Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

Applying green chemistry principles to iron catalysis: Mild and selective domino synthesis of pyrroles from nitroarenes

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1. General Information

All manipulations involving air- and moisture-sensitive compounds were carried out in an MBraun glovebox or using standard Schlenk techniques under an argon atmosphere. Iron(II) tetrafluoroborate hexahydrate was purchased from Sigma-Aldrich (now Merck), Tetraphos ligand from Strem or Sigma-Aldrich, Peptide **4m** from Bachem and complex **Fe-1** from Strem. All other chemicals were obtained commercially from typical suppliers (ABCR, Alfa Aesar, Ambeed, Combi-Blocks, Sigma-Aldrich, TCI) and were used without further purification, unless otherwise mentioned. Dry and oxygen-free solvents were collected from an Innovative Technologies PS-MD-6 solvent purification system and stored over 3 Å molecular sieves or bought from Acros Organics or VWR in anhydrous grade. Deuterated organic solvents were purchased from Euriso-Top. All hydrogenation experiments were carried out in a 300 mL autoclave (PARR Instrument Company) using high purity (99.999%) H_2 gas from Air Liquide. During screening conversion and yields were determined by gas chromatography (GC), on an HP 6890 machine with flame-ionization detector (FID), equipped with a HP-5 30 m x 250 mm x 0.25 µm column and using *n*-hexadecane as an internal standard. Mass spectra were recorded on a GC-MS Agilent 5973 Network equipped with a mass selective detector. HRMS measurements of unknown compounds were recorded on a Waters Xevo G2XS TOF MS for ESI (Electrospray Ionization) or a MAT 95XP spectrometer (70 eV, Thermo ELECTRON CORPORATION) for EI (Electron Ionization). NMR spectra were recorded on Bruker AV 300 or Bruker AV 400 spectrometers. All chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane and coupling constants (*J*) in hertz (Hz). The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). ^{19}F spectra are not calibrated by an internal reference. Abbreviations used in the reported NMR experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet etc. All measurements were carried out at room temperature unless otherwise stated. Thin layer chromatography (TLC) was performed on aluminum backed hand-cut silica plates (5 × 10 cm, pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV_{254}). If necessary, potassium permanganate (1.5 g of $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200mL water) was used as a developing stain. Ph-Tetraphos ligand was synthesized according to published procedures.[1] Complex **Fe-2** was synthesized by mixing ligand and metal precursor in THF according to published procedures.[1,2]

2. Reaction Optimization

Transferhydrogenation Optimization

General procedure: In a typical catalytic experiment, an 8 mL glass vial containing a stir bar was charged with the iron source (0.025 mmol, 5.0 mol%) and ligand (0.026 mmol, 5.2 mol%) under argon atmosphere (glove box). Afterwards, the reaction vial was capped with a septum cap and removed from the glovebox. The septum cap was pierced with a syringe needle connected to an argon line to avoid pressure build-up. Then, dry degassed solvent (2 mL), nitrobenzene substrate (0.5 mmol, 61.6 mg, 51.3 µL) and 2,5-hexane-dione (0.6 mmol, 68.5 mg, 70.6 µL) were sequentially introduced through the septum while stirring. The vial was set into a temperature-controlled alloy plate. Lastly, formic acid (4.5 equiv., 2.25 mmol, 103.6 mg, 84.9 µL) was added dropwise to the stirred mixture. The reaction was left to stir for the desired time at the desired temperature. Afterwards the reaction was cooled to room temperature (if necessary), diluted with EtOAc (2 mL) and internal standard *n*-hexadecane (50.0 mg) was added. The reaction mixture was then analyzed by calibrated GC-FID.

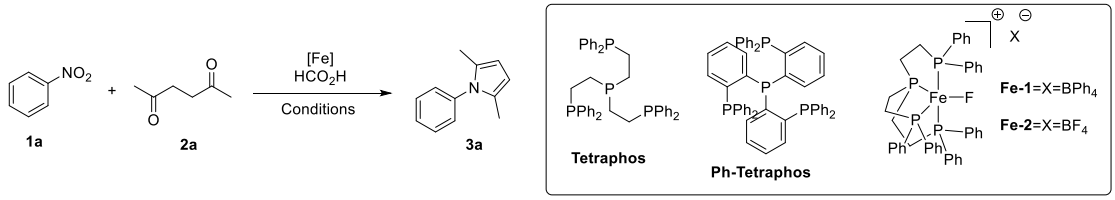


Table S1. Optimization of the Fe-catalyzed Transferhydrogenation/Paal-Knorr cascade.

Entry	Metal salt	Ligand	Solvent	Time	Temp.	Yield xy
1	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	EtOH	2 h	40 °C	99%
2	$Fe(BF_4)_2{\cdot}6H_2O$	Ph-Tetraphos	EtOH	2 h	40 °C	45%
3[a]	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	EtOH	2 h	40 °C	28%
4	$Fe(BF_4)_2{\cdot}6H_2O$	-	EtOH	5 h	25 °C	0%
5	-	Tetraphos	EtOH	5 h	25 °C	0%
6[b]	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	EtOH	5 h	25 °C	0%
7	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	EtOH	5 h	25 °C	97%
8	$Fe(OTf)_2$	Tetraphos	EtOH	5 h	25 °C	99%
9[a]	$Fe(OTf)_2$	Tetraphos	EtOH	2 h	40 °C	23%
10	$Fe(OAc)_2$	Tetraphos	EtOH	5 h	25 °C	0%
11	[Fe(Tetraphos)F][BPh_4]	-	EtOH	5 h	25 °C	24%
12	[Fe(Tetraphos)F][BF_4]	-	EtOH	5 h	25 °C	87%
13	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	*i*-PrOH	5 h	25 °C	89%
14	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	THF	5 h	25 °C	40%
15	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	Dioxane	5 h	25 °C	25%
16	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	DMC	5 h	25 °C	47%
17	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	H_2O	5 h	25 °C	0%
18	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	EtOAc	5 h	25 °C	37%
19[c]	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	EtOH/PhMe	5 h	25 °C	91%
20	$Fe(BF_4)_2{\cdot}6H_2O$	Tetraphos	NMP	5 h	25 °C	13%

[a] 1 mol% Metal and ligand. [b] Without formic acid. [c] Solvent ratio 1:1. Abbreviations: Tetrahydrofuran (THF), Dimethyl carbonate (DMC), N-methyl-2-pyrrolidinone (NMP).

Hydrogenation Optimization

General procedure: In a typical catalytic experiment, an 8 mL glass vial containing a stir bar was charged with $Fe(BF_4)_2 \cdot 6H_2O$ (3.4 mg, 0.01 mmol, 2.0 mol%) and ligand (0.01 mmol, 2.0 mol%) under argon atmosphere (glove box). Afterwards, the reaction vial was capped with a septum cap and removed from the glovebox. Then, sequentially dry degassed solvent (1.5 mL), nitrobenzene substrate (0.5 mmol, 61.6 mg, 51.3 µL), 2,5-hexane-dione (1.0 mmol, 114.1 mg, 120.0 µL) and the acid/additive was introduced through the septum while stirring. The vial was set into an alloy plate, which was then put inside an argon-flushed autoclave. Before closing the autoclave, the septum cap of each vial was pierced with a syringe needle to allow free gas flow. The closed autoclave was then sequentially flushed with nitrogen and hydrogen (3 x 20 bar each) and pressurized to the desired pressure (20 bar H_2). The autoclave was then put into an aluminum heating block and left to stir for the desired time at the desired temperature. Afterwards the autoclave was cooled to room temperature, the pressure was carefully(!) released and the autoclave was opened. The contents of each reaction vial were diluted with EtOAc (2 mL) and internal standard *n*-hexadecane (50.0 mg) was added. The reaction mixtures were then analyzed by calibrated GC-FID.

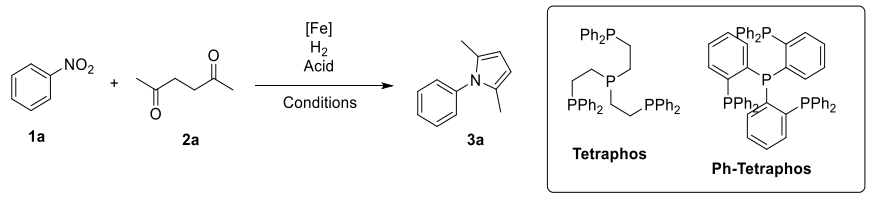


Table S2. Optimization of the Fe-catalyzed Hydrogenation/Paal-Knorr cascade.

Entry	Metal salt	Ligand	Solvent	Additive (mol%)	Time	Temp.	Yield xy
1	$Fe(BF_4)_2 \cdot 6H_2O$	Tetraphos	THF	TFA (50)	2 h	120 °C	16%
2	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (50)	2 h	120 °C	96%
3	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (50)	2 h	100 °C	84%
4	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (50)	6 h	100 °C	99%
5	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	-	2 h	120 °C	0%
6	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (3)	2 h	120 °C	4%
7	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (5)	2 h	120 °C	15%
8	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (10)	2 h	120 °C	26%
9	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (100)	2 h	120 °C	93%
10	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF	TFA (1200)	2 h	120 °C	3%
11	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	*t*-amylOH	TFA (50)	2 h	120 °C	91%
12	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	*t*-amylOH	TFA (100)	2 h	120 °C	92%
13[a]	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF/H_2O	TFA (50)	2 h	120 °C	0%
14[a]	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF/HOAc	TFA (50)	2 h	120 °C	62%
15[a]	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF/HOAc	-	2 h	120 °C	0%
16[a]	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF/HFIP	TFA (50)	2 h	120 °C	50%
17[a]	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF/TFE	TFA (50)	2 h	120 °C	78%
18[a]	$Fe(BF_4)_2 \cdot 6H_2O$	Ph-Tetraphos	THF/TFE	-	2 h	120 °C	3%

[a] Solvent ratio 3:1. Abbreviations: Tetrahydrofuran (THF), Trifluoroacetic acid (TFA), Hexafluoroisopropanol (HFIP), Trifluoroethanol (TFE).

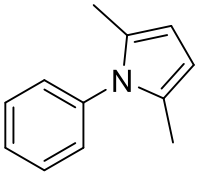
3. Synthesis and Characterization of Products

General Method A: In a typical catalytic experiment, an 8 mL glass vial containing a stir bar was sequentially charged with $Fe(BF_4)_2 \cdot 6H_2O$ (5.0 mol%, 0.025 mmol, 8.4 mg), Tetraphos ligand (5.2 mol%, 0.026 mmol, 17.4 mg), nitroarene substrate (0.5 mmol) and 1,4-dicarbonyl compound (0.6 mmol) under argon atmosphere (glove box). Afterwards, the reaction vial was capped with a septum cap and removed from the glovebox. The septum cap was pierced with a syringe needle connected to an argon line to avoid pressure build-up. Then, dry degassed solvent (2 mL) was introduced through the septum. The vial was set into a temperature-controlled alloy plate. Lastly, formic acid (4.5 equiv., 2.25 mmol, 103.6 mg, 84.9 µL) was added dropwise to the stirred mixture. The reaction was left to stir for 5 h at 25 °C (unless stated otherwise) and monitored using TLC or GC-MS. Upon completion of the reaction, the reaction mixture was concentrated and directly purified by flash column chromatography on silica gel to obtain isolated products.

General Method B (Basic Aq. Work-Up): In a typical catalytic experiment, an 8 mL glass vial containing a stir bar was sequentially charged with $Fe(BF_4)_2 \cdot 6H_2O$ (5.0 mol%, 0.025 mmol, 8.4 mg), Tetraphos ligand (5.2 mol%, 0.026 mmol, 17.4 mg), nitroarene substrate (0.5 mmol) and 1,4-dicarbonyl compound (0.6 mmol) under argon atmosphere (glove box). Afterwards, the reaction vial was capped with a septum cap and removed from the glovebox. The septum cap was pierced with a syringe needle connected to an argon line to avoid pressure build-up. Then, dry degassed solvent (2 mL) was introduced through the septum. The vial was set into a temperature-controlled alloy plate. Lastly, formic acid (4.5 equiv., 2.25 mmol, 103.6 mg, 84.9 µL) was added dropwise to the stirred mixture. The reaction was left to stir for 5 h at 25 °C (unless stated otherwise) and monitored using TLC or GC-MS. Upon completion of the reaction, the reaction mixture was diluted with EtOAc (~5 mL), treated with saturated aq. Na_2CO_3 (~5 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 5 mL), the combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated. The crude residue was then purified by flash column chromatography on silica gel to obtain isolated products.

General Method C (Hydrogenation): In a typical catalytic experiment, an 8 mL glass vial containing a stir bar was sequentially charged with $Fe(BF_4)_2 \cdot 6H_2O$ (2.0 mol%, 0.01 mmol, 3.4 mg), Ph-Tetraphos ligand (2.0 mol%, 0.01 mmol, 8.2 mg), nitroarene substrate (0.5 mmol) and 1,4-dicarbonyl compound (0.6 mmol) under argon atmosphere (glove box). Afterwards, the reaction vial was capped with a septum cap and removed from the glovebox. Then, dry degassed THF (1.5 mL) and TFA (50 mol%, 0.25 mmol, 28.5 mg, 19.2 µL) were introduced through the septum. The vial was set into an alloy plate, which was then put inside an argon-flushed autoclave. Before closing the autoclave, the septum cap of each vial was pierced with a syringe needle to allow free gas flow. The closed autoclave was then sequentially flushed with nitrogen and hydrogen (3 x 20 bar each) and pressurized to the desired pressure (20 bar H_2). The autoclave was then put into an aluminum heating block and left to stir for 20 h at 120 °C. Afterwards the autoclave was cooled to room temperature, the pressure was carefully(!) released and the autoclave was opened. The crude reaction mixture was then concentrated and directly purified by flash column chromatography on silica gel to obtain isolated products.

General Note: Several of the electron-rich pyrroles synthesized in this report are only moderately air-stable and should not be stored on air for longer periods of time. Oxidative degradation is especially prevalent in aerobic chloroform solutions.



3a

2,5-dimethyl-1-phenyl-1*H*-pyrrole (3a)[3]:

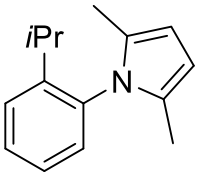
According to General Method A, **3a** was isolated in 78.2 mg (0.46 mmol, 91% yield) as a colorless solid.

TLC R_f = 0.56 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.45 – 7.38 (m, 1H), 7.26 – 7.21 (m, 2H), 5.93 (bs, 2H), 2.05 (s, 6H).

^{13}C NMR (101 MHz, CDCl3) δ 139.1, 129.2, 128.9, 128.4, 127.8, 105.7, 13.1.

GC-MS *m/z* 171 $[M]^+$.



3b

1-(2-isopropylphenyl)-2,5-dimethyl-1*H*-pyrrole (3b)[4]:

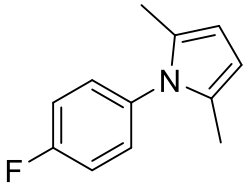
According to General Method A, **3b** was isolated after 24 h in 77.0 mg (0.36 mmol, 72% yield) as a colorless oil.

TLC R_f = 0.63 (5% EtOAc in Heptane).

^{1}H NMR (300 MHz, CDCl3) δ 7.48 – 7.37 (m, 2H), 7.32 – 7.21 (m, 1H), 7.15 – 7.09 (m, 1H), 5.88 (bs, 2H), 2.49 (sept, *J* = 6.9 Hz, 1H), 1.95 (s, 6H), 1.14 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 136.6, 129.1, 129.0, 128.9, 126.7, 126.5, 105.3, 27.5, 23.9, 12.9.

GC-MS *m/z* 213 $[M]^+$.



3c

1-(4-fluorophenyl)-2,5-dimethyl-1*H*-pyrrole (3c)[5]:

According to General Method A, **3c** was isolated in 72.0 mg (0.38 mmol, 76% yield) as a colorless crystalline solid.

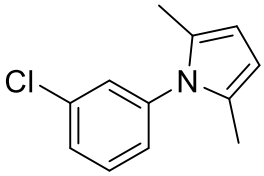
TLC R_f = 0.56 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 4H), 5.91 (bs, 2H), 2.03 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 247.3 Hz), 135.1 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 8.6 Hz), 129.0, 116.1 (d, *J* = 22.7 Hz), 105.9, 13.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.1.

GC-MS *m/z* 189 $[M]^+$.



3d

1-(3-chlorophenyl)-2,5-dimethyl-1*H*-pyrrole (3d)[6]:

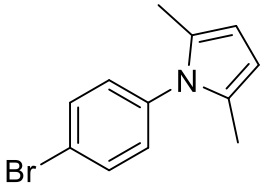
According to General Method A, **3d** was isolated in 84.0 mg (0.41 mmol, 82% yield) as a colorless crystalline solid.

TLC R_f = 0.60 (5% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.26 – 7.23 (m, 1H), 7.16 – 7.09 (m, 1H), 5.91 (s, 2H), 2.05 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 134.7, 130.1, 128.9, 128.7, 128.1, 126.7, 106.3, 13.1.

GC-MS *m/z* 204 $[M-H]^+$.



3e

1-(4-bromophenyl)-2,5-dimethyl-1*H*-pyrrole (3e)[7]:

According to General Method A, **3e** was isolated in 98.0 mg (0.39 mmol, 78% yield) as a colorless crystalline solid.

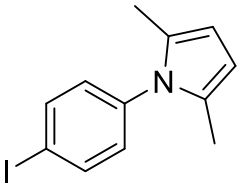
Additionally, **3e** could be synthesized according to a modified (3 mol% Fe-salt/Ligand) General Method C in 67 mg (0.27 mmol, 54% yield).

TLC R_f = 0.61 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 2H), 7.11 – 7.09 (m, 2H), 5.91 (s, 2H), 2.03 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 132.4, 130.0, 128.8, 121.7, 106.2, 13.1.

GC-MS *m/z* 250 $[M+H]^+$.



3f

1-(4-iodophenyl)-2,5-dimethyl-1*H*-pyrrole (3f)[8]:

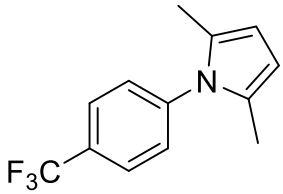
According to General Method A, **3f** was isolated after 24 h in 90.6 mg (0.31 mmol, 61% yield) as a colorless solid.

TLC R_f = 0.61 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 2H), 6.98 – 6.95 (m, 2H), 5.91 (s, 2H), 2.03 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.4, 130.3, 128.8, 106.3, 93.0, 13.1.

GC-MS *m/z* 297 $[M]^+$.



3g

2,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (3g)[9]:

According to General Method A, **3f** was isolated after 24 h in 87.0 mg (0.36 mmol, 73% yield) as a colorless crystalline solid.

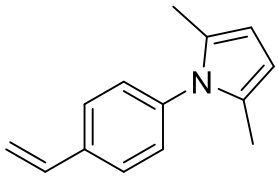
TLC R_f = 0.55 (5% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.65 (m, 2H), 7.41 – 7.30 (m, 2H), 5.94 (s, 2H), 2.05 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 130.1, 129.7, 128.8, 128.7, 126.5, 126.4, 126.4, 126.3, 125.8, 122.2, 106.7, 13.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.5.

GC-MS *m/z* 239 $[M]^+$.



3h

2,5-dimethyl-1-(4-vinylphenyl)-1*H*-pyrrole (3h)[10]:

According to General Method A, **3h** was isolated in 74.0 mg (0.38 mmol, 75% yield) as a light-yellow solid.

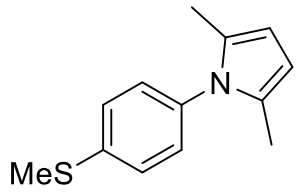
TLC R_f = 0.60 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.44 (m, 2H), 7.22 – 7.13 (m, 2H), 6.78 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.92 (s, 2H), 5.82 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.34 (dd, *J* = 10.9, 0.7 Hz, 1H), 2.06 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 137.0, 136.1, 128.9, 128.4, 126.9, 114.9, 105.9, 13.2.

GC-MS *m/z* 197 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{14}H_{15}N+H^+$: 198.1277 $[M+H]^+$; found: 198.1283.



3i

2,5-dimethyl-1-(4-(methylthio)phenyl)-1*H*-pyrrole (3i)[11]:

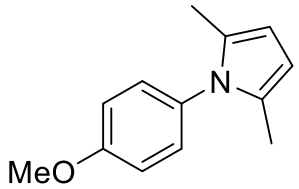
According to General Method A, **3i** was isolated in 104.0 mg (0.48 mmol, 96% yield) as a light-yellow crystalline solid.

TLC R_f = 0.46 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 2H), 7.19 – 7.09 (m, 2H), 5.91 (s, 2H), 2.55 (s, 3H), 2.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 136.0, 129.0, 128.7, 126.8, 105.8, 15.8, 13.1.

GC-MS *m/z* 217 $[M]^+$.



3j

1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (3j)[11]:

According to General Method A, **3j** was isolated after 24 h in 50.0 mg (0.25 mmol, 50% yield) as a colorless crystalline solid.

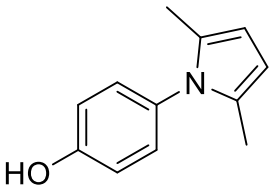
Additionally, **3j** could be synthesized according to General Method C, giving 40.1 mg (0.20 mmol, 40% yield).

TLC R_f = 0.41 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 2H), 7.02 – 6.92 (m, 2H), 5.87 (s, 2H), 3.87 (s, 3H), 2.02 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 131.9, 129.4, 129.2, 114.3, 105.4, 55.6, 13.1.

GC-MS *m/z* 201 $[M]^+$.



3k

4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenol (3k)[8]:

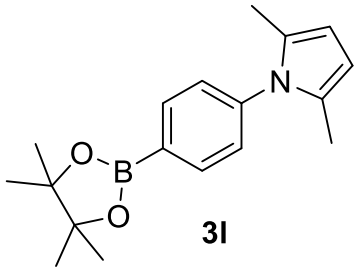
According to General Method A, **3k** was isolated in 71.0 mg (0.38 mmol, 76% yield) as a colorless crystalline solid.

TLC R_f = 0.30 (20% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 – 7.04 (m, 2H), 6.93 – 6.86 (m, 2H), 5.53 (s, 2H), 2.02 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 132.0, 129.6, 129.2, 115.9, 105.4, 13.1.

GC-MS *m/z* 187 $[M]^+$.



3l

2,5-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrrole (3l)[12]:

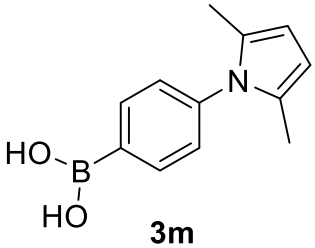
According to General Method A, **3l** was isolated in 97.3 mg (0.33 mmol, 66% yield) as a colorless crystalline solid.

TLC R_f = 0.37 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.25 – 7.18 (m, 2H), 5.91 (s, 2H), 2.03 (d, *J* = 0.8 Hz, 6H), 1.37 (d, *J* = 0.7 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 135.7, 128.8, 127.7, 106.0, 84.2, 25.0, 13.2. B-bound carbon was not detected.

GC-MS *m/z* 297 $[M]^+$.



3m

(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)boronic acid (3m)[13]:

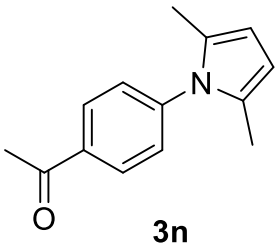
According to General Method A, **3m** was isolated after 24 h in 67.5 mg (0.31 mmol, 63% yield) as a sensitive colorless crystalline solid.

TLC R_f = 0.37 (50% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 – 8.32 (m, 2H), 7.49 – 7.34 (m, 2H), 5.98 (s, 2H), 2.12 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 136.7, 128.8, 128.0, 106.4, 13.2. B-bound carbon was not detected.

HRMS (ESI) *m/z* calcd for $C_{12}H_{14}BNO_2$+H^+: 216.1198 $[M+H]^+$; found: 216.1200.



3n

1-(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)ethan-1-one (3n)[14]:

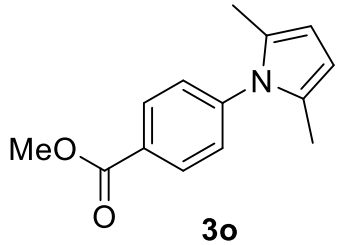
According to General Method A, **3n** was isolated after 24 h at 40 °C in 53.0 mg (0.25 mmol, 50% yield) as a colorless solid.

TLC R_f = 0.43 (20% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.00 (m, 2H), 7.36 – 7.28 (m, 2H), 5.94 (s, 2H), 2.66 (s, 3H), 2.06 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 143.4, 136.2, 129.4, 128.7, 128.4, 106.7, 26.8, 13.2.

GC-MS *m/z* 213 $[M]^+$.



3o

methyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzoate (3o)[15]:

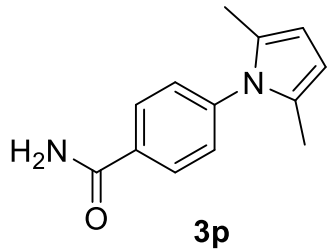
According to General Method A, **3o** was isolated after 24 h in 73.0 mg (0.32 mmol, 64% yield) as a colorless crystalline solid.

TLC R_f = 0.45 (10% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.09 (m, 2H), 7.35 – 7.26 (m, 2H), 5.93 (s, 2H), 3.96 (s, 3H), 2.05 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 143.3, 130.6, 129.4, 128.7, 128.2, 106.6, 52.4, 13.2.

GC-MS *m/z* 229 $[M]^+$.



3p

4-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzamide (3p):

According to General Method A, **3p** was isolated after 24 h in 63.0 mg (0.29 mmol, 59% yield) as a colorless solid.

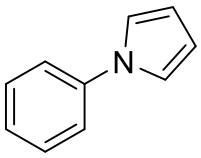
TLC R_f = 0.52 (100% EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H), 7.38 – 7.25 (m, 2H), 6.35 (s, 2H), 5.93 (s, 2H), 2.04 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 142.5, 132.5, 128.8, 128.5, 128.5, 106.6, 13.2.

GC-MS *m/z* 214 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2O+H^+$: 215.1184 $[M+H]^+$; found: 215.1187.



3q

1-phenyl-1*H*-pyrrole (3q)[3]:

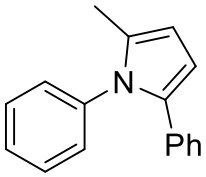
According to a modification of General Method B, **3q** was synthesized from 2,5-dimethoxytetrahydrofuran (*cis*/*trans*-mixture) as the 1,4-dicarbonyl source. After reacting for 5 h at room temperature, 1.5 mL of 50% aq. formic acid was added and the product was isolated after 24 h (total time) in 63.0 mg (0.44 mmol, 88% yield) as a volatile(!) colorless crystalline solid.

TLC R_f = 0.40 (100% Pentane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 4H), 7.30 – 7.23 (m, 1H), 7.16 – 7.07 (m, 2H), 6.42 – 6.31 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 129.7, 125.7, 120.7, 119.5, 110.5.

GC-MS *m/z* 143 $[M]^+$.



3r

2-methyl-1,5-diphenyl-1*H*-pyrrole (3r)[3]:

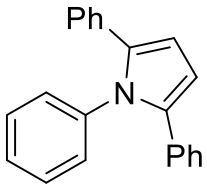
According to General Method A, **3r** was isolated after 24 h at 40 °C in 98.0 mg (0.42 mmol, 84% yield) as a colorless solid.

TLC R_f = 0.25 (5% Toluene in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 3H), 7.20 – 7.04 (m, 7H), 6.38 (d, *J* = 3.5 Hz, 1H), 6.12 (dq, *J* = 3.5, 0.9 Hz, 1H), 2.21 (d, *J* = 0.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 134.3, 133.7, 131.8, 129.1, 128.6, 128.1, 127.9, 127.5, 125.8, 108.8, 107.6, 13.5.

GC-MS *m/z* 233 $[M]^+$.



3s

1,2,5-triphenyl-1*H*-pyrrole (3s)[3]:

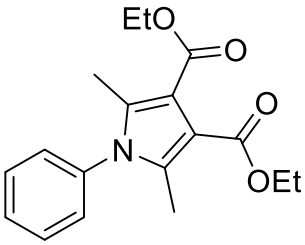
According to General Method C, **3s** was isolated after 20 h at 120 °C in 110.0 mg (0.37 mmol, 75% yield) as a colorless fluffy solid.

TLC R_f = 0.63 (10% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.01 (m, 15H), 6.49 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 135.9, 133.4, 129.0, 128.9, 128.8, 128.0, 127.4, 126.3, 110.1.

GC-MS *m/z* 295 $[M]^+$.



3t

diethyl 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3,4-dicarboxylate (3t)[16]:

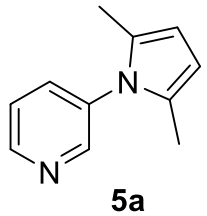
According to General Method A, **3t** was isolated in 128.0 mg (0.40 mmol, 81% yield) as a colorless viscous oil.

TLC R_f = 0.33 (20% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.40 (m, 3H), 7.20 – 7.06 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 4H), 2.13 (s, 6H), 1.34 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 137.0, 134.3, 129.8, 129.2, 128.3, 112.7, 60.3, 14.5, 11.9.

GC-MS *m/z* 315 $[M]^+$.



5a

3-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (5a)[11]:

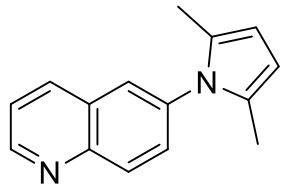
According to General Method B, **5a** was isolated after 24 h in 49.2 mg (0.29 mmol, 57% yield) as a faint-yellow oil.

TLC R_f = 0.36 (30% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.53 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.58 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1H), 7.43 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 5.94 (s, 2H), 2.04 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 148.8, 135.7 (probably 2C), 129.0, 123.8, 106.8, 13.1.

GC-MS *m/z* 172 $[M]^+$.



5b

6-(2,5-dimethyl-1*H*-pyrrol-1-yl)quinoline (5b)[17]:

According to General Method B, **5b** was isolated after 24 h in 65.0 mg (0.29 mmol, 59% yield) as a beige crystalline solid.

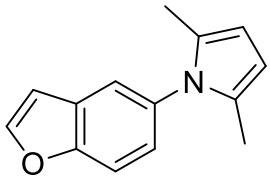
TLC R_f = 0.33 (30% EtOAc in Heptane).

^{1}H NMR (300 MHz, C_6D_6) δ 8.73 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.22 – 8.10 (m, 1H), 7.40 (ddd, *J* = 8.5, 1.9, 0.9 Hz, 1H), 7.11 – 6.99 (m, 2H), 6.73 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.19 (s, 2H), 1.98 (s, 6H).

^{13}C NMR (75 MHz, DMSO-d) δ 151.1, 146.6, 136.2, 136.2, 130.0, 129.8, 128.0, 127.8, 126.5, 122.1, 106.3, 12.9.

GC-MS *m/z* 222 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{15}H_{14}N_2+H^+$: 223.1230 $[M+H]^+$; found: 223.1233.



5c

1-(benzofuran-5-yl)-2,5-dimethyl-1*H*-pyrrole (5c):

According to General Method A, **5c** was isolated after 24 h in 78.0 mg (0.37 mmol, 74% yield) as a colorless solid.

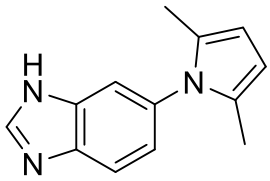
TLC R_f = 0.31 (1% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.2 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.17 – 7.10 (m, 1H), 6.83 (s, 1H), 5.90 (s, 2H), 2.03 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 146.4, 134.2, 129.3, 128.1, 124.7, 121.0, 111.8, 107.0, 105.5, 13.2.

GC-MS *m/z* 210 $[M-H]^+$.

HRMS (ESI) *m/z* calcd for $C_{14}H_{13}NO+H^+$: 212.1075 $[M+H]^+$; found: 212.1080.



5d

6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1*H*-benzo[*d*]imidazole (5d)[3]:

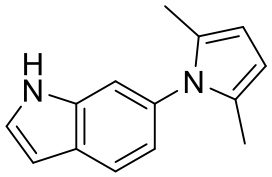
According to General Method B, **5d** was isolated after 24 h in 88.0 mg (0.42 mmol, 83% yield) as an off-white solid.

TLC R_f = 0.42 (99% EtOAc with 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 8.31 (s, 1H), 7.74 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.54 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.15 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.91 (s, 2H), 2.02 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 137.8, 136.7, 134.6, 129.3, 124.0, 115.6, 115.5, 105.6, 13.2.

GC-MS *m/z* 211 $[M]^+$.



5e

6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1*H*-indole (5e)[18]:

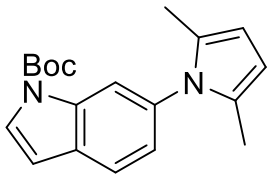
According to General Method A, **5e** was isolated after 24 h in 34.3 mg (0.16 mmol, 33% yield) as a colorless crystalline solid.

TLC R_f = 0.30 (20% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.69 (dt, *J* = 8.3, 0.7 Hz, 1H), 7.30 (dd, *J* = 3.3, 2.4 Hz, 1H), 7.23 (dt, *J* = 1.8, 0.8 Hz, 1H), 6.96 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.63 (ddd, *J* = 3.2, 2.0, 1.0 Hz, 1H), 5.93 (s, 2H), 2.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.6, 129.5, 127.4, 125.5, 121.0, 120.7, 111.0, 105.2, 102.9, 13.2.

GC-MS *m/z* 210 $[M]^+$.



5f

***tert*-butyl 6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1*H*-indole-1-carboxylate (5f):**

According to General Method A, **5f** was isolated after 24 h in 86.2 mg (0.28 mmol, 56% yield) as a colorless viscous oil.

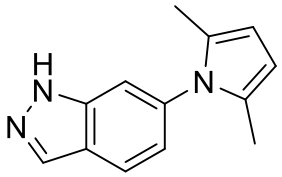
TLC R_f = 0.40 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.68 (d, *J* = 3.8 Hz, 1H), 7.62 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.10 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.64 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.93 (s, 2H), 2.08 (s, 6H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 135.5, 135.3, 129.8, 129.2, 127.1, 123.2, 121.0, 115.4, 107.1, 105.5, 84.1, 28.3, 13.3.

GC-MS *m/z* 310 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_2+H^+$: 311.1759 $[M+H]^+$; found: 311.1764.



5g

6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1*H*-indazole (5g):

According to General Method A, **5g** was isolated after 24 h at 40 °C in 88.0 mg (0.42 mmol, 83% yield) as a sensitive colorless solid.

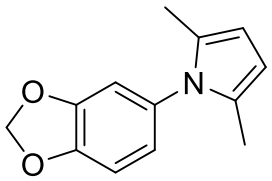
Additionally, **5g** could be synthesized according to General Method C, giving 39.1 mg (0.19 mmol, 37% yield).

TLC R_f = 0.35 (30% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.21 (d, *J* = 1.1 Hz, 1H), 7.85 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.42 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.06 (dd, *J* = 8.5, 1.6 Hz, 1H), 5.94 (s, 2H), 2.06 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 138.8, 134.2, 129.2, 122.7, 122.2, 121.7, 109.8, 106.2, 13.2.

GC-MS *m/z* 211 $[M]^+$.



5h

1-(benzo[*d*][1,3]dioxol-5-yl)-2,5-dimethyl-1*H*-pyrrole (5h)[19]:

According to General Method A, **5h** was isolated after 24 h in 37.0 mg (0.17 mmol, 34% yield) as a colorless oil.

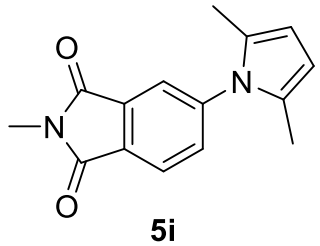
TLC R_f = 0.43 (5% EtOAc in Heptane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.84 (m, 1H), 6.72 – 6.63 (m, 2H), 6.05 (s, 2H), 5.87 (s, 2H), 2.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 147.2, 132.9, 129.2, 121.8, 109.3, 108.2, 105.5, 101.8, 13.0.

GC-MS *m/z* 215 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{13}H_{13}NO_2+H^+$: 216.1024 $[M+H]^+$; found: 216.1021.



5i

5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-methylisoindoline-1,3-dione (5i):

According to General Method A, **5i** was isolated after 24 h at 40 °C in 51.0 mg (0.20 mmol, 40% yield) as a light-yellow solid.

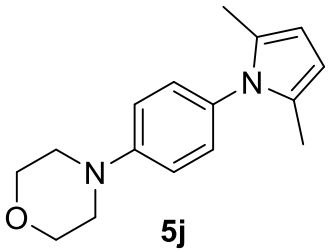
TLC R_f = 0.38 (20% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.68 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.95 (s, 2H), 3.22 (s, 3H), 2.06 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 167.7, 144.5, 133.7, 133.6, 130.9, 128.7, 124.2, 123.0, 107.4, 24.3, 13.3.

GC-MS *m/z* 254 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{15}H_{14}N_2O_2+H^+$: 255.1133 $[M+H]^+$; found: 255.1133.



5j

4-(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)morpholine (5j)[3]:

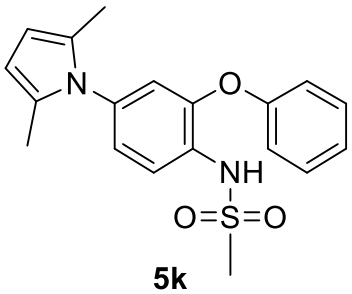
According to General Method B, **5j** was isolated after 24 h in 41.0 mg (0.16 mmol, 32% yield) or after 24 h at 40 °C in 61.0 mg (0.24 mmol, 48% yield) as a colorless solid.

TLC R_f = 0.50 (30% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.89 (s, 2H), 4.00 – 3.84 (m, 4H), 3.30 – 3.18 (m, 4H), 2.03 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 131.4, 129.2, 129.1, 115.9, 105.4, 66.9, 49.4, 13.1.

GC-MS *m/z* 256 $[M]^+$.



5k

***N*-(4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-phenoxyphenyl)methanesulfonamide (5k):**

According to General Method A, **5k** was isolated after 24 h in 106.0 mg (0.30 mmol, 60% yield) as a colorless solid.

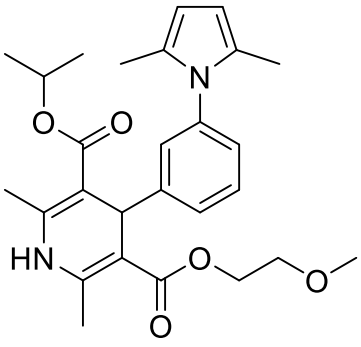
TLC R_f = 0.35 (30% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.24 – 7.17 (m, 1H), 7.09 – 7.01 (m, 3H), 6.98 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 5.85 (s, 2H), 3.12 (s, 3H), 2.00 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 147.9, 136.1, 130.5, 128.8, 127.2, 125.2, 123.6, 121.2, 119.4, 117.3, 106.1, 40.1, 13.1.

GC-MS *m/z* 356 $[M]^+$.

HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2O_3S+H^+$: 357.1273 $[M+H]^+$; found: 357.1273.



5l

3-isopropyl 5-(2-methoxyethyl) 4-(3-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5l)[17]:

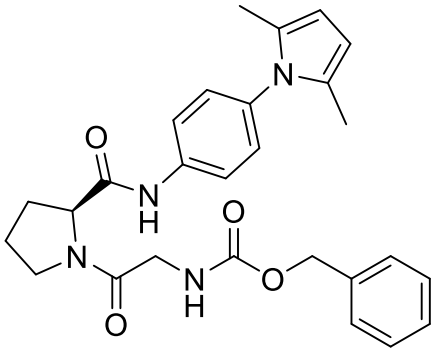
According to a down-scaled (0.25 mmol substrate, other reagents reduced accordingly except for solvent, which remained at 2 mL) General Method A, **5l** was isolated in 104.0 mg (0.23 mmol, 90% yield) as a colorless foamy solid.

TLC R_f = 0.45 (50% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.10 (t, *J* = 1.8 Hz, 1H), 6.95 (ddd, *J* = 7.7, 2.1, 1.3 Hz, 1H), 5.96 (s, 1H), 5.87 (s, 2H), 5.06 (s, 1H), 4.94 (sept, *J* = 6.2 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.55 (ddd, *J* = 6.2, 3.4, 0.9 Hz, 2H), 3.32 (s, 3H), 2.28 (d, *J* = 5.8 Hz 6H), 1.98 (s, 6H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 167.0, 149.1, 144.6, 144.0, 138.6, 128.8, 128.2, 127.7, 127.6, 125.7, 105.4, 104.2, 103.5, 70.7, 67.1, 62.9, 58.9, 39.7, 22.1, 21.8, 19.6, 19.4, 13.1.

GC-MS *m/z* 466 $[M]^+$.



5m

Benzyl (*S*)-(2-(2-((4-(2,5-dimethyl-1*H*-pyrrol-1-yl)phenyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (5m):

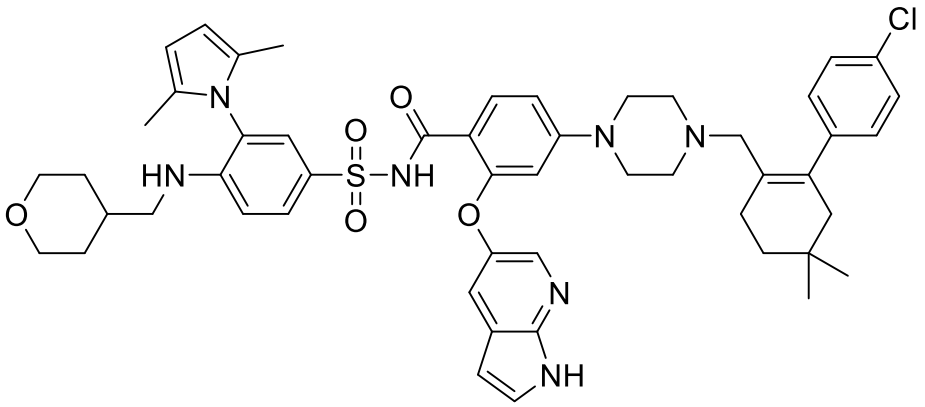
According to a down-scaled (0.25 mmol substrate, other reagents reduced accordingly except for solvent, which remained at 2 mL) General Method A, **5m** was isolated after 24 h in 105.6 mg (0.22 mmol, 89% yield) as a colorless solid.

TLC R_f = 0.42 (100% EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.28 (m, 5H), 7.18 – 7.03 (m, 2H), 5.87 (s, 2H), 5.75 (s, 1H), 5.13 (d, *J* = 2.6 Hz, 2H), 4.77 (d, *J* = 7.8 Hz, 1H), 4.15 – 3.92 (m, 2H), 3.59 (t, *J* = 8.6 Hz, 1H), 3.45 (q, *J* = 9.1 Hz, 1H), 2.57 – 7.51 (m, 1H), 2.31 – 2.15 (m, 1H), 2.12 – 2.02 (m, 1H), 1.99 (s, 6H), 1.95 – 1.88 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.8, 156.5, 137.6, 136.3, 134.7, 128.9, 128.7, 128.7, 128.3, 128.2, 120.2, 105.6, 67.2, 61.2, 46.8, 43.6, 27.2, 25.0, 13.1.

HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_4O_4+H^+$: 475.2345 $[M+H]^+$; found: 475.2349.



5n

2-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-*N*-((3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)phenyl)sulfonyl)benzamide (5n):

According to a slightly modified (solvent: 2 mL, 1:1 EtOH/Toluene) and down-scaled (0.25 mmol substrate, other reagents reduced accordingly) General Method A, **5n** was isolated after 36 h in 175.0 mg (0.19 mmol, 76% yield) as a faint yellow-green to off-white solid.

TLC R_f = 0.69 (100% EtOAc).

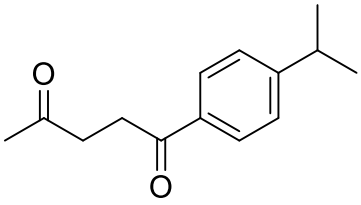
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 10.11 (s, 1H), 8.14 (d, *J* = 2.5 Hz, 1H), 8.03 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 3.5, 2.4 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.95 – 6.87 (m, 2H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.55 (dd, *J* = 9.2, 2.3 Hz, 1H), 6.51 (dd, *J* = 3.5, 1.9 Hz, 1H), 5.99 (d, *J* = 2.3 Hz, 1H), 5.92 (s, 2H), 3.97 – 3.89 (m, 3H), 3.33 (td, *J* = 11.8, 2.1 Hz, 2H), 3.18 (bs, 3H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.83 (bs, 1H), 2.26 (bs, 5H), 1.97 (s, 2H), 1.90 (s, 6H), 1.74 (dqd, *J* = 10.9, 7.0, 3.2 Hz, 1H), 1.52 (ddd, *J* = 12.7, 4.0, 1.9 Hz, 2H), 1.42 (t, *J* = 6.5 Hz, 2H), 1.25 (dtd, *J* = 13.3, 11.8, 4.6 Hz, 3H), 0.92 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 159.4, 155.3, 149.7, 149.7, 146.5, 146.4, 144.9, 141.7, 136.2, 133.9, 132.4, 131.1, 130.4, 129.6, 129.3, 128.6, 128.5, 128.3, 127.8, 125.0, 123.2, 123.1, 120.9, 120.9, 109.4, 107.0, 101.2, 67.5, 60.0, 52.0, 48.8, 47.1, 35.2, 34.7, 30.7, 29.7, 29.2, 28.2, 25.9, 12.4. Significant line-broadening is observed, possibly due to the existence of rotamers. ^{13}C-Peak assignments are tentative.

HRMS (ESI) *m/z* calcd for $C_{51}H_{58}ClN_7O_5S+H^+$: 916.3981 $[M+H]^+$; found: 916.3970.

4. Synthesis and Scale-Up of BM-635

Synthesis of the starting diketone



2c

1-(4-isopropylphenyl)pentane-1,4-dione (2c)[20]:

Modification of a literature Stetter reaction: A mixture of 4-isopropylbenzaldehyde (13.6 mL, 13.3 g, 0.09 mol), methyl vinyl ketone (7.6 mL, 6.3 g, 0.09 mol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (3.5 g, 0.014 mol) and triethylamine (19.5 mL, 14.1 g, 0.14 mol) was stirred at 70 °C over night. The mixture was then concentrated, diluted with 50 mL EtOAc and washed with 2 M aq. HCl (20 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). Then the combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$, H_2O, brine, dried with Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (10% to 20% EtOAc in Heptane) to obtain the isolated product in 9.8 g (0.045 mol, 50% yield) as a low melting light-orange crystalline solid.

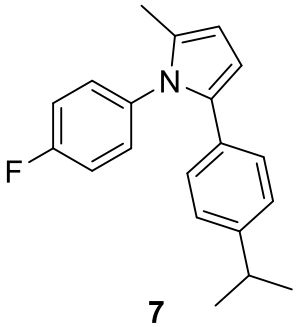
TLC R_f = 0.41 (25% EtOAc in Heptane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.85 (m, 2H), 7.34 – 7.27 (m, 2H), 3.25 (dd, *J* = 6.9, 5.8 Hz, 2H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.87 (dd, *J* = 7.0, 5.7 Hz, 2H), 2.25 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 198.3, 154.8, 134.6, 128.4, 126.8, 37.2, 34.4, 32.4, 30.2, 23.8.

GC-MS *m/z* 218 $[M]^+$.

Synthesis of the intermediate pyrrole



7

1-(4-fluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1*H*-pyrrole (7)[20]:

According to General Method A, **7** was isolated after 24 h in 107.0 mg (0.37 mmol, 73% yield) as a faint-yellow solid.

TLC R_f = 0.38 (1% EtOAc in Heptane).

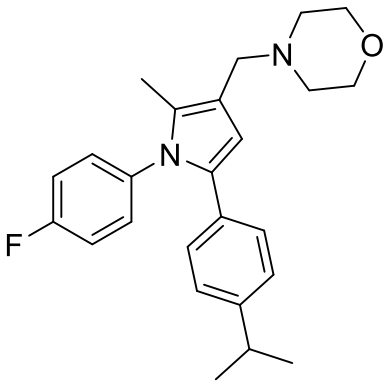
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 6.91 (m, 8H), 6.31 (d, *J* = 3.5 Hz, 1H), 6.08 (d, *J* = 3.4 Hz, 1H), 2.82 (sept, *J* = 7.0 Hz, 1H), 2.12 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (d, *J* = 246.8 Hz), 146.5, 135.6, 134.5, 131.5, 130.9, 130.2 (d, *J* = 8.5 Hz), 127.8, 126.2, 116.0 (d, *J* = 22.4 Hz), 108.4, 107.6, 33.8, 24.0, 13.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.3.

GC-MS *m/z* 293 $[M]^+$.

Scaled-up one-pot synthesis of BM-635



BM-635

4-((1-(4-fluorophenyl)-5-(4-isopropylphenyl)-2-methyl-1*H*-pyrrol-3-yl)methyl)morpholine (BM-635)[21]:

A 100 mL Schlenk flask containing a stir bar was charged with $Fe(BF_4)_2 \cdot 6H_2O$ (168 mg, 0.5 mmol), Tetraphos ligand (348 mg, 0.52 mmol) and diketone **2c** (2.62 g, 12.0 mmol) under argon atmosphere (glove box). The flask was then capped with a septum cap and removed from the glovebox. The Schlenk flash was connected to an inert gas manifold to avoid pressure build-up. Then, 40 mL dry degassed EtOH was introduced through the septum and the mixture was left to stir for 10 min at room temperature. Afterwards, 1-fluoro-4-nitrobenzene (1.42 g, 10.0 mmol) was added under argon counter flow, followed by dropwise addition of formic acid (1.8 mL, 2.2 g, 47.7 mmol). The mixture was then gently heated to 40 °C for 24 h. Next the reaction was cooled to room temperature and sequentially treated with formic acid (10 mL), morpholine **8** (1.2 mL, 1.2 g, 13.8 mmol) and aq. formaldehyde solution (37%, 1.0 mL, 1.09 g, 13.4 mmol). After stirring for further 4 h at room temperature, the reaction was diluted with 50 mL EtOAc and carefully(!) quenched with 100 mL sat. aq. Na_2CO_3 (gas generation!). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were then dried with Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (50% EtOAc and 1% Et_3N in Heptane) to obtain **BM-635** in 1.27 g (3.2 mmol, 32% yield) as a colorless crystalline solid.

TLC R_f = 0.20 (100% EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 6.92 (m, 8H), 6.34 (s, 1H), 3.80 – 3.68 (m, 4H), 3.45 (s, 2H), 2.81 (sept, *J* = 6.9 Hz, 1H), 2.60 – 2.45 (m, 4H), 2.07 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.68 (d, *J* = 247.3 Hz), 146.4, 135.74 (d, *J* = 3.2 Hz), 133.4, 130.6, 130.28 (d, *J* = 8.5 Hz), 129.6, 127.6, 126.2, 116.3, 115.98 (d, *J* = 22.7 Hz). 110.7, 67.2, 55.2, 53.6, 33.7, 24.0, 11.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -114.2.

GC-MS *m/z* 392 $[M]^+$.

5. NMR Spectra of Isolated Compounds

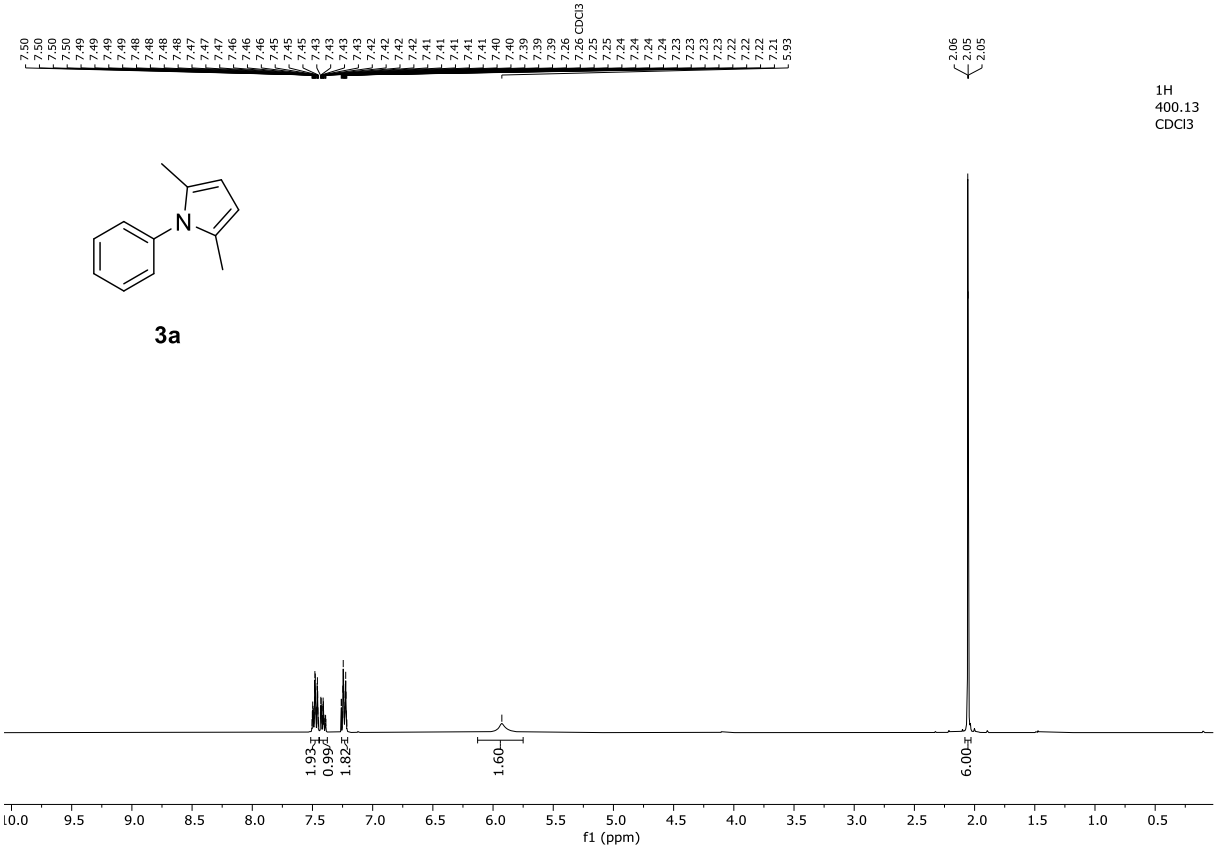


Figure S1. ^{1}H NMR (400 MHz, $CDCl_3$) of **3a**.

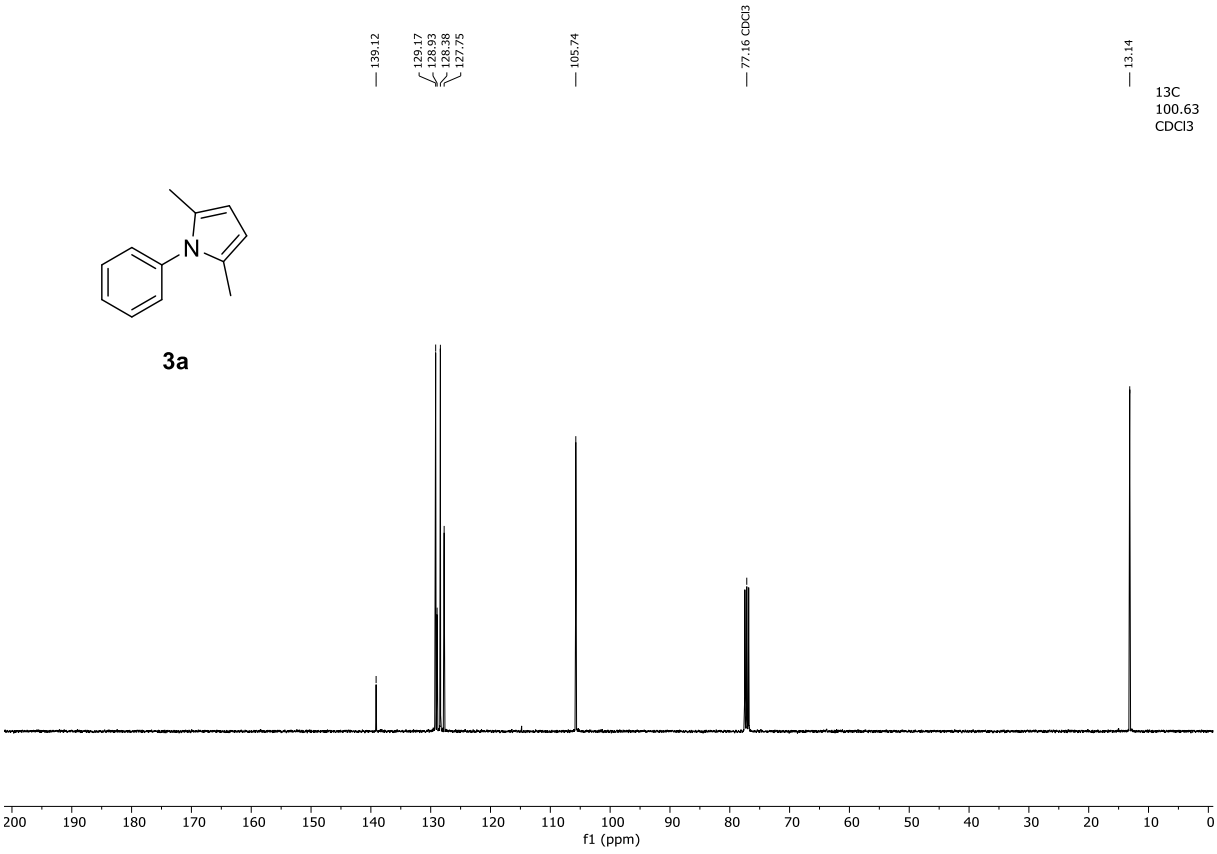


Figure S2. ^{13}C NMR (101 MHz, $CDCl_3$) of **3a**.

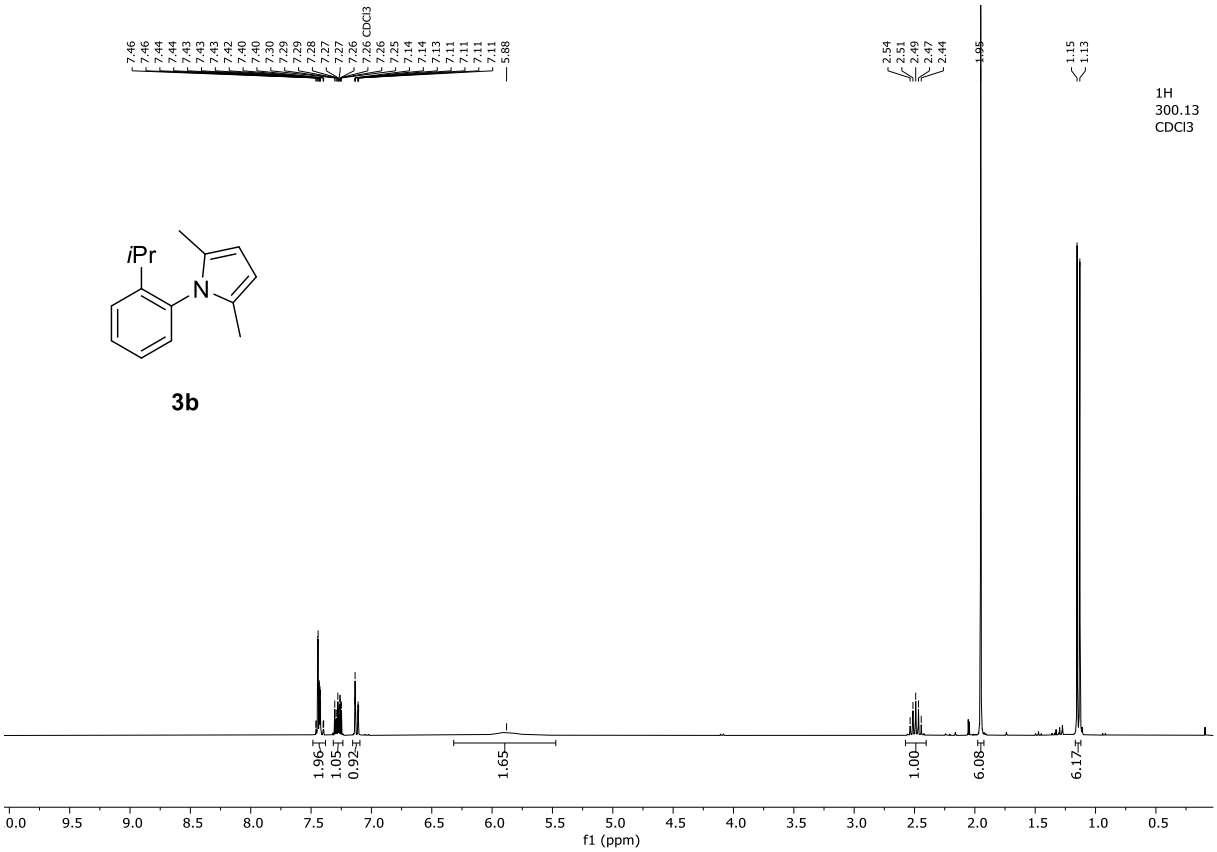


Figure S3. ^{1}H NMR (300 MHz, $CDCl_3$) of **3b**.

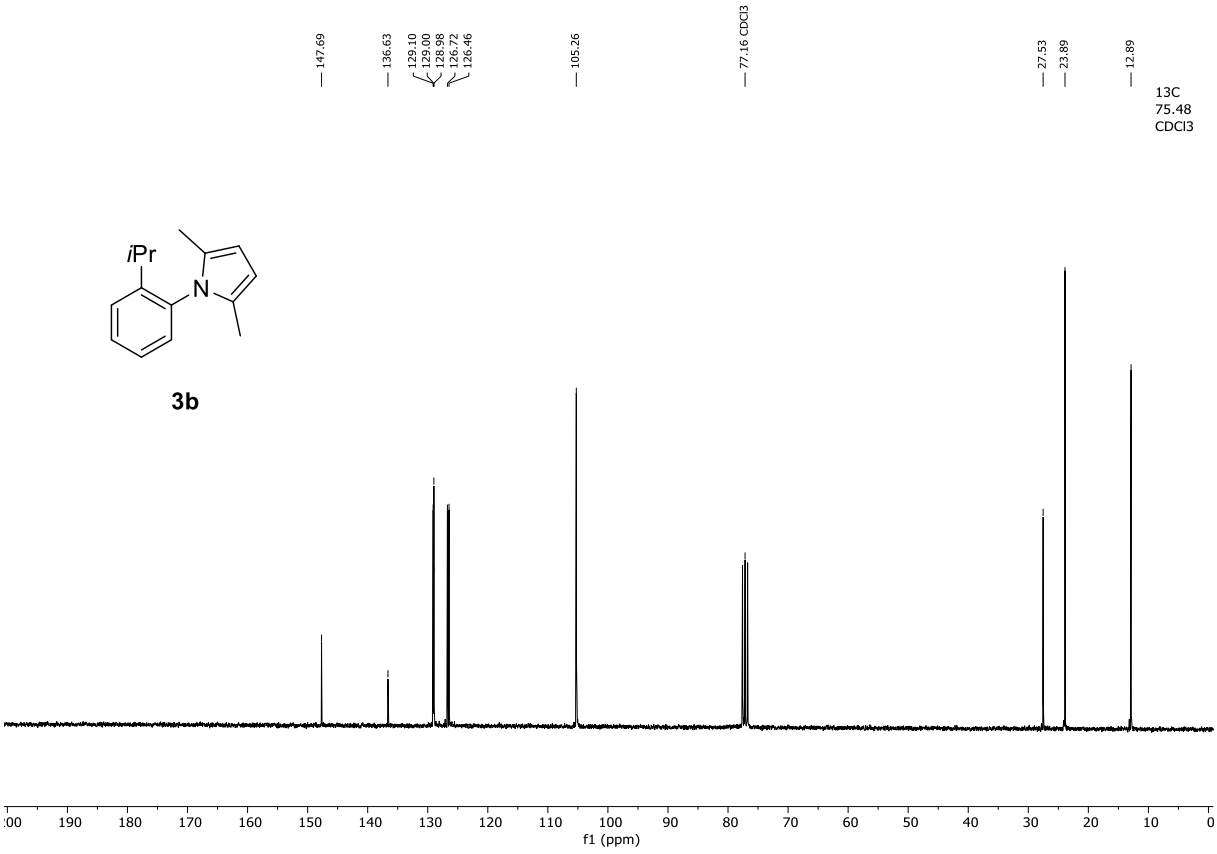


Figure S4. ^{13}C NMR (75 MHz, $CDCl_3$) of **3b**.

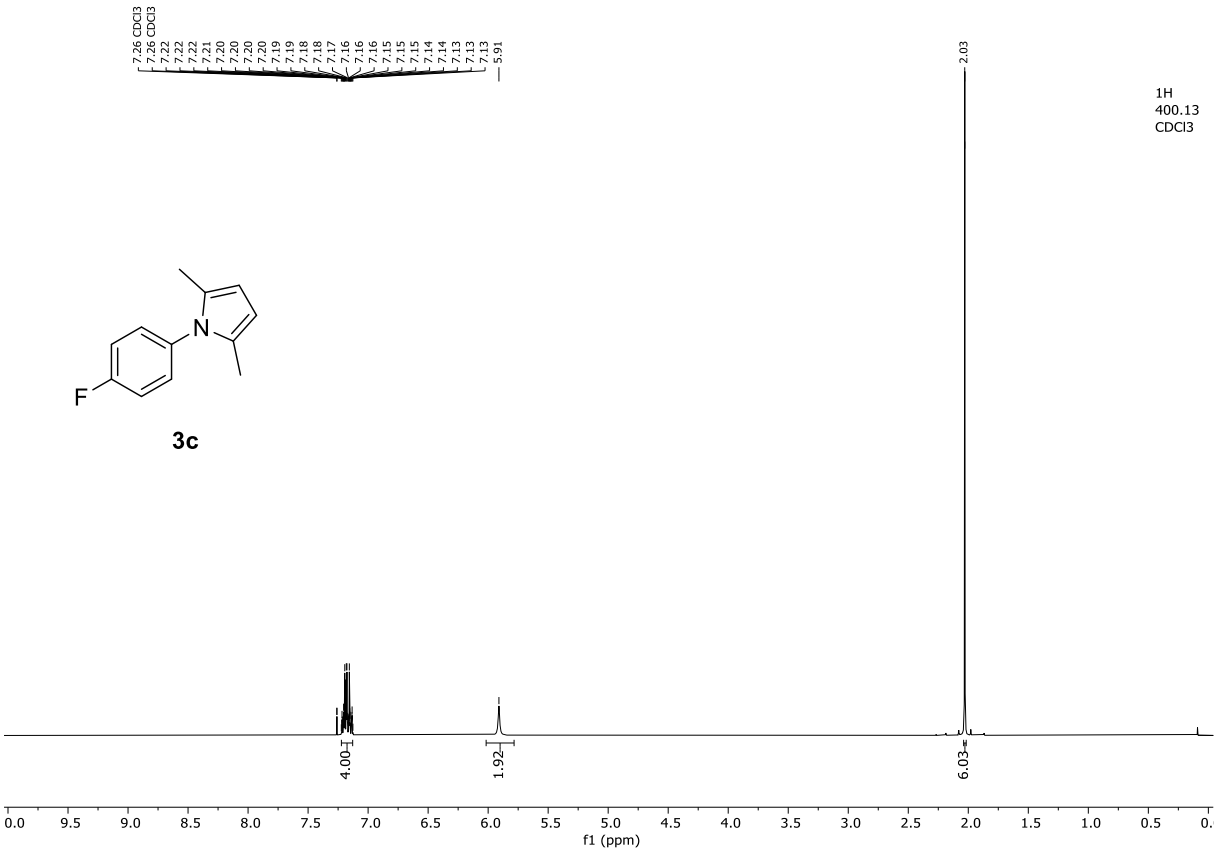


Figure S5. ^{1}H NMR (400 MHz, $CDCl_3$) of **3c**.

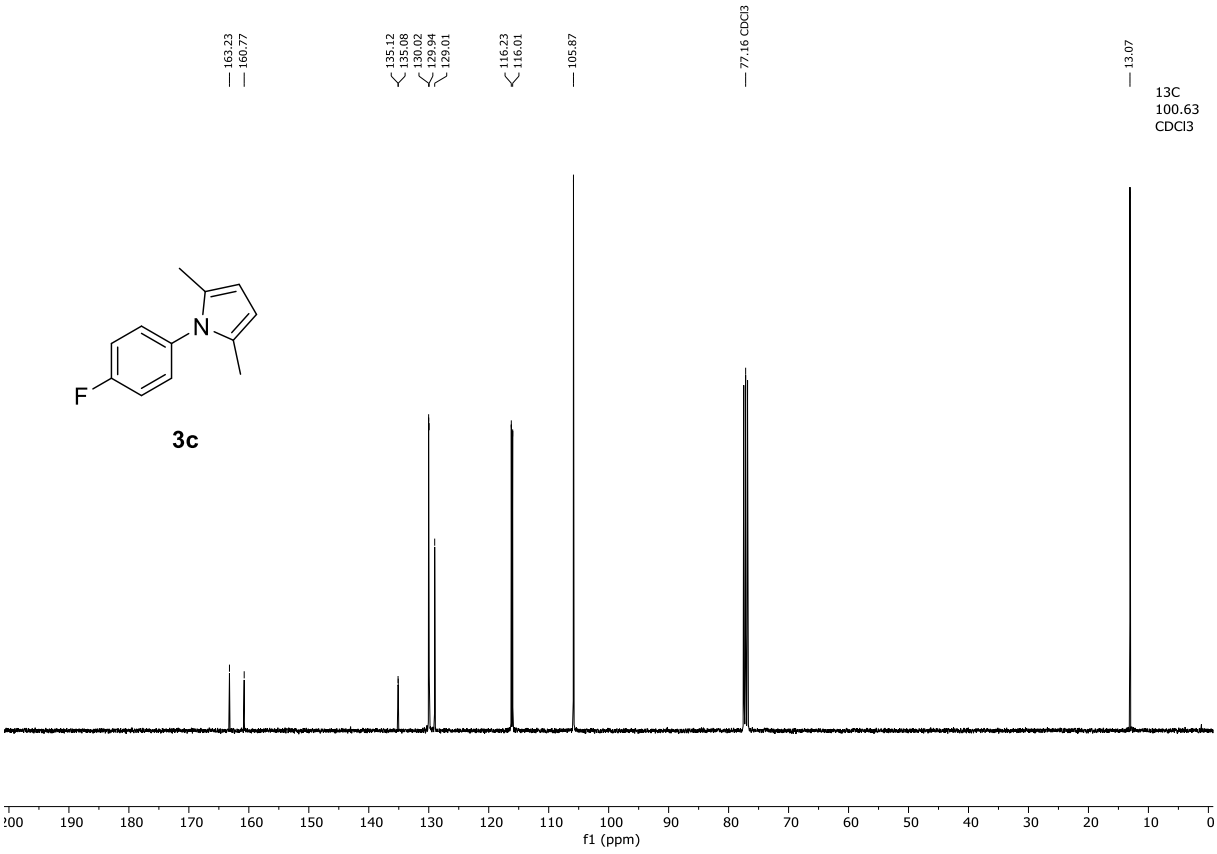


Figure S6. ^{13}C NMR (101 MHz, $CDCl_3$) of **3c**.

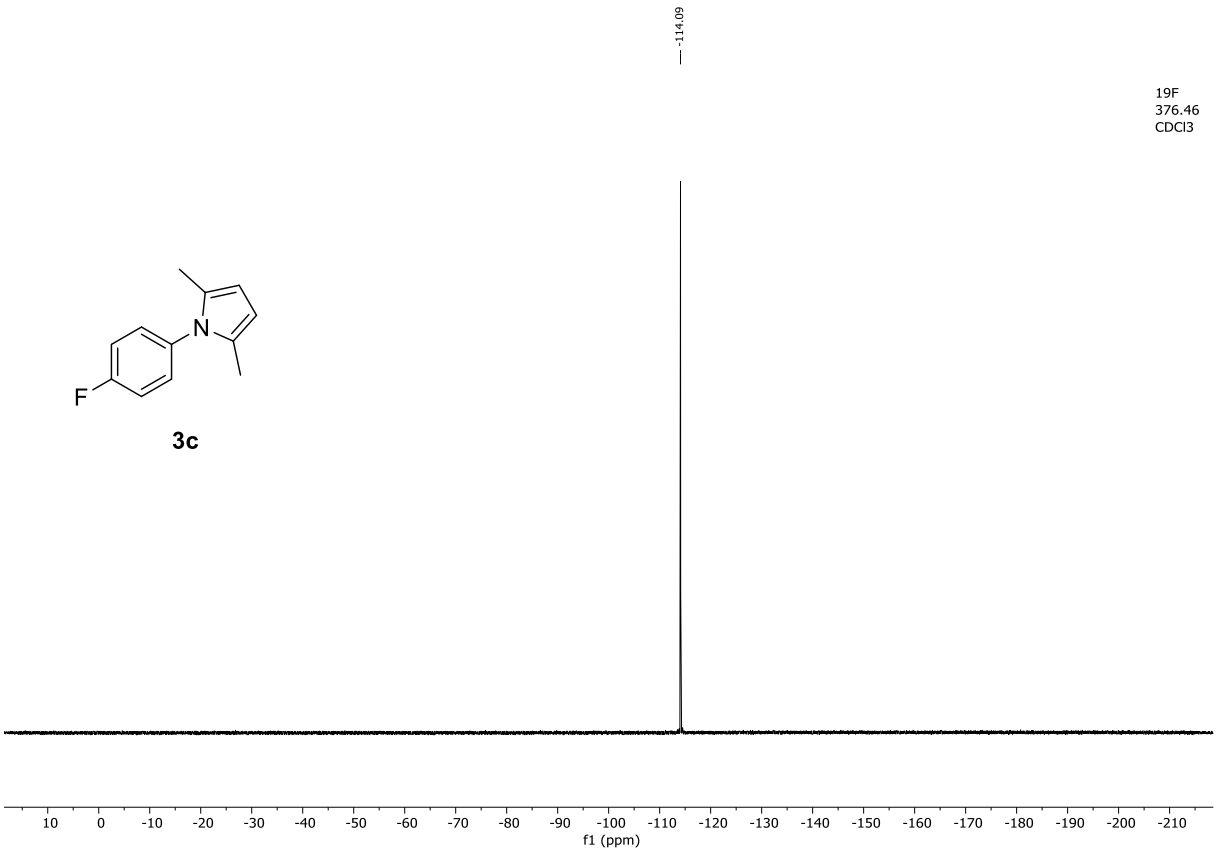


Figure S7. ^{19}F NMR (376 MHz, $CDCl_3$) of **3c**.

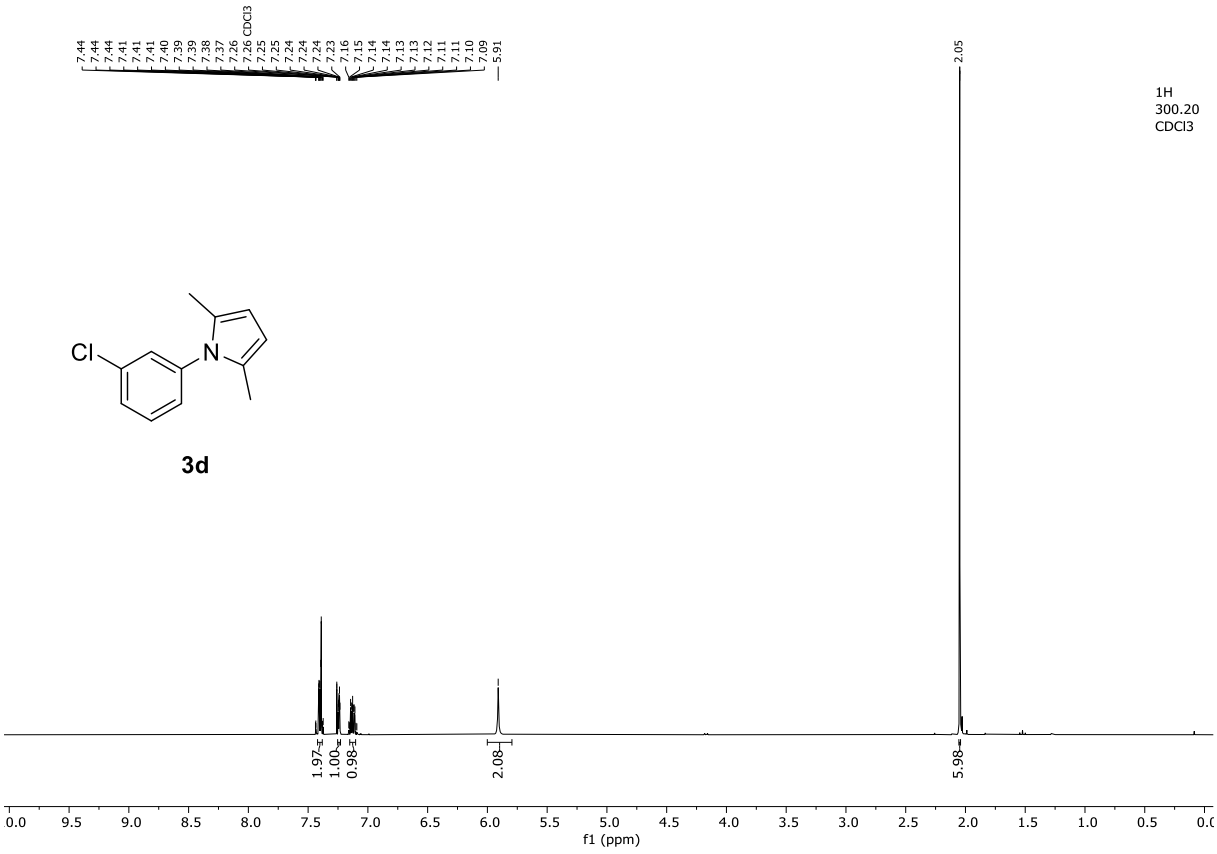


Figure S8. ^{1}H NMR (300 MHz, $CDCl_3$) of **3d**.

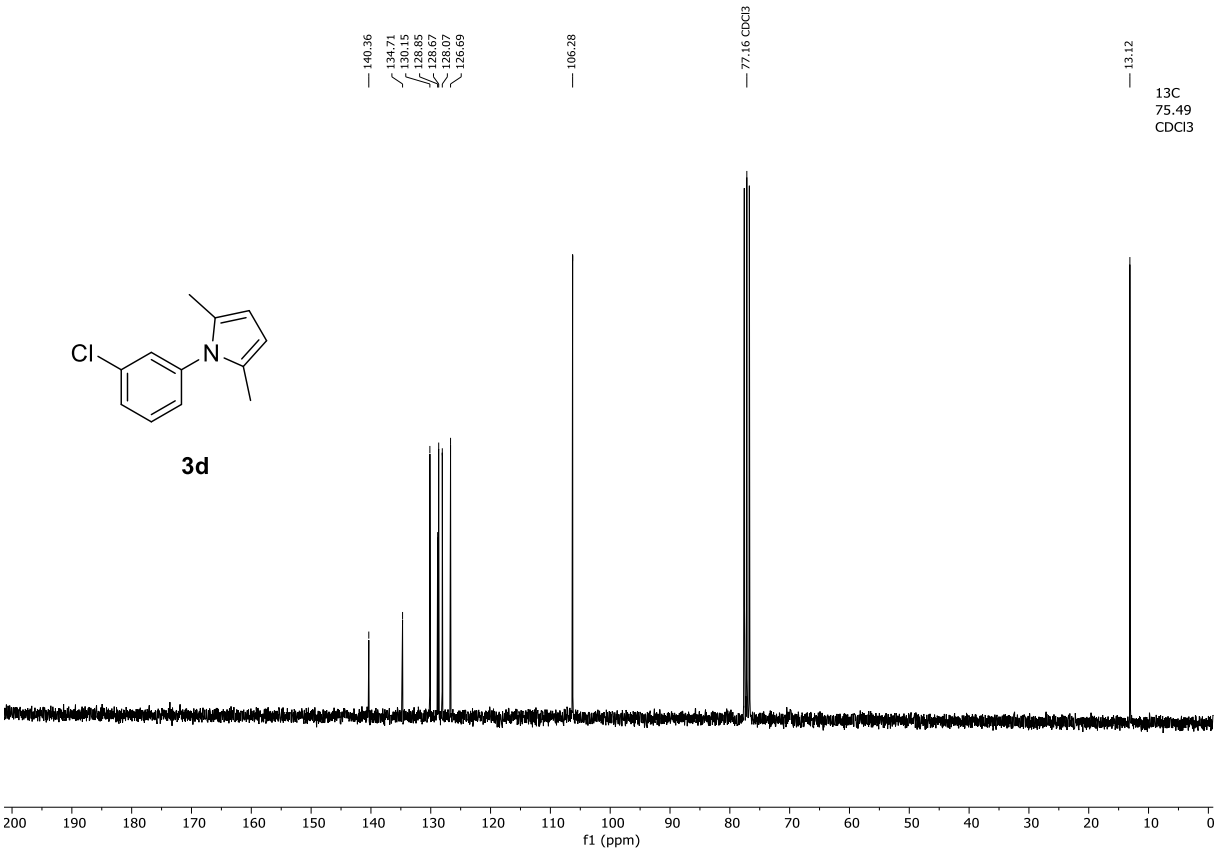


Figure S9. ^{13}C NMR (75 MHz, $CDCl_3$) of **3d**.

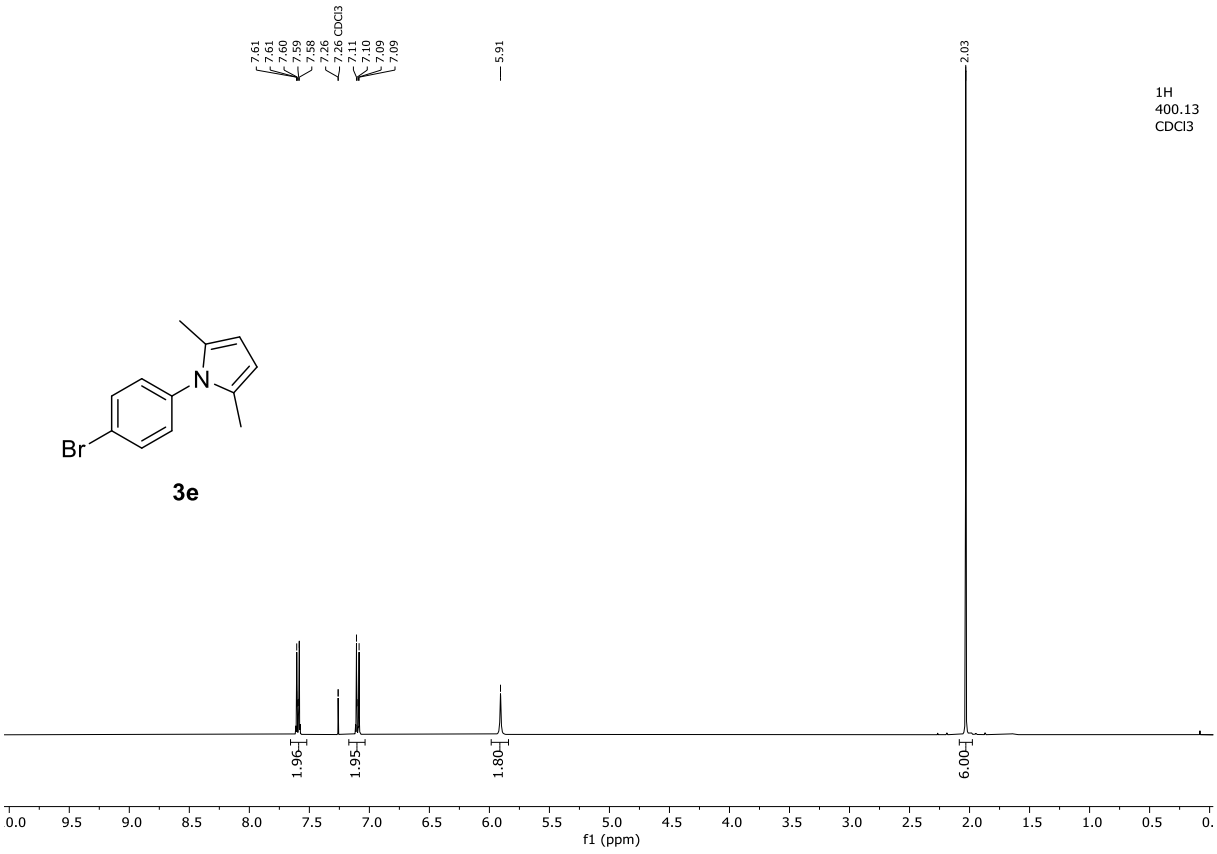


Figure S10. ^{1}H NMR (400 MHz, $CDCl_3$) of **3e**.

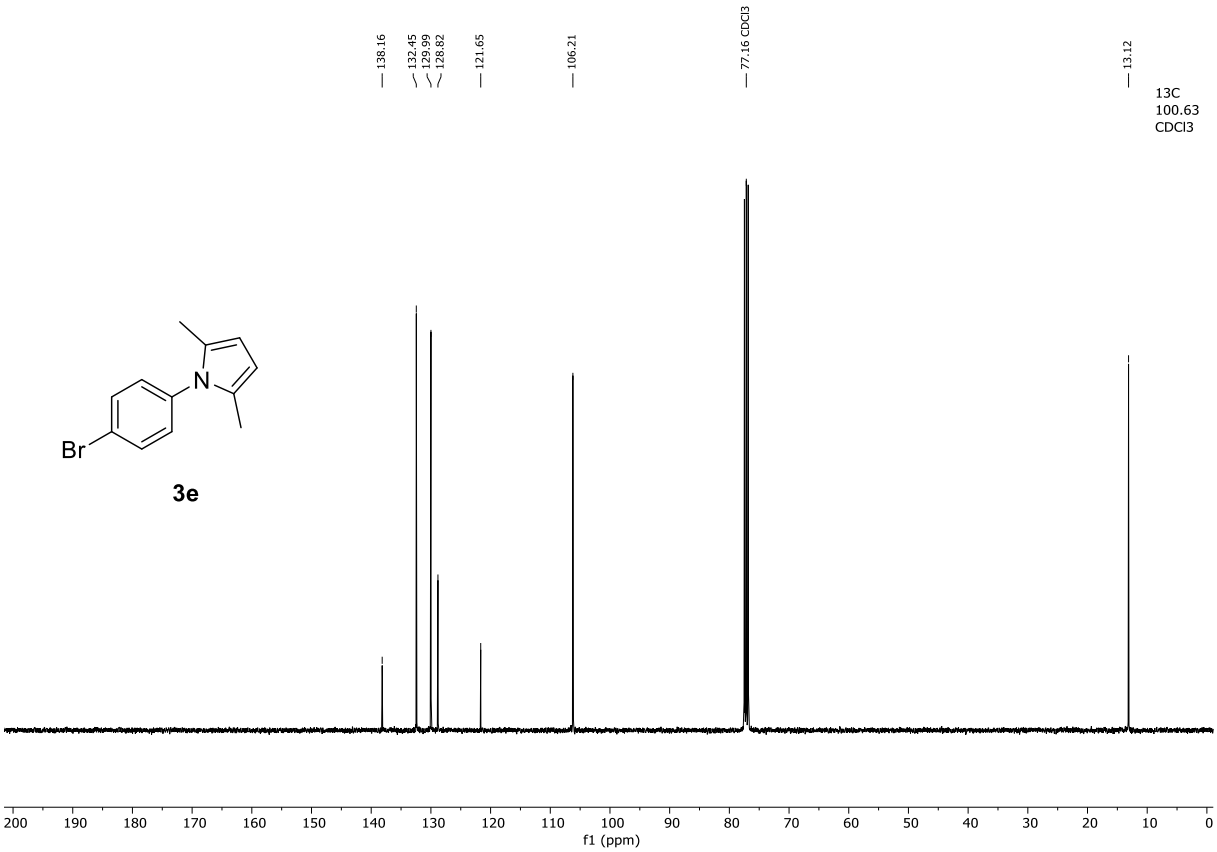


Figure S11. ^{13}C NMR (101 MHz, $CDCl_3$) of **3e**.

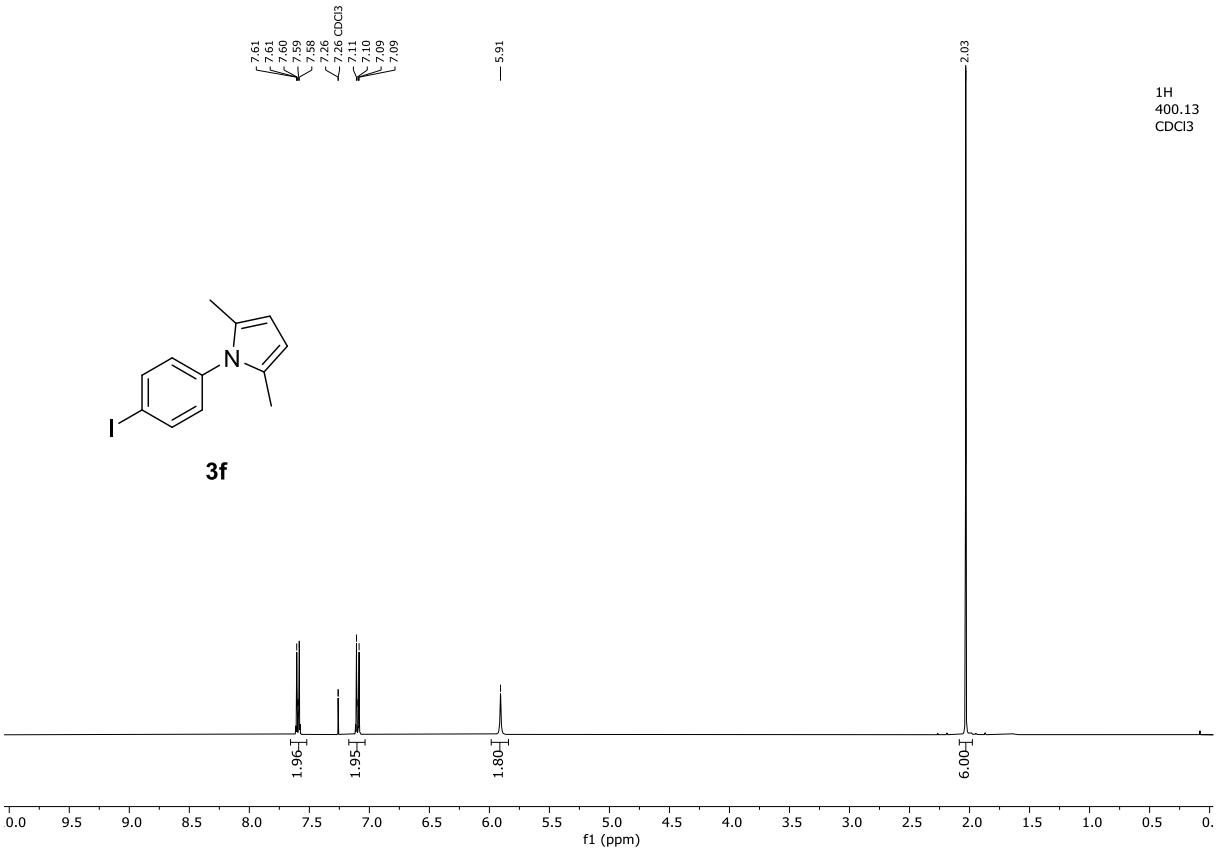


Figure S12. ^{1}H NMR (400 MHz, $CDCl_3$) of **3f**.

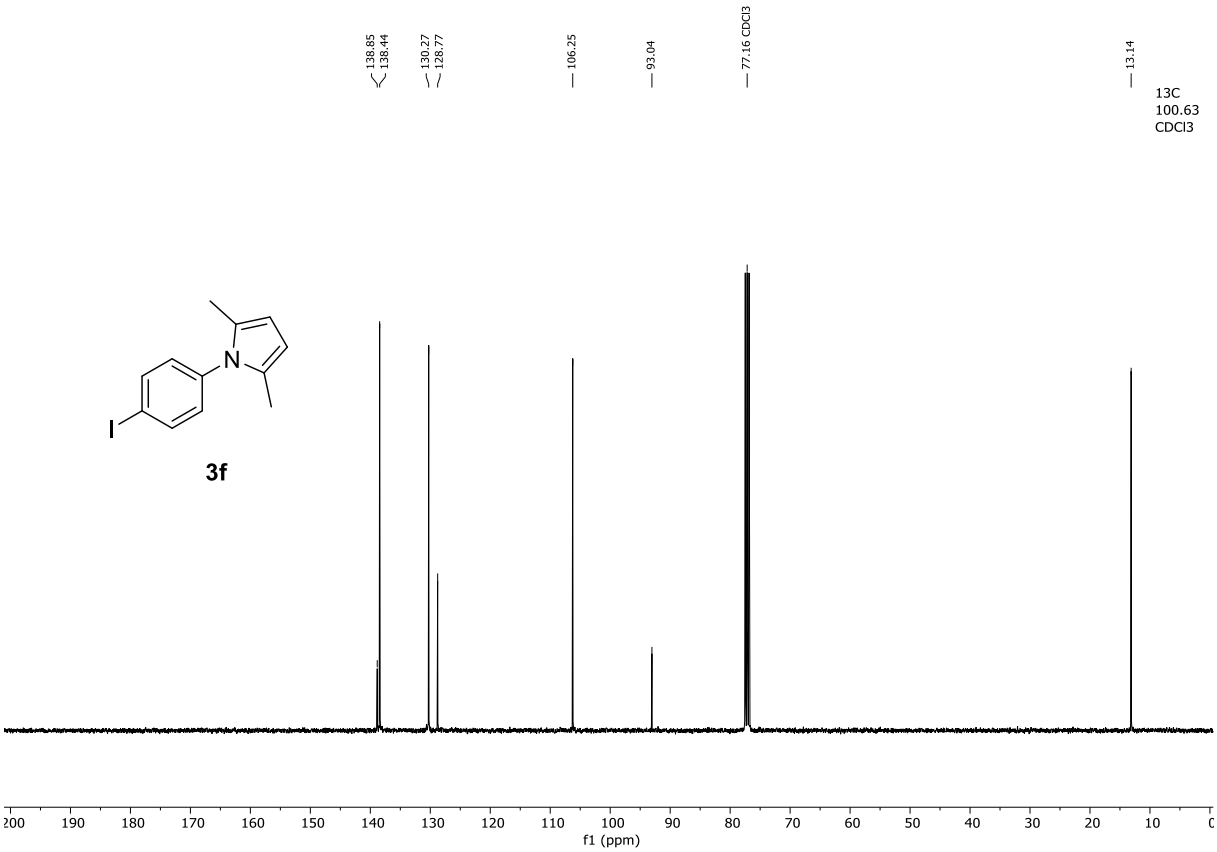


Figure S13. ^{13}C NMR (101 MHz, $CDCl_3$) of **3f**.

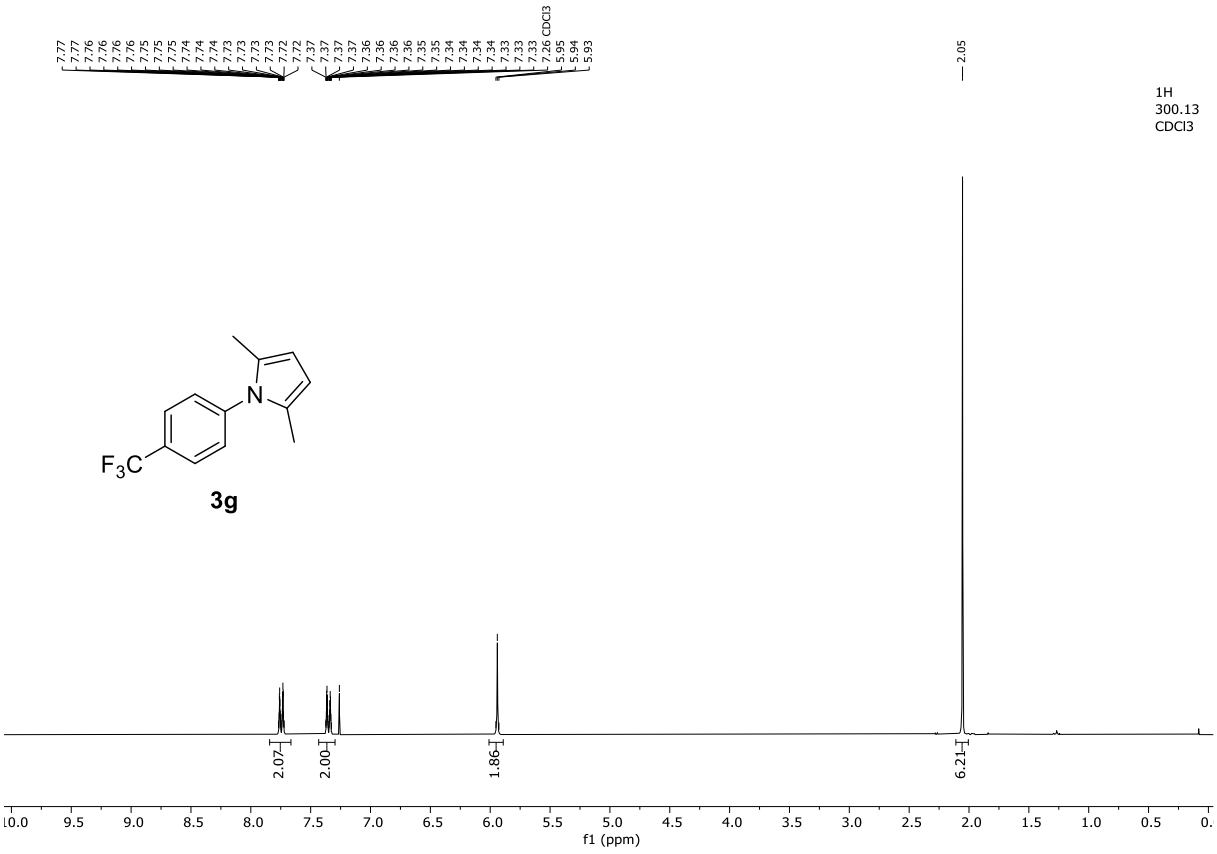


Figure S14. ^{1}H NMR (300 MHz, $CDCl_3$) of **3g**.

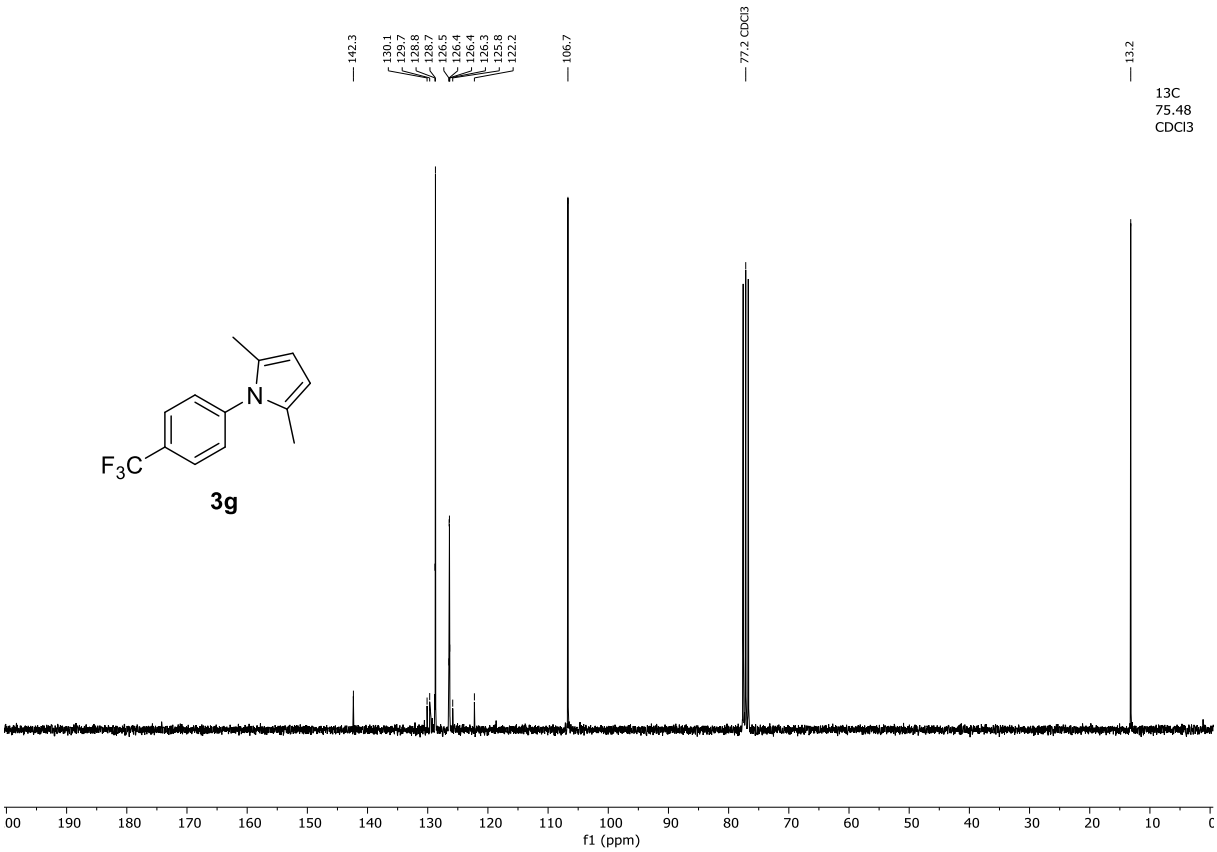


Figure S15. ^{13}C NMR (75 MHz, $CDCl_3$) of **3g**.

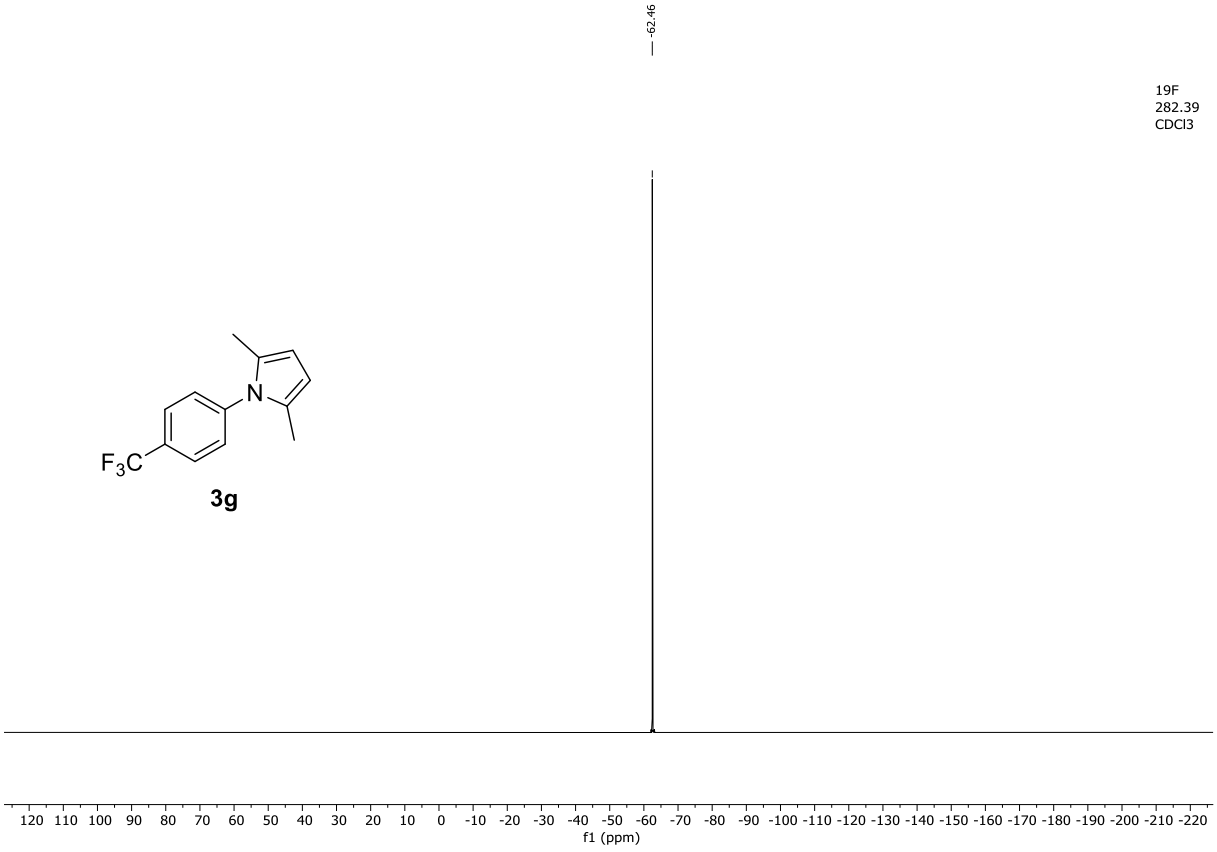


Figure S16. ^{19}F NMR (282 MHz, $CDCl_3$) of **3g**.

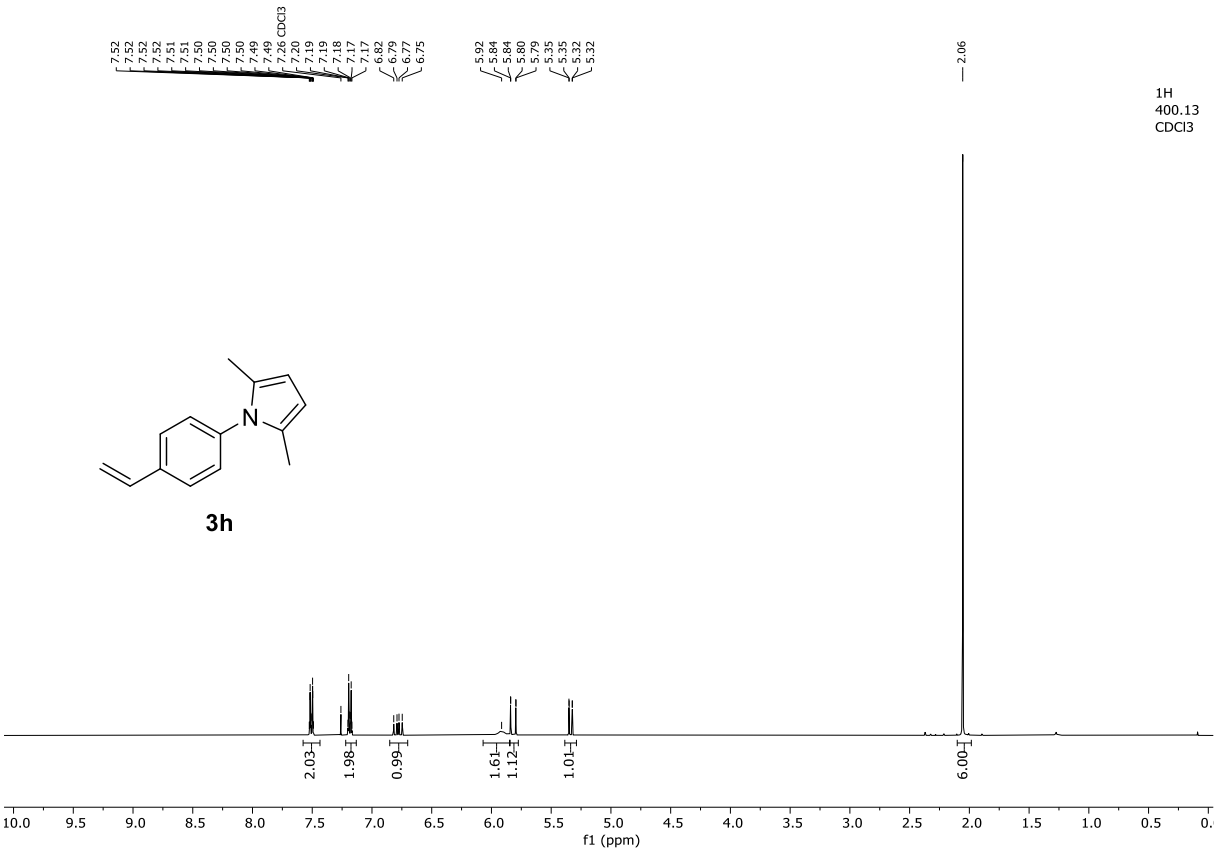


Figure S17. ^{1}H NMR (400 MHz, $CDCl_3$) of **3h**.

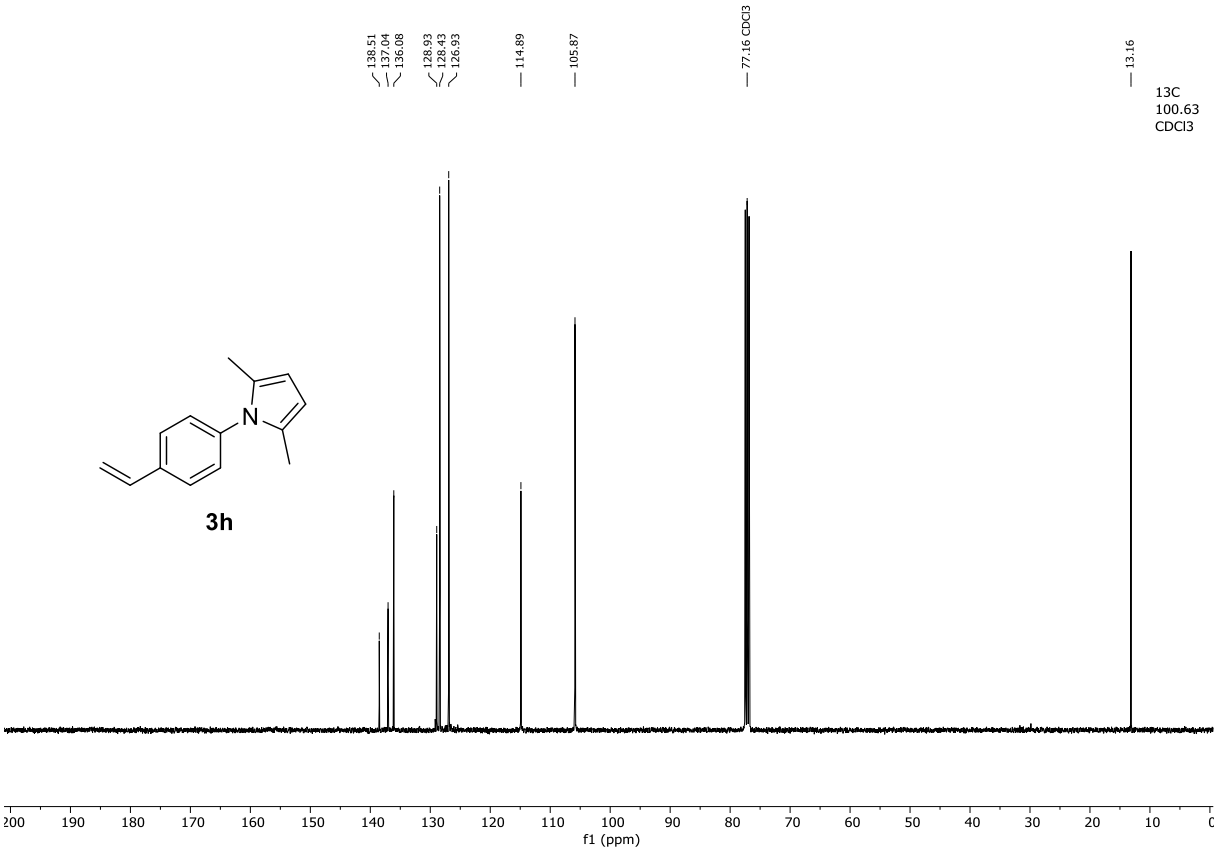


Figure S18. ^{13}C NMR (101 MHz, $CDCl_3$) of **3h**.

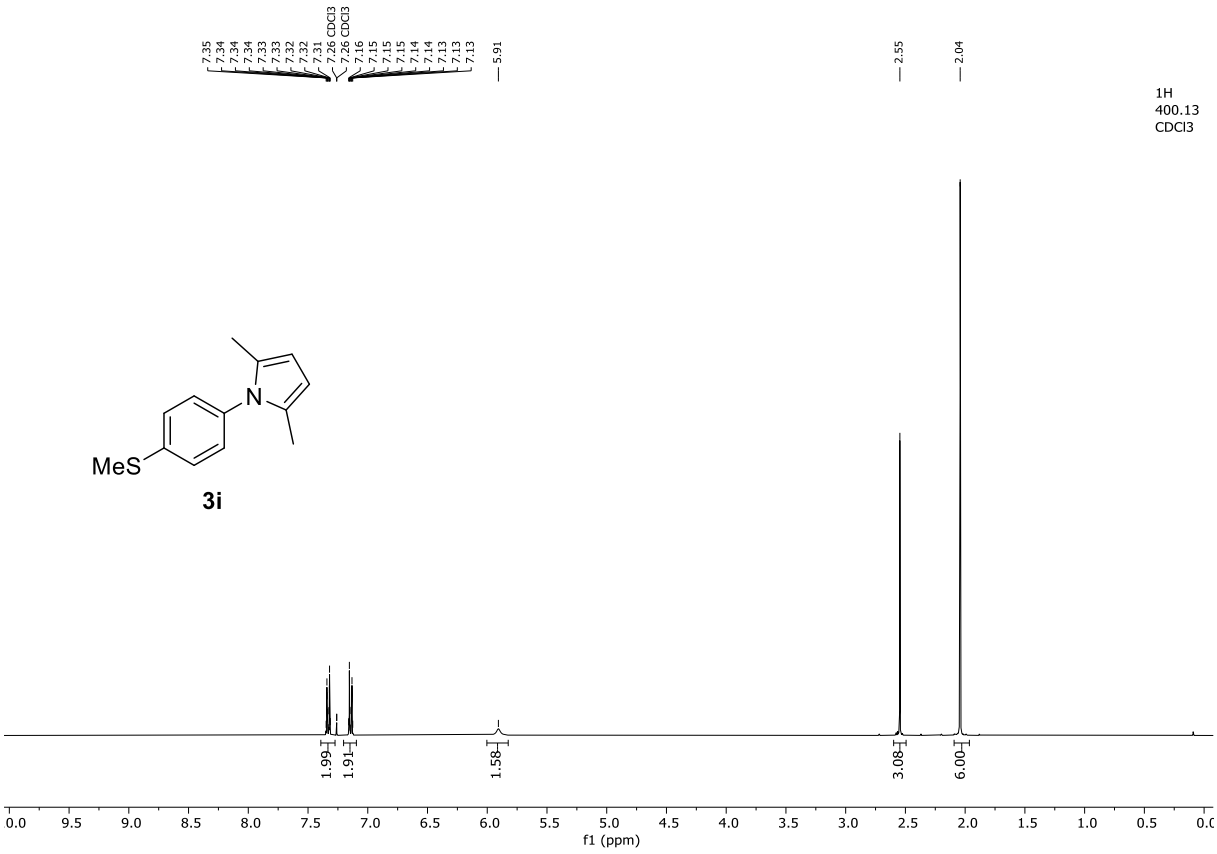


Figure S19. ^{1}H NMR (400 MHz, $CDCl_3$) of **3i**.

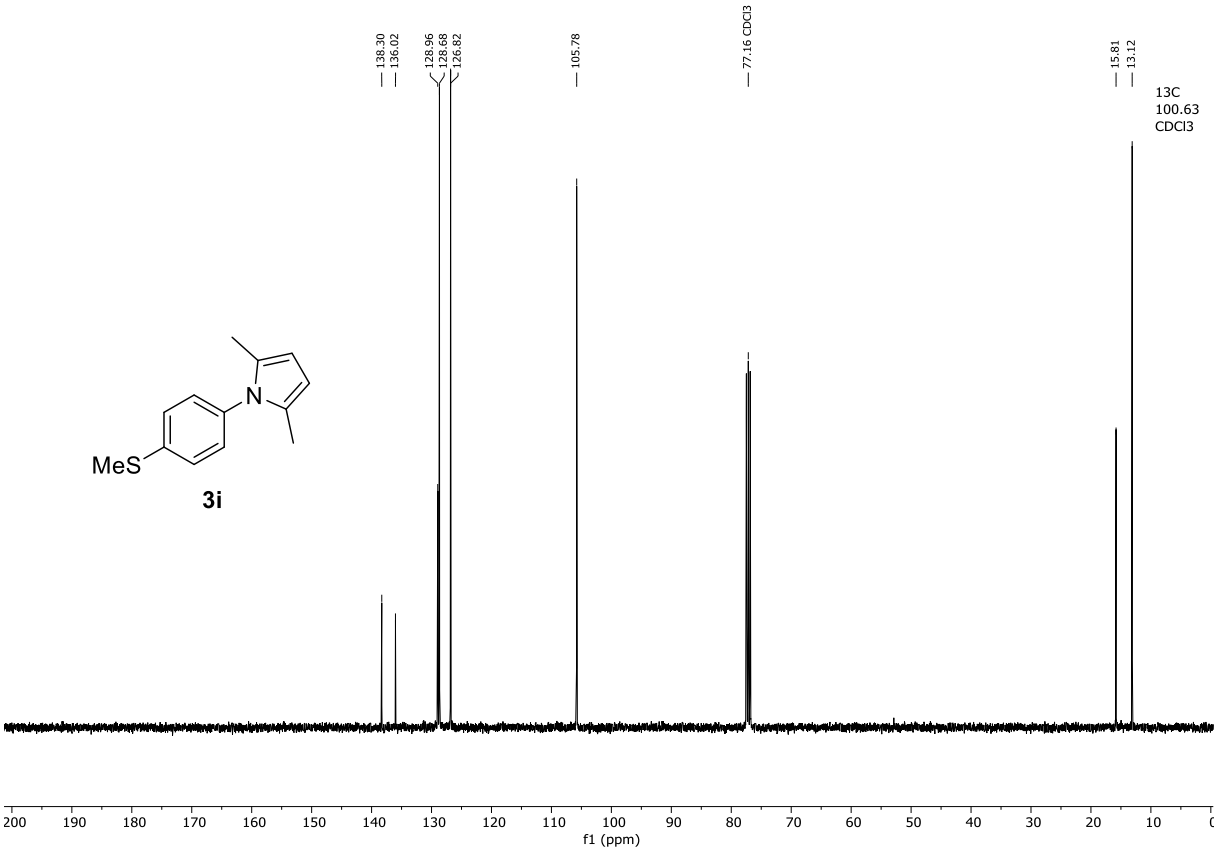


Figure S20. ^{13}C NMR (101 MHz, $CDCl_3$) of **3i**.

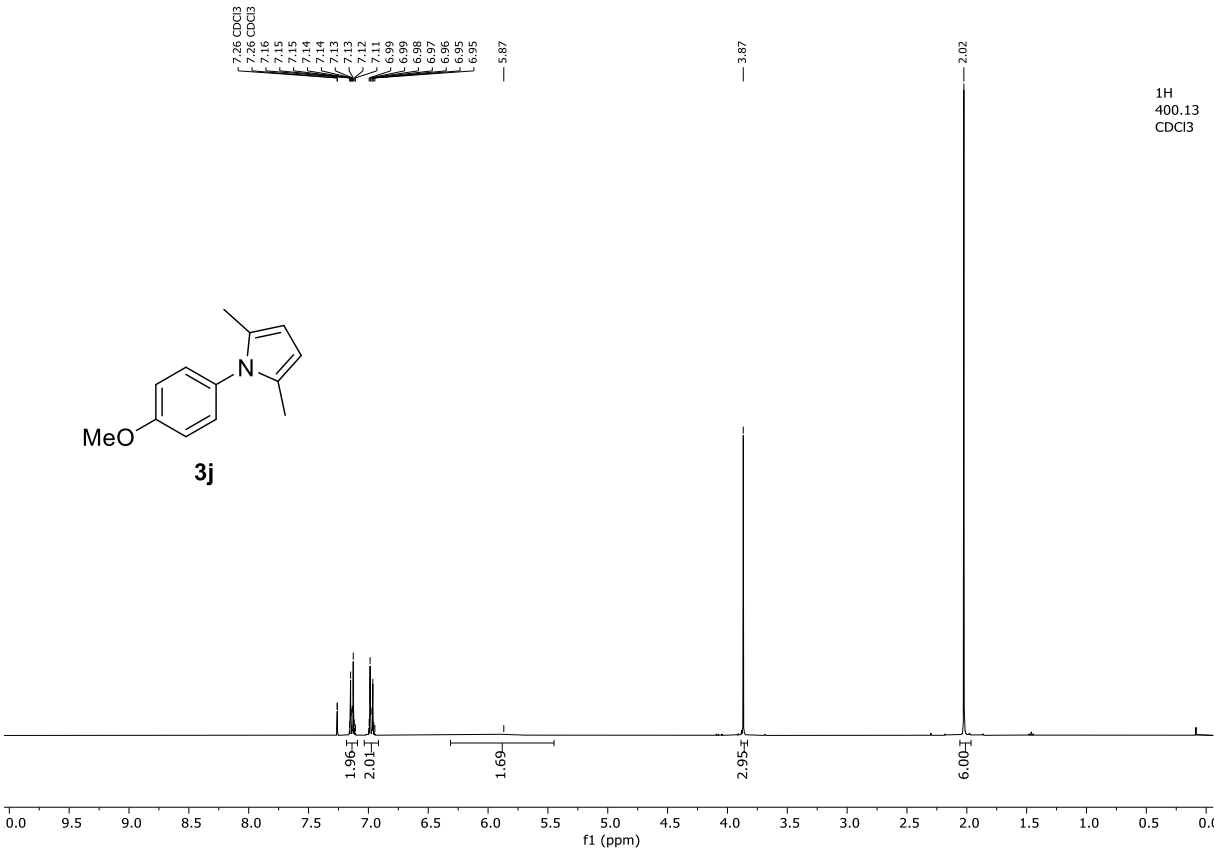


Figure S21. ^{1}H NMR (400 MHz, $CDCl_3$) of **3j**.

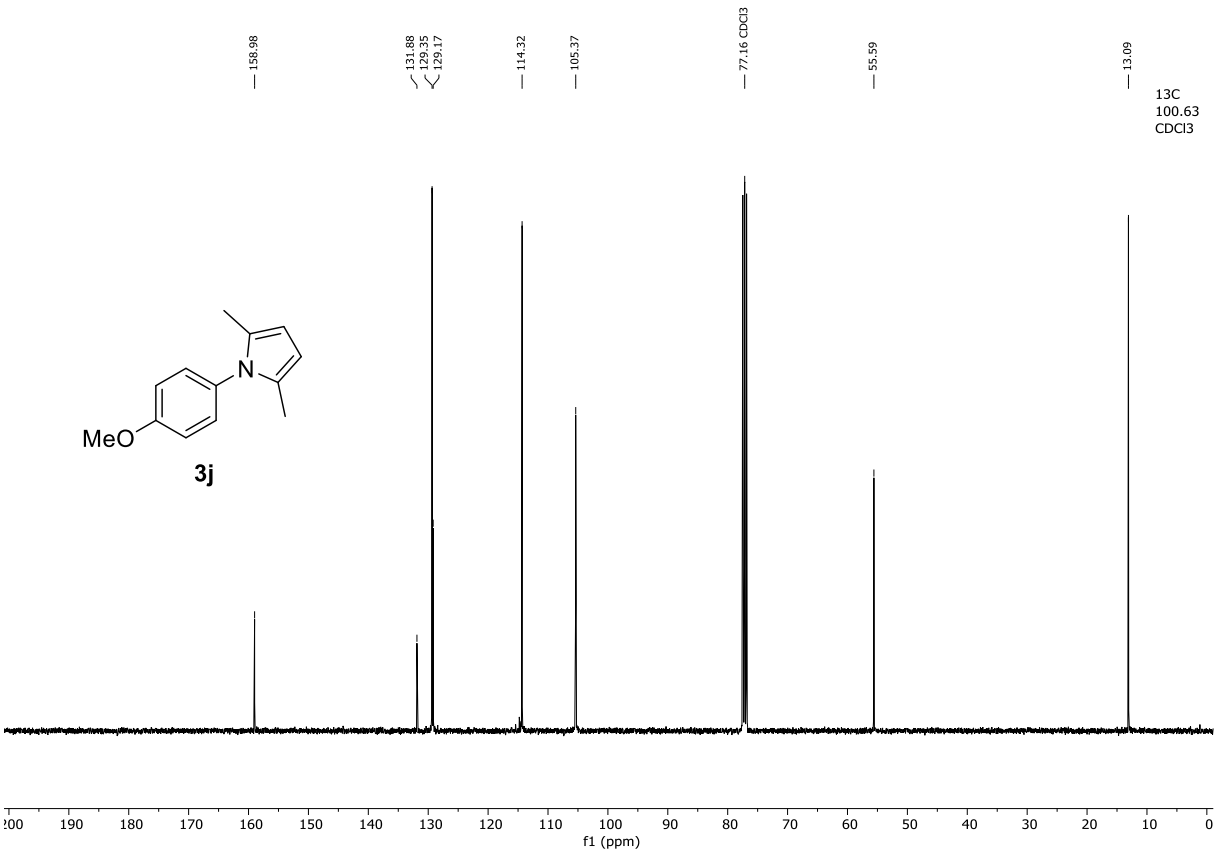


Figure S22. ^{13}C NMR (101 MHz, $CDCl_3$) of **3j**.

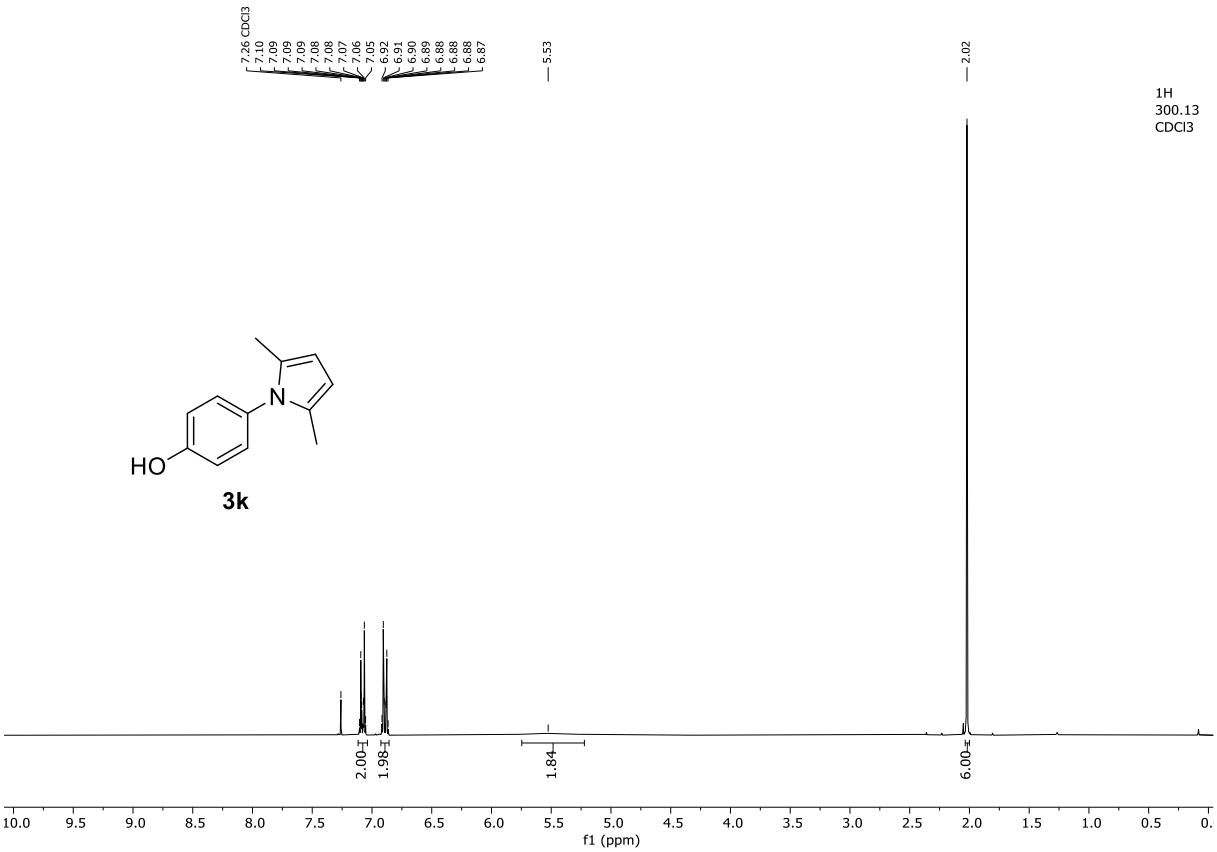


Figure S23. ^{1}H NMR (300 MHz, $CDCl_3$) of **3k**.

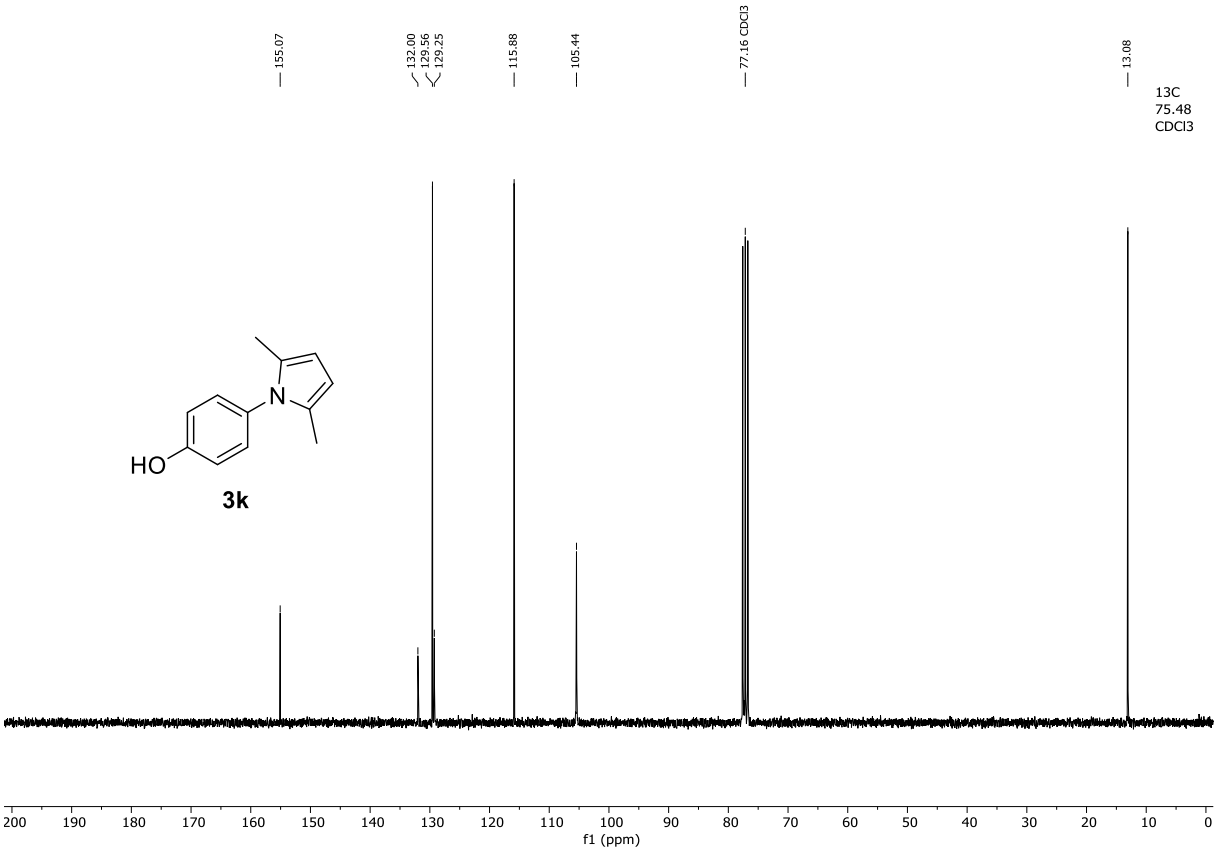


Figure S24. ^{13}C NMR (75 MHz, $CDCl_3$) of **3k**.

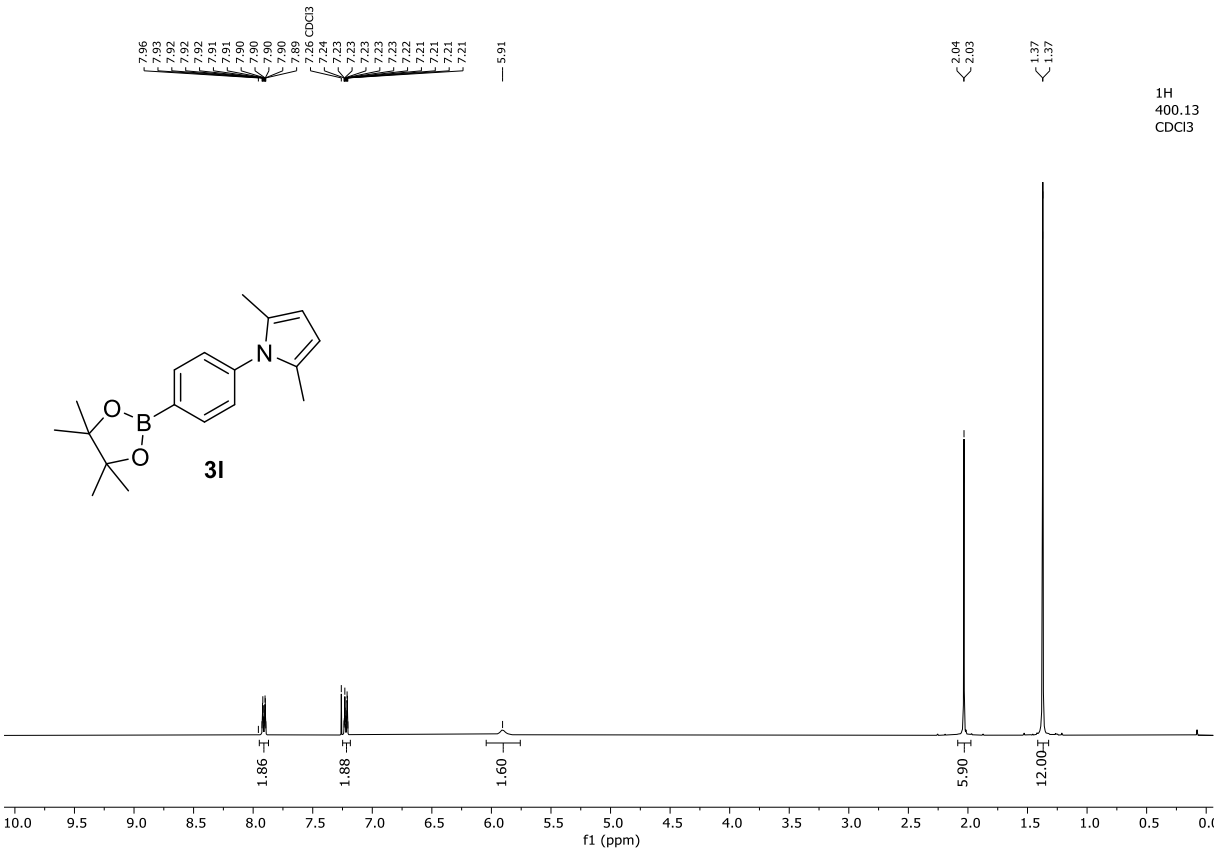


Figure S25. ^{1}H NMR (400 MHz, $CDCl_3$) of **3l**.

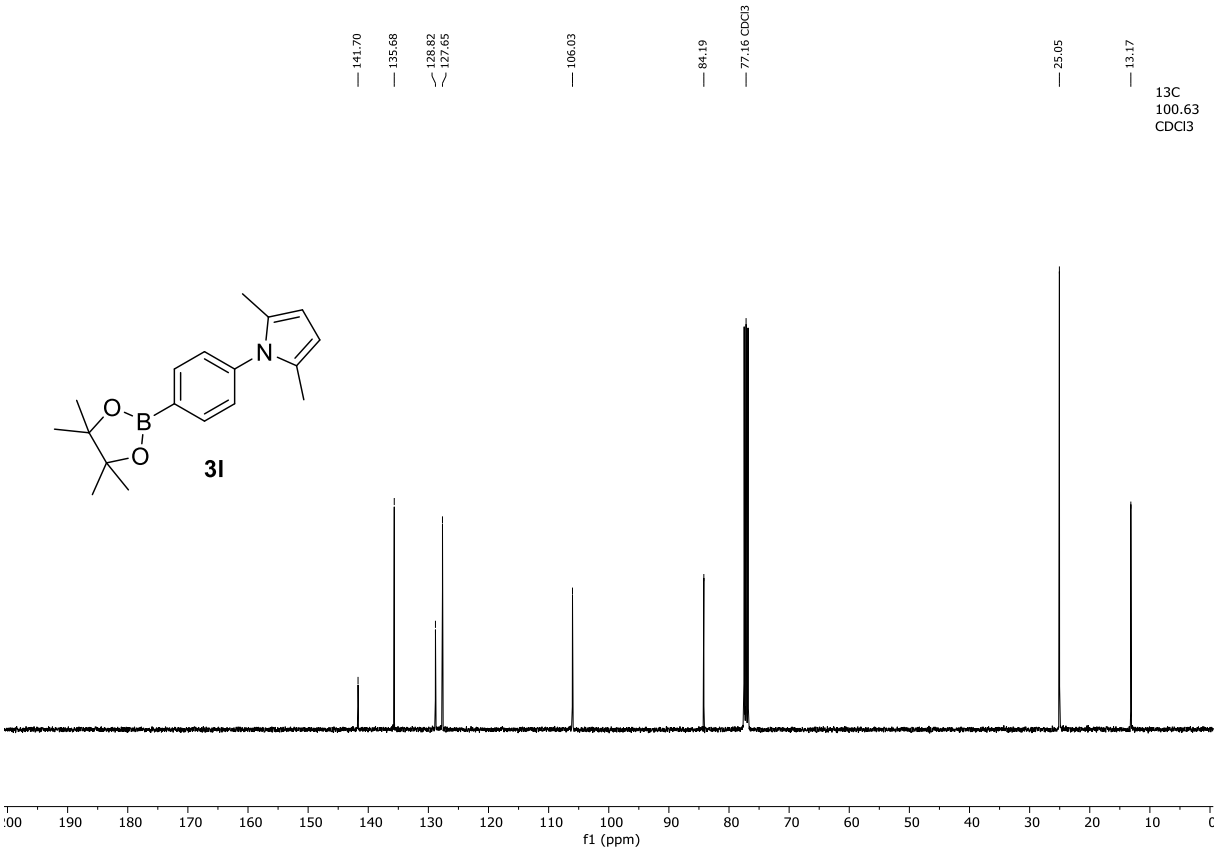


Figure S26. ^{13}C NMR (101 MHz, $CDCl_3$) of **3l**.

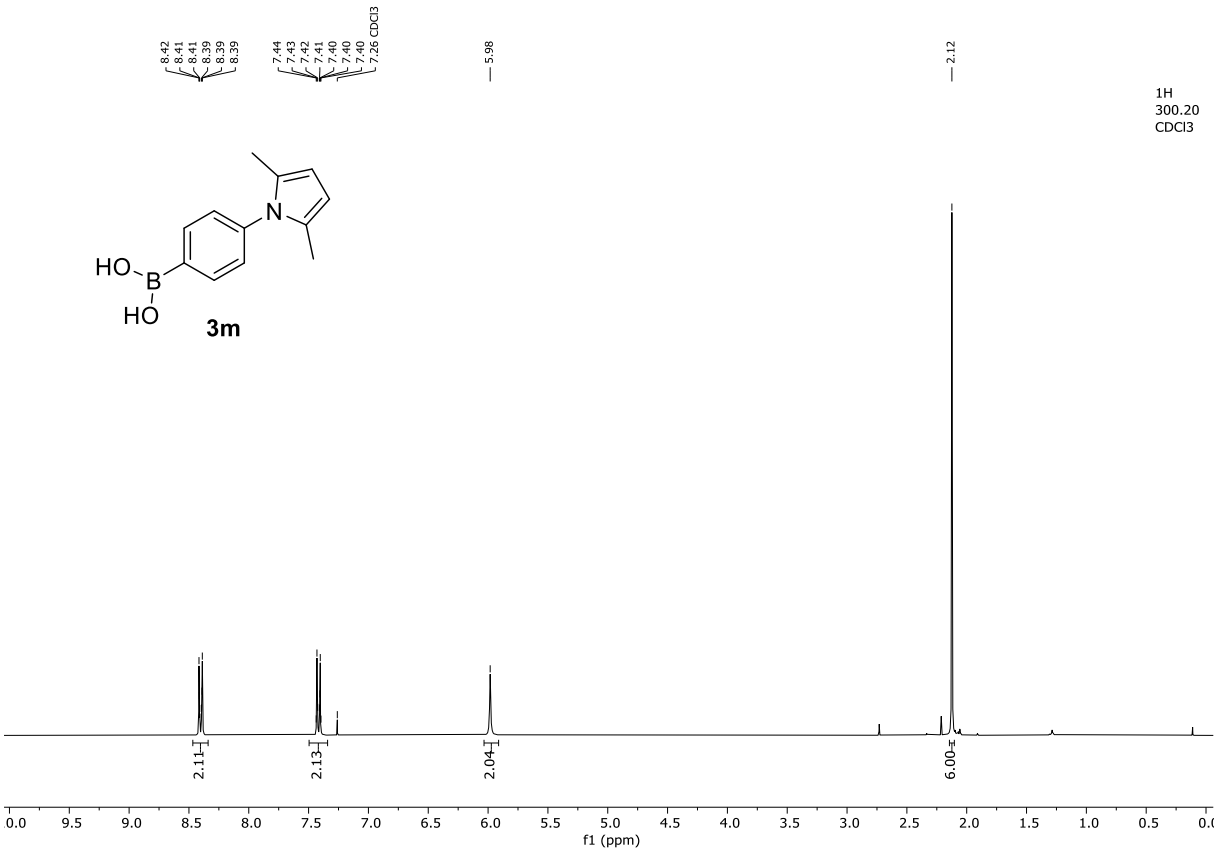


Figure S27. ^{1}H NMR (300 MHz, $CDCl_3$) of **3m**.

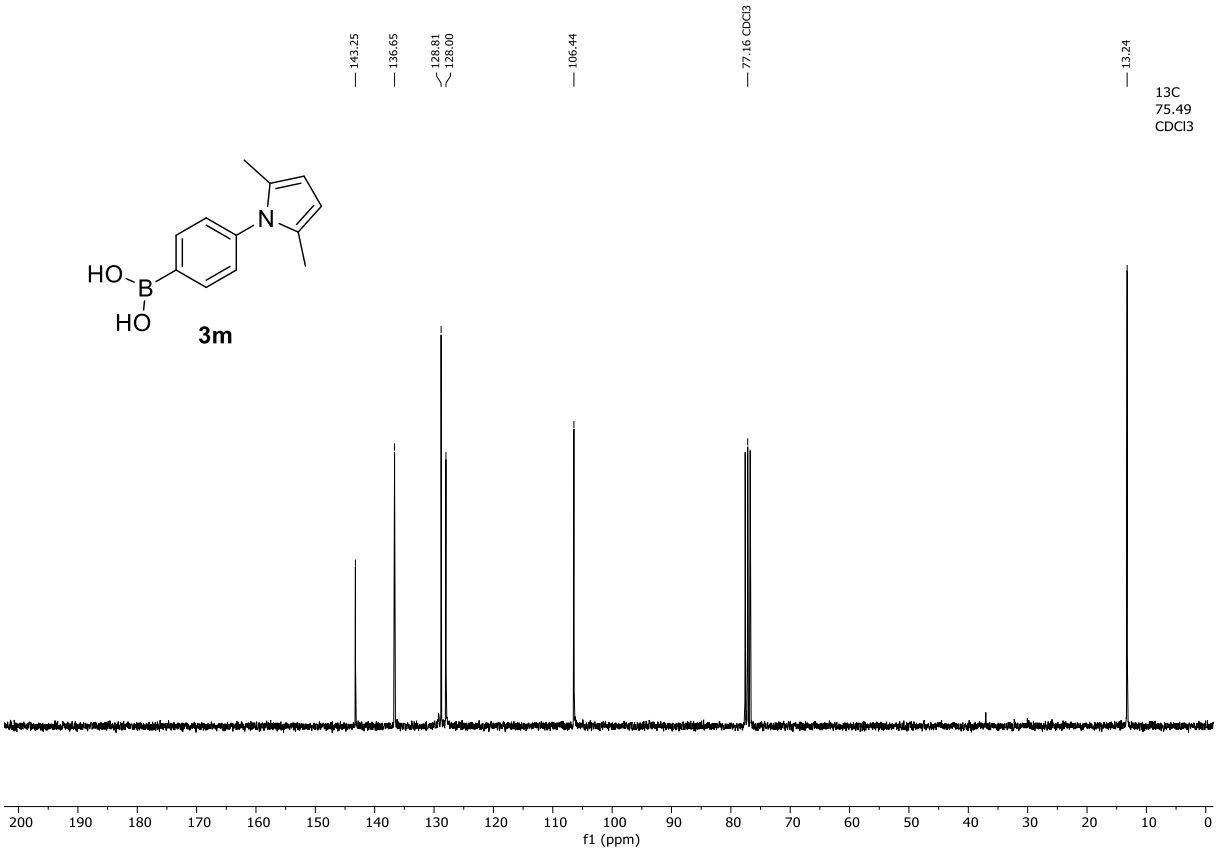


Figure S28. ^{13}C NMR (75 MHz, $CDCl_3$) of **3m**.

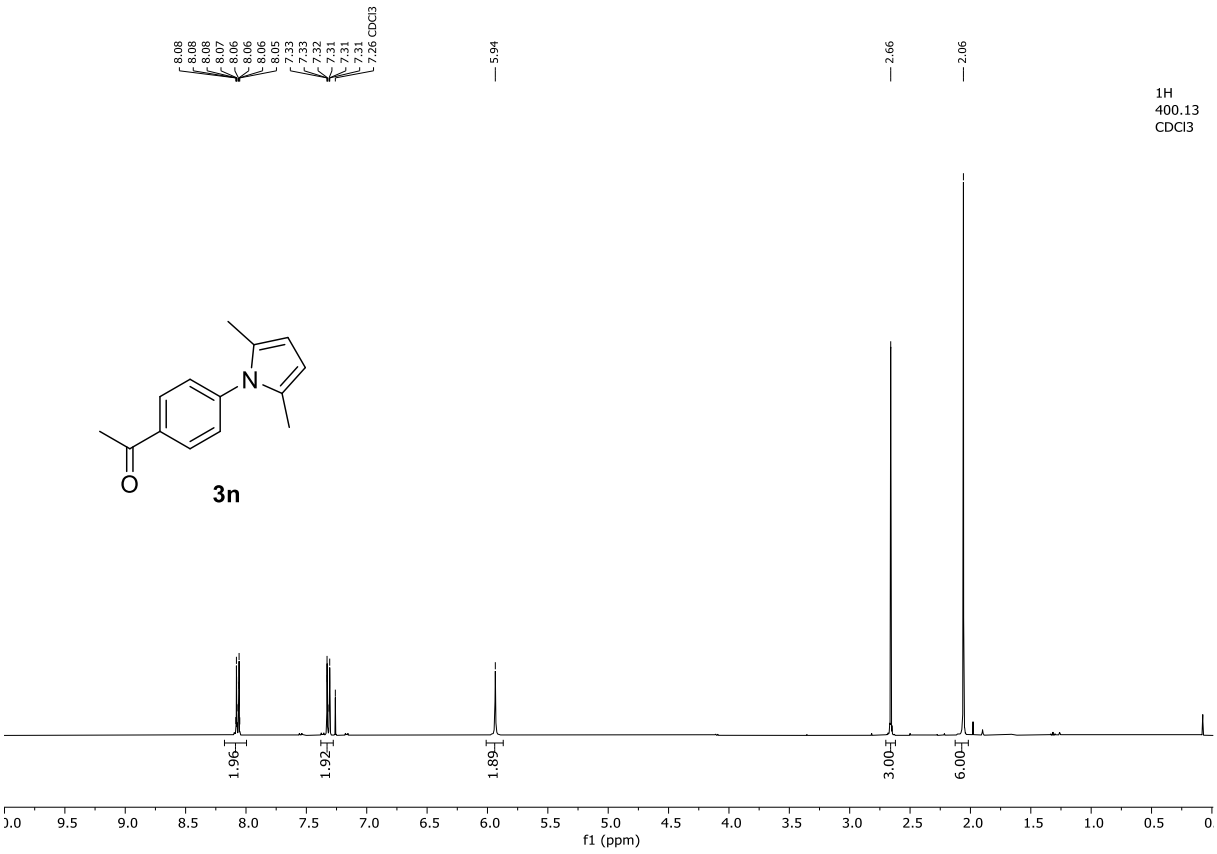


Figure S29. ^{1}H NMR (400 MHz, $CDCl_3$) of **3n**.

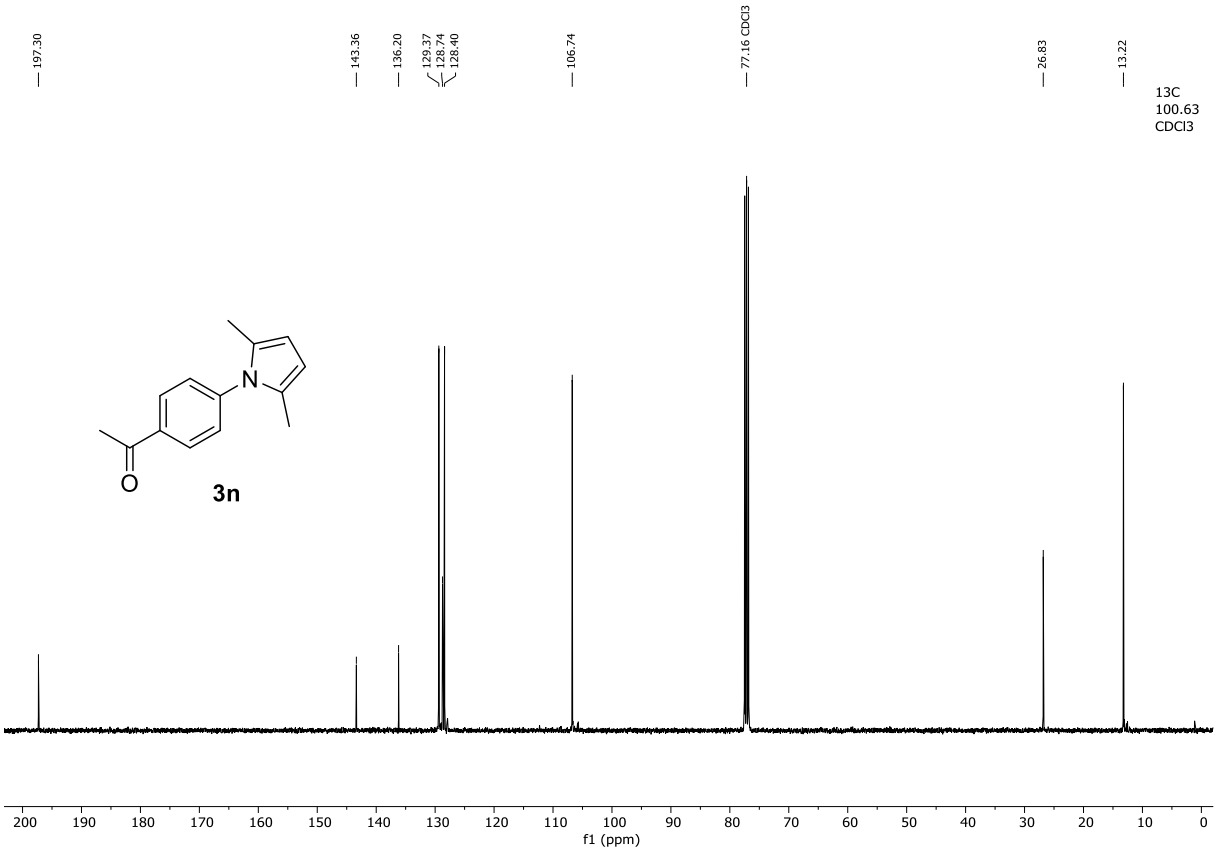


Figure S30. ^{13}C NMR (101 MHz, $CDCl_3$) of **3n**.

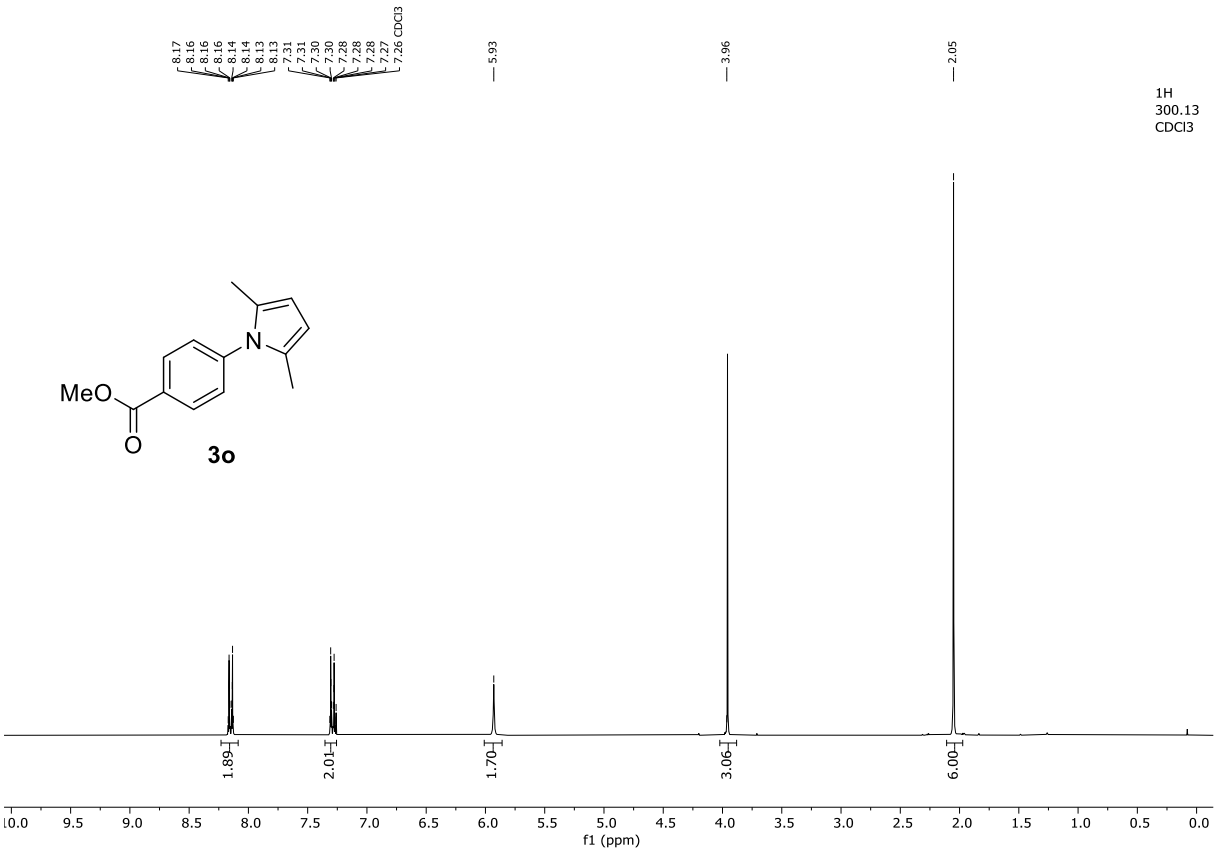


Figure S31. ^{1}H NMR (300 MHz, $CDCl_3$) of **3o**.

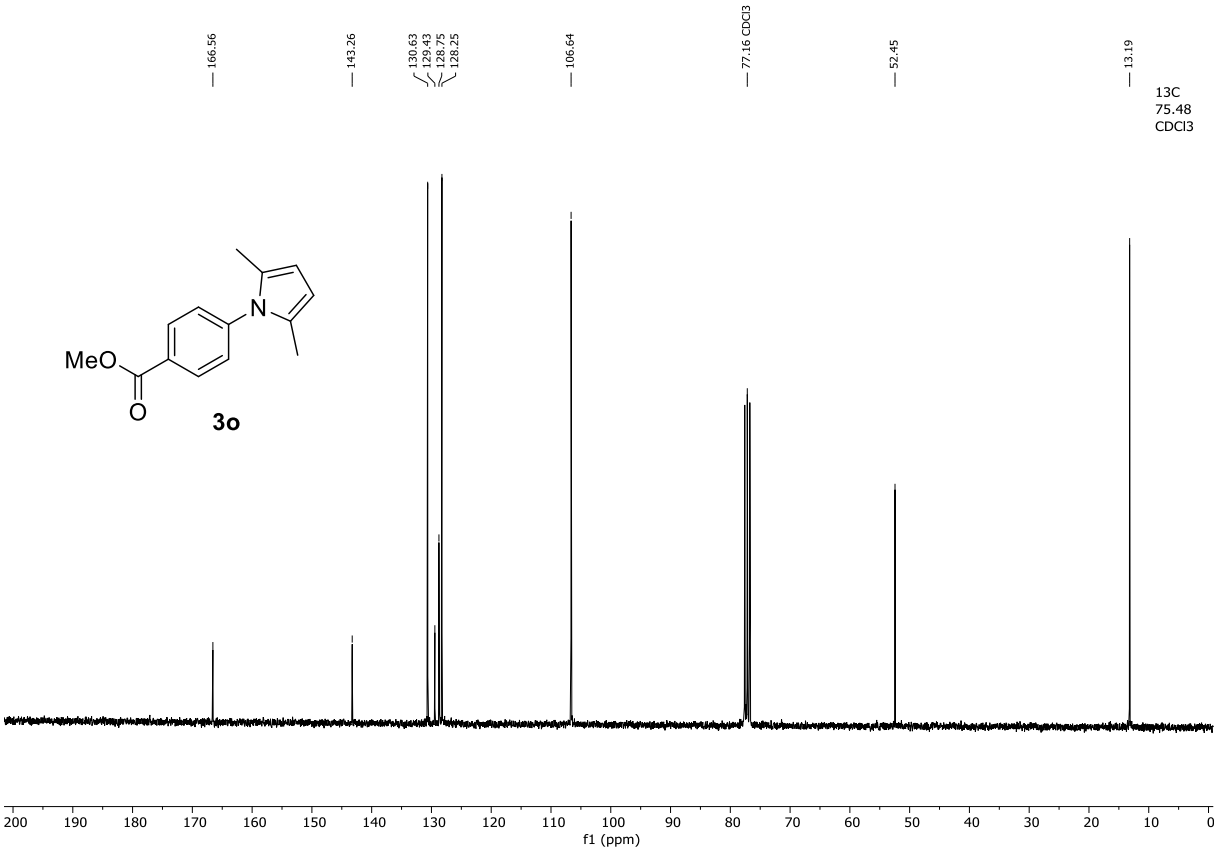


Figure S32. ^{13}C NMR (75 MHz, $CDCl_3$) of **3o**.

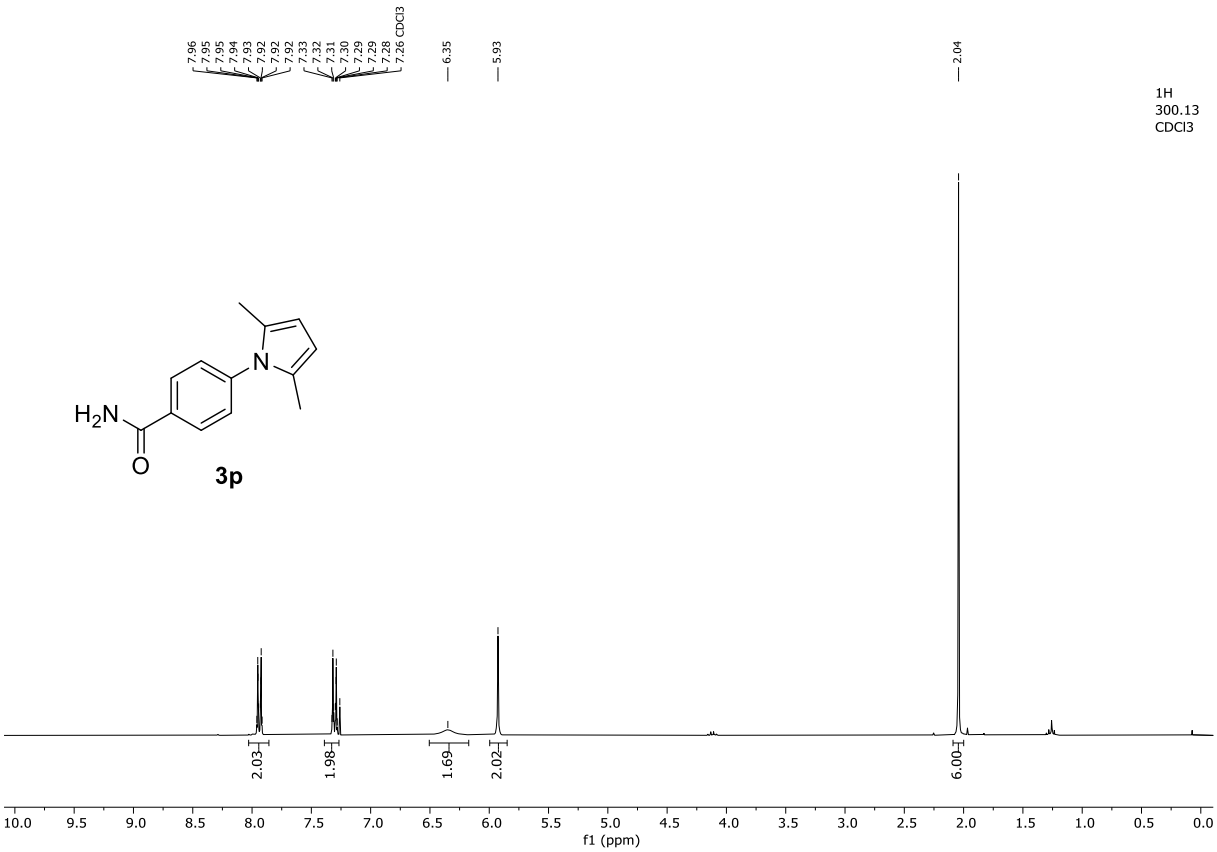


Figure S33. ^{1}H NMR (300 MHz, $CDCl_3$) of **3p**.

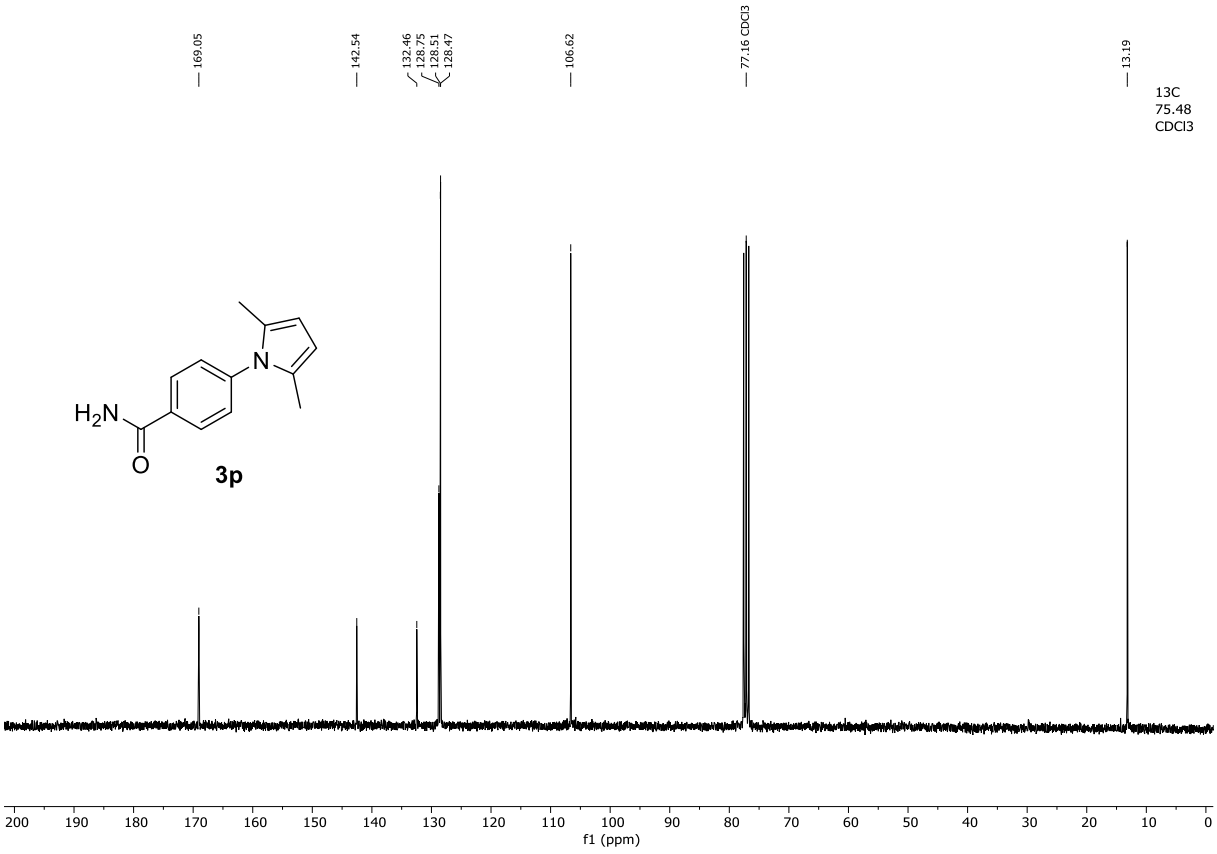


Figure S34. ^{13}C NMR (75 MHz, $CDCl_3$) of **3p**.

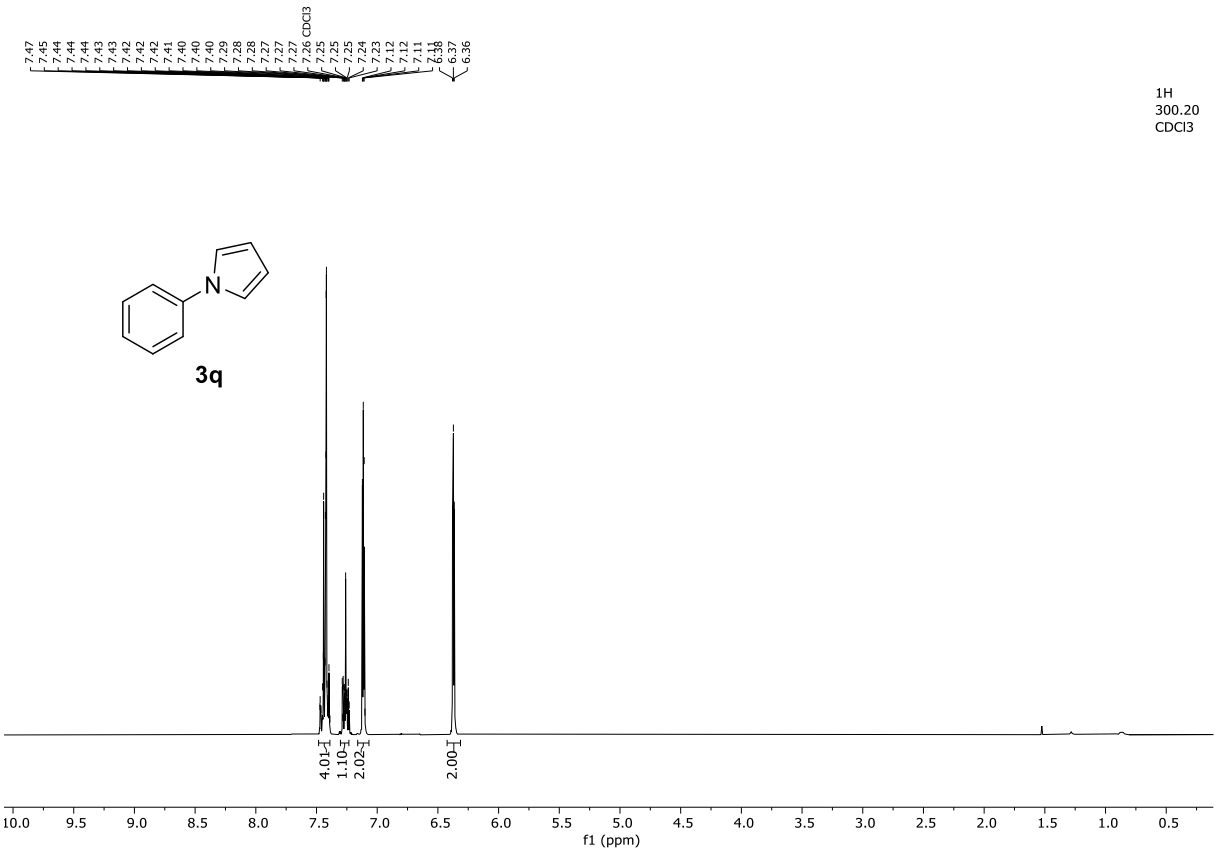


Figure S35. ^{1}H NMR (300 MHz, $CDCl_3$) of **3q**.

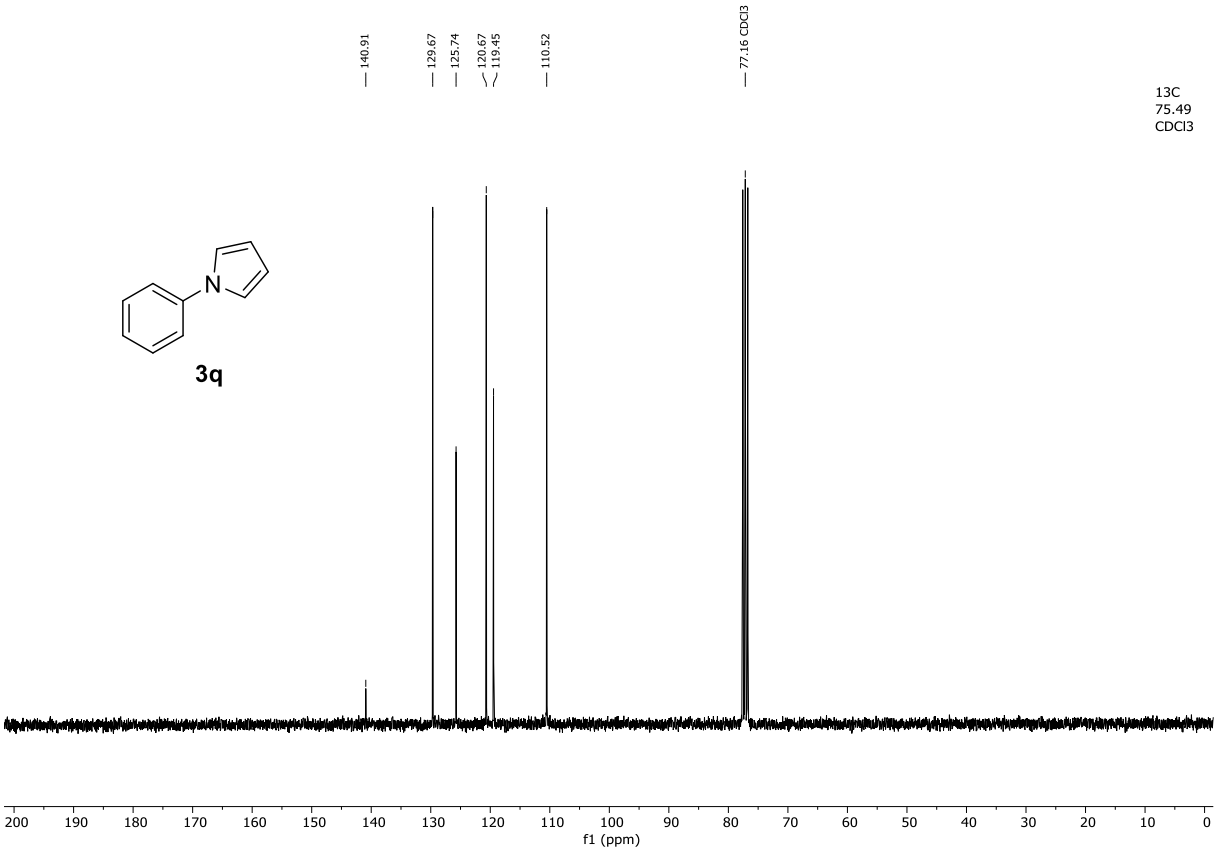


Figure S36. ^{13}C NMR (75 MHz, $CDCl_3$) of **3q**.

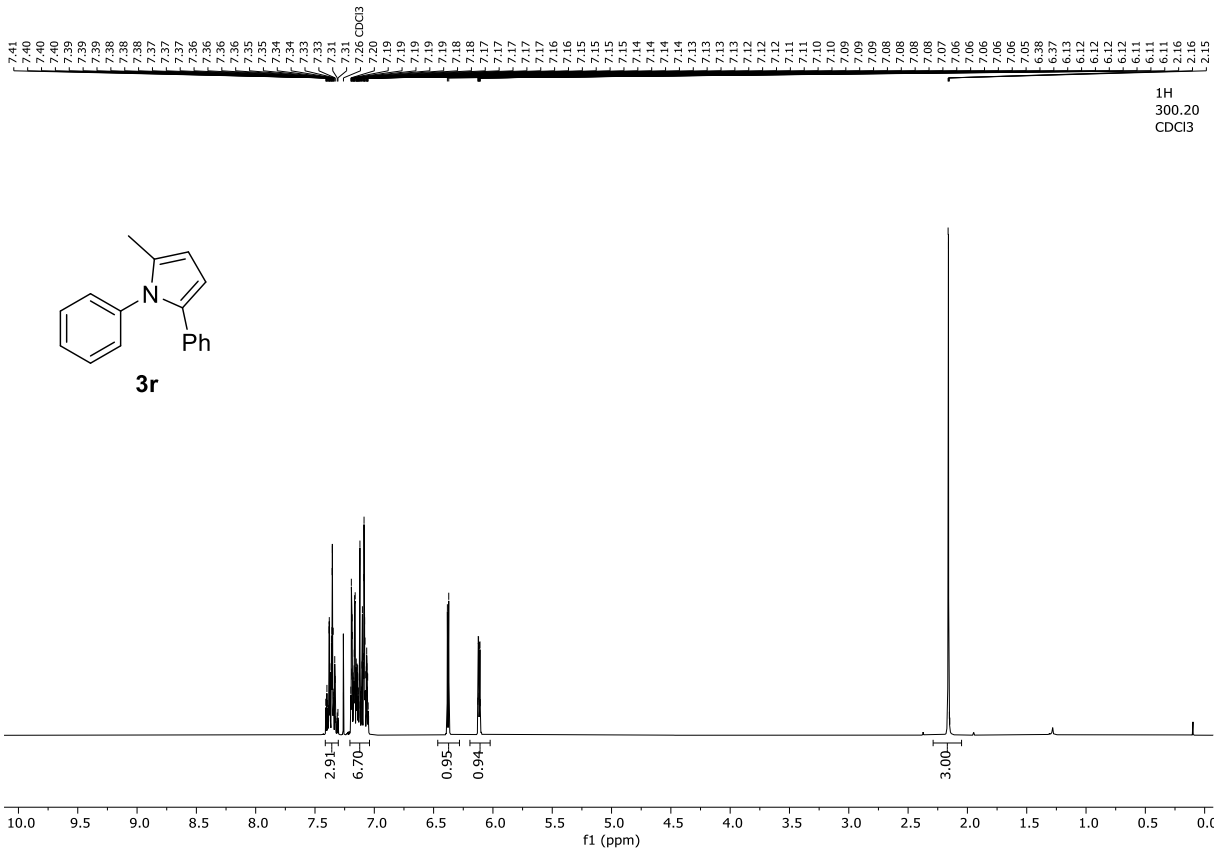


Figure S37. ^{1}H NMR (300 MHz, $CDCl_3$) of **3r**.

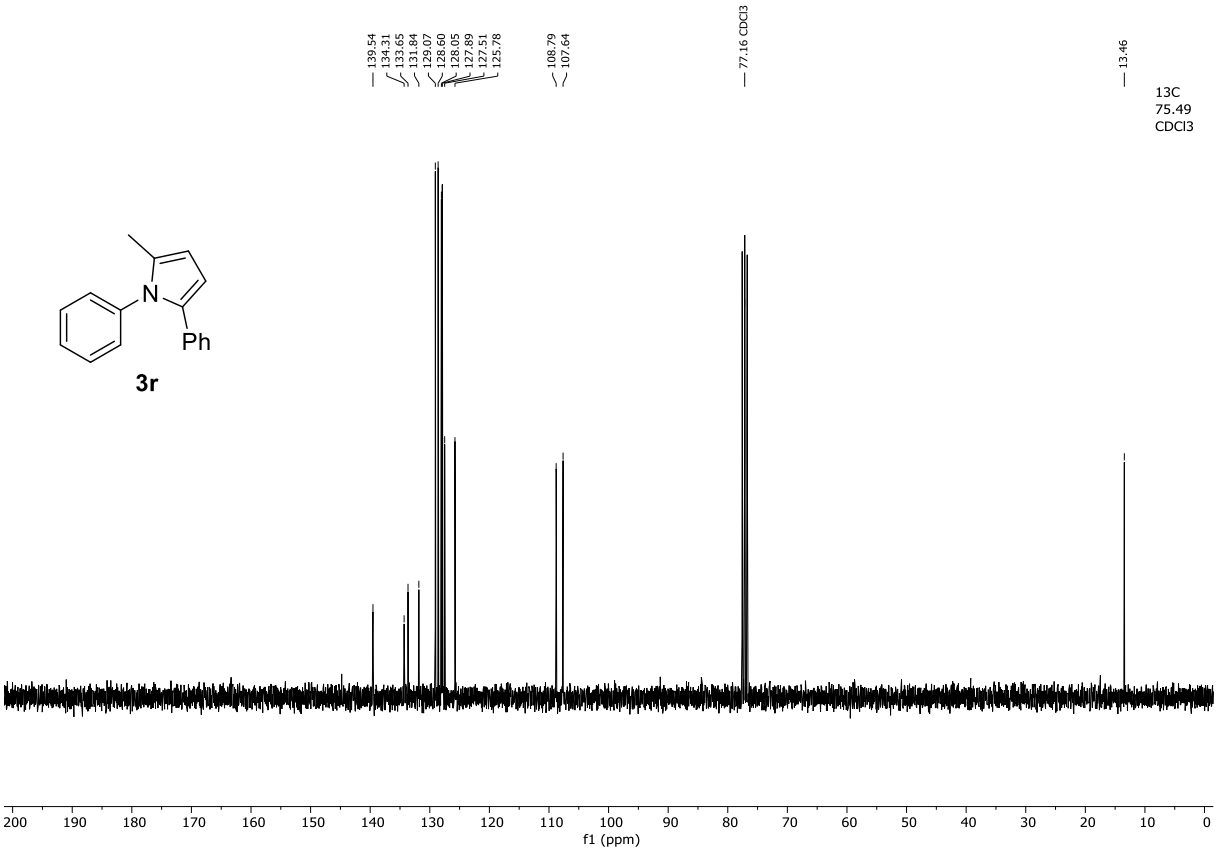


Figure S38. ^{13}C NMR (75 MHz, $CDCl_3$) of **3r**.

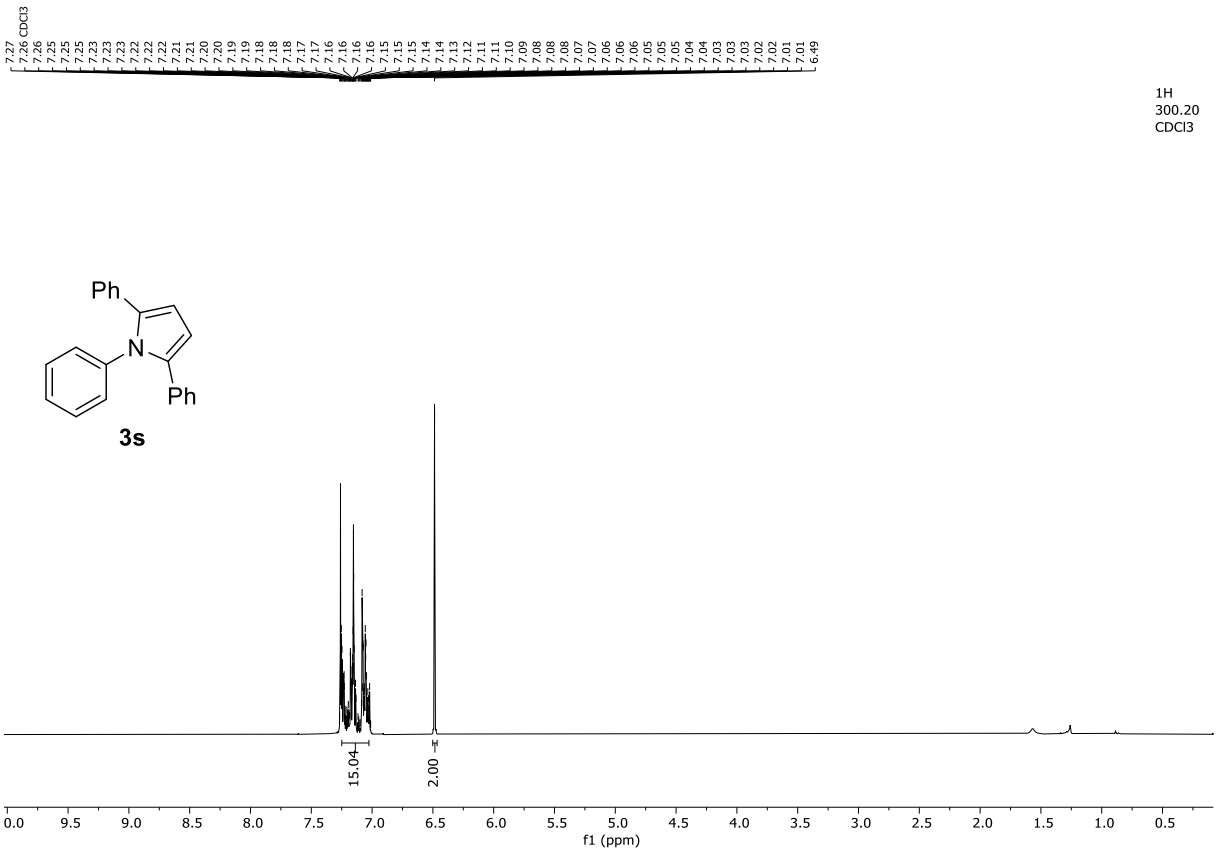


Figure S39. ^{1}H NMR (300 MHz, $CDCl_3$) of **3s**.

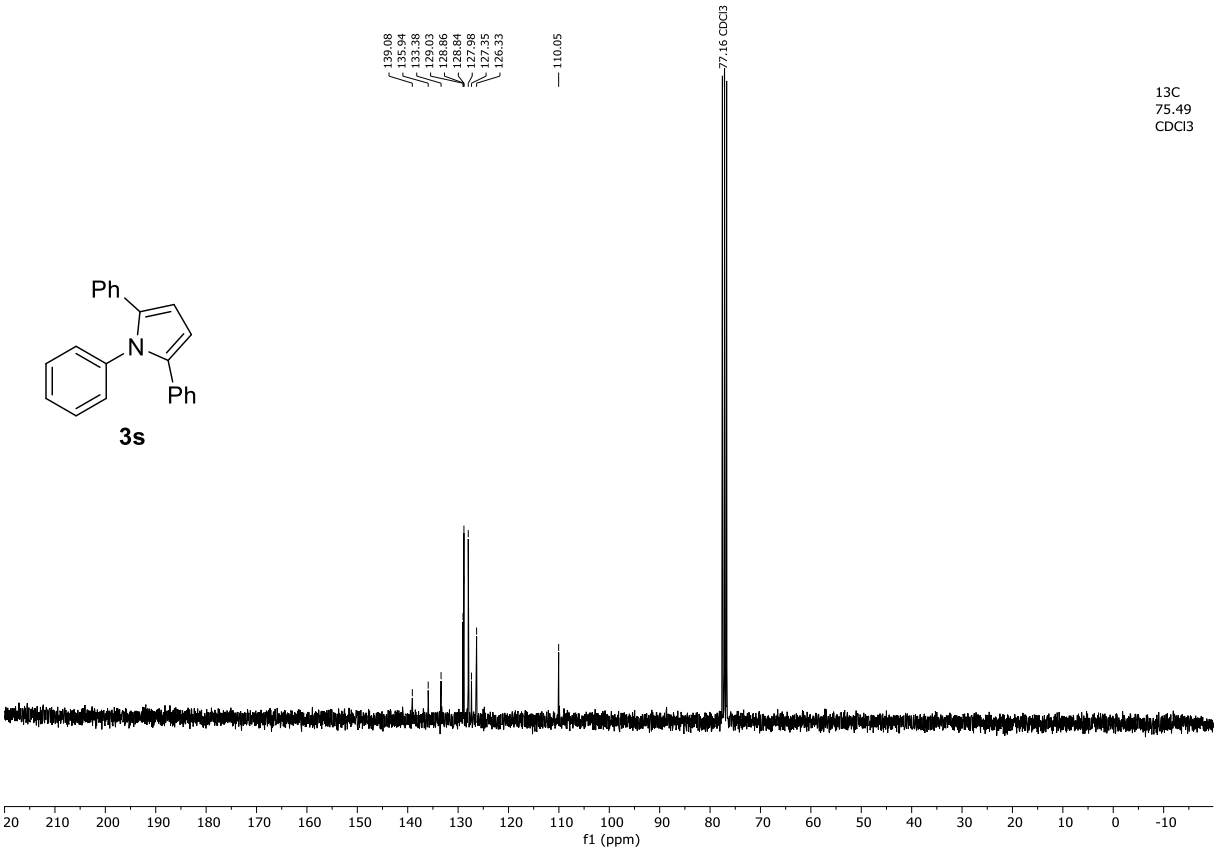


Figure S40. ^{13}C NMR (75 MHz, $CDCl_3$) of **3s**.

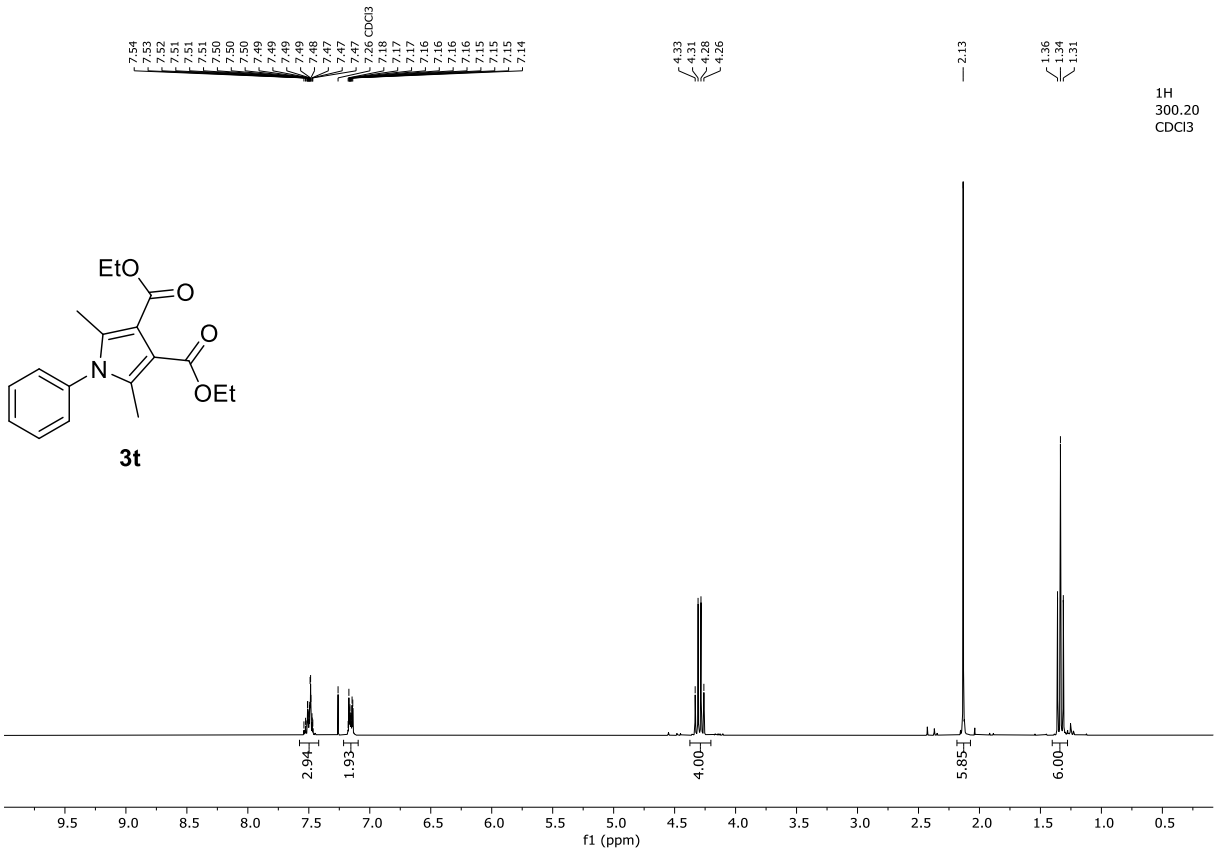


Figure S41. ^{1}H NMR (300 MHz, $CDCl_3$) of **3t**.

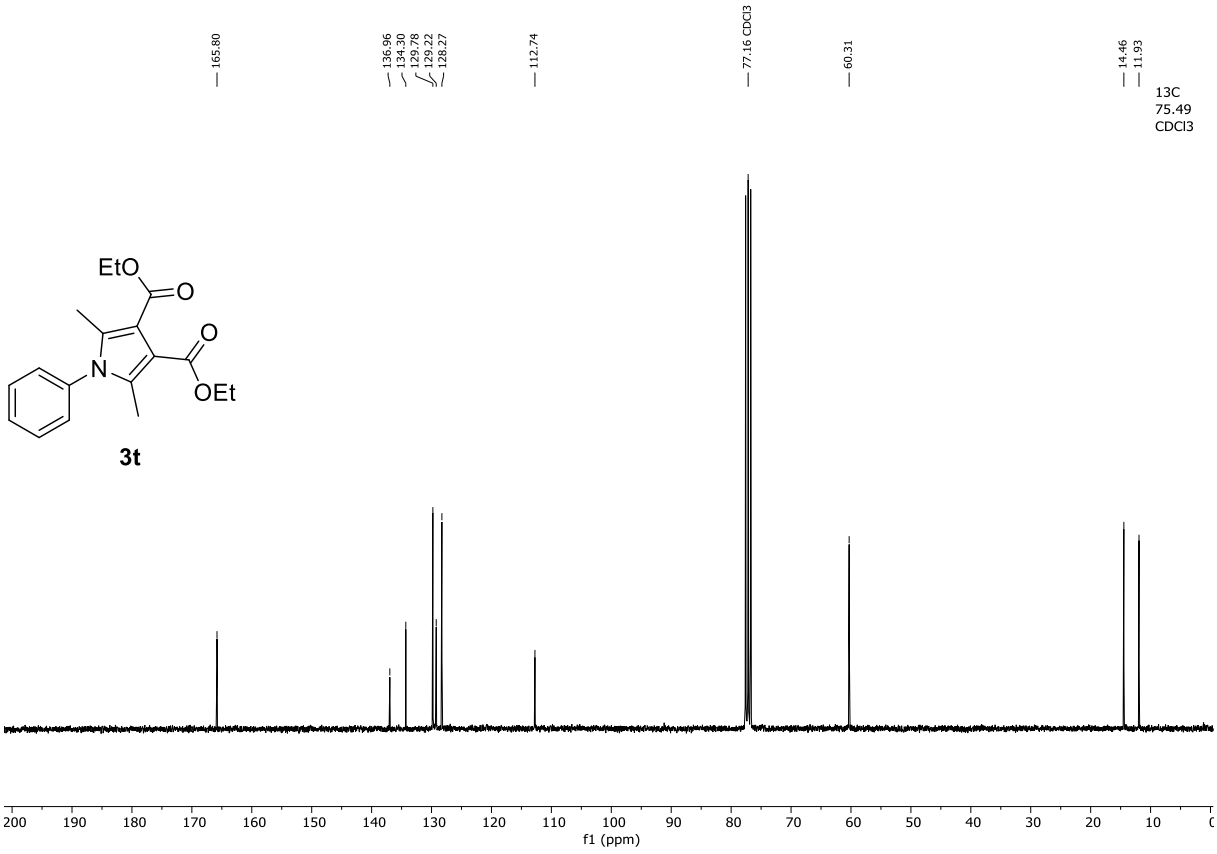


Figure S42. ^{13}C NMR (75 MHz, $CDCl_3$) of **3t**.

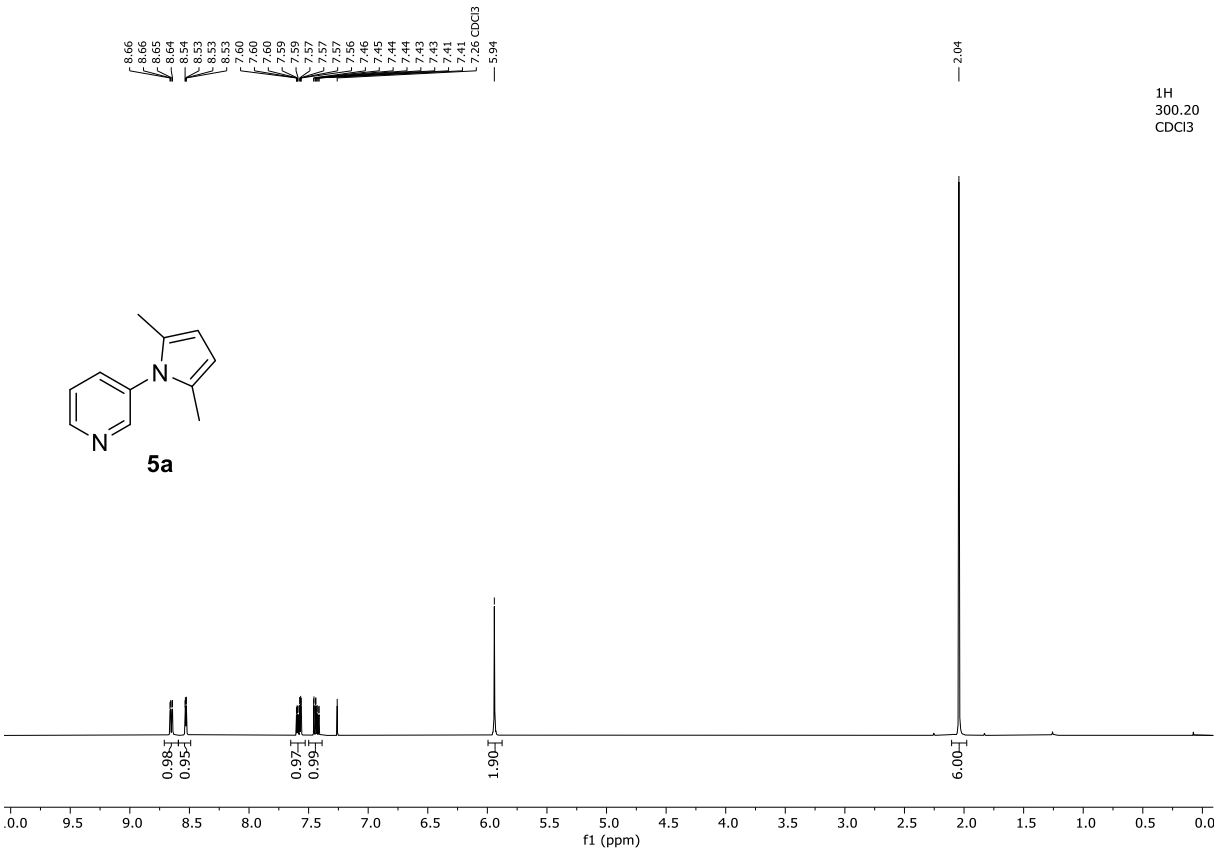


Figure S43. ^{1}H NMR (300 MHz, $CDCl_3$) of **5a**.

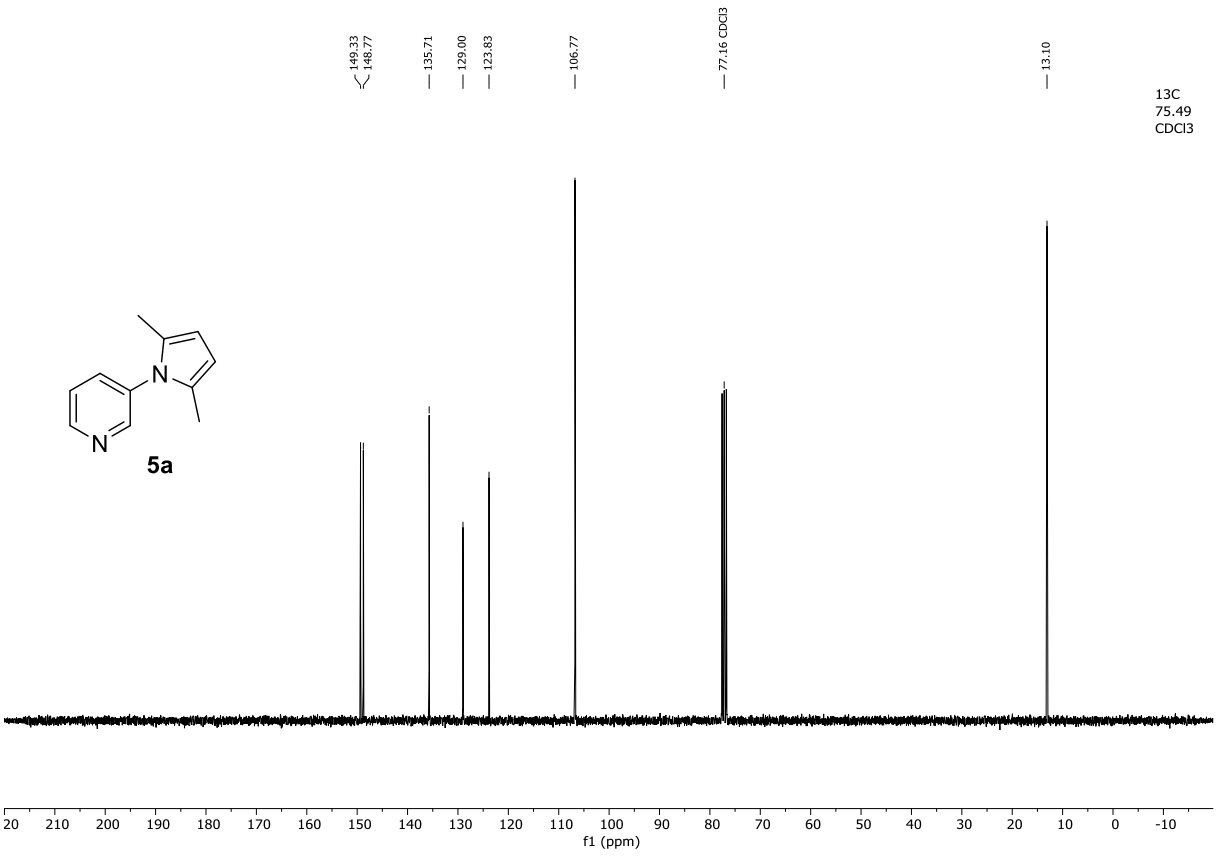


Figure S44. ^{13}C NMR (75 MHz, $CDCl_3$) of **5a**.

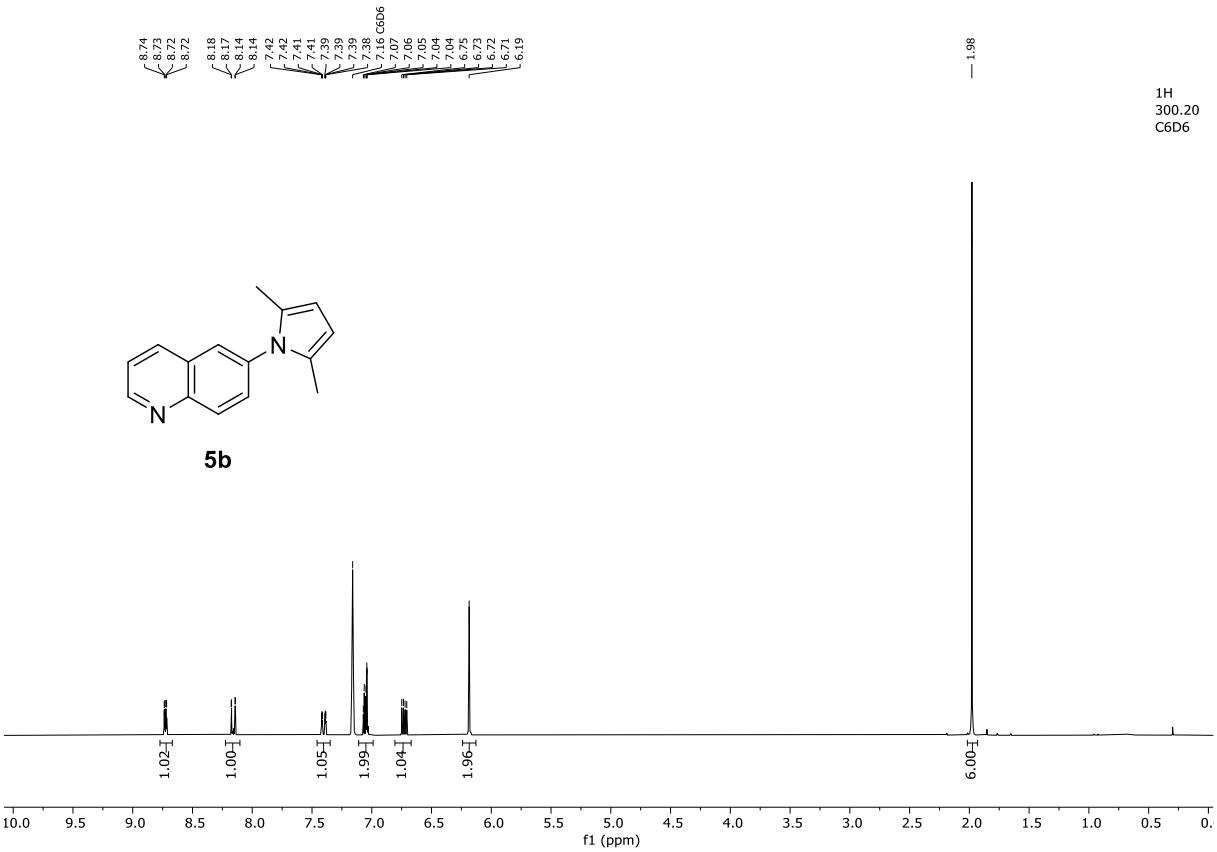


Figure S45. ^{1}H NMR (300 MHz, C_6D_6) of **5b**.

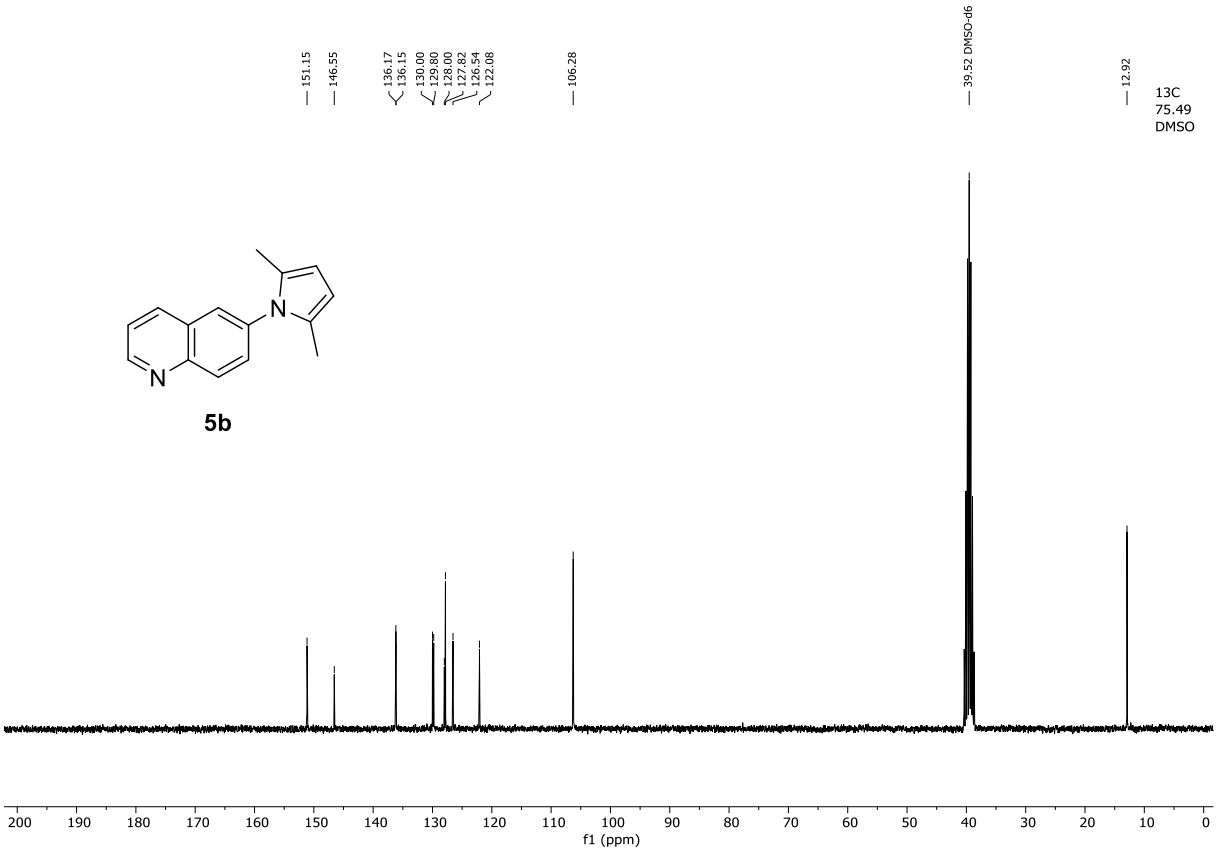
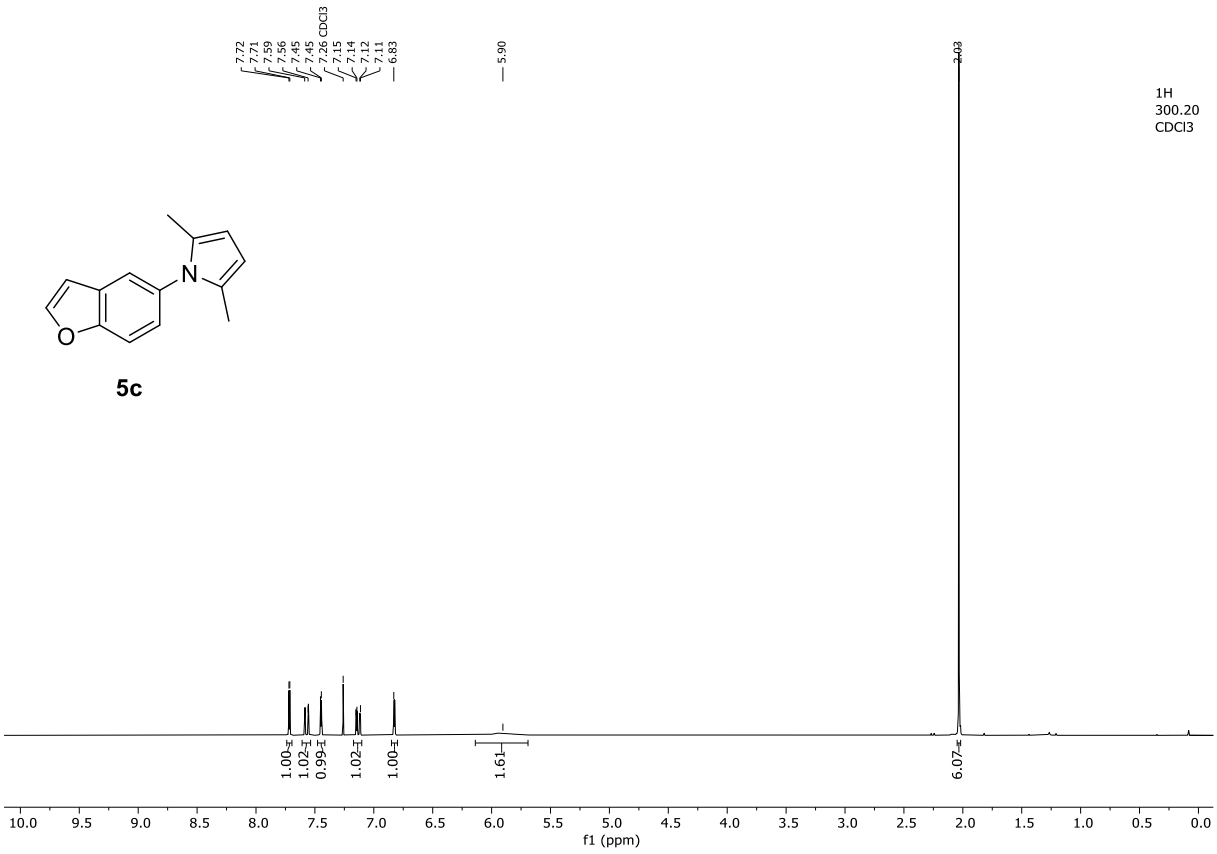
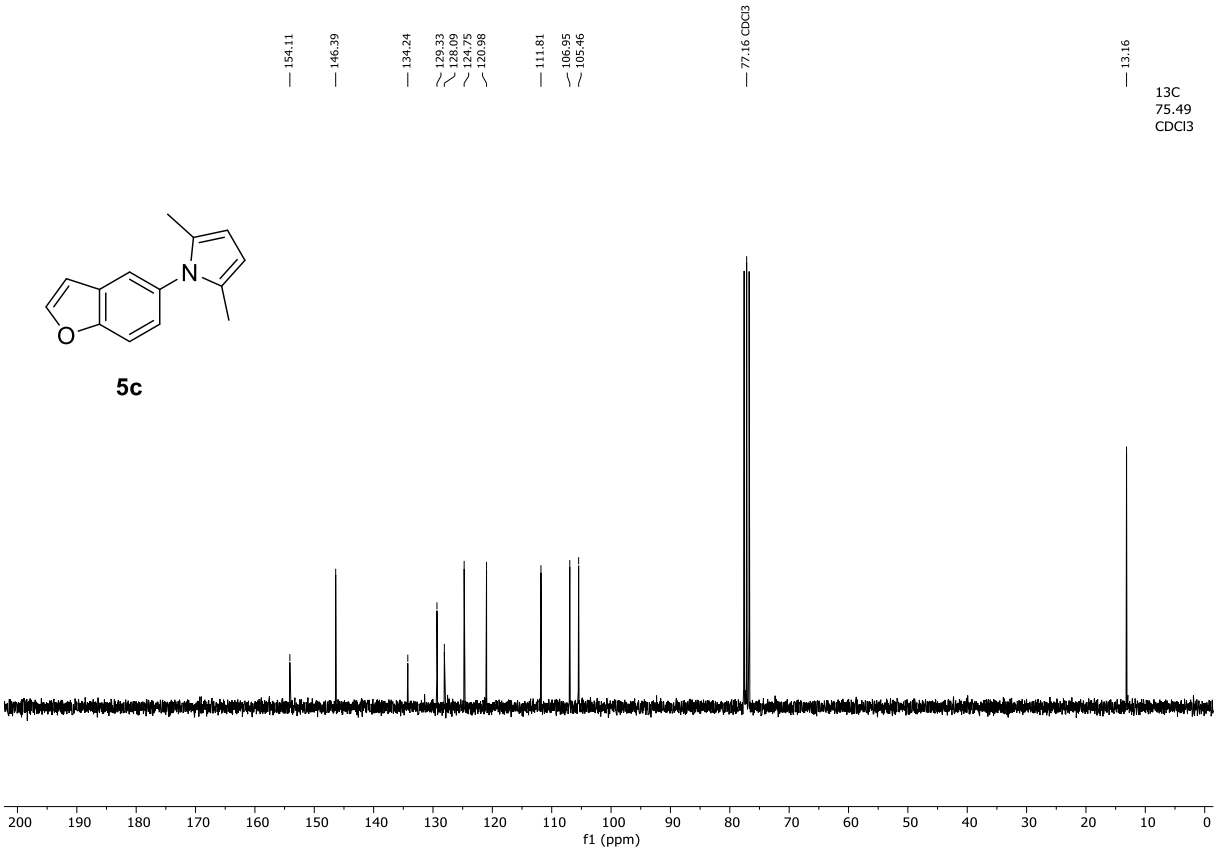


Figure S46. ^{13}C NMR (75 MHz, DMSO-d) of **5b**.



5c

Figure S47. ^{1}H NMR (300 MHz, $CDCl_3$) of **5c**.



5c

Figure S48. ^{13}C NMR (75 MHz, $CDCl_3$) of **5c**.

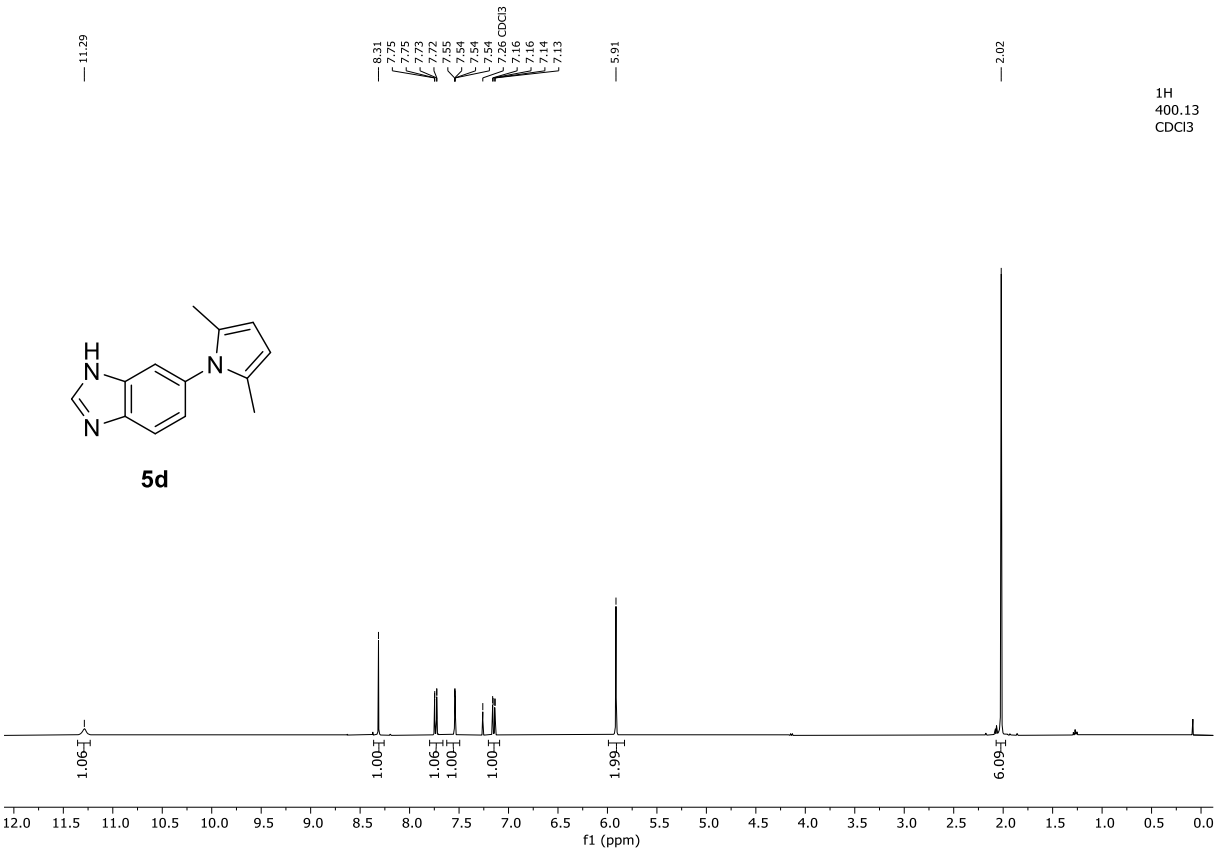


Figure S49. ^{1}H NMR (400 MHz, $CDCl_3$) of **5d**.

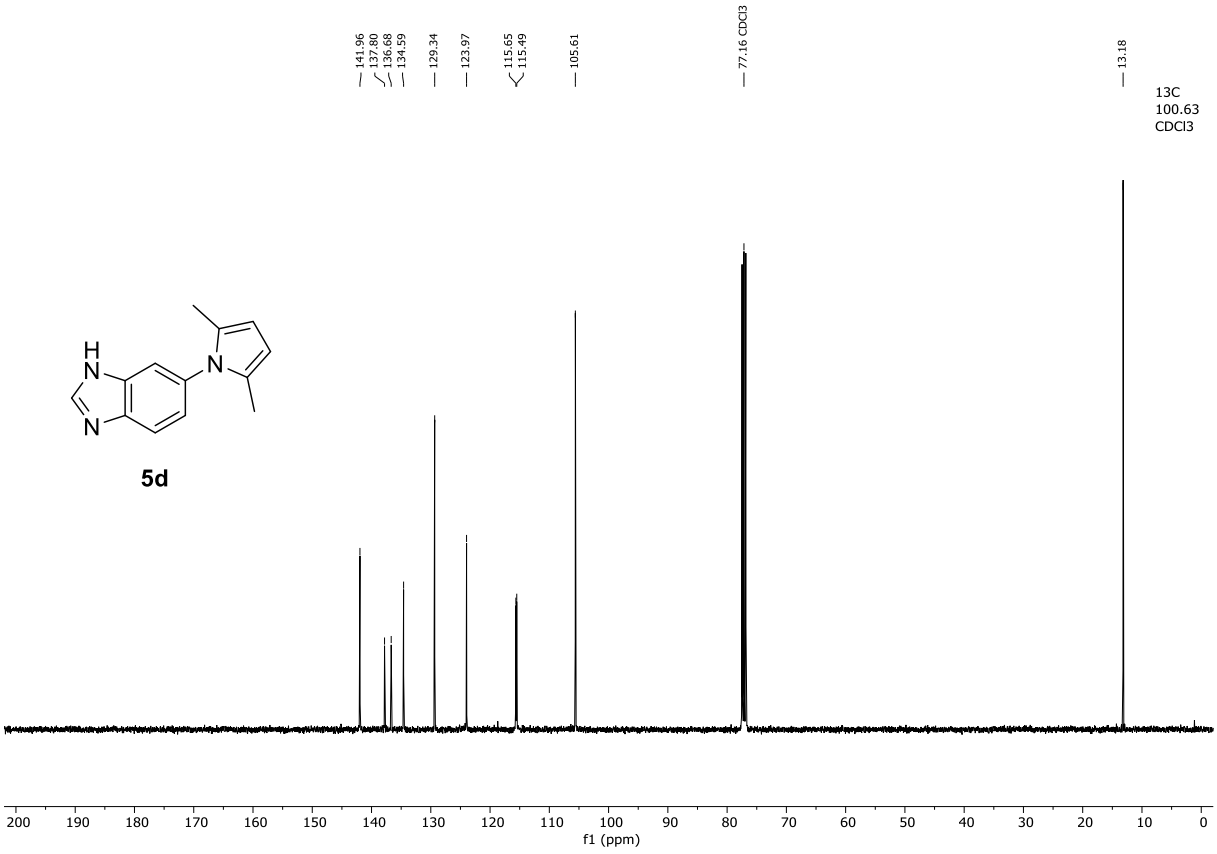
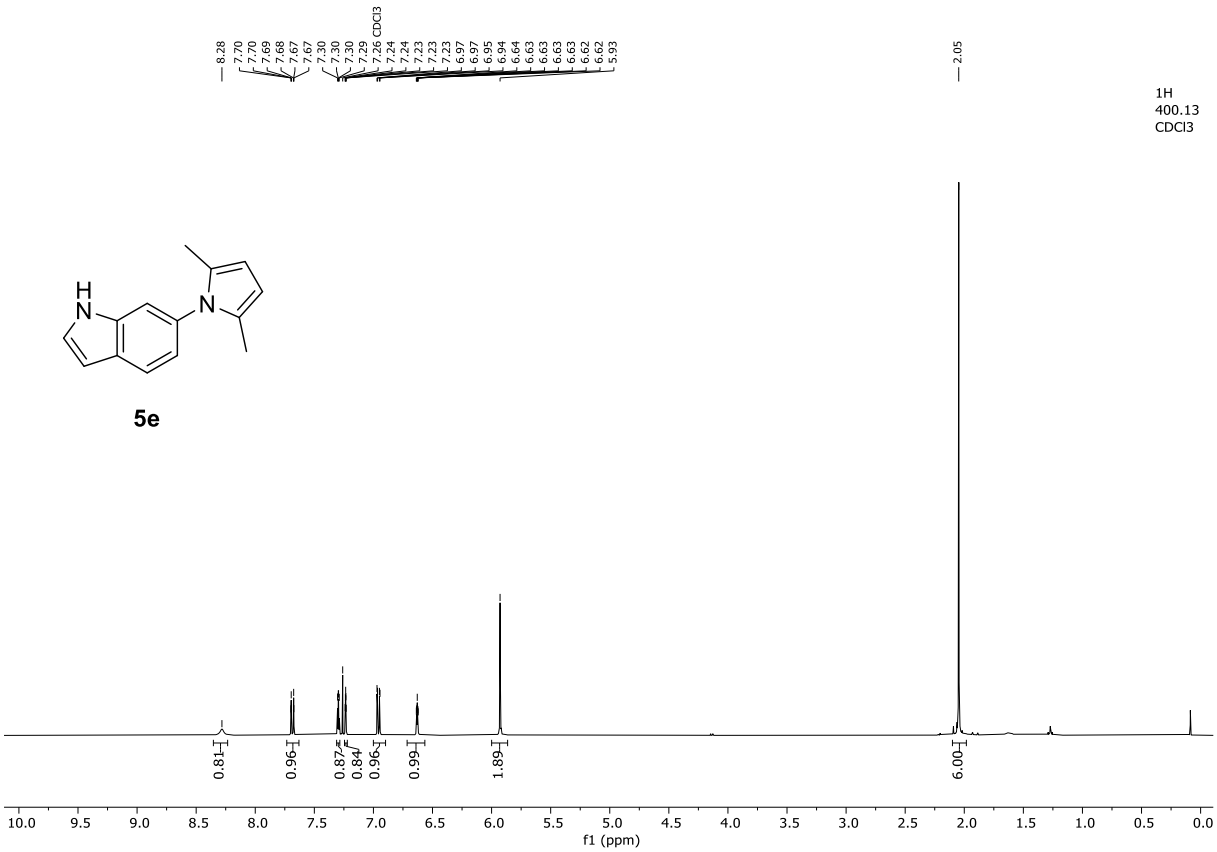
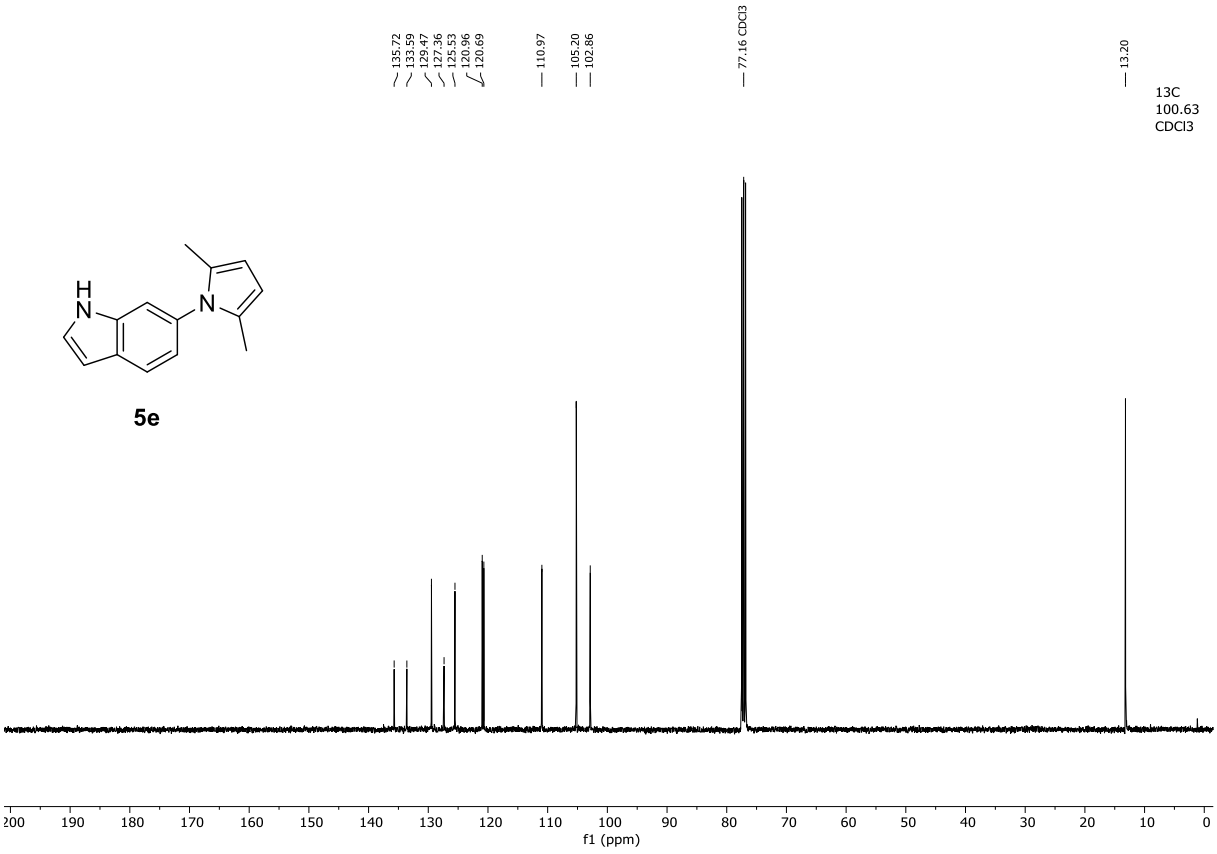


Figure S50. ^{13}C NMR (101 MHz, $CDCl_3$) of **5d**.



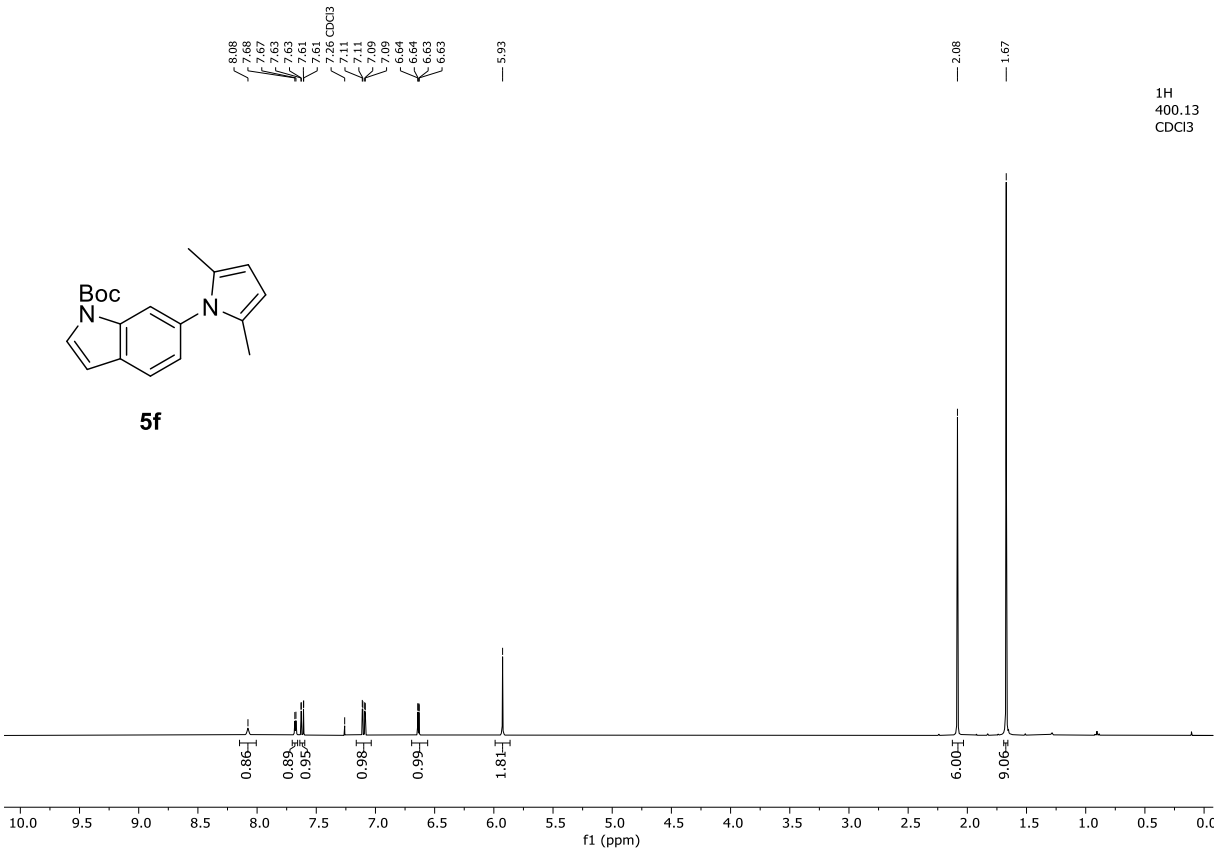
5e

Figure S51. ^{1}H NMR (400 MHz, $CDCl_3$) of **5e**.



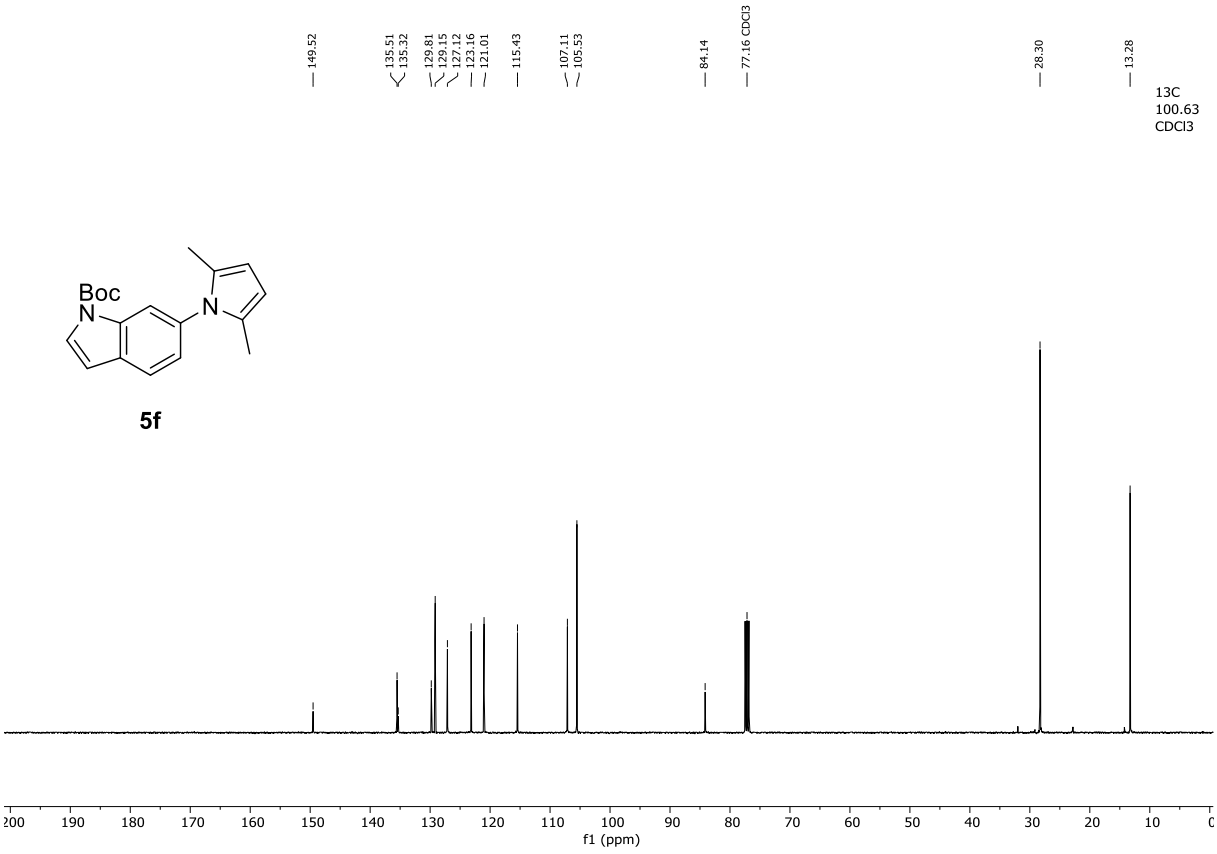
5e

Figure S52. ^{13}C NMR (101 MHz, $CDCl_3$) of **5e**.



5f

Figure S53. ^{1}H NMR (400 MHz, $CDCl_3$) of **5f**.



5f

Figure S54. ^{13}C NMR (101 MHz, $CDCl_3$) of **5f**.

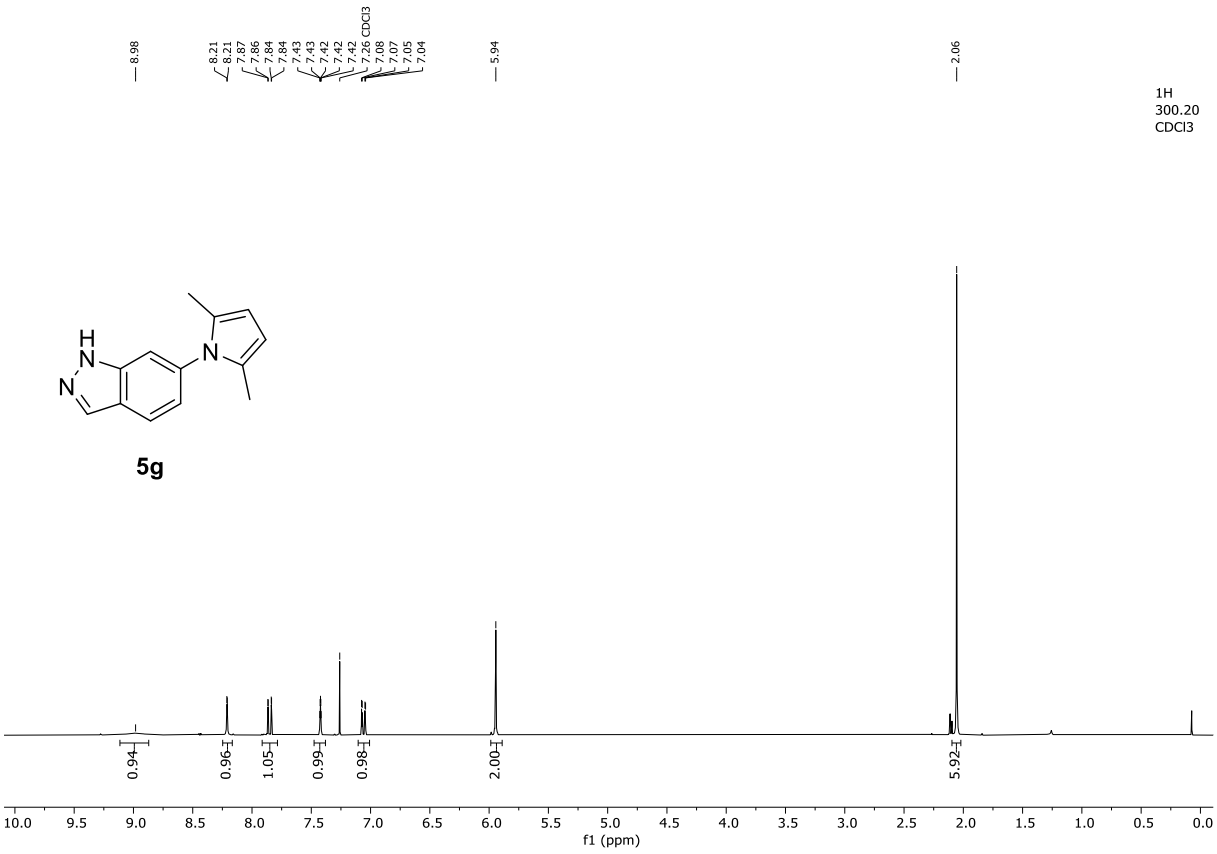


Figure S55. ^{1}H NMR (300 MHz, $CDCl_3$) of **5g**.

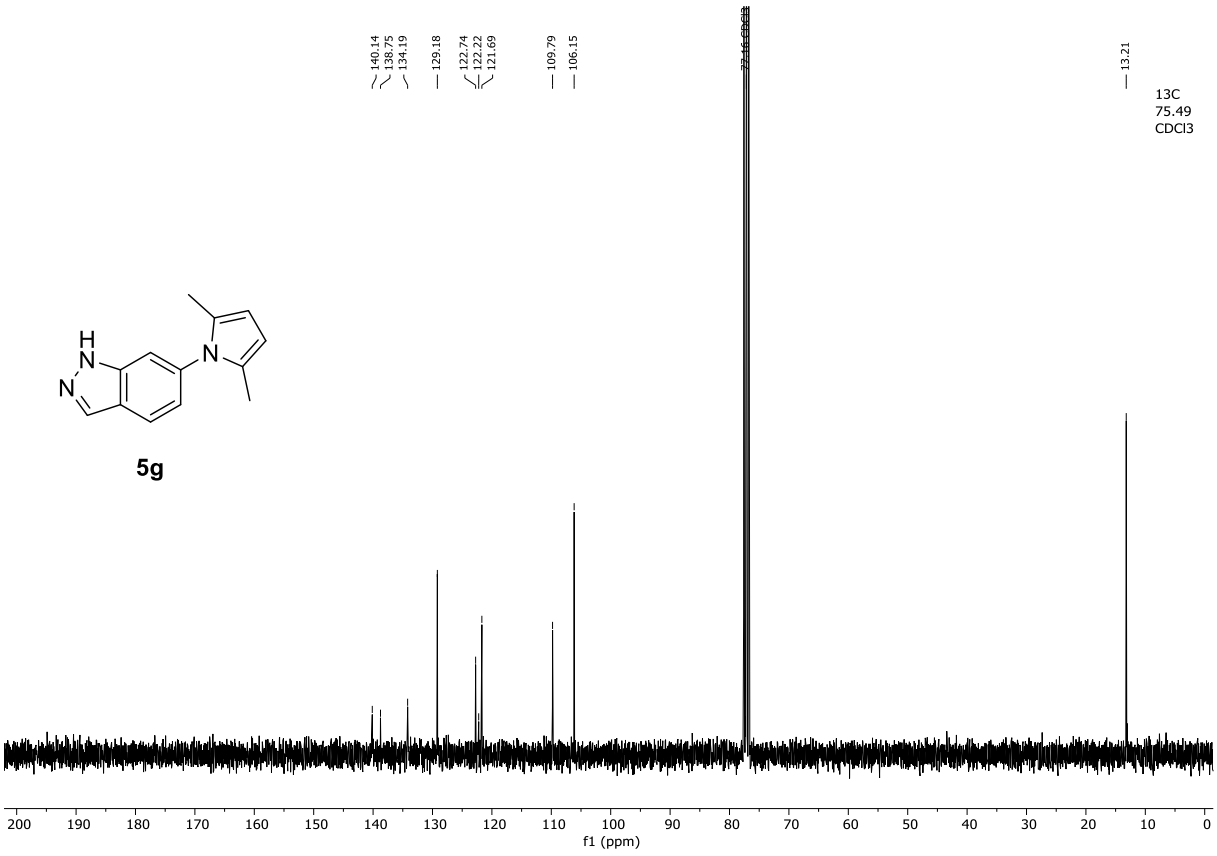


Figure S56. ^{13}C NMR (75 MHz, $CDCl_3$) of **5g**.

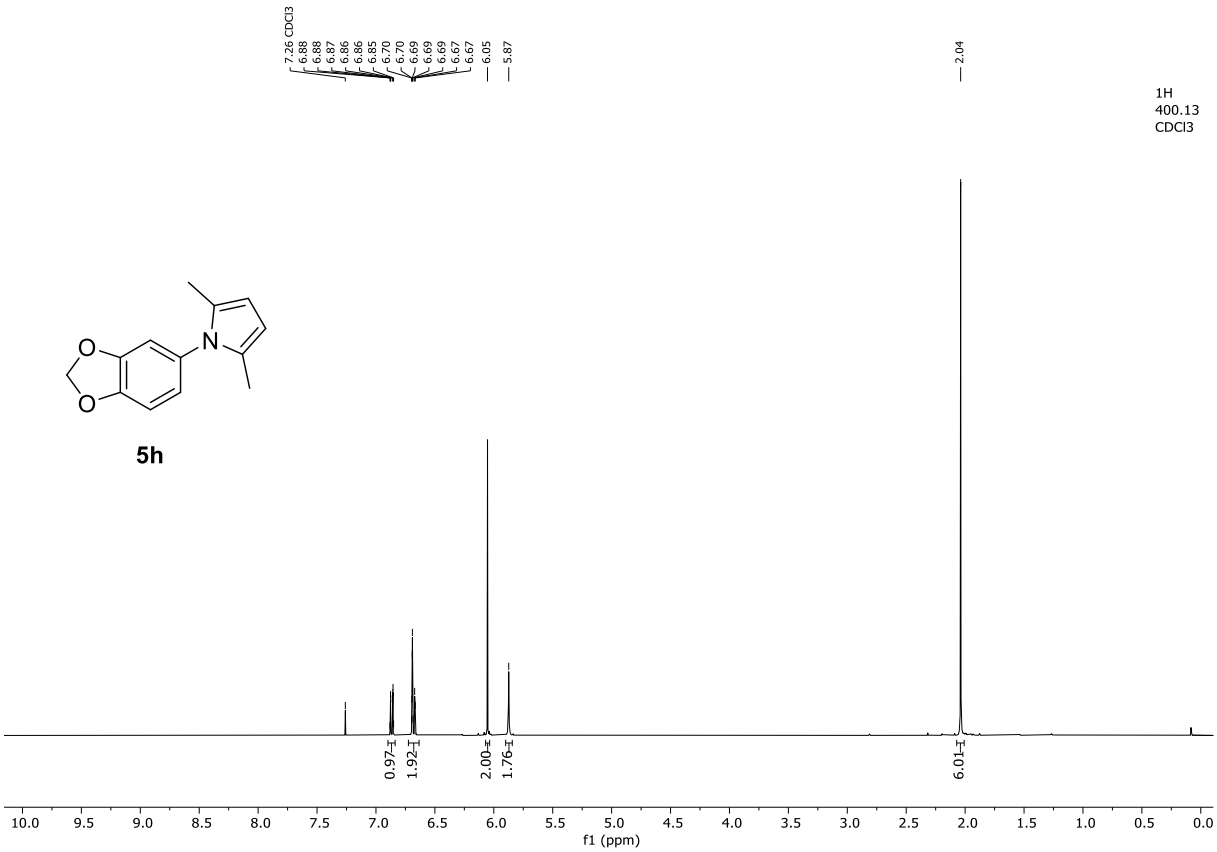


Figure S57. ^{1}H NMR (400 MHz, $CDCl_3$) of **5h**.

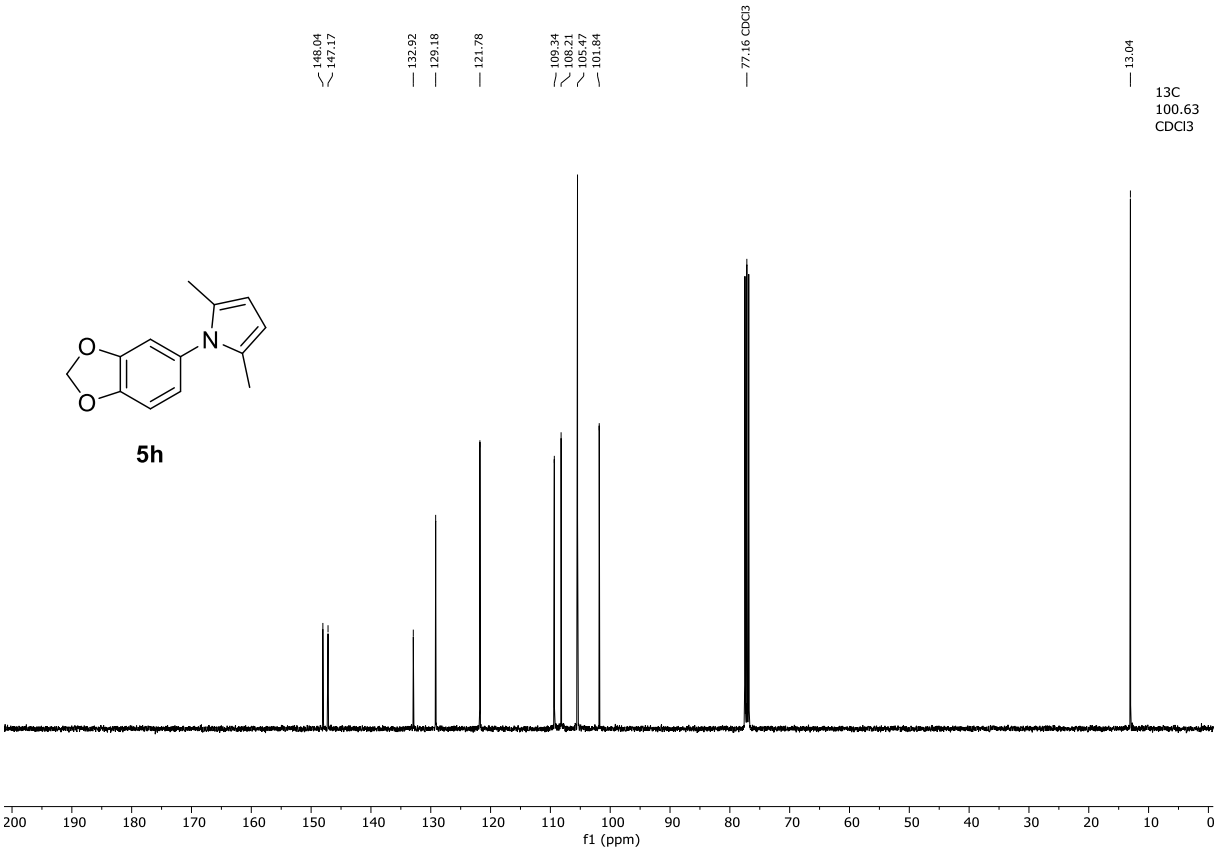


Figure S58. ^{13}C NMR (101 MHz, $CDCl_3$) of **5h**.

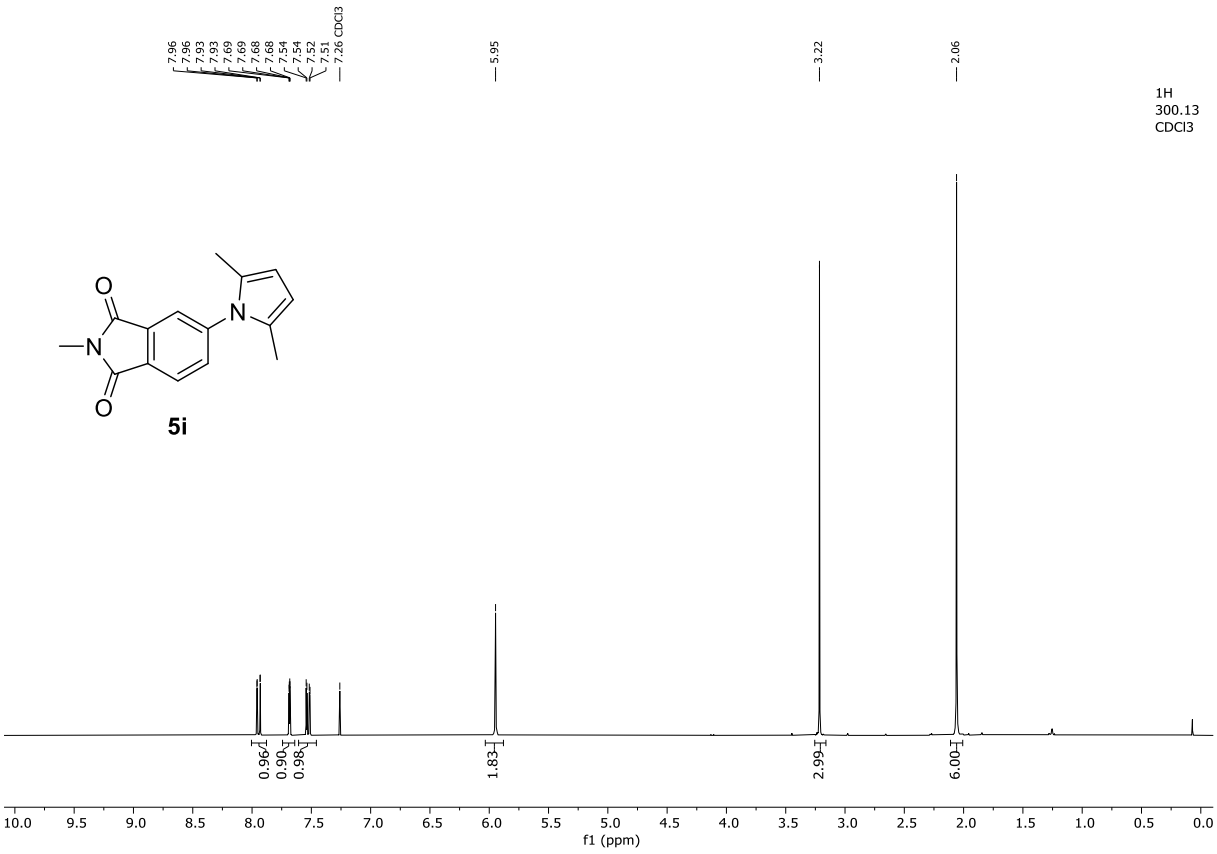


Figure S59. ^{1}H NMR (300 MHz, $CDCl_3$) of **5i**.

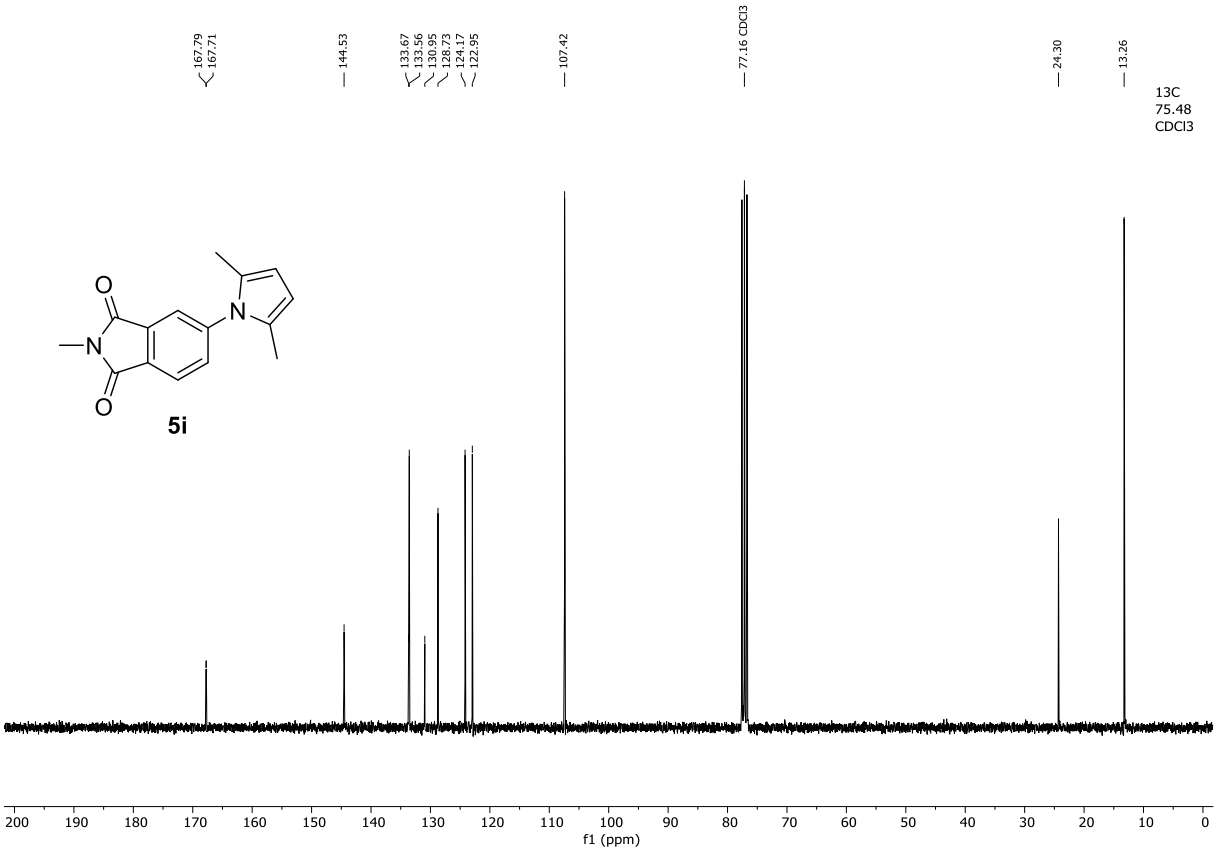


Figure S60. ^{13}C NMR (75 MHz, $CDCl_3$) of **5i**.

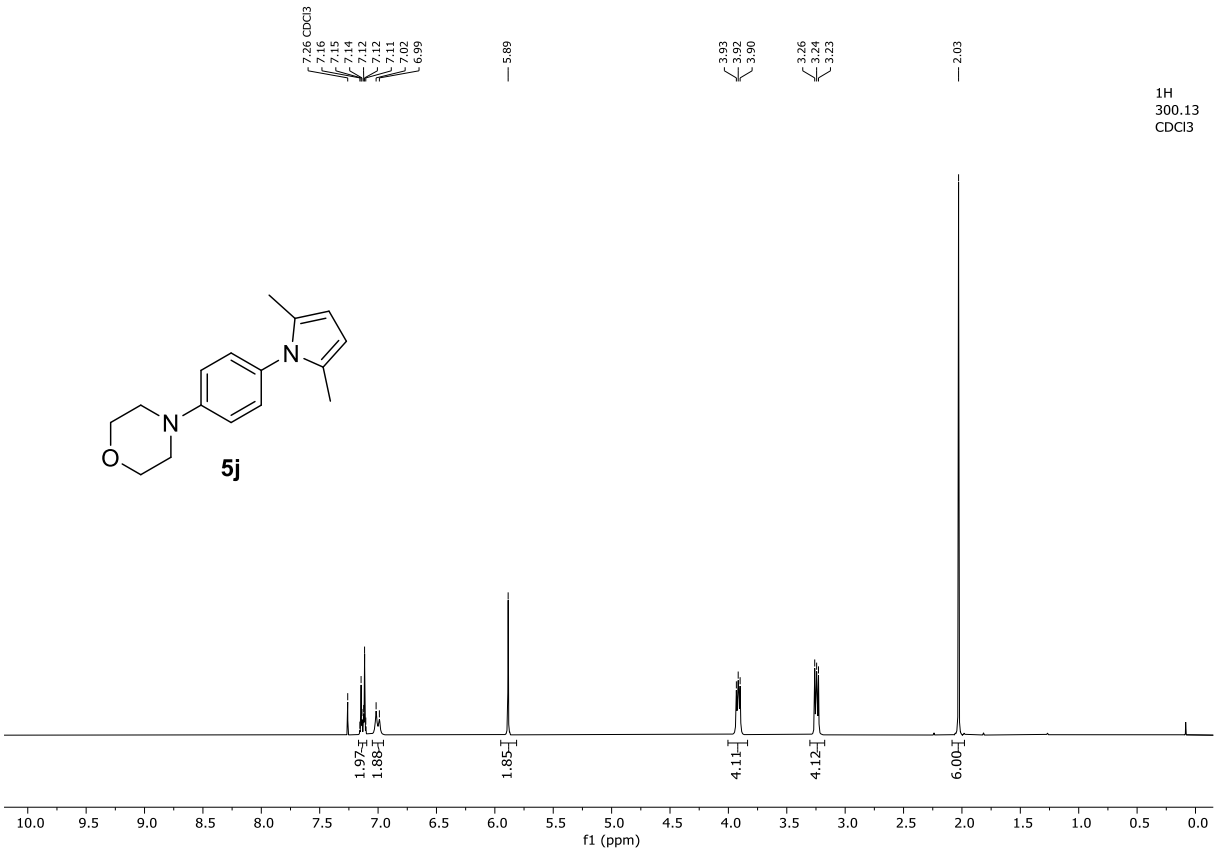


Figure S61. ^{1}H NMR (300 MHz, $CDCl_3$) of **5j**.

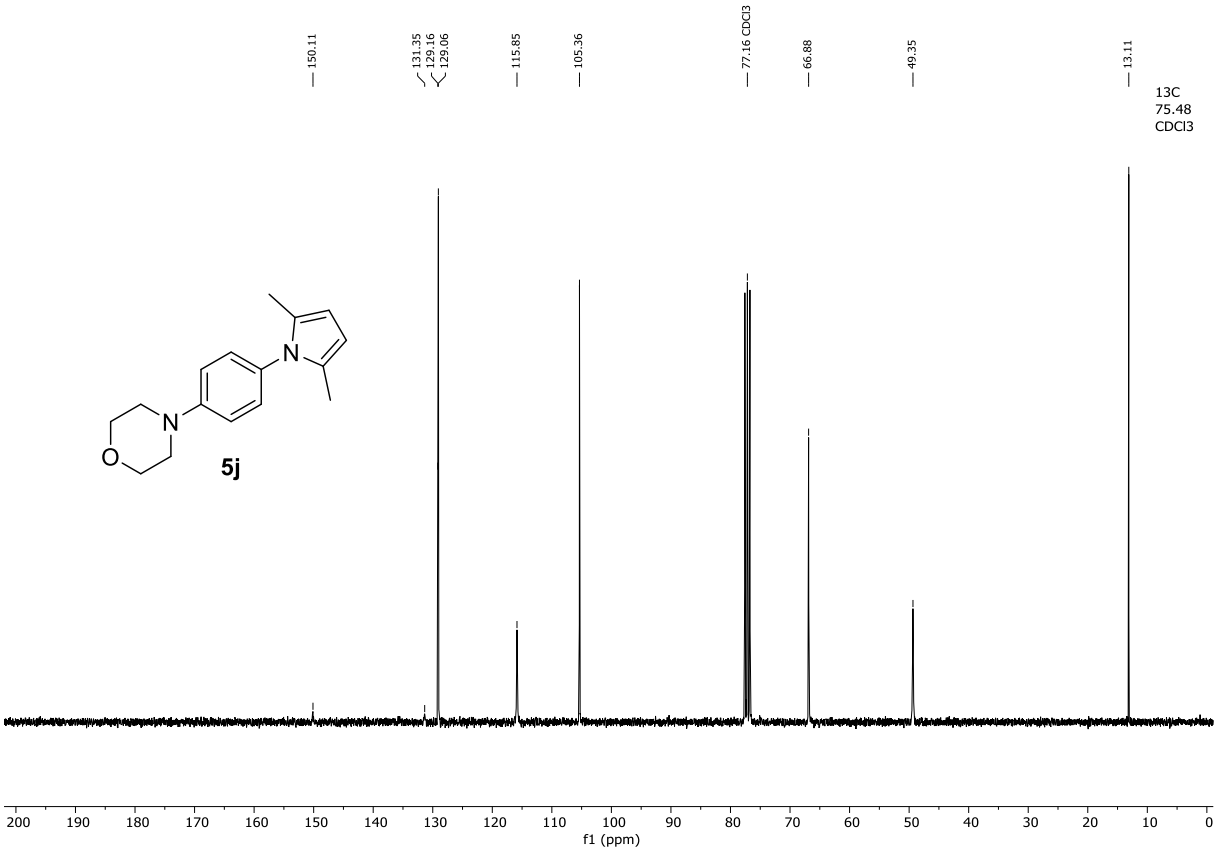


Figure S62. ^{13}C NMR (75 MHz, $CDCl_3$) of **5j**.

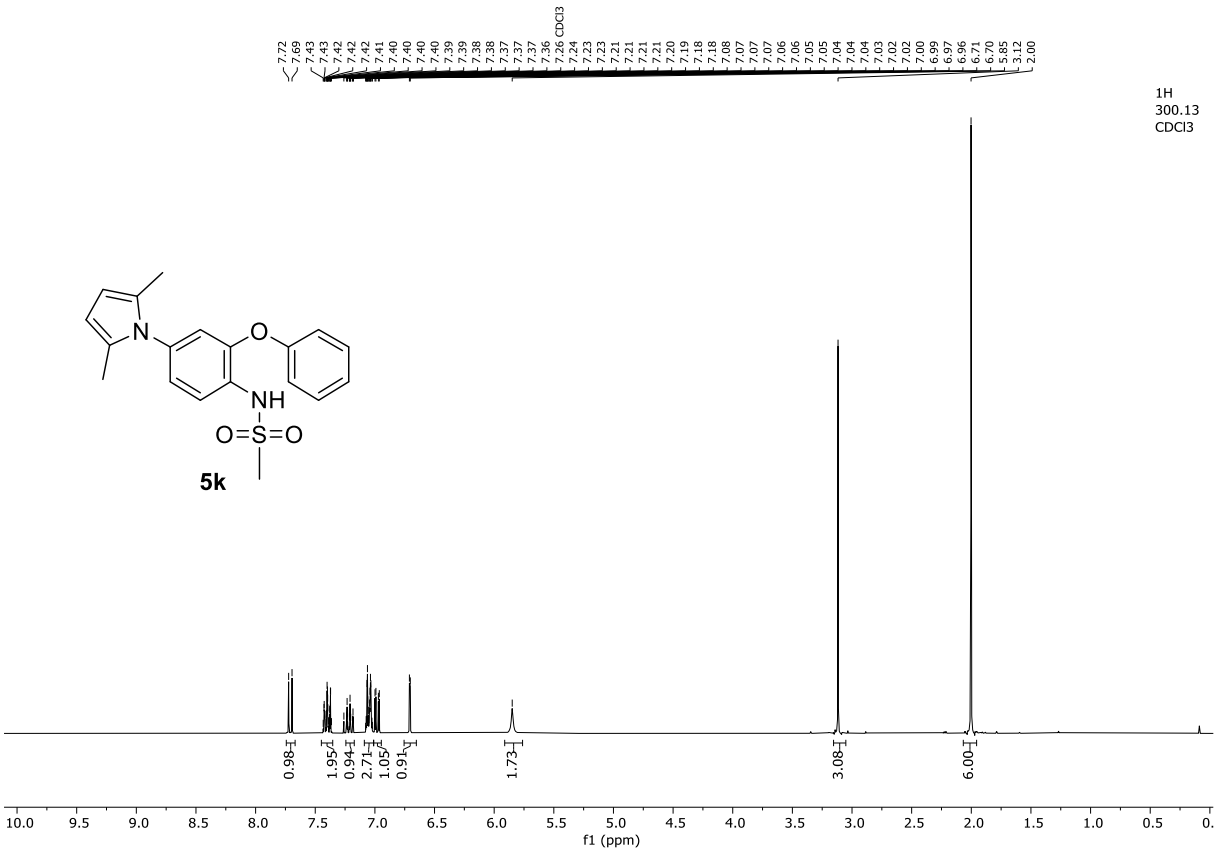


Figure S63. ^{1}H NMR (300 MHz, $CDCl_3$) of **5k**.

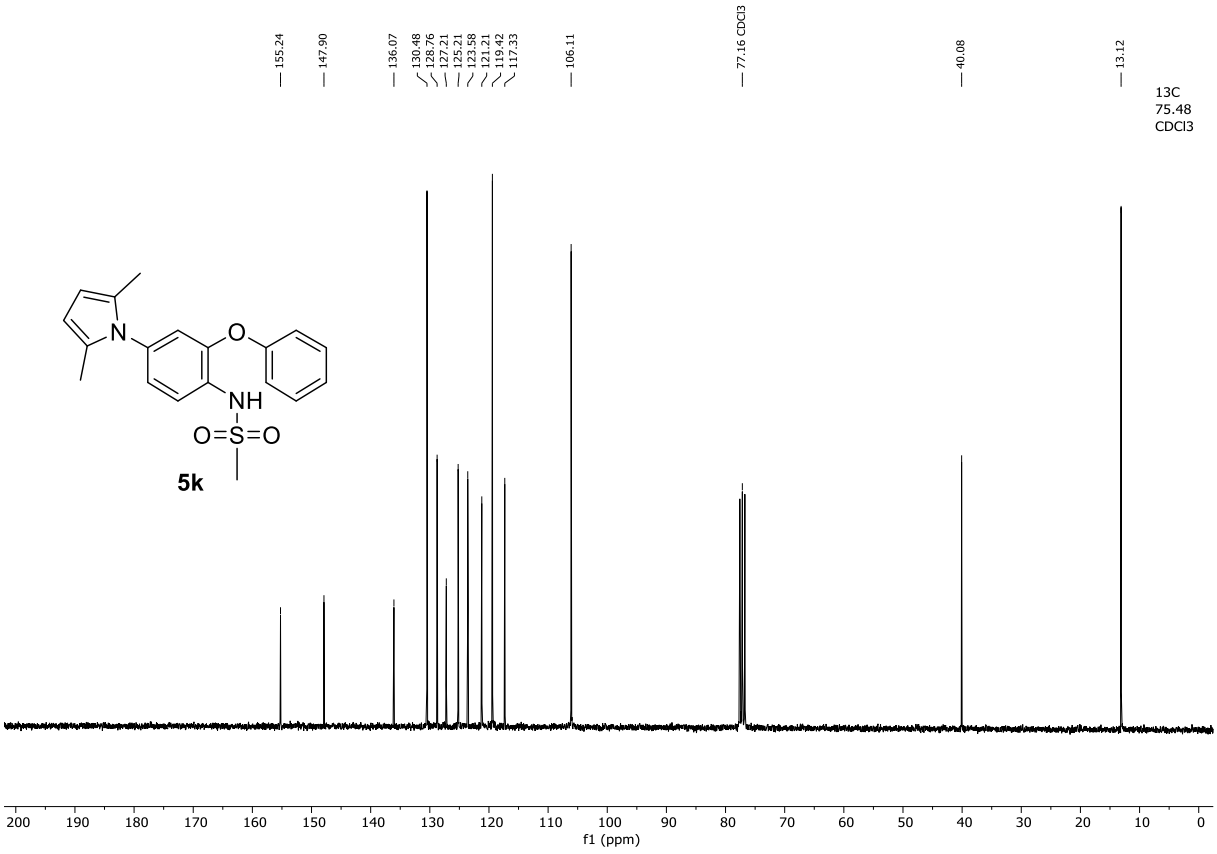


Figure S64. ^{13}C NMR (75 MHz, $CDCl_3$) of **5k**.

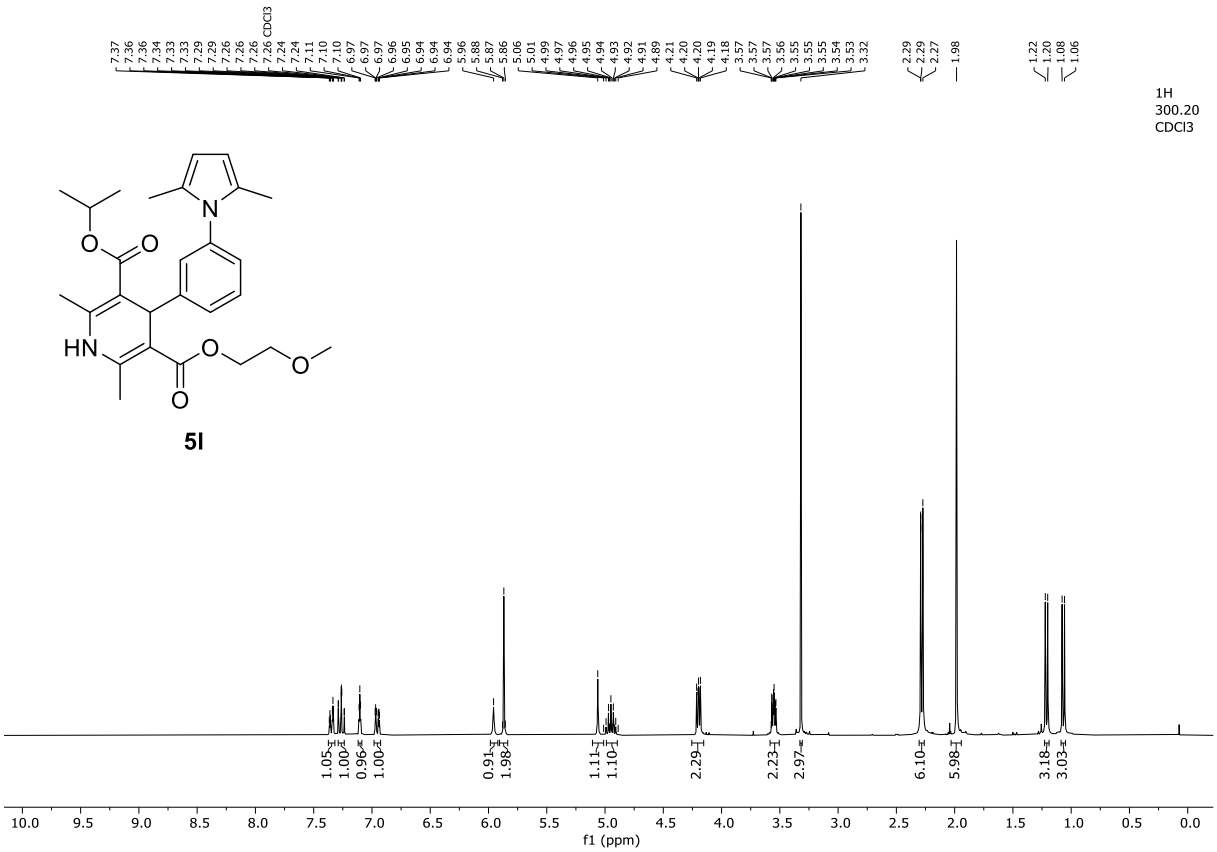


Figure S65. ^{1}H NMR (300 MHz, $CDCl_3$) of **5l**.

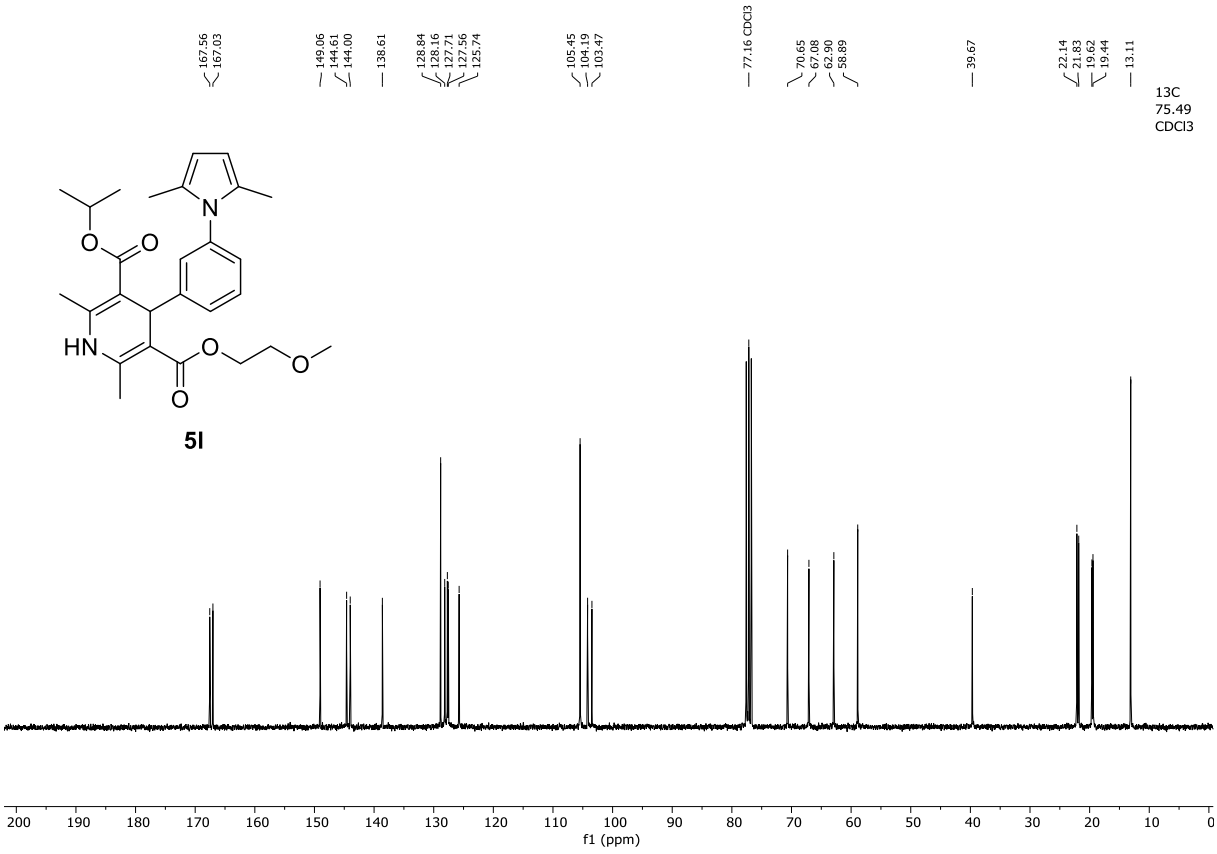


Figure S66. ^{13}C NMR (75 MHz, $CDCl_3$) of **5l**.

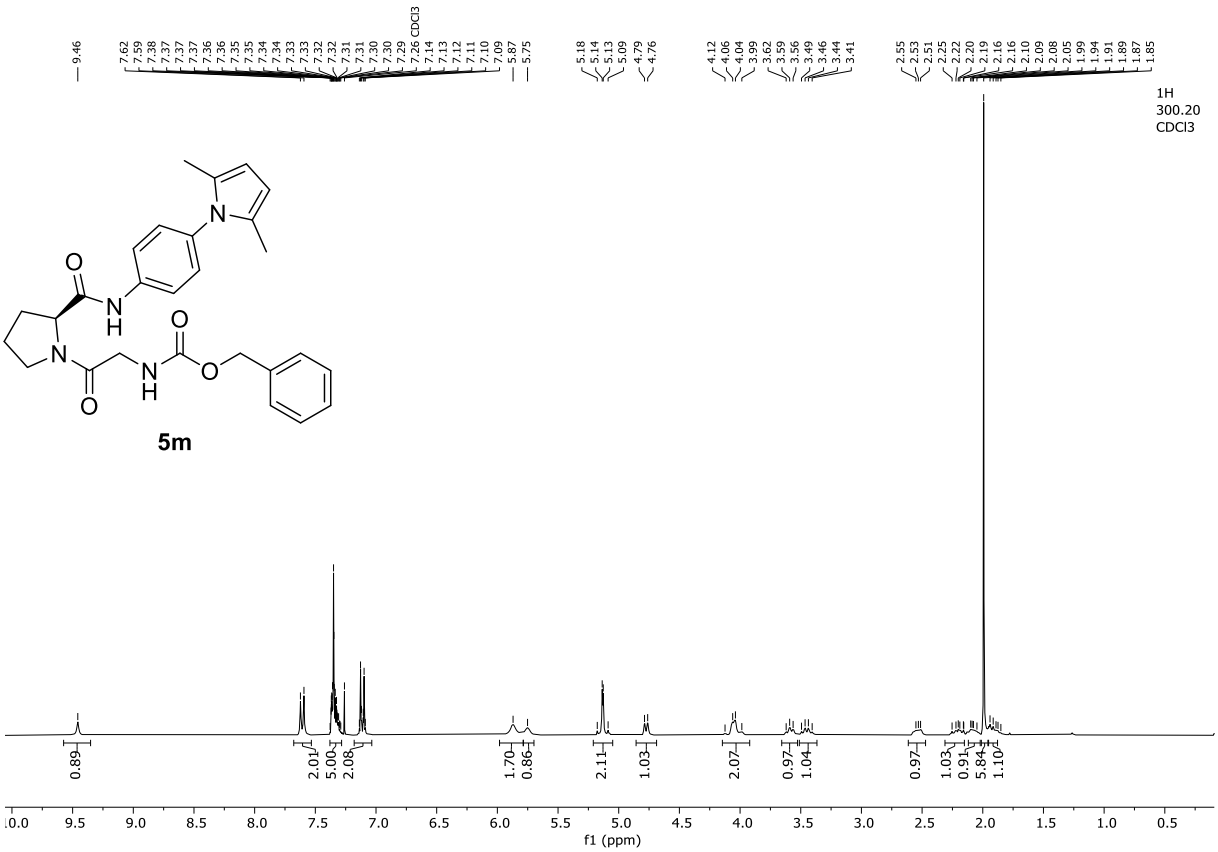


Figure S67. ^{1}H NMR (300 MHz, $CDCl_3$) of **5m**.

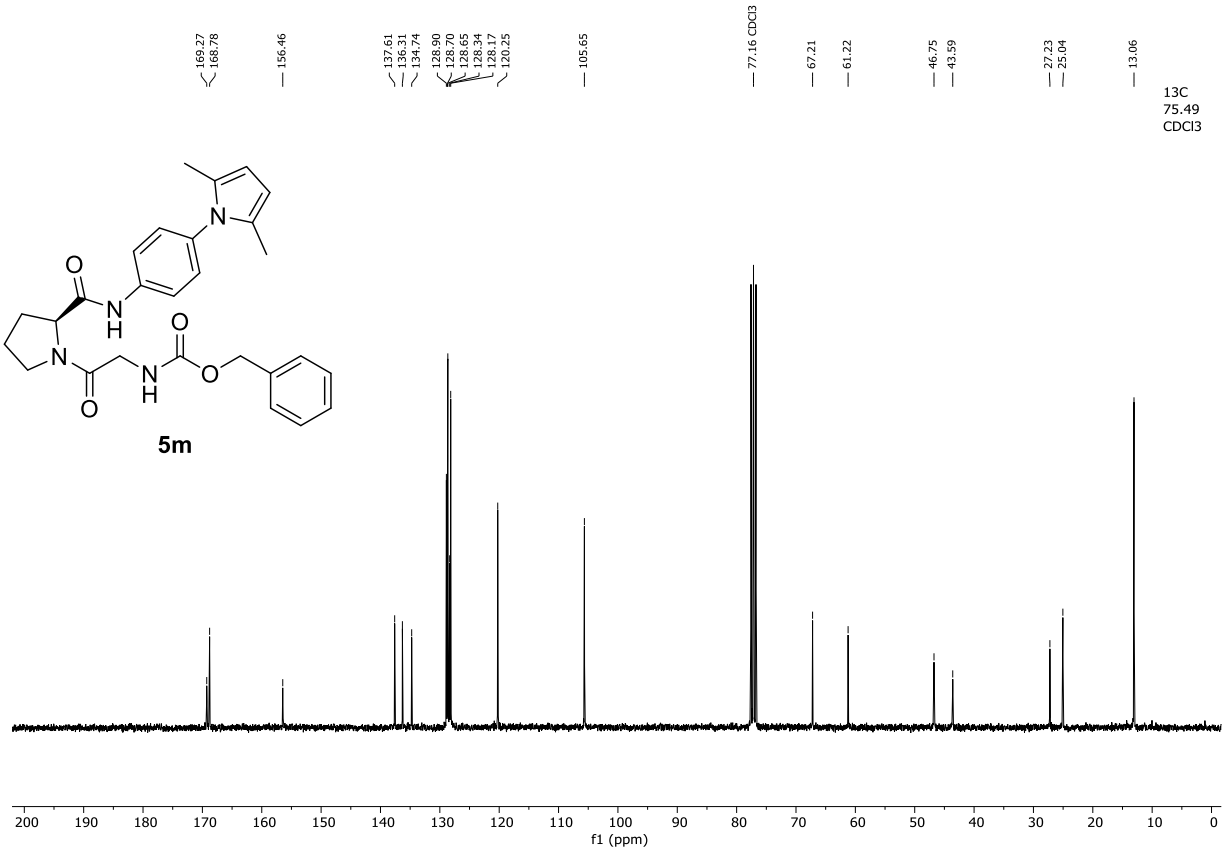


Figure S68. ^{13}C NMR (75 MHz, $CDCl_3$) of **5m**.

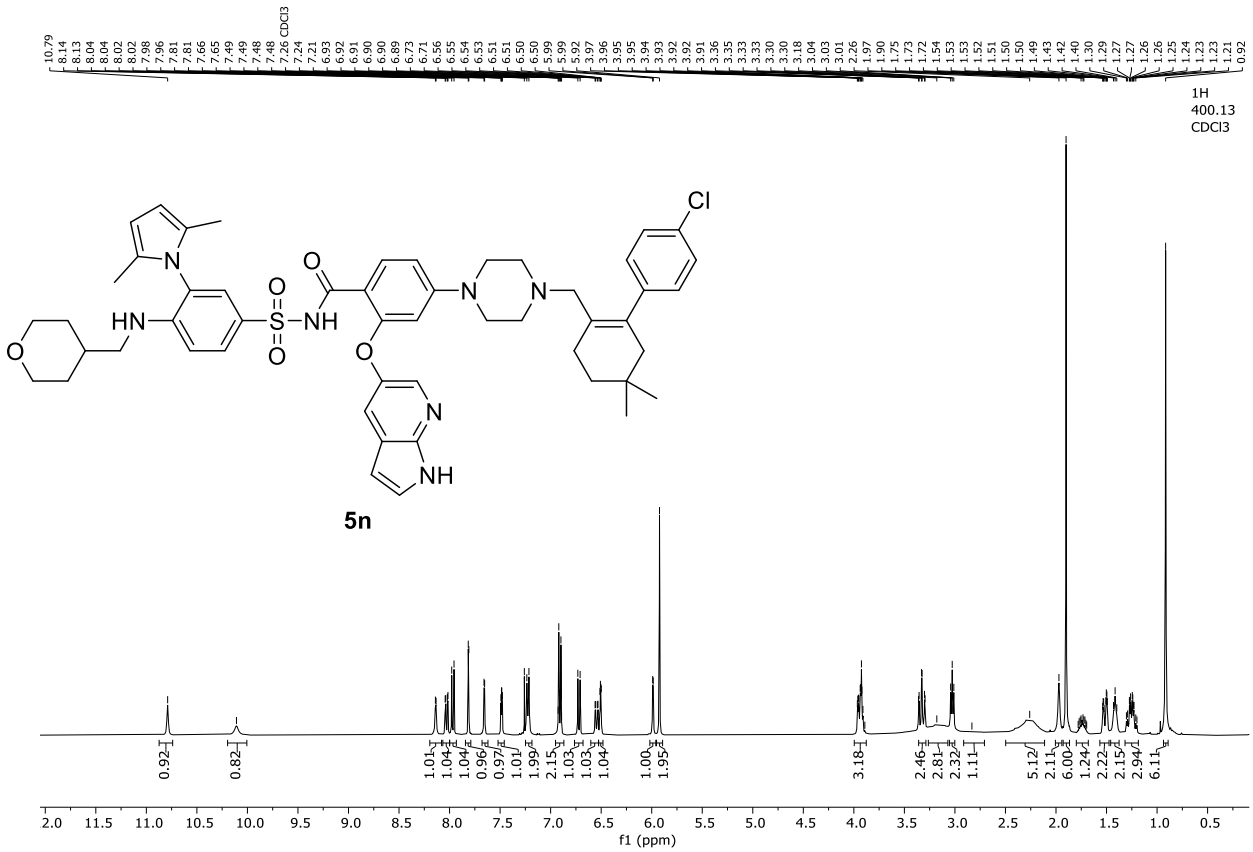


Figure S69. ^{1}H NMR (400 MHz, $CDCl_3$) of **5n**.

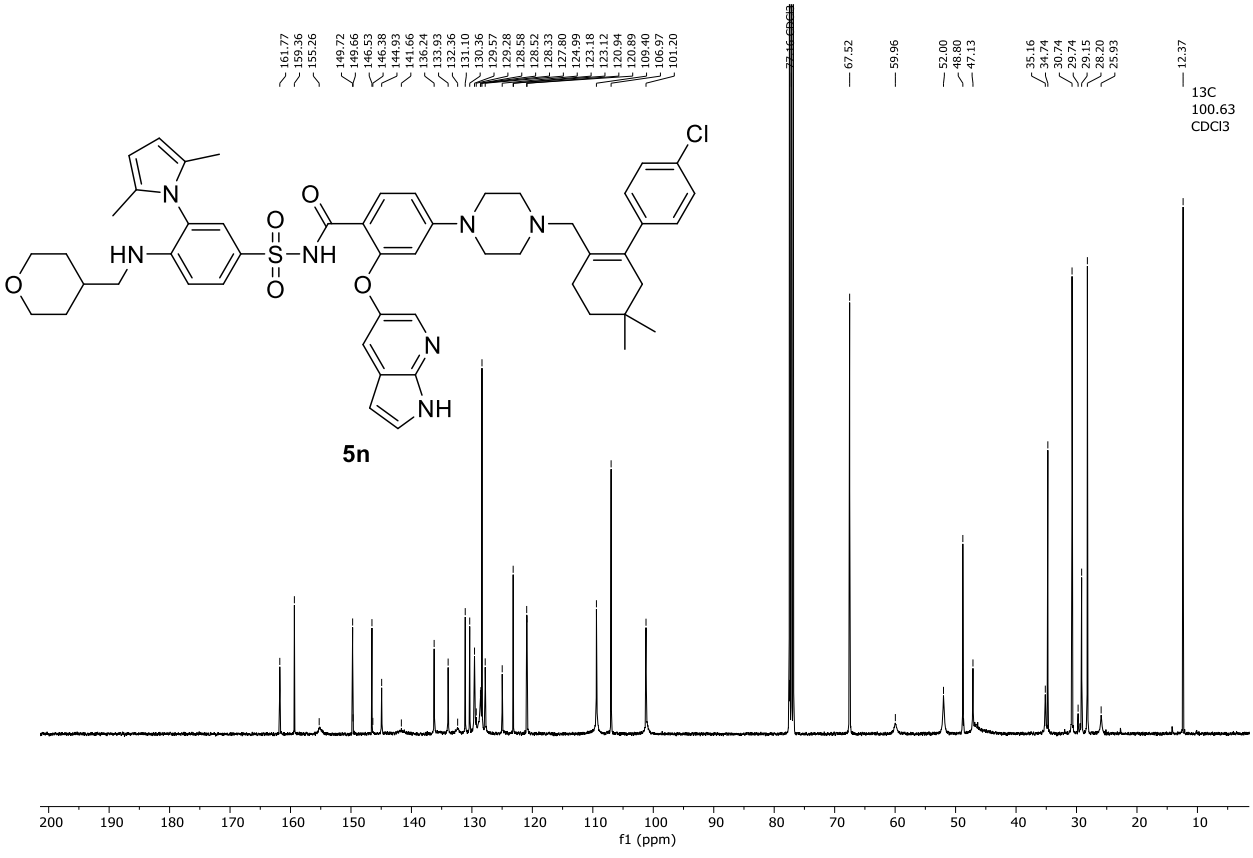


Figure S70. ^{13}C NMR (101 MHz, $CDCl_3$) of **5n**.

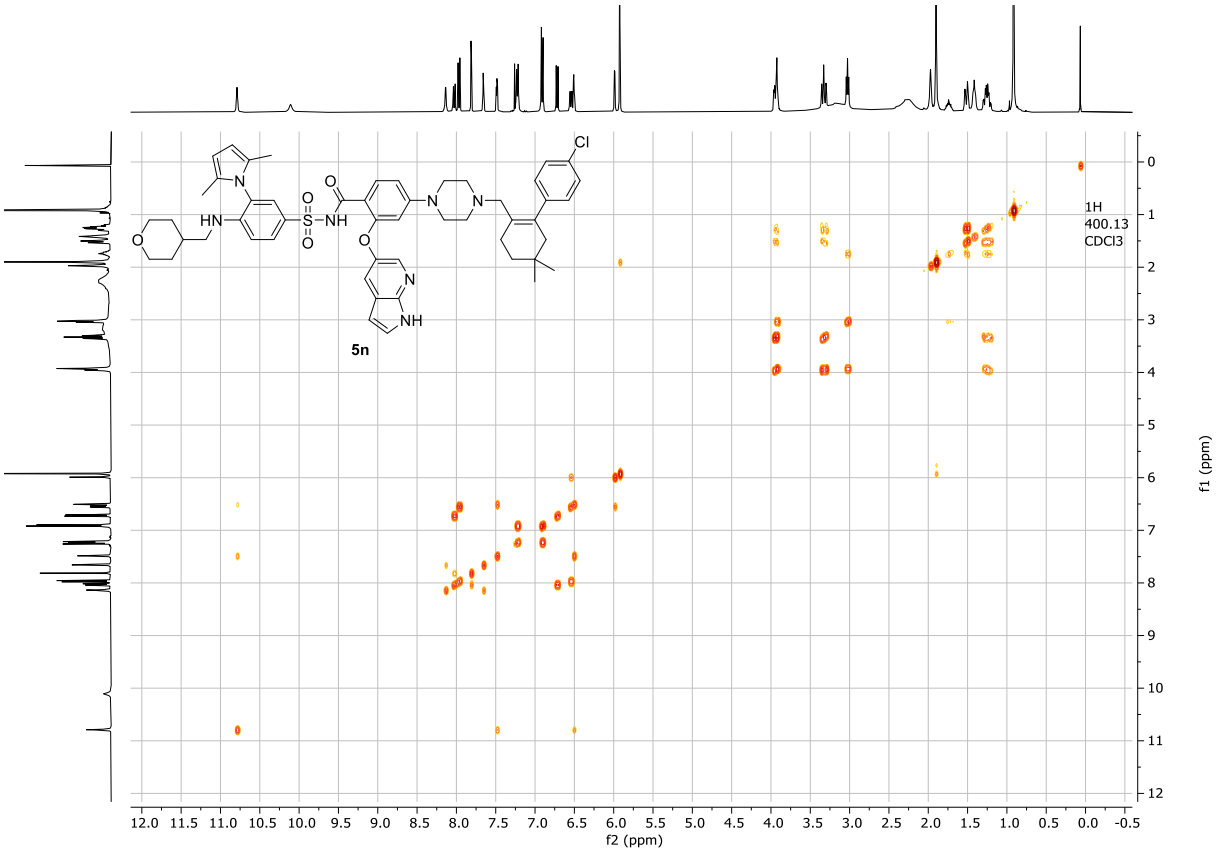


Figure S71. ^{1}H-COSY NMR (400 MHz, $CDCl_3$) of **5n**.

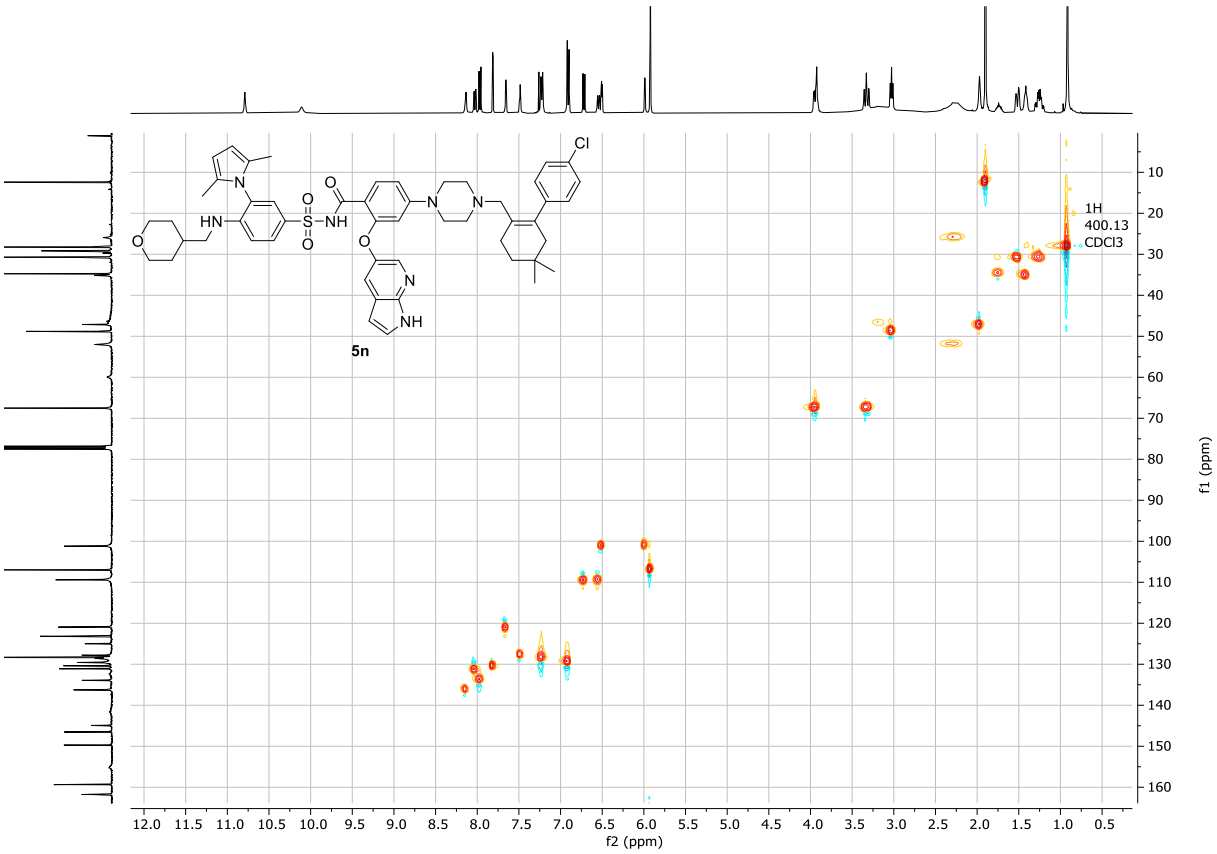


Figure S72. ^{1}H,^{13}C-HSQC NMR (400 MHz, $CDCl_3$) of **5n**.

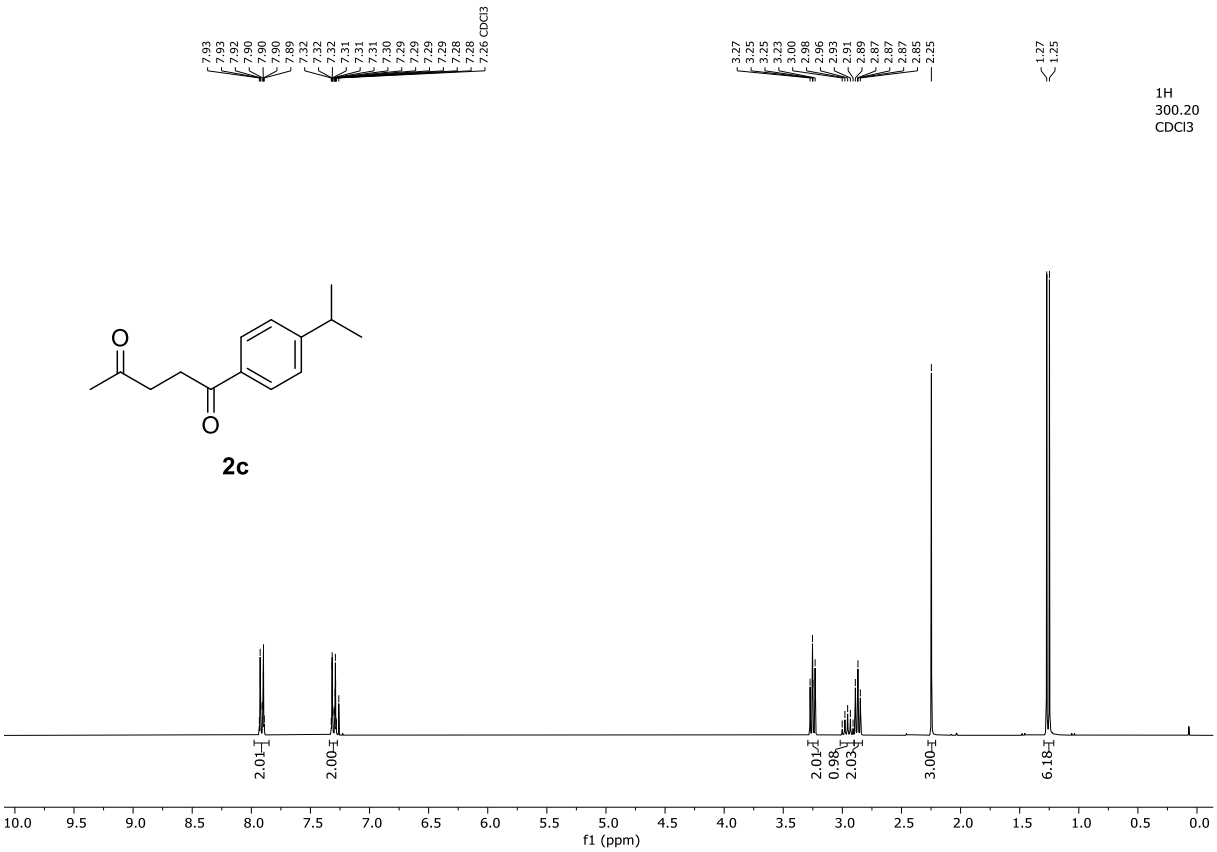


Figure S73. ^{1}H NMR (300 MHz, $CDCl_3$) of **2c**.

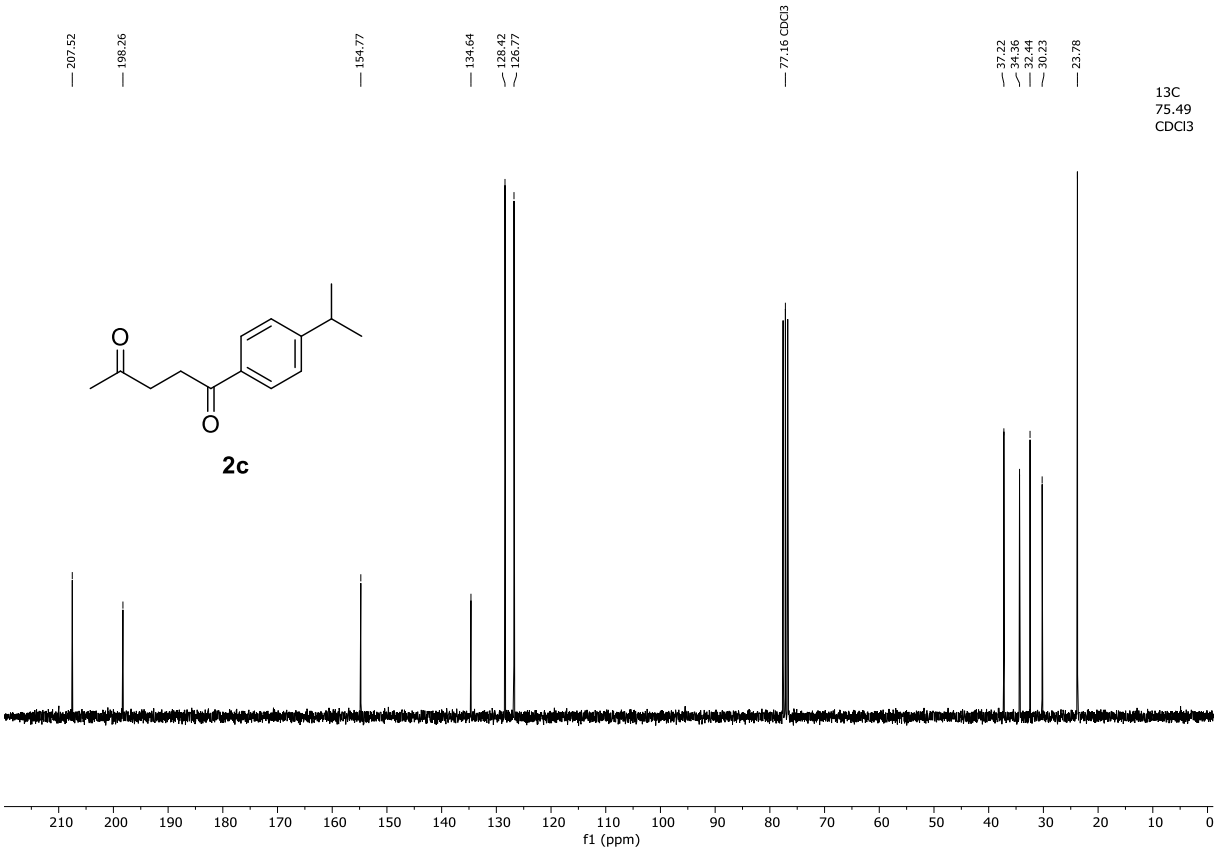


Figure S74. ^{13}C NMR (75 MHz, $CDCl_3$) of **2c**.

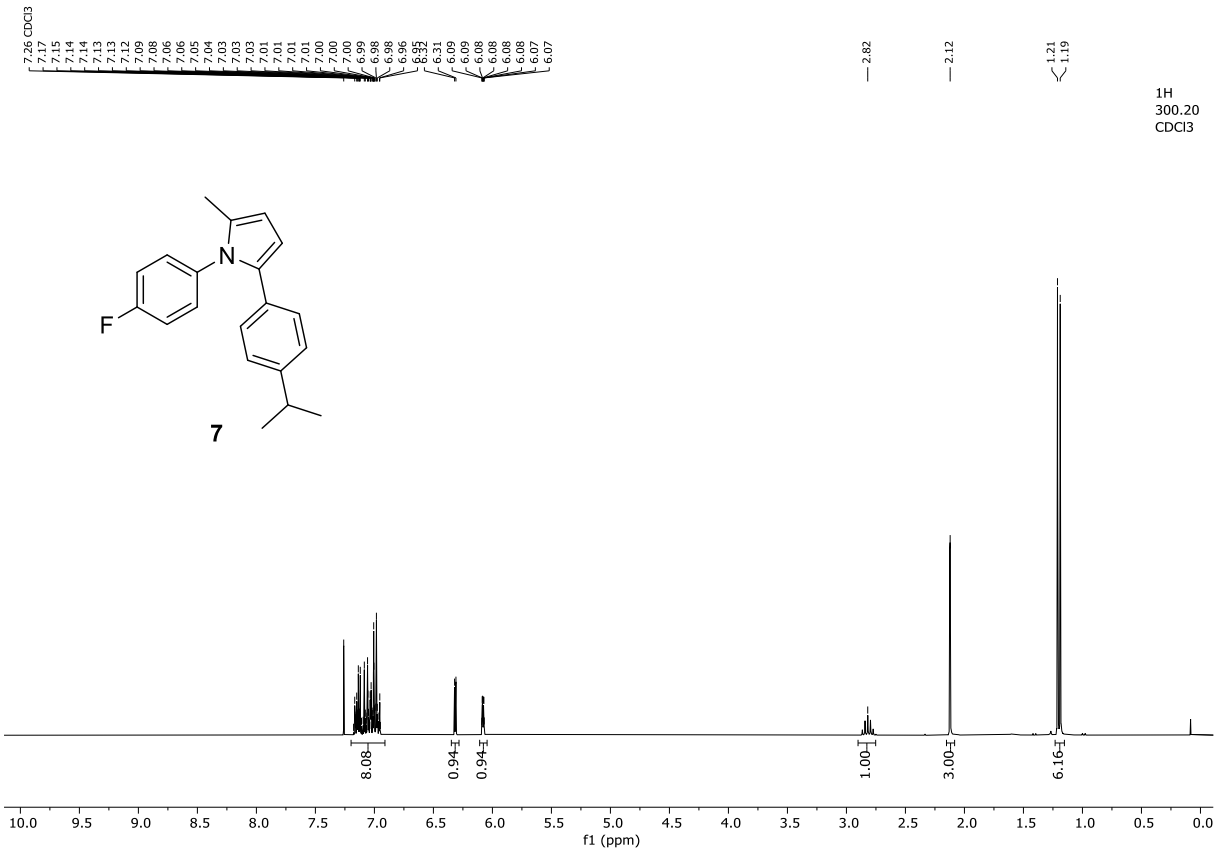


Figure S75. ^{1}H NMR (300 MHz, $CDCl_3$) of **7**.

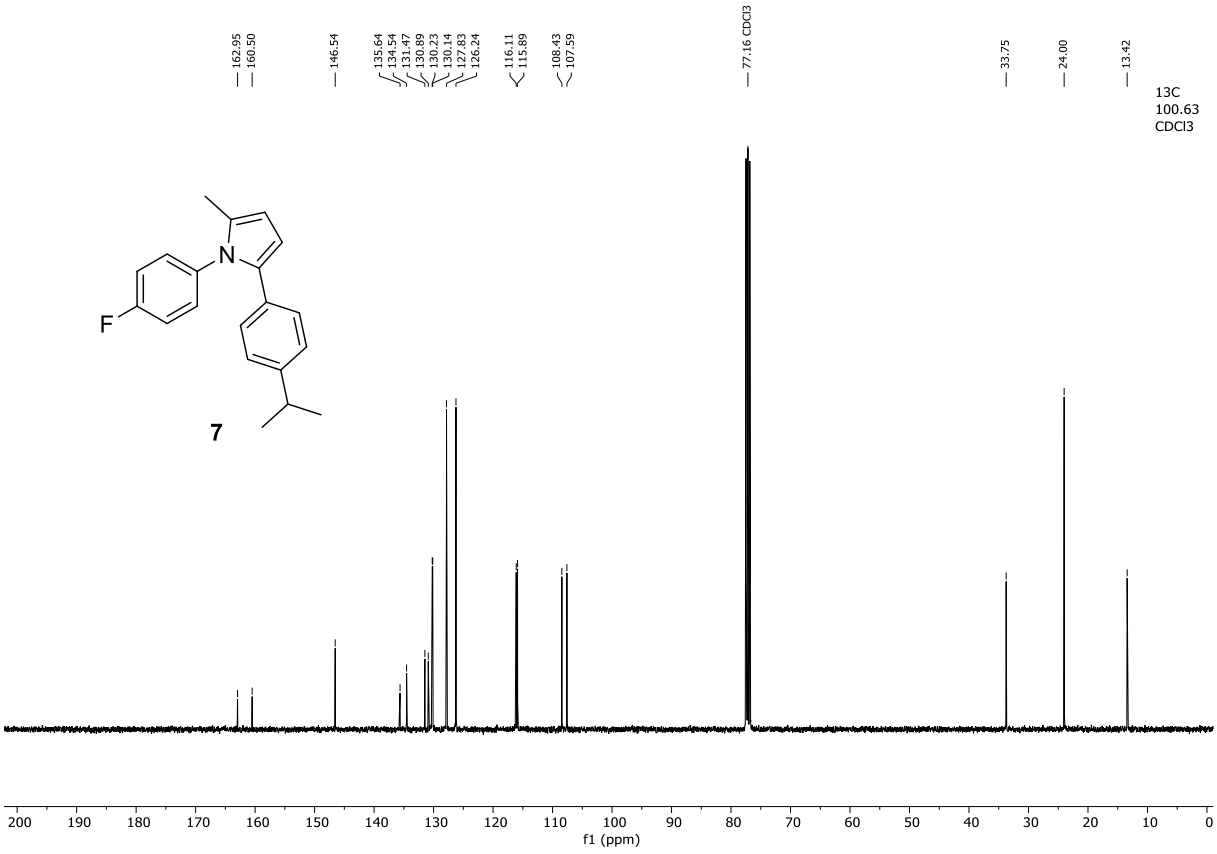


Figure S76. ^{13}C NMR (101 MHz, $CDCl_3$) of **7**.

Figure S77. ^{19}F NMR (282 MHz, $CDCl_3$) of **7**.

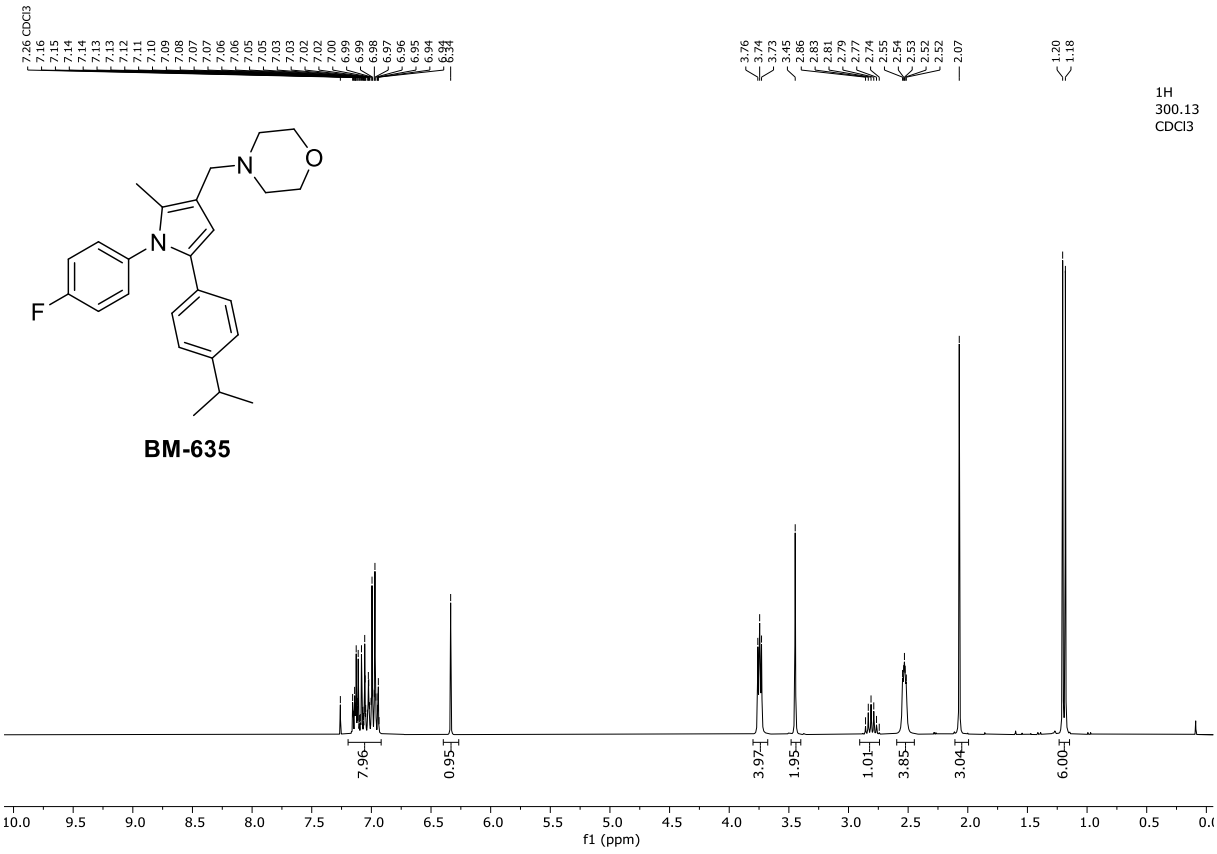


Figure S78. ^{1}H NMR (300 MHz, $CDCl_3$) of **BM-635**.

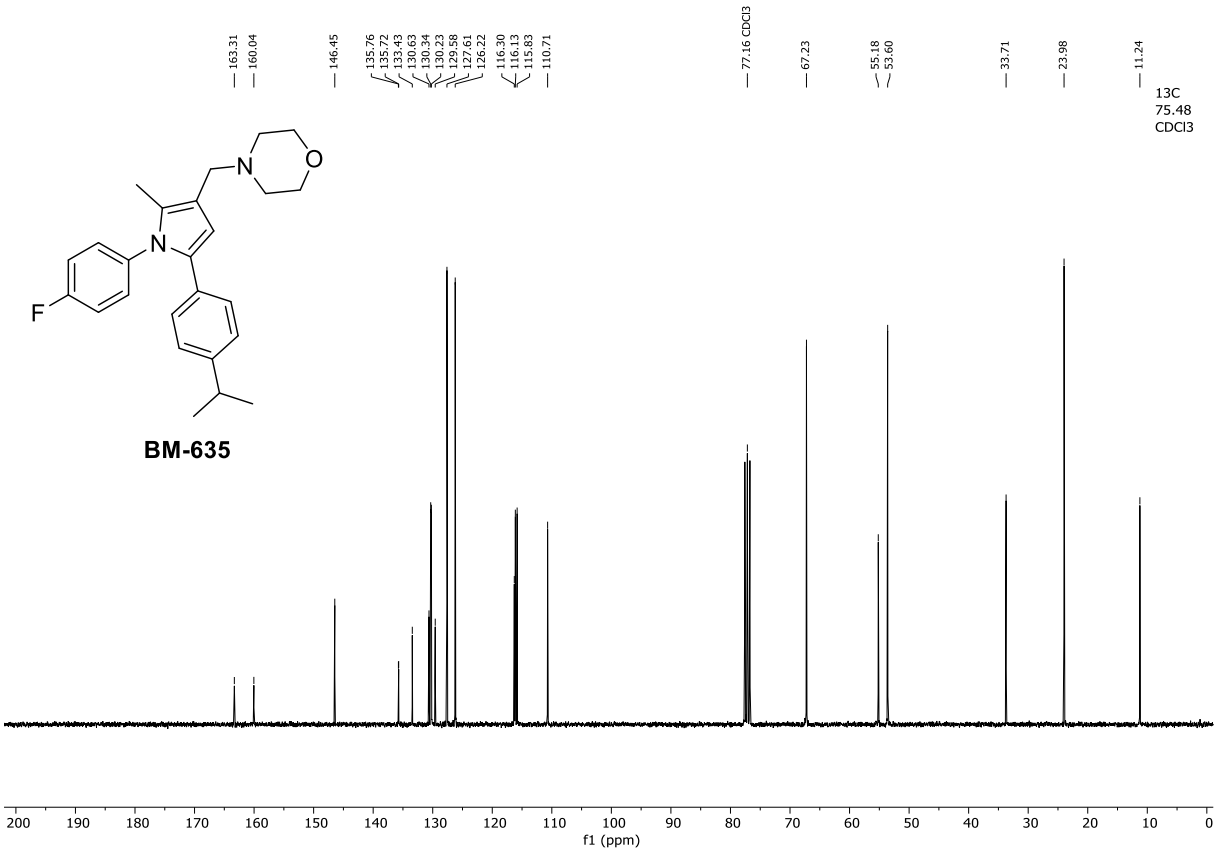


Figure S79. ^{13}C NMR (75 MHz, $CDCl_3$) of **BM-635**.

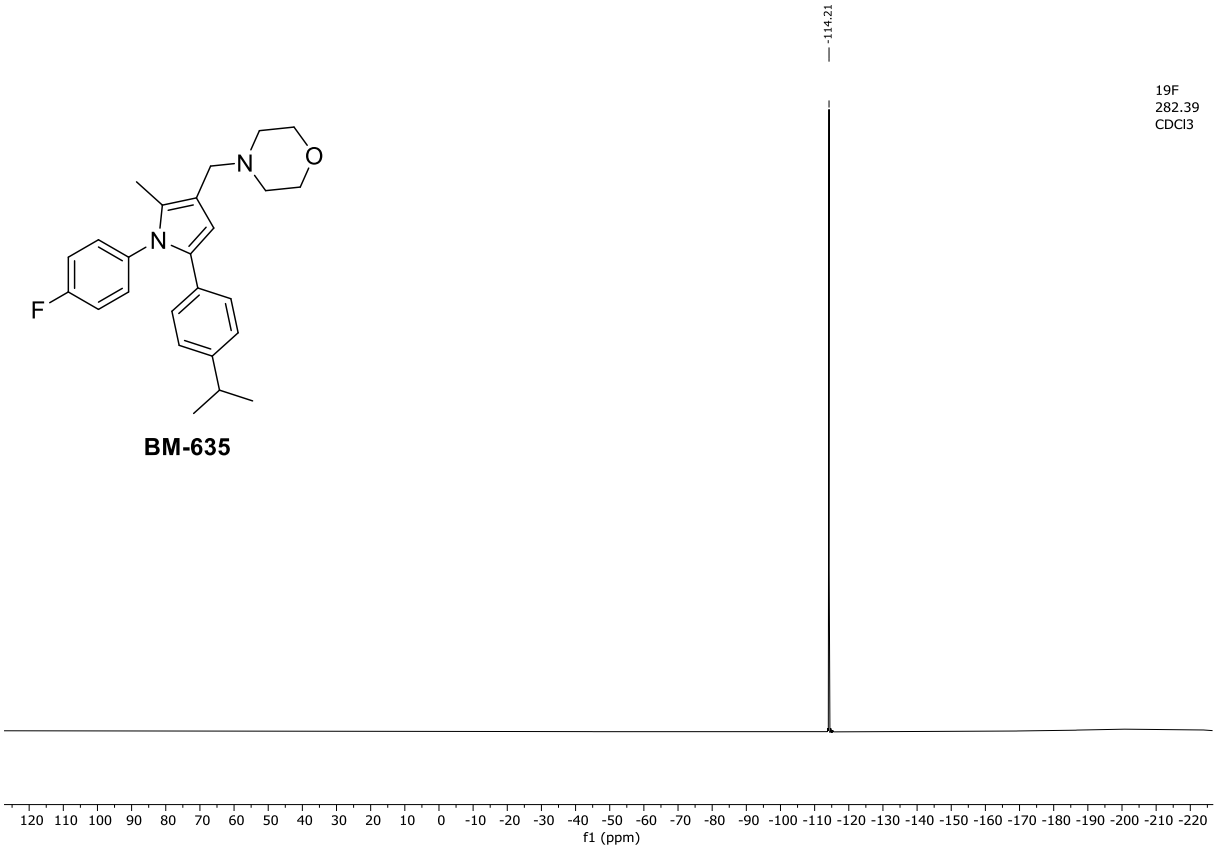


Figure S80. ^{19}F NMR (282 MHz, $CDCl_3$) of **BM-635**.

6. Literature References

[1] a) Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Verfahren zur Wasserstoffgewinnung durch katalytische Zersetzung von Ameisensäure. Patent DE102011007661A1, **2012**; b) C. Ziebart, C. Federsel, P. Anbarasan, R. Jackstell, W. Baumann, A. Spannenberg, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 20701–20704; c) A. Belyaev, T. M. Dau, J. Jänis, E. V. Grachova, S. P. Tunik, I. O. Koshevoy, *Organometallics* **2016**, *35*, 3763–3774.

[2] G. Wienhöfer, I. Sorribes, A. Boddien, F. Westerhaus, K. Junge, H. Junge, R. Llusar, M. Beller, *J. Am. Chem. Soc.* **2011**, *133*, 12875–12879.

[3] P. Ryabchuk, T. Leischner, C. Kreyenschulte, A. Spannenberg, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2020**, *59*, 18679–18685.

[4] L. Zhang, S.-H. Xiang, J. Wang, J. Xiao, J.-Q. Wang, B. Tan, *Nat. Commun.* **2019**, *10*, 566.

[5] F. Manetti, M. Magnani, D. Castagnolo, L. Passalacqua, M. Botta, F. Corelli, M. Saddi, D. Deidda, A. De Logu, *ChemMedChem* **2006**, *1*, 973–989.

[6] Y.-B. Huang, Y.-J. Luo, A. Del Rio Flores, L.-C. Li, F. Wang, *ACS Sustainable Chem. Eng.* **2020**, *8*, 12161–12167.

[7] H. Cho, R. Madden, B. Nisanci, B. Török, *Green Chem.* **2015**, *17*, 1088–1099.

[8] H. T. Nguyen, N.-P. T. Le, D.-K. N. Chau, P. H. Tran, *RSC Adv.* **2018**, *8*, 35681–35688.

[9] Y. Liu, Y. L. Hu, *J. Iran. Chem. Soc.* **2016**, *15*, 1033–1040.

[10] Z. Gong, Y. Lei, P. Zhou, Z. Zhang, *New J. Chem.* **2017**, *41*, 10613–10618.

[11] D. Murugesan, A. Mital, M. Kaiser, D. M. Shackleford, J. Morizzi, K. Katneni, M. Campbell, A. Hudson, S. A. Charman, C. Yeates, I. H. Gilbert, *J. Med. Chem.* **2013**, *56*, 2975–2990.

[12] B. S. Park, I. M. El-deeb, K. H. Yoo, D. K. Han, J. S. Tae, S. H. Lee, *Bull. Korean Chem. Soc.* **2012**, *33*, 3629–3634.

[13] Infinity Pharmaceuticals Inc, Inhibitors of fatty acid amide hydrolase. Patent WO2009/126691 A1 **2009**.

[14] U. A. More, S. D. Joshi, T. M. Aminabhavi, A. K. Gadad, M. N. Nadagouda, V. H. Kulkarni, *Eur. J. Med. Chem.* **2014**, *71*, 199–218.

[15] H. T. Nguyen, D.-K. N. Chau, P. H. Tran, *New J. Chem.* **2017**, *41*, 12481–12489.

[16] J.-C. Zeng, H. Xu, F. Yu, Z. Zhang, *Tetrahedron Lett.* **2017**, *58*, 674–678.

[17] Y. Lin, F. Wang, E. Ren, F. Zhu, Q. Zhang, G.-P. Lu, *J. Catal.* **2022**, *416*, 39–46.

[18] I. V. Taydakov, T. Y. Dutova, E. N. Sidorenko, S. S. Krasnoselsky, *Chem. Heterocycl. Compd.* **2011**, *47*, 425–434.

[19] TSD Life Sciences, Imidazopyridine derivative and pharmaceutical composition comprising same as active ingredient. Patent WO2021/040502 A1 **2021**.

[20] M. Biava, G. C. Porretta, G. Poce, A. De Logu, M. Saddi, R. Meleddu, F. Manetti, E. De Rossi, M. Botta, *J. Med. Chem.* **2008**, *51*, 3644–3648.

[21] G. Poce, R. H. Bates, S. Alfonso, M. Cocozza, G. C. Porretta, L. Ballell, J. Rullas, F. Ortega, A. D. Logu, E. Agus, V. La Rosa, M. R. Pasca, E. De Rossi, B. Wae, S. G. Franzblau, F. Manetti, M. Botta, M. Biava, *PLOS ONE* **2013**, *8*, e56980.