**Supporting Information**

# High-affinity small molecule inhibitors of the menin-Mixed Lineage Leukemia (MLL) interaction closely mimic a natural protein-protein interaction

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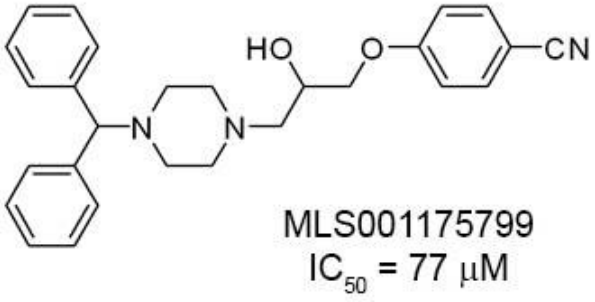
**Supplementary Figure 1.** Structure and activity of less potent HTS hit identified by screening for inhibitors of menin-MLL interaction.



**Supplementary Figure 2.** Structure and activity of the menin-MLL inhibitor **MIV-6**. a) Chemical structure of **MIV-6**. b) Titration curve from the competition FP experiment of **MIV-6R** with MLL for binding to menin. c) ITC titrations demonstrating direct binding of **MIV-6R** to menin.

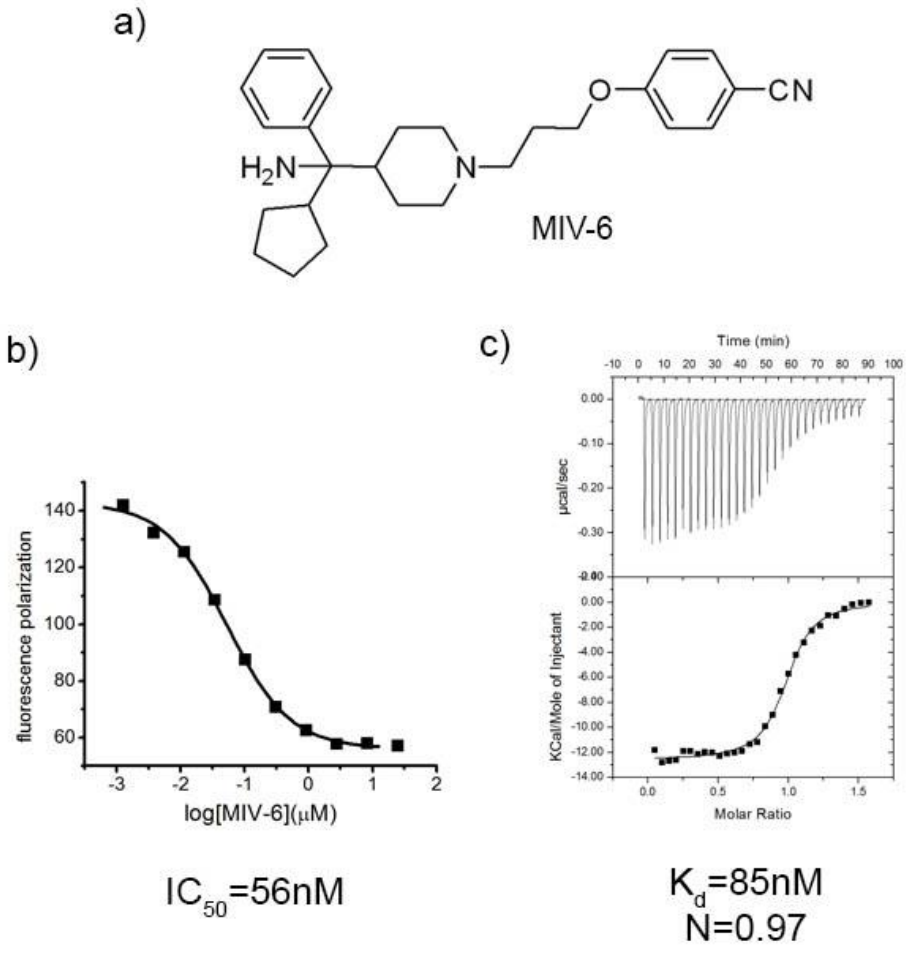
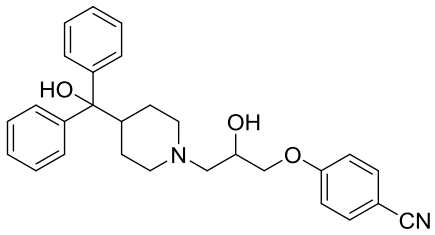


**Table S1**. Data collection and refinement statistics for menin-ligand complexes. Numbers in parenthesis refer to the highest resolution shell.

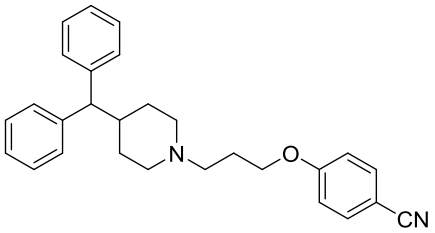
| **Structure** | **MIV-3S** | **MIV-3R** | **MIV-4** | **MIV-5** | **MIV-6** | **MIV-7** |
|---|---|---|---|---|---|---|
| **PDB code** | 4GO4 | 4GO3 | 4GO6 | 4GO5 | 4GO8 | 4GO7 |
| **Data collection** | | | | | | |
| Space group | P212121 | P212121 | P212121 | P212121 | P212121 | P212121 |
| Cell Dimensions | | | | | | |
| a, b, c (Å) | 48.9, 80.2, 124.7 | 48.9, 80.3, 124.7 | 48.6, 79.9, 124.5 | 48.7, 80.1, 124.5 | 48.8, 80.2, 124.7 | 48.0, 79.7, 124.8 |
| Solvent (%) | 45.2 | 45.2 | 44.5 | 44.8 | 45.1 | 43.9 |
| Resolution (Å) | 1.45 (1.48-1.45) | 2.01 (2.04-2.01) | 1.49 (1.52-1.49) | 1.63 (1.66-1.63) | 1.53 (1.56-1.53) | 2.08 (2.11-2.08) |
| Unique reflections | 87254 (4307) | 33475 (1648) | 74065 (3255) | 61076 (2957) | 73430 (3414) | 28805 (1401) |
| Total Reflections | 633852 | 242461 | 368758 | 410885 | 483441 | 189357 |
| $R_{sym}$ | 0.087 (0.700) | 0.145 (0.784) | 0.065 (0.596) | 0.068 (0.755) | 0.069 (0.584) | 0.125 (0.877) |
| $I / \sigma I$ | 36.5 (2.3) | 16.89 (2.45) | 22.85 (2.02) | 23.47 (2.03) | 28.38 (2.52) | 19.64 (2.21) |
| Completeness (%) | 100 (100) | 100 (100) | 92.8 (82.2) | 99.1 (98.4) | 98.5 (93.2) | 98.1 (99.3) |
| Redundancy | 7.3 (7.1) | 7.2 (7.2) | 5.0 (4.2) | 6.7 (6.4) | 6.6 (5.7) | 6.6 (6.3) |
| | | | | | | |
| **Refinement** | | | | | | |
| $R_{work}/R_{free}$ | 16.16/18.86 | 15.54/20.85 | 16.06/18.82 | 16.30/19.40 | 15.12/17.60 | 17.23/22.17 |
| No. atoms | | | | | | |
| Protein | 3742 | 3650 | 3763 | 3728 | 3742 | 3667 |
| Water | 461 | 322 | 463 | 373 | 429 | 168 |
| Mean B-factor ($Å^2$) | 25.07 | 26.3 | 19.98 | 24.08 | 20.16 | 34.97 |
| R.m.s. Dev. | | | | | | |
| Bond lengths (Å) | 0.018 | 0.018 | 0.017 | 0.017 | 0.016 | 0.017 |
| Bond angles(°) | 2.00 | 1.83 | 1.82 | 1.82 | 1.74 | 1.79 |
| **Ramachandran plot** | | | | | | |
| Most favored regions (%) | 98.06 | 98.27 | 98.27 | 98.06 | 98.06 | 98.06 |
| Additional allowed regions (%) | 1.94 | 1.73 | 1.73 | 1.94 | 1.94 | 1.94 |

**4. Procedures and Products**



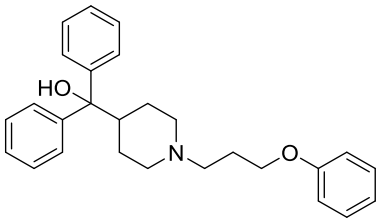

**4-(2-hydroxy-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propoxy)benzonitrile, 1 (MIV-1)**

In a round bottom flask equipped with a stir bar, diphenyl(piperidin-4-yl)methanol (500 mg, 1.77 mmol) was dissolved in DMF (3.54 mL). Potassium carbonate (294 mg, 2.12 mmol) was added in a single batch followed by epibromohydrin (291 mg, 2.12 mmol). The reaction mixture was warmed to 50 $^{o}$C and stirred for 6 h. 4-hydroxybenzonitrile (264 mg, 2.21 mmol) was then added in a single batch, and stirring was continued at 50 $^{o}$C for 18 h. The reaction was quenched with $H_2O$ and extracted with EtOAc. The combined organic layers were washed with brine, and dried over $Na_2SO_4$. Concentration *in vacuo* afforded the crude product as an oil, which was purified by flash chromatography (9:1 $CH_2Cl_2$/MeOH) to provide the desired product at as a clear amorphous solid in 509 mg (65%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (2H, d, *J* = 9 Hz), 7.47 (4H, d, *J* = 7.6 Hz), 7.30 (4H, t, *J* = 8 Hz), 7.19 (2H, t, *J* = 7.5 Hz), 6.96 (2H, d, *J* = 9 Hz), 4.07 (1H, m), 3.99 (2H, m), 3.05 (1H, d, *J* = 11 Hz), 2.89 (1H, d, *J* = 11 Hz), 2.49 (3H, m), 2.33 (2H, m), 2.05 (1H, dt, *J* = 11.5, 3 Hz), 1.53 (3H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.1, 145.9,134.1, 128.4, 126.8, 125.8, 119.3, 115.5, 104.4, 79.6, 70.7, 65.3, 60.5, 56.0, 52.9, 44.0, 26.7, 26.4; HRMS (ES+, M+H) calc. for $C_{28}H_{31}N_2O_3$: 443.2335, found: 443.2334



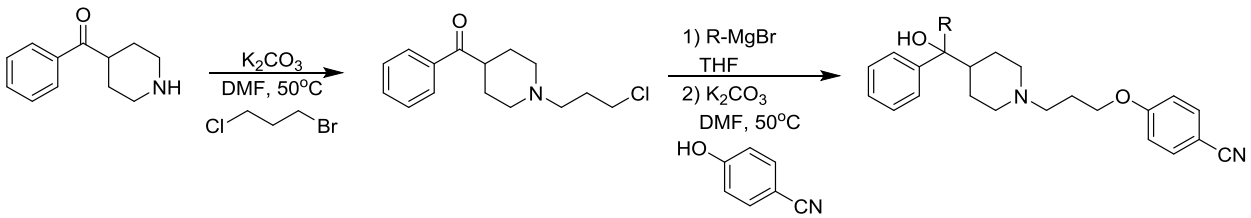

**4-(3-(4-benzhydrylpiperidin-1-yl)propoxy)benzonitrile, 3.**

In a round bottom flask equipped with a stir bar, 4-benzhydrylpiperidine (2.1 g, 8.46 mmol) was combined with $K_2CO_3$ (6.9 g, 50 mmol) in DMF (40 mL), followed by 1-bromo-3-chloropropane (1.6 g, 10 mmol). The reaction progress was monitored by LC-MS, and upon full consumption of starting material, 4-cyanophenol (1.3 g, 11 mmol) was added and the reaction allowed to stir overnight. The mixture was poured onto water and extracted with EtOAc, washed with brine and dried over $Na_2SO_4$. The volatiles were removed under reduced pressure and the crude mixture purified on silica gel (9:1 $CH_2Cl_2$/MeOH) to afford 2.7 g (78%) of 4-(3-(4-benzoylpiperidin-1-yl)propoxy)benzonitrile: $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (2H, d, *J* = 8.7 Hz), 7.29 (8H, m), 7.12 (2H, m), 6.94 (2H, m), 4.05 (2H, t, *J* = 6.5 Hz), 3.52 (1H, d, *J* = 10.9 Hz), 2.90 (2H, d, *J* = 11.7 Hz), 2.50 (2H, t, *J* = 7.2 Hz), 2.14 (1H, m), 1.97 (4H, m), 1.59 (2H, d, *J* = 13 Hz), 1.26 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.5, 143.9, 134.1, 128.6, 128.2, 126.3, 119.4, 115.3, 103.9, 66.9, 59.0, 55.4, 54.2, 39.7, 31.5, 26.8; HRMS (ES+, M+H) calc. for $C_{28}H_{30}N_2O$: 411.2436, found: 411.2434

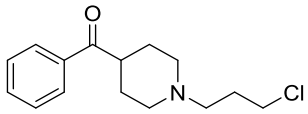



**(1-(3-phenoxypropyl)piperidin-4-yl)diphenylmethanol, 4.**

In a round bottom flask equipped with a stir bar, diphenyl(piperidin-4-yl)methanol (300 mg, 1.06 mmol) was dissolved in DMF (3.0 mL). Potassium carbonate (295 mg, 2.13 mmol) was added in a single batch followed by 1-bromo-3-chloropropane (184 mg, 1.17 mmol). The mixture was stirred for 6 h, at which point starting material was consumed by TLC observation. Phenol (190 mg, 1.60 mmol) was added to the stirring mixture, and the mixture was warmed to 50 $^{o}$C and stirred for 18 h. The reaction mixture was quenched with $H_2O$, and extracted with EtOAc. Combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration *in vacuo* afforded the crude product, which was purified by flash chromatography (9:1 $CH_2Cl_2$/MeOH) to provide the desired product in 399 mg (88%) as a white powder. $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51 (4H, d, *J* = 7.5 Hz), 7.31 (6H, m), 7.21 (2H, t, *J* = 7.5 Hz), 6.95 (1H, t, *J* = 7.5 Hz), 6.90 (2H, d, *J* = 8.2 Hz), 4.02 (2H, t, *J* = 6 Hz), 3.09 (2H, d, *J* = 11.5 Hz), 2.61 (2H, t, *J* = 7.4 Hz), 2.50 (1H, m), 2.16-2.00 (4H, m), 1.61 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 159.0, 146.1, 129.6, 128.4, 126.7, 120.8, 114.6, 79.6, 66.2, 55.5, 54.2, 44.1, 26.8, 26.2; HRMS (ES+, M+H) calc. for $C_{27}H_{32}NO_2$: 402.2433, found: 402.2433




**Scheme 1**. Synthesis of hydroxymethyl piperidine analogs 2, 5-10, 12.



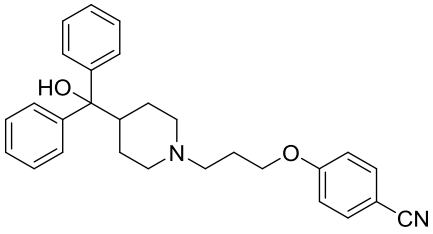

**(1-(3-chloropropyl)piperidin-4-yl)(phenyl)methanone, 23a.**

To a solution of phenyl(piperidin-4-yl)methanone (500 mg, 2.64 mmol) in dry DMF (8.8 mL) was added potassium carbonate (803 mg, 5.81 mmol) followed by 1-bromo-3-chloropropane (500 mg, 3.17 mmol). Mixture was warmed to 50 $^{o}$C and stirred for 4 h. The reaction was quenched with $H_2O$ and extracted three times with EtOAc. The organic layers were combined and washed with sat. aqueous NaCl, then dried over $Na_2SO_4$ and filtered. Concentration *in vacuo* provided the crude product which was purified by flash chromatography (9:1 $CH_2Cl_2$/MeOH) to yield the desired product in 533 mg (75%) as a white powder. $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (2H, d, *J* = 7.7 Hz), 7.54 (1H, t, *J* = 7.7 Hz), 7.45 (2H, t, *J* = 7.7 Hz), 3.59 (2H, t, *J* = 6.1 Hz), 3.23 (1H, m), 2.96 (2H, m), 2.49 (2H, t, *J* = 7.2 Hz), 2.11 (2H, td, *J* = 11.2, 3.5 Hz), 1.95 (2H, quintet, *J* = 6.6 Hz), 1.84 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 202.6, 136.0, 132.8, 128.6, 127.8, 55.5, 53.3, 43.6, 43.2, 30.0, 28.7; HRMS (ES+, M+H) calc. for $C_{15}H_{21}NOCl$: 266.1312, found: 266.1312

**General Procedure A:**

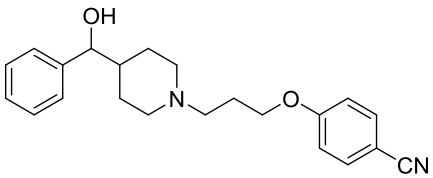
A solution of (1-(3-chloropropyl)piperidin-4-yl)(phenyl)methanone (100 mg, 0.35 mmol) in THF (1.4 mL) was cooled to 0 $^{o}$C. To this was added organomagnesium halide (2 equiv.) dropwise with stirring. The solution was then slowly warmed to ambient temperature, and stirring continued for 2 h, at which point starting material was consumed by TLC analysis. The reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layers were combined and dried over $Na_2SO_4$. Solution was then transferred to a round-bottom flask,

concentrated *in vacuo* to remove solvent, and then dissolved in DMF (1.0 mL). $K_2CO_3$ (98 mg) was added, followed by 4-hydroxybenzonitrile (63 mg, 0.53 mmol). Mixture was warmed to 50 $^oC$ and stirred for 6 h. The reaction mixture was quenched with $H_2O$ and extracted with EtOAc. The organic layers were combined and washed with sat. aqueous NaCl and dried over $Na_2SO_4$. Concentration *in vacuo* provided the crude product, which was purified by flash chromatography (9:1 $CH_2Cl_2$/MeOH) to provide the desired products **4-10, 13**.



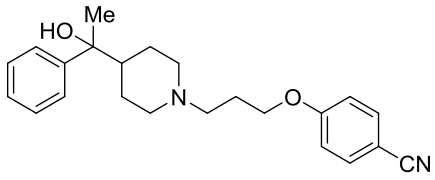

**4-(3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propoxy)benzonitrile, 2, MIV-2.**

Phenylmagnesium bromide (3.0 M in $Et_2O$) was used as described in general procedure A to provide the desired product in 99 mg (66%): $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, *J* = 8.7 Hz), 7.48 (4H, d, *J* = 7.7 Hz), 7.30 (4H, t, *J* = 7.7 Hz), 7.18 (2H, t, *J* = 7.7 Hz), 6.92 (2H, d, *J* = 8.7 Hz), 4.03 (2H, t, *J* = 6.2 Hz), 2.98 (2H, d, *J* = 11.8 Hz), 2.47 (3H, m), 2.30 (1H, br s), 1.98 (4H, m), 1.51 (4H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 146.05, 134.1, 128.4, 126.7, 125.9, 119.4, 115.3, 103.8, 79.6, 66.8, 55.1, 54.3, 44.2, 26.7, 26.5; HRMS (ES+, M+H) calc. for $C_{28}H_{31}N_2O_2$: 427.2386, found: 427.2390



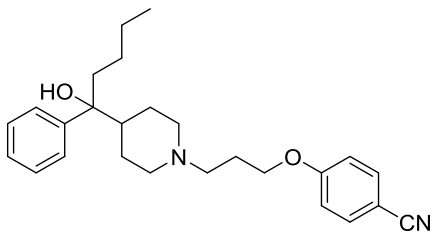

**4-(3-(4-(hydroxy(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 5.**

Cycolhexylmagnesium bromide (18% in THF) was used as described in general procedure A to provide the desired product in 36 mg (30%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, *J* = 8 Hz), 7.32 (5H, m), 6.92 (2H, d, *J* = 8 Hz), 4.38 (1H, d, *J* = 8 Hz), 4.03 (2H, t, *J* = 6 Hz), 3.02 (1H, d, *J* = 11 Hz), 2.89 (2H, d, *J* = 11 Hz), 1.96 (7H, m), 1.63 (1H, m), 1.46 (1H, m), 1.29 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.3, 143.3, 134.1, 128.5, 127.8, 126.7, 119.4, 115.3, 103.9, 78.9, 66.8, 55.3, 53.8, 53.7, 43.2, 28.5, 28.4, 26.6; HRMS (ES+, M+H) calc. for $C_{22}H_{27}N_2O_2$: 351.2073, found: 351.2074



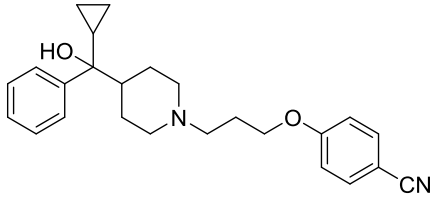

**4-(3-(4-(1-hydroxy-1-phenylethyl)piperidin-1-yl)propoxy)benzonitrile, 6.**

Methylmagnesium Bromide (3.0 M in $Et_2O$) was used as described in general procedure A to provide the desired product in 73 mg (58%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, *J* = 8.5 Hz), 7.40 (2H, d, *J* = 7.8 Hz), 7.33 (2H, t, *J* = 7.5 Hz), 7.24 (1H, t, *J* = 7.4 Hz), 6.92 (2H, d, *J* = 9 Hz), 4.02 (2H, t, *J* = 6.4 Hz), 2.97 (2H, t, *J* = 12 Hz), 2.47 (2H, t, *J* = 7.4 Hz), 1.97 (2H, m), 1.88 (2H, m), 1.63 (2H, m), 1.56 (3H, s), 1.51 (1H, m), 1.41 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 147.4, 134.0, 128.1, 126.8, 125.4, 119.4, 115.3, 103.9, 76.1, 66.9, 55.2, 54.3, 47.4, 26.7, 26.7, 26.6, 26.6; HRMS (ES+, M+H) calc. for $C_{23}H_{29}N_2O_2$: 365.2229, found: 365.2228



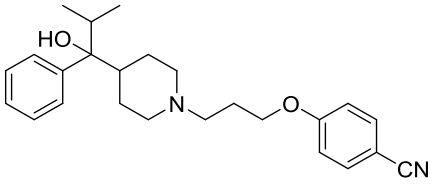
**4-(3-(4-(1-hydroxy-1-phenylpentyl)piperidin-1-yl)propoxy)benzonitrile, 7.**

*n*-Butylmagnesium chloride (2.0 M in THF) was used as described in general procedure A to provide the desired product in 64 mg (45%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (2H, d, *J* = 8 Hz), 7.33 (4H, m), 7.21 (1H, m), 6.91 (2H, d, *J* = 9.1 Hz), 4.02 (2H, t, *J* = 6.4 Hz), 3.01 (1H, d, *J* = 11.2 Hz), 2.90 (1H, d, *J* = 11.2), 2.45 (2H, t, *J* = 7.2 Hz), 1.95 (3H, m), 1.82 (4H, m), 1.62 (1H, m), 1.39 (3H, m), 1.25 (3H, m), 0.92 (1H, m), 0.82 (3H, t, *J* = 7.2 Hz); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.5, 145.1, 134.1, 128.0, 126.4, 125.9, 119.4, 115.3, 103.9, 78.4, 66.9, 55.2, 54.3, 46.9, 39.0, 26.7, 26.5, 26.1, 25.7, 23.3, 14.1; HRMS (ES+, M+H) calc. for $C_{26}H_{35}N_2O_2$: 407.2699, found: 407.2701



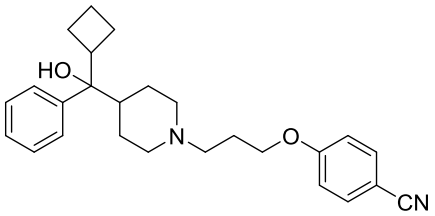

**4-(3-(4-(cyclopropyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 8.**

Cyclopropylmagnesium bromide (0.5 M in THF) was used as described in general procedure A to provide the desired product in 74 mg (56%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, *J* = 9 Hz), 7.45 (2H, d, *J* = 8 Hz), 7.33 (2H, t, *J* = 7.5 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 6.92 (2H, d, *J* = 9 Hz), 4.03 (2H, t, *J* = 6.2 Hz), 3.01 (1H, d, *J* = 11 Hz), 2.95 (1H, d, *J* = 11 Hz), 2.48 (2H, t, *J* = 7.2 Hz), 1.94 (4H, m), 1.79 (2H, m), 1.49 (3H, m), 1.35 (1H, m), 0.60 (1H, m), 0.53 (1H, m), 0.32 (1H, m), 0.09 (1H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 146.8, 134.1, 128.1, 134.1, 128.0, 126.7, 125.7, 119.4, 115.3, 103.9, 75.9, 66.9, 55.2, 54.4, 54.3, 48.0, 26.8, 26.7, 26.6, 18.2, 2.7, -0.1; HRMS (ES+, M+H) calc. for $C_{25}H_{31}N_2O_2$: 391.2386, found: 391.2383




**4-(3-(4-(1-hydroxy-2-methyl-1-phenylpropyl)piperidin-1-yl)propoxy)benzonitrile, 9.**

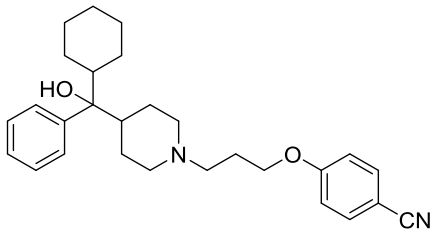
Isopropylmagnesium chloride (2.0 M in THF) was used as described in general procedure A to provide the desired product in 56 mg (41 %): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (2H, d, *J* = 9 Hz), 7.32 (4H, m), 7.21 (1H, t, *J* = 7 Hz), 6.90 (2H, d, *J* = 9 Hz), 4.00 (2H, t, *J* = 6 Hz), 3.00 (1H, d, *J* = 11.5 Hz), 2.97 (1H, d, *J* = 11.5 Hz), 2.50 (2H, t, *J* = 7 Hz), 2.32 (1H, sept, *J* = 7 Hz), 2.05-1.84 (6H, m), 1.45 (1H, m), 1.25 (3H, m), 0.87 (3H, d, *J* = 7 Hz), 0.76 (3H, d, *J* = 7 Hz); $^{13}$C NMR (125.8 MHz, $CDCl_3$) δ (ppm): 162.4, 142.8, 134.1, 127.7, 126.6, 126.5, 119.4, 115.3, 103.9, 80.3, 66.8, 55.2, 54.3, 54.2, 42.9, 33.3, 26.5, 25.9, 17.4, 16.4; HRMS (ES+, M+H) calc. for $C_{25}H_{33}N_2O_2$: 393.2542, found: 393.2542




**4-(3-(4-(cyclobutyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 10.**

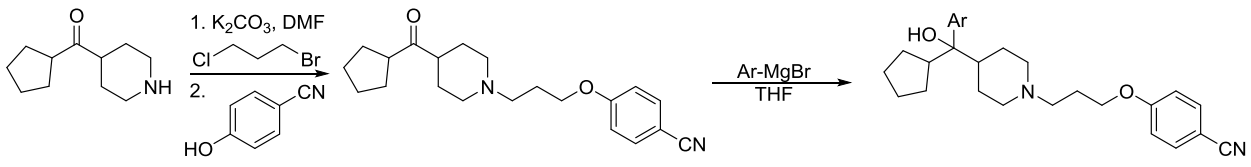
Cyclobutylmagnesium Bromide (0.2 M in THF) was prepared by dissolving cyclobutyl bromide (150 mg, 1.1 mmol) in THF (5.0 mL), followed by addition of magnesium (25 mg, 1.1 mmol) and a catalytic amount of iodine. The mixture was stirred for 2 h at ambient temperature, and was used as described in general procedure A to provide the desired product in 85 mg (60 %): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (2H, d, *J* = 8 Hz), 7.34 (2H, d, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 7.20 (1H, t, *J* = 7 Hz), 6.90 (2H, d, *J* = 9 Hz), 4.00 (2H, t, *J* = 6 Hz), 3.14 (1H, pent, *J* = 9 Hz), 2.97 (1H, d, *J* = 11 Hz), 2.89 (1H, d, *J* = 11 Hz), 2.44 (2H, t, *J* = 7.5 Hz), 2.14

(1H, pent, *J* = 9 Hz), 1.94 (4H, m), 1.80 (4H, m), 1.59 (4H, m), 1.41 (1H, m), 1.28 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 143.8, 134.1, 127.9, 126.6, 126.3, 119.2, 115.3, 103.9, 73.3, 68.8, 55.2, 54.3, 54.2, 45.5, 42.6, 26.9, 26.6, 26.4, 23.4, 23.1, 17.6; HRMS (ES+, M+H) calc. for $C_{26}H_{33}N_2O_2$: 405.2542, found: 405.2539

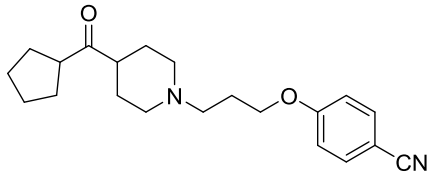



**4-(3-(4-(cyclohexyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 12.**

Cycolhexylmagnesium bromide (18% in THF) was used as described in general procedure A to provide the desired product in 59 mg (39%): $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (2H, d, *J* = 9 Hz), 7.31 (4H, m), 7.22 (1H, t, *J* = 7.5 Hz), 6.90 (2H, d, *J* = 9 Hz), 4.01 (2H, t, *J* = 6.5 Hz), 3.00 (1H, d, *J* = 11 Hz), 2.94 (1H, d, *J* = 11 Hz), 2.46 (2H, t, *J* = 7 Hz), 2.00-1.60 (12H, m), 1.50 (1H, d, *J* = 12 Hz), 1.29 (5H, m), 0.97 (2H, m), 0.77 (1H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 143.2, 134.1, 127.7, 126.5, 126.4, 119.4, 115.5, 103.9, 80.2, 68.9, 55.3, 54.4, 54.3, 44.2, 42.4, 27.5, 26.9, 26.8, 26.7, 26.6, 26.5, 26.4, 25.9; HRMS (ES+, M+H) calc. for $C_{28}H_{37}N_2O_2$: 433.2855, found: 433.2854




**Scheme 2.** Synthesis of hydroxymethyl piperidine derivatives 11, 13-17.



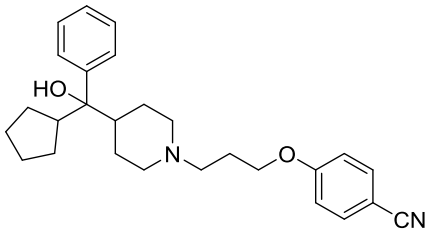

**4-(3-(4-(cyclopentanecarbonyl)piperidin-1-yl)propoxy)benzonitrile, 25.**

Cyclopentyl(piperidin-4-yl)methanone (2.70 g, 10.0 mmol) was combined with $K_2CO_3$ (6.9 g, 50.0 mmol) in DMF (40.0 mL), followed by 1-bromo-3-chloropropane (1.55 g, 10.0 mmol). The reaction progress was monitored by LC-MS and upon completion of the reaction 4-cyanophenol (1.3 g, 11.0 mmol) was added and the reaction allowed to stir overnight. The mixture was poured onto water and extracted with EtOAc, washed with brine and dried over $Na_2SO_4$. The volatiles were removed under reduced pressure and the crude mixture purified on silica gel (9:1 $CH_2Cl_2$/MeOH) to provide the desired product in 2.71g (78%) as a light yellow oil: $^1$H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.56 (2H, d, *J* = 9.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz), 4.05 (2H, t, *J* = 6.5 Hz), 3.00 (1H, quintet, *J* = 7.7 Hz), 2.94 (2H, m), 2.49 (2H, t, *J* = 7.1 Hz), 2.42 (1H, m), 1.99 (4H, m), 1.79 (4H, m), 1.68 (6H, m), 1.56 (2H, m); $^{13}$C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 215.7, 162.5, 134.1, 119.4, 115.3, 103.9, 66.8, 55.1, 53.4, 49.4, 48.2, 29.5, 28.1, 26.7, 26.2; HRMS (ES+, M+H) calc. for $C_{21}H_{29}N_2O_2$: 341.2229, found: 341.2228

**General procedure B:**

4-(3-(4-(cyclopentanecarbonyl)piperidin-1-yl)propoxy)benzonitrile (30 mg, 0.09 mmol) was dissolved in THF (0.7 mL). Organometallic (2 equiv.) was added dropwise to the solution with stirring. Reaction was then warmed to 50 °C, and stirring was continued for 2 h. Reaction was quenched with sat. aqueous $NH_4Cl$, and extracted with EtOAc. The combined organic fractions

were washed with saturated NaCl and dried over $Na_2SO_4$. Concentration *in vacuo* provided the crude product, which was purified by flash column chromatography (9:1 $CH_2Cl_2$/MeOH) to provide the desired products in 35 – 74% yield.

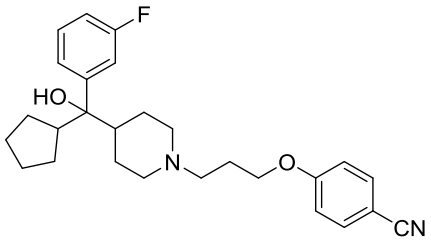



**4-(3-(4-(cyclopentyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 11 (MIV-3)**

Phenylmagnesium bromide (1.0 M in THF) was used as described in general procedure B to provide the desired product in 46 mg (74%): Chiral Separation: Semi-preparative purifications were carried out via stacked injections on a Waters Investigator SFC using a 10 x 250 mm Chiral Technologies CHIRALPAK IA column heated to 40 °C. The eluent was 55% EtOH (0.1% DEA) in $CO_2$ at a flow rate of 15 mL/minute. Backpressure was maintained at 100 bar. The *first* eluting peak (**11S**), retention time = 0.95 min was inferred as the *S* stereoisomer based upon the absolute configuration observed in the electron density map of the X-ray structure of the **MIV-3S**-Menin complex. The *second* eluting peak (11R), retention time = 2.3 min. was inferred as the *R* stereoisomer based upon the absolute configuration observed in the electron density map of the X-ray structure of the **MIV-3R**-Menin complex.

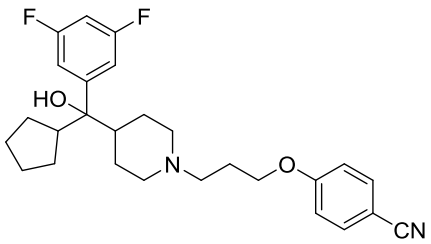
$^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (2H, d, *J* = 9 Hz), 7.37 (2H, d, *J* = 8 Hz), 7.30 (2H, t, *J* = 8 Hz), 7.22 (1H, t, *J* = 7 Hz), 6.88 (2H, d, *J* = 9 Hz), 4.07 (2H, t, *J* = 6 Hz), 3.21 (2H, m), 2.67 (3H, m), 2.19 (2H, m), 2.05 (2H, m), 1.95 (1H, m), 1.82 (1H, m), 1.72 (1H, m), 1.64 (1H, m), 1.59-1.40 (7H, m), 1.25 (1H, m), 1.07 (1H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 143.9, 134.0, 127.7, 126.5, 126.4, 119.4, 115.3, 103.8, 79.6, 68.9, 55.2, 54.5, 54.4, 45.8,

45.3, 27.5, 27.3, 26.7, 26.4, 26.1, 26.0, 25.6; HRMS (ES+, M+H) calc. for $C_{27}H_{35}N_2O_2$: 419.2699, found: 419.2698



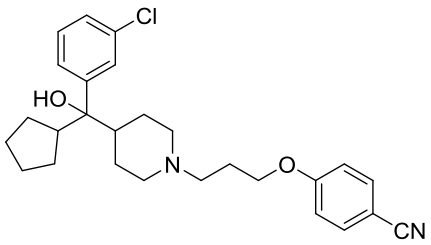

**4-(3-(4-(cyclopentyl(3-fluorophenyl)(hydroxy)methyl)piperidin-1-yl)propoxy)benzonitrile, 13 (MIV-4).**

3-Fluorophenylmagnesium bromide (1.0 M in THF) was used as described in general procedure B to provide the desired product in 22 mg (57%): $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, *J* = 9 Hz), 7.26 (1H, m), 7.13 (2H, m), 6.90 (3H, m), 4.02 (2H, t, *J* = 6 Hz), 3.06 (2H, m), 2.66 (1H, quintet, *J* = 8.5 Hz), 2.55 (2H, m), 2.03 (3H, m), 1.93 (1H, d, *J* = 13 Hz), 1.71 (4H, m), 1.57 (1H, m), 1.47 (6H, m), 1.10 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.8 (d, $J_{CF}$ = 247 Hz), 162.3, 146.8 (d, $J_{CF}$ = 6 Hz), 134.1, 129.1 (d, $J_{CF}$ = 8 Hz), 122.3 (d, $J_{CF}$ = 3 Hz), 119.4, 115.3, 114.1 (d, $J_{CF}$ = 24 Hz), 113.4 (d, $J_{CF}$ = 21 Hz), 103.9, 79.4, 66.7, 55.1, 54.2, 54.1, 46.0, 45.2, 27.4, 26.8, 26.3, 26.1, 26.0, 25.9, 25.5; HRMS (ES+, M+H) calc. for $C_{27}H_{34}N_2O_2F$: 437.2604, found: 437.2604



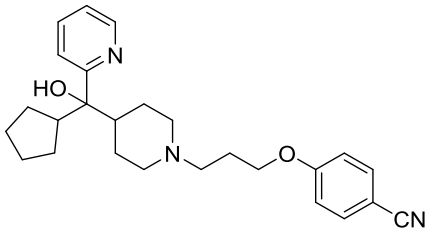

**4-(3-(4-(cyclopentyl(3,5difluorophenyl)(hydroxy)methyl) piperidin-1-yl)propoxy)benzonitrile, 14.**

3,5-Difluorophenylmagnesium bromide (0.5 M in THF) was used as described in general procedure B to provide the desired product in 15 mg (36%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (2H, d, *J* = 9 Hz), 6.91 (4H, t, *J* = 8 Hz), 6.66 (1H, tt, *J* = 9.0, 2.2 Hz), 4.00 (2H, t, *J* = 6.3 Hz), 2.99 (2H, d, *J* = 11 Hz), 2.60 (1H, quintet, *J* = 9 Hz), 2.47 (2H, t, *J* = 7 Hz), 1.93 (5H, m), 1.75 (1H, m), 1.68-1.32 (10H, m), 1.05 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.83 (dd, $J_{CF}$ = 247, 12 Hz), 162.3, 148.6 (t, $J_{CF}$ = 8 Hz), 134.1, 119.4, 115.3, 109.8 (d, $J_{CF}$ = 24 Hz), 104.0, 102.0 (t, $J_{CF}$ = 24 Hz), 79.5, 77.3, 66.7, 55.2, 54.2, 54.1, 46.1, 45.4, 27.3, 26.9, 26.4, 26.2, 25.9, 25.5; HRMS (ES+, M+H) calc. for $C_{27}H_{33}N_2O_2F_2$: 455.2510, found: 455.2513



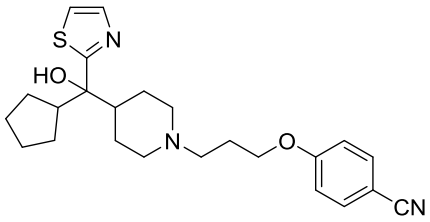

**4-(3-(4-((3-chlorophenyl)(cyclopentyl)(hydroxy)methyl) piperidin-1-yl)propoxy)benzonitrile, 15.**

3-Chlorophenylmagnesium bromide (0.5 M in THF) was used as described in general procedure B to provide the desired product in 24 mg (60%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (2H, d, *J* = 8.7 Hz), 7.42 (1H, s), 7.26 (2H, t, *J* = 7.6 Hz), 7.22 (1H, m), 6.92 (2H, d, *J* = 8.7 Hz), 4.02 (2H, t, *J* = 6.3 Hz), 2.97 (2H, d, *J* = 11 Hz), 2.70 (1H, quintet, *J* = 9 Hz), 2.47 (2H, t, *J* = 7 Hz), 1.95 (5H, m), 1.76 (1H, m), 1.71-1.41 (9H, m), 1.29 (1H, m), 1.04 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 162.4, 146.2, 134.1, 133.9, 128.9, 127.0, 126.8, 125.0, 119.4, 115.3, 103.9, 79.5, 66.8, 55.2, 54.3, 54.2, 45.9, 45.3, 27.5, 27.1, 26.5, 26.3, 26.1, 26.0, 25.6; HRMS (ES+, M+H) calc. for $C_{27}H_{34}N_2O_2Cl$: 453.2309, found: 453.2305




**4-(3-(4-(cyclopentyl(hydroxy)(pyridin-2-yl)methyl)piperidin-1-yl)propoxy)benzonitrile, 16 (MIV-5).**

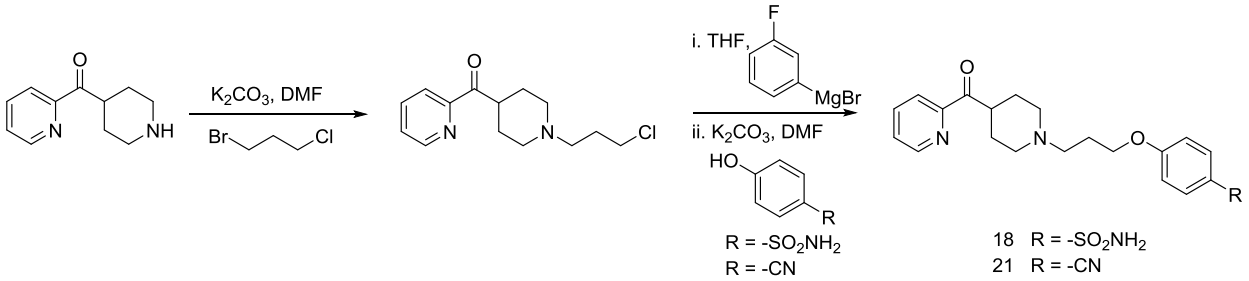
2-Pyridylmagnesium bromide (0.25 M) was used as described in general procedure B to provide the desired product in 13 mg (35%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.52 (1H, d, *J* = 5 Hz), 7.70 (2H, t, *J* = 8 Hz), 7.57 (2H, d, *J* = 8 Hz), 7.31 (1H, d, *J* = 8 Hz), 7.21 (1H, dd, *J* = 8, 5 Hz), 6.92 (2H, d, *J* = 8 Hz), 5.72 (1H, br s), 4.03 (2H, t, *J* = 6 Hz), 3.03 (1H, m), 2.56 (3H, m), 2.09-1.75 (7H, m), 1.65 (2H, m), 1.49 (4H, m), 1.15 (2H, m), 0.76 (1H, m); $^{13}$C NMR (125.8 MHz, $CDCl_3$) δ (ppm): 162.2, 161.5, 147.0, 136.6, 134.1, 122.2, 121.1, 119.3, 115.3, 104.1, 78.1, 66.6, 55.1, 54.3, 54.2, 45.8, 45.4, 29.8, 27.1, 26.5, 26.1, 25.7; HRMS (ES+, M+H) calc. for $C_{26}H_{34}N_3O_2$: 420.2651, found: 420.2650



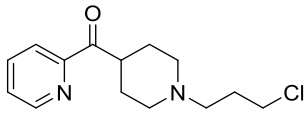

**4-(3-(4-(cyclopentyl(hydroxy)(thiazol-2-yl)methyl)piperidin-1-yl)propoxy)benzonitrile, 17.**

Thiazol-2-yllithium (0.15 M in THF) was prepared by dissolving 2-bromothiazole (72.2 mg, 0.44 mmol) in THF and cooling to -78 °C. *n*-Butyllithium (0.18 mL, 2.5 M in hexanes) was slowly added, and then stirred for 20 min. at -78 °C. The solution was then used as described in general procedure B to provide the desired product in 47 mg (75%): $^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (1H, d, *J* = 3.2 Hz), 7.54 (2H, d, *J* = 8.7 Hz), 7.28 (1H, d, *J* = 3.2 Hz), 6.91 (2H, d, *J*

= 8.7 Hz), 4.02 (2H, t, *J* = 6 Hz), 3.40 (1H, br s), 3.03 (2H, d, *J* = 11.2 Hz), 2.55 (3H, m), 2.05-1.85 (6H, m), 1.75 (2H, m), 1.47 (8H, m), 1.21 (1H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 175.7, 162.3, 114.6, 134.1, 141.6, 134.1, 119.4, 119.2, 115.3, 103.9, 80.9, 66.8, 55.1, 54.1, 47.5, 45.1, 26.7, 26.4, 26.3, 26.0, 25.8, 25.5; HRMS (ES+, M+H) calc. for $C_{24}H_{32}N_3O_2S$: 426.2215, found: 426.2212



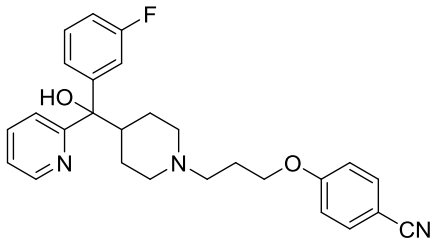

**Scheme 3.** Synthesis of **18** and **21**



**(1-(3-chloropropyl)piperidin-4-yl)(pyridin-2-yl)methanone, 23b.**

To a solution of piperidin-4-yl(pyridin-2-yl)methanone (791 mg, 2.72 mmol) in dry DMF (9.1 mL) was added potassium carbonate (1.13 g, 8.16 mmol) followed by 1-bromo-3-chloropropane (514 mg, 3.26 mmol). Mixture was warmed to 50 $^{o}$C and stirred for 4 h. The reaction was quenched with $H_2O$ and extracted three times with EtOAc. The organic layers were combined and washed with sat. aqueous NaCl, then dried over $Na_2SO_4$ and filtered. Concentration *in vacuo* provided the crude product which was purified by flash chromatography (9:1 $CH_2Cl_2$/MeOH) to yield the desired product in 790 mg (83%) as a light yellow oil: $^{1}$H NMR (400MHz,$CDCl_3$) δ (ppm): 8.66 (1H, d, *J* = 4.4 Hz), 8.01 (1H, d, *J* = 8.3 Hz), 7.82 (1H, t, *J* = 7.8

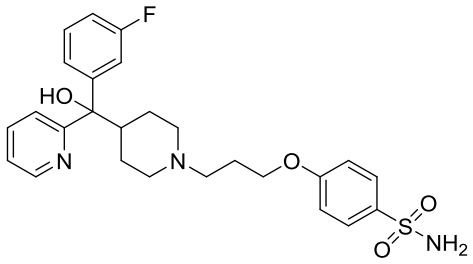
Hz), 7.44 (1H, m), 3.83 (1H, m), 3.59 (2H, t, *J* = 6.5 Hz), 2.95 (2H, d, *J* = 11.2 Hz), 2.50 (2H, t, *J* = 7.2 Hz), 2.16 (2H, m), 1.94 (4H, m), 1.77 (2H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 203.7, 152.7, 148.8, 136.9, 126.9, 122.4, 55.7, 53.2, 43.3, 42.2, 30.0, 28.1; HRMS (ES+, M+H) calc. for $C_{14}H_{20}N_2OCl$: 267.1264, found: 267.1263




**4-(3-(4-((3-fluorophenyl)(hydroxy)(pyridin-2-yl)methyl)piperidin-1-yl)propoxy)benzonitrile, 18.**

A solution of (1-(3-chloropropyl)piperidin-4-yl)(pyridin-2-yl)methanone (100 mg, 0.35 mmol.) in THF (1.41 mL) was cooled to 0 $^{o}$C. To this was added 3-Fluorophenylmagnesium bromide (1.0 M in THF) dropwise with stirring. The solution was then slowly warmed to ambient temperature, and stirring continued for 2 h, at which point starting material was consumed by TLC analysis. The reaction was quenched with sat. aqueous $NH_4Cl$ and extracted with EtOAc. The organic layers were combined and dried over $Na_2SO_4$. Solution was then transferred to a round-bottom flask, concentrated *in vacuo* to remove solvent, and then dissolved in DMF (1.0 mL). $K_2CO_3$ (76 mg, 0.55 mmol) was added, followed by 4-hydroxybenzonitrile (131 mg, 1.10 mmol). Mixture was warmed to 50 $^{o}$C and stirred for 6 h. The reaction mixture was quenched with $H_2O$ and extracted with EtOAc. The organic layers were combined and washed with sat. aqueous NaCl and dried over $Na_2SO_4$. Concentration *in vacuo* provided the crude product, which was purified by reverse-phase HPLC chromatography to provide the desired product as an off-white powder in 106 mg (65%). Chiral Separation: Semi-preparative purifications were carried out via stacked injections on a Waters Investigator SFC using a 10 x 250 mm Chiral

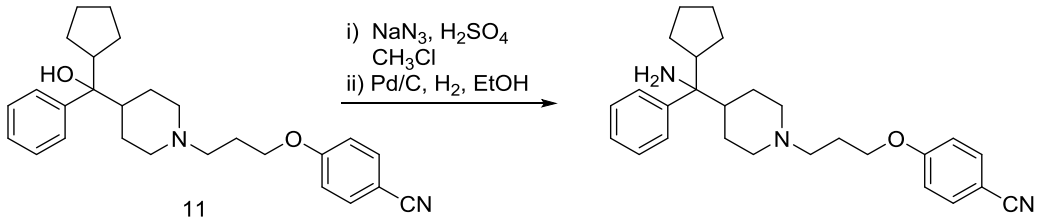
Technologies CHIRALPAK ID column heated to 40 °C. The eluent was 50% IPA (0.1% DEA) in $CO_2$ at a flow rate of 15 mL/minute. Backpressure was maintained at 100 bar. The *first* eluting peak (**18R**), retention time = 3.09 min. The *second* eluting peak (**18S**), retention time = 3.79 min. $^1$H NMR (500 MHz,$CDCl_3$) δ (ppm): 8.85 (1H, d, *J* = 6 Hz), 8.43 (1H, d, *J* = 7.4 Hz), 8.37 (1H, t, *J* = 7.4 Hz), 7.79 (1H, t, *J* = 6.6 Hz), 7.59 (4H, m), 7.37 (1H, dd, *J* = 16, 8 Hz), 6.96 (3H, m), 4.33 (1H, br s), 4.01 (2H, t, *J* = 6 Hz), 3.59 (3H, m), 3.25 (2H, m), 3.07 (1H, m), 2.58 (1H, m), 2.44 (3H, m), 1.72 (1H, d, *J* = 14 Hz), 1.59 (1H, d, *J* = 14 Hz); ); $^{13}$C NMR (125.8 MHz, $CDCl_3$) δ (ppm): 162.8 (d, $J_{CF}$ = 247 Hz), 162.2, 161.9, 148.4 (d, $J_{CF}$ = 6.2 Hz), 147.4, 137.4, 134.1, 129.8 (d, $J_{CF}$ = 8.1 Hz), 122.4, 121.5, 120.4, 119.4, 115.3, 113.9, 113.7, 113.5, 113.3, 104.0, 78.6, 66.7, 54.9, 54.0, 26.5, 25.6, 25.3; HRMS (ES+, M+H) calc. for $C_{27}H_{29}N_3O_2F$: 446.2244, found: 446.2248



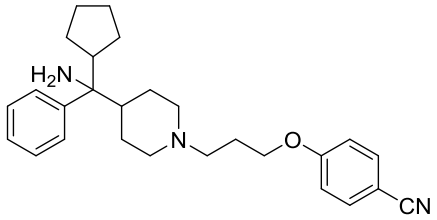

**4-(3-(4-((3-fluorophenyl)(hydroxy)(pyridin-2-yl)methyl)piperidin-1-yl)propoxy)benzenesulfonamide 21:**

A solution of (1-(3-chloropropyl)piperidin-4-yl)(pyridin-2-yl)methanone (100 mg, 0.35 mmol.) in THF (1.41 mL) was cooled to 0 $^o$C. To this was added 3-fluorophenylmagnesium bromide (1.0 M in THF) dropwise with stirring. The solution was then slowly warmed to ambient temperature, and stirring continued for 2 h, at which point starting material was consumed by TLC analysis. The reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layers were combined and dried over $Na_2SO_4$. Solution was then transferred to a round-

bottom flask, concentrated *in vacuo* to remove solvent, and then dissolved in DMF (1.0 mL). $K_2CO_3$ (76 mg, 0.55 mmol) was added, followed by 4-hydroxybenzenesulfonamide (190 mg, 1.10 mmol). Mixture was warmed to 50 $^oC$ and stirred for 6 h. The reaction mixture was quenched with $H_2O$ and extracted with EtOAc. The organic layers were combined and washed with sat. aqueous NaCl and dried over $Na_2SO_4$. Concentration *in vacuo* provided the crude product, which was purified by reverse-phase HPLC chromatography to provide the desired product as an off-white powder in 136 mg (74%): $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 8.47 (1H, d, *J* = 4.9 Hz), 7.82 (2H, d, *J* = 8.9 Hz), 7.67 (1H, td, *J* = 10, 7 Hz), 7.44 (1H, d, *J* = 8 Hz), 7.36 (2H, m), 7.26 (1H, m), 7.16 (1H, m), 6.93 (2H, d, *J* = 9 Hz), 6.87 (1H, m), 6.05 (1H, br s), 5.10 (1H, br s), 4.02 (2H, t, *J* = 6 Hz), 2.92 (2H, m), 2.46 (2H, t, *J* = 7 Hz), 2.36 (1H, t, *J* = 11 Hz), 1.94 (4H, m), 1.62 (2H, m), 1.45 (1H, d, *J* = 13 Hz), 0.97 (1H, d, *J* = 13 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ (ppm): 163.1 (d, $J_{CF}$ = 242 Hz), 162.5, 162.1, 148.4 (d, $J_{CF}$ = 7 Hz), 147.3, 137.4, 133.8, 129.8 (d, $J_{CF}$ = 8 Hz), 128.6, 122.3, 121.5, 120.4, 114.8, 113.7 (d, $J_{CF}$ = 21 Hz), 113.4 (d, $J_{CF}$ = 22 Hz), 78.6, 66.9, 55.0, 54.1, 54.0, 44.7, 26.7, 26.0, 25.8; HRMS (ES+, M+H) calc. for $C_{26}H_{31}N_3O_4SF$: 500.2019, found: 500.2020




**Scheme 4.** Synthesis of aminomethyl piperidine **19**



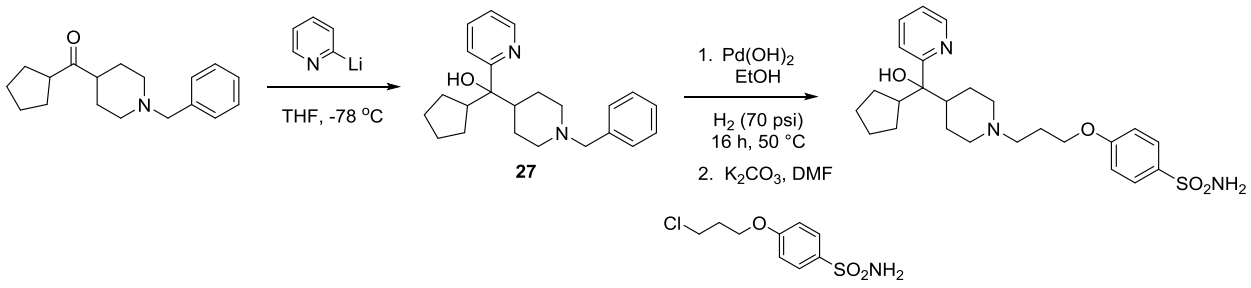

**4-(3-(4-(cyclopentyl(amino)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 19 (MIV-6).**

A $CHCl_3$ (4.78 mL, 0.25 M) solution of 4-(3-(4-(cyclopentyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile (1.0 g, 2.39 mmol) and sodium azide (1.16 g, 17.9 mmol) was cooled to 0 $^oC$. To the solution $H_2SO_4$ was added dropwise (0.28 mL, 9.3 mmol). The mixture was allowed to warm to rt over 4h with stirring, then cooled to 0 $^oC$ and treated with $NH_4OH$ until pH was basic. The biphasic solution was extracted with $CH_2Cl_2$ (3x) and the organic layers combined and dried over $MgSO_4$. Concentration under reduced pressure and concentration *in vacuo* afforded a crude oil which was purified by flash column chromatography (9:1 $CH_2Cl_2$/MeOH) to afford a colorless oil comprising an inseperable mixture of the desired azide and an elimination byproduct in 30 mg that was carried on to the next step.

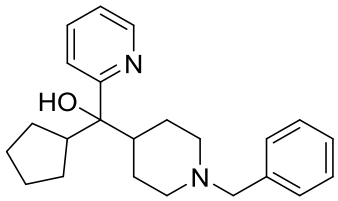
4-(3-(4-(Azido(cyclopentyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile (30 mg, 0.07 mmol) was dissolved in degassed EtOH (0.5 mL) and Pd/C (2.7 mg) added in one portion. Reaction was placed under a balloon of $H_2$ gas and allowed to stir for 4 h at ambient temperature. The reaction was filtered over Celite and rinsed with MeOH. The filtrate was concentrated to afford an oil. RP-HPLC preparative purification afforded the desired product as a TFA salt. The mixture was treated with a StratoSpheres SPE MP-carbonate resin cartridge to give title compound as a free base in 20 mg (2%). Chiral Separation: Semi-preparative purifications were carried out via stacked injections on a Waters Investigator SFC using a 10 x 250 mm Chiral Technologies CHIRALPAK ID column heated to 40 °C. The eluent was 50% MeOH (0.1%

DEA) in $CO_2$ at a flow rate of 15 mL/minute. Backpressure was maintained at 100 bar. The *first* eluting peak (**19S**), retention time = 3.97 min. was inferred as the *S* stereoisomer based upon the absolute configuration observed in the electron density map of the X-ray structure of the **MIV-6R**-Menin complex. The *second* eluting peak (**19R**), retention time = 5.38 min. was inferred as the *R* stereoisomer based upon the absolute configuration observed in the electron density map of the X-ray structure of the **MIV-6R**-Menin complex.

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 6.0 Hz), 7.43 (2H, d, *J* = 7.2 Hz), 7.31 (2H, t, *J*=7.2 Hz), 7.22 (1H, t, *J* = 7.2 Hz), 6.91 (2H, d, *J* = 6.0 Hz), 4.02 (2H, t, *J* = 8.4 Hz), 3.05-2.96 (2H, m), 2.62 (1H, m), 2.47 (2H , br s), 1.96-1.89 (4H, m), 1.73 (1H, m), 1.62-1.40 (9H, m), 1.29-1.24 (2H, m), 1.13-1.05 (2H, m); $^{13}$C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 162.4, 144.5, 134.1, 127.6, 127.5, 126.1, 119.42, 115.3, 103.9, 66.9, 61.3, 55.2, 54.7, 54.6, 46.4, 45.6, 27.6, 27.1, 26.7, 26.6, 26.5, 25.9, 25.6; HRMS (ES+, M+H) calc. for $C_{28}H_{30}N_2O_2$: 418.858, found: 418.2857

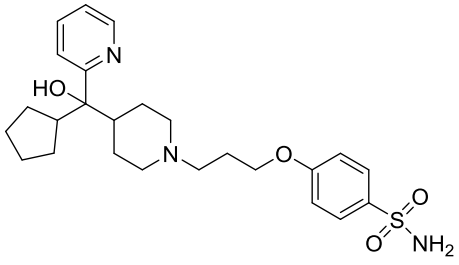



**Scheme 5**. Synthesis of hydroxymethyl piperidine **22**.




**(1-benzylpiperidin-4-yl)(cyclopentyl)(pyridin-2-yl)methanol, 27.**

2-Bromopyridine (873 mg, 5.54 mmol), was dissolved in THF (30 mL), and cooled to -78 °C. To this solution was added *n*-butlyllithium (2.2 mL, 2.5 M in hexanes, 5.53 mmol) dropwise with stirring. Stirring was continued for 20 min. (1-Benzylpiperidin-4-yl)(cyclopentyl)methanone (500 mg, 1.84 mmol) dissolved in THF (2.0 mL), was added dropwise to stirring solution of pyridin-2-yllithium at -78 °C. The mixture was stirred for 20 min. and then slowly warmed to room temperature. Reaction was stirred for 2 h, then quenched with sat. aqueous $NH_4Cl$. The mixture was extracted with EtOAc, and the organic layers combined and washed with sat. aqueous NaCl and dried over $Na_2SO_4$. Concentration *in vacuo* provided the crude product, which was purified by flash column chromatography (9:1 $CH_2Cl_2$/MeOH) to provide the desired product as a white solid in 599 mg (93%): $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.51 (1H, d, *J* = 4.7 Hz), 7.66 (1H, t, *J* = 8.1 Hz), 7.30-7.17 (7H, m), 5.66 (1H, br s), 3.45 (2H, d, *J* = 2.0 Hz), 2.90 (2H, m), 2.62 (1H, quintet, *J* = 8.5 Hz), 1.97-1.61 (8H, m), 1.47 (4H, m), 1.14 (2H, m), 0.69 (1H, m); $^{13}$C NMR (125.8 MHz, $CDCl_3$) δ (ppm): 162.1, 146.9, 138.5, 136.3, 129.3, 128.2, 127.0, 121.9, 121.2, 78.3, 63.5, 54.5, 54.3, 46.0, 45.8, 27.9, 27.1, 26.6, 26.5, 26.2, 25.7; HRMS (ES+, M+H) calcd for $C_{23}H_{31}N_2O$: 351.2436, found: 351.2433



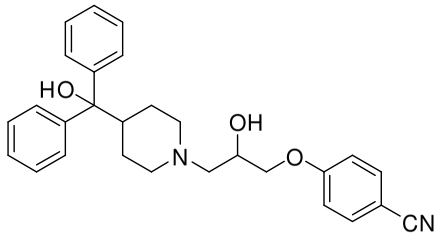
**4-(3-(4-(cyclopentyl(hydroxy)(pyridin-2-yl)methyl)piperidin-1-yl)propoxy)benzenesulfonamide, 20 (MIV-7).**

In a Parr vessel, (1-benzylpiperidin-4-yl)(cyclopentyl)(pyridin-2-yl)methanol (500 mg, 1.84 mmol) was dissolved in EtOH (10 mL). The solution was degassed by bubbling Argon through the solution for 10 min. $Pd(OH)_2$ was then added and the vessel was quickly inserted into the Parr Shaker apparatus. The system was purged with $H_2$ three times, and $H_2$ pressure was then set to 70 psi. The vessel was heated to 50 °C, and shaken for 12-24 h. When the reaction progress was complete by LCMS, the mixture was filtered through a celited pad and washed with EtOH. The filtrate was concentrated *in vacuo* to yield the crude product, which was carried forward to the next step.

Cyclopentyl(piperidin-4-yl)(pyridin-2-yl)methanol (30 mg, 0.12 mmol) was dissolved in DMF (1.0 mL). 4-(3-chloropropoxy)benzenesulfonamide (29 mg, 0.12 mmol) and $K_2CO_3$ (32 mg, 0.23 mmol) were added and reaction was wamred to 50 °C. Stirring was continued overnight. The reaction mixture was quenched with aqueous $NH_4Cl$. The mixture was extracted with EtOAc, and the organic layers combined and washed with sat. aqueous NaCl and dried over $Na_2SO_4$. Concentration *in vacuo* provided the crude product, which was purified by RP-HPLC to provide the desired product as a white solid in 23 mg (42%): $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.45 (1H, d, *J* = 4.7 Hz), 7.80 (2H, d, *J* = 8.4 Hz), 7.65 (1H, t, *J* = 7.8 Hz), 7.27 (1H, d, *J* = 7.8 Hz), 7.17 (1H, t, *J* = 6.1 Hz), 6.90 (2H, d, *J* = 7.8 Hz), 5.66 (1H, br s), 5.06 (2H, br s), 3.98 (2H, t, *J* = 6.4 Hz), 2.98 (1H, d, *J* = 10.2 Hz), 2.91 (1H, d, *J* = 10.2 Hz), 2.58 (1H, m), 2.44 (2H, m), 1.96-1.69 (8H, m), 1.60-1.42 (6H, m), 1.12 (2H, m), 0.69 (1H, m); $^{13}$C NMR (125.8 MHz, $CDCl_3$) δ (ppm): 162.4, 161.8, 147.0, 136.5, 133.8, 128.6, 122.0, 121.2, 114.8, 78.3, 66.9,

55.2, 54.5, 54.4, 45.8, 45.7, 27.6, 27.1, 26.6, 26.5, 26.4, 26.1, 25.7; HRMS (ES+, M+H) calc. for $C_{25}H_{36}N_3O_4S$: 474.2427, found: 474.2430

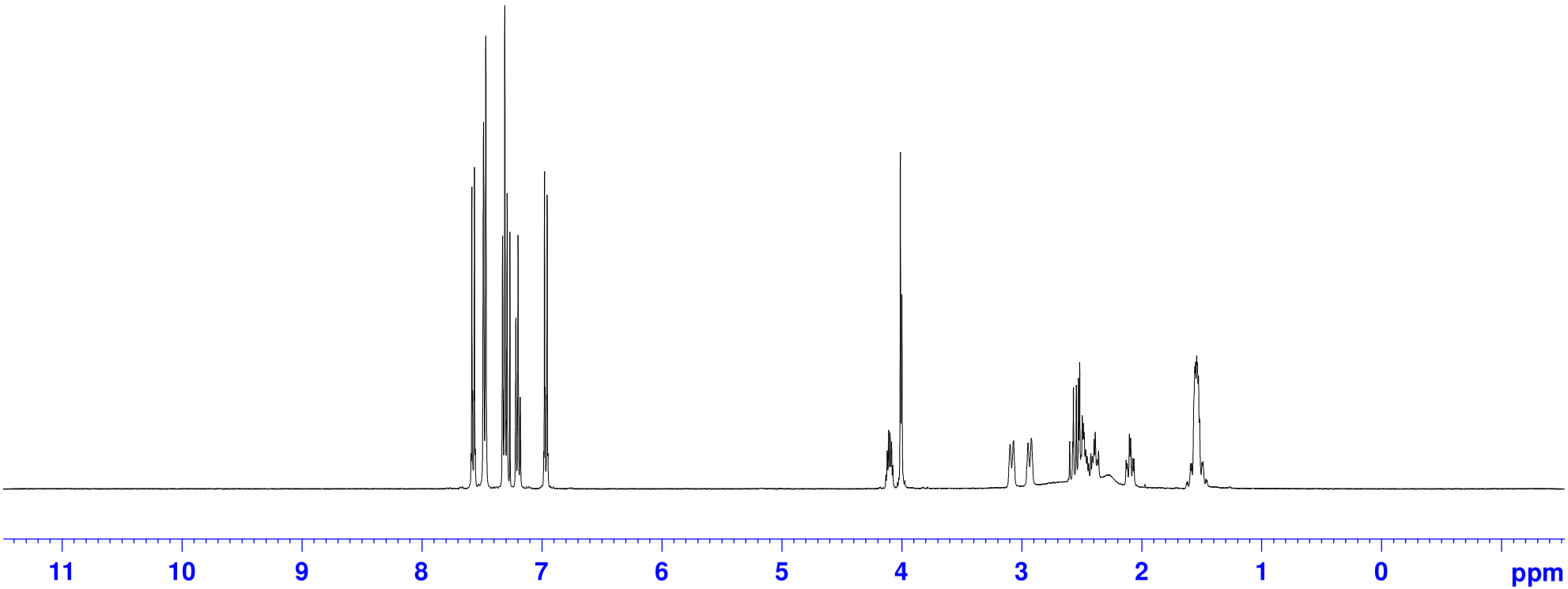
## 5. $^{1}H$ and $^{13}C$ NMR spectra

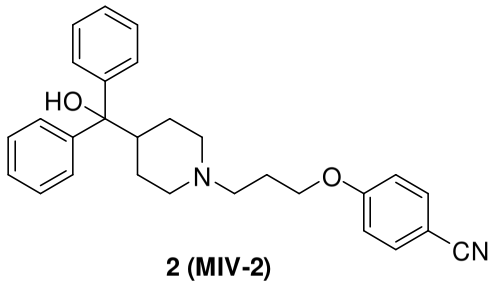



**1 (MIV-1)**

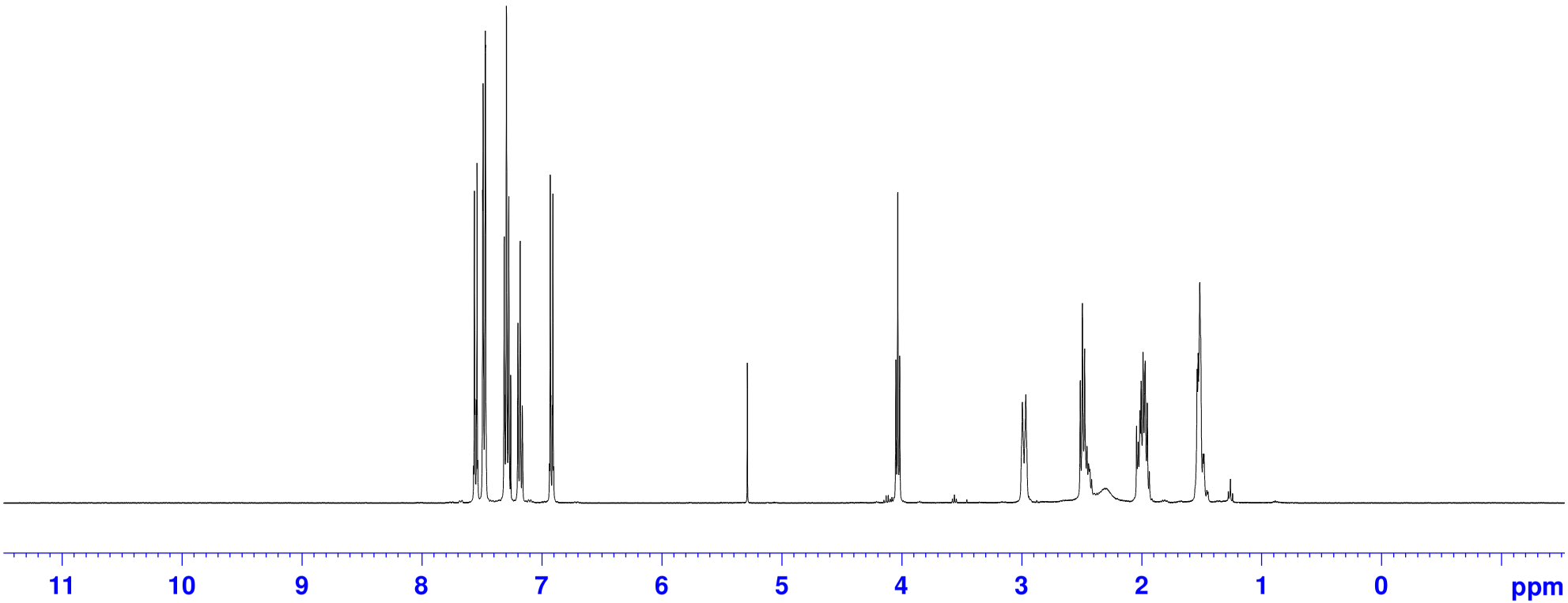
**$^1$H NMR Spectrum**

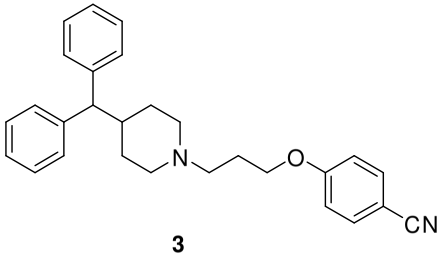
**(400 MHz, $CDCl_3$)**






**2 (MIV-2)**
**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

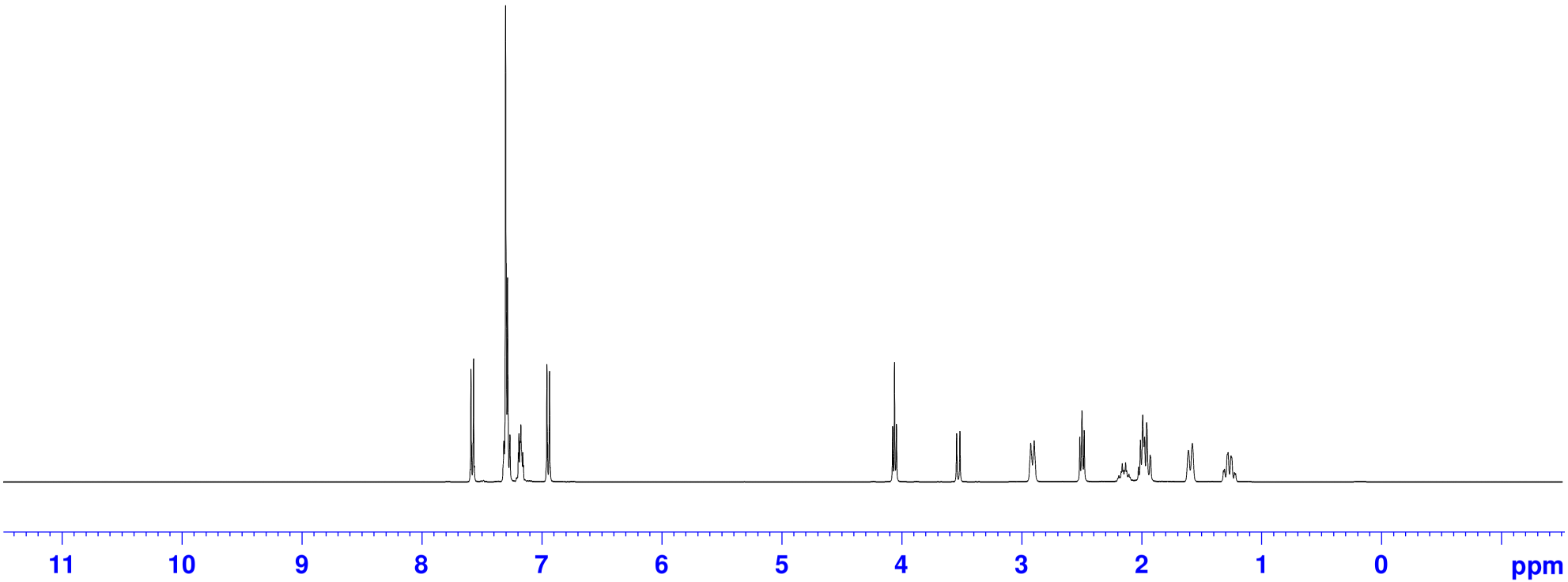


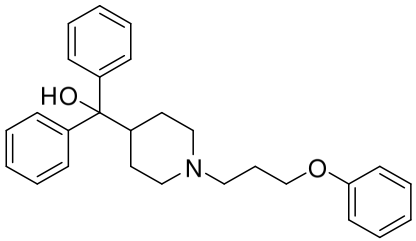



**3**

**$^1$H NMR Spectrum**

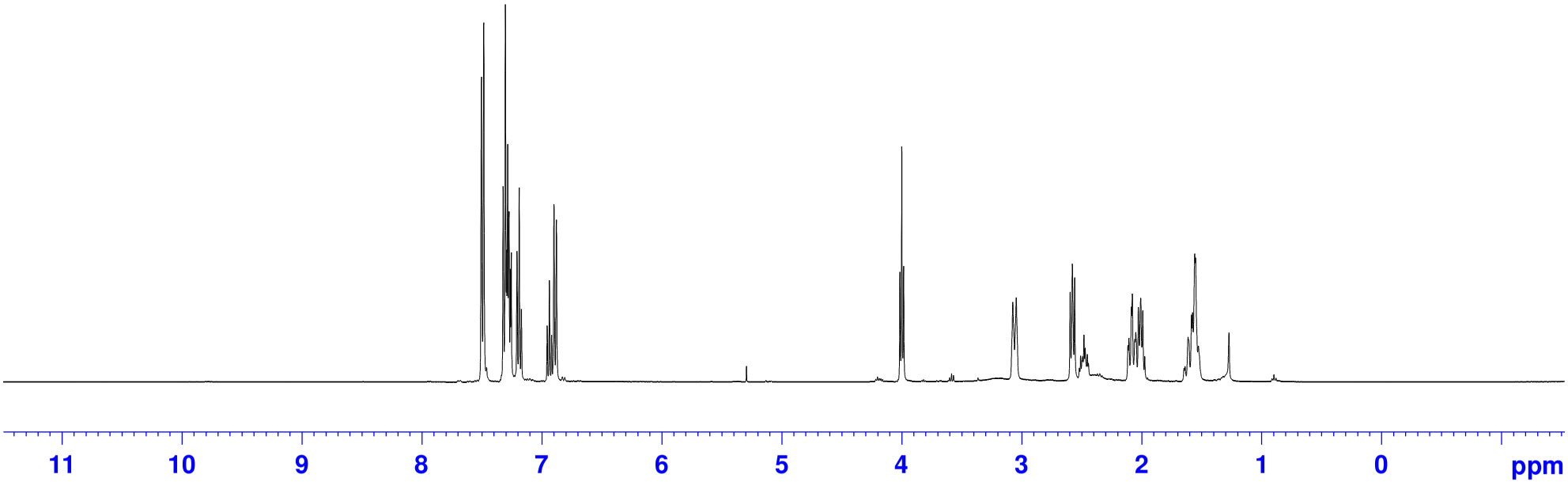
**(400 MHz, $CDCl_3$)**

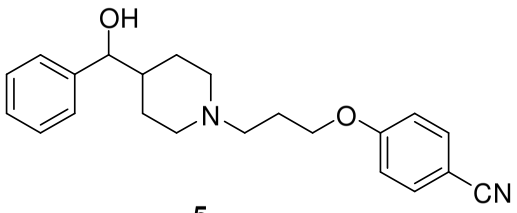





**4**

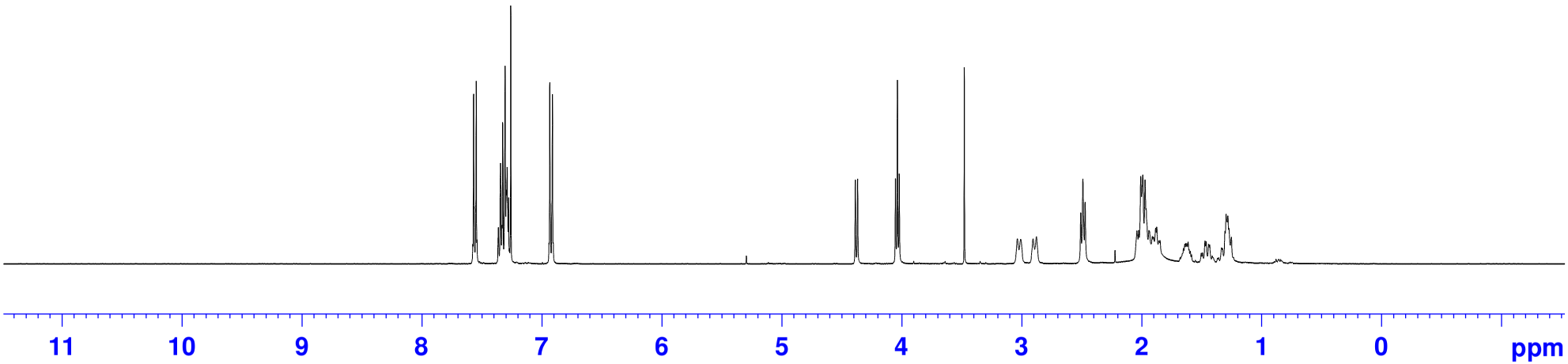
**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

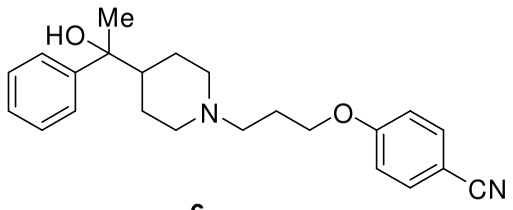





**5**

**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

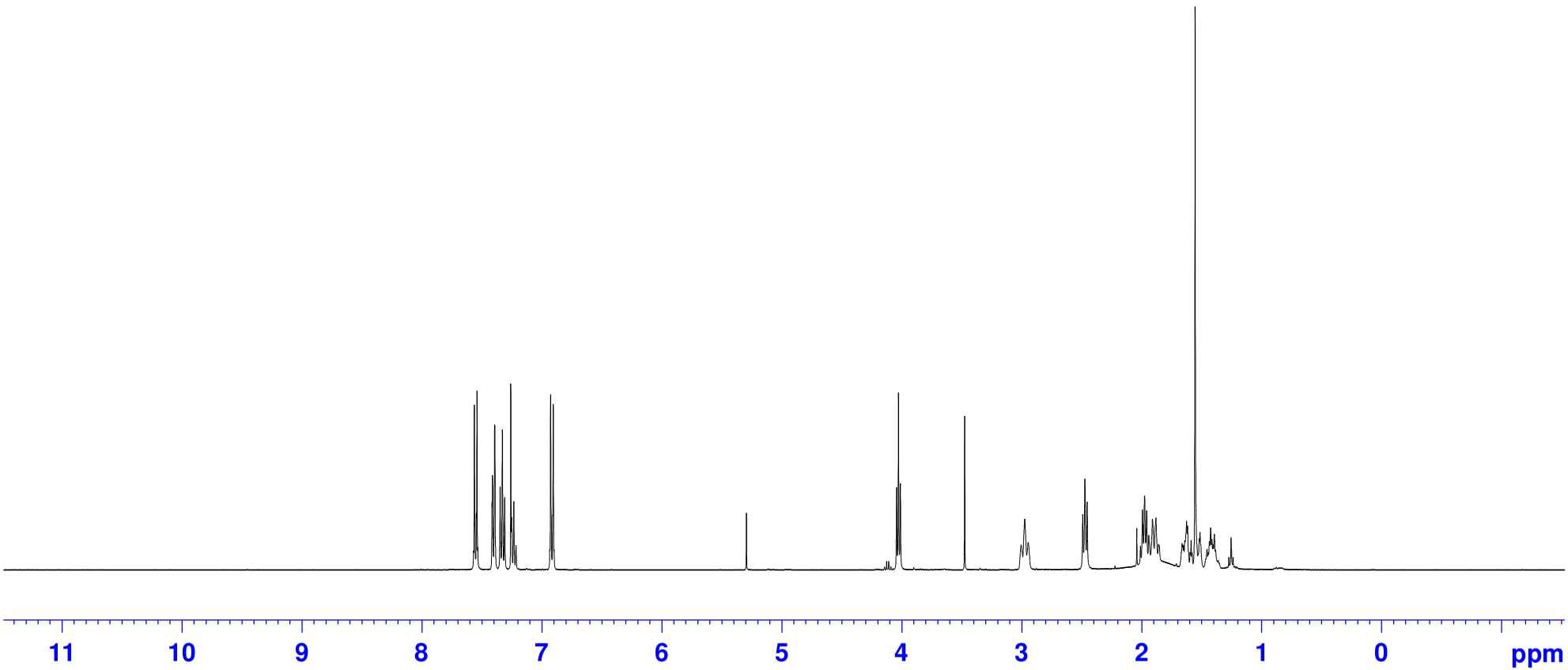


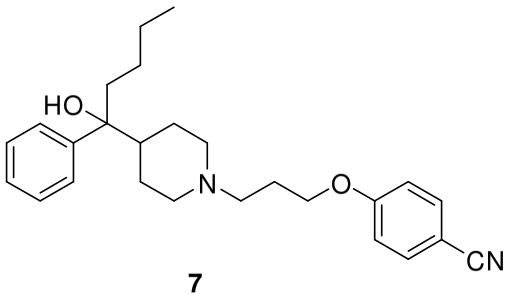



**6**

**$^1$H NMR Spectrum**

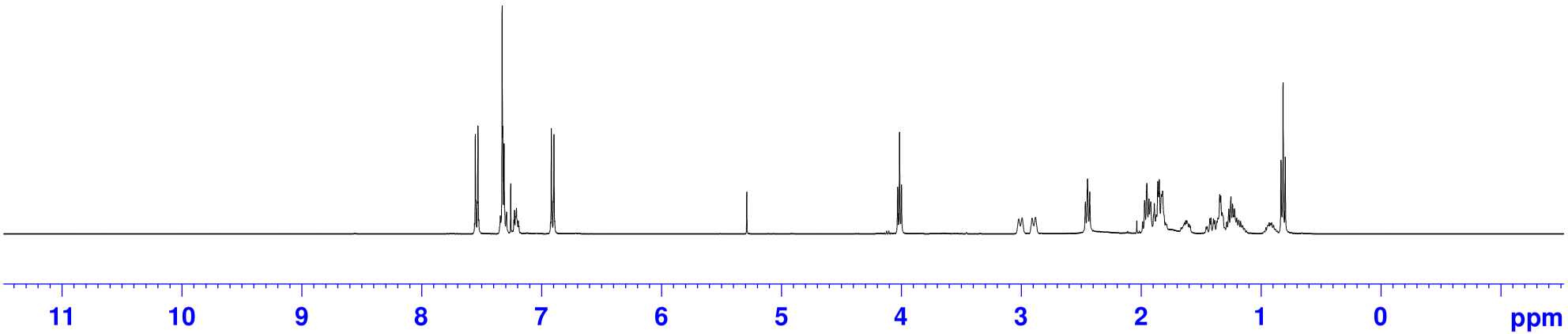
**(400 MHz, $CDCl_3$)**

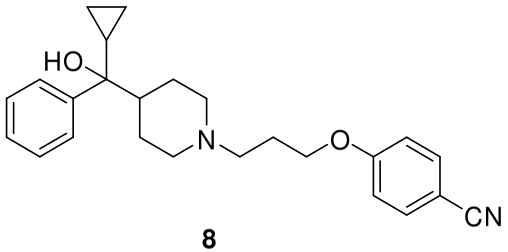





**7**

**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

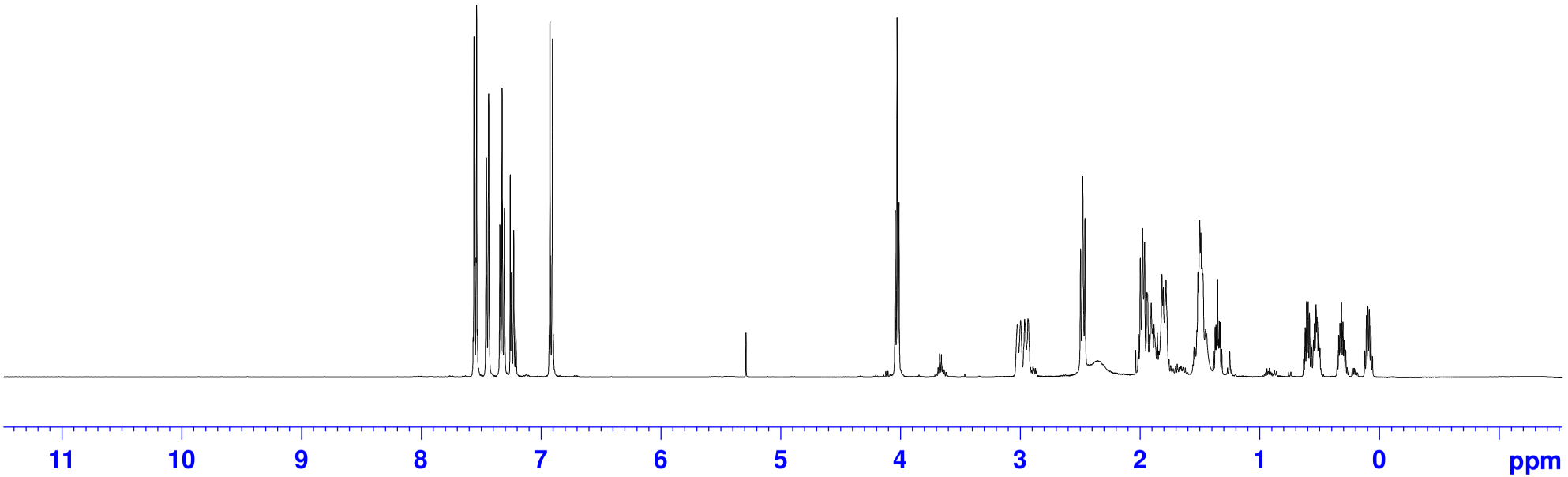


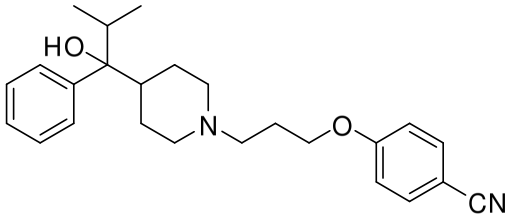



**8**

**$^1$H NMR Spectrum**

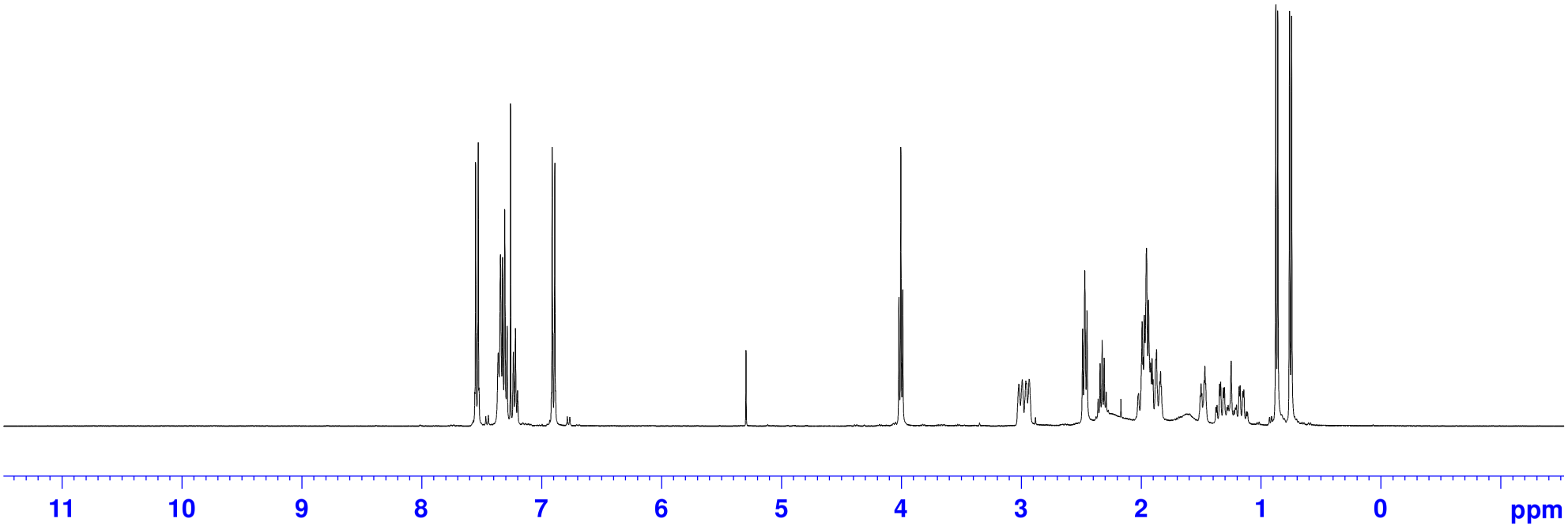
**(400 MHz, $CDCl_3$)**

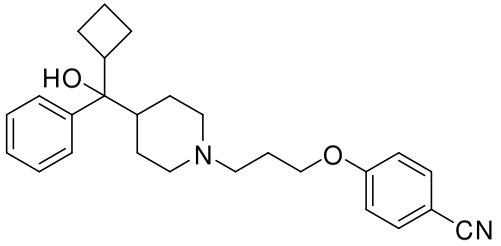





**9**

**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

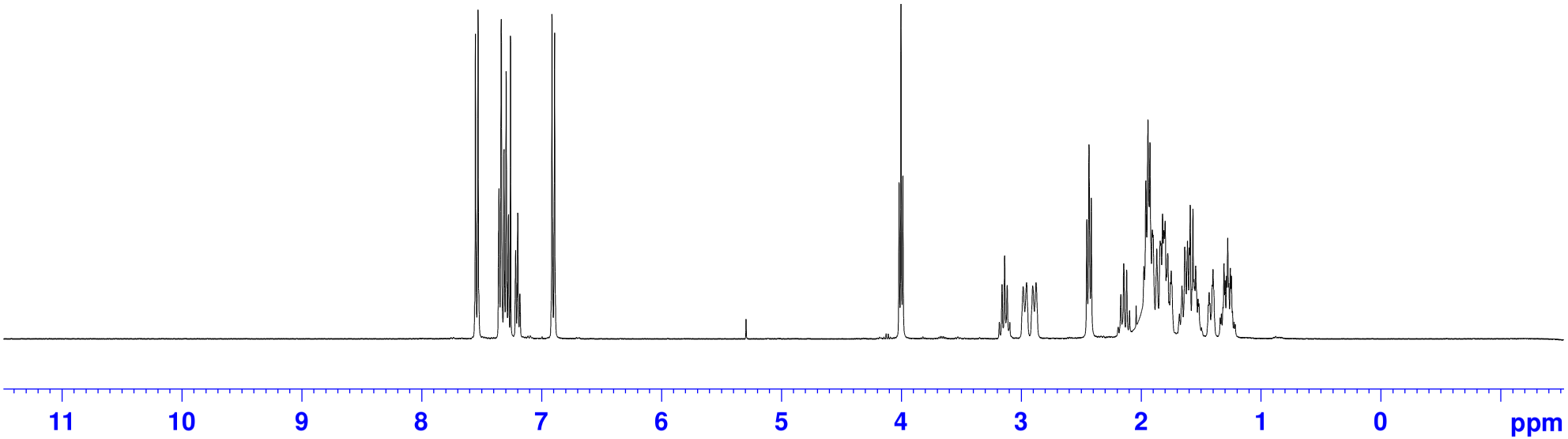


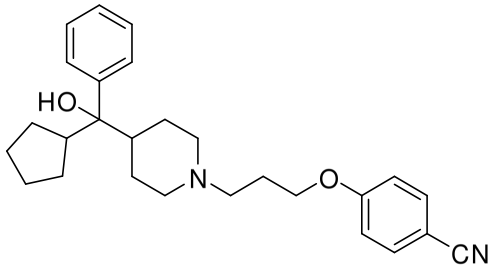



**10**

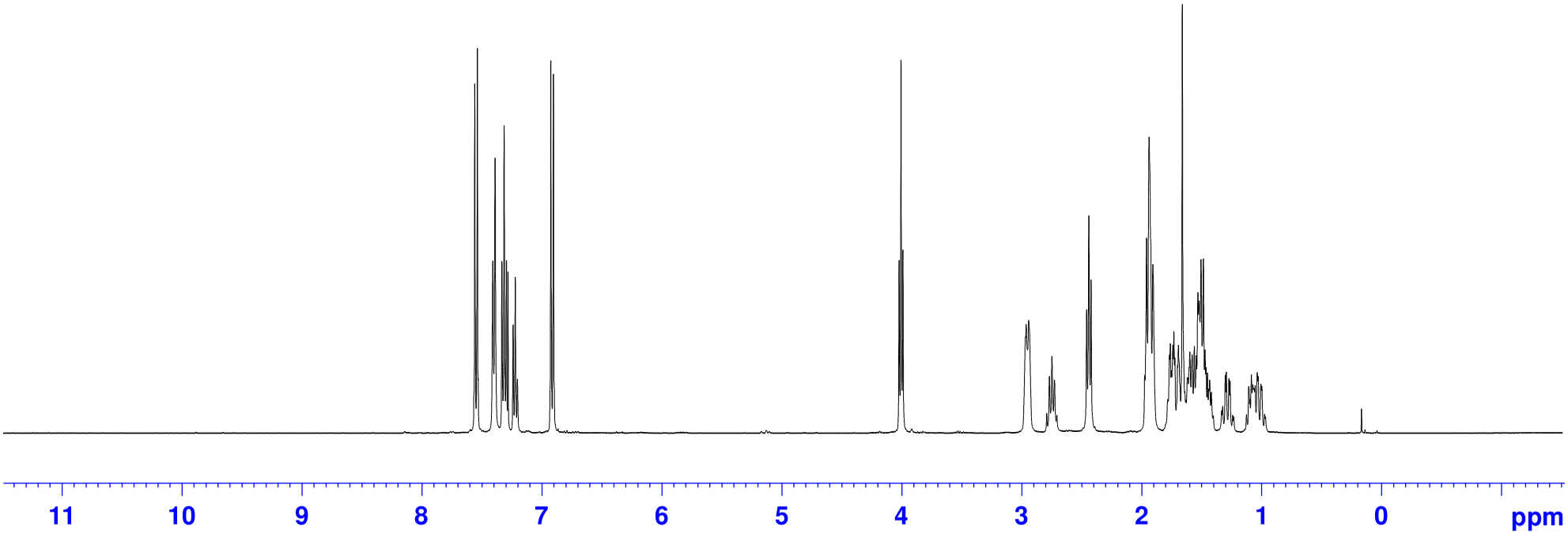
**$^1$H NMR Spectrum**

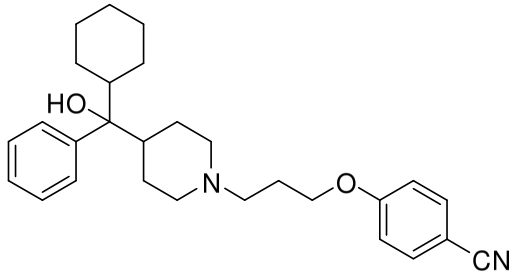
**(400 MHz, $CDCl_3$)**






**11 (MIV-3)**
**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

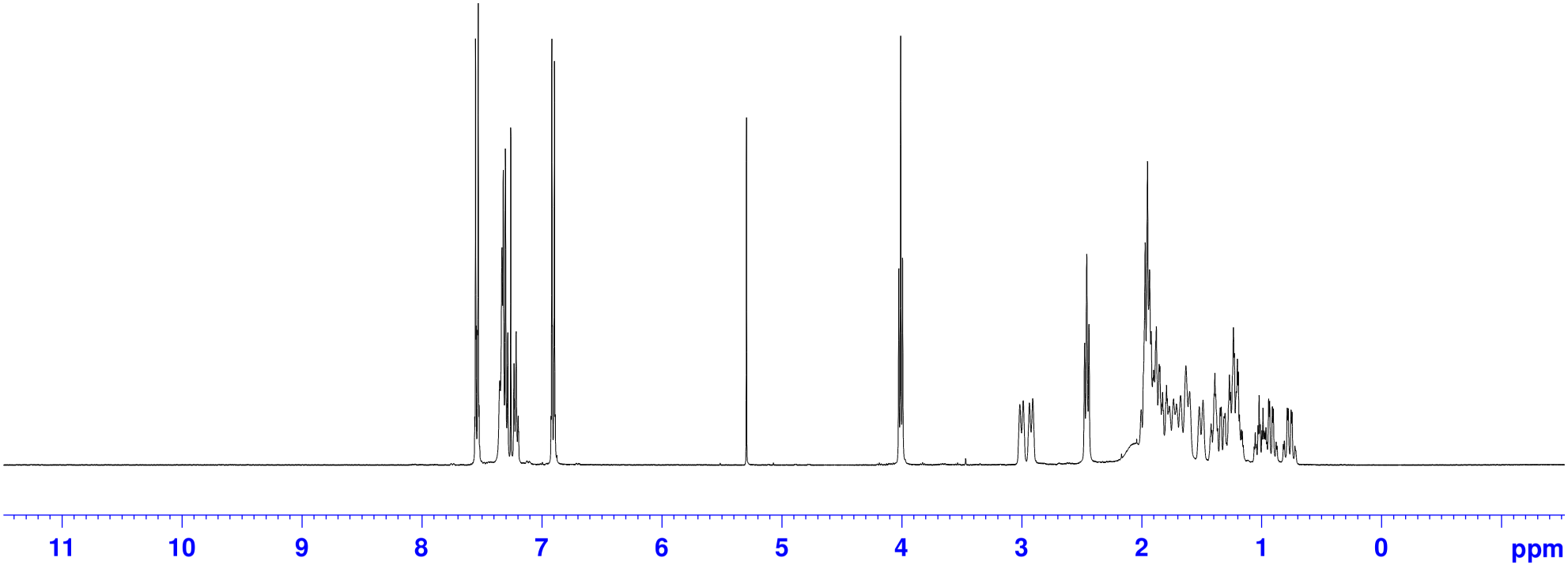


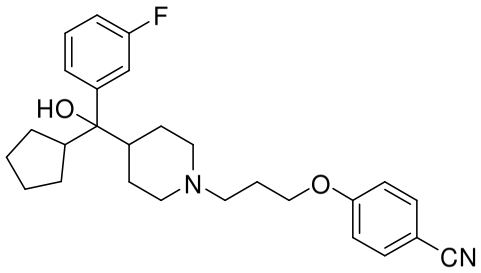



**12**

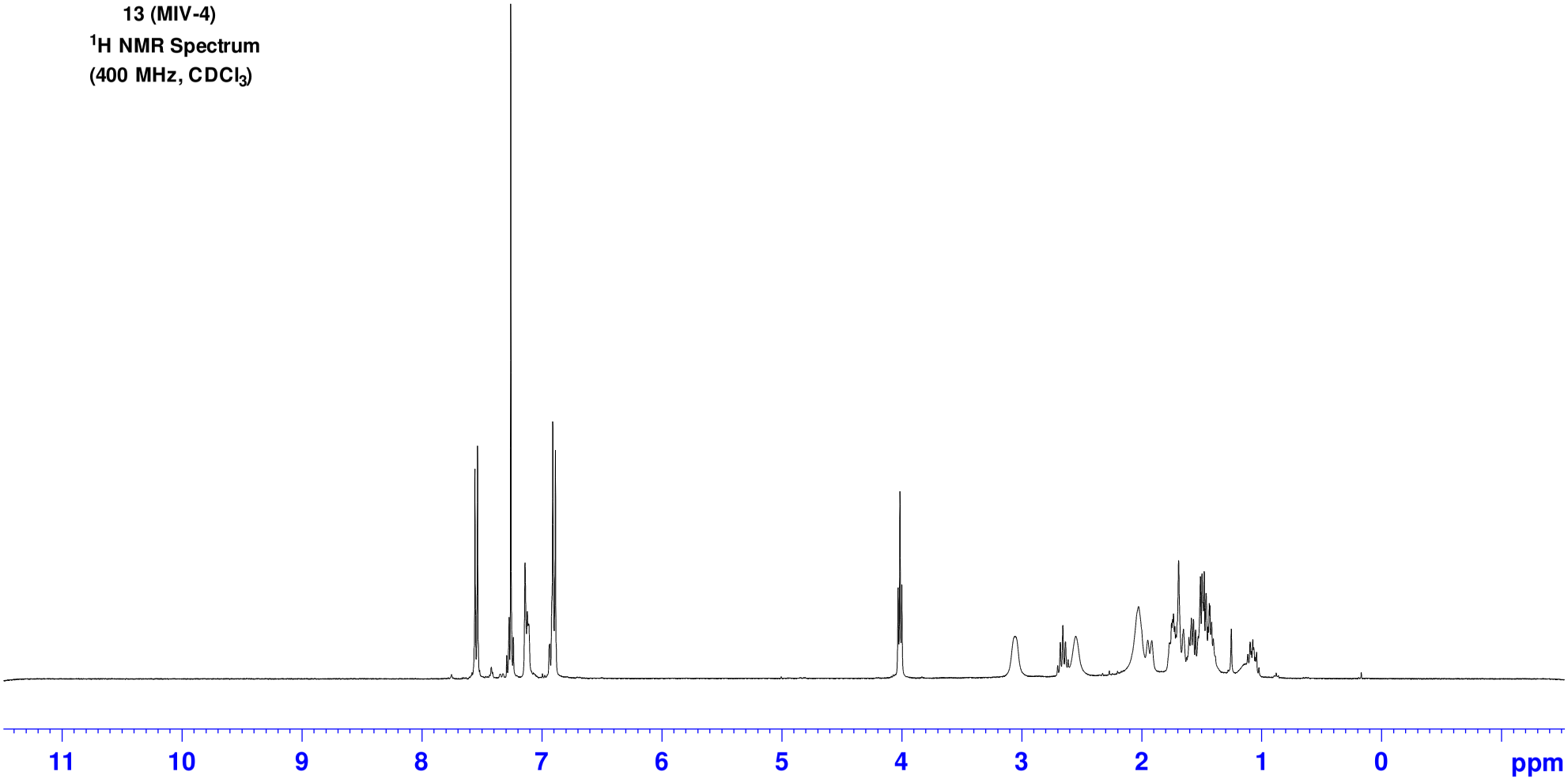
**$^1$H NMR Spectrum**

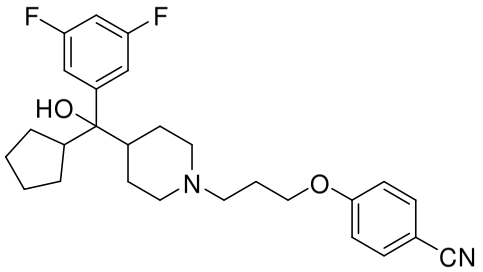
**(400 MHz, $CDCl_3$)**






**13 (MIV-4)**
**$^1$H NMR Spectrum**
**(400 MHz, $CDCl_3$)**

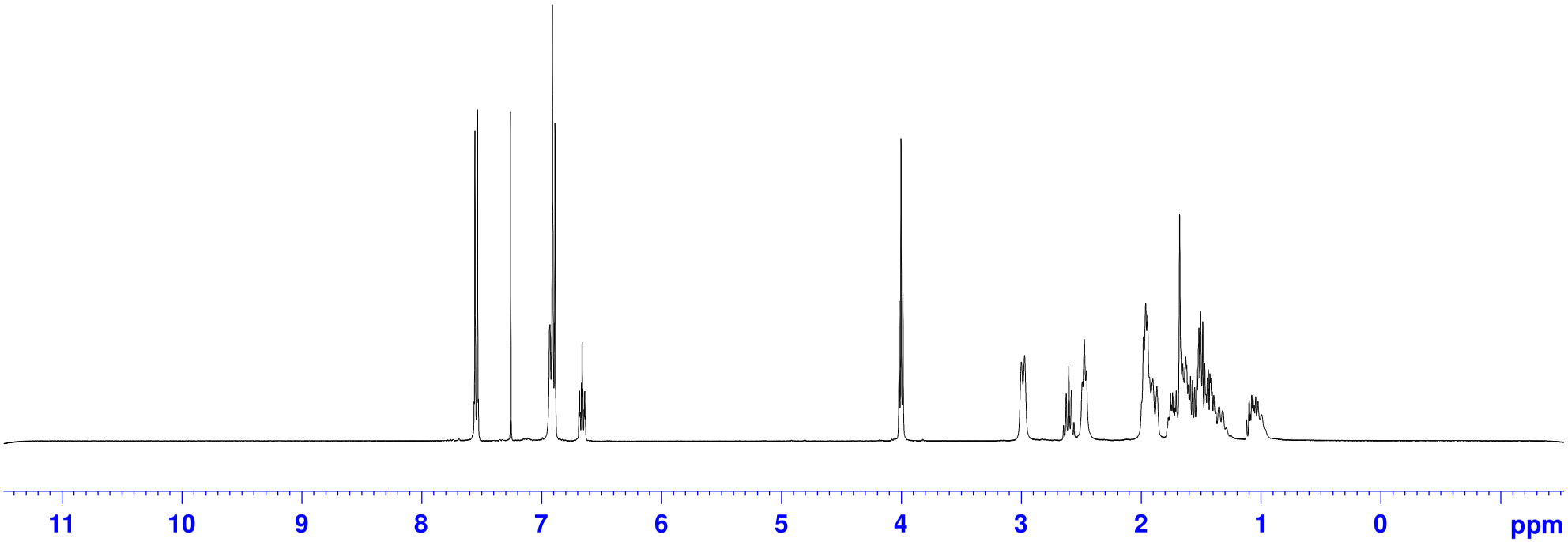


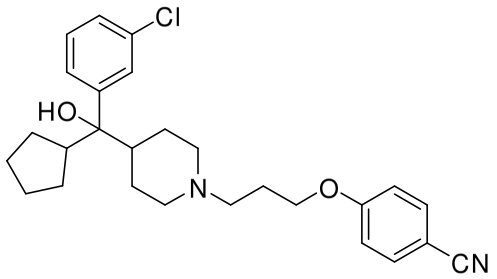



**14**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

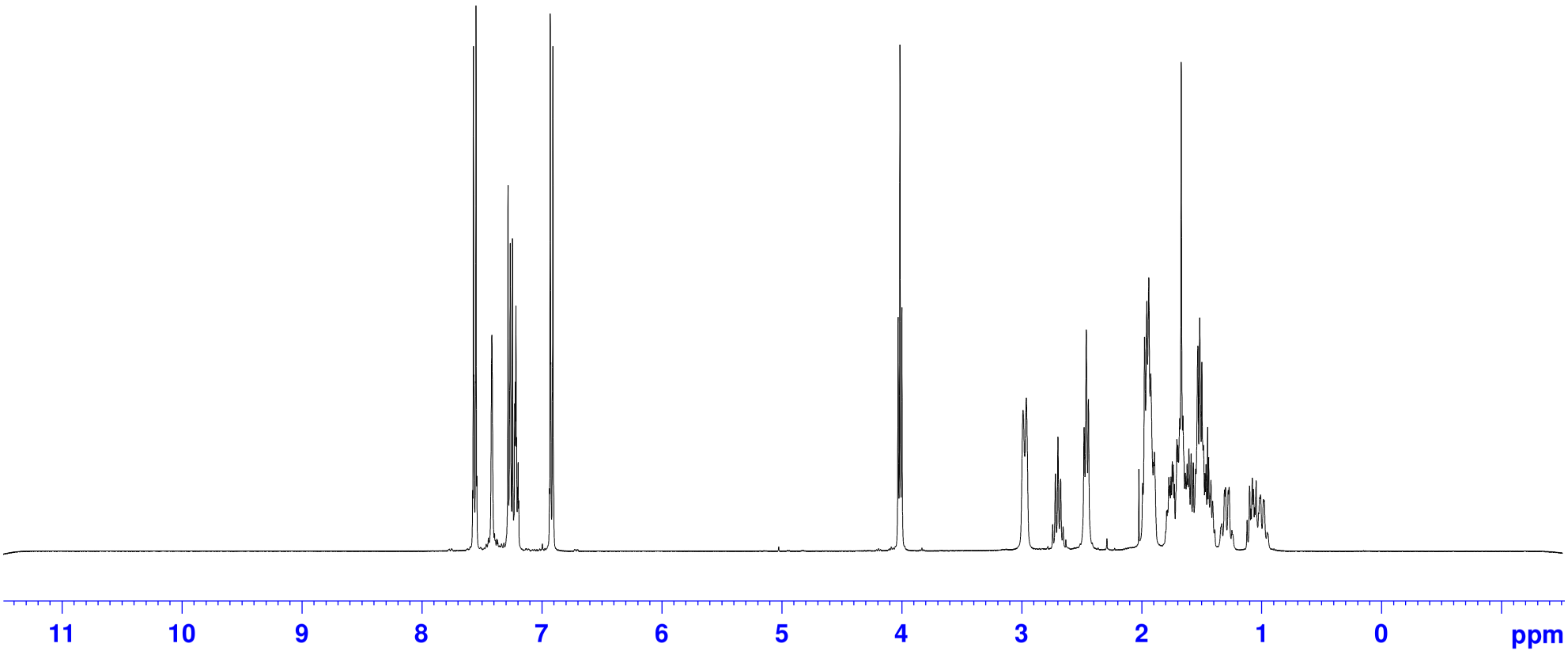


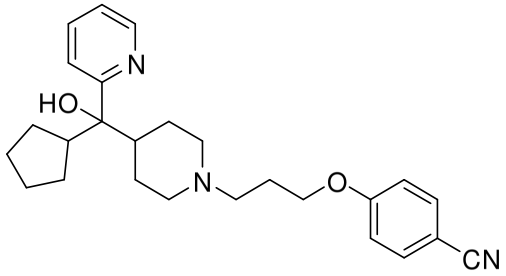



**15**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

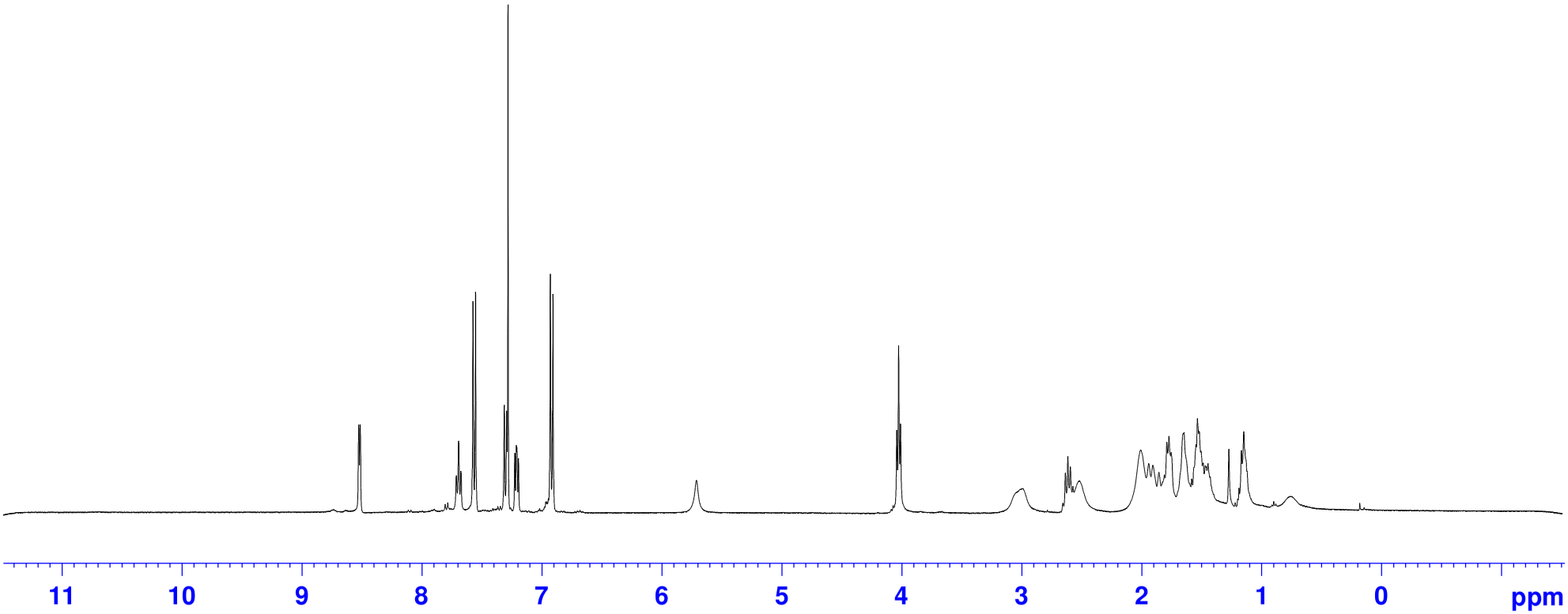


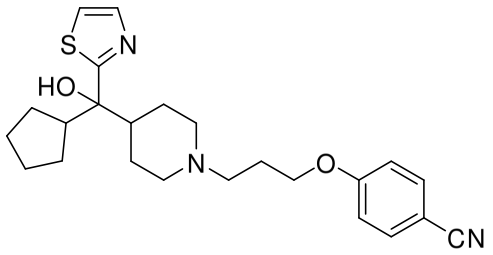



**16 (MIV-5)**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

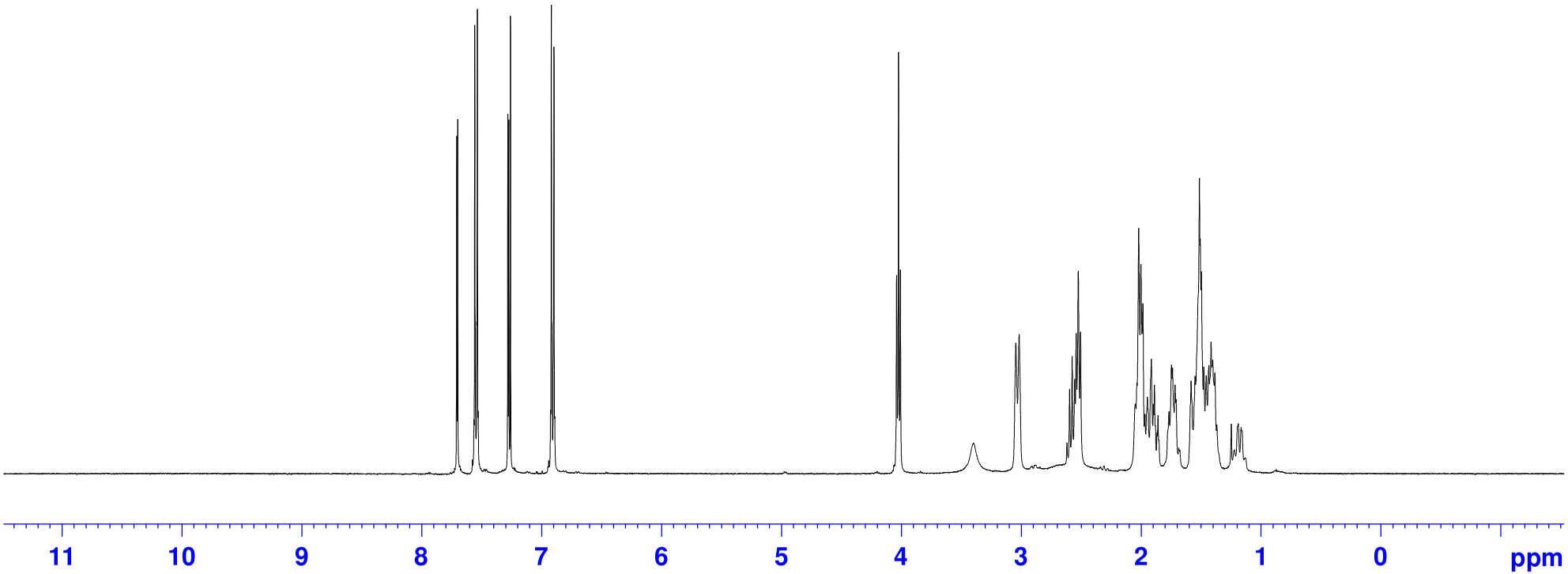


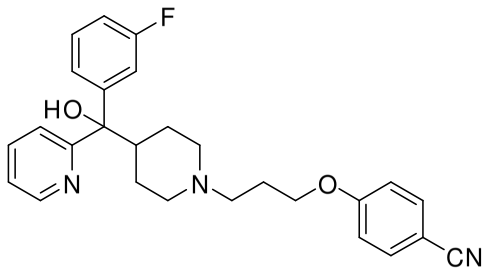



**17**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

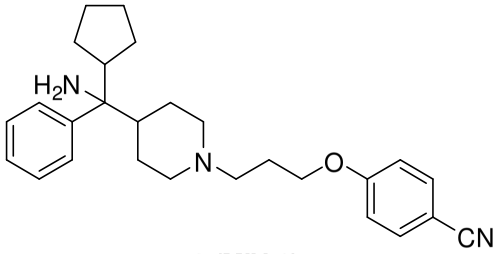





**18**

**$^1$H NMR Spectrum**

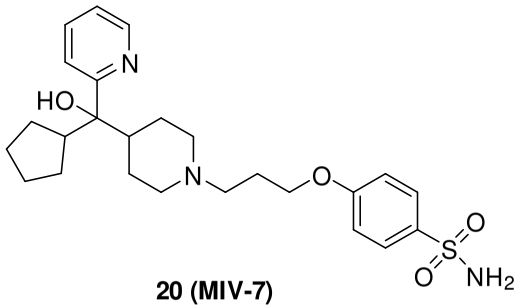
**(500 MHz, $CDCl_3$)**




**19 (MIV-6)**

**$^1$H NMR Spectrum**

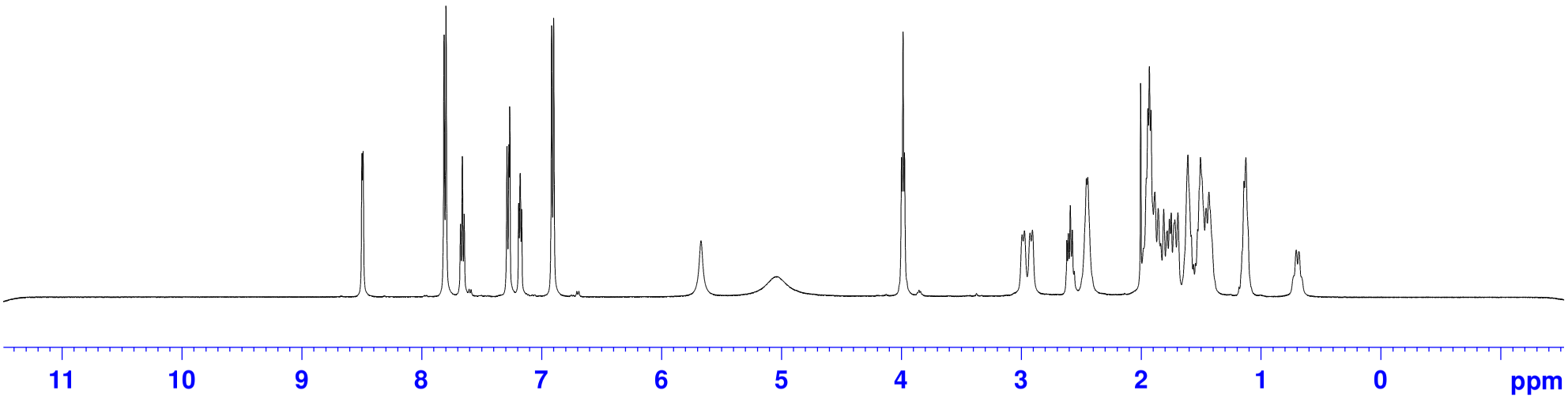
**(600 MHz, $CDCl_3$)**

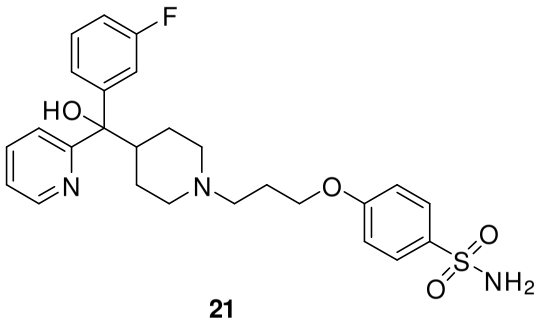



**20 (MIV-7)**

**$^1$H NMR Spectrum**

**(500 MHz, $CDCl_3$)**

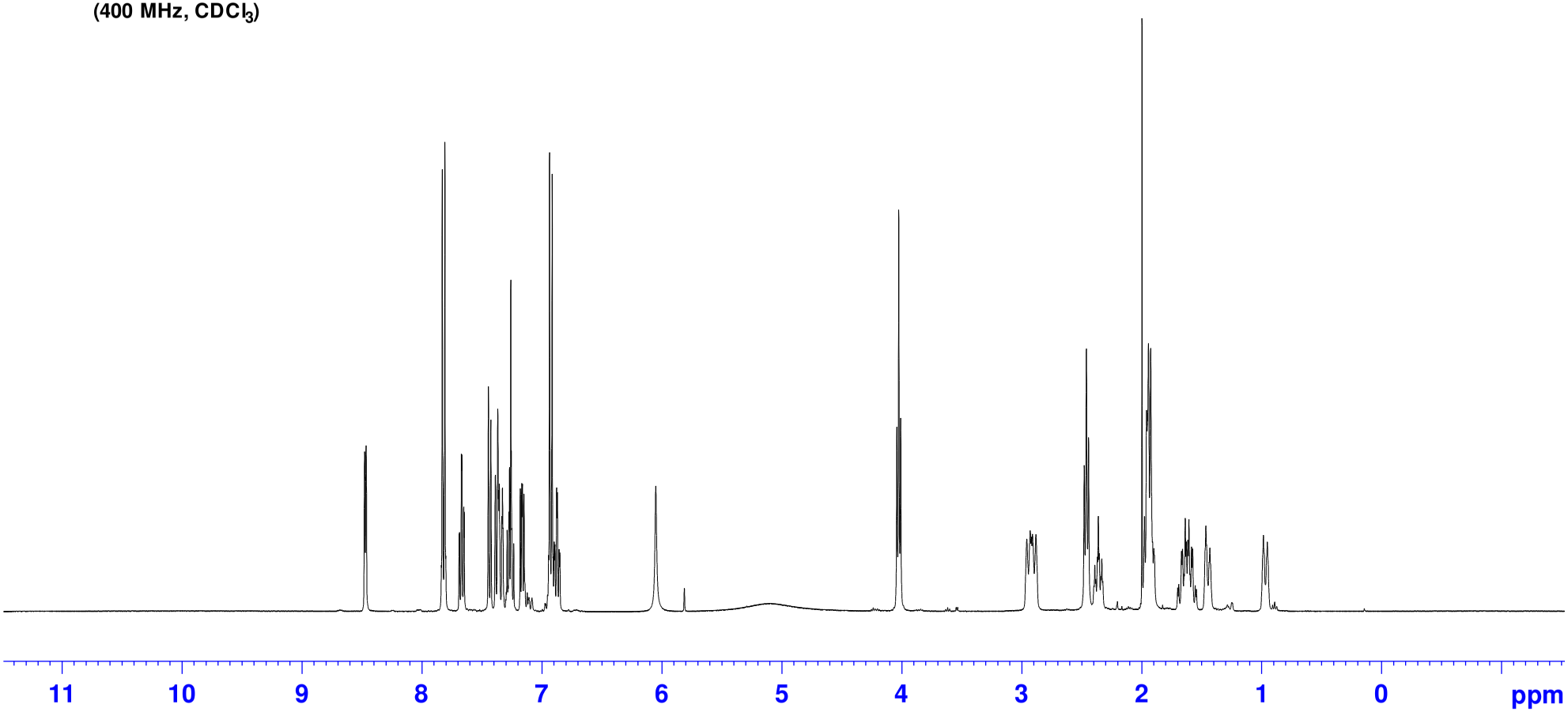


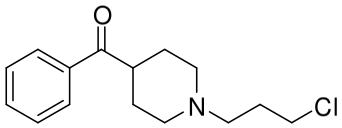



**21**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

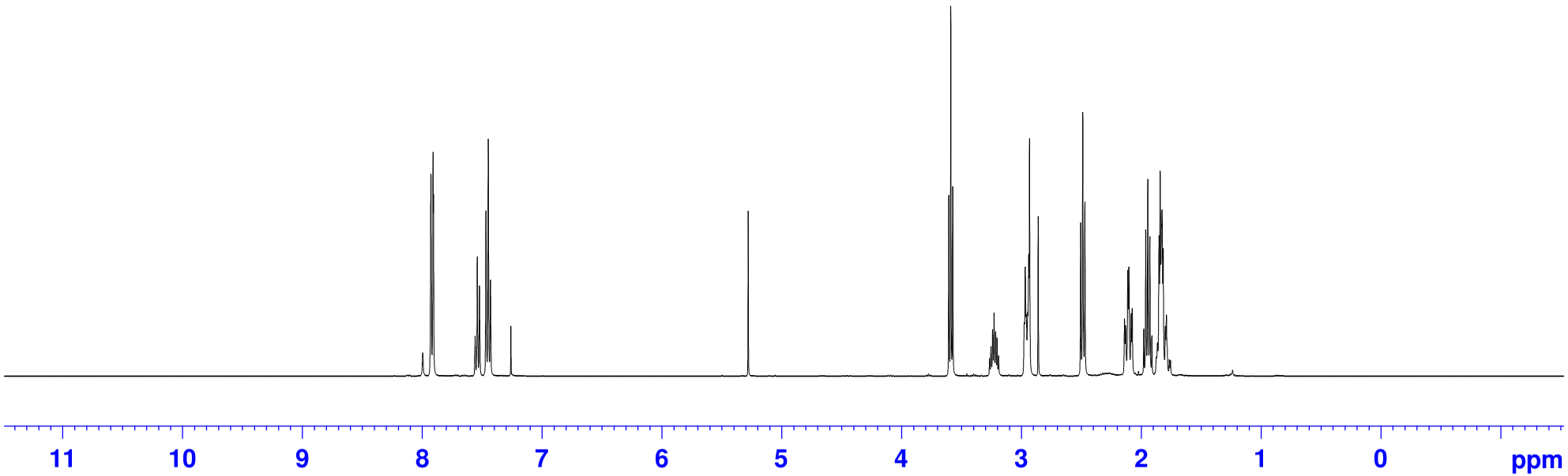


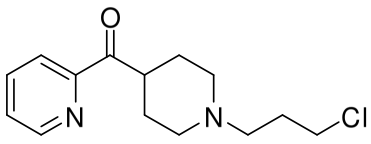



**23a**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

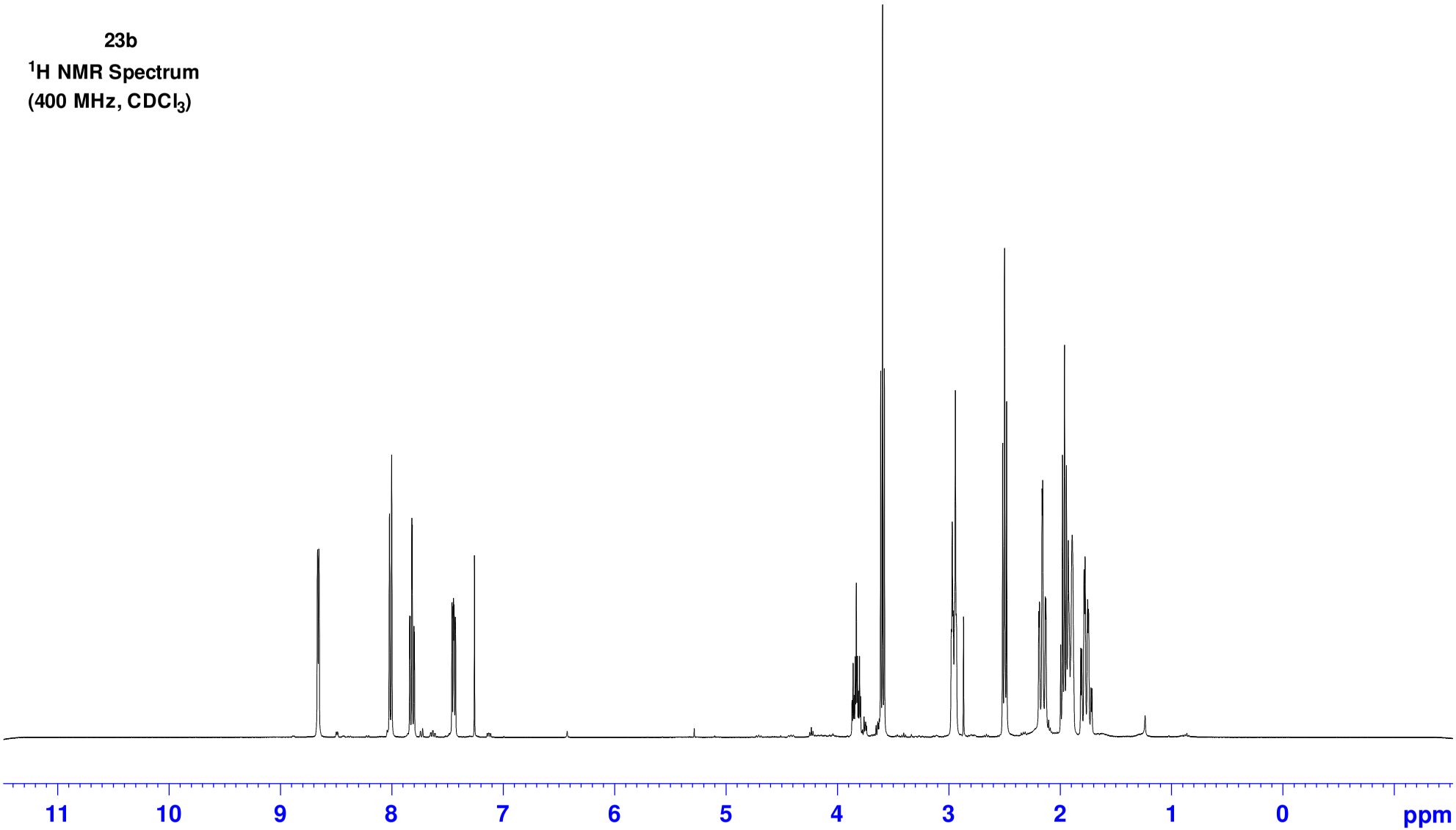


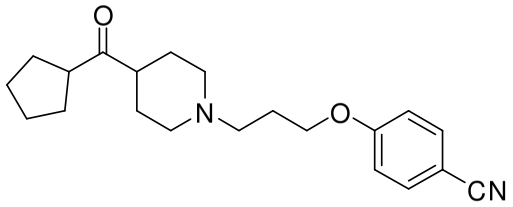



**23b**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

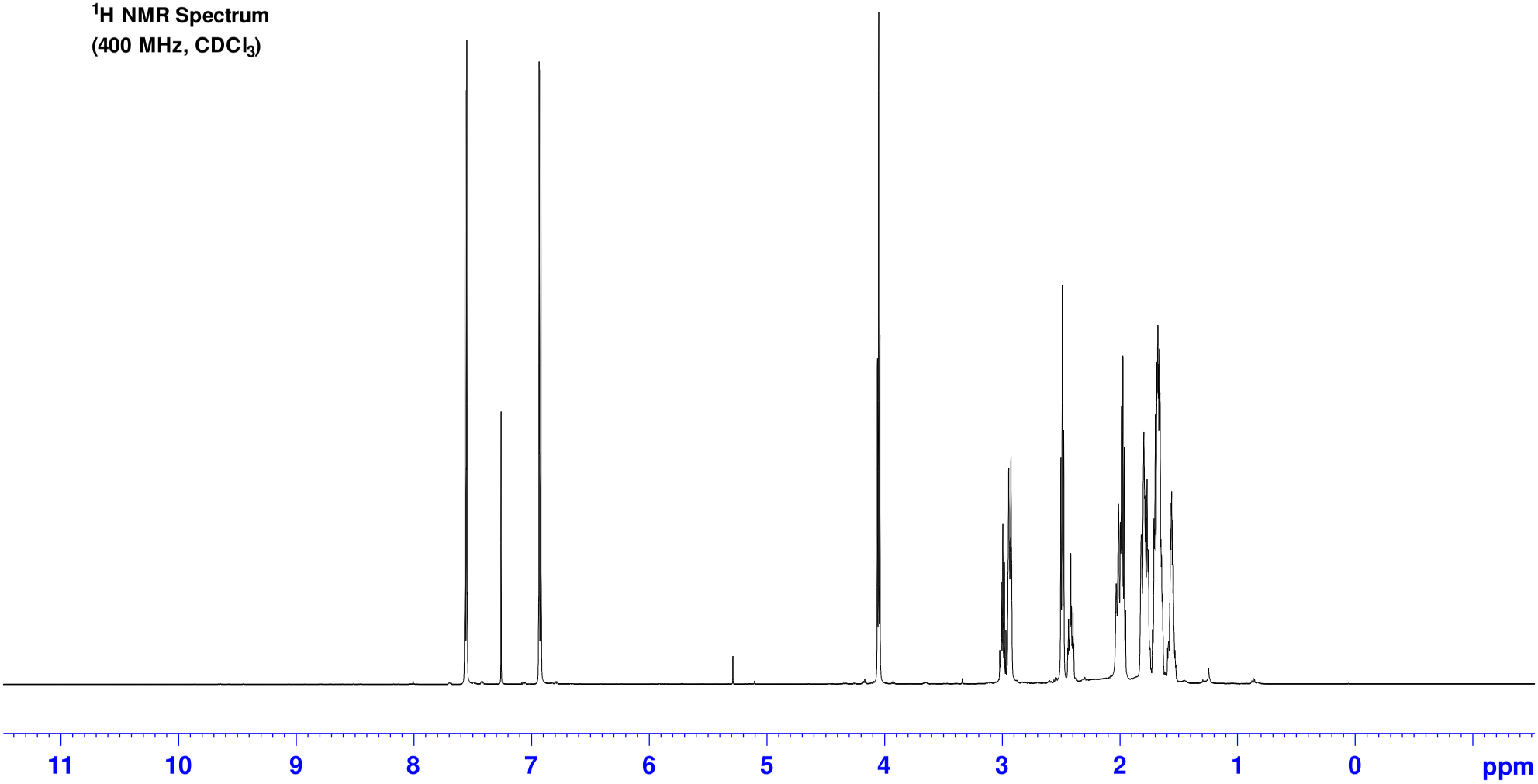


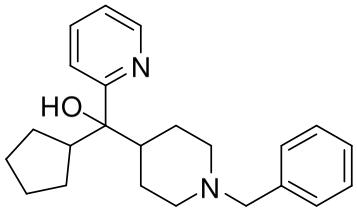



**25**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

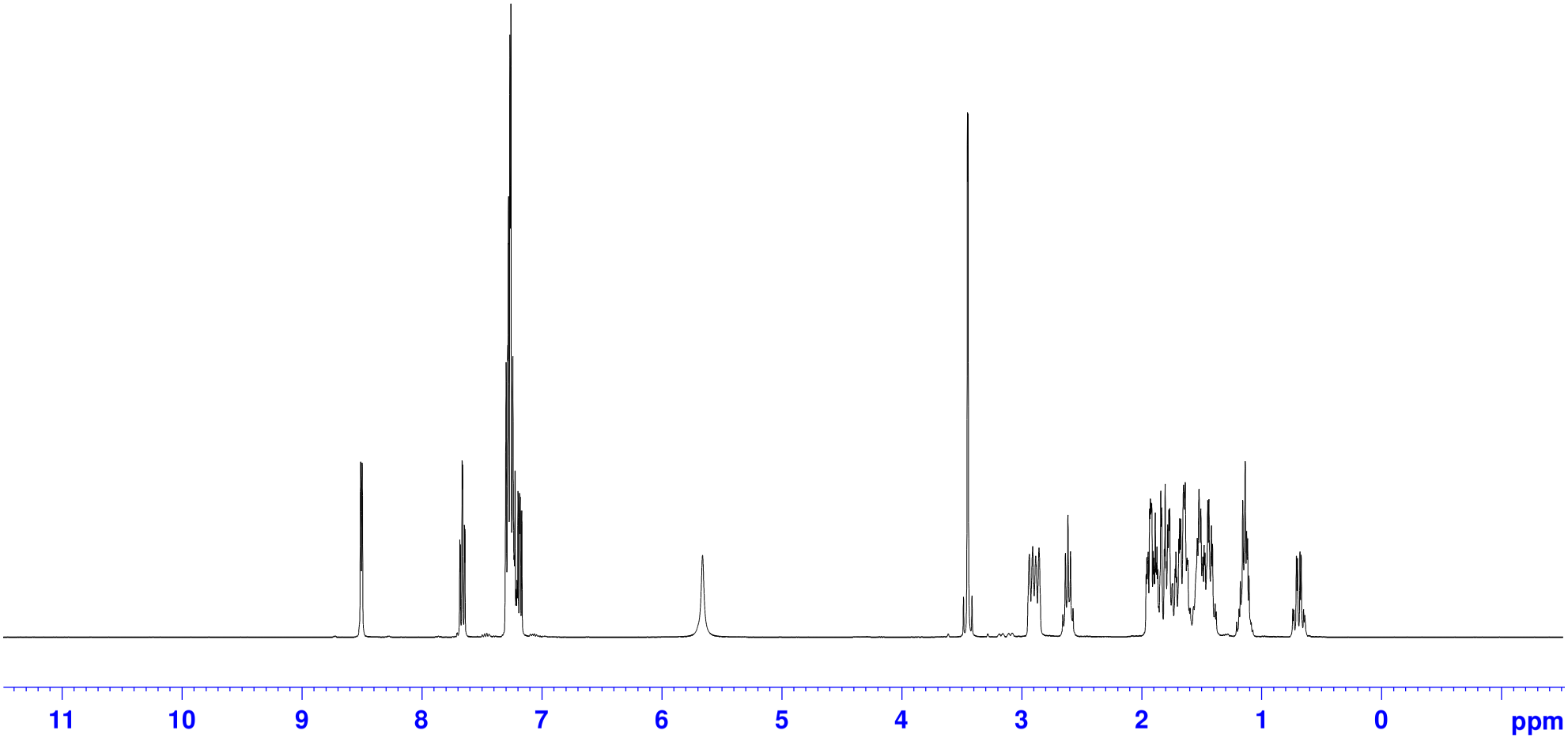


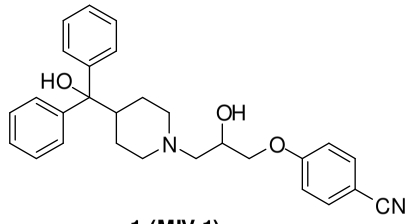



**27**

**$^1$H NMR Spectrum**

**(400 MHz, $CDCl_3$)**

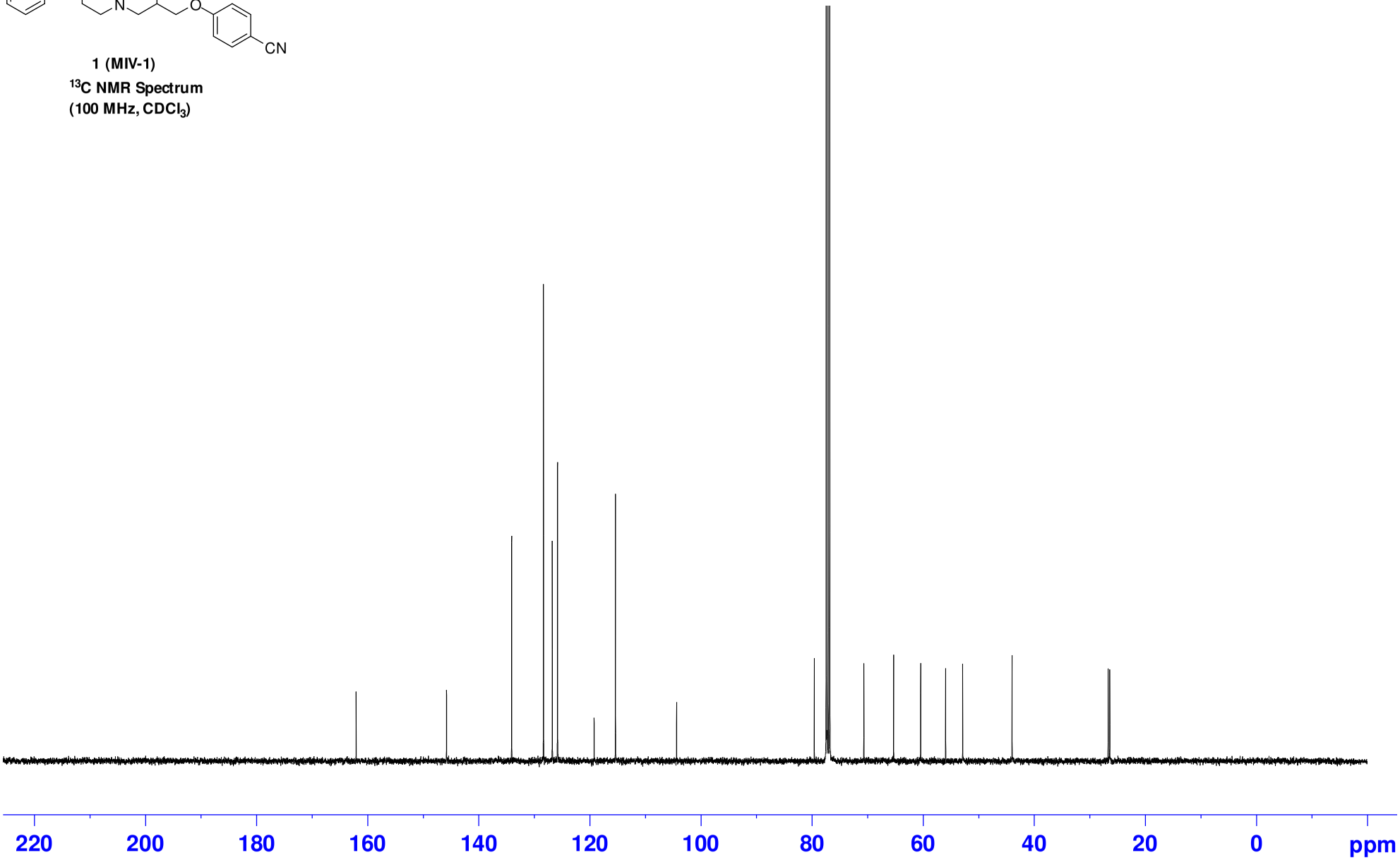


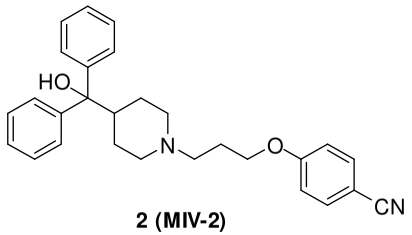



**1 (MIV-1)**

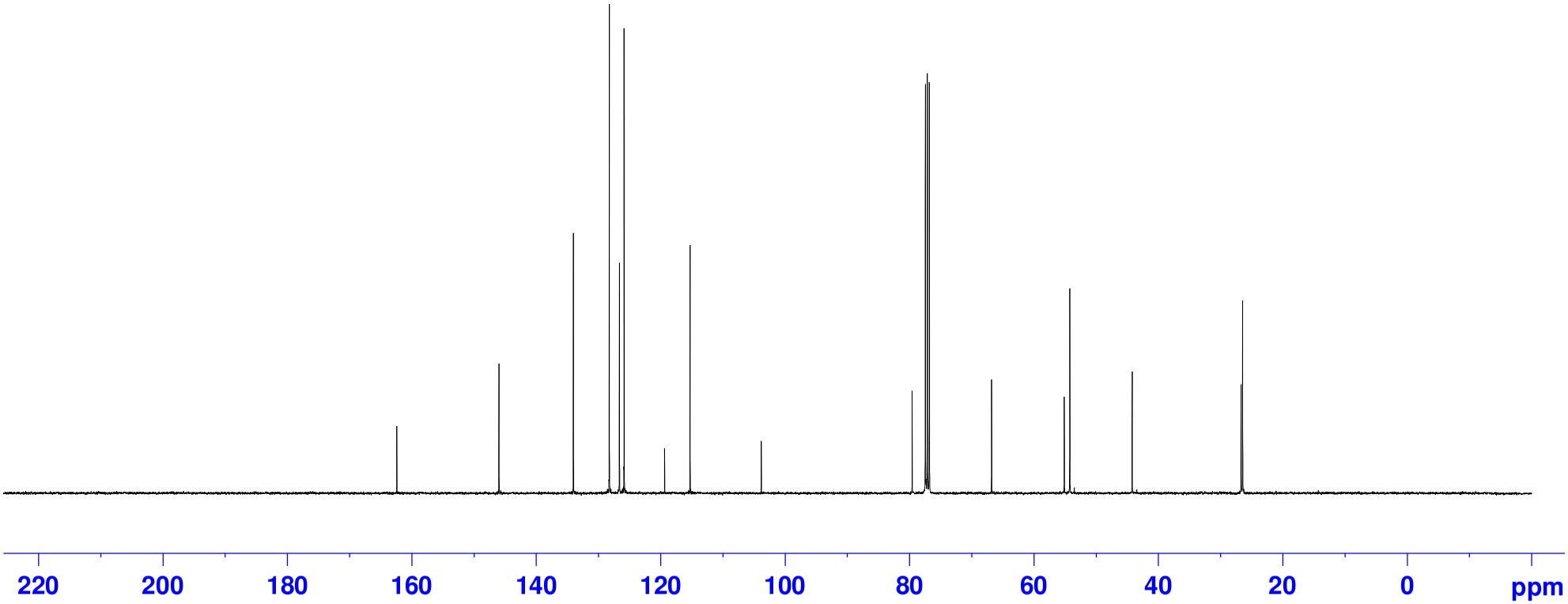
**$^{13}$C NMR Spectrum**

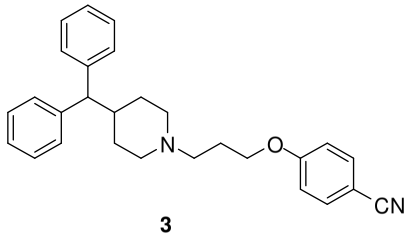
**(100 MHz, $CDCl_3$)**





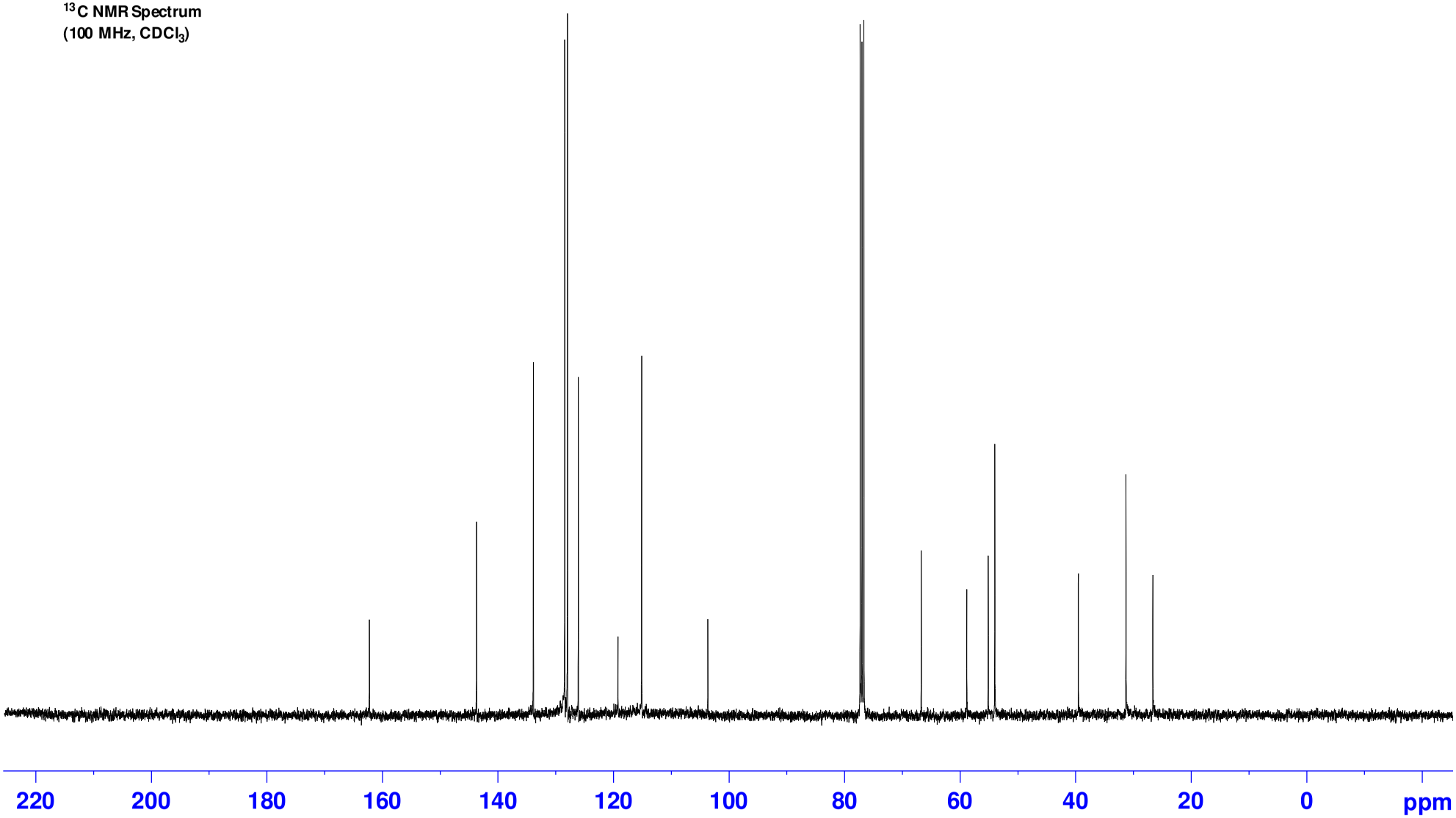

**2 (MIV-2)**
**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

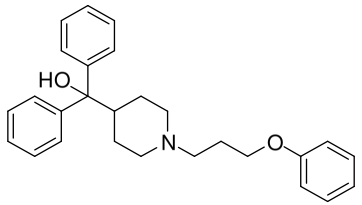





**3**

**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

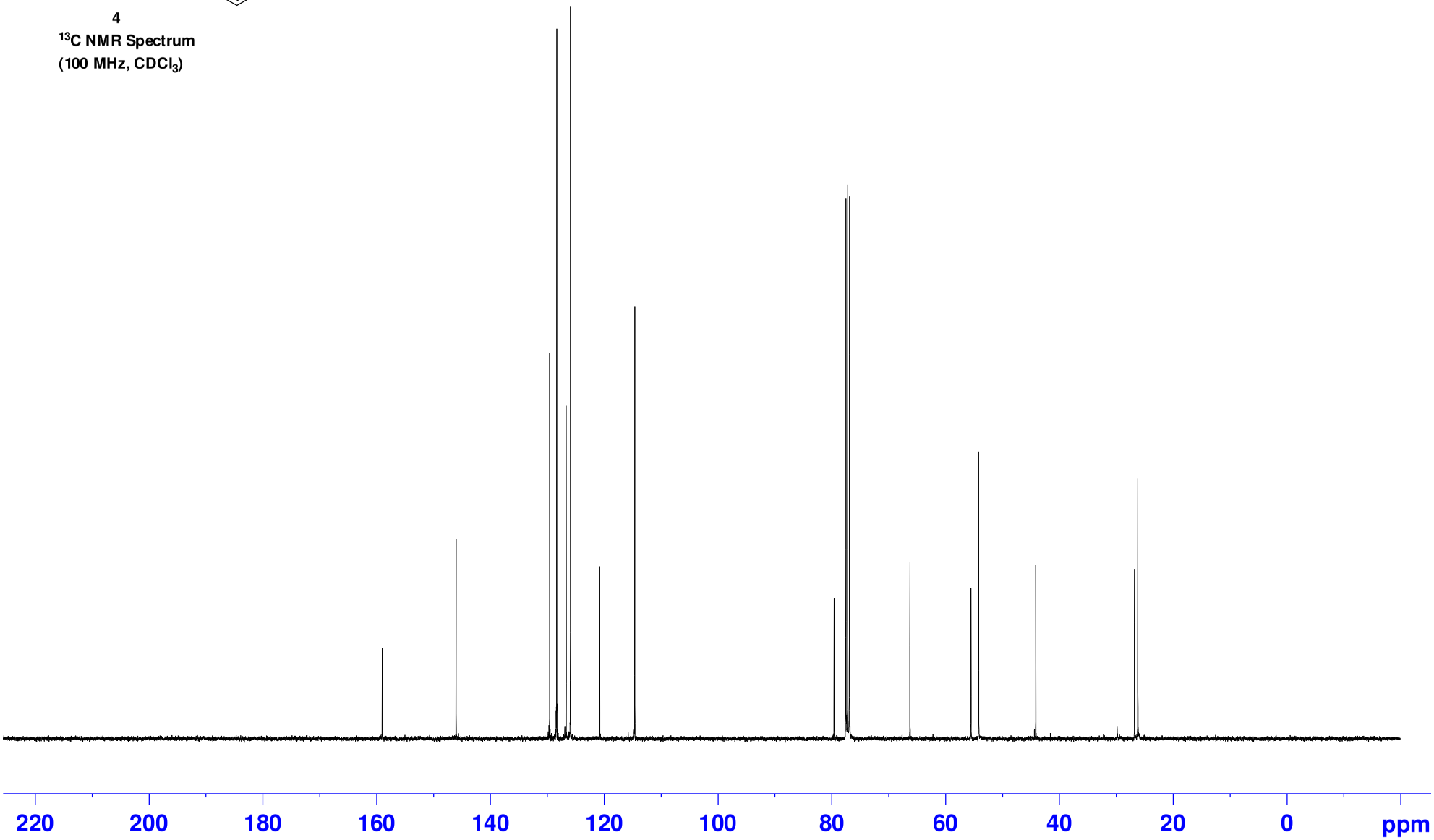


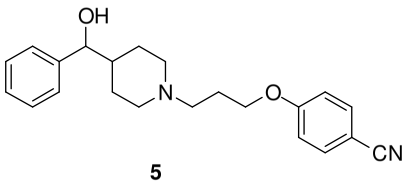



**4**

**$^{13}$C NMR Spectrum**

**(100 MHz, $CDCl_3$)**

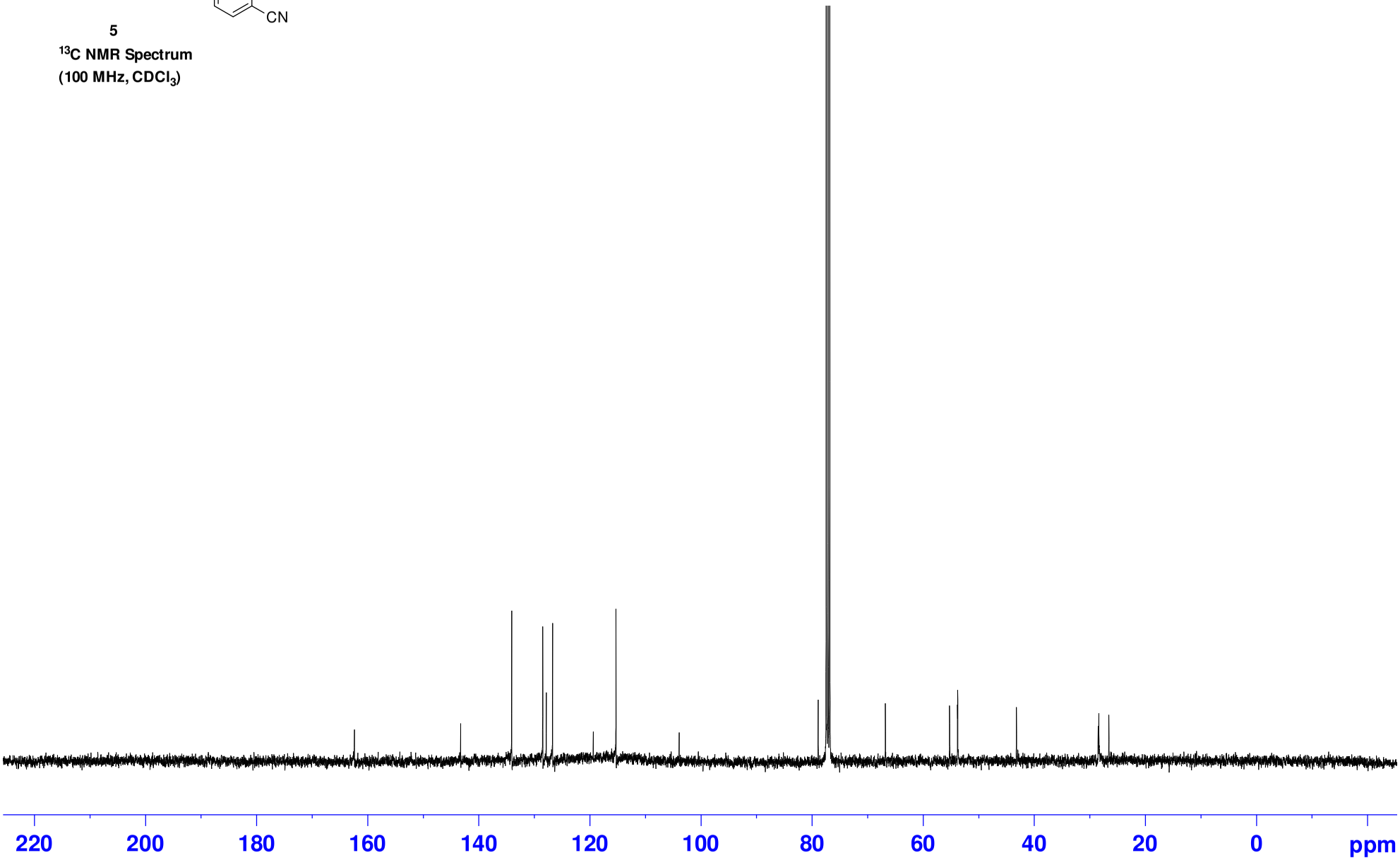


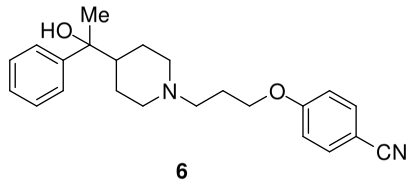



**5**

**$^{13}$C NMR Spectrum**

**(100 MHz, $CDCl_3$)**

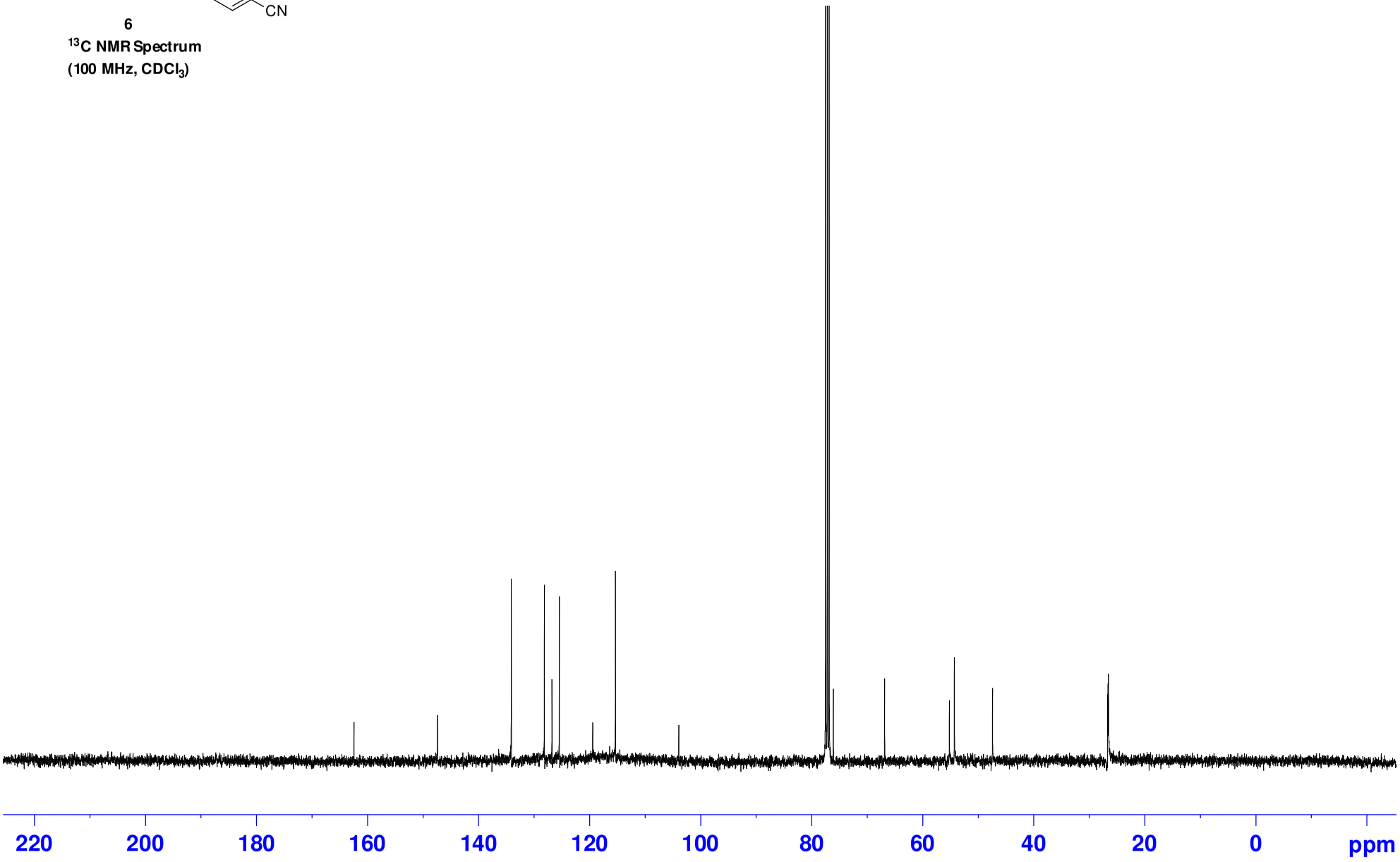


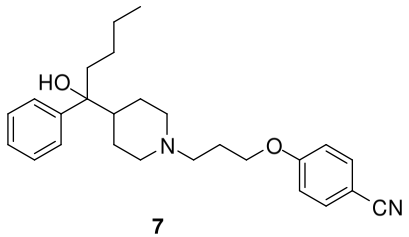



**6**

**$^{13}$C NMR Spectrum**

**(100 MHz, $CDCl_3$)**

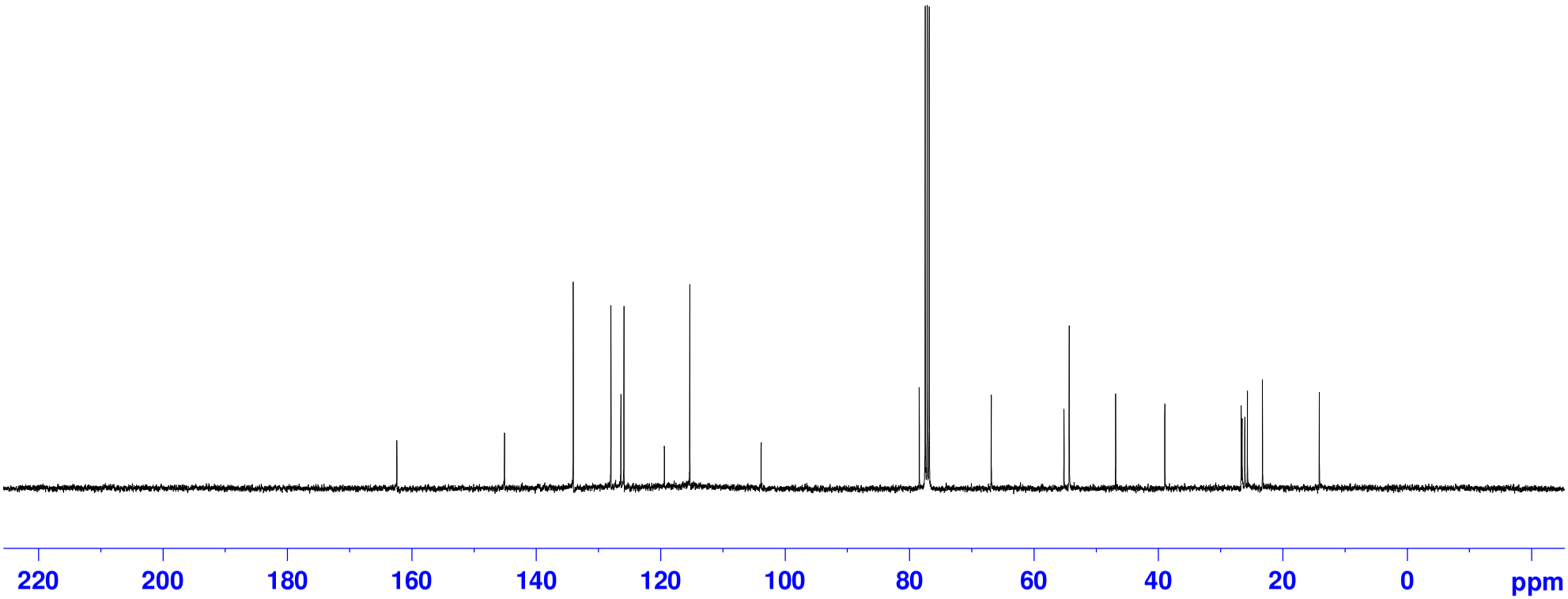


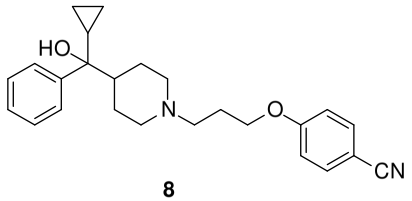



**7**

**$^{13}$C NMR Spectrum**

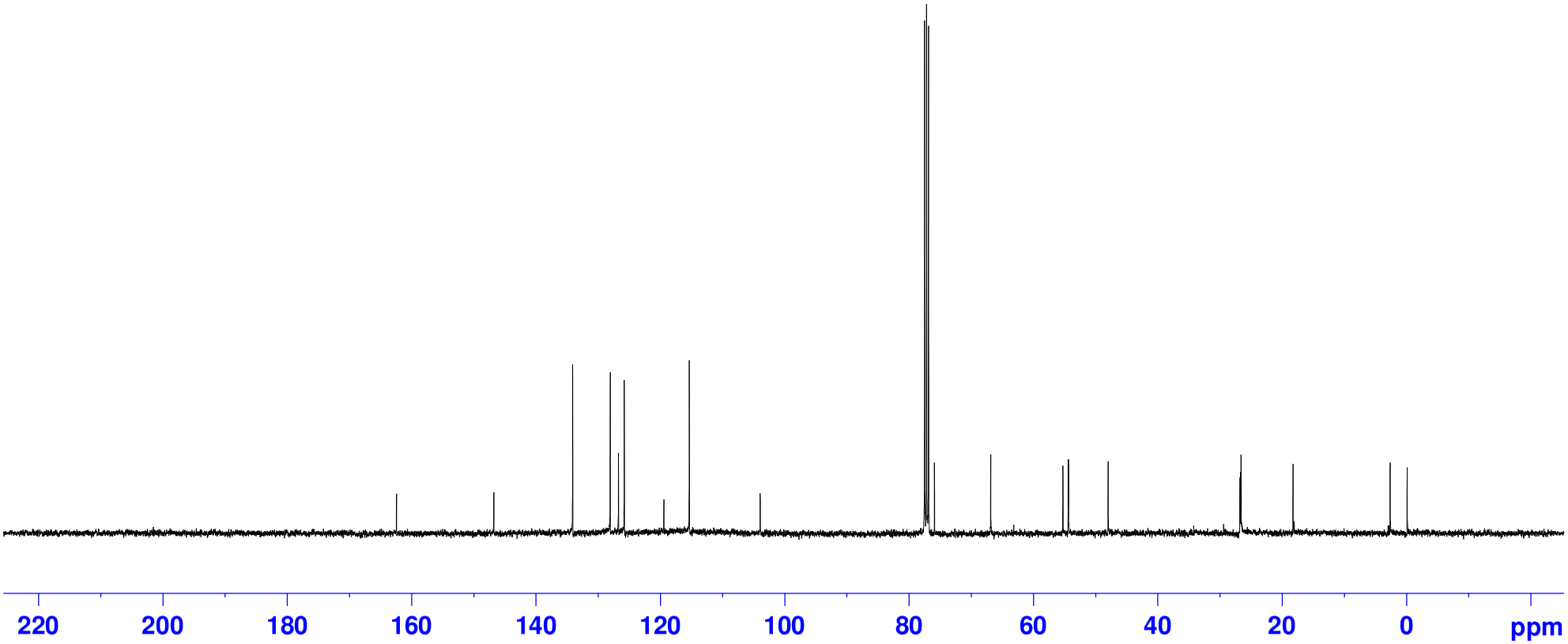
**(100 MHz, $CDCl_3$)**

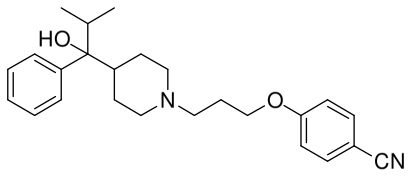





**8**

**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

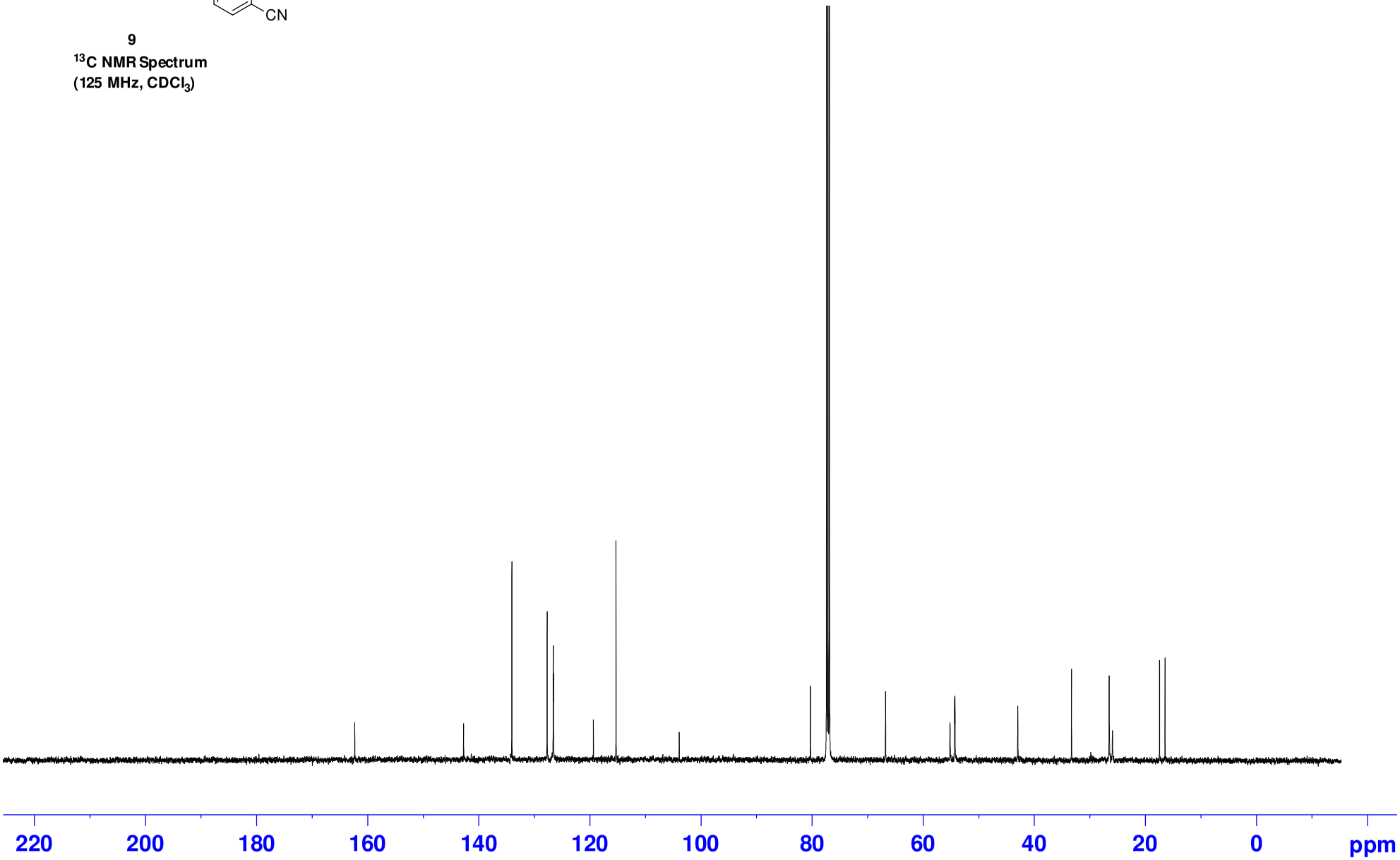


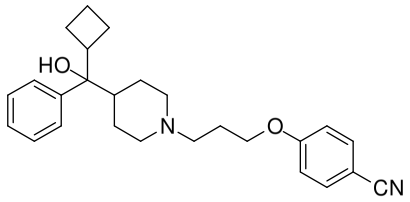



**9**

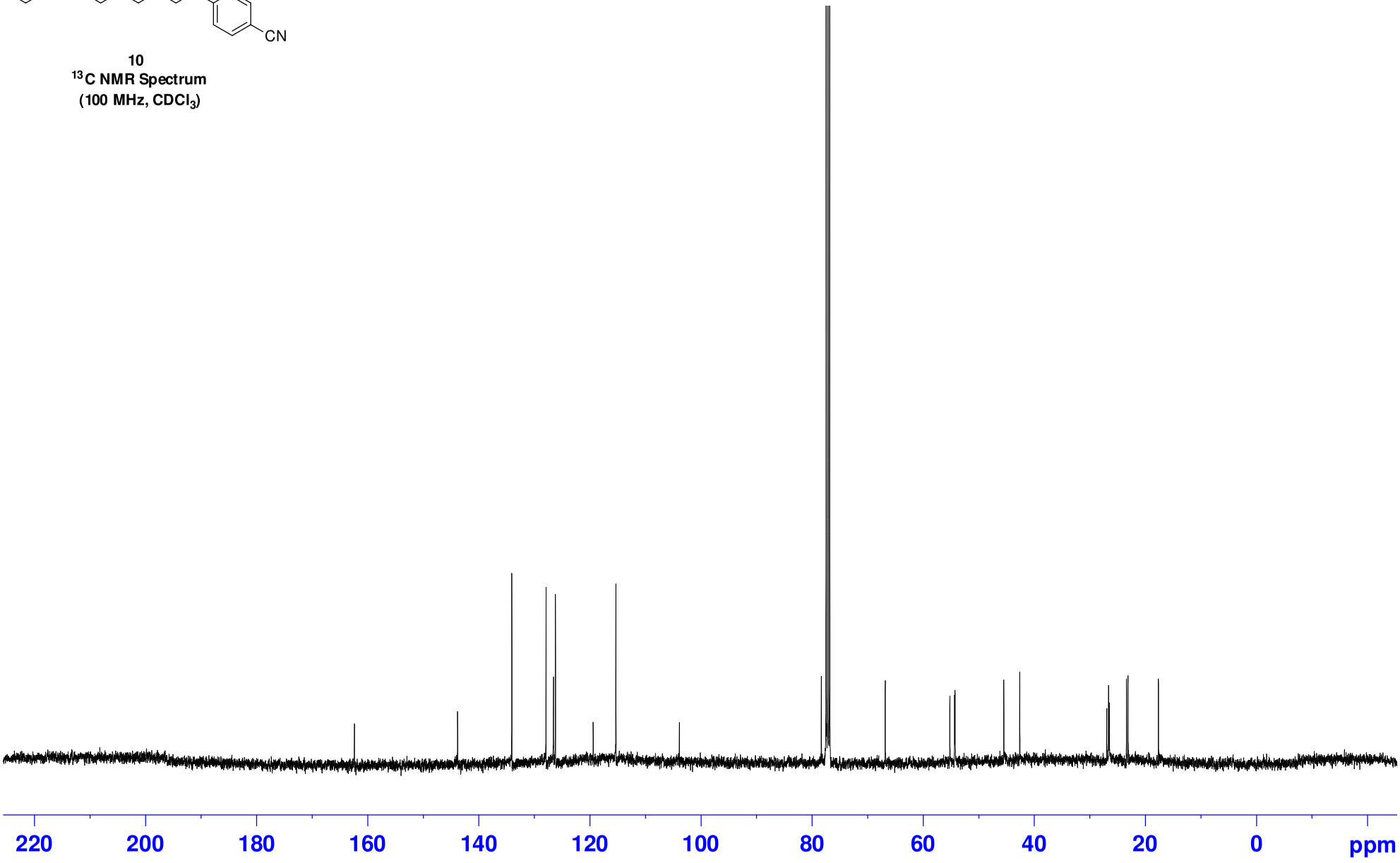
**$^{13}$C NMR Spectrum**

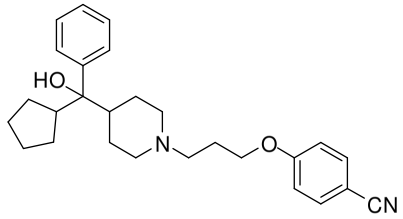
**(125 MHz, $CDCl_3$)**






**10**
**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

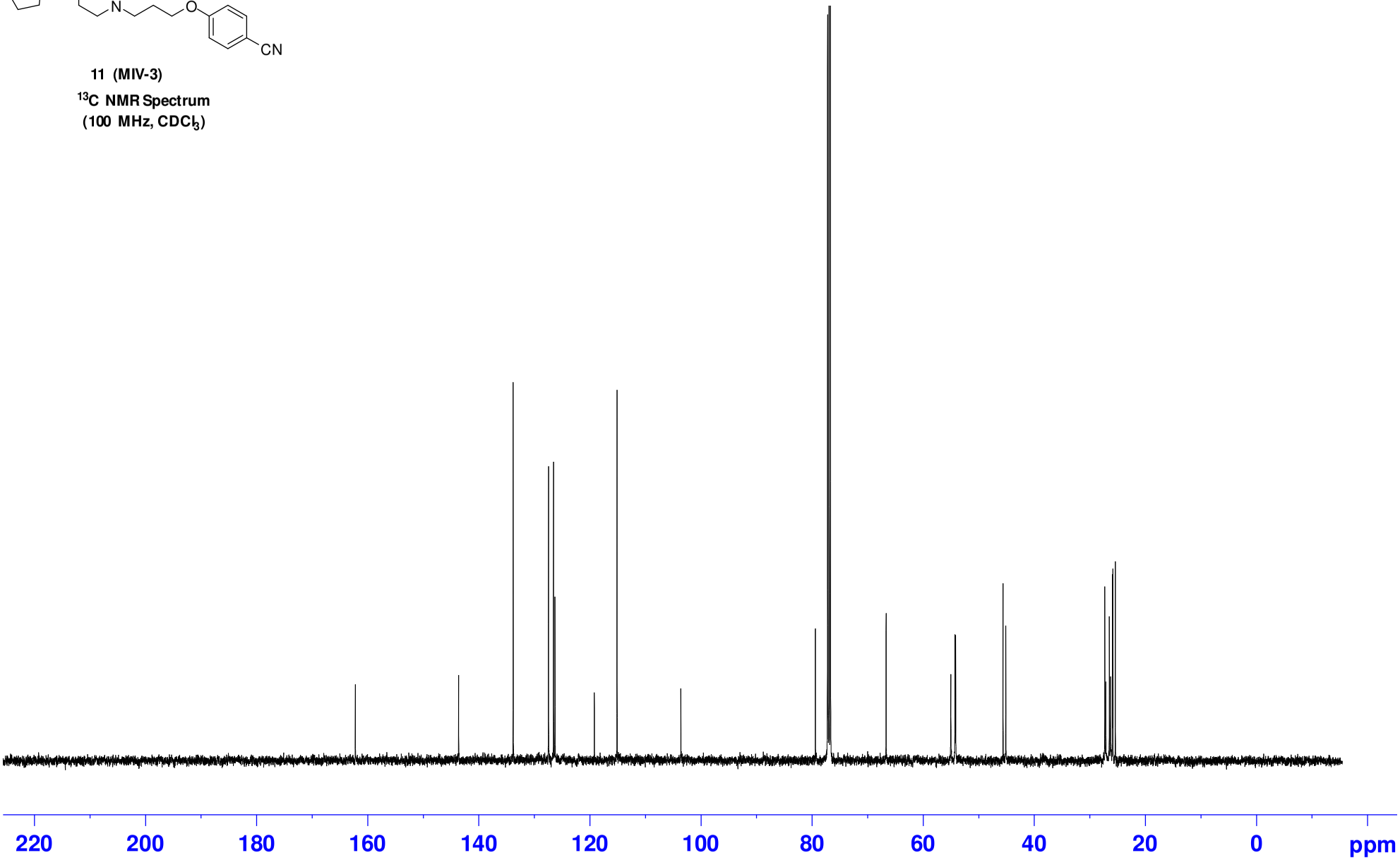


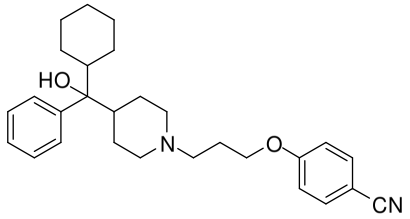



**11 (MIV-3)**

**$^{13}$C NMR Spectrum**

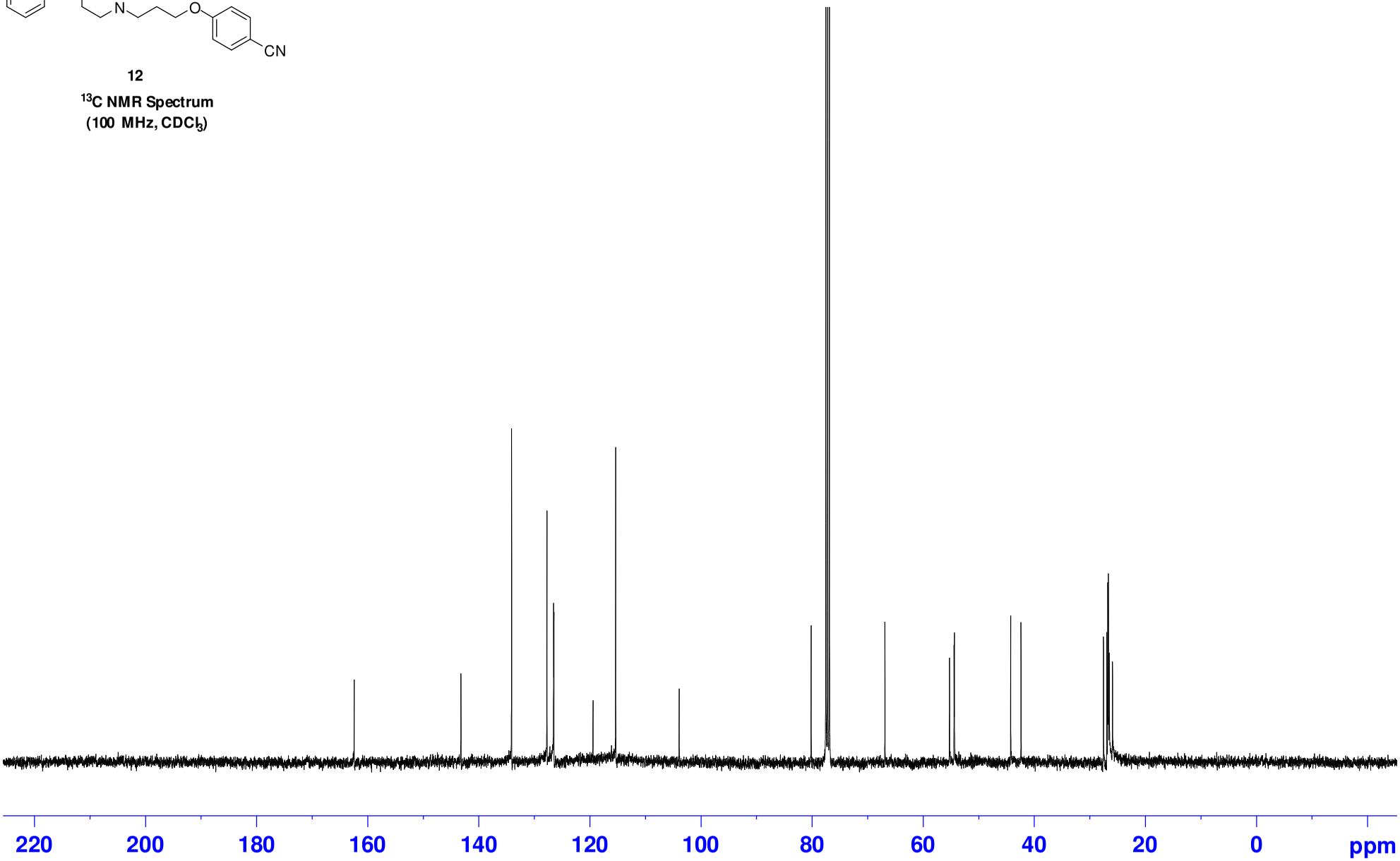
**(100 MHz, $CDCl_3$)**

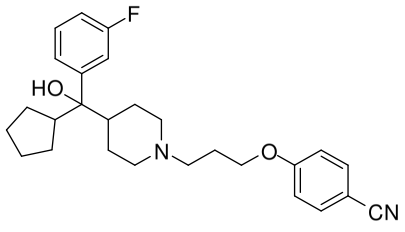




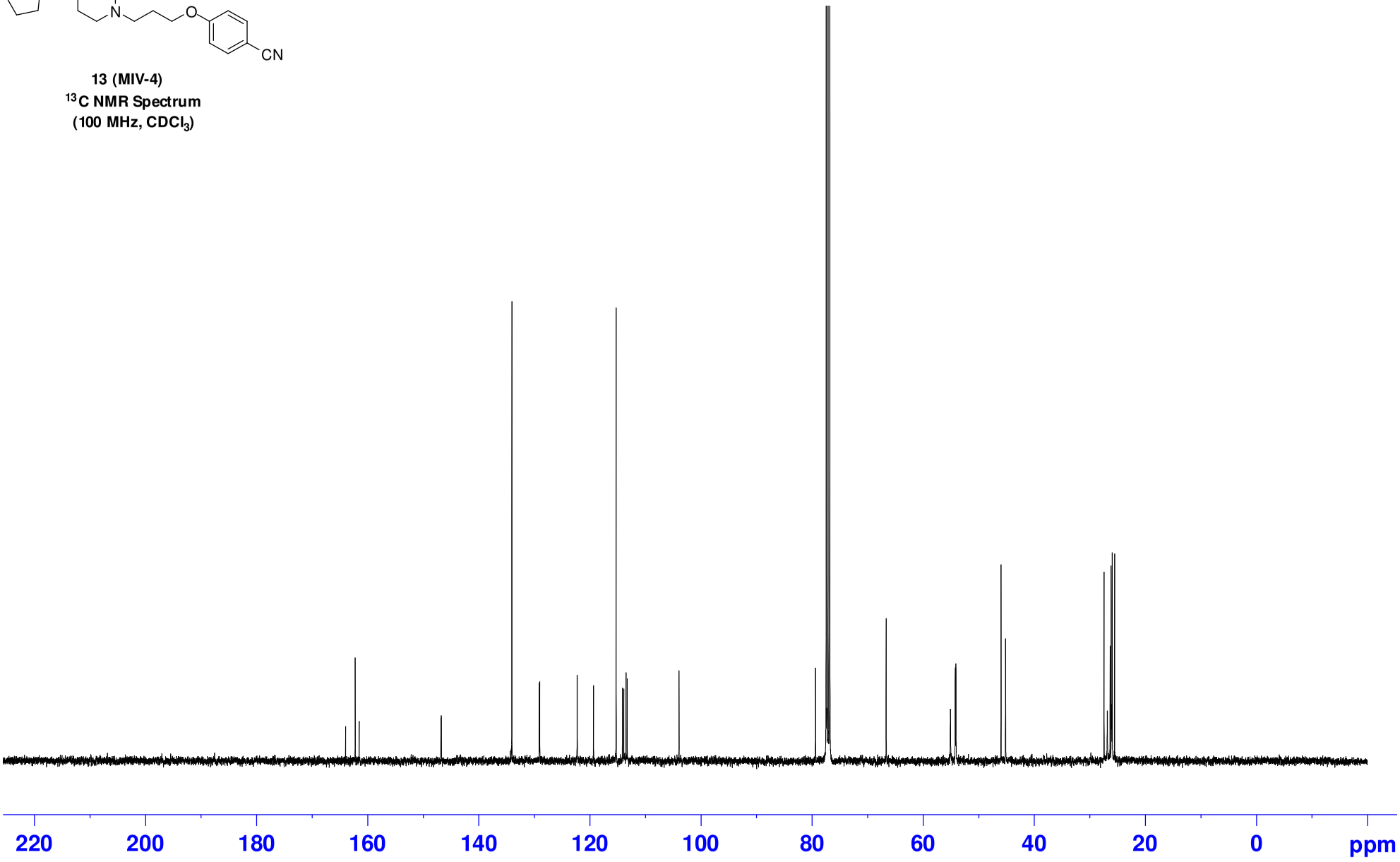

**12**

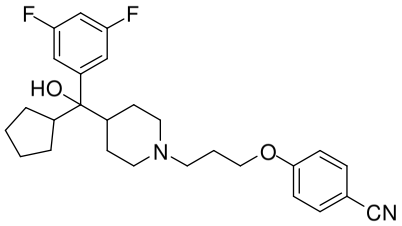
**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**






**13 (MIV-4)**
**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

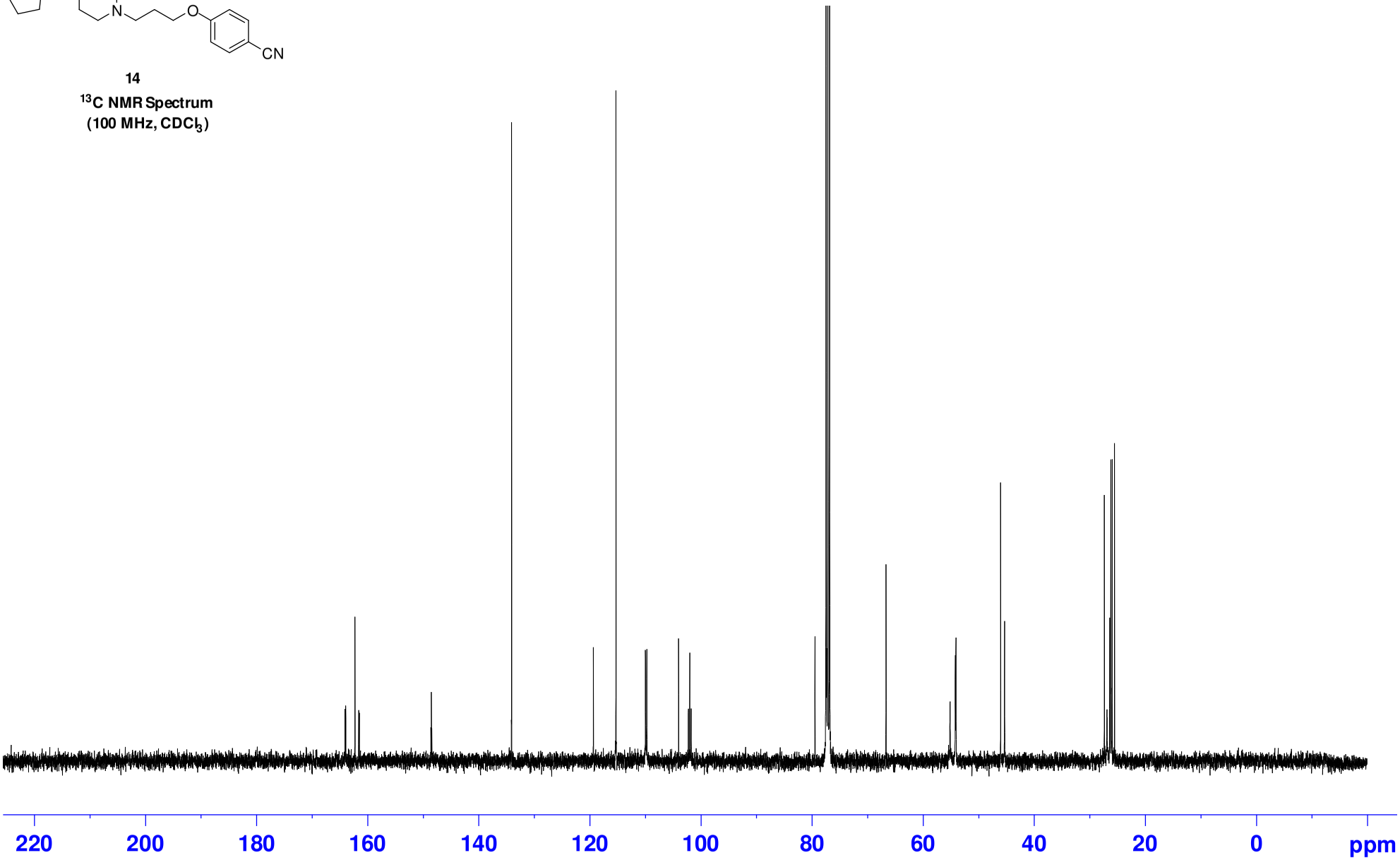


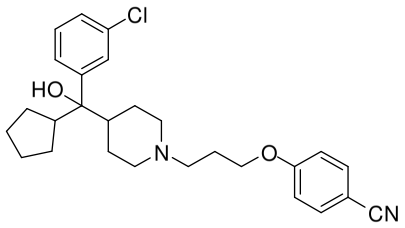



**14**

**$^{13}$C NMR Spectrum**

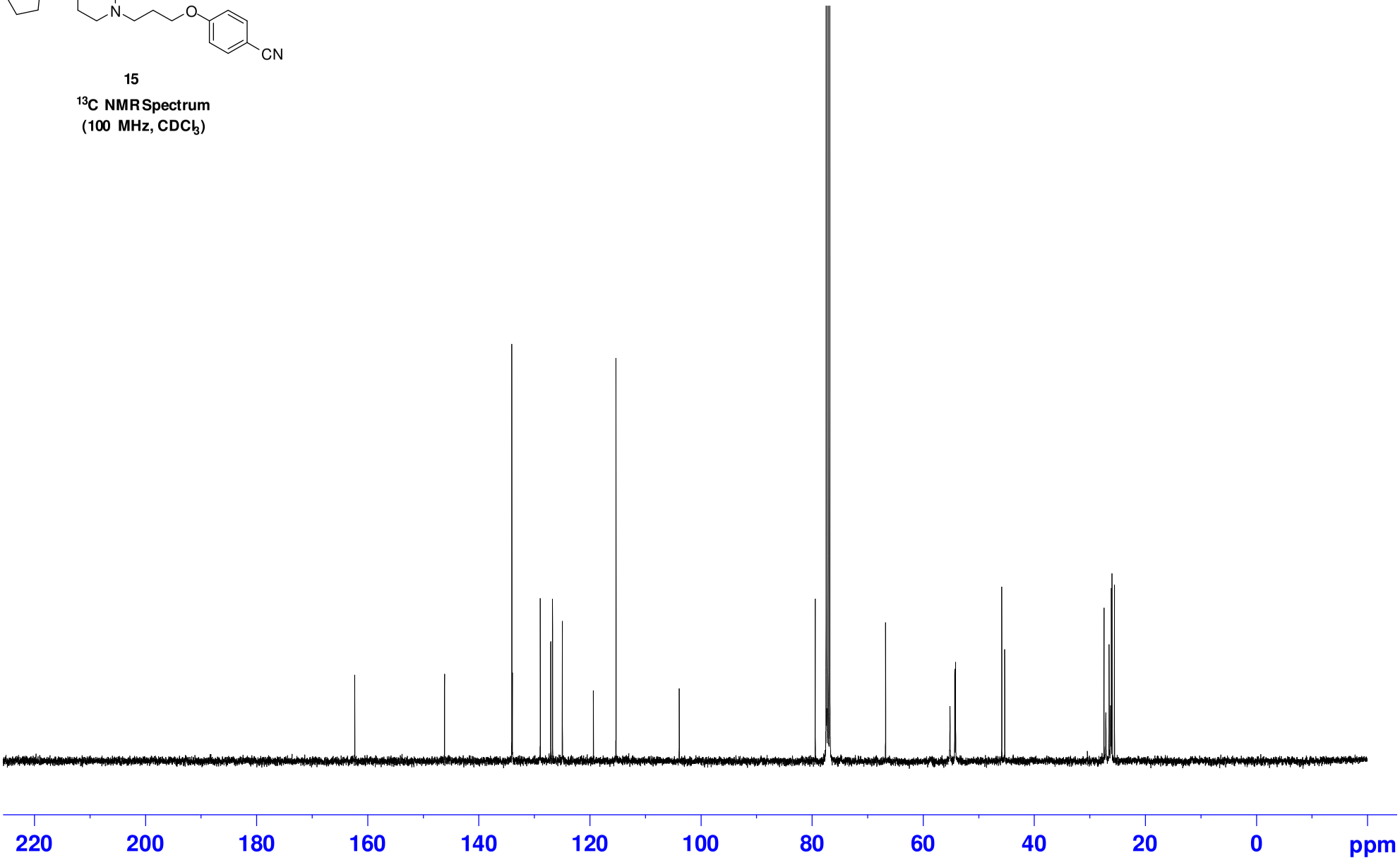
**(100 MHz, $CDCl_3$)**

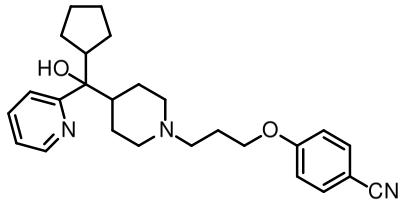





**15**

**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

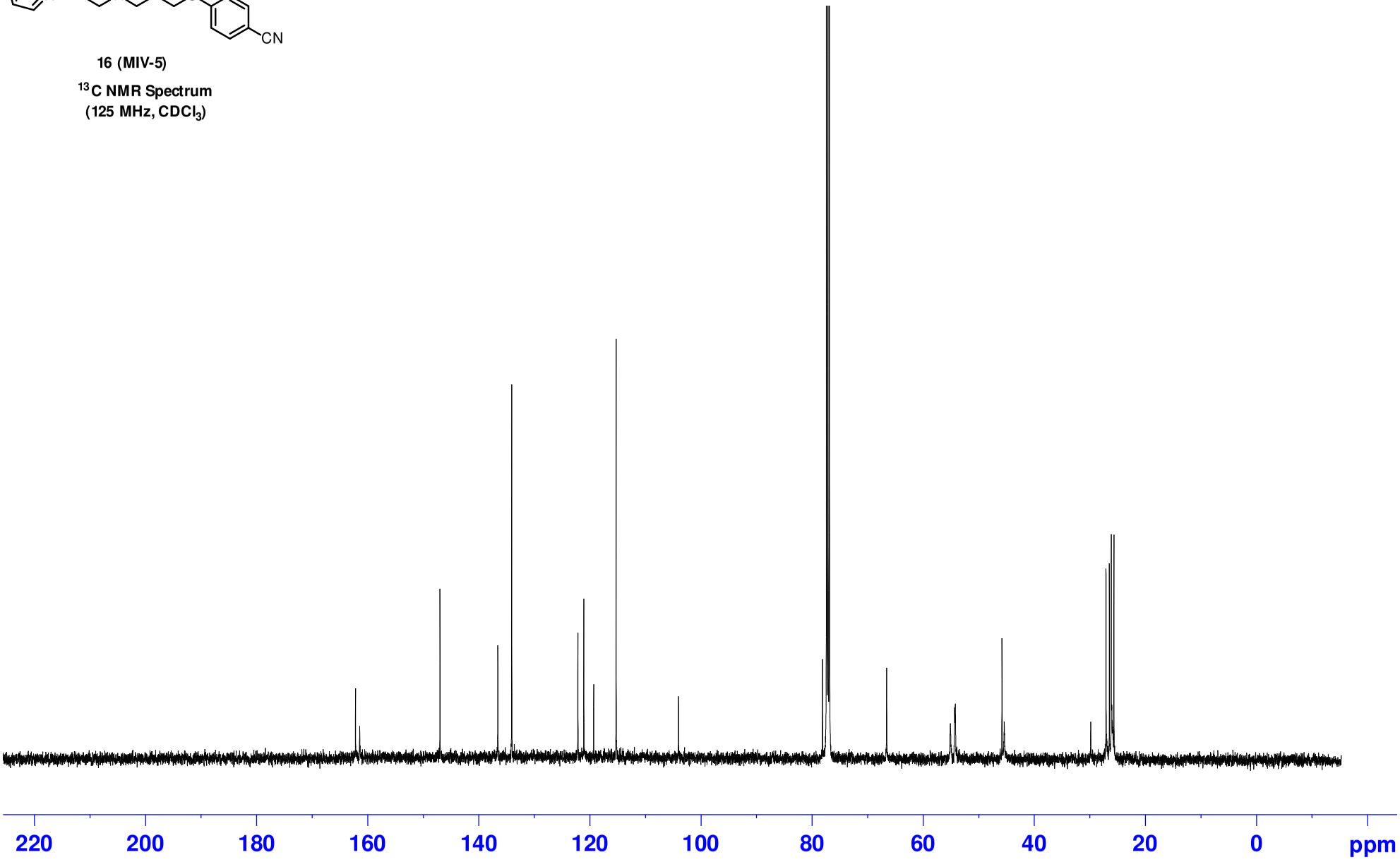


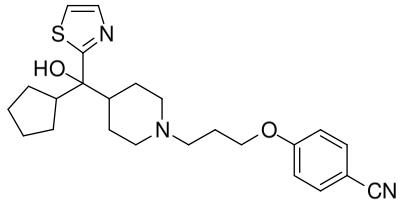



**16 (MIV-5)**

**$^{13}$C NMR Spectrum**

**(125 MHz, $CDCl_3$)**

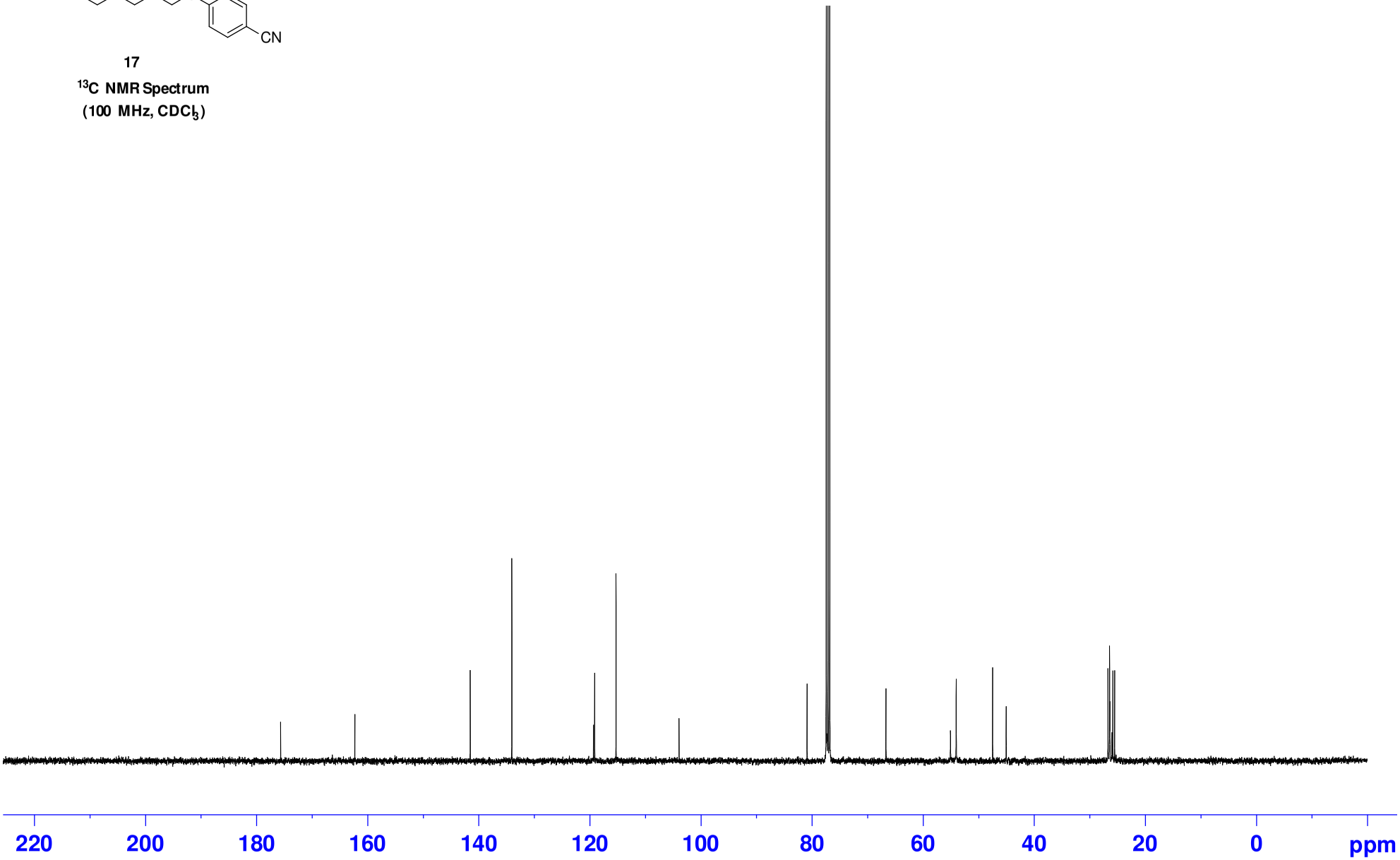


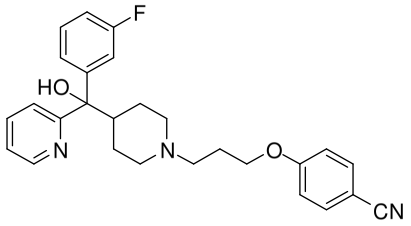



**17**

**$^{13}$C NMR Spectrum**

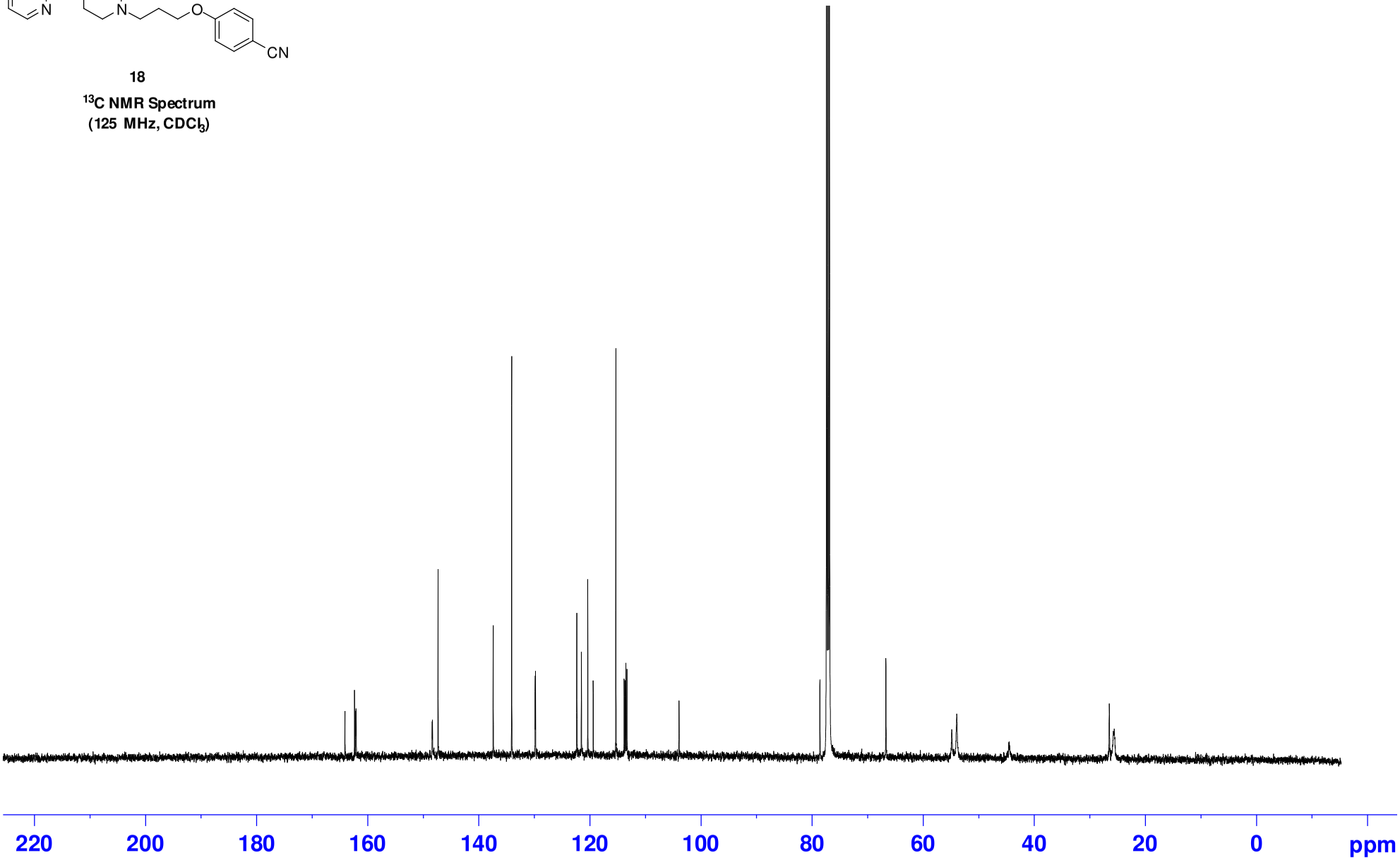
**(100 MHz, $CDCl_3$)**

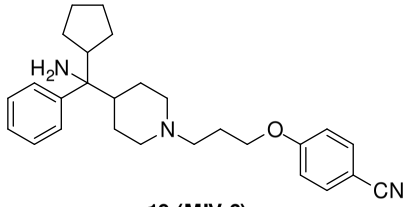




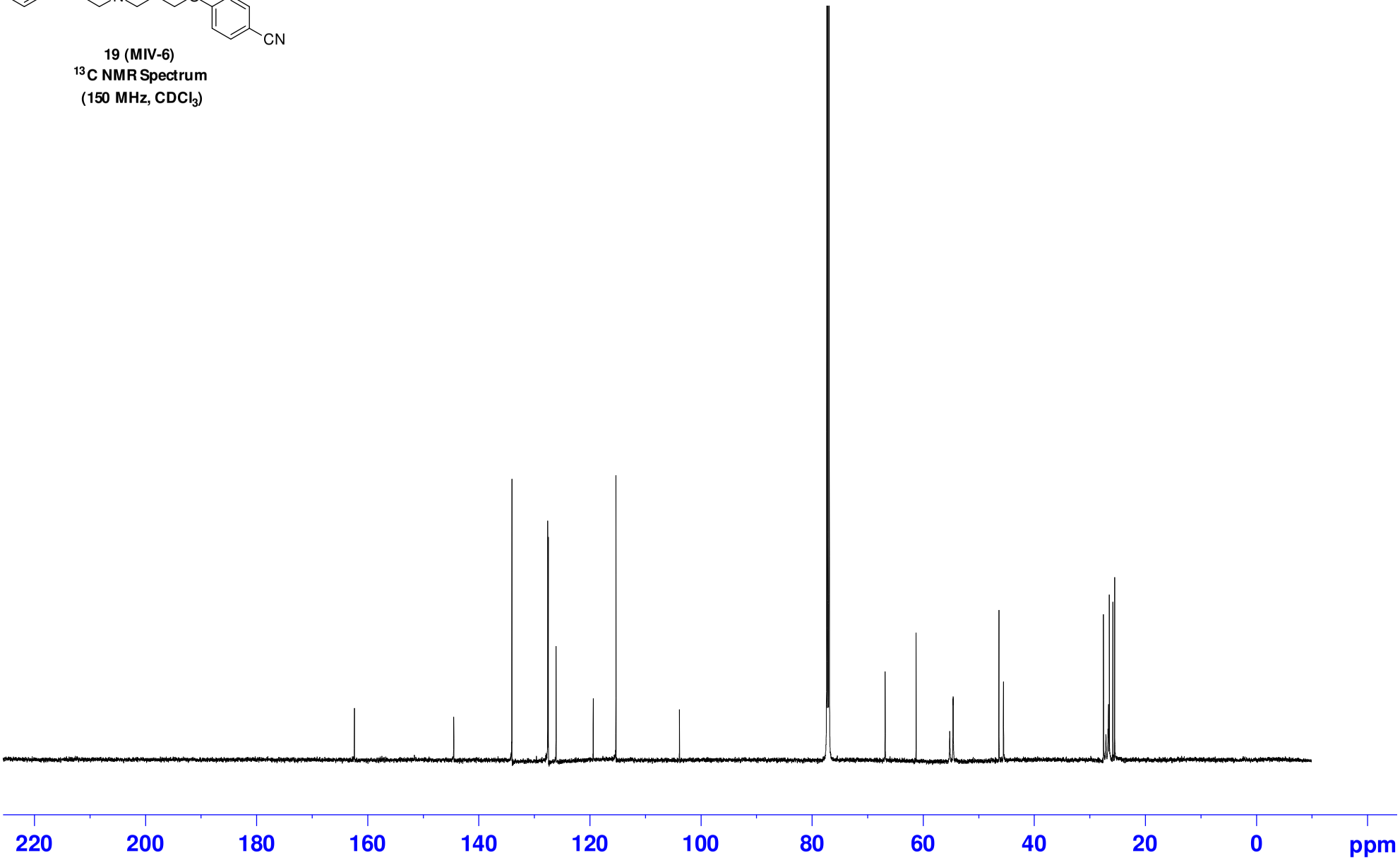

**18**

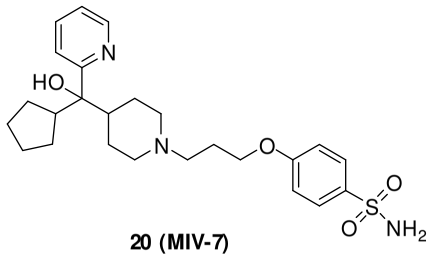
**$^{13}$C NMR Spectrum**
**(125 MHz, $CDCl_3$)**






**19 (MIV-6)**
**$^{13}$C NMR Spectrum**
**(150 MHz, $CDCl_3$)**

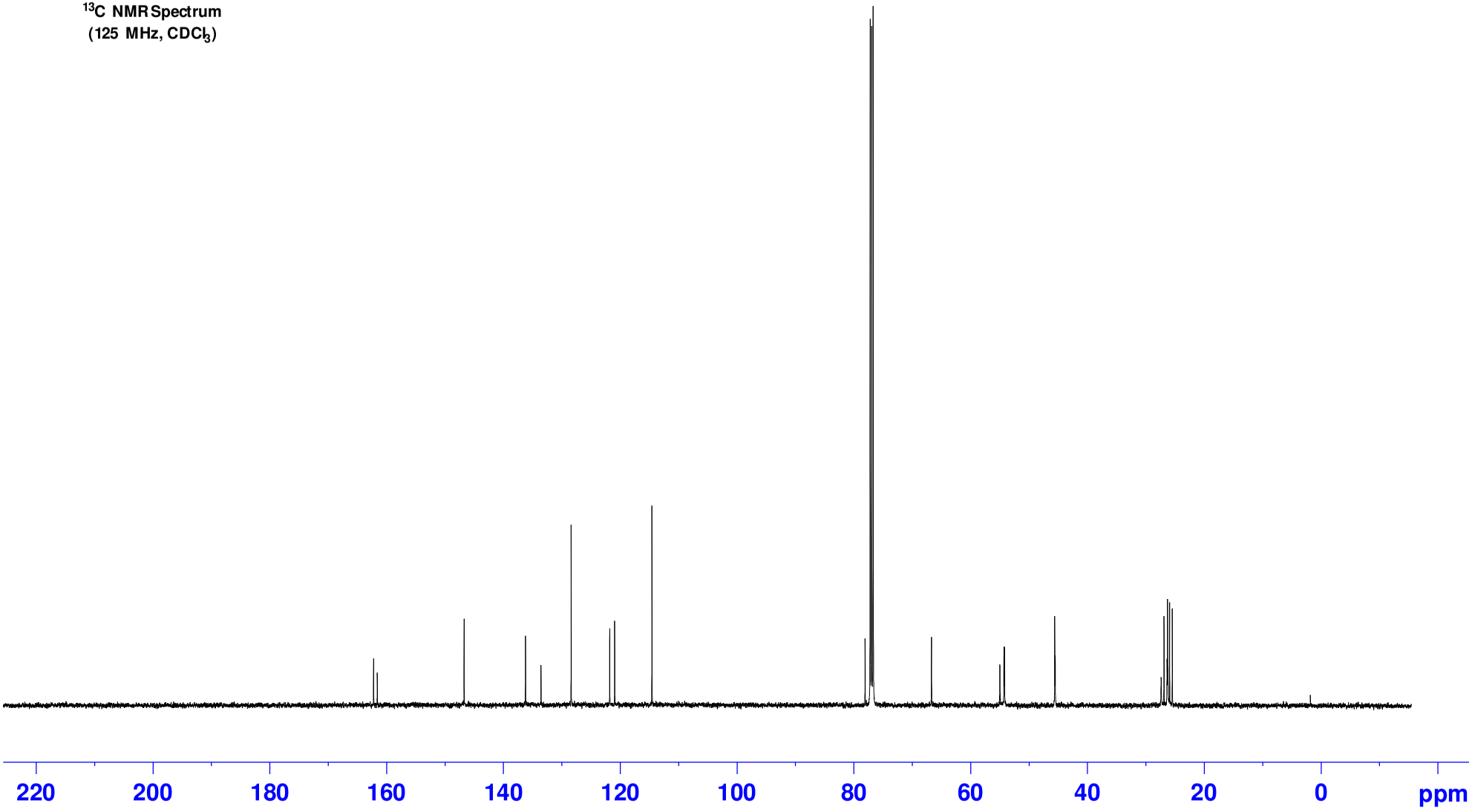


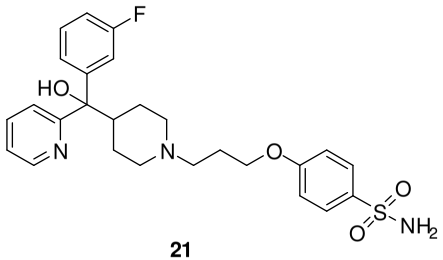



**20 (MIV-7)**

**$^{13}$C NMR Spectrum**

**(125 MHz, $CDCl_3$)**

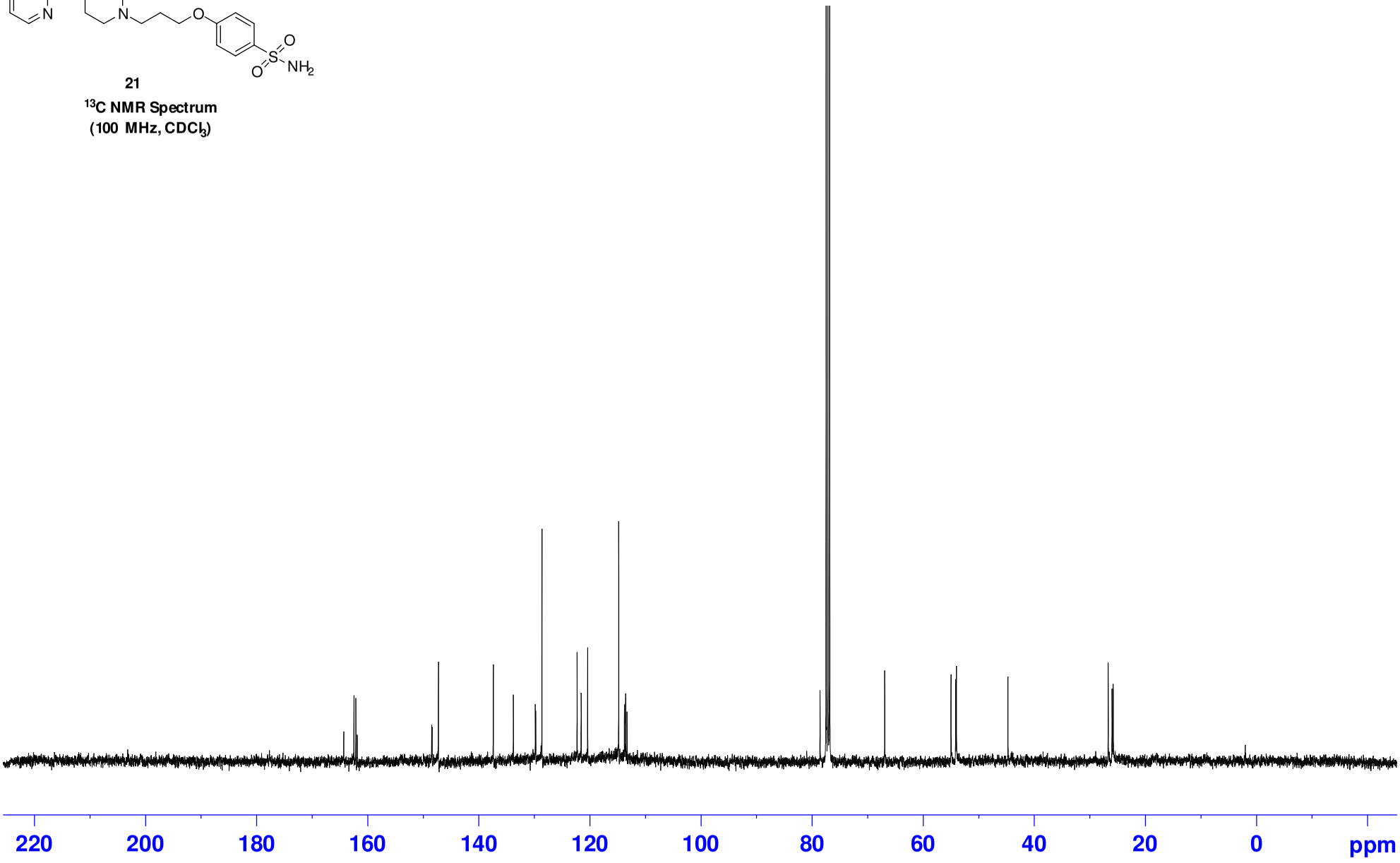


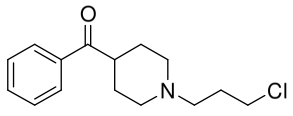



**21**

**$^{13}$C NMR Spectrum**

**(100 MHz, $CDCl_3$)**

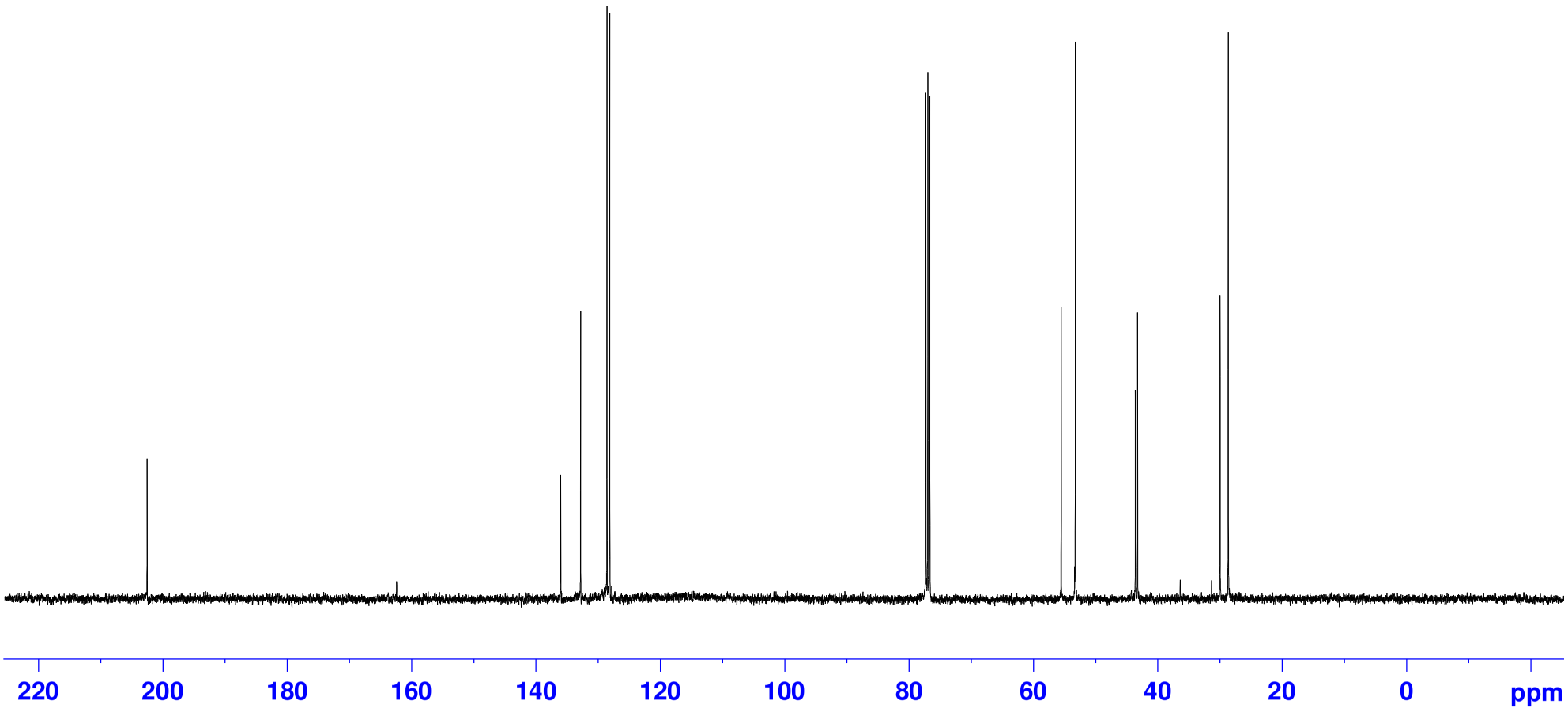


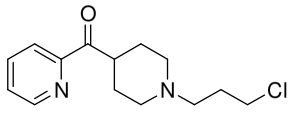



**23a**

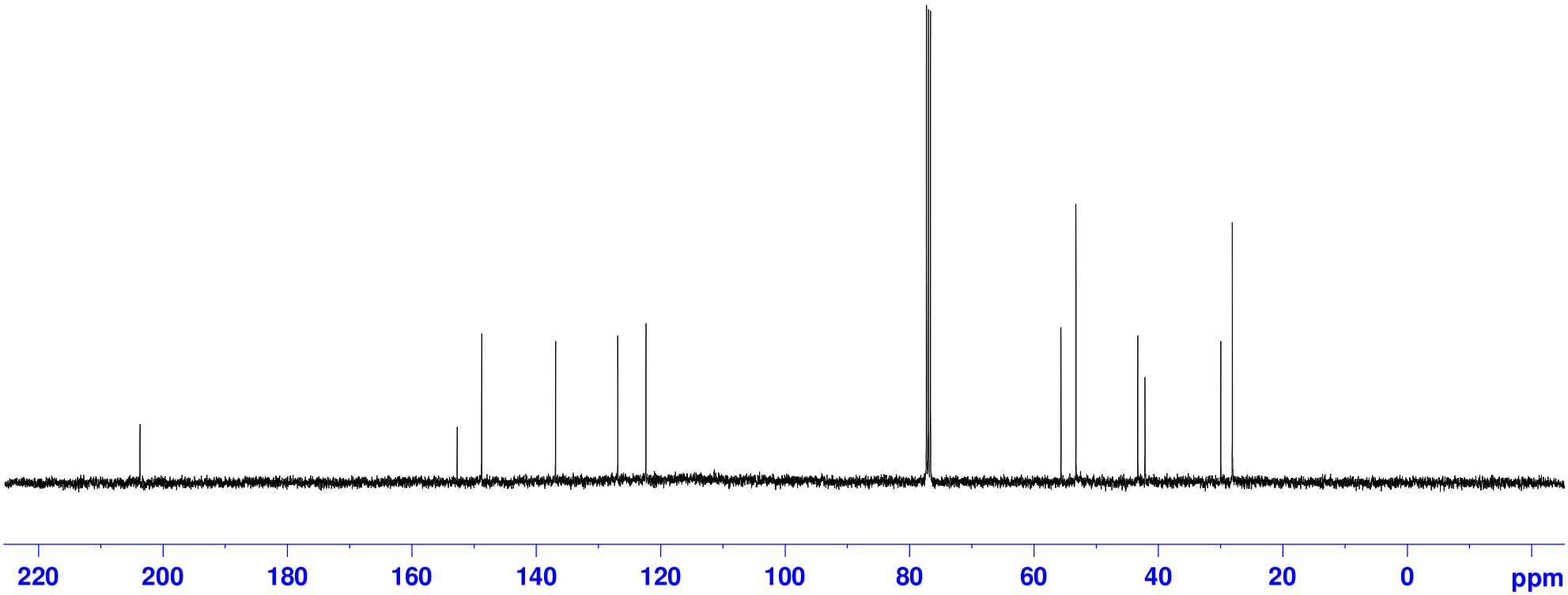
**$^{13}$C NMR Spectrum**

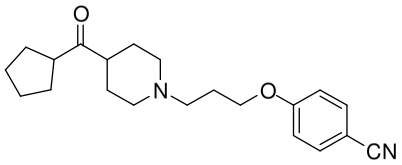
**(100 MHz, $CDCl_3$)**






**23b**
**$^{13}$C NMR Spectrum**
**(100 MHz, $CDCl_3$)**

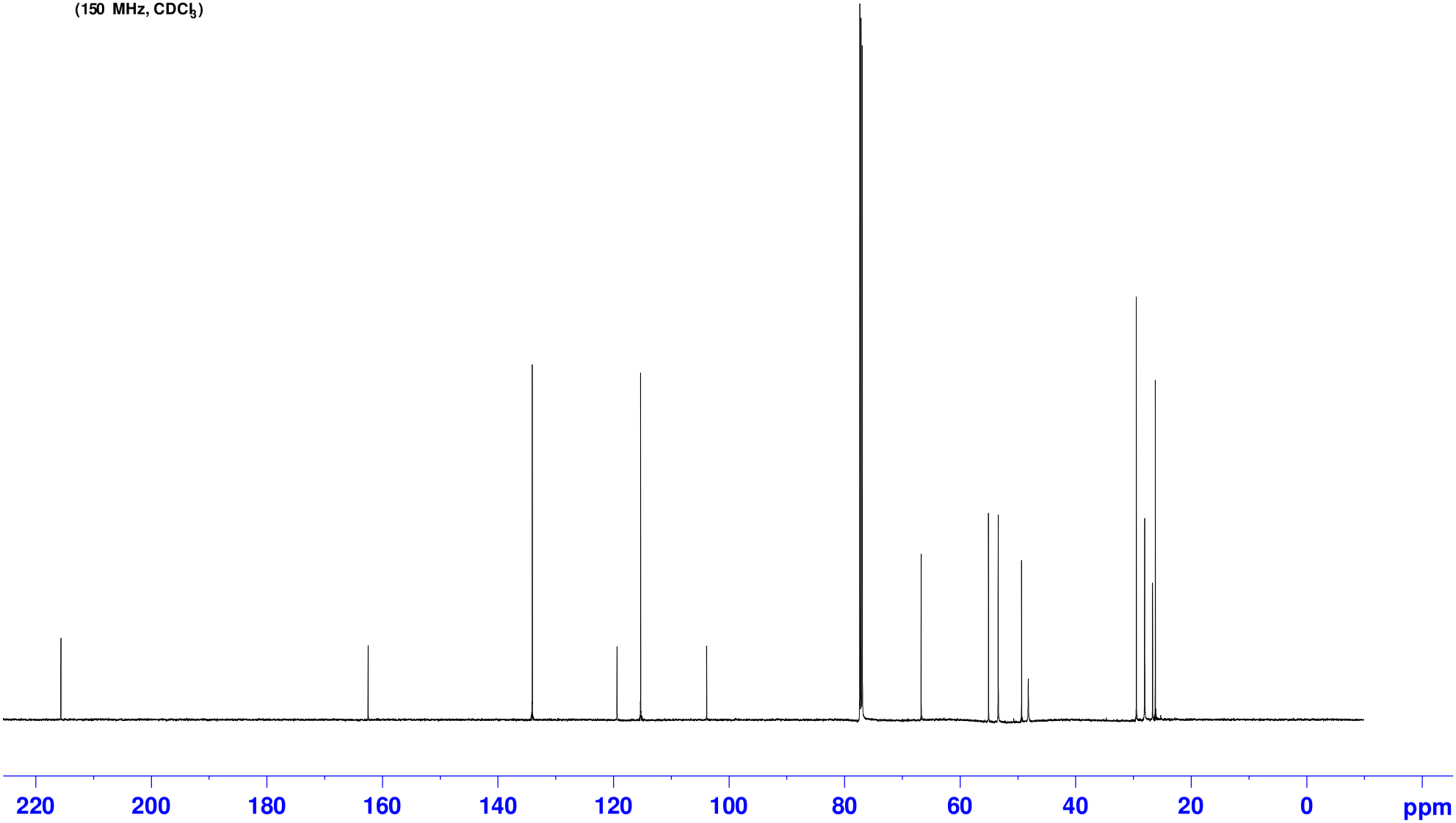


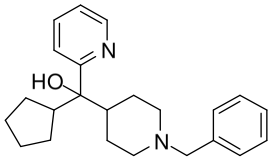



**25**

**$^{13}$C NMR Spectrum**

**(150 MHz, $CDCl_3$)**

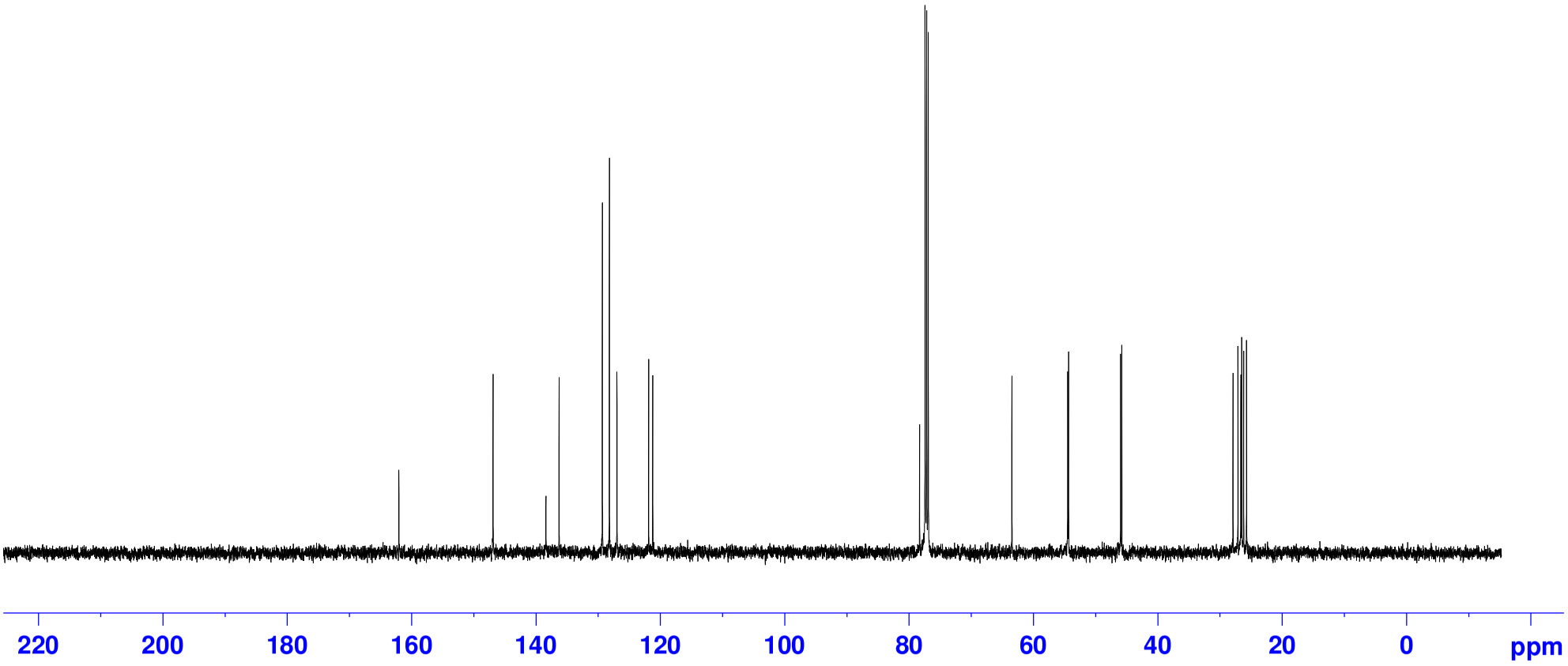




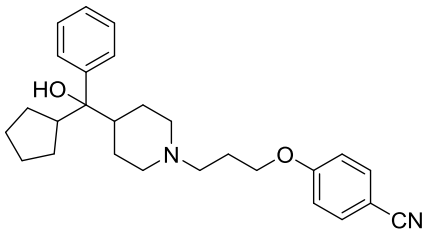

27

$^{13}C$ NMR Spectrum

(100 MHz, $CDCl_3$)

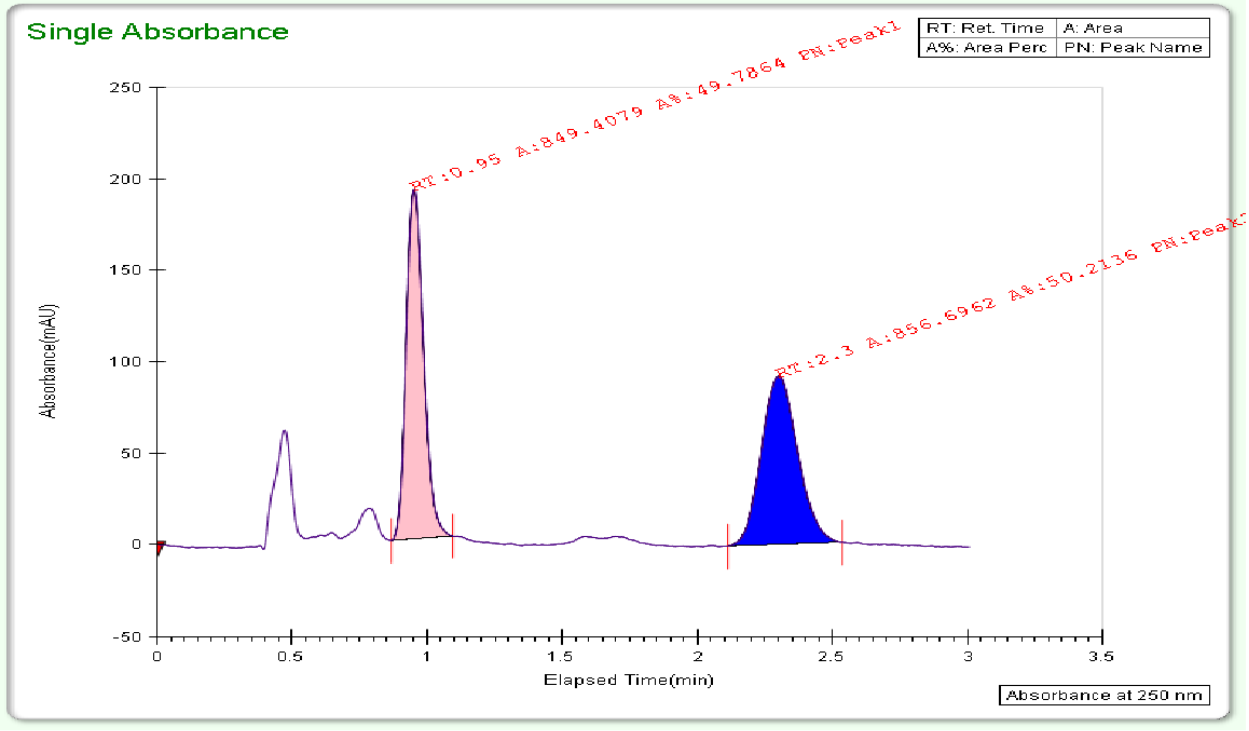


## 6. Chiral SFC Traces

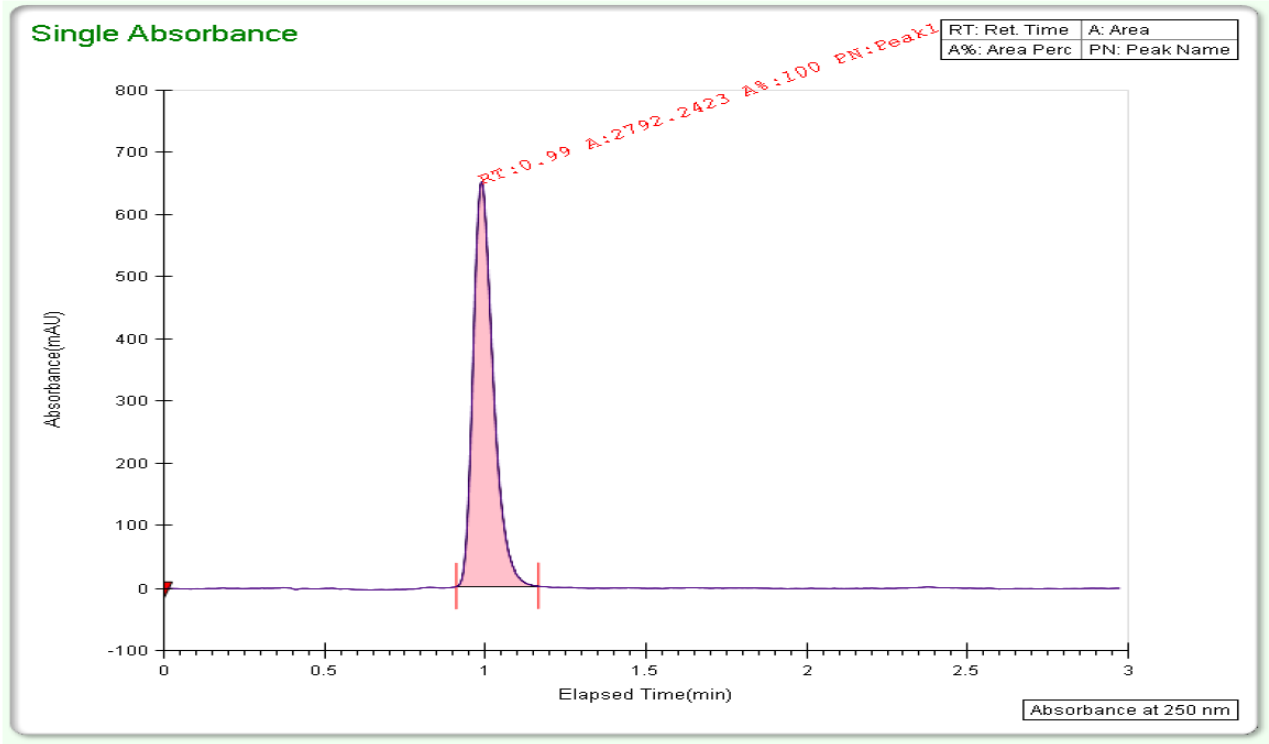



**4-(3-(4-(cyclopentyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 11 (MIV-3):**

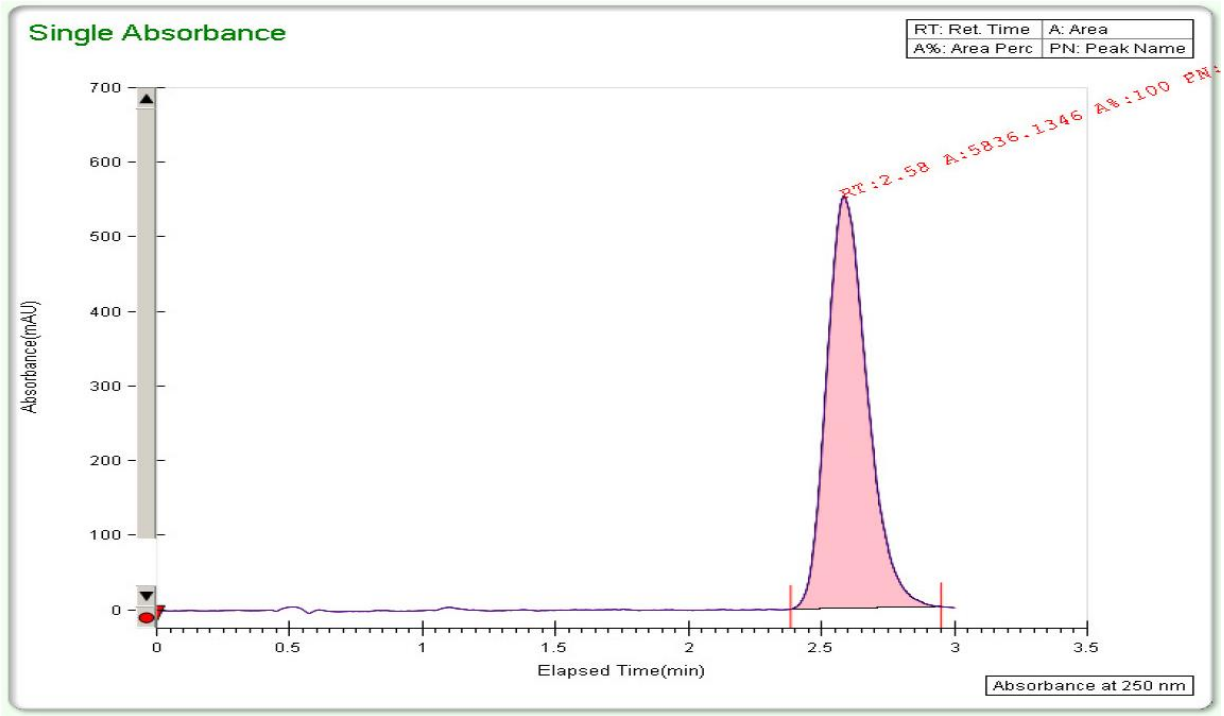
Semi-preparative purification:

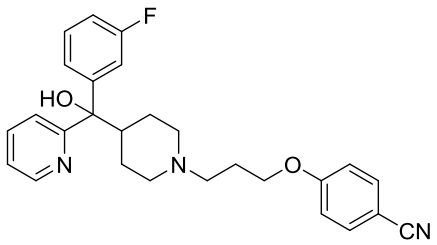


First Eluting Peak:



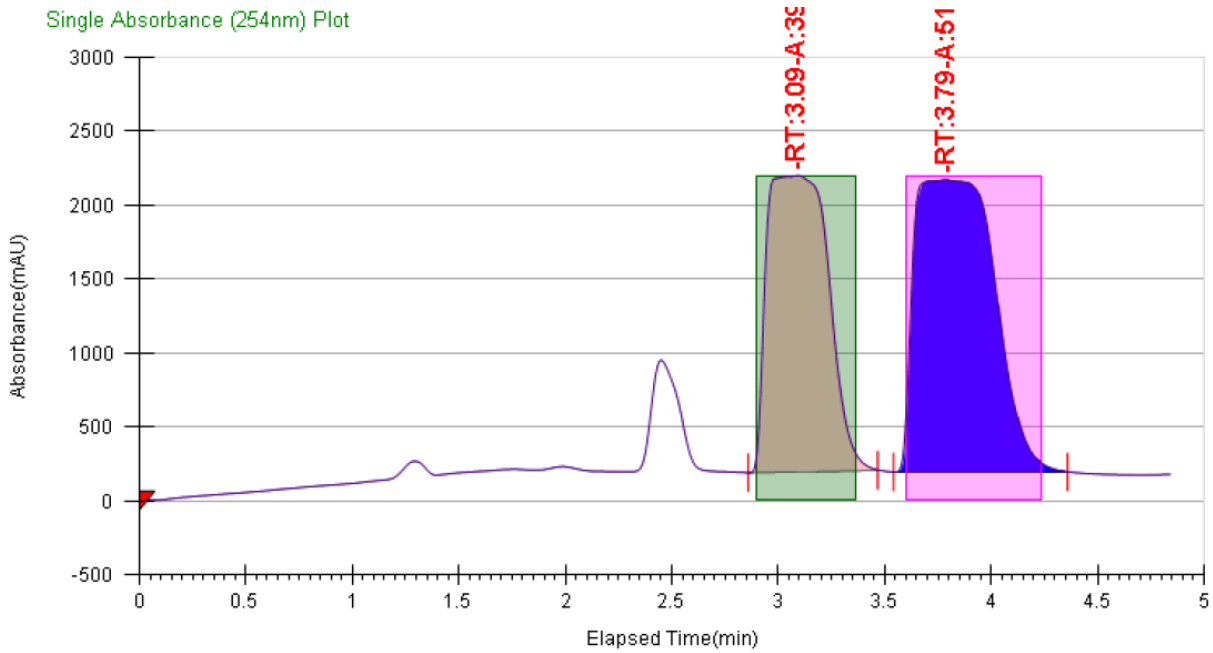

Second Eluting Peak:



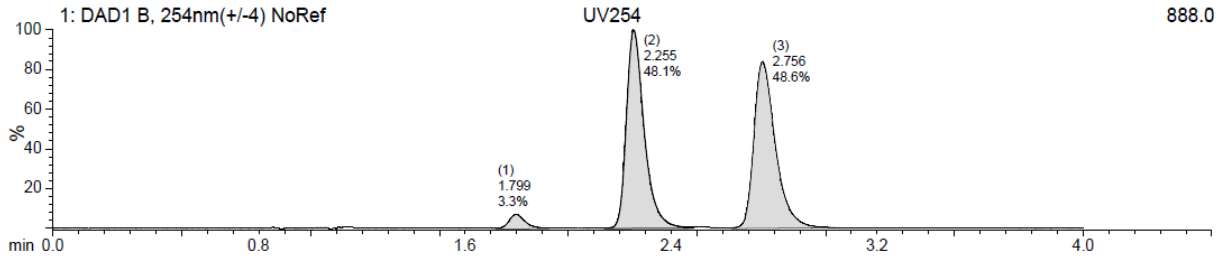



**4-(3-(4-((3-fluorophenyl)(hydroxy)(pyridin-2-yl)methyl)piperidin-1-yl)propoxy)benzonitrile, 18.**

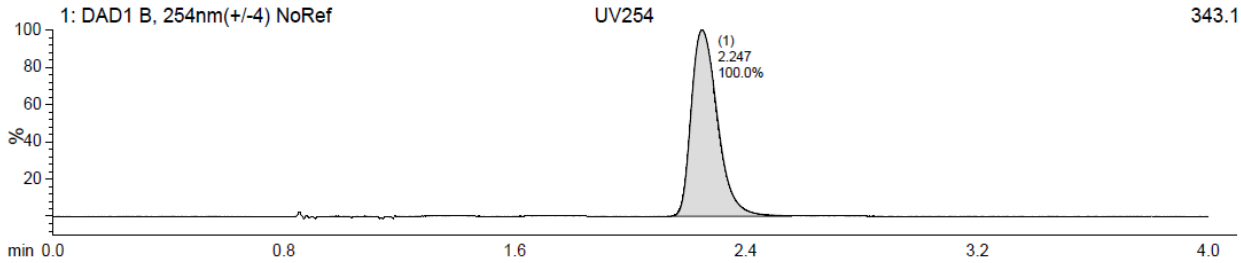
Semi-preparative purification:



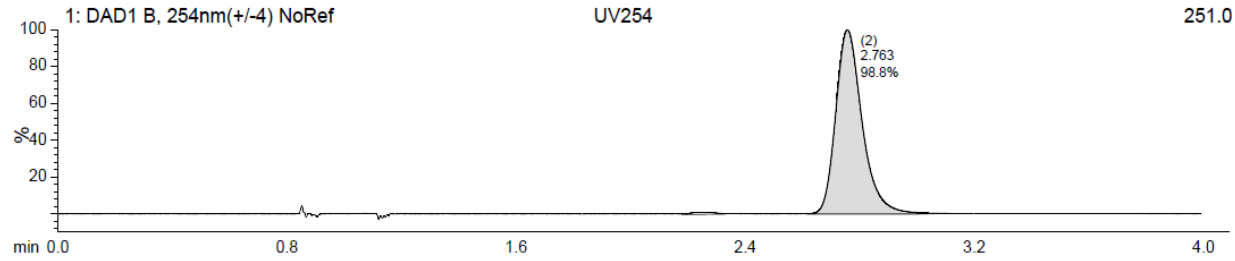
Racemic Analytical Chiral SFCMS:

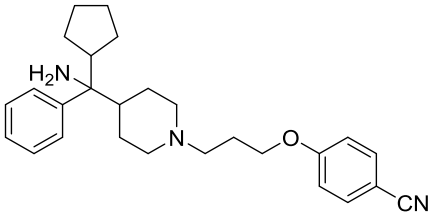



First Eluting Peak:



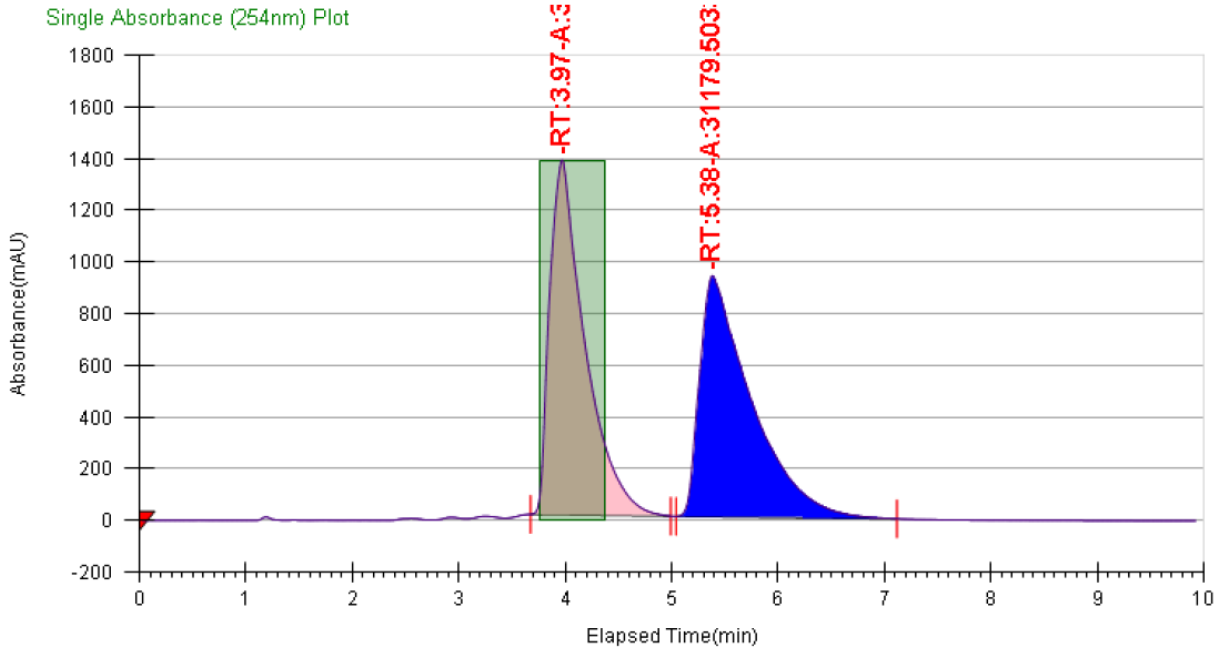

Second Eluting Peak:



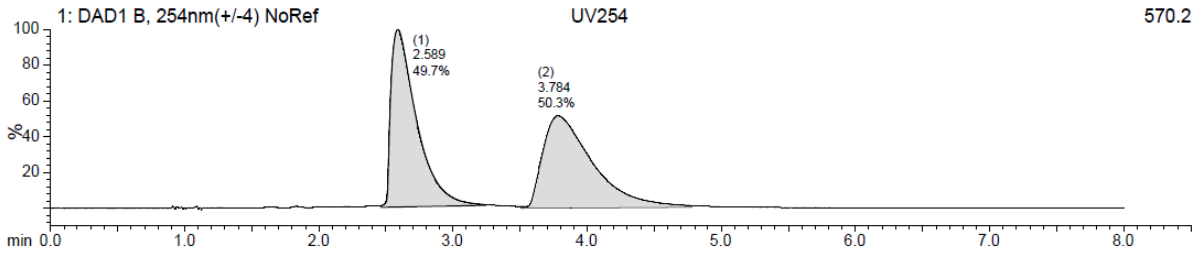



**4-(3-(4-(cyclopentyl(hydroxy)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile, 19 (MIV-6).**

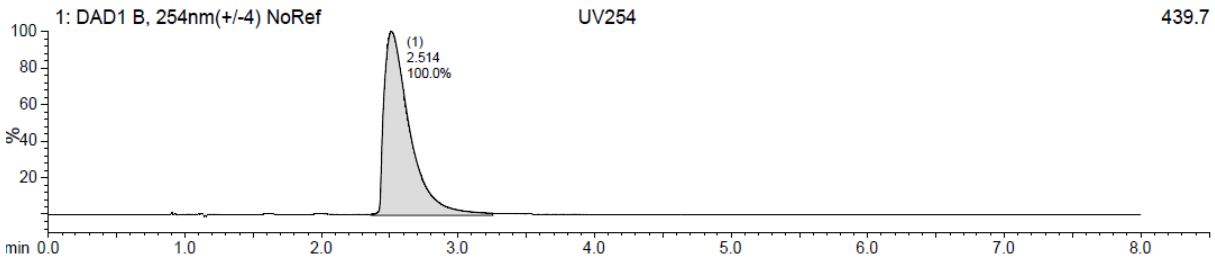
Semi-preparative purification:




Racemic Analytical Chiral SFCMS:



First Eluting Peak:




Second Eluting Peak: