Supporting information

Selective Synthesis of Spirooxindoles by an Intramolecular Heck-Mizoroki Reaction

Tamal Roy[†], Peter Brandt[†], Alexander Wetzel[‡], Joakim Bergman[‡], Jonas Brånalt[‡], Jonas Sävmarker[#], Mats Larhed[¤,*]

[†] Department of Medicinal Chemistry, BMC, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden.

[‡] Department of Medicinal Chemistry, Cardiovascular and Metabolic Diseases, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Pepparedsleden 1, Mölndal, 431 83, Sweden.

[#] The Beijer Laboratory, Department of Medicinal Chemistry, BMC, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden.

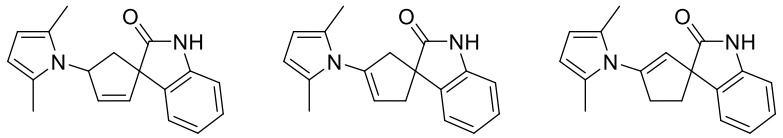
[¤] Department of Medicinal Chemistry, Science for Life Laboratory, BMC, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden.

Table of Contents

Computational details

The density functional calculations were performed in Jaguar version 9.4, release 15, Schrodinger, Inc., New York, NY, 2016.[1]

Geometries and energies. Geometries were optimized using the LACVP* basis set[2] and the B3LYP-D3 *a posteriori*-corrected functional.[3] Vibrational analyses were performed to characterize the stationary points identified and to calculate zero point energies. The contributions to the free energies were calculated at a temperature of 353.15 K (80 °C) using the B3LYP-D3/LACVP* geometries. Solvation energies were calculated using B3LYP-D3/LACVP** and the standard Poisson-Boltzmann continuum solvation model[4] for DMF using the B3LYP-D3/LACVP* geometries. The final solvated free energies were calculated by adding the total free energy contributions and solvation energies to the energy calculated by B3LYP-D3/LACVP**++. The results are shown in Tables S1 and S2.



2a **2a-4a** **4a**

Table S1. Relative energies (kcal mol^{-1}) of the two products **2a** and **4a** observed in the reaction together with a presumptive intermediate **2a-4a**.

Species	Gas Phase Energy LACVP*	Total Free Energy at 353.15K	Free energy contribution	Gas Phase Energy LACVP**	Solvation and LACVP**	Solvation effect	Gas Phase Energy LACVP**++	Relative free energy in DMF at 80 °C
2a	2.8	4.6	1.8	2.7	2.0	-0.7	2.8	3.9
2a-4a	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
4a	0.2	0.5	0.4	0.2	-0.2	-0.3	0.1	0.1

Table S1 shows that **2a** is less stable than the isomerized byproduct **4a**. Further, **4a** is found to be isoenergetic with a hypothetical intermediate **2a-4a** that would be an intermediate on a pathway consisting of repeating β-elimination, alkene rotation, and reinsertion. Therefore, it can be concluded that the selective formation of **2a** and **4a** must be under kinetic control.

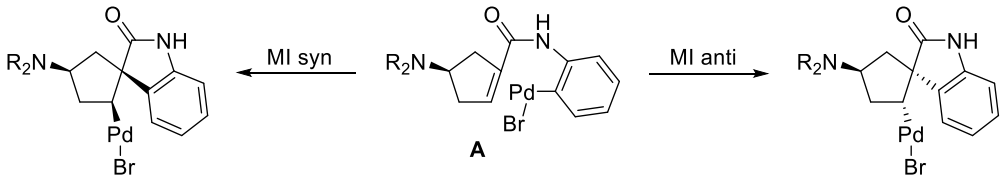


Table S2. Relative B3LYP-D3 energies (kcal mol^{-1}) of the two diastereomeric migratory insertions investigated. Triphenyl phosphine excluded for sake of clarity; R_2N = 2,5-dimethylpyrrole.

Entry	Aryl vs.Br	Aryl vs. PPh_3	Species	Gas Phase Energy LACVP*	Total Free Energy at 353.15K	Free energy contribution	Gas Phase Energy LACVP**	Solvation and LACVP**	Solvation effect	Gas Phase Energy LACVP**++	Relative free energy in DMF at 80 °C
s1	Cis	Cis	**A**	-13.2	-16.0	-2.8	-13.2	-9.5	3.7	-12.6	-11.8
s2	Cis	Trans	**A**	2.4	-0.7	-3.1	2.4	9.0	6.6	1.6	5.1
s3‡	Cis	Trans	**A**	-3.7	-3.5	0.2	-3.8	-0.8	3.0	-3.9	-0.7
s4	Trans	Cis	**A**	-16.6	-17.9	-1.3	-16.6	-13.2	3.4	-16.0	-13.9
s5	Cis→ Trans	Cis	**s1→s4**	-11.2	-13.3	-2.0	-11.2	-7.7	3.6	-10.4	-8.9
s6	Cis	Cis→ Trans	**s1→s2**	9.0	4.8	-4.2	9.0	15.9	6.9	9.1	11.7
s7	Cis	Trans	**MI anti**	0	0	0	0	0	0	0	0
s8	Cis	Trans	**MI syn**	3.5	1.9	-1.6	3.5	3.6	0.0	3.6	2.1
s9	Trans	Cis	**MI anti**	-0.1	-1.5	-1.4	-0.3	1.3	1.6	0.4	0.6
s10	Trans	Cis	**MI syn**	4.2	2.9	-1.4	4.0	5.4	1.4	4.6	4.6

†) The bromide is cis to the uncoordinated olefin. ‡) The bromide is trans to the coordinated olefin.

The cis-trans isomerization of the initially formed cis Br-Pd-aryl σ-complex (**s1**) to the trans Br-Pd-aryl σ-complex (**s4)** was found to be very fast with a transition state (**s5**) barrier of only 2.8 kcal mol^{-1} (see values in Table S2). The resulting trans Br-Pd-aryl σ-complex (**s4)** was found to be more stable by 2.1 kcal mol^{-1}. A cis Br-Pd-aryl configuration with the phosphine trans to the aryl (**s2**) was found to be high in energy; 19.0 kcal mol^{-1} above **s4**. This species could isomerize to a lower energy conformation with the bromide trans to a Pd-coordinated olefin (s3) but the energy was still found to be relatively high (13.2 above **s4**). This higher energy Pd-aryl complex corresponds to migratory insertion **s7**. However, the barrier (**s6**; 25.6 kcal mol^{-1} above **s4**) for reaching this olefin complex was found to be considerably higher than the migratory insertion **s9** from **s4** leading to the observed product **2a**. Thus, migratory insertions **s7** and **s8** will not be involved in the production of Heck products and the anti-syn selectivity can be calculated to 4.0 kcal mol^{-1}.

NOE

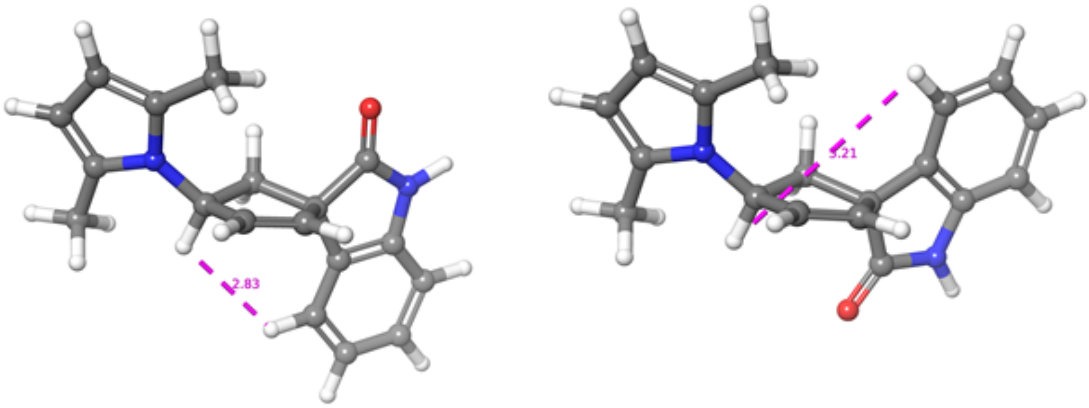


Figure S3. Distances between characteristic protons for **2a** (left) and the **diastereomer of 2a** (right). Geometries are from molecular mechanics calculations using the OPLS3 force field.

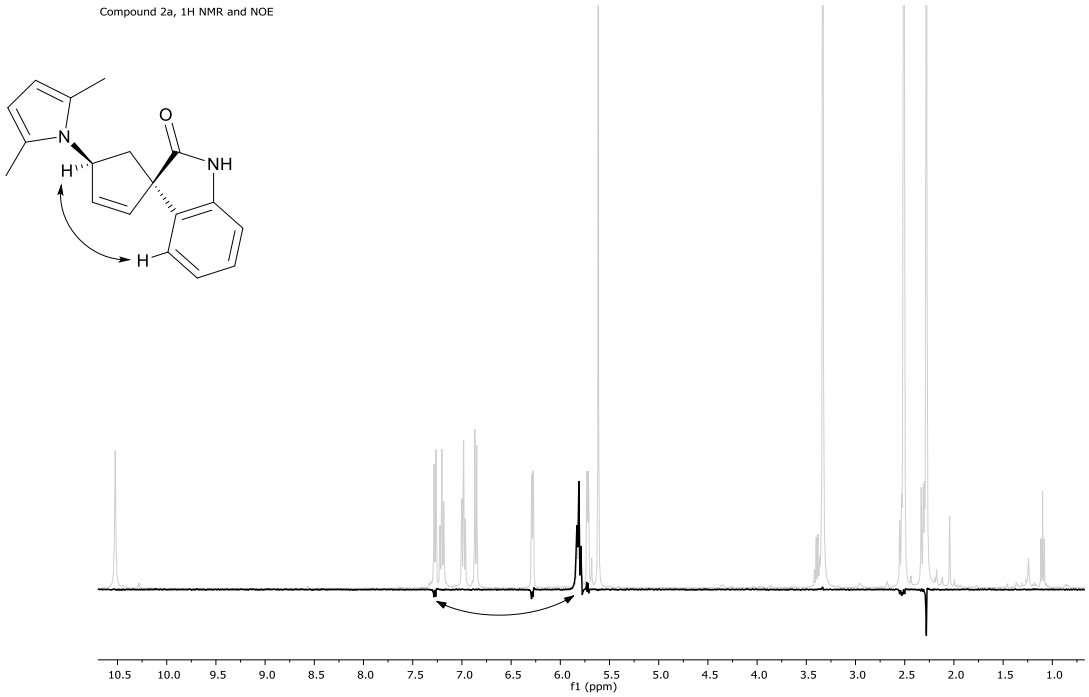


Figure S4. ^{1}H NMR (grey) and NOEDIFF (black) of compound **2a** superimposed. The NOEDIFF experiment was recorded with selective irradiation of the allylic proton. The arrow indicates the NOE observed between the characteristic protons, which would be in agreement with the diastereomer to the left in figure S3.

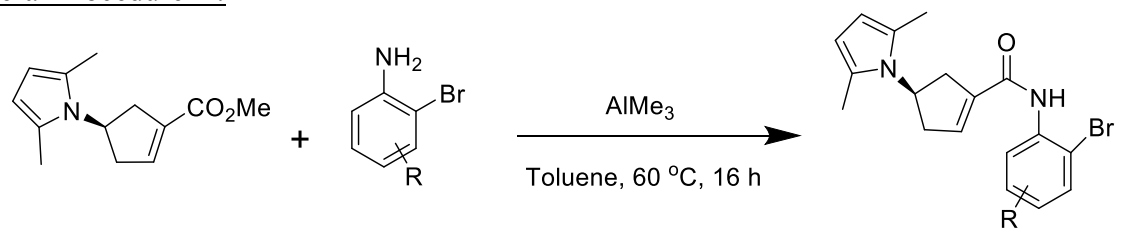
General methods

All the reagents were purchased in their highest purity and were used without further purification. Yields of the reactions were referred as isolated and conversion was determined by ^{1}H NMR analysis. The progress of the reactions were monitored by analytical RPLC-MS in a gradient mode with UV (214 and 254 nm) and MS (ESI) detection. The NMR spectra were recorded on a Bruker instrument at 25 ^{o}C and chemical shifts (d) are reported in ppm and referenced indirectly to TMS via the solvent (or residual solvent) signals. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, or as a combination of them. Molecular mass values were determined on a mass spectrometer equipped with an electrospray ion source and TOF detector. The microwave reactions were performed in the sealed reaction vial in a Biotage Initiator single mode reactor with inbuilt IR sensor for temperature detection. Optical rotations were recorded on a Rudolph Autopol II automated polarimeter instrument.

Synthetic procedures

I. Synthesis of substrates for intramolecular Heck-Mizoroki reaction[5,6]

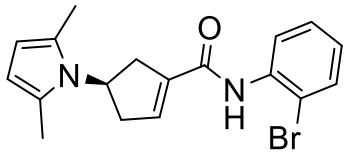
General Procedure A:



Isolated Yield 65-85%

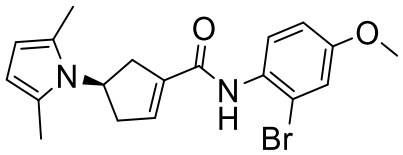
In a flame dried round bottom flask, trimethylaluminium (2 M in toluene, 0.50 mL, 0.98 mmol, 1.2 equiv) was added to 1.5 mL dry toluene under nitrogen atmosphere. The mixture was cooled to 0 °C and 2-bromooaniline derivative (0.90 mmol) in 1.5 mL dry toluene was added dropwise to the above mixture. The mixture was stirred for another 10 minutes at the same temperature. The ice bath was then removed and the mixture was allowed to stir for 20 minutes at room temperature. The mixture was cooled again to 0 °C and the ester (0.8 mmol) in 1.5 mL dry toluene was added dropwise over 2 minutes to the mixture. After stirring for 10 minutes at 0 °C, the mixture was heated to 60 °C and stirring was continued for 16 hours. After cooling to room temperature, HCl (1 M, 4 mL) was added. (Caution: gas evaluation, heat development). The mixture was stirred for 15 minutes and then, 30 mL water and 30 mL EtOAc were added. The mixture was transfered to a separation funnel, the organic phase was separated and the aqueous phase was extracted once more with 30 mL EtOAc. The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed in a rotatory evaporator and the crude mixture was purified by column chromatography.

(*R*)-*N*-(2-bromophenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1a**)



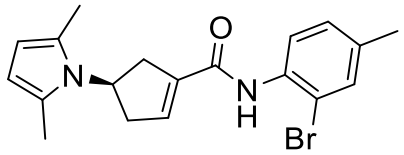
Compound **1a** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (230 mg, 82%). $[\alpha]_D^{23}$ = (+) 4.7 (c = 0.72, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.38 (s, 1H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.41 (td, *J* = 7.7, 1.5 Hz, 1H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H), 6.78 (t, *J* = 2.2 Hz, 1H), 5.63 (s, 2H), 5.11 (tt, *J* = 10.3, 6.3 Hz, 1H), 3.26 – 2.98 (m, 2H), 2.88 – 2.65 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.01, 137.63, 136.95, 136.57, 133.07, 128.59, 128.52, 128.06, 127.38, 120.21, 106.63, 52.17, 40.46, 40.43, 38.91, 13.88. HRMS: calcd. for $C_{18}H_{20}N_2OBr$ $[M+H]^+$ 359.0759; found: 359.0767.

(*R*)-*N*-(2-bromo-4-methoxyphenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1b**)



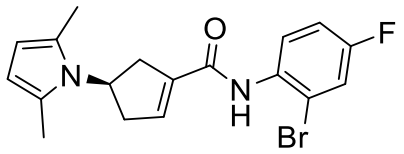
Compound **1b** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (260 mg, 84%). $[\alpha]_D^{23}$ = (+) 0.14 (c = 0.72, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.33 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 2.8 Hz, 1H), 6.98 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.76 – 6.66 (m, 1H), 5.63 (s, 2H), 5.10 (tt, *J* = 10.2, 6.3 Hz, 1H), 3.79 (s, 3H), 3.24 – 3.01 (m, 2H), 2.87-2.64 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.28, 158.33, 137.73, 136.41, 129.97, 129.44, 127.37, 121.70, 117.74, 114.38, 106.62, 56.17, 52.19, 38.97, 13.88. HRMS: calcd. for $C_{19}H_{22}N_2O_2Br$ $[M+H]^+$ 389.0865; found: 389.0872.

(*R*)-*N*-(2-bromo-4-methylphenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1c**)



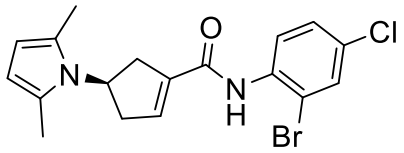
Compound **1c** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (244 mg, 82%). $[\alpha]_D^{23}$ = (+) 1.14 (c = 0.7, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.32 (s, 1H), 7.53 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 6.75 (t, *J* = 2.3 Hz, 1H), 5.63 (s, 2H), 5.10 (tt, *J* = 10.3, 6.3 Hz, 1H), 3.22-3.02 (m, 2H), 2.89-2.63 (m, 2H), 2.31 (s, 3H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.07, 137.89, 137.70, 136.66, 133.94, 133.16, 129.10, 128.46, 127.37, 120.20, 106.62, 52.18, 40.43, 38.93, 20.58, 13.88. HRMS: calcd. for $C_{19}H_{22}N_2OBr$ $[M+H]^+$ 373.0915; found: 373.0917.

(*R*)-*N*-(2-bromo-4-fluorophenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1d**)



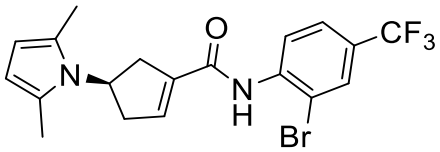
Compound **1d** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (234 mg, 78%). $[\alpha]_D^{23}$ = (-) 0.43 (c = 0.7, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.45 (s, 1H), 7.68 (dd, *J* = 8.4, 2.9 Hz, 1H), 7.54 (dd, *J* = 8.9, 5.8 Hz, 1H), 7.30 (ddd, *J* = 8.9, 8.2, 2.9 Hz, 1H), 6.77 (q, *J* = 2.2 Hz, 1H), 5.63 (s, 2H), 5.10 (tt, *J* = 10.3, 6.3 Hz, 1H), 3.28 – 3.00 (m, 2H), 2.89 – 2.59 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.21, 161.30, 158.84, 137.51, 136.94, 133.37, 133.34, 130.34, 130.26, 127.37, 121.40, 121.30, 120.13, 119.88, 115.61, 115.39, 106.63, 52.15, 40.64, 40.44, 39.64, 38.94, 13.88. ^{19}F NMR (376 MHz, DMSO) δ -114.26. HRMS: calcd. for $C_{18}H_{19}N_2OBrF$ $[M+H]^+$ 377.0665; found: 377.0671.

(*R*)-*N*-(2-bromo-4-chlorophenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1carboxamide (**1e**)



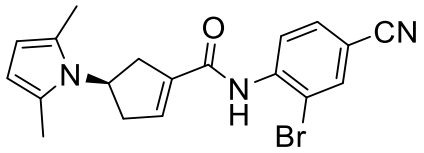
Compound **1e** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (234 mg, 78%). $[\alpha]_D^{23}$ = (+) 3.75 (c = 0.72, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.44 (s, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.79 (p, *J* = 2.2 Hz, 1H), 5.63 (s, 2H), 5.11 (tt, *J* = 10.0, 6.2 Hz, 1H), 3.24 – 2.93 (m, 2H), 2.91 – 2.59 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.05, 137.43, 137.30, 135.84, 132.31, 131.12, 129.58, 128.57, 127.38, 120.92, 106.64, 52.14, 40.64, 40.47, 40.43, 39.64, 38.88, 13.88. HRMS: calcd. for $C_{18}H_{19}N_2OClBr$ $[M+H]^+$ 393.0369; found: 393.0366.

(*R*)-*N*-(2-bromo-4-(trifluoromethyl)phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1f**)



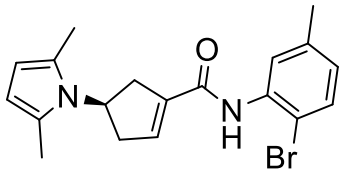
Compound **1f** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (262 mg, 77%). $[\alpha]_D^{23}$ = (-) 18.31 (c = 0.65, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.50 (s, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.84 – 7.72 (m, 1H), 6.84 (t, *J* = 2.3 Hz, 1H), 5.63 (s, 2H), 5.12 (tt, *J* = 10.3, 6.4 Hz, 1H), 3.26 – 3.06 (m, 2H), 2.92-2.69 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 162.99, 140.49, 138.02, 137.29, 130.08, 130.04, 127.81, 127.68, 127.39, 125.63, 125.59, 125.06, 122.35, 119.38, 106.66, 52.13, 40.51, 38.82, 13.88. ^{19}F NMR (376 MHz, DMSO) δ -60.74. HRMS: calcd. for $C_{19}H_{17}N_2OBrF_3$ $[M-H]^-$ 425.0476; found: 425.0486.

(*R*)-N-(2-bromo-4-cyanophenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1g**)



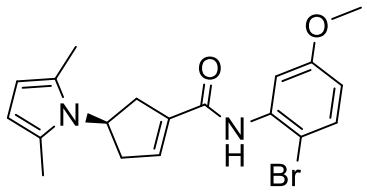
Compound **1g** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (245 mg, 80%). $[\alpha]_D^{23}$ = (+) 12.54 (c = 0.67, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.45 (s, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 7.93 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.85 (t, *J* = 2.2 Hz, 1H), 5.63 (s, 2H), 5.12 (tt, *J* = 10.2, 6.3 Hz, 1H), 3.26 – 3.02 (m, 2H), 2.95-2.62 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 162.90, 141.13, 138.40, 137.21, 136.79, 132.65, 127.71, 127.40, 126.98, 118.63, 117.90, 109.43, 106.66, 52.12, 40.65, 40.53, 40.44, 39.65, 38.76, 14.28, 13.89. HRMS: calcd. for $C_{19}H_{19}N_3OBr$ $[M+H]^+$ 384.0711; found: 384.0700.

(*R*)-*N*-(2-bromo-5-methylphenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1h**)



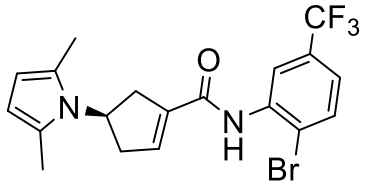
Compound **1h** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (238 mg, 80%). $[\alpha]_D^{23}$ = (-) 0.28 (c = 0.63, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.32 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.40 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.02 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H), 6.76 (q, *J* = 2.3 Hz, 1H), 5.63 (s, 2H), 5.11 (tt, *J* = 10.2, 6.3 Hz, 1H), 3.22 – 3.01 (m, 2H), 2.86 – 2.62 (m, 2H), 2.29 (d, *J* = 0.9 Hz, 3H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.00, 138.16, 137.67, 136.79, 136.24, 132.63, 129.08, 128.77, 127.37, 116.82, 106.63, 52.15, 40.64, 40.47, 38.94, 20.88, 13.87. HRMS: calcd. for $C_{19}H_{22}N_2OBr$ $[M+H]^+$ 373.0915; found: 373.0917.

(*R*)-*N*-(2-bromo-5-methoxyphenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1i**)



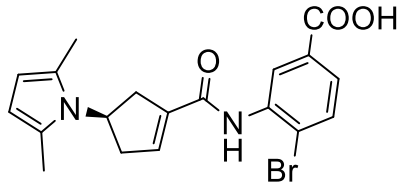
Compound **1i** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (227 mg, 73%). $[\alpha]_D^{23}$ = (-) 2.59 (c = 0.81, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.26 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 3.0 Hz, 1H), 6.83 – 6.76 (m, 2H), 5.63 (s, 2H), 5.11 (tt, *J* = 10.2, 6.4 Hz, 1H), 3.76 (s, 3H), 3.25 – 3.02 (m, 2H), 2.89 – 2.65 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 162.92, 159.24, 137.62, 137.26, 137.10, 133.32, 133.26, 127.71, 127.39, 113.78, 113.44, 109.92, 106.63, 106.37, 56.00, 52.19, 40.64, 40.44, 39.42, 38.84, 14.30, 13.88. HRMS: calcd. for $C_{19}H_{22}N_2O_2Br$ $[M+H]^+$ 389.0865; found: 389.0867.

(*R*)-*N*-(2-bromo-5-(trifluoromethyl)phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamide (**1j**)



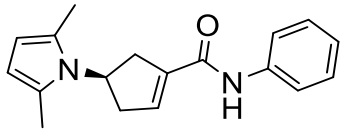
Compound **1j** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 5:1) a white solid was obtained (262 mg, 77%). $[\alpha]_D^{23}$ = (-) 21.39 (c = 0.65, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.58 (s, 1H), 8.00 – 7.94 (m, 2H), 7.55 (m, 1H), 6.88 – 6.73 (m, 1H), 5.63 (s, 2H), 5.12 (tt, *J* = 10.2, 6.3 Hz, 1H), 3.25 – 3.07 (m, 2H), 2.91 – 2.66 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.16, 137.77, 137.61, 137.27, 134.44, 129.27, 128.95, 127.61, 127.39, 125.46, 124.48, 124.34, 124.18, 122.75, 106.65, 52.12, 40.51, 38.86, 13.88. ^{19}F NMR (376 MHz, DMSO) δ -61.27. HRMS: calcd. for $C_{19}H_{19}N_2OBrF_3$ $[M+H]^+$ 427.0633 ; found: 427.0611.

(*R*)-4-bromo-3-(4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-1-ene-1-carboxamido)benzoic acid (**1k**)



Compound **1k** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 4:1) a yellow solid was obtained (180 mg, 56%). $[\alpha]_D^{23}$ = (-) 7.89 (c = 0.7, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.54 (s, 1H), 8.10 (d, *J* = 2.1 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.81 (q, *J* = 2.2 Hz, 1H), 5.63 (s, 2H), 5.12 (tt, *J* = 10.2, 6.3 Hz, 1H), 3.24 – 3.04 (m, 2H), 2.90 – 2.67 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.88, 163.11, 137.43, 137.37, 136.89, 133.51, 128.78, 128.31, 127.39, 125.03, 106.64, 52.14, 40.63, 40.50, 38.90, 13.88. HRMS: calcd. for $C_{19}H_{20}N_2O_3Br$ $[M+H]^+$ 403.0657 ; found: 403.0650.

(*R*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-phenylcyclopent-1-ene-1-carboxamide (**1l**)



Compound **1l** was synthesized according to general procedure A. After column chromatography (isohexane/EtOAc 4:1) a white solid was obtained (159 mg, 71%). $[\alpha]_D^{23}$ = (+) 10.04 (c = 0.75, THF). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.68 (s, 1H), 7.77 – 7.63 (m, 2H), 7.42 – 7.24 (m, 2H), 7.11 – 6.98 (m, 1H), 6.74 (q, *J* = 2.2 Hz, 1H), 5.63 (s, 2H), 5.08 (tt, *J* = 10.2, 6.3 Hz, 1H), 3.22 – 3.02 (m, 2H), 2.92 – 2.63 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 163.25, 139.41, 138.30, 135.99, 129.02, 127.36, 123.89, 120.50, 106.61, 52.04, 40.47, 39.14, 13.87. HRMS: calcd. for $C_{18}H_{21}N_2O$ $[M+H]^+$ 281.1654; found: 281.1646.

II. Intramolecular Heck-Mizoroki reaction of aryl bromides

General procedure B1

In a flame dried reaction vial, $Pd(OAc)_2$ (0.01 mmol), DPPF (0.02 mmol) and NEt_3 (0.36 mmol) were taken together. The vial was evacuated and flashed with nitrogen three times. Dry DMF (500 μL) was introduced in the reaction vial and the solution was allowed to stir at room temperature for 10 min. Subsequently, the substrate (0.20 mmol in 500 μL) was introduced in the reaction mixture and the heating was started. The progress of the reaction was monitored using LC-MS.

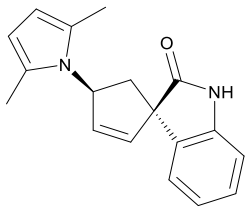
After completion of the reaction, the reaction mixture was quenched with water (5 mL) and the product was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with a saturated solution of brine and dried over anhydrous $MgSO_4$. The volatile component was partially removed under the reduced pressure and then passed through a plug of silica (using 1:3 ethyl acetate: hexanes as an eluent) to remove the palladium source and the ligand. After complete removal of the solvent the crude product was analyzed as such on ^1H NMR to determine the conversion and purity of the product.

General procedure B2

In a reaction vial, $Pd(OAc)_2$ (0.02 mmol), triphenylphosphine (0.04 mmol), NEt_3 (0.36 mmol) and the substrate (0.20 mmol) were taken together. A mixture of DMF and water (1000 μL) was introduced in the reaction vial and the heating was started. The progress of the reaction was monitored using LC-MS.

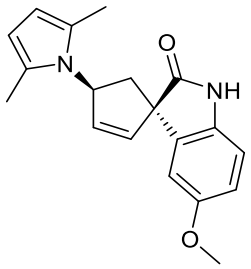
After completion of the reaction, the reaction mixture was quenched with water (5 mL) and the product was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with a saturated solution of brine and dried over anhydrous $MgSO_4$. The volatile component was partially removed under the reduced pressure and then passed through a plug of silica (using 1:3 ethyl acetate: hexanes as an eluent) to remove the palladium source and the ligand. After complete removal of the solvent the crude product was analyzed as such on ^1H NMR to determine the conversion and purity of the product.

(1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)spiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2a**)



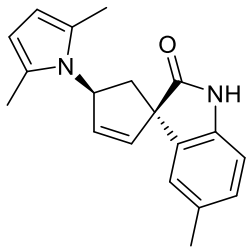
Compound **2a** was synthesized according to general procedure B1. White solid (42 mg, 76%). $[\alpha]_D^{23}$ = (-) 350.79 (c = 0.6, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.27 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.27 (dd, *J* = 5.4, 1.9 Hz, 1H), 5.83-5.77 (m, 1H), 5.71 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.60 (s, 2H), 2.53 (m, 1H), 2.31 (m, 1H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.07, 141.80, 136.28, 133.73, 133.18, 128.61, 127.91, 123.93, 122.32, 109.95, 106.56, 61.28, 60.32, 42.54, 14.47. HRMS: calcd. for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1497 ; found: 279.1496.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-5'-methoxyspiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2b**)



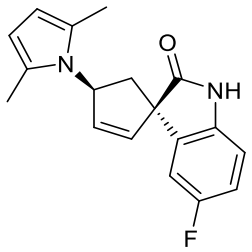
Compound **2b** was synthesized according to general procedure B1. White solid (50 mg, 81%). $[\alpha]_D^{23}$ = (-) 331.19 (c = 0.56, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 6.90 (dd, *J* = 2.0, 0.9 Hz, 1H), 6.76 (t, *J* = 1.5 Hz, 2H), 6.27 (dd, *J* = 5.4, 1.9 Hz, 1H), 5.86-5.81 (m, 1H), 5.69 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.60 (s, 2H), 3.71 (s, 3H), 2.53 (m, 1H), 2.29-2.24 (m, 1H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 179.95, 155.67, 136.42, 135.10, 135.07, 133.09, 127.95, 112.94, 111.35, 110.20, 106.52, 61.23, 60.86, 56.07, 42.49, 14.50. HRMS: calcd. for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1603 ; found: 309.1603.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-5'-methylspiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2c**)



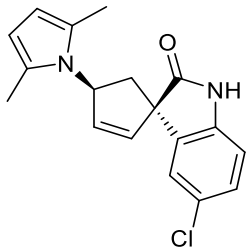
Compound **2c** was synthesized according to general procedure B1. White solid (46 mg, 79%). $[\alpha]_D^{23}$ = (-) 351.57 (c = 0.62, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.09 (d, *J* = 1.7 Hz, 1H), 7.02-6.98 (m, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.26 (dd, *J* = 5.4, 1.9 Hz, 1H), 5.82-5.77 (m, 1H), 5.69 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.60 (s, 2H), 2.54 (m, 1H), 2.30-2.23 (m, 1H), 2.27 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 180.07, 139.31, 136.10, 133.79, 133.36, 131.27, 128.80, 127.93, 124.51, 109.66, 106.53, 61.32, 60.44, 42.43, 21.16, 14.53. HRMS: calcd. for $C_{19}H_{21}N_2O$ $[M+H]^+$ 293.1654 ; found: 293.1663.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-5'-fluorospiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2d**)



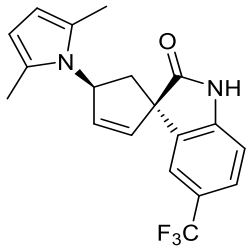
Compound **2d** was synthesized according to general procedure B1. White solid (47 mg, 80%). $[\alpha]_D^{23}$ = (-) 280.79 (c = 0.72, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.29 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.06-7.00 (m, 1H), 6.83 (dd, *J* = 8.5, 4.4 Hz, 1H), 6.29 (dd, *J* = 5.4, 1.9 Hz, 1H), 5.91-5.87 (m, 1H), 5.71 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.61 (s, 2H), 2.55 (dd, *J* = 12.2, 7.2 Hz, 1H), 2.30-2.25 (m, 1H), 2.28 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.05, 159.96, 157.61, 138.00, 137.98, 136.96, 135.54, 135.46, 132.51, 127.97, 114.92, 114.68, 112.11, 111.86, 110.63, 110.55, 106.55, 42.25, 14.50. ^{19}F NMR (376 MHz, DMSO) δ -121.74. HRMS: calcd. for $C_{18}H_{18}N_2OF$ $[M+H]^+$ 297.1403 ; found: 297.1415.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-5'-chlorospiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2e**)



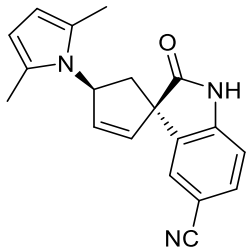
Compound **2e** was synthesized according to general procedure B1. White solid (51 mg, 82%). $[\alpha]_D^{23}$ = (-) 323.98 (c = 0.75, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.3, 2.2 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.28 (dd, J = 5.4, 1.9 Hz, 1H), 5.91-5.87 (m, 1H), 5.69 (dd, J = 5.4, 2.6 Hz, 1H), 5.60 (s, 2H), 2.56 (dd, J = 13.1, 8.2 Hz, 1H), 2.28-2.23 (m, 1H), 2.27 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 179.85, 140.78, 137.06, 135.82, 132.39, 128.45, 128.00, 126.40, 124.26, 111.30, 106.53, 61.20, 60.68, 42.12, 14.54. HRMS: calcd. for $C_{18}H_{18}N_2OCl$ $[M+H]^+$ 313.1108 ; found: 313.1113.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-5'-(trifluoromethyl)spiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2f**)



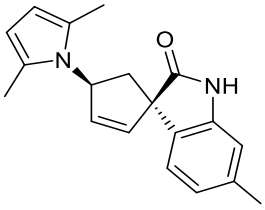
Compound **2f** was synthesized according to general procedure B1. White solid (53 mg, 77%). $[\alpha]_D^{23}$ = (-) 263.97 (c = 0.59, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.61-7.57 (m, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.33 (dd, J = 5.4, 1.9 Hz, 1H), 5.99-5.92 (m, 1H), 5.72 (dd, J = 5.4, 2.6 Hz, 1H), 5.61 (s, 2H), 2.61 (dd, J = 13.3, 8.2 Hz, 1H), 2.31-2.27 (m, 1H), 2.29 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.25, 145.64, 137.33, 134.66, 132.21, 128.01, 126.53, 126.44, 126.40, 123.83, 123.09, 122.77, 121.08, 121.04, 110.11, 106.54, 61.28, 60.45, 42.06, 14.55. ^{19}F NMR (376 MHz, DMSO) δ -59.29. HRMS: calcd. for $C_{19}H_{18}N_2OF_3$ $[M+H]^+$ 347.1371 ; found: 347.1385.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-5'-carbonitrile (**2g**)



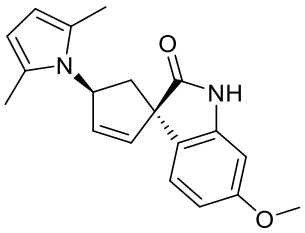
Compound **2g** was synthesized according to general procedure B1. White solid (49 mg, 80%). $[\alpha]_D^{23}$ = (-) 341.79 (c = 0.6, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.88 (d, *J* = 1.7 Hz, 1H), 7.69 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.32 (dd, *J* = 5.5, 1.9 Hz, 1H), 5.97-5.93 (m, 1H), 5.71 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.61 (s, 2H), 2.58 (dd, *J* = 13.2, 8.1 Hz, 1H), 2.30-2.26 (m, 1H), 2.28 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.09, 146.32, 137.47, 134.89, 133.98, 131.95, 128.00, 127.80, 119.96, 110.70, 106.58, 104.30, 61.14, 60.13, 42.10, 14.53. HRMS: calcd. for $C_{19}H_{18}N_3O$ $[M+H]^+$ 304.1450 ; found: 304.1452.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-6'-methylspiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2h**)



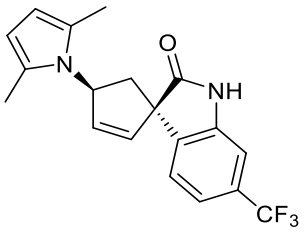
Compound **2h** was synthesized according to general procedure B1. White solid (45 mg, 77%). $[\alpha]_D^{23}$ = (-) 305.44 (c = 0.6, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.66 (s, 1H), 6.25 (dd, *J* = 5.5, 1.9 Hz, 1H), 5.80-5.76 (m, 1H), 5.68 (dd, *J* = 5.5, 2.6 Hz, 1H), 5.60 (s, 2H), 2.48-2.44 (m, 1H), 2.30-2.25 (m, 1H), 2.27 (s, 3H), 2.26 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.34, 141.87, 138.13, 136.03, 133.31, 130.76, 127.89, 123.64, 122.78, 110.62, 106.54, 61.25, 60.09, 42.56, 21.72, 14.47. $C_{19}H_{21}N_2O$ $[M+H]^+$ 293.1654 ; found: 293.1660.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-6'-methoxyspiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2i**)



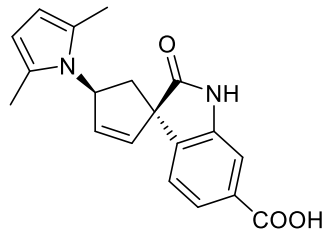
Compound **2i** was synthesized according to general procedure B1. White solid (49 mg, 80%). $[\alpha]_D^{23}$ = (-) 248.89 (c = 0.6, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.51 (dd, J = 8.2, 2.4 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.23 (dd, J = 5.4, 1.9 Hz, 1H), 5.80-5.74 (m, 1H), 5.67 (dd, J = 5.4, 2.6 Hz, 1H), 5.60 (s, 2H), 3.72 (s, 3H), 2.48-2.43 (m, 1H), 2.29-2.24 (m, 1H), 2.26 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.63, 160.10, 142.96, 135.86, 133.39, 127.89, 125.51, 124.59, 107.13, 106.54, 96.95, 61.19, 59.81, 55.73, 42.68, 14.47. HRMS: calcd. for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1606 ; found: 309.1603.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-6'-(trifluoromethyl)spiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**2j**)



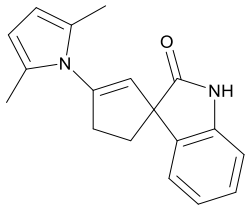
Compound **2j** was synthesized according to general procedure B1 (54 mg, 78%). White solid. $[\alpha]_D^{23}$ = (-) 265.99 (c = 0.61, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.30-7.27 (m, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.28 (dd, J = 5.4, 1.9 Hz, 1H), 5.81-5.75 (m, 1H), 5.68 (dd, J = 5.4, 2.6 Hz, 1H), 5.54 (s, 2H), 2.52 (dd, J = 13.2, 8.1 Hz, 1H), 2.25-2.21 (m, 1H), 2.20 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 179.79, 142.77, 138.33, 137.30, 132.25, 129.39, 129.08, 127.93, 125.95, 124.79, 123.24, 119.26, 106.62, 106.02, 99.99, 61.22, 60.35, 42.29, 14.46. ^{19}F NMR (376 MHz, DMSO) δ -60.92. HRMS: calcd. for $C_{19}H_{18}N_2OF_3$ $[M+H]^+$ 347.1371 ; found: 347.1377.

(1*R*,4*S*)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-6'-carboxylic acid (**2k**)



Compound **2k** was synthesized according to general procedure B1 (45 mg, 70%). White solid. $[\alpha]_D^{23}$ = (-) 355.32 (c = 0.51, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 10.65 (s, 1H), 7.54 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.40 (m, 2H), 6.25 (dd, *J* = 5.5, 1.9 Hz, 1H), 5.79-5.74 (m, 1H), 5.67 (dd, *J* = 5.4, 2.6 Hz, 1H), 5.54 (s, 2H), 2.50 (dd, *J* = 13.1, 8.1 Hz, 1H), 2.26-2.22 (m, 1H), 2.20 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 179.83, 167.49, 142.17, 138.72, 136.99, 132.53, 131.99, 131.90, 131.17, 129.29, 129.17, 127.93, 124.00, 123.91, 110.17, 106.61, 61.27, 60.50, 42.29, 14.48. HRMS: calcd. for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1396 ; found: 323.1410.

3-(2,5-dimethyl-1H-pyrrol-1-yl)spiro[cyclopentane-1,3'-indolin]-2-en-2'-one (**4a**)



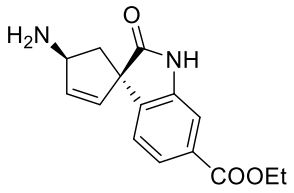
Compound **4a** was synthesized according to general procedure B1 using JohnPhos as a ligand and after HPLC purification was obtained as off white solid (22 mg, 40%). $[\alpha]_D^{23}$ = (-) 42.11 (c = 0.62, THF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 7.22-7.20 (m, 1H), 7.16-7.11 (m, 1H), 6.96-6.91 (m, 1H), 6.81-6.78 (m, 1H), 5.64 (s, 2H), 5.42 (t, *J* = 1.8 Hz, 1H), 2.90-2.12 (m, 4H), 2.10 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 180.50, 144.03, 141.95, 134.22, 128.69, 128.50, 127.61, 123.91, 122.39, 109.91, 106.59, 59.19, 34.57, 34.48, 13.20. HRMS: calcd. for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1497 ; found: 279.1495.

III. Procedure for the removal of the protection group[7]

General procedure C

The product (1 mmol) was taken in a dry microwave vial and EtOH (3 mL) was added into the vial. To this suspension, conc. HCl (0.3 mL) was added and the reaction mixture was heated in the microwave irradiator for 60 min at 120 ^{o}C. After completion of the reaction (checked on LC-MS), the reaction mixture was cooled down to 0 ^{o}C and saturated $NaHCO_3$ solution (10 mL) was added to it. The product was then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography.

Ethyl (1*R*,4*S*)-4-amino-2'-oxospiro[cyclopentane-1,3'-indolin]-2-ene-6'-carboxylate (**6**)

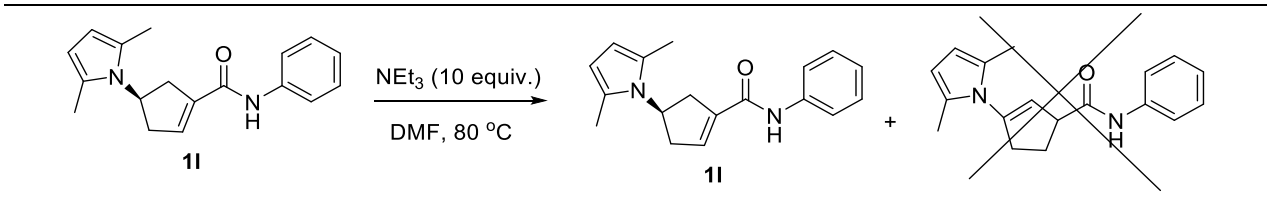


Compound **6** was synthesized according to general procedure C. After column chromatography (MeOH/EtOAc/NEt_3 25:75:1) a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.13 (s, 2H), 7.64 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.21 (dd, *J* = 5.4, 2.1 Hz, 1H), 5.95 (dd, *J* = 5.5, 1.4 Hz, 1H), 4.65 (d, *J* = 6.5 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.53-2.48 (m, 1H), 2.26 (dd, *J* = 13.8, 4.6 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 179.69, 165.80, 142.71, 138.43, 137.51, 133.56, 130.70, 124.21, 123.99, 110.26, 61.38, 61.11, 56.40, 40.64, 14.62. HRMS: calcd. for $C_{15}H_{17}N_2O_3$ $[M+H]^+$ 273.1239 ; found: 273.1247.

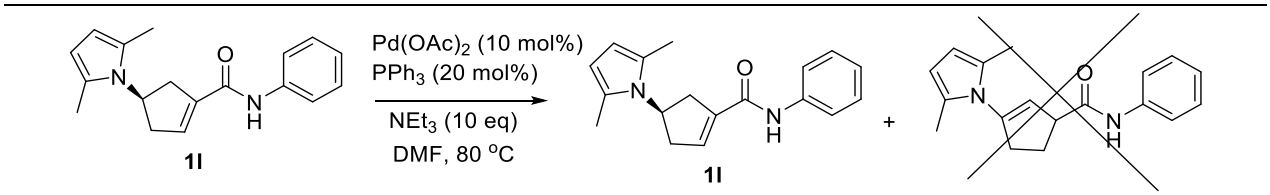
(Note: too dark sample to determine optical rotation)

IV. Controlled experiments to check the double-bond migration for intramolecular Heck-Mizoroki reaction

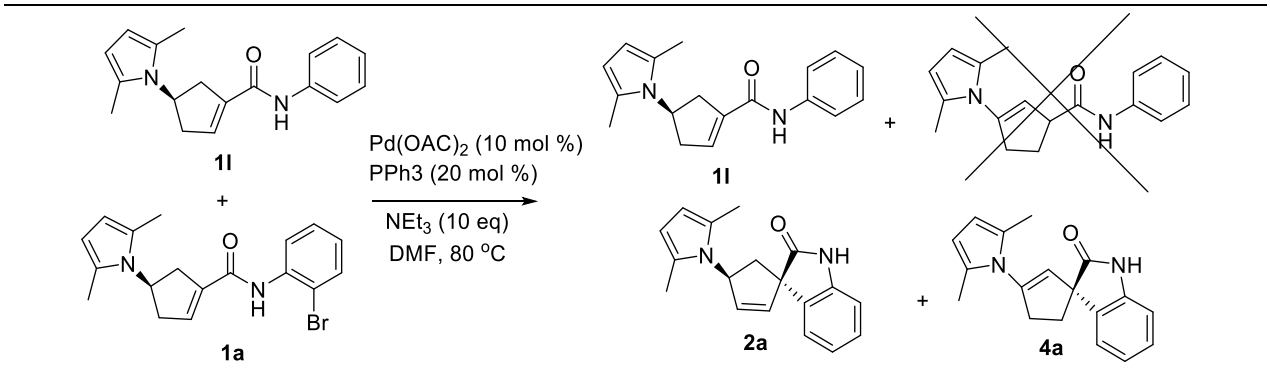
We performed a number of control experiments to pinpoint a plausible mechanism for formation of isomerized product **4**. To start with, no isomerization of the non-halogen substituted olefin **1l** could be detected using the reaction conditions reported in entry 1 (Table 1). This indicates that isomerization is effected by species formed in the Heck-Mizoroki reaction. Further, no isomerization of **1l** was detected after adding this substrate to a reaction with **1a**. This suggests that isomerization takes place intramolecularely after oxidative addition of the aryl bromide to Pd(o). To exclude a base-mediated deprotonation-reprotonation pathway, D_2O was added to the reaction mixture (see Table 2). However, this did completely suppress the isomerization (*vide infra*) and could therefore indicate a depletion of the species responsible for isomerization.



Reaction condition: substrate **1l** (0.2 mmol), Net_3 (2 mmol), DMF (1 mL).

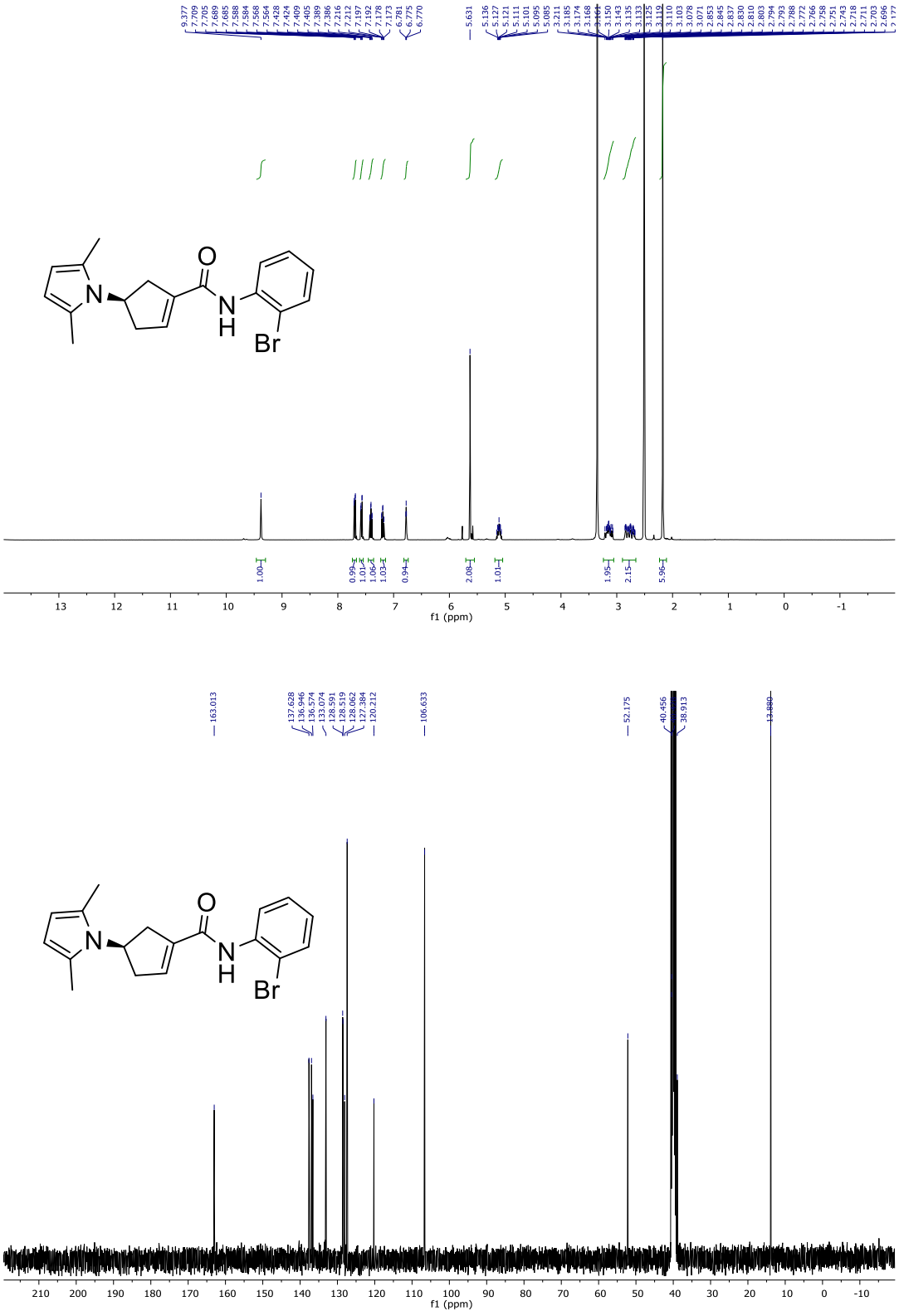


Reaction condition: substrate **1l** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.04 mmol), Net_3 (2 mmol), DMF (1 mL).

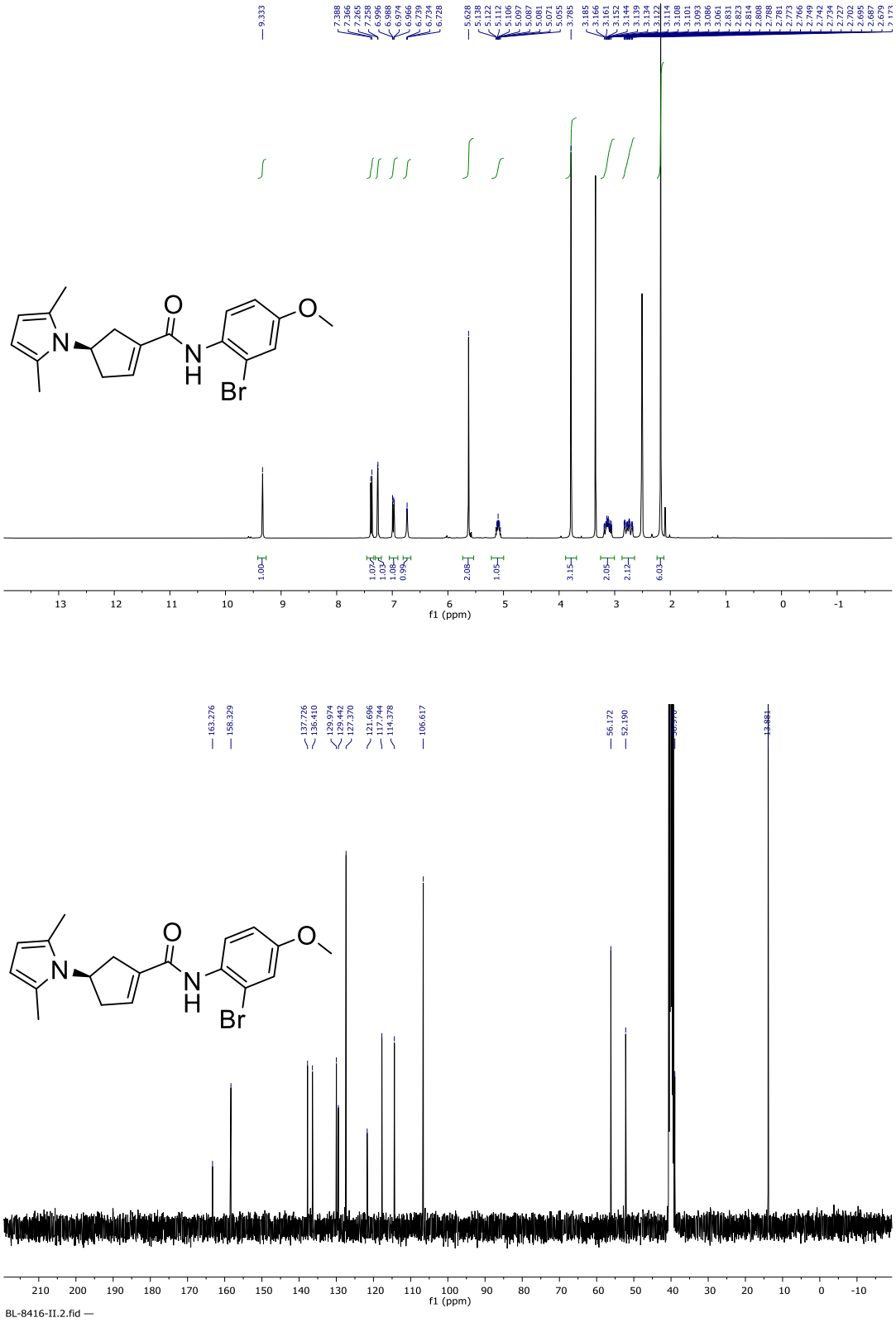


Reaction condition: substrate **1l** (0.2 mmol), substrate **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.04 mmol), Net_3 (2 mmol), DMF (1 mL).

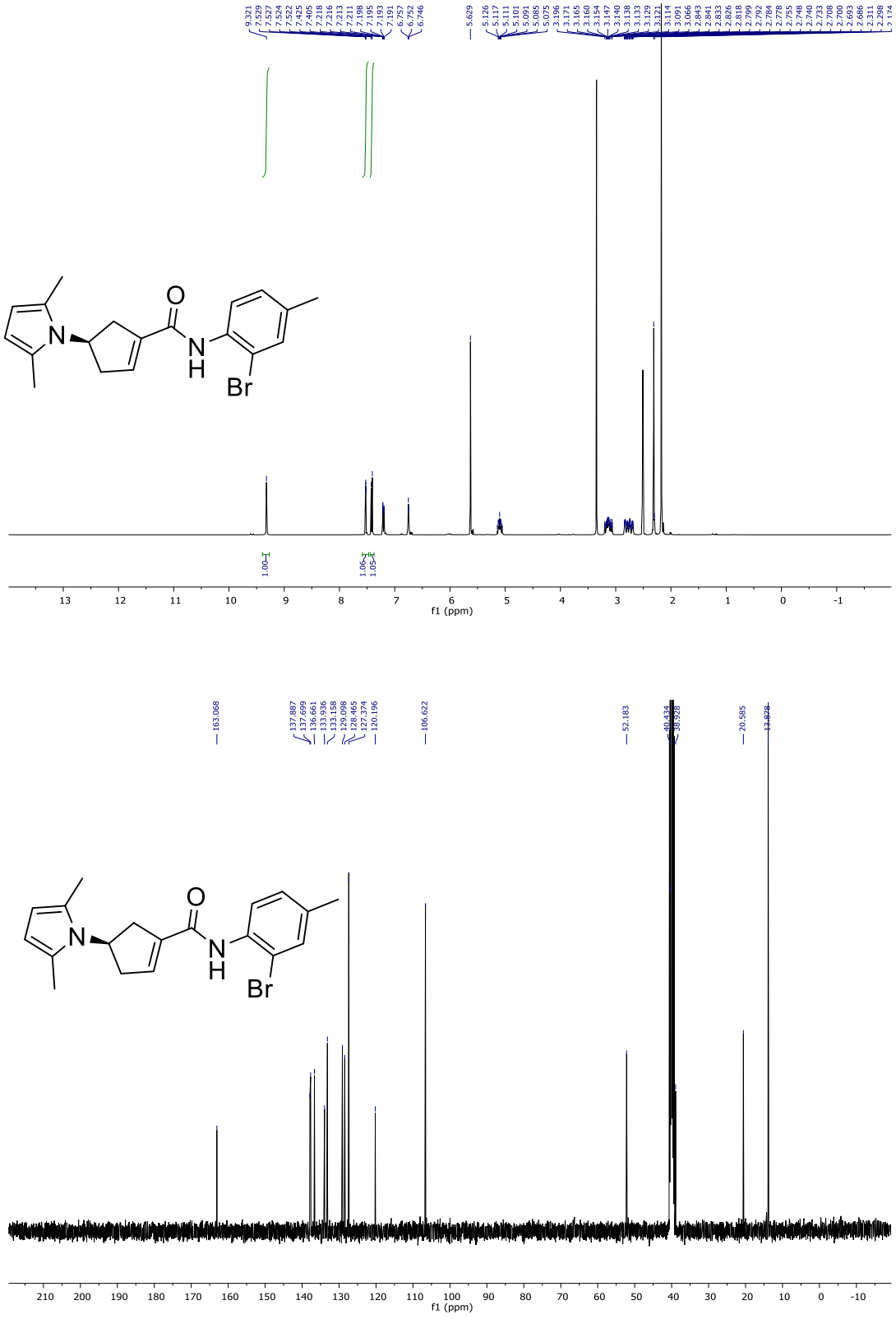
NMR Spectra



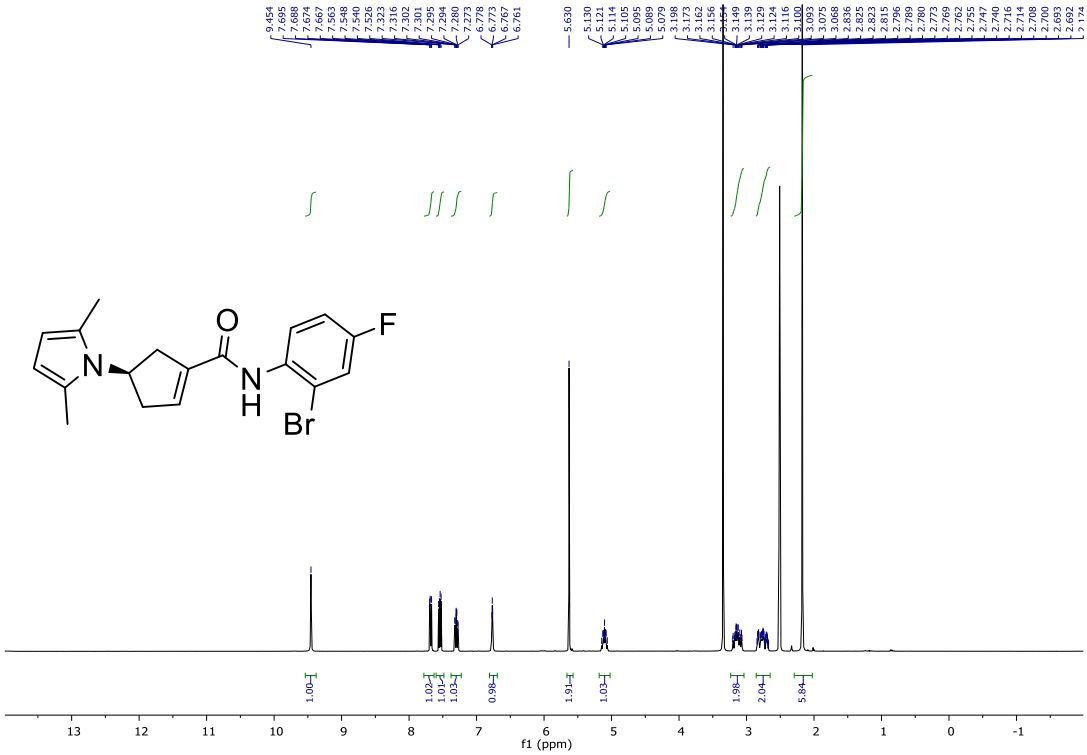
^{1}H and ^{13}C NMR spectra of compound **1a**

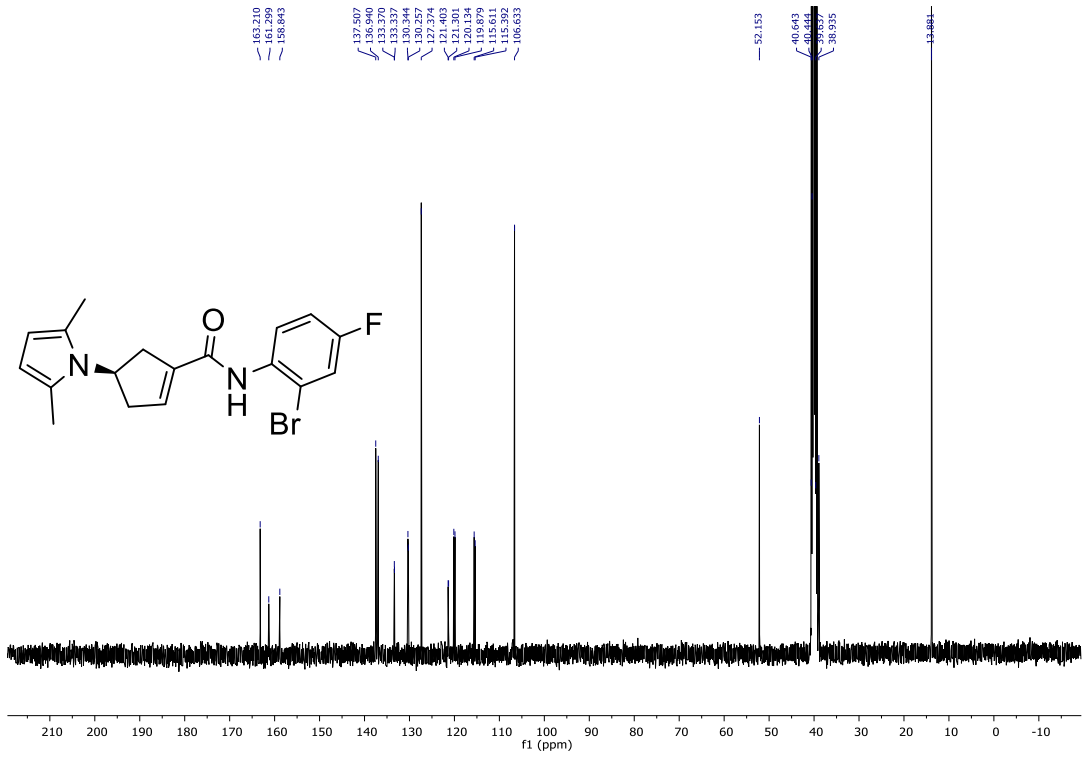


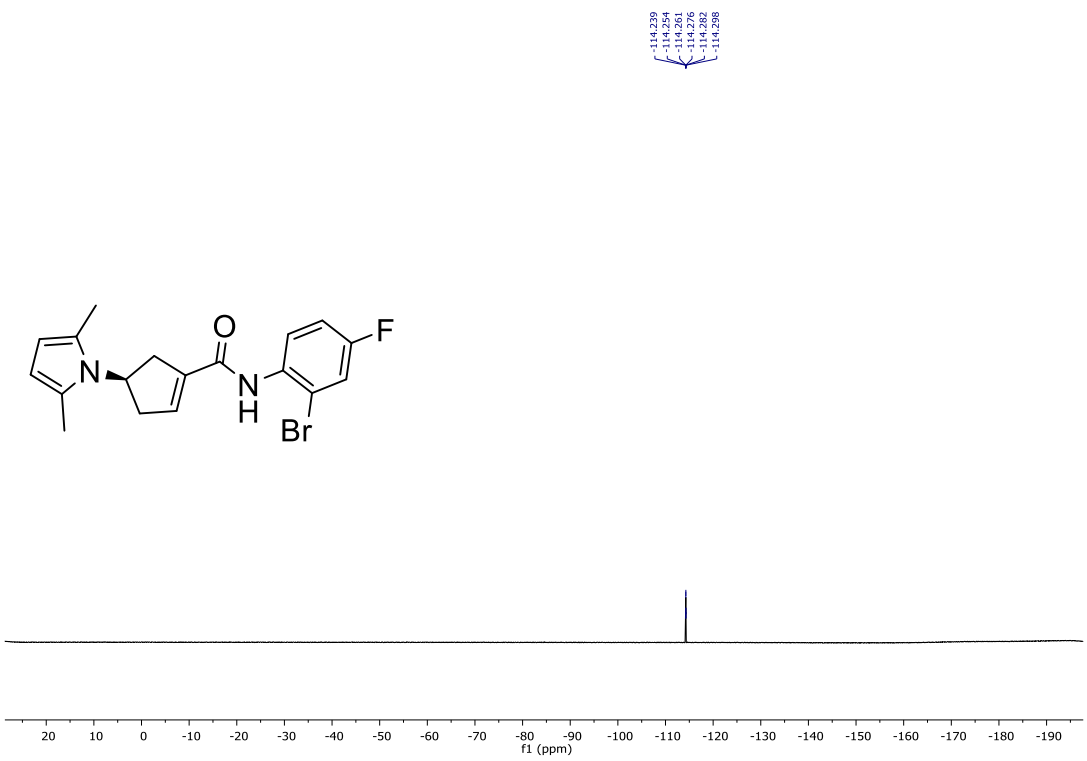
^{1}H and ^{13}C NMR spectra of compound **1b**



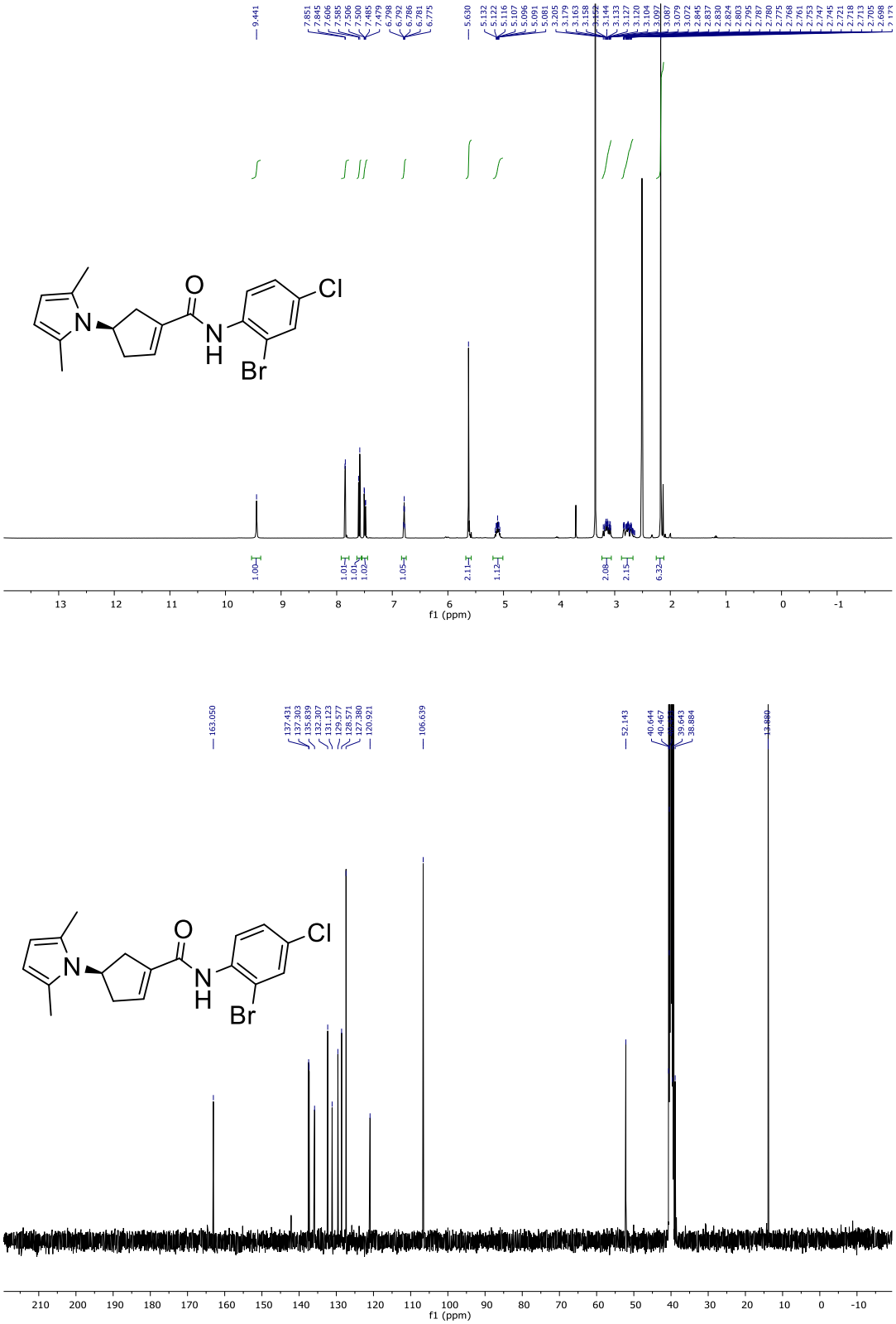
^{1}H and ^{13}C NMR spectra of compound **1c**


9.454
7.695
7.688
7.674
7.667
7.563
7.548
7.540
7.526
7.323
7.316
7.302
7.301
7.295
7.294
7.280
7.273
6.778
6.773
6.767
6.761
5.630
5.130
5.121
5.114
5.105
5.095
5.089
5.079
3.198
3.173
3.162
3.156
3.149
3.139
3.129
3.124
3.116
3.100
3.093
3.075
3.068
2.836
2.825
2.823
2.815
2.796
2.789
2.780
2.773
2.769
2.762
2.755
2.747
2.740
2.716
2.714
2.708
2.700
2.693
2.692
2.174
O
N
H
N
F
Br
1.00
1.02
1.02
1.03
0.98
1.91
1.03
1.98
2.04
5.84
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

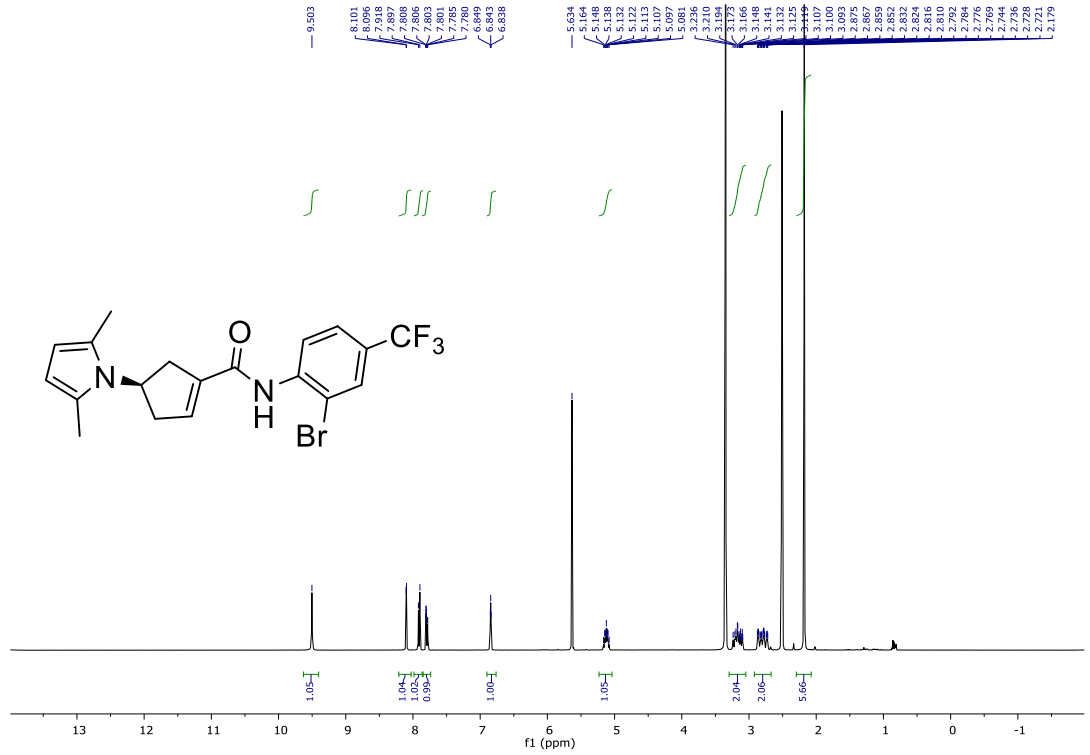

163.210
161.299
158.843
137.507
136.940
133.370
133.337
130.344
130.257
127.374
121.403
121.301
120.134
119.879
115.611
115.392
106.633
52.153
40.643
40.434
40.227
38.935
13.881
O
N
H
N
F
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

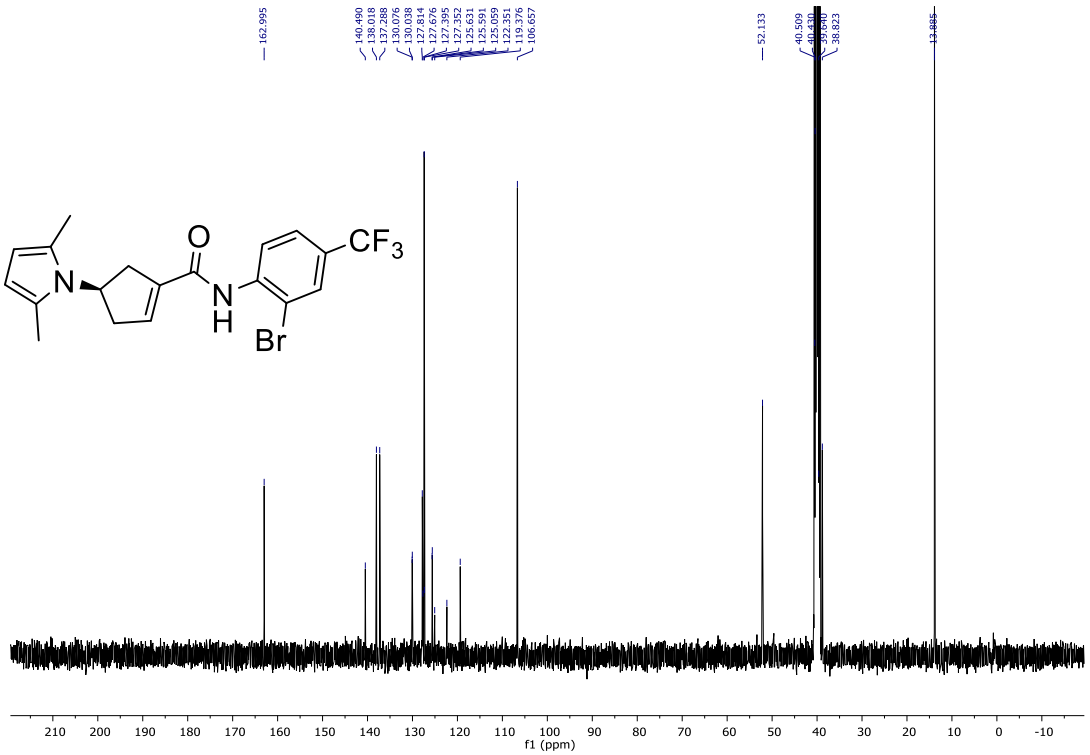


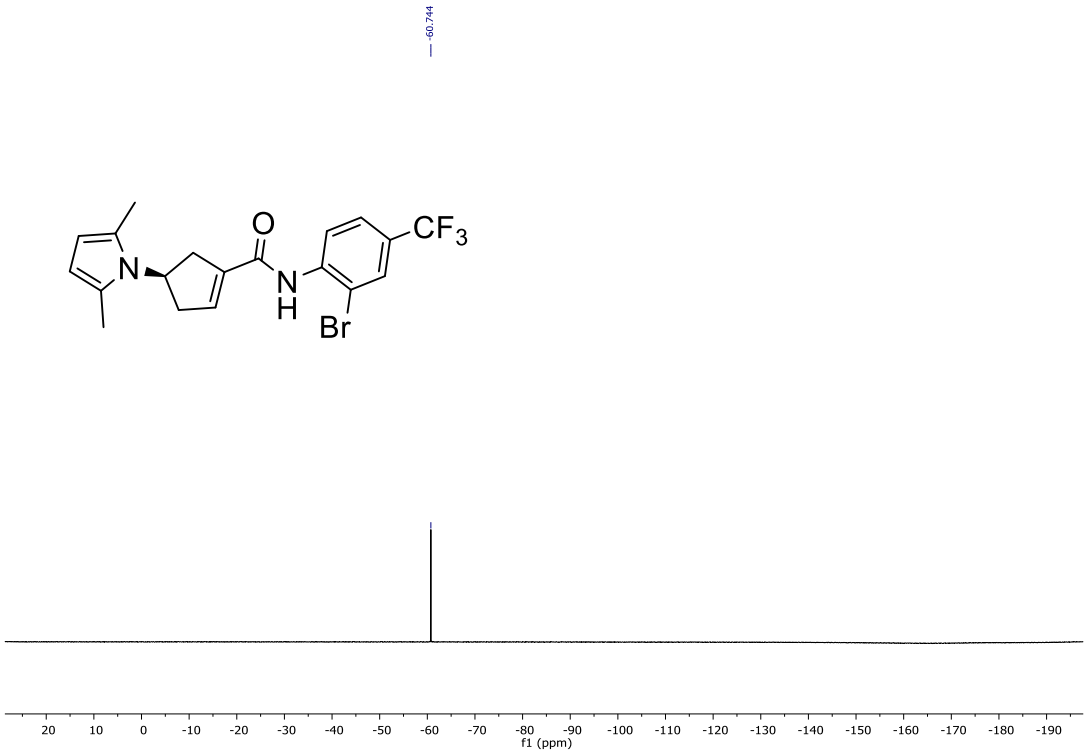
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **1d**



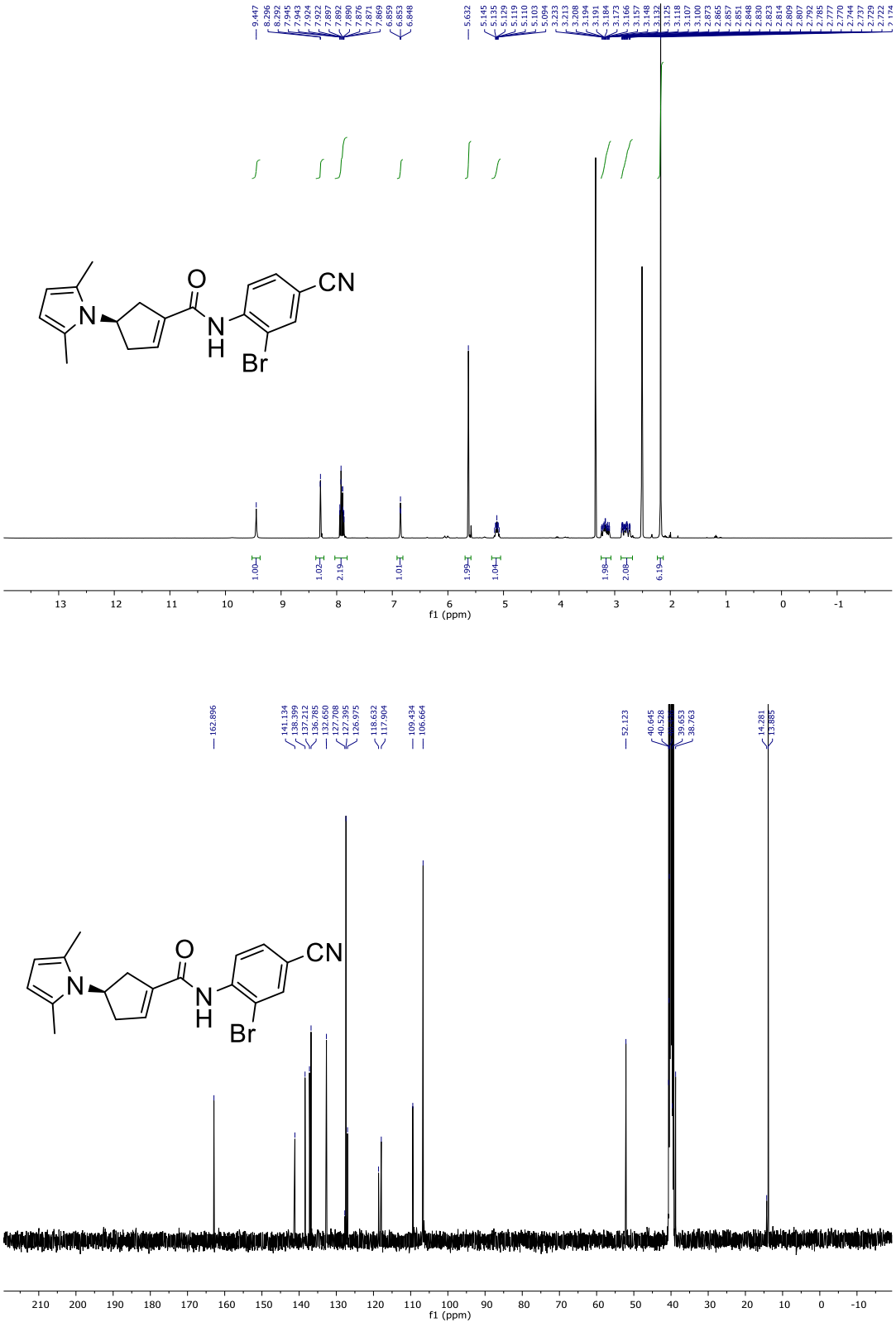
^{1}H and ^{13}C NMR spectra of compound **1e**


9.503
8.101
8.096
7.918
7.897
7.808
7.806
7.803
7.801
7.785
7.780
6.849
6.843
6.838
5.634
5.164
5.148
5.138
5.132
5.122
5.113
5.107
5.097
5.081
3.236
3.210
3.194
3.173
3.166
3.148
3.141
3.132
3.125
3.119
3.107
3.100
3.093
2.875
2.867
2.858
2.852
2.832
2.824
2.816
2.810
2.792
2.784
2.776
2.769
2.744
2.736
2.728
2.721
2.179
1.05
1.04
1.02
0.99
1.00
1.05
2.04
2.06
5.66
f1 (ppm)

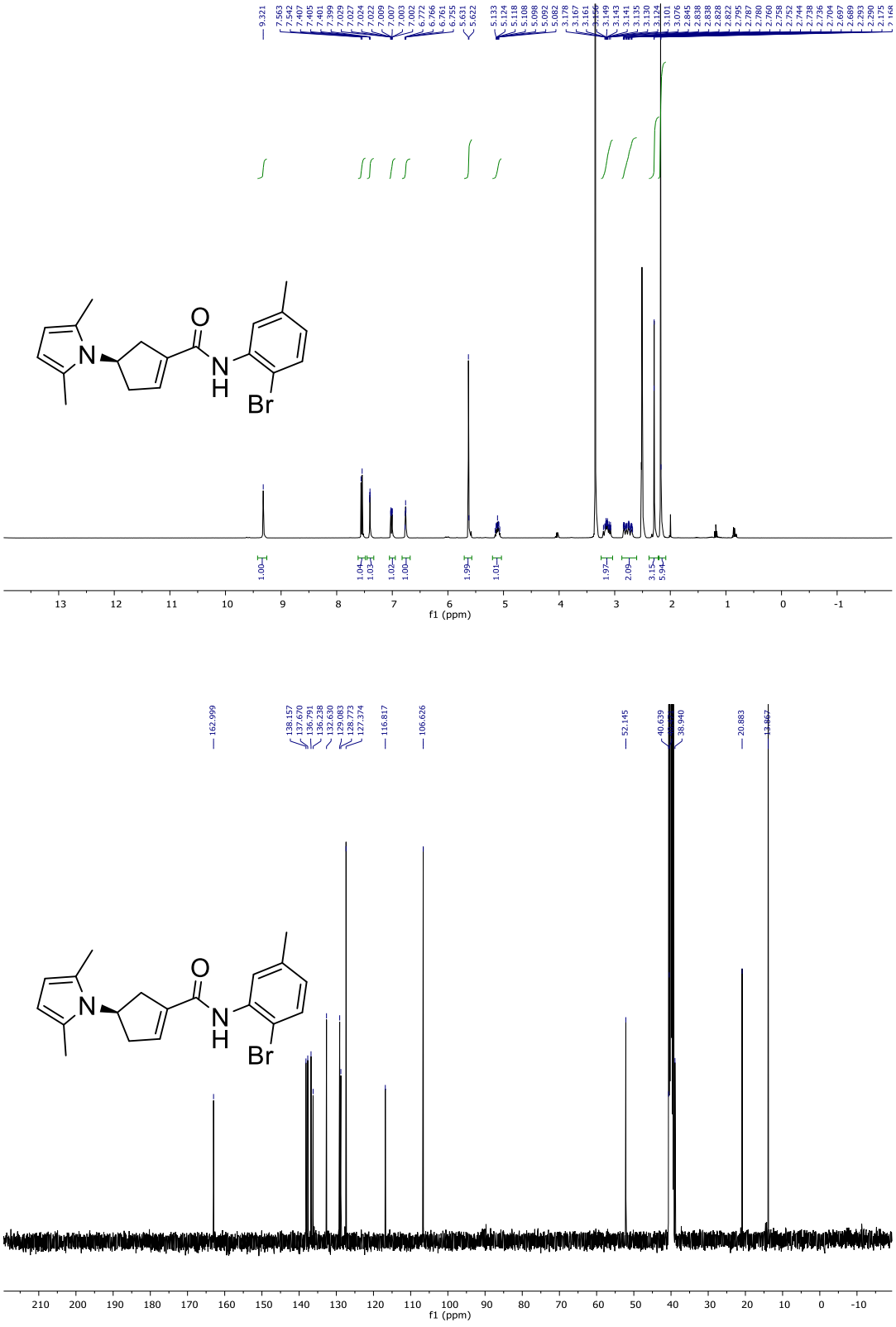

162.995
140.490
138.018
137.288
130.076
130.038
127.814
127.676
127.395
127.352
125.631
125.591
125.059
122.351
119.376
106.657
52.133
40.509
40.298
39.880
38.823
13.885
f1 (ppm)



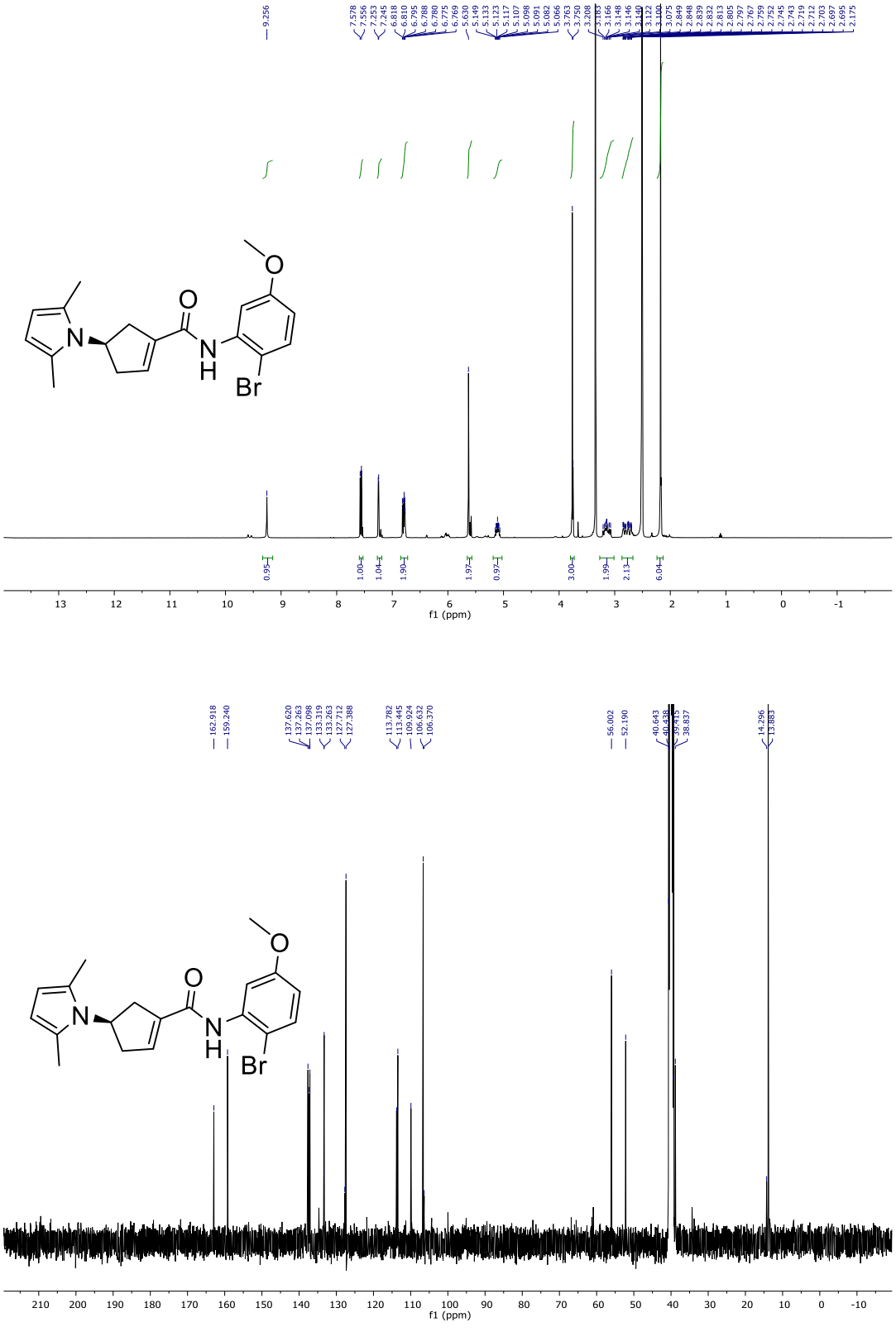
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **1f**



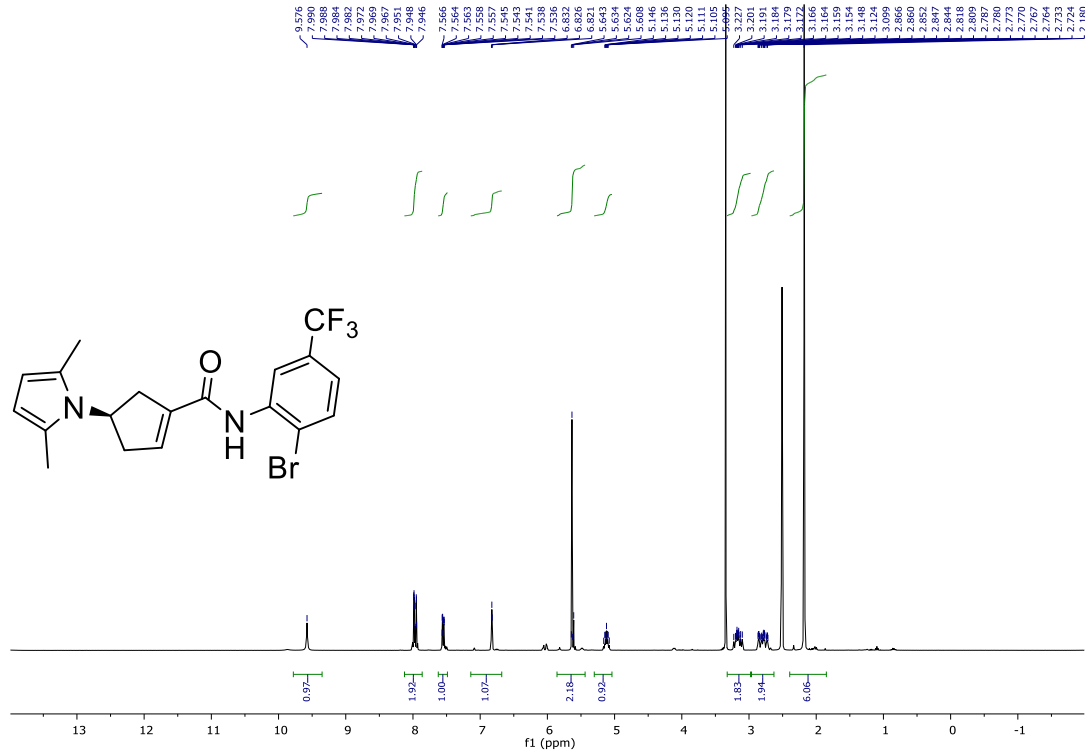
^{1}H and ^{13}C NMR spectra of compound **1g**

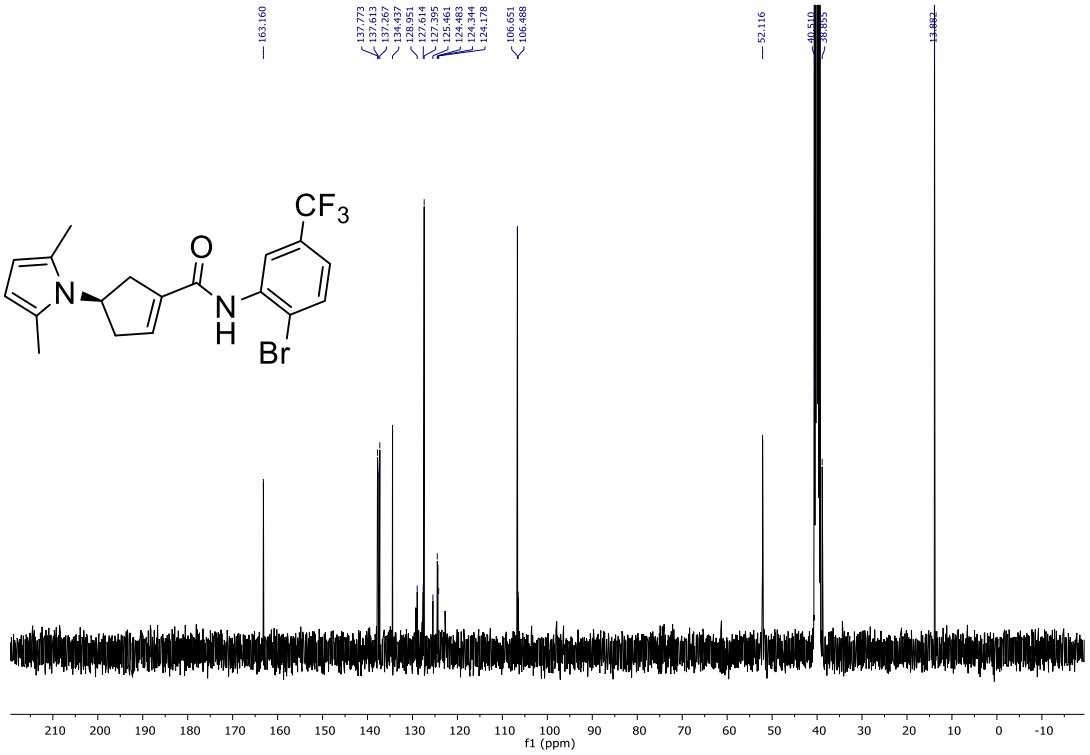


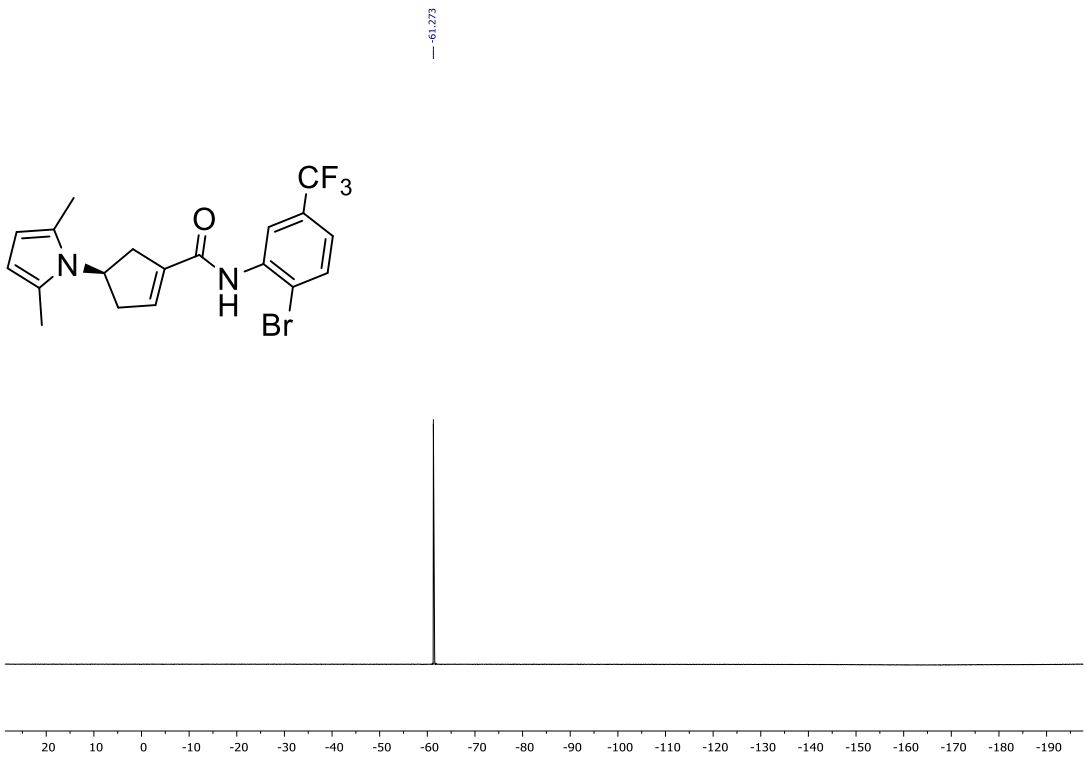
^{1}H and ^{13}C NMR spectra of compound **1h**



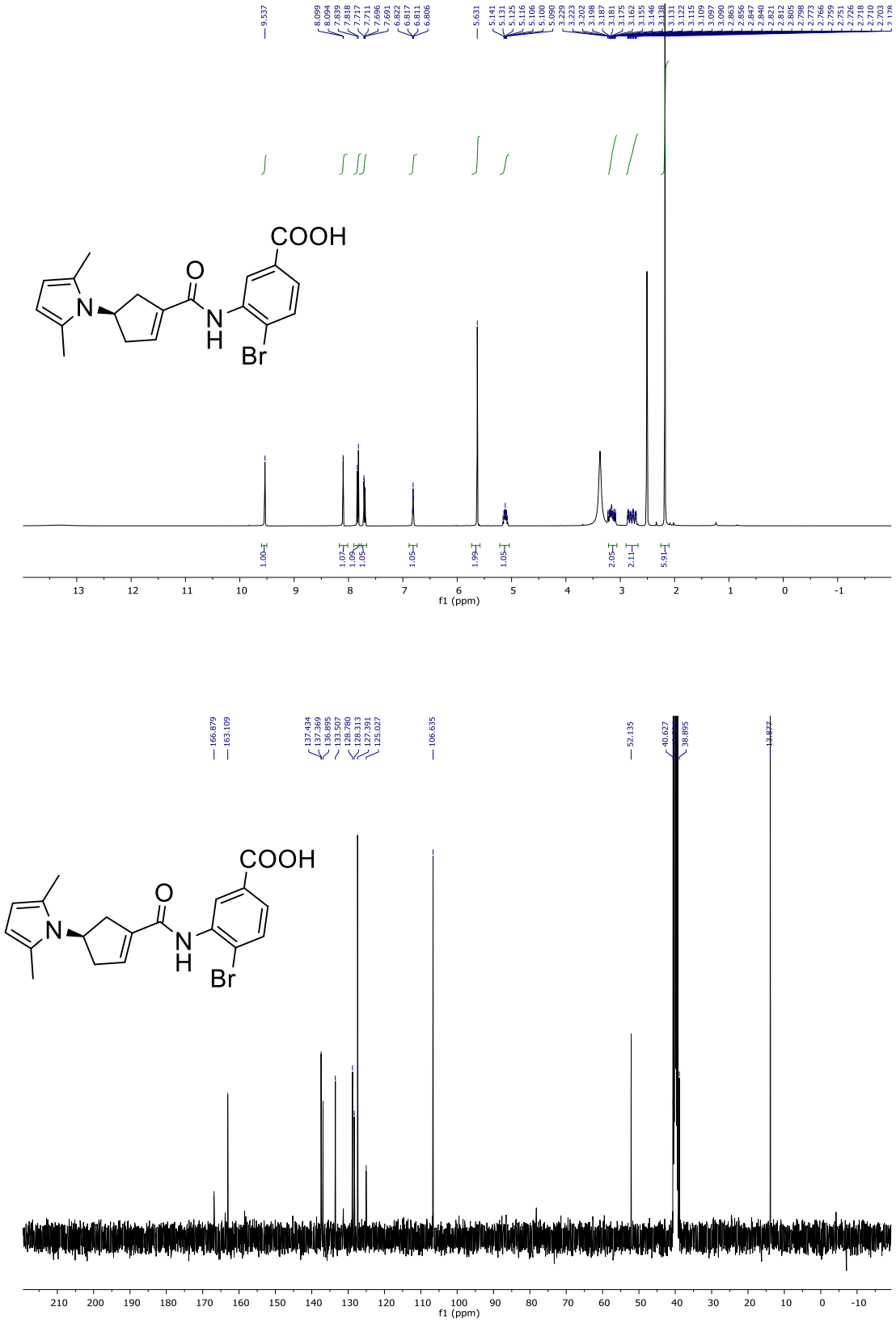
^{1}H and ^{13}C NMR spectra of compound **1i**


CF3
O
N
H
Br
f1 (ppm)

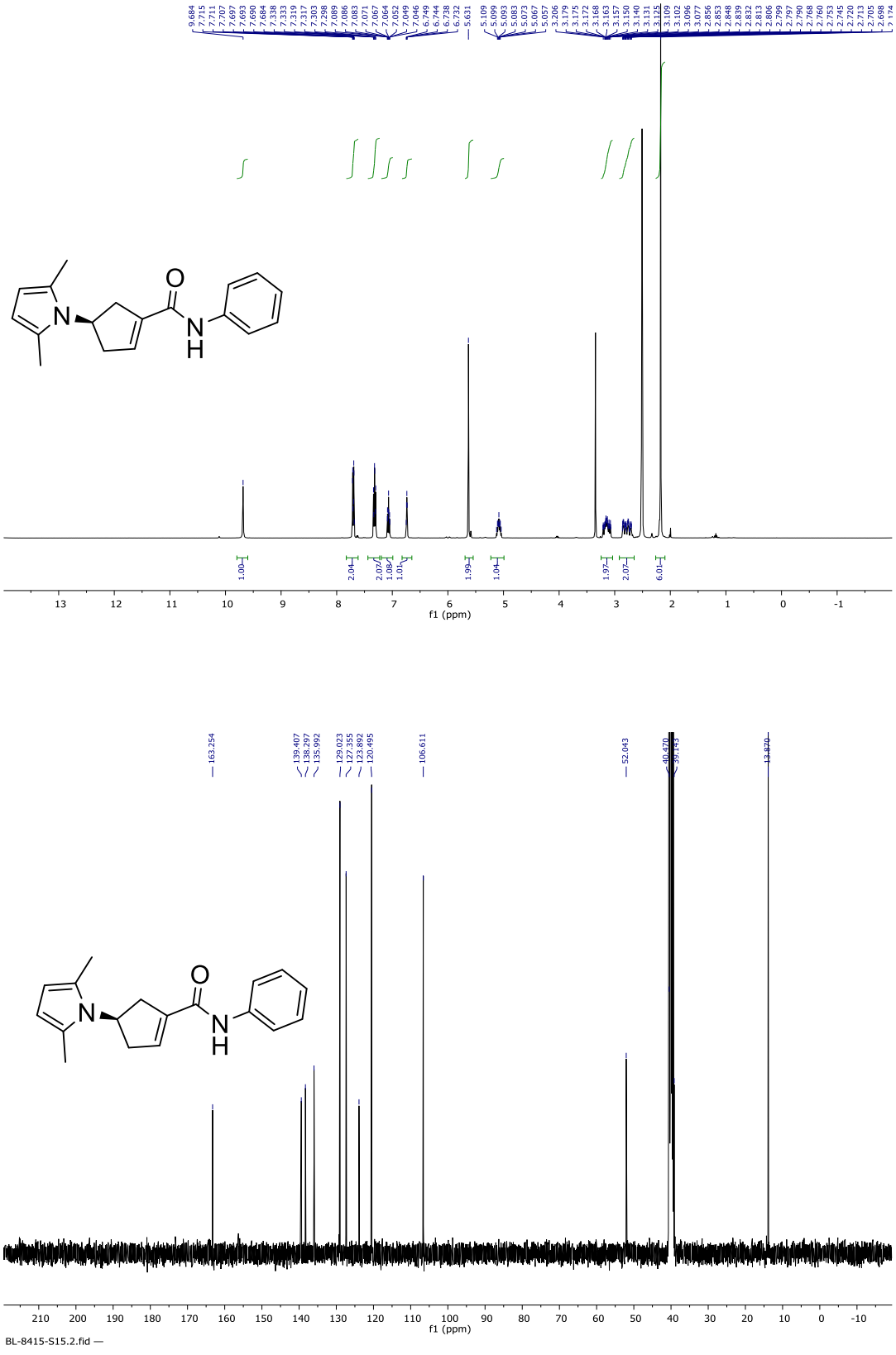

CF3
O
N
H
Br
f1 (ppm)



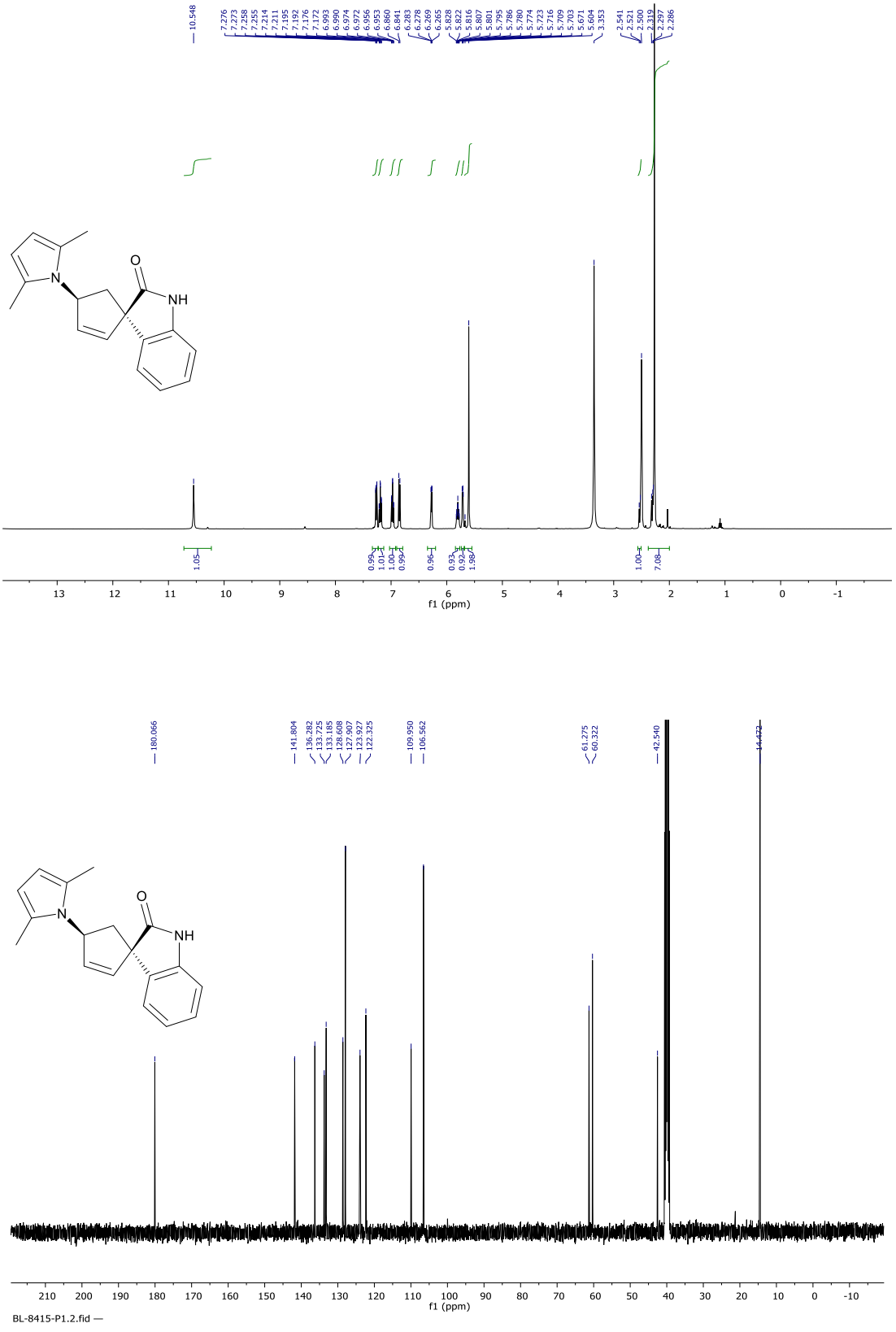
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **1j**



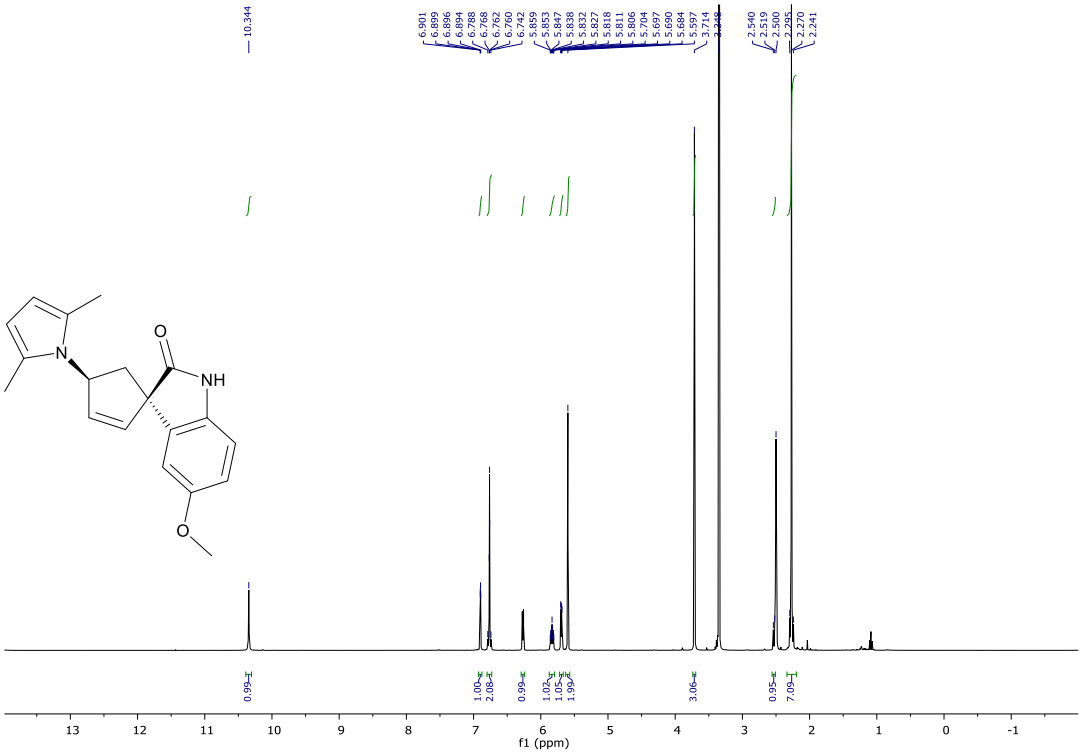
^{1}H and ^{13}C NMR spectra of compound **1k**

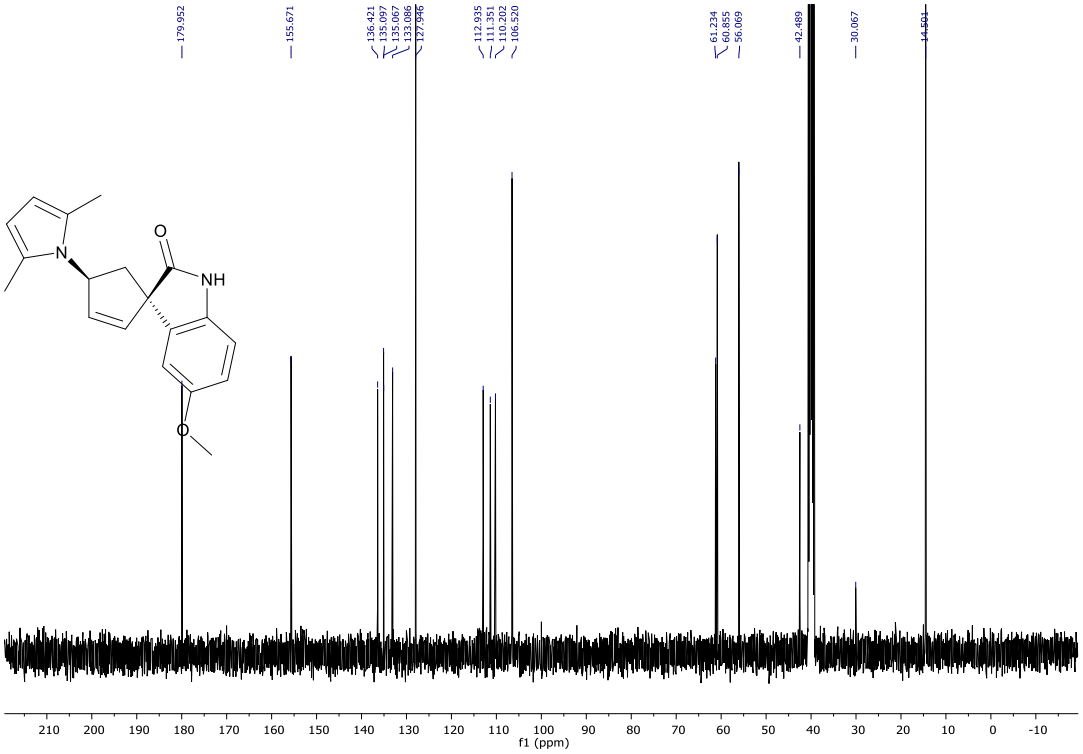


^{1}H and ^{13}C NMR spectra of compound **1l**

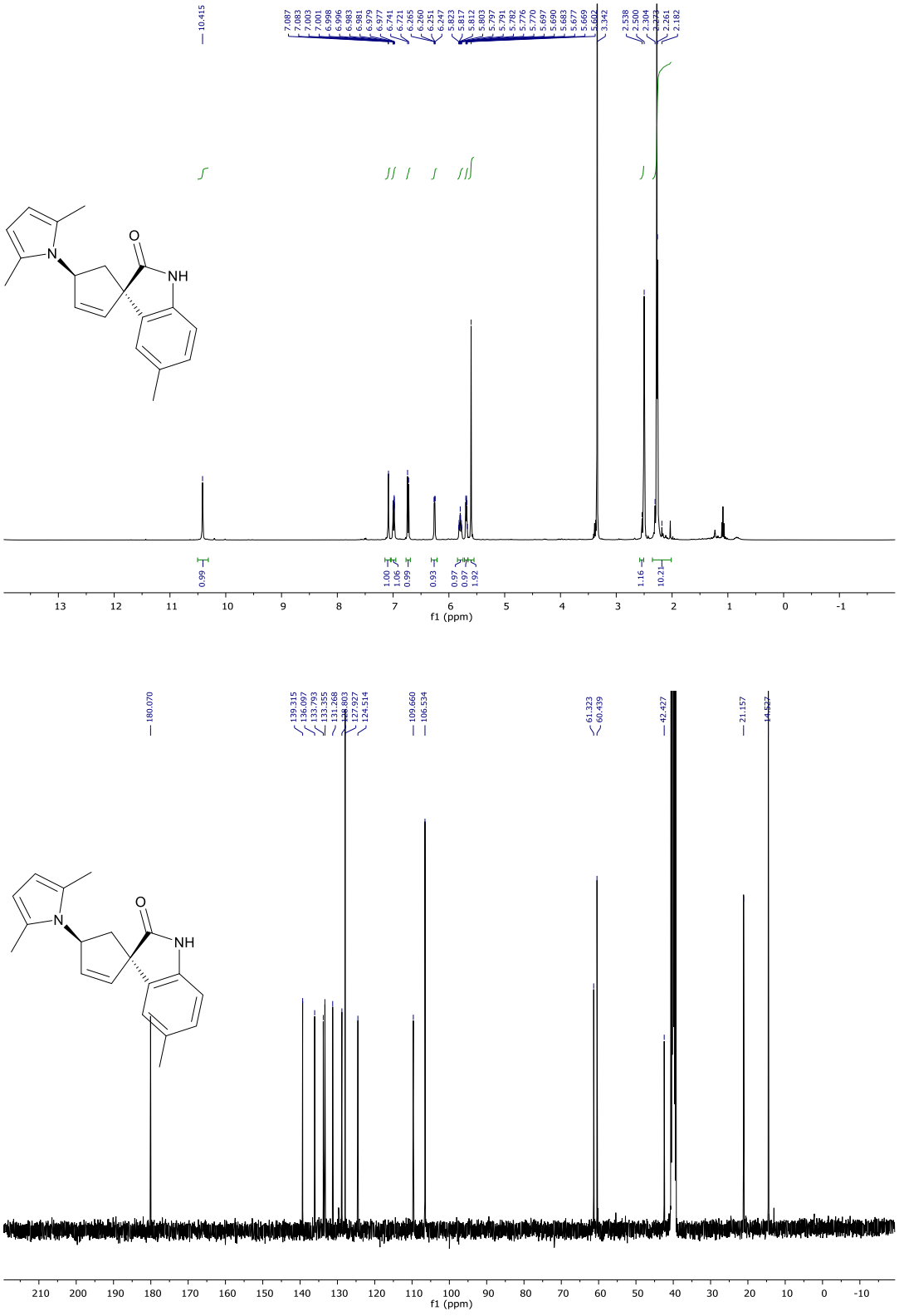


^{1}H and ^{13}C NMR spectra of compound **2a**

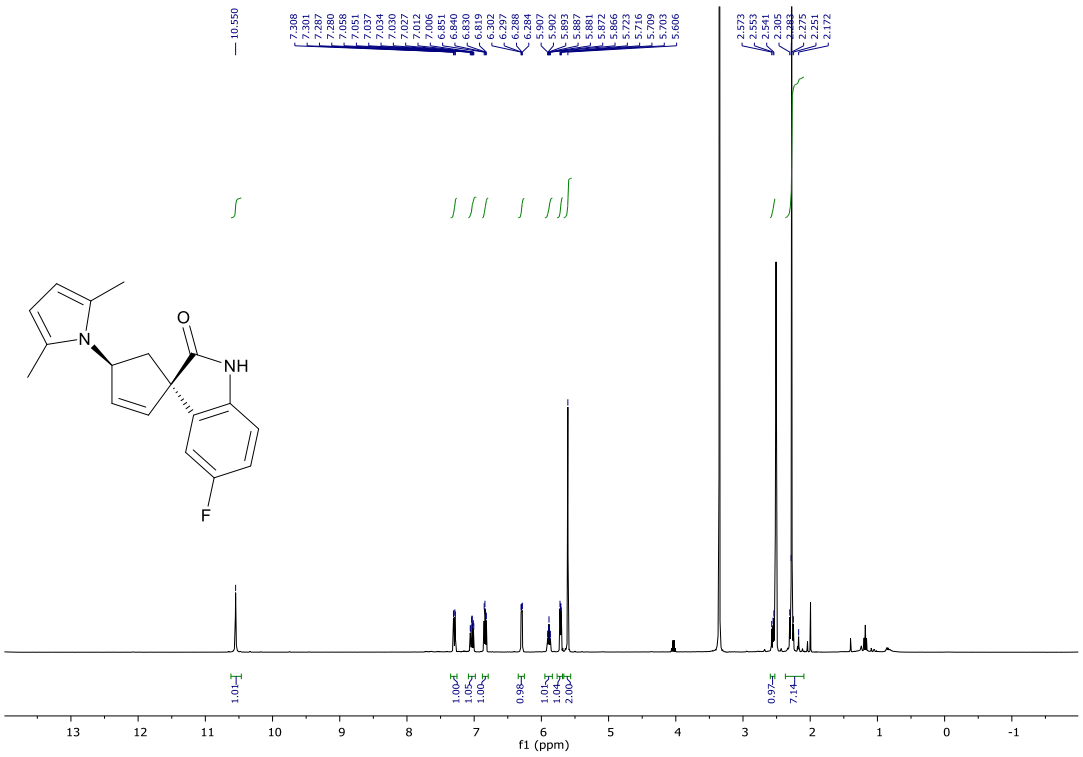


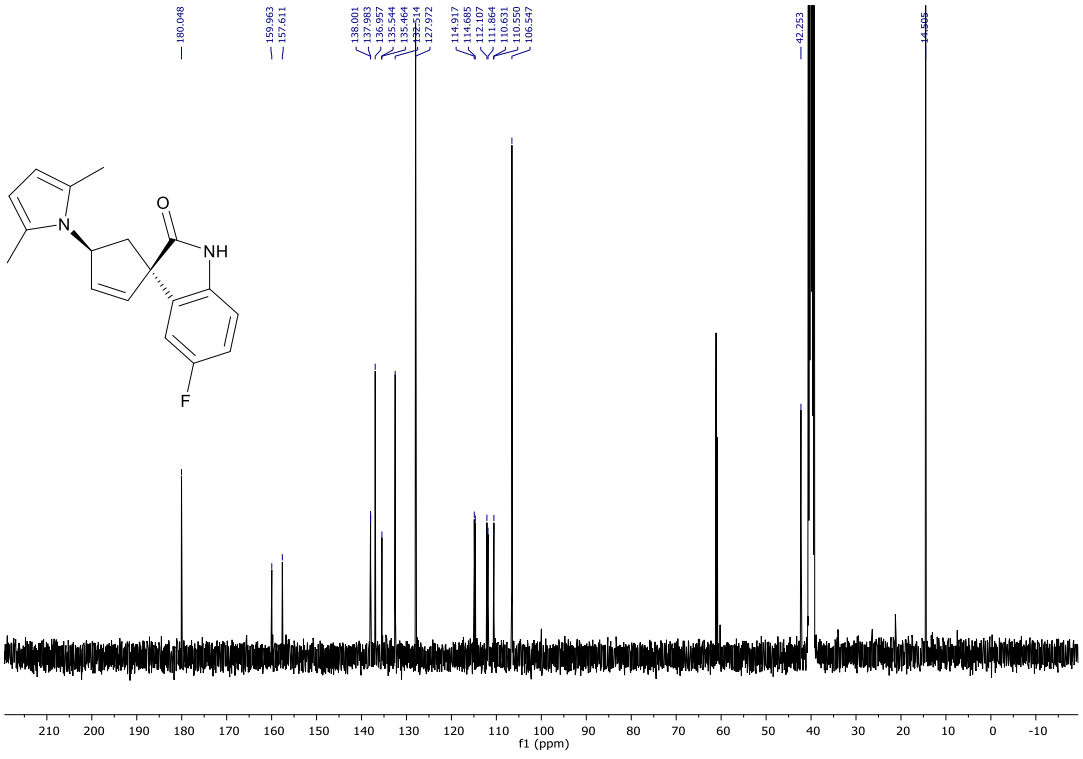


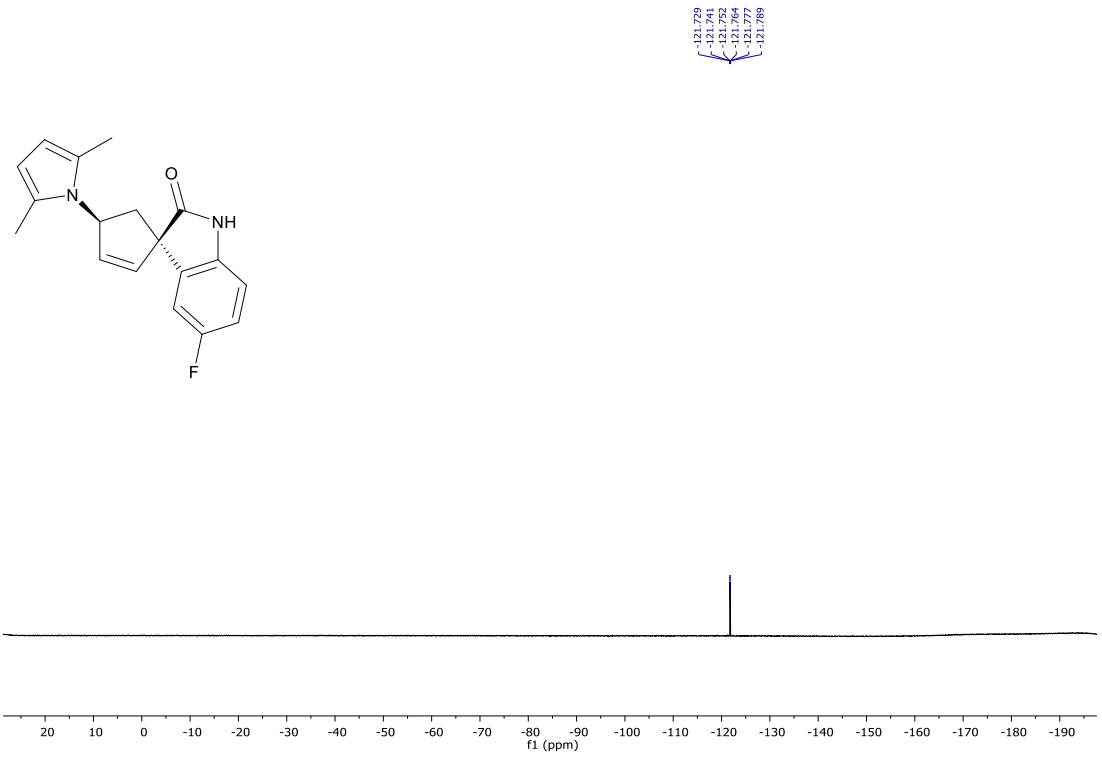
^{1}H and ^{13}C NMR spectra of compound **2b**



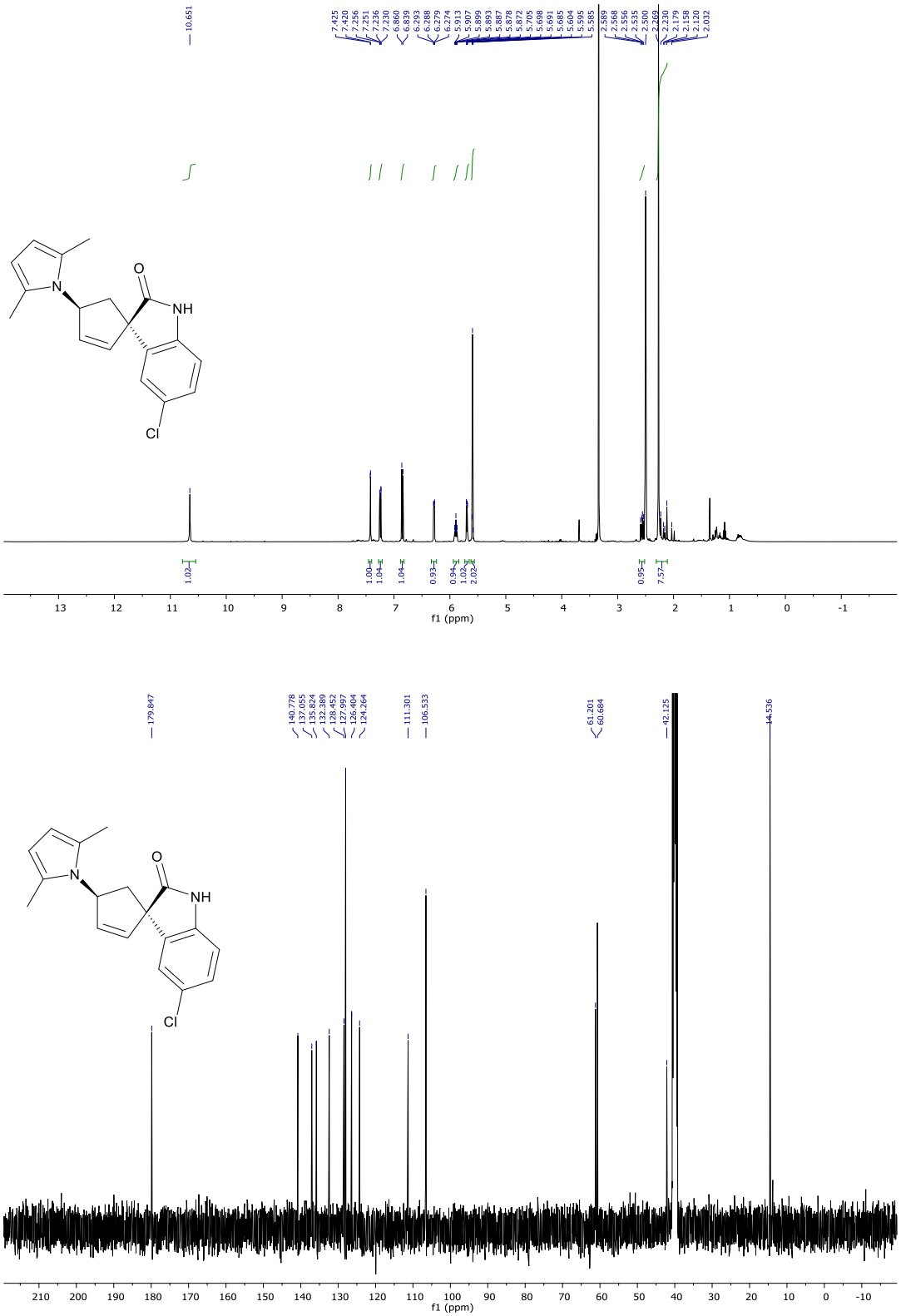
^{1}H and ^{13}C NMR spectra of compound **2c**


10.550
7.308
7.301
7.287
7.280
7.058
7.051
7.037
7.034
7.030
7.027
7.012
7.006
6.851
6.840
6.830
6.819
6.302
6.297
6.288
6.284
5.907
5.902
5.893
5.887
5.881
5.872
5.866
5.723
5.716
5.709
5.703
5.606
2.573
2.553
2.541
2.305
2.293
2.275
2.251
2.172
O
NH
N
F
1.01
1.00
1.05
1.00
0.98
1.01
1.04
2.00
0.97
7.14
f1 (ppm)

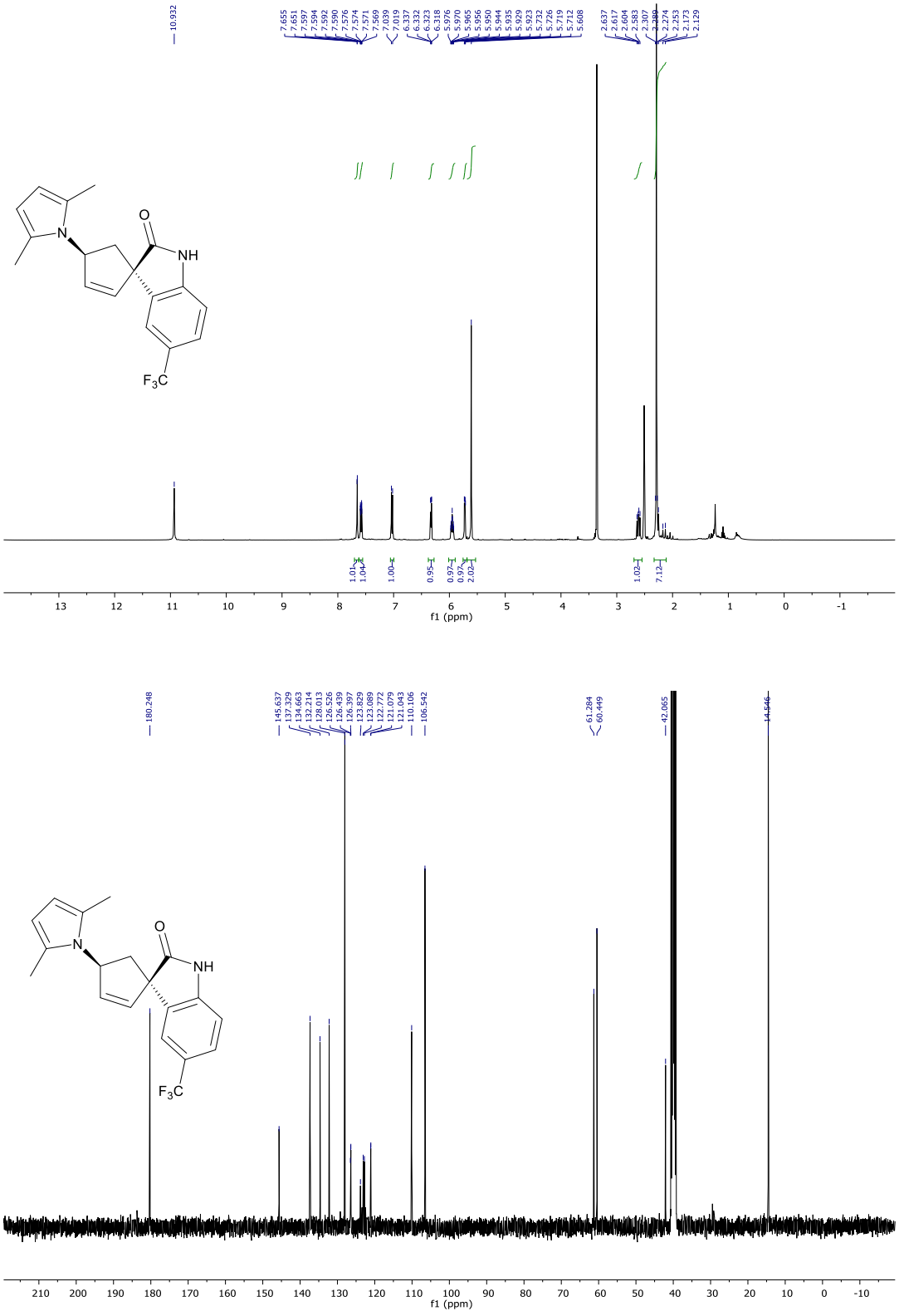

180.048
159.963
157.611
138.001
137.983
136.957
135.544
135.464
132.514
127.972
114.917
114.695
112.107
111.864
110.631
110.550
106.547
42.253
14.595
O
NH
N
F
f1 (ppm)



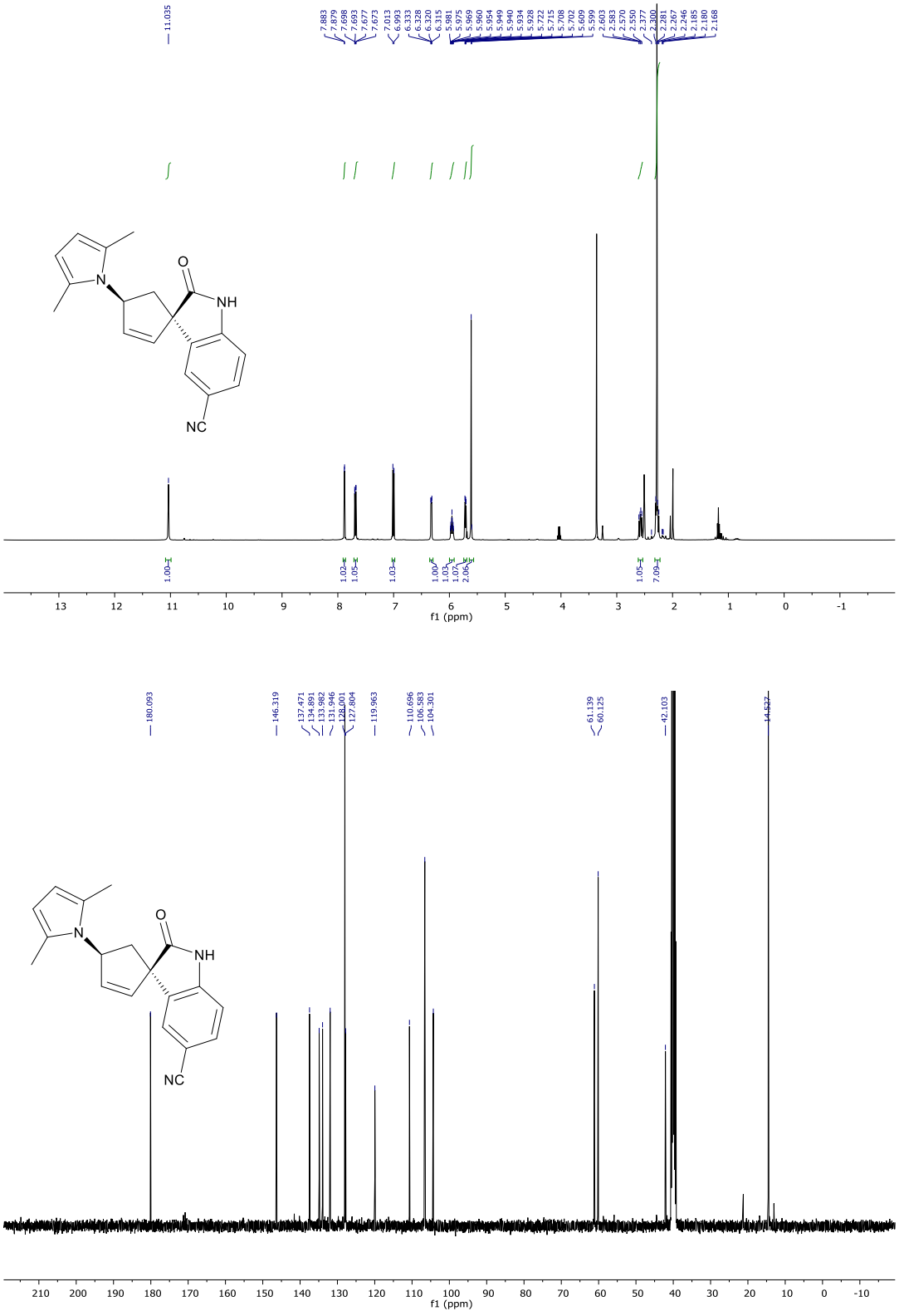
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **2d**



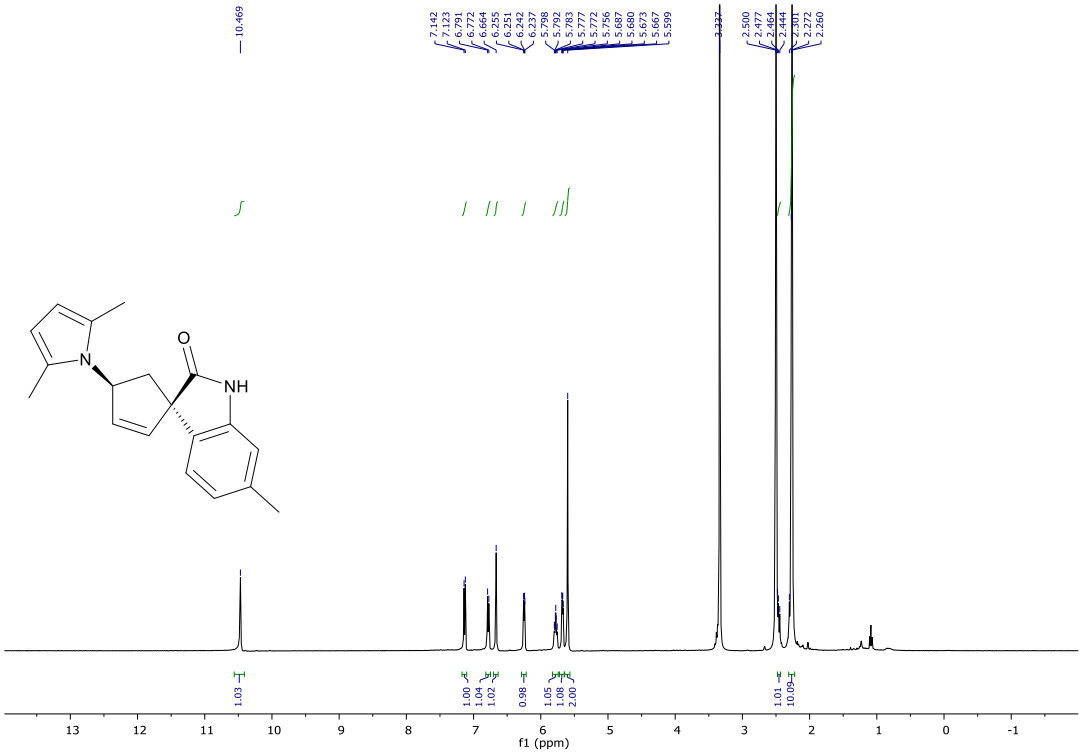
^{1}H and ^{13}C spectra of compound **2e**

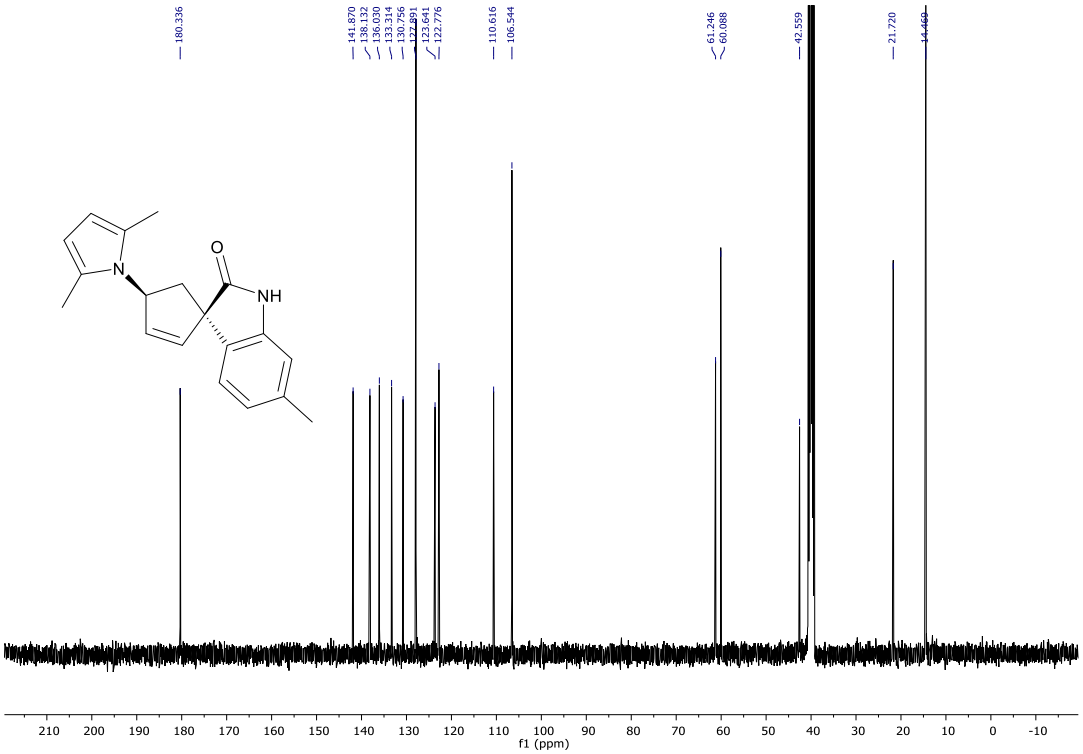


^{1}H, ^{13}C and ^{19}F NMR spectra of compound **2f**

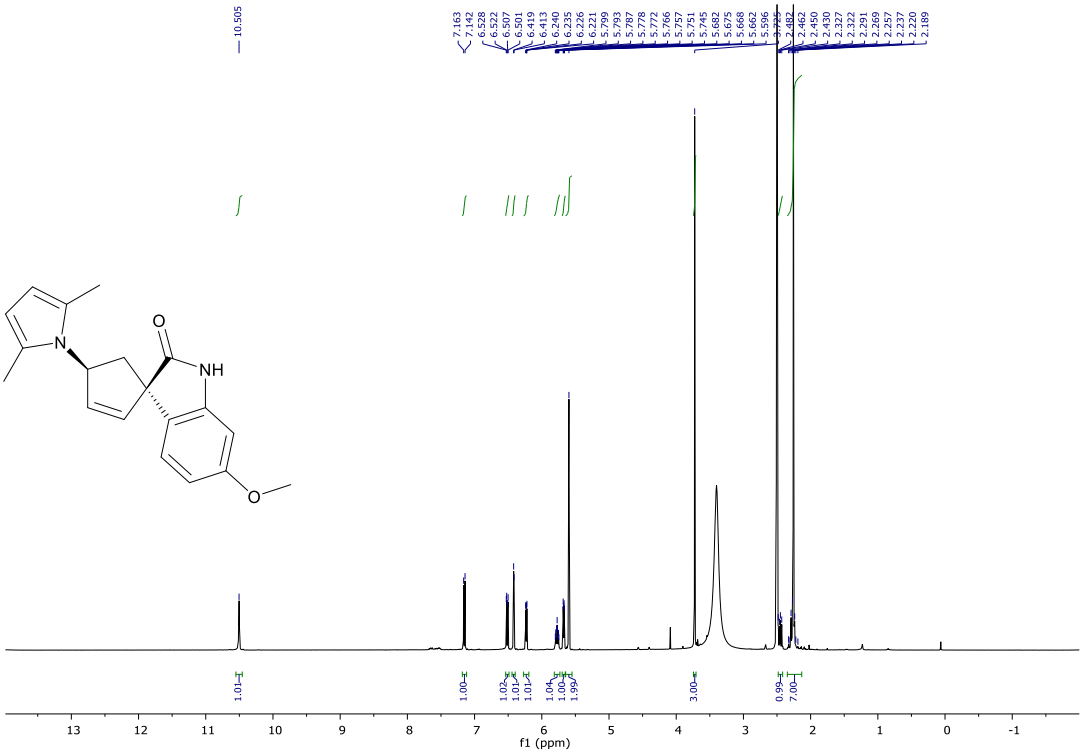


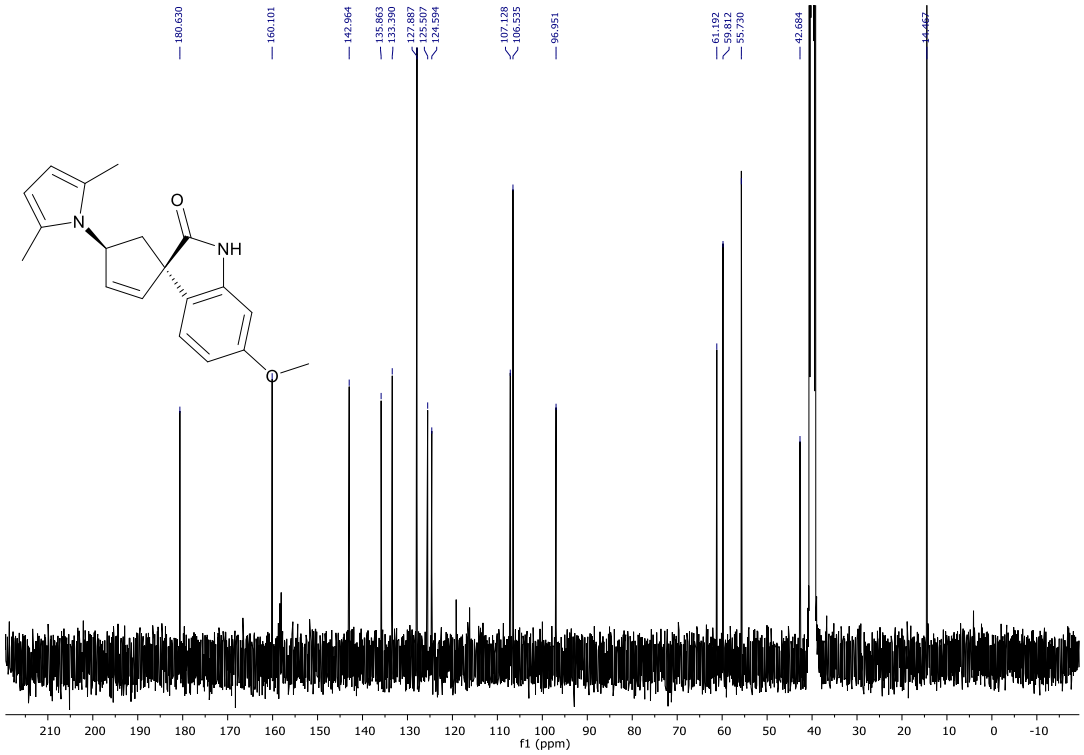
^{1}H and ^{13}C NMR spectra of compound **2g**



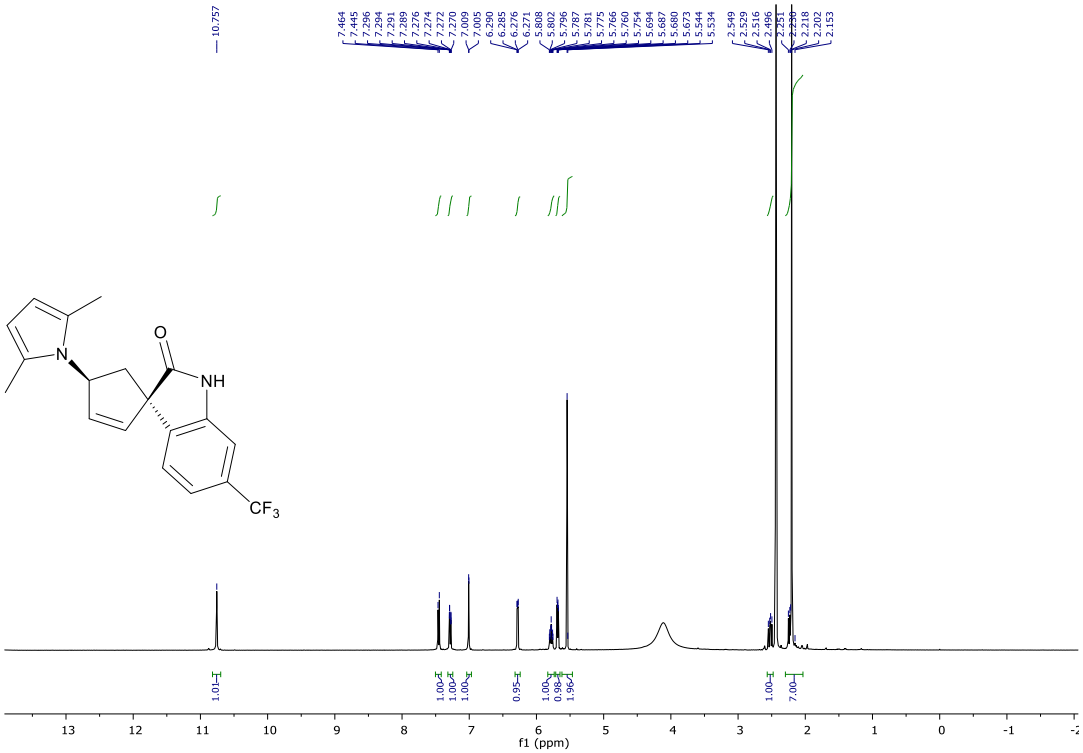


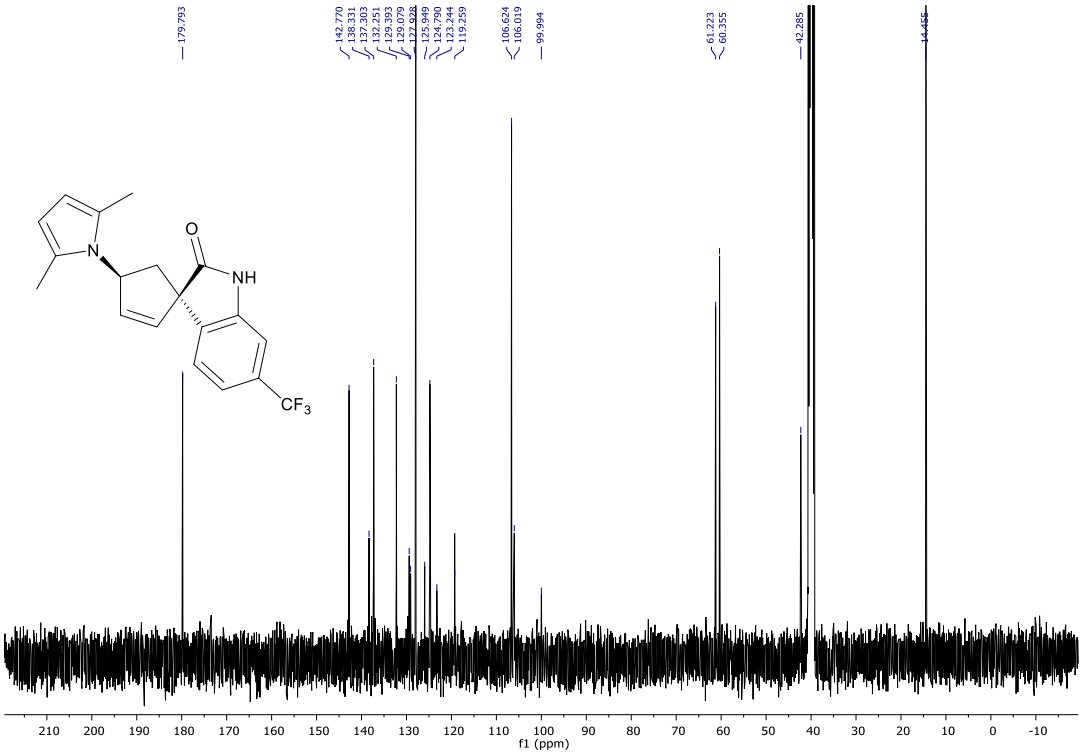
^{1}H and ^{13}C NMR spectra of compound **2h**

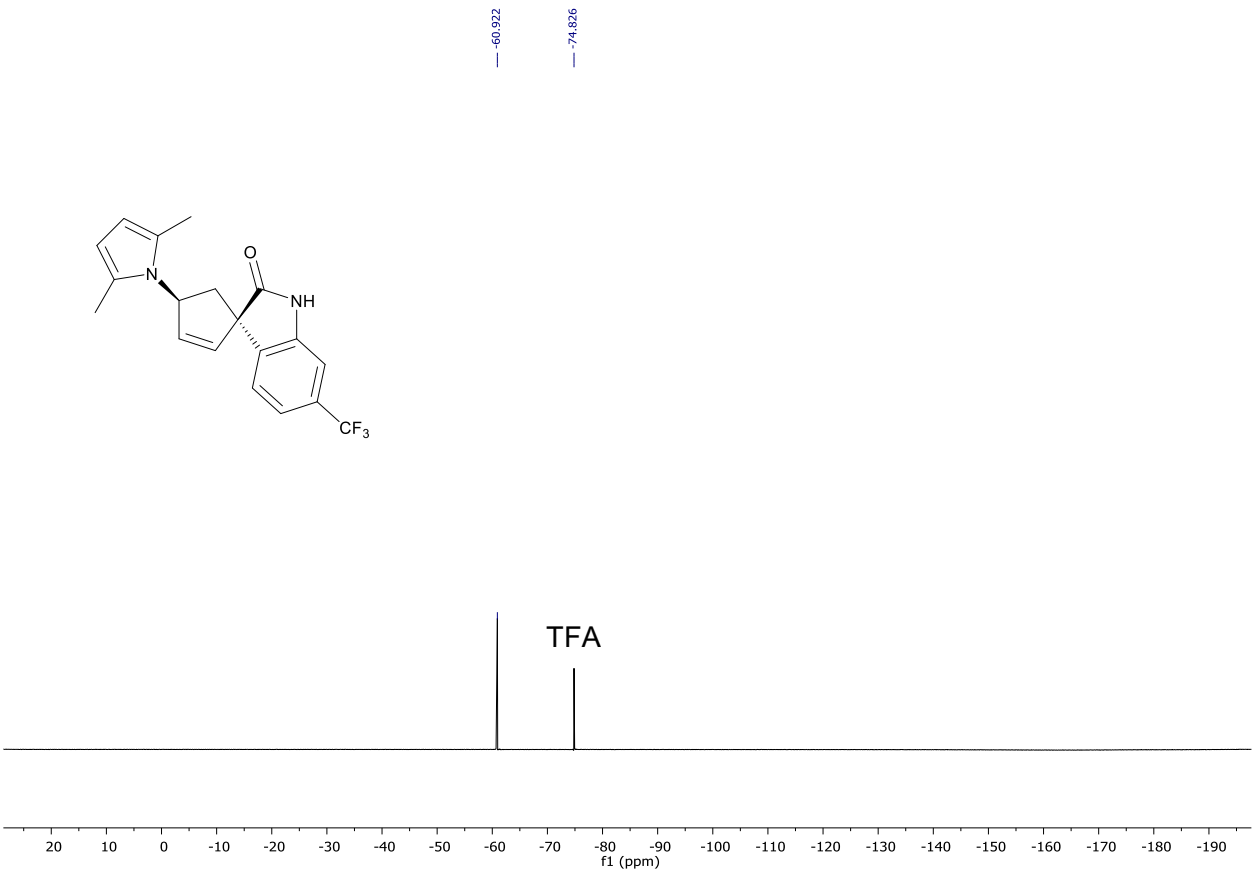




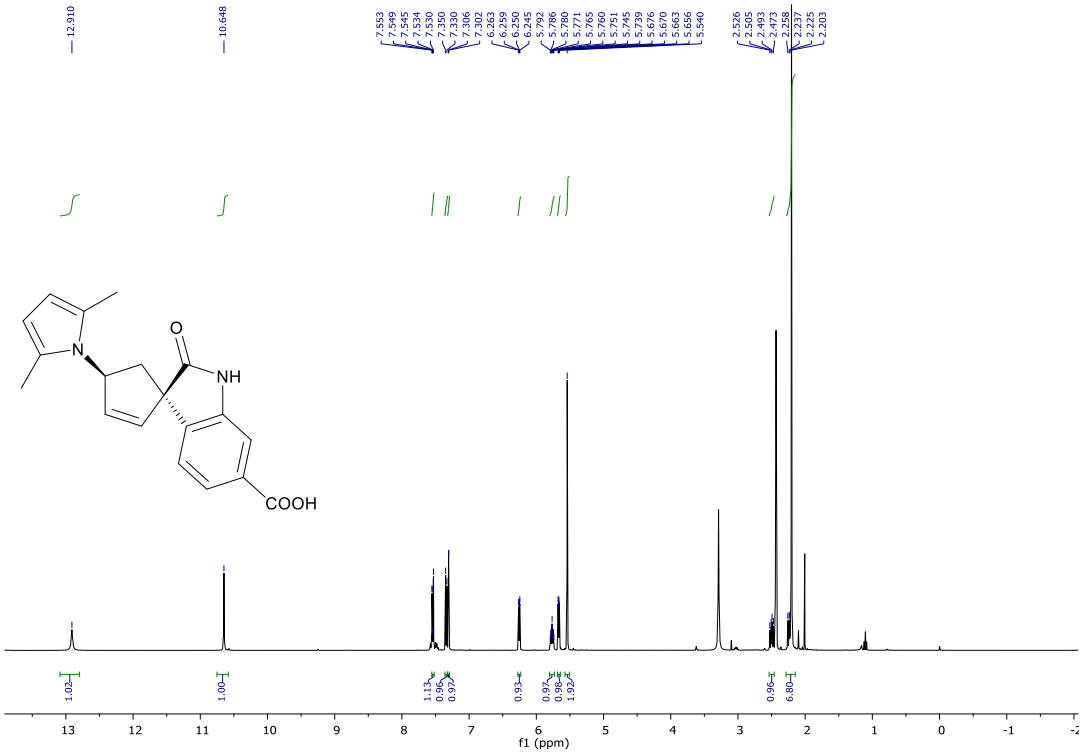
^{1}H and ^{13}C NMR spectra of compound **2i**

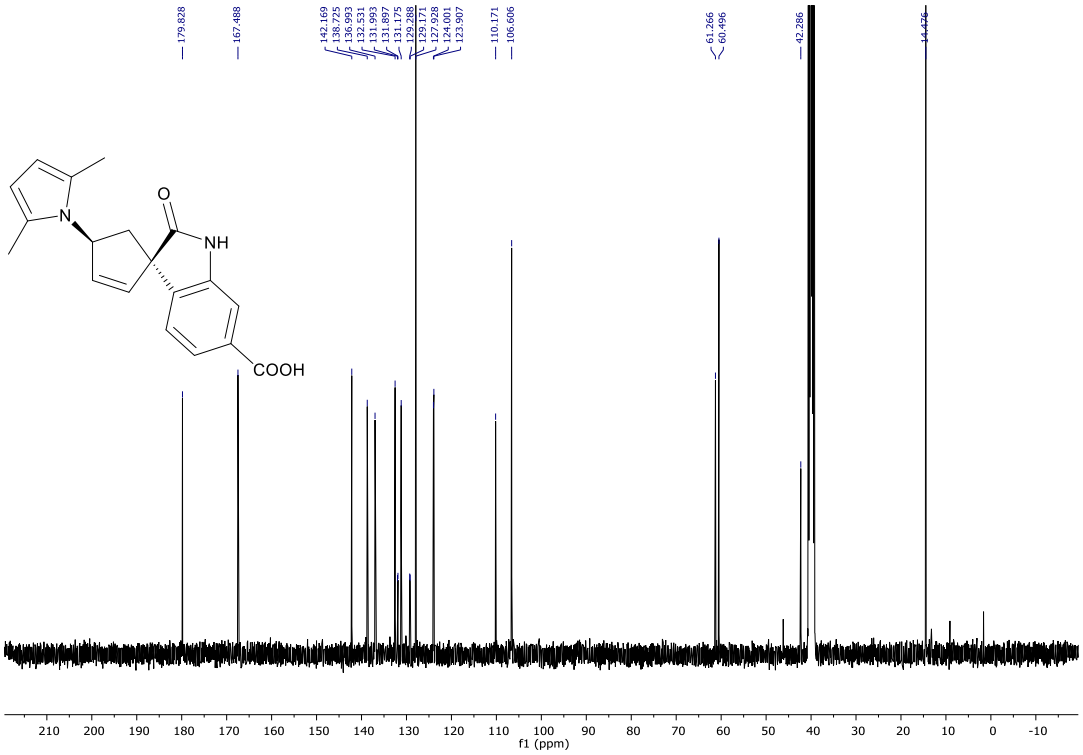

10.757
7.464
7.445
7.296
7.294
7.291
7.289
7.276
7.274
7.272
7.270
7.009
7.005
6.290
6.285
6.276
6.271
5.808
5.802
5.796
5.787
5.781
5.775
5.766
5.760
5.754
5.684
5.680
5.673
5.544
5.534
2.549
2.529
2.516
2.496
2.251
2.230
2.218
2.202
2.153
1.01
1.00
1.00
1.00
0.95
1.00
0.98
1.96
1.00
7.00
O
NH
N
CF3
f1 (ppm)


179.793
142.770
138.331
137.303
132.251
129.393
129.079
125.496
124.790
123.244
119.259
106.624
106.019
99.994
61.223
60.355
42.285
14.455
O
NH
N
CF3
f1 (ppm)

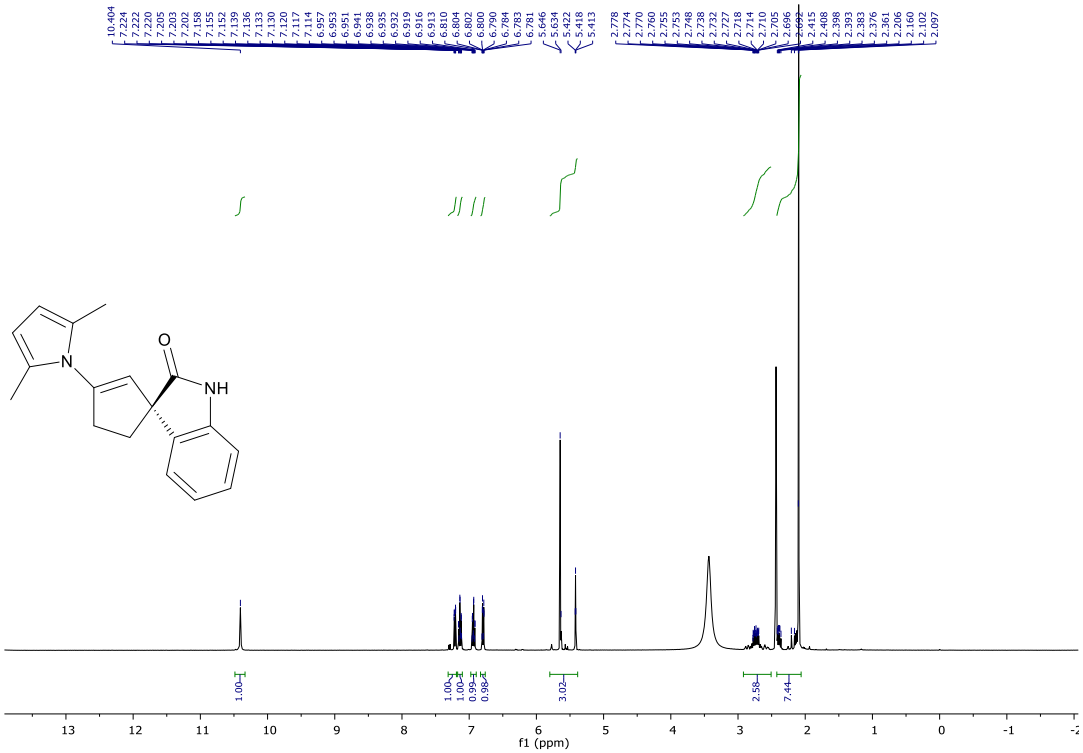


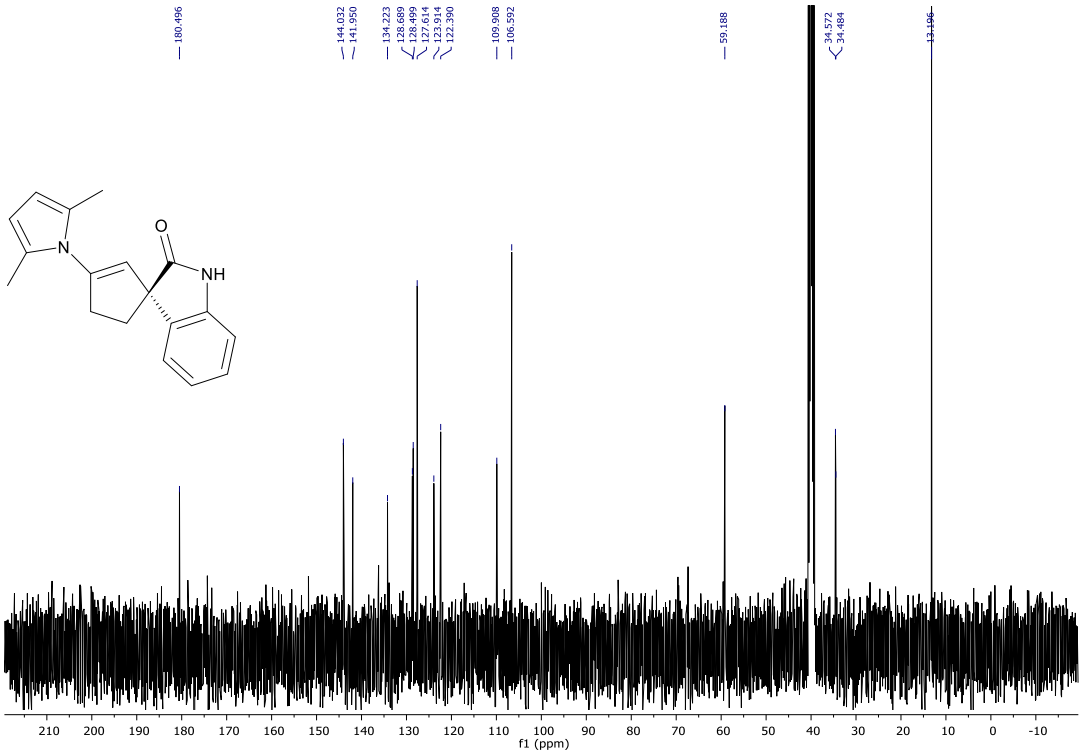
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **2j**



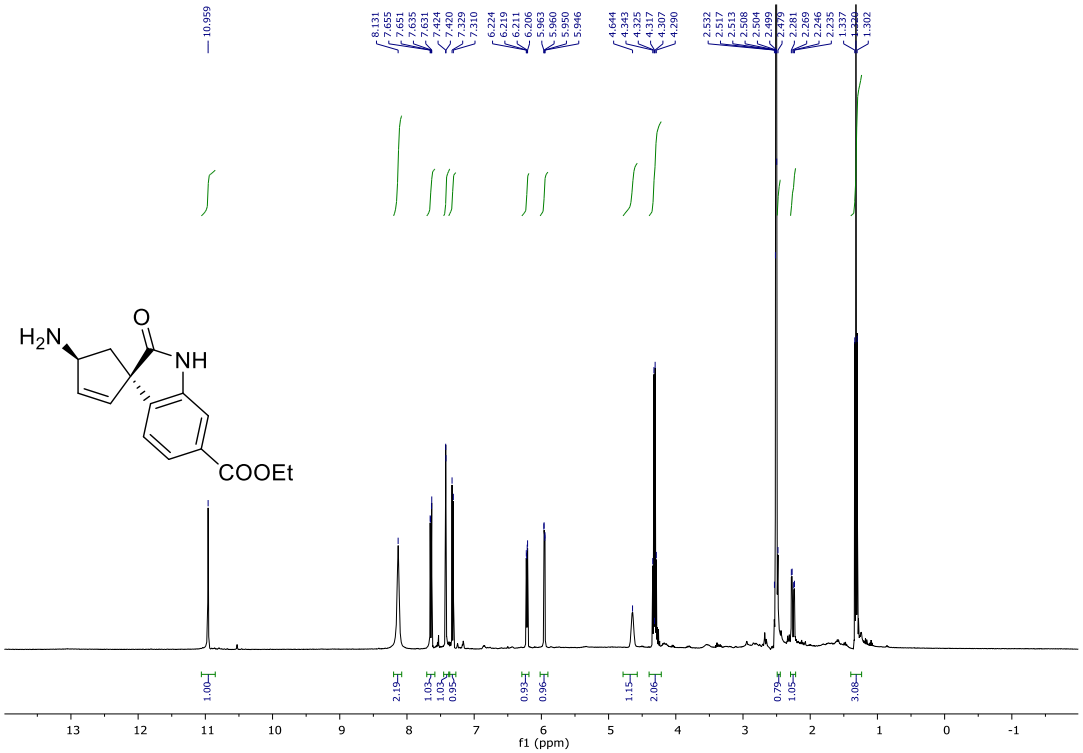


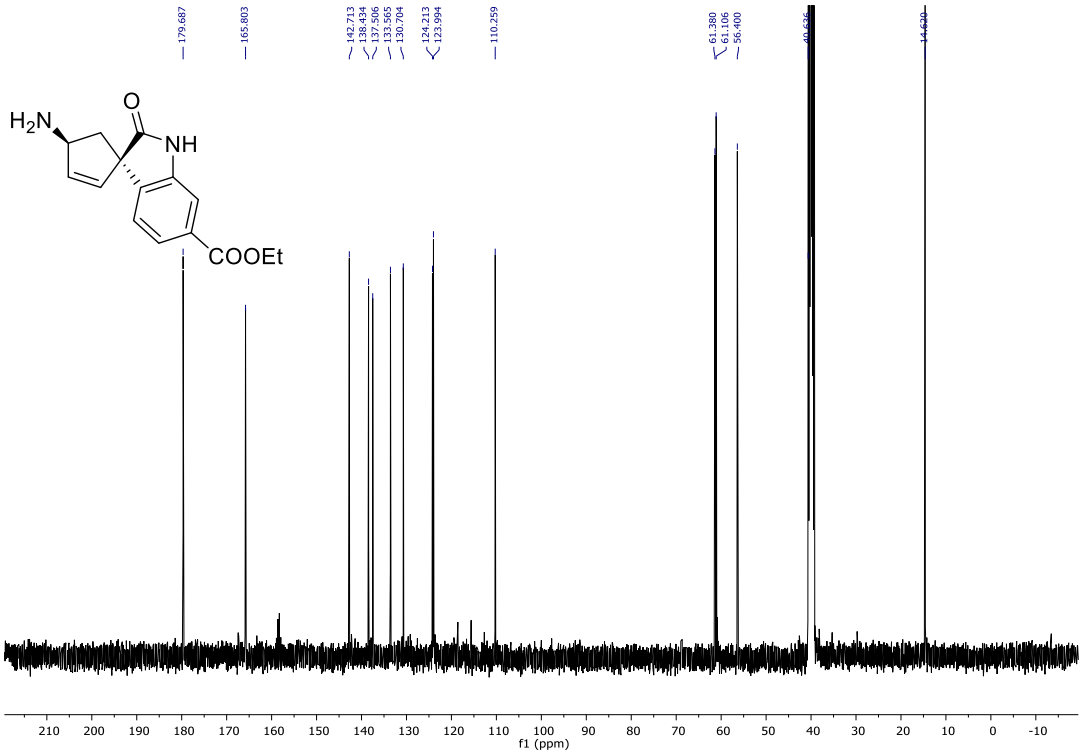
^{1}H and ^{13}C NMR spectra of compound **2k**





^{1}H and ^{13}C NMR spectra of compound **4a**





^{1}H and ^{13}C NMR spectra of compound **6**

References

(1) Bochevarov, A. D.; Harder, E.; Hughes, T. F.; Greenwood, J. R.; Braden, D. A.; Philipp, D. M.; Rinaldo, D.; Halls, M. D.; Zhang, J.; Friesner, R. A. *Int. J. Quantum Chem.* **2013**, *113*, 2110.

(2) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(3) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.

(4) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775.

(5) Bray, B. L.; Dolan, S. C.; Halter, B.; Lackey, J. W.; Schilling, M. B.; Tapolczay, D. J. *Tetrahedron Lett.* **1995**, *36*, 4483.

(6) Smith, M. E. B.; Derrien, N.; Lloyd, M. C.; Taylor, S. J. C.; Chaplin, D. a; Mccague, R. *Tetrahedron Lett.* **2001**, *42*, 1347.

(7) Walia, A.; Kang, S.; Silverman, R. B. *J. Org. Chem.* **2013**, *78*, 10931.