Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A concise formation of *N*-substituted 3,4-diarylpyrroles – synthesis and cytotoxic activity.

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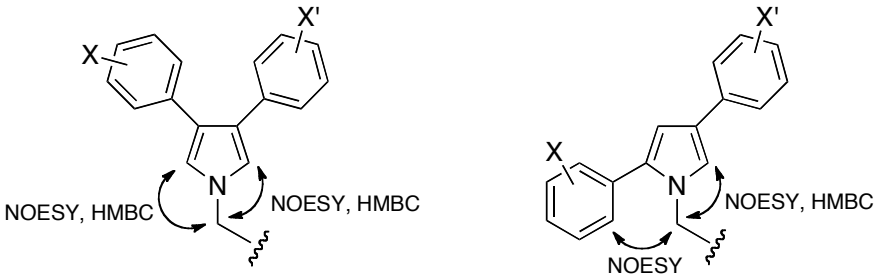
Contents

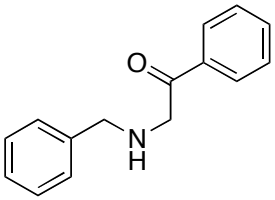
Chemistry

Note. The structures of pyrroles were unambiguously proved by NMR spectroscopy using especially HMBC and NOESY experiments, the most important correlations being shown in the following scheme.



Experimental procedures

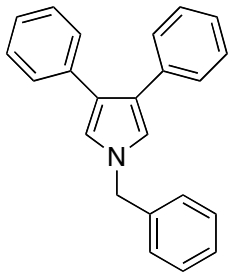
Two-step synthesis of pyrrole 2
2-(Benzylamino)-1-phenylethanone 1



To a solution of benzylamine (1.5 g, 14.0 mmol) in diethyl ether (8 mL) at -78 °C under argon, a solution of 2-bromoacetophenone (1 g, 5.03 mmol) in diethyl ether (2 mL) was gradually added during 15 min. The reaction mixture was stirred for 1 h at this temperature, warmed gradually to RT and stirred for 2 h. The resulting mixture was extracted with diethyl ether and the organic phase was washed with 10% $NaHCO_3$, brine, dried over Na_2SO_4, evaporated under reduced pressure at 0 to -10 °C to give aminoketone **1** as a light yellow

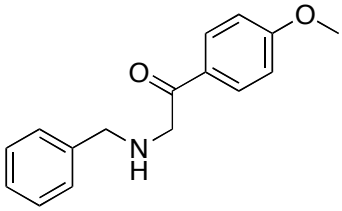
unstable oil (1.1 g, 97%), which was rapidly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.94 (2 H, d, J = 8.0 Hz), 7.59 (1 H, t, J = 7.0 Hz), 7.48 (2 H, t, J = 7.5 Hz), 7.42–7.34 (4 H, m), 7.29 (1 H, t, J = 7.0 Hz), 4.15 (2 H, s), 3.92 (2 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 197.9, 139.6, 133.5, 128.7, 128.5, 128.2, 127.7, 127.2, 54.7, 53.4.

1-Benzyl-3,4-diphenyl-1*H*-pyrrole 2[11]



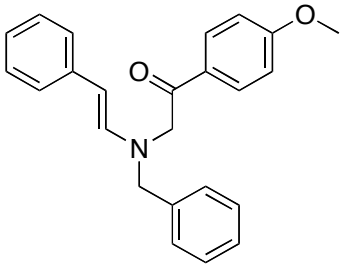
A solution of **1** (0.55 g, 2.44 mmol) from the previous step and phenylacetaldehyde (0.59 g, 4.88 mmol) in methanol (4 mL) was stirred for 16 h at RT under argon. The resulting mixture was concentrated under reduced pressure and chromatographed on silica gel (elution gradient from pentane to pentane/diethyl ether 10:1) to give **2** as a light yellow oil (0.73 g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.30–7.04 (15 H, m), 6.71 (2 H, s), 4.99 (2 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 137.4, 135.9, 128.9, 128.4, 128.2, 128.0, 127.5, 125.6, 123.6, 120.8, 53.6. IR (neat) ν_{max} cm^{-1} 3027, 1699, 1600, 1537, 1170, 760, 697. HRMS (MALDI) (m/z) $[M]^+$ calcd for $C_{23}H_{19}N$ 309.1517, found 309.1512.

2-(Benzylamino)-1-(4-methoxyphenyl)ethanone 3



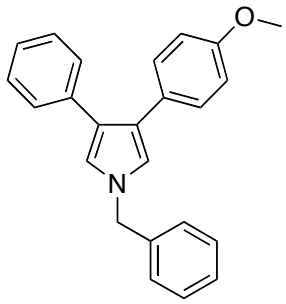
To a solution of benzylamine (1.4 g, 13.1 mmol) in diethyl ether (3 mL), a solution of 2-bromo-4'-methoxyacetophenone (1 g, 4.4 mmol) in diethyl ether/THF 1/1 (4 mL) was gradually added during 5 min at -78 °C under argon. The mixture was stirred for 1 h at this temperature, warmed gradually to RT and stirred for 2 h. The resulting mixture was extracted with diethyl ether and the organic phase was washed with a 10% solution of $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated under reduced pressure at 0 to -10 °C to give aminoketone **3** as a light yellow unstable oil (1.1 g, 99%), which was rapidly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.91 (2 H, d, J = 8.5 Hz), 7.45–7.23 (5 H, m), 6.94 (2 H, d, J = 8.5 Hz), 4.07 (2 H, s), 3.91 (2 H, s), 3.88 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 196.3, 163.7, 139.7, 130.0, 129.2, 128.4, 128.2, 127.2, 113.9, 55.5, 54.3, 53.5.

(*E*)-2-(benzyl(styryl)amino)-1-(4-methoxyphenyl)ethanone 4



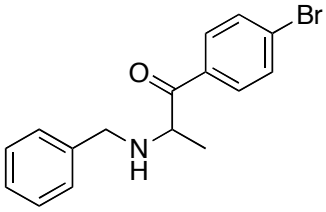
A solution of **3** (0.35 g, 1.36 mmol) from the previous step and phenylacetaldehyde (163 mg, 1.36 mmol) in methanol (2 mL) was stirred for 16 h at RT under argon. Yellow crystals were formed and were filtered, washed by methanol and dried (0.39 g, 80%), mp 123–125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.94 (2 H, d, J = 9.0 Hz), 7.43–7.28 (5 H, m), 7.25–7.12 (4 H, m), 7.06–6.92 (4 H, m), 5.26 (1 H, d, J = 14.1 Hz), 4.49 (2 H, s), 4.46 (2 H, s), 3.89 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 194.0, 163.9, 139.2, 138.7, 137.7, 130.1, 128.7, 128.4, 127.9, 127.5, 123.9, 123.6, 113.9, 98.8, 56.9, 55.5, 55.3. IR (neat) ν_{max} cm^{-1} 2909, 1677, 1630, 1598, 1572, 1396, 1232, 1172, 928, 742, 693. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{24}H_{24}NO_2$ 358.1807, found 358.1805.

1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole 5



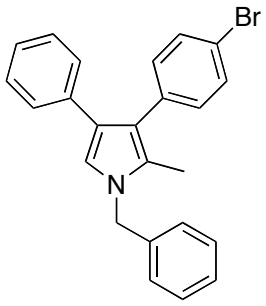
A solution of the enamine **4** (0.25 g, 0.70 mmol) in methanol (20 mL) was stirred for 2 h at 50 °C under argon. The solvent was removed under reduced pressure to give **5** as a light yellow oil (0.23 g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.32–7.06 (12 H, m), 6.76–6.68 (3 H, m), 6.66 (1 H, d, J = 2.4 Hz), 4.99 (2 H, s), 3.70 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 157.8, 137.5, 136.0, 129.5, 128.8, 128.4, 128.3, 128.1, 127.9, 127.5, 125.5, 123.4, 123.3, 120.5, 120.3, 113.6, 55.2, 53.6. IR (neat) ν_{max} cm^{-1} 3029, 1699, 1680, 1601, 1540, 1243, 1172, 1029, 833, 770, 728, 698. HRMS (MALDI) (m/z) $[M]^+$ calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1626.

2-(Benzylamino)-1-(4-bromophenyl)propan-1-one 6



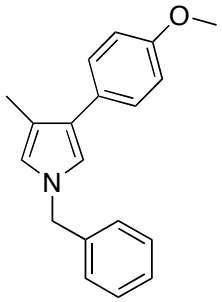
To a solution of benzylamine (0.55 g, 5.1 mmol) in THF (3 mL) at -78 °C under argon, was gradually added a solution of 2,4'-dibromopropiophenone (0.5 g, 1.7 mmol) in THF (3 mL). The reaction was stirred for 1 h at this temperature, warmed gradually to RT and stirred for 5 h. The resulting mixture was extracted with diethyl ether and the organic phase was washed with a 10% solution of $NaHCO_3$, brine, dried over Na_2SO_4, evaporated under reduced pressure at 0 to -10 °C to give aminoketone **6** as a light yellow unstable oil (0.53 g, 98%), which was rapidly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.80 (2 H, d, J = 8.5 Hz), 7.61 (2 H, d, J = 8.5 Hz), 7.38–7.21 (5 H, m), 4.28 (1 H, q, J = 7.0 Hz), 3.83 (1 H, d, J = 13.0 Hz), 3.67 (1 H, d, J = 13.0 Hz), 2.19 (1 H, s), 1.33 (3 H, d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 202.9, 140.3, 134.8, 132.5, 130.8, 130.3, 128.9, 128.7, 127.5, 57.5, 52.3, 20.2.

1-Benzyl-3-(4-bromophenyl)-2-methyl-4-phenyl-1*H*-pyrrole 7



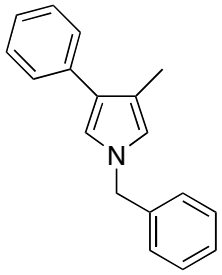
A solution of **6** (0.30 g, 0.94 mmol) from the previous step and phenylacetaldehyde (0.11 g, 0.94 mmol) in methanol (3 mL) was stirred for 16 h at RT under argon. Yellow crystals of the intermediate enamine were formed. Methanol (40 mL) was added and the reaction mixture was stirred for 4 h at 60 °C under argon. The solvent was removed under reduced pressure to give **7** as a yellow oil (0.37 g, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.36–6.95 (14 H, m), 6.73 (1 H, s), 5.02 (2 H, s), 2.07 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 137.6, 135.6, 135.4, 132.2, 131.1, 128.9, 128.2, 128.0, 127.6, 127.2, 126.7, 125.4, 123.1, 119.5, 119.2, 50.8, 10.5. IR (neat) ν_{max} cm^{-1} 2922, 1689, 1601, 1534, 1485, 1452, 1392, 1178, 1070, 912, 837, 744, 699. HRMS (MALDI) (*m*/*z*) $[M+H]^+$ calcd for $C_{24}H_{21}BrN$ 402.0852, found 402.0871.

1-Benzyl-3-(4-methoxyphenyl)-4-methyl-1*H*-pyrrole 8



It was prepared as **2**, starting from **3** (0.35 g, 1.4 mmol) and propionaldehyde (99 μL, 1.4 mmol) in methanol (2 mL). The light yellow oil **8** (20 mg, 5%) was obtained. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.32–7.17 (6 H, m), 7.11 (2 H, d, J = 7.0 Hz), 6.82 (2 H, d, J = 7.0 Hz), 6.63 (1 H, s), 6.42 (1 H, s), 4.92 (2 H, s), 3.74 (3 H, s), 2.11 (3 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 157.6, 138.1, 129.2, 128.7, 128.6, 127.7, 127.3, 124.3, 120.3, 118.8, 116.9, 113.8, 55.3, 53.3, 11.6. IR (neat) ν_{max} cm^{-1} 2926, 1679, 1606, 1538, 1246, 832, 831. HRMS (MALDI) (*m*/*z*) $[M]^+$ calcd for $C_{19}H_{19}NO$ 277.1467, found 277.1457.

One-step synthesis of 1-benzyl-3-methyl-4-phenyl-1*H*-pyrrole 9

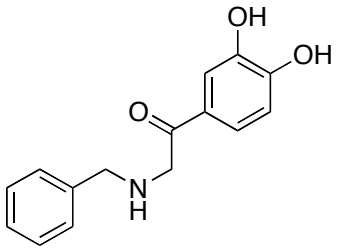


To the mixture of benzylamine (1.34 g, 12.5 mmol), TEA (3.5 mL, 25 mmol) and a catalytic amount of NaI in THF (10 mL) under argon, chloroacetone (1 mL, 12.5 mmol) was gradually added at -78 °C. The reaction mixture was warmed gradually to RT and stirred for 3 h. A solution of phenylacetaldehyde (1.5 mL, 12.5 mmol) in methanol (10 mL) was added and the reaction mixture was stirred for 16 h at RT under argon. The resulting mixture was extracted

with diethyl ether and the organic phase was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure and chromatographed on silica gel (elution gradient from pentane to pentane/diethyl ether 10:1) to give **9** as a light yellow oil (2.08 g, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39–7.06 (10 H, m), 6.70 (1 H, d, J = 2.4 Hz), 6.44 (1 H, dq, J = 2.4, 0.9 Hz), 4.93 (2 H, s), 2.14 (3 H, d, J = 0.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 138.0, 136.6, 128.8, 128.3, 127.7, 127.4, 127.2, 125.2, 124.6, 120.6, 119.4, 117.1, 53.4, 11.7. IR (neat) ν_{max} cm^{-1} 2921, 1702, 1601, 1535, 1452, 1353, 1147, 761, 697. HRMS (ES) (*m*/*z*) $[M+H]^+$ calcd for $C_{18}H_{18}N$ 248.1439, found 248.1443.

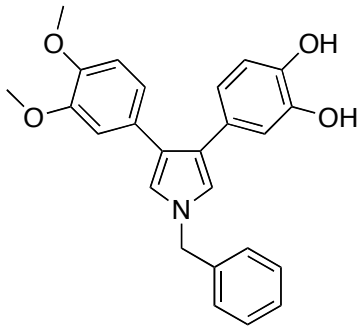
Two-step synthesis of pyrrole 12

2-(Benzylamino)-1-(3,4-dihydroxyphenyl)ethanone 11



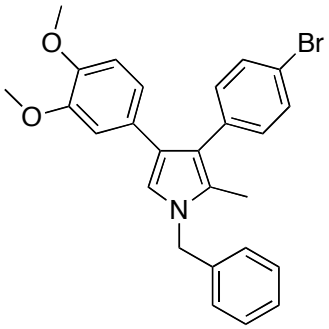
To the mixture of 2-chloro-3',4'-dihydroxyacetophenone (0.5 g, 2.7 mmol) and a catalytic amount of NaI at RT under argon, a solution of benzylamine (0.86 g, 8.0 mmol) in DMF (10 mL) was added and the reaction mixture was stirred for 16 h. The resulting mixture was extracted with diethyl ether and the organic phase was washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, evaporated under reduced pressure at 0 to -10 °C to give aminoketone **11** as a light yellow unstable oil (0.50 g, 73%), which was rapidly used in the next step. ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm) 7.43–7.24 (7 H, m), 6.80 (1 H, d, J = 8.4 Hz), 4.04 (2 H, s), 3.83 (2 H, s). ^{13}C NMR (CD_3OD, 75 MHz) δ (ppm) 195.6, 152.8, 145.7, 138.6, 128.2, 127.1, 126.6, 121.4, 114.8, 113.7, 52.9, 52.6.

4-(1-Benzyl-4-(3,4-dimethoxyphenyl)-1*H*-pyrrol-3-yl)benzene-1,2-diol 12



A solution of **11** (0.45 g, 1.75 mmol) and 2-(3,4-dimethoxyphenyl)acetaldehyde[4] (0.32 g, 1.75 mmol) in methanol (3 mL) was stirred for 16 h at RT. The resulting mixture was concentrated under reduced pressure to give pyrrole **12** as a brown oil (0.67 g, 95%). If necessary, **12** can be purified by the chromatography on silica gel (elution gradient from pentane to diethyl ether). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.31–7.14 (5 H, m), 6.77 (1 H, d, J = 8.0 Hz), 6.72–6.60 (7 H, m), 4.98 (2 H, s), 3.77 (3 H, s), 3.59 (3 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 147.4, 146.1, 142.1, 140.9, 136.5, 128.0, 127.8, 126.9, 126.4, 122.1, 122.0, 120.3, 119.3, 119.2, 119.0, 114.6, 114.1, 111.2, 110.2, 54.9, 54.6, 52.6. IR (neat) ν_{max} cm^{-1} 3401, 2930, 1598, 1543, 1509, 1261, 1025, 728. HRMS (ES) (*m*/*z*) $[M + Na]^+$ calcd for $C_{25}H_{23}NNaO_4$ 424.1525, found 424.1529.

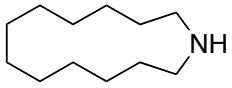
1-Benzyl-3-(4-bromophenyl)-4-(3,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole 13



It was prepared as **7**, starting from a solution of **6** (0.30 g, 0.94 mmol) and 3,4-dimethoxyphenylaldehyde[14] (0.17 g, 0.94 mmol) in methanol (3 mL). **13** (0.37 g, 84%) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.46–7.26 (5 H, m), 7.20–7.07 (4 H, m), 6.81 (1 H, s), 6.76 (2 H, s), 6.62 (1 H, s), 5.11 (2 H, s), 3.87 (3 H, s), 3.63 (3 H, s), 2.17 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 148.4, 147.0, 137.7, 135.6, 132.3, 131.1, 128.9, 128.5, 127.6, 127.0, 126.7, 122.9, 119.9, 119.7, 119.5, 118.5, 111.8, 111.2, 55.9, 55.5, 50.8, 10.5. IR (neat) ν_{max} cm^{-1} 2933, 1693, 1513, 1453, 1260, 1246, 1169, 1140, 1026, 910, 730. HRMS (ES) (*m*/*z*) $[M+H]^+$ calcd for $C_{26}H_{25}BrNO_2$, 462.1069 found 462.1114.

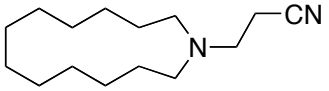
Preparation of 3-(azacyclotridecan-1-yl)propan-1-amine 14

Azacyclotridecane[2]



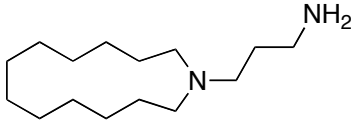
To the solution of azacyclotridecan-2-one (4.3 g, 21.8 mmol) in THF (100 mL) at RT under argon, $LiAlH_4$ (1.5 g, 39.5 mmol) was added gradually and the reaction mixture was refluxed during 16 h. Then, a saturated solution of Na_2SO_4 was added gradually at 0 °C to neutralize the excess of $LiAlH_4$, followed diethyl ether/pentane 1:1 (200 mL) and excess of solid K_2CO_3 to absorb the whole aqueous phase. The organic phase was decanted and the precipitate was washed three times with diethyl ether/pentane 1:1. The solvent was removed under reduced pressure to give azacyclotridecane (3.9 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.62 (4 H, t, J = 5.1 Hz), 1.57–1.25 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 47.9, 27.9, 26.5, 26.0, 25.4, 24.6.

3-(Azacyclotridecan-1-yl)propanenitrile



To a solution of azacyclotridecane (3.8 g, 20.7 mmol) and triethylamine (50 μL, 0.35 mmol) in DMF (15 mL) under argon, acrylonitrile (7.7 mL, 115 mmol) was added and the reaction mixture was stirred during 16 h at 70 °C. The reaction mixture was extracted with diethyl ether, organic phase was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure to give 3(-azacyclotridecan-1-yl)propanenitrile as a colorless oil (4.64 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.76 (2 H, t, J = 7.2 Hz), 2.50–2.35 (6 H, m), 1.55–1.28 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 53.7, 49.7, 26.5, 26.2, 25.23, 25.18, 15.7.

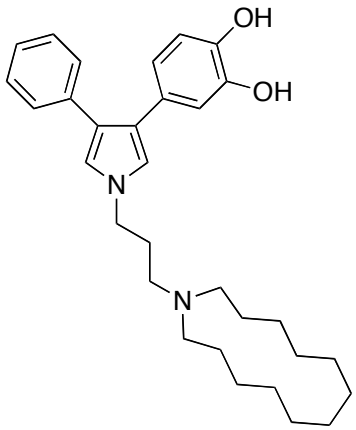
3-(Azacyclotridecan-1-yl)propan-1-amine 14[3]



To the solution of 3-(azacyclotridecan-1-yl)propanenitrile (0.5 g, 2.1 mmol) in diethyl ether (15 mL) at 0 °C under argon, $LiAlH_4$ (0.3 g, 7.9 mmol) was added gradually and the reaction mixture was stirred at 33 °C during 15 min. Then, a saturated solution of Na_2SO_4 was added gradually at 0 °C to neutralize the excess of $LiAlH_4$, followed by solid K_2CO_3 to absorb the whole aqueous phase. The organic phase was decanted and the precipitate was washed three times with diethyl ether. The solvent was removed under reduced pressure to give **14** (0.49 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 2.74 (2 H, t, J = 7.0 Hz), 2.40–2.28 (6 H, m), 1.57 (2 H, quint, J = 7.0 Hz), 1.44–1.32 (22 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 54.4, 52.8, 41.2, 31.7, 26.7, 26.5, 26.3, 25.8, 25.6.

General procedure for the synthesis of 3,4-diarylpyrroles 15.
A mixture of phenacyl halide (0.42 mmol) and NaI (320 mg, 2.1 mmol) in THF (2 mL) under argon was stirred during 25 min at RT. Then, amine **14** (0.42 mmol) was added followed by $NaHCO_3$ (150 mg, 1.8 mmol) and the reaction mixture was stirred during 1 h at RT. Phenylacetaldehyde (50 μL, 0.42 mmol) (or its 3,4-dimethoxy- or 3,4-methylenedioxy-derivatives[4]) in methanol (3 mL) was added and the mixture was stirred during 30 min. TEA (60 μL 0.42 mmol) was added and the reaction mixture was stirred for 16 h at 45 °C. It was extracted with diethyl ether/chloroform 5:1 and the organic phase was washed with a $NaHCO_3$/NaCl solution and brine, dried over Na_2SO_4, evaporated under reduced pressure and chromatographed on silica gel to give pyrrole **15**. The corresponding hydrochloride was prepared by diluting a solution of **15** in a minimal volume of chloroform containing 2 M HCl in methanol (5 equiv) with diethyl ether or Et_2O/pentane 1:1. Then the precipitate was filtered and dried under argon. Its NMR spectrum can be recorded in DMSO-d_6. CD_3OD is not convenient for this purpose because in the presence of HCl the pyrrole protons are totally exchanged by deuterium within 10 min.

Pyrrole 15a

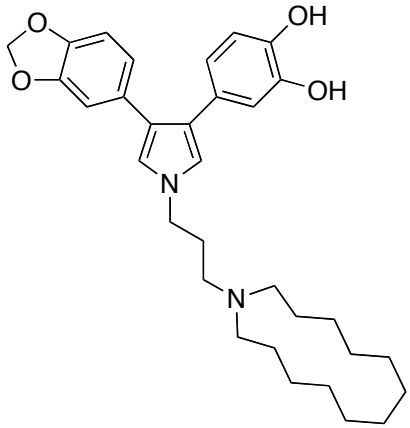


Yield 24%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.19 (2 H, d, J = 8.0 Hz), 7.13 (2 H, t, J = 8.0 Hz), 7.04 (1 H, t, J = 8.0 Hz), 6.72 (1 H, d, J = 2.0 Hz), 6.67 (1 H, d, J = 8.0 Hz), 6.63 (1 H, d, J = 2.5 Hz), 6.58–6.51 (2 H, m), 3.83 (2 H, t, J = 7.5 Hz), 2.42–2.30 (6 H, m), 1.88 (2 H, quint, J = 6.5 Hz), 1.43–1.23 (20 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 144.2, 142.8, 136.3, 128.4, 128.2, 128.1, 125.2, 123.1, 122.8, 120.5, 119.9, 115.7, 115.2, 53.7, 51.7, 47.9, 29.0, 26.0, 25.8, 25.5, 25.4. IR (neat) ν_{max} cm^{-1} 3054, 2926, 2854, 1599, 1541, 1444, 1360, 1287, 1023, 768, 699. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{31}H_{43}N_2O_2$ 475.3325, found 475.3337.

Hydrochloride 15a•HCl

Mp 169-172 °C (dec). ^{1}H NMR (DMSO-d_6 500 MHz) δ (ppm) 7.25–7.17 (4 H, m), 7.11 (1 H, t, J = 8.0 Hz), 6.99 (1 H, d, J = 2.0 Hz), 6.84 (1 H, d, J = 2.0 Hz), 6.69–6.60 (2 H, m), 6.44 (1 H, dd, J = 7.5, 1.5 Hz), 3.99 (2 H, t, J = 6.5 Hz), 3.15–2.94 (6 H, m), 2.27 (2 H, quint, J = 7.0 Hz), 1.80–1.60 (4 H, m), 1.50–1.25 (16 H, m). ^{13}C NMR (DMSO-d_6 125 MHz) δ (ppm) 144.9, 143.4, 136.1, 128.0, 127.5, 127.2, 125.0, 122.6, 121.8, 120.1, 120.0, 119.1, 115.9, 115.5, 51.4, 50.5, 46.1, 25.4, 25.3, 24.5, 24.2, 24.0, 20.3. IR (neat) ν_{max} cm^{-1} 3158, 2927, 2856, 2750, 1597, 1503, 1445, 1371, 1286, 1243, 1176, 1112, 1032, 931, 810. HRMS (ES) (m/z) [M-Cl]$^{+}$ calcd for $C_{31}H_{43}N_2O_2$ 475.3325, found 475.3306.

Pyrrole 15b

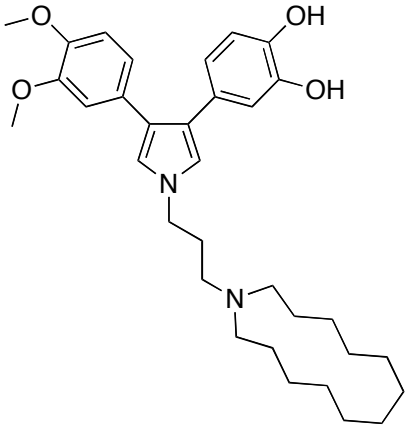


Yield 20%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.77–6.40 (8 H, m), 5.79 (2 H, s), 3.74 (2 H, t, J = 6.6 Hz), 2.50–2.24 (6 H, m), 1.86 (2 H, quint, J = 6.9 Hz), 1.44–1.16 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 147.2, 145.4, 144.4, 142.9, 130.3, 128.3, 122.9, 122.6, 121.5, 120.5, 119.6, 115.8, 115.5, 109.1, 108.1, 100.6, 53.2, 51.8, 47.7, 28.7, 25.8, 25.5, 25.3, 24.6. IR (neat) ν_{max} cm^{-1} 3050, 2926, 2855, 1652, 1604, 1542, 1501, 1484, 1440, 1358, 1232, 1102, 1038, 935, 906, 862, 810, 730. HRMS (ES) (m/z) [M+H]$^{+}$ calcd for $C_{32}H_{43}N_2O_4$ 519.3223, found 519.3223.

Hydrochloride 15b•HCl

Mp 146–149 °C. ^{1}H NMR (DMSO-d_6 500 MHz) δ (ppm) 6.92 (1 H, d, J = 2.5 Hz), 6.84–6.76 (2 H, m), 6.70–6.56 (4 H, m), 6.44 (1 H, d, J = 6.5 Hz), 5.95 (2 H, s), 3.96 (2 H, t, J = 6.5 Hz), 3.22–2.95 (6 H, m), 2.24 (2 H, quint, J = 7.5 Hz), 1.75–1.59 (4 H, m), 1.50–1.26 (16 H, m). ^{13}C NMR (DMSO-d_6 75 MHz) δ (ppm) 147.4, 145.3, 143.8, 130.6, 127.6, 122.9, 122.1, 121.1, 120.3, 120.2, 119.6, 116.3, 116.0, 108.6, 101.0, 51.9, 51.0, 46.5, 25.9, 25.8, 24.9, 24.7, 24.5, 20.8. IR (neat) ν_{max} cm^{-1} 3100, 2929, 2858, 2581, 1604, 1540, 1502, 1444, 1242, 1179, 1028, 808. HRMS (ES) (m/z) [M-Cl]$^{+}$ calcd for $C_{32}H_{43}N_2O_4$ 519.3223, found 519.3201.

Pyrrole 15c

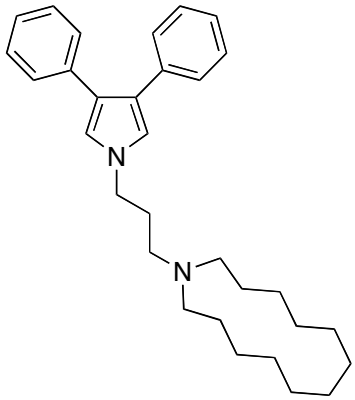


Yield 19%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.86–6.70 (5 H, m), 6.70–6.61 (2 H, m), 6.57 (1 H, d, J = 1.8 Hz), 3.85 (3 H, s), 3.67 (3 H, s), 2.58–2.38 (6 H, m), 1.97 (2 H, quint, J = 6.6 Hz), 1.54–1.25 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 148.3, 147.0, 144.1, 142.7, 129.0, 128.6, 122.9, 122.6, 120.8, 120.2, 119.6, 119.4, 115.8, 115.2, 112.2, 111.1, 55.8, 55.6, 53.2, 51.8, 47.7, 28.8, 25.8, 25.5, 25.3, 24.5. IR (neat) ν_{max} cm^{-1} 3150, 2928, 2855, 1584, 1541, 1505, 1462, 1250, 1162, 1027, 782, 730. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{33}H_{47}N_2O_4$ 535.3536, found 535.3531.

Hydrochloride 15c•HCl

Mp 142–144 °C. ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm) 6.94 (1 H, d, J = 2.4 Hz), 6.85–6.78 (2 H, m), 6.77–6.68 (2 H, m), 6.66–6.57 (2 H, m), 6.46 (1 H, dd, J = 8.1, 1.8 Hz), 3.96 (2 H, t, J = 6.6 Hz), 3.71 (3 H, s), 3.56 (3 H, s), 3.22–2.92 (6 H, m), 2.24 (2 H, quint, J = 7.5 Hz), 1.80–1.52 (4 H, m), 1.50–1.22 (16 H, m). ^{13}C NMR (DMSO-d_6 75 MHz) δ (ppm) 148.1, 146.6, 144.8, 143.3, 128.8, 127.2, 122.4, 121.7, 119.7, 119.51, 119.48, 119.2, 115.9, 115.4, 111.8, 111.7, 55.4, 55.1, 51.4, 50.5, 46.0, 25.4, 24.4, 24.2, 24.0, 20.3. IR (neat) ν_{max} cm^{-1} 3112, 2929, 2858, 2601, 1599, 1541, 1503, 1445, 1245, 1163, 1025, 808, 764. HRMS (ES) (m/z) $[M-Cl]^+$ calcd for $C_{33}H_{47}N_2O_4$ 535.3536, found 535.3528.

Pyrrole 15d

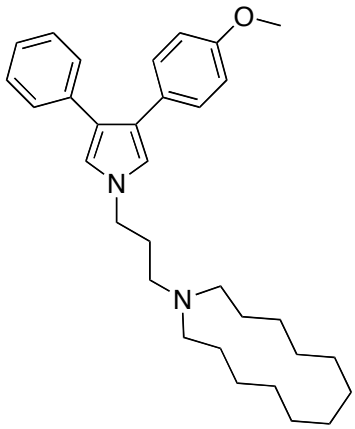


Yield 61%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.21–7.05 (10 H, m), 6.69 (2 H, s), 3.91 (2 H, t, J = 6.5 Hz), 2.42–2.28 (6 H, m), 1.92 (2 H, quint, J = 7.0 Hz), 1.43–1.23 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 136.1, 128.4, 128.2, 125.5, 123.1, 120.3, 54.3, 51.7, 48.1, 29.4, 26.5, 26.2, 26.0, 25.6, 25.3. IR (neat) ν_{max} cm^{-1} 3026, 2923, 2852, 1632, 1600, 1539, 1453, 1176, 759, 697. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{31}H_{43}N_2$ 443.3426, found 443.3448.

Hydrochloride 15d•HCl

Mp 105–107 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.31–7.11 (10 H, m), 7.04 (2 H, s), 4.03 (2 H, t, J = 6.6 Hz), 3.20–2.93 (6 H, m), 2.28 (2 H, quint, J = 6.6 Hz), 1.77–1.60 (4 H, m), 1.40–1.21 (16 H, m). ^{13}C NMR (DMSO-d_6 75 MHz) δ (ppm) 135.8, 128.1, 127.8, 125.4, 122.0, 120.7, 51.3, 50.5, 46.1, 25.4, 25.3, 24.4, 24.2, 24.0, 20.3. IR (neat) ν_{max} cm^{-1} 3145, 2928, 2857, 2578, 1600, 1540, 1503, 1445, 1244, 1178, 1026, 761, 697. HRMS (ES) (m/z) [M-Cl]$^{+}$ calcd for $C_{31}H_{43}N_2$ 443.3426, found 443.3430.

Pyrrole 15e

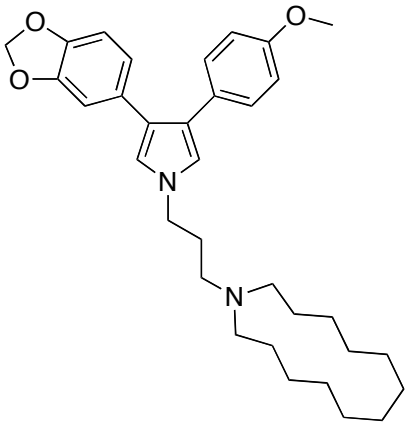


Yield 52%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.20–7.12 (5 H, m), 7.10 (2 H, d, J = 8.7 Hz), 6.73 (2 H, d, J = 8.7 Hz), 6.69 (1 H, d, J = 2.4 Hz), 6.64 (1 H, d, J = 2.4 Hz), 3.90 (2 H, t, J = 6.9 Hz), 3.71 (3 H, s), 2.45–2.28 (6 H, m), 1.92 (2 H, quint, J = 6.9 Hz), 1.42–1.23 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 157.7, 136.1, 129.5, 128.6, 128.3, 128.1, 125.4, 122.9, 122.8, 120.0, 119.8, 113.6, 55.2, 53.9, 51.7, 47.9, 29.1, 26.1, 25.9, 25.5, 25.4. IR (neat) ν_{max} cm^{-1} 3028, 2924, 2852, 1674, 1600, 1541, 1501, 1454, 1242, 1174, 1033, 832, 769, 697. HRMS (ES) (m/z) [M+H]$^{+}$ calcd for $C_{32}H_{45}N_2O$ 473.3532, found 473.3534.

Hydrochloride 15e•HCl

Mp 103–106 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 7.26–7.10 (5 H, m), 7.09 (2 H, d, J = 7.5 Hz), 7.02 (1 H, d, J = 1.0 Hz), 6.95 (1 H, d, J = 1.0 Hz), 6.82 (2 H, d, J = 8.0 Hz), 4.02 (2 H, t, J = 7.0 Hz), 3.73 (3 H, s), 3.15–2.96 (6 H, m), 2.29 (2 H, quint, J = 7.5 Hz), 1.78–1.61 (4 H, m), 1.51–1.26 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 157.8, 136.4, 129.4, 128.7, 128.6, 128.1, 125.7, 122.4, 122.3, 120.9, 120.7, 114.1, 55.4, 51.8, 51.0, 46.6, 25.9, 25.8, 24.9, 24.7, 24.5, 20.8. IR (neat) ν_{max} cm^{-1} 3116, 2927, 2856, 2700, 1599, 1445, 1286, 1242, 1176, 1112, 758, 699. HRMS (ES) (m/z) [M-Cl]$^{+}$ calcd for $C_{32}H_{45}N_2O$ 473.3532, found 473.3552.

Pyrrole 15f

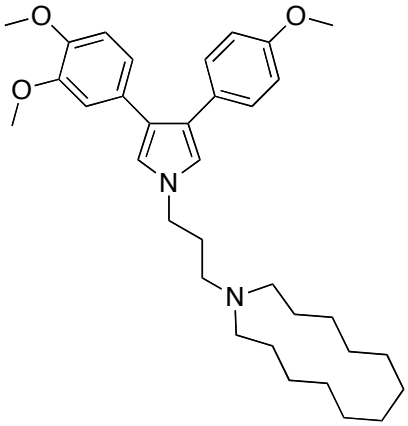


Yield 29%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.22 (2 H, d, J = 8.5 Hz), 6.84 (2 H, d, J = 9.0 Hz), 6.82–6.70 (5 H, m), 5.94 (2 H, s), 3.99 (2 H, t, J = 8.0 Hz), 3.83 (3 H, s), 2.50–2.35 (6 H, m), 1.99 (2 H, quint, J = 7.5 Hz), 1.55–1.35 (20 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 157.8, 147.4, 145.5, 130.3, 129.5, 128.5, 122.7, 122.6, 121.5, 119.7, 119.6, 113.7, 109.1, 108.1, 100.7, 55.2, 54.3, 51.7, 48.0, 29.4, 26.4, 26.2, 26.0, 25.7, 25.6, 25.3. IR (neat) ν_{max} cm^{-1} 2926, 2854, 1608, 1542, 1501, 1484, 1440, 1244, 1225, 1177, 1038, 937, 811. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{33}H_{45}N_2O_3$ 517.3430, found 517.3405.

Hydrochloride 15f•HCl

Mp 119–121 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 7.10 (2 H, d, J = 8.5 Hz), 6.95 (1 H, d, J = 2.5 Hz), 6.91 (1 H, d, J = 2.5 Hz), 6.88–6.76 (3 H, m), 6.71–6.59 (2 H, m), 5.96 (2 H, s), 3.99 (2 H, t, J = 6.0 Hz), 3.72 (3 H, s), 3.17–2.93 (6 H, m), 2.26 (2 H, quint, J = 6.5 Hz), 1.76–1.60 (4 H, m), 1.52–1.28 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 157.8, 147.5, 145.5, 130.5, 129.4, 128.6, 122.1, 121.3, 120.6, 120.4, 114.2, 108.7, 108.6, 101.1, 55.4, 51.8, 51.0, 46.6, 25.9, 25.8, 24.9, 24.7, 24.5, 20.8. IR (neat) ν_{max} cm^{-1} 3120, 2928, 2857, 1599, 1444, 1371, 1286, 1242, 1176, 1111, 1032, 931, 809. HRMS (ES) (m/z) $[M-Cl]^+$ calcd for $C_{33}H_{45}N_2O_3$ 517.3430, found 517.3413.

Pyrrole 15g



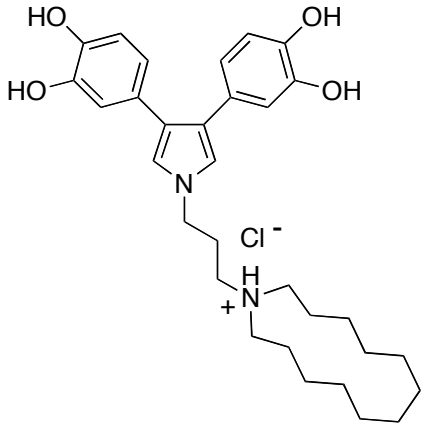
Yield 37%, amorphous semisolid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.23 (2 H, d, J = 7.0 Hz), 6.91–6.72 (7 H, m), 4.00 (2 H, t, J = 7.0 Hz), 3.90 (3 H, s), 3.82 (3 H, s), 3.70 (3 H, s), 2.50–2.36 (6 H, m), 2.00 (2 H, quint, J = 7.5 Hz), 1.55–1.37 (20 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 157.8, 148.4, 147.0, 129.6, 129.1, 128.7, 122.7, 122.6, 120.2, 119.6, 119.5, 113.6, 112.2, 111.2, 55.9, 55.6, 55.2, 54.2, 51.7, 48.0, 29.4, 26.4, 26.2, 26.0, 25.6, 25.3.

IR (neat) ν_{max} cm^{-1} 2927, 2852, 1608, 1541, 1500, 1461, 1241, 1219, 1178, 1162, 1136, 1028, 832, 729. HRMS (ES) (*m*/*z*) [M+H]$^+$ calcd for $C_{34}H_{49}N_2O_3$ 533.3743, found 533.3777.

Hydrochloride 15g•HCl

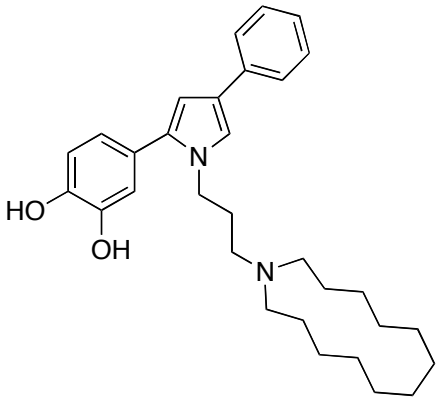
Mp 116–119 °C (dec). ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 7.11 (2 H, d, J = 8.5 Hz), 6.97 (1 H, d, J = 1.5 Hz), 6.92 (1 H, d, J = 1.5 Hz), 6.88–6.80 (3 H, m), 6.75–6.63 (2 H, m), 3.98 (2 H, t, J = 6.5 Hz), 3.72 (3 H, s), 3.71 (3 H, s), 3.56 (3 H, s), 3.21–2.98 (6 H, m), 2.24 (2 H, quint, J = 6.5 Hz), 1.85–1.50 (4 H, m), 1.49–1.23 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 157.8, 148.7, 147.2, 129.5, 129.2, 128.8, 122.3, 122.2, 120.4, 120.2, 114.0, 112.5, 112.3, 55.9, 55.6, 55.5, 51.8, 50.9, 46.6, 25.9, 25.8, 24.9, 24.7, 24.5, 20.8. IR (neat) ν_{max} cm^{-1} 3250, 2929, 2858, 2579, 1605, 1539, 1503, 1462, 1242, 1220, 1177, 1137, 1025, 860, 832, 807, 793, 763. HRMS (ES) (*m*/*z*) [M-Cl]$^+$ calcd for $C_{34}H_{49}N_2O_3$ 533.3743, found 533.3765.

Pyrrole 15h•HCl



To a hydrochloride **15c•**HCl solution (15 mg, 0.026 mmol) in CH_2Cl_2 (2 mL) under argon at 0 °C, BBr_3 (1 M solution in CH_2Cl_2, 0.5 mL, 0.5 mmol) was added. The reaction mixture was stirred and warmed gradually to RT during 2 h. It was diluted with a phosphate buffer (pH = 7), extracted with chloroform/methanol 3:1, dried over Na_2SO_4, filtered through silica gel (2 cm^3), eluted with the same solvent mixture and evaporated under reduced pressure. The residue was dissolved in methanol (0.5 mL) and diluted with diethyl ether (25 mL) containing HCl (2 M solution in methanol, 67 μL, 0.13 mmol). The precipitate was filtered, washed with diethyl ether and dried to give hydrochloride **15h•**HCl (12 mg, 84%), mp 195–197 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 6.77 (2 H, s), 6.70–6.53 (4 H, m), 6.43 (2 H, dd, J = 8.1, 2.1 Hz), 3.95 (2 H, t, J = 6.6 Hz), 3.24–2.92 (6 H, m), 2.24 (2 H, quint, J = 6.5 Hz), 1.82–1.55 (4 H, m), 1.52–1.20 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 145.2, 143.6, 127.9, 122.7, 119.8, 119.4, 116.2, 116.0, 51.9, 50.9, 46.4, 25.9, 24.9, 24.7, 24.5, 20.8. IR (neat), cm^{-1} ν_{max} 3158, 2927, 2856, 2730, 1597, 1503, 1445, 1366, 1286, 1242, 1177, 1111, 1032, 812. HRMS (ES) (*m*/*z*) [M-Cl]$^+$ calcd for $C_{31}H_{43}N_2O_4$ 507.3223, found 507.3262.

Pyrrole 16

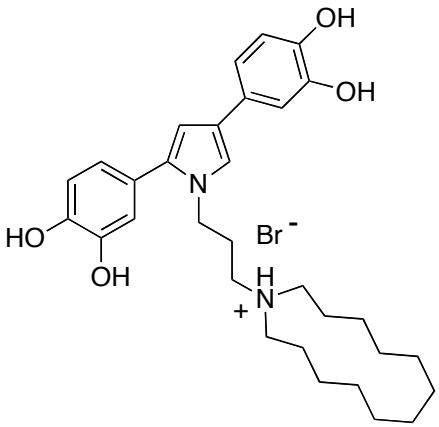


To a mixture of 2-chloro-3',4'-dihydroxyacetophenone (0.77 g, 4.2 mmol) and a catalytic amount of NaI under argon, DMF (50 mL) was added, followed by amine **14** (1 g, 4.2 mmol), and the reaction mixture was stirred during 5 min at RT. Then, phenylacetaldehyde (0.5 mL, 4.2 mmol) was added and the reaction mixture was stirred during 16 h at RT. It was extracted with diethyl ether/chloroform 5:1 and the organic phase was washed with a phosphate buffer (pH = 7), brine, dried over Na_2SO_4, evaporated under reduced pressure and chromatographed on silica gel (elution gradient from pentane to diethyl ether) to give **16** (258 mg, 13%) as an amorphous semisolid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39 (2 H, d, J = 7.5 Hz), 7.21 (2 H, t, J = 7.5 Hz), 7.04 (1 H, t, J = 7.5 Hz), 6.88–6.80 (2 H, m), 6.76 (1 H, d, J = 8.1 Hz), 6.64 (1 H, d, J = 8.4 Hz), 6.26 (1 H, d, J = 1.5 Hz), 3.80 (2 H, t, J = 7.0 Hz), 2.43–2.28 (6 H, m), 1.74 (2 H, quint, J = 7.5 Hz), 1.38–1.15 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 145.4, 145.2, 135.7, 135.6, 128.6, 125.3, 124.9, 124.8, 123.9, 120.8, 118.1, 116.3, 115.7, 106.0, 52.5, 51.8, 45.4, 28.3, 25.63, 25.60, 25.4, 25.1, 23.6. IR (neat) ν_{max} cm^{-1} 3029, 2925, 2854, 1650, 1602, 1490, 1453, 1360, 1279, 1257, 1200, 907, 731. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{31}H_{43}N_2O_2$ 475.3325, found 475.3308.

Hydrochloride 16•HCl

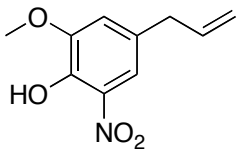
It was obtained as described for **15**. Mp 145–147 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.53 (2 H, d, J = 7.2 Hz), 7.36 (1 H, d, J = 1.8 Hz), 7.31 (2 H, t, J = 7.5 Hz), 7.11 (1 H, t, J = 7.2 Hz), 6.87 (1 H, d, J = 1.8 Hz), 6.82 (1 H, d, J = 8.1 Hz), 6.70 (1 H, dd, J = 7.8, 1.8 Hz), 6.37 (1 H, d, J = 1.8 Hz), 3.99 (2 H, t, J = 6.6 Hz), 3.10–2.82 (6 H, m), 2.10 (2 H, quint, J = 7.4 Hz), 1.77–1.50 (4 H, m), 1.45–1.20 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 145.2, 144.9, 135.5, 135.1, 128.5, 125.0, 124.2, 123.7, 122.9, 119.7, 118.7, 116.1, 115.8, 105.4, 51.1, 50.4, 44.0, 25.4, 25.3, 24.4, 24.2, 23.9, 20.3. IR (neat) ν_{max} cm^{-1} 3111, 2929, 2859, 2601, 1678, 1601, 1496, 1445, 1366, 1285, 1196, 1111, 815, 757, 696. HRMS (ES) (m/z) $[M-Cl]^+$ calcd for $C_{31}H_{43}N_2O_2$ 475.3325, found 475.3349.

Pyrrole 17 (hydrobromide salt)



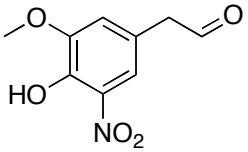
Hydrochloride **15c** (20 mg, 0.035 mmol) was stirred in 48% HBr (0.5 mL) during 2 h at 150 °C under argon in a sealed tube in the dark. Then water (7 mL) was added at RT and the precipitate was filtered and dissolved in methanol (0.5 mL). The resulting solution was diluted with diethyl ether (30 mL) and the precipitate was filtered, washed with diethyl ether and dried under argon to give **17** (18 mg, 87%), mp 185–188 °C (dec). ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) 7.10 (1 H, s), 6.90 (1 H, s), 6.86–6.75 (3 H, m), 6.70–6.63 (2 H, m), 6.17 (1 H, s), 3.96 (2 H, t, J = 6.0 Hz), 3.10–2.85 (6 H, m), 2.01 (2 H, quint, J = 7.5 Hz), 1.70–1.46 (4 H, m), 1.42–1.22 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 145.74, 145.67, 145.3, 143.6, 135.1, 127.7, 124.4, 124.1, 120.1, 117.9, 116.6, 116.3, 116.2, 116.0, 112.7, 105.8, 51.9, 51.2, 44.3, 25.8, 24.9, 24.7, 24.3, 20.9. IR (neat) ν_{max} cm^{-1} 3119, 2928, 2857, 2745, 1590, 1503, 1446, 1371, 1287, 1192, 1113, 869, 813, 696. HRMS (ES) (m/z) [M-Br]$^{+}$ calcd for $C_{31}H_{43}N_2O_4$ 507.3223, found 507.3249.

4-Allyl-2-methoxy-6-nitrophenol 18[5]



To a solution of eugenol (6.76 g, 41.2 mmol) in acetic acid (100 mL) at RT, 70% HNO_3 (2.8 mL, 44.2 mmol) was added. The reaction mixture was stirred during 15 min, extracted with diethyl ether, washed thoroughly with brine, and finally with a phosphate buffer (pH = 7). The ether solution was diluted with the same volume of pentane, filtered through silica gel and evaporated under reduced pressure to give **18** (6.36 g, 79%) as a dark red oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 10.61 (1 H, br s), 7.48 (1 H, d, J = 1.5 Hz), 6.96 (1 H, d, J = 1.5 Hz), 5.91 (1 H, m), 5.20–5.08 (2 H, m), 3.92 (3 H, s), 3.35 (2 H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 149.8, 144.8, 135.9, 133.6, 131.2, 118.6, 117.1, 115.0, 56.7, 39.4. IR (neat) ν_{max} cm^{-1} 3225, 3080, 2976, 2939, 1639, 1539, 1428, 1390, 1326, 1259, 1133, 1061, 916, 763. HRMS (ES) (m/z) [M+Na]$^{+}$ calcd for $C_{10}H_{11}NNaO_4$ 232.0586, found 232.0578.

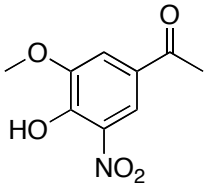
2-(4-Hydroxy-3-methoxy-5-nitrophenyl)acetaldehyde 19



To a solution of **18** (2.0 g, 9.6 mmol) in THF (23 mL) and water (8 mL) at 0 °C, a 0.166 M solution of osmium tetroxide (23 mg, 0.09 mmol) in THF/water 7:5 (0.55 mL) was added. After 5 min, $NaIO_4$ (4.8 g, 22 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C, warmed gradually to RT during 1 h, extracted with CH_2Cl_2/diethyl ether 1:1 and the

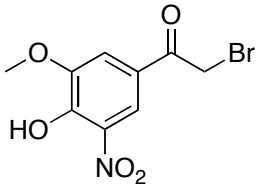
organic phase was washed once with brine, dried over Na_2SO_4, evaporated under reduced pressure at 25 °C. The residue was dissolved in the minimal volume of CH_2Cl_2 and pentane/diethyl ether 1:1 was added. The solvent was evaporated under reduced pressure at 25 °C till yellow crystal formation; pentane was added and the solution was concentrated once more. The crystals were filtered to give **19** (1.66 g, 82%), mp 130–132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 10.71 (1 H, s), 9.80 (1 H, t, J = 1.8 Hz), 7.57 (1 H, d, J = 1.8 Hz), 6.97 (1 H, d, J = 1.8 Hz), 3.96 (3 H, s), 3.74 (2 H, d, J = 1.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 197.8, 150.4, 145.8, 133.8, 123.1, 119.0, 116.6, 56.8, 49.5. IR (neat) ν_{max} cm^{-1}: 3226, 1720, 1583, 1449, 1333, 1264, 1238, 1134, 1064, 921, 764. HRMS (ES) (m/z) [M-H]$^-$ calcd for $C_9H_8NO_5$ 210.0402, found 210.0399.

1-(4-Hydroxy-3-methoxy-5-nitrophenyl)ethanone 20[6]



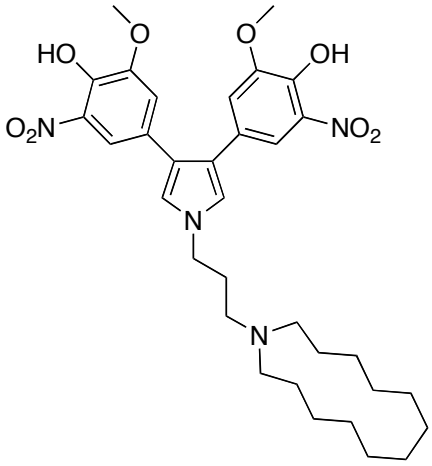
To a solution of 4'hydroxy-3'-methoxyacetophenone (10 g, 60.2 mmol) in acetic acid (140 mL) at RT, 70% HNO_3 (4.2 mL, 66.3 mmol) was added. The reaction mixture was stirred during 30 min and the yellow crystals were filtered, washed with diethyl ether and dried to give **20** (10.5 g, 83%), mp 158–159 °C (lit.,[5b] 159–161 °C from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 11.09 (1 H, s), 8.30 (1 H, d, J = 1.5 Hz), 7.75 (1 H, d, J = 1.5 Hz), 4.01 (3 H, s), 2.62 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 194.9, 150.4, 150.1, 133.0, 128.3, 117.7, 115.3, 56.9, 26.0. IR (neat) ν_{max} cm^{-1} 3228, 3091, 2988, 2925, 1676, 1612, 1535, 1413, 1378, 1350, 1329, 1218, 1136, 1047, 869, 735, 709. HRMS (ES) (m/z) [M-H]$^-$ calcd for $C_9H_8NO_5$ 210.0402, found 210.0404.

2-Bromo-1-(4-hydroxy-3-methoxy-5-nitrophenyl)ethanone 21[7]



To a solution of **20** (9.6 g, 45.5 mmol) in CH_2Cl_2 (200 mL) at RT, bromine (2.4 mL, 46.8 mmol) was added gradually and the reaction mixture was stirred during 10 min. During this period the color of bromine disappeared totally. Then, pentane (400 mL) was added. After 10 min the yellow crystals were filtered in the hood, washed with pentane/diethyl ether 1:1, dried to give **21** (10 g, 76%), mp 143–145 °C (lit.,[6] 147–149 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 11.18 (1 H, s), 8.36 (1 H, d, J = 1.8 Hz), 7.77 (1 H, d, J = 1.8 Hz), 4.44 (2 H, s), 4.03 (3 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 188.7, 150.7, 150.6, 133.0, 125.0, 118.3, 115.9, 57.0, 29.4. IR (neat) ν_{max} cm^{-1} 3366, 3093, 2991, 2942, 1765, 1689, 1608, 1535, 1386, 1246, 1151, 1060, 912, 887, 850, 762. HRMS (ES) (m/z) [M-H]$^-$ calcd for $C_9H_7{}^{79}BrNO_5$ 287.9508, found 287.9480.

Pyrrole 22

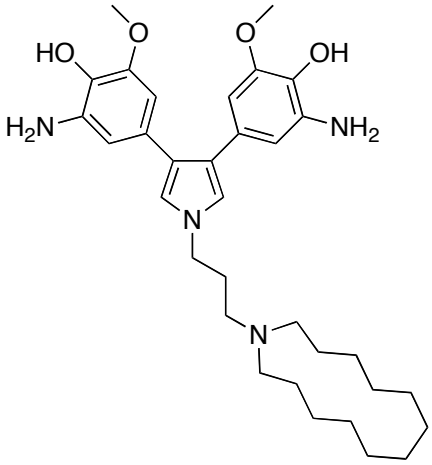


Phenacyl bromide **21** (1.23 g, 4.2 mmol) and NaI (3.2 g, 21 mmol) were added to a solution of the amine **14** (1 g, 4.2 mmol) in DMSO (20 mL) at RT under argon and the reaction mixture was stirred during 15 min at RT. Then a solution of aldehyde **19** (900 mg, 4.3 mmol) in methanol (60 mL) was added and the reaction mixture was stirred during 16 h at RT. It was extracted with CH_2Cl_2 and the organic phase was washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, evaporated under reduced pressure and chromatographed on silica gel (elution gradient from CH_2Cl_2 to CH_2Cl_2/MeOH 80:1) to give **22** (682 mg, 26%) as an amorphous red solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.65 (2 H, d, J = 2.0 Hz), 7.01 (2 H, d, J = 2.0 Hz), 6.87 (2 H, s), 4.05 (2 H, t, J = 7.0 Hz), 3.77 (6 H, s), 2.70–2.43 (6 H, m), 2.15 (2 H, quint, J = 7.5 Hz), 1.66–1.34 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 149.7, 144.8, 133.9, 126.7, 121.0, 120.7, 118.7, 114.5, 56.8, 53.0, 51.7, 47.7, 27.9, 25.7, 25.6, 25.5, 25.2, 23.9. IR (neat) ν_{max} cm^{-1} 3255, 2930, 2859, 1552, 1522, 1464, 1337, 1240, 1156, 919, 732. HRMS (ES) (m/z) $[M+H]^+$ calcd for $C_{33}H_{45}N_4O_8$ 625.3237, found 625.3228.

Hydrochloride 22•HCl

It was obtained as described for **15**, mp 122–125 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.26 (2 H, d, J = 1.5 Hz), 7.20 (2 H, s), 7.08 (2 H, d, J = 1.5 Hz), 4.02 (2 H, t, J = 6.3 Hz), 3.74 (6 H, s), 3.20–3.00 (6 H, m), 2.27 (2 H, quint, J = 7.8 Hz), 1.76–1.60 (4 H, m), 1.45–1.27 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 149.7, 141.1, 137.6, 126.5, 121.7, 120.5, 116.7, 114.8, 56.9, 51.9, 51.2, 46.7, 25.9, 25.7, 25.0, 24.8, 24.4, 20.9. IR (neat) ν_{max} cm^{-1} 3245, 2930, 2859, 2596, 1622, 1552, 1523, 1455, 1315, 1234, 1146, 1054, 798, 763. HRMS (ES) (m/z) $[M-Cl]^+$ calcd for $C_{33}H_{45}N_4O_8$ 625.3237, found 625.3261.

Pyrrole 23

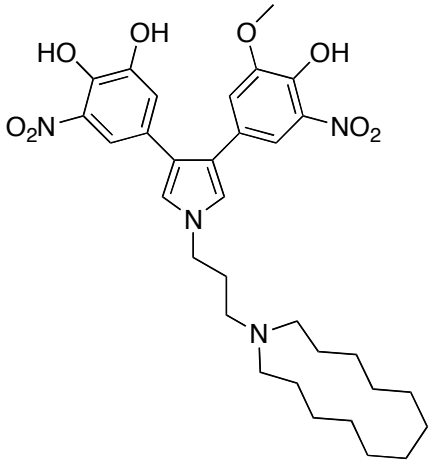


Compound **22** (0.28 g, 0.45 mmol) was hydrogenated (H_2, 3.5 bar) in EtOAc (70 mL) in the presence of 10% Pd/C (150 mg) at RT during 16 h. Then, the solution was degassed under argon and reduced pressure, filtered through silica gel, concentrated at reduced pressure and chromatographed on silica gel (elution gradient from CH_2Cl_2 to CH_2Cl_2/methanol 20:1) to give **23** (196 mg, 77%) as an amorphous colorless semisolid which became rapidly violet in the presence of the air. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.70 (2 H, br s), 6.40 (2 H, br s), 6.31 (2 H, br s), 3.95 (2 H, m), 3.69 (6 H, br s), 2.59 (6 H, br s), 2.12 (2 H, m), 1.60–1.27 (20 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 146.4, 133.7, 131.3, 127.8, 123.3, 119.4, 109.5, 102.7, 56.0, 53.3, 51.9, 47.6, 28.3, 25.7, 25.6, 25.5, 25.3, 24.4. IR (neat) ν_{max} cm^{-1} 3345, 2928, 2856, 1614, 1541, 1508, 1462, 1406, 1346, 1208, 1091, 729. HRMS (ES) (*m*/*z*) $[M+H]^+$ calcd for $C_{33}H_{49}N_4O_4$ 565.3754, found 565.3786.

Hydrochloride 23•3 HCl

It was obtained as described for **15**. Mp 218–226 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.02 (2 H, br s), 6.83 (2 H, br s), 6.77 (2 H, br s), 4.02 (2 H, m), 3.74 (6 H, s), 3.22–2.93 (6 H, m), 2.28 (2 H, m), 1.80–1.60 (4 H, m), 1.58–1.15 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 148.6, 138.5, 127.4, 121.5, 120.9, 119.9, 115.5, 111.8, 56.5, 51.9, 51.1, 46.7, 25.9, 25.8, 25.0, 24.8, 24.5, 20.9. IR (neat) ν_{max} cm^{-1} 3346, 2929, 2859, 2594, 1548, 1523, 1462, 1409, 1239, 1087, 1050, 862, 798. HRMS (ES) (*m*/*z*): $[M-2HCl-Cl]^+$ calcd for $C_{33}H_{49}N_4O_4$ 565.3754, found 565.3774.

Pyrrole 24

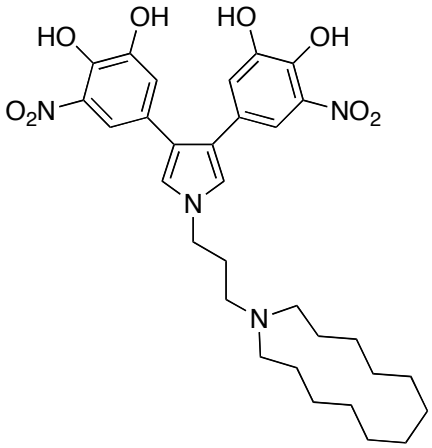


To a solution of **22** (50 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) under argon at -78 °C, BBr_3 (1 M solution in CH_2Cl_2, 0.64 mL, 0.64 mmol) was added. The reaction mixture was stirred and warmed gradually to RT during 1 h and then stirred for 3 h at RT. It was diluted with a phosphate buffer (pH = 7), extracted with chloroform/methanol 3:1, dried over Na_2SO_4, evaporated under reduced pressure and chromatographed on silica gel (elution gradient from CH_2Cl_2 to CH_2Cl_2/methanol 20:1) to give **24** (6 mg, 12%) and **25** (5 mg, 10%) as red-orange oils. **24**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ, (ppm) 7.53 (1 H, br s), 7.47 (1 H, br s), 7.11 (1 H, br s), 7.03 (1 H, br s), 6.87 (1 H, br s), 6.83 (1 H, br s), 4.10 (2 H, t, J = 6.0 Hz), 3.78 (3 H, s), 3.20–2.90 (6 H, m), 2.47 (2 H, m), 1.90–1.67 (4 H, m), 1.57–1.30 (16 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 149.7, 146.7, 144.8, 142.1, 133.8, 133.6, 127.0, 126.5, 121.9, 121.4, 121.2, 120.7, 120.6, 118.8, 114.5, 114.3, 56.8, 52.1, 51.4, 47.1, 26.4, 25.9, 25.0, 24.8, 24.7, 20.7. IR (neat) ν_{max} cm^{-1} 3230, 2931, 2860, 2507, 1552, 1528, 1467, 1237. HRMS (ES) (*m*/*z*) $[M+H]^+$ calcd for $C_{32}H_{43}N_4O_8$ 611.3081, found 611.3109.

Hydrochloride 24•HCl

It was obtained as described for **15**. Mp 154–159 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.28 (1 H, d, J = 3.0 Hz), 7.22 (1 H, d, J = 3.0 Hz), 7.17 (1 H, d, J = 3.0 Hz), 7.10 (1 H, d, J = 3.0 Hz), 7.02 (1 H, d, J = 3.0 Hz), 6.93 (1 H, d, J = 3.0 Hz), 4.01 (2 H, t, J = 6.0 Hz), 3.71 (3 H, s), 3.20–3.00 (6 H, m), 2.23 (2 H, quint, J = 7.0 Hz), 1.73–1.51 (4 H, m), 1.43–1.30 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 149.7, 147.9, 141.1, 140.4, 137.64, 137.57, 126.6, 121.5, 121.4, 120.5, 120.4, 120.1, 116.6, 114.6, 113.6, 56.8, 52.0, 51.3, 46.7, 25.9, 25.8, 24.9, 24.7, 24.4, 21.0. IR (neat) ν_{max} cm^{-1} 3111, 2930, 2861, 2705, 1553, 1463, 1313, 1234, 1061, 866, 801, 763. HRMS (ES) (m/z) [M-HCl-H]$^-$ calcd for $C_{32}H_{41}N_4O_8$ 609.2924, found 609.2916.

Pyrrole 25

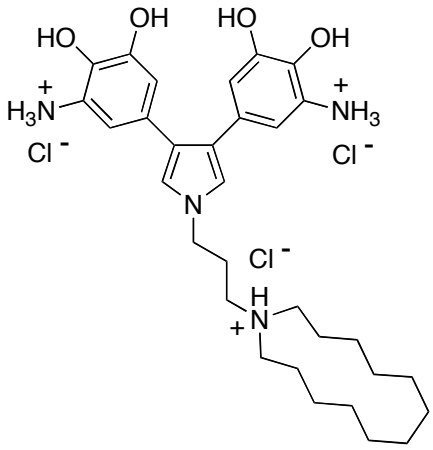


To the amorphous solid **22** (50 mg, 0.080 mmol) under argon at RT, BBr_3 (1 M solution in CH_2Cl_2, 2 mL, 2 mmol) was added. The heterogeneous mixture was stirred during 30 min at RT. A mixture CH_2Cl_2/pentane 1:1 (30 mL) was added and, after 5 min, the precipitate was separated, washed by the same solvents mixture and dissolved in the minimal volume of CH_2Cl_2/ethanol 10:1. The solution was introduced on a column with silica gel, eluted with CH_2Cl_2/ethanol 20:1 and evaporated under reduced pressure to give the amorphous red-orange solid **25** (44 mg, 92%). ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm) 7.44 (2 H, d, J = 1.8 Hz), 7.00 (2 H, s), 6.97 (2 H, d, J = 1.8 Hz), 4.12 (2 H, t, J = 6.3 Hz), 3.30–3.12 (6 H, m), 2.32 (2 H, quint, J = 6.0 Hz), 1.85–1.70 (4 H, m), 1.60–1.39 (16 H, m). ^{13}C NMR (CD_3OD, 75 MHz) δ (ppm) 147.5, 141.9, 134.7, 127.0, 121.4, 121.3, 120.5, 113.5, 52.4, 52.0, 46.1, 25.9, 25.3, 24.6, 24.2, 23.9, 21.2. IR (neat) ν_{max} cm^{-1} 3379, 2932, 1621, 1555, 1471, 1300, 1236, 803, 762, 667. HRMS (ES) (m/z) [M+H]$^+$ calcd for $C_{31}H_{41}N_4O_8$ 597.2924, found 597.2938.

Hydrochloride 25•HCl

It was obtained as described for **15**. Mp 179–184 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.19 (2 H, d, J = 3.0 Hz), 7.06 (2 H, s), 6.90 (2 H, d, J = 3.0 Hz), 4.00 (2 H, t, J = 6.0 Hz), 3.15–2.97 (6 H, m), 2.24 (2 H, quint, J = 6.0 Hz), 1.75–1.58 (4 H, m), 1.44–1.28 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 148.0, 140.4, 137.7, 126.7, 121.3, 120.5, 120.1, 113.5, 51.9, 51.2, 46.7, 25.9, 25.7, 24.9, 24.7, 24.4, 20.9. IR (neat) ν_{max} cm^{-1} 3111, 2930, 2861, 1552, 1463, 1293, 1233, 1061, 866, 801, 762. HRMS (ES) (m/z) [M-HCl-H]$^-$ calcd for $C_{31}H_{39}N_4O_8$ 595.2768, found 595.2773.

Pyrrole 26



Compound **25** (44 mg, 0.074 mmol) was hydrogenated (H_2, atmospheric pressure) in ethanol (7 mL) in the presence of 10% Pd/C (30 mg) at RT during 16 h. Then, the solution was degassed under argon and reduced pressure, CH_2Cl_2 (10 mL) and pentane (3 mL) were added and the resulting mixture was filtered through silica gel, eluted with CH_2Cl_2/methanol 5:3. The obtained solution was collected directly in the flask containing HCl (2 M solution in methanol, 1 mL). Then, it was diluted with diethyl ether to form a white precipitate of **26** (43 mg, 90%), mp 234–242 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 6.86 (2 H, br s), 6.72 (2 H, br s), 6.64 (2 H, br s), 4.01 (2 H, t, J = 7.2 Hz), 3.17–2.90 (6 H, m), 2.25 (2 H, m), 1.80–1.54 (4 H, m), 1.52–1.20 (16 H, m). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 146.4, 137.7, 127.5, 121.6, 120.6, 120.0, 115.7, 114.3, 51.9, 51.0, 46.6, 25.89, 25.86, 24.9, 24.7, 24.5, 20.8. IR (neat) ν_{max} cm^{-1} 3405, 3150, 2927, 2857, 2588, 1578, 1503, 1438, 1295, 1238, 1206, 1165, 1091, 998, 864, 796, 725. HRMS (ES) (m/z) [M-2HCl-Cl]$^+$ calcd for $C_{31}H_{45}N_4O_4$ 537.3441, found 537.3416.

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2 (*a*) J. E. Baldwin, H. R. Vollmer, V. Lee, *Tetrahedron Lett.*, 1999, **40**, 5401–5404; (*b*) M. H. Weston, K. Nakajima, T. G. Back, *J. Org. Chem.*, 2008, **73**, 4630–4637.
3 (*a*) G. Koren-Goldshlager, Y. Kashman, M. Schleyer, *J. Nat. Prod.*, 1998, **61**, 282–284; (*b*) D. E. Williams, K. S. Craig, B. Patrick, L. M. McHardy, R. van Soest, M. Roberge, R. J. Andersen, *J. Org. Chem.*, 2002, **67**, 245–258.
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5 D. E. Lewin, A. Lowy, *J. Am. Chem. Soc.*, 1933, **55**, 1995–2000.
6 (*a*) L. E. Kiss, H. S. Ferreira, L. Torrão, M. J. Bonifácio, P. N. Palma, P. Soares-da-Silva, D. A. Learnmonth, *J. Med. Chem.*, 2010, **53**, 3396–3411; (*b*) X. Lu, S. Wan, J. Jiang, X. Jiang, W. Yang, P. Yu, L. Xu, Z. Zhang, G. Zhang, L. Shan, Y. Wang, *Eur. J. Med. Chem.*, 2011, **46**, 2691–2698.
7 J. Borgulya, H. Bruderer, K. Bernauer, G. Zürcher, M. Da Prada, *Helv. Chim. Acta*, 1989, **72**, 952–968.

Cytotoxic studies

Cell culture

Cancer cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. Briefly, human cell lines HCT-116 (colon cancer) and K562 (leukemia cancer) were grown in RPMI-1640 supplemented with 10% heat-inactivated fetal bovine serum, penicillin (50 U/mL) and streptomycin (50 µg/mL). U87 (glioblastoma) and MDA-MB-231 (breast cancer) were grown

in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum, penicillin (50 U/mL) and streptomycin (50 µg/mL).
The human cell lines KB3-1 (mouth epidermis carcinoma) originated from the NCI, HepG2 (hepatocarcinoma) and MiaPaca (pancreas carcinoma) provided from ECACC were grown in D-MEM medium supplemented with 10% fetal calf serum, in the presence of penicillin, streptomycin and fungizone in a 75 cm² flask under 5% of CO_2. HL60 (acute promyelocytic leukaemia), K562 (chronic myelocytic leukemia), OVCAR8 (ovary adenocarcinoma), MCF7 (breast adenocarcinoma), and PC3 (prostate carcinoma) obtained from ATCC were grown in RPMI medium supplemented with 10% fetal calf serum, in the presence of penicillin, streptomycin and fungizone in a 75 cm² flask under 5% of CO_2. Resistant HL60R was obtained by prolonged treatment with doxorubicin.

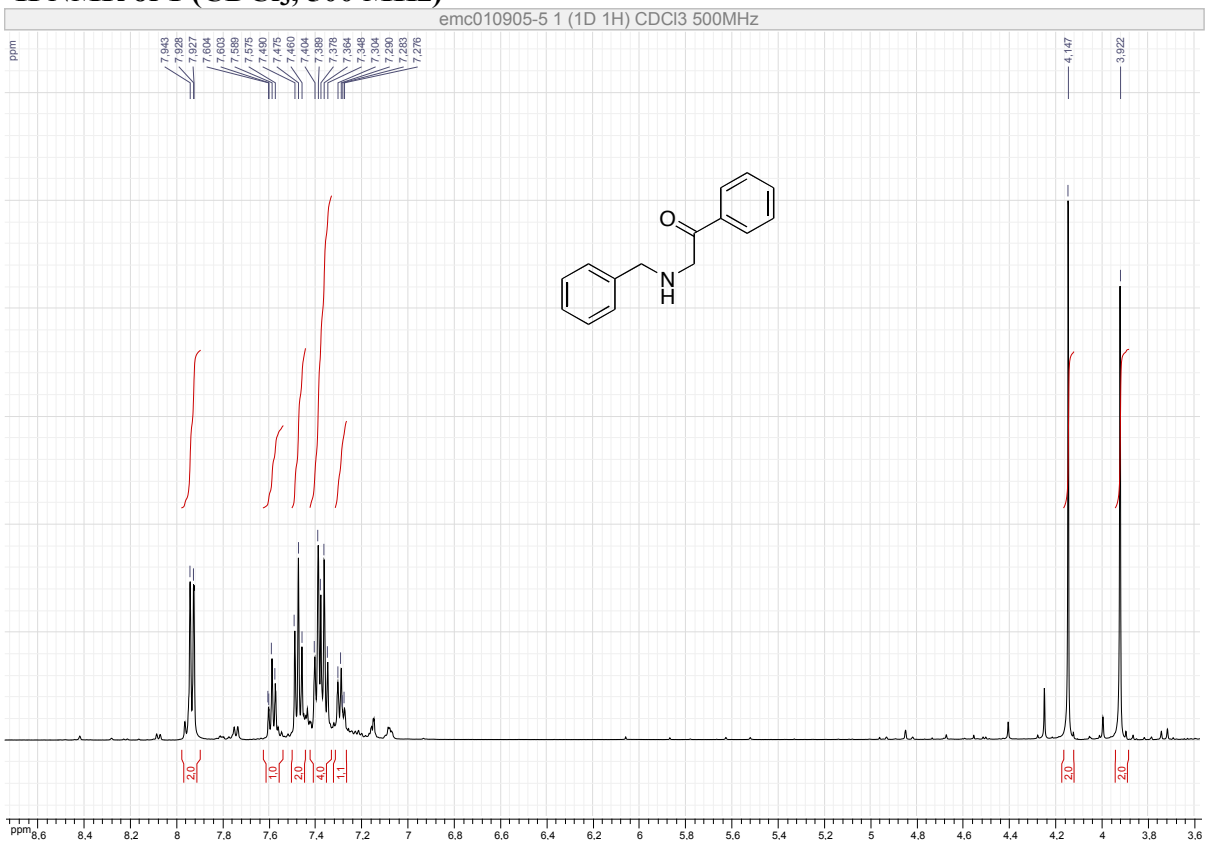
Proliferation assay
For cell proliferation assays, cells were plated in 96-well tissue culture plates in 200 µL of medium and treated 24 h later with 2 µL of a stock solution of compounds dissolved in DMSO using a Biomek 3000 (Beckman-Coulter). Controls received the same volume of DMSO (1% of final volume). After 72 h of exposure, MTS reagent (Celltiter 96AQeous One, Promega) was added and incubated for 3 h at 37 °C: the absorbance was monitored at 490 nm and results expressed as the inhibition of cell proliferation calculated as the ratio [(1-(OD490 treated/OD490 control)) × 100] in triplicate experiments. For IC_{50} determination [50% inhibition of cell proliferation], cells were incubated for 72 h following the same protocol with compound concentrations ranging from 5 nM to 100 µM in separate duplicate experiments.
Cell viability was determined by using Promega celltiter blue reagent according to the manufacturer's instructions. Briefly, cells were seeded in 96-well microtiter plates at a density of 2500 cells/well containing 50 µL of growth medium. After 24 h, 50 µL of the studied compounds dissolved in DMSO (< 0.1%) were added at different concentrations, ranging from 10^{-8} to 10^{-4} M. After 72 h of incubation, resazurin (20 µL) was added for 1 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (PerkinElmer, USA). The IC_{50} value corresponds to the concentration of the studied compound that caused a 50% decreased in fluorescence of drug-treated cells relative to untreated cells. Experiments were performed in triplicates.

Cell culture and apoptosis assay
Cancer cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. HCT-116 colorectal carcinoma cells were grown in RPMI 1640 supplemented with 10% fetal calf serum (FCS) and 1% penicillin-streptomycin. Cell line was maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Apoptosis was measured by the Apo-one homogeneous caspase-3/7 assay (Promega Co, WI) according to the manufacturer's recommendations. Briefly, HCT-116 cells were subcultured on a 96-well plate with 2.5×10^3 cells/well in 50 µL medium. After 24 h of culture, the cells were supplemented with 50 µL of medium containing different concentrations of the tested compound dissolved in DMSO (less than 0.1% in each preparation). The treated cells were incubated for 24 h, each well then received 100 µL of a mixture of caspase substrate and Apo-one caspase 3/7 buffer. After 1 h of incubation, the fluorescence of sample was measured using a Victor microtiter plate fluorimeter (Perkin–Elmer, USA) at 527 nm. Experiments were performed in triplicate.

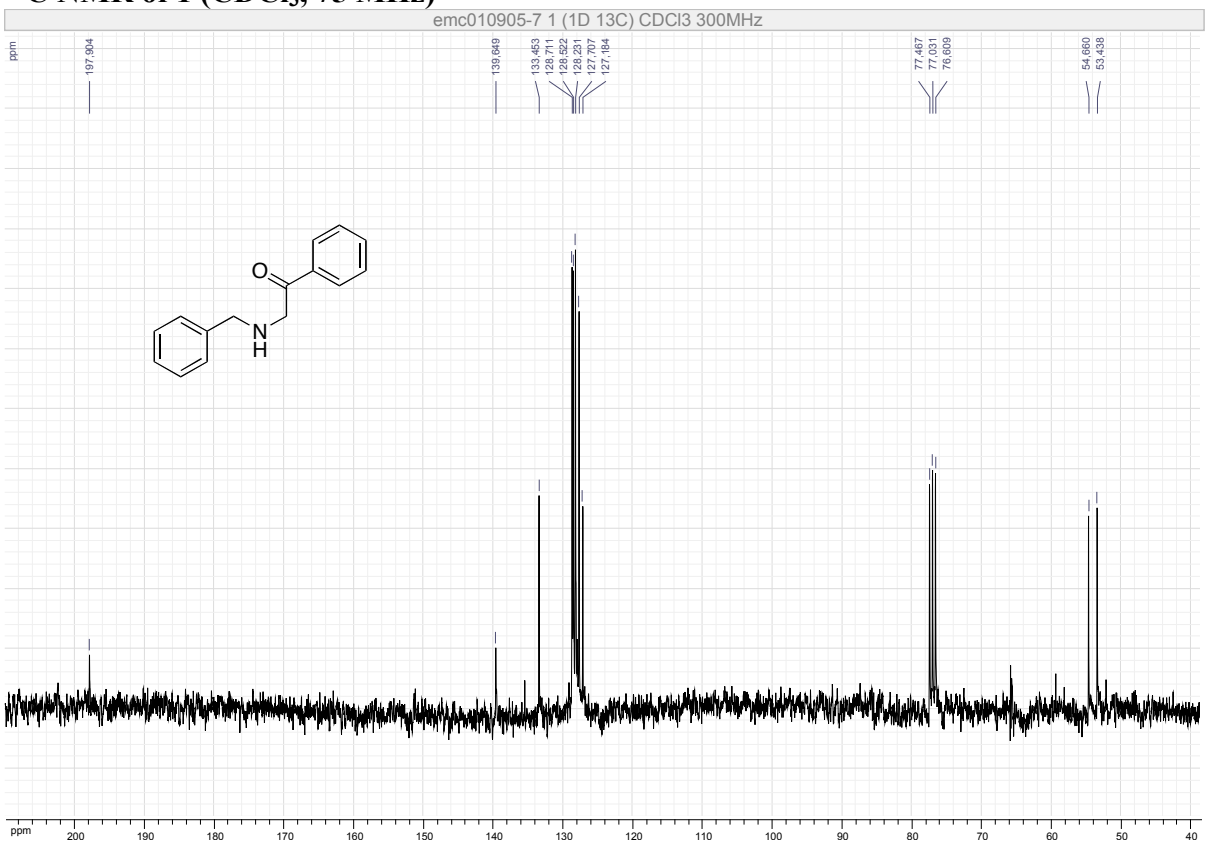
SDS-PAGE and Western blot analysis

HCT-116 cells were plated in 10 cm diameter culture Petri dishes at a density of 3×10^5 cells/dish. After 24 h of culture, compound **25** was added at the final concentrations of 5, 10, 25, 50 and 100 nM. After 24 h, cells were then washed twice with cold DPBS and lysed in the cell lysis buffer containing 20 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM Na_2EDTA, 1 mM EGTA, 1% Triton, 2.5 mM sodium pyrophosphate, 1 mM β-glycerophosphate, 1 mM Na_3VO_4, 1 μL leupeptin and a protease inhibitor cocktail. The cell lysates were collected by centrifugation; 20 μg protein from each cell lysate was diluted in Laemmli buffer, heating during 10 min at 90 °C, subjected to SDS-PAGE (Biorad TGX any KD) polyacrylamide gel electrophoresis and transferred into PDVF membrane. The membrane was blocked with 5% skim milk in 0.1% Tween-PBS (T-PBS) for 2 h at room temperature and incubated overnight with either rabbit-anti-LC3 (dilution 1/1000, Sigma-Aldrich) or rabbit anti-β tubulin (dilution 1/1200, Cell Signaling Technology) primary antibodies at 4 °C. After rinsing with T-PBS blots were incubated for 1 h 30 min with the respective secondary antibody (goat anti-rabbit, dilution 1/20000) conjugated with horse radish peroxidase (HRP) diluted in blocking solution. Membranes were washed in T-PBS and followed by development with Immobilon Western (Millipore) Chemiluminescent HRP substrate reagent.

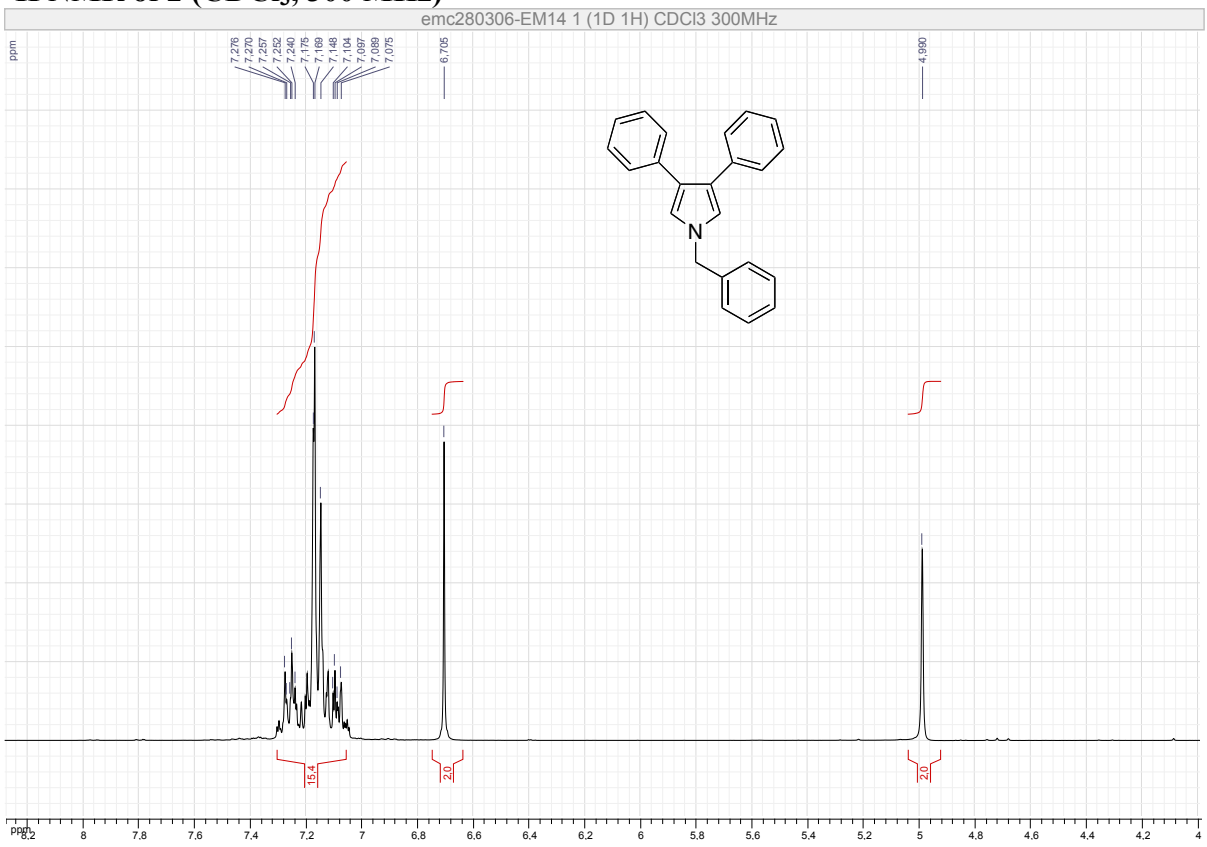
^{1}H NMR of 1 ($CDCl_3$, 500 MHz)



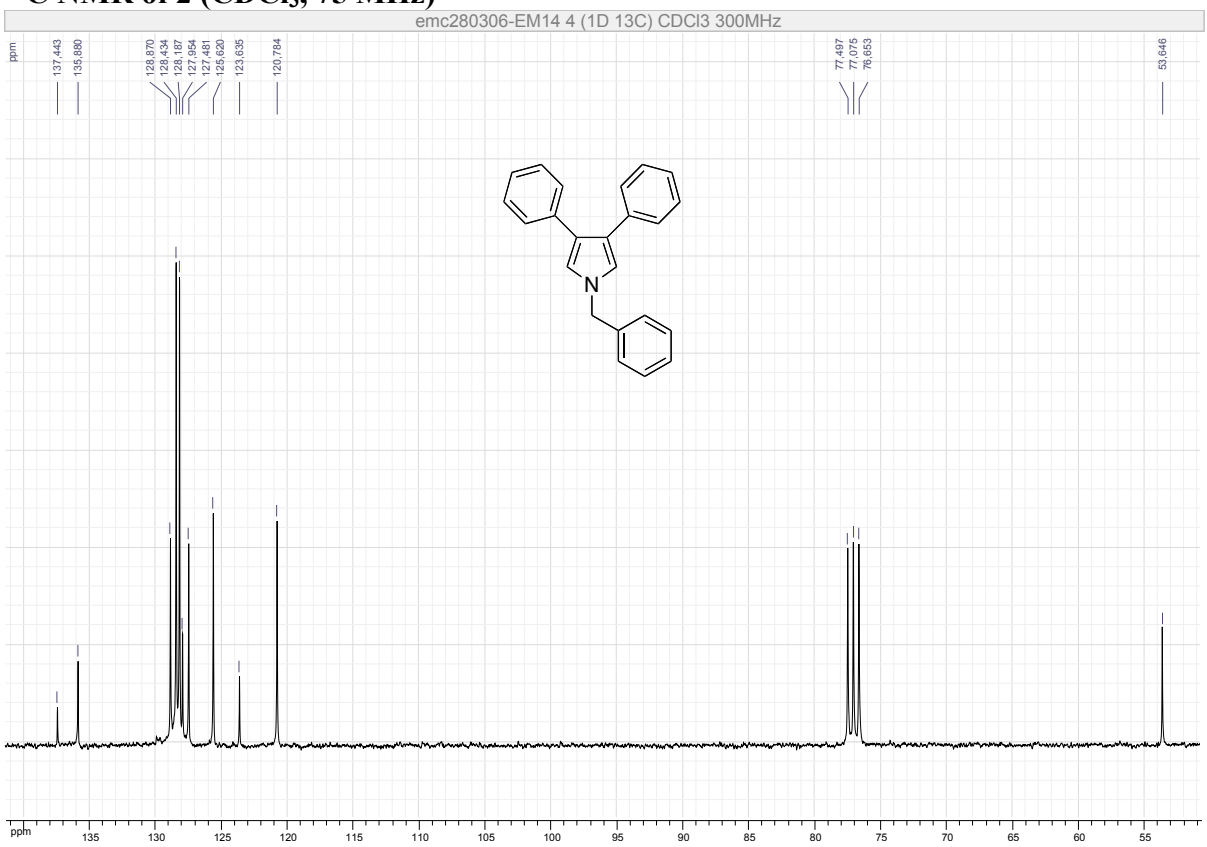
^{13}C NMR of 1 ($CDCl_3$, 75 MHz)



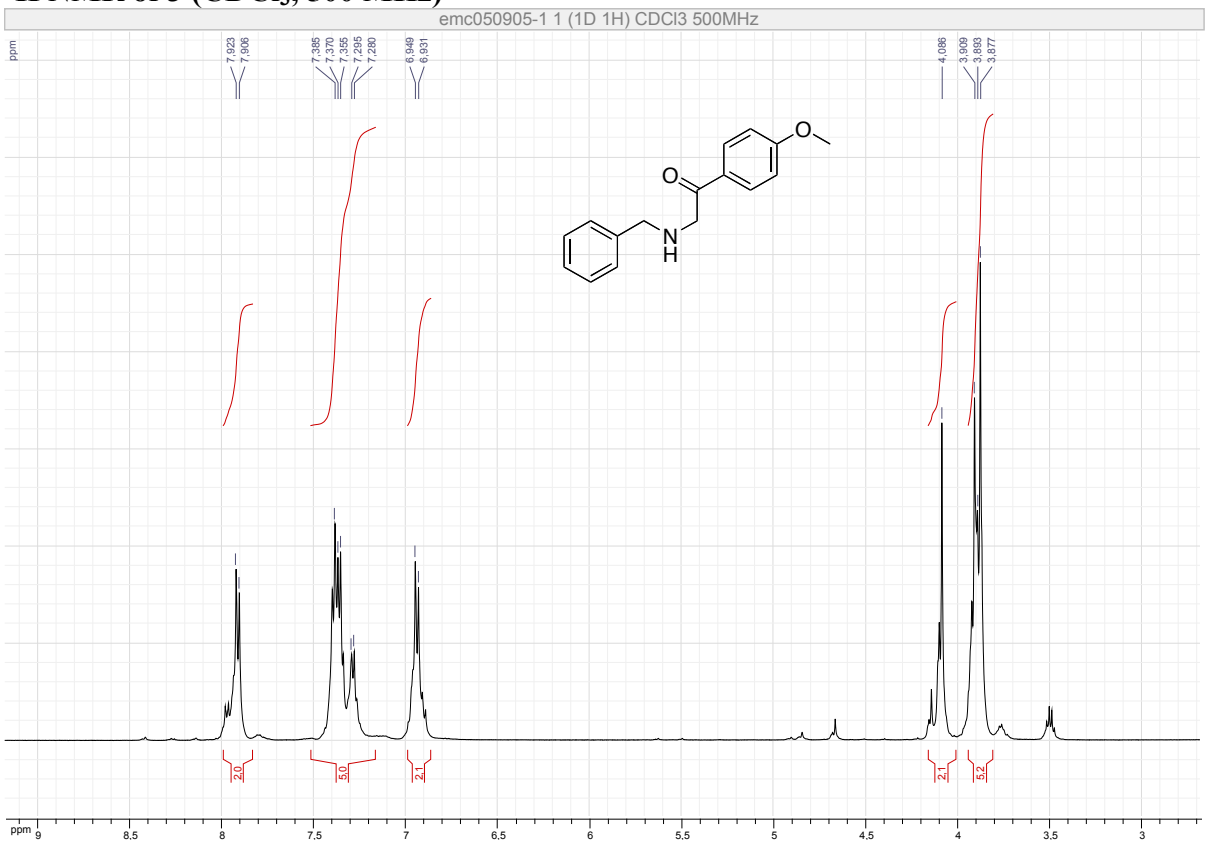
^{1}H NMR of 2 ($CDCl_3$, 300 MHz)



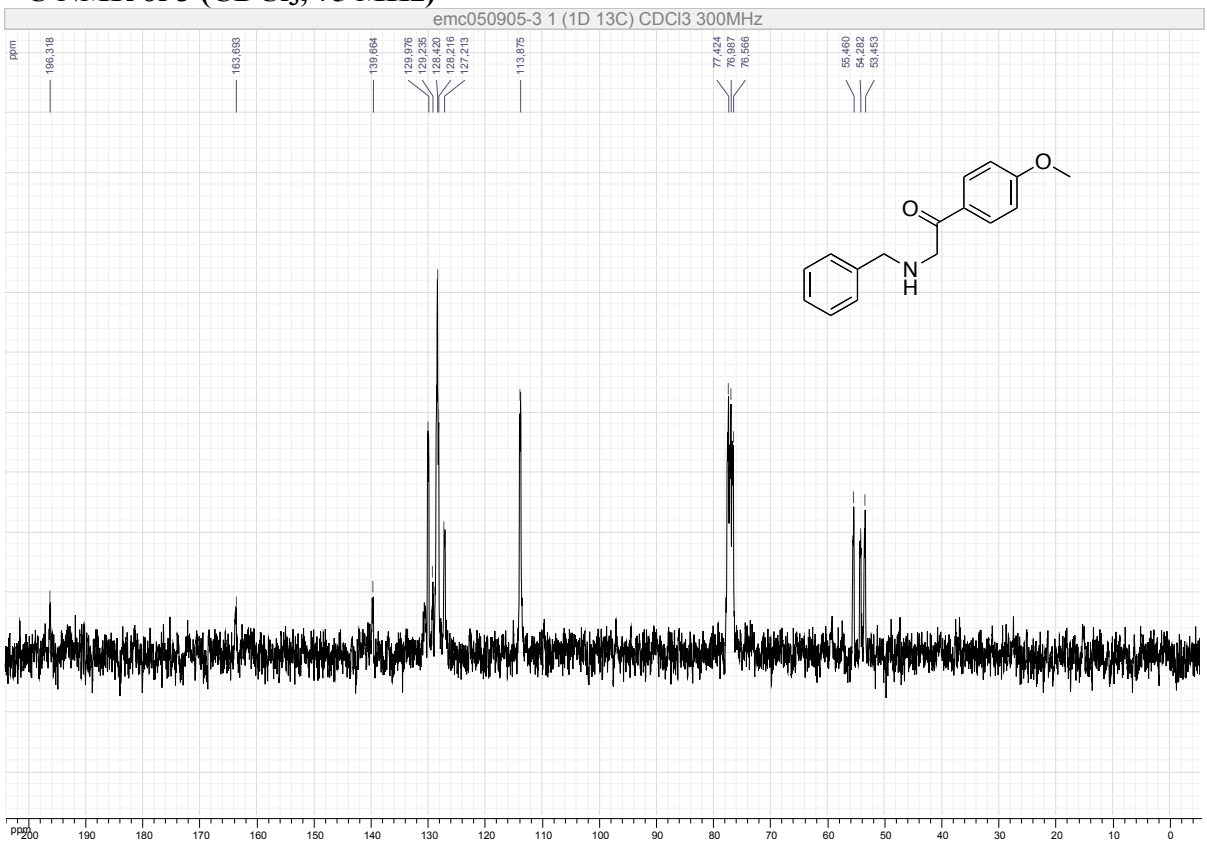
^{13}C NMR of 2 ($CDCl_3$, 75 MHz)



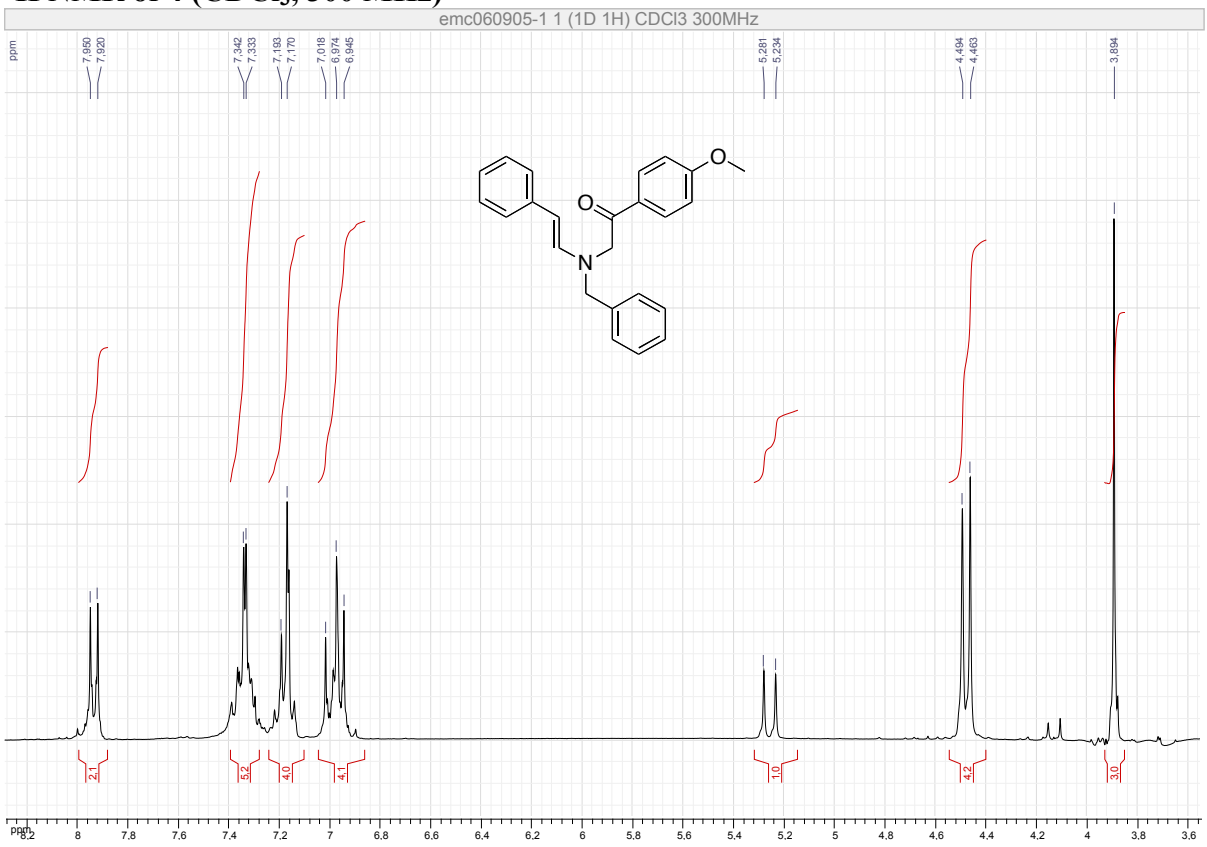
^{1}H NMR of 3 ($CDCl_3$, 500 MHz)



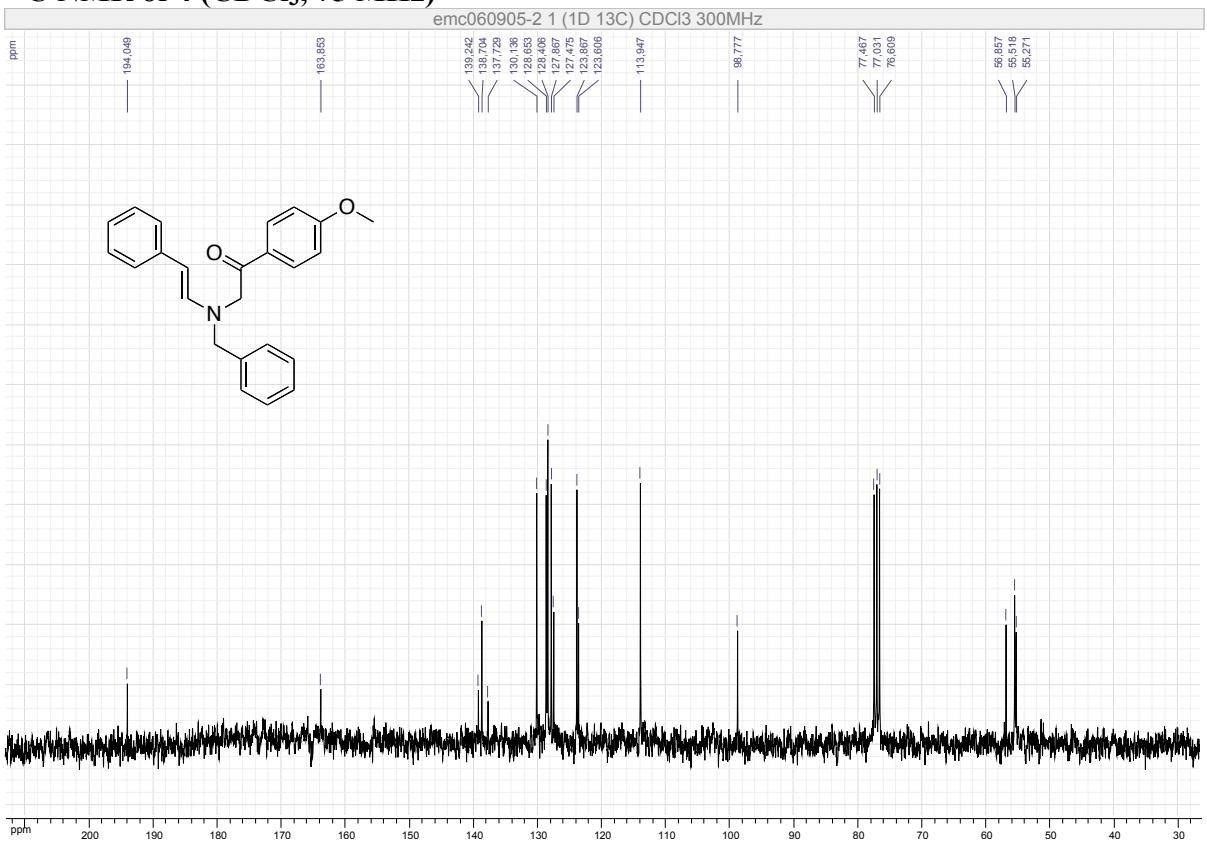
^{13}C NMR of 3 ($CDCl_3$, 75 MHz)



^{1}H NMR of 4 ($CDCl_3$, 300 MHz)



^{13}C NMR of 4 ($CDCl_3$, 75 MHz)



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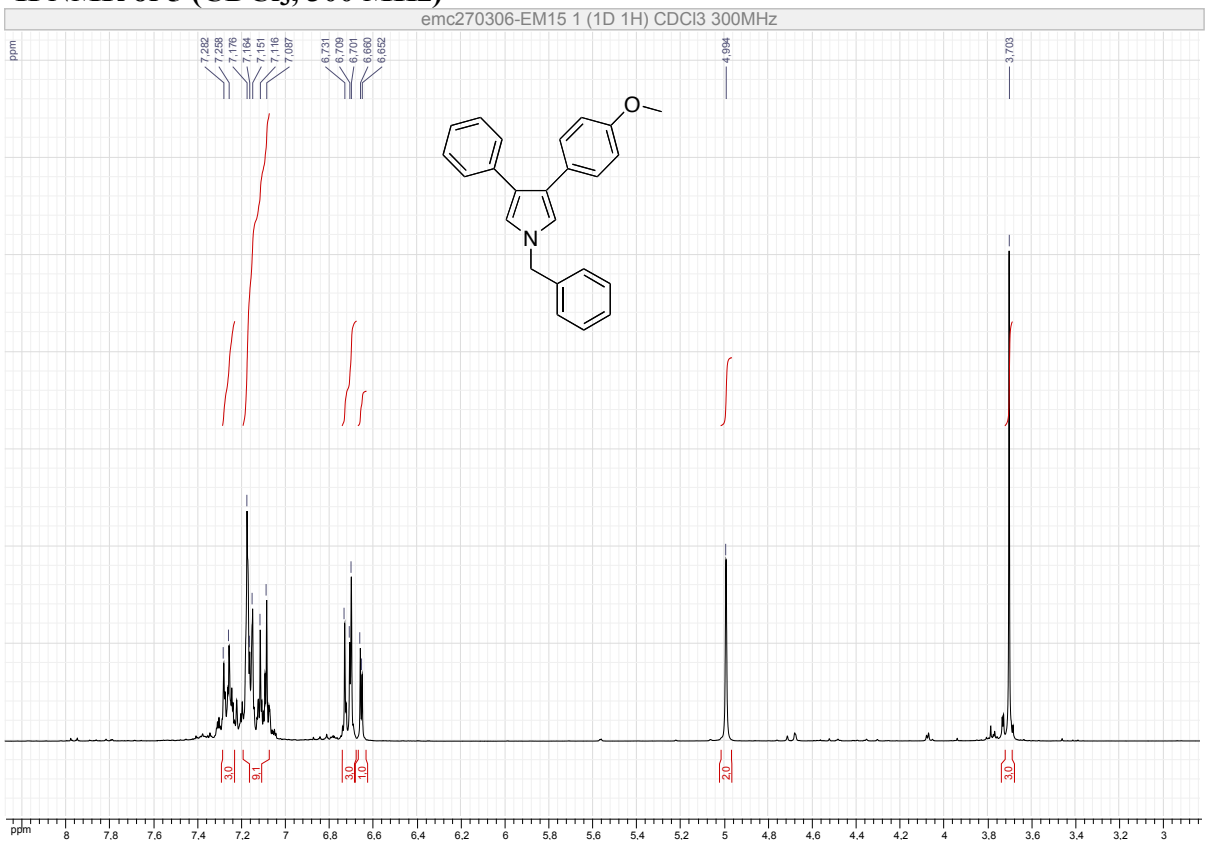
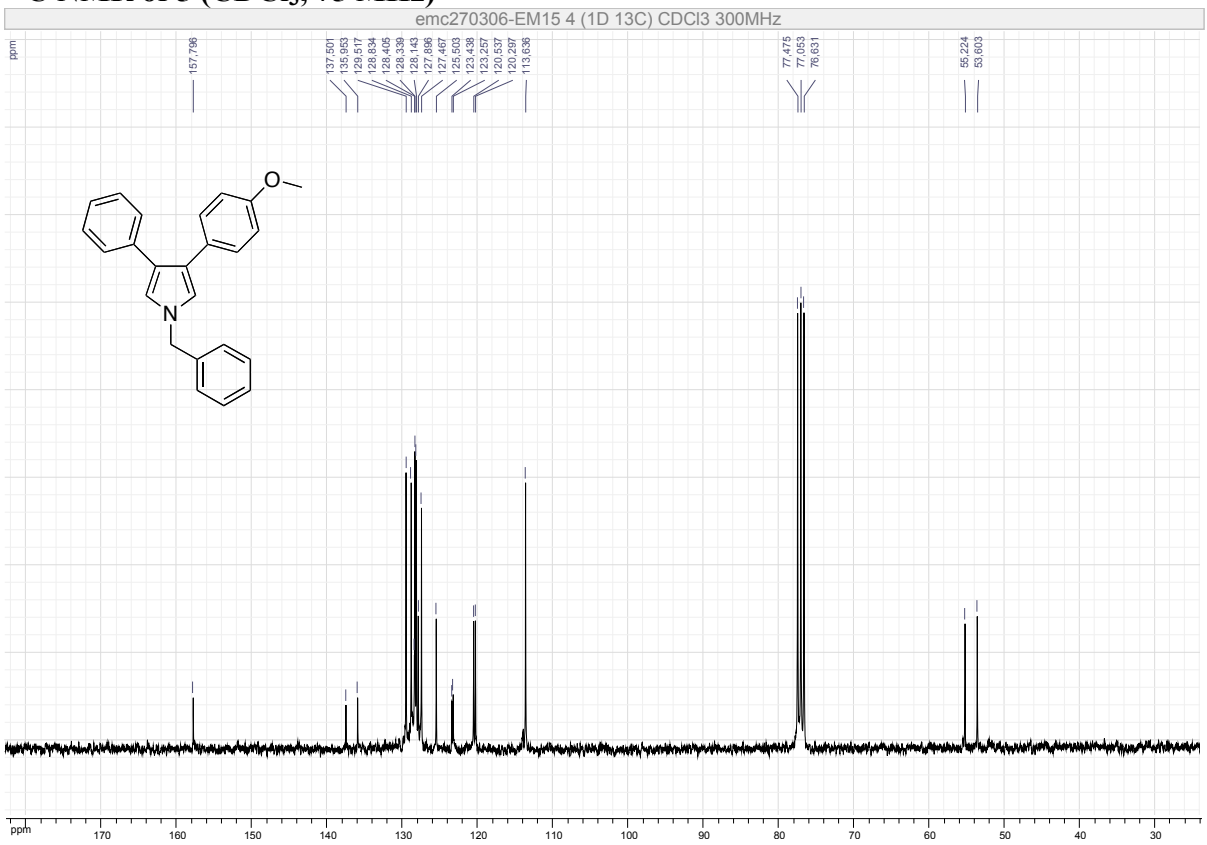
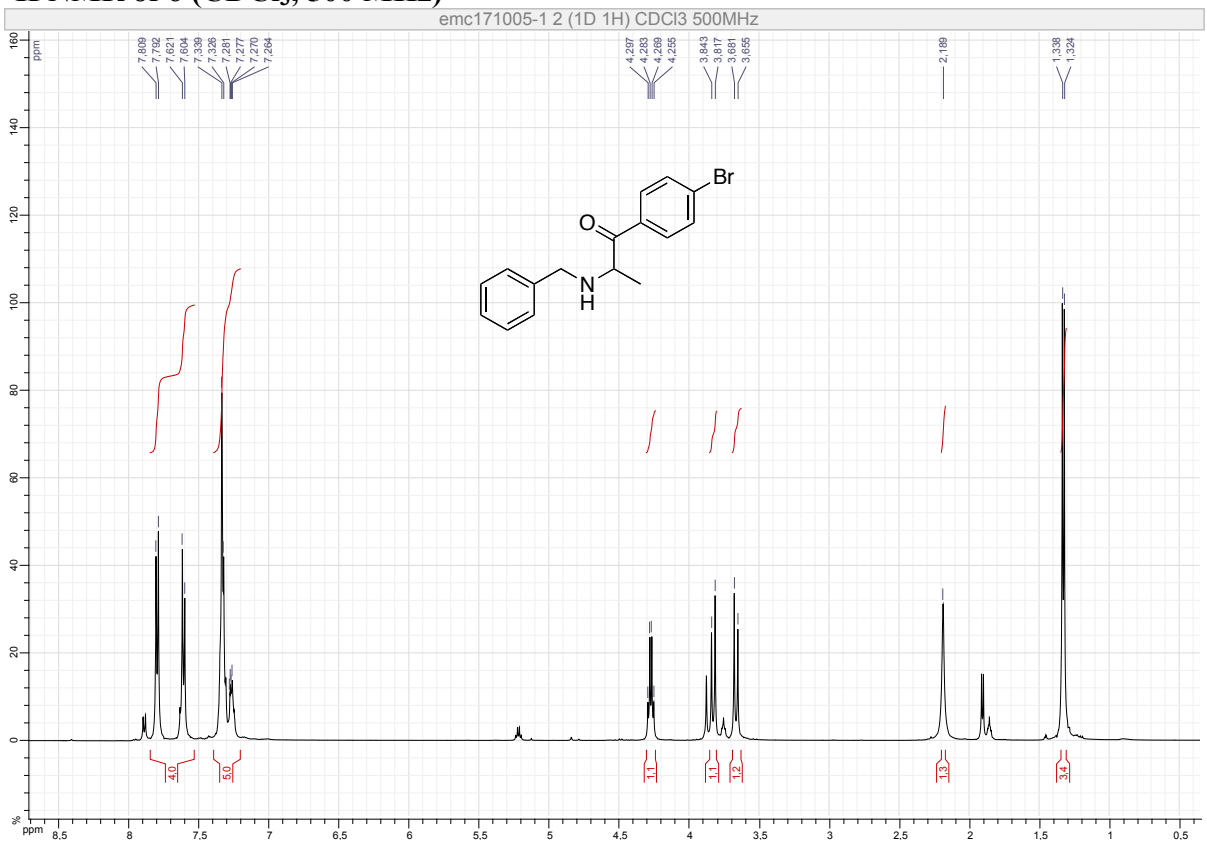


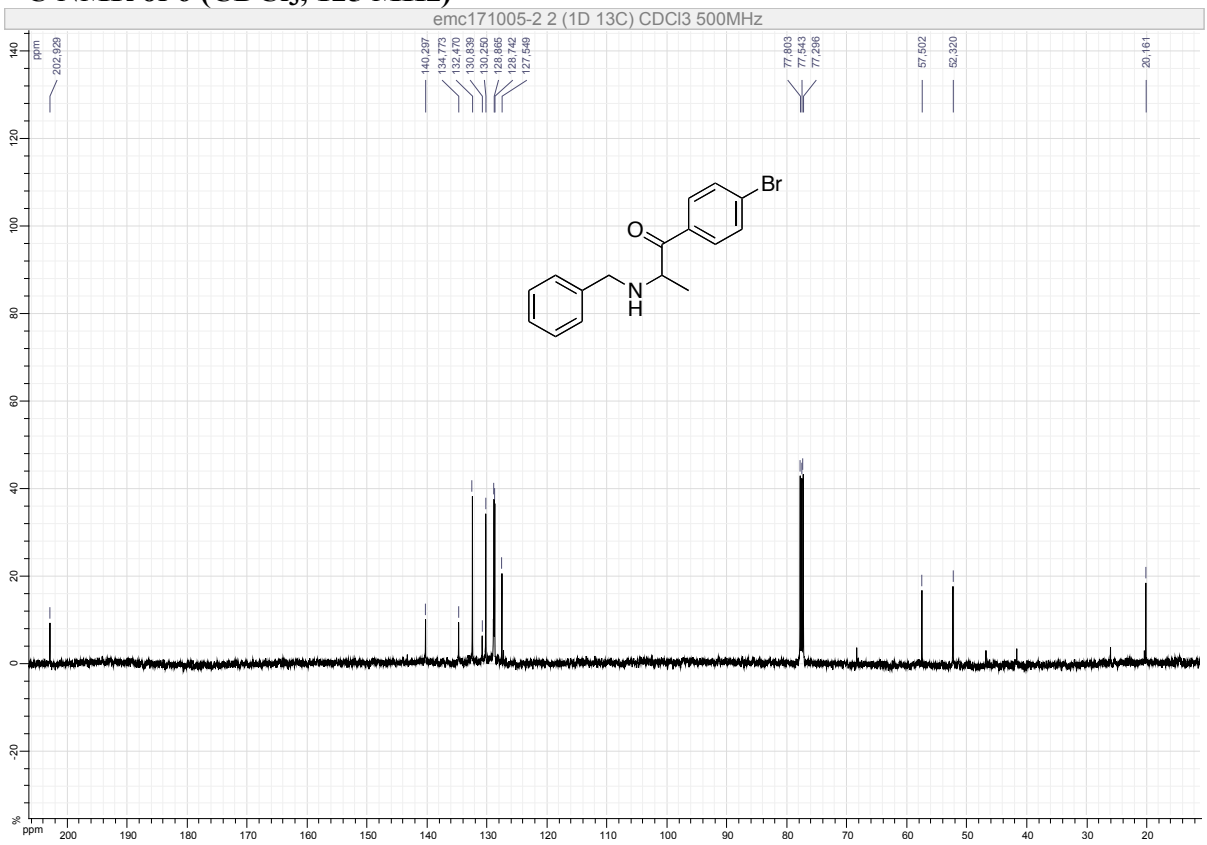
^{13}C NMR of 5 ($CDCl_3$, 75 MHz)



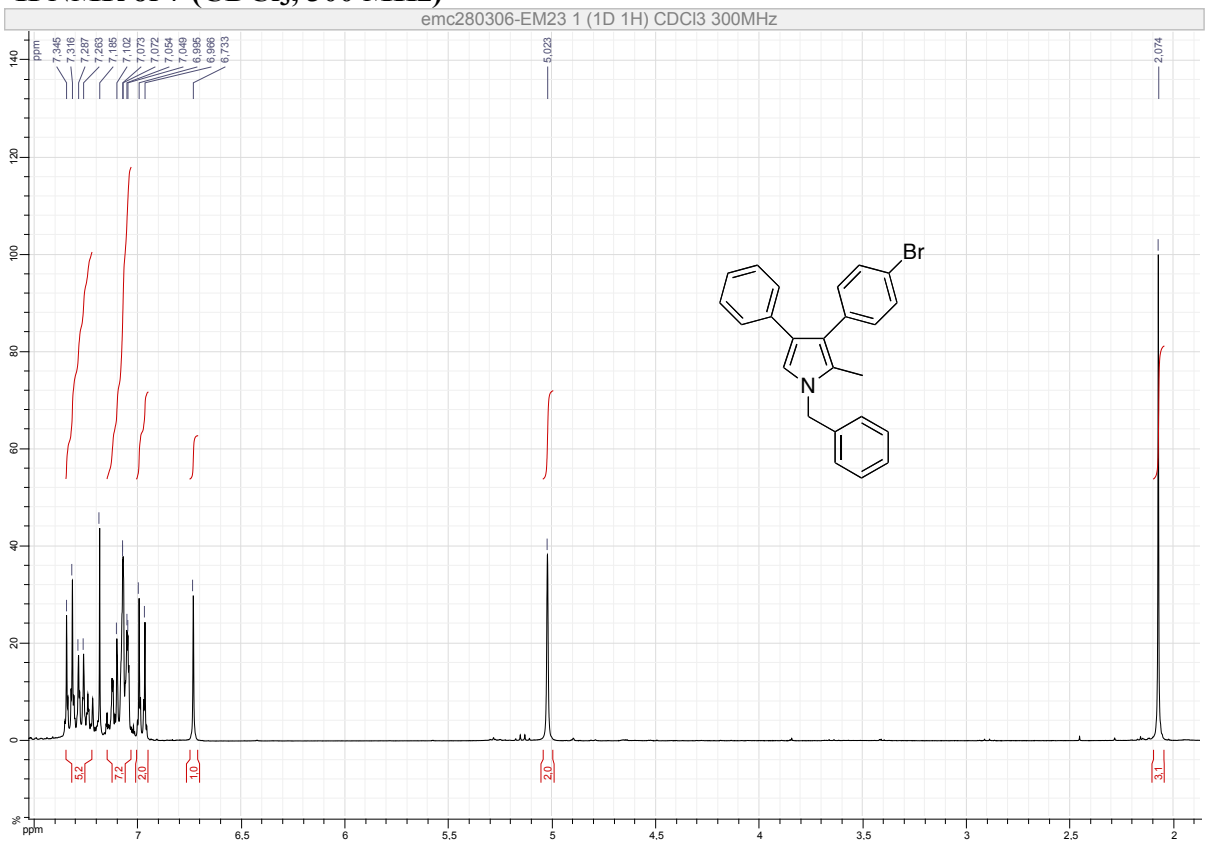
^{1}H NMR of 6 ($CDCl_3$, 500 MHz)



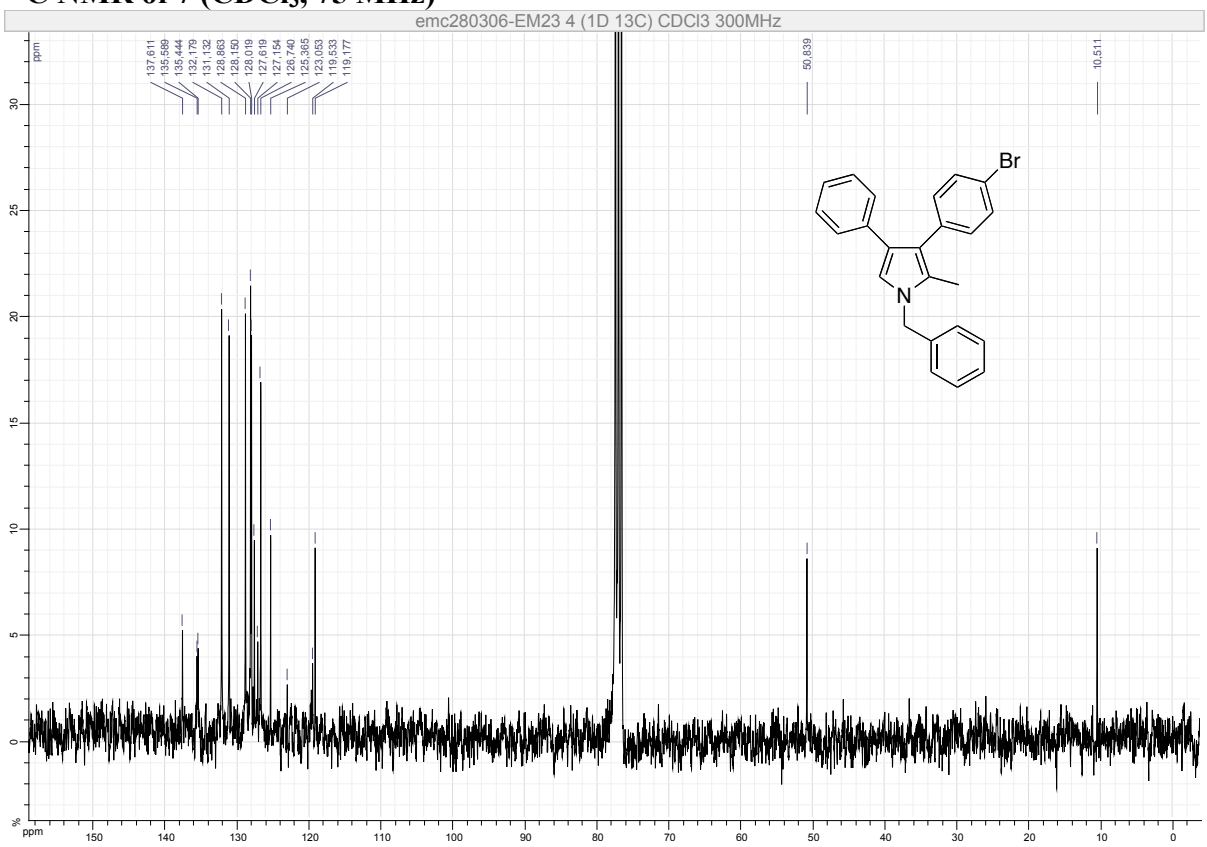
^{13}C NMR of 6 ($CDCl_3$, 125 MHz)



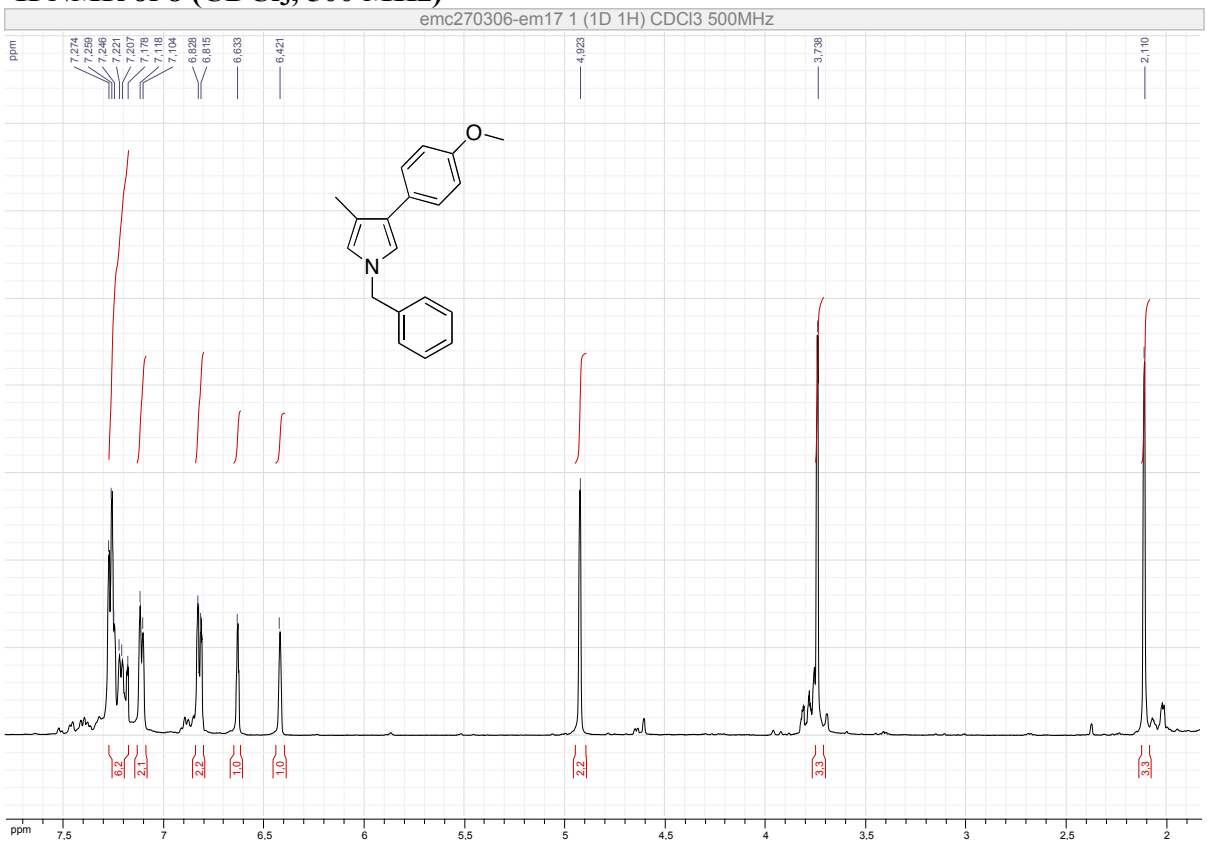
^{1}H NMR of 7 ($CDCl_3$, 300 MHz)



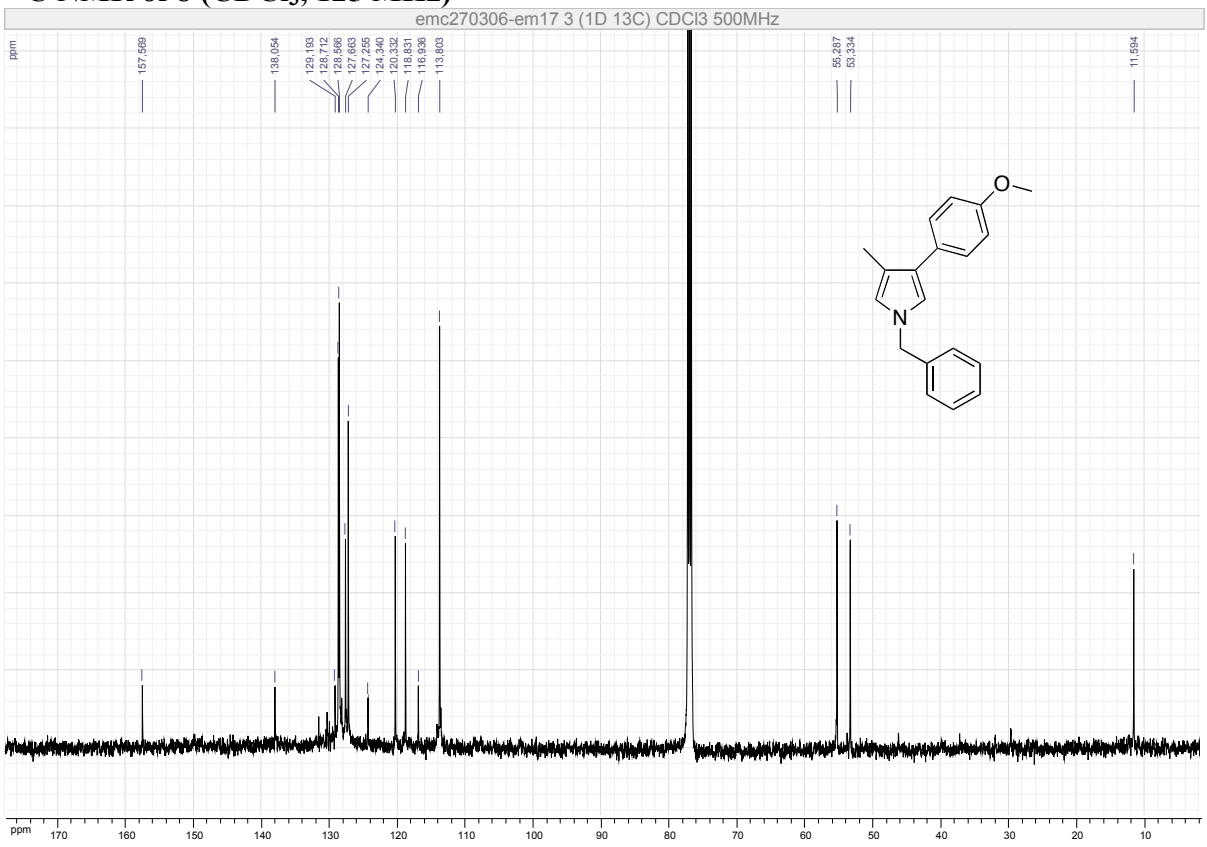
^{13}C NMR of 7 ($CDCl_3$, 75 MHz)



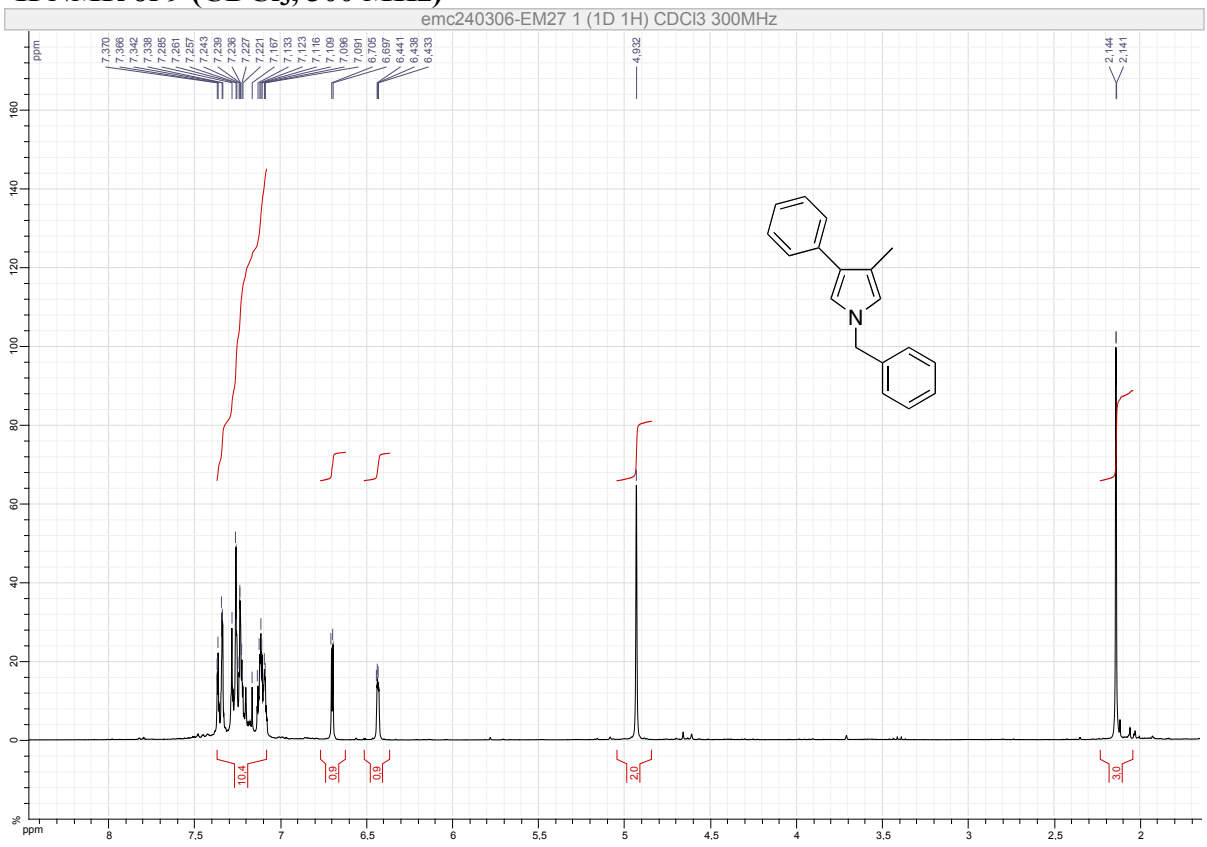
^{1}H NMR of 8 ($CDCl_3$, 500 MHz)



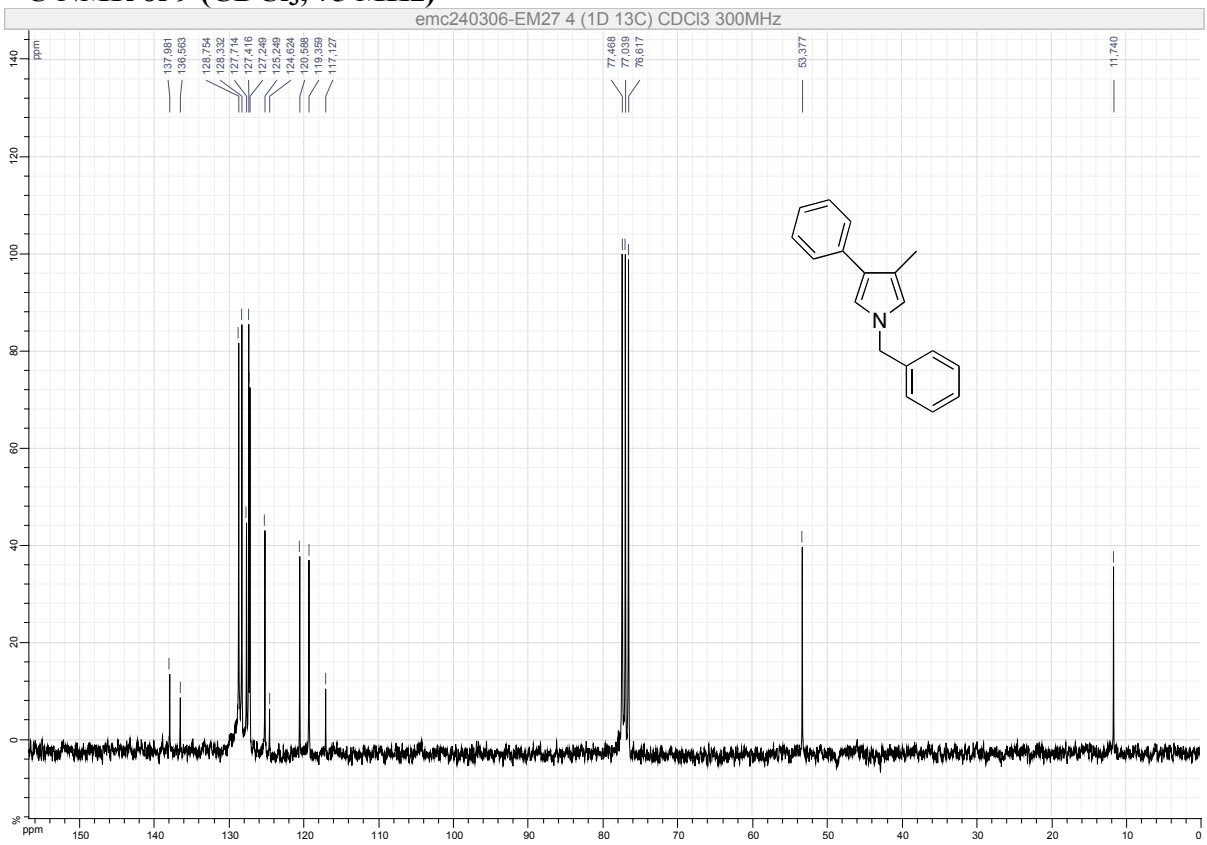
^{13}C NMR of 8 ($CDCl_3$, 125 MHz)



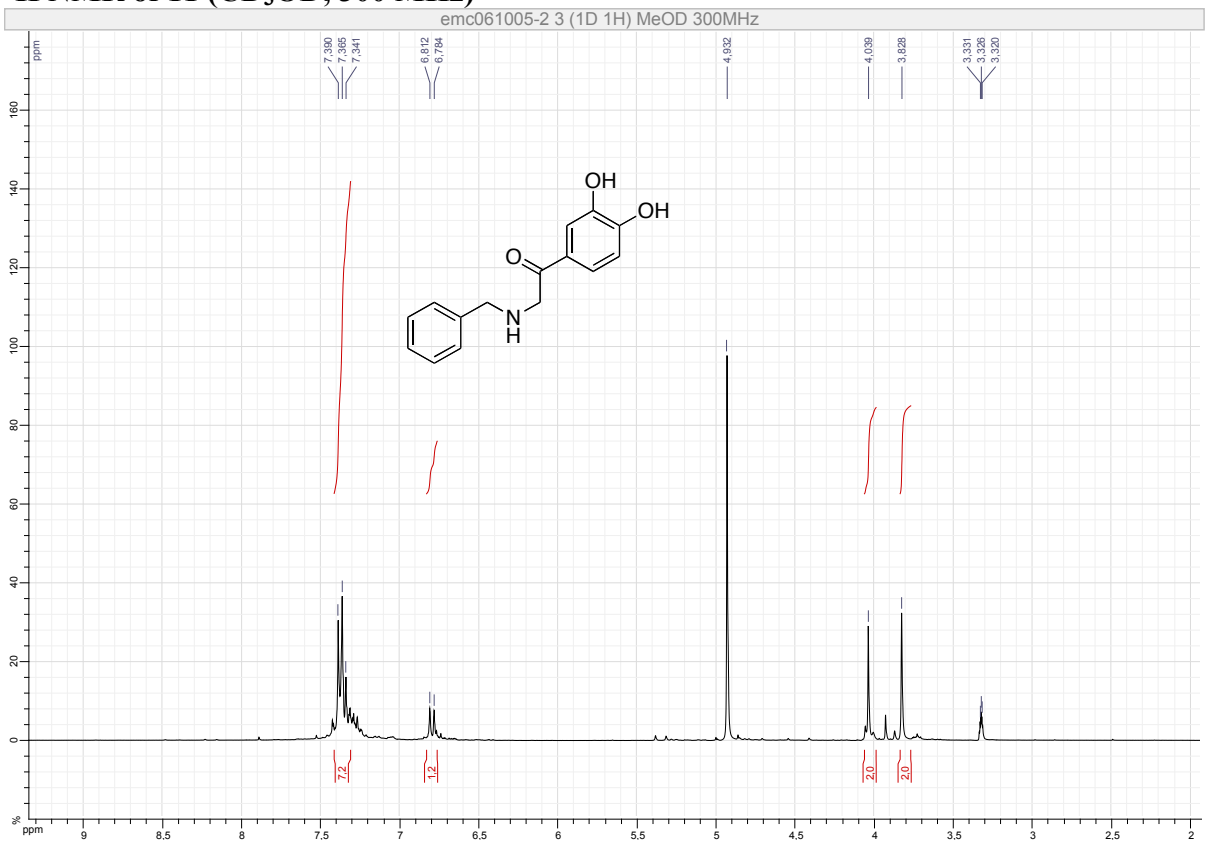
^{1}H NMR of 9 ($CDCl_3$, 300 MHz)



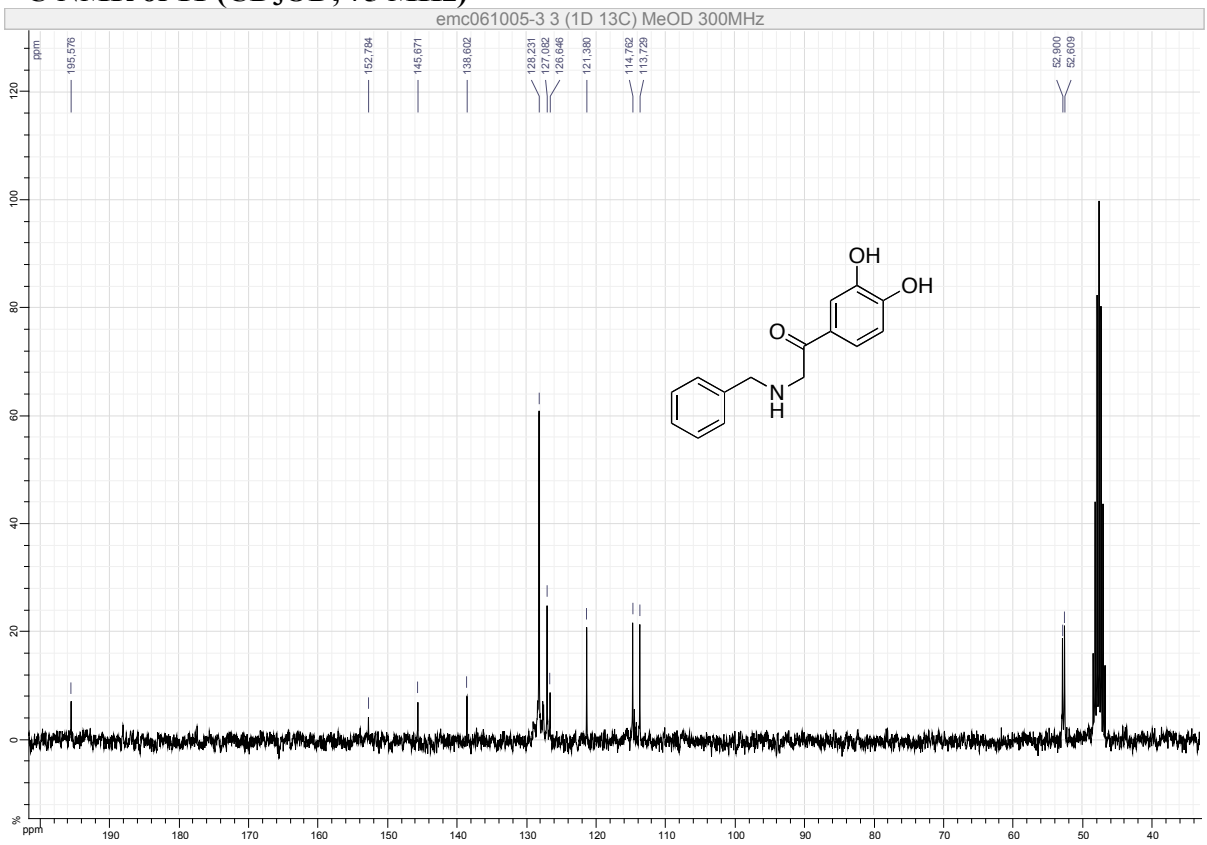
^{13}C NMR of 9 ($CDCl_3$, 75 MHz)



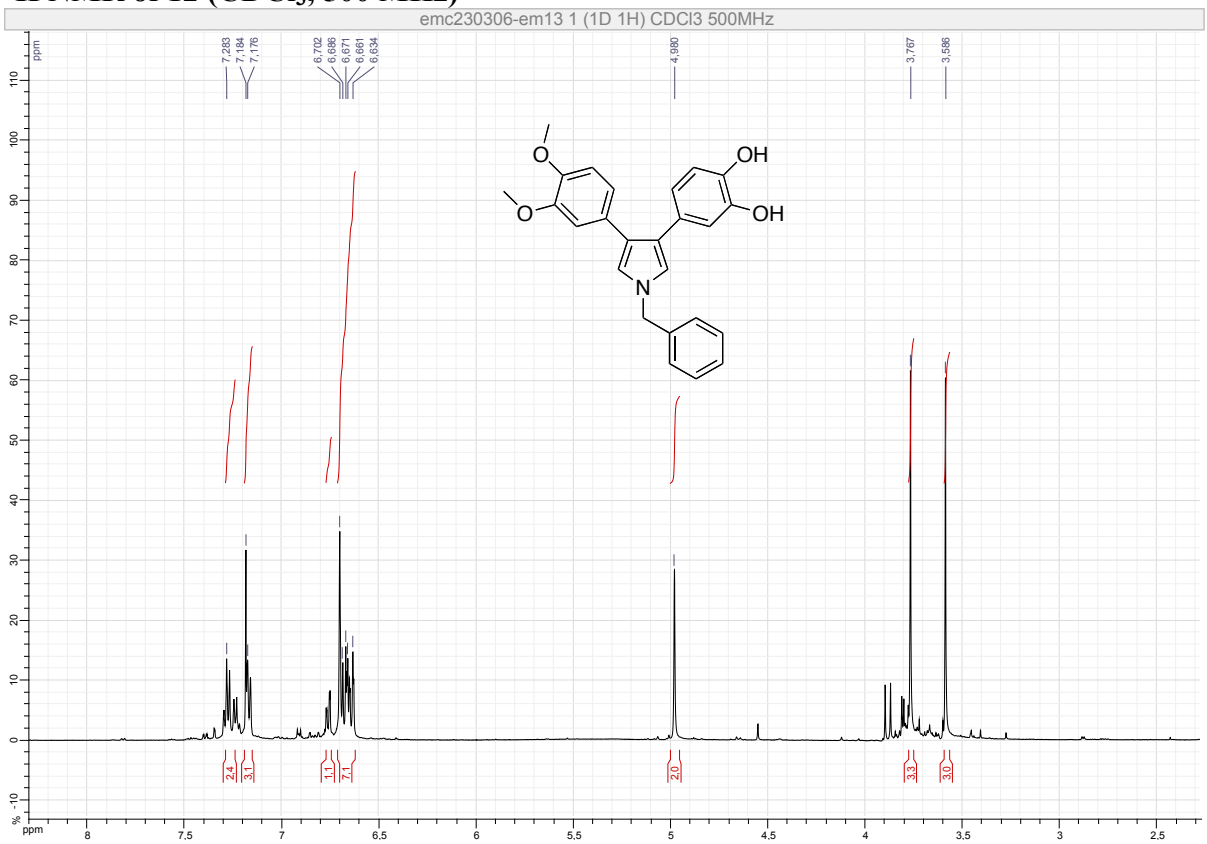
^{1}H NMR of 11 (CD_3OD, 300 MHz)



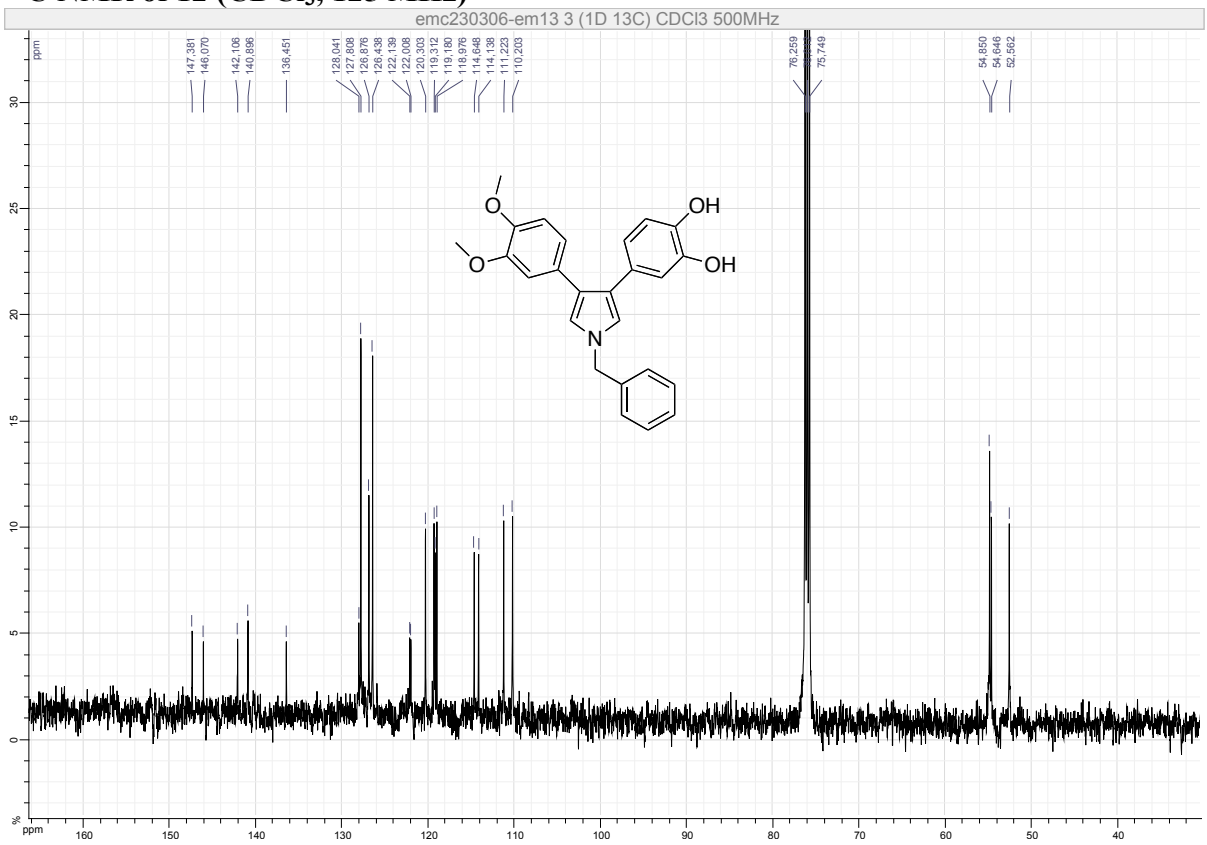
^{13}C NMR of 11 (CD_3OD, 75 MHz)



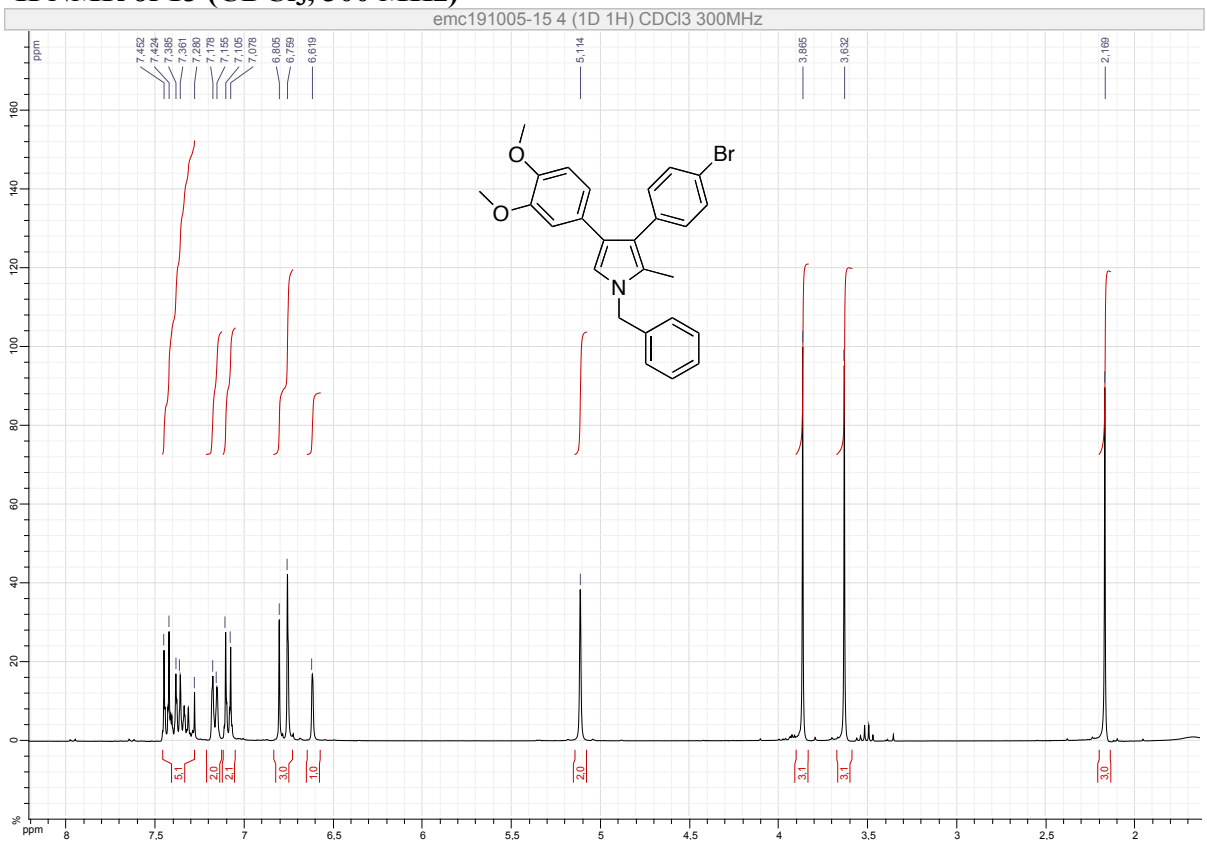
^{1}H NMR of 12 ($CDCl_3$, 500 MHz)



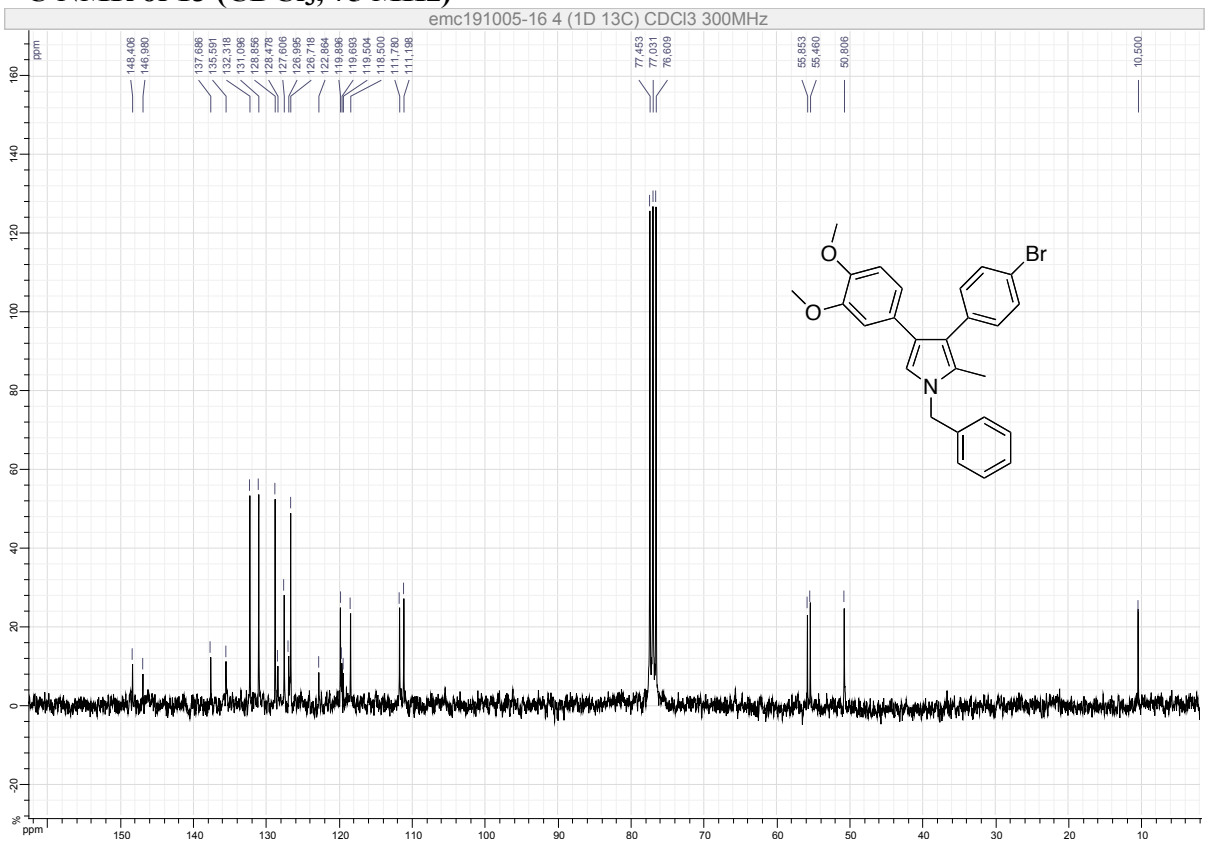
^{13}C NMR of 12 ($CDCl_3$, 125 MHz)



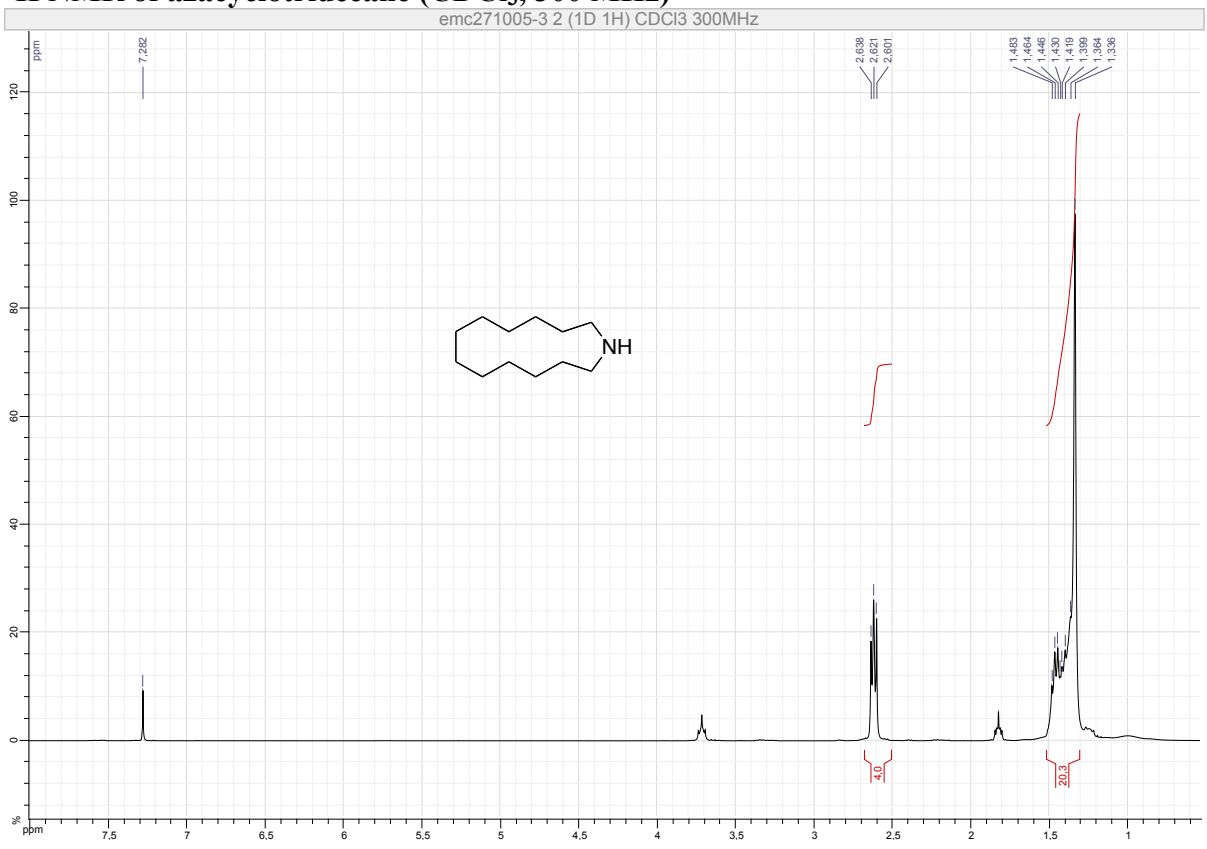
^{1}H NMR of 13 ($CDCl_3$, 300 MHz)



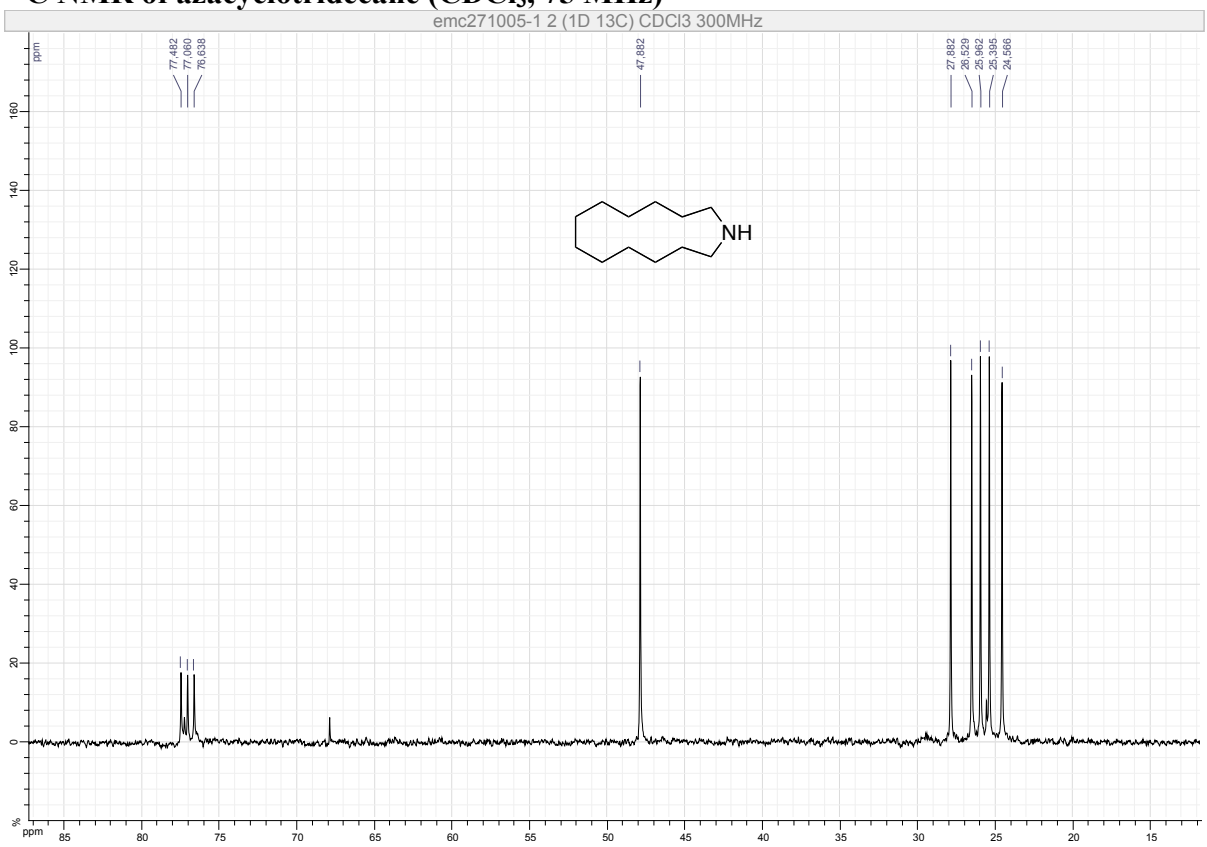
^{13}C NMR of 13 ($CDCl_3$, 75 MHz)



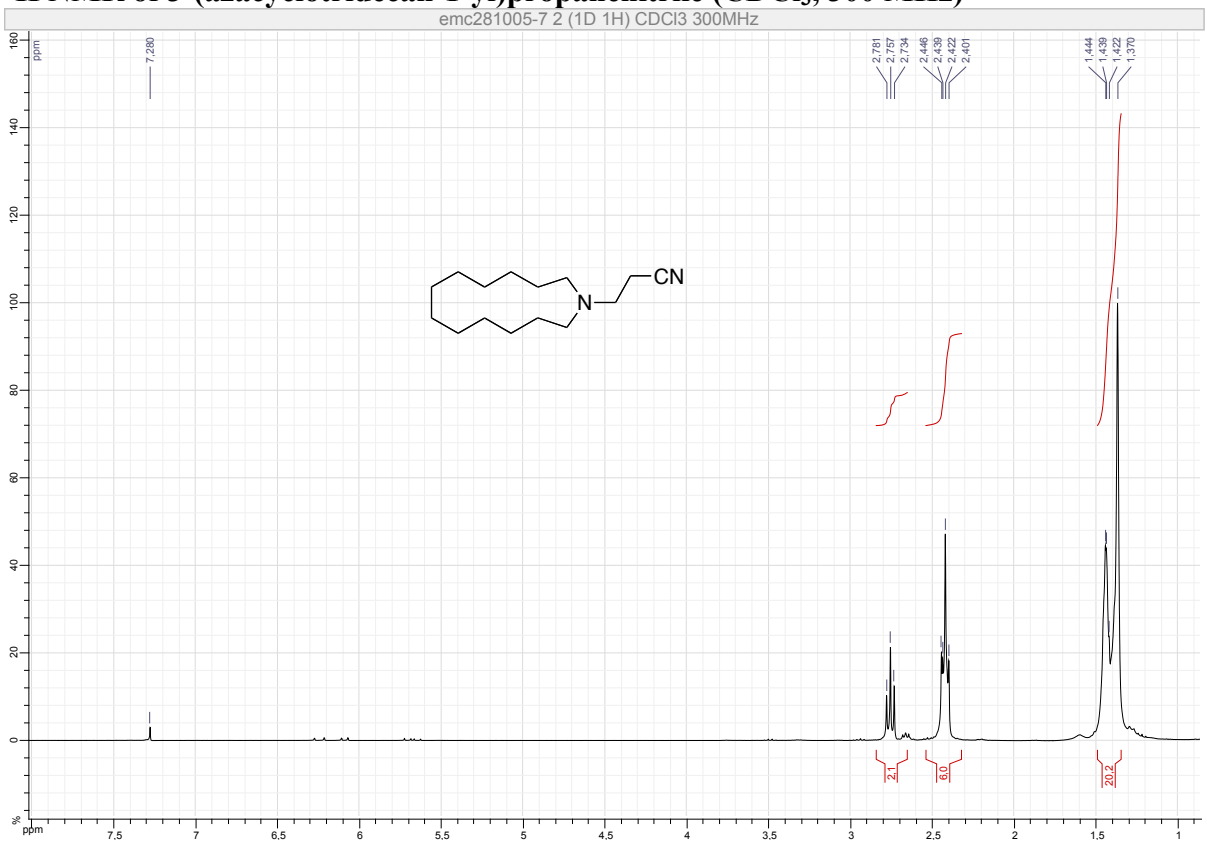
^{1}H NMR of azacyclotridecane ($CDCl_3$, 300 MHz)



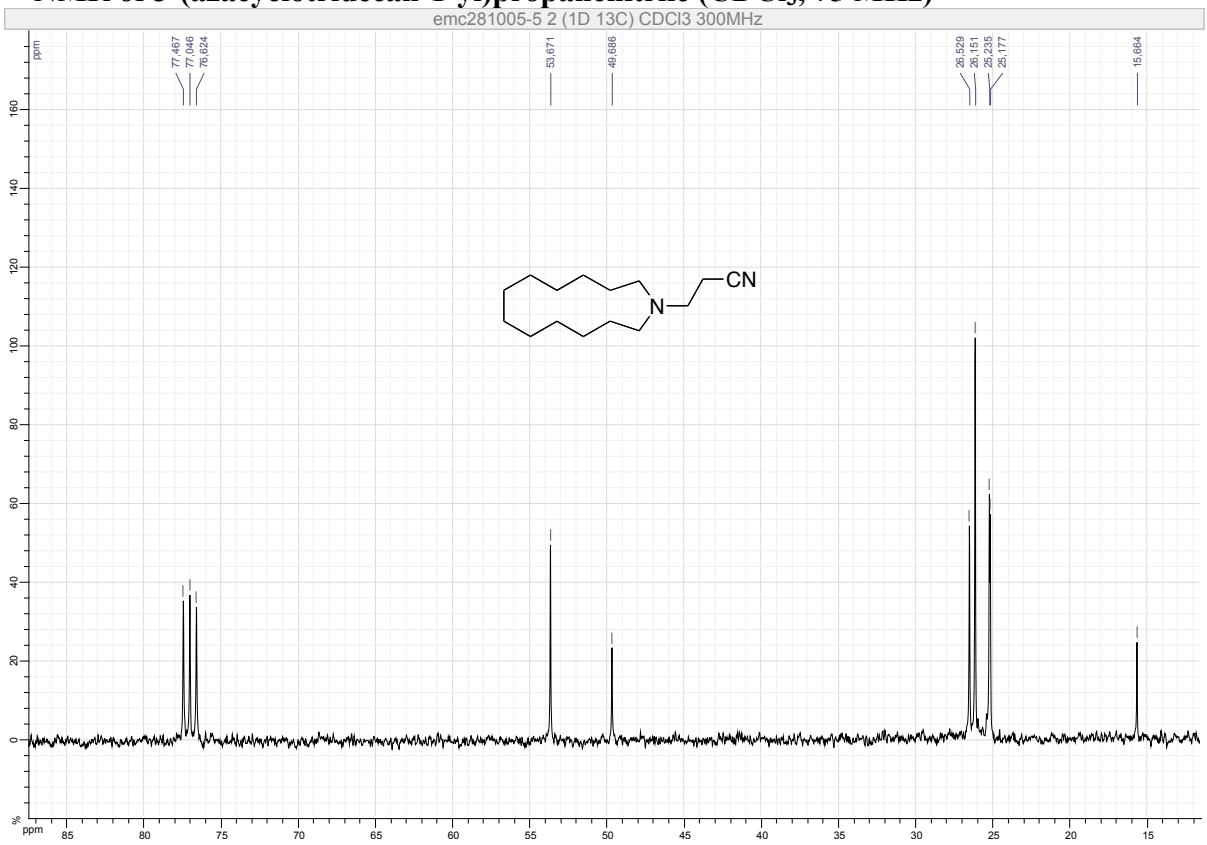
^{13}C NMR of azacyclotridecane ($CDCl_3$, 75 MHz)



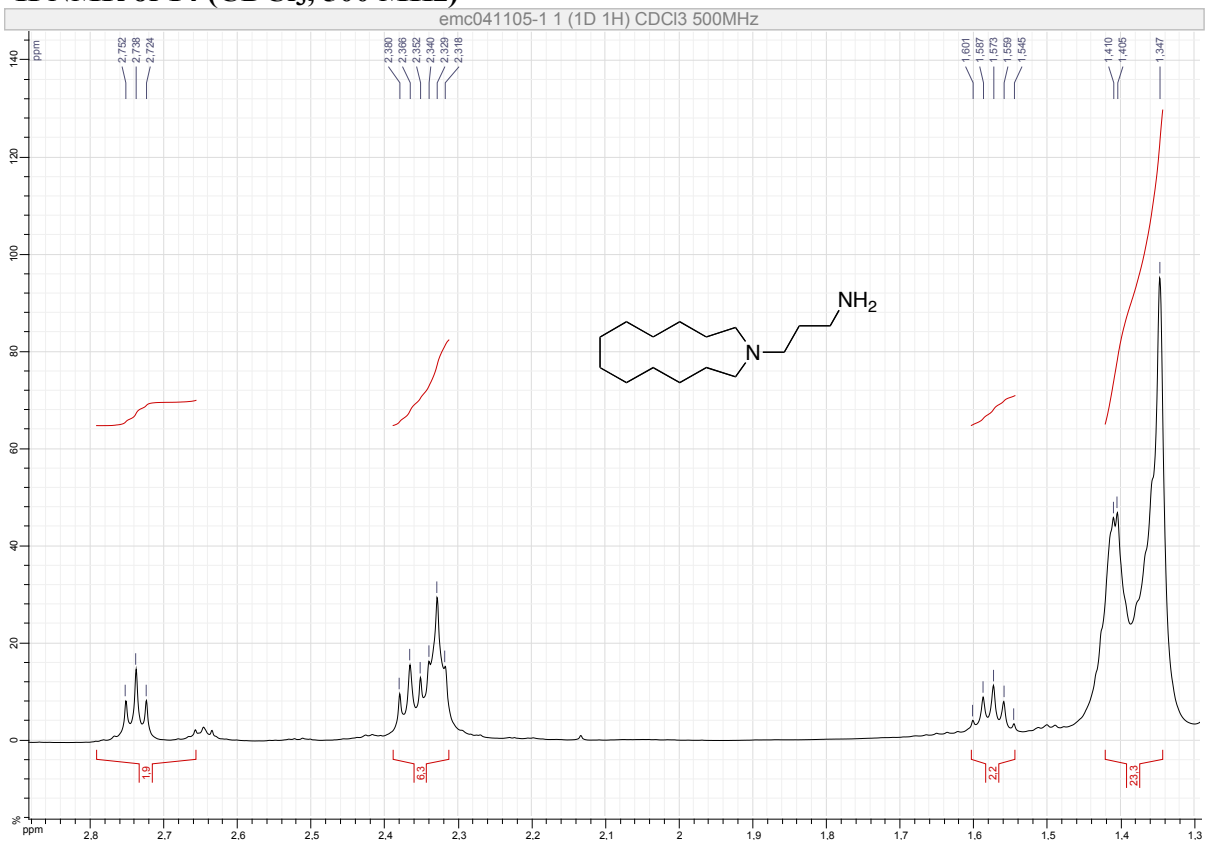
^{1}H NMR of 3-(azacyclotridecan-1-yl)propanenitrile ($CDCl_3$, 300 MHz)



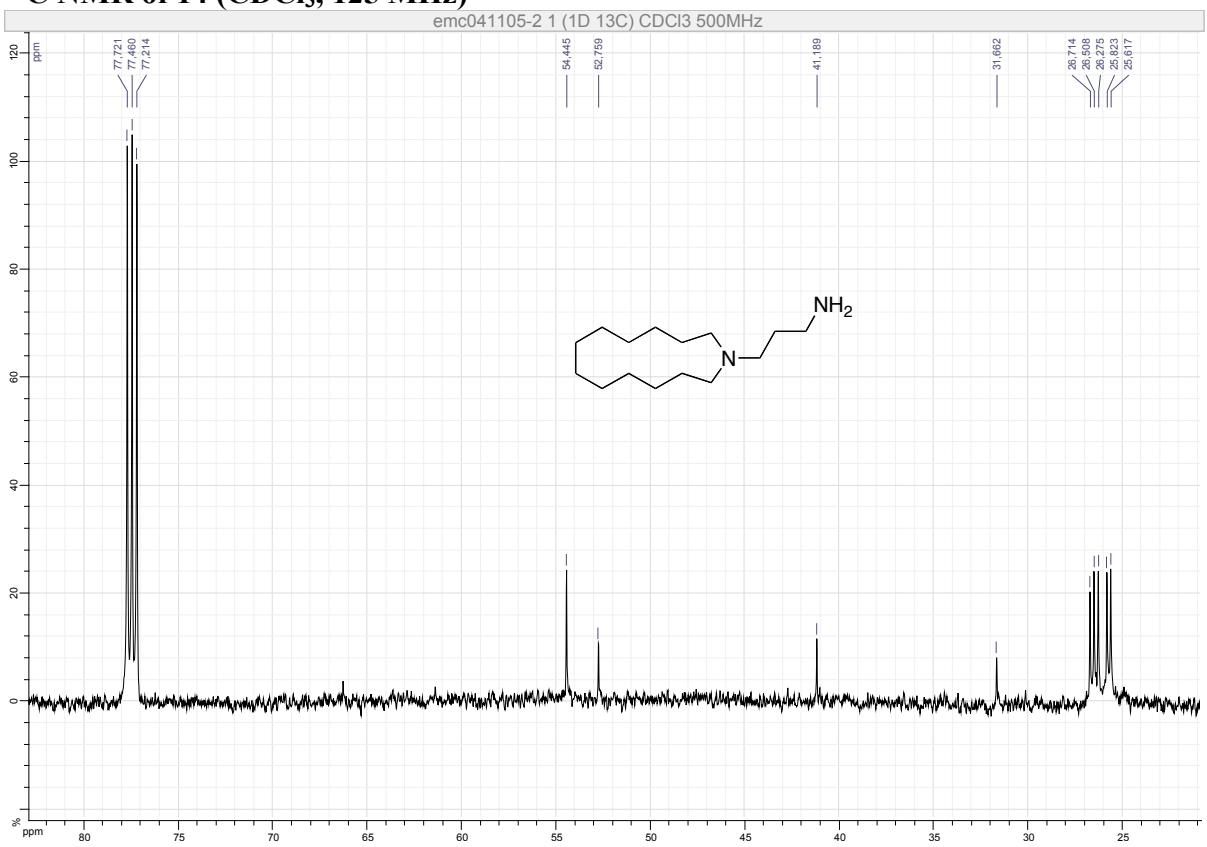
^{13} NMR of 3-(azacyclotridecan-1-yl)propanenitrile ($CDCl_3$, 75 MHz)



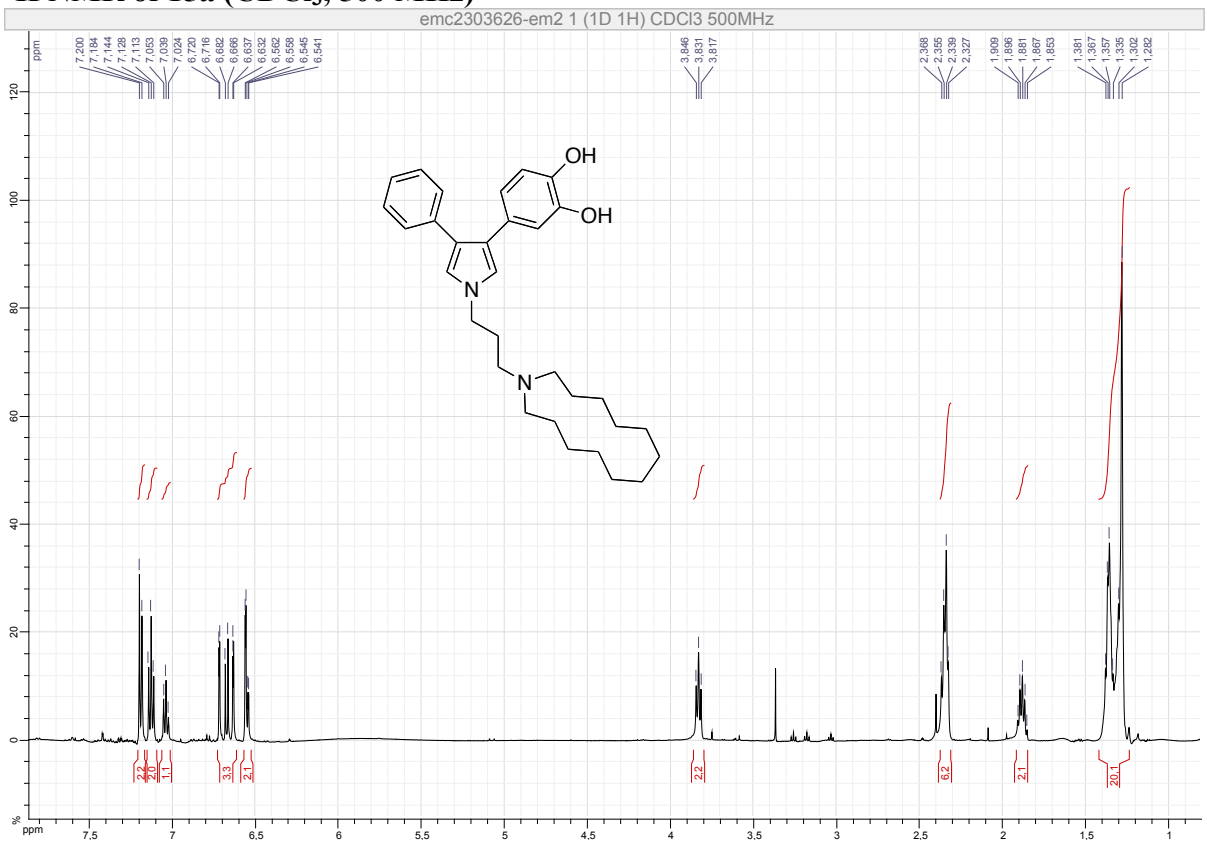
^{1}H NMR of 14 ($CDCl_3$, 500 MHz)



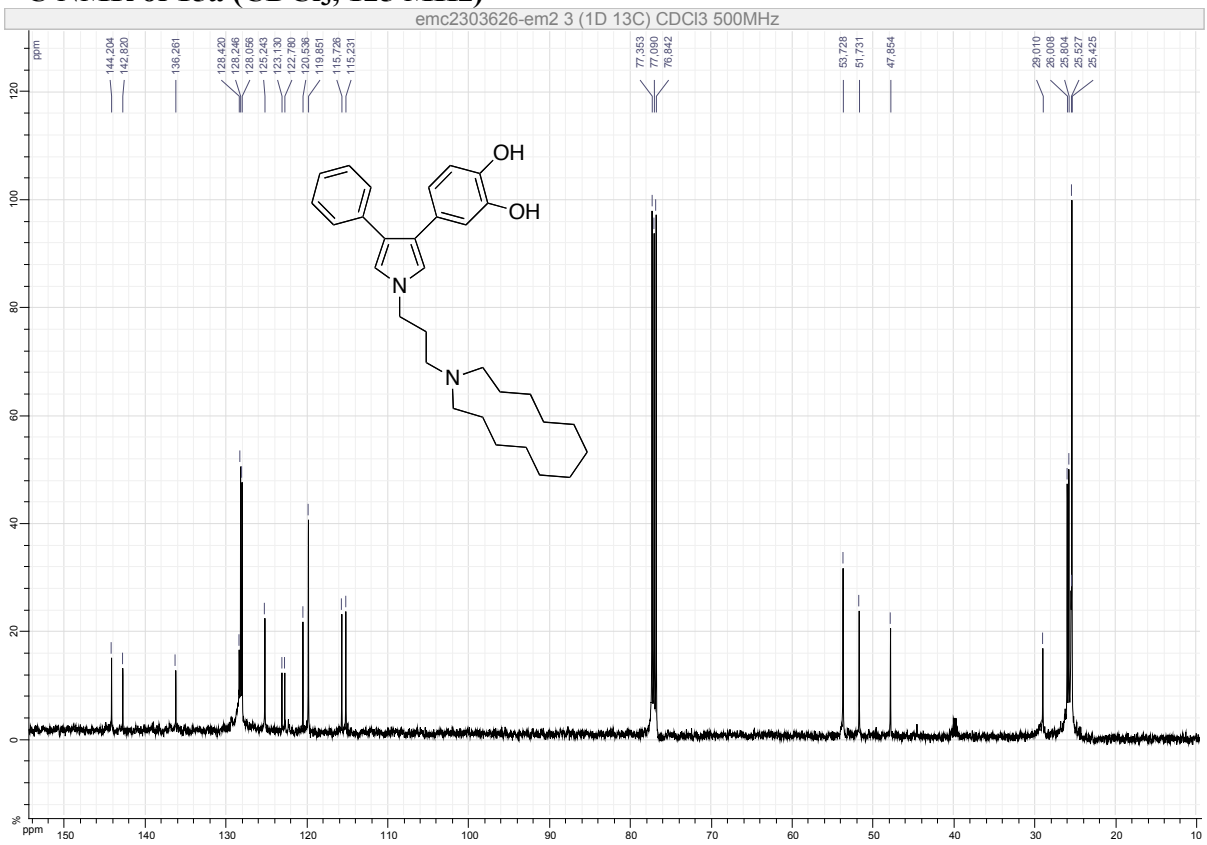
^{13}C NMR of 14 ($CDCl_3$, 125 MHz)



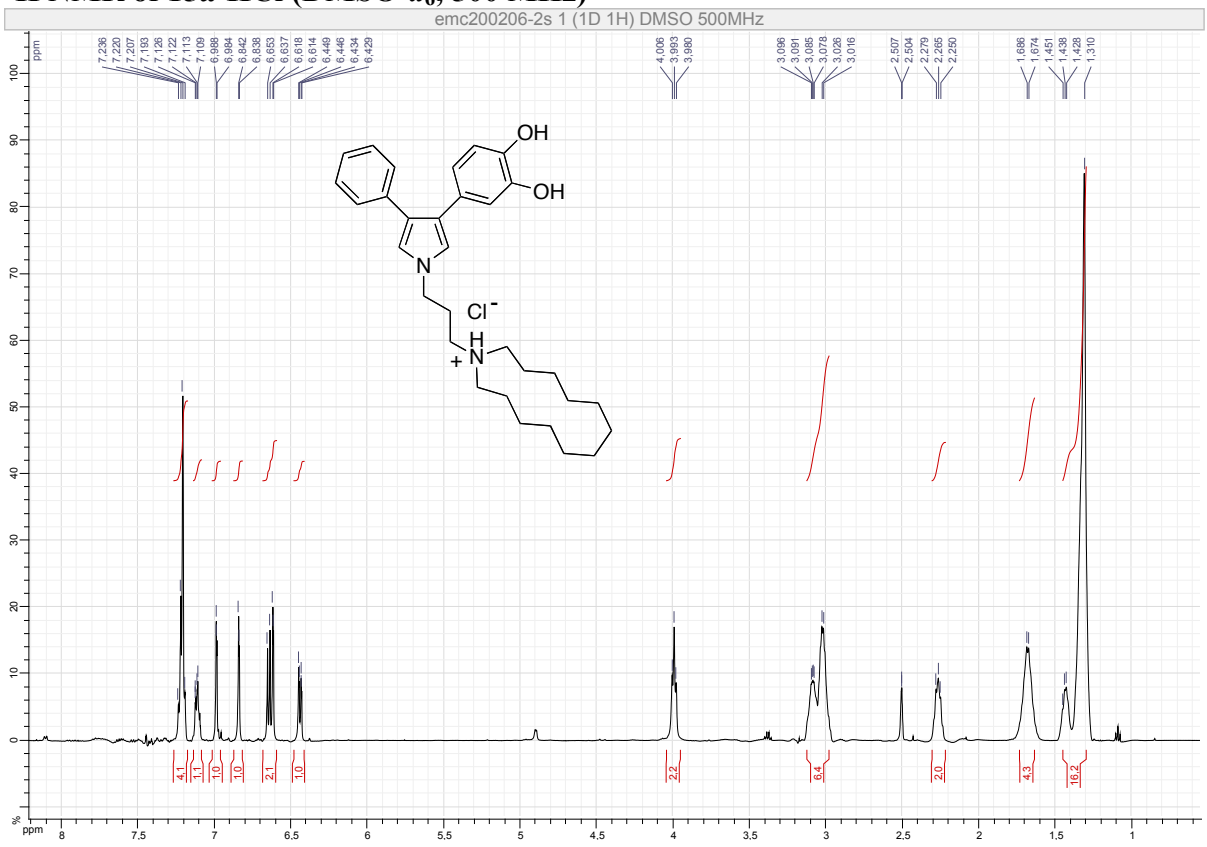
^{1}H NMR of 15a ($CDCl_3$, 500 MHz)



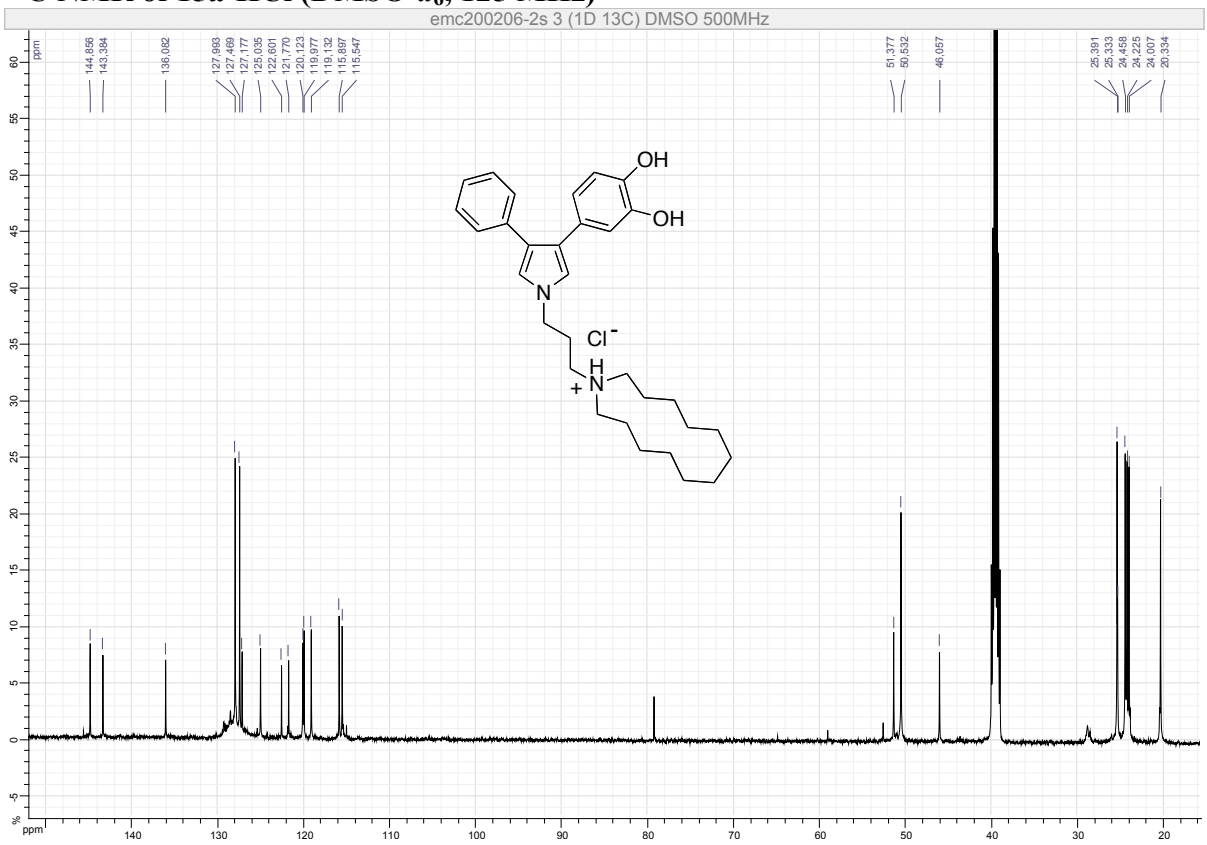
^{13}C NMR of 15a ($CDCl_3$, 125 MHz)



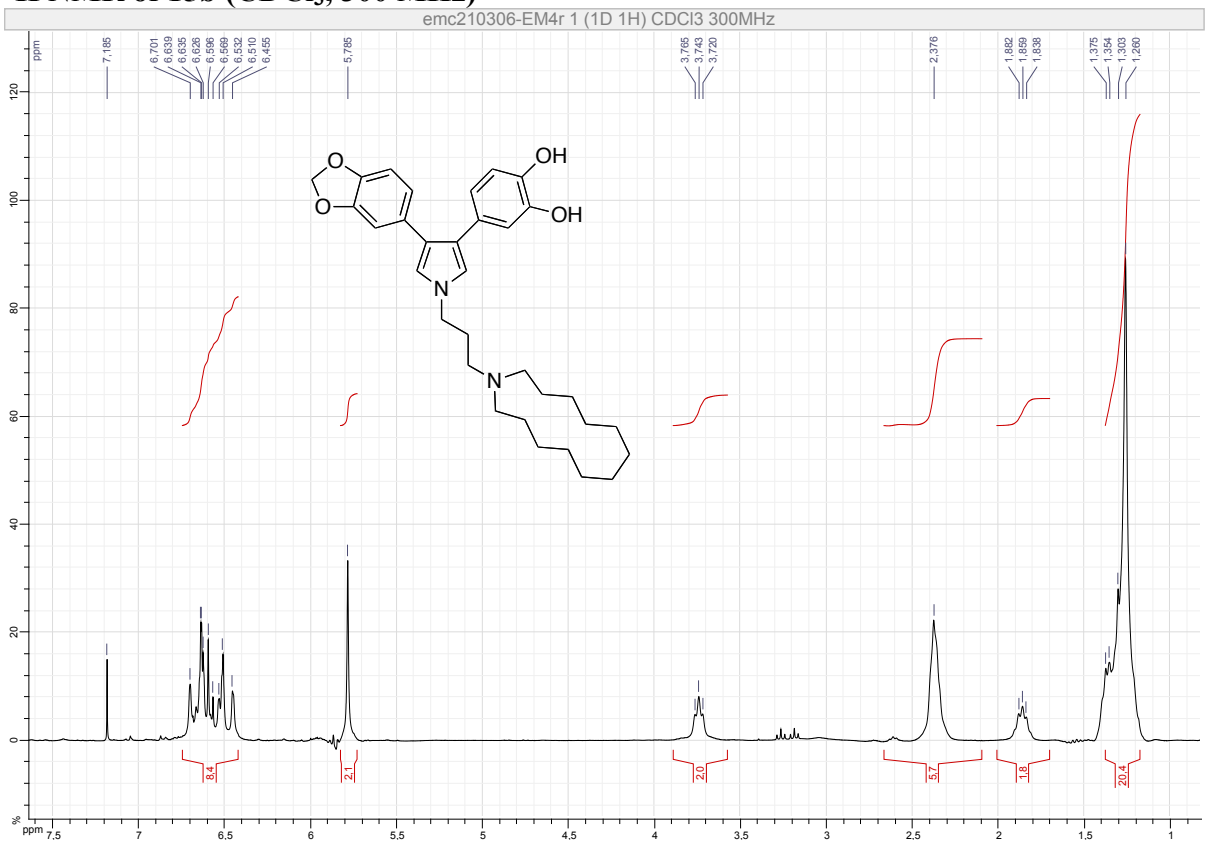
^{1}H NMR of 15a•HCl (DMSO-d_6, 500 MHz)



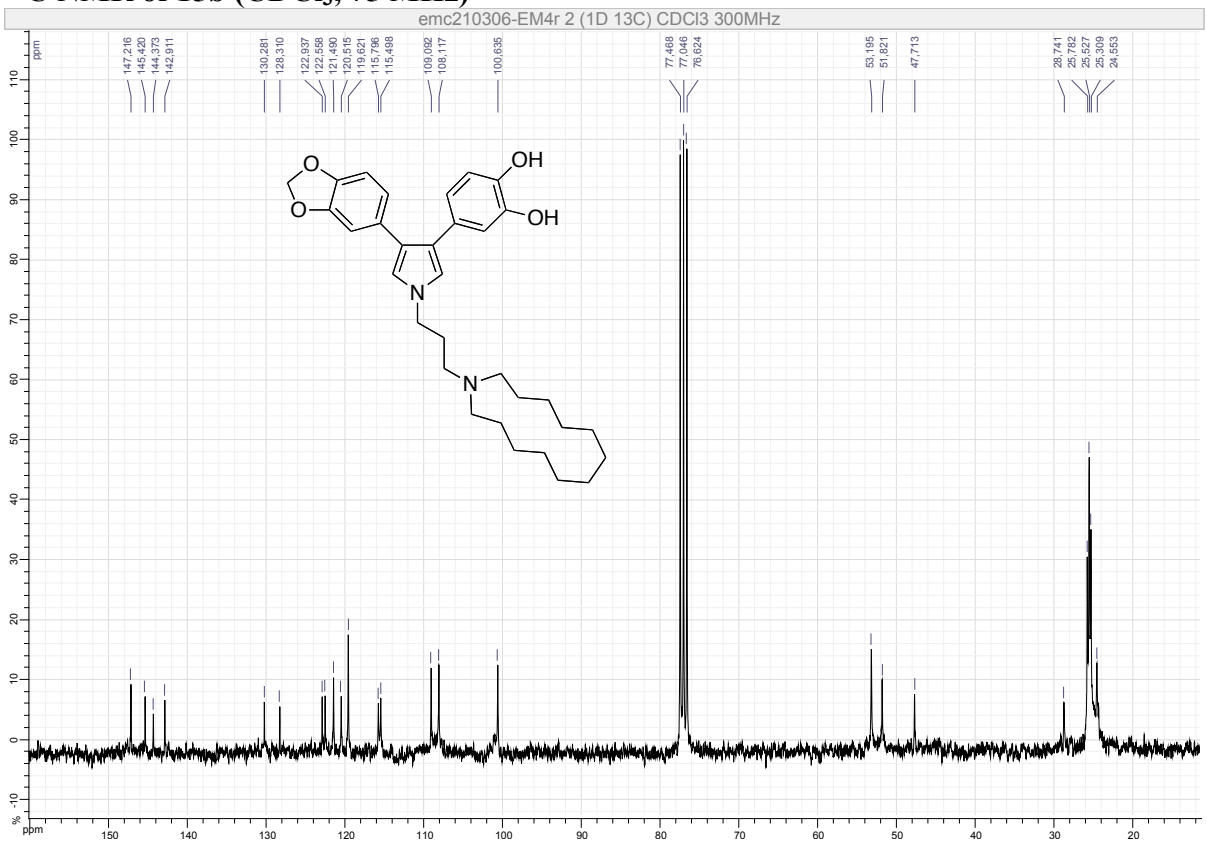
^{13}C NMR of 15a•HCl (DMSO-d_6, 125 MHz)



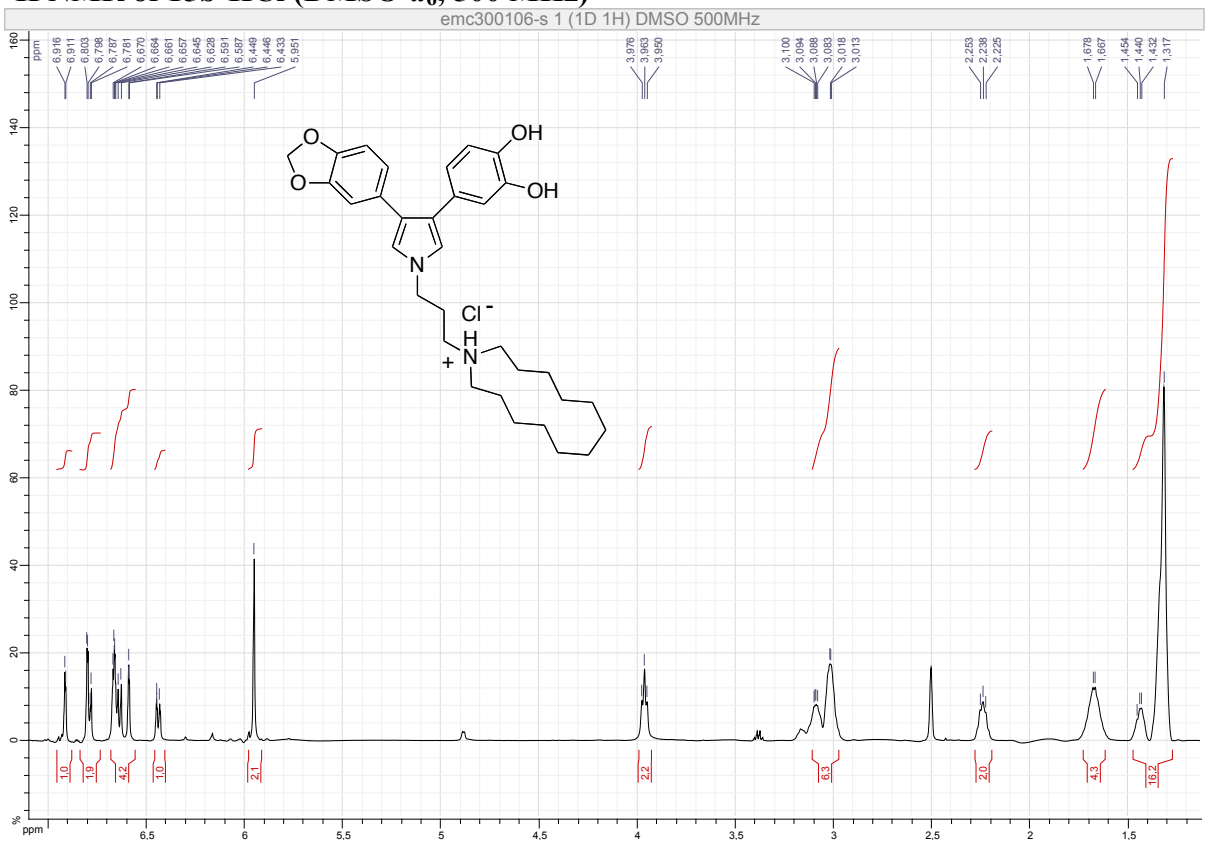
^{1}H NMR of 15b ($CDCl_3$, 300 MHz)



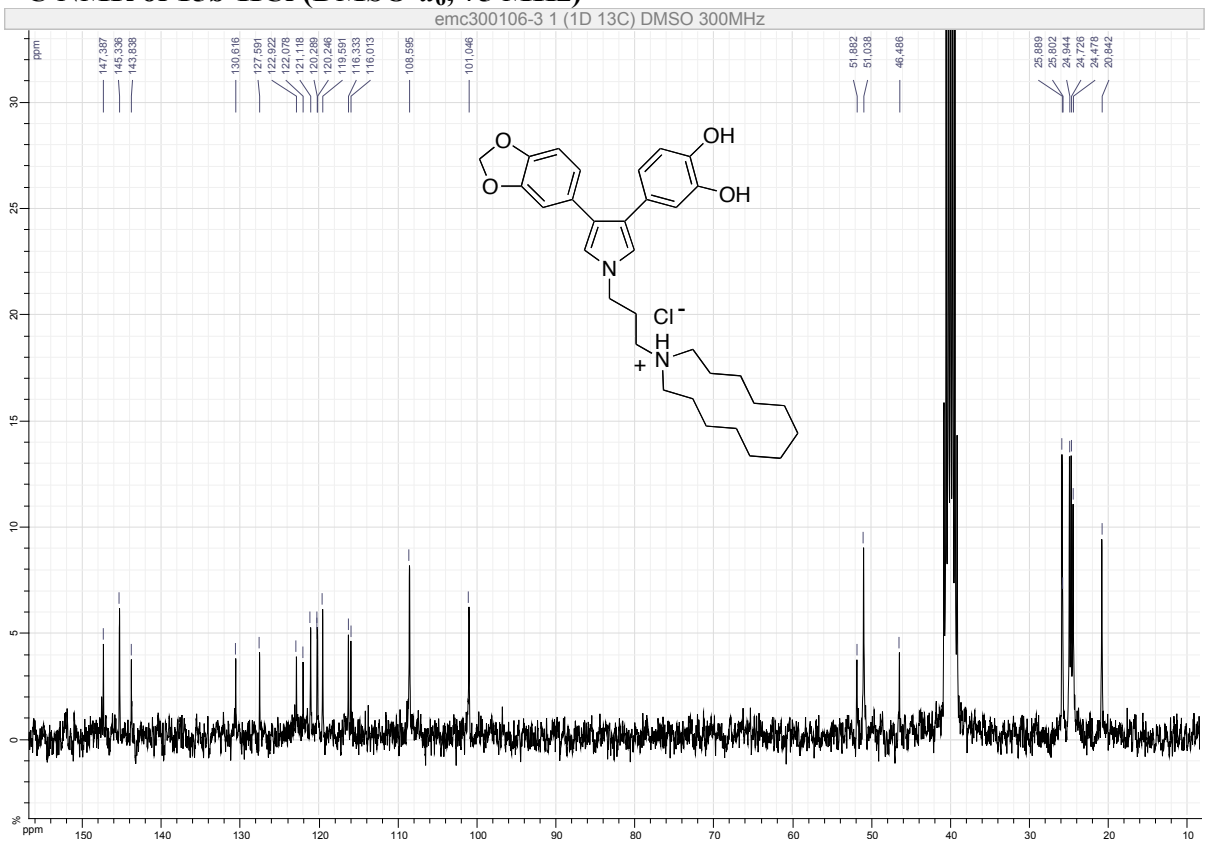
^{13}C NMR of 15b ($CDCl_3$, 75 MHz)



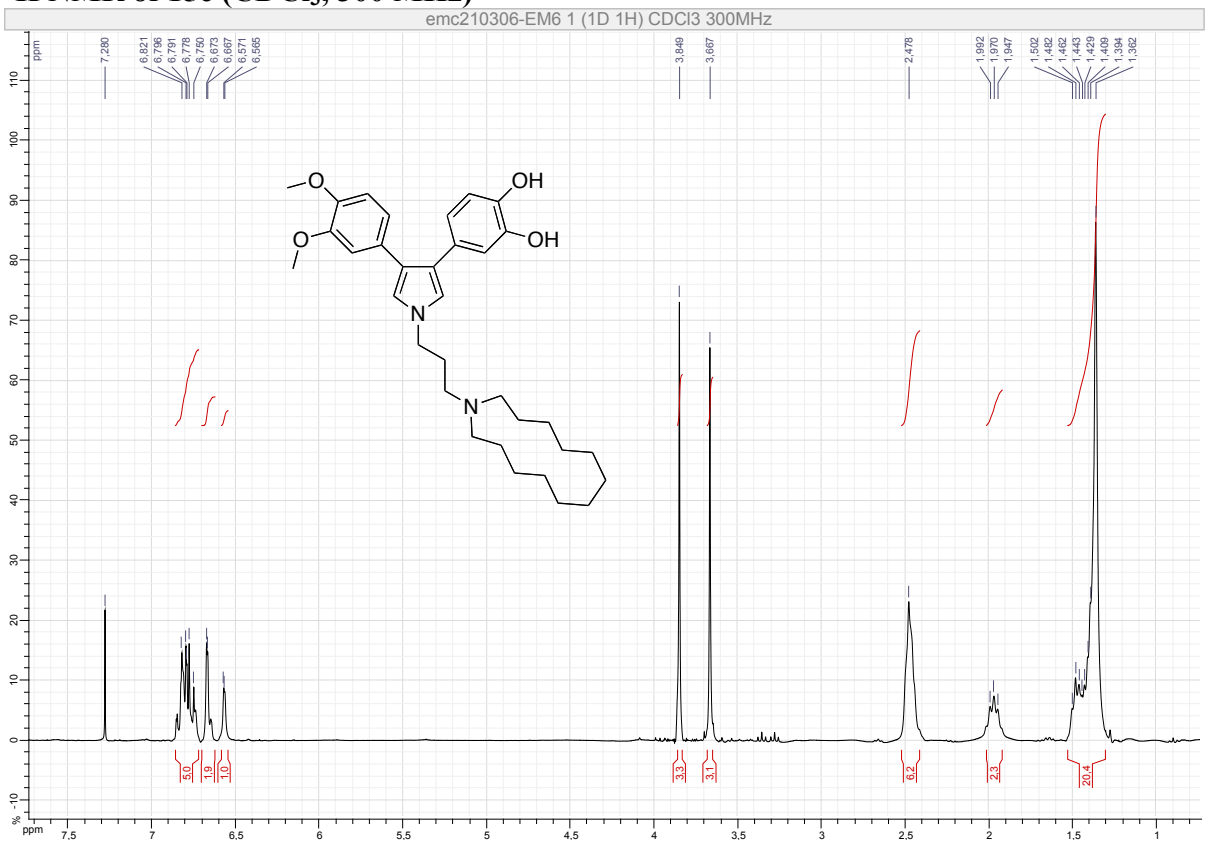
^{1}H NMR of 15b•HCl (DMSO-d_6, 500 MHz)



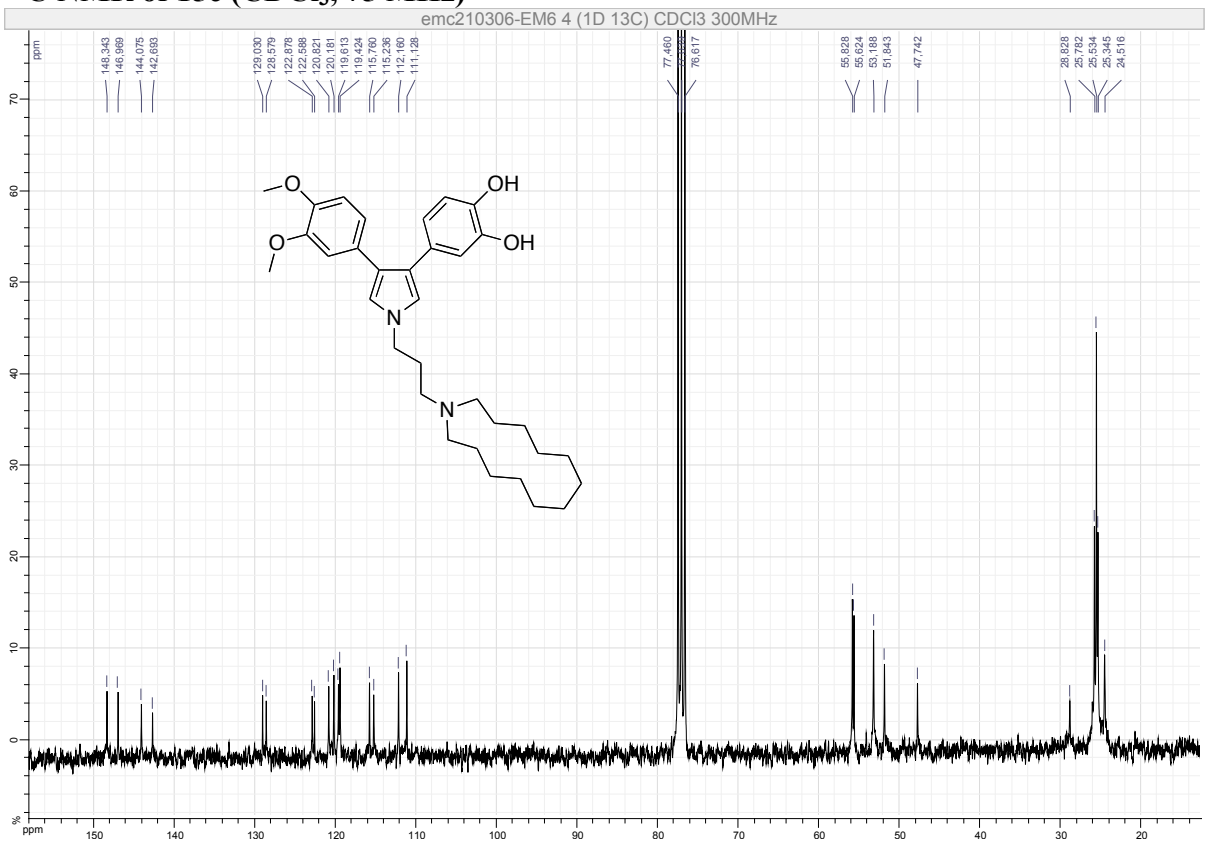
^{13}C NMR of 15b•HCl (DMSO-d_6, 75 MHz)



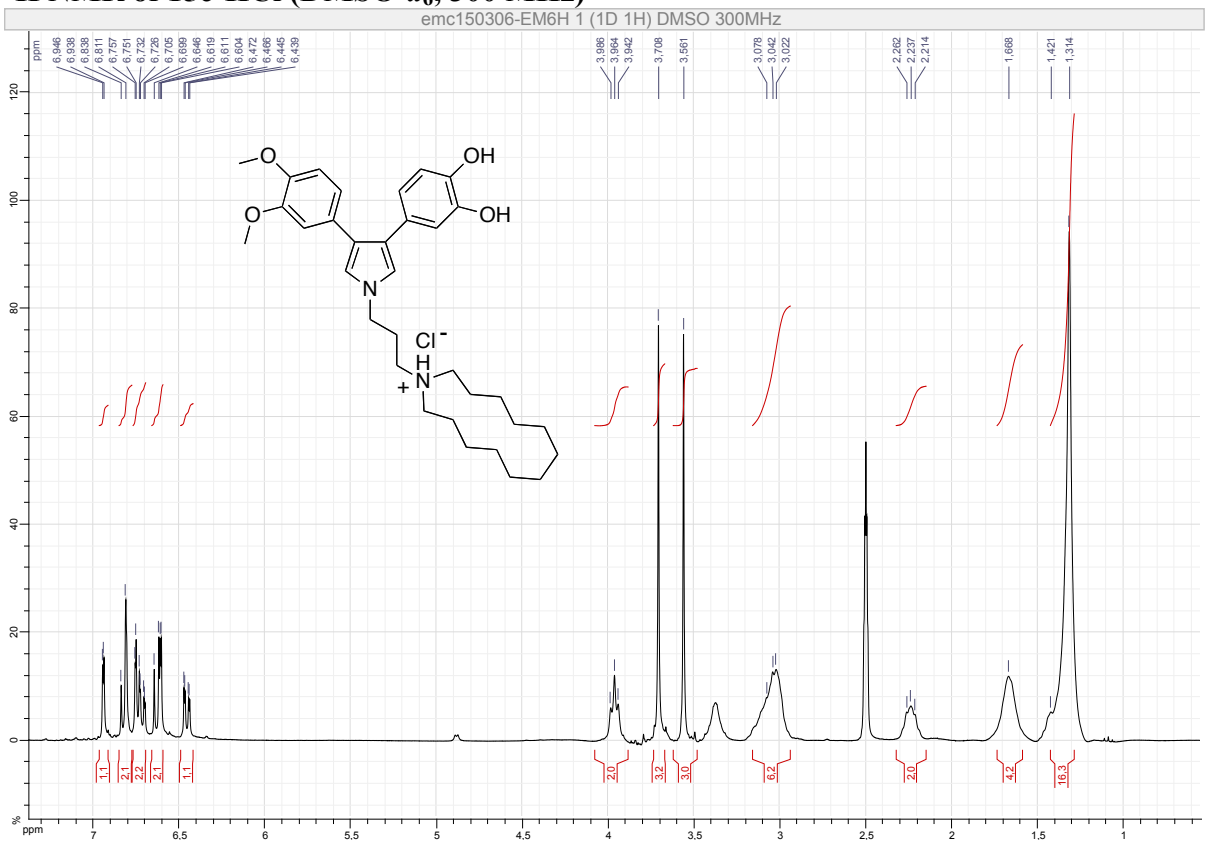
^{1}H NMR of 15c ($CDCl_3$, 300 MHz)



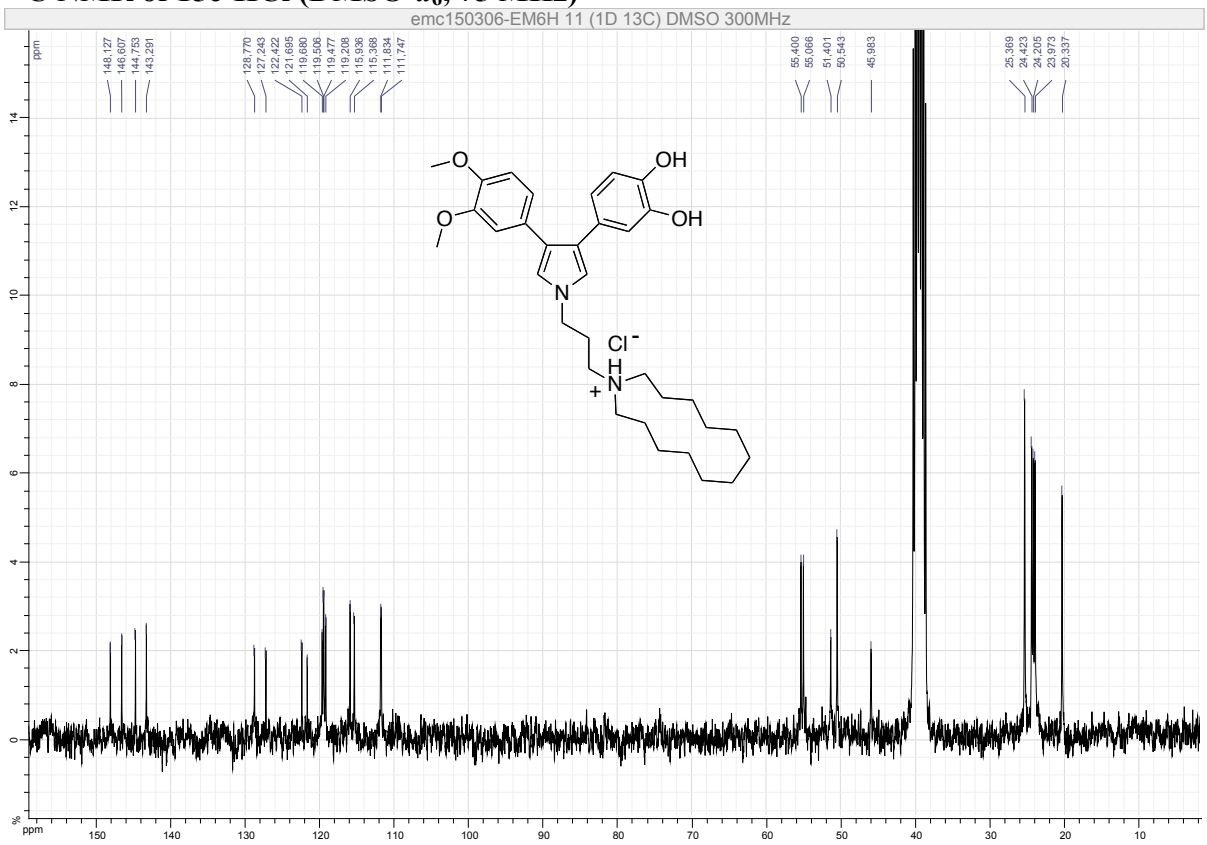
^{13}C NMR of 15c ($CDCl_3$, 75 MHz)



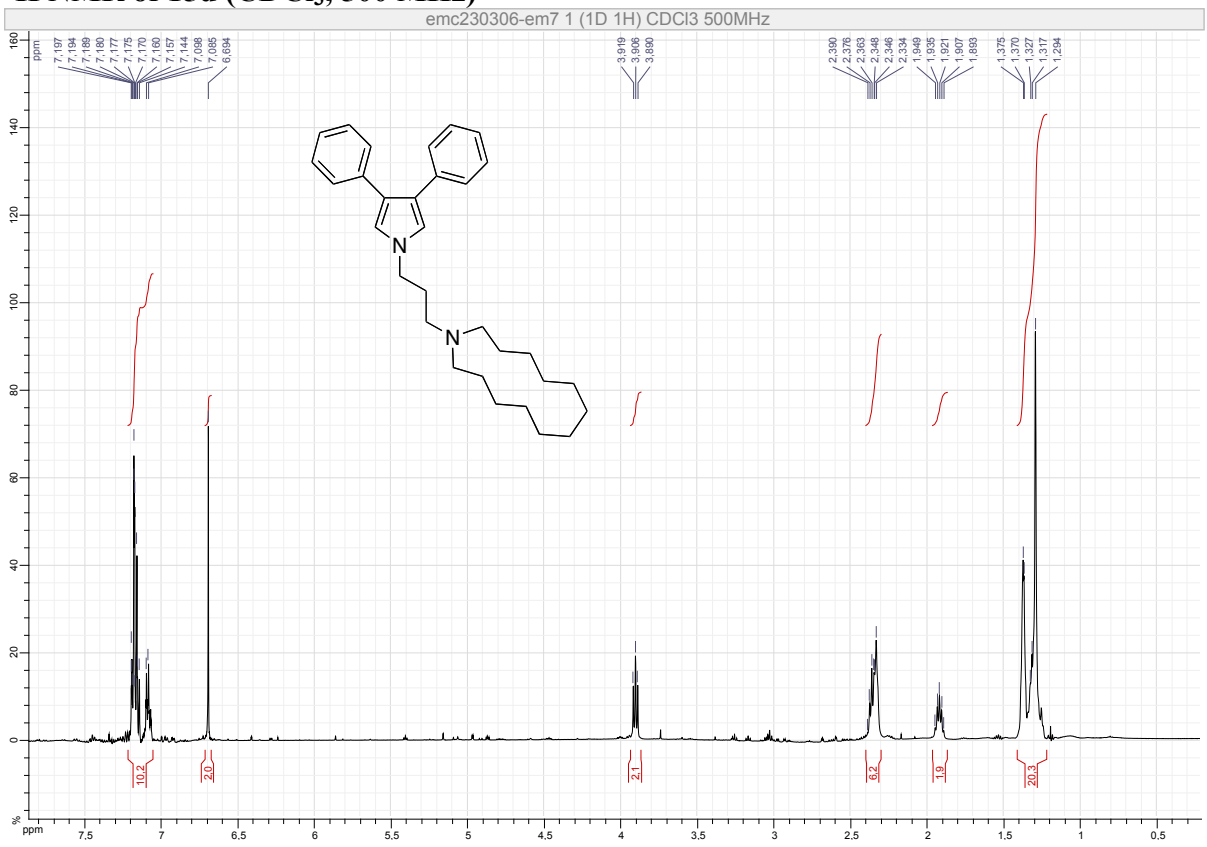
^{1}H NMR of 15c•HCl (DMSO-d_6, 300 MHz)



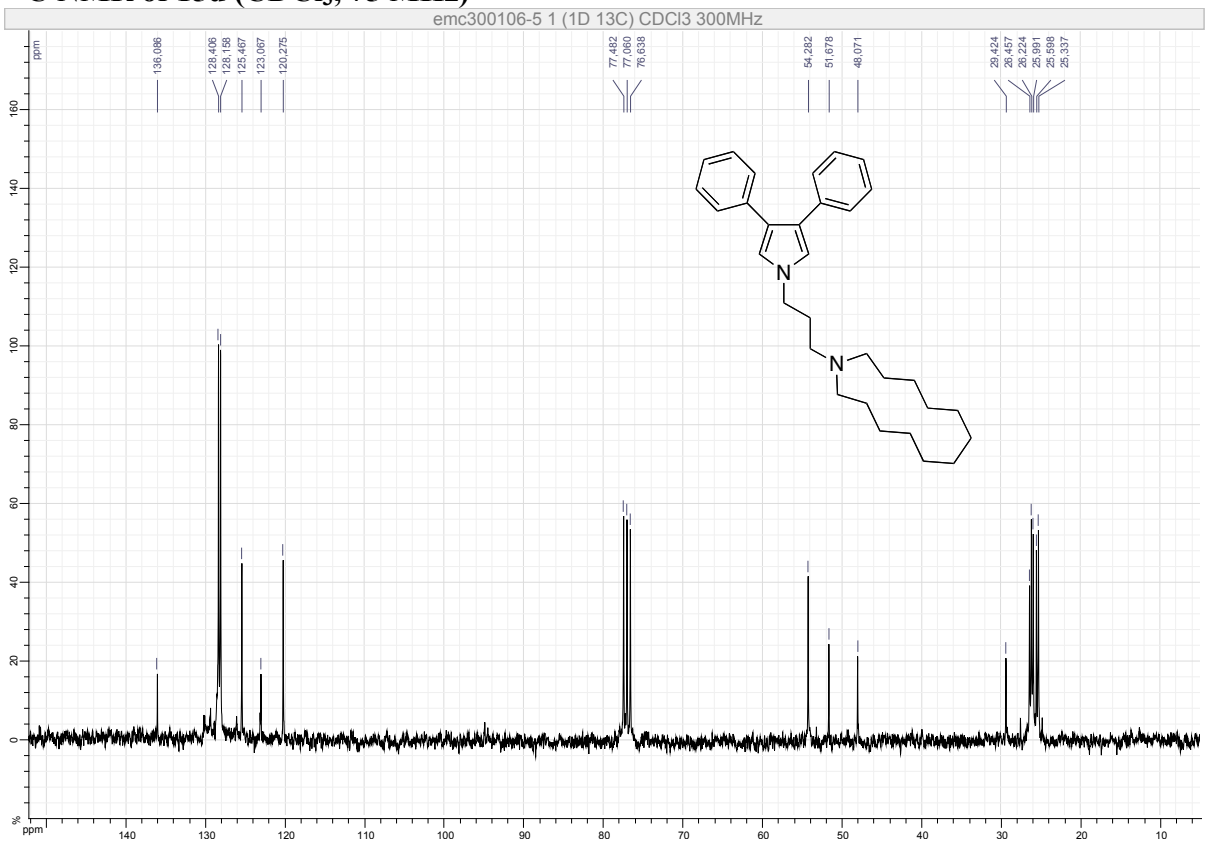
^{13}C NMR of 15c•HCl (DMSO-d_6, 75 MHz)



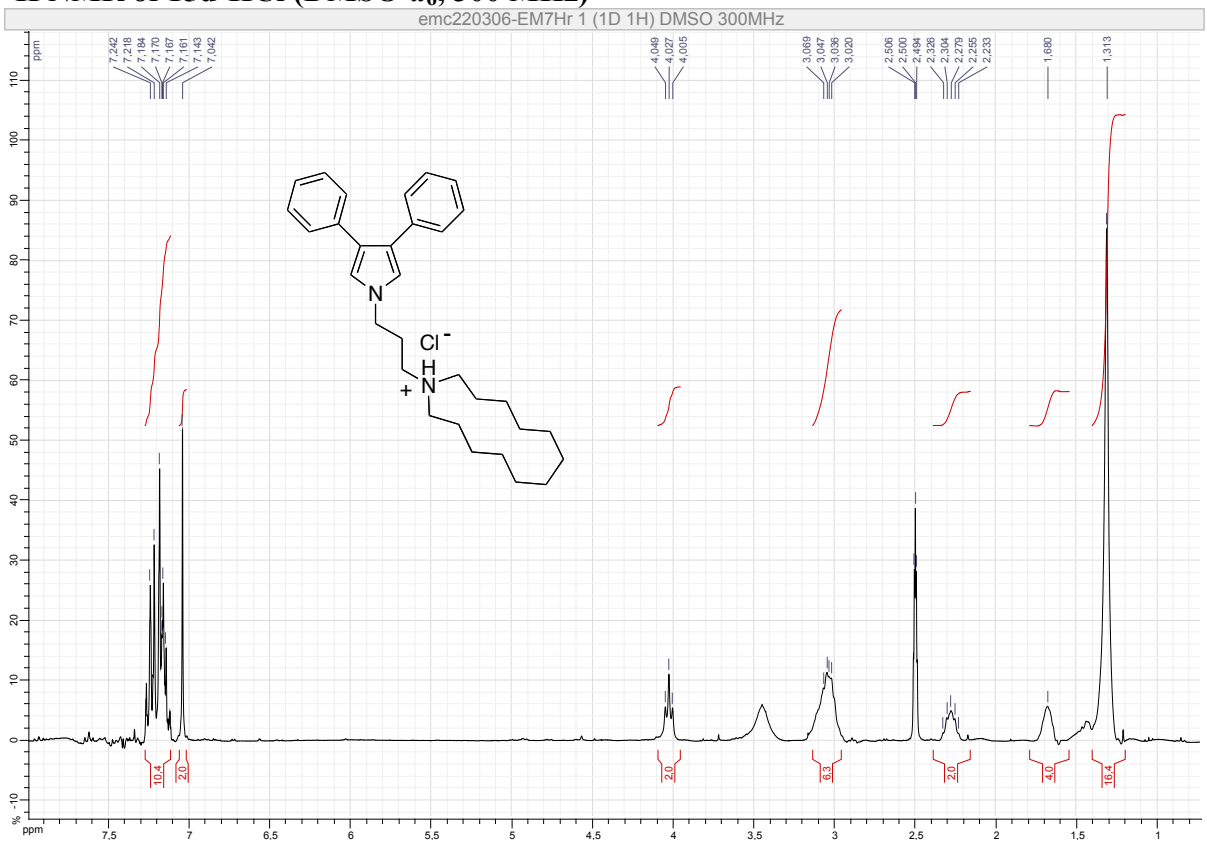
^{1}H NMR of 15d ($CDCl_3$, 500 MHz)



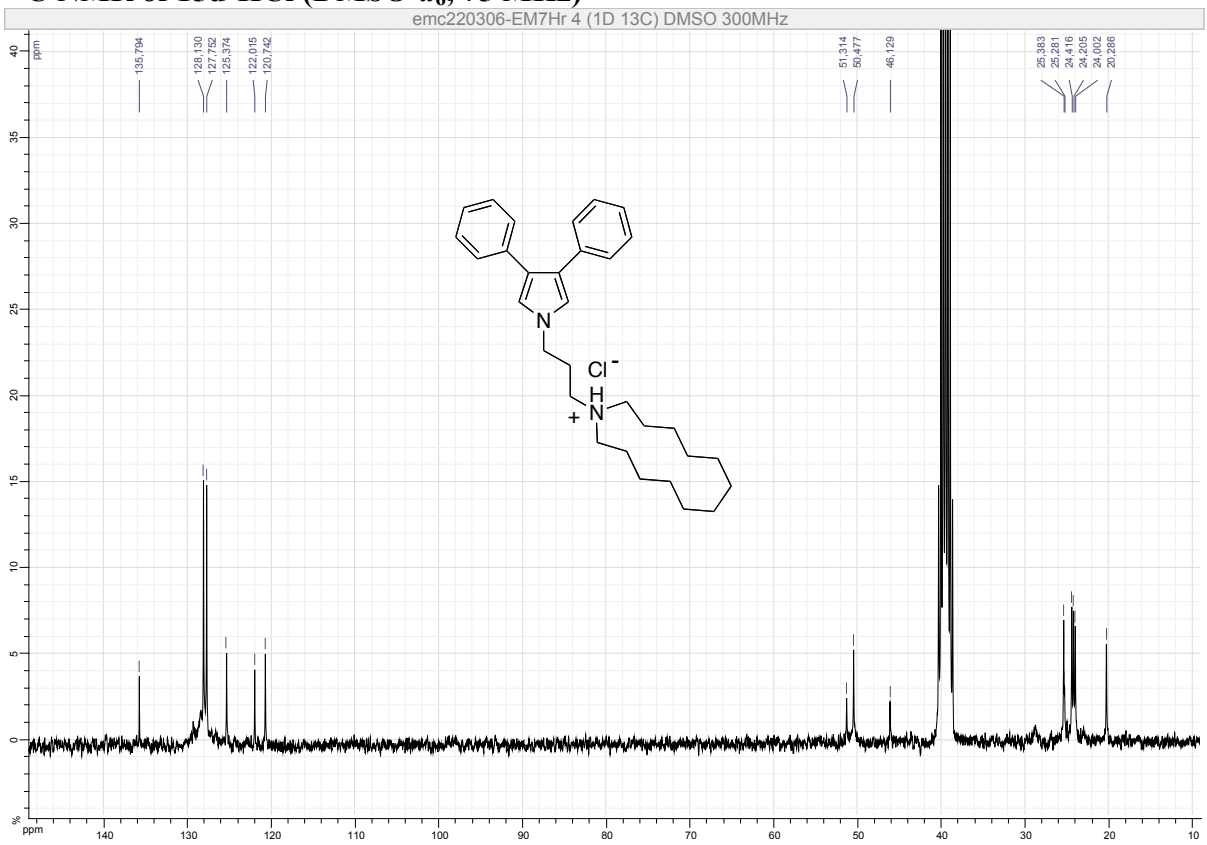
^{13}C NMR of 15d ($CDCl_3$, 75 MHz)



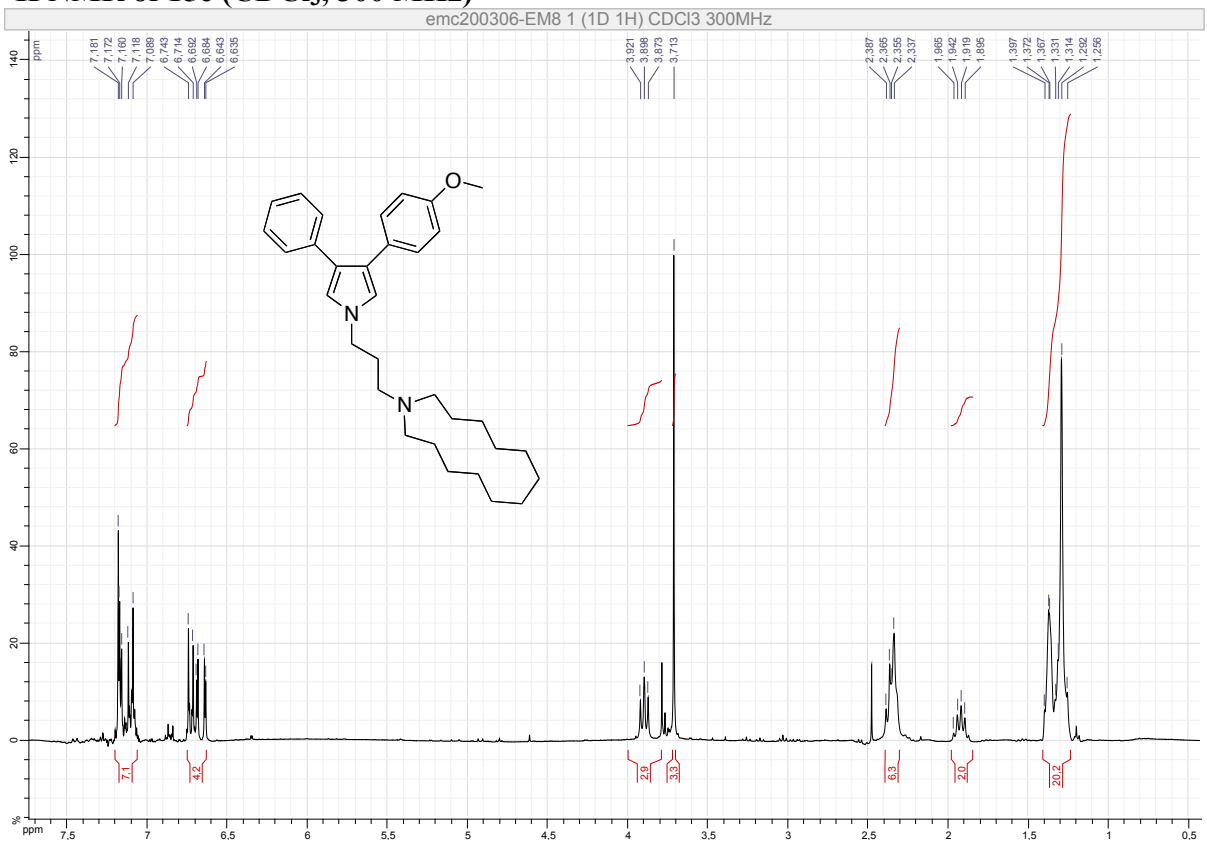
^{1}H NMR of 15d•HCl (DMSO-d_6, 300 MHz)



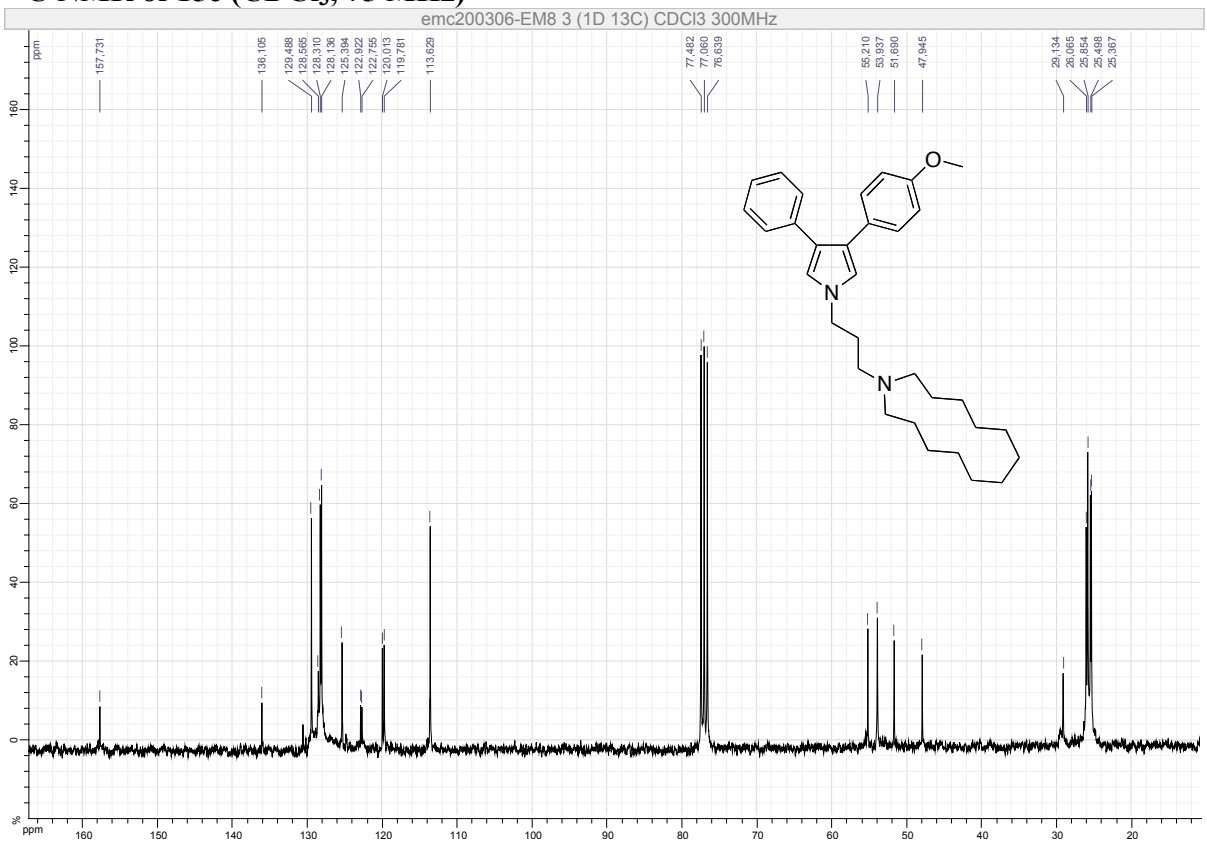
^{13}C NMR of 15d•HCl (DMSO-d_6, 75 MHz)



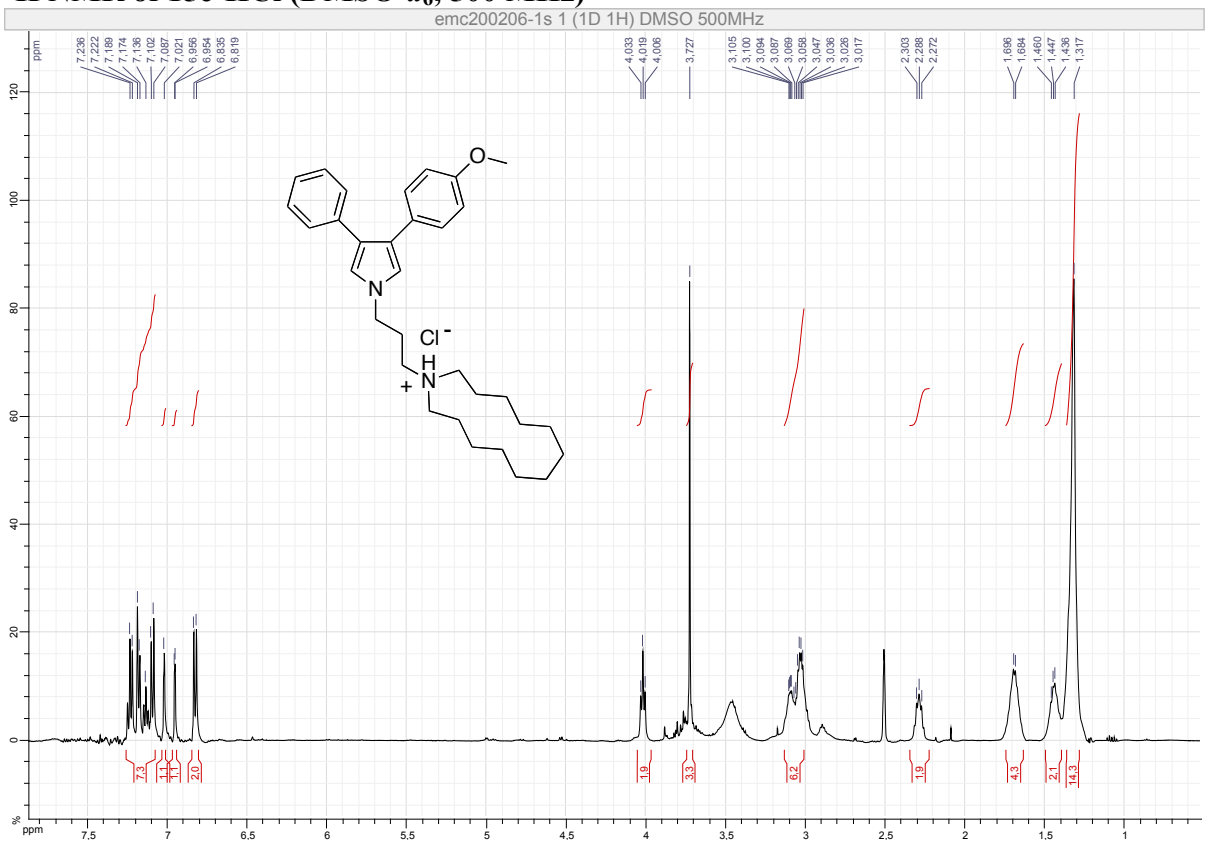
^{1}H NMR of 15e ($CDCl_3$, 300 MHz)



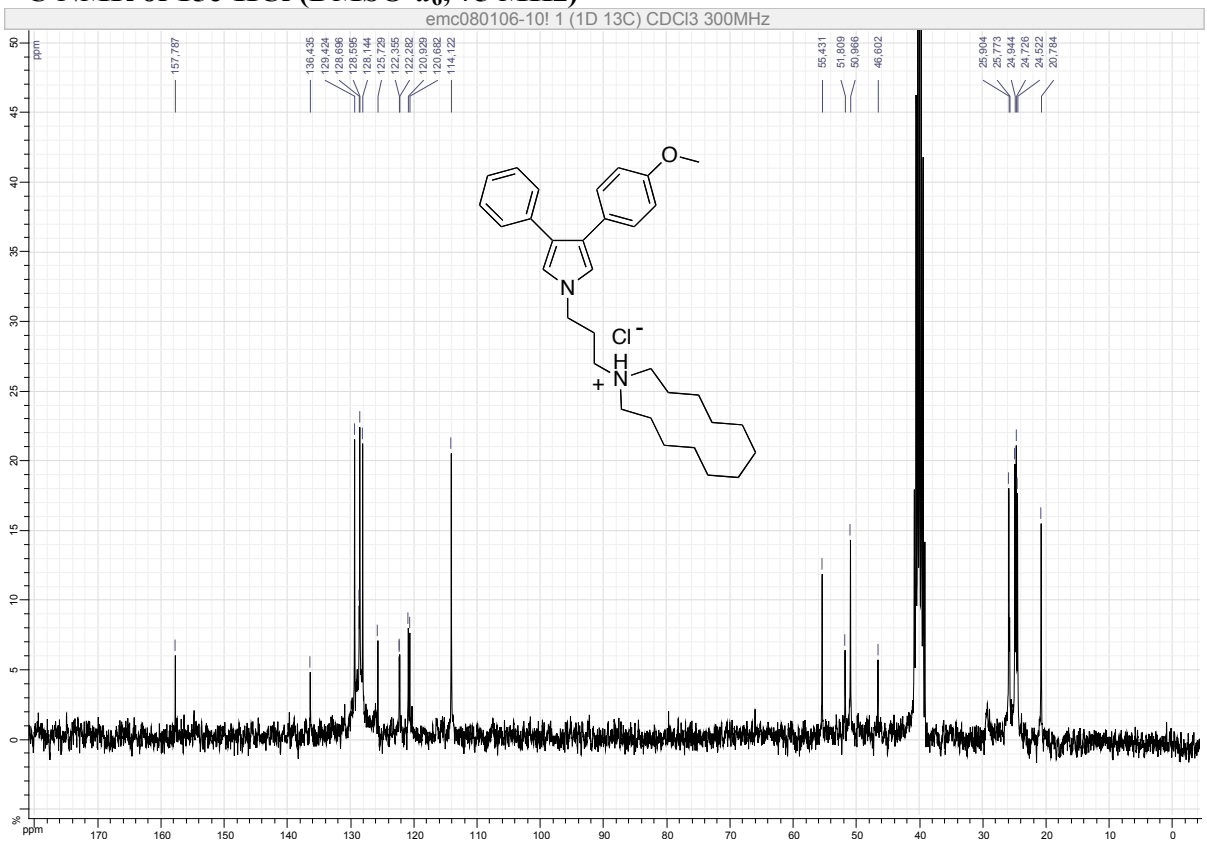
^{13}C NMR of 15e ($CDCl_3$, 75 MHz)



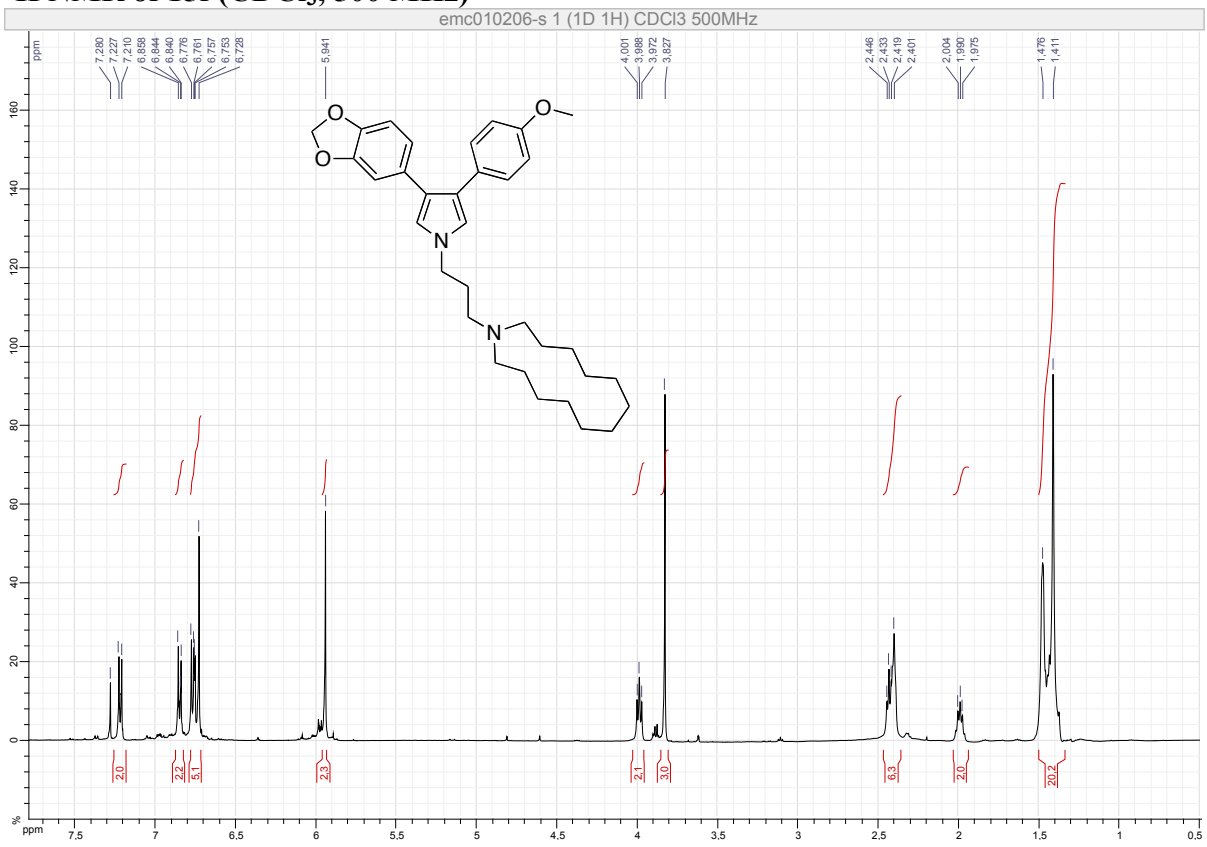
^{1}H NMR of 15e•HCl (DMSO-d_6, 500 MHz)



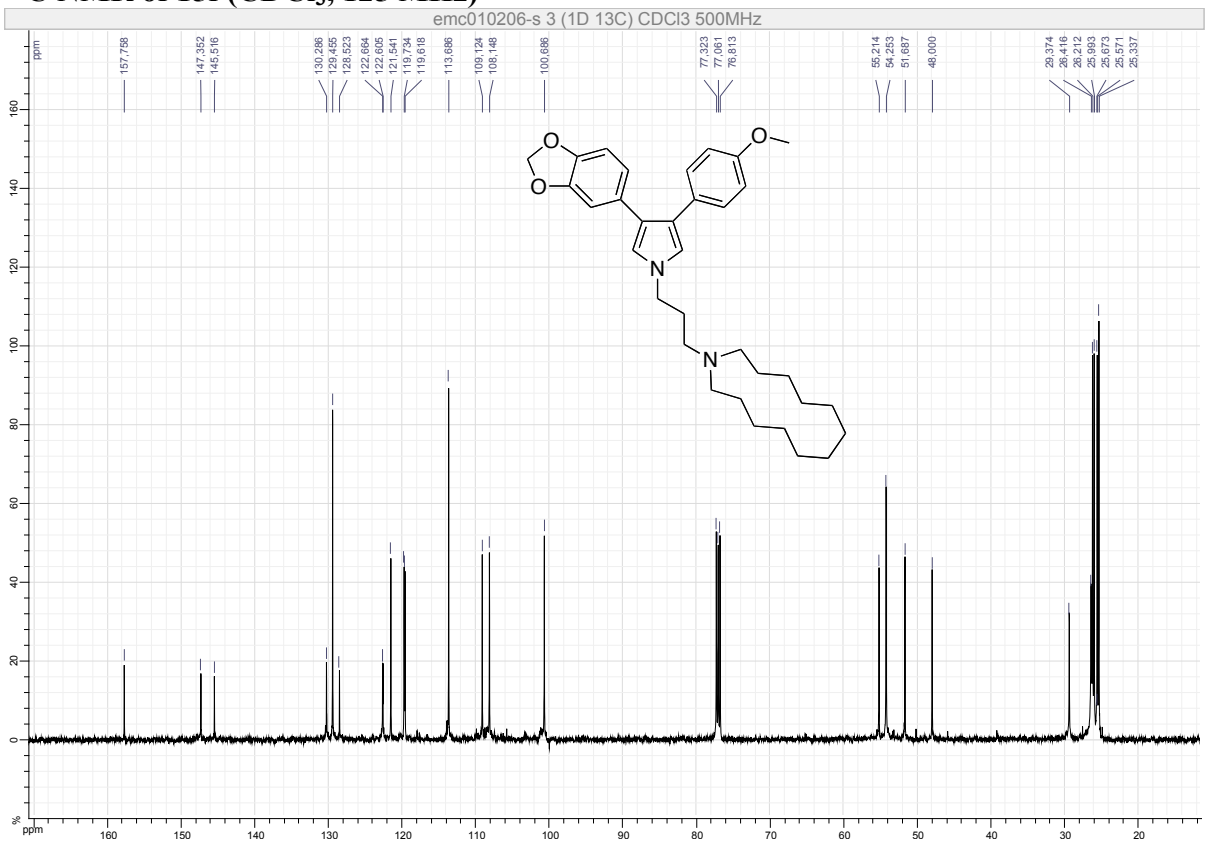
^{13}C NMR of 15e•HCl (DMSO-d_6, 75 MHz)



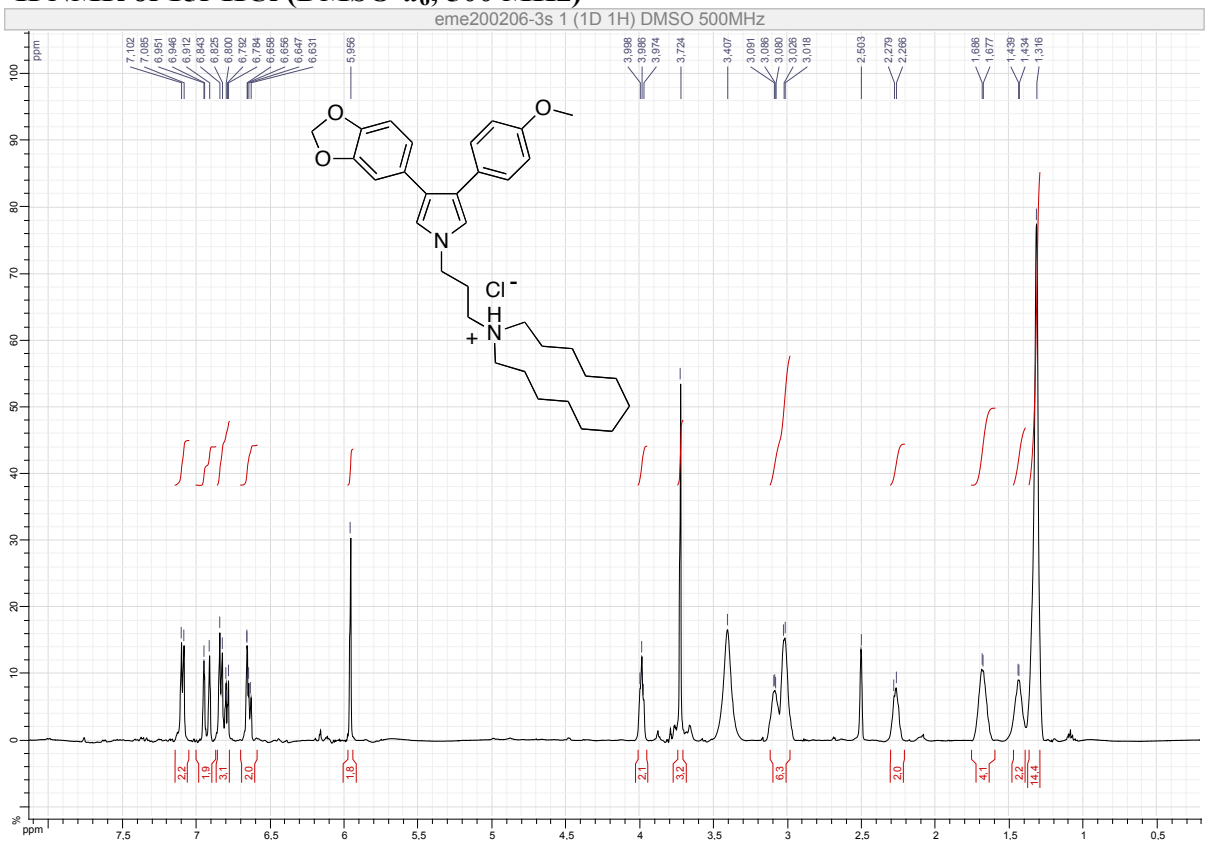
^{1}H NMR of 15f ($CDCl_3$, 500 MHz)



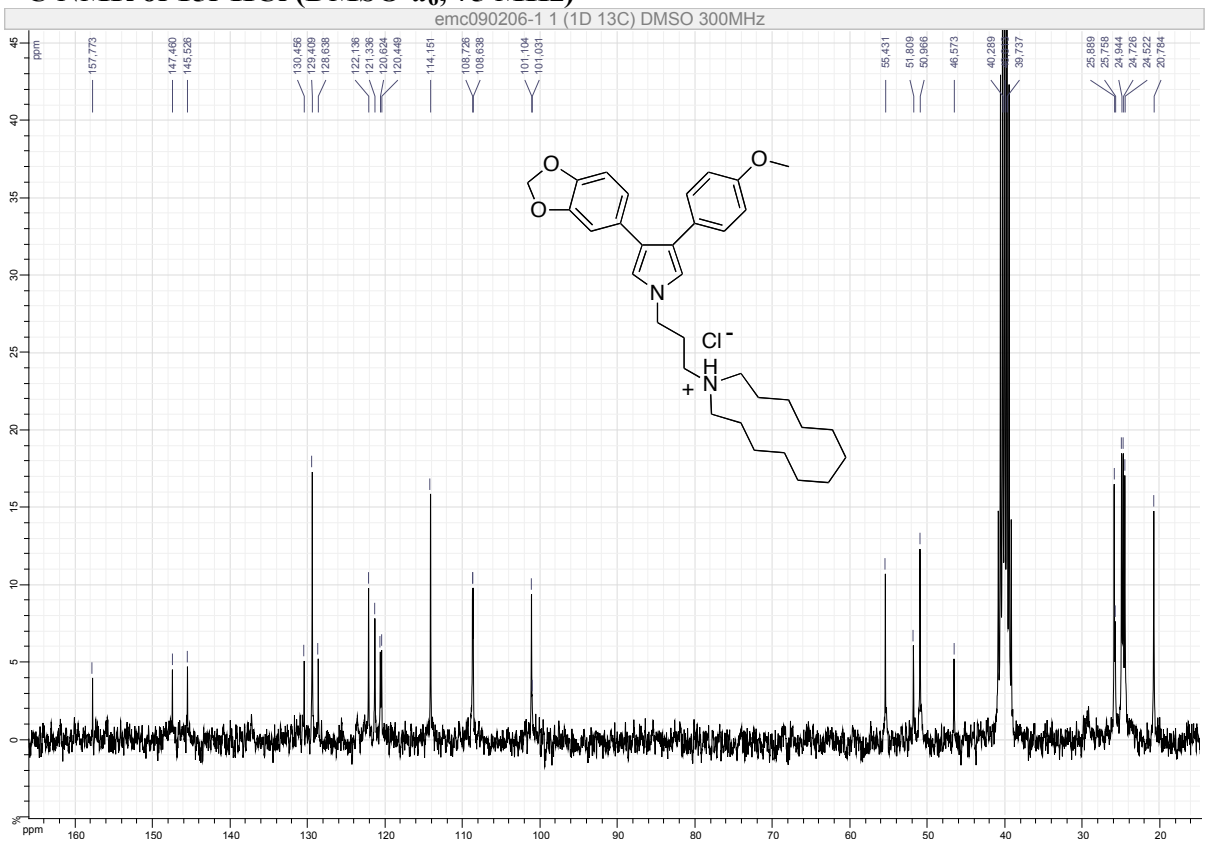
^{13}C NMR of 15f ($CDCl_3$, 125 MHz)



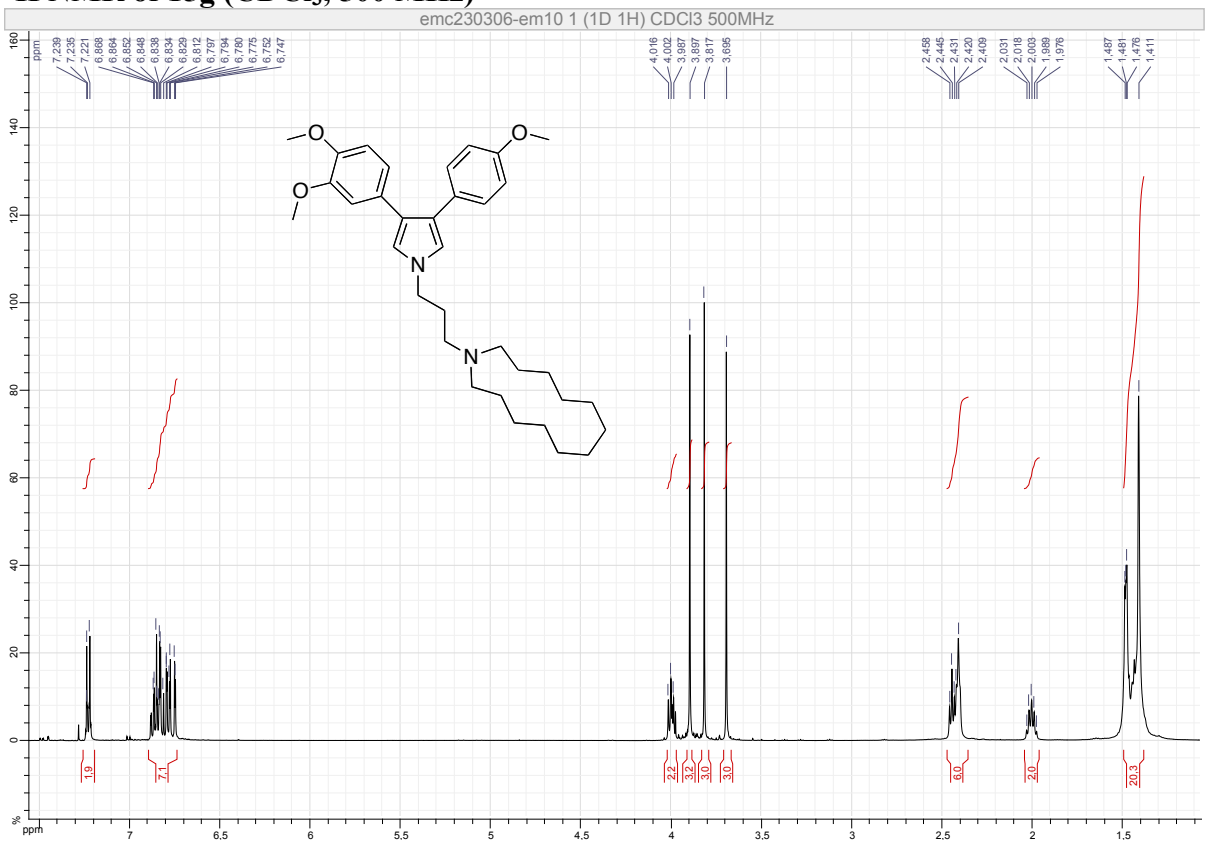
^{1}H NMR of 15f•HCl (DMSO-d_6, 500 MHz)



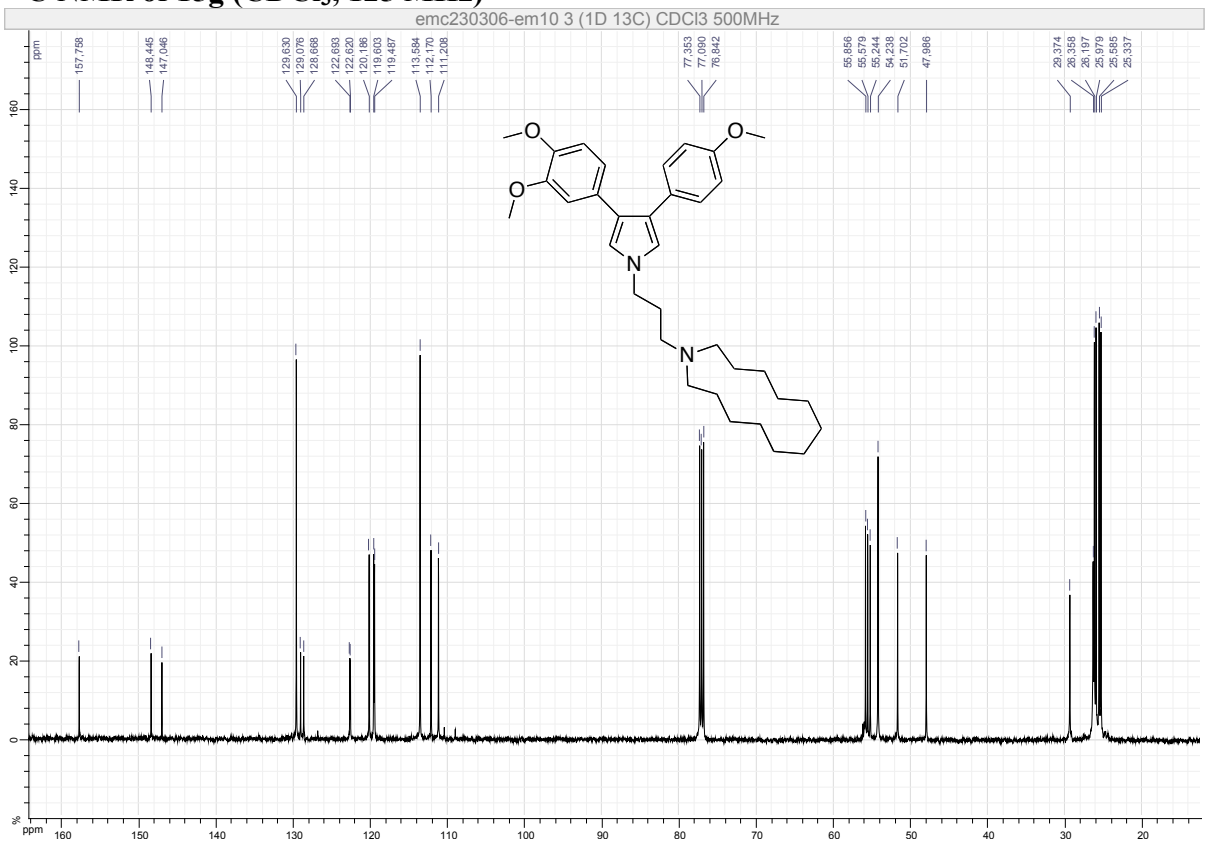
^{13}C NMR of 15f•HCl (DMSO-d_6, 75 MHz)



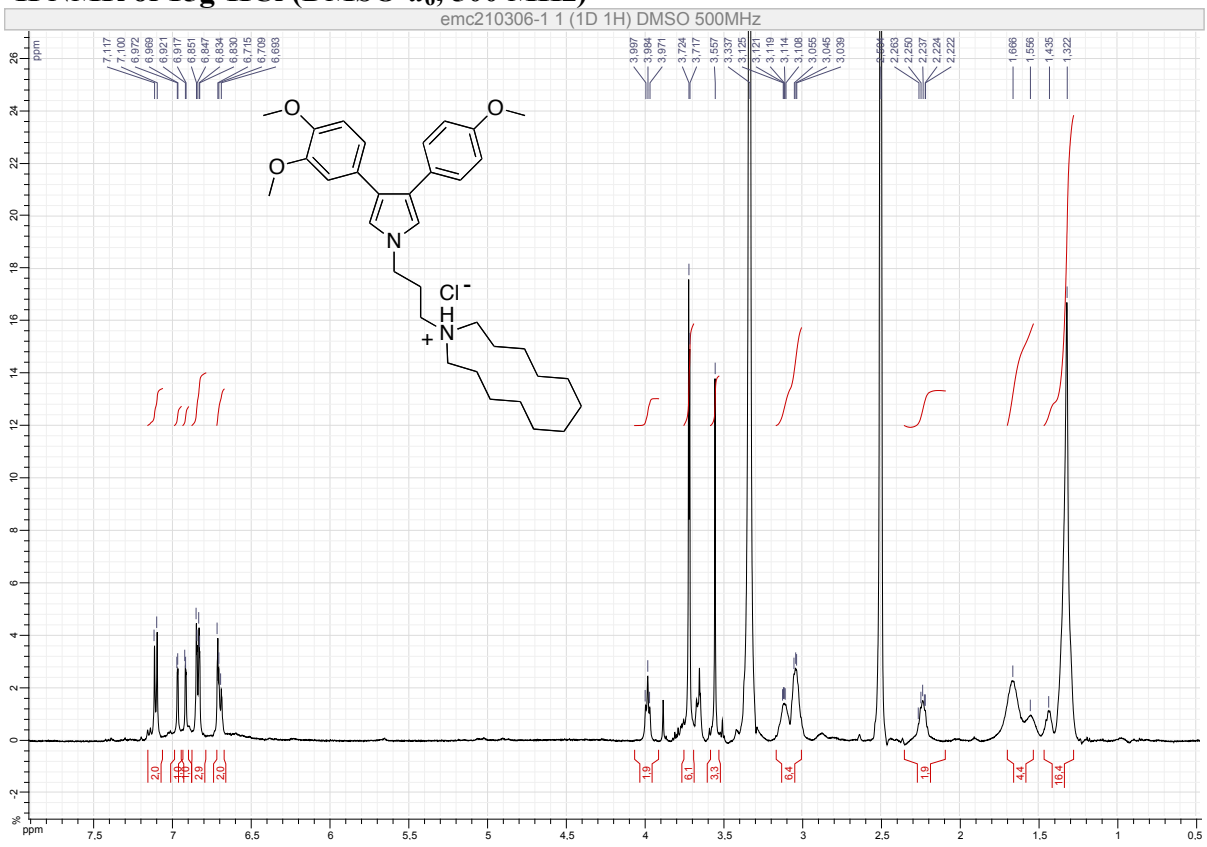
^{1}H NMR of 15g ($CDCl_3$, 500 MHz)



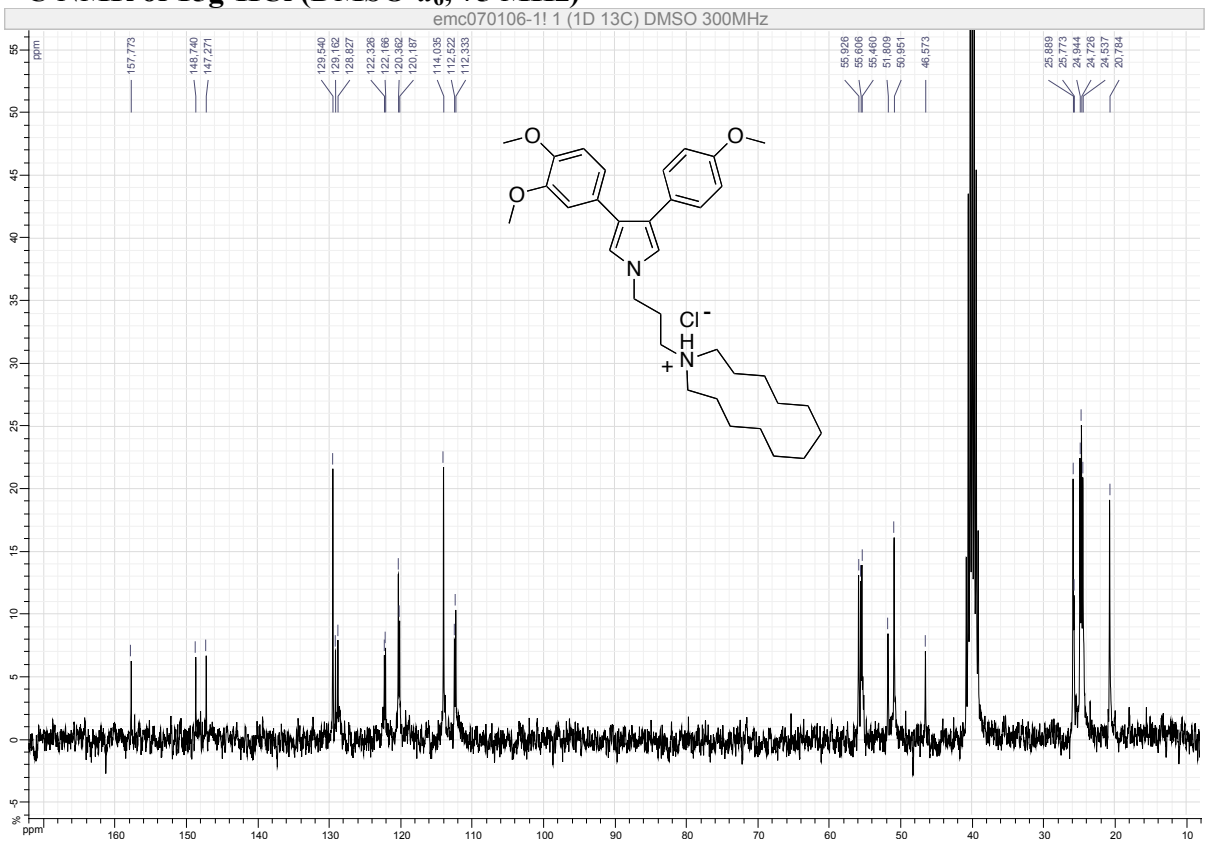
^{13}C NMR of 15g ($CDCl_3$, 125 MHz)



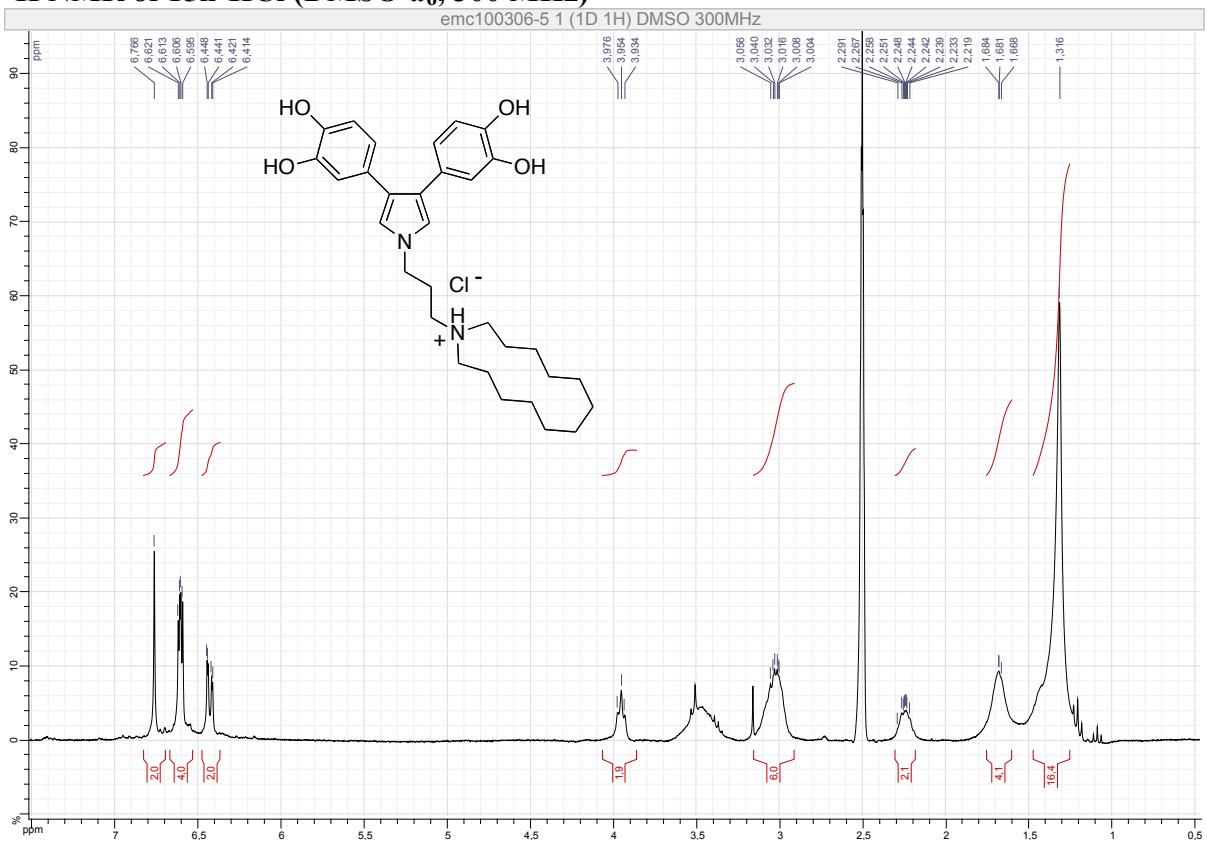
^{1}H NMR of 15g•HCl (DMSO-d_6, 500 MHz)



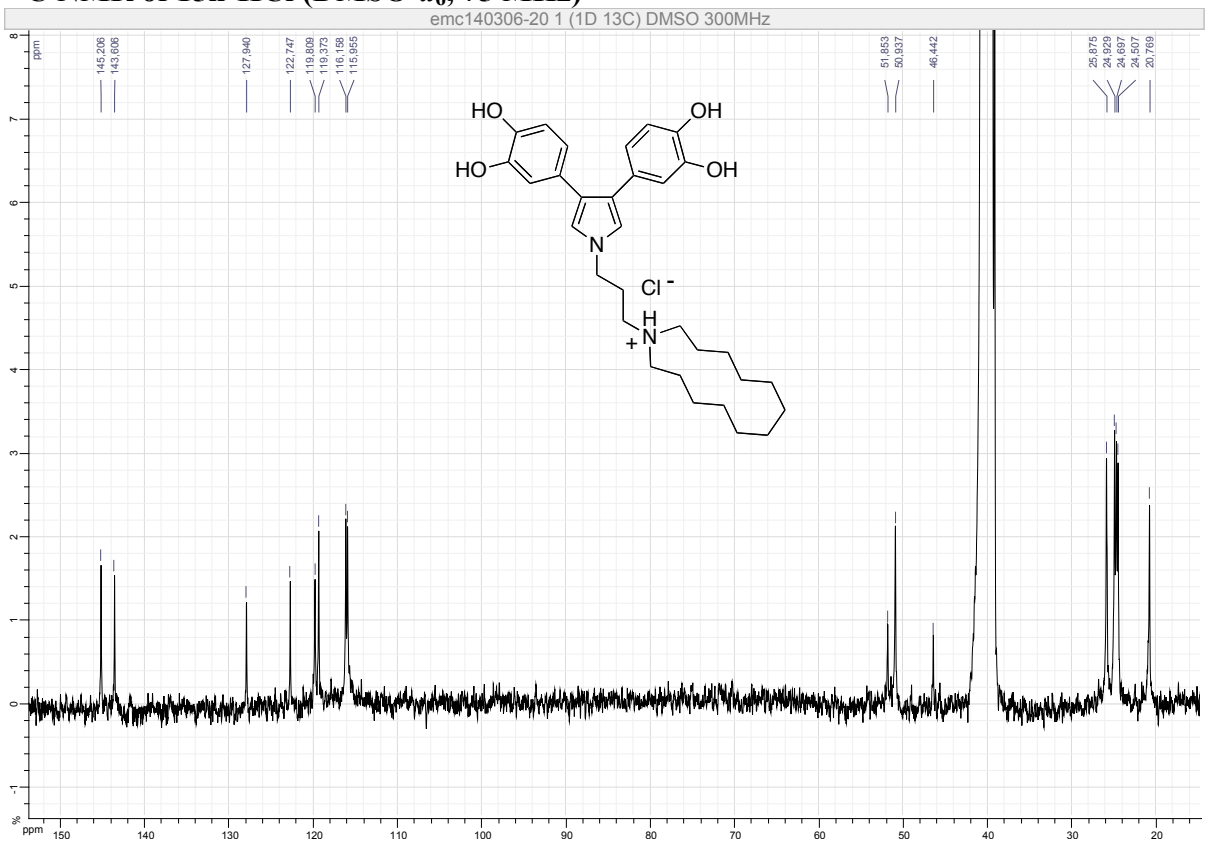
^{13}C NMR of 15g•HCl (DMSO-d_6, 75 MHz)



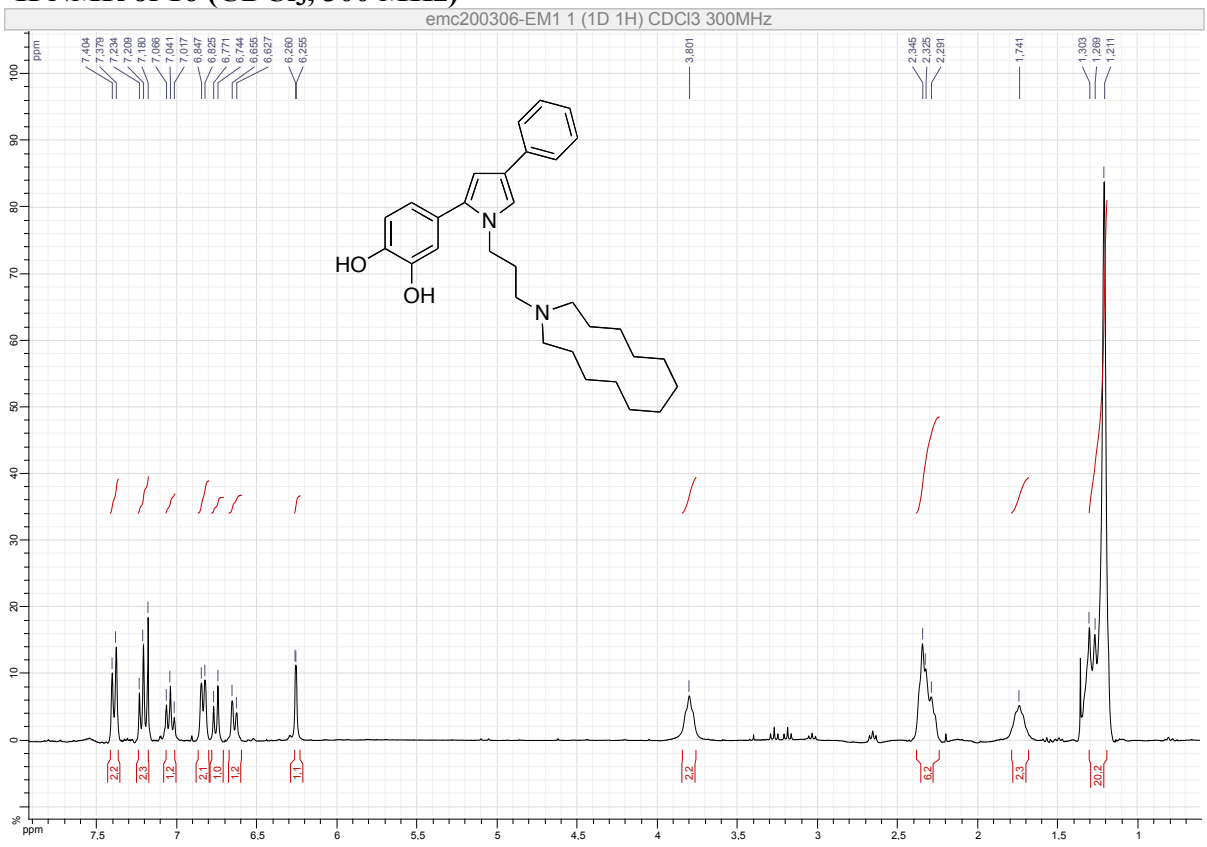
^{1}H NMR of 15h•HCl (DMSO-d_6, 300 MHz)



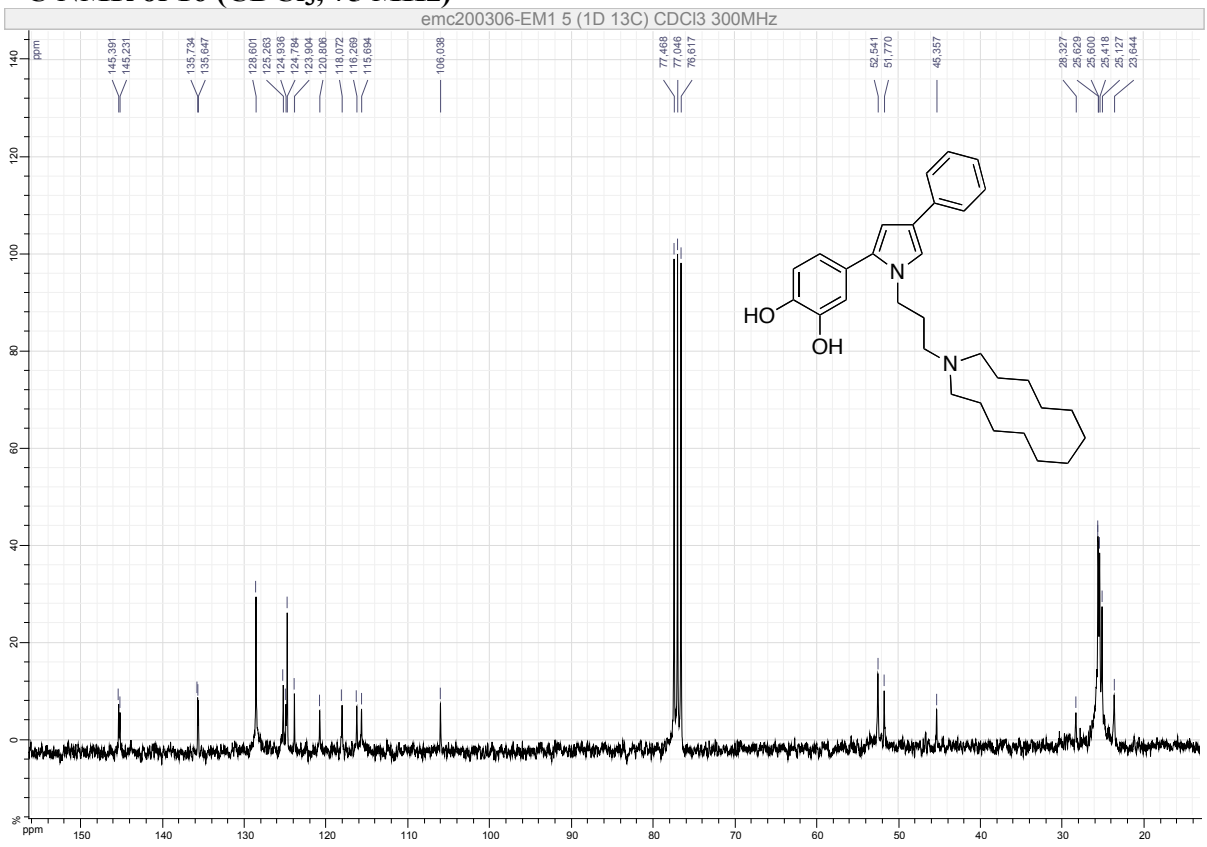
^{13}C NMR of 15h•HCl (DMSO-d_6, 75 MHz)



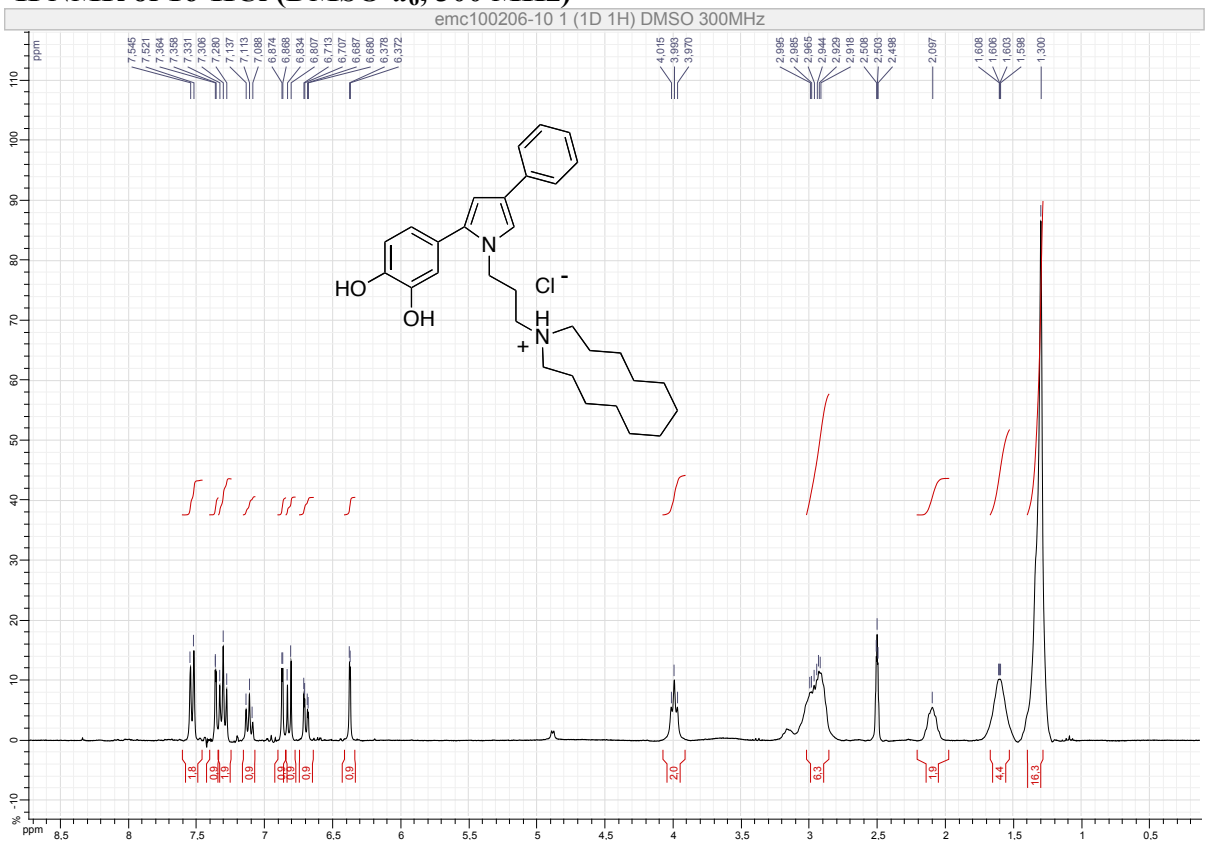
^{1}H NMR of 16 ($CDCl_3$, 300 MHz)



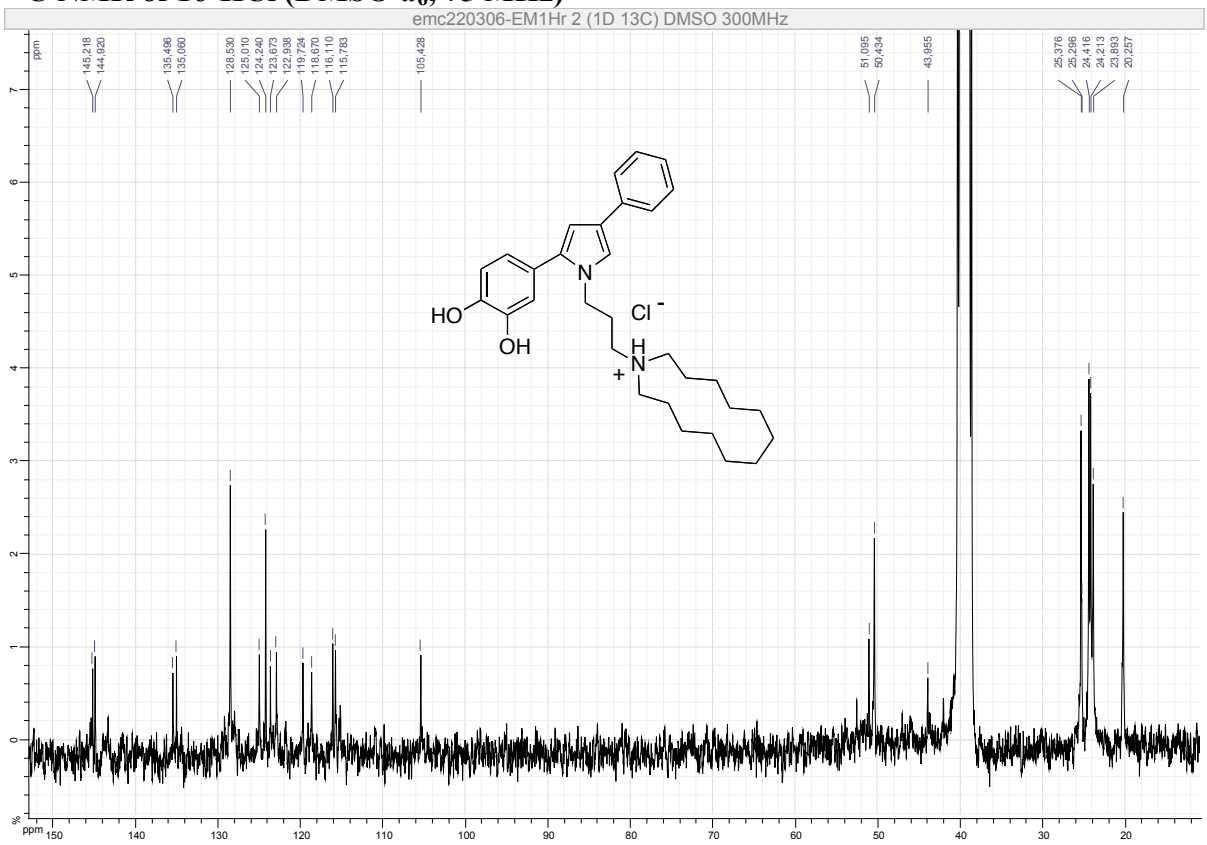
^{13}C NMR of 16 ($CDCl_3$, 75 MHz)



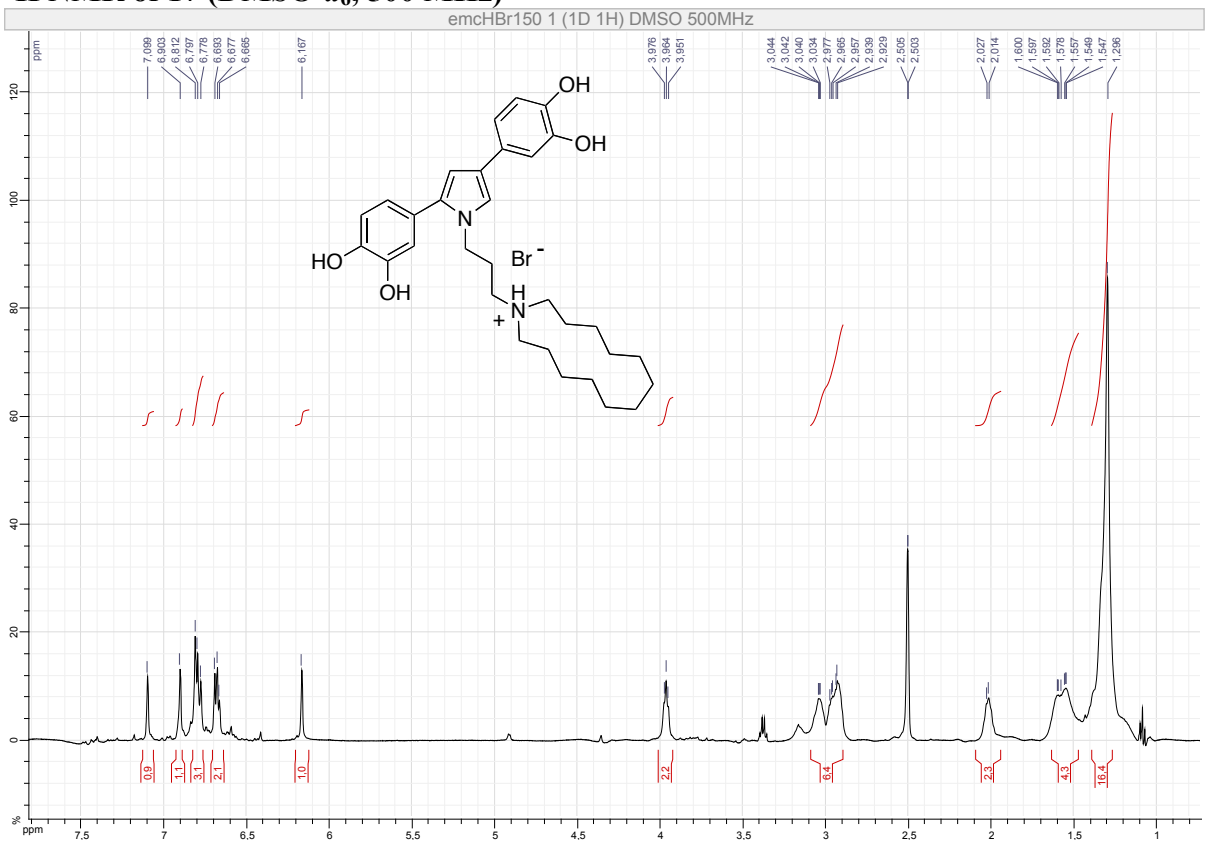
^{1}H NMR of 16•HCl (DMSO-d_6, 300 MHz)



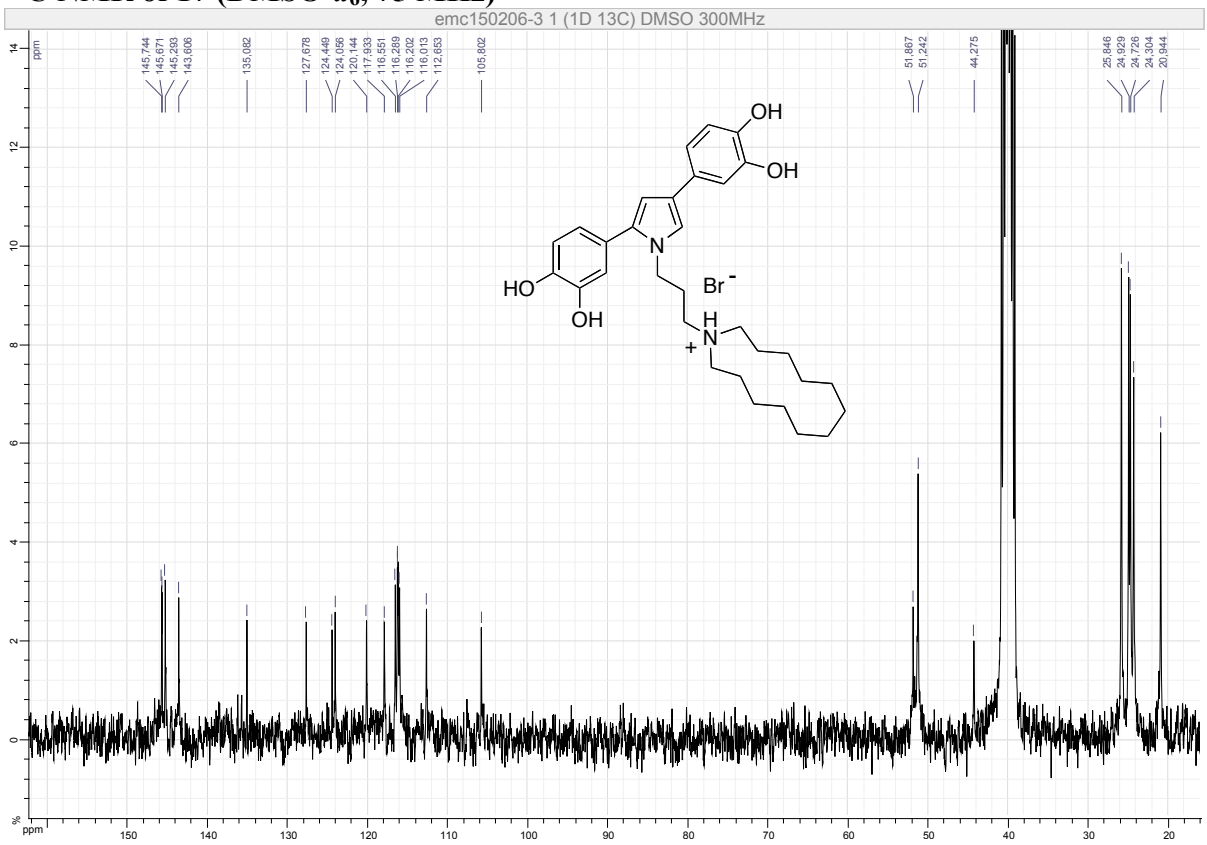
^{13}C NMR of 16•HCl (DMSO-d_6, 75 MHz)



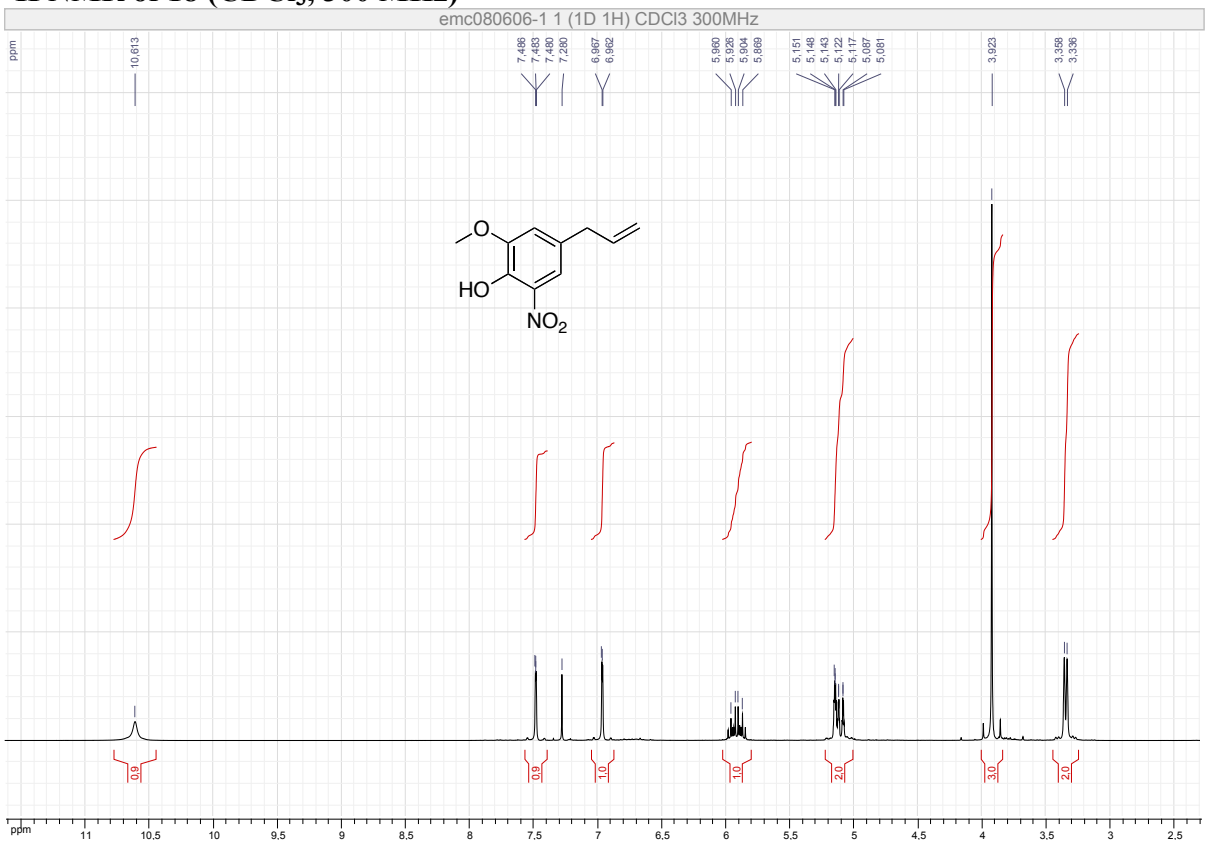
^{1}H NMR of 17 (DMSO-d_6, 500 MHz)



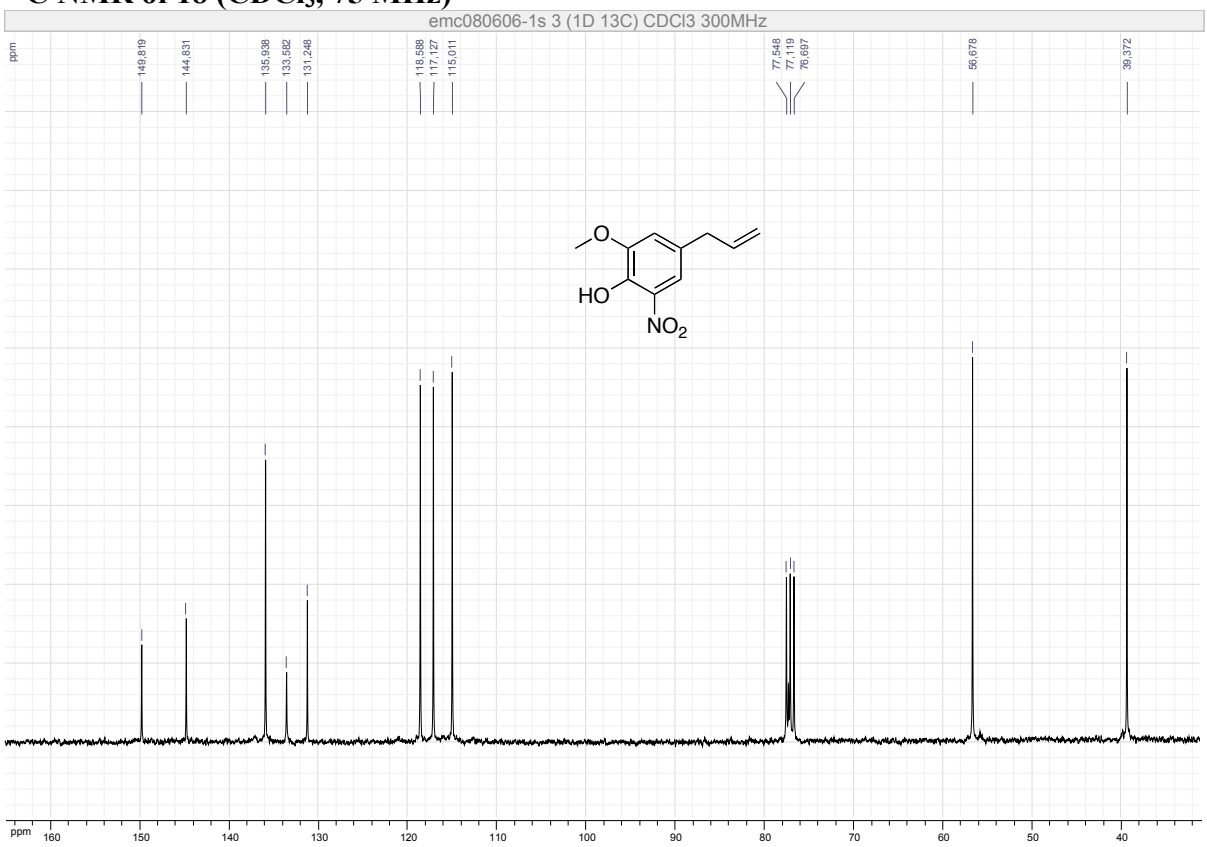
^{13}C NMR of 17 (DMSO-d_6, 75 MHz)



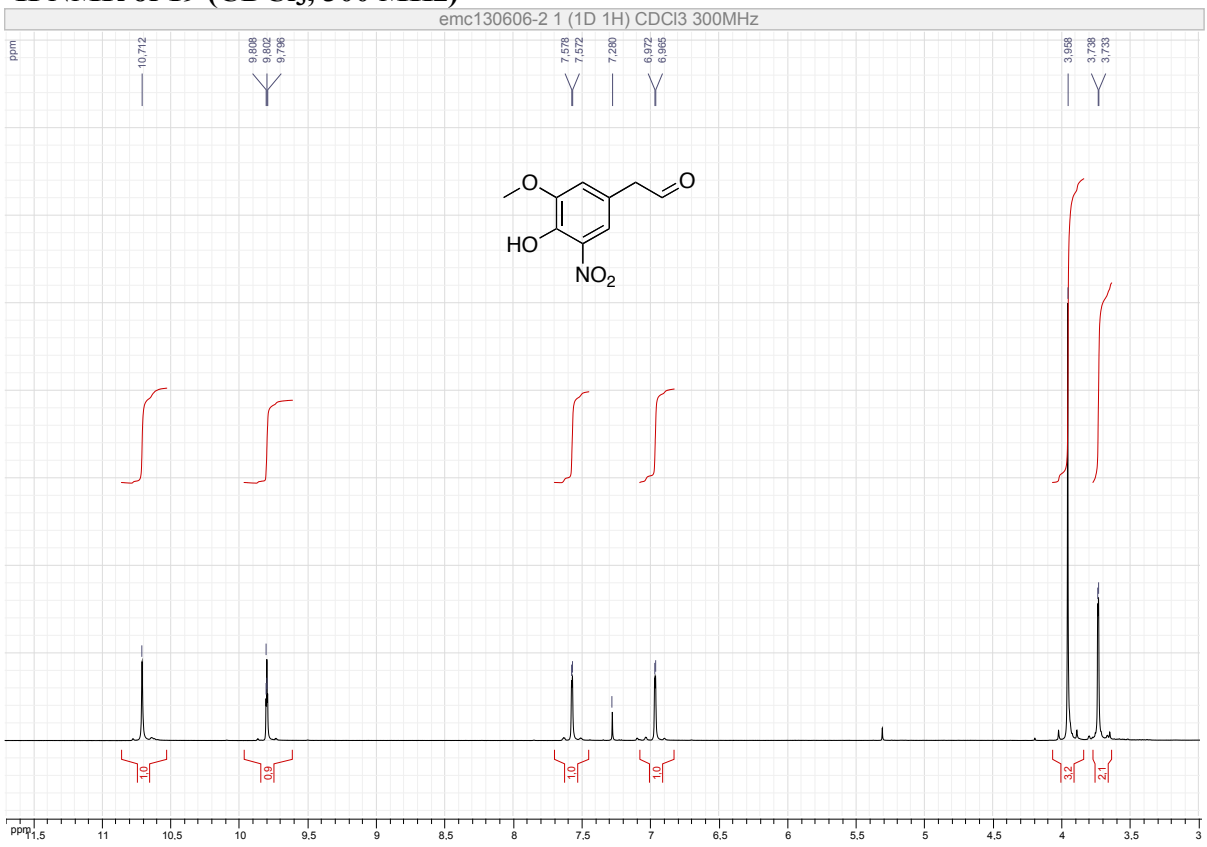
^{1}H NMR of 18 ($CDCl_3$, 300 MHz)



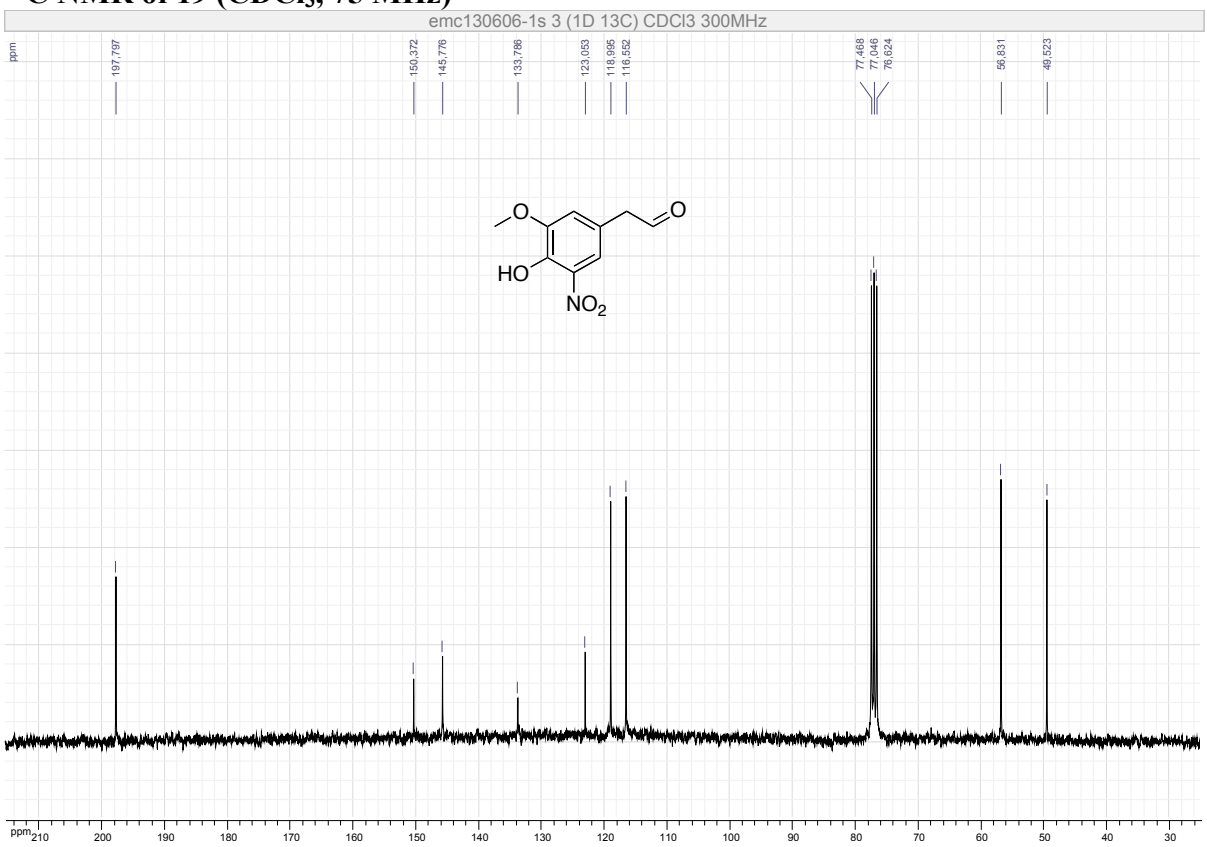
^{13}C NMR of 18 ($CDCl_3$, 75 MHz)



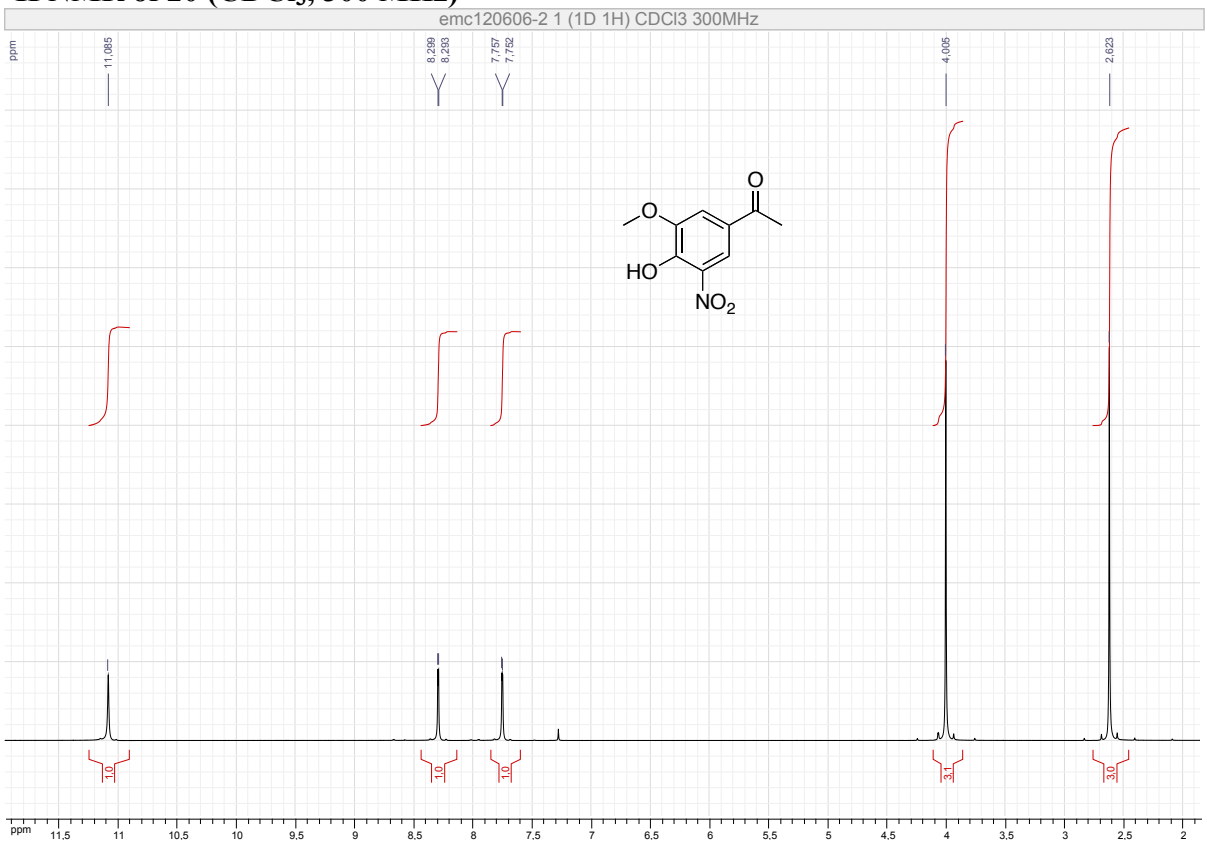
^{1}H NMR of 19 ($CDCl_3$, 300 MHz)



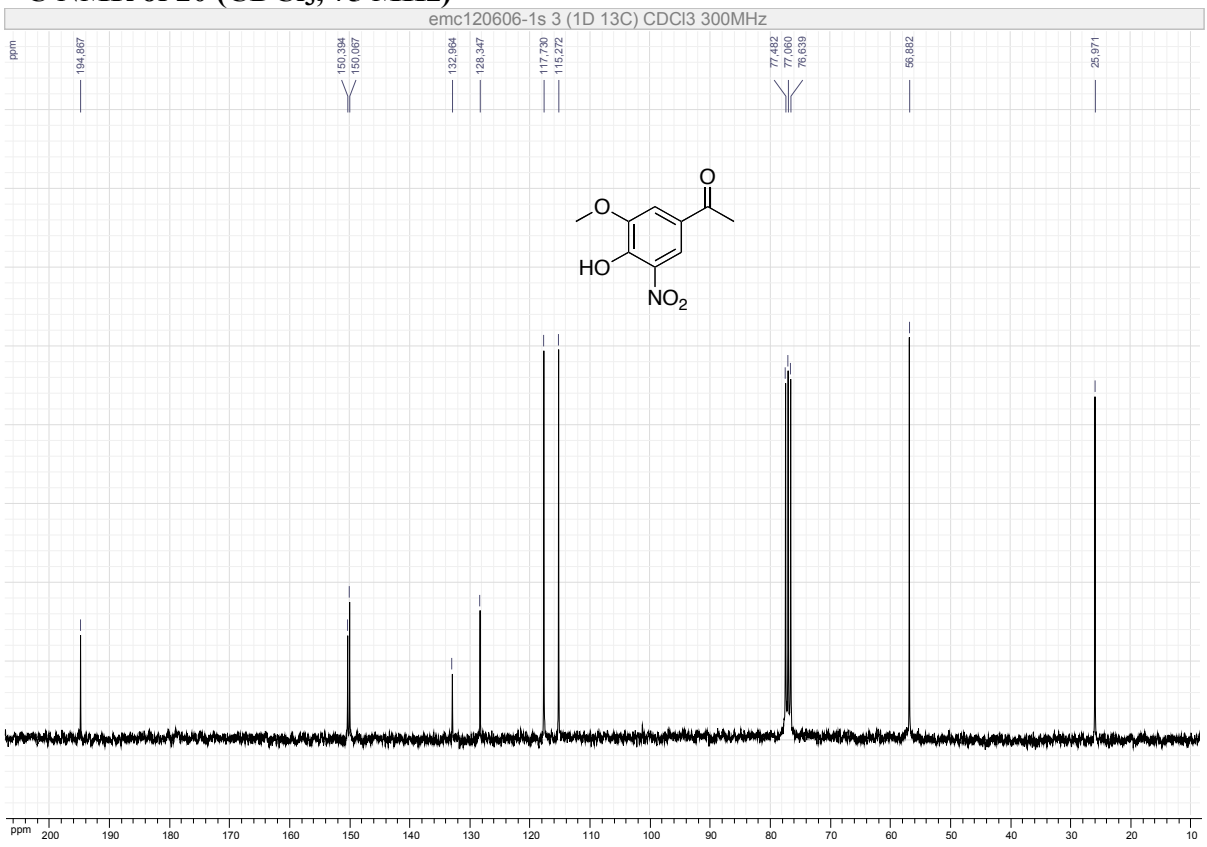
^{13}C NMR of 19 ($CDCl_3$, 75 MHz)



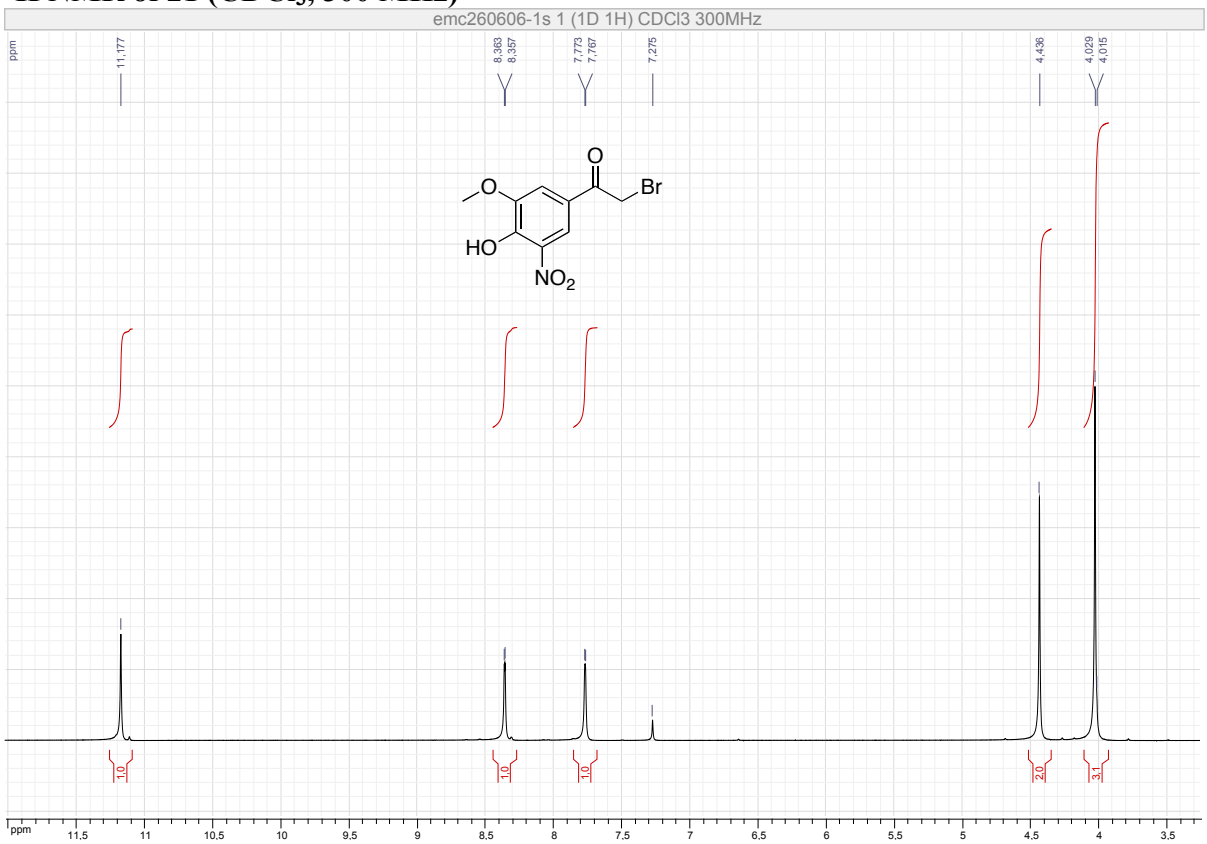
^{1}H NMR of 20 ($CDCl_3$, 300 MHz)



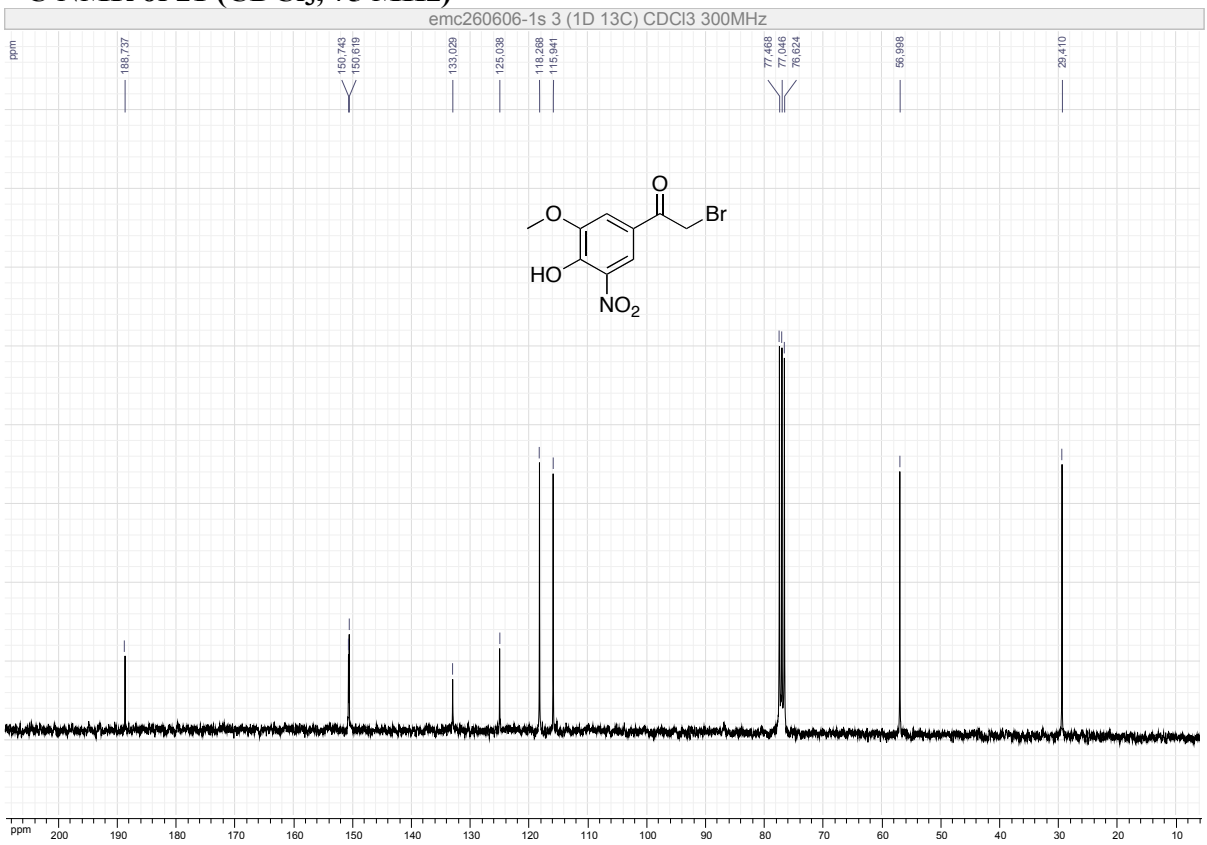
^{13}C NMR of 20 ($CDCl_3$, 75 MHz)



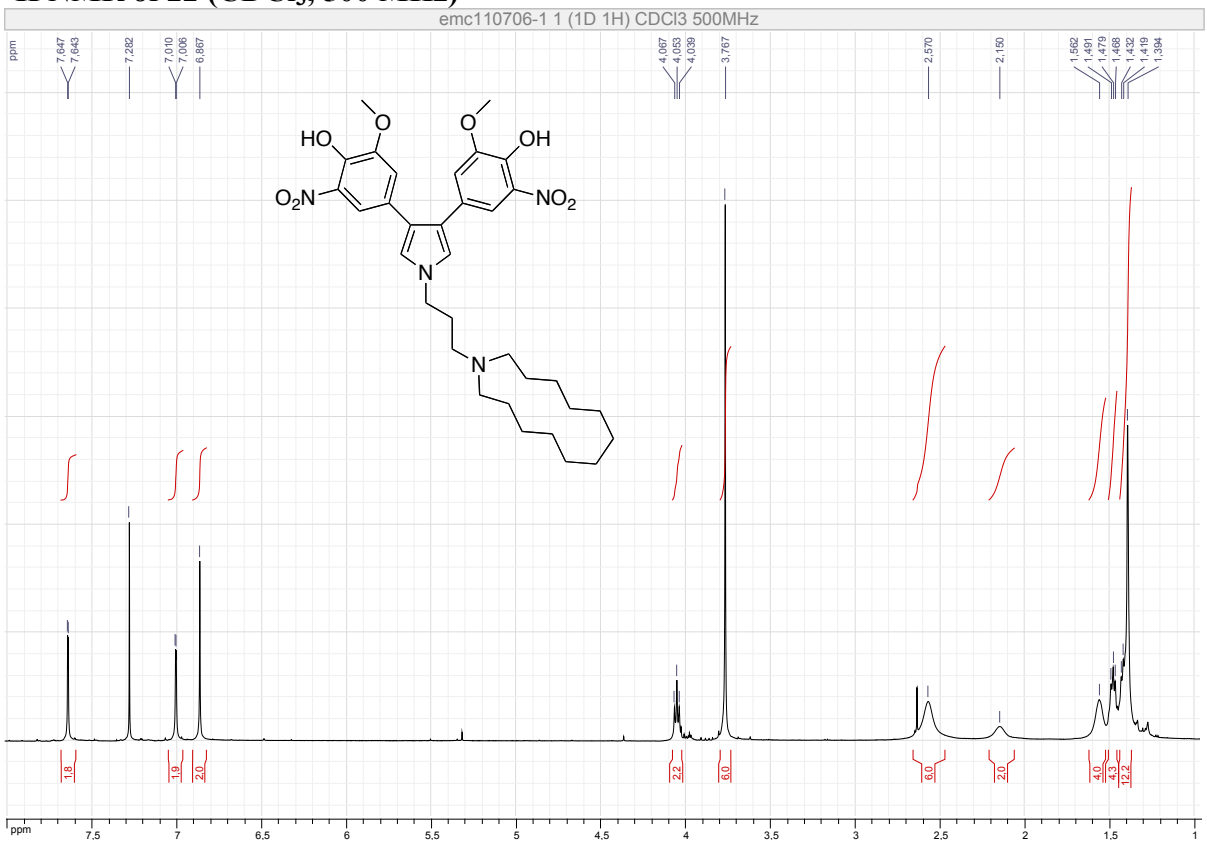
^{1}H NMR of 21 ($CDCl_3$, 300 MHz)



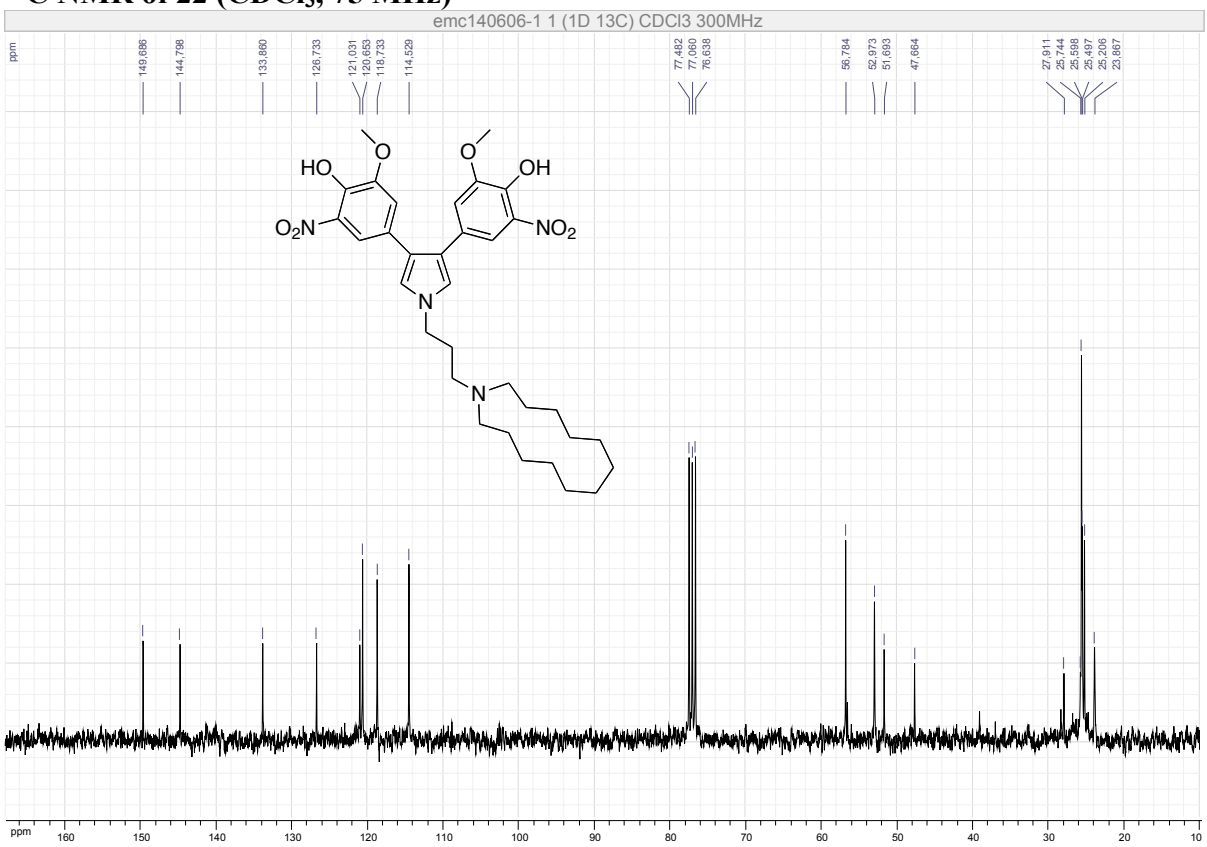
^{13}C NMR of 21 ($CDCl_3$, 75 MHz)



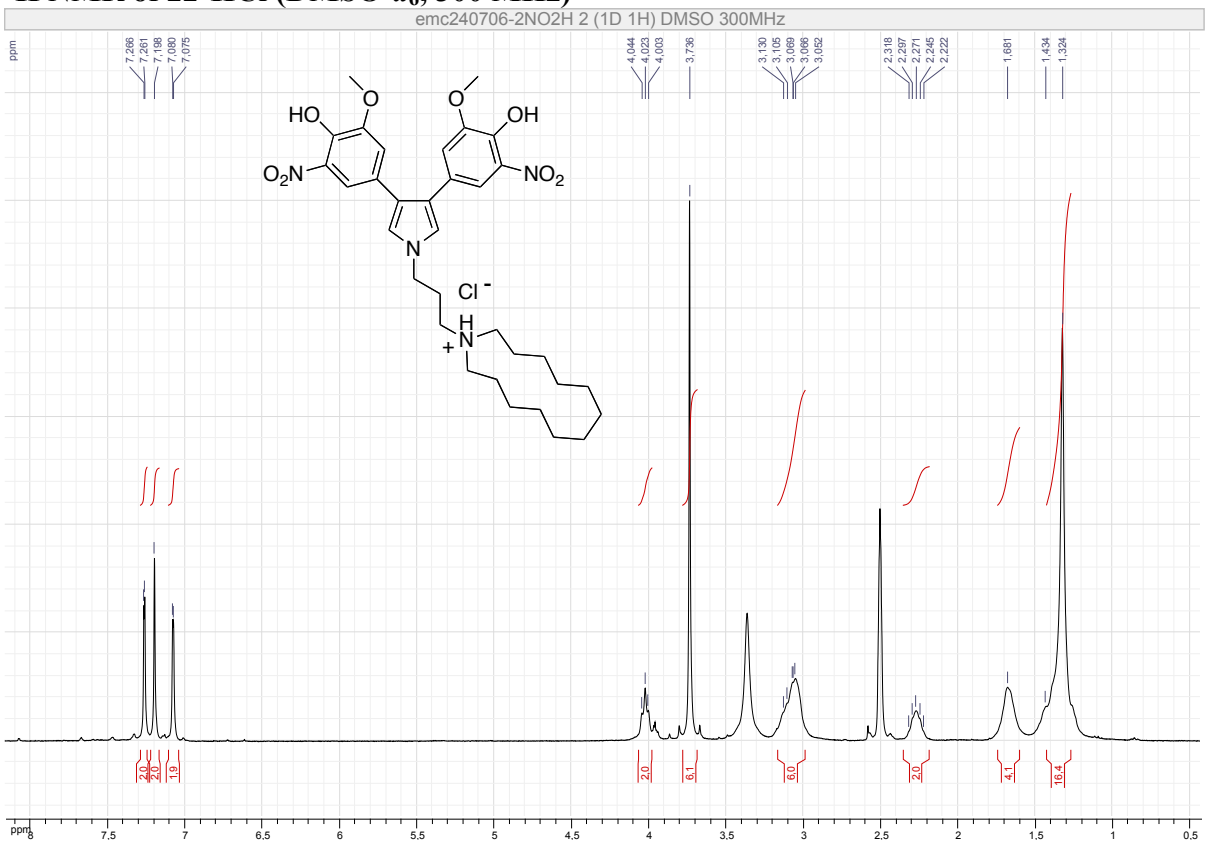
^{1}H NMR of 22 ($CDCl_3$, 500 MHz)



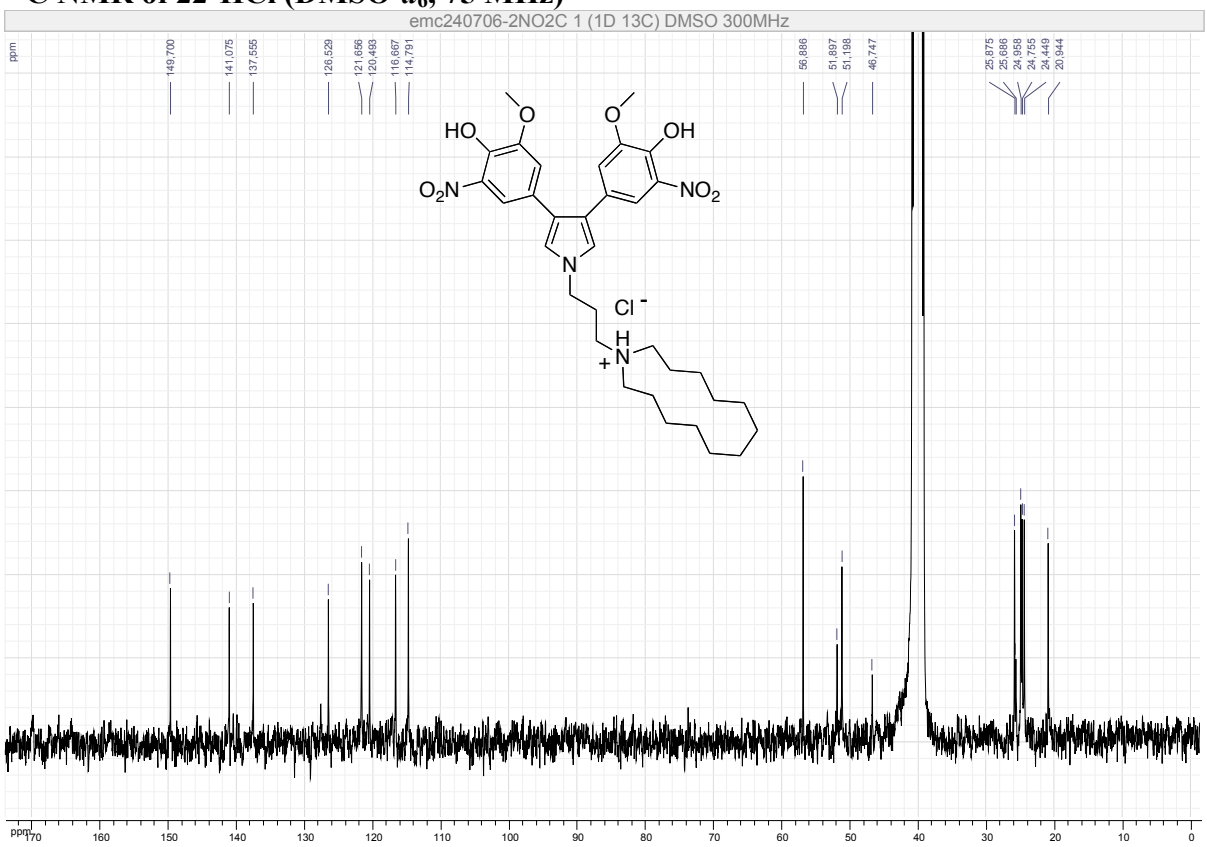
^{13}C NMR of 22 ($CDCl_3$, 75 MHz)



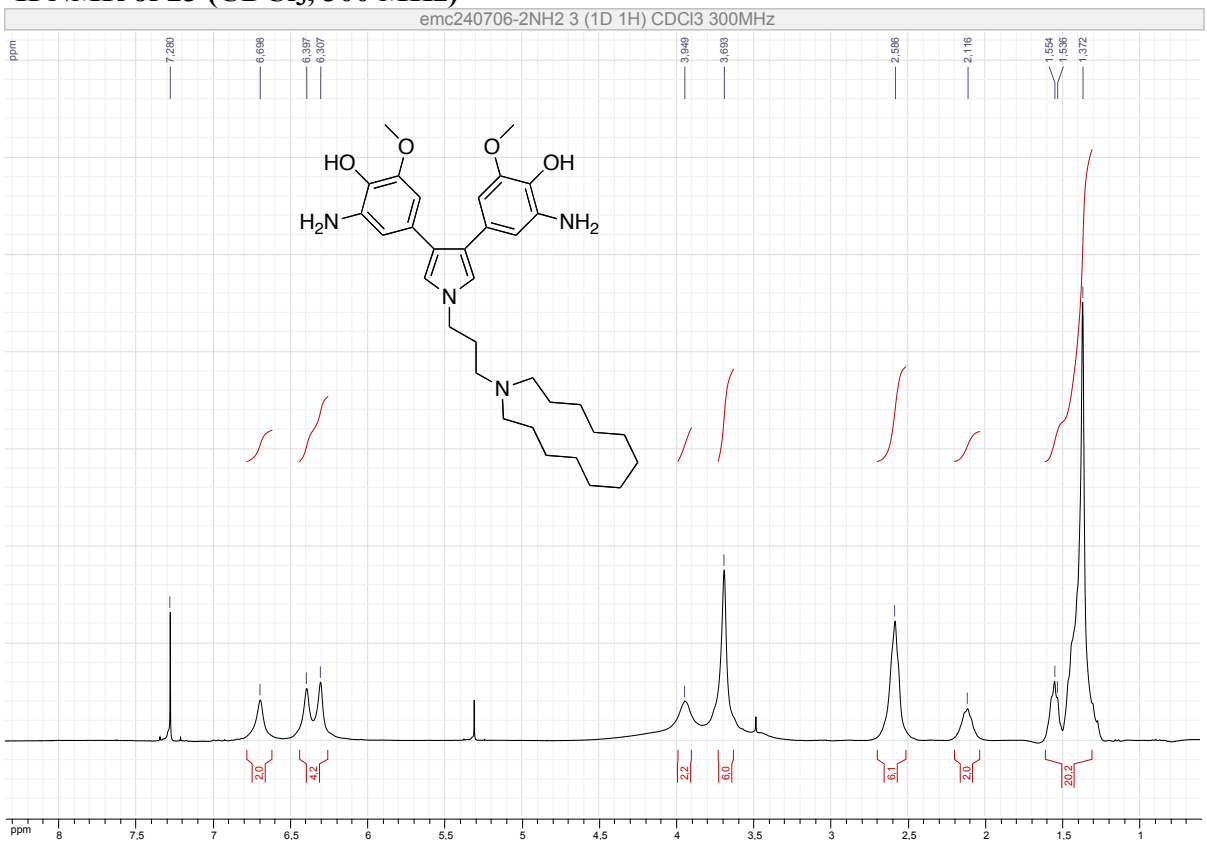
^{1}H NMR of 22•HCl (DMSO-d_6, 300 MHz)



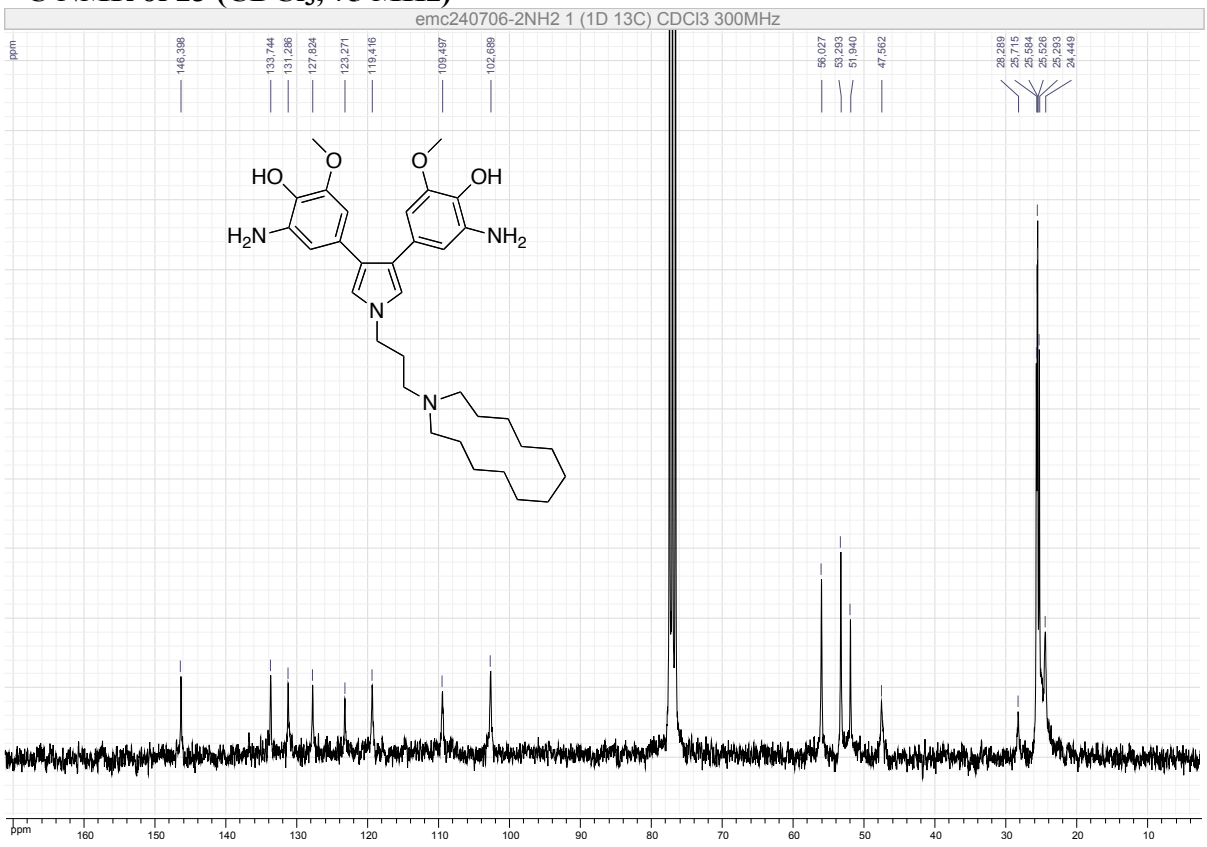
^{13}C NMR of 22•HCl (DMSO-d_6, 75 MHz)



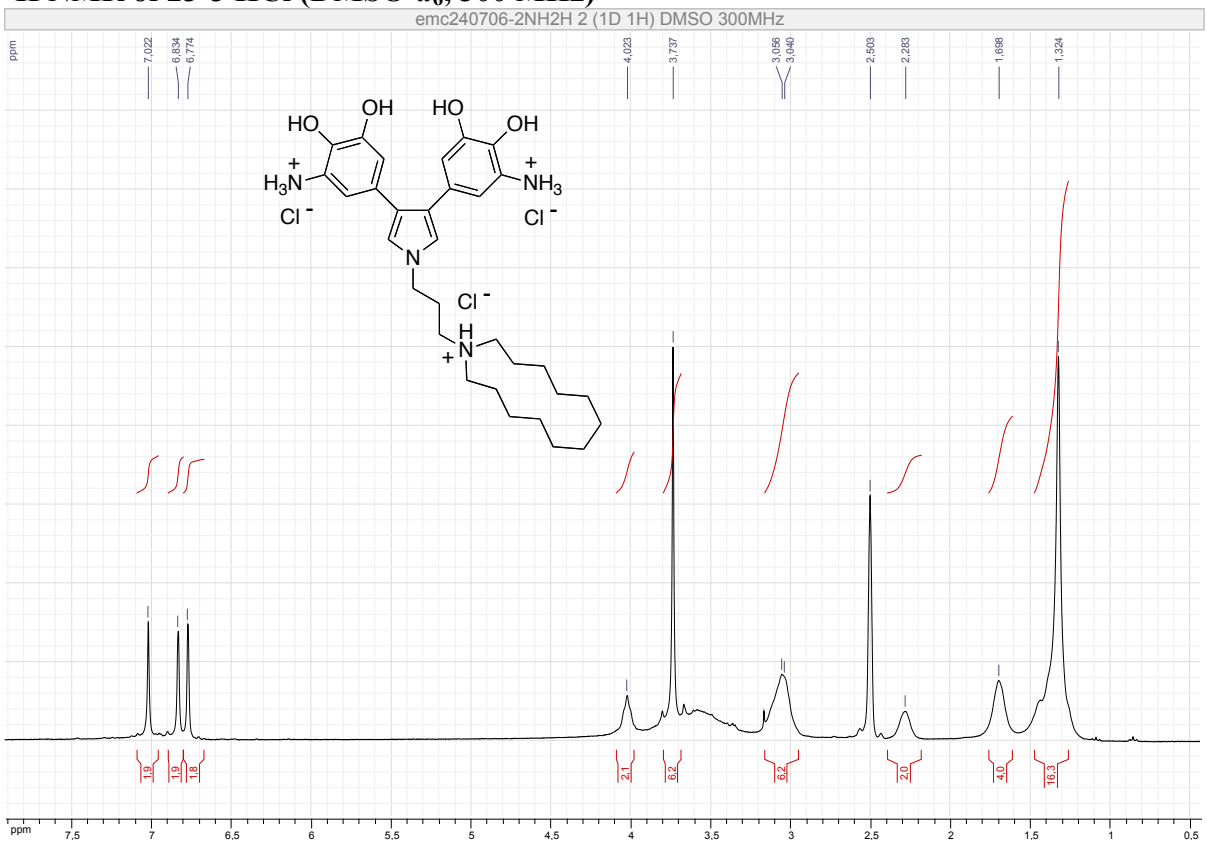
^{1}H NMR of 23 ($CDCl_3$, 300 MHz)



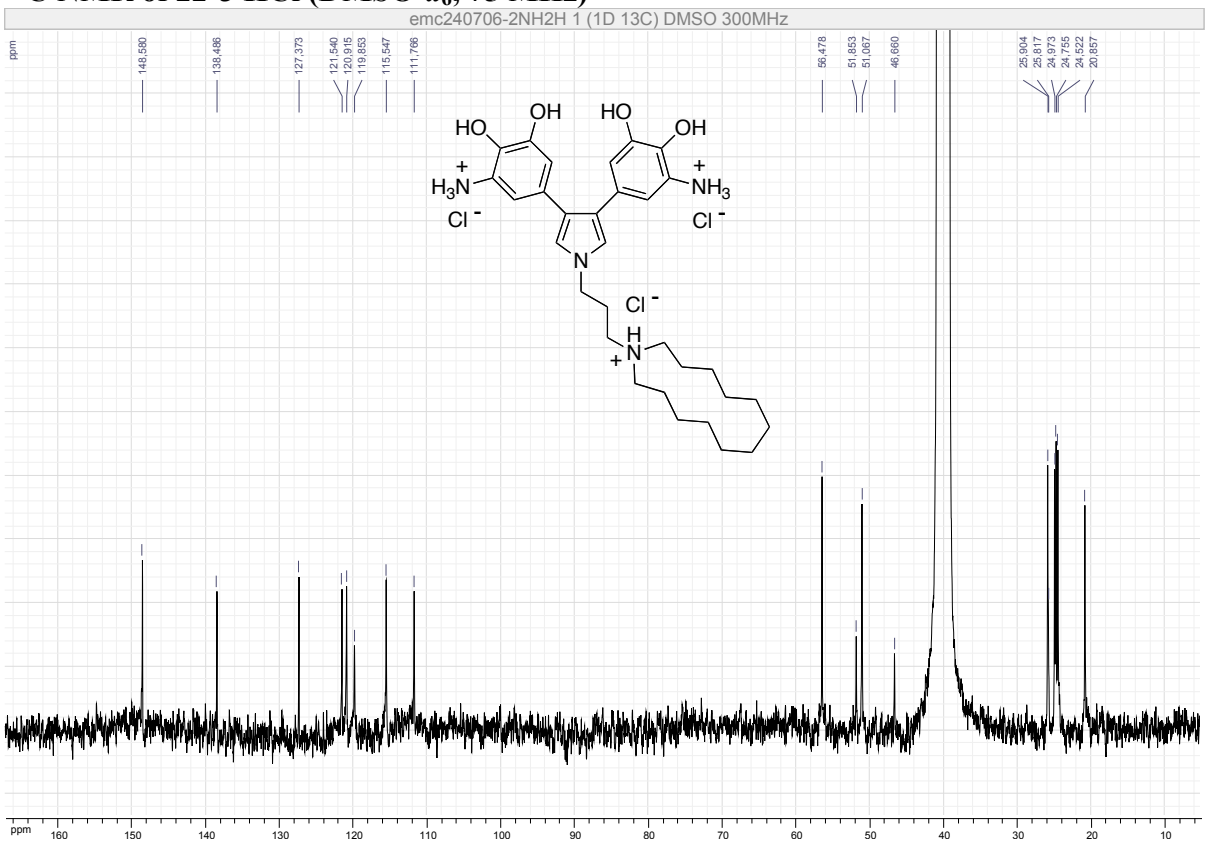
^{13}C NMR of 23 ($CDCl_3$, 75 MHz)



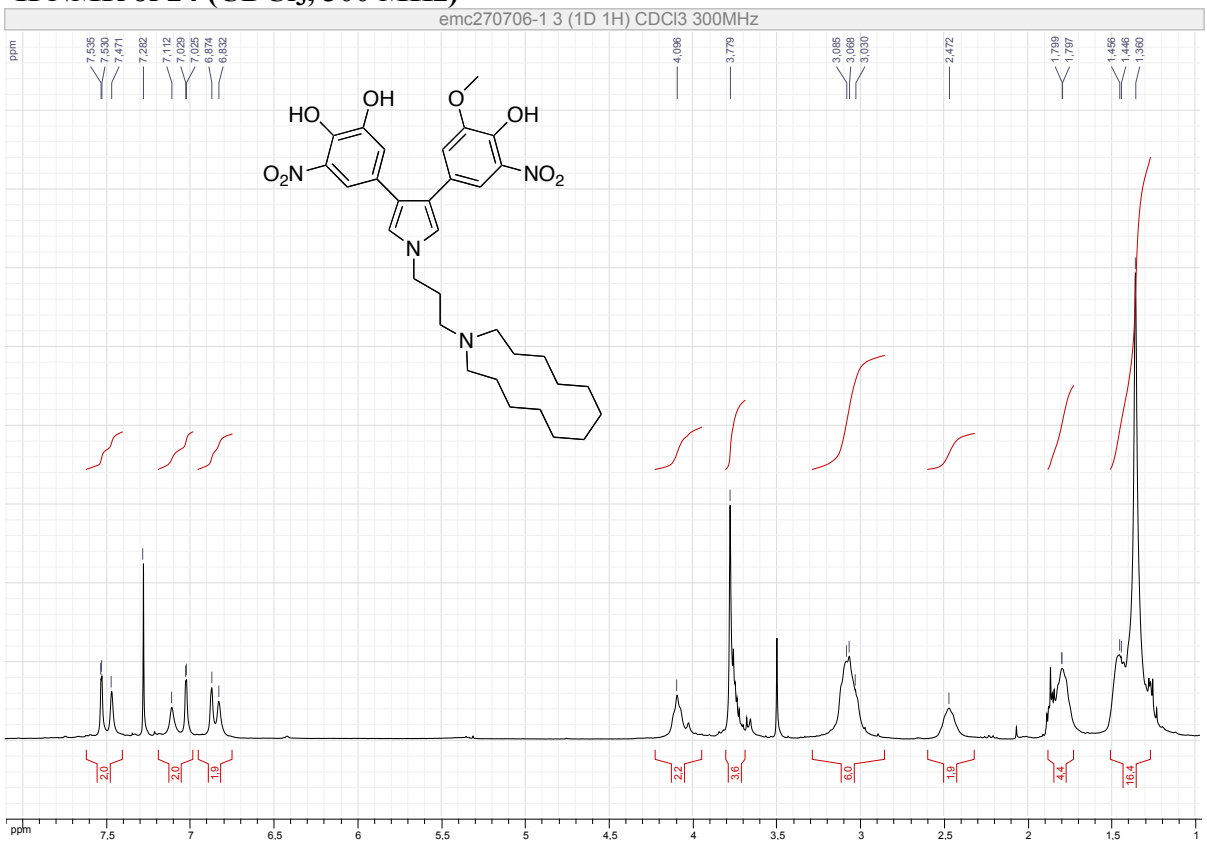
^{1}H NMR of 23•3 HCl (DMSO-d_6, 300 MHz)



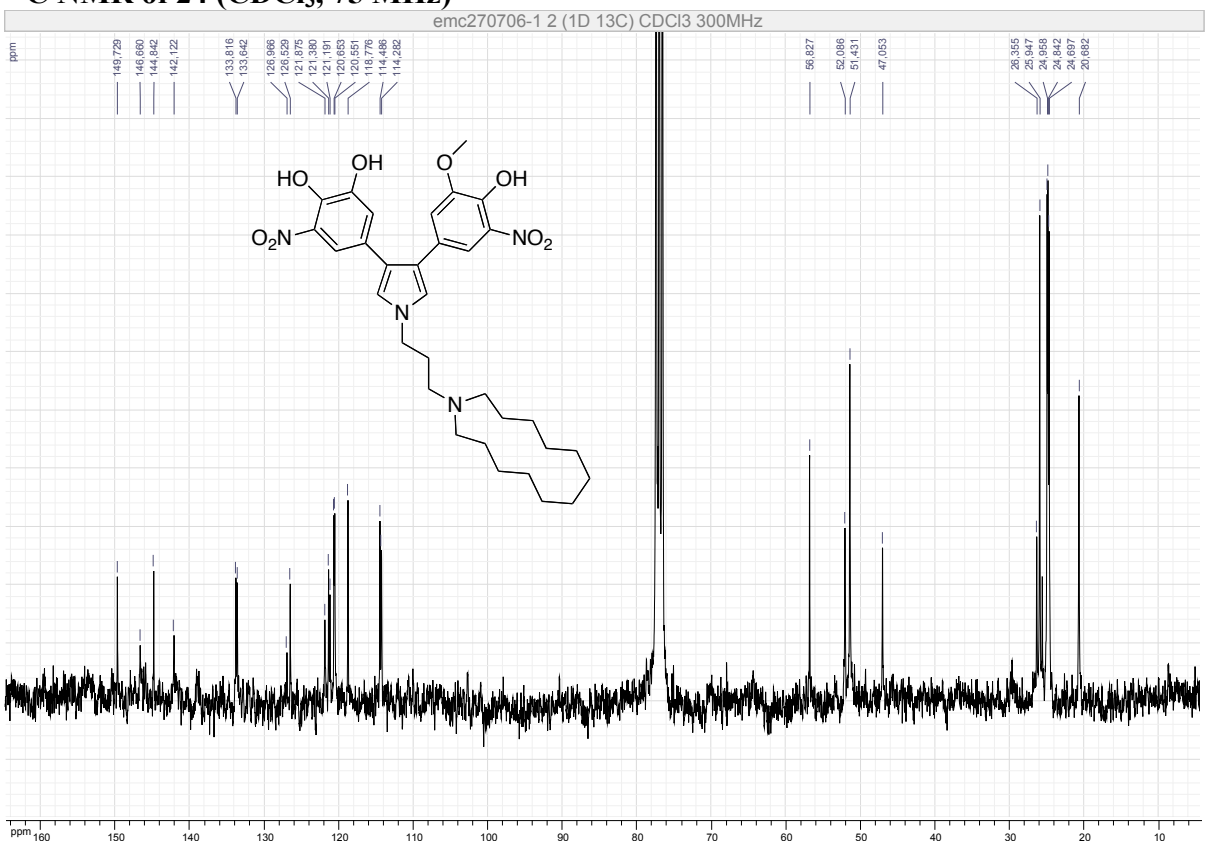
^{13}C NMR of 22•3 HCl (DMSO-d_6, 75 MHz)



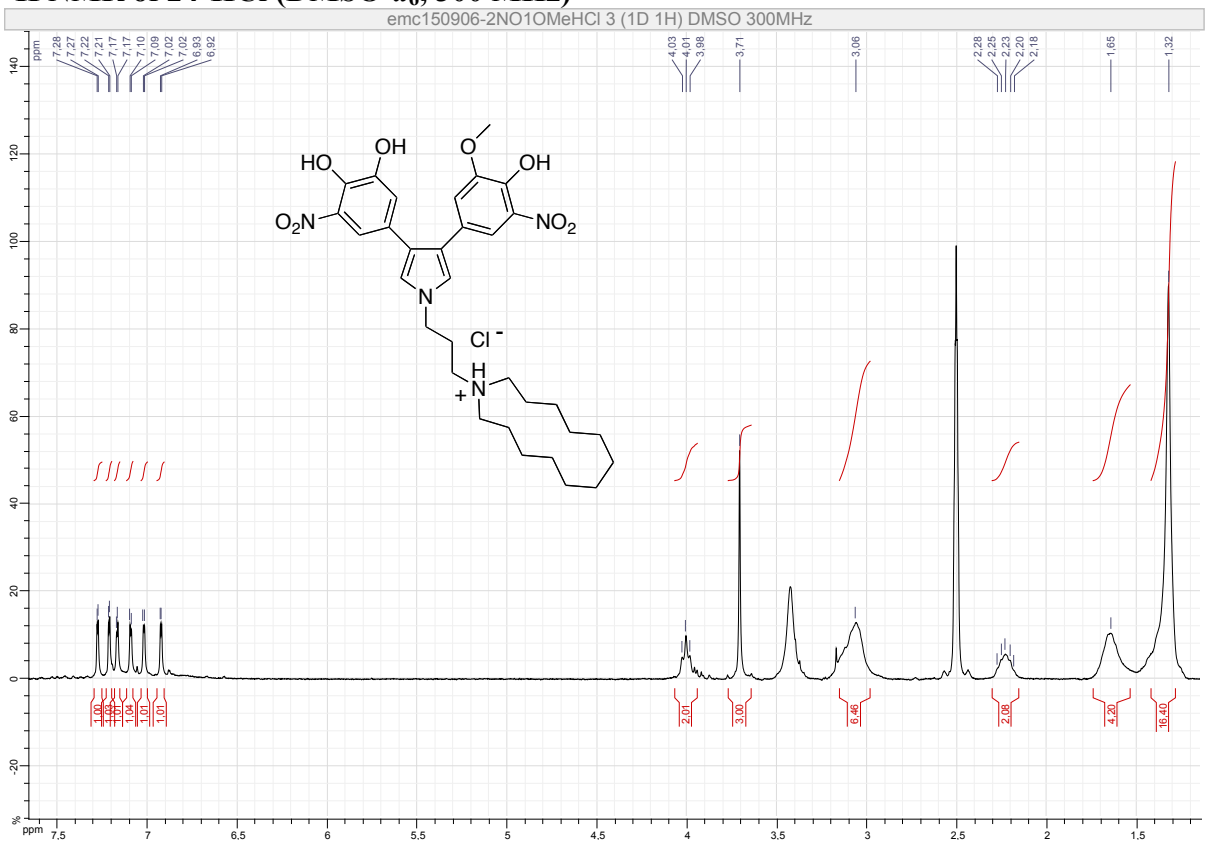
^{1}H NMR of 24 ($CDCl_3$, 300 MHz)



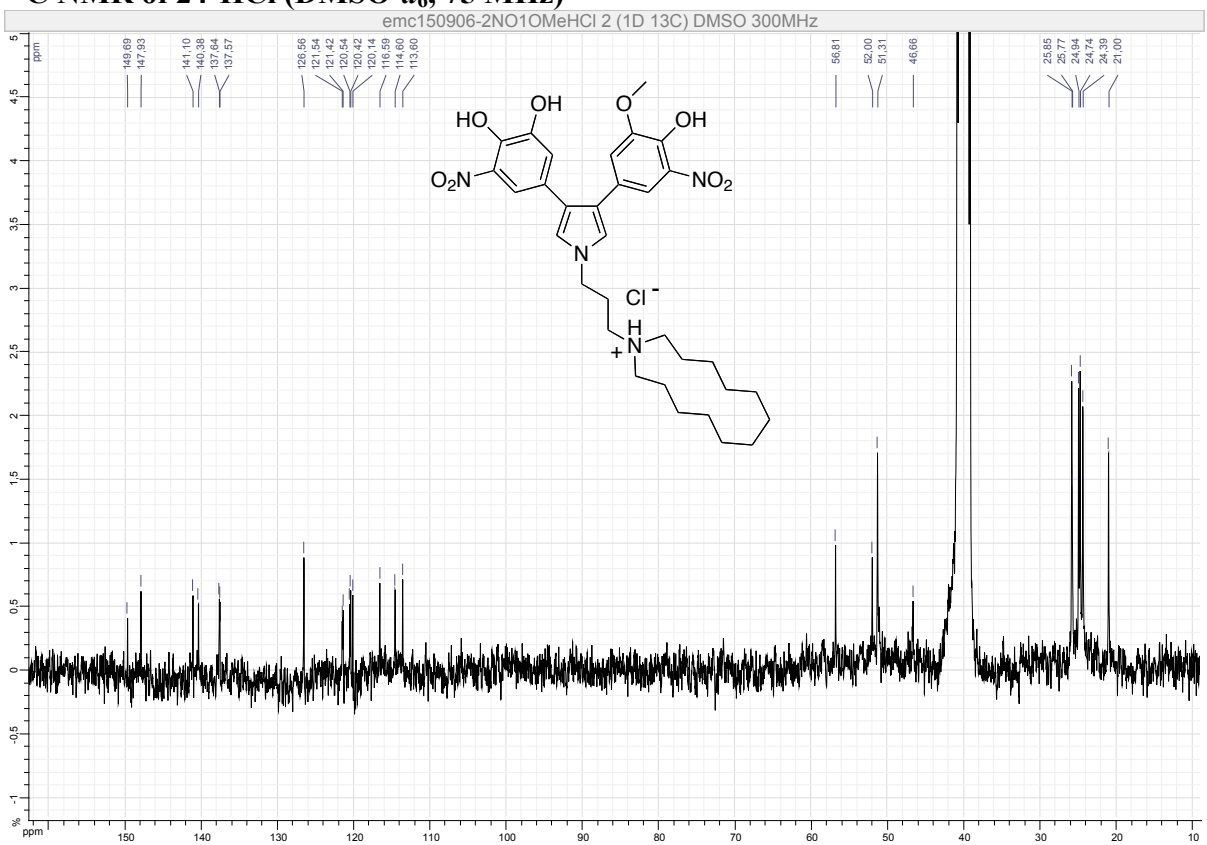
^{13}C NMR of 24 ($CDCl_3$, 75 MHz)



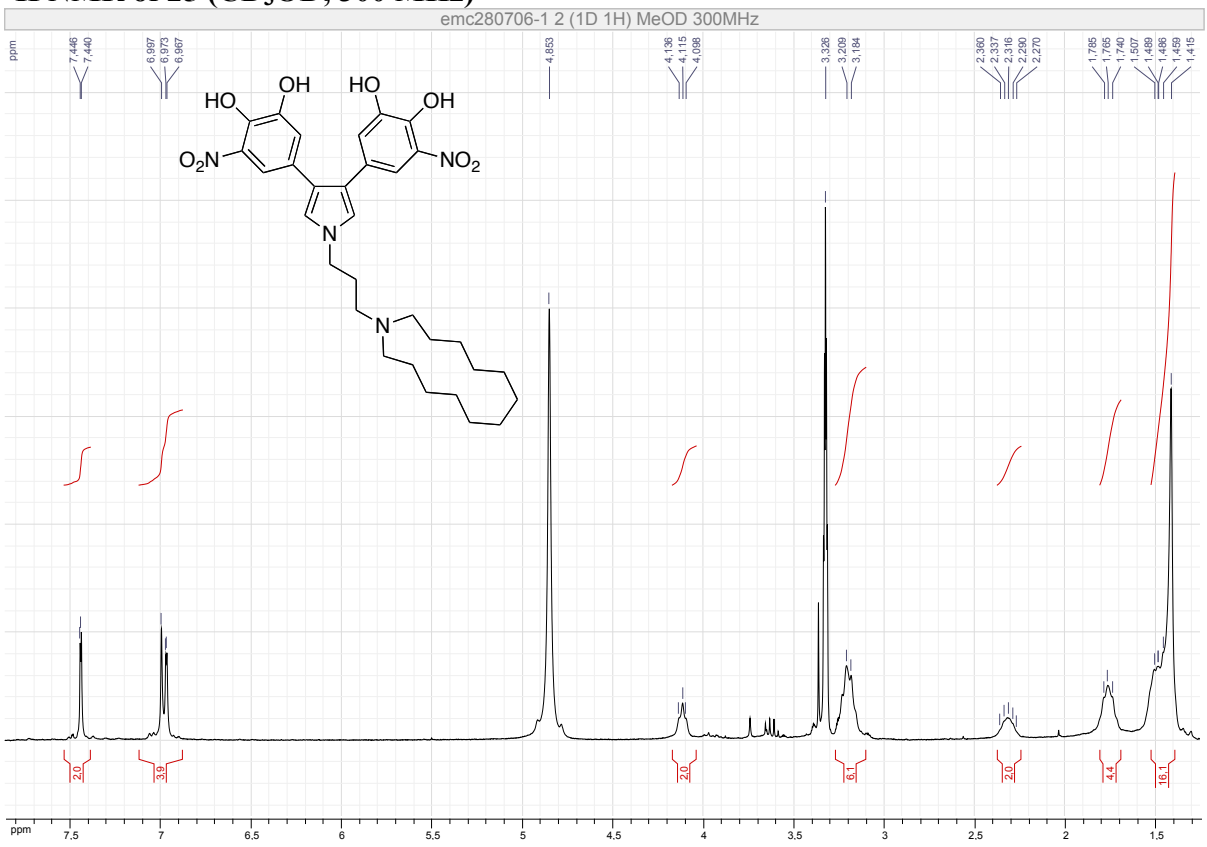
^{1}H NMR of 24•HCl (DMSO-d_6, 300 MHz)



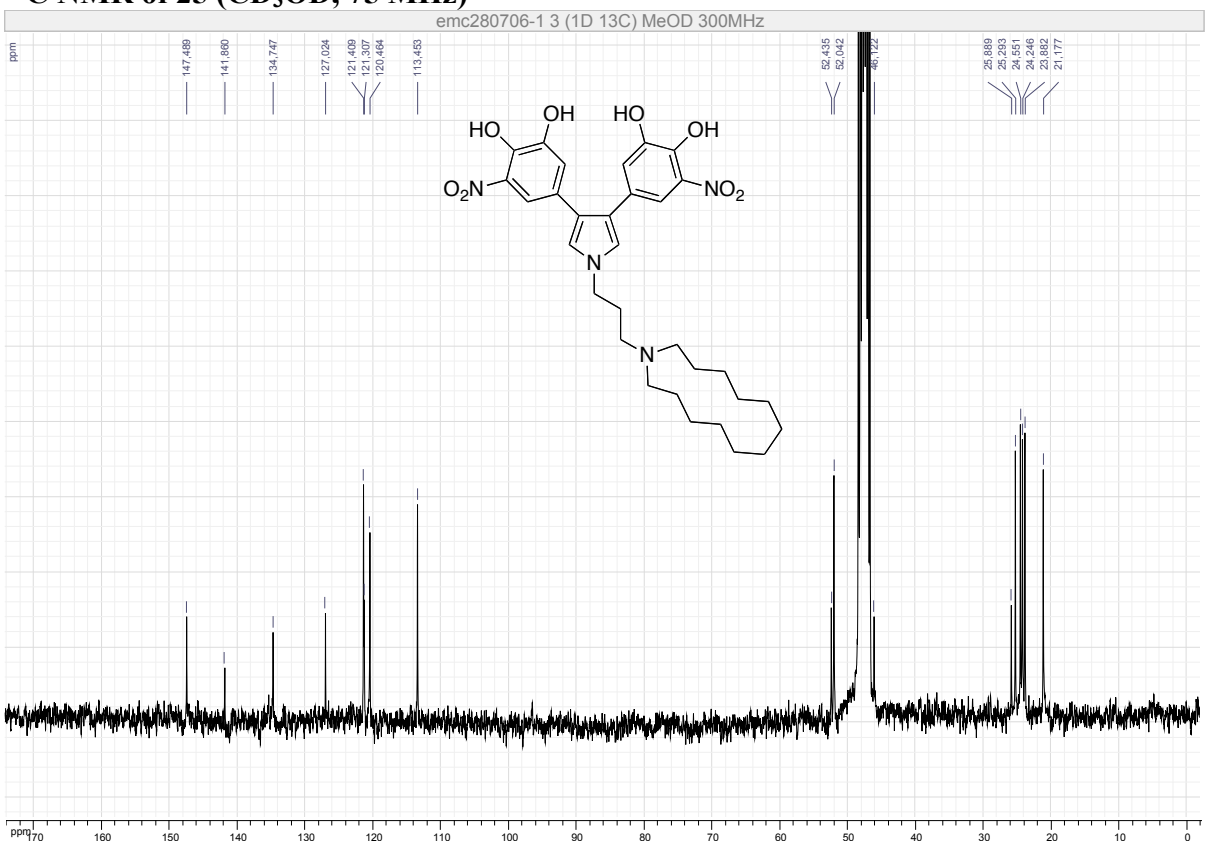
^{13}C NMR of 24•HCl (DMSO-d_6, 75 MHz)



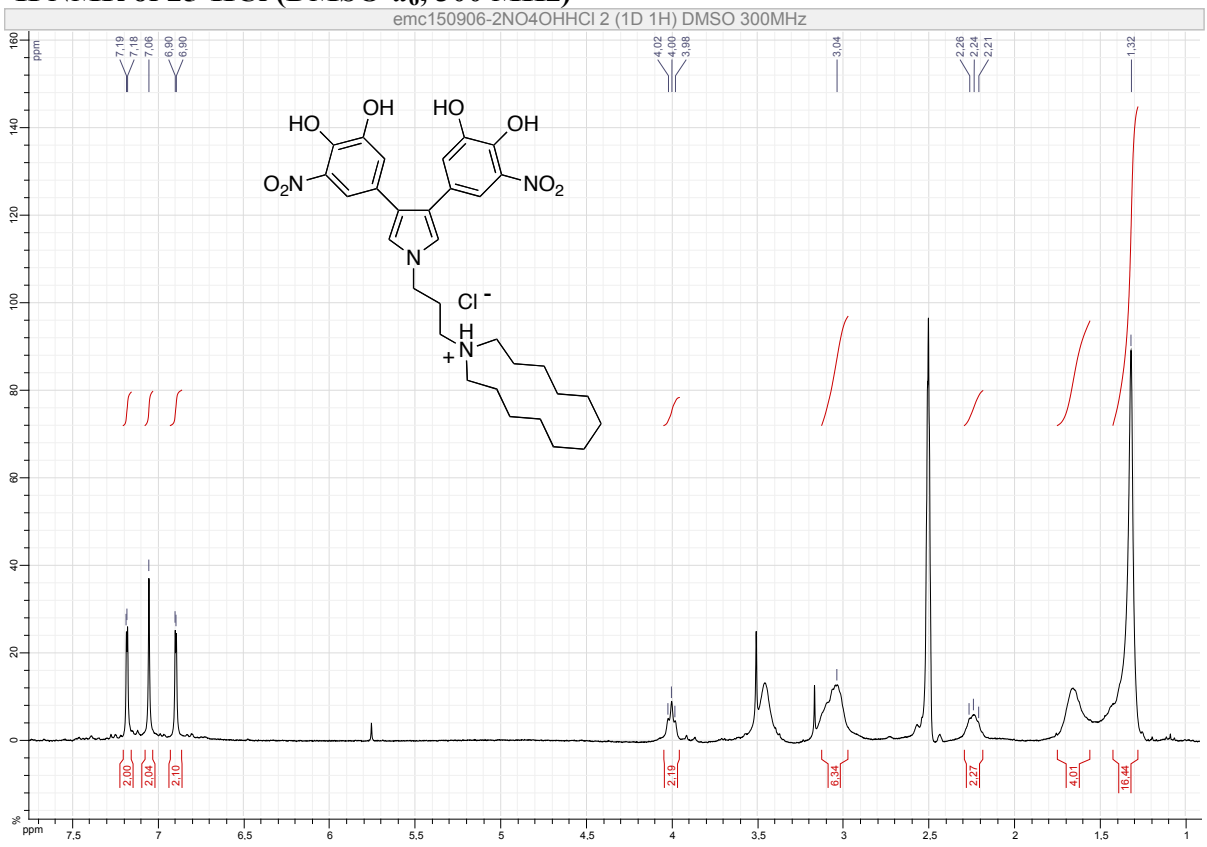
^{1}H NMR of 25 (CD_3OD, 300 MHz)



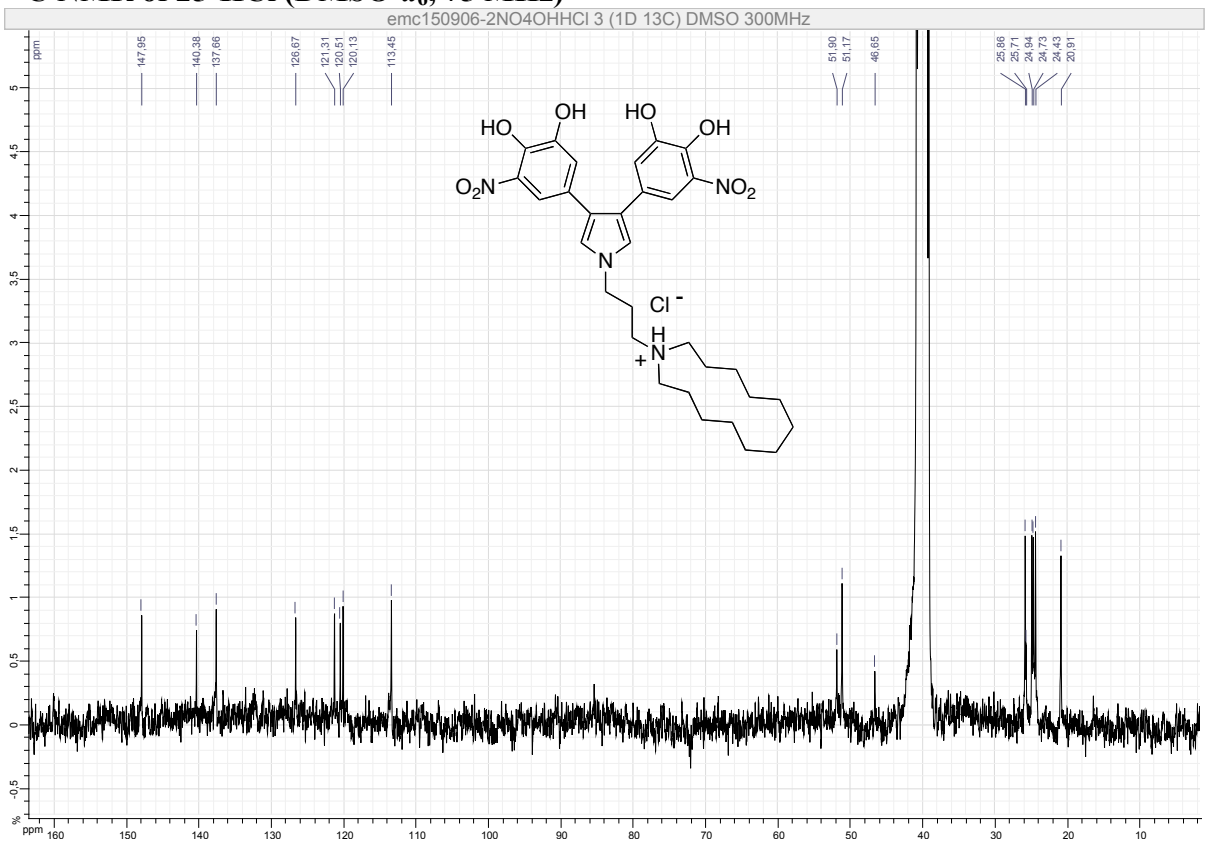
^{13}C NMR of 25 (CD_3OD, 75 MHz)



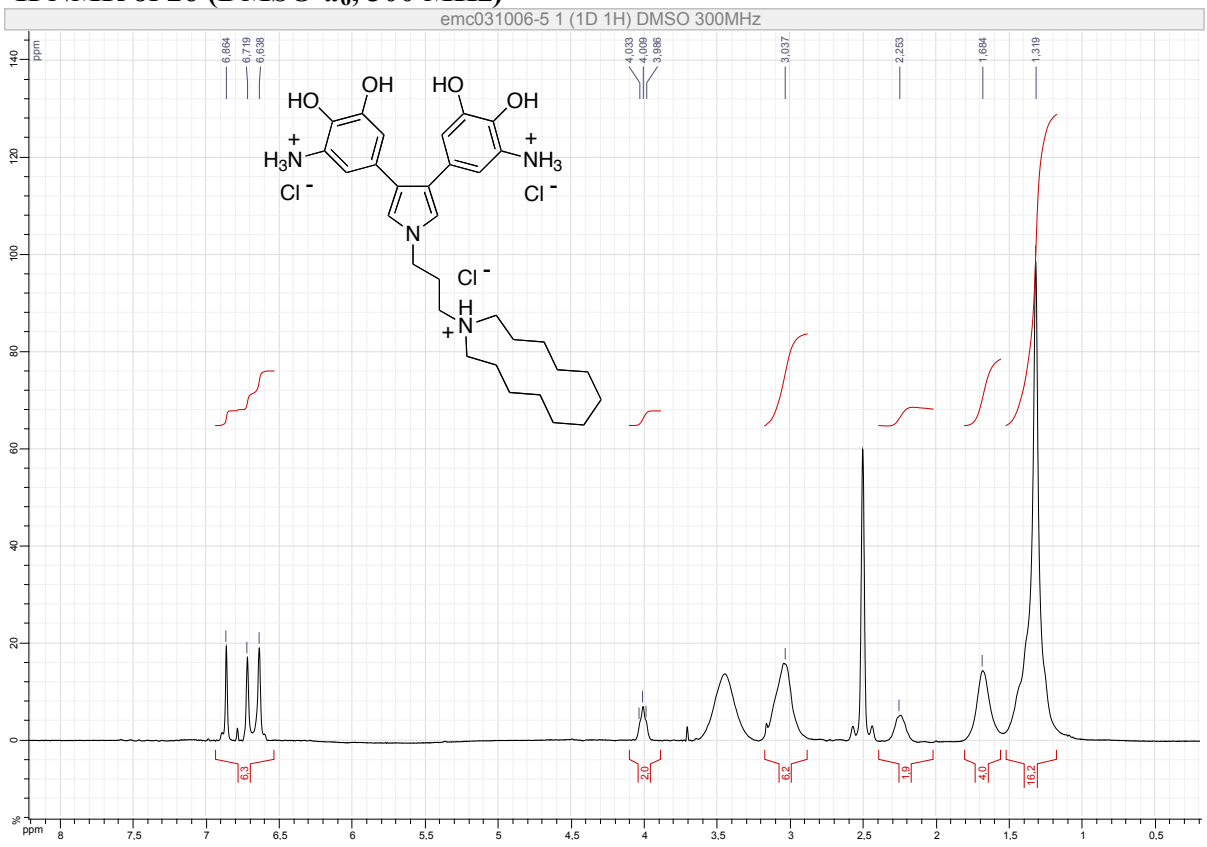
^{1}H NMR of 25•HCl (DMSO-d_6, 300 MHz)



^{13}C NMR of 25•HCl (DMSO-d_6, 75 MHz)



^{1}H NMR of 26 (DMSO-d_6, 300 MHz)



^{13}C NMR of 26 (DMSO-d_6, 75 MHz)