SUPPORTING INFORMATION

Synthesis and potassium K_V7 channel opening activity of thioether analogues of the analgesic flupirtine

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Contents

Experimental

All commercial reagents and solvents were used without further purification.

Reaction control via TLC was performed on silica gel 60 F_{254} aluminium plates from Merck using UV-light (254 nm and 366 nm) for visualization.

NMR spectra were recorded with a Bruker Avance III instrument at 400 MHz (^{1}H-NMR) and 101 MHz (^{13}C-NMR), respectively. The samples were found in DMSO-d_6 solution with tetramethylsilane as an internal standard at 25 °C.

HRMS were obtained with an LCMS-IT-TOF (Shimadzu) by using electrospray ionization.

IR spectra were recorded on an ALPHA FT-IR spectrometer from Bruker with the help of ATR technology.

Melting points were found automatically with the Melting Point M-565 (Büchi).

The compound purities were determined by HPLC with DAD (100 % method at 220 nm).

Flash chromatography was performed (unless stated otherwise) on a glass column using silica gel 60 from Carl Roth GmbH + Co. KG with a particle size of 20–45 µm. The flow rate was adjusted to approximately 25 mL/min by applying pressure with compressed air.

6-Chloro-3-nitropyridin-2-amine: 2,6-Dichloro-3-nitropyridine (100 mmol, 19.2 g) was suspended in 200 mL ethanol and cooled to 0 °C. Ammonia gas was bubbled into the suspension for 3 hours while the temperature was kept at 0 °C. Afterwards the flask was sealed with a stopper and the reaction stirred at r.t. overnight. The product was precipitated with 400 mL water and filtered off. The yellow coloured solid was washed with 200 mL water, 200 mL *n*-hexane and dried at 70 °C in the oven. Yellow solid (m.p.: 190–192 °C). Yield: 16.2 g (93.6%). R_f = 0.80 (cyclohexane/ethanol/Et_3N 6:2:2). ^{1}H-NMR [ppm]: δ = 6.77 (d, 1H, *J* = 8.6 Hz), 8.25 (s, 2H), 8.39 (d, 1H, *J* = 8.6 Hz). ^{13}C-NMR [ppm]: δ = 112.0, 126.1, 138.3, 153.4, 155.0. IR [cm^{-1}]: $\tilde{\nu}$ = 1552, 1594, 3157, 3364, 3442.

6-Amino-5-nitropyridine-2-thiol (5): A mixture of 6-chloro-3-nitropyridin-2-amine (30 mmol, 5.2 g), sulfur (0.9 eq, 27 mmol, 0.86 g), $Na_2S{\cdot}9H_2O$ (0.9 eq, 27 mmol, 6.49 g) and NaOH (1 eq, 30 mmol, 1.2 g) were suspended in 125 mL ethanol and refluxed for 2.5 hours. The crude product was evaporated to dryness and the residue dissolved in 400 mL water. The aqueous phase was extracted twice with 200 mL dichloromethane and subsequently acidified with 1 M HCl until pH 2. The product precipitated as an orange coloured solid and could be collected by filtration. Drying was achieved by heating to 70 °C in the oven for 5 hours. Orange solid (m.p.: 180–183 °C). Yield: 4.76 g (92.7%). R_f = 0.36 (*n*-hexane/ethyl acetate 4:6). ^{1}H-NMR [ppm]: δ = 6.49 (d, 1H, *J* = 9.5 Hz), 7.53 (bs, 1H), 7.92 (d, 1H, *J* = 9.5 Hz), 8.66 (bs, 1H), 12.61 (s, 1H). ^{13}C-NMR [ppm]: δ = 118.8, 119.5, 131.9, 149.5, 183.8. IR [cm^{-1}]: $\tilde{\nu}$ = 1087, 1570, 3247, 3387.

General procedure for synthesizing compounds **5a**–**5d**: 1 eq of **5** was dissolved in DMF (4 mL per mmol of **5**) and 1 eq of NaOH (as 3 M solution in water) was added to form a dark brown coloured solution. 1 eq of a suitable substituted benzyl bromide was added whereby the solution changed to orange. The reaction was stirred at r.t.

and monitored by TLC. After completion the mixture was poured into water. The resulting yellow precipitate was filtered off, washed with water and dried under reduced pressure at 40 °C.

6-[(4-Fluorobenzyl)thio]-3-nitropyridin-2-amine (5a): 5 (10 mmol, 1.71 g) was reacted with 4-fluorobenzyl bromide (10 mmol, 1.25 mL) and 4.3 mL 3 M NaOH. The reaction was completed after 3 hours. Yellow solid (m.p.: 139–141 °C). Yield: 1.98 g (70.0%). R_f = 0.35 (*n*-hexane/ethyl acetate 9:1). ^{1}H-NMR [ppm]: δ = 4.46 (s, 2H), 6.61 (d, 1H, *J* = 8.8 Hz), 7.13 (m, 2H), 7.53 (m, 2H), 8.15 (d, 1H, *J* = 8.8 Hz), 8.18 (bs, 2H). ^{13}C-NMR [ppm]: δ = 32.2, 110.3, 115.1 (d, 2C, $^2J_{C,F}$ = 22 Hz), 123.5, 131.1 (d, 2C, $^3J_{C,F}$ = 8 Hz), 134.2 (d, $^4J_{C,F}$ = 3 Hz), 134.5, 153.1, 160.1 and 162.5 (d, $^1J_{C,F}$ = 242 Hz), 166.3. IR [cm^{-1}]: $\tilde{\nu}$ = 1342, 1558, 3332, 3456.

6-(Benzylthio)-3-nitropyridin-2-amine (5b): 5 (3 mmol, 0.51 g) was reacted with benzyl bromide (3 mmol, 0.36 mL) and 1.3 mL 3 M NaOH. The reaction was completed after 3 hours. Yellow solid (m.p.: 151–153 °C). Yield: 0.65 g (82.9%). R_f = 0.53 (*n*-hexane/ethyl acetate 9:1). ^{1}H-NMR [ppm]: δ = 4.47 (s, 2H), 6.62 (d, 1H, *J* = 8.8 Hz), 7.22–7.26 (m, 1H), 7.29–7.33 (m, 2H), 7.47 (d, 2H, *J* = 7.2 Hz), 8.08–8.23 (bs, 2H), 8.16 (d, 1H, *J* = 8.7 Hz). ^{13}C-NMR [ppm]: δ = 33.1, 110.2, 123.4, 127.1, 128.4 (2C), 129.1 (2C), 134.4, 137.7, 153.1, 166.6. IR [cm^{-1}]: $\tilde{\nu}$ = 1144, 1345, 1560, 3335, 3459.

6-[(3,4-Difluorobenzyl)thio]-3-nitropyridin-2-amine (5c): **5 (**5 mmol, 0.85 g) was reacted with 3,4-difluorobenzyl bromide (5 mmol, 0.64 mL) and 2.2 mL 3 M NaOH. After 2 hours additional 3,4-difluorobenzyl bromide (1 mmol, 0.13 mL) were added. After further 2 hours the reaction was completed. Yellow solid (m.p.: 135–138 °C). Yield: 1.44 g (97.0%). R_f = 0.75 (cyclohexane/ethanol/Et_3N 6:2:2). ^{1}H-NMR [ppm]: δ = 4.44 (s, 2H), 6.61 (d, 1H, *J* = 8.8 Hz), 7.34–7.38 (m, 2H), 7.59–7.65 (m, 2H), 8.16 (d, 1H, *J* = 8.8 Hz), 8.21 (bs, 2H). ^{13}C-NMR [ppm]: δ = 31.9, 110.3, 117.3 (d, $^2J_{C,F}$ = 17 Hz), 118.2 (d, $^2J_{C,F}$ = 17 Hz), 123.5, 126.1 (dd, $^3J_{C,F}$ = 6 Hz, $^4J_{C,F}$ = 3 Hz), 134.6, 136.1 (dd, $^3J_{C,F}$ = 6 Hz, $^4J_{C,F}$ = 4 Hz), 147.3 and 149.7 (dd, $^1J_{C,F}$ = 245 Hz, $^2J_{C,F}$ = 13 Hz), 147.8 and 150.2 (dd, $^1J_{C,F}$ = 245 Hz, $^2J_{C,F}$ = 13 Hz), 153.1, 165.8. IR [cm^{-1}]: $\tilde{\nu}$ = 1149, 1165, 1346, 1560, 3331, 3464.

3-Nitro-6-{[4-(trifluoromethyl)benzyl]thio}pyridin-2-amine (5d): 5 (5 mmol, 0.85 g) was reacted with 4-(trifluoromethyl)benzyl bromide (5 mmol, 0.77 mL) and 2.2 mL 3 M NaOH. After 45 min additional of 4-(trifluoromethyl)benzyl bromide (1.5 mmol, 0.23 mL) were added. The reaction was completed after further 30 min. Yellow solid (m.p.: 128–130 °C). Yield: 1.67 g (101.2%, due to some bisalkylated by-product). ^{1}H-NMR [ppm]: δ = 4.55 (s, 2H), 6.63 (d, 1H, *J* = 8.8 Hz), 7.67 (d, 2H, *J* = 8.2 Hz), 7.74 (d, 2H, *J* = 8.2 Hz), 8.16 (d, 1H, *J* = 8.8 Hz), 8.19 (bs, 2H). ^{13}C-NMR [ppm]: δ = 32.3, 110.2, 122.8 and 125.5 (d, 2H, $^1J_{C,F}$ = 270 Hz), 123.5, 125.1 (q, 2C, $^4J_{C,F}$ = 4 Hz), 127.6 (q, 2C, $^2J_{C,F}$ = 32 Hz), 129.9 (2C), 134.5, 143.1, 153.0, 165.7. IR [cm^{-1}]: $\tilde{\nu}$ = 1122, 1341, 1560, 3335, 3460.

Ethyl-{2-amino-6-[(4-fluorobenzyl)thio]pyridin-3-yl}carbamate (6a):

Method A: A three-neck round-bottom flask was equipped with **5a** (3.65 mmol, 1.02 g), $SnCl_2 \cdot 2H_2O$ (5.1 eq, 18.6 mmol, 4.2 g) and 40 mL ethanol. The mixture was put under an argon atmosphere and heated to 70 °C for 25 hours. Afterwards, the temperature was lowered to 40 °C and Et_3N (10.2 eq, 37.2 mmol, 5.16 mL), as well as ethyl chloroformate (1.26 eq, 4.6 mmol 0.44 mL), were added slowly to the suspension. After 30 min the temperature was increased to 55 °C and kept for one additional hour. After cooling to r.t. the mixture was filtered

through a pad of celite and washed with ethanol. The filtrate was evaporated to dryness and distributed between water and dichloromethane. The organic layer was evaporated to dryness and the residue washed with *n*-hexane. White solid (m.p.: 138–140 °C). Yield: 0.86 g (73.0%).

Method B: **5a** (5 mmol, 1.4 g) was suspended in 30 mL water and 50 mL 2-propanol. Iron powder (3 eq, 15 mmol, 0.84 g) and NH_4Cl (4.5 eq, 22.5 mmol, 1.2 g) were added and the suspension refluxed for 5 hours. The resulting dark brown mixture was filtered and evaporated to dryness. The residue was diluted with 150 mL water and extracted three times with 60 mL ethyl acetate. The combined organic layers were washed with 150 mL saturated brine and dried over Na_2SO_4. Et_3N (1.4 eq, 7 mmol, 0.97 mL) was added and the solution cooled to 0 °C. A solution of ethyl chloroformate (1.2 eq, 6 mmol, 0.57 mL) in 5 mL ethyl acetate was added drop wise. After 2 hours additional ethyl chloroformate (1.2 eq, 6 mmol, 0.57 mL) were added at r.t., 5 hours later, ethyl chloroformate (0.6 eq, 3 mmol, 0,29 mL) and Et_3N (0.7 eq, 3.5 mmol, 0.49 mL) were added. After 2 hours the reaction was completed and the solution washed with 200 mL water and 200 mL saturated brine. After drying with Na_2SO_4 and evaporation to dryness the resulting solid was recrystallized from DCM. The product was dried at 40 °C under reduced pressure. Brown solid (m.p.: 140–142). Yield: 0.75 g (47%). Compound purity: 100.0%. R_f = 0.83 (cyclohexane/ ethanol/Et_3N 6:2:2). ^{1}H-NMR [ppm]: δ = 1.22 (t, 3H, *J* = 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.29 (s, 2H), 5.94 (s, 2H), 6.43 (d, 1H, *J* = 8.0 Hz), 7.07–7.12 (m, 2 H), 7.40–7.45 (m, 3H), 8.57 (m, 1H). ^{13}C-NMR [ppm]: δ = 14.5, 32.6, 60.3, 109.3, 115.0 (d, 2C, $^2J_{C,F}$ = 21 Hz), 115.2, 130.7 (d, 2C, $^3J_{C,F}$ = 8 Hz), 131.8, 135.0 (d, $^4J_{C,F}$ = 3 Hz), 150.2, 152.8, 154.4, 159.9 and 162.3 (d, $^1J_{C,F}$ = 243 Hz). IR [cm^{-1}]: $\tilde{\nu}$ = 1454, 1678, 2984, 3145, 3260, 3403. HRMS: $[C_{15}H_{16}N_3O_2FS + H]^+$ req.: 322.1020, found: 322.1027.

Ethyl-[2-amino-6-(benzylthio)pyridin-3-yl]carbamate (6b): **5b** (2.31 mmol, 0.60 g) was suspended in a mixture of 15 mL water and 25 mL 2-propanol. Iron powder (3 eq, 6.93 mmol, 0.39 g) and NH_4Cl (4.5 eq, 10.4 mmol, 0.56 g) were added and the suspension refluxed for 6 hours. The resulting dark brown mixture was filtered and the residue washed with 50 mL 2-propanol. Et_3N (6.0 eq, 13.9 mmol, 1.91 mL) and ethyl chlorofomate (2.4 eq, 5.54 mmol, 0.53 mL) were added. The solution was stirred at 40 °C and reaction progress monitored by TLC. After 1 hour and after 2 hours ethyl chlorofomate (2.4 eq, 5.54 mmol, 0.53 mL) were added to complete the reaction. The solution was evaporated to dryness and the resulting solid dissolved in 100 mL ethyl acetate. The organic phase was washed with 2×100 mL water as well as 100 mL saturated brine. After drying with Na_2SO_4 the crude product was purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate 7:3). The resulting brown solid was washed with small quantities of ice-cold diethyl ether and dried at 40 °C under reduced pressure. Light blue solid (m.p.: 100–101 °C). Yield: 0.23 g (33.0%). Compound purity: 100.0%. R_f = 0.72 (cyclohexane/ethanol/Et_3N 6:2:2). ^{1}H-NMR [ppm]: δ = 1.22 (t, 3H, *J* = 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.30 (s, 2H), 5.93 (s, 2H), 6.44 (d, 1H, *J* = 8.0 Hz), 7.21 (t, 1H, *J* = 7.3 Hz), 7.28 (t, 2H, *J* = 7.3 Hz), 7.39–7.41 (m, 3H), 8.57 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.5, 33.5, 60.3, 109.2, 115.2, 126.8, 128.3 (2C), 128.8 (2C), 131.8, 138.6, 150.5, 152.7, 154.4. IR [cm^{-1}]: $\tilde{\nu}$ = 1457, 1681, 2975, 3140, 3281, 3405. HRMS: $[C_{15}H_{17}N_3O_2S + H]^+$ calculated: 304.1114, found: 304.1099.

Ethyl-{2-amino-6-[(3,4-difluorobenzyl)thio]pyridin-3-yl}carbamate (6c): **5c** (5 mmol, 1.49 g) was suspended in a mixture of 30 mL water and 50 mL 2-propanol. Iron powder (3 eq, 15 mmol, 0.84 g) and NH_4Cl (4.5 eq,

22.5 mmol, 1.2 g) were added and the suspension refluxed for 3.5 hours. The resulting dark brown mixture was filtered and the residue washed with 100 mL 2-propanol. Et_3N (3.0 eq, 15 mmol, 2.07 mL) and ethyl chlorofomate (1.2 eq, 6 mmol, 0.57 mL) were added. The solution was stirred for 2 hours at 40 °C. Since TLC monitoring showed no complete conversion ethyl chlorofomate (0.6 eq, 3 mmol, 0.29 mL) were added and additional ethyl chloroformate (0.5 eq, 2.5 mmol, 0.24 mL) as well as Et_3N (1 eq, 5 mmol, 0.69 mL) after further 2 hours. After 5 hours the reaction was completed and the solution evaporated to dryness. The solid was dissolved in 100 mL ethyl acetate and the solution washed with 2×100 mL water as well as 100 mL saturated brine. After drying with Na_2SO_4 the crude product was dissolved in 50 mL isopropanol and precipitated with 100 mL water. The crude product was purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate 7:3) and dried at 40 °C under reduced pressure. White solid (m.p.: 137–140 °C). Yield: 0.95 g (56.0%). Compound purity: 100.0%. R_f = 0.39 (*n*-hexane/ethyl acetate 7:3). ^{1}H-NMR [ppm]: δ = 1.22 (t, 3H, *J* = 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.29 (s, 2H), 5.99 (s, 2H), 6.42 (d, 1H, *J* = 8.0 Hz), 7.24–7.36 (m, 2H), 7.4 (d, 1H, *J* = 6.3 Hz), 7.45–7.50 (m, 1H), 8.57 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.5, 32.2, 60.4, 109.3, 115.3, 117.1 (d, $^2J_{C,F}$ = 17 Hz), 117.8 (d, $^2J_{C,F}$ = 17 Hz), 125.7 (dd, $^3J_{C,F}$ = 6 Hz, $^4J_{C,F}$ = 3 Hz), 132.0, 137.0 (dd, $^3J_{C,F}$ = 6 Hz, $^4J_{C,F}$ = 4 Hz), 147.2 and 149.6 (dd, $^1J_{C,F}$ = 245 Hz, $^2J_{C,F}$ = 13 Hz). 147.8 and 150.2 (dd, $^1J_{C,F}$ = 245 Hz, $^2J_{C,F}$ = 13 Hz), 152.9, 154.4. IR [cm^{-1}]: $\tilde{\nu}$ = 1203, 1454, 1510, 1674, 2991, 3149, 3272, 3396. HRMS: $[C_{15}H_{15}N_3O_2F_2S + H]^+$ calculated: 340.0926, found: 340.0919.

Ethyl-(2-amino-6-{[4-(trifluoromethyl)benzyl]thio}pyridin-3-yl)carbamate (6d):

Method A: A three-neck round-bottom flask was equipped with **5d** (1.52 mmol, 0.50 g), $SnCl_2 \bullet 2H_2O$ (5.2 eq, 7.9 mmol, 1.79 g) and 20 mL ethanol. The mixture was put under an argon atmosphere and heated to 70 °C for 23 hours. Afterwards, the temperature was lowered to 40 °C and Et_3N (10.2 eq, 15.4 mmol, 2.14 mL), as well as ethyl chloroformate (1.27 eq, 1.9 mmol, 0.18 mL), were added slowly to the suspension. After 30 min the temperature was increased to 55 °C and kept for one additional hour. After cooling to r.t. the mixture was filtered through a pad of celite and washed with ethanol. The filtrate was evaporated to dryness and distributed between water and dichloromethane. The organic layer was evaporated to dryness and the residue washed with *n*-hexane. The product was dried at 40 °C under reduced pressure. White solid (m.p.: 166–168 °C). Yield: 0.42 g (74.0%).

Method B: **5c** (5 mmol, 1.65 g) was suspended in a mixture of 30 mL water and 50 mL 2-propanol. Iron powder (3 eq, 15 mmol, 0.84 g) and NH_4Cl (4.5 eq, 22.5 mmol, 1.2 g) were added and the suspension refluxed for 4 hours. The resulting dark brown mixture was filtered and the residue washed with 100 mL 2-propanol. Et_3N (5.0 eq, 25 mmol, 3.45 mL) and ethyl chlorofomate (1.2 eq, 6 mmol, 0.57 mL) were added. The solution was stirred for 3 hours at 40 °C. Since TLC monitoring showed no complete conversion ethyl chlorofomate (1.2 eq, 6 mmol, 0.57 mL) and Et_3N (1 eq, 5 mmol, 0.69 mL) were added. After 7 hours ethyl chloroformate (0.6 eq, 3 mmol, 0.29 mL) and Et_3N (0.6 eq, 3 mmol, 0.41 mL) were added again. The reaction was completed after 2 more hours and the solution evaporated to dryness. The solid was dissolved in 150 mL ethyl acetate and the solution washed with 2×100 mL water as well as 100 mL saturated brine. After drying with Na_2SO_4 the crude product was purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate 7:3). The resulting brown solid was washed with small quantities of ice-cold diethyl ether and dried at 40 °C under reduced pressure. White solid (m.p.: 170–171 °C). Yield: 0.71 g (38.2%). Compound purity: 100.0%. R_f = 0.58 (*n*-hexane/ethyl acetate 7:3). ^{1}H-NMR [ppm]: δ = 1.22 (t, 3H, *J* = 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.39 (s, 2H), 5.97 (s, 2H), 6.44 (d, 1H, *J* = 8.0 Hz), 7.41 (d, 1H,

J = 5.6 Hz), 7.64 (s, 4H), 8.57 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.5, 32.8, 60.4, 109.3, 115.3, 122.9 and 125.6, 125.1 (q, 2C, $^{4}J_{C,F}$ = 4 Hz), 127.4 (q, $^{2}J_{C,F}$ = 32 Hz), 129.6 (2C), 131.8, 144.1, 149.6, 152.7, 154.4. IR [cm^{-1}]: $\tilde{\nu}$ = 1113, 1460, 1685, 2980, 3174, 3307, 3423. HRMS: $[C_{16}H_{16}N_3O_2F_3S + H]^+$ calculated: 372.0988, found: 372.0970.

Ethyl-{2-amino-6-[(4-fluorobenzyl)sulfinyl]pyridin-3-yl}carbamate (7a): **6a** (0.5 mmol, 0.17 g) was dissolved in 10 mL DCM and cooled to 0 °C. *meta*-Chloroperoxybenzoic acid (*m*CPBA, 1.1 eq, 0.55 mmol, 0.17 g of a 55% mixture with water) were dissolved in 10 mL DCM and added dropwise within 30 min. The solution was stirred for 3 hours while the product precipitated as a white solid. The suspension was evaporated to dryness and purified by flash chromatography (mobile phase: DCM/MeOH 95:5). The product was washed with diethyl ether, sat. $NaHCO_3$ solution and water and dried under reduced pressure at 40 °C. Light pink solid (m.p.: 202–204 °C). Yield: 0.11 g (65.1%). Compound purity: 100.0%. R_f = 0.58 (*n*-hexane/ethyl acetate 5:5). ^{1}H-NMR [ppm]: δ = 1.25 (t, 3H, *J* = 7.1), 3.99 (d, 1H, *J* = 13.0 Hz), 4.14 (q, 2H, *J* = 7.0 Hz), 4.32 (d, 1H, *J* = 13.0 Hz), 6.38 (s, 2H), 6.72 (d, 1H, *J* = 7.9 Hz), 7.05–7.12 (m, 4H), 7.82 (d, 1H, *J* = 7.5 Hz), 8.86 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.5, 57.6, 60.7, 108.7, 114.9 (d, 2C, $^{2}J_{C,F}$ = 21 Hz), 120.5, 126.6 (d, $^{4}J_{C,F}$ = 3 Hz), 129.5, 132.2 (d, 2C, $^{3}J_{C,F}$ = 8 Hz), 152.0, 154.2, 154.6, 160.7 and 163.0 (d, $^{1}J_{C,F}$ = 244 Hz). IR [cm^{-1}]: $\tilde{\nu}$ = 1219, 1466, 1532, 1731, 2978, 3213, 3294, 3347. HRMS: $[C_{15}H_{16}N_3O_3FS + H]^+$ req.: 338.0969, found: 338.0978.

Ethyl-[2-amino-6-(benzylsulfinyl)pyridin-3-yl]carbamate (7b): **6b** (1 mmol, 0.30 g) was dissolved in 20 mL DCM and cooled to 0 °C. *m*CPBA (1.1 eq, 1.1 mmol, 0.34 g of a 55% mixture with water) was dissolved in 30 mL DCM and added drop wise over a period of 2 hours. The resulting solution was stirred for further 3 hours. After evaporation of approximately 50% of the solvent a white precipitate was formed. The precipitation was completed by storage of the suspension at 4 °C for 72 hours. The solid was filtered off and washed with sat. $NaHCO_3$ solution. The crude product was purified by flash chromatography (mobile phase: *n*-hexane/ethyl acetate 5:5 until the starting material eluted, afterwards the mobile phase was changed to methanol and the product eluted). The solid was dried under reduced pressure at 40 °C. White solid (m.p.: 183–186 °C). Yield: 0.05 g (16.0%). Compound purity: 100.0%. R_f = 0.21 (cyclohexane/ethanol/Et_3N 6:2:2). ^{1}H-NMR [ppm]: δ = 1.26 (t, 3H, *J* = 7.1 Hz), 3.97 (d, 1H, *J* = 12.9 Hz), 4.14 (q, 2H, *J* = 7.1 Hz), 4.31 (d, 1H, *J* = 12.9 Hz), 6.38 (s, 2H), 6.78 (d, 1H, *J* = 7.9 Hz), 7.08–7.10 (m, 2H), 7.28–7.29 (m, 3H), 7.82 (d, 1H, *J* = 7.8 Hz), 8.87 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.5, 59.0, 60.7, 108.6, 120.5, 127.7, 128.2 (2C), 129.6, 130.2 (2C), 130.7, 152.0, 154.2, 154.9. IR [cm^{-1}]: $\tilde{\nu}$ = 1220, 1463, 1533, 1728, 2975, 3212, 3341. HRMS: $[C_{15}H_{17}N_3O_3S + H]^+$ calculated: 320.1063, found: 320.1052.

Ethyl-{2-amino-6-[(3,4-difluorobenzyl)sulfinyl]pyridin-3-yl}carbamate (7c): **6d** (1 mmol, 0.34 g) was dissolved in 20 mL DCM and cooled to 0 °C. *m*CPBA (1.1 eq, 1.1 mmol, 0.35 g of a 55% mixture with water) was dissolved in 20 mL DCM and added drop wise within 30 min. The solution was stirred for further 20 min and afterwards diluted with 60 mL DCM. The organic phase was washed with 3×100 mL sat. $NaHCO_3$ solution as well as 100 mL saturated brine and dried with Na_2SO_4. After evaporation the crude product was recrystallized from ethyl acetate and dried under reduced pressure at 40 °C. Beige solid (m.p.: 196–198 °C). Yield: 0.13 g (37.3%). Compound purity: 100.0%. R_f = 0.27 (*n*-hexane/ethyl acetate 4:6). ^{1}H-NMR [ppm]: δ = 1.25 (t, 3H, *J* = 7.1 Hz), 4.00 (d, 1H, *J* = 13.0 Hz), 4.33 (d, 1H, *J* = 13.0 Hz), 6.37 (s, 2H), 6.70 (d, 1H, *J* = 7.9 Hz), 6.82–6.85 (m, 1H), 7.03–7.08 (m, 1H), 7.29–7.36 (m, 1H), 7.82 (d, 1H, *J* = 7.6 Hz), 8.87 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.4, 57.0, 60.7, 108.8, 117.0 (d,

$^{2}J_{C,F}$ = 17 Hz), 119.1 (d, $^{2}J_{C,F}$ = 17 Hz), 120.6, 127.2 (dd, $^{3}J_{C,F}$ = 6 Hz, $^{4}J_{C,F}$ = 3 Hz), 128.0 (dd, $^{3}J_{C,F}$ = 6 Hz, $^{4}J_{C,F}$ = 4 Hz), 129.4, 147.6 and 150.0 (dd, $^{1}J_{C,F}$ = 245 Hz, $^{2}J_{C,F}$ = 12 Hz), 147.9 and 150.3 (dd, $^{1}J_{C,F}$ = 245 Hz, $^{2}J_{C,F}$ = 12 Hz), 151.9, 154.1, 154.2. IR [cm^{-1}]: $\tilde{\nu}$ = 1221, 1463, 1672, 1724, 2979, 3215, 3343. HRMS: $[C_{15}H_{15}N_3O_3F_2S + H]^+$ calculated: 356.0875, found: 356.0881.

Ethyl-(2-amino-6-{[4-(trifluoromethyl)benzyl]sulfinyl}pyridin-3-yl)carbamate (7d): **6c** (0.40 mmol, 0.15 g) was dissolved in 12 mL DCM and cooled to 0 °C. *m*CPBA (1.0 eq, 0.40 mmol, 0.13 g of a 55% mixture with water) was added to the solution. Within 30 minutes the product started to precipitate. Since the reaction was not completed after one hour, *m*CPBA (0.5 eq, 0.20 mmol, 0.07 g of a 55% mixture with water) was added. The suspension was stirred for one more hour, filtrated and the product dried under reduced pressure at 40 °C. White solid (m.p.: 187–189 °C). Yield: 0.05 g (35.0%). Compound purity: 100.0%. R_f = 0.19 (*n*-hexane/ ethyl acetate 4:6). ^{1}H-NMR [ppm]: δ = 1.26 (t, 3H, *J* = 7.1 Hz), 4.11 (d, 1H, *J* = 12.8 Hz), 4.15 (q, 2H, *J* = 7.0 Hz), 4.45 (d, 1H, *J* = 12.8 Hz), 6.37 (s, 2H), 6.72 (d, 1H, *J* = 7.9 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.63 (d, 2H, *J* = 8.1 Hz), 7.82 (d, 1H, *J* = 7.9 Hz), 8.85 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.4, 57.8, 60.7, 108.7, 120.6, 122.9 and 125.6 (q, $^{1}J_{C,F}$ = 270 Hz), 124.8 (q, $^{4}J_{C,F}$ = 4 Hz), 128.2 (q, 2C, $^{2}J_{C,F}$ = 31.8), 129.5, 131.1 (2C), 135.3, 152.0, 154.1, 154.2. IR [cm^{-1}]: $\tilde{\nu}$ = 1122, 1466, 1659, 1730, 2979, 3216, 3305, 3343. HRMS: $[C_{15}H_{16}N_3O_3FS - H]^-$ calculated: 386.0792, found: 386.0781.

Ethyl-{2-amino-6-[(4-fluorobenzyl)sulfonyl]pyridin-3-yl}carbamate (8a): **6a** (1 mmol, 0.32 g) was dissolved in 20 mL DCM and cooled to 0 °C. *m*CPBA (2 eq, 2 mmol, 0.63 g of a 55% mixture with water) was dissolved in 20 mL DCM and added drop wise over a period of 1 hour. The solution was stirred for further 45 min at 0 °C. The resulting suspension was filtered and the residue washed with DCM. The filtrate was washed with 3×100 mL sat. $NaHCO_3$ solution and 100 mL brine. The organic phase was evaporated and purified by flash chromatography (puriFlash® 450 system from Interchim, 25 g silica column, mobile phase: *n*-hexane/ethyl acetate, gradient: 1 CV 10% ethyl acetate, 10 CV 10–80% ethyl acetate, 5 CV 80% ethyl acetate). The solid was washed with small quantities of diethyl ether and dried under reduced pressure at 40 °C. Pink solid (m.p.: 168–171 °C). Yield: 0.09 g (25.5%). Compound purity: 100.0%. R_f = 0.41 (-hexane/ethyl acetate). ^{1}H-NMR [ppm]: δ = 1.26 (t, 3H, *J* = 7.0 Hz), 4.16 (q, 2H, *J* = 7.0 Hz), 4.61 (s, 2H), 6.64 (s, 2H), 7.00 (d, 1H, *J* = 8.0 Hz), 7.13–7.17 (m, 2H), 7.22–7.25 (m, 2H), 7.95 (d, 1H, *J* = 7.8 Hz), 9.05 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.4, 56.1, 60.9, 111.5, 115.2 (d, 2C, $^{2}J_{C,F}$ = 22 Hz), 123.3, 124.8 (d, $^{4}J_{C,F}$ = 3 Hz), 127.4, 133.0 (d, 2C, $^{3}J_{C,F}$ = 8 Hz), 147.3, 151.3, 153.9, 160.9 and 163.3 (d, $^{1}J_{C,F}$ = 245 Hz). IR [cm^{-1}]: $\tilde{\nu}$ = 1232, 1462, 1511, 1634, 1714, 2979, 3305, 3445. HRMS: $[C_{15}H_{16}N_3O_4FS + H]^+$ req.: 354.0918, found: 354.0930.

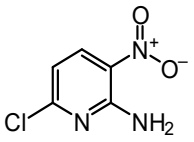
Ethyl-[2-amino-6-(benzylsulfonyl)pyridin-3-yl]carbamate (8b): **6b** (1 mmol, 0.30 g) was dissolved in 20 mL DCM and cooled to 0 °C. *m*CPBA (2.2 eq, 2.2 mmol, 0.69 g of a 55% mixture with water) was dissolved in 40 mL DCM and added drop wise within 1 hour. Since TLC monitoring showed no complete conversion after 1 additional hour *m*CPBA (0.5 eq, 0.5 mmol, 0.35 g of a 55% mixture with water) was dissolved in 5 mL DCM and added drop wise. After 30 min the solution was extracted with 2×100 mL sat. $NaHCO_3$ solution and 100 mL saturated brine. After drying with $NaSO_4$ the product was purified via flash chromatography (mobile phase: *n*-hexane/ethyl acetate 5:5), washed with diethyl ether and dried under reduced pressure at 40 °C. Light pink solid (m.p.: 164–166 °C).

Yield: 0.19 g (55.2%). Compound purity: 100.0%. R_f = 0.46 (*n*-hexane/ethyl acetate 4:6). ^{1}H-NMR [ppm]: δ = 1.26 (t, 3H, *J* = 7.1 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 4.60 (s, 2H), 6.64 (s, 2H), 7.00 (d, 1H, *J* = 8.0 Hz), 7.18–7.20 (m, 2H), 7.30–7.31 (m, 2H), 7.94 (d, 1H, *J* = 8.0 Hz), 9.05 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.4, 57.0, 60.9, 111.4, 123.3, 127.4, 128.2, 128.3 (2C), 128.4, 131.0 (2C), 147.5, 151.4, 153.9. IR [cm^{-1}]: $\tilde{\nu}$ = 1229, 1464, 1518, 1633, 1713, 2972, 3299, 3449. HRMS: $[C_{15}H_{17}N_3O_4S + H]^+$ calculated: 336.1013, found: 336.1029.

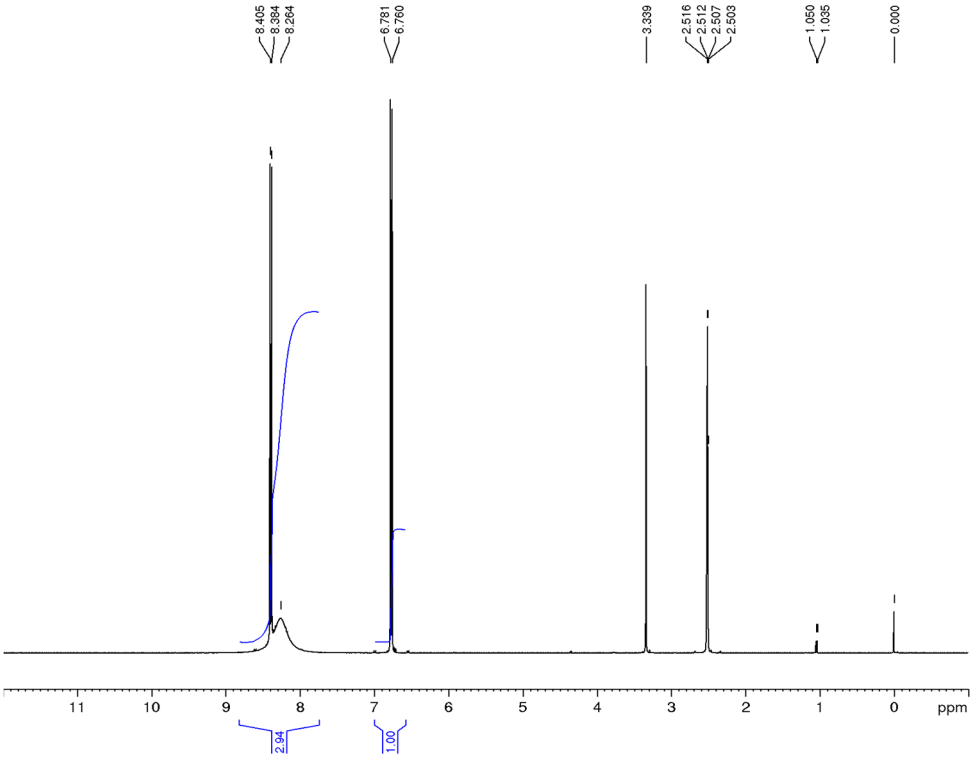
Ethyl-{2-amino-6-[(3,4-difluorobenzyl)sulfonyl]pyridin-3-yl}carbamate (8c): **6d** (1 mmol, 0.34 g) was dissolved in 20 mL DCM and cooled to 0 °C. *m*CPBA (2 eq, 2 mmol, 0.63 g of a 55% mixture with water) was dissolved in 20 mL DCM and added drop wise. Since TLC still showed starting material after 3 hours *m*CPBA (0.5 eq, 0.5 mmol, 0.32 g of a 55% mixture with water) was dissolved in 5 mL DCM and added drop wise again. After 4 additional hours the suspension was extracted with 2×50 mL sat. $NaHCO_3$ solution, 50 mL water and 50 mL saturated brine. The product was purified by flash chromatography (*n*-hexane/ethyl acetate 5:5) washed with diethyl ether and dried under reduced pressure at 40 °C. White solid (m.p.: 186–188 °C). Yield: 0.19 g (51.2%). Compound purity: 100.0%. R_f = 0.57 (*n*-hexane/ethyl acetate 4:6). ^{1}H-NMR [ppm]: δ = 1.26 (t, 3H, *J* = 7.1 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 4.65 (s, 2H), 6.64 (s, 2H), 7.02 (d, 1H, *J* = 8.0 Hz), 7.01–7.05 (m, 1H), 7.24–7.29 (m, 1H), 7.35–7.42 (m, 1H), 7.96 (d, 1H, *J* = 8.0 Hz), 9.06 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.4, 55.9, 60.9, 111.5, 117.4 (d, $^2J_{C,F}$ = 17 Hz), 119.9 (d, $^2J_{C,F}$ = 17 Hz), 123.4, 126.3 (dd, $^3J_{C,F}$ = 6 Hz, $^4J_{C,F}$ = 4 Hz), 127.4, 128.1 (dd, $^3J_{C,F}$ = 7 Hz, $^4J_{C,F}$ = 3 Hz), 147.1, 147.7 and 150.2 (dd, $^1J_{C,F}$ = 249 Hz, $^2J_{C,F}$ = 16 Hz), 148.2 and 150.7 (dd, $^1J_{C,F}$ = 255 Hz, $^2J_{C,F}$ = 20 Hz), 151.4, 153.9. IR [cm^{-1}]: $\tilde{\nu}$ = 1231, 1464, 1519, 1713, 2975, 3299, 3449. HRMS: $[C_{15}H_{15}F_2N_3O_4S + H]^+$ calculated: 372.0824, found: 372.0832.

Ethyl-(2-amino-6-{[4-(trifluoromethyl)benzyl]sulfonyl}pyridin-3-yl)carbamate (8d): **6c** (0.75 mmol, 0.28 g) was dissolved in 15 mL DCM and cooled to 0 °C. *m*CPBA (2 eq, 1.5 mmol, 0.47 g of a 55% mixture with water) was dissolved in 15 mL DCM and added drop wise within 1 hour. After additional 100 min the reaction is completed and the solution extracted with 3×50 mL sat. $NaHCO_3$ solution as well as 50 mL saturated brine. After drying with Na_2SO_4 the product was purified by flash chromatography (puriFlash® 450 system from Interchim, 25 g silica column, mobile phase: *n*-hexane/ethyl acetate, gradient: 1 CV 10% ethyl acetate, 10 CV 10–70% ethyl acetate, 5 CV 70% ethyl acetate). The product was washed with small quantities diethyl ether. Light orange solid (m.p.: 184–186 °C). Yield: 0.13 g (41.3%). Compound purity: 100.0%. R_f = 0.49 (*n*-hexane/ethyl acetate 5:5). ^{1}H-NMR [ppm]: δ = 1.26 (t, 3H, *J* = 7.1 Hz), 4.17 (q, 2H, *J* = 7.1 Hz), 4.76 (s, 2H), 6.66 (s, 2H), 7.03 (d, 1H, *J* = 8.0 Hz), 7.44 (d, 2H, *J* = 7.9 Hz), 7.70 (d, 2H, *J* = 8.0 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 9.07 (s, 1H). ^{13}C-NMR [ppm]: δ = 14.4, 56.5, 61.0, 111.4, 120.1 + 122.7 + 125.4 + 128.2 (q, $^1J_{C,F}$ = 272 Hz), 123.5, 125.1 (q, 2C, $^4J_{C,F}$ = 4 Hz), 127.3, 128.7 (q, $^2J_{C,F}$ = 32 Hz), 131.8 (2C), 133.4, 147.2, 151.4, 153.9. IR [cm^{-1}]: $\tilde{\nu}$ = 1234, 1470, 1529, 1649, 1700, 2939, 3345, 3430. HRMS: $[C_{16}H_{16}F_3N_3O_4S - H]^-$ calculated: 402.0741, found: 402.0750.

Spectra of 6-chloro-3-nitropyridin-2-amine



TK 02 (1H-NMR, DMSO-d6)

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EXPNO                        5
PROCNO                       1

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INSTRUM                spect
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PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                       101
DW                    60.800 usec
DE                    10.00 usec
TE                    296.2 K
D1                 1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                      1H
P1                      9.75 usec
PL1                    -4.50 dB
PL1W              26.90193939 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1299984 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
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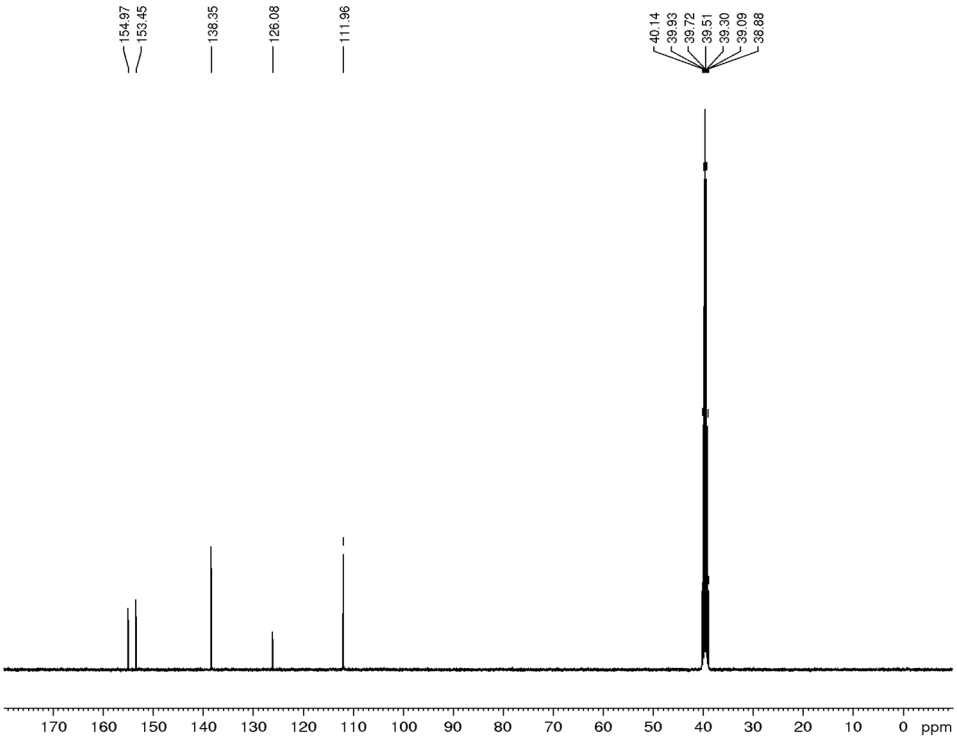
TK 02 (13C-NMR, DMSO-d6)

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Current Data Parameters
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EXPNO                        6
PROCNO                       1

F2 - Acquisition Parameters
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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 usec
DE                    10.00 usec
TE                    298.5 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                          1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                      1H
PCPD2                 60.00 usec
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 MHz

F2 - Processing parameters
SI                       32768
SF                100.6128179 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
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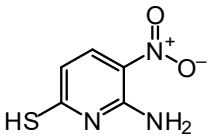
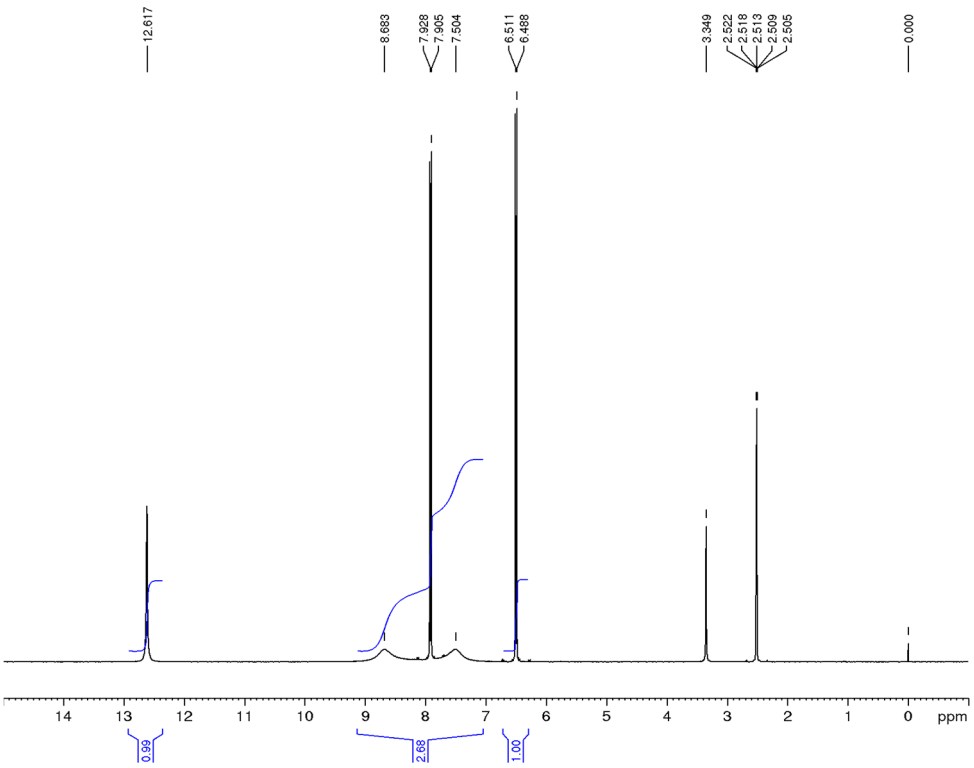
Spectra of 5



TK 03 (1H-NMR, DMSO-d6)

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Current Data Parameters
NAME                  T. Kasch
EXPNO                        7
PROCNO                       1

F2 - Acquisition Parameters
Date_               20150518
Time                   10.36
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                      90.5
DW                    60.800 usec
DE                    10.00 usec
TE                    296.3 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                        9.75 usec
PL1                      -4.50 dB
PL1W               26.90193939 W
SFO1              400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1299981 MHz
WDW                         EM
SSB          0
LB                        0.30 Hz
GB           0
PC                        1.00
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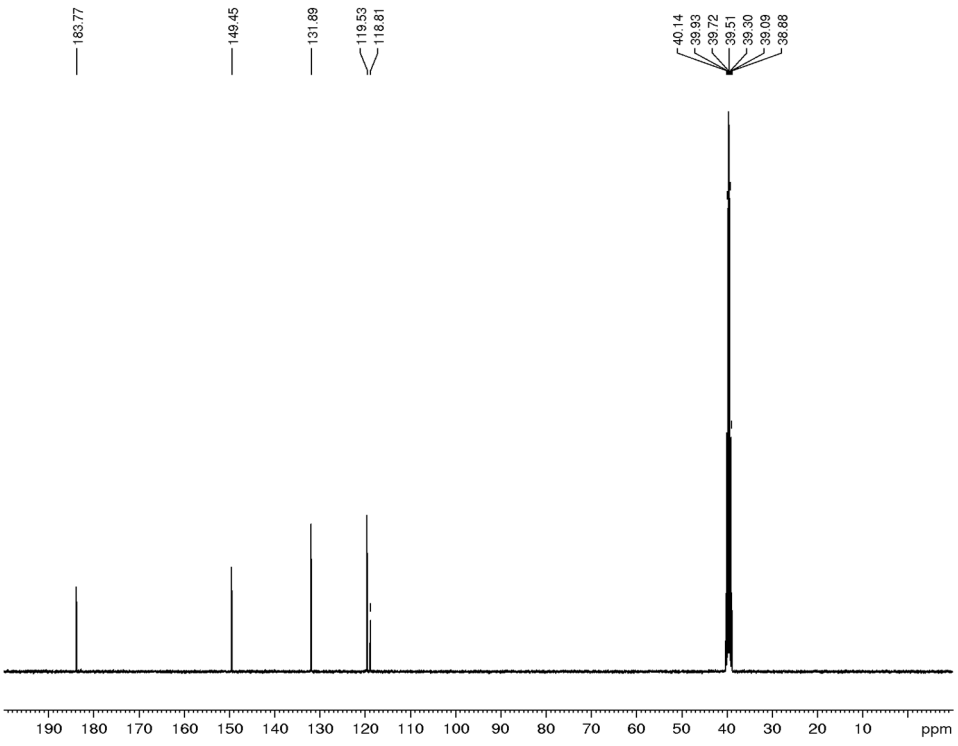
TK 03 (13C-NMR, DMSO-d6)

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Current Data Parameters
NAME                  T. Kasch
EXPNO                        8
PROCNO                       1

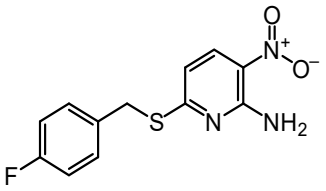
F2 - Acquisition Parameters
Date_               20150518
Time                   14.01
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                     65536
SOLVENT                 DMSO
NS                      1024
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                      2050
DW                    20.800 usec
DE                    10.00 usec
TE                    298.1 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

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

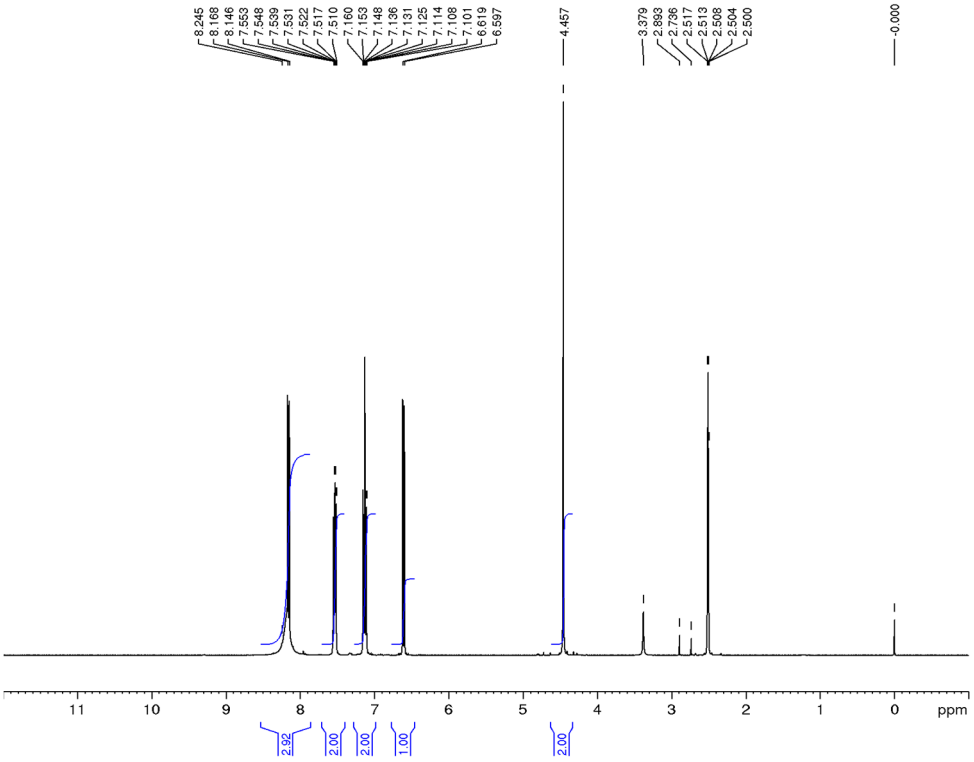
======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                        1H
PCPD2                 60.00 usec
PL2                      -4.50 dB
PL12                     11.28 dB
PL13                     15.00 dB
PL2W               26.90193939 W
PL12W               0.71085924 W
PL13W     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

F2 - Processing parameters
SI                       32768
SF                100.6128167 MHz
WDW                         EM
SSB          0
LB                        1.00 Hz
GB           0
PC                        1.40
```

Spectra of 5a



TK 04 (1H-NMR, DMSO-d6)

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Current Data Parameters
NAME                  T. Kasch
EXPNO                       10
PROCNO                       1

F2 - Acquisition Parameters
Date_               20150519
Time                   13.39
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                 3.9845889 sec
RG                      101
DW                 60.800 usec
DE                 10.00 usec
TE                 296.1 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                     1H
P1                    9.75 usec
PL1                  -4.50 dB
PL1W           26.90193939 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF              400.1300001 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```
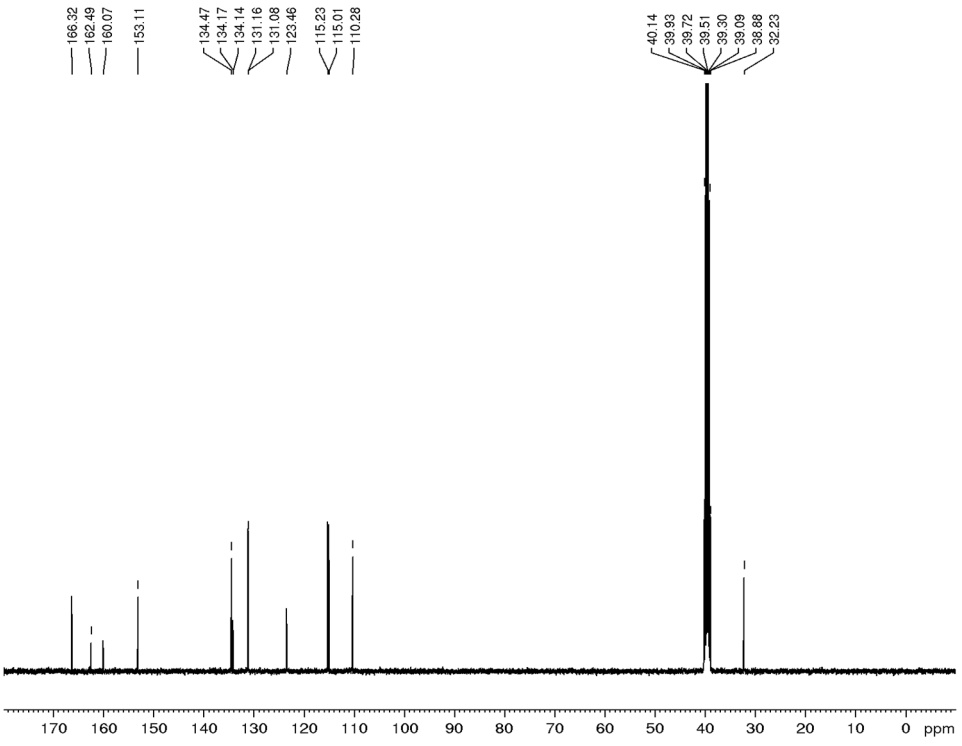

TK 04 (13C-NMR, DMSO-d6)

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Current Data Parameters
NAME                  T. Kasch
EXPNO                       15
PROCNO                       1

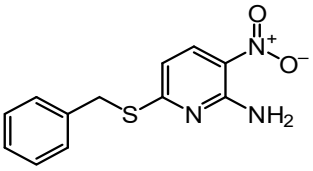
F2 - Acquisition Parameters
Date_               20150527
Time                   12.18
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                 1.3631488 sec
RG                     2050
DW                 20.800 usec
DE                 10.00 usec
TE                 297.9 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                      1

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

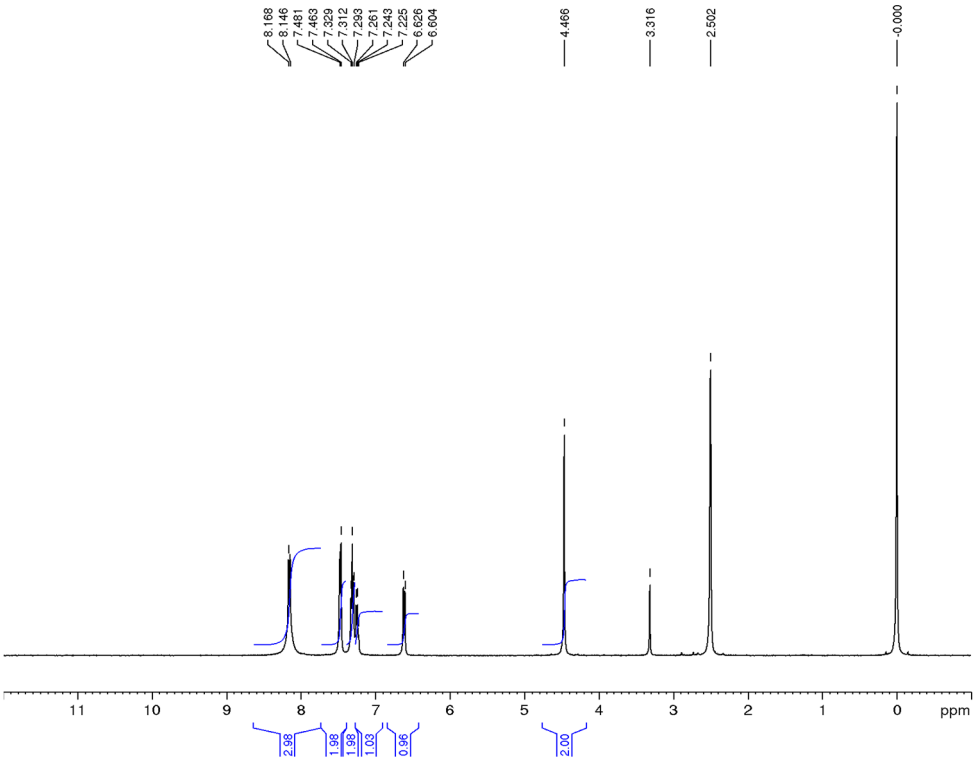
======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                     1H
PCPD2                60.00 usec
PL2                  -4.50 dB
PL12                 11.28 dB
PL13                 15.00 dB
PL2W           26.90193939 W
PL12W           0.71085924 W
PL13W           0.30184472 W
SFO2  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

F2 - Processing parameters
SI                    32768
SF             100.6128178 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

Spectra of 5b



AS-19 (1H-NMR, DMSO-d6)

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Current Data Parameters
NAME                  A. Surur
EXPNO                      111
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170111
Time                   14.24
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9845889 sec
RG                       114
DW                  60.800 usec
DE                  10.00 usec
TE                  297.2 K
D1              1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       1H
P1                    9.75 usec
PL1                  -5.00 dB
PL1W          30.18447304 W
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF             400.1300017 MHz
WDW                         EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```
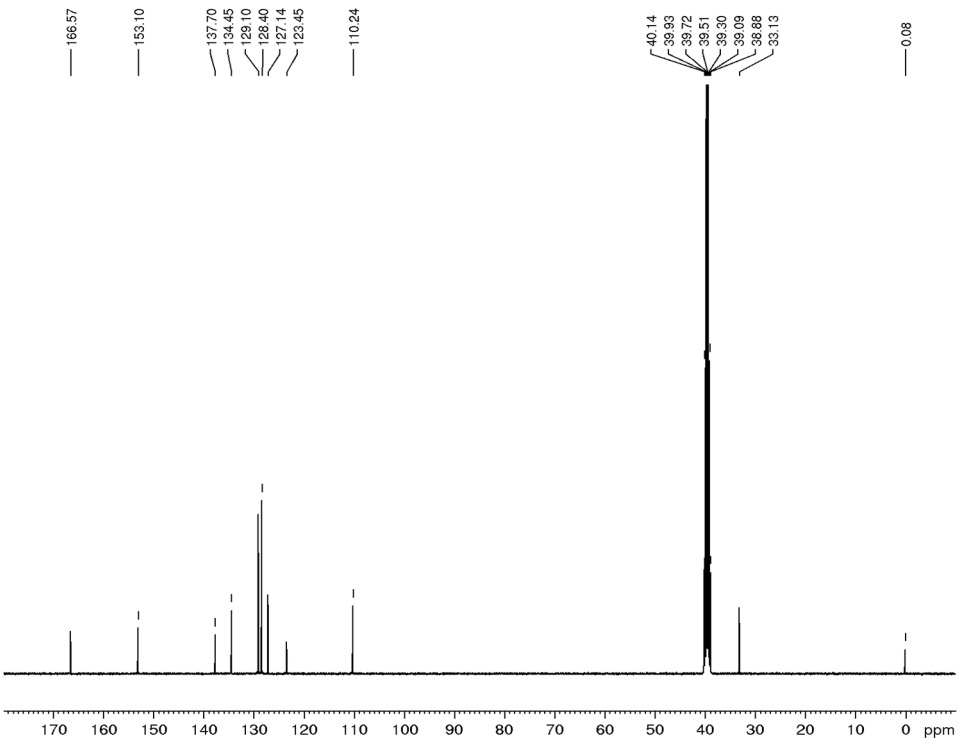
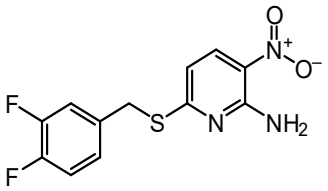

AS-19 (13C-NMR, DMSO-d6)

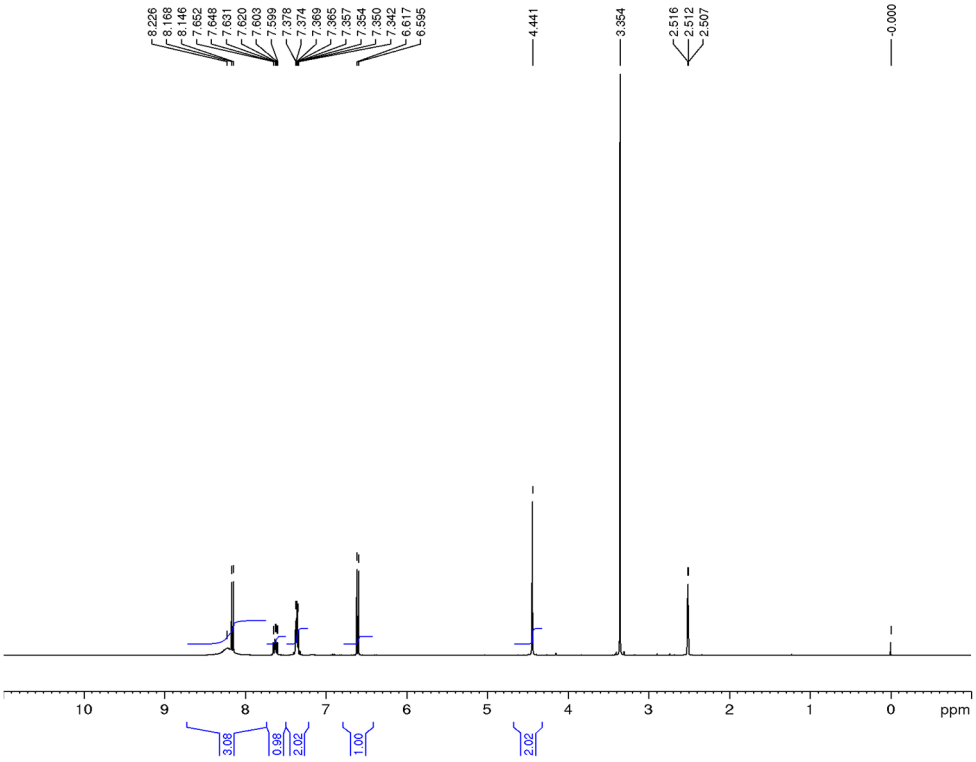



```
Current Data Parameters
NAME                  A. Surur
EXPNO                      113
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170113
Time                    6.52
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 usec
DE                  10.00 usec
TE                  298.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                          1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2               60.00 usec
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
LB                    1.00 Hz
GB           0
PC                    1.40
```

Spectra of 5c

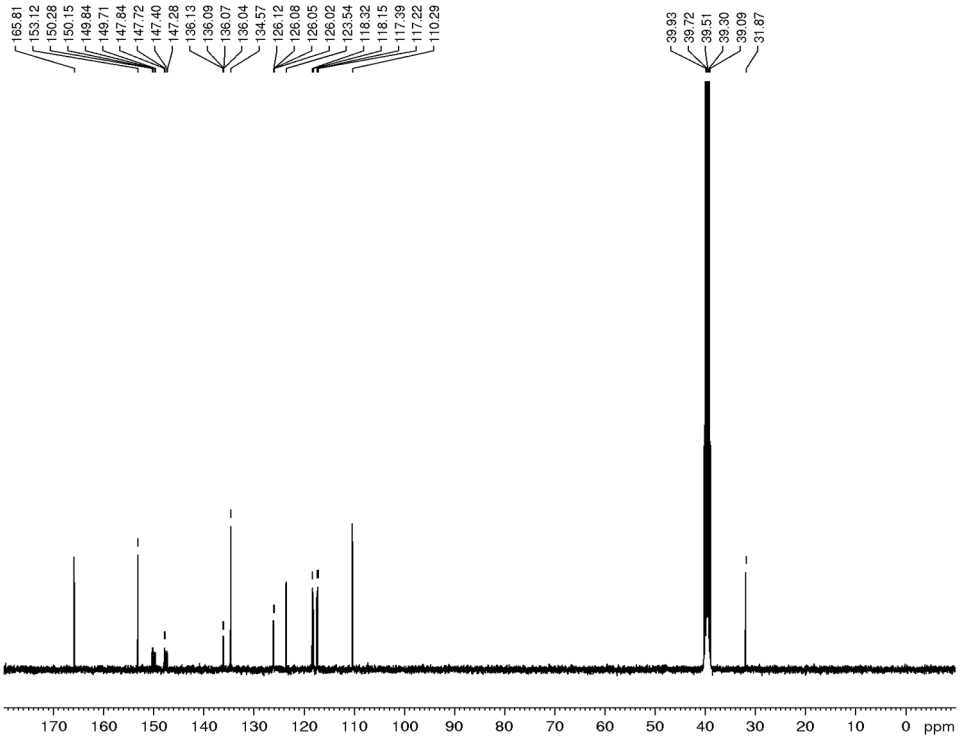


TK23.1 (1H-NMR, DMSO-d6)



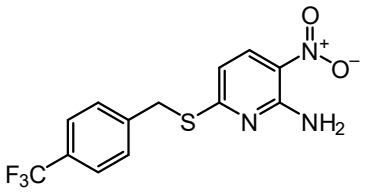

```
Current Data Parameters
NAME                  T. Kasch
EXPNO                       99
PROCNO                       1

F2 - Acquisition Parameters
Date_               20151009
Time                    8.37
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                       101
DW                    60.800 usec
DE                    10.00 usec
TE                    283.8 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.75 usec
PL1                    -4.50 dB
PL1W             26.90193939 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                  400.1299984 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

TK23.1 (13CNMR, DMSO-d6)

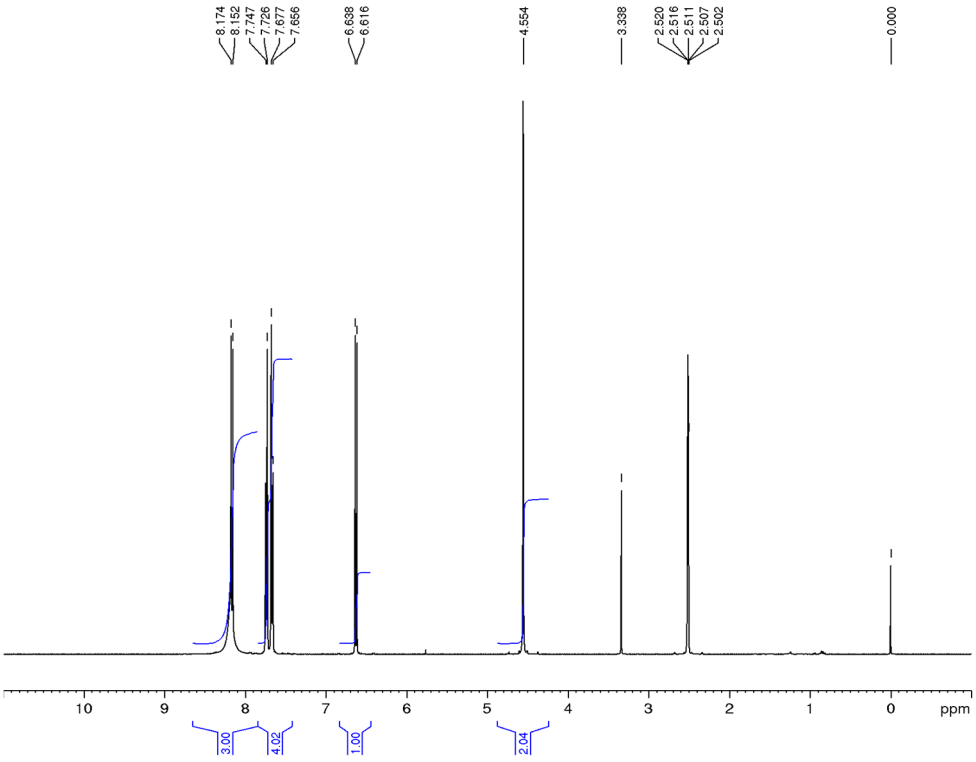



```
Current Data Parameters
NAME                  T. Kasch
EXPNO                      100
PROCNO                       1

F2 - Acquisition Parameters
Date_               20151009
Time                    9.39
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 usec
DE                    10.00 usec
TE                    285.3 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                 60.00 usec
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 MHz

F2 - Processing parameters
SI                       32768
SF                  100.6128165 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

Spectra of 5d

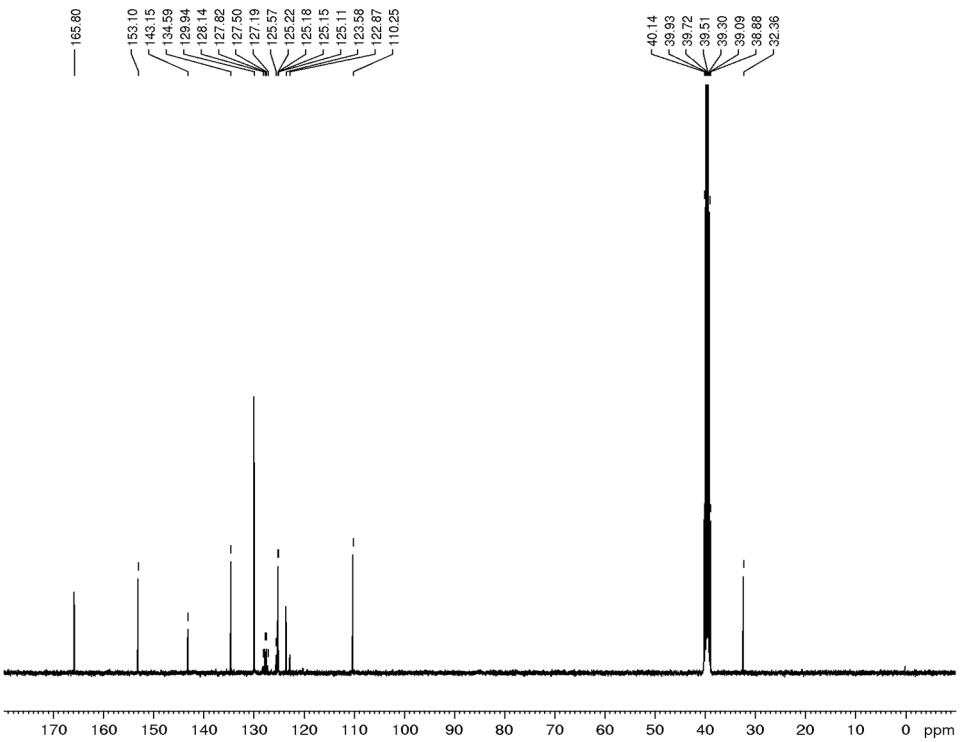


ELB 010 UK (1H-NMR, DMSO-d6)



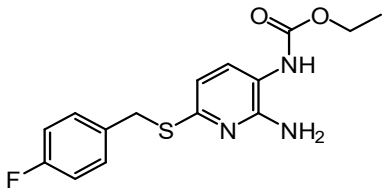

```
Current Data Parameters
NAME                  C. Bock
EXPNO                      32
PROCNO                      1

F2 - Acquisition Parameters
Date_               20150323
Time                   13.39
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                       101
DW                  60.800 usec
DE                  10.00 usec
TE                  297.4 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     9.75 usec
PL1                   -4.50 dB
PL1W            26.90193939 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                400.1299984 MHz
WDW                          EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

ELB 010 UK (13C-NMR, DMSO-d6)

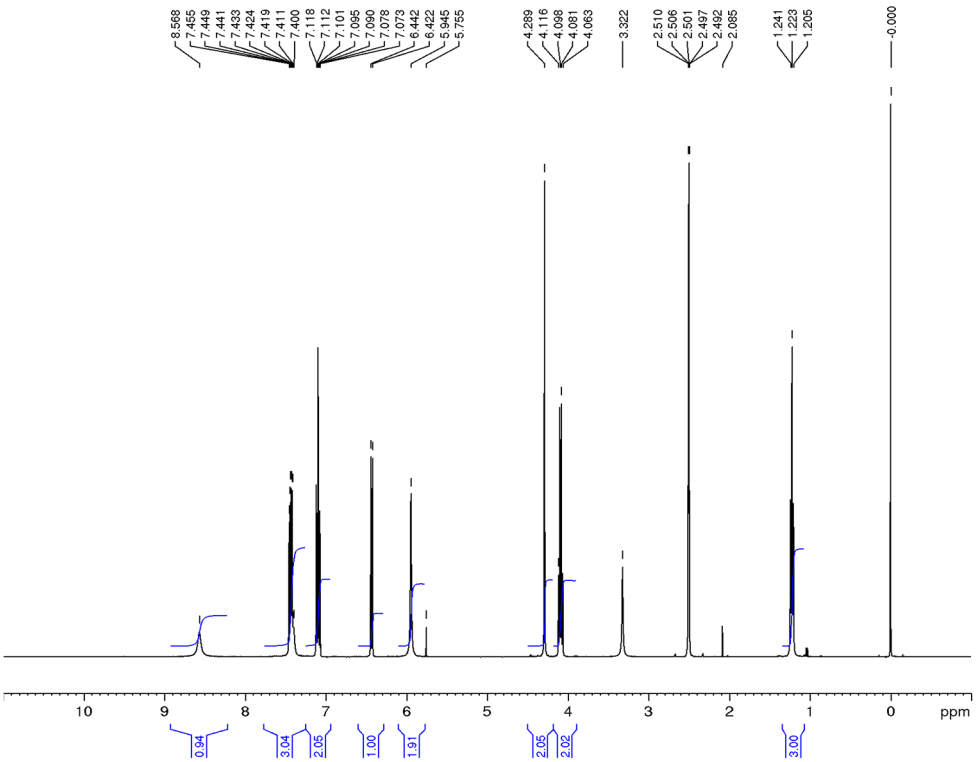



```
Current Data Parameters
NAME                  C. Bock
EXPNO                      38
PROCNO                      1

F2 - Acquisition Parameters
Date_               20150324
Time                   10.56
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 usec
DE                  10.00 usec
TE                  297.7 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                      1H
PCPD2                 60.00 usec
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 MHz

F2 - Processing parameters
SI                        32768
SF                100.6128175 MHz
WDW                          EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Spectra of 6a

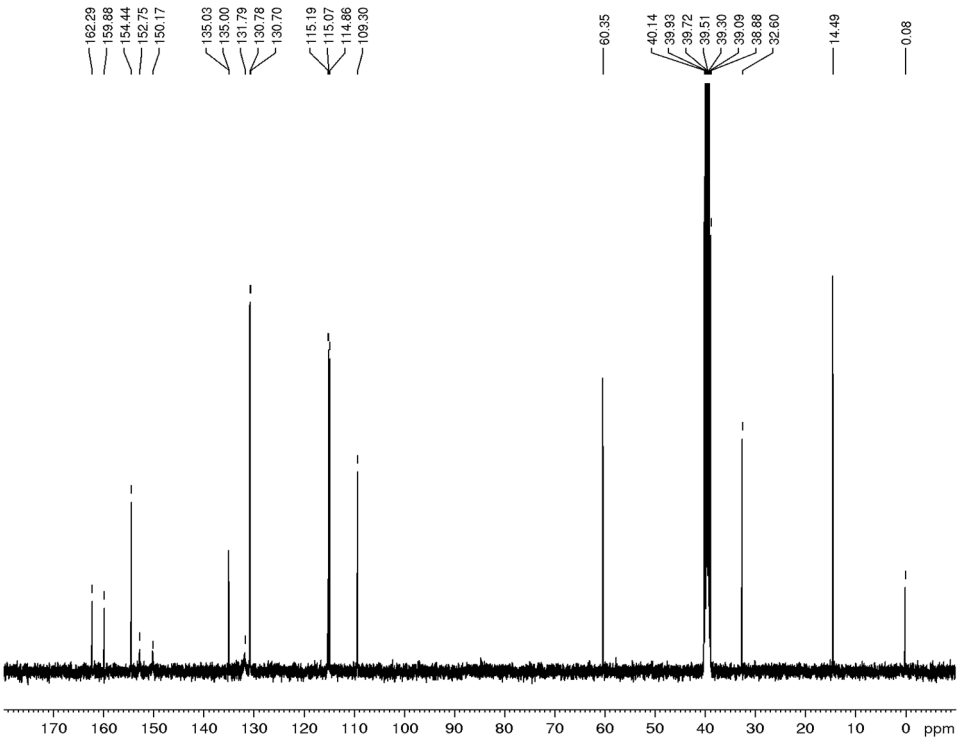


ELB079 (1H-NMR, DMSO-d6)



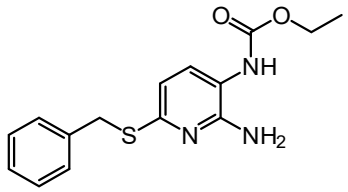

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     348
PROCNO                      1

F2 - Acquisition Parameters
Date_               20171103
Time                   10.42
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                       90.5
DW                   60.800 usec
DE                   10.00 usec
TE                    298.4 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.75 usec
PL1                    -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                400.1300027 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

ELB079 (13C-NMR, DMSO-d6)

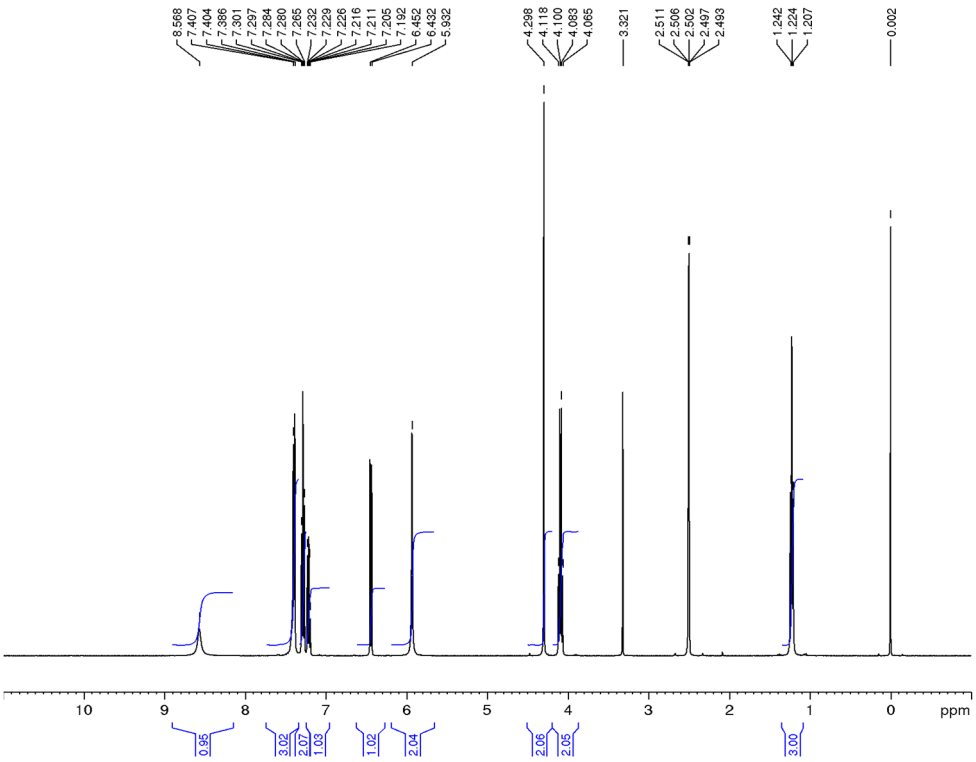



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     423
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180123
Time                   14.11
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 usec
DE                   10.00 usec
TE                    298.3 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                60.00 usec
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
GB           0
PC                      1.40
```

Spectra of 6b

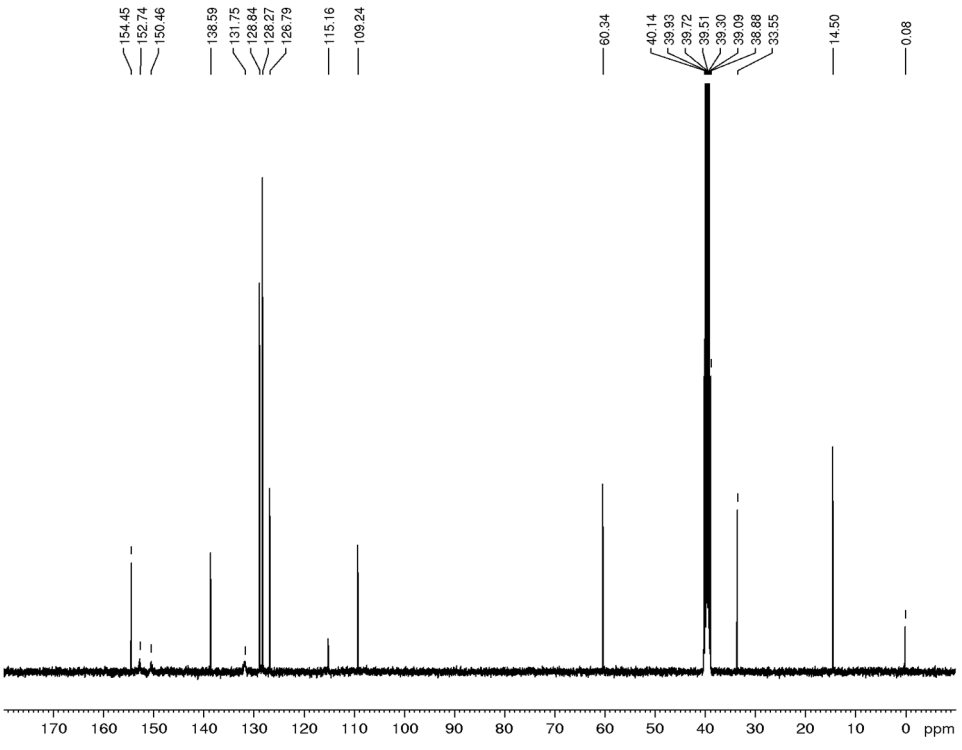


ELB108 (1H-NMR, DMSO-d6)



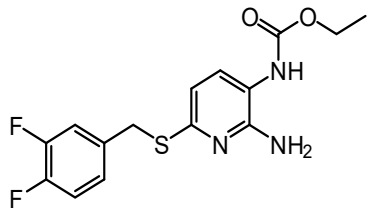

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     445
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180209
Time                   10.24
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      114
DW                   60.800 usec
DE                   10.00 usec
TE                   298.4 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                       9.75 usec
PL1                     -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF              400.1300023 MHz
WDW                         EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

ELB108 (13C-NMR, DMSO-d6)

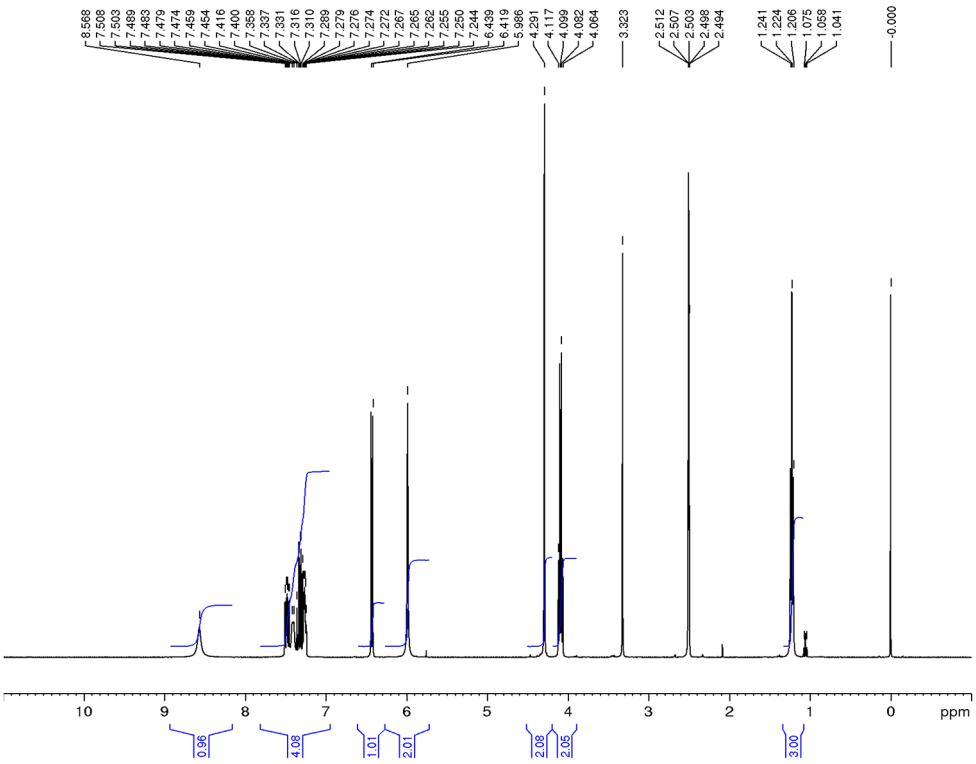



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     446
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180209
Time                   12.58
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 sec
RG                     2050
DW                   20.800 usec
DE                   10.00 usec
TE                   298.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                  60.00 usec
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
LB                    1.00 Hz
GB           0
PC                    1.40
```

Spectra of 6c

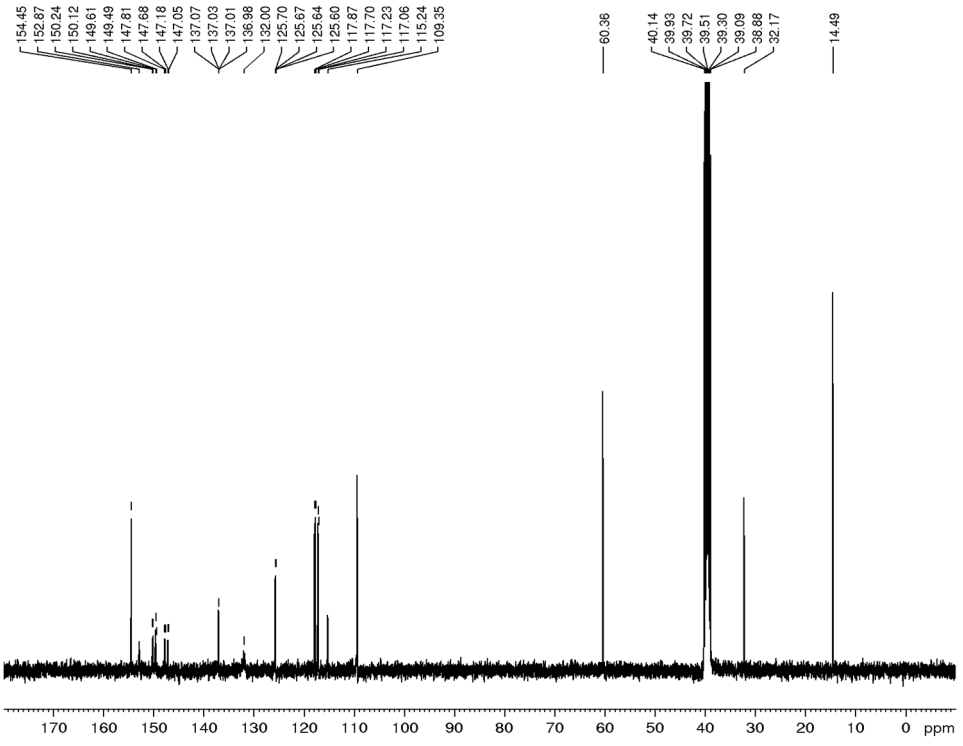


ELB083 (1H-NMR, DMSO-d6)



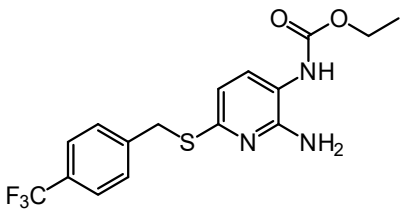

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     353
PROCNO                      1

F2 - Acquisition Parameters
Date_              20171113
Time                    9.47
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      90.5
DW                    60.800 usec
DE                    10.00 usec
TE                    298.1 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.75 usec
PL1                    -5.00 dB
PL1W            30.18447304 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                      32768
SF                 400.1300020 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

ELB083 (13C-NMR, DMSO-d6)

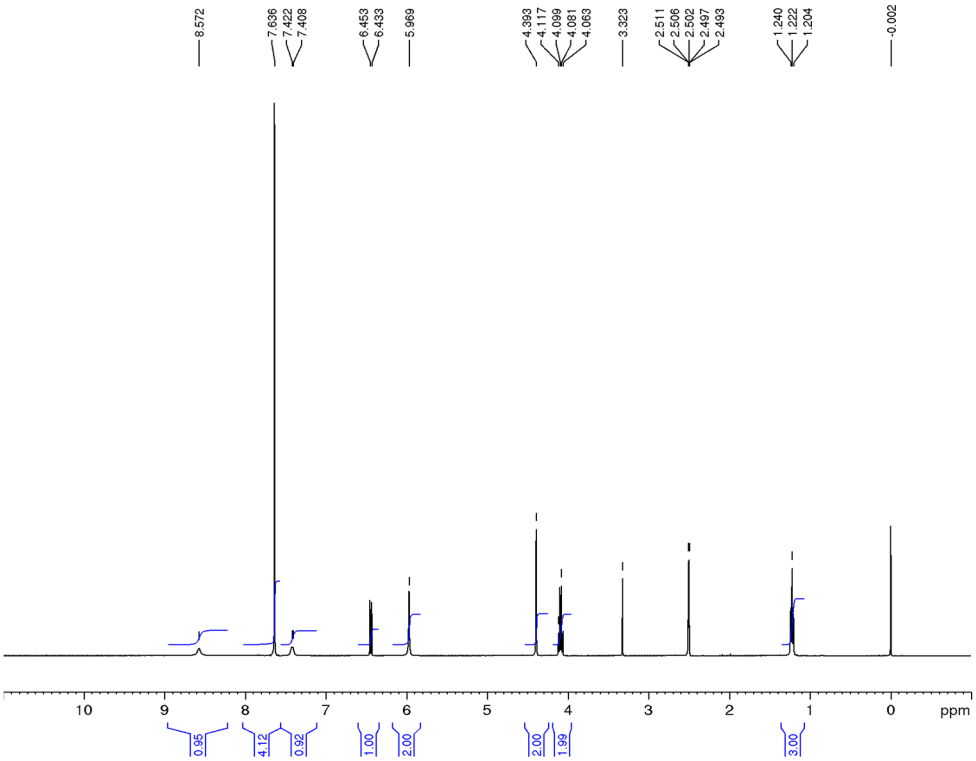



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     362
PROCNO                      1

F2 - Acquisition Parameters
Date_              20171121
Time                    9.36
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 usec
DE                    10.00 usec
TE                    298.3 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                 60.00 usec
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
LB                      1.00 Hz
GB           0
PC                      1.40
```

Spectra of 6d

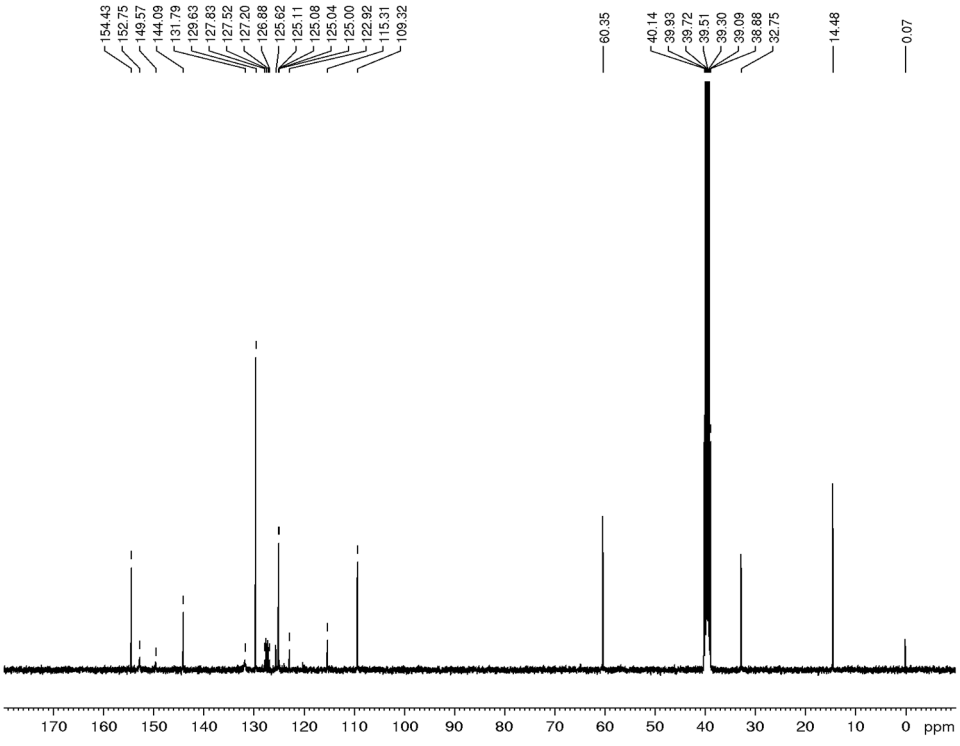


ELB017.2 (1H-NMR, DMSO-d6)



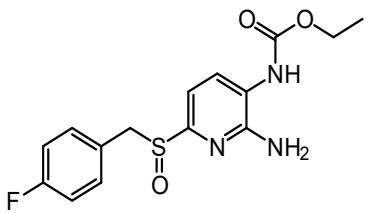

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     442
PROCNO                      1

F2 - Acquisition Parameters
Date_              20180208
Time                  15.16
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9845889 sec
RG                      114
DW                 60.800 usec
DE                 10.00 usec
TE                 298.4 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                   9.75 usec
PL1                  -5.00 dB
PL1W          30.18447304 W
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF            400.1300023 MHz
WDW                     EM
SSB       0
LB                   0.30 Hz
GB        0
PC                    1.00
```

ELB017.2 (13C-NMR, DMSO-d6)

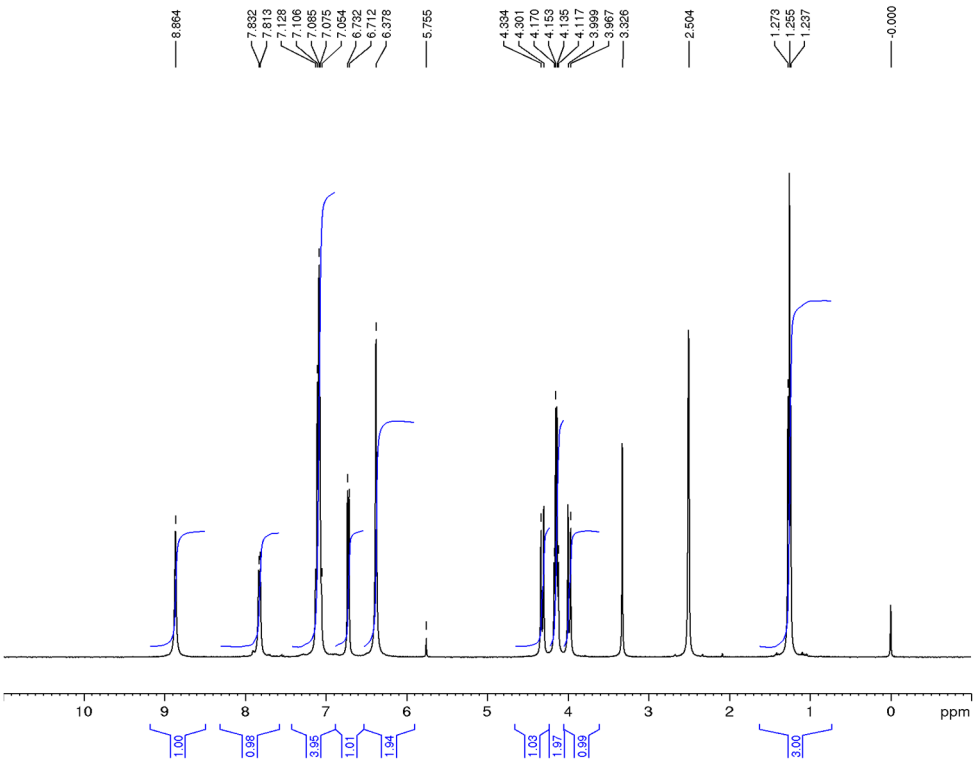



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     443
PROCNO                      1

F2 - Acquisition Parameters
Date_              20180209
Time                   9.41
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 sec
RG                     2050
DW                 20.800 usec
DE                 10.00 usec
TE                 298.1 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

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

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                    1H
PCPD2               60.00 usec
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
GB        0
PC                    1.40
```

Spectra of 7a

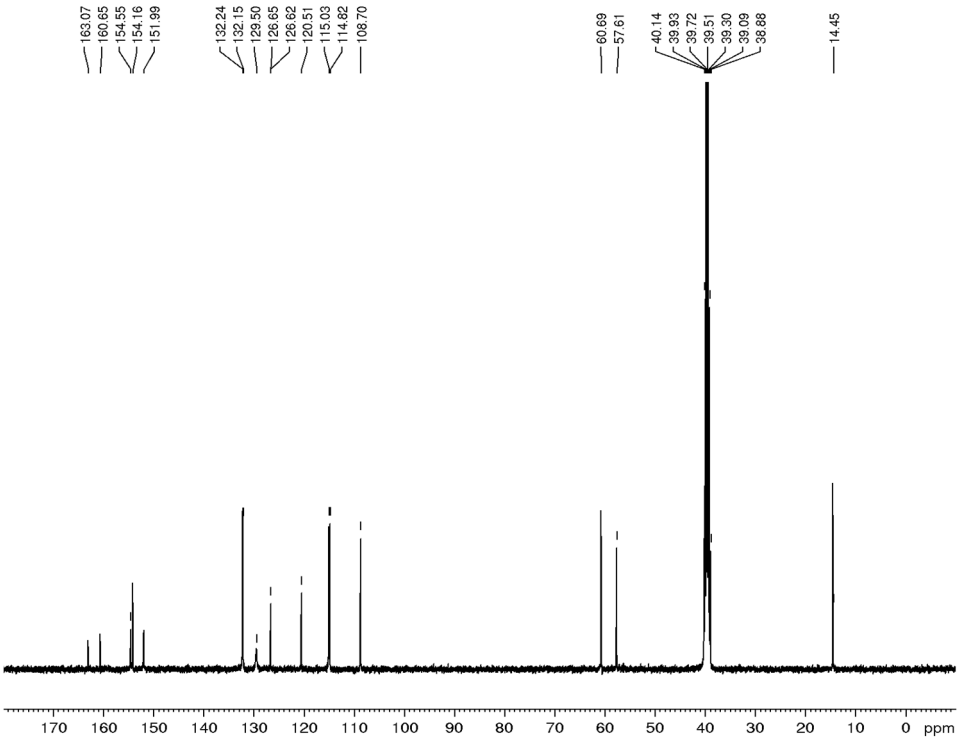


ELB084 (1H-NMR, DMSO-d6)



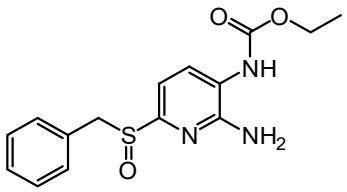

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     374
PROCNO                      1

F2 - Acquisition Parameters
Date_               20171205
Time                   14.50
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      90.5
DW                   60.800 usec
DE                   10.00 usec
TE                   298.3 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                       9.75 usec
PL1                     -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300014 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```

ELB084 (13C-NMR, DMSO-d6)

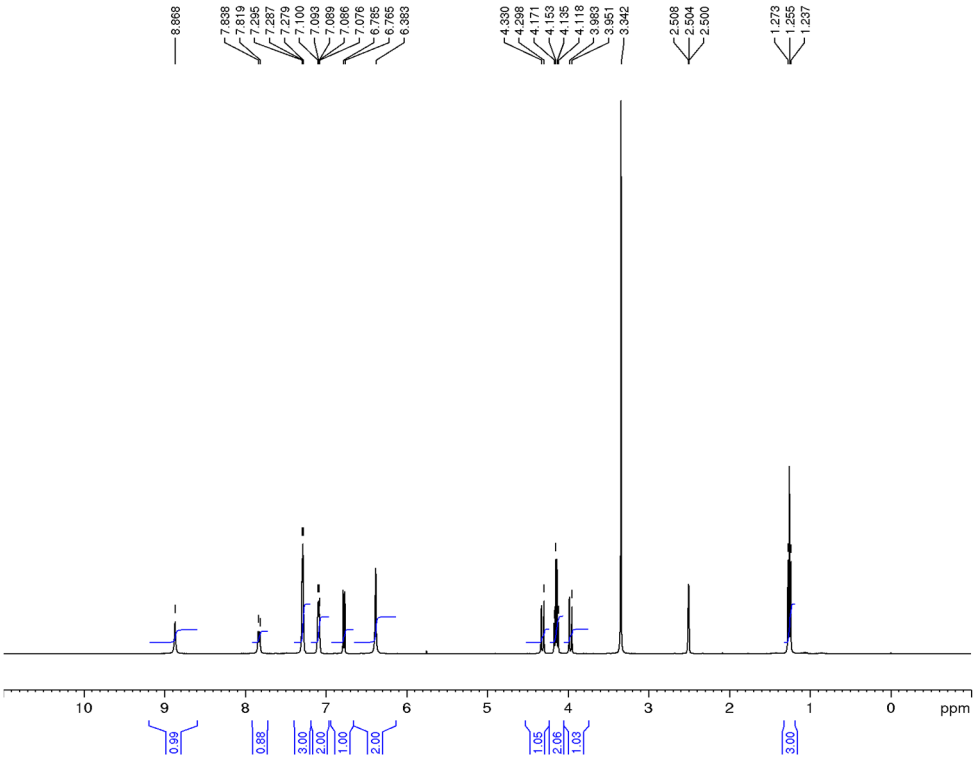



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     383
PROCNO                      1

F2 - Acquisition Parameters
Date_               20171218
Time                    9.12
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 usec
DE                   10.00 usec
TE                   298.3 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2           waltz16
NUC2                       1H
PCPD2                  60.00 usec
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               100.6128163 MHz
WDW                         EM
SSB          0
LB                     1.00 Hz
GB           0
PC                       1.40
```

Spectra of 7b



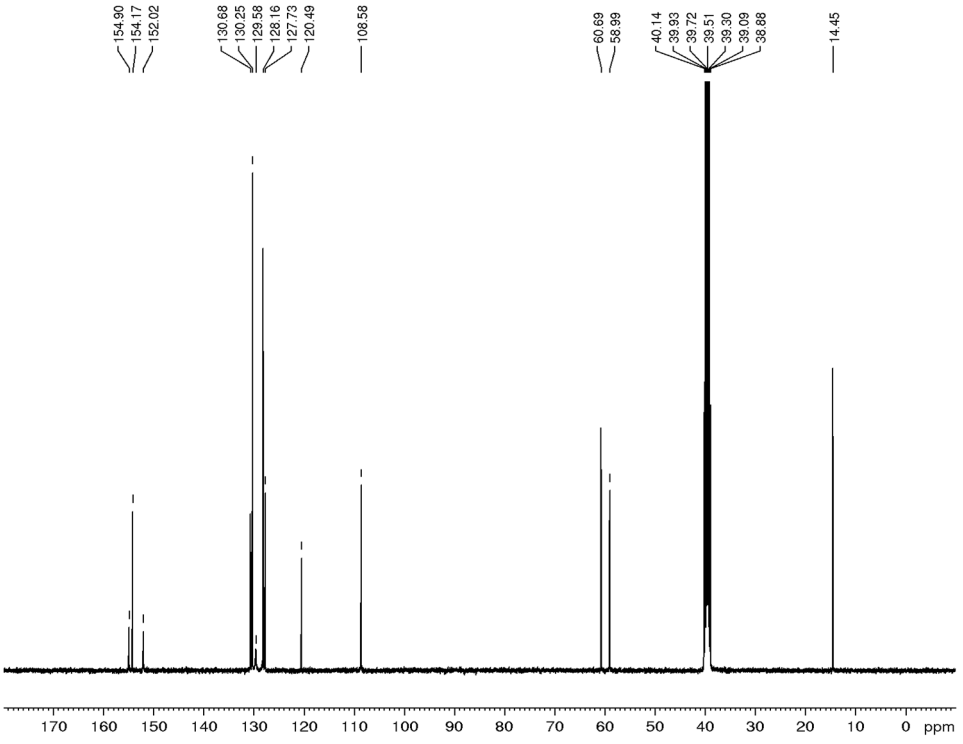
AS-29 (1H-NMR, DMSO-d6)



BRUKER

```
Current Data Parameters
NAME                  A. Surur
EXPNO                      262
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170505
Time                    8.08
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                      71.8
DW                    60.800 usec
DE                    10.00 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.75 usec
PL1                    -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                  400.1300016 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

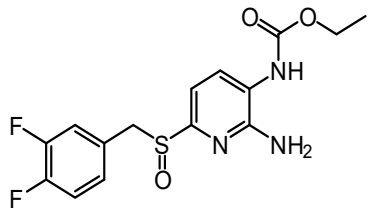
AS-29 (13C-NMR, DMSO-d6)



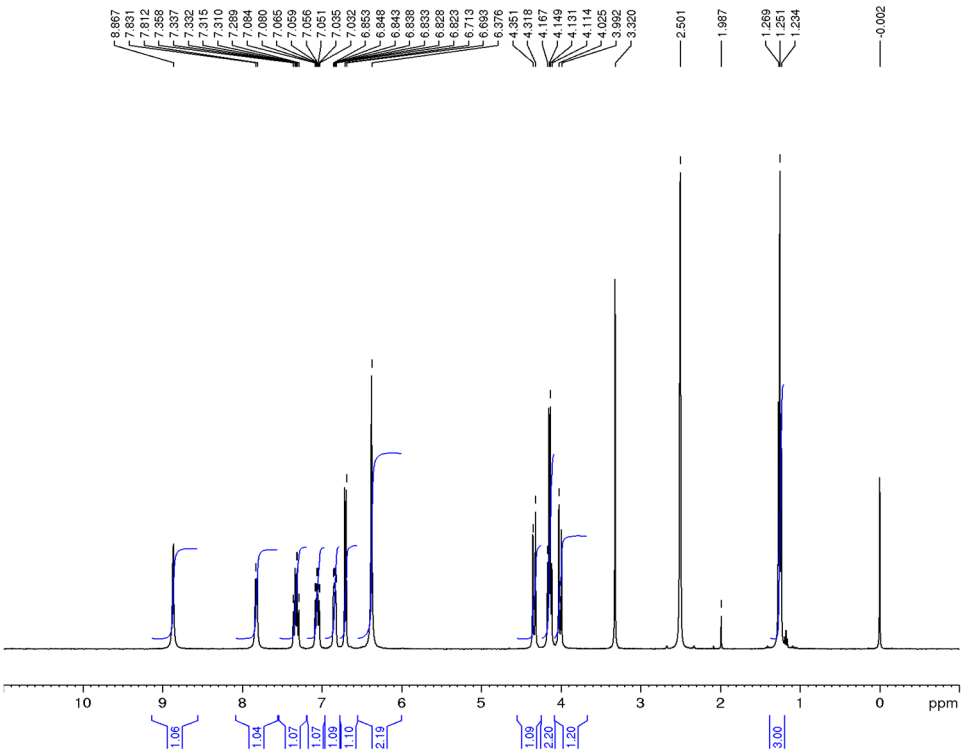
BRUKER

```
Current Data Parameters
NAME                  A. Surur
EXPNO                      265
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170505
Time                   17.54
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 usec
DE                    10.00 usec
TE                    299.2 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                          1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                 60.00 usec
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                  100.6128172 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

Spectra of 7c

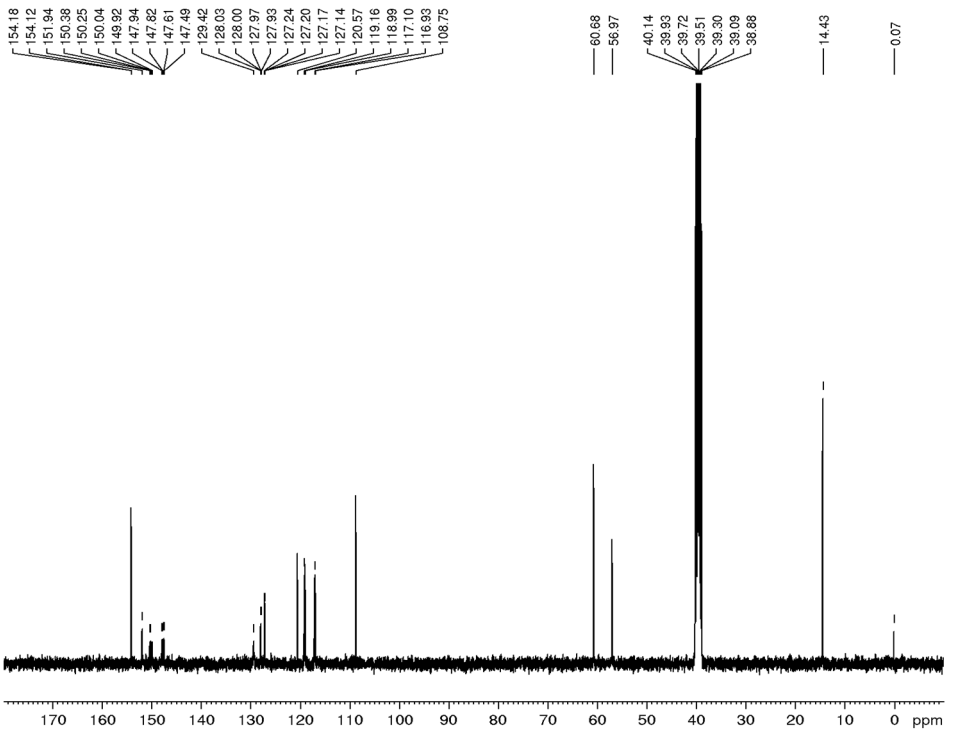


ELB109 (1H-NMR, DMSO-d6)



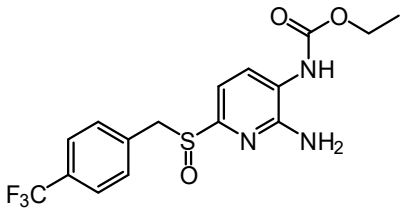

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     454
PROCNO                      1

F2 - Acquisition Parameters
Date_              20180213
Time                    9.49
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      114
DW                   60.800 usec
DE                   10.00 usec
TE                   298.5 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                       9.75 usec
PL1                     -5.00 dB
PL1W             30.18447304 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF               400.1300023 MHz
WDW                          EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```

ELB109 (13C-NMR, DMSO-d6)

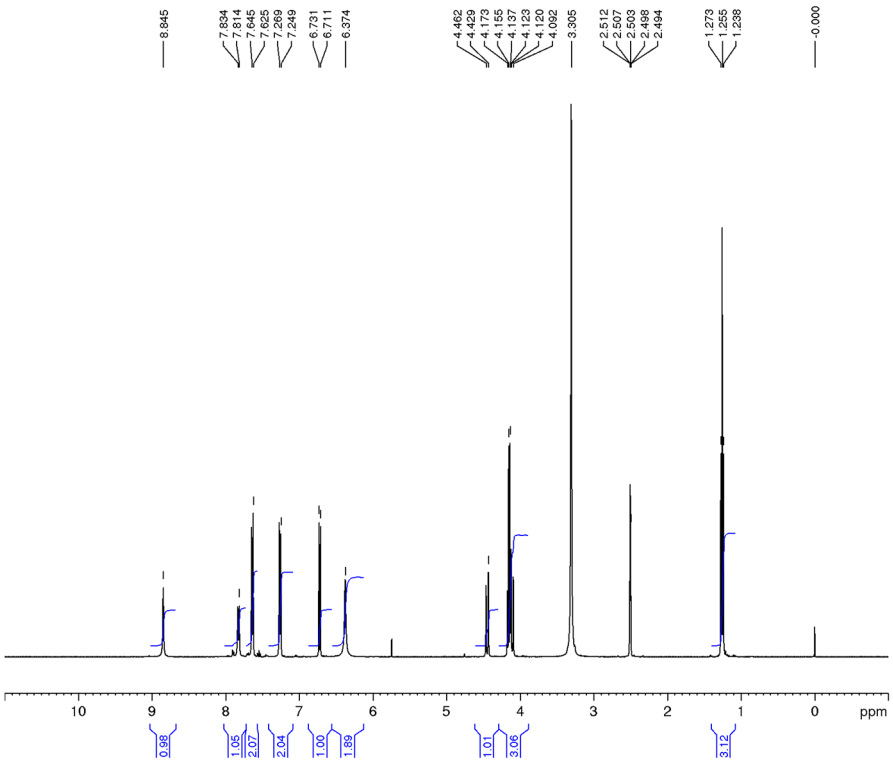



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     455
PROCNO                      1

F2 - Acquisition Parameters
Date_              20180213
Time                   12.47
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 sec
RG                      2050
DW                   20.800 usec
DE                   10.00 usec
TE                   298.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                  60.00 usec
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               100.6128180 MHz
WDW                          EM
SSB          0
LB                       1.00 Hz
GB           0
PC                       1.40
```

Spectra of 7d

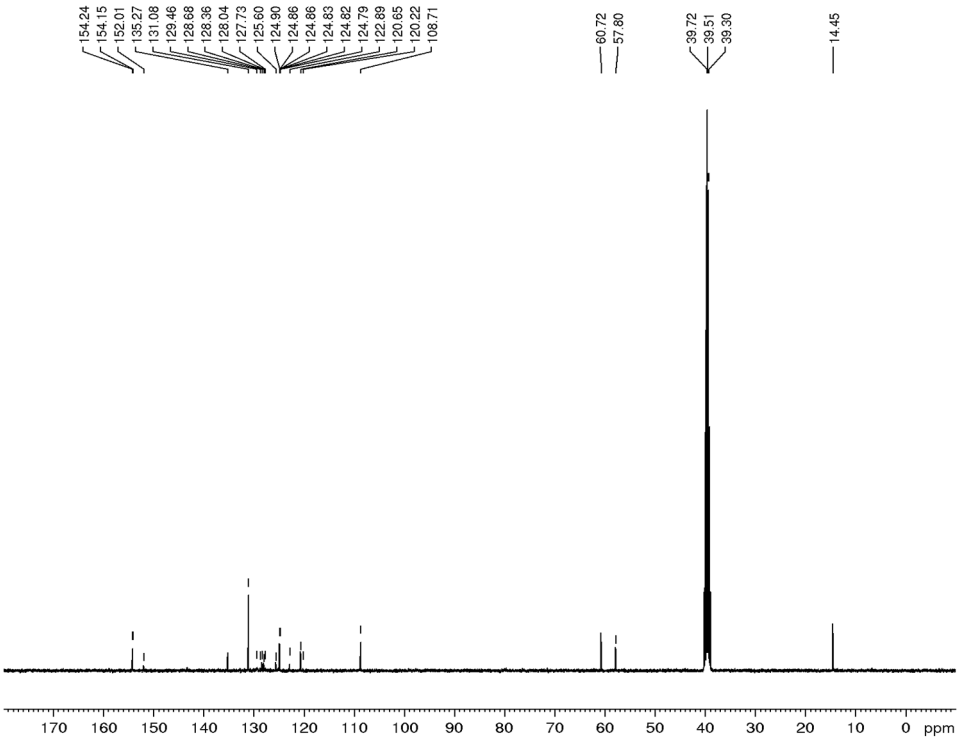


TK21 (1H-NMR, DMSO-d6)



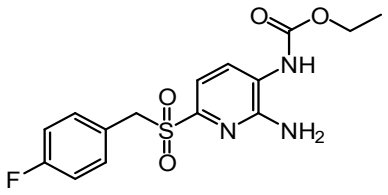

```
Current Data Parameters
NAME            T. Kasch
EXPNO                 90
PROCNO                 1

F2 - Acquisition Parameters
Date_          20151001
Time              11.00
INSTRUM           spect
PROBHD    5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   16
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ             3.9845889 sec
RG                 90.5
DW                60.800 usec
DE                10.00 usec
TE                295.1 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 9.75 usec
PL1               -4.50 dB
PL1W        26.90193939 W
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300024 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

TK21 (13C-NMR, DMSO-d6)

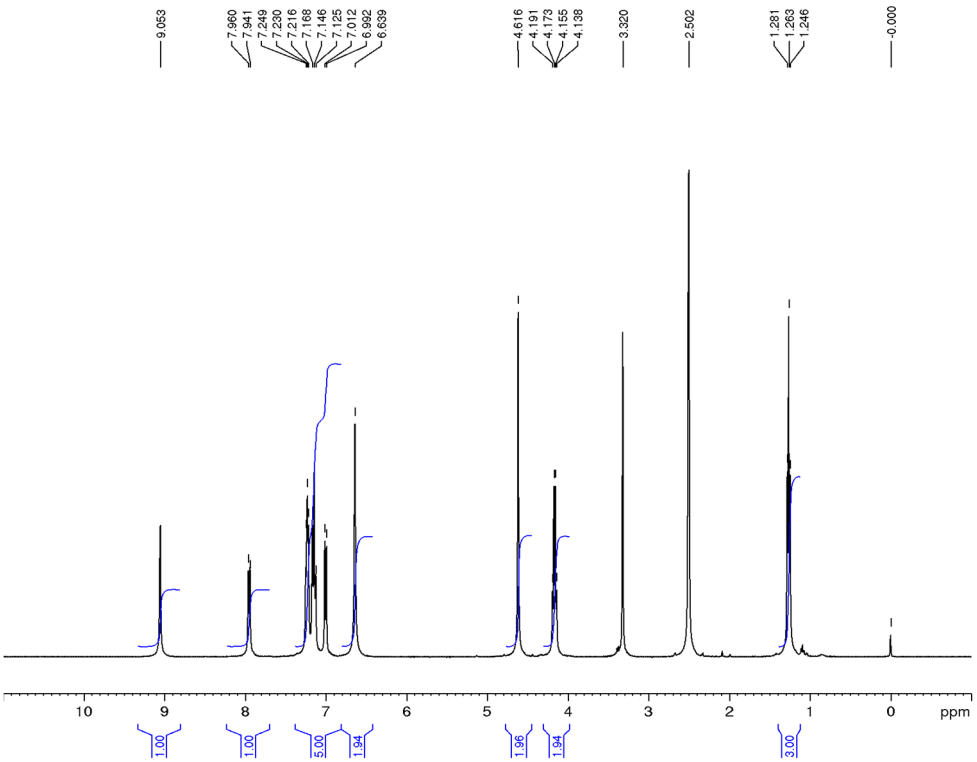



```
Current Data Parameters
NAME            T. Kasch
EXPNO                 93
PROCNO                 1

F2 - Acquisition Parameters
Date_          20151006
Time              10.01
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 usec
DE                10.00 usec
TE                285.4 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

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

======== CHANNEL f2 ========
CPDPRG[2        waltz16
NUC2                  1H
PCPD2             60.00 usec
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 MHz

F2 - Processing parameters
SI                 32768
SF          100.6128155 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

Spectra of 8a

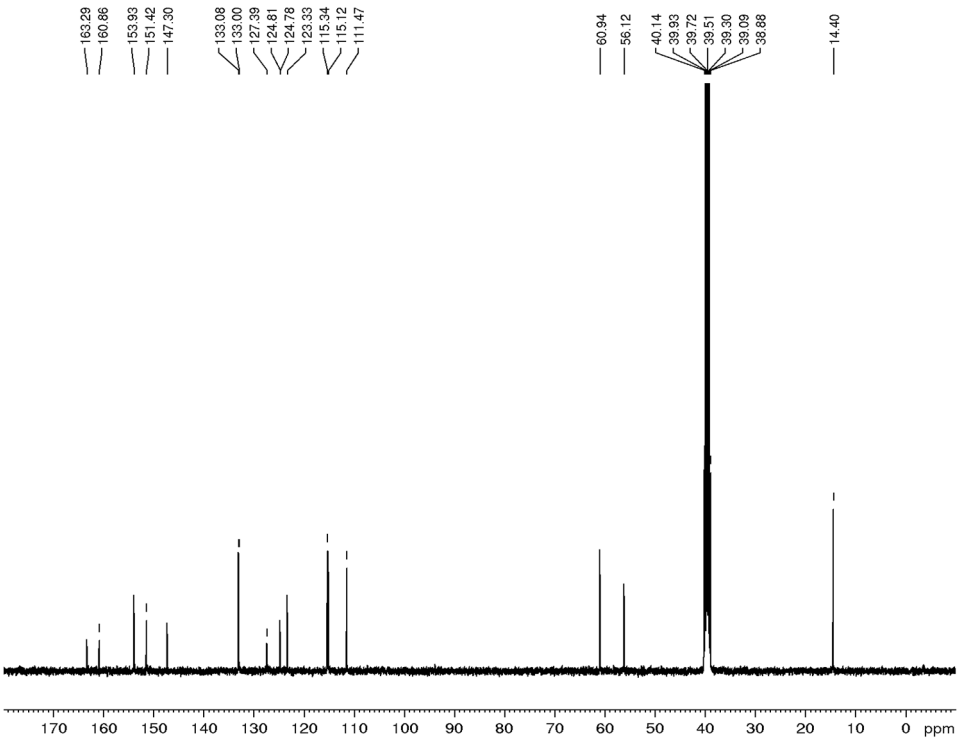


ELB100 (1H-NMR, DMSO-d6)



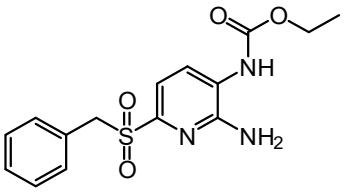

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     389
PROCNO                      1

F2 - Acquisition Parameters
Date_               20171219
Time                   13.45
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                       90.5
DW                   60.800 usec
DE                   10.00 usec
TE                    298.5 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     9.75 usec
PL1                   -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                400.1300017 MHz
WDW                          EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

ELB100 (13C-NMR, DMSO-d6)

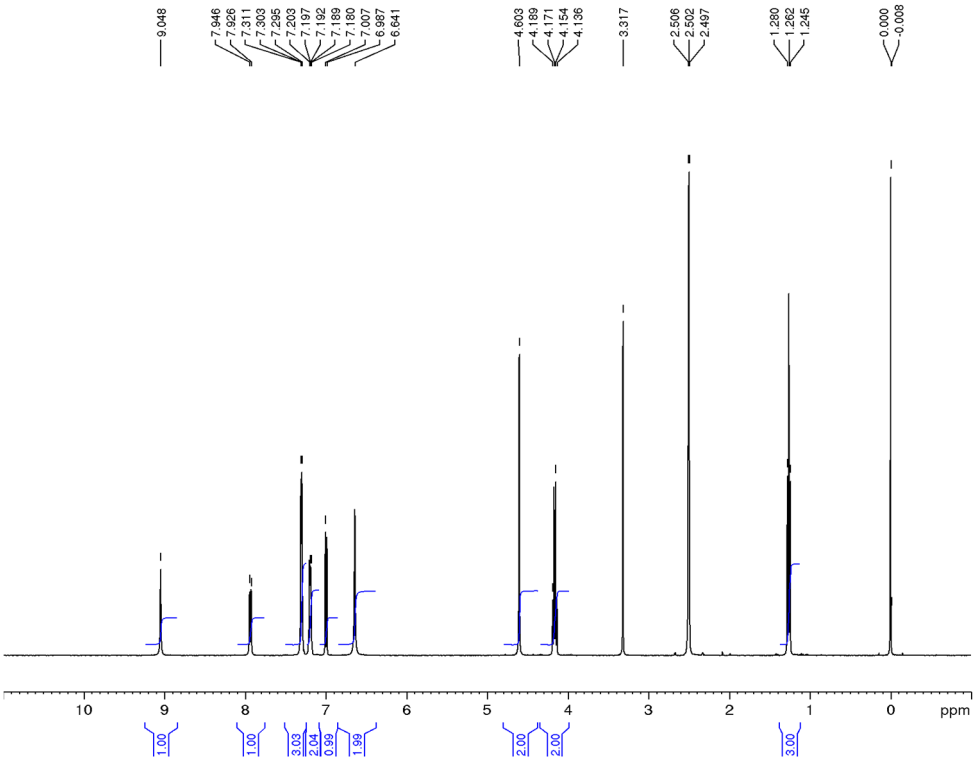



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     398
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180108
Time                   14.33
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 usec
DE                   10.00 usec
TE                    298.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1

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

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                      1H
PCPD2                60.00 usec
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                100.6128162 MHz
WDW                          EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Spectra of 8b

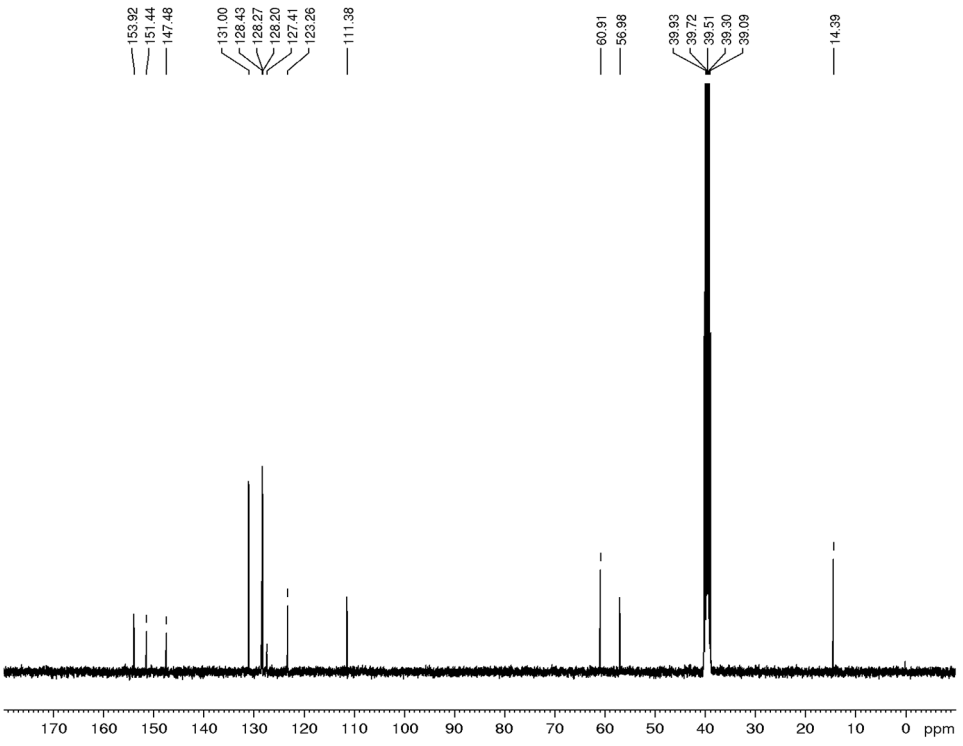


ELB110 (1H-NMR, DMSO-d6)



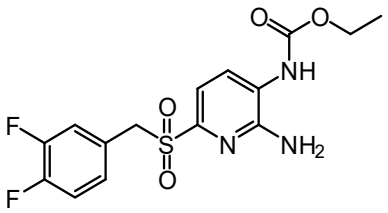

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     452
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180213
Time                    9.37
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      114
DW                   60.800 usec
DE                   10.00 usec
TE                   298.4 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      9.75 usec
PL1                    -5.00 dB
PL1W            30.18447304 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                      32768
SF             400.1300023 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

ELB110 (13C-NMR, DMSO-d6)

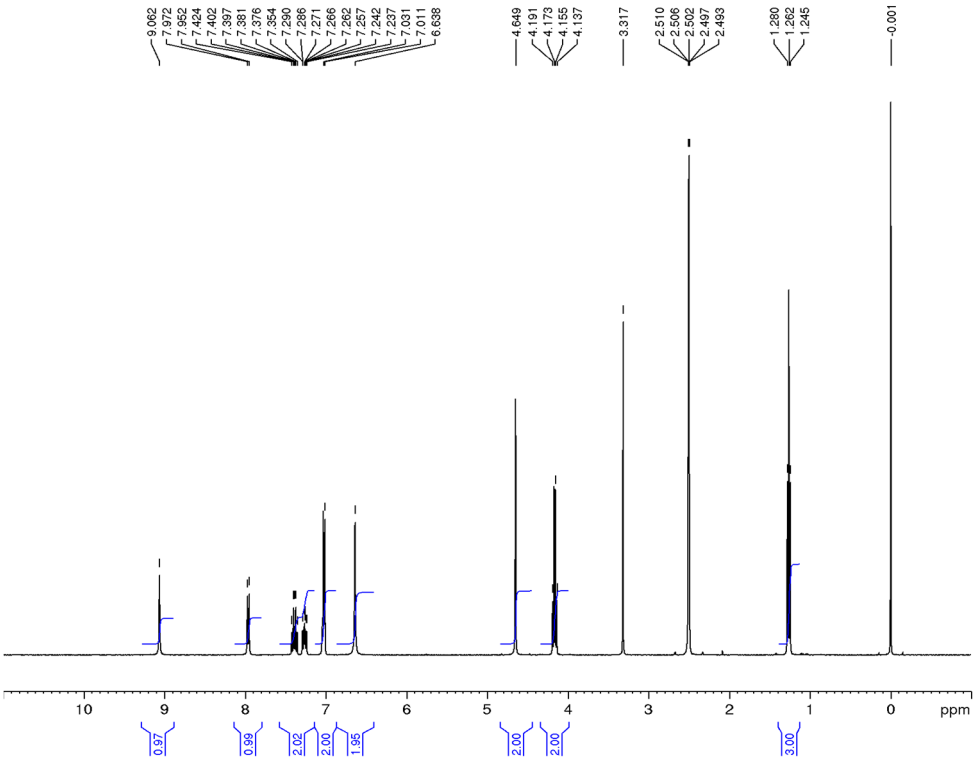



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     457
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180215
Time                   13.58
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 sec
RG                     2050
DW                   20.800 usec
DE                   10.00 usec
TE                   298.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                  60.00 usec
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
GB           0
PC                      1.40
```

Spectra of 8c

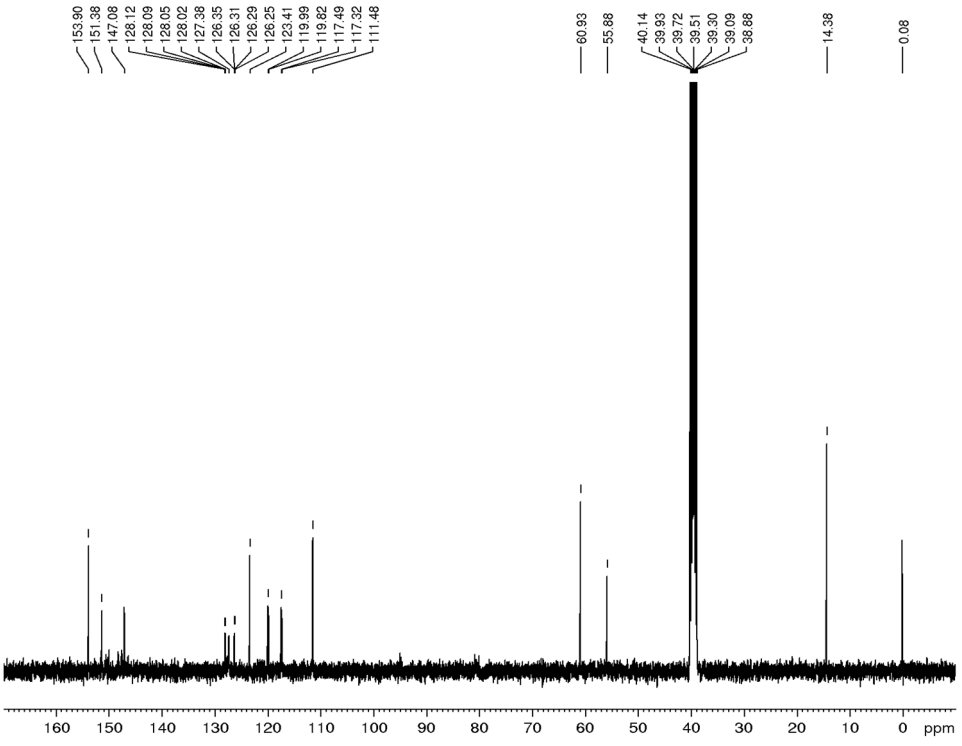


ELB097.2 (1H-NMR, DMSO-d6)



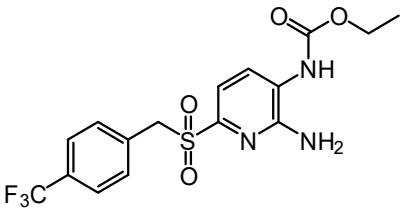

```
Current Data Parameters
NAME                  C. Bock
EXPNO                     438
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180206
Time                   11.25
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      128
DW                   60.800 usec
DE                   10.00 usec
TE                   298.5 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                       9.75 usec
PL1                     -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300023 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```

ELB097.2 (13C-NMR, DMSO-d6)

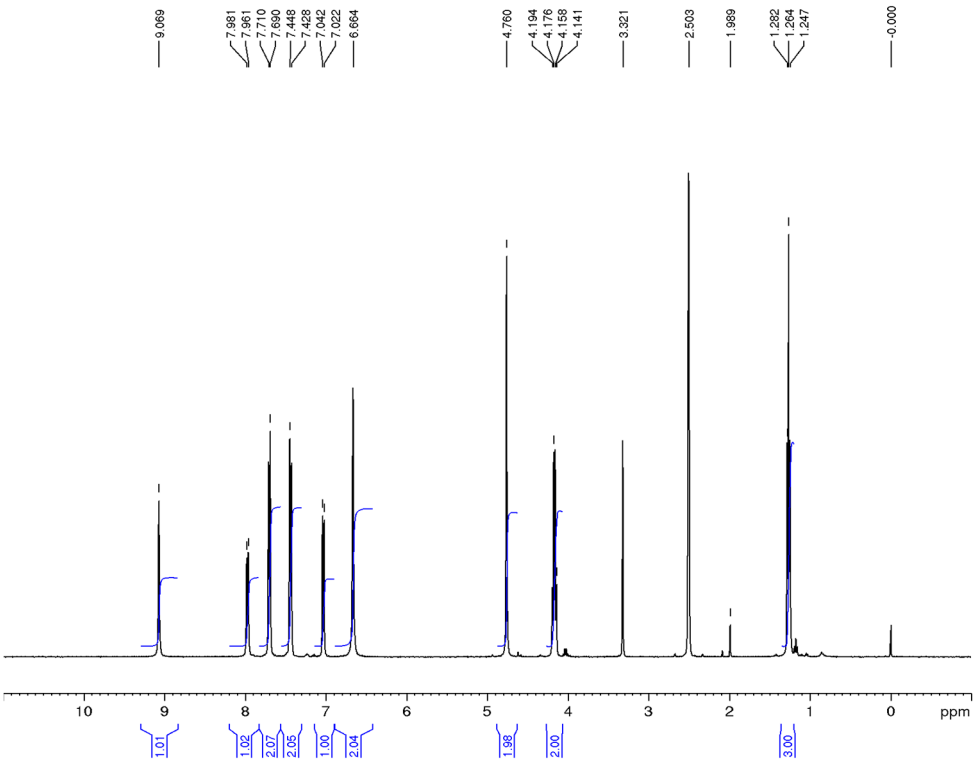



```
Current Data Parameters
NAME                  C. Bock
EXPNO                     439
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180206
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 sec
RG                      2050
DW                   20.800 usec
DE                   10.00 usec
TE                   298.4 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                 60.00 usec
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
LB                       1.00 Hz
GB           0
PC                       1.40
```

Spectra of 8d

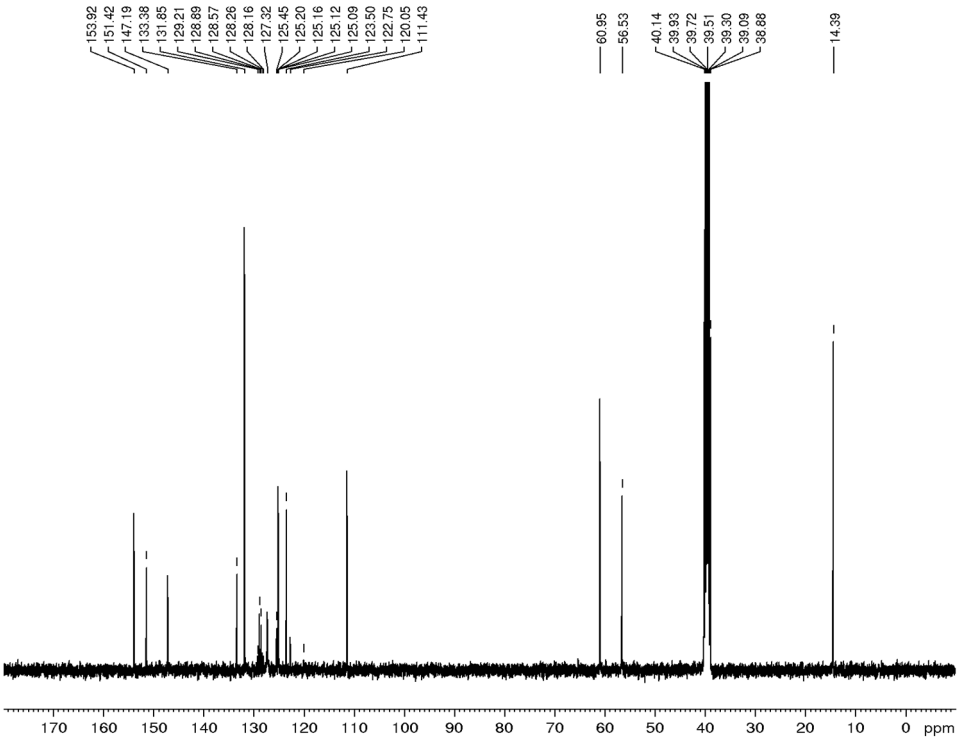


ELB099 (1H-NMR, DMSO-d6)




```
Current Data Parameters
NAME                  C. Bock
EXPNO                     388
PROCNO                      1

F2 - Acquisition Parameters
Date_               20171219
Time                   13.40
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9845889 sec
RG                      90.5
DW                   60.800 usec
DE                   10.00 usec
TE                   297.9 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                       9.75 usec
PL1                     -5.00 dB
PL1W             30.18447304 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300015 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```

ELB099 (13C-NMR, DMSO-d6)




```
Current Data Parameters
NAME                  C. Bock
EXPNO                     400
PROCNO                      1

F2 - Acquisition Parameters
Date_               20180109
Time                    8.50
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 usec
DE                   10.00 usec
TE                   298.1 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

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

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                  60.00 usec
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                100.6128162 MHz
WDW                         EM
SSB          0
LB                     1.00 Hz
GB           0
PC                       1.40
```

Biological Evaluations

Cell culture

TGF-α transgenic mouse hepatocytes (TAMH) were provided by Sidney D. Nelson (formerly Department of Medicinal Chemistry, University of Washington, Seattle, USA). HEK293 cells expressing $K_v7.2/3$ were purchased from SB Drug Discovery (Glasgow, UK). TAMH cells were maintained in a T75 flask with Dulbecco's Modified Eagle's Medium/Nutrient Mixture F-12 (DMEM/F12 1:1 mix) (PAN Biotech), supplemented with 5 % PANEXIN NTA (PAN Biotech), 10 mM nicotinamide (Sigma Aldrich) and 10 µg/mL gentamicin sulfate (PAN Biotech). HEK293 cells were cultured in a T75 flask with minimum essential medium with non-essential amino acids (MEM) (Thermo Fisher Scientific), supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Sigma Aldrich), 2 mM L-glutamine (Sigma Aldrich), 4 µg/mL blasticidin S-HCl (Merck), 1% penicillin/streptomycin (Thermo Fisher Scientific) and 0.78 mg/mL G418 sulfate (Carl Roth). Both cell lines were incubated at 37 °C in a humidified incubator with 95% air/5% CO_2.

MTT assay

TAMH cells were detached from flask when ~90% confluent with Trypsin-EDTA (Sigma Aldrich), resuspended in the presence of 0.25 mg/mL soybean trypsin inhibitor (Sigma Aldrich) in DMEM/F12. After centrifugation, the cell pellet was resuspended in DMEM/F12 media. Cells were counted with an EVE™ Automated Cell Counter (NanoEnTek) and 20 000 cells/well/200 µL DMEM/F12 media were seeded into 96 well plates (#83.3924.300, Sarstedt). Plates were incubated until cells became confluent (usually 48 h after seeding). In triplicate, medium was removed and replaced by 200 µL/well DMEM/F12 media containing a serial dilution series of test compounds (5-9 concentrations) prepared in DMSO (BioScience-grade) (Carl Roth). Untreated controls contained 1% DMSO and wells lacking cells were used to determine background signal. After 24 h exposure to the test compounds, medium was aspirated off, 125 µL DMEM/F12 media supplemented with 20% (V/V) of 2.5 mg/mL solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) (Alfa Aesar) in phosphate-buffered saline (PBS) was added to wells and plates were incubated 2.5-4 h in a humidified incubator at 37 °C. After removing the medium and generated formazan crystals were dissolved in 50 µL DMSO (for synthesis) (Carl Roth). Absorbance was measured at λ = 570 nm with SpectraMax 190 microplate reader (Molecular Devices). Cell viability (T/C_{corr}) was obtained by dividing absorbance values for each treatment condition through that measured for control wells expressed in % (both corrected for background without cells). The LD_{50} is the estimated concentration that reduces the T/C_{corr} by 50%. This value was determined by plotting (log)concentration of test compound versus T/C_{corr} and performing linear regression analysis in Microsoft Excel (2013). When even the highest tested soluble concentration of a compound could not reduce cell viability to or below 50%, LD_{50} was indicated as greater than the highest tested concentration. Determined values are the mean of at least three independent experiments ± standard deviation (SD).

Kv7.2/3 channel opening assay

HEK293 cells were detached from flask by TrypLE Express (Thermo Fisher Scientific) when ~80% confluent and resuspended in MEM media. After centrifugation the cell pellet was again resuspended in MEM media. Cells were counted with an EVE™ Automated Cell Counter and 60 000 cells/well/100 µL MEM media were seeded into

black walled 96 well plates with clear bottom (4titude). Cells were allowed to attach for 24 h in a humidified incubator at 37 °C, forming a near confluent monolayer. FLIPR® Potassium Assay Kit (Molecular Devices) was used to determine K_v7.2/3 channel opening activity of test compounds according to manufacturer's instructions. Briefly, equal amount of Loading Buffer containing 5 mM probenecid (Santa Cruz Biotechnology) (pH 7.4) was added to wells and incubated for 1 h at room temperature in the dark. Serial diution series of test compounds (5-9 concentrations) were prepared in DMSO (BioScience-grade) (Carl Roth) and incubated with cells for another 30 min at room temperature in the dark. Control wells contained 1% DMSO. Plates were placed in an Infinite® F200 Pro plate reader (Tecan) and background fluorescence (baseline) for each well was bottom read at excitation/emmission wavelength: 485nm/535 nm for approximately 20 s. Then, 50 µL Stimulus Buffer ($c(K^+)$ = 25 mM, $c(Tl^+)$ = 15 mM) was added to each well and fluorescence intensity was recorded immediately every 2.5-3 s continuously for further 2 min. The recorded data were transfered to Microsoft Excel (2013). The ratio readout of maximal fluorescence intensity change of a compound's concentration at a specific timepoint was divided through the average of fluorescence intensities of baseline (ΔF/F) and analogous determined value for control was substracted (corr. ΔF/F). At the chosen specific time point the sum of ΔF/F of all concentrations belonging to a dilution series of a compound became maximal. Corr. ΔF/F were plotted versus log(concentration) of a compound, fitted to a four parameter logistic equation and EC_{50} values were calculated according to the software GraphPad Prism 6 (La Jolla, California, USA). Indicated EC_{50} values are the mean of at least three independent experiments ± standard deviation (SD).

Log$D_{7.4}$ determination

Log$D_{7.4}$ values were determined using a HPLC method. Column: Phenomenex Kinetex PFP 2.6 µM 75×4.6 mm, flow rate 0.5 mL/min, mobile phase: **A**: 95 % ammonium formiate buffer (21.05 mM, pH 7.4) and 5 % methanol, **B** 5 % ammonium formiate buffer (0.36 mM, pH 7.4) and 95 % methanol, gradient: 0-50 min 0→100 % **B**, 50-52 min 100→0 % **B**, 52-60 min 0 % **B**.

Table of reference compounds with known log*P* and measured log*k'*

reference	ret1	ret2	ret3	ret4	mean	k'	log*k'*	log*P* (lit.)
uracil	2.71	2.72	2.72	2.72	2.72			
pyridine	11.92	11.92	11.92	11.92	11.92	3.39	0.53	0.65
benzyl alcohol	14.95	14.96	14.95	14.95	14.95	4.50	0.65	1.1
acetanilide	16.26	16.26	16.26	16.25	16.26	4.98	0.70	1.16
picoline	19.09	19.10	19.09	19.08	19.09	6.02	0.78	1.2
acetophenone	24.15	24.16	24.16	24.15	24.15	7.89	0.90	1.7
methyl benzoate	29.39	29.40	29.39	29.39	29.39	9.82	1.00	2.1
ethyl benzoatee	33.65	33.65	33.65	33.65	33.65	11.38	1.06	2.6
benzophenone	37.19	37.18	37.18	37.18	37.18	12.68	1.10	3.2
phenyl benzoate	39.18	39.17	39.18	39.18	39.18	13.42	1.13	3.6
diphenyl ether	40,85	40,85	40,85	40,85	40,85	14,03	1,15	4,2
bibenzyl	43,95	43,94	43,95	43,95	43,95	15,17	1,18	4,8
triphenylamine	47,87	47,86	47,87	47,87	47,87	16,61	1,22	5,7

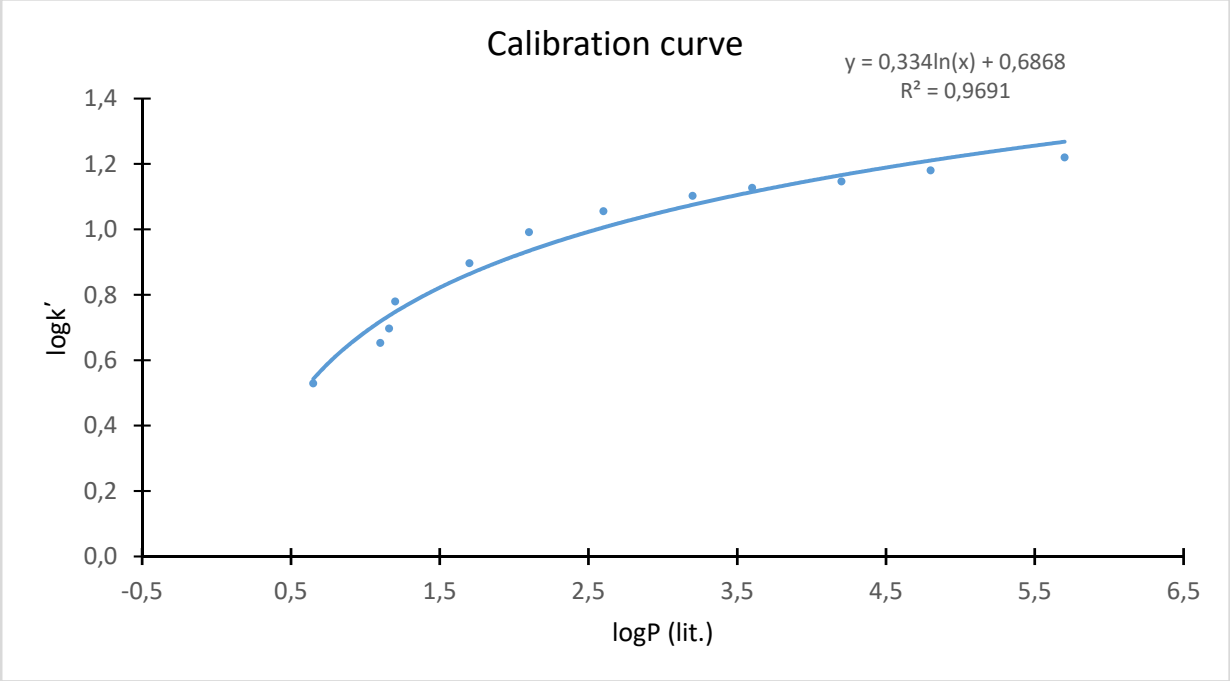
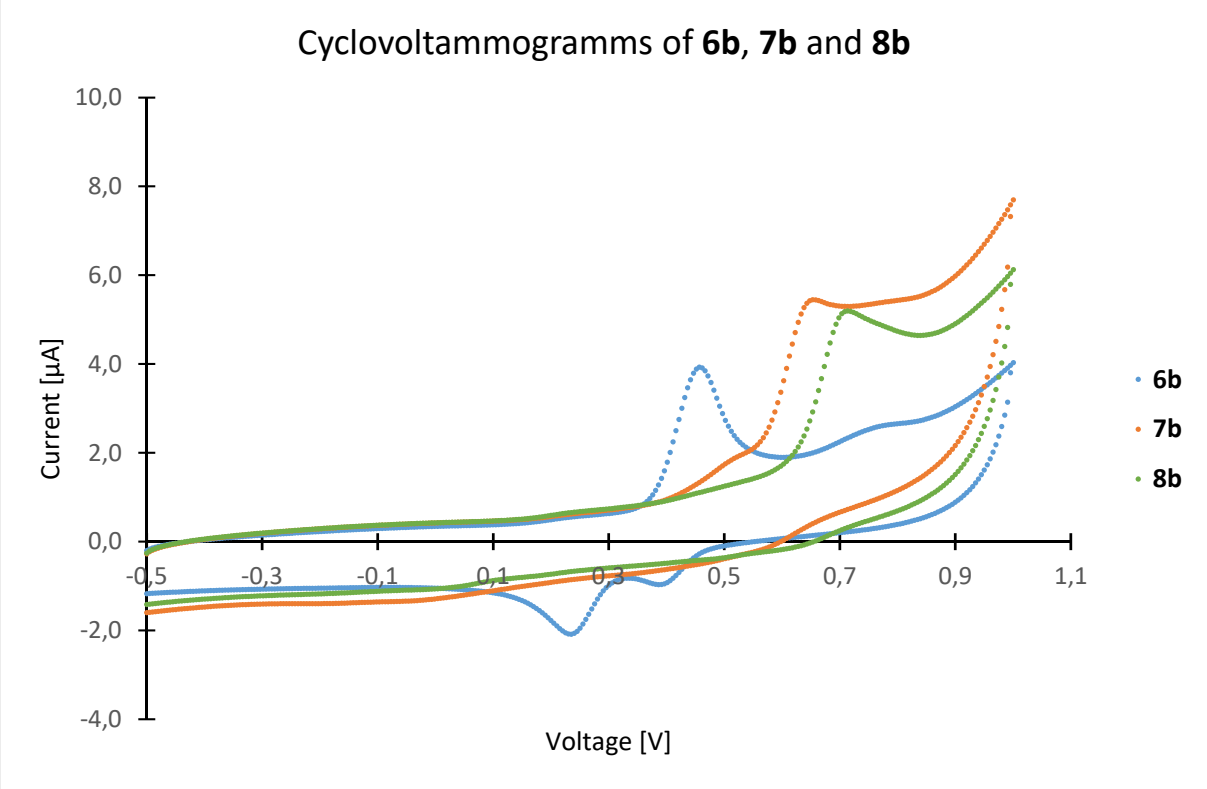


Table of synthesized compounds with measured log*k'* and calculated log$D_{7.4}$

cmpd	ret 1	ret 2	ret3	mean	k'	log*k'*	log$D_{7.4}$
1	33.78	33.66	n.d.	33.72	11.21	1.05	2.96
6a	38.22	38.23	38.23	38.226	12.84	1.11	3.54
6b	37.54	37.53	37.54	37.54	12.60	1.10	3.45
6c	39.19	39.21	n.d.	39.20	13.20	1.12	3.66
6d	41.08	41.08	41.07	41.08	13.88	1.14	3.91
7a	31.07	31.08	31.08	31.08	10.26	1.01	2.64
7b	29.94	29.95	29.96	29.95	9.85	0.99	2.50
7c	32.37	32.37	32.38	32.37	10.72	1.03	2.80
7d	35.63	35.63	35.62	35.63	11.90	1.08	3.20
8a	33.26	33.25	33.25	33.25	11.04	1.04	2.91
8b	32.02	32.01	32.02	32.02	10.60	1.03	2.75
8c	34.59	34.59	34.58	34.59	11.53	1.06	3.07
8d	37.29	37.29	37.29	37.29	12.51	1.10	3.42

Cyclic voltammetry

Oxidation potentials of the compounds were obtained using the 797 VA Computrace from Metrohm. Working electrode: glassy carbon, reference electrode: Ag/AgCl/KCl 3 M, auxiliary electrode: Pt. 10 µmol of the compound were suspended in 10 mL of TRIS buffer (pH 7.4) and sonicated for 3 min. The mixture was poured into the glass vial and degassed by nitrogen for 3 min. Starting at –0.5 V the voltage was increased to 1.0 V with a speed of 0.1 V/s, while the current was recorded in 0.05 V steps. Once 1.0 V was reached, the voltage was inverted until –0.5 V with the same speed to obtain a full cycle. 5 of those cycles were recorded but only the first sweep was used to determine the anodic peak potential ($E_{P.A.}$) as it gave the strongest signal. The consecutive cycles showed lower currents, most likely because of polymerization of the oxidized compounds on the surface of the working electrode. Thus the graphite surface had to be polished after every measurement with an alumina oxide suspension in water which was distributed on a patch of cloth. The $E_{P.A.}$ was determined automatically using the software: 797 VA Computrace 1.3.1.



	1. measurement		2. measurement		3. measurement		mean	s.d.
cmpd.	E_{pa} [mV]	I_{pa} [µA]	E_{pa} [mV]	I_{pa} [µA]	E_{pa} [mV]	I_{pa} [µA]	E_{pa} [mV]	E_{pa} [mV]
1	255	6.21	220	0.46	225	1.36	233.33	18.93
6a	472	1.05	467	0.355	452	0.106	463.67	10.41
6b	457	0.34	462	0.41	457	0.48	458.67	2.89
6c	457	0.81	462	0.67	462	0.4	460.33	2.89
6d	457	2.74	457	1.42	452	1.89	455.33	2.89
7a	653	1.13	648	0.61	658	0.48	653.00	5.00

7b	628	0.14	628	0.15	623	0.29	626.33	2.89
7c	633	0.35	633	0.38	652	0.28	639.33	10.97
7d	633	1.34	653	0.69	648	2.2	644.67	10.41
8a	714	1.35	709	1.39	729	1.24	717.33	10.41
8b	709	0.95	714	1.07	709	1.49	710.67	2.89
8c	729	2.59	714	3.11	714	4.21	719.00	8.66
8d	709	1.75	714	2.27	704	2.32	709.00	5.00

Computational methods

All calculations were performed using the Molecular Operating Environment (MOE) software suite (version 2018.01). The default parameters were used if not explicitly specified.

Heteromeric K_v7.2/7.3 multimer homology modeling

The sequences of the voltage-gated potassium channels K_v7.2 and K_v7.3 were taken from the UniProt entries O43526 and O43525. Both were aligned to the Kv1.2 template (PDB 2R9R) in an alternating manner. Only the first 351 amino acids, containing the membrane-associated S1-S6 subunits, were taken into account. All four, pore-forming chains were modeled at once to prevent unusual sidechain positions. A total of 10 main chain models with 10 sidechain models each were calculated at a temperature of 300K. The final homology model was protonated with Protonate3D and energy-optimized.

Docking

The binding site was defined as all residues within 4.5 Å of residue W265, which was previously described as an important amino acid for the binding of closely related drug retigabine. The placement of 30 poses was performed using the Triangle Matcher with London dG scoring and flexible ligands. All generated binding poses were refined with an Induced Fit and MM/GBVI scoring. A total of 10 final poses for each ligand was calculated, visually inspected and cross-checked with additional 20 compounds from literature and patents using the same procedure and the obtained retigabine binding mode as template.