ELECTRONIC SUPPLEMENTARY INFORMATION FOR

New Reagent Space and New Scope for the Castagnoli-Cushman Reaction of Oximes

Anton Bannykh,[a] Ekaterina Levashova,[a] Olga Bakulina,[a] and Mikhail Krasavin*[,a,b]

[a] Saint Petersburg State University, Saint Petersburg 199034, Russian Federation

[b] Immanuel Kant Baltic Federal University, Kaliningrad 236016, Russian Federation

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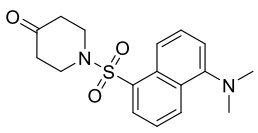
General Information

NMR spectroscopic data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) and Bruker Avance 500 spectrometer (500.03 for ^{1}H and 125 MHz for ^{13}C) in DMSO-d_6 and in $CDCl_3$ and were referenced to residual solvent proton signals (δH = 2.50 and 7.26 ppm, respectively) and solvent carbon signals (δC = 39.5 and 77.0 ppm, respectively). Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Flash column chromatography on silica was performed with Biotage Isolera Prime instrument using Biotage SNAP KP-Sil 25g cartridges. TLC was performed with Macherey-Nagel «Alugram Sil G/UV254» plates. Melting points were determined with a Stuart SMP50 instrument in open capillary tubes and are uncorrected. All commercial reagents and solvents were used without further purification. All reactions were performed in air. Oximes were synthesized according to known procedures as *E/Z* isomeric mixtures.[1] Synthesis of 4-aryl-2*H*-pyran-2,6(3*H*)-diones **9** was performed from the corresponding dicarboxylic acids according to known procedures.[2] For synthesis of compounds **12** and **13** was used HPLC grade DMSO (dried over MS 4Å for at least 48h).

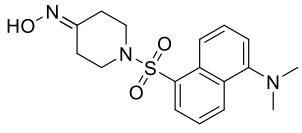
Procedure for synthesis of 1-((5-(Dimethylamino)naphthalen-1-yl)sulfonyl)piperidin-4-one [3]



To the bi-phasic solution of 4-pipiridone hydrochloride (244 mg, 1.8 mmol) and K_2CO_3 (180 mg, 1.3 mmol) in 15 mL MeCN-H_2O (1:1) 5-(dimethylamino)naphthalene-1-sulfonyl chloride (512 mg, 1.9 mmol) was added in one portion. Orange suspension was stirred overnight at room temperature. Conversion was monitored by TLC with cerium-ammonium-molybdate (CAM) staining. The reaction mixture was diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was then separated and dried over Na_2SO_4, filtered and concentrated in vacuo to give the title product as white solid.

Yield 780 mg (64%), white solid, m.p. 147-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.5 Hz, 1H), 8.34 (d, *J* = 8.7 Hz, 1H), 8.27 (d, *J* = 7.3 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 3.59 (t, *J* = 6.1 Hz, 4H), 2.89 (s, 6H), 2.51 (t, *J* = 6.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 133.3, 131.1, 130.7, 130.2, 130.2, 128.4, 123.4, 119.4, 115.6, 45.6, 45.3, 41.2. HRMS *m/z* $[M+H]^+$ 333.1267 calculated for $C_{17}H_{21}N_2O_3S^+$, found 333.1271.

Procedure for synthesis of 1-((5-(Dimethylamino)naphthalen-1-yl)sulfonyl)piperidin-4-one oxime [1]



To a solution of corresponding ketone (0.535 mg, 1.6 mmol) and pyridine (0.607 mL, 7.3 mmol) in EtOH (3 mL) was added $NH_2OH \cdot HCl$

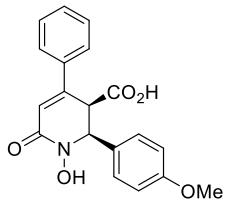
(0.393 mg, 5.5 mmol) at ambient temperature. The mixture was stirred at 60 °C for 10 h. After being cooled to room temperature, EtOH was removed under reduced pressure. Water was added to the residue, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give pure title product.

Yield 475 mg (85 %), white solid, m.p. 162-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.5 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.25 – 8.19 (m, 1H), 7.66 (s, 1H), 7.58 – 7.48 (m, 2H), 7.22 – 7.14 (m, 1H), 3.39 (t, *J* = 5.9 Hz, 2H), 3.34 (t, *J* = 6.1 Hz, 2H), 2.88 (s, 6H), 2.66 (t, *J* = 6.1 Hz, 2H), 2.41 – 2.34 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 151.9, 133.3, 130.9, 130.6, 130.3, 130.2, 128.3, 123.3, 119.6, 115.5, 46.0, 45.6, 44.7, 31.3, 24.4. HRMS *m/z* $[M+Na]^+$ calculated for $C_{17}H_{21}N_3O_3SNa^+$ 370.1196, found 370.1201.

Synthesis of compound 12a.

To a stirred solution of phenylglutaconic anhydride (1 mmol) in DMSO (1 mL) in a screw-cap vial the corresponding oxime (1 mmol) was added at room temperature. The resulting mixture was stirred at room temperature for 48 h. Oxime conversion was controlled by ^{1}H NMR. The reaction mixture was diluted with DCM (10 mL) and extracted with saturated aq. $NaHCO_3$ (10 mL/mmol). The aqueous layer was separated and washed with DCM (5 mL/mmol). The pH of aqueous phase was then adjusted to 1 with concentrated aq. HCl at 0 °C. The formed precipitate was collected, washed with small amount of water and dried in air to afford pure products.

(2*SR*, 3*RS*)-1-Hydroxy-2-(4-methoxyphenyl)-6-oxo-4-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylic acid (12a)



Yield 213 mg (63%), beige solid, m.p. 155-156 °C (decomposition). Mixture of *cis*/*trans* isomers 5:1. Major isomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 9.27 (s, 1H), 7.69 – 7.60 (m, 2H), 7.46 – 7.40 (m, 3H), 7.37 – 7.31 (m, 2H), 6.93 – 6.86 (m, 2H), 6.47 (s, 1H), 5.19 (d, *J* = 6.0 Hz, 1H), 4.23 (d, *J* = 6.1 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.8, 166.5, 158.7, 146.3, 135.7, 129.8, 129.0, 128.9, 128.9, 126.2, 120.4, 113.2, 64.7, 55.1, 52.2. HRMS m/z $[M+Na]^+$ calculated for $C_{19}H_{17}NNaO_5^+$ 362.0999, found 362.0998.

General procedure 1 for synthesis of 1-hydroxypyridin-2(3*H*)-ones 13 (GP1)

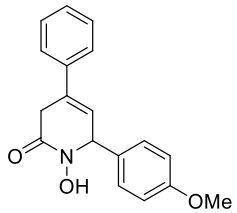
To a stirred solution of corresponding arylglutaconic anhydride **9** (0.5 mmol) in dry DMSO (0.5 mL) in a screw-cap vial the corresponding oxime (0.5 mmol) was added at room temperature. The resulting mixture was heated at 110 °C for 16 h (oil bath) under magnetic stirring. After

cooling to room temperature, the reaction mixture was diluted with water (10 mL) and ethyl acetate (15 mL). The organic layer was separated, washed with water (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with methanol - dichloromethane mixture (2%−40% of MeOH) to provide pure product **13**.

General procedure 2 for synthesis of 1-hydroxypyridin-2(3*H*)-ones 13 (GP2)

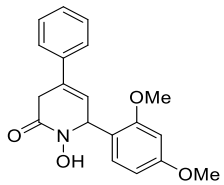
To a stirred solution of corresponding arylglutaconic anhydride **9** (0.5 mmol) in dry DMSO (0.5 mL) in a screw-cap vial the corresponding oxime (0.5 mmol) was added at room temperature. The resulting mixture was heated at 110 °C for 16 h (oil bath) under magnetic stirring. After cooling to room temperature, the reaction mixture was diluted with water (10 mL). The products were precipitated from reaction mixture as amorphous solid, filtered, washed with water (2*10 ml) and dried at room temperature on air to provide the pure compound **13**.

1-Hydroxy-6-(4-methoxyphenyl)-4-phenyl-3,6-dihydropyridin-2(1*H*)-one (13a)



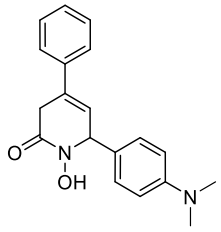
Synthesized according to GP1. Yield 95 mg (64%), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.47 – 7.30 (m, 5H), 7.29 – 7.23 (m, 2H), 6.97 – 6.87 (m, 2H), 6.10 (s, 1H), 5.45 (s, 1H), 3.80 (s, 3H), 3.70 – 3.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 160.0, 137.6, 130.8, 130.2, 128.9, 128.8, 128.6, 125.2, 121.1, 114.5, 63.7, 55.5, 33.5. HRMS m/z $[M-H]^-$ calculated for $C_{18}H_{16}NO_3^-$ 294.1136, found 294.1109.

6-(2,4-Dimethoxyphenyl)-1-hydroxy-4-phenyl-3,6-dihydropyridin-2(1*H*)-one (13b)



Synthesized according to GP1.Yield 73 mg (45%), amorphous beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 7.14 – 7.01 (m, 1H), 6.48 (s, 2H), 6.10 (s, 1H), 5.88 – 5.76 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.61 – 3.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 161.0, 158.1, 137.9, 130.0, 128.7, 128.4, 128.2, 125.1, 120.6, 118.5, 104.9, 99.1, 59.2, 55.8, 55.5, 33.5. HRMS m/z $[M+Na]^+$ calculated for $C_{19}H_{19}NNaO_4^+$ 348.1206, found 348.1210.

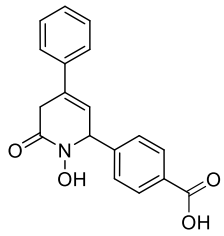
6-(4-(Dimethylamino)phenyl)-1-hydroxy-4-phenyl-1,6-dihydropyridin-2(3*H*)-one (13c)



Synthesized according to GP1. Yield 69 mg (45%), brown amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.44 – 7.30 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 2H), 6.14 – 6.09 (m, 1H), 5.40 (q, *J* = 4.3 Hz, 1H), 3.71 – 3.55 (m, 2H), 2.96 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 150.8,

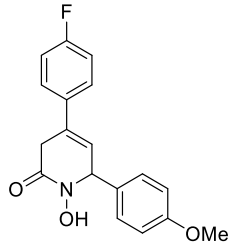
137.8, 130.4, 128.8, 128.5, 128.4, 125.5, 125.2, 121.5, 112.8, 63.7, 40.7, 33.4. HRMS m/z $[M+H]^+$ calculated for $C_{19}H_{21}N_2O_2^+$ 309.1598, found 309.1602.

4-(1-Hydroxy-6-oxo-4-phenyl-1,2,5,6-tetrahydropyridin-2-yl)benzoic acid (13d)



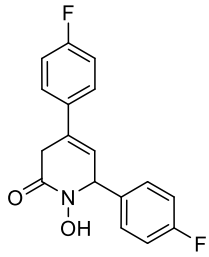
Synthesized according to GP2. Yield 82 mg (53%), beige solid, m.p. 245-246 °C. This synthesis was also performed on a larger scale (6.4 mmol), yield 1.02 g (52%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.93 (s, 1H), 9.76 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.41 (m, 4H), 7.42 – 7.25 (m, 3H), 6.26 – 6.16 (m, 1H), 5.55 – 5.46 (m, 1H), 3.80 – 3.66 (m, 1H), 3.53 – 3.41 (m, 1H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.0, 162.2, 144.9, 137.3, 130.8, 130.3, 129.7, 128.5, 128.1, 127.3, 125.1, 120.8, 65.1, 34.4. HRMS m/z $[M-H]^-$ calculated for $C_{18}H_{14}NO_4^-$ 308.0928, found 308.0916.

4-(4-Fluorophenyl)-1-hydroxy-6-(4-methoxyphenyl)-1,6-dihydropyridin-2(3*H*)-one (13e)



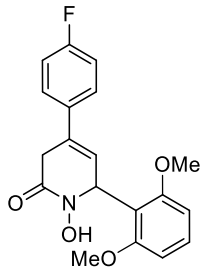
Synthesized according to GP1. Yield 78 mg (50%), white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H), 7.28 – 7.24 (m, 2H), 7.13 – 7.03 (m, 2H), 6.99 – 6.91 (m, 2H), 6.10 – 6.02 (m, 1H), 5.46 (q, *J* = 4.3 Hz, 1H), 3.84 (s, 3H), 3.71 – 3.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.4 Hz), 160.0, 133.7 (d, *J* = 3.3 Hz), 130.0, 129.8, 128.8, 127.0 (d, *J* = 8.1 Hz), 121.1, 115.8 (d, *J* = 21.6 Hz), 114.5, 114.1, 63.9, 55.5, 33.6. HRMS *m/z* $[M+Na]^+$ calculated for $C_{18}H_{16}FNNaO_3^+$ 336.1006, found 336.1012.

4,6-Bis(4-fluorophenyl)-1-hydroxy-1,6-dihydropyridin-2(3*H*)-one (13f)



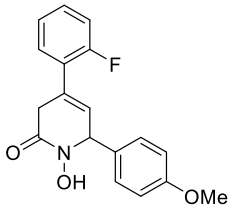
Synthesized according to GP1. Yield 84 mg (56%), beige solid, m.p. 123-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.46 – 7.27 (m, 4H), 7.20 – 6.98 (m, 4H), 6.01 (s, 1H), 5.47 (s, 1H), 3.72 – 3.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (d, *J* = 251.7 Hz), 163.0 (d, *J* = 245.1 Hz), 161.5, 133.9 (d, *J* = 3.0 Hz),133.6 (d, *J* = 3.1 Hz), 130.4, 129.2 (d, *J* = 8.3 Hz), 127.0 (d, *J* = 8.1 Hz), 120.6, 116.1 (d, *J* = 21.0 Hz), 115.9 (d, *J* = 20.8 Hz), 63.5, 33.5. HRMS m/z $[M+Na]^+$ 324.0807 calculated for $C_{17}H_{13}F_2NNaO_2^+$, found 324.0812.

6-(2,6-Dimethoxyphenyl)-4-(4-fluorophenyl)-1-hydroxy-3,6-dihydropyridin-2(1*H*)-one 13g)



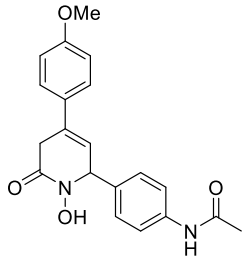
Synthesized according to GP1. Yield 69 mg (40%), brown solid, m.p. 205-206 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 7.60 – 7.48 (m, 2H), 7.23 (t, J = 8.3 Hz, 1H), 7.15 (t, J = 8.7 Hz, 2H), 6.66 (s, 2H), 5.96 (d, J = 2.6 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.55 – 3.37 (m, 1H), 3.36 – 3.21 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 161.3 (d, J = 245.2 Hz), 158.4, 134.3, 129.8, 128.6, 126.5 (d, J = 8.1 Hz), 118.9, 114.5 (d, J = 21.3 Hz), 114.2, 104.8, 55.8, 55.3, 34.7. HRMS m/z [M+Na]$^+$ calculated for $C_{19}H_{18}FNNaO_4^+$ 366.1112, found 366.1119.

4-(2-Fluorophenyl)-1-hydroxy-6-(4-methoxyphenyl)-3,6-dihydropyridin-2(1*H*)-one (13h)



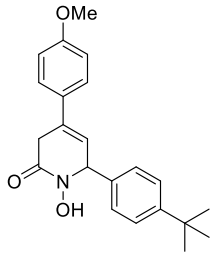
Synthesized according to GP1. Yield 83 mg (53%), beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 9.72 (s, 1H), 7.37 – 7.18 (m, 4H), 7.18 – 6.98 (m, 2H), 6.87 (d, J = 7.3 Hz, 2H), 5.96 (s, 1H), 5.33 (s, 1H), 3.76 (s, 3H), 3.62 (d, J = 21.3 Hz, 1H), 3.54 – 3.37 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$ + DMSO-d_6) δ 161.0, 158.8 (d, J = 248.1 Hz), 158.4, 129.9, 128.7 (d, J = 8.5 Hz), 128.0 (d, J = 3.7 Hz), 127.7, 126.4, 125.3 (d, J = 12.9 Hz), 124.7 (d, J = 4.2 Hz), 123.4 (d, J = 3.1 Hz), 115.0 (d, J = 22.7 Hz), 113.0, 64.0, 54.2, 34.6 (d, J = 4.2 Hz). HRMS m/z [M+Na]$^+$ calculated for $C_{18}H_{16}FNNaO_3^+$ 336.1006, found 336.1009.

***N*-(4-(1-Hydroxy-4-(4-methoxyphenyl)-6-oxo-1,2,5,6-tetrahydropyridin-2-yl)phenyl)acetamide (13i)**



Synthesized according to GP2. Yield 44 mg (25%), brown solid, m.p. 222-224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.58 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 6.12 – 6.03 (m, 1H), 5.34 – 5.24 (m, 1H), 3.75 (s, 3H), 3.70 – 3.60 (m, 1H), 3.45 – 3.35 (m, 1H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 162.0, 159.1, 138.9, 134.6, 129.8, 129.5, 127.6, 126.3, 119.6, 119.1, 113.8, 64.9, 55.1, 34.4, 23.9. HRMS m/z [M+Na]$^+$ calculated for $C_{20}H_{20}N_2NaO_4^+$ 375.1315, found 375.1320.

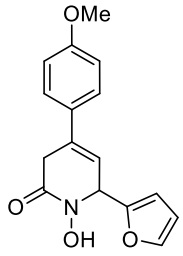
6-(4-(*tert*-Butyl)phenyl)-1-hydroxy-4-(4-methoxyphenyl)-3,6-dihydropyridin-2(1*H*)-one (13j)



Synthesized according to GP1. Yield 109 mg (62%), brown solid, m.p. 119-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.01 (s, 1H), 5.45 (s, 1H), 3.81 (s, 3H), 3.69 – 3.54 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 159.9, 151.7, 135.4, 130.1, 130.1, 127.1, 126.4, 126.0, 119.4, 114.2,

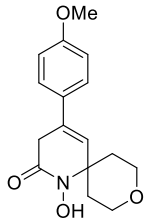
63.8, 55.5, 34.7, 33.5, 31.4. HRMS m/z $[M+Na]^+$ calculated for $C_{22}H_{25}NNaO_3^+$ 374.1727, found 374.1728.

6-(Furan-2-yl)-1-hydroxy-4-(4-methoxyphenyl)-3,6-dihydropyridin-2(1H)-one (13k)



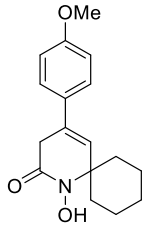
Synthesized according to GP1 at 70 °C. Yield 36 mg (25%), amorphous beige solid. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 9.24 (s, 1H), 7.19 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 6.71 – 6.64 (m, 2H), 6.21 – 6.10 (m, 2H), 5.86 – 5.77 (m, 1H), 5.27 (q, *J* = 4.0 Hz, 1H), 3.60 (s, 3H), 3.46 – 3.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$ + DMSO-d_6) δ 162.7, 159.3, 150.7, 142.3, 131.7, 129.6, 125.9, 116.0, 113.6, 110.2, 108.2, 58.5, 54.9, 34.3. HRMS m/z $[M+Na]^+$ calculated for $C_{16}H_{15}NNaO_4^+$ 308.0894, found 308.0898.

1-Hydroxy-4-(4-methoxyphenyl)-9-oxa-1-azaspiro[5.5]undec-4-en-2-one (13l)



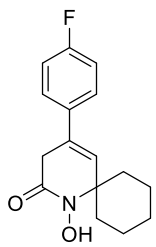
Synthesized according to GP2. Yield 110 mg (76%), beige solid, m.p. 182-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.45 (s, 1H), 4.12 – 3.98 (m, 2H), 3.83 (s, 3H), 3.78 – 3.67 (m, 2H), 3.48 (s, 2H), 2.74 – 2.62 (m, 2H), 1.59 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 160.0, 130.4, 130.2, 126.5, 120.4, 114.3, 64.5, 60.7, 55.5, 34.8, 33.4. HRMS m/z $[M+Na]^+$ calculated for $C_{16}H_{19}NNaO_4^+$ 312.1206, found 312.1208.

1-Hydroxy-4-(4-methoxyphenyl)-1-azaspiro[5.5]undec-4-en-2-one (13m)



Synthesized according to GP1. Yield 112 mg (78%), brown amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.39 – 7.30 (m, 2H), 6.93 – 6.86 (m, 2H), 6.42 (s, 1H), 3.83 (s, 3H), 3.46 (s, 2H), 2.39 – 2.26 (m, 2H), 1.87 – 1.71 (m, 4H), 1.71 – 1.51 (m, 4H), 1.38 – 1.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 159.8, 130.9, 128.8, 126.4, 122.0, 114.2, 63.4, 55.5, 34.9, 33.3, 25.1, 22.8. HRMS m/z $[M+Na]^+$ calculated for $C_{17}H_{21}NNaO_3^+$ 310.1414, found 310.1415.

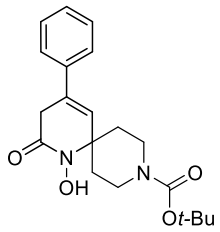
4-(4-Fluorophenyl)-1-hydroxy-1-azaspiro[5.5]undec-4-en-2-one (13n)



Synthesized according to GP1. Yield 83 mg (60%), beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.35 (s, 2H), 7.06 (t, *J* = 7.6 Hz, 2H), 6.44 (s, 1H), 3.44 (s, 2H), 2.43 – 2.25 (m, 2H), 1.88 – 1.71 (m, 3H), 1.70 – 1.48 (m, 4H), 1.38 – 1.18 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (d, *J* = 248.0 Hz), 162.1, 134.6 (d, *J* = 3.3 Hz), 128.6, 127.0 (d, *J* = 8.0 Hz), 123.7 (d, *J* = 1.4 Hz), 115.7 (d, *J* = 21.5

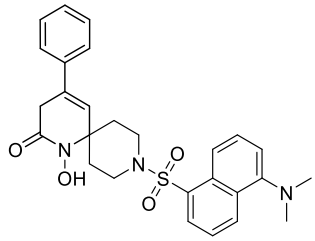
Hz), 63.5, 34.7, 33.5, 25.0, 22.8. HRMS *m/z* $[M+Na]^+$ calculated for $C_{16}H_{18}FNNaO_2^+$ 298.1214, found 298.1220.

***tert*-Butyl 1-hydroxy-2-oxo-4-phenyl-1,9-diazaspiro[5.5]undec-4-ene-9-carboxylate (13o)**



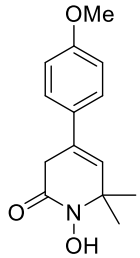
Synthesized according to GP2. Yield 129 mg (72%), beige solid, m.p. 178-179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H), 6.41 (s, 1H), 4.14 (d, *J* = 13.7 Hz, 2H), 3.53 (d, *J* = 1.6 Hz, 2H), 3.20 – 3.06 (m, 2H), 2.49 (td, *J* = 12.7, 4.9 Hz, 2H), 1.66 (d, *J* = 13.5 Hz, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 154.8, 137.9, 131.1, 128.9, 128.7, 125.9, 125.3, 121.9, 80.1, 61.6, 34.1, 33.3, 28.6. HRMS m/z $[M+Na]^+$ calculated for $C_{20}H_{26}N_2O_4Na^+$ 381.1785, found – 381.1770.

9-((5-(Dimethylamino)naphthalen-1-yl)sulfonyl)-1-hydroxy-4-phenyl-1,9-diazaspiro[5.5]undec-4-en-2-one (13p)



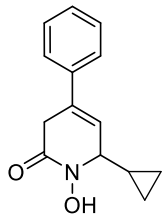
Synthesized according to GP2. Yield 234 mg (95%), beige solid, m.p. 212-214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.52 (d, *J* = 8.3 Hz, 1H), 8.30 – 8.11 (m, 2H), 7.71 – 7.58 (m, 2H), 7.58 – 7.48 (m, 2H), 7.38 – 7.22 (m, 4H), 6.60 (s, 1H), 3.76 (d, *J* = 12.4 Hz, 2H), 3.40 (s, 2H), 3.34 – 3.21 (m, 2H), 2.84 (s, 6H), 2.30 (t, *J* = 10.5 Hz, 2H), 1.58 (d, *J* = 12.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 152.0, 137.7, 133.3, 131.6, 131.0, 130.7, 130.4, 130.3, 128.9, 128.9, 128.4, 125.3, 123.3, 121.7, 119.6, 115.5, 60.7, 45.6, 42.2, 34.2, 33.1. HRMS m/z $[M+H]^+$ calculated for $C_{27}H_{30}N_3O_4S^+$ 492.1952, found 492.1964.

1-Hydroxy-4-(4-methoxyphenyl)-6,6-dimethyl-3,6-dihydropyridin-2(1*H*)-one (13q)



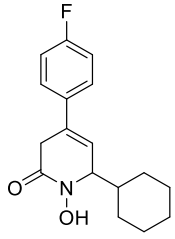
Synthesized according to GP2 at 70 °C. Yield 103 mg (83%), amorphous beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.89 (t, *J* = 1.6 Hz, 1H), 3.82 (s, 3H), 3.45 (d, *J* = 1.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 159.8, 130.3, 128.0, 126.29, 126.27, 114.2, 61.0, 55.5, 33.2, 27.2. HRMS m/z $[M+Na]^+$ calculated for $C_{14}H_{17}NNaO_3^+$ 270.1101, found 270.1105.

6-Cyclopropyl-1-hydroxy-4-phenyl-1,6-dihydropyridin-2(3*H*)-one (13r)



Synthesized according to GP1. Yield 70 mg (61%), beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.47 – 7.29 (m, 5H), 6.07 (d, *J* = 3.4 Hz, 1H), 3.95 – 3.81 (m, 1H), 3.60 – 3.39 (m, 2H), 1.18 – 1.06 (m, 1H), 0.80 – 0.66 (m, 2H), 0.63 – 0.49 (m, 1H), 0.36 – 0.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 137.9, 131.9, 128.8, 128.5, 125.2, 119.9, 64.1, 33.5, 15.3, 4.8, 0.9. HRMS m/z $[M+H]^+$ calculated for $C_{14}H_{16}NO_2^+$ 230.1176, found 230.1179.

6-Cyclohexyl-4-(4-fluorophenyl)-1-hydroxy-1,6-dihydropyridin-2(3*H*)-one (13s)

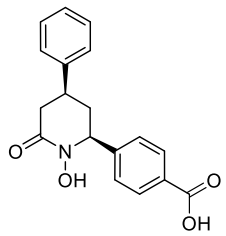


Synthesized according to GP1. Yield 62 mg (43%), yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.64 – 7.48 (m, 2H), 7.25 – 7.13 (m, 2H), 6.19 – 6.07 (m, 1H), 4.26 – 4.14 (m, 1H), 3.49 – 3.19 (m, 2H), 2.13 – 1.96 (m, 1H), 1.81 – 1.56 (m, 4H), 1.49 (d, *J* = 12.7 Hz, 1H), 1.26 – 1.01 (m, 4H), 1.01 – 0.90 (m, 1H). ^{13}C NMR (101 MHz, DMSO- *d6*) δ 162.1, 161.8 (d, *J* = 244.8 Hz), 134.4 (d, *J* = 3.2 Hz), 131.6, 127.2 (d, *J* = 8.1 Hz), 119.0 (d, *J* = 1.5 Hz), 115.2 (d, *J* = 21.3 Hz), 65.5, 40.2, 34.7, 28.4, 26.2, 26.1, 25.9, 25.5. HRMS *m/z* $[M-H]^-$ calculated for $C_{17}H_{19}FNO_2^-$ 288.1405, found 288.1412.

General procedure for hydrogenation of 13d.

To a stirred solution of compound **13d** (150 mg, 0.485 mmol) in MeOH-THF (10:1, 11 mL) Pd/C (5 mg of 10%wt) was added. The resulting suspension was stirred under the atmosphere of hydrogen gas (1 atm) for 24 h at room temperature. The reaction mixture was filtered through a pad of Celite to remove catalyst, washed with MeOH and THF, concentrated and purified by flash column chromatography eluting with DCM-MeOH (2%−20% of MeOH) to provide pure product **20**.

(±)-(*cis*)-4-(1-Hydroxy-6-oxo-4-phenylpiperidin-2-yl)benzoic acid (20)

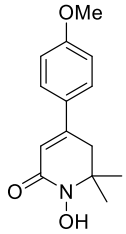


Yield 145 mg (96%), amorphous beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 9.31 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.25 (m, 4H), 7.25 – 7.16 (m, 1H), 4.96 – 4.84 (m, 1H), 3.28 – 3.20 (m, 1H), 2.91 – 2.75 (m, 1H), 2.32 – 2.17 (m, 1H), 2.14 – 1.97 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.1, 166.5, 146.6, 143.2, 129.8, 129.4, 128.5, 126.9, 126.7, 126.6, 64.8, 40.8, 39.8, 37.5. HRMS *m/z* $[M-H]^-$ calculated for $C_{18}H_{16}NO_4$ 310.1074, found 310.1060.

General procedure for isomerization of compound 13q.

The solution of compound **13q** (100 mg, 0.404 mmol) and DBU (184 mg, 1.215 mmol) in dry toluene (1.5 mL) was heated at 110 °C for 9 h (controlled by ^{1}H NMR). Upon cooling to room temperature, the mixture was diluted with 5 mL of DCM, washed with 3% HCl and water, dried over Na_2SO_4, and evaporated to dryness to afford pure title compound.

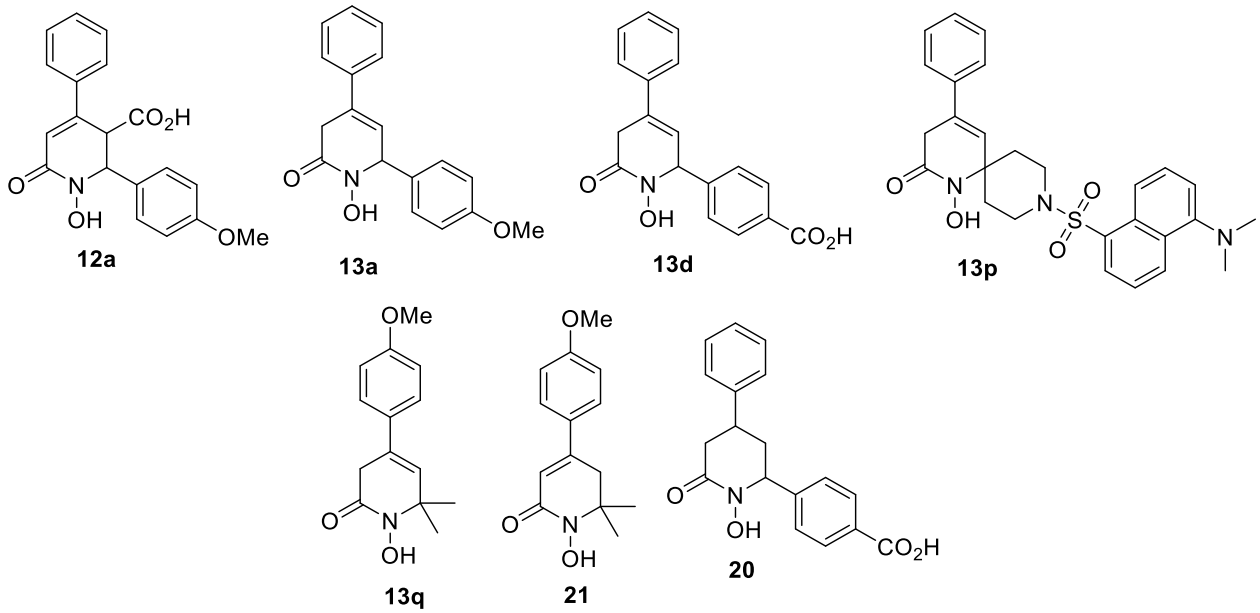
1-Hydroxy-4-(4-methoxyphenyl)-6,6-dimethyl-5,6-dihydropyridin-2(1*H*)-one (21)



Yield 98 mg (98%), beige solid, m.p. 145-150 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.25 (s, 1H), 3.84 (s, 3H), 2.88 (d, *J* = 1.2 Hz, 2H), 1.43 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 161.2, 147.7, 129.6, 127.4, 126.3, 114.4, 60.5, 55.5, 41.7, 24.5. HRMS *m/z* $[M+H]^+$ calculated for $C_{14}H_{18}NO_3^+$ 248.1281, found 248.1277.

Spectrophotometrical investigation of compounds 12,13,20,21 and their complexation with iron(III) chloride

Spectrophotometric measurements were performed on a UV-1900 Shimadzu double beam spectrophotometer using 10.00 mm quartz cells. MeOH or DMSO were used as solvents for compounds **13a, 13p, 12a** and **13d, 13t, 21, 20** respectively. All measurements were performed at room temperature (25 °C) in stoppered cells. For experiments with Fe^{3+} complexation, $Fe(NO_3)_3 \cdot 9H_2O$ was used as an iron source.



Absorbance spectra

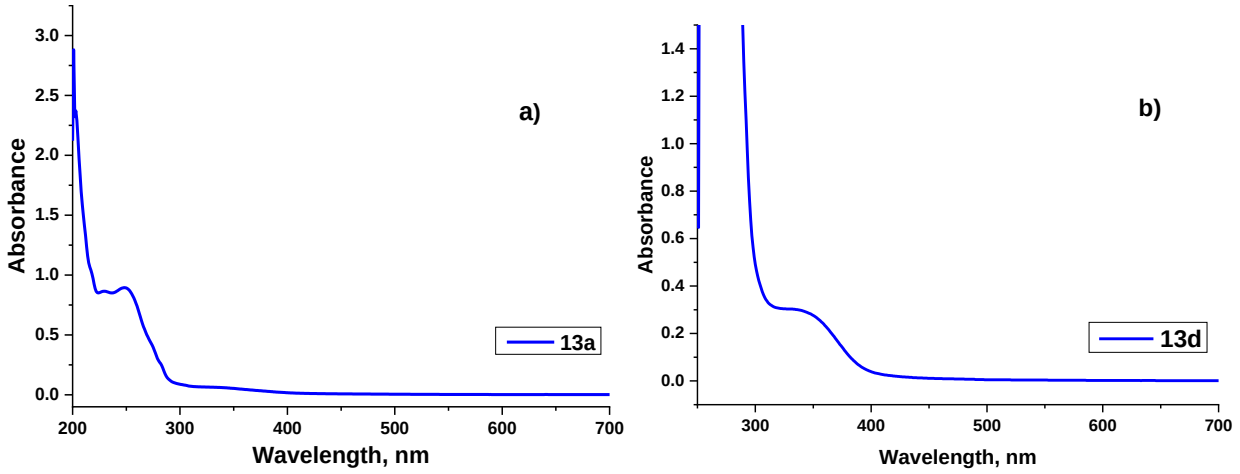


Figure S1. a) UV-Vis absorbance spectrum of compound **13a** recorded in MeOH ($C = 6.7\times10^{-5}$ M); b) UV-Vis absorbance spectrum of compound **13d** recorded in DMSO ($C = 5\times10^{-4}$ M);

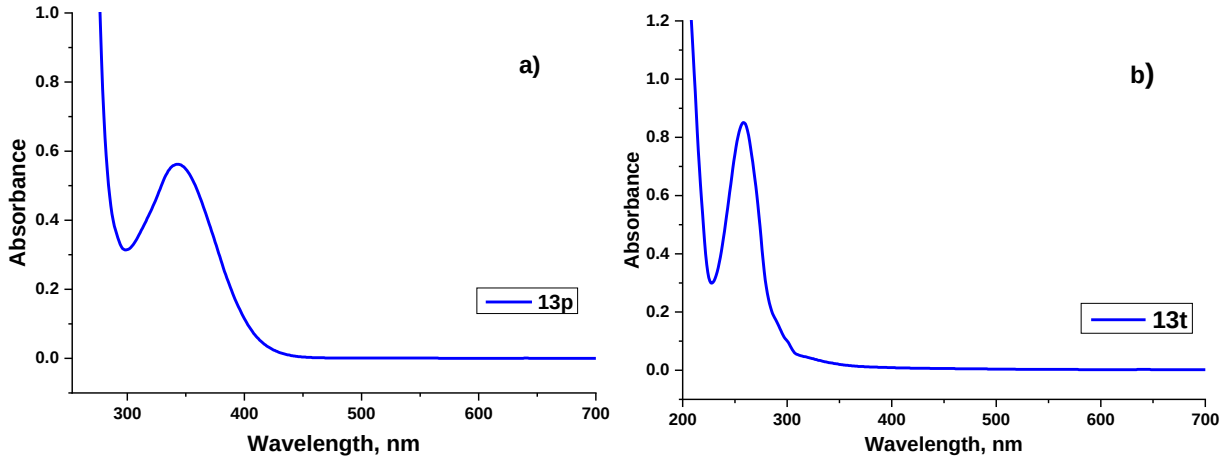


Figure S2. a) UV-Vis absorbance spectrum of compound **13p** recorded in MeOH (C = 6.7×10^{-5} M); b) UV-Vis absorbance spectrum of compound **13t** recorded in DMSO (C = 10^{-4} M);

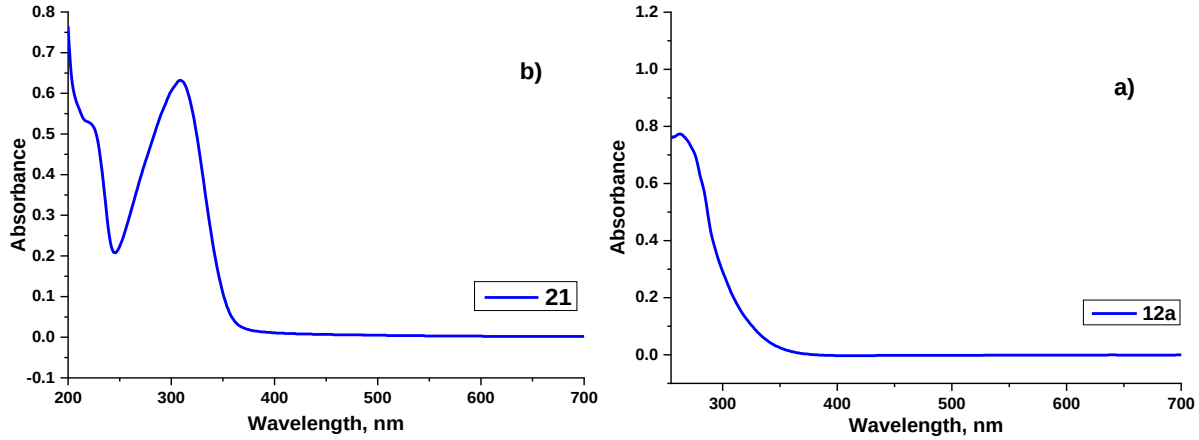


Figure S3. a) UV-Vis absorbance spectrum of compound **21** recorded in DMSO (C = 6.7×10^{-5} M); b) UV-Vis absorbance spectrum of compound **12a** recorded in MeOH (C = 6.7×10^{-5} M);

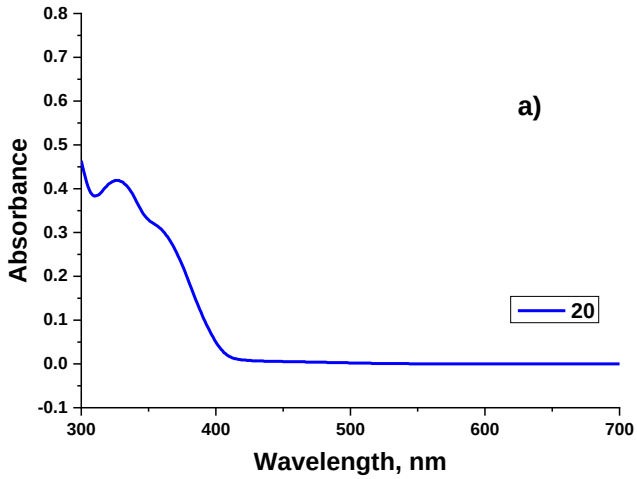


Figure S4.; a) UV-Vis absorbance spectrum of compound **20** recorded in DMSO (C = 6.7×10^{-5} M)

Electronic absorption spectra of compounds 12,13,20,21 in the presence of increasing concentration of Fe^{3+} and corresponding mole ratio plots

Sample preparation for UV-Vis titrations: a 150 μL aliquot of 0.01 M stock solution of compound in MeOH or DMSO was placed in a 10.00 mm quartz cuvette equipped with magnetic stir bar and diluted to 3 mL with 450 uL of water and 2400 uL of MeOH or DMSO to obtain solution in 85% aq. MeOH or DMSO ($C_L = 5\times10^{-4}$ M). 10 uL Aliquots of 7.5×10^{-3} M, 1.5×10^{-2} M and 7.5×10^{-2} M aqueous $Fe(NO_3)_3$ were added to the cell with calibrated micropipette in stepwise manner ($C_M = 0.25\times10^{-4}$ to 10×10^{-4} M). In the case of compound **21**, concentration of the ligand in 85% aq. DMSO was 2.5×10^{-4} M, with subsequent stepwise addition of 10 uL aliquots of 3.75×10^{-3} M, 7.5×10^{-3} M and 3.75×10^{-2} M aqueous $Fe(NO_3)_3$. The solution was vigorously stirred after addition of each aliquot followed by registration of absorbance spectrum (Fig.S5a-11a) over the wavelength range of 300–700 nm vs. 85% aq. MeOH or DMSO (all measurement were performed in stoppered cuvettes). Color of the solution was changed from colorless to purple. The absorbance at selected wavelength was plotted as a function of $[Fe^{3+}]$/[ligand] ratio to give binding isotherms presented on Fig.S5b-11b. The maxima of these curves correspond to the maximum formation of complexes and indicate to the stoichiometry of the complexes. The average stoichiometry of complex is estimated from the point where this curve changes its slope (this point is the intersect point of bilinear fitting of experimental curve). Formation constants K_1 and K_2 (Table S1) were calculated from curves presented on Fig.5b-11b using following equations:

$$K = \frac{[ML_X]}{[M][L]^X} \qquad (eq.1)$$

$$K_1K_2[L]^3 + K_1\big(1 + K_2(2C_M - C_L)\big)[L]^2 + \big(1 + K_1(C_M - C_L)\big)[L] = 0 \qquad (eq.2)$$

$$\Delta A_{obs} = \frac{\varepsilon_{\Delta ML}(C_M)K_1[L] + 2\varepsilon_{\Delta ML2}(C_M)K_1K_2[L]^2}{1 + K_1[L] + K_1K_2[L]^2} \qquad (eq.3)$$

X is a number of moles of ligand per-mol of metal ion, C_L and C_M are analytical concentrations of ligand and Fe^{3+} correspondingly.

Experimental curves were fitted to eq. 3 corresponding to 1:2 metal-to-ligand complex formation using nonlinear curve-fitting performed in ThordarsonFittingProgram.[4-5] The program is based on the iterative adjustment of calculated values of absorbance (A) to observed values using eq. 3 previously derived from eq. 1 and 2, where K_1 and K_2 are stepwise formation constants (also K_f in Table S1); $\varepsilon_{\Delta ML}=\varepsilon_{ML}-\varepsilon_L$ and $\varepsilon_{\Delta ML2}=\varepsilon_{ML2}-\varepsilon_{ML}$,where ε_i are molar absorptivities of corresponding species; C_L and C_M are analytical concentrations of ligand and Fe^{3+} respectively and L is free

ligand concentration. Other stoichiometries like 1:1 or 2:1 were also tested during curve fitting, but these models provided very low correlation to experimental data.

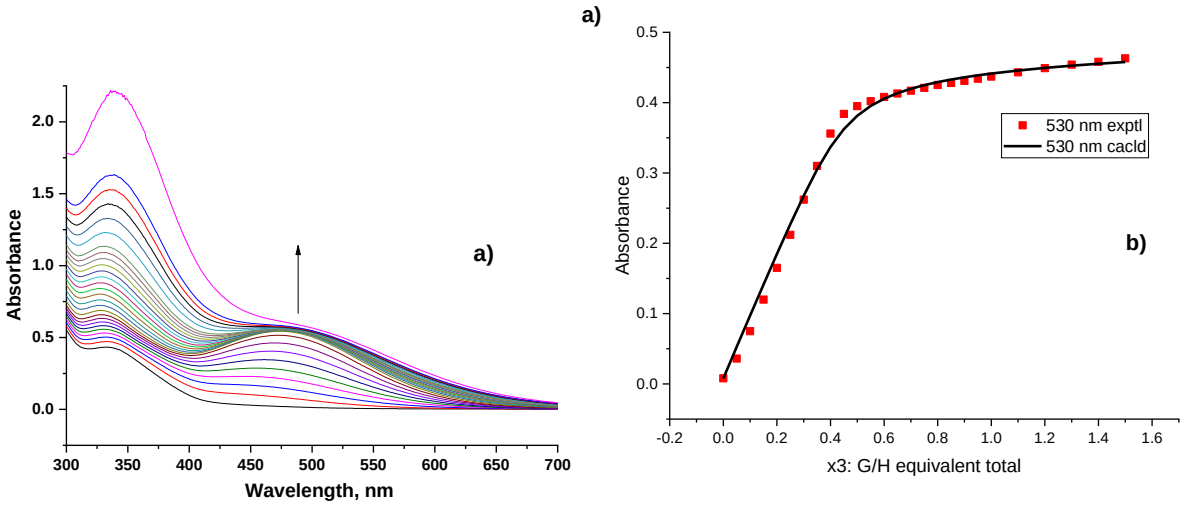


Figure S5. (a) Changes in UV-Vis spectrum of compound **13a** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plots in MeOH (red squares – experimental data, black line – nonlinear curve-fitting according to eq. 3).

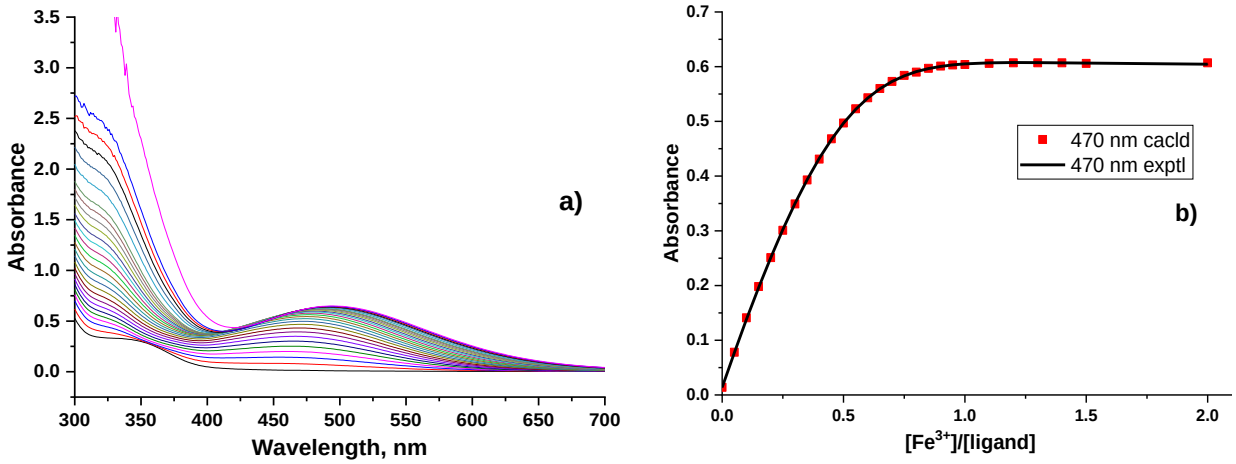


Figure S6. (a) Changes in UV-Vis spectrum of compound **13d** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plot (470 nm) in DMSO 85% (red squares – experimental data, black line – nonlinear curve-fitting according to eq. 3).

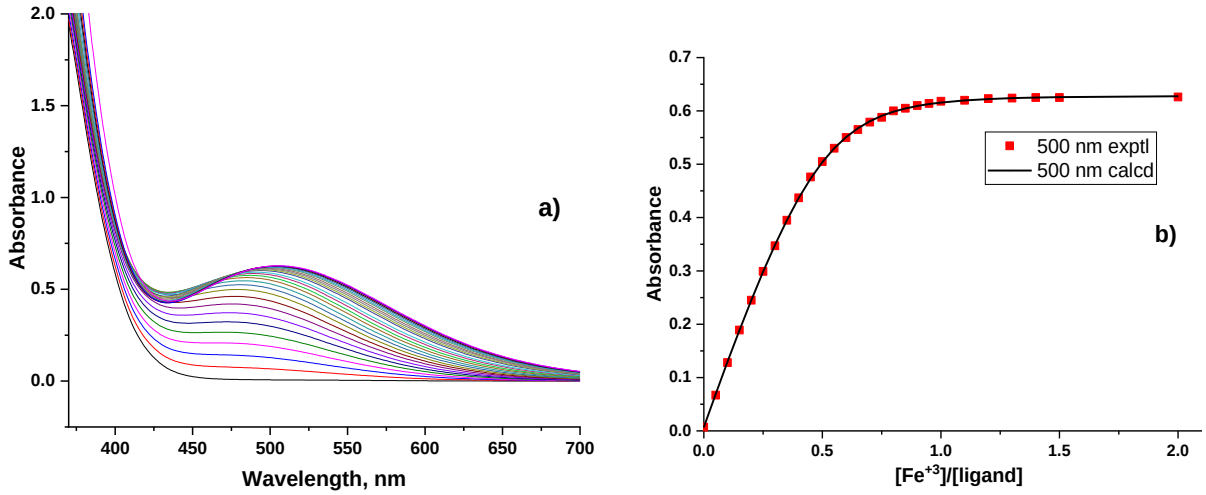


Figure S7. (a) Changes in UV-Vis spectrum of compound **13p** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plot (500 nm) in DMSO 85% (red squares – experimental data, black line – nonlinear curve-fitting according to eq. 3).

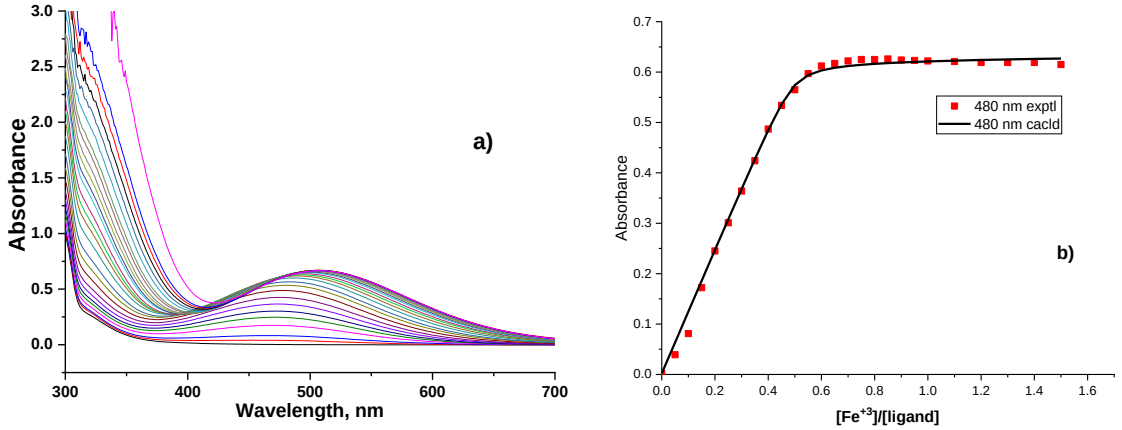


Figure S8. (a) Changes in UV-Vis spectrum of compound **13q** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plot (480 nm) in DMSO 85% (red squares – experimental data, black line – nonlinear curve-fitting according to eq. 3).

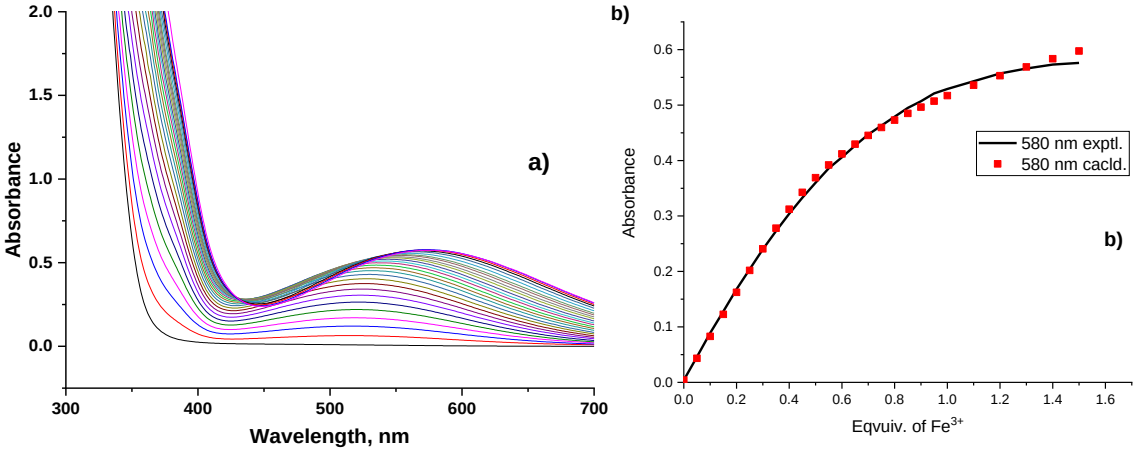


Figure S9. (a) Changes in UV-Vis spectrum of compound **21** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plot (580 nm) in DMSO 85% (red squares – experimental data, black line – nonlinear curve-fitting according to eq. 3).

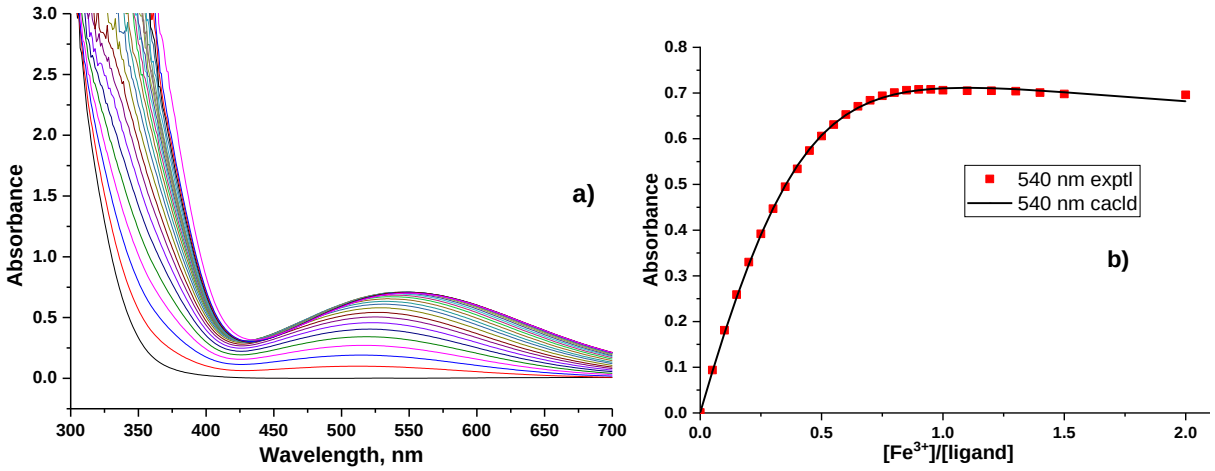


Figure S10. (a) Changes in UV-Vis spectrum of compound **12a** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plot (540 nm) in DMSO 85% (red asterisks – experimental data, black line – nonlinear curve-fitting according to eq. 3).

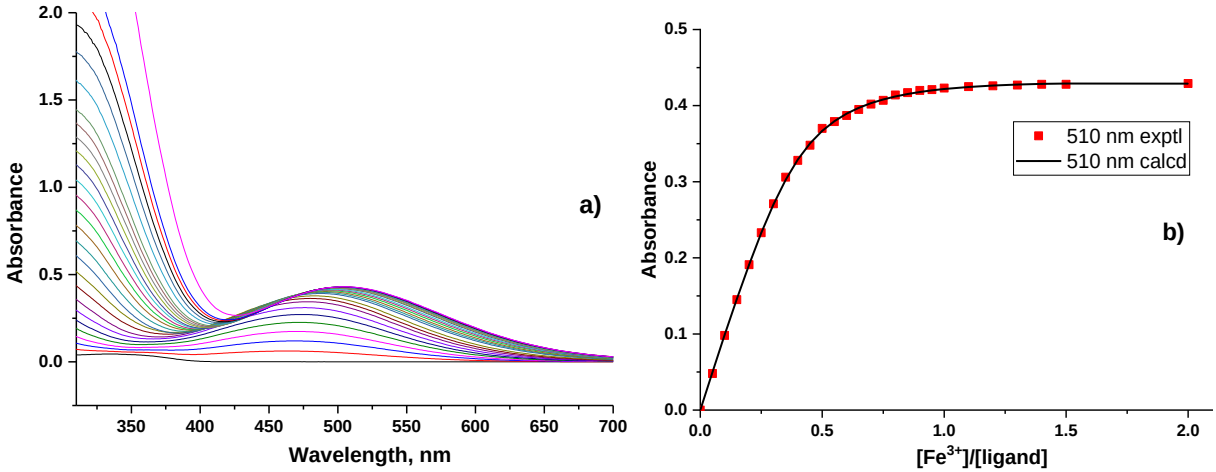


Figure S11. (a) Changes in UV-Vis spectrum of compound **20** upon addition of $Fe(NO_3)_3$; (b) corresponding mole ratio plot (510 nm) in DMSO 85% (red asterisks – experimental data, black line – nonlinear curve-fitting according to eq. 3).

Table S1. Results of UV-Vis titration of compound **12**,**13**,**20** and **21** with iron(III) ions. K*f* – stepwise formation constants, M:L – stoichiometry of the complex (M – metal, L - ligand). λ_{max} - absorbance maximum of Fe-complexes formed upon titration.

Ligand	Solvent	M:L	K*f*, M^{-1}	log K_f	λ_{max}, nm
13a	MeOH	1:1	3.79×10^3	3.58	480
		1:2	1.42×10^5	5.15	
13d	DMSO	1:1	8.22×10^4	4.91	470
		1:2	3.85×10^3	3.59	
13p	DMSO	1:1	7.90×10^4	4.90	500

		1:2	7.89×10^3	3.90	
13q	DMSO	1:1	1.63×10^5	5.21	500
		1:2	1.98×10^5	5.30	
12a	DMSO	1:1	1.15×10^4	4.06	540
		1:2	4.32×10^3	3.64	
20	DMSO	1:1	2.71×10^3	3.43	510
		1:2	5.12×10^4	4.71	
21	DMSO	1:1	1.45×10^3	3.17	550
		1:2	6.98×10^5	5.84	

Fluorescence measurements

Emission and excitation spectra (Fig.S12) were acquired for compound **13p** using Shimadzu RF-6000 spectrofluorimeter (10.00 mm stoppered quartz cell, ambient temperature) in DMSO+ 15%vol of 0.1M HEPES buffer solution (pH 7.0; concentration of **13p** 10 μM). Fluorescence quenching was observed upon addition of metal ions aliquotes (10 equiv. in 10 μL of 0.03 M aq. solution of $Pb(NO_3)_2$, $Cu(OAc)_2$, $Fe(NO_3)_3*9H_2O$, $Zn(NO_3)2*9H_2O$, NaCl, $MgCl_2$, $Co(OAc)_2*4H_2O$, $Ni(OAc)_2*2H_2O$, $Al(NO_3)_3*9H_2O$, $Mn(OAc)_2$, $CrCl_3$, $Cd(NO_3)_2*4H_2O$, $AgNO_3$, $Zr(NO_3)_4$, $Sc(OTf)_3$, $La(NO_3)_3$) to the solution of compound **13p** and the resulting F/F_0 (at 550 nm) values are presented on Fig.S13.

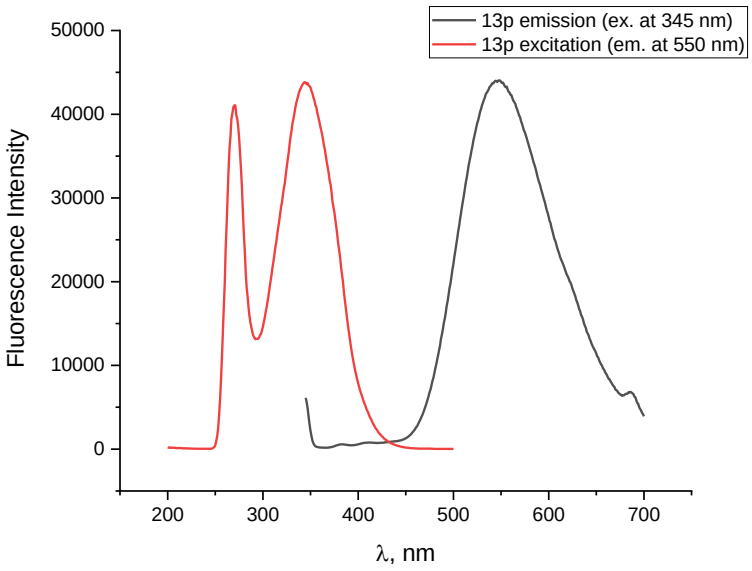


Fig.S12. Excitation and emission spectra of compound **13p** (aq.DMSO, 10μM). λ_{ex} = 345 nm, λ_{em} = 550 nm

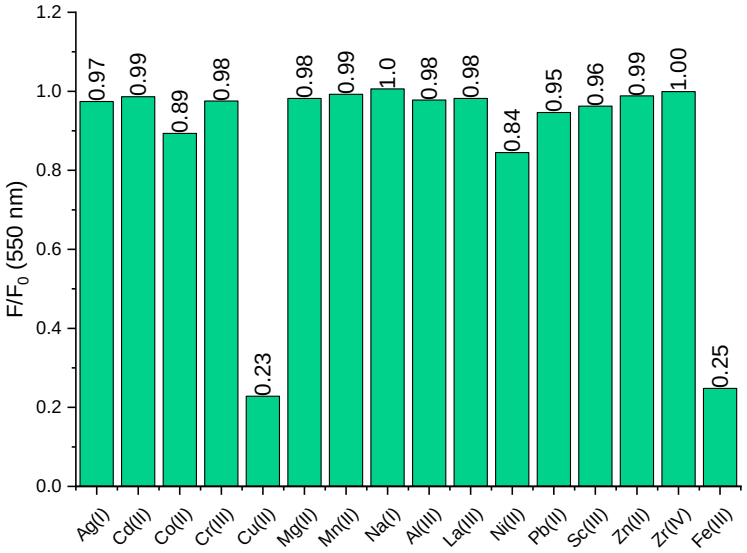


Fig.S13. Fluorescence quenching for compound **13p** upon addition of 10 equiv. of metal ions.

Crystallographic data

Single crystal X-ray data were obtained using Rigaku XtaLAB Synergy diffractometer. The crystals were kept at 100 K during data collection. Using Olex2 [6], the structure was solved with the SHELXT [7] structure solution program using Intrinsic Phasing and refined with the SHELXL [8] refinement package using Least Squares minimisation.

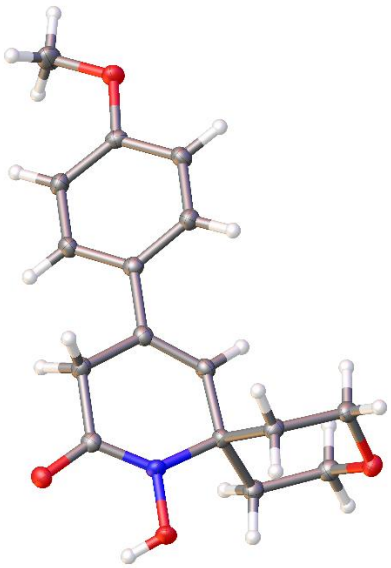


Figure S14. ORTEP representation of compound **13l** drawn at 50% probability level

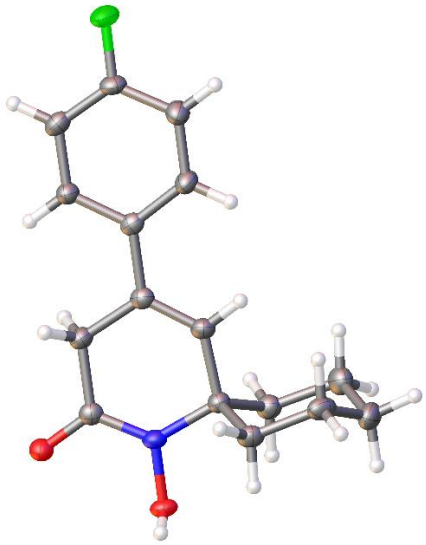


Figure S15. ORTEP representation of compound **13n** drawn at 50% probability level

Table S2. Crystal data and structure refinement for **13l** and **13n**

Identification code	**13l**	**13n**
Empirical formula	$C_{16}H_{19}NO_4$	$C_{16}H_{18}FNO_2$
Formula weight	289.32	275.31
Temperature/K	100.00(10)	100.15
Crystal system	monoclinic	trigonal
Space group	$P2_1$	$P3_1$
a/Å	7.8108(2)	9.9484(3)
b/Å	6.5963(2)	9.9484(3)
c/Å	13.6805(4)	11.8653(4)
α/°	90	90
β/°	96.914(2)	90
γ/°	90	120
Volume/Å^3	699.73(3)	1016.99(7)

Z	2	3
ρ_{calc}g/cm^3	1.373	1.349
μ/mm^{-1}	0.812	0.805
F(000)	308	438
Crystal size/mm^3	0.16 × 0.08 × 0.04	0.24 × 0.12 × 0.1
Radiation	Cu Kα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.508 to 154.434	10.268 to 159.654
Index ranges	-8 ≤ h ≤ 9, -8 ≤ k ≤ 8, -17 ≤ l ≤ 17	-12 ≤ h ≤ 12, -12 ≤ k ≤ 11, -12 ≤ l ≤ 14
Reflections collected	9975	10563
Independent reflections	2903 [R_{int} = 0.0386, R_{sigma} = 0.0384]	2685 [R_{int} = 0.0436, R_{sigma} = 0.0376]
Data/restraints/parameters	2903/1/192	2685/1/183
Goodness-of-fit on F^2	1.064	1.084
Final R indexes [I>=2σ (I)]	R_1 = 0.0322, wR_2 = 0.0834	R_1 = 0.0324, wR_2 = 0.0817
Final R indexes [all data]	R_1 = 0.0328, wR_2 = 0.0840	R_1 = 0.0344, wR_2 = 0.0827
Largest diff. peak/hole / e Å^{-3}	0.18/-0.25	0.18/-0.14
Flack parameter	-0.06(8)	0.17(12)
CCDC	2056273	2165922

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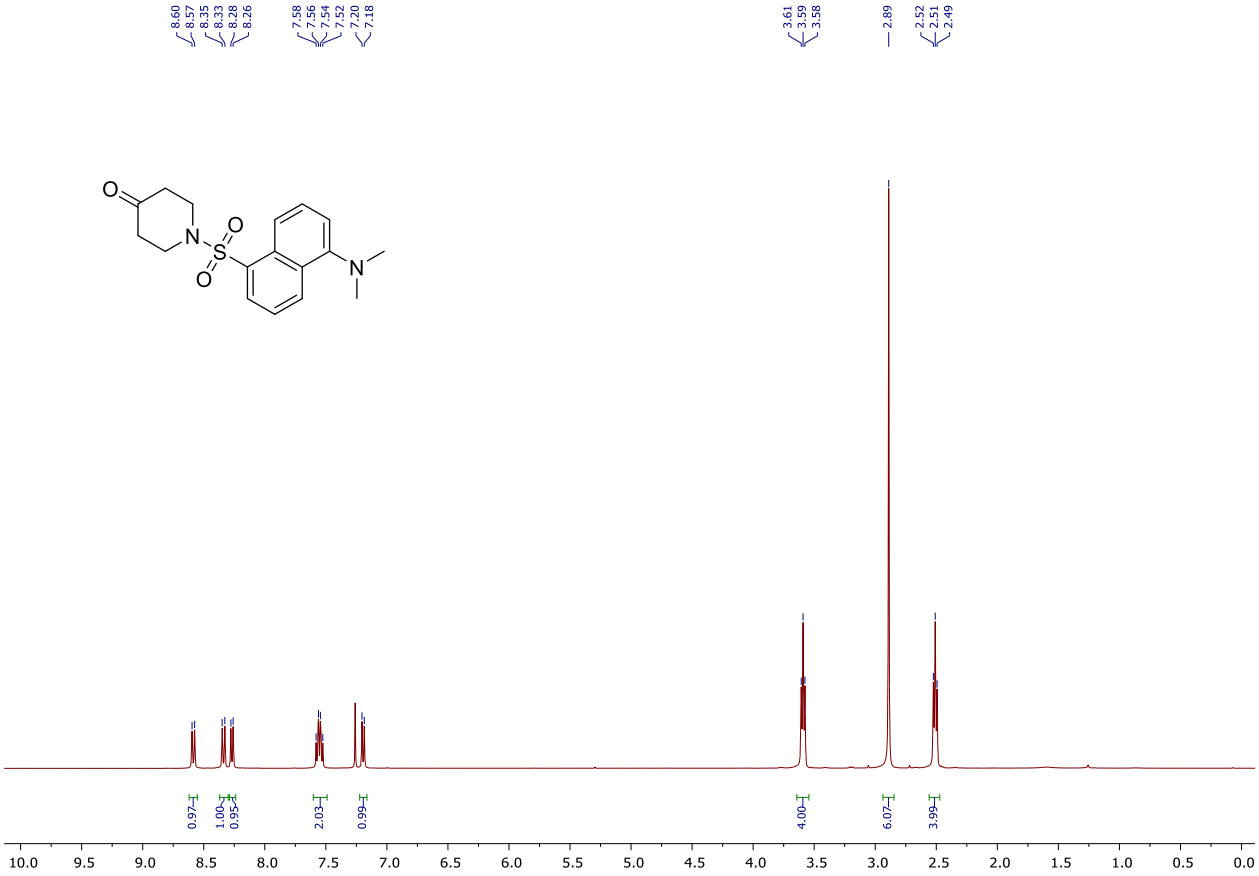
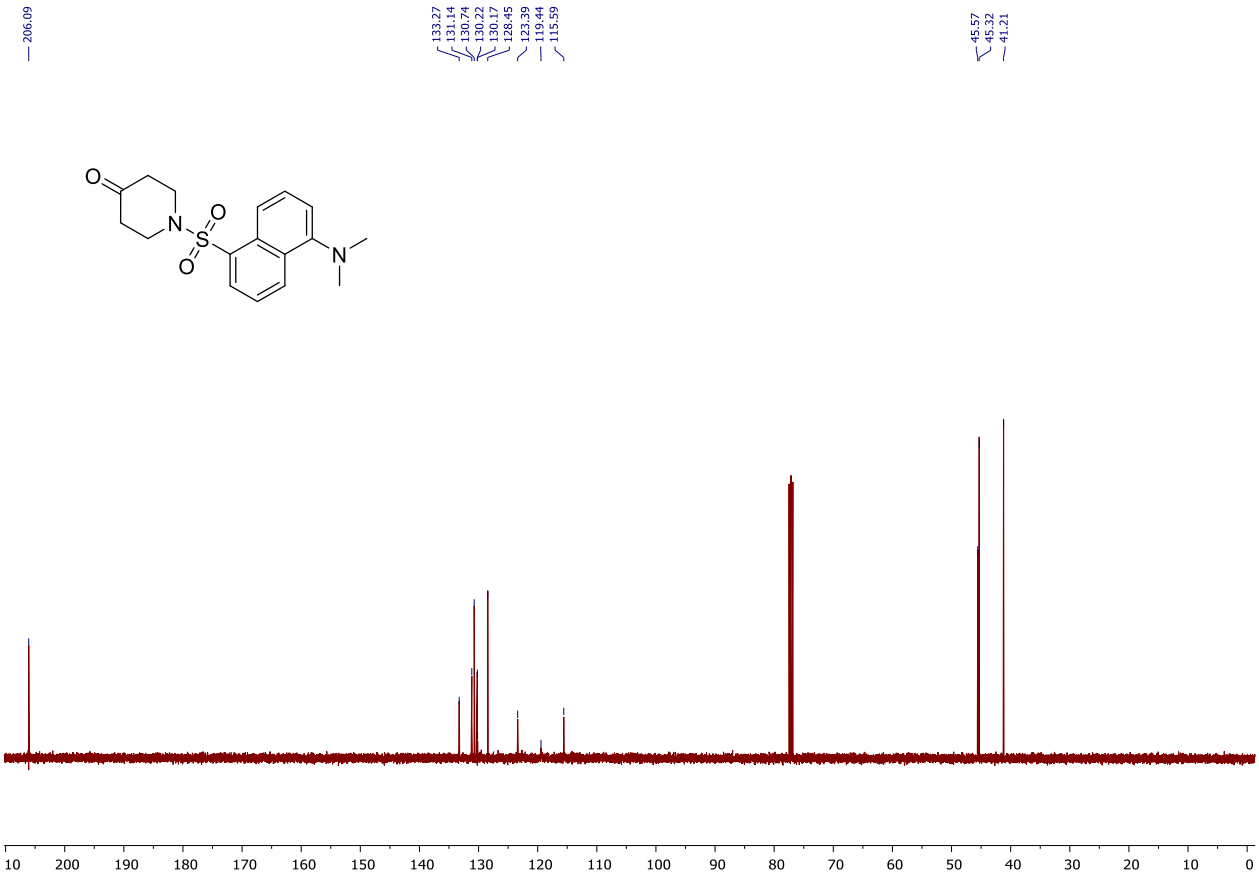
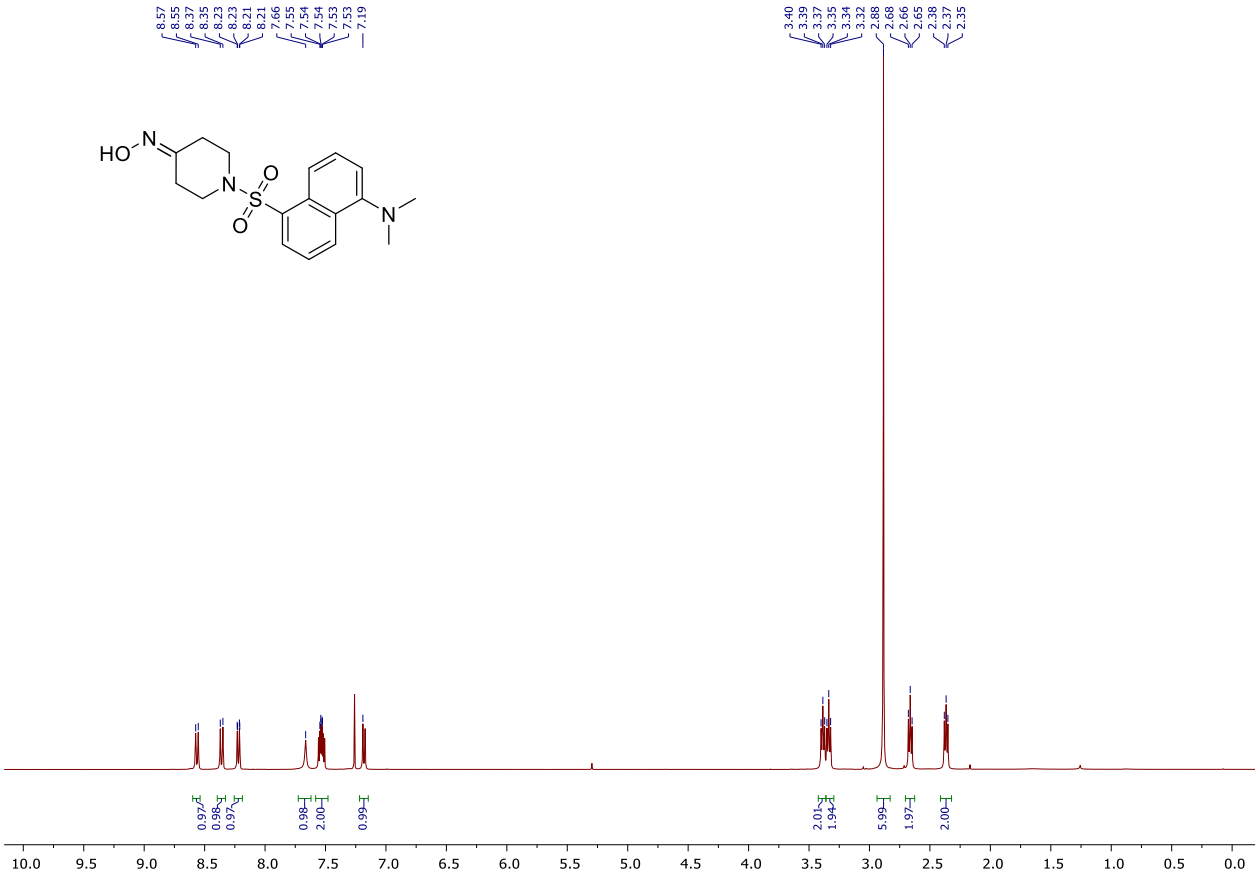
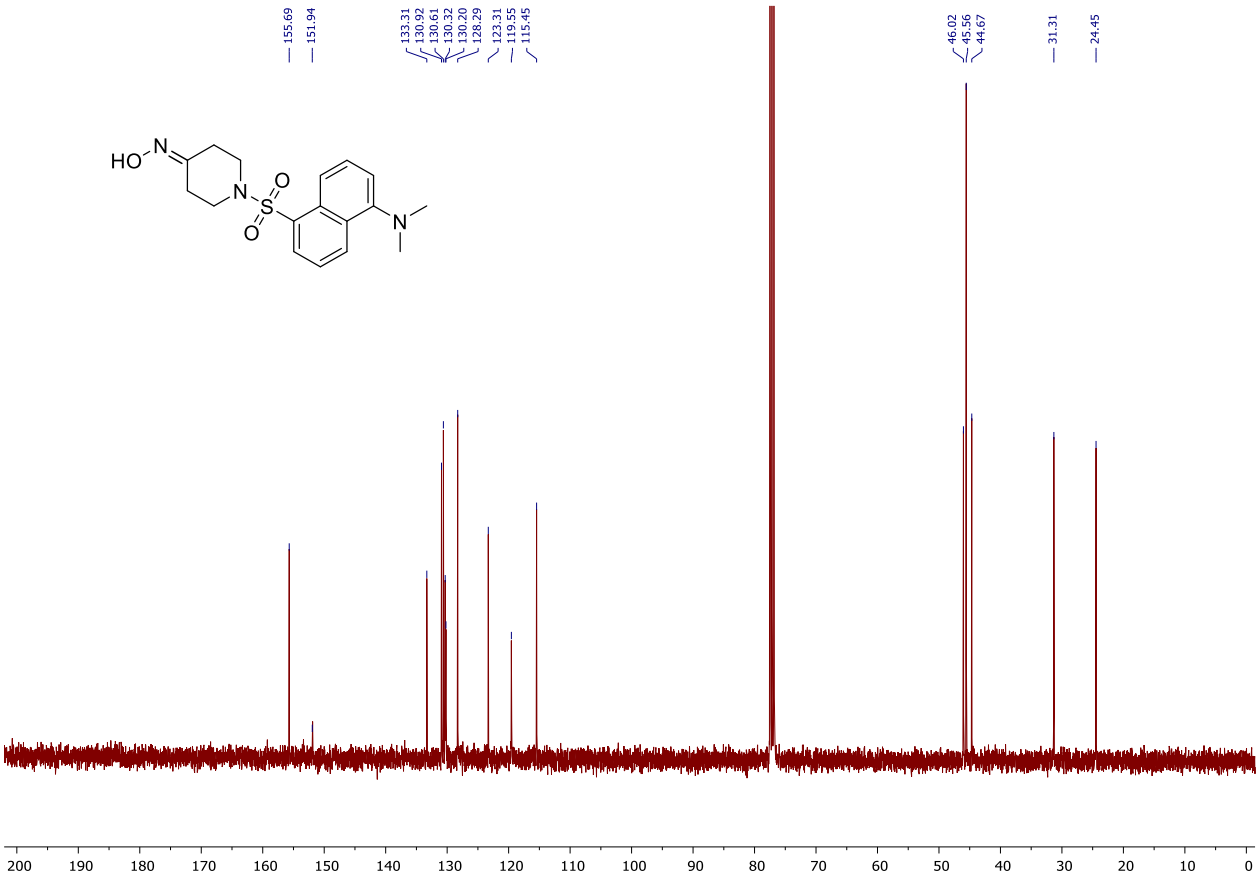
^{1}H and ^{13}C NMR spectra of 1-((5-(dimethylamino)naphthalen-1-yl)sulfonyl)piperidin-4-one



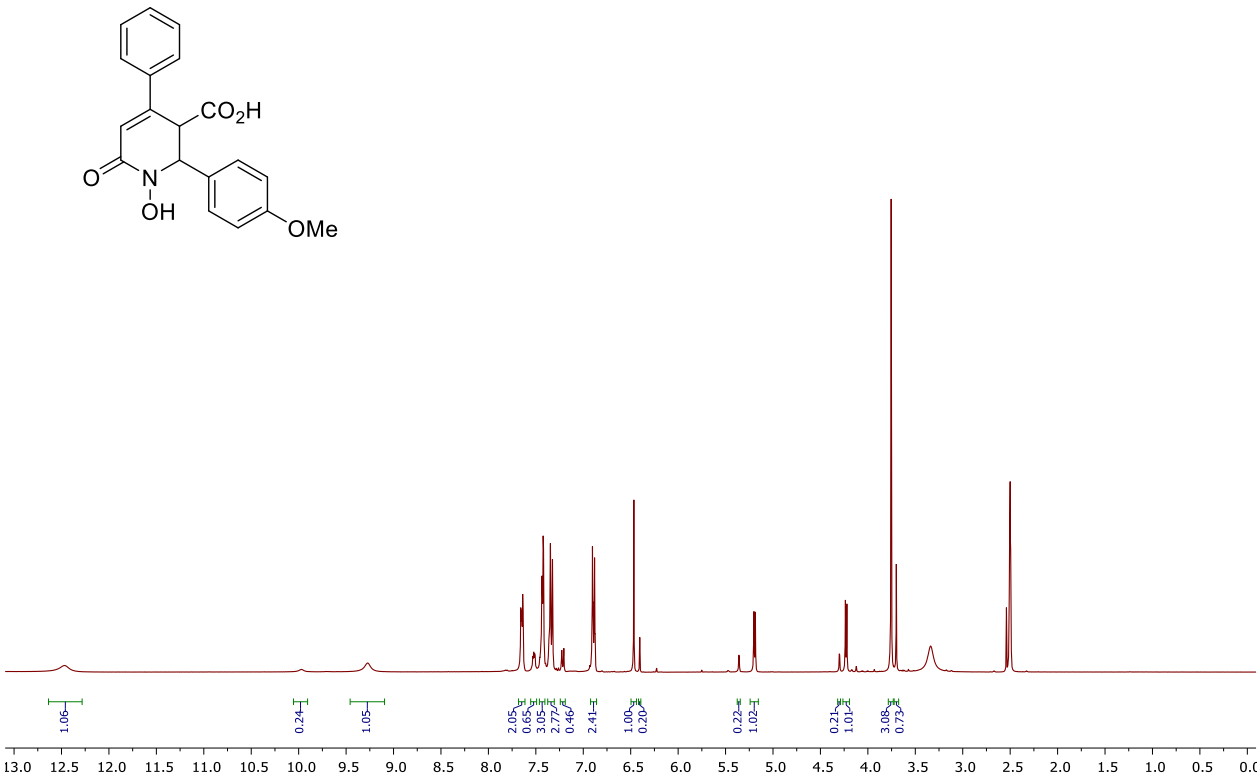


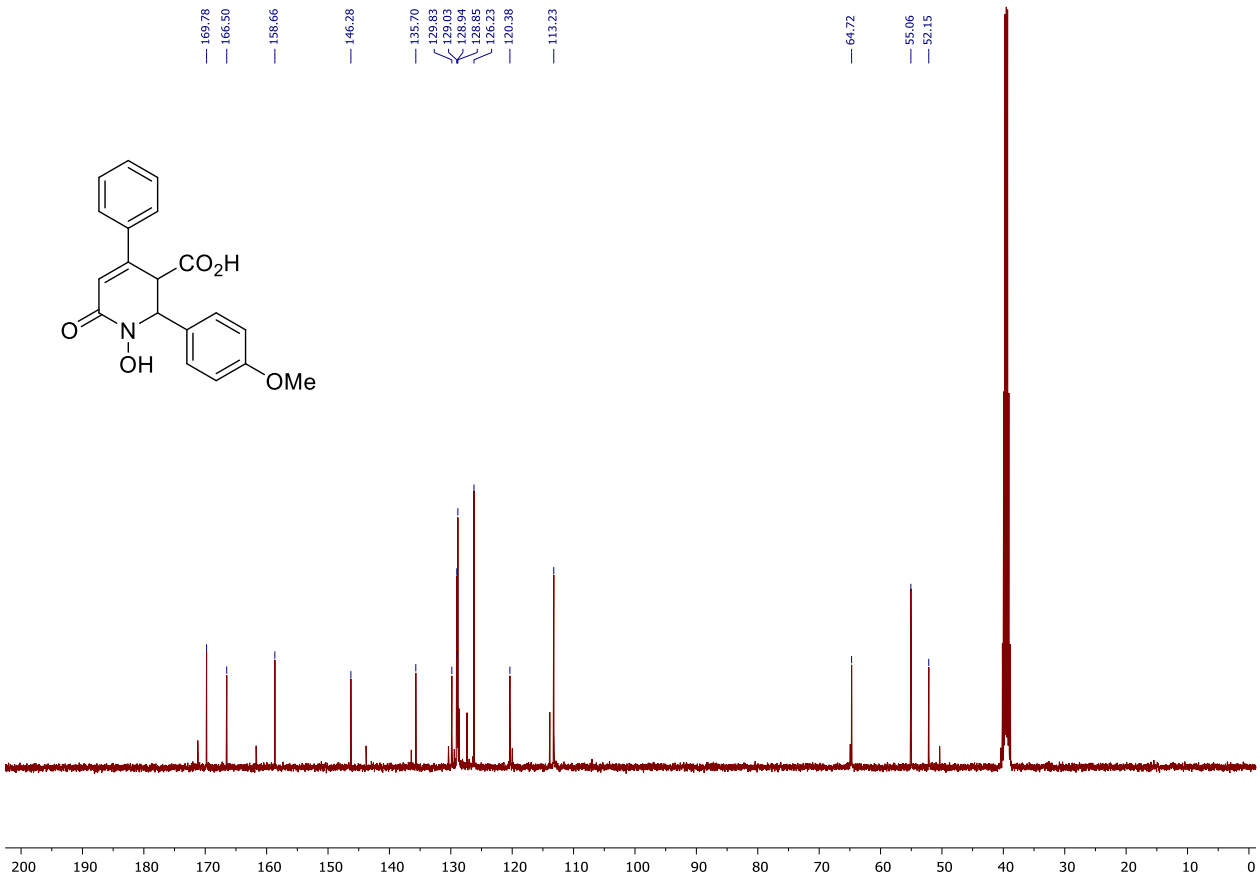
^{1}H and ^{13}C NMR spectra of 1-((5-(dimethylamino)naphthalen-1-yl)sulfonyl)piperidin-4-one oxime



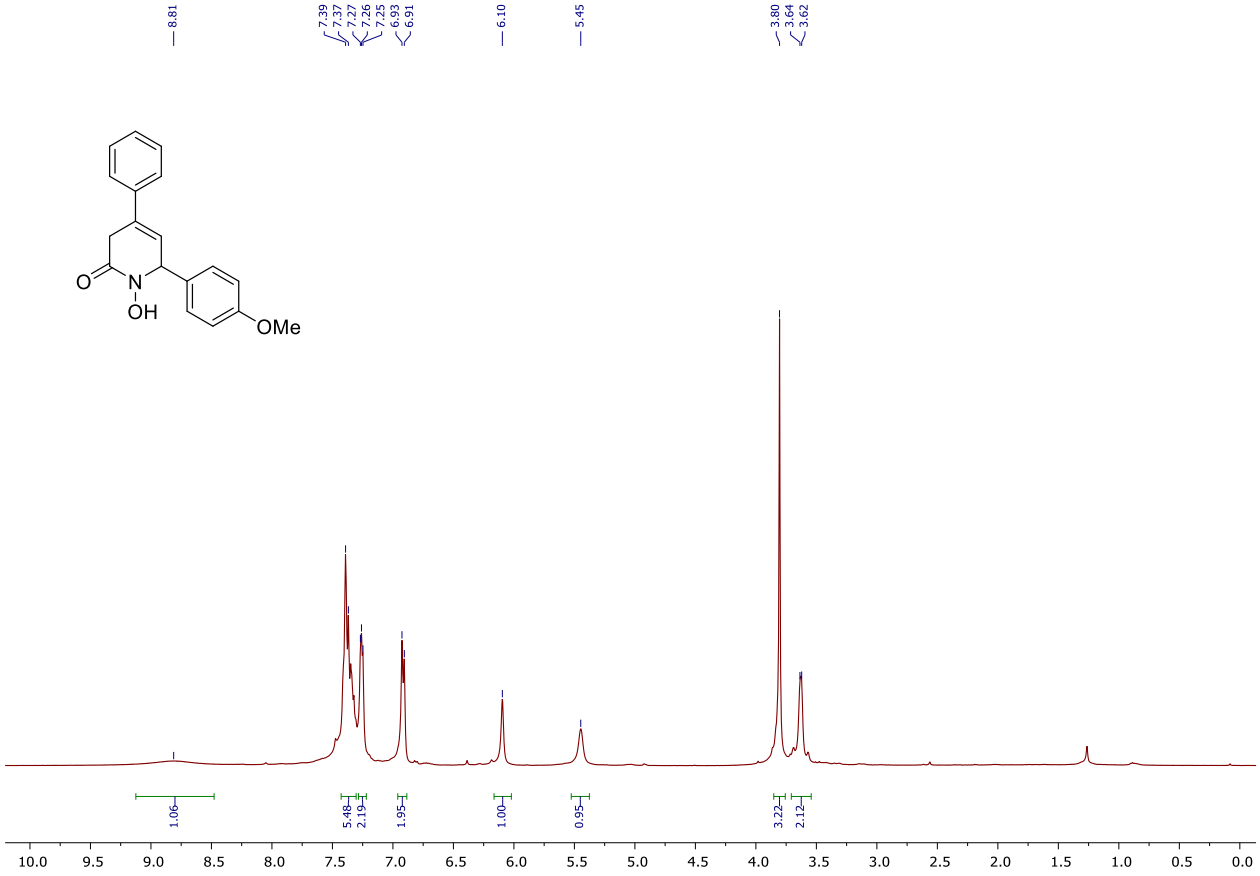


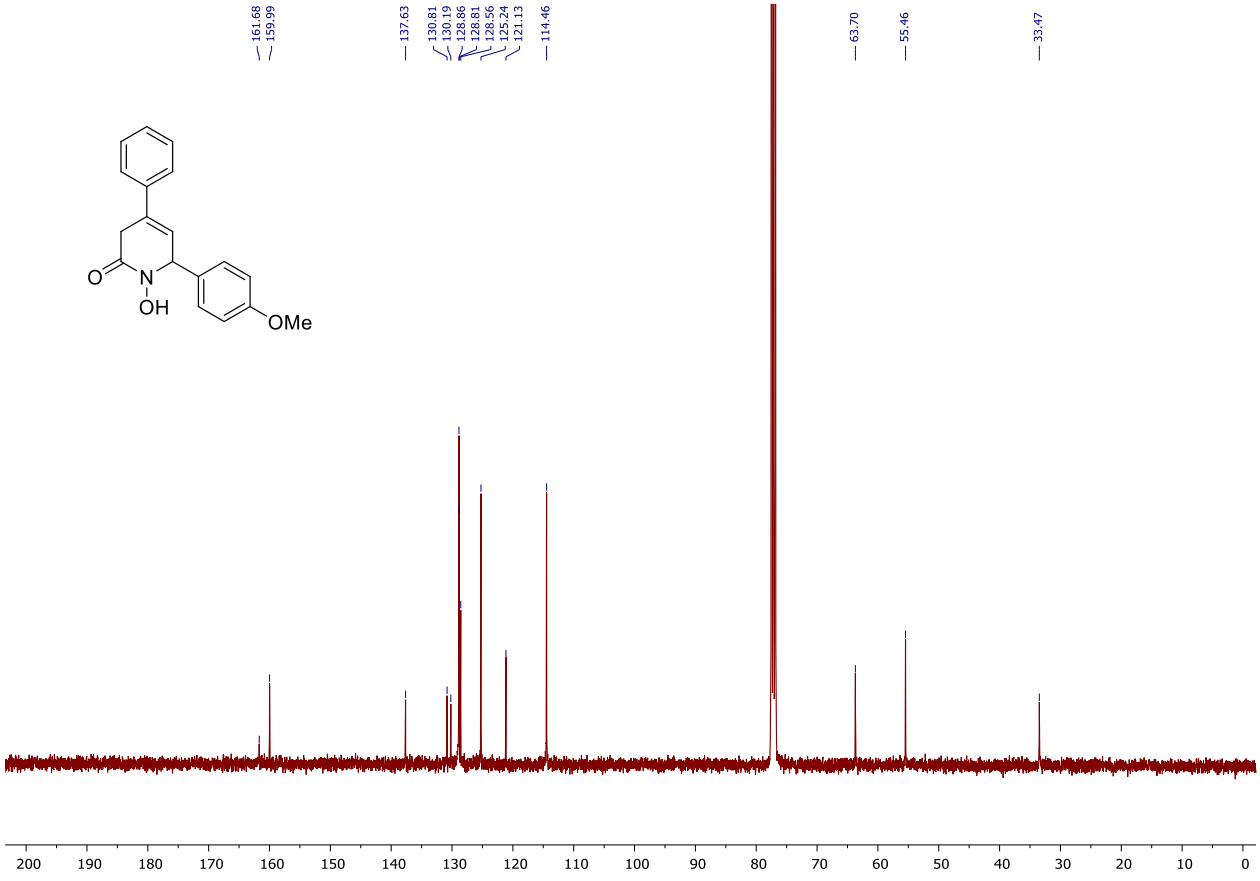
^{1}H and ^{13}C NMR spectra of compound 12a



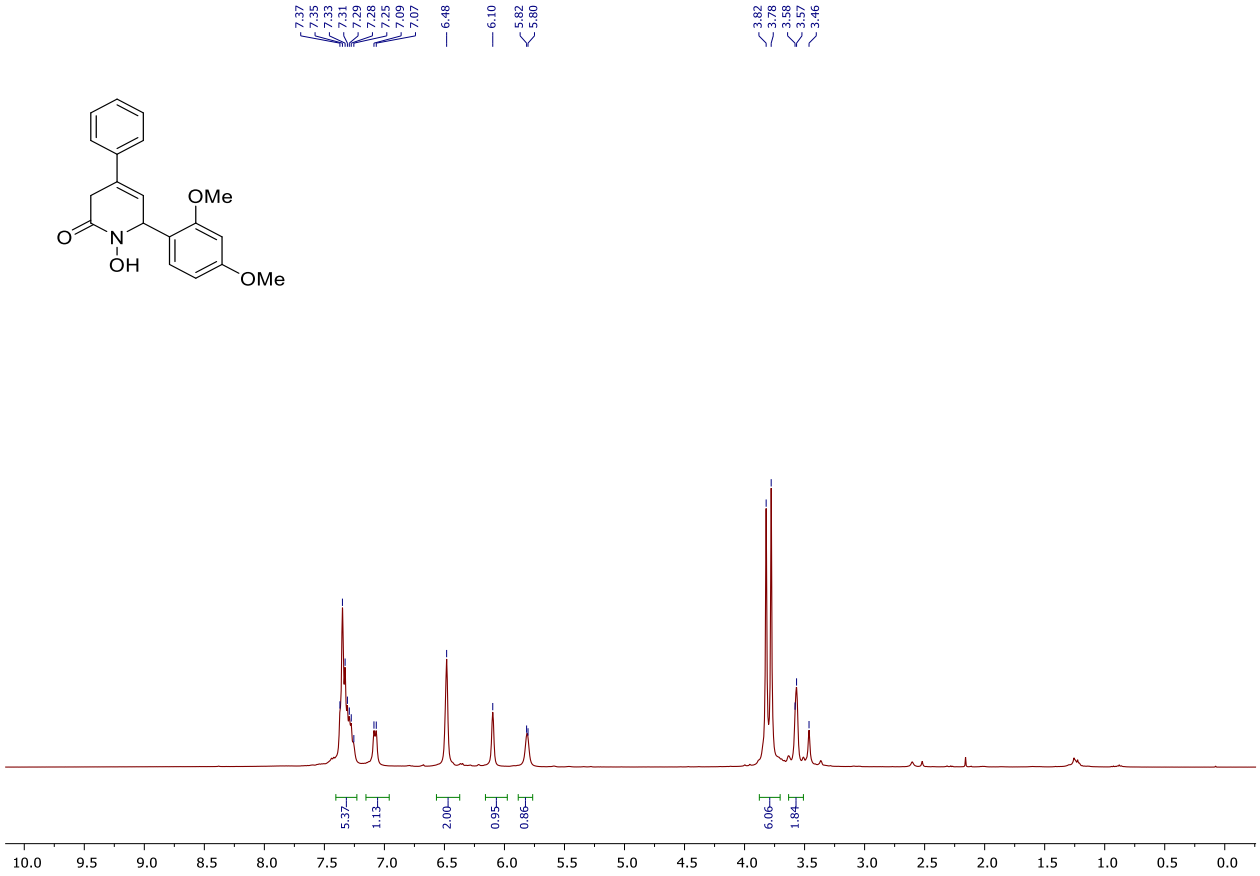


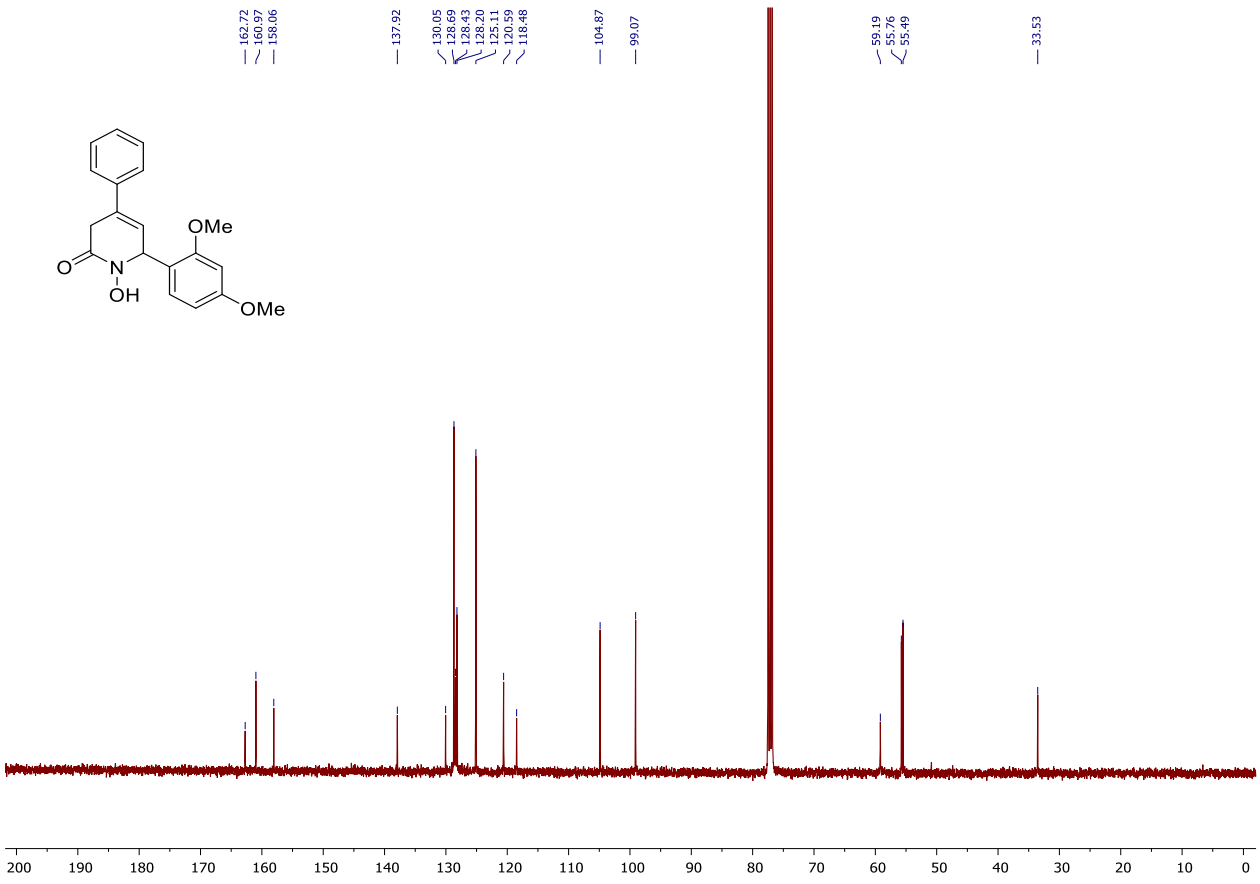
^{1}H and ^{13}C NMR spectra of compound 13a



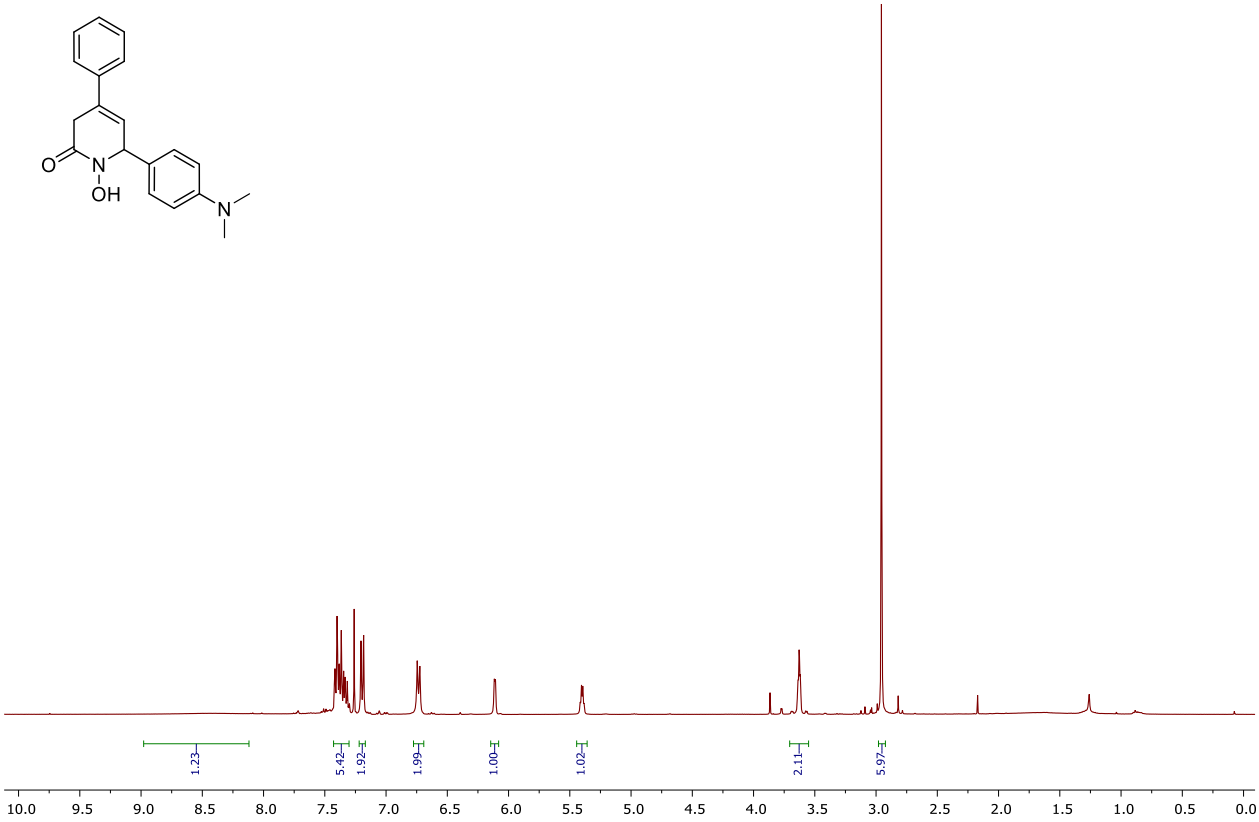


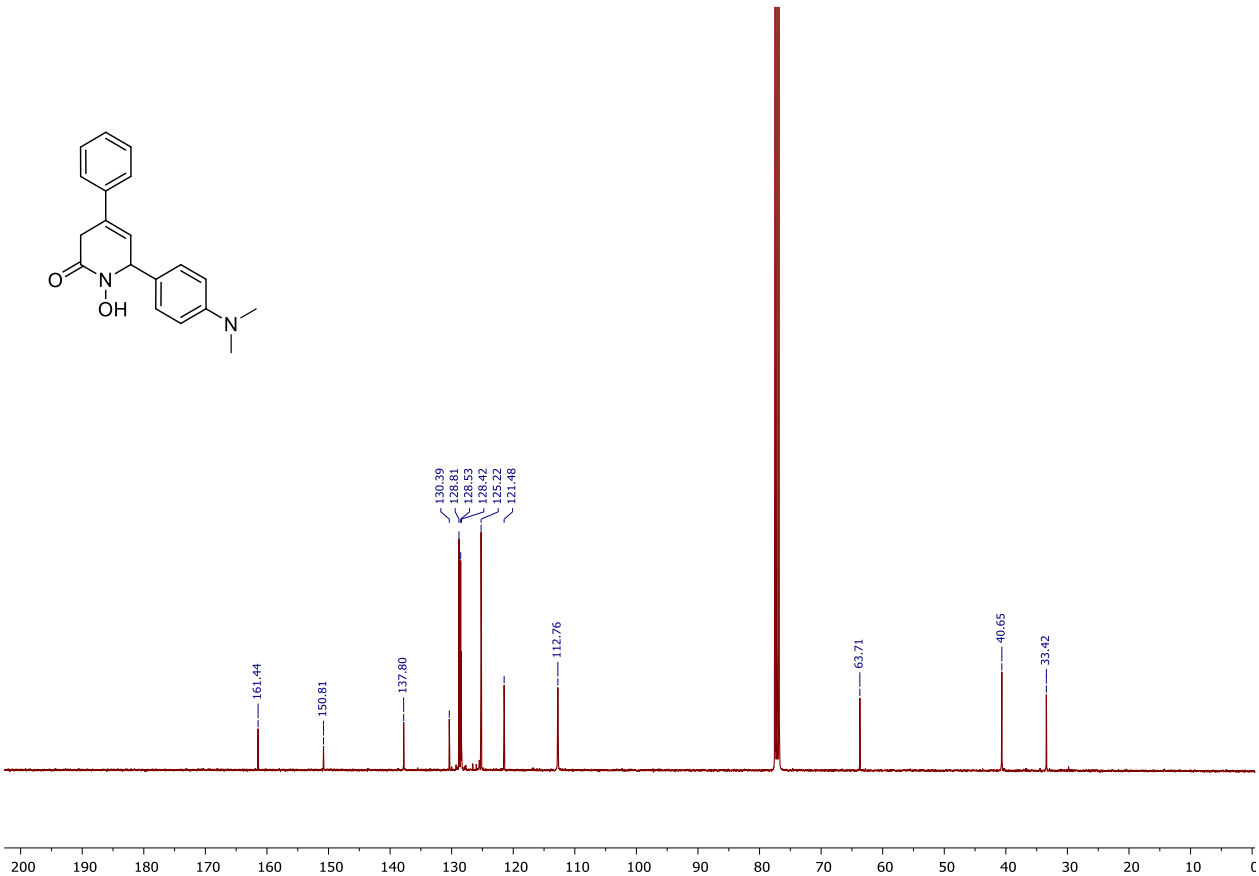
^{1}H and ^{13}C NMR spectra of compound 13b



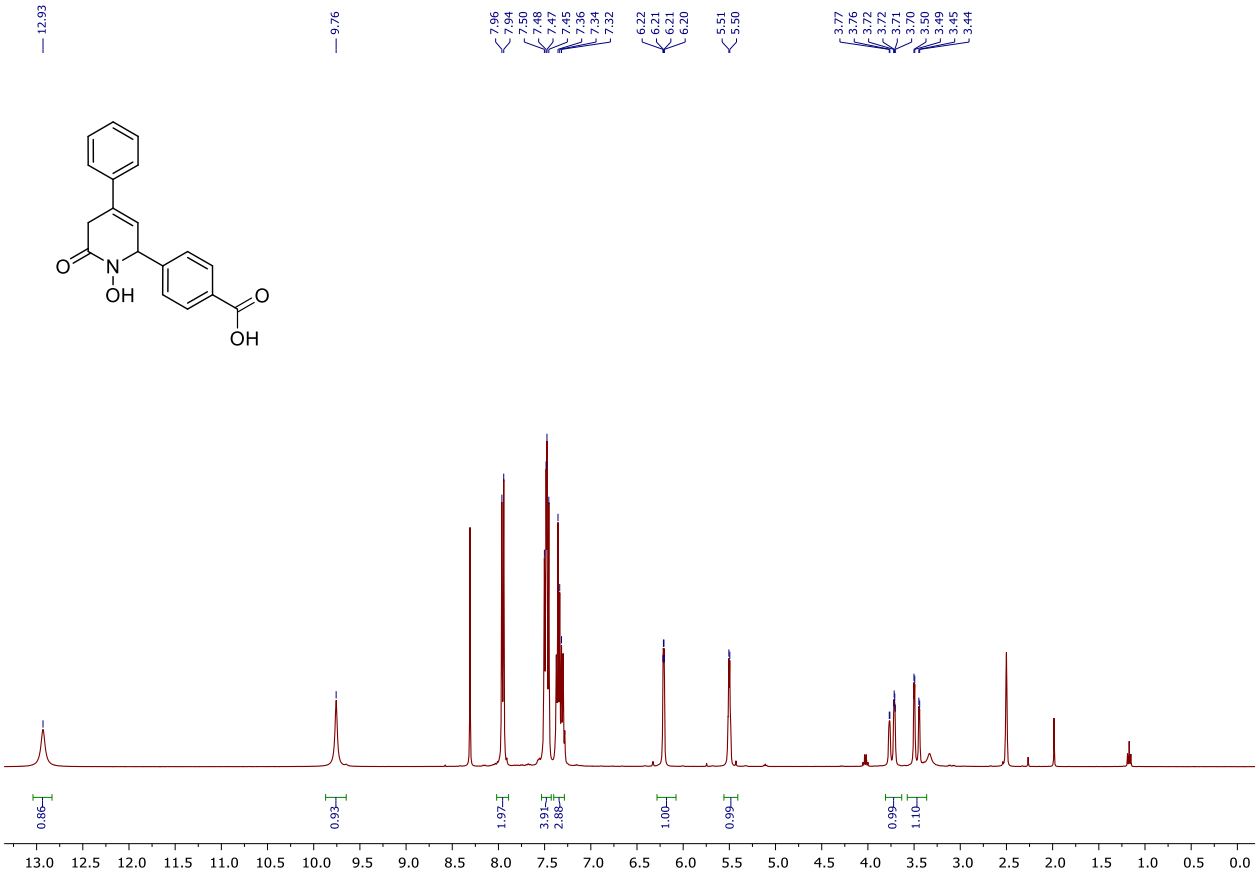


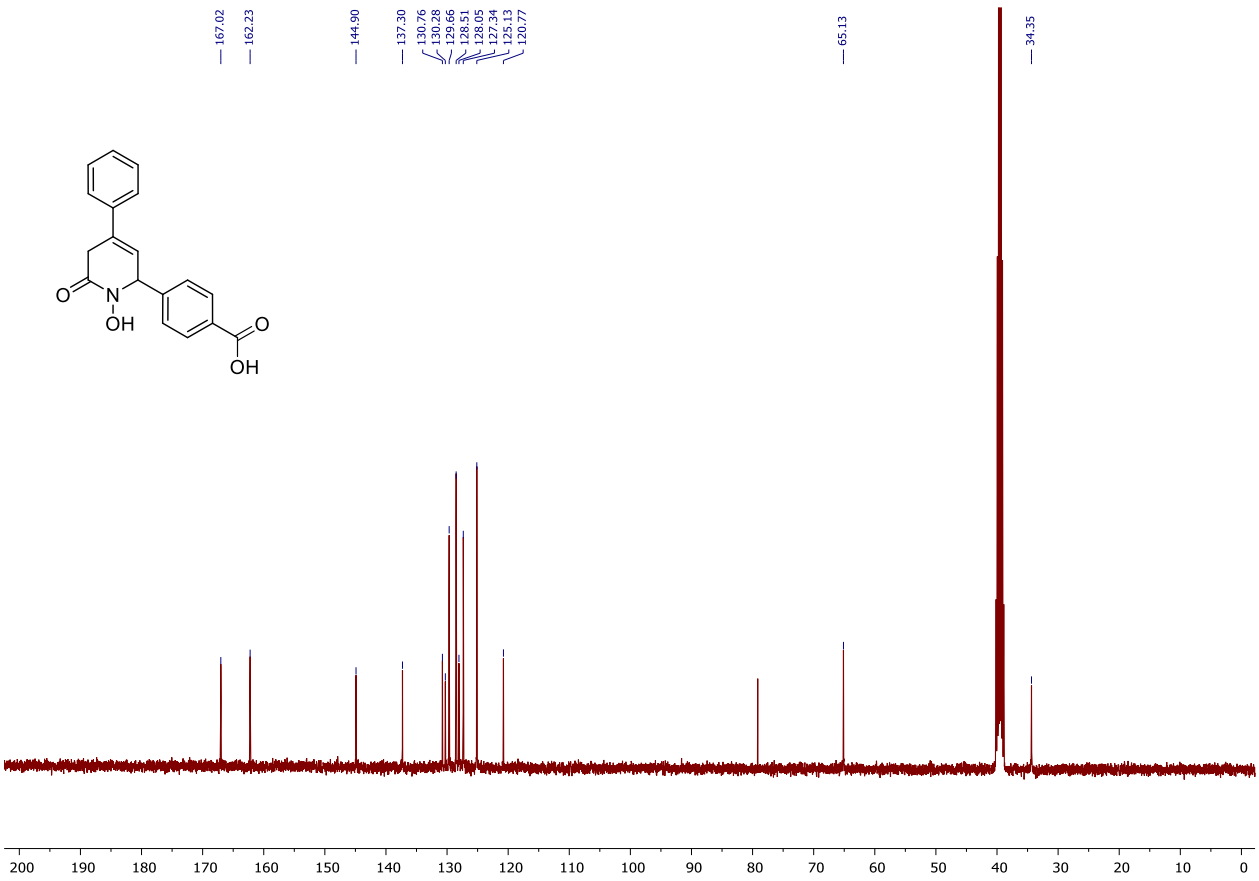
^{1}H and ^{13}C NMR spectra of compound 13c



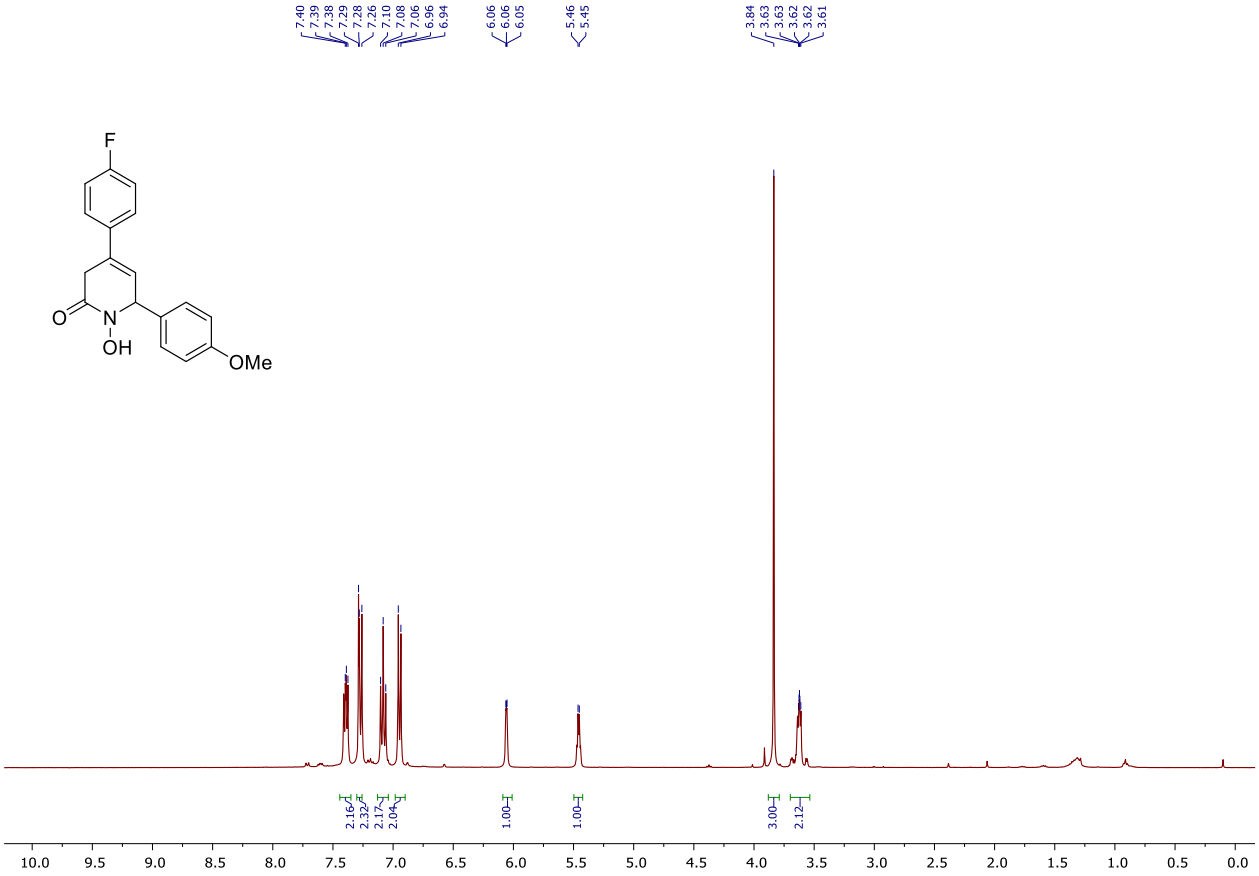


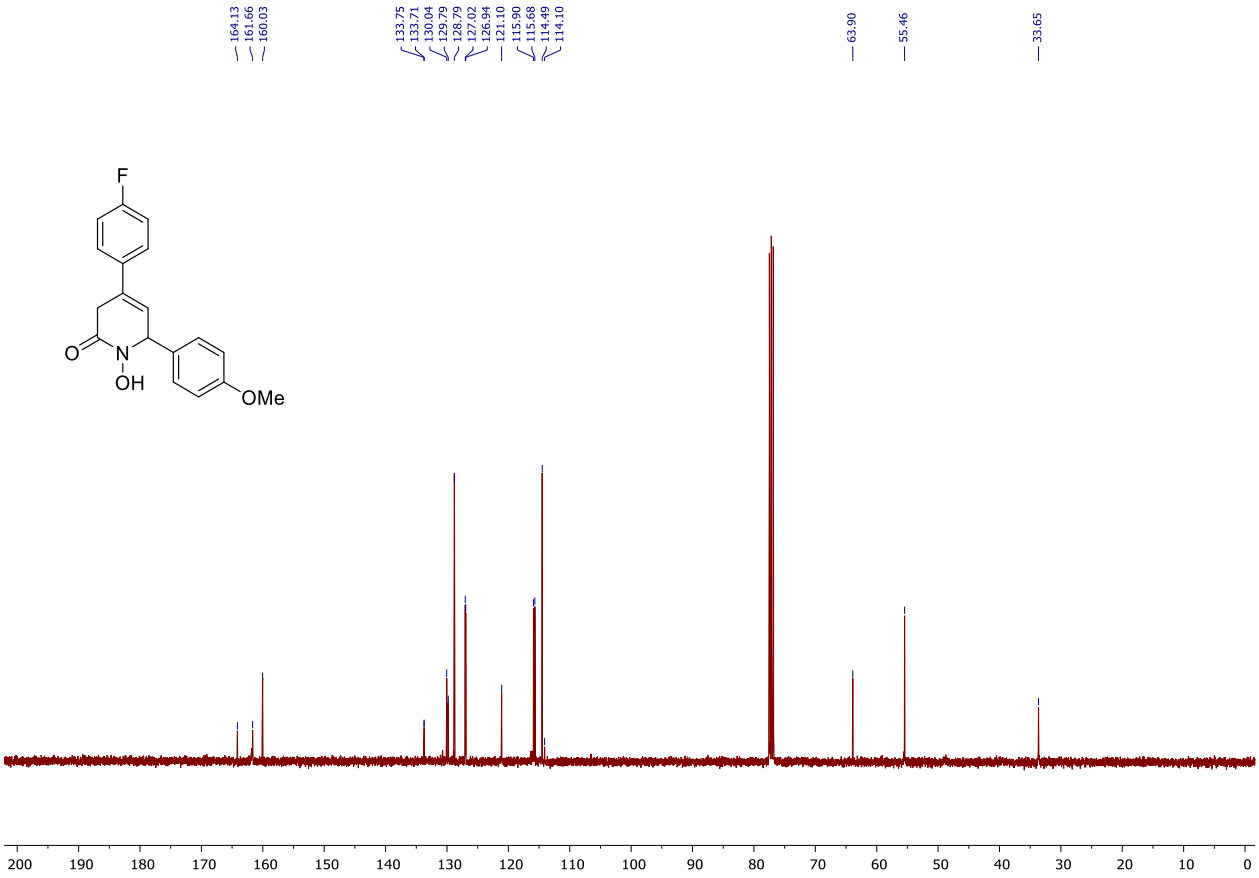
^{1}H and ^{13}C NMR spectra of compound 13d



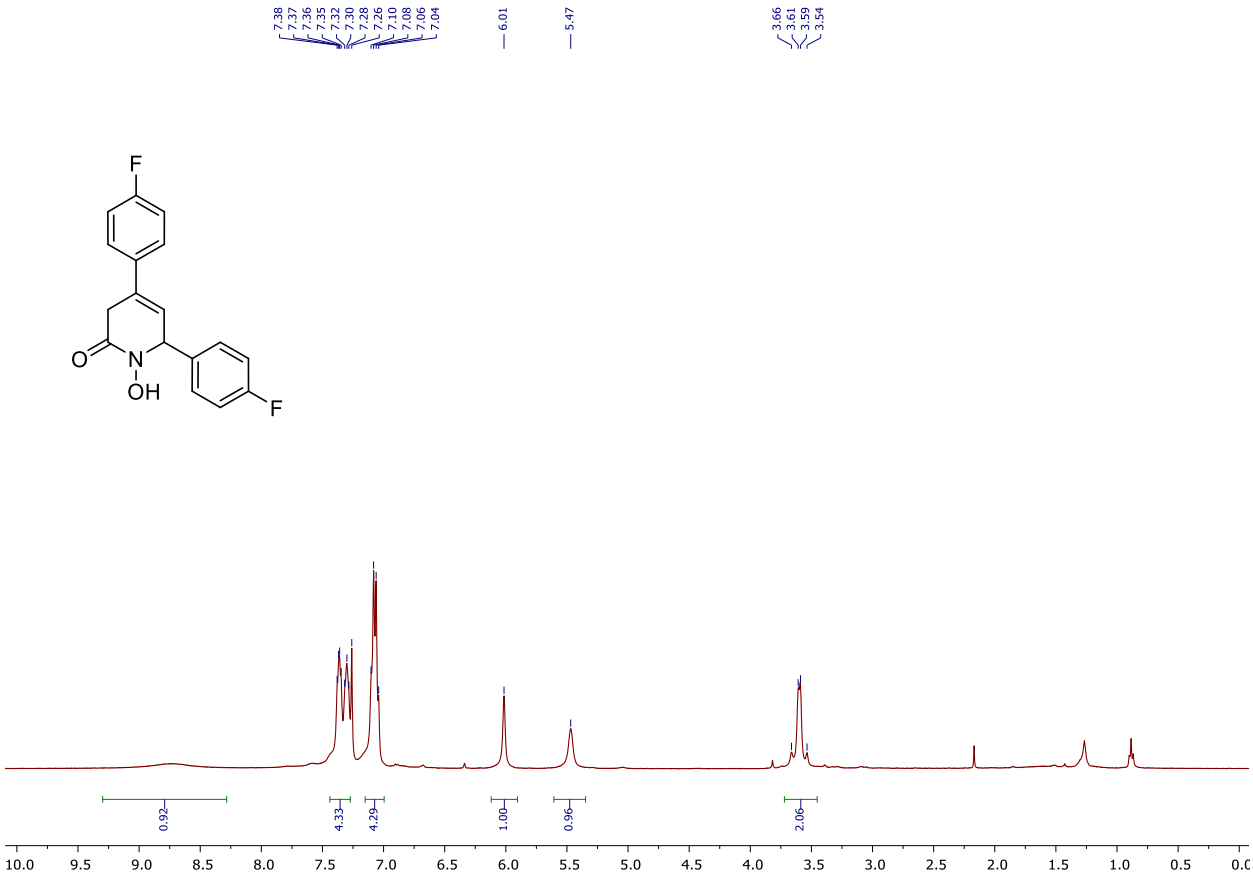


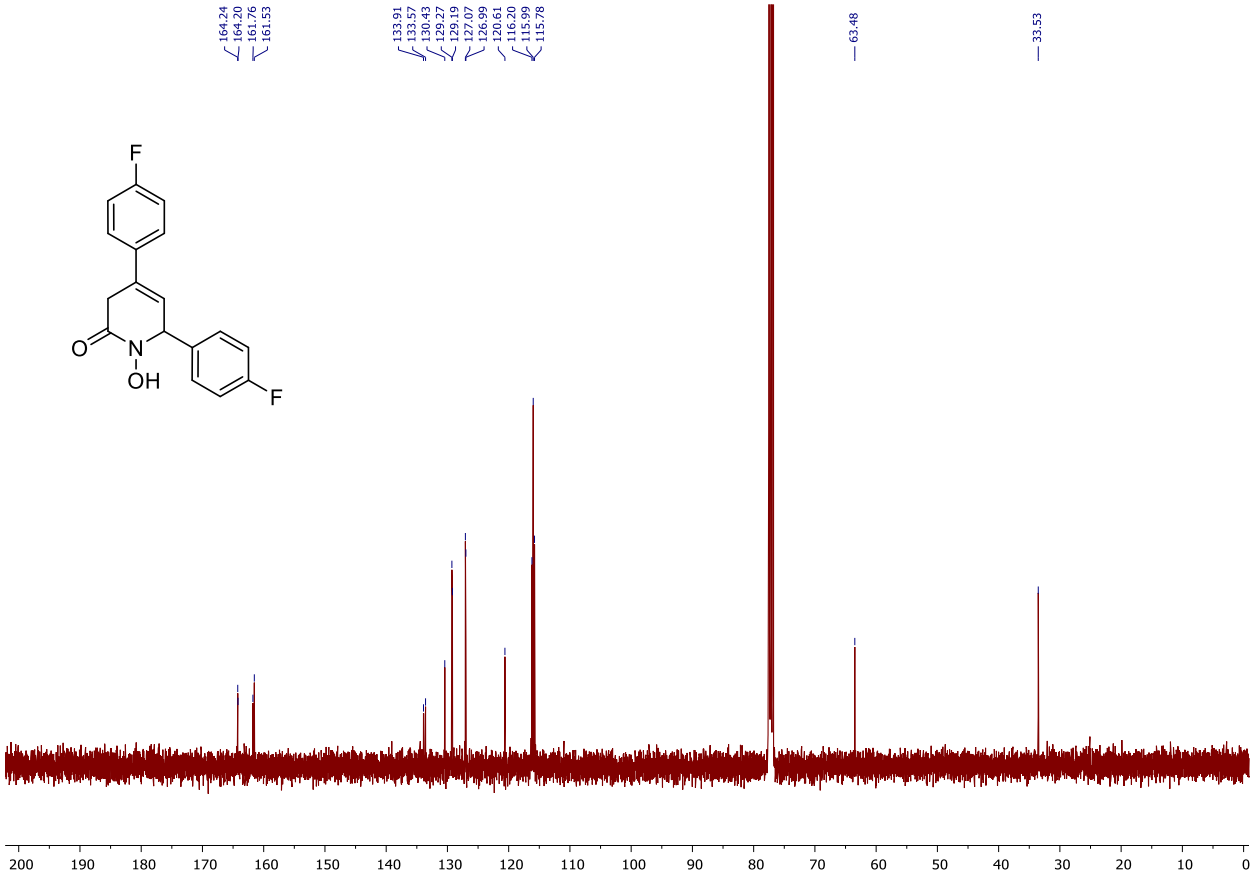
^{1}H and ^{13}C NMR spectra of compound 13e



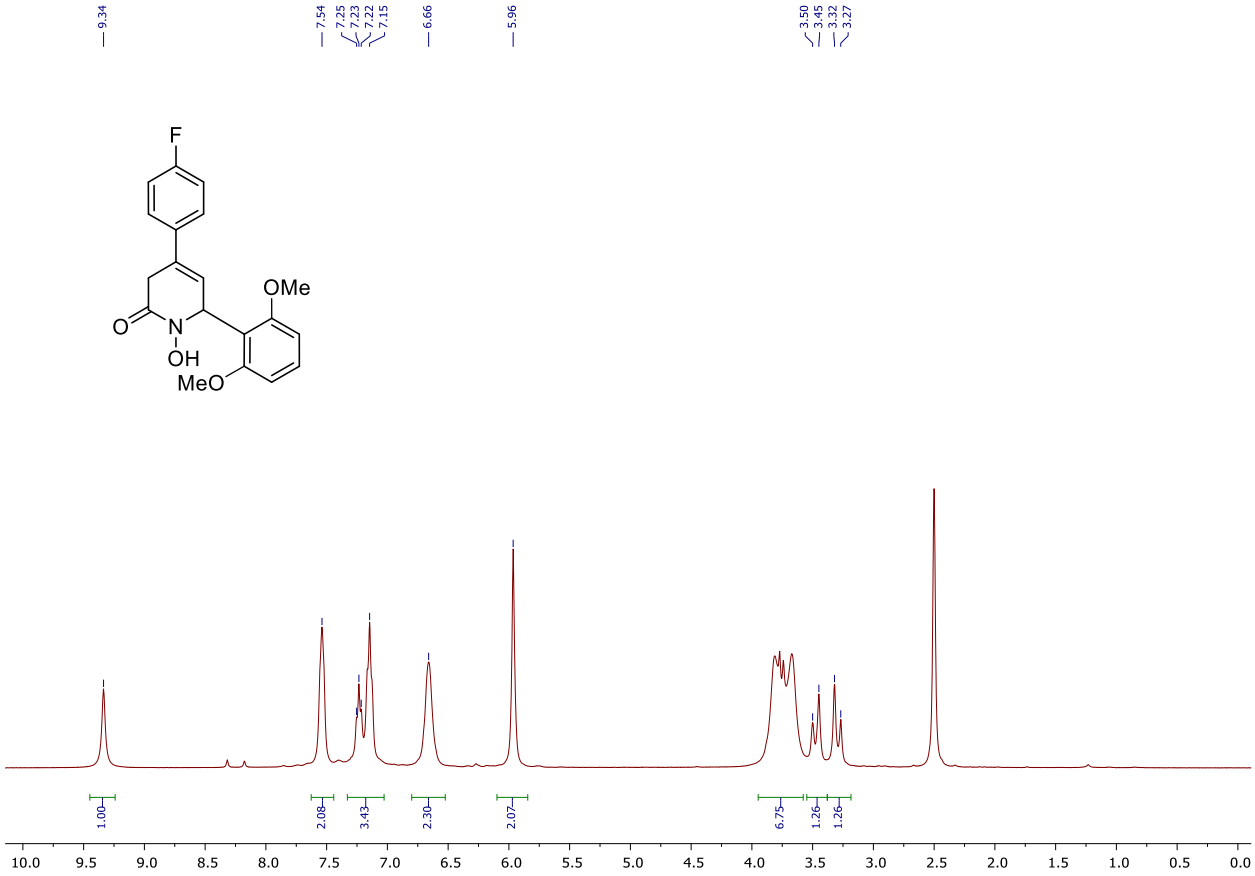


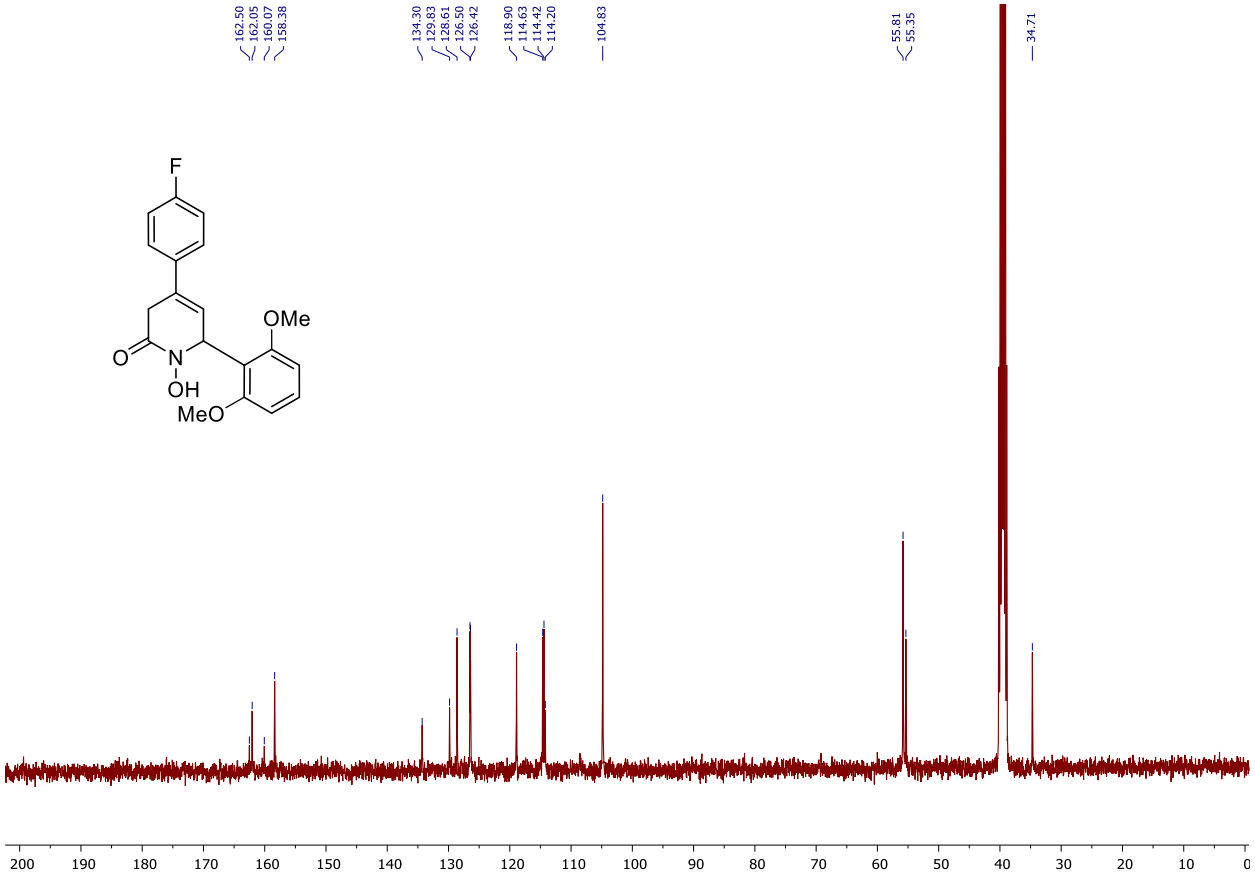
^{1}H and ^{13}C NMR spectra of compound 13f



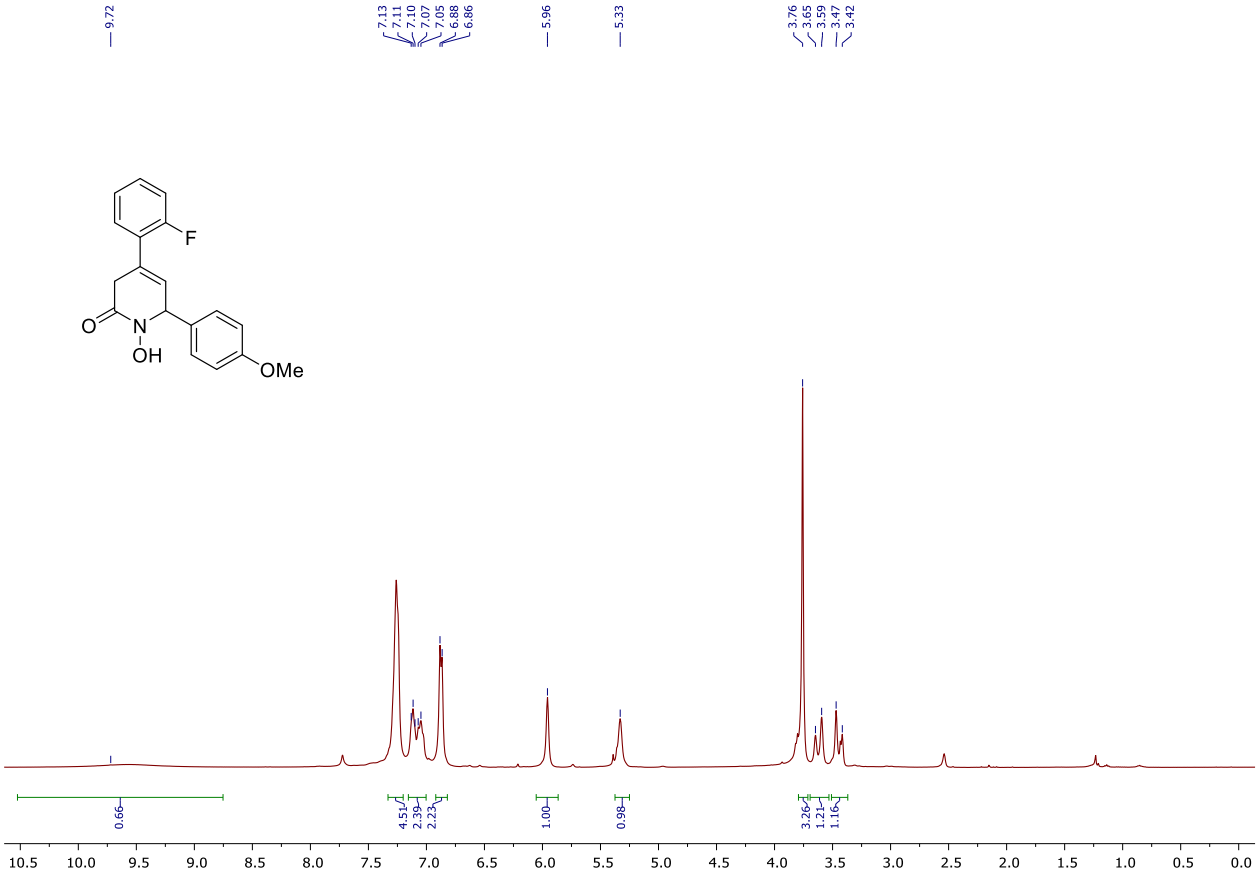


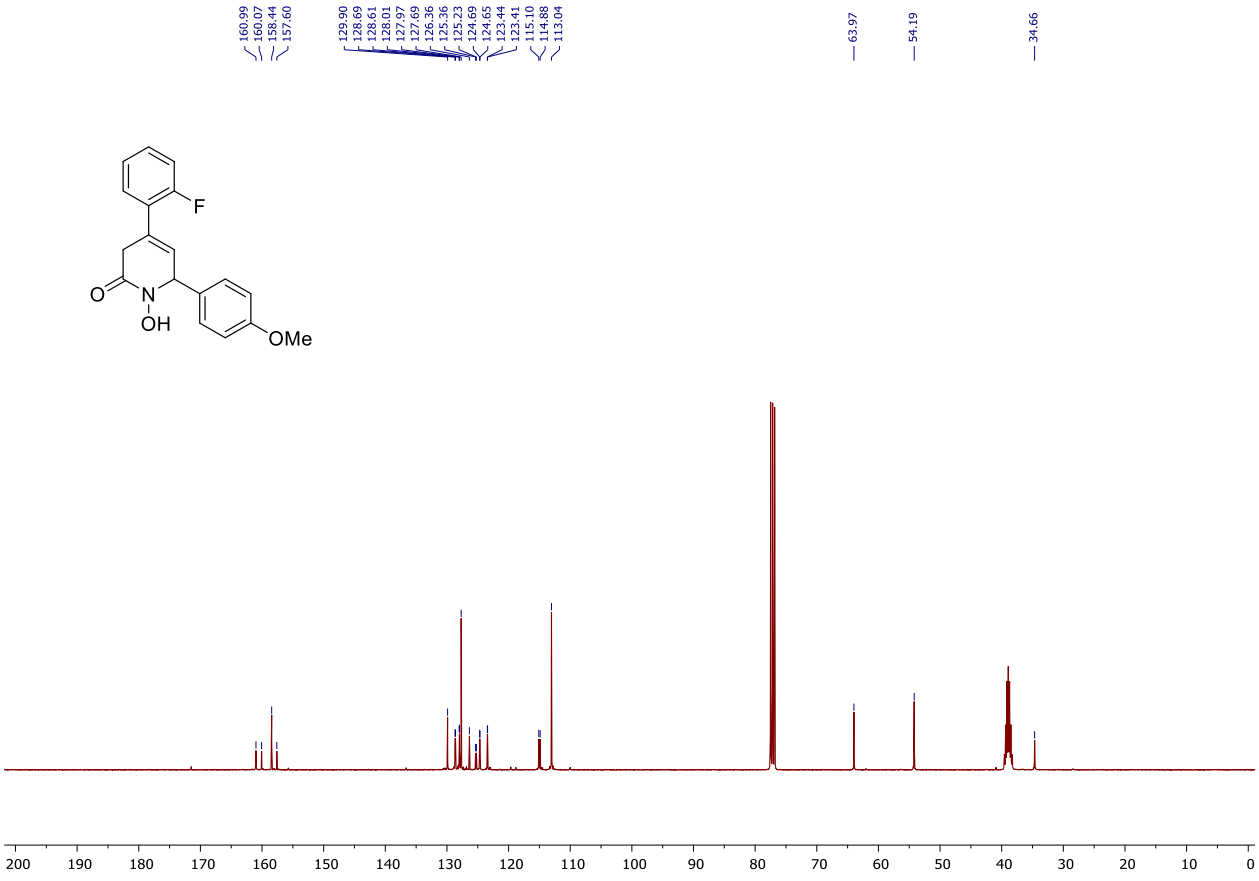
^{1}H and ^{13}C NMR spectra of compound 13g



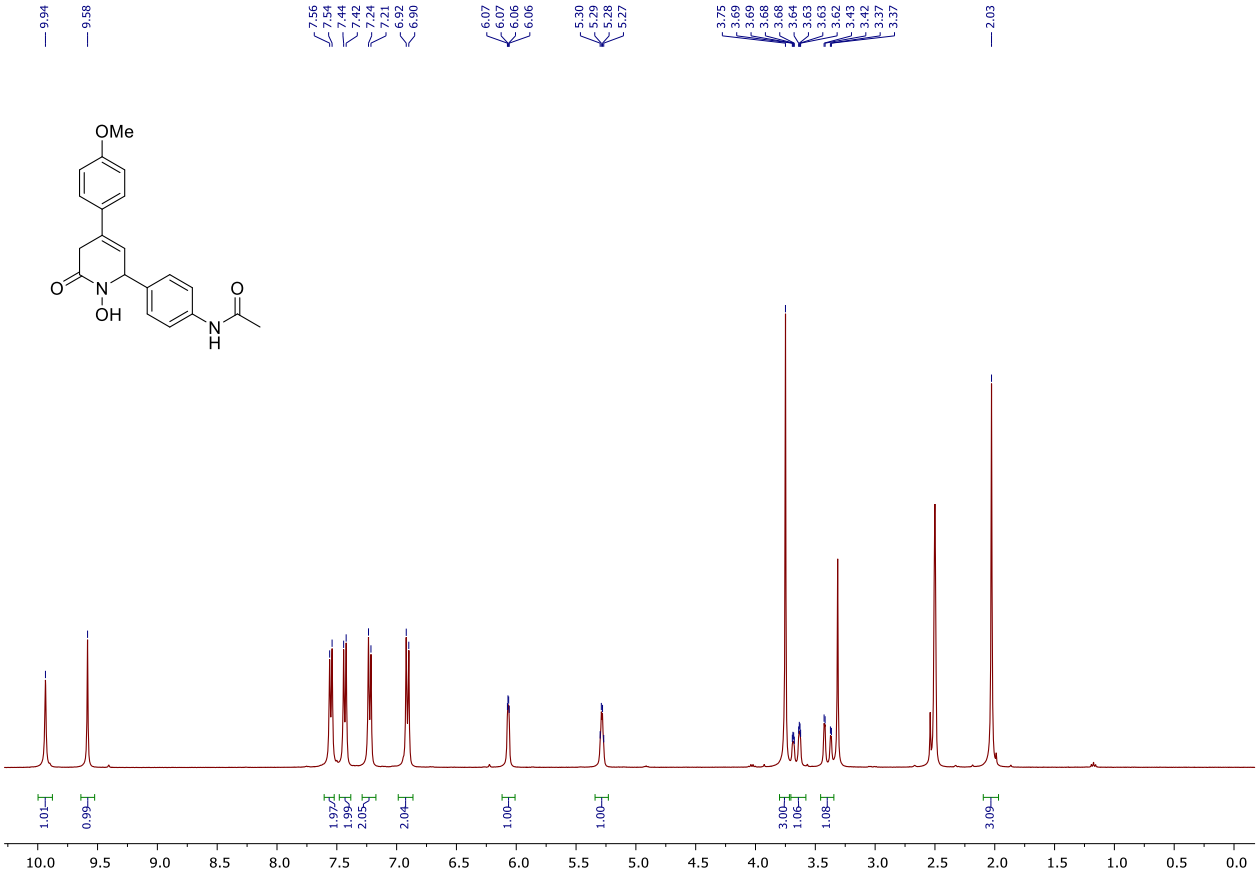


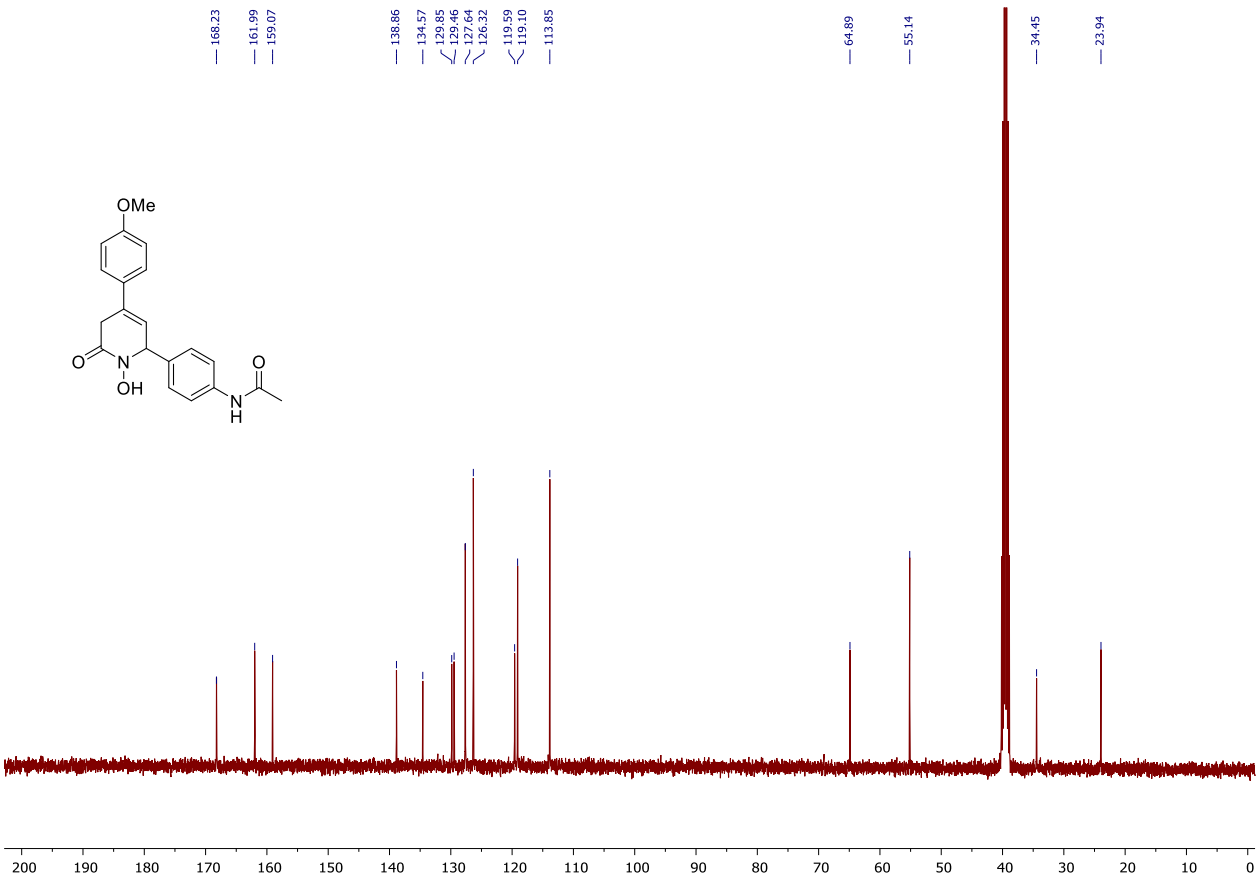
^{1}H and ^{13}C NMR spectra of compound 13h



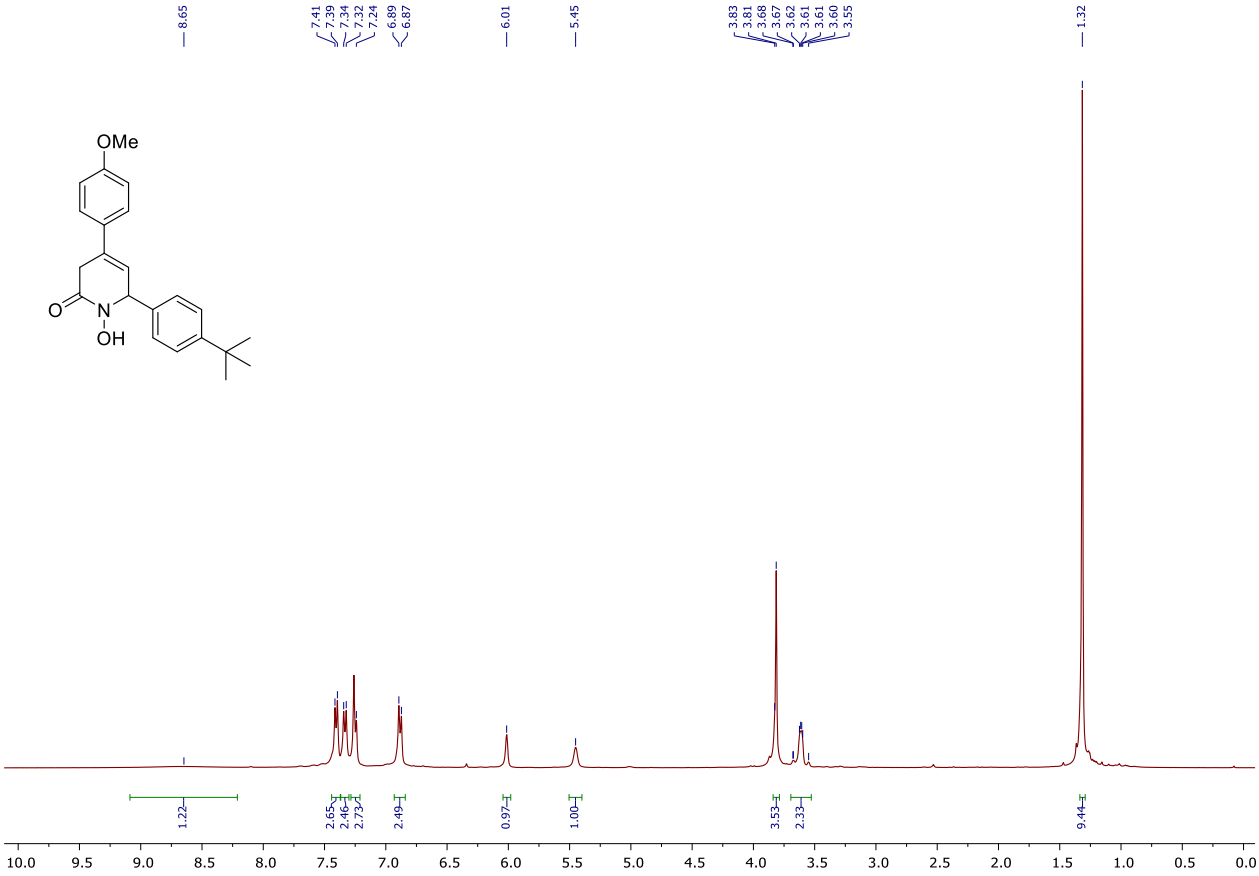


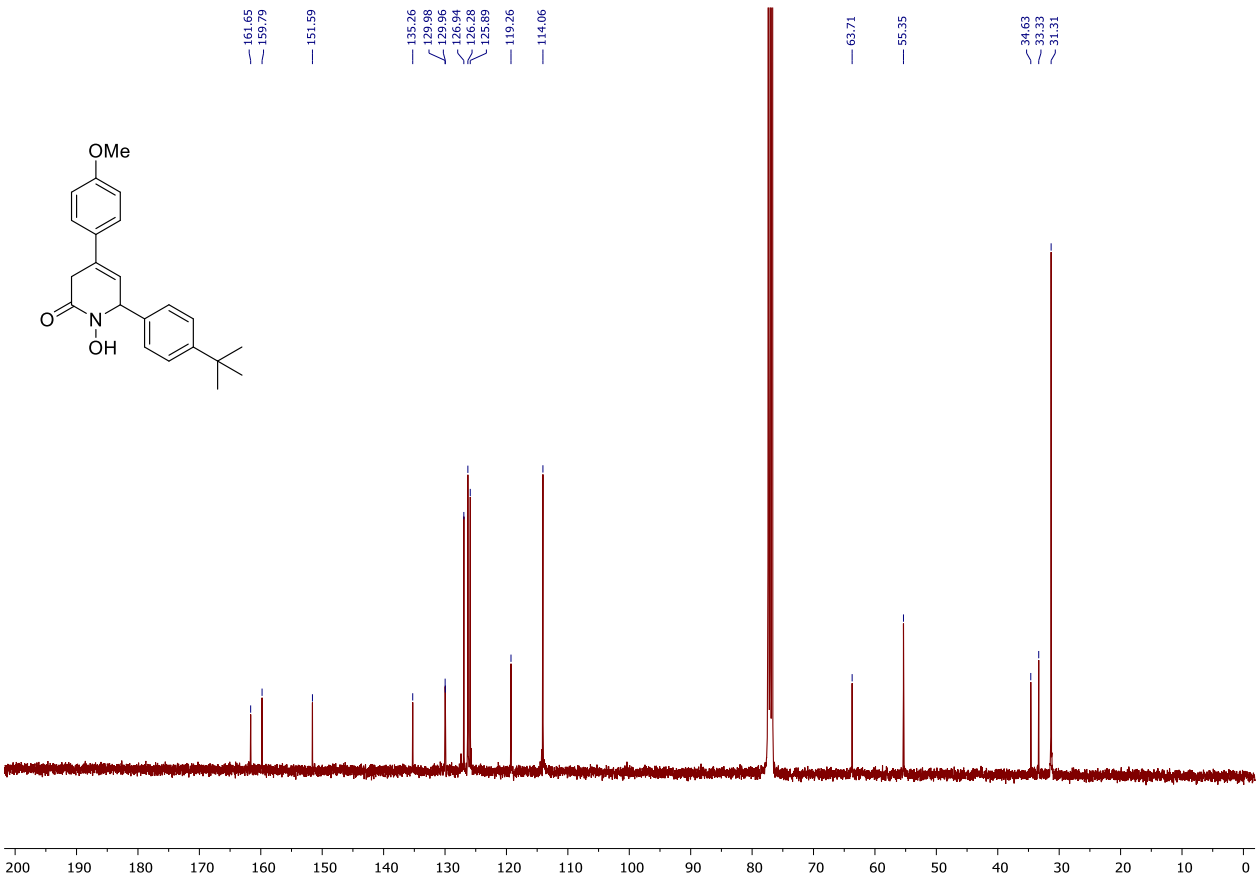
^{1}H and ^{13}C NMR spectra of compound 13i



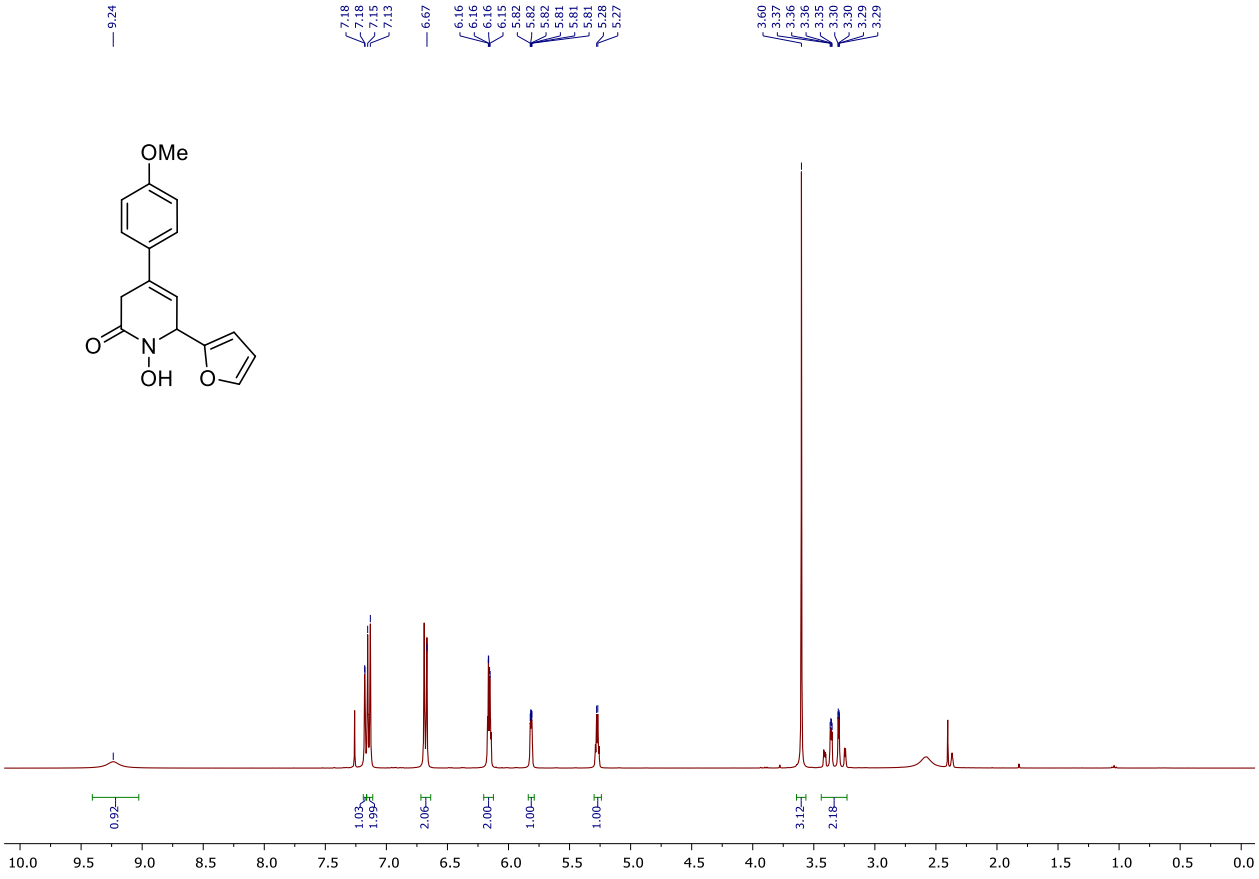


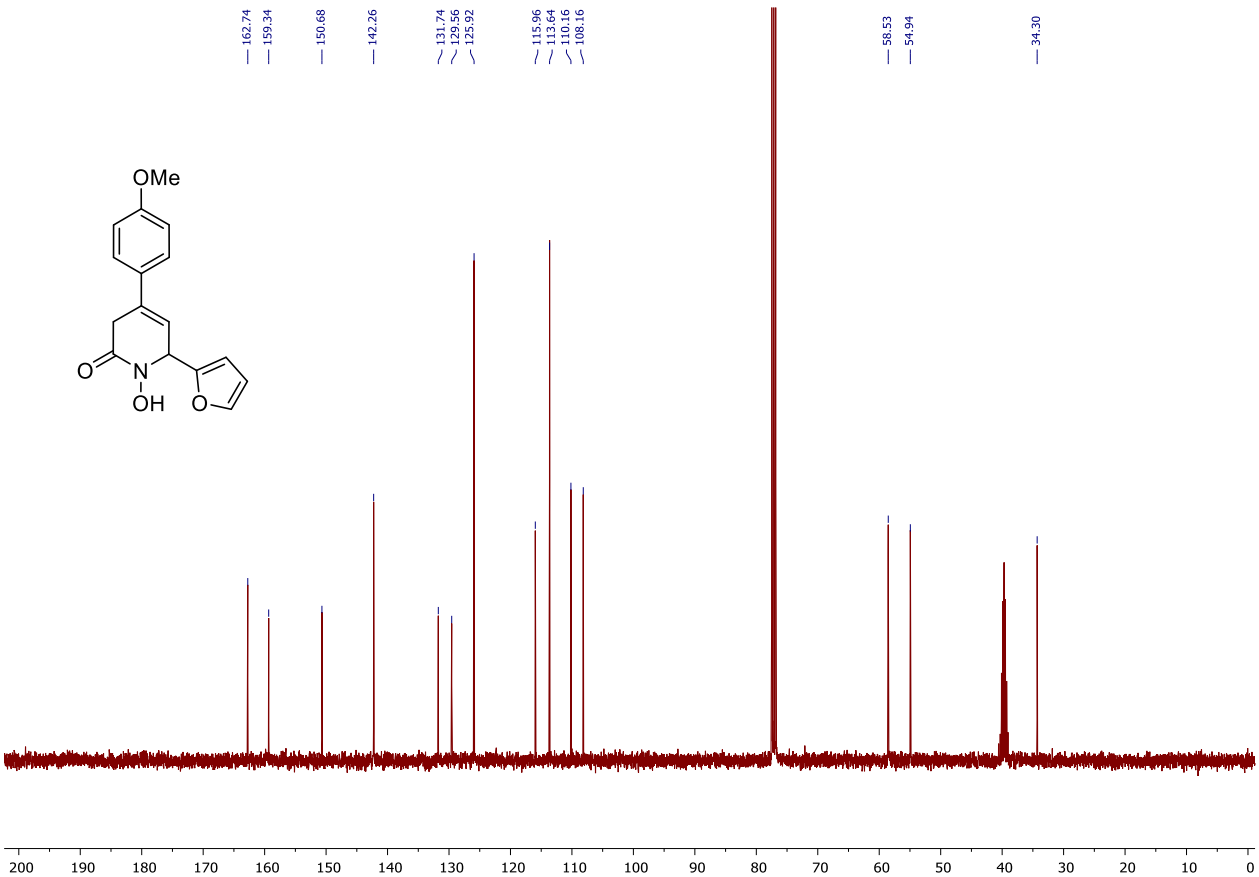
^{1}H and ^{13}C NMR spectra of compound 13j



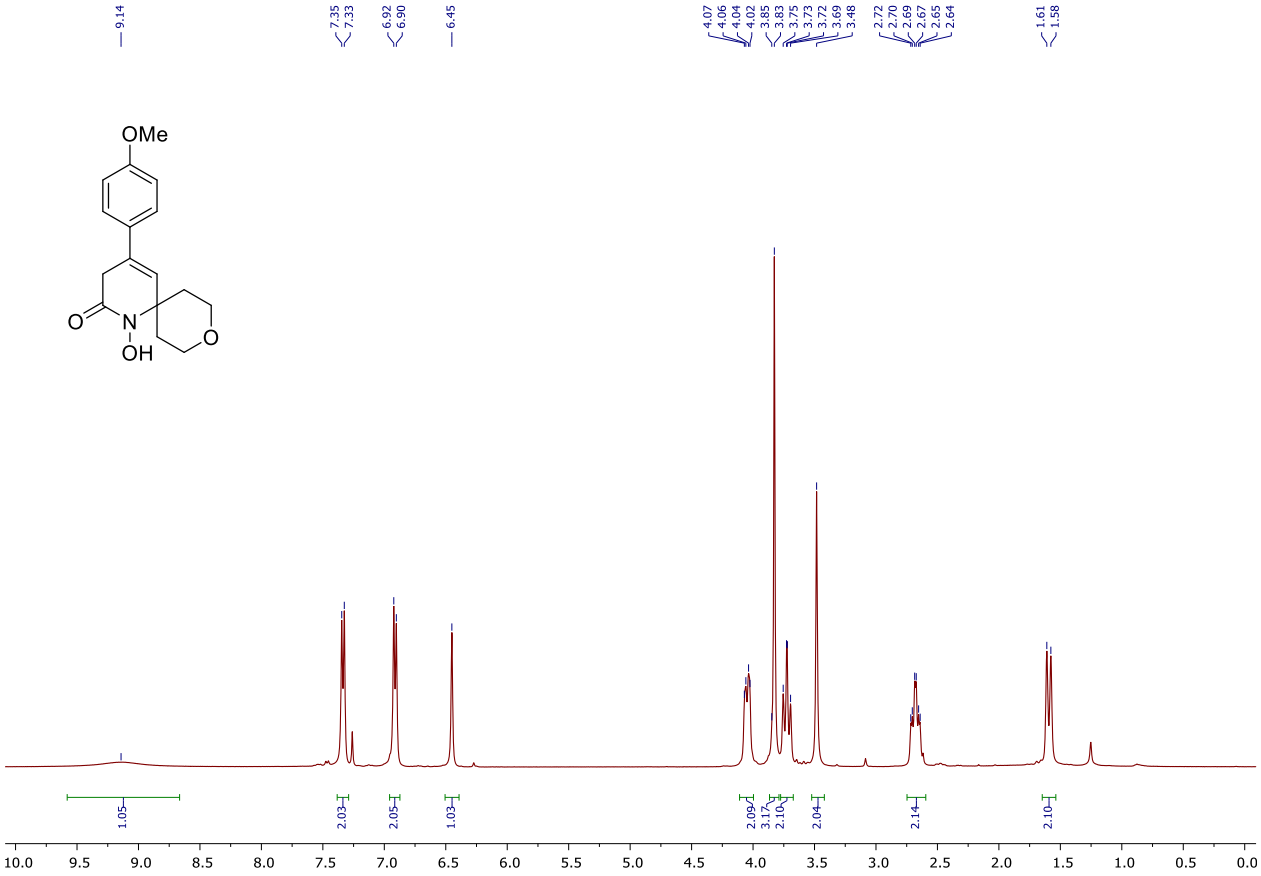


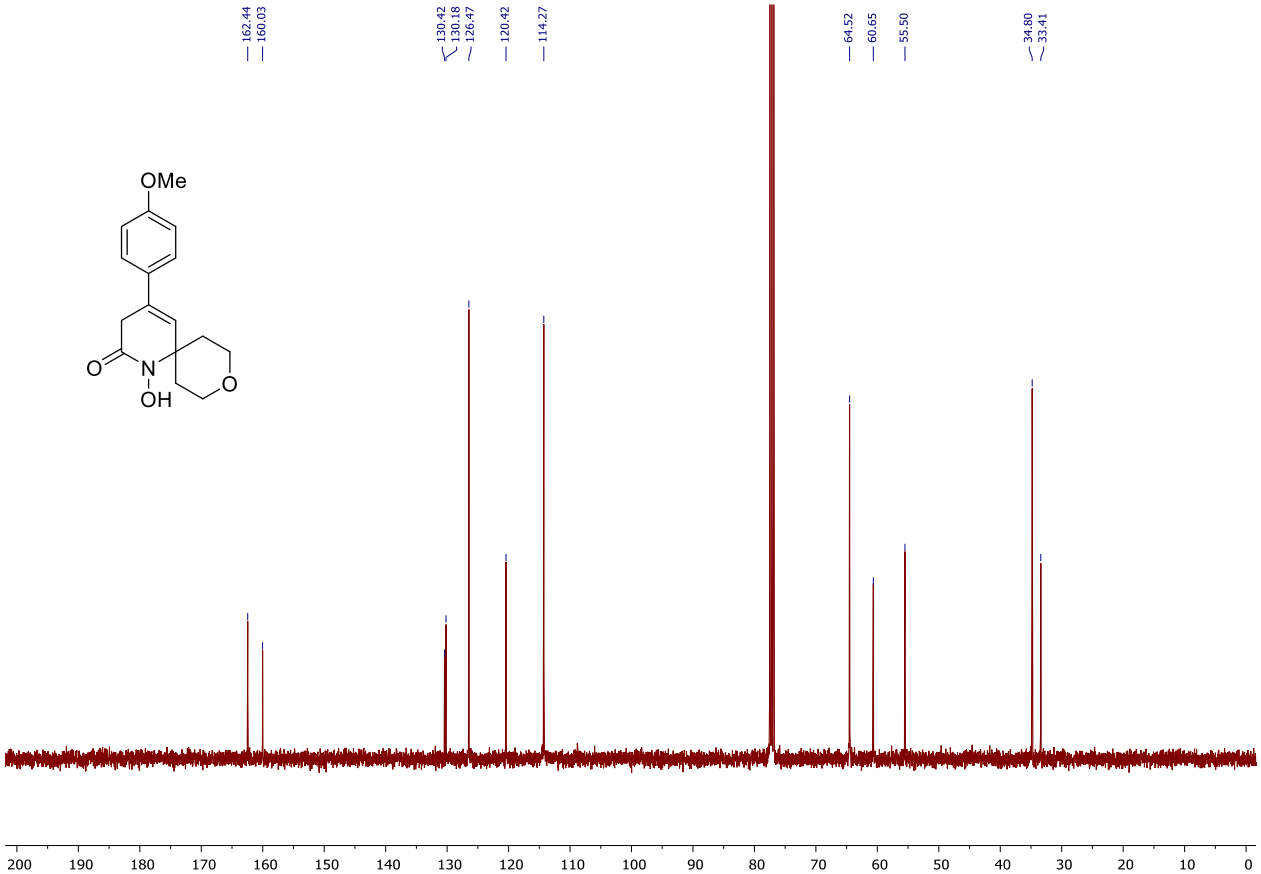
^{1}H and ^{13}C NMR spectra of compound 13k



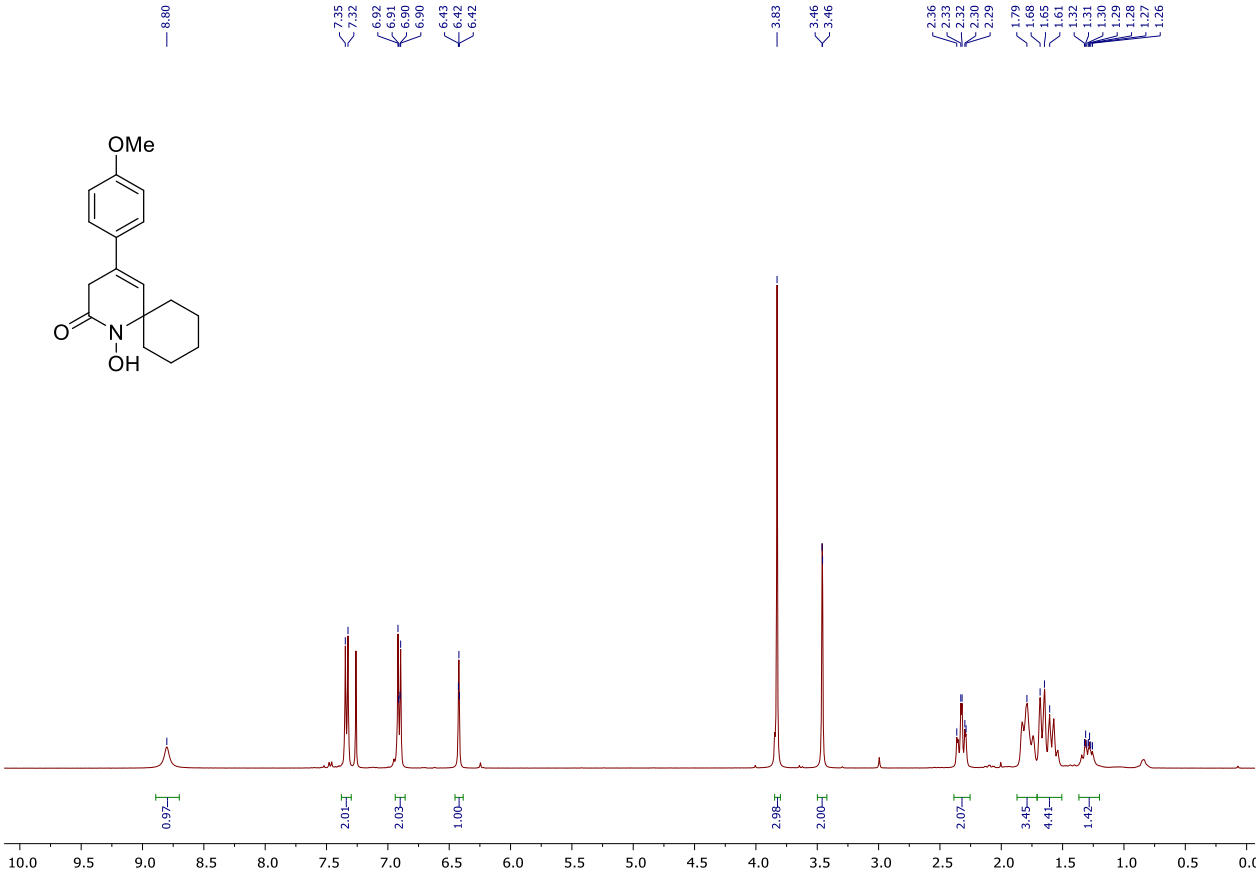


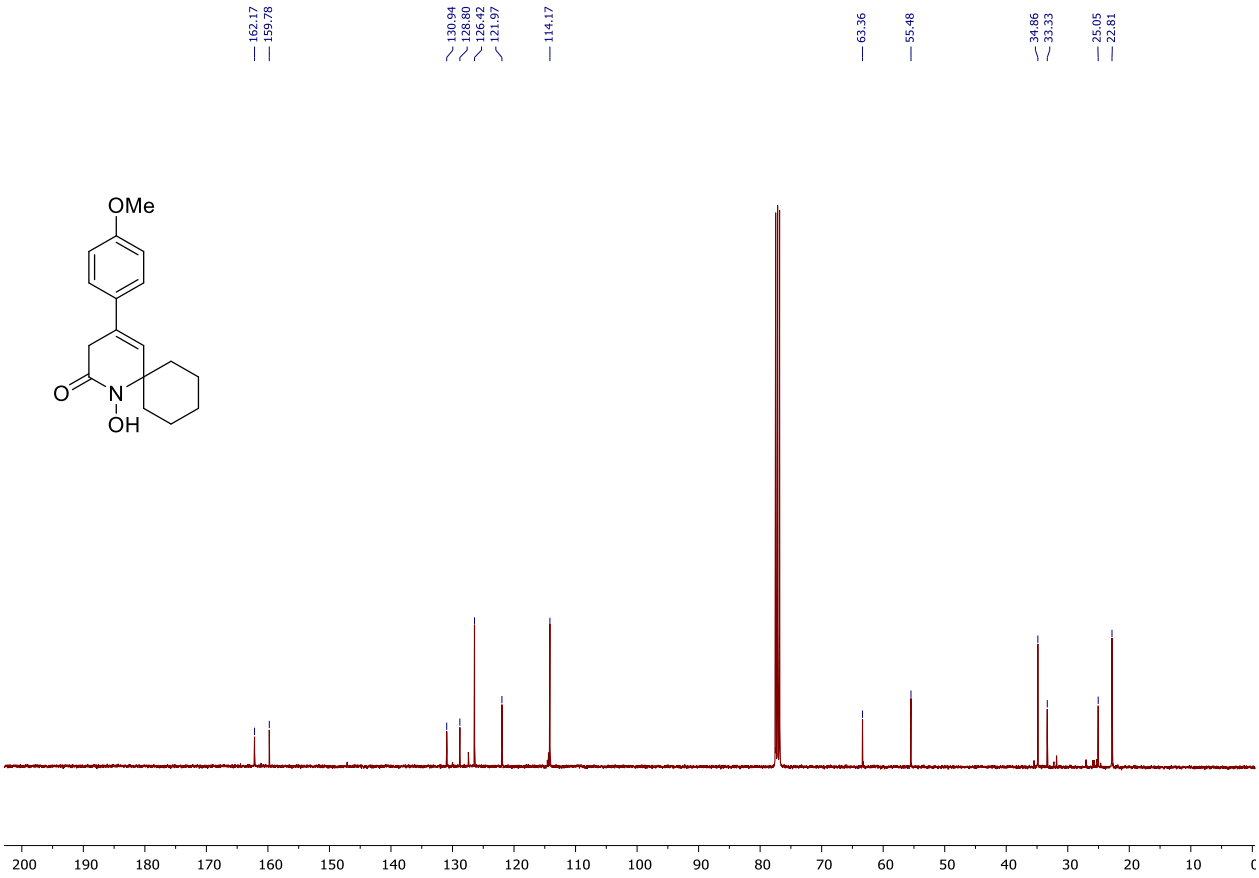
^{1}H and ^{13}C NMR spectra of compound 13l



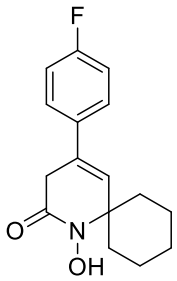


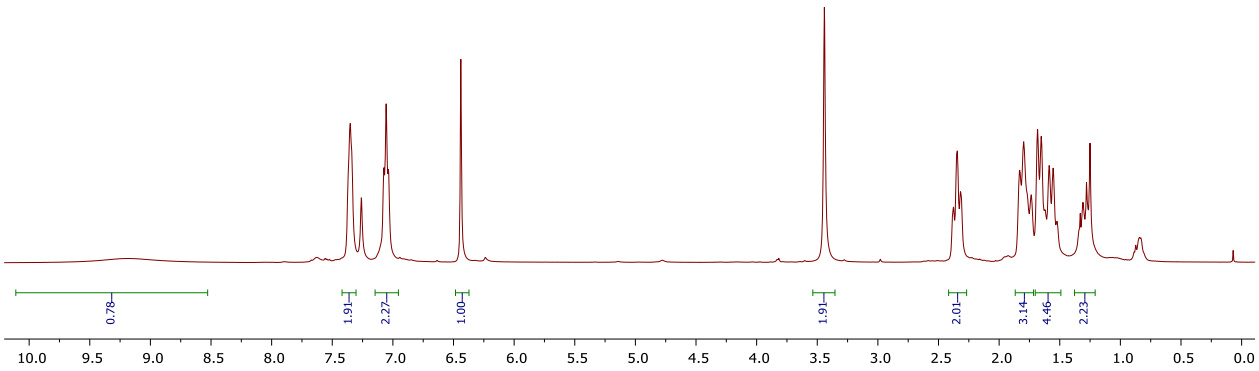
^{1}H and ^{13}C NMR spectra of compound 13m

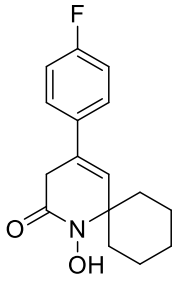




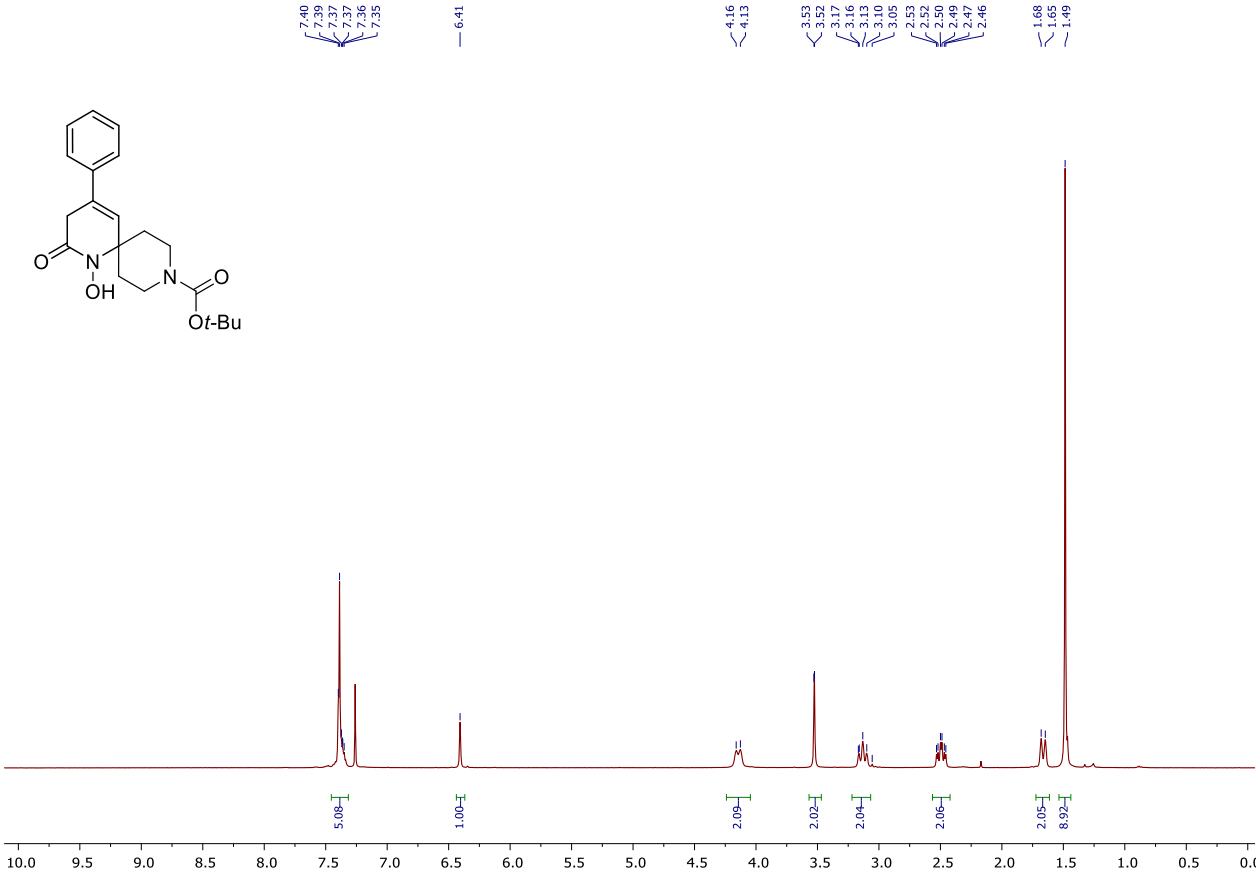
^{1}H and ^{13}C NMR spectra of compound 13n

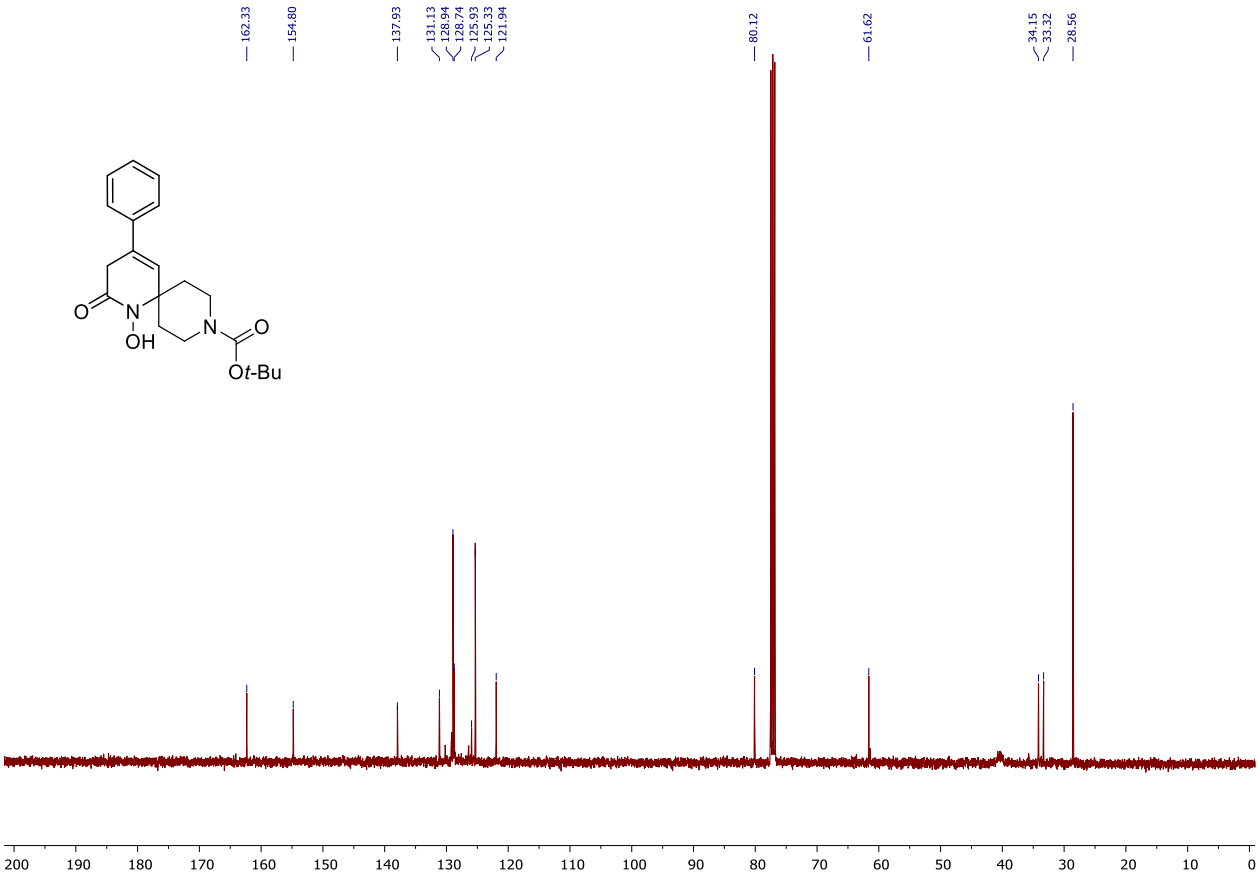




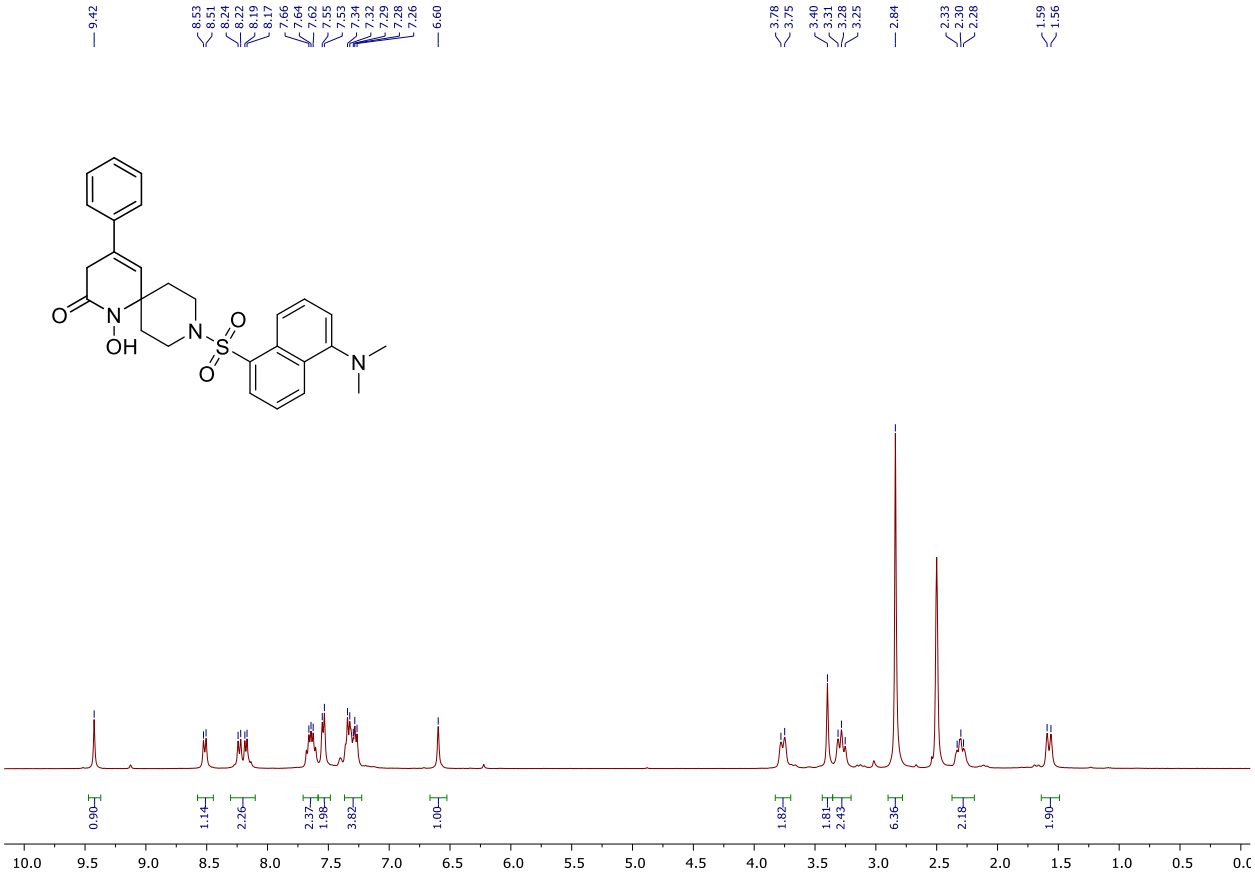


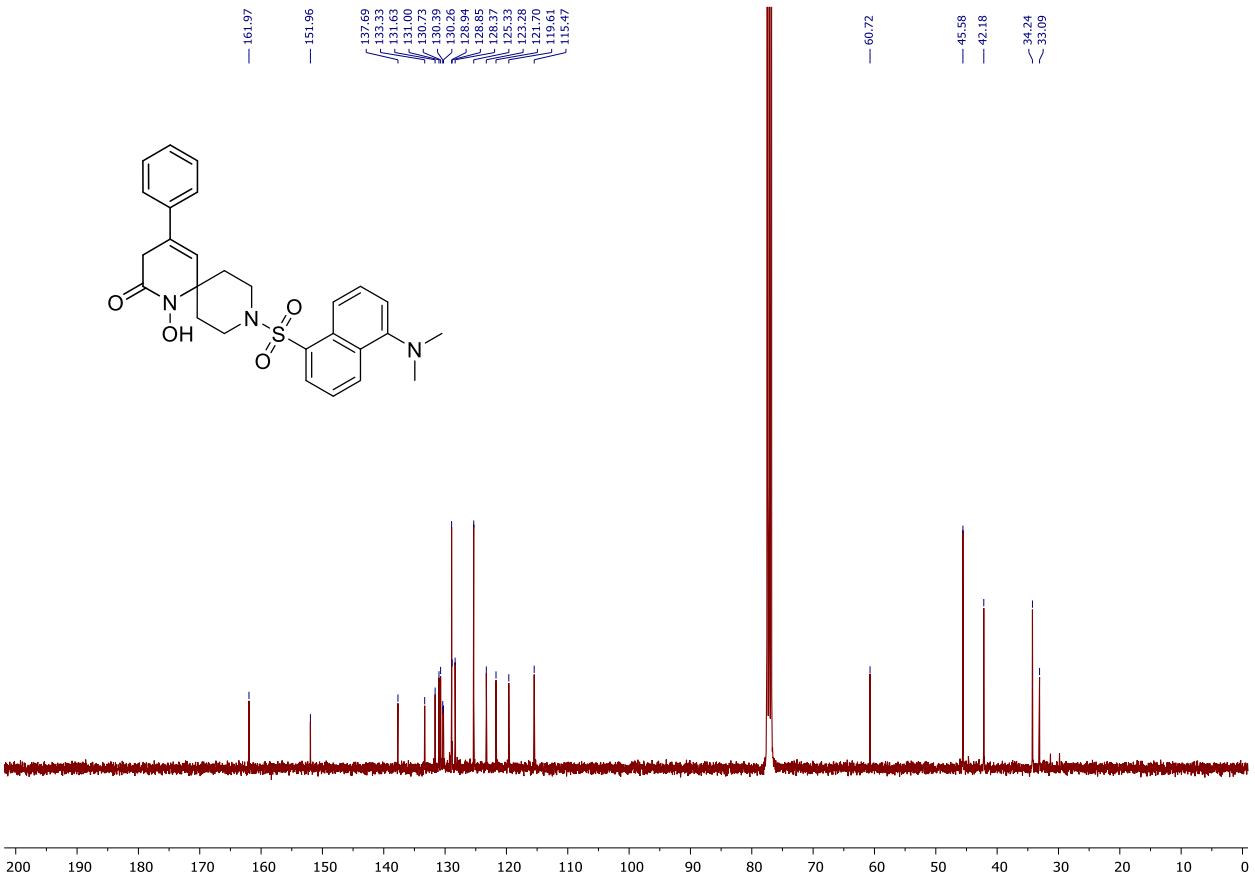
^{1}H and ^{13}C NMR spectra of compound 13o



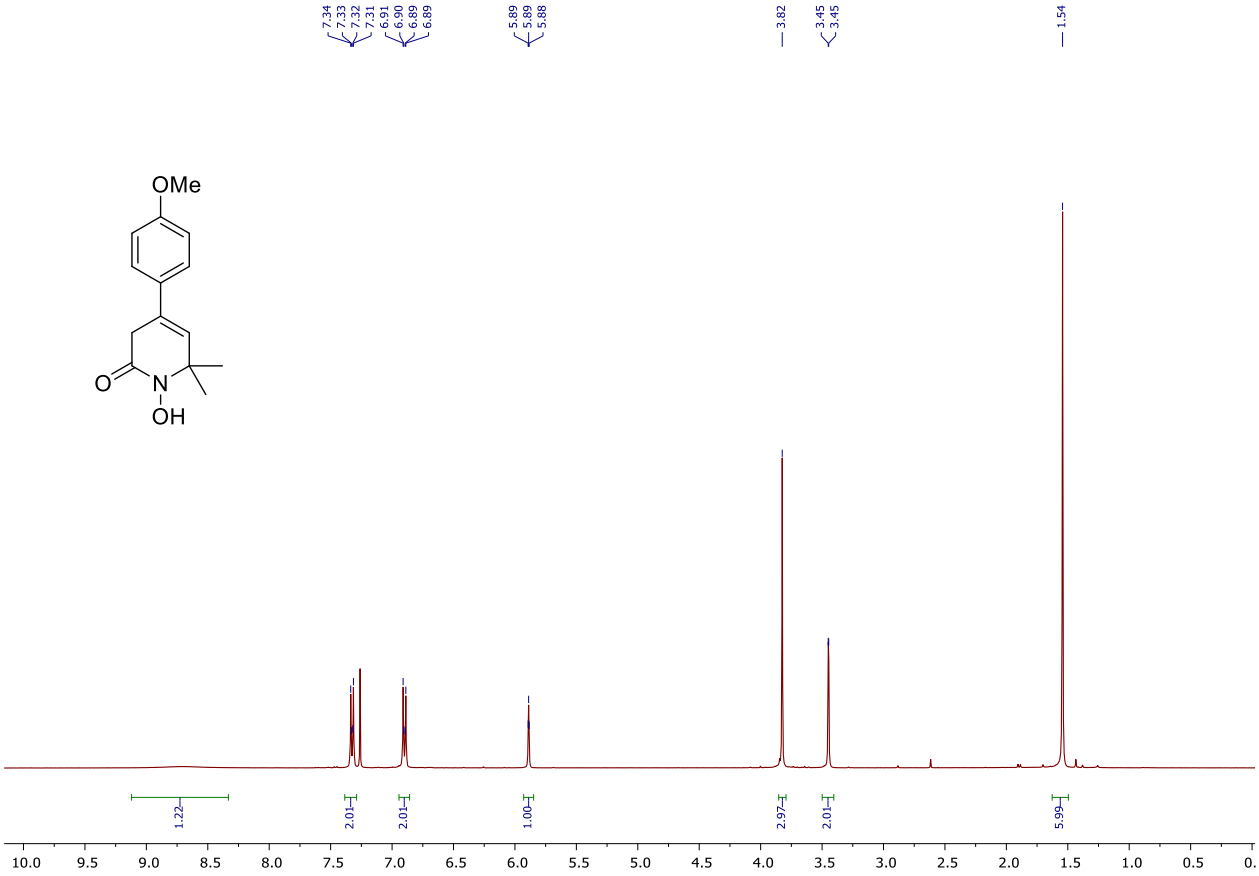


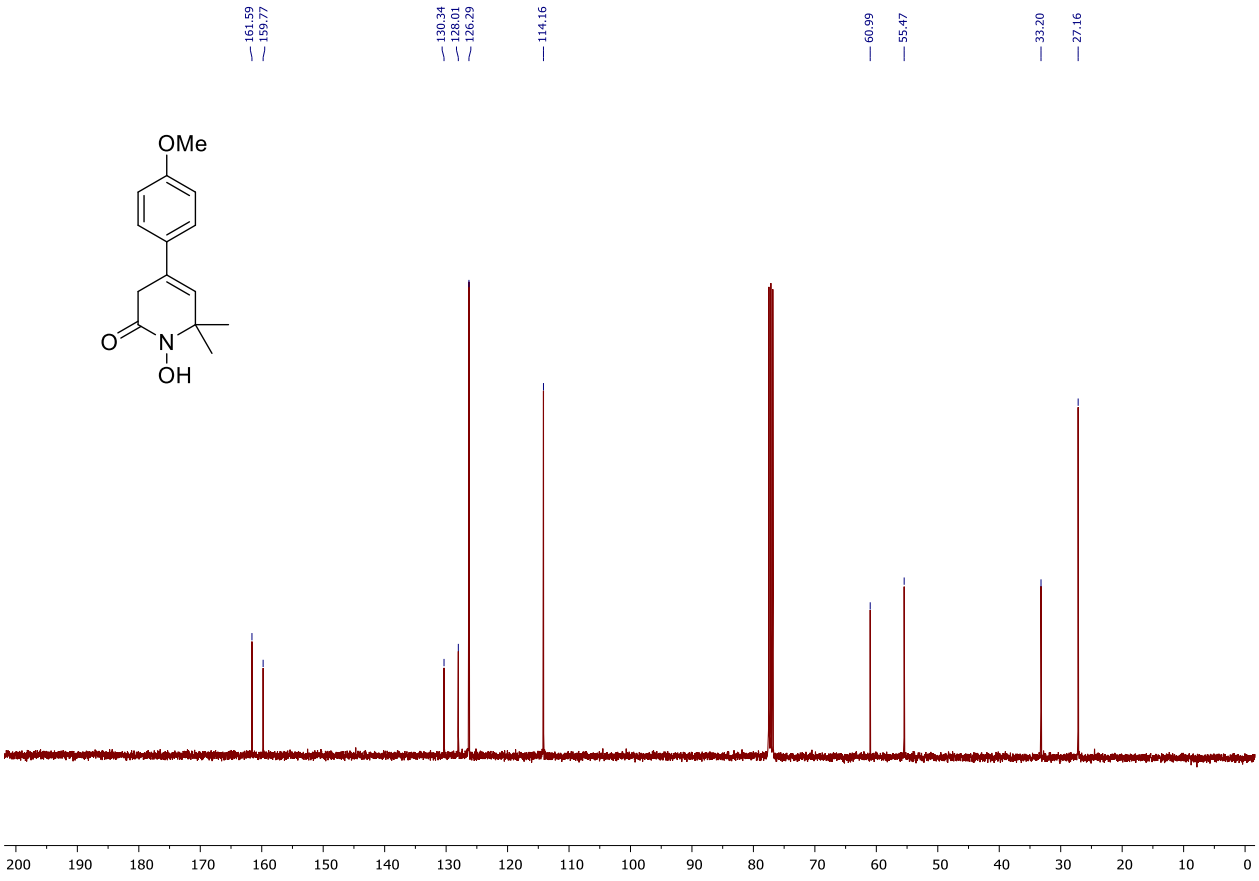
^{1}H and ^{13}C NMR spectra of compound 13p



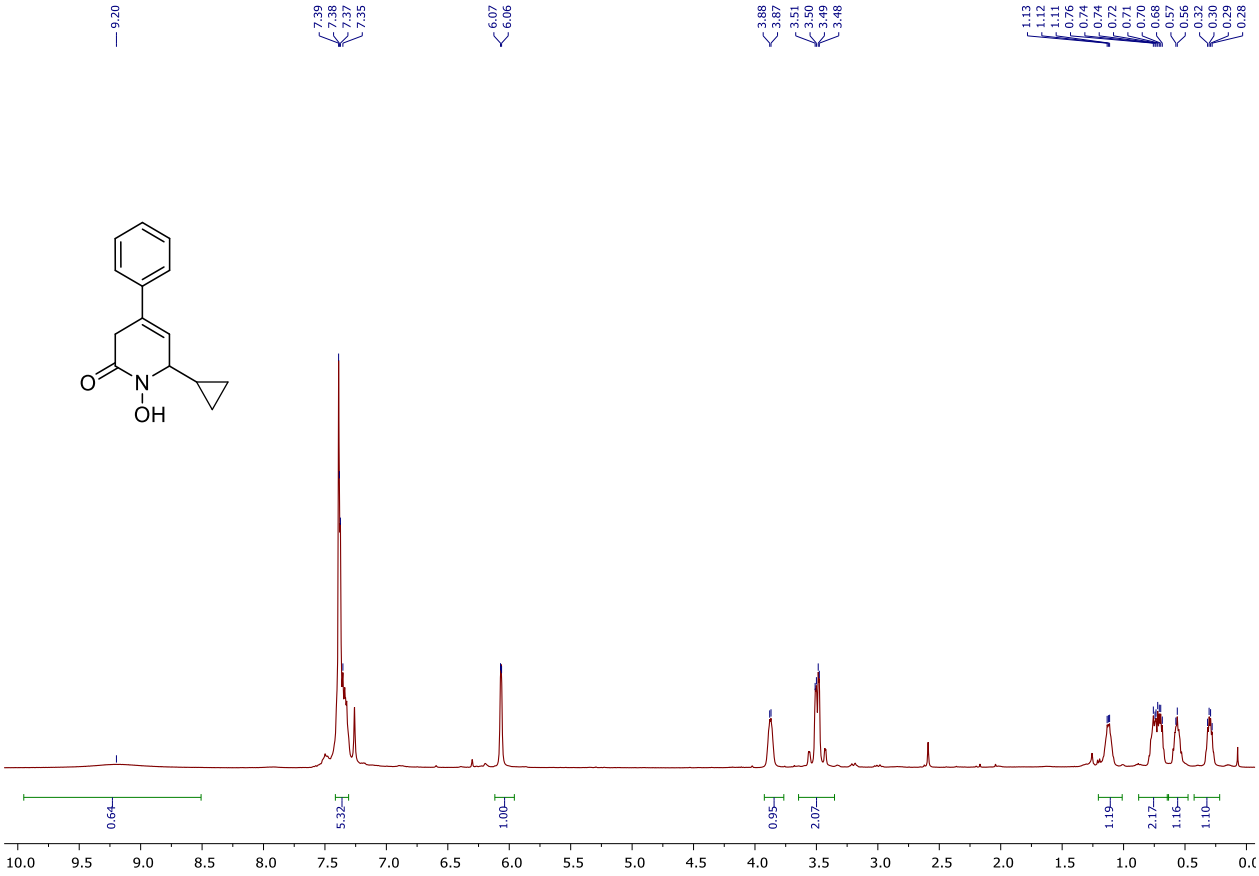


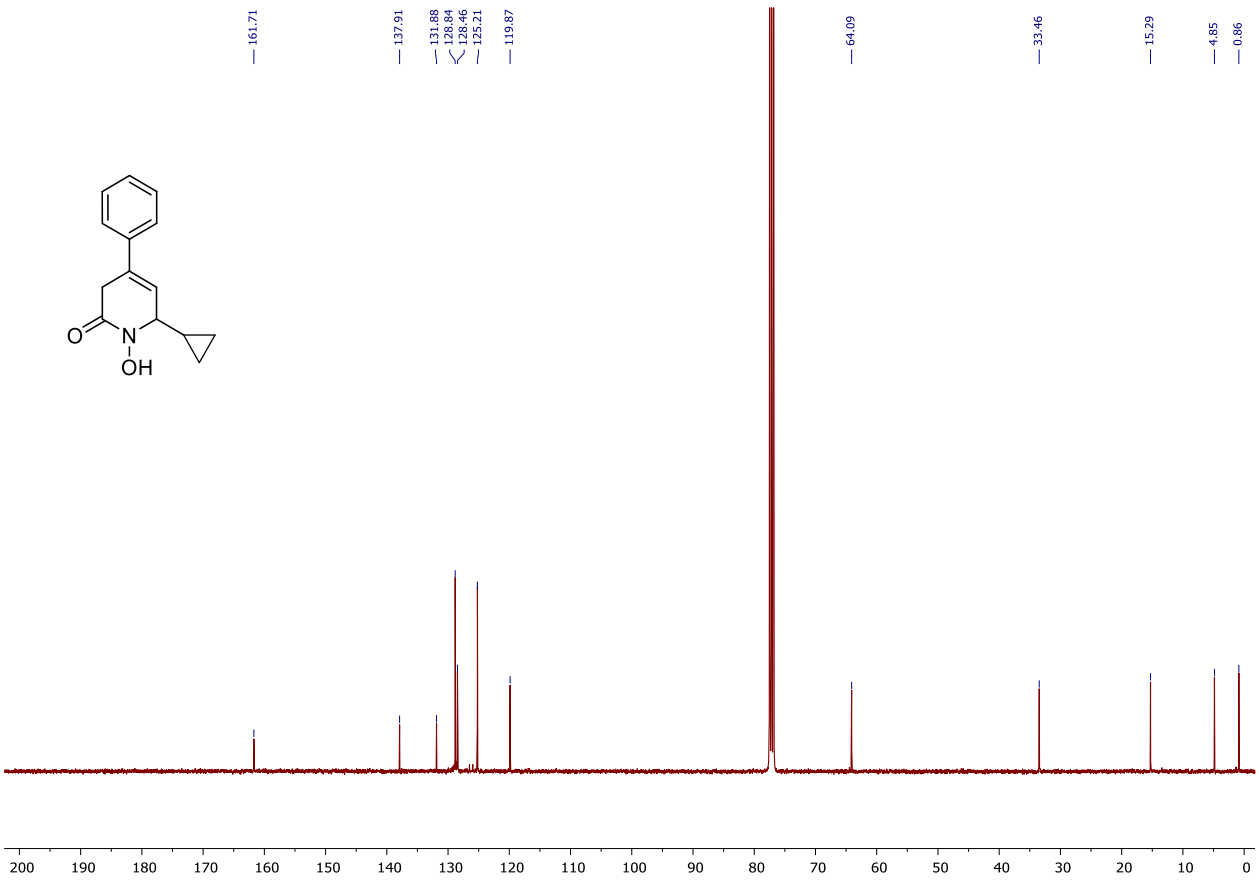
^{1}H and ^{13}C NMR spectra of compound 13q



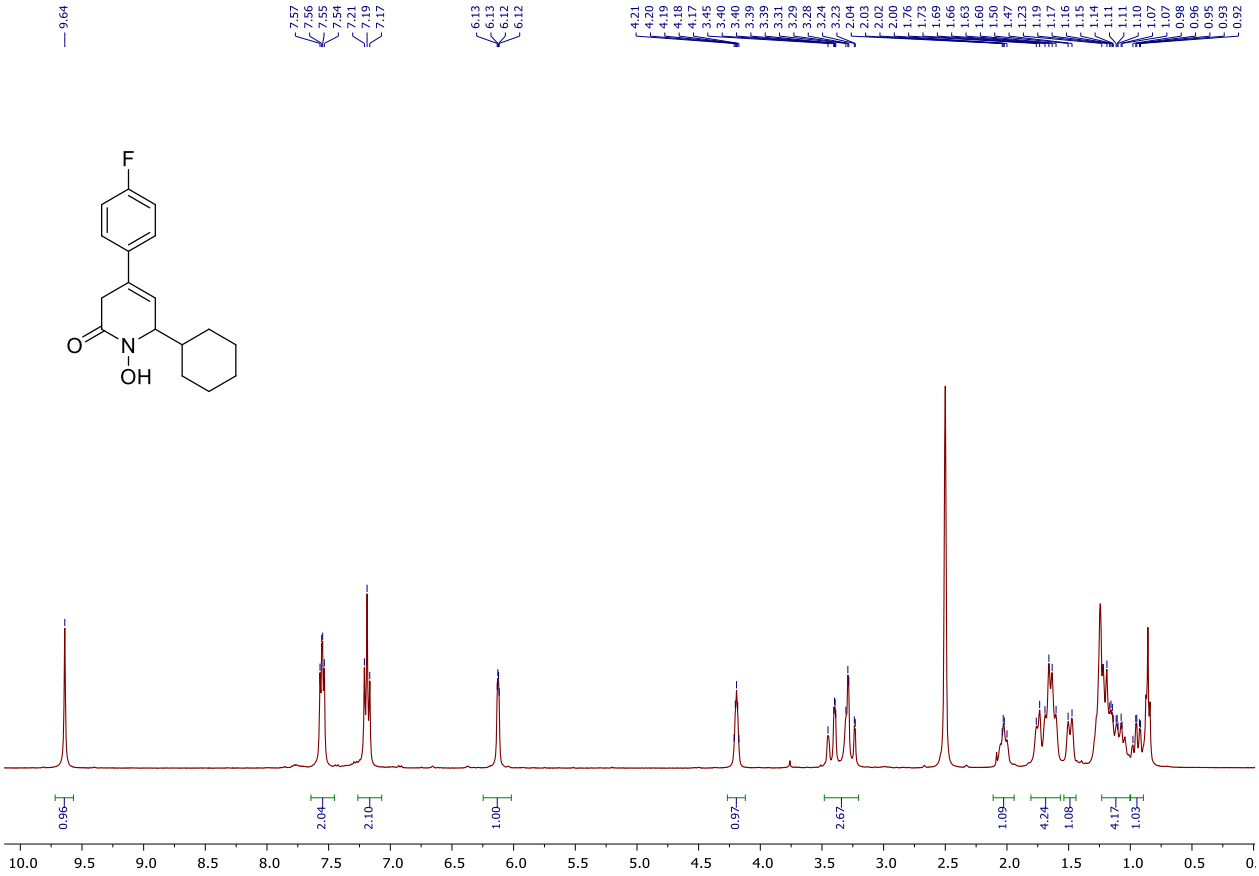


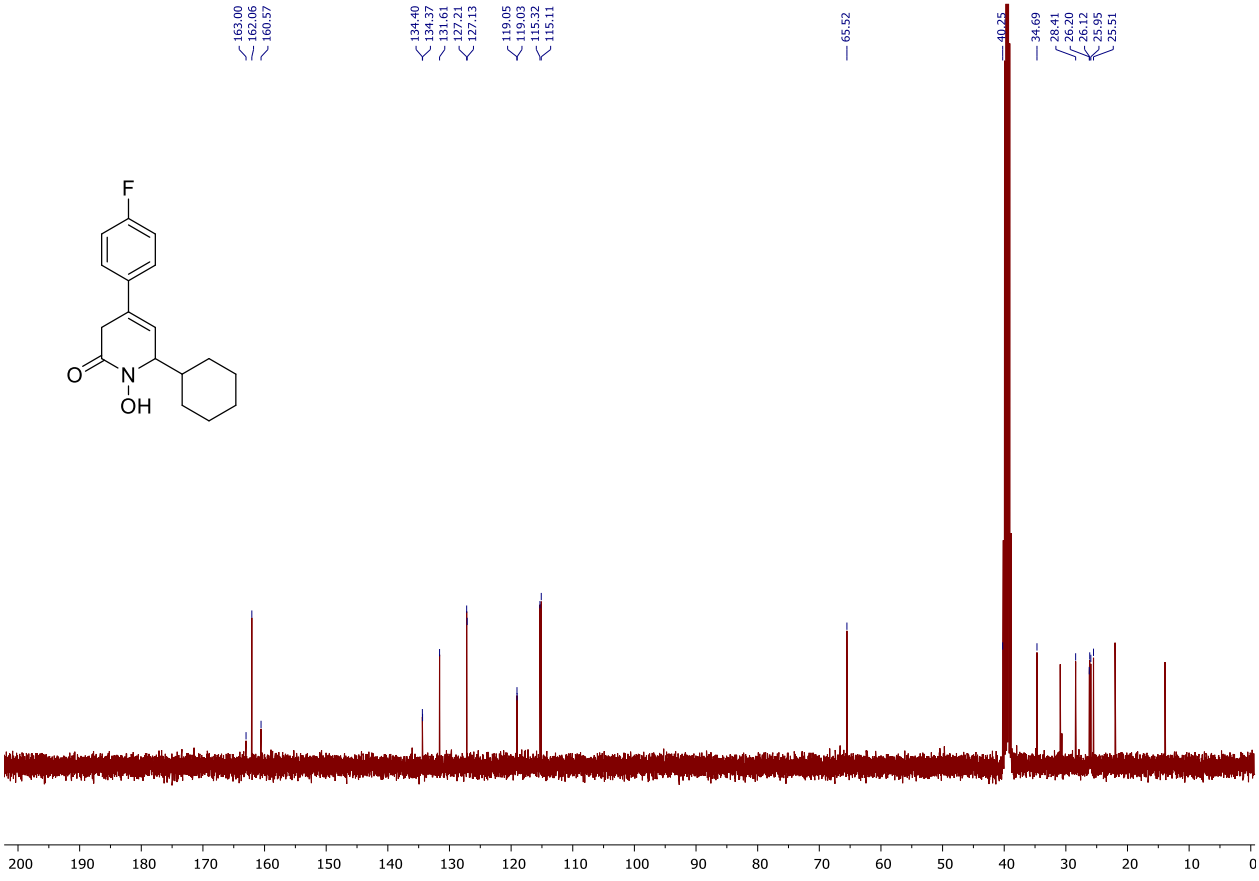
^{1}H and ^{13}C NMR spectra of compound 13r



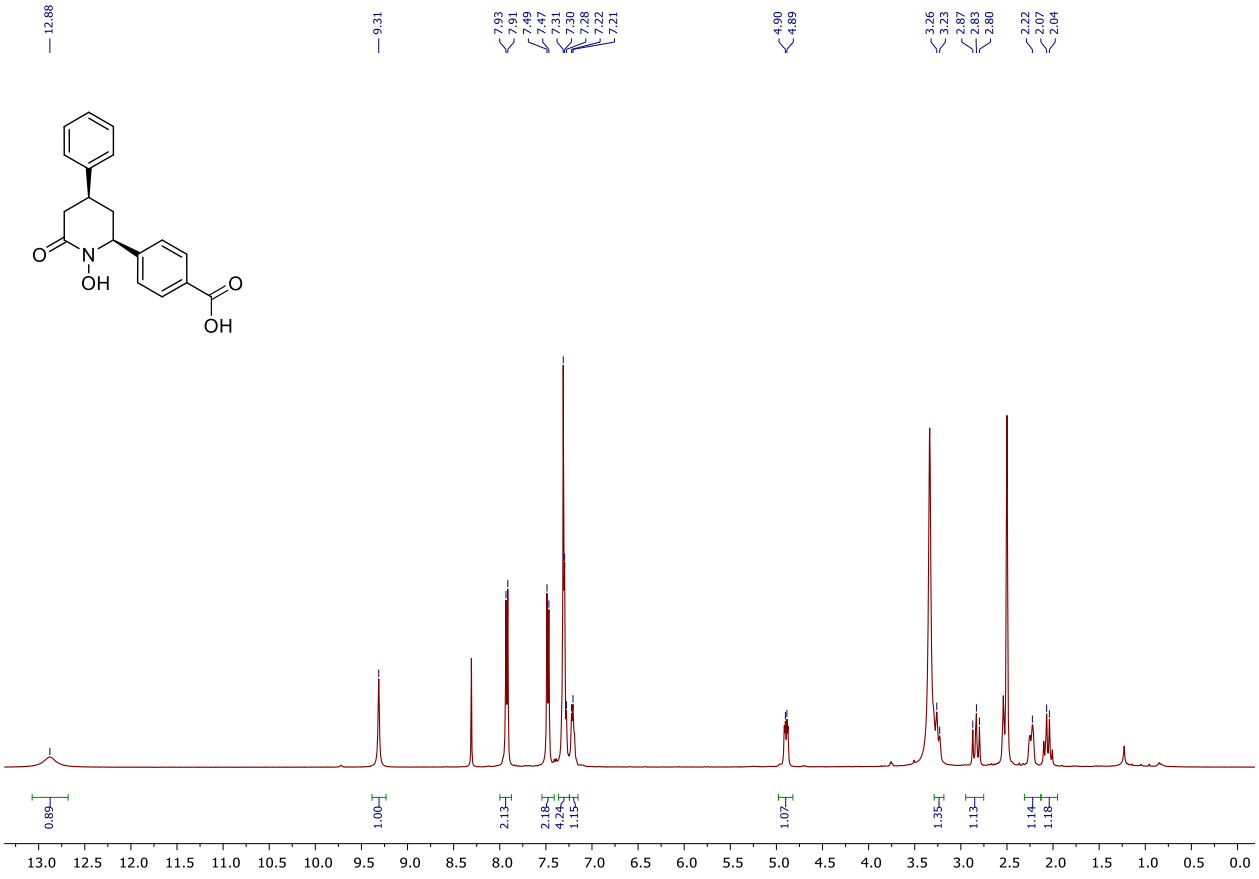


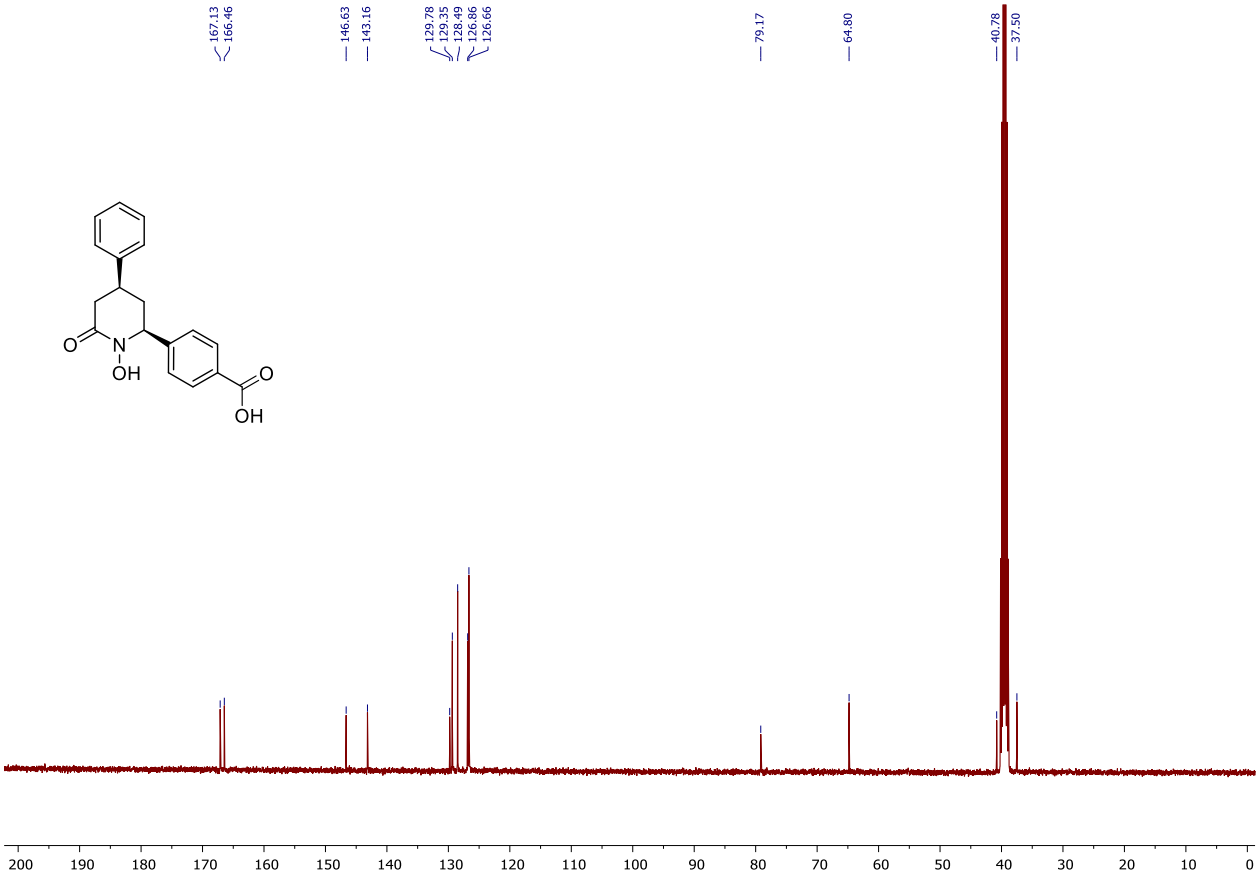
^{1}H and ^{13}C NMR spectra of compound 13s





^{1}H and ^{13}C NMR spectra of compound 20





^{1}H and ^{13}C NMR spectra of compound 21