Electronic Supplementary Material (ESI) for New Journal of Chemistry.

SUPPORTING INFORMATION

Highly diastereoselective Heck-Matsuda reaction with pyrazolyl-diazonium salts

F. Bellina[a,b], F. Berti[a], S.M. Bertozzi[c], T. Bandiera[a], F. Bertozzi[a,*]

[a]D3-PharmaChemistry, Fondazione Istituto Italiano di Tecnologia, Via Morego 30, 16163 Genoa (Italy)

[b]Department of Chemistry and Industrial Chemistry, University of Genova, 16146 Genoa (Italy)

[c]Analytical Chemistry Facility, Fondazione Istituto Italiano di Tecnologia, Via Morego 30, 16163 Genoa (Italy)

Table of Contents

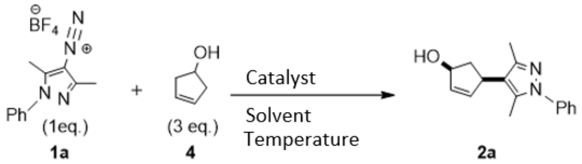
1 Experimental part

Material and Methods.

All reagents were obtained from commercial suppliers and used without further purification, unless indicated otherwise. The anhydrous solvents were used as purchased from commercial suppliers; ethanol was in absolute grade purity and used without any previous anhydrification. The reactions were carried out in round-bottom flasks or in sealed reaction tubes and heated with metal mantel or by sand bath, when necessary. Automated column chromatography purifications were performed on either a Teledyne ISCO (CombiFlash® R_f) or Biotage apparatus, using pre-packed silica gel columns of different sizes (Redisep or Biotage). The reactions were monitored using both thin layer chromatography (TLC), applying UV/Vis wavelengths (254/366 nm) and/or $KNMO_4$, *p*-anisaldehyde, ninidrine and β-naphthol as staining solutions, and by ULPC-MS analysis (see below). NMR experiments were run at 300 K on a Bruker Avance III 400 system (400.13 MHz for ^1H, and 100.62 MHz for ^{13}C), equipped with a BBI probe and Z-gradients, and Bruker FT NMR Avance III 600 MHz spectrometer equipped with a 5 mm CryoProbeTM QCI $^1H/^{19}F–^{13}C/^{15}N–D$ quadruple resonance, a shielded z-gradient coil and the automatic sample changer SampleJet™ NMR system (400 and 600 MHz for ^1H, 101 and 151 MHz for ^{13}C and 376 and 565 MHz for ^{19}F). Chemical shifts for ^1H, ^{13}C and ^{19}F spectra were reported in parts per million (ppm), calibrating the residual non-deuterated solvent peak for the ^1H and ^{13}C, respectively to 7.26 ppm and 77.16 ppm for $CDCl_3$ and 2.50 ppm and 39.52 ppm for DMSO-d_6. UPLC-MS analyses were performed on a Waters ACQUITY UPLC-MS system consisting of a single quadrupole detector (SQD) mass spectrometer equipped with an electrospray ionization interface and a photodiode array detector (PDA) from Waters Inc. (Milford, MA, USA). Electrospray ionization in positive and negative mode was applied in the mass scan range 100-500 Da. The PDA range was 210-400 nm. The mobile phase was 10 mM NH_4OAc in H_2O at pH 5 adjusted with AcOH (A) and 10 mM NH_4OAc in CH_3CN-H_2O (95:5) at pH 5 (B) with 0.5 mL/min as flow rate. *For intermediates*, the analyses were run on an ACQUITY UPLC BEH C18 column (50 x 2.1 mm ID, particle size 1.7 µm) with a VanGuard BEH C18 pre-column (5 x 2.1 mm ID, particle size 1.7 µm). A linear gradient was applied: 0-0.2 min: 5% B; 0.2-2.2 min: 5-95% B; 2.2-2.3 min: 95-100% B; 2.3-3.0 min: 100% B. *For final compounds and diastereomeric ratio determinations*, the analyses were run on an ACQUITY UPLC BEH C18 column (100 x 2.1 mm ID, particle size 1.7 µm) with a VanGuard BEH C18 pre-column (5 x 2.1 mm ID, particle size 1.7 µm). A linear gradient was applied: 0-0.2 min: 10% B; 0.2-6.2 min: 10-90% B; 6.2-6.3 min: 90-100% B; 6.3-6.5 min: 100% B. Accurate mass measurements were performed on a Waters Synapt G2 Q-ToF mass spectrometer equipped with an electrospray ionization interface and coupled to a Waters ACQUITY UPLC from Waters Inc. (Milford, MA, USA). Leucine enkephalin (2 ng/mL) was used as lock mass reference compound for spectral recalibration. The analyses were run on an ACQUITY UPLC BEH C18 column (100 x 2.1 mm ID, particle size 1.7 µm), using H_2O + 0.1% HCOOH (A) and CH_3CN + 0.1% HCOOH as mobile phase. A linear gradient was applied: 0-0.2 min: 10% B; 0.2-6.2 min: 10-90% B; 6.2-6.3 min: 90-100% B; 6.3-6.5 min: 100% B. *For enantiomeric ratio determinations*, the analytical chiral separations were performed on a Waters Alliance HPLC instrument consisting of an e2695 separation module and a 2998 photodiode array detector (PDA) from Waters Inc. (Milford, MA, USA). The PDA range was 210-400 nm. The analyses were run in isocratic mode on a Daicel ChiralPak AD column (250 x 4.6 mm ID, particle size 10 µm) at room temperature. The mobile phase was heptane-EtOH (75:25) with a flow rate = 1.0 mL/min. A thermogravimetric analysis (TGA) was performed under nitrogen flow (50 mL min_1) by heating the sample from 30°C to 250°C at a rate of 10°C min_1 through a TGAQ500 from TA instruments.

2 Optimization of Heck-Matsuda reaction conditions.

Table S1. Evaluation of reaction parameters.

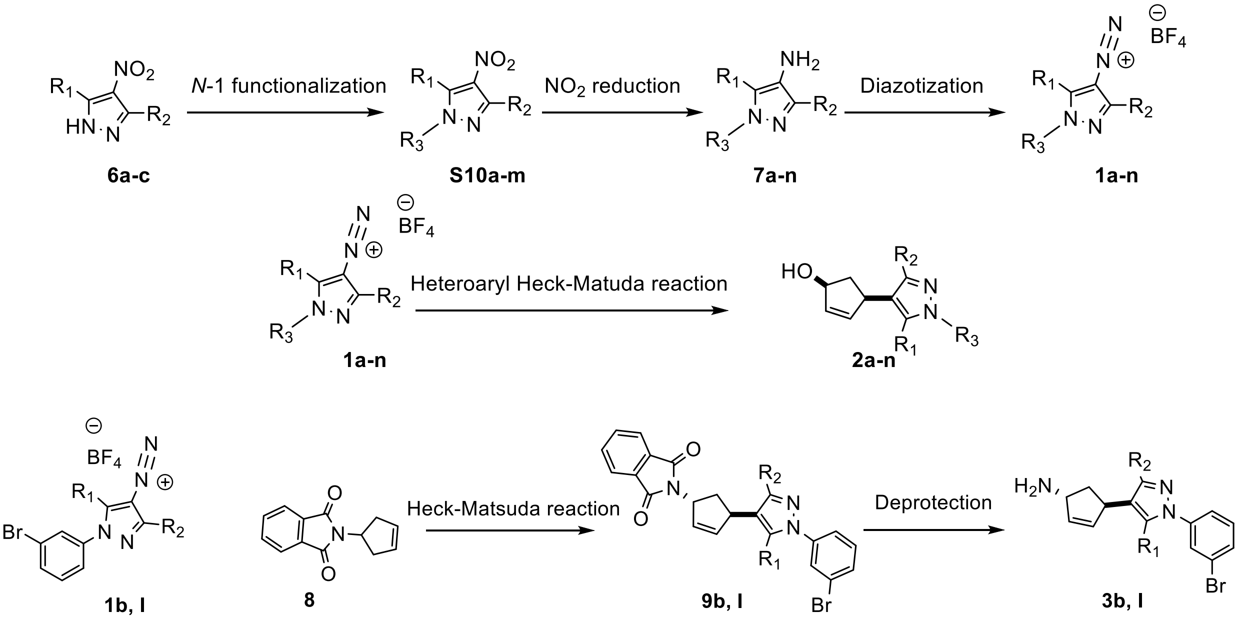


Entry	Solvent	Catalyst	Temperature	Time*	Yield**	d.r.***
1	DCM[a,b]	$Pd(dba)_2$ (5%)	r.t.	1h	<5%	///
2	MeCN[a,b]	$Pd(dba)_2$ (5%)	r.t.	1h	<5%	///
3	EtOH	$Pd(dba)_2$ (10%)	60°C	< 30 min	50%	98.8: 1.2
4	EtOH	$Pd(dba)_2$ (10%)	40°C	3 h	53%	99.4:0.6
5	EtOH	$Pd(dba)_2$ (10%)	r.t.	24 h	25%	99.6:0.4
6	EtOH	$Pd(dba)_2$ (5%)	40°C	7h	32%	///
7	EtOH[c]	$Pd(dba)_2$ (10%)	40°C	6 h	31%	///
8	EtOH	None	40°C	///	No reaction	///
9	EtOH	$Pd_2(dba)_3$ (10%)	40°C	4h	39%	97.9:2.1
10	EtOH	$Pd(OAc)_2$ (10%)	40°C	8 h	30%	99.9:0.1
11	MeOH	$Pd(dba)_2$ (10%)	40°C	2h	38%	97.0:3.0
12	*i*PrOH	$Pd(dba)_2$(10%)	40°C	28h	17%	98.1:1.9
13	MeCN	$Pd(dba)_2$(10%)	40°C	24h	///	///
14	EtOH[d]	$Pd(dba)_2$ (10%)	40°C	3.5 h	50%	99.3:0.7
15	EtOH[e]	$Pd(dba)_2$ (10%)	40°C	3.5 h	54%	99.2: 0.8
16	MeOH[d]	$Pd(dba)_2$ (10%)	40°C	2h	51%	98.9:1.1

*Time to reach full conversion/disappearance of diazonium salt; **Isolated yield; ***Calculated by UPLC-MS analysis for *cis*-isomer; *a)* **4** (2.0 eq.) and NaOAc (3.0 eq.); *b)* see Reference 1; *c)* **4** (1.5 eq.); *c)* $CaCO_3$ (1.1 eq.) was added; *d)* 2,6-di-*tert*-butyl-4-methylpyridine (1.1 eq.) was added.

3 General synthesis of 4-pyrazol-1-cyclopentenols **2a-n** and 4-pyrazol-1-cyclopentenamines **3b,l**

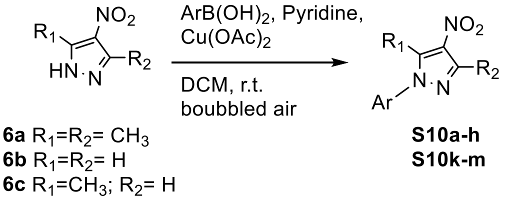
Scheme S1. General synthesis of 4-pyrazol-1-cyclopenten-ols/-amines using novel pyrazolyl diazonium tetrafluoroborates.



3.1 Synthesis of *N*-1 substituted 4-nitro-pyrazoles **S10a-m**

3.1.1 General Procedure **1A** (Cham-Lam reaction)

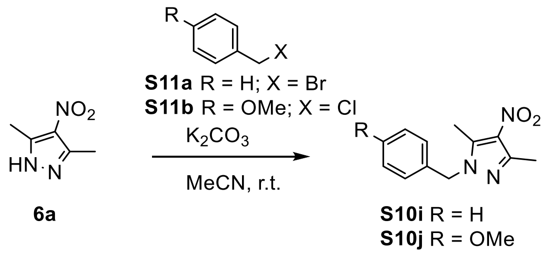
Scheme S2. Synthesis of pyrazoles **S10a-h,k-m** by Cham-Lam reaction.



A two-neck round-bottom flask was charged with substituted 4-nitro pyrazole (1.0 eq.), arylboronic acid (1.5 eq.), pyridine (2.8 mL, 5.0 eq.), $Cu(OAc)_2$ (0.5 eq.) and DCM (3.33 mL/mmol). Under vigorous stirring, the mixture was bubbled with air and the reaction was allowed to run at room temperature overnight. The crude reaction was filtered on a short pad of silica gel mixed with Celite® and washed with DCM. The organic phase was transferred into a separatory funnel, washed with HCl (1.0 M) (3 x 10 mL), NaOH (1.0 M) (3x 10 mL) and brine, and finally dried over Na_2SO_4. The organics were then removed under vacuum to afford the crude product. The resulting *N*-1-substituted pyrazole was used without any further purification in the following step.

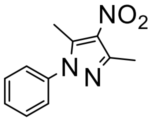
3.1.2 General procedure **1B**

Scheme S3. Synthesis of *N*-benzyl substituted pyrazoles **S10i-j**.



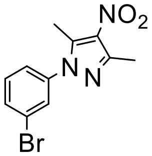
A round-bottom flask was charged with 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 eq.) and K_2CO_3 (5.0 eq.) followed by MeCN (3.3 mL/mmol) and benzyl halide (1.2 eq.). The reaction was stirred at room temperature overnight. The crude mixture was diluted with AcOEt and transferred into a separatory funnel. The organic phase was washed with brine, dried over Na_2SO_4 and the organics removed under vacuum. The resulting *N*-1-benzyl substituted pyrazole was used without any further purification in the following step.

*3,5-Dimethyl-4-nitro-1-phenyl-1H-pyrazole (**S10a**).*



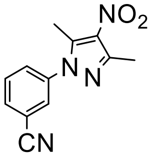
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.38 g, 90%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). ^{1}**H NMR** (400 MHz, DMSO-*d*$_6$): δ 8.19 – 7.26 (m, 5H), 2.57 (s, 3H), 2.51 (s, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 146.3, 141.8, 138.1, 131.9, 129.9, 129.8, 126.1, 115.7, 14.3, 13.2.

*1-(3-Bromophenyl)-3,5-dimethyl-4-nitro-1H-pyrazole (**S10b**).*



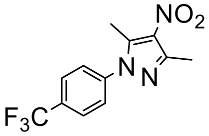
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.53 g, 93%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, DMSO-*d_6*): δ 7.84 (t, *J* = 2.0 Hz, 1H), 7.78 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H), 7.61 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 2.59 (s, 3H), 2.51 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-*d_6*): δ 146.6, 142.3, 139.3, 132.7, 131.8, 128.9, 125.3, 122.3, 14.3, 13.1.

*3-(3,5-Dimethyl-4-nitro-1H-pyrazol-1-yl)benzonitrile (**S10c**).*



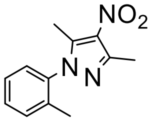
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.63 g, 95%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 – 7.68 (m, 2H), 7.66 – 7.58 (m, 2H), 2.62 (s, 3H), 2.54 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.9, 141.0, 138.9, 132.8, 132.3, 130.6, 129.8, 129.1, 117.3, 114.2, 14.2, 13.2.

*3,5-Dimethyl-4-nitro-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**S10d**).*



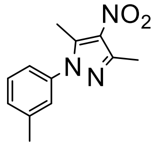
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.76 g, 87%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 2.62 (s, 3H), 2.54 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 145.73, 137.43, 137.15, 135.92, 133.81, 128.68, 127.42, 126.64, 118.10, 77.25, 52.65, 42.85, 39.75, 29.71, 12.61, 9.91. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.7.

*3,5-Dimethyl-4-nitro-1-(o-tolyl)-1H-pyrazole (**S10e**).*



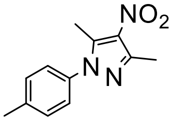
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.54 g, 94%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 – 7.22 (m, 3H), 7.15 (d, *J* = 1.4 Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H), 2.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.74, 141.79, 136.74, 135.77, 131.36, 130.33, 127.52, 127.06, 17.20, 14.23, 12.31.

*3,5-Dimethyl-4-nitro-1-(m-tolyl)-1H-pyrazole (**S10f**).*



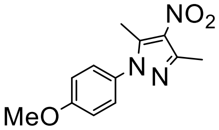
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.47 g, 90%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.08 (m, 2H), 2.55 (s, 3H), 2.53 (s, 3H), 2.37 (s, 3H).

*3,5-Dimethyl-4-nitro-1-(p-tolyl)-1H-pyrazole (**S10g**).*



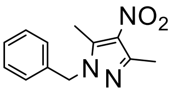
Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.57 g, 96%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 – 7.16 (m, 4H), 2.54 (s, 3H), 2.52 (s, 3H), 2.37 (s, 3H).

*1-(4-Methoxyphenyl)-3,5-dimethyl-4-nitro-1H-pyrazole (**S10h**).*



Following the General Procedure **1A**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), the title compound (1.59 g, 91%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (Cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 2H), 7.07 – 7.01 (m, 2H), 3.89 (s, 3H), 2.61 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.20, 146.68, 140.94, 131.93, 130.81, 127.06, 114.62, 77.23, 55.65, 14.14, 12.89.

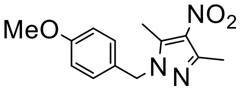
*1-Benzyl-3,5-dimethyl-4-nitro-1H-pyrazole (**S10i**).*



Following the General Procedure **1B**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol) and **S11a** (0.9 g, 8.5 mmol), the title compound (1.59 g, 97%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (cyclohexane/TBME 50%). **^{1}H**

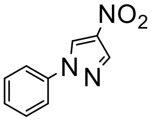
NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.19 (m, 3H), 7.10 – 7.03 (m, 2H), 5.19 (s, 2H), 2.49 (s, 3H), 2.47 (s, 3H).

*1-(4-Methoxybenzyl)-3,5-dimethyl-4-nitro-1H-pyrazole (**S10j**).*



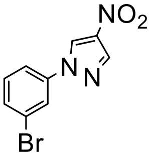
Following the General Procedure **1B**, starting from 3,5-dimethyl-4-nitro-1H-pyrazole (**6a**) (1.0 g, 7.09 mmol), and **S11b** (1.3 g, 8.5 mmol), the title compound (1.48 g, 80%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (cyclohexane/TBME 50%).^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.11 (s, 2H), 3.72 (s, 3H), 2.50 (s, 3H), 2.46 (s, 3H).

*4-Nitro-1-phenyl-1H-pyrazole (**S10k**).*



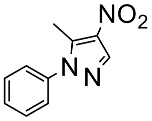
Following the General Procedure **1A**, starting from 4-nitro-1H-pyrazole (**6b**) (1.0 g, 8.85 mmol), the title compound (1.57 g, 94%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (cyclohexane/TBME 50%). ^{1}**H NMR** (400 MHz, DMSO-d_6): δ 7.42-7.52 (s, 1H), 7.54-7.64 (m, 2H), 7.92-8.00 (m, 2H,), 8.36 (s, 1H, H), 9.26 (s, 1H).

*1-(3-Bromophenyl)-4-nitro-1H-pyrazole (**S10l**).*



Following the General Procedure **1A**, starting from 4-nitro-1H-pyrazole (**6b**) (1.0 g, 8.85 mmol), the title compound (1.58 g, 89%) was synthesized as white solid and used in the following step without any further purification. TLC: R_f 0.7 (cyclohexane/TBME 50%). ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.21 (s, 1H), 7.87 (t, *J* = 2.0 Hz, 1H), 7.58 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H), 7.50 (ddd, *J* = 8.1, 1.9, 1.0 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H).

*5-Methyl-4-nitro-1-phenyl-1H-pyrazole (**S10m**).*

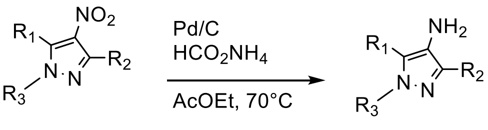


Following the General Procedure **1A**, starting from 4-nitro-1H-pyrazole (**6c**) (1.0 g, 7.87 mmol), the crude product, as a 84:16 mixture of two regioisomers, was purified by flash column chromatography with cyclohexane/AcOEt 3% to give the title compound as the major pure isomer (identified by confronting with literature spectra[1]). TLC: R_f 0.7 (cyclohexane/TBME 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.51 – 7.42 (m, 3H), 7.37 – 7.32 (m, 2H), 2.59 (s, 3H).

3.2 Synthesis of 4-amino-pyrazoles **7a-m**

3.2.1 General Procedure **2A** (*in situ* hydrogenation).

Scheme S4. General synthesis of pyrazoles **7a, d-h, k, m**



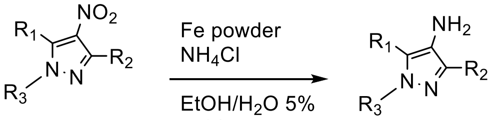
S10a, d-h, k,m

7a, d-h, k,m

In a sealed reaction tube 4-nitro-pyrazole **S10** (1 eq.), ammonium formate (5-10 eq.), Pd/C (10%) and AcOEt (3.33 mL/mmol) were sequentially added. The tube was sealed and heated at 70°C until full conversion of the starting material (ca. 3-6 h, monitored by TLC). The crude reaction was filtered on a short pat of Celite® and washed with AcOEt. The organic phase was transferred into a flask and dried under vacuum to give the crude product **7**, which was used in the next step without any further purification.

3.2.2 General Procedure **2B**.

Scheme S5. General synthesis of pyrazoles **7b-c, i-j, l**.

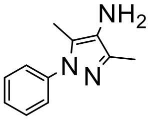


S10b-c, i-j, l

7b-c, i-j, l

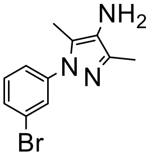
In a round-bottom flask 4-nitro-pyrazole **S10** (1 eq.), ammonium chloride (5 eq.) were added to a mixture EtOH/H_2O (5%) (10 mL/mmol). The reaction was heated at 80°C and iron powder (4 eq.) was then added. Upon full conversion of the starting material (ca. 2-4h, monitored by TLC), the crude reaction was filtered on Celite® and washed with EtOH. The organic phase was transferred into a flask and the solvent partially removed under vacuum. The organic phase was further diluted with AcOEt, transferred into a separatory funnel, washed with brine, dried over Na_2SO_4 and the organics removed under vacuum. The crude product **7** was used in the next step without any further purification.

*3,5-Dimethyl-1-phenyl-1H-pyrazol-4-*amine *(**7a**).*



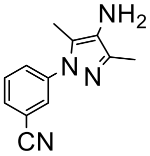
Following the General Procedure **2A**, starting from 3,5-dimethyl-4-nitro-1-phenyl-1H-pyrazole (**S10a**) (1.27 g, 5.87 mmol), the title compound (1.1 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, DMSO-*d_6*): δ 7.48 – 7.40 (m, 4H), 7.30 – 7.25 (m, 1H), 2.20 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d_6*) δ 140.4, 139.3, 128.9, 127.5, 125.7, 123.6, 122.8, 11.0, 10.3.

*1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazol-4-amine (**7b**).*



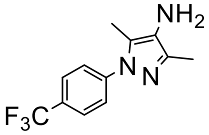
Following the General Procedure **2B**, starting from 1-(3-bromophenyl)-3,5-dimethyl-4-nitro-1H-pyrazole (**S10b)** (5.75 g, 19.5 mmol), the title compound (5.2 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (t, *J* = 2.0 Hz, 1H), 7.44 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 2.28 (d, J = 3.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 141.6, 141.4, 130.2, 129.6, 126.8, 125.4, 122.6, 122.2, 10.9, 10.5.

*3-(4-Amino-3,5-dimethyl-1H-pyrazol-1-yl)benzonitrile (**7c**).*



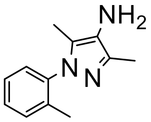
Following the General Procedure **2B**, starting from 3-(3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)benzonitrile (**S10c**) (1.82 g, 7.5 mmol), the title compound (1.6 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 1.9 Hz, 1H), 7.62 (dt, *J* = 7.5, 2.0 Hz, 1H), 7.52 – 7.38 (m, 2H), 2.24 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 142.3, 141.0, 130.0, 129.5, 127.4, 126.5, 126.3, 126.2, 118.2, 113.2, 11.0, 10.6, 1.0.

*3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-amine (**7d**).*



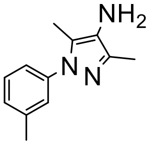
Following the General Procedure **2A**, starting from 3,5-dimethyl-4-nitro-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**S10d**) (1.53 g, 5.3 mmol), the title compound (1.32 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 2.18 (d, *J* = 12.0 Hz, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.3, 142.1, 128.3, 127.9, 126.5, 126.3, 126.2, 126.2, 126.2, 126.1, 125.4, 123.5, 123.2, 122.7, 10.9, 10.7. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.27.

*3,5-Dimethyl-1-(o-tolyl)-1H-pyrazol-4-amine (**7e**).*



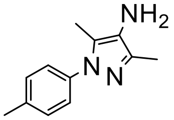
Following the General Procedure **2A**, starting from 3,5-dimethyl-4-nitro-1-(o-tolyl)-1H-pyrazole (**S10e**) (0.92 g, 4.0 mmol), the title compound (0.81 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR (**400 MHz, $CDCl_3$): δ 7.48 – 7.28 (m, 3H), 7.34 – 7.19 (m, 2H), 2.33 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H).

*3,5-Dimethyl-1-(m-tolyl)-1H-pyrazol-4-amine (**7f**).*



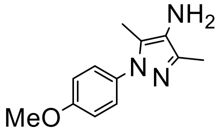
Following the General Procedure **2A**, starting from 3,5-dimethyl-4-nitro-1-(m-tolyl)-1H-pyrazole (**S10f**) (1.24 g, 5.3 mmol), the title compound (1.01 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 – 7.15 (m, 2H), 7.12 – 7.00 (m, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H).

*3,5-Dimethyl-1-(p-tolyl)-1H-pyrazol-4-amine (**7g**).*



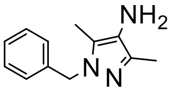
Following the General Procedure **2A**, starting from 3,5-dimethyl-4-nitro-1-(*p*-tolyl)-1H-pyrazole (**S10g**) (0.71 g, 3.08 mmol), the title compound (0.61 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 – 7.17 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 2.31 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H).

*1-(4-Methoxyphenyl)-3,5-dimethyl-1H-pyrazol-4-amine (**7h**).*



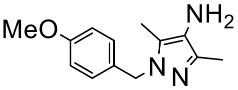
Following the General Procedure **2A**, starting from 1-(4-methoxyphenyl)-3,5-dimethyl-4-nitro-1H-pyrazole (**S10h**) (0.42 g, 1.7 mmol), the title compound (0.37 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 2H), 6.98 – 6.92 (m, 2H), 3.85 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.5, 140.4, 133.51, 127.4, 125.9, 124.3, 114.2, 55.5, 10.9, 10.1.

*1-Benzyl-3,5-dimethyl-1H-pyrazol-4-amine (**7i**).*



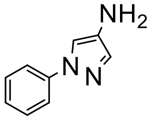
Following the General Procedure **2B**, starting from 1-benzyl-3,5-dimethyl-4-nitro-1H-pyrazole (**S10i**) (1.0 g, 4.4 mmol), the title compound (0.75 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 – 7.12 (m, 3H), 7.01 – 6.91 (m, 2H), 5.10 (s, 2H), 2.44 (s, 3H), 2.13 (s, 3H).

*1-(4-Methoxybenzyl)-3,5-dimethyl-1H-pyrazol-4-amine (**7j**).*



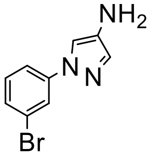
Following the General Procedure **2B**, starting from 1-(4-methoxybenzyl)-3,5-dimethyl-4-nitro-1H-pyrazole (**S10j**) (0.25 g, 0.95 mmol), the title compound (0.18 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.3 Hz, 1H), 6.94 – 6.88 (m, 1H), 5.27 (s, 1H), 3.79 (s, 1H), 2.34 (d, *J* = 4.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.1, 142.2, 136.2, 129.6, 115.8, 115.3, 110.8, 68.1, 55.8, 53.7, 27.2, 10.6, 9.2.

*1-Phenyl-1H-pyrazol-4-amine (**7k**).*



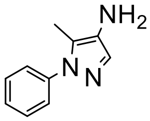
Following the General Procedure **2A**, starting 4-nitro-1-phenyl-1H-pyrazole (**S10k**) (1.0 g, 5.9 mmol), the title compound (0.95 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 – 7.57 (m, 2H), 7.54 (s, 1H), 7.50 – 7.39 (m, 3H), 7.24 (td, *J* = 7.3, 1.3 Hz, 1H).

*1-(3-Bromophenyl)-1H-pyrazol-4-amine (**7l**).*



Following the General Procedure **2B**, starting from 1-(3-bromophenyl)-4-nitro-1H-pyrazole (**S10l**) (0.8 g, 3.0 mmol), the title compound (0.71 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (t, *J* = 2.0 Hz, 1H), 7.44 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.40 (d, *J* = 0.8 Hz, 1H), 7.32 (s, 1H), 7.29 – 7.23 (m, 1H), 7.21 – 7.14 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 141.3, 134.06, 130.6, 128.5, 123.1, 121.3, 116.5, 114.2.

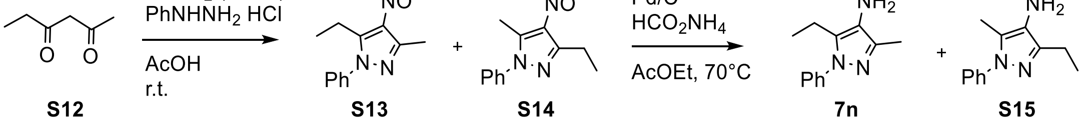
*5-Methyl-1-phenyl-1H-pyrazol-4-amine (**7m**).*



Following the General Procedure **2A**, starting from 5-methyl-4-nitro-1-phenyl-1H-pyrazole (**S10m**) (0.87 g, 4.2 mmol), the title compound (0.65 g, *quant.*) was synthesized as red oil and used in the following step without any further purification. TLC R_f 0.13 (cyclohexane/AcOEt 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 – 7.37 (m, 2H), 7.37 – 7.23 (m, 3H), 7.16 – 7.01 (m, 1H), 2.82 (s, 2H), 2.18 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 141.7, 140.3, 129.3, 128.8, 125.1, 117.8, 114.9, 10.8.

*5-Ethyl-3-methyl-1-phenyl-pyrazol-4-amine (7**n**).*

Scheme S6. Synthesis of substituted pyrazole **7n**.



Step 1. *5-Ethyl-3-methyl-4-nitroso-1-phenyl-pyrazole (**S13**) and 3-ethyl-5-methyl-4-nitroso-1-phenyl-pyrazole (**S14**).*

In a round-bottom flask to a solution of hexane-2,4-dione (**S12**) (0.5 g, 4.4 mmol, 1.0 eq.) in AcOH (14 mL, 3.3 mL/mmol), an aqueous $NaNO_2$ solution (0.1M) (48 mL) was dropwise added. The reaction was stirred at room temperature for 20 min, then phenyl hydrazine hydrochloride (0.698 g, 4.8 mmol, 1.1 eq.) was added and the reaction stirred at room temperature for 2 h. The crude mixture was transferred into a separatory funnel and diluted with water. The aqueous phase was extracted with Et_2O (3x 30 mL). The combined organic phase was washed with NaOH (1M) and brine, dried over Na_2SO_4 and concentrated under vacuum to afford the corresponding nitroso-pyrazoles **S13** and **S14** (0.25 g), as a mixture of regioisomers.

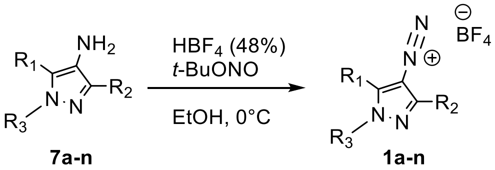
Step 2. *5-Ethyl-3-methyl-1-phenyl-pyrazol-4-amine (**7n**) and 3-ethyl-5-methyl-1-phenyl-pyrazol-4-amine (**S15**).*

The crude mixture of nitroso-pyrazoles **S13** and **S14** was charged into a pressure tube followed by AcOEt (17 mL), 10% Pd/C (0.09 g) and ammonium formate (1.4 g, 40 mmol). The tube was sealed and heated at 70°C for 4 h. The crude reaction was filtered on a short pad of Celite® and the corresponding organic phase evaporated under reduced pressure. The crude product was subjected to flash column chromatography, using cyclohexane/AcOEt 50%, as eluent, to afford the title compound **7n** (0.2 g, 22%), as a black oil, as a pure regioisomer. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.5 – 7.3 (m, 5H), 2.6 (q, *J* = 7.6 Hz, 2H), 2.2 (s, 3H), 1.1 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.9, 140.5, 133.0, 129.1, 127.3, 125.0, 124.3, 17.6, 13.2, 11.0.

The structure of the desired product **7n**, as the major isomer, was determined by 2D ^{1}H NOESY, looking at the cross signals between the protons of the CH_2-CH_3 residue and the ones of the phenyl ring (see Paragraph 5.3 in this Section).

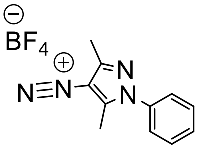
3.3 Synthesis of pyrazolyl diazonium tetrafluoroborate salts 1a-n (General Procedure 3)

Scheme S7. Synthesis of pyrazolyl diazonium tetrafluoroborates **1a-n**.



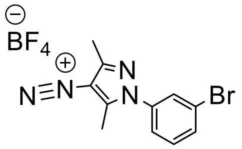
In a round-bottom flask substituted 4-amino pyrazole **7a-n** (1.0 eq.) was dissolved in EtOH (2.0 mL/mmol). The solution was cooled to 0°C and aqueous HBF_4 (48%) (1.5 eq.) was added dropwise. The reaction was stirred for 2 min, then *t*-BuONO (1.5 eq.) was dropwise added. The corresponding mixture was stirred at 0°C for 30 min, then for further 30 min at room temperature. To promote precipitation of the crude product, TBME (2.0 mL/mmol) was added and the reaction stirred at room temperature for 5 min. The diazonium tetrafluoroborate **1a-n**, as pure compound, was collected by filtration washing the corresponding precipitate with TBME.

*3,5-Dimethyl-1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1a**).*



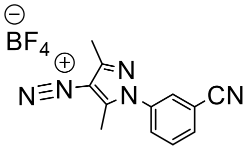
Following the General Procedure **3**, starting from 3,5-dimethyl-1-phenyl-1H-pyrazol-4-amine (**7a**) (0.82 g, 4.4 mmol), the pure title compound (1.01 g, 80%) was synthesized as grey solid. UPLC-MS: t_R = 0.99 min (generic method); MS (ESI) *m/z* calcd. for $C_{11}H_{11}N_4^+$ [M+H]$^+$: 199.10, found: 199.01. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.73 – 7.60 (m, 5H), 2.77 (s, 3H), 2.64 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 153.6, 153.3, 136.3, 130.6, 129.9, 125.2, 92.2, 12.3, 12.3. **^{19}F NMR** (565 MHz, DMSO-d_6): δ -147.23, -147.29 (m).

*1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1b**).*



Following the General Procedure **3**, starting from 1-(3-bromophenyl)-3,5-dimethyl-1H-pyrazol-4-amine (**7b**) (5.0 g, 18.8 mmol), the pure title compound (5.5 g, 70%) was synthesized as grey solid. UPLC-MS: t_R = 1.34 min (generic method); MS (ESI) *m/z* calcd. for $C_{11}H_{10}BrN_4^+$ [M+H]$^+$:277.0, found: 277.0. **^{1}H NMR** (600 MHz, DMSO-d_6): δ 7.97 (t, *J* = 2.0 Hz, 1H), 7.88 (ddd, *J* = 8.1, 1.9, 1.0 Hz, 1H), 7.73 – 7.71 (m, 1H), 7.62 (t, *J* = 8.1 Hz, 1H), 2.79 (s, 3H), 2.63 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6): δ 154.2, 153.4, 137.4, 133.6, 131.7, 128.0, 124.5, 122.1, 92.6, 48.6, 12.3. **^{19}F NMR** (565 MHz, DMSO-d_6): δ -147.24, -147.30 (m).

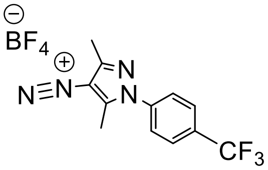
*1-(3-Cyanophenyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1c**).*



Following the General Procedure **3**, starting from 3-(4-amino-3,5-dimethyl-1H-pyrazol-1-yl)benzonitrile (**7c**) (1.5 g, 6.2 mmol), after running the diazonization reaction at room temperature for 4 h the pure title compound (1.1 g, 84%) was synthesized as light pink solid. UPLC-MS: t_R = 1.01 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{10}N_5^+$ [M+H]$^+$: 224.09, found: 224.1. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.29

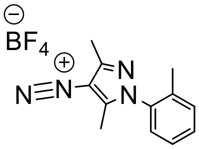
(t, J = 1.9 Hz, 1H), 8.14 (dt, J = 7.8, 1.3 Hz, 1H), 8.04 (ddd, J = 8.3, 2.2, 1.1 Hz, 1H), 7.88 (t, J = 8.0 Hz, 1H), 2.78 (d, J = 15.9 Hz, 3H), 2.64 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 154.4, 153.5, 136.8, 134.4, 131.3, 130.3, 128.8, 117.5, 112.8, 93.0, 12.3, 12.3. **^{19}F NMR** (376 MHz, DMSO-d_6): δ -148.14 -148.45 (m).

*3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1d**).*



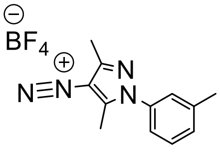
Following the General Procedure **3**, starting from 3,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-amine (**7d**) (1.32 g, 5.2 mmol), the pure title compound (0.1 g, 10%) was synthesized as white solid. UPLC-MS: t_R = 1.47 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{10}F_3N_5^+$ [M+H]$^+$: 267.08, found: 267.0. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.06 (d, J = 8.6 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H), 2.83 (s, 3H), 2.65 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 154.4, 153.5, 127.1, 127.1, 126.2, 12.4, 12.3. **^{19}F NMR** (376 MHz, DMSO-d_6): δ -61.3, -148.2 -148.4 (m).

*3,5-Dimethyl-1-(o-tolyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1e**).*



Following the General Procedure **3**, starting from 3,5-dimethyl-1-(o-tolyl)-1H-pyrazol-4-amine (**7e**) (0.386 g, 1.92 mmol), the pure title compound (0.458 g, 80%) was synthesized as white solid. UPLC-MS: t_R = 1.16 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{13}N_4^+$ [M+H]$^+$: 213.11, found: 213.0. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.63 – 7.52 (m, 2H), 7.52 – 7.44 (m, 2H), 2.62 (s, 3H), 2.56 (s, 3H), 2.08 (d, J = 0.6 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 154.9, 153.2, 135.0, 134.9, 131.7, 131.4, 127.5, 127.1, 91.4, 16.6, 12.3, 11.7. **^{19}F NMR** (376 MHz, DMSO-d_6): δ -148.24 – -148.39 (m).

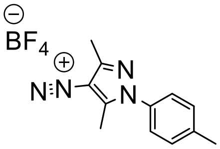
*3,5-Dimethyl-1-(m-tolyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1f**).*



Following the General Procedure **3**, starting from 3,5-dimethyl-1-(*m*-tolyl)-1H-pyrazol-4-amine (**7f**) (1.0 g, 5.02 mmol), the pure title compound (1.3 g, 89%) was synthesized as white solid. UPLC-MS: t_R = 1.16 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{13}N_4^+$ [M+H]$^+$: 213.11, found: 213.0. **^{1}H NMR** (400

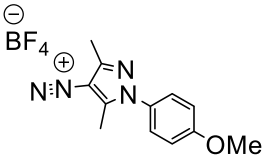
MHz, DMSO-*d*$_6$): δ 7.59 – 7.42 (m, 4H), 2.76 (s, 3H), 2.63 (s, 3H), 2.43 (s, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 153.5, 153.3, 139.9, 136.2, 131.2, 129.6, 125.5, 122.2, 92.1, 20.7, 12.3, 12.3. ^{19}**F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.01 – -148.54 (m).

*3,5-Dimethyl-1-(p-tolyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1g**).*



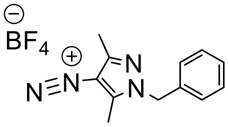
Following the General Procedure **3**, starting from 3,5-dimethyl-1-(*p*-tolyl)-1H-pyrazol-4-amine (**7g**) (0.61 g, 3.03 mmol), the pure title compound (0.4 g, 44%) was synthesized as white solid. UPLC-MS: t$_R$ = 1.16 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{13}N_4^+$ [M+H]$^+$: 213.11, found: 213.0. ^{1}**H NMR** (400 MHz, DMSO-*d*$_6$): δ 7.6 – 7.5 (m, 2H), 7.5 – 7.4 (m, 2H), 2.7 (s, 3H), 2.6 (s, 3H), 2.4 (s, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 153.4, 153.3, 140.6, 133.9, 130.3, 125.0, 91.9, 20.8, 12.3. ^{19}**F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.22-148.39 (m).

*1-(4-Methoxyphenyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1h**).*



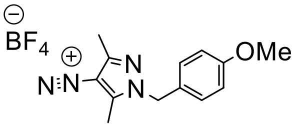
Following the General Procedure **3**, starting from 1-(4-methoxyphenyl)-3,5-dimethyl-1H-pyrazol-4-amine (**1h**) (0.37 g, 1.7 mmol), the pure title compound (0.214 g, 44%) was synthesized as black solid. UPLC-MS: t$_R$ = 1.16 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{13}N_4O^+$ [M+H]$^+$: 229.1, found: 229.1. ^{1}**H NMR** (400 MHz, DMSO-*d*$_6$): δ 7.60 – 7.56 (m, 2H), 7.19 – 7.14 (m, 2H), 3.85 (s, 3H), 2.72 (s, 3H), 2.61 (s, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 160.5, 153.4, 153.2, 129.0, 126.8, 114.9, 55.7, 12.3, 12.2. ^{19}**F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.22 -148.39 (m).

*1-Benzyl-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1i**).*



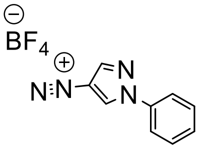
Following the General Procedure **3**, starting from 1-benzyl-3,5-dimethyl-1H-pyrazol-4--amine (**7i**) (0.745 g, 3.7 mmol), the pure title compound (0.943 g, 85%) was synthesized as grey solid. UPLC-MS: t$_R$ = 1.17 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{13}N_4^+$ [M+H]$^+$: 213.11, found: 213.0. ^{1}**H NMR** (400 MHz, DMSO-*d*$_6$): δ 7.46 – 7.27 (m, 5H), 5.50 (s, 2H), 2.79 (s, 3H), 2.53 (s, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 153.5, 153.2, 134.1, 128.9, 128.5, 128.0, 90.6, 53.8, 12.3, 11.2. **^{19}F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.15 – -148.39 (m).

*1-(4-Methoxybenzyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1j**).*



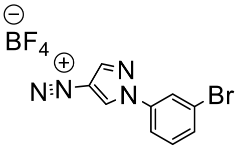
Following the General Procedure **3**, starting from 1-(4-methoxybenzyl)-3,5-dimethyl-1H-pyrazol-4-amine (**7j**) (0.177 g, 0.77 mmol), the pure title compound (0.205 g, 80%) was synthesized as black solid. UPLC-MS: t_R = 1.29 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{15}N_4O^+$ [M+H]$^+$: 243.12, found: 243.1. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$): δ 7.35 – 7.24 (m, 2H), 7.02 – 6.90 (m, 2H), 5.40 (s, 2H), 3.75 (s, 3H), 2.79 (s, 3H), 2.51 (d, *J* = 2.7 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$): δ 159.4, 153.1, 153.1, 129.8, 125.9, 114.3, 55.2, 53.4, 12.3, 11.2. **^{19}F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.23, -148.25 – -148.31 (m).

*1-Phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1k**).*



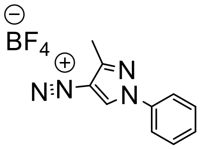
Following the General Procedure **3**, starting from 1-phenyl-1H-pyrazol-4-amine (**7k**) (0.527 g, 3.33 mmol), the pure title compound (0.78 g, 62%) was synthesized as light purple solid. UPLC-MS: t_R = 1.0 min (generic method); MS (ESI) *m/z* calcd. for $C_9H_7N_4^+$ [M+H]$^+$: 171.07, found: 171.1. **^{1}H NMR (**400 MHz, DMSO-*d*$_6$): δ 10.09 (s, 1H), 9.12 (s, 1H), 8.03 – 7.86 (m, 2H), 7.76 – 7.56 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$): δ 145.7, 140.0, 137.3, 130.2, 125.2, 120.9, 94.2. **^{19}F NMR** (376 MHz, DMSO-*d*$_6$): δ -147.93 – -148.51 (m).

*1-(3-Bromophenyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1l**).*



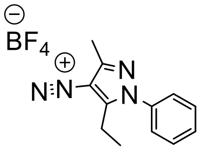
Following the General Procedure **3**, starting from 1-(3-bromophenyl)-1H-pyrazol-4-amine (**7l**) (0.37 g, 1.55 mmol), the pure title compound (0.35 g, 67%) was synthesized as orange solid. UPLC-MS: t_R = 1.30 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{15}N_4O^+$ [M+H]$^+$: 248.98, found: 248.9. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$): δ 10.16 (s, 1H), 9.12 (s, 1H), 8.21 (t, *J* = 2.1 Hz, 1H), 7.98 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 7.82 (ddd, *J* = 8.1, 1.9, 0.9 Hz, 1H), 7.63 (t, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$): δ 145.8, 140.5, 138.4, 132.9, 132.0, 123.7, 122.4, 120.2, 94.7. ^{19}**F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.16, 148.18 – -148.28 (m).

*3-Methyl-1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1m**).*



Following the General Procedure **3**, starting from 5-methyl-1-phenyl-1H-pyrazol-4-amine (**7m**) (0.5 g, 2.9 mmol), the pure title compound (0.35 g, 44%) was synthesized as orange solid. UPLC-MS: t_R = 1.08 min (generic method); MS (ESI) *m/z* calcd. for $C_{10}H_9N_4^+$ [M+H]$^+$: 185.08, found: 185.0. ^{1}**H NMR** (400 MHz, DMSO-*d*$_6$): δ 9.94 (s, 1H), 7.95 – 7.88 (m, 2H), 7.66 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.64 – 7.57 (m, 1H), 2.69 (s, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 155.8, 140.4, 130.6, 130.5, 130.1, 121.2, 12.9. ^{19}**F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.20 -148.24 – -148.29 (m).

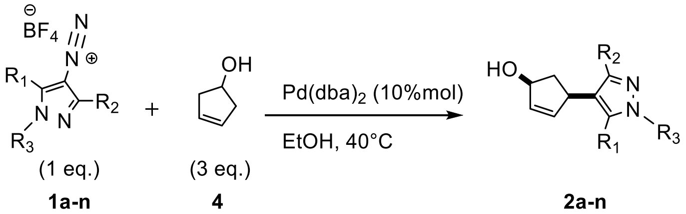
*5-Ethyl-3-methyl-1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1n**).*



Following the General Procedure **3**, starting from 5-ethyl-3-methyl-1-phenyl-pyrazol-4-amine (**7n**) (0.05 g, 0.25 mmol), the pure title compound (0.037 g, 50%) was synthesized as light purple solid. UPLC-MS: t_R = 1.15 min (generic method); MS (ESI) *m/z* calcd. for $C_{12}H_{13}N_4^+$ [M+H]$^+$: 213.11, found: 213.1. ^{1}**H NMR** (400 MHz, DMSO-*d*$_6$): δ 7.44 – 7.35 (m, 5H), 2.79 (q, *J* = 7.5 Hz, 2H), 2.50 (s, 3H), 1.04 (t, *J* = 7.5 Hz, 3H). ^{13}**C NMR** (101 MHz, DMSO-*d*$_6$): δ 157.61, 153.76, 136.32, 130.63, 129.90, 125.25, 19.81, 12.33, 10.99. ^{19}**F NMR** (376 MHz, DMSO-*d*$_6$): δ -148.20 – -148.39 (m).

3.4 Synthesis of 4-pyrazolyl-cyclopent-2-en-1-ols **2a-n** via heteroaryl Heck-Matsuda reaction (General Procedure **4**)

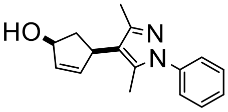
Scheme S8. Synthesis of 4-pyrazolyl-cyclopentenols **2a-n** via Heck-Matsuda reaction.



In a round-bottom flask Pd(dba)$_2$ (10% mol) was mixed with EtOH (12.5 mL/mmol). The mixture was heated at 40°C and cyclopent-3-en-1-ol (**2**) (3.0 eq.) was added, followed by the heteroaryl diazonium salt **1a-n** (1.0 eq.). The reaction was monitored by TLC (using β-naphthol spot test*) until disappearance of the diazonium salt (ca. 1-4 h). The reaction was quenched with NaHCO$_3$ (3.0 eq.) and the crude mixture filtered over a short pad of Celite® washing few times with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na$_2$SO$_4$ and the solvent removed under vacuum. The crude product was purified by flash column chromatography using cyclohexane/AcOEt 30% to give desired 4-pyrazolyl-cyclopentenol.

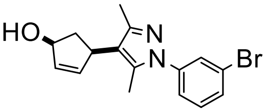
[*A small aliquot of the reaction mixture was spotted on a TLC plate and a drop of β-naphthol solution in MeOH was added. If the diazonium salt were present, a red/orange coloration would appear].

(1S,4R*)-4-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2a**).*



Following the General Procedure **4**, starting from 3,5-dimethyl-1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1a**) (0.1 g, 0.34 mmol), after 3 h the pure title compound (0.04 g, 53%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 99.4 : 0.6). TLC: R$_f$ 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t$_R$ = 1.65 min (generic method); MS (ESI) *m/z* calcd. for $C_{16}H_{18}N_2O$ [M+H]$^+$: 254.14, found: 255.1. HRMS-ESI: m/z [M+NH$_4$]$^+$ calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 255.1499. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.48 – 7.31 (m, 5H), 5.96 – 5.89 (m, 2H), 4.96 (td, *J* = 6.7, 1.9 Hz, 1H), 3.75 (ddt, *J* = 7.9, 6.4, 1.3 Hz, 1H), 2.83 (ddd, *J* = 13.4, 8.2, 7.5 Hz, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 1.60 (ddd, *J* = 13.3, 7.8, 6.4 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ 147.5, 139.9, 136.9, 136.2, 134.2, 129.1, 127.4, 125.2, 119.2, 77.4, 42.6, 39.9, 12.8, 11.3, 1.1.

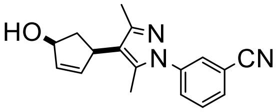
(1S,4R*)-4-(1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2b**).*



Following the General Procedure **4**, starting from 1-(3-bromophenyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1b**) (5.3 g, 13.7 mmol), after 3h the pure title compound (1.35 g, 30%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* > 99 : 1). TLC: R$_f$ 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t$_R$ = 2.10 min (generic method); MS (ESI) *m/z* calcd. for $C_{16}H_{17}BrN_2O$ [M+H]$^+$: 332.05, found: 333.0. HRMS-ESI: m/z [M+NH$_4$]$^+$ calcd. for $C_{16}H_{17}BrN_2O$: 332.0524, found: 333.0606. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.5 – 7.3 (m, 5H), 6.0 – 5.9 (m, 2H), 5.0 (td, *J* = 6.7, 1.9 Hz, 1H), 3.8 (ddt, *J* = 7.9, 6.4, 1.3 Hz, 1H), 2.8 (ddd, *J* = 13.4, 8.2, 7.5 Hz, 1H), 2.3 (s, 3H), 2.2

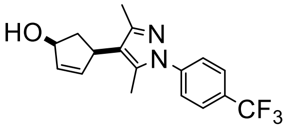
(s, 3H), 1.6 (ddd, *J* = 13.3, 7.8, 6.4 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 148.2, 141.1, 136.7, 136.2, 134.3, 130.3, 130.3, 128.2, 123.4, 122.6, 119.7, 77.4, 42.5, 39.8, 12.8, 11.3.

3-(4-((1R,4S*)-4-Hydroxycyclopent-2-en-1-yl)-3,5-dimethyl-1H-pyrazol-1-yl)benzonitrile (**2c**).*



Following the General Procedure **4**, starting from 1-(3-cyanophenyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1c**) (0.8 g, 2.57 mmol), after 4h the pure title compound (0.344 g, 48%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* > 99 : 1). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 1.20 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{17}N_3O$ $[M+H]^+$: 279.14, found: 280.0. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{17}N_3O$: 279.1372, found: 280.1446. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 1.9 Hz, 1H), 7.62 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.59 – 7.39 (m, 2H), 5.93 – 5.76 (m, 2H), 4.92 (t, *J* = 7.1 Hz, 1H), 3.69 (td, *J* = 8.1, 2.1 Hz, 1H), 2.77 (dt, *J* = 13.4, 7.9 Hz, 1H), 2.22 (d, *J* = 8.5 Hz, 6H), 1.52 (ddd, *J* = 13.7, 7.8, 6.3 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 149.0, 140.7, 136.4, 136.2, 134.5, 130.4, 130.1, 128.8, 127.9, 120.4, 118.1, 113.3, 77.3, 42.4, 39.7, 12.8, 11.4, 1.1.

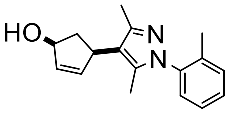
(1S,4R*)-4-(3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2d**).*



Following the General Procedure **4**, starting from 3,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1d**) (0.1 g, 0.28 mmol), after 2 h the pure title compound (0.045 g, 50%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 92.3 : 7.7). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 2.14 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{17}F_3N_2O$ $[M+H]^+$: 322.13, found: 323.0. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{17}F_3N_2O$: 322.1293 found: 132.1373. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 5.86 (qd, *J* = 5.6, 3.0 Hz, 2H), 4.91 (t, *J* = 6.9 Hz, 1H), 3.69 (td, *J* = 8.1, 2.0 Hz, 1H), 2.77 (dt, *J* = 13.5, 7.9 Hz, 1H), 2.22 (d, *J* = 9.1 Hz, 6H), 1.53 (ddd, *J* = 13.7, 7.8, 6.4 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 148.7, 142.8, 136.7, 136.3, 134.4, 126.4, 126.3, 124.7, 120.3, 77.4, 53.6, 42.5, 39.8, 12.8, 11.5. ^{19}**F NMR** (376 MHz, $CDCl_3$) δ -62.36.

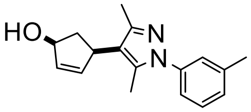
[For the one-pot protocol to prepare compound **2d**, see Paragraph 3.5 in this Section].

(1S,4R*)-4-(3,5-Dimethyl-1-(o-tolyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2e**).*



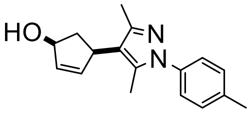
Following the General Procedure **4**, starting from 3,5-dimethyl-1-(*o*-tolyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1e**) (0.3 g, 1.0 mmol), after 3 h the pure title compound (0.15 g, 56%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 97.5: 2.5). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 1.81 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{20}N_2O$ $[M+H]^+$: 268.16, found: 269.1. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{20}N_2O$: 268.1576, found: 269.1652. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 – 7.21 (m, 5H), 6.01 – 5.93 (m, 2H), 5.02 – 4.96 (m, 1H), 3.80 (tq, *J* = 8.0, 2.2 Hz, 1H), 2.88 (dt, *J* = 13.3, 7.9 Hz, 1H), 2.32 (s, 3H), 2.07 (d, *J* = 10.8 Hz, 6H), 1.69 – 1.60 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 146.8, 138.9, 137.1, 137.1, 136.5, 134.0, 130.9, 129.0, 128.2, 126.5, 117.7, 77.4, 42.8, 39.9, 17.4, 12.8, 10.3.

(1S,4R*)-4-(3,5-Dimethyl-1-(m-tolyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2f**).*



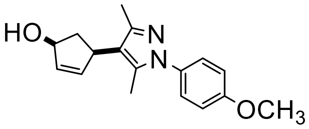
Following the General Procedure **4**, starting from 3,5-dimethyl-1-(*m*-tolyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1f**) (0.8 g, 2.15 mmol), after 3 h the pure title compound (0.3 g, 52%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 88.2 : 11.8). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 1.81 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{20}N_2O$ $[M+H]^+$: 268.16, found: 269.1. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{20}N_2O$: 268.1576, found: 269.1652. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 – 7.12 (m, 3H), 7.12 – 7.05 (m, 2H), 5.84 (d, *J* = 2.4 Hz, 2H), 4.93 – 4.77 (m, 1H), 4.05 (q, *J* = 7.1 Hz, 1H), 3.73 – 3.64 (m, 1H), 2.74 (dt, *J* = 13.4, 7.9 Hz, 1H), 2.32 (s, 4H), 2.20 (s, 3H), 2.16 (s, 3H), 1.52 (ddd, *J* = 13.4, 7.9, 6.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.4, 139.8, 139.2, 137.0, 136.2, 134.1, 128.8, 128.2, 126.0, 122.1, 119.0, 77.5, 42.7, 39.9, 21.4, 12.8, 11.3.

(1S,4R*)-4-(3,5-Dimethyl-1-(p-tolyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2g**).*



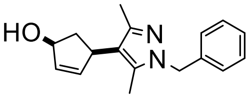
Following the General Procedure **4**, starting from 3,5-dimethyl-1-(*p*-tolyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1g**) (0.05 g, 0.12 mmol), after 3 h the pure title compound (0.025 g, 78%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 88.6 : 11.4). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 1.81 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{20}N_2O$ $[M+H]^+$: 268.16, found: 269.1. HRMS-ESI: m/z $[M+NH_4]_+$ calcd. for $C_{17}H_{20}N_2O$: 268.1576, found: 269.1655. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 – 7.14 (m, 5H), 5.85 (d, *J* = 2.6 Hz, 2H), 4.88 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.67 (dd, *J* = 9.3, 6.5 Hz, 1H), 2.75 (dt, *J* = 13.3, 7.9 Hz, 1H), 2.32 (s, 3H), 2.20 (s, 4H), 2.14 (s, 3H), 1.52 (ddd, *J* = 13.8, 7.8, 6.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.1, 137.2, 137.0, 136.1, 133.9, 129.6, 125.0, 118.8, 77.2, 42.6, 39.8, 21.1, 12.7, 11.1.

(1S,4R*)-4-(1-(4-Methoxyphenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2h**).*



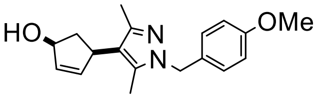
Following the General Procedure **4**, starting from 1-(4-methoxyphenyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1h**) (0.17 g, 0.52 mmol), after 3h the pure title compound (0.03 g, 20%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 97.5 : 2.5). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 1.66 min (generic method); MS (ESI) *m/z* calcd. $C_{17}H_{20}N_2O_2$ $[M+H]^+$: 284.15, found: 285.1. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{20}N_2O_2$: 284.1525, found: 285.1605. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 – 7.26 (m, 2H), 7.02 – 6.92 (m, 2H), 5.92 (p, *J* = 1.5 Hz, 2H), 4.96 (t, *J* = 7.0 Hz, 1H), 3.84 (d, *J* = 1.9 Hz, 3H), 3.74 (dd, *J* = 9.6, 6.9 Hz, 1H), 2.83 (dt, *J* = 13.4, 7.9 Hz, 1H), 2.26 (d, *J* = 1.9 Hz, 3H), 2.18 (d, *J* = 2.0 Hz, 3H), 1.59 (ddd, *J* = 13.6, 7.8, 6.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.8, 146.9, 136.9, 136.3, 134.0, 133.0, 126.6, 118.5, 114.1, 77.3, 42.6, 39.8, 12.6, 11.0.

(1S,4R*)-4-(1-Benzyl-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2i**).*



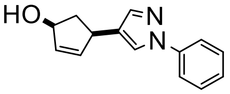
Following the General Procedure **4**, starting from 1-benzyl-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1i**) (0.6 g, 2.0 mmol), after 3 h the pure title compound (0.279 g, 52%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 97.4 : 2.6). TLC: R_f 0.5 (cycloexane/AcOEt 55%). UPLC-MS: t_R = 1.78 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{20}N_2O$ $[M+H]^+$: 268.16, found: 269.1. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{20}N_2O$: 268.1576, found: 269.1660. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 3H), 7.09 – 7.03 (m, 2H), 5.90 – 5.85 (m, 2H), 5.20 (s, 2H), 4.93 (t, *J* = 7.3 Hz, 1H), 3.68 (td, *J* = 7.9, 3.4 Hz, 1H), 2.79 (dt, *J* = 13.3, 7.9 Hz, 1H), 2.22 (s, 4H), 2.10 (s, 3H), 1.54 – 1.48 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 145.8, 137.5, 137.2, 136.1, 133.9, 128.8, 127.5, 126.8, 118.2, 77.5, 43.0, 39.9, 12.7, 10.0.

(1S,4R*)-4-(1-(4-Methoxybenzyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2j**).*



Following the General Procedure **4**, starting from 1-(4-methoxybenzyl)-3,5-dimethyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1j**) (0.18 g, 0.54 mmol), after 3 h the pure title compound (0.032 g, 20%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* = 92.7 : 7.3). TLC: R_f 0.5 (cycloexane/AcOEt 55%). UPLC-MS: t_R = 1.77 min (generic method); MS (ESI) *m/z* calcd. for $C_{18}H_{22}N_2O_2$ $[M+H]^+$: 298.17, found: 299.4. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{18}H_{22}N_2O_2$: 299.1760, found: 299.1766. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.00 – 6.91 (m, 2H), 6.81 – 6.71 (m, 2H), 5.88 – 5.75 (m, 2H), 5.06 (s, 2H), 4.86 (t, *J* = 6.9 Hz, 1H), 3.71 (s, 3H), 3.60 (td, *J* = 8.0, 1.7 Hz, 1H), 2.71 (dt, *J* = 13.3, 7.9 Hz, 1H), 2.15 (s, 3H), 2.04 (s, 3H), 1.43 (ddd, *J* = 13.7, 7.8, 6.4 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 159.1, 145.6, 137.3, 135.9, 133.9, 129.5, 128.2, 118.2, 114.2, 77.4, 55.4, 52.3, 43.0, 39.9, 12.7, 10.1.

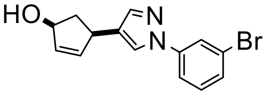
(1S,4R*)-4-(1-Phenyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2k**).*



Following the General Procedure **4**, starting from 1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1k**) (0.15 g, 0.58 mmol), after 3 h the pure title compound (0.042 g, 32%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* > 99:1). TLC: R_f 0.5 (cycloexane/AcOEt 55%). UPLC-MS: t_R = 1.62 min (generic method); MS (ESI) *m/z* calcd. for $C_{14}H_{14}N_2O$ $[M+H]^+$: 226.11, found: 227.0. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{14}H_{14}N_2O$: 226.1106 found: 227.1182. ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.57 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.50 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.25 – 7.14 (m, 1H), 5.97 – 5.83 (m, 2H), 4.84 (ddt, *J* = 6.5, 4.8, 1.6 Hz, 1H), 3.72 (ddq, *J* = 8.0, 5.7, 2.0 Hz, 1H), 2.74 (dt, *J* = 13.5, 7.8 Hz, 1H), 1.58 (dt, *J* = 13.6, 5.3 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 140.3, 140.0, 137.2, 134.1, 129.5, 127.8, 126.3, 119.0, 77.3, 43.4, 39.8.

Along with compound **2k**, a side-product (**S16**) was also isolated (ca. 10%) and fully characterized (see Paragraph 4.3 in this Section).

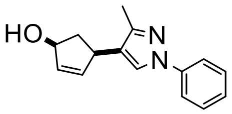
(1S,4R*)-4-(1-(3-Bromophenyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2l**).*



Following the General Procedure **4**, starting from 1-(3-bromophenyl)-1H-pyrazole-4-diazonium tetrafluoroborate (**1l**) (0.33 g, 0.97 mmol), after 3 h the pure title compound (0.13 g, 44%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* > 99:1). TLC: R_f 0.5 (cycloexane/AcOEt 55%).

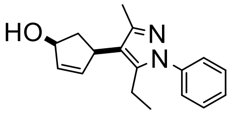
UPLC-MS: t_R = 2.08 min (generic method); MS (ESI) *m/z* calcd. for $C_{14}H_{13}BrN_2O$ $[M+H]^+$: 304.02, found: 304.9. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{14}H_{13}BrN_2O$: 304.0211 found: 304.0288. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (t, *J* = 2.0 Hz, 1H), 7.66 (s, 1H), 7.57 – 7.47 (m, 2H), 7.40 – 7.18 (m, 3H), 5.90 (qd, *J* = 5.8, 3.0 Hz, 2H), 4.86 (ddq, *J* = 6.1, 4.7, 1.5 Hz, 1H), 3.81 – 3.63 (m, 1H), 2.75 (ddd, *J* = 13.6, 8.3, 7.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.6, 137.1, 134.2, 130.8, 129.2, 128.4, 124.4, 123.2, 122.1, 117.3, 77.3, 43.3, 39.7.

(1S,4R*)-4-(3-Methyl-1-phenyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2m**).*



Following the General Procedure **4**, starting from 3-methyl-1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1m**) (0.2 g, 0.74 mmol), after 2 h the pure title compound (0.12 g, 67%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* > 99:1). TLC: R_f 0.5 (cycloexane/AcOEt 55%). UPLC-MS: t_R = 1.72 min (generic method); MS (ESI) *m/z* calcd. for $C_{15}H_{16}N_2O$ $[M+H]^+$: 240.13, found: 241.1. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{15}H_{16}N_2O$: 240.1263 found: 241.1337. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 – 7.56 (m, 3H), 7.43 – 7.35 (m, 2H), 7.21 (td, *J* = 7.3, 1.1 Hz, 1H), 6.05 – 5.93 (m, 2H), 4.93 (ddt, *J* = 7.8, 4.8, 1.6 Hz, 1H), 3.73 (ddq, *J* = 7.9, 5.7, 1.9 Hz, 1H), 2.90 – 2.78 (m, 1H), 2.33 (s, 3H), 1.61 (ddd, *J* = 13.5, 5.8, 4.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 148.4, 140.2, 136.9, 134.1, 129.4, 125.8, 125.7, 124.9, 118.6, 77.4, 42.7, 39.5, 12.4.

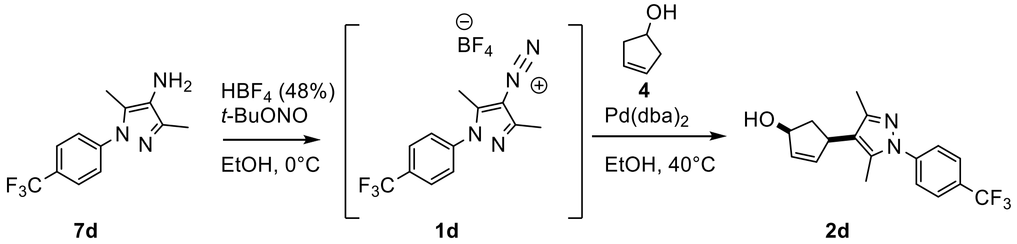
(1S,4R*)-4-(5-Ethyl-3-methyl-1-phenyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2n**).*



Following the General Procedure **4**, starting from 5-ethyl-3-methyl-1-phenyl-1H-pyrazole-4-diazonium tetrafluoroborate (**1n**) (0.01 g, 0.03 mmol), after 4.5 h the pure title compound (0.004 g, 44%) was synthesized as brown glass, as mixture of *cis*- and *trans*-isomers (*d.r.* > 99:1). TLC: R_f 0.5 (cycloexane/AcOEt 55%). UPLC-MS: t_R = 1.88 min (generic method); MS (ESI) *m/z* calcd. for $C_{17}H_{20}N_2O$ $[M+H]^+$: 268.16, found: 269.1. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{17}H_{20}N_2O$: 268.1654 found: 269.1661. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 – 7.37 (m, 5H), 7.37 – 7.29 (m, 1H), 5.93 (qt, *J* = 5.5, 1.8 Hz, 2H), 4.99 – 4.91 (m, 1H), 3.77 (tq, *J* = 8.1, 2.1 Hz, 1H), 2.94 – 2.79 (m, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.24 (s, 3H), 1.61 (ddd, *J* = 13.4, 8.0, 6.4 Hz, 1H), 1.26 (dd, *J* = 9.1, 5.9 Hz, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.0, 140.0, 137.2, 136.3, 134.0, 129.1, 127.4, 125.3, 118.5, 77.5, 43.1, 39.8, 20.3, 14.5, 11.5.

3.5 Synthesis of pyrazolyl-cyclopentenol **2d** by one-pot Heck-Matsuda reaction

Scheme S9. One-pot Heck-Matsuda reaction.

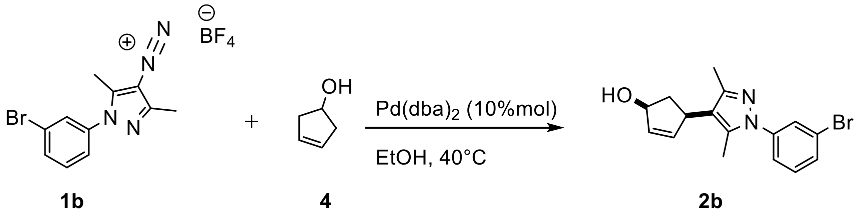


In a round-bottom flask 4-amino-pyrazole **7d** (0.545 g, 2.13 mmol, 1.0 eq.) was dissolved in EtOH (4.3 mL) and the solution cooled to 0°C. An aqueous HBF_4 solution (48%) (333 µL, 2.55 mmol, 1.2 eq.) was added dropwise and the resulting mixture stirred for few minutes. *t*-BuONO (303 µL, 2.55 mmol, 1.2 eq.) was added dropwise and the reaction stirred at 0°C for 2 h. Upon completion of the reaction, the solution was transferred into a flask previously charged with $Pd(dba)_2$ (0.122 g, 0.21 mmol, 10%mol), EtOH (16 mL) and the cyclopent-3-en-1-ol (**4**) (0.5 g, 6.39 mmol, 3.0 eq.) and the mixture heated at 40°C. Additional EtOH (6 mL) was used to fully transfer the crude into the new reaction flask. The reaction was monitored by TLC (using β-naphthol spot test*) until full conversion of the diazonium salt (ca 1.5 h). The reaction was quenched with $NaHCO_3$ (0.15 g) and the corresponding crude mixture filtered over a short pad of Celite® and washed few times with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was purified by flash column chromatography using cyclohexane/AcOEt 30% to give desired 4-pyrazole-cyclopentenol **2d** (0.122 g, 38%).

[*A small aliquot of the reaction mixture was spotted on a TLC plate and a drop of β-naphthol solution in MeOH was added. If the diazonium salt were present, a red/orange coloration would appear].

3.6 Multigram synthesis of pyrazolyl-cyclopentenol **2b** by Heck-Matsuda reaction

Scheme S10. Multigram synthesis of cyclopentenol **2b**.

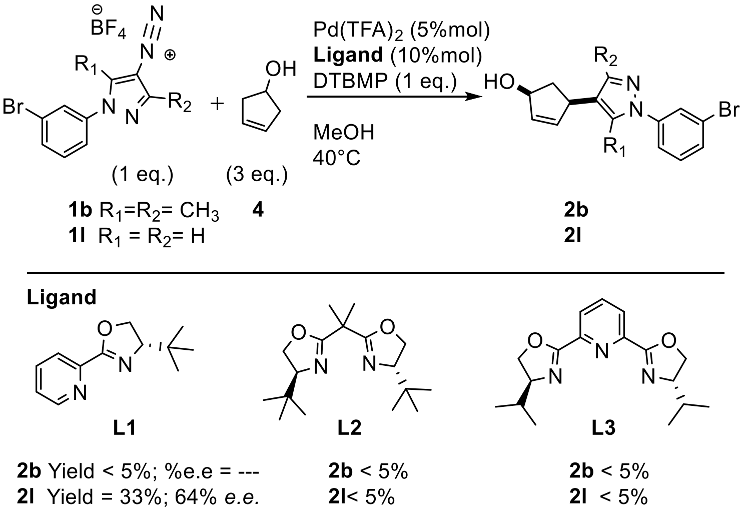


In a round-bottom flask Pd(dba)$_2$ (0.77 g, 1.34 mmol, 10% mol) was mixed with EtOH (170 mL, 12.5 mL/mmol). The mixture was heated at 40°C and cyclopent-3-en-1-ol (**4**) (2.3 g, 27.4 mmol, 2.0 eq.) was added, followed by pyrazolyl diazonium salt **1b** (5.0 g, 13.7 mmol, 1.0 eq.). The reaction was monitored by TLC (using β-naphthol spot test*) until disappearance of the diazonium salt after 3 h. The reaction was quenched with NaHCO$_3$ (1.5 g) and the solvent partially removed under vacuum. The crude was diluted with AcOEt, filtered over a short pad of Celite® and finally washed few times with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na$_2$SO$_4$ and the solvent removed under vacuum. The crude product was purified by flash column chromatography using cyclohexane/AcOEt 30% to give the pure title compound **2b** (1.35 g, 30%).

[*A small aliquot of the reaction mixture was spotted on a TLC plate and a drop of β-naphthol solution in MeOH was added. If the diazonium salt were present, a red/orange coloration would appear].

3.7 Enantioselective synthesis of pyrazolyl-cyclopentenol **2l** by Heck-Matsuda reaction

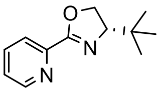
Scheme S11. Enantioselective Heck-Matsuda reaction using diazonium salts **1b,l**.



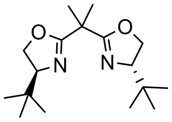
In a round-bottom flask Pd(TFA)$_2$ (5%mol) and the chiral ligand **L1-3** (10% mol) were mixed in dry MeOH (14.3 mL/mmol). The mixture was heated at 40°C and vigorously stirred for 15 min before addition of cyclopent-3-en-1-ol (**4**) (3.0 eq.) and the 2,6-di-*tert*-butyl-4-methylpyridine (1.0 eq.), followed by the pyrazolyl diazonium salts **1b,l** (1.0 eq.). The reaction was monitored by TLC (using β-naphthol spot test) until disappearance of the diazonium salt after 2 h. Upon completion of the reaction, the solvent was removed under vacuum, the crude mixture diluted with AcOEt, filtered on a pad of Celite® and finally washed with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na$_2$SO$_4$ and the solvent removed under vacuum. The crude mixture was purified by flash column chromatography, using cyclohexane/AcOEt 35%, to give the desired product. Enantiomeric excess (*%ee*) of the purified compound was then assessed by chiral HPLC analysis, using a Daicel ChiralPak AD column with heptane-EtOH (75:25) as a mobile phase (flow rate = 1.0 mL/min).

3.7.1 Chiral ligands tested in the enantioselective Heck-Matsuda protocol

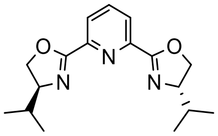
*(S)-4-(tert-butyl)-2-(pyridine-2-yl)-4,5-dihydrooxazole (**L1**)*



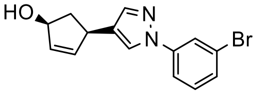
*(4S,4'S)-2,-2'-(propane-2,2-diyl)bis(4-(tert-butyl)-4,5.dihydrooxazole) (**L2**)*



*2,6-bis((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)pyridiene (**L3**)*



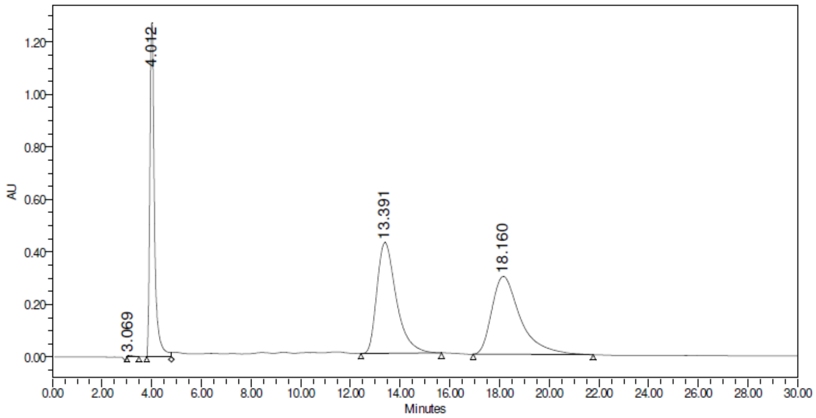
*(1S,4R)- or (1R,4S)-4-(1-(3-Bromophenyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**2l**).*



or enantiomer

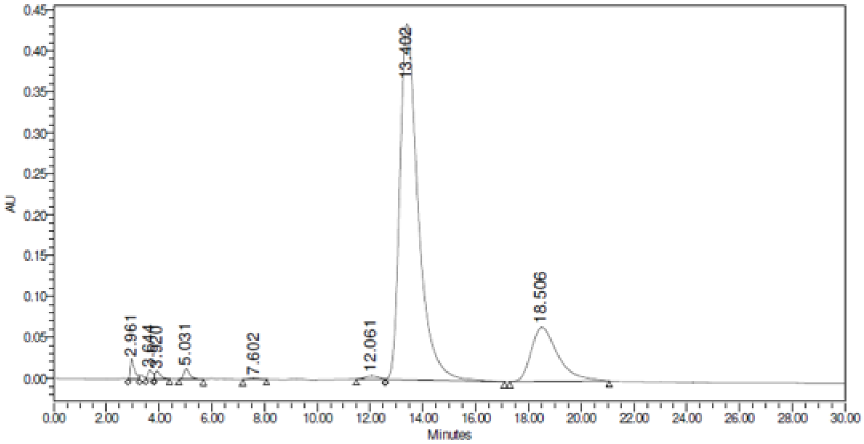
Following the General Procedure, using $Pd(TFA)_2$ (0.0025 g, 0.007 mmol, 5% mol), chiral ligand **L1** (0.0031 g, 0.015 mmol, 10%mol), cyclopent-3-en-1-ol (**4**) (0.038 g, 0.45 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.031 g, 0.15 mmol) and heteroaryl diazonium salt **1l** (0.05 g, 0.15 mmol) in dry MeOH (2.15 mL, 14.3 mL/mmol), the pure title compound (0.016 g, 33%) was obtained and purified as a *cis*-isomer with a 64%*e.e.*

Figure S1. Chiral HPLC analysis of racemic compound **2l**.



	RT	Area	% Area	Height
1	3.069	78408	0.12	5512
2	4.012	16539455	26.14	1273593
3	13.391	22881916	36.16	422312
4	18.160	23781888	37.58	297224

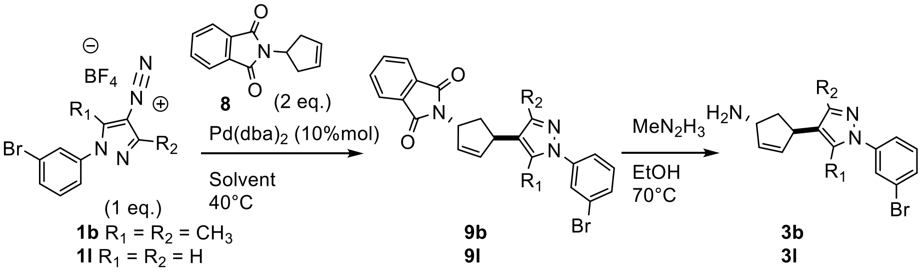
Figure S2. Chiral HPLC analysis of enantio-enriched compound **2l.**



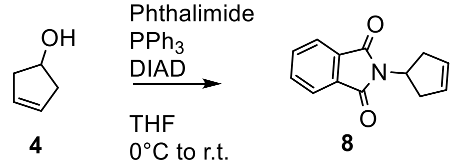
	RT	Area	% Area	Height
1	2.961	265675	1.00	24184
2	3.644	130277	0.49	10453
3	3.920	136633	0.51	9554
4	5.031	202101	0.76	12576
5	7.602	55913	0.21	1881
6	12.061	159267	0.60	4135
7	13.402	21024024	78.96	435018
8	18.506	4653294	17.48	65847

3.8 Synthesis of 4-pyrazolylcyclopent-2-en-1-amines **3b,l**.

Scheme S12. General synthesis of 4-pyrazolyl-cyclopentenamines **3b,l** via Heck-Matsuda reaction.



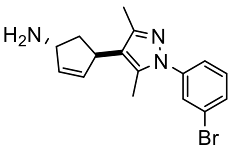
*2-(3-Cyclopenten-1-yl)-1H-isoindole-1,3(2H)-dione (**8**)*



In a round-bottom flash cyclopenten-1-ol (**4**) (0.2 g, 2.38 mmol, 1.0 eq.), phthalimide (0.418 g, 2.85 mmol, 1.2 eq.) and PPh$_3$ (0.746 g, 2.85 mmol, 1.2 eq.) were sequentially added under argon atmosphere. The reagents were dissolved in THF (23 mL, 10 mL/mmol) and the system cooled at 0°C, then DIAD (559 µL, 1.2 eq.) was added dropwise. The reaction was monitored by TLC until complete conversion of **4** (ca. 60 min). TBME (50 mL) was added and the crude mixture transferred into a separatory funnel. The organic phase was washed (3x) with NaOH (1M) and brine, dried over Na$_2$SO$_4$ and evaporated under vacuum. The crude mixture was purified by flash column chromatography, using cyclohexane/TBME 10%, to give the pure product **8** (0.328 g, 65%). **^{1}H NMR** (400 MHz, CDCl3) δ 7.88 – 7.78 (m, 2H), 7.71 (td, J = 4.9, 2.5 Hz, 2H), 5.80 (d, J = 6.3 Hz, 2H), 5.01 (tt, J = 9.7, 7.3 Hz, 1H), 2.85 (dd, J = 14.6, 7.3 Hz, 2H), 2.68 (ddd, J = 14.2, 9.8, 4.8 Hz, 1H).

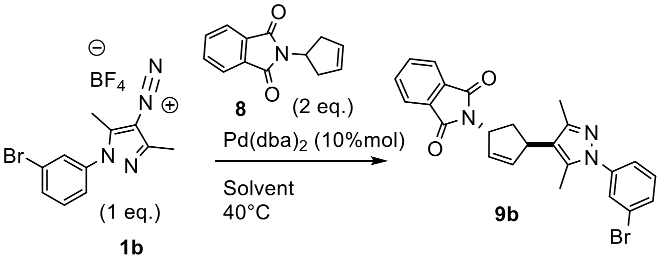
[^{1}H NMR data as reported in the literature.][2]

(1R,4R*)-4-(1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-amine (**3b**)*



Step 1. *2-((1R*,4R*)-4-(1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-yl) isoindoline-1,3-dione (**9b**)*

Scheme S13. Synthesis of protected phthalamido-cyclopentene **9b** via Heck-Matsuda reaction.



In a round-bottom flask Pd(dba)$_2$ (0.008 g, 0.014 mmol, 10% mol) and **8** (0.058 g, 0.27 mmol, 2.0 eq.), were mixed with the selected solvent (EtOH, DMA or MeCN/H$_2$O (1:1)) (12.5 mL/mmol). The mixture was heated at 40°C and the diazonium salt **1b** (0.05 g, 0.14mmol, 1.0 eq.) was added. The reaction was monitored by TLC (using β-naphthol spot test) and left to run for the described time (Table S1). The reaction was quenched with NaHCO$_3$ (3.0 eq.) and the crude mixture filtered over a short pad of Celite® washing few times with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na$_2$SO$_4$ and the solvent removed under vacuum. The crude product was purified by flash column chromatography using cyclohexane/TBME 15% to give desired 4-pyrazolyl-cyclopentenamine **9b**.

Table S2. Synthesis of **9b** via heteroaryl Heck-Matsuda reaction using diazonium salt **1b.**

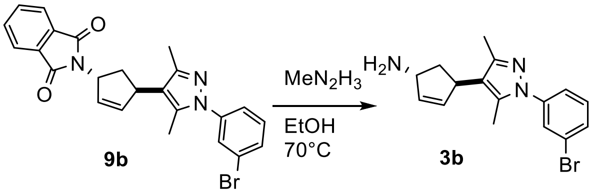
Entry	Solvent	time (h)	Yield	d.r. (*cis*:*trans)*
1	EtOH	20	23%	77 : 23
2	DMA	4	50%	25 : 75
3	MeCN/H$_2$O (1:1)	20	21%	<1 : 99

2-((1R,4R*)-4-(1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-yl)isoindoline-1,3-dione (**9b**) (entry 3, Table S2)*

In a round-bottom flask Pd(dba)$_2$ (0.008 g, 0.014 mmol, 10% mol) and **8** (0.058 g, 0.27 mmol, 2.0 eq.), were mixed with MeCN/H$_2$O (1:1) (12.5 mL/mmol) (entry 3, Table S2). The mixture was heated at 40°C and the diazonium salt **1b** (0.05 g, 0.14 mmol, 1.0 eq.) was added. The reaction was monitored by TLC (using β-naphthol spot test) and left to run for 20h. The reaction was quenched with NaHCO$_3$ (3.0 eq.) and the crude mixture filtered over a short pad of Celite® washing few times with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na$_2$SO$_4$ and the solvent removed under vacuum. The crude product was purified by flash column chromatography using cyclohexane/TBME 15% to give desired 4-pyrazolyl-cyclopentenamine **9b** (0.013 g, 21%), as a *trans*-diastereoisomer (*cis*:*trans* *d.r.* < 1 : 99). TLC: R_f 0.3 (cycloexane/TBME 30%). UPLC-MS: t_R = 1.89 min (apolar method); MS (ESI) *m/z* calcd. for $C_{24}H_{20}BrN_3O_2$ $[M+H]^+$: 462.34, found: 462.9. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{24}H_{20}BrN_3O_2$: 462.0812 found: 462.0817. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.89 – 7.75 (m, 2H), 7.75 – 7.66

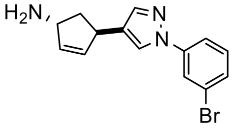
(m, 2H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.34 (dt, *J* = 15.6, 7.9 Hz, 2H), 6.09 (d, *J* = 5.5 Hz, 1H), 5.73 (dt, *J* = 5.4, 2.6 Hz, 1H), 5.61 (d, *J* = 9.8 Hz, 1H), 4.54 (s, 1H), 2.55 (ddd, *J* = 14.4, 8.8, 2.7 Hz, 1H), 2.28 (d, *J* = 2.4 Hz, 7H). **^{13}C NMR** (101 MHz, CDCl$_3$): δ 168.2, 148.3, 141.2, 139.9, 136.4, 134.1, 132.2, 130.3, 128.1, 127.5, 123.4, 123.3, 122.6, 119.6, 56.0, 41.4, 36.4, 27.0, 12.8, 11.3.

Step 2. *(1R*,4R*)-4-(1-(3-Bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-amine (**3b**)*

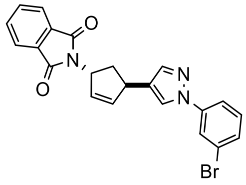


In a round-bottom flash compound **9b** (0.013 g, 0.028 mmol, 1.0 eq.) was suspended with EtOH (0.3 mL, 10 mL/mmol) and methylhydrazine (5 µL, 0.084 mmol, 3 eq.) was added. The reaction was heated at 70°C overnight. Upon full conversion of the starting material (monitored by TLC), the solvent was evaporated under vacuum and the crude product purified by flash chromatographic column, using DCM/MeOH 5% (ca 1% NH$_3$) to give the pure product **3b** (0.009 g, *quant.*), as yellow oil, as a *trans*-diastereoisomer. TLC: R$_f$ 0.15 (DCM/MeOH 10%). UPLC-MS: t$_R$ = 1.65 min (generic method); MS (ESI) *m/z* calcd. for C$_{16}$H$_{18}$BrN$_3$ [M+H]$^+$: 331.07, found: 332.9. HRMS-ESI: m/z [M-NH$_2$+H]$^+$ calcd. for C$_{16}$H$_{18}$BrN$_3$: 315.0491 found 315.0489. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.56 (t, *J* = 1.9 Hz, 1H), 7.42 (dt, *J* = 7.4, 1.7 Hz, 1H), 7.35 – 7.24 (m, 2H), 5.87 (dt, *J* = 5.2, 2.4 Hz, 1H), 5.77 (dt, *J* = 5.4, 1.6 Hz, 1H), 4.17 (s, 1H), 4.05 (tt, *J* = 6.7, 2.4 Hz, 1H), 2.18 (d, *J* = 3.7 Hz, 6H), 2.13 – 1.93 (m, 2H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 141.2, 135.8, 135.3, 130.2, 128.1, 123.4, 122.6, 119.9, 58.0, 42.5, 39.8, 12.69, 11.2.

(1R,4R*)-4-(1-(3-Bromophenyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-amine (**3l**)*



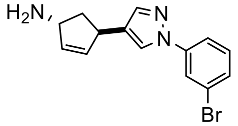
Step 1. *2-((1R*,4R*)-4-(1-(3-Bromophenyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-yl)isoindoline-1,3-dione (**9l**)*



In a round-bottom flask Pd(dba)$_2$ (0.009 g, 0.015 mmol, 10% mol) and **8** (0.063 g, 0.30 mmol, 2 eq.), were mixed with MeCN/H$_2$O (1:1) (12.5 mL/mmol). The mixture was heated at 40°C and the heteroaryl diazonium salt **1l** (0.05 g, 0.15 mmol, 1.0 eq.) was added. The reaction was monitored by TLC (using β-naphthol spot test) and kept to run for 5h. Despite the reaction was not complete, it was quenched with

$NaHCO_3$ (3.0 eq.) and the crude mixture filtered over a short pad of Celite® washing few times with AcOEt. The organic phase was transferred into a separatory funnel, washed with brine, dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was purified by flash column chromatography using cyclohexane/TBME 15% to give desired 4-pyrazole-cyclopentenamine (0.032 g, 50%), as white solid, as a *trans*-diastereoisomer (*cis:trans d.r.* < 1 : 99) TLC: R_f 0.21 (cycloexane/TBME 30%). UPLC-MS: t_R = 1.87 min (apolar method); MS (ESI) m/z calcd. for $C_{22}H_{16}BrN_3O_2$ $[M+H]^+$: 434.28, found: 434.9. HRMS-ESI: m/z $[M+NH_4]^+$ calcd. for $C_{22}H_{16}BrN_3O_2$: 434.0499 found: 434.0502. ^{1}**H NMR** (400 MHz, CDCl3): δ 7.88 (t, J = 2.3 Hz, 1H), 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.75 – 7.70 (m, 3H), 7.60 (s, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 6.16 (dt, J = 5.6, 2.1 Hz, 1H), 5.78 (dt, J = 5.2, 2.4 Hz, 1H), 5.57 (ddd, J = 9.1, 4.2, 2.1 Hz, 1H), 4.53 – 4.45 (m, 1H), 2.64 (ddd, J = 13.1, 8.6, 4.1 Hz, 1H), 2.25 (ddd, J = 14.2, 9.3, 5.4 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 168.2, 141.3, 140.6, 138.9, 134.5, 134.1, 132.2, 129.2, 128.6, 127.6, 124.3, 123.7, 123.3, 122.1, 117.3, 55.8, 41.1, 38.1.

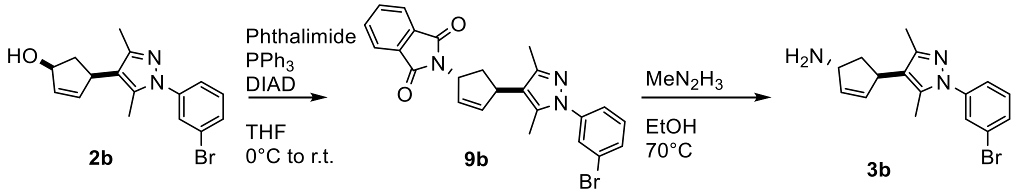
Step 2. *(1R*,4R*)-4-(1-(3-Bromophenyl)-1H-pyrazol-4-yl)cyclopent-2-en-1-amine (**3l**).*



In a round-bottom flash compound **9l** (0.032 g, 0.075 mmol, 1 eq.) was suspended with EtOH (0.8 mL, 10 mL/mmol), and methylhydrazine (12 µL, 0.225 mmol, 3 eq.) were added. The reaction is heat at 70°C for one night. The next day, the reaction was monitored by TLC to control the full conversion of starting material and reactive intermediates. The solvent in evaporated under vacuum and the crude was purified by flash chromatographic column, using DCM/MeOH 5% (1% of NH_3) to give pure product **3l** (0.022 g, *quant.*), as yellow oil, as a *trans*-diastereoisomer. TLC: R_f 0.15 (DCM/MeOH 10%). UPLC-MS: t_R = 1.38 min (generic method); MS (ESI) m/z calcd. for $C_{14}H_{14}BrN_3$ [M+H]+: 304.18, found: 304.9. HRMS-ESI: m/z $[M-NH_2+H]^+$ calcd. for $C_{14}H_{14}BrN_3$: 287.0178 found: 287.0183 ^{1}**H NMR** (400 MHz, $CDCl_3$): 7.84 (t, J = 2.0 Hz, 1H), 7.65 (s, 1H), 7.58 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 7.52 (s, 1H), 7.37 (dt, J = 8.2, 1.3 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 5.89 (s, 2H), 4.17 (dd, J = 7.6, 4.5 Hz, 1H), 4.08 – 4.02 (m, 1H), 2.19 (ddd, J = 13.3, 7.5, 4.7 Hz, 1H), 2.02 (ddd, J = 13.2, 8.4, 4.6 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 141.2, 140.5, 136.7, 134.7, 130.7, 128.1, 123.9, 123.1, 121.9, 117.1, 77.2, 57.5, 44.2, 39.7.

3.8.1 Alternative synthesis of (1*R**,4*R**)-4-[1-(3-bromophenyl)-3,5-dimethyl-pyrazol-4-yl]cyclopent-2-en-1-amine (**3b**) via Mitsunobu reaction

Scheme S14. Synthesis of *trans*-cyclopentenamine **3b**.



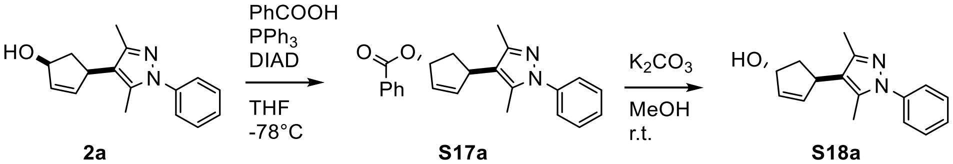
Step 1. In a round-bottom flash *cis*-cyclopenten-1-ol **2b** (0.052 g, 0.155 mmol, 1.0 eq.), phthalimide (0.027 g, 0.186 mmol, 1.2 eq.) and PPh_3 (0.049 g, 0.186 mmol, 1.2 eq.) were sequentially added under argon atmosphere. The reagents were dissolved in THF (1.6 mL, 10 mL/mmol) and the system cooled at 0°C, then DIAD (37 µL, 1.2 eq.) was added dropwise. The reaction was monitored by TLC until complete conversion of **2b** (ca. 30 min). TBME (10 mL) was added and the crude mixture transferred into a separatory funnel. The organic phase was washed (3x) with NaOH (1M) and brine, dried over Na_2SO_4 and evaporated under vacuum. The crude mixture was purified by flash column chromatography, using cyclohexane/TBME 15%, to give the pure product **9b** (0.043 g, 60%), as a *trans*-diastereoisomer.

Step 2. In a round-bottom flash compound **9b** (0.043 g, 0.093 mmol, 1.0 eq.) was suspended with EtOH (0.9 mL, 10 mL/mmol) and methylhydrazine (15 µL, 0.279 mmol, 3 eq.) was added. The reaction was heated at 70°C overnight. Upon full conversion of the starting material (monitored by TLC), the solvent was evaporated under vacuum and the crude product purified by flash chromatographic column, using DCM/MeOH 5% (ca. 1% NH_3) to give the pure product **3b** (0.03 g, *quant.*).

4 Miscellaneous reactions

4.1 Synthesis of *trans*-4-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**S18a**) via Mitsunobu reaction

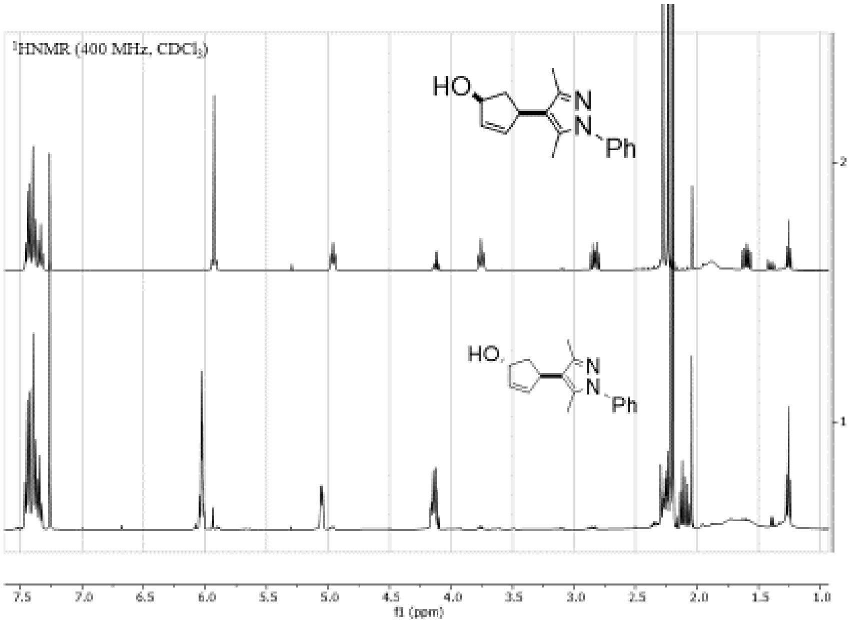
Scheme S12. Synthesis of *trans*-cyclopentenol **S18a.**



Step 1. In a round-bottom flash cyclopenten-1-ol **2a** (0.029 g, 0.11 mmol, 1.0 eq.), PhCOOH (0.022 g, 0.18 mmol, 1.5 eq.) and PPh_3 (0.047 g, 0.18 mmol, 1.5 eq.) were sequentially added under argon atmosphere. The reagents were dissolved in THF (0.8 mL, 6.6 mL/mmol) and the system cooled at -78°C, then DIAD (35 µL, 1.5 eq.) was added dropwise. The reaction was monitored by TLC until complete conversion of staring alcohol (ca. 30 min). $NaHCO_3$ (aq.) was added and the crude mixture transferred into a separatory funnel. The water phase was extracted with AcOEt, then the combined organic phase washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude mixture was purified by flash column chromatography, using cyclohexane/TBME 10%, to give pure product **S17a** (0.036 g, 90%).

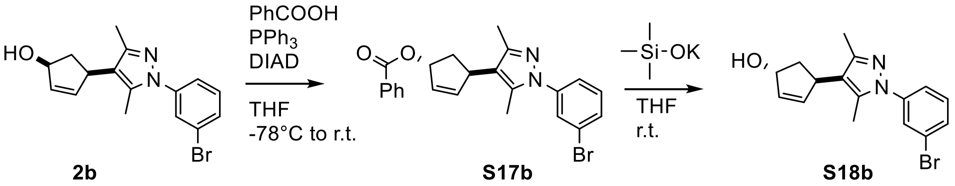
Step 2. In a round-bottom flash benzoic ester **S17a**, K_2CO_3 (0.028 g, 2.0 eq.) and methanol (0.2 mL, 2 mml/mmol) were mixed. The reaction was kept at room temperature for 3 h, then quenched with H_2O and the corresponding crude mixture transferred into a separatory funnel adding AcOEt. The separated organic phase was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash column chromatography, using cyclohexane/AcOEt 30% to give the title compound **S18a** (0.021 g, 80%), as a brown glass, as *trans*-diastereoisomer (*cis*:*trans d.r.* > 1 : 99). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 1.65 min; MS (ESI) m/z $(M+H)^+$ found: 255.1. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 – 7.35 (m, 5H), 6.07 – 6.00 (m, 2H), 5.05 (dq, *J* = 6.9, 1.9 Hz, 1H), 4.15 (tt, *J* = 6.9, 1.6 Hz, 1H), 2.33 – 2.19 (m, 8H), 2.20 (d, *J* = 8.9 Hz, 6H), 2.11 – 2.05 (m, 1H).

Figure S3. ^{1}H NMR spectra of *cis*-**2a** and *trans*-**S18a**.



4.2 Synthesis of *trans*-4-(1-(3-bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)cyclopent-2-en-1-ol (**S18b**) via Mitsunobu reaction.

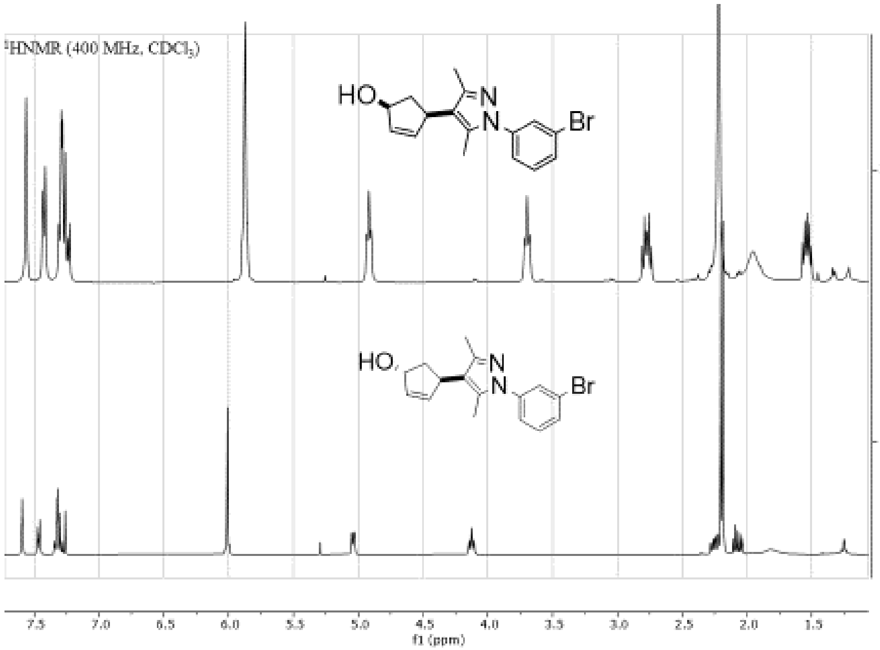
Scheme S13. Synthesis of *trans*-cyclopentenol **S18b**.



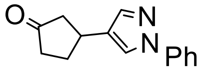
Step 1. In a round-bottom flash cyclopenten-1-ol **2b** (0.134 g, 0.40 mmol, 1.0 eq.), PhCOOH (0.053 g, 0.44 mmol, 1.5 eq.) and PPh_3 (0.115 g, 0.44 mmol, 1.5 eq.) were sequentially added under argon atmosphere. The reagents were dissolved in THF (0.8 mL, 6.6 mL/mmol) and the system cooled at -78°C, then DIAD (130 µL, 0.44 mmol, 1.5 eq.) was added dropwise. The reaction was monitored by TLC until complete conversion of staring alcohol (ca. 30 min). $NaHCO_3$ (aq.) was added and the crude mixture transferred into a separatory funnel. The water phase was extracted with AcOEt, then the combined organic phase washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude mixture was purified by flash column chromatography, using cyclohexane/TBME 10%, to give pure product **S17b** (0.138 g, 76%).

Step 2. In a round-bottom flash benzoic ester **S17b** (0.138 g, 0.3 mmol, 1.0 eq.) was dissolved in THF (6.0 ml, 20 mL/mmol). Potassium trimethylsilanolate (0.194 g, 1.5 mmol, 5.0 eq.) was added and the reaction was left at room temperature until the complete conversion of the starting alcohol (ca. 12 h). The crude reaction was quenched with H_2O and the corresponding crude mixture transferred into a separatory funnel adding AcOEt. The separated organic phase was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by flash column chromatography, using cyclohexane/AcOEt 30%, to give the title compound **S18b** (0.043 g, 43%), as a brown glass, as *trans*-diastereoisomer (*cis*:*trans* *d.r.* > 1 : 99). TLC: R_f 0.5 (cycloexane/AcOEt 50%). UPLC-MS: t_R = 2.10 min; MS (ESI) m/z $(M+H)^+$ found: 333.0. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 1.9 Hz, 1H), 7.40 (dt, *J* = 7.2, 1.8 Hz, 1H), 7.30 – 7.18 (m, 1H), 5.94 (d, *J* = 2.1 Hz, 2H), 5.01 – 4.91 (m, 1H), 4.11 – 3.94 (m, 1H), 2.25 – 2.10 (m, 7H), 2.05 – 1.98 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.94, 140.92, 139.04, 136.07, 130.23 (d, *J* = 6.1 Hz), 128.05, 123.33, 122.53, 119.13, 41.88, 39.52, 12.54, 11.08.

Figure S4. ^{1}H NMR spectra of *cis*-**2b** and *trans*-**S18b**.



4.3 3-(1-Phenyl-1*H*-pyrazol-4-yl)cyclopentan-1-one (**S16**)

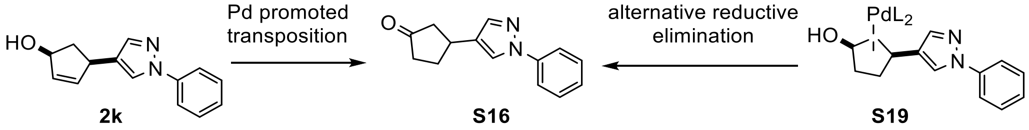


The compound was isolated as a side-product of the reaction and isolated (ca. 10%) after column flash chromatography (see compound **2k**, Paragraph 3.4 in this Section). Brown glass; TLC R_f: 0.5 (cycloexane/AcOEt 20%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.71 – 7.64 (m, 2H), 7.61 (s, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 3.43 (tt, *J* = 9.7, 6.6 Hz, 1H), 2.78 – 2.63 (m, 1H), 2.52 –

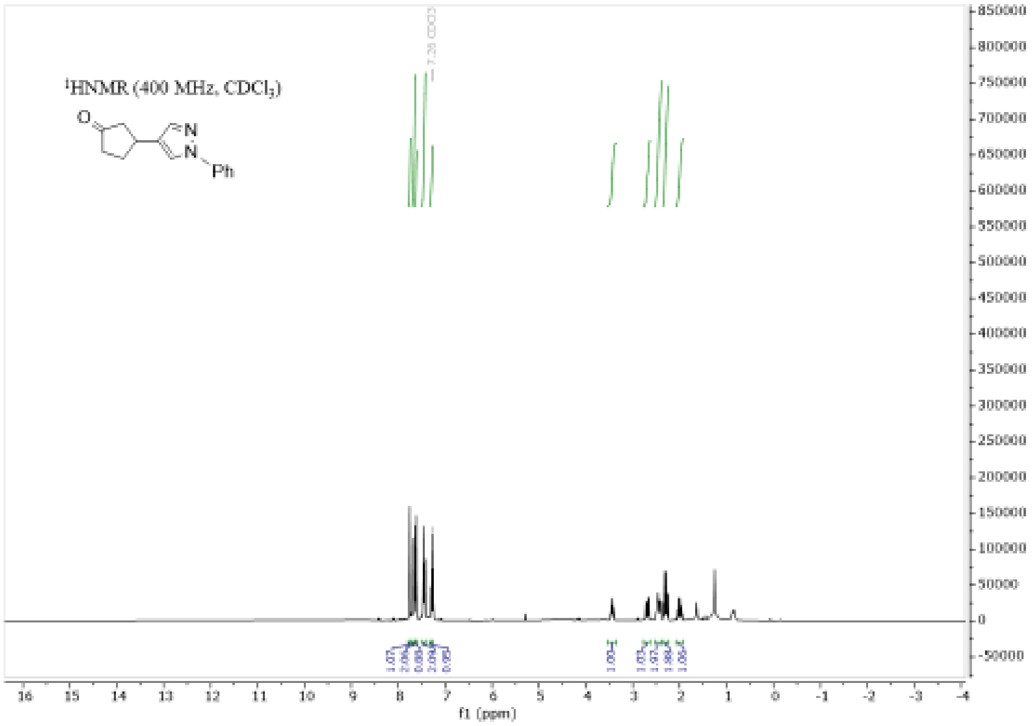
2.38 (m, 2H), 2.36 – 2.23 (m, 2H), 2.08 – 1.92 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 140.10, 139.45, 129.46, 126.45, 126.03, 123.99, 119.24, 118.98, 45.94, 38.27, 32.56, 31.08, 29.71.

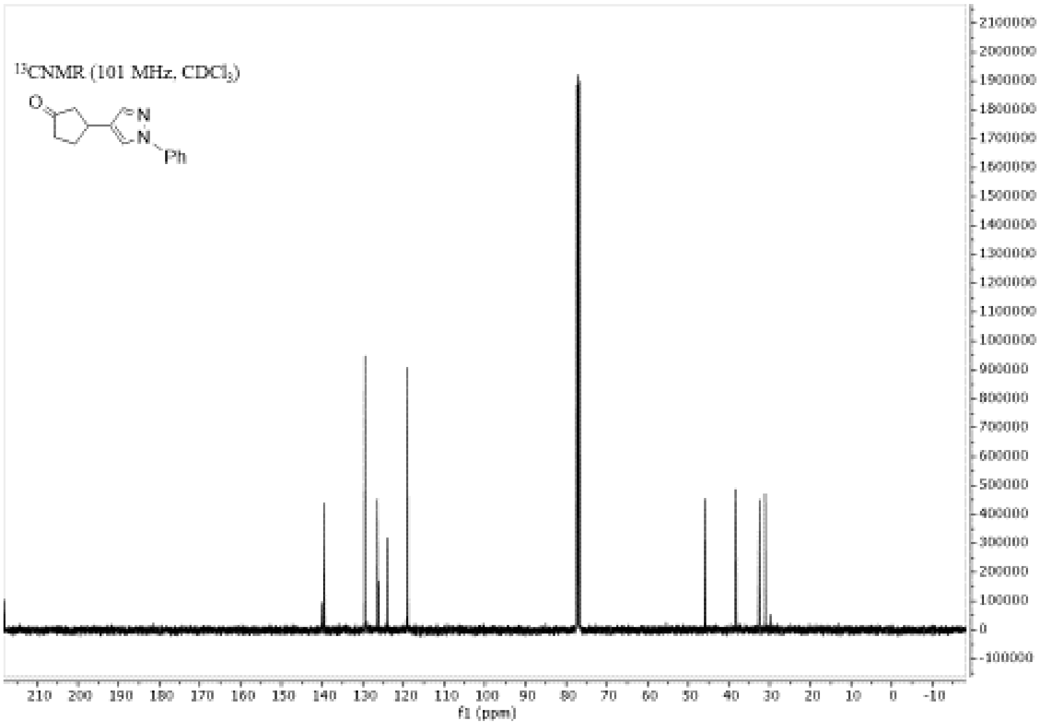
With the limited observations available, it is worth assuming that compound **S16** may derive either from a Pd "walking chain transposition"[3] post the Heck-Matsuda reaction or as an alternative reductive elimination side-product during the C-C bond formation (Scheme S17).[4]

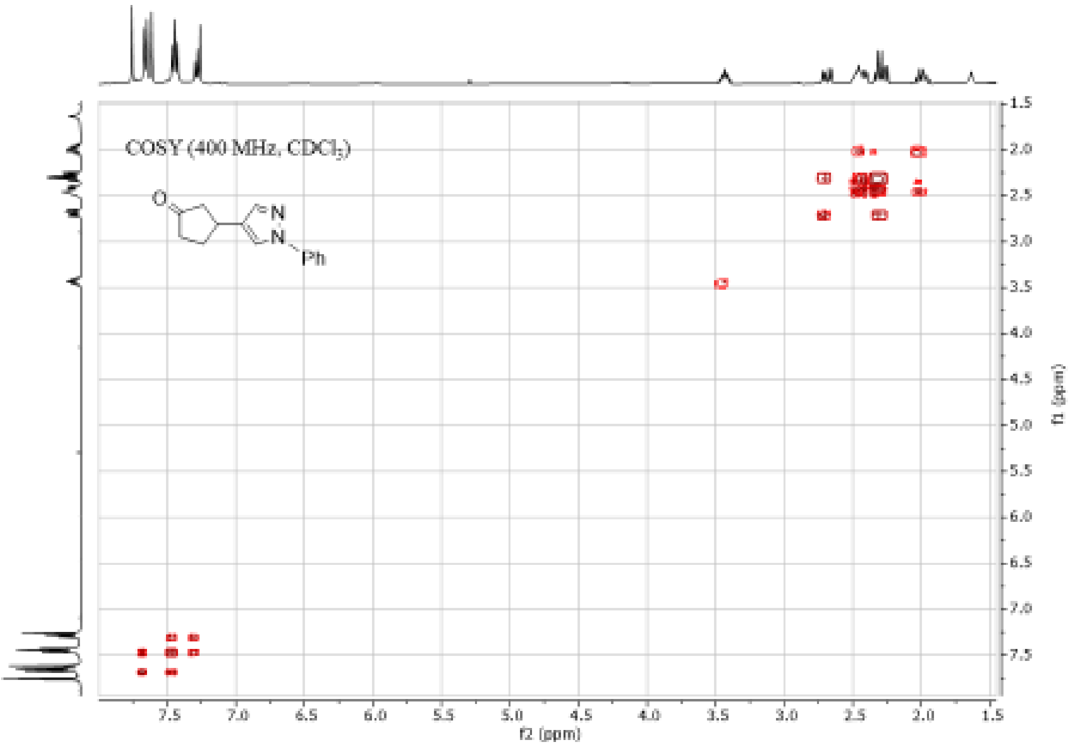
Scheme S14. Postulated, possible formation of side-product **S16.**

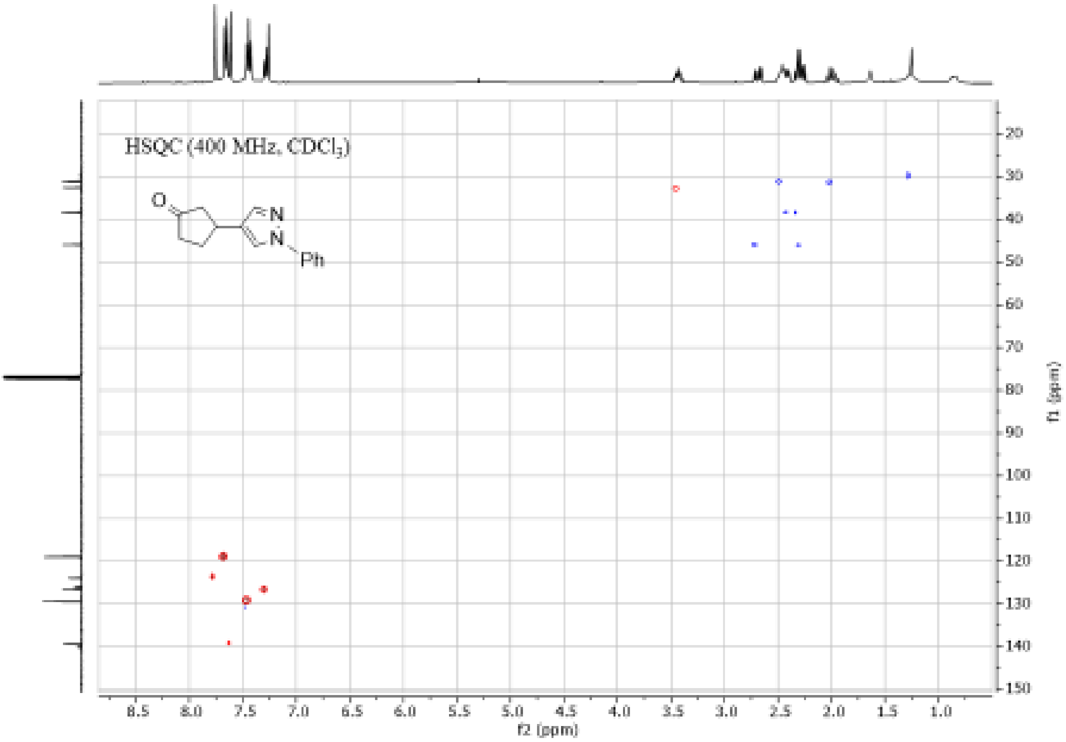


4.3.1 Full characterization by NMR (^{1}H, ^{13}C, COSY and HSQC) of compound **S16**.





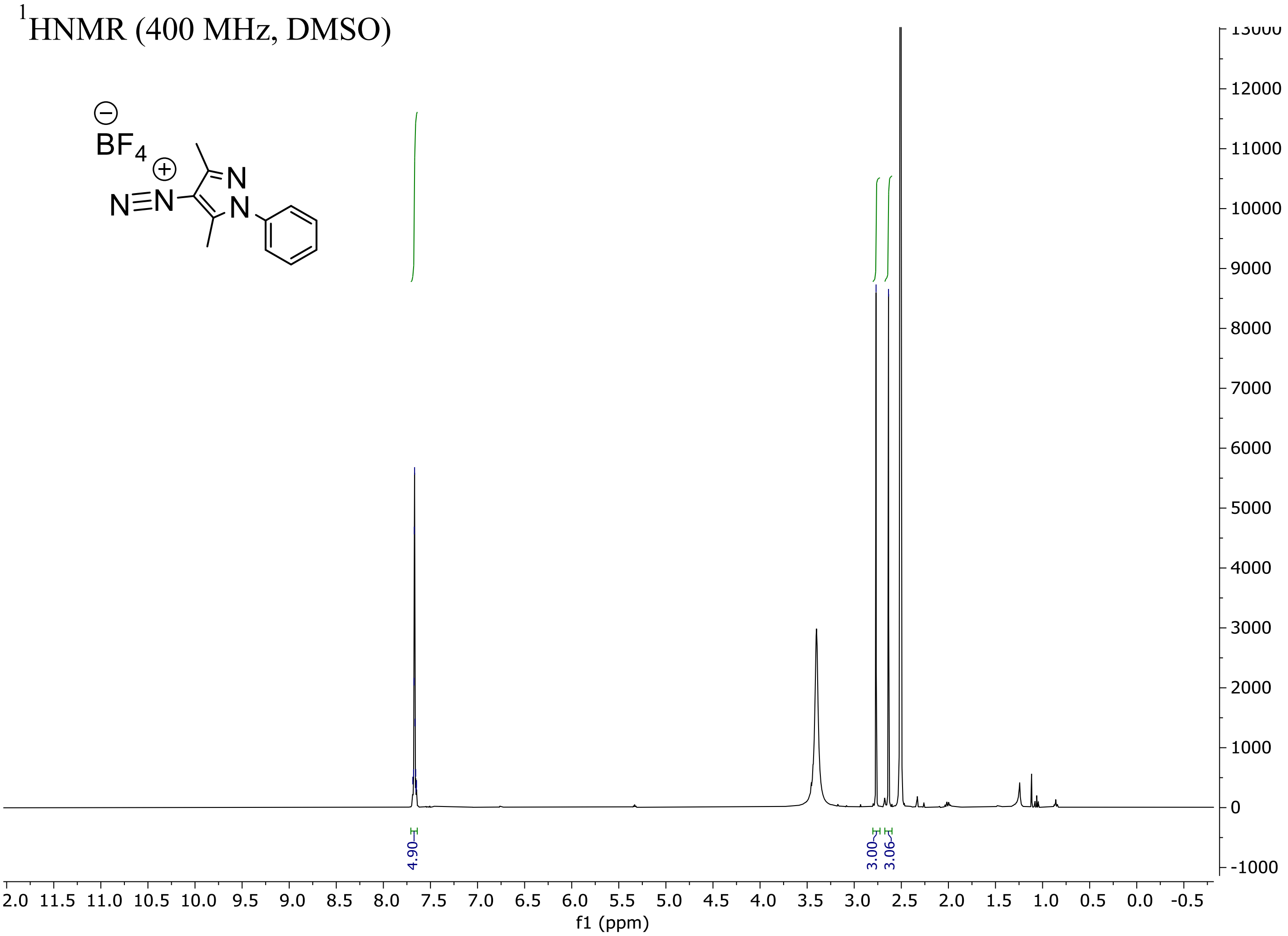

COSY (400 MHz, CDCl3)
O
N
N
Ph
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


HSQC (400 MHz, CDCl3)
O
N
N
Ph
f2 (ppm)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
20
30
40
50
60
70
80
90
100
110
120
130
140
150

5 NMR characterization of pyrazolyl diazonium tetrafluoroborate salts **1a-n**, 4-pyrazolyl-cyclopent-2-en-1-ols **2a-n** and 4-pyrazolyl-cyclopent-2-enamines **3b,l**.

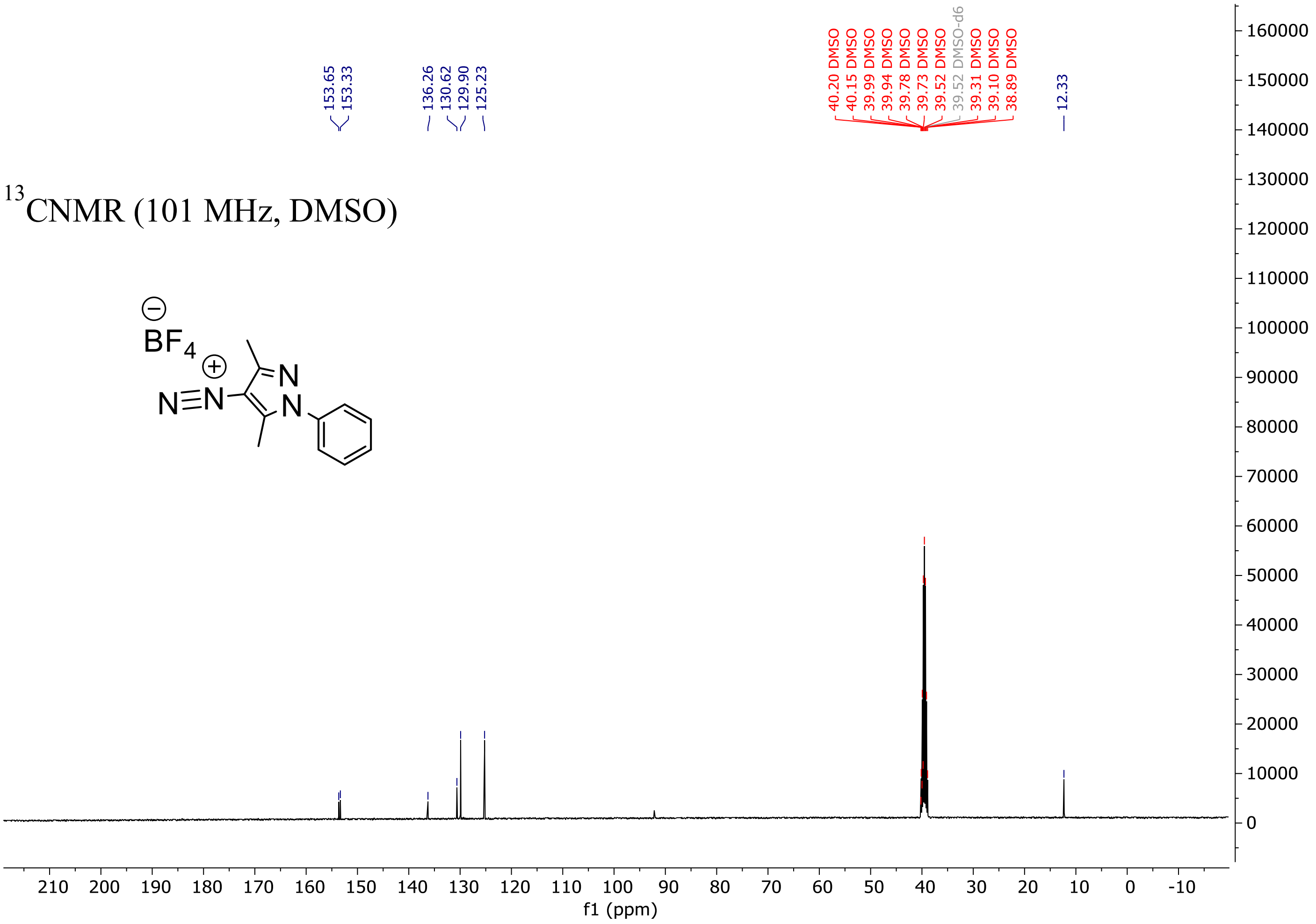
5.1 Pyrazolyl diazonium tetrafluoroborate salts **1a-n**

Compound 1a

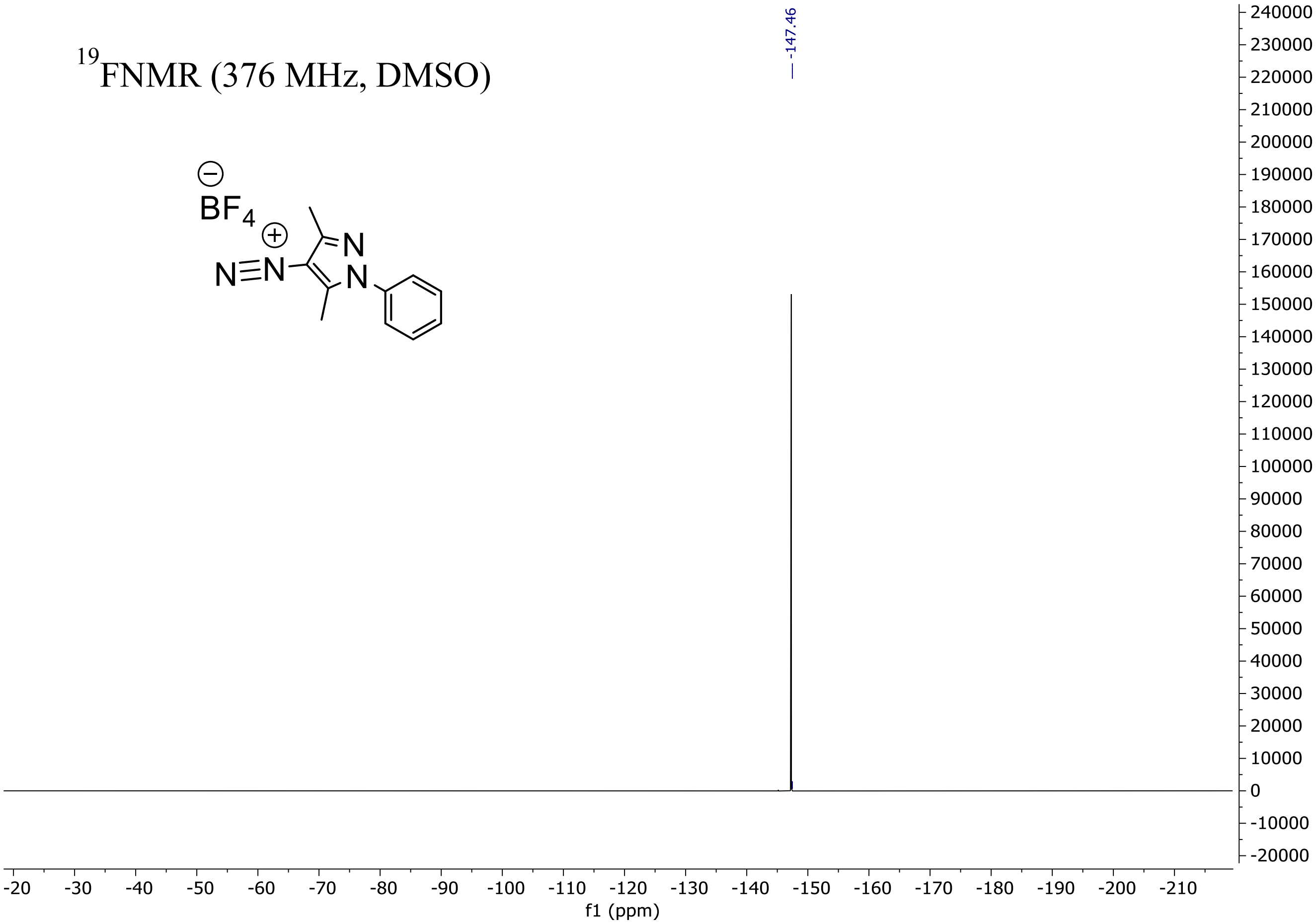


^{1}HNMR (400 MHz, DMSO)

^{13}CNMR (101 MHz, DMSO)

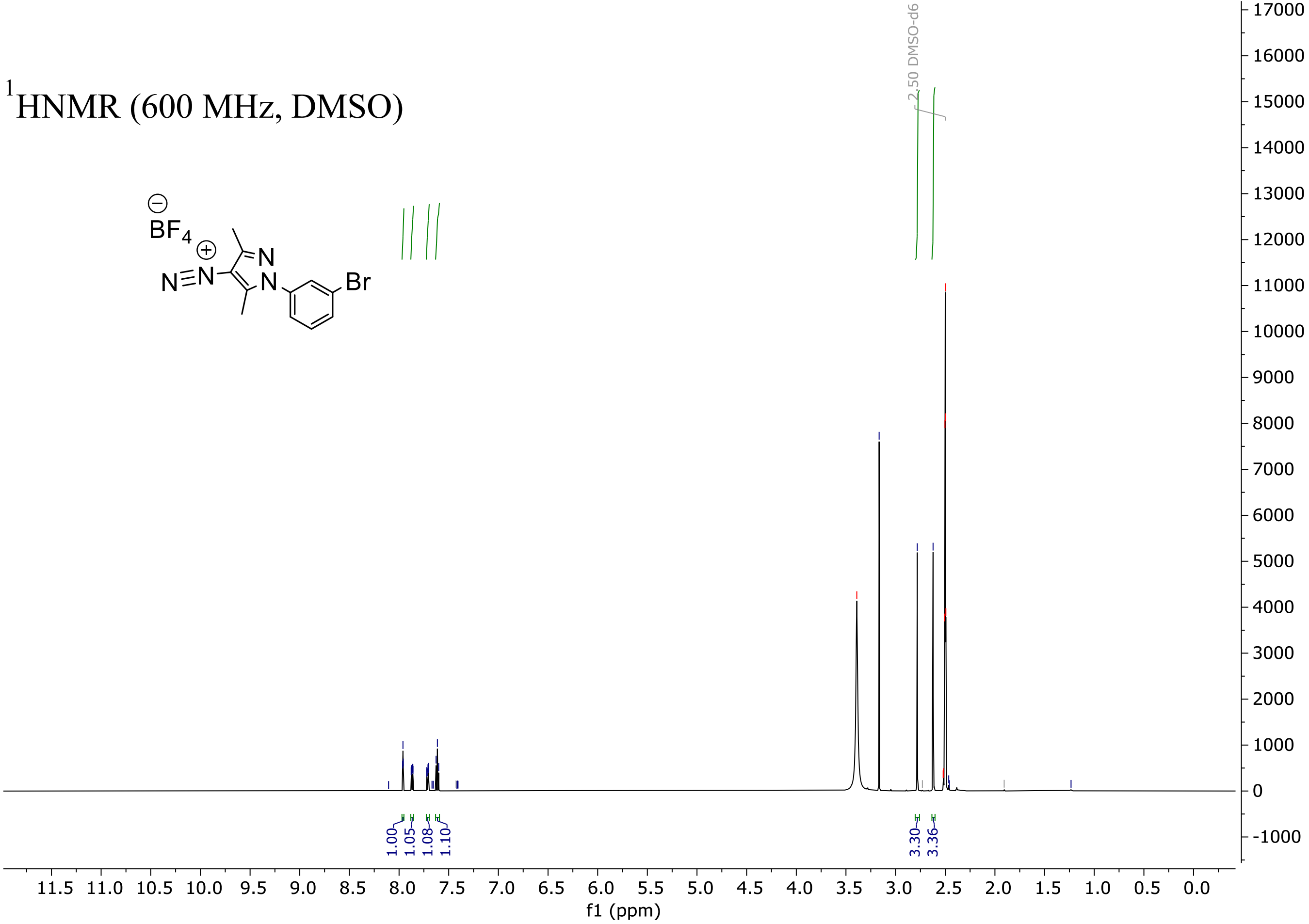


^{19}FNMR (376 MHz, DMSO)

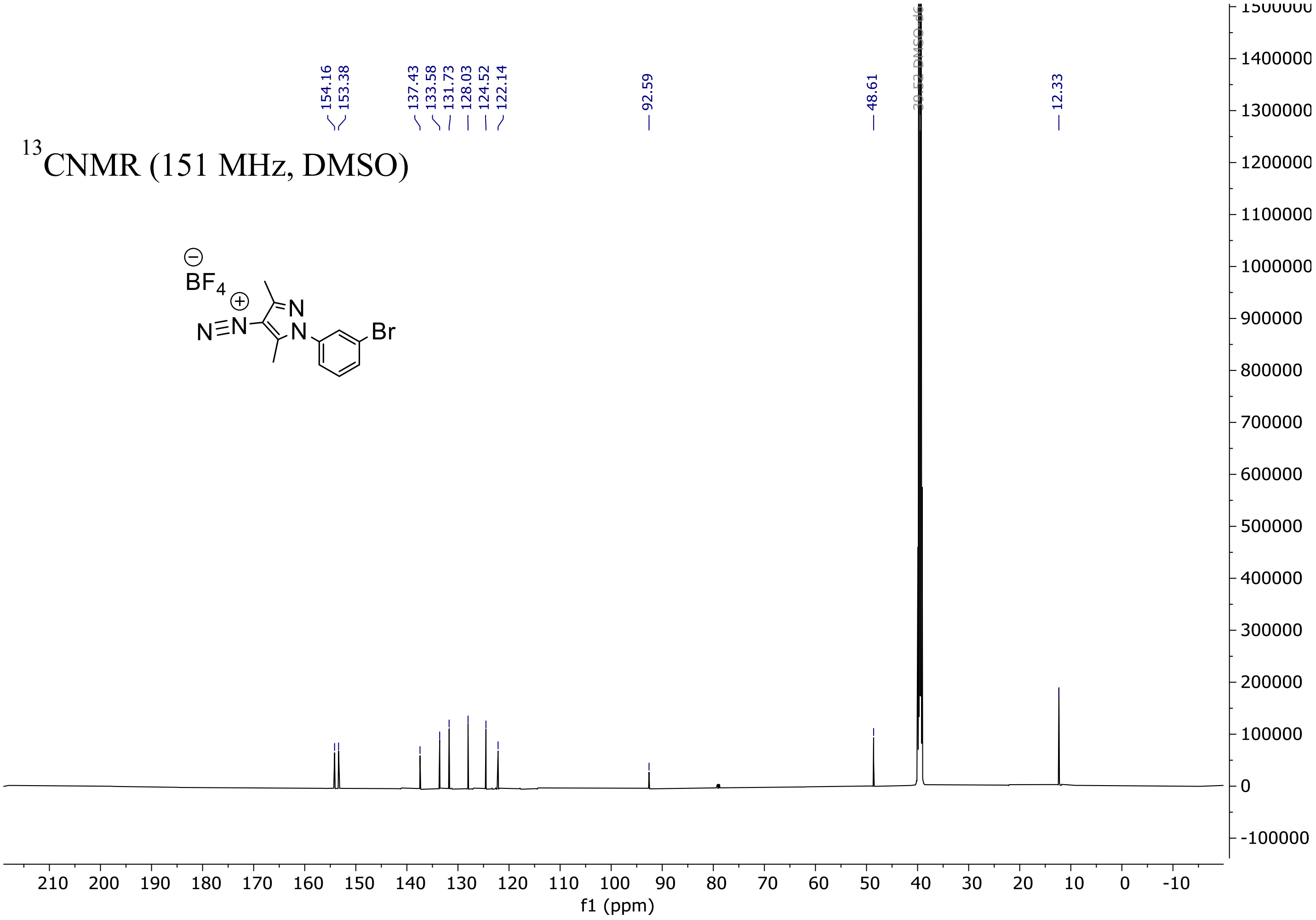


Compound 1b

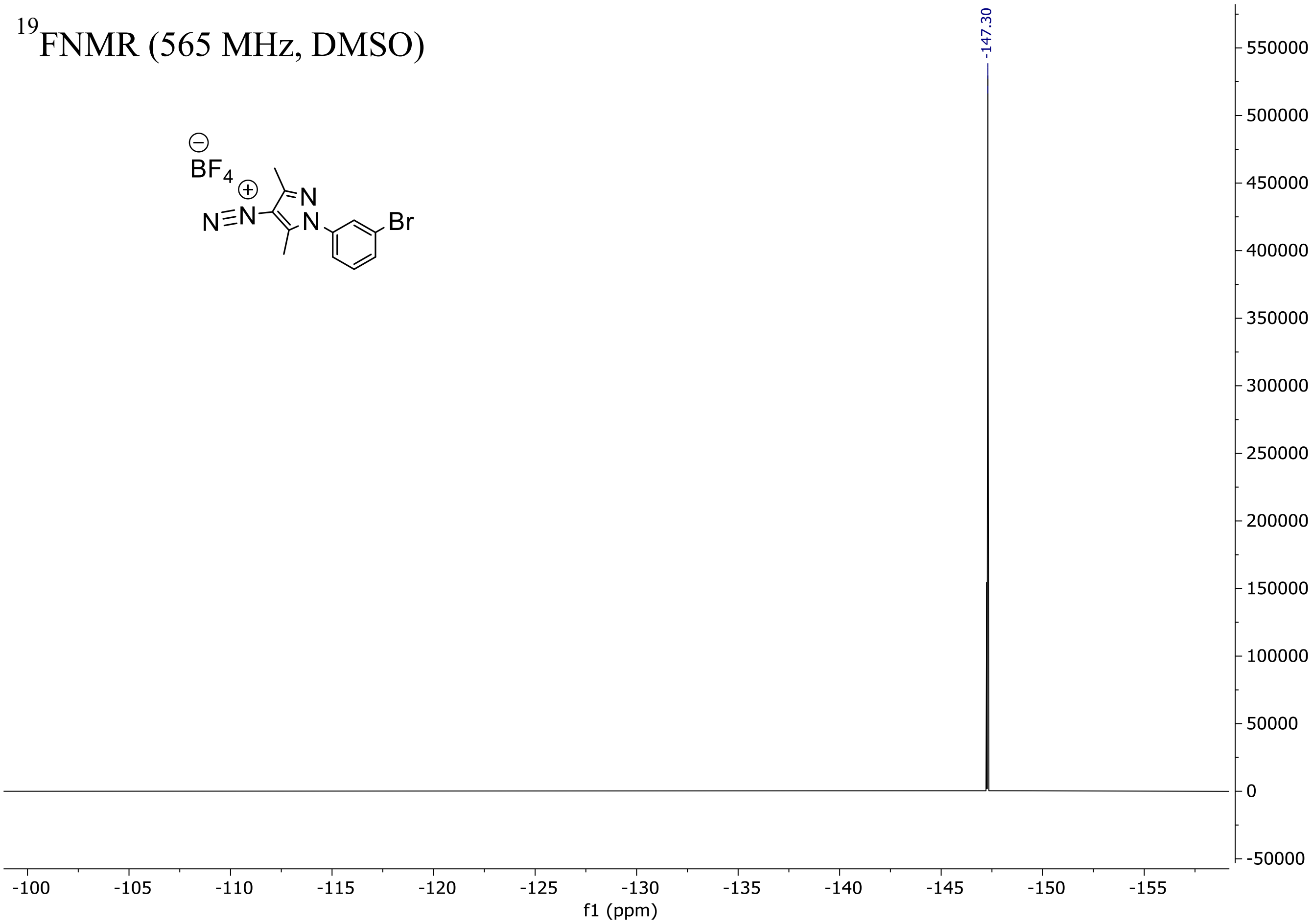
^{1}HNMR (600 MHz, DMSO)



^{13}CNMR (151 MHz, DMSO)

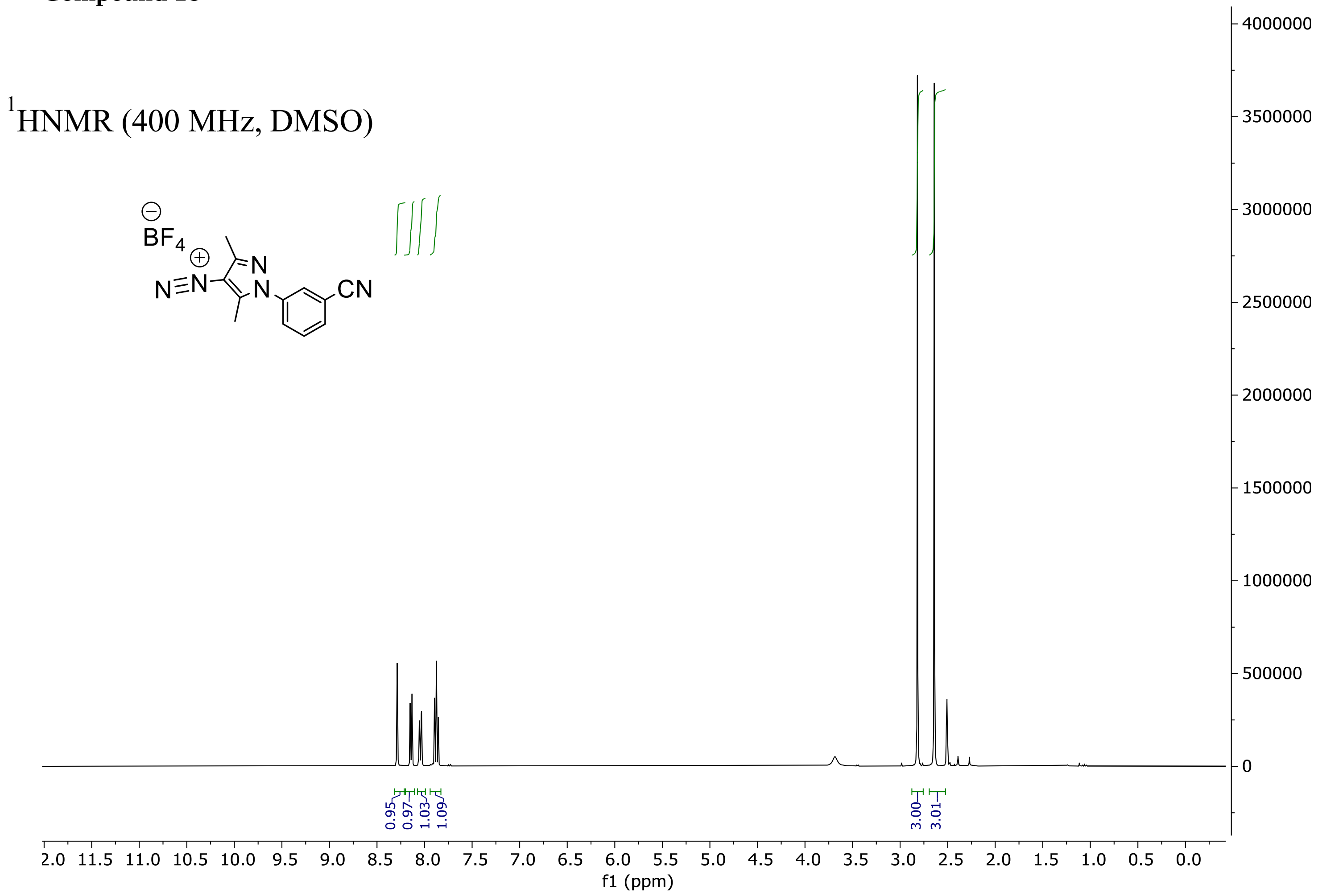


^{19}FNMR (565 MHz, DMSO)

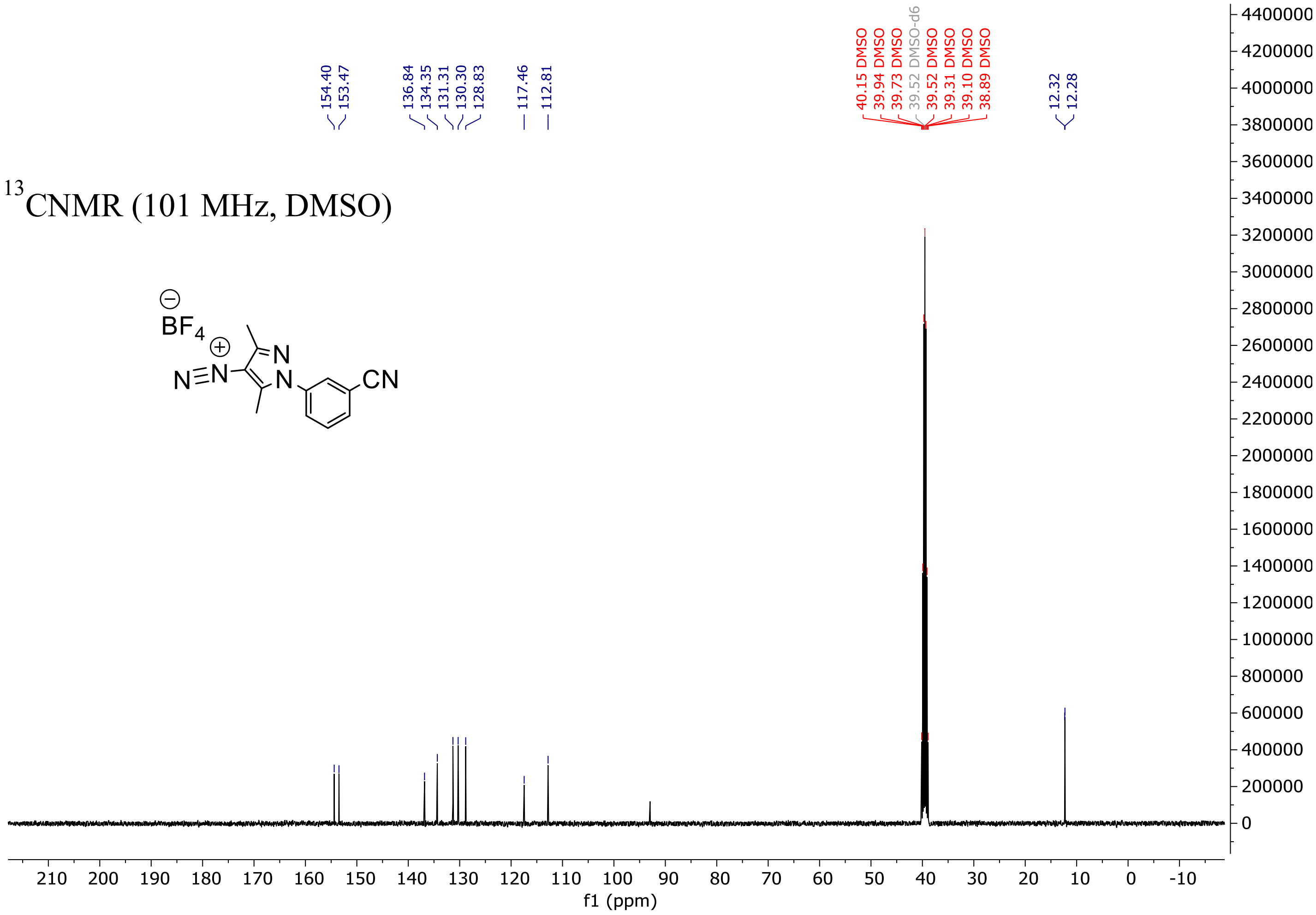


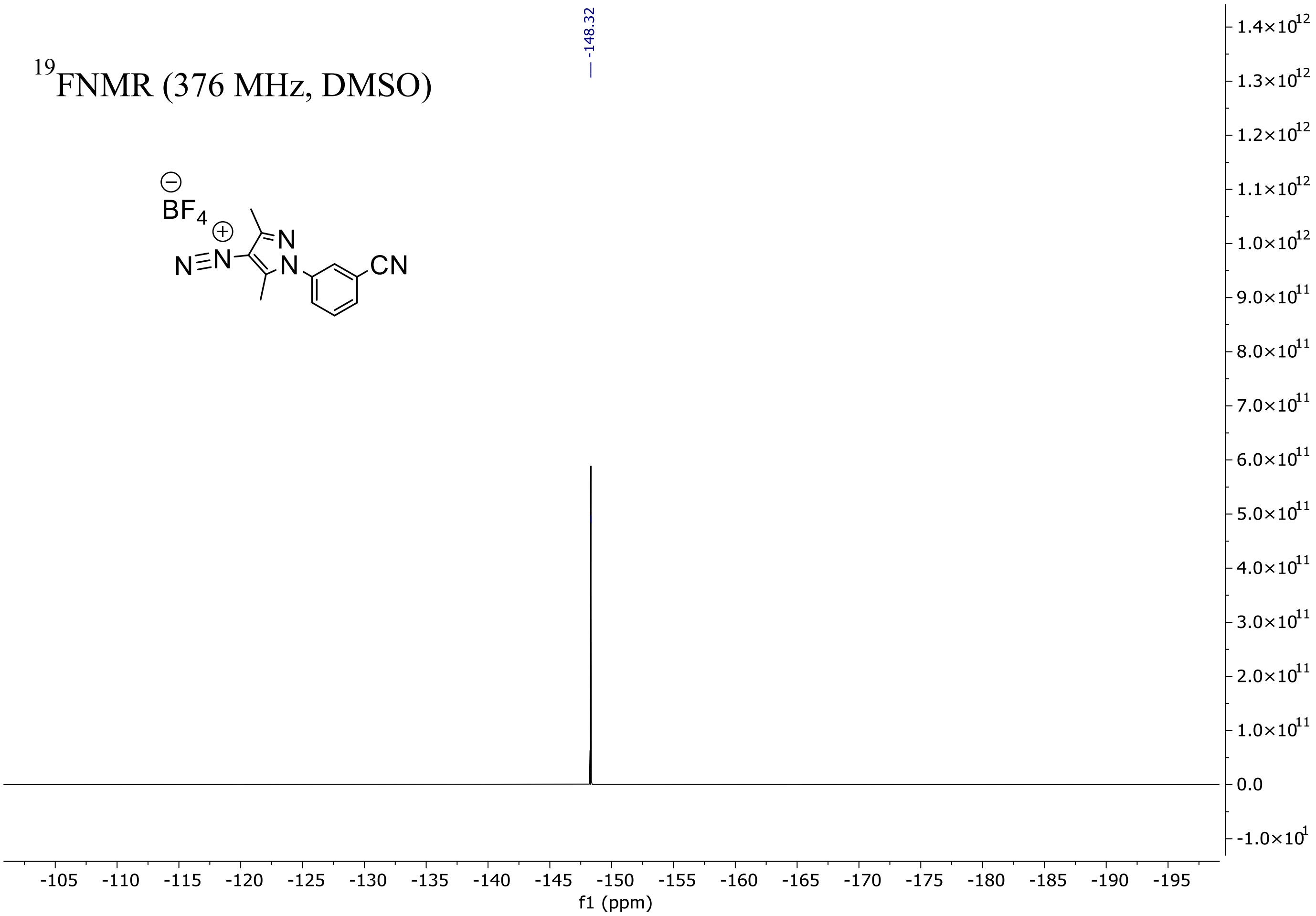
Compound 1c

^{1}HNMR (400 MHz, DMSO)



^{13}CNMR (101 MHz, DMSO)

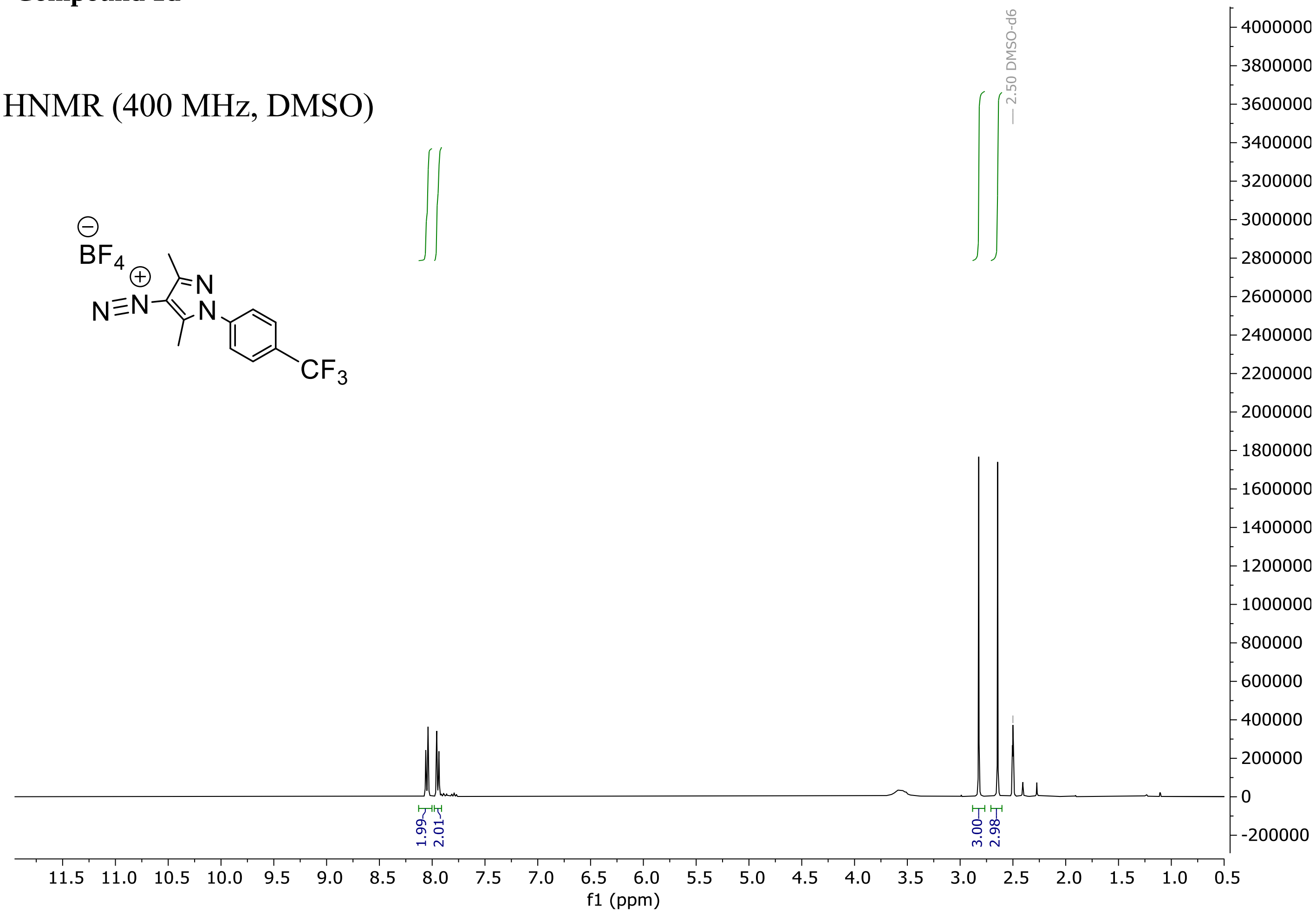


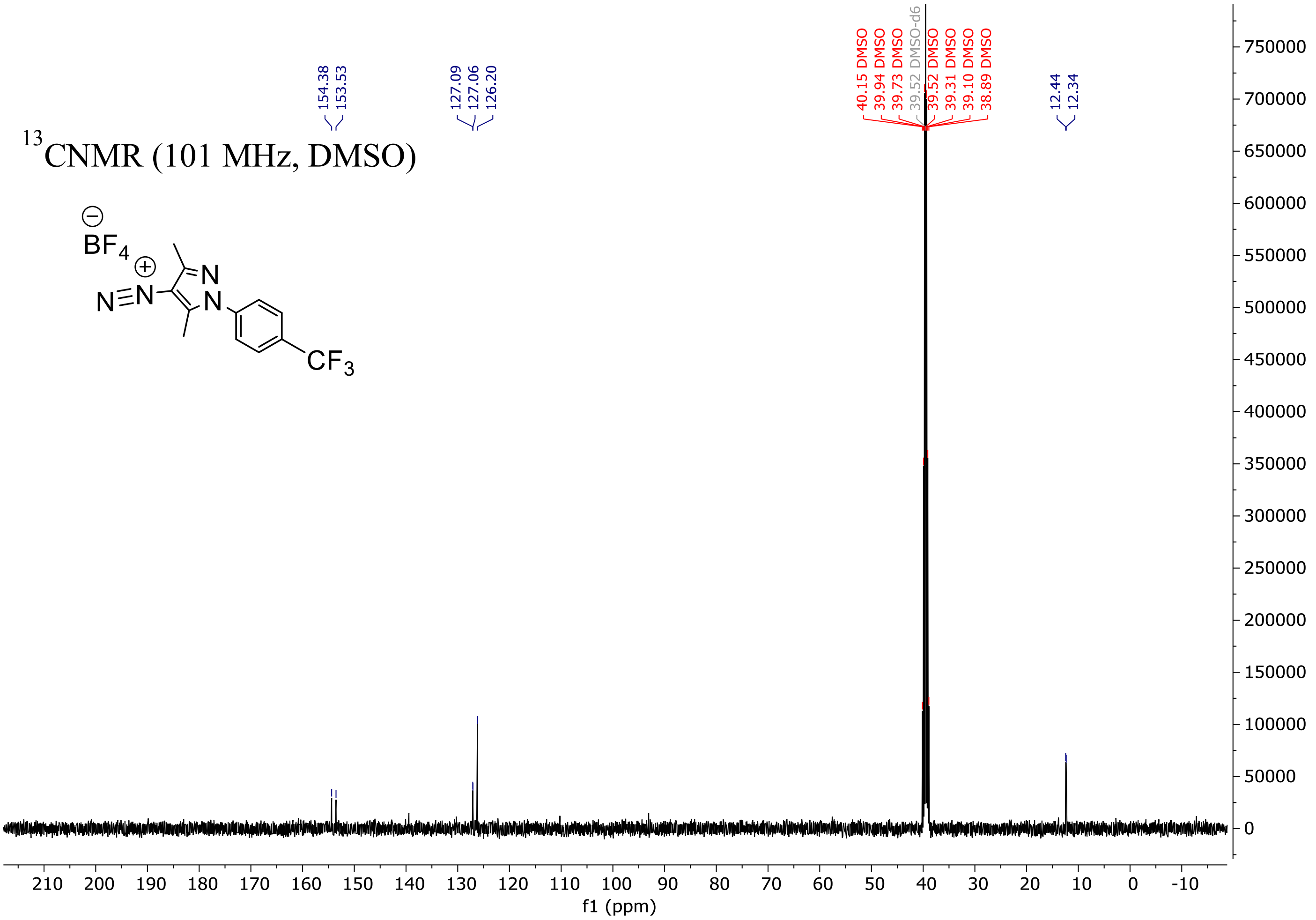


19FNMR (376 MHz, DMSO)
-148.32
BF4
N≡N
N
N
CN
1.4×10^12
1.3×10^12
1.2×10^12
1.1×10^12
1.0×10^12
9.0×10^11
8.0×10^11
7.0×10^11
6.0×10^11
5.0×10^11
4.0×10^11
3.0×10^11
2.0×10^11
1.0×10^11
0.0
-1.0×10^1
-105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195
f1 (ppm)

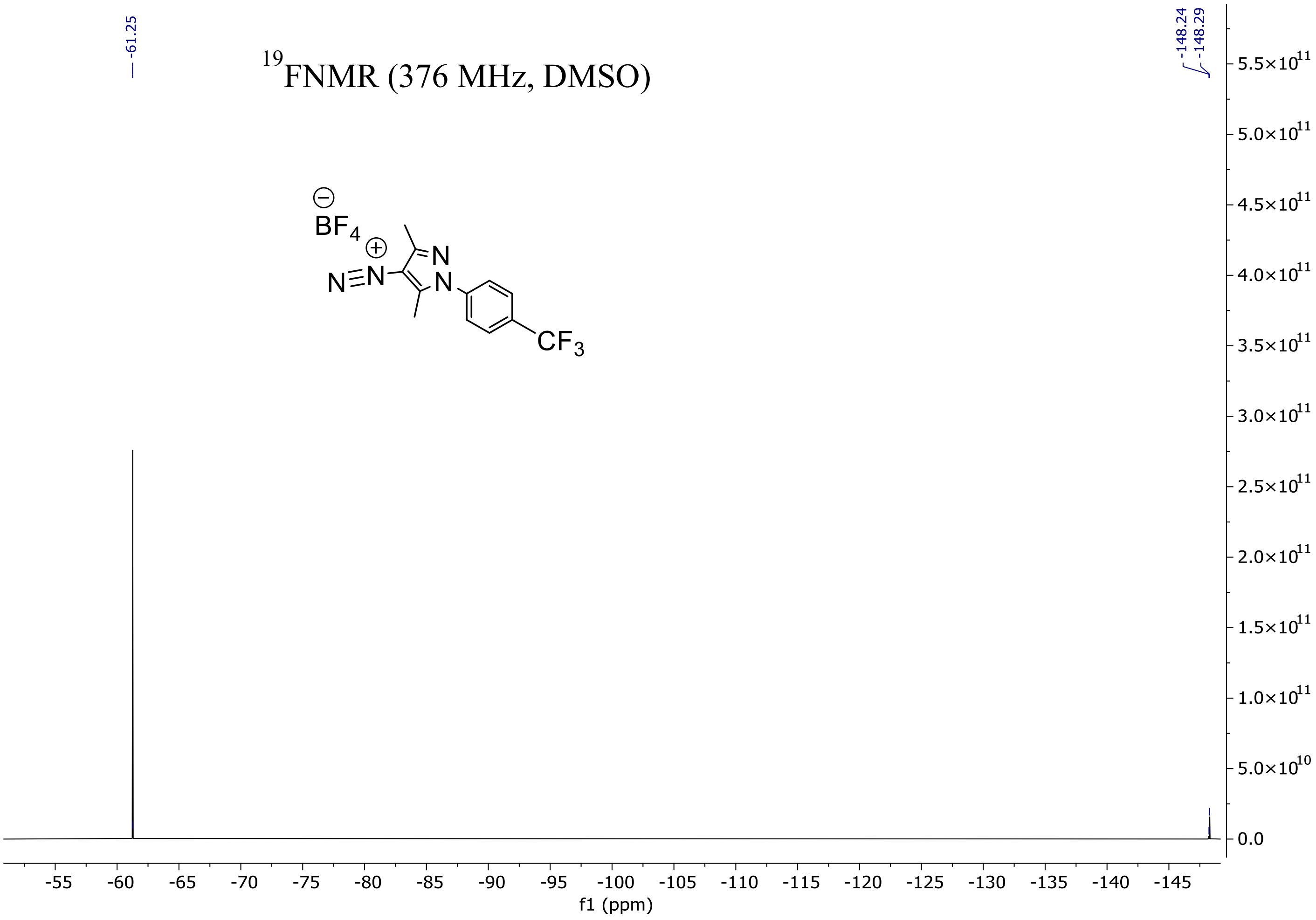
Compound 1d

^{1}HNMR (400 MHz, DMSO)

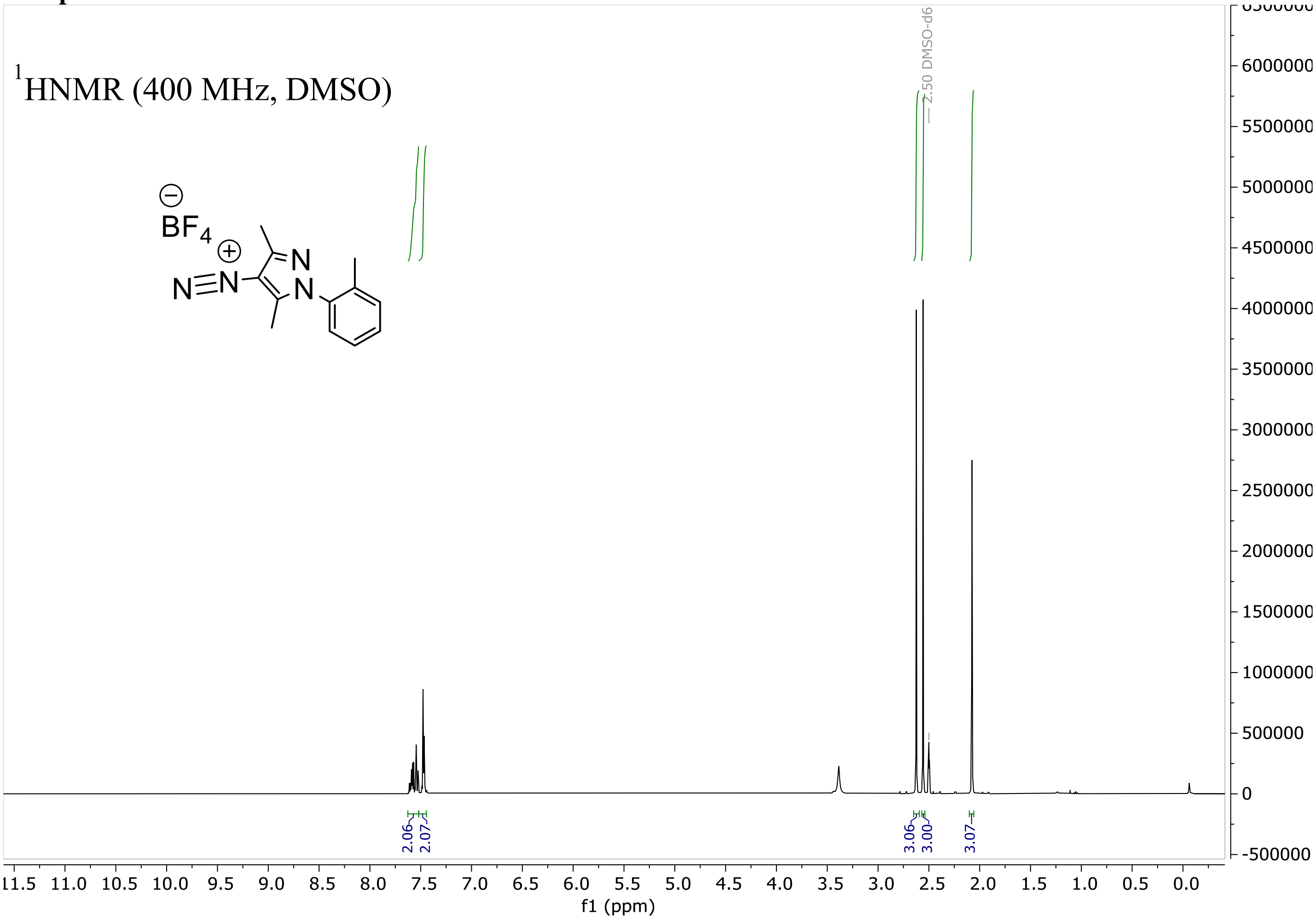




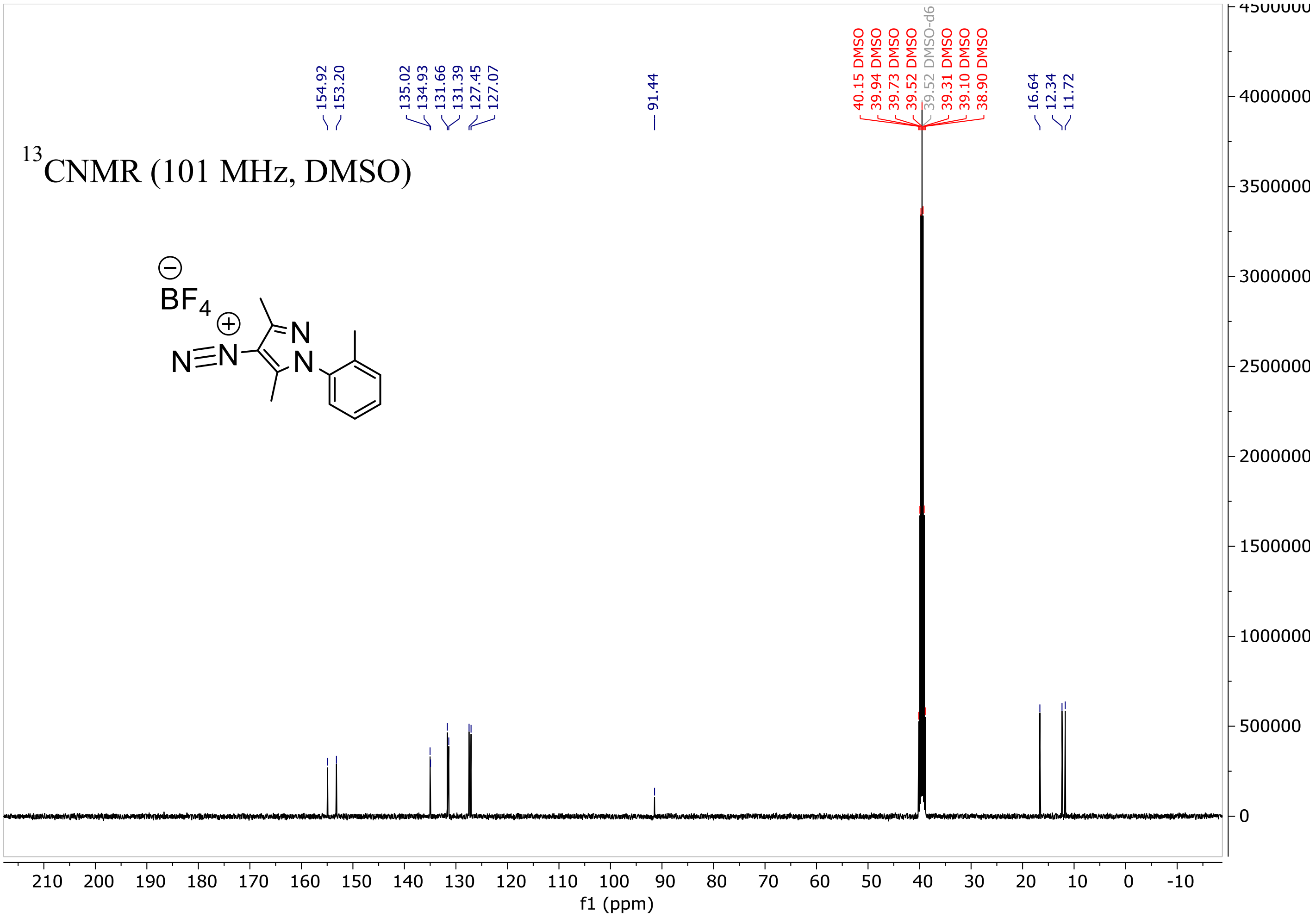
^{13}CNMR (101 MHz, DMSO)

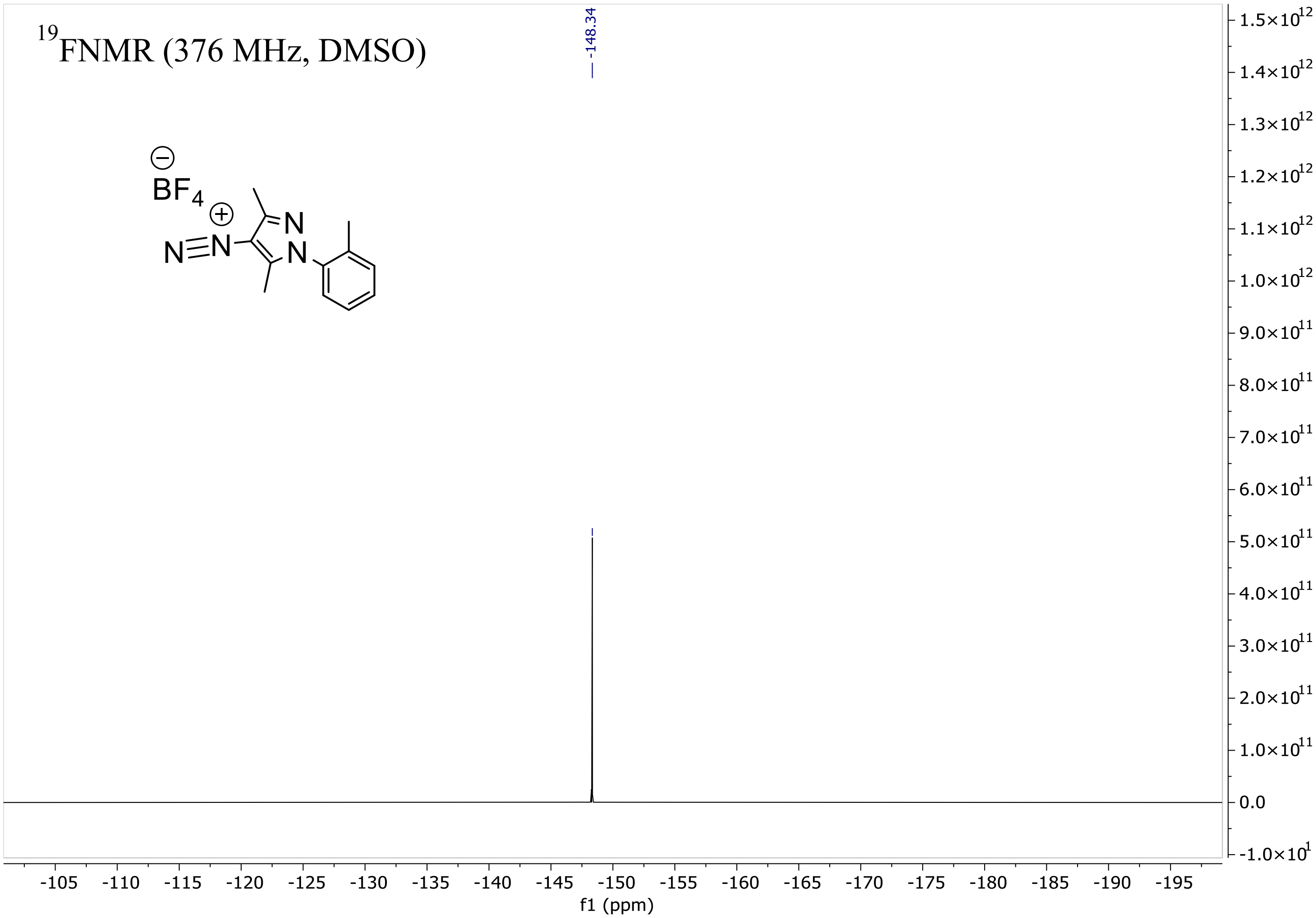

-61.25
-148.24
-148.29
19FNMR (376 MHz, DMSO)
BF4
N≡N
N
N
CF3
5.5×10^11
5.0×10^11
4.5×10^11
4.0×10^11
3.5×10^11
3.0×10^11
2.5×10^11
2.0×10^11
1.5×10^11
1.0×10^11
5.0×10^10
0.0
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

Compound 1e



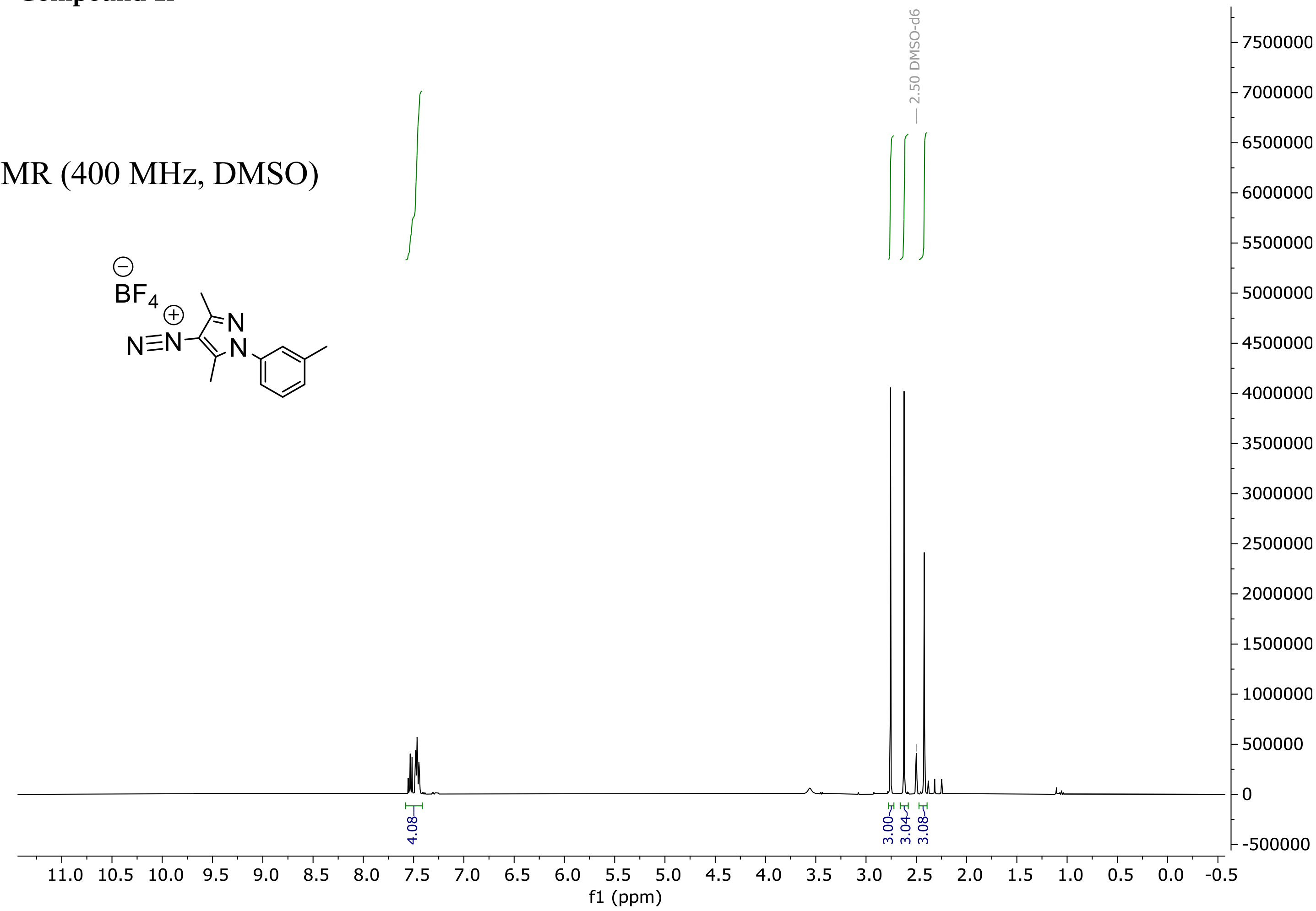
^{1}HNMR (400 MHz, DMSO)
BF$_4$
N≡N
N
N
2.50 DMSO-d6
2.06
2.07
3.06
3.00
3.07
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

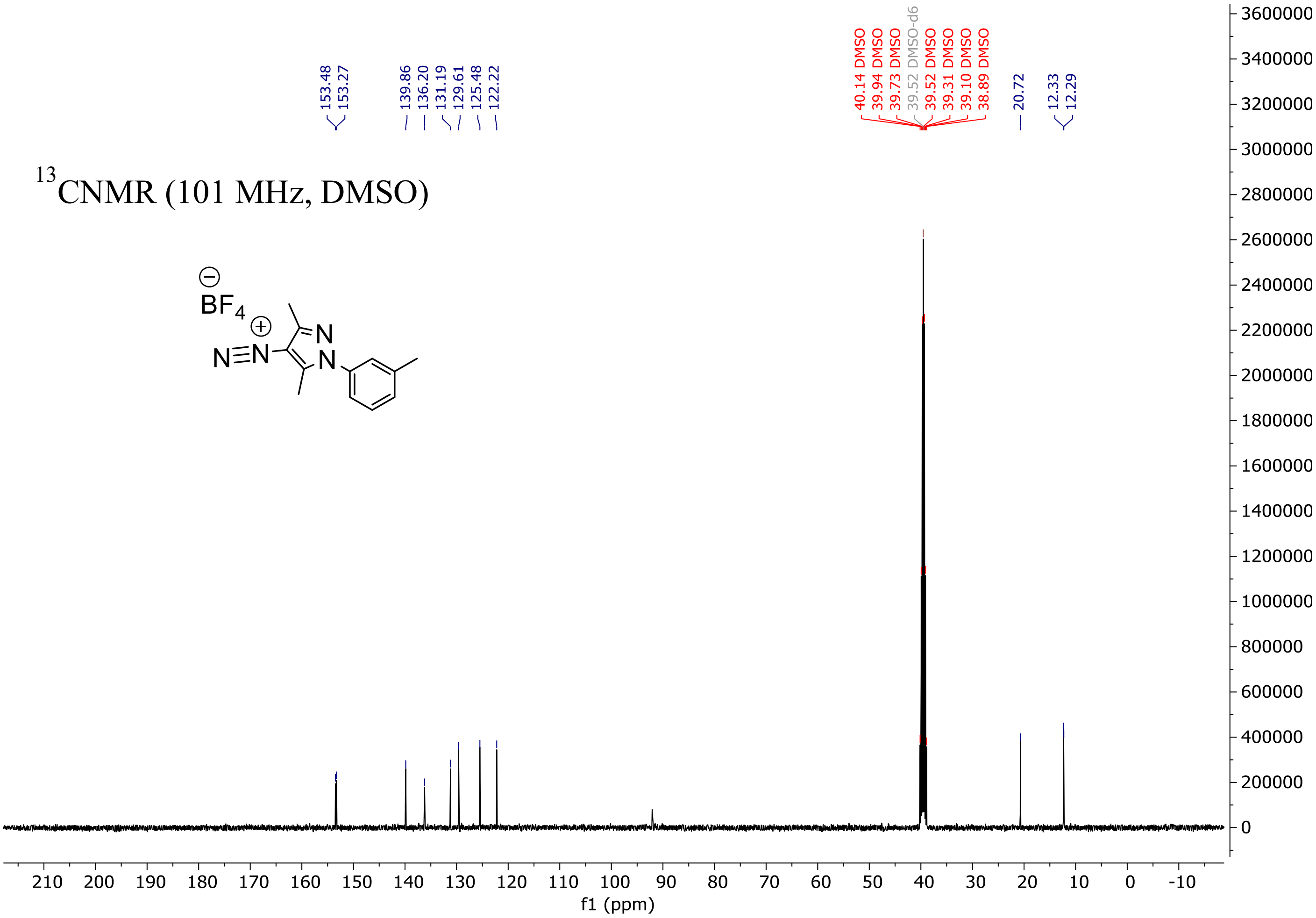

13CNMR (101 MHz, DMSO)
BF4
N≡N
N
N
154.92
153.20
135.02
134.93
131.66
131.39
127.45
127.07
91.44
40.15 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO
39.52 DMSO-d6
39.31 DMSO
39.10 DMSO
38.90 DMSO
16.64
12.34
11.72
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


^{19}FNMR (376 MHz, DMSO)
-148.34
BF_4
N≡N
N
N
1.5×10^12
1.4×10^12
1.3×10^12
1.2×10^12
1.1×10^12
1.0×10^12
9.0×10^11
8.0×10^11
7.0×10^11
6.0×10^11
5.0×10^11
4.0×10^11
3.0×10^11
2.0×10^11
1.0×10^11
0.0
-1.0×10^1
-105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195
f1 (ppm)

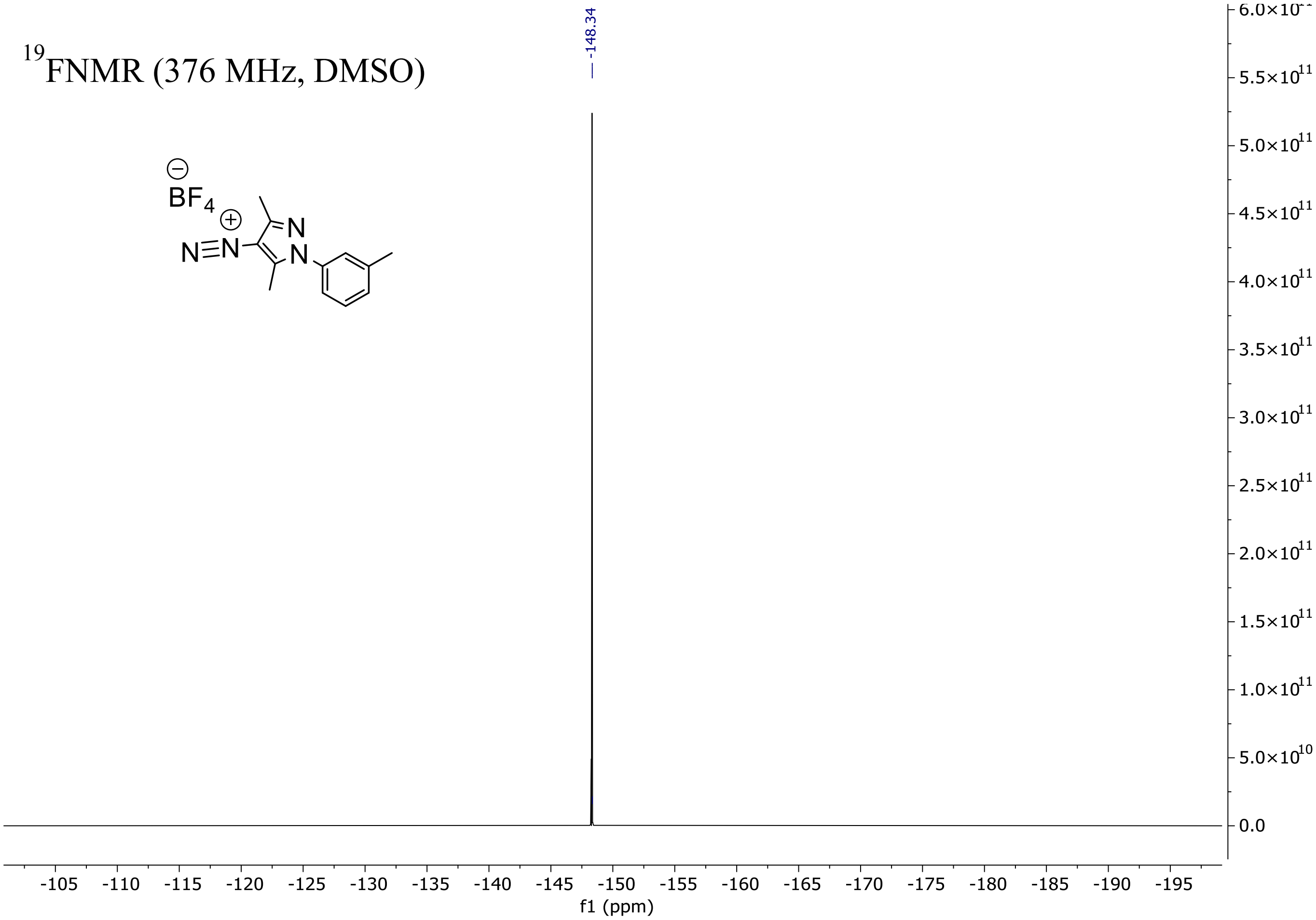
Compound 1f

^{1}HNMR (400 MHz, DMSO)



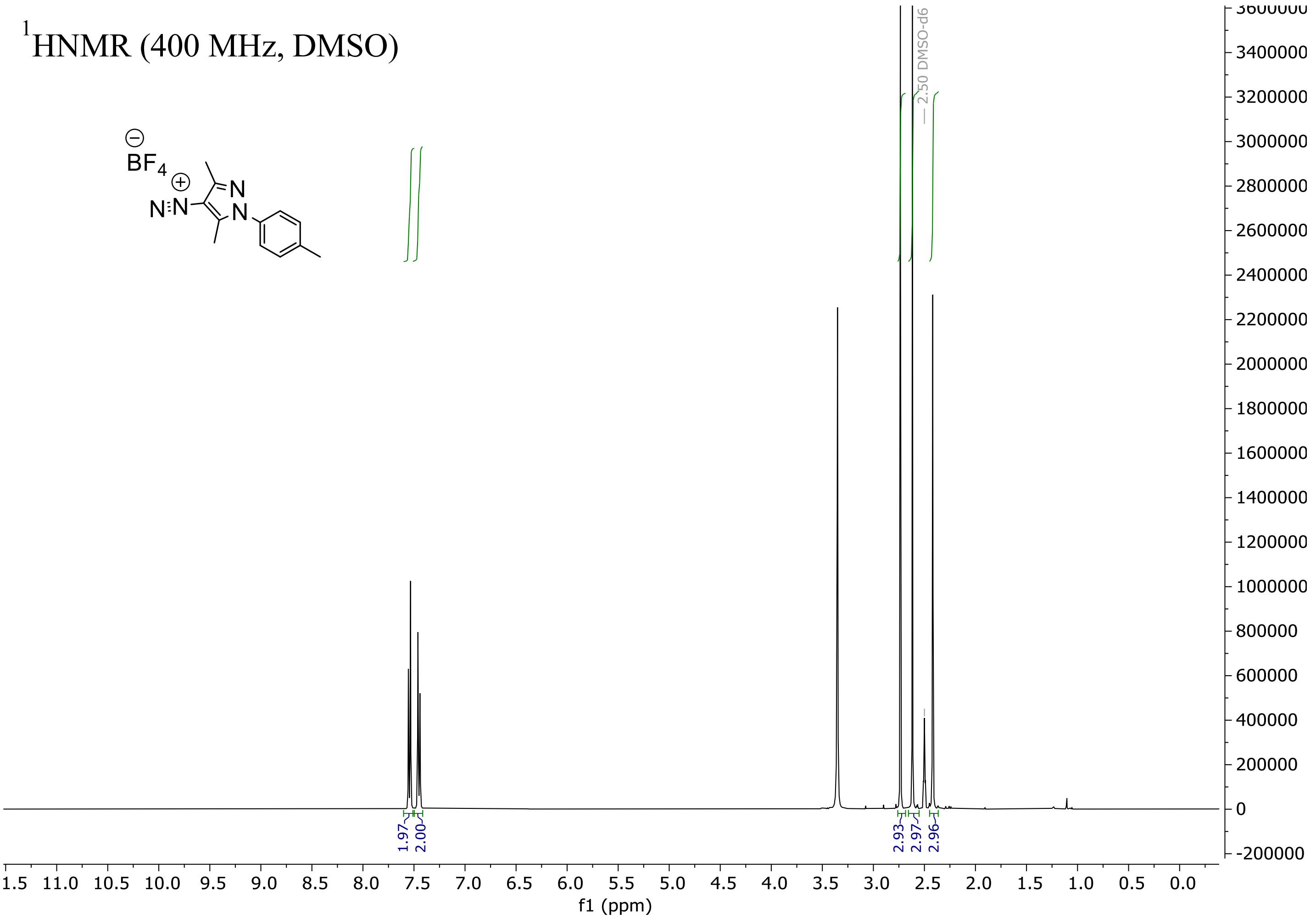


^{13}CNMR (101 MHz, DMSO)
BF4
N≡N
N
N
153.48
153.27
139.86
136.20
131.19
129.61
125.48
122.22
40.14 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO-d6
39.52 DMSO
39.31 DMSO
39.10 DMSO
38.89 DMSO
20.72
12.33
12.29
3600000
3400000
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



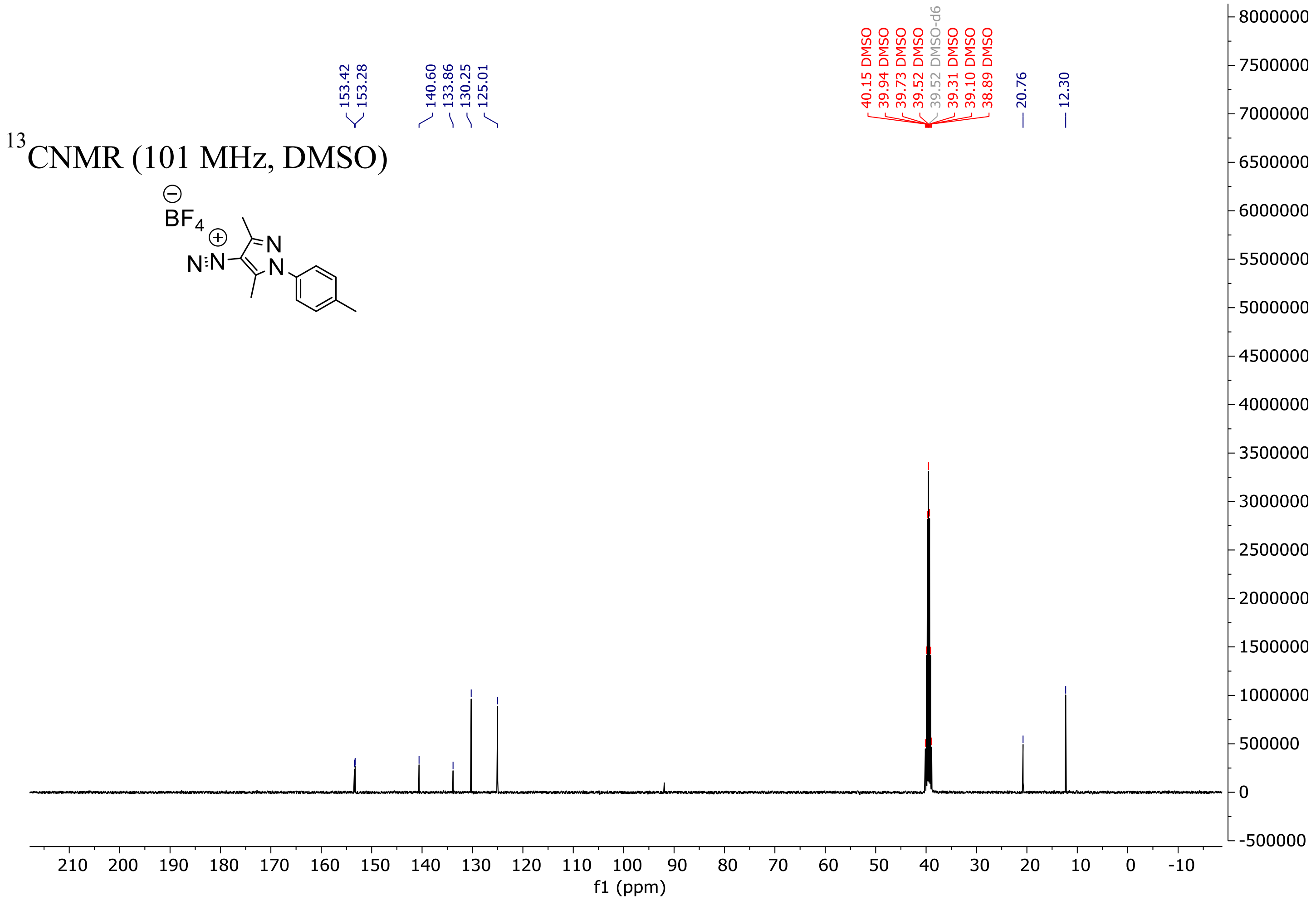
^{19}FNMR (376 MHz, DMSO)

Compound 1g

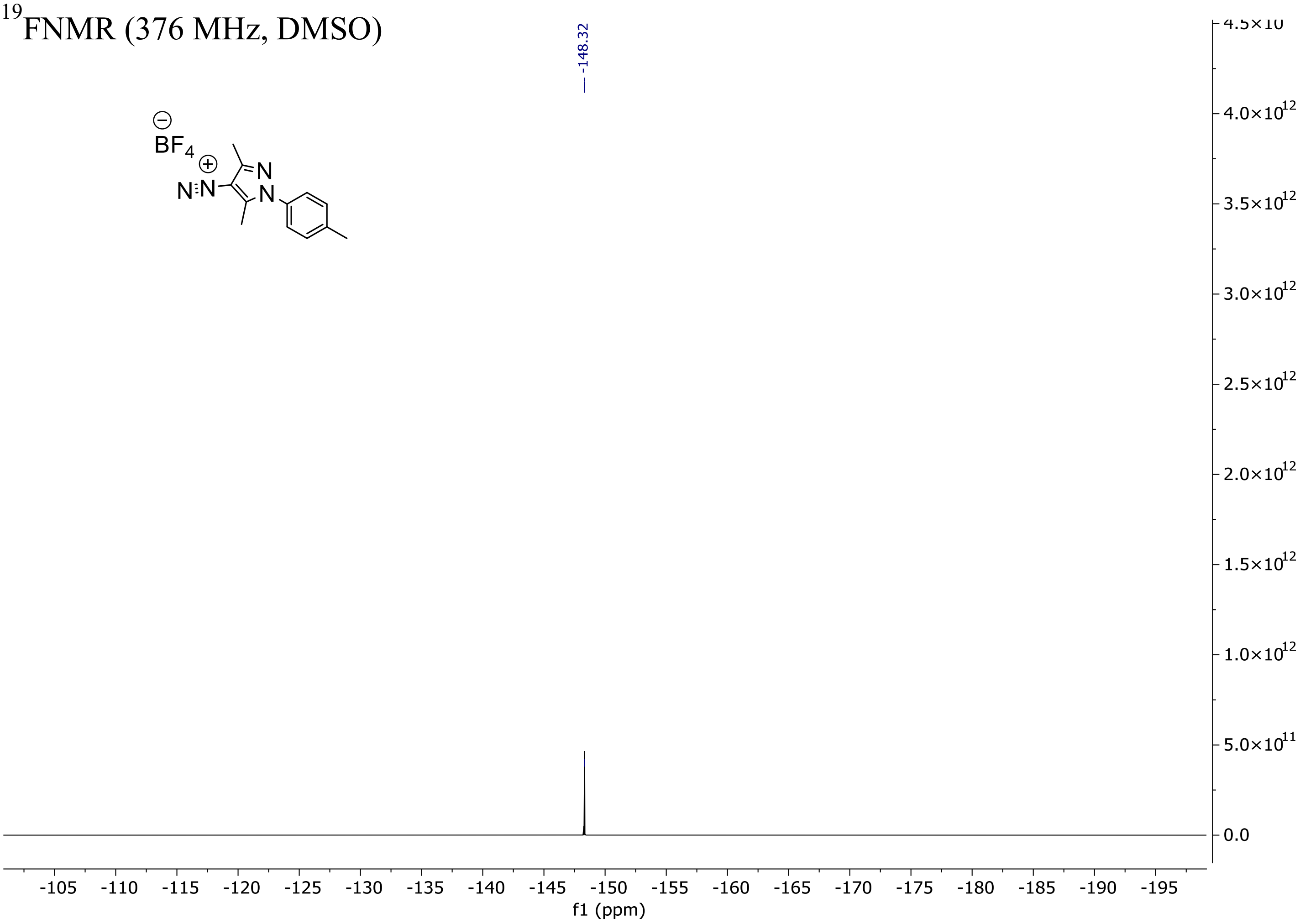


^{1}HNMR (400 MHz, DMSO)
BF4
N≡N
N
N
2.50 DMSO-d6
1.97
2.00
2.93
2.97
2.96
3600000
3400000
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

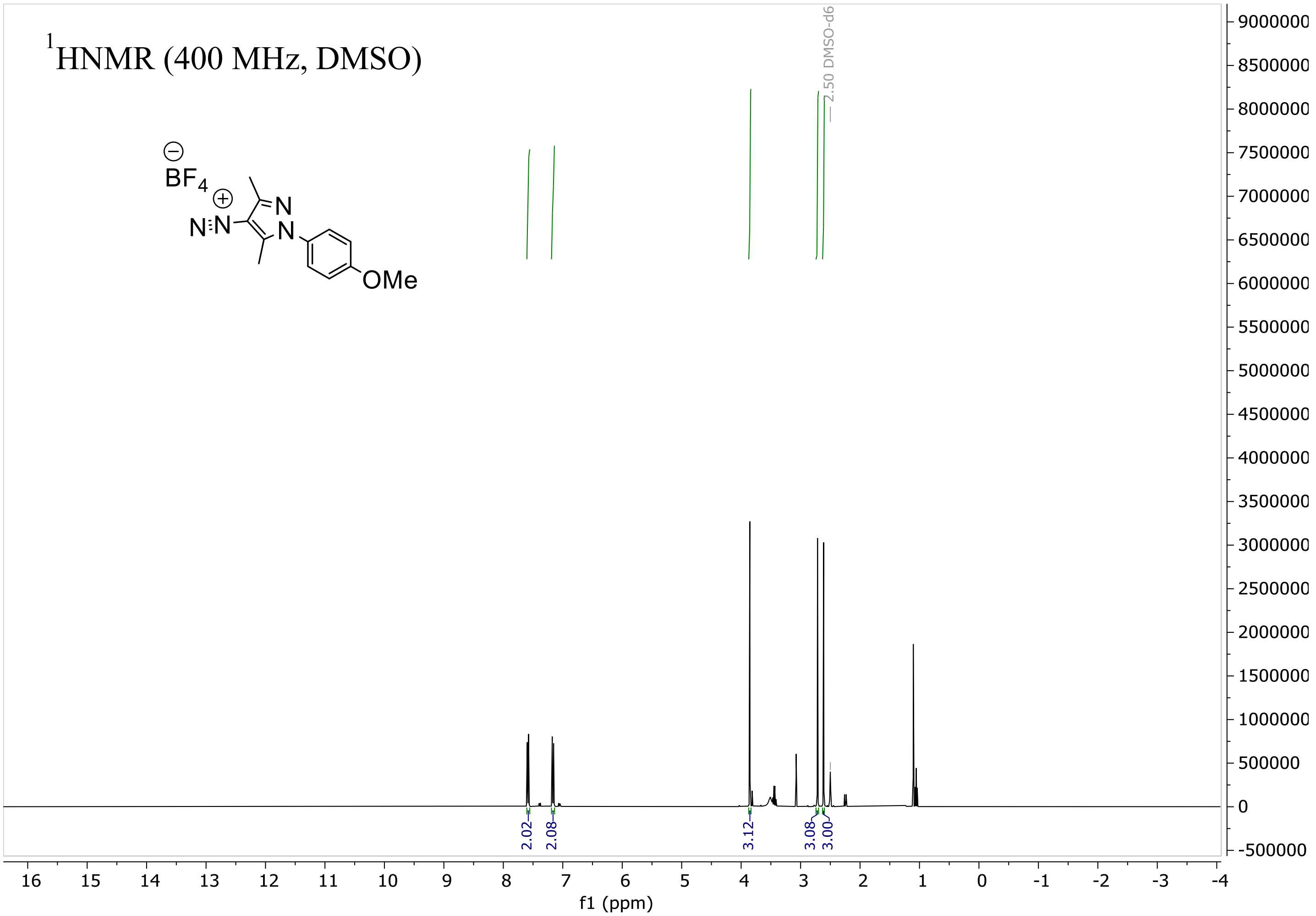
^{13}CNMR (101 MHz, DMSO)



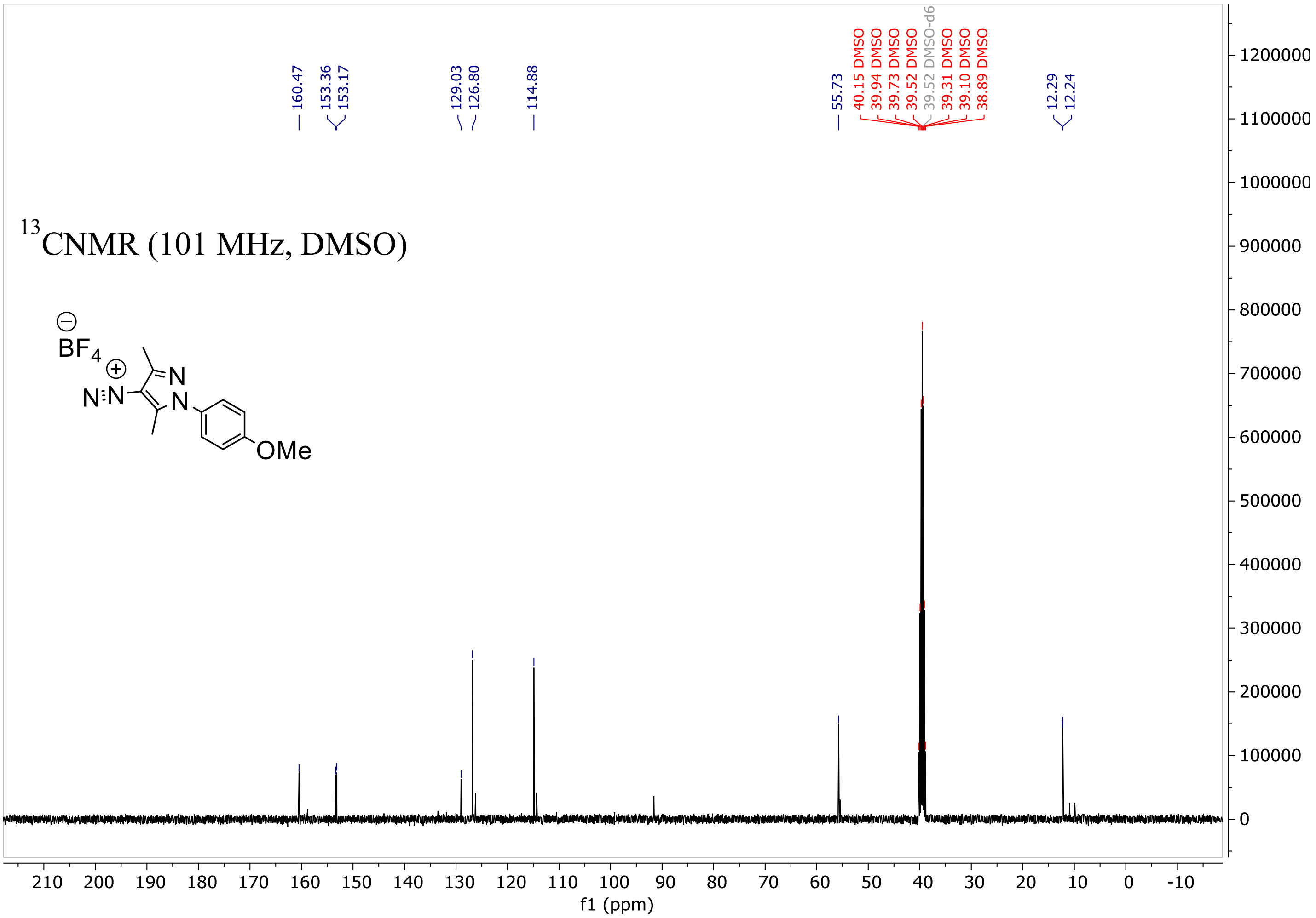
^{19}FNMR (376 MHz, DMSO)

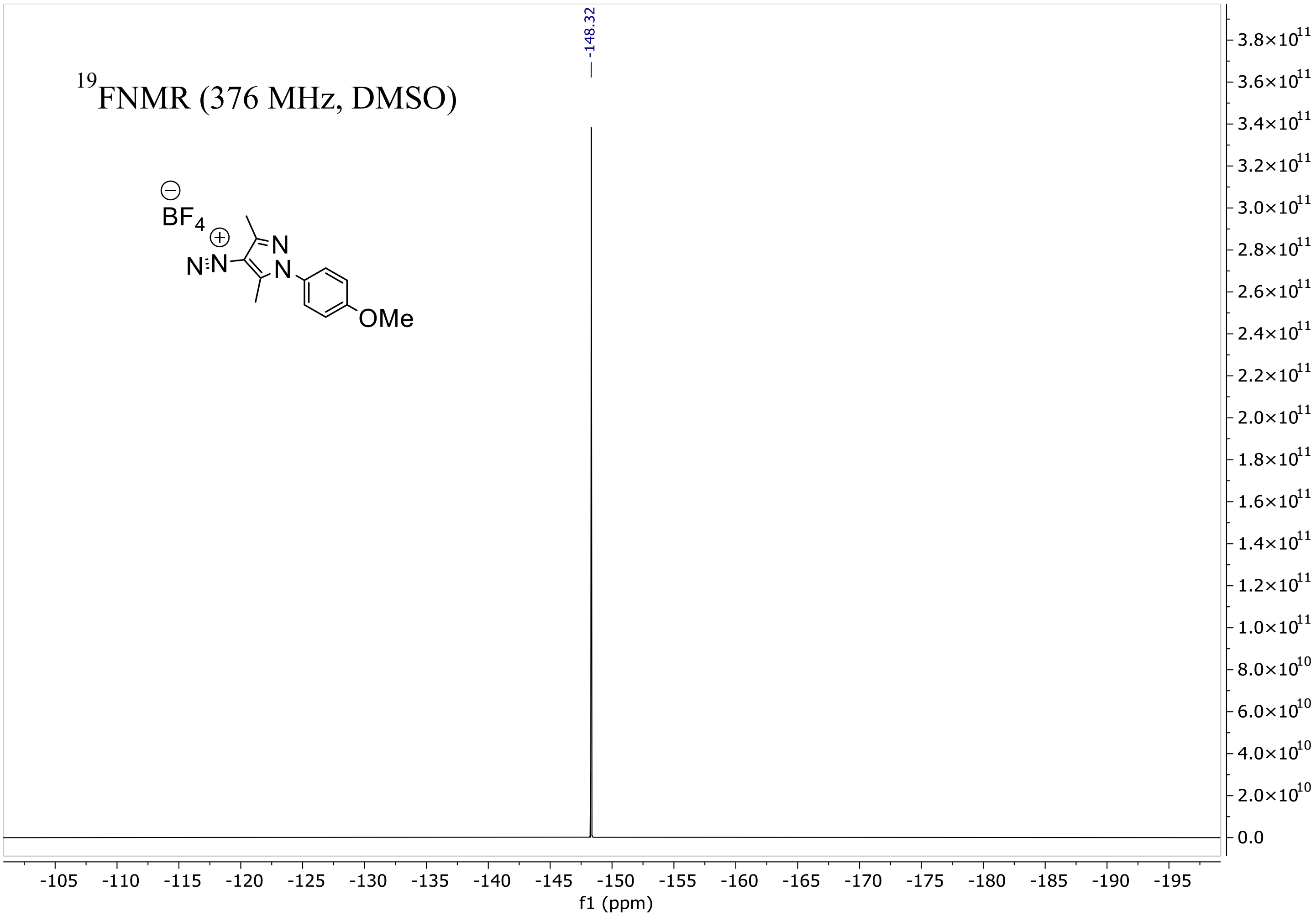


Compound 1h

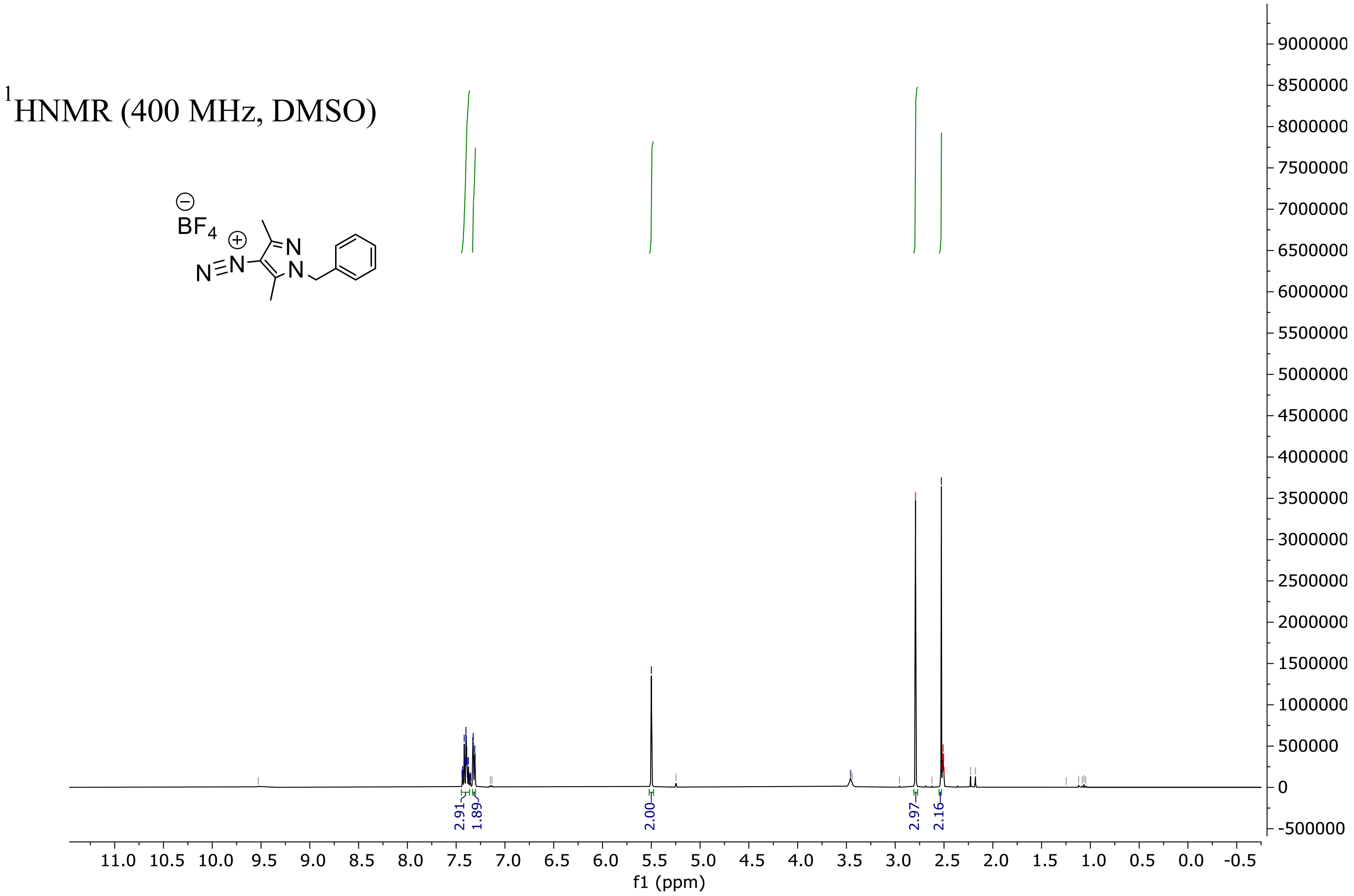


^{1}HNMR (400 MHz, DMSO)
BF4
N
N
OMe
2.50 DMSO-d6
2.02
2.08
3.12
3.08
3.00
f1 (ppm)
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
9000000
8500000
8000000
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000

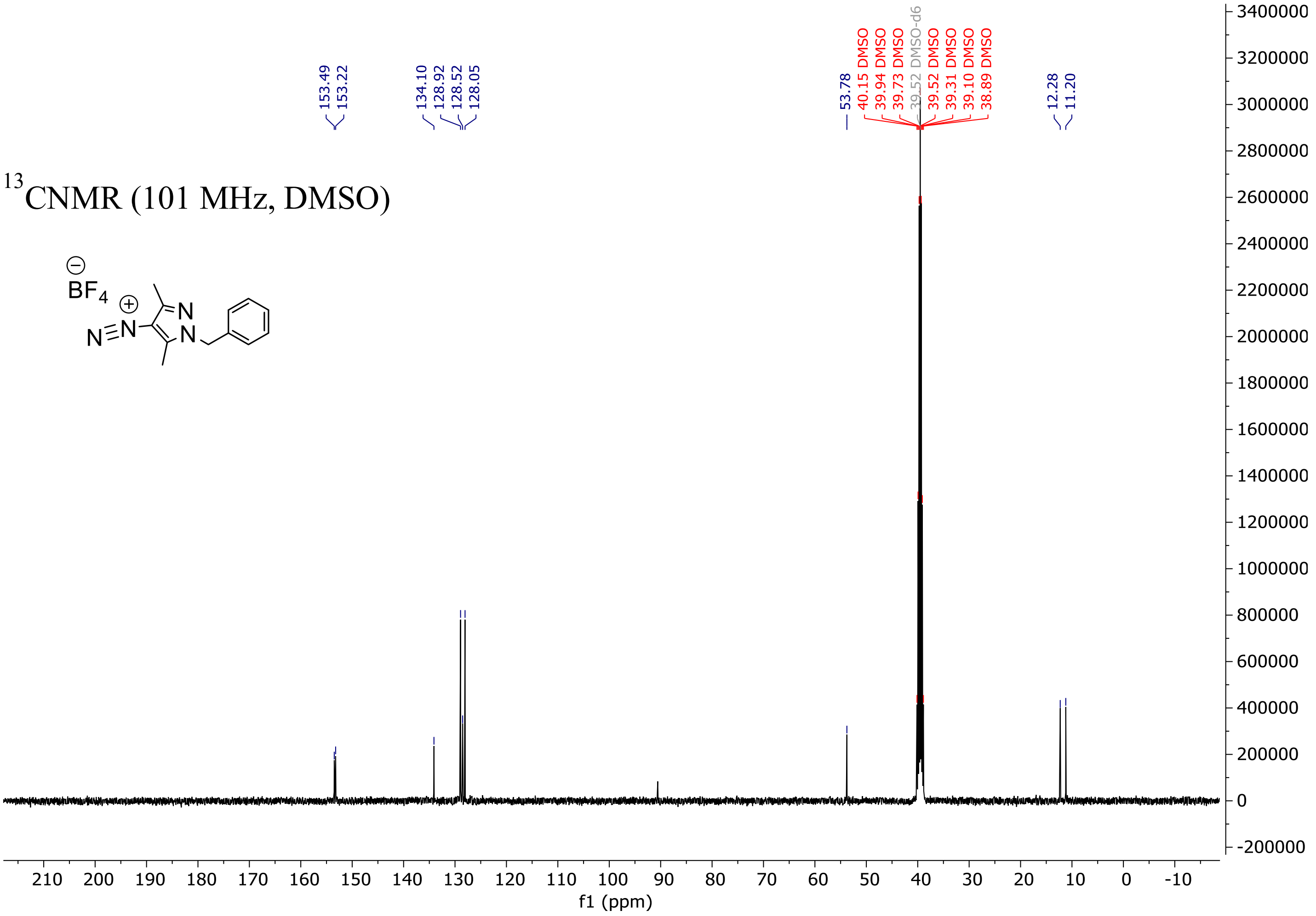

^{13}CNMR (101 MHz, DMSO)
BF$_4^-$
N≡N$^+$
N
N
OMe
160.47
153.36
153.17
129.03
126.80
114.88
55.73
40.15 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO
39.52 DMSO-d6
39.31 DMSO
39.10 DMSO
38.89 DMSO
12.29
12.24
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

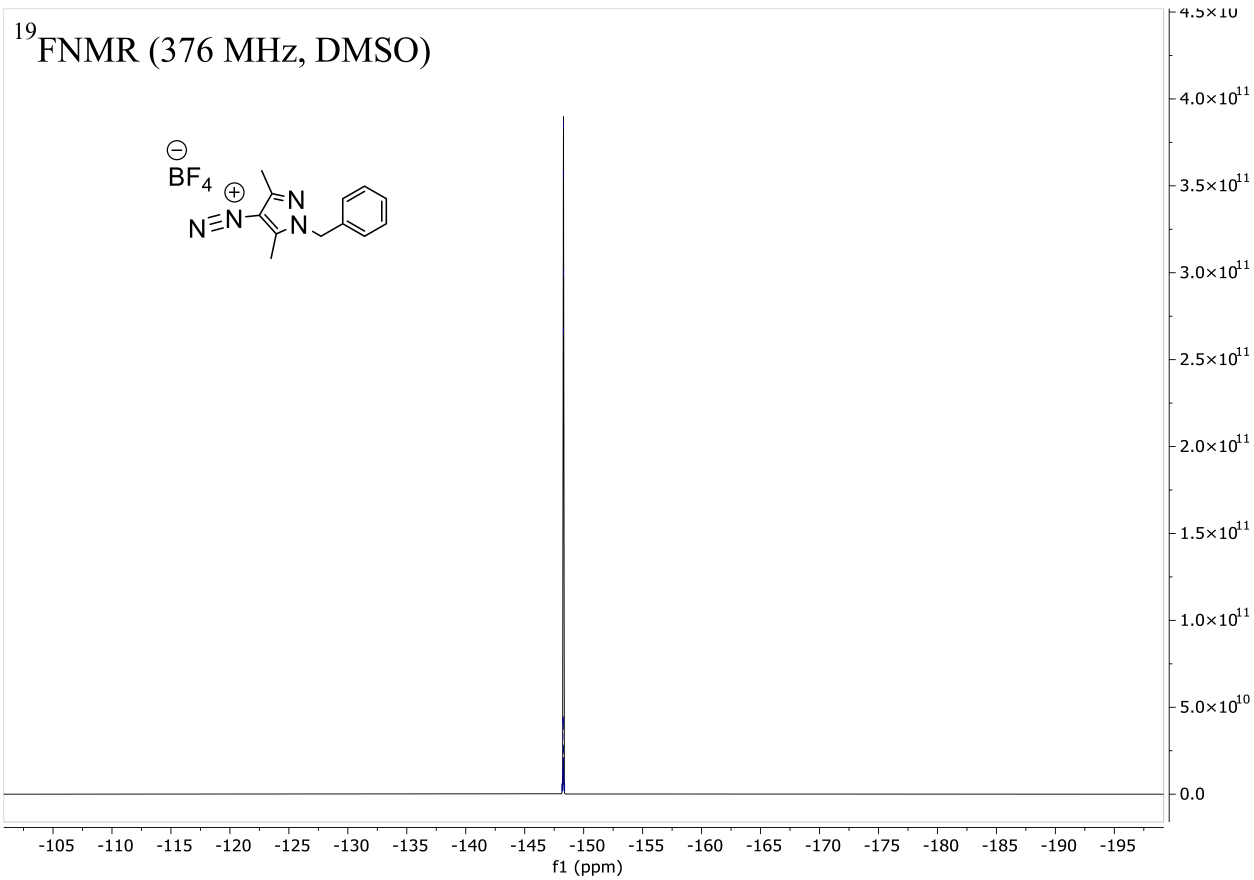

^{19}FNMR (376 MHz, DMSO)
BF4
N
N
N
N
OMe
-148.32
3.8×10^11
3.6×10^11
3.4×10^11
3.2×10^11
3.0×10^11
2.8×10^11
2.6×10^11
2.4×10^11
2.2×10^11
2.0×10^11
1.8×10^11
1.6×10^11
1.4×10^11
1.2×10^11
1.0×10^11
8.0×10^10
6.0×10^10
4.0×10^10
2.0×10^10
0.0
-105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195
f1 (ppm)

Compound 1i

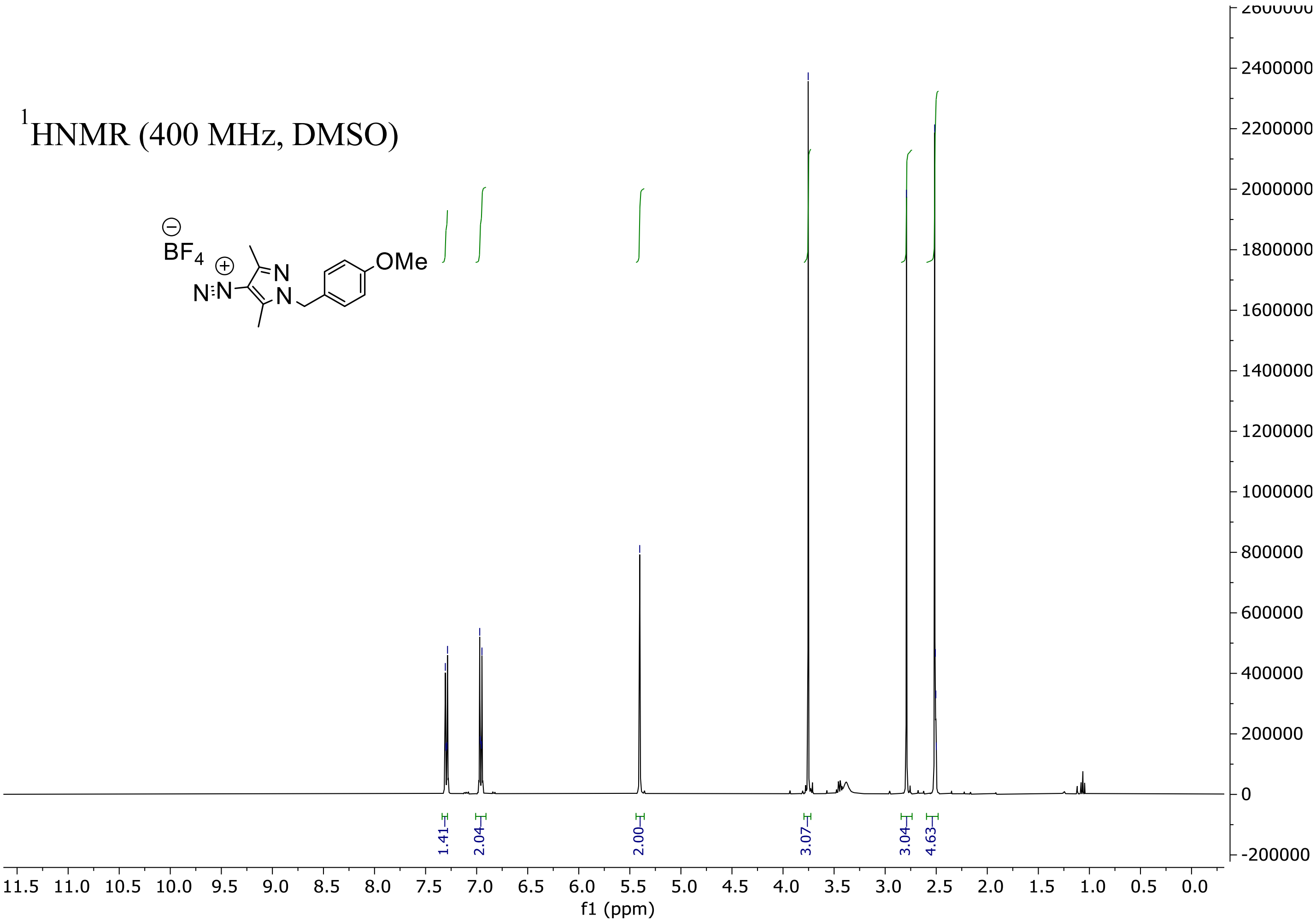

^{1}HNMR (400 MHz, DMSO)
$BF_4^{\ominus}$
N≡N⊕
N
N
2.91
1.89
2.00
2.97
2.16
9000000
8500000
8000000
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

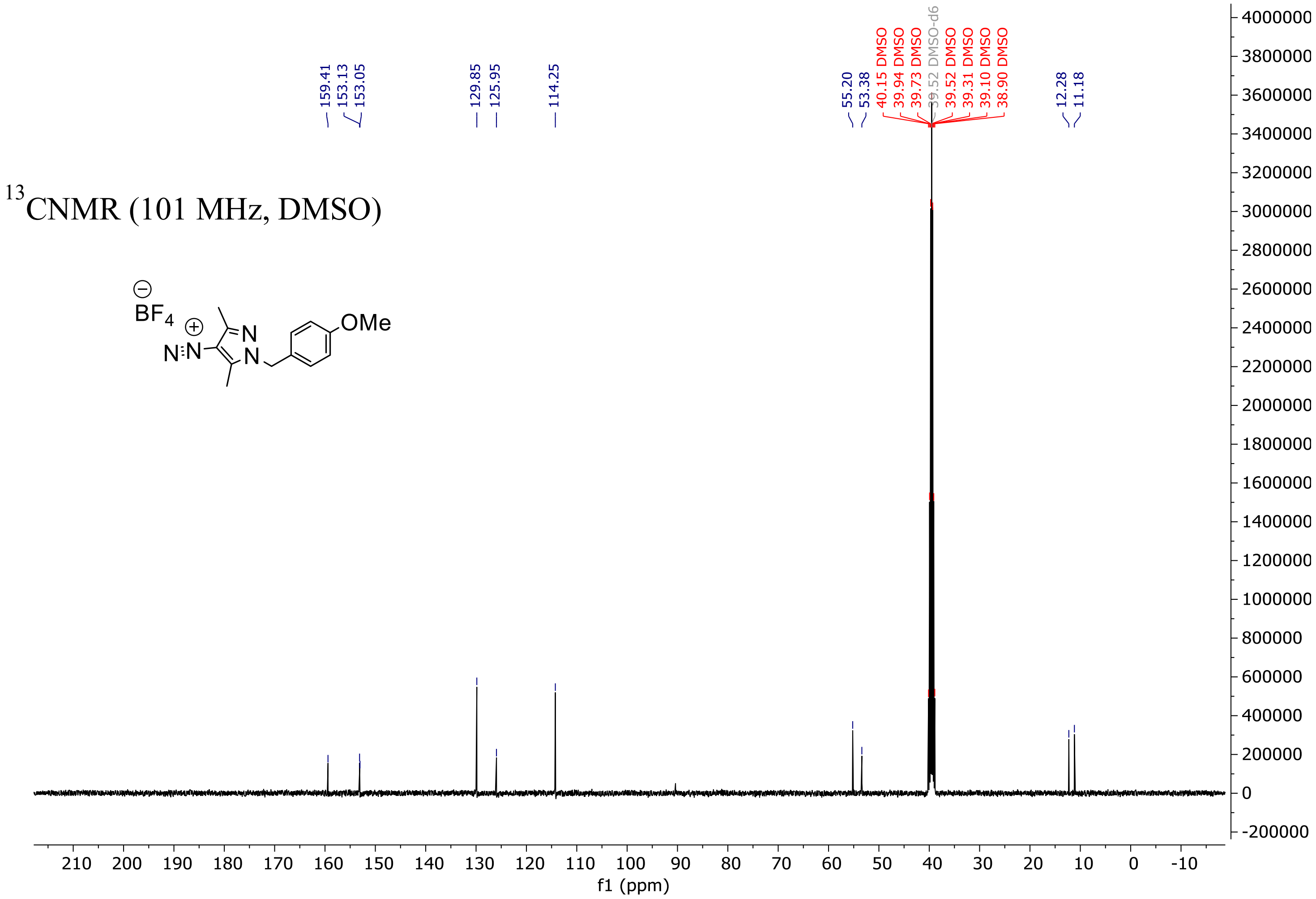
^{13}CNMR (101 MHz, DMSO)




^{19}FNMR (376 MHz, DMSO)

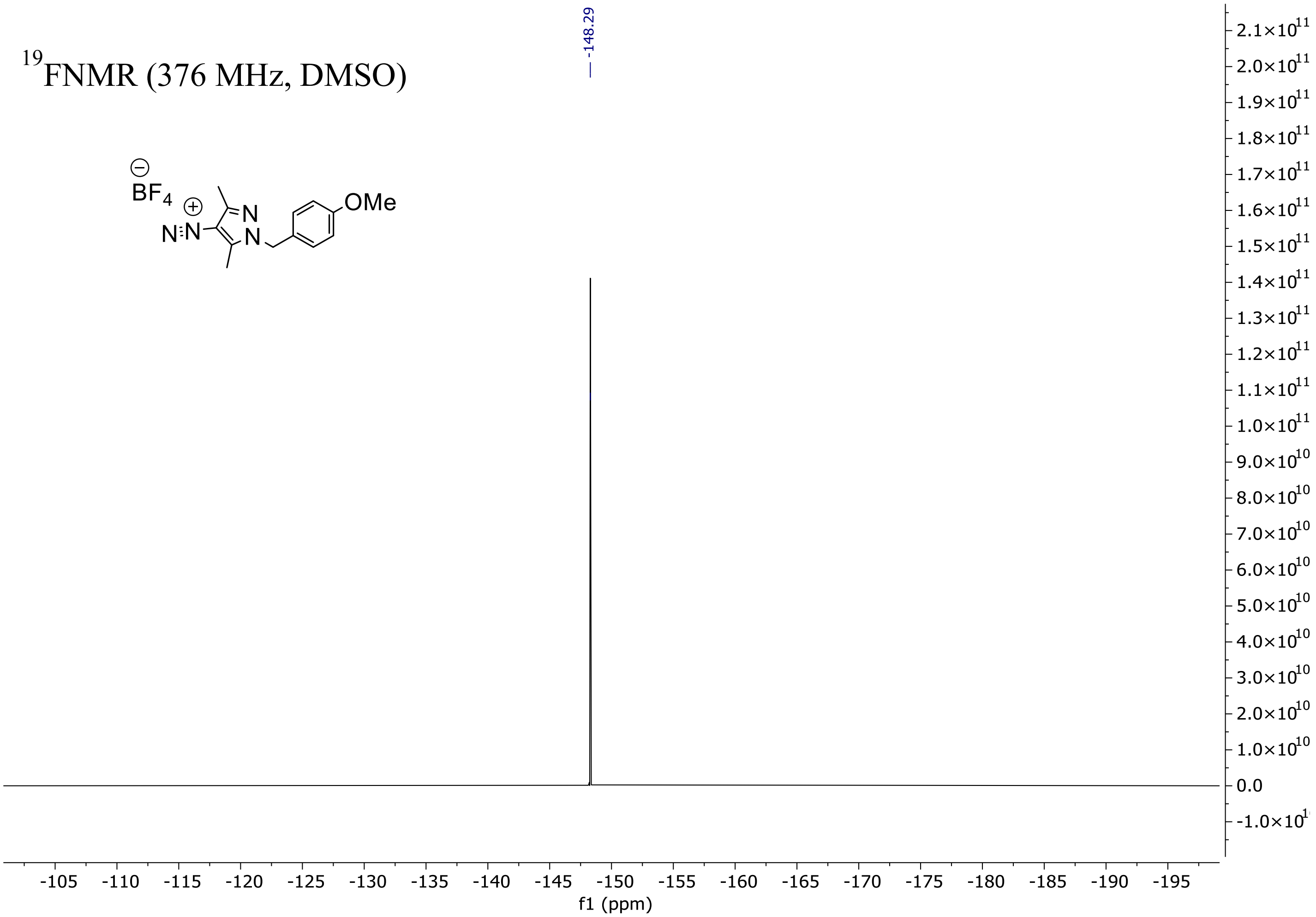
Compound 1j


^{1}HNMR (400 MHz, DMSO)
BF$_4$
N
N
N
N
OMe
1.41
2.04
2.00
3.07
3.04
4.63
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000

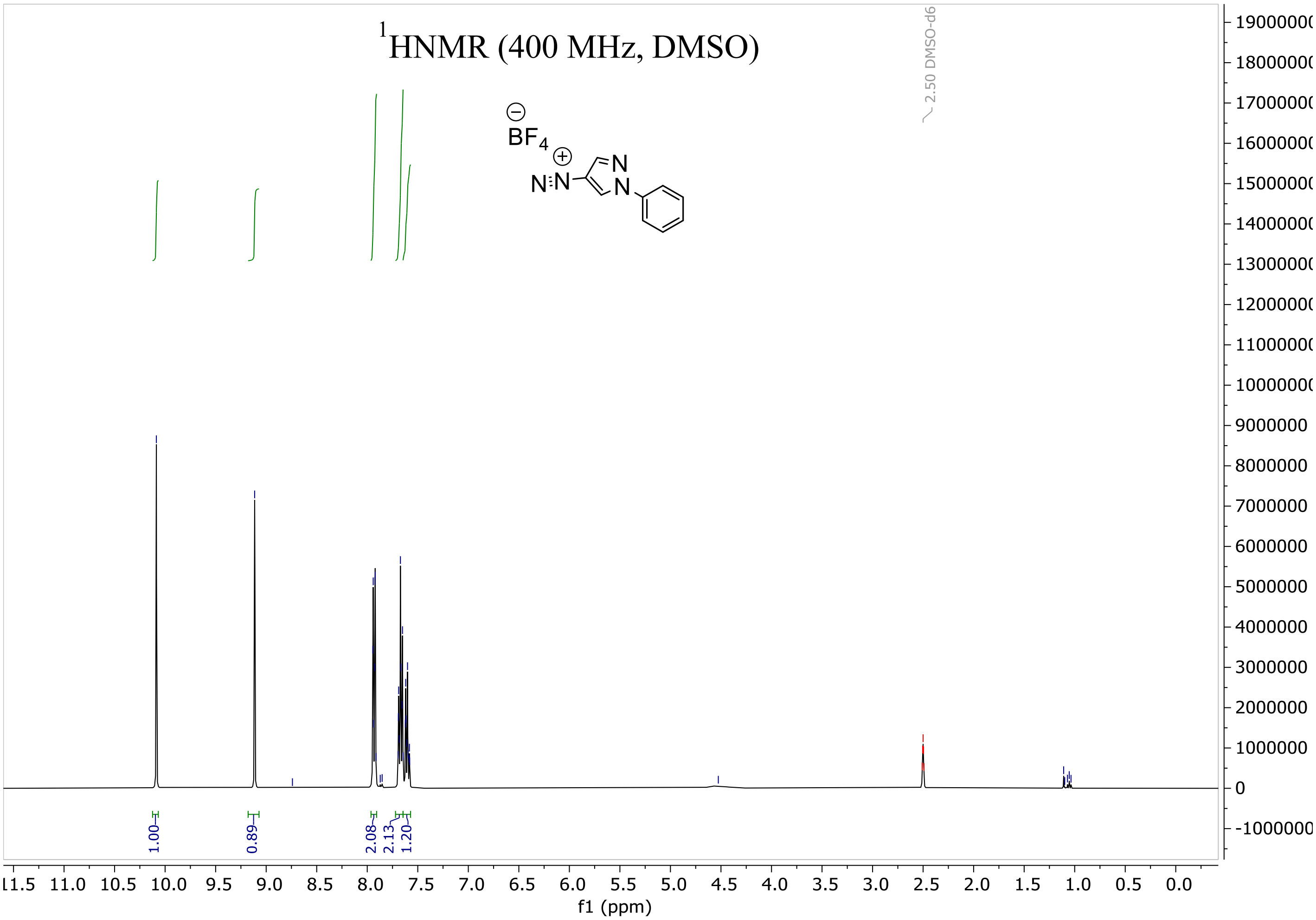


^{13}CNMR (101 MHz, DMSO)

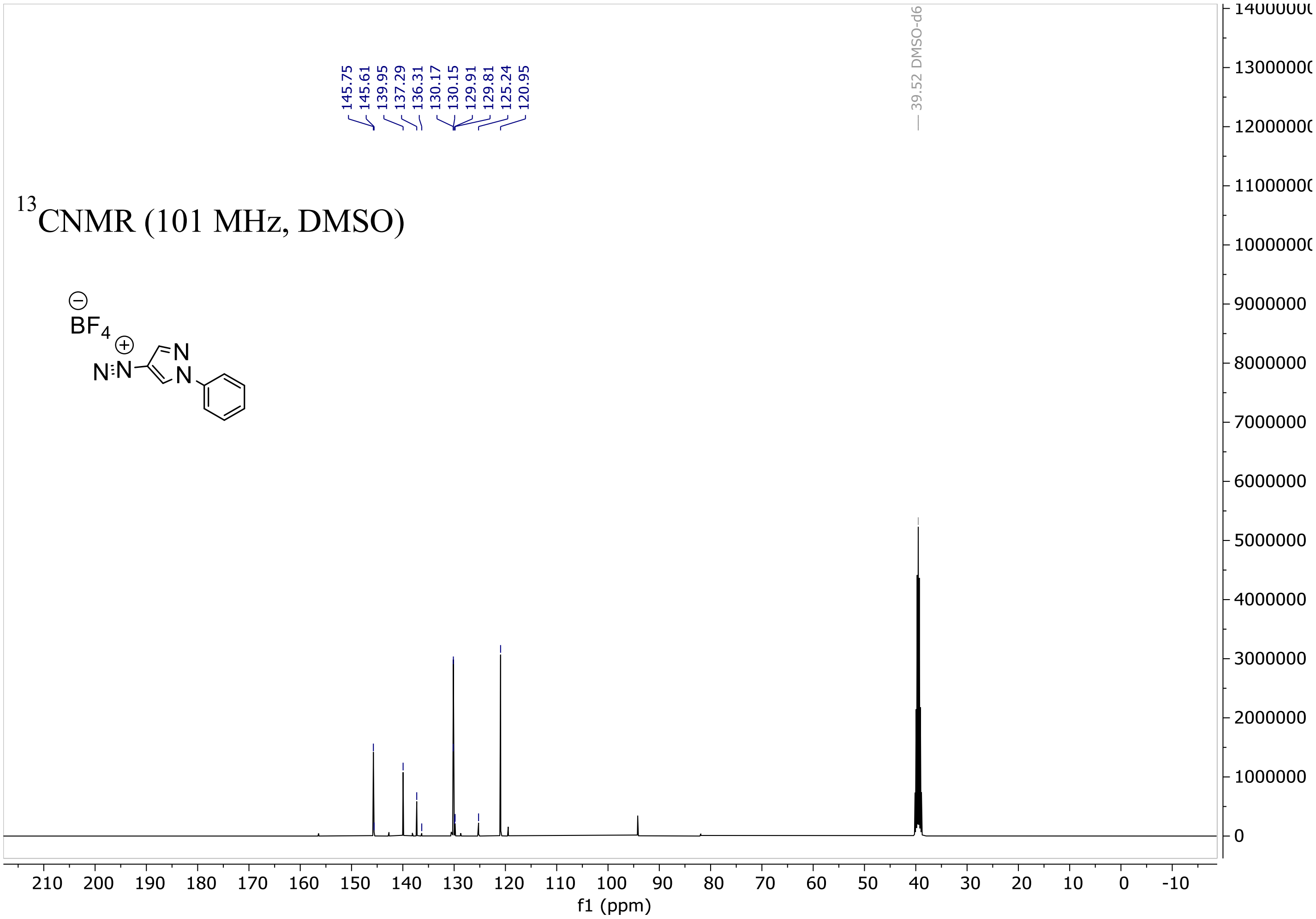
^{19}FNMR (376 MHz, DMSO)



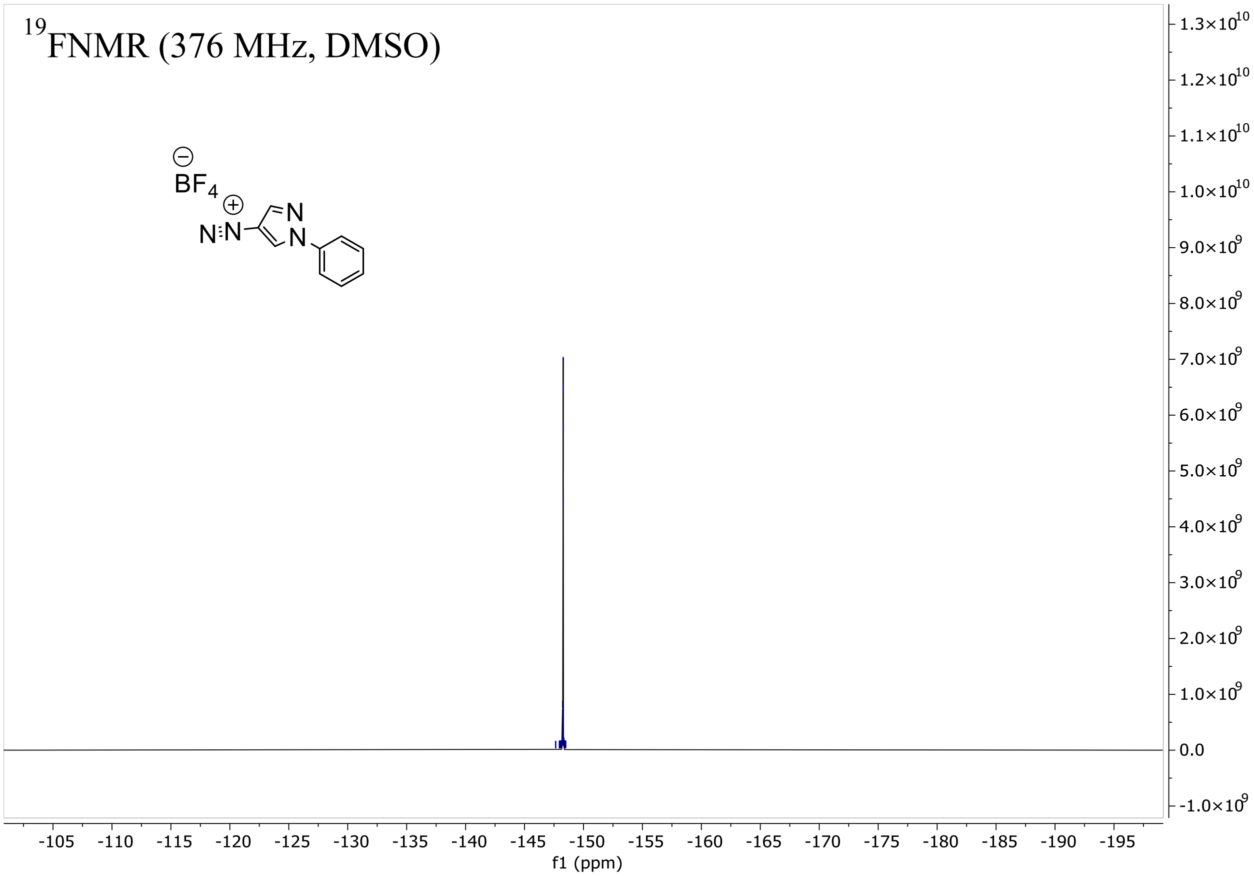
Compound 1k



^{1}HNMR (400 MHz, DMSO)
2.50 DMSO-d6
$BF_4^{\ominus}$
N
N
N
N
1.00
0.89
2.08
2.13
1.20
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
19000000
18000000
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000

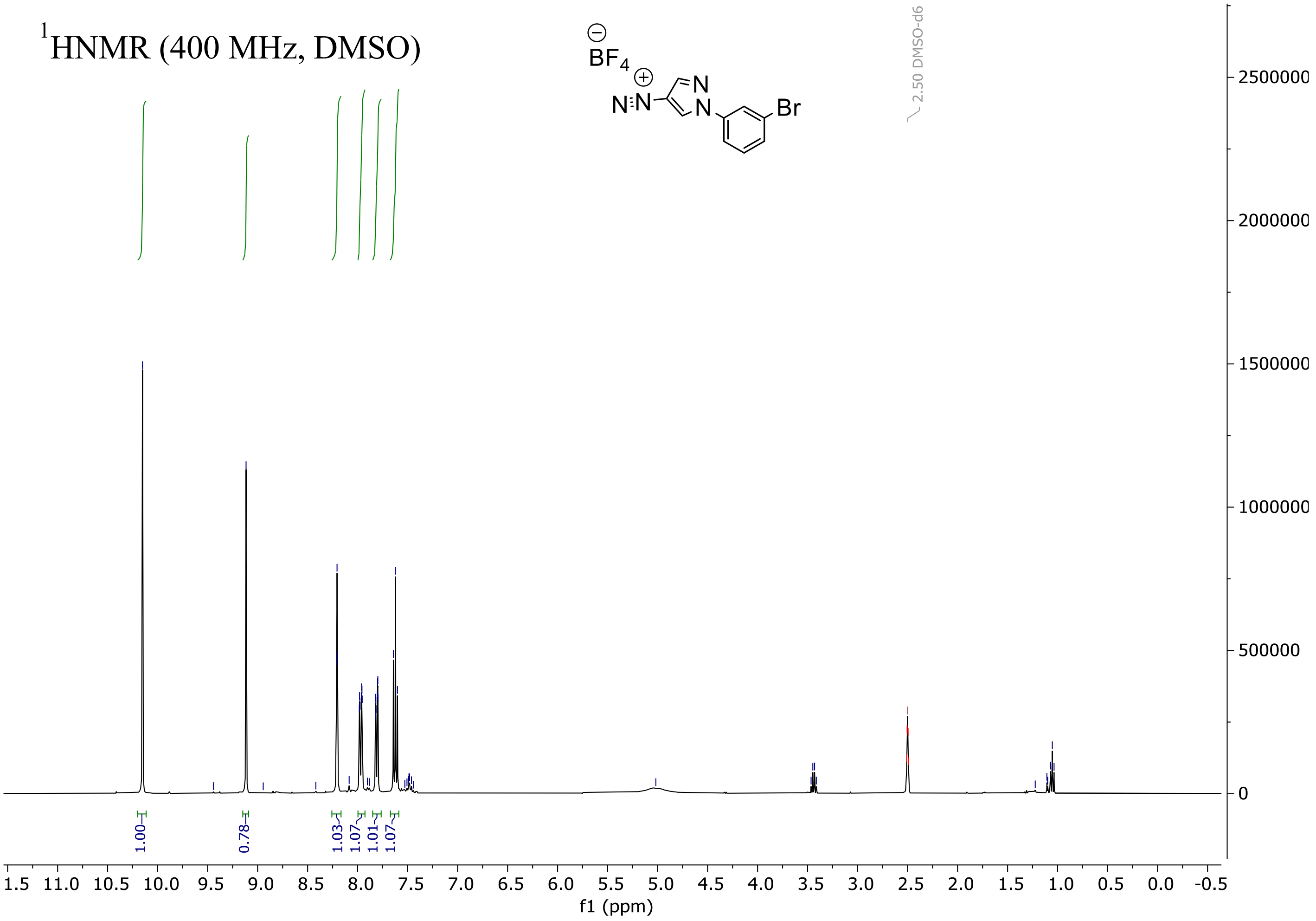


^{13}CNMR (101 MHz, DMSO)



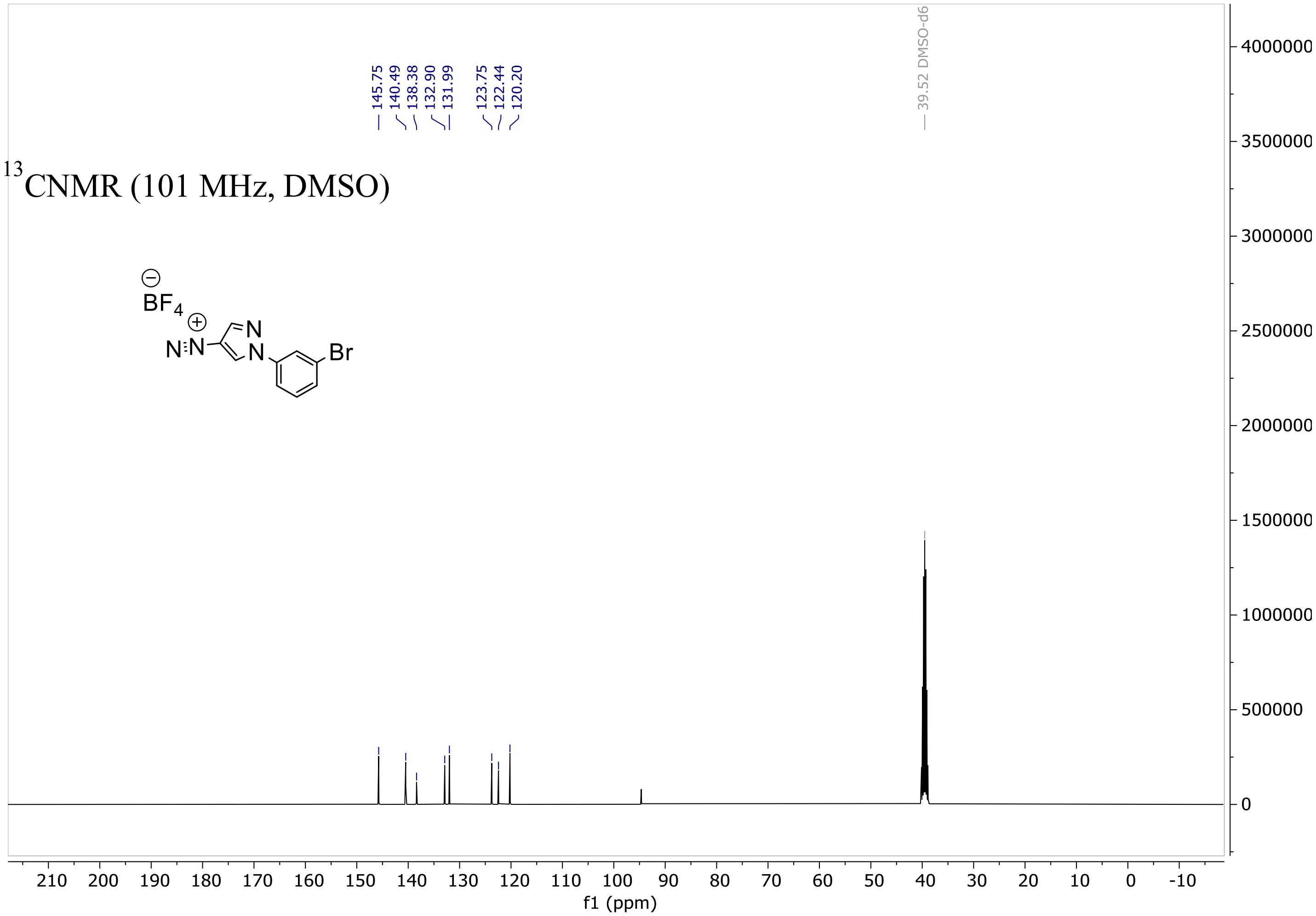
^{19}FNMR (376 MHz, DMSO)
BF4
N≡N
N
N
1.3×10^10
1.2×10^10
1.1×10^10
1.0×10^10
9.0×10^9
8.0×10^9
7.0×10^9
6.0×10^9
5.0×10^9
4.0×10^9
3.0×10^9
2.0×10^9
1.0×10^9
0.0
-1.0×10^9
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
f1 (ppm)

Compound 1l

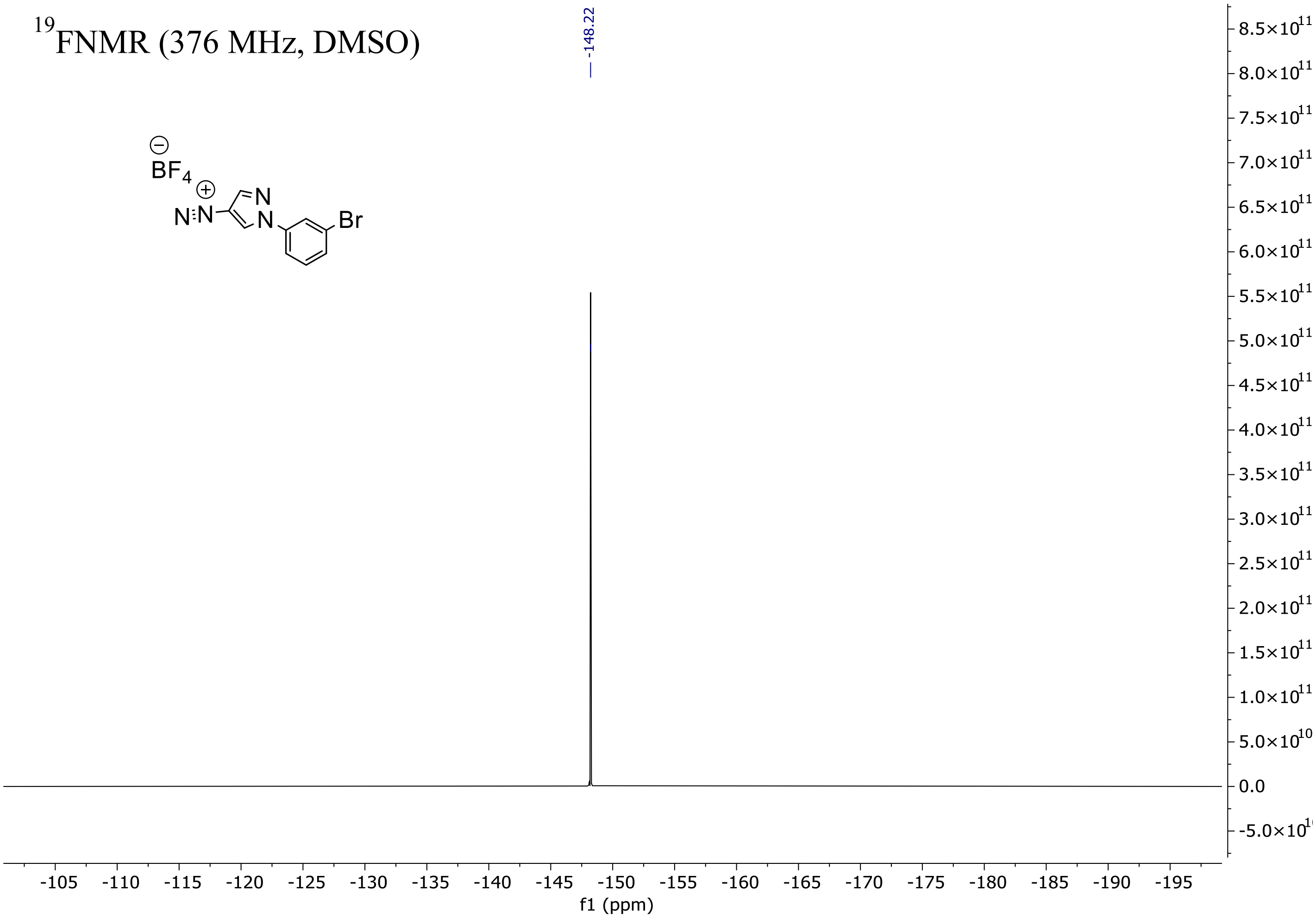


^{1}HNMR (400 MHz, DMSO)
BF_4
N
N
N
N
Br
2.50 DMSO-d6
1.00
0.78
1.03
1.07
1.01
1.07
1.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
2500000
2000000
1500000
1000000
500000
0

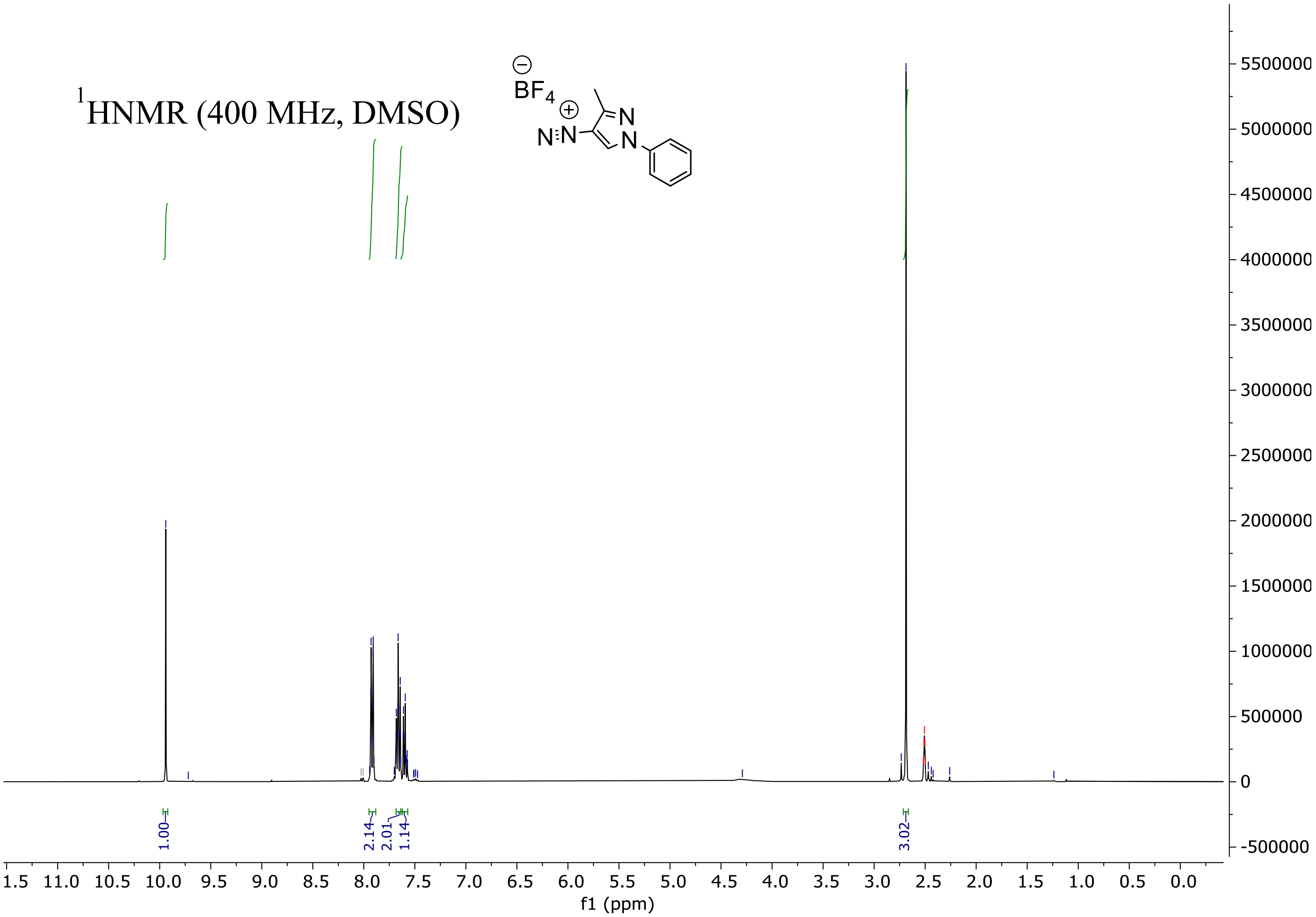
^{13}CNMR (101 MHz, DMSO)



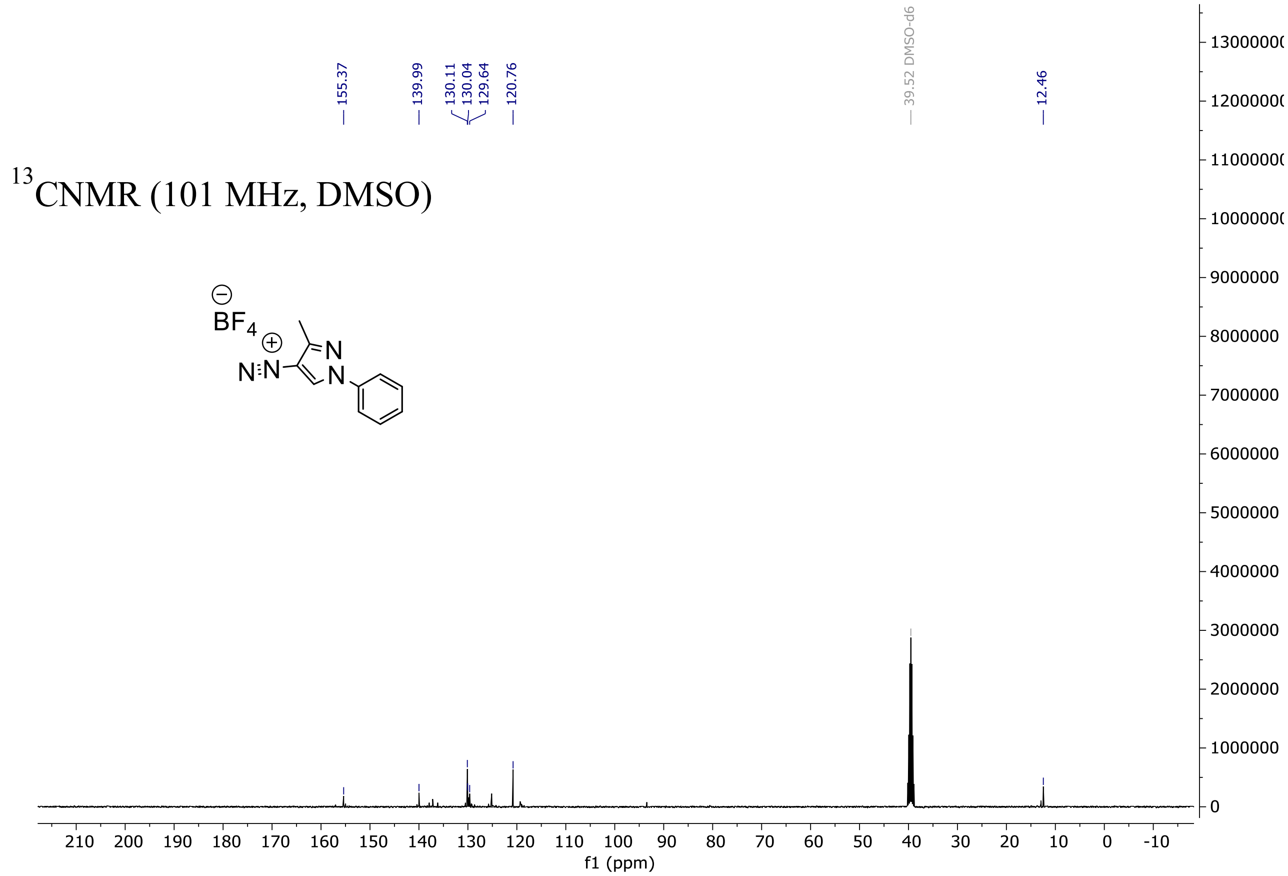
^{19}FNMR (376 MHz, DMSO)



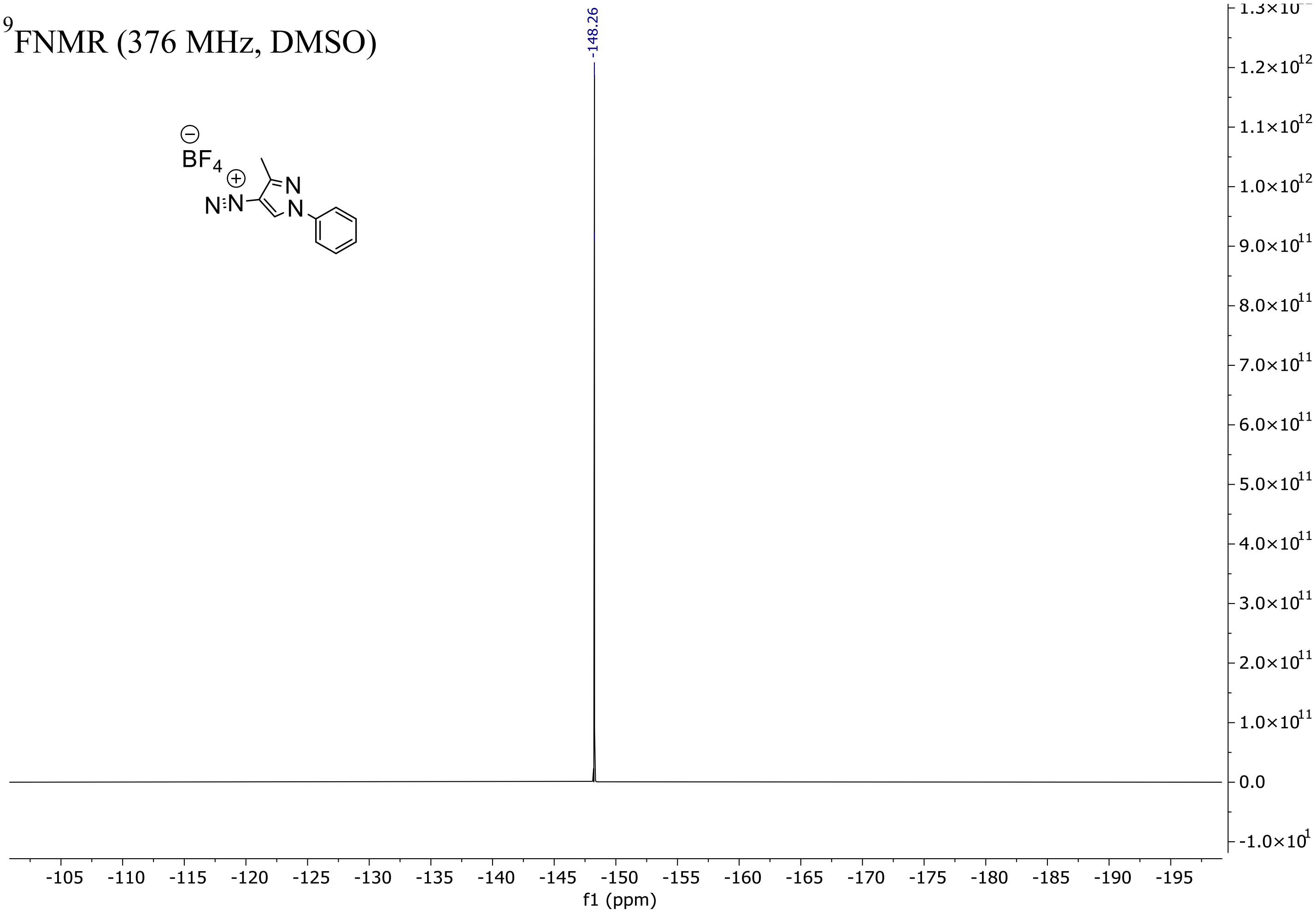
Compound 1m



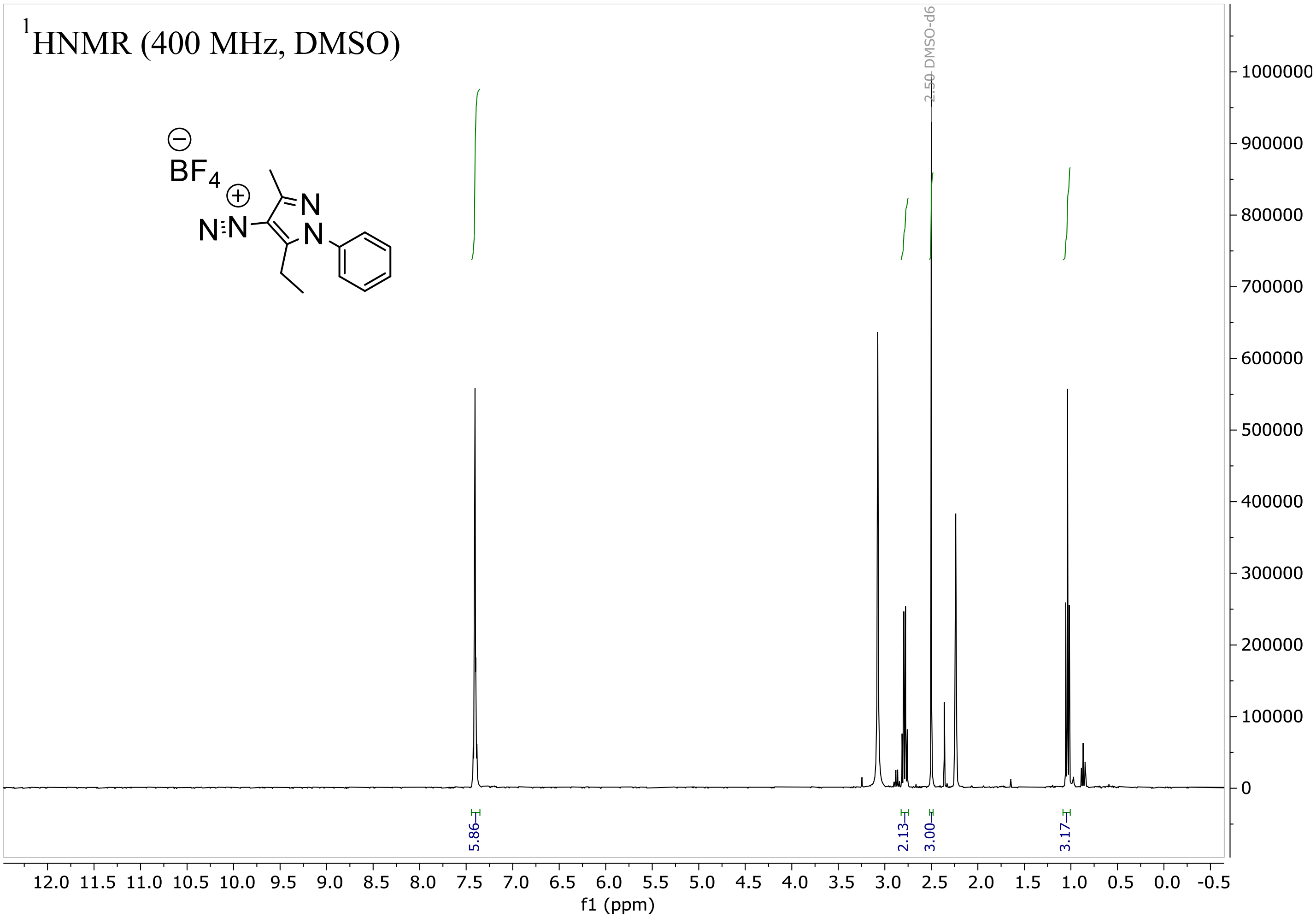
^{1}HNMR (400 MHz, DMSO)
BF4
N
N
N
N
1.00
2.14
2.01
1.14
3.02
f1 (ppm)
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


155.37
139.99
130.11
130.04
129.64
120.76
39.52 DMSO-d6
12.46
13CNMR (101 MHz, DMSO)
BF4
N
N
N
N
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

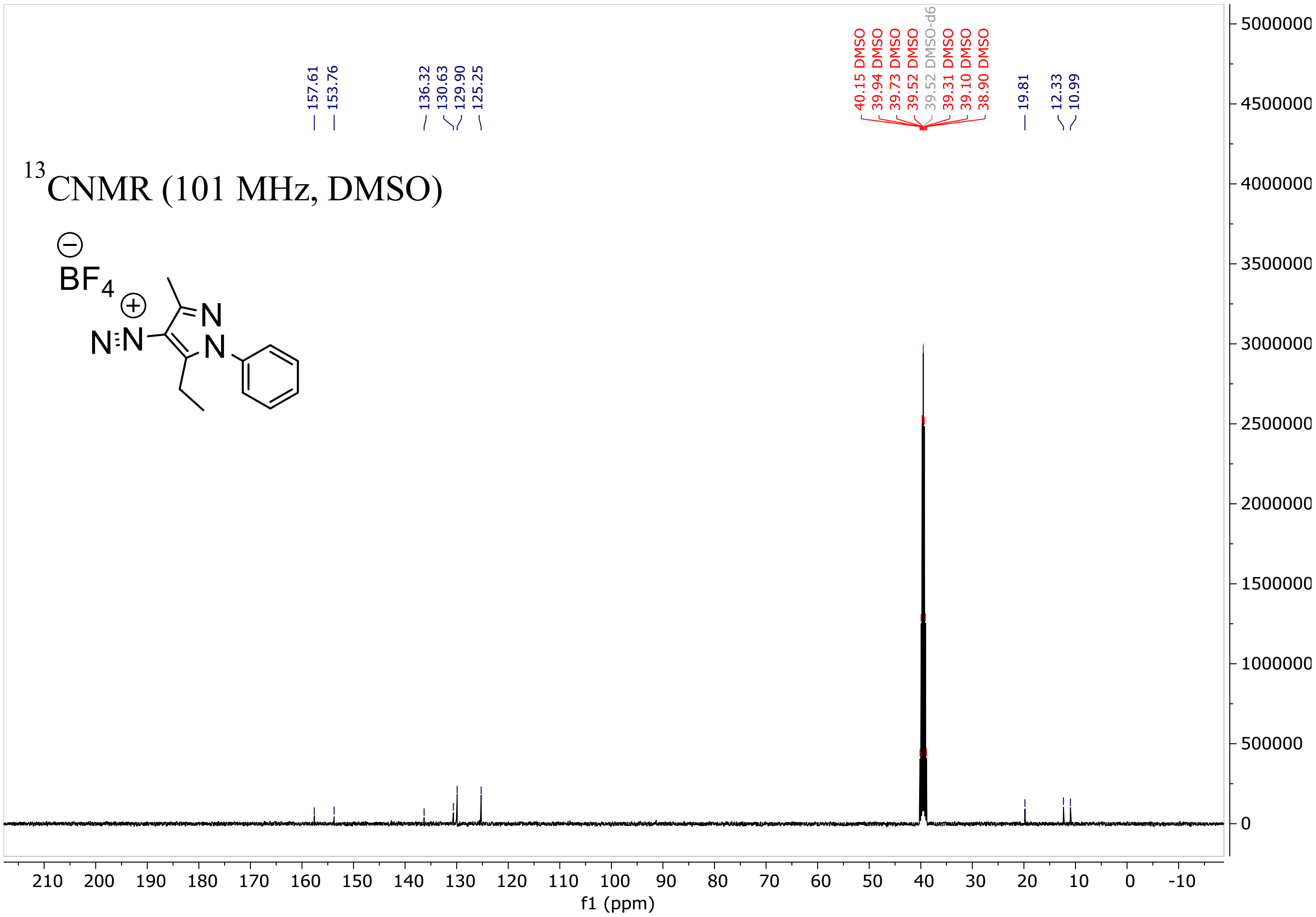
^{19}FNMR (376 MHz, DMSO)



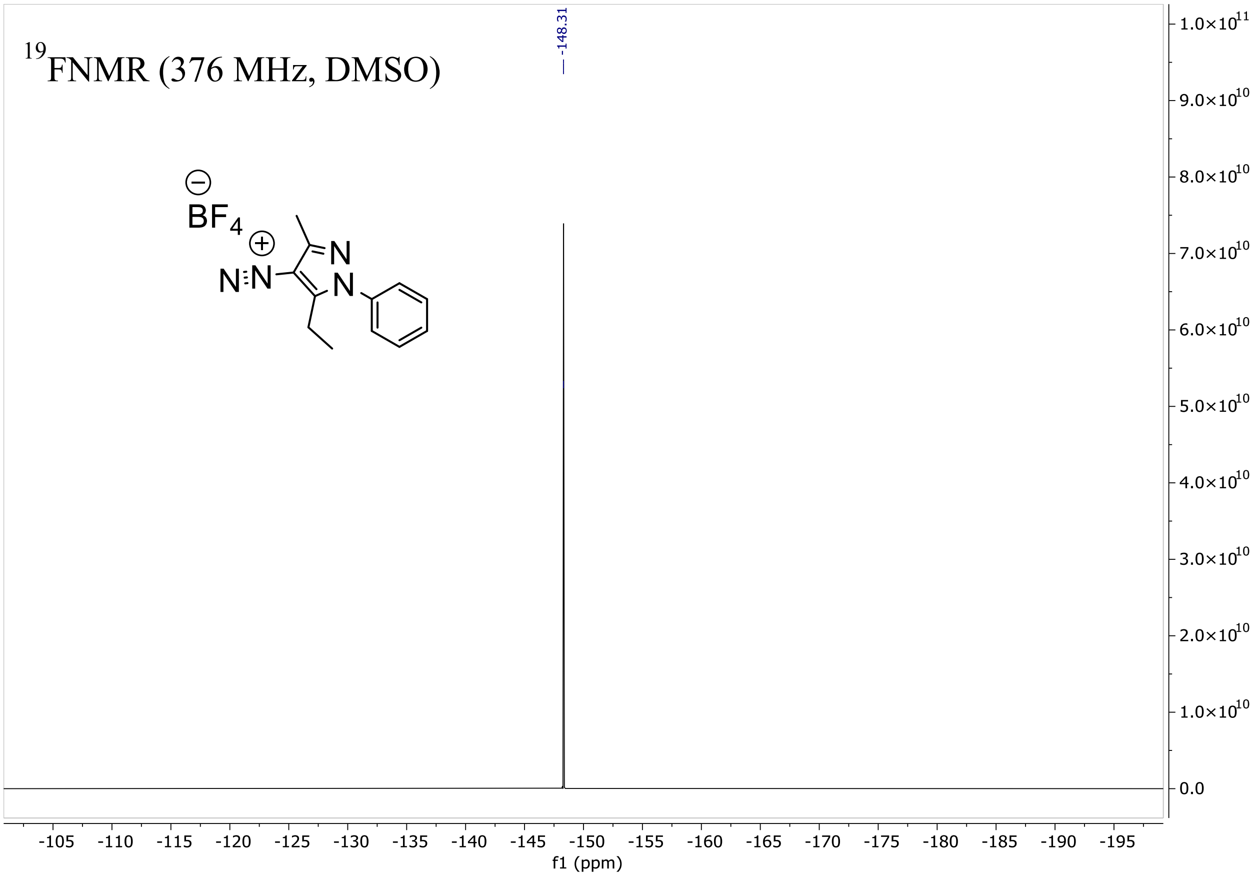
Compound 1n



^{1}HNMR (400 MHz, DMSO)
BF_4
N
N
N
N
2.50 DMSO-d6
5.86
2.13
3.00
3.17
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

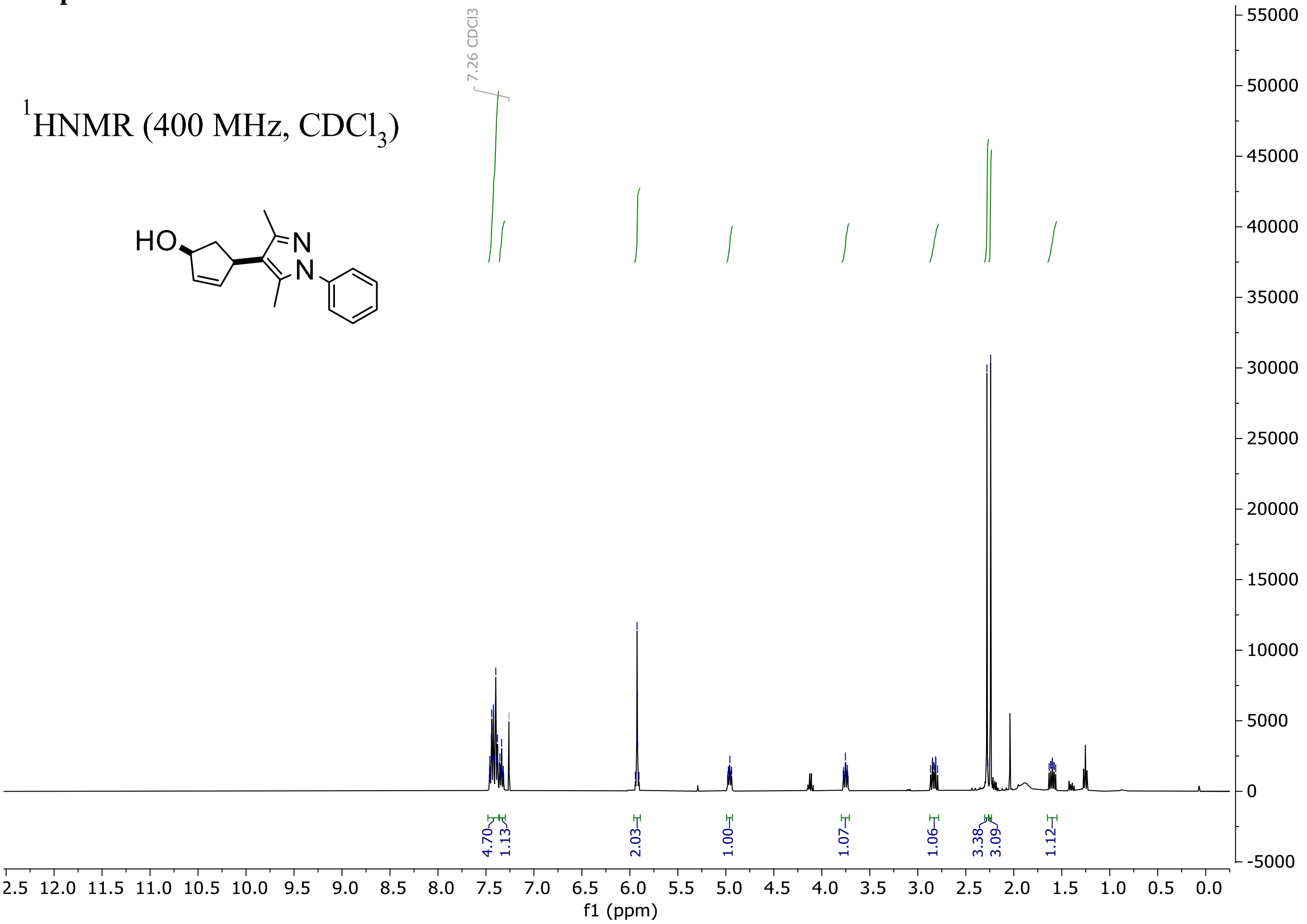


^{13}CNMR (101 MHz, DMSO)


^{19}FNMR (376 MHz, DMSO)
-148.31
BF4
N≡N
N
N
1.0×10^11
9.0×10^10
8.0×10^10
7.0×10^10
6.0×10^10
5.0×10^10
4.0×10^10
3.0×10^10
2.0×10^10
1.0×10^10
0.0
-105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195
f1 (ppm)

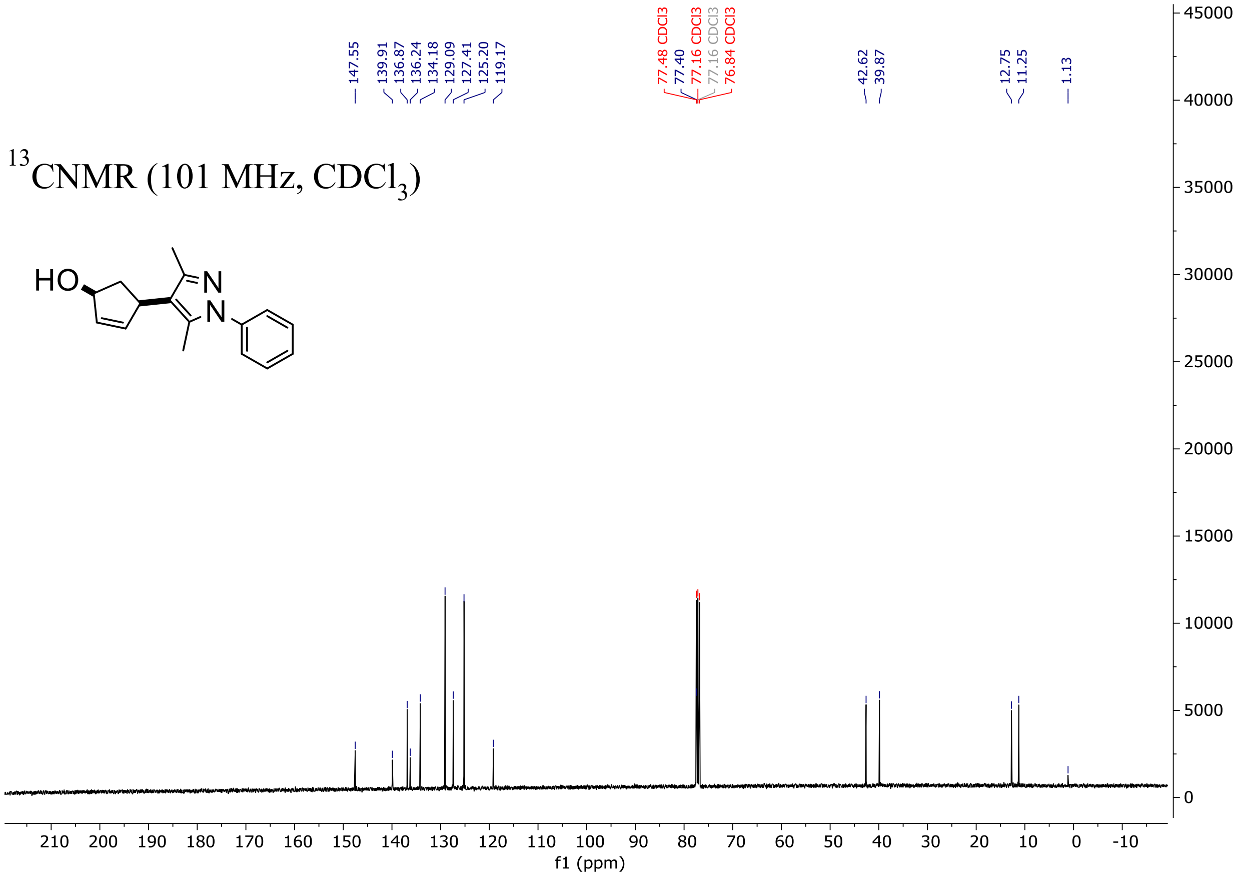
5.2 4-Pyrazolyl-cyclopent-2-en-1-ols **2a-n**

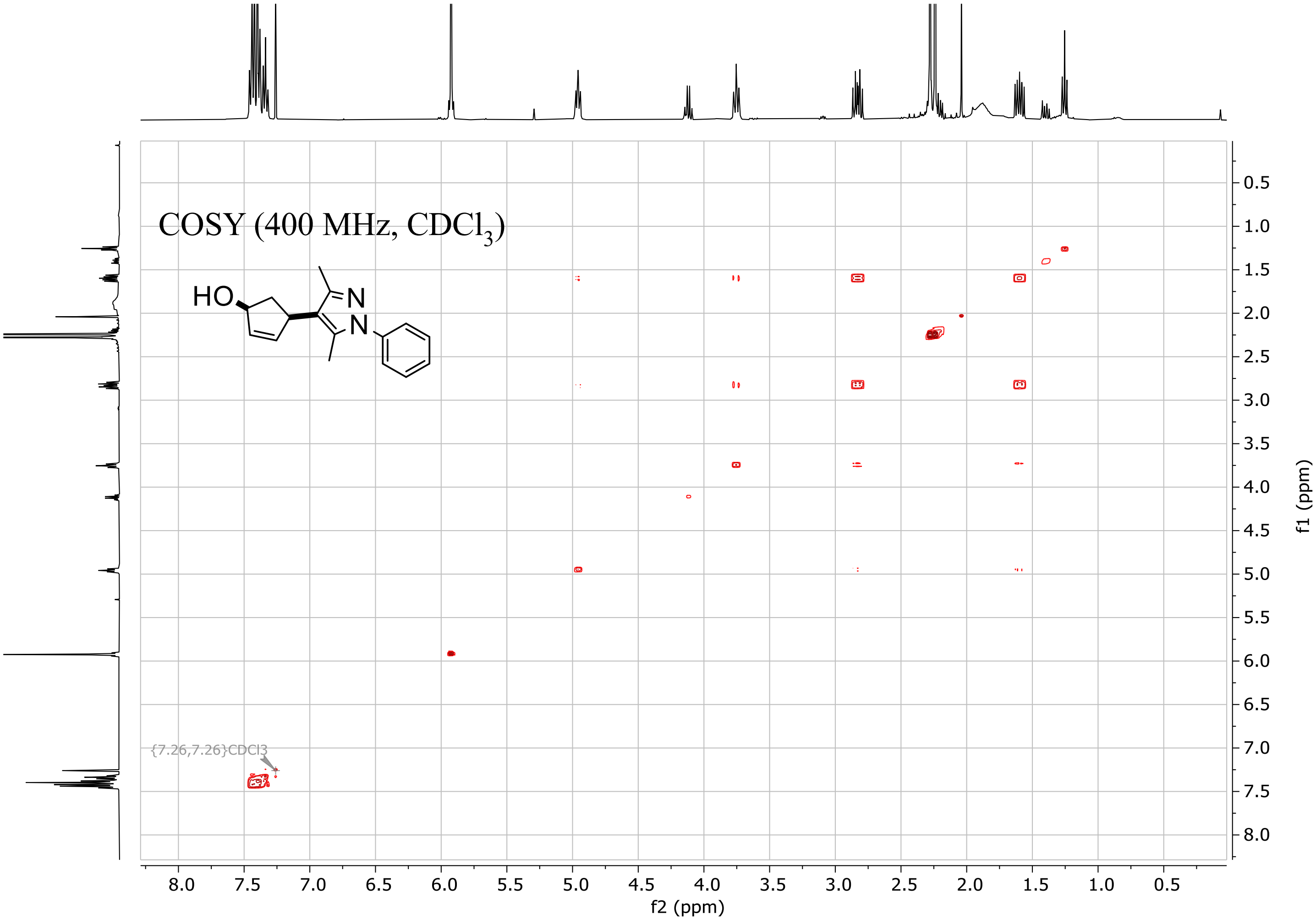
Compound 2a

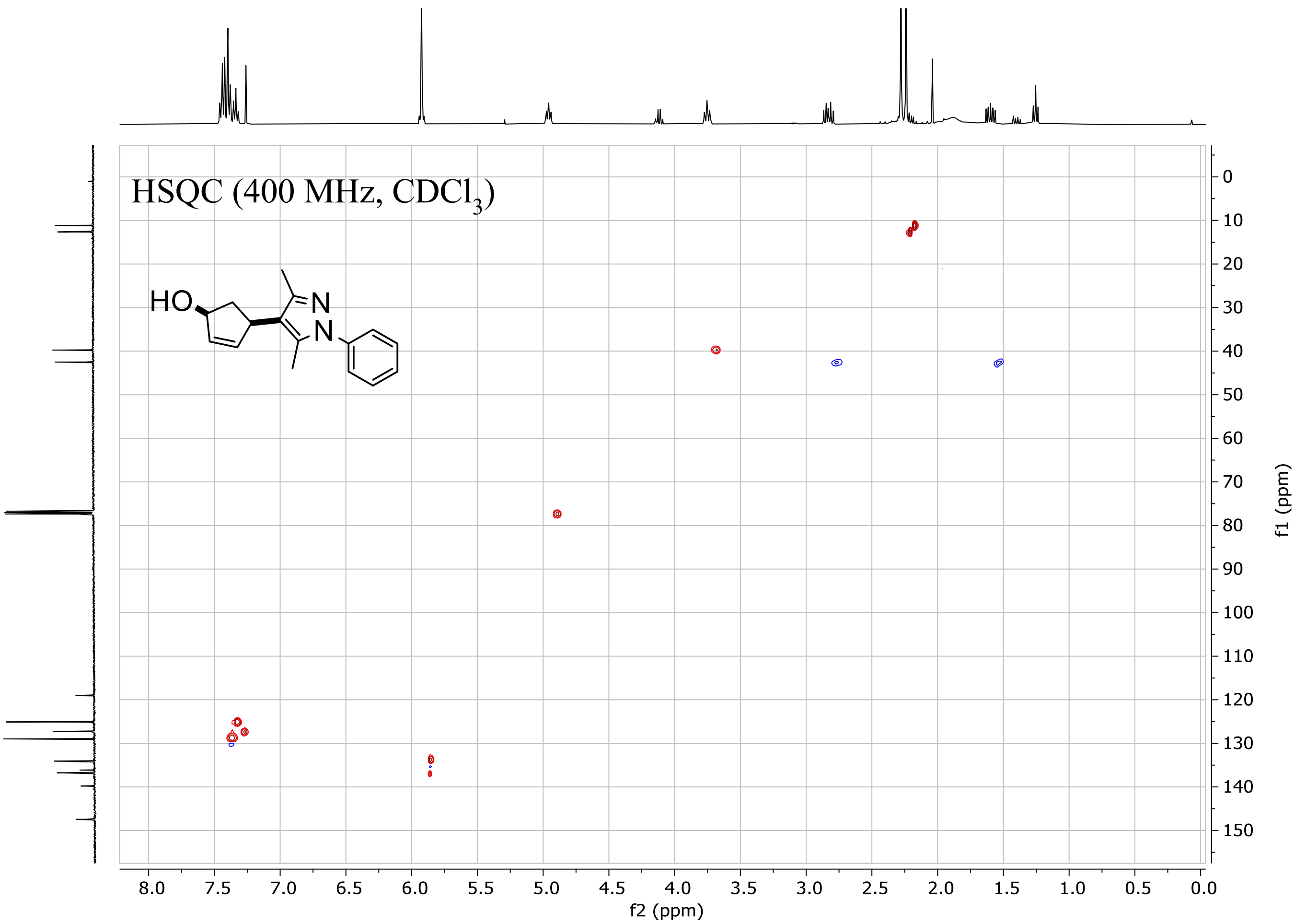


^{1}HNMR (400 MHz, $CDCl_3$)

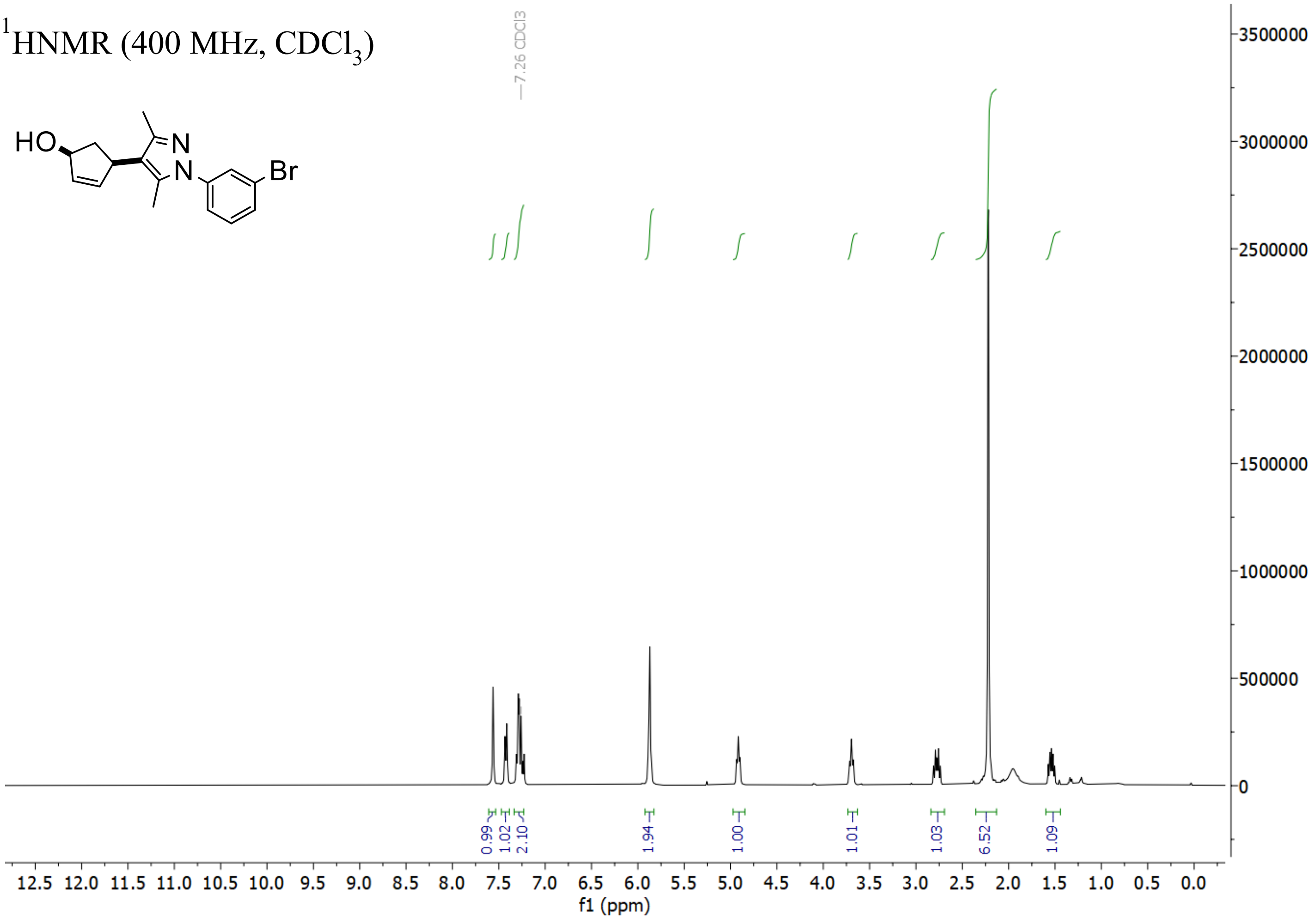
^{13}CNMR (101 MHz, $CDCl_3$)

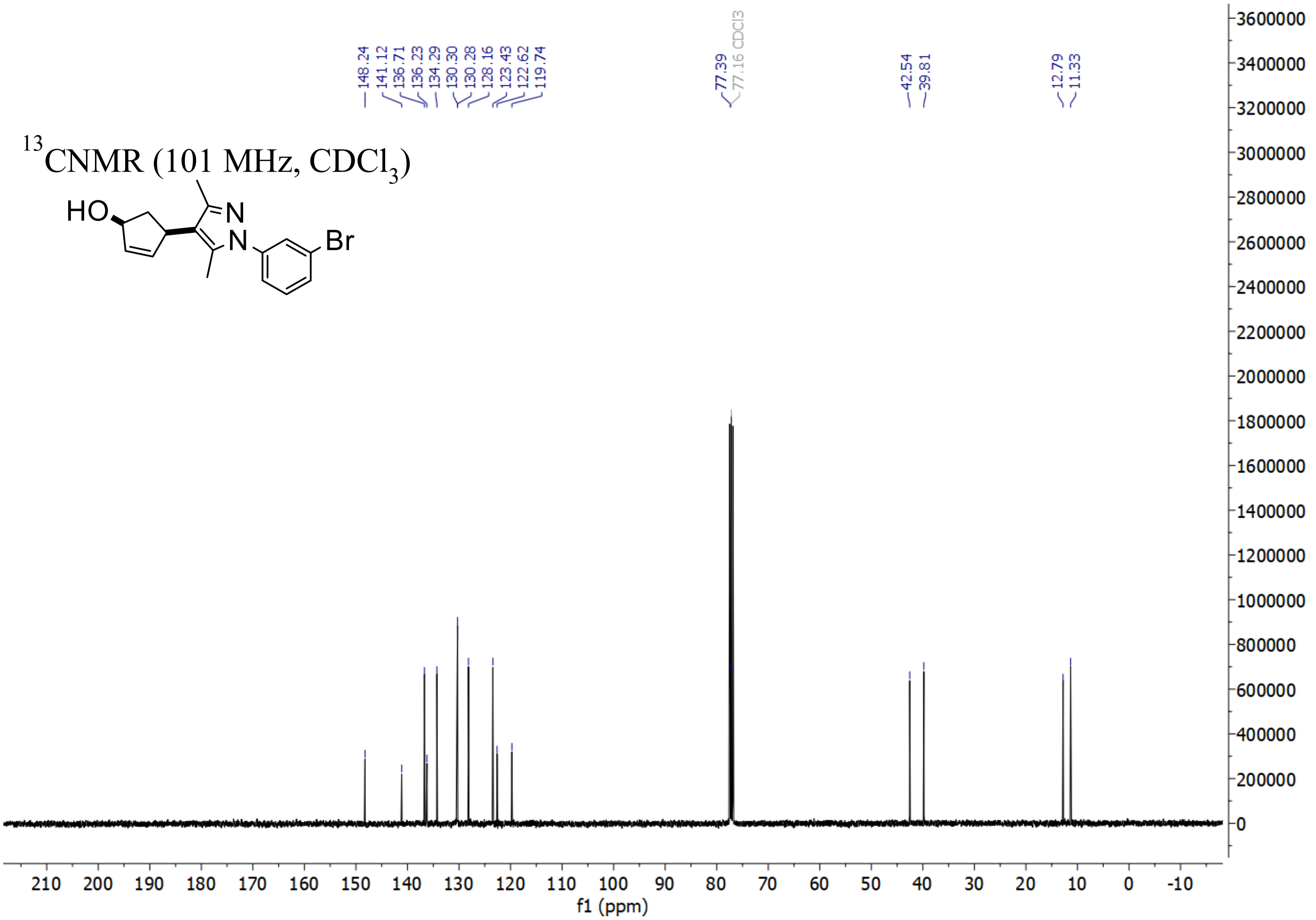



COSY (400 MHz, CDCl3)
HO
N
N
{7.26,7.26}CDCl3
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

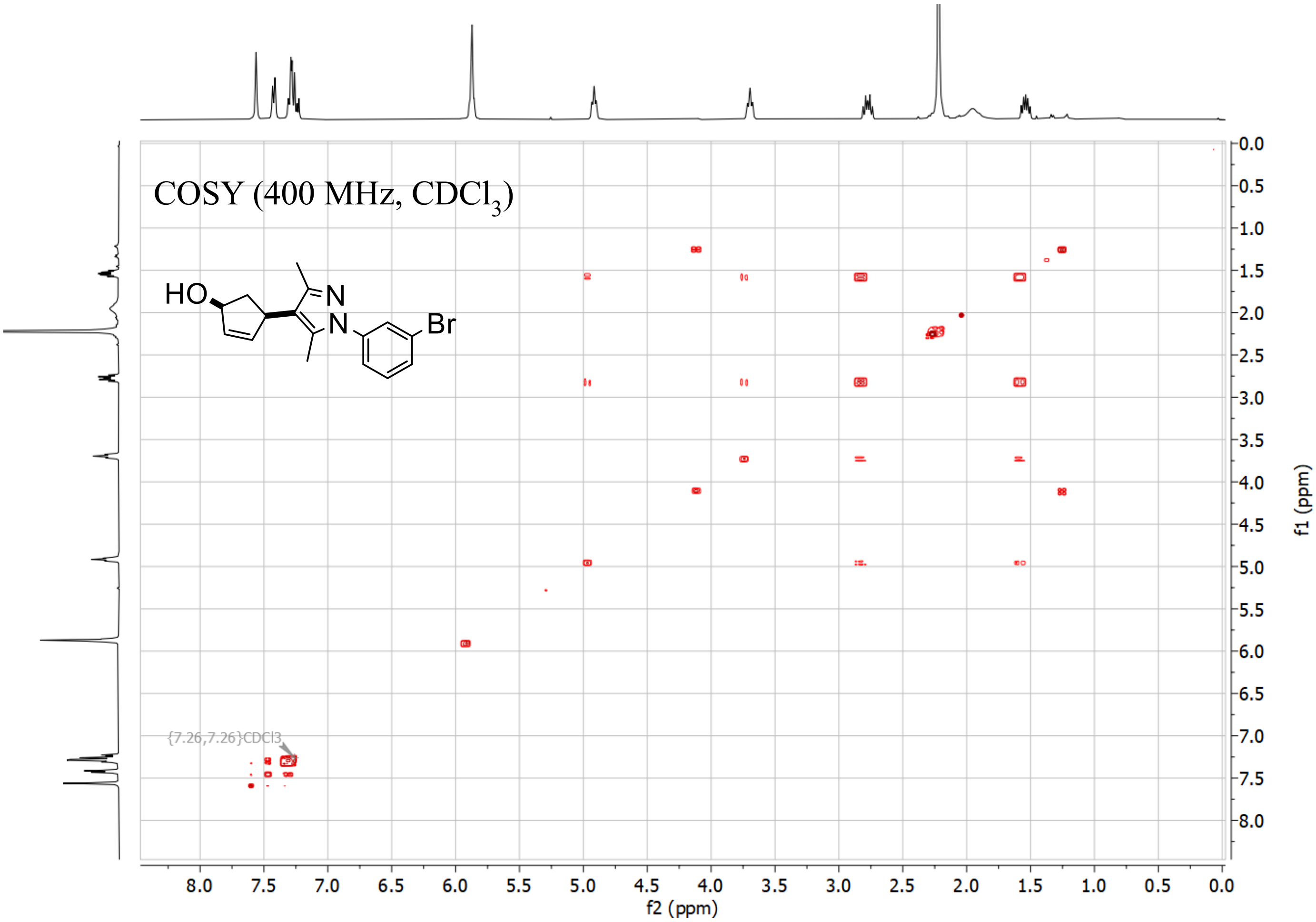

HSQC (400 MHz, CDCl$_3$)
HO
N
N
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

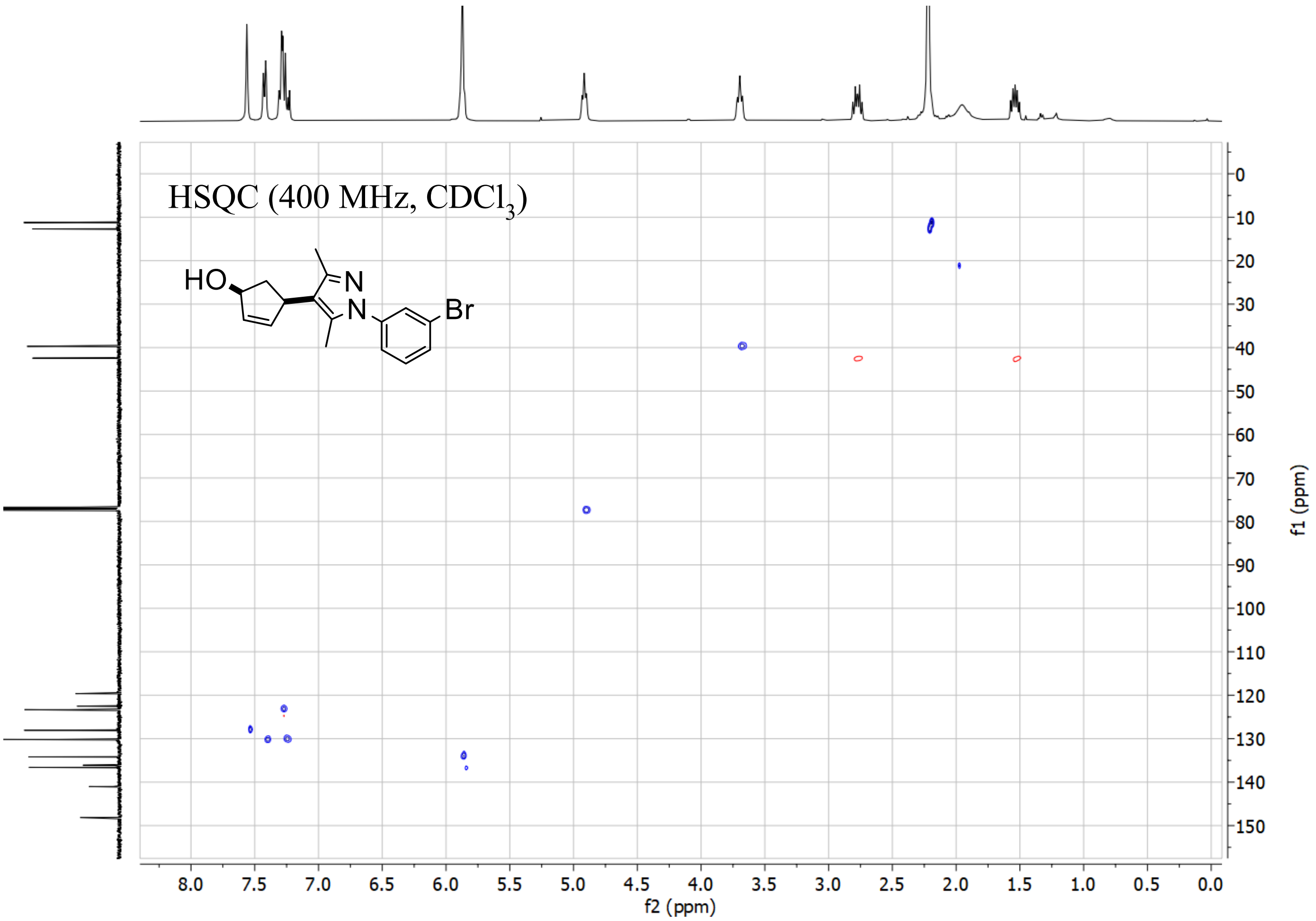
Compound 2b


^{1}HNMR (400 MHz, $CDCl_3$)

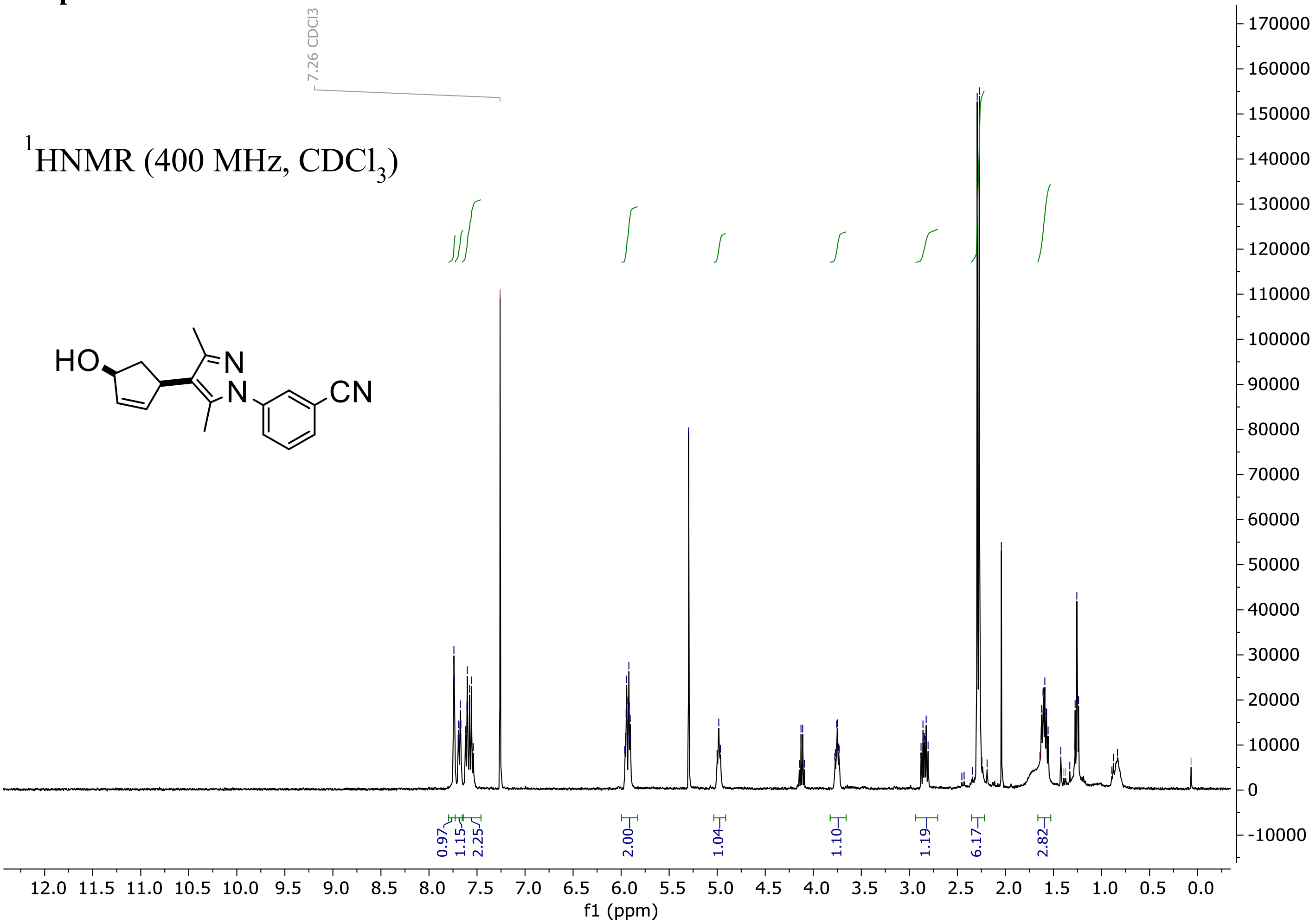


^{13}CNMR (101 MHz, $CDCl_3$)


COSY (400 MHz, CDCl$_3$)
HO
N
N
Br
{7.26,7.26}CDCl3
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

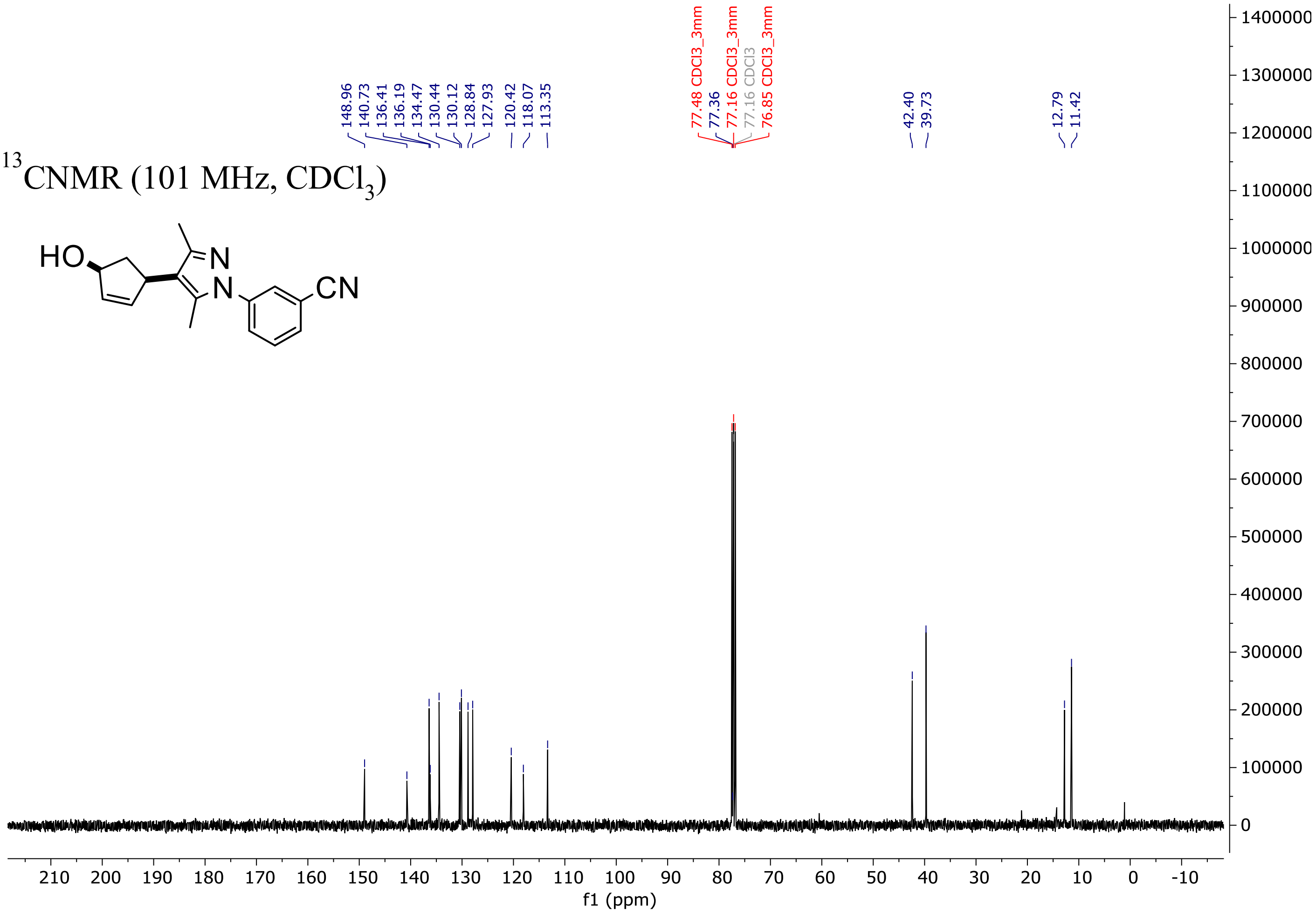

HSQC (400 MHz, CDCl$_3$)
HO
N
N
Br
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)

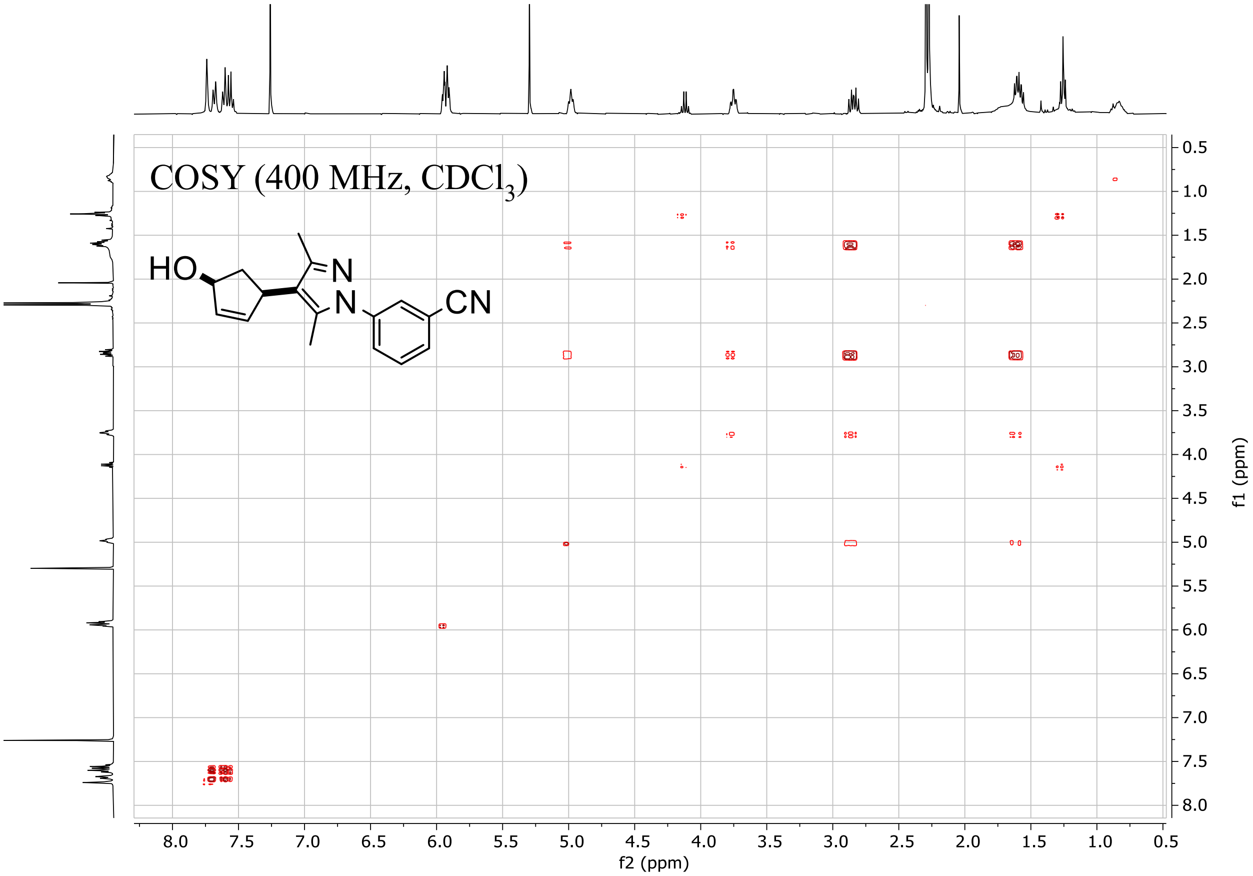
Compound 2c

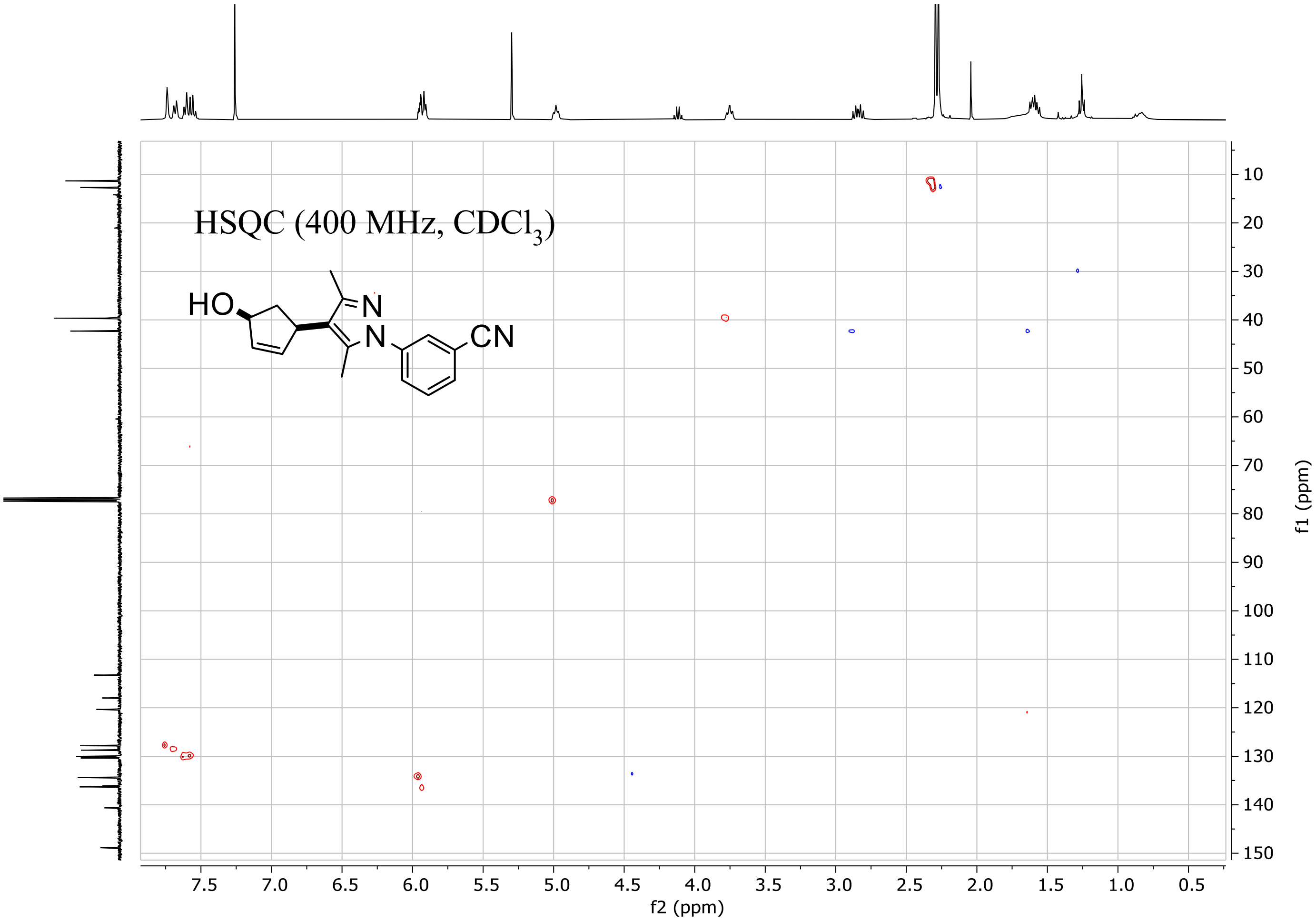


7.26 CDCl3
^{1}HNMR (400 MHz, CDCl$_3$)
HO
N
N
CN
0.97
1.15
2.25
2.00
1.04
1.10
1.19
6.17
2.82
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

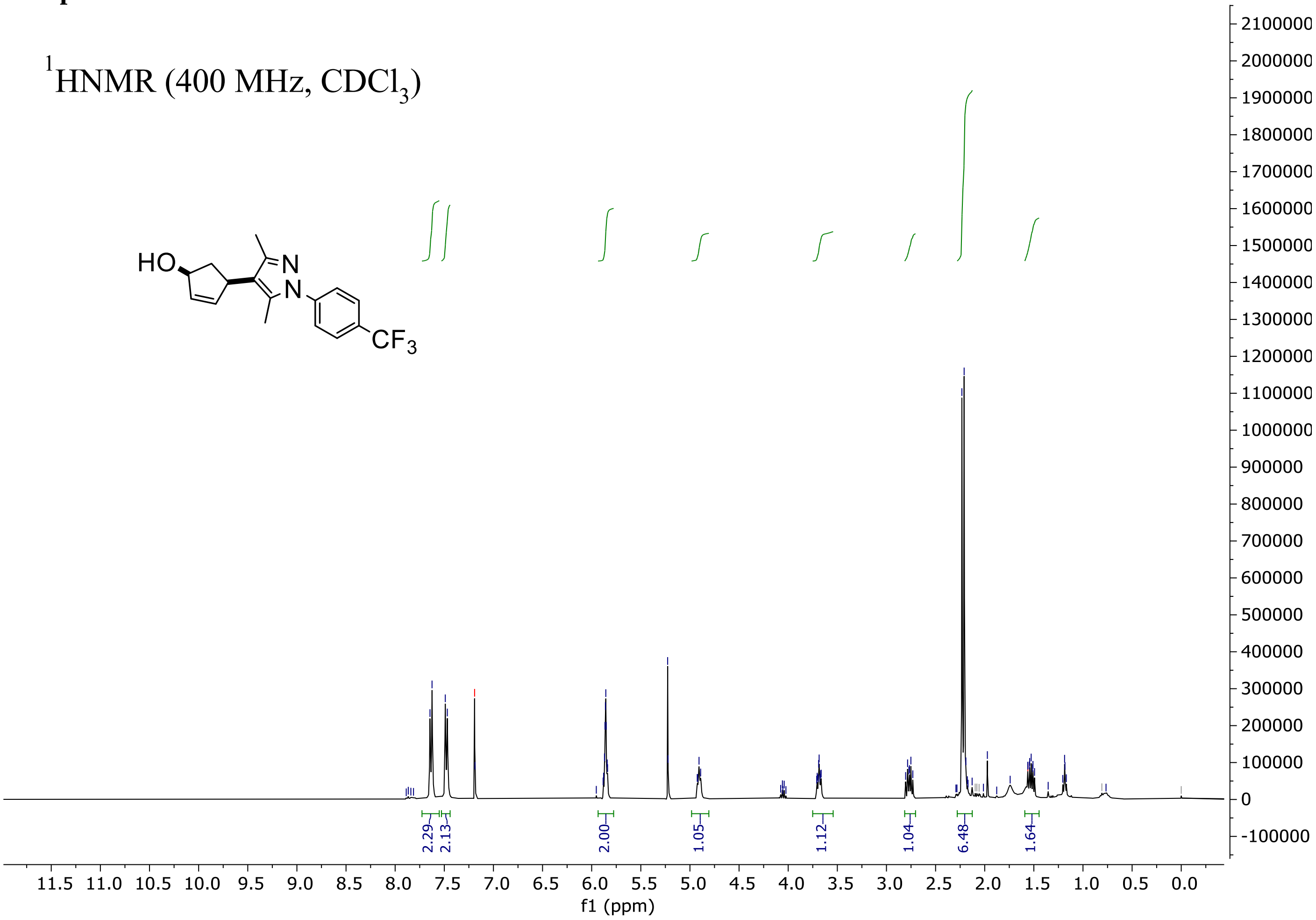
^{13}CNMR (101 MHz, $CDCl_3$)



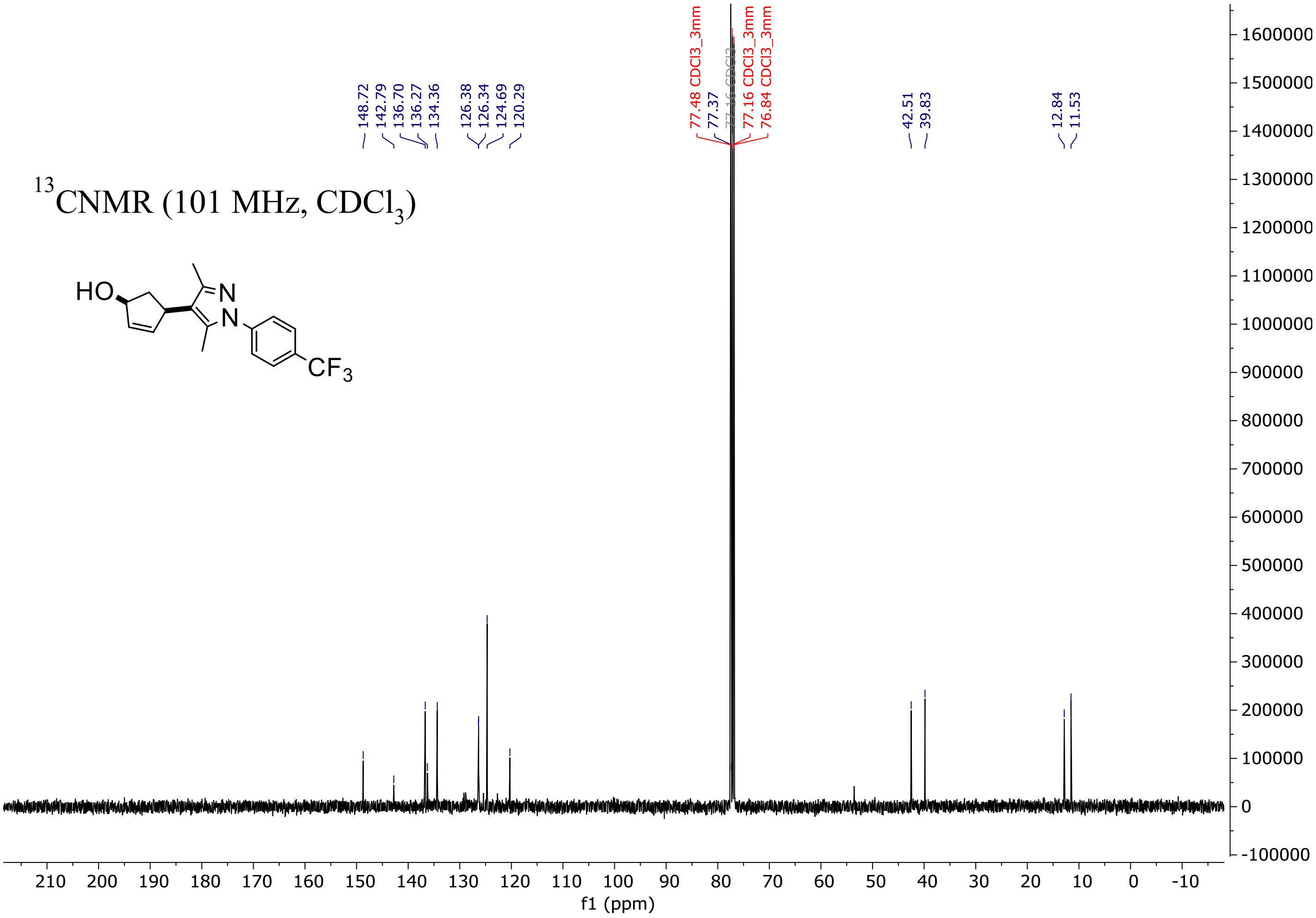

COSY (400 MHz, CDCl$_3$)
HO
N
N
CN
f1 (ppm)
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0


HSQC (400 MHz, CDCl$_3$)
HO
N
N
CN
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

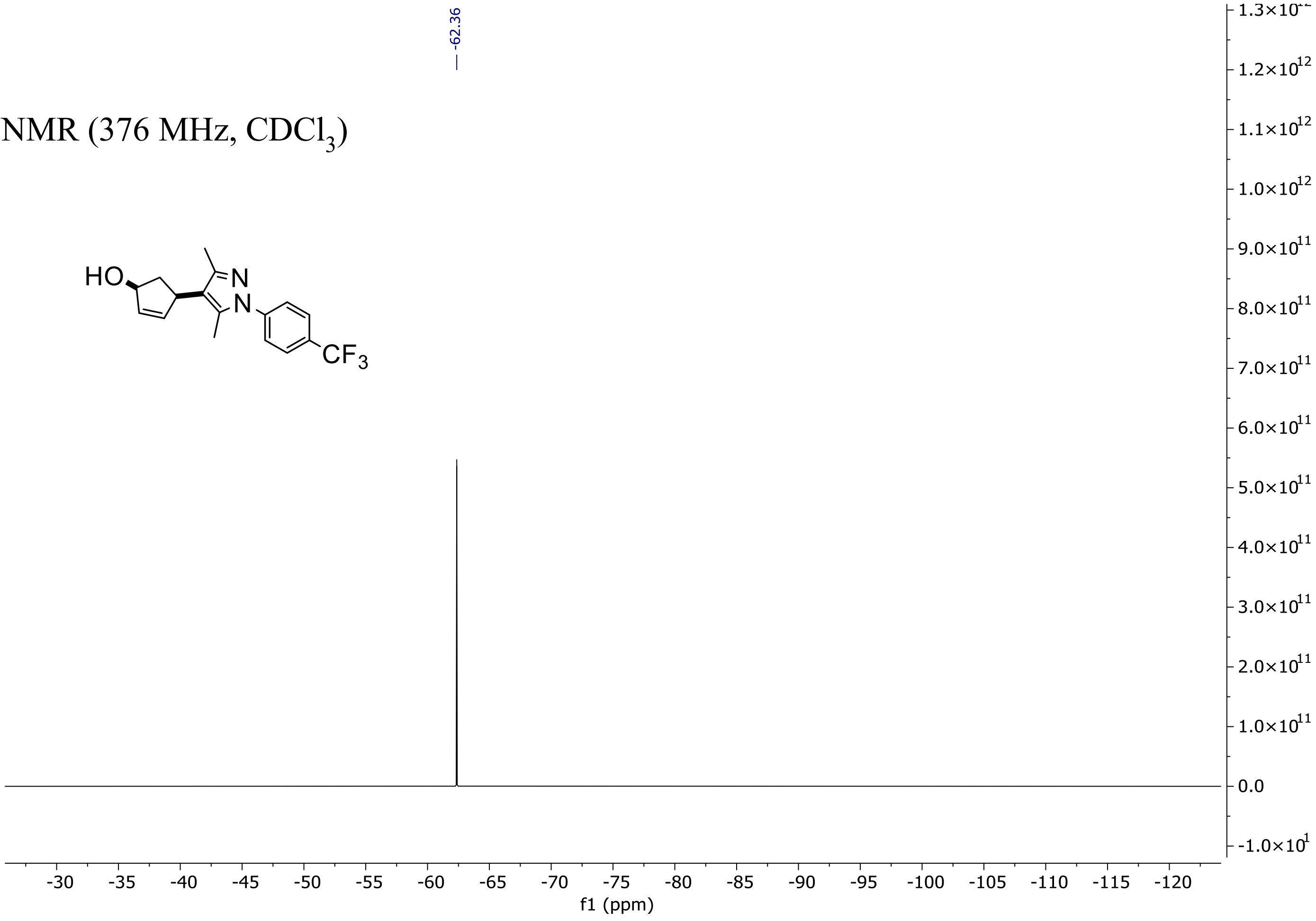
Compound 2d

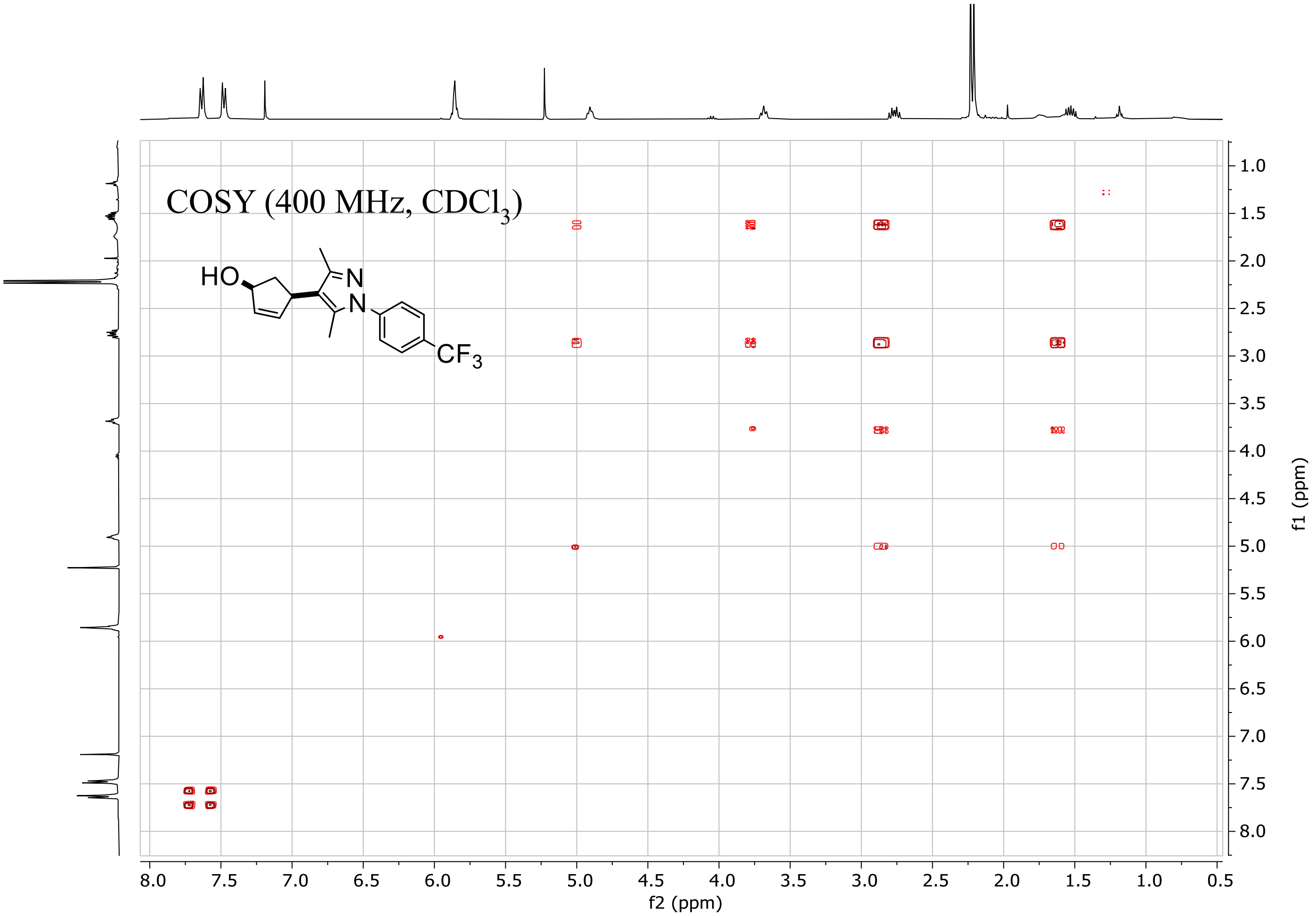

^{1}HNMR (400 MHz, $CDCl_3$)
HO
N
N
CF_3
2100000
2000000
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
2.29
2.13
2.00
1.05
1.12
1.04
6.48
1.64
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

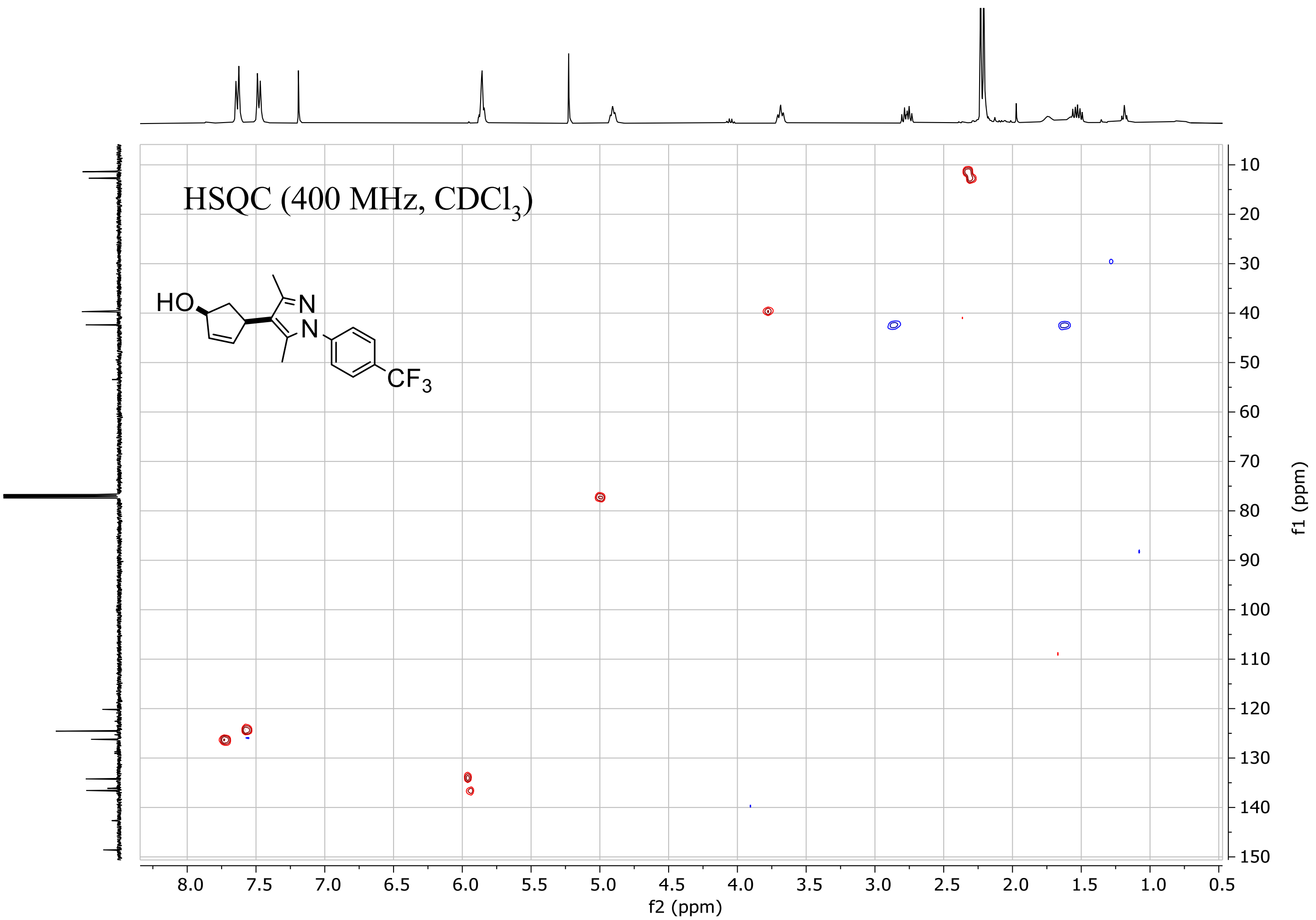
^{13}CNMR (101 MHz, $CDCl_3$)



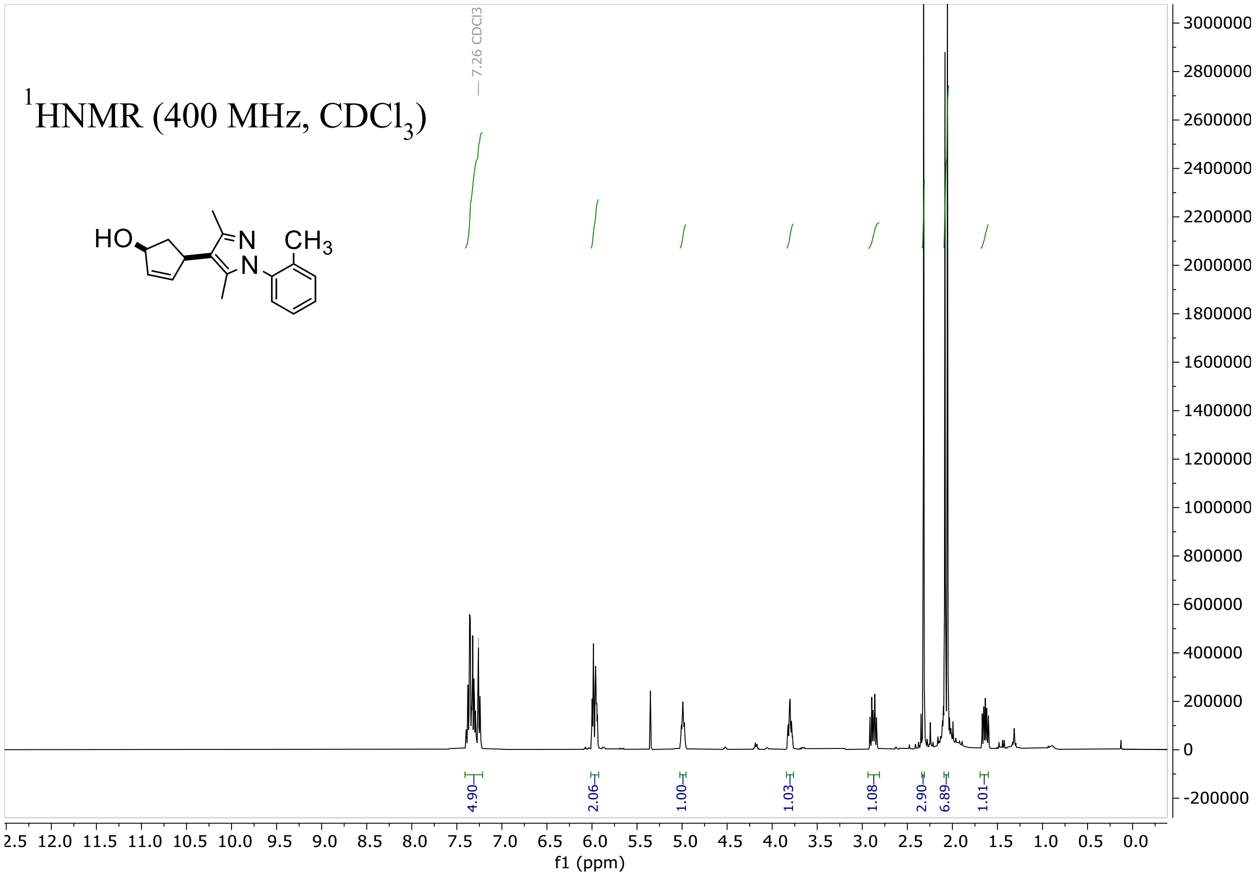
^{19}FNMR (376 MHz, $CDCl_3$)

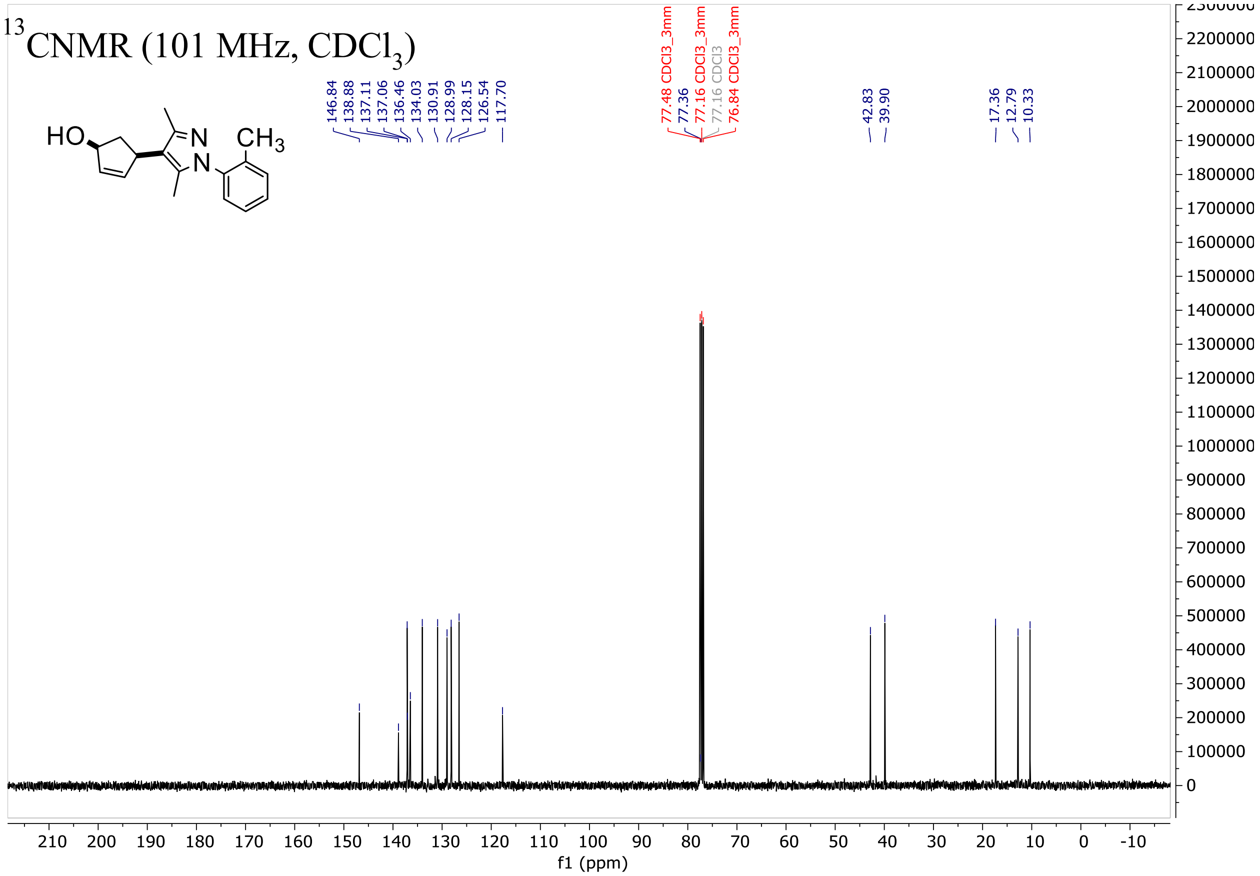



COSY (400 MHz, CDCl$_3$)
HO
N
N
CF$_3$
f1 (ppm)
f2 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

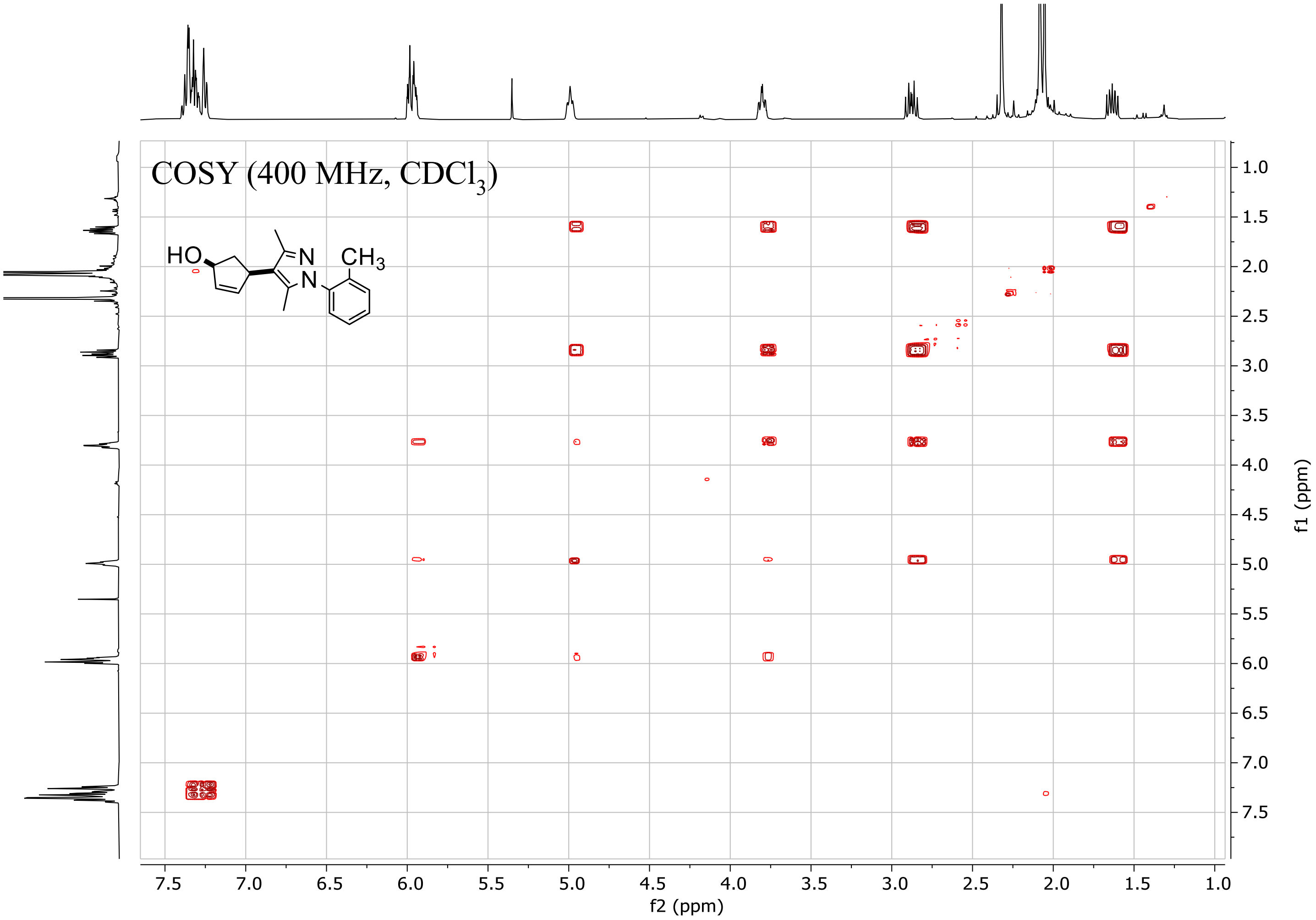

HSQC (400 MHz, $CDCl_3$)
HO
N
N
CF_3
f2 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150

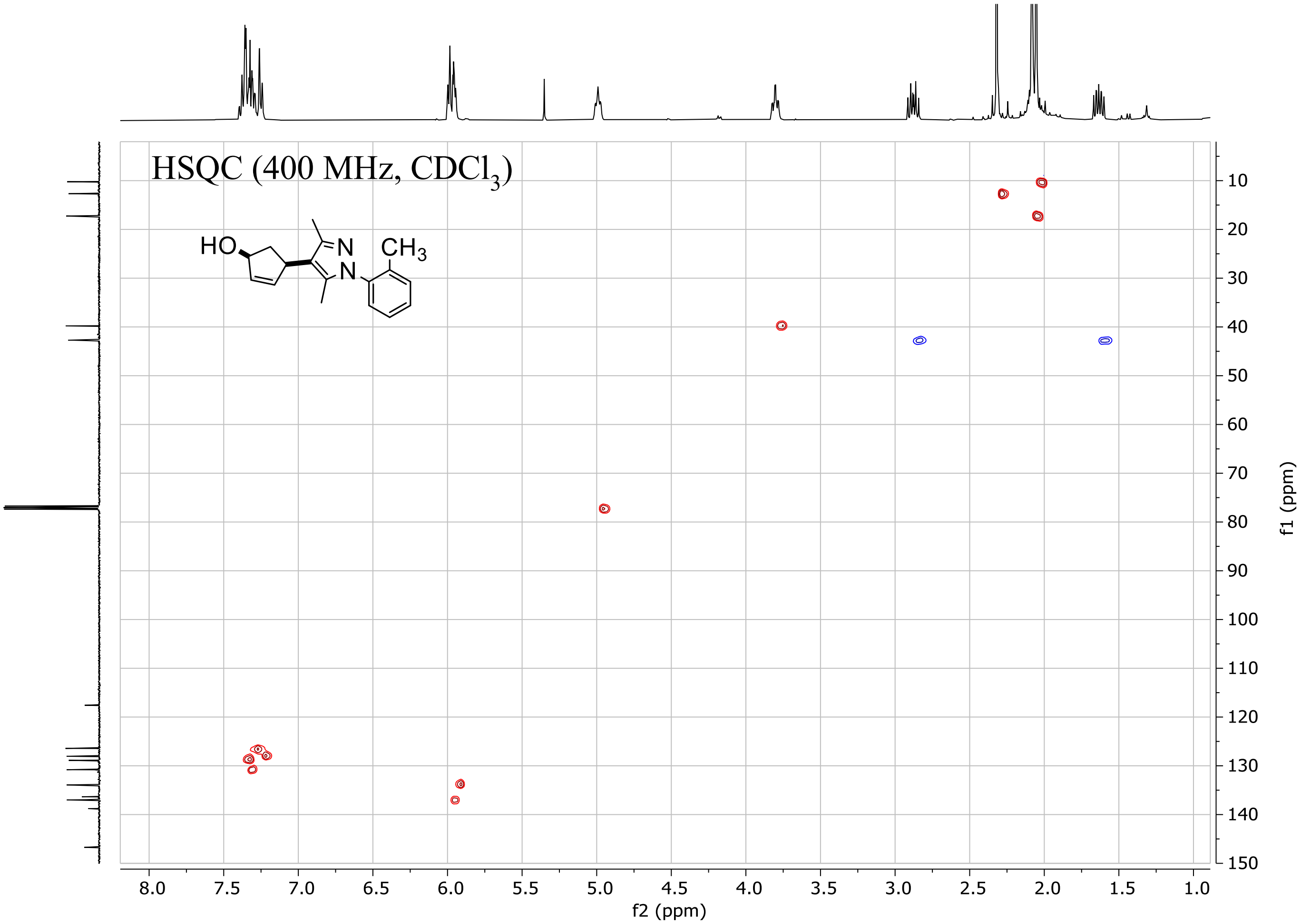
Compound 2e


^{1}HNMR (400 MHz, $CDCl_3$)
7.26 CDCl3
HO
N
N
CH3
4.90
2.06
1.00
1.03
1.08
2.90
6.89
1.01
2.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000

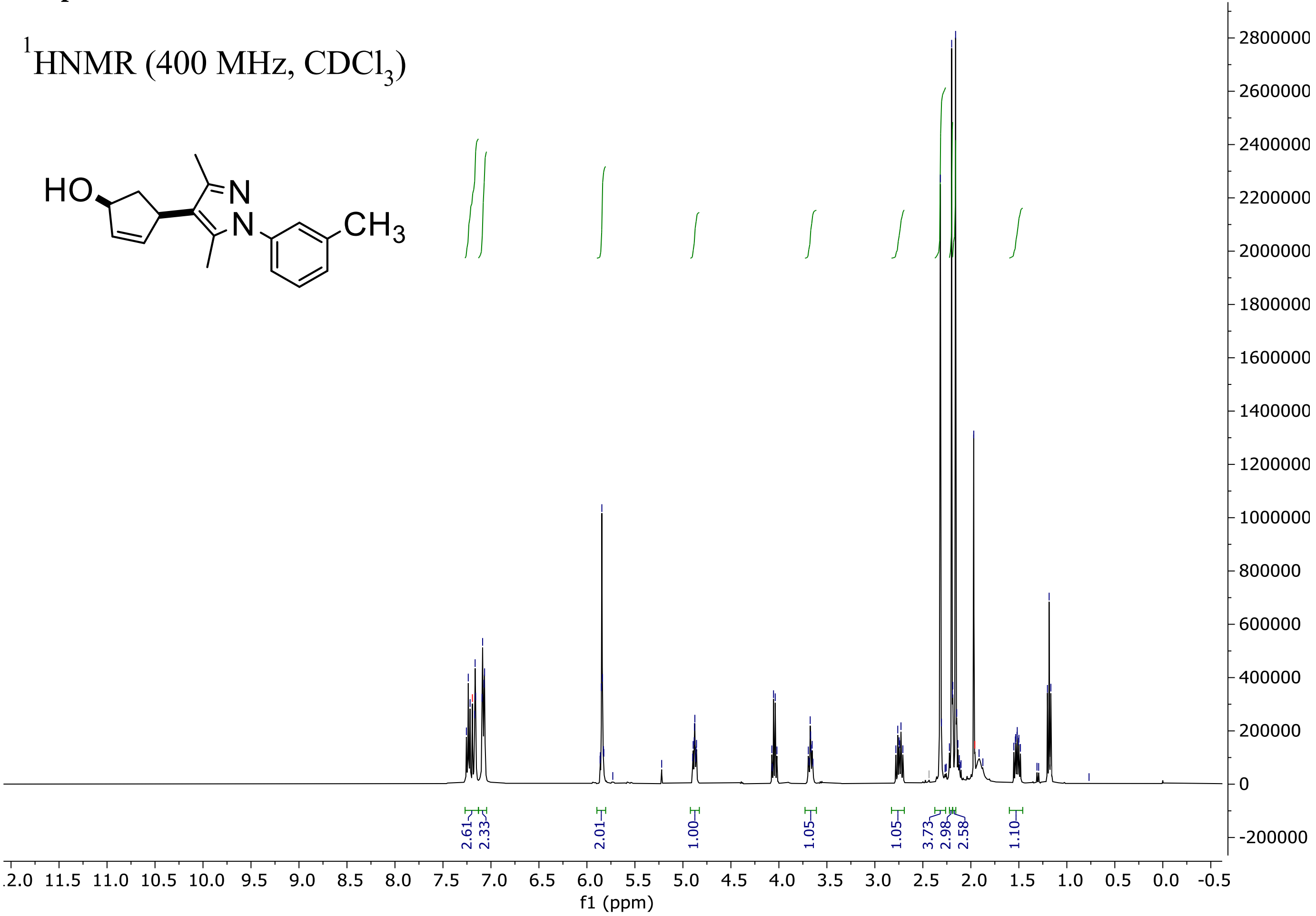


^{13}CNMR (101 MHz, $CDCl_3$)

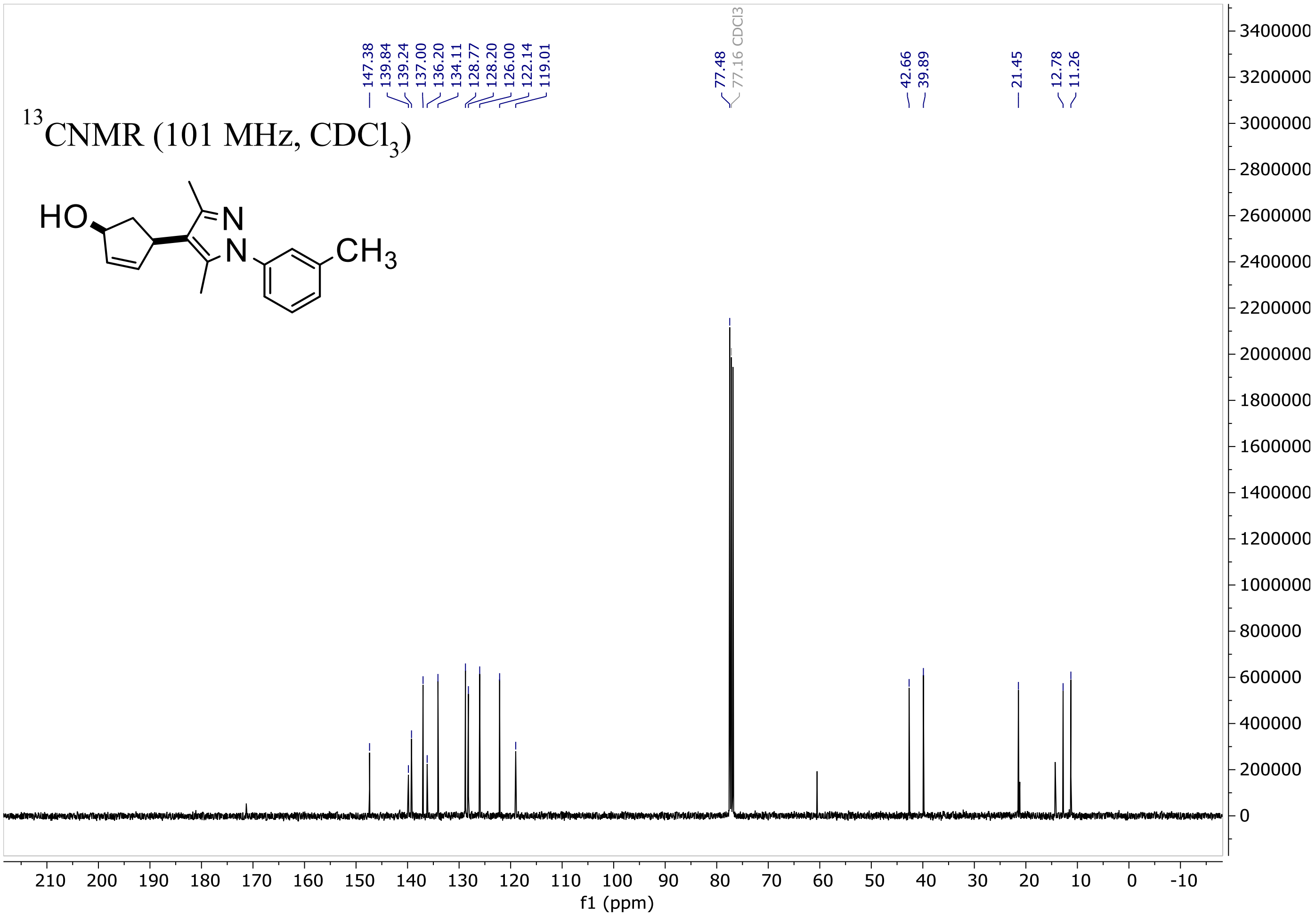

COSY (400 MHz, $CDCl_3$)
HO
N
N
CH_3
f1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f2 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

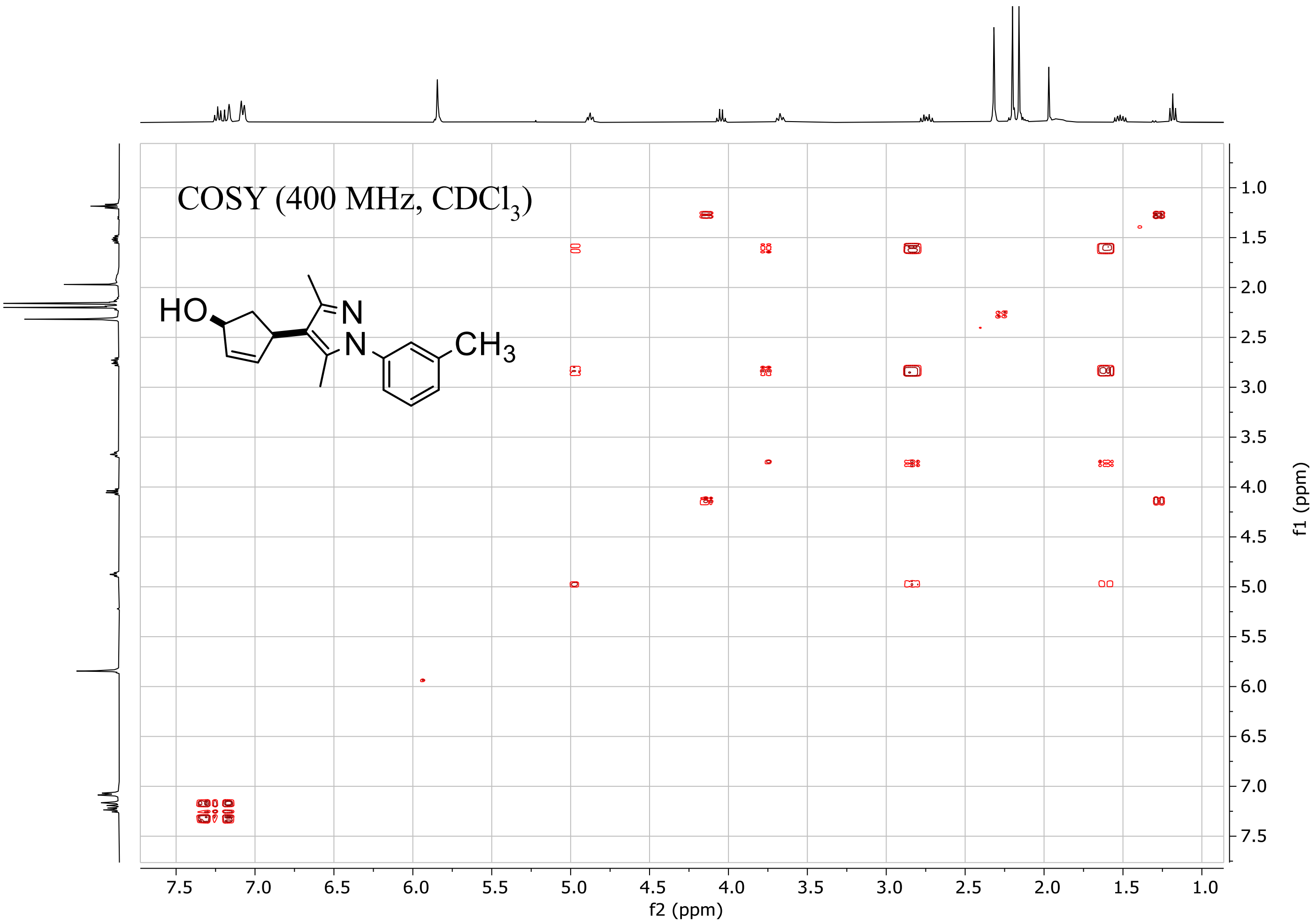

HSQC (400 MHz, CDCl$_3$)
HO
N
N
CH$_3$
f1 (ppm)
f2 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

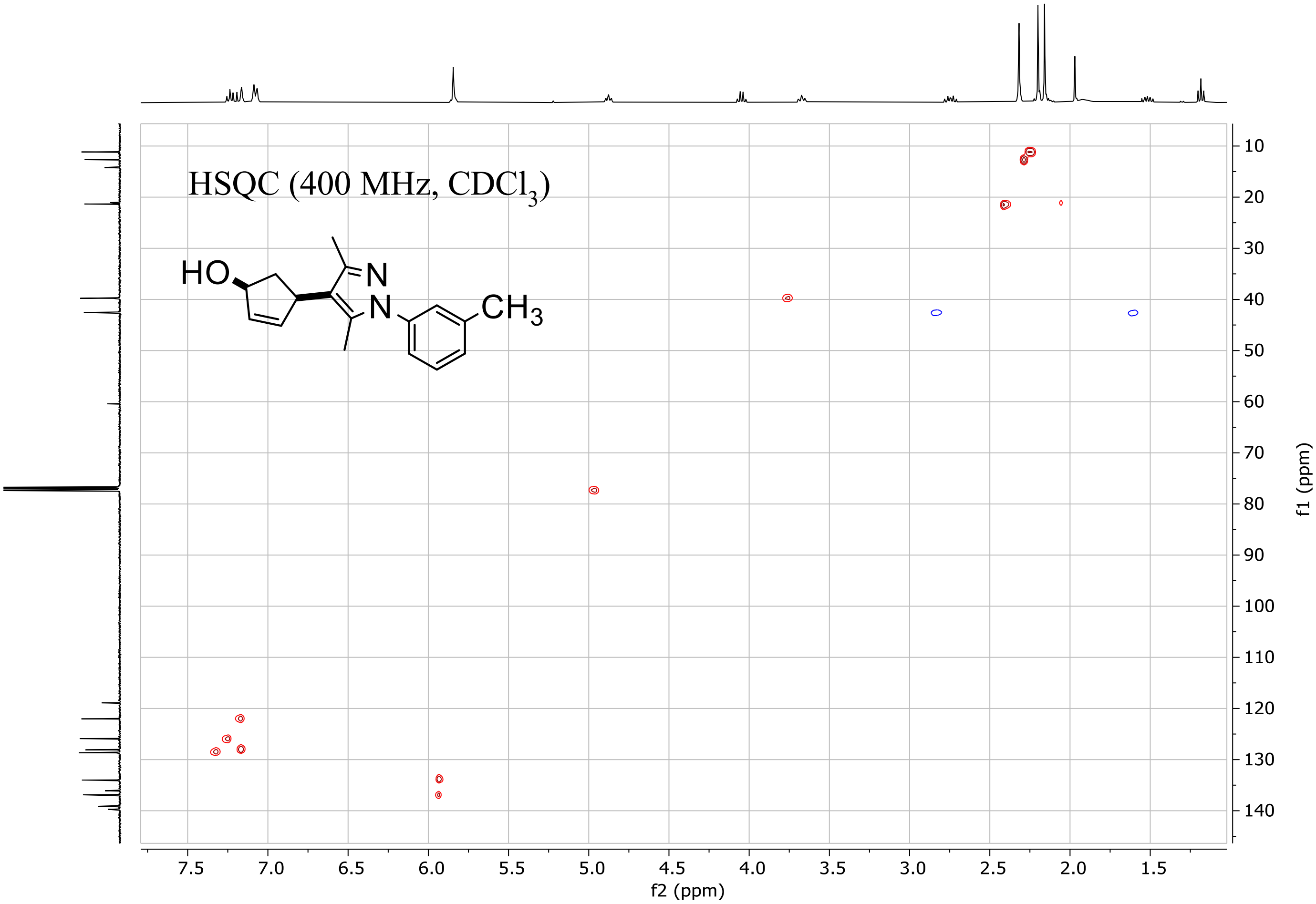
Compound 2f



^{1}HNMR (400 MHz, CDCl$_3$)

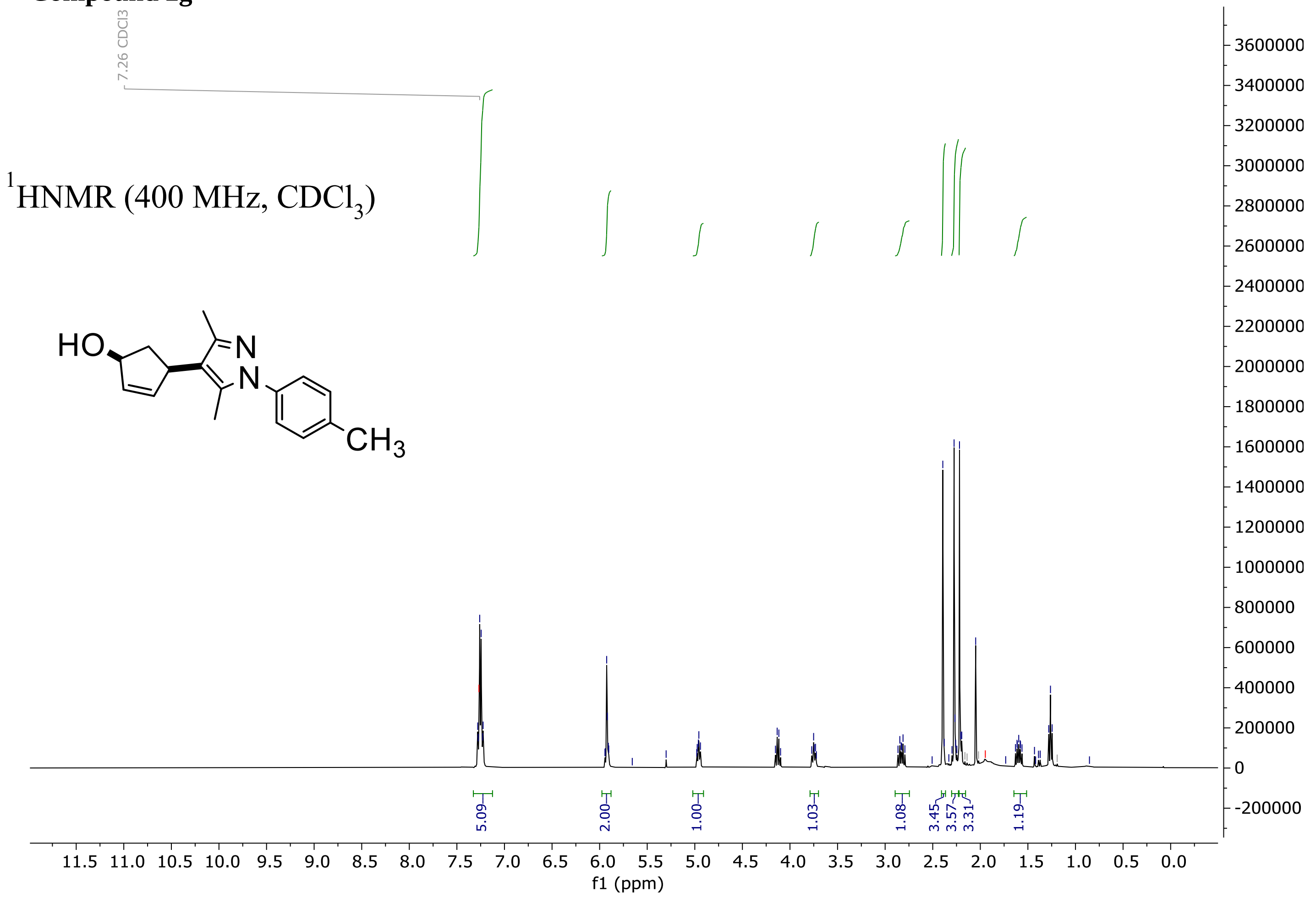

^{13}CNMR (101 MHz, CDCl$_3$)
HO
N
N
CH$_3$
147.38
139.84
139.24
137.00
136.20
134.11
128.77
128.20
126.00
122.14
119.01
77.48
77.16 CDCl3
42.66
39.89
21.45
12.78
11.26
3400000
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

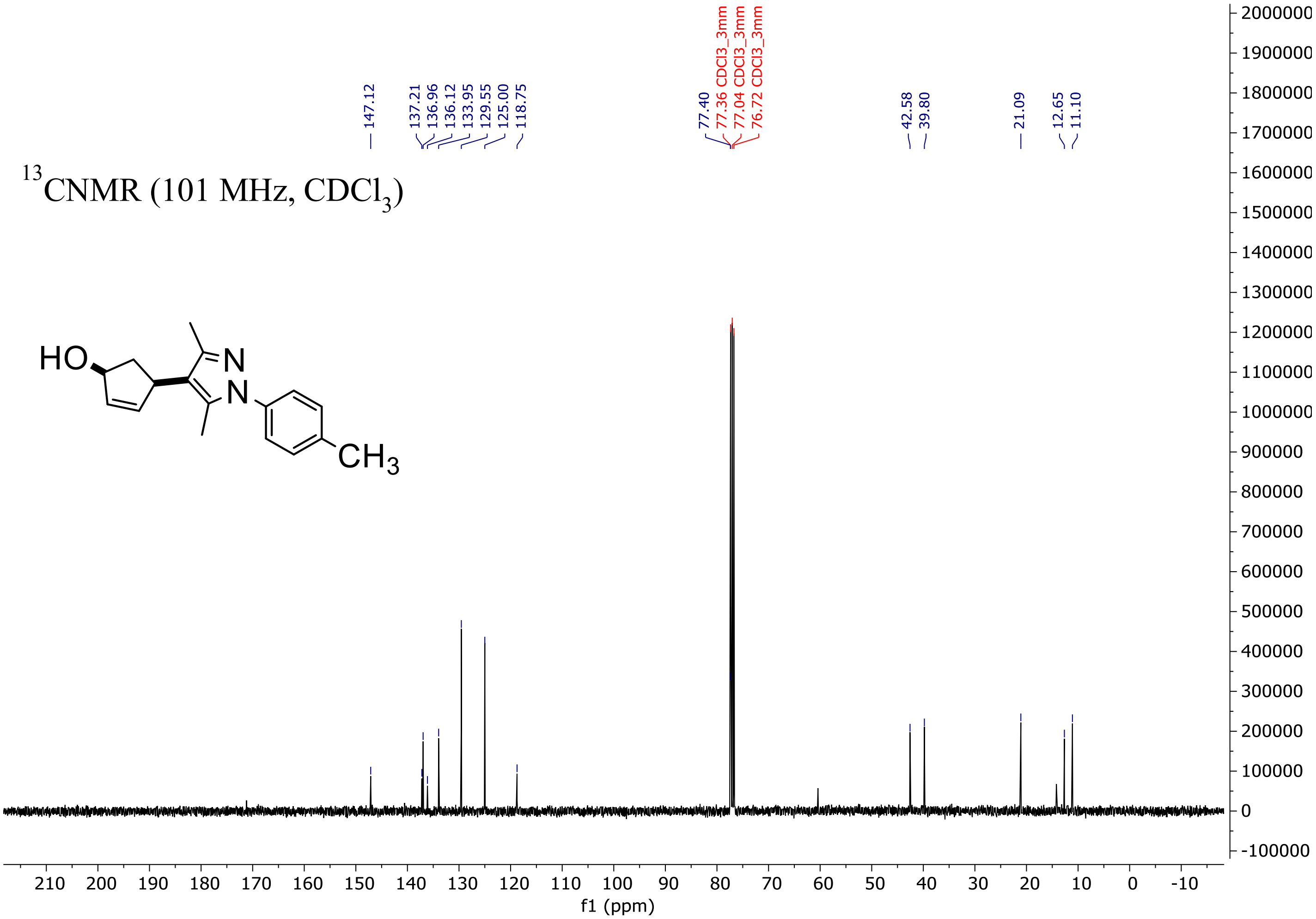

COSY (400 MHz, CDCl$_3$)
HO
N
N
CH$_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


HSQC (400 MHz, CDCl$_3$)
HO
N
N
CH$_3$
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)

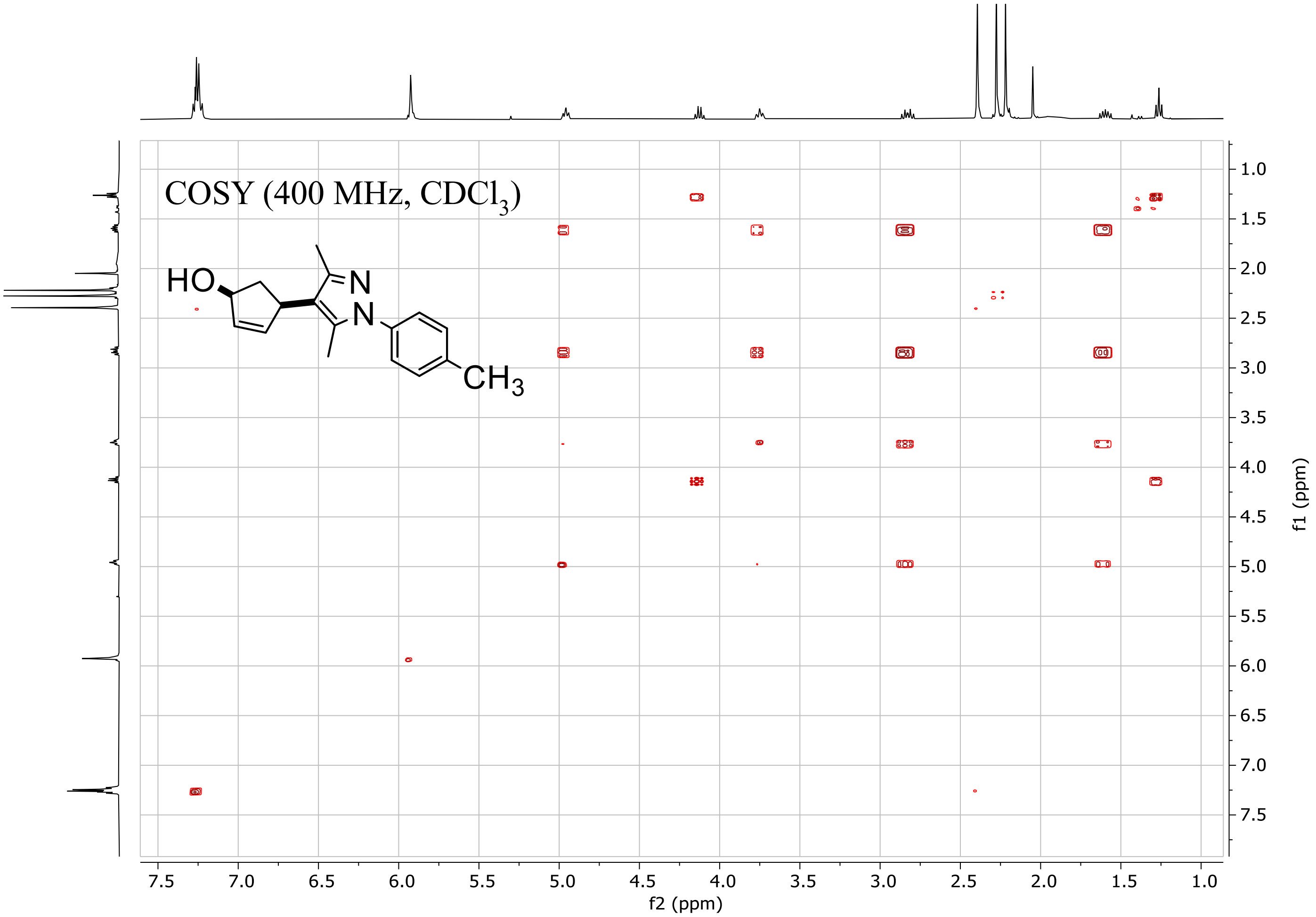
Compound 2g

^{1}HNMR (400 MHz, $CDCl_3$)

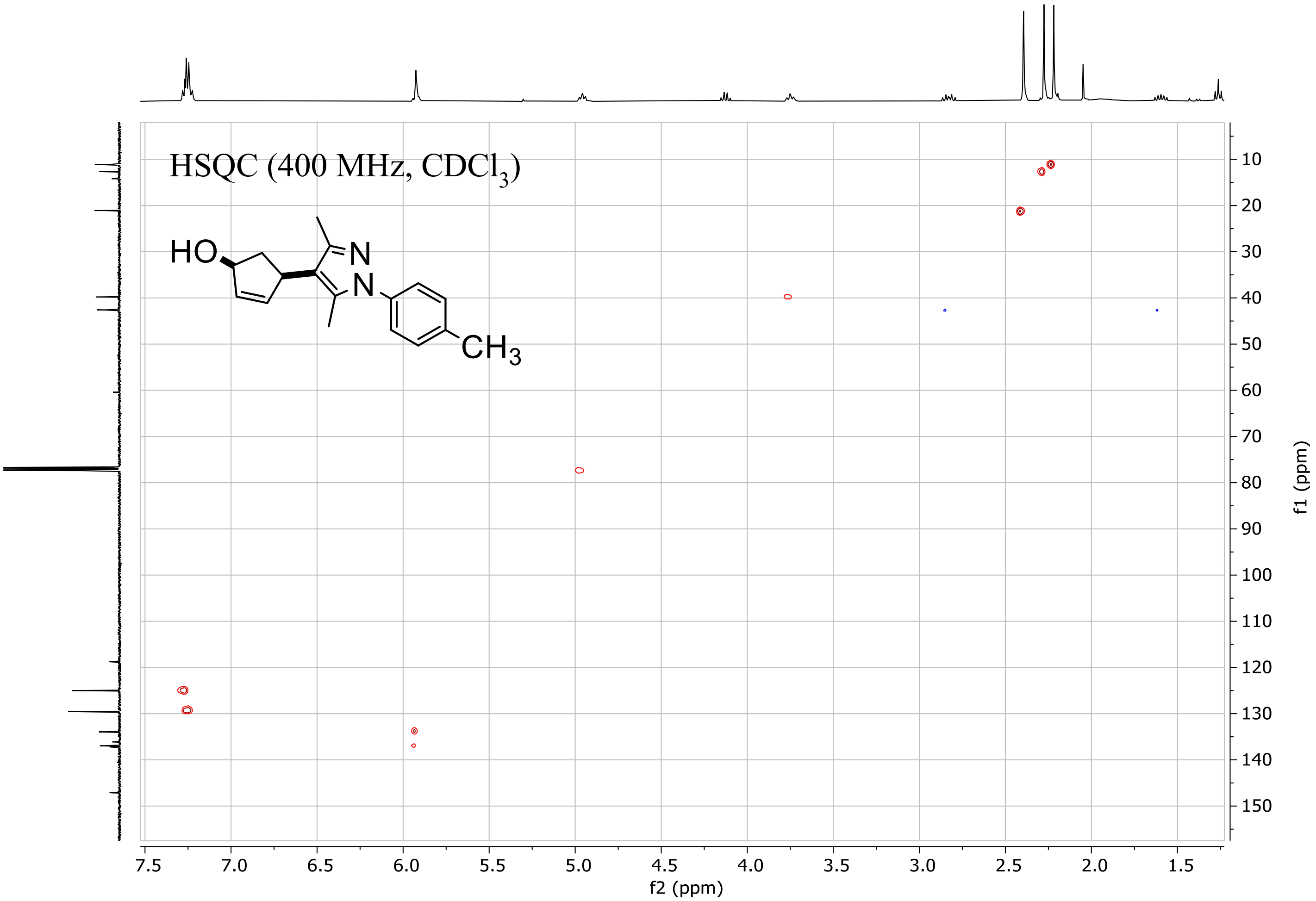




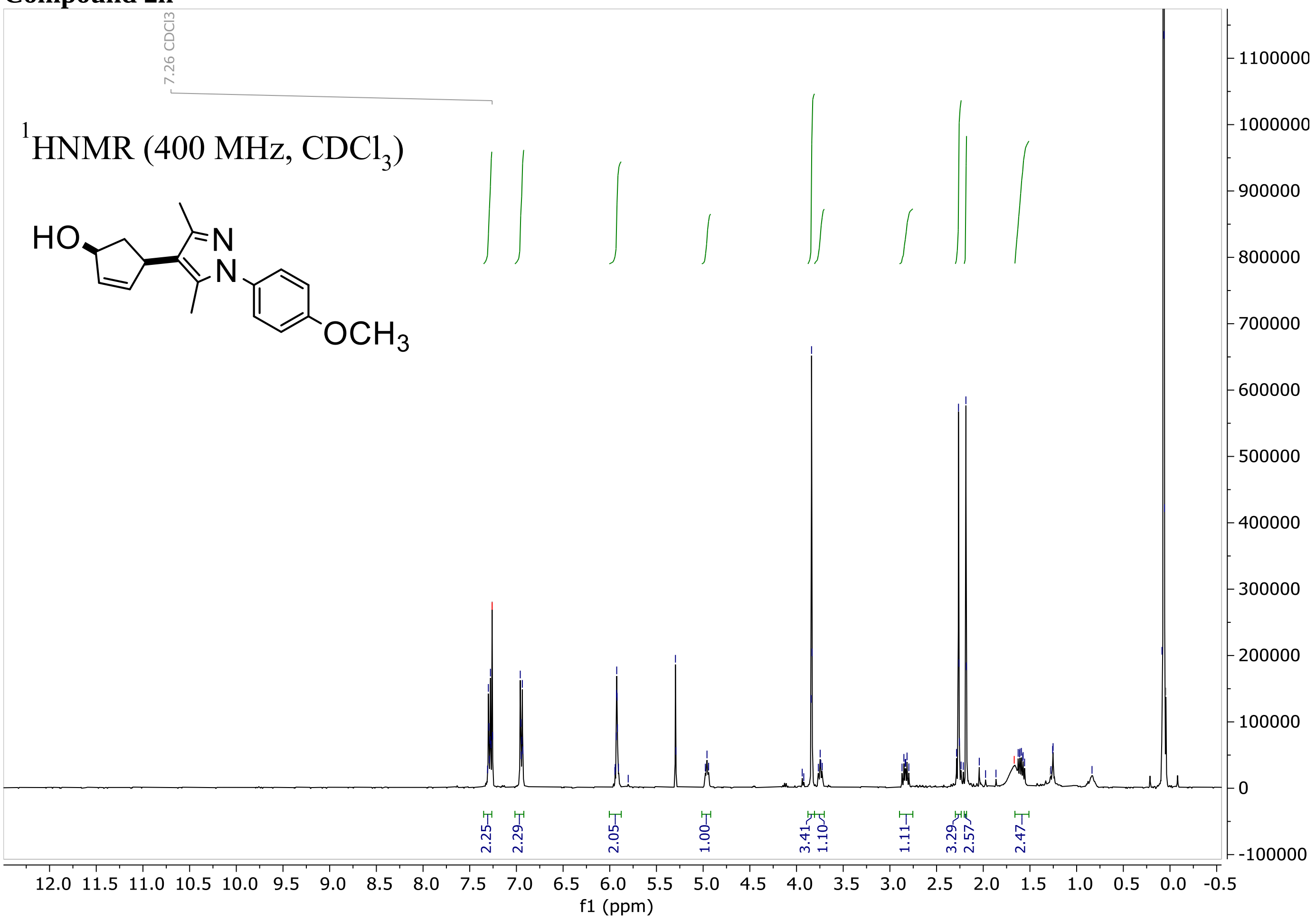
^{13}CNMR (101 MHz, $CDCl_3$)

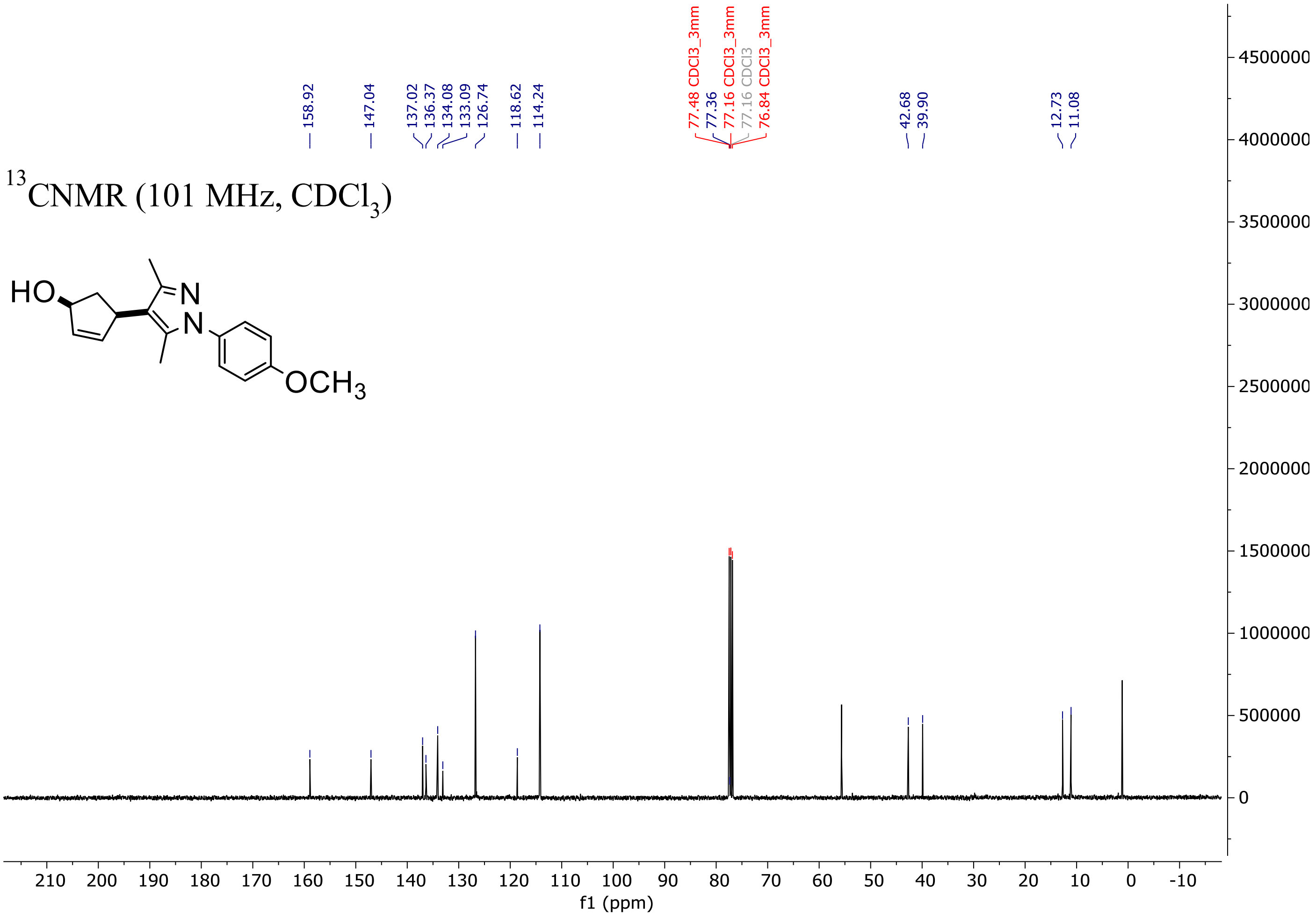


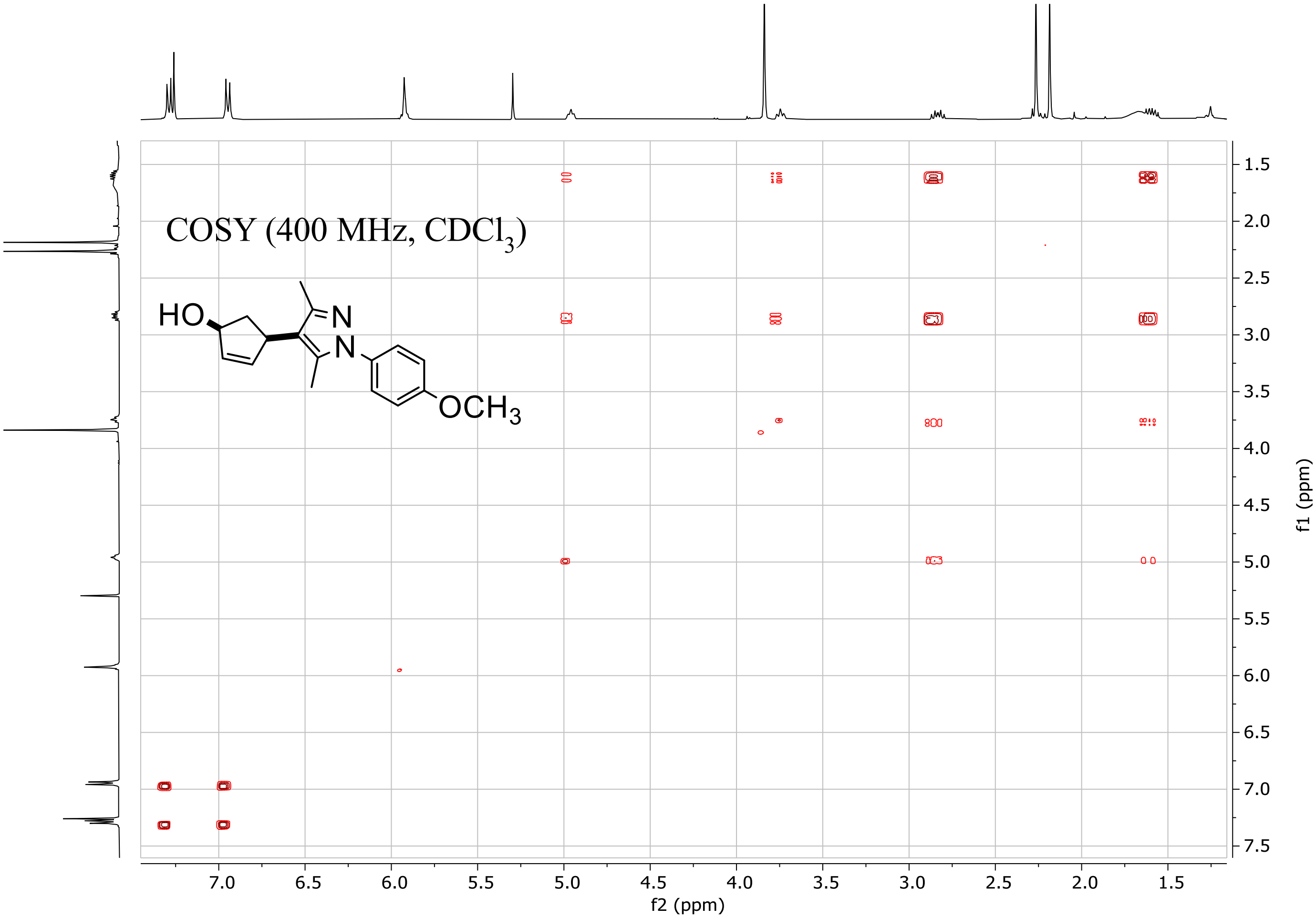
COSY (400 MHz, $CDCl_3$)


HSQC (400 MHz, CDCl$_3$)
HO
N
N
CH$_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

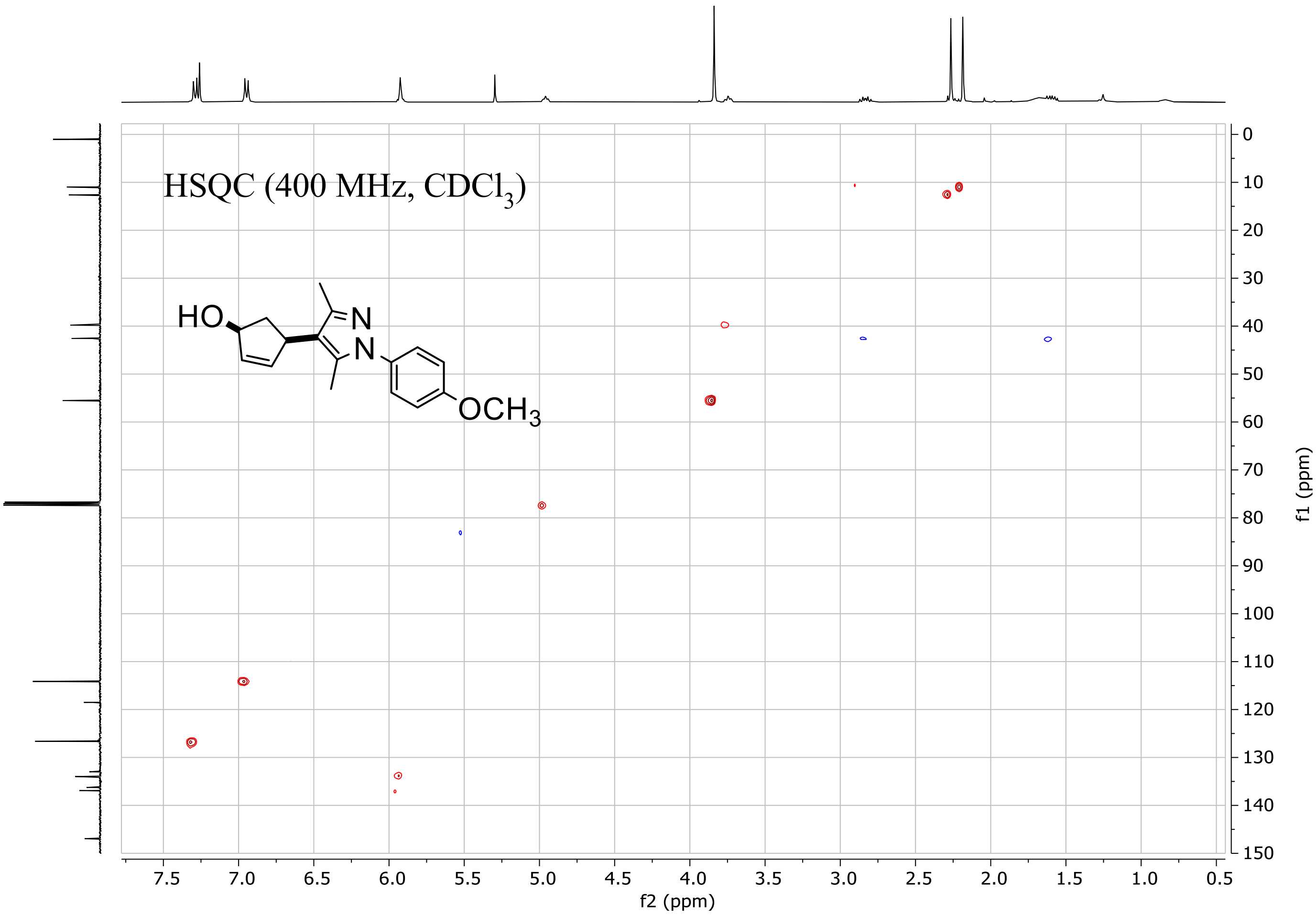
Compound 2h


7.26 CDCl3
^{1}HNMR (400 MHz, CDCl$_3$)
HO
N
N
OCH$_3$
2.25
2.29
2.05
1.00
3.41
1.10
1.11
3.29
2.57
2.47
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


^{13}CNMR (101 MHz, $CDCl_3$)

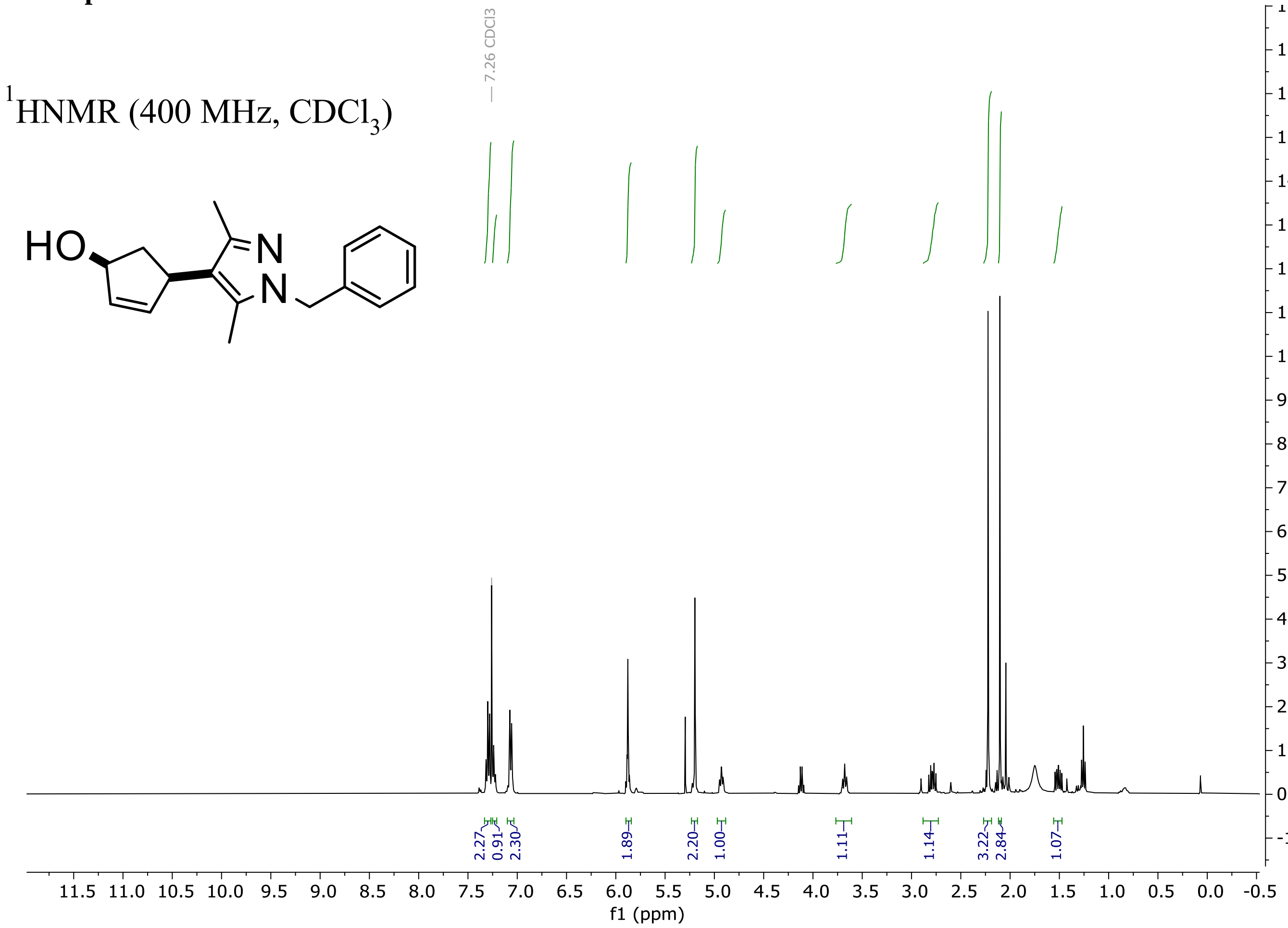


COSY (400 MHz, $CDCl_3$)
HO
N
N
OCH_3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

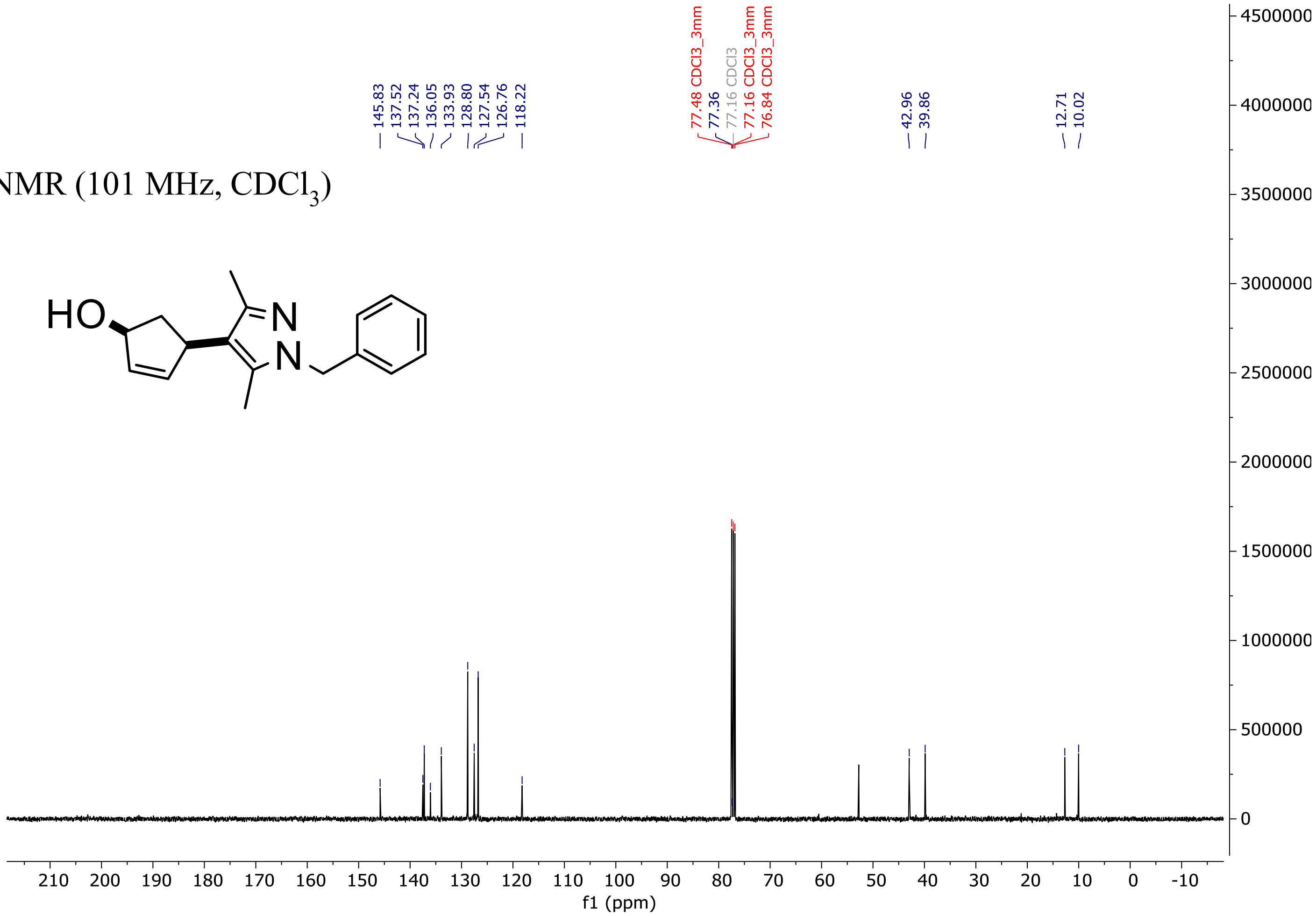

HSQC (400 MHz, CDCl$_3$)
HO
N
N
OCH$_3$
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

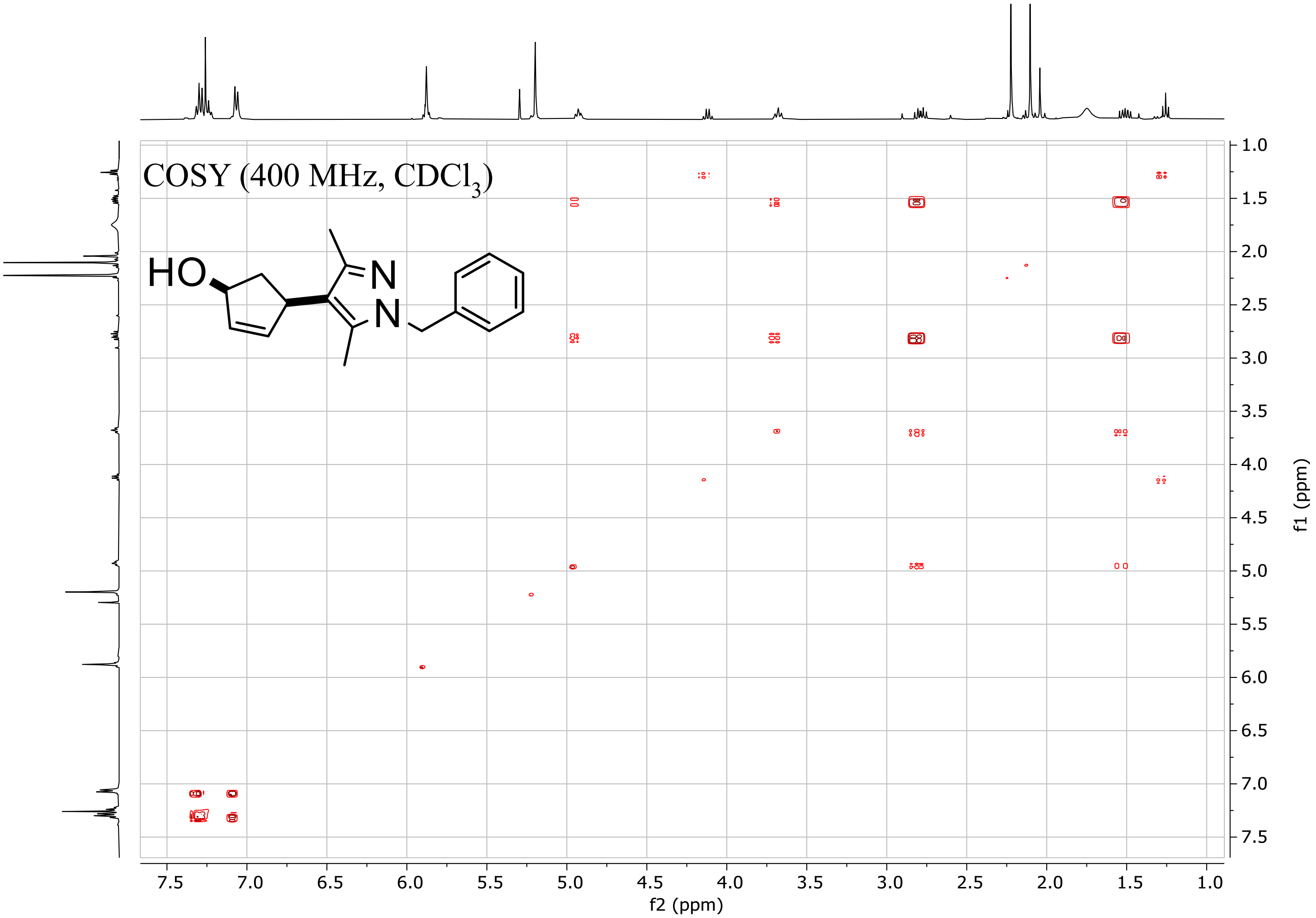
Compound 2i

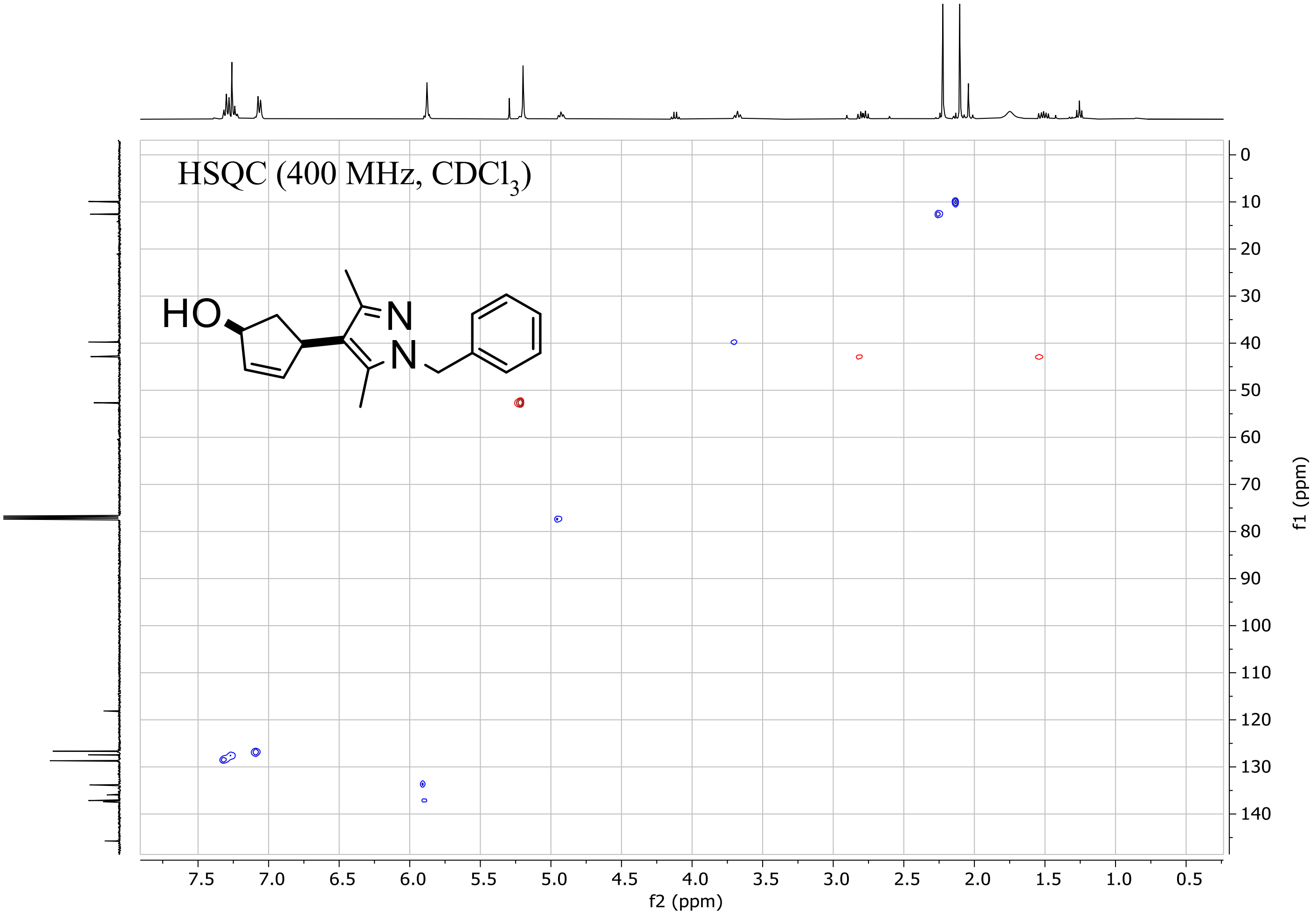
^{1}HNMR (400 MHz, $CDCl_3$)



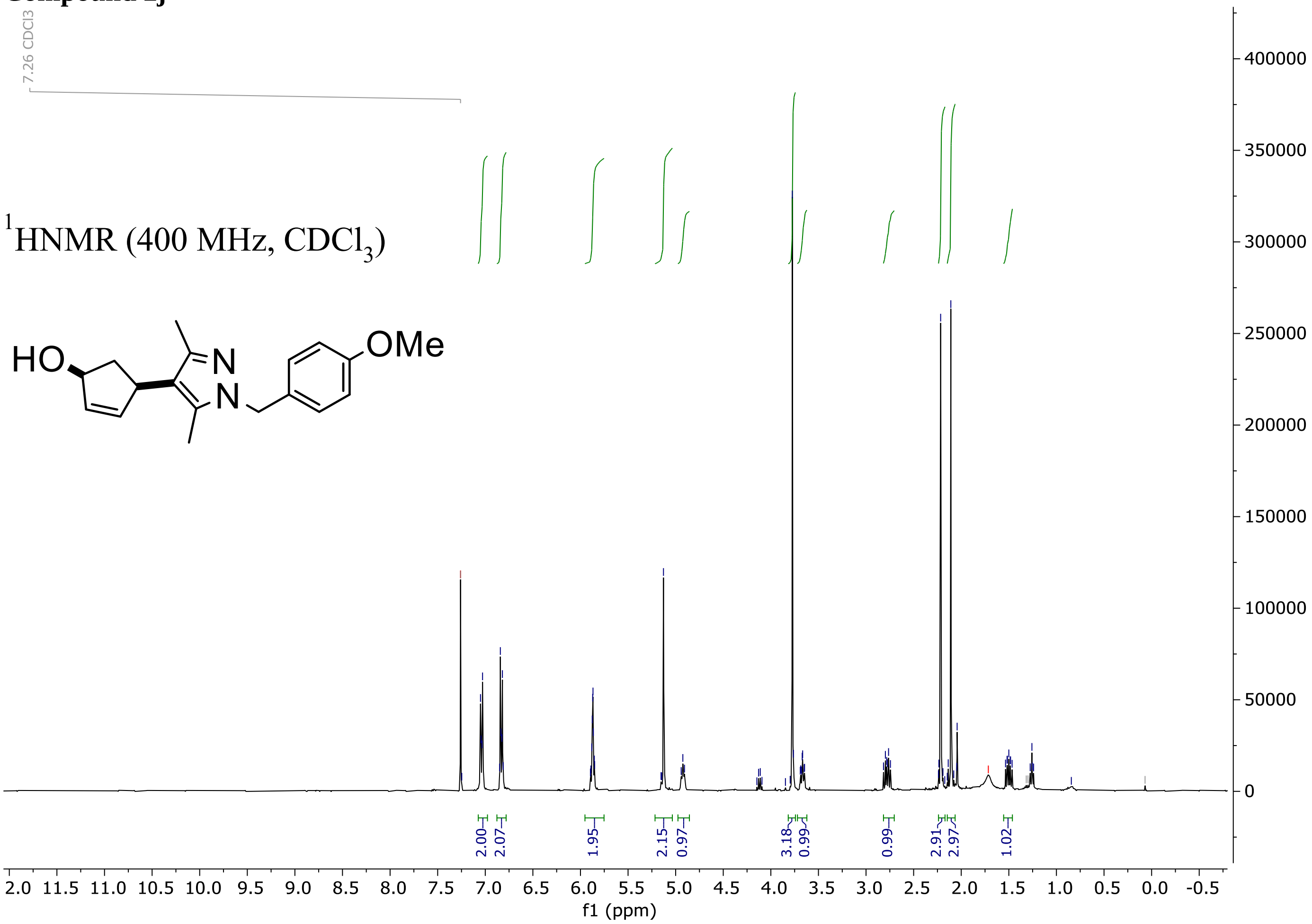
^{13}CNMR (101 MHz, $CDCl_3$)



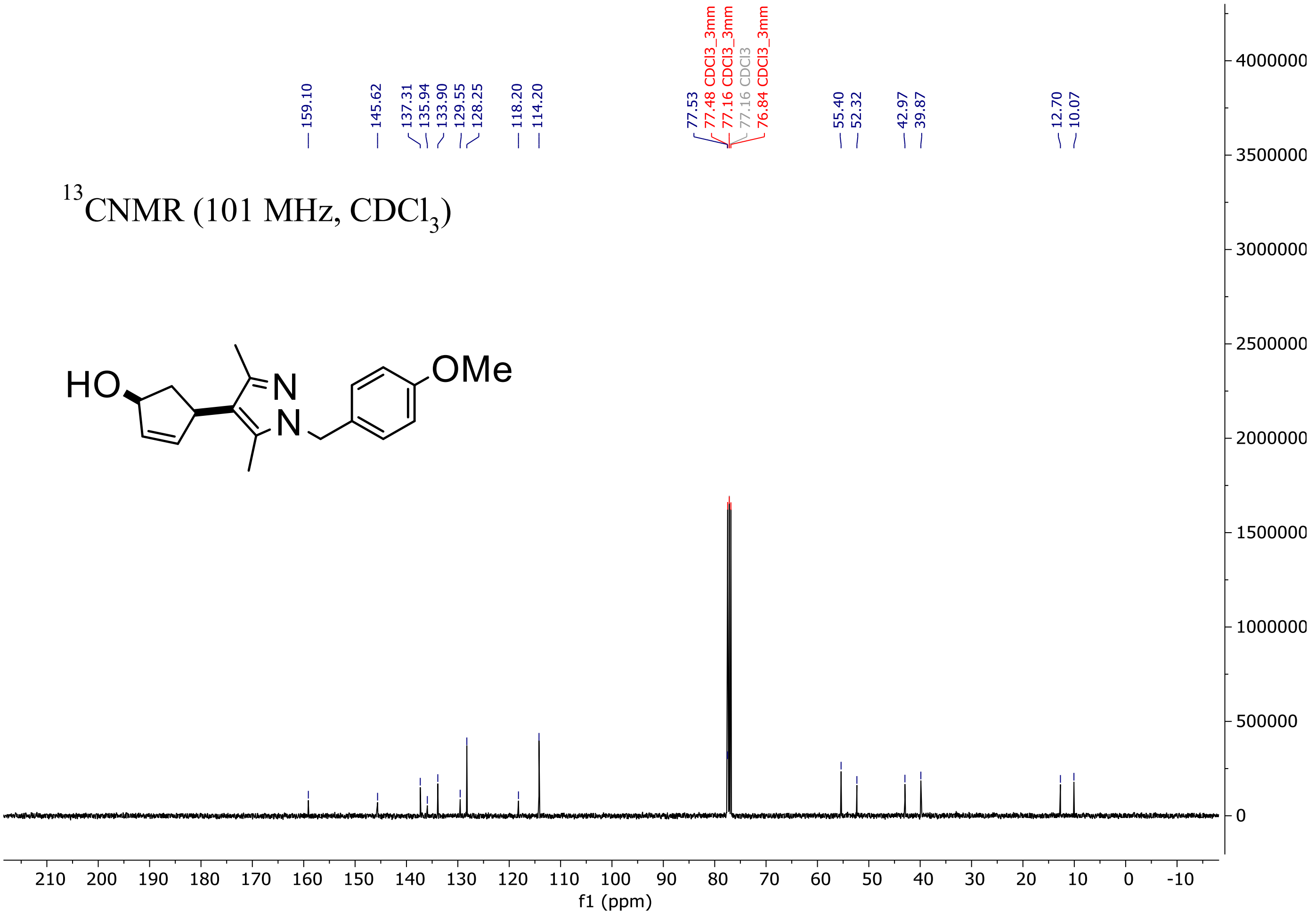

COSY (400 MHz, CDCl$_3$)
HO
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


HSQC (400 MHz, CDCl$_3$)
HO
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)

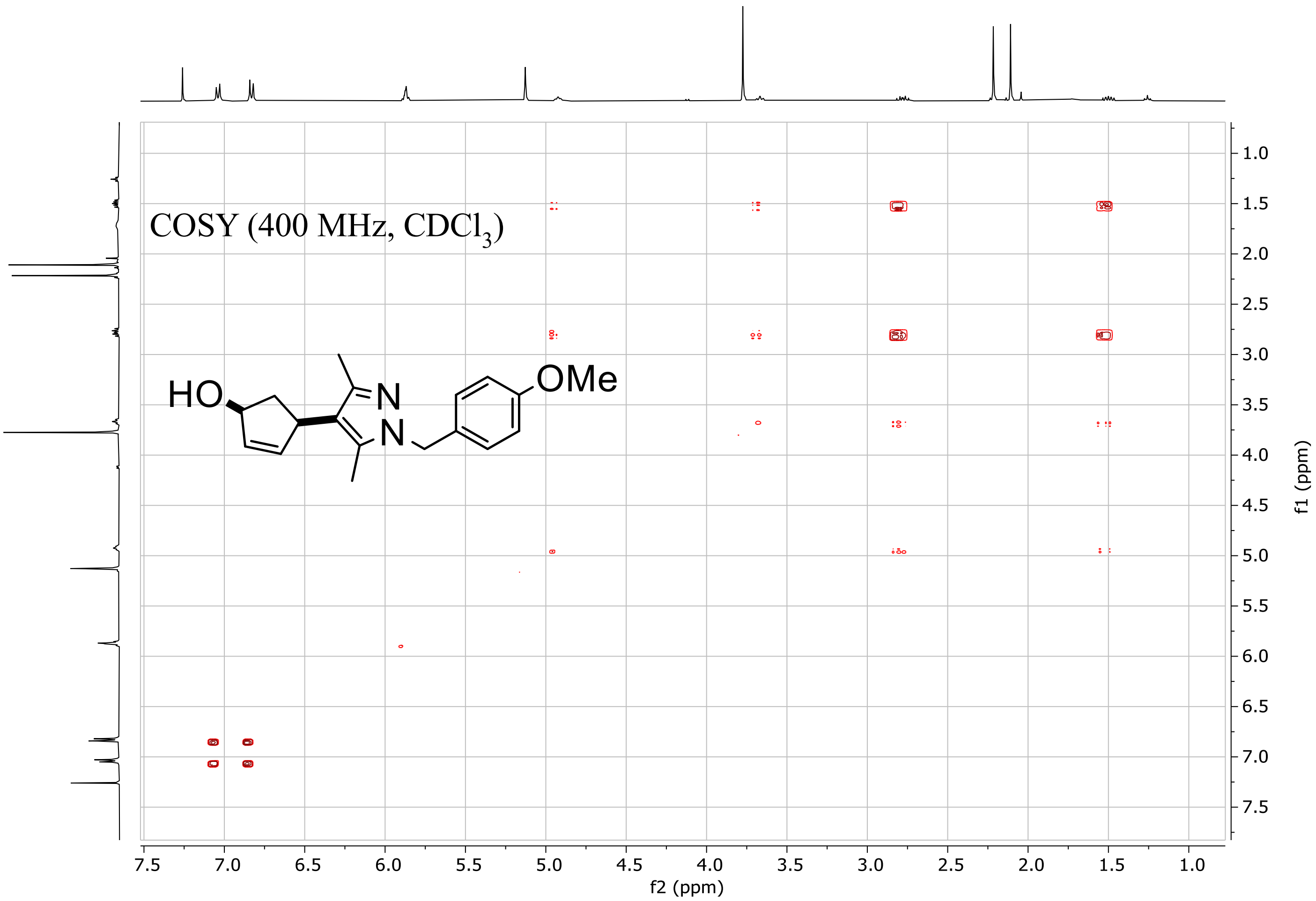
Compound 2j

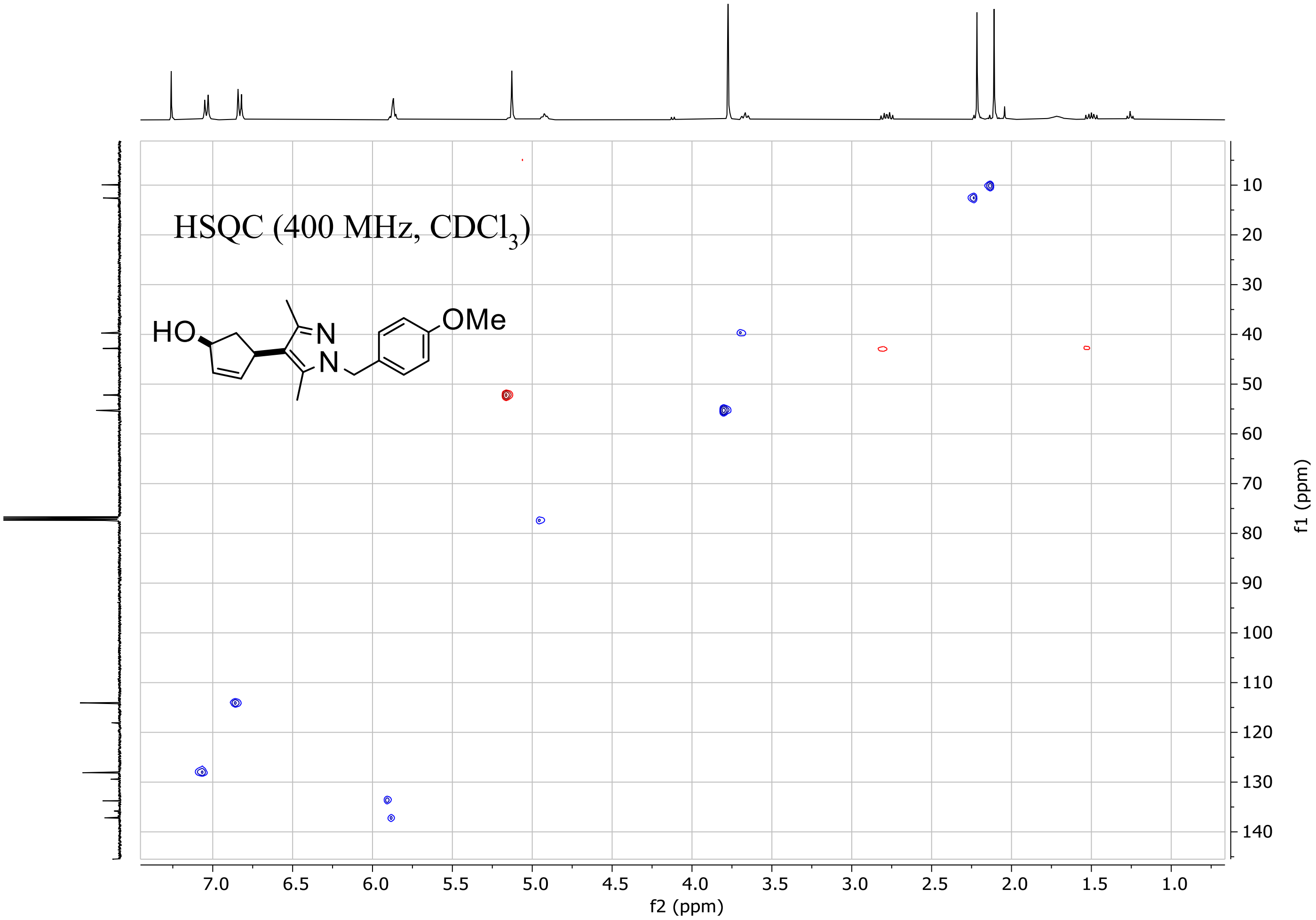


^{1}HNMR (400 MHz, $CDCl_3$)



^{13}CNMR (101 MHz, $CDCl_3$)

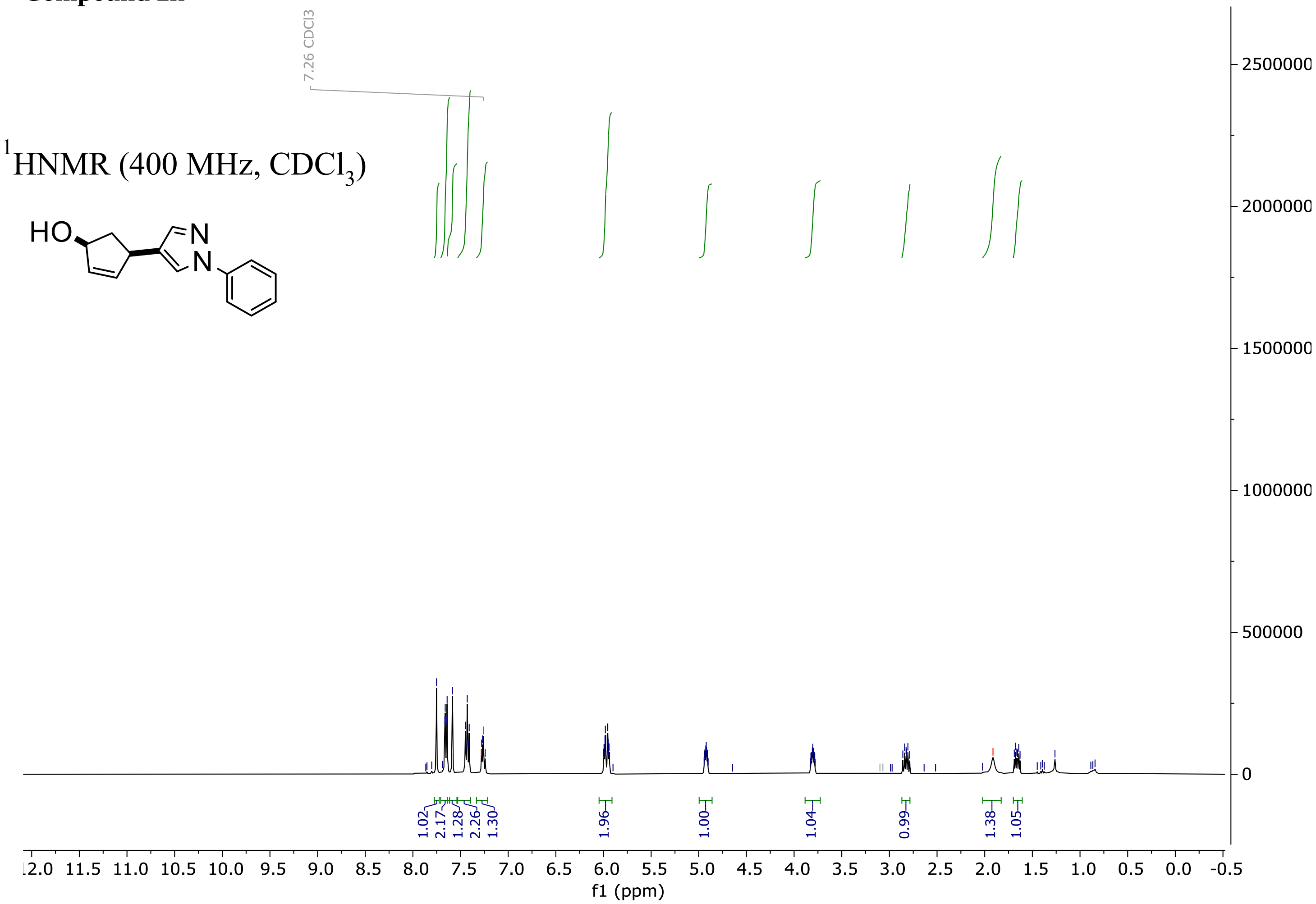

COSY (400 MHz, CDCl$_3$)
HO
N
N
OMe
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

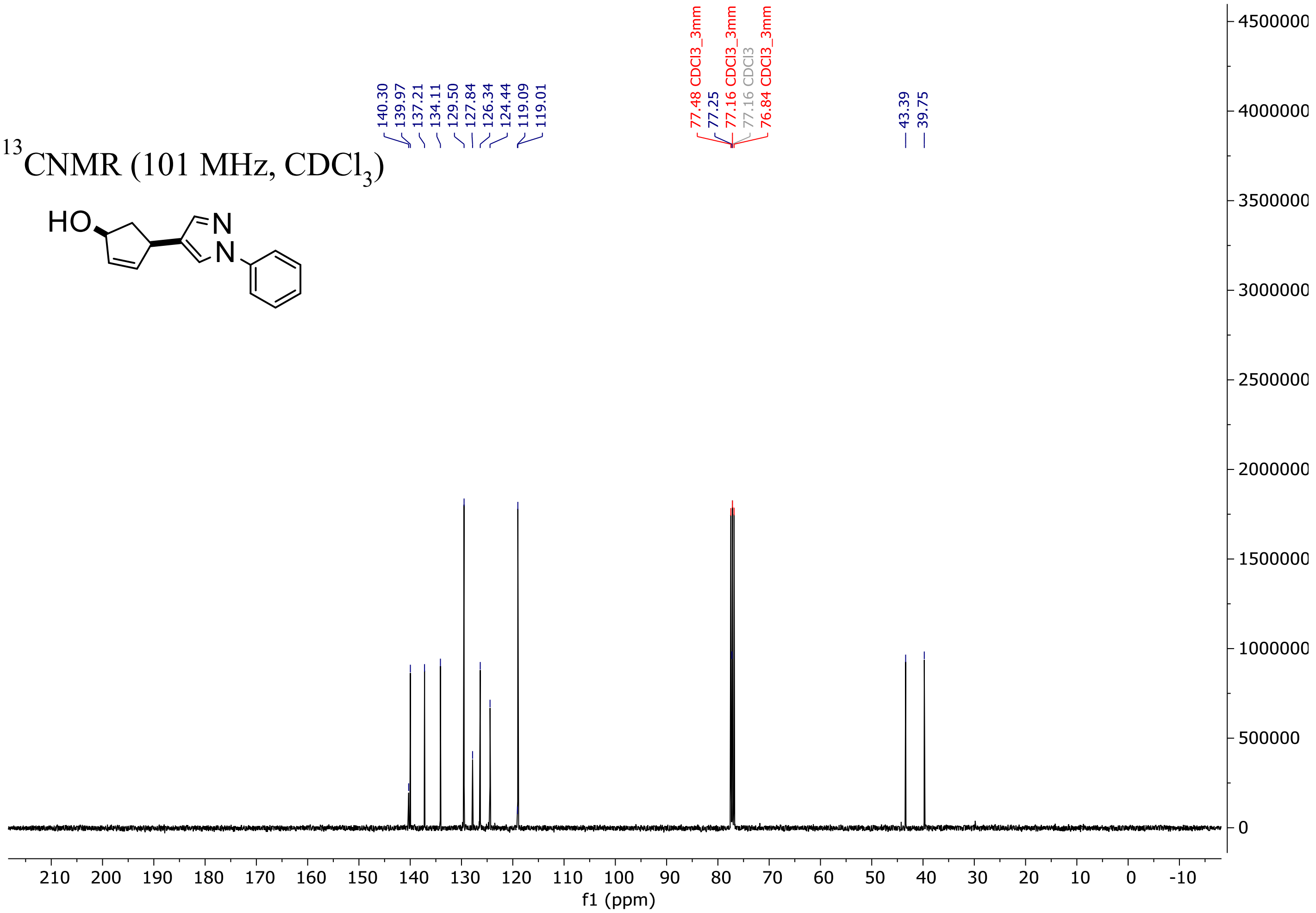


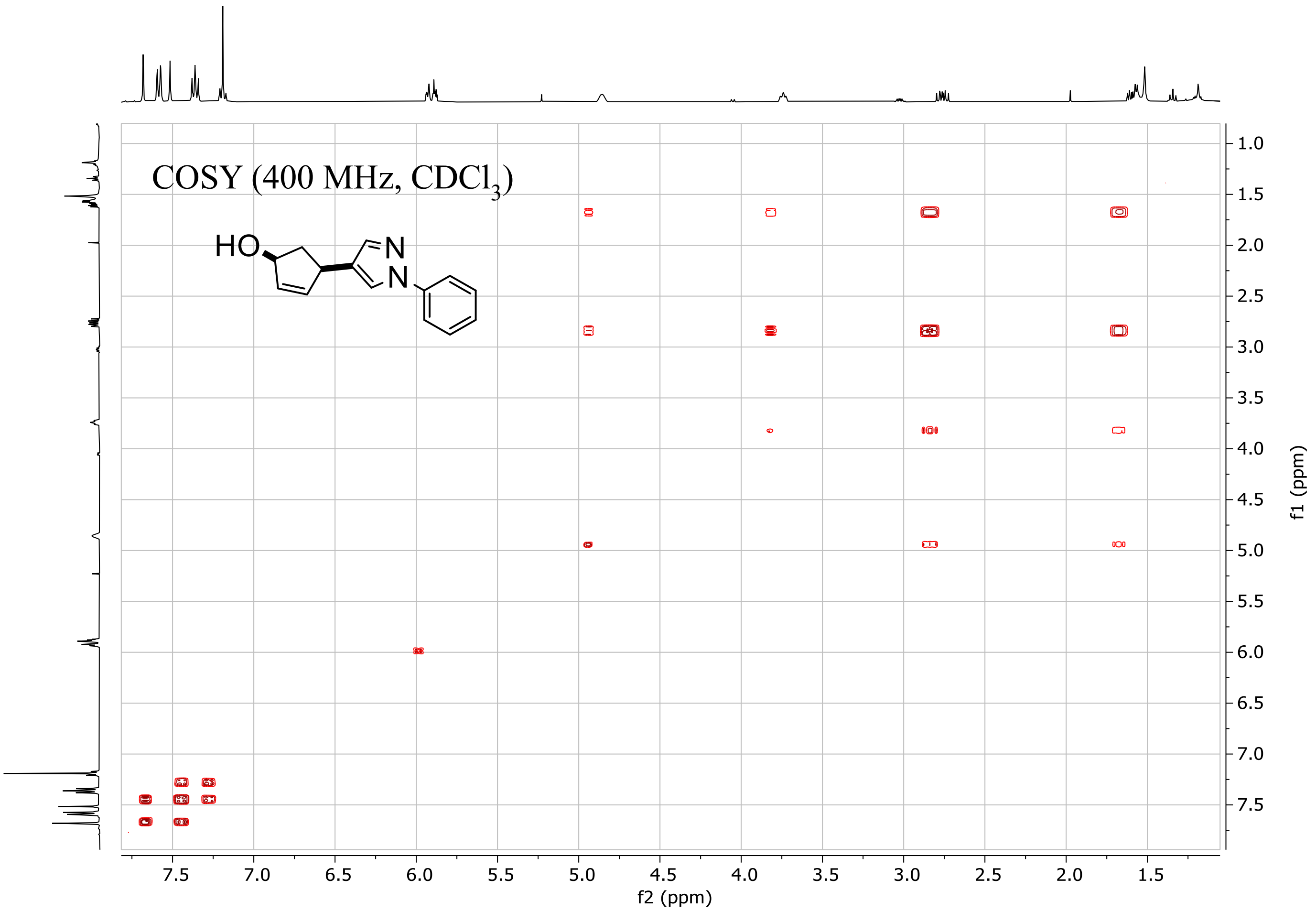
HSQC (400 MHz, CDCl3)
HO
N
N
OMe
f1 (ppm)
f2 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

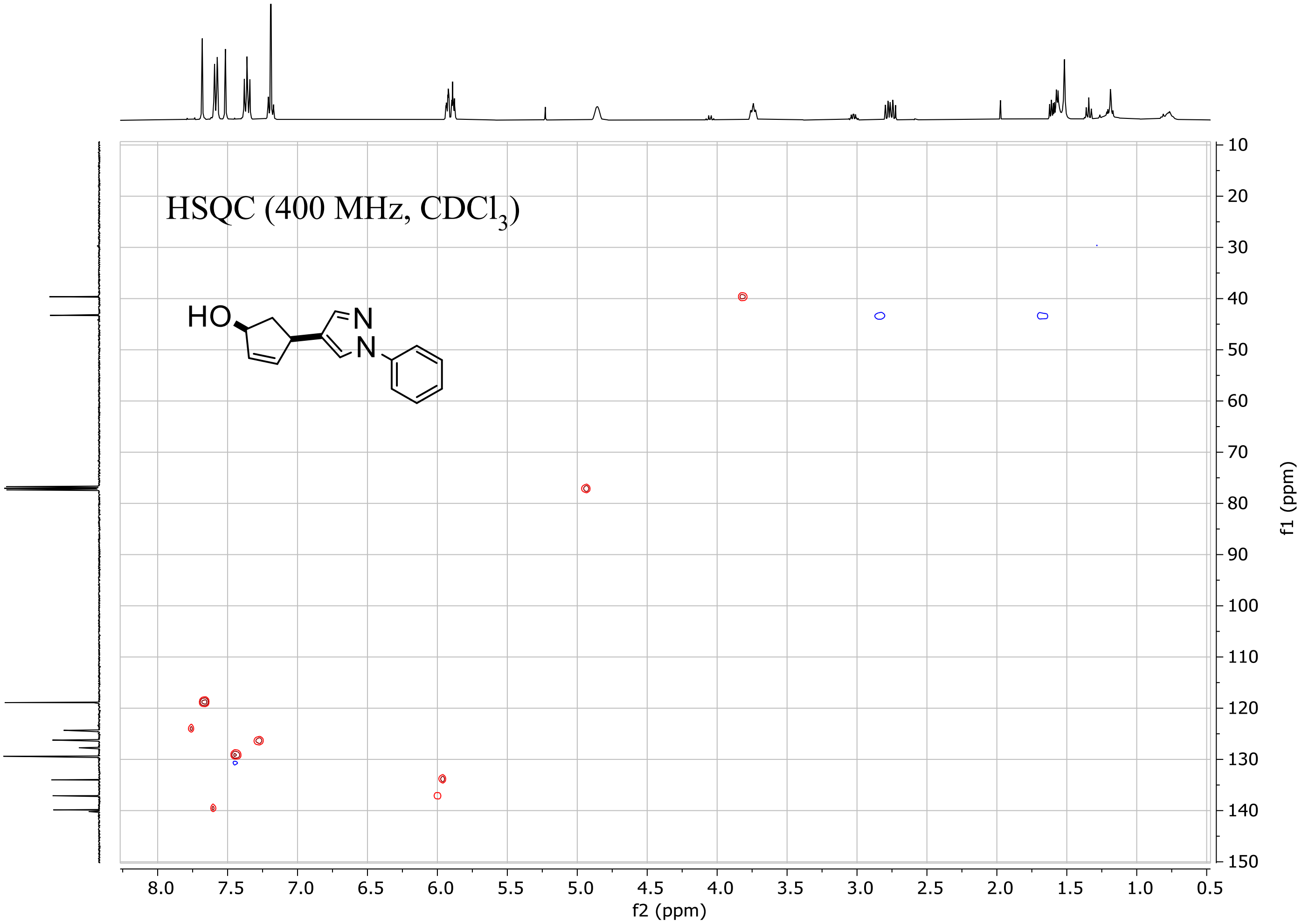
Compound 2k

^{1}HNMR (400 MHz, $CDCl_3$)



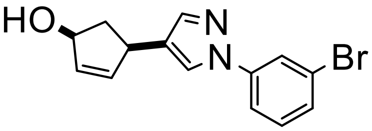

^{13}CNMR (101 MHz, $CDCl_3$)

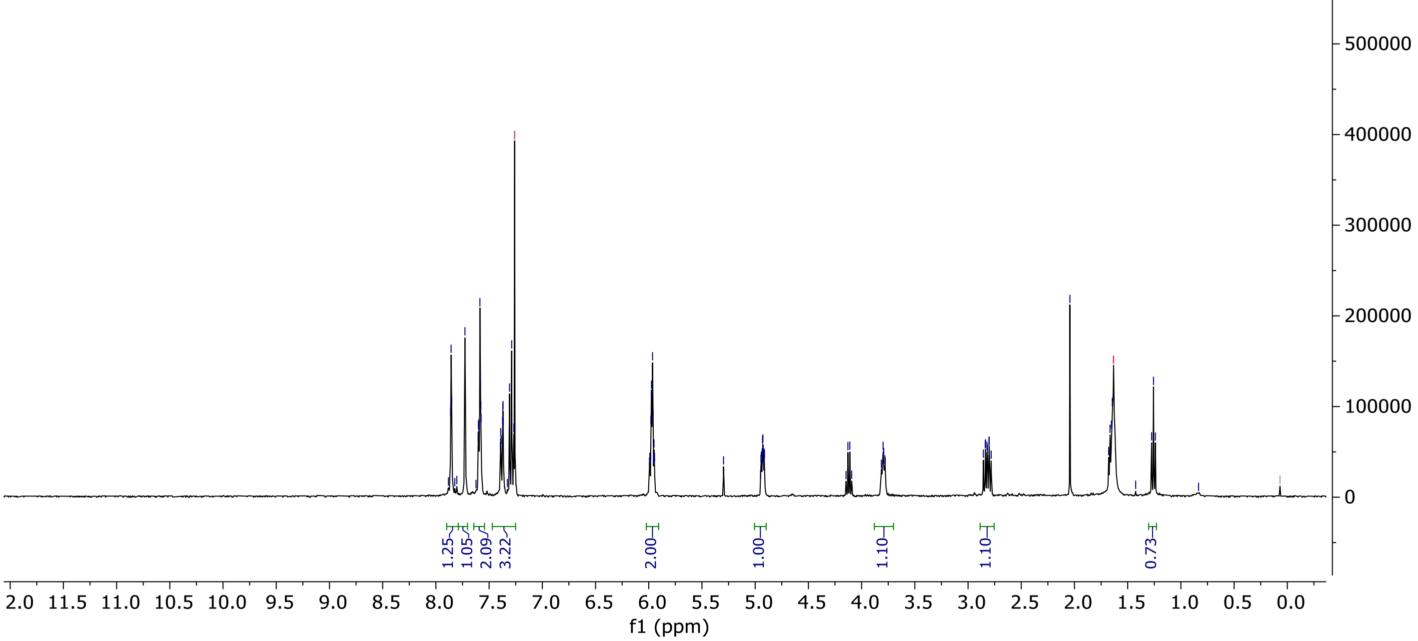

COSY (400 MHz, CDCl3)
HO
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


HSQC (400 MHz, CDCl$_3$)
HO
N
N
f2 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

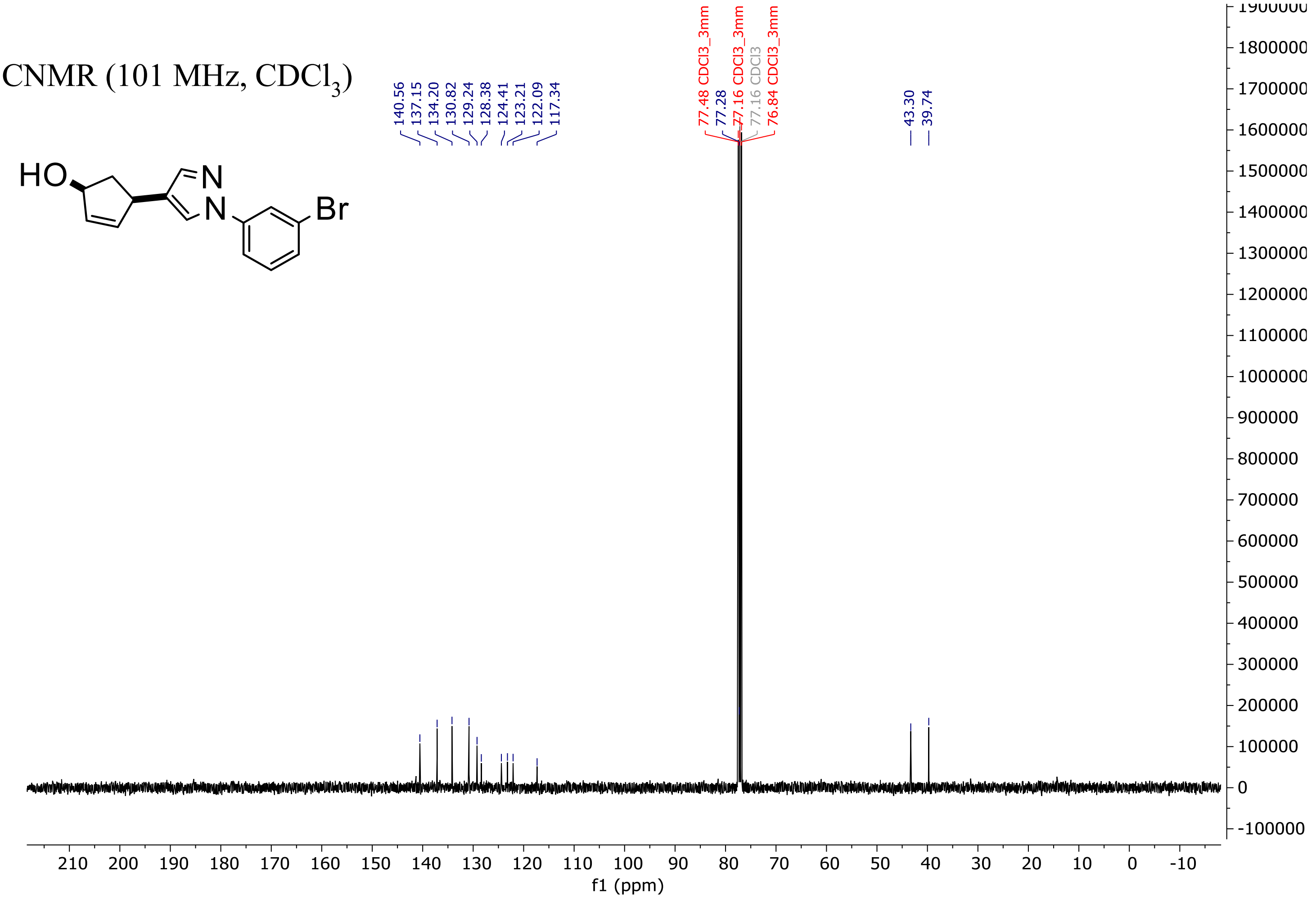
Compound 2l

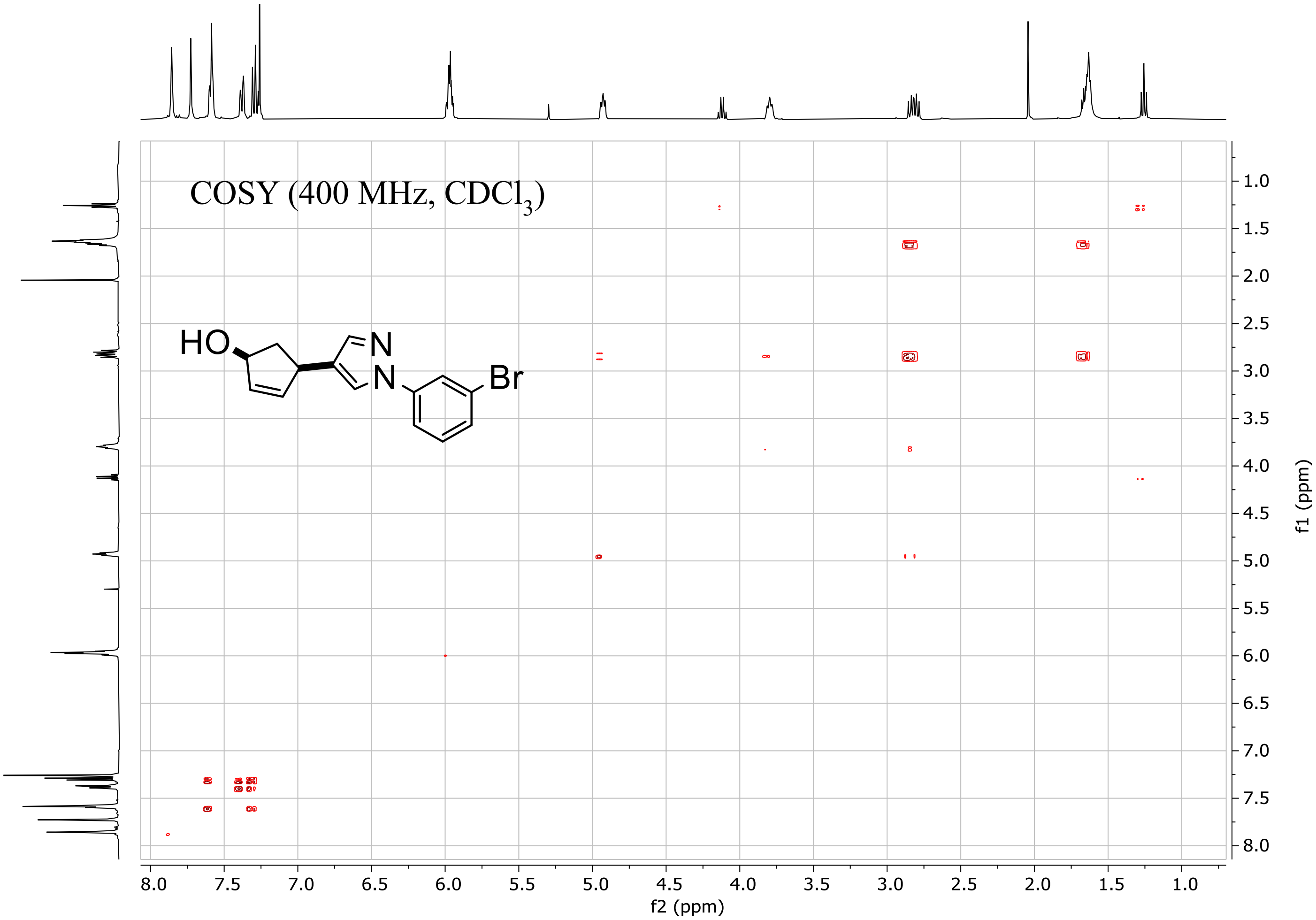
^{1}HNMR (400 MHz, $CDCl_3$)

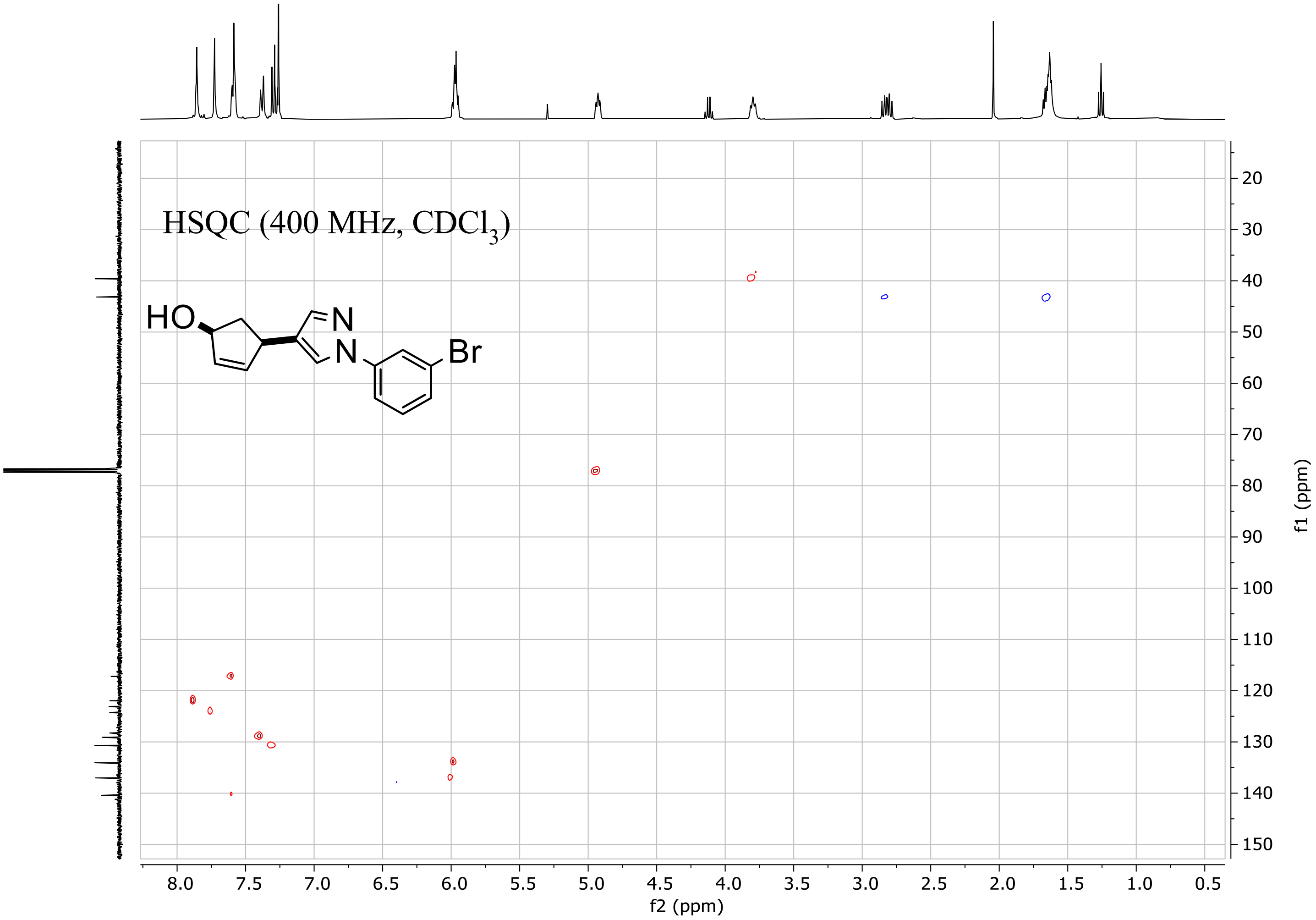




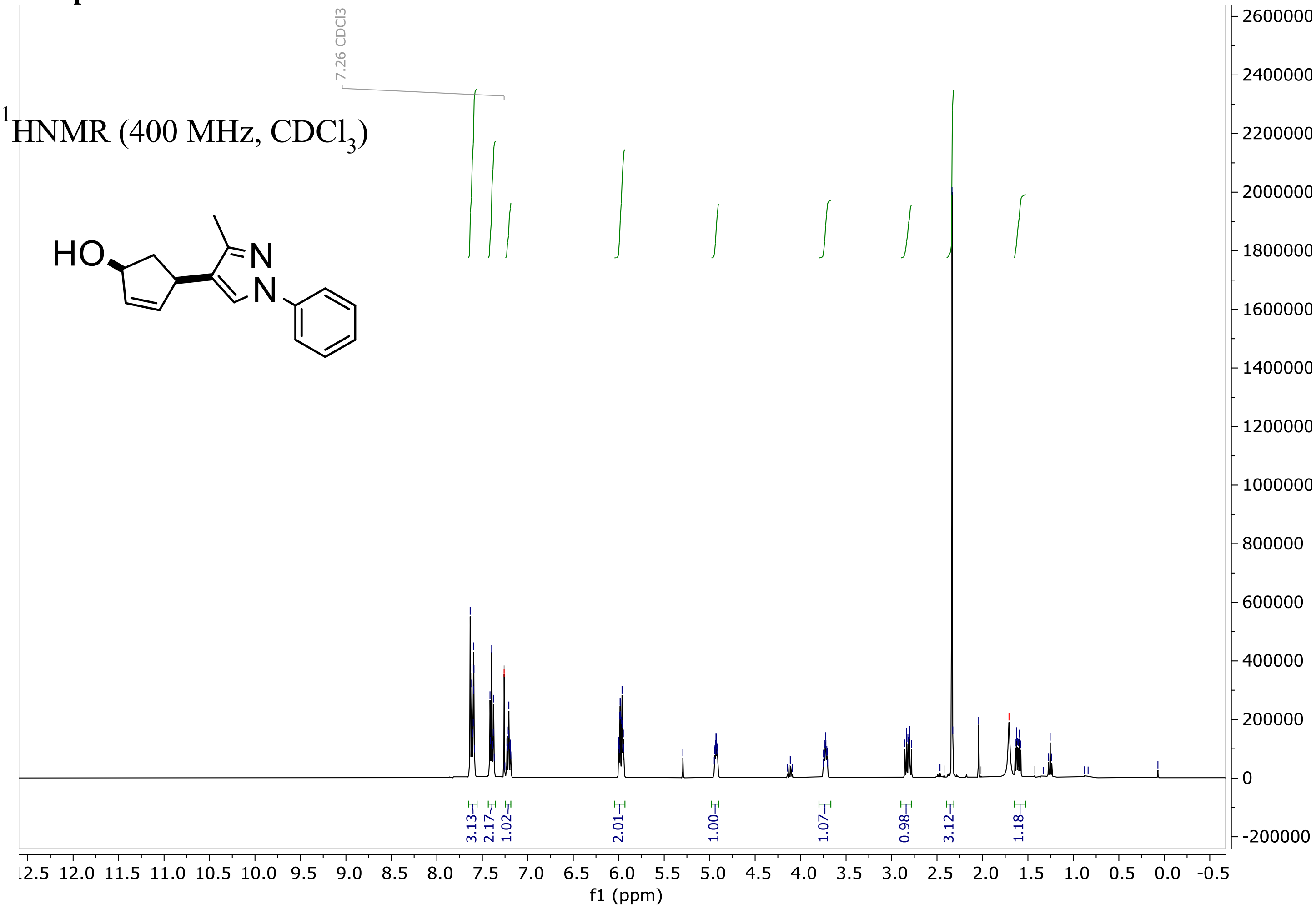
^{13}CNMR (101 MHz, $CDCl_3$)



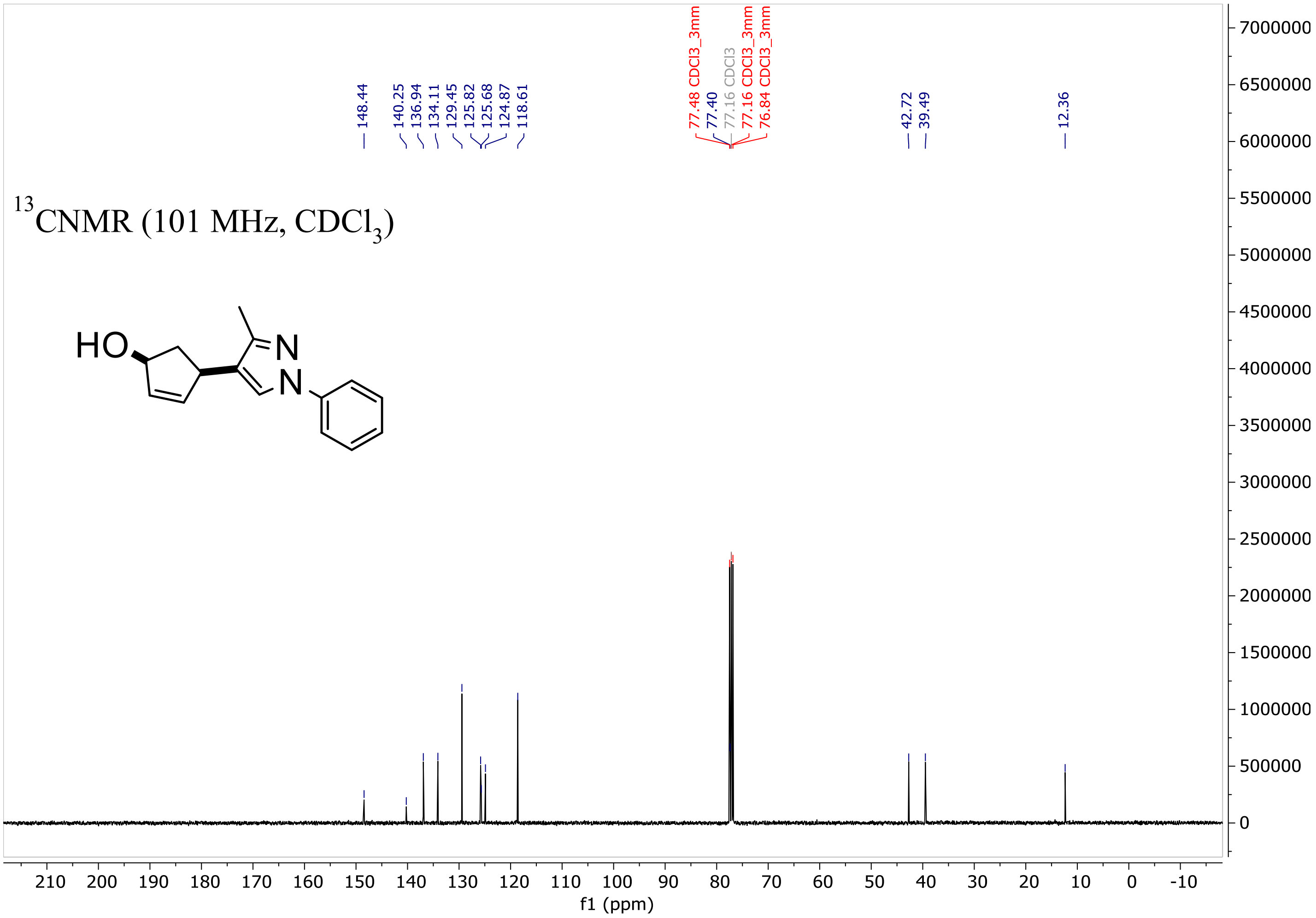

COSY (400 MHz, CDCl$_3$)
HO
N
N
Br
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

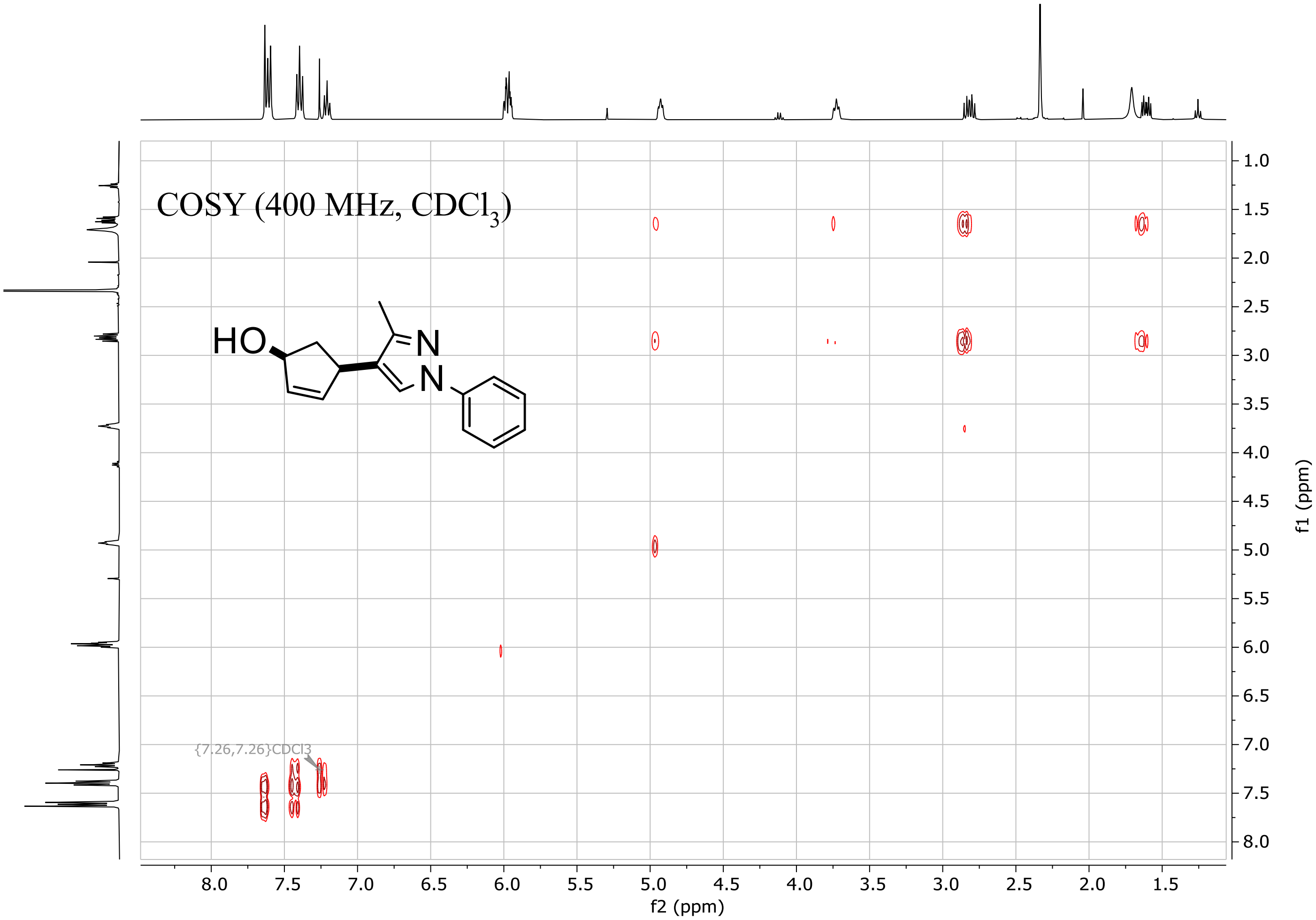

HSQC (400 MHz, CDCl3)
HO
N
N
Br
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

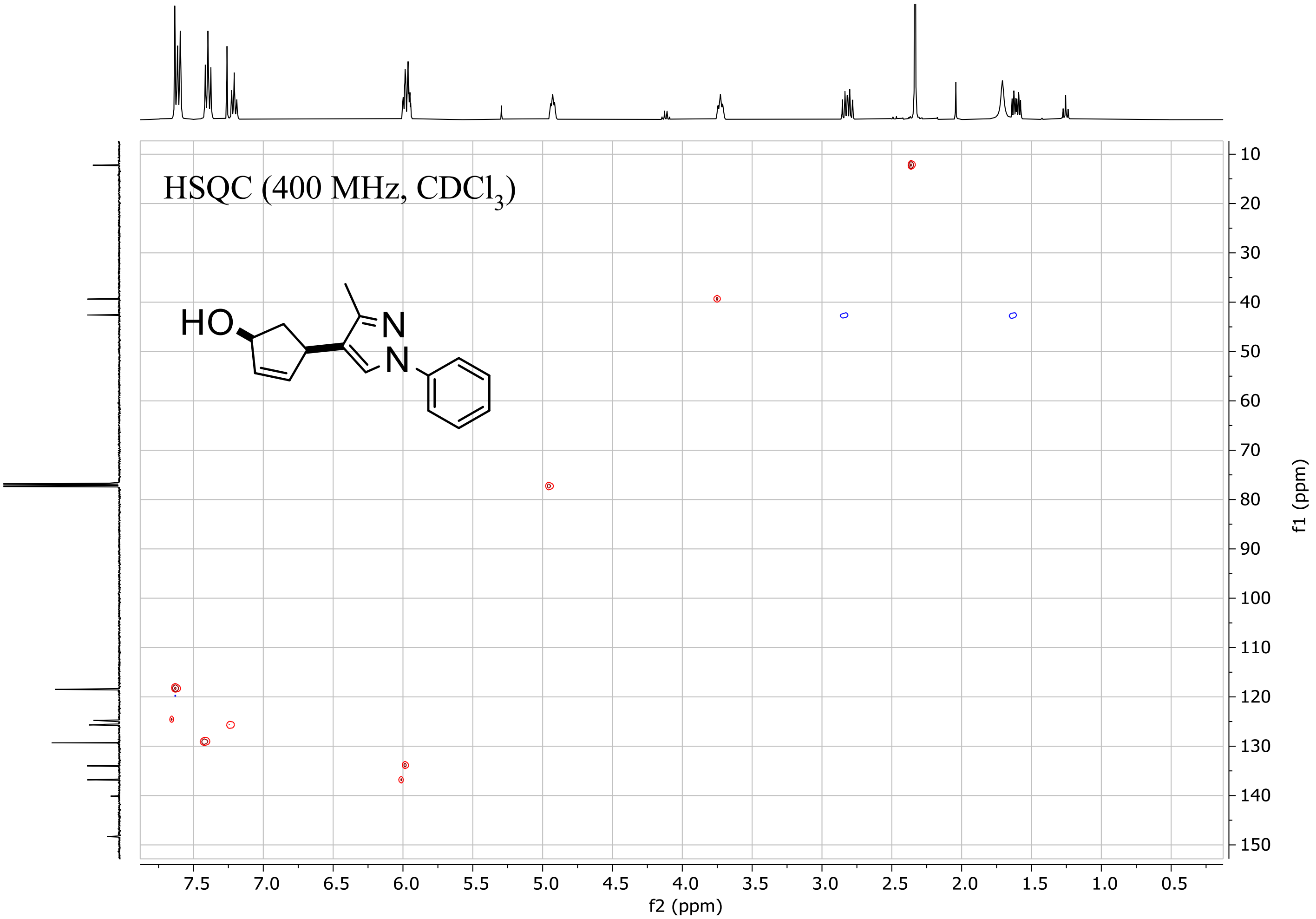
Compound 2m



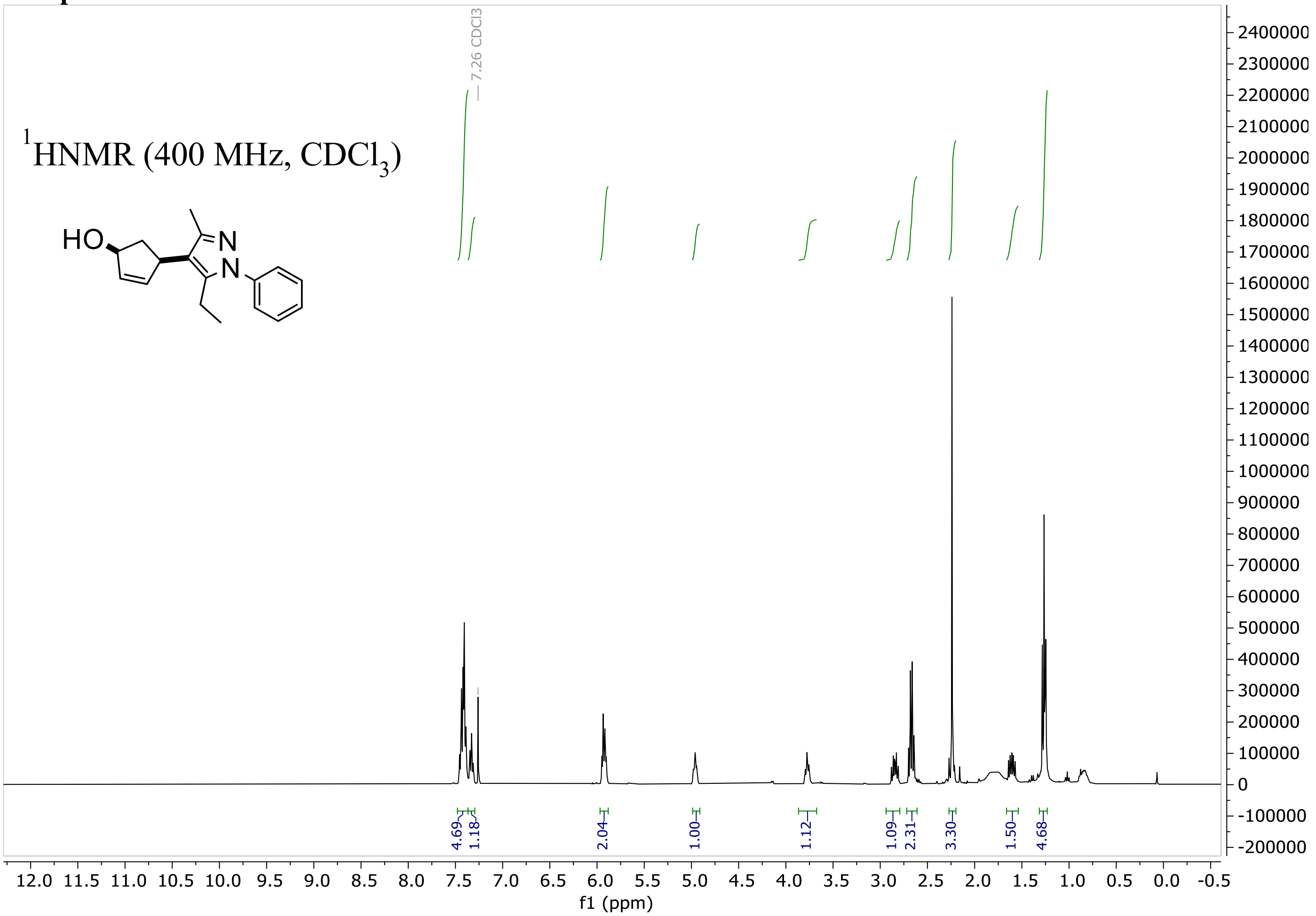
^{1}HNMR (400 MHz, CDCl$_3$)
HO
N
N
7.26 CDCl3
3.13
2.17
1.02
2.01
1.00
1.07
0.98
3.12
1.18
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000


^{13}CNMR (101 MHz, $CDCl_3$)

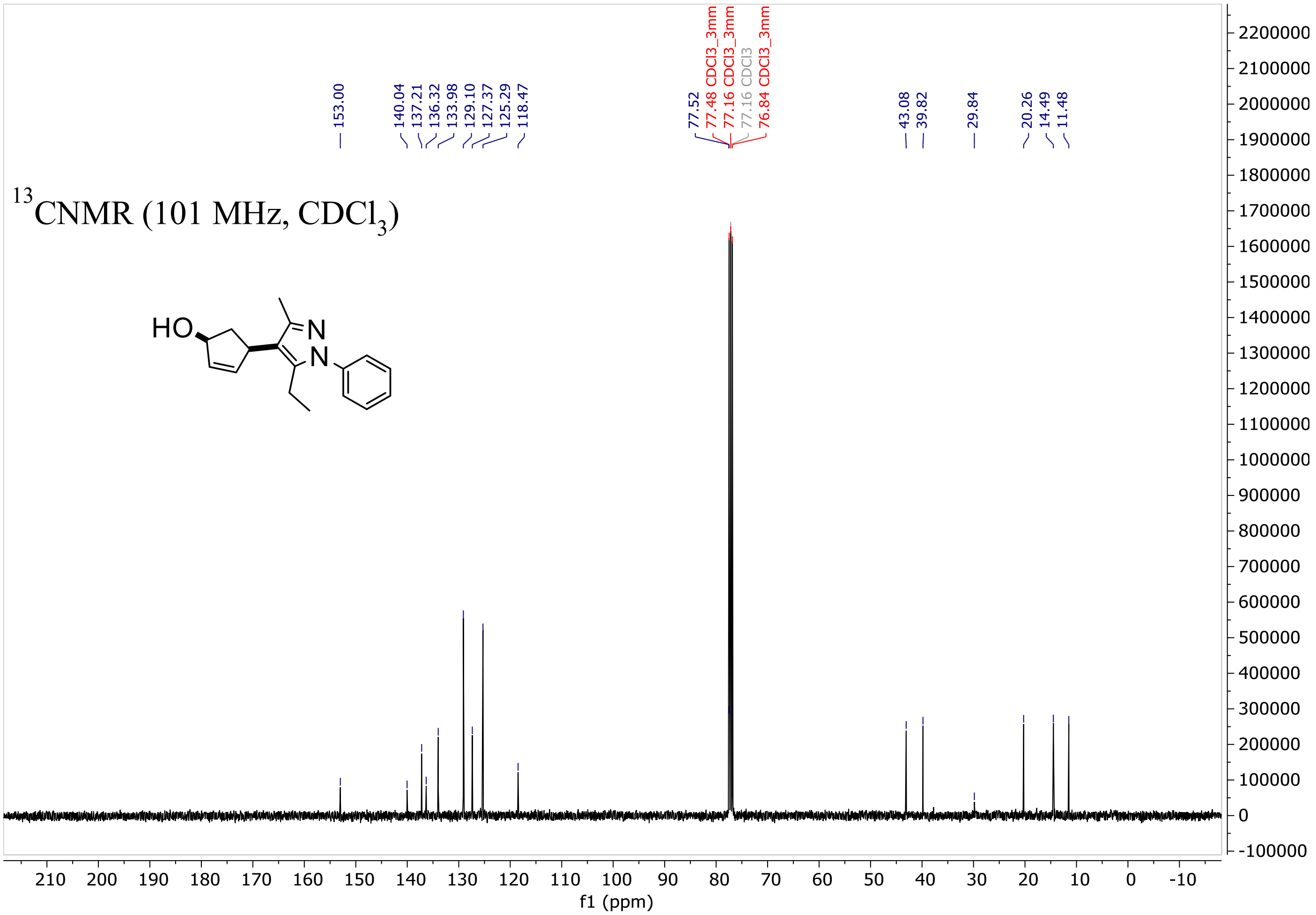

COSY (400 MHz, CDCl3)
HO
N
N
{7.26,7.26}CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


HSQC (400 MHz, $CDCl_3$)

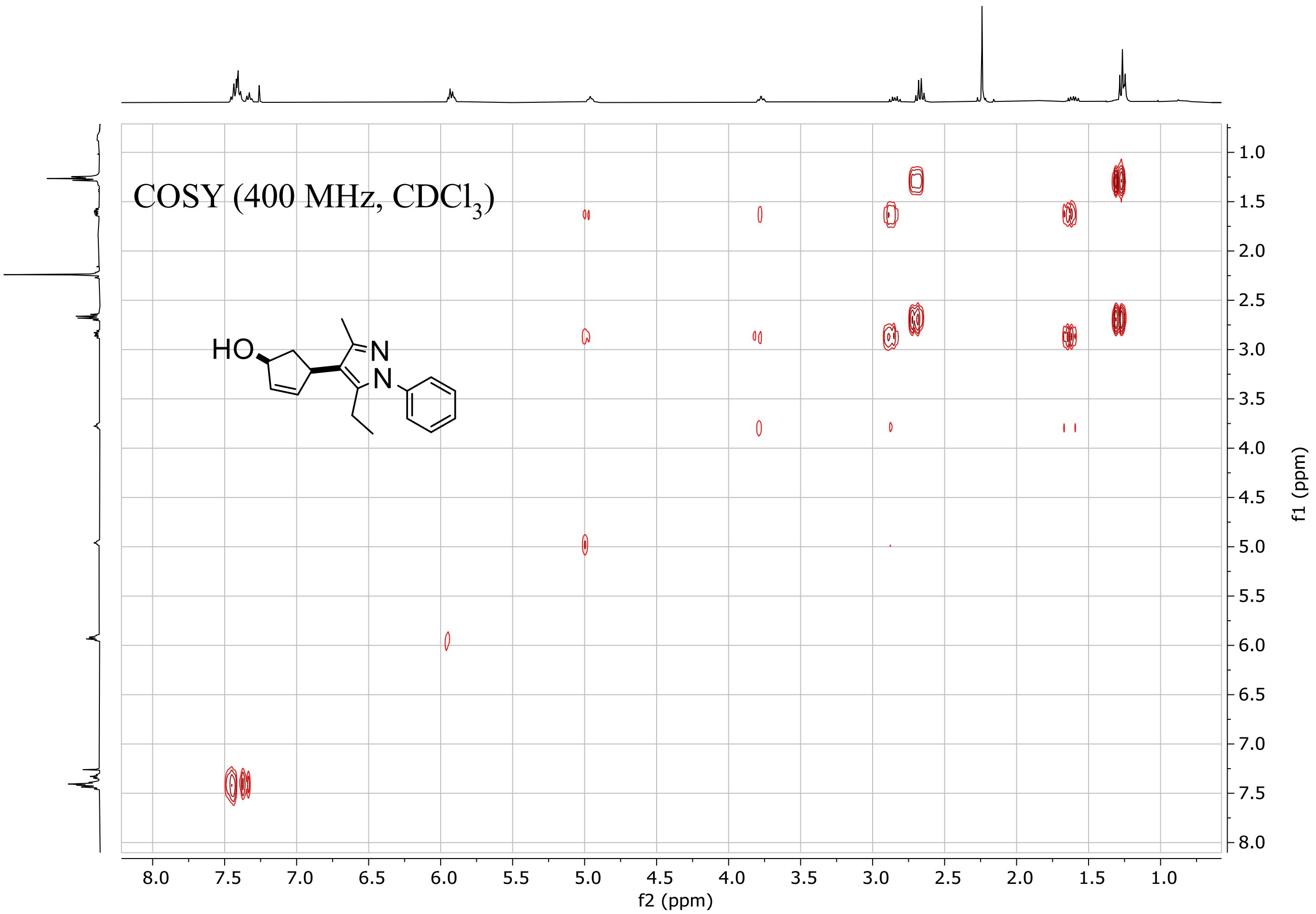
Compound 2n

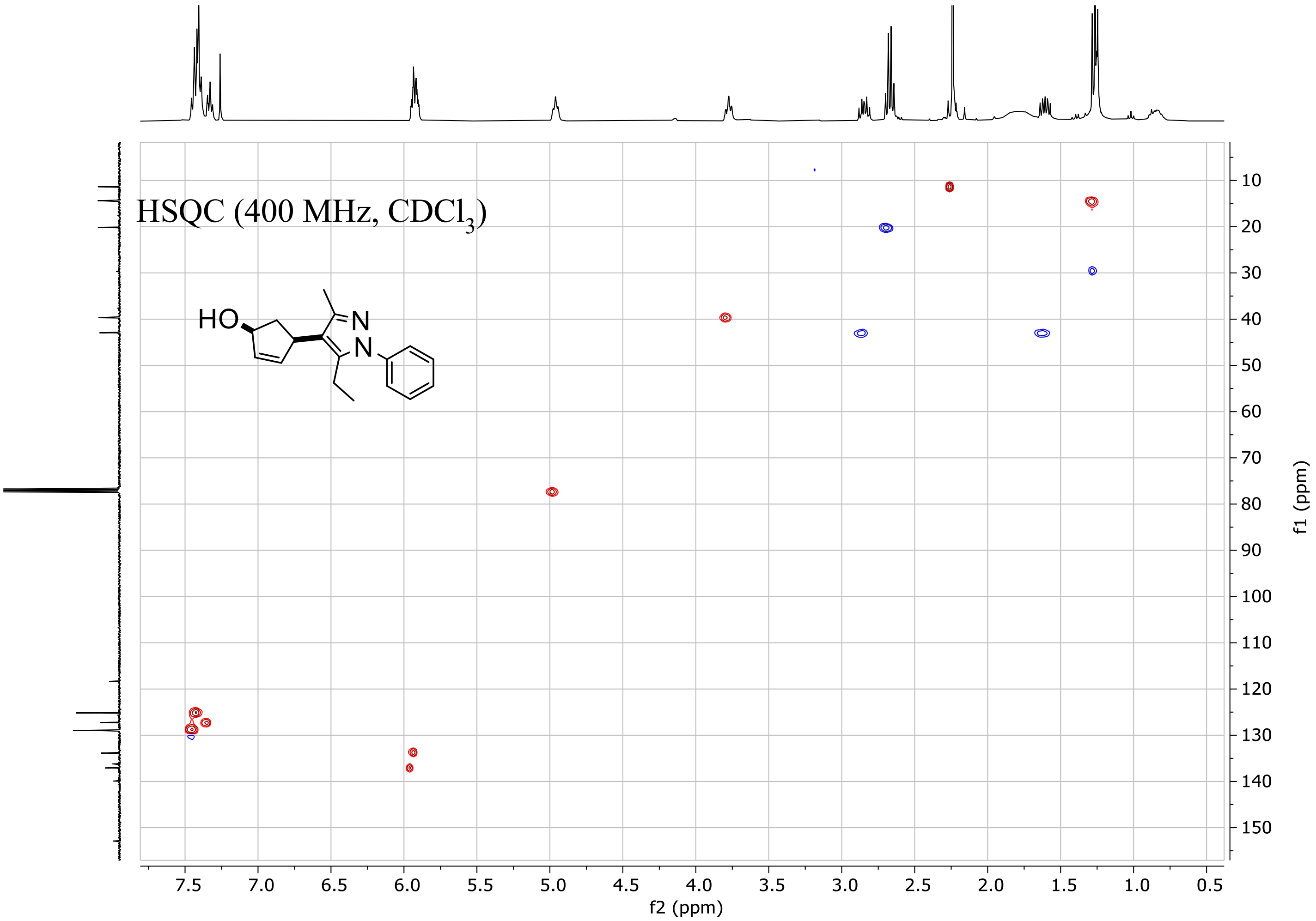


^{1}HNMR (400 MHz, $CDCl_3$)
7.26 CDCl3
HO
N
N
4.69
1.18
2.04
1.00
1.12
1.09
2.31
3.30
1.50
4.68
2400000
2300000
2200000
2100000
2000000
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



^{13}CNMR (101 MHz, CDCl$_3$)
HO
N
N
153.00
140.04
137.21
136.32
133.98
129.10
127.37
125.29
118.47
77.52
77.48 CDCl3_3mm
77.16 CDCl3_3mm
77.16 CDCl3
76.84 CDCl3_3mm
43.08
39.82
29.84
20.26
14.49
11.48
2200000
2100000
2000000
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

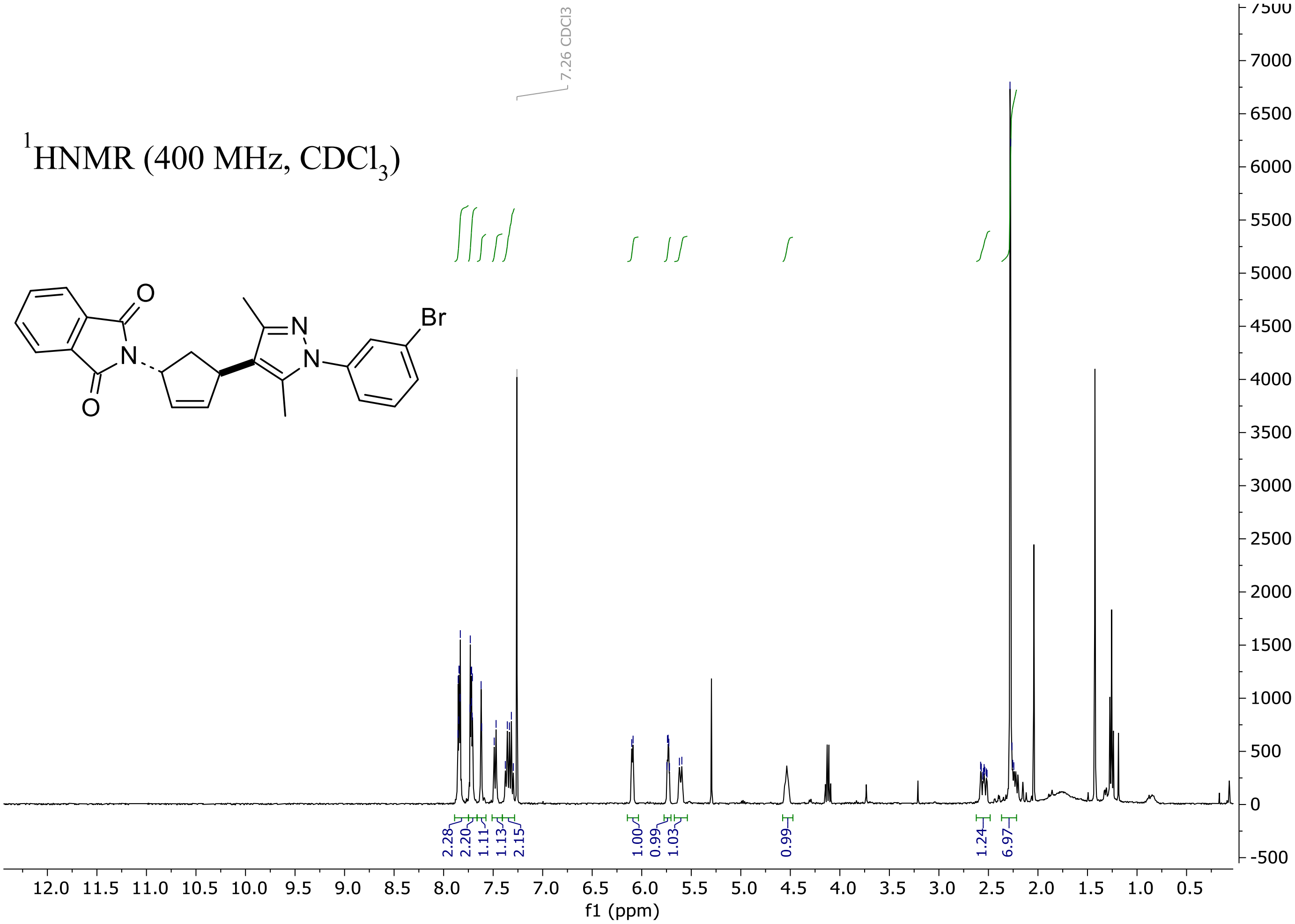

COSY (400 MHz, $CDCl_3$)
HO
N
N
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


HSQC (400 MHz, $CDCl_3$)
HO
N
N
f1 (ppm)
f2 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

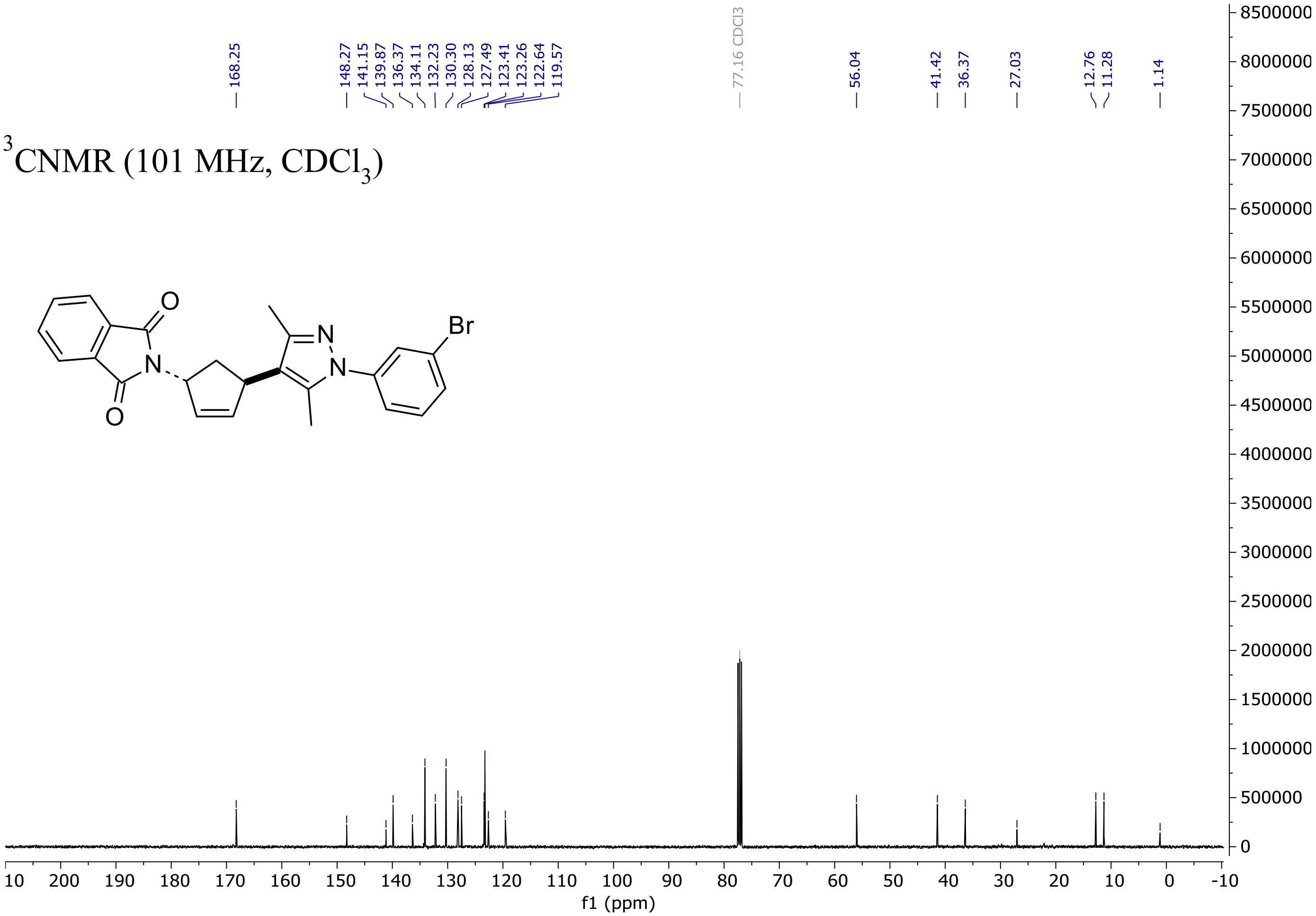
5.3 4-Pyrazolyl-cyclopent-2-en-amines **3b,l**

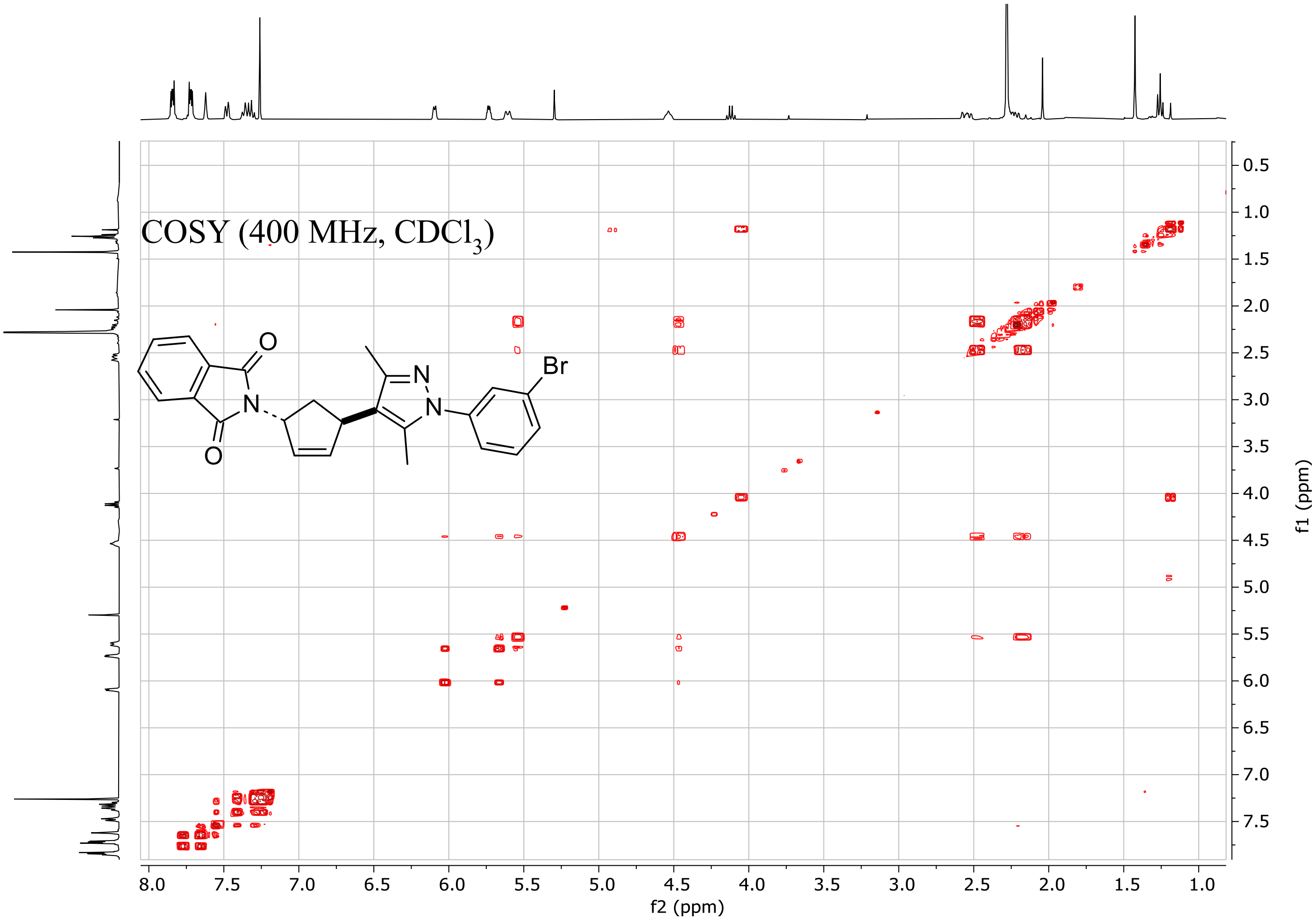
5.3.1 Phthalamido derivatives **9b,l**

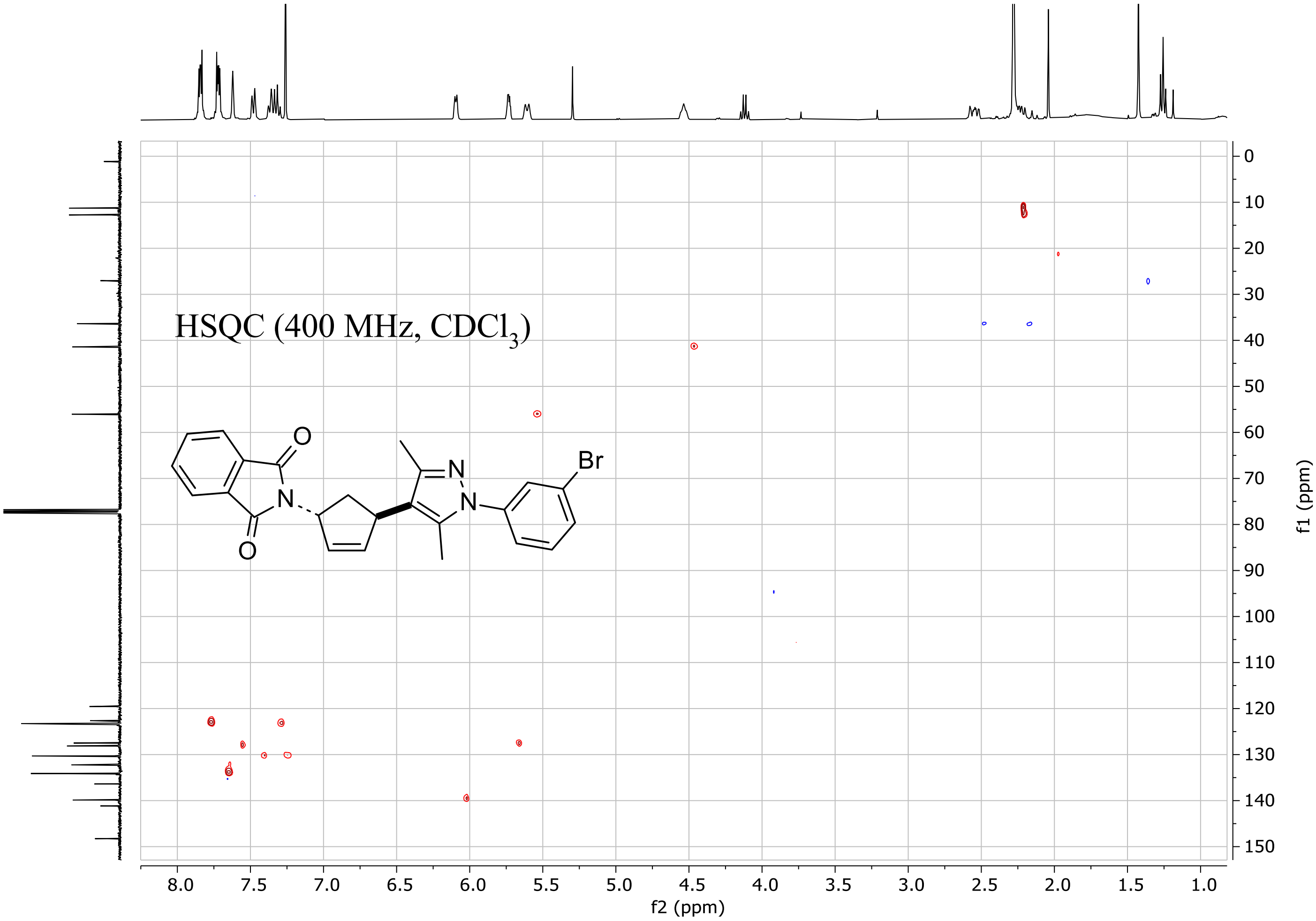
Compound 9b



^{13}CNMR (101 MHz, $CDCl_3$)

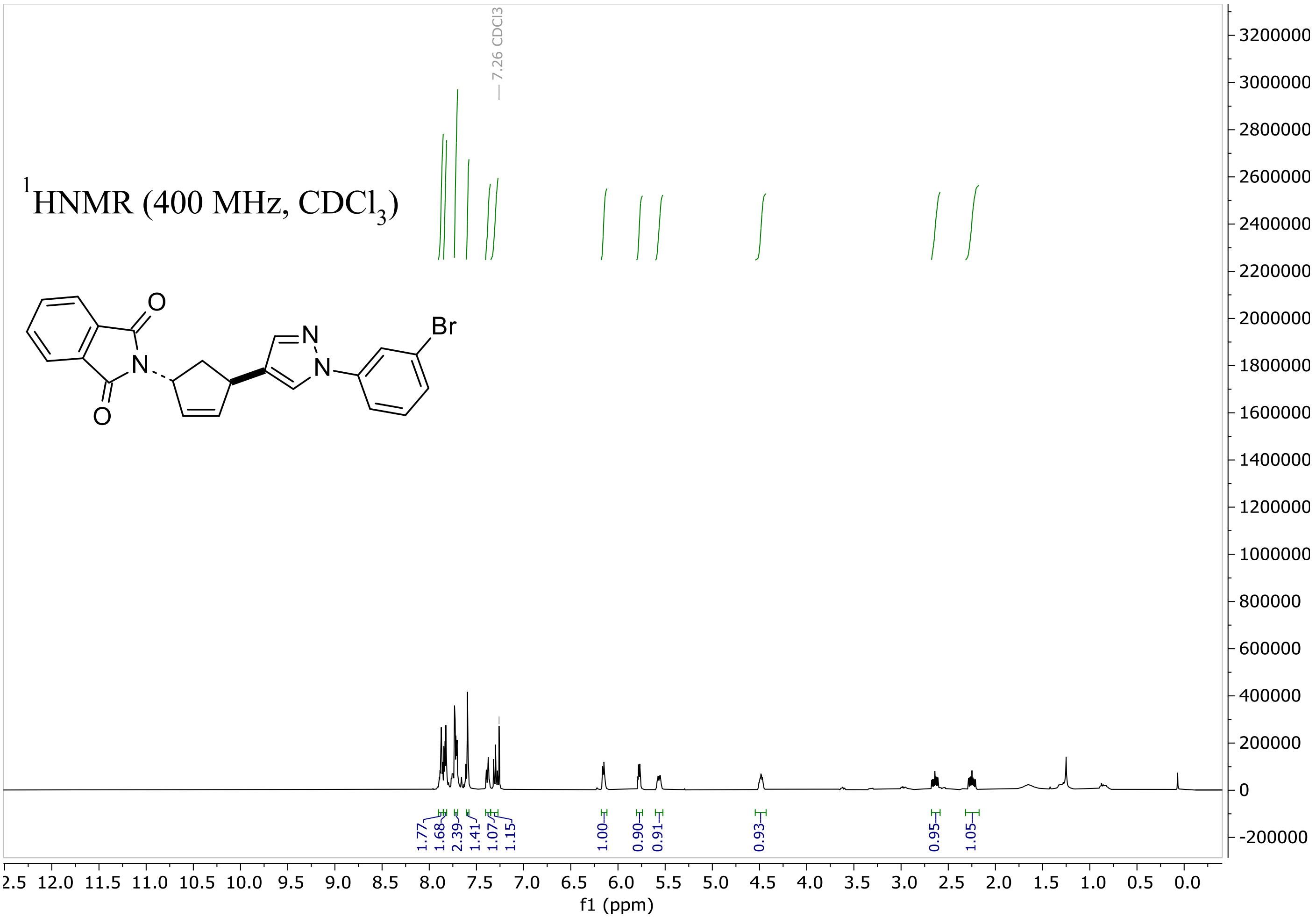


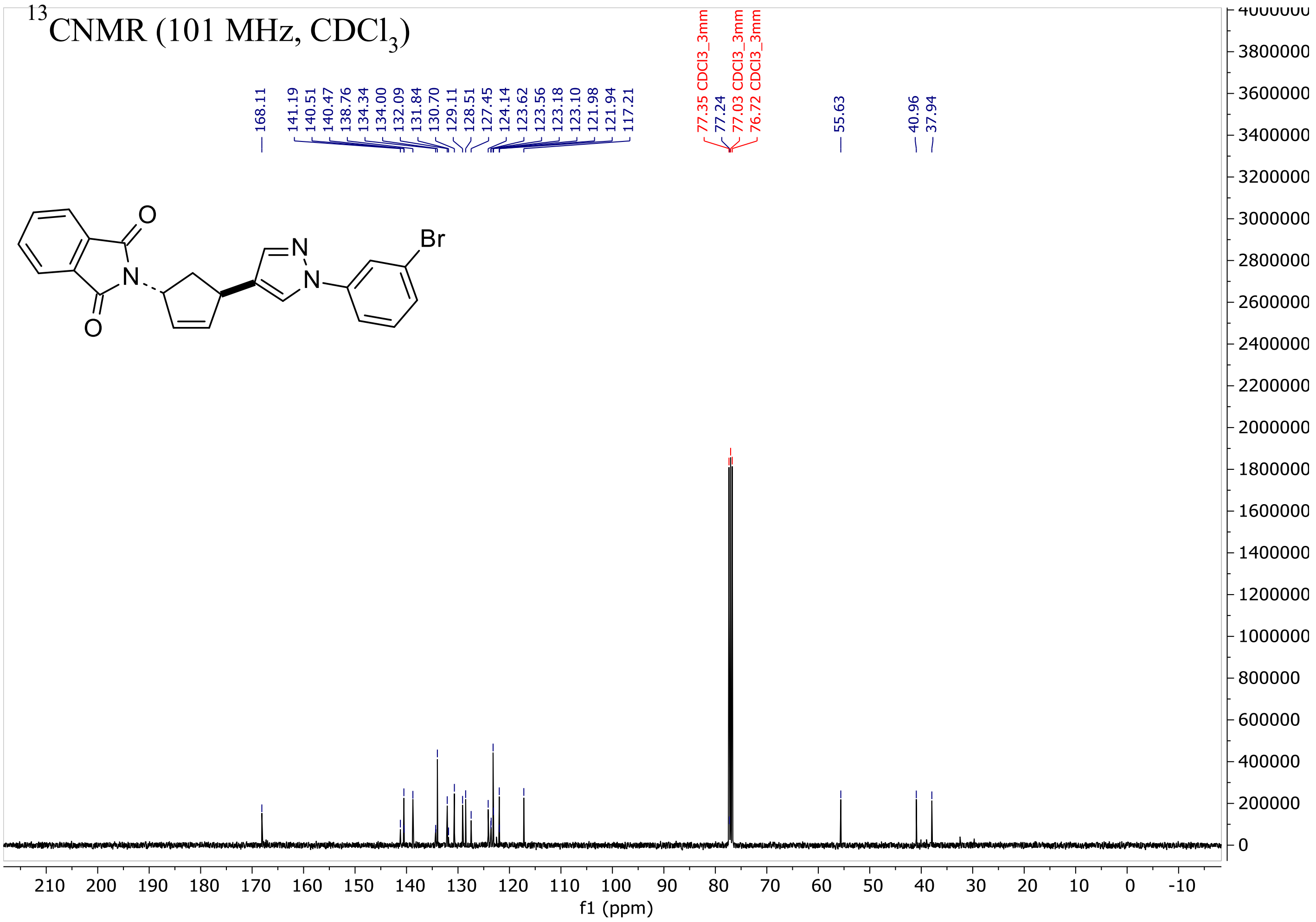

COSY (400 MHz, $CDCl_3$)
O
N
O
N
N
Br
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5



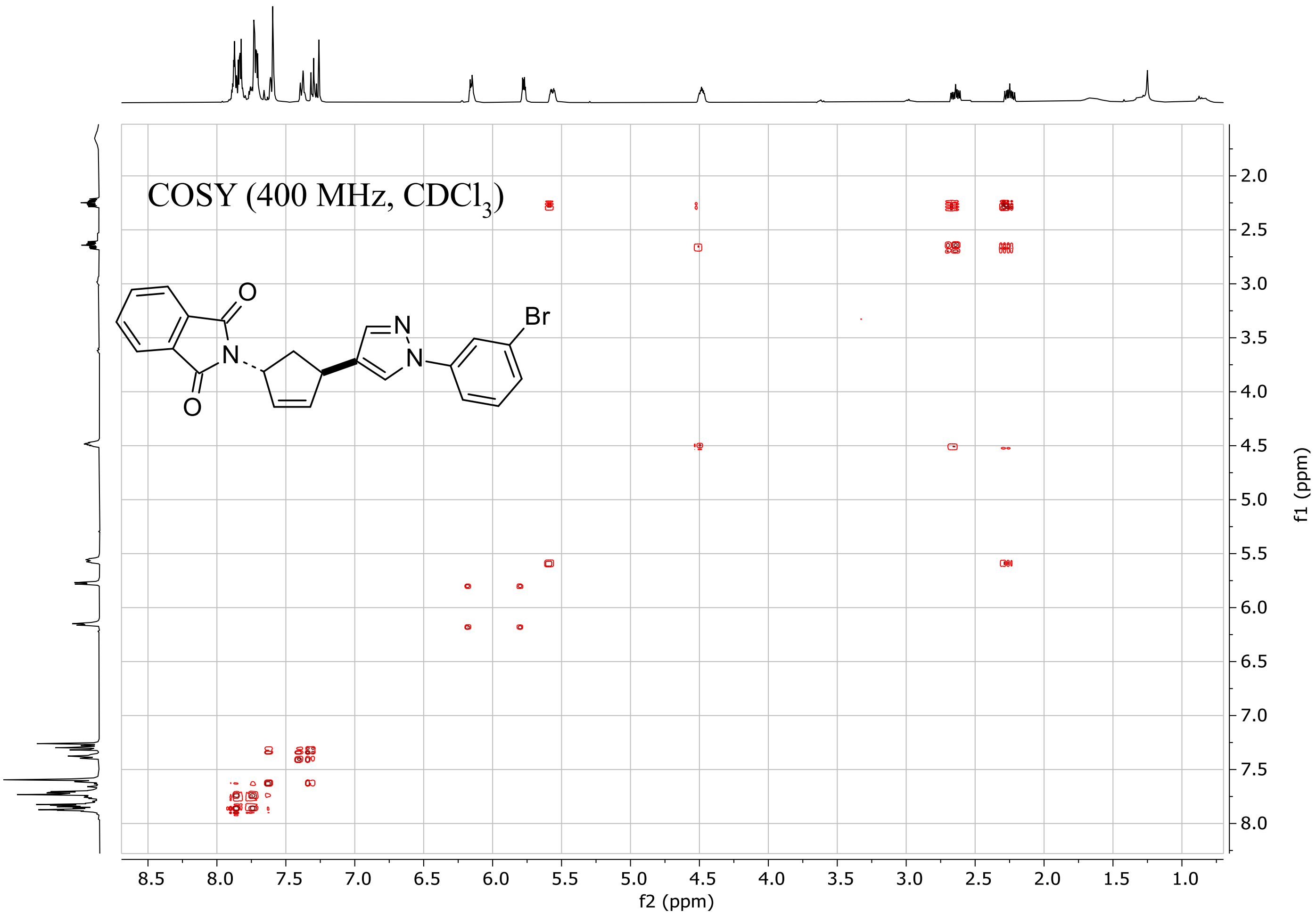
HSQC (400 MHz, $CDCl_3$)

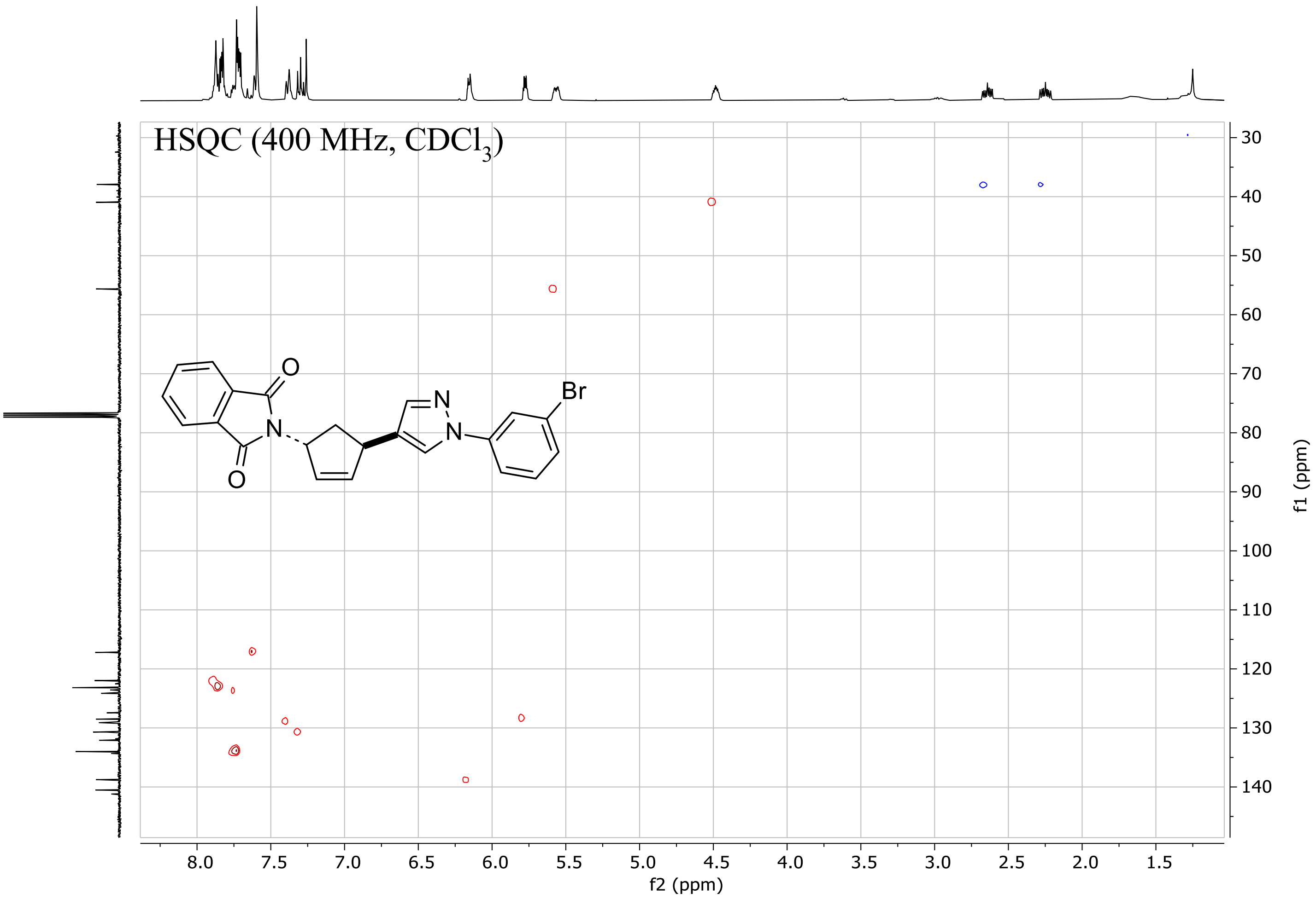
Compound 9l


^{1}HNMR (400 MHz, CDCl$_3$)
7.26 CDCl3
O
N
O
N
N
Br
1.77
1.68
2.39
1.41
1.07
1.15
1.00
0.90
0.91
0.93
0.95
1.05
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



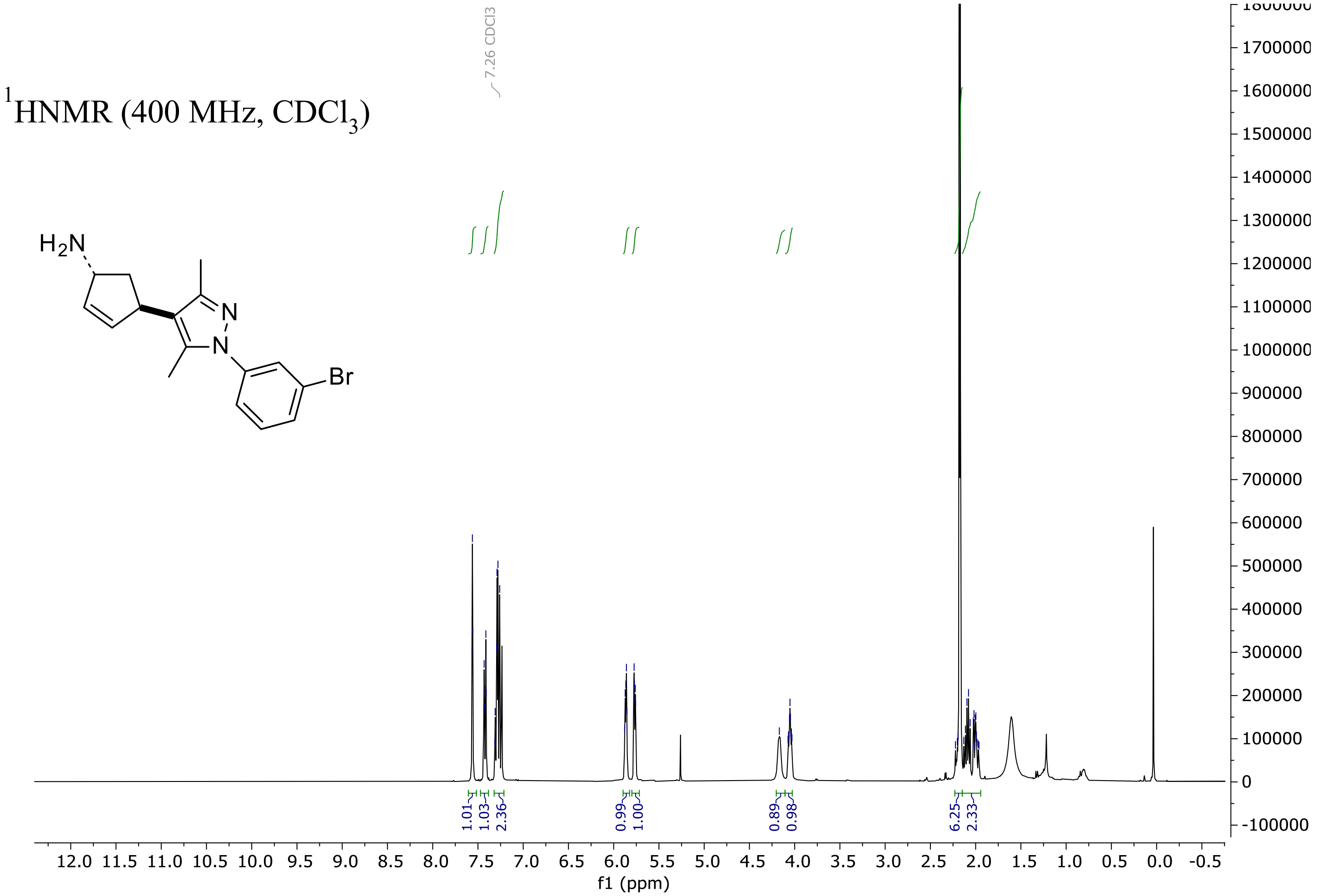
^{13}CNMR (101 MHz, $CDCl_3$)


COSY (400 MHz, CDCl$_3$)
O
N
O
N
N
Br
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)

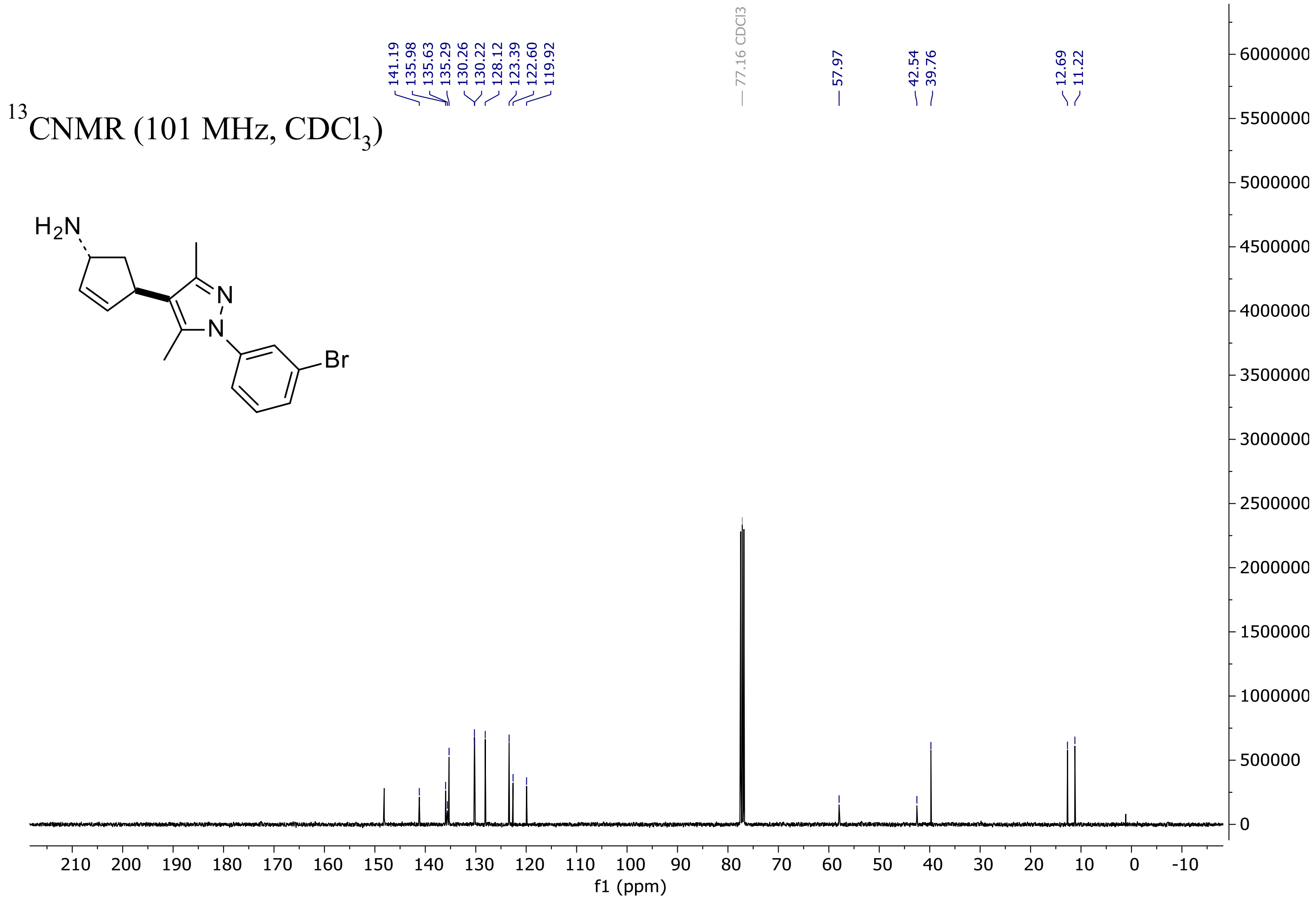


HSQC (400 MHz, CDCl$_3$)
O
N
O
N
N
Br
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)

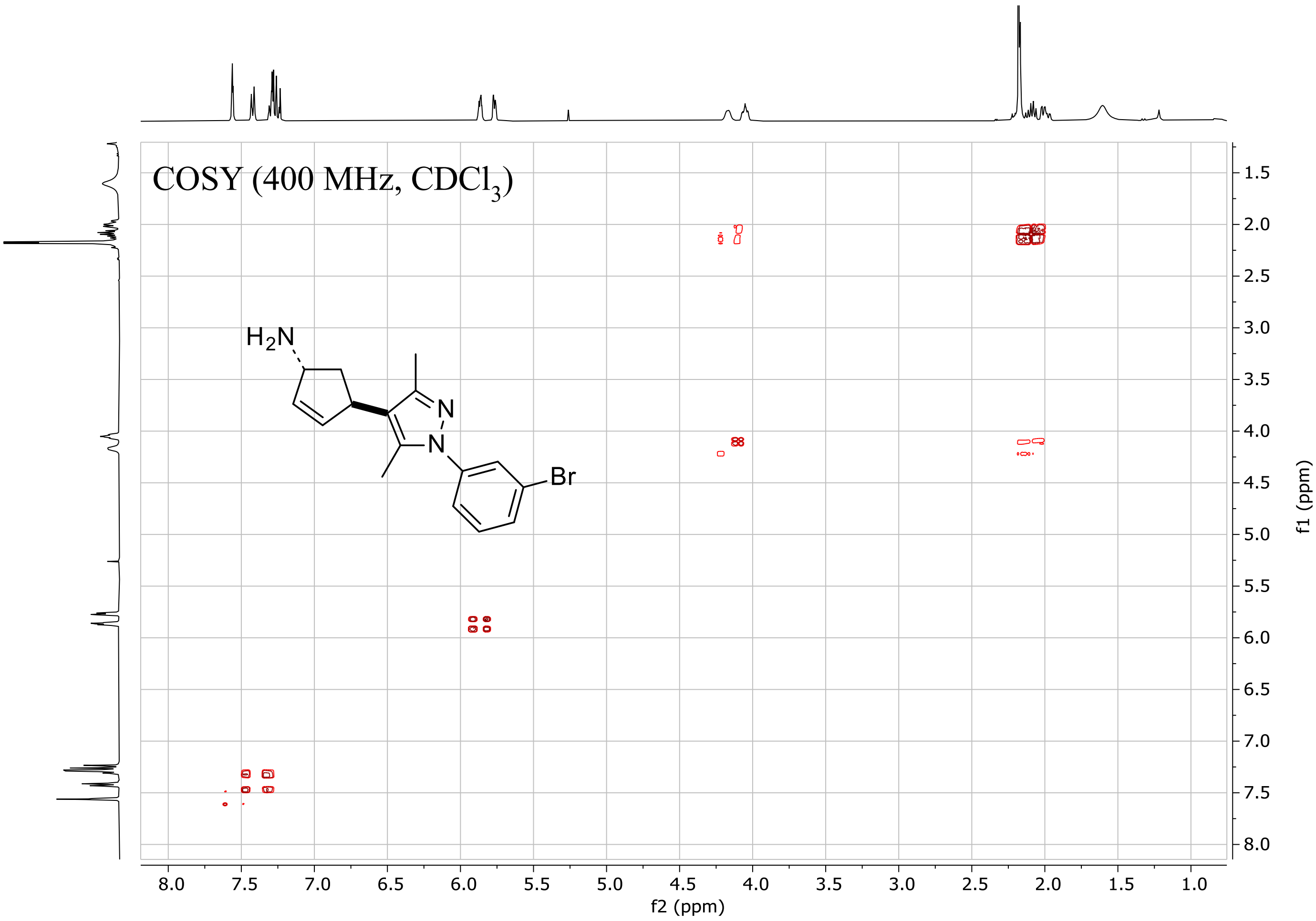
Compound 3b

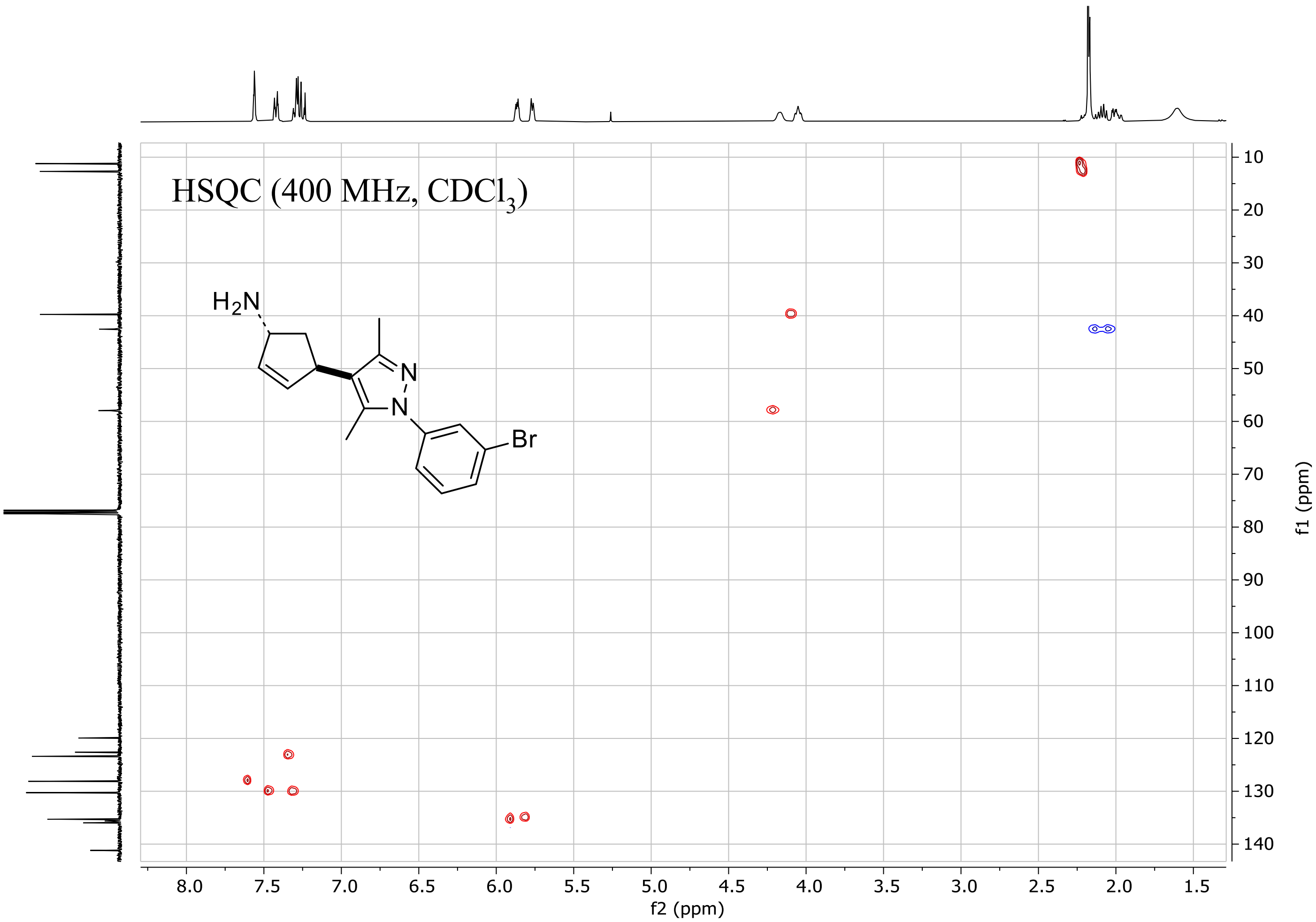


^{1}HNMR (400 MHz, $CDCl_3$)

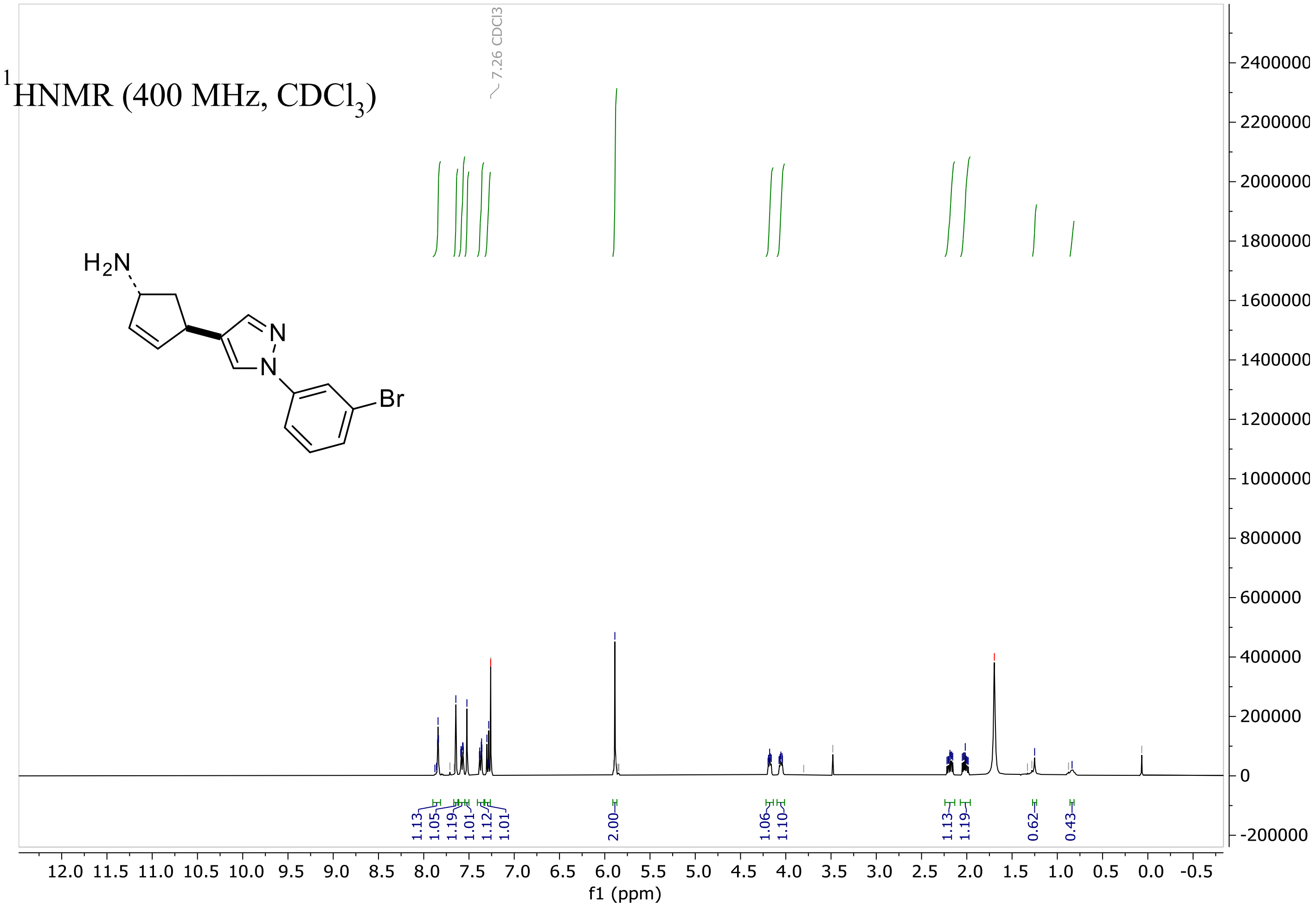


^{13}CNMR (101 MHz, $CDCl_3$)


COSY (400 MHz, CDCl$_3$)
H$_2$N
N
N
Br
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)

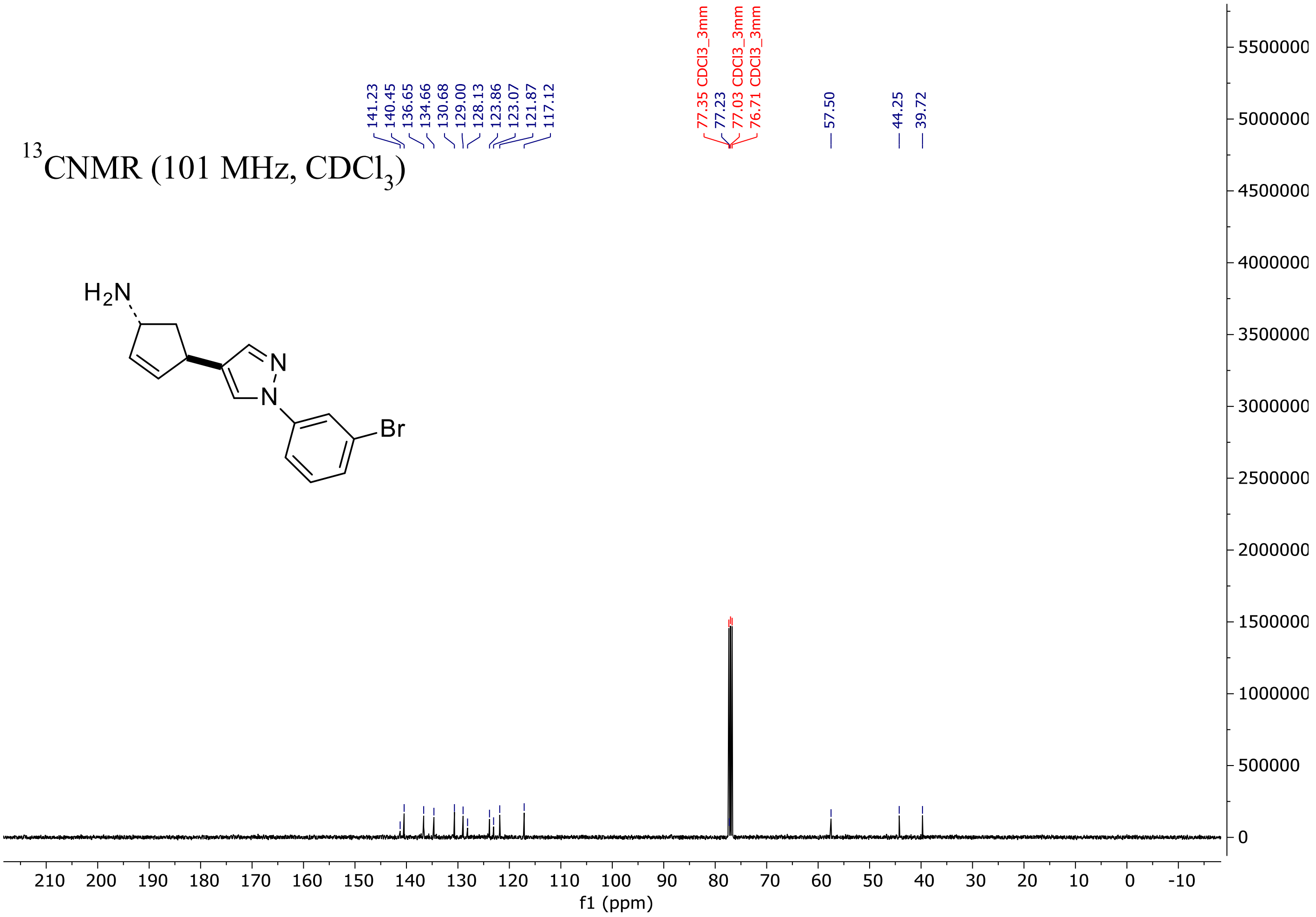

HSQC (400 MHz, $CDCl_3$)
H_2N
N
N
Br
f2 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140

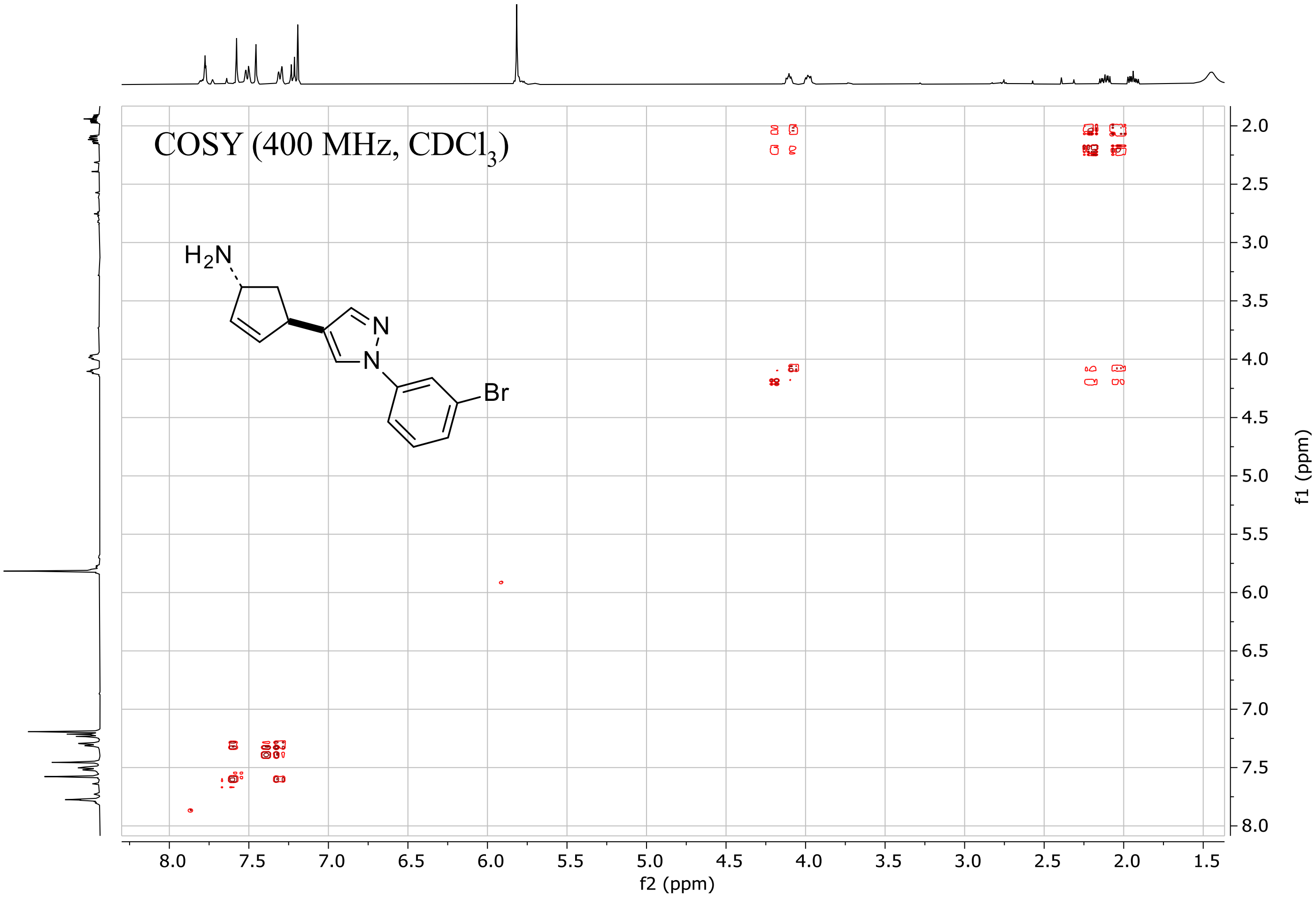
Compound 3l

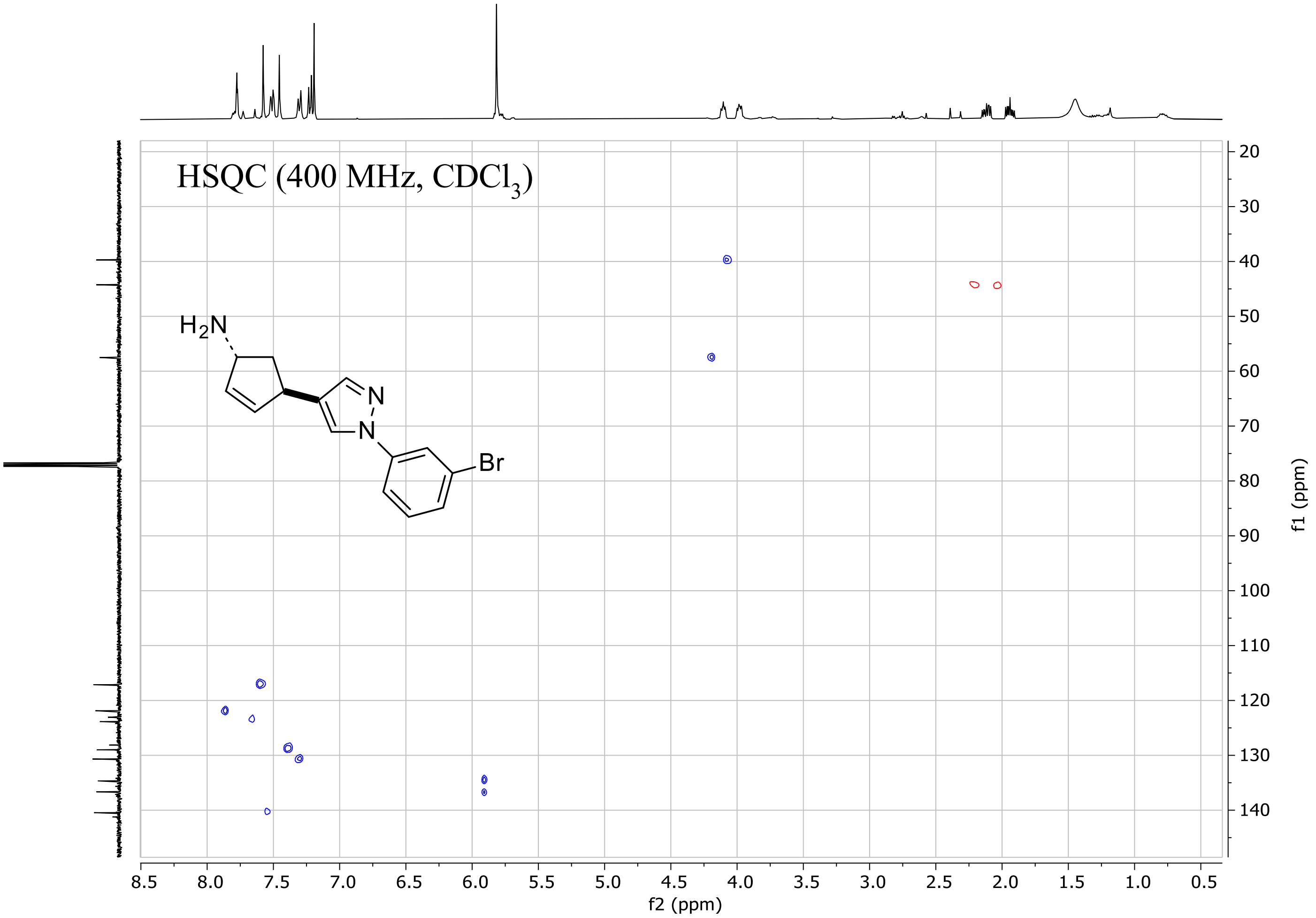


^{1}HNMR (400 MHz, CDCl$_3$)
7.26 CDCl3
H$_2$N
N
N
Br
1.13
1.05
1.19
1.01
1.12
1.01
2.00
1.06
1.10
1.13
1.19
0.62
0.43
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000

^{13}CNMR (101 MHz, $CDCl_3$)

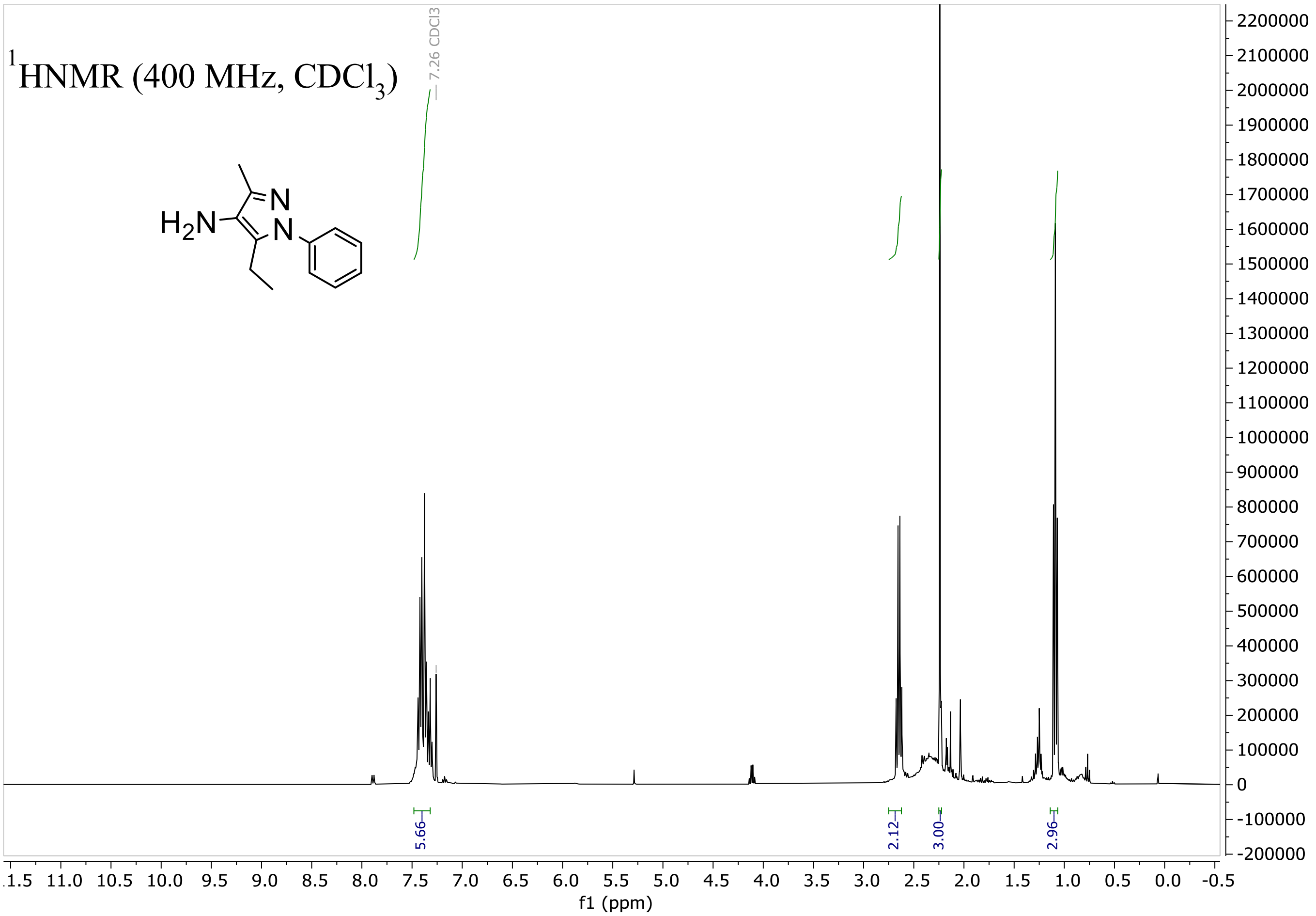


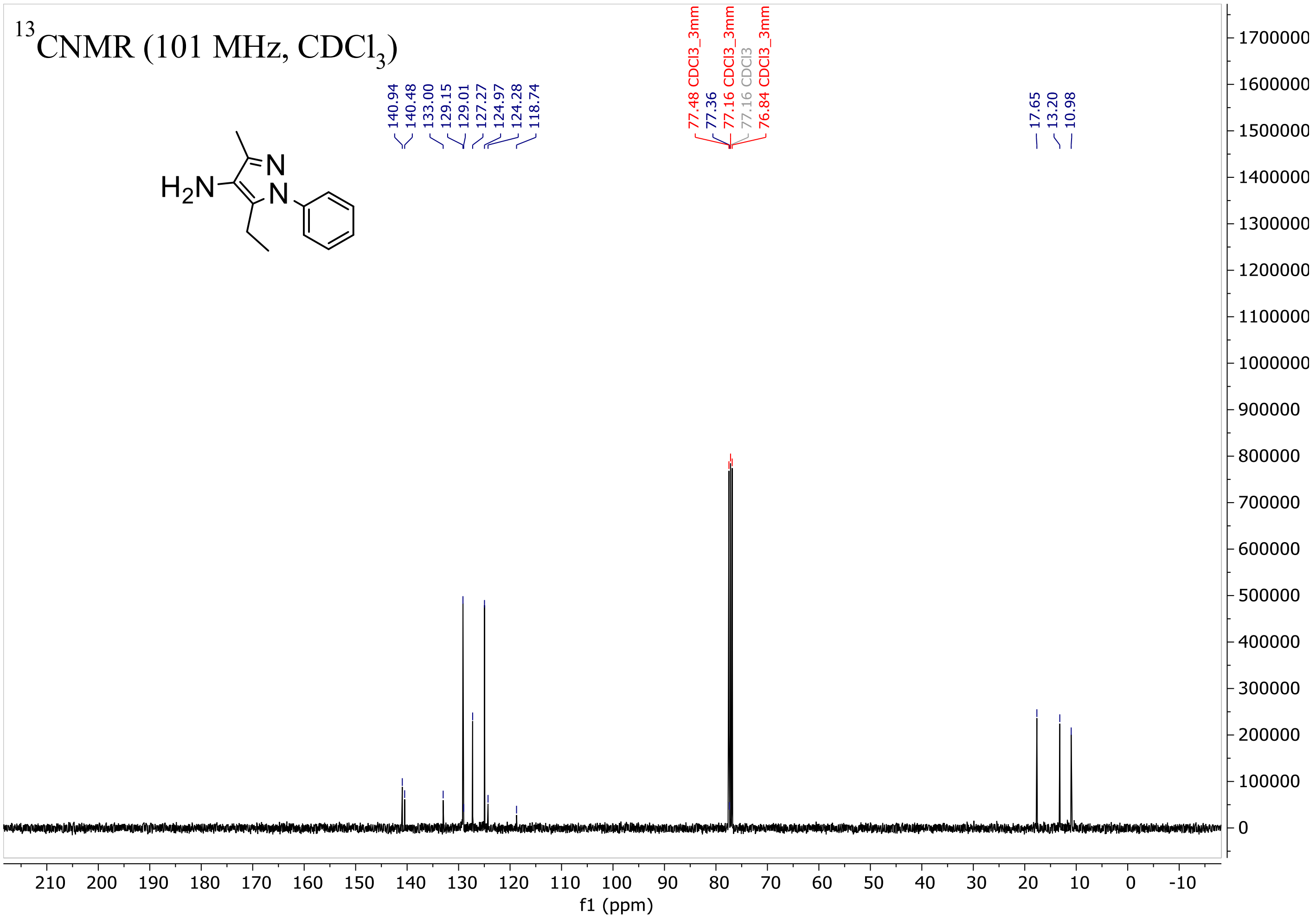

COSY (400 MHz, CDCl$_3$)
H$_2$N
N
N
Br
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


HSQC (400 MHz, CDCl3)
H2N
N
N
Br
f2 (ppm)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
20
30
40
50
60
70
80
90
100
110
120
130
140

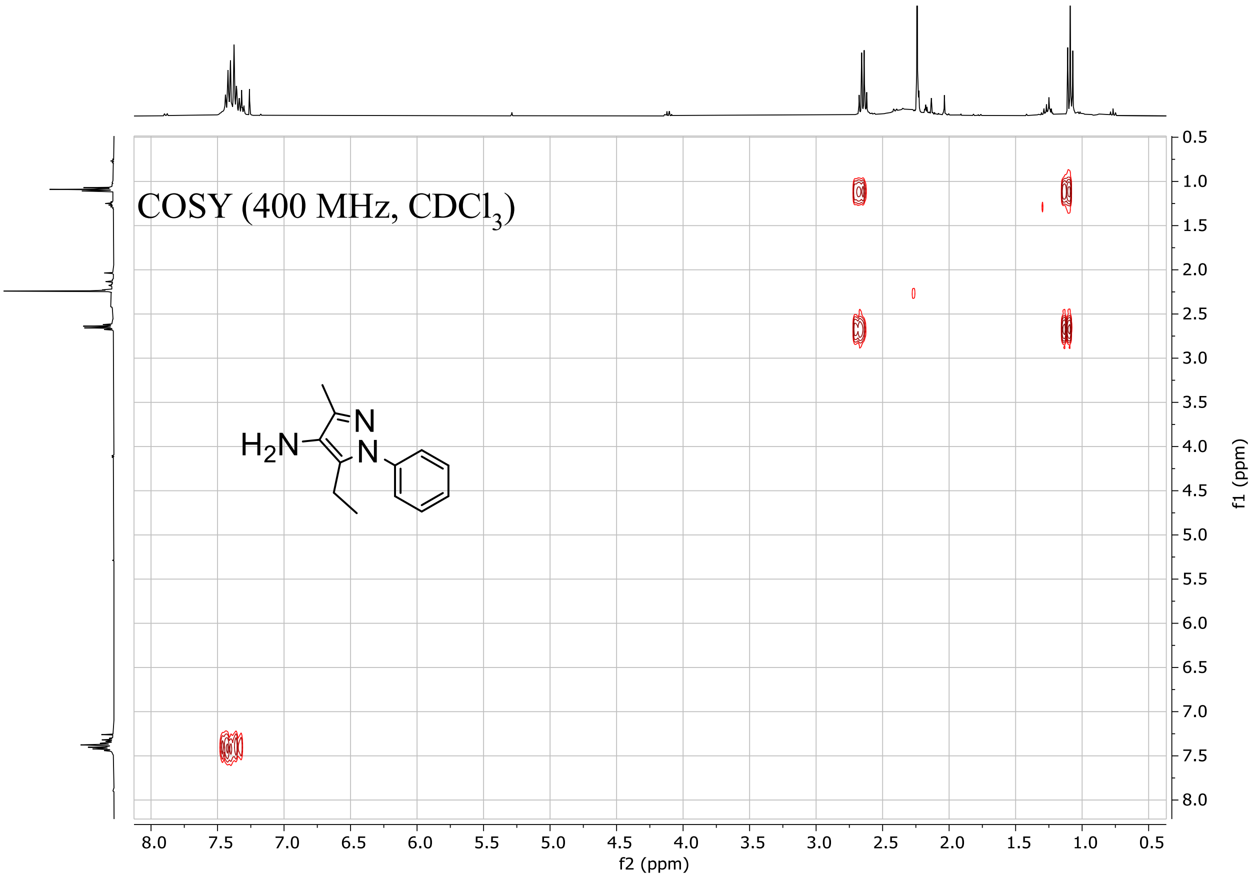
5.4 Other spectra

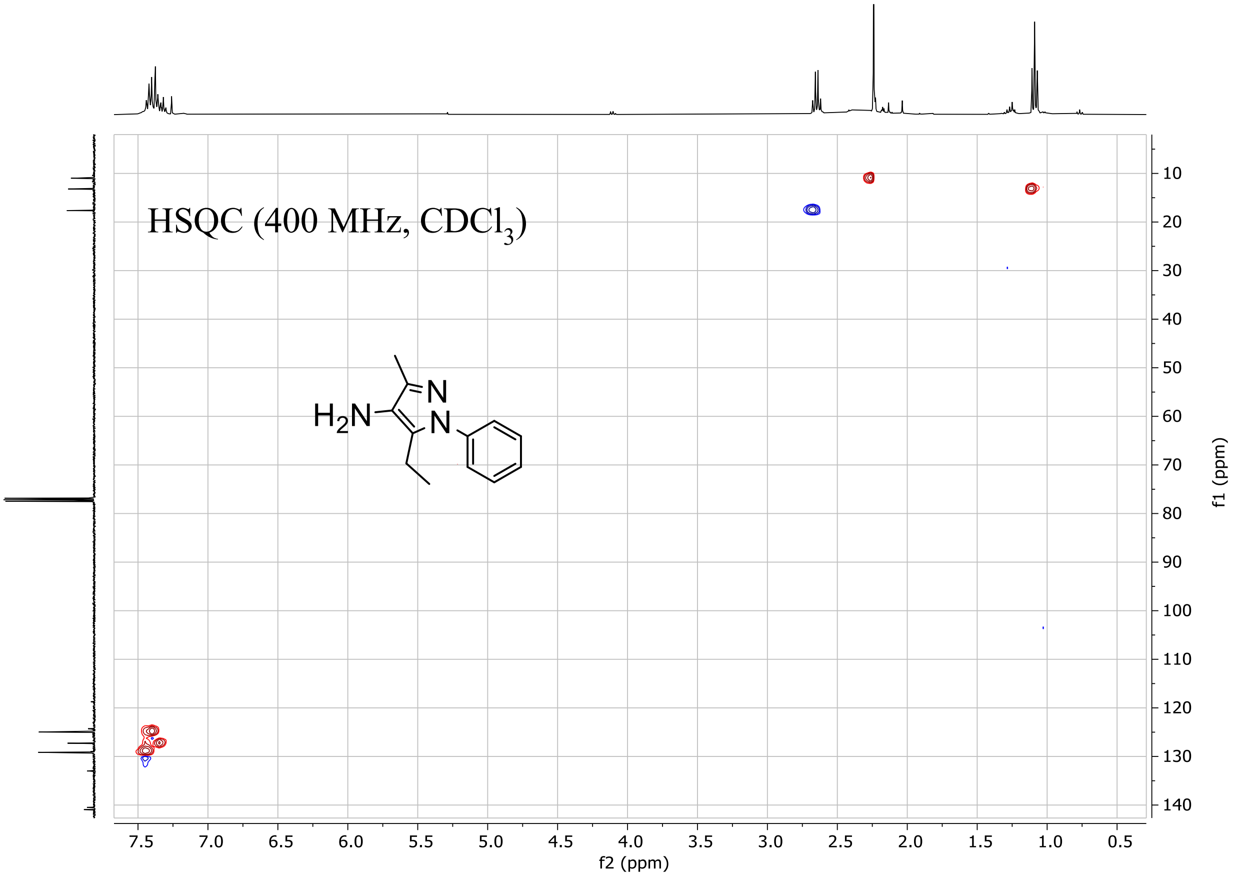
Compound 7n

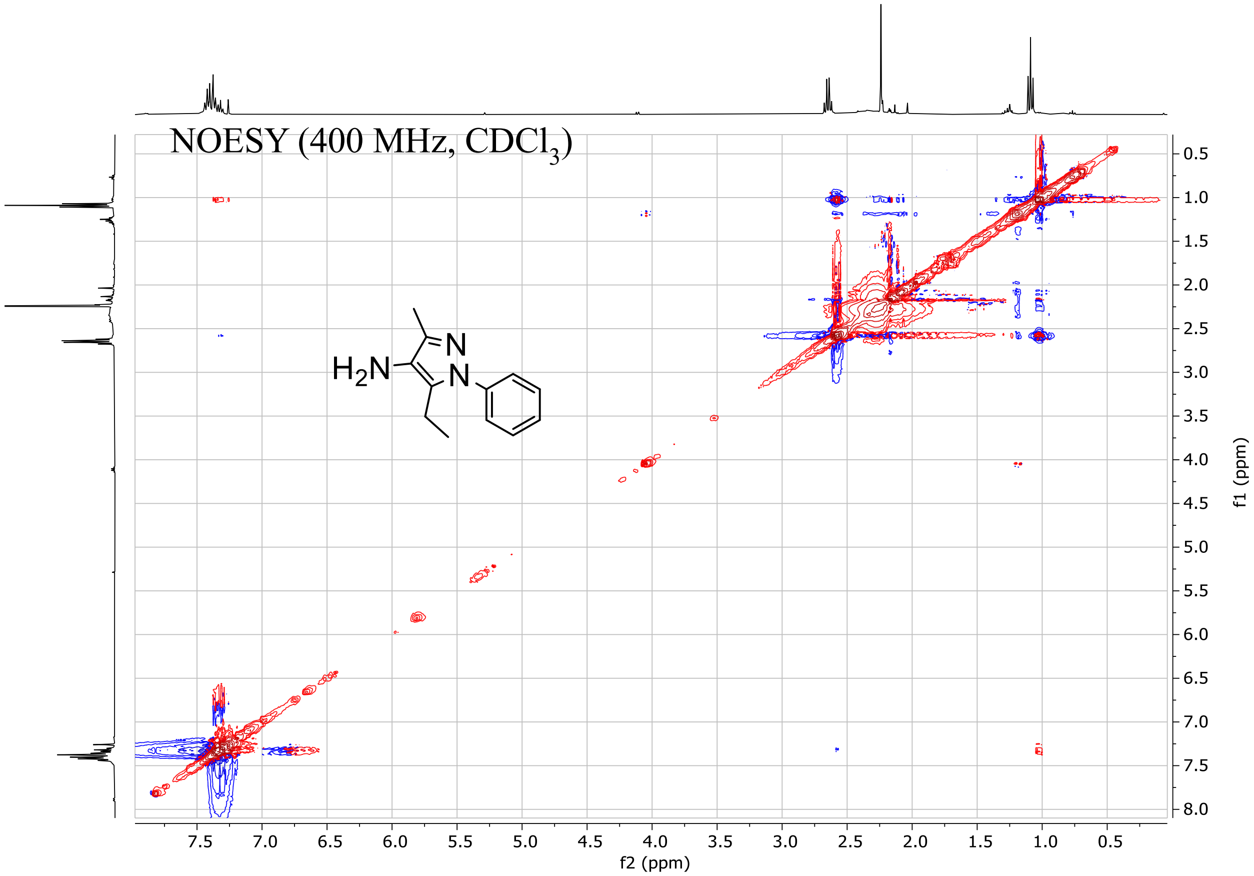




^{13}CNMR (101 MHz, $CDCl_3$)


COSY (400 MHz, CDCl$_3$)
H_2N
N
N
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


HSQC (400 MHz, CDCl$_3$)
H$_2$N
N
N
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)


NOESY (400 MHz, CDCl$_3$)
H_2N
N
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
f1 (ppm)

6 TGA analyses of tetrafluoroborate diazonium salts **1a,d,f,i,k-m**.

Table 1. Summary of TGA analyses of tetrafluoroborate diazonium salts **1a,d,f,i,k-m**.

Sample	Starting of decomposition (°C)	TC1 (°C)	TC2 (°C)	TC3 (°C)
1a	186	215		
1d	162	223		
1f	165	217		
1i	172	226		
1k	167	199	230	
1l	150	173	197	225
1m	146	196	223	

Figure S5. TGA analysis of **1a**.

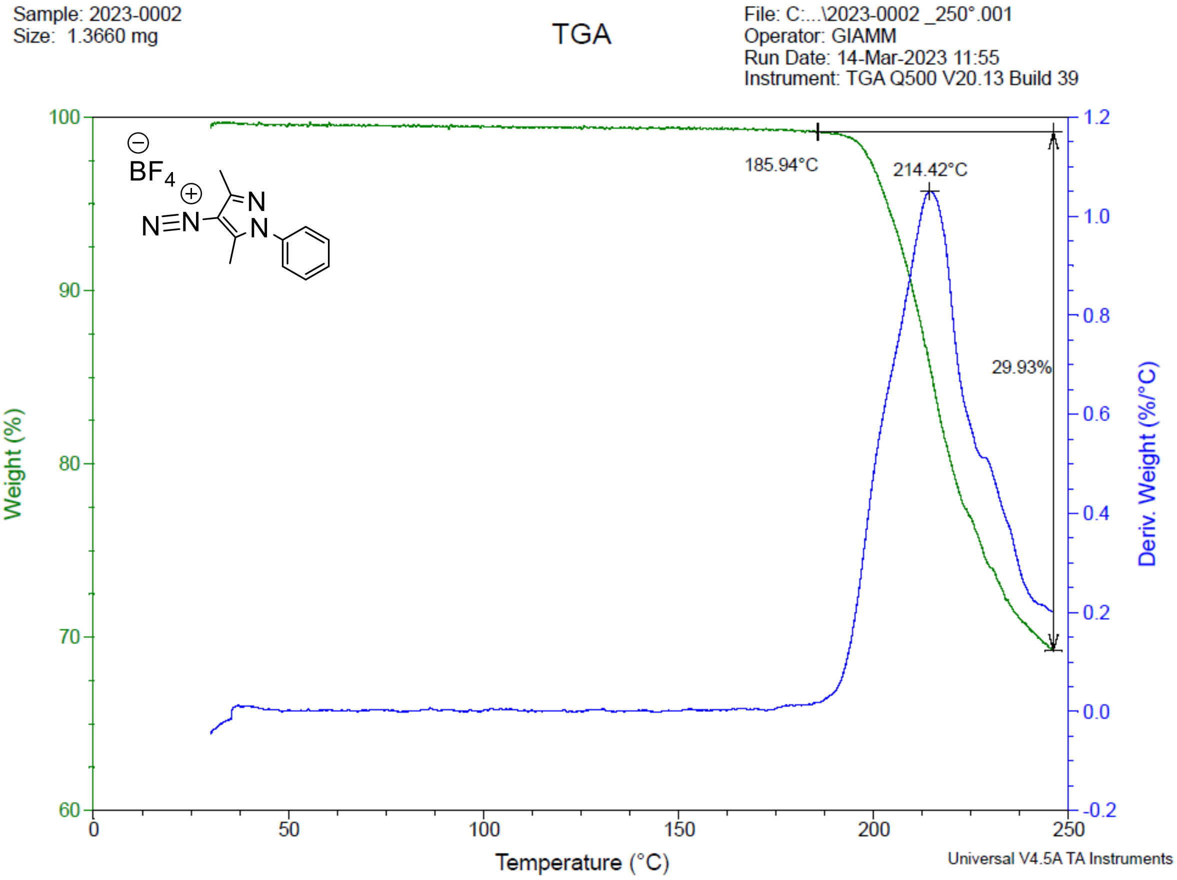


Figure S6. TGA analysis of **1d**.

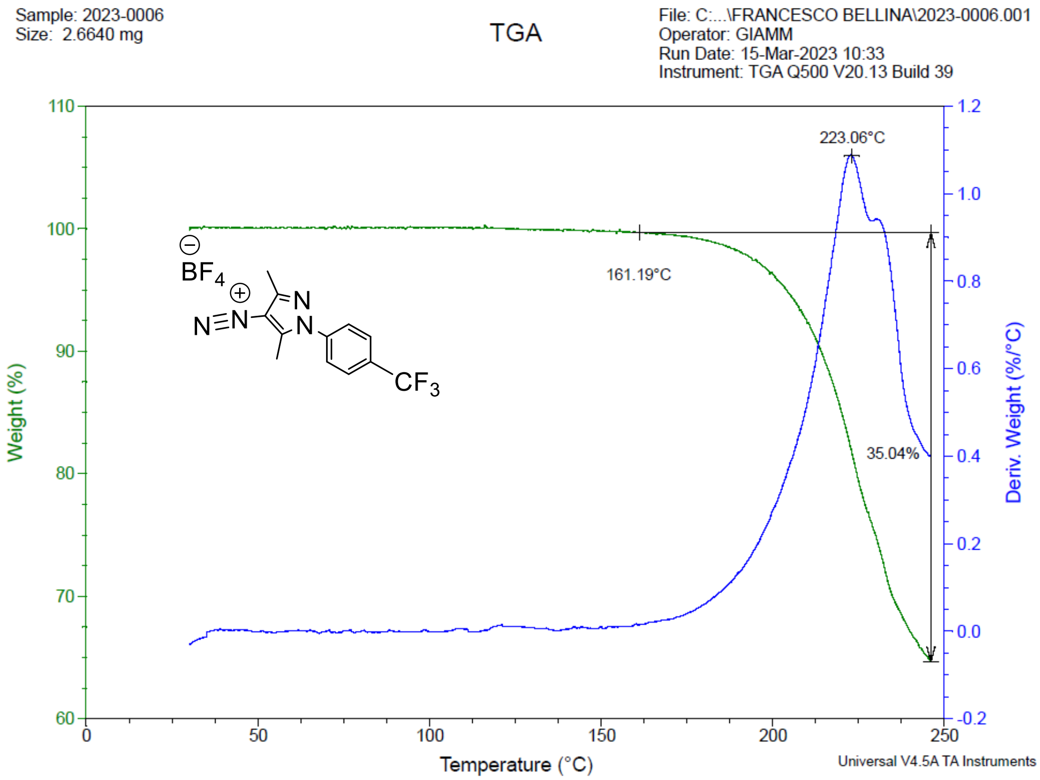


Figure S7. TGA analysis of **1f**.

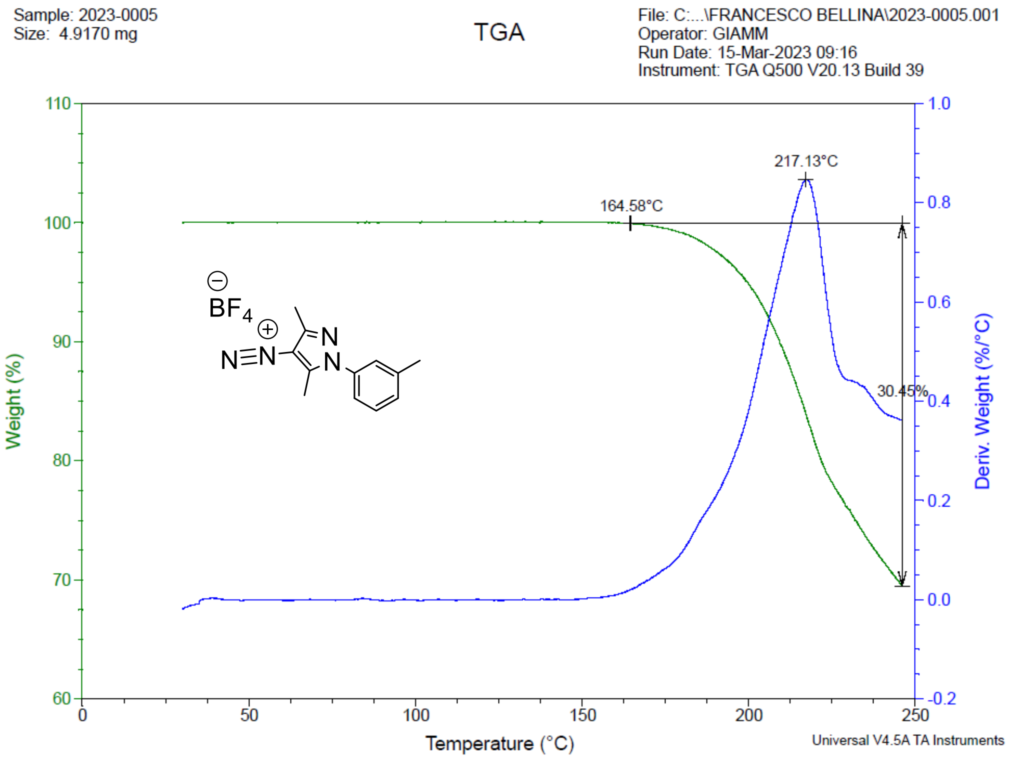


Figure S8.TGA analysis of **1i**.

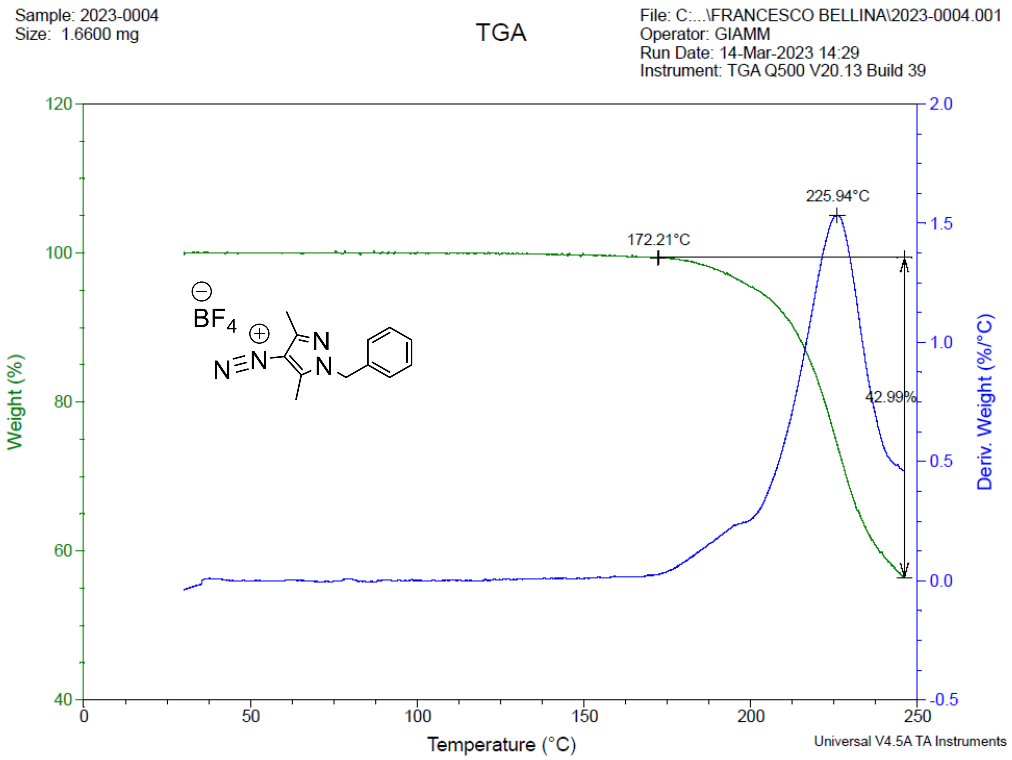


Figure S9. TGA analysis of **1k**.

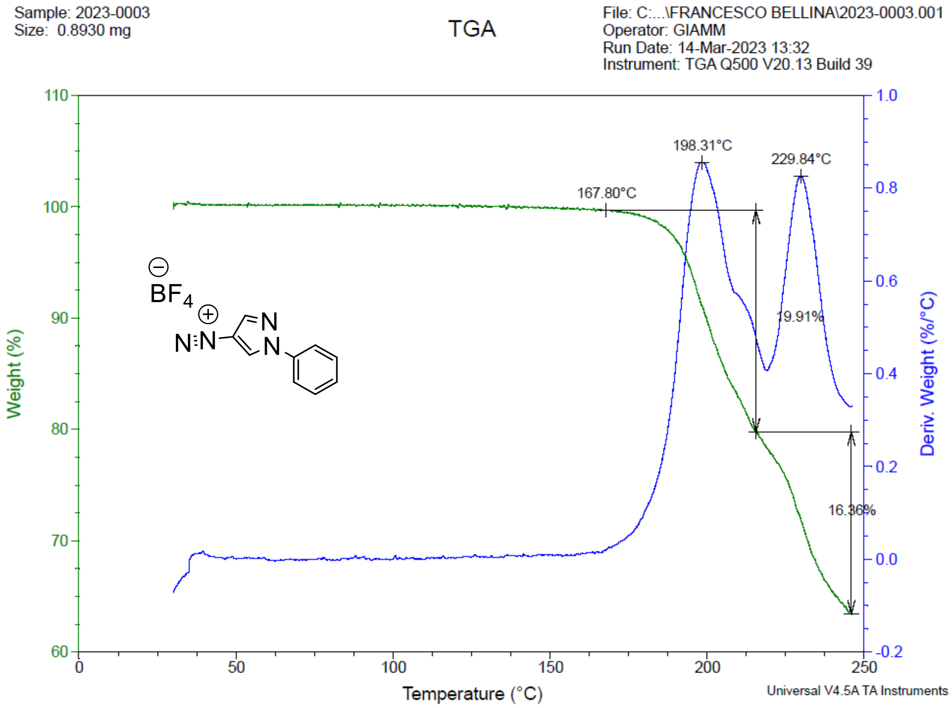


Figure S10. TGA analysis of **1l**.

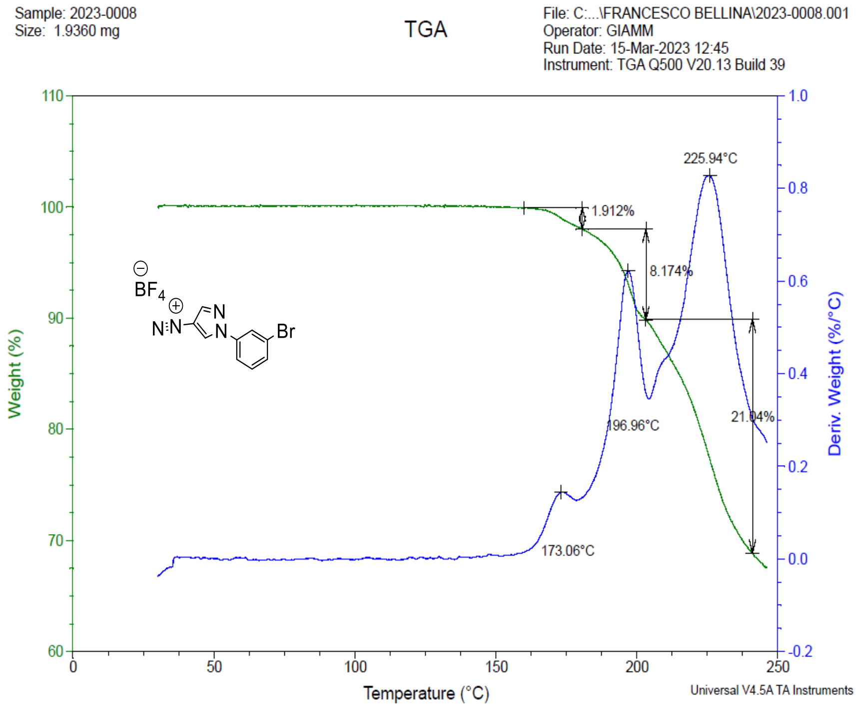
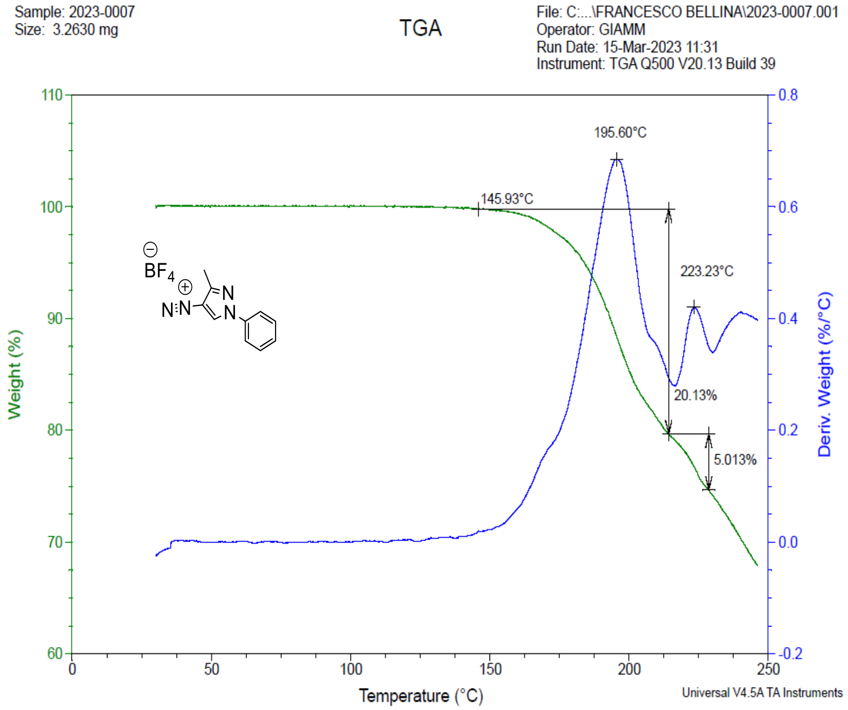


Figure S11. TGA analysis of **1m**.



7 References

1. V.A. Chertkov, A. K. Shestakova, D.V. Davydov, *Chem. Heter. Comp.* 2011, **47**, 45-54.

2. Y. Guan, C. Bissantz, D.E. Bergstrom, A. Link, *Archiv der Pharmazie* 2012, **345**, 677-686.

3. *a)* E. Larionov, L. Lin, L. Guénée, C. Mazet, *J. Am. Chem. Soc.* 2014, **136**, 16882-16894; *b)* R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* 2003, **103**, 27-52.

4. R.A. Angnes, J.M. Oliveira, C.C. Oliveira, N.C. Martins, C.R.D. Correia, *Chem. -Eur. J.* 2014, **20**, 13117-13121.