SUPPORTING INFORMATION

Novel Aza-analogous Ergoline Derived Scaffolds as potent Serotonin 5-HT_6 and dopamine D_2 Receptor Ligands.

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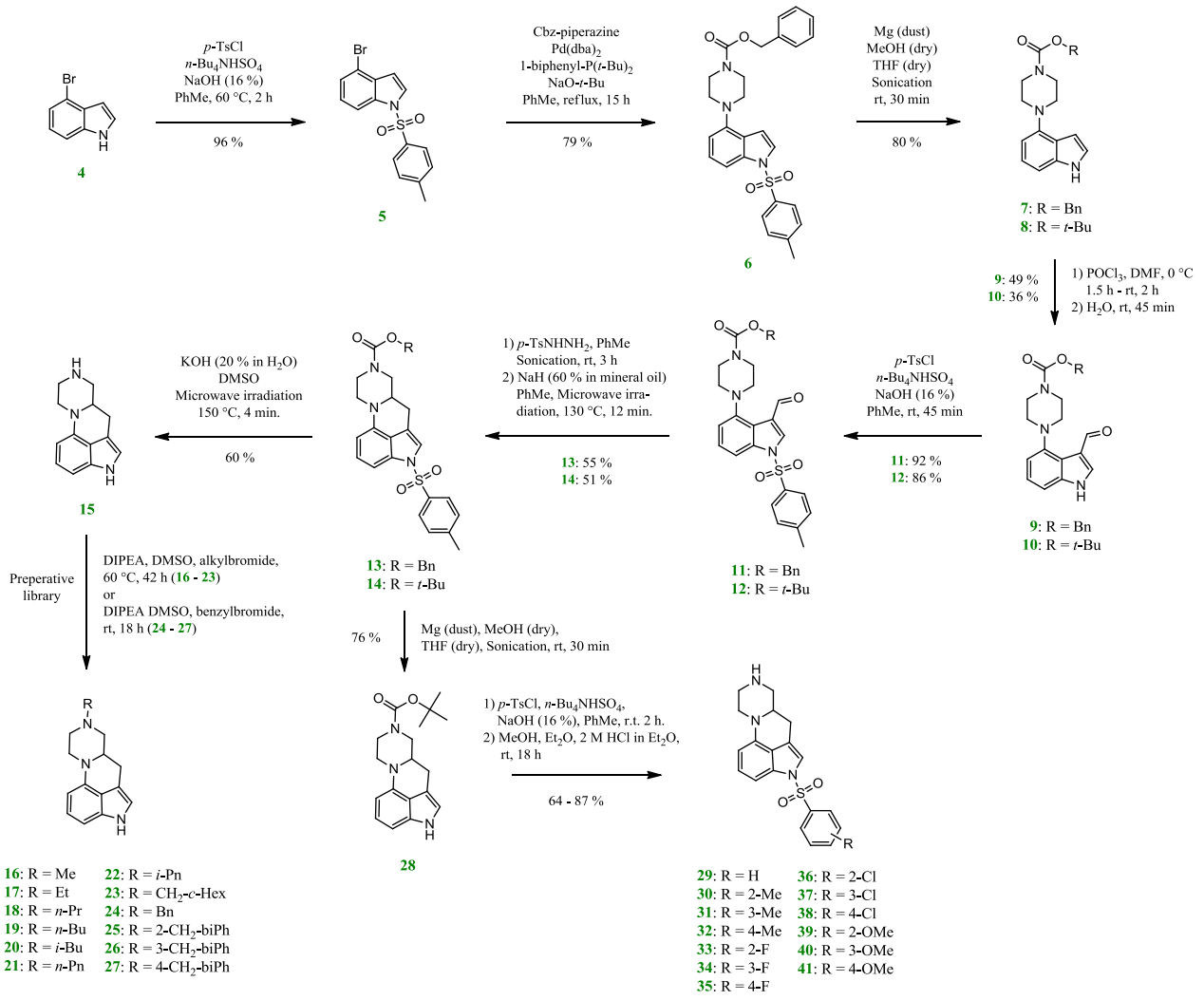
CHEMISTRY

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AV-500 at 500 MHz for H nuclei and 125 MHz for C nuclei using either deuterated chloroform ($CDCl_3$) or DMSO ($(CD_3)_2SO$) as solvents. Multiplicities of H^1 NMR signals are given as follows: s, singlet; bs, broad singlet; m(s), multiplet that appears as a singlet; d, doublet; bd, broad doublet; t, triplet; q, quartet; quin, quintet; se, sextet; h, heptet; o, octet; n, nonet. Microwave-assisted reactions were performed using the following instruments: Emrys Optimizer (300 w), Emrys Synthesizer (300 w), Biotage Initiater (400 w) or Biotage Advancer (300 w). The purification by chromatography were performed using one of the following instruments: FlashMasterII from JonesChromatography with prepacked IST (international sorbent technology) columns or ISCO Companion 4X. Reactions and product mixtures were analyzed by thin layer chromatography (TLC) on Merck 60 F_{254} 0.25 mm silica gel plates and visualized under UV light and $KMnO_4$ stain or by use of an analytical LC-MS system. The LC-MS analysis were performed using a one of two apparatuses: Sciex API150ex apparatus (Method 111) from Applied Biosystems with the following equipment: Applied Biosystems API150ex single quadrupole mass spectrometer with atmospheric pressure photo ionization (APPI) ionsource, Shimatsu LC10ADvp LC pumps (3X), shimatsu SPD-M20A photodiode array detector, Shimatsu CBM-20A system controller, Gilson 215 autosampler, Gilson 864 degasser, SEDERE SEDEX 85, The system is controlled by Analyst software. MS: Ion source: APPI, temp. 450 °C, OR/RNG 20/200 V, OR/RNG 5/100 V, Mass: 100-1000 amu. HPLC: Column: C-18 4,6x30 mm 3.5 mm Symmetry, column temperature: 60 °C, gradient, reverse phase with ion pairing, solvent A: 99.95 % H_2O, 0.05 % TFA, solvent B: 95 % CH_3CN, 5 % H_2O, 0.035 % TFA, flow 3.3 mL/min. Injection volumen 10 µL (1 µL on column), gradient 10 % to 100 % B in 2.4 min., 10 % B in 0.4 min., total run time: 2.8 min. UV: 254 nm, LSD: Glass tube: 21 °C, evaporation chamber: 50 °C, pressure 4.4 bar. The other apparatus was a Sciex API300 (Method 350) from Applied Biosystems with the following equipment: Applied Biosystems API300 triple quadrupole mass spectrometer with atmospheric pressure photoionization (APPI) ionsource, Shimatsu LC10ADvp LC pumps (3X), acquity UPLC core system w/column manager (including UPLC binary solvent manager), acquity UPLC sampler organizer, acquity UPLC PDA detector with an analytical flow cell, acquity UPLC ELS detector. The system is controlled by analyst software and Waters plug-in control to analyst. *Methods 350*: Duration: 1.15 min., column: Acquity UPLC BEH C_{18} 1.7 mm, 2.1 x 50 mm (waters), column temperature: 60 °C, ion source: APPI, neubulizer temperature: 60 °C, OR/RNG: 20/200, mass: 100-1000, flow: 1.20 mL/min. Solvent A: 99.95 % H_2O, 0.05 % TFA. Solvent B: 95 % CH_3CN, 5 % H_2O, 0.035 % TFA. Gradient: time: 0.00 (10 % B), 1.00 (100 % B), 1.01 (10 % B), 1.15 (10 % B), make-up flow: 0.7 mL/min. ethanol/toluene (90/10), UV: 254, ELSD: Evaporation: 50 °C, nebuliser: RT. The HRMS performed in-house were generated on an Agilent/Bruker Daltonics LC-SPE-MS consisting of the following components: Agilent 1100 quaternary pump with degasser, Agilent 1100 automatic sample injector, Agilent 1100 variable wavelength detector (VWD), Agilent diode-array detector (DAD), Agilent 1200 column oven, Spark ProspectII automatic cartridge exchanger (ACE) and high-pressure dilutor (HPD) for peak trapping on solid-phase-exchange (SPE) cartridges.

Bruker Daltronics microTOF mass spectrometer with ESI and APPI ionsources, LC packings ACURATE splitter 1/1000, Varian vacuum pump. The system is controlled by Hystar software. The methods have not been described since only the MS part has been used for HRMS determination.



4-Bromo-1-(toluene-4-sulfonyl)-1*H*-indole (**5**): 4-Bromoindole **4** (14.8 g, 75.2 mmol, 1.00 eq), *p*-tosyl chloride (17.2 g, 90.2 mmol, 1.20 eq) and tetrabutylammonium hydrogensulfate (1.25 g, 3.69 mmol, 0.05 eq) were dissolved in toluene (90 mL) and subsequently added 28 % NaOH (90 mL) and water (30 mL). The mixture was stirred vigorously for 10 min. at room temperature before the temperature was raised to 60 °C for 2.5 h. The mixture was diluted with toluene (400 mL) and water (250 mL) and the phases were separated. The organic phase was washed with water (250 mL), brine (250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The brownish solid was crystallised (EtOAc and small amount of MeOH with heptane) to yield 23.4 g (89 %) of compound **5** as a slightly off white solid that turned pink over time. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.35 (3H, s), 6.72 (1H, d, *J* = 4 Hz), 7.17 (1H, t, *J* = 8 Hz), 7.24 (2H, t, *J* = 9 Hz), 7.38 (1H, d, *J* = 8 Hz), 7.62 (1H, d, *J* = 4 Hz), 7.75 (2H, d, *J* = 8 Hz), 7.94 (1H, d, *J* = 9 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 22.0 , 109.2 ,

113.0 , 115.4 , 125.9 , 126.6 , 127.3 , 130.4 , 131.8 , 135.4 , 145.8; **LC-MS** (Method 111)**:** UV = 100 % (t_R = 1.84), ELS = 100 % (t_R = 1.90), m/z ($M+H^+$) = 351.4 (95 %) / 349.1 (100 %) (t_R = 1.89 min). **TLC:** R_f = 0.32 (heptane : EtOAc, 10 : 1). The characterisation is consistent with existing literature.[1]

Benzyl 4-[1-(Toluene-4-sulfonyl)-1H-indol-4-yl]-piperazine-1-carboxylate (**6**)**:** Tosyl protected indole **5** (2.01 g, 5.74 mmol, 1.00 eq), benzyl (1-piperazinyl)carboxylate (1.27 mL, 6.58 mmol, 1.15 eq) and sodium *t*-butoxide (680 mg, 7.07 mmol, 1.23 eq) were suspended in toluene (20 mL) and the suspension was purged with argon for 20 min. $Pd(dba)_2$ (125 mg, 0.22 mmol, 0.04 eq) and 1-bifenyl-P(*t*-Bu)$_2$ (117 mg, 0.39 mmol, 0.07 eq) were added to the mixture and the suspension was purged with argon for another 10 min. The vial was sealed and heated to 85 °C for 18 h. The yellow/reddish suspension was filtered through a plug of celite. The vial was washed with EtOAc (3 x 5 mL), which were afterwards filtered through the same celite plug. The solution was concentrated *in vacuo*, dissolved in acetone, concentrated *in vacuo* and purified by flash chromatography to yield 2.21 g (79 %) of compound **6** as a light brownish foam. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.33 (3H, s), 3.08 (4H, m), 3.70 (4H, m), 5.16 (2H, s), 6.65 (1H, d, *J* = 5 Hz), 6.70 (1H, d, *J* = 8 Hz), 7.20 (3H, m), 7.30 – 7.40 (5H, m), 7.54 (1H, d, *J* = 4 Hz), 7.67 (1H, d, *J* = 9 Hz), 7.75 (2H, m); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 21.5, 44.1, 52.4, 67.3, 106.9, 108.4, 111.0, 124.3, 125.1, 125.4, 126.9, 128.0, 128.1, 128.5, 129.9, 135.2, 135.9, 136.6, 145.0, 145.7, 155.3; **LC-MS:** (Method 111) UV = 100 % (t_R = 1.88 min), ELS = 100 % (t_R = 1.94), m/z = 490.5 (t_R = 1.92 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{27}H_{28}N_3O_4S$) Calculated: 490.1795, Found: 490.1803; **TLC:** R_f = 0.42 (heptane : EtOAc, 1 : 1).

Benzyl 4-(1H-Indol-4-yl)-piperazine-1-carboxylate (7): Protected piperazino indole **6** (1.22 g, 2.50 mmol, 1.00 eq) was dissolved in dry THF (5 mL), added dry MeOH (15 mL) under argon. The mixture was cooled to 0 °C and added magnesium powder (300 mg, 12.3 mmol, 4.92 eq). The mixture was left to stir for 15 min and was then sonicated for 30 min at room temperature. During the first 15 min the mixture was removed several times from the sonication and placed in an ice-bath for short periods of time due to the exothermic reaction that resulted in reflux of the solvent. The mixture was filtered through celite and concentrated *in vacuo.* The concentration was stopped when a white gel began to form. The reaction mixture was transferred to a separatory funnel containing 0.1 M HCl (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL). The combined organic phases were washed with sat. $NaHCO_3$ (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and purified by flash chromatography to yield 658 mg (80 %) of compound **7** as a clear, colorless oil. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 3.18 (4H, bs), 3.74 (4H, bt, *J* = 5 Hz), 5.18 (2H, s), 6.50 (1H, m), 6.56 (1H, dm, *J* = 8 Hz), 7.06 (1H, dm, *J* = 8 Hz), 7.10 (1H, t, *J* = 8 Hz), 7.11 (1H, t, *J* = 3 Hz), 7.3 – 7.4 (5H, m), 8.33 (1H, s); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 44.2, 51.0, 67.2, 100.4, 106.5, 106.7, 121.2, 122.3, 123.1, 127.8, 128.0, 128.5, 136.5, 136.9, 145.1, 155.4; **LC-MS:** (Method 111) UV = 100 % (t_R = 1.14), ELS = 100 % (t_R = 1.20), m/z = 336.6 (t_R = 1.19 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_2$) Calculated: 336.1707, Found: 336.1701; **TLC:** R_f = 0.30 (heptane : EtOAc, 2 : 1).

Benzyl 4-(3-Formyl-1*H*-indol-4-yl)-piperazine-1-carboxylate (**9**)**:** Deprotected piperazino indole **7** (9.20 g, 27.4 mmol, 1.00 eq) was dissolved in DMF (30 mL). The mixture was purged with and placed under argon and afterwards cooled to 0 °C. $POCl_3$ (2.80 mL, 30.0 mmol, 1.09 eq) was added dropwise to the reaction mixure over 15 min. The mixture was left at 0 °C for 1.5 h and then stirred at room temperature for 1 h. Additional $POCl_3$ (0.28 mL, 3.00 mmol, 0.11 eq) was added and the reaction mixture stirred at room temperature for another 1 h. To the reaction mixture was slowly added water (12 mL) and the mixture stirred at room temperature for 45 min. The mixture was poured into a large separatory funnel and added a mixture of Et_2O (400 mL), sat. $NaHCO_3$ (200 mL) and ice some ice (Warning! Quenching of $POCl_3$ can be violent). The aqueous phase was extracted with Et_2O (200 mL). The combined organic phases were washed with a mixture of brine and water (1:1) (200 mL), brine (200 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield 4.49 g (45 %) of compound **9** as a clear, colorless oil. **^{1}H NMR**: (500 MHz, $CDCl_3$) δ: 2.9 – 3.2 (4H, bs), 3.3 – 4.2 (4H, vbs), 5.18 (2H, s), 6.91 (1H, dd, *J* = 7 Hz, 2 Hz), 7.18 – 23 (2H, m), 7.3 – 7.4 (5H, m), 7.94 (1H, d, *J* = 3 Hz), 9.49 (1H, bs), 10.50 (1H, s); **^{13}C NMR**: (125 MHz, $CDCl_3$) δ: 44.1, 52.3, 67.4, 108.8, 112.1, 119.1, 119.9, 124.2, 127.9, 128.2, 128.6, 131.9, 136.5, 138.4, 147.0, 155.5, 187.5; **LC-MS** (Method 111)**:** UV = 99.1 % (t_R = 0.75), ELS = 100 % (t_R = 0.80), m/z = 364.7 (100 %) (t_R = 0.80 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{21}H_{22}N_3O_3$) Calculated: 364.1656, Found: 364.1654; **TLC:** R_f = 0.30 (heptane : EtOAc, 2 : 1).

***tert*-Butyl 4-(3-formyl-1H-indol-4-yl)-piperazine-1-carboxylate** (**10**): DMF (10 mL) was cooled to 0 °C and dropwise added $POCl_3$ (3.71 mL, 39.82 mmol, 1.20 eq). The mixture was then stirred at room temperature for 30 min. In another flask indole **8** (10.0 g, 33.18 mmol, 1.00 eq) was dissolved in DMF (25 mL) under argon, cooled to 0 °C and added drop wise the solution containing the preformed formamidinium chloride over the course of 15 min. The mixture was stirred at 0 °C for 2 hours. The mixture was carefully added 2M NaOH (15 mL) and stirred at room temperature for 30 min. The mixture was transferred to a large separatory funnel containing EtOAc (250 mL), sat. $NaHCO_3$ (250 mL) and ice (Warning! Quenching of $POCl_3$ can be violent). After the gas production had ceased Et_2O (500 mL) was added. The aqueous phase was reextracted with Et_2O (200 mL). The combined organic phases were washed with 50 % brine (2 x 250 mL), brine (200 mL), dried over $MgSO_4$, filtered, concentrated in vacuo and purified by flash chromatography to yield 3.93 g (36 %) of compound **10** as a colorless foam. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.49 (9H, s), 2.9 – 3.2 (4H, bs), 3.2 – 4.2 (4H, bs), 6.92 (1H, m), 7.18 – 7.24 (2H, m), 7.95 (1H, d, *J* = 3 Hz), 9.75 (1H, bs), 10.51 (1H, s); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 28.5, 43.4, 44.4, 52.2, 80.2, 108.7, 111.9, 118.9, 119.9, 124.1, 132.2, 138.5, 147.0, 155.0, 187.5; **LC-MS** (Method 111)**:** UV = 99.5 % (t_R = 0.66 min), ELS = 100 % (t_R = 0.72 min), m/z = 330.4 (100 %), 274.4 (81 %), 230.6 (52 %) (t_R = 0.74 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{18}H_{23}N_3O_3$) Calculated: 330.1812, Found: 330.1819; **TLC:** R_f = 0.10 (heptane : EtOAc, 1 : 1).

Benzyl 4-[3-Formyl-1-(toluene-4-sulfonyl)-1*H*-indol-4-yl]-piperazine-1-carboxylate (**11**)**:** 3-Formylated indole **9** (450 mg, 1.19 mmol, 1.00 eq), *p*-tosyl chloride (300 mg, 1.57 mmol, 1.32 eq) and benzyltriethylammonium chloride (20 mg, 0.09 mmol, 0.08 eq) were dissolved in toluene (10 mL) and water (5 mL) and added 28 % NaOH (5 mL). The mixture was stirred vigorously for 45 min at room temperature. The mixture was then diluted with EtOAc (50 mL) and poured into water (50 mL). The organic phase was washed with brine (50 mL), dried with $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield 563 mg (92 %) of compound **11** as a white foam. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.36 (3H, s), 2.99 (4H, bs), 3.0-4.6 (4H, vbs), 5.16 (2H, s), 6.99 (1H, d, *J* = 8 Hz), 7.25-7.38 (8H, m), 7.75 (1H, d, *J* = 8 Hz), 7.84 (2H, d, *J* = 9 Hz), 8.31 (1H, s), 10.60 (1H, s); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 21.5, 43.8, 52.3, 67.1, 109.7, 114.6, 121.90, 121.93, 126.2, 127.2, 127.8, 128.0, 128.4, 130.2, 130.5, 134.1, 136.2, 136.5, 146.0, 147.3, 155.1, 187.4; **LC-MS** (Method 111)**:** UV = 98.9 % (t_R = 1.51), ELS = 100 % (t_R = 1.57), m/z = 518.5 (100 %) (t_R = 1.56 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{28}H_{28}N_3O_5S$) Calculated: 518.1744, Found: 518.1728; **TLC:** R_f = 0.31 (heptane : EtOAc, 1 : 1).

***tert*-Butyl 4-[3-Formyl-1-(toluene-4-sulfonyl)-1*H*-indol-4-yl]-piperazine-1-carboxylate (12):** 3-Formyl indole **10** (1.29 g, 3.90 mmol, 1.00 eq), tosyl chloride (855 mg, 4.49 mmol, 1.15 eq) and benzyltriethylammonium chloride (60 mg, 0.26 mmol, 0.07 eq) were dissolved in toluene (20 mL) and added water (10 mL) and 28 % NaOH (10 mL). The mixture was stirred vigorously for 45 min at room temperature. The mixture was added EtOAc (100 mL) and poured into water (100 mL). The organic phase was washed with brine (50 mL), dried with $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield 1.62 g (86 %) of compound **12** as a white foam. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.48 (9H, s), 2.38 (3H, s), 2.99 (4H, bs), 3.0 – 4.5 (4H, vbs), 7.01 (1H, d, *J* = 8 Hz), 7.26 – 7.35 (3H, m), 7.75 (1H, d, *J* = 9 Hz), 7.84 (2H, d, *J* = 8 Hz), 8.31 (1H, s), 10. 61 (1H, s); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 21.8, 28.5, 43.5, 44.3, 52.6, 80.1, 109.8, 114.7, 122.1, 122.2, 126.3, 127.4, 130.37, 130.44, 134.4, 136.4, 146.2, 147.7, 154.8, 187.9; **LC-MS** (Method 111)**:** UV = 99.4 % (t_R = 1.36 min), ELS = 100 % (t_R = 1.41 min), m/z = 484.3 (79 %), 428.2 (40 %), 384.4 (100 %). (t_R = 1.43 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{25}H_{29}N_3O_5S$) Calculated: 484.1901, Found: 484.1896; **TLC:** R_f = 0.37 (heptane : EtOAc, 1 : 1).

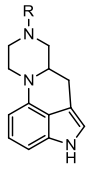
Benzyl 4-(Toluene-4-sulfonyl)-4,6,6a,7,9,10-hexahydro-4,8,10a-triaza-acephenanthrylene-8-carboxylate (13): Diprotected formyl indole **11** (540 mg, 1.04 mmol, 1.00 eq) and *p*-tosylhydrazide (200 mg, 1.07 mmol, 1.03 eq) were suspended in toluene (15 mL). The mixture was sonicated for 3 hours at room temperature. To the reaction mixture was added $MgSO_4$ and after 15 min filtered (in cases where the compound had precipitated, the product was dried azeotropically with toluene). The resulting solution was transferred to a microwave vial and added toluene to a total volume of 20 mL. To the mixture was carefully added NaH (60 %) (44 mg, 1.10 mmol, 1.06 eq), which was afterwards purged with argon for 30 min until gas formation had ceased. The vial was sealed and heated using microwave irradiation for 12 min at 130 °C. The resulting thick suspension was transferred to a separatory funnel with EtOAc (100 mL) and sat. $NaHCO_3$ (100 mL). The organic

phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield 285 mg (54 %) of compound **13** as a white foam. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.33 (3H, s), 2,6 – 3,2 (6H, bm), 3.73 (1H, bm), 4,15 – 4,35 (2H, bm), 5.15 (2H, s), 6,47 (1H, m), 7.06 (1H, bs), 7.19 (3H, m), 7.3 – 7.4 (6H, m), 7.74 (2H, d, *J* = 9 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 22.0, 27.0, 43.7, 46.4, 49.5, 55.6, 67.8, 104.3, 105.4, 115.5, 117.5, 120.3, 127.2, 128.4, 128.6, 129.0, 130.2, 134.5, 136.0, 136.9, 142.2, 145.1, 155.3; **LC-MS** (Method 111)**:** UV = 100 % (t_R = 1.84 min), ELS = 100 % (t_R = 1.90 min), m/z = 502.5 (100 %) (t_R = 1.88 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{28}H_{28}N_3O_4S$) Calculated: 502.1795, Found: 502.1772; **TLC:** R_f = 0.40 (heptane : EtOAc, 1 : 1).

***tert*-butyl 4-tosyl-6a,7,9,10-tetrahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline-8(6*H*)-carboxylate (14):** Diprotected formyl indole **12** (498 mg, 1.03 mmol, 1.00 eq) and tosylhydrazide (200 mg, 1.07 mmol, 1.04 eq) was suspended in toluene (15 mL). The reaction mixture was subjected to sonication for 3 hours at room temperature. The reaction mixture was added $MgSO_4$ (in cases where the compound had precipitated, the product was dried azeotropically with toluene) and after 15 min filtered. The resulting solution was transferred to a microwave vial and added toluene to a total volume of 20 mL. To the mixture was carefully added NaH (60 %) (45 mg, 1.13 mmol, 1.10 eq), which was afterwards purged with argon for 30 min until gas formation had ceased. The vial was sealed and heated using microwave irradiation for 12 min at 130 °C. The resulting thick mash was transferred to a separatory funnel with EtOAc (100 mL) and sat. $NaHCO_3$ (100 mL). The organic phase was washed with brine (75 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield 246 mg (51 %) of compound **14** as a white foam. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.47 (9H, s), 2.31 (3H, s), 2.65 (1H, ddd, *J* = 16, 11, 2 Hz), 2.72 (1H, dt, *J* = 12, 3 Hz), 2.65 – 2.88 (1H, m), 2.88 – 3.18 (3H, m), 3.70 (1H, dm, *J* = 12 Hz), 4.00 – 4.38 (2H, bs), 6.47 (1H, d, *J* = 8 Hz), 7.05 (1H, d, *J* = 1 Hz), 7.15 – 7.21 (3H, m), 7.36 (1H, d, *J* = 9 Hz), 7.74 (2H, d, J = 9 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 21.6, 26.7, 28.5, 42.7, 43.7, 46.1, 48.7, 49.5, 55.3, 80.3, 103.9, 105.0, 115.4, 117.1, 120.0, 126.8, 129.8, 134.2, 135.6, 142.1, 144.7, 154.4; **LC-MS** (Method 111)**:** UV = 97.5 % (t_R = 1.81 min), ELS = 100 % (t_R = 1.87 min), m/z = 467.2 (5 %), 412.4 (29 %), 368.4 (100 %) (t_R = 1.87 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{25}H_{29}N_3O_4S$) Calculated: 468.1952, Found: 468.1939; **TLC:** R_f = 0.41 (heptane : EtOAc, 1 : 1).

6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (15): Diprotected tetracycle **13** (245 mg, 0.49 mmol) was dissolved in DMSO (3 mL) and 20 % KOH (1.5 mL) added. The mixture was heated using microwave irradiation at 150 °C for 4 min. The mixture was subsequently added a large amount of EtOAc (300 mL) and washed with a combination of sat. NH_4Cl (75 mL) and sat. $NaHCO_3$ (75 mL), brine (2 x 150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The pale light-brown solid was further dried at 60 °C under high vacuum to give 63 mg (60 %) of compound **15** as an amorphous solid. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.53 – 2.64 (3H, m), 2.77 – 2.91 (3H, m), 3.01 – 3.11 (2H, m), 3.2 (1H, bs), 3.65 (1H, dm, *J* = 12 Hz), 6.18 (1H, d, *J* = 8 Hz), 6.69 (1H, d, *J* = 8 Hz), 6.77 (1H, m), 6.88 (1H, t, *J* = 8 Hz), 10.49 (1H, s); **^{13}C NMR:**

(125 MHz, $CDCl_3$) δ: 27.7, 45.3, 46.7, 52.2, 56.8, 97.8, 101.9, 107.7, 115.4, 117.7, 122.9, 134.0, 142.4 HRMS: ($M+H^+$: $C_{13}H_{16}N_3$) Calculated: 214.1339, Found: 214.1341, deviation: 0.9 ppm; **LC-MS** (Method 111)**:** UV = 100 % (t_R = 0.29 min), ELS = 100 % (t_R = 0.35 min), m/z = 214.1 (100 %) (t_R = 0.34 min, ESI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{13}H_{16}N_3$) Calculated: 214.1339, Found: 214.1341; **TLC:** R_f = 0.32 (EtOAc : MeOH : TEA, 3 : 2 : 1) (Excessive heating of TLC plate results in a black spot).



16-27

No	R	MW Calc.	MW Found	Purity UV	Purity ELSD
16	Me	228.1495	228.1501	92.0	100
17	Et	242.1652	242.1656	87.2	94.5
18	*n*-Pr	256.1808	256.1812	98.6	99.1
19	*n*-Bu	270.1965	270.1956	99.0	100
20	*i*-Bu	270.1965	270.1964	85.1	96.7
21	*n*-Pn	284.2121	284.2111	100	100
22	*i*-Pn	284.2121	284.2114	99.4	100
23	CH_2-*c*-Hex	310.2278	310.2261	100	100
24	Bn	304.1808	304.1806	87.6	99.2
25	2-CH_2-biPh	380.2121	380.2112	99.6	99.4
26	3-CH_2-biPh	380.2121	380.2116	97.0	99.7
27	4-CH_2-biPh	380.2121	380.2116	99.1	99.9

Table 1: The analytical data available for the *N*-alkylated and *N*-benzylated derivatives of tetracyclic compound **15**. Compound **16** – **23** were prepared using **Method A** while compound **24** – **27** were prepared using **Method B**.

Method A (General procedure for alkylating compound **15):** Tetracyclic compound **15** (15 mg, 0.07 mmol, 1.00 eq) was dissolved in DMSO (2 mL) and added DIPEA (20 µL, 0.11 mmol, 1.64 eq.) and alkyl bromide (1.6 eq.). The mixture was heated to 60 °C and stirred over night in a sealed vial under argon. Additional alkyl bromide (0.8 eq.) was added and reaction mixture stirred at 60 °C for 24 h. The mixtures was purified through a SCX cation-exchange column, concentrated *in vacuo* on a centrifuge, dissolved in 180 µL DMSO and purified using preparative LC-MS.

Method B (General procedure for benzylating compound **15):** Tetracyclic compound **15** (15 mg, 0.07 mmol, 1.00 eq) was dissolved in DMSO (2 mL) and added DIPEA (20 µL, 0.11 mmol, 1.64 eq.) and benzyl bromide (1.6 eq.). The reaction mixture was stirred over night at room temperature. The mixtures was purified through a SCX cation-exchange column, concentrated *in vacuo* on a centrifuge, dissolved in 180 µL DMSO and purified using preparative LC-MS.

8-propyl-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (18): Tetracyclic compound **15** (120 mg, 0.56 mmol, 1.00 eq) was dissolved in THF (3 mL) and DMSO (3 mL). The solution was added DIPEA (120 µL, 0.69 mmol, 1.23 eq) and *n*-propyl bromide (65 µL, 0.72 mmol, 1.29 eq). The reaction mixture was heated to 60 °C in a sealed tube and stirred over night. The mixture was transferred to a separatory funnel containing EtOAc (75 mL) and $NaHCO_3$ (75 mL). The phases were separated and the organic phase was washed with brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified using flash chromatography to yield 69 mg (48 %) of compound **18** as a pale white, glassy oil. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7 Hz), 1.49 (2H, se, *J* = 8 Hz), 1.94 (1H, t, *J* = 11 Hz), 2.15 (1H, dt, *J* = 12, 3 Hz), 2.29 (2H, t, *J* = 7 Hz), 2.67 (2H, m), 2.9-3.1 (4H, m), 3.70 (1H, dm, *J* = 12 Hz), 6.19 (1H, d, *J* = 8 Hz), 6.69 (1H, d, *J* = 9 Hz), 6.78 (1H, m), 6.88 (1H, t, *J* = 8 Hz), 10,50 (1H, s); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 11.8, 19.5, 27.1, 45.9, 52.5, 56.1, 59.7, 59.8, 98.0, 102.0, 107.7, 115.5, 117.8, 122.9, 134.0, 142.0; **LC-MS** (Method 111)**:** UV = 99.4 % (t_R = 0.35 min), ELS = 100 % (t_R = 0.37 min), m/z = 255.9 (100 %) (t_R = 0.40 min, APPI, ($M+H^+$)). **HRMS:** ($M+H^+$: $C_{16}H_{22}N_3$) Calculated: 256.1808, Found: 256.1812; **TLC:** R_f = 0.28 (EtOAc : Heptane : TEA, 12 : 8 : 1).

***tert*-butyl 6a,7,9,10-tetrahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline-8(6*H*)-carboxy-late (28):):** Diprotected tetracyclic compound **14** (1.17 g, 2.50 mmol, 1.00 eq) was dissolved in dry THF (5 mL), added dry MeOH (15 mL) under argon. The mixture was cooled to 0 °C and added magnesium powder (300 mg, 12.3 mmol, 4.92 eq). The mixture was left to stir for 15 min and was then sonicated for 30 min at room temperature. During the first 15 min the mixture was removed several times from the sonication and placed in an ice-bath for short periods of time due to the exothermic reaction that resulted resulted in reflux of the solvent. The mixture was filtered through celite and concentrated *in vacuo.* The concentration was stopped when a white gel began to form. The reaction mixture was transferred to a separatory funnel containing 0.1 M HCl (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL). The combined organic phases were washed with sat. $NaHCO_3$ (150 mL), brine (150 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield 595 mg (76 %) of compound **28** as a clear, colorless oil. **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.53 (9H, s), 2.77 – 2.99 (3H, m), 3.00 – 3.27 (3H, m), 3.82 (1H, dm, *J* = 12 Hz), 4.03 – 4.45 (2H, bm), 6.37 (1H, d, *J* = 8 Hz), 6.71 (1H, s), 6.82 (1H, d, *J* = 8 Hz), 7.11 (1H, t, *J* = 8 Hz), 8.10 (1H, bs); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.1, 28.5, 42.8, 43.9, 46.3, 48.9, 49.9, 56.1, 80.1, 99.3, 102.5, 108.6, 115.4, 118.0, 124.0, 134.4, 141.8, 154.7; **LC-MS** (Method 111)**:** UV = 97.9 % (t_R = 1.32 min), ELS = 100 % (t_R = 1.37 min), m/z =

314.3 (10 %), 258.5 (31 %), 214.2 (100 %) (t_R = 1.39 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{18}H_{23}N_3O_2$) Calculated: 314.1863, Found: 314.1855; **TLC:** R_f = 0.48 (heptane : EtOAc, 1 : 1).

Method C (General procedure for sulphonation and deprotection of compound **28**): Boc-protected tetracyclic compound **28** (75 mg, 0.24 mmol, 1.00 eq) was weight out in a 4 mL vial, added toluene (1.2 mL) and tetrabutylammonium hydrogensulfate (8 mg, 0.02 mmol, 0.10 eq). The substituted benzenesulfonyl chloride (1.25 eq) and 16 % NaOH (1 mL) was added sequentially. The vial was sealed and the mixture was stirred vigorously at room temperature for 2 – 3 h. The organic phase was isolated and the aqueous phase was reextracted with toluene (2 x 2 mL). The organic phases were combined, washed with brine (2 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield a clear oil.

The oil was redissolved in Et_2O (1.5 mL) and MeOH (1.5 mL) before 2M HCl in Et_2O (1.5 mL) was added. The mixture was stirred at room temperature for 24 h under argon. The mixture was concentrated *in vacuo*, dissolved in water (8 mL), added 2M NaOH (2 mL) and EtOAc (10 mL). After thorough mixing the mixture was filtered due to a black, insoluble impurity that made it difficult to determine the transition between the phases. The organic phase was isolated and the aqueous phase reextracted with EtOAc (10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

4-(phenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (29): Prepared using **Method C**. Clear, colorless oil (68 mg, 80 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.03 (1H, bs), 2.60 (1H, ddd, *J* = 16, 12, 2 Hz), 2.64 – 2.74 (2H, m), 2.82 (1H, dd, *J* = 16, 4 Hz), 2.89 – 2.99 (2H, m), 3.10 – 3.18 (2H, m), 3.66 (1H, dm, *J* = 12 Hz), 6.45 (1H, d, *J* = 8 Hz), 7.03 (1H, s(m)), 7.18 (1H, t, *J* = 8 Hz), 7.34 (1H, d, *J* = 9 Hz), 7.38 (2H, t, *J* = 8 Hz), 7.47 (1H, t, *J* = 8 Hz), 7.85 (2H, d, *J* = 8 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.0, 52.5, 56.4, 103.5, 104.5, 116.2, 116.7, 119.9, 126.7, 126.8, 129.2, 133.6, 134.2, 138.6, 142.8; **LC-MS** (Method 111)**:** UV = 98.2 % (t_R = 0.84 min), ELS = 100 % (t_R = 0.89 min), m/z = 354.5 (100 %) (t_R = 0.91 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{20}N_3O_2S$) Calculated: 354.1271, Found: 354.1266; **TLC:** R_f = 0.46 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(*o*-tolylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (30): Prepared using **Method C**. Clear, colorless oil (56 mg, 64 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.44 (1H, bs), 2.55 (3H, s), 2.65 – 2.80 (3H, m), 2.89 (1H, dd, *J* = 16, 4 Hz), 2.96 – 3.06 (2H, m), 3.15 – 3.23 (2H, m), 3.71 (1H, dm, *J* = 12 Hz), 6.45 (1H, d, *J* = 8 Hz), 7.06 – 7.16 (3H, m), 7.21 (1H, d, *J* = 8 Hz), 7.25 (1H, t, *J* = 8 Hz), 7.40 (1H, t, *J* = 8 Hz), 7.74 (1H, d, *J* = 8 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 20.5, 27.0, 45.6, 47.0, 52.4, 56.4, 103.3, 104.3, 114.5, 117.5, 119.5, 126.5, 126.7, 128.8, 132.9, 133.6, 134.2, 137.88, 137.94, 142.8; **LC-MS** (Method 111)**:** UV = 96.9 % (t_R = 0.90 min), ELS = 100 % (t_R = 0.96 min), m/z = 368.4 (100 %) (t_R = 0.97 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_2S$) Calculated: 368.1427, Found: 368.1426; **TLC:** R_f = 0.51 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(*m*-tolylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (31): Prepared using **Method C**. Light braunish solid (58 mg, 66 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.08 (1H, bs), 2.33 (3H, s), 2.62 (1H, ddd, *J* = 16, 11, 2 Hz), 2.66 – 2.76 (2H, m), 2.84 (1H, dd, *J* = 16, 4 Hz), 2.91 – 3.01 (2H, m), 3.11 – 3.20 (2H, m), 3.68 (1H, dm, *J* = 12 Hz), 6.45 (1H, d, *J* = 8 Hz), 7.04 (1H, d, *J* = 1 Hz), 7.18 (1H, t, *J* = 8 Hz), 7.24 – 7.30 (2H, m), 7.34 (1H, d, *J* = 9 Hz), 7.63 – 7.70 (2H, m); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 21.4, 27.0, 45.7, 47.0, 52.5, 56.4, 103.4, 104.5, 115.9, 116.8, 119.9, 124.0, 126.8, 127.0, 129.1, 134.2, 134.5, 138.5, 139.5, 142.7; **LC-MS** (Method 111)**:** UV = 97.8 % (t_R = 0.92 min), ELS = 100 % (t_R = 0.97 min), m/z = 368.4 (100 %) (t_R = 0.99 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_2S$) Calculated: 368.1427, Found: 368.1433; **TLC:** R_f = 0.47 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(*p*-tolylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (32): Prepared using **Method C** (0.24 mmol of tetracyclic compound **11** was exposed to the deprotection part of **Method C**). Clear, colorless oil (42 mg, 48 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.44 (1H, bs), 2.55 (3H, s), 2.65 – 2.80 (3H, m), 2.89 (1H, dd, *J* = 16, 4 Hz), 2.96 – 3.06 (2H, m), 3.15 – 3.23 (2H, m), 3.71 (1H, dm, *J* = 12 Hz), 6.45 (1H, d, *J* = 8 Hz), 7.06 – 7.16 (3H, m), 7.21 (1H, d, *J* = 8 Hz), 7.25 (1H, t, *J* = 8 Hz), 7.40 (1H, t, *J* = 8 Hz), 7.74 (1H, d, *J* = 8 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 20.5, 27.0, 45.6, 47.0, 52.4, 56.4, 103.3, 104.3, 114.5, 117.5, 119.5, 126.5, 126.7, 128.8, 132.9, 133.6, 134.2, 137.88, 137.94, 142.8; **LC-MS** (Method 111)**:** UV = 96.9 % (t_R = 0.90 min), ELS = 100 % (t_R = 0.96 min), m/z = 368.4 (100 %) (t_R = 0.97 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_2S$) Calculated: 368.1427, Found: 368.1426; **TLC:** R_f = 0.45 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(2-Fluorophenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (33): Prepared using **Method C**. Clear, colorless oil (65 mg, 73 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.95 (1H, bs), 2.63 – 2.78 (3H, m), 2.89 (1H, dd, *J* = 16, 3 Hz), 2.95 – 3.04 (2H, m), 3.17 (2H, dm, *J* = 12 Hz), 3.70 (1H, dm, *J* = 12 Hz), 6.47 (1H, d, *J* = 8 Hz), 7.07 (1H, t, *J* = 9 Hz), 7.11 – 7.17 (2H, m), 7.18 – 7.26 (2H, m), 7.47 – 7.54 (1H, m), 7.99 (1H, t, *J* = 7 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.1, 45.8, 47.1, 52.6, 56.5, 103.6, 104.4, 115.3, 117.3, 117.5, 117.7, 119.8, 124.5, 124.6, 126.7, 130.2, 133.9, 136.06, 136.13, 142.8, 158.1, 160.2; **LC-MS** (Method 111)**:** UV = 98.4 % (t_R = 0.84 min), ELS = 100 % (t_R = 0.90 min), m/z = 372.3 (100 %) (t_R = 0.90 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{19}FN_3O_2S$) Calculated: 372.1177, Found: 372.1173; **TLC:** R_f = 0.22 (EtOAc : MeOH : TEA, 8 : 4 : 1).

4-(3-Fluorophenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (34): Prepared using **Method C**. Clear, colorless oil (67 mg, 75 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.83 (1H, bs), 2.63 (1H, ddd, *J* = 16, 12, 2 Hz), 2.67 – 2.76 (2H, m), 2.85 (1H, dd, *J* = 16, 4 Hz), 2.92 – 3.02 (2H, m), 3.12 – 3.19 (2H, m), 3.68 (1H, dm, *J* = 12 Hz), 6.48 (1H, d, *J* = 8 Hz), 7.01 (1H, s(m)) 7.15 – 7.23 (2H, m), 7.32 (1H, d, *J* = 8 Hz), 7.35 – 7.41 (1H, m), 7.56 (1H, dm, *J* = 8 Hz), 7.65 (1H, d, *J* = 8 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.8, 47.1, 52.6, 56.4, 103.8, 104.4, 114.1, 114.3, 116.6, 116.8, 120.0, 121.0, 122.61, 122.63, 127.1, 131.0, 131.1, 134.2, 140.28,

140.34, 142.9, 161.2, 163.2; **LC-MS:** (Method 350) UV = 99.7 % (t_R = 0.56 min), ELS = 100 % (t_R = 0.58 min), m/z = 371.8 (100 %) (t_R = 0.62 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{19}FN_3O_2S$) Calculated: 372.1177, Found: 372.1180; **TLC:** R_f = 0.24 (EtOAc : MeOH : TEA, 8 : 4 : 1).

4-(4-Fluorophenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (35): Prepared using **Method C**. Clear, colorless oil (62 mg, 70 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.22 (1H, bs), 2.64 (1H, ddd, *J* = 16, 12, 2 Hz), 2.69 – 2.78 (2H, m), 2.86 (1H, dd, *J* = 16, 4 Hz), 2.94 – 3.03 (2H, m), 3.13 – 3.20 (2H, m), 3.70 (1H, dm, *J* = 12 Hz), 6.47 (1H, d, *J* = 8 Hz), 7.01 (1H, s(m)), 7.07 (2H, t, *J* = 9 Hz), 7.19 (1H, t, *J* = 8 Hz), 7.32 (1H, d, *J* = 8 Hz), 7.85-7.90 (2H, m); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.1, 45.7, 47.1, 52.5, 56.4, 103.8, 104.5, 116.5, 116.56, 116.69. 116.71, 120.0, 127.0, 129.6, 129.7, 134.2, 134.6, 142.8, 164.6, 166.7; **LC-MS:** (Method 350) UV = 93.0 % (t_R = 0.55 min), ELS = 99.7 % (t_R = 0.57 min), m/z = 371.7 (100 %) (t_R = 0.61 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{19}FN_3O_2S$) Calculated: 372.1177, Found: 372.1170; **TLC:** R_f = 0.25 (EtOAc : MeOH : TEA, 8 : 4 : 1).

4-(2-Chlorophenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (36): Prepared using **Method C**. Slightly yellow oil (62 mg, 67 %). **^{1}H NMR:** (500 MHz, $CDCl_3$): δ: 2.19 (1H, bs), 2.66 (1H, ddd, *J* = 16, 12, 2 Hz), 2.69 – 2.77 (2H, m), 2.88 (1H, dd, *J* = 16, 4 Hz), 2.95 (2H, m), 3.17 (2H, dm, *J* = 12 Hz), 3.69 (1H, dm, *J* = 12 Hz), 6.45 (1H, d, *J* = 8 Hz), 7.06 (1H, d, *J* = 8 Hz), 7.11 (1H, t, *J* = 8 Hz), 7.20 (1H, d, *J* = 1 Hz), 7.35 (1H, td, *J* = 8, 2 Hz), 7.37 (2H, m), 8.00 (1H, dd, *J* = 8, 1 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.0, 52.4, 56.5, 103.5, 104.1, 114.4, 118.3, 119.6, 126.6, 127.2, 130.9, 132.3, 132.7, 133.9, 134.6, 136.7, 142.9; **LC-MS:** (Method 111) UV = 98.7 % (t_R = 0.86 min), ELS = 100 % (t_R = 0.92 min), m/z = 390.5 (57 %) (t_R = 0.94 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{19}ClN_3O_2S$) Calculated: 388.0881, Found: 388.0880; **TLC:** R_f = 0.53 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(3-Chlorophenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (37): Prepared using **Method C**. Slightly yellow oil (61 mg, 65 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.16 (1H, bs), 2.62 (1H, ddd, *J* = 16, 12, 2 Hz), 2.66 – 2.75 (2H, m), 2.85 (1H, dd, *J* = 16, 4 Hz), 2.91 – 3.01 (2H, m), 3.12 – 3.20 (2H, m), 3.68 (1H, dm, *J* = 12 Hz), 6.47 (1H, d, *J* = 8 Hz), 7.00 (1H, d, *J* = 1 Hz), 7.20 (1H, t, *J* = 8 Hz), 7.28 – 7.35 (2H, m), 7.44 (1H, dm, *J* = 8 Hz), 7.73 (1H, dm, *J* = 8 Hz), 7.85 (1H, m); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.0, 52.4, 56.3, 103.8, 104.4, 116.6, 116.8, 119.9, 124.9, 126.8, 127.1, 130.5, 133.8, 134.1, 135.3, 140.0, 142.8; **LC-MS:** (Method 111) UV = 97.8 % (t_R = 0.94 min), ELS = 100 % (t_R = 0.99 min), m/z = 390.5 (50 %), 388.4 (100 %) (t_R = 0.99 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{19}ClN_3O_2S$) Calculated: 388.0881, Found: 388.0880; **TLC:** R_f = 0.56 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(4-Chlorophenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]quinoline (38): Prepared using **Method C**. Slightly yellow oil (65 mg, 70 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.05 (1H, bs), 2.61 (1H, ddd, *J* = 16, 12, 2 Hz), 2.66 – 2.75 (2H, m), 2.84 (1H, dd, *J* = 16, 4 Hz), 2.91

– 3.00 (2H, m), 3.11 – 3.19 (2H, m), 3.67 (1H, dm, *J* = 12 Hz), 6.46 (1H, d, *J* = 8 Hz), 6.99 (1H, d, *J* = 1 Hz), 7.19 (1H, t, *J* = 8 Hz), 7.28 – 7.37 (3H, m), 7.77 (2H, d, *J* = 8 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.0, 52.5, 56.3, 103.8, 104.4, 116.6, 116.7, 120.0, 127.0, 128.2, 129.5, 134.1, 136.8, 140.2, 142.9; **LC-MS:** (Method 111) UV = 97.4 % (t_R = 0.93 min), ELS = 100 % (t_R = 0.99 min), m/z = 390.5 (55 %), 388.4 (100 %) (t_R = 0.99 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{19}H_{19}ClN_3O_2S$) Calculated: 388.0881, Found: 388.0876; **TLC:** R_f = 0.55 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(2-Methoxyphenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]-quinoline (39): Prepared using **Method C**. Clear, colorless oil (75 mg, 82 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.06 (1H, bs), 2.65 (1H, ddd, *J* = 16, 12, 2 Hz), 2.68 – 2.74 (2H, m), 2.86 (1H, dd, *J* = 16, 4 Hz), 2.91 – 3.01 (2H, m), 3.15 (2H, dm, *J* = 12 Hz), 3.66 (3H, s), 3.66 – 3.71 (1H, m), 6.42 (1H, d, *J* = 8 Hz), 6.82 (1H, d, *J* = 9 Hz), 6.99 (1H, t, *J* = 8 Hz), 7.07 – 7.16 (3H, m), 7.44 (1H, dt, *J* = 8, 2 Hz), 7.97 (1H, dd, *J* = 8, 1 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.1, 52.5, 55.9, 56.6, 103.0, 104.5, 112.6, 113.5, 118.3, 119.4, 120.3, 126.1, 126.8, 130.3, 134.2, 135.6, 142.6, 157.4; **LC-MS:** (Method 111) UV = 97.7 % (t_R = 0.81 min), ELS = 100 % (t_R = 0.86 min), m/z = 384.4 (100 %) (t_R = 0.87 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_3S$) Calculated: 384.1376, Found: 384.1392; **TLC:** R_f = 0.45 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(3-Methoxyphenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]-quinoline (40): Prepared using **Method C**. Clear, colorless oil (72 mg, 78 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 2.03 (1H, bs), 2.60 (1H, ddd, *J* = 16, 12, 2 Hz), 2.65 – 2.74 (2H, m), 2.82 (1H, dd, *J* = 16, 4 Hz), 2.90 – 2.99 (2H, m), 3.14 (2H, dm, *J* = 12 Hz), 3.67 (1H, dm, *J* = 12 Hz), 3.74 (3H, s), 6.45 (1H, d, *J* = 8 Hz), 6.96 – 7.03 (2H, m), 7.18 (1H, t, *J* = 8 Hz), 7.27 (1H, t, *J* = 8 Hz), 7.34 (1H, d, *J* = 8 Hz), 7.36 (1H, m), 7.42 (1H, dm, *J* = 8 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.0, 52.5, 55.6, 56.4, 103.5, 104.5, 111.7, 116.2, 116.8, 118.8, 119.7, 119.9, 126.8, 130.3, 134.2, 139.6, 142.8, 159.8; **LC-MS:** (Method 111) UV = 96.8 % (t_R = 0.87 min), ELS = 100 % (t_R = 0.92 min), m/z = 384.4 (100 %) (t_R = 0.94 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_3S$) Calculated: 384.1376, Found: 384.1369; **TLC:** R_f = 0.49 (EtOAc : MeOH : TEA, 8 : 2 : 1).

4-(4-Methoxyphenylsulfonyl)-6,6a,7,8,9,10-hexahydro-4*H*-pyrazino[1,2-*a*]pyrrolo[4,3,2-*de*]-quinoline (41): Prepared using **Method C**. Clear, colorless oil (80 mg, 87 %). **^{1}H NMR:** (500 MHz, $CDCl_3$) δ: 1.94 (1H, bs), 2.59 (1H, ddd, *J* = 16, 12, 2 Hz), 2.63 – 2.71 (2H, m), 2.81 (1H, dd, *J* = 16, 4 Hz), 2.86 – 2.97 (2H, m), 3.08 – 3.15 (2H, tm, *J* = 11 Hz), 3.64 (1H, dm, *J* = 12 Hz), 3.71 (3H, s), 6.43 (1H, d, *J* = 8 Hz), 6.79 (2H, d, *J* = 9 Hz), 7.01 (1H, s), 7.16 (1H, t, *J* = 8 Hz), 7.32 (1H, d, *J* = 9 Hz), 7.77 (2H, d, *J* = 9 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$) δ: 27.0, 45.7, 47.0, 52.5, 55.6, 56.3, 103.3, 104.4, 114.3, 115.9, 116.7, 119.9, 126.6, 128.9, 130.0, 134.1, 142.7, 163.5; **LC-MS**: (Method 111) UV = 98.8 % (t_R = 0.85 min), ELS = 100 % (t_R = 0.90 min), m/z = 384.4 (100 %) (t_R = 0.90 min, APPI, ($M+H^+$)); **HRMS:** ($M+H^+$: $C_{20}H_{22}N_3O_3S$) Calculated: 384.1376, Found: 384.1372; **TLC:** R_f = 0.47 (EtOAc : MeOH : TEA, 8 : 2 : 1).

PHARMACOLOGY

General methods:

D_2 receptor binding affinity assay:

The affinity of the compounds for the D_2 receptor were measured by the addition of a serial dilution of compound to a membrane preparation from CHO cells transfected with the human D_2 receptor in a mixture of 50 mM Tris-HCl, 120 mM NaCl, 4 mM $MgCl_2$ and 0.1 nM [^{3}H]spiperone in a total volume of 1 ml. The mixture was incubated for 30' at 37 °C, cooled briefly on ice where after unbound radioactivity were removed by passing the binding reaction through a Packard CF/C filter pre-treated with 0.1 % polyethylenime, The filters was dried and the remaining radioactivity was measured by scintillation counting.

Cell culture and transfections. CHO-K1a cells stably expressing the human dopamine 2L receptor (Cell-line established at Lundbeck, clone 0603C-8-3-11) were cultured at 37 °C in a humidified 5% CO_2 incubator in culture medium [RPMI 1640 Medium w. GlutaMAX1 supplemented with penicillin (100 U/ml), streptomycin (100 µg/ml) 1 mg/mL G418 and 10 % Foetal Bovine Serum]. Cells were grown to 80-90% confluence, and harvested using a cell scraper.

[^{3}H]Raclopride Binding: Competition binding to membranes of CHO-K1a-hD2L cells stably expressing the human D_2L receptor using [^{3}H]raclopride ([*methoxy*-^{3}H]raclopride, 62,2.0 Ci/mmol, Perkin Elmer) was performed. Cells were harvested and scraped into TRIS, pH = 7.7, + 125 mM NaCl, homogenized using an UltraTurrax for 20 sec, centrifuged and frozen. Cell pellets were resuspended in fresh assay buffer (50 mM TRIS pH = 7,4 + 120 mM NaCl + 5 mM KCl + 4 mM $MgCl_2$ + 1 mM EDTA) and the cell membranes were incubated with 1,5 nM [^{3}H]raclopride in the presence of various concentrations of compounds and SPA beads in total assay volumes of 80 µl (10 µL testcompound, 20 µL membrane, 20µL SPA beads (GE healthcare; RPNQ0001) and 30 µL [^{3}H]raclopride). Nonspecific binding was determined in reactions with 10 µM haloperidol. The reactions were incubated for 180 min at room temperature on a shaker. The amount of bound radioactivity was determined in a scintillation counter (Wallac MicroBeta 1450).

D_2 receptor functional efficacy assay

Cells were seeded in 96 well plates at a concentration of 8000 cells/well 3 days prior to the experiment. At the day of the experiment the cells were washed once in preheated G buffer (1 mM $MgCl_2$, 0.9 mM $CaCl_2$, 1 mM IBMX in PBS) and the assay was initiated by addition of *Antagonists:* 100 µl of a mixture of 1 µM quinpirole, 10 µM forskolin and test compound in G buffer. *Agonists:* 100 µl of a mixture of 10 µM forskolin and test compound in G buffer. The cells were incubated 20 minutes at 37 °C and the reaction was stopped by the addition of 100 µl S buffer (0.1 M HCl and 0.1 mM $CaCl_2$) and the plates were placed at 4 °C for 1 hour. 68 µl N buffer (0.15 M NaOH and 60 mM NaAc) were added and the plates were shaken for 10 minutes. 60 µl of the reaction were transferred to cAMP FlashPlates (DuPont NEN) containing 40 µl 60 mM NaAc pH

6.2 and 100 µl IC mix (50 mM NaAc pH 6.2, 0.1 % NaAzid, 12 mM $CaCl_2$, 1% BSA and 0.15 µCi/ml ^{125}I-cAMP) were added. Following an 18-hour incubation at 4 °C the plates were washed once and counted in a Wallac TriLux counter.

5-HT_{2C} receptor binding affinity assay

Cell culture and transient transfections. The tsA-201 cells were maintained at 37 °C in a humidified 5% CO_2 incubator in culture medium [Dulbecco's Modified Eagle Medium supplemented with penicillin (100 U/ml), streptomycin (100 mg/ml) and 10 % fetal bovine serum]. The cells were split into 10 cm tissue culture dishes and the following day transfected with 5-HT_{2C}-pcDNA3.1 using PolyFect® (Qiagen, West Sussex, UK) as a DNA carrier according to the manufacturer's protocol. 16-24 h later the culture medium were changed and 40-48 h after transfection the cells were used for the binding assay.

[^{3}H]Mesulergine Binding. Competition binding to membranes of tsA201 cells transiently expressing the human 5-HT_{2C} receptor using [^{3}H]mesulergine ([*N*^{6}-methyl-^{3}H]mesulergine, 74.0 Ci/mmol, GE Healthcare, Buckinghamshire, UK) was performed essentially as reported previously.[2] Cells were harvested and scraped into assay buffer [50 mM Tris-HCl (pH 7.4)], homogenized using a polytron for 10 sec and centrifuged for 20 min at 50.000 × *g*. Cell pellets were resuspended in fresh assay buffer, homogenized and centrifuged at 50.000 × *g* for another 20 min. Then the cell pellet were resuspended in assay buffer, and the cell membranes were incubated with 0.5 nM [^{3}H]mesulergine in the presence of various concentrations of compounds in total assay volumes of 800 µl. Nonspecific binding was determined in reactions with 10 µM mianserin. The reactions were incubated for 1 h at 37 °C. Whatman GF/C filters were presoaked for 1 h in a 0.2 % polyethyleneimine solution, and binding was terminated by filtration through these filters using a 48-well cell harvester and washing with 3 × 4 ml ice-cold isotonic NaCl solution. Following this, the filters were dried, 3 ml Opti-Fluor™ (Packard) was added, and the amount of bound radioactivity was determined in a scintillation counter. The fraction of specifically bound radioligand was always <5% of the total amount of radioligand. The binding experiments were performed at least three times for each compound.

5-HT_6 receptor binding affinity assay

Cell culture and transient transfections. The BHK cells were maintained at 37 °C in a humidified 5% CO_2 incubator in culture medium [Dulbecco's Modified Eagle Medium supplemented with penicillin (100 U/ml), streptomycin (100 µg/ml) and 10 % FetaClone1 serum]. The cells were split into 14 cm tissue culture dishes and the following day transfected with h5HT_6-pCR4-TOPO (Guthrie HTR0600000-01) using Lipofectamine 2000® (InVitrogen, Carlsbad, CA) as a DNA carrier according to the manufacturer's protocol. 4-6 h later the culture medium was changed. Cells were grown to 90-95% confluence, and harvested using a cell scraper.

[^{3}H]LSD Binding. Competition binding to membranes of BHK-h5HT$_6$ cells transiently expressing the human 5-HT$_6$ receptor using [^{3}H]LSD ([*N*-methyl-^{3}H]Lysergic acid deithylamide, 81.0 Ci/mmol, GE Healthcare, Buckinghamshire, UK) was performed. Cells were harvested and scraped into d-PBS, homogenized using an UltraTurrax for 20 sec, centrifuged 40 min at 40000 x g and frozen. Cell pellets were resuspended in fresh assay buffer (50 mM TRIS, pH = 7.7), and the cell membranes were incubated with 1.0 nM [^{3}H]LSD in the presence of various concentrations of compounds in total assay volumes of 200 µl. Nonspecific binding was determined in reactions with 10 µM LU25103. The reactions were incubated for 60 min at RT. Whatman GF/B filters were presoaked for 30 min in a 0.5 % polyethyleneimine solution, and binding was terminated by filtration through these filters using a 96-well cell harvester and washing with 2 × 0,5 ml ice-cold TRIS, pH = 7.7. Following this, the filters were dried, 50 µl OptiPhase SuperMix™ (Perkin Elmer) was added, and the amount of bound radioactivity was determined in a scintillation counter (Wallac MicroBeta 1450). The fraction of specifically bound radioligand was always <5% of the total amount of radioligand.

D_2 receptor functional efficacy assay

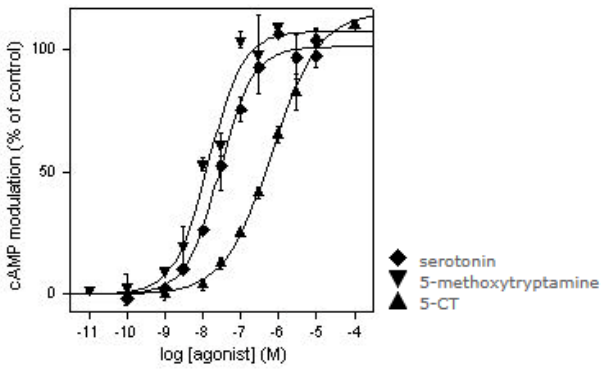
The functional data was purchased and performed by CEREP. The assays were setup and performed as previously described in the literature.[3]

cellular assay

5-HT6 (agonist effect)

Ref. 1627

Standard Turnaround Time	15 days
Source	human recombinant (CHO cells)
Stimulant	none (10 µM serotonin for control)
Measured component	cAMP
Incubation	30 min/37°C
Detection method	HTRF
Reference:	serotonin (EC_{50}:55 nM)

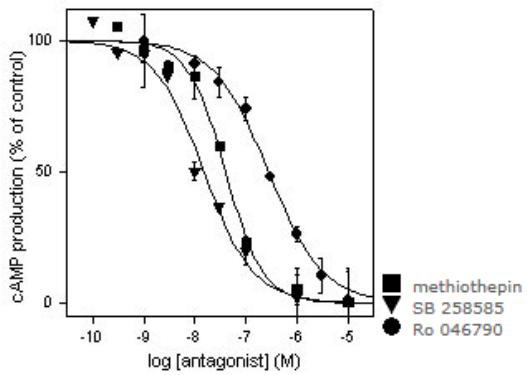


cellular assay

5-HT6 (antagonist effect)

Ref. 1628

Standard Turnaround Time	15 days
Source	human recombinant (CHO cells)
Stimulant	serotonin
Stimulant concentration	300 nM
Measured component	cAMP
Incubation	30 min/37°C
Detection method	HTRF
Reference:	methiothepin (IC_{50}:10.7 nM)



PHARMACOKINETICS

General methods:

Microsomal Stability Determination

Microsomal intrinsic clearance was determined by assessing the elimination of test compound over the incubation time. The test compounds were incubated at 1 µM with human liver microsomes (BD Biosciences) for 60 min, using NADPH as cofactor. An NADPH regenerating system containing NADP+, glucose-6-phosphate dehydrogenase, glucose-6-phosphate, sodium citrate, and $MgCl_2$ (cofactor mix) was used as a source of NADPH. The microsomes were stored at −80 °C, and test tubes with prepared cofactor mix were stored in the freezer until use. Human liver microsomes were thawed at room temperature, and cofactor mix was added. The mixture was vortex mixed and put in a water bath at 37 °C for 10 min. The reaction was initiated by adding test compound (final concentration 1 µM, 0.5 mg of protein/mL). The samples were was incubated for 0, 5, 15, 30, and 60 min, and the reactions were stopped by adding 100 µL of acetonitrile and transferred to a 96 well stop plate. The stop plates were centrifuged for 10 min at 3300 rpm and 4 °C, before being analyzed by liquid-chromatography coupled to a tandem mass spectrometer (LC-MS/MS, Waters QuattroMicro, Manchester, UK). Reference litterature.[4]

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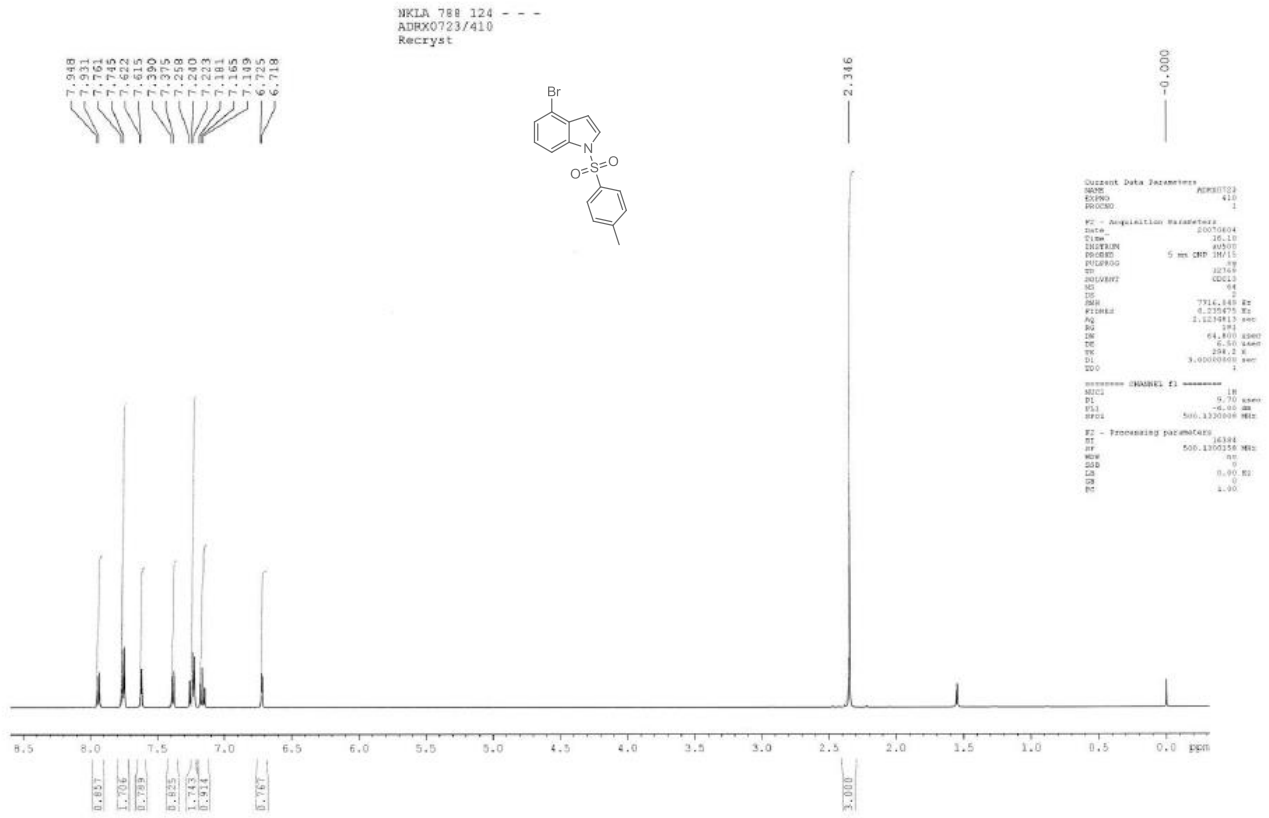
(4) Obach R. S; The prediction of human clearance from hepatic microsomal metabolism data. *Curr. Opin. Drug Discov. Devel.* **2001**, *4*, 36-44.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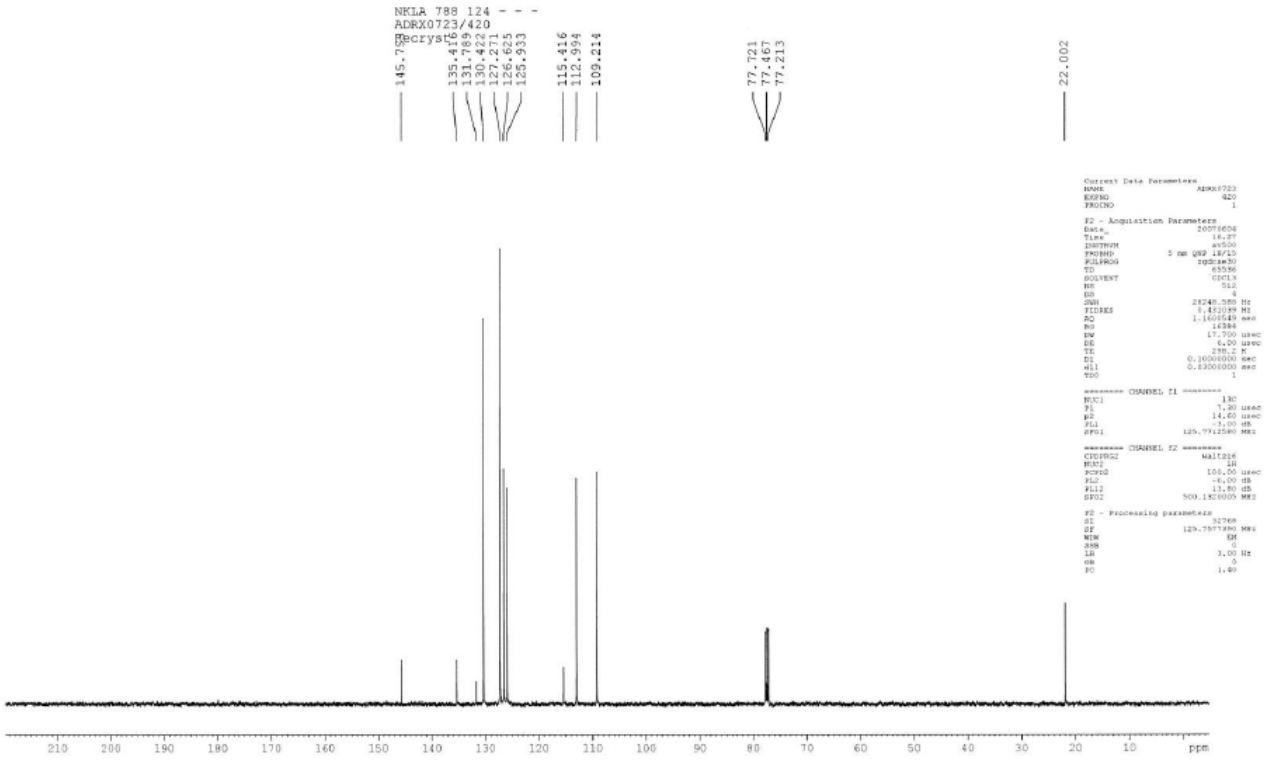
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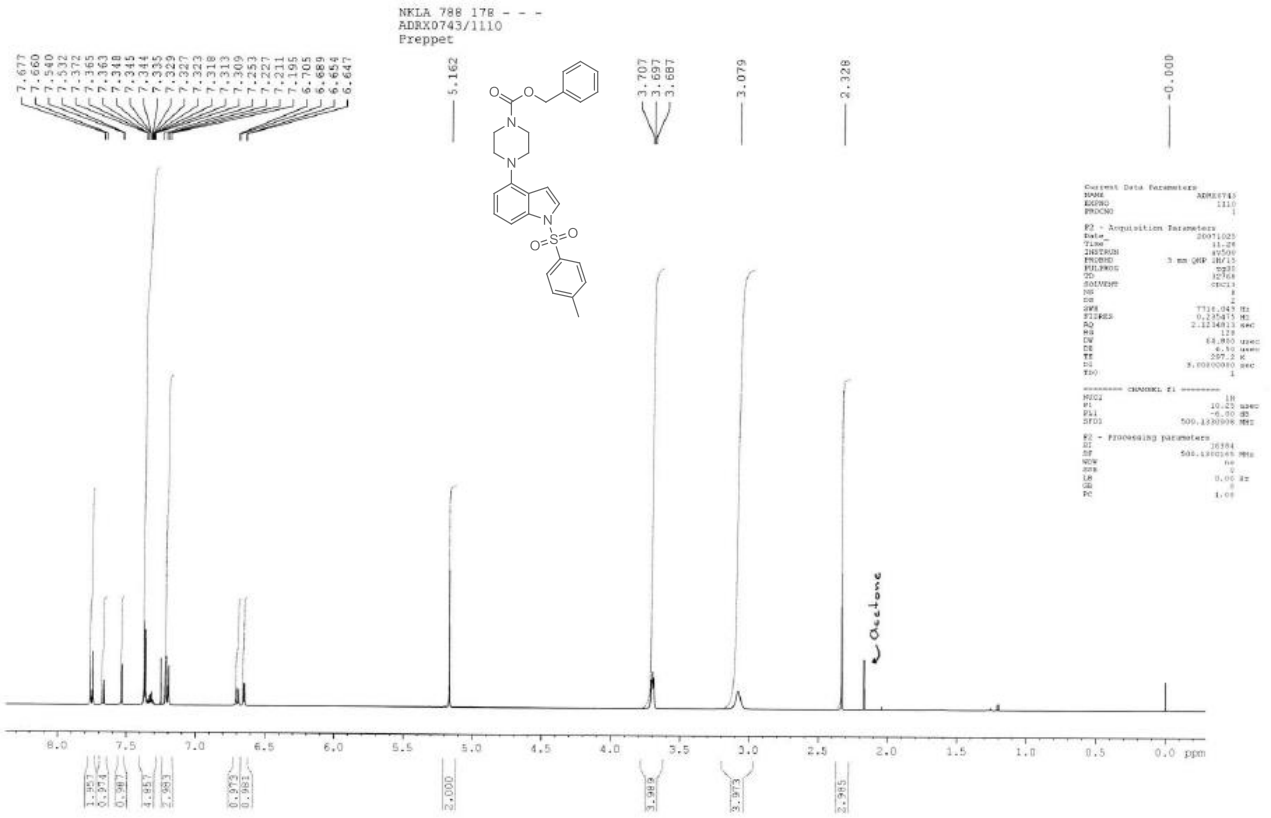
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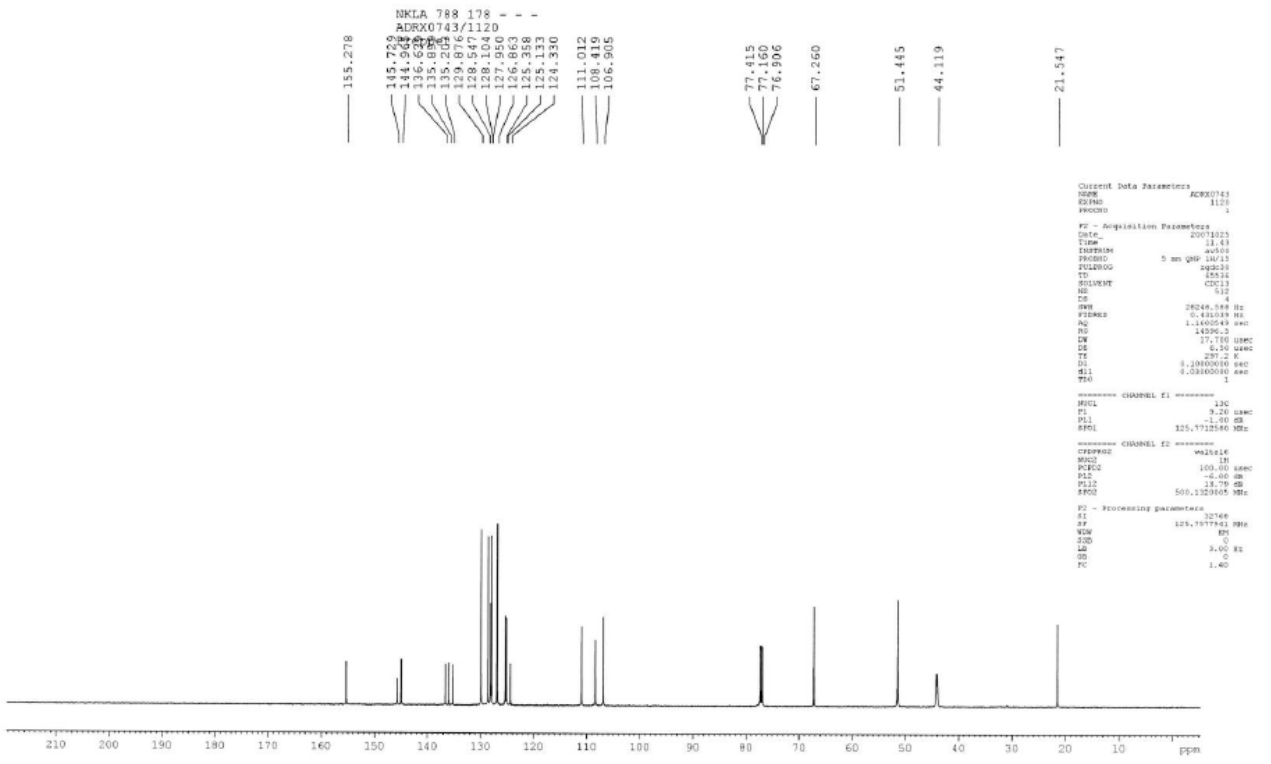
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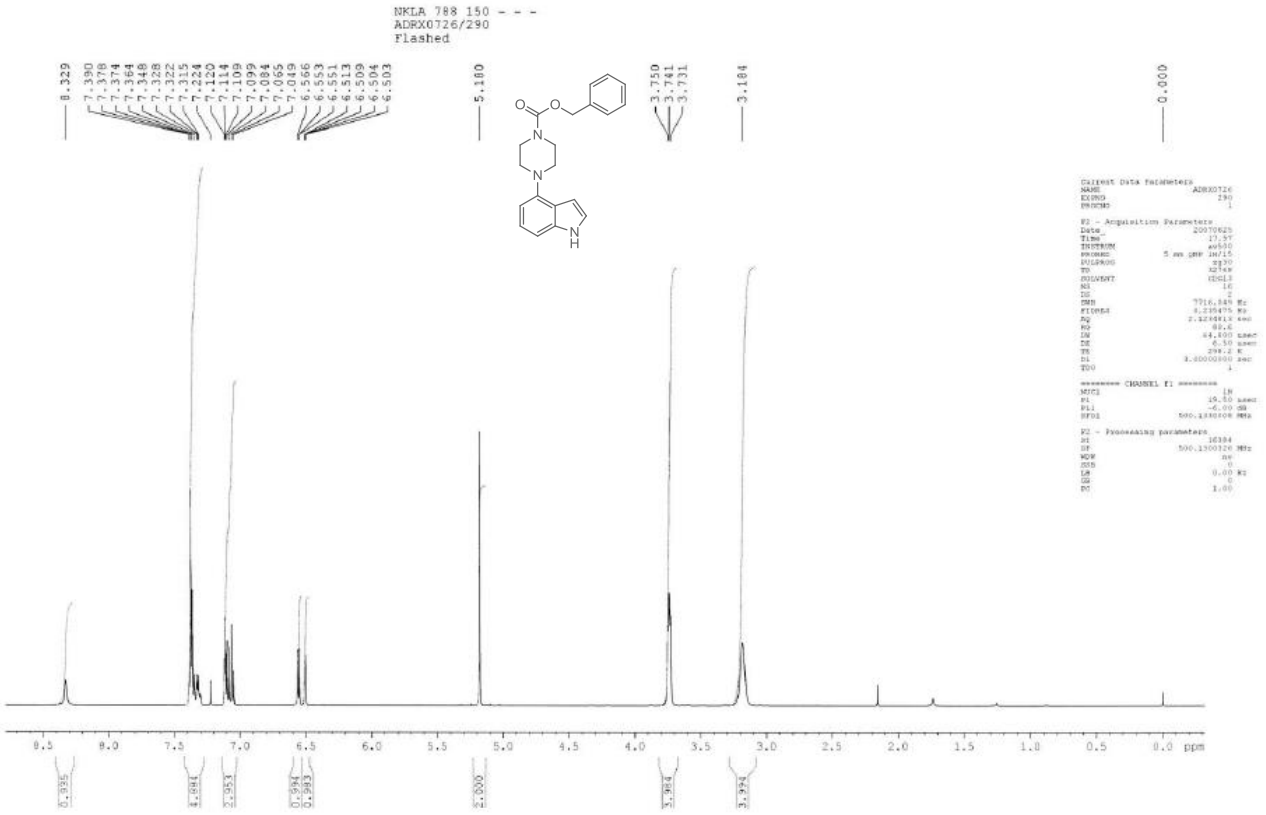
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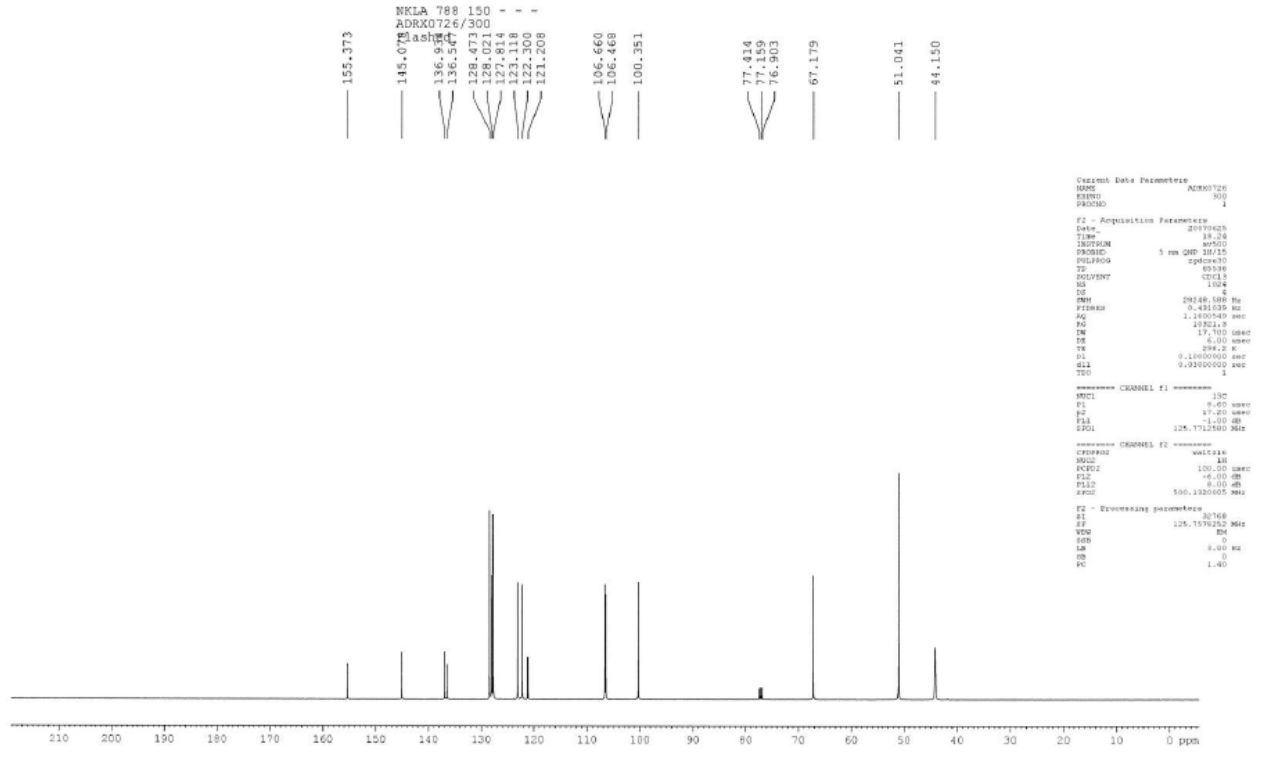
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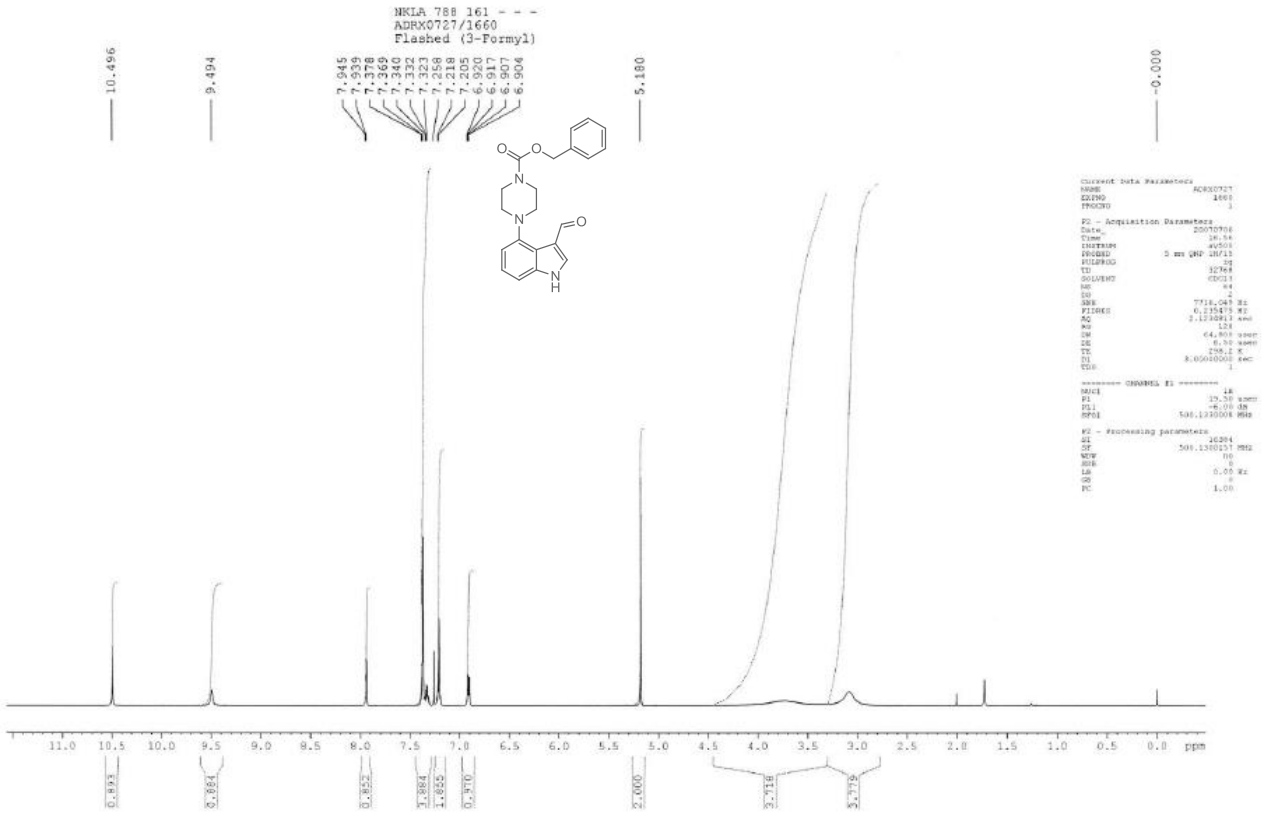
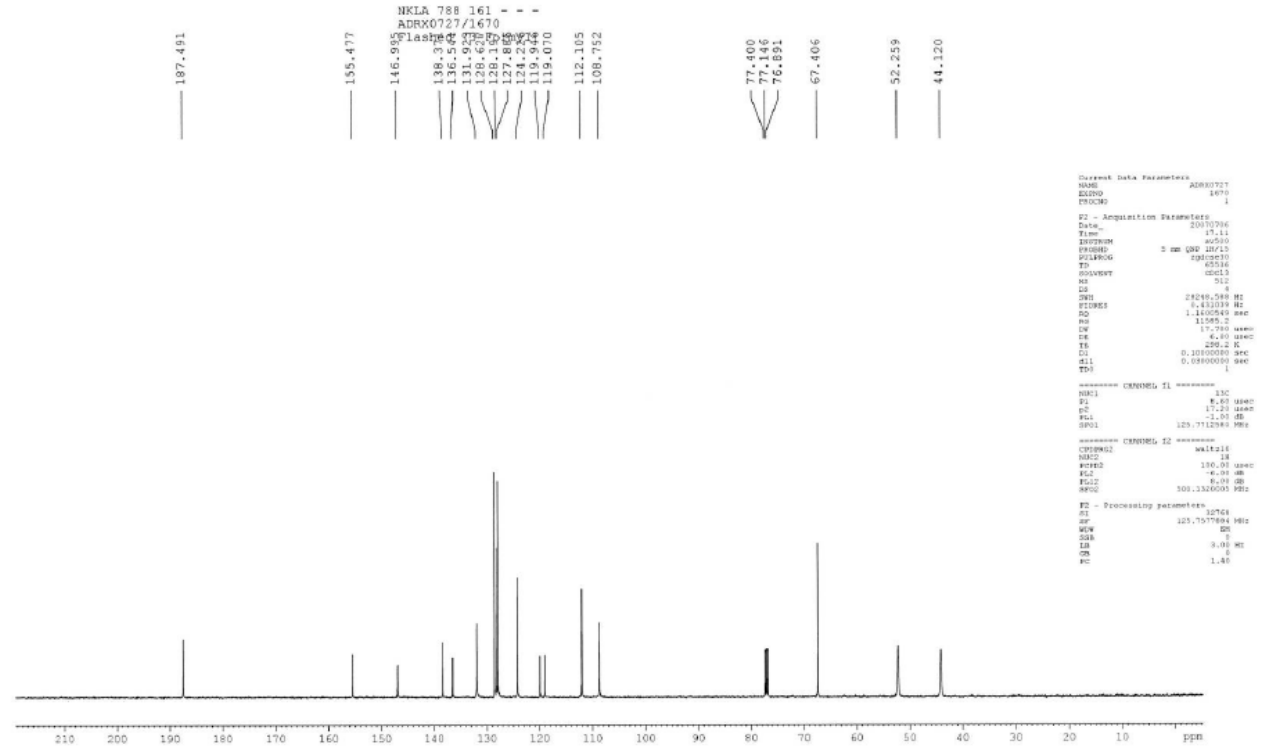
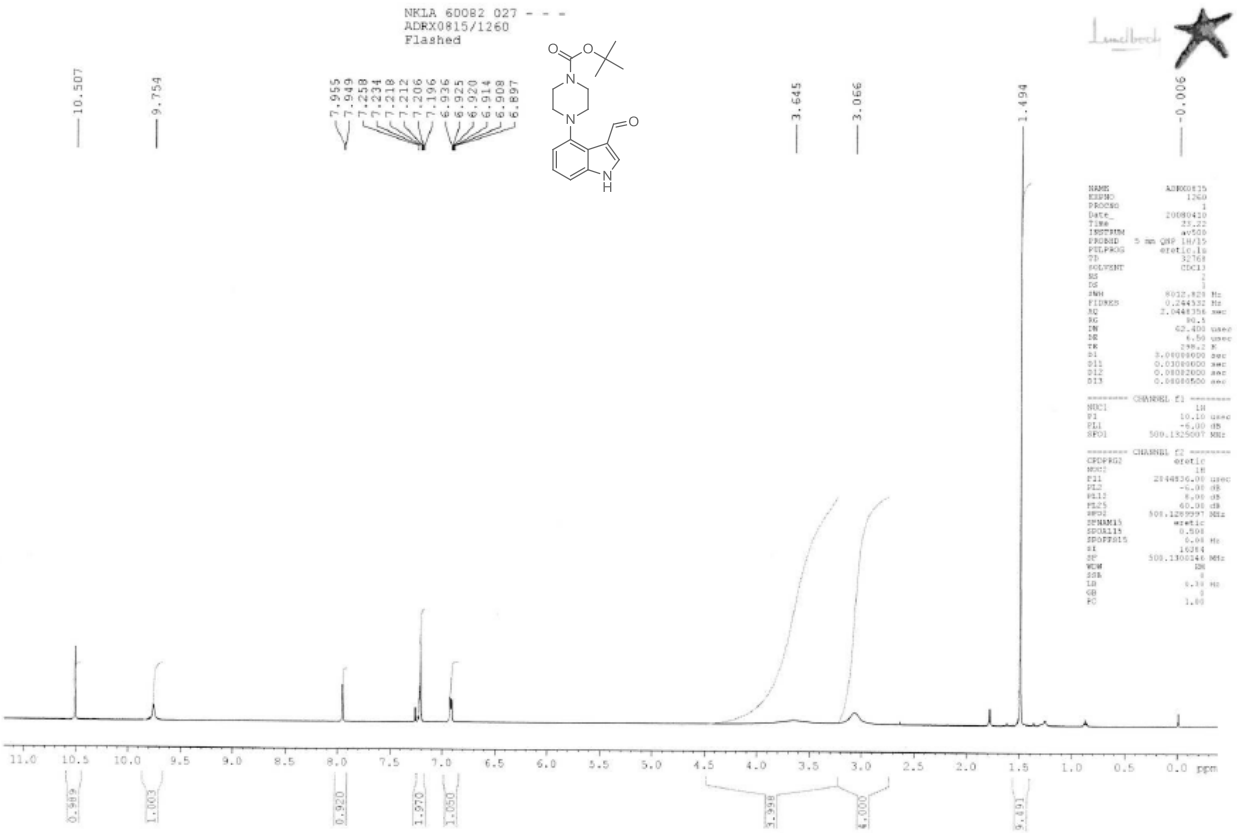
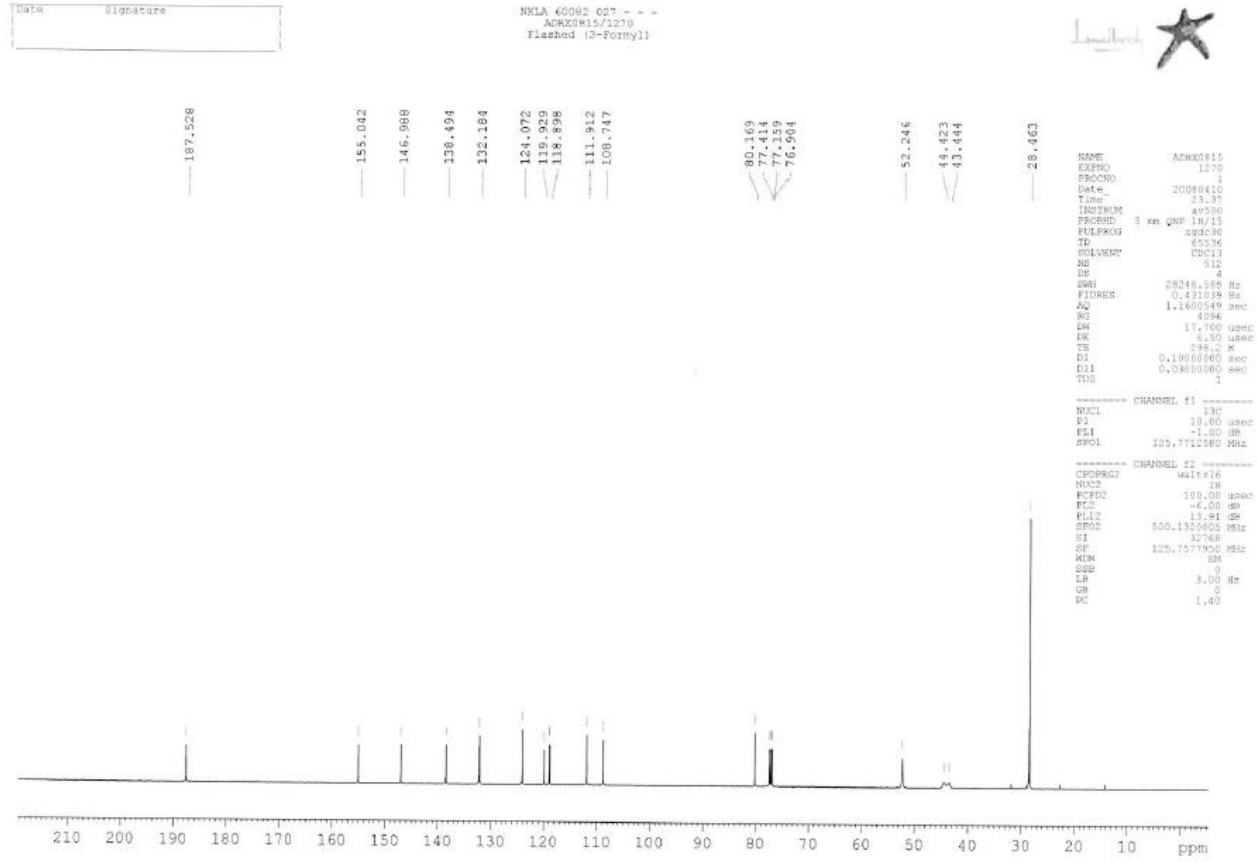
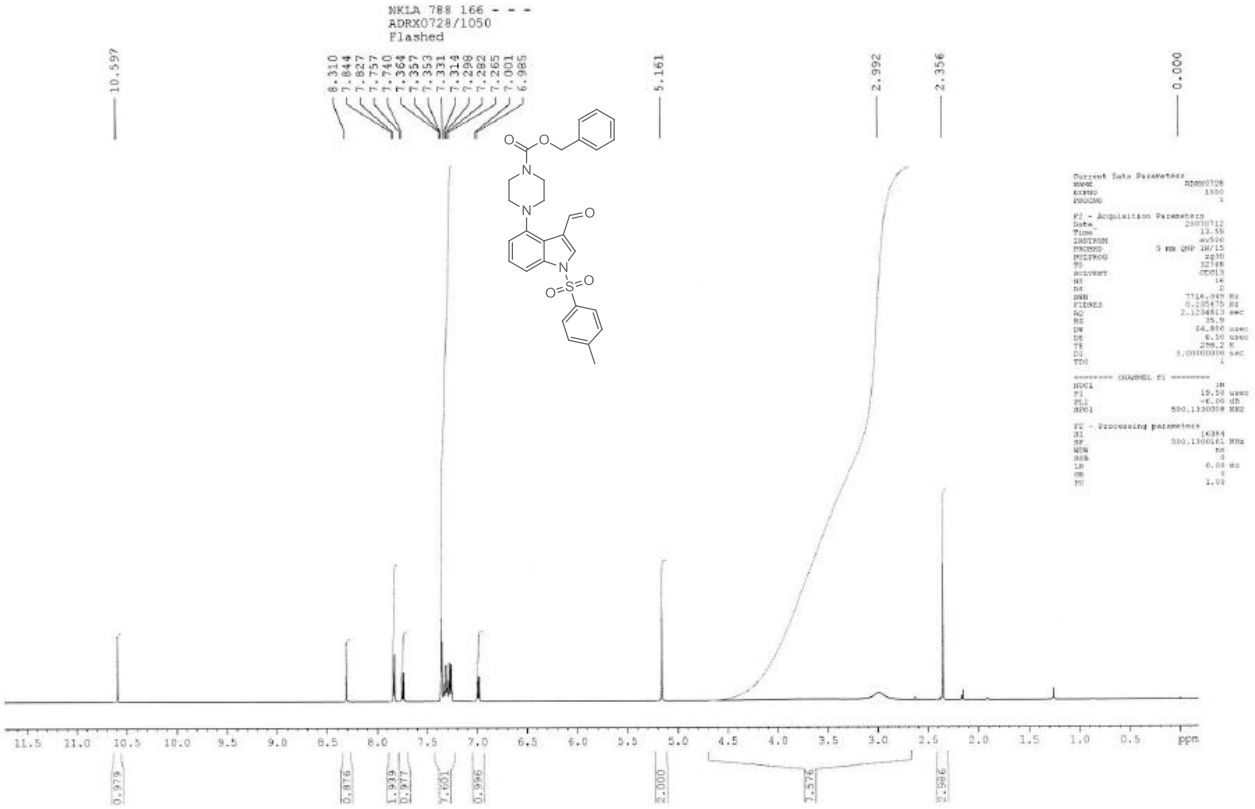
10
0 ppm

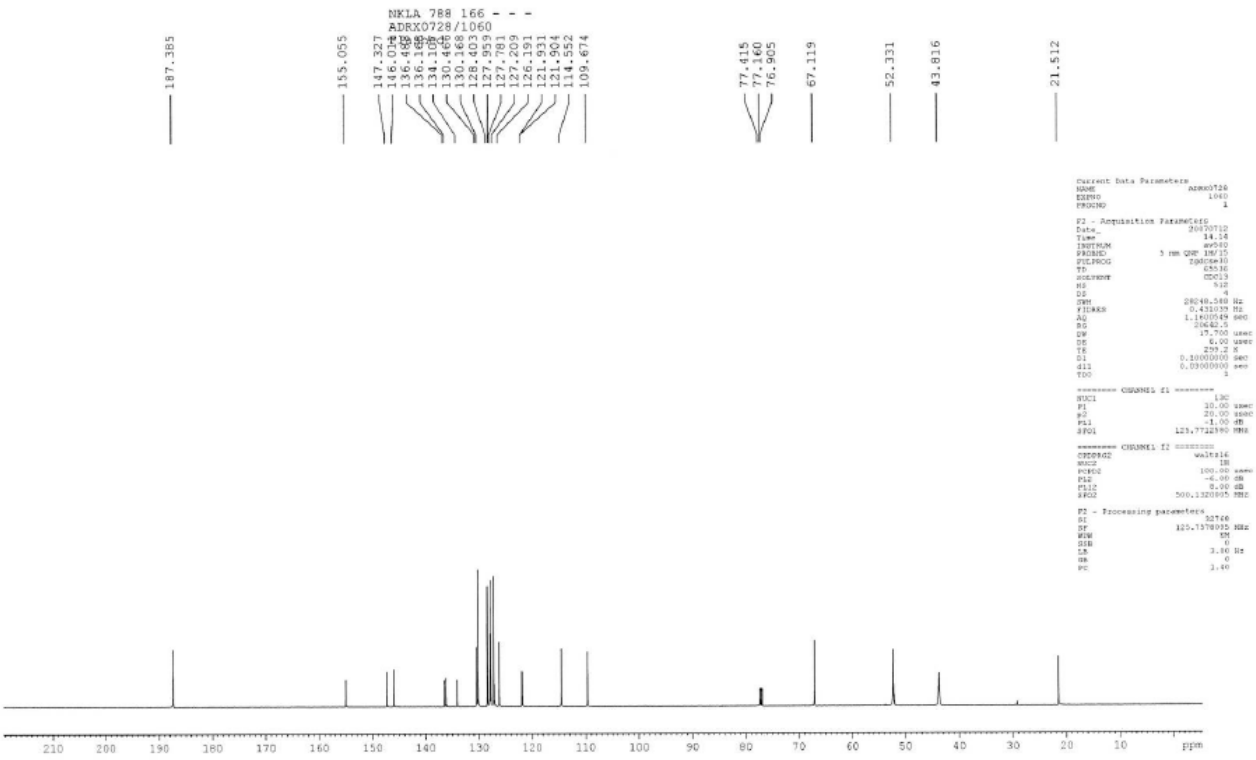

NKLA 788 161 - - -
ADRX0727/1660
Flashed (3-Formyl)
10.496
9.494
7.945
7.939
7.378
7.369
7.340
7.332
7.323
7.268
7.265
6.917
6.907
6.906
5.180
-0.000
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.893
0.884
0.852
1.884
1.656
0.970
2.000
3.718
3.779

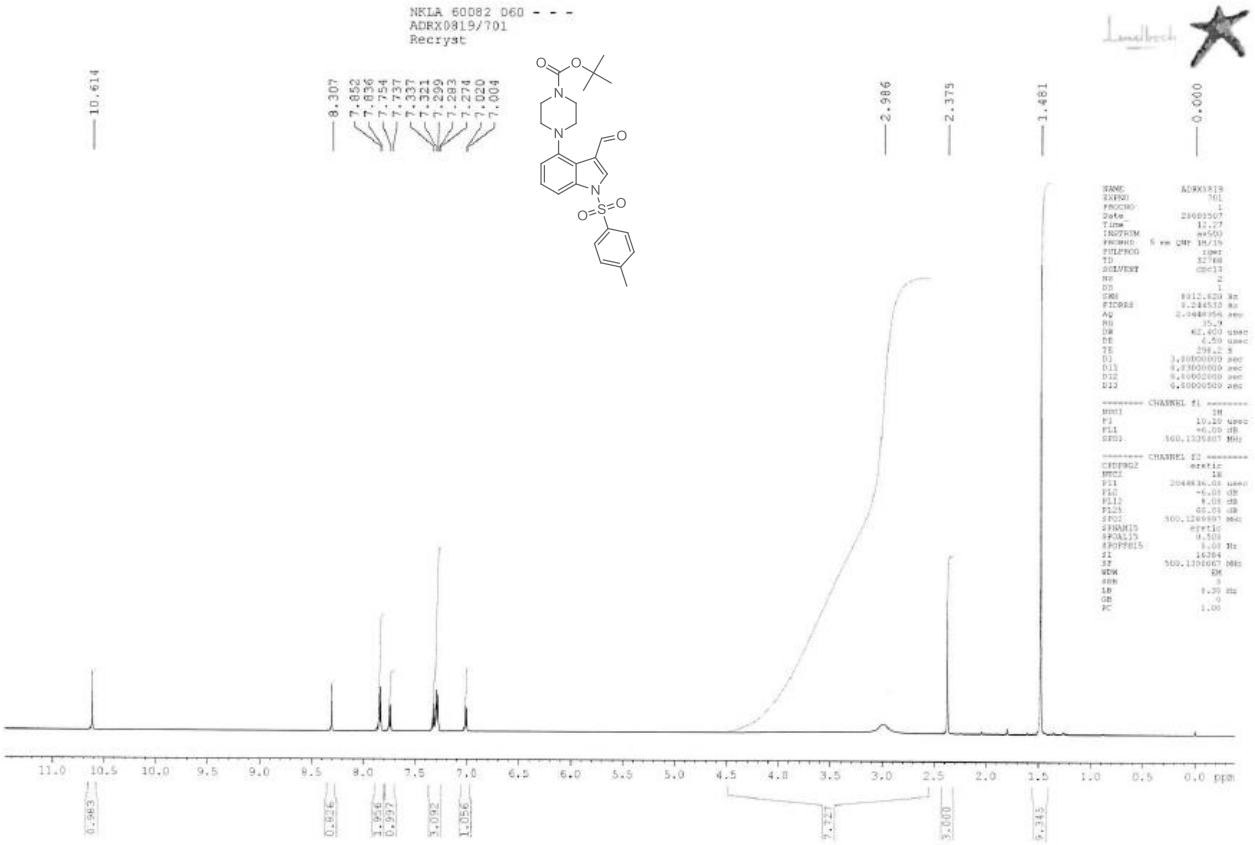

NKLA 788 161 - - -
ADRX0727/1670
187.491
155.477
146.905
138.3
136.5
131.9
128.6
128.1
127.8
124.2
119.9
119.0
112.105
108.752
77.400
77.146
76.891
67.406
52.259
44.120
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


NKLA 60082 027 - - -
ADRX0815/1260
Flashed
10.507
9.754
7.955
7.949
7.258
7.234
7.218
7.212
7.206
7.196
6.936
6.925
6.920
6.914
6.908
6.897
3.645
3.066
1.494
-0.006
0.989
1.003
0.920
1.970
1.050
3.998
4.000
9.491
ppm

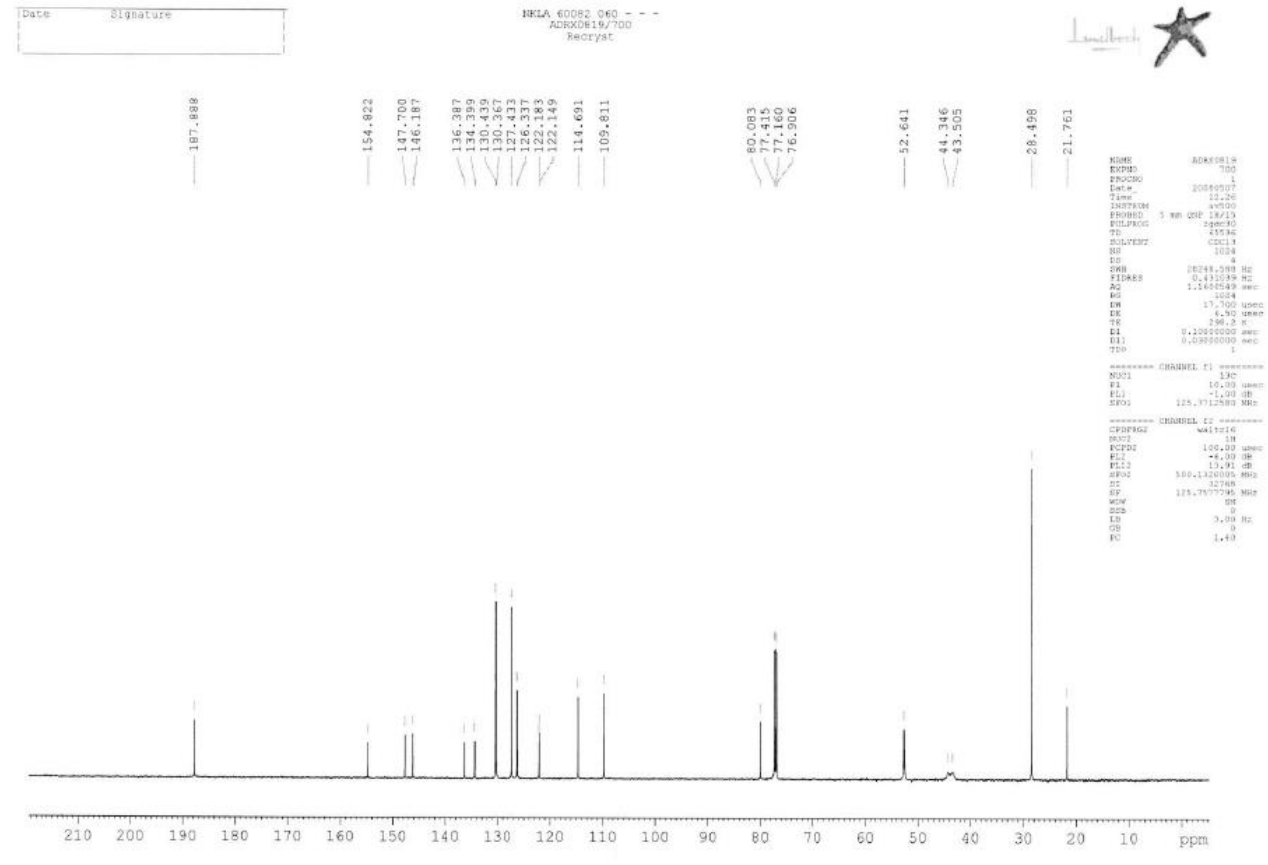

Date Signature
NKLA 60082 027 - - -
ADRX0815/1270
Flashed (3-Formyl)
187.528
155.042
146.988
130.494
132.180
124.072
119.929
118.898
111.912
108.747
80.169
77.414
77.159
76.904
52.246
44.423
43.444
28.463
ppm

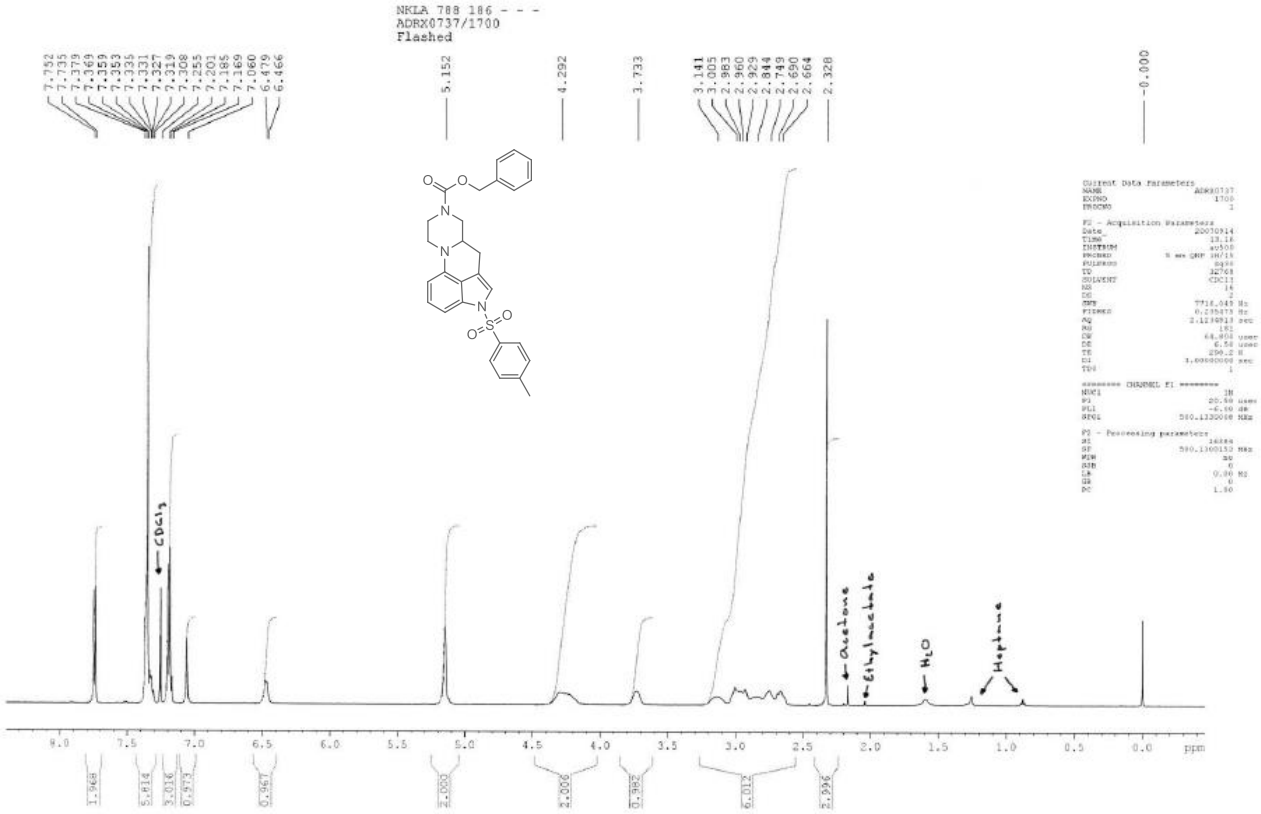

NKLA 788 166 - - -
ADRX0728/1050
Flashed
10.597
8.310
7.844
7.827
7.757
7.740
7.364
7.357
7.333
7.314
7.298
7.282
7.265
7.001
6.985
5.161
2.992
2.356
0.000
ppm

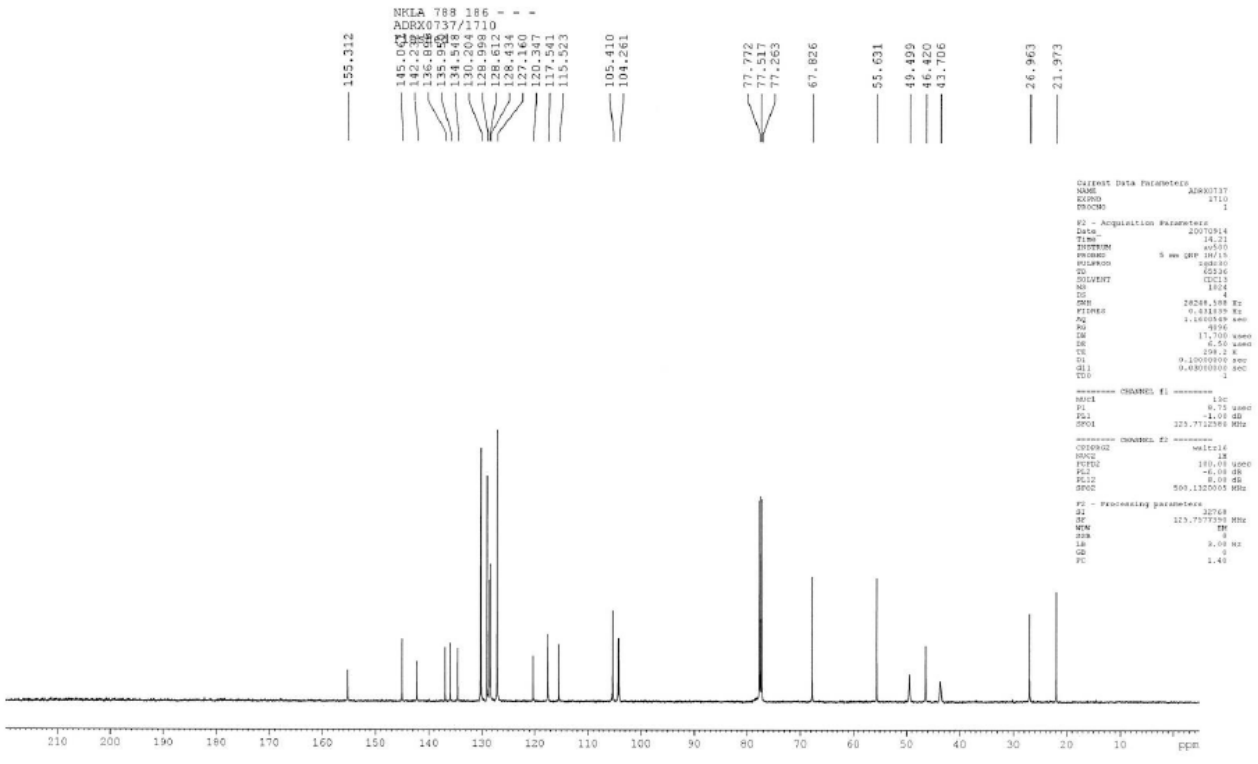

NKLA 788 166 - - -
ADRX0728/1060
187.385
155.055
147.327
136.188
134.106
130.466
130.168
128.403
127.959
127.701
127.209
126.191
121.931
121.904
114.552
109.674
77.415
77.160
76.905
67.119
52.331
43.816
21.512
ppm

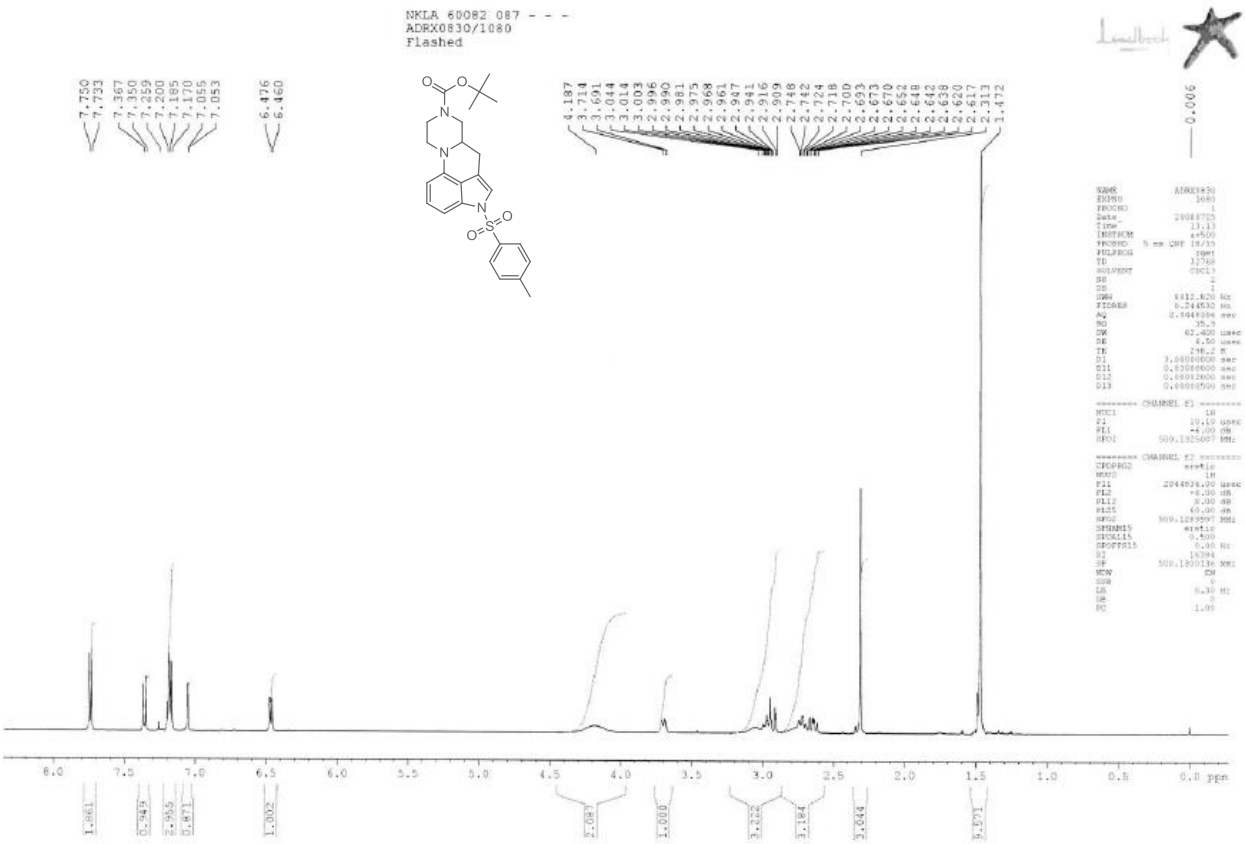


Date Signature

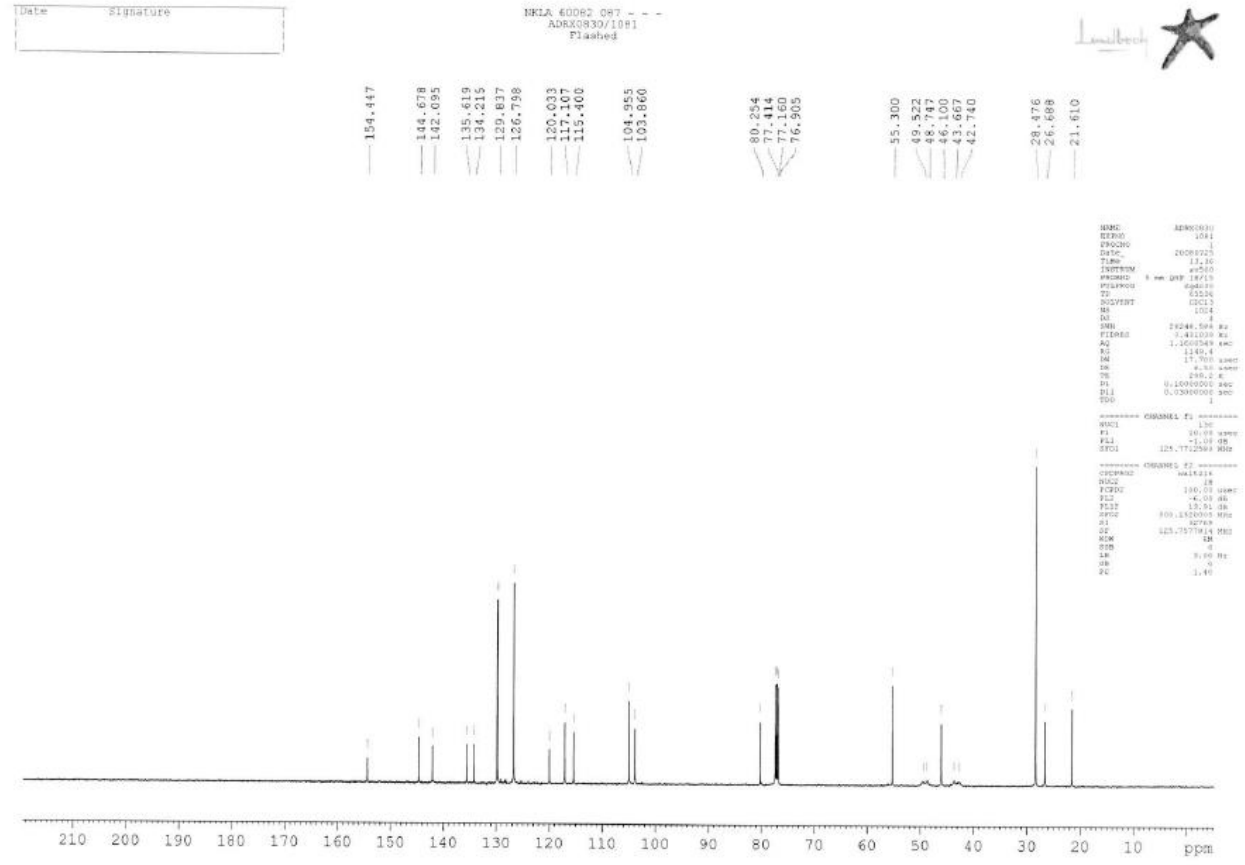


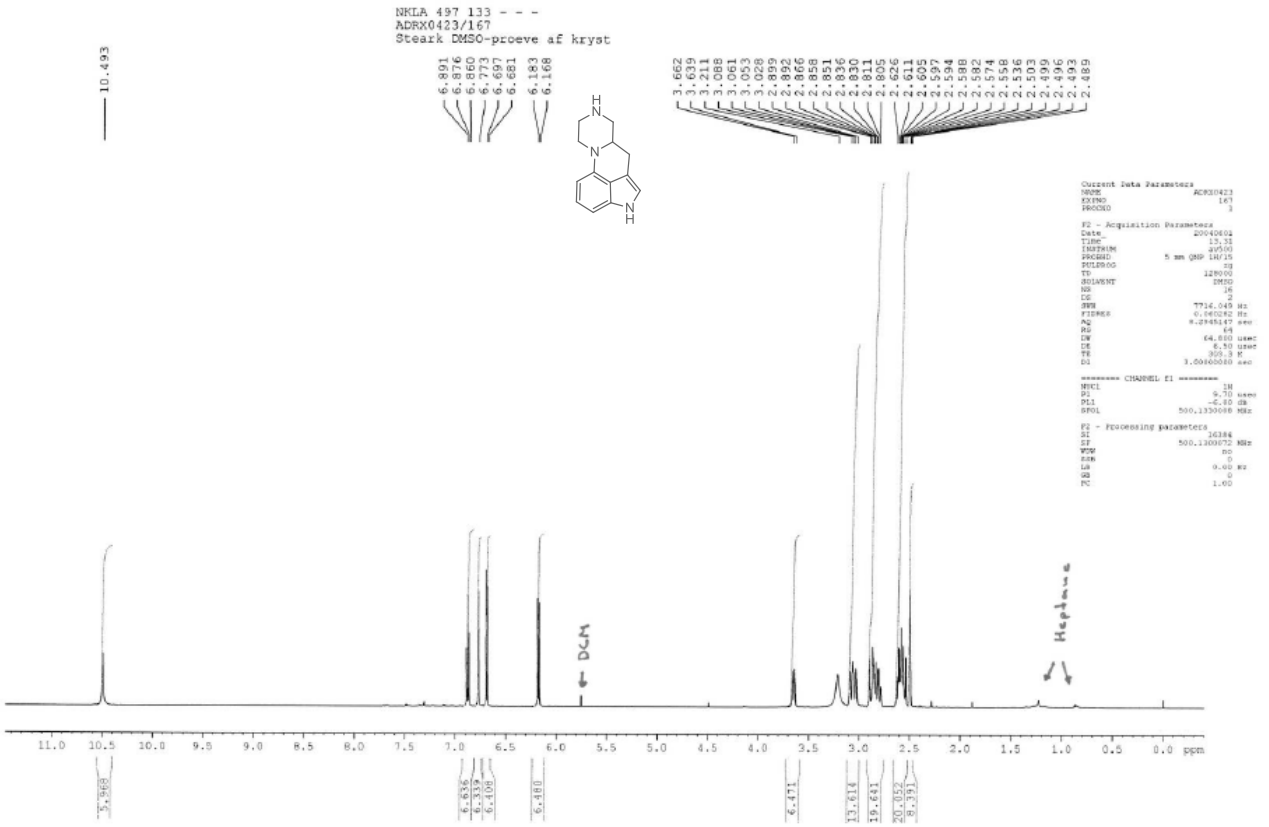

NKLA 788 186 - - -
ADRX0737/1700
Flashed
7.752
7.735
7.379
7.369
7.359
7.353
7.335
7.331
7.327
7.309
7.268
7.255
7.201
7.185
7.169
7.060
6.479
6.466
5.152
4.292
3.733
3.141
3.005
2.983
2.960
2.929
2.844
2.749
2.690
2.664
2.328
0.000
CDCl3
Acetone
Ethylacetate
H2O
Heptane
1.968
5.814
3.016
6.973
0.967
2.000
4.006
0.982
6.012
2.996
ppm

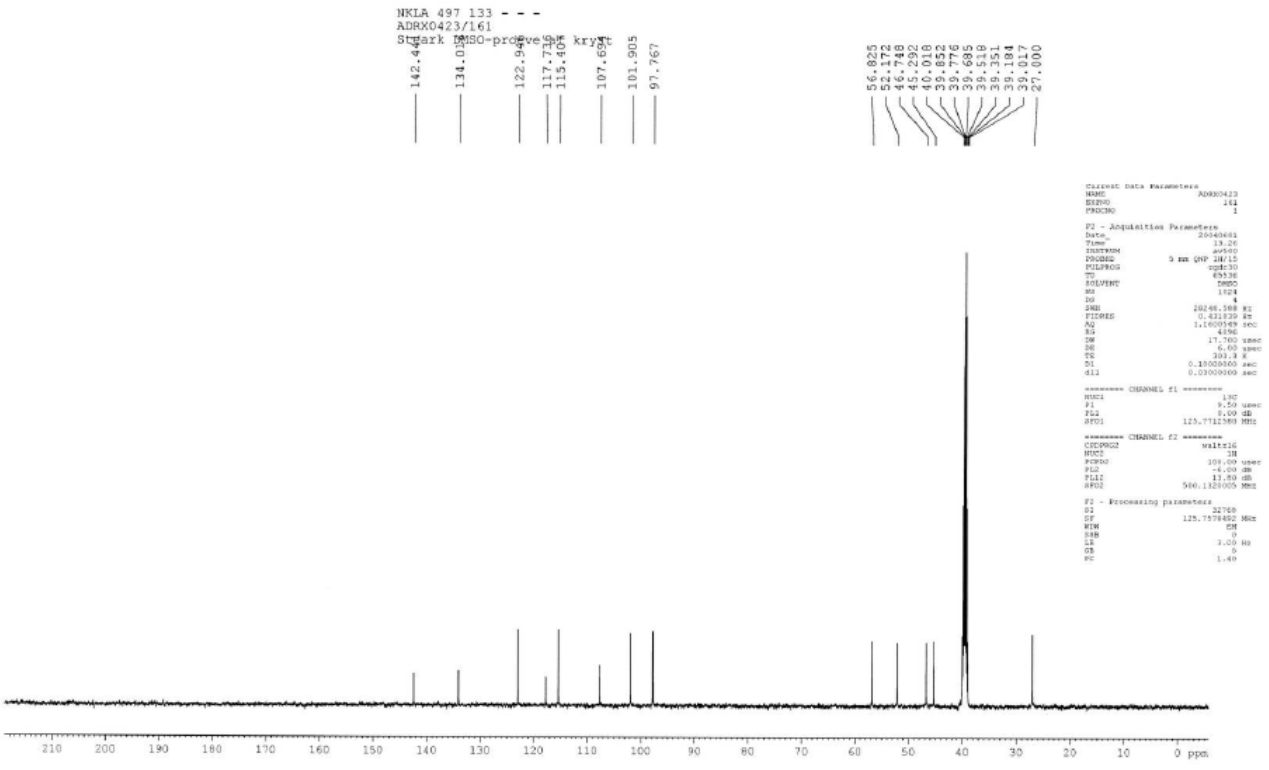

NKLA 788 186 - - -
ADRX0737/1710
155.312
145.062
142.230
136.898
135.952
134.548
130.204
128.998
128.612
128.434
127.160
120.347
117.541
115.523
105.410
104.261
77.772
77.517
77.263
67.826
55.631
49.499
46.420
43.706
26.963
21.973
ppm

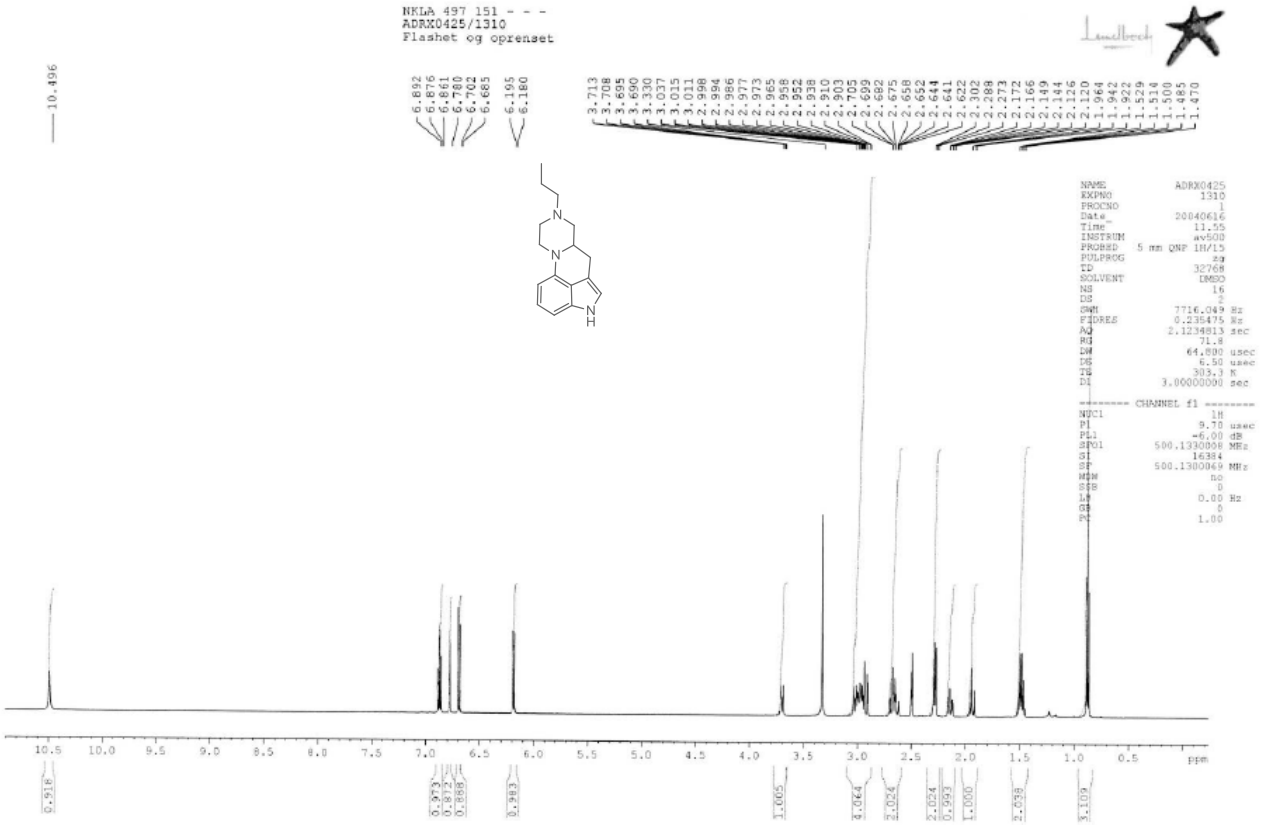


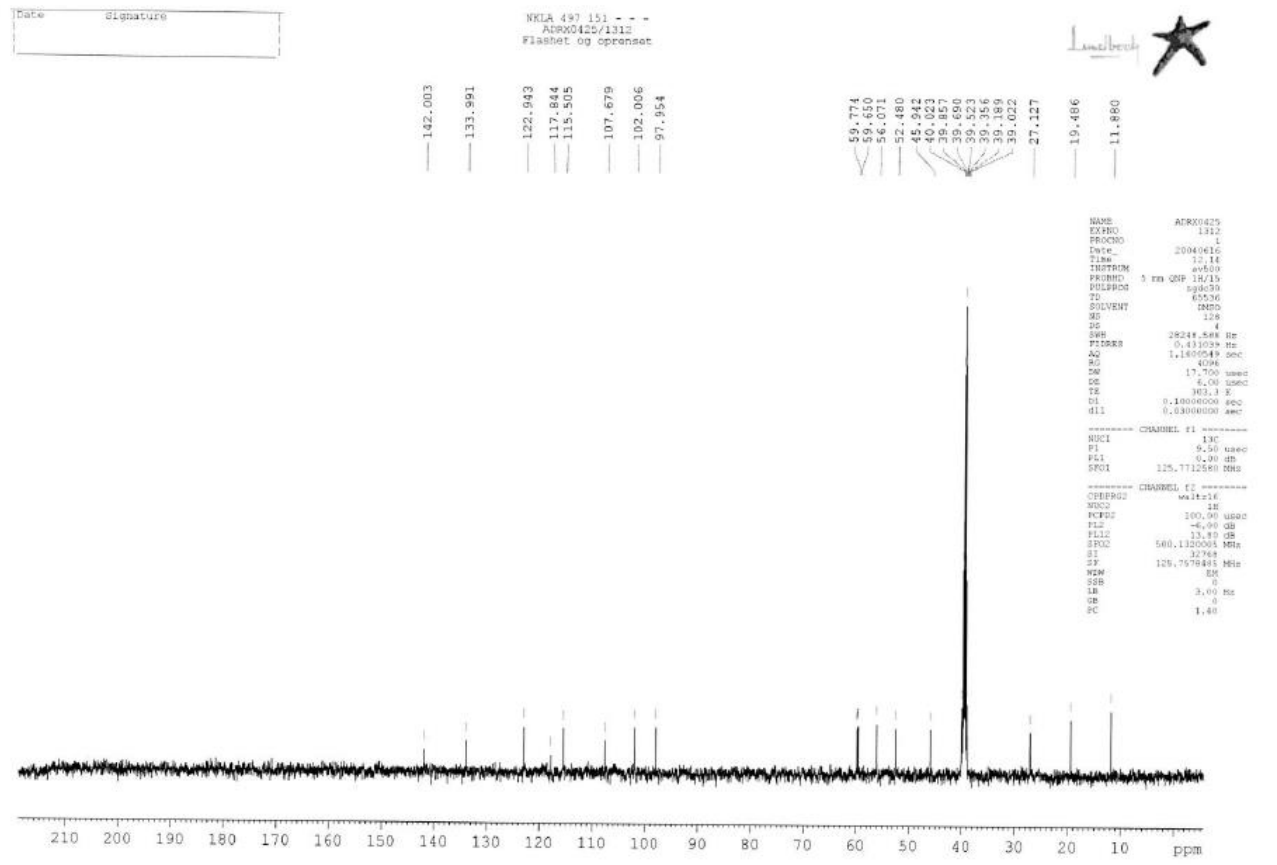
Date Signature

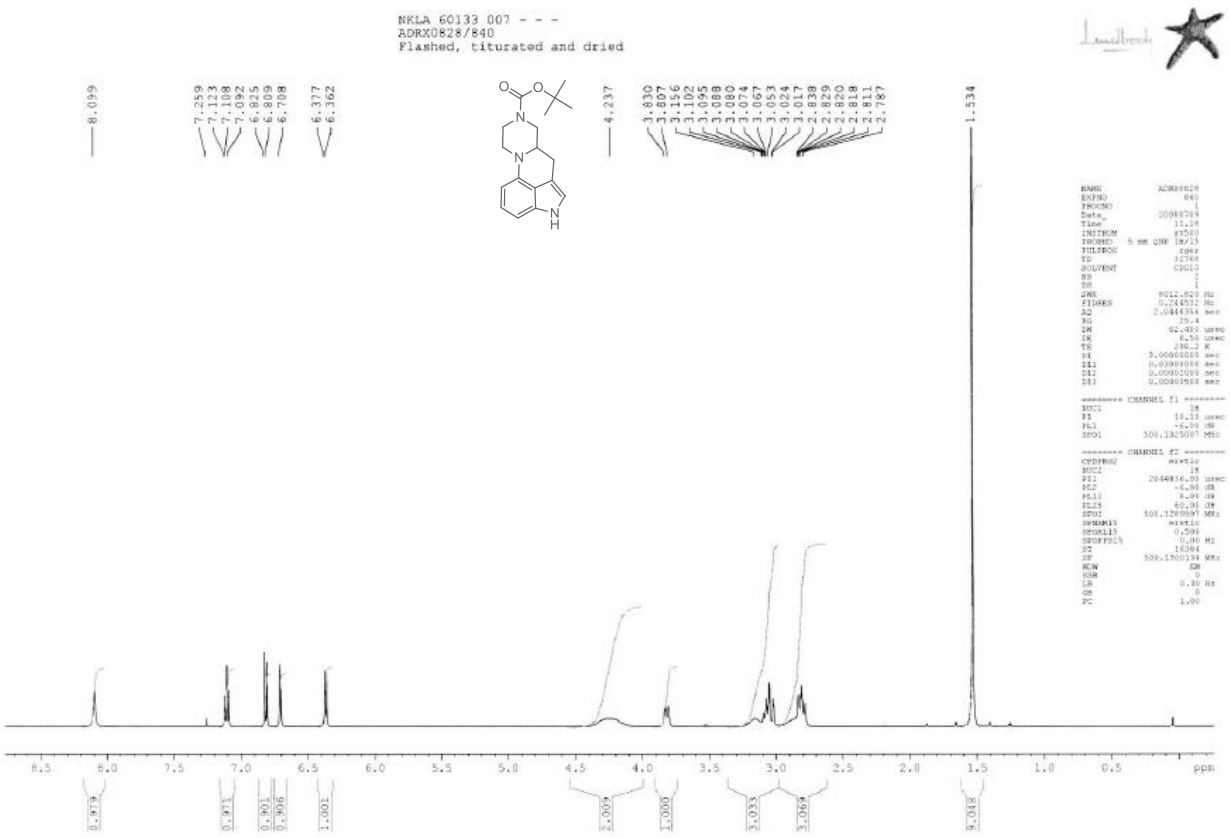


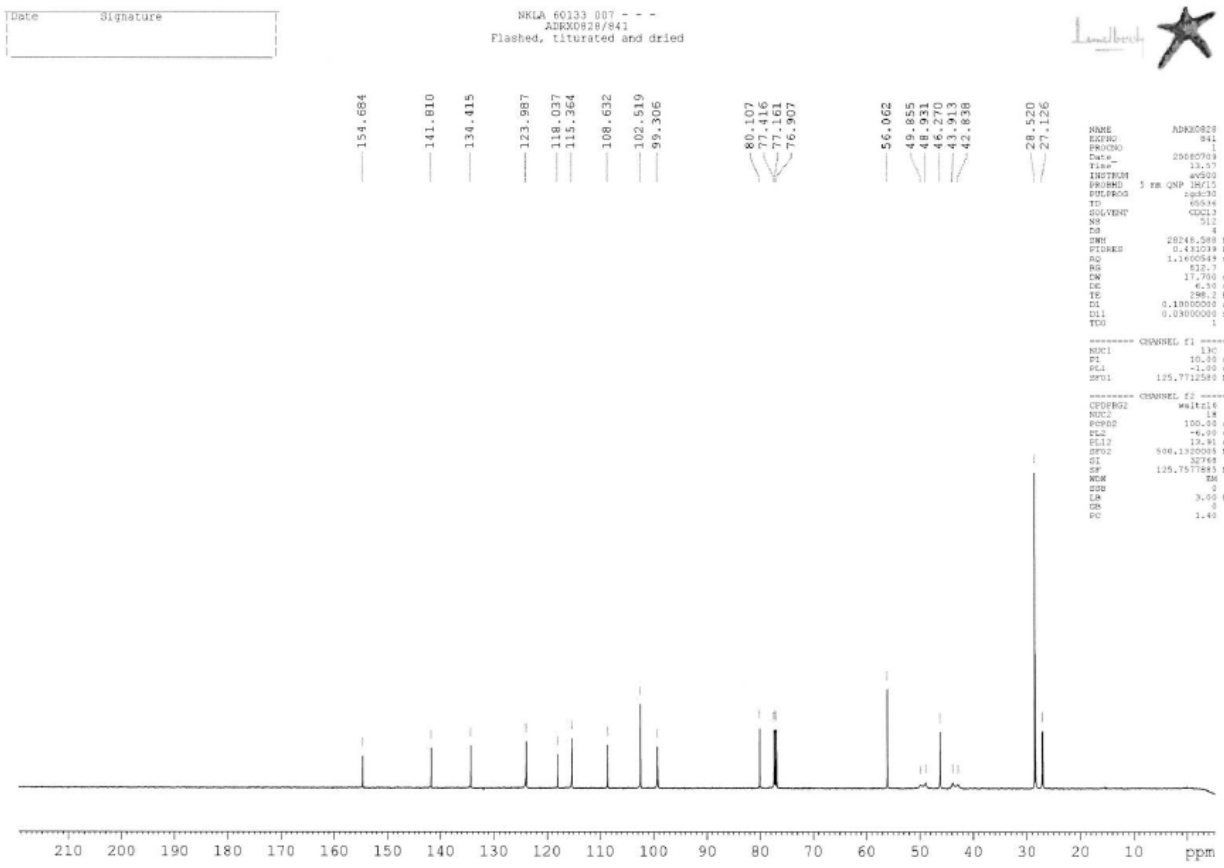

NKLA 497 133 - - -
ADRX0423/167
Steark DMSO-proeve af kryst
DCM
Heptane
ppm

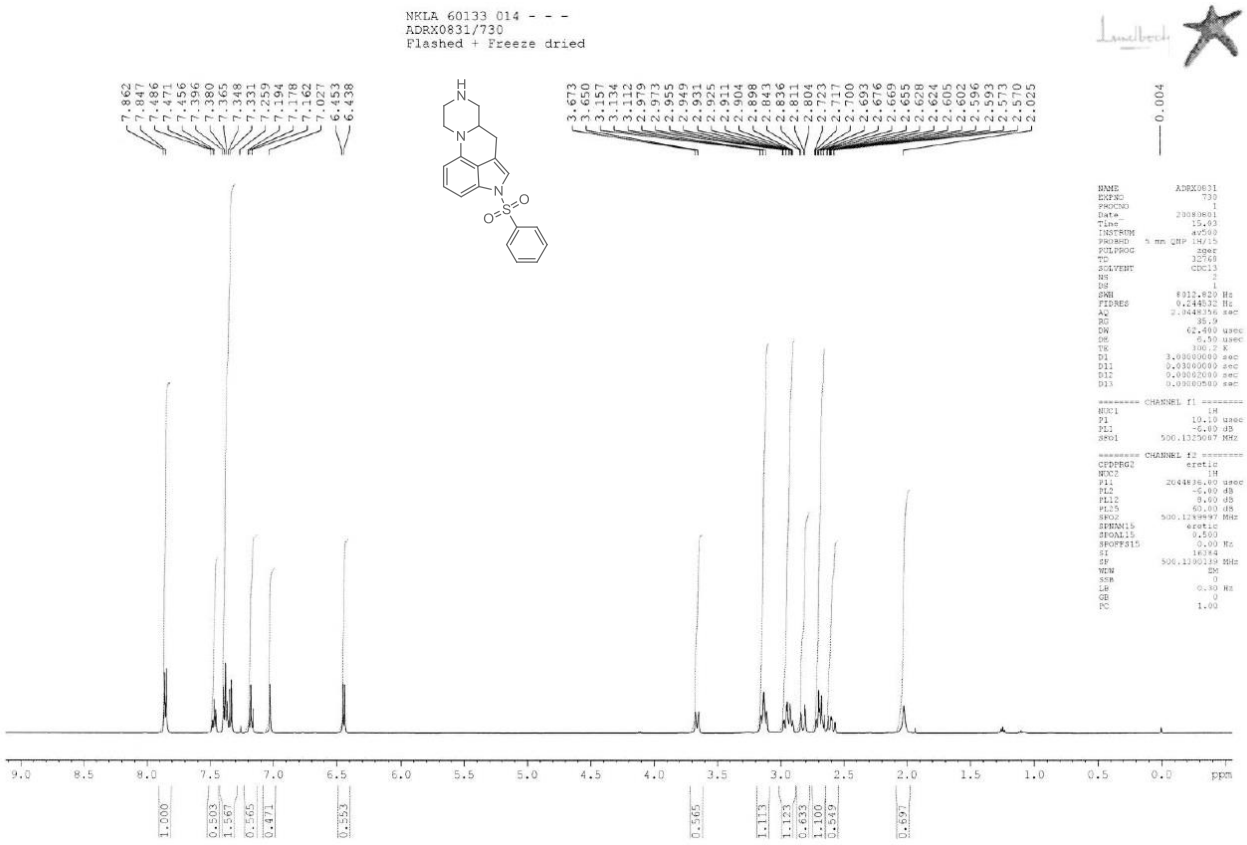

NKLA 497 133 - - -
ADRX0423/161
ppm


NKLA 497 151 - - -
ADRX0425/1310
Flashet og oprenset


Date Signature
NKLA 497 151 - - -
ADRX0425/1312
Flashet og oprenset

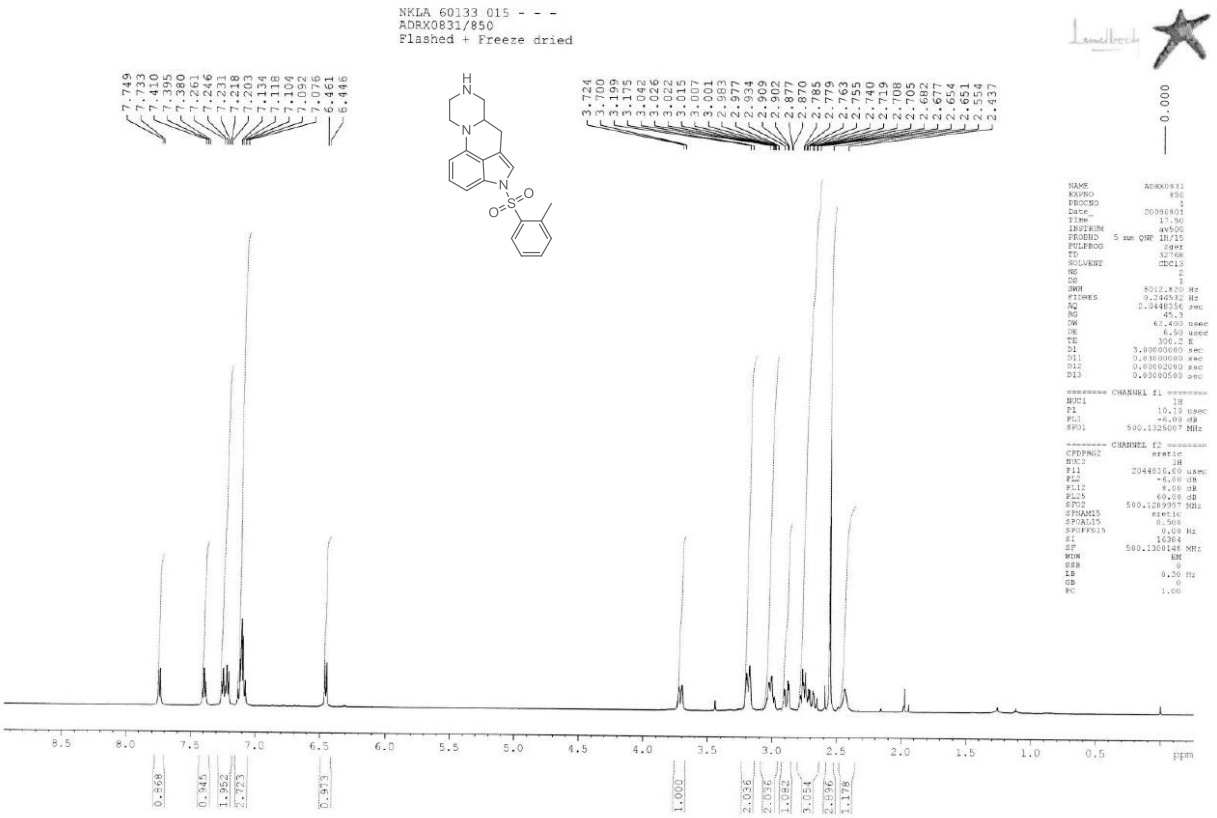

NKLA 60133 007 - - -
ADRX0828/840
Flashed, titurated and dried
8.099
7.259
7.123
7.108
7.092
6.825
6.809
6.708
6.377
6.362
4.237
3.830
3.807
3.156
3.102
3.095
3.088
3.080
3.074
3.067
3.053
3.024
3.017
2.838
2.829
2.820
2.818
2.811
2.787
1.534
0.979
0.971
0.901
0.906
1.001
2.009
1.000
3.033
3.069
9.018
ppm


Date Signature
NKLA 60133 007 - - -
ADRX0828/841
Flashed, titurated and dried
154.684
141.810
134.415
123.987
118.037
115.364
108.632
102.519
99.306
80.107
77.416
77.161
76.907
56.062
49.855
48.931
46.270
43.913
42.838
28.520
27.126
ppm

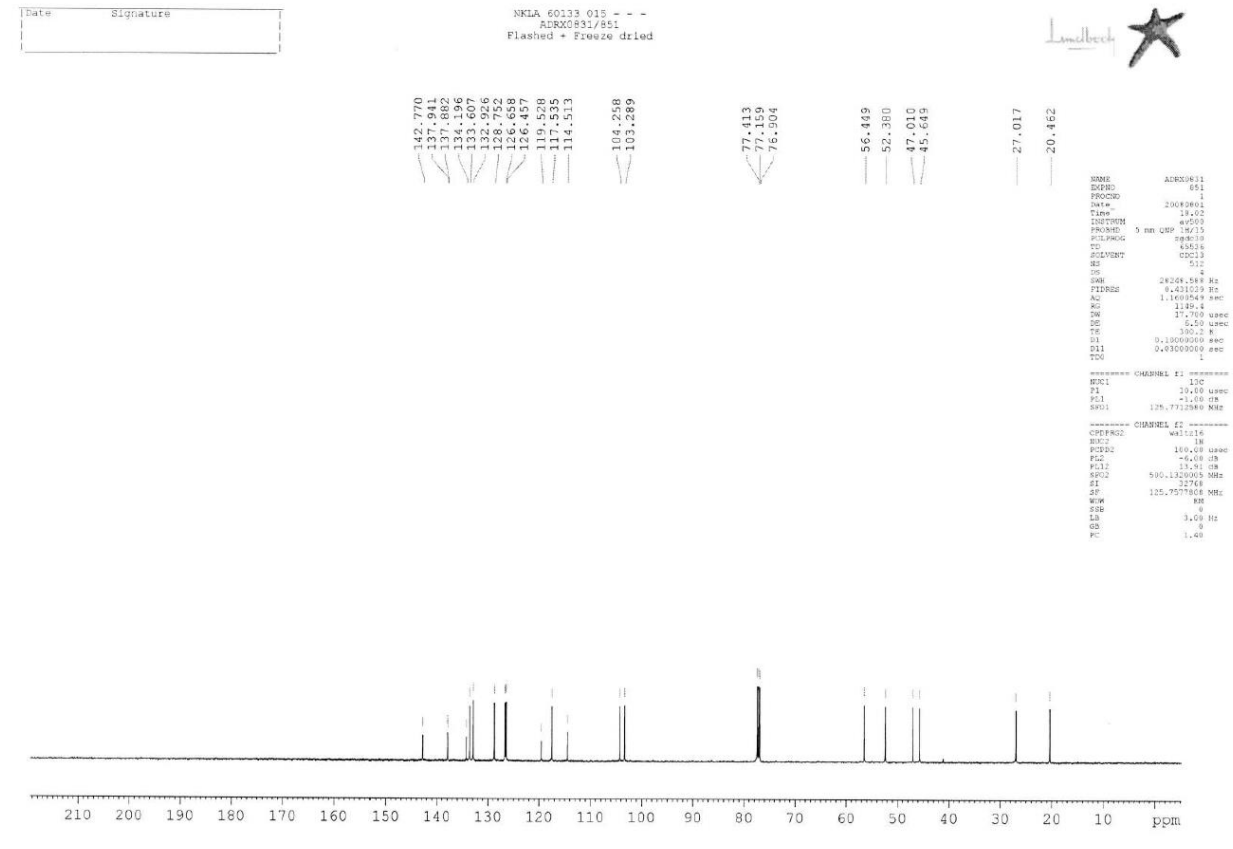

NKLA 60133 014 - - -
ADRX0831/730
Flashed + Freeze dried

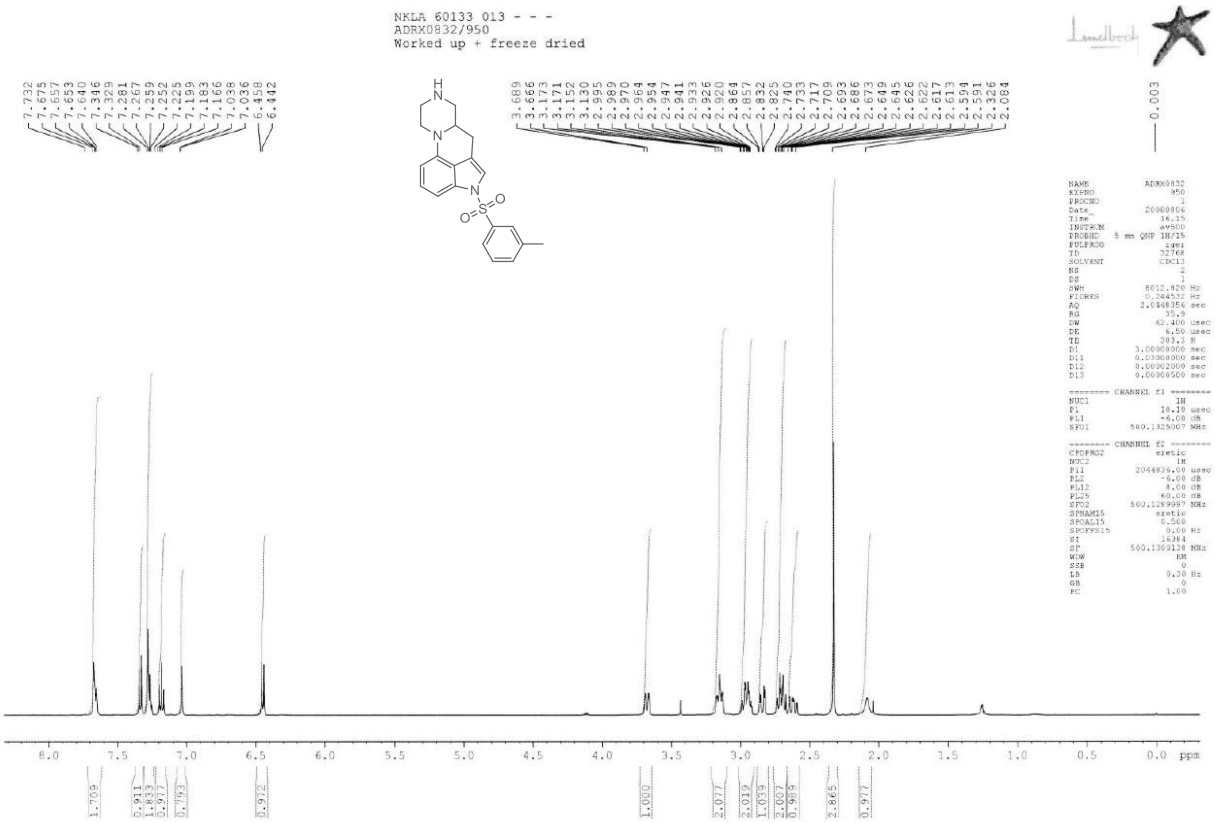

Date
Signature

NKLA 60133 014 - - -
ADRX0831/731
Flashed + Freeze dried

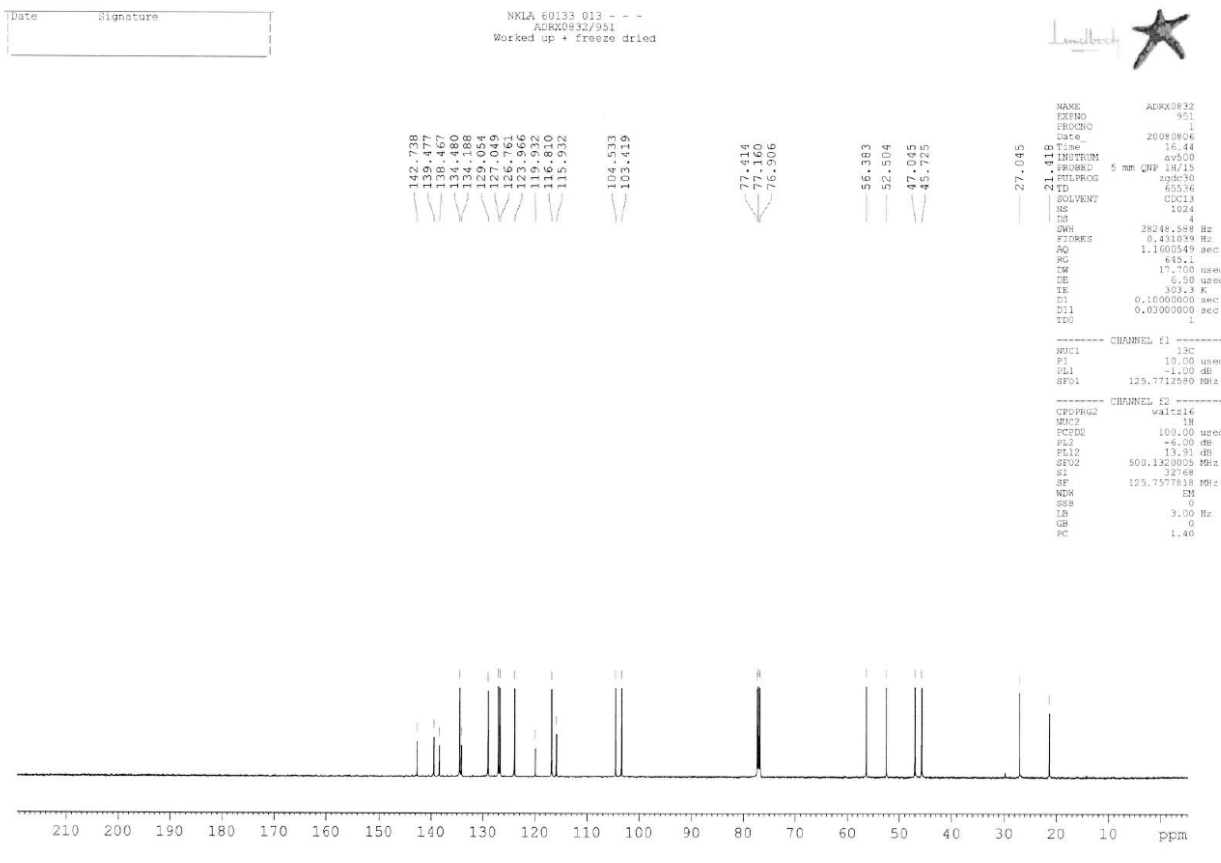


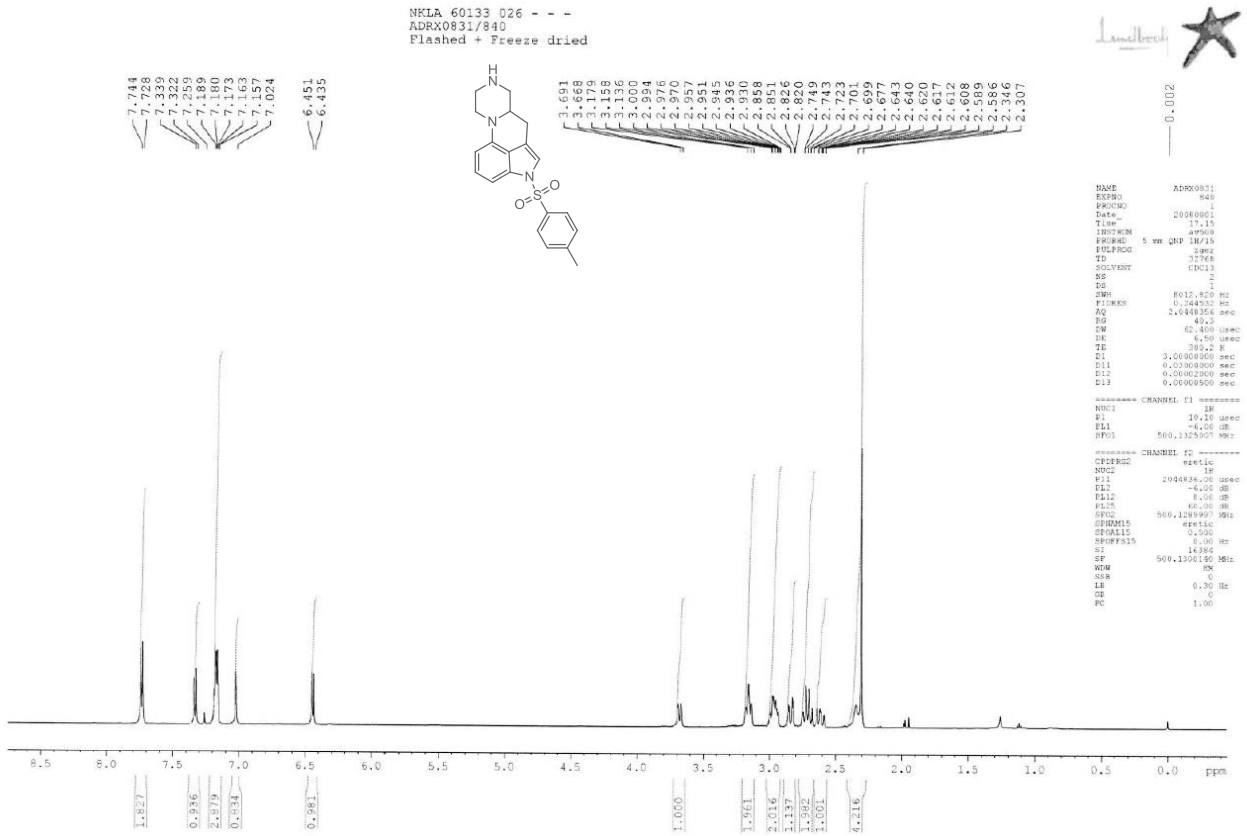
Date Signature



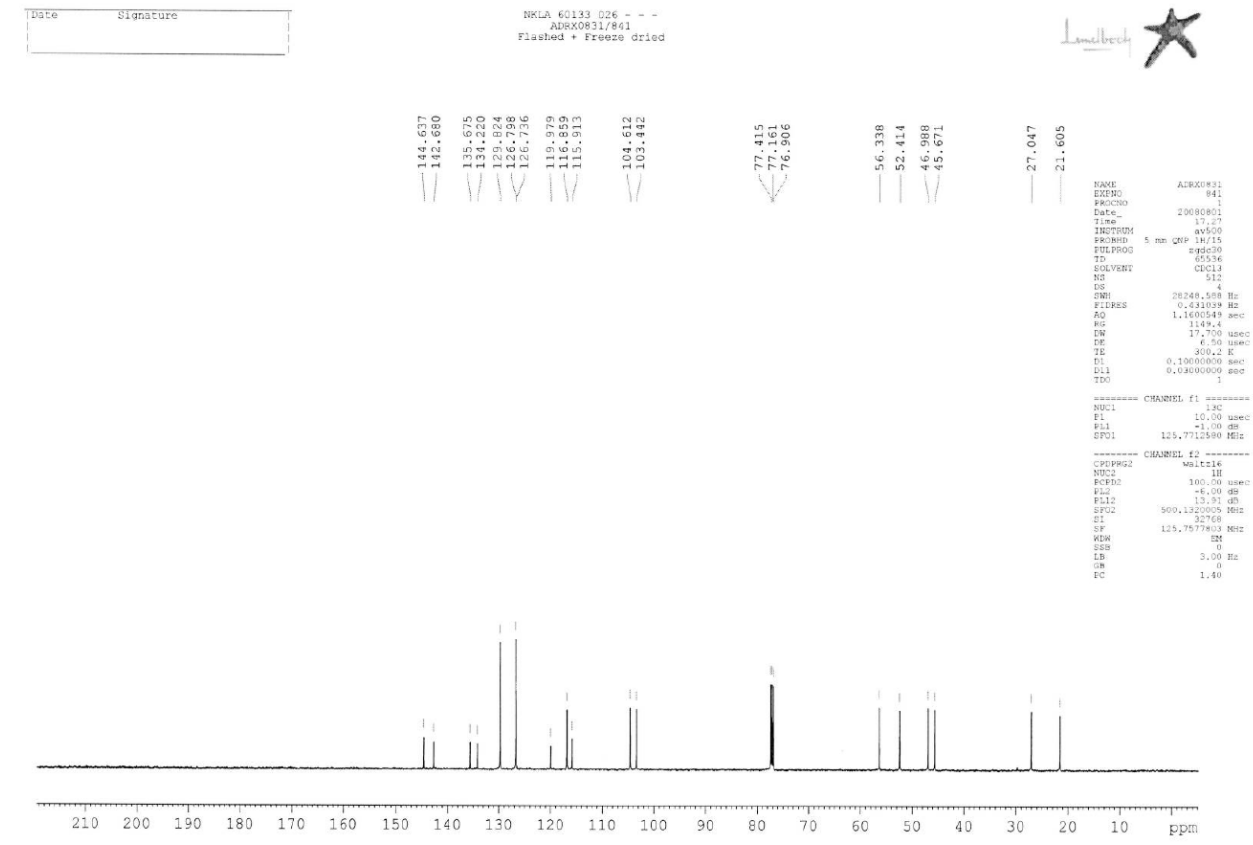


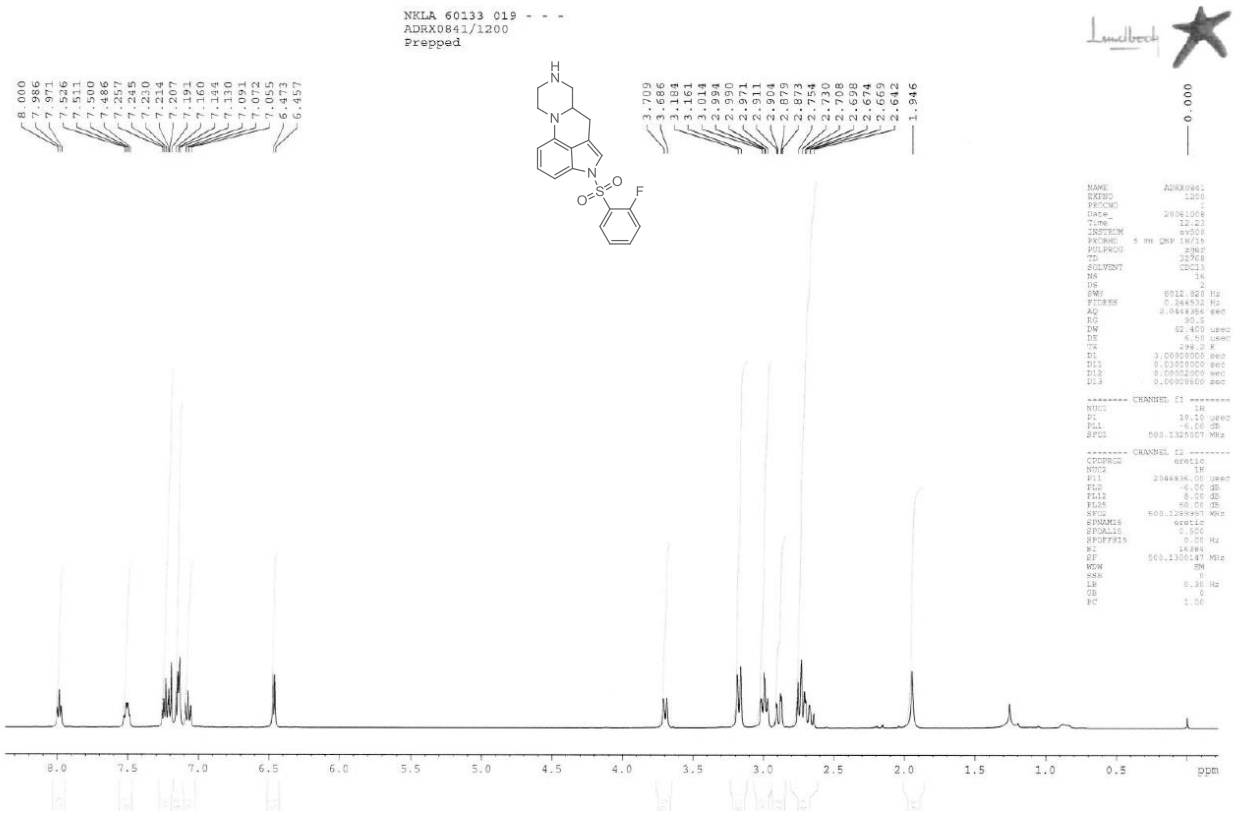
Date Signature



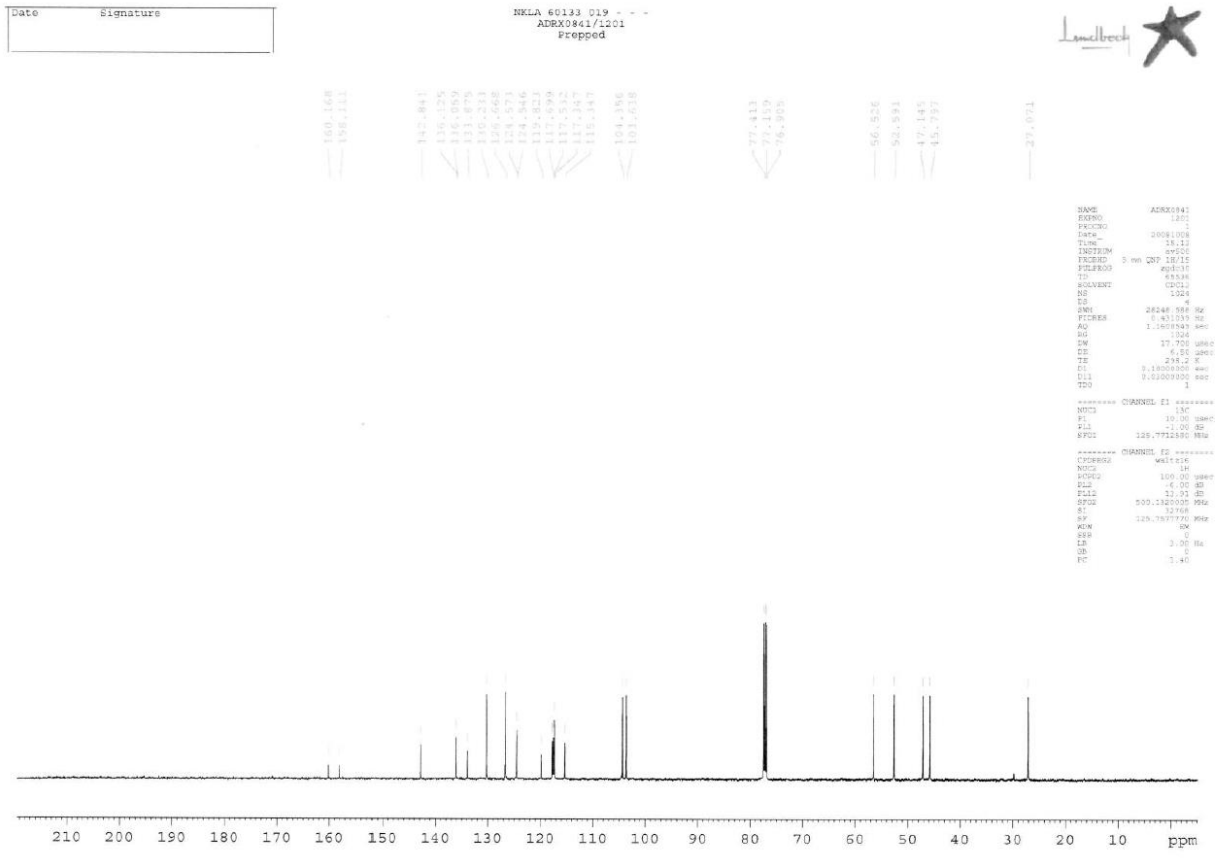


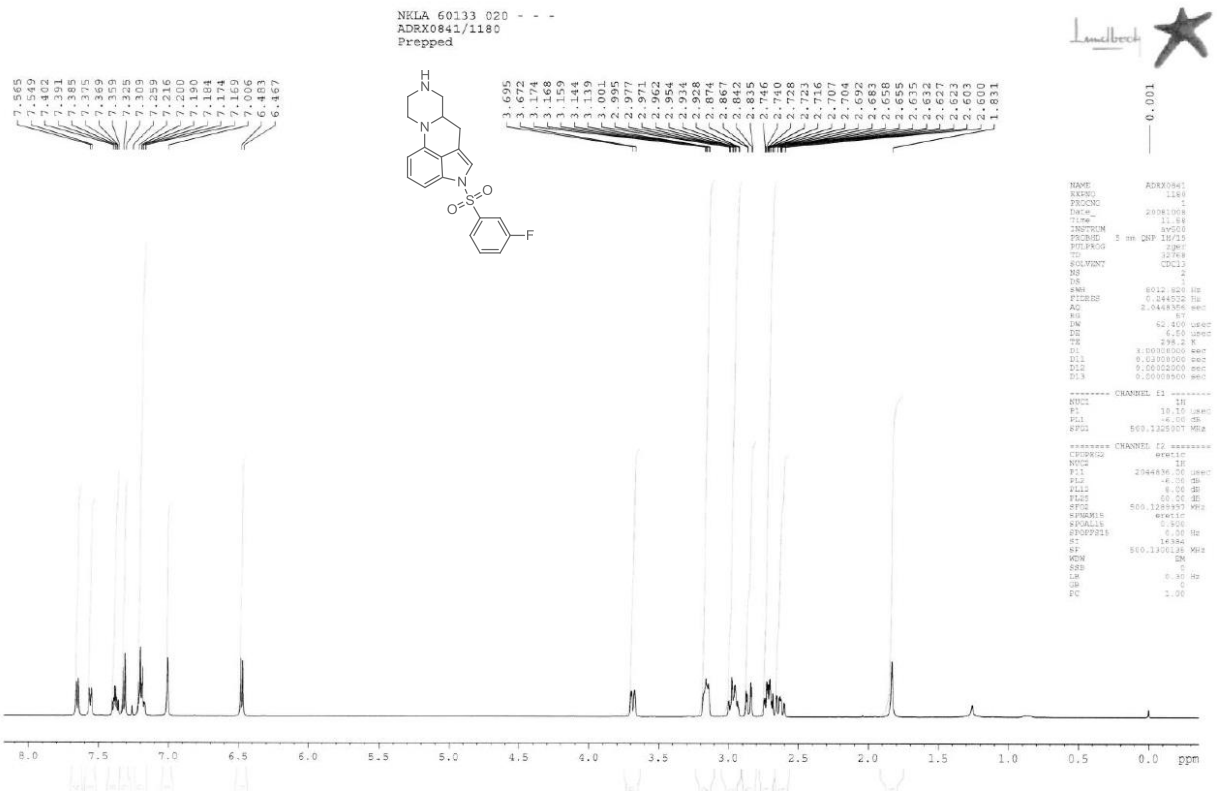
Date Signature



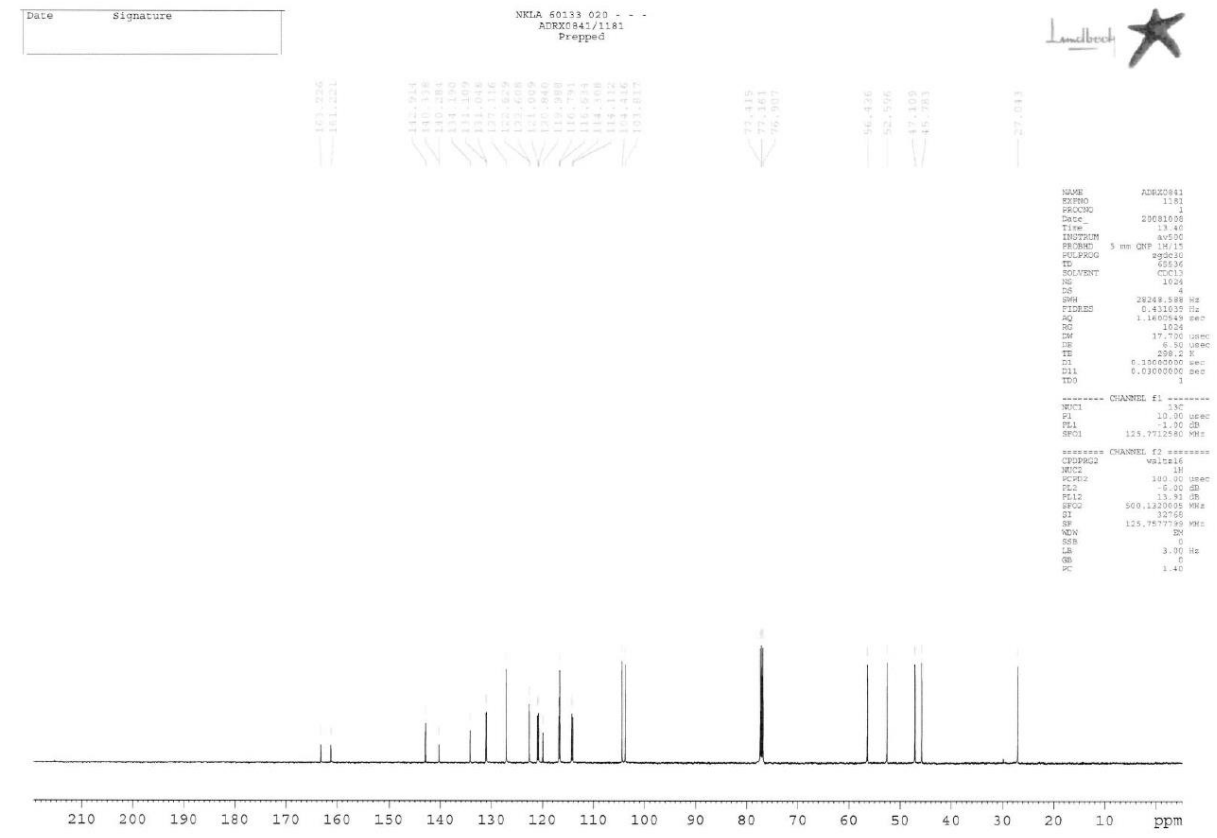


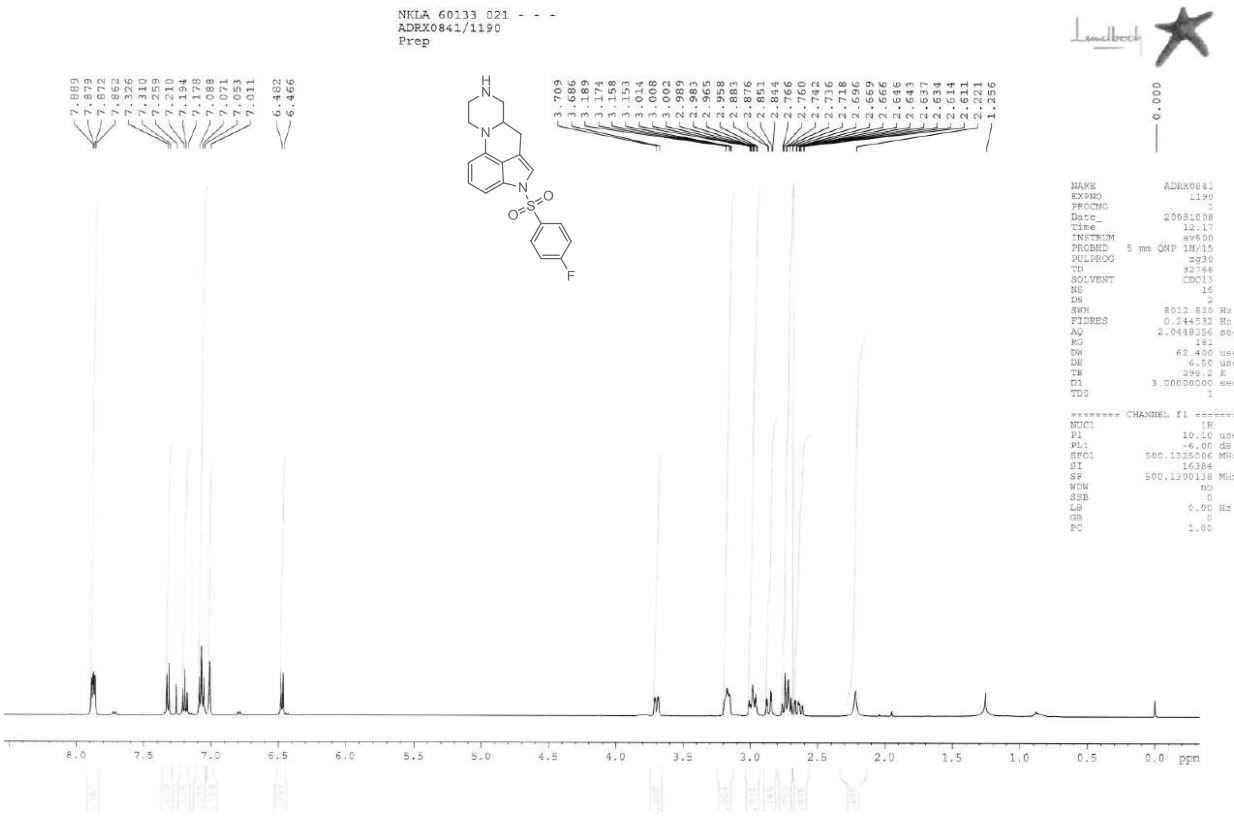
Date Signature



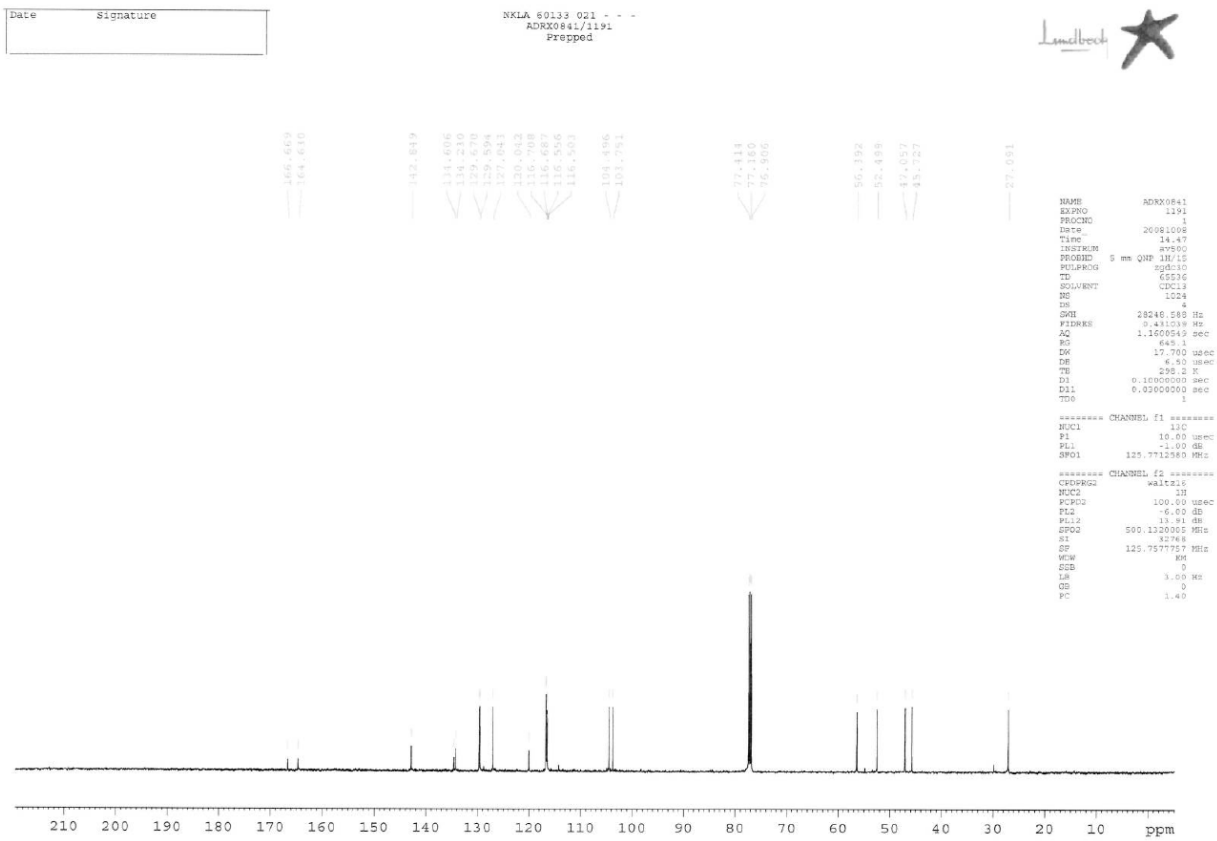


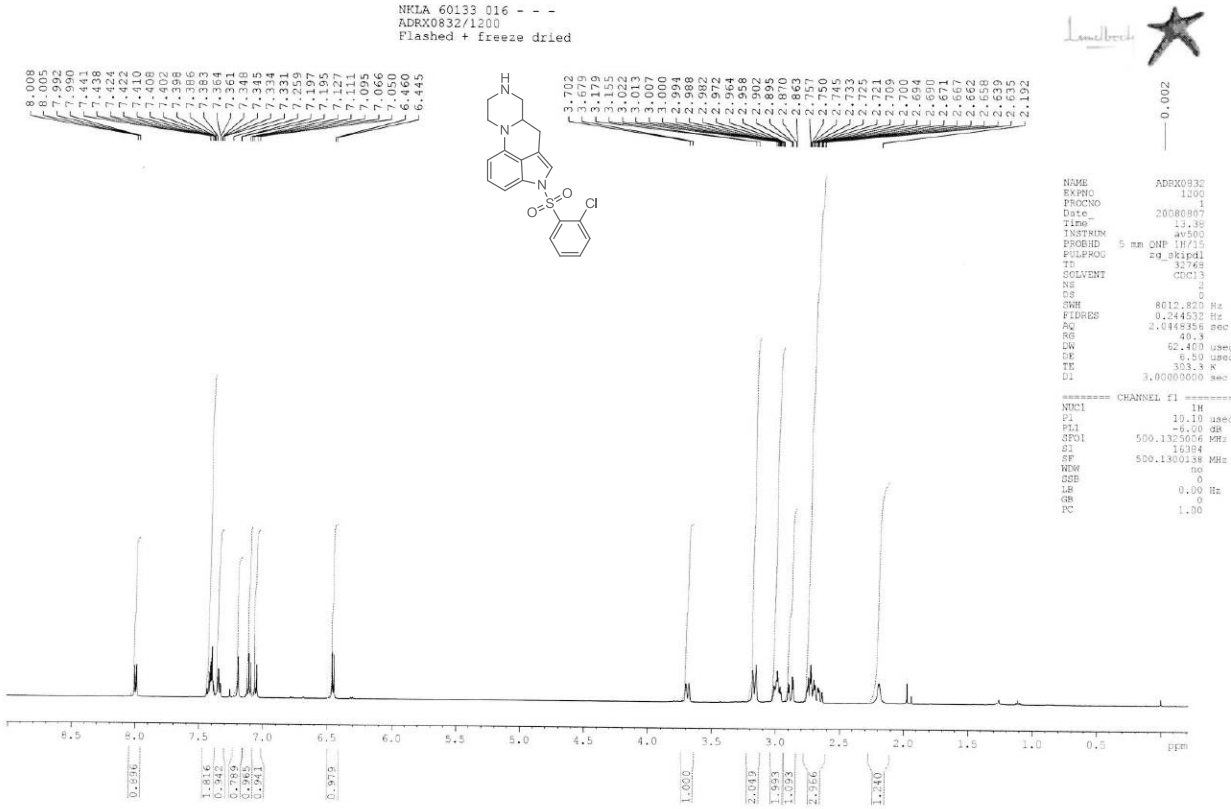
Date Signature

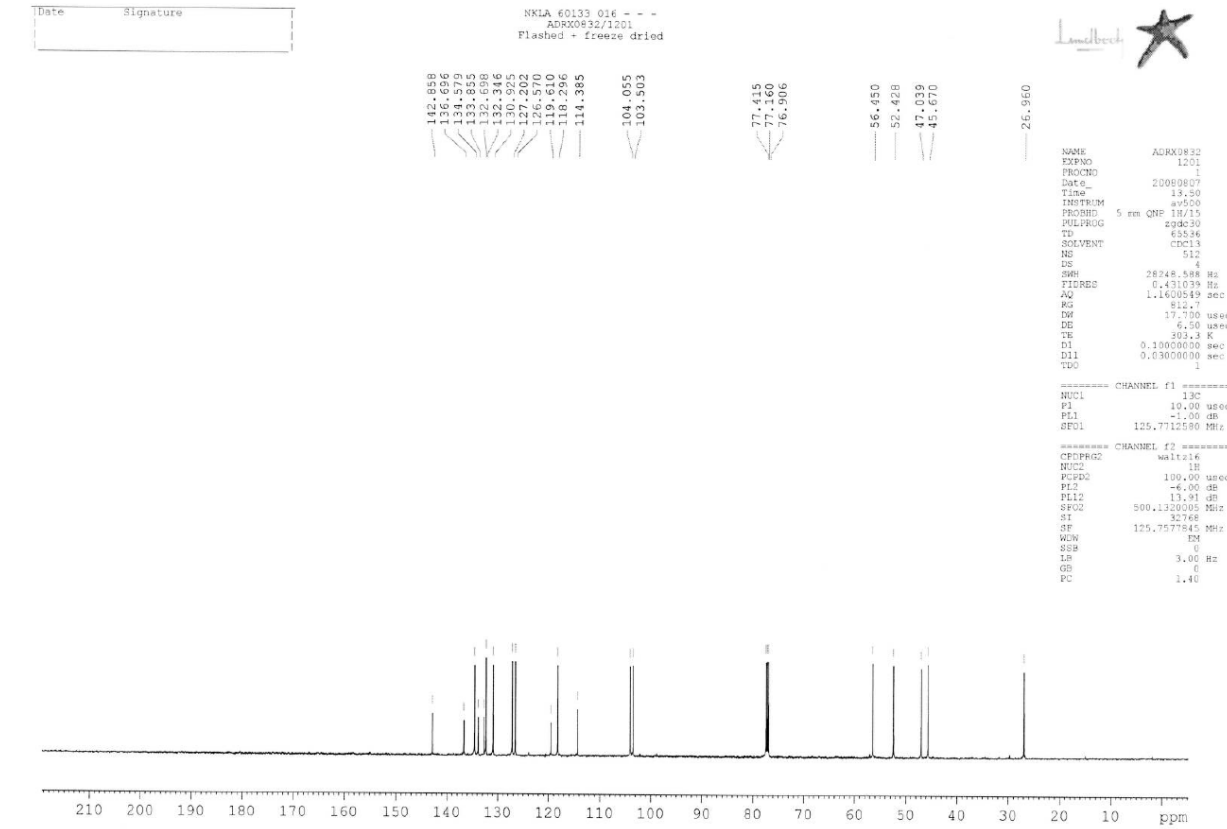


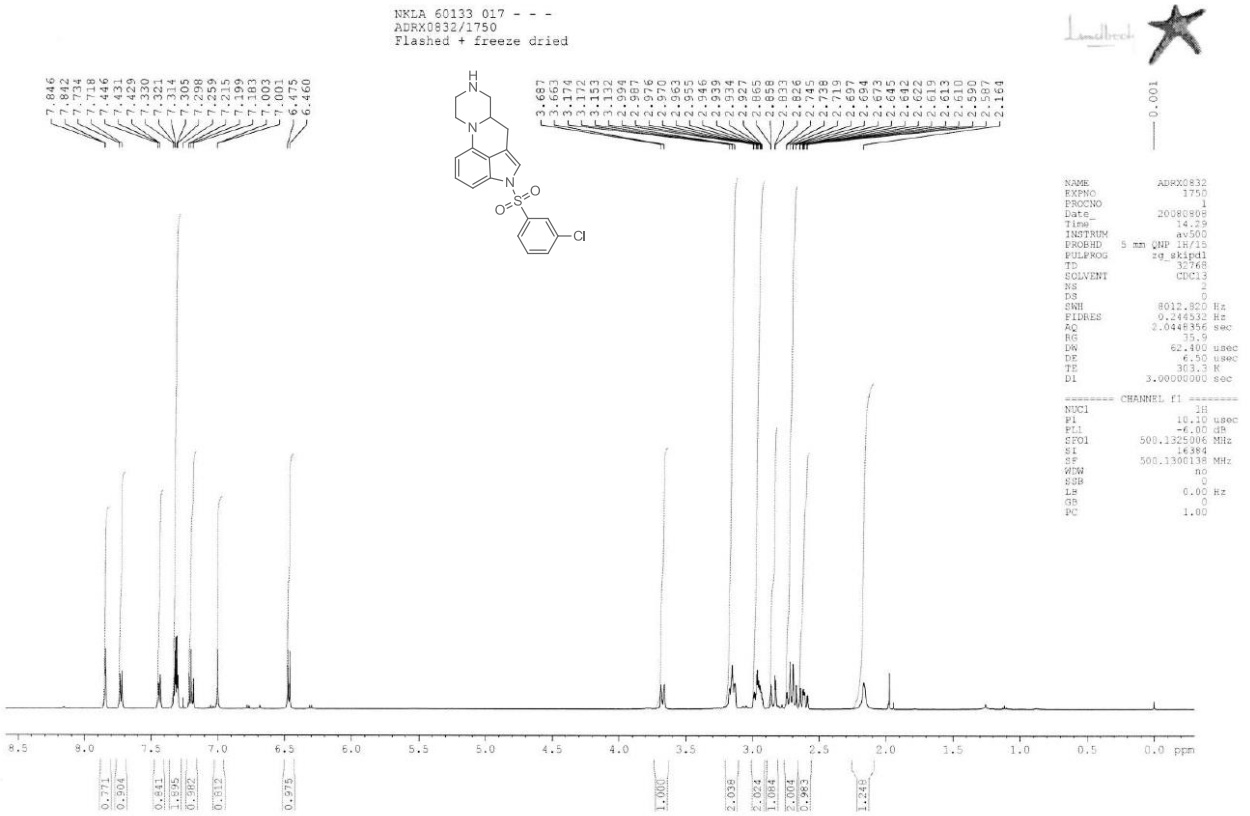


Date Signature

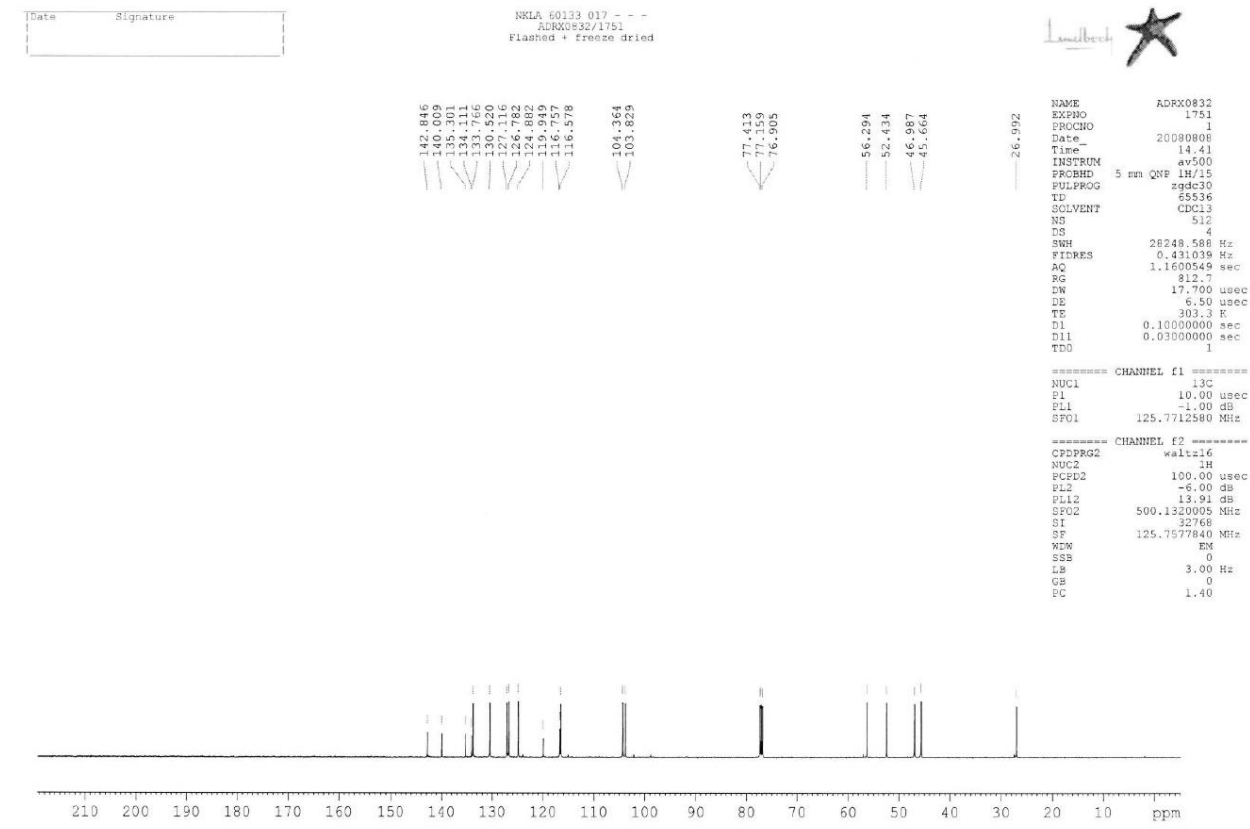


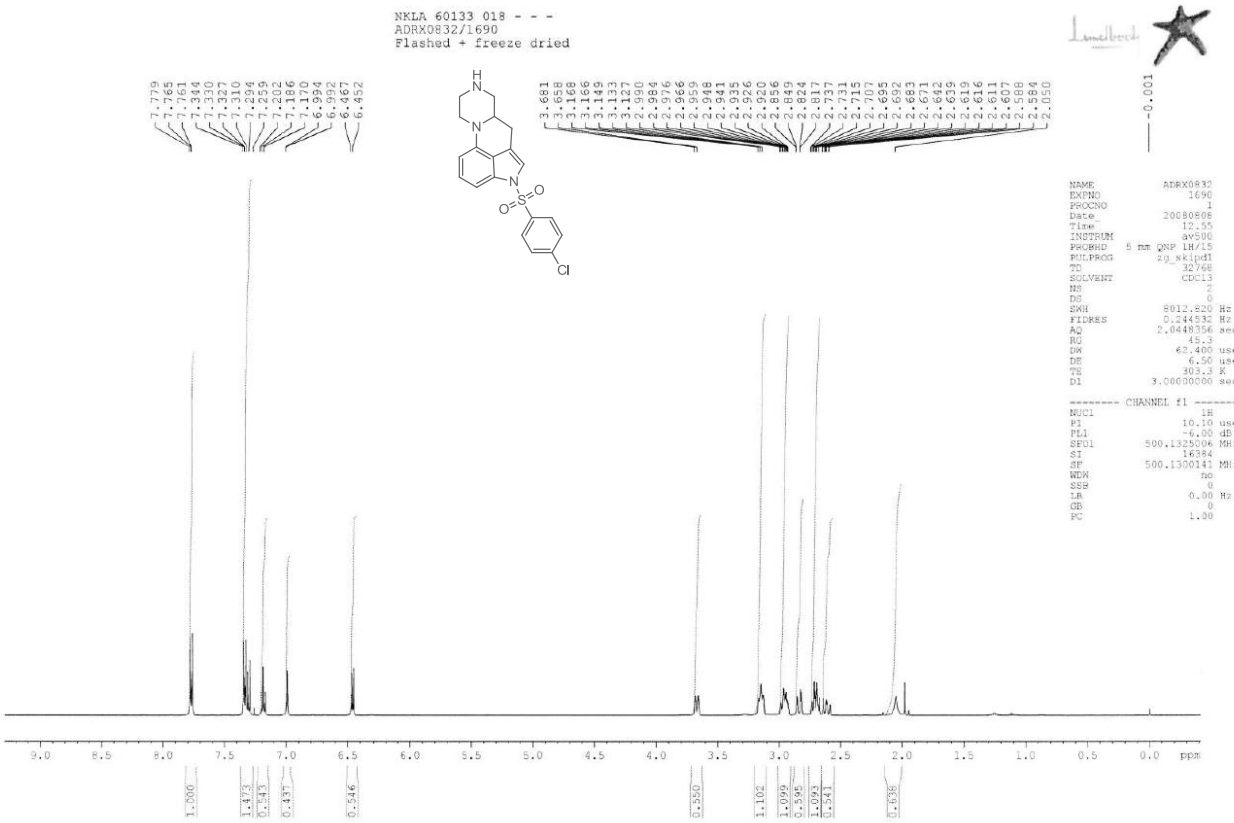

NKLA 60133 016 - - -
ADRX0832/1200
Flashed + freeze dried
8.008
8.005
7.992
7.990
7.441
7.438
7.424
7.422
7.410
7.408
7.402
7.398
7.386
7.383
7.364
7.361
7.348
7.345
7.334
7.331
7.259
7.187
7.185
7.127
7.111
7.095
7.066
7.050
6.460
6.445
3.702
3.679
3.179
3.155
3.022
3.013
3.007
3.000
2.994
2.988
2.972
2.964
2.958
2.902
2.895
2.870
2.863
2.757
2.750
2.745
2.733
2.725
2.721
2.709
2.700
2.694
2.690
2.671
2.667
2.662
2.658
2.639
2.635
2.192
0.002
NAME ADRX0832
EXPNO 1200
PROCNO 1
Date_ 20080807
Time 13.38
INSTRUM av500
PROBHD 5 mm QNP 1H/15
PULPROG zg_skipdl
TD 32768
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 40.3
DW 62.400 usec
DE 6.50 usec
TE 303.3 K
D1 3.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
PL1 -6.00 dB
SFO1 500.1325006 MHz
SI 16384
SF 500.1300138 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.896
1.816
0.942
0.789
0.965
0.941
0.979
1.000
2.049
1.983
1.093
2.966
1.240

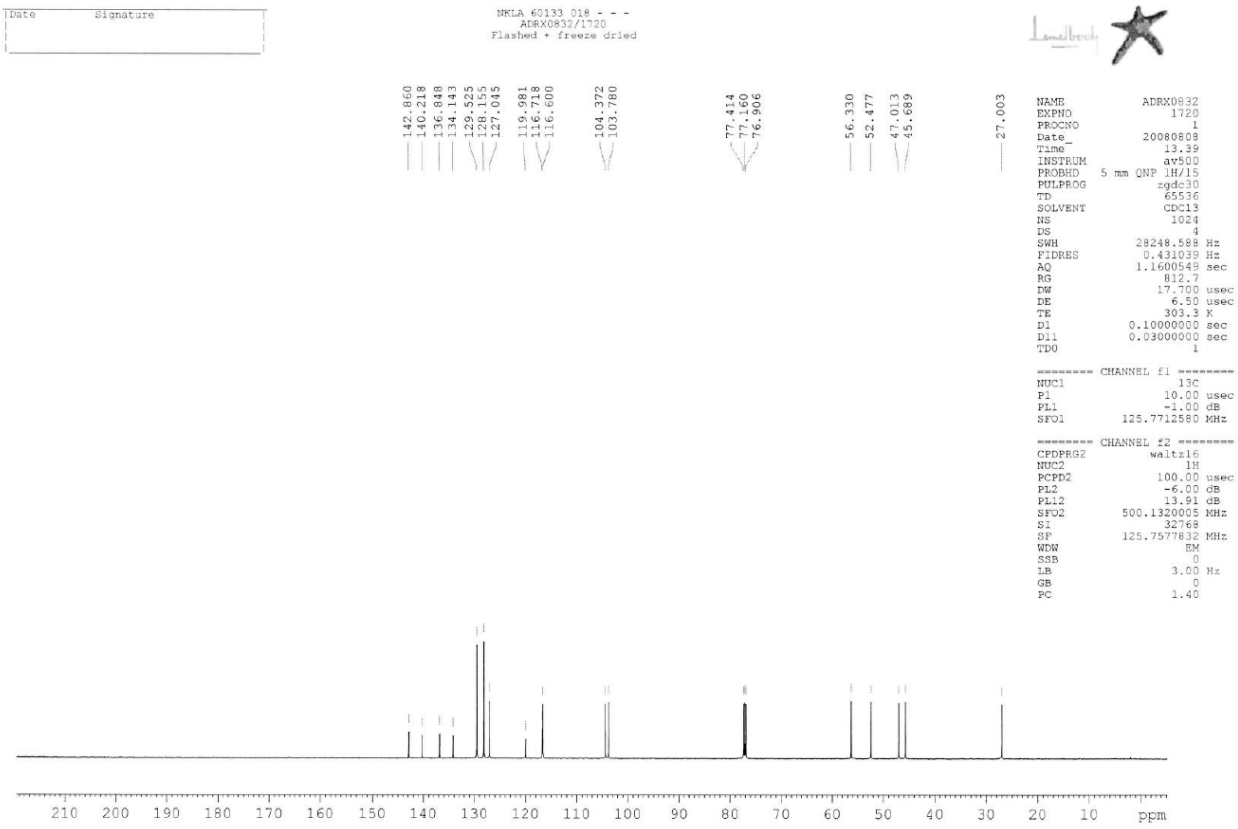

Date Signature
NKLA 60133 016 - - -
ADRX0832/1201
Flashed + freeze dried
142.858
136.696
134.579
133.855
132.698
132.346
130.925
127.202
126.570
119.610
118.296
114.385
104.055
103.503
77.415
77.160
76.906
56.450
52.428
47.039
45.670
26.960
NAME ADRX0832
EXPNO 1201
PROCNO 1
Date_ 20080807
Time 13.50
INSTRUM av500
PROBHD 5 mm QNP 1H/15
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 28248.588 Hz
FIDRES 0.431039 Hz
AQ 1.1600549 sec
RG 812.7
DW 17.700 usec
DE 6.50 usec
TE 303.3 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 -1.00 dB
SFO1 125.7712580 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.91 dB
SFO2 500.1320005 MHz
SI 32768
SF 125.7577845 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

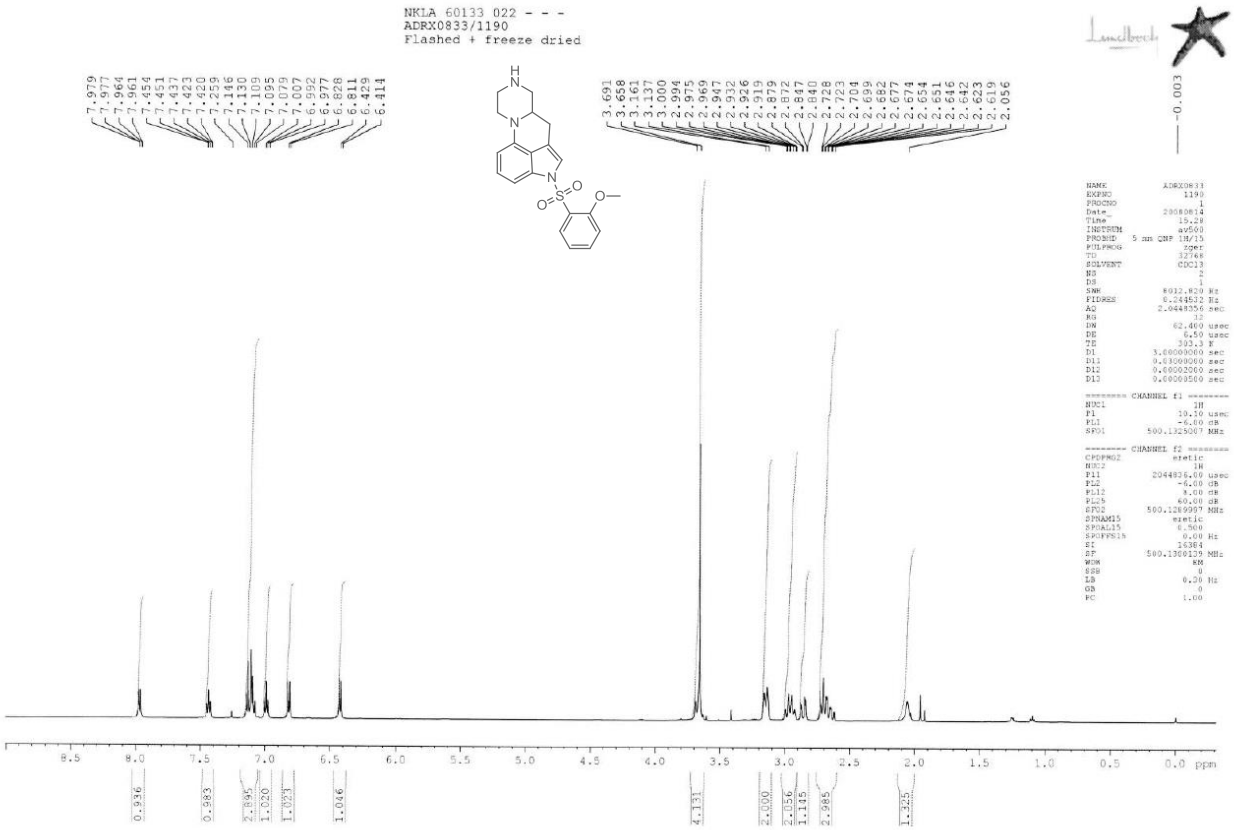


Date	Signature

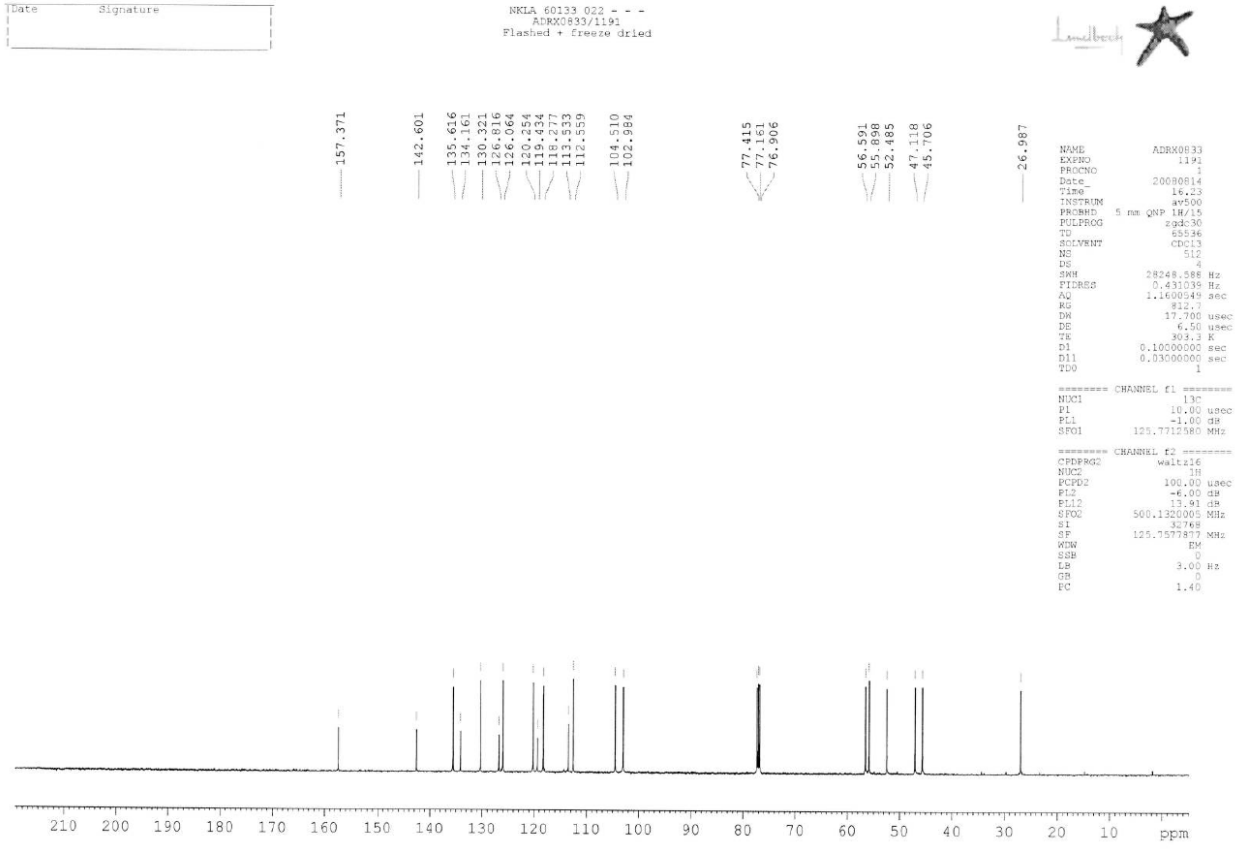


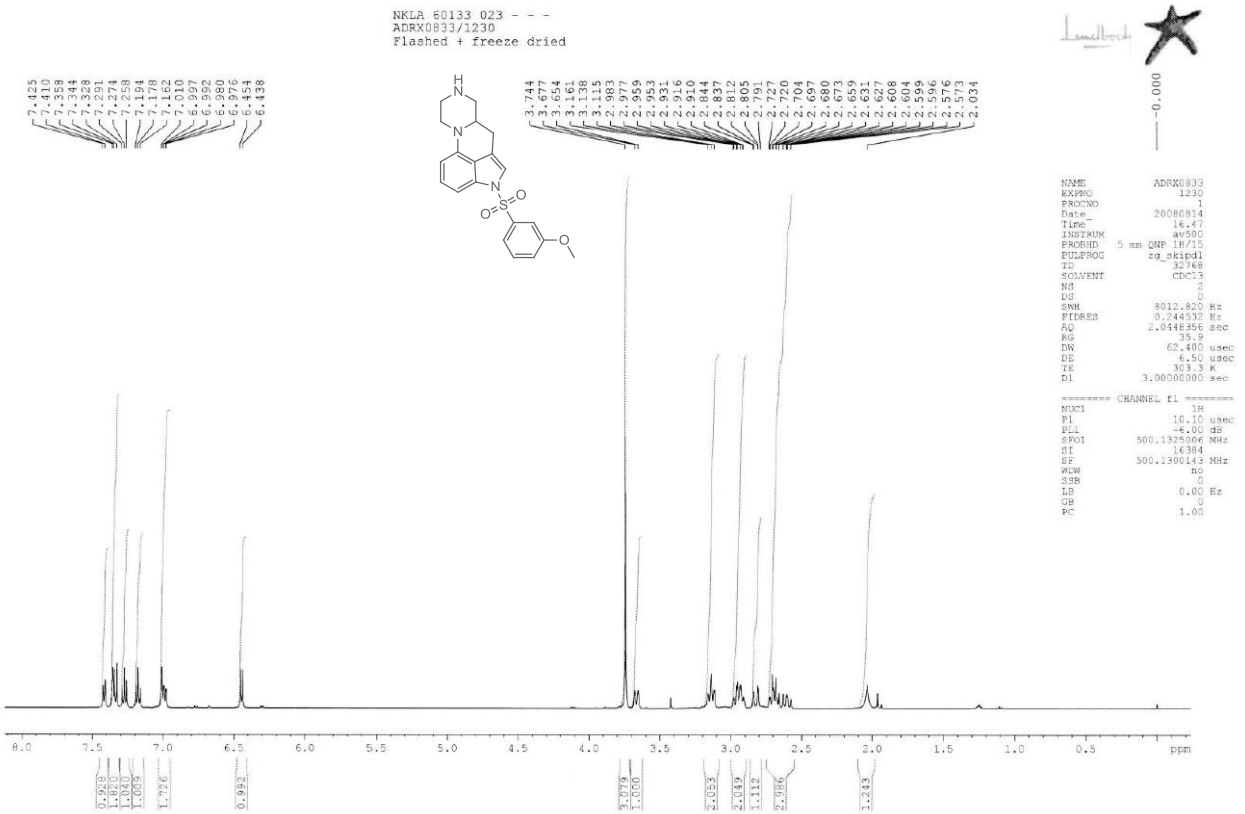

NKLA 60133 018 - - -
ADRX0832/1690
Flashed + freeze dried
7.779
7.765
7.761
7.344
7.330
7.327
7.310
7.294
7.259
7.202
7.186
7.170
6.994
6.992
6.467
6.452
3.681
3.658
3.168
3.166
3.149
3.133
3.127
2.990
2.984
2.976
2.966
2.959
2.948
2.941
2.935
2.926
2.920
2.886
2.859
2.834
2.817
2.737
2.731
2.715
2.707
2.695
2.692
2.683
2.671
2.642
2.639
2.619
2.616
2.611
2.607
2.588
2.584
2.050
-0.001
NAME ADRX0832
EXPNO 1690
PROCNO 1
Date_ 20080808
Time_ 12.55
INSTRUM av500
PROBHD 5 mm QNP 1H/15
PULPROG zg_skipd1
TD 32768
SOLVENT CDCl3
NS 2
DS 0
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 45.3
DW 62.400 usec
DE 6.50 usec
TE 303.3 K
D1 3.00000000 sec
CHANNEL f1
NUC1 1H
P1 10.10 usec
PL1 -6.00 dB
SFO1 500.1325006 MHz
SI 16384
SF 500.1300141 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.000
1.473
0.543
0.437
0.546
0.550
1.102
1.099
0.595
1.093
0.541
0.638


Date Signature
NKLA 60133 018 - - -
ADRX0832/1720
Flashed + freeze dried
142.860
140.218
136.848
134.143
129.525
128.155
127.045
119.981
116.718
116.600
104.372
103.780
77.414
77.160
76.906
56.330
52.477
47.013
45.689
27.003
NAME ADRX0832
EXPNO 1720
PROCNO 1
Date_ 20080808
Time_ 13.39
INSTRUM av500
PROBHD 5 mm QNP 1H/15
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 28248.588 Hz
FIDRES 0.431039 Hz
AQ 1.1600549 sec
RG 812.7
DW 17.700 usec
DE 6.50 usec
TE 303.3 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 10.00 usec
PL1 -1.00 dB
SFO1 125.7712580 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.91 dB
SFO2 500.1320005 MHz
SI 32768
SF 125.7577832 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

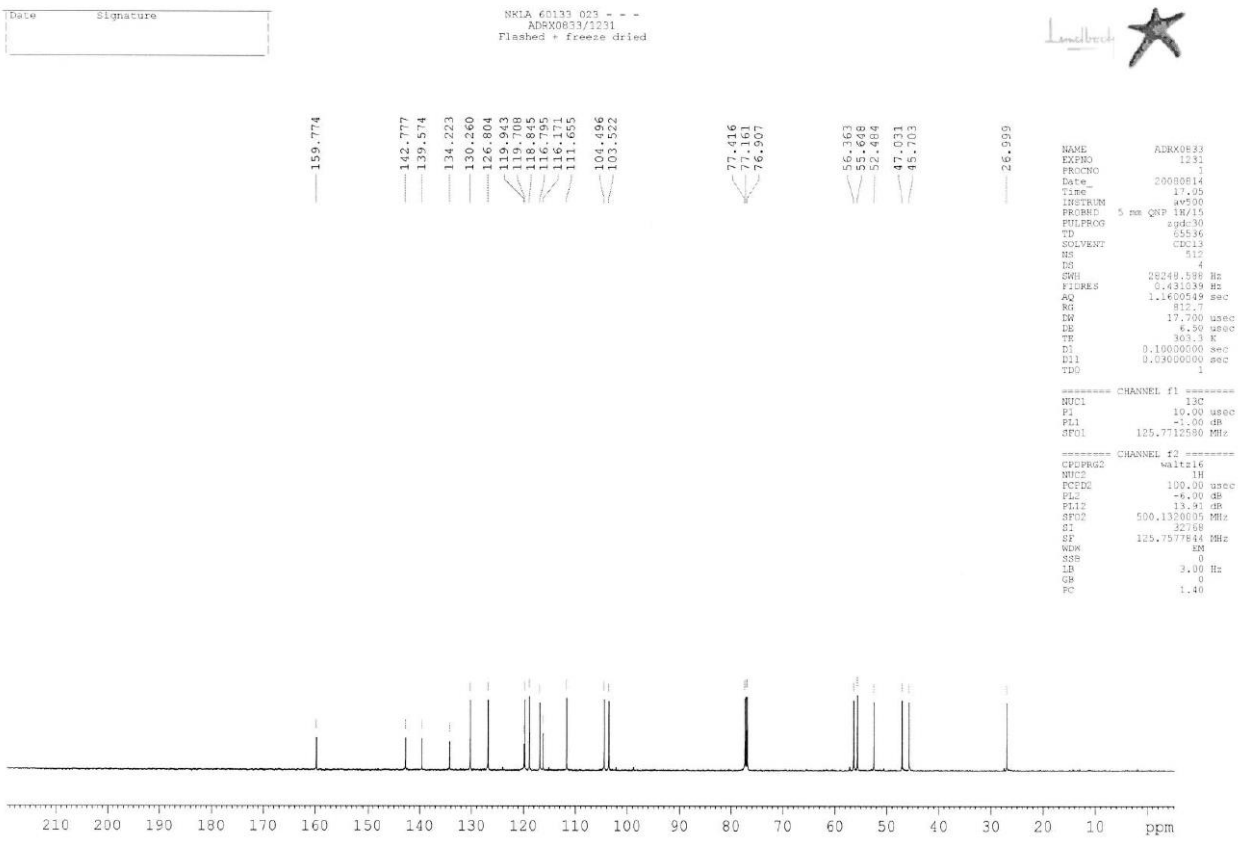


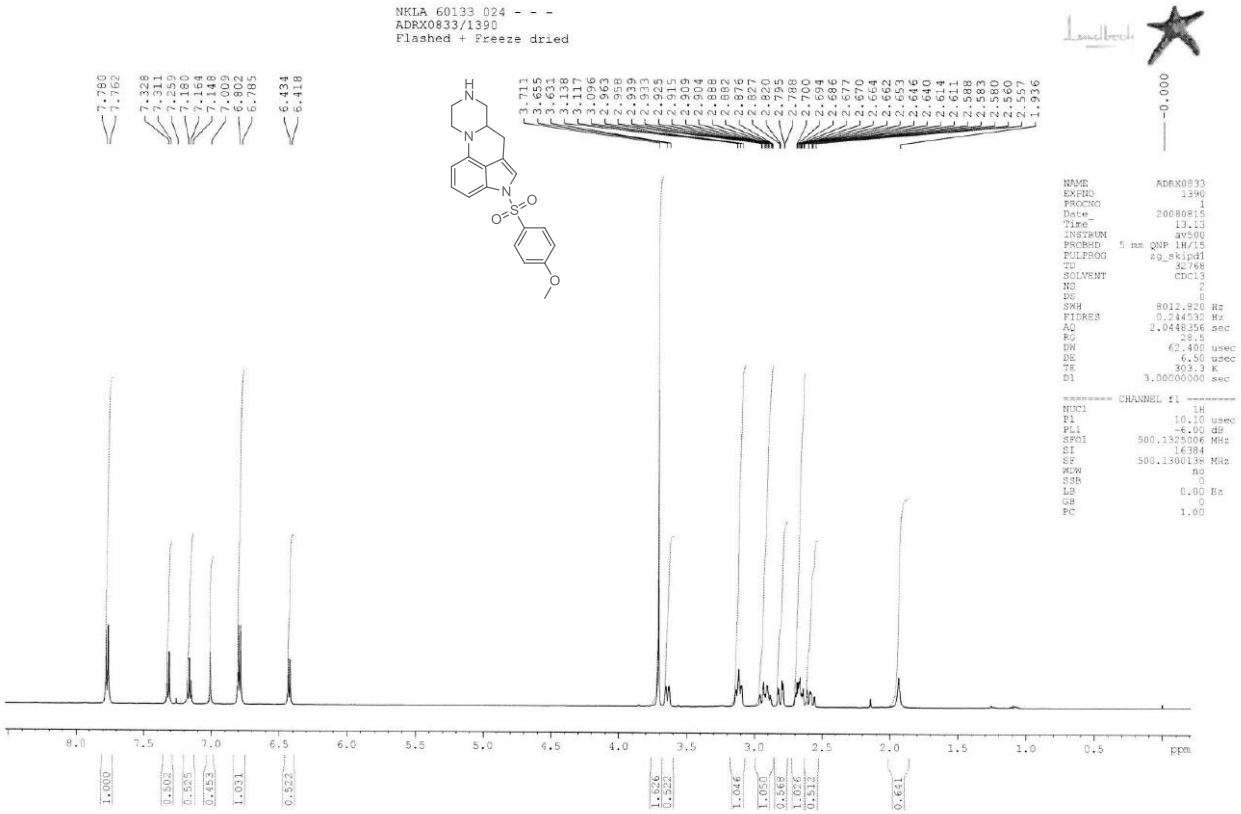
Date Signature

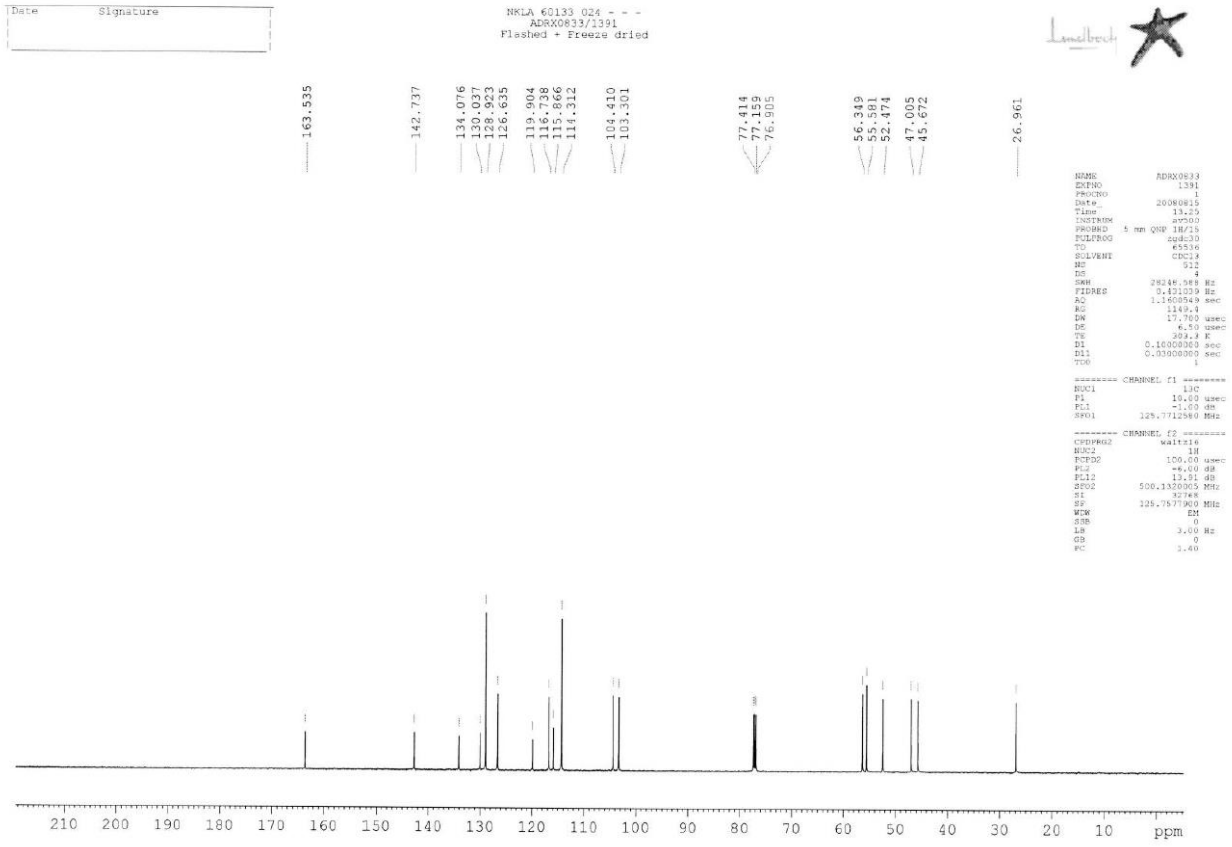




Date Signature




NKLA 60133 024 - - -
ADRX0833/1390
Flashed + Freeze dried
7.780
7.762
7.328
7.311
7.259
7.160
7.148
7.009
6.802
6.785
6.434
6.418
3.711
3.655
3.631
3.138
3.117
3.096
2.963
2.958
2.939
2.933
2.925
2.915
2.909
2.904
2.888
2.882
2.876
2.827
2.820
2.795
2.788
2.700
2.694
2.686
2.677
2.670
2.664
2.662
2.653
2.646
2.640
2.614
2.611
2.588
2.583
2.580
2.560
2.557
1.936
-0.000
NAME ADRX0833
EXPNO 1390
PROCNO 1
Date_ 20080815
Time 13.13
INSTRUM av500
PROBHD 5 mm QNP 1H/15
PULPROG zg_skipd1
TD 32768
SOLVENT CDCl3
NS 2
DS 0
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0448356 sec
RG 28.5
DW 62.400 usec
DE 6.50 usec
TE 303.3 K
D1 3.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
PL1 -6.00 dB
SFO1 500.1325006 MHz
SI 16384
SF 500.1300138 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.502
0.585
0.453
1.031
0.522
1.626
0.522
1.046
1.050
0.568
1.026
0.512
0.641


Date Signature
NKLA 60133 024 - - -
ADRX0833/1391
Flashed + Freeze dried
163.535
142.737
134.076
130.037
128.923
126.635
119.904
116.738
115.866
114.312
104.410
103.301
77.414
77.159
76.905
56.349
55.581
52.474
47.005
45.672
26.961
NAME ADRX0833
EXPNO 1391
PROCNO 1
Date_ 20080815
Time 13.25
INSTRUM av500
PROBHD 5 mm QNP 1H/15
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 29285.588 Hz
FIDRES 0.421039 Hz
AQ 1.1600549 sec
RG 1149.4
DW 17.700 usec
DE 6.50 usec
TE 309.1 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 -1.00 dB
SFO1 125.7712560 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 +6.00 dB
PL12 19.91 dB
SFO2 500.1320005 MHz
SI 32768
SF 125.7577900 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm