Supplementary Information

Structural basis of vilazodone dual binding mode to the serotonin transporter

Iris E. Kalenderoglou, Andreas Nygaard, Caleb D. Vogt, Anton Turaev, Tillmann Pape, Nathan B.P. Adams, Amy Hauck Newman, Claus J. Loland

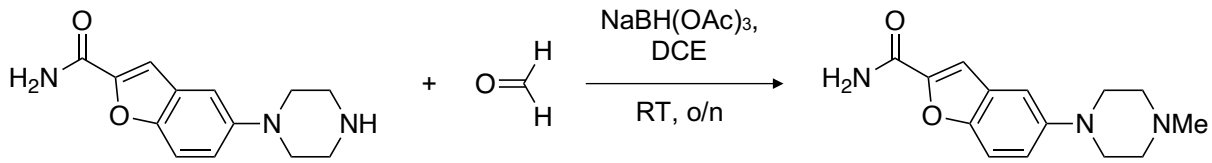
General Information. Chemicals and solvents were purchased from commercial suppliers and used as received. Unless stated otherwise, reactions were performed under ambient conditions and monitored by thin-layer chromatography using Analtech silica gel GHLF (250 microns) coated glass plates, which were visualized with either phosphomolybdic acid, potassium permanganate, or vanillin stain. Normal phase column chromatography was conducted with a Teledyne Isco Combiflash Rf or EZ-Prep purification system. All nuclear magnetic resonance (NMR) spectra (^{1}H and ^{13}C) were acquired in deuterated solvents ($CDCl_3$) on a Varian Mercury Plus 400 or JEOL JNM-ECLS 400S spectrometer. Chemical shifts are reported in parts per million (ppm) and were adjusted using the residual undertreated solvent ($CHCl_3$: 7.26 ppm for ^{1}H NMR, 77.2 ppm for ^{13}C NMR) as an internal reference. Coupling constants are reported in Hertz (Hz) and peak multiplicities as either a singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Infrared (IR) spectra were acquired on a Perkin Elmer Spectrum Two FT-IR spectrometer. Melting points were determined on an Optimelt MPA100 instrument and are uncorrected. High-resolution mass spectrometry (HRMS) data were collected on a Thermo Scientific LTQ-Orbitrap Velos spectrometer using electrospray ionization (ESI). Gas chromatography–mass spectrometry (GC–MS) data was acquired on an Agilent Technologies 7890B GC equipped with an HP-5MS column (cross-linked 5% PH ME siloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness) and a 5977B mass-selective ion detector in electron-impact mode. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively. All samples were prepared at a concentration of ca. 4 mg/mL in DCM, and 1 μL of each solution was injected onto the column. The temperature gradient was as follows: the initial temperature (70 °C) was held for 1 min, then increased to 300 °C over 11.5 min, and finally held at 300 °C for 4 min. Compound purity was determined from the total ion chromatogram based on peak integration (area under the curve). Elemental analysis was performed by Robertson Microlit Laboratories (Ledgewood, NJ). All tested compounds were >95% pure by GC–MS or elemental analysis.

General Procedure A for Reductive Amination.[1] To a mixture of 5-(piperazin-1-yl)benzofuran-2-carboxamide (0.200 g, 0.816 mmol) in anhydrous DCE (2.9 mL) was added the appropriate aldehyde (1.1 equiv). The reaction was stirred for 30 min, and $NaBH(OAc)_3$ (1.4 equiv) was added. After stirring overnight, the reaction mixture was washed with a saturated aq solution of $NaHCO_3$ (15 mL), and the aq layer was

extracted with DCM (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography as described.

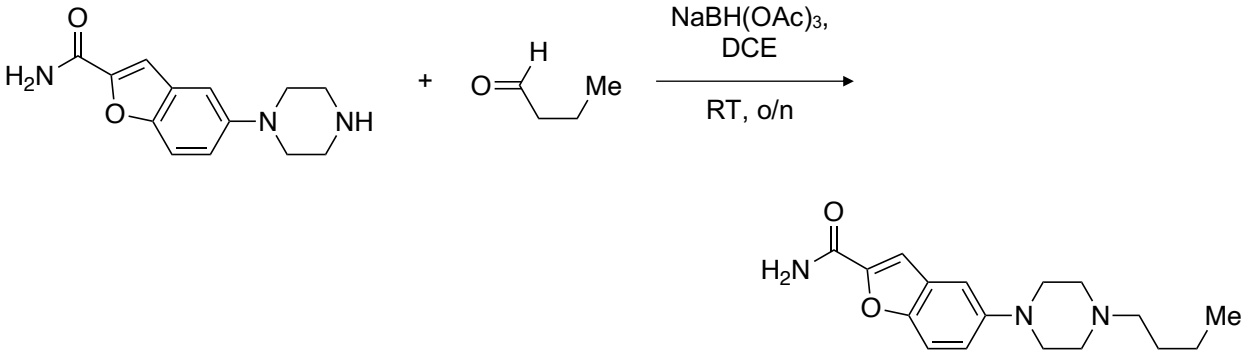
General Procedure B for Nucleophilic Displacement.[2] In a pressure flask, a mixture of **CDV-2-94** (1.20 g, 3.11 mmol), the appropriate nucleophile (2.0 equiv), NEt_3 (2.0 equiv), K_2CO_3 (2.0 equiv), and KI (0.1 equiv) in MeCN (14.5 mL) was heated to 100 °C. After stirring overnight, the reaction was allowed to cool to RT and concentrated. The resulting material was suspended in DCM (50 mL), washed with H_2O (50 mL), and the aq layer was extracted with DCM (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography as described.

General Procedure C for Tosyl Deprotection.[2] In a pressure flask, a solution of the starting material (1.0 equiv), NaOH (4.0 equiv), and MeOH (0.1 M) was heated to 70 °C. After stirring for 4 h, the reaction was allowed to cool to RT and concentrated. The residue was suspended in DCM, washed with H_2O, and the aq layer was extracted with DCM (2 ×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography as described.



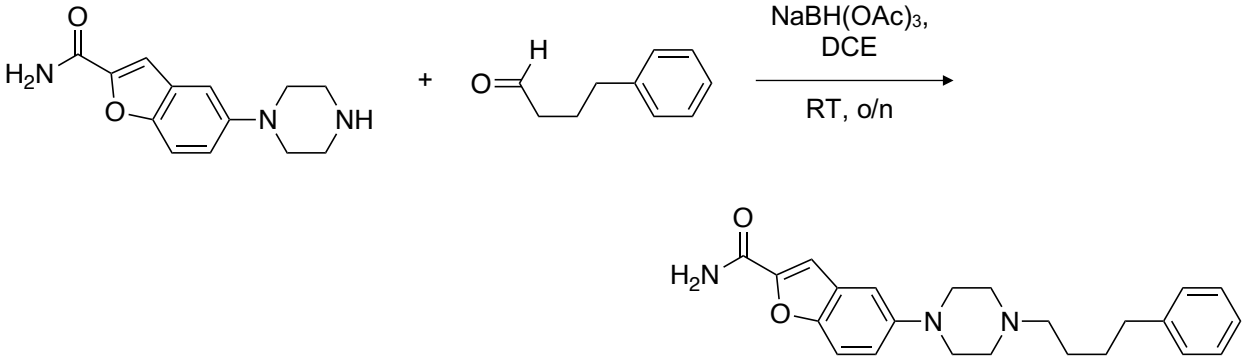
CDV-2-29 (39% yield)

5-(4-Methylpiperazin-1-yl)benzofuran-2-carboxamide (CDV-2-29). General procedure A was followed using a 37 wt% aq solution of formaldehyde (67 µL, 0.90 mmol). After work-up, the crude product was purified by chromatography (24 g of silica gel, 0–10% MeOH/DCM) to afford **CDV-2-29** (82.7 mg, 0.319 mmol, 39% yield) as a white, amorphous solid. R_f = 0.2 (10% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.35 (m, 2H), 7.20–7.08 (m, 2H), 6.50 (s, 1H), 5.92 (s, 1H), 3.27–3.13 (m, 4H), 2.69–2.56 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 150.3, 148.9, 148.6, 128.3, 119.5, 112.2, 111.6, 108.8, 55.3 (2C), 50.9 (2C), 46.2; IR (film) 3158, 1675 cm^{-1}; mp 232–234 °C (dec); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}N_3O_2$ 260.1394, found 260.1389. Anal. calcd for $C_{14}H_{17}N_3O_2 \cdot 0.25H_2O$: C, 63.74; H, 6.69; N, 15.93. Found: C, 63.71; H, 6.56; N, 15.61.



CDV-2-26 (87% yield)

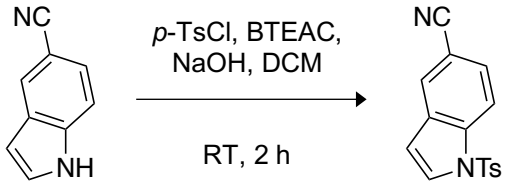
5-(4-Butylpiperazin-1-yl)benzofuran-2-carboxamide (CDV-2-26). General procedure A was followed using butyraldehyde (81 µL, 0.90 mmol). After work-up, the crude product was purified by chromatography (24 g of silica gel, 0–5% MeOH/$CHCl_3$) to afford **CDV-2-26** (0.213 g, 0.707 mmol, 87% yield) as a white, amorphous solid. R_f = 0.1 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.35 (m, 2H), 7.17–7.09 (m, 2H), 6.50 (s, 1H), 5.88 (s, 1H), 3.25–3.16 (m, 4H), 2.69–2.59 (m, 4H), 2.45–2.37 (m, 2H), 1.57–1.47 (m, 2H), 1.41–1.30 (m, 2H), 0.97–0.90 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 150.3, 149.0, 148.6, 128.3, 119.5, 112.1, 111.6, 108.7, 58.6, 53.5 (2C), 50.9 (2C), 29.2, 21.0, 14.2; IR (film) 3419, 3184, 1657 cm^{-1}; mp 185–186 °C (dec); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}N_3O_2$ 302.1863, found 302.1857. Anal. calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.40; H, 7.76; N, 13.90.



CDV-2-32 (50% yield)

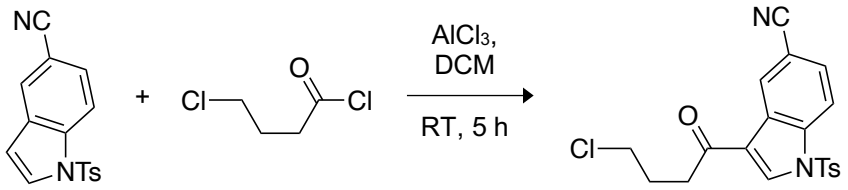
5-(4-(4-Phenylbutyl)piperazin-1-yl)benzofuran-2-carboxamide (CDV-2-32). General procedure A was followed using 4-phenylbutanal (0.135 g, 0.910 mmol). After work-up, the crude product was purified by normal phase flash chromatography (24 g of silica gel, 0–10% MeOH/DCM) to afford **CDV-2-32** (0.156 g, 0.413 mmol, 50% yield) as a yellow, amorphous solid. R_f = 0.5 (10% MeOH/DCM); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.45–7.35 (m, 2H), 7.31–7.25 (m, 2H), 7.22–7.08 (m, 5H), 6.49 (s, 1H), 5.92 (s, 1H), 3.21–3.15 (m, 4H), 2.69–2.58 (m, 6H), 2.46–2.39 (m, 2H), 1.72–1.63 (m, 2H), 1.62–1.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 150.3, 149.0, 148.6, 142.6, 128.5, 128.4, 128.3, 125.9, 119.4, 112.1, 111.6, 108.7, 58.7, 53.5 (2C), 50.9 (2C), 36.0, 29.5, 26.7; IR (film) 3438, 3187, 1661 cm^{-1}; mp 217–218 °C (dec); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}N_3O_2$ 378.2176, found 378.2170. Anal. calcd for $C_{23}H_{27}N_3O_2 \cdot 0.25H_2O$: C, 72.32; H, 7.26; N, 11.00. Found: C, 72.66; H, 7.12; N, 11.00.



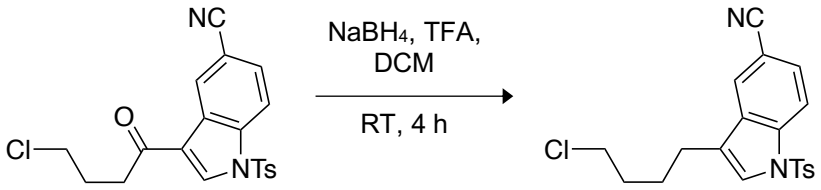
CDV-2-52 (89% yield)

1-Tosyl-1*H*-indole-5-carbonitrile (CDV-2-52).[3] To a mixture of 1*H*-indole-5-carbonitrile (3.00 g, 21.1 mmol), benzyltriethylammonium chloride (BTEAC) (0.483 g, 2.12 mmol), NaOH (1.55 g, 39 mmol), and anhydrous DCM (105 mL). Then, *p*-TsCl (4.83 g, 25.3 mmol) was added, and the reaction mixture was stirred for 2 h. H_2O (200 mL) was added, and the aq layer was extracted with DCM (2 × 90 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by recrystallization from EtOH (slow cooling of hot solvent) to afford **CDV-2-52** (5.55 g, 18.7 mmol, 89% yield) as a white, crystalline solid. R_f = 0.5 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 1H), 7.87 (dd, *J* = 1.4, 0.5 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 3.7 Hz, 1H), 7.55 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.71 (dd, *J* = 3.7, 0.7 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 136.5, 134.9, 130.8, 130.3 (2C), 128.6, 127.7, 127.0 (2C), 126.5, 119.5, 114.4, 108.6, 107.0, 21.8; IR (neat) 2225, 1610, 1595 cm^{-1}; mp 132–133 °C (EtOH), lit.[4] 130–131 °C; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}N_2O_2S$ 297.0692, found 297.0686.



CDV-2-52 **CDV-2-56** (83% yield)

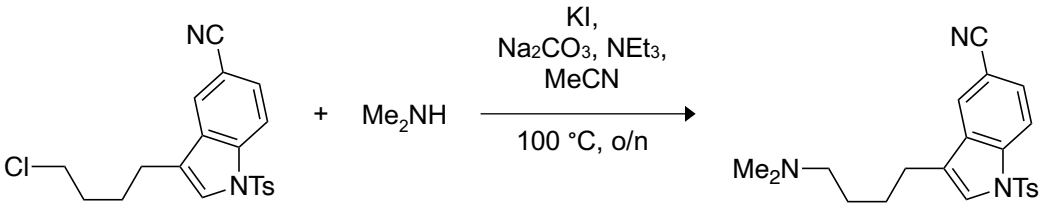
3-(4-Chlorobutanoyl)-1-tosyl-1*H*-indole-5-carbonitrile (CDV-2-56).[2] To a mixture of $AlCl_3$ (5.00 g, 37.5 mmol) in anhydrous DCM (92 mL) was added 4-chlorobutanoyl chloride (2.5 mL, 22 mmol) followed by **CDV-2-52** (5.55 g, 18.7 mmol). After stirring for 5 h, the reaction was poured into ice-cold H_2O (100 mL), and the aq layer was extracted with DCM (3 × 100 mL). The combined organic layers were washed with a saturated aq solution of $NaHCO_3$ (150 mL) followed by brine (150 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by recrystallization from *i*-PrOH (slow cooling of hot solvent) to afford **CDV-2-56** (6.22 g, 15.5 mmol, 83% yield) as a fluffy, white solid. R_f = 0.4 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 1.6 Hz, 1H), 8.36 (s, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.62 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 3.69 (t, *J* = 6.1 Hz, 2H), 3.12 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 2.29–2.21 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 146.9, 136.5, 134.0, 133.3, 130.7 (2C), 128.9, 128.4, 127.8, 127.4 (2C), 120.6, 119.0, 114.2, 108.8, 44.6, 36.6, 26.7, 21.9; IR (neat) 2227, 1661, 1608, 1597 cm^{-1}; mp 164–165 °C (*i*-PrOH), lit.[2] 154–156 °C (*i*-PrOH); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{18}ClN_2O_3S$ 401.0721, found 401.0713.



CDV-2-56 **CDV-2-94** (69% yield)

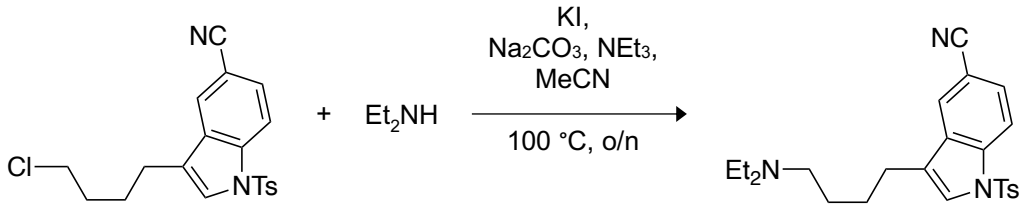
3-(4-Chlorobutyl)-1-tosyl-1*H*-indole-5-carbonitrile (CDV-2-94).[2] TFA (120 mL, 1.57 mol) was cooled to 0 °C, and $NaBH_4$ (8.86 g, 234 mmol) was added slowly portion wise. Caution: $NaBH_4$ reacts violently with TFA! After stirring for 10 min, a solution of **CDV-2-56** (6.22 g, 15.5 mmol) in DCM (150 mL) was added over 5 min. The reaction was allowed to warm to RT and stirred for 4 h. Afterward, ice-cold H_2O (200 mL) was added slowly, and the aq layer was extracted with DCM (3 × 100 mL). The combined organic

layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by recrystallization from MeOH (slow cooling of hot solvent) to afford **CDV-2-94** (4.12 g, 10.6 mmol, 69% yield) as a white, crystalline solid. R_f = 0.6 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.56 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.45 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 3.60–3.52 (m, 2H), 2.75–2.64 (m, 2H), 2.36 (s, 3H), 1.89–1.78 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 137.1, 134.9, 131.0, 130.3 (2C), 127.8, 126.9 (2C), 124.9, 124.6, 122.4, 119.5, 114.7, 106.8, 44.7, 32.2, 26.2, 24.1, 21.8; IR (neat) 2224, 1606, 1597 cm^{-1}; mp 126–127 °C (MeOH), lit.[2] 110–112 °C (MeOH); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}ClN_2O_2S$ 387.0929, found 387.0927.



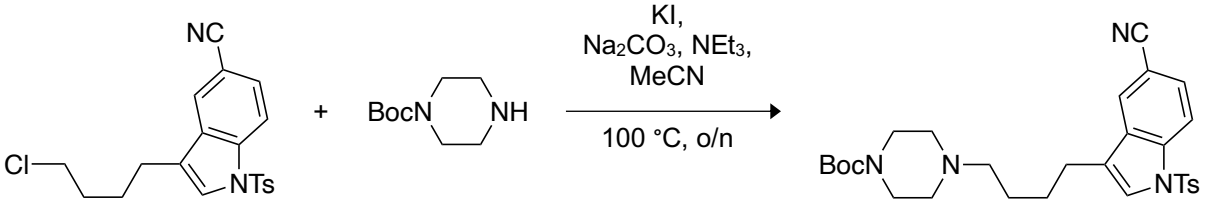
CDV-2-94 **CDV-2-76** (72% yield)

3-(4-(Dimethylamino)butyl)-1-tosyl-1*H*-indole-5-carbonitrile (CDV-2-76). General procedure B was followed using dimethylamine•HCl (0.506 g, 6.21 mmol). After work-up, the crude product was purified by chromatography (80 g of silica gel, 0–10% MeOH containing 10% NH_4OH/DCM) to afford **CDV-2-76** (0.890 g, 2.25 mmol, 72% yield) as a white, amorphous solid. R_f = 0.3 (10% MeOH containing 10% NH_4OH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H), 7.83, (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.44 (s, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.36 (s, 3H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.21 (s, 6H), 1.75–1.65 (m, 2H), 1.59–1.49 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 137.1, 135.1, 131.2, 130.2 (2C), 127.7, 126.9 (2C), 124.8, 124.7, 123.0, 119.5, 114.6, 106.7, 59.5, 45.6 (2C), 27.6, 26.9, 24.7, 21.7; IR (film) 2226 cm^{-1}; mp 93–94 °C; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_3O_2S$ 396.1740, found 396.1735.



CDV-2-94 **CDV-2-73** (34% yield)

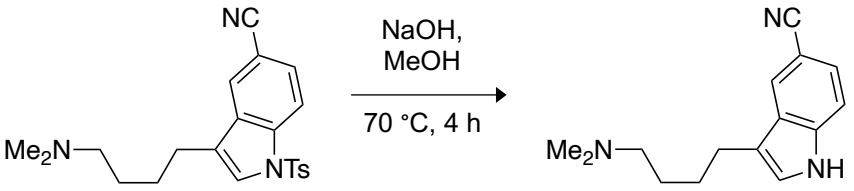
3-(4-(Diethylamino)butyl)-1-tosyl-1*H*-indole-5-carbonitrile (CDV-2-73). General procedure B was followed using diethylamine (0.64 mL, 6.2 mmol). After work-up, the crude product was purified by chromatography (80 g of silica gel, 0–10% MeOH containing 10% NH_4OH/DCM) to afford **CDV-2-73** (0.445 g, 1.05 mmol, 34% yield) as a white, amorphous solid. R_f = 0.3 (10% MeOH containing 10% NH_4OH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 1H), 7.83 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.44 (s, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.52 (q, *J* = 7.1 Hz, 4H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.36 (s, 3H), 1.73–1.63 (m, 2H), 1.58–1.47 (m, 2H), 1.02 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 137.2, 135.1, 131.3, 130.2 (2C), 127.7, 126.9 (2C), 124.8 (2C), 123.1, 119.5, 114.6, 106.7, 52.7, 47.1 (2C), 27.1 (2C), 24.8, 21.7, 11.8 (2C); IR (film) 2226 cm^{-1}; mp 71–72 °C; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{24}H_{30}N_3O_2S$ 424.2053, found 424.2048.



CDV-2-94 **CDV-2-89** (54% yield)

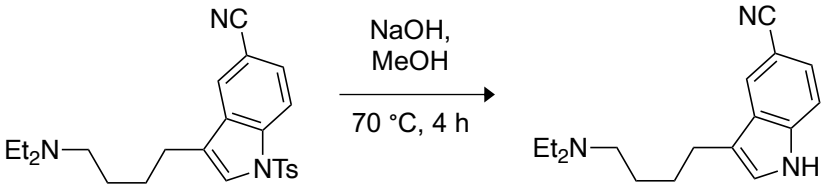
***tert*-Butyl 4-(4-(5-cyano-1-tosyl-1*H*-indol-3-yl)butyl)piperazine-1-carboxylate (CDV-2-89).** General procedure B was followed using *tert*-butyl piperazine-1-carboxylate (1.16 g, 6.21 mmol). After work-up, the crude product was purified by chromatography (80 g of silica gel, 0–75% EtOAc/hexanes) to afford **CDV-2-89** (0.894 g, 1.67 mmol, 54% yield) as a white, amorphous solid. R_f = 0.4 (75% EtOA/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.44 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 3.49–3.38 (m, 4H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.41–2.31 (m, 9H), 1.76–1.65 (m, 2H), 1.61–1.51 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 145.7, 137.2, 135.1, 131.2, 130.2 (2C), 127.7, 126.9 (2C), 124.8, 124.7, 122.9, 119.5, 114.6, 106.7, 79.7, 58.3, 53.2 (2C),

43.7 (2C), 28.6 (3C), 26.9, 26.6, 24.7, 21.8; IR (film) 2226, 1690 cm^{-1}; mp 110–112 °C; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{29}H_{37}N_4O_4S$ 537.2530, found 537.2523.



CDV-2-76 **CDV-2-81** (54% yield)

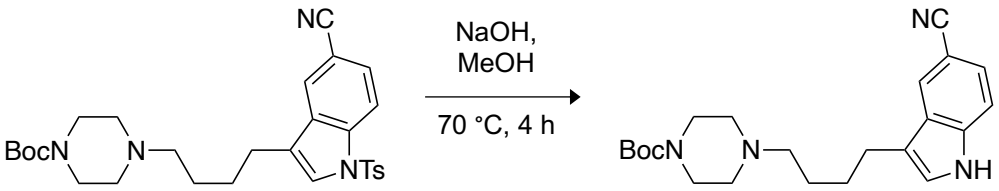
3-(4-(Dimethylamino)butyl)-1*H*-indole-5-carbonitrile (CDV-2-81). General procedure C was followed using **CDV-2-76** (0.866 g, 2.19 mmol) in MeOH (14.5 mL). After work-up, the crude product was purified by chromatography (24 g of silica gel, 0–10% MeOH containing 10% NH_4OH/DCM) to afford **CDV-2-81** (0.288 g, 1.19 mmol, 54% yield) as a white, amorphous solid. R_f = 0.3 (10% MeOH containing 10% NH_4OH/DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.93 (s, 1H), 7.41–7.31 (m, 2H), 7.01 (s, 1H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.26 (s, 6H), 1.78–1.67 (m, 2H), 1.63–1.53 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 127.6, 124.79, 124.76, 123.6, 121.1, 117.6, 112.1, 102.1, 59.8, 45.6 (2C), 27.9, 27.7, 24.9; IR (film) 3327, 3118, 2217 cm^{-1}; mp 100–102 °C; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}N_3$ 242.1652, found 242.1648; ^{t}R = 12.20 min (GC–MS, 98% pure).



CDV-2-73 **CDV-3-2** (87% yield)

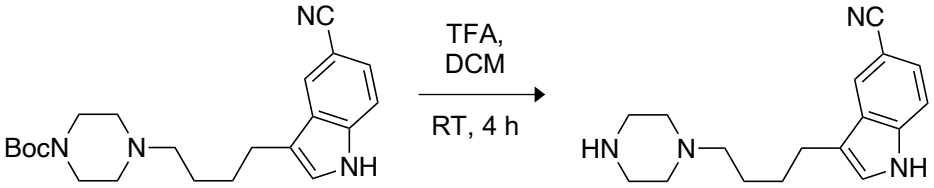
3-(4-(Diethylamino)butyl)-1*H*-indole-5-carbonitrile (CDV-3-2). General procedure C was followed using **CDV-2-73** (0.438 g, 1.04 mmol) in MeOH (7.0 mL). After work-up, the crude product was purified by chromatography (24 g of silica gel, 0–10% MeOH containing 10% NH_4OH/DCM) to afford **CDV-3-2** (0.243 g, 0.902 mmol, 87% yield) as a clear, colorless oil. R_f = 0.2 (10% MeOH containing 10% NH_4OH/DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.94 (s, 1H), 7.41–7.33 (m, 2H), 7.04 (s, 1H), 2.76 (t, *J* = 7.4 Hz, 2H), 2.56 (q, *J* = 7.1 Hz, 4H), 2.51–2.45 (m, 2H), 1.75–1.65 (m, 2H), 1.60–1.50 (m, 2H), 1.02 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 127.6, 124.9, 124.8, 123.5, 121.1, 117.8,

112.0, 102.2, 53.0, 47.0 (2C), 28.2, 27.2, 25.0, 11.7 (2C); IR (film) 3331, 3117, 2218 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}N_3$ 270.1965, found 270.1960; ^tR = 12.81 min (GC–MS, 96% pure).



CDV-2-89 **CDV-2-97** (91% yield)

***tert*-Butyl 4-(4-(5-cyano-1*H*-indol-3-yl)butyl)piperazine-1-carboxylate (CDV-2-97).** General procedure C was followed using **CDV-2-89** (0.887 g, 1.65 mmol) in MeOH (15.5 mL). After work-up, the crude product was purified by chromatography (40 g of silica gel, 0–75% EtOAc/hexanes) to afford **CDV-2-97** (0.574 g, 1.50 mmol, 91% yield) as a clear, colorless oil. R_f = 0.3 (75% EtOA/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.94 (s, 1H), 7.43–7.36 (m, 2H), 7.09 (s, 1H), 3.48–3.38 (m, 4H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.42–2.32 (m, 6H), 1.77–1.66 (m, 2H), 1.63–1.52 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 138.1, 127.6, 124.9, 124.8, 123.4, 121.0, 117.7, 112.1, 102.3, 79.8, 58.6, 53.2 (2C), 43.8 (2C), 28.6 (3C), 28.0, 26.7, 24.9; IR (film) 3300, 2218, 1670 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{31}N_4O_2$ 383.2442, found 383.2437.



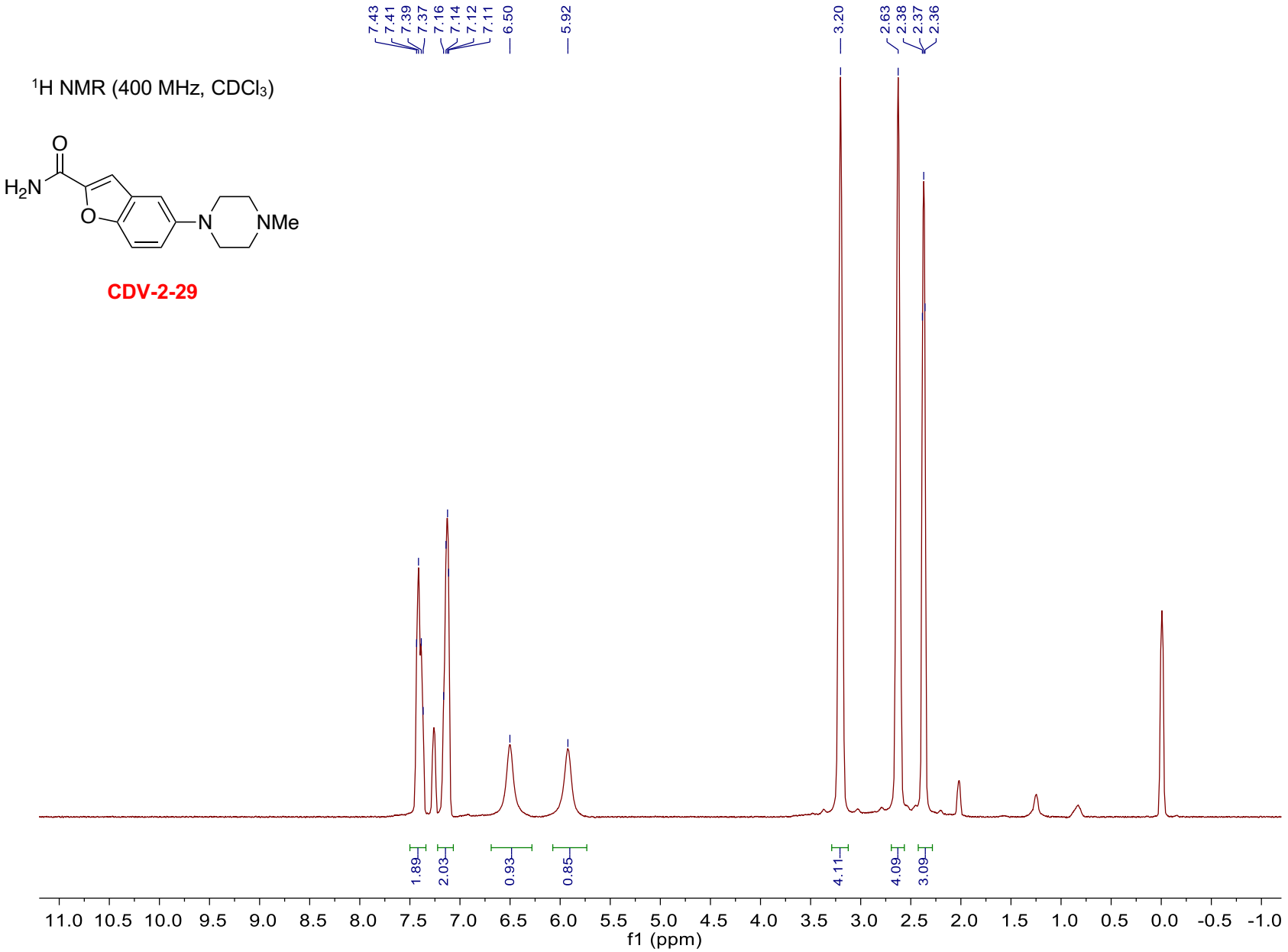
CDV-2-97 **CDV-3-1** (90% yield)

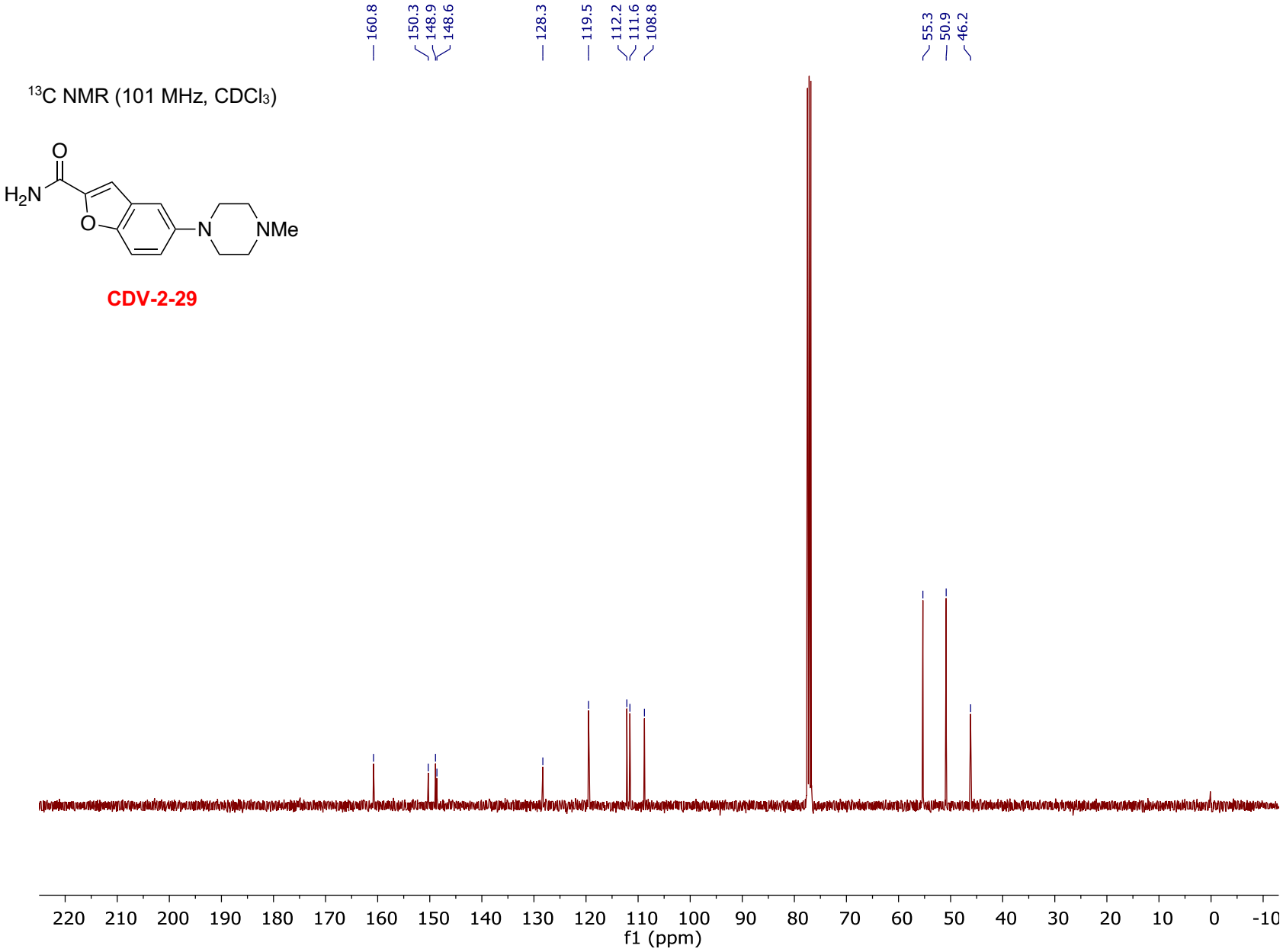
3-(4-(Piperazin-1-yl)butyl)-1H-indole-5-carbonitrile (CDV-3-1). To a solution of **CDV-2-97** (0.562 g, 1.47 mmol) in DCM (10 mL) was added TFA (4.5 mL, 59 mmol). The reaction was stirred for 4 h and then concentrated. After suspending the resulting residue in a 1.0 M aq solution of NaOH (30 mL), the aq layer was extracted with DCM (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (12 g of silica gel, 0–10% MeOH containing 10% NH_4OH/DCM) to afford **CDV-3-1** (0.375 g, 1.33 mmol, 90% yield) as a clear, colorless oil. R_f = 0.1 (10% MeOH containing 10% NH_4OH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.95 (s,

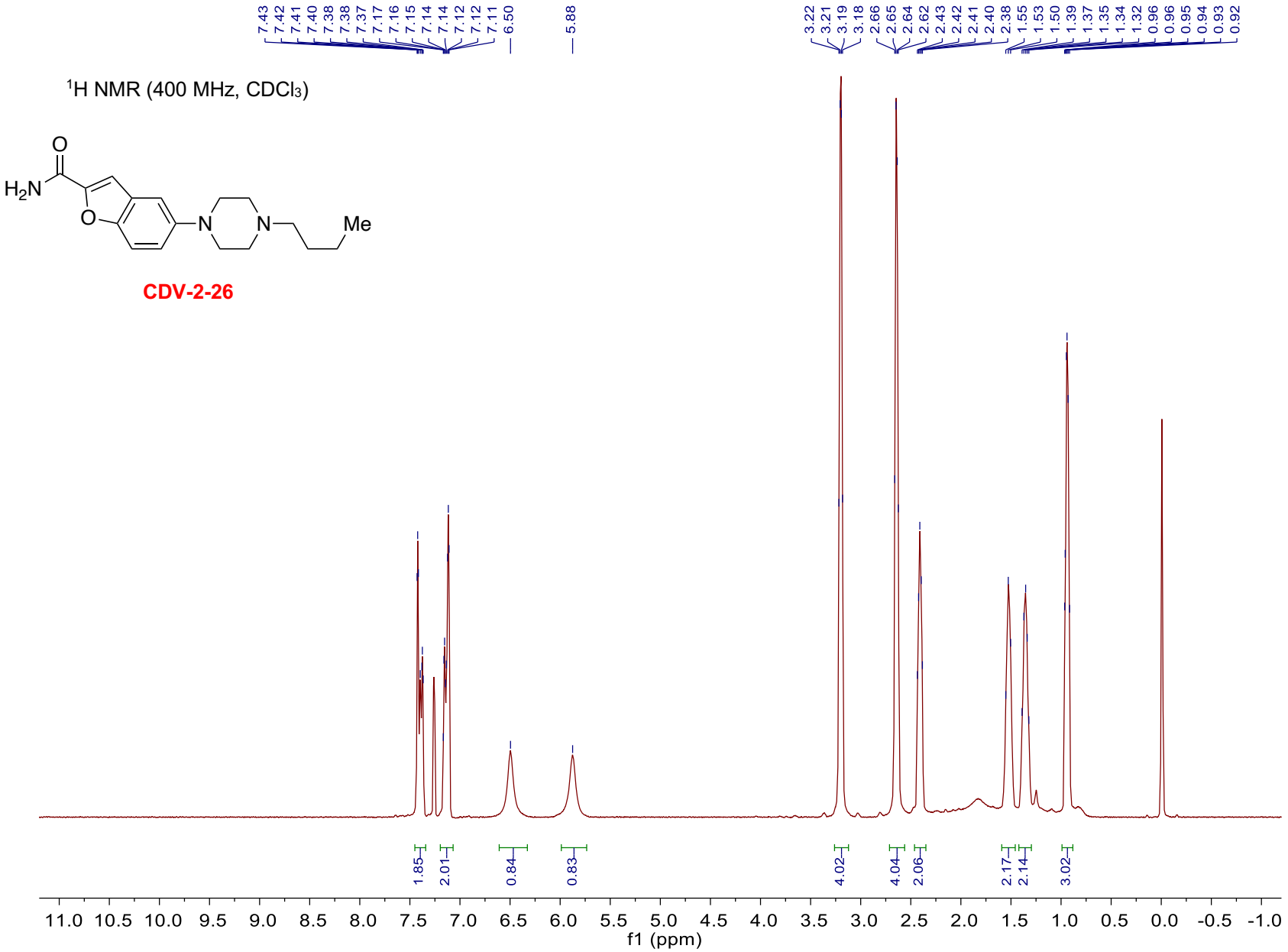
1H), 7.42–7.34 (m, 2H), 7.07 (s, 1H), 2.96–2.86 (m, 4H), 2.76 (t, J = 6.4 Hz, 2H), 2.60–2.28 (m, 6H), 1.90 (s, 1H), 1.77–1.65 (m, 2H), 1.63–1.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 127.6, 124.9 (2C), 123.4, 121.0, 117.8, 112.0, 102.3, 59.2, 54.7 (2C), 46.2 (2C), 28.1, 26.6, 24.9; IR (film) 3120, 2217 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}N_4$ 283.1917, found 283.1912; ^{t}R = 14.32 min (GC–MS, 97% pure).

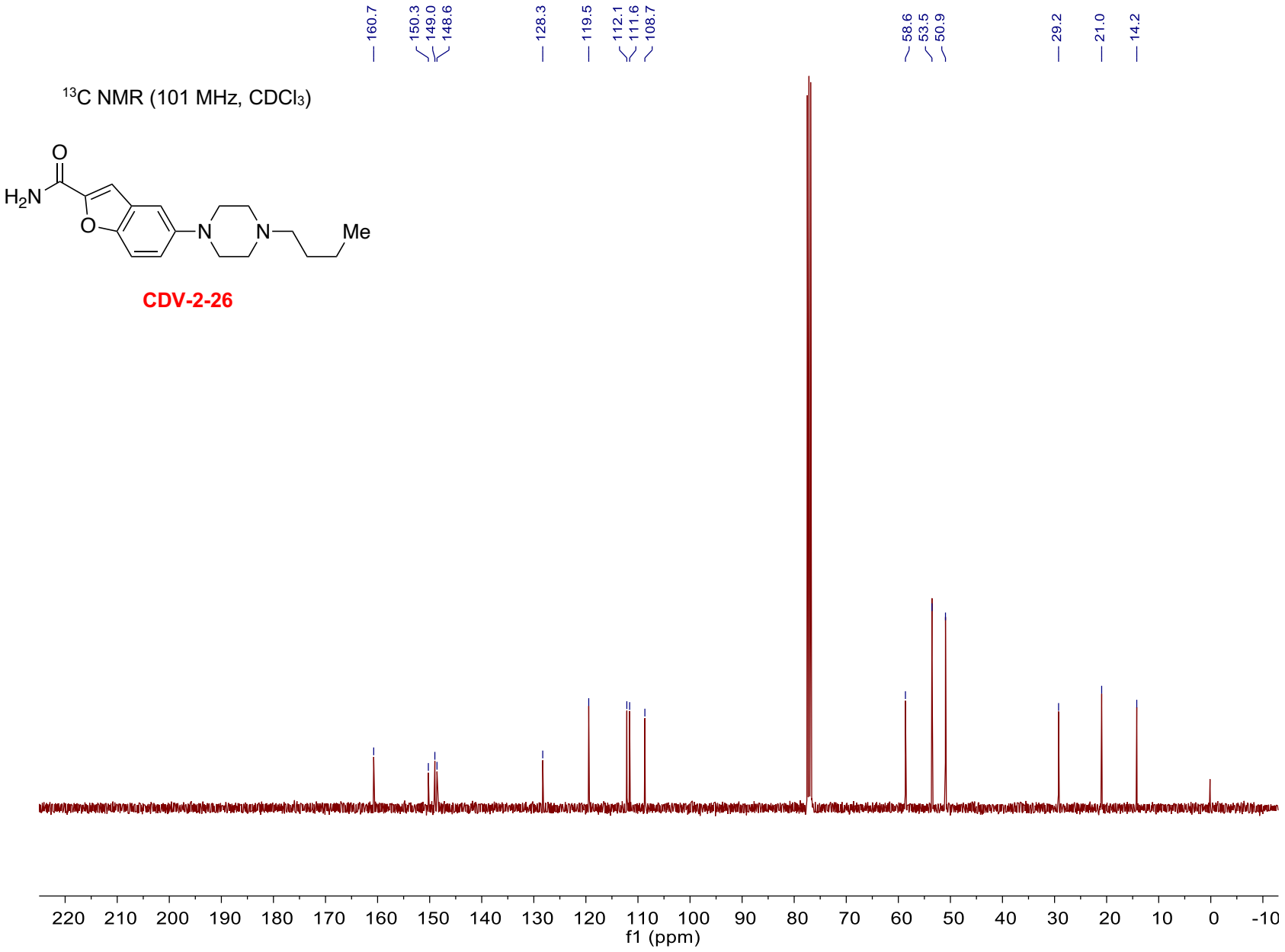
References

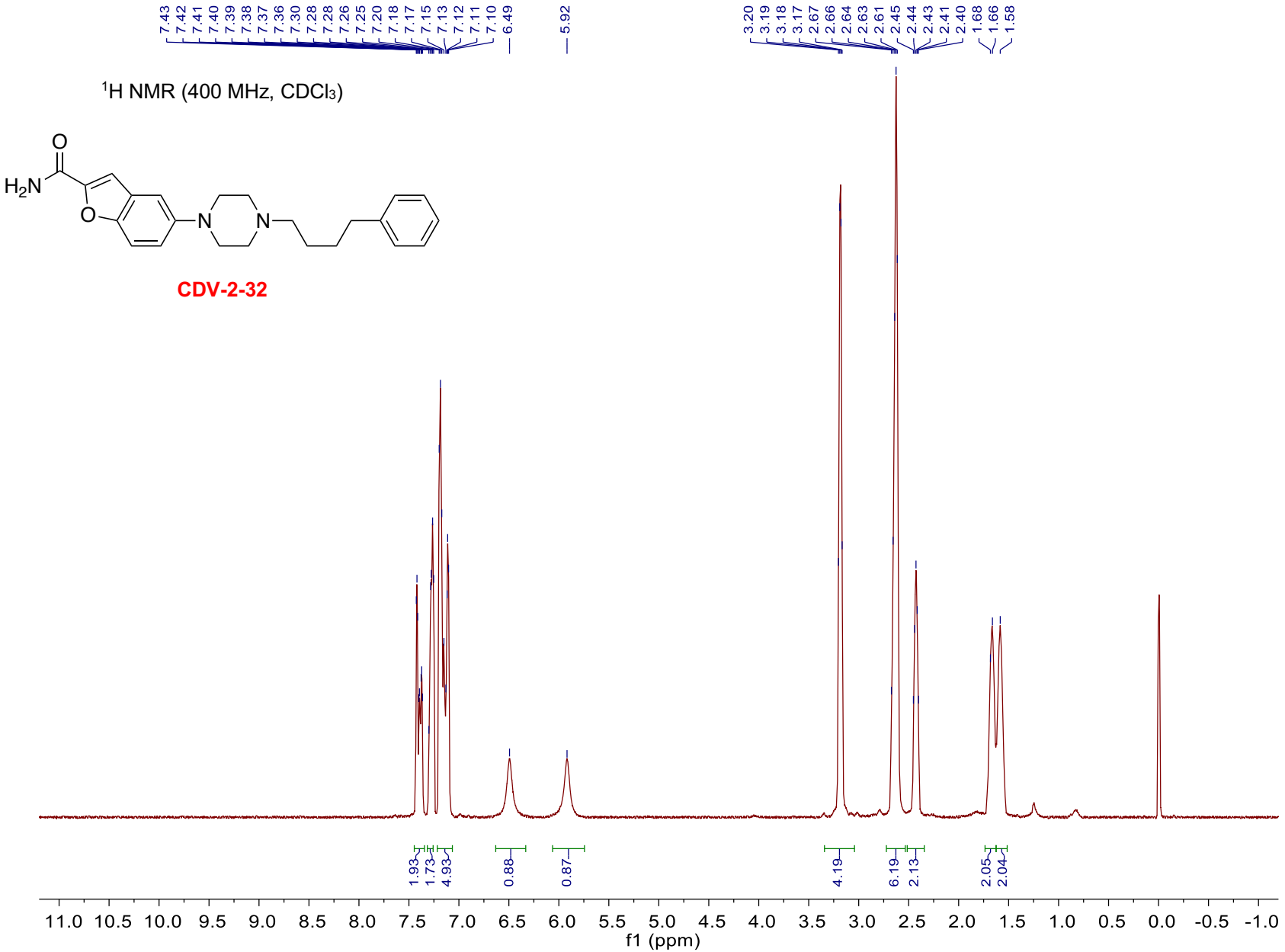
1. Abdel-Magid, A. F., Carson, K. G., Harris, B. D., Maryanoff, C. A. & Shah, R. D. Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. *J. Org. Chem.* **61**, (1996).
2. Hu, B., Song, Q. & Xu, Y. Scale-up synthesis of antidepressant drug vilazodone. *Org Process Res Dev* **16**, (2012).
3. Che, Z. *et al.* Synthesis and quantitative structure-activity relationship (QSAR) study of novel N-arylsulfonyl-3-acylindole arylcarbonyl hydrazone derivatives as nematicidal agents. *J. Agric. Food Chem.* **61**, (2013).
4. Zanon, J., Klapars, A. & Buchwald, S. L. Copper-catalyzed domino halide exchange-cyanation of aryl bromides. *J. Am. Chem. Soc.* **125**, (2003).

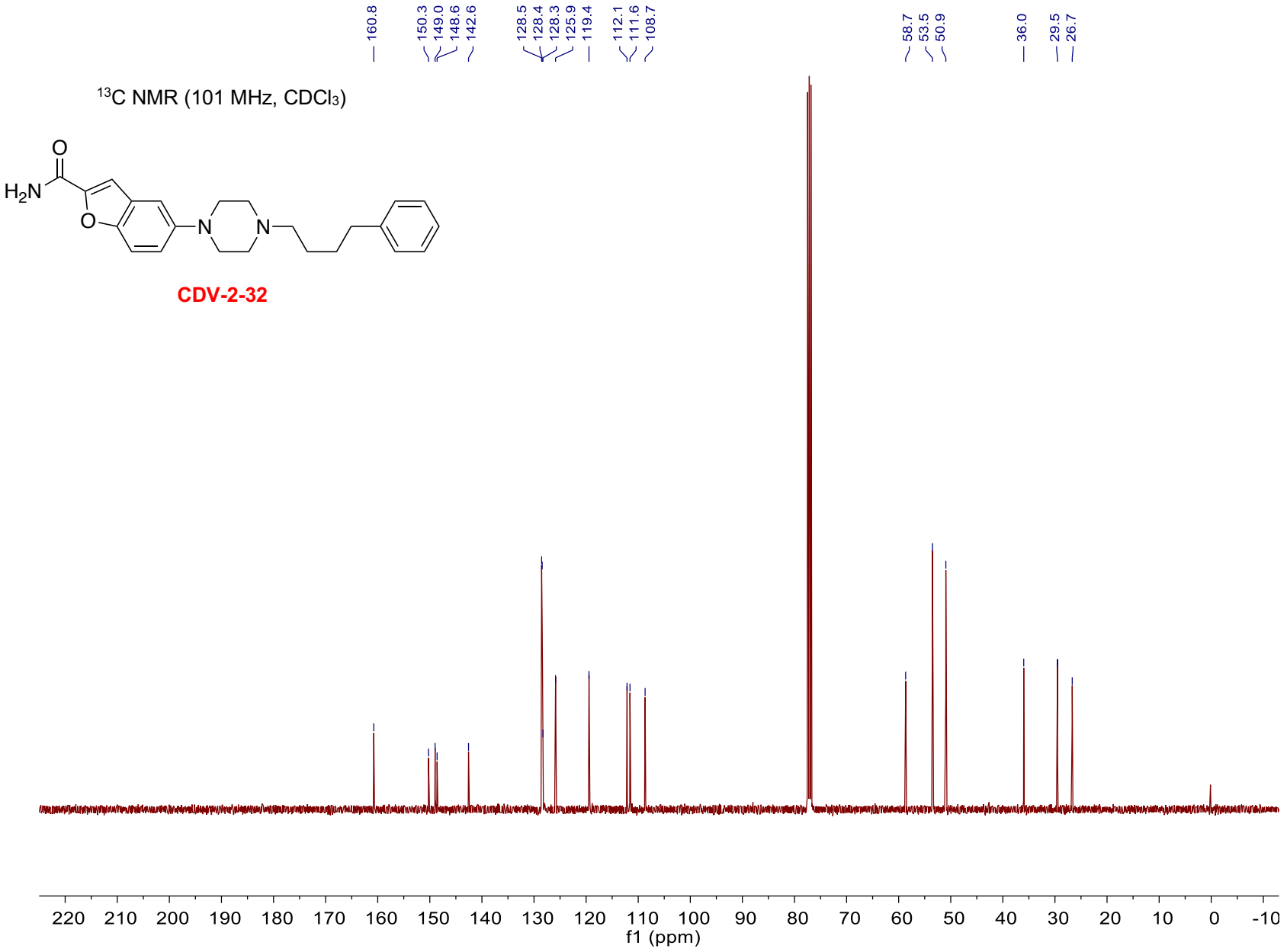

7.43
7.41
7.39
7.37
7.16
7.14
7.12
7.11
6.50
5.92
3.20
2.63
2.38
2.37
2.36
^{1}H NMR (400 MHz, $CDCl_3$)
O
H_2N
O
N
NMe
CDV-2-29
1.89
2.03
0.93
0.85
4.11
4.09
3.09
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


160.8
150.3
148.9
148.6
128.3
119.5
112.2
111.6
108.8
55.3
50.9
46.2
13C NMR (101 MHz, CDCl3)
O
H2N
O
N
NMe
CDV-2-29
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

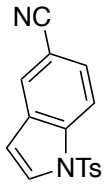

7.43
7.42
7.41
7.40
7.38
7.38
7.37
7.17
7.16
7.15
7.14
7.14
7.12
7.12
7.11
6.50
5.88
3.22
3.21
3.19
3.18
2.66
2.65
2.64
2.62
2.43
2.42
2.41
2.40
2.38
1.55
1.53
1.50
1.39
1.37
1.35
1.34
1.32
0.96
0.96
0.95
0.94
0.93
0.92
^{1}H NMR (400 MHz, $CDCl_3$)
O
H_2N
O
N
N
Me
CDV-2-26
1.85
2.01
0.84
0.83
4.02
4.04
2.06
2.17
2.14
3.02
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 -0.5 -1.0
f1 (ppm)


160.7
150.3
149.0
148.6
128.3
119.5
112.1
111.6
108.7
58.6
53.5
50.9
29.2
21.0
14.2
13C NMR (101 MHz, CDCl3)
O
H2N
O
N
N
Me
CDV-2-26
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.30
7.28
7.28
7.26
7.25
7.20
7.18
7.17
7.15
7.13
7.12
7.11
7.10
6.49
5.92
3.20
3.19
3.18
3.17
2.67
2.66
2.64
2.63
2.61
2.45
2.44
2.43
2.41
2.40
1.68
1.66
1.58
1H NMR (400 MHz, CDCl3)
O
H2N
O
N
N
CDV-2-32
1.93
1.73
4.93
0.88
0.87
4.19
6.19
2.13
2.05
2.04
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 -0.5 -1.0
f1 (ppm)

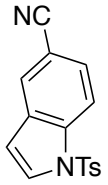

160.8
150.3
149.0
148.6
142.6
128.5
128.4
128.3
125.9
119.4
112.1
111.6
108.7
58.7
53.5
50.9
36.0
29.5
26.7
13C NMR (101 MHz, CDCl3)
O
H2N
O
N
N
CDV-2-32
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1H NMR (400 MHz, CDCl3)



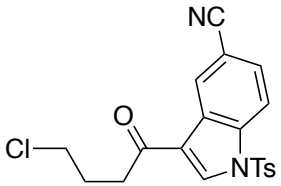
CDV-2-52

^{13}C NMR (101 MHz, $CDCl_3$)



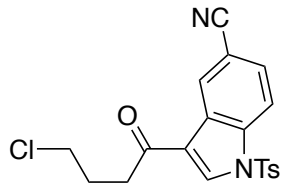
CDV-2-52

^{1}H NMR (400 MHz, $CDCl_3$)



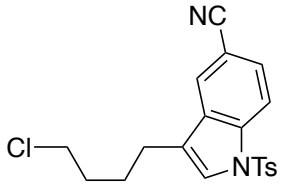
CDV-2-56

^{13}C NMR (101 MHz, $CDCl_3$)



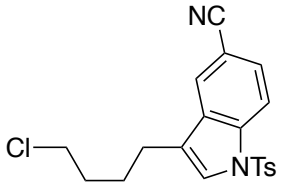
CDV-2-56

^{1}H NMR (400 MHz, $CDCl_3$)



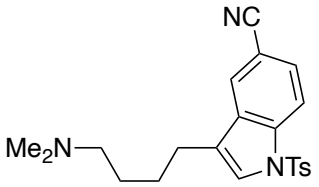
CDV-2-94

^{13}C NMR (101 MHz, $CDCl_3$)



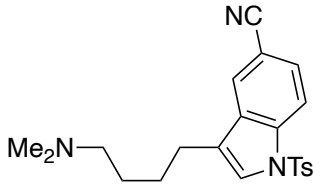
CDV-2-94

^{1}H NMR (400 MHz, $CDCl_3$)



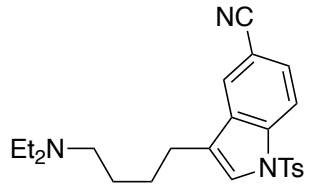
CDV-2-76

^{13}C NMR (101 MHz, $CDCl_3$)



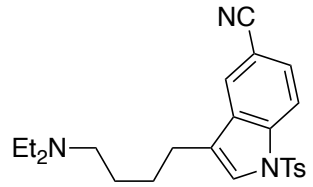
CDV-2-76

^{1}H NMR (400 MHz, $CDCl_3$)



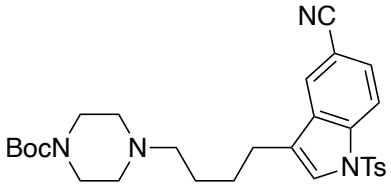
CDV-2-73

^{13}C NMR (101 MHz, $CDCl_3$)

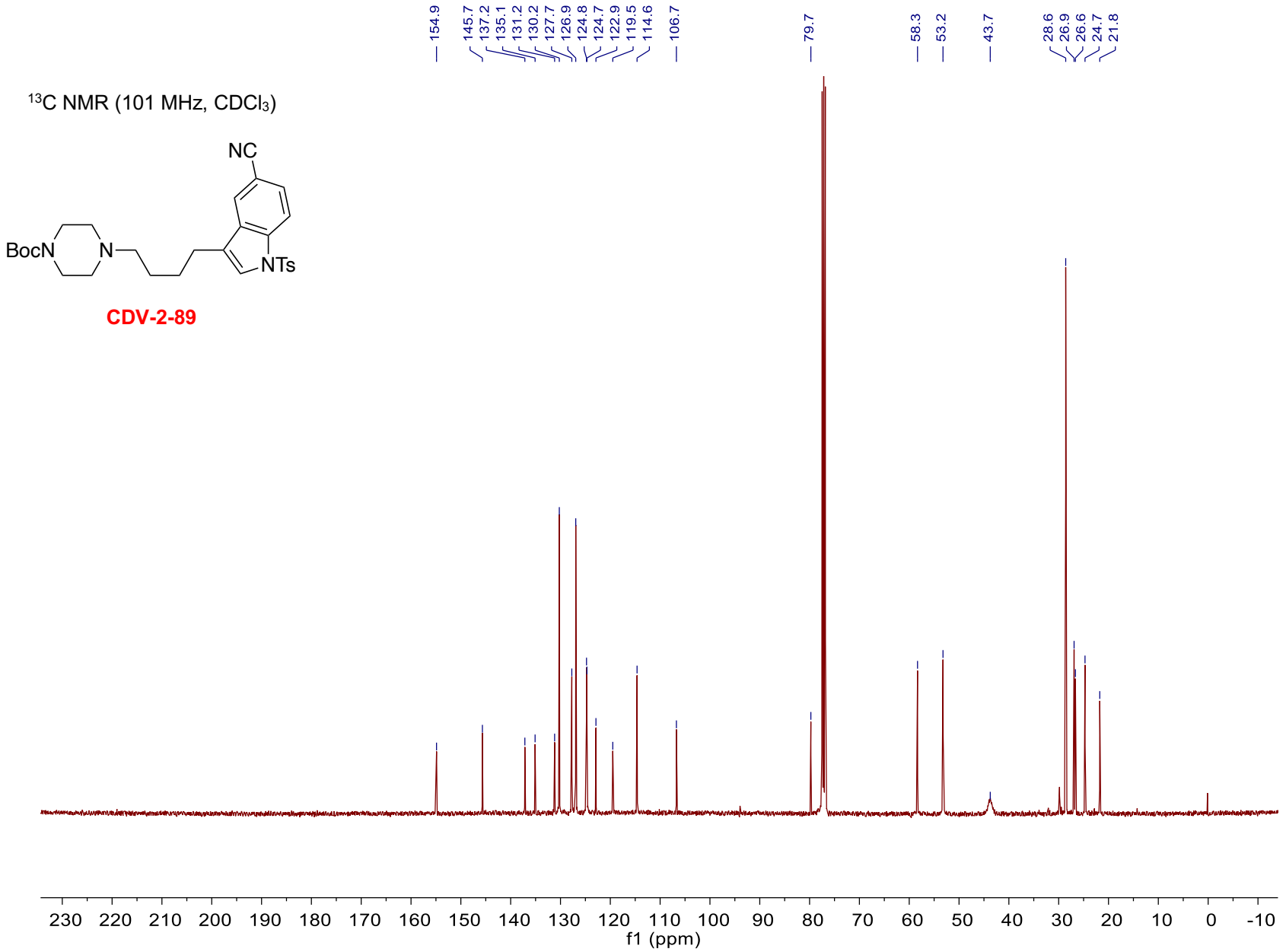


CDV-2-73

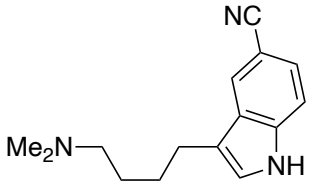
^{1}H NMR (400 MHz, $CDCl_3$)



CDV-2-89

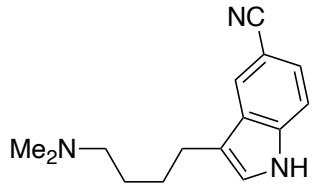

154.9
145.7
137.2
135.1
131.2
130.2
127.7
126.9
124.8
124.7
122.9
119.5
114.6
106.7
79.7
58.3
53.2
43.7
28.6
26.9
26.6
24.7
21.8
^{13}C NMR (101 MHz, CDCl$_3$)
NC
BocN
N
NTs
CDV-2-89
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



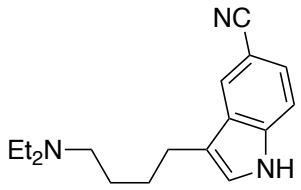
CDV-2-81

^{13}C NMR (101 MHz, $CDCl_3$)



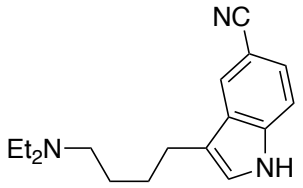
CDV-2-81

^{1}H NMR (400 MHz, $CDCl_3$)

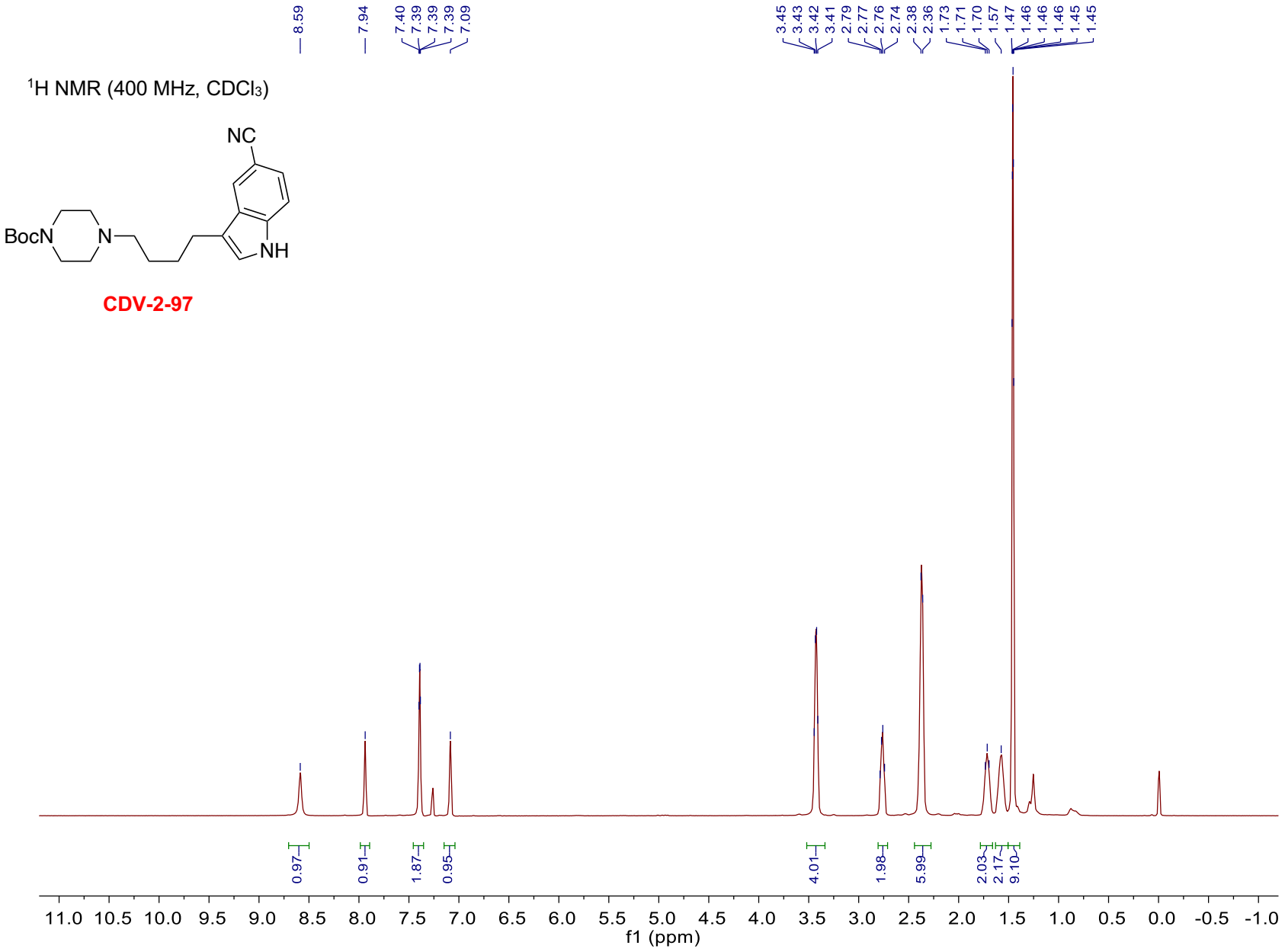


CDV-3-2

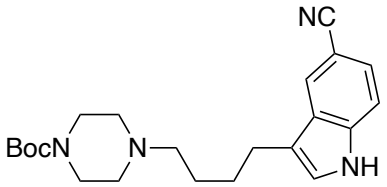
^{13}C NMR (101 MHz, $CDCl_3$)



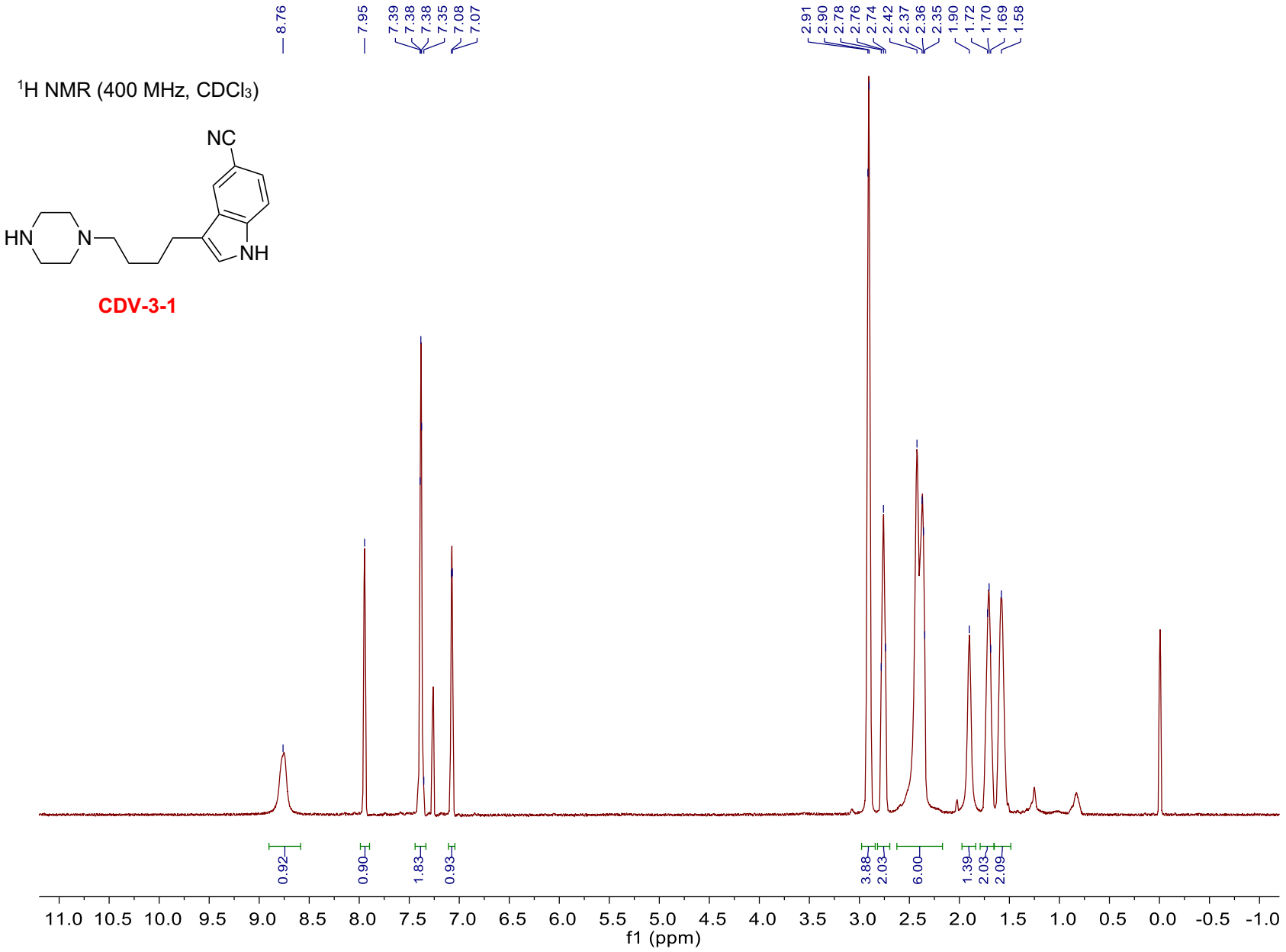
CDV-3-2


8.59
7.94
7.40
7.39
7.39
7.39
7.09
3.45
3.43
3.42
3.41
2.79
2.77
2.76
2.74
2.38
2.36
1.73
1.71
1.70
1.57
1.47
1.46
1.46
1.46
1.45
1.45
^{1}H NMR (400 MHz, $CDCl_3$)
NC
BocN
N
NH
CDV-2-97
0.97
0.91
1.87
0.95
4.01
1.98
5.99
2.03
2.17
9.10
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 -0.5 -1.0
f1 (ppm)

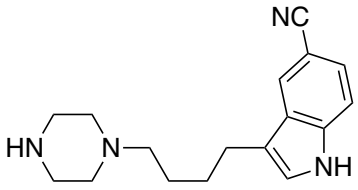
^{13}C NMR (101 MHz, $CDCl_3$)



CDV-2-97


8.76
7.95
7.39
7.38
7.38
7.35
7.08
7.07
2.91
2.90
2.78
2.76
2.74
2.42
2.37
2.36
2.35
1.90
1.72
1.70
1.69
1.58
^{1}H NMR (400 MHz, CDCl$_3$)
NC
HN
N
NH
CDV-3-1
0.92
0.90
1.83
0.93
3.88
2.03
6.00
1.39
2.03
2.09
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 -0.5 -1.0
f1 (ppm)

^{13}C NMR (101 MHz, $CDCl_3$)

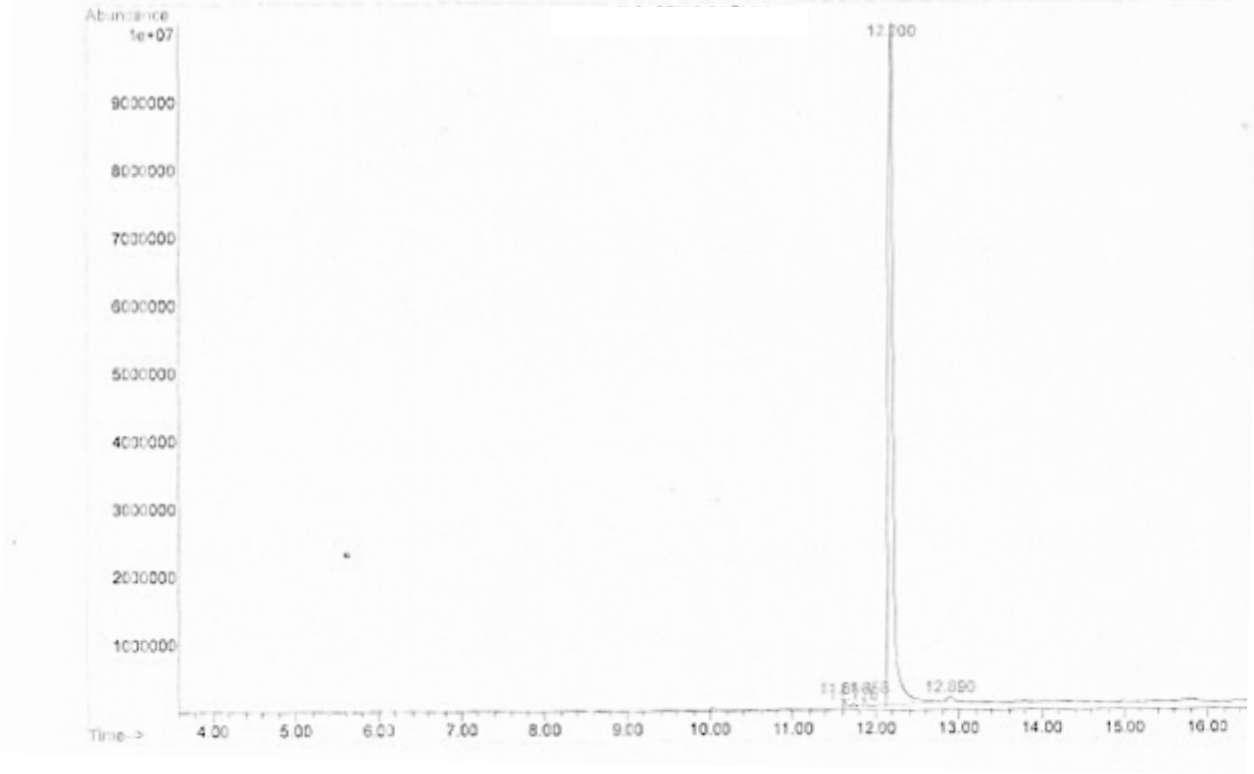


CDV-3-1

CDV-2-81 (GC–MS):

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	11.616	761	763	771	M3	140242	2819254	0.70%	0.689%
2	11.726	771	774	782	M2	44277	1072679	0.27%	0.262%
3	11.858	783	786	793	M	125796	2024244	0.51%	0.495%
4	12.200	810	819	868	M	10750215	399897328	100.00%	97.730%
5	12.890	877	884	894	M3	69798	3370785	0.84%	0.824%

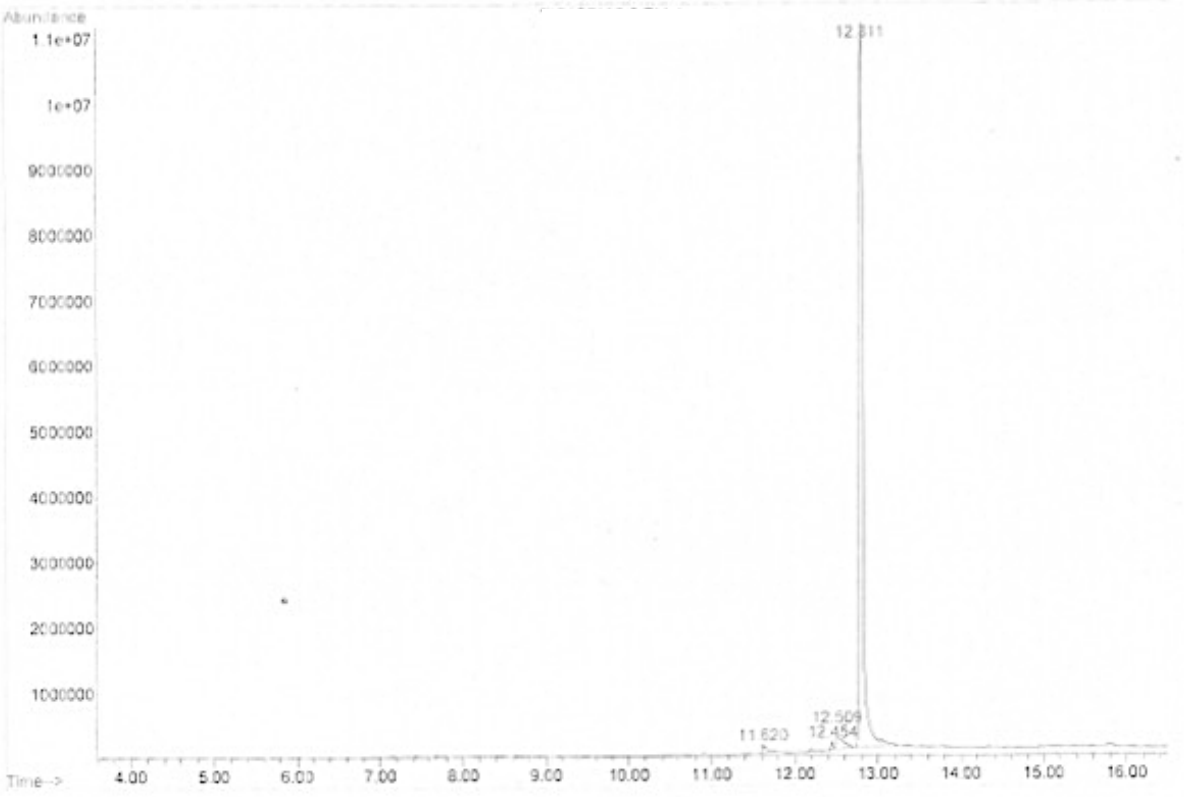
Sum of corrected areas: 409184289



CDV-3-2 (GC–MS):

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	11.620	755	763	774	BV 3	122926	4110866	0.98%	0.942%
2	12.454	828	843	845	BV	116556	1258975	0.30%	0.288%
3	12.509	845	848	868	VV	341841	13078534	3.13%	2.996%
4	12.811	870	877	921	M	11537551	418160526	100.00%	95.775%

Sum of corrected areas: 436608901



CDV-3-1 (GC–MS):

peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	11.641	755	765	775	BV 2	156458	5679493	1.05%	1.017%
2	12.188	807	817	828	BV	251452	6542359	1.21%	1.172%
3	12.895	875	885	897	M3	78122	3488534	0.65%	0.625%
4	14.614	1045	1048	1065	M	97711	2933883	0.54%	0.525%
5	14.923	1067	1077	1223	M	7399705	539671742	100.00%	96.661%

Sum of corrected areas: 558315932