Supporting Information

Flupirtine Analogues: Explorative Synthesis and Influence of Chemical Structure on $K_V7.2/K_V7.3$ Channel Opening Activity

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Contents

Specific procedures and characterization

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

2,6-Dichloro-3-nitropyridine (40 mmol, 7.72g) was dissolved in 2-propanol (300 mL). An excess of aqueous ammonia (20 mL, 25%) was added. The reaction mixture was then warmed to 35 °C and stirred for 5 days. A light yellow precipitate was collected by filtration, which was washed with water (2 x 50 mL) and dried using desiccator. Light yellow solid (yield= 77%); mp: 194-195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.40 (d, *J*= 8.6 Hz, 1H), 8.26 (br s, 2H), 6.78 (d, *J*= 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 155.0, 153.5, 138.4, 126.1, 112.0; IR: $\tilde{\nu}$ = 3442, 3277, 1633, 1556, 1495, 1422, 1338, 1234, 1148, 946, 762, 502 cm^{-1}.

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

2,6-Dichloro-3-nitropyridine (5 mmol, 1.0 g) was dissolved in acetonitrile (20 mL). After adding triethylamine (7.5 mmol, 1 mL), the mixture was cooled to about 0 °C. Methylamine (6 mmol, 613 µL) was dissolved in acetonitrile (10 mL) and added slowly over a period of 30 min. After complete addition of methylamine, the mixture was stirred for 10 min at about 0 ^{0}C and then allowed to rise to room temperature. The mixture was stirred at room temperature for 30 min. The product was purified using silica gel chromatography (solvent: toluene). Yellow solid (yield= 68%); mp: 119-120 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.72 (d, *J*= 3.1 Hz, 1H), 8.43 (d, *J*= 8.6 Hz, 1H), 6.78 (d, *J*= 8.6 Hz, 1H), 3.01 (d, *J*= 4.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 155.2, 152.1, 138.4, 126.9, 111.0, 28.5; IR: $\tilde{\nu}$ = 3397, 3111, 1567, 1504, 1375, 1217, 758 cm^{-1}.

6-Amino-5-nitropyridine-2-thiol (**7a**)

Compound **6a** (4.2 mmol, 730 mg), sulfur (3.1 mmol, 103 mg), $Na_2S.9H_20$ (3 mmol, 702mg) and sodium hydroxide (4.2 mmol, 168 mg) were added to a round bottom flask. After adding ethanol (30 mL), the mixture was held under reflux for 5 hours. The reaction mixture was poured into ice-cooled water (100 mL) and then washed with dichloromethane (3 x 50 mL). The mixture was acidified (pH=4) with stepwise addition of 10% HCl, which resulted in precipitation of the product. Eventually, an orange coloured product was collected by filtration and dried using desiccator. Orange coloured solid (yield= 80%); mp: 190-191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 12.64 (s,

1H), 8.69 (br d, *J*= 7.0 Hz, 1H), 7.93 (d, *J*= 9.4 Hz, 1H), 7.61 (br d, *J*= 10.4 Hz, 1H), 6.51 (d, *J*= 9.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 183.8, 149.5, 131.9, 119.5, 118.8; IR: $\tilde{\nu}$ = 3386, 3243, 1631, 1593, 1258, 1090, 755 cm^{-1}.

6-(Methylamino)-5-nitropyridine-2-thiol (**7b**)

Compound **6b** (7.34 mmol, 1.38 mg), sulfur (5.35 mmol, 171 mg), $Na_2S.9H_20$ (5.29 mmol, 1.25 g) and sodium hydroxide (7.34 mmol, 294 mg) were added to a round bottom flask. After adding ethanol (30 mL), the mixture was heated under reflux for 6 hours. The reaction mixture was poured into ice-cooled water (100 mL) and then washed with dichloromethane (3 x 50 mL). The mixture was acidified to pH=4 with stepwise addition of 10% HCl. Eventually, the product was collected by filtration and dried using desiccator. Orange coloured solid (yield= 48%); mp: 193-194 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 11.92 (br s, 1H), 9.62 (d, *J*= 4.7 Hz, 1H), 7.94 (d, *J*= 9.5 Hz, 1H), 6.52 (d, *J*= 9.5 Hz, 1H), 3.17 (d, *J*= 5.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 185.0, 149.4, 131.4, 119.3, 119.1, 29.5; IR: $\tilde{\nu}$ = 3246, 1623, 1581, 1338, 1140, 748, 529 cm^{-1}.

6-Methyl-5-nitropyridine-2-thiol (**7c**)

Compound **6c** (10 mmol, 2.17 g), sulfur (7.29 mmol, 234 mg), $Na_2S.9H_20$ (7.2 mmol, 1.73 g) and sodium hydroxide (10 mmol, 400 mg) were added to a round bottom flask. After adding ethanol (40 mL), the mixture was heated under reflux for 3 hours. The reaction mixture was poured into ice-cooled water (100 mL) and then washed with dichloromethane (3 x 50 mL). The pH of the solution was adjusted to 4 with stepwise addition of 10% HCl. Eventually, the product was collected by filtration. Brown solid (yield= 32%); mp: 175-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 13.95 (br s, 1H), 7.99 (d, *J*= 9.5 Hz, 1H), 7.20 (d, *J*= 9.6 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 183.2, 150.6, 135.5, 130.9, 130.6, 19.0; IR: $\tilde{\nu}$ = 3196, 1585, 1327, 1210, 1069, 830, 510 cm^{-1}.

6-[(4-Fluorobenzyl)thio]-3-nitropyridin-2-amine (**8a**)

Compound **7a** (6 mmol, 1.03 g) was dissolved in dimethylformamide (10 mL). This was followed by the addition of 10% KOH (6 mmol, 3.1 mL) and 4-fluorobenzyl bromide (6 mmol, 740 µL). The reaction was completed after 1 hour of stirring at room temperature. The product was

precipitated with addition of water. A yellow product was collected by filtration and then washed with n-hexane and ethanol. Yellow solid (yield = 85%); mp: 139-140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.16 (d, *J*= 8.8 Hz, 3H), 7.55 (m, 2H), 7.15 (m, 2H), 6.62 (d, *J*= 8.8 Hz, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 166.3, 162.5 (d, *J*= 243 Hz, 1C), 153.1, 134.5, 134.2 (d, *J*= 3 Hz, 1C), 131.2 (d, *J*= 8 Hz, 1C), 123.5, 115.2 (d, *J*= 21 Hz, 1C), 110.3, 32.2; IR: $\tilde{\nu}$ = 3458, 3333, 1558, 1345, 1220, 1144, 763 cm^{-1}.

6-[(1,1'-Biphenyl-4-yl)methylthio]-3-nitropyridin-2-amine (**8b**)

Compound **7a** (2.5 mmol, 430 mg) was dissolved in dimethylformamide (10 mL), to which 10% KOH (2.5 mmol, 1.4 mL) and 4-(bromomethyl)biphenyl (2.5 mmol, 668 mg) were added respectively. The reaction was completed after 1 hour of stirring at room temperature. Water was added to precipitate the product. The product was filtered and washed with n-hexane and ethanol. Yellow solid (yield= 90%); mp: 179-181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.18 (d, J= 8.8 Hz, 3H), 7.66 (m, 6H), 7.45 (m, 2H), 7.37 (m, 1H), 6.65 (d, *J*= 8.8 Hz, 1H) 4.45 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 166.4, 153.1, 139.7, 139.0, 136.9, 134.4, 129.6 (2C), 128.8 (2C), 127.3, 126.6 (2C), 126.5 (2C), 123.4, 110.2, 32.7; IR: $\tilde{\nu}$ = 3463, 3324, 1595, 1335, 1166, 1144, 763, 740 cm^{-1}.

6-[(3,5-Dimethoxybenzyl)thio]-3-nitropyridin-2-amine (**8c**)

Compound **7a** (2 mmol, 344 mg) was dissolved in dimethylformamide (10 mL). 10% KOH (2 mmol, 1.1 mL) and dimethoxybenzyl bromide (2 mmol, 463 mg) were added respectively to the reaction solution, which was stirred for 1 hour at room temperature. Water was added in order to precipitate the product. The product was washed with ethanol and n-hexane. Yellow solid (yield = 76%); mp: 124-125 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.17 (d, *J*= 8.8 Hz, 1H), 6.65 (d, *J*= 2.2 Hz, 2H), 6.62 (d, *J*= 8.8 Hz, 1H), 6.38 (t, 1H), 4.39 (s, 2H), 3.71 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 166.5, 160.4 (2C), 153.1, 139.9, 134.4, 123.4, 110.2, 107.1 (2C), 99.0, 55.1 (2C), 33.2; IR: $\tilde{\nu}$ = 3488, 3362, 2834, 1577, 1462, 1204, 1145, 1052 cm^{-1}.

3-Nitro-6-[(pyridin-2-ylmethyl)thio]pyridin-2-amine (**8d**)

Compound **7a** (2 mmol, 344 mg) was dissolved in dimethylformamide (10 mL). 10% KOH (3 mmol, 1.8 mL) and 2-(bromomethyl)pyridine HBr (2 mmol, 502 mg) were added respectively to the reaction solution. The reaction was completed after 1 hour of stirring at room temperature. The product was precipitated with the addition of water. Eventually, the product was filtered and washed with n-hexane. Saffron coloured solid (yield = 88%); mp: 121-123 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.78 (d, *J*= 5.0 Hz, 1H), 8.34 (t, 1H), 8.19 (d, *J*= 8.8 Hz, 1H), 8.11 (d, *J*= 8.0 Hz, 1H), 7.78 (t, 1H), 6.70 (d, *J*= 8.8 Hz, 1H), 4.70 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 166.5, 157.0, 153.1, 149.2, 136.8, 134.5, 123.5, 122.4, 110.2, 35.3; IR: $\tilde{\nu}$ = 3404, 3242, 2595, 1606, 1569, 1243, 1143, 749 cm^{-1}.

S-(6-Amino-5-nitropyridin-2-yl) 4-fluorobenzothioate (**8e**)

Compound **7a** (2 mmol, 344 mg) was dissolved in 2-propanol (15 mL). Triethylamine (4 mmol, 560 µL) and 4-benzoyl chloride (2 mmol, 120 µL) were added to the reaction solution. The mixture was held at reflux for overnight. Water was added to precipitate the product. The precipitate was filtered and washed with water and n-hexane. Eventually, the product was recrystallized from ethyl acetate. Yellow solid (yield = 82%); mp: 168-169 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.49 (d, *J*= 8.6 Hz, 1H), 8.12 (s, 2H), 8.10 (m, 2H), 7.48 (m, 2H), 7.18 (d, *J*= 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 186.3, 167.1 (d, *J*= 254 Hz, 1C), 157.8, 153.3, 152.9, 136.1, 133.5, 132.4 (d, *J*= 3 Hz, 1C), 130.4 (d, *J*= 10 Hz, 2C), 126.6, 117.0 (t, *J*= 24 Hz, 2C), 107.2; IR: $\tilde{\nu}$ = 3489, 3067, 1674, 1549, 1477, 1236, 765 cm^{-1}.

3-Nitro-6-{[2-(piperidin-1-yl)ethyl]thio}pyridin-2-amine (**8f**)

Aqueous KOH 10% (3 mmol, 1.8 mL) was added to the round bottom flask that contains compound **7a** (2 mmol, 344 mg) and 1-(2-chloroethyl)piperidine HCl. Dimethylformamide (10 mL) was added to put the above compounds into a solution. The solution was stirred for 1 hour at room temperature. The product was precipitated by the addition of water. The precipitate was then washed with *n*-hexane and aqueous NaOH 10%. Saffron coloured solid (yield= 87%); mp: 108-109 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.15 (d, *J*= 8.8 Hz, 1H), 8.04 (s, 2H), 6.62 (d, *J*= 8.8 Hz, 1H), 3.32 (t, 2H), 2.56 (t, 2H), 2.40 (m, 4H), 1.51 (m, 4H), 1.40 (m, 2H); ^{13}C NMR (100 MHz,

DMSO-d_6): δ= 167.7, 153.2, 134.1, 123.2, 110.6, 57.41, 53.8 (2C), 27.1, 25.5 (2C), 24.0; IR: $\tilde{\nu}$ = 3457, 3328, 2933, 2760, 1607, 1557, 1347, 1229, 1141, 766 cm^{-1}.

6-(Benzylthio)-*N*-methyl-3-nitropyridin-2-amine (**8g**)

Compound **7b** (3.25 mmol, 602 mg) was dissolved in dimethylformamide (10 mL). 10% KOH (3.25 mmol, 2 mL) and benzyl bromide (3.25 mmol, 387 µL) were added sequentially to the above mixture. The mixture was stirred for 1 hour and a yellow product was precipitated with the addition of water. The precipitate was washed with ethanol and n-hexane. Yellow solid (yield= 89%); mp: 133-134 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.76 (d, *J*= 4.4 Hz, 1H), 8.20 (d, *J*= 8.8 Hz, 1H), 7.44 (m, 2H), 7.35 (m, 2H), 7.23 (m, 1H), 6.65 (d, *J*= 8.8 Hz, 1H), 4.53 (s, 1H), 3.09 (d, *J*= 4.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 166.8, 151.8, 137.4, 134.6, 128.7 (2C), 128.5 (2C), 127.2, 124.1, 109.3, 33.4, 28.3; IR: $\tilde{\nu}$ = 3374, 1577, 1374, 1212, 1036, 928, 760 cm^{-1}.

6[(4-Fluorobenzyl)thio]-2-methyl-3-nitropyridine (**8h**)

Compound **7c** (3 mmol, 510 mg) was dissolved in dimethylformamide (10 mL). This was followed by the addition of aqueous KOH 10% (3 mmol, 1.68 mL) and 4-fluorobenzyl bromide (3 mmol, 374 µL) respectively. After 1 hour of stirring at room temperature, the reaction was complete. The product was precipitated with the addition of water. Eventually, the product was filtered and further purified by washing with n-hexane. Pale yellow solid (yield= 66%); mp: 66-67 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.23 (d, *J*= 8.7 Hz, 1H), 7.51 (m, 2H), 7.42 (d, *J*= 8.8 Hz, 1H), 7.12 (m, 2H), 4.50 (s, 2H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 163.4, 162.5 (d, *J*= 243 Hz, 1C), 153.4, 142.1, 133.7 (d, *J*= 3 Hz, 1C), 133.1, 131.0 (d, *J*= 8 Hz, 2C), 119.6, 115.3 (d, *J*= 22 Hz, 2C), 32.8, 23.9; IR: $\tilde{\nu}$ = 3074, 1566, 1499, 1324, 1066, 753, 530 cm^{-1}.

N-{2-Amino-6-[(4-fluorobenzyl)thio]pyridin-3-yl}-3,4-difluorobenzamide (**9a**)

Compound **8a** (5 mmol, 1.4 g), iron powder (50 mmol, 2.8 g) and ammonium chloride (50 mmol, 2.675 g) were suspended in 4:1 ethanol/water (15 mL). The suspension was stirred at 100 °C for 1 hour. The suspension was filtered through a glass filter protected with 1 cm layer of diatomaceous earth and washed with ethyl acetate (2 x 50 mL). The filtrate was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). Triethylamine (7.5 mmol, 1.05 mL)

was added to the combined filtrate. The solution was cooled to about 0 ^{0}C and 3,4-difluorobenzyl chloride (5 mmol, 630 µL) was added slowly over a period of 30 min. After complete addition of 3,4-difluorobenzyl bromide, the mixture was stirred for 1 hour at room temperature. Eventually, the mixture was concentrated and left in the refrigerator to allow precipitation of the product. The product was further purified by recrystallization from dichloromethane. White solid (yield= 35%); purity 99%; mp: 150-151 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 9.64 (s, 1H), 8.08 (m, 1H), 7.86 (d, *J*= 2.0 Hz, 1H), 7.63 (m, 1H), 7.56 (m, 2H), 7.34 (d, 1H), 7.13 (m, 2H), 6.49 (d, *J*= 7.9 Hz, 1H), 6.09 (s, 2H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 167.3, 162.3 (d, *J*= 241 Hz, 1C), 154.6, 152.5, 150.3, 147.8, 135.2, 135.0 (d, *J*= 3 Hz, 1C), 130.8 (d, *J*= 8 Hz, 2C), 125.4, 117.5 (d, *J*= 9 Hz, 1C), 117.3 (d, *J*= 9 Hz, 1C), 115.1 (d, *J*= 21 Hz, 2C), 114.1, 109.0 , 32.5; IR: $\tilde{\nu}$ = 3396, 3298, 3150, 1629, 1504, 1462, 1226, 750 cm^{-1}; HRMS-ESI m/z [M-H]$^-$ calcd for $C_{19}H_{14}N_3OF_3S$: 388.0737, found: 388.0747.

Ethyl-{6-[(1,1'-biphenyl-4-yl)methylthio]-2-aminopyridin-3-yl}carbamate (**9b**)

Compound **8b** (2 mmol, 675 mg) and tin (II) chloride dihydrate (10 mmol, 2.26 g) were suspended in absolute ethanol (20 mL). The suspension was carefully set under an argon atmosphere and stirred at 70 °C. After 24 hours, the temperature was reduced to 40 ^{0}C and then triethylamine (20.4 mmol, 2.85 mL) and ethyl chloroformate (2.6 mmol, 248 µL) were added respectively. The reaction was stirred for overnight. The suspension was filtered through a protected glass filter and washed with ethanol (2 x 30 mL). The filtrate was concentrated and water was added to precipitate the product. The product was further purified by recrystallization from dichloromethane. Beige coloured solid (yield = 38%); purity 97%; mp: 165-167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.58 (s, 1H), 7.65 (m, 2H), 7.60 (m, 2H), 7.50 (m, 5H), 7.56 (m, 1H), 6.48 (d, *J*= 8.0 Hz, 1H), 5.96 (s, 2H), 4.35 (s, 2H), 4.12 (q, *J*= 7.1 Hz, 2H), 1,24 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 154.9, 154.2, 152.0, 139.6, 139.5, 130.8 (2C), 129.9, 128.9 (2C), 127.5, 126.5 (2C), 126.4 (2C), 120.1, 108.6, 60.6, 58.7, 14.4; IR: $\tilde{\nu}$ = 3484, 3290, 3161, 1703, 1622, 1460, 1219, 1065, 747 cm^{-1}; HRMS-ESI m/z [M-H]$^-$ calcd for $C_{21}H_{21}N_3O_2S$: 378.1282, found: 378.1272.

Ethyl-{2-amino-6-[(3,5-dimethoxybenzylthio)pyridin-3-yl]}carbamate (**9c**)

Compound **8c** (2.5 mmol, 800 mg) and tin (II) chloride dihydrate (12.5 mmol, 2.82 g) were suspended in absolute alcohol (20 mL). The suspension was carefully set under an argon atmosphere and stirred at 70 °C for overnight. The temperature was lowered to 40 °C. Triethylamine (25.5 mmol, 3.5 mL) and ethyl chloroformate (3.25 mmol, 310 µL) were added sequentially and the mixture was stirred for 4 hours. The mixture was then filtered through a protected glass filter and washed with ethanol (3x 20 mL). The product was separated using column flash chromatography (solvent: n-hexane and ethyl acetate). The fractions that contain the product were combined and evaporated to dryness. The product was dissolved in ethanol and then precipitated with the addition of water. Off-white solid (yield = 52%); purity 100%; mp: 84-85 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.57 (br s, 1H), 7.41 (d, *J*= 5.1 Hz, 1H), 6.57 (d, *J*= 2.1 Hz, 2H), 6.44 (d, *J*= 8.0 Hz, 1H), 6.34 (t, 1H), 5.94 (s, 2H), 4.22 (s, 2H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.70 (s, 6H), 1.24 (t, *J*= 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 160.2 (2C), 154.4, 152.8, 150.4, 140.9, 131.8, 115.2, 109.4, 106.7 (2C), 98.7, 60.3, 55.1 (2C), 33.7, 14.5; IR: $\tilde{\nu}$ = 3475, 3285, 3163, 2935, 1685, 1598, 1520, 1460, 1202, 1148, 1057 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{17}H_{21}N_3O_4S$: 364.1326, found: 364.1317.

Ethyl-{2-amino-6-[(pyridin-2-ylmethylthio)pyridin-3-yl]}carbamate (**9d**)

Compound **8d** (1 mmol, 263 mg) and tin (II) chloride dihydrate (4.6 mmol, 1.04 g) were suspended in ethanol (10 mL). The suspension was carefully set under an argon atmosphere and then stirred at 70 °C for 22 hours. The temperature was lowered to 40 °C. Triethylamine (10.2 mmol, 1.4 mL) and ethyl chloroformate (1.3 mmol, 120 µL) were added respectively and stirred overnight. The filtrate was concentrated and water was added. The product was then partitioned into dichloromethane and packed for flash column chromatography (solvent: dichloromethane and methanol). The fractions containing the product were combined and evaporated to dryness. Brown solid (yield= 30%); purity 100%; mp: 129-131 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.57 (s, 1H), 8.49 (d, *J*= 4.3 Hz, 1H), 7.73 (m, 1H), 7.50 (d, *J*= 7.8 Hz, 1H), 7.41 (d, *J*= 6.0 Hz, 1H), 7.25 (m, 1H), 6.49 (d, *J*= 8.0 Hz, 1H), 5.94 (s, 2H), 4.39 (s, 2H), 4.12 (q, *J*= 7.1 Hz, 2H), 1.24 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 158.2, 154.5, 152.8, 150.3, 149.0, 136.7, 131.9, 130.1, 123.1,

122.1, 115.2, 109.2, 60.4, 45.6, 35.7, 14.5; IR: $\tilde{\nu}$ = 3361, 3227, 2979, 2929, 1721, 1524, 1456, 1245, 1221, 1071 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_4O_2S$: 305.1067, found: 305.1061.

S-{6-Amino-5-[(ethoxycarbonyl)amino]pyridin-2-yl} 4-fluorobenzothioate (**9e**)

Compound **8e** (1 mmol, 293 mg) and tin (II) chloride dihydrate (5 mmol, 1.13 g) were suspended in absolute ethanol (10 mL). The suspension was carefully set under argon atmosphere. The suspension was stirred at 70 °C for 48 hours. The temperature was lowered to 40 °C. Triethylamine (10.2 mmol, 1.4 mL) and ethyl chloroformate (2.6 mmol, 240 µL) were added respectively. After 4 hours of stirring at 40 °C, the reaction was complete. The mixture was filtered through a protected glass filter and washed with ethanol (3 x 20 mL). The product was separated by flash column chromatography (solvent: dichloromethane and ethanol). The product was further purified using preparative HPLC (water and methanol). Off-white solid (yield= 28%); purity 100%; mp: 156-157 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.84 (s, 1H), 8.03 (m, 2H), 7.81 (d, *J*= 7.2 Hz, 1H), 7.44 (m, 2H), 6.92 (d, *J*= 7.8 Hz, 1H), 6.19 (s, 2H), 4.18 (q, *J*= 6.8 Hz, 2H), 1.28 (t, *J*= 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 188.2, 166.7 (d, *J*= 251 Hz, 1C), 154.2, 132.8, 130.0 (d, *J*= 10 Hz, 1C), 119.8, 119.4, 116.5 (d, *J*= 23 Hz, 1C), 60.6, 14.4; IR: $\tilde{\nu}$ = 3434, 3377, 3161, 1736, 1649, 1505, 1470, 1201, 906 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{15}H_{14}N_3O_3FS$: 336.0813, found: 336.0816.

Ethyl {2-amino-6-([2-(piperidin-1-yl)ethylthio]pyridin-3-yl}carbamate (**9f**)

Compound **8f** (1 mmol, 282 mg) and tin (II) chloride dihydrate (4.6 mmol, 1.02g) were suspended in absolute ethanol (10 mL). After carefully setting under argon atmosphere, the suspension was stirred at 70 °C for 25 hours. The temperature was lowered to 40 °C. Triethylamine (10.2 mmol, 1.4 mL) and ethyl chloroformate (2.6 mmol, 240 µL) were added and the mixture was stirred for 3 hours. The mixture was filtered and washed with ethanol (3 x 20 mL). The filtrate was concentrated and poured into water (50 mL). The product was partitioned into dichloromethane, which was evaporated to dryness in order to give a pure product. Brown coloured solid (yield= 32%); purity 100%; mp: 136-137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.55 (s, 1H), 7.40 (d, *J*= 6.1 Hz, 1H), 6.44 (d, *J*= 8.0 Hz, 1H), 5.82 (s, 2H), 4.12 (q, *J*= 7.1 Hz, 2H), 3.14 (q, *J*= 8.8 Hz, 2H), 2.50 (m, 2H), 2.38 (m, 4H), 1.51 (m, 4H), 1.39 (m, 2H), 1.24 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-

d_6): δ= 154.5, 152.8, 151.1, 131.9, 114.9, 109.3, 60.3, 58.2, 53.8 (2C), 26.9, 25.5 (2), 24.0, 14.5; IR: $\tilde{\nu}$ = 3341, 3212, 2934, 1713, 1530, 1452, 1214, 1065 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{15}H_{24}N_4O_2S$: 325.1693, found: 325.1698.

N-[6-(Benzylthio)-2-(methylamino)pyridin-3-yl]-2-(3,5-difluorophenyl)acetamide (**9g**)

Compound **8g** (2.8 mmol, 771 mg), iron powder (28 mmol, 1.57 g) and ammonium chloride (28 mmol, 1.5 g) were suspended in 15 mL ethanol 20%. The suspension was stirred at 100 °C for 2 hours, filtered over diatomaceous earth, and the filter washed with ethyl acetate. The filtrate was poured into water. The collected precipitate was washed with ethyl acetate. 2,6-Dichlorophenyl acetic acid (2.8 mmol, 600 mg) and *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*,*N*'-tetramethyluroniumhexafluorophosphate (HATU, 5.6 mmol, 2.1 g) were added and the mixture was stirred at 40 °C overnight. The product was separated using silica gel chromatography (solvent: ethyl acetate/hexane). The combined product containing fractions were evaporated to dryness. The residue was dissolved in ethanol and water was added to precipitate the product. Lavender coloured solid (yield = 8%); purity 100%; mp: 201-202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 9.25 (s, 1H), 7.40 (m, 2H), 7.30 (m, 4H), 7.13 (m, 3H), 6.41 (d, *J*= 7.8 Hz, 1H), 6.23 (d, *J*= 4.6 Hz, 2H), 4.38 (s, 2H), 3.70 (s, 2H), 2.89 (d, *J*= 4.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 168.7, 163.4 (dd, *J*= 13 Hz, *J*= 244Hz, 2C), 153.2, 151.6, 140.4 (t, *J*= 10 Hz, 1C), 138.9, 133.2, 128.6 (2C), 128.3 (2C), 126.8, 115.1, 112.7 (dd, *J*= 6 Hz, *J*= 17Hz, 2C), 107.9, 102.2 (t, *J*= 26 Hz, 1C), 41.8, 33.3, 27.9; IR: $\tilde{\nu}$ = 3442, 3404, 3269, 1652, 1591, 1496, 1389, 1230, 1119, 991, 696 cm^{-1}; HRMS-ESI m/z $[M-H]^-$ calcd for $C_{14}H_{16}N_4O_2S$: 398.1144, found: 398.1157.

Ethyl [6-(4-fluorobenzylthio)-2-methylpyridin-3-yl]carbamate (**9h**)

Compound **8h** (1.8 mmol, 501 mg) and tin (II) chloride dihydrate (9 mmol, 2.03 g) were suspended in absolute ethanol (20 mL). The suspension was carefully set under argon atmosphere. The mixture was stirred at 70 °C for overnight. The temperature was then lowered to 40 °C. Triethylamine (18.36 mmol, 2.56 mL) and ethyl chloroformate (2.34 mmol, 223 µL) were added respectively. The reaction mixture was vigorously stirred for 3 hours and then filtered through a glass filter protected with 1 cm layer of diatomaceous earth. The mixture was washed with ethanol (3 x 10 mL). Eventually, the mixture was concentrated and water added to precipitate

the product. Beige coloured solid (yield = 84%); purity 100%; mp: 102-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.99 (s, 1H), 7.60 (d, *J*= 8.4 Hz, 1H), 7.46 (m, 2H), 7.13 (m, 3H), 4.36 (s, 2H), 4.13 (q, *J*= 7.1 Hz, 2H), 2.40 (s, 3H), 1.25 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 162.3 (d, *J*= 243 Hz, 1C), 154.4, 152.0, 134.7 (d, *J*= 3 Hz, 1C), 132.8, 130.8 (d, *J*= 8 Hz, 2C), 129.5, 119.5, 115.1 (d, *J*=21 Hz, 2C), 60.43, 32.8, 20.8, 14.5; IR: $\tilde{\nu}$ = 3284, 2980, 1689, 1509, 1442, 1250, 1061 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_2FS$: 321.1068, found: 321.1060.

N-[2-Amino-6-(4-fluorobenzylsulfinyl)pyridin-3-yl]-3,4-difluorobenzamide (**10a**)

Compound **9a** (1 mmol, 390 mg) was dissolved in dichloromethane (15 mL) and was allowed to cool using an ice-cold water bath. 3-chloroperbenzoic acid (1.1 mmol, 190 mg) was dissolved in dichloromethane (15 mL) and was added slowly to the reaction mixture. Following the complete addition of 3-chloroperbenzoic acid, the solution was stirred for 1 hour. The solution was concentrated and left in the refrigerator for overnight. The product was collected by filtration and washed with 10% $NaHCO_3$. The product was further purified by recrystallization from ethanol. Beige coloured solid (yield = 30%); purity 100%; mp: 118-119 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 9.81 (s, 1H), 8.12 (m, 1H), 7.91 (m, 1H), 7.70 (d, *J*= 7.8 Hz, 1H), 7.65 (m, 1H), 7.12 (m, 4H), 6.77 (d, *J*= 7.8 Hz, 1H), 6.51 (s, 2H), 4.38 (d, *J*= 13.0 Hz, 1H), 4.05 (d, *J*= 13.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 163.9, 163.1 (d, *J*= 243 Hz, 1C), 157.5, 154.6, 134.7, 132.3 (d, *J*= 8 Hz, 1C), 131.7, 126.6, 125.6, 119.3, 117.6, 117.4, 115.1 (d, *J*= 21 Hz, 2C), 108.1, 57.6; IR: $\tilde{\nu}$ = 3470, 3349, 3234, 1657, 1596, 1494, 1456, 1289, 1229, 1042 cm^{-1}; HRMS-ESI m/z $[M-H]^-$ calcd for $C_{19}H_{14}N_3O_2F_3S$: 404.0686, found: 404.0701.

Ethyl {6-[(1,1'-biphenyl-4-yl)methylsulfinyl]-2-aminopyridin-3-yl}carbamate (**10b**)

Compound **9b** (0.64 mmol, 241 mg) was dissolved in dichloromethane (15 mL) and was cooled in an ice-cold water bath. 3-chloroperbenzoic acid (0.71 mmol, 122mg) was dissolved in dichloromethane (15 mL) and added slowly to the reaction solution. The solution was stirred for an additional 1 hr, which was then concentrated and left in the refrigerator to allow precipitation of the product. The product was collected by filtration, which was washed with 10% $NaHCO_3$. Off-white solid (yield = 88%); purity 100%; mp: 224-225 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.90 (br s, 1H), 7.86 (d, *J*= 7.8 Hz, 1H), 7.66 (d, *J*= 7.3 Hz, 2H), 7.60 (d, *J*= 8.2 Hz, 2H), 7.45 (t, 2H), 7.38 (t,

1H), 7.19 (d, *J*= 8.2 Hz, 2H), 6.82 (d, *J*= 7.9 Hz, 1H), 6.39 (s, 2H), 4.39 (d, *J*= 12.9 Hz, 1H), 4.16 (q, *J*= 7.1 Hz, 2H), 4.04 (d, *J*= 12.9 Hz, 1H), 1.27 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 154.9, 154.1, 152, 139.6, 139.5, 130.8 (2C), 129.9, 128.9 (2C), 127.5, 126.6 (2C), 126.4 (2C), 120.6, 108.6, 60.6, 58.7, 14.4; IR: $\tilde{\nu}$ = 3341, 3211, 2988, 1725, 1530, 1465, 1220, 1030, 762 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{21}H_{21}N_3O_3S$: 396.1376, found: 396.1366.

Ethyl [2-amino-6-(3,5-dimethoxybenzylsulfinyl)pyridin-3-yl]carbamate (**10c**)

Compound **9c** (0.8 mmol, 291 mg) was dissolved in dichloromethane (15 mL) and was cooled in an ice-cold water bath. 3-chloroperbenzoic acid (0.88 mmol, 152 mg) was dissolved in dichloromethane (15 mL) and was added to the reaction mixture over a period on 1 hour. After full addition of 3-chloroperbenzoic acid, the solution stirred for 1 hr, concentrated and left in the refrigerator for overnight. The precipitate was collected by filtration and washed with 10% $NaHCO_3$. The product was separated using flash column chromatography (solvent: dichloromethane and ethanol).White solid (yield = 18%); purity 100%; mp: 200-202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 8.88 (s, 1H), 7.84 (d, *J*= 7.8 Hz, 1H), 6.83 (d, *J*= 7.9 Hz, 1H), 6.40 (t, 1H), 6.37 (s, 2H), 6.23 (d, *J*= 2.2 Hz, 2H), 4.25 (d, *J*= 12.8 Hz, 1H), 4.17 (q, *J*= 7.1 Hz, 2H), 3.93 (d, *J*= 12.8 Hz, 1H), 3.65 (s, 6H), 1.27 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 160.0 (2C), 154.9, 154.2, 152.1, 132.7, 129.7, 120.5, 108.7, 108.1 (2C), 99.8, 60.7, 59.1, 55.1 (2C), 14.4; IR: $\tilde{\nu}$ = 3340, 3210, 1732, 1595, 1524, 1208, 1036 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{17}H_{21}N_3O_5S$: 380.1275, found: 380.1274.

Ethyl [6-(4-fluorobenzylsulfinyl)-2-methylpyridin-3-yl]carbamate (**10d**)

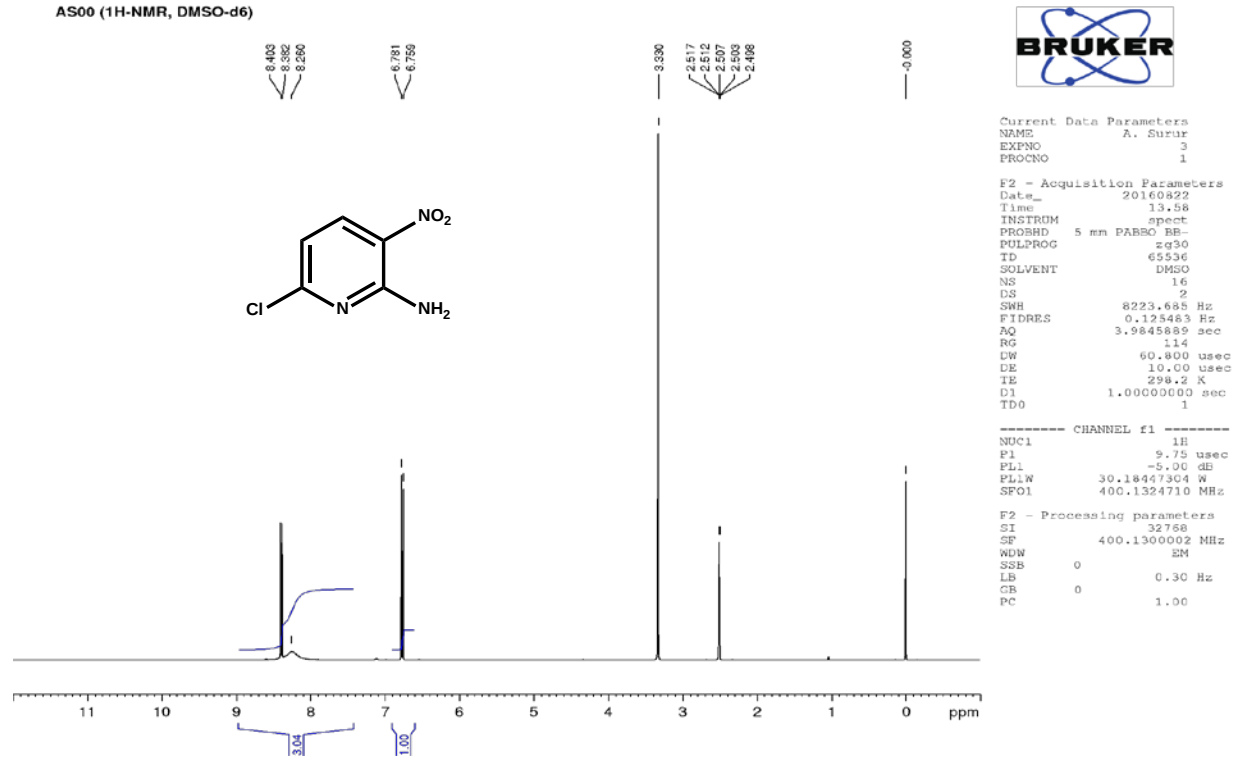
Compound **9d** (0.8 mmol, 275 mg) was dissolved in dichloromethane (15 mL). The solution was put in an ice-cold water bath. 3-Chloroperbenzoic acid (0.88 mmol, 152 mg) was dissolved in dichloromethane (15 mL) and added to the reaction solution slowly over a period of 1 hour. After complete addition, the solution was stirred for another 1 hour. The solution was then concentrated and left in the refrigerator to allow the precipitation of the product. The product was washed with 10% $NaHCO_3$ and dried under reduced pressure. White solid (yield = 25%); purity 100%; mp: 155-156 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 9.28 (s, 1H), 8.03 (d, *J*= 8.4 Hz, 1H), 7.37 (d, *J*= 8.3 Hz, 1H), 7.10 (m, 4H), 4.39 (d, *J*= 13.08 Hz, 1H), 4.19 (q, *J*= 7.1 Hz, 2H), 4.07 (d,

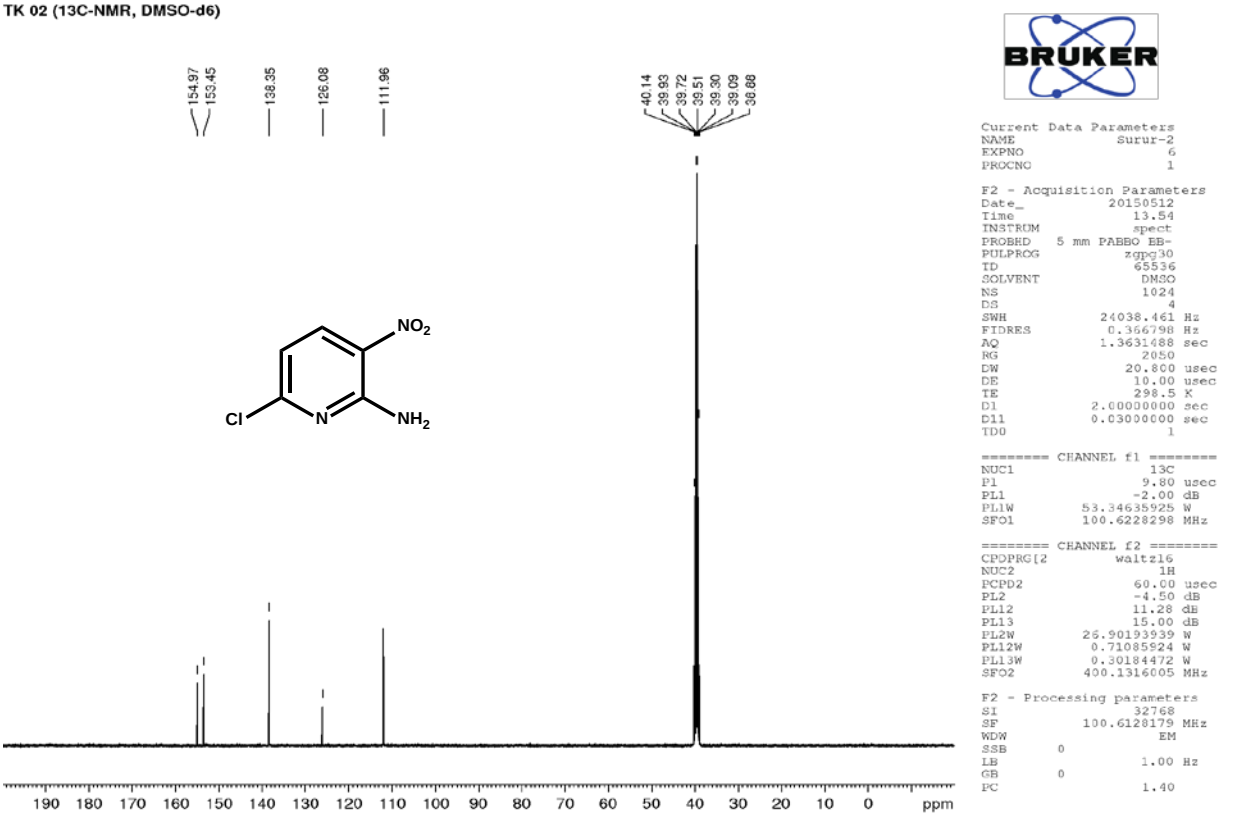
J= 13.08 Hz, 1H), 1.28 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 163.1 (d, *J*= 244 Hz, 1C), 156.6, 154.1, 151.3, 134.2, 132.3 (d, *J*= 8 Hz, 2C), 131.4, 126.3 (d, *J*= 3 Hz, 1C), 118.2, 115.0 (d, *J*= 22 Hz, 2C), 60.8, 57.9, 21.0, 14.4; IR: $\tilde{\nu}$ = 3164, 3058, 2994, 1712, 1528, 1231, 1040, 870 cm^{-1}; HRMS-ESI m/z $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_3FS$: 337.1017, found: 337.1008.

Determination of $LogD_{7.4}$

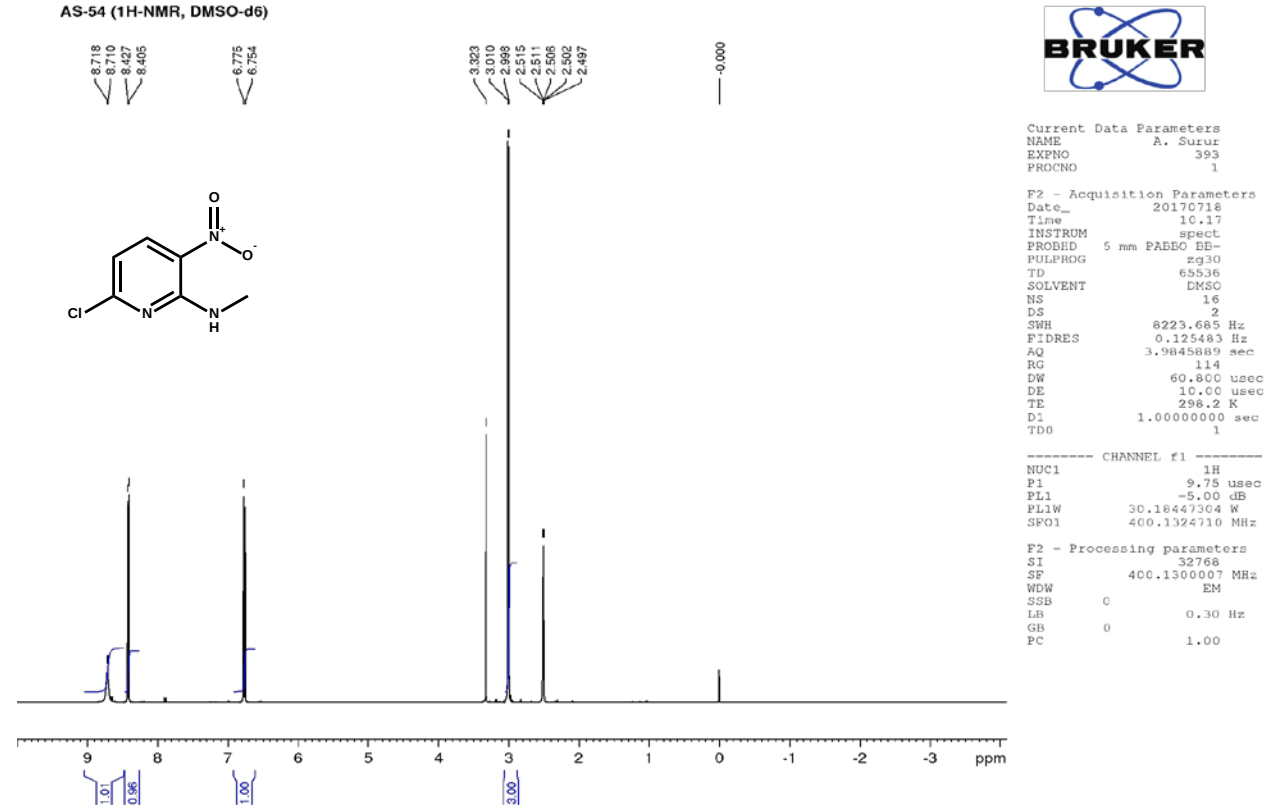
$LogD_{7.4}$ values were determined using a HPLC method. Column: Phenomenex Kinetex PFP 2.6 µM 75×4.6 mm, flow rate 0.5 mL/min, mobile phase: **A**: 95% ammonium formate buffer (21.05 mM, pH 7.4) and 5% methanol, **B** 5% ammonium formate buffer (0.36 mM, pH 7.4) and 95% methanol, gradient: 0-50 min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

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





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



BRUKER

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PROCNO                       1

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TD                     65536
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SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9845889 sec
RG                       114
DW                    60.800 usec
DE                    10.00 usec
TE                    298.2 K
D1                  1.00000000 sec
TD0                          1

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

F2 - Processing parameters
SI                       32768
SF                400.1300007 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
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BRUKER

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Current Data Parameters
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EXPNO                      399
PROCNO                       1

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TD                     65536
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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
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SF                100.6128187 MHz
WDW                         EM
SSB          0
LB                       1.00 Hz
GB           0
PC                       1.40
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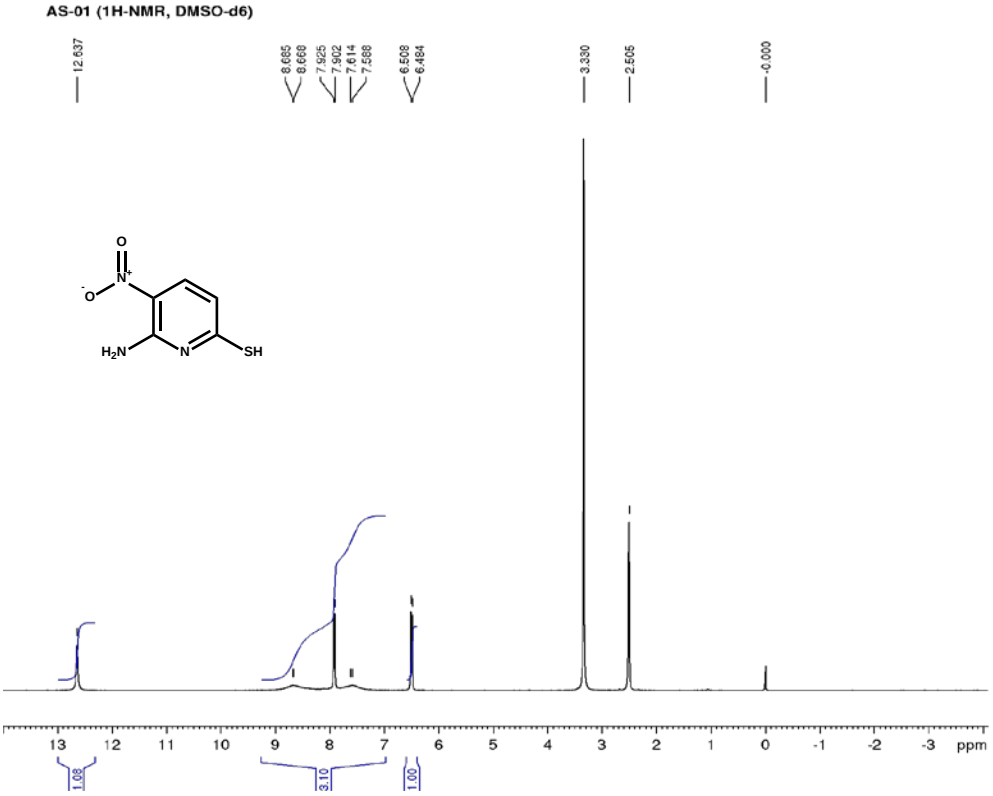
6-Amino-5-nitropyridine-2-thiol (**7a**)

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EXPNO                      193
PROCNO                       1

F2 - Acquisition Parameters
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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                       114
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                400.1300010 MHz
WDW                           EM
SSB                0
LB                    0.30 Hz
GB                 0
PC                    1.00
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Current Data Parameters
NAME                  Surur-2
EXPNO                       8
PROCNO                      1

F2 - Acquisition Parameters
Date_               20150518
Time                   14.01
INSTRUM                spect
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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
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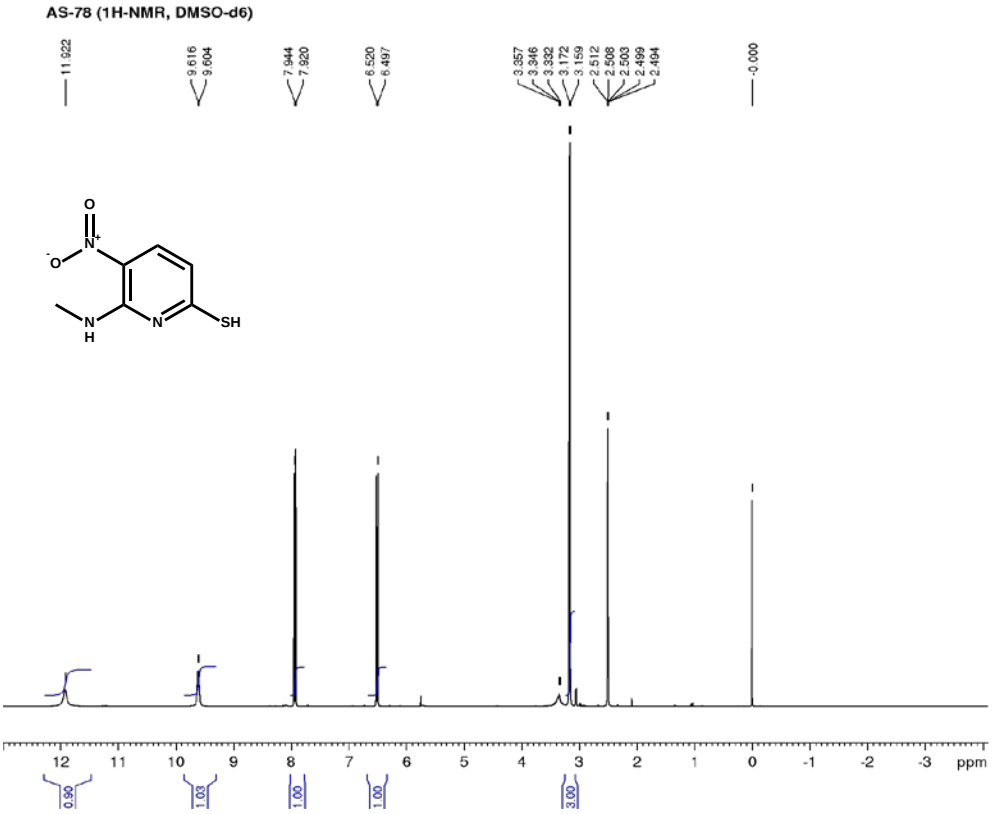
6-(Methylamino)-5-nitropyridine-2-thiol (**7b**)

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EXPNO                      518
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                  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                400.1300017 MHz
WDW                         EM
SSB                0
LB                       0.30 Hz
GB                 0
PC                       1.00
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Current Data Parameters
NAME                  A. Surur
EXPNO                      541
PROCNO                       1

F2 - Acquisition Parameters
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Time                   11.21
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
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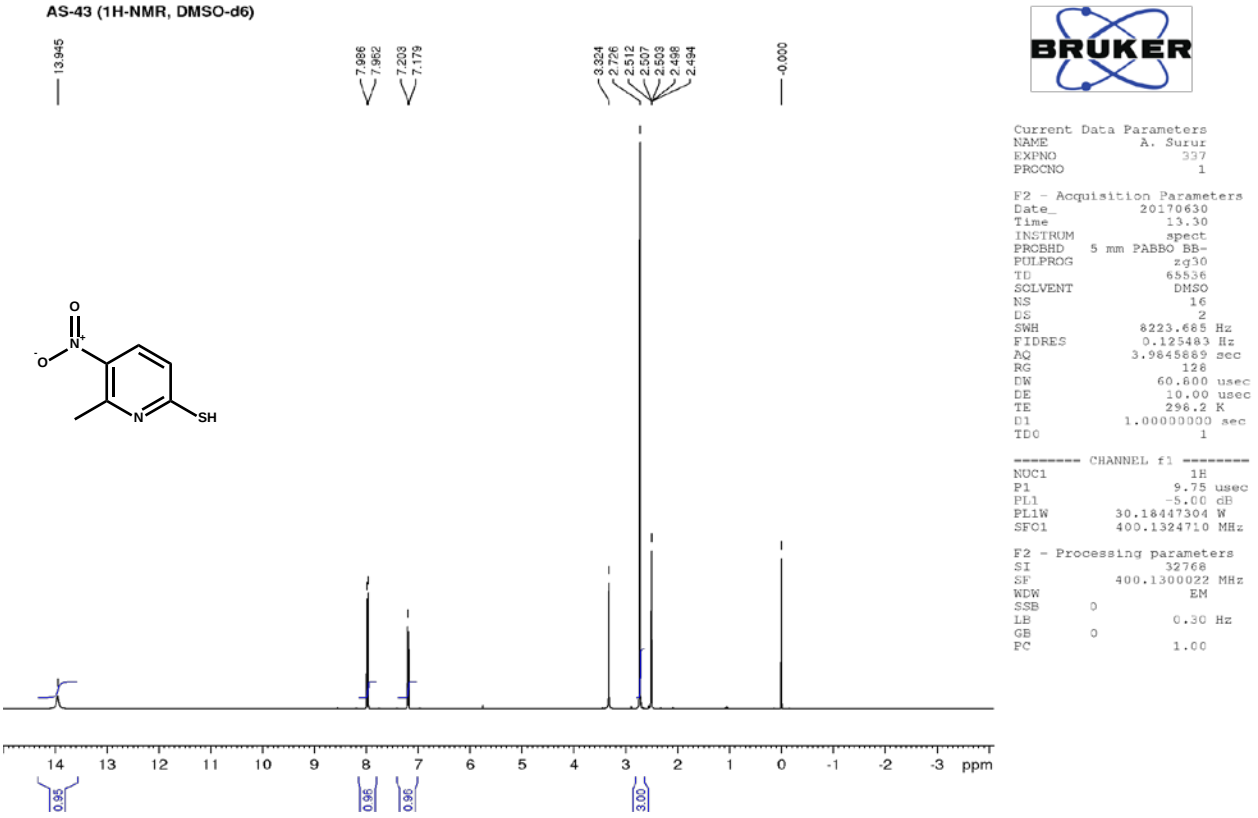
6-Methyl-5-nitropyridine-2-thiol (**7c**)



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Current Data Parameters
NAME                  A. Surur
EXPNO                      337
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170630
Time                   13.30
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                    296.2 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                400.1300022 MHz
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LB                      0.30 Hz
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PC                      1.00
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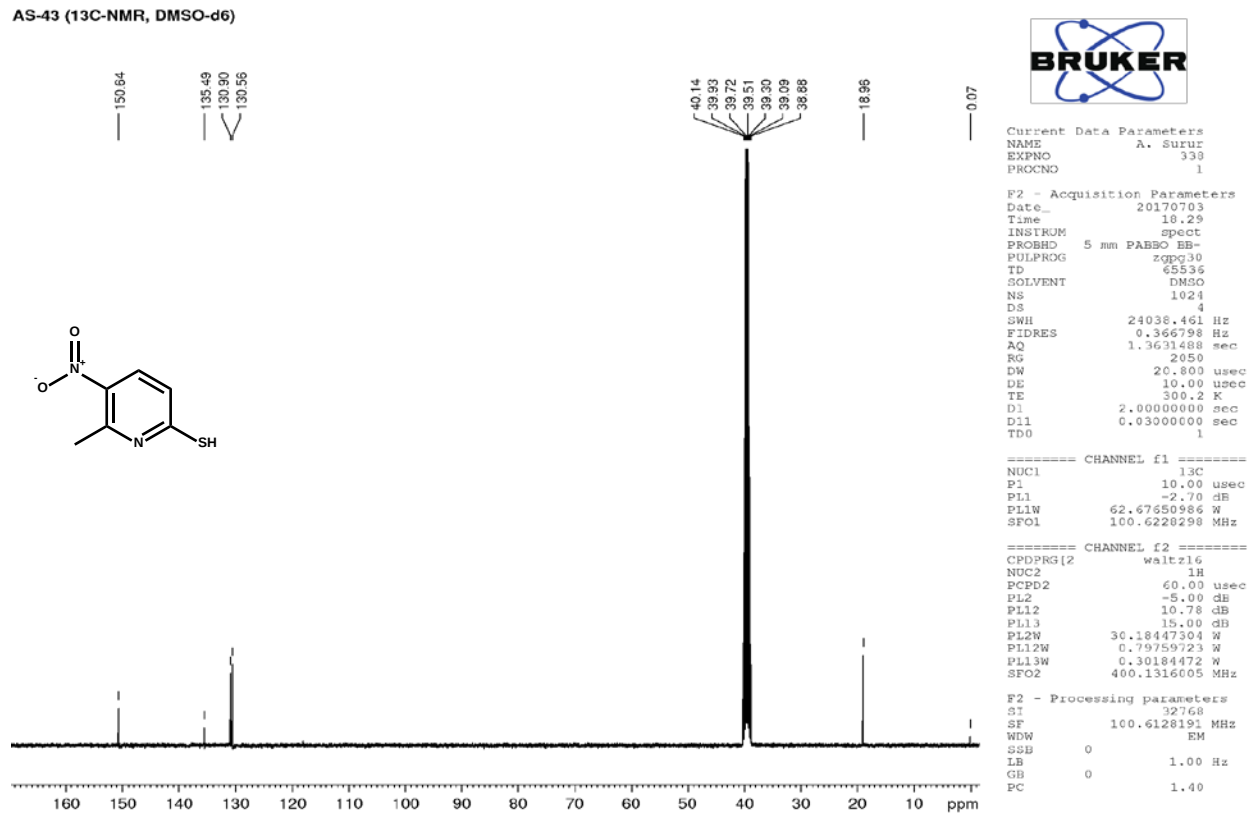

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Current Data Parameters
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EXPNO                      330
PROCNO                       1

F2 - Acquisition Parameters
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Time                   18.29
INSTRUM                spect
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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                    300.2 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              0.79759923 W
PL13W              0.30184472 W
SFO2              400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                100.6128191 MHz
WDW                          EM
SSB                0
LB                      1.00 Hz
GB                 0
PC                      1.40
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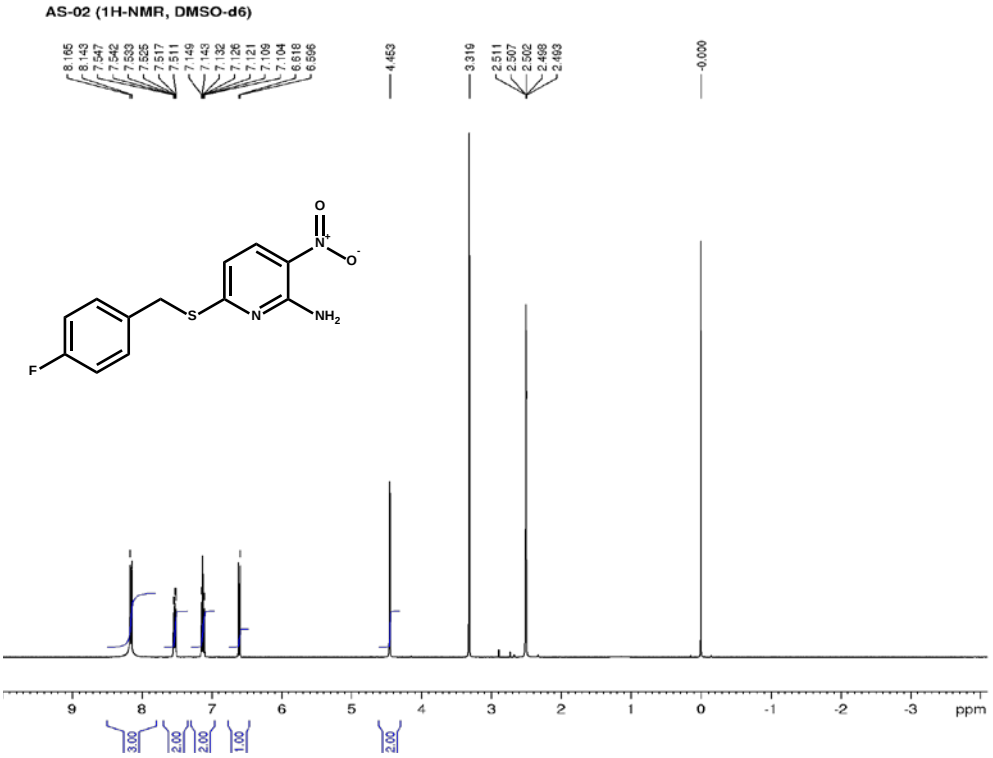
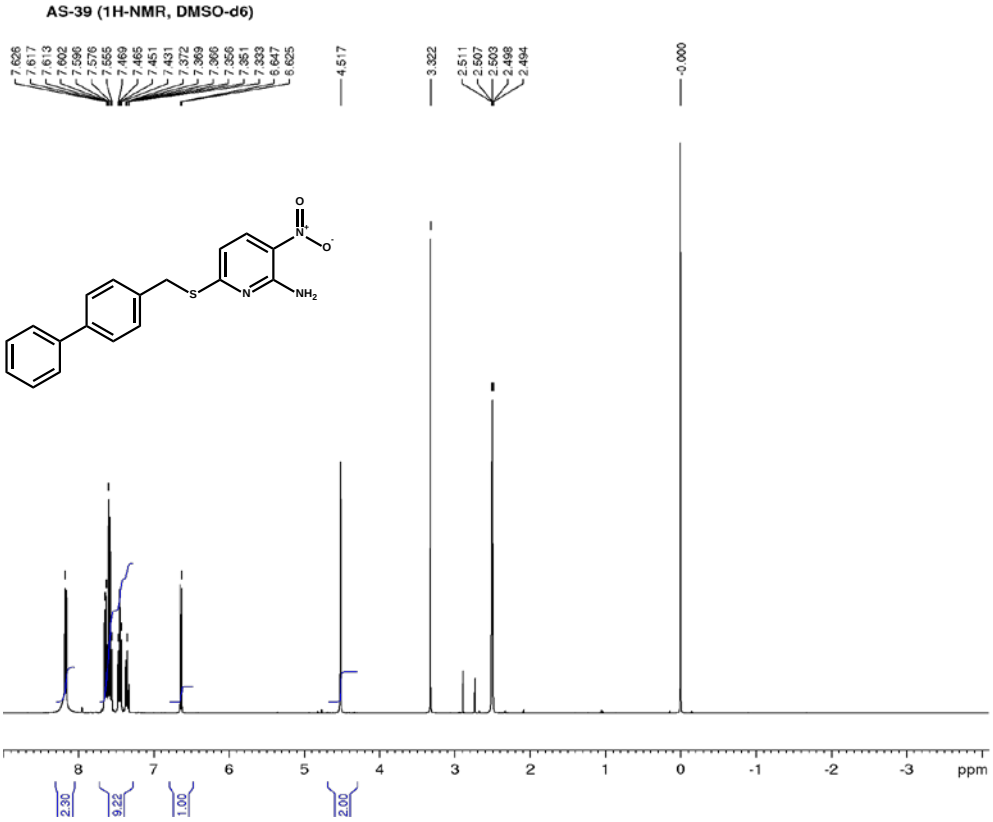
6-[(4-Fluorobenzyl)thio]-3-nitropyridin-2-amine (**8a**)



6-[(1,1'-Biphenyl-4-yl)methylthio]-3-nitropyridin-2-amine (**8b**)



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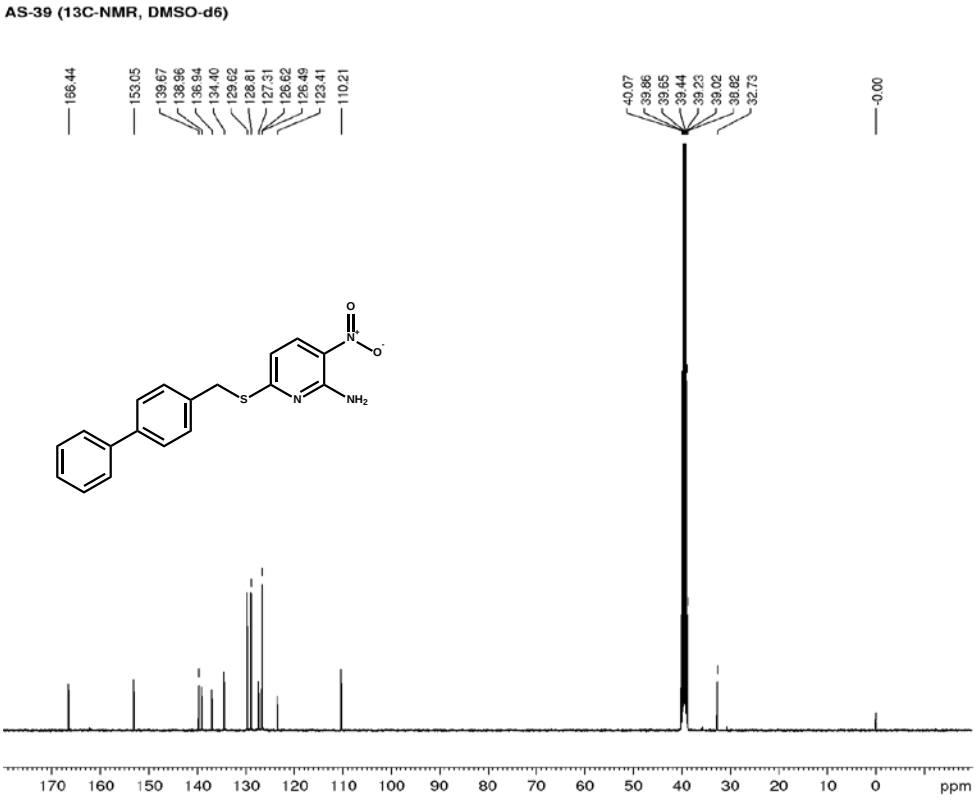
Current Data Parameters
NAME                  A. Surur
EXPNO                      313
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170608
Time                      9.54
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                    298.2 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                400.1300021 MHz
WDW                         EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```



```
Current Data Parameters
NAME                  A. Surur
EXPNO                      314
PROCNO                       1

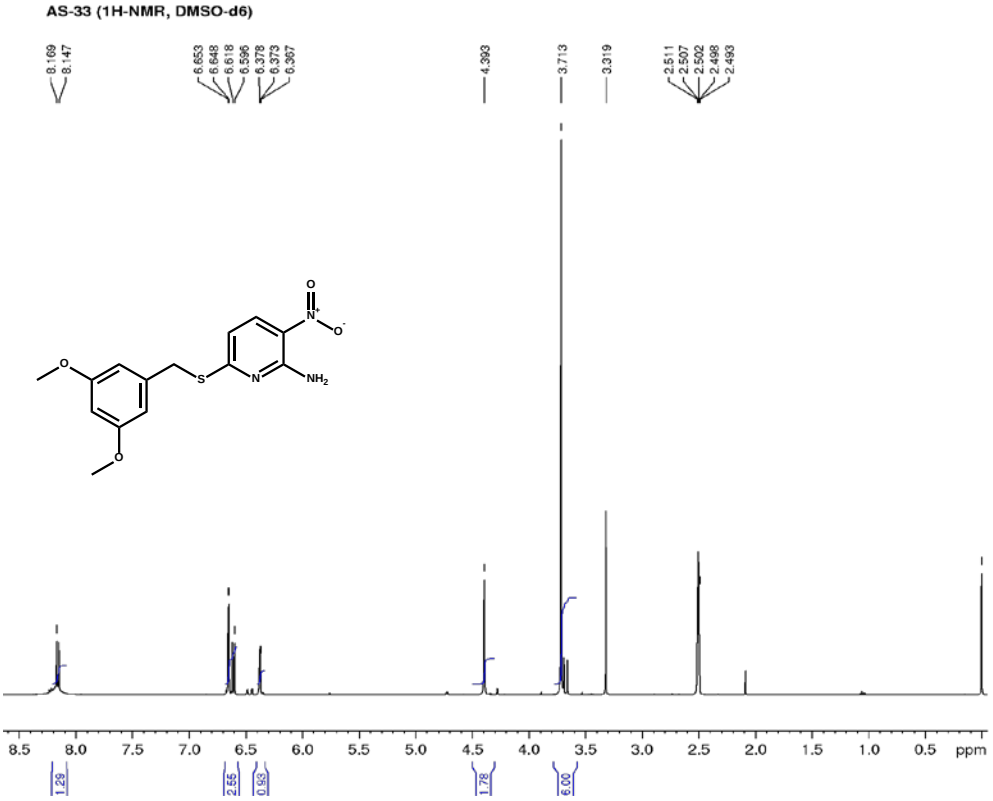
F2 - Acquisition Parameters
Date_                 20170608
Time                     20.19
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                         5000
DS                          4
SWH                 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                100.6128263 MHz
WDW                         EM
SSB                  0
LB                        1.00 Hz
GB                   0
PC                        1.40
```

6-[(3,5-Dimethoxybenzyl)thio]-3-nitropyridin-2-amine (**8c**)

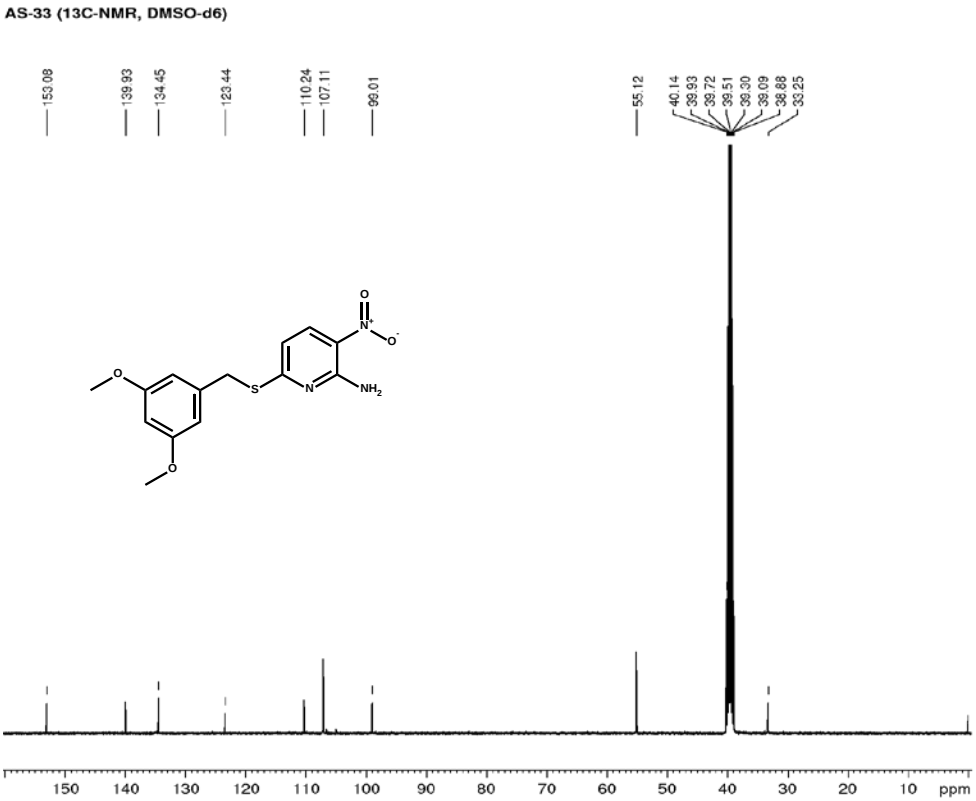


```
Current Data Parameters
NAME                  A. Surur
EXPNO                      280
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170515
Time                      9.28
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                     298.2 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                 400.1300023 MHz
WDW                          EM
SSB                 0
LB                       0.30 Hz
GB                  0
PC                       1.00
```



```
Current Data Parameters
NAME                  A. Surur
EXPNO                      281
PROCNO                       1

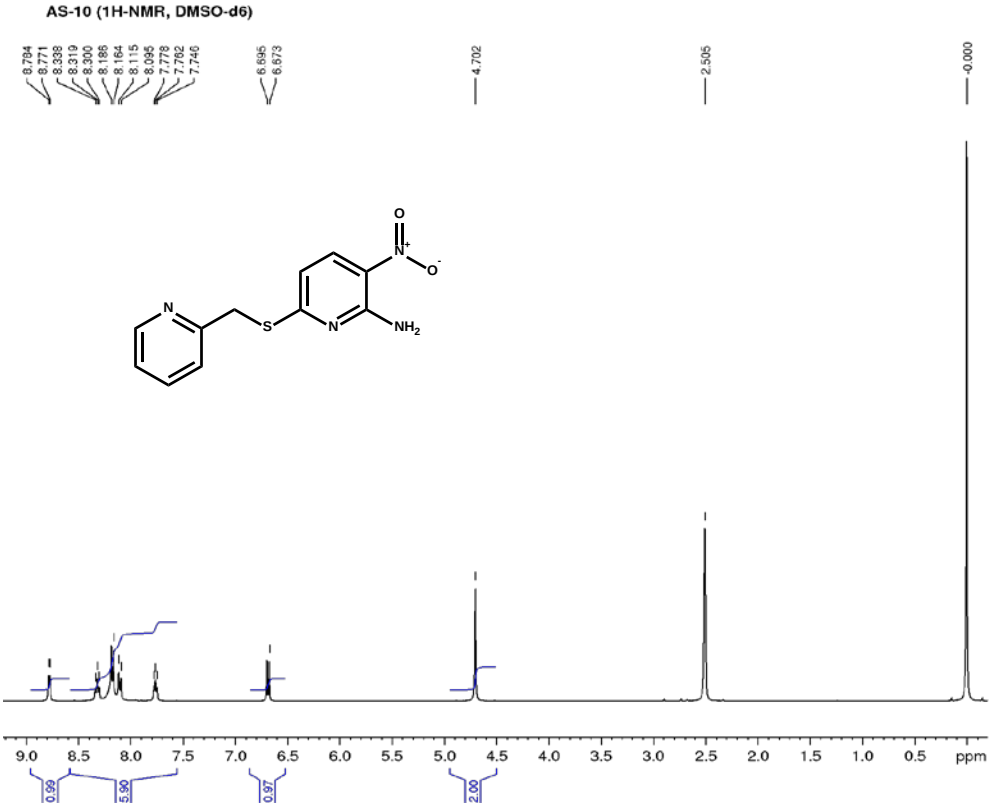
F2 - Acquisition Parameters
Date_                 20170515
Time                     19.22
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                         4000
DS                            4
SWH                 24038.461 Hz
FIDRES               0.366798 Hz
AQ                   1.3631488 sec
RG                         2050
DW                     20.800 usec
DE                     10.00 usec
TE                     301.2 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                 100.6128199 MHz
WDW                          EM
SSB                 0
LB                       1.00 Hz
GB                  0
PC                       1.40
```

3-Nitro-6-[(pyridin-2-ylmethyl)thio]pyridin-2-amine (**8d**)



BRUKER

```
Current Data Parameters
NAME                  A. Surur
EXPNO                      103
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170105
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                       101
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                400.1300008 MHz
WDW                           EM
SSB                0
LB                         0.30 Hz
GB                 0
PC                         1.00
```

BRUKER

```
Current Data Parameters
NAME                  A. Surur
EXPNO                       49
PROCNO                       1

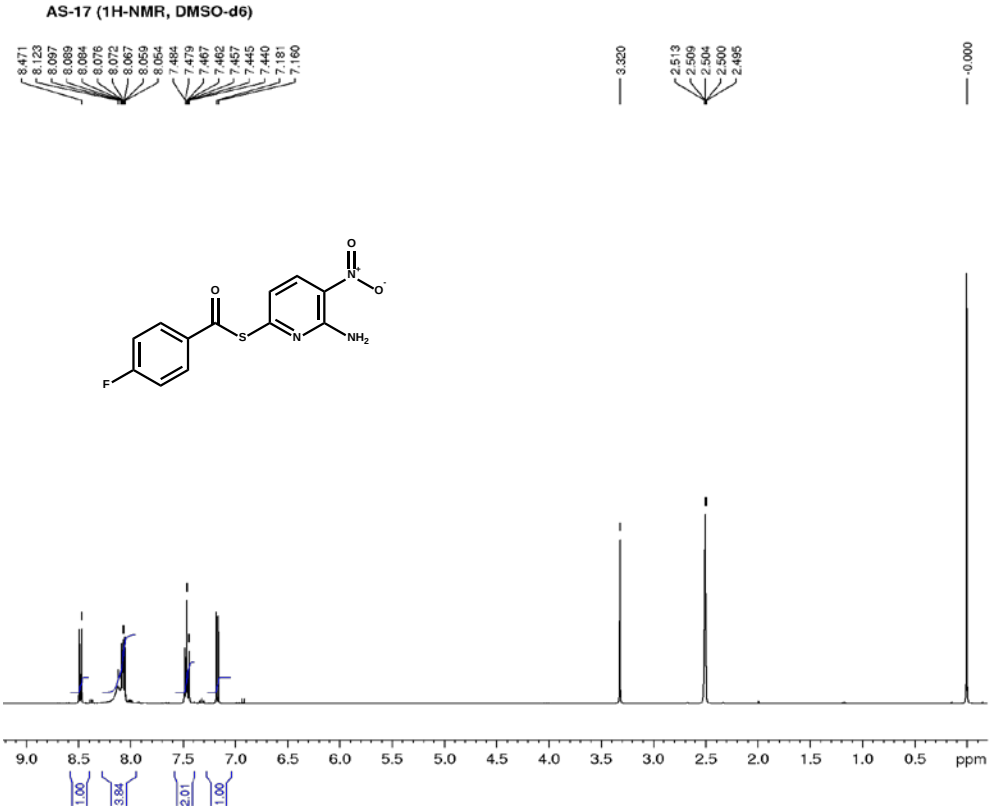
F2 - Acquisition Parameters
Date_               20161121
Time                    12.16
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                     65536
SOLVENT                 DMSO
NS                       1024
DS                          4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       2050
DW                    20.800 usec
DE                    10.00 usec
TE                    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                100.6128189 MHz
WDW                           EM
SSB                0
LB                         1.00 Hz
GB                 0
PC                         1.40
```

S-(6-Amino-5-nitropyridin-2-yl) 4-fluorobenzothioate (**8e**)




```
Current Data Parameters
NAME                  A. Surur
EXPNO                      159
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170220
Time                    10.23
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                    298.2 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
```


```
Current Data Parameters
NAME                  A. Surur
EXPNO                      128
PROCNO                       1

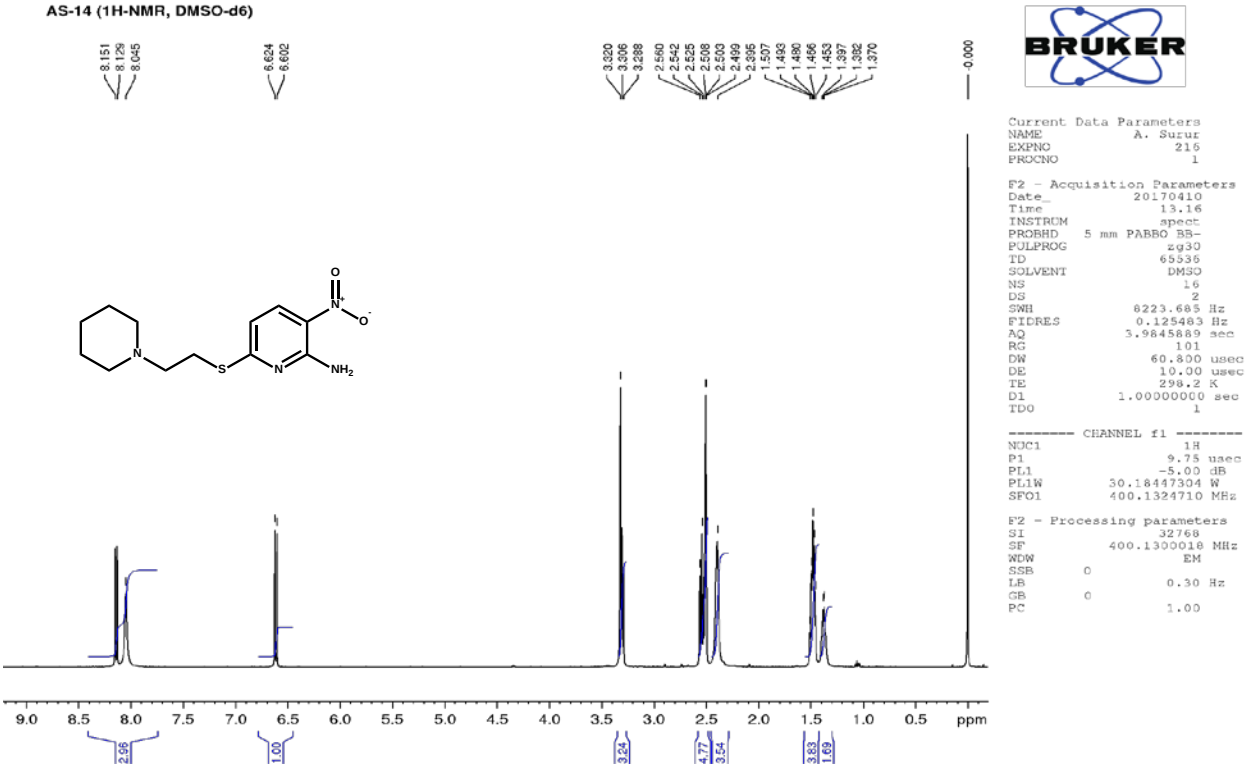
F2 - Acquisition Parameters
Date_               20170120
Time                    14.52
INSTRUM                 spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                     65536
SOLVENT                 DMSO
NS                       1024
DS                          4
SWH                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

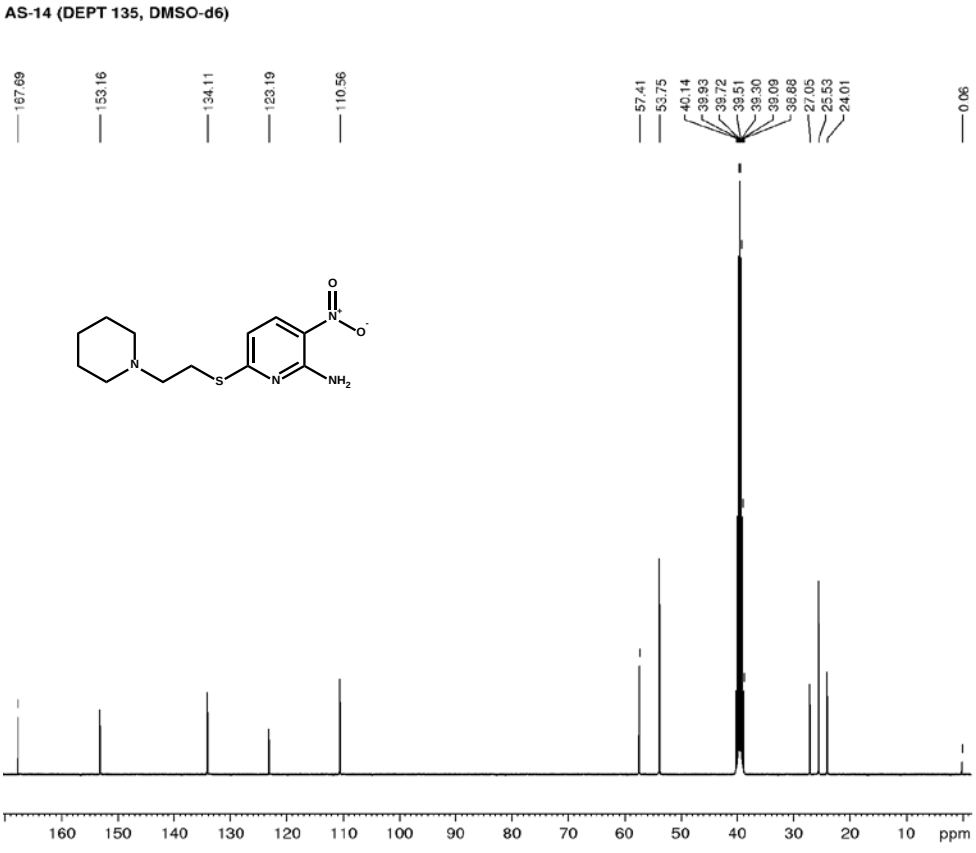
======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
PL1                   -2.70 dB
PL1W            62.67650986 W
SFO1           100.6228298 MHz

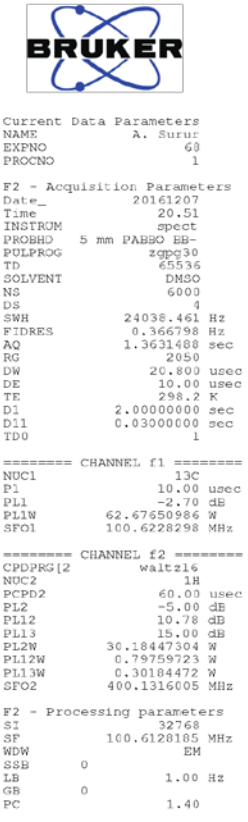
======== CHANNEL f2 ========
CPDPRG[2              waltz16
NUC2                      1H
PCPD2                 60.00 usec
PL2                   -5.00 dB
PL12                  10.78 dB
PL13                  15.00 dB
PL2W            30.18447304 W
PL12W            0.79759723 W
PL13W            0.30184472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

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

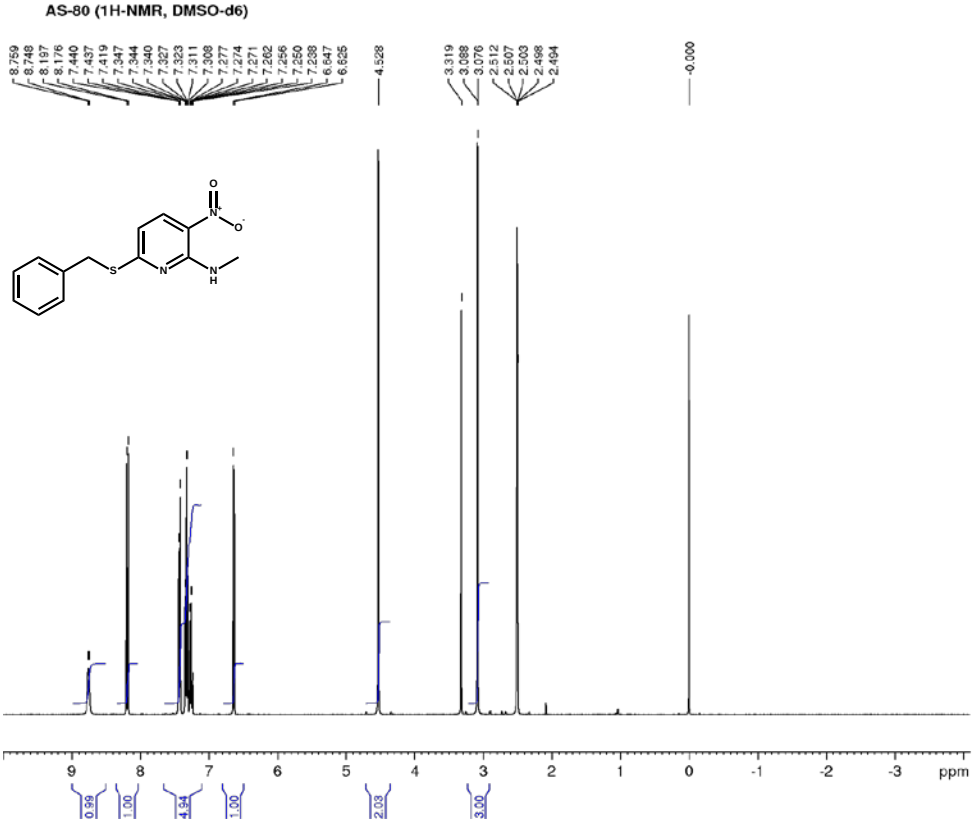
3-Nitro-6-{[2-(piperidin-1-yl)ethyl]thio}pyridin-2-amine (**8f**)







6-(Benzylthio)-*N*-methyl-3-nitropyridin-2-amine (**8g**)



```
Current Data Parameters
NAME                  A. Surur
EXPNO                      523
PROCNO                       1

F2 - Acquisition Parameters
Date_               20171110
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                       114
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                400.1300019 MHz
WDW                         EM
SSB             0
LB                       0.30 Hz
GB              0
PC                       1.00
```

```
Current Data Parameters
NAME                  A. Surur
EXPNO                      549
PROCNO                       1

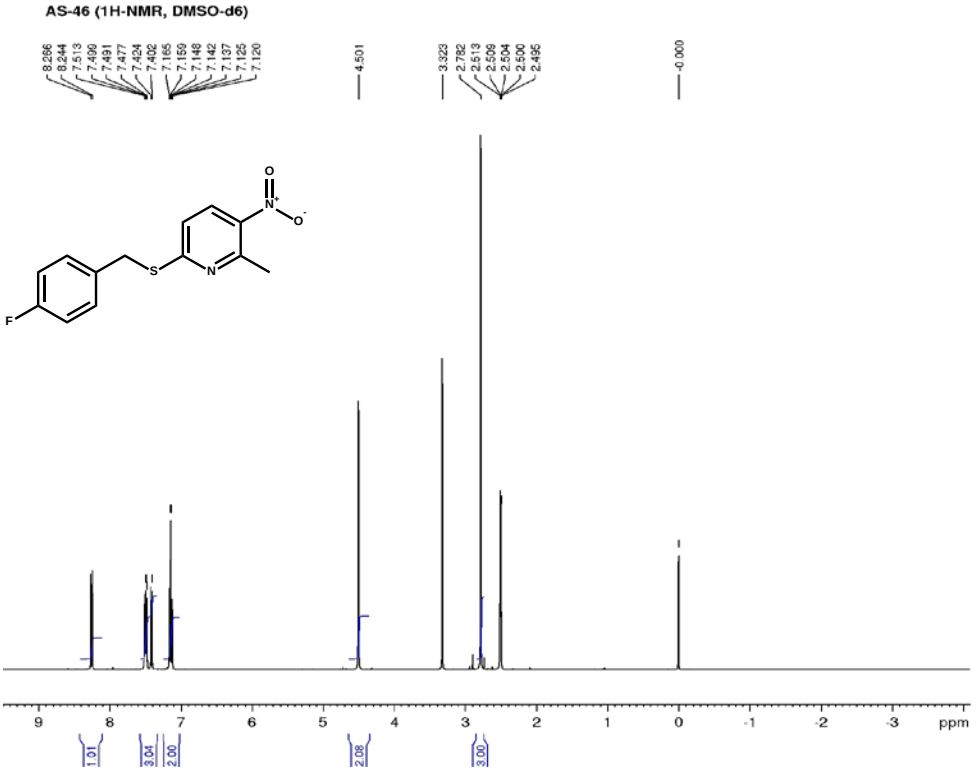
F2 - Acquisition Parameters
Date_               20171124
Time                    9.59
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     1024
DS                        4
SWH               24038.461 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                100.6128175 MHz
WDW                         EM
SSB             0
LB                       1.00 Hz
GB              0
PC                       1.40
```

6[(4-Fluorobenzyl)thio]-2-methyl-3-nitropyridine (**8h**)



Current Data Parameters
NAME A. Surur
EXPNO 343
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170704
Time 10.29
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125463 Hz
AQ 3.9845889 sec
RG 101
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 400.1300013 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Current Data Parameters
NAME A. Surur
EXPNO 349
PROCNO 1

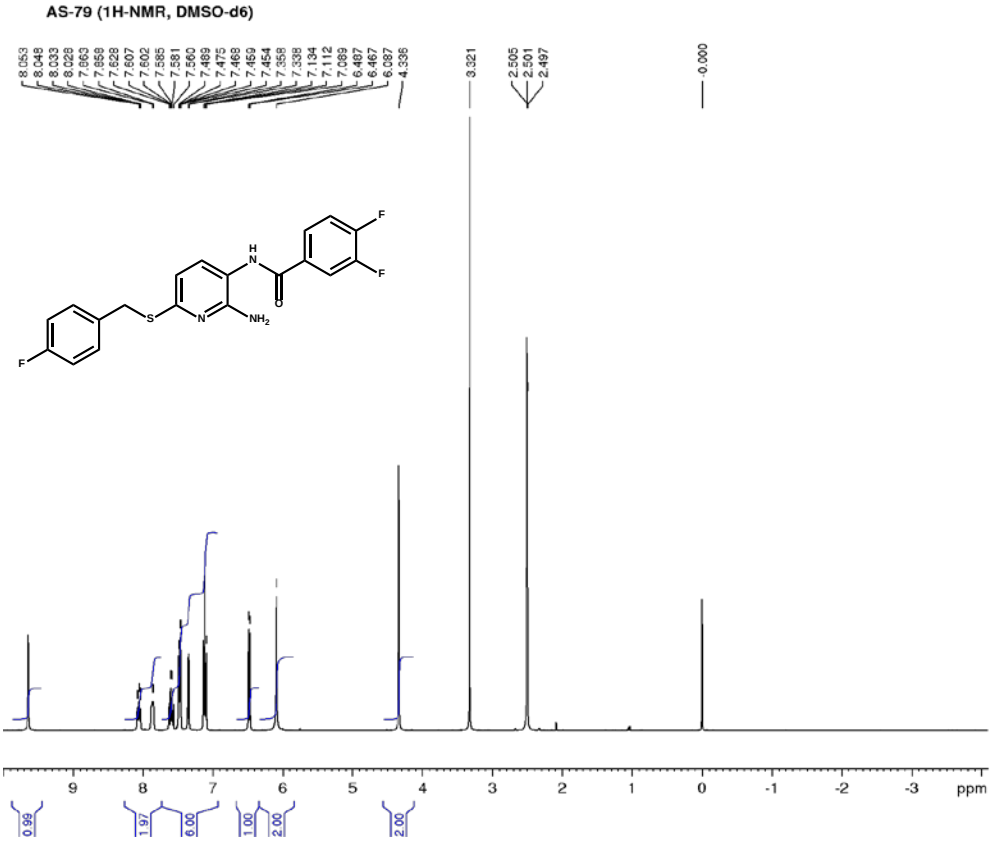
F2 - Acquisition Parameters
Date_ 20170705
Time 4.01
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3000
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 2050
DW 20.800 usec
DE 10.00 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== 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 100.6128185 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

N-{2-Amino-6-[(4-fluorobenzyl)thio]pyridin-3-yl}-3,4-difluorobenzamide (**9a**)




```
Current Data Parameters
NAME                  A. Surur
EXPNO                      529
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20171115
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                       114
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              400.1300027 MHz
WDW                         EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```


```
Current Data Parameters
NAME                  A. Surur
EXPNO                      554
PROCNO                       1

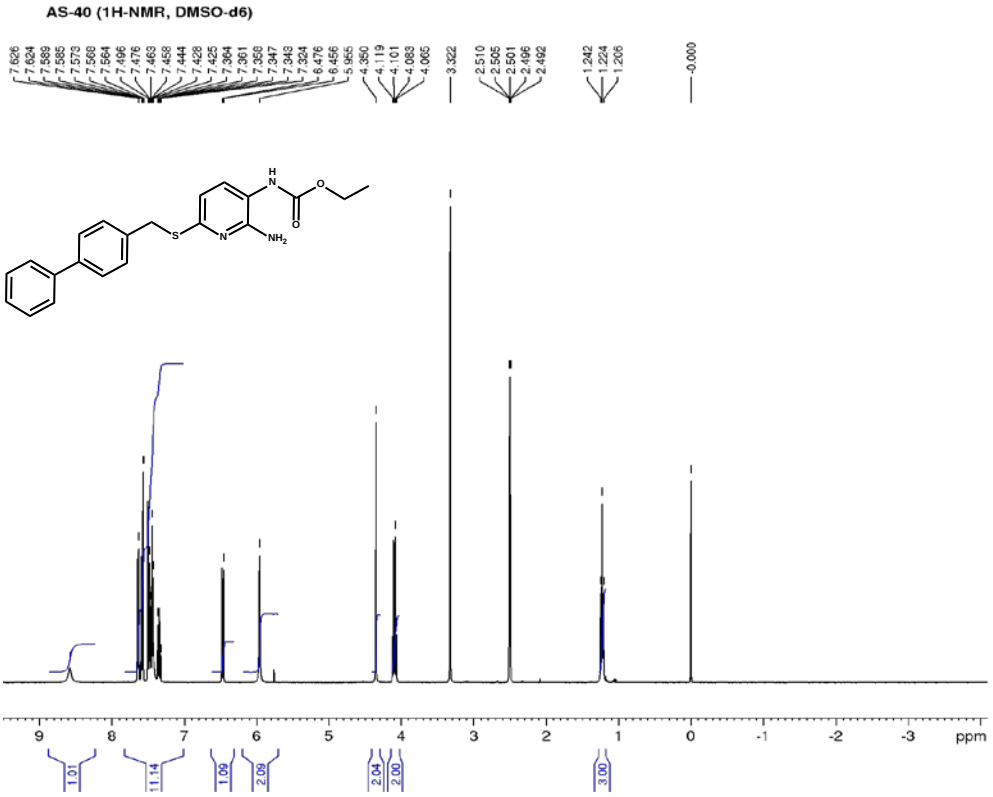
F2 - Acquisition Parameters
Date_                 20171127
Time                     11.53
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                        1024
DS                           4
SWH               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              100.6128177 MHz
WDW                         EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

Ethyl-{6-[(1,1'-biphenyl-4-yl)methylthio]-2-aminopyridin-3-yl}carbamate (**9b**)

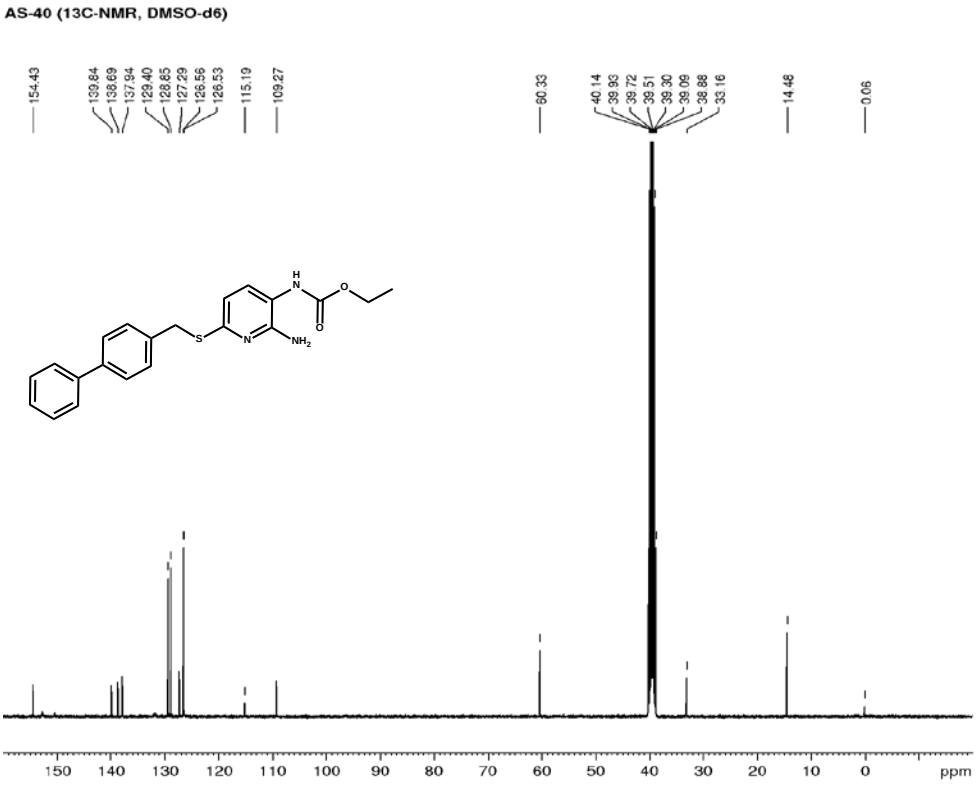



```
Current Data Parameters
NAME                  A. Surur
EXPNO                      325
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170622
Time                   14.01
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                   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               400.1300030 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```




```
Current Data Parameters
NAME                  A. Surur
EXPNO                      326
PROCNO                       1

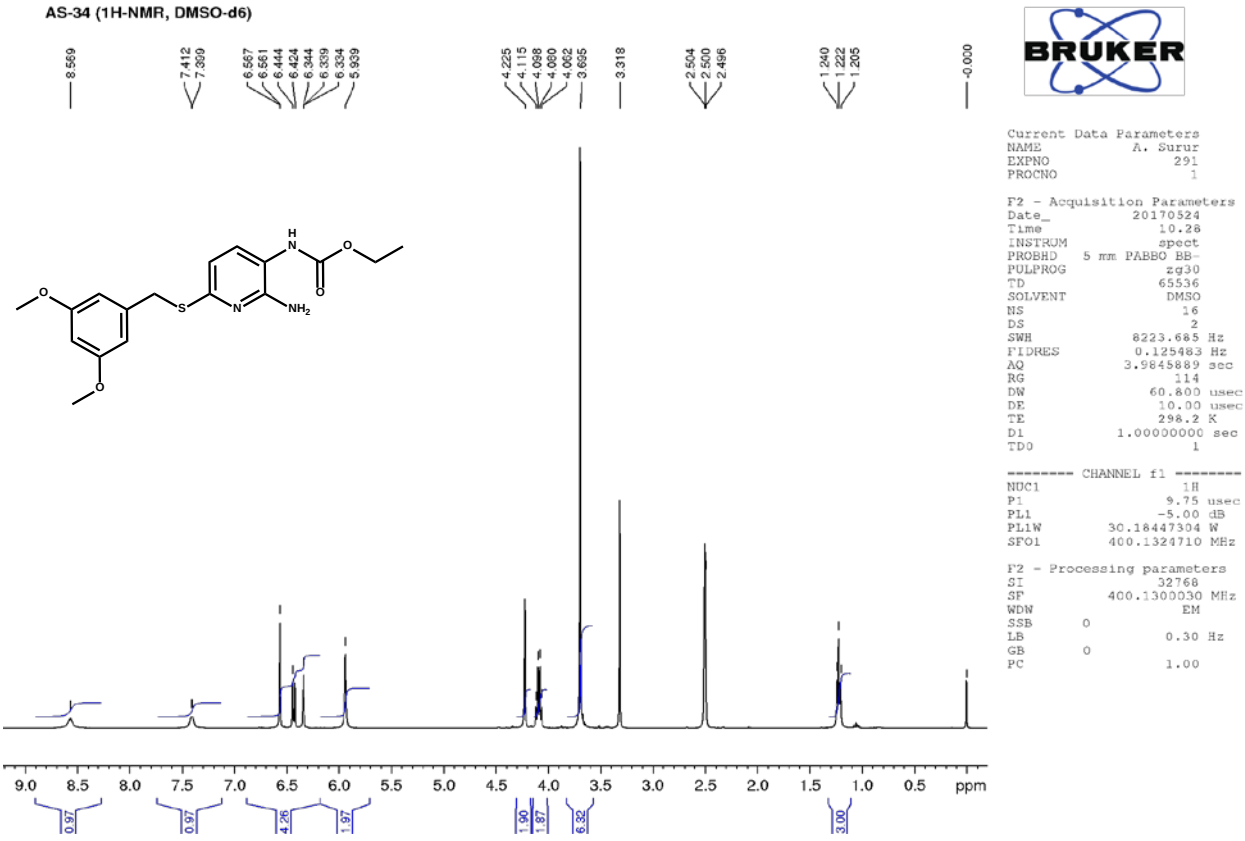
F2 - Acquisition Parameters
Date_               20170622
Time                   18.49
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                     4000
DS                        4
SWH               24038.461 Hz
FIDRES            0.366798 Hz
AQ                1.3631488 sec
RG                      2050
DW                   20.800 usec
DE                   10.00 usec
TE                   301.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

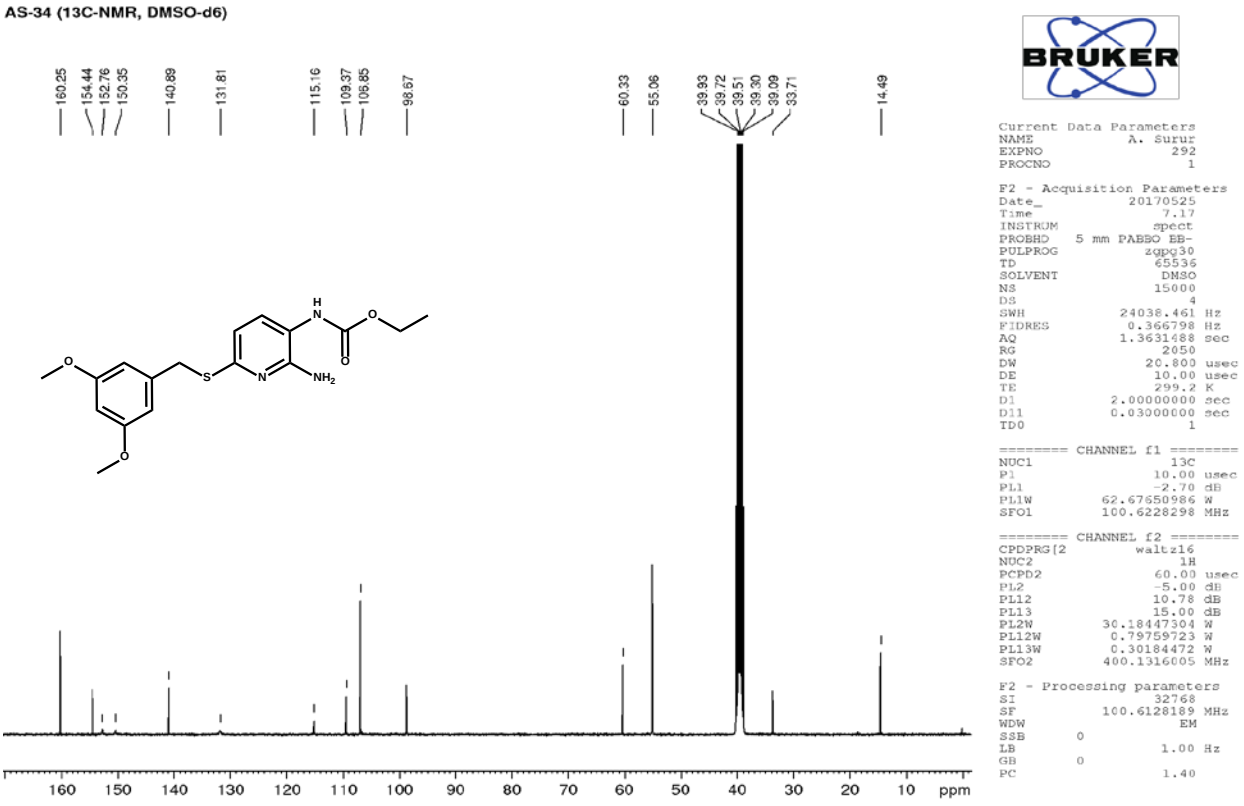
======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
PL1                   -2.70 dB
PL1W            62.67650986 W
SFO1           100.6228298 MHz

======== 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

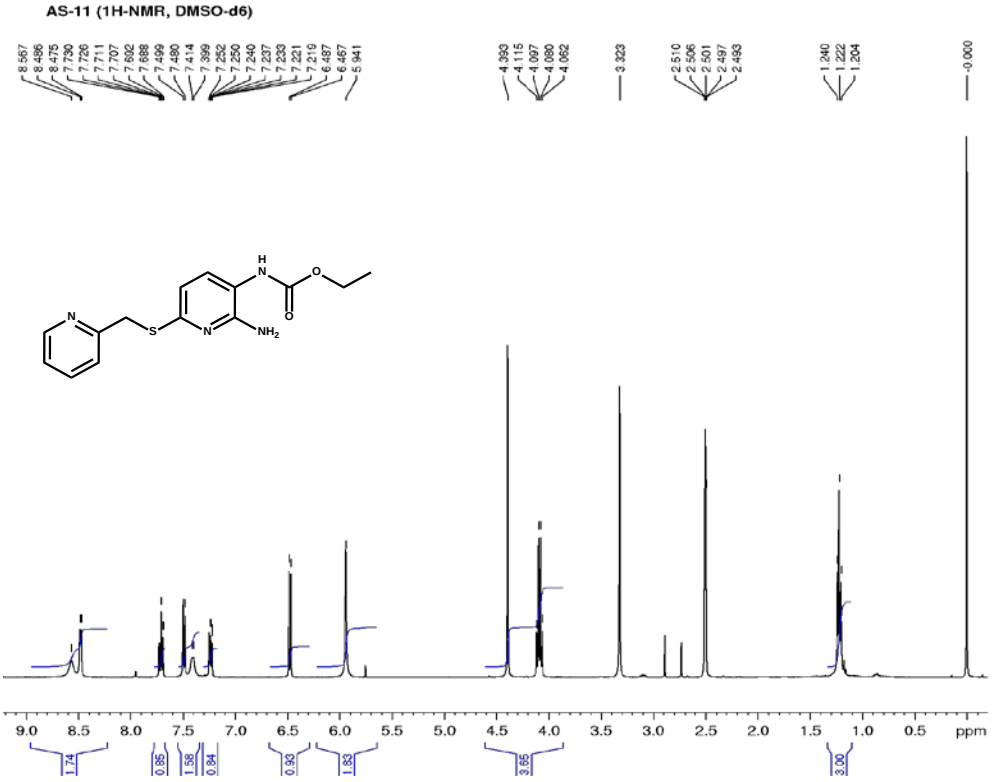
F2 - Processing parameters
SI                    32768
SF               100.6128202 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

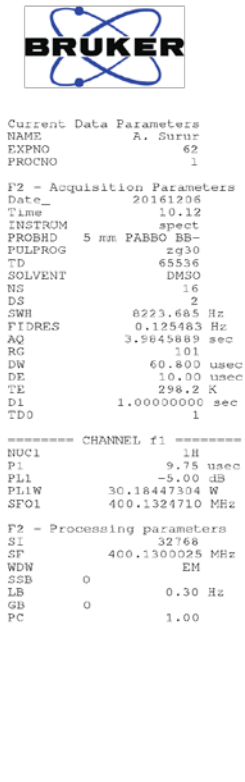
Ethyl-{2-amino-6-[(3,5-dimethoxybenzylthio)pyridin-3-yl]}carbamate (**9c**)

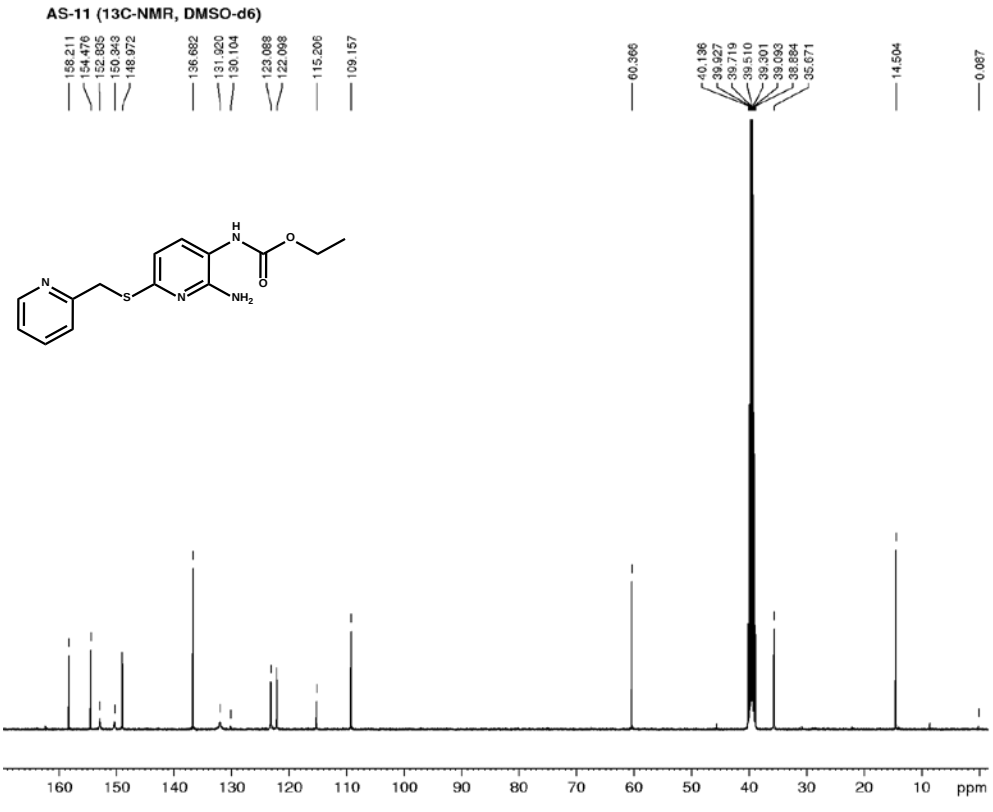


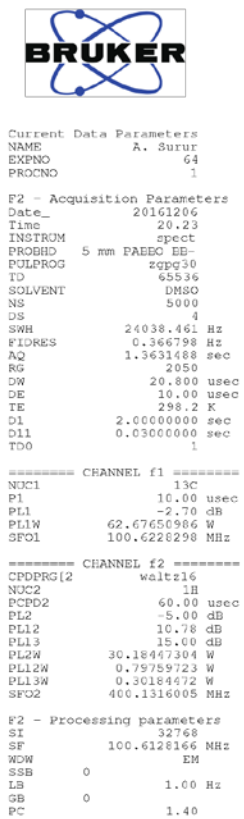


Ethyl-{2-amino-6-[(pyridin-2-ylmethylthio)pyridin-3-yl]}carbamate (**9d**)

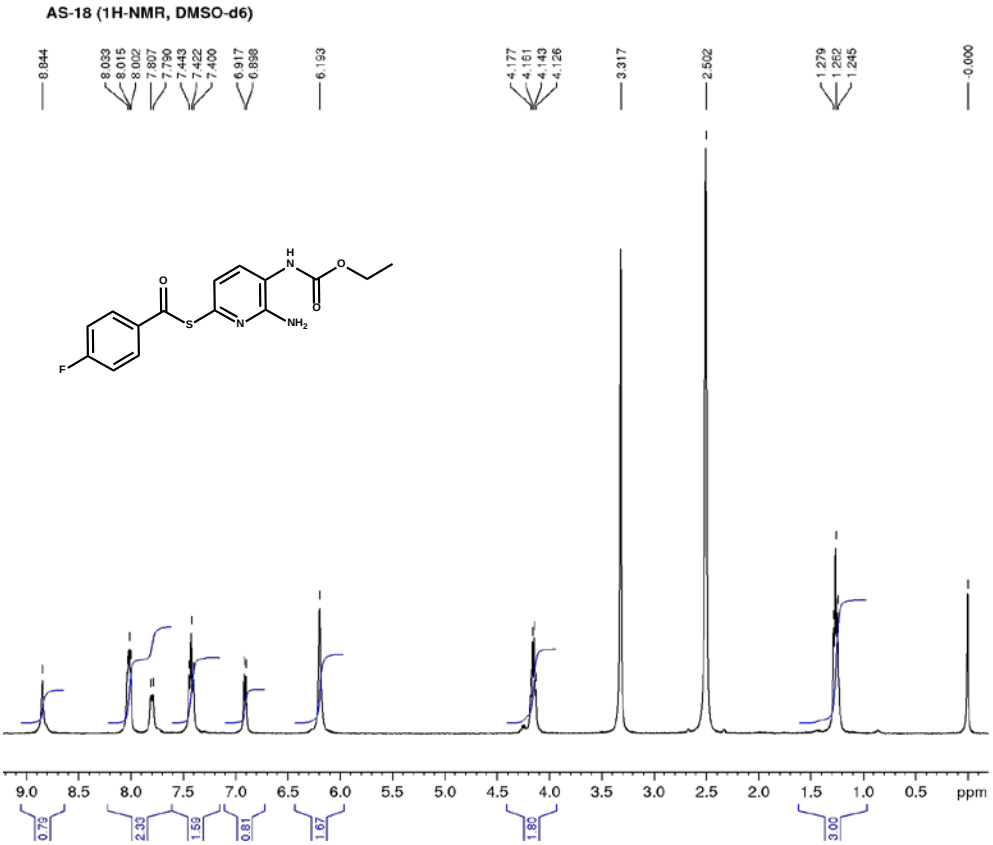


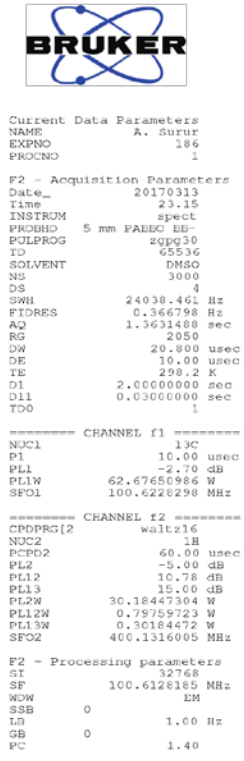




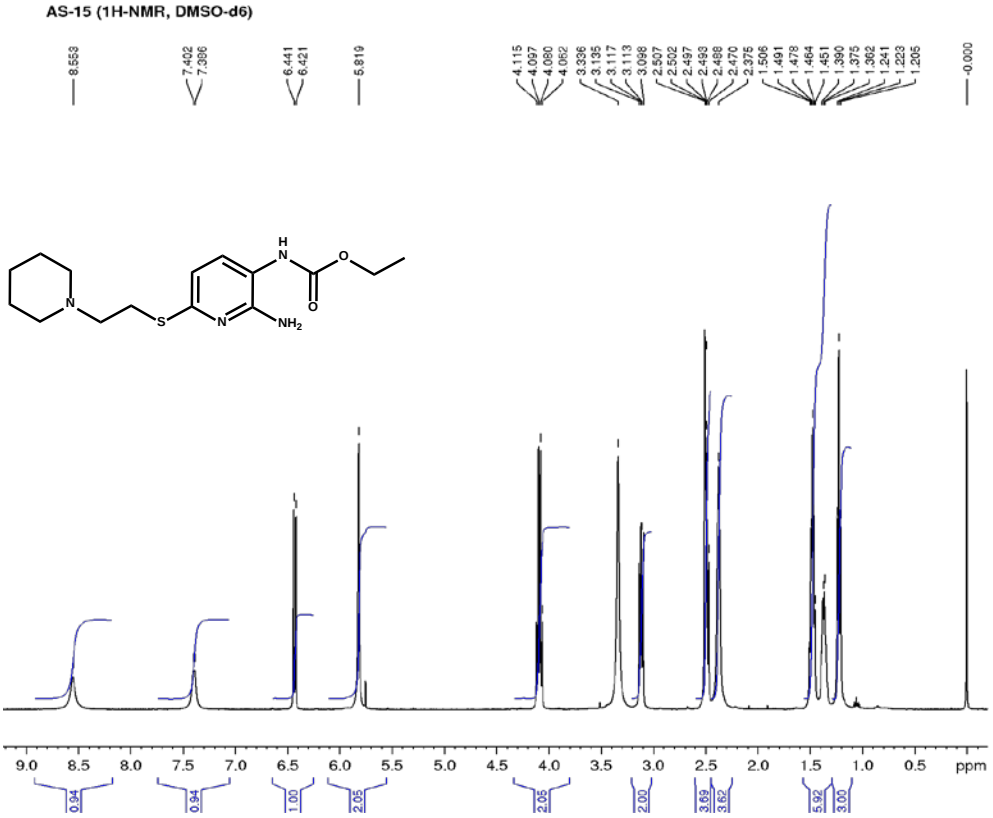


S-{6-Amino-5-[(ethoxycarbonyl)amino]pyridin-2-yl} 4-fluorobenzothioate (**9e**)





Ethyl {2-amino-6-([2-(piperidin-1-yl)ethylthio]pyridin-3-yl}carbamate (**9f**)

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Current Data Parameters
NAME                  A. Surur
EXPNO                      229
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170412
Time                    10.56
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                 400.1300024 MHz
WDW                        EM
SSB                 0
LB                      0.30 Hz
GB                  0
PC                      1.00
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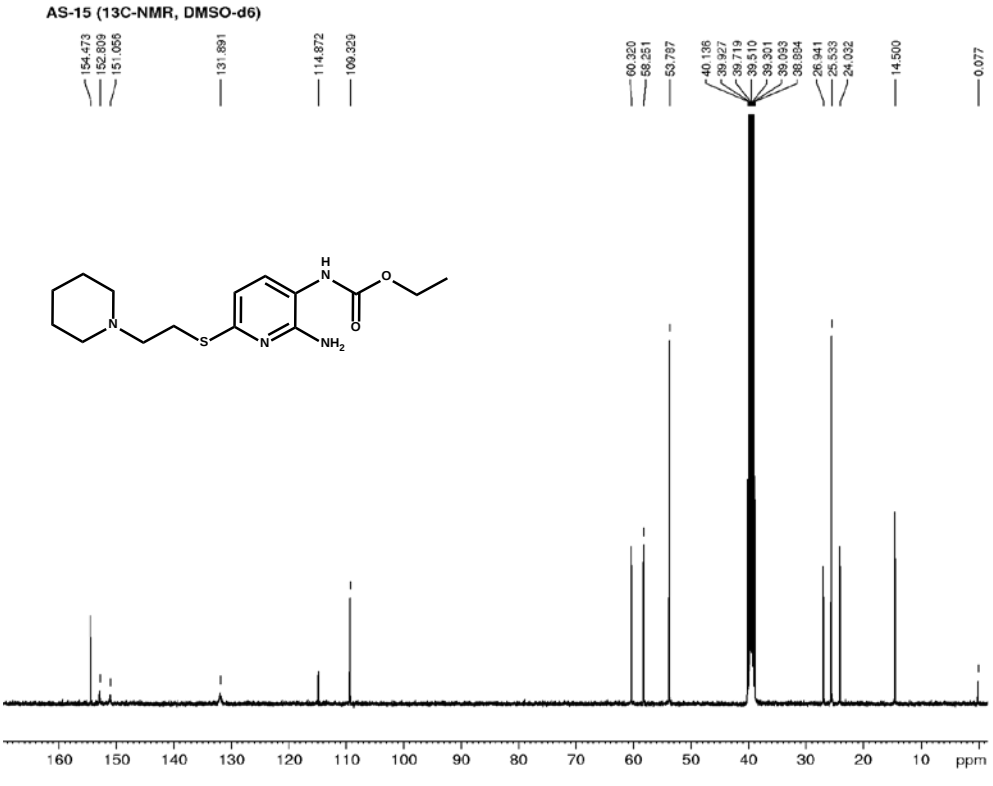


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Current Data Parameters
NAME                  A. Surur
EXPNO                      230
PROCNO                       1

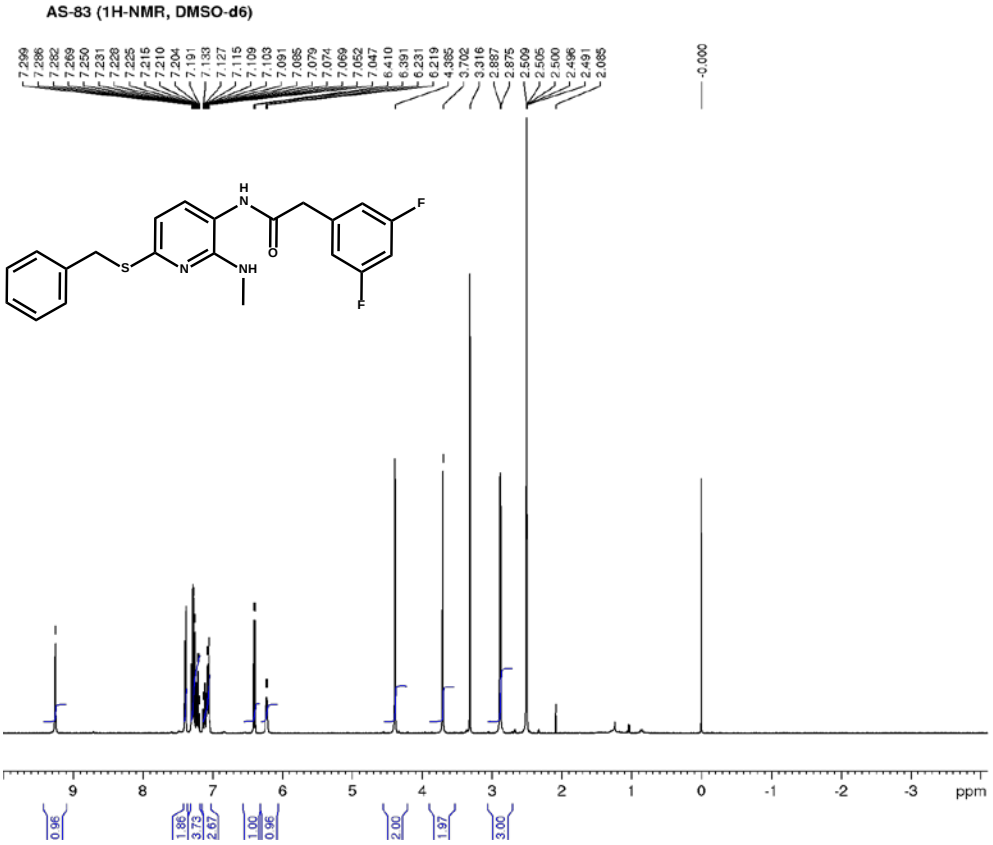
F2 - Acquisition Parameters
Date_               20170412
Time                    18.18
INSTRUM                 spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgpg30
TD                      65536
SOLVENT                 DMSO
NS                        3000
DS                           4
SWH                 24038.461 Hz
FIDRES               0.366798 Hz
AQ                   1.3631488 sec
RG                        2050
DW                      20.800 usec
DE                      10.00 usec
TE                      299.2 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                         1

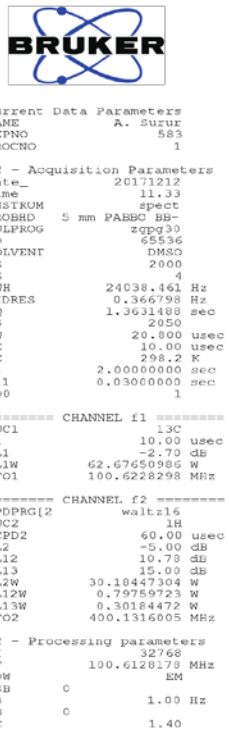
======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
PL1                     -2.70 dB
PL1W                62.67650986 W
SFO1               100.6228298 MHz

======== 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                0.79755723 W
PL13W                0.30184472 W
SFO2               400.1316005 MHz

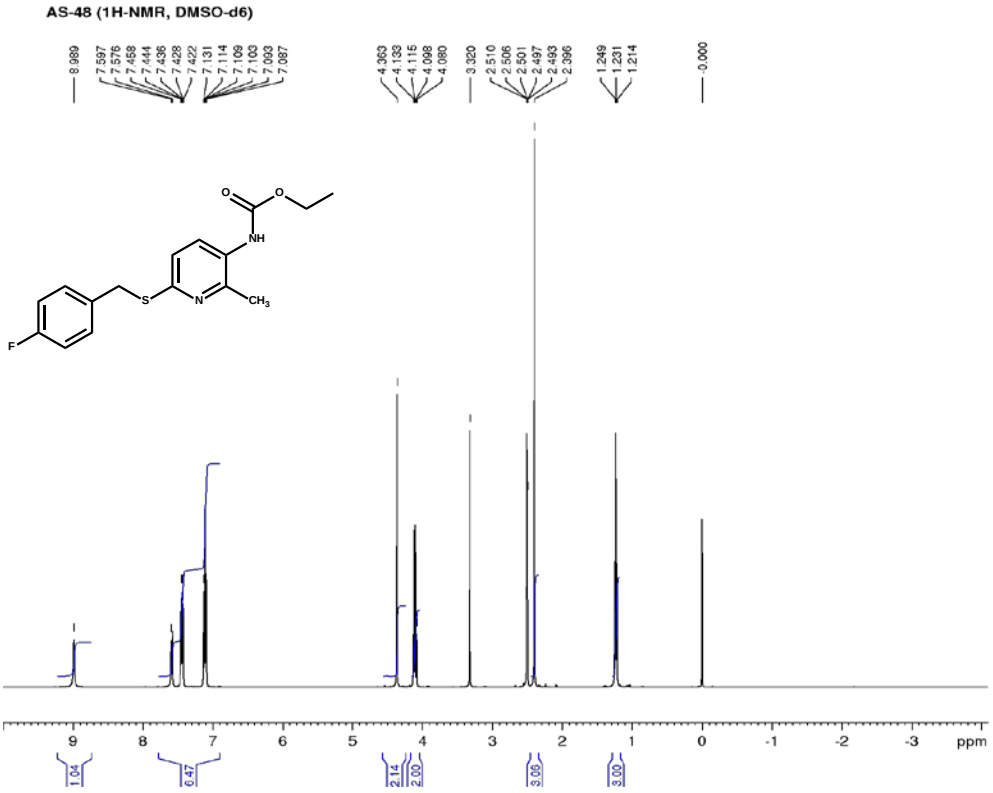
F2 - Processing parameters
SI                      32768
SF                 100.6128182 MHz
WDW                        EM
SSB                 0
LB                      1.00 Hz
GB                  0
PC                      1.40
```

N-[6-(Benzylthio)-2-(methylamino)pyridin-3-yl]-2-(3,5-difluorophenyl)acetamide (**9g**)





Ethyl [6-(4-fluorobenzylthio)-2-methylpyridin-3-yl]carbamate (**9h**)

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Current Data Parameters
NAME                  A. Surur
EXPNO                      361
PROCNO                       1

F2 - Acquisition Parameters
Date_               20170710
Time                   10.13
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                  298.2 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                 400.1300027 MHz
WDW                         EM
SSB                  0
LB                     0.30 Hz
GB                   0
PC                     1.00
```


```
Current Data Parameters
NAME                  A. Surur
EXPNO                      362
PROCNO                       1

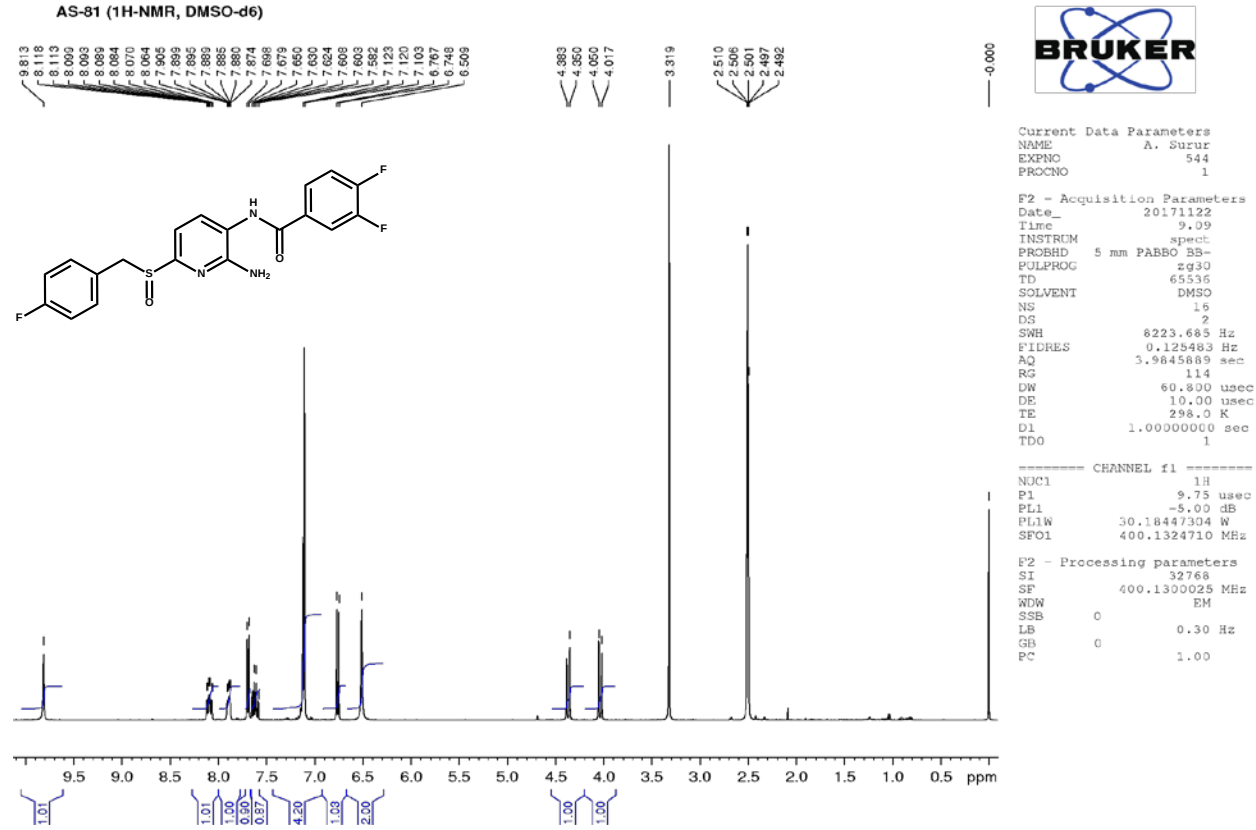
F2 - Acquisition Parameters
Date_               20170710
Time                   23.31
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                      4000
DS                         4
SWH               24038.461 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

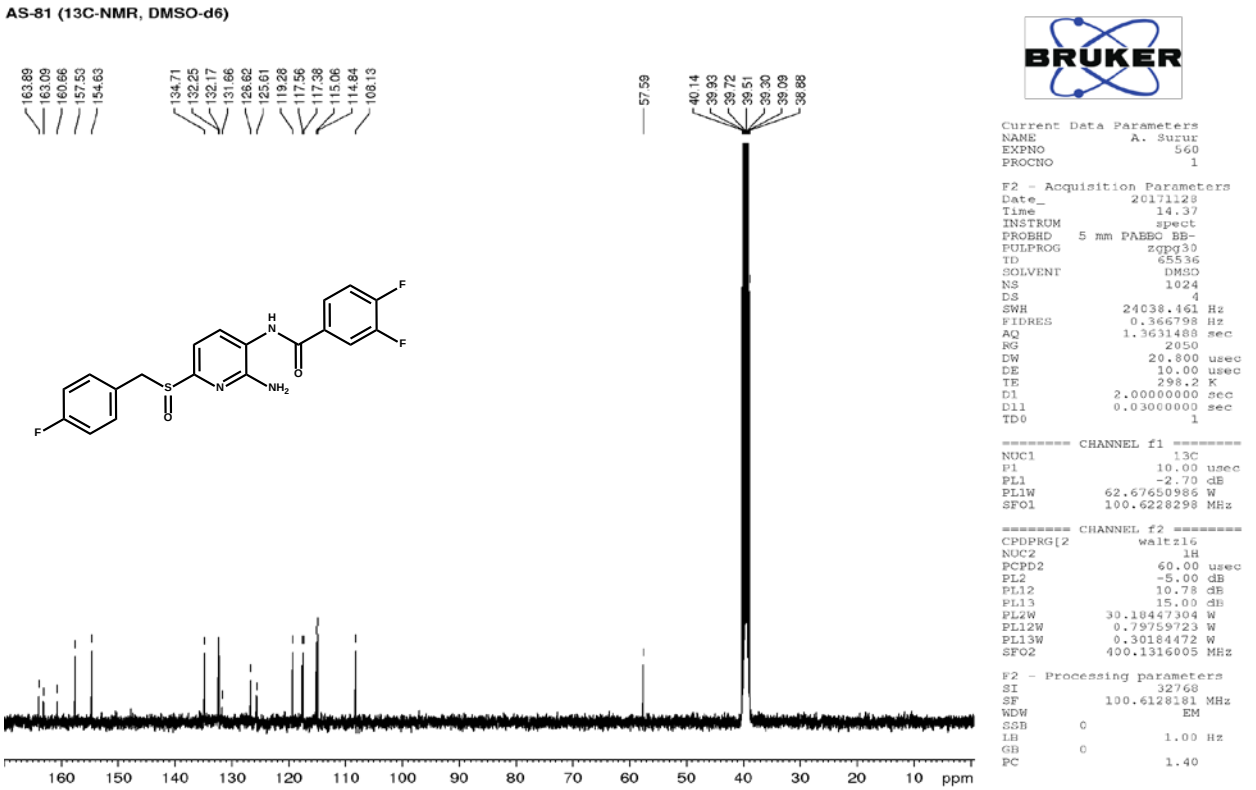
======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
PL1                    -2.70 dB
PL1W            62.67650986 W
SFO1           100.6228298 MHz

======== 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

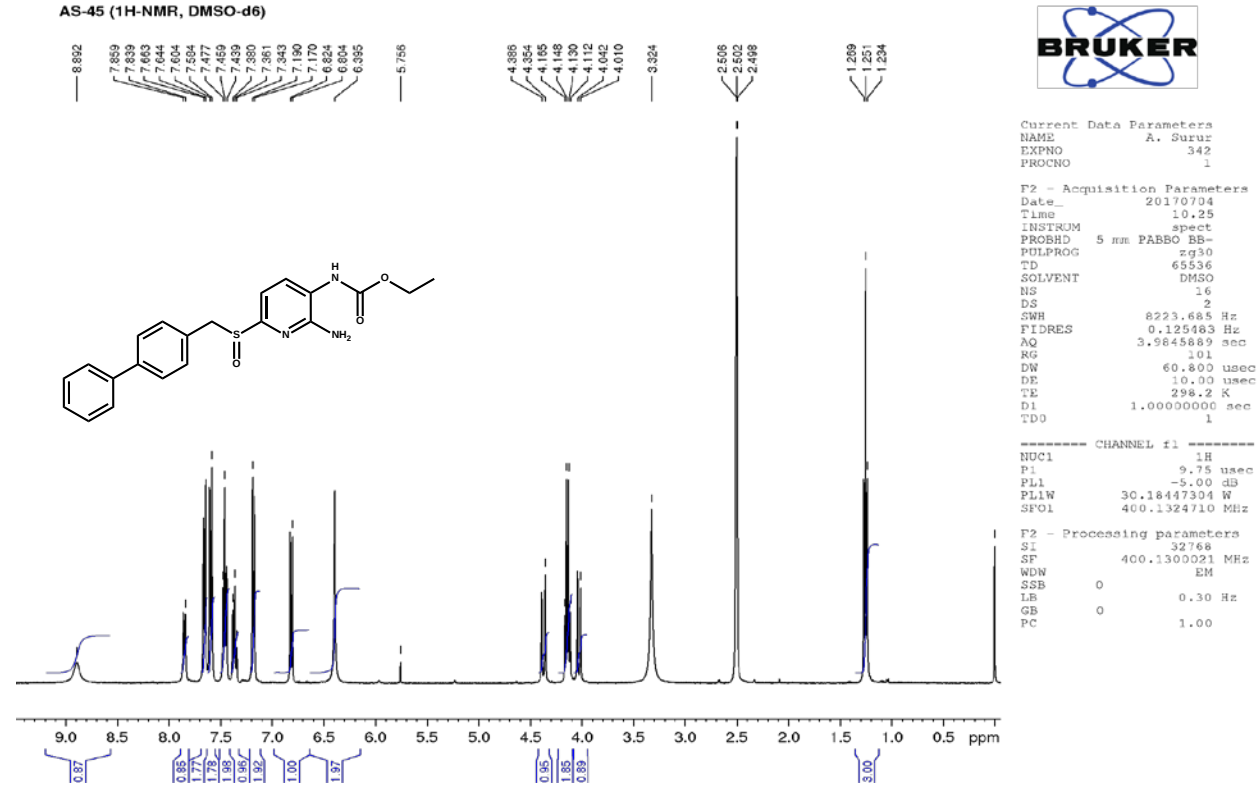
F2 - Processing parameters
SI                       32768
SF                 100.6128185 MHz
WDW                         EM
SSB                  0
LB                     1.00 Hz
GB                   0
PC                     1.40
```

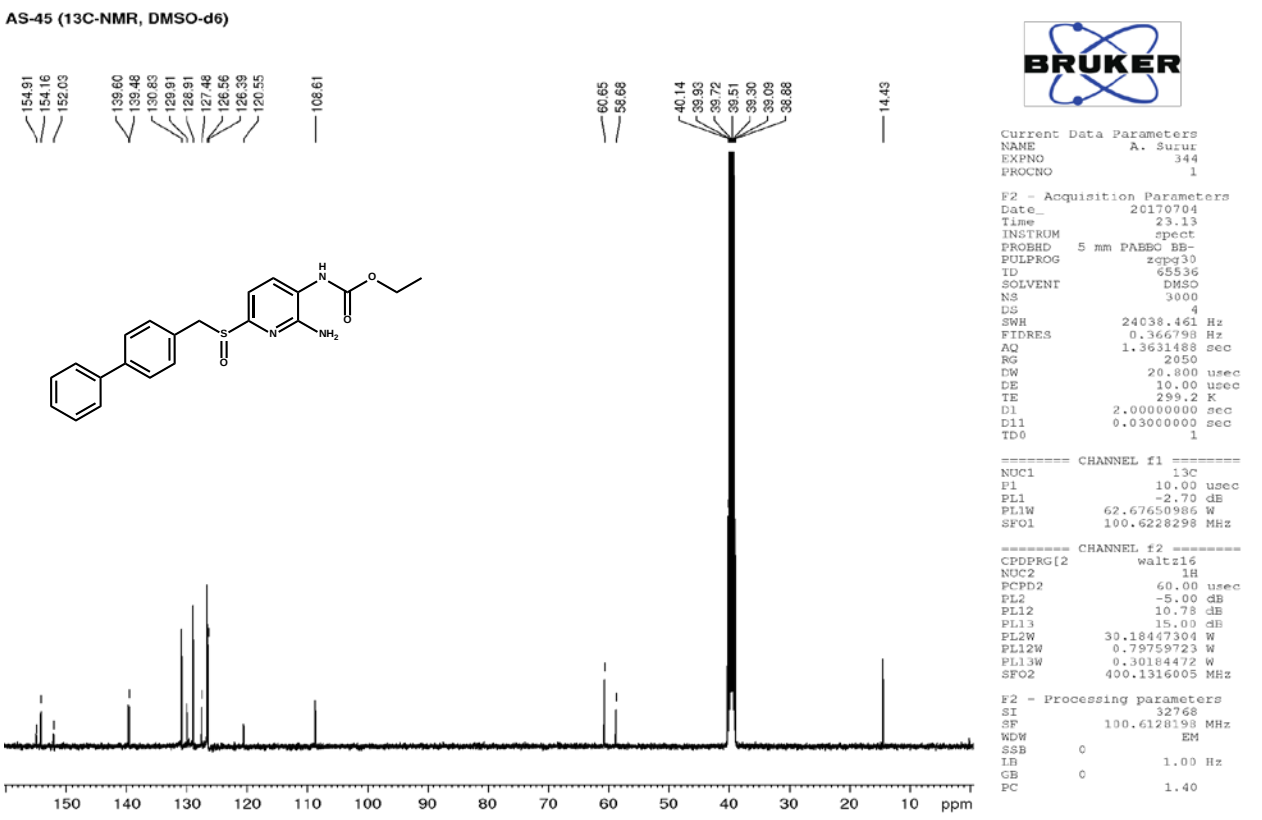
N-[2-Amino-6-(4-fluorobenzylsulfinyl)pyridin-3-yl]-3,4-difluorobenzamide (**10a**)



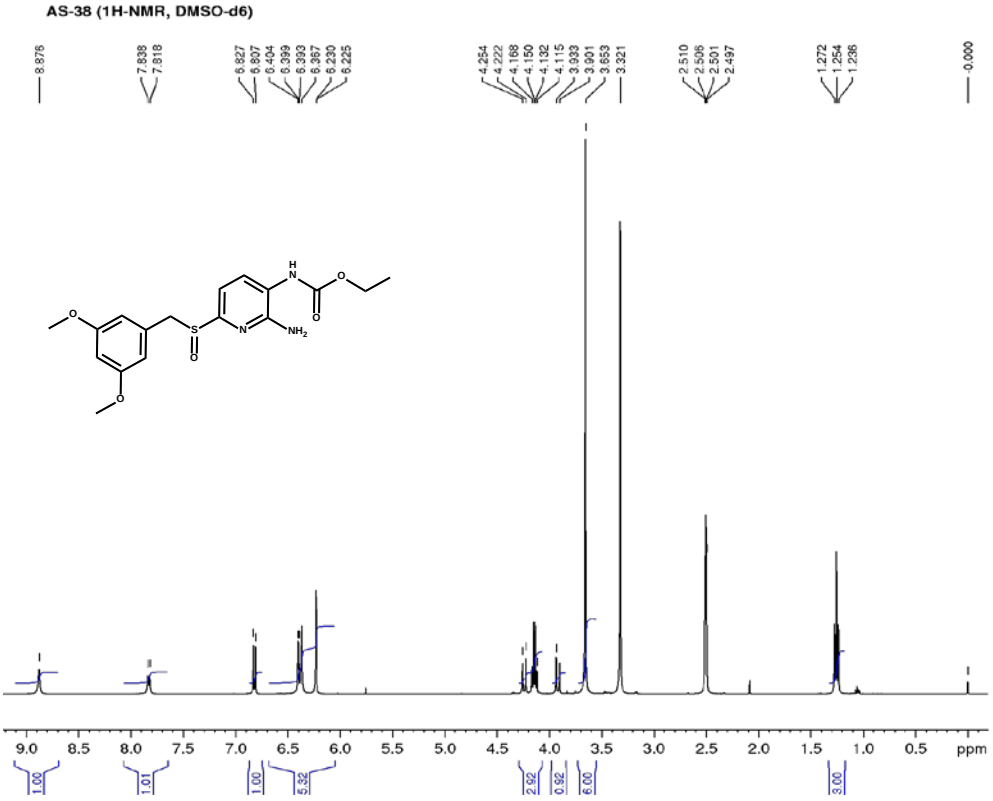


Ethyl {6-[(1,1'-biphenyl-4-yl)methylsulfinyl]-2-aminopyridin-3-yl}carbamate (**10b**)





Ethyl [2-amino-6-(3,5-dimethoxybenzylsulfinyl)pyridin-3-yl]carbamate (**10c**)

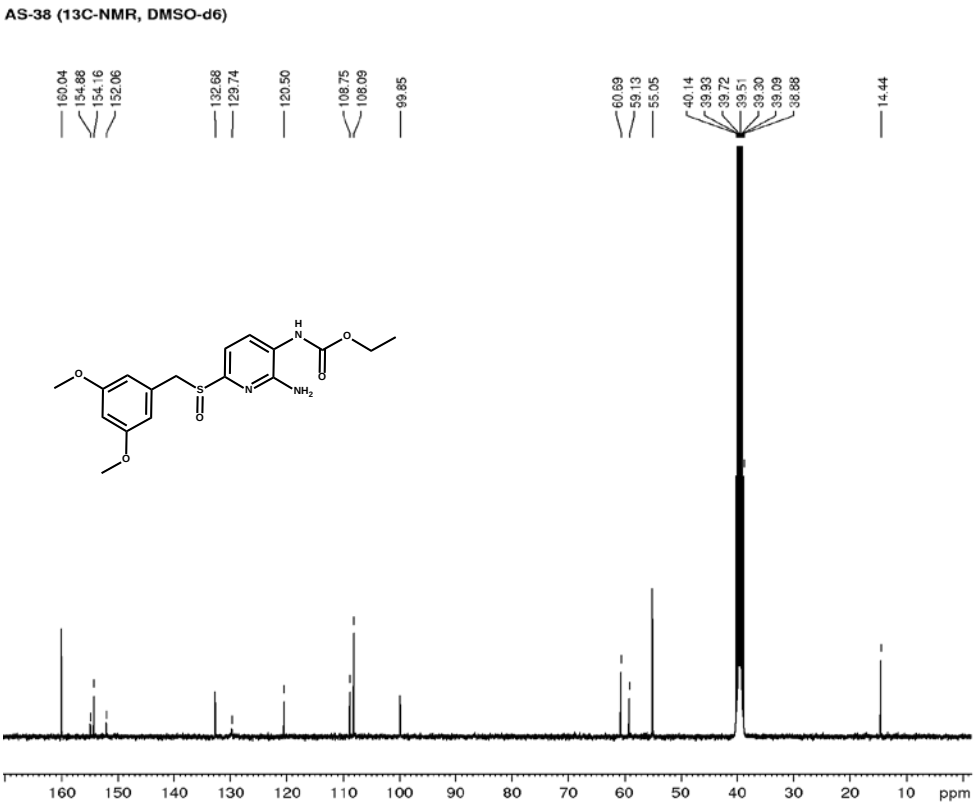


```
Current Data Parameters
NAME                  A. Surur
EXPNO                      300
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170602
Time                      8.17
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                      298.2 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                  400.1300027 MHz
WDW                         EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```



```
Current Data Parameters
NAME                  A. Surur
EXPNO                      303
PROCNO                       1

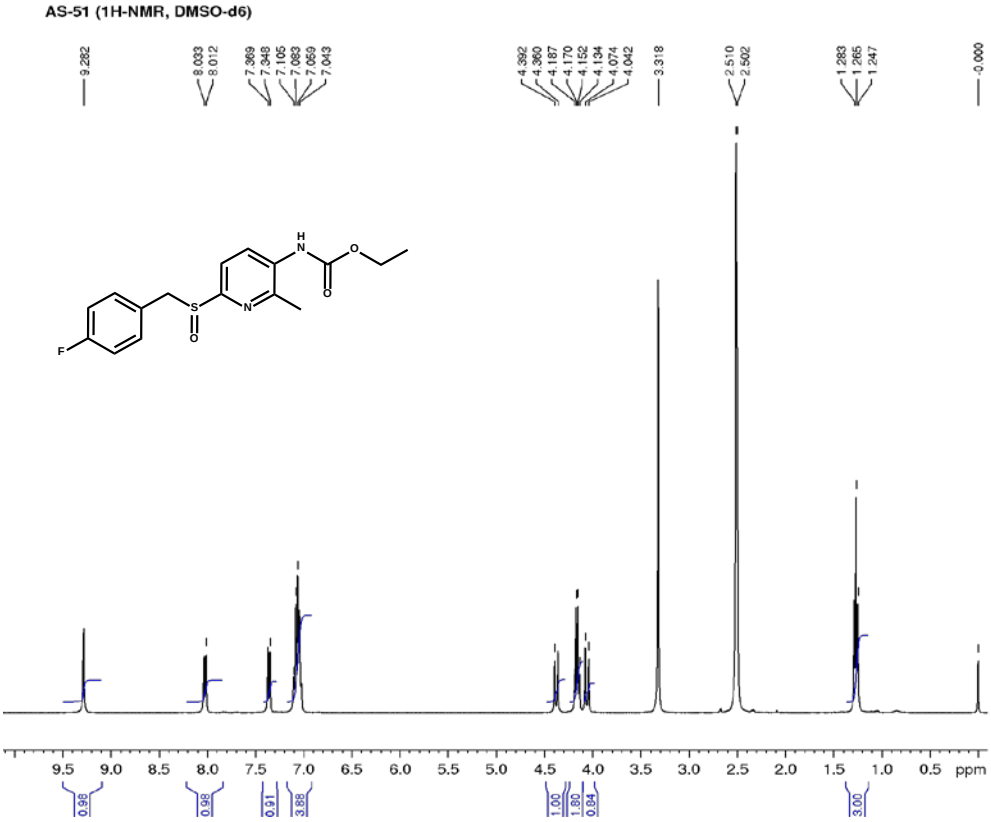
F2 - Acquisition Parameters
Date_                 20170607
Time                         0
INSTRUM                   spect
PROBHD    5 mm PABBO BB-
PULPROG                 zgpg30
TD                       65536
SOLVENT                   DMSO
NS                         4000
DS                           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                 100.6128174 MHz
WDW                         EM
SSB                  0
LB                        1.00 Hz
GB                   0
PC                        1.40
```

Ethyl [6-(4-fluorobenzylsulfinyl)-2-methylpyridin-3-yl]carbamate (**10d**)




```
Current Data Parameters
NAME                  A. Surur
EXPNO                      381
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170717
Time                      8.45
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                         114
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                  400.1300027 MHz
WDW                         EM
SSB                  0
LB                       0.30 Hz
GB                   0
PC                       1.00
```


```
Current Data Parameters
NAME                  A. Surur
EXPNO                      387
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170717
Time                     23.03
INSTRUM                  spect
PROBHD     5 mm PABBO BB-
PULPROG                zgpg30
TD                      65536
SOLVENT                  DMSO
NS                        3000
DS                           4
SWH                 24038.461 Hz
FIDRES               0.366798 Hz
AQ                   1.3631488 sec
RG                        2050
DW                      20.800 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

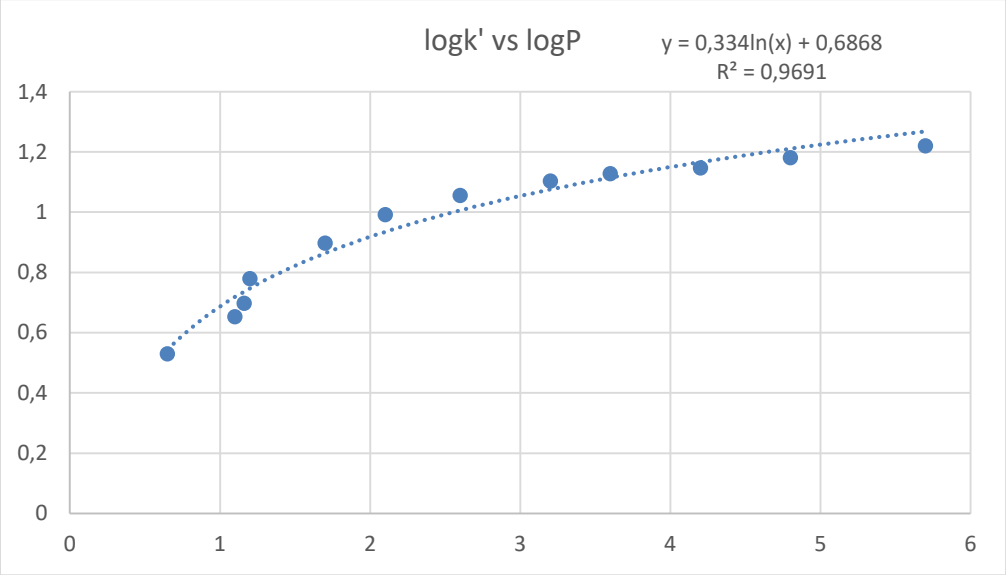
F2 - Processing parameters
SI                       32768
SF                  100.6128191 MHz
WDW                         EM
SSB                  0
LB                       1.00 Hz
GB                   0
PC                       1.40
```

Calibration curve and retention times for $LogD_{7.4}$ determination

Retention time, retention factor and literature LogP values of references

Reference	Retention time (mean)	k'	Logk'	LogP (Lit.)
Uracil	2.72			
Pyridine	11.92	3.38	0.53	0.65
Benzyl alcohol	14.95	4.50	0.65	1.1
Acetanilide	16.25	4.98	0.70	1.16
Picoline	19.09	6.02	0.78	1.2
Acetophenone	24.15	7.88	0.90	1.7
Methyl benzoate	29.39	9.82	0.99	2.1
Ethyl benzoate	33.65	11.38	1.06	2.6
Benzophenone	37.18	12.68	1.10	3.2
Phenyl benzoate	39.18	13.42	1.13	3.6
Diphenyl ether	40.85	14.03	1.15	4.2
Diphenyl ethane	43.94	15.17	1.18	4.8
Triphenylamine	47.87	16.62	1.22	5.7

Calibration curve



Retention time, retention factor and $LogD_{7.4}$ of synthesized compounds

Compounds	Retention time (mean)	k'	Logk'	$LogD_{7.4}$
9a	41.00	13.85	1.14	3.90
9b	44.26	15.03	1.18	4.34
9c	38.76	13.04	1.12	3.61
9d	30.39	10.18	1.01	2.62
9e	34.00	11.31	1.05	3.00
9f	25.99	8.41	0.92	2.04
9g	43.73	14.84	1.17	4.27
9h	40.64	13.72	1.14	3.85
10a	35.88	12.00	1.08	3.24
10b	39.61	13.34	1.12	3.72
10c	32.50	10.77	1.03	2.81
10d	34.18	11.38	1.06	3.02

Biological Evaluations

MTT cell viability assay

The TAMH and HEP-G2 cell lines were a gift of Dr. Sidney D. Nelson (University of Washington, Seattle, USA) and purchased from the Leibniz-Institute DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany), respectively. Cultivation of TAMH cell line and the determination of the LD_{50} values with the MTT cell viability assay have been described elsewhere [1]. The HEP-G2 cell line was cultured in T75 flask (Sarstedt) with RPMI 1640 (PAN Biotech), supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Sigma Aldrich) and 1% penicillin/streptomycin (PAN-Biotech) and were incubated at 37 °C in a humidified incubator with 95% air/5% CO_2. The HEP-G2 cells were detached from flask by Trypsin-EDTA (Sigma Aldrich) when ~70% confluent and suspended in RPMI 1640. Cells were counted with an EVE™ Automated Cell Counter (NanoEntek) and 15000 cells/well/100 µL RPMI 1640 media were seeded into 96 well plates (Sarstedt). Cells were allowed to attach for 24 h in a humidified incubator at 37 °C. Test compounds and controls were then added to the wells of the plates as previously described for TAMH cells [1]. Both cell lines were exposed for 48 h to the test compounds that had shown activity in $K_V7.2/3$ channel opening assay (were a EC_{50} value could be generated). The LD_{25} is the estimated concentration that reduces the T/C_{corr} by 75% and was determined by plotting (log)concentration of test compound versus T/C_{corr} and performing linear regression analysis in Microsoft Excel (2013). Determined values are the mean of at least three independent experiments ± standard deviation (SD).

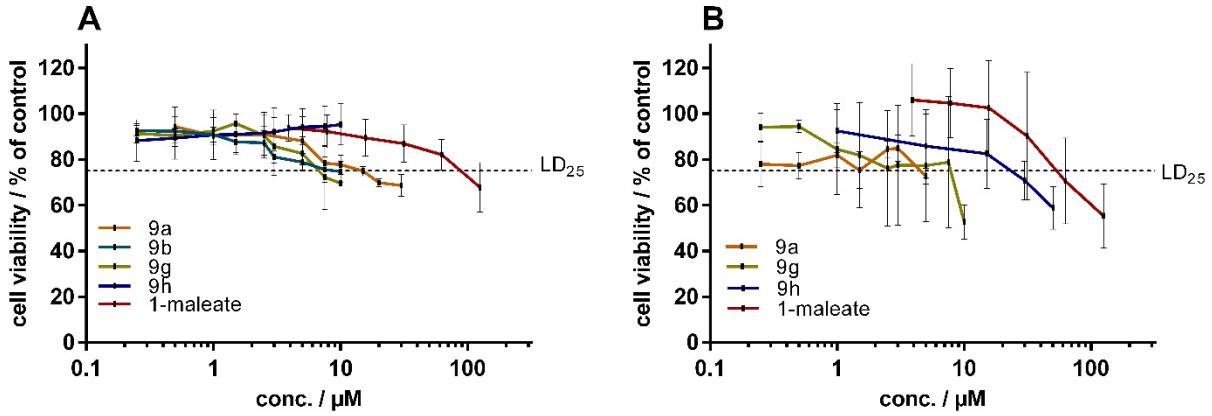


Figure 1. Cell viability as a function of compound concentration in TAMH (A) and HEP-G2 cell line (B) after a 48 h exposure, determined by MTT assay; values are the mean ± SD from ≥3 independent experiments.

K_V7.2/3 channel opening assay

Cultivation of HEK293 cells expressing K_V7.2/3 and K_V7.2/3 channel opening assay were performed as descibed [1]. E_{max} value indicates intrinsic activity of a compound relative to flupirtine. It was determined by calculating the difference of lowest and highest corr. ΔF/F value of an obtained sigmoidal curve of a compound when corr. ΔF/F were plotted versus log(concentration) and related to E_{max} of flupirtine maleate that was defined as 100%. E_{max} value of a compound is the mean of at least three independent experiments ± standard deviation (SD).

Toxicity/Activity ratio

To estimate the therapeutic ratio between pharmacological activity (i.e., K_V7.2/3 channel opening activity) and toxicity (i.e., reduced viability in either the TAMH and HEP-G2 cell lines), a toxicity/activity ratio was calculated following the known safety index [2]. Here, the average LD_{25} value by the MTT assay after a 48 h exposure of compound in either the TAMH or HEP-G2 cell lines was divided by the average EC_{50} value obtained in K_V7.2/3 channel opening assay with transfected HEK293 cells.

[1] C. Bock, K. Beirow, A. S. Surur, L. Schulig, A. Bodtke, P. J. Bednarski, A. Link, *Org. Biomol. Chem.* **2018**, DOI: 10.1039/c8ob02530d.

[2] Y. Y. Pang, W. K. Yeo, K. Y. Loh, M. L. Go, H. K. Ho. *Food Chem. Toxicol*. **2014**, 71, 207-216.