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Supporting Information

Inhibitors of Human Divalent Metal Transporters DMT1 (SLC11A2) and ZIP8 (SLC39A8) from a GDB-17 Fragment Library

Jonai Pujol-Giménez, Marion Poirier, Sven Bühlmann, Céline Schuppisser, Rajesh Bhardwaj, Mahendra Awale, Ricardo Visini, Sacha Javor, Matthias A. Hediger,* and Jean-Louis Reymond*

Supporting Information

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Analogs of *rac*-3

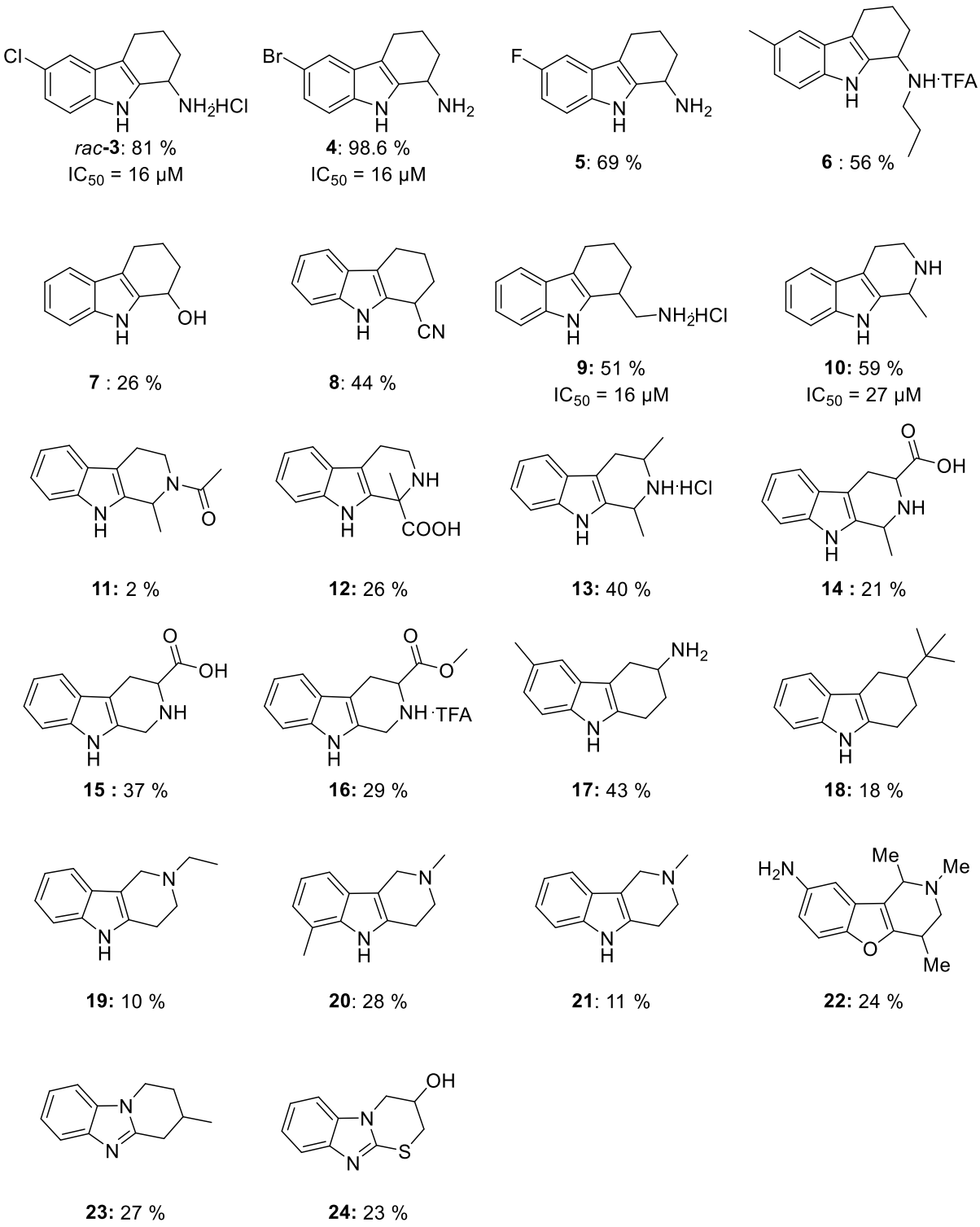


Figure S1. Analogs of compound *rac*-**3** tested for ZIP8 inhition. The % inhibition observed is in the ZIP8 screening given, as well as the IC_{50} value when measured.

Chemistry

All reagents were purchased from commercial sources and were used without further purification. Flash chromatography purifications were performed with silica Gel 60 (Sigma, 0.040–0.063 nm, 230–400 mesh ASTM). Low resolution mass spectra were obtained by electron spray ionization (ESI-MS) in the positive mode on a Thermo Scientific LCQ Fleet. High resolution mass spectra were obtained by electron spray ionization (HR-ESI-MS) in the positive mode recorded on a Thermo Scientific LTQ Orbitrap XL. ^{1}H and ^{13}C-NMR spectra were measured on a Bruker Avance 300 spectrometer (at 300 MHz and 75 MHz, respectively) or on a Bruker Avance II 400 spectrometer (at 400 MHz and 101 MHz, respectively). ^{1}H and ^{13}C chemical shifts are given in ppm (δ) relative to the solvent proton impurity signals, and resonance multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet); br = broad peak. Compound purities were assessed by analytical reversed phase HPLC (RP-HPLC) at a detection wavelength of 214 nm. Analytical RP-HPLC was performed on a Dionex Ultimate 3000 RSLC System (DAD-3000 RS Photodiode Array Detector) using a Dionex Acclaim RSLC 120 column (C18, 3.0 x 50 mm, particle size 2.2 μm, 120 Å pore size) and a flow rate of 1.2 mL min^{-1}. Data were recorded and processed with Xcalibur (version 2.2, Thermo Scientific). Eluents for analytical RP-HPLC were as follows: (A) milliQ-deionized water containing 0.05% TFA, (D) HPLC-grade acetonitrile/milliQ-deionized water (9:1) containing 0.05% TFA. Conditions for analytical RP-HPLC were as follows: in 2.2 min from 100 % A to 100 % D, then staying on 100 % D (method A), in 7.5 min from 100 % A to 100 % D, then staying on 100 % D (method B). Optical rotations were recorded in cells with 10 cm path length on a Polartronic H532 (Gerber Instruments) digital polarimeter. Preparative RP-HPLC were performed with a Waters Prep LC System Controller with a Dr. Maisch GmbH Reprospher column (C18-DE, 100×30 mm, particle size 5 μm, pore size 100 Å, flow rate 40 mL/min). Compounds were detected by UV absorption at 214 nm using Waters 2489 UV/Vis detector. The elution solutions were: (A) MilliQ deionized water containing 0.1% TFA; (D) MilliQ deionized water / acetonitrile (10 / 90) containing 0.1% TFA. Commercial compounds were purchased as 1 mg solid and dissolved in DMSO to get a 10 mM stock solution that was used for screening. The purity of the most active compounds was checked by LC-MS and they were purchased in higher amount (usually 25 mg) and analysed by NMR and HR-MS. The purity was determined by RP-UPLC at 214 nm.

4-((trifluoromethyl)sulfonyl)phenol (1a): Compound **1a** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 4.67 min (method B). ^{1}H NMR (300 MHz, DMSO): δ 11.49 (1H, br s), 8.03 – 7.83 (2H, m), 7.24 – 7.02 (2H, m). ^{13}C NMR (101 MHz, DMSO): δ 165.8, 133.3 (CH_{ar}), 119.6 (q, *J* = 325.9 Hz, CF_3), 117.9, 117.0 (CH_{ar}). HR-MS calculated for $C_7H_4F_3O_3S$: *m/z* 224.9839, *m/z* found 224.0004.

4-((trifluoromethyl)sulfonyl)aniline (1b): Compound **1b** was purchased as a 25 mg solid form from Enamine. RP-UPLC: t_R = 2.24 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 7.69 – 7.56 (2H, m), 6.92 (2H, s), 6.81 – 6.70 (2H, m). HR-MS calculated for $C_7H_7O_2NF_3S$: *m/z* 226.0144, *m/z* found 226.9790.

2,4-bis((trifluoromethyl)sulfonyl)phenol (1c): Compound **1c** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 2.41 min (method A). HR-MS calculated for $C_8H_3F_6O_5S_2$: *m/z* 356.9332, *m/z* found 356.9323.

4-(methylsulfonyl)phenol (1d): Compound **1d** was purchased as a 25 mg solid form from Alpha Aesar. RP-UPLC: t_R = 1.43 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 10.56 (1H, s), 7.81 – 7.64 (2H, m), 7.04 – 6.84 (2H, m), 3.11 (3H, s). HR-MS calculated for $C_7H_5O_3S$: *m/z* 171.0121, *m/z* found 171.0128.

2-fluoro-4-(methylsulfonyl)phenol (1e): Compound **1e** was purchased as a 1 mg solid form from Ambiter. RP-UPLC: t_R = 1.48 min (method A). HR-MS calculated for $C_7H_6FO_3S$: *m/z* 189.0027, *m/z* found 189.0025.

N-(5-(ethylsulfonyl)-2-hydroxyphenyl)methanesulfonamide (1f): Compound **1f** was purchased as a 1 mg solid form from Ambiter. RP-UPLC: t_R = 1.72 min (method A). HR-MS calculated for $C_9H_{12}NO_5S_2$: *m/z* 278.0162, *m/z* found 278.0157.

N-(5-(ethylsulfonyl)-2-hydroxyphenyl)isobutyramide (1g): Compound **1g** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 1.78min (method A). HR-MS calculated for $C_{12}H_{18}NO_4S$: *m/z* 272.0951, *m/z* found 272.0949.

N-(5-(ethylsulfonyl)-2-hydroxyphenyl)-2-methylcyclopropane-1-carboxamide (1h): Compound **1h** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 1.89 min (method A). HR-MS calculated for $C_{13}H_{18}NO_4S$: *m/z* 284.0951, *m/z* found 284.0948.

4-hydroxybenzenesulfonamide (1i): Compound **1i** was purchased as a 25 mg solid form from Acros organics. RP-UPLC: t_R = 1.17 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 7.79 – 7.54 (2H, m), 7.08 (2H, br s), 6.99 – 6.73 (2H, m). HR-MS calculated for $C_6H_6NO_3S$: *m/z* 172.0074, *m/z* found 172.0079.

4,4'-sulfonyldiphenol (1j): Compound **1j** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 1.73 min (method A). HR-MS calculated for $C_{12}H_{11}O_4S$: *m/z* 251.0373, *m/z* found 251.0371.

3,5-dichloro-4-hydroxybenzenesulfonic acid (1k): Compound **1k** was purchased as a 1 mg solid form from Ambiter. RP-UPLC: t_R = 1.11 min (method A). HR-MS calculated for $C_6H_3Cl_2O_4S$: *m/z* 240.9135, *m/z* found 240.9132.

sodium 4,4'-sulfonylbis(2,6-dichlorophenolate) (1l): Compound **1l** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 2.30 min (method A). HR-MS calculated for $C_{12}H_4Cl_4O_4S$: *m/z* 384.8668, *m/z* found 384.9348.

2-chloro-4-(morpholinosulfonyl)phenol (1m): Compound **1m** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 1.90 min (method A). HR-MS calculated for $C_{10}H_{11}ClNO_4S$: *m/z* 276.0103, *m/z* found 276.0099.

2-hydroxy-5-(pyrrolidin-1-ylsulfonyl)benzamide (1n): Compound **1n** was purchased as a 1 mg solid form from Enamine. RP-UPLC: t_R = 1.83 min (method A). HR-MS calculated for $C_{11}H_{13}N_2O_4S$: *m/z* 269.0602, *m/z* found 269.0599.

5-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic acid (2): Compound **2** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 2.21 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 12.76 (1H, s), 7.39 (1H, s), 2.97 – 2.57 (3H, m), 2.14 (1H, dd, *J* = 15.9, 10.0 Hz), 1.94 – 1.65 (2H, m), 1.39 (1H, m), 1.02 (3H, d, *J* = 6.5 Hz). ^{13}C NMR (101 MHz, DMSO): δ 163.0, 142.8, 136.4, 133.6 (CH_{ar}), 130.6, 33.1 (CH_2), 30.8 (CH_2), 28.3 (CH), 24.5 (CH_2), 21.2 (CH_3). HR-MS calculated for $C_{10}H_{13}O_2S$: *m/z* 197.0631, *m/z* found 197.0629.

6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine, HCl salt (*rac*-3): Compound ***rac*-3** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.83 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.48 (1H, d, *J* = 2.0 Hz, H_{ar}), 7.36 (1H, d, *J* = 8.7 Hz, H_{ar}), 7.14 (1H, dd, *J* = 8.7, 2.1 Hz, H_{ar}), 4.61 (1H, t, *J* = 4.9 Hz), 2.88 – 2.63 (2H, m),

2.33 – 2.19 (1H, m), 2.14 – 1.93 (3H, m). ^{13}C NMR (101 MHz, MeOD): δ 136.7, 130.7, 129.0, 126.2, 124.1 (CH_{ar}), 119.2 (CH_{ar}), 114.9, 113.7 (CH_{ar}), 45.9 (CH), 29.3 (CH_2), 21.3 (CH_2), 20.0 (CH_2). HR-MS calculated for $C_{12}H_{11}ClN$: *m/z* 204.0575, m/z found 204.0571.

(*S*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine, HCl salt ((*S*)-3): Compound (*S*)-**7** (126 mg, 0.32 mmol, 1.0 eq) was suspended in DCM (2 mL) in a two-necks flask. BCl_3 (0.81 mL, 1 M in DCM, 0.81 mmol, 3.0 eq) was added dropwise. The solution was stirred at room temperature for 5 h and then at 10 °C for 15 h. KOH (7 mL) 20% w/v was slowly added dropwise with the temperature kept at 10 °C. The solution was then warmed up to room temperature. The two phases were separated. The aqueous phase was extracted twice with 10 mL 9/1 DCM/MeOH. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (gradient MeOH / DCM). The residue was dissolved in HCl 1.25 M in MeOH, and the white precipitate was removed. The solvent was removed to afford (*S*)-**3** (51 mg, 0.15 mmol, 47%) as a brownish solid. α_D = - 1.3 (c 0.053, MeOH). RP-UPLC: t_R = 1.85 min (method A). ^{1}H NMR (400 MHz, MeOD): δ 7.48 (1H, dd, *J* = 2.1, 0.6 Hz), 7.36 (1H, dd, *J* = 8.6, 0.6 Hz), 7.14 (1H, dd, *J* = 8.7, 2.1 Hz), 4.61 (1H, t, *J* = 5.0 Hz), 2.88 – 2.77 (1H, m), 2.75 – 2.66 (1H, m), 2.34 – 2.21 (1H, m), 2.16 – 1.91 (2H, m). ^{13}C NMR (101 MHz, MeOD) δ 136.7, 130.7, 129.0, 126.2, 124.1 (CH_{ar}), 119.2 (CH_{ar}), 114.9 (CH_{ar}), 113.7, 45.9 (CH), 29.3 (CH_2), 21.3 (CH_2), 20.1 (CH_2). HR-MS calculated for $C_{12}H_{11}ClN$: *m/z* 204.0575, m/z found 204.0573.

(*R*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine, HCl salt ((*R*)-3): The procedure described above for (S)-**3** was applied starting from (*R*)-**7** (82 mg, 0.21 mmol, 1.0 eq) to afford (*R*)-**3** (18 mg, 0.070 mmol, 33%) as a brownish solid, α_D = 1.03 (c 0.053, MeOH). RP-UPLC: t_R = 1.84 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.37 (1H, d, *J* = 2.0 Hz), 7.26 (1H, d, *J* = 8.5 Hz), 7.03 (1H, dd, *J* = 8.6, 2.1 Hz), 4.13 – 4.07 (1H, m), 2.72 – 2.62 (2H, m), 2.25 – 2.14 (1H, m), 2.11 – 2.02 (1H, m), 1.90 – 1.67 (2H, m). ^{13}C NMR (101 MHz, MeOD): δ 139.6, 136.2, 129.7, 125.3, 122.2 (CH_{ar}), 118.5 (CH_{ar}), 112.9 (CH_{ar}), 111.1, 46.5 (CH), 34.0 (CH_2), 22.1 (CH_2), 21.9 (CH_2). HR-MS calculated for $C_{12}H_{14}ClN_2$: *m/z* 221.0840, m/z found 221.0833.

6-bromo-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (4): Compound **4** was purchased as a 25 mg solid form from Enamine. RP-UPLC: t_R = 1.89 min (method A). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (1H, s), 7.58 (1H, d, *J* = 1.8 Hz), 7.23 – 7.16 (2H, m), 4.08 – 4.04 (1H, m), 2.67 – 2.63 (2H, m), 2.24 – 2.16 (1H, m), 2.06 – 1.99 (1H, m), 1.89 – 1.72 (1H, m), 1.63 – 1.54 (1H, m), 1.48 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 134.6, 129.5, 124.4 (CH), 121.2 (CH),

112.5, 112.3 (CH), 110.7, 46.9 (CH), 36.9 (CH_2), 21.8 (CH_2), 20.9 (CH_2). HR-MS calculated for $C_{12}H_{11}NBr$: *m/z* 248.0075, *m/z* found 248.0077.

6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (5): Compound **5** was purchased as a 25 mg solid form from Enamine. RP-UPLC: t_R = 1.73 min (method A). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H, NH), 7.21 (1H, dd, *J* = 8.8, 4.4 Hz, H_{ar}), 7.11 (1H, dd, *J* = 9.6, 2.6 Hz, H_{ar}), 6.88 (1H, td, *J* = 9.1, 2.5 Hz, H_{ar}), 4.09 – 4.05 (1H, m), 2.68 – 2.64 (2H, m), 2.23 – 2.16 (1H, m), 2.07 – 1.99 (1H, m), 1.89 – 1.77 (m, 1H), 1.65 – 1.55 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (d, J = 234 Hz, CF), 139.2, 132.4, 128.0 (d, J = 10.1 Hz), 111.4 (d, J = 9.1 Hz, CH), 111.2 (d, J = 4 Hz), 109.7 (d, J = 26.3 Hz, CH), 103.5 (d, J = 23.3 Hz, CH), 46.9 (CH), 36.9 (CH_2), 21.8 (CH_2), 20.0 (CH_2). HR-MS calculated for $C_{12}H_{11}FN$: *m/z* 188,0876 *m/z* found 188.0875.

6-methyl-*N*-propyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine, TFA salt (6): Compound **6** was purchased as a 25 mg solid form from Enamine. Compound was purified by preparative HPLC (gradient from 70/30 A/D to 55/45 A/D in 18 minutes, t_R = 35 % D) to afford **6** as a white powder. RP-UPLC: t_R = 1.94 min (method A). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (1H, s, NH), 9.46 (2H, d, *J* = 223.2 Hz, NH_2), 7.27 (1H, m, Har), 7.24 (1H, d, *J* = 8.3 Hz, H_{ar}), 7.01 (1H, dd, *J* = 8.3, 1.7 Hz, H_{ar}), 4.63 – 4.58 (1H, m), 2.90 – 2.78 (1H, m), 2.74 – 2.62 (3H, m), 2.43 (3H, s, CH_3), 2.31 – 2.19 (1H, m), 2.12 – 1.97 (1H, m), 1.84 – 1.73 (1H, m), 1.71 – 1.56 (2H, m), 0.88 (3H, t, *J* = 7.4 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.2, 129.0, 126.7, 125.7, 124.9 (CH), 118.5 (CH), 115.9, 111.5 (CH), 52.0 (CH), 44.3 (CH_2), 25.5 (CH_2), 21.6 (CH_3), 21.6 (CH_2), 20.7 (CH_2), 20.1 (CH_2), 11.2 (CH_3). HR-MS calculated for $C_{16}H_{23}N_2$: *m/z* 243.1853, *m/z* found 243.1855.

2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (7): Compound **7** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 2.16 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.40 (1H, dt, *J* = 7.7, 1.1 Hz, H_{ar}), 7.30 (1H, dt, *J* = 8.1, 0.9 Hz, H_{ar}), 7.05 (1H, ddd, *J* = 8.2, 7.0, 1.3 Hz, H_{ar}), 6.95 (1H, ddd, *J* = 8.0, 7.0, 1.1 Hz, H_{ar}), 4.89 – 4.85 (1H, m), 2.84 – 2.55 (2H, m), 2.16 – 2.00 (m, 2H), 1.97 – 1.77 (m, 2H). HR-MS calculated for $C_{12}H_{17}NO$: *m/z* 186.0924, *m/z* found 186.0926.

2,3,4,9-tetrahydro-1*H*-carbazole-1-carbonitrile (8): Compound **8** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 2.33 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.42 (1H, dt, *J* = 7.7, 1.0 Hz, H_{ar}), 7.31 (1H, dt, *J* = 8.1, 0.9 Hz,

H_{ar}), 7.10 (1H, ddd, *J* = 8.2, 7.1, 1.3 Hz, H_{ar}), 7.00 (1H, ddd, *J* = 8.0, 7.1, 1.1 Hz, H_{ar}), 4.19 (1H, tt, *J* = 5.5, 1.4 Hz), 2.87 – 2.58 (2H, m), 2.36 – 2.12 (2H, m), 2.13 – 1.88 (2H, m). HR-MS calculated for $C_{13}H_{11}DN_2Na$: *m/z* 220.0955, *m/z* found 220.0956.

(2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)methanamine (9): Compound **9** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.71 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.40 (1H, d, *J* = 7.7 Hz), 7.29 (1H, d, *J* = 8.0 Hz), 7.07 (1H, ddd, *J* = 8.2, 7.1, 1.3 Hz), 6.98 (1H, ddd, *J* = 8.1, 7.1, 1.1 Hz), 3.47 (1H, dd, *J* = 12.6, 3.7 Hz), 3.13 (1H, dd, *J* = 12.6, 9.4 Hz), 2.80 – 2.62 (2H, m), 3.31 – 3.23 (1H, m), 2.22 – 1.97 (2H, m), 1.96 – 1.69 (2H, m). ^{13}C NMR (101 MHz, MeOD): δ 138.1, 132.8, 128.6, 122.5 (CH_{ar}), 119.8 (CH_{ar}), 118.8 (CH_{ar}), 112.4, 111.8 (CH_{ar}), 43.9 (CH_2), 33.8 (CH), 27.7 (CH_2), 22.1 (CH_2), 21.9 (CH_2). HR-MS calculated for $C_{13}H_{17}N_2$: *m/z* 201.1386, *m/z* found 201.1391.

1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole (10): Compound **10** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.51 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.38 (1H, d, *J* = 7.6 Hz, H_{ar}), 7.27 (1H, d, *J* = 7.9 Hz, H_{ar}), 7.06 – 7.00 (1H, m, H_{ar}), 6.98 - 6.93 (1H, m, H_{ar}), 4.13 (1H, dt, *J* = 6.7, 1.9 Hz), 3.35 – 3.27 (1H, m), 3.03 - 2.92 (1H, m), 2.88 – 2.62 (2H, m), 1.48 (3H, d, *J* = 6.7 Hz, CH_3). ^{13}C NMR (101 MHz, MeOD): δ 137.8, 137.7, 128.6, 121.9 (CH_{ar}), 119.6 (CH_{ar}), 118.6 (CH_{ar}), 111.8 (CH_{ar}), 108.1, 49.53 (CH), 43.6 (CH_2), 22.9 (CH_2), 20.3 (CH_3). HR-MS calculated for $C_{12}H_{14}DN_2$: *m/z* 188.1298, *m/z* found 188.1292.

1-(1-methyl-1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethan-1-one (11) : Compound **11** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 2.00 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.40 (1H, d, *J* = 7.7, H_{ar}), 7.33 – 7.24 (1H, m, H_{ar}), 7.12 – 6.93 (2H, m, H_{ar}), 5.66 (1H, q, *J* = 6.7 Hz), 5.15 (q, *J* = 6.7 Hz, 0H), 4.20 – 4.04 (1H, m), 3.52 (1H, ddd, *J* = 13.9, 10.0, 6.0 Hz), 3.15 – 2.96 (m, 0H), 2.93 – 2.66 (3H, m), 2.23 (4H, d, *J* = 1.5 Hz), 1.61 (1H, d, *J* = 6.7 Hz, 1H), 1.48 (2H, d, *J* = 6.8 Hz, 2H). HR-MS calculated for $C_{14}H_{17}N_2O$: *m/z* 229.1335, *m/z* found 229.1331.

1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid (12): Compound **12** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.31 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 10.86 (1H, s), 7.39 (2H, d, *J* = 8.8 Hz, H_{ar}), 7.04 (1H, t, *J* = 7.4 Hz, H_{ar}), 6.95 (1H, t, *J* = 7.0 Hz, H_{ar}), 3.4 – 3.2 (2H, m), 2.86 (2H, q,

J = 5.8 Hz), 1.71 (3H, s, CH_3). HR-MS calculated for $C_{13}H_{13}N_2O_2$: *m/z* 229.0983, *m/z* found 229.0986.

1,3-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole, HCl salt (13) : Compound **13** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.56 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.47 (1H, dt, *J* = 7.8, 1.1 Hz, H_{ar}), 7.36 (1H, dt, *J* = 8.1, 1.0 Hz, H_{ar}), 7.15 (1H, ddd, *J* = 8.2, 7.1, 1.3 Hz, H_{ar}), 7.06 (1H, ddd, *J* = 8.1, 7.1, 1.1 Hz, H_{ar}), 4.84 – 4.74 (1H, m) 3.83 – 3.68 (1H, m), 3.16 (1H, ddd, *J* = 16.3, 4.7, 1.5 Hz), 2.83 (1H, ddd, *J* = 16.4, 11.4, 2.5 Hz), 1.75 (3H, d, *J* = 6.8 Hz, CH_3), 1.59 (3H, d, *J* = 6.5 Hz, CH_3). HR-MS calculated for $C_{13}H_{16}DN_2$: *m/z* 202.1449, *m/z* found 202.1455.

1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (14): Compound **14** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.45 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 11.05 (1H, s), 7.45 (1H, d, *J* = 7.7 Hz, H_{ar}), 7.33 (1H, d, *J* = 8.0 Hz, H_{ar}), 7.14 – 7.05 (1H, m, H_{ar}), 7.03 – 6.95 (1H, m, H_{ar}), 4.50 (1H, d, *J* = 7.0 Hz), 3.59 (1H, dd, *J* = 11.9, 4.8 Hz), 3.15 (1H, dd, *J* = 15.9, 4.8 Hz), 2.76 (1H, ddd, *J* = 16.0, 11.9, 2.4 Hz), 1.60 (3H, d, *J* = 6.7 Hz, CH_3). HR-MS calculated for $C_{13}H_{15}N_2O_2$: *m/z* 231.1128, *m/z* found 231.1126.

2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (15): Compound **15** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.43 min (method A). ^{1}H NMR (300 MHz, DMSO): δ 10.93 (1H, s), 7.44 (1H, d, *J* = 7.7 Hz, H_{ar}), 7.33 (1H, d, *J* = 8.0 Hz, H_{ar}), 7.11 – 7.02 (1H, m, H_{ar}), 7.02 – 6.93 (1H, m, H_{ar}), 4.30 – 4.10 (2H, m), 3.60 (1H, dd, *J* = 10.4, 5.0 Hz), 3.13 (1H, dd, *J* = 16.2, 5.0 Hz), 2.81 (1H, dd, *J* = 16.2, 10.5 Hz). HR-MS calculated for $C_{12}H_{13}N_2O_2$: *m/z* 217.0972, *m/z* found 217.0970.

methyl 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (16): Compound **16** was purchased as a 25 mg solid form from Princeton Biomolecular Research. Compound was purified by preparative HPLC (gradient from 90/10 A/D to 70/30 A/D in 18 minutes, t_R = 24 %) to afford **16** as a white powder. RP-UPLC: t_R = 1.64 min (method A). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (1H, s, NH), 7.45 – 7.39 (1H, m, H_{ar}), 7.24 (1H, t, *J* = 1.1 Hz, H_{ar}), 7.19 – 7.11 (2H, m), 4.52 (1H, d, *J* = 15.7 Hz), 4.26 (1H, d, *J* = 15.7 Hz), 4.14 (1H, dd, *J* = 9.3, 5.5 Hz), 3.75 (3H, s, CH3), 3.39 – 3.11 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 136.8, 126.0, 125.2, 122.9 (CH_{ar}), 120.1 (CH_{ar}), 118.2 (CH_{ar}), 111.8 (CH_{ar}), 105.2, 54.9 (CH), 53.6 (CH_3), 40.7 (CH_2), 22.2 (CH_2). HR-MS calculated for $C_{13}H_{15}N_2O_2$: *m/z* 231.1128, *m/z* found 231.1132.

6-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-3-amine (17): Compound **17** was purchased as a 25 mg solid form from Enamine. RP-UPLC: t_R = 1.67 min (method A). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, s, NH), 7.23 (1H, m, H_{ar}), 7.16 (1H, d, *J* = 8.2 Hz, H_{ar}), 6.94 (1H, dd, *J* = 8.2, 1.6 Hz, H_{ar}), 3.29 (1H, dddd, *J* = 9.8, 8.2, 5.1, 3.0 Hz), 3.07 – 2.95 (1H, m), 2.86 – 2.77 (2H, m), 2.48 – 2.38 (4H, m), 2.15 – 1.99 (1H, m), 1.79 (1H, ddt, *J* = 12.7, 9.8, 7.7 Hz), 1.52 (2H, s, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 134.7, 133.3, 128.6, 128.1, 122.8 (CH_{ar}), 117.7 (CH_{ar}), 110.2 (CH_{ar}), 108.3, 48.0 (CH), 32.9 (CH_2), 31.4 (CH_2), 21.8 (CH_2), 21.6 (CH_3). HR-MS calculated for $C_{13}H_{18}DN_2$: *m/z* 204.1606, *m/z* found 204.1605.

3-(tert-butyl)-2,3,4,9-tetrahydro-1*H*-carbazole (18): Compound **18** was purchased as a 25 mg solid form from Princeton Biomolecular Research. ^{1}H NMR (300 MHz, DMSO): δ 10.58 (1H, s, NH), 7.33 (1H, d, *J* = 7.5 Hz, H_{ar}), 7.25 – 7.17 (1H, m, H_{ar}), 6.96 (1H, td, *J* = 7.9, 7.5, 1.4 Hz, H_{ar}), 6.90 (1H, td, *J* = 7.3, 1.3 Hz, H_{ar}), 2.85 – 2.59 (3H, m), 2.37 – 2.23 (1H, m), 2.14 – 1.98 (1H, m), 1.59 – 1.28 (2H, m), 0.98 (9H, s, tBu). HR-MS calculated for $C_{16}H_{21}N$: *m/z* 228.1747, *m/z* found 228.1705.

2-ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (19): Compound **19** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.55 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.38 – 7.31 (1H, m, H_{ar}), 7.26 (1H, dt, *J* = 8.0, 1.0 Hz, H_{ar}), 7.03 (1H, ddd, *J* = 8.1, 7.1, 1.4 Hz, H_{ar}), 6.96 (1H, ddd, *J* = 8.2, 7.1, 1.2 Hz, H_{ar}), 3.71 (2H, d, *J* = 1.5 Hz), 2.92 (4H, s), 2.73 (2H, q, *J* = 7.2 Hz), 1.25 (3H, t, *J* = 7.2 Hz, CH_3). HR-MS calculated for $C_{13}H_{16}DN_2$: *m/z* 202.1449, *m/z* found 202.1451.

2,6-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (20): Compound **20'** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.55 min (method A). ^{1}H NMR (300 MHz, MeOD) δ 7.25 (1H, dd, *J* = 6.9, 2.1 Hz, H_{ar}), 7.06 – 6.84 (2H, m, H_{ar}), 4.51 (2H, s), 3.71 (2H, s), 3.25 (2H, t, *J* = 6.3 Hz), 3.12 (3H, s, CH_3), 2.47 (3H, s, CH_3). HR-MS calculated for $C_{13}H_{15}D_2N_2$: *m/z* 203.1512, *m/z* found 203.1514.

2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (21): Compound **21** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.43 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.35 – 7.31 (1H, m, H_{ar}), 7.26 (1H, dt, *J* = 8.1, 1.0 Hz, H_{ar}), 7.06 – 6.92 (2H, m, H_{ar}), 3.68 (2H, t, *J* = 1.5 Hz), 2.98 – 2.81 (4H, m), 2.54 (3H, s, CH_3). HR-MS calculated for $C_{12}H_{14}DN_2$: *m/z* 188.1293, *m/z* found 188.1293.

1,2,4-trimethyl-1,2,3,4-tetrahydrobenzofuro[3,2-*c*]pyridin-8-amine (22): Compound **22** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 1.00 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.27 (1H, d, *J* = 8.7 Hz, H_{ar}), 6.92 (1H, d, *J* = 2.2 Hz, H_{ar}), 6.78 (1H, dd, *J* = 8.7, 2.3 Hz, H_{ar}), 6.25 (2H, s, NH_2), 4.71 – 4.56 (1H, m), 3.79 (1H, dd, *J* = 12.2, 5.5 Hz), 3.52 – 3.39 (1H, m), 3.29 – 3.23 (1H, m), 3.08 (3H, s, CH_3), 1.79 (3H, d, *J* = 6.7 Hz, CH_3), 1.39 (3H, d, *J* = 6.8 Hz, CH_3). HR-MS calculated for $C_{14}H_{19}N_2O$: *m/z* 231.1492, *m/z* found 231.1492.

3-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine (23): Compound **23** was purchased as a 25 mg solid form from Princeton Biomolecular Research. RP-UPLC: t_R = 2.27 min (method B). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 – 7.83 (1H, m), 7.49 (1H, d, *J* = 7.0 Hz), 4.51 – 4.26 (1H, m), 4.26 – 4.01 (1H, m), 3.86 – 3.62 (1H, m), 2.92 (1H, dd, *J* = 18.4, 9.9 Hz), 2.42 – 2.12 (2H, m), 2.02 – 1.77 (1H, m), 1.25 (3H, t, *J* = 5.9 Hz). MS calculated for $C_{12}H_{15}N_2$: *m/z* 187.12, *m/z* found 187.03.

3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazin-3-ol (24): Compound **24** was purchased as a 25 mg solid form from Princeton Biomolecular Research.RP-UPLC: t_R = 1.20 min (method A). ^{1}H NMR (300 MHz, MeOD): δ 7.49 – 7.43 (1H, m, H_{ar}), 7.41 – 7.34 (1H, m, H_{ar}), 7.21 (2H, dd, *J* = 6.0, 3.2 Hz, H_{ar}), 4.65 – 4.55 (1H, m), 4.34 – 4.10 (2H, m), 3.45 (1H, ddd, *J* = 12.8, 2.5, 0.9 Hz), 3.29 – 3.21 (1H, m). HR-MS calculated for $C_{10}H_{11}N_2OS$: *m/z* 207.0587, *m/z* found 207.0588.

(*S*)-6-chloro-*N*-((*S*)-1-(4-methoxyphenyl)ethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine, HCl salt ((*S*)-26): 6-chloro-2,3,4,9-tetrahydrocarbazol-1-one (282 mg, 1.3 mmol, 1.0 eq) was suspended in dry toluene (4 mL) under argon. (1*S*)-1-(4-methoxyphenyl)ethanamine (0.2 mL, 1.3 mmol, 1.0 eq) and HCl *conc* (10 µL) were added in presence of activated 4A molecular sieves. The mixture was stirred at 112 °C during 6 h before it was allowed to cool down to room temperature. The mixture was added dropwise to a solution of $NaBH_4$ (48 mg, 1.3 mmol, 1.0 eq) in ethanol (3.4 mL) at - 30 °C. The flask was washed twice with 0.5 mL of dried toluene. The mixture was stirred at -30 °C for 14.5 h before warming up slowly at room temperature. Acetone (1 mL) was added and the solution was stirred at room temperature for 30 minutes before the removal of few milliliters of solvent. Ethyl acetate and water were added. The two phases were separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with water, then with brine, dried over Na_2SO_4 and concentrated. The yellow oil was then dissolved in toluene (2 mL) and cooled down to - 5 °C.

1.4 mL HCl (1.25 M in MeOH) were added and the solution was stirred at - 5 °C for 30 minutes. The white precipitate was filtered, washed with TBME and dried *in vacuo* to afford (*S*)-**26** (297 mg, 0.76 mmol, 59%) as a white solid, α_D = - 9.5 (c 0.055, MeOH). RP-UPLC: t_R = 4.61 min (method B). ^{1}H NMR (400 MHz, DMSO): δ 11.75 (1H, s), 9.87 (1H, d, *J* = 10.0 Hz), 9.24 (1H, dd, *J* = 12.0, 6.4 Hz), 7.71 (2H, d, *J* = 8.5 Hz), 7.52 (1H, d, *J* = 2.1 Hz), 7.41 (1H, d, *J* = 8.6 Hz), 7.14 (1H, dt, *J* = 8.7, 4.3 Hz), 6.99 (2H, d, *J* = 8.7 Hz), 4.70 (1H, q, *J* = 6.4 Hz), 4.65 – 4.49 (1H, m), 3.76 (3H, s), 2.64 (2H, q, *J* = 6.0, 5.5 Hz), 2.18 – 2.08 (1H, m), 2.04 – 1.90 (2H, m), 1.86 – 1.68 (1H, m), 1.67 (3H, d, *J* = 6.7 Hz). ^{13}C NMR (101 MHz, DMSO): δ 159.6, 134.4, 130.0, 129.7, 129.5 (CH_{ar}), 128.9, 128.2, 127.1, 123.5, 122.2 (CH_{ar}), 117.8 (CH_{ar}), 114.1 (CH_{ar}), 113.1, 113.0 (CH_{ar}), 55.2 (CH), 55.2 (CH), 49.1 (CH_3), 25.9 (CH_2), 20.1 (CH_2), 19.5 (CH_2), 18.9 (CH_3). HR-MS calculated for $C_{21}H_{24}N_2OCl$: *m/z* 355.1572, *m/z* found 355.1577.

(*R*)-6-chloro-*N*-((*R*)-1-(4-methoxyphenyl)ethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine, HCl salt ((*R*)-26): The procedure described above for (*S*)-**26** starting with (1*R*)-1-(4-methoxyphenyl)ethanamine (0.2 mL, 1.3 mmol, 1.0 eq) afforded (*R*)-**7** (328 mg, 0.84 mmol, 66%) as a white solid. α_D = +10.2 (c 0.055, MeOH). RP-UPLC: t_R = 4.61 min (method B). ^{1}H NMR (400 MHz, DMSO): δ 11.75 (1H, s), 9.87 (1H, d, *J* = 10.0 Hz), 9.24 (1H, dd, *J* = 12.0, 6.4 Hz), 7.71 (2H, d, *J* = 8.5 Hz), 7.52 (1H, d, *J* = 2.1 Hz), 7.41 (1H, d, *J* = 8.6 Hz), 7.14 (1H, dt, *J* = 8.7, 4.3 Hz), 6.99 (2H, d, *J* = 8.7 Hz), 4.70 (1H, q, *J* = 6.4 Hz), 4.65 – 4.49 (1H, m), 3.76 (3H, s), 2.64 (2H, q, *J* = 6.0, 5.5 Hz), 2.18 – 2.08 (1H, m), 2.04 – 1.90 (2H, m), 1.86 – 1.68 (1H, m), 1.67 (3H, d, *J* = 6.7 Hz). ^{13}C NMR (101 MHz, DMSO): δ 159.6, 134.4, 130.0, 129.7, 129.5 (CH_{ar}), 128.9, 128.2, 127.1, 123.5, 122.2 (CH_{ar}), 117.8 (CH_{ar}), 114.1 (CH_{ar}), 113.1, 113.0 (CH_{ar}), 55.2 (CH), 55.2 (CH), 49.1 (CH_3), 25.9 (CH_2), 20.1 (CH_2), 19.5 (CH_2), 18.9 (CH_3). HR-MS calculated for $C_{21}H_{24}N_2OCl$: *m/z* 355.1572, *m/z* found 355.1581.

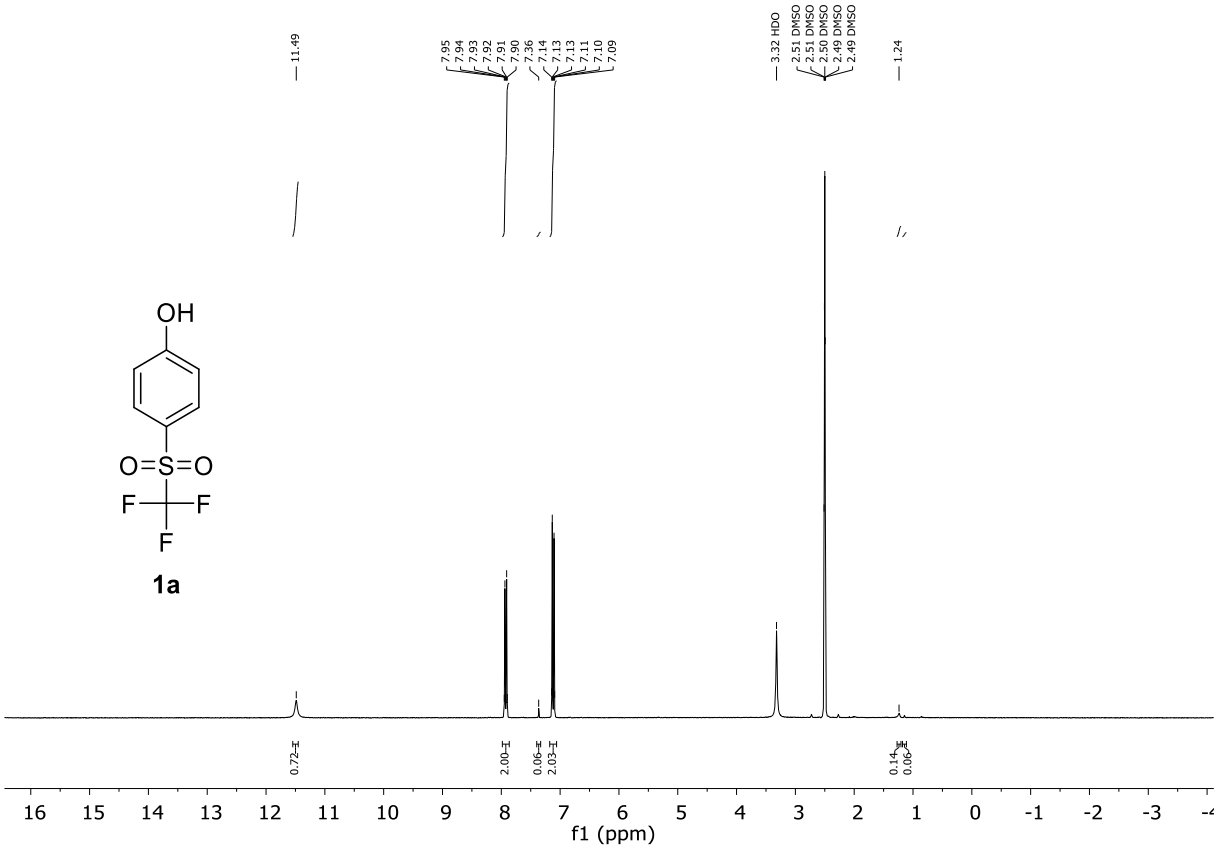
HPLC purity of final compounds

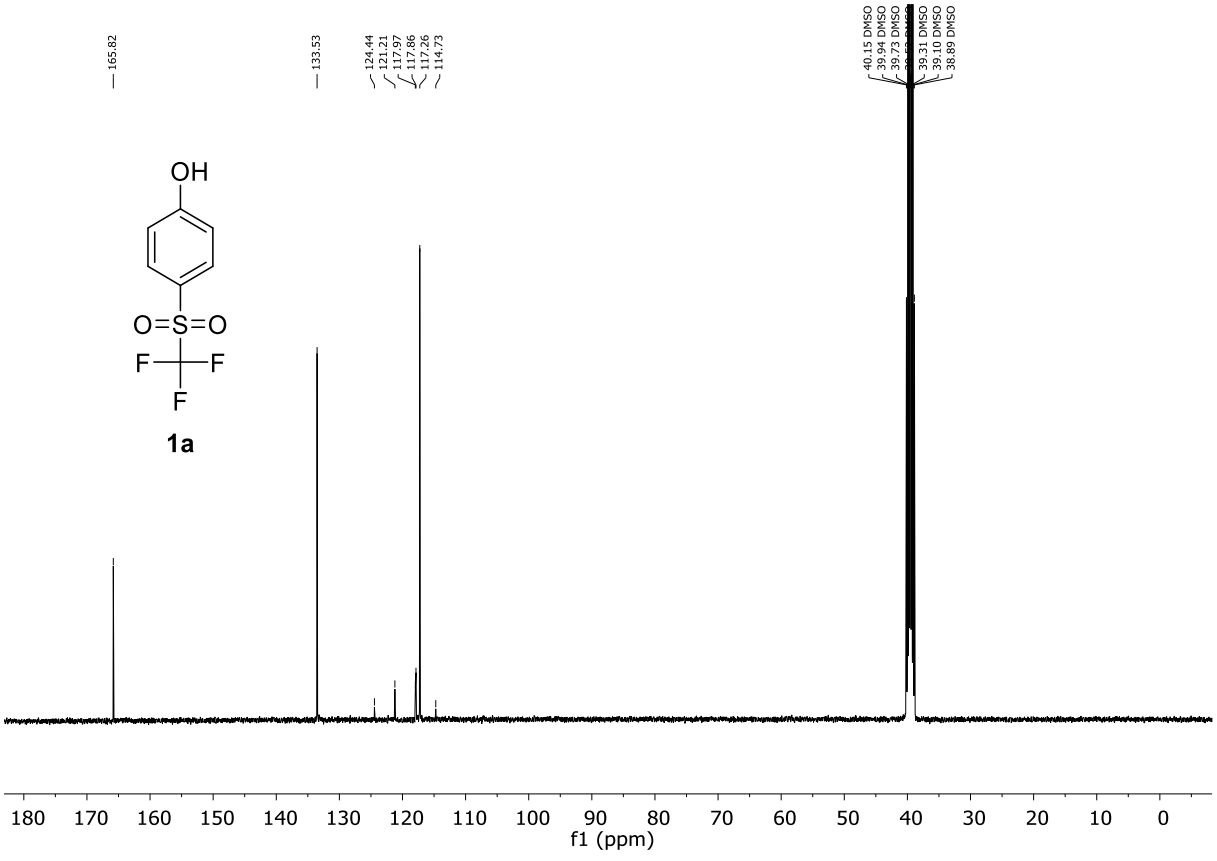
***Table 1**: Purity of the final compounds*

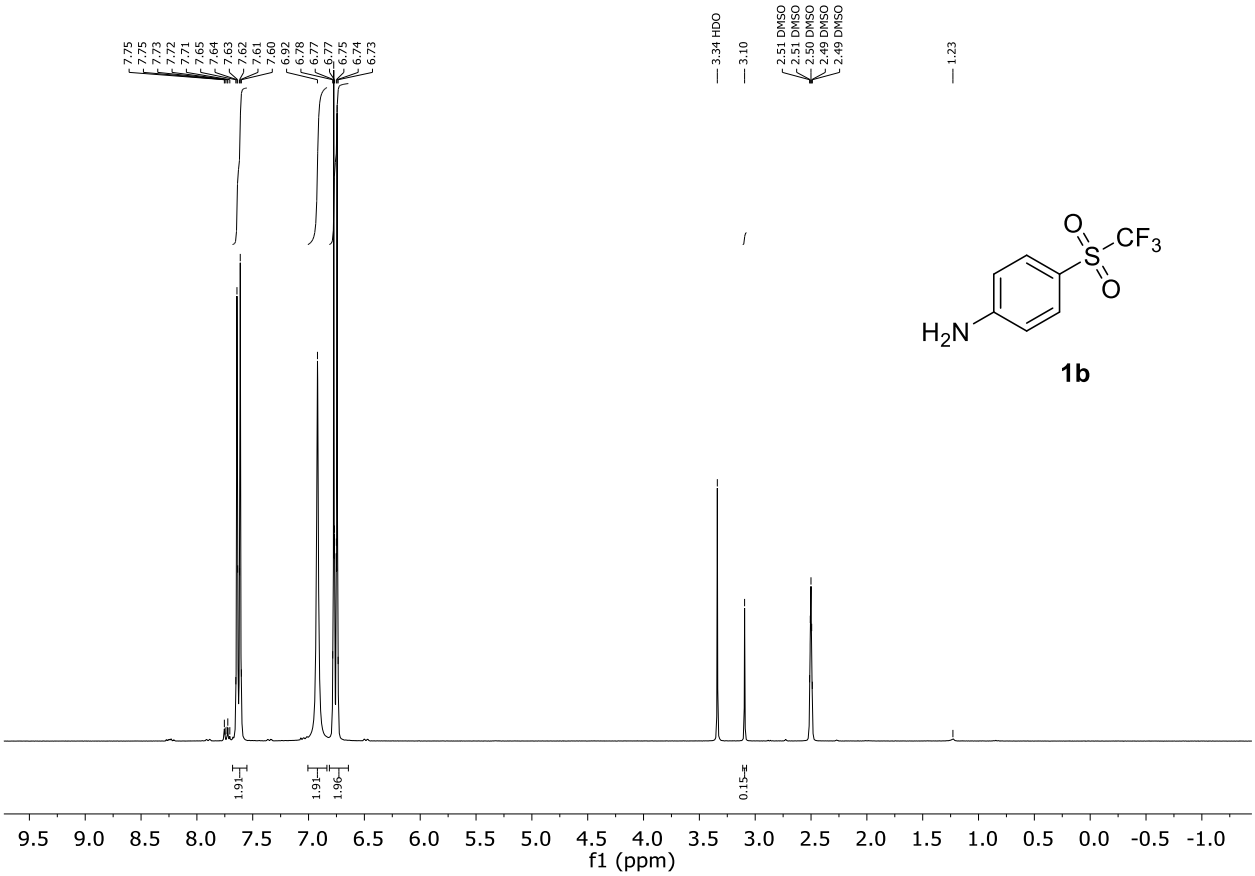
Compound	Retention time	Purity [%]	HPLC Method[a]
1a	4.67 min	99	B
1b	2.24 min	97	A
1c	2.41 min	99	A
1d	1.43 min	99	A
1e	1.48 min	99	A
1f	1.72 min	99	A
1g	1.78min	99	A
1h	1.89 min	99	A
1i	1.17 min	98	A
1j	1.73 min	99	A
1k	1.11 min	99	A
1l	2.30 min	99	A
1m	1.90 min	87	A
1n	1.83 min	99	A
2	2.21 min	99	A
***rac*-3**	1.83 min	99	A
***(S)*-3**	1.85 min	99	A
***(R)*-3**	1.84 min	98	A
4	1.89 min	99	A
5	1.73 min	99	A
6	1.94 min	99	A
7	2.16 min	99	A
8	2.33 min	99	A
9	1.71 min	99	A
10	1.51 min	99	A
11	2.00 min	99	A
12	1.31 min	99	A
13	1.56 min	99	A
14	1.45 min	99	A
15	1.43 min	90	A
16	1.64 min	99	A
17	1.67 min	99	A
18	ND[b]	ND[b]	A
19	1.55 min	99	A
20	1.55 min	99	A
21	1.43 min	99	A
22	1.00 min	96	A
23	2.27 min	99	B
24	1.20 min	99	A

[a] method A: from 100 % A to 100 % D in 2.2 min, then 100 % D. Method B: from 100 % A to 100% D in 7.5 min, then 100 % D. [b] ND = Not Determined. The compound was not soluble in acetonitrile/water.

^{1}H and ^{13}C NMR spectra



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1.91
1.96
0.15
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O
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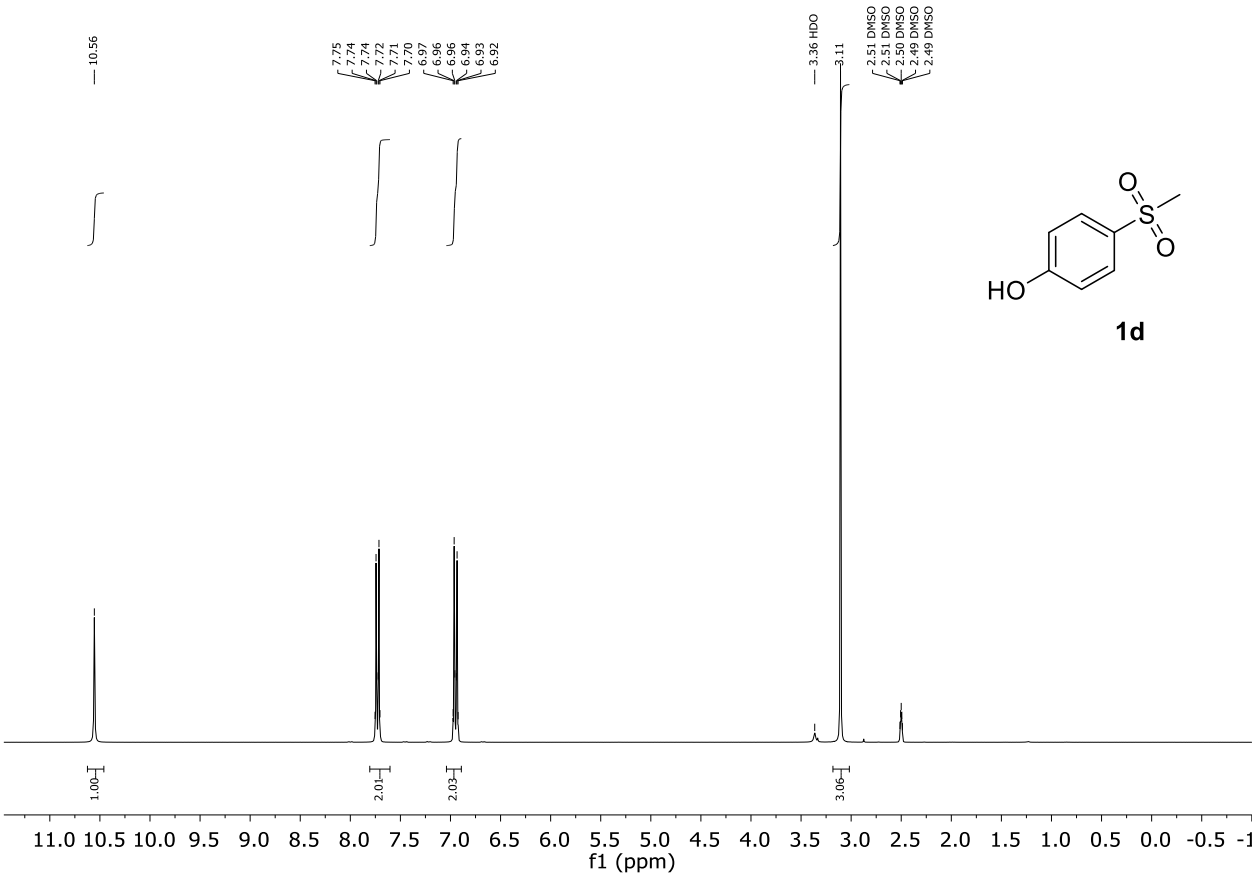
1b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2.51 DMSO
2.50 DMSO
2.49 DMSO
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2.03
3.06
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f1 (ppm)

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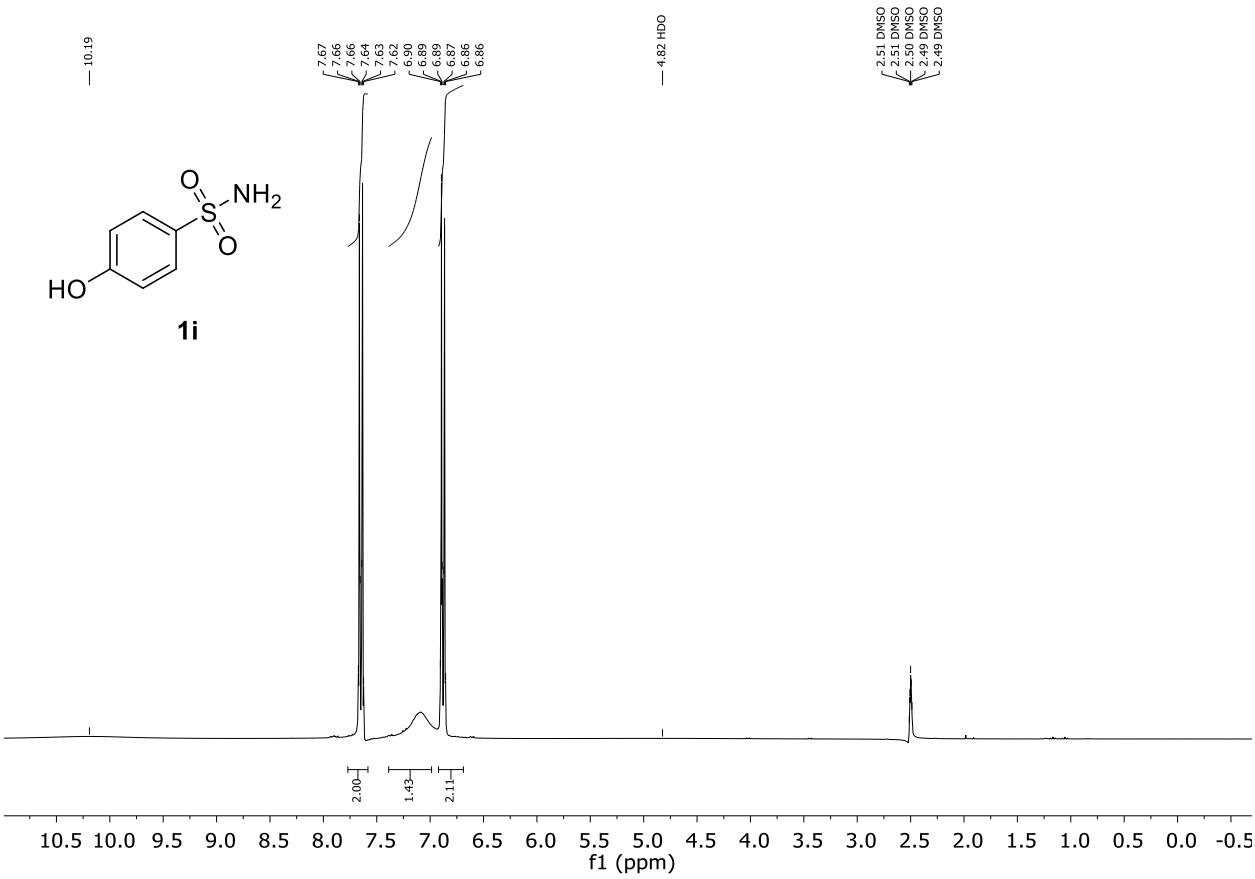
S
O
HO

1d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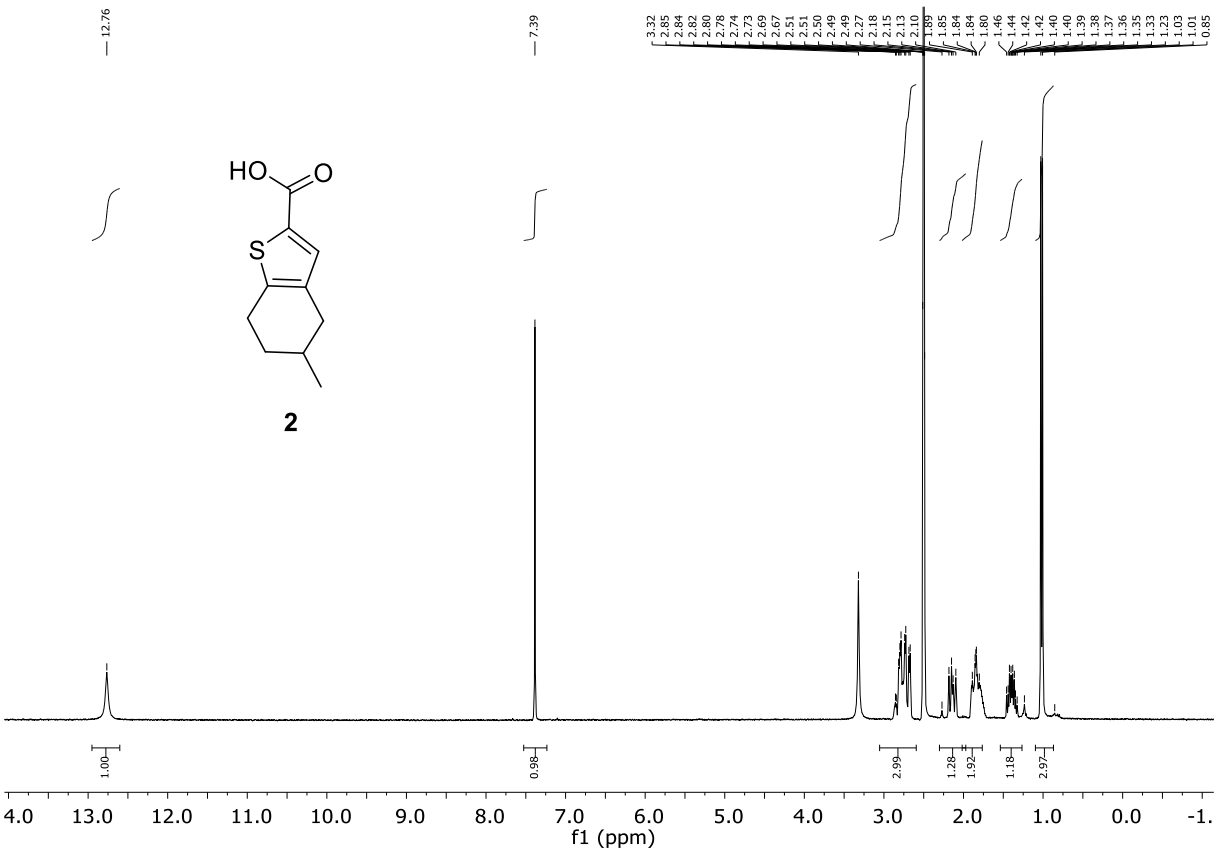
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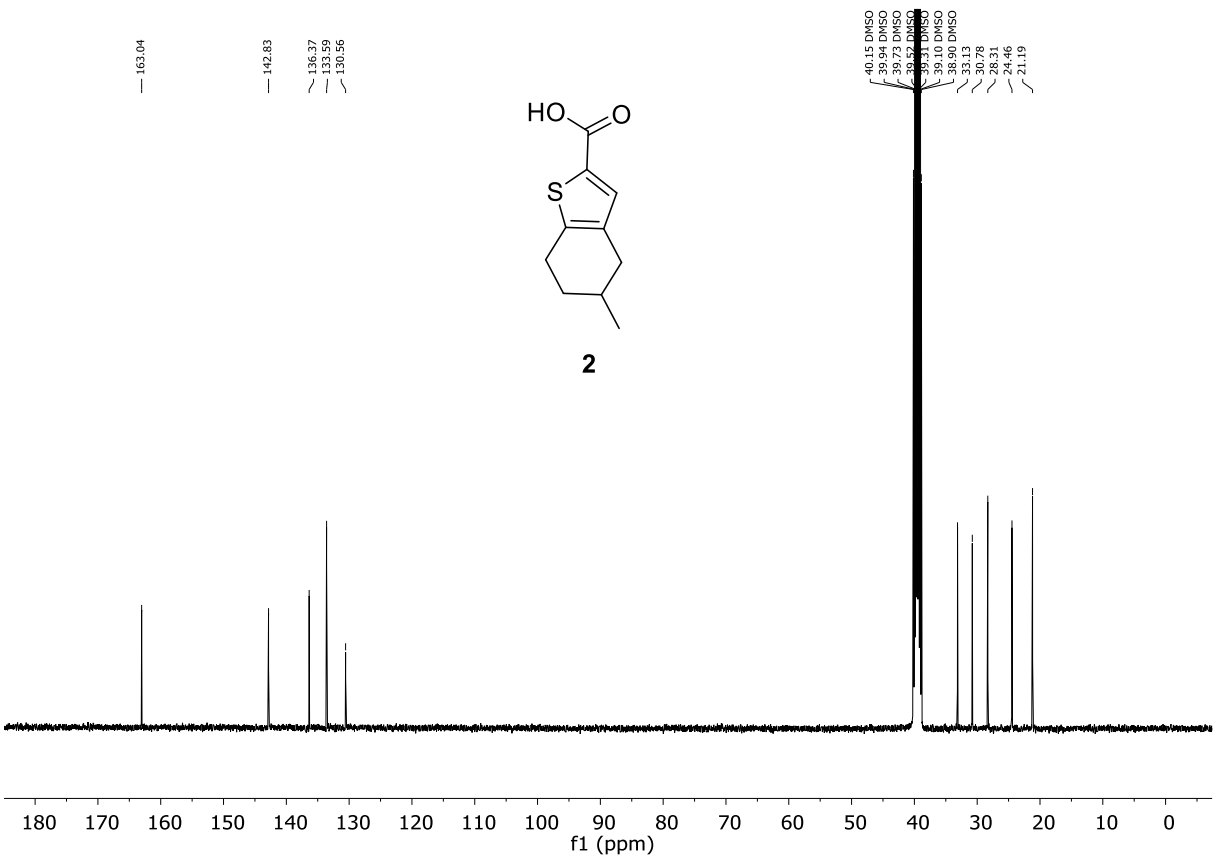
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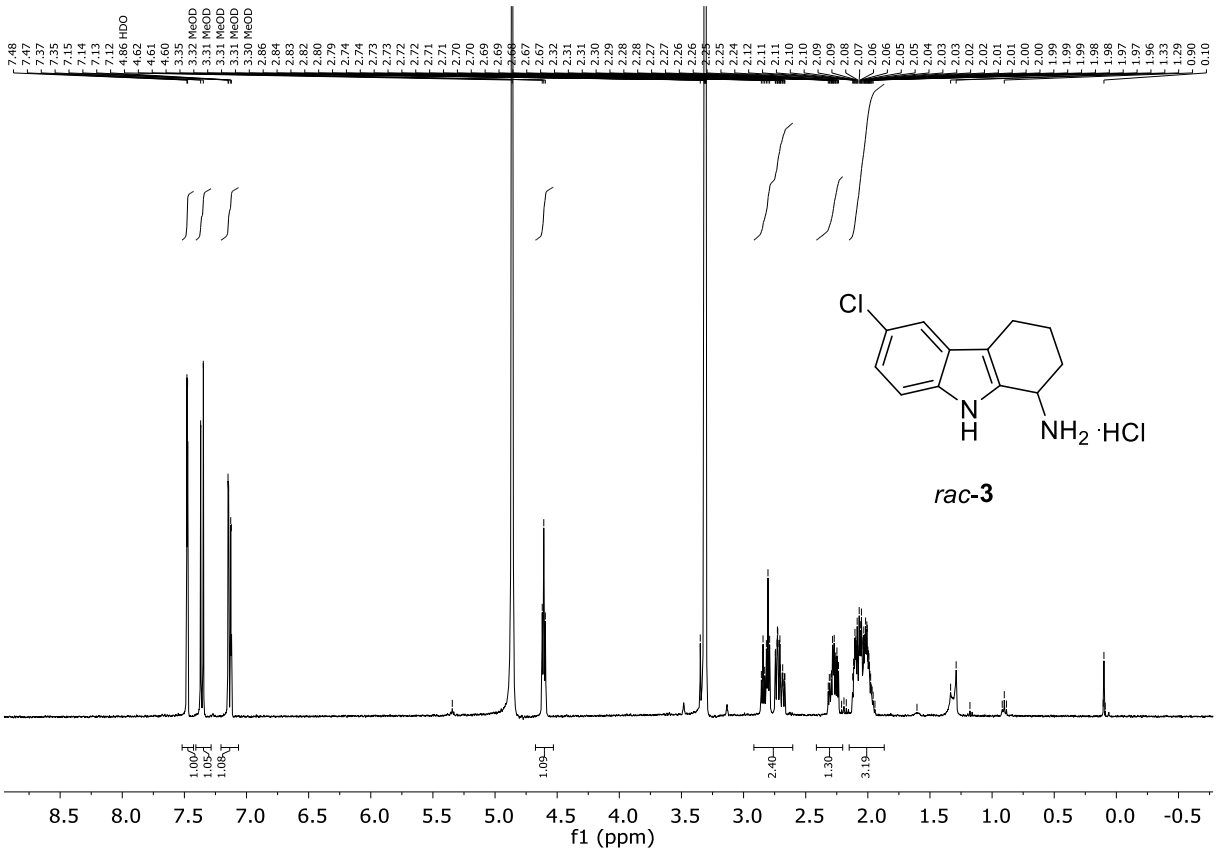
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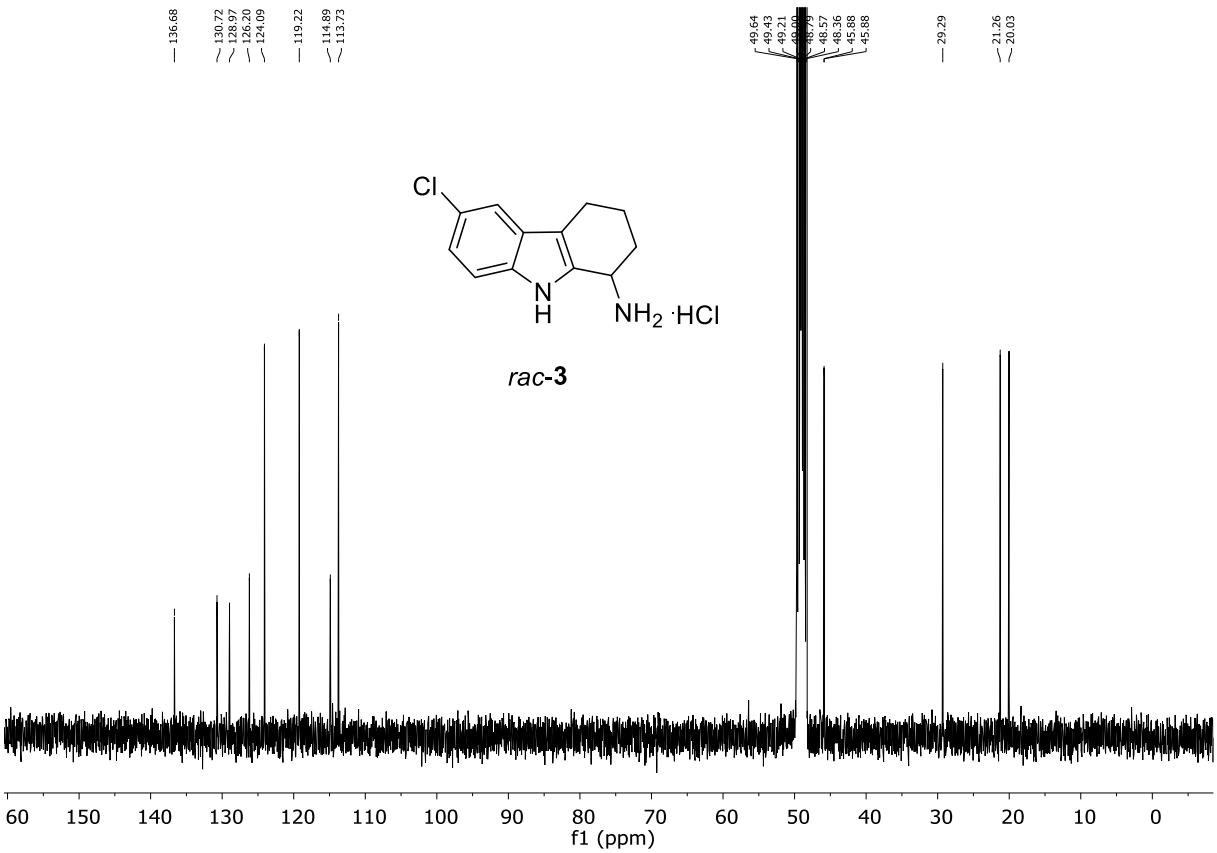
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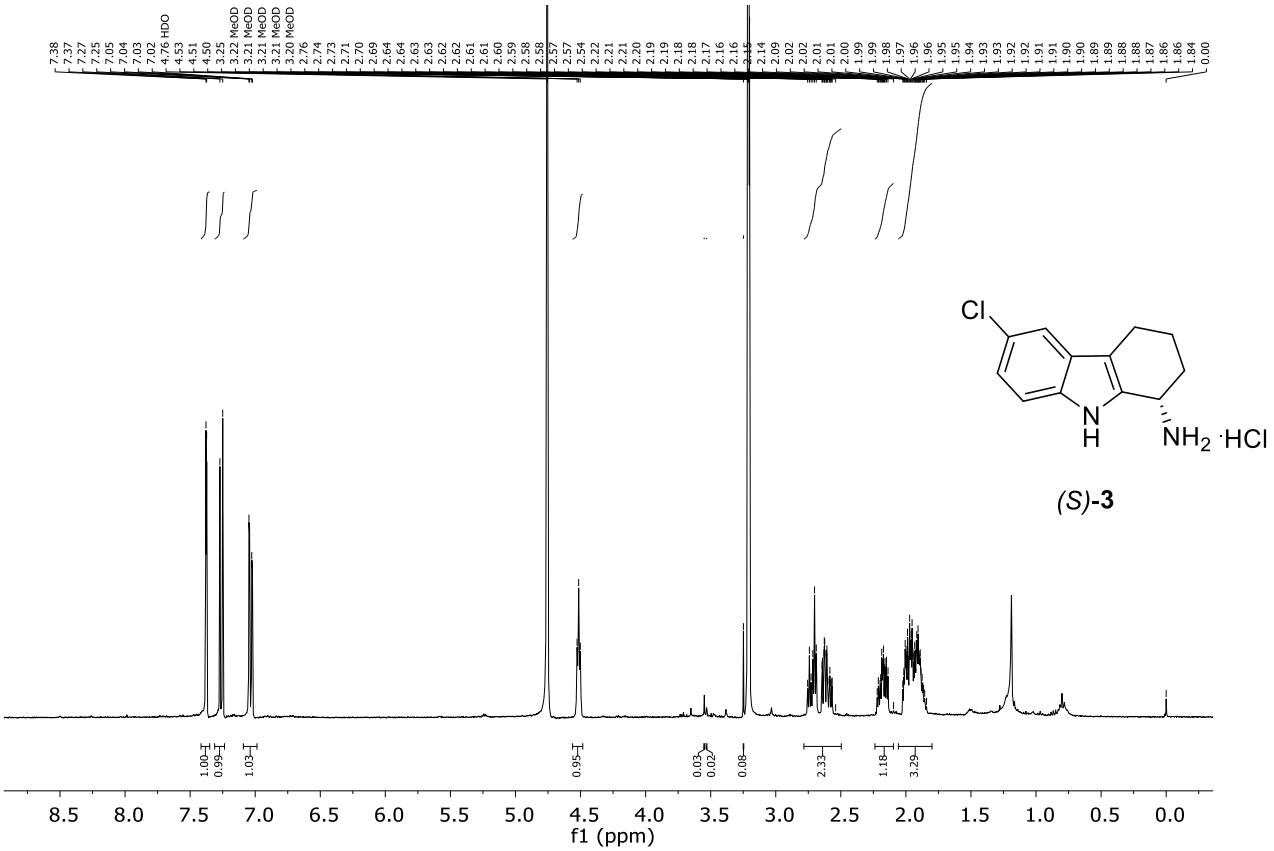
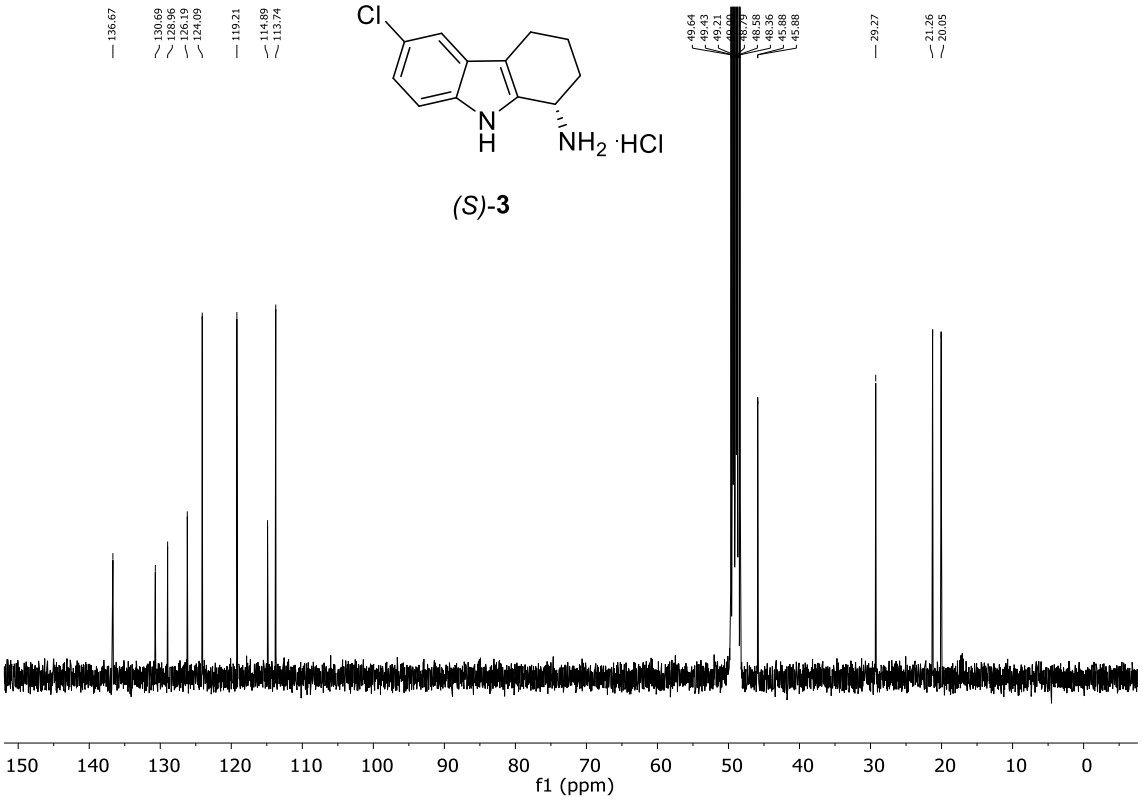
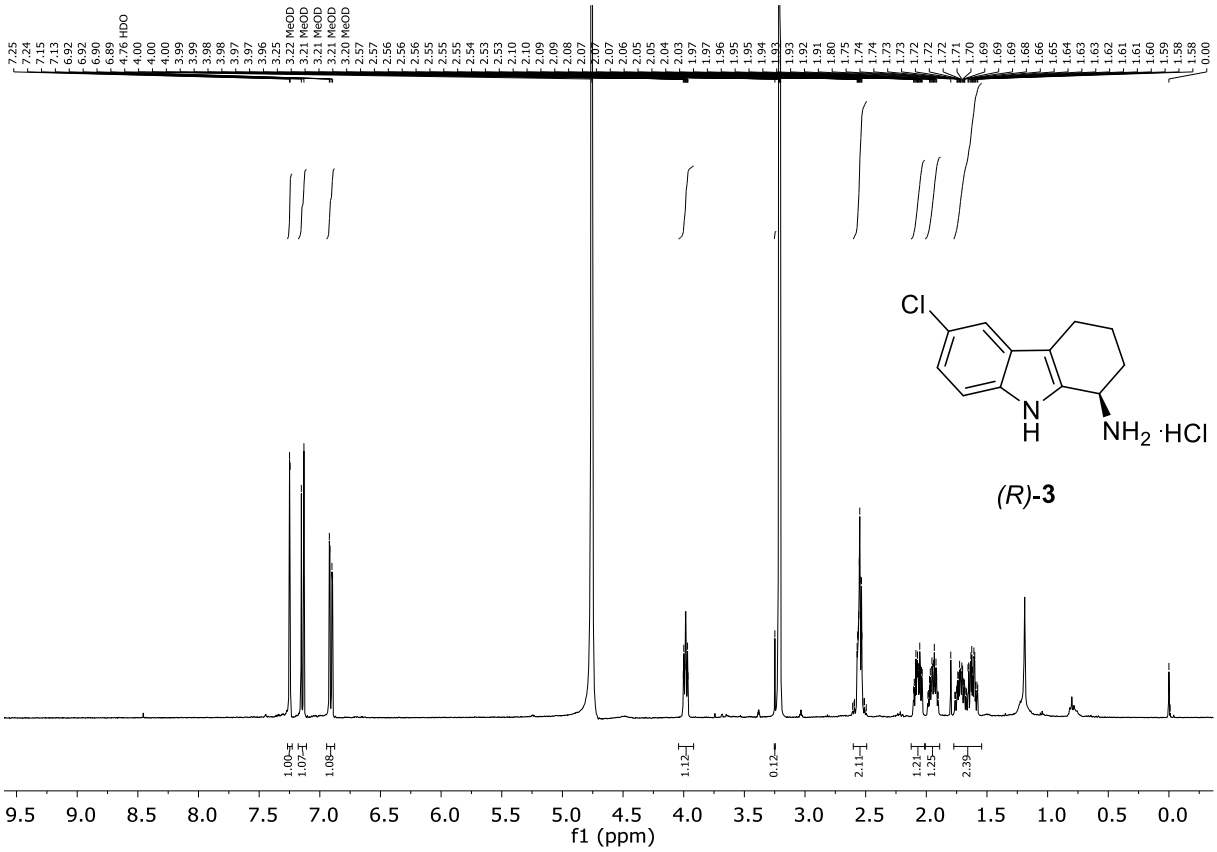
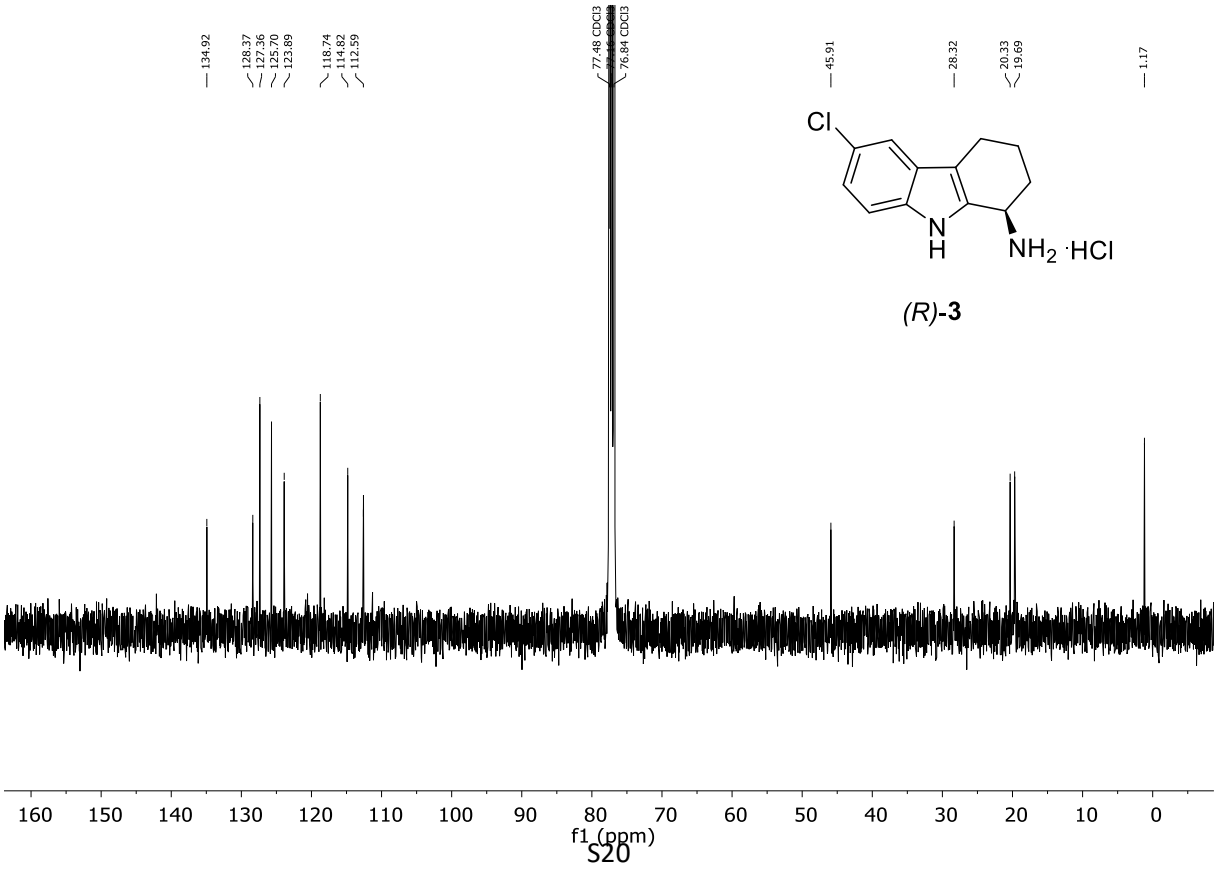
rac-3
f1 (ppm)


Cl
N
H
NH2 ·HCl
(S)-3
f1 (ppm)

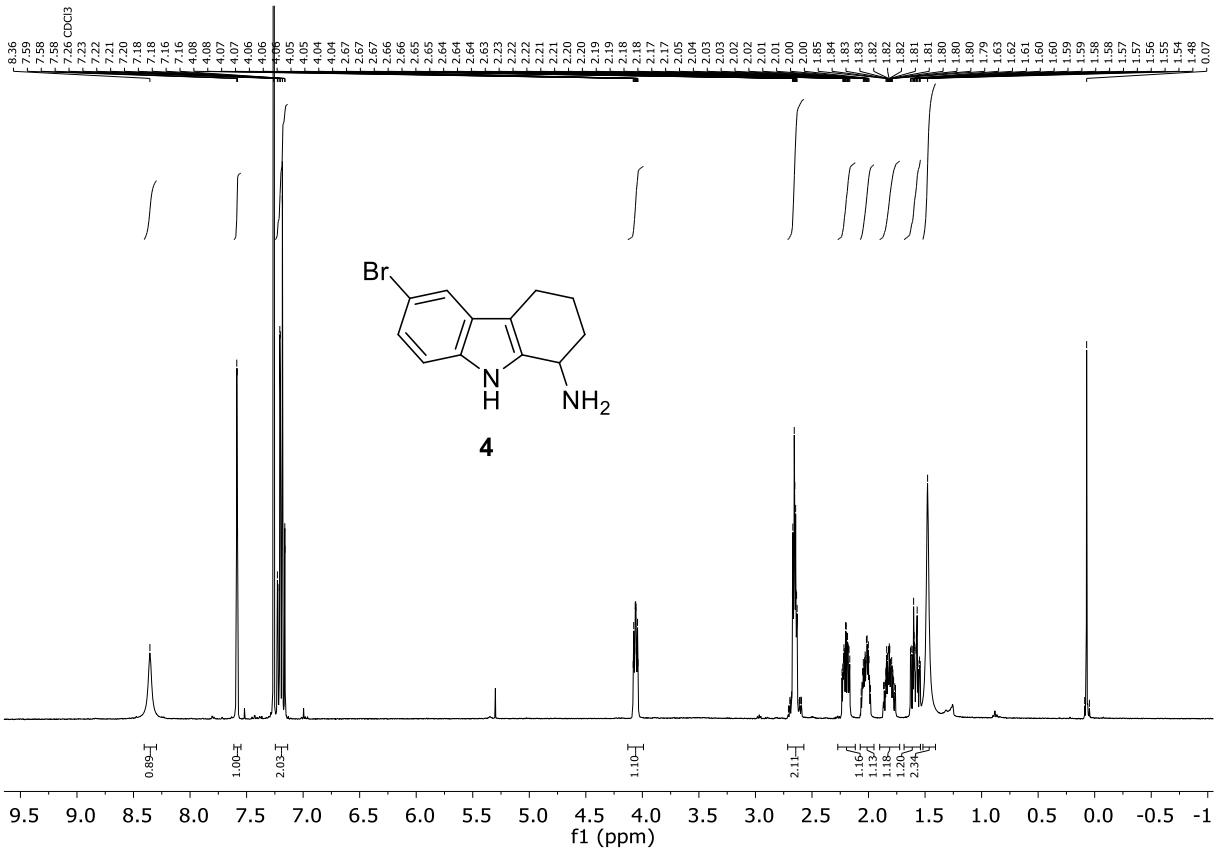

Cl
N
H
NH2 ·HCl
(S)-3
f1 (ppm)

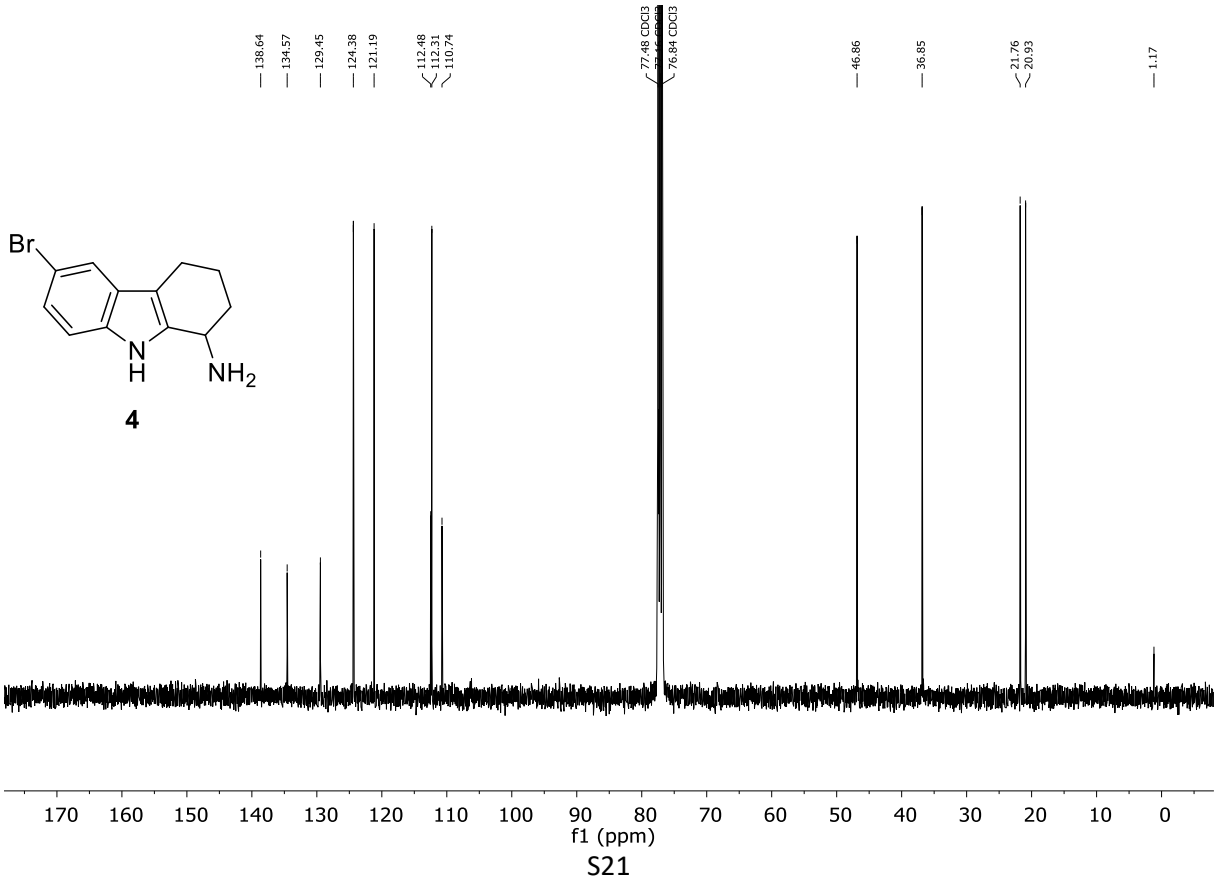


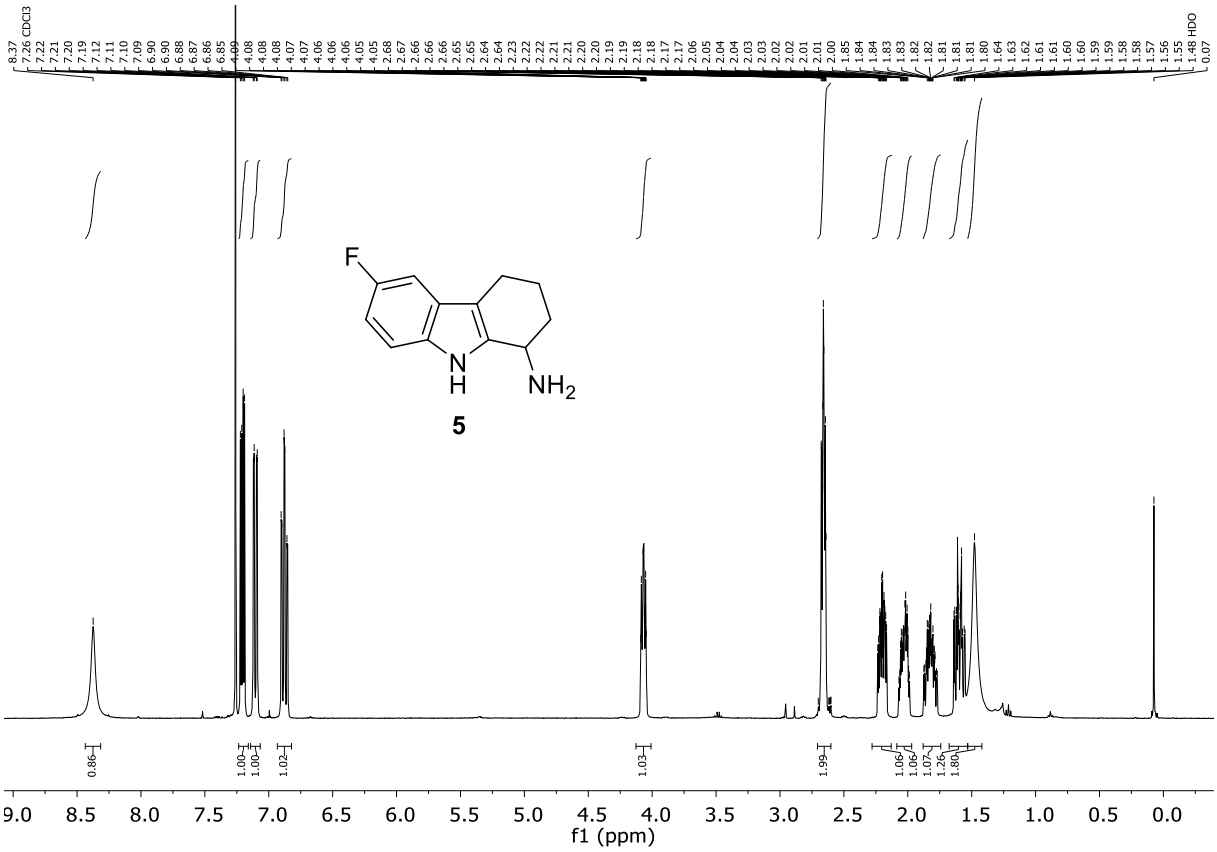
(R)-**3**

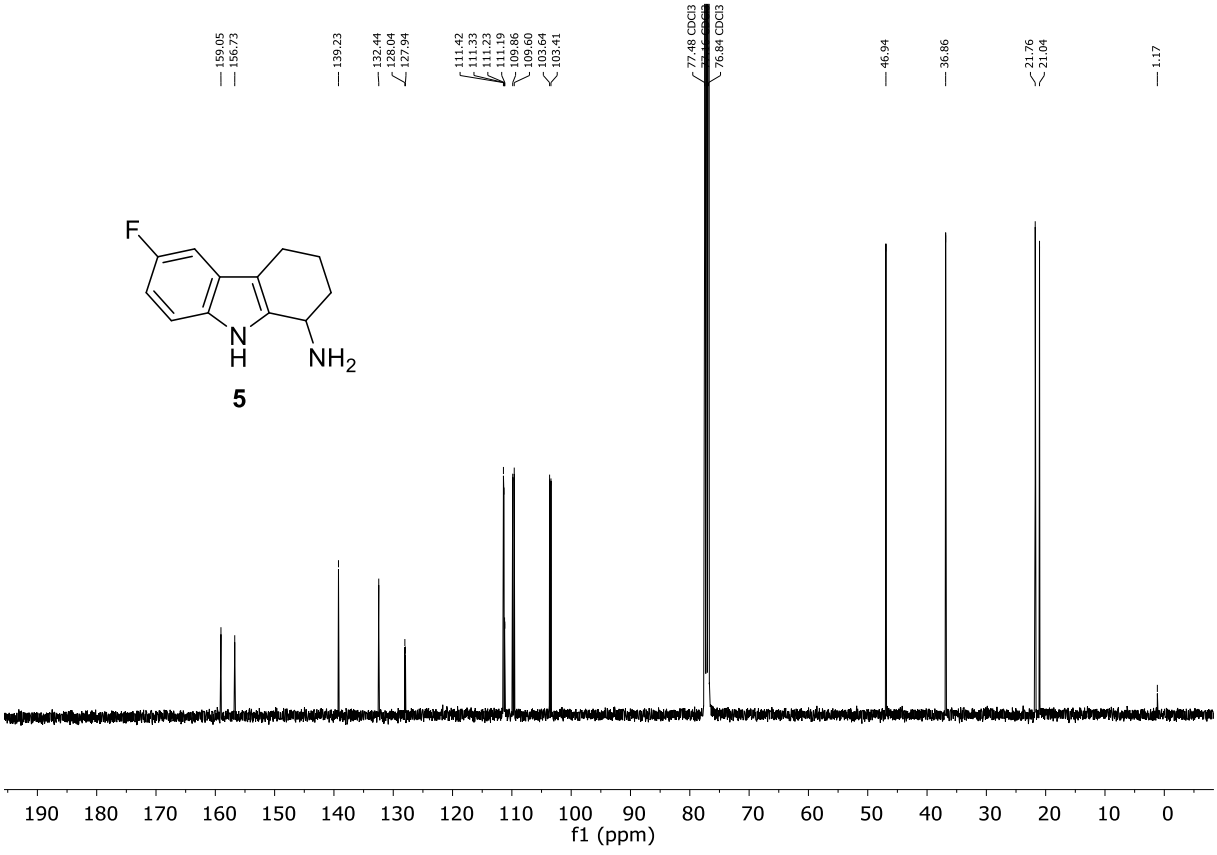


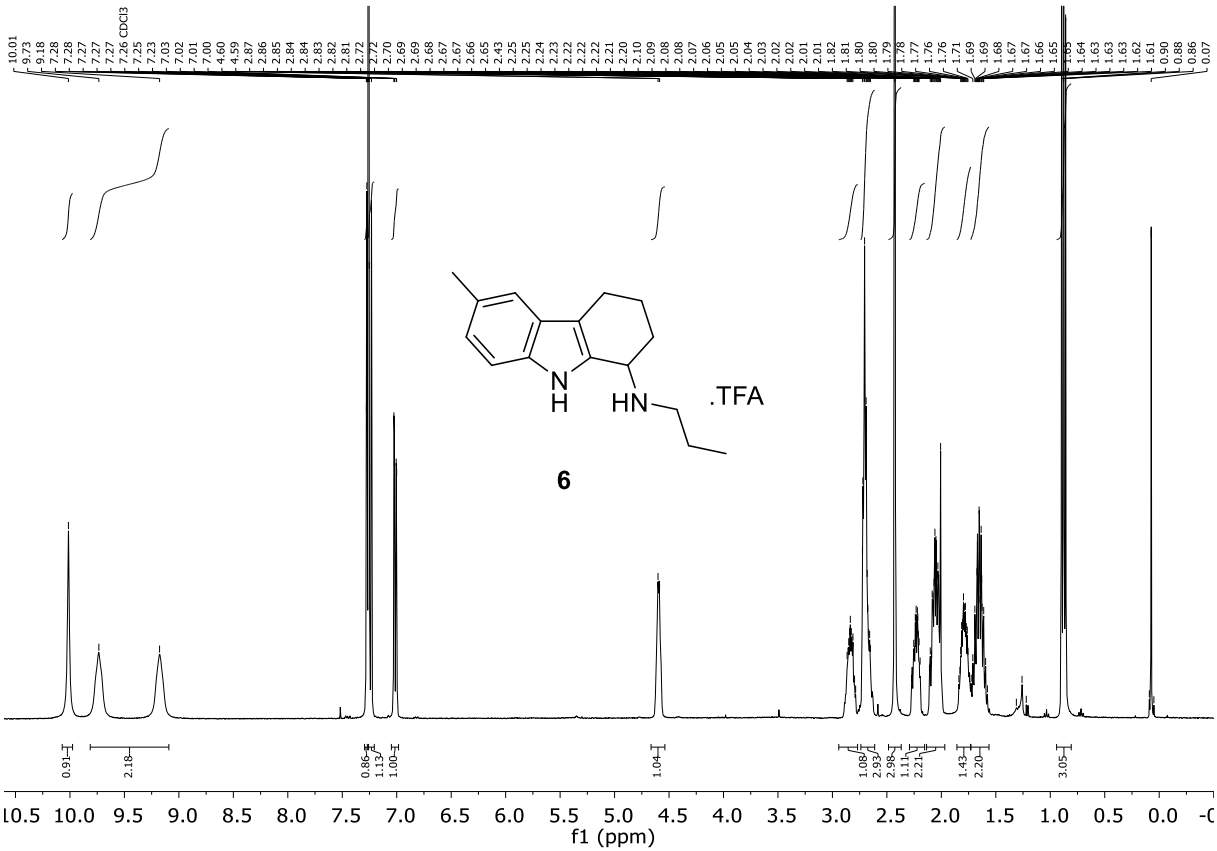
(R)-**3**

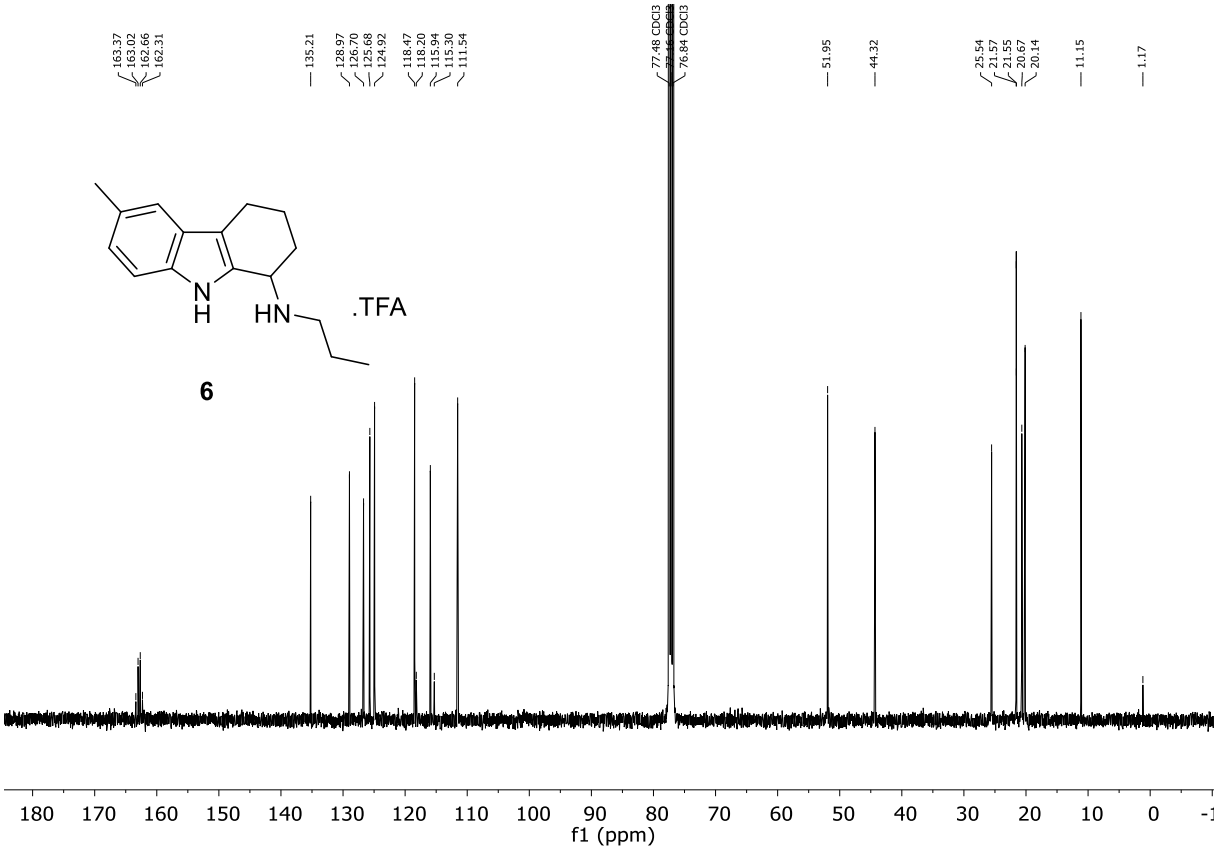

Br
N
H
NH2
4
f1 (ppm)

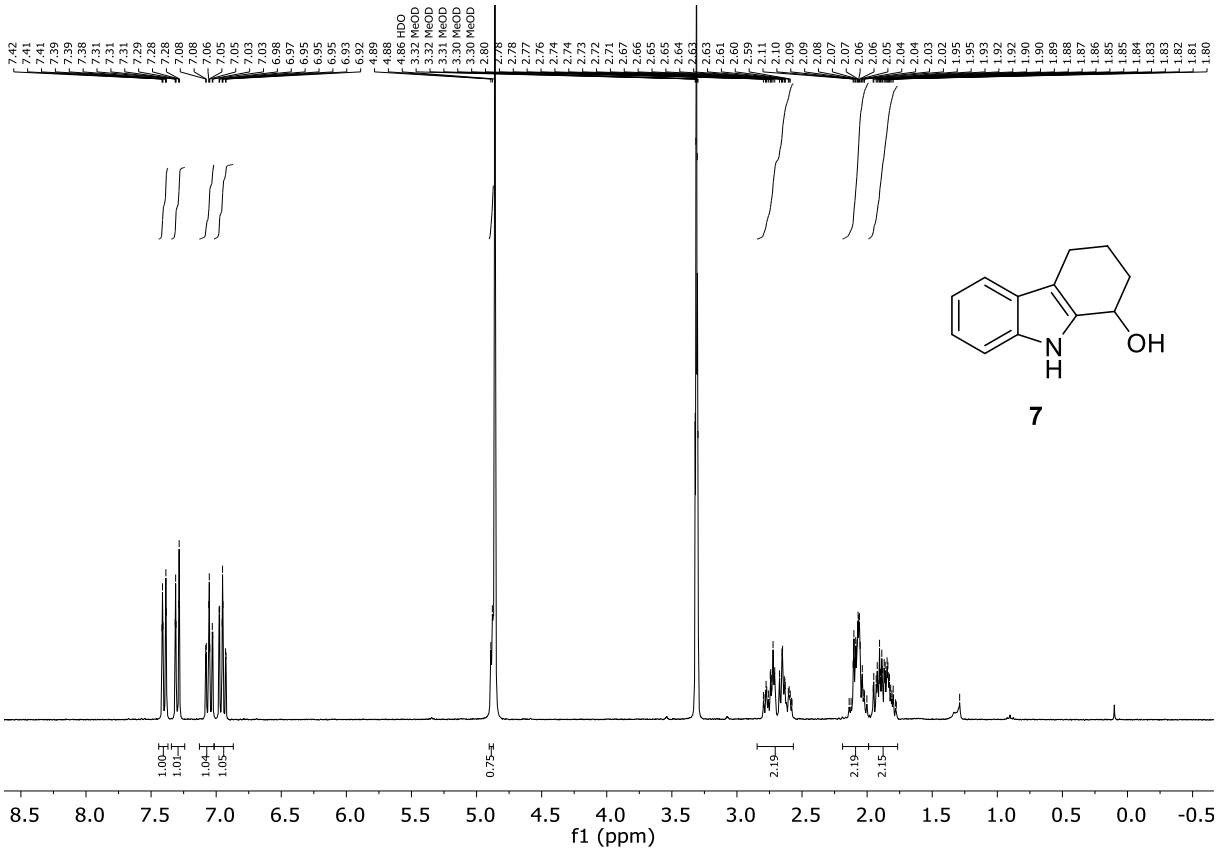

Br
N
H
NH2
4
f1 (ppm)


F
N
H
NH2
5
f1 (ppm)


F
N
H
NH2
5
f1 (ppm)


.TFA
6
f1 (ppm)


.TFA
6
f1 (ppm)



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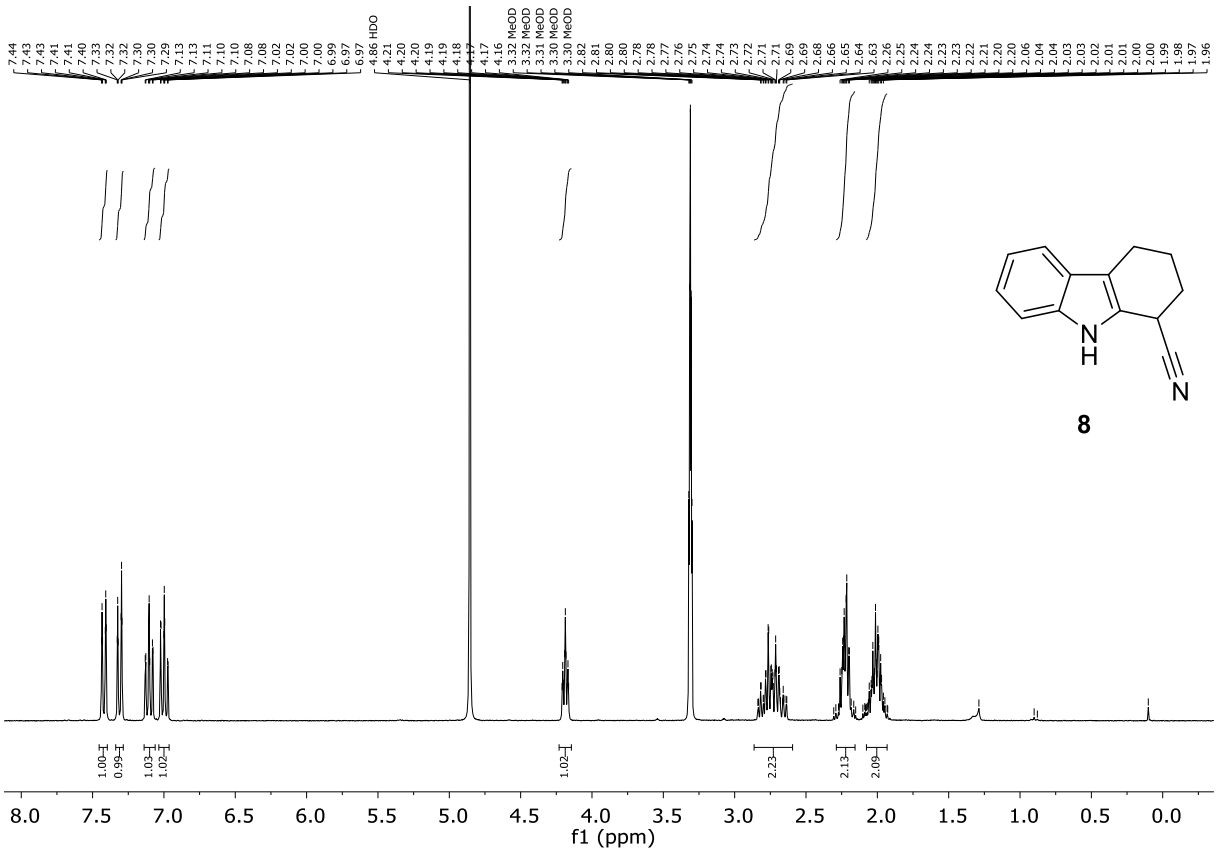

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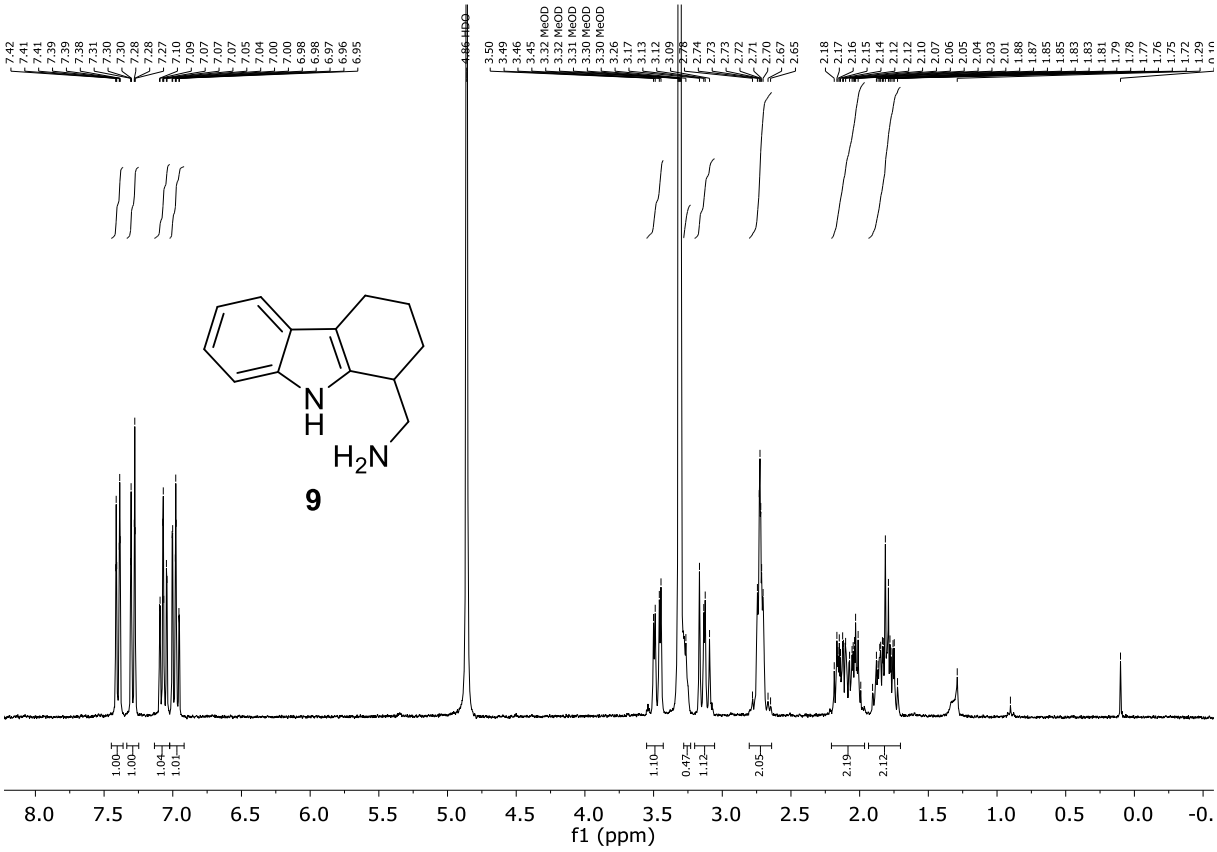
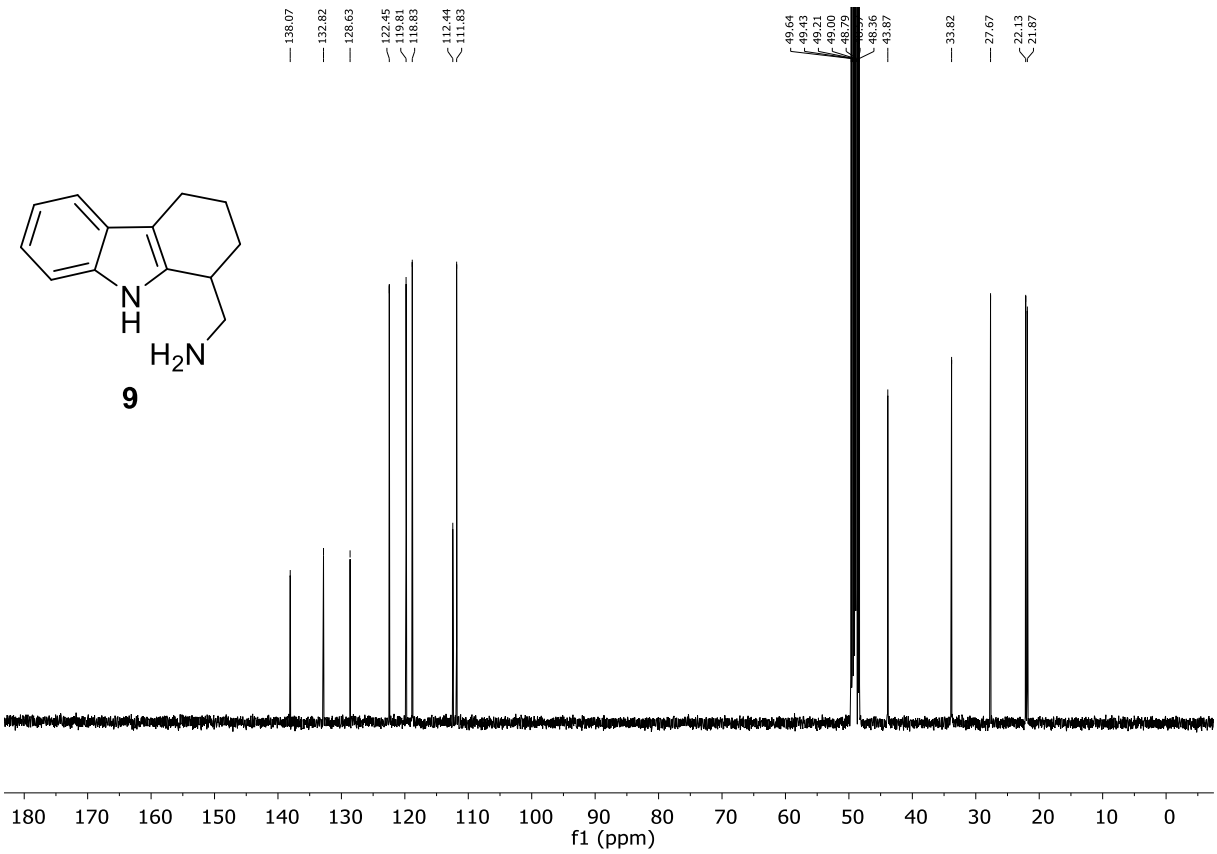
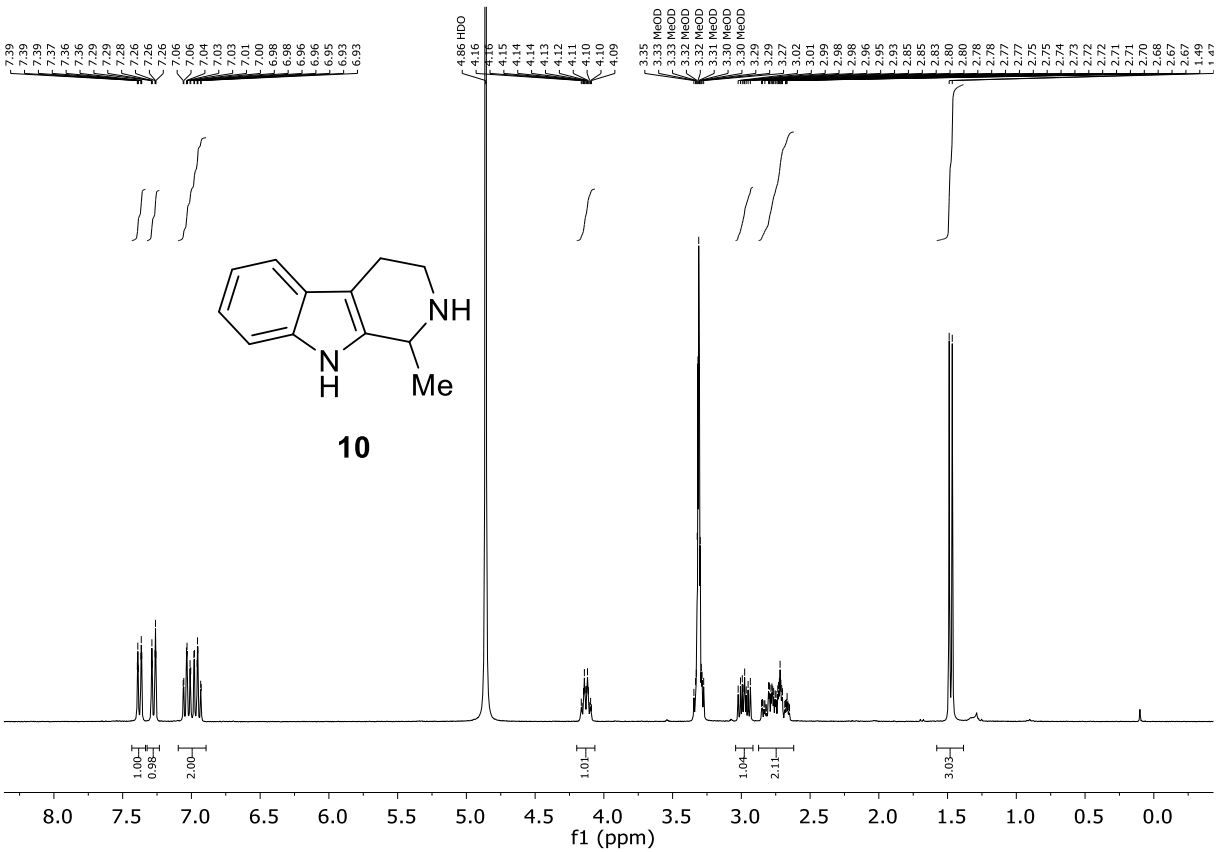

4.86 HDO
MeOD
1.00
1.00
1.04
1.01
1.10
0.47
1.12
2.05
2.19
2.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
N
H
H2N
9


138.07
132.82
128.63
122.45
119.81
118.83
112.44
111.83
49.64
49.43
49.21
49.00
48.79
48.57
48.36
43.87
33.82
27.67
22.13
21.87
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
N
H
H2N
9



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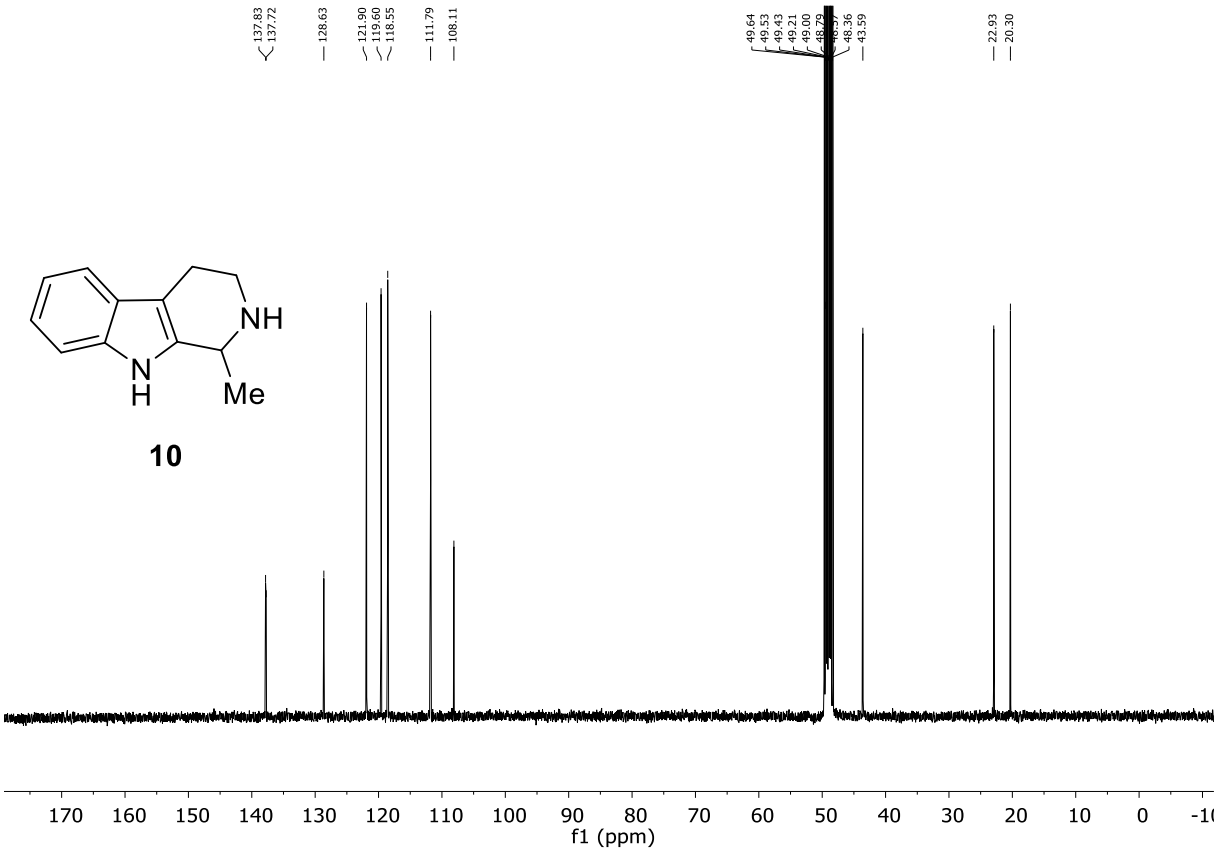

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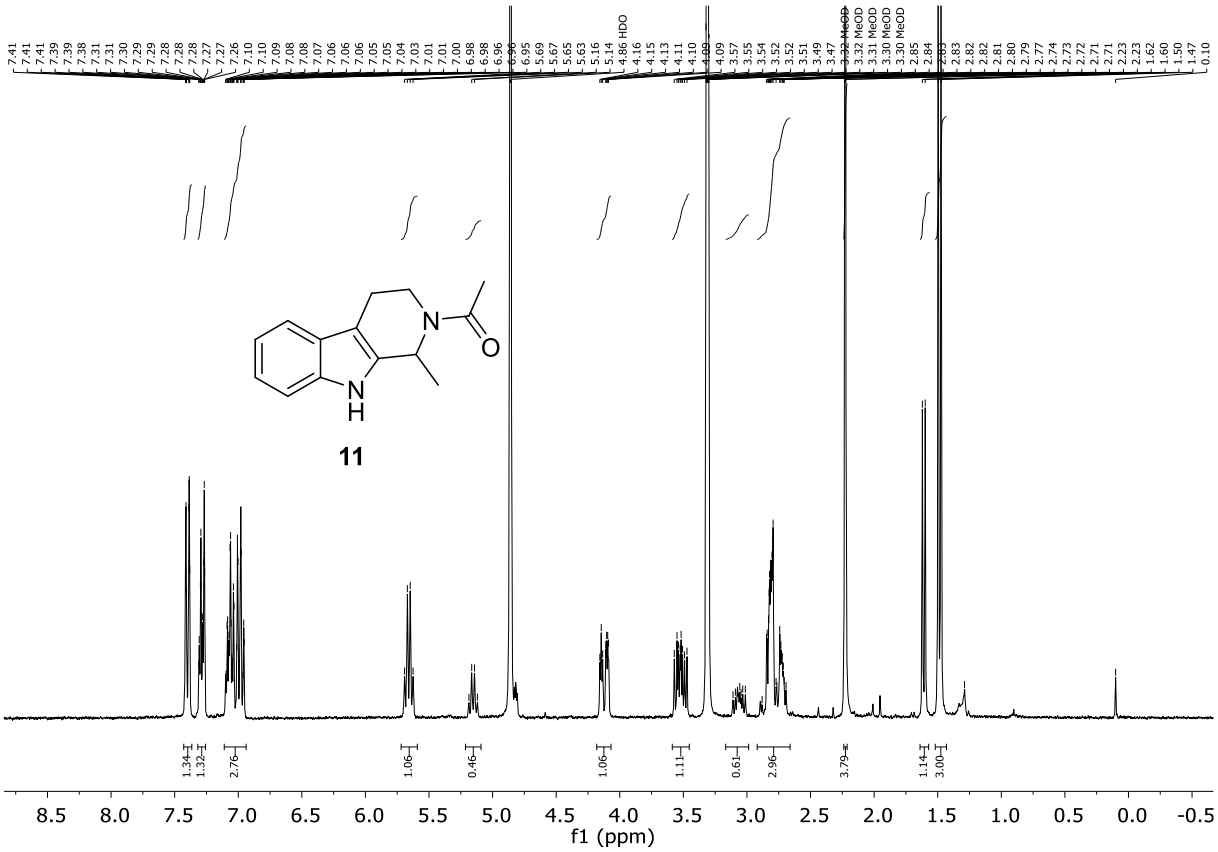
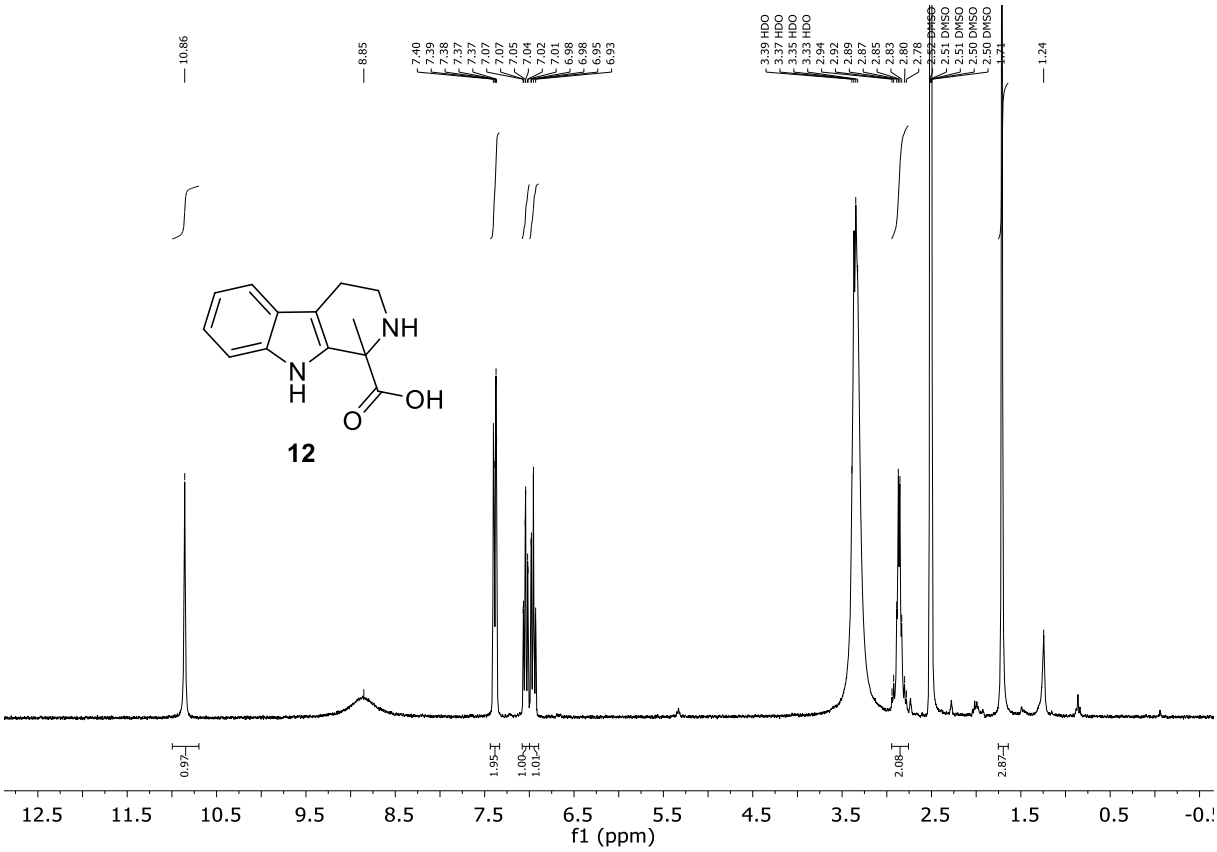
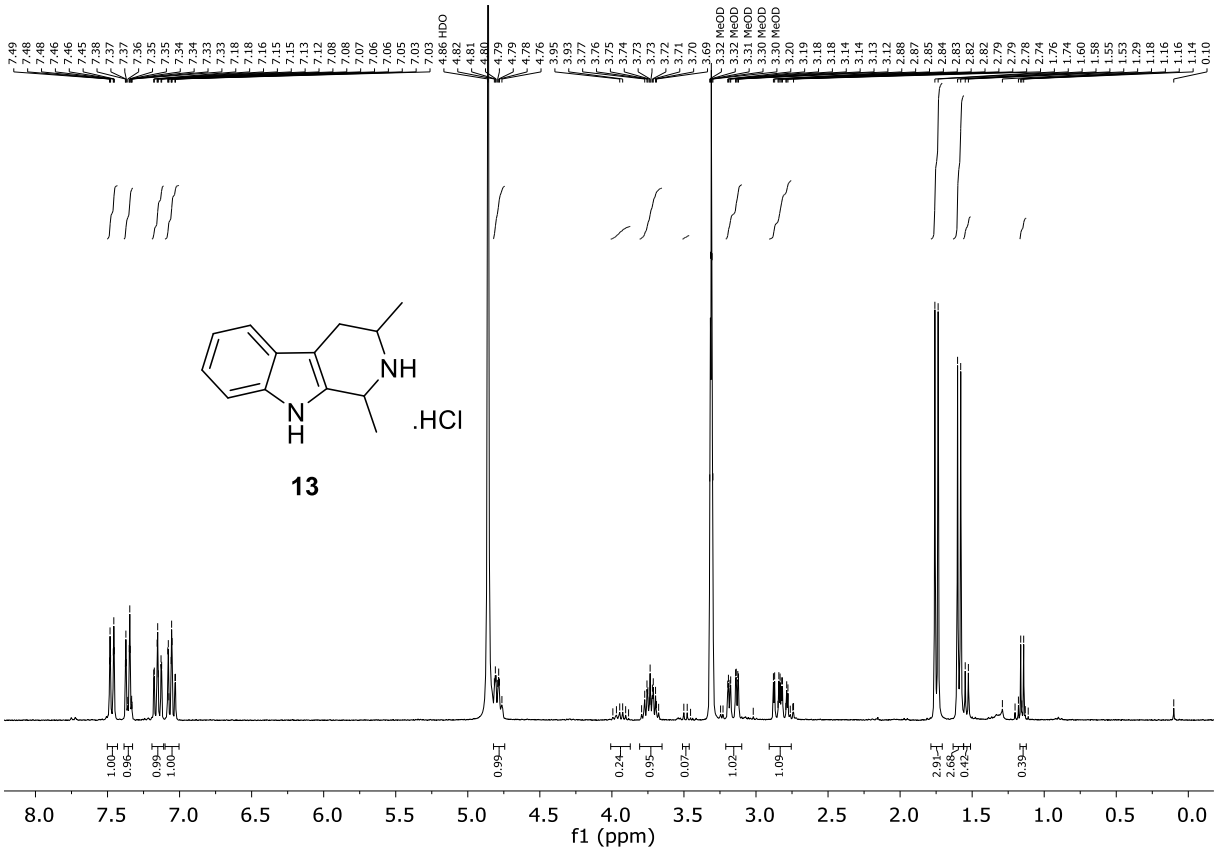

11
f1 (ppm)


12
f1 (ppm)



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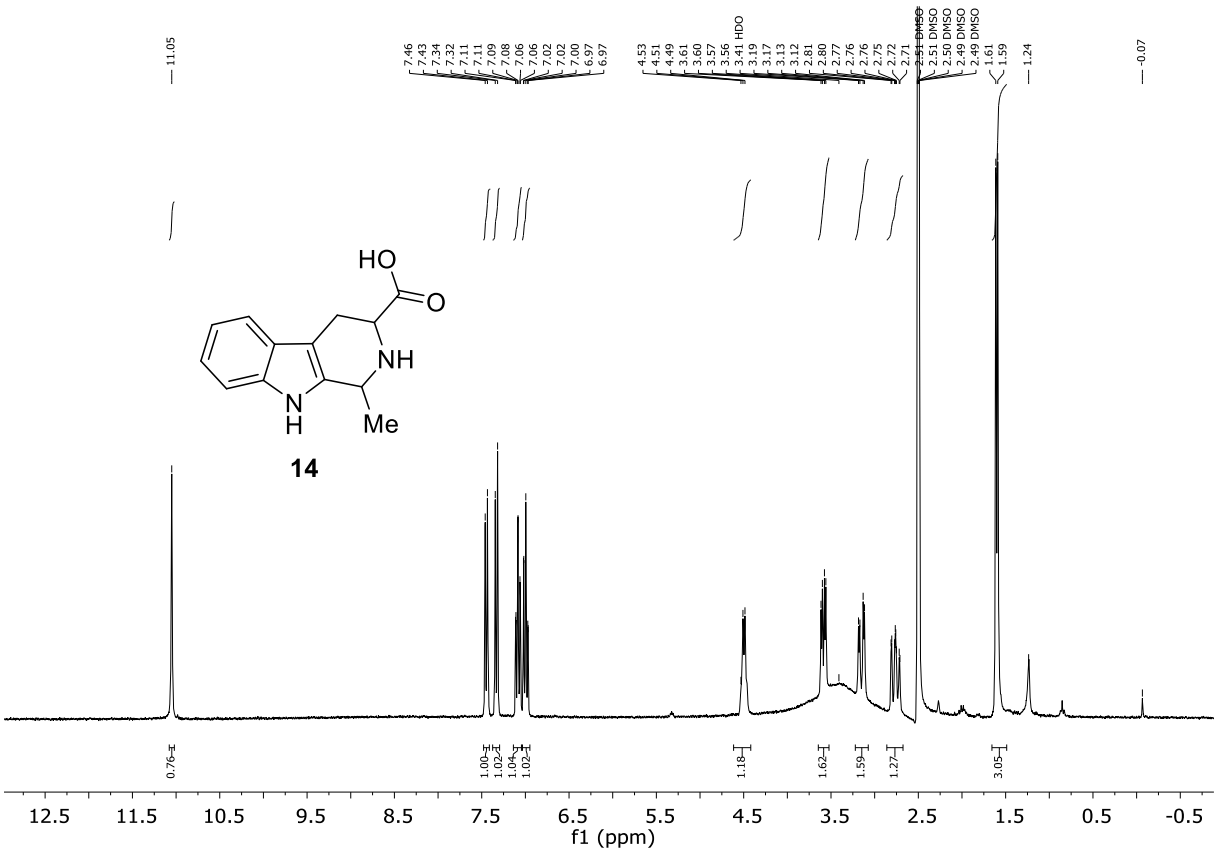

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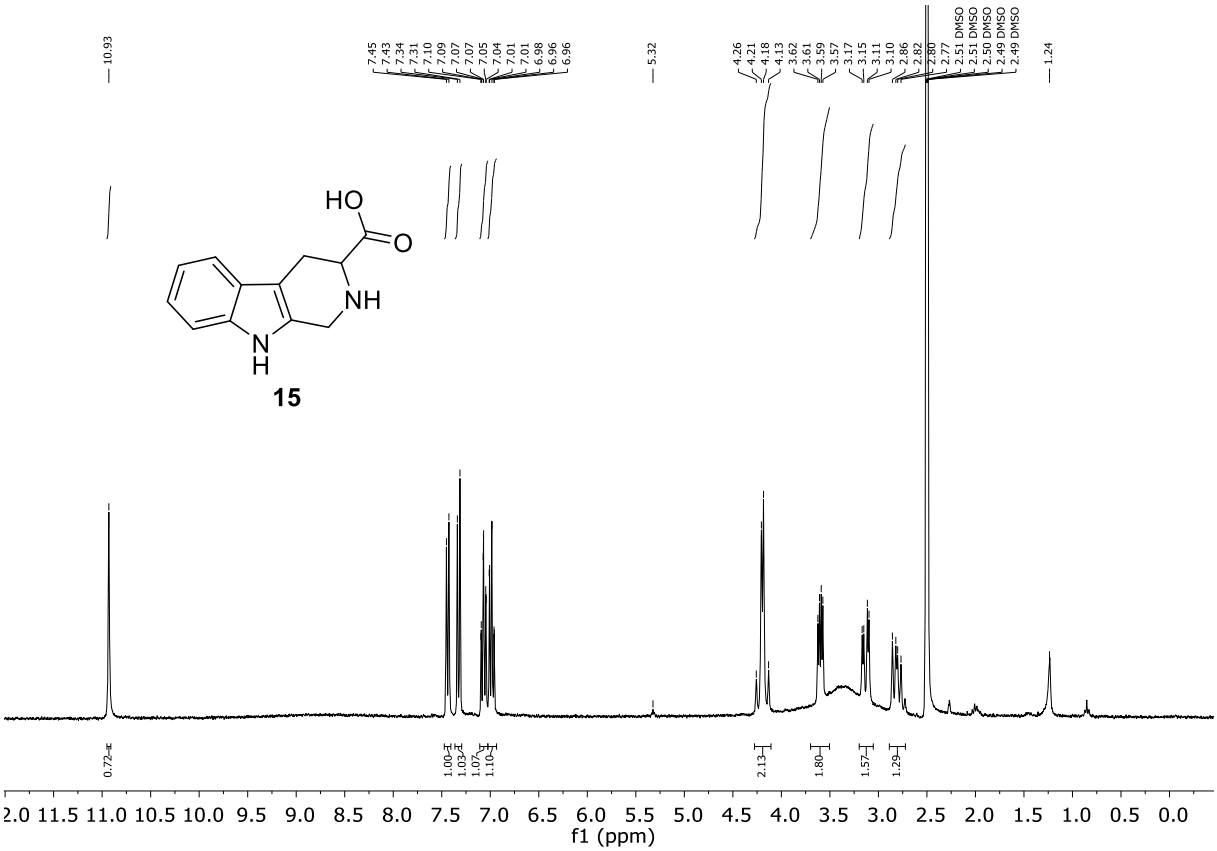
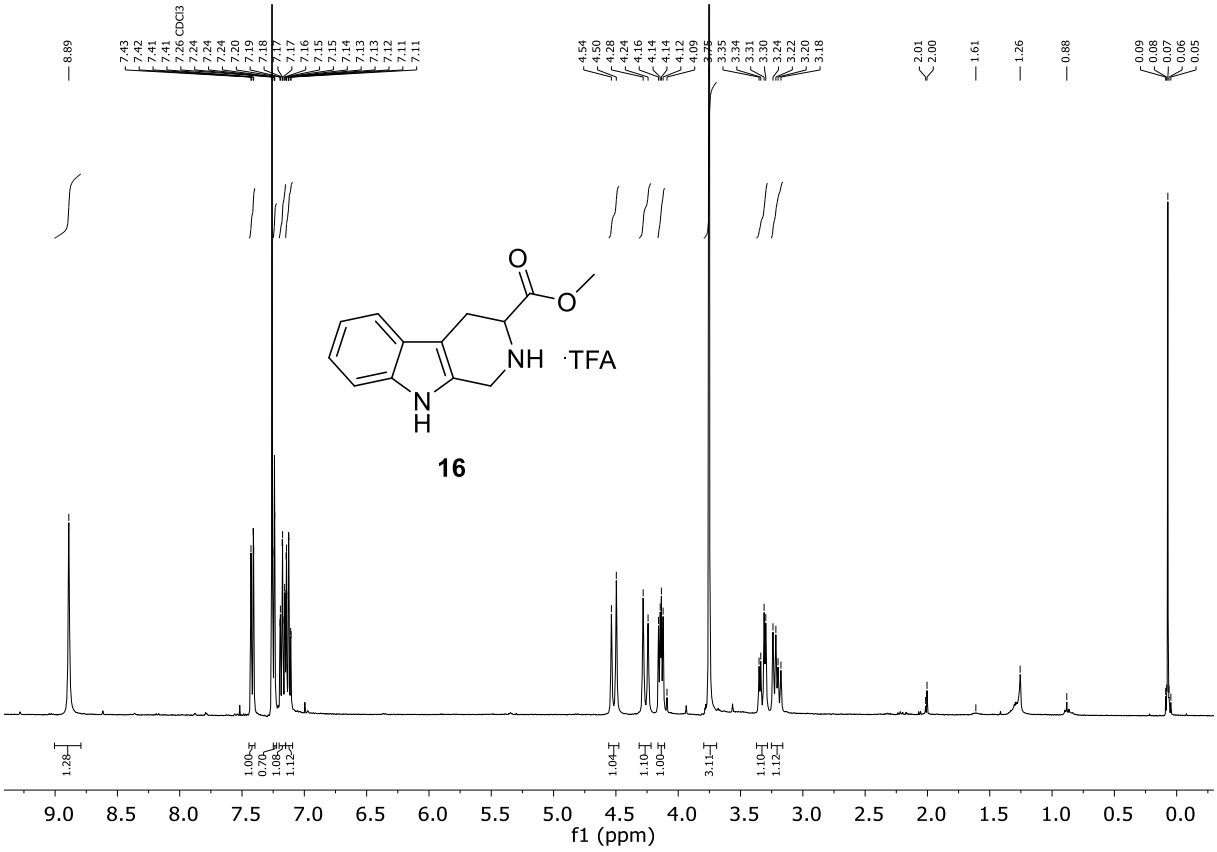
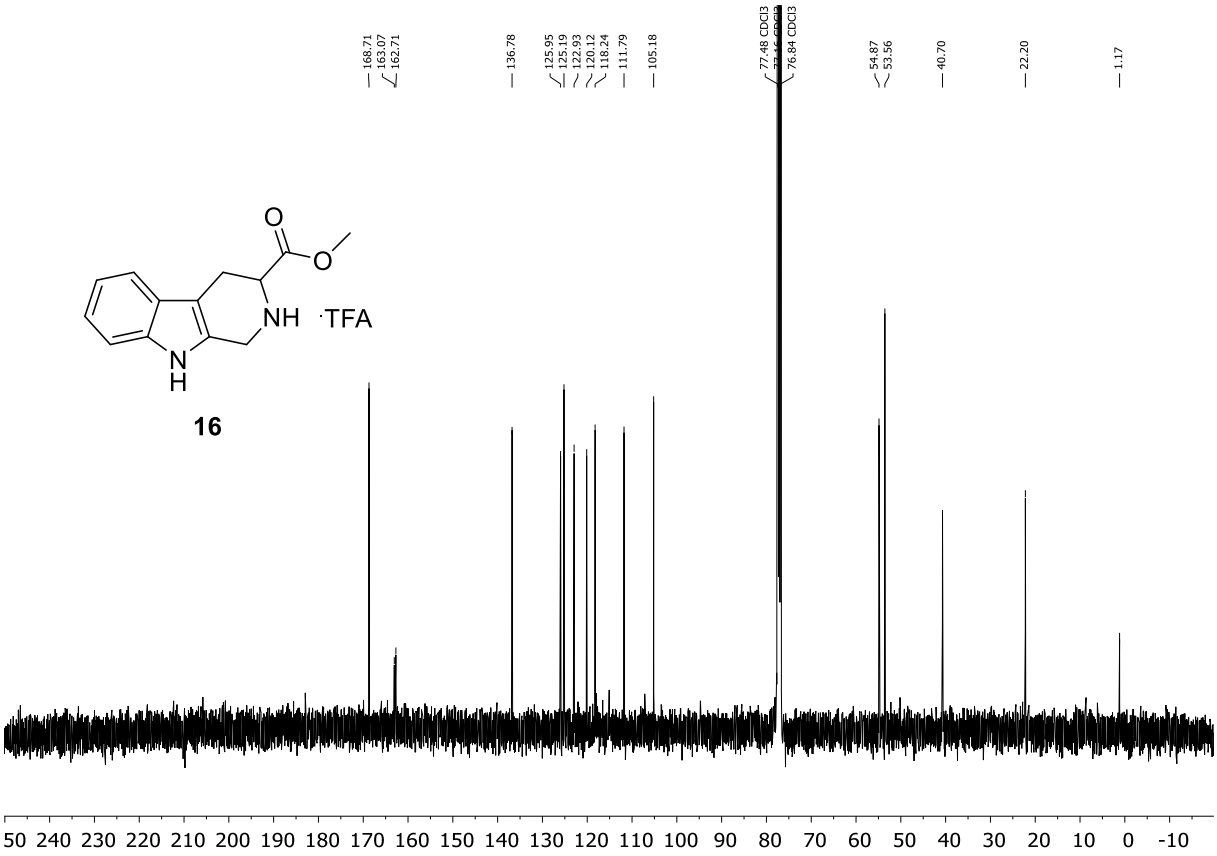
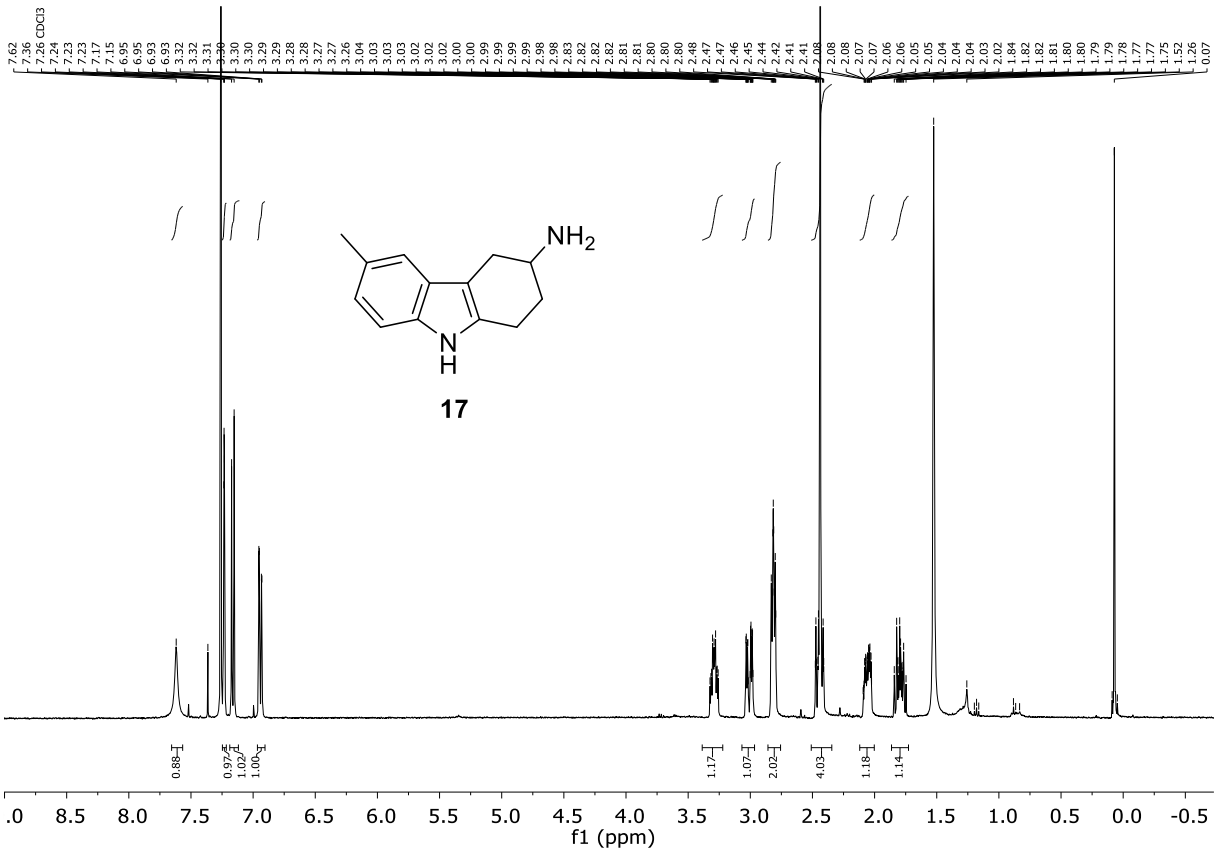
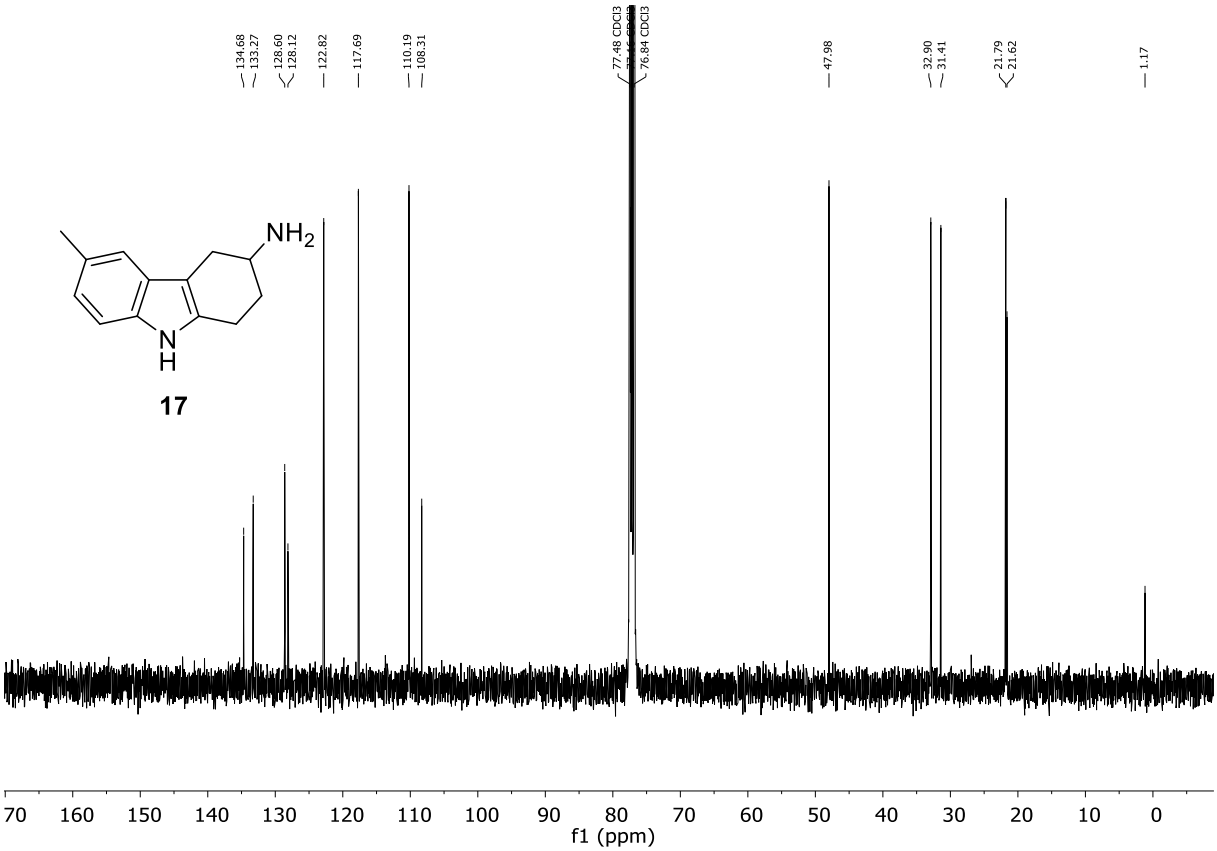

HO
O
NH
N
H
15
f1 (ppm)


O
O
NH ·TFA
N
H
16
f1 (ppm)


168.71
163.07
162.71
136.78
125.95
125.19
122.93
120.12
118.24
111.79
105.18
77.48 CDCl3
76.84 CDCl3
54.87
53.56
40.70
22.20
1.17
O
O
NH ·TFA
N
H
16
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


7.62
7.36
CDCl3
7.26
7.24
7.23
7.23
7.17
7.15
6.95
6.95
6.93
6.93
3.32
3.32
3.31
3.31
3.30
3.30
3.29
3.29
3.28
3.28
3.27
3.27
3.26
3.04
3.03
3.03
3.03
3.02
3.02
3.02
3.00
3.00
2.99
2.99
2.99
2.98
2.98
2.98
2.83
2.82
2.82
2.82
2.81
2.81
2.80
2.80
2.80
2.48
2.47
2.47
2.46
2.45
2.44
2.42
2.41
2.41
2.08
2.08
2.08
2.07
2.07
2.06
2.06
2.05
2.05
2.04
2.04
2.04
2.03
2.02
1.84
1.82
1.82
1.81
1.80
1.80
1.79
1.79
1.78
1.77
1.77
1.75
1.52
1.26
0.07
NH2
N
H
17
0.88
0.97
1.02
1.00
1.17
1.07
2.02
4.03
1.18
1.14
.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 -0.5
f1 (ppm)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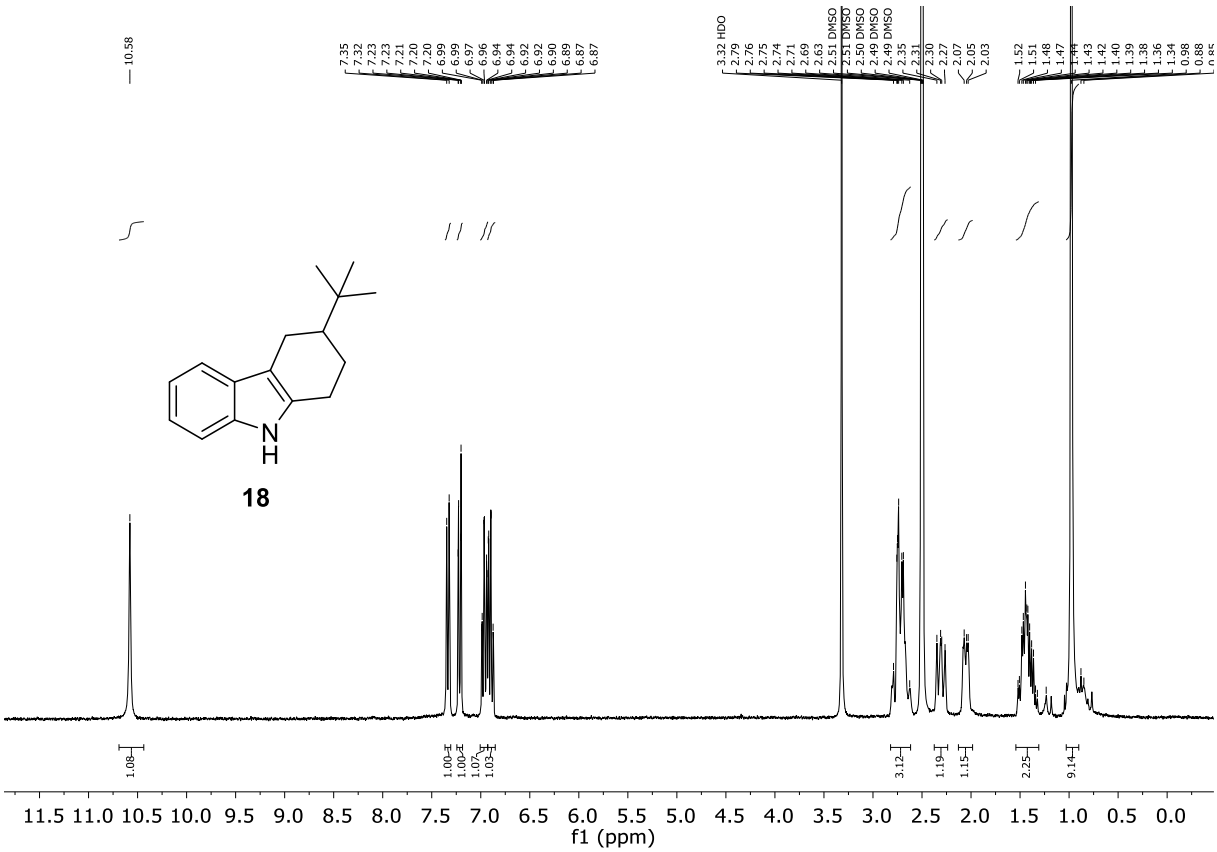
133.27
128.60
128.12
122.82
117.69
110.19
108.31
77.48 CDCl3
76.84 CDCl3
47.98
32.90
31.41
21.79
21.62
1.17
NH2
N
H
17
f1 (ppm)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7.32
7.23
7.21
7.20
6.99
6.97
6.96
6.94
6.92
6.90
6.89
6.87
3.32 HDO
2.79
2.76
2.75
2.74
2.71
2.69
2.63
2.51 DMSO
2.50 DMSO
2.49 DMSO
2.35
2.31
2.30
2.27
2.07
2.05
2.03
1.52
1.51
1.48
1.47
1.43
1.42
1.40
1.39
1.38
1.36
1.34
0.98
0.88
1.08
1.00
1.00
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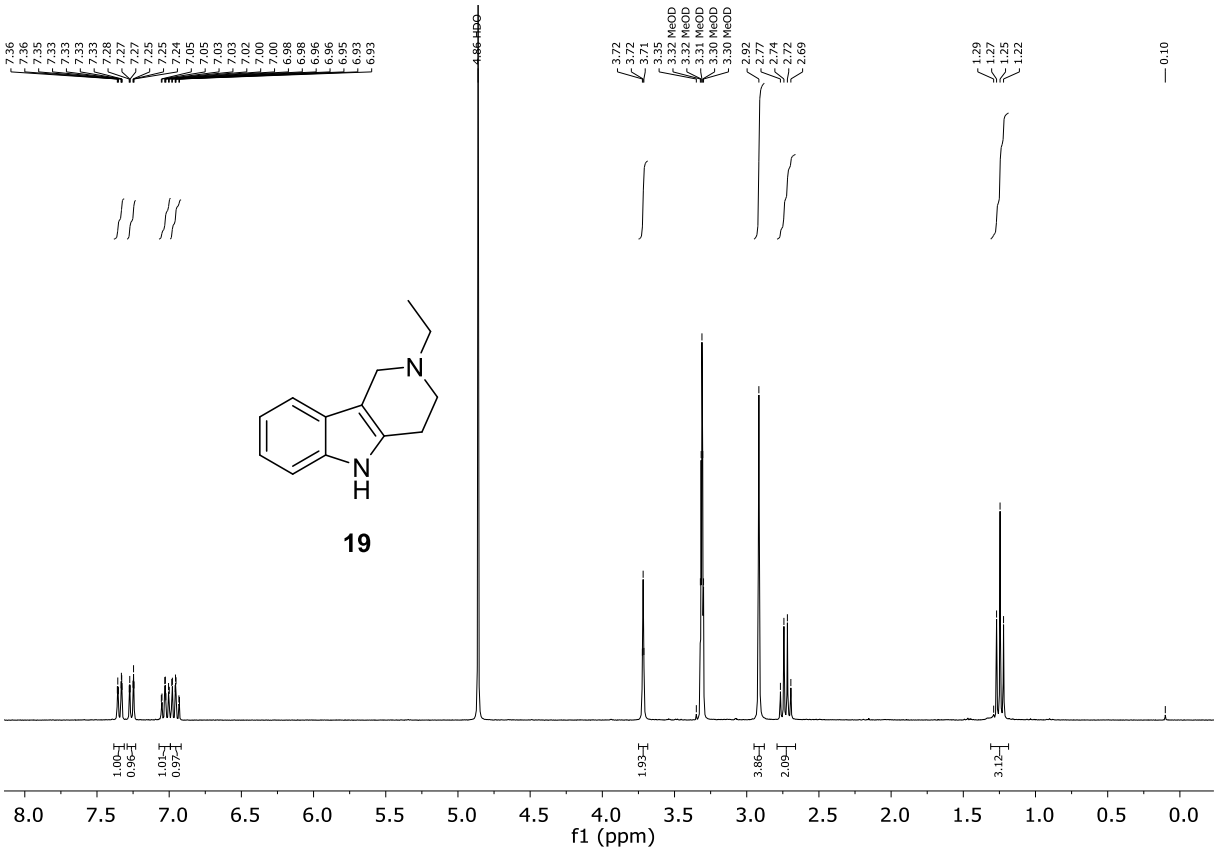
1.03
3.12
1.19
1.15
2.25
9.14
N
H
18
f1 (ppm)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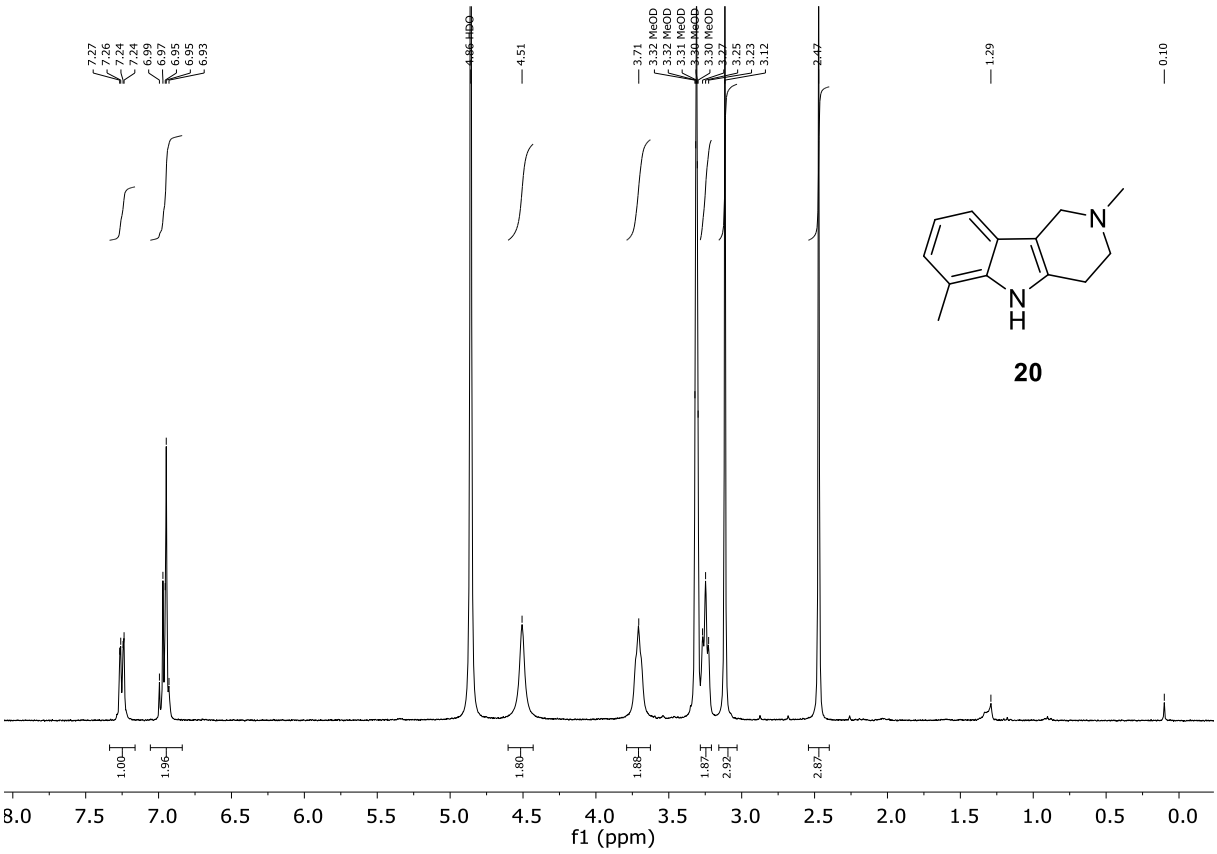
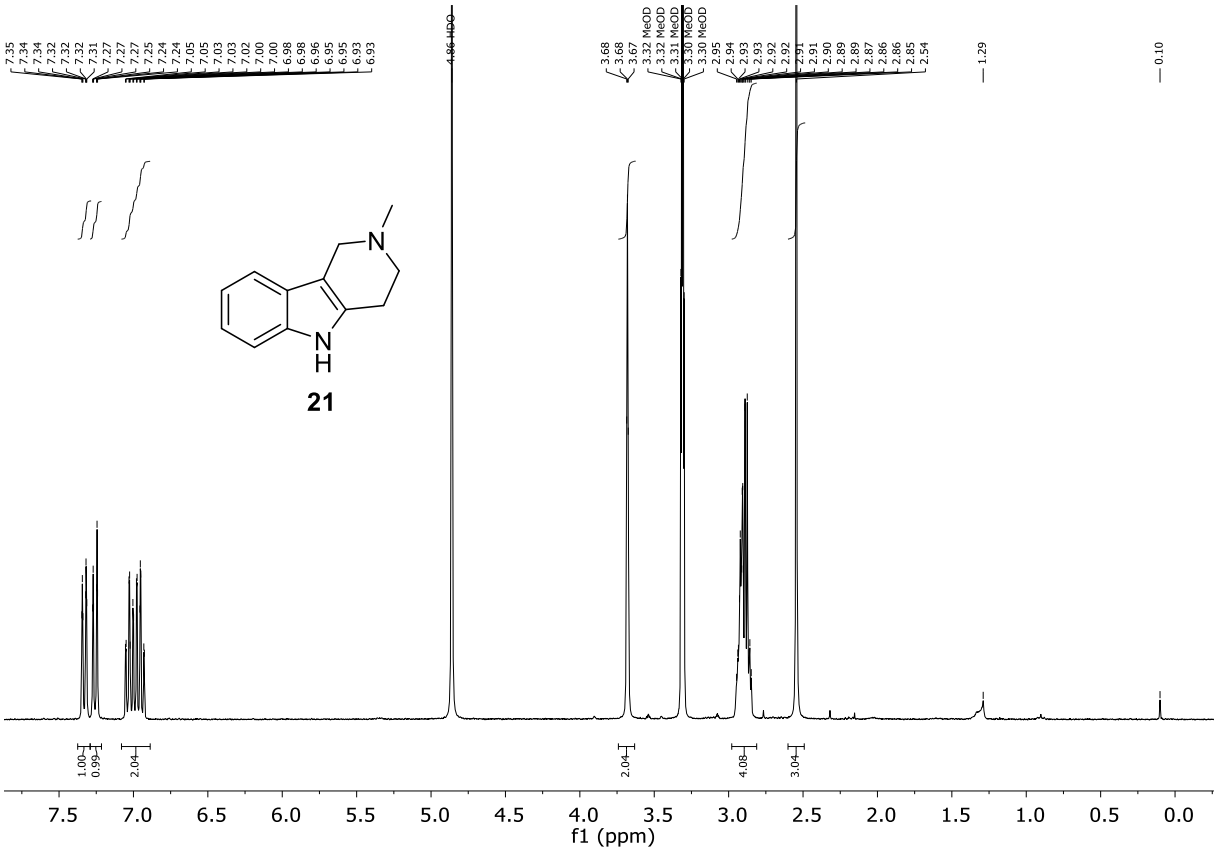
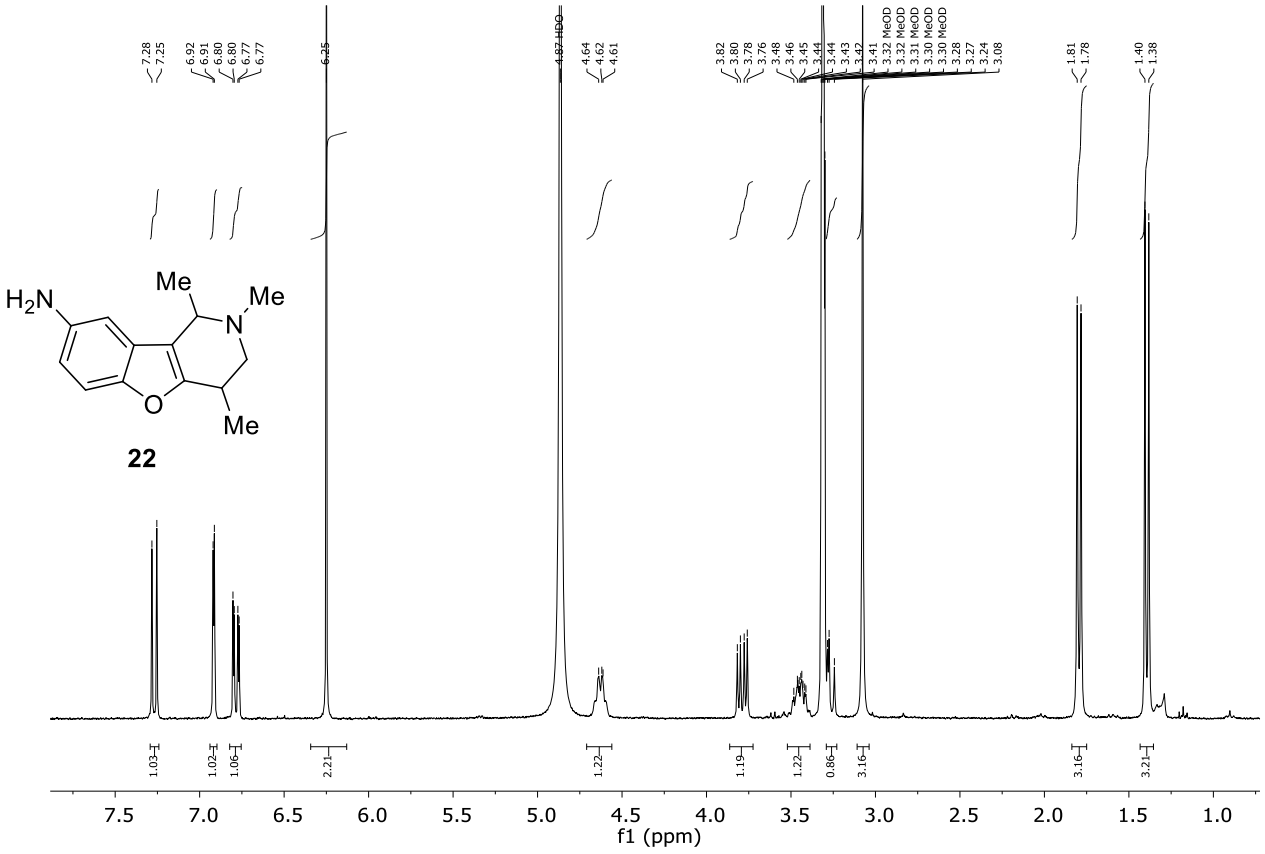
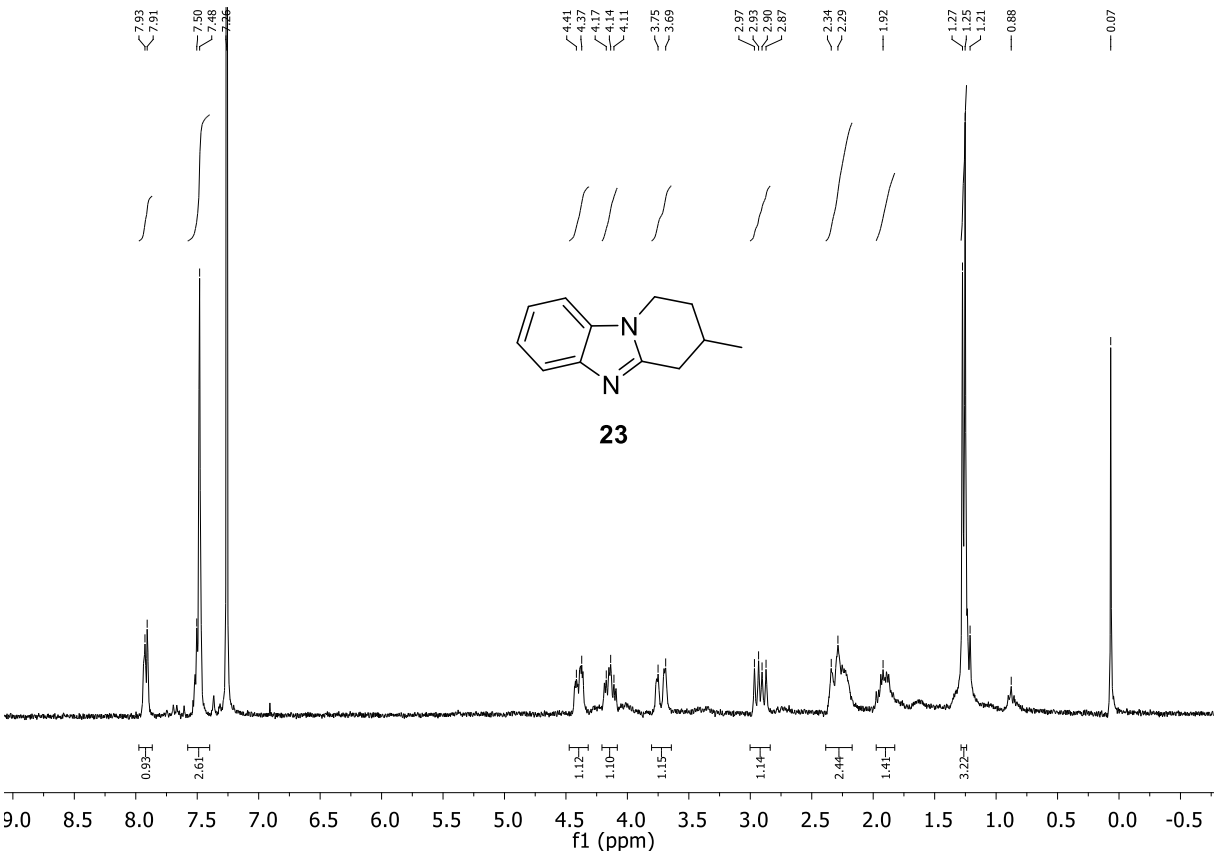
7.33
7.33
7.28
7.27
7.27
7.25
7.25
7.24
7.05
7.05
7.05
7.03
7.03
7.02
7.00
7.00
6.98
6.98
6.96
6.96
6.95
6.93
6.93
4.86 HDO
3.72
3.72
3.71
3.35
3.32 MeOD
3.32 MeOD
3.31 MeOD
3.30 MeOD
3.30 MeOD
2.92
2.77
2.74
2.72
2.69
1.29
1.27
1.25
1.22
0.10
N
N
H
19
1.00
0.96
1.01
0.97
1.93
3.86
2.09
3.12
8.0
7.5
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
f1 (ppm)

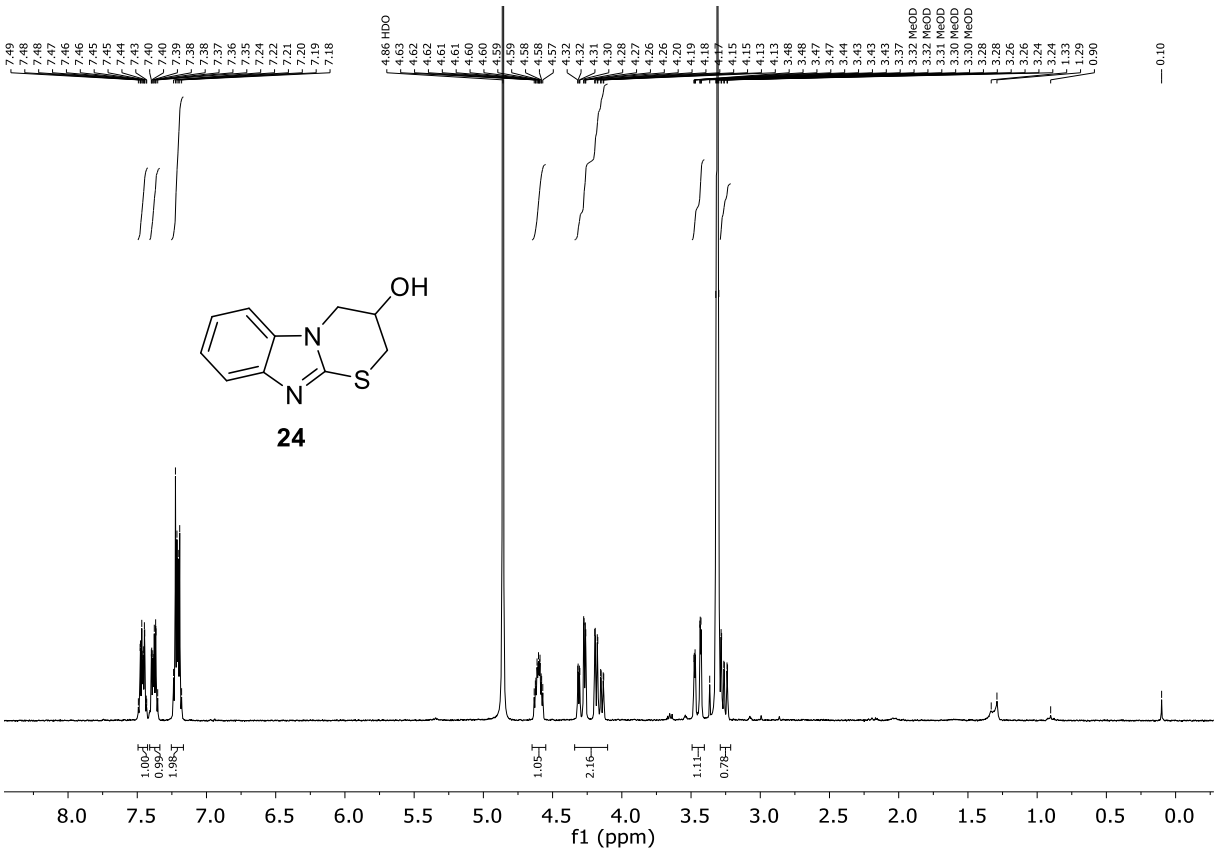

7.27
7.26
7.24
7.24
6.99
6.97
6.95
6.95
6.93
4.86 HDO
4.51
3.71
3.32 MeOD
3.32 MeOD
3.31 MeOD
3.30 MeOD
3.30 MeOD
3.27
3.25
3.23
3.12
2.47
1.29
0.10
N
N
H
20
1.00
1.96
1.80
1.88
1.87
2.92
2.87
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


21
f1 (ppm)


22
f1 (ppm)


7.93
7.91
7.50
7.48
7.26
4.41
4.37
4.17
4.14
4.11
3.75
3.69
2.97
2.93
2.90
2.87
2.34
2.29
1.92
1.27
1.25
1.21
0.88
0.07
N
N
0.93
2.61
1.12
1.10
1.15
1.14
2.44
1.41
3.22
f1 (ppm)

23


4.86 HDO
3.32 MeOD
3.31 MeOD
3.30 MeOD
0.10
OH
N
N
S
1.00
0.99
1.98
1.05
2.16
1.11
0.78
f1 (ppm)

24

Complexation attempts with *rac*-**3**

A stock solution of $(NH_4)_2Fe(SO_4)_2$•6 H_2O (0.45 M) in D_2O was prepared. The compound ***rac*-3** was dissolved in D_2O to form a 6.4 mM solution in the NMR tube. Then, stock solution was successively added to result in 0.5, 1, 2, 5, 10 equivalents of Fe(II). Before each measurement, the NMR tube was shaken for 30 s. No shifts of the ^{1}H NMR signals of **3**, potentially indicating complexation by iron, could be detected.

Selected IC_{50} curves for inhibition of ZIP8

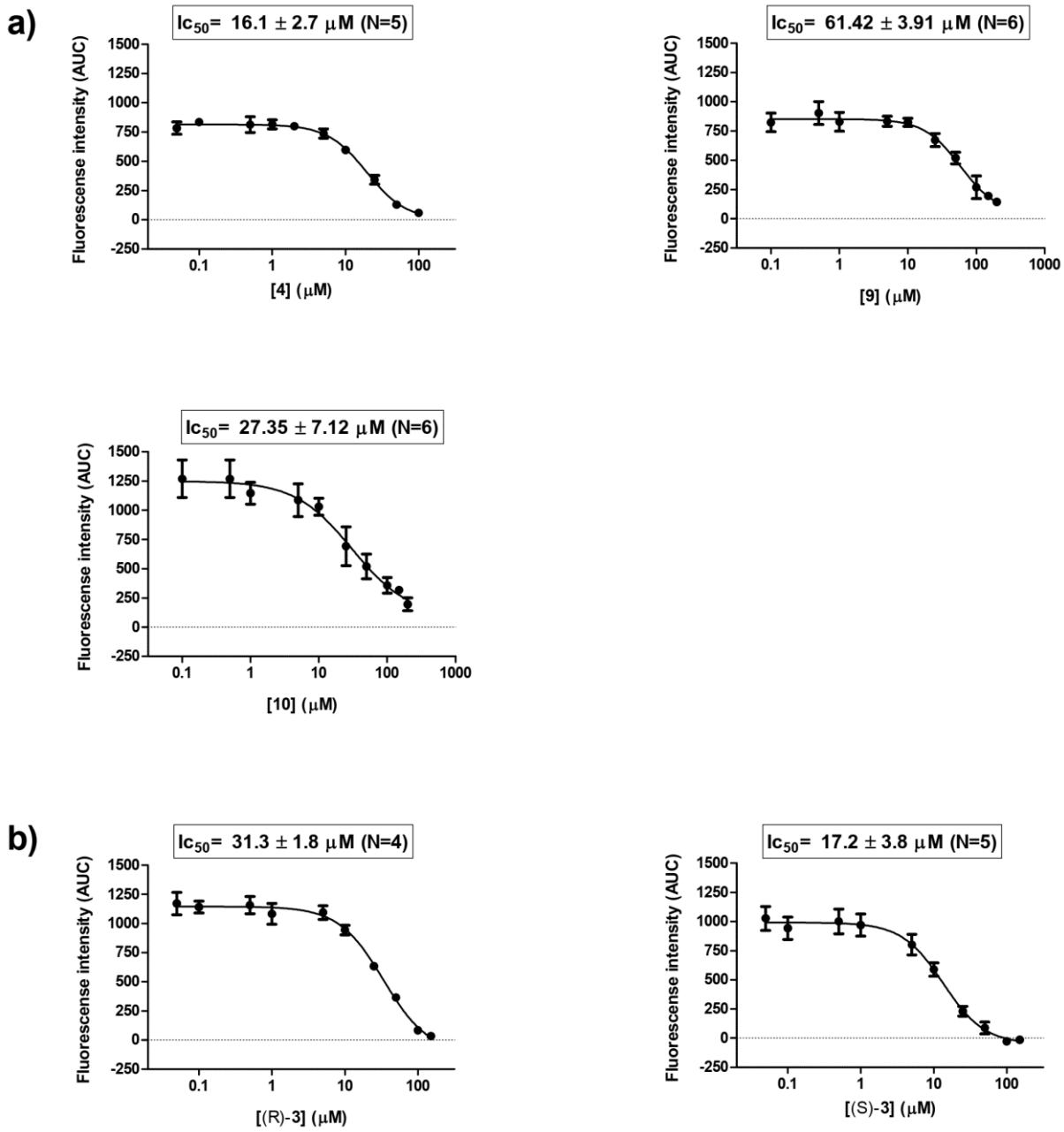


Figure S2. Representative Ic_{50} curves for *rac*-**3** analogues (**a**) and enantiomers (**b**) in ZIP8 transiently transfected HEK293T cells. Cd^{2+}-uptake (5μM) was measured as the Area Under the curve (AUC) in the presence of the indicated compound concentrations using the Calcium 5 fluorescent dye. Each data point represents the Mean ± SD (N=6-8) of the AUC determined in the presence of each compound concentration. IC_{50} values were calculated from 2 independent experiments performed in triplicate and are represented as the Mean ± SD (N=4-6). See Methods for details.