

Supporting Information for

**Multicomponent Synthesis and Biological Evaluation
of a Piperazine-Based Dopamine Receptor Ligands Library**

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General Methods.

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were run under N₂, unless otherwise indicated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with 1% aqueous KMnO₄ solution. Products were purified by flash chromatography on silica gel 60 (230 - 400 mesh).

NMR spectra were recorded with 300 or 400 MHz spectrometers. Chemical shifts (δ) are expressed in ppm relative to TMS at $\delta = 0$ ppm for ¹H NMR and relative to CDCl₃ at $\delta = 77.16$ ppm for ¹³C NMR. ¹³C NMR spectra have been recorded using the APT pulse sequence; the signals of CH and CH₃ are positive while CH₂ and quaternary carbons are negative. High-resolution MS spectra were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source.

Synthetic procedures and characterization data for compounds 1-35

Formamides,¹ isocyanides² and *N*-MOM protected indoles³ were prepared according to the literature.

General procedure A: split-Ugi reaction

To a solution of piperazine (3 mmol, 1.0 eq.) in methanol (3 mL), paraformaldehyde (4.5 mmol, 1.5 eq.), carboxylic acid (3 mmol, 1.0 eq.) and isocyanide (3 mmol, 1.0 eq.) were added. The mixture was refluxed for 15 minutes, then cooled to room temperature and stirred for 1 hour. Isolation and purification are described for each individual compound.

Compound 1

General procedure A, 2-carboxy indole and 1-isocyano-4-methoxybenzene were used. The product was collected by filtration (70% yield). ¹H NMR (300 MHz, CDCl₃): δ 9.37 (br, m, 1H), 8.86 (br, m, 1H), 7.64 (br, d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 8.9$ Hz, 2H), 7.42 (br, d, $J = 7.8$ Hz, 1H), 7.28 (br, t, $J = 7.5$ Hz, 1H), 7.13 (br, t, $J = 7.5$ Hz, 1H), 6.89 (d, $J = 8.9$ Hz, 2H), 6.77 (s, 1H), 4.01 (br, m, 4H), 3.80 (s, 3H), 3.20 (s, 2H), 2.72 (br, t, $J = 4.9$ Hz, 4H). ¹³C NMR (75 MHz, CDCl₃): δ 167.4, 162.6, 156.4, 135.7, 130.5, 128.8, 127.4, 124.5, 121.9, 121.3 (2C), 120.7, 114.2 (2C), 111.8, 105.3, 61.9, 55.4, 53.5 (2C), 43.6* (2C). HRMS (ESI): calcd for [C₂₂H₂₅N₄O₃]⁺ 393.1921, found 393.1933 [MH⁺].

Compound 2

General procedure A, 2-carboxy indole and 1-bromo-4-isocyanobenzene were used. The product was collected by filtration (73% yield). ¹H NMR (300 MHz, CDCl₃): δ 9.31 (br, m, 1H), 9.02 (br, m, 1H), 7.64 (br, d, $J = 7.7$ Hz, 1H), 7.55 – 7.38 (m, 5H), 7.29 (br, t, $J = 7.6$ Hz, 1H), 7.14 (br, t, $J = 7.5$ Hz, 1H), 6.77 (s, 1H), 4.02 (br, m, 4H), 3.22 (s, 2H), (br, m, 4H). ¹³C NMR (75 MHz, DMF-*d*₇): δ 169.3, 162.9, 138.6, 136.7, 131.9 (2C), 130.7, 127.6, 123.5, 121.9 (3C), 120.2, 115.4, 112.3, 104.6, 62.1, 53.4 (2C), 45.8* (2C). HRMS (ESI): calcd for [C₂₁H₂₁BrN₄NaO₂]⁺ 463.0740, found 463.0734 [MNa⁺].

Compound 3

General procedure A, 1-(methoxymethyl)-indole-2-carboxylic acid and 1-isocyano-4-methoxybenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (EtOAc/Hex 8/2) (70% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.90 (br, m, 1H), 7.62 (br, d, $J = 7.7$ Hz, 1H), 7.51 (br, d, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 8.9$ Hz,

¹ (a) Elders, N.; Schmitz, R.; de Kanter, F.; Ruijter, E.; Groen, B. M.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135-6142. (b) Shekhar, A. C.; Kumar, A. R.; Sathaiyah, G.; Paul, V. L.; Sridhar, M.; Rao, P. S. *Tetrahedron Lett.* **2009**, *50*, 7099-7101.

² Zhu, J.; Wu, X.; Danishefsky, S. *Tetrahedron Letters* **2009**, *50*, 577-579.

³ Putey, A.; Joucla, L.; Picot, L.; Besson, T.; Joseph, B. *Tetrahedron Letters* **2007**, *63*, 867-879.

2H), 7.32 (br, t, $J = 7.6$ Hz, 1H), 7.18 (br, t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 8.9$ Hz, 2H), 6.65 (s, 1H), 5.65 (s, 2H), 3.87 (br, m, 4H), 3.79 (s, 3H), 3.24 (s, 3H), 3.22 (s, 2H), 2.70 (br, m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 163.0 (2C), 156.6, 137.9, 130.4 (2C), 126.5, 124.1, 121.5, 121.0 (3C), 114.0 (2C), 110.3, 105.5, 74.7, 61.5, 56.0, 55.5, 53.4 (2C), 49.0*, 43.6*. HRMS (ESI): calcd for $[\text{C}_{24}\text{H}_{28}\text{N}_4\text{NaO}_4]^+$ 459.2003, found 459.2014 $[\text{MNa}^+]$.

Compound 4

General procedure A, 1-(methoxymethyl)-indole-2-carboxylic acid and 1-bromo-4-isocyanobenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (EtOAc/Hex 8/2) (75% yield). ^1H NMR (400 MHz, CDCl_3): δ 9.06 (br, m, 1H), 7.66 (br, d, $J = 7.7$ Hz, 1H), 7.55 (br, d, $J = 7.8$ Hz, 1H), 7.51 (d, $J = 8.9$ Hz, 2H), 7.47 (d, $J = 8.9$ Hz, 2H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 6.68 (s, 1H), 5.68 (s, 2H), 3.91 (br, m, 4H), 3.25 (br, s, 2H), 3.27 (s, 3H), 2.74 (br, m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 163.8, 137.3, 135.2, 132.7 (2C), 127.5, 124.7, 122.2, 121.8 (3C), 117.7, 111.1, 107.0, 106.0, 75.7, 62.6, 56.6, 54.2 (2C), 45.5 (2C). HRMS (ESI): calcd for $[\text{C}_{23}\text{H}_{25}\text{BrN}_4\text{NaO}_3]^+$ 507.1002, found 506.9987 $[\text{MNa}^+]$.

Compound 17

General procedure A, 2-(1H-indol-3-yl)acetic acid and 1-isocyano-4-methoxybenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (82% yield). ^1H NMR (300 MHz, CDCl_3): δ 8.77 (br, m, 1H), 8.35 (br, m, 1H), 7.61 (br, d, $J = 7.8$ Hz, 1H), 7.42 (d, $J = 8.9$ Hz, 2H), 7.36 (br, d, $J = 7.8$ Hz, 1H), 7.20 (br, t, $J = 7.6$ Hz, 1H), 7.12 (br, t, $J = 7.6$ Hz, 1H), 7.08 (s, 1H), 6.84 (d, $J = 8.9$ Hz, 2H), 3.85 (s, 2H), 3.77 (s, 3H), 3.70 (br, m, 2H), 3.53 (br, m, 2H), 3.05 (s, 2H), 2.55 (br, m, 2H), 2.36 (br, m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.3, 167.4, 156.1, 136.1, 130.6, 126.7, 122.5, 122.2, 121.3 (2C), 119.6, 118.6, 114.1 (2C), 111.5, 108.7, 61.8, 55.5, 53.3, 53.2, 46.1, 41.8, 31.5. HRMS (ESI): calcd for $[\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_3]^+$ 407.2078, found 407.2076 $[\text{MH}^+]$.

Compound 18

General procedure A, 2-(1H-indol-3-yl)acetic acid and 1-bromo-4-isocyanobenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (82% yield). ^1H NMR (300 MHz, CDCl_3): δ 8.92 (br, m, 1H), 8.30 (br, m, 1H), 7.61 (br, d, $J = 7.7$ Hz, 1H), 7.41 (br, m, 4H), 7.36 (br, d, $J = 7.8$ Hz, 1H), 7.21 (br, t, $J = 7.6$ Hz, 1H), 7.12 (br, t, $J = 7.6$ Hz, 1H), 7.09 (br, s, 1H), 3.85 (s, 2H), 3.72 (br, m, 2H), 3.53 (br, m, 2H), 3.06 (s, 2H), 2.55 (br, m, 2H), 2.37 (br, m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.5 (2C), 136.8, 136.5, 132.4 (2C), 127.3, 122.8, 121.5 (2C), 120.1 (2C), 119.0, 117.4, 111.8, 109.2, 61.9, 53.6, 53.5, 46.1, 41.9, 31.7. HRMS (ESI): calcd for $[\text{C}_{22}\text{H}_{23}\text{BrN}_4\text{NaO}_2]^+$ 478.3368, found 478.3364 $[\text{MNa}^+]$.

Compound 19

General procedure A, 2-(1-(methoxymethyl)-indol-3-yl)acetic acid and 1-isocyano-4-methoxybenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (87% yield). ^1H NMR (300 MHz, CDCl_3): δ 8.78 (br, m, 1H), 7.60 (br, d, $J = 7.9$ Hz, 1H), 7.46 (br, d, $J = 7.8$ Hz, 1H), 7.42 (d, $J = 9.0$ Hz, 2H), 7.26 (br, t, $J = 7.6$ Hz, 1H), 7.16 (br, t, $J = 7.5$ Hz, 1H), 7.10 (s, 1H), 6.85 (d, $J = 9.0$ Hz, 2H), 5.41 (s, 2H), 3.84 (s, 2H), 3.78 (s, 3H), 3.73 (br, m, 2H), 3.56 (br, m, 2H), 3.23 (s, 3H), 3.08 (s, 2H), 2.56 (br, m, 2H), 2.39 (br, m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 169.7, 167.2, 156.4, 136.5, 130.5, 128.0, 126.1, 122.8, 121.2 (2C), 120.3, 118.8, 114.3 (2C), 110.0, 109.2, 77.2, 61.8, 56.0, 55.4, 53.4, 53.2, 46.1, 41.7, 31.1. HRMS (ESI): calcd for $[\text{C}_{25}\text{H}_{30}\text{N}_4\text{NaO}_4]^+$ 473.2159, found 473.2126 $[\text{MNa}^+]$.

Compound 20

General procedure A, 2-(1-(methoxymethyl)-indol-3-yl)acetic acid and 1-bromo-4-isocyanobenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (72% yield). ^1H NMR (300 MHz, CDCl_3): δ 9.01 (br, m, 1H), 7.59 (br, d, $J = 7.8$ Hz, 1H), 7.52 – 7.37 (m, 5H), 7.26 (br, t, $J = 7.4$ Hz, 1H), 7.16 (br,

t, $J = 7.4$ Hz, 1H), 7.09 (s, 1H), 5.40 (s, 2H), 3.84 (s, 2H), 3.74 (br, m, 2H), 3.60 (br, m, 2H), 3.22 (s, 3H), 3.19 (br, s, 2H), 2.67 (br, m, 2H), 2.49 (br, m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.2 (2C), 137.0, 136.6, 132.3 (2C), 128.4, 126.5, 123.1, 121.4 (2C), 120.7, 119.2, 117.3, 110.4, 109.3, 76.9, 62.2 and 61.8 (1C), 56.3, 53.7 (2C), 46.4 and 46.1 (1C), 42.0 and 41.8 (1C), 31.5. HRMS (ESI): calcd for $[\text{C}_{24}\text{H}_{27}\text{BrN}_4\text{NaO}_3]^+$ 521.1159, found 521.1141 $[\text{MNa}^+]$.

Compound 27

General procedure A, 2-carboxy indole and 1-(isocyanomethyl)-4-methoxybenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (78% yield). ^1H NMR (300 MHz, CDCl_3): δ 9.51 (br, m, 1H), 7.63 (br, d, $J = 7.7$ Hz, 1H), 7.41 (br, d, $J = 7.8$ Hz, 1H), 7.35 (br, m, 1H), 7.27 (br, t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 2H), 7.12 (br, t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.73 (s, 1H), 4.43 (d, $J = 5.9$ Hz, 2H), 3.92 (br, m, 4H), 3.79 (s, 3H), 3.14 (s, 2H), 2.63 (br, m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 162.5 (2C), 159.0, 135.8, 130.3, 129.1 (2C), 128.7, 127.1, 124.4, 121.9, 120.7, 114.0 (2C), 111.7, 105.4, 61.3, 55.2, 53.3 (2C), 46.8*, 42.6, 43.1*. HRMS (ESI): calcd for $[\text{C}_{23}\text{H}_{26}\text{N}_4\text{NaO}_3]^+$ 429.1897, found 429.1891 $[\text{MNa}^+]$.

Compound 28

General procedure A, 2-carboxy indole and 1-bromo-4-(isocyanomethyl)benzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (85% yield). ^1H NMR (300 MHz, CDCl_3): δ 9.50 (br, m, 1H), 7.63 (br, d, $J = 7.8$ Hz, 1H), 7.54 – 7.34 (m, 4H), 7.27 (br, t, $J = 7.6$ Hz, 1H), 7.18 – 7.03 (m, 3H), 6.74 (s, 1H), 4.45 (d, $J = 6.1$ Hz, 2H), 3.92 (br, m, 4H), 3.13 (s, 2H), 2.61 (br, m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 167.6, 162.5, 137.4, 135.6, 131.8, 129.5 (2C), 129.0, 127.4, 124.5 (2C), 122.0, 121.8, 120.7, 111.7, 105.3, 61.4, 53.5 (2C), 46.1*, 42.5, 43.3*. HRMS (ESI): calcd for $[\text{C}_{22}\text{H}_{23}\text{N}_4\text{NaO}_2]^+$ 477.0897, found 477.0884 $[\text{MNa}^+]$.

Compound 29

General procedure A, 1-(methoxymethyl)-indole-2-carboxylic acid and 1-(isocyanomethyl)-4-methoxybenzene were used. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($\text{EtOAc}/\text{Et}_3\text{N}$ 99/1) (79% yield). ^1H NMR (300 MHz, CDCl_3): δ 7.61 (br, d, $J = 7.9$ Hz, 1H), 7.50 (br, d, $J = 7.8$ Hz, 1H), 7.31 (br, t, $J = 7.7$ Hz, 1H), 7.20 (d, $J = 8.6$ Hz, 2H), 7.17 (br, t, $J = 7.7$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.60 (s, 1H), 5.62 (s, 2H), 4.41 (d, $J = 5.9$ Hz, 2H), 3.79 (s, 3H), 3.77 (br, m, 4H), 3.21 (s, 3H), 3.13 (br, s, 2H), 2.59 (br, m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 163.1 (2C), 159.1, 137.8, 130.8, 130.2, 129.1 (2C), 126.7, 124.2, 121.6, 121.2, 114.3 (2C), 110.4, 105.5, 75.0, 61.3, 56.1, 55.3, 53.3 (2C), 46.9*, 42.6, 41.8*. HRMS (ESI): calcd for $[\text{C}_{25}\text{H}_{30}\text{N}_4\text{NaO}_4]^+$ 473.2159, found 473.2152 $[\text{MNa}^+]$.

General procedure B: reduction of amides

LiAlH_4 (1M in THF, 1.95 mmol) was dissolved in anhydrous THF (2 mL) at 40 °C under N_2 atmosphere and a solution of compound **1** (or **2**, **17**, **18**, **27**, **28**) (0.65 mmol) in anhydrous THF (10 mL) was slowly added. After 15 minutes, the solution was refluxed until full conversion (monitored by TLC). Then the reaction was cooled to room temperature, quenched with H_2O , NaOH 15% and H_2O (n. g of LiAlH_4 require n. mL of H_2O , n. mL of NaOH 15%, and 3n. mL of H_2O added in succession) and stirred vigorously overnight. The precipitate was removed by filtration over celite and the solvent was evaporated under reduced pressure.

Compound 5

General procedure B. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2) (87% yield). ^1H NMR (300 MHz, CDCl_3): δ 8.65 (br, m, 1H), 7.55 (br, d, $J = 7.7$ Hz, 1H), 7.33 (br, d, $J = 7.8$ Hz, 1H), 7.14 (br, t, $J = 7.5$ Hz, 1H), 7.07 (br, t, $J = 7.6$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 2H), 6.61 (d, $J = 8.8$ Hz, 2H), 6.36 (s, 1H), 3.74 (s, 3H), 3.68 (s, 2H), 3.11 (t, $J = 5.9$ Hz, 2H), 2.62 (t, $J = 5.9$ Hz, 2H), 2.52 (br, m, 9H). ^{13}C NMR (75 MHz, CDCl_3): δ 148.1, 138.7, 132.1, 131.2, 124.3, 117.6, 116.2, 115.7, 111.0 (2C), 110.3 (2C), 106.8, 97.7, 52.93, 52.1, 51.7, 49.1 (2C), 48.6 (2C), 37.3. HRMS (ESI): calcd for $[\text{C}_{22}\text{H}_{29}\text{N}_4\text{O}]^+$ 365.2336, found 365.2322 $[\text{MH}^+]$.

Compound 6

General procedure B. The residue was purified by flash chromatography (CH₂Cl₂/CH₃OH 98/2) (90% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.60 (br, m, 1H), 7.55 (br, d, *J* = 7.7 Hz, 1H), 7.33 (br, d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.15 (br, t, *J* = 7.4 Hz, 1H), 7.07 (br, t, *J* = 7.4 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 1H), 4.31 (br, m, 1H), 3.70 (s, 2H), 3.10 (br, q, *J* = 5.5 Hz, 2H), 2.62 (t, *J* = 5.7 Hz, 2H), 2.53 (br, m, 8H). ¹³C NMR (75 MHz, CDCl₃): δ 147.3, 136.0, 135.0, 132.0 (2C), 128.3, 121.7, 120.2, 119.6, 114.5 (2C), 110.8, 108.8, 101.9, 56.3, 55.7, 52.9 (2C), 52.5 (2C), 40.2. HRMS (ESI): calcd for [C₂₁H₂₆BrN₄]⁺ 413.1335, found 413.1342 [MH⁺].

Compound 21

General procedure B. The residue was purified by flash chromatography (CH₂Cl₂/CH₃OH/Et₃N 97/2/1) (87% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.09 (br, m, 1H), 7.61 (br, d, *J* = 7.7 Hz, 1H), 7.35 (br, d, *J* = 7.8 Hz, 1H), 7.18 (br, t, *J* = 7.4 Hz, 1H), 7.11 (br, t, *J* = 7.5 Hz, 1H), 7.04 (br, s, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.14 (t, *J* = 5.9 Hz, 2H), 3.02 (m, 2H), 2.78 (m, 2H), 2.67 (t, *J* = 5.9 Hz, 2H), 2.63 (br, m, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 152.4, 143.1, 136.5, 127.9, 122.4, 122.1, 119.7, 119.2, 115.4 (2C), 114.7 (2C), 114.3, 111.6, 59.6, 57.2, 56.3, 53.6 (2C), 53.1 (2C), 41.7, 23.2. HRMS (ESI): calcd for [C₂₃H₃₁N₄O]⁺ 379.2492, found 379.2483 [MH⁺].

Compound 22

General procedure B. The residue was purified by flash chromatography (CH₂Cl₂/CH₃OH/Et₃N 97/2/1) (88% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.15 (br, m, 1H), 7.61 (br, d, *J* = 7.7 Hz, 1H), 7.35 (br, d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.18 (br, t, *J* = 7.5 Hz, 1H), 7.10 (br, t, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 6.50 (d, *J* = 8.8 Hz, 2H), 4.36 (br, m, 1H), 3.12 (m, 2H), 3.04 – 2.89 (m, 2H), 2.74 (m, 2H), 2.70 – 2.44 (m, 10H). ¹³C NMR (75 MHz, CDCl₃): δ 147.3, 136.1, 132.0 (2C), 127.4, 122.0, 121.7, 119.2, 118.7, 114.5 (2C), 113.8, 111.2, 108.8, 59.0, 56.3, 52.9 (2C), 52.4 (2C), 40.2, 22.6. HRMS (ESI): calcd for [C₂₂H₂₈BrN₄]⁺ 427.1492, found 427.1478 [MH⁺].

Compound 30

General procedure B. The residue was purified by flash chromatography (EtOAc/CH₃OH/Et₃N 90/9/1) (90% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.80 (br, m, 1H), 7.53 (br, d, *J* = 7.6 Hz, 1H), 7.32 (br, d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.13 (br, t, *J* = 7.6 Hz, 1H), 7.06 (br, t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.34 (s, 1H), 3.75 (s, 3H), 3.66 (s, 2H), 3.46 (s, 2H), 2.78 (br, m, 4H), 2.72 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.49 (br, m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 159.2, 136.2, 135.2, 130.4, 129.9 (2C), 128.2, 121.6, 120.2, 119.6, 114.1 (2C), 110.8, 101.9, 56.7, 55.7, 55.3, 53.1 (2C), 52.9 (2C), 52.7, 44.7. HRMS (ESI): calcd for [C₂₃H₃₁N₄O]⁺ 379.2492, found 379.2481 [MH⁺].

Compound 31

General procedure B. The residue was purified by flash chromatography (EtOAc/CH₃OH/Et₃N 90/9/1) (93% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.69 (br, m, 1H), 7.54 (br, d, *J* = 7.6 Hz, 1H), 7.44 – 7.19 (m, 5H), 7.14 (br, t, *J* = 7.4 Hz, 1H), 7.06 (br, t, *J* = 7.4 Hz, 1H), 6.35 (s, 1H), 3.86 (s, 2H), 3.69 (s, 2H), 3.64 (br, m, 1H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.66 – 2.39 (m, 10H). ¹³C NMR (75 MHz, CDCl₃): δ 139.4, 136.1, 135.3 (2C), 128.4, 128.2, 127.1, 121.4 (2C), 120.0, 119.5, 111.3, 110.7, 101.7, 57.2, 55.7, 53.6, 53.1 (2C), 53.0 (2C), 45.2. HRMS (ESI): calcd for [C₂₂H₂₈BrN₄]⁺ 427.1492, found 427.1481 [MH⁺].

General procedure C: reductive amination

To a solution of compound **5** (or **6**, **21**, **22**, **30**, **31**) (0.26 mmol) in CH₂Cl₂ (1.5 mL) sodium triacetoxyboronhydride (0.31 mmol, 1.2 eq.) and propionaldehyde (0.29 mmol, 1.1 eq.) were added. The resulting mixture was stirred at room temperature until full conversion (monitored by TLC). The reaction was quenched with saturated aq. NaHCO₃ (5 mL) and the organic layer was separated. The aqueous phase was then extracted with CH₂Cl₂ (3 x 5 mL), the combined organic layer was dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure.

Compound 7

General procedure C, 95% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.61 (br, m, 1H), 7.54 (br, d, $J = 7.7$ Hz, 1H), 7.33 (br, d, $J = 7.8$ Hz, 1H), 7.15 (br, t, $J = 7.5$ Hz, 1H), 7.07 (br, t, $J = 7.4$ Hz, 1H), 6.80 (d, $J = 8.9$ Hz, 2H), 6.65 (d, $J = 8.9$ Hz, 2H), 6.36 (s, 1H), 3.74 (s, 3H), 3.68 (s, 2H), 3.40 (t, $J = 7.5$ Hz, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 2.66 – 2.40 (m, 10H), 1.55 (br, sext, $J = 7.4$ Hz, 2H), 0.89 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 151.3, 143.1, 136.4, 135.5, 128.5, 121.8, 120.3, 119.6, 115.1 (2C), 114.5 (2C), 110.9, 101.9, 56.0, 55.9, 55.7, 54.2, 53.7 (2C), 53.3 (2C), 49.7, 20.6, 11.7. HRMS (ESI): calcd for $[\text{C}_{25}\text{H}_{35}\text{N}_4\text{O}]^+$ 407.2805, found 407.2788 $[\text{MH}^+]$.

Compound 8

General procedure C, 92% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.73 (br, m, 1H), 7.60 (br, d, $J = 7.8$ Hz, 1H), 7.37 (br, d, $J = 7.8$ Hz, 1H), 7.29 (d, $J = 9.0$ Hz, 2H), 7.19 (br, t, $J = 7.5$ Hz, 1H), 7.12 (br, t, $J = 7.4$ Hz, 1H), 6.56 (d, $J = 9.0$ Hz, 2H), 6.41 (s, 1H), 3.72 (s, 2H), 3.45 (t, $J = 7.5$ Hz, 2H), 3.24 (t, $J = 7.5$ Hz, 2H), 2.68 – 2.42 (m, 10H), 1.63 (br, sext, $J = 7.4$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 147.0, 136.3, 135.3, 131.9 (2C), 128.3, 121.7, 120.2, 119.7, 113.4 (2C), 110.8, 107.3, 101.9, 55.8, 55.0, 53.5 (2C), 53.1 (3C), 48.9, 20.3, 11.4. HRMS (ESI): calcd for $[\text{C}_{24}\text{H}_{32}\text{BrN}_4]^+$ 455.1805, found 455.1806 $[\text{MH}^+]$.

Compound 23

General procedure C, 90% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.45 (br, m, 1H), 7.67 (br, d, $J = 7.8$ Hz, 1H), 7.36 (br, d, $J = 7.7$ Hz, 1H), 7.23 (br, t, $J = 7.5$ Hz, 1H), 7.17 (br, t, $J = 7.5$ Hz, 1H), 7.03 (s, 1H), 6.88 (d, $J = 8.9$ Hz, 2H), 6.73 (d, $J = 8.9$ Hz, 2H), 3.81 (s, 3H), 3.48 (t, $J = 7.5$ Hz, 2H), 3.24 (t, $J = 7.5$ Hz, 2H), 3.01 (m, 2H), 2.79 (m, 2H), 2.69 (br, m, 8H), 2.61 (m, 2H), 1.63 (br, sext, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.3, 143.1, 136.3, 127.5, 121.9, 121.7, 119.2, 118.8, 115.0 (2C), 114.4 (2C), 114.2, 111.2, 59.3, 55.9, 55.6, 54.1, 53.7 (2C), 53.2 (2C), 49.5, 22.9, 20.6, 11.6. HRMS (ESI): calcd for $[\text{C}_{26}\text{H}_{37}\text{N}_4\text{O}]^+$ 421.2962, found 421.2950 $[\text{MH}^+]$.

Compound 24

General procedure C, 91% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.06 (br, m, 1H), 7.61 (br, d, $J = 7.7$ Hz, 1H), 7.35 (br, d, $J = 7.7$ Hz, 1H), 7.25 (d, $J = 8.9$ Hz, 2H), 7.18 (br, t, $J = 7.4$ Hz, 1H), 7.11 (br, t, $J = 7.5$ Hz, 1H), 7.04 (s, 1H), 6.52 (d, $J = 8.9$ Hz, 2H), 3.43 (t, $J = 8.0$ Hz, 2H), 3.19 (t, $J = 7.9$ Hz, 2H), 3.03 (m, 2H), 2.88 – 2.47 (m, 12H), 1.58 (br, sext, $J = 7.7$ Hz, 2H), 0.91 (t, $J = 7.7$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 147.3, 136.3, 132.0 (2C), 127.6, 122.1 and 121.8 (1C), 119.4, 119.0, 114.3, 113.6 (2C), 112.0, 111.4, 107.5, 59.4, 55.3, 53.8 (2C), 53.3 (3C), 49.0, 23.0, 20.5, 11.6. HRMS (ESI): calcd for $[\text{C}_{25}\text{H}_{34}\text{BrN}_4]^+$ 469.961, found 469.1982 $[\text{MH}^+]$.

Compound 32

General procedure C, 90% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.63 (br, m, 1H), 7.57 (br, d, $J = 7.7$ Hz, 1H), 7.35 (br, d, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.17 (br, t, $J = 7.6$ Hz, 1H), 7.10 (br, t, $J = 7.6$ Hz, 1H), 6.86 (d, $J = 8.5$ Hz, 2H), 6.38 (s, 1H), 3.82 (s, 3H), 3.68 (s, 2H), 3.56 (s, 2H), 2.71 – 2.36 (m, 14H), 1.51 (br, sext, $J = 7.4$ Hz, 2H), 0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 159.5, 137.0, 136.5, 133.0, 130.4 (2C), 129.3, 122.2, 120.8, 120.3, 114.4 (2C), 111.2, 102.2, 59.3, 57.3, 57.2, 56.4, 55.9, 54.1 (2C), 53.9 (2C), 52.1, 21.1, 12.2. HRMS (ESI): calcd for $[\text{C}_{26}\text{H}_{37}\text{N}_4\text{O}]^+$ 421.2962, found 421.2977 $[\text{MH}^+]$.

Compound 33

General procedure C, 92% yield. ^1H NMR (400 MHz, CDCl_3): δ 8.93 (br, m, 1H), 7.62 (br, d, $J = 7.8$ Hz, 1H), 7.42 – 7.25 (m, 5H), 7.20 (br, td, $J = 7.6$ and 1.2 Hz, 1H), 7.14 (br, td, $J = 7.7$ and 1.2 Hz, 1H), 6.41 (br, s, 1H), 3.67 (s, 2H), 3.65 (s, 2H), 2.70 – 2.45 (m, 14H), 1.55 (br, sext, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 140.1, 136.4, 135.6, 128.9 (2C), 128.5 (2C), 128.2 (2C), 121.6, 120.3, 119.7, 110.9, 101.9, 59.2, 56.7, 56.5, 55.9, 53.6 (2C), 53.3 (2C), 51.3, 20.4, 12.0. HRMS (ESI): calcd for $[\text{C}_{25}\text{H}_{34}\text{BrN}_4]^+$ 469.1961, found 469.1945 $[\text{MH}^+]$.

General procedure D: N-alkylation

To a suspension of NaH (80% in mineral oil, 5.5 mmol, 1.1 eq.) in anhydrous DMF (3 mL), cooled to 0 °C under N_2 atmosphere, a solution of compound **3** (or **4**, **19**, **20**, **29**) (5 mmol) in anhydrous

DMF (7 mL) was added and the mixture was stirred for 15 minutes. After dropwise addition of the alkylating agent (6 mmol, 1.2 eq.), the solution was warmed to room temperature and stirred until full conversion (monitored by TLC). The reaction was quenched with H₂O (10 mL), and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with saturated aq. NaCl (5 x 10 mL) and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure.

Compound 9

General procedure D. The residue was purified by flash chromatography (EtOAc) (89% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.53 (br, d, *J* = 7.8 Hz, 1H), 7.32 (br, t, *J* = 7.7 Hz, 1H), 7.19 (br, t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.63 (s, 1H), 5.65 (s, 2H), 3.86 (s, 3H), 3.83 (br, m, 4H), 3.63 (m, 2H), 3.24 (s, 3H), 2.99 (br, s, 2H), 2.62 (br, m, 4H), 1.56 (br, sext, *J* = 7.6 Hz, 2H), 0.91 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 162.9, 159.3, 137.8, 134.2, 131.3, 129.3 (2C), 127.0, 123.9, 121.6, 121.1, 114.9 (2C), 110.6, 105.2, 74.9, 59.1, 56.0, 55.5, 53.1 (2C), 51.1, 47.5*, 41.8*, 20.9, 11.2. HRMS (ESI): calcd for [C₂₇H₃₄N₄NaO₄]⁺ 501.2472, found 501.2488 [MNa⁺].

Compound 10

General procedure D. The residue was purified by flash chromatography (EtOAc) (76% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.32 (br, t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.62 (s, 1H), 5.64 (s, 2H), 5.23 (br, t, *J* = 7.3 Hz, 1H), 4.26 (d, *J* = 7.3 Hz, 2H), 3.85 (s, 3H), 3.82 (br, m, 4H), 3.23 (s, 3H), 2.98 (s, 2H), 2.59 (br, m, 4H), 1.69 (s, 3H), 1.46 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 168.4, 162.9, 159.2, 138.1, 136.6, 134.2, 131.4, 129.4 (2C), 126.6, 123.9, 121.6, 121.1, 119.0, 114.7 (2C), 110.6, 105.2, 75.2, 59.1, 55.9, 55.5, 53.2 (2C), 47.5*, 47.2, 42.0*, 25.7, 17.7. HRMS (ESI): calcd for [C₂₉H₃₆N₄NaO₄]⁺ 527.2629, found 527.2637 [MNa⁺].

Compound 11

General procedure D. The residue was purified by flash chromatography (EtOAc) (80% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.60 (br, d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.49 (br, d, *J* = 7.8 Hz, 1H), 7.29 (br, t, *J* = 7.5 Hz, 1H), 7.16 (br, t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.59 (s, 1H), 5.61 (s, 2H), 3.79 (br, m, 4H), 3.60 (m, 2H), 3.20 (s, 3H), 2.95 (br, s, 2H), 2.56 (br, m, 4H), 1.50 (br, sext, *J* = 7.4 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 163.3 (2C), 138.0, 136.4, 132.1 (2C), 126.7, 124.2, 121.7, 121.3, 121.1 (2C), 117.1, 111.4, 110.4, 105.6, 74.8, 61.7, 56.1, 53.4 (2C), 47.3*, 41.0*, 29.7, 20.1, 11.0. HRMS (ESI): calcd for [C₂₆H₃₁BrN₄NaO₃]⁺ 549.1472, found 549.1479 [MNa⁺].

Compound 12

General procedure D. The residue was purified by flash chromatography (EtOAc) (75% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.59 (br, d, *J* = 7.8 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.28 (br, t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.59 (s, 1H), 5.61 (s, 2H), 5.17 (br, t, *J* = 7.8 Hz, 1H), 4.24 (br, d, *J* = 7.8 Hz, 2H), 3.76 (br, m, 4H), 3.19 (s, 3H), 2.91 (s, 2H), 2.51 (br, m, 4H), 1.65 (s, 3H), 1.42 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.9, 162.7, 140.6, 138.0, 137.1, 132.9 (2C), 131.5, 130.1 (2C), 126.7, 123.9, 121.8, 121.6, 121.1, 118.7, 110.7, 105.3, 75.0, 59.5, 55.9, 53.3 (2C), 47.2, 44.2*, 40.6*, 25.8, 17.8. HRMS (ESI): calcd for [C₂₈H₃₃BrN₄NaO₃]⁺ 575.1628, found 575.1636 [MNa⁺].

Compound 25

General procedure D. The residue was purified by flash chromatography (CH₂Cl₂/CH₃OH/Et₃N 98/1/1) (72% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.60 (br, d, *J* = 7.8 Hz, 1H), 7.47 (br, d, *J* = 7.8 Hz, 1H), 7.26 (br, t, *J* = 7.5 Hz, 1H), 7.17 (br, t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.42 (s, 2H), 3.84 (s, 3H), 3.81 (s, 2H), 3.73 (br, m, 2H), 3.60 (m, 2H), 3.55 (br, m, 2H), 3.22 (s, 3H), 2.91 (br, s, 2H), 2.53 (br, m, 2H), 2.44 (br, m, 2H), 1.52 (br, sext, *J* = 7.6 Hz, 2H), 0.89 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 169.4, 167.9, 158.9, 136.3, 133.8, 129.0 (2C), 127.7, 126.0, 122.3, 119.9, 118.6, 114.6 (2C), 109.7, 109.0, 77.1, 58.6,

55.6, 55.2, 52.6, 52.4, 50.8, 45.5, 41.0, 30.7, 20.5, 10.9. HRMS (ESI): calcd for $[C_{28}H_{37}N_4O_4]^+$ 493.2809, found 493.3707 $[MH^+]$.

Compound 26

General procedure D. The residue was purified by flash chromatography ($CH_2Cl_2/CH_3OH/Et_3N$ 98/1/1) (78% yield). 1H NMR (400 MHz, $CDCl_3$): δ 7.60 (br, d, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 2H), 7.46 (br, d, $J = 7.7$ Hz, 1H), 7.26 (br, t, $J = 7.5$ Hz, 1H), 7.17 (br, t, $J = 7.5$ Hz, 1H), 7.09 (s, 1H), 7.04 (d, $J = 8.5$ Hz, 2H), 5.42 (s, 2H), 3.81 (s, 2H), 3.69 (br, m, 2H), 3.61 (br, t, $J = 7.6$ Hz, 2H), 3.51 (br, m, 2H), 3.22 (s, 3H), 2.87 (s, 2H), 2.46 (br, m, 2H), 2.35 (br, m, 2H), 1.50 (sext, $J = 7.6$ Hz, 2H), 0.88 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 168.6, 141.4, 137.3, 133.6 (2C), 130.6 (2C), 128.9, 126.9, 123.2, 122.7, 120.9, 119.6, 110.7, 109.7, 78.0, 60.0, 56.6, 53.6, 53.4, 51.7, 46.5, 42.1, 31.6, 21.5, 11.8. HRMS (ESI): calcd for $[C_{27}H_{33}BrN_4NaO_3]^+$ 563.1628, found 563.1624 $[MNa^+]$.

Compound 34

General procedure D. The residue was purified by flash chromatography (EtOAc/Hex 9/1) (87% yield). 1H NMR (300 MHz, $CDCl_3$, mixture of 2 conformers in ratio 1:1): δ 7.62 (br, d, $J = 7.8$ Hz, 1H), 7.51 (br, d, $J = 7.8$ Hz, 1H), 7.30 (br, t, $J = 7.7$ Hz, 1H), 7.25 – 7.13 (m, 2H), 7.08 (d, $J = 8.6$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz, 1H), 6.83 (d, $J = 8.6$ Hz, 1H), 6.64 (s, 0.5H), 6.62 (s, 0.5H), 5.64 (s, 1H), 5.62 (s, 1H), 4.54 (s, 1H), 4.52 (s, 1H), 3.97 – 3.72 (br, m, 4H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 3.42 – 3.11 (m, 7H), 2.85 – 2.61 (br, m, 4H), 1.56 (m, 2H), 0.98 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 and 168.5 (1C), 162.9, 159.1 and 159.0 (1C), 137.8, 131.2, 129.5, 128.8, 127.5, 126.8, 124.0, 121.6, 121.2, 114.3, 113.7, 110.5, 105.3, 74.9, 60.3 and 59.8 (1C), 56.0, 55.2, 53.5 (2C), 50.2 and 48.0 (1C), 47.7 and 47.5 (1C), 47.1, 42.6, 21.7 and 20.7 (1C), 11.3. HRMS (ESI): calcd for $[C_{28}H_{36}N_4NaO_4]^+$ 515.2629, found 515.2610 $[MNa^+]$.

General procedure E: MOM-deprotection

To a solution of **9** (or **10**, **11**, **12**, **25**, **26**, **34**) (0.26 mmol) in THF (2 mL) HCl 3N (10 mL) was added and the solution was stirred at room temperature until full conversion (monitored by TLC). The solution was made basic (pH > 12) with KOH 20% and then the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The reunited organic phases were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure.

Compound 13

General procedure E. The residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 98.5/1.5) (95% yield). 1H NMR (300 MHz, $CDCl_3$): δ 9.43 (br, m, 1H), 7.61 (br, d, $J = 7.8$ Hz, 1H), 7.36 (br, d, $J = 7.8$ Hz, 1H), 7.25 (br, t, $J = 7.8$ Hz, 1H), 7.11 (br, t, $J = 7.8$ Hz, 1H), 7.07 (br, d, $J = 8.7$ Hz, 2H), 6.91 (br, d, $J = 8.7$ Hz, 2H), 6.71 (s, 1H), 4.04 (br, m, 4H), 3.82 (s, 3H), 3.61 (dd, $J = 7.8$ and 5.8 Hz, 2H), 2.95 (s, 2H), 2.60 (br, m, 4H), 1.53 (m, 2H), 0.92 (t, 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 162.1, 159.1, 135.6, 134.2, 129.4 (2C), 127.4, 124.4, 121.9, 120.4, 114.6 (2C), 111.9, 111.4, 104.9, 59.2, 55.5, 53.1 (2C), 51.1, 41.8*, 39.9*, 20.8, 11.2. HRMS (ESI): calcd for $[C_{25}H_{31}N_4O_3]^+$ 435.2391, found 435.2409 $[MH^+]$.

Compound 14

General procedure E. The residue was purified by flash chromatography ($CH_2Cl_2/CH_3OH/Et_3N$ 98/1/1) (85% yield). 1H NMR (300 MHz, $CDCl_3$): δ 9.76 (br, m, 1H), 7.60 (br, d, $J = 7.8$ Hz, 1H), 7.40 (br, d, $J = 7.8$ Hz, 1H), 7.23 (br, t, $J = 7.5$ Hz, 1H), 7.08 (br, t, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.70 (br, s, 1H), 5.21 (br, t, $J = 7.7$ Hz, 1H), 4.22 (d, $J = 7.7$ Hz, 2H), 3.93 (br, m, 4H), 3.80 (s, 3H), 2.93 (s, 2H), 2.57 (br, m, 4H), 1.65 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 162.2, 159.1, 136.4, 135.7, 134.0, 129.5 (2C), 127.3, 124.2, 121.8, 120.3, 118.8, 114.7 (2C), 111.9, 111.5, 105.1, 59.3, 55.3, 53.2 (2C), 47.1, 42.9* (2C), 25.6, 17.7. HRMS (ESI): calcd for $[C_{27}H_{32}N_4NaO_3]^+$ 483.2367, found 483.2343 $[MNa^+]$.

Compound 15

General procedure E. The residue was purified by flash chromatography ($CH_2Cl_2/CH_3OH/Et_3N$ 98/1/1) (78% yield). 1H NMR (300 MHz, $CDCl_3$): δ 9.41 (br, m, 1H), 7.61 (br, d, $J = 7.8$ Hz, 1H),

7.55 (d, $J = 8.5$ Hz, 2H), 7.40 (br, d, $J = 7.8$ Hz, 1H), 7.25 (br, t, $J = 7.8$ Hz, 1H), 7.11 (br, t, $J = 7.6$ Hz, 1H), 7.06 (d, $J = 8.5$ Hz, 2H), 6.72 (br, s, 1H), 3.92 (br, m, 4H), 3.62 (br, t, $J = 7.8$ Hz, 2H), 2.94 (s, 2H), 2.56 (br, m, 4H), 1.52 (sext, $J = 7.8$ Hz, 2H), 0.88 (t, $J = 7.8$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 168.1, 162.5, 140.8, 135.5, 132.9, 129.9 (2C), 129.0, 127.3, 124.4, 122.1, 121.9 (2C), 120.6, 111.9, 105.3, 59.6, 52.7 (2C), 51.4, 42.8*, 40.0*, 20.7, 10.9. HRMS (ESI): calcd for $[\text{C}_{24}\text{H}_{28}\text{BrN}_4\text{O}_2]^+$ 483.1390, found 483.1377 $[\text{MH}^+]$.

Compound 16

General procedure E. The residue was purified by flash chromatography ($\text{EtOAc}/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (85% yield). ^1H NMR (300 MHz, CDCl_3): δ 9.69 (br, m, 1H), 7.61 (br, d, $J = 7.8$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.40 (br, d, $J = 7.8$ Hz, 1H), 7.24 (br, t, $J = 7.8$ Hz, 1H), 7.10 (br, t, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.72 (br, s, 1H), 5.19 (br, t, $J = 7.8$ Hz, 1H), 4.25 (br, d, $J = 7.8$ Hz, 2H), 3.93 (br, m, 4H), 2.94 (s, 2H), 2.58 (br, m, 4H), 1.66 (s, 3H), 1.43 (br, s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 167.4, 162.4, 140.4, 137.2, 135.7, 132.9 (2C), 130.0, 129.0, 127.3, 124.4, 122.2, 121.8 (2C), 120.5, 118.5, 111.8, 105.3, 59.0, 52.9 (2C), 47.1, 45.8*, 40.0*, 25.7, 17.7. HRMS (ESI): calcd for $[\text{C}_{26}\text{H}_{29}\text{BrN}_4\text{NaO}_2]^+$ 531.1366, found 531.1341 $[\text{MNa}^+]$.

Compound 35

General procedure E. The residue was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ 98/1/1) (90% yield). ^1H NMR (400 MHz, CDCl_3 , mixture of 2 conformers in ratio 1:1): δ 9.88 (br, m, 0.5H), 9.86 (br, m, 0.5H), 7.65 (dd, $J = 8.2$ and 2.4 Hz, 1H), 7.45 (dd, $J = 8.2$ and 2.6 Hz, 1H), 7.27 (br, t, $J = 7.7$ Hz, 1H), 7.23 – 7.08 (m, 3H), 6.95 – 6.83 (m, 2H), 6.78 (br, s, 0.5H), 6.76 (br, s, 0.5H), 4.58 (s, 1H), 4.56 (s, 1H), 4.02 (br, m, 2H), 3.97 (br, m, 2H), 3.82 (br, s, 3H), 3.40 – 3.29 (m, 3H), 3.20 (br, t, $J = 7.6$ Hz, 1H), 2.76 (br, m, 2H), 2.69 (br, m, 2H), 1.59 (m, 2H), 0.90 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.5, 163.1, 159.1, 136.6, 131.2, 125.0 (2C), 124.6, 122.4, 121.7, 121.2, 120.0, 116.1 (2C), 112.4 and 110.7 (1C), 106.9 and 105.8 (1C), 60.8 and 60.4 (1C), 55.9, 53.8 (2C), 48.9 and 48.6 (1C), 48.1*, 43.0*, 45.5, 21.6, 11.8. HRMS (ESI): calcd for $[\text{C}_{26}\text{H}_{33}\text{N}_4\text{O}_3]^+$ 449.2547, found 449.2535 $[\text{MH}^+]$.

* Chemical shifts values from 2D HSQC experiments.

Computational data for selected compounds 22-24

Docking studies.

The selected ligands were first submitted to a Monte Carlo conformational search with the MMFF94 force field *in vacuo* with Spartan '08.⁴ The obtained conformers were used for docking studies. Docking was performed using AutoDock⁵ using the default docking parameters supplied with AutoDock in the 'examples' subdirectory, and point charges initially assigned according to the AMBER03 force field,⁶ and then damped to mimic the less polar Gasteiger charges used to optimize the AutoDock scoring function. The setup was done with the YASARA molecular modeling program⁷ (Krieger E et al, 2002). For each ligands 50 Autodock LGA runs were executed. Results, were sorted by binding energy (more positive energies indicate stronger binding, and negative energies mean no binding). After clustering the 50 runs, the resulting complex conformations were originated (they all differ by at least 5.0 Å heavy atom RMSD). Binding energy are reported in kcal/mol and predicted dissociation constant in pM units. Contacting receptor residues are also listed.

D2 receptor

Compound **22**. Three clusters were originated:

Clu	Bind.energy	Dissoc. constant	Contacting receptor residues
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001	000011.2300	00000000005910.0000	VAL A 91 LEU A 94 GLU A 95 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 118 CYS A 182 ILE A 183 ILE A 184 VAL A 190 SER A 193 SER A 194 SER A 197 TRP A 386 PHE A 389 PHE A 390 HIS A 393 TYR A 408 THR A 412 TYR A 416
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002	000011.0800	00000000007530.0000	LEU A 41 TRP A 90 VAL A 91 LEU A 94 GLU A 95 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 182 ILE A 183 ILE A 184 VAL A 190 SER A 193 SER A 194 TRP A 386 PHE A 389 PHE A 390 HIS A 393 ILE A 394 TYR A 408 SER A 409 THR A 412 TYR A 416
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003	000009.1700	00000000188850.0000	LEU A 41 VAL A 91 LEU A 94 GLU A 95 VAL A 97 GLY A 98 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 182 ILE A 183 ILE A 184 PHE A 389 HIS A 393 TYR A 408 SER A 409 THR A 412 TRP A 413
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Compound **24**. Five clusters were originated:

Clu	Bind.energy	Dissoc. constant	Contacting receptor residues
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001	000011.5900	00000000003170.0000	LEU A 41 VAL A 91 LEU A 94 GLU A 95 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 118 GLU A 181 CYS A 182 ILE A 183 ILE A 184 VAL A 190 SER A 193 SER A 194 SER A 197 TRP A 386 PHE A 389 PHE A 390 HIS A 393 TYR A 408 SER A 409 THR A 412 TRP A 413
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002	000011.5200	00000000003600.0000	VAL A 91 LEU A 94 VAL A 97 GLY A 98 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 118 THR A 119 ILE A 122 GLU A 181 CYS A 182 ILE A 183 ILE A 184 VAL A 190 SER A 193 SER A 194 SER A 197 TRP A 386 PHE A 389 PHE A 390 HIS A 393 ILE A 394 TYR A 408 THR A 412 TYR A 416
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⁴ Spartan'08. Wavefunction, Inc. Irvine, CA

⁵ Morris, G.M.; Huey, R.; Lindstrom, W.; Sanner, M.F.; Belew, R.K.; Goodsell, D.S.; Olson, A.J. *J.Comput.Chem.* **209**, 30, 2785-91

⁶ Duan, Y.; Wu, C.; Chowdhury, S.; Lee, M.C.; Xiong, G.; Zhang, W.; Yang, R.; Cieplak, P.; Luo, R.; Lee, T. *J.Comput.Chem.* **2003**, 24, 1999-2012

⁷ (a) Krieger, E.; Vriend, G.; *Bioinformatics* **2014**, 30, 2981-2982. (b) Krieger, E.; Darden, T.; Nabuurs, S.; Finkelstein, A.; Vriend, G. *Proteins* **2004**, 57, 678-683

003 | 000010.0900 | 00000000040030.0000 | LEU A 41 VAL A 87 VAL A 91 LEU A 94 GLU A 95 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 182 ILE A 183 ILE A 184 VAL A 190 PHE A 389 HIS A 393 TYR A 408 SER A 409 THR A 412 TRP A 413 TYR A 416
004 | 000009.5400 | 00000000102030.0000 | TYR A 34 LEU A 41 VAL A 91 LEU A 94 GLU A 95 VAL A 97 GLY A 98 PHE A 110 VAL A 111 ASP A 114 VAL A 115 CYS A 182 ILE A 183 ILE A 184 PHE A 389 HIS A 393 TYR A 408 SER A 409 THR A 412 TRP A 413
005 | 000008.6100 | 00000000489850.0000 | VAL A 91 LEU A 94 GLU A 95 VAL A 97 GLY A 98 GLU A 99 TRP A 100 PHE A 110 VAL A 111 ASP A 114 VAL A 115 ASN A 180 GLU A 181 CYS A 182 ILE A 183 ILE A 184 TRP A 386 PHE A 389 TYR A 408 SER A 409 THR A 412 TYR A 416

D3 receptor

Compound **22**. Five clusters were originated:

Clu	Bind.energy	Dissoc. constant	Contacting receptor residues
001	000011.4600	00000000003990.0000	ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 94 PHE A 106 VAL A 107 ASP A 110 VAL A 111 CYS A 114 THR A 115 SER A 182 ILE A 183 VAL A 189 SER A 192 SER A 193 SER A 196 TRP A 342 PHE A 345 PHE A 346 HIS A 349 TYR A 365 SER A 366 THR A 369 TRP A 370 TYR A 373
002	000011.0500	00000000007980.0000	ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 94 PHE A 106 VAL A 107 ASP A 110 VAL A 111 CYS A 114 THR A 115 CYS A 181 SER A 182 ILE A 183 VAL A 189 SER A 192 SER A 196 TRP A 342 PHE A 345 PHE A 346 HIS A 349 TYR A 365 SER A 366 THR A 369 TRP A 370 TYR A 373
003	000008.8100	000000000345950.0000	TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 94 PHE A 106 VAL A 107 ASP A 110 CYS A 181 SER A 182 ILE A 183 PHE A 345 PRO A 362 TYR A 365 SER A 366 THR A 369 TYR A 373
004	000008.6400	000000000460910.0000	ARG A 27 TYR A 32 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 93 GLY A 94 PHE A 106 VAL A 107 ASP A 110 VAL A 111 CYS A 181 SER A 182 ILE A 183 PHE A 345 HIS A 349 TYR A 365 SER A 366 THR A 369 TYR A 373
005	000007.8400	000000001800000.0000	ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 THR A 92 GLY A 93 GLY A 94 VAL A 95 VAL A 180 CYS A 181 SER A 182 PRO A 362 TYR A 365 SER A 366 THR A 369 TYR A 373

Compound **22**. Seven clusters were originated:

Clu	Bind.energy	Dissoc. constant	Contacting receptor residues
001	000011.0600	00000000007840.0000	ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 94 PHE A 106 VAL A 107 ASP A 110 VAL A 111 CYS A 114 THR A 115 CYS A 181 SER A 182 ILE A 183 VAL A 189 SER A 192 SER A 196 TRP A 342 PHE A 345 PHE A 346 HIS A 349 PRO A 362 TYR A 365 SER A 366 THR A 369 TYR A 373
002	000010.5200	00000000019370.0000	ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 PHE A 106 VAL A 107 ASP A 110 VAL A 111 CYS A 114 CYS A 181 SER A 182 ILE A 183 VAL A 189 SER A 192 TRP A 342 PHE A 345 PHE A 346 HIS A 349 PRO A 362 TYR A 365 SER A 366 THR A 369 GLY A 372 TYR A 373
003	000009.8800	000000000057660.0000	ARG A 27 TYR A 36 VAL A 82 VAL A 86 LEU A 89 GLU A 90 GLY A 94 PHE A 106 VAL A 107 ASP A 110 CYS A 181 SER A 182 ILE A 183 PHE A 345 HIS A 349 PRO A 362 TYR A 365 SER A 366 THR A 369 TYR A 373
004	000008.6600	000000000451390.0000	ARG A 27 VAL A 86 LEU A 89 GLU A 90 GLY A 93 GLY A 94 PHE A 106 VAL A 107 ASP A 110 CYS A 181 SER A 182 ILE A 183 PHE

A 345 HIS A 349 ASN A 352 VAL A 360 SER A 361 PRO A 362 TYR A 365 SER A 366 THR A 369 TYR A 373

005 | 000008.3000 | 00000000820720.0000 | ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 94 PHE A 106 VAL A 107 ASP A 110 CYS A 181 SER A 182 PRO A 362 TYR A 365 SER A 366 THR A 369 TRP A 370 TYR A 373

006 | 000008.1400 | 00000001080000.0000 | ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 94 VAL A 95 TRP A 96 PHE A 106 THR A 179 VAL A 180 CYS A 181 SER A 182 PRO A 362 TYR A 365 SER A 366 THR A 369 TYR A 373

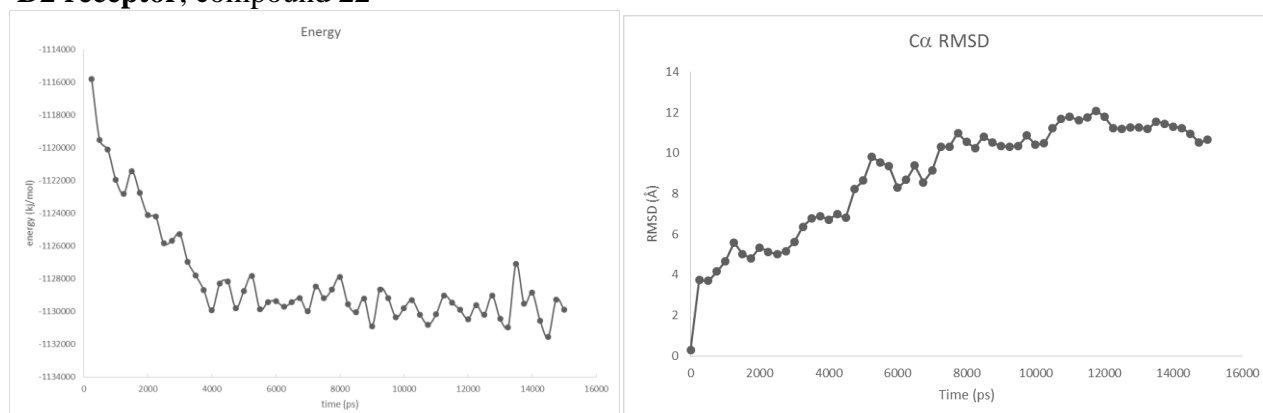
007 | 000007.9100 | 00000001600000.0000 | ARG A 27 TYR A 36 VAL A 86 LEU A 89 GLU A 90 GLY A 93 GLY A 94 PHE A 106 VAL A 107 ASP A 110 CYS A 181 SER A 182 PHE A 345 VAL A 360 SER A 361 PRO A 362 GLU A 363 TYR A 365 SER A 366 THR A 369 TYR A 373

Molecular dynamics studies

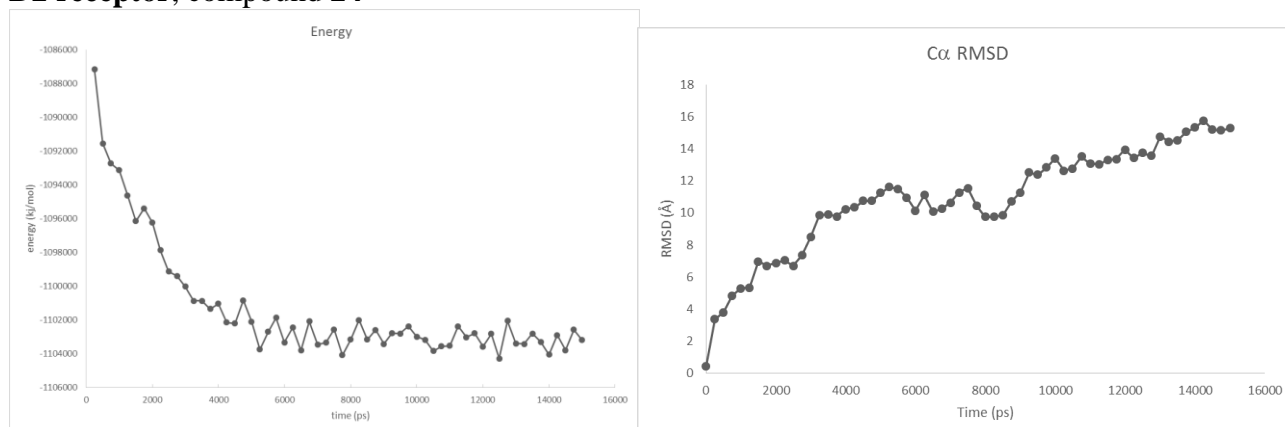
The highest binding energy complex of each ligand was then submitted to molecular dynamics studies. Simulations were run at 298K and 1 bar in a protein membrane of phosphatidylethanolamine (PEA) with the AMBER03 ForceField. The protein was scanned for secondary structure elements with hydrophobic surface residues and oriented accordingly and embedded in the membrane. Water was then added as 0.9% NaCl physiological solution. A 250 ps restrained equilibration simulation was run, which ensures that the membrane can adapt to the newly embedded protein. Then a simulation was run for 15 ns (5 fs timestep, simulation snapshots saved every 250000 fs).

Plots of the energy and the C α RMSD profiles after MD simulations

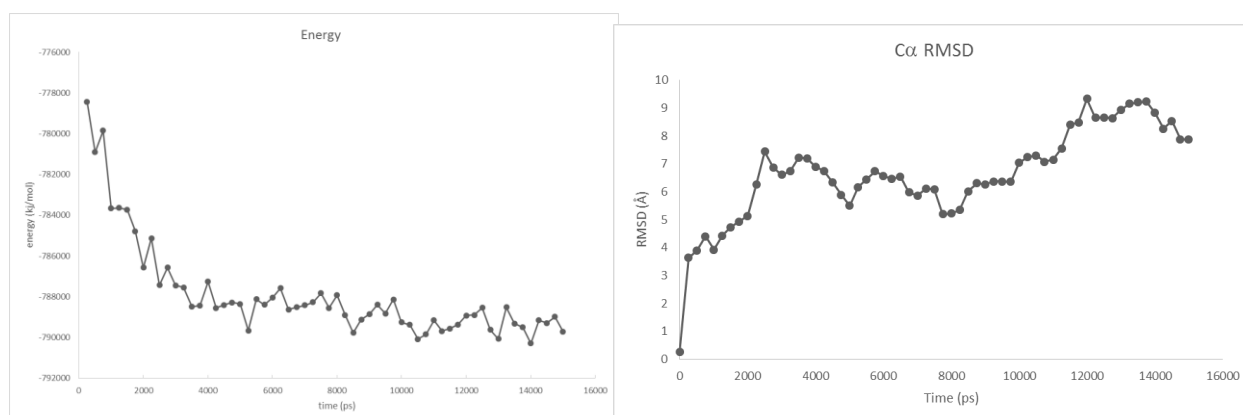
D2 receptor, compound 22



D2 receptor, compound 24



D3 receptor, compound 22



D3 receptor, compound 24

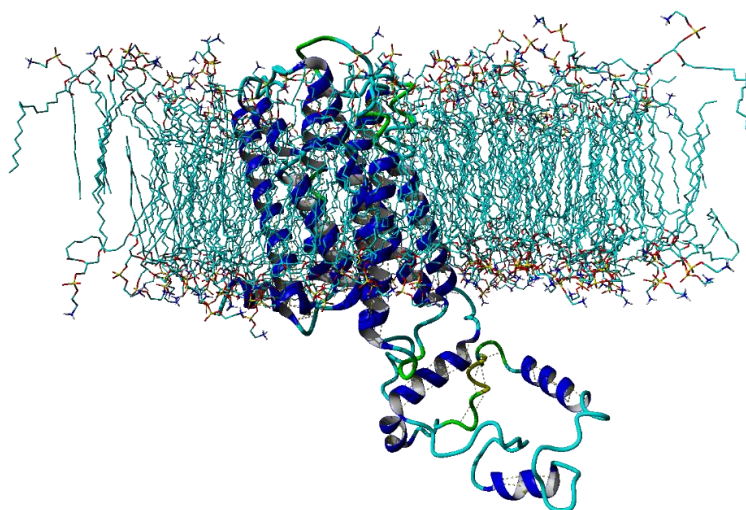
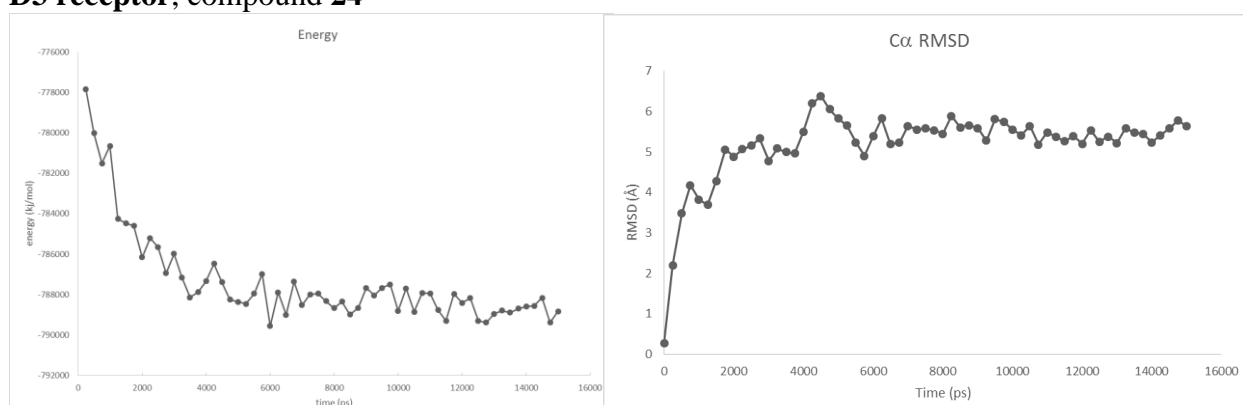


Figure 1. The D3 receptor embedded in the membrane

For each compound, the lowest energy complex from MD simulations was further minimized with the same force field. The binding energy of the obtained complex was then recalculated with Autodock, giving the following results (binding energy are reported in kcal/mol):

	D2	D3
22	10.79	9.30
24	10.66	11.97
23	9.20	8.83
21	9.66	8.50

Biological data for compounds 1-35

Receptor Binding Studies. Dopamine receptor binding was determined by competition binding experiments with membranes from CHO cells stably expressing the human D_{2L}, D_{2S}, D₃ and D₄ receptor displacing the radioligand [³H]spiperone. Affinities for the D₁ and D₅ receptor were performed using transiently transfected HEK cells expressing the appropriate receptor and the radioligand [³H]SCH23390. K_i values of the test compounds 1-4, 9-20 and 25-35 are displayed in Table S1.

Table S1. Radioligand binding data for the compounds 1-4, 9-20, 25-29 and 34-35 employing the human D_{2L} and D₃ receptors

<i>K_i ± (SD) [nM]^a</i>					
compd	[³ H]spiperone		compd	[³ H]spiperone	
	hD _{2L}	hD ₃		hD _{2L}	hD ₃
1	69000 ± 45000	75000 ± 4200	17	36000 ± 22000	6500 ± 300
2	24000 ± 7800	100000 ± 0	18	2800 ± 800	4200 ± 150
3	44000 ± 17000	72000 ± 29000	19	60000 ± 40000	8000 ± 3100
4	44000 ± 17000	72000 ± 29000	20	4200 ± 2500	2600 ± 450
9	68000 ± 8000	100000 ± 0	25	14000 ± 3000	5600 ± 1000
10	14000 ± 4400	5600 ± 950	26	16000 ± 10000	4500 ± 500
11	42000 ± 3000	100000 ± 0	27	100000 ± 0	87000 ± 8100
12	4500 ± 1800	3300 ± 300	28	11000 ± 0	6600 ± 2300
13	91000 ± 13000	100000 ± 0	29	100000 ± 0	100000 ± 0
14	3400 ± 750	2600 ± 0	34	60000 ± 2000	82000 ± 18000
15	28000 ± 8500	49000 ± 20000 ^b	35	33000 ± 1000	48000 ± 3000
16	19000 ± 5500	35000 ± 19000			

^a*K_i* values in nM ± standard deviation (SD) derived from two individual experiments each performed in triplicate. ^b*K_i* values in nM ± standard error of mean (SEM) derived from 3 individual experiments each performed in triplicate.

Receptor binding studies were carried out as described previously.^{S1} In brief, competition binding experiments with the human D_{2L}^{S2}, D_{2S}^{S2}, D₃^{S3} and D₄^{S4} receptor were done with preparations of membranes from CHO cells stably expressing the corresponding receptor and the radioligand [³H]spiperone (specific activity = 81 Ci/mmol, PerkinElmer, Rodgau, Germany) at a final concentration of 0.10 nM, 0.15 nM, 0.20-0.50 nM and 0.30 nM for D_{2L}, D_{2S}, D₃ and D₄ binding, respectively. The assays were carried out at a protein concentration of 1-6 µg/assay tube, K_D values of 0.058 nM, 0.032 nM, 0.20-0.50 nM and 0.25 nM and corresponding B_{max} values of 910 fmol/mg, 8500 fmol/mg, 4200-5000 fmol/mg and 1300 fmol/mg for D_{2L}, D_{2S}, D₃ and D₄, respectively. Human D₁ and D₅ binding was achieved using homogenates of membranes from HEK 293 cells, which were transiently transfected with the pcDNA3.1 vector containing the appropriate human gene (from Missouri S&T cDNA Resource Center (UMR), Rolla, MO) by the calcium phosphate method^{S5} and worked up as described.^{S1} Binding assays were performed using the radioligand [³H]SCH23390 (specific activity 80 Ci/mmol; Biotrend, Cologne, Germany) at 0.40 nM and 0.50 nM with membranes expressing the receptors at a density of 4500 fmol/mg and 2300 fmol/mg, a protein content of 3 µg/well and 6 µg/well and K_D values of 0.34 nM and 0.43 nM for D₁ and D₅, respectively. Unspecific binding was determined for all receptors in the presence of haloperidol (10 µM). Protein concentration was established by the method of Lowry using bovine serum albumin as standard.^{S6} The resulting competition curves of the receptor binding experiments were analyzed by nonlinear regression using the algorithms in PRISM 5.0 (GraphPad Software, San Diego, CA). The data were initially fit using a sigmoid model to

provide an IC_{50} value, representing the concentration corresponding to 50% of maximal inhibition. IC_{50} values were transformed to K_i values according to the equation of Cheng and Prusoff.^{S7}

cAMP BRET Assay. HEK293T cells were transiently co-transfected with pcDNA3L-His-CAMYEL (purchased from ATCC via LGC Standards, Wesel, Germany) and D_{2s} , respectively. Twentyfour hours after transfection cells were split into white half-area 96-well plates at 20×10^4 cells/well and grown overnight. On the following day phenol red free medium was removed and replaced by phosphate buffered saline (PBS) and cells were serum starved for 1 hour before treatment. The assay was started by adding 10 μ l coelenterazine-h (Promega, Mannheim, Germany) to each well at a final concentration of 5 μ M. After 5 minutes incubation time compounds were added containing 50 μ M forskolin (final concentration 10 μ M). Determination of BRET signals started 15 minutes after agonist addition using a CLARIOstar plate reader (BMG LabTech, Ortenberg, Germany). Emission signals from Renilla Luciferase and YFP were measured simultaneously using a BRET filter set (475-30nm/535-30nm).^{S8}

S1. Huebner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. Conjugated enynes as nonaromatic catechol bioisosteres: Synthesis, binding experiments, and computational studies of novel dopamine receptor agonists recognizing preferentially the D-3 subtype. *J. Med. Chem.* **2000**, *43*, 756-762.

S2. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. Structural subtypes of the dopamine D2 receptor are functionally distinct: Expression of the cloned D2A and D2B subtypes in a heterologous cell line. *Mol. Endocrinol.* **1992**, *6*, 920-926.

S3. Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L.; Schwartz, J. C. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature* **1990**, *347*, 146-151.

S4. Asghari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *J. Neurochem.* **1995**, *65*, 1157-1165.

S5. Jordan, M.; Schallhorn, A.; Wurm, F. M. Transfecting mammalian cells: Optimization of critical parameters affecting calcium-phosphate precipitate formation. *Nucleic. Acids Res.* **1996**, *24*, 596-601.

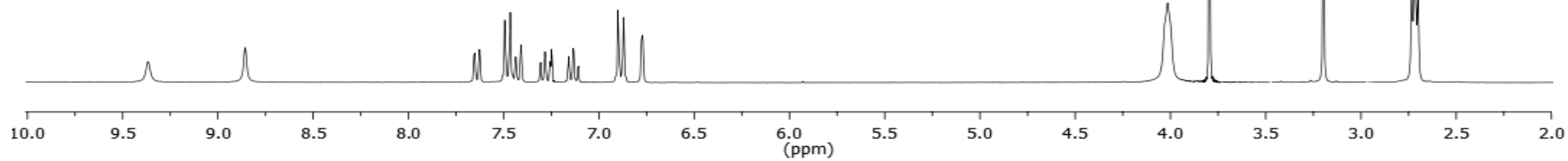
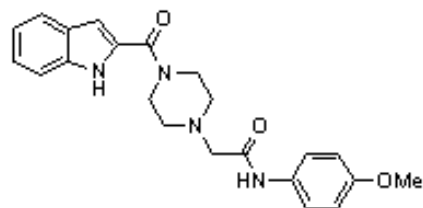
S6. Lowry, O. H.; Rosebrough, N. J.; Farr, A. L.; Randall, R. J. Protein measurement with the folin phenol reagent. *J. Biol. Chem.* **1951**, *193*, 265-275.

S7. Cheng, Y.-C.; Prusoff, W. H. Relation between the inhibition constant K_1 and the concentration of inhibitor which causes fifty per cent inhibition (I_{50}) of an enzymic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.

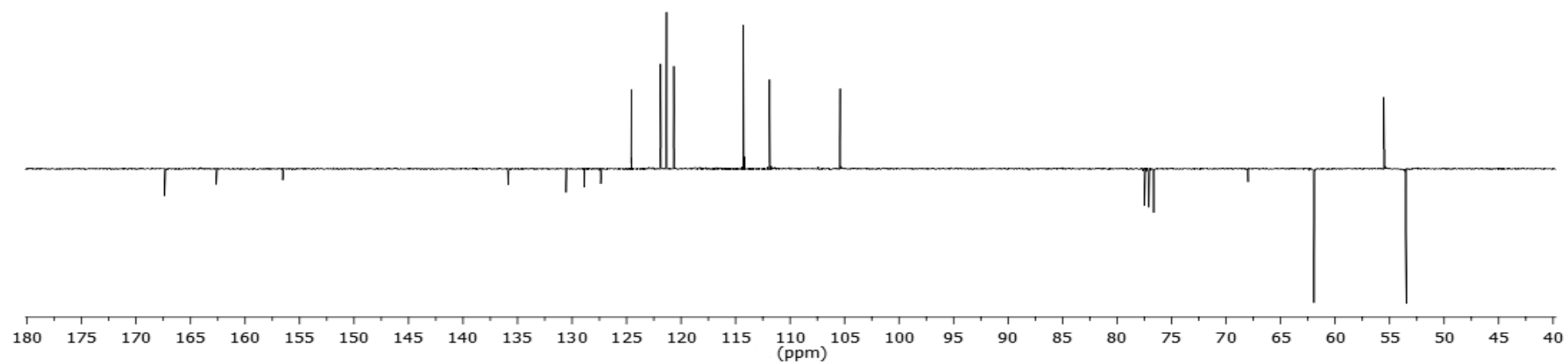
S8. Jiang, L.I.; Collins, J.; Davis, R.; Lin, K.-M.; DeCamp, D.; Roach, T.; Hsueh, R.; Rebres, R.A.; Ross, E.M.; Taussig, R.; Fraser, I.; Sternweis, P.C. Use of cAMP BRET sensor to characterize a novel regulation of cAMP by sphingosine-1-phosphate/G13 pathway. *J. Biol. Chem.* **2007**, *282*, 10576-10584.

Compound 1

^1H NMR, 300 MHz, CDCl_3

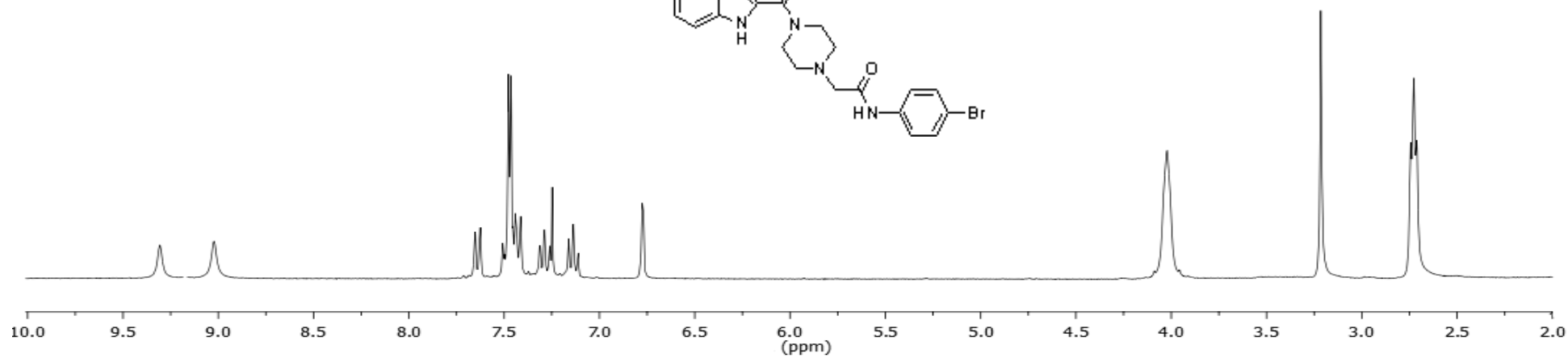
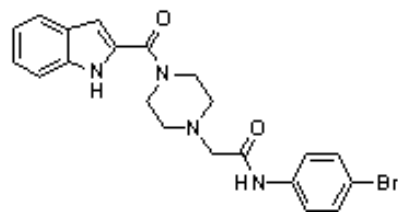


^{13}C NMR, 75 MHz, CDCl_3

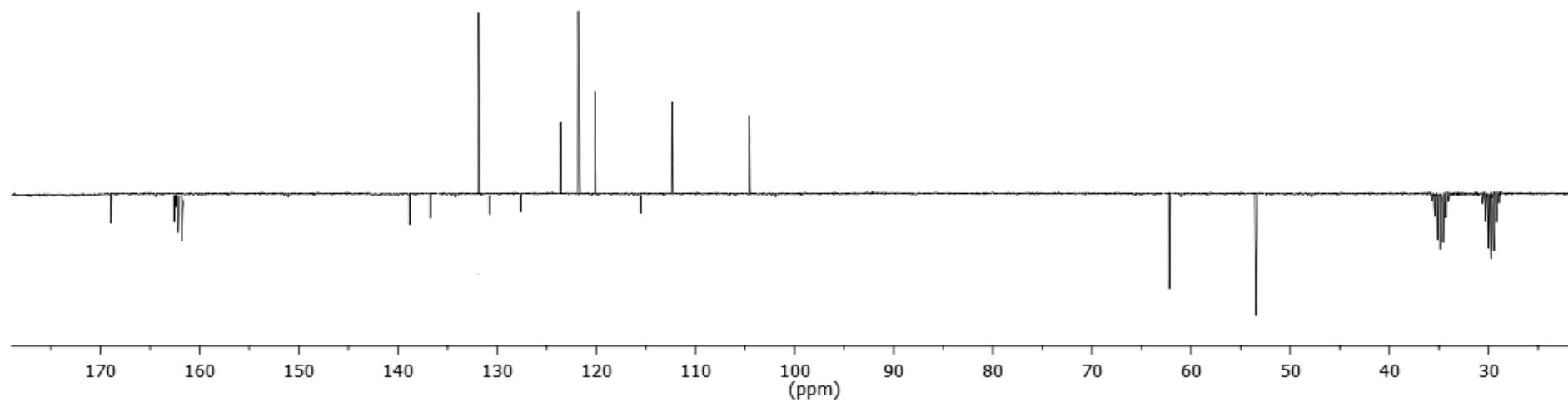


Compound 2

^1H NMR, 300 MHz, CDCl_3

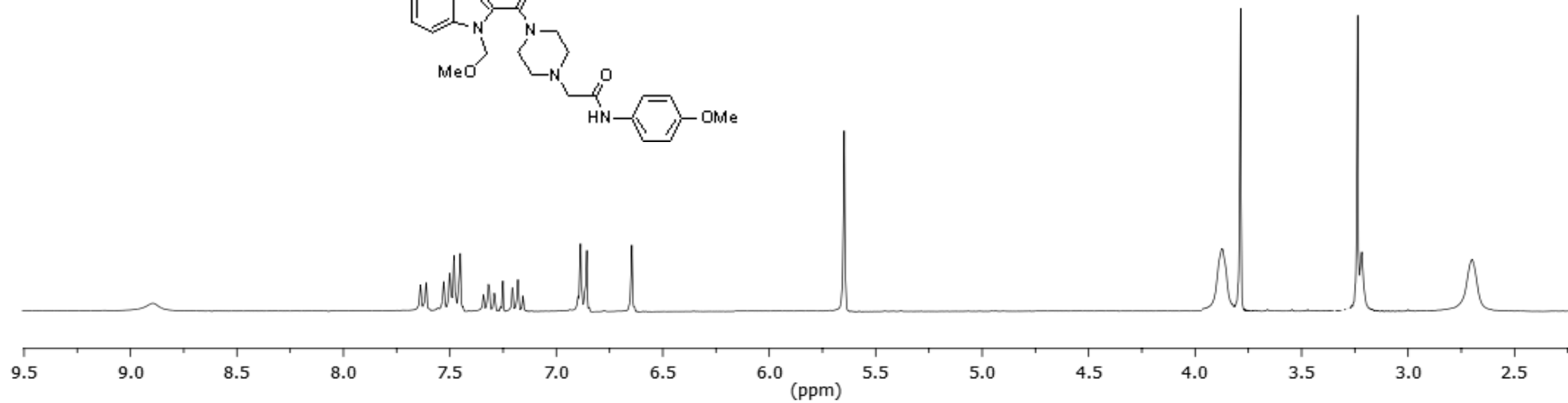
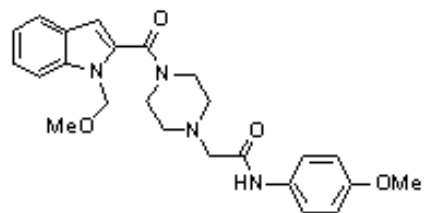


^{13}C NMR, 75 MHz, $\text{DMF-}d_7$

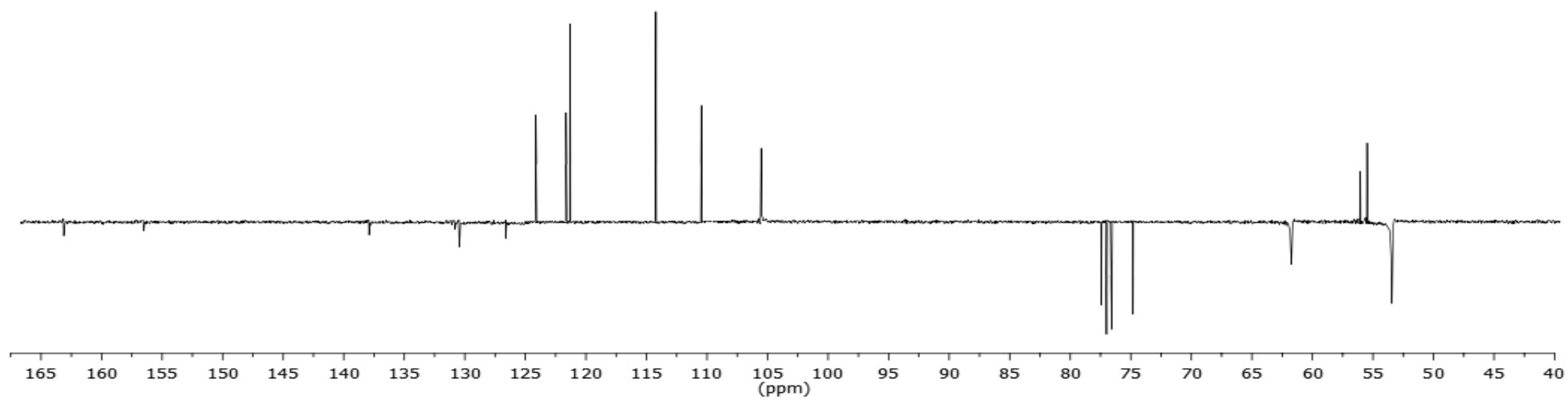


Compound 3

^1H NMR, 300 MHz, CDCl_3

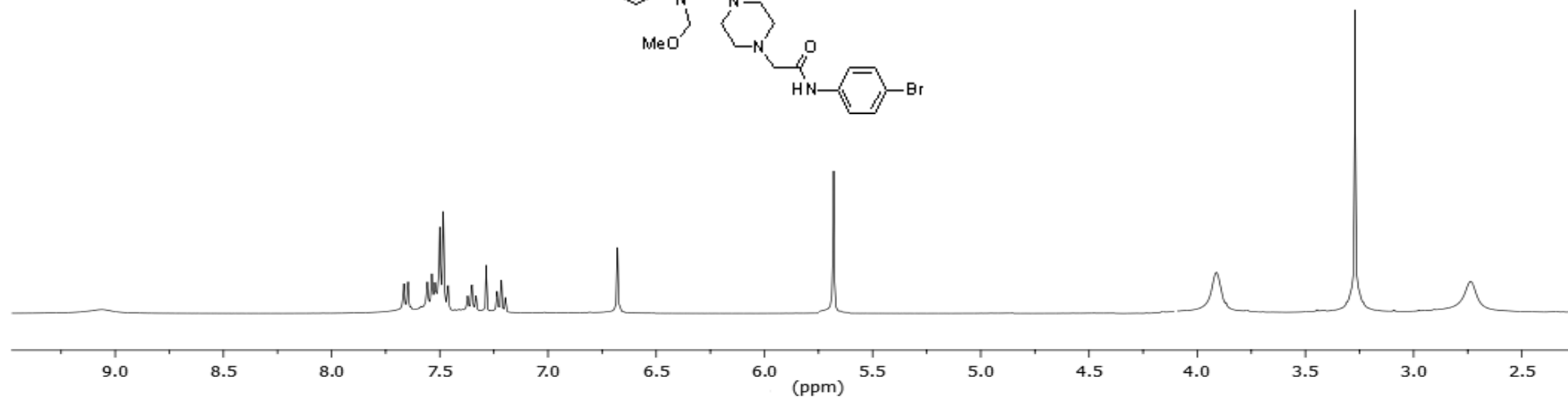
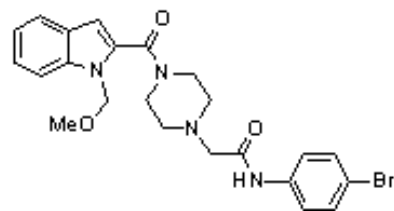


^{13}C NMR, 75 MHz, CDCl_3

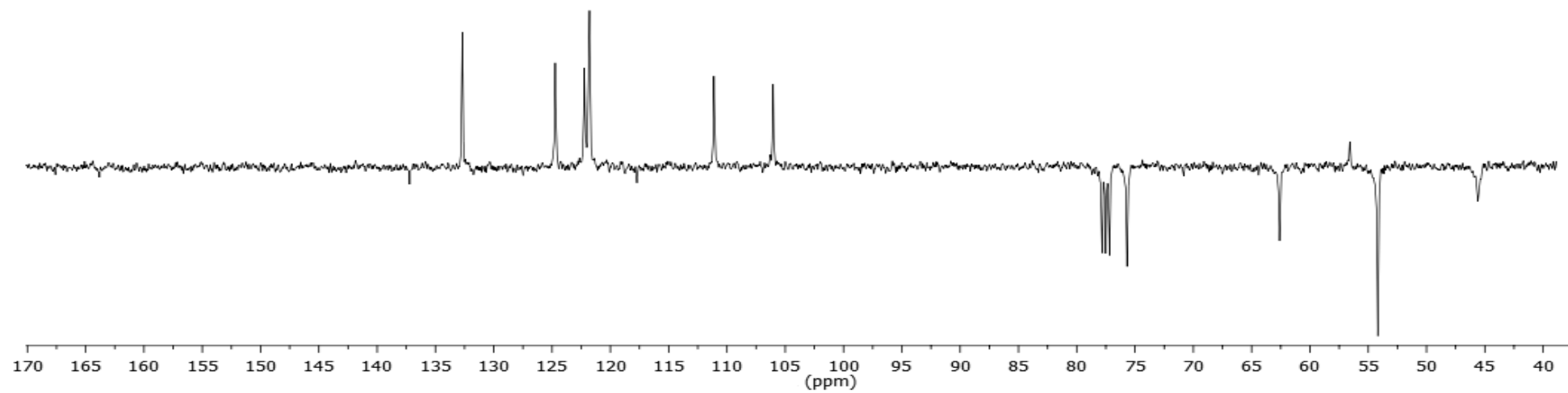


Compound 4

^1H NMR, 400 MHz, CDCl_3

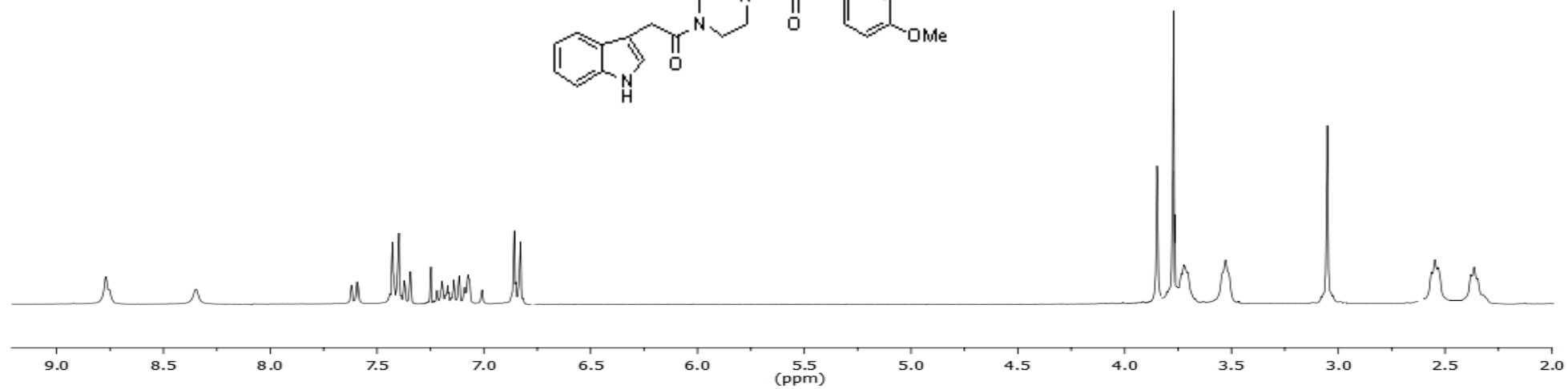
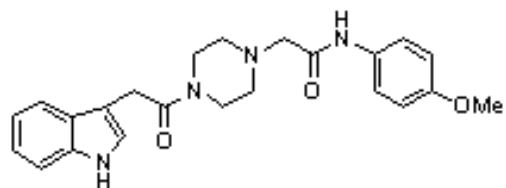


^{13}C NMR, 100 MHz, CDCl_3

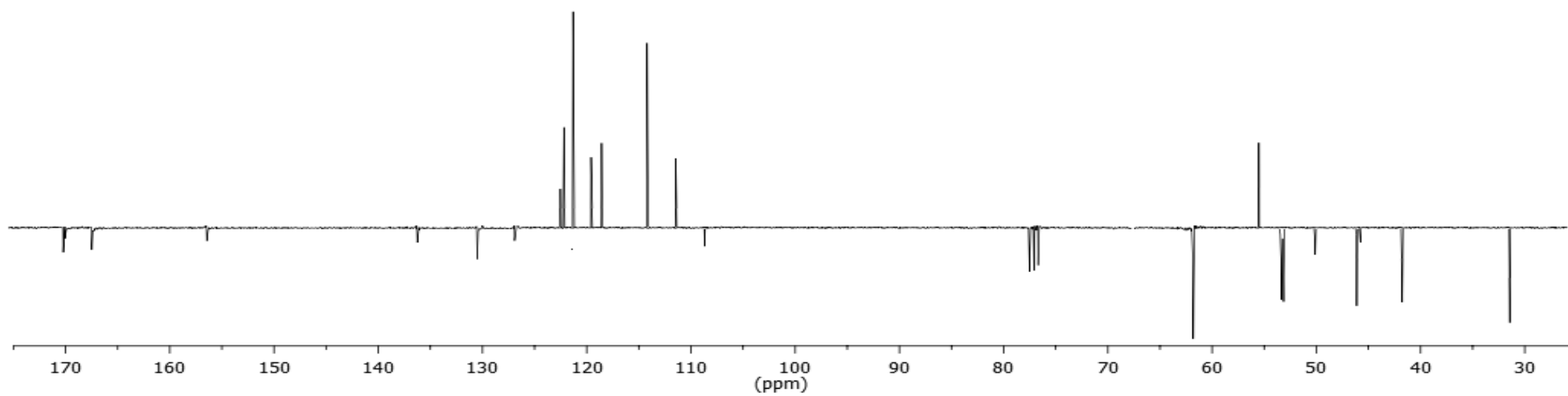


Compound 17

^1H NMR, 300 MHz, CDCl_3

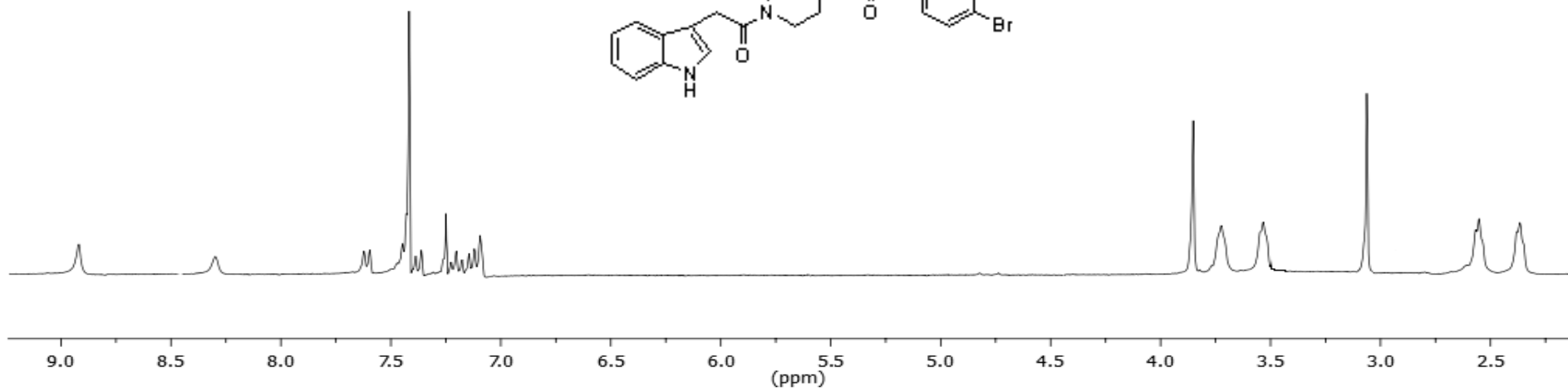
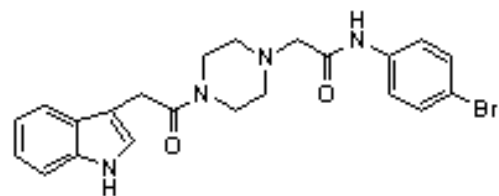


^{13}C NMR, 75 MHz, CDCl_3

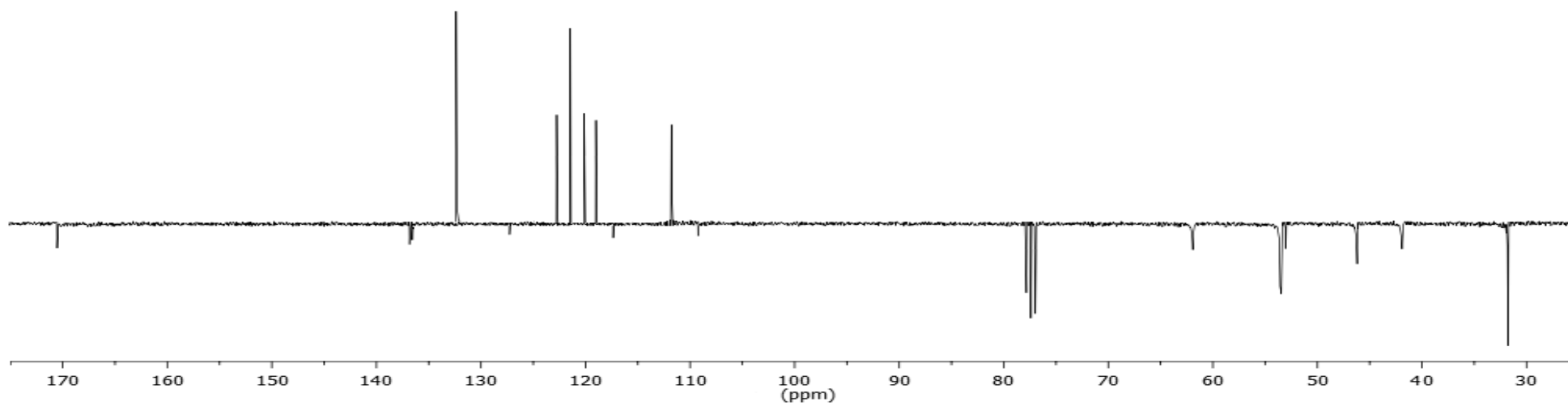


Compound 18

^1H NMR, 300 MHz, CDCl_3

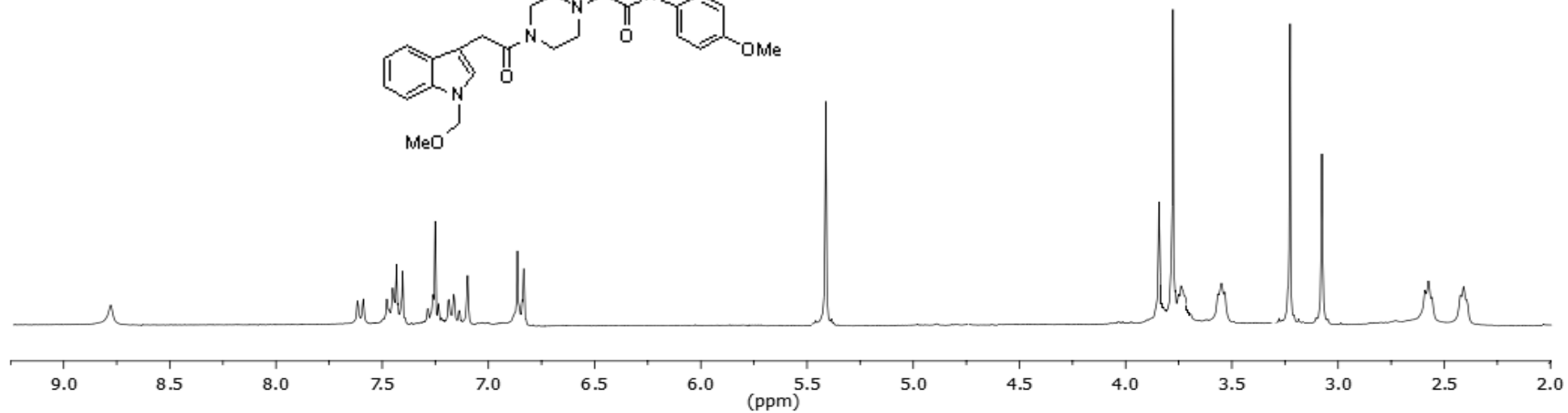
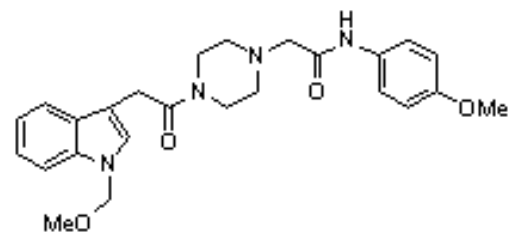


^{13}C NMR, 75 MHz, CDCl_3

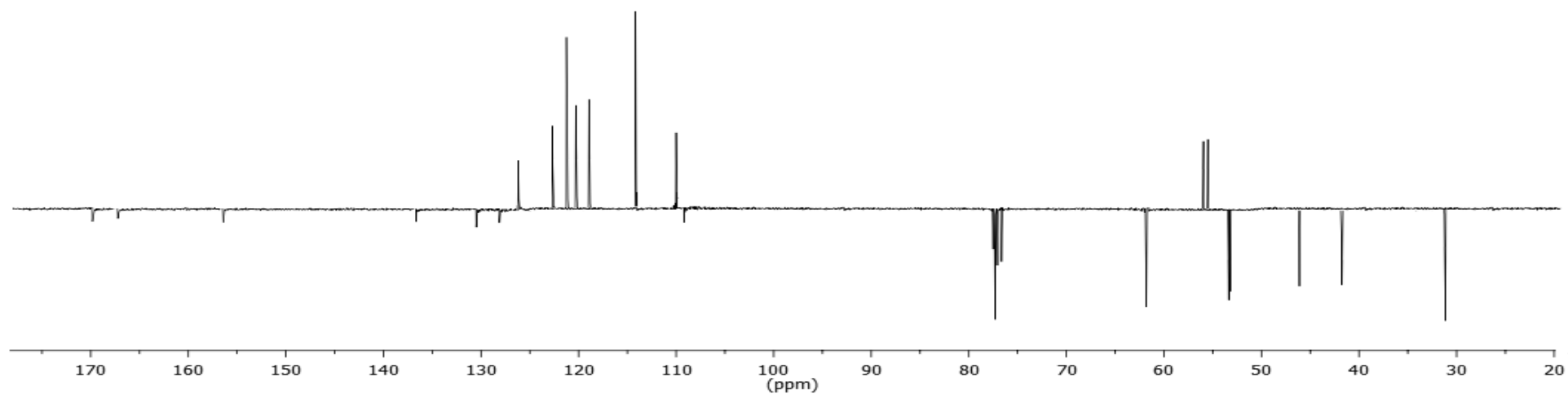


Compound 19

^1H NMR, 300 MHz, CDCl_3

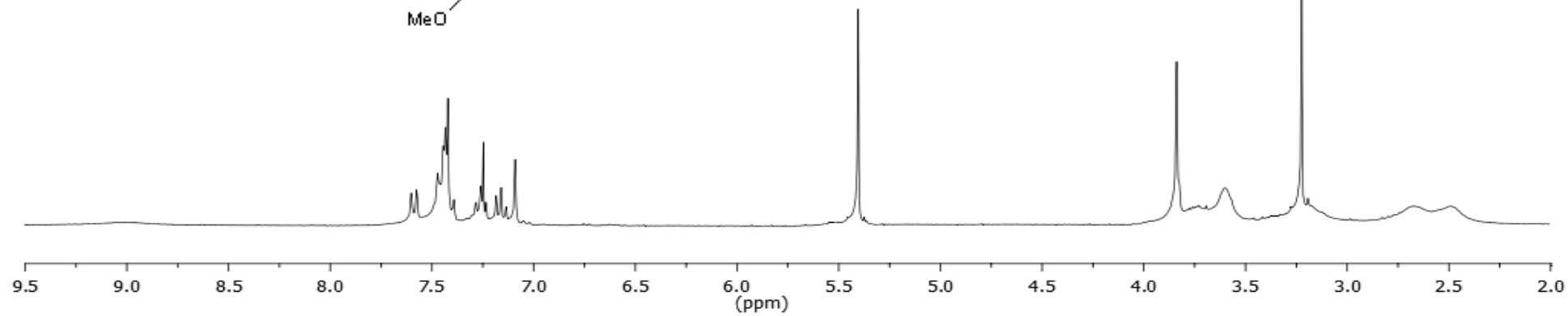
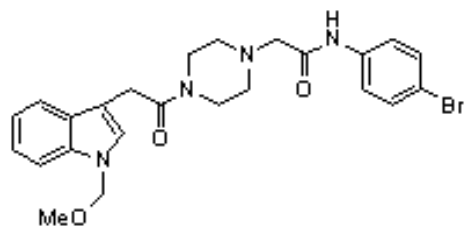


^{13}C NMR, 75 MHz, CDCl_3

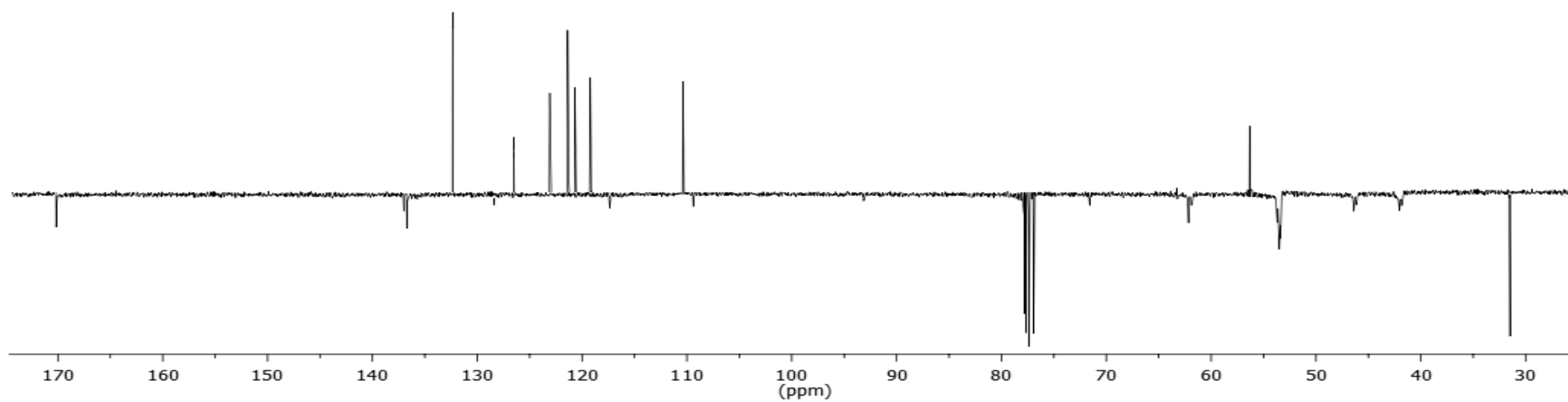


Compound 20

^1H NMR, 300 MHz, CDCl_3

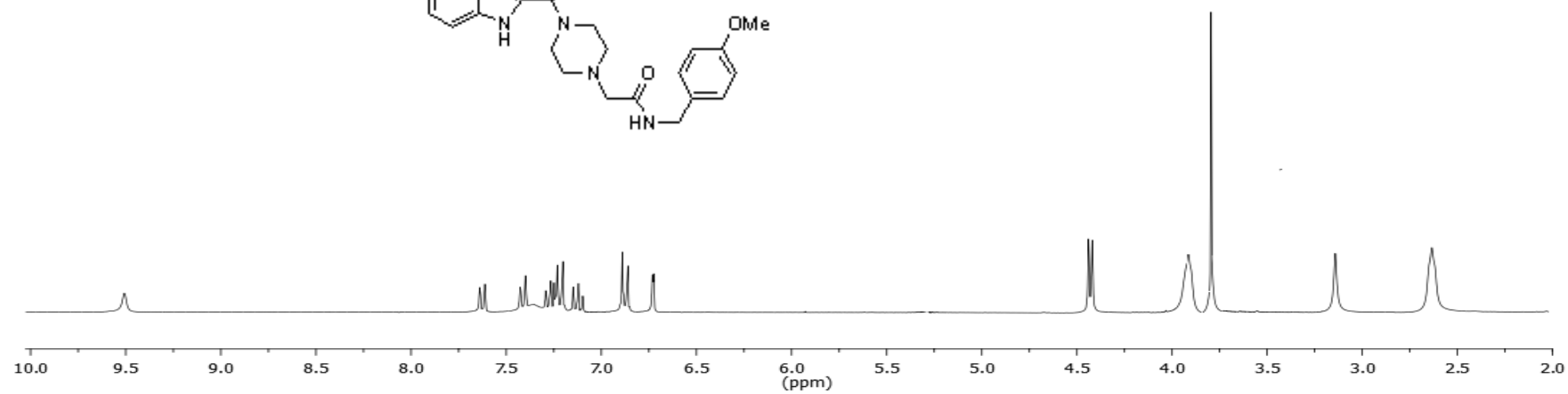
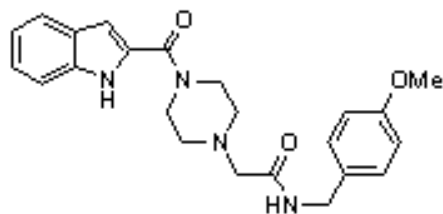


^{13}C NMR, 75 MHz, CDCl_3

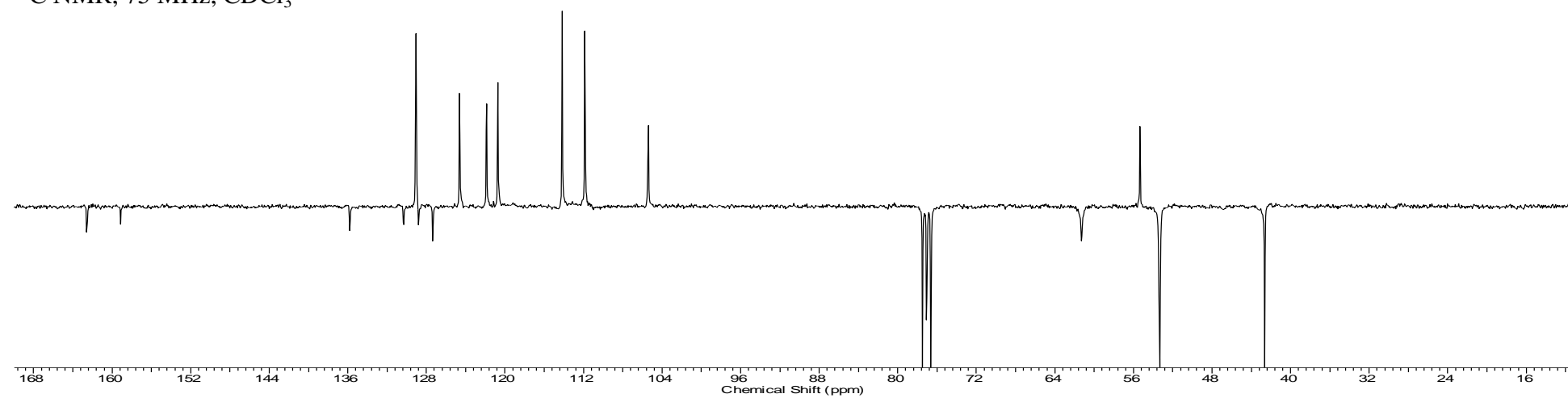


Compound 27

¹H NMR, 300 MHz, CDCl₃

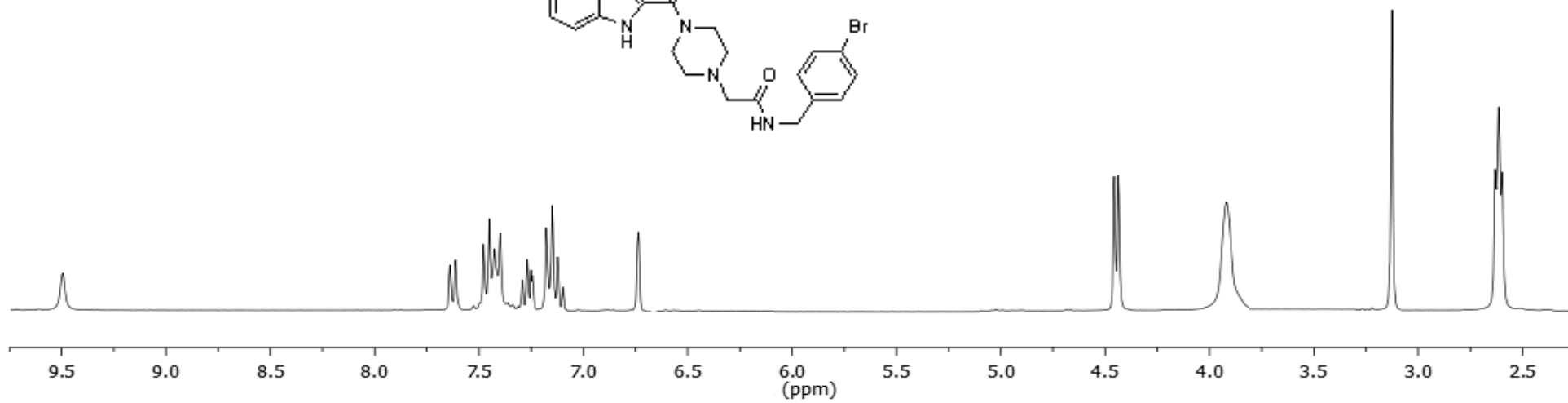
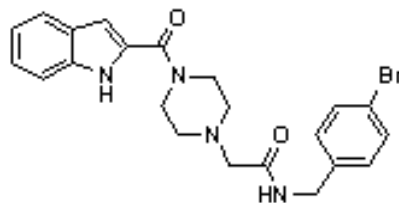


¹³C NMR, 75 MHz, CDCl₃

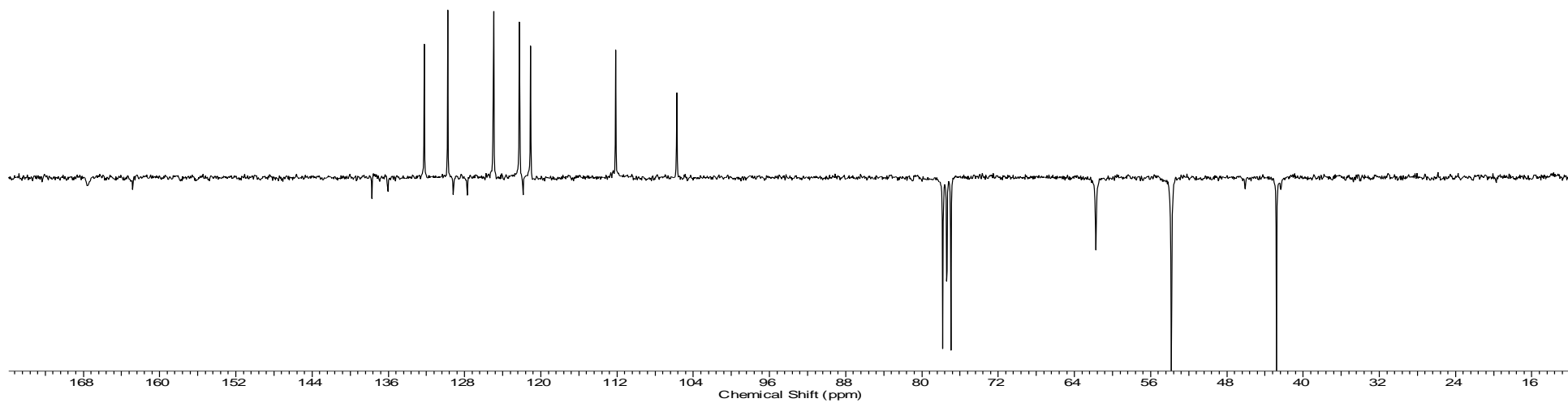


Compound 28

^1H NMR, 300 MHz, CDCl_3

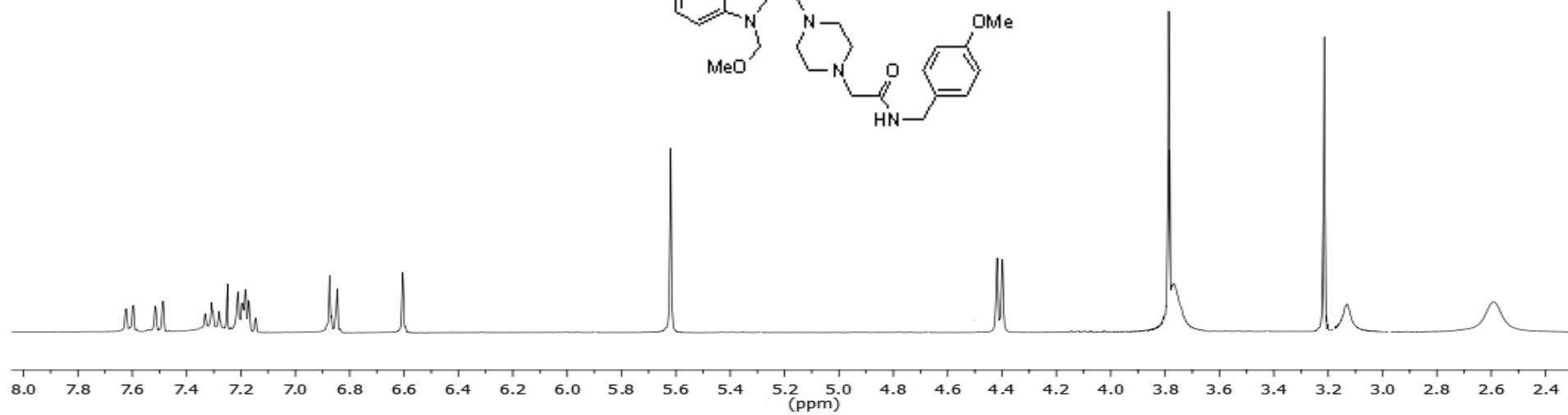
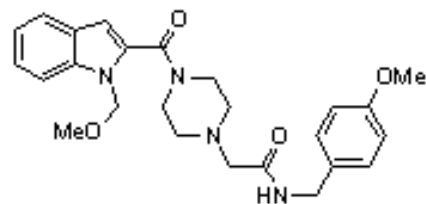


^{13}C NMR, 75 MHz, CDCl_3

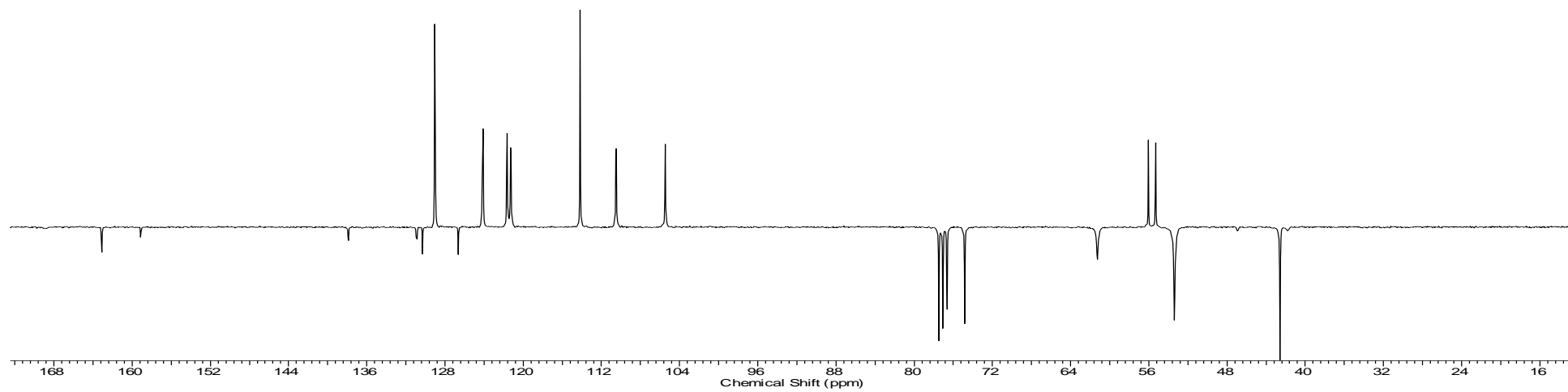


Compound 29

^1H NMR, 300 MHz, CDCl_3

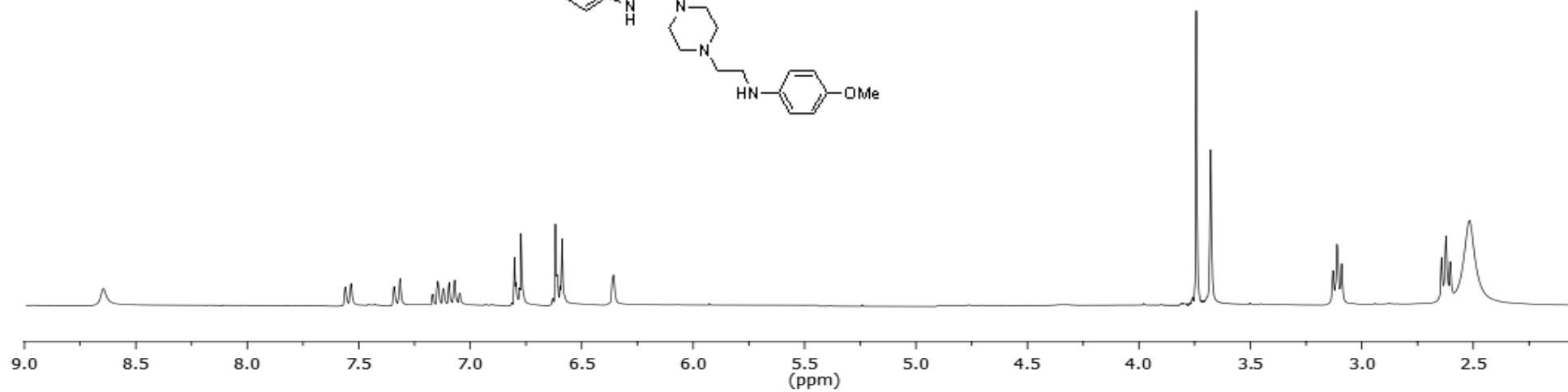
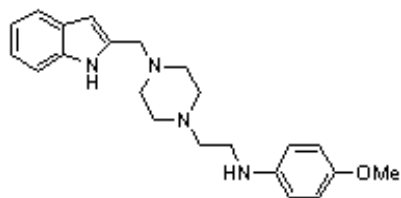


^{13}C NMR, 75 MHz, CDCl_3

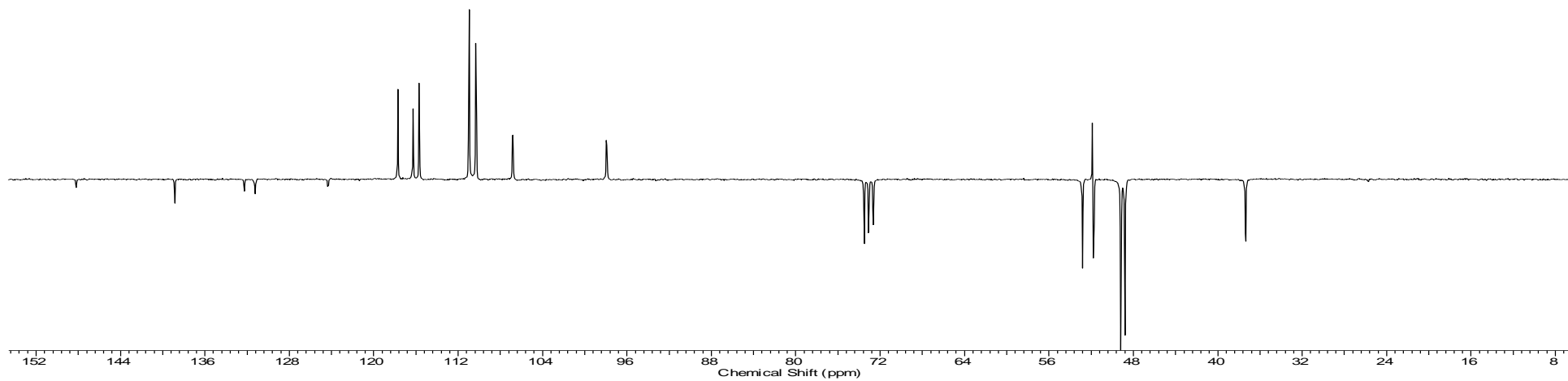


Compound 5

^1H NMR, 300 MHz, CDCl_3

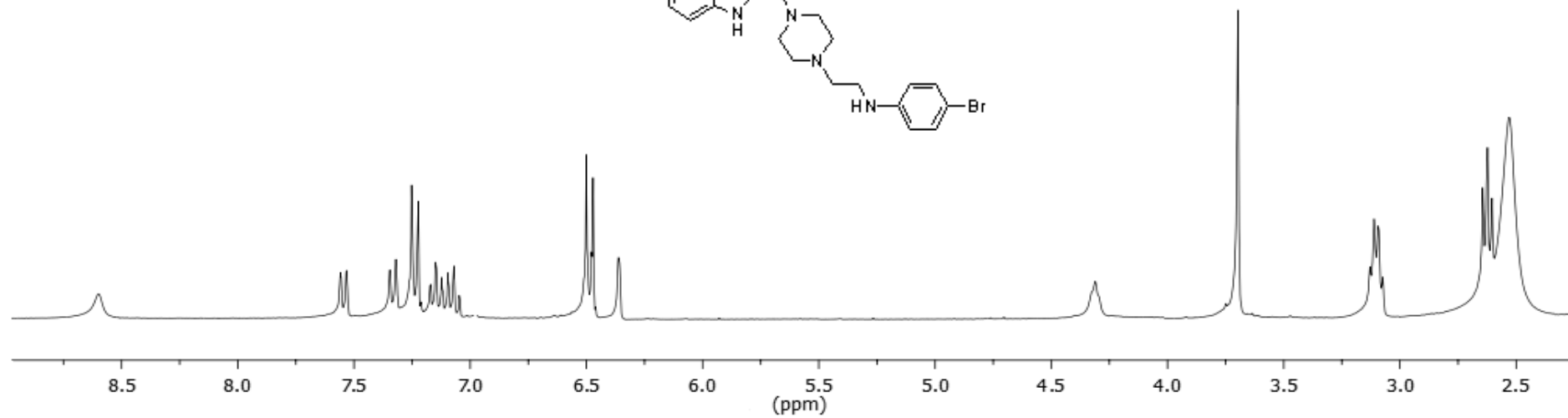
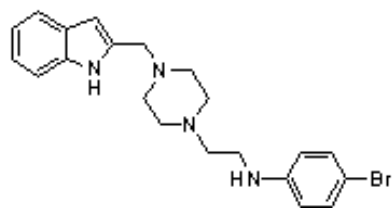


^{13}C NMR, 75 MHz, CDCl_3

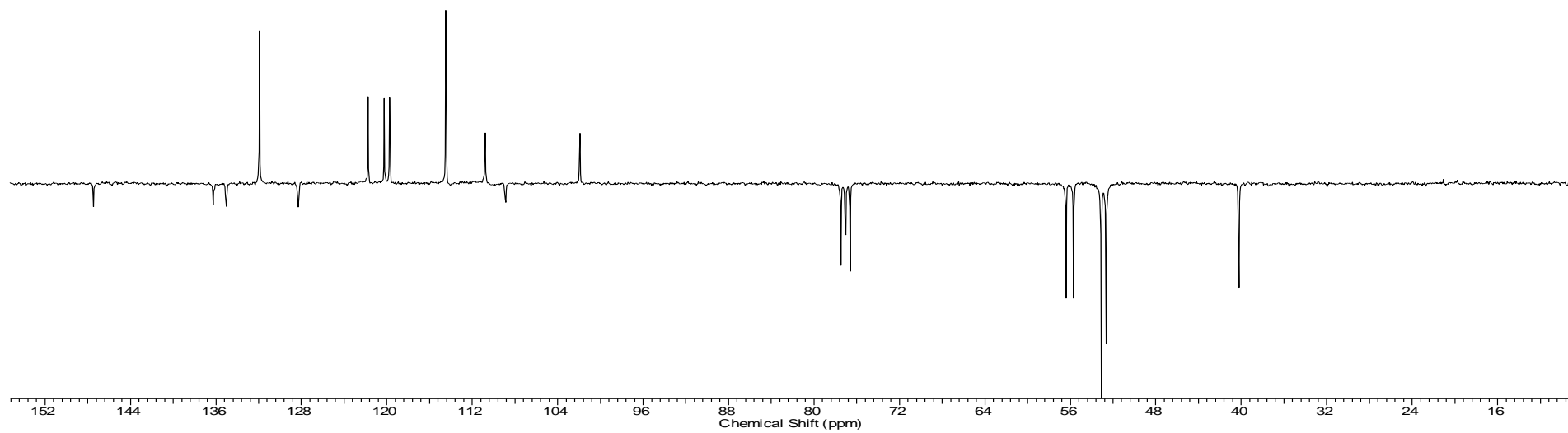


Compound 6

^1H NMR, 300 MHz, CDCl_3

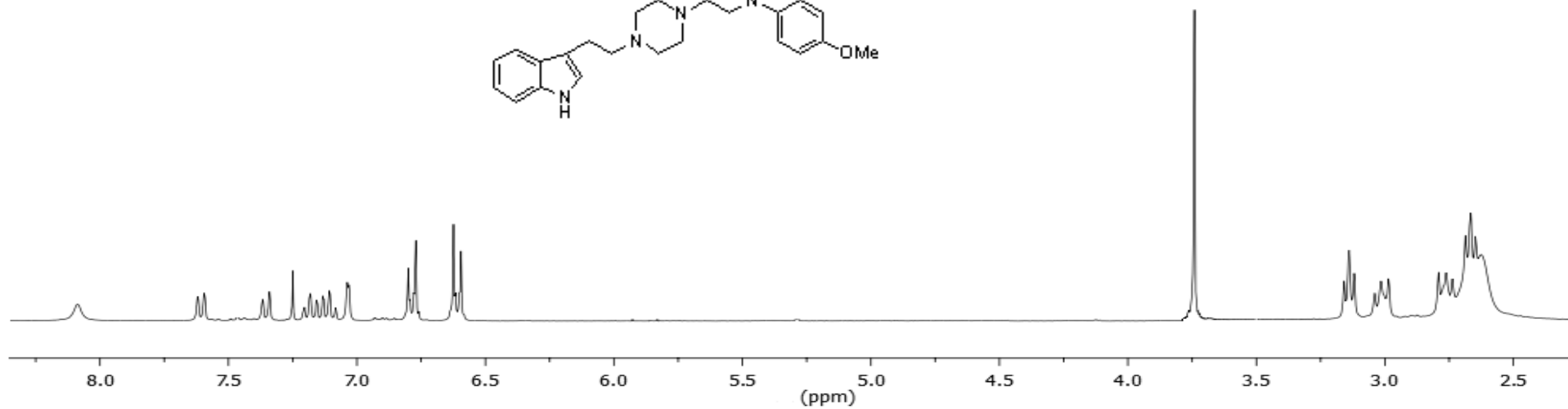
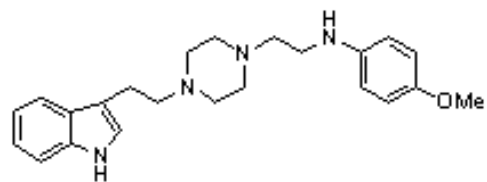


^{13}C NMR, 75 MHz, CDCl_3

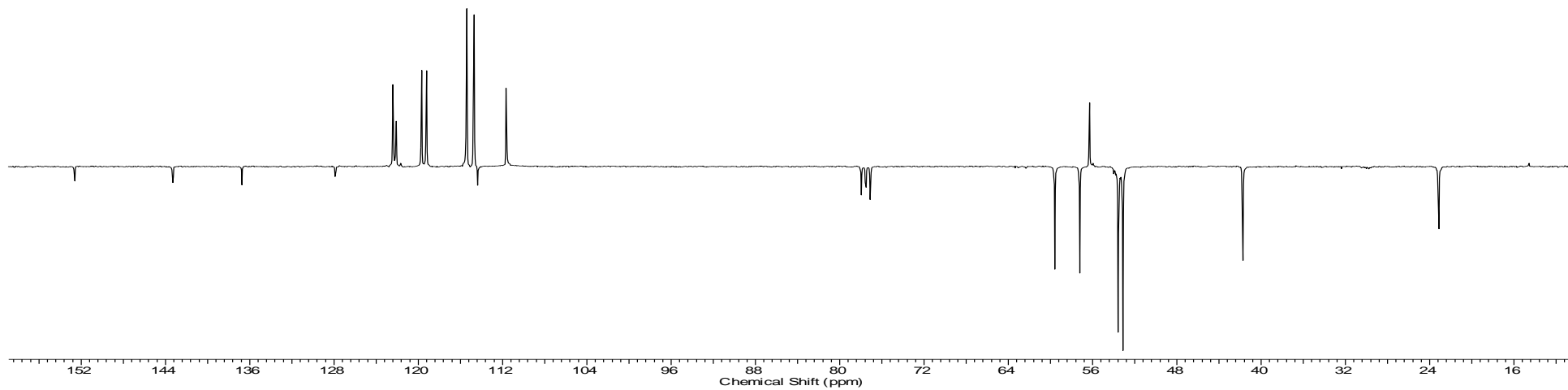


Compound 21

¹H NMR, 300 MHz, CDCl₃

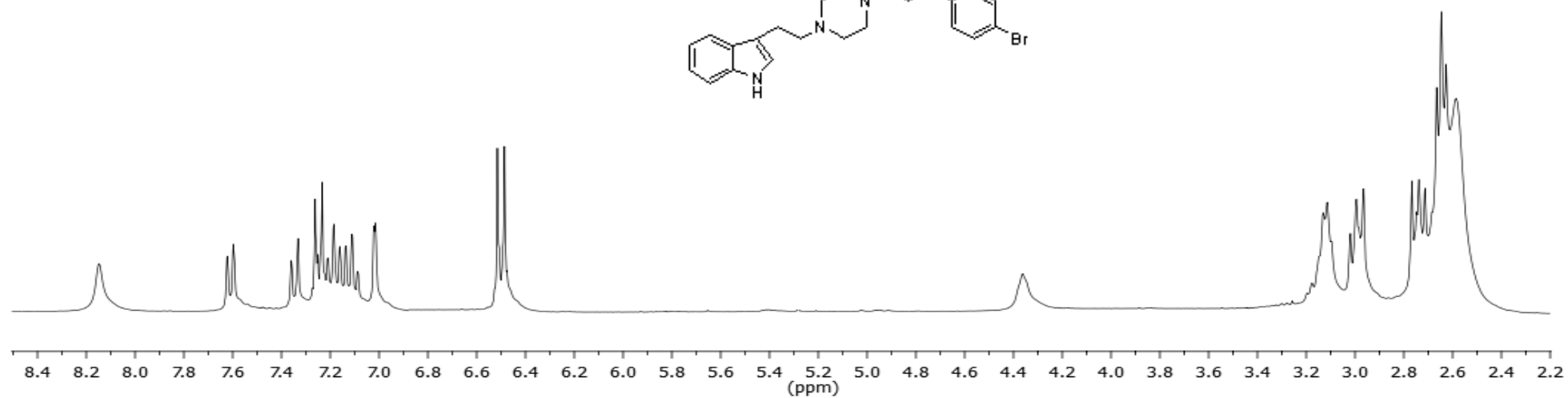
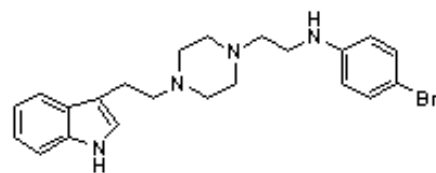


¹³C NMR, 75 MHz, CDCl₃

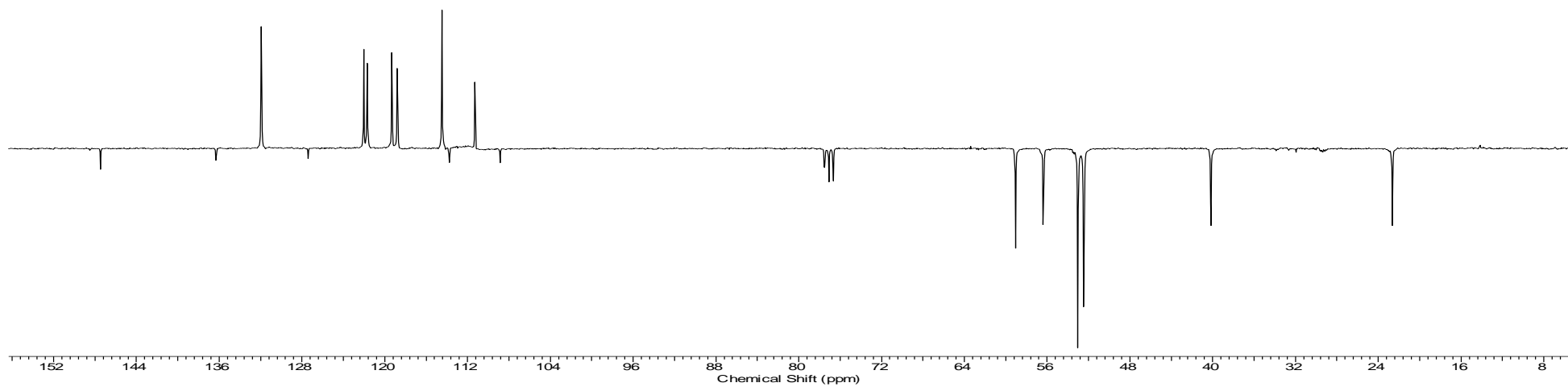


Compound 22

¹H NMR, 300 MHz, CDCl₃

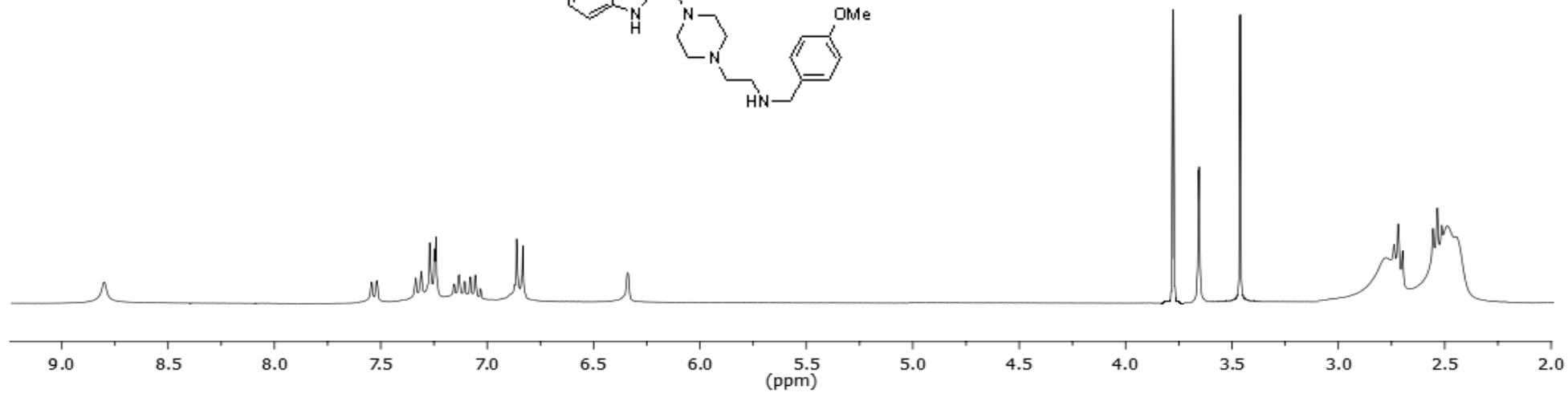
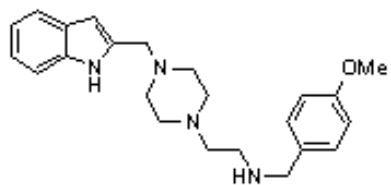


¹³C NMR, 75 MHz, CDCl₃

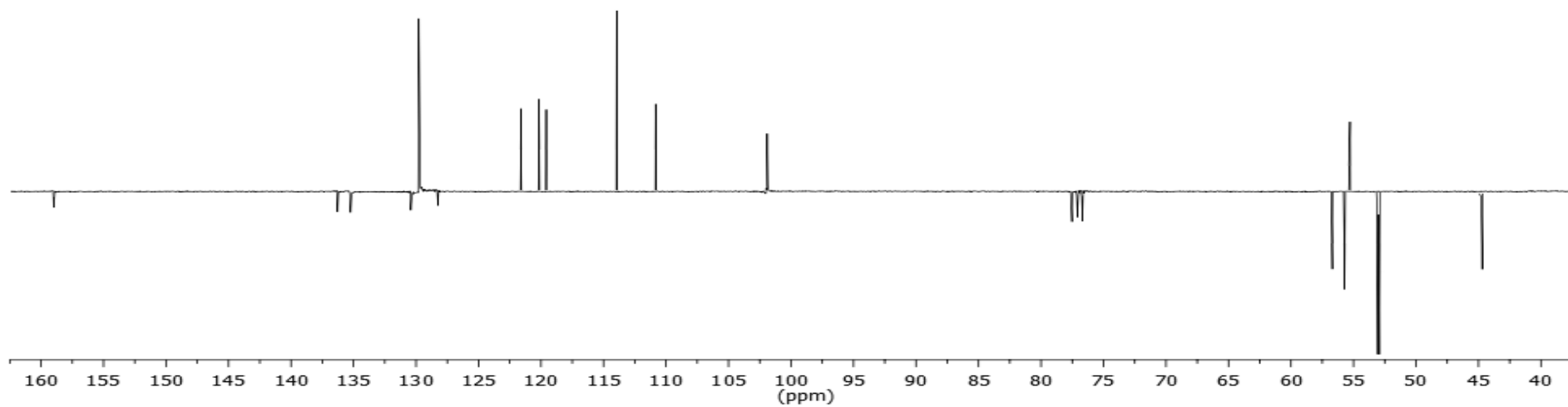


Compound 30

^1H NMR, 300 MHz, CDCl_3

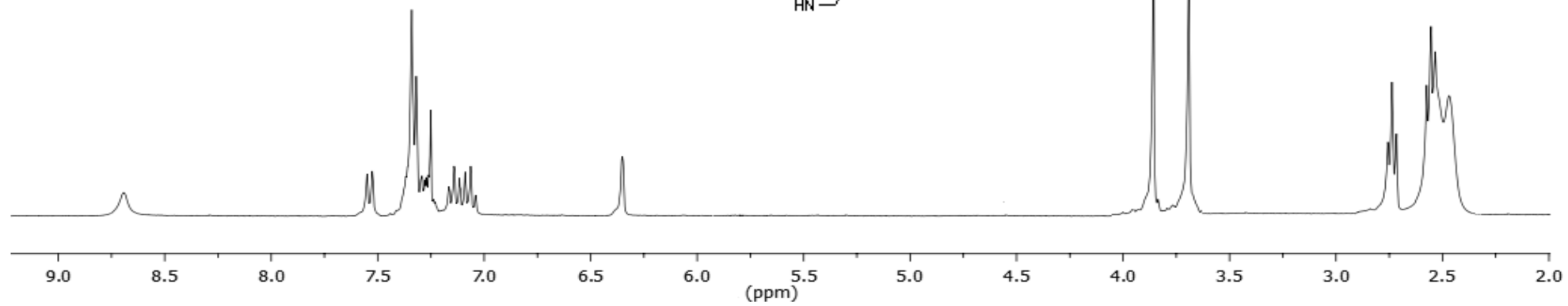
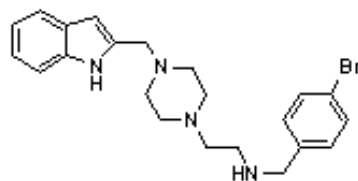


^{13}C NMR, 75 MHz, CDCl_3

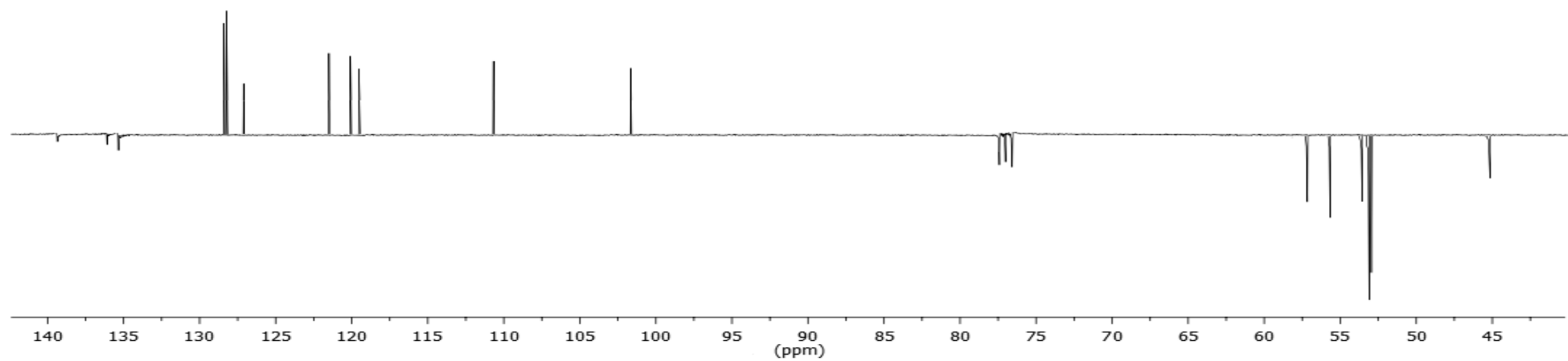


Compound 31

¹H NMR, 300 MHz, CDCl₃

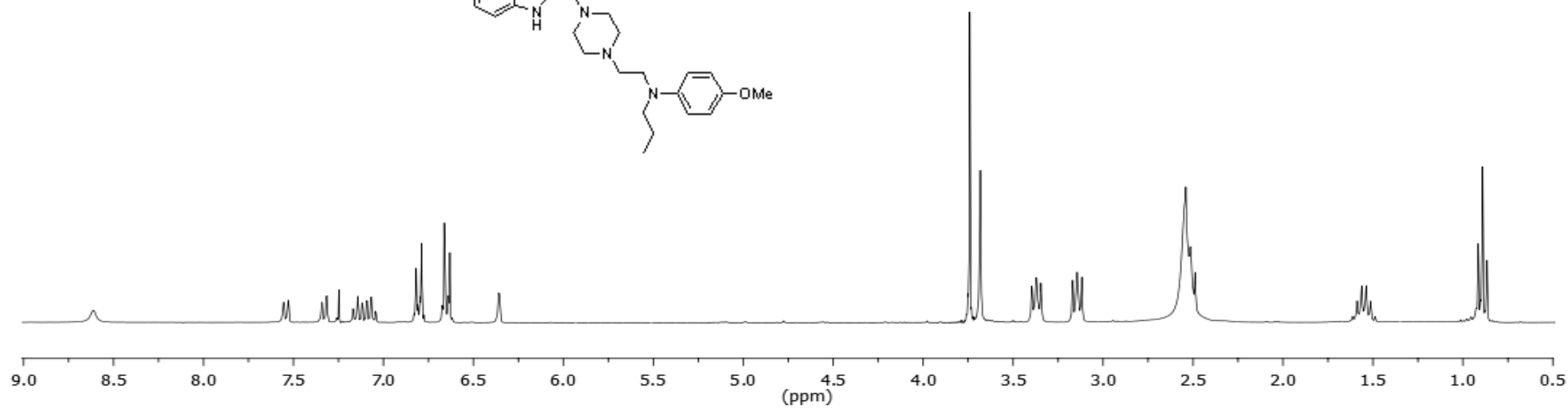
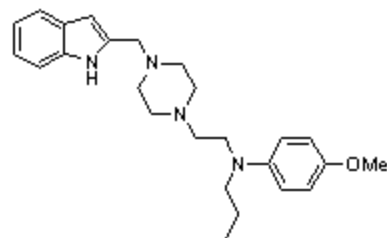


¹³C NMR, 75 MHz, CDCl₃

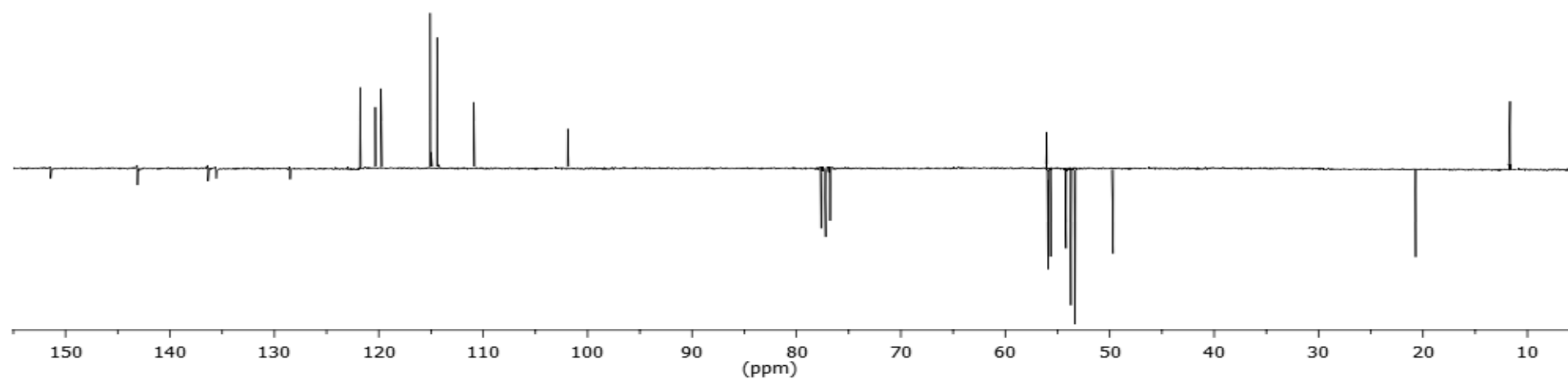


Compound 7

^1H NMR, 300 MHz, CDCl_3

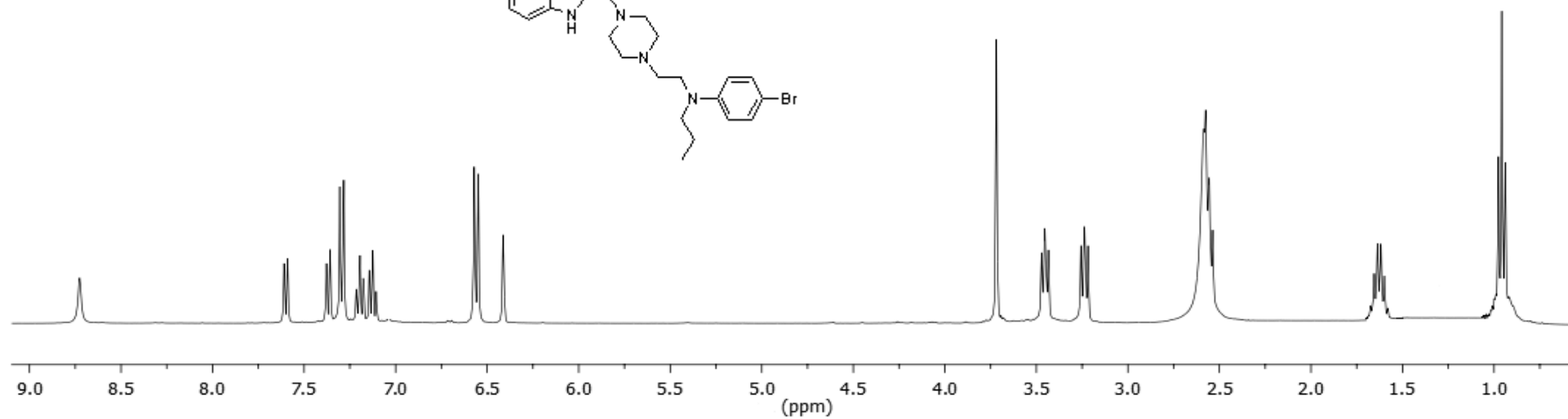
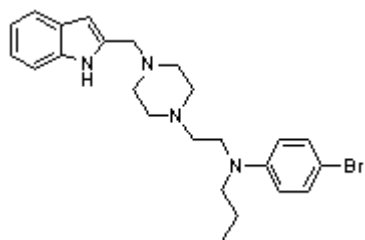


^{13}C NMR, 75 MHz, CDCl_3

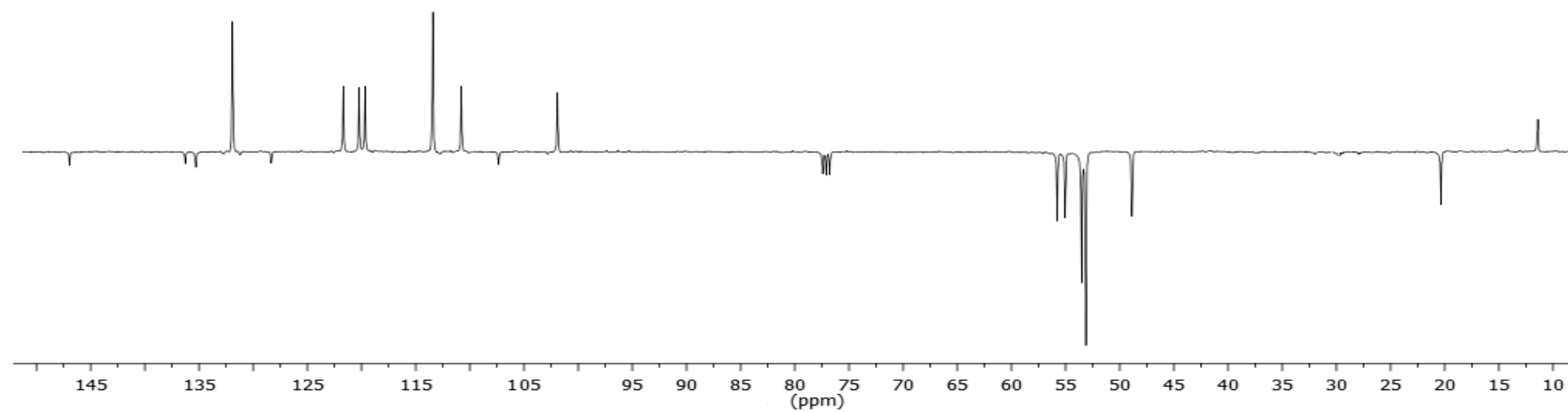


Compound 8

^1H NMR, 400 MHz, CDCl_3

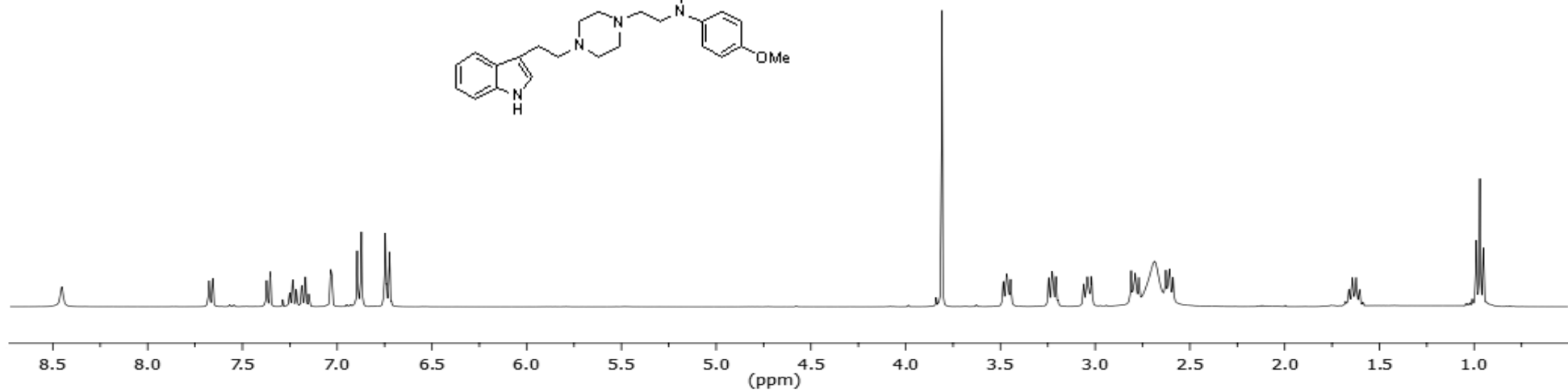
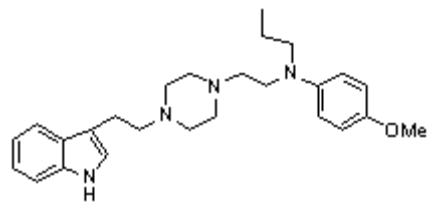


^{13}C NMR, 100 MHz, CDCl_3

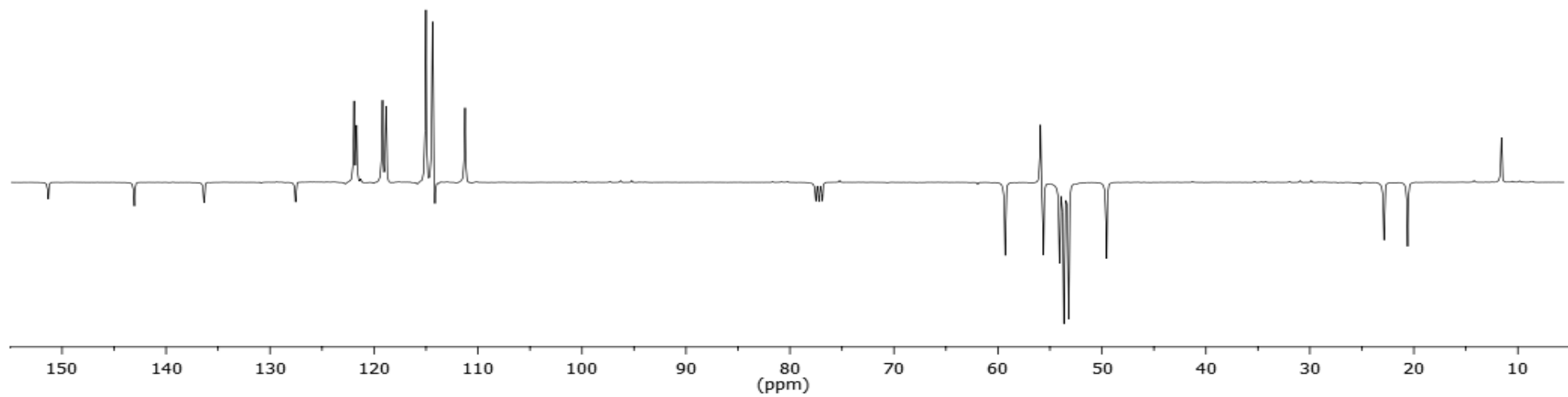


Compound 23

^1H NMR, 400 MHz, CDCl_3

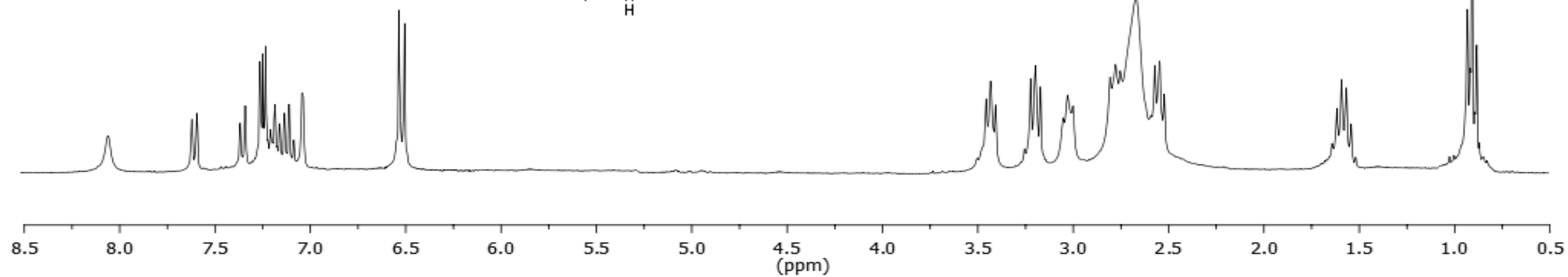
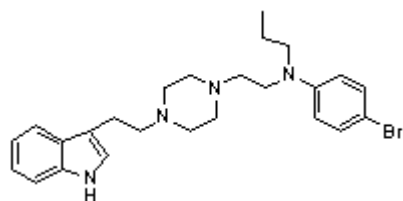


^{13}C NMR, 100 MHz, CDCl_3

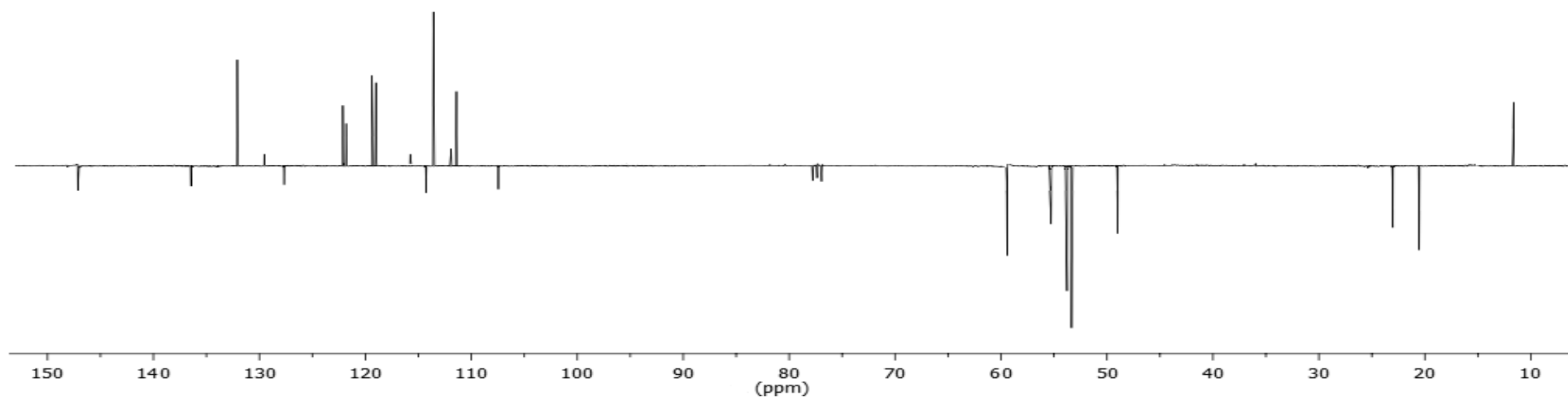


Compound 24

^1H NMR, 300 MHz, CDCl_3

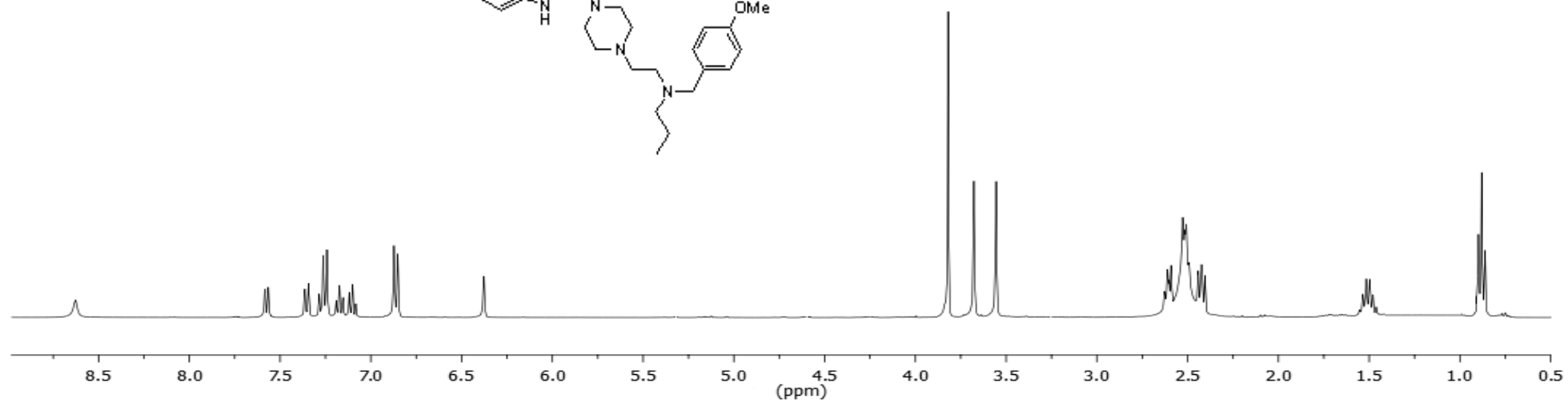
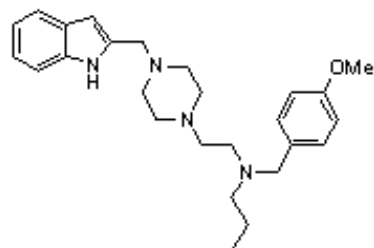


^{13}C NMR, 75 MHz, CDCl_3

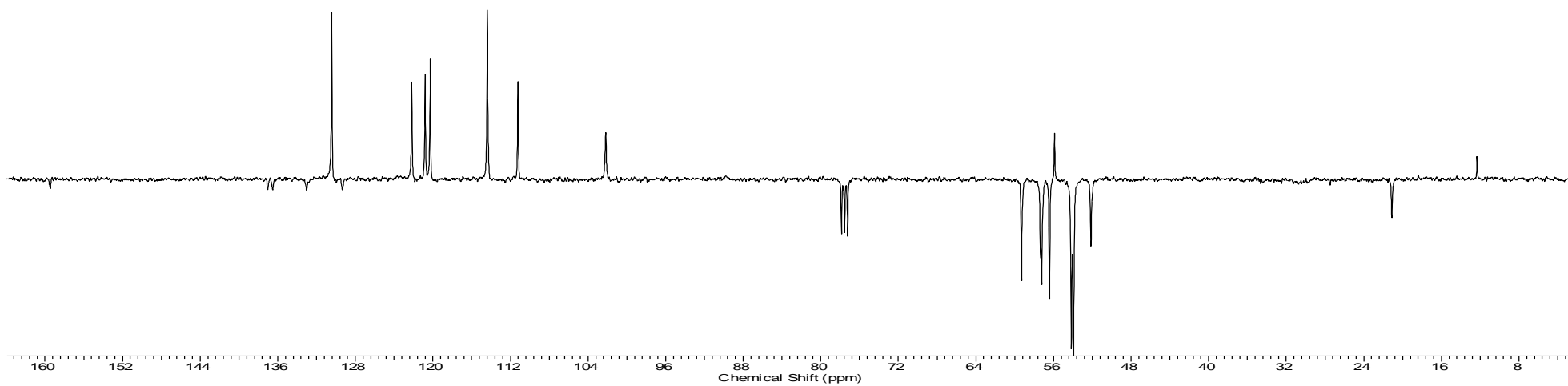


Compound 32

^1H NMR, 400 MHz, CDCl_3

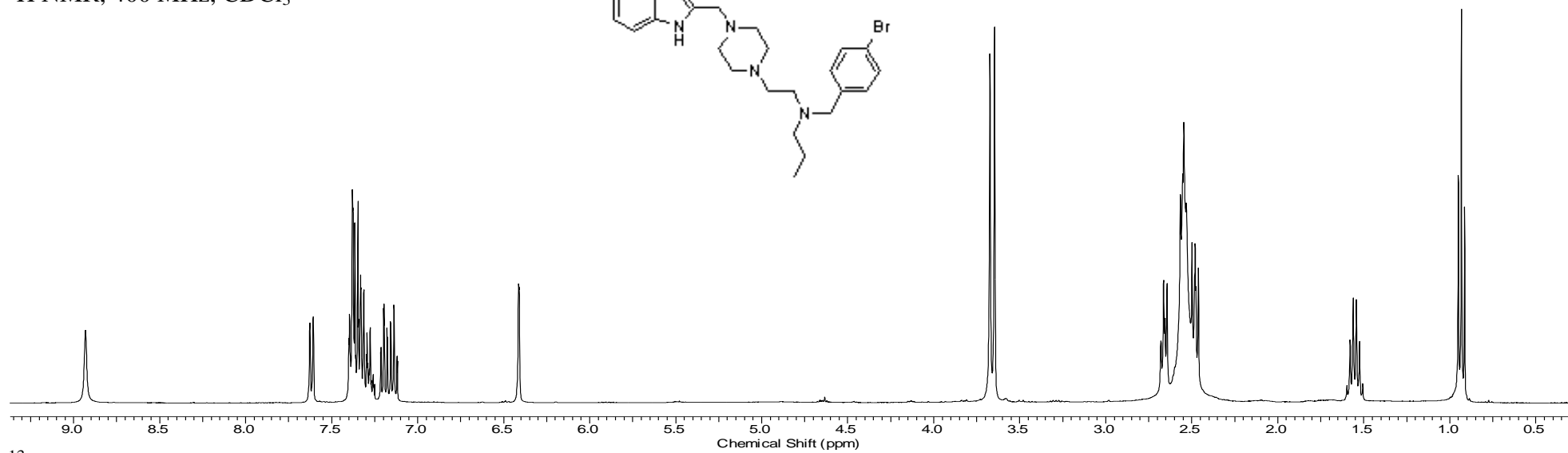
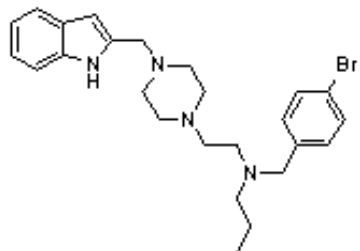


^{13}C NMR, 100 MHz, CDCl_3

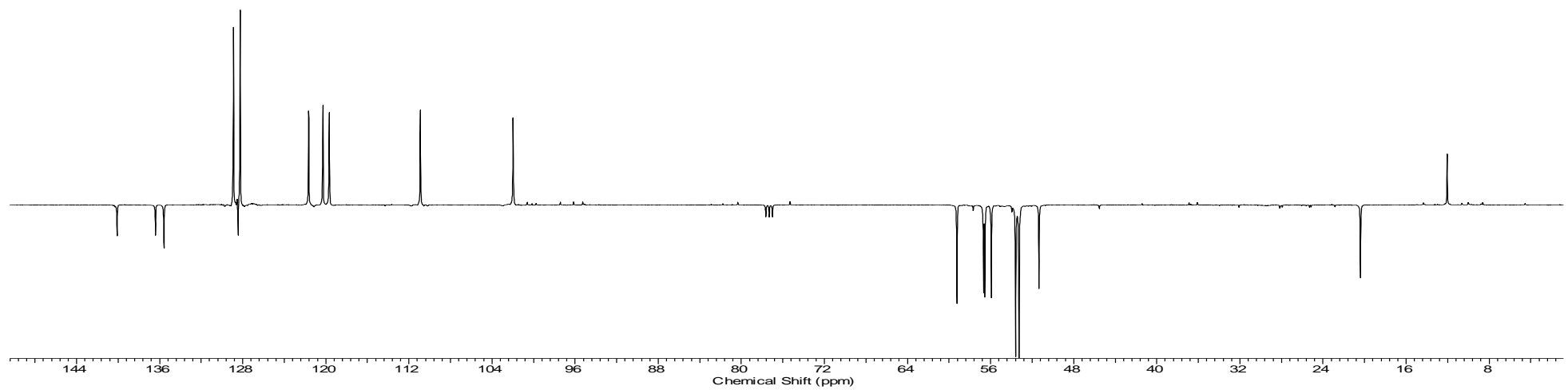


Compound 33

^1H NMR, 400 MHz, CDCl_3

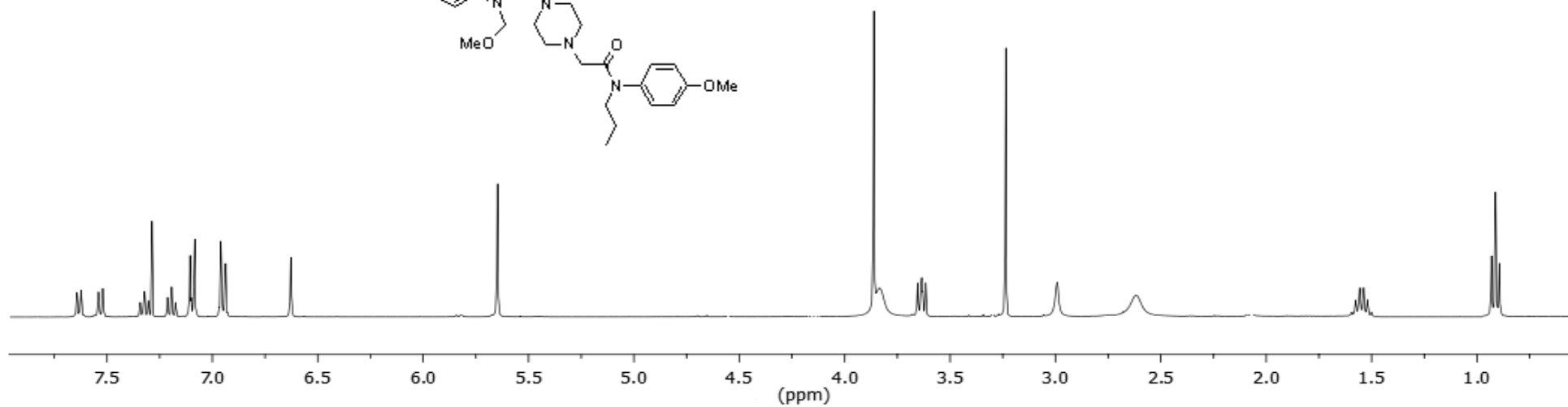
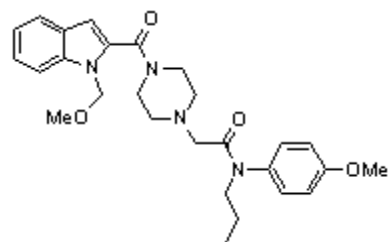


^{13}C NMR, 100 MHz, CDCl_3

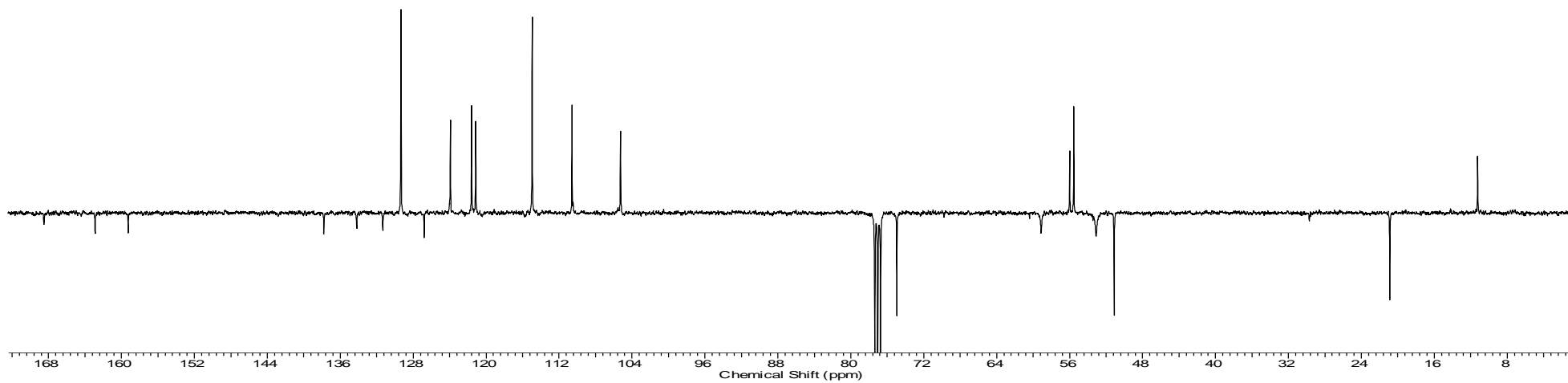


Compound 9

^1H NMR, 400 MHz, CDCl_3

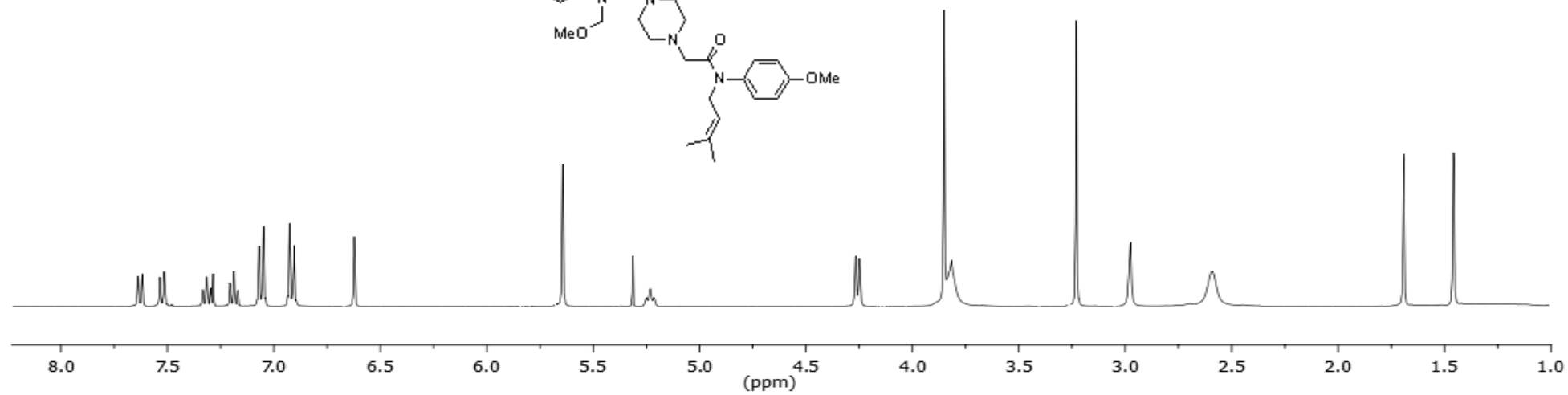
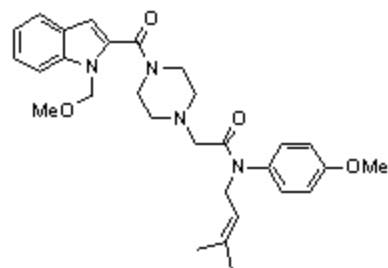


^{13}C NMR, 100 MHz, CDCl_3

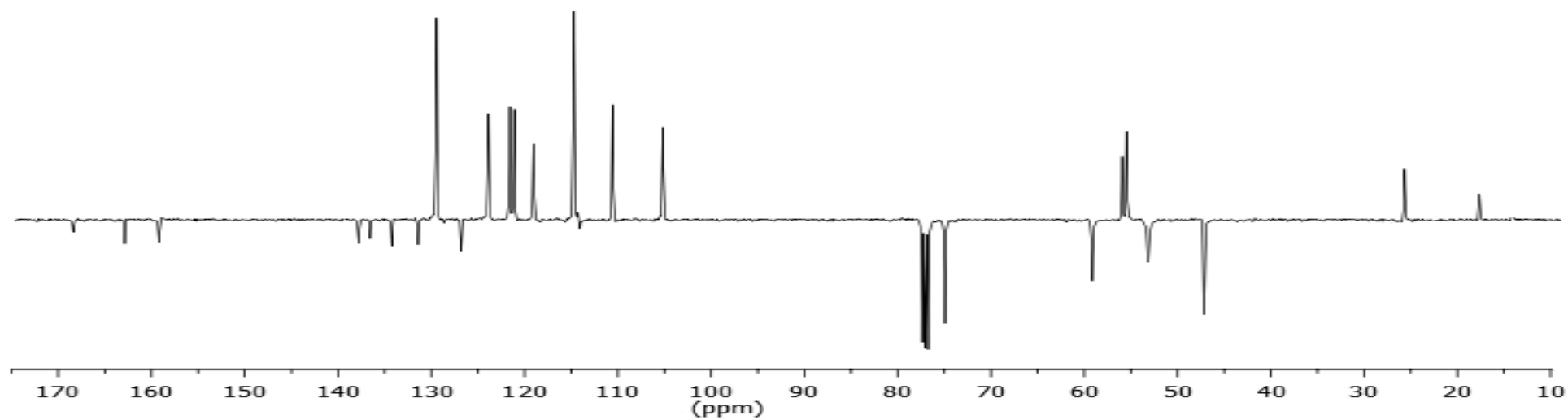


Compound 10

¹H NMR, 400 MHz, CDCl₃

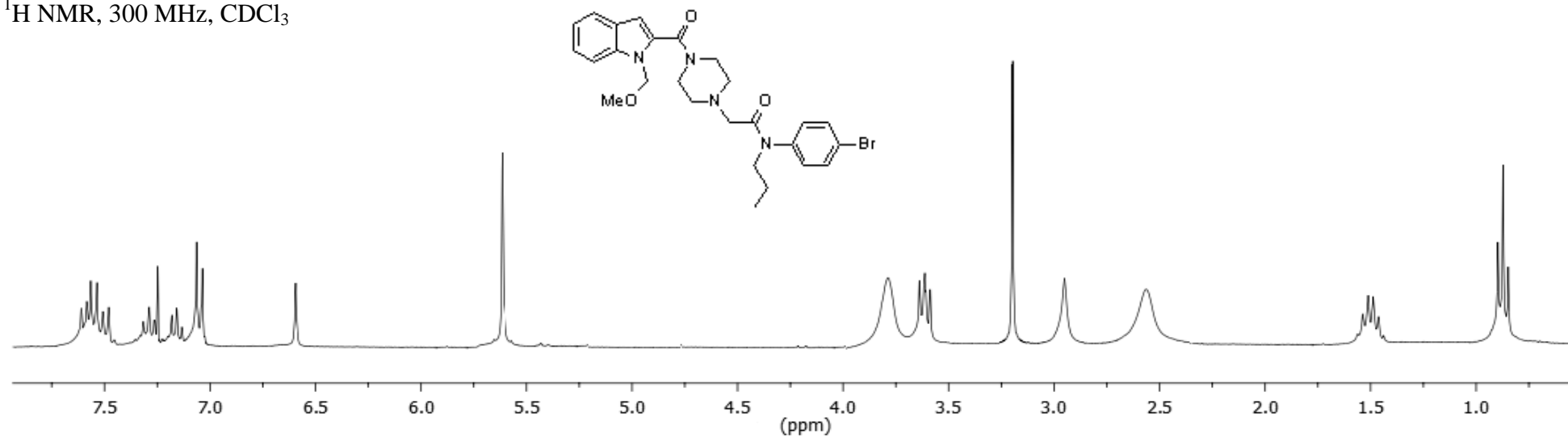


¹³C NMR, 100 MHz, CDCl₃

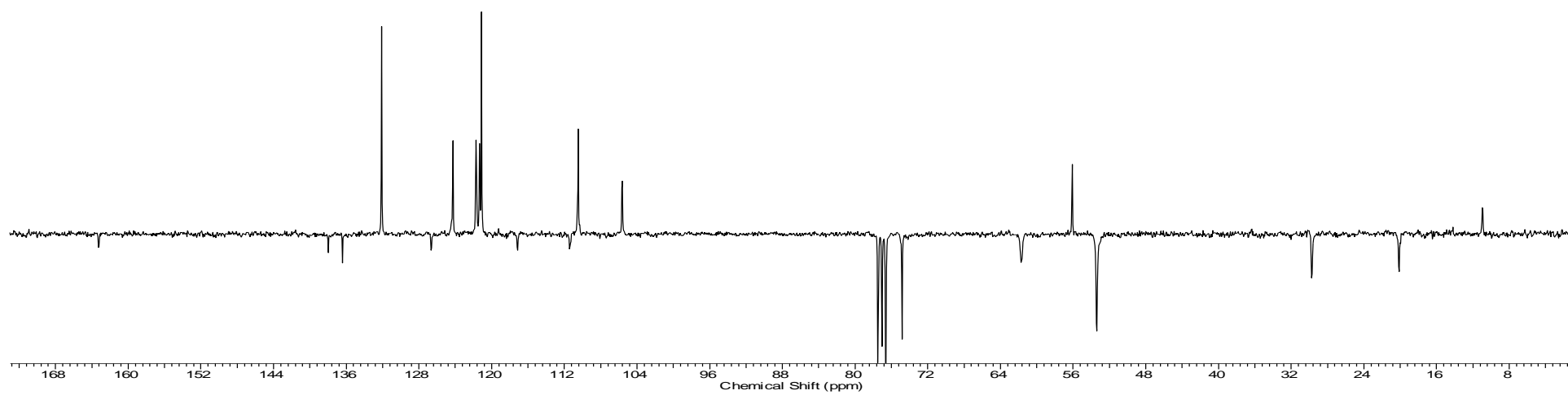


Compound 11

^1H NMR, 300 MHz, CDCl_3

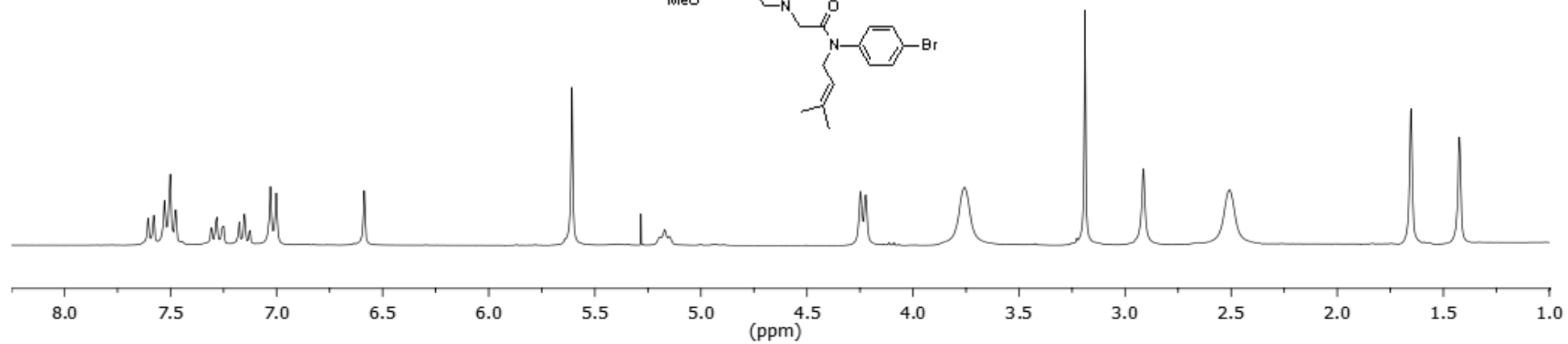
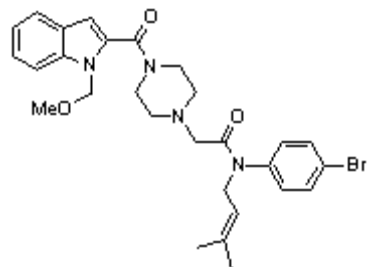


^{13}C NMR, 75 MHz, CDCl_3

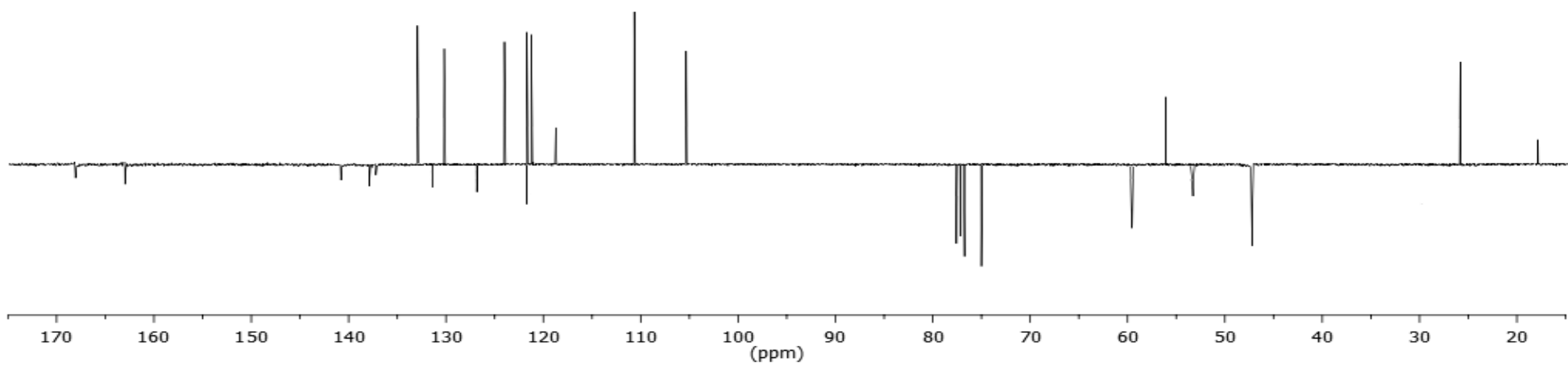


Compound 12

^1H NMR, 300 MHz, CDCl_3

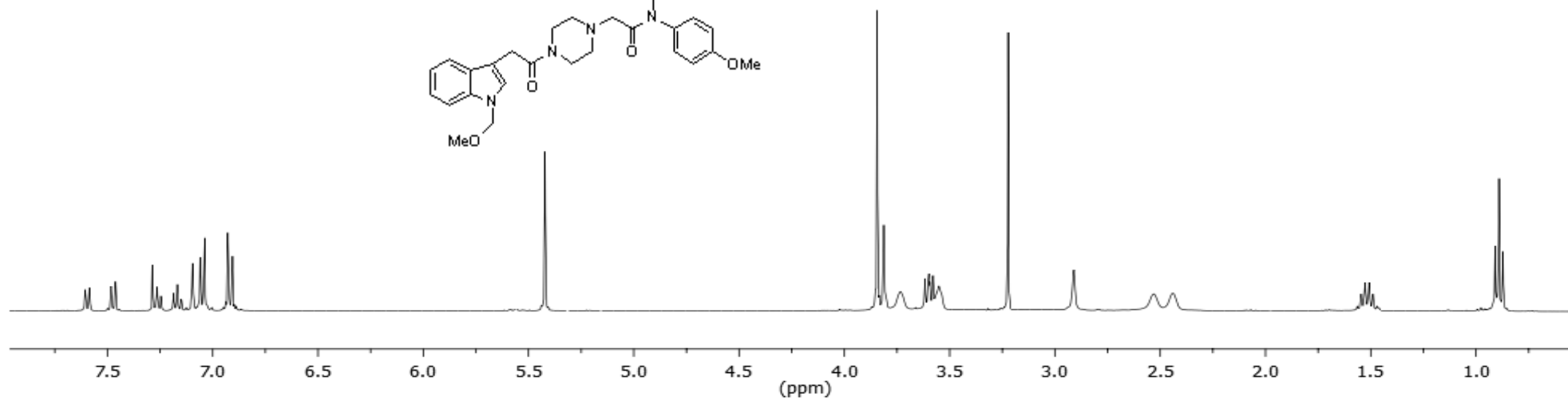
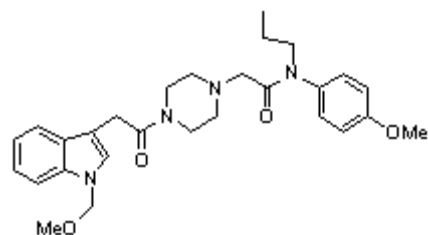


^{13}C NMR, 75 MHz, CDCl_3

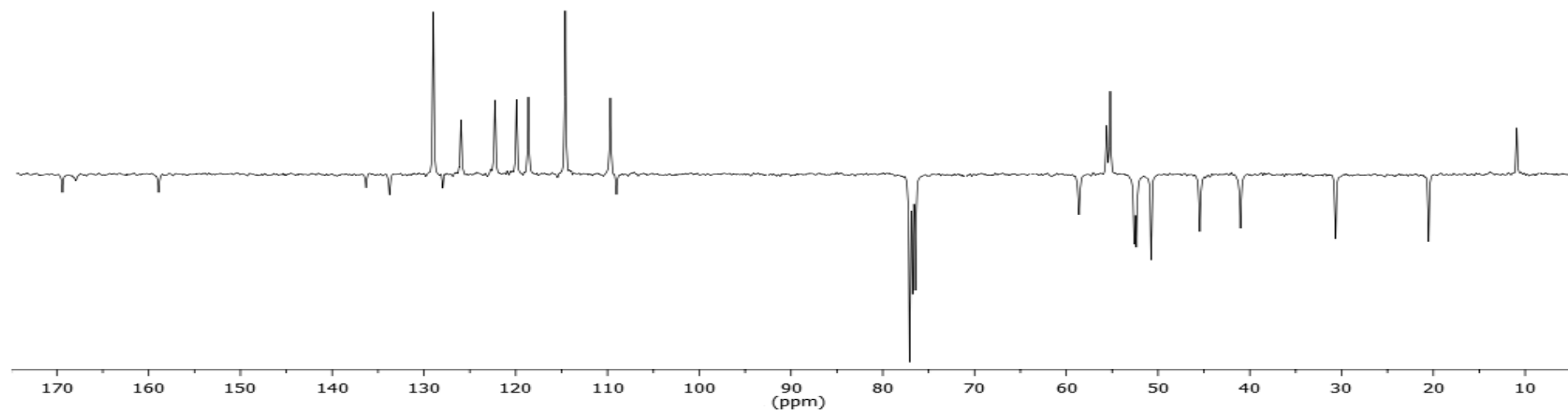


Compound 25

^1H NMR, 400 MHz, CDCl_3

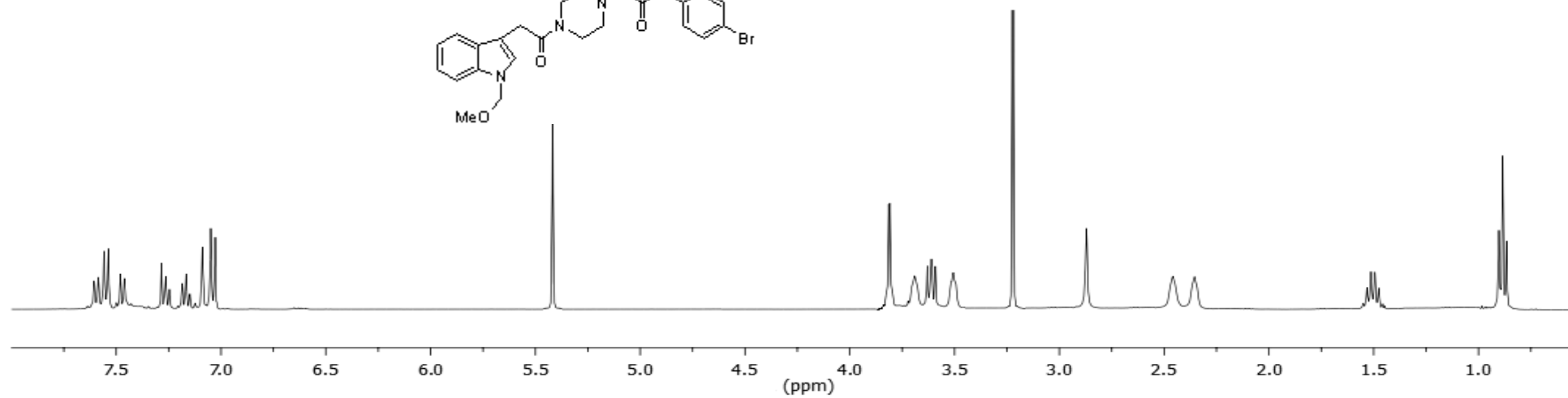
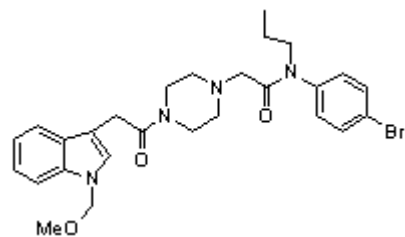


^{13}C NMR, 100 MHz, CDCl_3

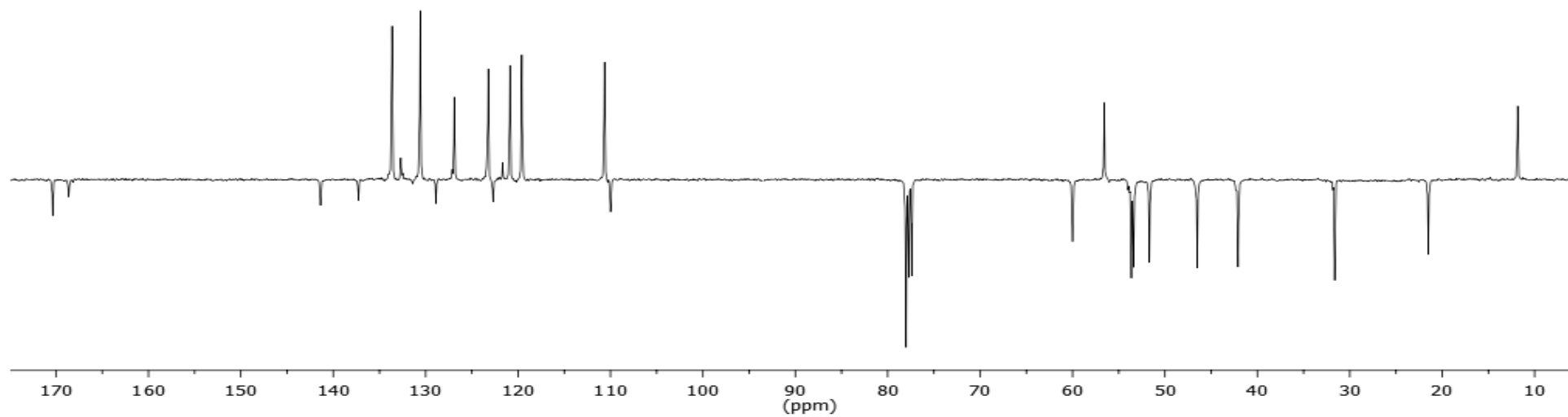


Compound 26

^1H NMR, 400 MHz, CDCl_3

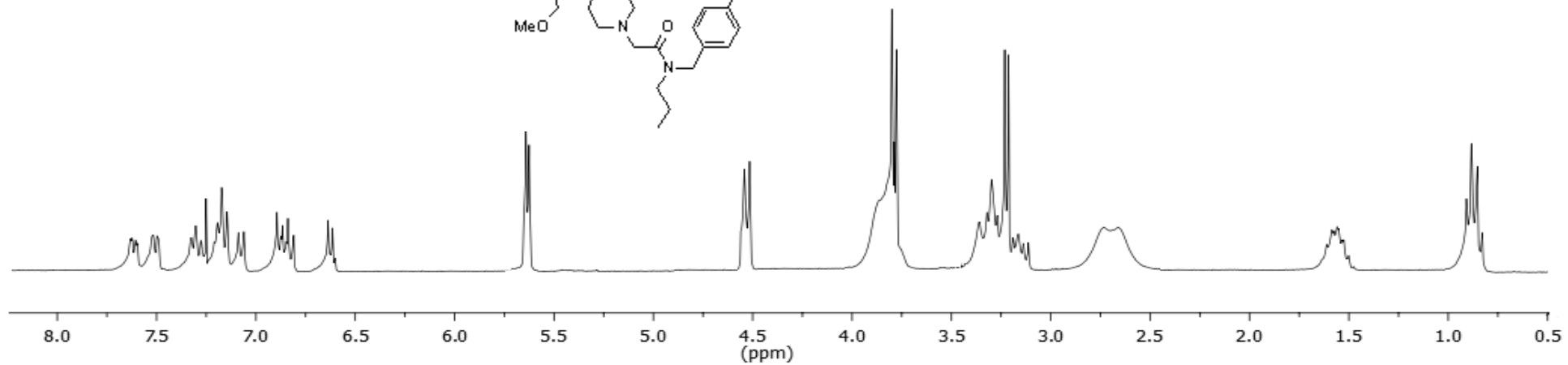
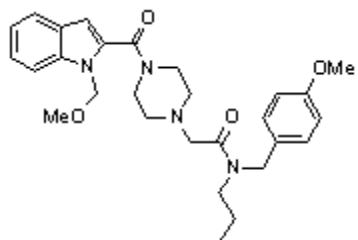


^{13}C NMR, 100 MHz, CDCl_3

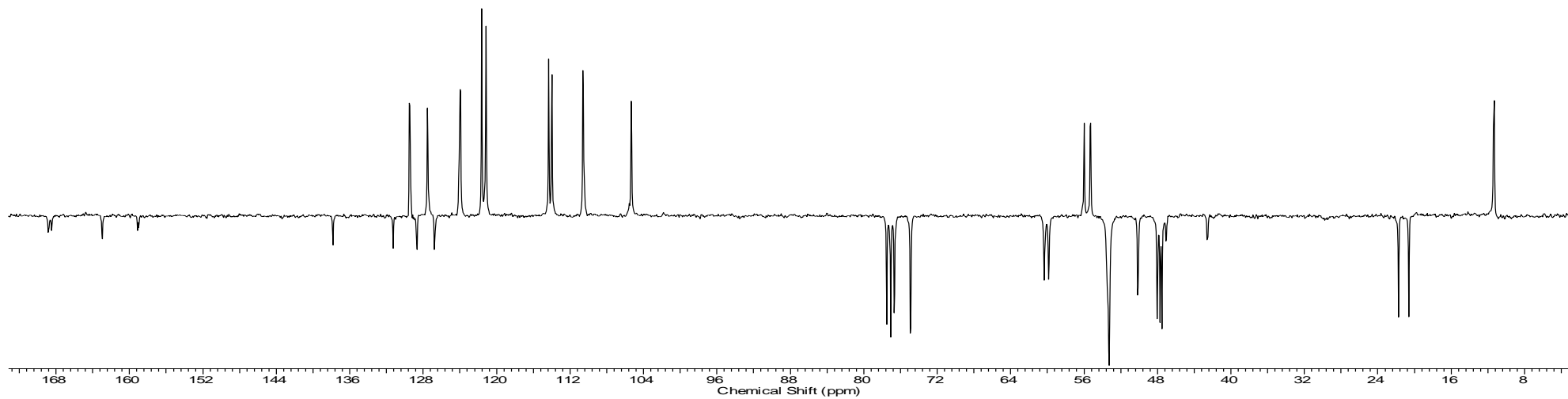


Compound 34

^1H NMR, 300 MHz, CDCl_3

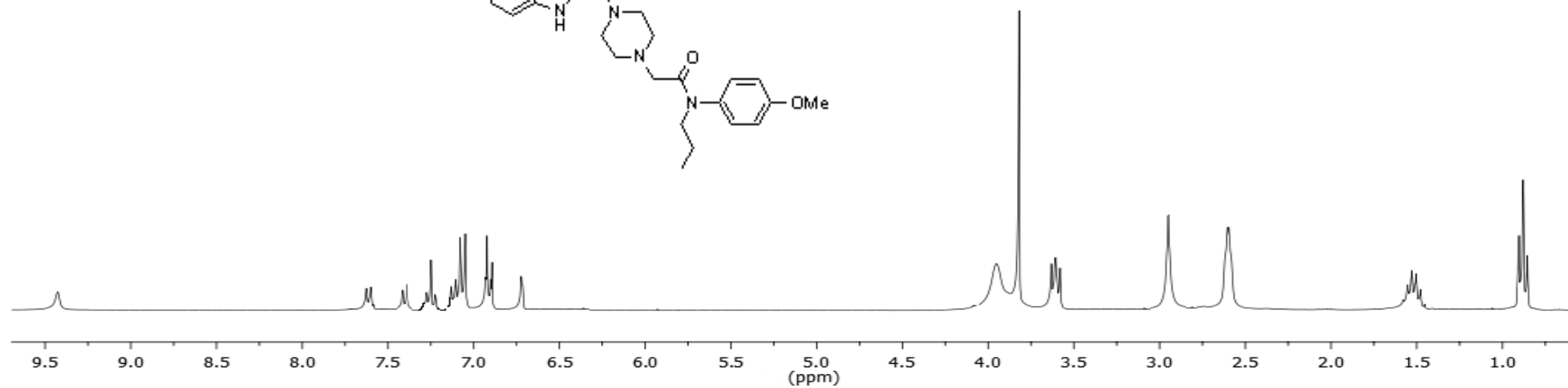
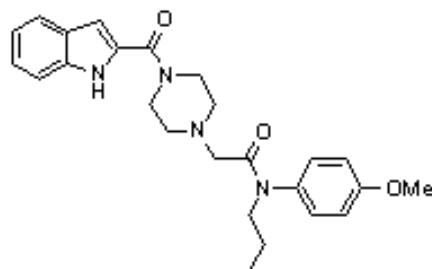


^{13}C NMR, 75 MHz, CDCl_3

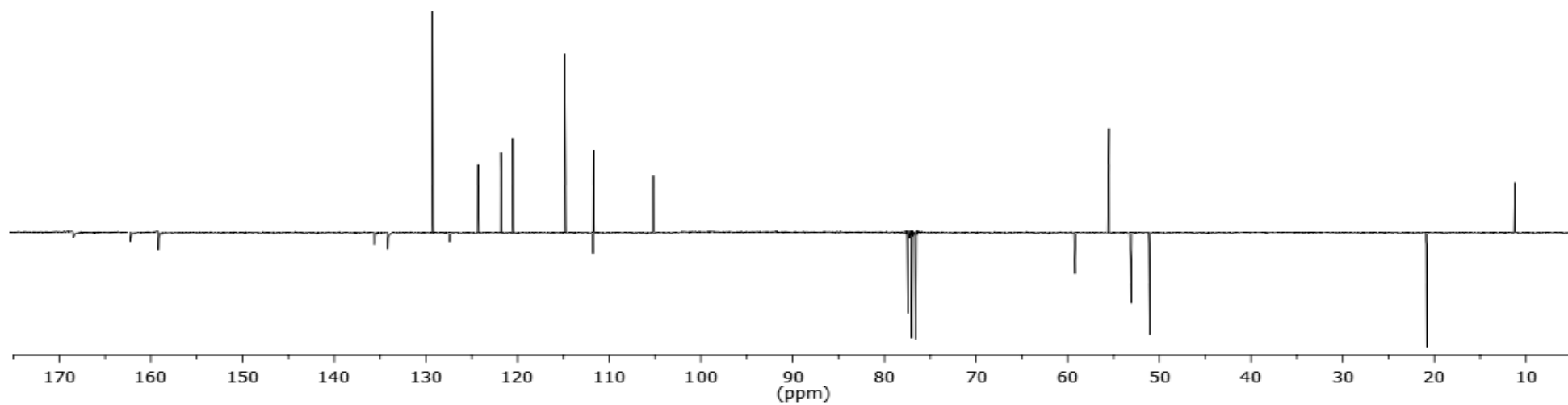


Compound 13

^1H NMR, 300 MHz, CDCl_3

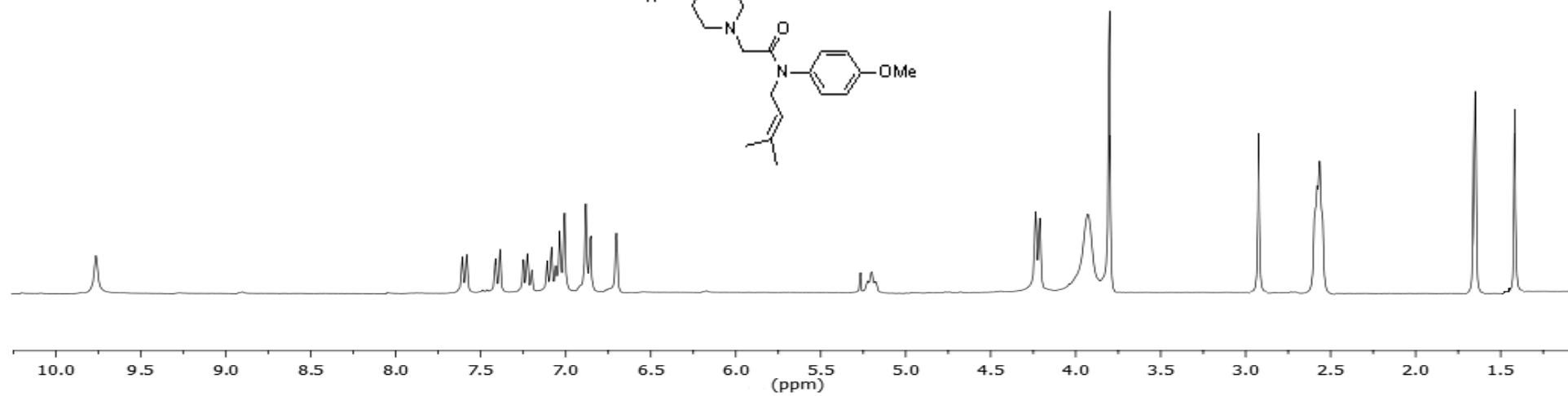
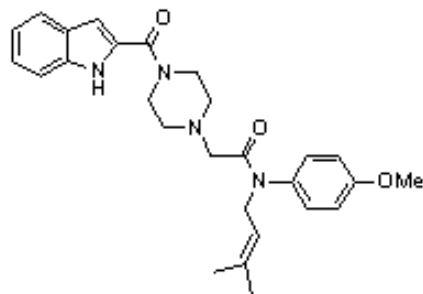


^{13}C NMR, 75 MHz, CDCl_3

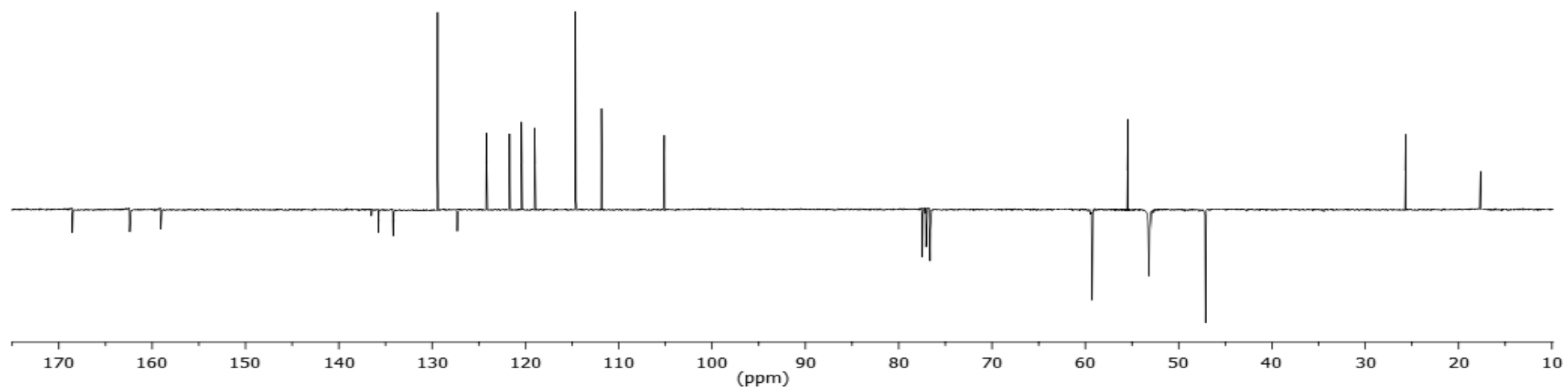


Compound 14

^1H NMR, 300 MHz, CDCl_3

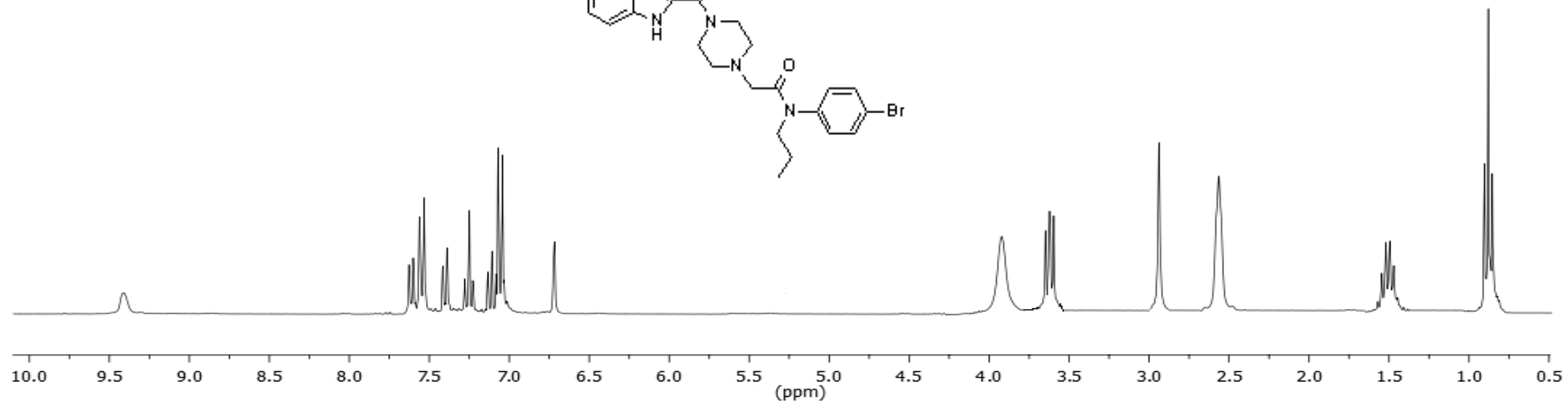
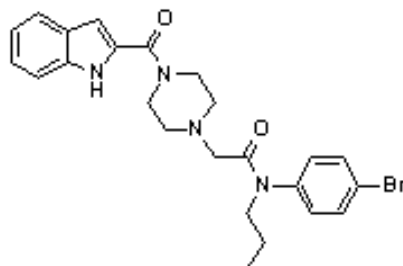


^{13}C NMR, 75 MHz, CDCl_3

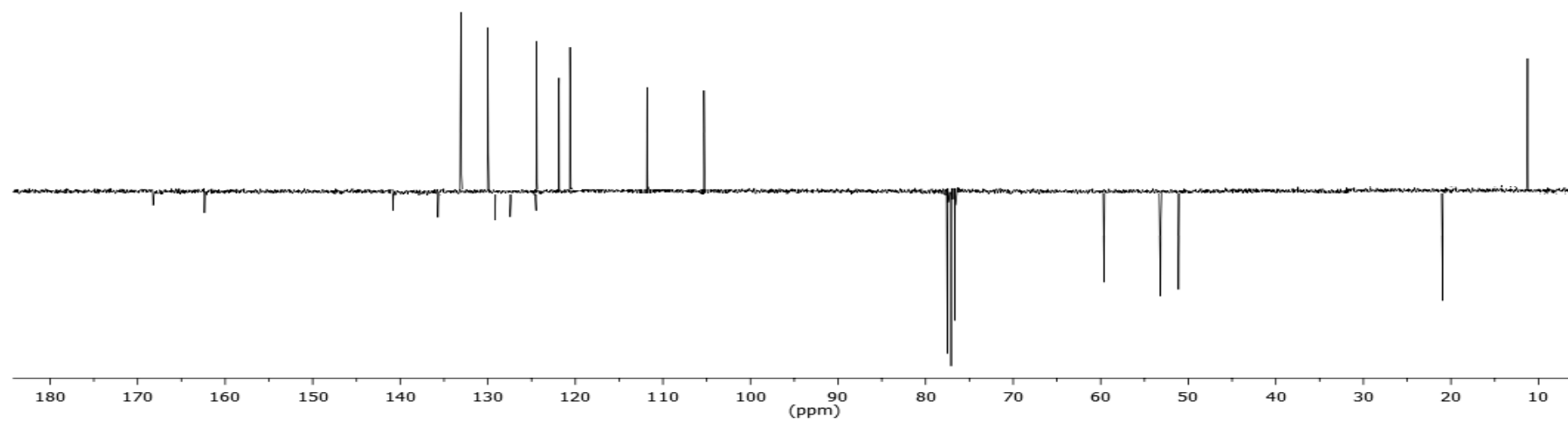


Compound 15

¹H NMR, 300 MHz, CDCl₃

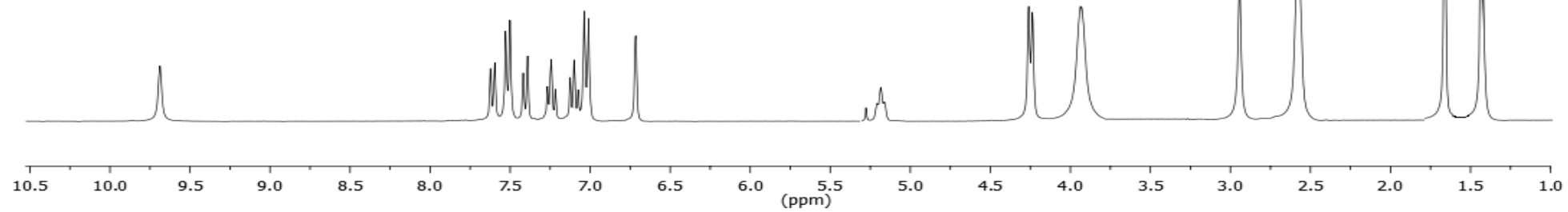
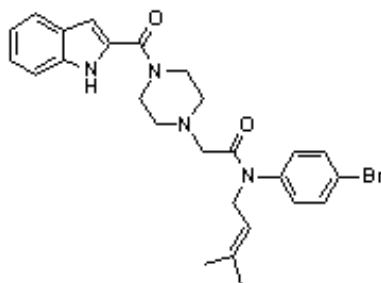


¹³C NMR, 75 MHz, CDCl₃

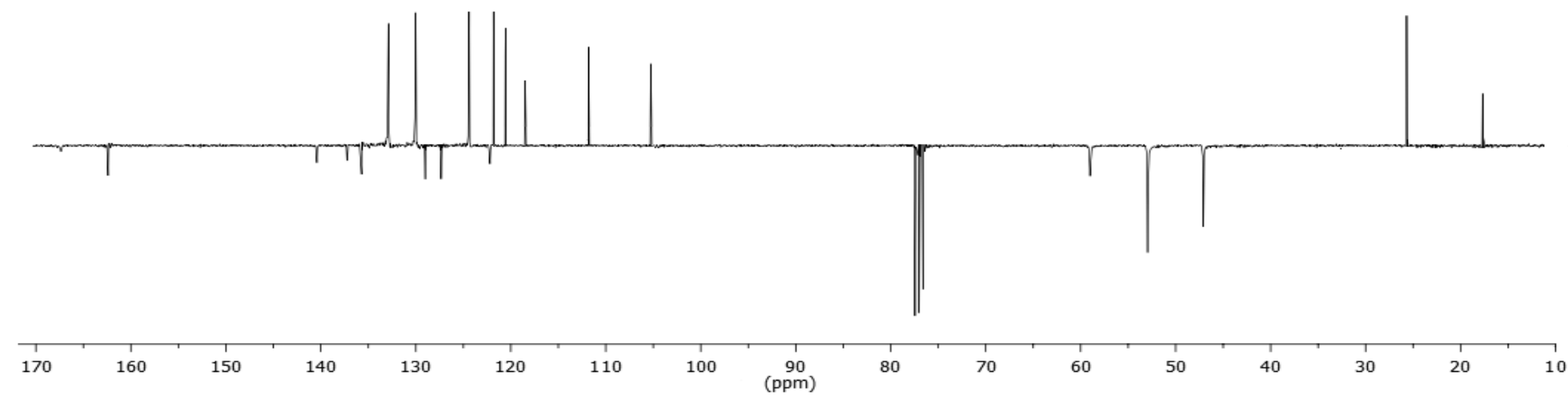


Compound 16

^1H NMR, 300 MHz, CDCl_3

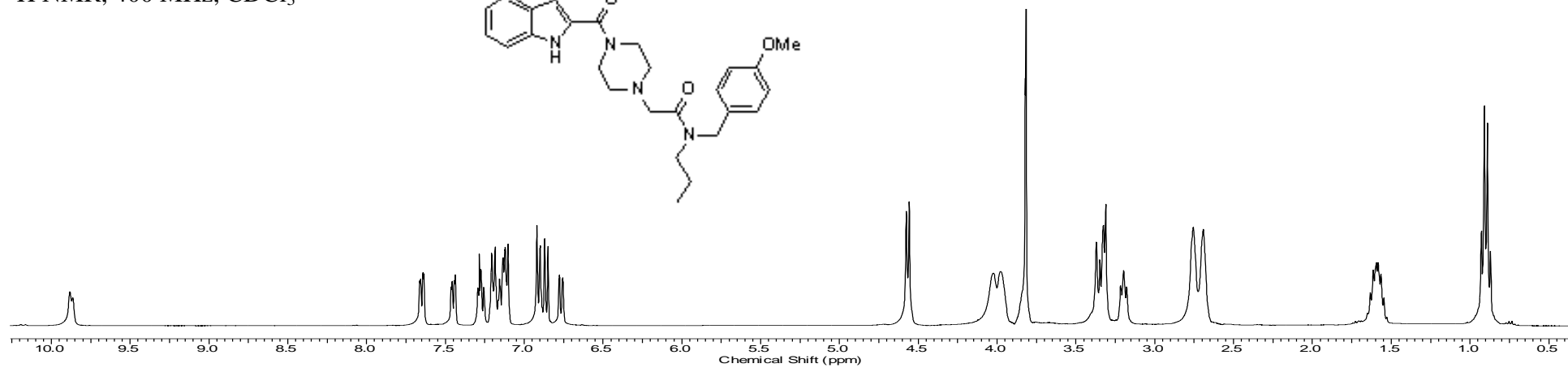
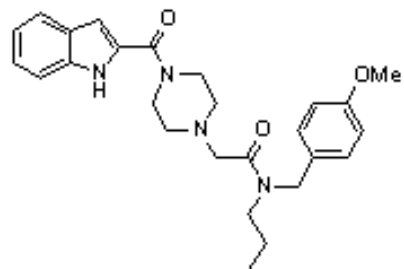


^{13}C NMR, 75 MHz, CDCl_3



Compound 35

^1H NMR, 400 MHz, CDCl_3



^{13}C NMR, 100 MHz, CDCl_3

