

Palladium-Catalyzed Dicarbonylative Synthesis of Tetracycle Quinazolinones

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1. General considerations

Nuclear Magnetic Resonance spectra were recorded on Bruker Avance 300 and Bruker ARX 400 spectrometers. All ¹H NMR experiments were reported in δ units, parts per million (ppm), and were measured relative to residual CHCl₃ (7.26 ppm) in the deuterated solvent. All ¹³C NMR spectra were reported in ppm relative to deuterochloroform (77.0 ppm) and all were obtained with ¹H decoupling. All coupling constants J were reported in Hz. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet and br s = broad singlet. All measurements were carried out at room temperature unless otherwise stated. Electron impact (EI) mass spectra were recorded on AMD 402 mass spectrometer (70 eV). High resolution mass spectra (HRMS) were recorded on Agilent 6210. The data were given as mass units per charge (m/z). Gas chromatography analysis was performed on an Agilent HP-5890 instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5 % phenyl groups, 30 m, 0.32 mm i.d., 0.25 μ m film thickness) using argon as carrier gas. The products were isolated from the reaction mixture by column chromatography on silica gel 60, 0.063-0.2 mm, 70-230 mesh (Merck).

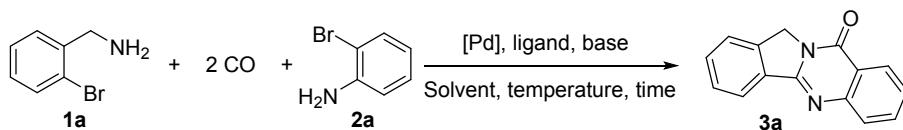
2. Materials

DMSO, NMP, toluene, 1,4-dioxane, DMF, DMAc (anhydrous) was purchased from Sigma-Aldrich and Fluka and used without further purification. All Chemicals were commercial available and were used without further purification unless otherwise noted.

3. Representative procedure for the synthesis of isoindolo[1,2-b]quinazolin-10(12H)-one

A vial (6 mL) was charged with Pd(OAc)₂ (2 mol%), BuPAd₂ (6 mol%), Na₂CO₃ (1.5 mmol) and a magnetic stirring bar. Then, DMAc (2.0 mL), 2-bromoaniline (0.6 mmol), and 2-bromobenzylamine (0.5 mmol) were injected under argon by using a syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 5 bar of CO was adjusted at ambient temperature. Then, the reaction was performed for 16 h at 120°C. After the reaction was complete, the autoclave was cooled down with ice-water mixture to room temperature and the pressure was released carefully. The solution was diluted with ethyl acetate and then silica gel was added into the solution. After evaporation of the organic solvent, the crude product was purified by column chromatography using ethyl acetate/n-pentane.

Table S1. Optimization of Reaction Conditions.^a

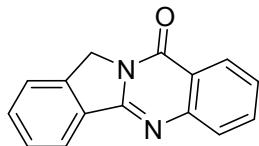


Entry	[Pd]	Ligand	Base	Solvent	CO Pressure (bar)	Temperature (°C)	Time (h)	Yield ^b
1	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv K ₂ CO ₃	DMAc	10	120	16	11%
2	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv K ₂ CO ₃	DMF	10	120	16	8%
3	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	69% (66%)
4	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Cs ₂ CO ₃	DMAc	10	120	16	0%
5	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv K ₃ PO ₄	DMAc	10	120	16	28%
6	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv K ₂ CO ₃	NMP	10	120	16	0%
7	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMF	10	120	16	41%
8	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	Toluene	10	120	16	0%
9	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	1,4-Dioxane	10	120	16	16%
10	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMSO	10	120	16	21%
11	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	5.0 equiv Na ₂ CO ₃	DMAc	10	120	16	72%
12	2 mol% Pd(OAc) ₂	6 mol% PCy ₃	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	32%

13	2 mol% Pd(OAc) ₂	6 mol% PPh ₃	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	0%
14	2 mol% Pd(OAc) ₂	6 mol% Xantphos	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	17%
15	2 mol% Pd(OAc) ₂	6 mol% DPPP	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	53%
16	1 mol% Pd(OAc) ₂	3 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	57%
17	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	32	72%
18	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc ^c	10	120	16	51%
19	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	82% (79%)
20 ^d	2 mol% Pd(TFA) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	63%
21	1 mol% Pd ₂ (dba) ₃	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	68%
22	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	5	120	16	80% (78%)
23 ^d	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	100	16	44%
24 ^d	2 mol% Pd(OAc) ₂	6 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	2	120	16	77%
25 ^d	1 mol% Pd(OAc) ₂	3 mol% BuPAd ₂	3.0 equiv Na ₂ CO ₃	DMAc	10	120	16	57%

^aUnless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol of **1a**, 0.5 mmol of **2a**, 2 mL solvent). ^bGC yields with *n*-hexadecane as an internal standard, isolated yields in parentheses. ^c4mL DMAc. ^d0.50 mmol of **1a**, 0.60 mmol of **2a**.

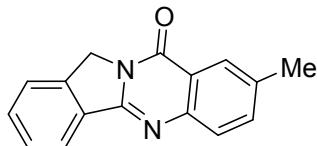
4. Analytic data



Isoindolo[1,2-b]quinazolin-10(12H)-one (3a)¹

¹H NMR (300 MHz, CDCl₃): δ = 8.35-8.32 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 7.84-7.80 (m, 1H), 7.77-7.71 (m, 1H), 7.62-7.52 (m, 3H), 7.48-7.43 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): δ = 160.63, 154.94, 149.47, 139.63, 134.25, 132.68, 132.33, 128.89, 127.39, 126.48, 126.40, 123.53, 123.48, 120.59, 49.78.



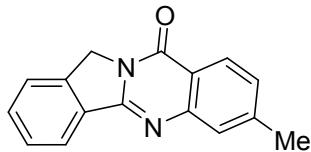
8-Methylisoindolo[1,2-b]quinazolin-10(12H)-one (3b)

¹H NMR (300 MHz, CDCl₃): δ = 8.12-8.10 (m, 2H), 7.67 (d, 1H), 7.58-7.48 (m, 4H), 5.09 (s, 2H), 2.45 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 160.69, 154.29, 139.56, 136.71, 135.79, 132.80, 132.19, 128.90, 127.20, 125.99, 123.52, 123.46, 120.35, 49.82, 21.38.

GC-MS (EI, 70eV): m/z (%) = 249 (M⁺, 100), 234 (41), 220 (12) .

HRMS (ESI): calcd. for [C₁₆H₁₂N₂O + H]⁺ 249.10224; found 249.10200.



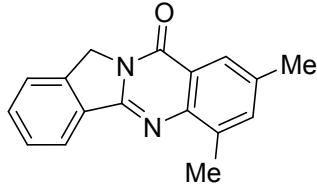
7-Methylisoindolo[1,2-b]quinazolin-10(12H)-one (3c)

¹H NMR (300 MHz, CDCl₃): δ = 8.21-8.14 (m, 2H), 7.60-7.50 (m, 4H), (d, *J* = 8.1 Hz, 2H), 5.08 (s, 2H), 2.46 (s, 3H)

¹³C NMR (75 MHz, CDCl₃): δ = 160.51, 155.08, 145.39, 139.72, 132.60, 132.40, 128.93, 128.13, 126.96, 126.33, 123.71, 123.49, 118.13, 77.45, 77.03, 76.61, 49.82, 21.96.

GC-MS (EI, 70eV): m/z (%) = 248 (M⁺, 100), 89(23), 77 (12), 62 (15).

HRMS (EI): calcd. for [C₁₆H₁₂ON₂]⁺ 248.09441; found 248.09421.



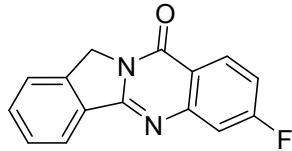
6,8-Dimethylisoindolo[1,2-b]quinazolin-10(12H)-one (3d)

¹H NMR (300 MHz, CDCl₃): δ = 8.12 (d, *J* = 6.9 Hz, 2H), 7.95 (s, 1H), 7.55-7.47 (m, 3H), 7.40 (s, 1H), 5.07 (s, 2H), 2.63 (s, 3H), 2.40 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 161.08, 152.95, 139.41, 136.42, 135.98, 135.74, 133.23, 131.91, 128.72, 123.61, 123.58, 123.44, 120.31, 49.68, 21.31, 17.55.

GC-MS (EI, 70eV): m/z (%) = 262 (M⁺, 100), 247 (46), 233 (10), 218 (6), 131 (8), 116 (10), 89 (8).

HRMS (EI): calcd. for [C₁₇H₁₄ON₂]⁺ 262.11006, found 262.10942.



7-Fluoroisoindolo[1,2-b]quinazolin-10(12H)-one (3e)

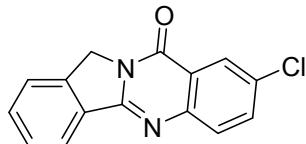
¹H NMR (300 MHz, CDCl₃): δ = 8.43 (dd, *J* = 6.3 Hz, 9.0 Hz, 1H), 8.22 (dd, *J* = 1.2 Hz, 7.8 Hz, 1H), 7.75-7.62 (m, 3H), 7.52 (dd, *J* = 2.4 Hz, 9.9 Hz, 1H), 7.31-7.22 (m, 1H), 5.20 (s, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 166.51 (d, *J* = 252 Hz), 159.97, 156.18, 139.85, 132.72, 132.45, 129.12 (d, *J* = 10.5 Hz), 129.05, 123.77, 123.57, 117.37, 117.35, 115.14 (d, *J* = 23.3 Hz), 112.73 (d, *J* = 21.8 Hz), 49.87.

¹⁹F NMR (282 Hz, CDCl₃): δ = -103.26 (q, *J* = 8.5 Hz).

GC-MS (EI, 70eV): m/z (%) = 252 (M⁺, 100), 223 (15), 197 (7).

HRMS (EI): calcd. for [C₁₅H₉ON₂F]⁺ 252.06934; found 252.06937.



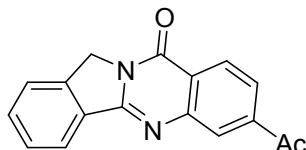
8-Chloroisoindolo[1,2-b]quinazolin-10(12H)-one (3f)

¹H NMR (300 MHz, CDCl₃): δ = 8.27 (d, *J* = 2.4 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.68-7.51 (m, 4H), 5.11 (s, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 159.43, 155.31, 139.70, 134.82, 132.87, 132.36, 132.03, 129.17, 128.64, 126.00, 125.96, 124.00, 123.56, 121.50, 50.07.

GC-MS (EI, 70eV): m/z (%) = 268 (M⁺, 100), 233 (45), 205 (14), 177 (11), 89 (10), 75 (10).

HRMS (ESI): calcd. for [C₁₅H₉³⁵ClN₂O + H]⁺ 269.04762, found 269.04; calcd. for [C₁₅H₉³⁷ClN₂O + H]⁺ 271.04509, found 271.04484.



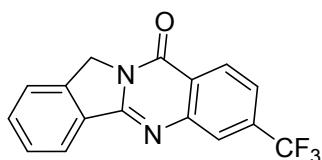
7-Acetylisoindolo[1,2-b]quinazolin-10(12H)-one (3g)¹

¹H NMR (400 MHz, CDCl₃): δ = 8.38 (d, *J* = 8.0 Hz, 1H), 8.32-8.31 (m, 1H), 8.16-8.14 (m, 1H), 7.97 (dd, *J* = 1.6 Hz, 8.2 Hz, 1H), 7.64-7.55 (m, 3H), 5.12 (s, 2H), 2.67 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 197.53, 160.04, 141.63, 139.76, 132.85, 129.17, 128.17, 127.13, 124.89, 123.80, 123.76, 123.63, 123.49, 50.02, 27.09.

GC-MS (EI, 70eV): m/z (%) = 276 (M⁺, 100), 261 (83), 233(67), 205 (23), 116 (37), 43 (34).

HRMS (EI): calcd. for [C₁₇H₁₂O₂N₂]⁺ 276.08933; found 276.08929.



7-(Trifluoromethyl)isoindolo[1,2-b]quinazolin-10(12H)-one (3h)²

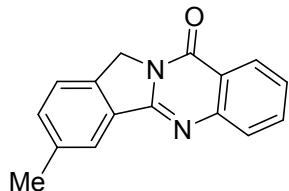
¹H NMR (300 MHz, CDCl₃): δ = 8.40 (dt, *J* = 0.9 Hz, 8.1 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 8.04 (t, *J* = 0.9 Hz, 1H), 7.63-7.51 (m, 4H), 5.10 (s, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 159.81, 156.22, 149.46, 135.87 (q, *J* = 32.6 Hz), 135.21, 132.95, 132.19, 129.19, 127.67, 124.92 (q, *J* = 3.8 Hz), 123.85, 123.59, 123.51 (q, *J* = 271.3 Hz), 122.83, 122.37 (q, *J* = 3.5 Hz), 50.02.

¹⁹F NMR (282 Hz, CDCl₃): δ = -62.73 (s).

GC-MS (EI, 70eV): m/z (%) = 302 (M⁺, 100), 273 (10), 233 (9), 205 (8), 170 (9), 89 (11), 75 (17).

HRMS (EI): calcd. for [C₁₆H₉ONF₃]⁺ 302.06615; found 302.06619.



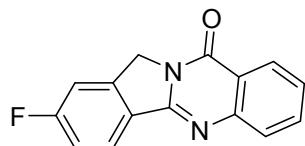
3-Methylisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3i)

¹H NMR (400 MHz, CDCl₃): δ = 8.42 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 8.03 (s, 1H), 7.88-7.80 (m, 2H), 7.55-7.46 (m, 3H), 5.14 (s, 2H), 2.54 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 160.67, 155.11, 149.48, 139.13, 136.91, 134.24, 133.50, 132.75, 127.35, 126.51, 126.34, 123.69, 123.19, 120.62, 49.64, 21.39.

GC-MS (EI, 70eV): m/z (%) = 248 (M⁺, 100), 233 (51), 219 (9), 77 (9).

HRMS (EI): calcd. for [C₁₆H₁₂O N₂]⁺ 248.09441, found 248.09437



2-Fluoroisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (3j)

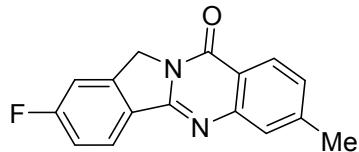
¹H NMR (300 MHz, CDCl₃): δ = 8.30-8.27 (m, 1H), (dd, *J* = 4.8 Hz, 8.6 Hz, 1H), 7.75-7.68 (m, 2H), 7.75-7.39 (m, 2H), 7.27-7.18 (m, 2H), 5.06 (s, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 165.49 (d, *J* = 252.8 Hz), 160.49, 153.94, 149.36, 141.99 (d, *J* = 10.5 Hz), 134.42, 128.75, 127.32, 126.54, 125.61 (d, *J* = 9.0 Hz), 124.98, 120.35, 117.04 (d, *J* = 24.0 Hz), 111.03 (d, *J* = 24.0 Hz), 49.59 (d, *J* = 3.0 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ = -104.90

GC-MS (EI, 70eV): m/z (%) = 252 (100), 224 (17), 223 (18), 197 (9).

HRMS (EI): calcd. for [C₁₅H₉N₂OF]⁺ 252.06934, found 252.06931



2-Fluoro-7-methylisoindolo[1,2-b]quinazolin-10(12H)-one (3k)

¹H NMR (300 MHz, CDCl₃): δ = 8.29 (d, *J* = 8.1 Hz, 1H), 8.23-8.19 (m, 1H), 7.65 (s, 1H), 7.39-7.31 (m, 3H), 5.17 (s, 2H), 2.57 (s, 3H).

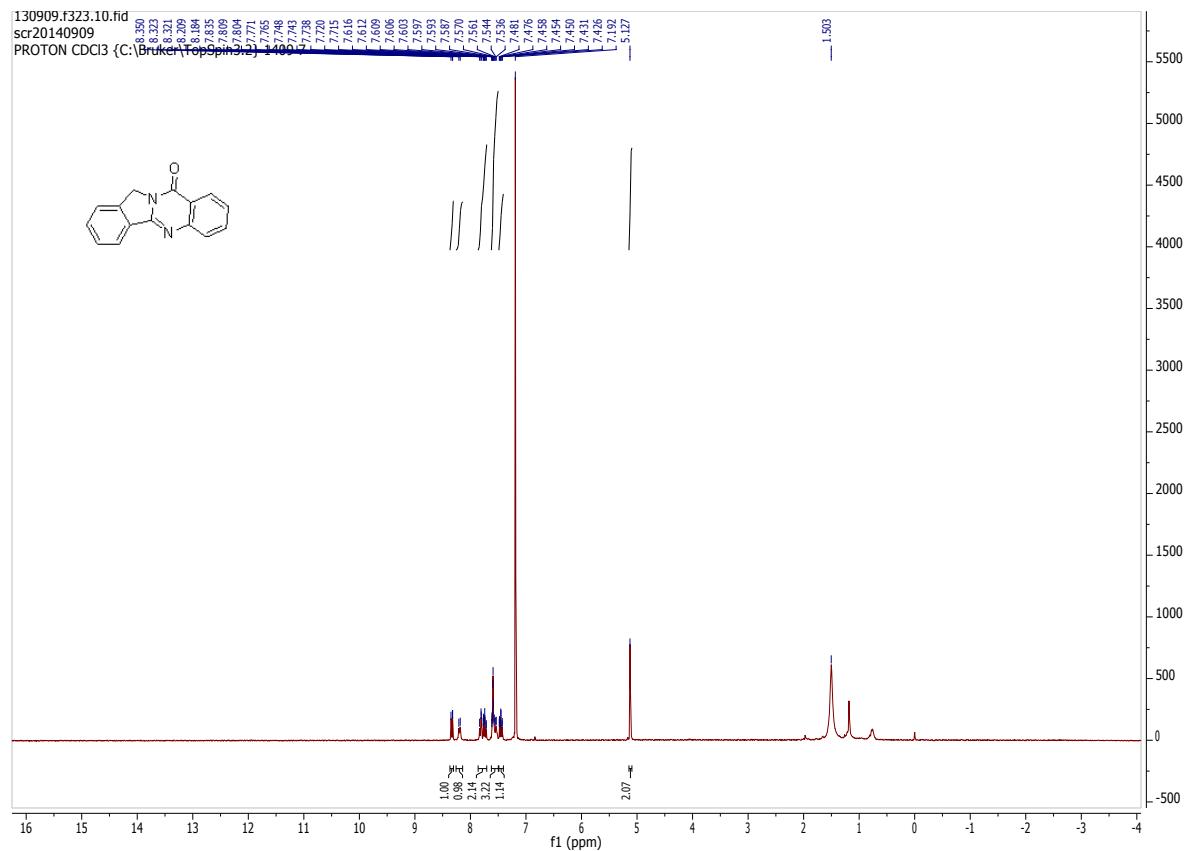
¹³C NMR (75 MHz, CDCl₃): δ = 165.45 (d, *J* = 251.3 Hz), 160.44, 154.03, 145.45, 142.03 (d, *J* = 10.5 Hz), 128.83, 128.81, 128.15, 127.07, 126.34, 125.59 (d, *J* = 9.0 Hz), 117.96, 116.99 (d, *J* = 24.0 Hz), 111.00 (d, *J* = 24.8 Hz), 49.54 (d, *J* = 3.0 Hz), 21.96.

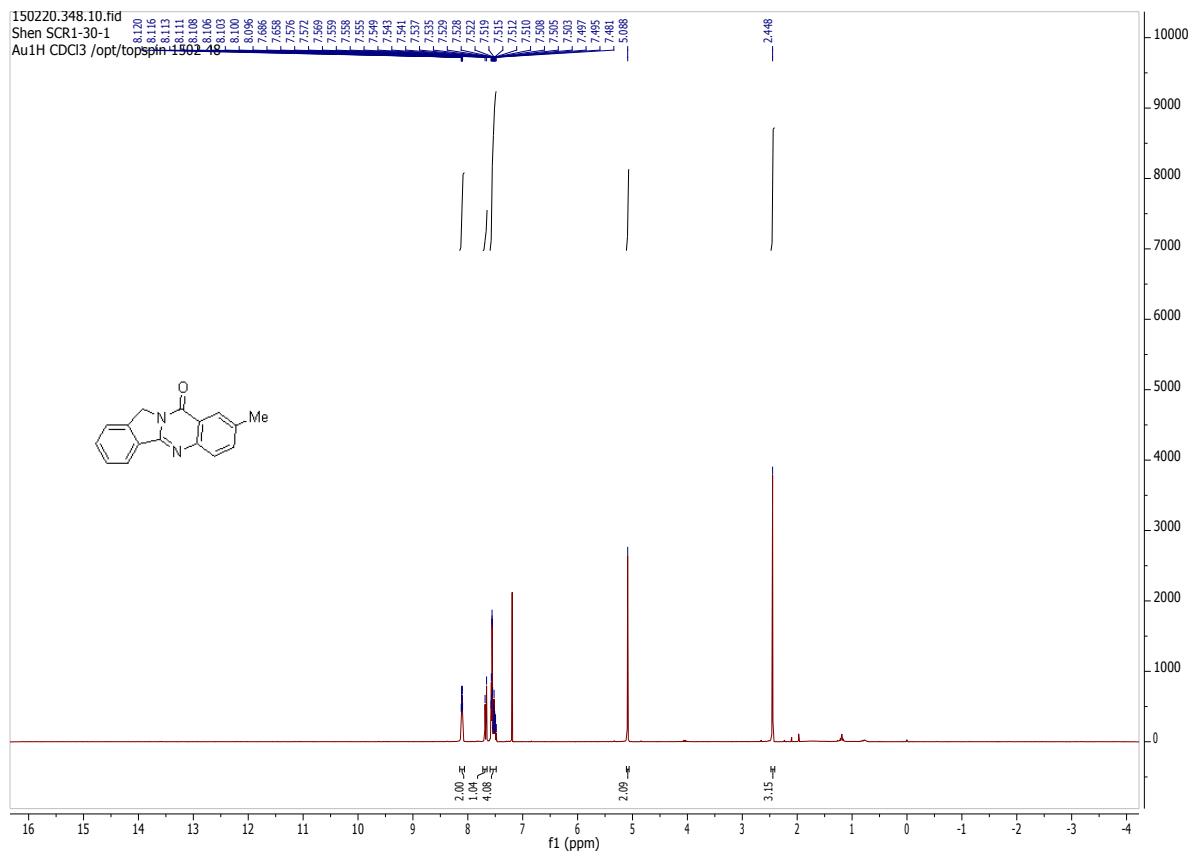
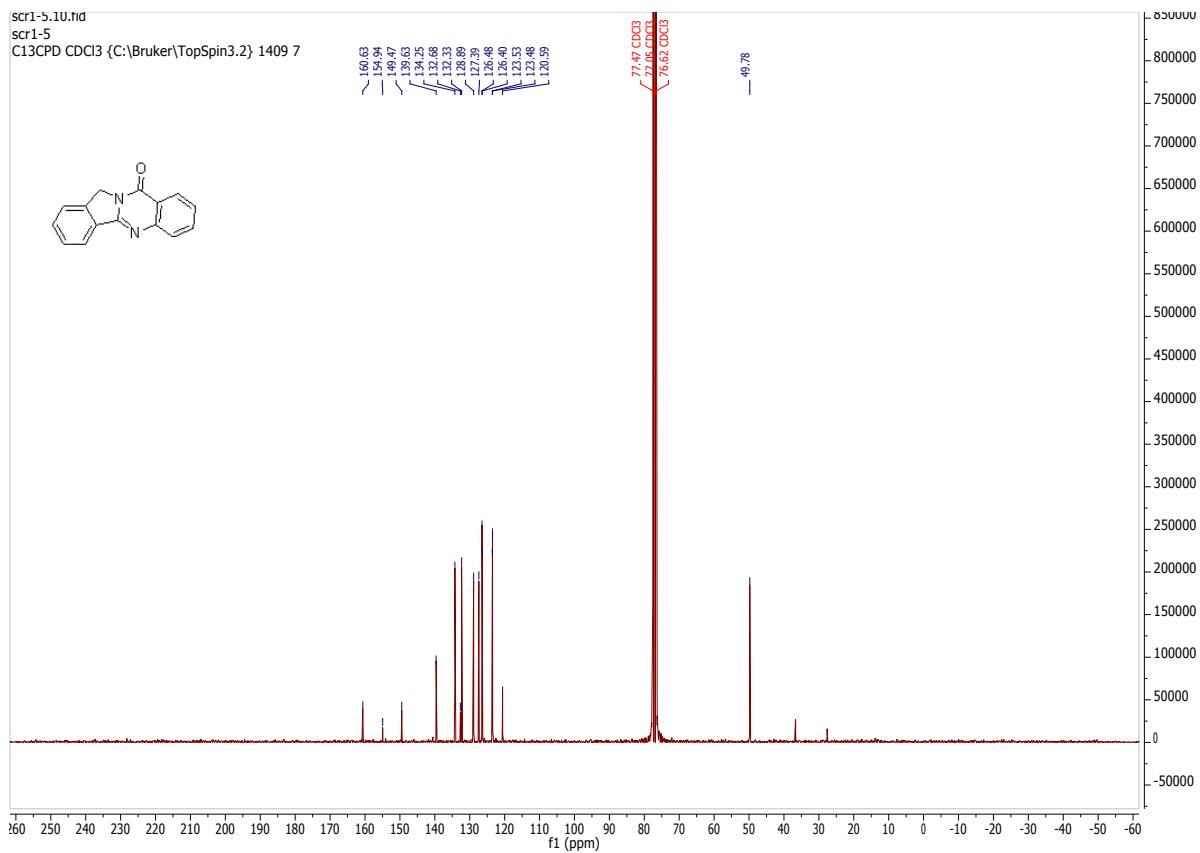
¹⁹F NMR (282 MHz, CDCl₃): δ = -105.11.

GC-MS (EI, 70eV): m/z (%) = 266 (M⁺, 100), 251 (13), 237 (12), 223 (9), 120 (9).

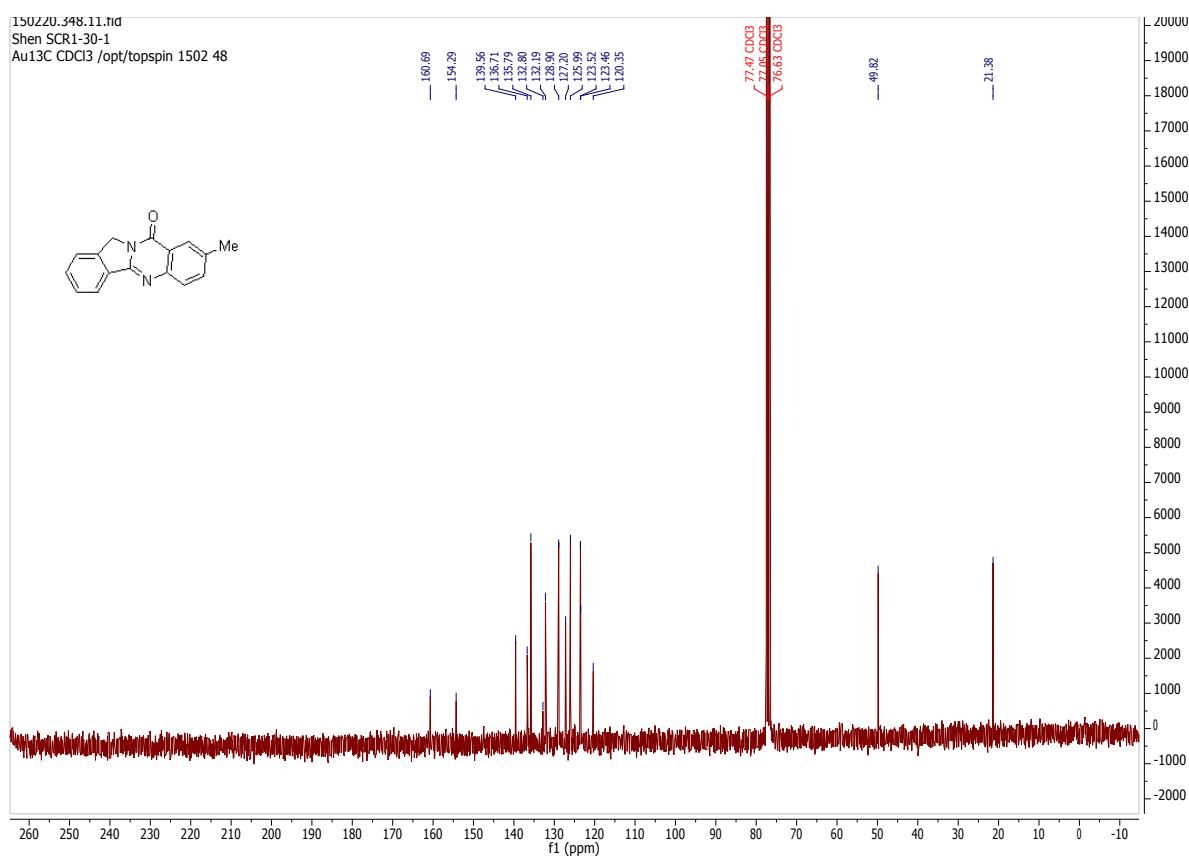
HRMS (EI): caclcd. for [C₁₆H₁₁O N₂F]⁺ 266.08554, found 266.08563.

5. Spectrum Copies

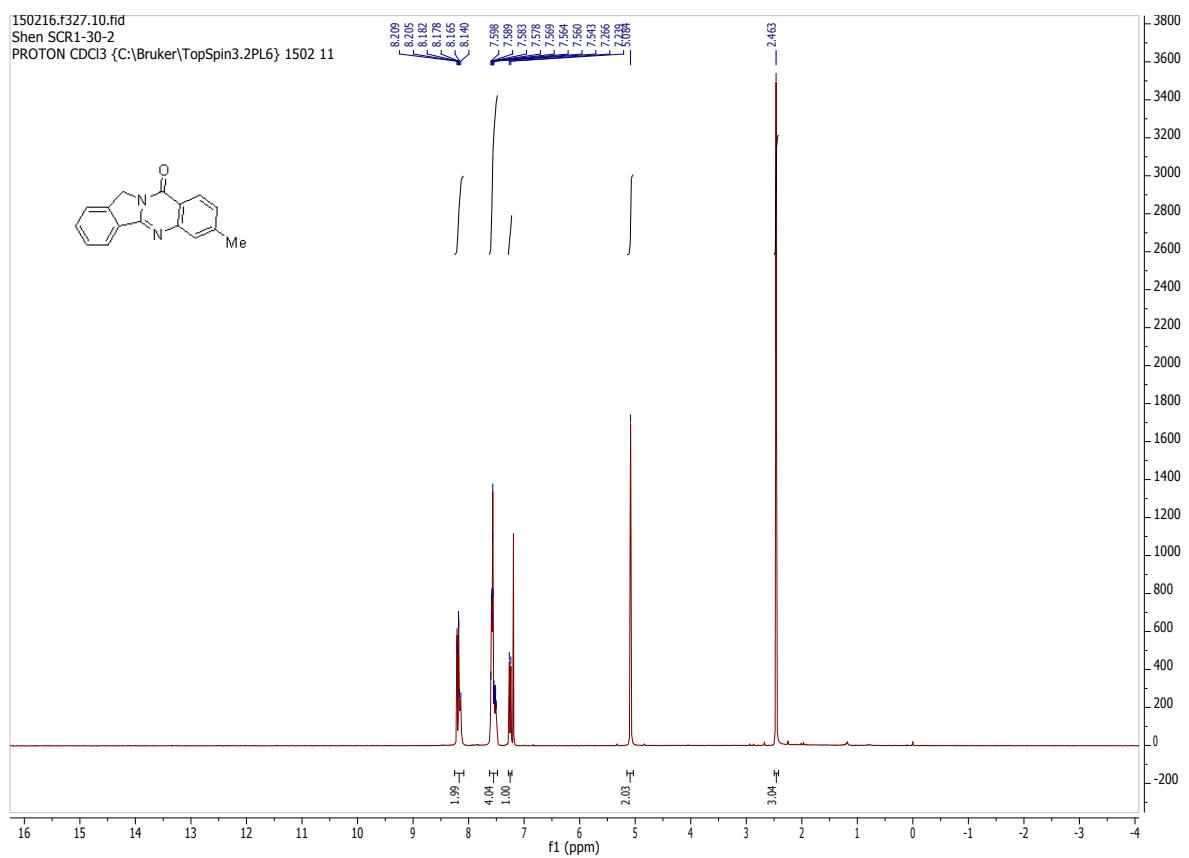


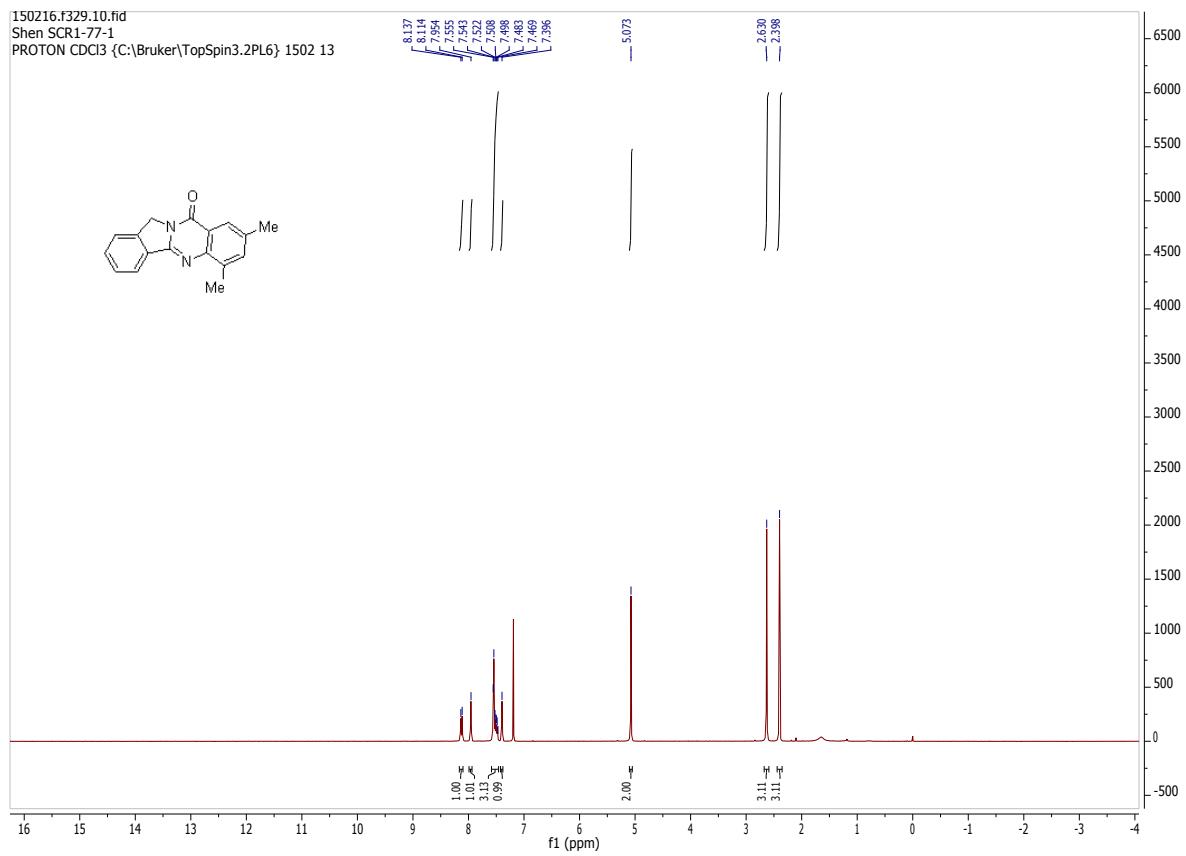
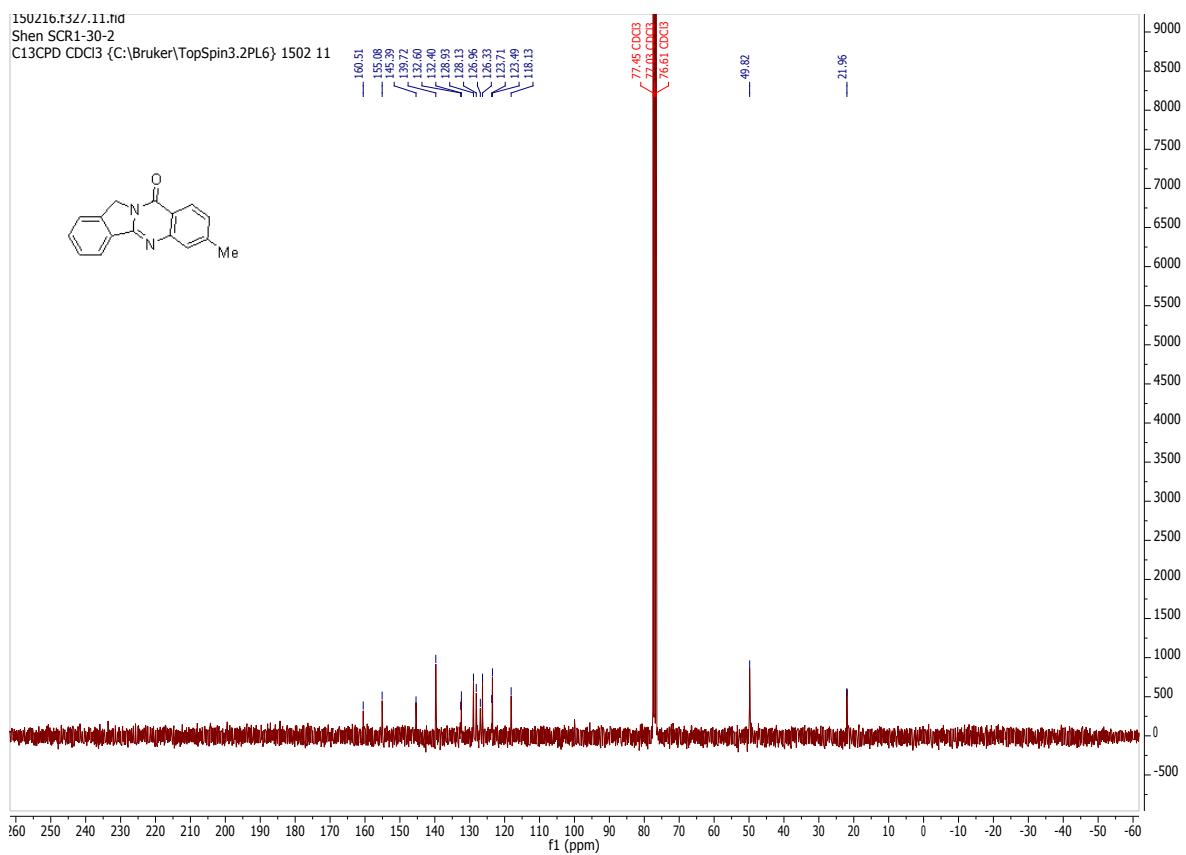


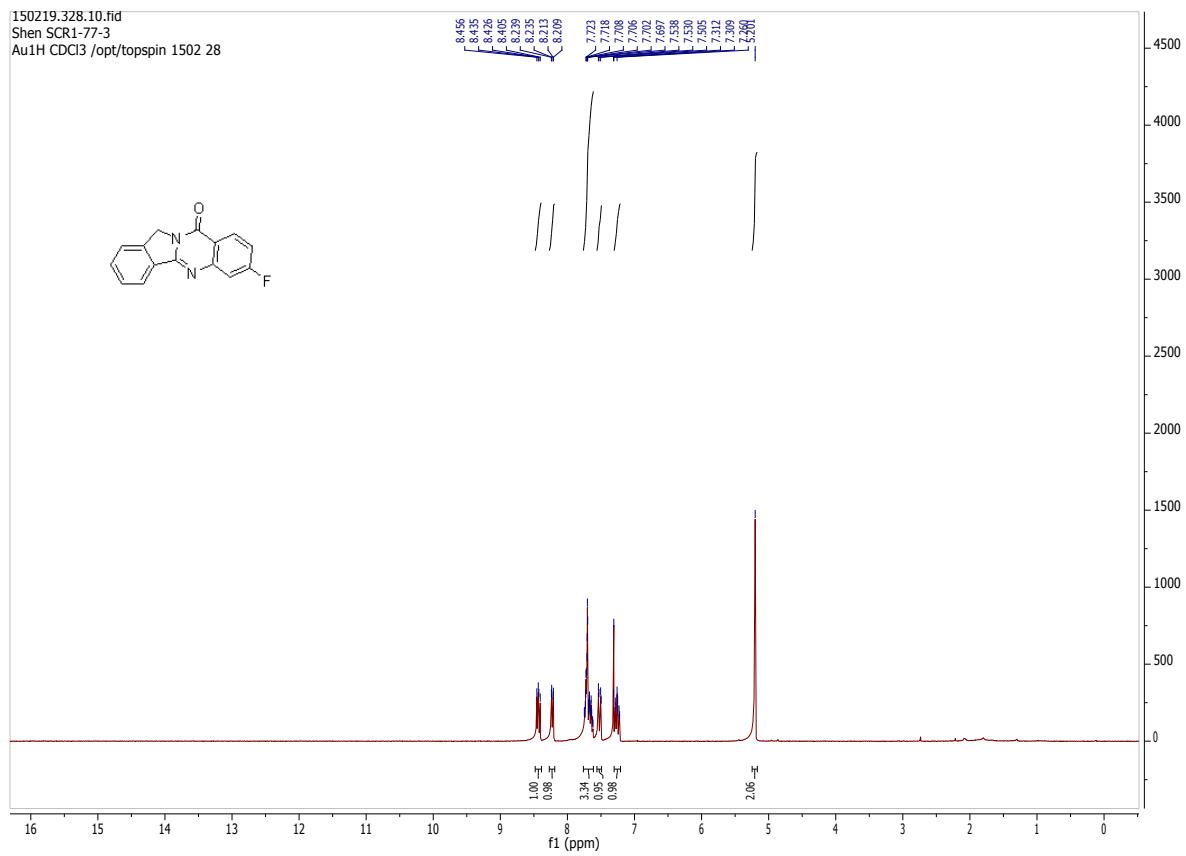
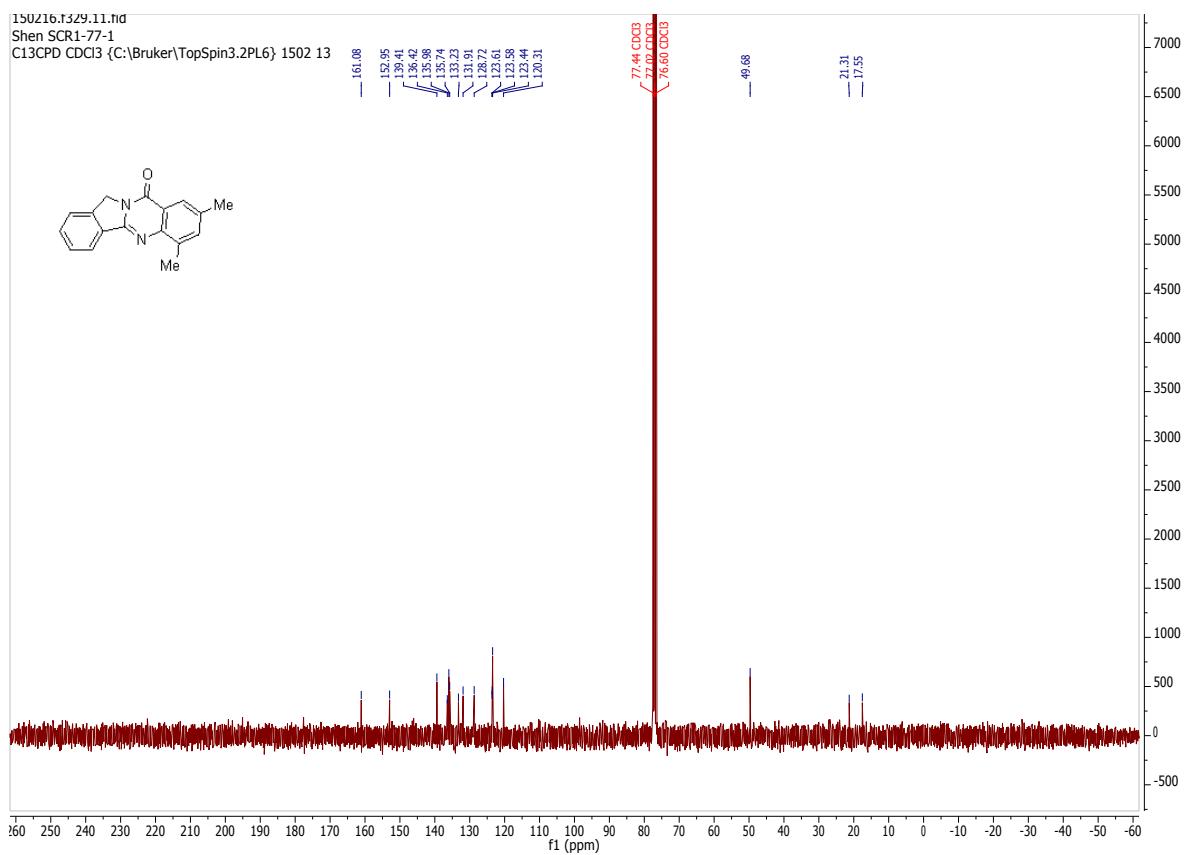
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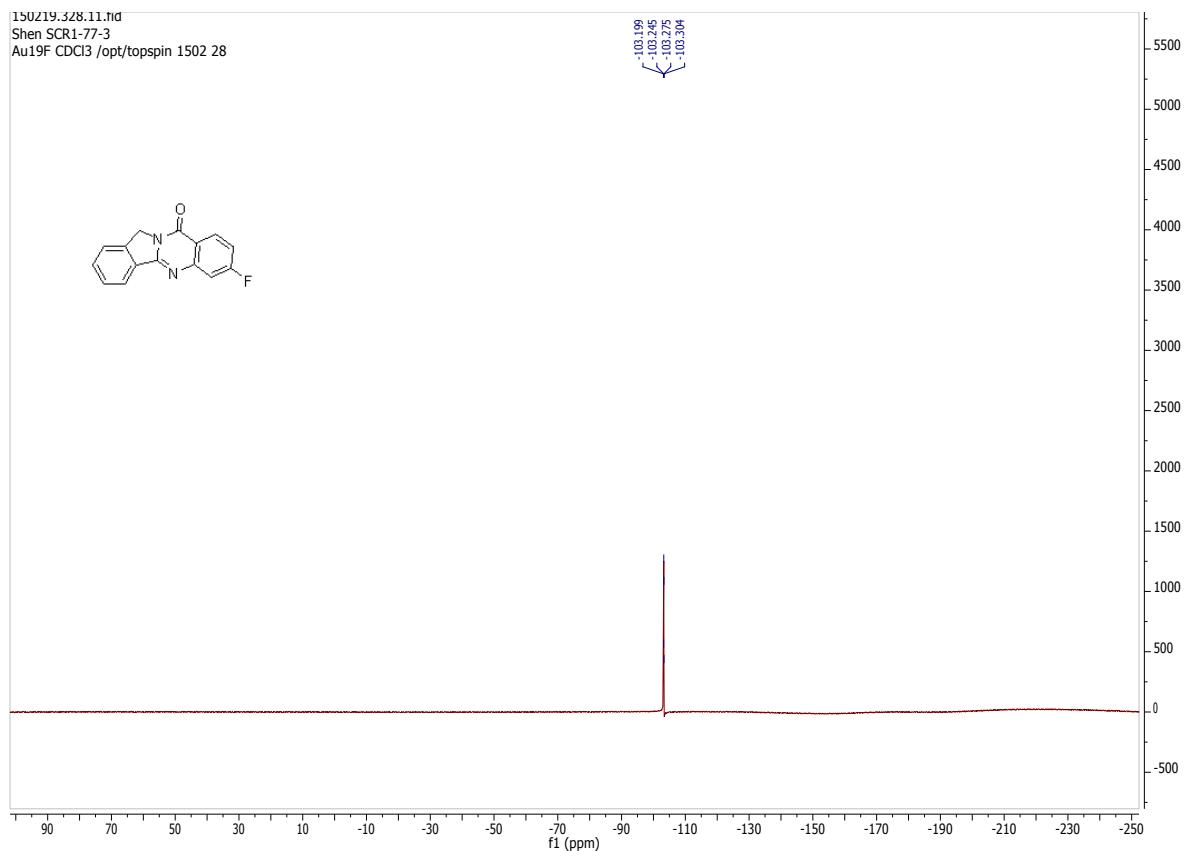
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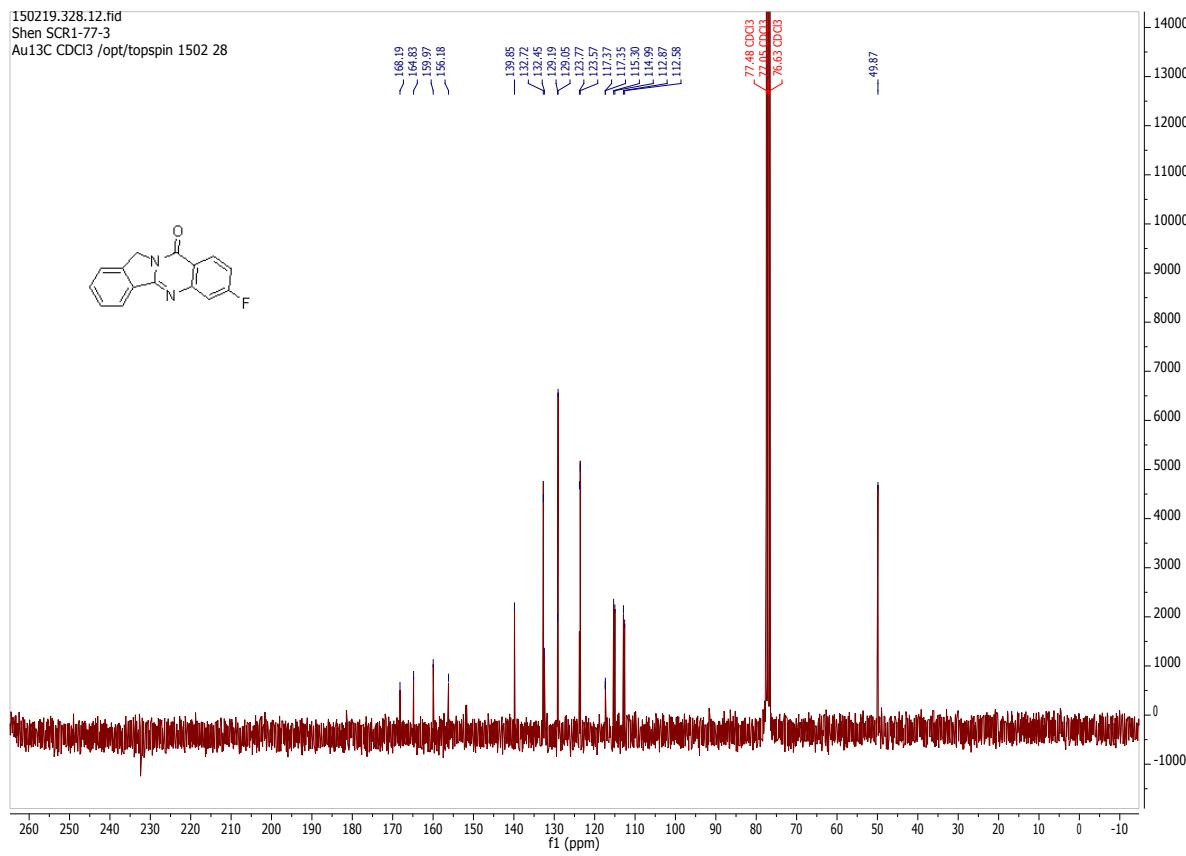


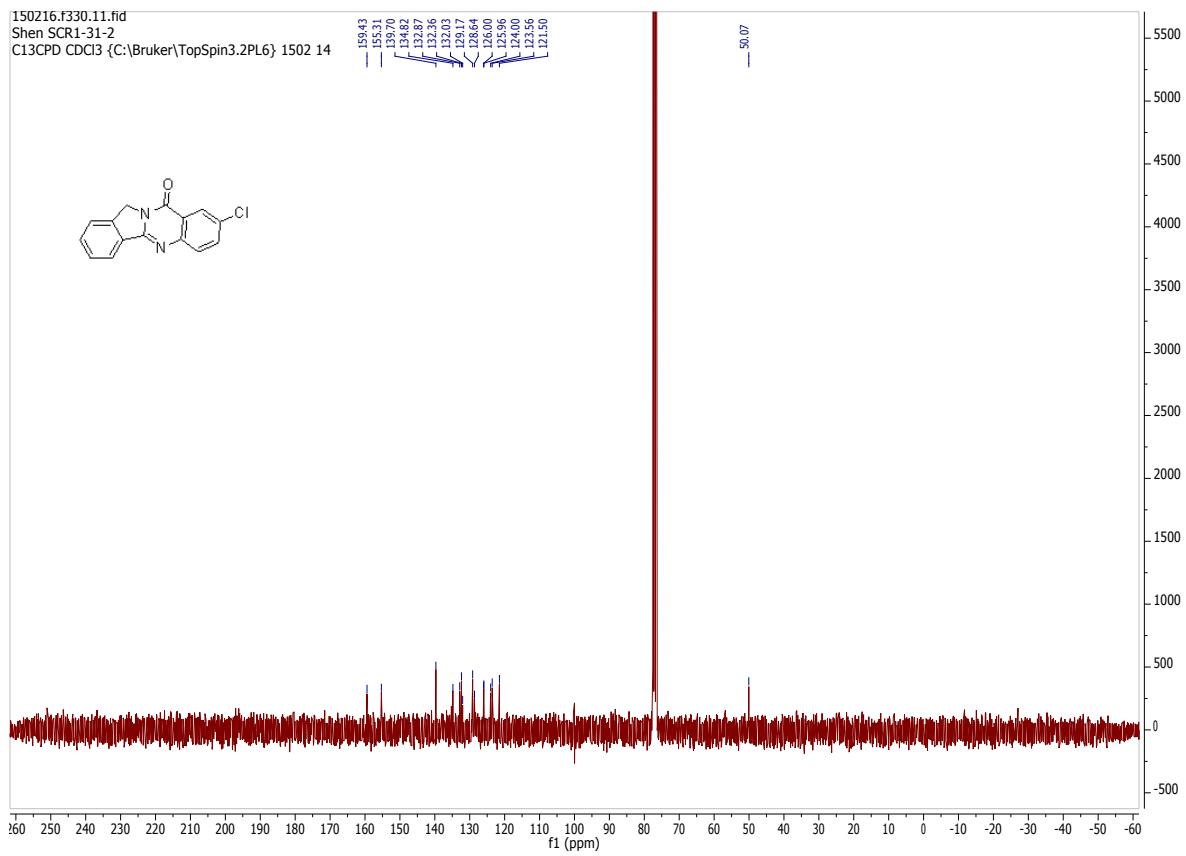
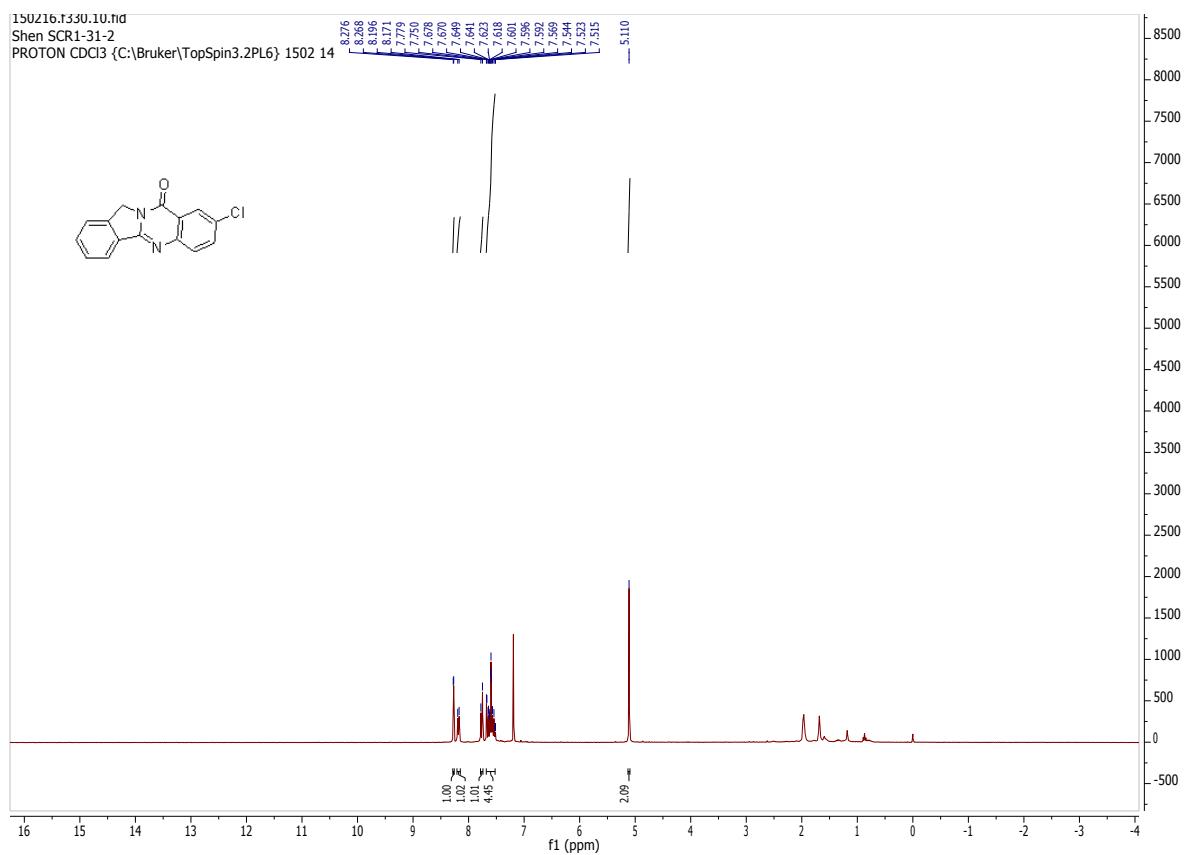


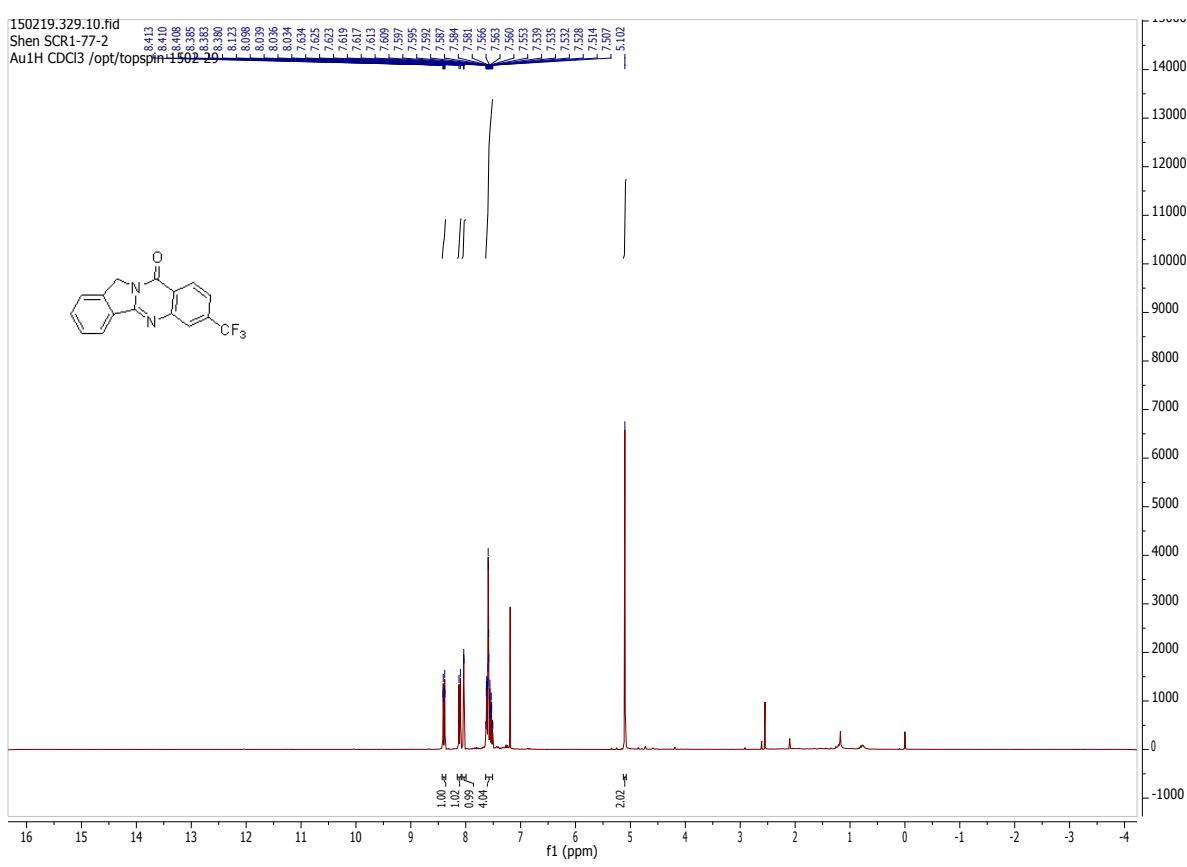
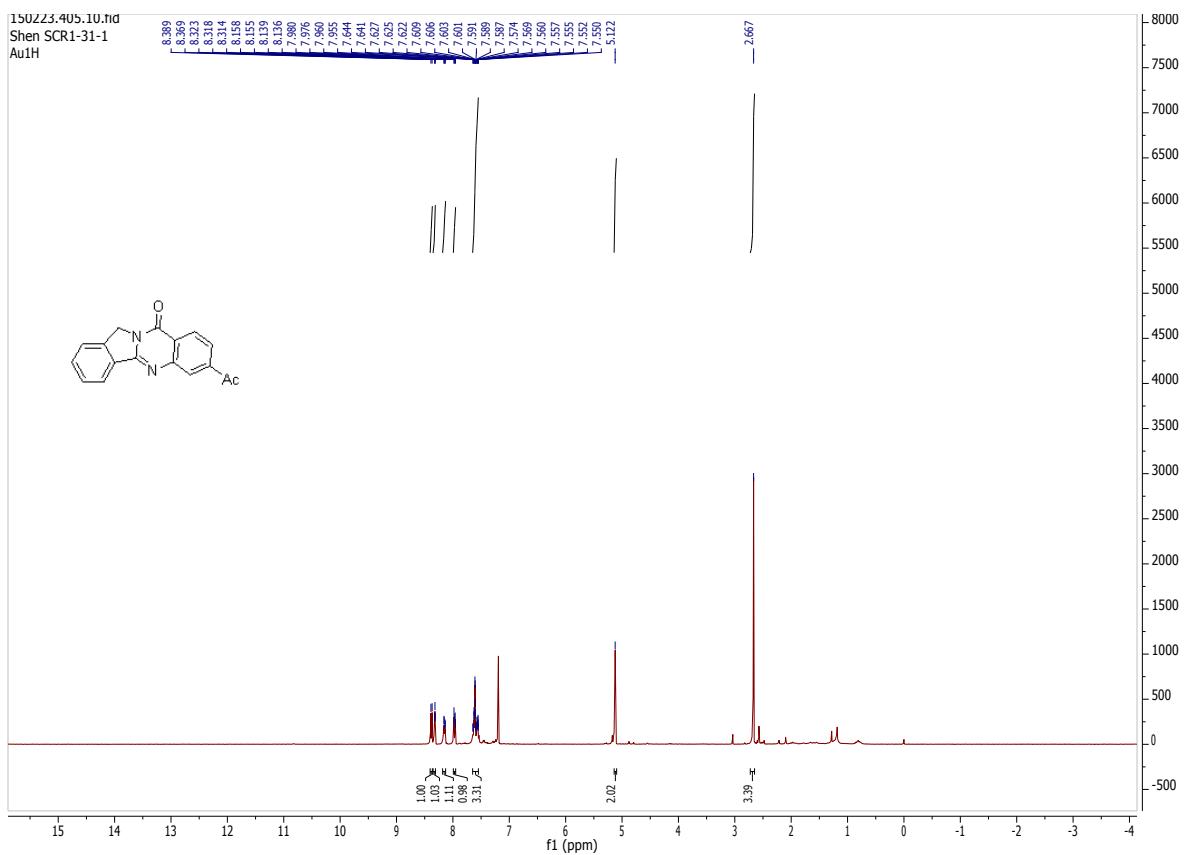
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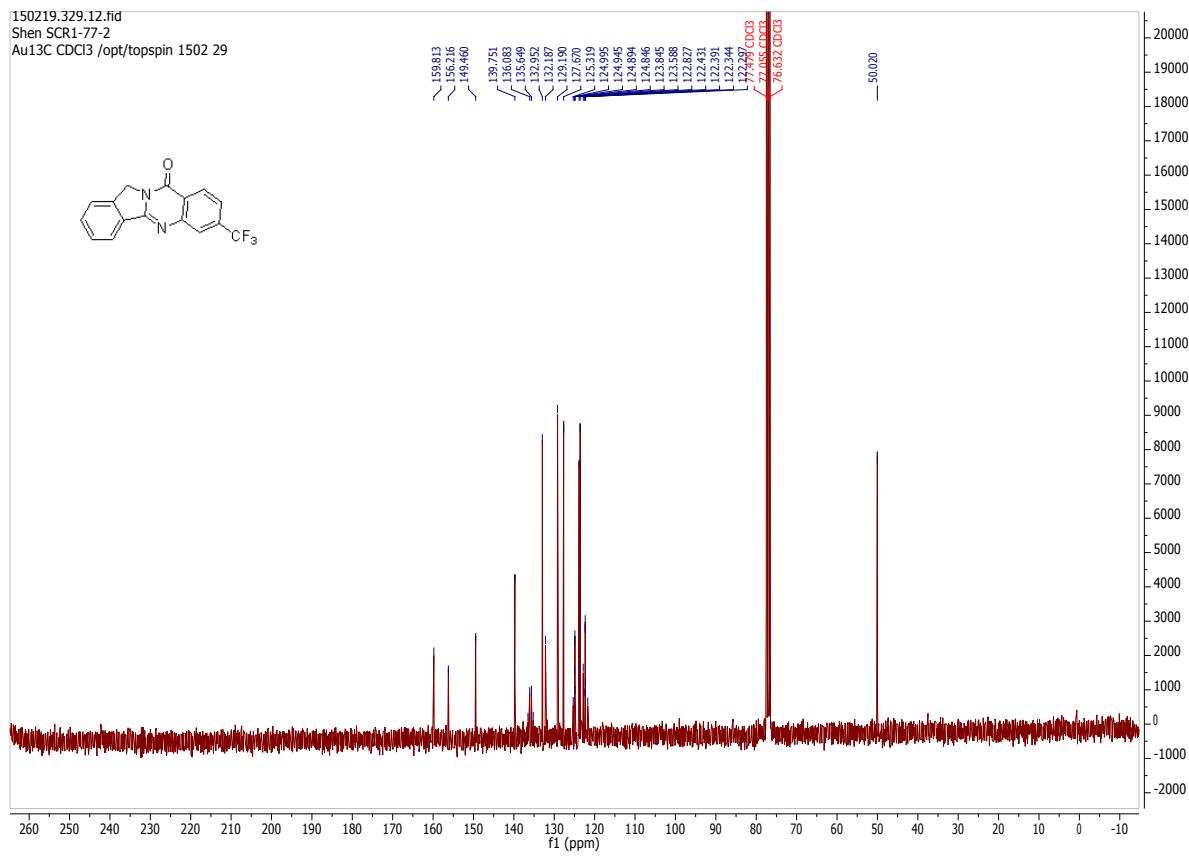
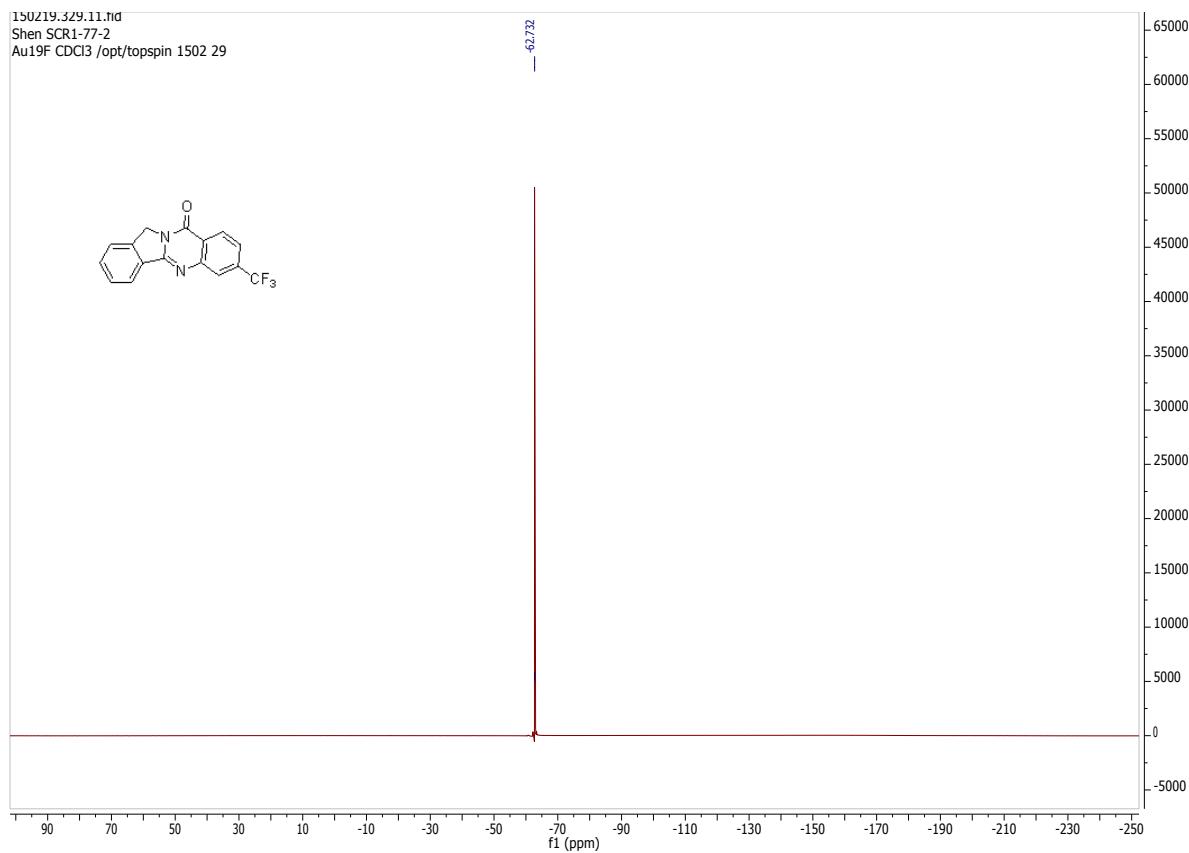


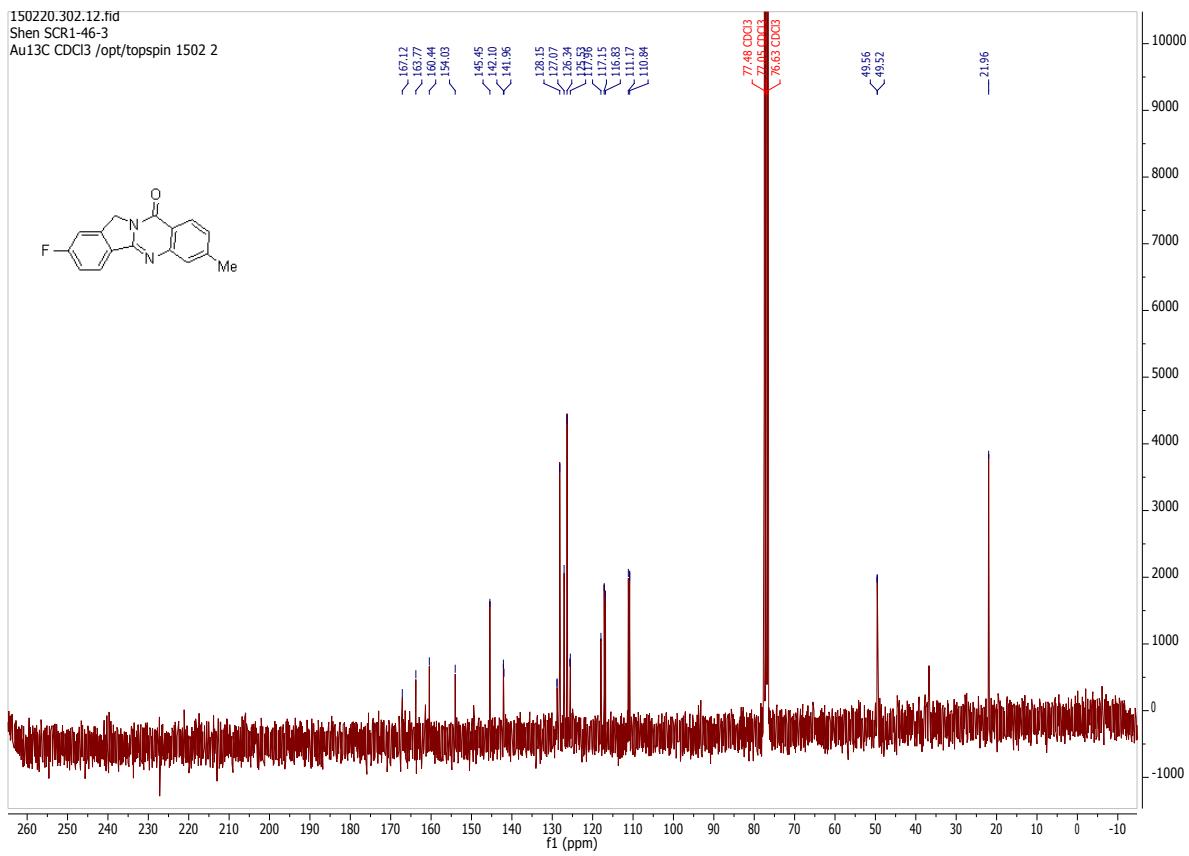
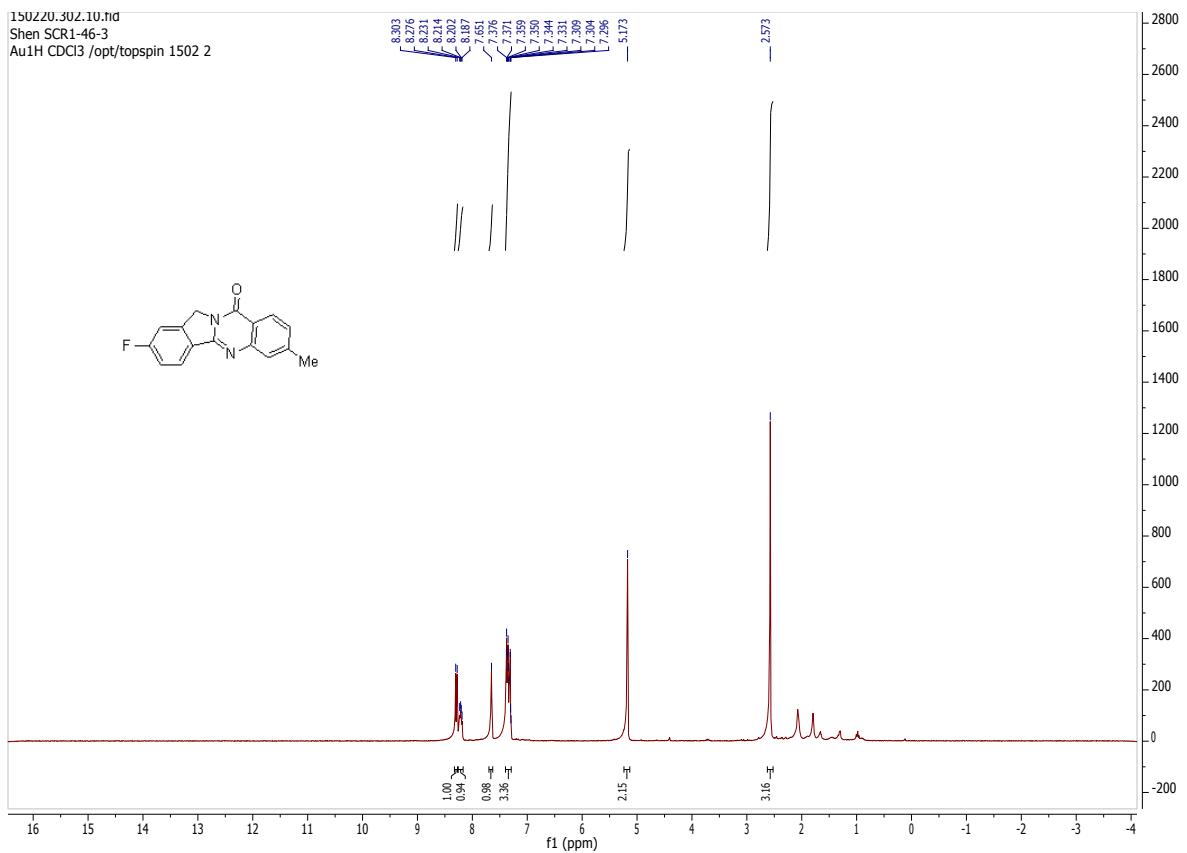
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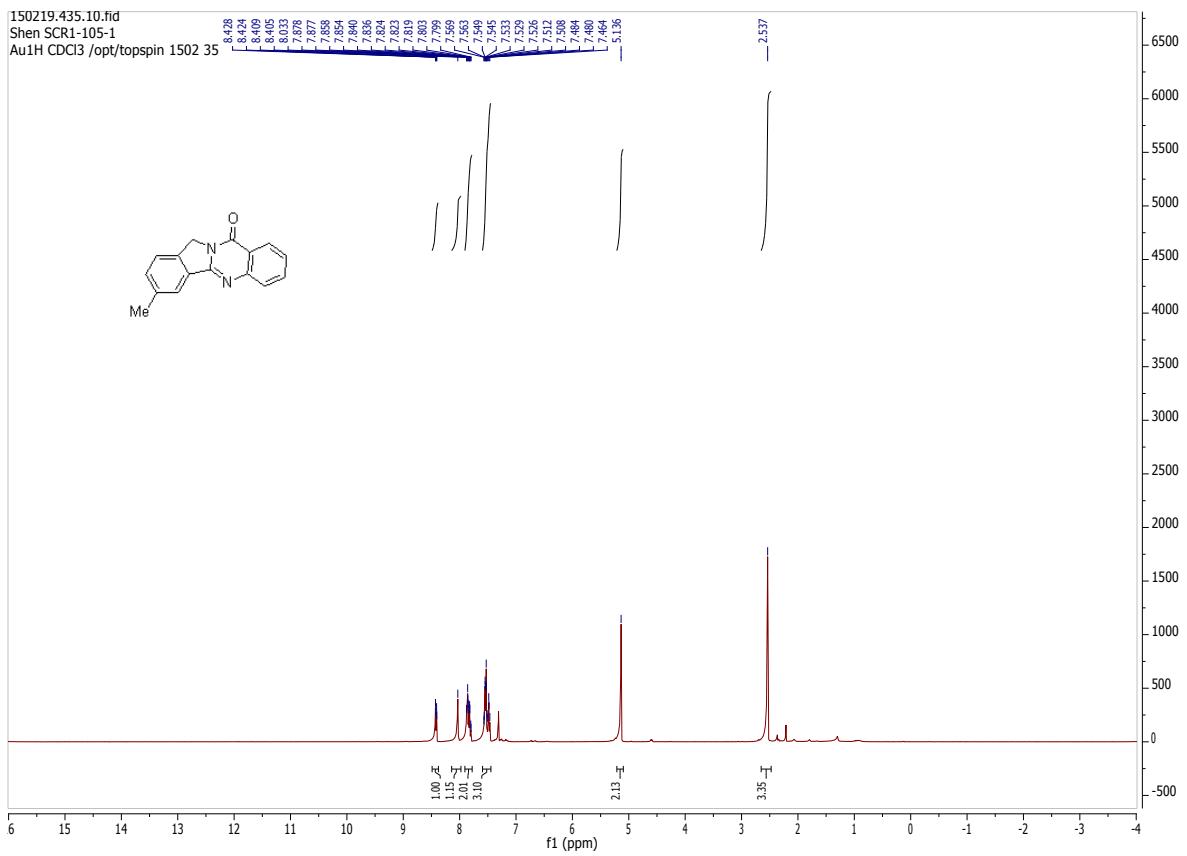
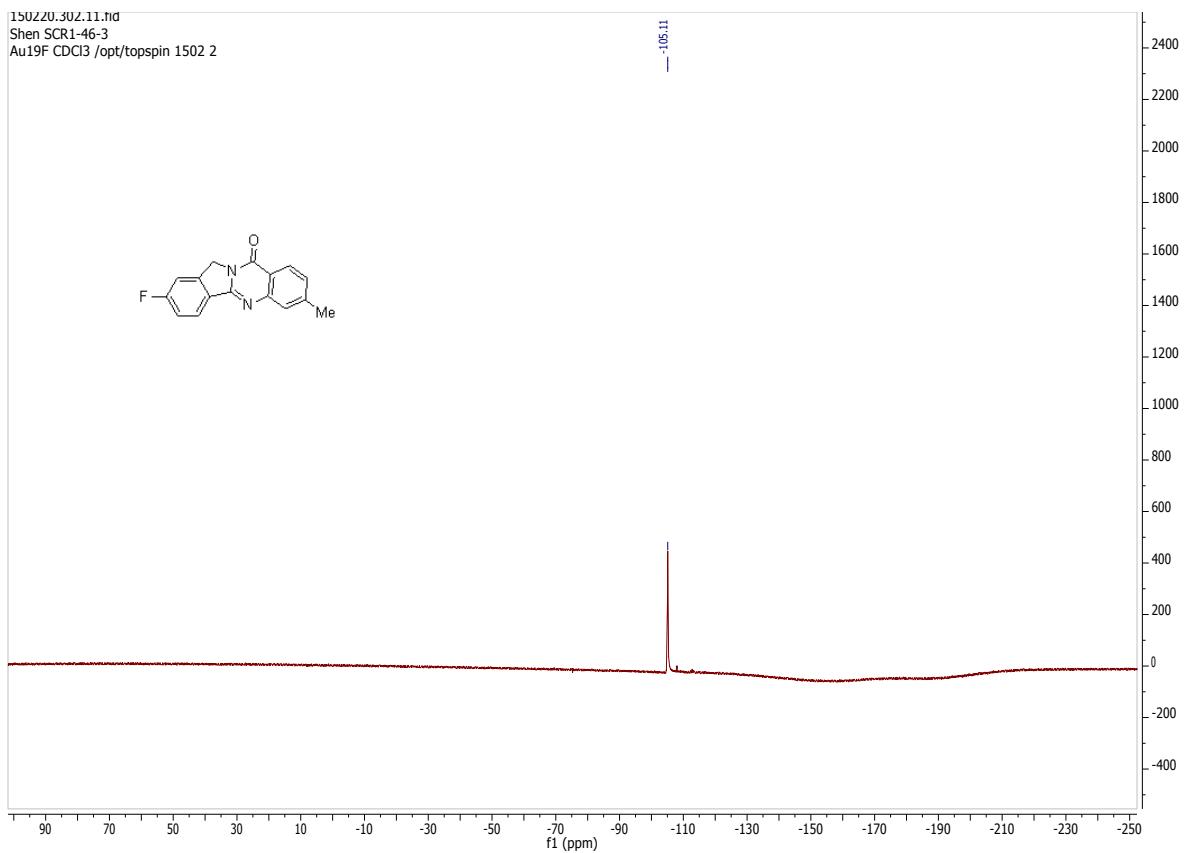


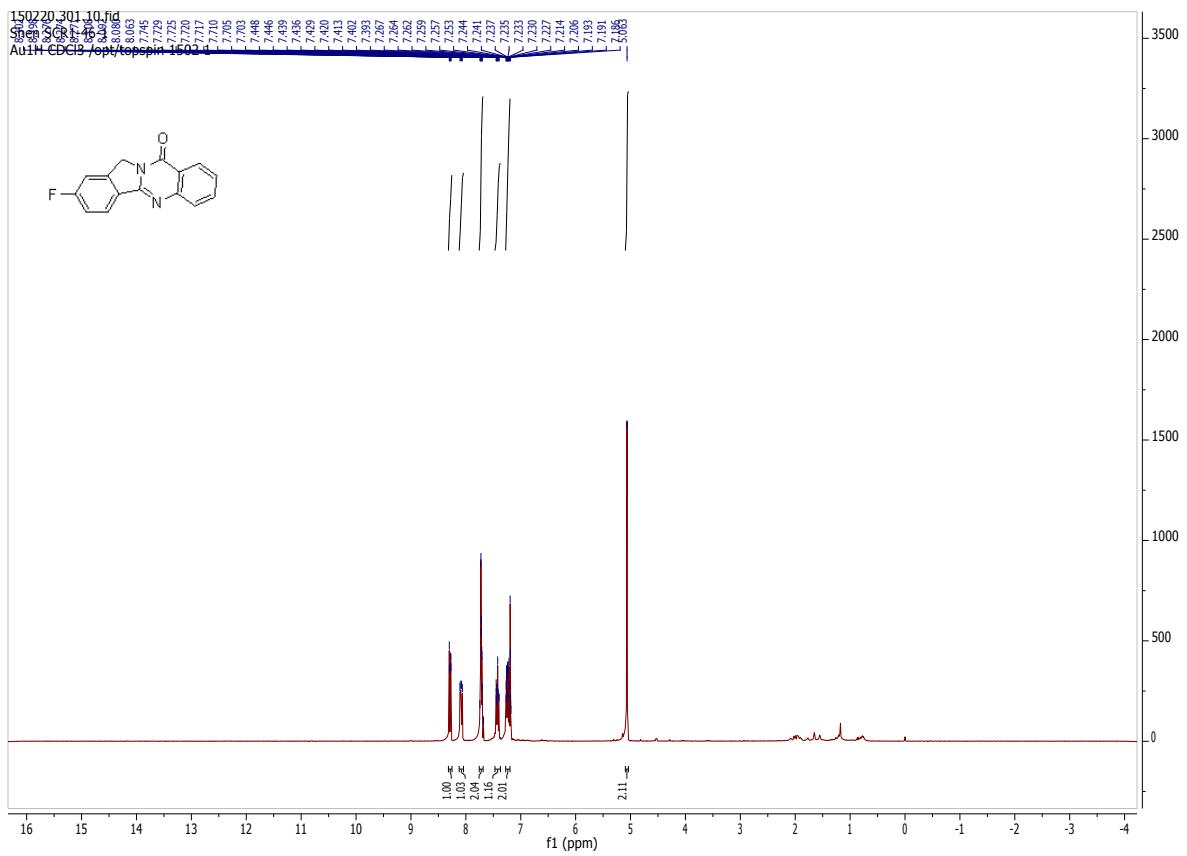
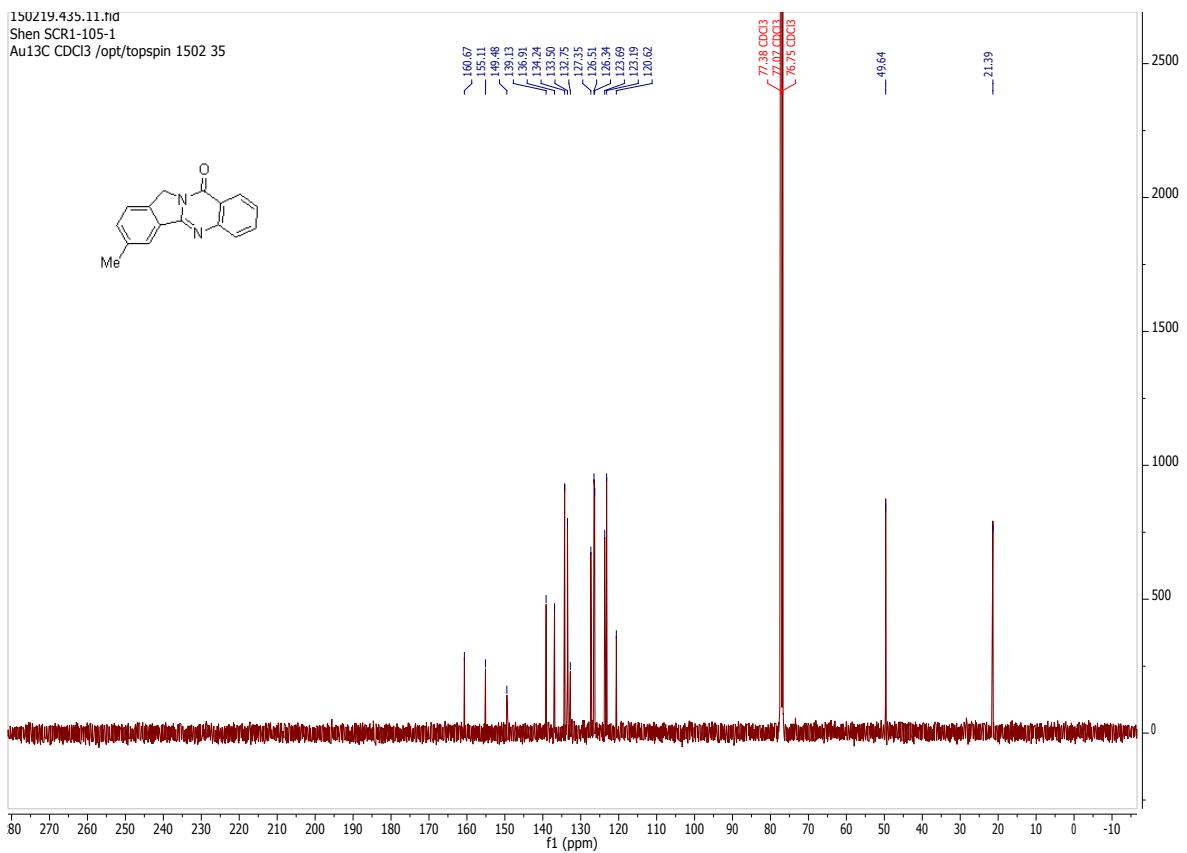


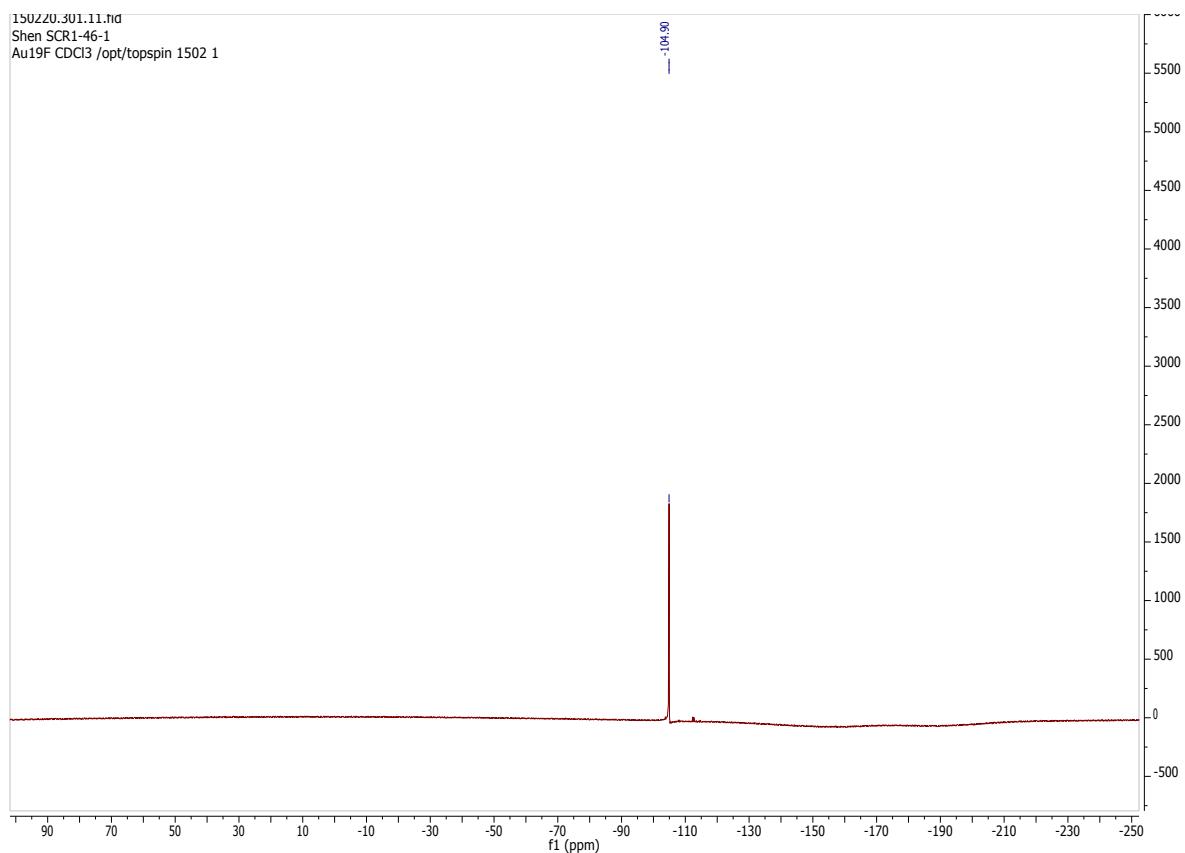












6. Reference

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