal
NUC2
PCPD2                6
PL2                  -
PL12                 1
PL13                 1
PL2W          30.1844
PL12W          0.7975
PL13W          0.3018
SFO2          400.131

F2 - Processing par
SI                   3
SF            100.612
WDW
```

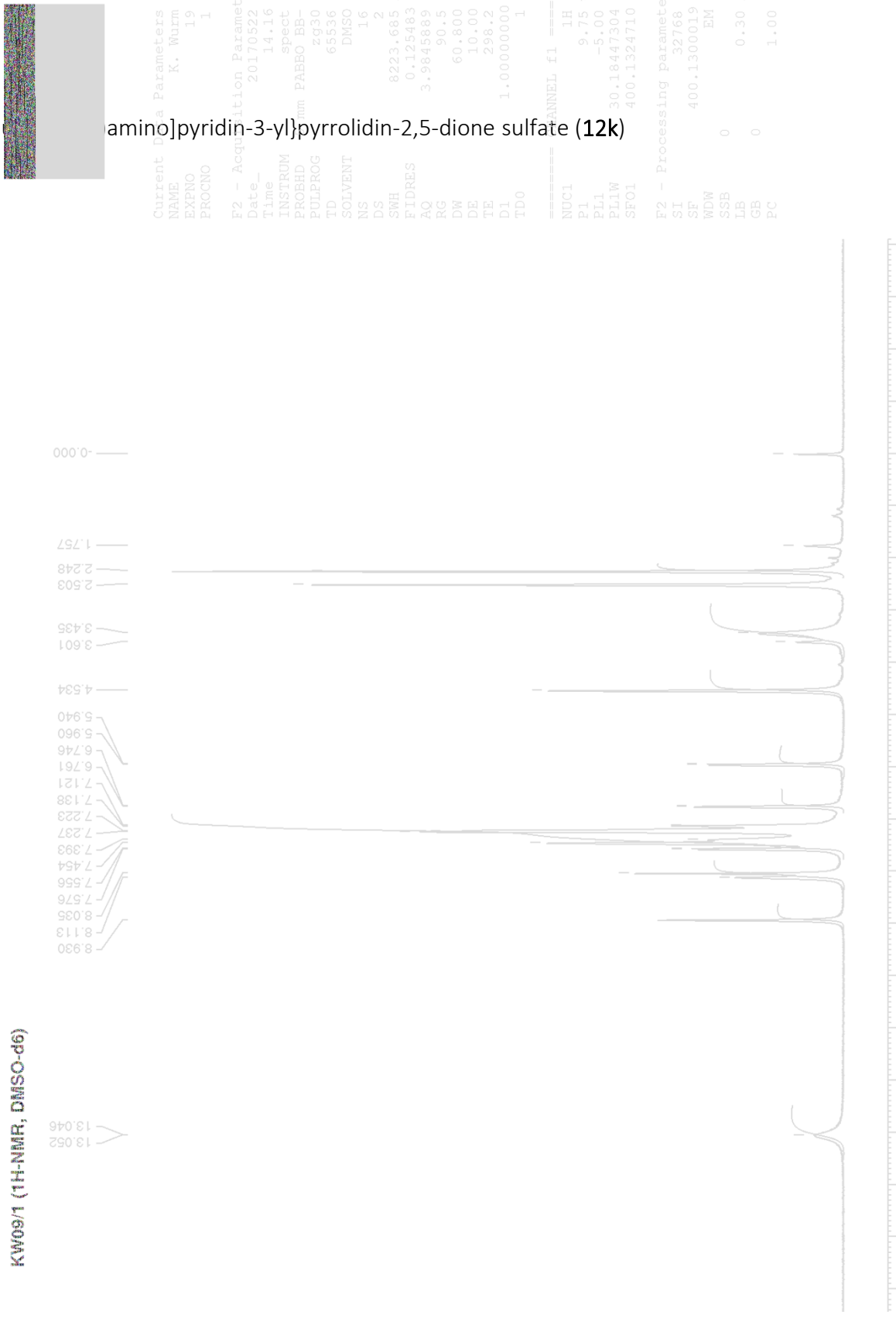
1-{2-Amino-6-[(4-fluorophenyl)amino]pyridin-3-yl}-3-[*m*-tolyl)thiourea hydrochloride (12j)



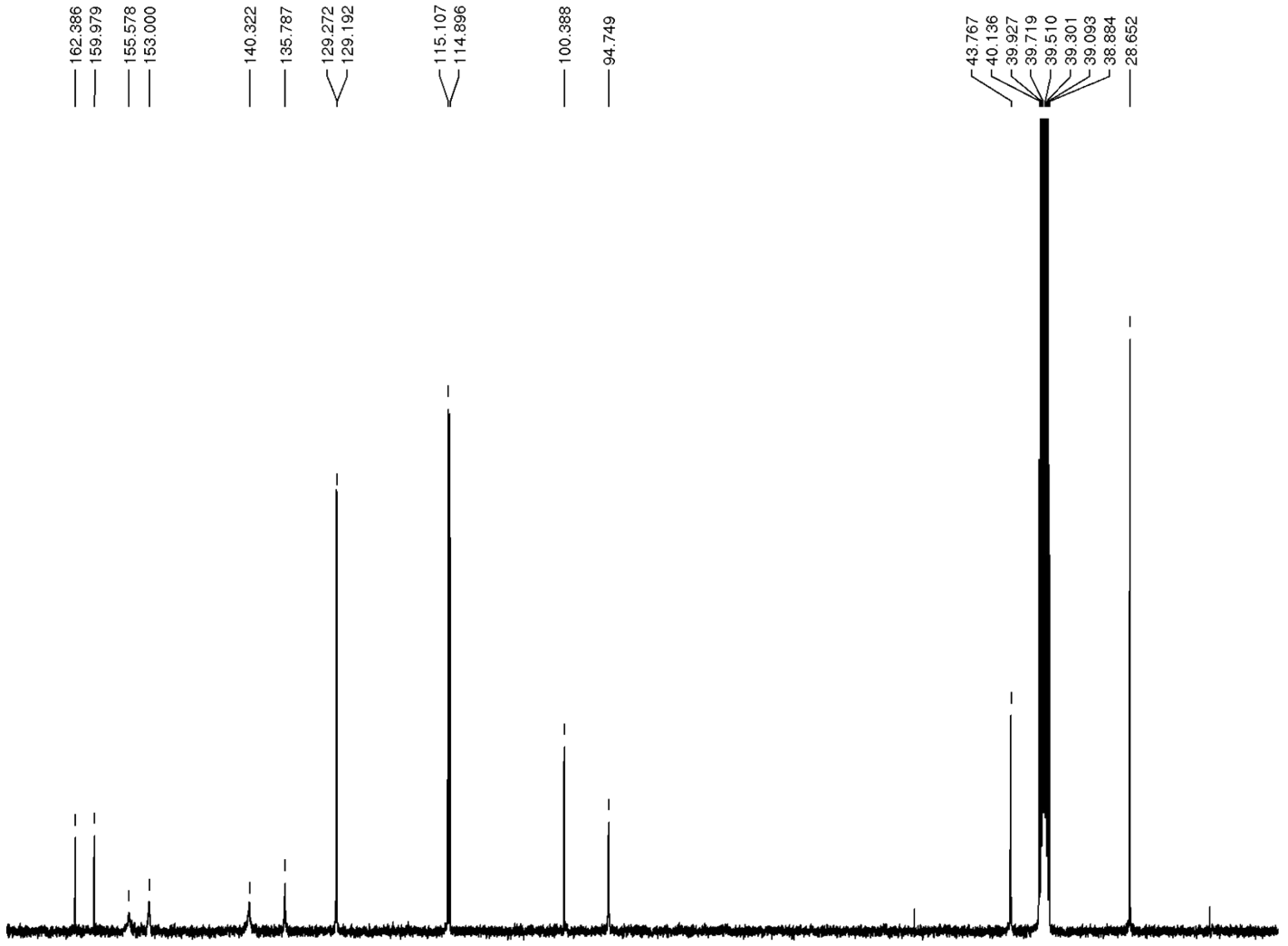


KW53 (13C-NMR, DMSO-d6)

1-{2-Amino-6-[(4-fl amino]pyridin-3-yl}pyrrolidin-2,5-dione sulfate (**12k**)



KW61 (13C-NMR, DMSO-d6)



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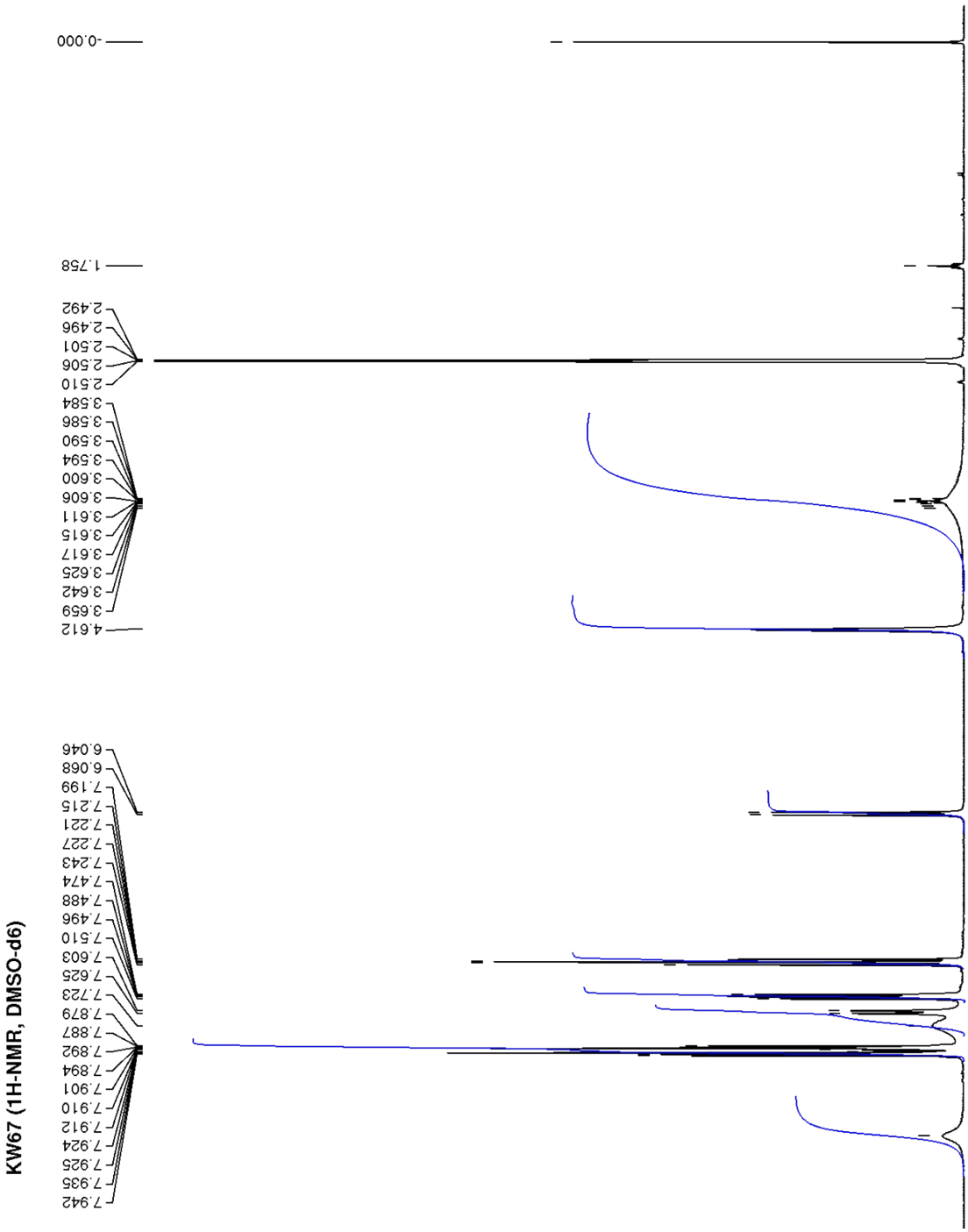
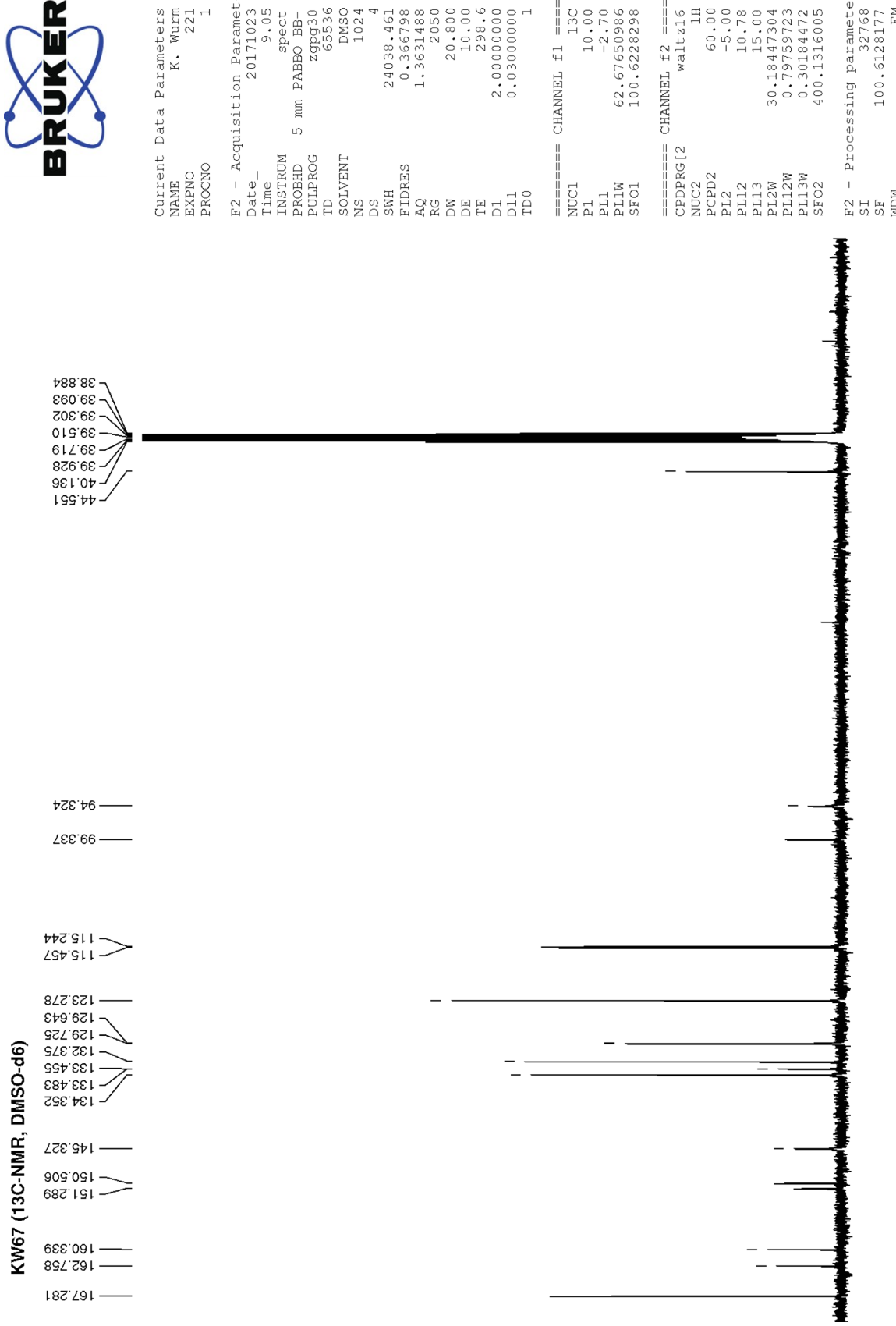
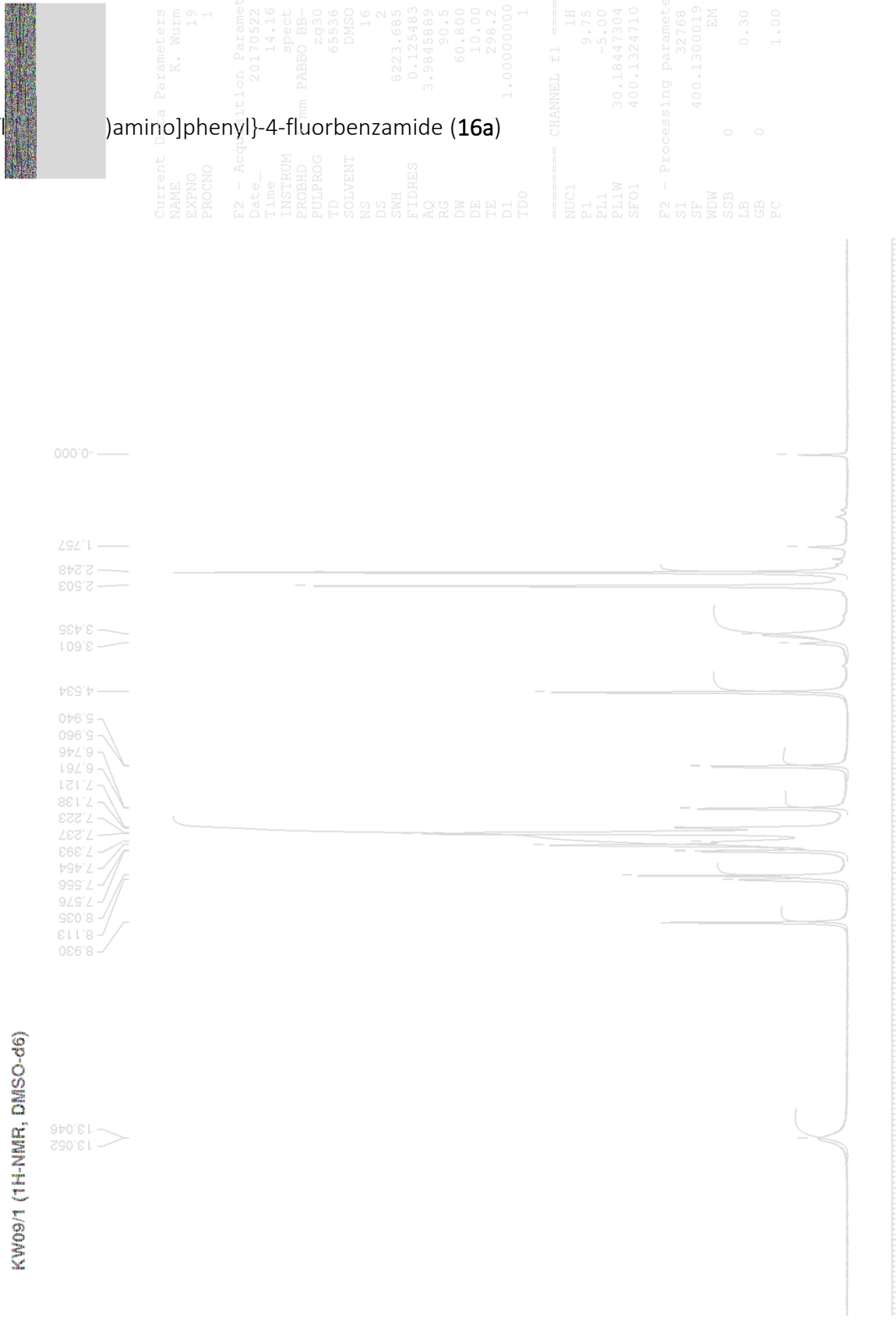
```
Current Data Parameters
NAME                 K. Wurm
EXPNO                     187
PROCNO                      1

F2 - Acquisition Parame
Date_              20170912
Time                   2.01
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                     65536
SOLVENT                DMSO
NS                       200
DS                         4
SWH                24038.461
FIDRES              0.366798
AQ                  1.363148
RG                       205
DW                     20.800
DE                     10.00
TE                     299.2
D1                2.00000000
D11               0.03000000
TD0                        1

======== CHANNEL f1 ===
NUC1                      13C
P1                      10.00
PL1                     -2.70
PL1W             62.67650986
SFO1            100.6228298

======== CHANNEL f2 ===
CPDPRG[2              waltz16
NUC2                       1H
PCPD2                   60.00
PL2                     -5.00
PL12                    10.78
PL13                    15.00
PL2W             30.18447304
PL12W             0.79759721
PL13W             0.30184472
SFO2            400.1316005

F2 - Processing paramet
SI                       32768
SF              100.6128174
WDW                         EM
```

2-{2-Amino-6-[(4-flu amino]pyridin-3-yl}isoindolin-1,3-dione hydrochloride (**12l**)

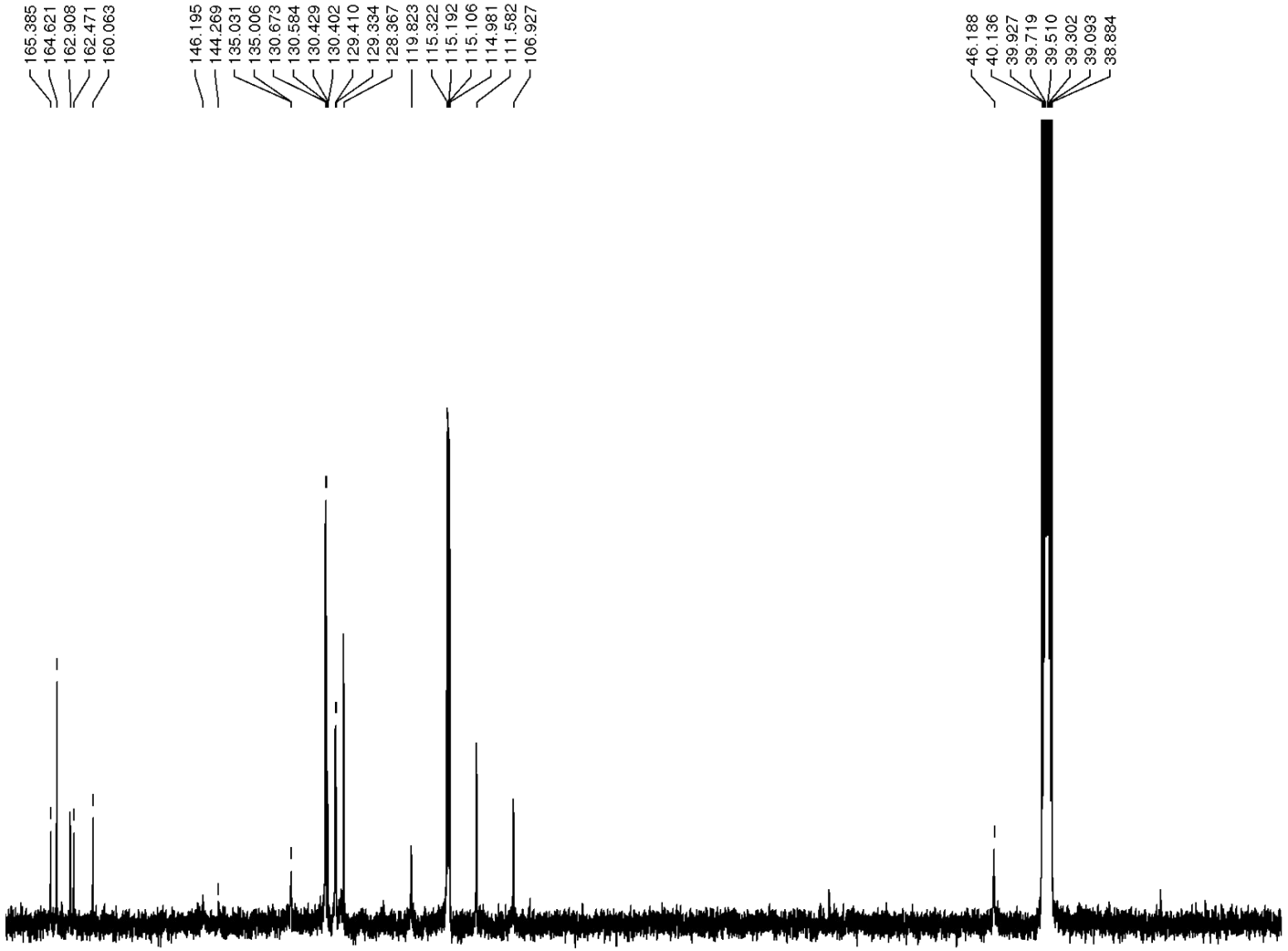



Current Data Parameters
NAME K. Wurm
EXPNO 221
PROCNO 1
F2 - Acquisition Parameter
Date_ 20171023
Time_ 9.05
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.461
FIDRES 0.366798
AQ 1.3631488
RG 2050
DW 20.800
DE 10.00
TE 298.6
D1 2.00000000
D11 0.03000000
TD0 1
CHANNEL f1
NUC1 13C
P1 10.00
PL1 -2.70
PL1W 62.67650986
SFO1 100.6228298
CHANNEL f2
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00
PL2 -5.00
PL12 10.78
PL13 15.00
PL2W 30.18447304
PL12W 0.79759723
PL13W 0.30184472
SFO2 400.1316005
F2 - Processing parameter
SI 32768
SF 100.6128177
38.884
39.093
39.302
39.510
39.719
39.928
40.136
44.551
94.324
99.337
115.244
115.457
123.278
129.643
129.725
132.375
133.455
133.483
134.352
145.327
150.506
151.289
160.339
162.758
167.281
KW67 (13C-NMR, DMSO-d6)

N-{2-Amino-4-[(4-fl)amino]phenyl}-4-fluorbenzamide (**16a**)



ELB093 (13C-NMR, DMSO-d6)



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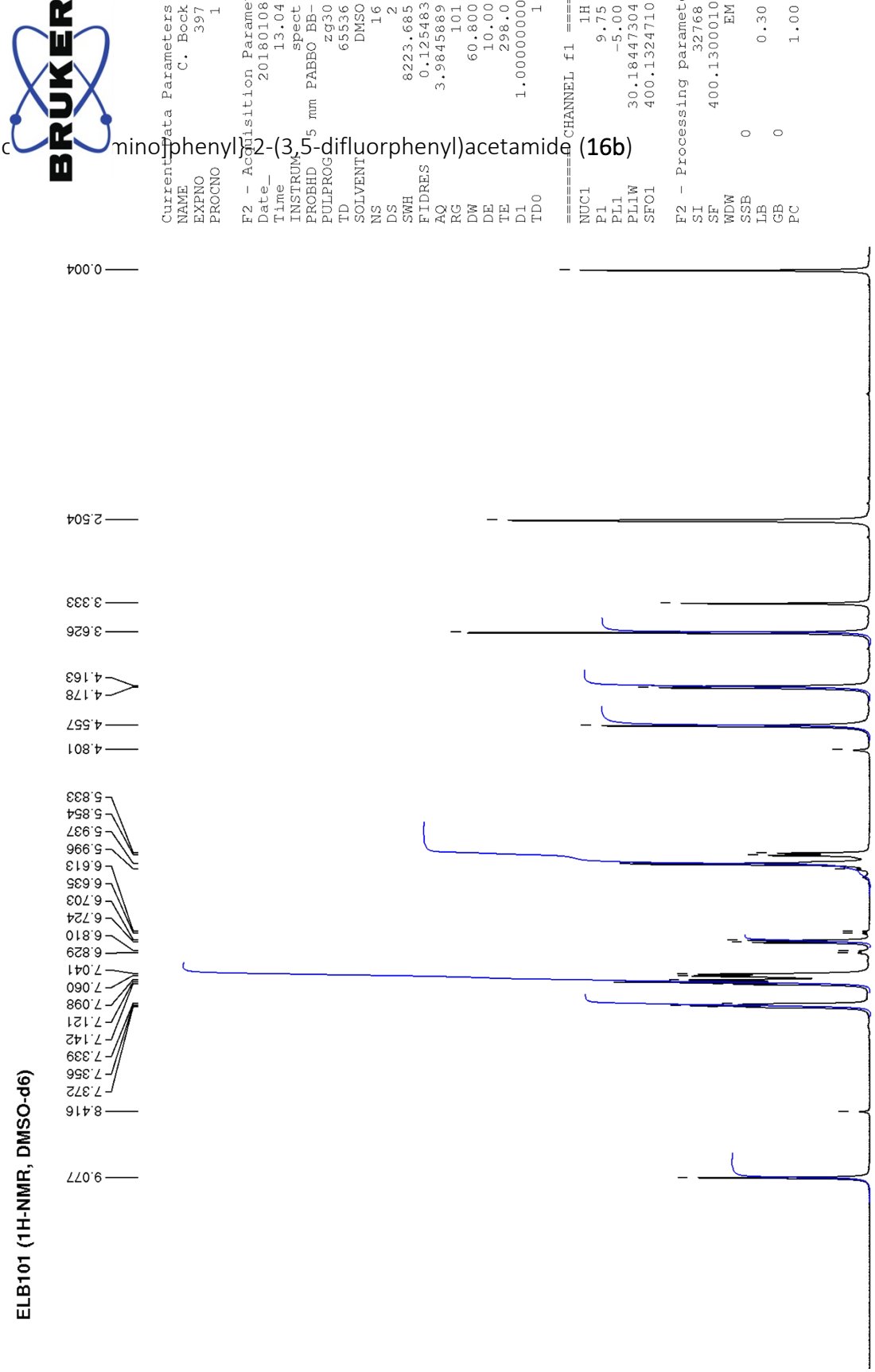
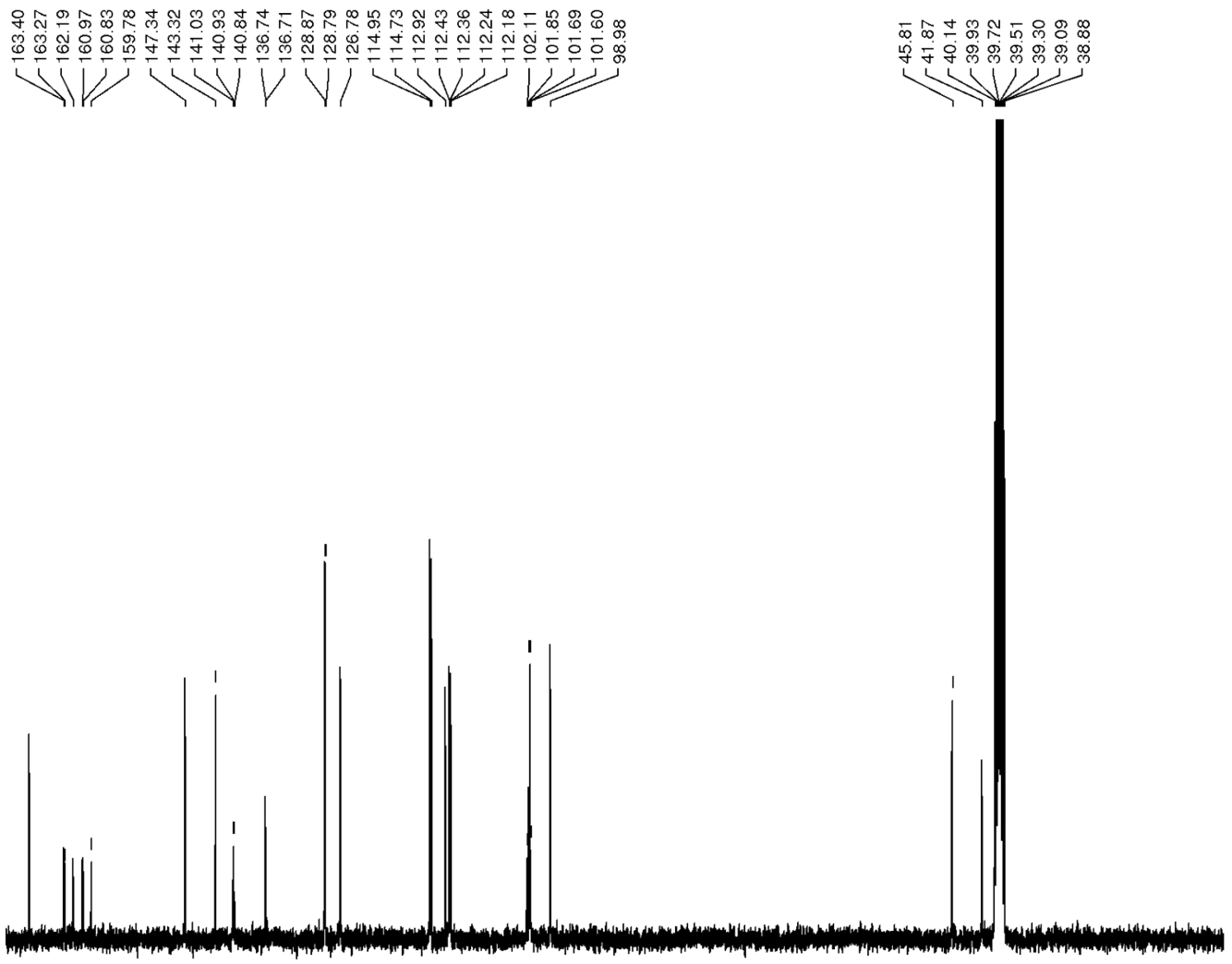
```
Current Data Parameters
NAME                 C. Bock
EXPNO                     380
PROCNO                      1

F2 - Acquisition Paramet
Date_               20171215
Time                   14.06
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                       800
DS                         4
SWH                24038.461
FIDRES              0.366798
AQ                 1.3631488
RG                      2050
DW                     20.800
DE                     10.00
TE                     298.2
D1                2.00000000
D11               0.03000000
TD0                         1

======== CHANNEL f1 ====
NUC1                     13C
P1                     10.00
PL1                    -2.70
PL1W            62.67650986
SFO1            100.6228298

======== CHANNEL f2 ====
CPDPRG[2            waltz16
NUC2                     1H
PCPD2                  60.00
PL2                    -5.00
PL12                   10.78
PL13                   15.00
PL2W            30.18447304
PL12W            0.79759723
PL13W            0.30184472
SFO2            400.1316005

F2 - Processing paramete
SI                       32768
SF              100.6128162
```

N-{2-Amino-4-[(4-fluo[illegible]mino]phenyl}-2-(3,5-difluorphenyl)acetamide (**16b**)

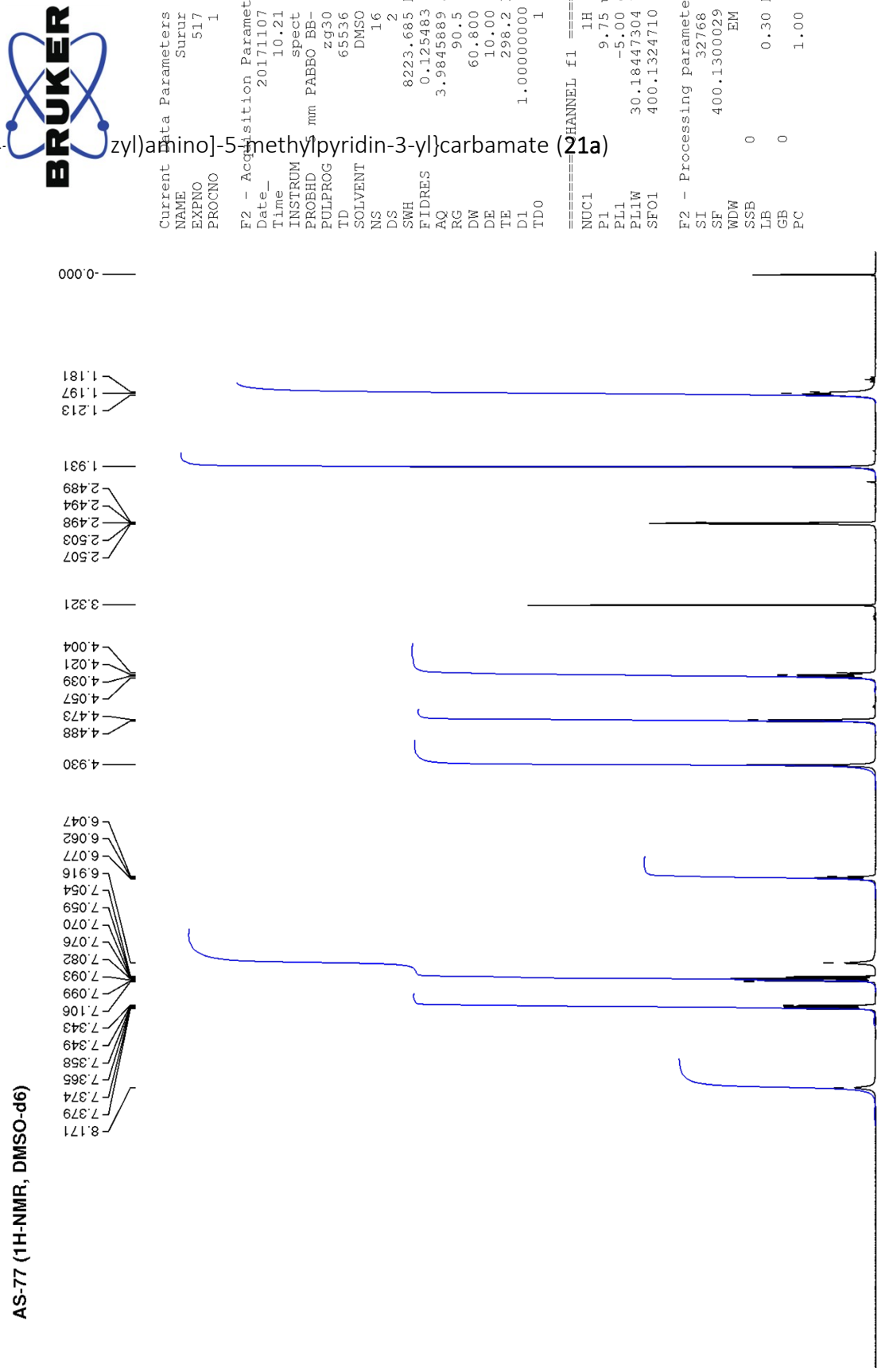


ELB101 (13C-NMR, DMSO-d6)

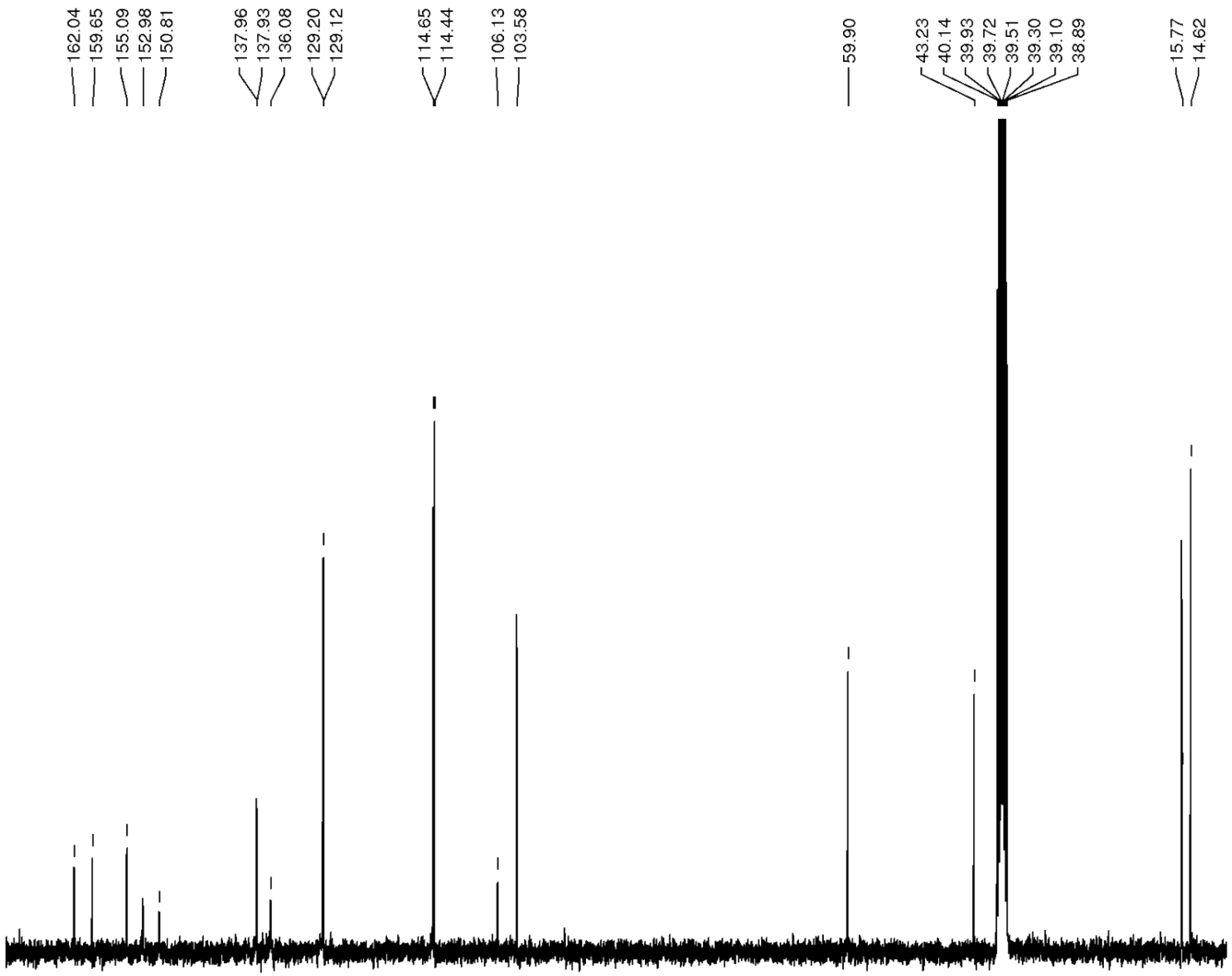



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     404
PROCNO                      1

F2 - Acquisition Parameters
Date_                20180115
Time                    15.22
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                   DMSO
NS                         800
DS                           4
SWH                 24038.461 Hz
FIDRES                0.366798 Hz
AQ                    1.3631488 sec
RG                         2050
DW                       20.800 use
DE                       10.00 use
TE                       298.2 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

======== CHANNEL f1 =======
NUC1                       13C
P1                       10.00 use
PL1                      -2.70 dB
PL1W                62.67650986 W
SFO1               100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2                waltz16
NUC2                        1H
PCPD2                    60.00 use
PL2                      -5.00 dB
PL12                     10.78 dB
PL13                     15.00 dB
PL2W                30.18447304 W
PL12W                0.79759723 W
PL13W                0.30184472 W
SFO2               400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                 100.6128175 MHz
WDW                           EM
SSB          0
LB                        1.00 Hz
```

Ethyl {2-amino-6-[(4-[illegible]zyl)amino]-5-methylpyridin-3-yl}carbamate (**21a**)

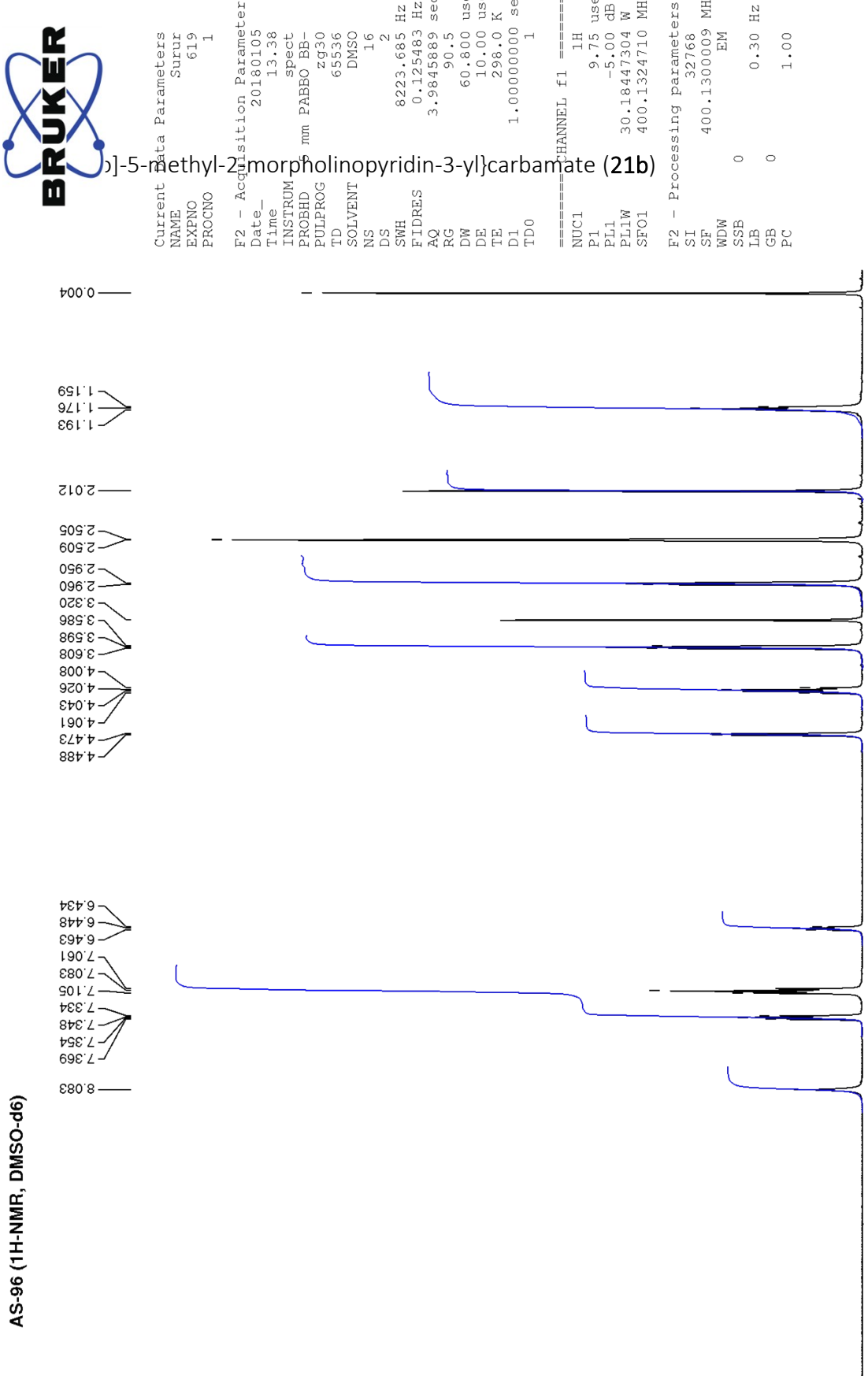


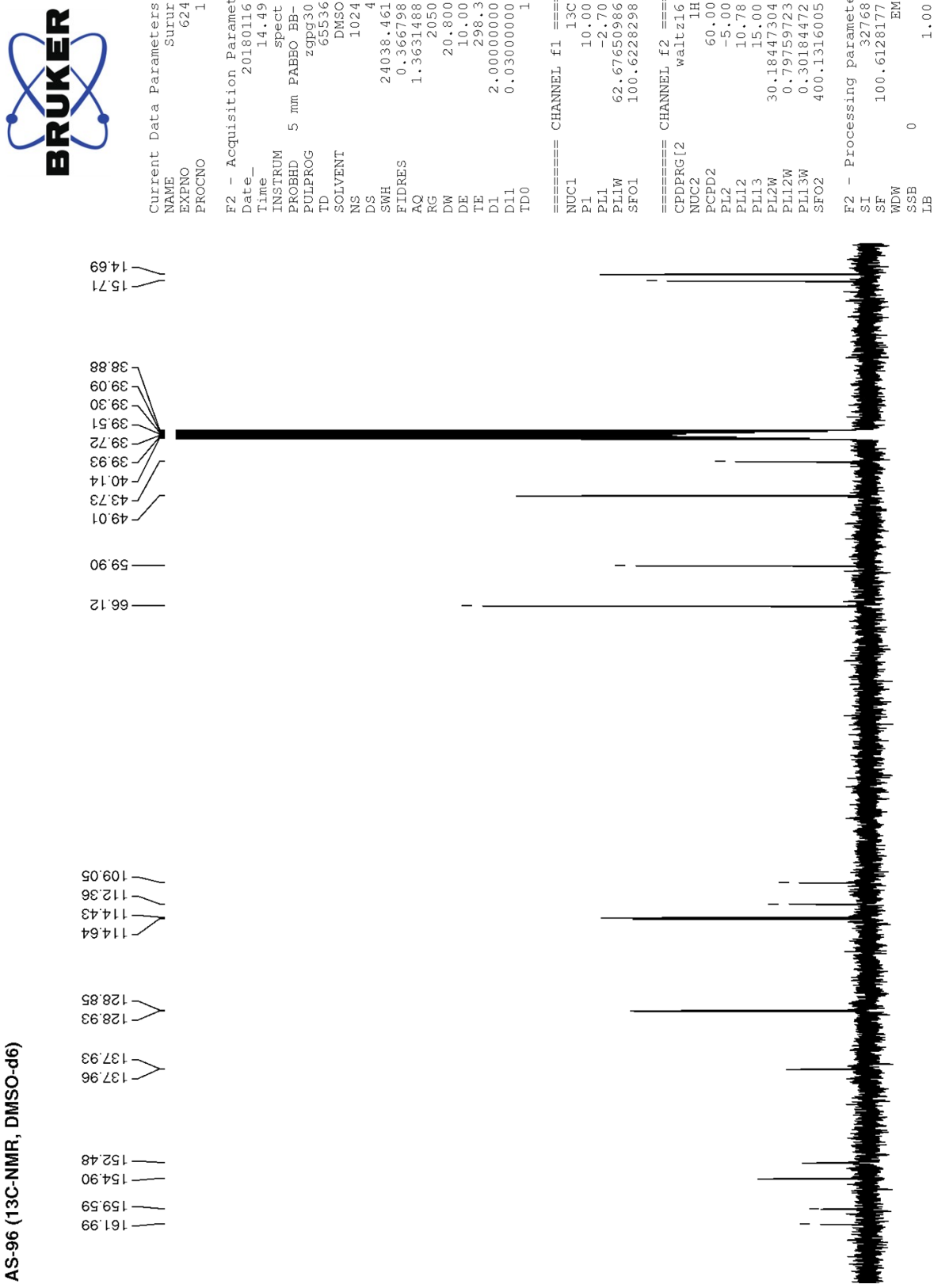
AS-77 (13C-NMR, DMSO-d6)



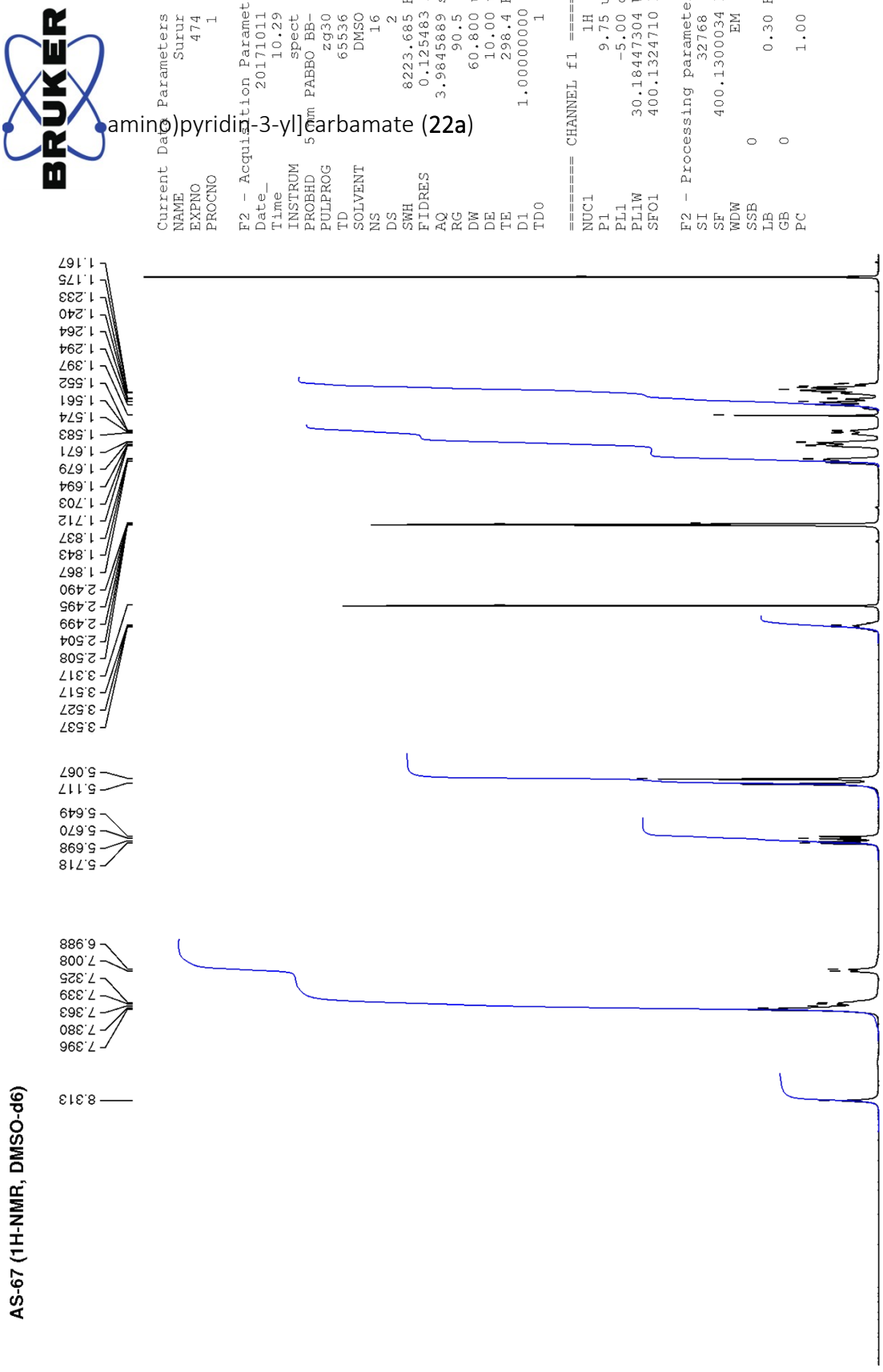

```
Current Data Parameters
NAME                  Surur
EXPNO                   535
PROCNO                    1

F2 - Acquisition Parameters
Date_              20171120
Time                   9.21
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                      1024
DS                         4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                      2050
DW                  20.800 use
DE                  10.00 use
TE                  298.1 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 =======
NUC1                    13C
P1                  10.00 use
PL1                 -2.70 dB
PL1W          62.67650986 W
SFO1         100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2           waltz16
NUC2                    1H
PCPD2                60.00 use
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W          30.18447304 W
PL12W          0.79759723 W
PL13W          0.30184472 W
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF           100.6128166 MHz
WDW                      EM
SSB       0
```

Ethyl {6-[(4-fluorobe]-5-methyl-2-morpholinopyridin-3-yl}carbamate (**21b**)

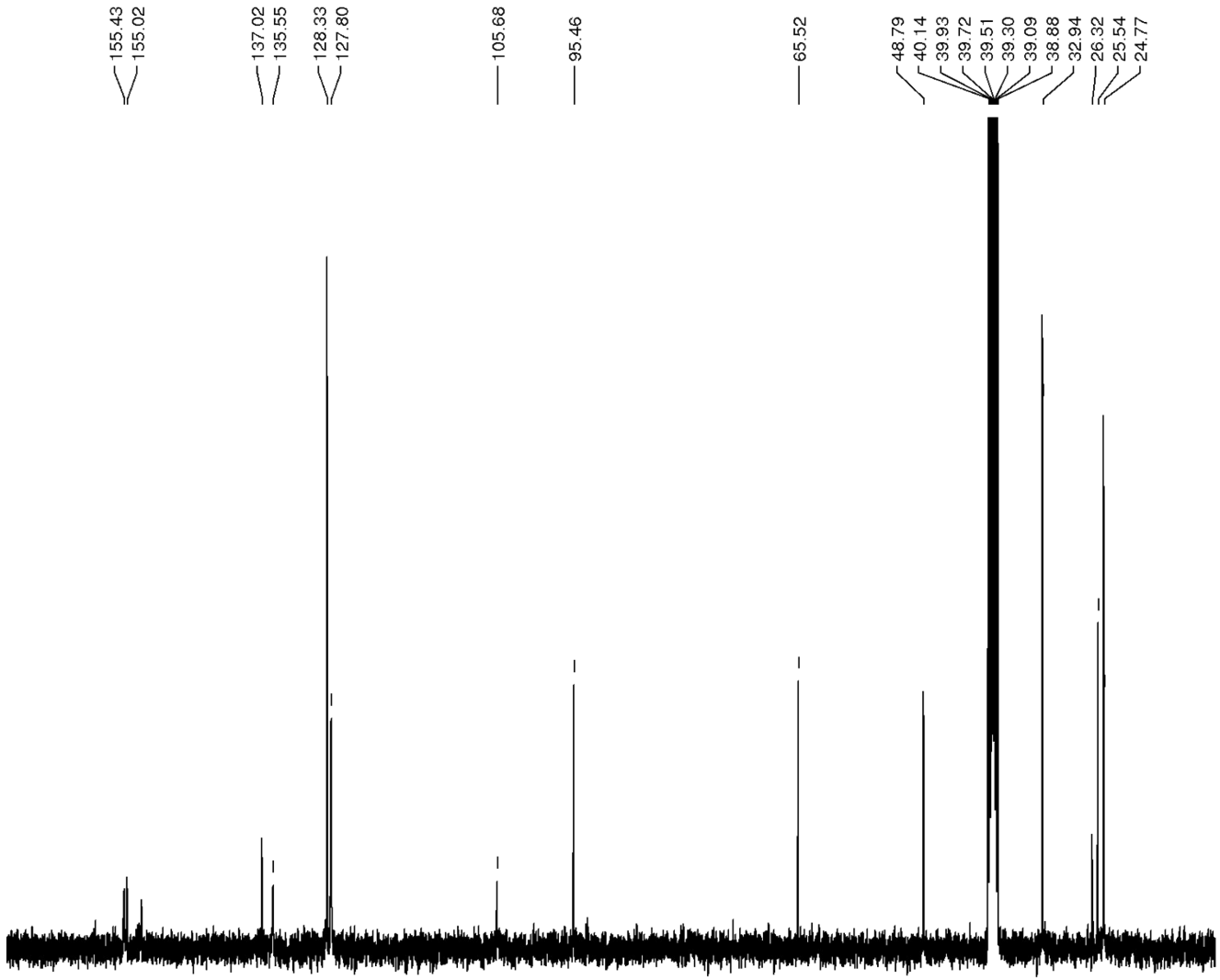



Current Data Parameters
NAME Surur
EXPNO 624
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180116
Time_ 14.49
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 2050
DW 20.800 use
DE 10.00 use
TE 298.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 use
PL1 -2.70 dB
PL1W 62.67650986 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 60.00 use
PL2 -5.00 dB
PL12 10.78 dB
PL13 15.00 dB
PL2W 30.18447304 W
PL12W 0.79759723 W
PL13W 0.30184472 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128177 MHz
WDW EM
SSB 0
LB 1.00 Hz
14.69
15.71
38.88
39.09
39.30
39.51
39.72
39.93
40.14
43.73
49.01
59.90
66.12
109.05
112.36
114.43
114.64
128.85
128.93
137.93
137.96
152.48
154.90
159.59
161.99
AS-96 (13C-NMR, DMSO-d6)

Benzyl [2-amino-6-(amino)pyridin-3-yl]carbamate (**22a**)

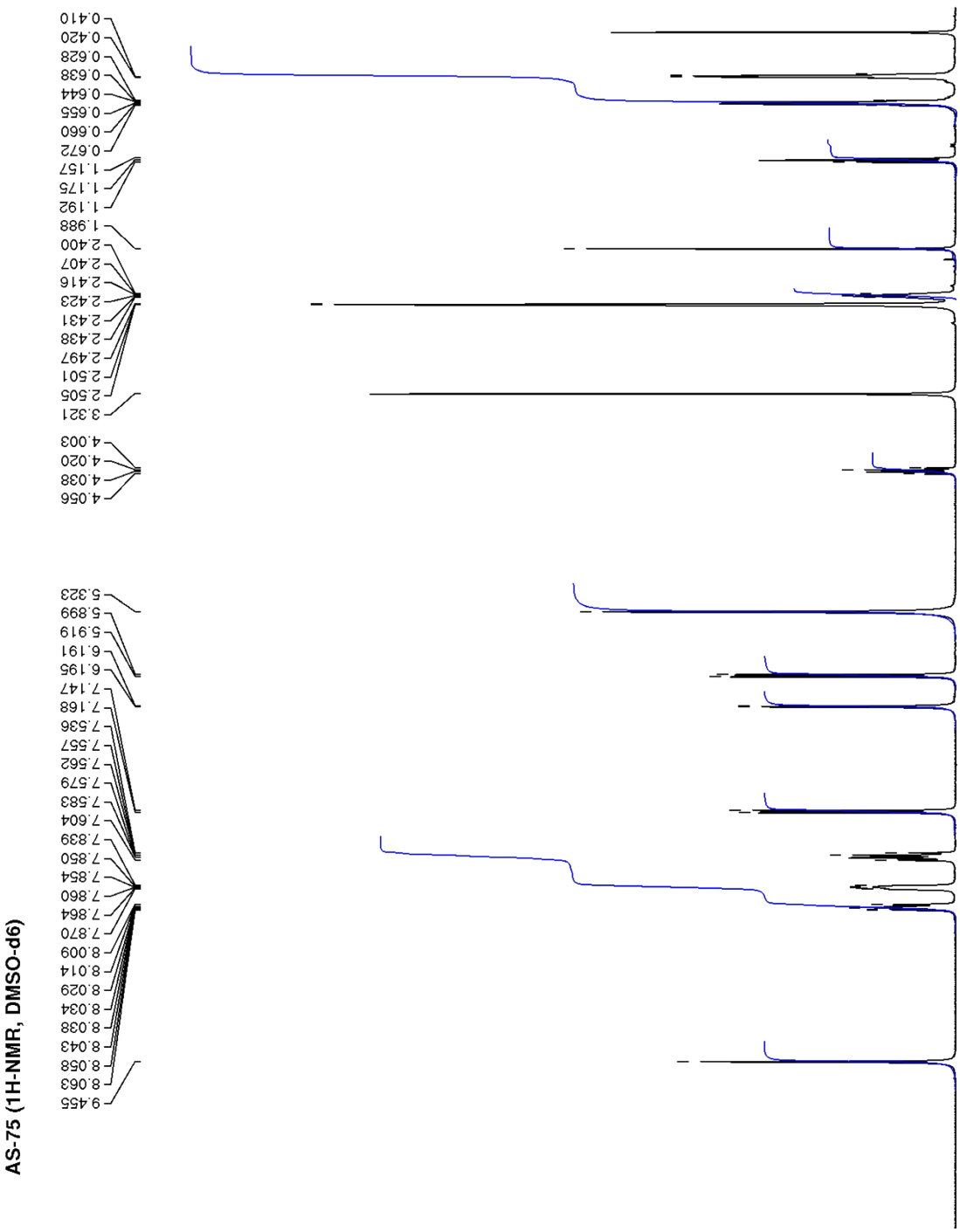


AS-67 (13C-NMR, DMSO-d6)

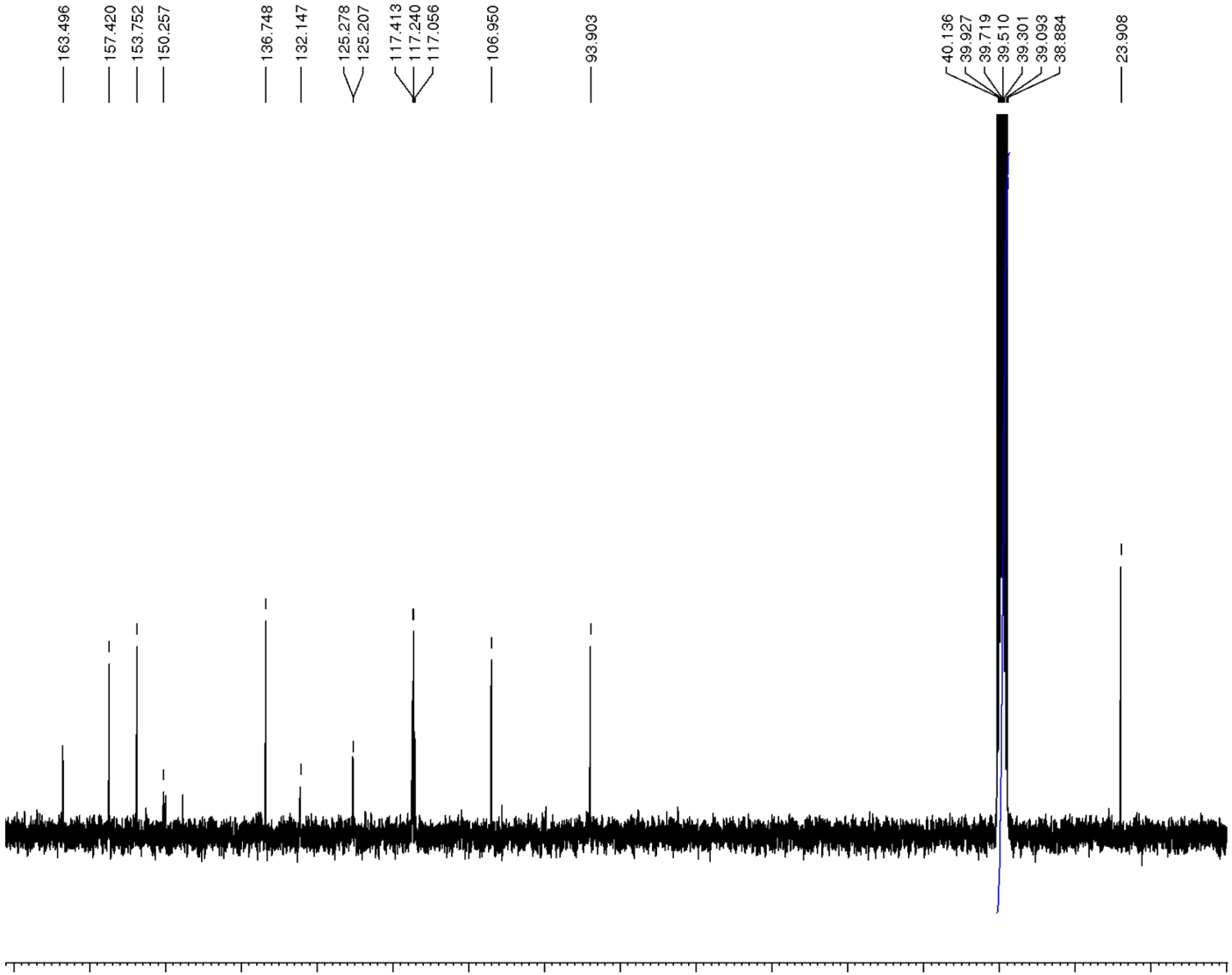



```
Current Data Parameters
NAME                  Surur
EXPNO                   480
PROCNO                    1

F2 - Acquisition Parameters
Date_              20171016
Time                   8.55
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ               1.3631488 sec
RG                     2050
DW                   20.800 use
DE                   10.00 use
TE                   298.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                       1

======== CHANNEL f1 =======
NUC1                    13C
P1                   10.00 use
PL1                  -2.70 dB
PL1W           62.67650986 W
SFO1          100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2           waltz16
NUC2                    1H
PCPD2                60.00 use
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF            100.6128186 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
```

N-[2-Amino-6-(cyclo[illegible]no)pyridin-3-yl]-3,4-difluorobenzamide (**22c**)

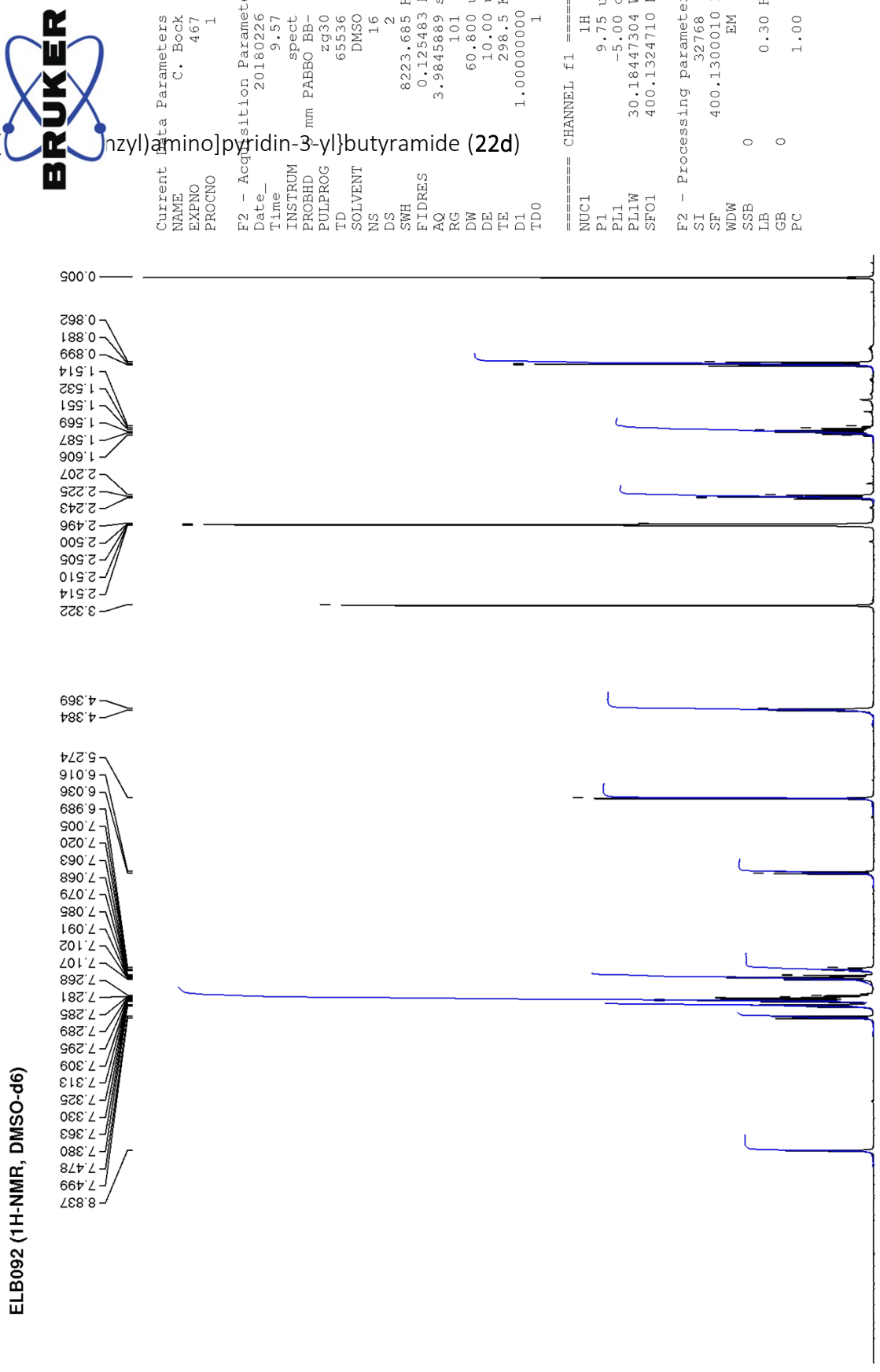


AS-75 (13C-NMR, DMSO-d6)

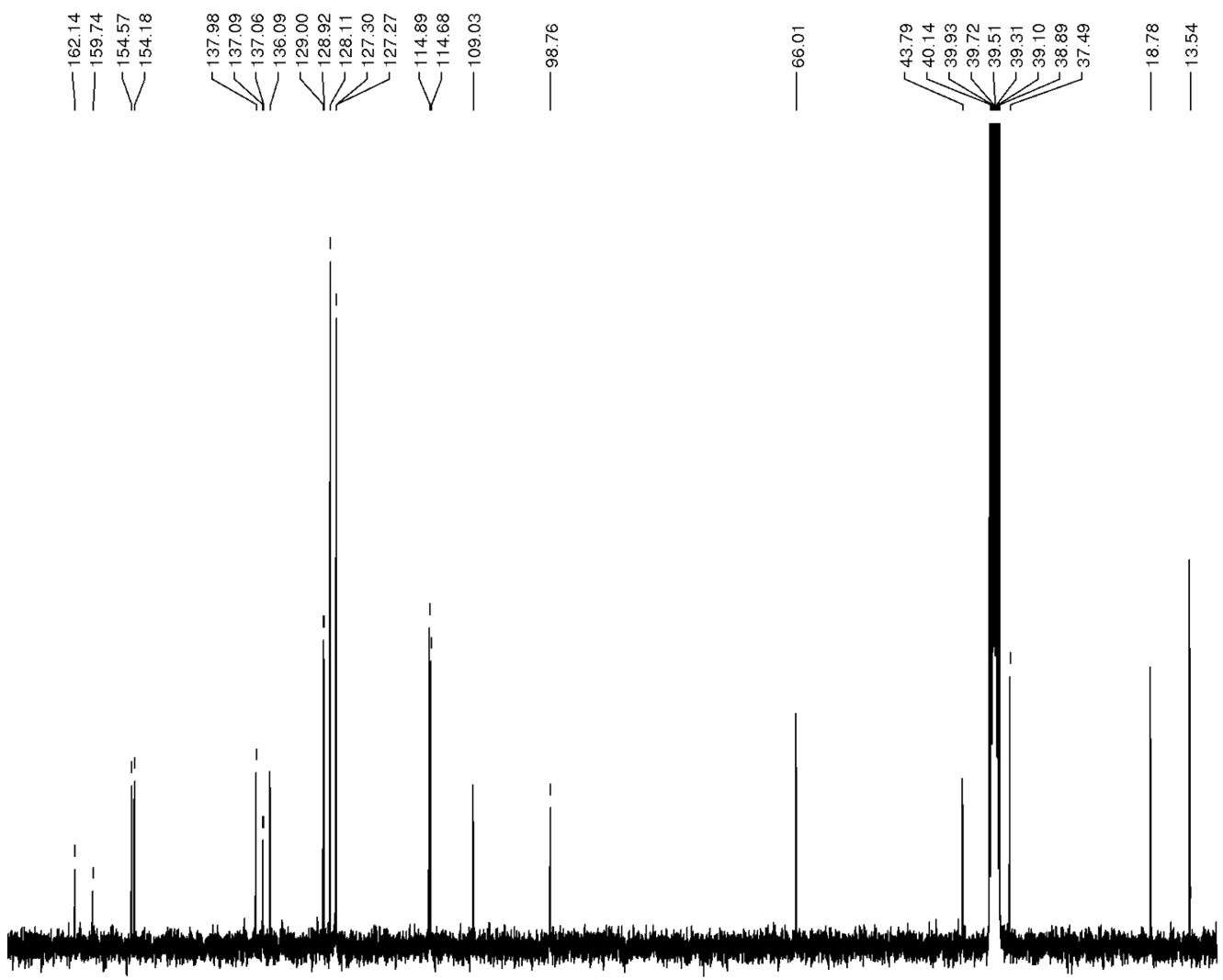



```
Current Data Parameters
NAME                  Surur
EXPNO                   528
PROCNO                    1

F2 - Acquisition Paramete
Date_              20171114
Time                  12.13
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH               24038.461 H
FIDRES             0.366798 H
AQ                 1.3631488 s
RG                      2050
DW                    20.800 u
DE                    10.00 u
TE                    298.6 K
D1              2.00000000 s
D11             0.03000000 s
TD0                       1

======== CHANNEL f1 =====
NUC1                    13C
P1                    10.00 u
PL1                   -2.70 d
PL1W           62.67650986 W
SFO1          100.6228298 M

======== CHANNEL f2 =====
CPDPRG[2            waltz16
NUC2                    1H
PCPD2                 60.00 u
PL2                   -5.00 d
PL12                  10.78 d
PL13                  15.00 d
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2          400.1316005 M

F2 - Processing parameter
SI                    32768
SF            100.6128173 M
WDW                      EM
SSB                       0
```

N-{2-(Benzyloxy)-6-[(benzyl)amino]pyridin-3-yl}butyramide (**22d**)



ELB092 (13C-NMR, DMSO-d6)



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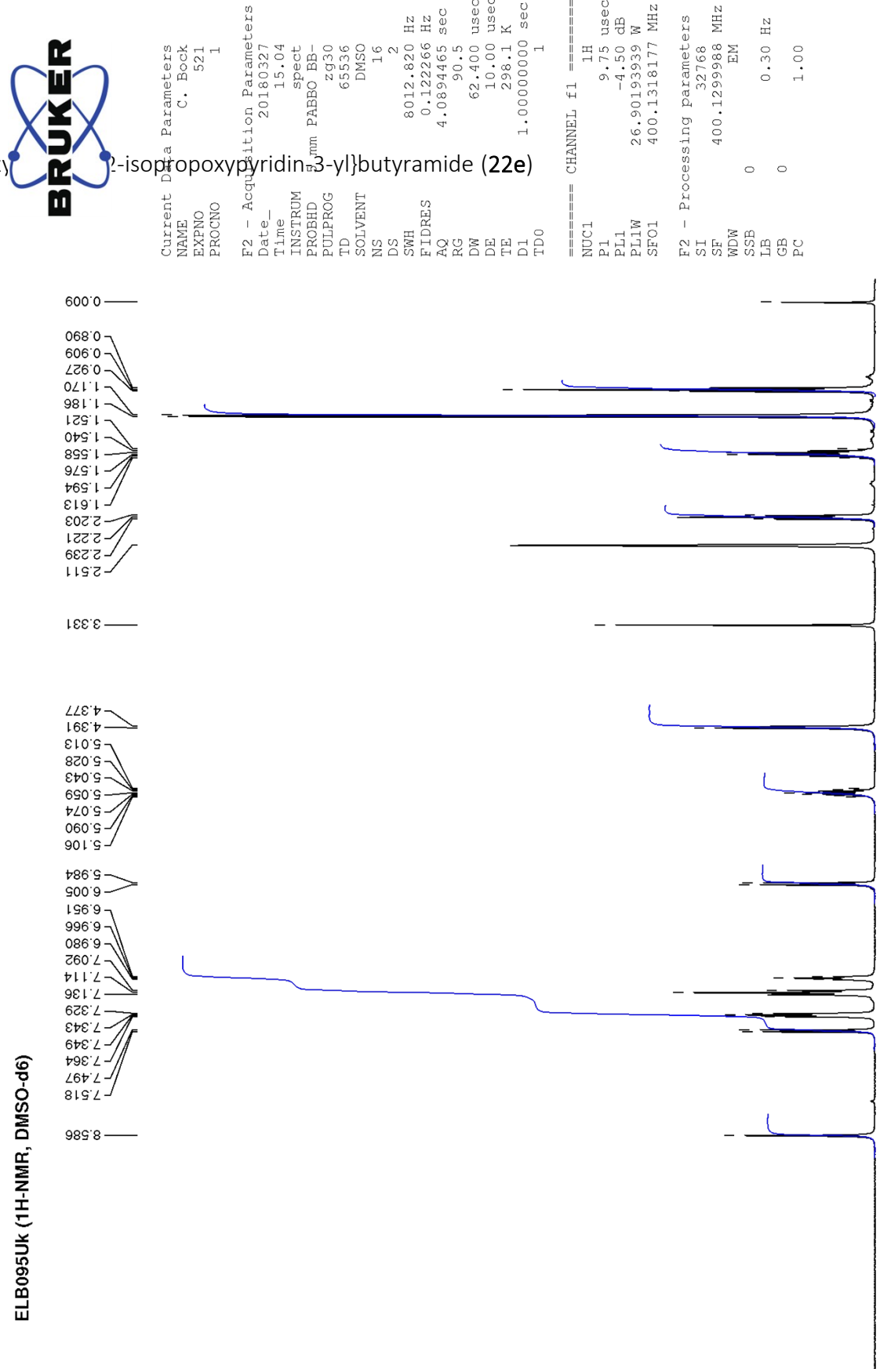
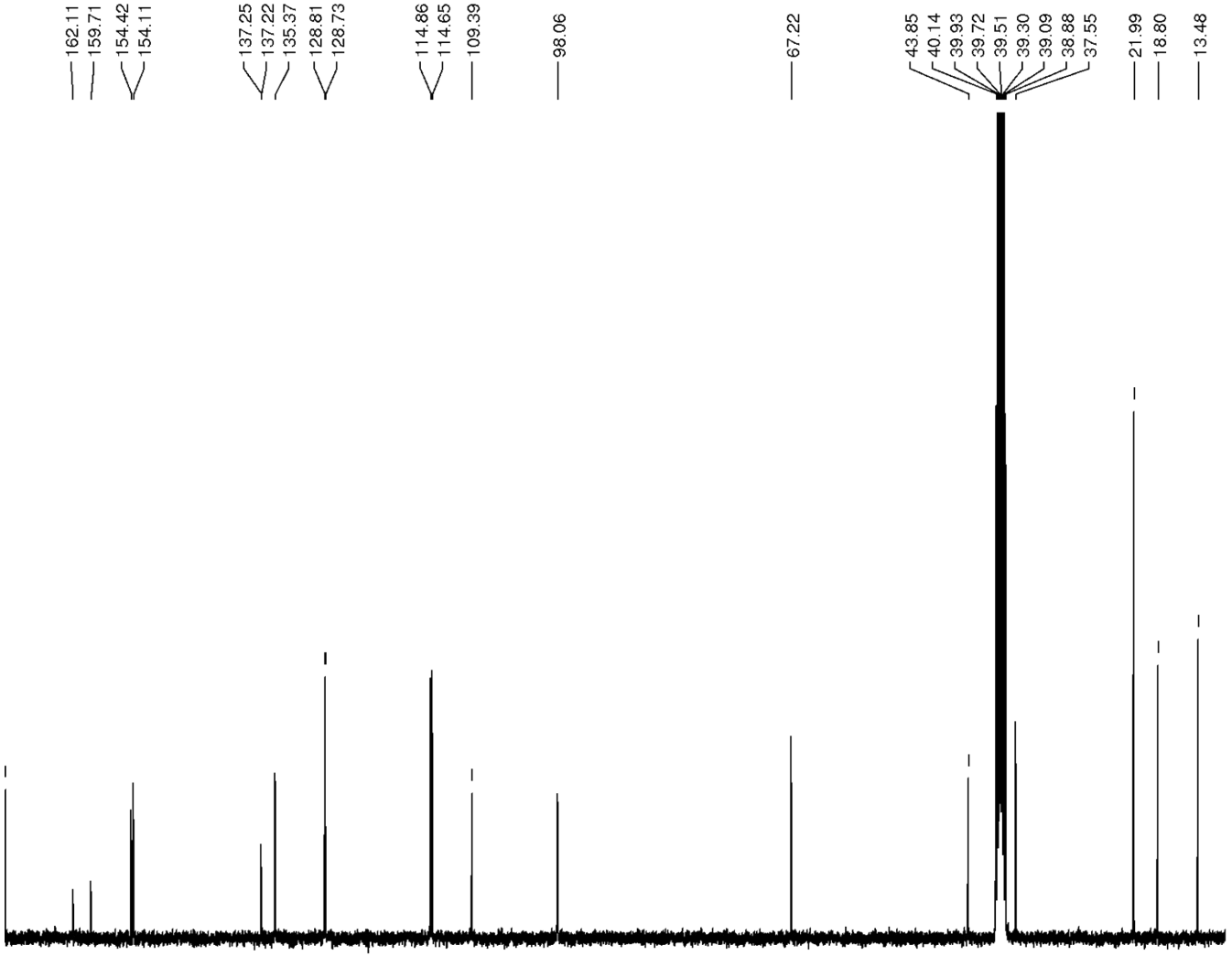
```
Current Data Parameters
NAME                  C. Bock
EXPNO                     468
PROCNO                      1

F2 - Acquisition Parameters
Date_                20180226
Time                    13.05
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                       2000
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       2050
DW                     20.800 use
DE                     10.00 use
TE                     298.9 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

======== CHANNEL f1 =======
NUC1                      13C
P1                     10.00 use
PL1                    -2.70 dB
PL1W              62.67650986 W
SFO1             100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2               waltz16
NUC2                       1H
PCPD2                  60.00 use
PL2                    -5.00 dB
PL12                   10.78 dB
PL13                   15.00 dB
PL2W              30.18447304 W
PL12W              0.79759723 W
PL13W              0.30184472 W
SFO2             400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF               100.6128182 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
```

N-{6-[(4-Fluorbenzyl)oxy]-2-isopropoxypyridin-3-yl}butyramide (**22e**)

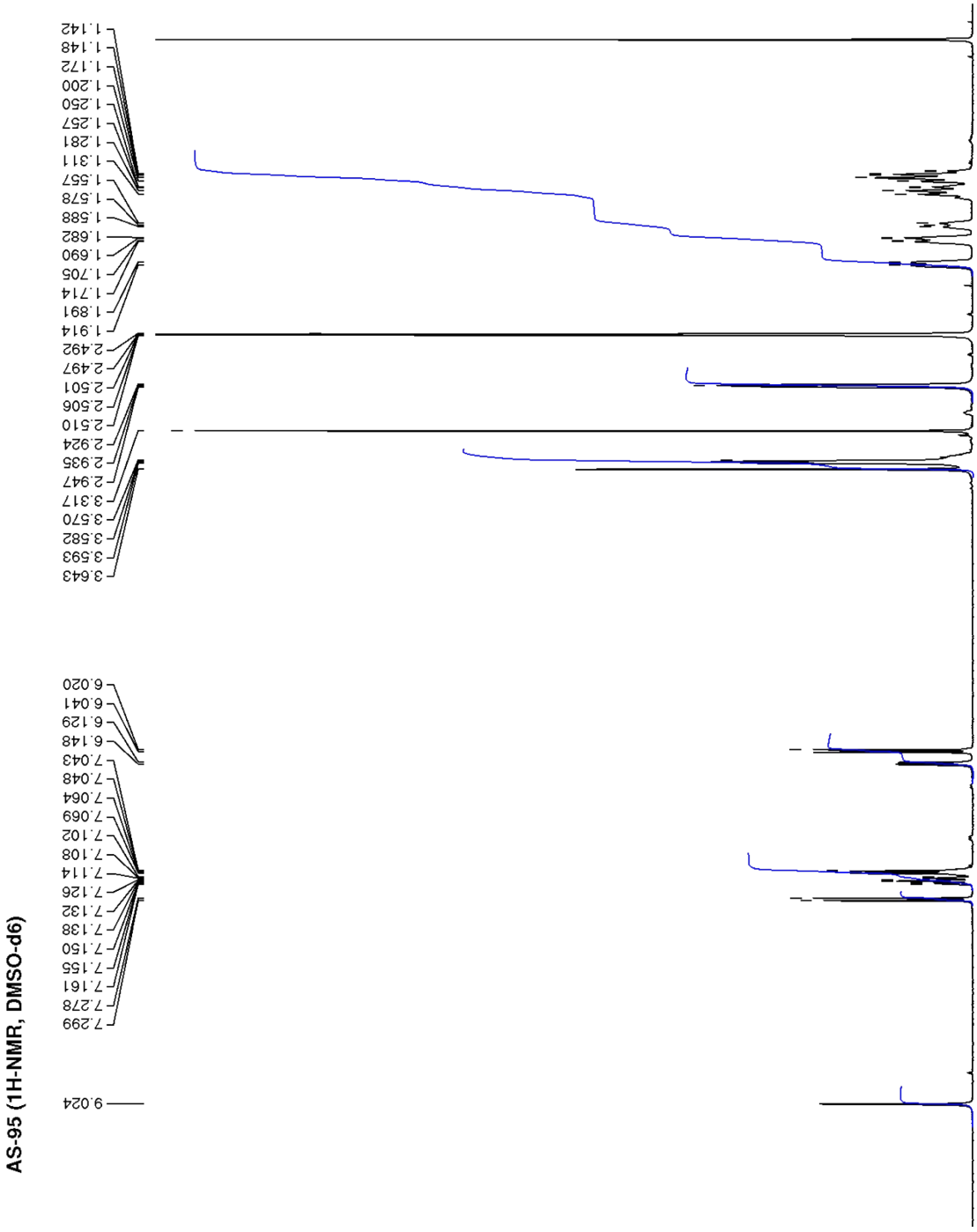


ELB095Uk (13C-NMR, DMSO-d6)

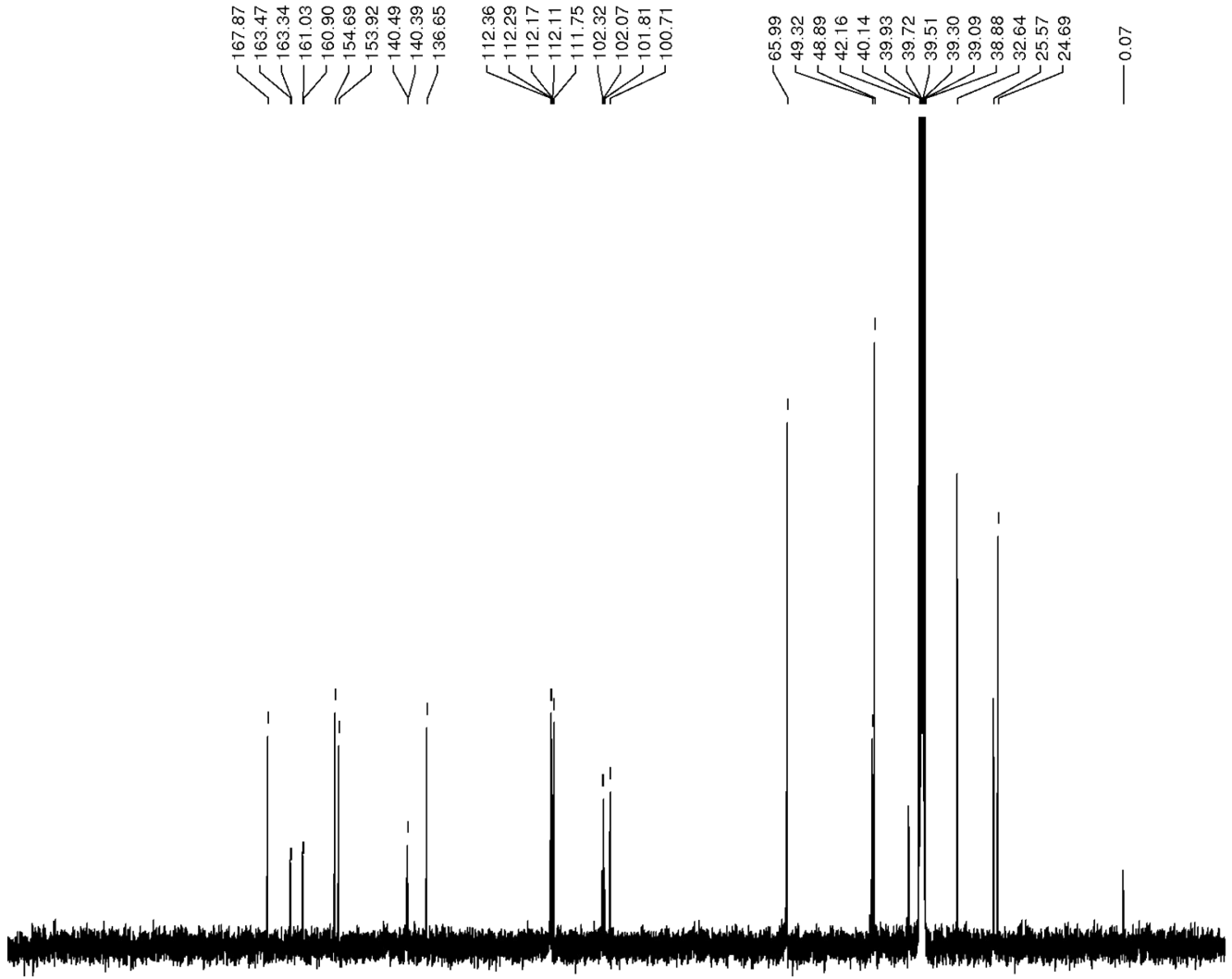



```
Current Data Parameters
NAME                 C. Bock
EXPNO                    524
PROCNO                     1

F2 - Acquisition Parameter
Date_             20180329
Time                  9.48
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT              DMSO
NS                    1500
DS                       4
SWH            24038.461 H
FIDRES          0.366798 H
AQ             1.3631488 se
RG                    2050
DW                 20.800 us
DE                 10.00 us
TE                 298.2 K
D1            2.00000000 se
D11           0.03000000 se
TD0                      1

======== CHANNEL f1 ======
NUC1                  13C
P1                  9.80 us
PL1                -2.00 dB
PL1W         53.34635925 W
SFO1        100.6228298 MH

======== CHANNEL f2 ======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              60.00 us
PL2                -4.50 dB
PL12               11.28 dB
PL13               15.00 dB
PL2W         26.90193939 W
PL12W         0.71085924 W
PL13W         0.30184472 W
SFO2        400.1316005 MH

F2 - Processing parameters
SI                 32768
SF          100.6128181 MH
WDW                   EM
SSB       0
```

N-[6-(Cyclohexylamino)-4-morpholinopyridin-3-yl]-2-(3,5-difluorophenyl)acetamide (25a)

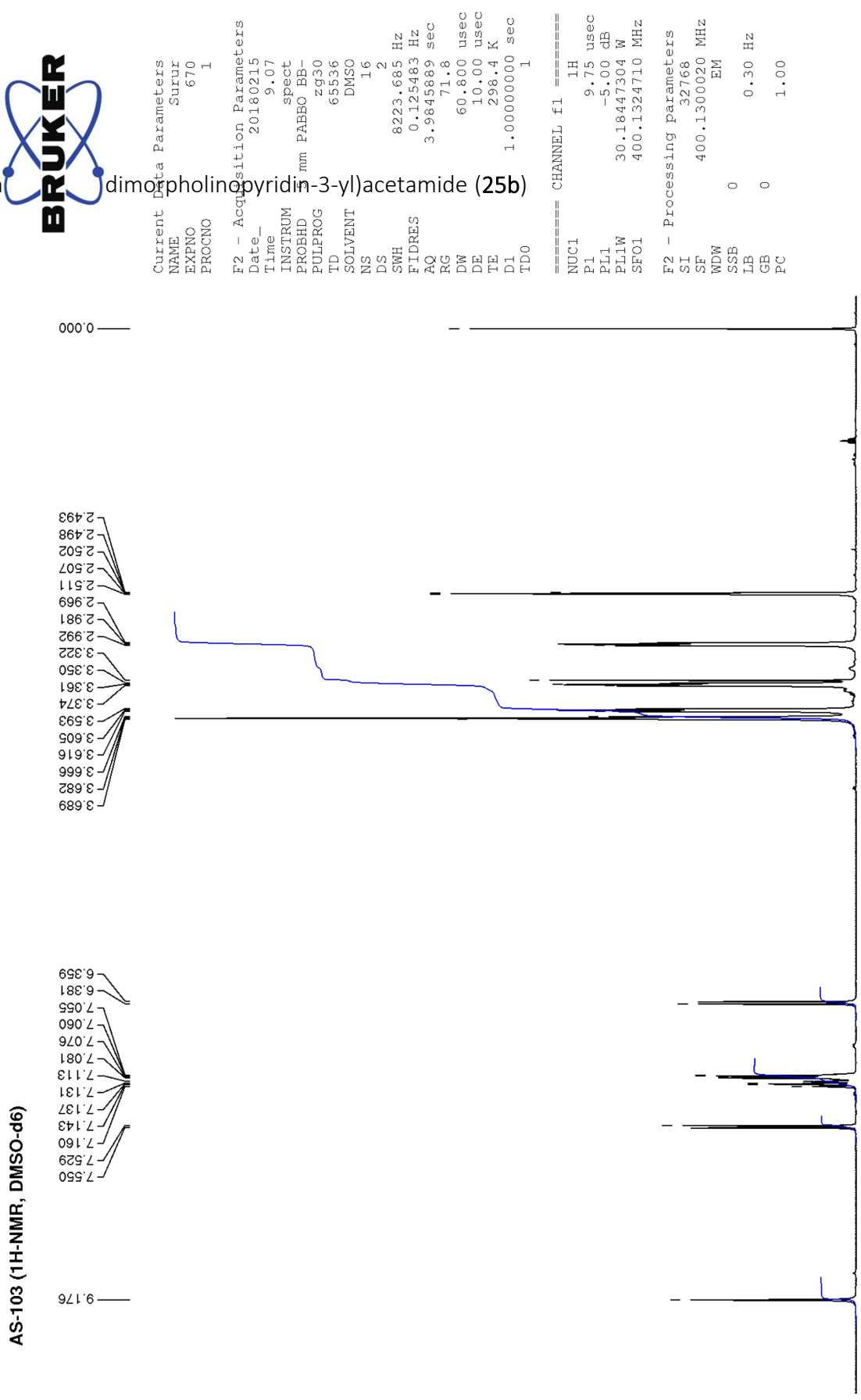


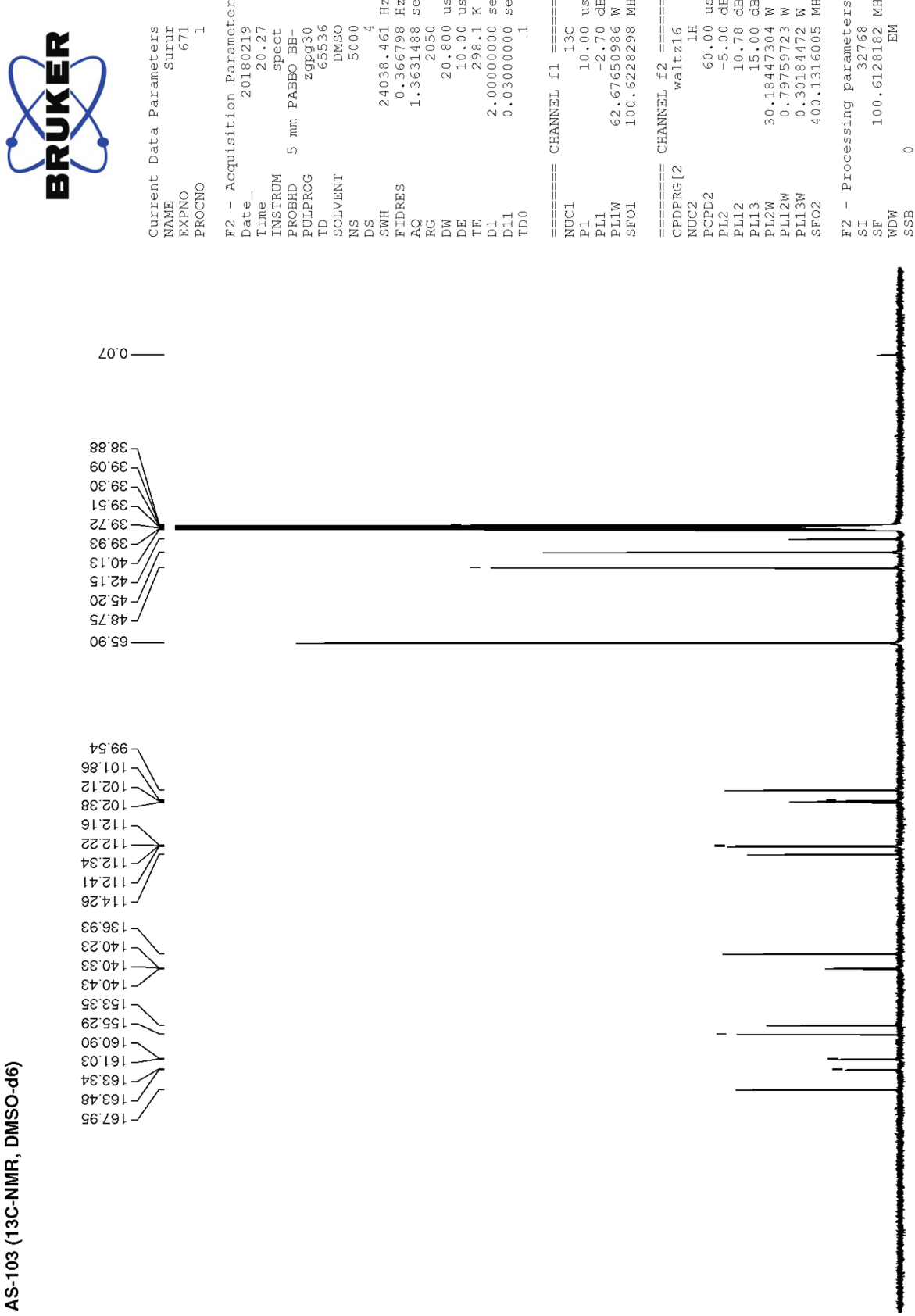
AS-95 (13C-NMR, DMSO-d6)




```
Current Data Parameters
NAME                  Surur
EXPNO                   636
PROCNO                    1

F2 - Acquisition Parameters
Date_              20180119
Time                   8.44
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                     2050
DW                   20.800 use
DE                   10.00 use
TE                   298.1 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 =======
NUC1                    13C
P1                   10.00 use
PL1                  -2.70 dB
PL1W           62.67650986 W
SFO1          100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG[2           waltz16
NUC2                    1H
PCPD2                60.00 use
PL2                  -5.00 dB
PL12                 10.78 dB
PL13                 15.00 dB
PL2W           30.18447304 W
PL12W           0.79759723 W
PL13W           0.30184472 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF            100.6128178 MHz
WDW                      EM
SSB       0
```

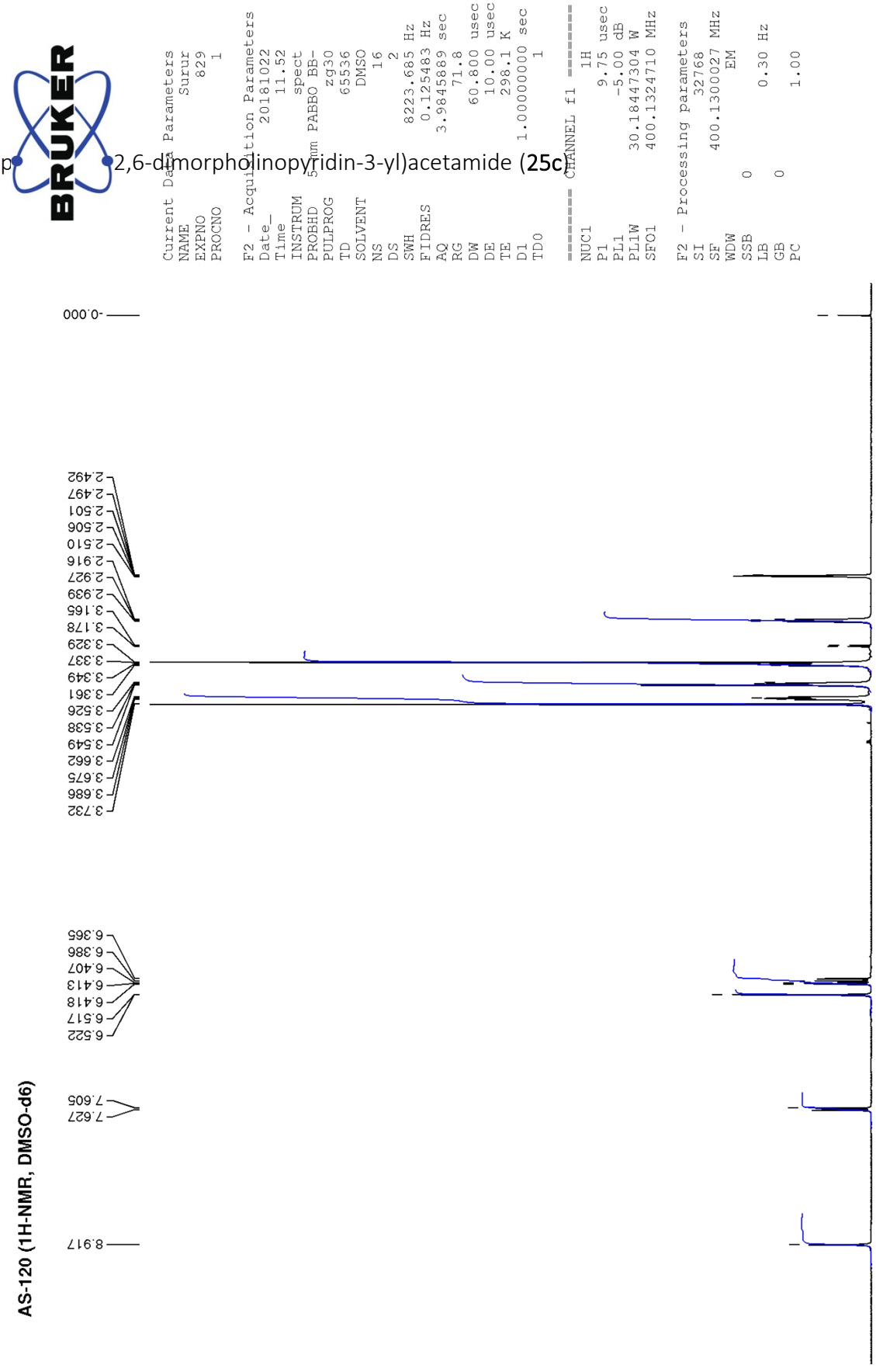
2-(3,5-Difluorophen dimorpholinopyridin-3-yl)acetamide (**25b**)



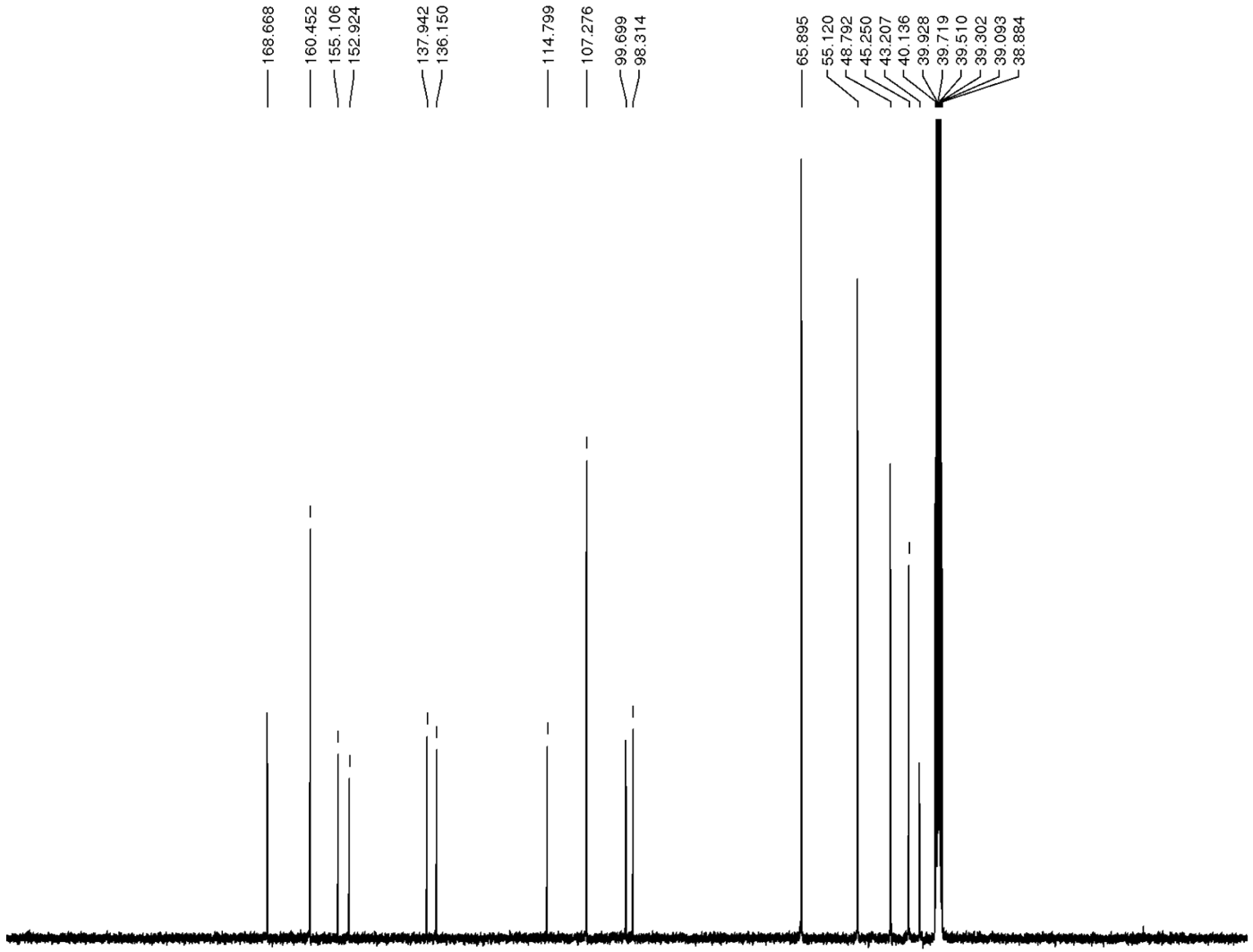


AS-103 (13C-NMR, DMSO-d6)

2-(3,5-Dimethoxyp[illegible]2,6-dimorpholinopyridin-3-yl)acetamide (**25c**)



AS-120 (13C-NMR, DMSO-d6)




```
Current Data Parameters
NAME                  Surur
EXPNO                   830
PROCNO                    1

F2 - Acquisition Paramete
Date_              20181023
Time                  10.47
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                     2500
DS                        4
SWH               24038.461
FIDRES             0.366798
AQ                1.3631488
RG                     2050
DW                   20.800
DE                   10.00
TE                   298.2
D1                2.00000000
D11               0.03000000
TD0                       1

======== CHANNEL f1 =====
NUC1                    13C
P1                    10.00
PL1                   -2.70
PL1W           62.67650986
SFO1           100.6228298

======== CHANNEL f2 =====
CPDPRG[2            waltz16
NUC2                    1H
PCPD2                60.00
PL2                  -5.00
PL12                 10.78
PL13                 15.00
PL2W           30.18447304
PL12W           0.79759723
PL13W           0.30184472
SFO2           400.1316005

F2 - Processing paramete
SI                    32768
SF             100.6128175
WDW                      EM
```