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External oxidant-free oxidation/[3+2] cycloaddition/ aromatization cascade: electrochemical synthesis of polycyclic N-heterocycles

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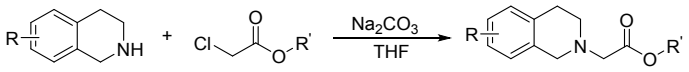
Contents

General Methods

All reactions were carried out under atmospheric conditions with dry solvents unless otherwise stated. Reagents and solvents were purchased commercially and used directly as received. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Advance 400 or 600 instrument. The chemical shifts (δ) were given in part per million and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm ^{1}HNMR, 77.2 ppm ^{13}C NMR). Multiplicities were reported by use of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. High–resolution mass spectra (HRMS) were recorded on an Agilent LCMS TOF mass spectrometer by electrospray positive ionization time-of-flight (ESI-TOF) reflectron experiments.

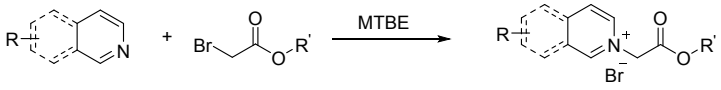
1. General Methods for the Preparation of substrates

1.1 Synthesis of 2-(3,4-Dihydroisoquinolin-2-yl)acetates[1]



A 200 mL round bottom flask was charged with 1,2,3,4-tetrahydroisoquinoline (10.0 mmol),Na_2CO_3 (12.0 mmol) and THF (60 mL). After stirring for 5 minutes, 2-chloroacetate (11.0 mmol) was added slowly. The mixture was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc/PE as the eluent to give corresponding products.

1.2 Synthesis of Pyridinium and Isoquinolinium Salts



Pyridine or isoquinoline (10 mmol) was dissolved in 20 mL methyl tert-butyl ether (MTBE) in a 100 mL round bottom flask. After stirring for 5 min, bromoacetate (15 mmol) was added dropwise over 10 min. The resulting mixture was stirred at room temperature for 12 h. The precipitate was filtered and washed by MTBE (5 mL × 3), dried in vacuum to afford the corresponding products.

2. General Procedure for the Electrochemical Oxidative Cascade Reaction

2.1 Synthesis of 4-43

Table S1. Optimization of the conditions for the electrochemical cascade reaction[a]

1 2 3 4

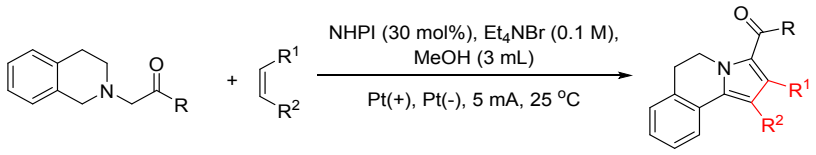
Entry	Catalyst	Electrolyte	Anode/cathode	Solvent	Yield (%)[b] **3**/**4**
1	-	$LiClO_4$	Pt(+)/Pt(-)	MeOH	13/ trace
2	-	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	25/trace
3	LiBr	$LiClO_4$	Pt(+)/Pt(-)	MeOH	20/trace
4	TEMPO	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	52/trace
5	NHPI	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	11/62
6	NHPI	$^nBu_4NI$	Pt(+)/Pt(-)	MeOH	23/45
7	NHPI	$^nBu_4NBF_4$	Pt(+)/Pt(-)	MeOH	21/26
8	NHPI	Et_4NBr	Pt(+)/Pt(-)	MeOH	trace/83
9	TEMPO	Et_4NBr	Pt(+)/Pt(-)	MeOH	51/trace
10	-	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	27/trace
11	NHSI	Et_4NBr	Pt(+)/Pt(-)	MeOH	20/16
12	NHPI	Et_4NBr	C(+)/C(-)	MeOH	16/61
13	NHPI	Et_4NBr	Pt(+)/C(-)	MeOH	trace/63
14	NHPI	Et_4NBr	Pt(+)/Fe(-)	MeOH	trace/71
15	NHPI	Et_4NBr	Pt(+)/Ni(-)	MeOH	trace/77
16	NHPI	Et_4NBr	Pt(+)/Pt(-)	CH_3CN	26/43
17	NHPI	Et_4NBr	Pt(+)/Pt(-)	THF	21/33
18[c]	NHPI	Et_4NBr	Pt(+)/Pt(-)	MeOH	trace/79
19[d]	NHPI	Et_4NBr	Pt(+)/Pt(-)	MeOH	trace/trace

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.26 mmol), catalyst (0.06 mmol), electrolyte (0.3 mmol), solvent (3 mL), undivided cell, 25 °C, 12 h. [b] Isolated yield. [c] Under N_2. [d] No electricity.

With $LiClO_4$ or Bu_4NBr as the electrolyte in a simple undivided cell under 5 mA constant current for 12 h, the oxidation/ [3 + 2] cycloaddition occurred and afforded the nonaromatic heterocycle **3** albeit in poor yields (Table S1, entries 1, 2). We speculated that the methine in **3** may have high redox potentials, thus subsequent oxidative dehydrogenation of the desired C−H bonds might be problematic under direct electrolysis condition. To circumvent the problem, the redox mediator

mediated electrochemical oxidation was applied for the accomplishment of the oxidation/ [3 + 2] cycloaddition/ aromatization cascade reaction. Hopefully, the redox mediator could be oxidized anodically to generate a reactive species, which could facilitate further oxidative aromatization.[1] To our delight, although the mediators such as LiBr and TEMPO showed no reactivity at all, NHPI (*N*-hydroxyphthalimide) provided the desired product **4** in promising yields (entries 3-5). However, structurally similar NHSI (*N*-Hydroxysuccinimide) gave a much inferior result (entry 11). An extensive study found Et_4NBr was the optimal and inexpensive electrolyte, which was able to realize the oxidative aromatization of **3** and afford **4** in 83% yield (entries 5-10). Other electrode materials were also examined. Graphite, iron and nickel were found to be inferior in efficiency to platinum, which provide good current efficiency and sufficient corrosion resistance (entries 12-15). The protic solvent MeOH was the most efficient as compared with CH_3CN (entry 16) and THF (entry 17), which resulted in lower yields. It should be mentioned that NHPI/O_2 system has been widely used in the aerobic activation of hydrocarbons. However, good yield was still observed under inert atmosphere (entry 18), which indicated atmospheric oxygen may not act as the terminal oxidant. Consequently, the final optimal reaction conditions were established as electrolyzing **1** and **2** in the presence of 30 mol% NHPI in an undivided cell with a supporting electrolyte solution of Et_4NBr (0.1 M in MeOH) under 5 mA constant currentin the air. In addition, the control experiment carried out in the absence of electricity showed the catalyst system was totally inactive, demonstrating the pivotal role of the electricity (entry 19).

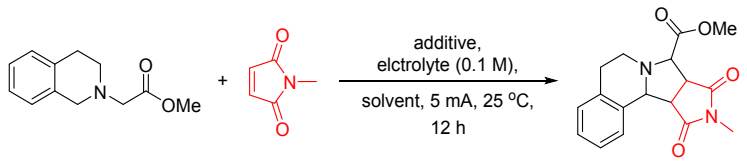
Procedure for the Synthesis of 4 - 43



A 10 mL three necked round bottom flask installed with two platinum electrodes (1.0 x 1.0 cm^2) as the cathode and anode respectively was used as the electrochemical reactor. Without any precaution to exclude air or moisture, the falsk was charged with 2-(3,4-dihydroisoquinolin-2(1*H*-yl)acetate (0.2 mmol, 1 equiv.), dipolarophile (0.26 mmol, 1.3 equiv.), NHPI (0.06 mmol, 0.0098 g), Et_4NBr (0.3 mmol, 0.0630 g) and MeOH (3 mL). After being stirred for 5 minutes, the reaction mixture was electrolyzed under a constant current of 5 mA (the cell voltage ranges from 2.2 to 3.5 V without reference electrode) at 25 °C for 12 h. Then the solvent was removed in vacuum, and the residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to afford the desired product.

2.2. Synthesis of 3

Table S2. Optimization Reaction Conditions for the Synthesis of 3[a]



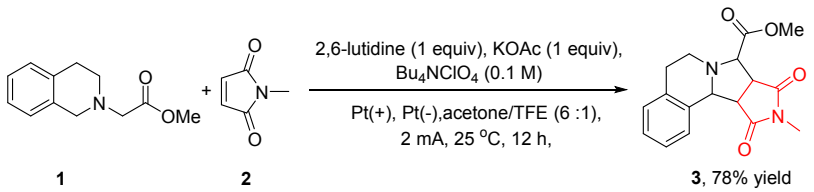
1 2 3

entry	Additive (equiv.)	electrolyte	anode/cathode	solvent	yield (%)[b]
1	-	$LiClO_4$	Pt(+)/Pt(-)	MeOH	13
2	-	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	25
3	LiBr (0.3)	$LiClO_4$	Pt(+)/Pt(-)	MeOH	20
4	TEMPO (0.3)	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	52
5	NHPI (0.3)	$^nBu_4NBr$	Pt(+)/Pt(-)	MeOH	11
6	NHPI (0.3)	$^nBu_4NI$	Pt(+)/Pt(-)	MeOH	23
7	NHPI (0.3)	$^nBu_4NBF_4$	Pt(+)/Pt(-)	MeOH	21
8	KOAc (1.0)	Et_4NBr	Pt(+)/Pt(-)	MeOH	39
9	2,6-lutidine (1.0)	Et_4NBr	Pt(+)/Pt(-)	MeOH	53
10	2,6-lutidine (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	MeOH	57
11	2,6-lutidine (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	acetone	65
12	2,6-lutidine (1.0), KOAc (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	acetone/MeOH (6 :1)	70
13	2,6-lutidine (1.0), KOAc (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	acetone/TFE (6 :1)	73
14	2,6-lutidine (1.0), KOAc (1.0)	Et_4NClO_4	Pt(+)/Pt(-)	acetone/TFE (6 :1)	65
15[c]	2,6-lutidine (1.0), KOAc (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	acetone/TFE (6 :1)	78
16	2,6-lutidine (1.0), KOAc (1.0)	Bu_4NClO_4	C(+)/C(-)	acetone/TFE (6 :1)	57
17[d]	2,6-lutidine (1.0), KOAc (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	acetone/TFE (6 :1)	trace

[a] Reaction conditions : undivided cell, **1** (0.2 mmol), **2** (0.26 mmol), additive, electrolyte (0.3 mmol), solvent (3 mL) , constant current, 25 °C, 12h. [b] Isolated yield. [c] Constant current was 2 mA. [d] Without electricity.

The final optimal reaction conditions were established as electrolyzing **1** and **2** in the presence of 2,6-lutidine (1.0 equiv.) and KOAc (1.0 equiv.) in an undivided cell equipped with Pt plate cathode and anode with a supporting electrolyte solution of $^nBu_4NClO_4$ (0.1 M in acetone/TFE = 6 :1) under 2 mA constant current under atmospheric conditions (Table S2, entry 15).

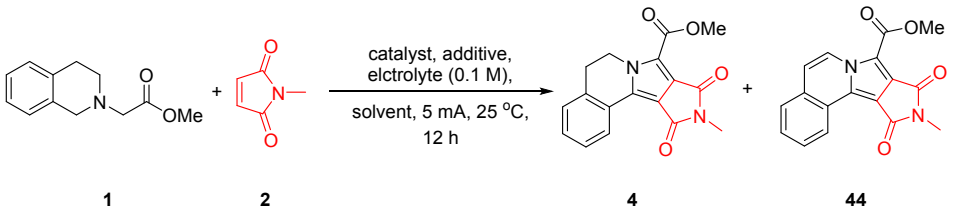
Procedure for the Synthesis of 3



A 10 mL three necked round bottom flask which was charged with a stir bar and installed platinum electrodes (1.0 x 1.0 cm^2) as the cathode and anode respectively was used as electrolysis setup. With no precautions to exclude air or moisture, the device was charged sequentially with methyl 2-(3,4-dihydroisoquinolin-2(1H-yl)acetate **1** (0.2 mmol, 0.0410 g), *N*-methylmaleimide (0.26 mmol, 0.0289 g), 2,6-lutidine (0.2 mmol, 0.0215 g), KOAc (0.2 mmol, 0.0196 g), $^{n}Bu_4NClO_4$ (0.3 mmol, 0.1025 g) and mixed solvent of acetone/TFE (6 :1, 3 mL). After being stirred for 5 minutes, the reaction mixture was electrolyzed under a constant current of 2 mA (the cell voltage ranges from 2.0 to 2.8 V without reference electrode) at 25 °C for 12 h. Then the solvent was removed in vacuum, and the crude product was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to afford the **3** (49.0 mg, 78%).

2.3 Synthesis of 44 from 1

Table S3. Optimization Reaction Conditions for the Synthesis of **44** from **1**[a]



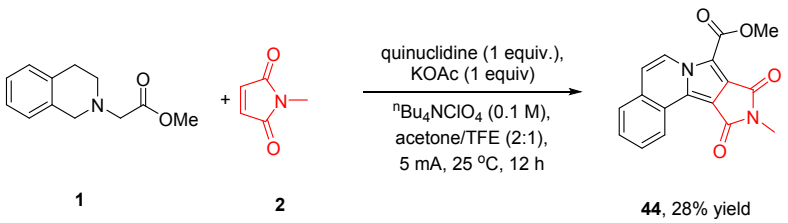
entry	Catalyst (equiv)	Additive (equiv)	electrolyte	anode/ cathode	solvent	yield (%)[b] **4**/**44**
1	Cl_4NHPI (0.3)	-	Et_4NBr	Pt(+)/Pt(-)	MeOH	76/trace
2	Cl_4NHPI (0.3)	-	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone	59/5
3	quinuclidine (0.3)	-	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone	62/13
4	quinuclidine (0.3)	pyridine (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone	66/15
5	quinuclidine (0.3)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone	71/18
6	quinuclidine (0.3)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone/TFE (2 :1)	53/22
7	quinuclidine (1.0)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone/TFE (2 :1)	55/28

8	quinuclidine (1.0)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone/MeOH (2 :1)	75/17
9	quinuclidine (1.0)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	DMF/TFE (2 :1)	61/25
10	TBPA (1.0)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone/MeOH (2 :1)	70/25
11[c]	quinuclidine (1.0)	KOAc (1.0)	$^{n}Bu_4NClO_4$	Pt(+)/Pt(-)	acetone/TFE (2 :1)	trace

[a] Reaction conditions : undivided cell, **1** (0.2 mmol), **2** (0.26 mmol), catalyst, additive, electrolyte (0.3 mmol), solvent (3 mL), constant current, 25 °C, 12h. [b] Isolated yield. [c] Without electricity. Cl_4NHPI = tetrachloro-*N*-hydroxyphthalimide; TBPA = tris(4-bromophenyl)amine.

The final optimal reaction conditions were established as electrolyzing **1** and **2** in the presence of quinuclidine (1.0 equiv.) and KOAc (1.0 equiv.) in an undivided cell equipped with Pt plate cathode and anode with a supporting electrolyte solution of $^{n}Bu_4NClO_4$ (0.1 M in acetone/TFE = 2 :1) under 2 mA constant currentin the air (Table S3, entry 7).

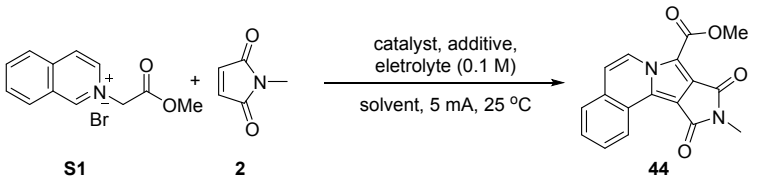
Procedure for the Synthesis of 44 from 1



A 10 mL three necked round bottom flask which was charged with a stir bar and installed platinum electrodes (1.0 x 1.0 cm^2) as cathode and anode respectively was used as electrolysis setup. With no precautions to exclude air or moisture, the device was added methyl 2-(3,4-dihydroisoquinolin-2(1H-yl)acetate **1** (0.2 mmol, 0.0410 g), *N*-methylmaleimide (0.26 mmol, 0.0289 g), quinuclidine (0.2 mmol, 0.0222 g), KOAc (0.2 mmol, 0.0196 g), then followed by $^{n}Bu_4NClO_4$ (0.3 mmol, 0.1025 g) as electrolyte. Next, 3 mL of acetone/TFE (2 :1) were added by syringes. After stirring the solution for 5 minutes, the reaction mixture was electrolyzed under a constant current of 5 mA (the cell voltage ranges from 2.7 to 3.5 V without reference electrode) at 25 °C for 12 h. Then the solvent was removed in vacuum, and the crude mixture was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to afford the **44** (17.3 mg, 28%).

2.4 Synthesis of 44 - 56

Table S4. Optimization Reaction Conditions for the Synthesis of **44** from **S1**[a]

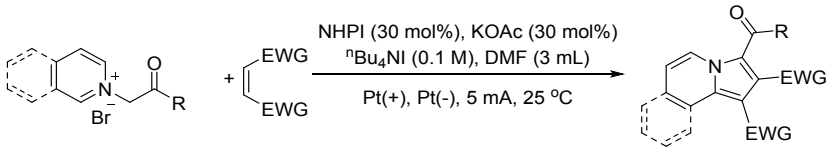


entry	Catalyst (equiv)	Additive (equiv)	electrolyte	anode/ cathode	solvent	yield (%)[b]
1	-	-	Et_4NBr	Pt(+)/Pt(-)	MeOH	trace
2	NHPI (0.3)	-	Et_4NBr	Pt(+)/Pt(-)	MeOH	22
3	NHPI (0.3)	KOAc (1.0)	Et_4NBr	Pt(+)/Pt(-)	MeOH	35
4	NHPI (0.3)	KOAc (1.0)	Et_4NBr	Pt(+)/Pt(-)	CH_3CN	39
5	NHPI (0.3)	KOAc (1.0)	Et_4NBr	Pt(+)/Pt(-)	THF	trace
6	NHPI (0.3)	KOAc (1.0)	Et_4NBr	Pt(+)/Pt(-)	DMF	63
7	NHPI (0.3)	KOAc (1.0)	$^nBu_4NI$	Pt(+)/Pt(-)	DMF	91
8	NHPI (0.3)	KOAc (1.0)	$^nBu_4NClO_4$	Pt(+)/Pt(-)	DMF	20
9	NHPI (0.3)	KOAc (1.0)	NaI	Pt(+)/Pt(-)	DMF	65
10	NHPI (0.3)	KOAc (1.0)	$^nBu_4NI$	C(+)/C(-)	DMF	78
11[c]	NHPI (0.3)	KOAc (1.0)	$^nBu_4NI$	Pt(+)/Pt(-)	DMF	trace

[a] Reaction conditions: undivided cell, **S1** (0.2 mmol), **2** (0.26 mmol), catalyst, additive, electrolyte (0.3 mmol), solvent (3 mL), constant current, 25 °C, 12h. [b] Isolated yield. [c] Without electricity

The final optimal reaction conditions were established as electrolyzing **1** and **2** in the presence of NHPI (0.3 equiv.) and KOAc (1.0 equiv.) in an undivided cell equipped with Pt plate cathode and anode with a supporting electrolyte solution of $^nBu_4NI$ (0.1 M in DMF) under 2 mA constant current under atmospheric conditions (Table S4, entry 7).

Procedure for the synthesis of 44 - 56



A 10 mL three necked round bottom flask which was charged with a stir bar and installed platinum electrodes (1.0 x 1.0 cm^2) as cathode and anode respectively was used as electrolysis setup. With no precautions to exclude air or moisture, the device was added pyridinium salts or isoquinolinium salt (0.2 mmol, 1 equiv.), dipolarophile (0.26 mmol, 1.3 equiv.), NHPI (0.06 mmol, 0.0098 g), KOAc (0.2 mmol, 0.0196 g), then followed by $^nBu_4NI$ (0.3 mmol, 0.1108 g) as electrolyte. Next, 3 mL of DMF was added by syringe. After stirring the solution for 5 minutes, the reaction mixture was electrolyzed under a constant current of 5 mA (the cell voltage ranges from 2.2 to 3.7 V without reference electrode) at 25 ^oC for 12 h. Then the reaction mixture was diluted by CH_2Cl_2 (70 mL), washed successively with water (2×50 mL and brine (1×50 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to afford the final product.

3. X-ray crystallography

Single crystals of **18** was obtained by slow evaporation of its solution in methylene chloride at 22 ^oC.

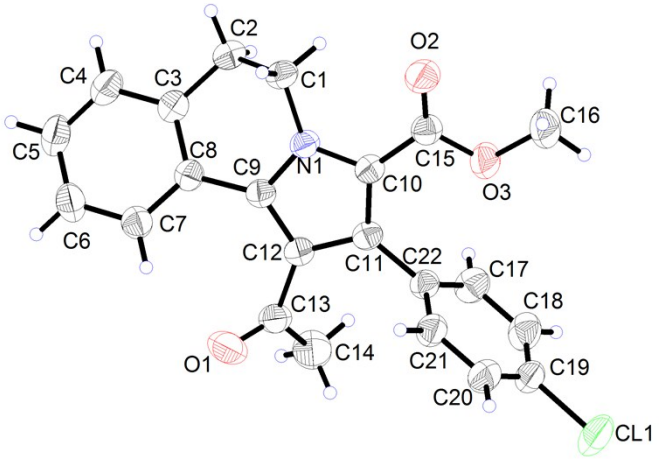


Figure S1. Crystal structure of **18**

Table S5. Crystal data and structure refinement for **18**.

Identification code	a	
Empirical formula	C22 H18 N O3 Cl	
Formula weight	379.82	
Temperature	295.47 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	
Unit cell dimensions	a = 9.7422(7) Å	□= 90°

	b = 8.7533(5) Å □= 96.623(3)°
	c = 21.6004(14) Å □ = 90°
Volume	1829.7(2) $Å^3$
Z	4
Density (calculated)	1.379 Mg/m^3
Absorption coefficient	0.232 mm^{-1}
F(000)	792.0
Crystal size	0.180 x 0.150 x 0.110 mm^3
Theta range for data collection	5.026 to 55.038°
Index ranges	-10<=h<=12, -11<=k<=11, -27<=l<=28
Reflections collected	13175
Independent reflections	4168 [R(int) = 0.0284]
Completeness to theta = 25.242?	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.946 and 0.973
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4168 / 0 / 244
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0431, wR2 = 0.1247
R indices (all data)	R1 = 0.0474, wR2 = 0.1281
Extinction coefficient	n/a
Largest diff. peak and hole	0.27 and -0.28 e $Å^{-3}$

Table S6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (?^{2}x 10^3) for cd16058. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl1	349.9(7)	2282.4(7)	4547.6(3)	78.1(2)
O1	2500.5(14)	-1121.3(15)	1623.1(6)	60.9(3)
O2	4002.3(14)	-5817.2(14)	4148.4(5)	56.1(3)
O3	2565.6(14)	-3945.8(15)	4349.9(5)	58.2(3)
N1	3364.9(12)	-5083.8(13)	2828.9(5)	35.2(3)
C1	4013.0(16)	-6607.2(17)	2839.4(7)	42.8(3)
C2	3376.7(18)	-7490.0(17)	2276.2(8)	45.2(4)
C3	3492.9(15)	-6603.7(17)	1687.5(7)	39.9(3)
C4	3714.9(18)	-7329(2)	1135.9(8)	50.1(4)
C5	3827.4(19)	-6495(2)	601.2(8)	56.4(4)
C6	3747.3(19)	-4921(2)	615.1(8)	53.9(4)
C7	3535.5(16)	-4170.4(19)	1161.4(7)	44.0(3)
C8	3375.3(13)	-4999.0(17)	1701.0(7)	36.4(3)
C9	3066.2(13)	-4282.4(15)	2287.6(6)	34.3(3)
C10	2936.0(14)	-4279.1(16)	3322.3(6)	35.5(3)
C11	2311.5(13)	-2940.4(16)	3085.0(7)	35.1(3)
C12	2399.2(14)	-2928.4(16)	2434.2(6)	34.9(3)
C13	1835.2(16)	-1690.4(17)	2003.9(7)	41.8(3)
C14	385(2)	-1155(3)	2052.0(9)	65.0(5)
C15	3239.7(15)	-4784.7(17)	3970.8(7)	39.1(3)
C16	2812(2)	-4290(2)	5005.5(8)	62.9(5)
C17	519.6(16)	-1716(2)	3675.0(8)	48.5(4)
C18	65.7(17)	-506(2)	4011.4(8)	52.9(4)
C19	907.0(18)	750.7(19)	4126.0(7)	48.6(4)
C20	2193(2)	819.6(19)	3920.9(8)	51.9(4)
C21	2627.9(16)	-387.2(18)	3578.6(7)	44.2(3)
C22	1802.4(14)	-1667.4(16)	3451.0(6)	36.2(3)

Table S7. Bond lengths (Å) and angles (°) for**18**.

Cl1	C19	1.7423(16)
O1	C13	1.212(2)
O2	C15	1.2042(18)
O3	C15	1.3286(19)
O3	C16	1.4408(19)
N1	C1	1.4745(18)
N1	C9	1.3658(18)
N1	C10	1.3817(17)
C1	C2	1.512(2)
C2	C3	1.505(2)
C3	C4	1.389(2)
C3	C8	1.410(2)
C4	C5	1.381(3)
C5	C6	1.381(3)
C6	C7	1.386(2)
C7	C8	1.397(2)
C8	C9	1.4756(19)
C9	C12	1.4052(19)
C10	C11	1.3907(19)
C10	C15	1.466(2)
C11	C12	1.418(2)
C11	C22	1.4842(19)
C12	C13	1.491(2)
C13	C14	1.503(2)
C17	C18	1.385(2)
C17	C22	1.392(2)
C18	C19	1.377(3)
C19	C20	1.377(2)
C20	C21	1.384(2)
C21	C22	1.388(2)

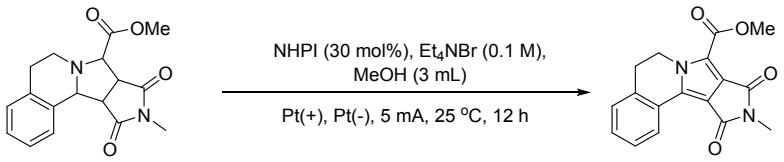
C15	O3	C16	116.88(13)
C9	N1	C1	121.75(12)
C9	N1	C10	110.18(11)
C10	N1	C1	128.04(12)
N1	C1	C2	108.34(12)
C3	C2	C1	110.64(13)
C4	C3	C2	121.58(14)

C4	C3	C8	119.62(15)
C8	C3	C2	118.80(13)
C5	C4	C3	120.72(16)
C6	C5	C4	119.95(15)
C5	C6	C7	120.37(16)
C6	C7	C8	120.41(16)
C3	C8	C9	117.80(13)
C7	C8	C3	118.87(13)
C7	C8	C9	123.32(13)
N1	C9	C8	118.18(12)
N1	C9	C12	107.38(12)
C12	C9	C8	134.23(13)
N1	C10	C11	107.68(12)
N1	C10	C15	122.50(12)
C10	C11	C12	107.32(12)
C10	C11	C22	126.52(13)
C12	C11	C22	125.76(12)
C9	C12	C11	107.42(12)
C9	C12	C13	128.27(13)
C11	C12	C13	124.29(12)
O1	C13	C12	122.32(14)
O1	C13	C14	119.96(15)
C12	C13	C14	117.73(14)
O2	C15	O3	123.30(14)
O2	C15	C10	125.46(14)
O3	C15	C10	111.24(12)
C18	C17	C22	120.86(16)
C19	C18	C17	119.05(15)
C18	C19	Cl1	119.59(13)
C18	C19	C20	121.44(15)
C20	C19	Cl1	118.96(14)
C19	C20	C21	118.99(16)
C20	C21	C22	121.07(14)
C17	C22	C11	122.07(13)
C21	C22	C11	119.36(13)
C11	C10	C15	129.64(13)
C21	C22	C17	118.57(14)

Symmetry transformations used to generate equivalent atoms:

4. Mechanistic studies

4.1 Electrochemical oxidative aromatization of 3



3
0.12 mmol

4, 75%

A 10 mL three necked round bottom flask which was charged with a stir bar and installed platinum electrodes (1.0 x 1.0 cm^2) as cathode and anode respectively was used as electrolysis setup. With no precautions to exclude air or moisture, compound **3** (0.12 mmol, 0.0377 g), NHPI (0.036 mmol, 0.0059 g), and Et_4NBr (0.3 mmol, 0.0630 g) were added. Next, 3 mL of MeOH was added by syringe. The reaction mixture was stirred and electrolyzed at a constant current of 5 mA at 25 °C for 12 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to afford **4** (27.9 mg, 75%).

4.2. The determination of H_2 emission in the reaction

Under the standard procedure for the synthesis of **4**, the mixture was flushed with N_2 for 10 min before being electrolyzed for 12 h, then 600 uL of the gaseous phase was taken out by micro-syringe and analyzed by GC with a TCD detector.

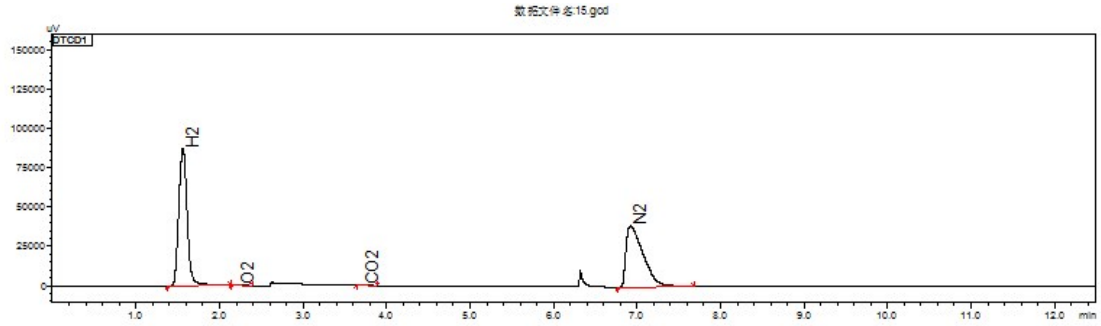


Figure S2. Gaseous phase analysis

4.3 Procedure for the sampling experiments

A 10 mL three necked round bottom flask which was charged with a stir bar and installed platinum electrodes (1.0 x 1.0 cm^2) as cathode and anode respectively was used as electrolysis setup. With no precautions to exclude air or moisture, the device was added methyl 2-(3,4-dihydroisoquinolin-2(1H)-yl)acetate (0.2 mmol, 0.0411 g), *N*-methylmaleimide (0.26 mmol, 0.0289 g), NHPI (0.06 mmol, 0.0098 g), followed by Et_4NBr (0.3 mmol, 0.0630 g) as electrolyte. Next, 3 mL of MeOH was added by syringe. The reaction mixture was stirred and electrolyzed at a constant current of 5 mA at 25 °C. 10 uL of reaction solution was taken out and mixed with 10 uL the solution of 1,3,5-

trimethoxy-benzene (0.2 mmol in 3 mL MeOH), then the sample was analyzed by GC-MS. By using the above procedure, a similar sets of experiments were conducted without NHPI.

Reaction time (min)	0	10	20	40	70
Yield of 3 with NHPI (%)	0	15.2	29.9	35.5	49.6
Yield of 3 without NHPI (%)	0	9.1	14.2	15.1	20.0

Table S8. The yields of **3** determined by GC-MS

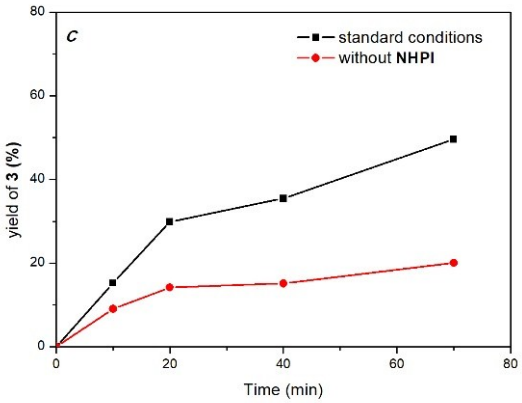
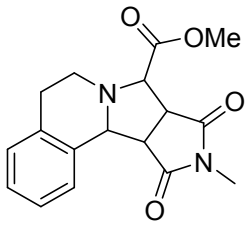


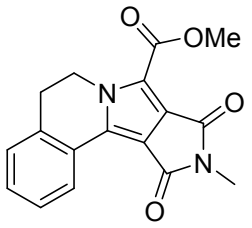
Figure S3. Kinetic study of oxidation/cycloaddition cascade

Characterization Data for the Electrolysis Products



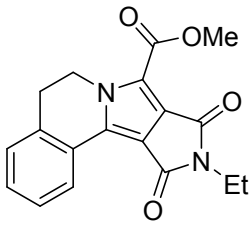
3

methyl 10-methyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 78%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.17 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 4.50 (d, *J* = 7.5 Hz, 1H), 4.22 (s, 1H), 3.76 (s, 3H), 3.71 (t, *J* = 7.6 Hz, 1H), 3.61 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.12 (ddd, *J* = 11.1, 5.7, 2.6 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.91 – 2.78 (m, 4H), 2.75 – 2.64 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.7, 175.5, 170.4, 134.2, 131.93, 128.8, 128.3, 126.8, 125.1, 66.5, 62.1, 51.9, 47.6, 46.5, 45.2, 30.0, 25.2. HRMS (ESI) calculated for $C_{17}H_{18}N_2O_4$ [M+H]+: 315.1345; found: 315.1350.



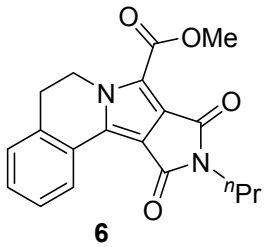
4

methyl 10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 83%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 4.74 – 4.64 (m, 2H), 3.96 (s, 3H), 3.13 (m, 2H), 3.07 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.0, 162.8, 160.1, 133.0, 132.3, 130.2, 127.9, 127.8, 127.6, 125.9, 125.6, 117.6, 116.6, 52.3, 43.2, 28.2, 24.2. HRMS (ESI) calculated for $C_{17}H_{14}N_2O_4$ [M+H]+: 311.1032; found: 311.1030.



5

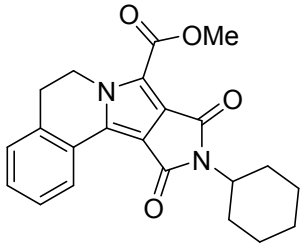
methyl 10-ethyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 82%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 5.6, 1.8 Hz, 1H), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H), 7.35 (td, *J* = 7.4, 1.5 Hz, 1H), 7.28 – 7.22 (m, 1H), 4.79 – 4.50 (m, 2H), 4.13 – 3.86 (m, 3H), 3.80 – 3.54 (m, 2H), 3.13 (t, *J* = 6.5 Hz, 2H), 1.23 (td, *J* = 7.1, 1.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 162.7, 160.2, 133.0, 132.3, 130.2, 127.9, 127.8, 127.6, 125.9, 125.5, 117.5, 116.7, 52.3, 43.2, 33.1, 28.3, 14.0. HRMS (ESI) calculated for $C_{18}H_{16}N_2O_4$ [M+H]+: 325.1188; found: 325.1189.



6

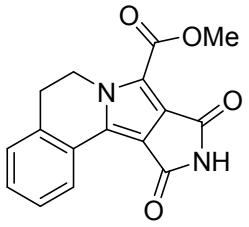
methyl 9,11-dioxo-10-propyl-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 70%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.25 (m, 1H), 4.76 – 4.61 (m, 2H), 3.97 (m, 3H), 3.57 (t, *J* = 8.7 Hz, 2H), 3.14 (t, *J* = 6.5 Hz, 2H), 1.67 (dd, *J* = 14.5, 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 162.9, 160.2, 133.0, 132.3, 130.2, 127.9, 127.8, 127.6, 125.9,

125.6, 117.5, 116.7, 52.3, 43.3, 39.9, 28.3, 21.9, 11.4. HRMS (ESI) calculated for $C_{19}H_{18}N_2O_4$ [M+H]+: 339.1345; found: 339.1345.



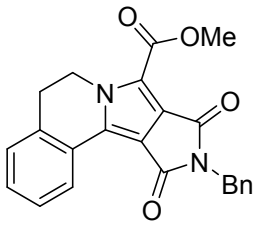
7

methyl 10-cyclohexyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 80%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 4.75 (t, *J* = 6.9 Hz, 2H), 4.08 (tt, *J* = 12.3, 3.8 Hz, 1H), 4.01 (s, 3H), 3.17 (t, *J* = 6.8 Hz, 2H), 2.25 (qd, *J* = 12.6, 3.3 Hz, 2H), 1.87 (d, *J* = 13.2 Hz, 2H), 1.74 (d, *J* = 11.1 Hz, 2H), 1.70 (d, *J* = 12.9 Hz, 1H), 1.37 (dd, *J* = 26.3, 13.1 Hz, 2H), 1.27 (ddd, *J* = 12.8, 9.7, 3.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2, 163.0, 160.3, 132.9, 132.3, 130.2, 127.96, 127.9, 127.6, 125.8, 125.7, 117.4, 116.8, 52.32, 5.10, 43.3, 29.9, 28.3, 26.2, 25.3. HRMS (ESI) calculated for $C_{22}H_{22}N2O4$ [M+H]+: 379.1658; found: 379.1658.



8

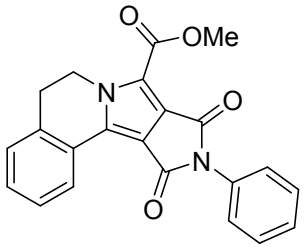
methyl 9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 62%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.38 (dd, *J* = 7.3, 6.3 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 4.75 (t, *J* = 6.9 Hz, 2H), 3.99 (s, 3H), 3.17 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.5, 162.2, 160.1, 133.4, 132.3, 130.4, 128.1, 127.9, 127.7, 126.2, 125.5, 117.8, 117.1, 52.5, 43.5, 28.3. HRMS (ESI) calculated for $C_{16}H_{12}N_2O_4$ [M+H]+: 297.0875; found: 297.0877.



9

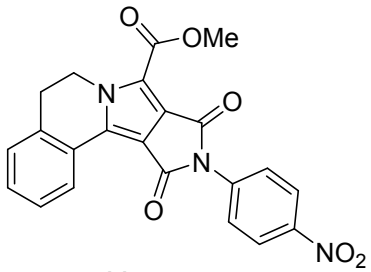
methyl 10-benzyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 88%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.26 (m, 2H), 4.81 (s, 2H), 4.74 (t, *J* = 6.9 Hz, 2H), 4.00 (s, 3H), 3.16 (t, *J* = 6.8 Hz, 2H). ^{13}C

NMR (151 MHz, $CDCl_3$) δ 163.8, 162.5, 160.1, 137.1, 133.3, 132.3, 130.3, 128.6, 128.6, 128.0, 127.9, 127.7, 127.6, 125.7, 125.5, 117.8, 116.6, 52.4, 43.3, 41.9, 28.3. HRMS (ESI) calculated for $C_{23}H_{18}N_2O_4$ [M+H]+: 387.1345; found: 387.1343.



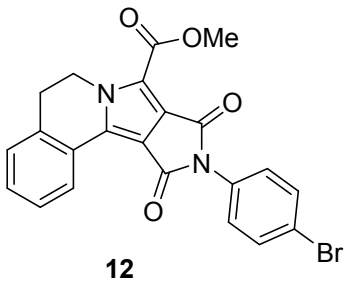
10

methyl 9,11-dioxo-10-phenyl-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 71%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 7.0 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.41 (m, 5H), 7.31 (d, *J* = 6.6 Hz, 1H), 4.79 (t, *J* = 6.8 Hz, 2H), 4.00 (s, 3H), 3.20 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0, 161.7, 160.1, 133.7, 132.6, 132.5, 130.4, 128.9, 128.0, 128.0, 127.8, 127.7, 127.0, 125.5, 125.3, 118.2, 116.3, 52.3, 43.4, 28.3. HRMS (ESI) calculated for $C_{22}H_{16}N_2O_4$ [M+H]+: 373.1188; found: 373.1188.



11

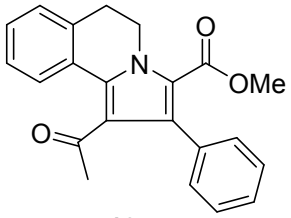
methyl 10-(4-nitrophenyl)-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 69%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 6.5 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.45 (m, 2H), 7.34 (d, *J* = 6.3 Hz, 1H), 4.82 (t, *J* = 6.7 Hz, 2H), 4.03 (s, 3H), 3.22 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.1, 160.6, 159.8, 146.0, 138.5, 134.3, 132.6, 130.8, 128.2, 127.9, 127.8, 126.8, 125.2, 124.6, 124.2, 118.8, 115.7, 52.6, 43.6, 28.3. HRMS (ESI) calculated for $C_{22}H_{15}N_3O_6$ [M+H]+: 418.1039; found: 418.1037.



12

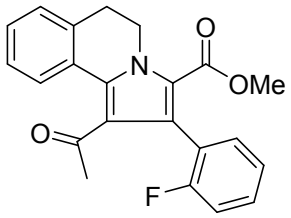
methyl 10-(4-bromophenyl)-9,11-dioxo-5,9,10,11-tetrahydro-6H-

pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 72%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 – 8.51 (m, 1H), 7.65 – 7.58 (m, 2H), 7.40 (dtd, *J* = 14.5, 7.4, 1.2 Hz, 2H), 7.33 – 7.29 (m, 3H), 4.77 (t, *J* = 6.9 Hz, 2H), 3.99 (s, 3H), 3.19 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.6, 161.3, 160.0, 133.9, 132.5, 132.0, 131.6, 130.6, 128.4, 128.1, 127.9, 127.8, 125.4, 125.1, 121.4, 118.3, 116.0, 52.4, 43.5, 28.3. HRMS (ESI) calculated for $C_{22}H_{15}BrN_2O_4$ [M+H]+: 451.0293; found: 451.0291.



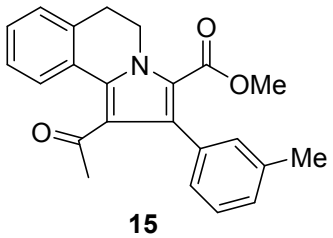
13

methyl 1-acetyl-2-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 80%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 6.8 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.31 (d, *J* = 7.1 Hz, 2H), 7.30 – 7.26 (m, 3H), 4.69 – 4.52 (m, 2H), 3.58 (s, 3H), 3.14 – 3.05 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.7, 161.9, 135.2, 133.9, 133.3, 132.8, 129.9, 128.6, 127.8, 127.7, 127.3, 127.2, 127.0, 126.6, 123.9, 118.9, 51.1, 42.7, 32.2, 29.4. HRMS (ESI) calculated for $C_{22}H_{19}NO_3$ [M+H]+: 346.1443; found: 346.1445.



14

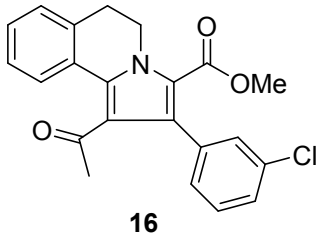
methyl 1-acetyl-2-(2-fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 65%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 1H), 7.37 (ddd, *J* = 7.2, 6.3, 1.8 Hz, 1H), 7.33 – 7.22 (m, 4H), 7.21 – 7.10 (m, 2H), 4.67 – 4.52 (m, 2H), 3.60 (s, 3H), 3.39 – 3.06 (m, 2H), 2.13 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.6, 161.6, 160.0 (d, *J* = 246.1 Hz), 134.0, 133.9, 132.0 (d, *J* = 3.0 Hz), 129.5 (d, *J* = 7.6 Hz), 128.7, 127.8, 127.2, 126.9, 126.8, 125.4, 123.7, 123.6 (d, *J* = 3.0 Hz), 123.1 (d, *J* = 15.1Hz), 119.7, 115.1 (d, *J* = 21.1 Hz), 51.3, 42.8, 31.6, 29.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ -114.25. HRMS (ESI) calculated for $C_{22}H_{18}FNO_3$ [M+H]+: 364.1349; found: 364.1350.



15

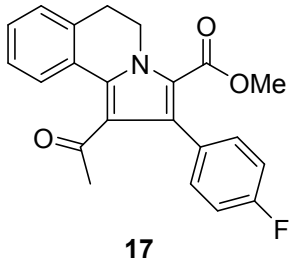
methyl 1-acetyl-2-(m-tolyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield =

73%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.63 (m, 1H), 7.34 – 7.24 (m, 4H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.11 (m, 2H), 4.71 – 4.51 (m, 2H), 3.59 (s, 3H), 3.30 – 2.93 (m, 2H), 2.40 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.8, 161.9, 137.3, 135.0, 133.9, 133.3, 132.9, 130.6, 128.5, 128.15, 127.7, 127.6, 127.2, 127.1, 126.6, 123.9, 118.9, 51.1, 42.8, 32.2, 29.4, 21.5. HRMS (ESI) calculated for $C_{23}H_{21}NO_3$ [M+H]+: 360.1600; found: 360.1602.



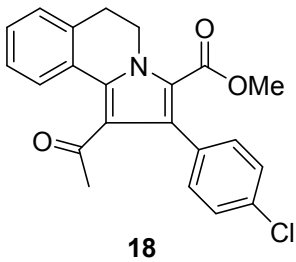
16

methyl 1-acetyl-2-(3-chlorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 71%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 1H), 7.37 – 7.33 (m, 3H), 7.32 – 7.26 (m, 3H), 7.20 (dd, *J* = 5.0, 3.4 Hz, 1H), 4.68 – 4.48 (m, 2H), 3.61 (s, 3H), 3.16 – 3.06 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.0, 161.6, 137.0, 133.9, 133.6 133.5, 131.0, 130.1, 128.9, 128.7, 128.3, 127.7, 127.5, 127.2, 126.8, 126.6, 123.7, 119.1, 51.2, 42.8, 32.3, 29.3. HRMS (ESI) calculated for $C_{22}H_{18}ClNO_3$ [M+H]+: 380.1053; found: 380.1053.



17

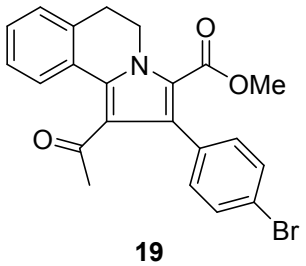
methyl 1-acetyl-2-(4-fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 71%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 1H), 7.35 – 7.24 (m, 5H), 7.14 – 7.03 (m, 2H), 4.77 – 4.44 (m, 2H), 3.60 (s, 3H), 3.16 – 3.03 (m, 2H), 2.06 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.2, 162.3 (d, *J* = 255.2 Hz), 161.7, 133.9, 133.4, 131.6 (d, *J* = 7.6 Hz), 131.5, 131.0, 128.6, 127.8, 127.2, 126.9, 126.6, 123.9, 119.1, 114.7 (d, *J* = 21.4 Hz), 51.2, 42.7, 32.2, 29.3. HRMS (ESI) calculated for $C_{22}H_{18}FNO_3$ [M+H]+: 364.1349; found: 364.1351.



18

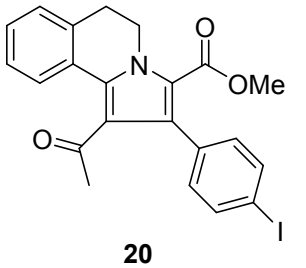
methyl 1-acetyl-2-(4-chlorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 76%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 1H), 7.41 – 7.35 (m, 2H), 7.32 – 7.23 (m, 5H), 4.78 – 4.48 (m, 2H), 3.61 (s,3H), 3.24 – 3.00 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.3, 161.7, 133.9, 133.6, 133.5, 133.4, 131.3, 131.3, 128.7, 127.9, 127.8, 127.2, 126.9,

126.6, 123.9, 119.0, 51.2, 42.8, 32.3, 29.3. HRMS (ESI) calculated for $C_{22}H_{18}ClNO_3$ [M+H]+: 380.1053; found: 380.1052.



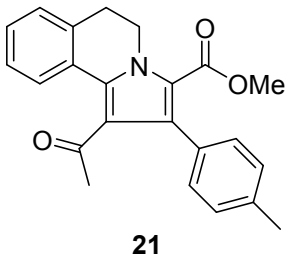
19

methyl 1-acetyl-2-(4-bromophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 72%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 1H), 7.57 – 7.50 (m, 2H), 7.31 – 7.25 (m, 3H), 7.24 – 7.16 (m, 2H), 4.64 – 4.48 (m, 2H), 3.61 (s, 3H), 3.15 – 2.99 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.3, 161.7, 134.1, 133.9, 133.5, 131.7, 131.3, 130.9, 128.7, 127.8, 127.2, 126.9, 126.6, 123.8, 121.6, 118.9, 51.3, 42.8, 32.3, 29.3. HRMS (ESI) calculated for $C_{22}H_{18}BrNO_3$ [M+H]+: 424.0548; found: 424.0551.



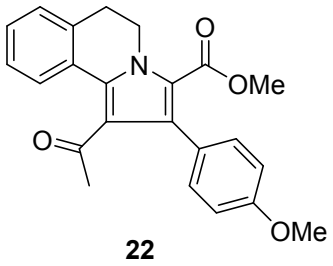
20

methyl 1-acetyl-2-(4-iodophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 77%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.65 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.06 (d, *J* = 8.3 Hz, 2H), 4.71 – 4.53 (m, 2H), 3.61 (s, 3H), 3.10 (t, *J* = 6.5 Hz, 2H), 2.07 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.3, 161.7, 136.9, 134.7, 133.8, 133.5, 131.3, 131.3, 128.7, 127.8, 127.2, 126.8, 126.6, 123.8, 118.9, 93.3, 51.3, 42.8, 32.3, 29.3. HRMS (ESI) calculated for $C_{22}H_{18}INO_3$ [M+H]+: 472.0410; found: 472.0413.



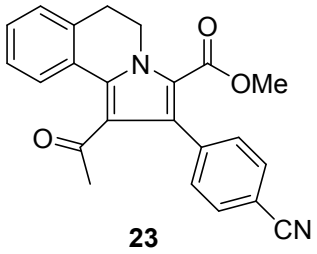
21

methyl 1-acetyl-2-(p-tolyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 81%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 6.1, 2.1 Hz, 1H), 7.34 – 7.25 (m, 3H), 7.20 (m, 4H), 4.65 – 4.53 (m, 2H), 3.61 (s, 3H), 3.15 – 3.04 (m, 2H), 2.42 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.9, 137.0, 133.9, 133.2, 132.9, 131.9, 129.8, 128.5, 128.5, 127.6, 127.1, 127.1, 126.6, 124.0, 118.9, 51.1, 42.7, 32.2, 29.4, 21.3. HRMS (ESI) calculated for $C_{23}H_{21}NO_3$ [M+H]+: 360.1600; found: 360.1602.



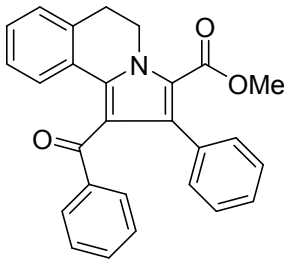
22

methyl 1-acetyl-2-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 76%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 1H), 7.31 – 7.26 (m, 3H), 7.26 – 7.21 (m, 2H), 6.97 – 6.89 (m, 2H), 4.71 – 4.45 (m, 2H), 3.88 (s, 3H), 3.62 (s, 3H), 3.23 – 2.96 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.8, 161.9, 158.9, 133.9, 133.2, 132.5, 131.1, 128.5, 127.7, 127.2, 127.2, 127.1, 126.6, 124.1, 118.9, 113.2, 55.2, 51.2, 42.7, 32.2, 29.4. HRMS (ESI) calculated for $C_{23}H_{21}NO_4$ [M+H]+: 376.1549; found: 376.1550.



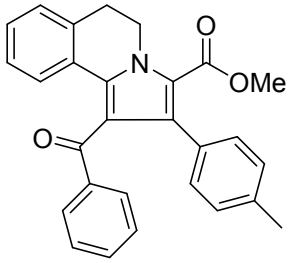
23

methyl 1-acetyl-2-(4-cyanophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 71%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.33 – 7.27 (m, 3H), 4.68 – 4.43 (m, 2H), 3.57 (s, 3H), 3.26 – 3.03 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.6, 161.3, 140.4, 133.9, 133.9, 131.4, 130.9, 130.5, 128.9, 127.9, 127.3, 126.8, 126.6, 123.6, 119.1, 118.9, 111.1, 51.3, 42.9, 32.3, 29.3. HRMS (ESI) calculated for $C_{23}H_{18}N_2O_3$ [M+H]+: 371.1396; found: 371.1395.



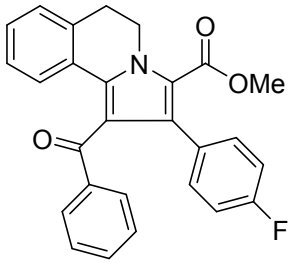
24

methyl 1-benzoyl-2-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 70%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.23 (m, 3H), 7.15 (m, 5H), 7.12 – 7.08 (m, 1H), 7.04 (dd, J = 11.1, 4.1 Hz, 1H), 4.72 – 4.61 (m, 2H), 3.60 (s, 3H), 3.15 (t, J = 6.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.3, 162.1, 138.2, 134.3, 133.5, 133.3, 132.9, 130.1, 129.8, 128.2, 128.1, 127.8, 127.2, 127.15, 126.9, 126.9, 126.2, 121.2, 118.9, 99.9, 51.2, 42.8, 29.3. HRMS (ESI) calculated for $C_{27}H_{21}NO_3$ [M+H]+: 408.1600; found: 408.1602.



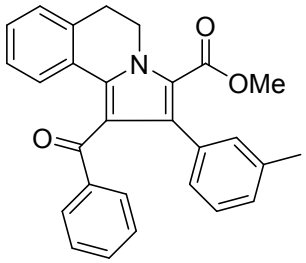
25

methyl 1-benzoyl-2-(p-tolyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 66%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.29 (m, 4H), 7.19 (t, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 2H), 4.85 – 4.61 (m, 2H), 3.66 (s, 3H), 3.18 (t, *J* = 6.5 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.4, 162.2, 138.2, 136.3, 133.4, 133.3, 132.9, 131.2, 129.9, 129.9, 128.1, 128.1, 128.0, 127.8, 127.1, 126.9, 126.3, 121.2, 118.9, 51.2, 42.9, 29.3, 21.2. HRMS (ESI) calculated for $C_{28}H_{23}NO_3$ [M+H]+: 422.1756; found: 422.1756.



26

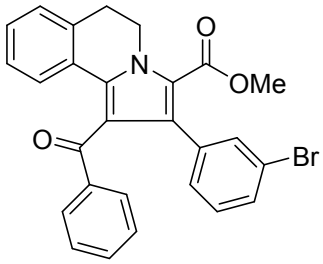
methyl 1-benzoyl-2-(4-fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 63%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.25 – 7.12 (m, 7H), 7.08 (dd, *J* = 16.2, 8.1 Hz, 2H), 4.70 (t, *J* = 6.5 Hz, 2H), 3.62 (s, 3H), 3.18 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.9, 162.3 (d, *J* = 247.6 Hz), 162.0, 140.4, 134.2, 133.8, 133.3 (d, *J* = 13.6 Hz), 130.1, 129.7 (d, *J* = 7.6 Hz), 128.3, 127.8, 127.3, 127.1 (d, *J* = 30.2 Hz), 126.7, 126.2, 125.6, 120.7, 119.8 (d, *J* = 22.6 Hz), 118.9, 116.2 (d, *J* = 22.6 Hz), 51.2, 42.9, 29.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ -112.81. HRMS (ESI) calculated for $C_{27}H_{20}FNO_3$ [M+H]+: 426.1505; found: 426.1502.



27

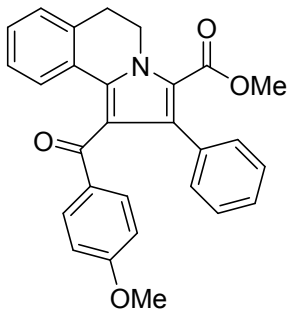
methyl 1-benzoyl-2-(m-tolyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 62%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.33

(d, *J* = 7.8 Hz, 1H), 7.25 m, 3H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.98 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 4.76 – 4.57 (m, 2H), 3.63 (s, 3H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.4, 162.2, 138.3, 136.6, 134.1, 133.5, 133.3, 132.8, 130.8, 129.7, 128.1, 128.0, 127.7, 127.6, 127.2, 127.1, 127.1, 126.9, 126.2, 121.2, 118.8, 51.1, 42.9, 29.3, 21.3. HRMS (ESI) calculated for $C_{28}H_{23}NO_3$ [M+H]+: 422.1756; found: 422.1755.



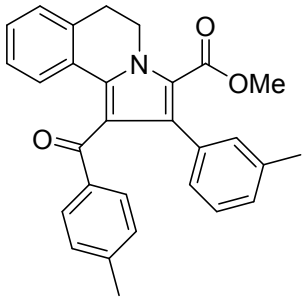
28

methyl 1-benzoyl-2-(3-bromophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 70%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 1.7 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 7.20 (td, *J* = 7.5, 0.9 Hz, 1H), 7.12 – 7.09 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 4.77 – 4.59 (m, 2H), 3.64 (s, 3H), 3.17 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.9, 161.8, 138.2, 136.4, 133.8, 133.3, 133.2, 133.1, 131.6, 129.9, 129.7, 128.8, 128.7, 128.5, 128.3, 128.2, 127.8, 127.2, 126.7, 126.3, 121.1, 118.9, 51.3, 42.9, 29.3. HRMS (ESI) calculated for $C_{27}H_{20}BrNO_3$ [M+H]+: 486.0705; found: 486.0707.



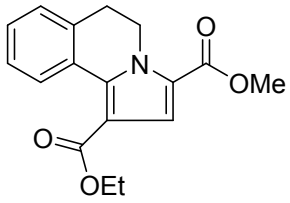
29

methyl 1-(4-methoxybenzoyl)-2-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 61%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.20 – 7.18 (m, 2H), 7.16 (m, 3H), 7.12 (dd, *J* = 8.4, 5.8 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 4.69 – 4.61 (m, 2H), 3.76 (s, 3H), 3.60 (s, 3H), 3.14 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.0, 163.5, 162.2, 134.3, 133.2, 132.9, 132.8, 132.3, 131.3, 130.0, 128.0, 127.8, 127.3, 127.2, 127.0, 126.8, 126.0, 121.5, 118.7, 113.4, 55.4, 51.1, 42.8, 29.3. HRMS (ESI) calculated for $C_{28}H_{23}NO_4$ [M+H]+: 438.1705; found: 438.1703.



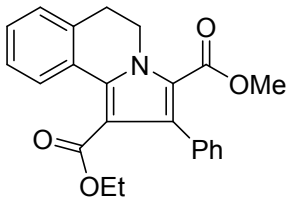
30

methyl 1-(4-methylbenzoyl)-2-(m-tolyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate. Yield = 75%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.1 Hz, 1H), 7.09 – 7.03 (m, 4H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 4.76 – 4.60 (m, 2H), 3.63 (s, 3H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.2, 162.2, 143.7, 136.6, 135.8, 134.1, 133.3, 133.2, 133.0, 130.8, 129.9, 128.9, 127.9, 127.7, 127.6, 127.2, 127.1, 127.1, 127.0, 126.2, 121.4, 118.8, 51.1, 42.8, 29.3, 21.7, 21.3. HRMS (ESI) calculated for $C_{29}H_{25}NO_3$ [M+H]+: 436.1913; found: 436.1912.



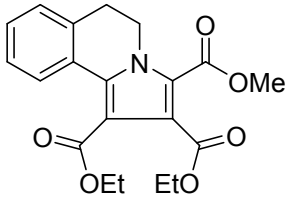
31

1-ethyl 3-methyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate. Yield = 82%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.5 Hz, 1H), 7.52 (s, 1H), 7.33 (ddt, *J* = 8.6, 7.3, 3.7 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 1H), 4.80 – 4.54 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.19 – 2.92 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 161.4, 137.9, 134.1, 128.9, 128.6, 127.3, 127.1, 126.9, 121.5, 120.7, 112.4, 60.3, 51.5, 42.3, 29.5, 14.4. HRMS (ESI) calculated for $C_{17}H_{17}NO_4$ [M+H]+: 300.1236; found: 300.1237.



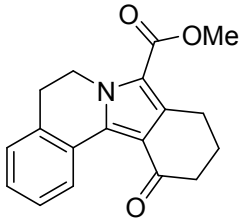
32

1-ethyl 3-methyl 2-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate. Yield = 56%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 4.8, 3.7 Hz, 1H), 7.33 (m, 3H), 7.30 – 7.24 (m, 5H), 4.73 – 4.34 (m, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.55 (s, 3H), 3.16 – 2.99 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 161.9, 135.5, 134.6, 134.1, 133.8, 129.7, 128.5, 127.6, 127.2, 127.0, 126.9, 126.8, 126.8, 119.2, 113.9, 60.5, 51.1, 42.8, 29.4, 13.5. HRMS (ESI) calculated for $C_{23}H_{21}NO_4$ [M+H]+: 376.1549; found: 376.1550.



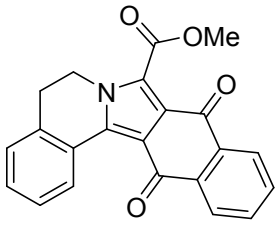
33

1,2-diethyl 3-methyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate. Yield = 87%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 6.1, 3.0 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.28 – 7.22 (m, 1H), 4.55 (t, *J* = 6.5 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.10 – 2.98 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 163.4, 160.3, 136.8, 134.3, 129.3, 128.5, 127.3, 127.1, 126.9, 126.3, 118.8, 110.7, 61.5, 60.8, 51.9, 42.6, 29.3, 14.3, 14.0. HRMS (ESI) calculated for $C_{20}H_{21}NO_6$ [M+H]+: 372.1447; found: 372.1445.



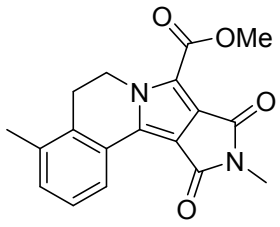
34

methyl 12-oxo-5,6,9,10,11,12-hexahydroisoindolo[1,2-a]isoquinoline-8-carboxylate. Yield = 62%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (d, *J* = 7.6 Hz, 1H), 7.35 (dd, *J* = 11.1, 4.2 Hz, 1H), 7.31 (td, *J* = 7.4, 1.1 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 4.90 – 4.46 (m, 2H), 3.89 (s, 3H), 3.05 (t, *J* = 6.2 Hz, 2H), 3.03 – 2.98 (m, 2H), 2.64 – 2.54 (m, 2H), 2.13 – 2.05 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.5, 162.2, 138.2, 137.1, 134.0, 129.3, 128.9, 127.1, 127.0, 127.0, 118.2, 117.4, 51.3, 42.6, 40.3, 29.3, 24.1, 23.8. HRMS (ESI) calculated for $C_{18}H_{17}NO_3$ [M+H]+: 296.1287; found: 296.1283.



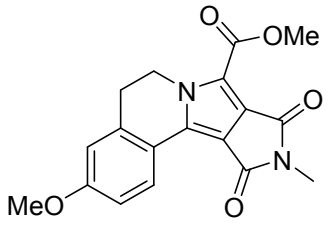
35

methyl 9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate. Yield = 71%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.97 (d, *J* = 7.8 Hz, 1H), 8.32 – 8.25 (m, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.07 (s, 3H), 3.09 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.7, 179.6, 161.9, 135.9, 135.6, 134.7, 133.7, 133.4, 133.1, 130.2, 128.9, 127.5, 127.5, 127.3, 126.6, 126.3, 125.5, 123.5, 117.5, 53.2, 43.2, 29.1. HRMS (ESI) calculated for $C_{22}H_{15}NO_4$ [M+H]+: 358.1079; found: 358.1079.



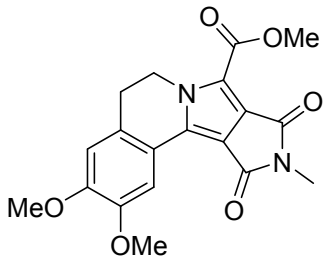
36

methyl 4,10-dimethyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 81%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 4.72 (t, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 3.11 (s, 3H), 3.09 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 162.9, 160.2, 135.2, 133.6, 132.0, 130.9, 127.6, 126.1, 125.9, 125.5, 117.3, 116.6, 52.3, 42.9, 24.8, 24.3, 19.5. HRMS (ESI) calculated for $C_{18}H_{16}N_2O_4$ [M+H]+: 325.1188; found: 325.1189.



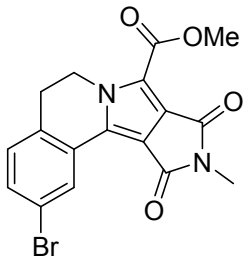
37

methyl 3-methoxy-10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 79%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.6 Hz, 1H), 6.94 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 4.69 (t, *J* = 6.9 Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.18 – 3.04 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2, 162.9, 161.1, 160.2, 134.4, 133.5, 129.7, 125.9, 118.5, 117.1, 115.3, 113.3, 113.2, 55.5, 52.2, 43.0, 28.6, 24.2. HRMS (ESI) calculated for $C_{18}H_{16}N_2O_5$ [M+H]+: 341.1137; found: 341.1136.



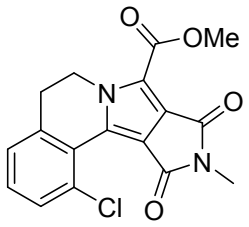
38

methyl 2,3-dimethoxy-10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 77%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.0 Hz, 1H), 6.70 (s, 1H), 4.64 (dd, *J* = 9.8, 4.2 Hz, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.05 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 162.8, 160.1, 150.6, 148.5, 133.6, 125.7, 125.5, 118.1, 117.3, 115.2, 110.3, 110.2, 56.1, 56.0, 52.2, 43.3, 27.8, 24.1. HRMS (ESI) calculated for $C_{19}H_{18}N_2O_6$ [M+H]+: 371.1243; found: 371.1245.



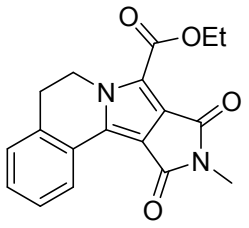
39

methyl 2-bromo-10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 91%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.0 Hz, 1H), 7.47 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 4.78 – 4.68 (m, 2H), 3.98 (s, 3H), 3.17 – 3.07 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 162.6, 160.0, 133.0, 131.3, 130.9, 130.3, 129.2, 127.3, 125.8, 121.6, 118.1, 117.3, 52.4, 43.1, 27.9, 24.3. HRMS (ESI) calculated for $C_{17}H_{13}BrN_2O_4$ [M+H]+: 389.0137; found: 389.0137.



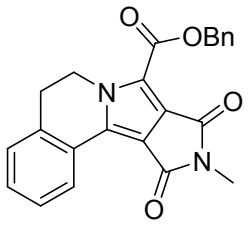
40

methyl 1-chloro-10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 73%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 1H), 4.61 (m, 2H), 3.99 (s, 3H), 3.10 (s, 3H), 3.00 (t, *J* = 6.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 162.7, 160.1, 137.8, 133.1, 130.3, 130.0, 128.1, 125.9, 125.7, 125.3, 119.1, 117.9, 52.5, 42.5, 30.5, 24.3. HRMS (ESI) calculated for $C_{17}H_{13}ClN_2O_4$ [M+H]+: 345.0642; found: 345.0642.



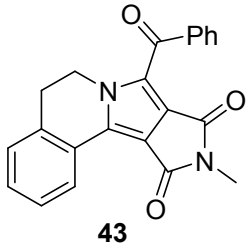
41

ethyl 10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 76%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.4 Hz, 1H), 7.38 (m, 2H), 7.25 (m, 1H), 4.70 (t, *J* = 6.9 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 3.10 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 162.8, 159.7, 132.9, 132.3, 130.2, 127.9, 127.8, 127.6, 125.8, 125.6, 118.1, 116.7, 61.6, 43.2, 28.3, 24.2, 14.2. HRMS (ESI) calculated for $C_{18}H_{16}N_2O_4$ [M+H]+: 325.1188; found: 325.1189.



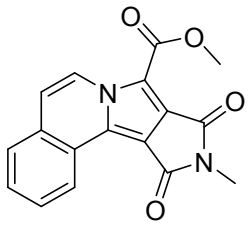
42

benzyl 10-methyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 81%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.46 – 7.30 (m, 5H), 7.23 (d, *J* = 7.1 Hz, 1H), 5.41 (s, 2H), 4.66 (t, *J* = 6.8 Hz, 2H), 3.15 – 2.97 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.0, 162.6, 159.4, 135.5, 132.9, 132.3, 130.2, 128.6, 128.9, 128.3, 127.9, 127.8, 127.6, 126.0, 125.5, 117.6, 116.7, 66.9, 43.2, 28.2, 24.3. HRMS (ESI) calculated for $C_{23}H_{18}N_2O_4$ [M+H]+: 387.1345; found: 387.1346.



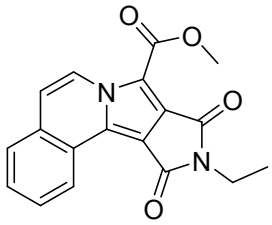
43

8-benzoyl-10-methyl-5,6-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(10H)-dione. Yield = 80%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.96 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.74 – 7.66 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.42 (td, *J* = 7.5, 1.3 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 4.72 – 4.39 (m, 2H), 3.22 (t, *J* = 6.9 Hz, 2H), 3.05 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.6, 164.2, 162.8, 137.8, 133.7, 133.5, 132.7, 130.3, 129.9, 128.3, 128.1, 127.8, 125.8, 125.5, 125.2, 116.3, 43.9, 28.5, 24.2. HRMS (ESI) calculated for $C_{22}H_{16}N_2O_3$ [M+H]+: 357.1239; found: 357.1239.



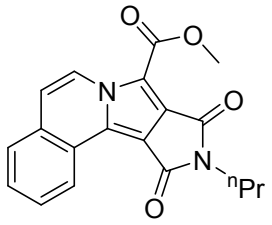
44

methyl 10-methyl-9,11-dioxo-10,11-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 91%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (d, *J* = 7.6 Hz, 1H), 9.07 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.54 (m, 3H), 7.14 (d, *J* = 7.6 Hz, 1H), 4.04 (s, 3H), 3.16 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 162.9, 160.3, 131.1, 130.2, 129.1, 128.9, 128.5, 127.3, 126.6, 124.7, 123.7, 115.9, 113.1, 111.5, 52.3, 24.4. HRMS (ESI) calculated for $C_{17}H_{12}N_2O_4$ [M+H]+: 309.0875; found: 309.0873.



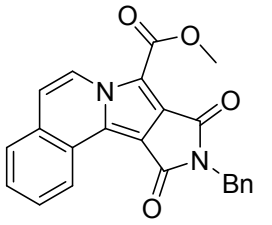
45

methyl 10-ethyl-9,11-dioxo-10,11-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 87%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.23 (d, *J* = 7.6 Hz, 1H), 9.14 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.46 (m, 3H), 7.18 (d, *J* = 7.6 Hz, 1H), 4.05 (s, 3H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.7, 162.8, 160.4, 131.2, 130.2, 129.2, 128.9, 128.6, 127.3, 126.5, 124.7, 123.8, 115.9, 113.2, 111.5, 52.3, 33.3, 14.1. HRMS (ESI) calculated for $C_{18}H_{14}N_2O_4$ [M+H]+: 323.1032; found: 323.1032.



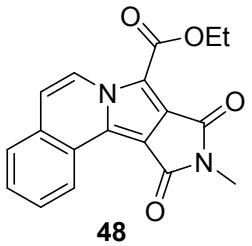
46

methyl 9,11-dioxo-10-propyl-10,11-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 88%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (d, *J* = 7.6 Hz, 1H), 8.99 (dd, *J* = 6.0, 3.6 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.04 (s, 3H), 3.75 – 3.54 (m, 2H), 1.74 (dd, *J* = 14.7, 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.7, 162.7, 160.2, 130.8, 130.1, 128.9, 128.8, 128.3, 127.2, 126.4, 124.5, 123.5, 115.8, 112.9, 111.3, 52.2, 40.1, 22.0, 11.4. HRMS (ESI) calculated for $C_{19}H_{16}N_2O_4$ [M+H]+: 337.1188; found: 337.1187.



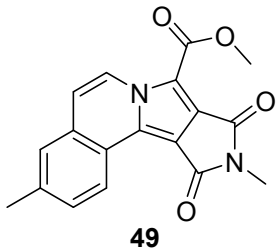
47

methyl 10-benzyl-9,11-dioxo-10,11-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 79%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (d, *J* = 7.6 Hz, 1H), 9.08 (d, *J* = 7.8 Hz, 1H), 7.69 – 7.59 (m, 3H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 4.85 (s, 2H), 4.04 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.6, 162.5, 160.3, 137.0, 131.3, 130.2, 129.1, 128.9, 128.7, 128.6, 128.2, 127.6, 127.3, 126.5, 124.7, 123.6, 116.1, 112.8, 111.6, 52.3, 42.1. HRMS (ESI) calculated for $C_{23}H_{16}N_2O_4$ [M+H]+: 385.1188; found: 385.1189.



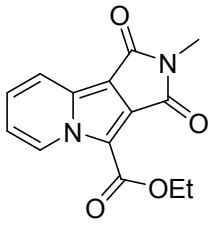
48

ethyl 10-methyl-9,11-dioxo-10,11-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 86%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.06 (d, *J* = 6.5 Hz, 1H), 8.95 (m, 1H), 7.60 (m, 3H), 7.03 (d, *J* = 6.6 Hz, 1H), 4.45 (d, *J* = 6.9 Hz, 2H), 3.12 (s, 3H), 1.52 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.0, 162.9, 159.8, 130.05, 129.0, 128.8, 128.2, 127.2, 126.5, 124.6, 123.6, 115.7, 112.9, 111.9, 61.5, 29.71, 24.3, 14.2. HRMS (ESI) calculated for $C_{18}H_{14}N_2O_4$ [M+H]+: 323.1032; found: 323.1033.



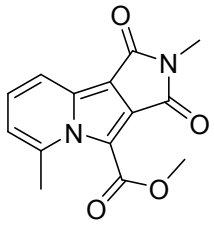
49

methyl 3,10-dimethyl-9,11-dioxo-10,11-dihydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate. Yield = 82%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (d, *J* = 7.6 Hz, 1H), 8.88 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.42 (s, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 4.03 (s, 3H), 3.15 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 162.9, 160.3, 140.7, 131.2, 130.5, 129.2, 128.4, 127.1, 126.2, 124.6, 121.4, 115.7, 112.3, 111.2, 52.2, 24.3, 21.8. HRMS (ESI) calculated for $C_{18}H_{14}N_2O_4$ [M+H]+: 323.1032; found: 323.1031.



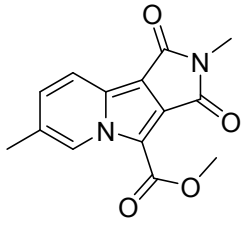
50

ethyl 2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate. Yield = 73%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.50 (dt, *J* = 7.2, 1.0 Hz, 1H), 7.81 (dt, *J* = 8.9, 1.2 Hz, 1H), 7.34 (ddd, *J* = 8.9, 6.8, 1.0 Hz, 1H), 7.00 (td, *J* = 7.1, 1.3 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.11 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 163.2, 160.0, 131.3, 130.2, 129.1, 127.0, 118.6, 115.5, 110.6, 110.0, 61.3, 24.1, 14.3. HRMS (ESI) calculated for $C_{14}H_{12}N_2O_4$ [M+H]+: 273.0875; found: 273.0873.



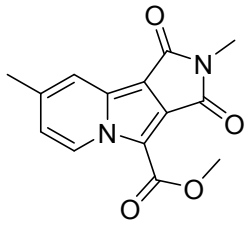
51

methyl 2,6-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate. Yield = 65%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 1H), 7.32 (dd, *J* = 8.8, 7.0 Hz, 1H), 6.83 (d, *J* = 6.9 Hz, 1H), 4.06 (s, 3H), 3.13 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8, 163.7, 160.2, 139.7, 133.2, 130.7, 127.2, 117.1, 116.5, 112.6, 109.8, 52.8, 24.1, 22.3. HRMS (ESI) calculated for $C_{14}H_{12}N_2O_4$ [M+H]+: 273.0875; found: 273.0876.



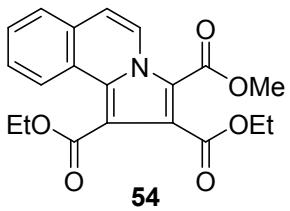
52

methyl 2,7-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate. Yield = 71%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.42 (d, *J* = 7.1 Hz, 1H), 7.19 – 7.10 (m, 1H), 6.96 (t, *J* = 7.1 Hz, 1H), 4.04 (s, 3H), 3.15 (s, 3H), 2.80 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.6, 163.2, 160.5, 133.3, 130.4, 129.9, 126.7, 126.3, 115.9, 111.1, 109.6, 52.1, 24.3, 19.5. HRMS (ESI) calculated for $C_{14}H_{12}N_2O_4$ [M+H]+: 273.0875; found: 273.0876.



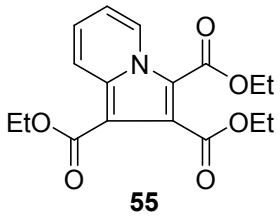
53

methyl 2,8-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate. Yield = 63%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.42 (d, *J* = 7.3 Hz, 1H), 7.64 (s, 1H), 6.88 (dd, *J* = 7.3, 1.7 Hz, 1H), 4.03 (s, 3H), 3.13 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.9, 163.4, 160.5, 138.9, 132.0, 130.5, 128.4, 118.5, 117.2, 109.3, 109.2, 52.1, 24.1, 21.3. HRMS (ESI) calculated for C14H12N2O4 [M+H]+: 273.0875; found: 273.0875.



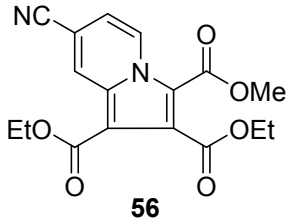
54

1,2-diethyl 3-methyl pyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate. Yield = 93%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.39 (dd, *J* = 6.3, 2.9 Hz, 1H), 9.26 (d, *J* = 7.5 Hz, 1H), 7.72 – 7.60 (m, 1H), 7.60 – 7.53 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 4.43 (dd, *J* = 14.3, 7.1 Hz, 2H), 4.40 (dd, *J* = 14.3, 7.1 Hz, 2H), 3.90 (s, 3H), 1.42 (t, *J* = 7.4 Hz, 3H), 1.39 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.2, 163.9, 160.4, 134.5, 130.4, 129.7, 129.1, 127.9, 127.2, 126.9, 124.3, 123.8, 115.9, 113.2, 107.9, 61.6, 61.1, 51.9, 14.3, 14.1. HRMS (ESI) calculated for $C_{20}H_{19}NO_6$ [M+H]+: 370.1291; found: 370.1289.



55

triethyl indolizine-1,2,3-tricarboxylate. Yield = 78%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.53 (d, *J* = 7.1 Hz, 1H), 8.35 (d, *J* = 9.0 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.03 (t, *J* = 6.6 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 4.41 – 4.34 (m, 4H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.38 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 162.9, 160.2, 137.9, 130.6, 127.9, 126.6, 119.9, 115.3, 111.8, 103.1, 61.8, 60.8, 60.3, 14.3, 14.1, 14.1. HRMS (ESI) calculated for $C_{17}H_{19}NO_6$ [M+H]+: 334.1291; found: 334.1292.



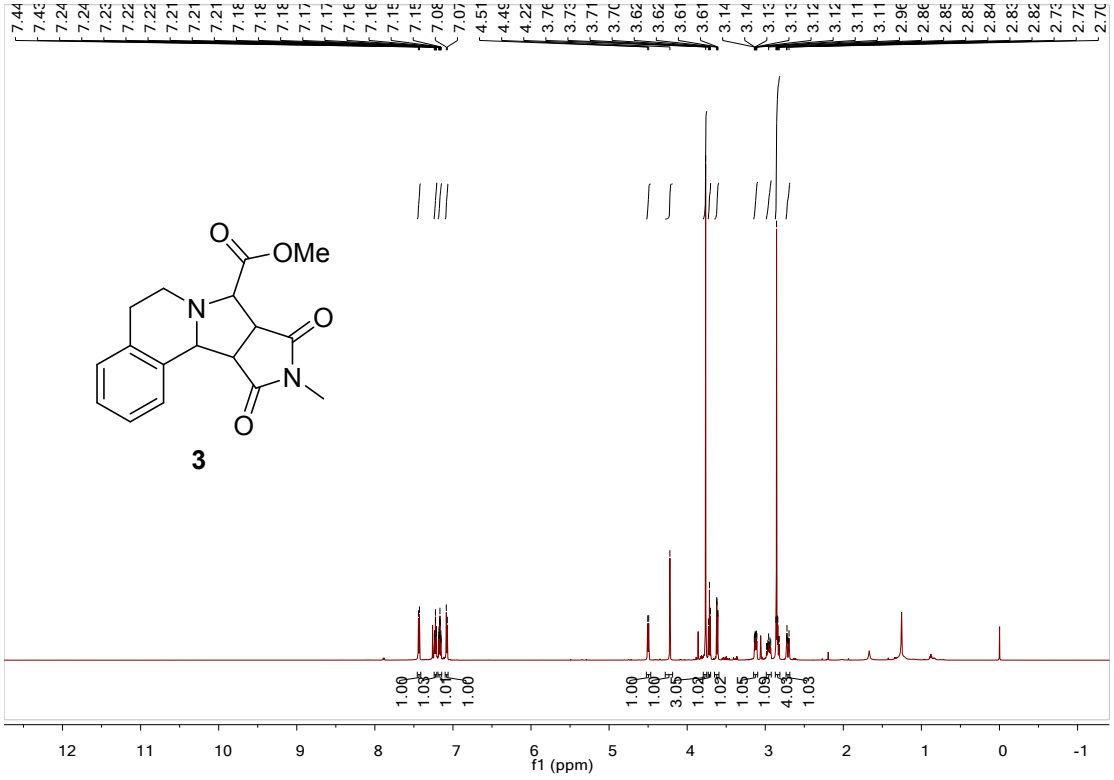
56

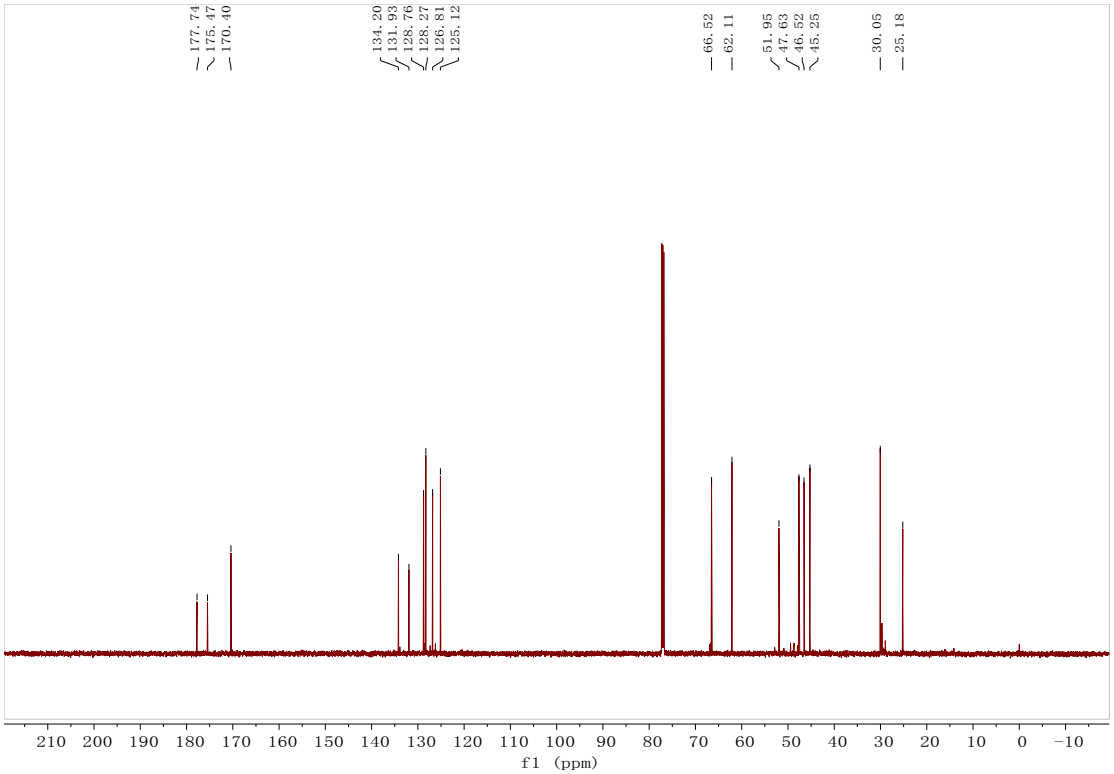
methyl 7-cyanoindolizine-1,2,3-tricarboxylate. Yield = 71%; White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.56 (dd, *J* = 7.4, 0.6 Hz, 1H), 8.72 (s, 1H), 7.11 (dd, *J* = 7.4, 1.8 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.59, 161.99, 160.03, 135.09, 131.44, 128.30, 126.09, 117.04, 115.01, 114.00, 109.23, 106.48, 62.14, 61.10, 52.31, 14.25, 14.18. HRMS (ESI) calculated for $C_{18}H_{18}N_2O_6$ [M+H]+: 359.1243; found: 359.1243.

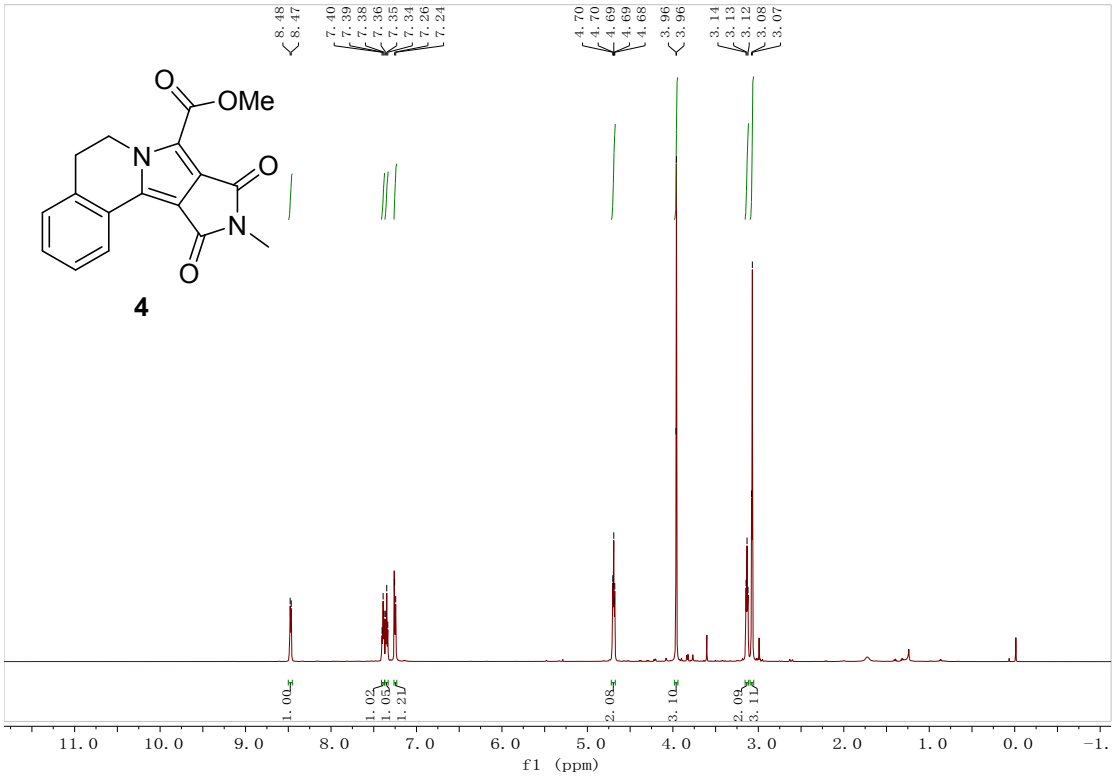
References

1. S. Guo, H. Zhang, L. Huang, Z. Guo, G. Xiong and J. Zhao, *Chem. Commun.*, 2013, **49**, 8689-8691.
2. (a) R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492-2521; (b) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230-13319; (c) J. E. Nutting, M. Rafiee and S. S. Stahl, *Chem. Rev.*, 2018, **118**, 4834-4885; (d) X.-Y. Qian, S.-Q. Li, J. Song and H.-C. Xu, *ACS Catalysis*, 2017, **7**, 2730-2734.

Copies of Product NMR Spectra



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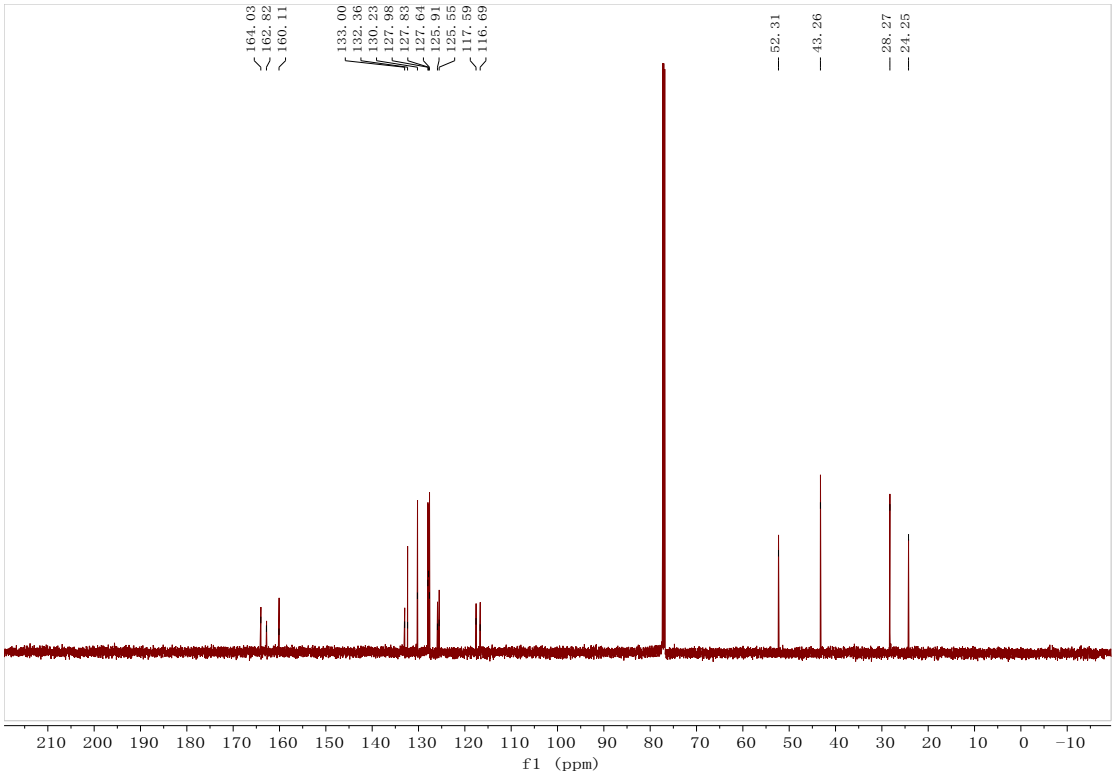
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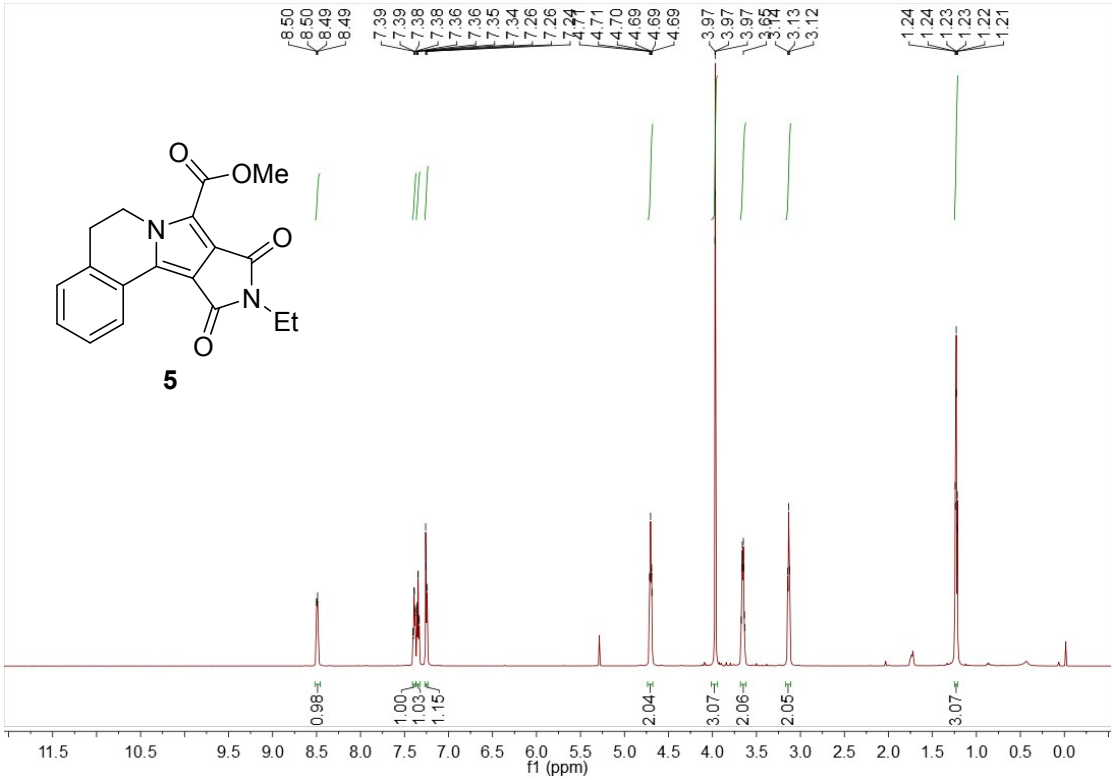
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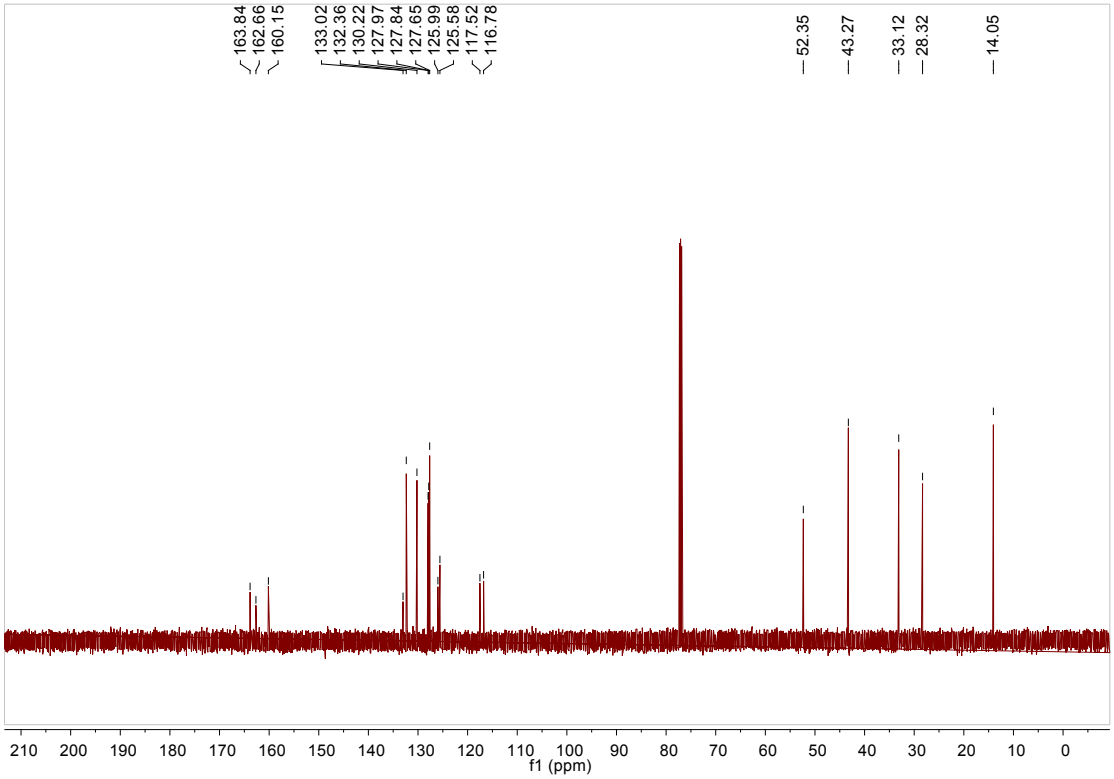
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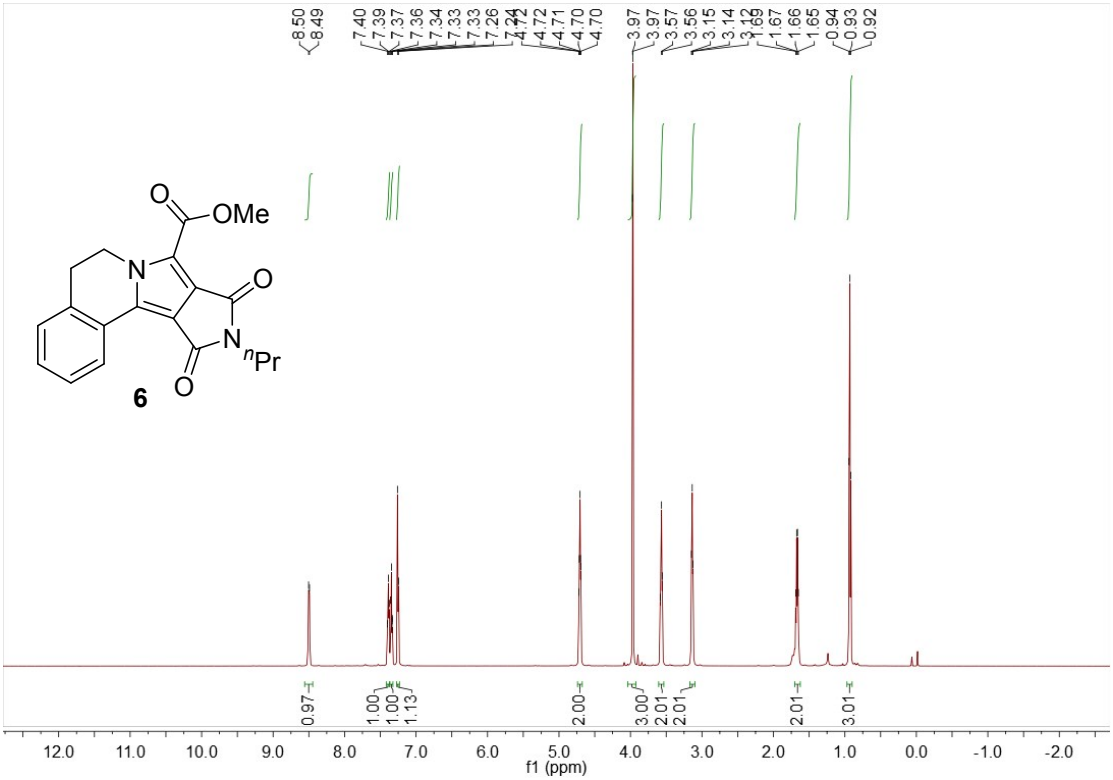
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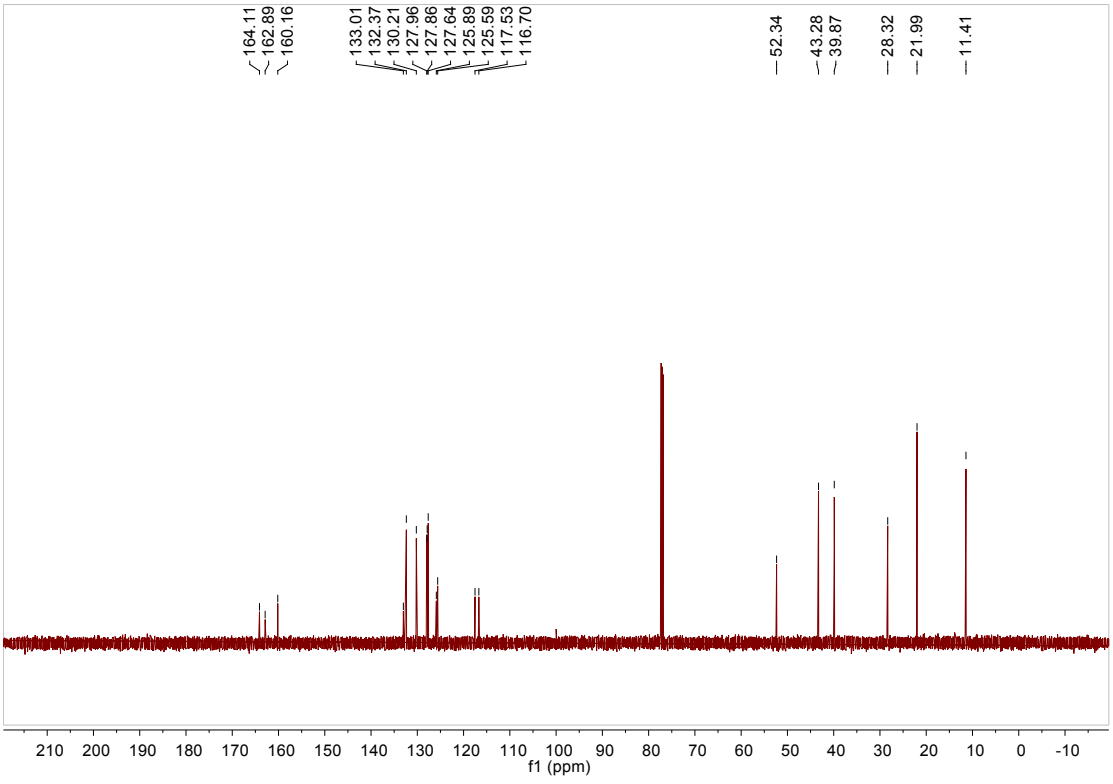
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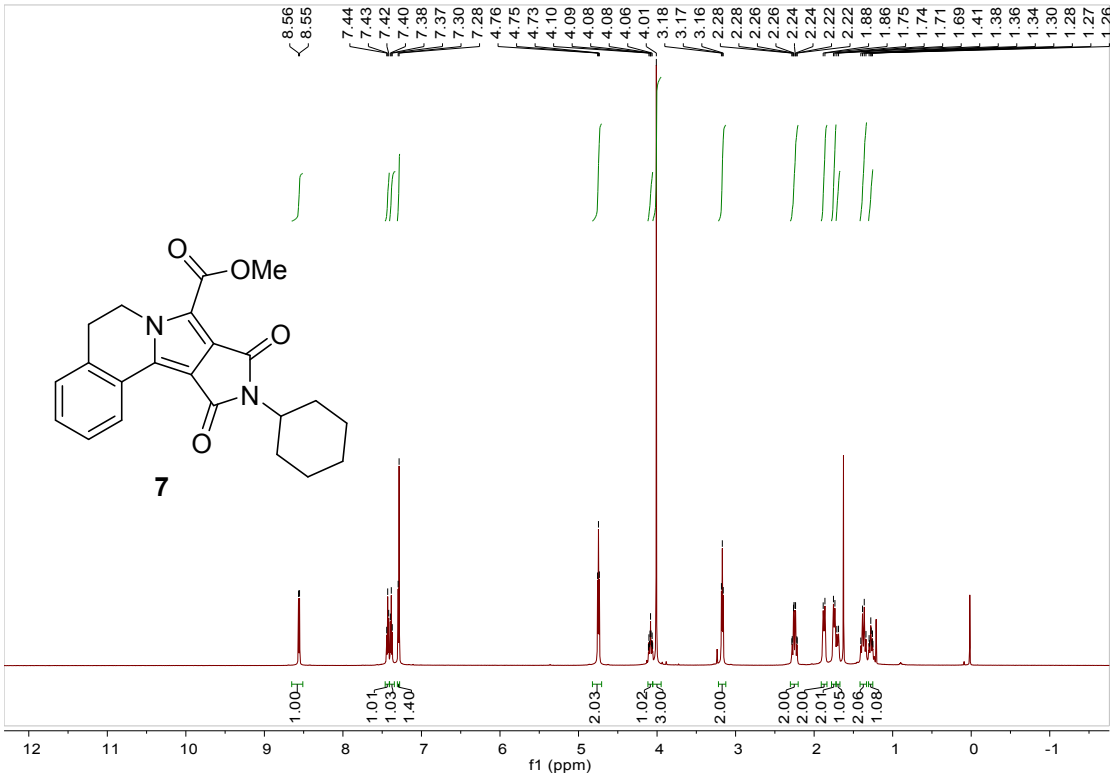
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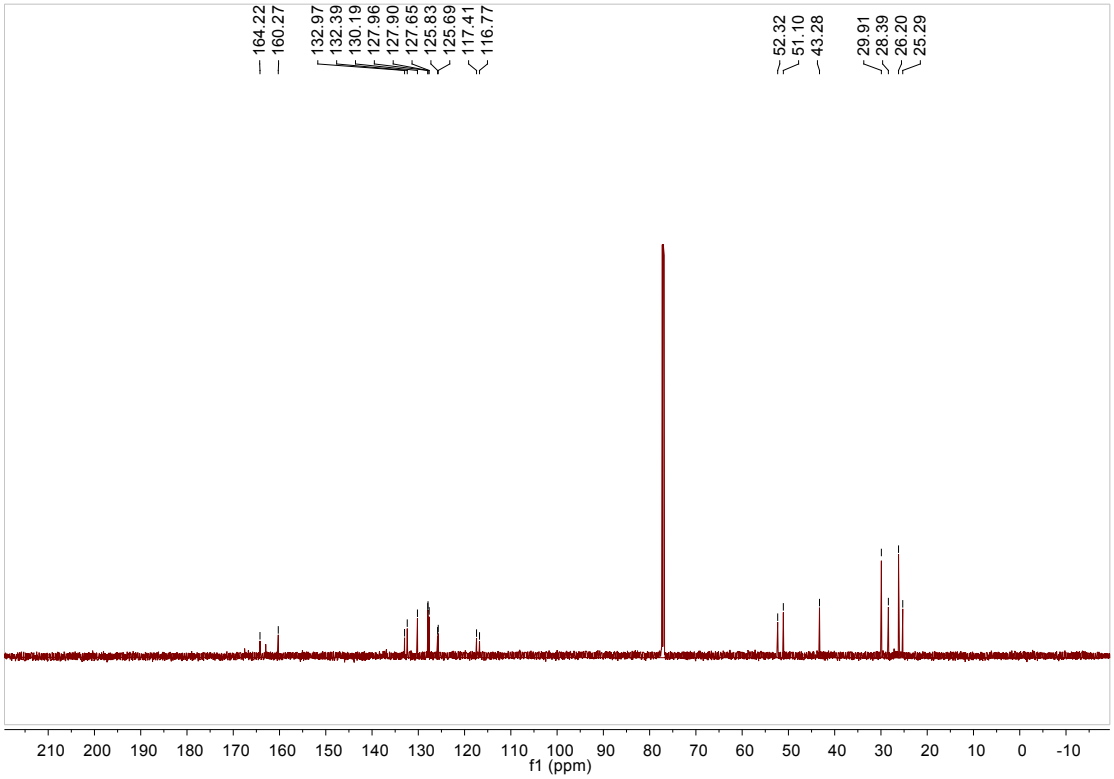
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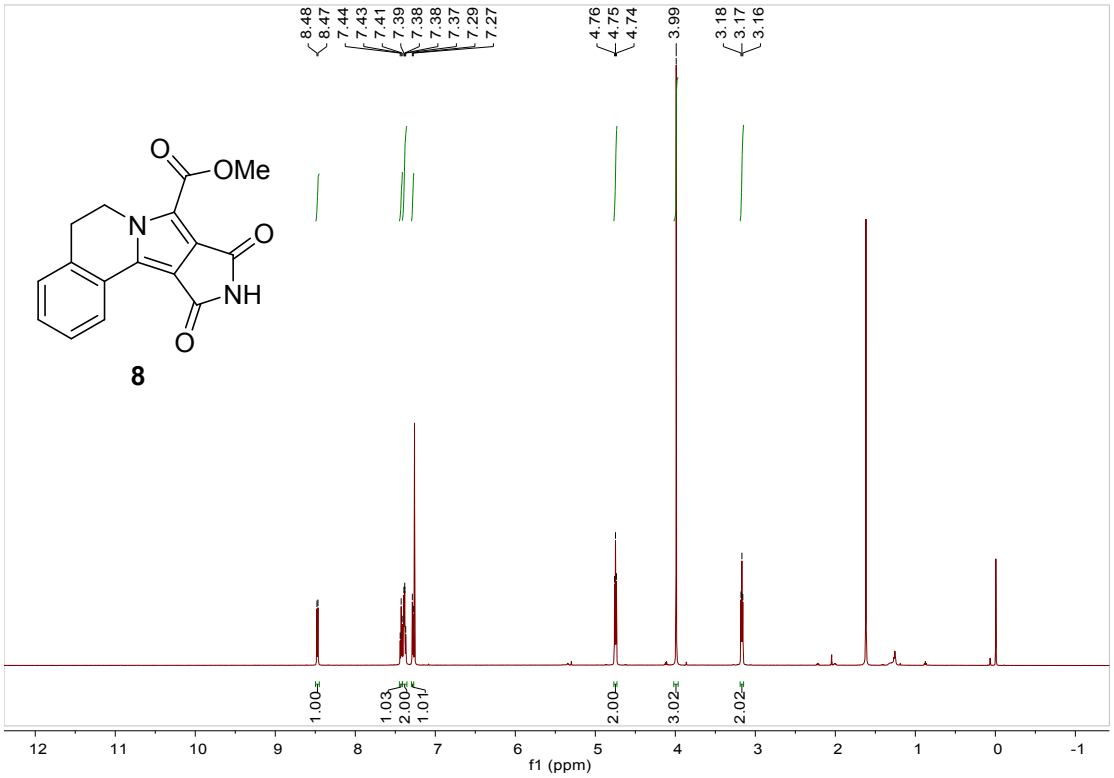
f1 (ppm)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7.38
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7.27
4.76
4.75
4.74
3.99
3.18
3.17
3.16
O
OMe
N
O
NH
O
1.00
1.03
2.00
1.01
2.00
3.02
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10
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8
7
6
5
4
3
2
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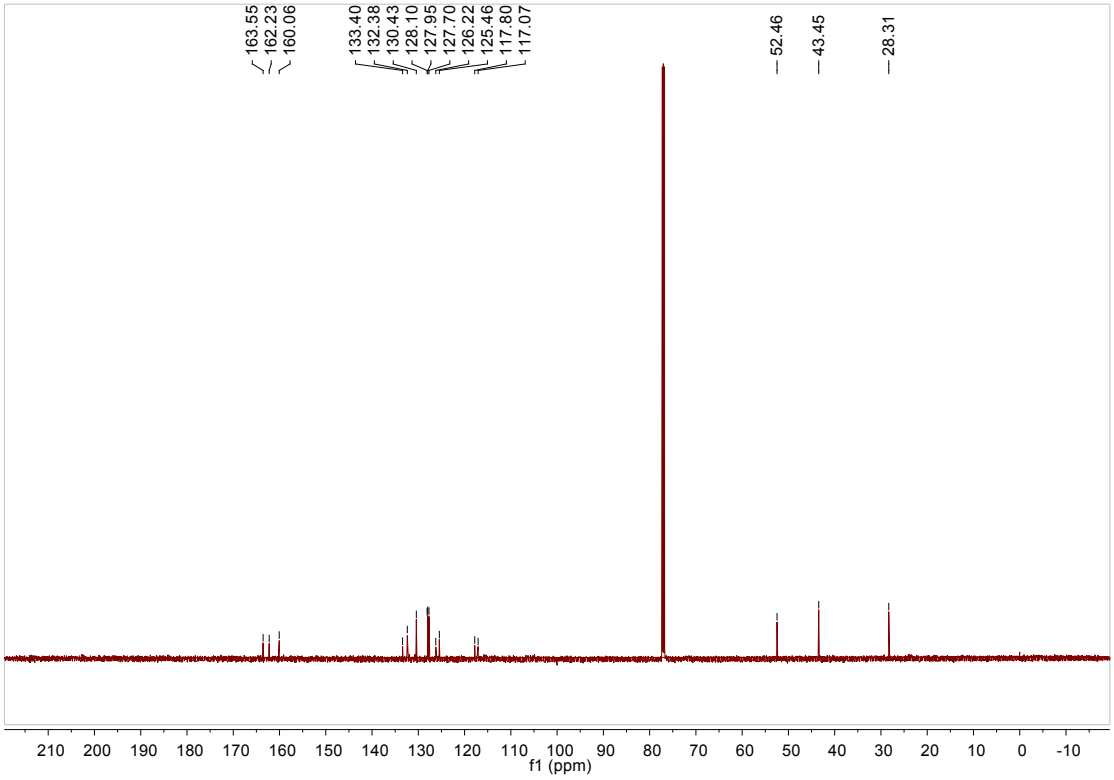
0
-1
f1 (ppm)

8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117.07
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43.45
28.31
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200
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180
170
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30
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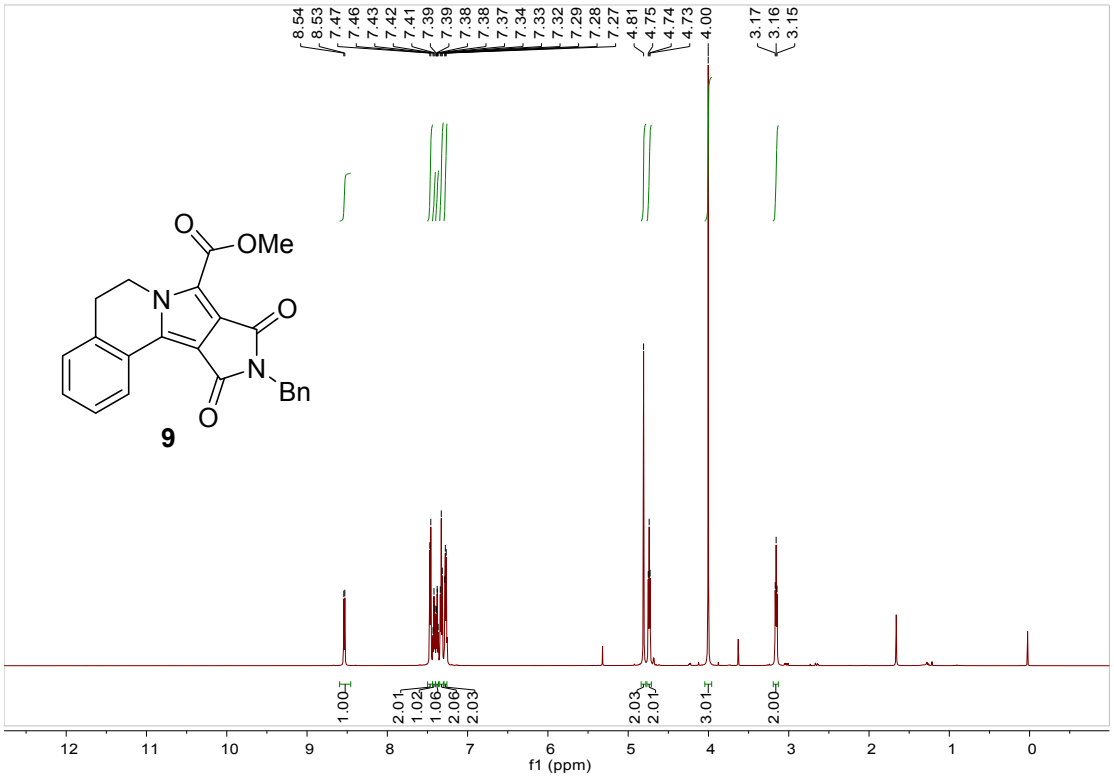
f1 (ppm)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7.33
7.32
7.29
7.28
7.27
4.81
4.75
4.74
4.73
4.00
3.17
3.16
3.15
O
OMe
N
O
N
Bn
O
9
1.00
2.01
1.02
1.06
2.06
2.03
2.03
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7
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5
4
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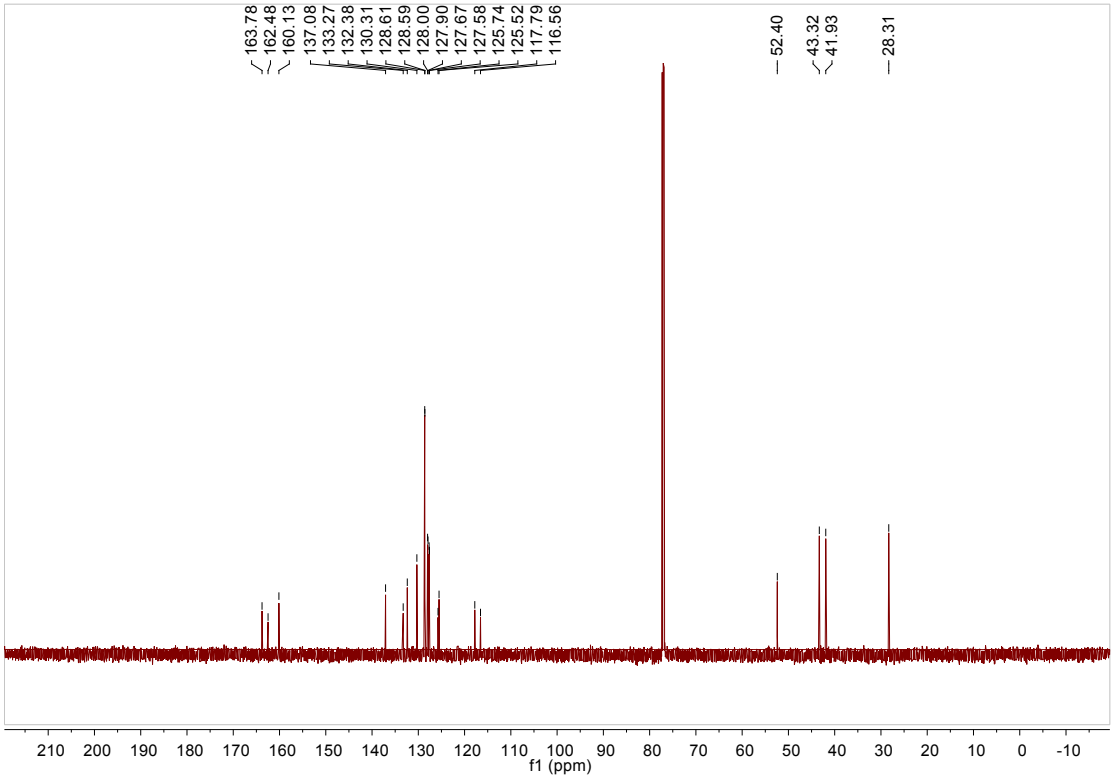
f1 (ppm)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125.52
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52.40
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41.93
28.31
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200
190
180
170
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80
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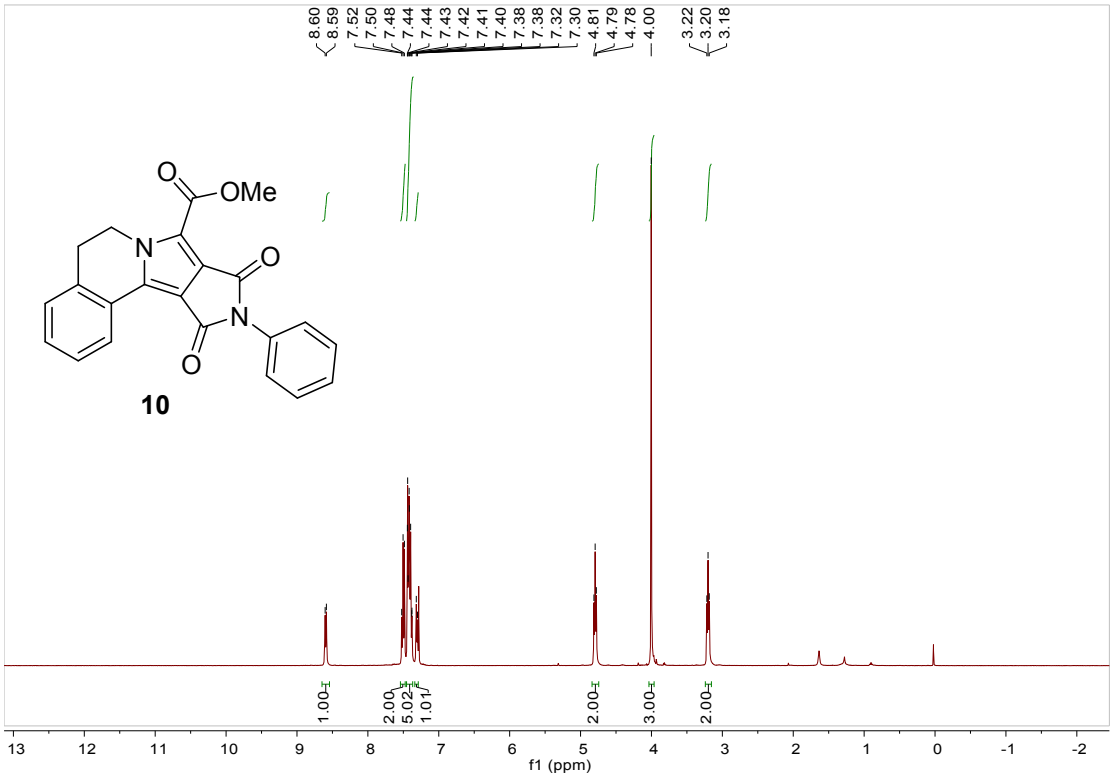
-10
f1 (ppm)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7.43
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7.41
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7.38
7.38
7.32
7.30
4.81
4.79
4.78
4.00
3.22
3.20
3.18
O
OMe
N
O
N
O
10
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2.00
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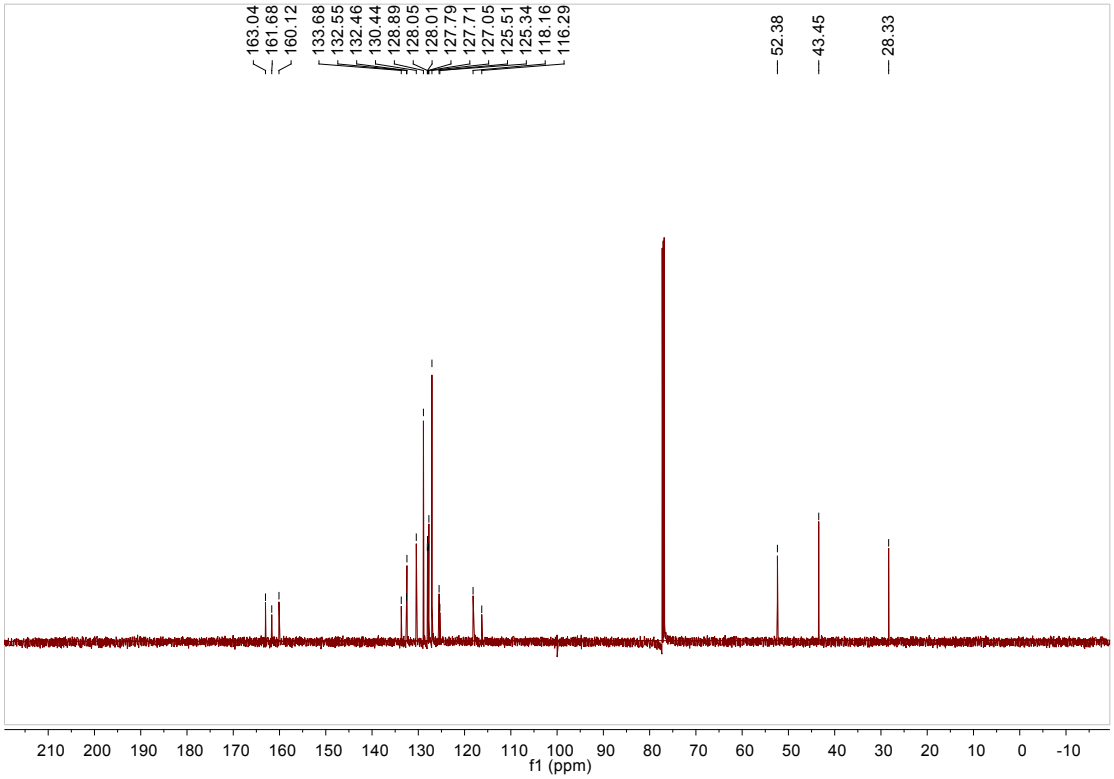
1.01
2.00
3.00
2.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)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128.01
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127.71
127.05
125.51
125.34
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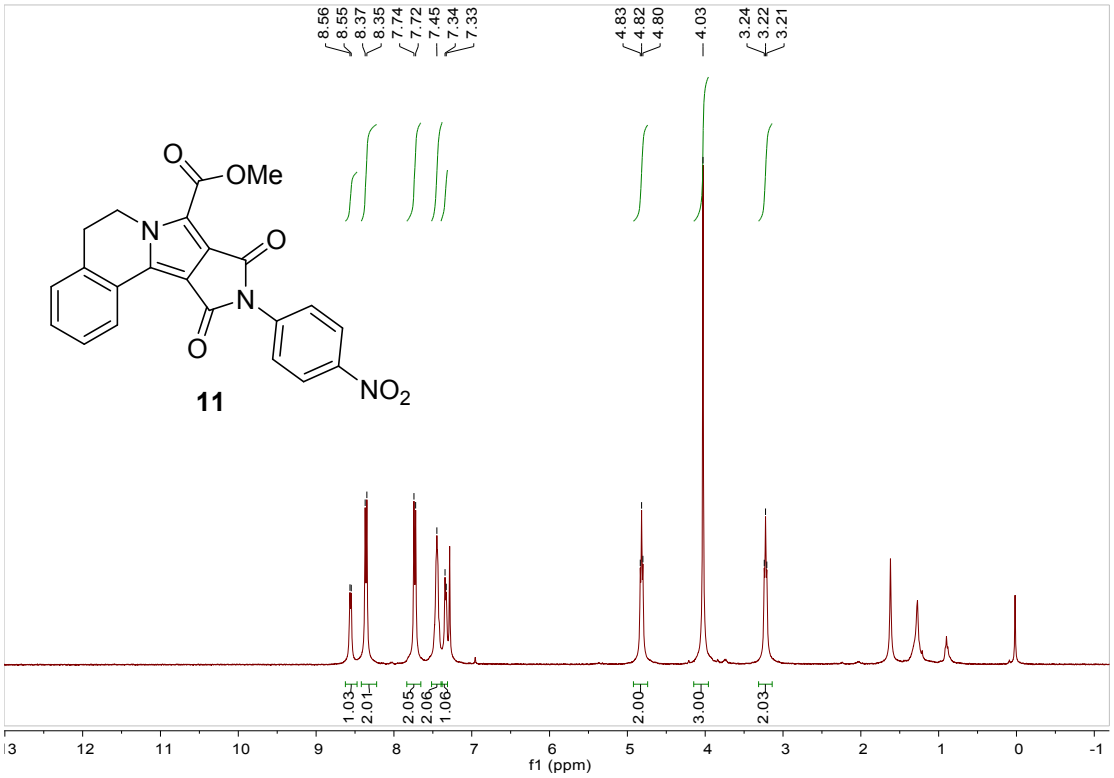
52.38
43.45
28.33
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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4.80
4.03
3.24
3.22
3.21
O
OMe
N
O
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O
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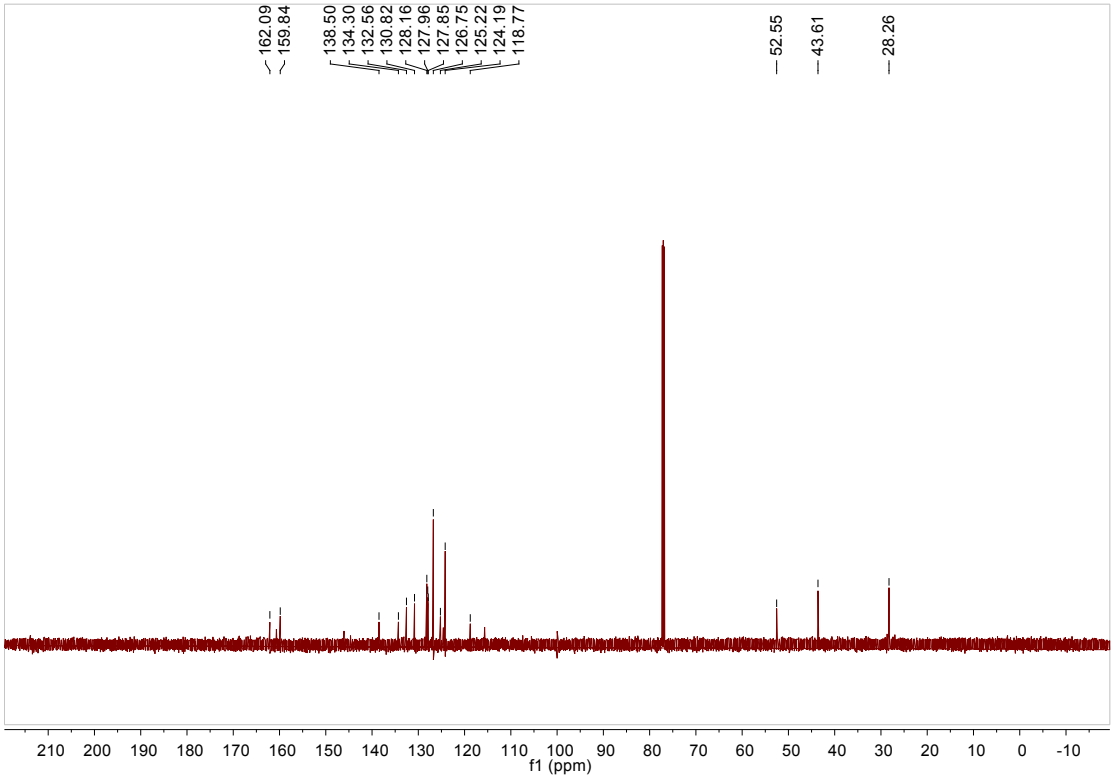
1.03
2.01
2.05
2.06
1.06
2.00
3.00
2.03
f1 (ppm)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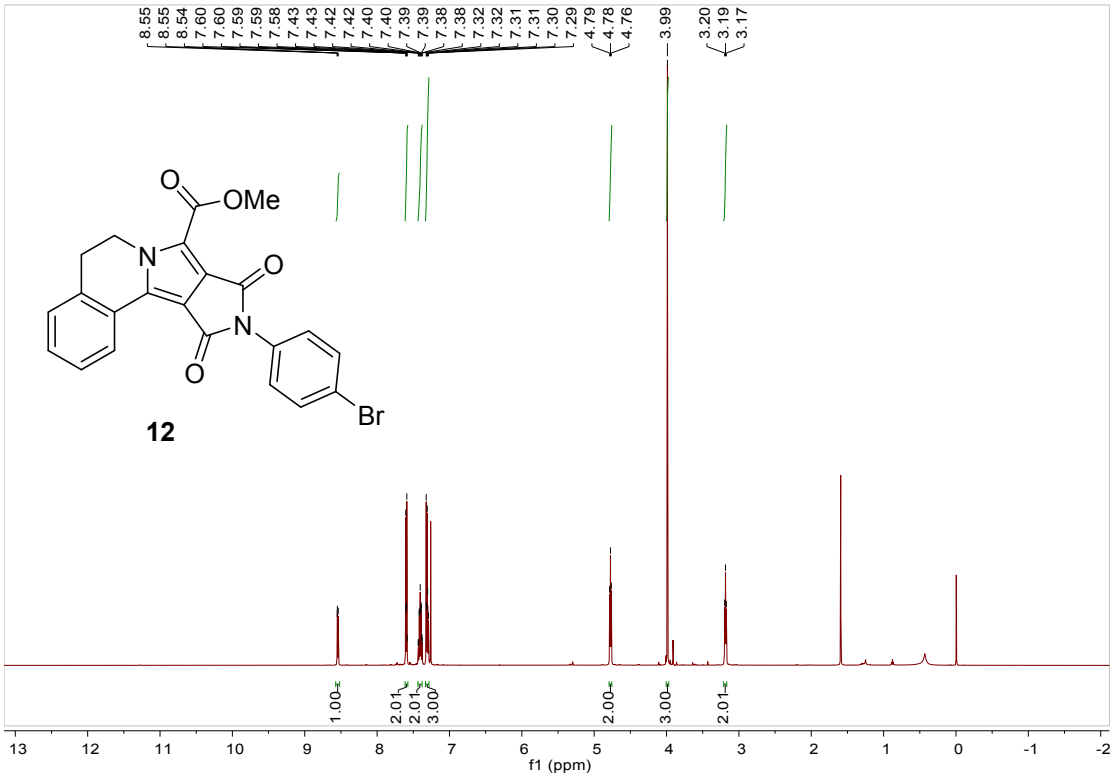
52.55
43.61
28.26
f1 (ppm)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7.31
7.30
7.29
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4.78
4.76
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3.19
3.17
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N
O
N
O
Br
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2.01
3.00
2.00
3.00
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4
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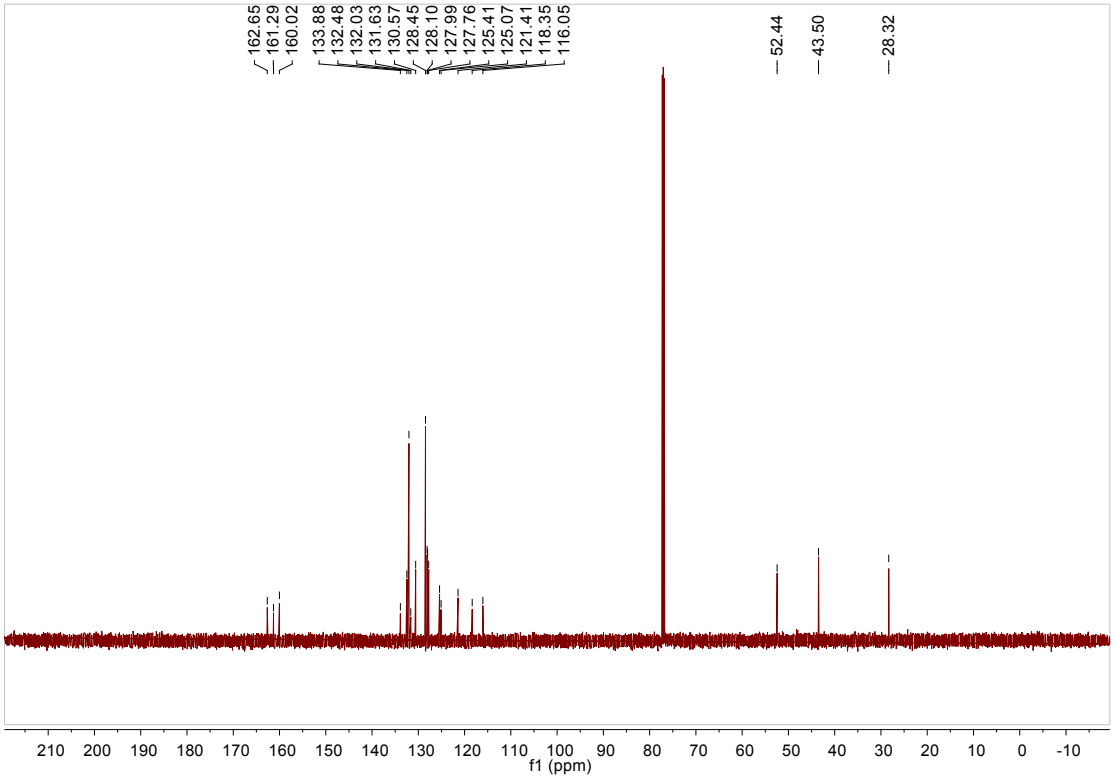
-2
f1 (ppm)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43.50
28.32
210
200
190
180
170
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120
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100
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80
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60
50
40
30
20
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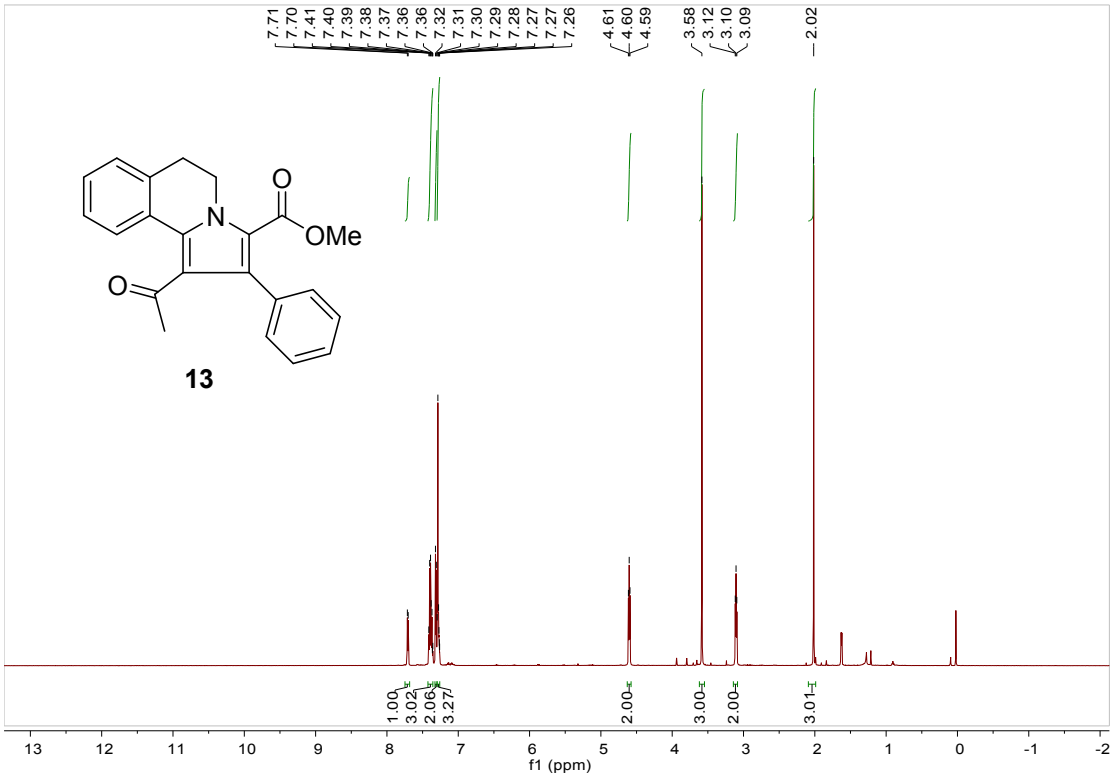
0
-10
f1 (ppm)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7.27
7.26
4.61
4.60
4.59
3.58
3.12
3.10
3.09
2.02
O
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OMe
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1.00
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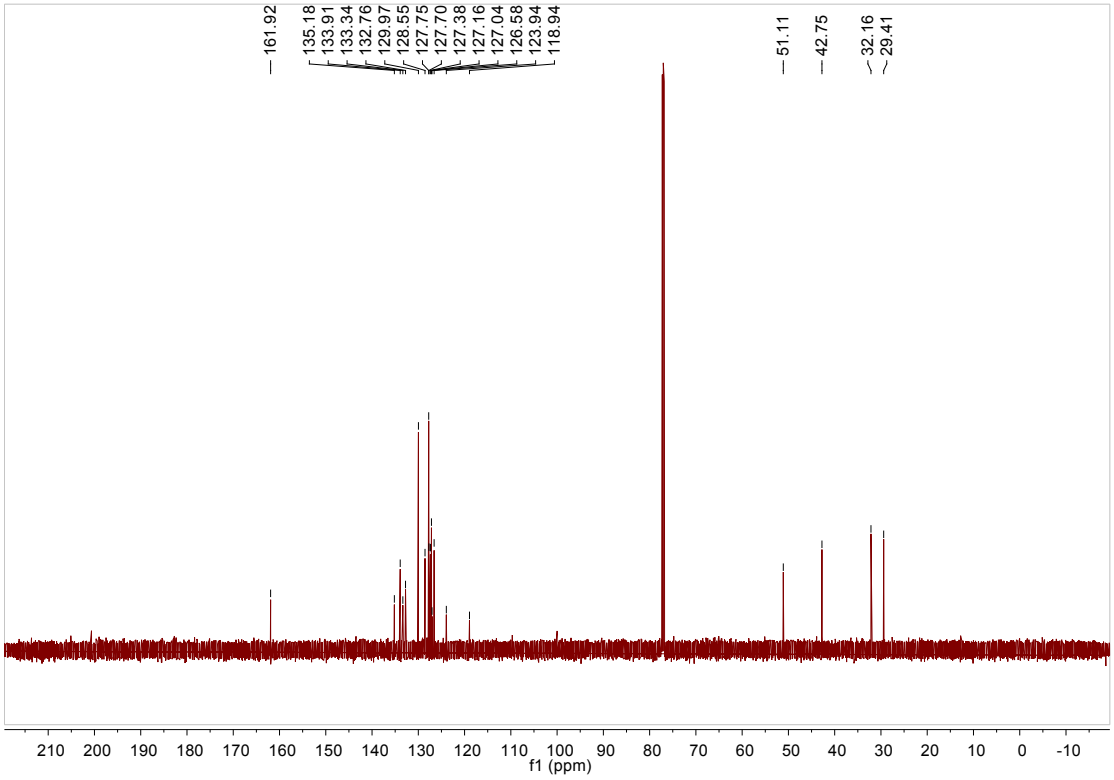
3.00
2.00
3.01
f1 (ppm)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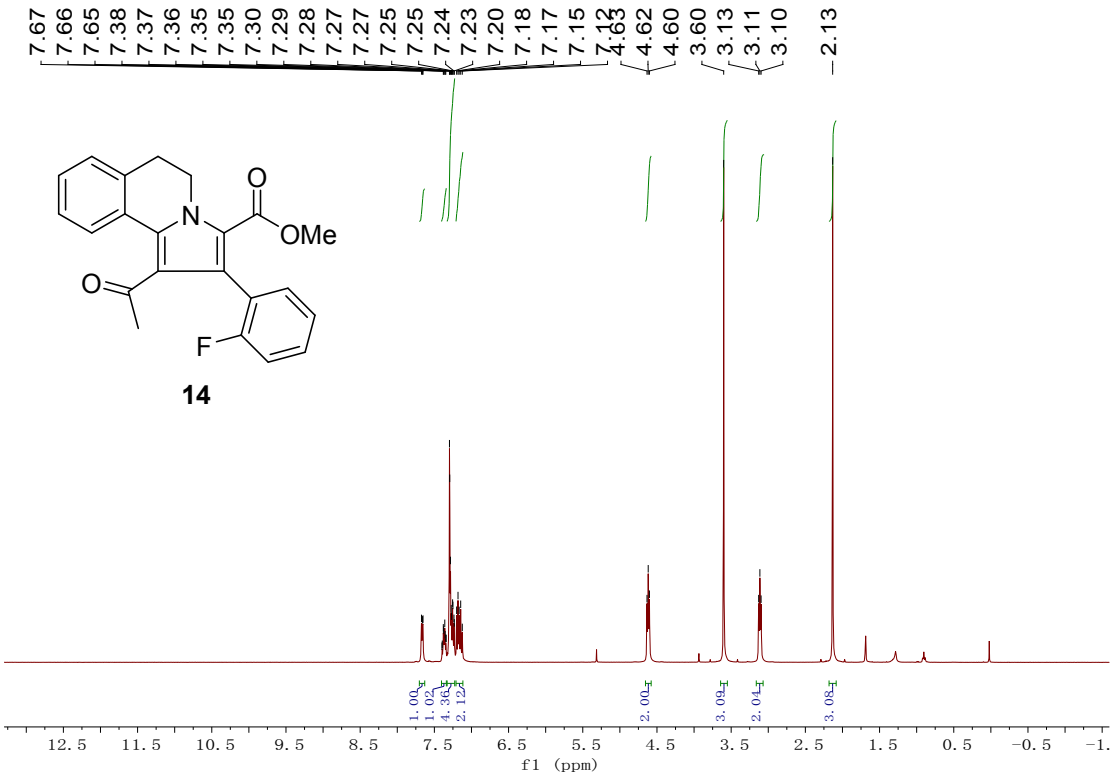
29.41
f1 (ppm)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7.25
7.24
7.23
7.20
7.18
7.17
7.15
7.12
4.63
4.62
4.60
3.60
3.13
3.11
3.10
2.13
O
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OMe
O
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1.02
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2.00
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3.08
12.5
11.5
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9.5
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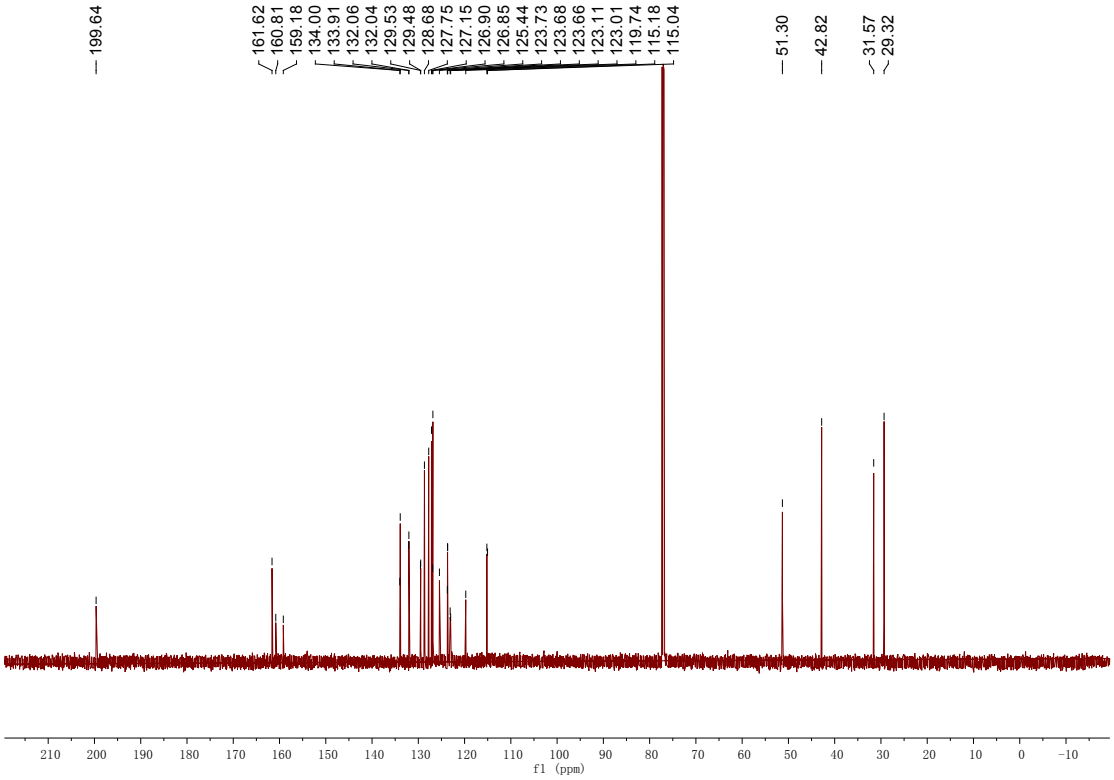
−1.
f1 (ppm)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126.90
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125.44
123.73
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123.66
123.11
123.01
119.74
115.18
115.04
51.30
42.82
31.57
29.32
210
200
190
180
170
160
150
140
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120
110
100
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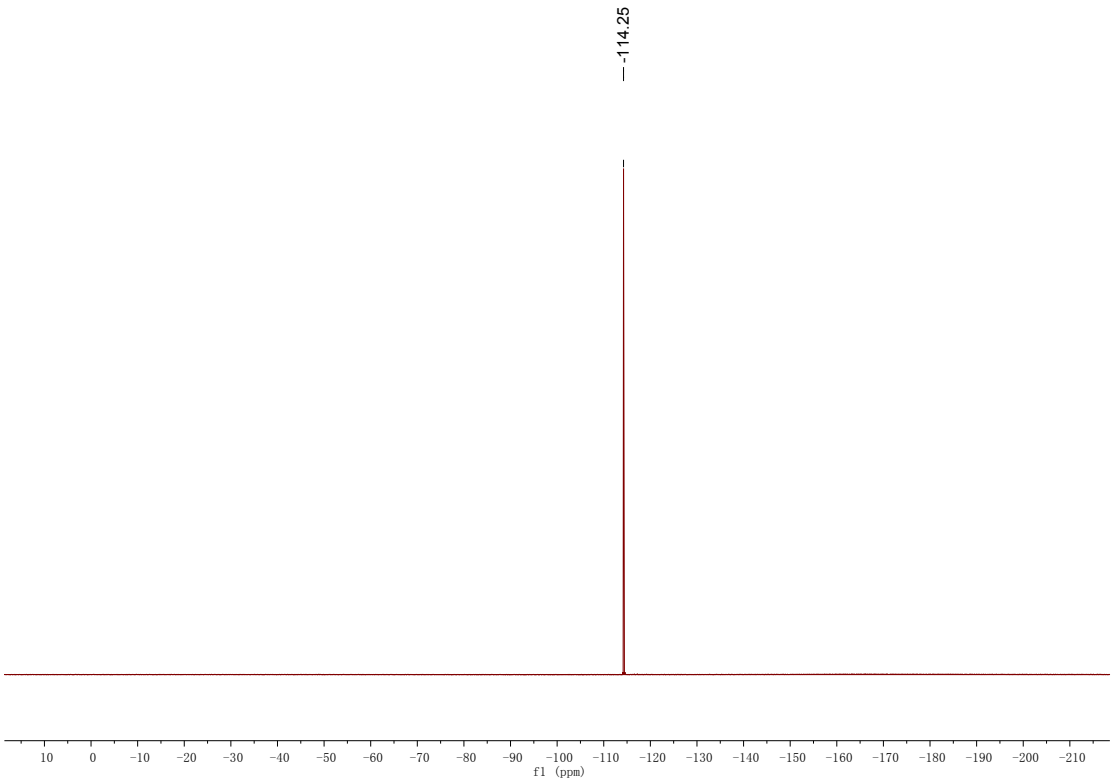
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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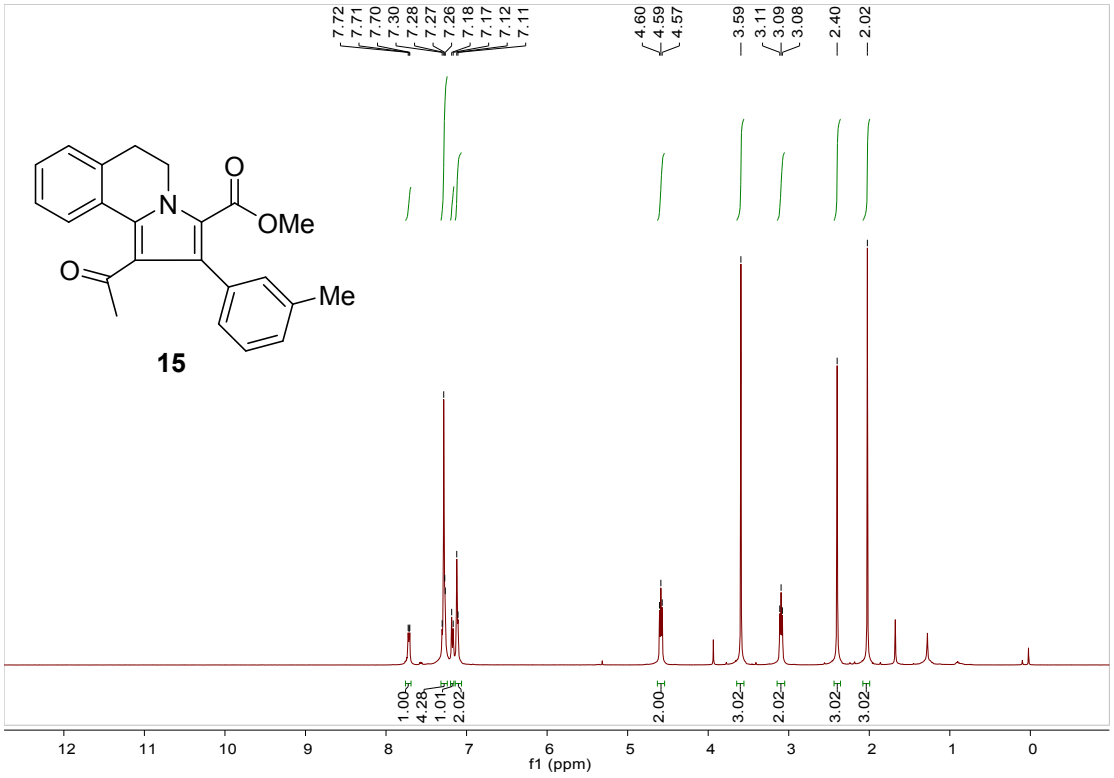
10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210
f1 (ppm)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7.11
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4.59
4.57
3.59
3.11
3.09
3.08
2.40
2.02
O
N
OMe
O
Me
15
1.00
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1.01
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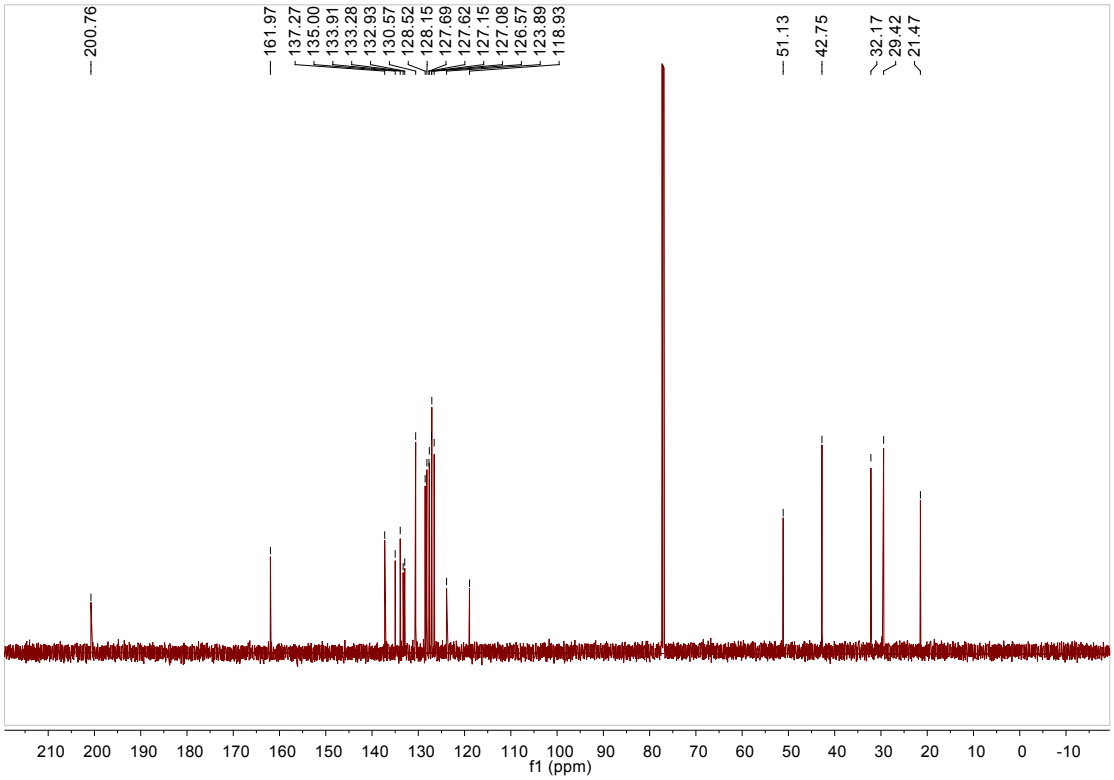
2.00
3.02
2.02
3.02
3.02
12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)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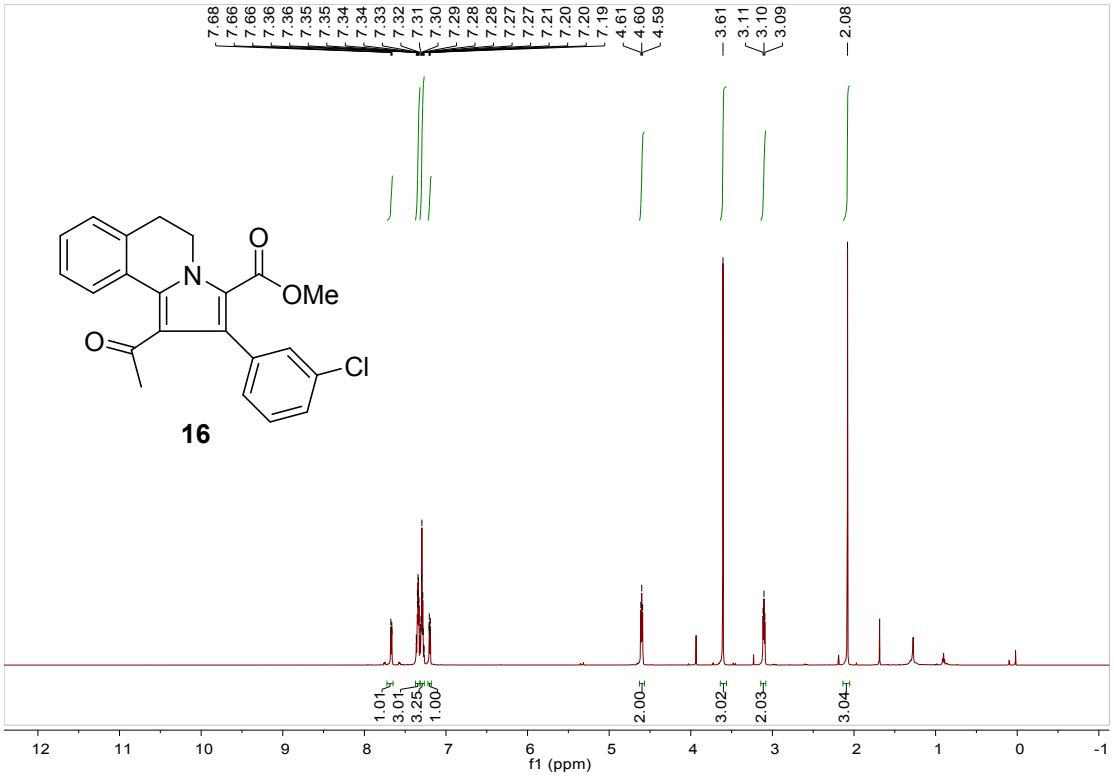
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7.28
7.27
7.27
7.21
7.20
7.20
7.19
4.61
4.60
4.59
3.61
3.11
3.10
3.09
2.08
O
N
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O
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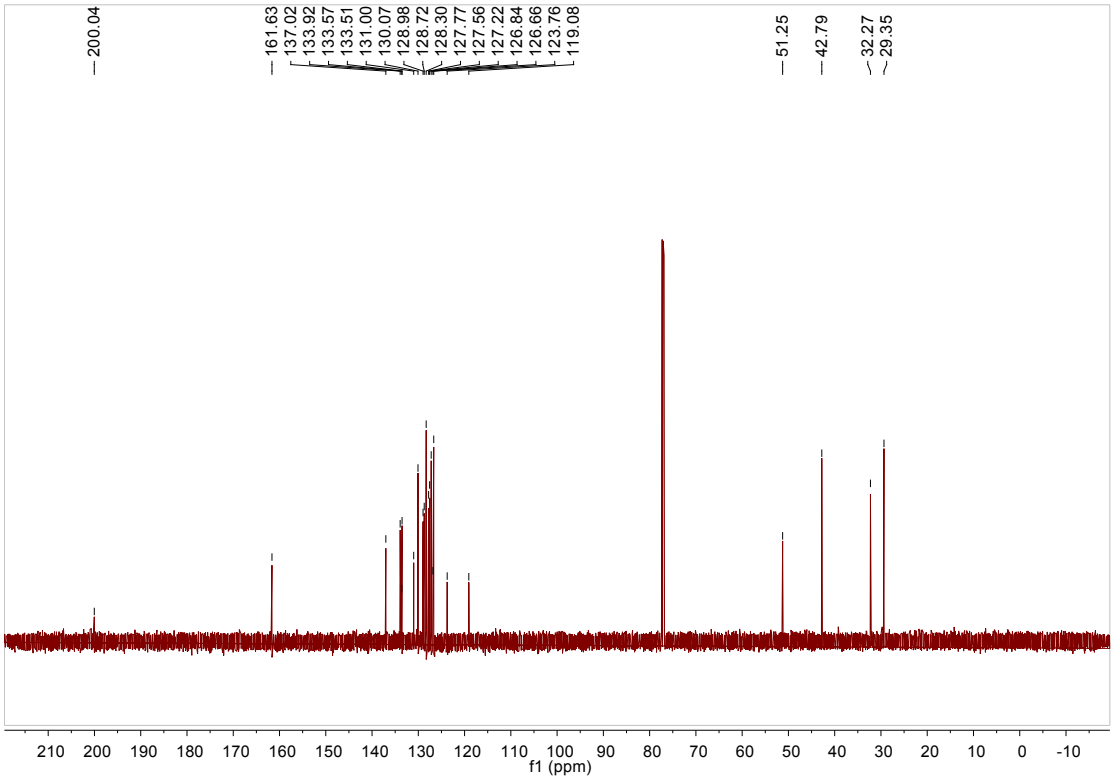
3.04
f1 (ppm)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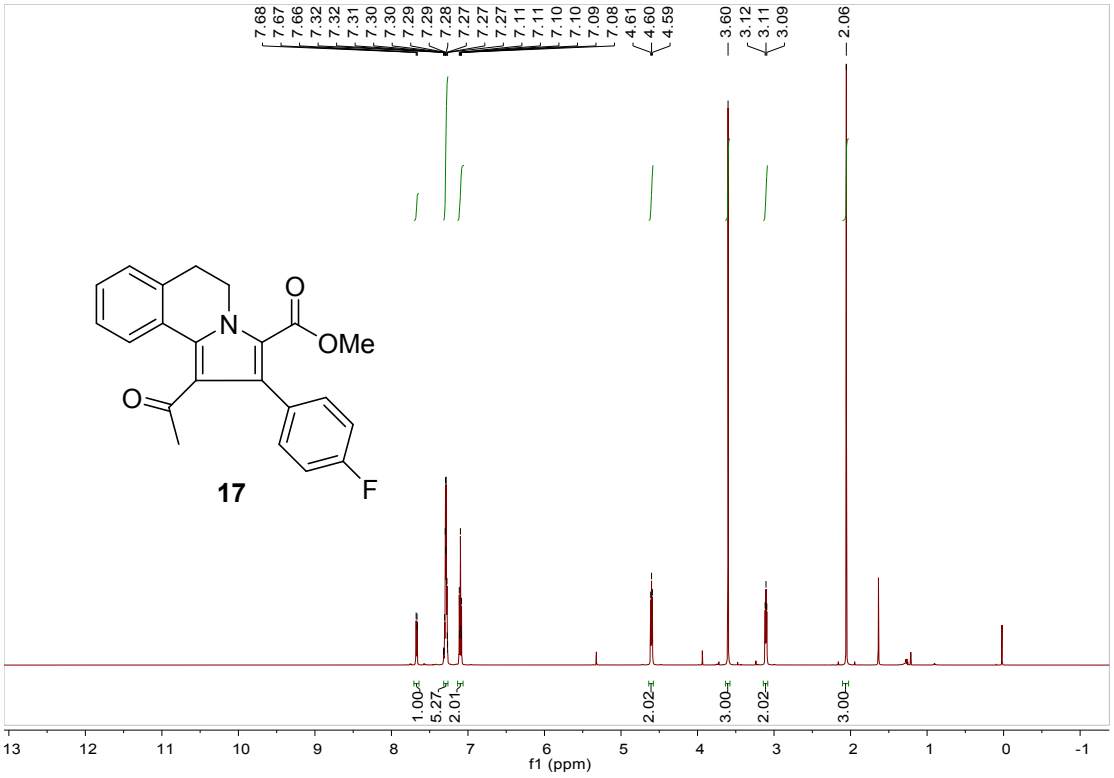
42.79
32.27
29.35
f1 (ppm)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7.27
7.11
7.11
7.10
7.10
7.09
7.08
4.61
4.60
4.59
3.60
3.12
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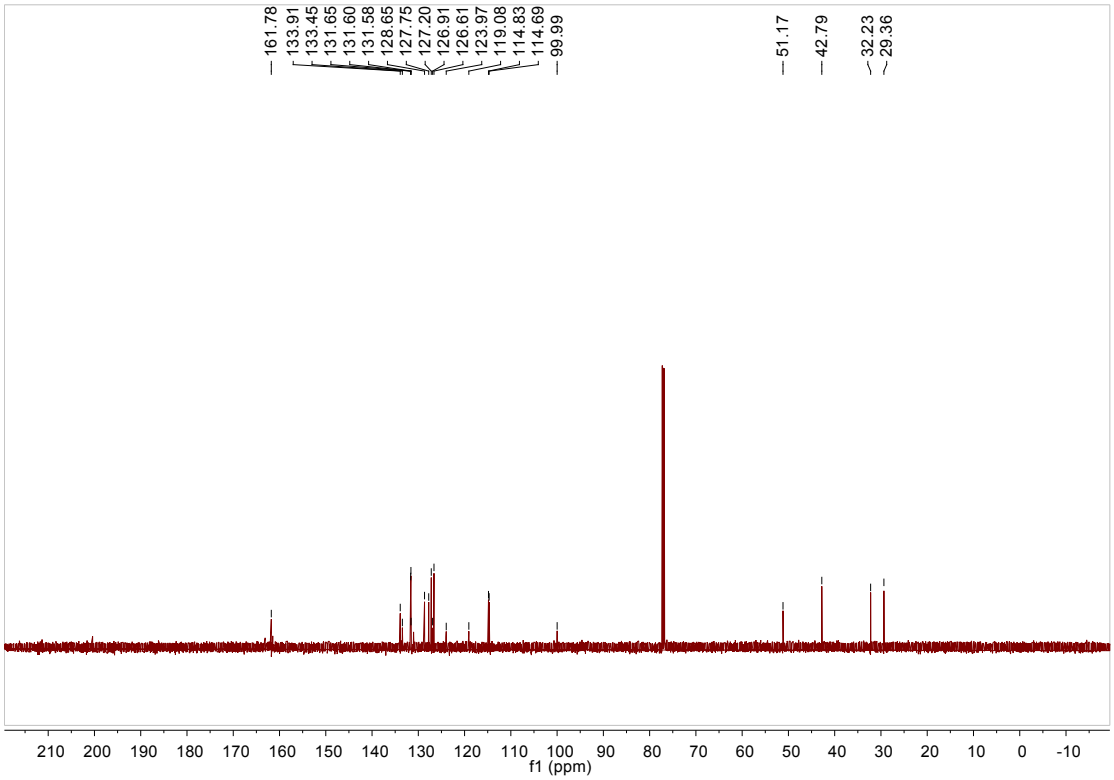
3.00
2.02
3.00
f1 (ppm)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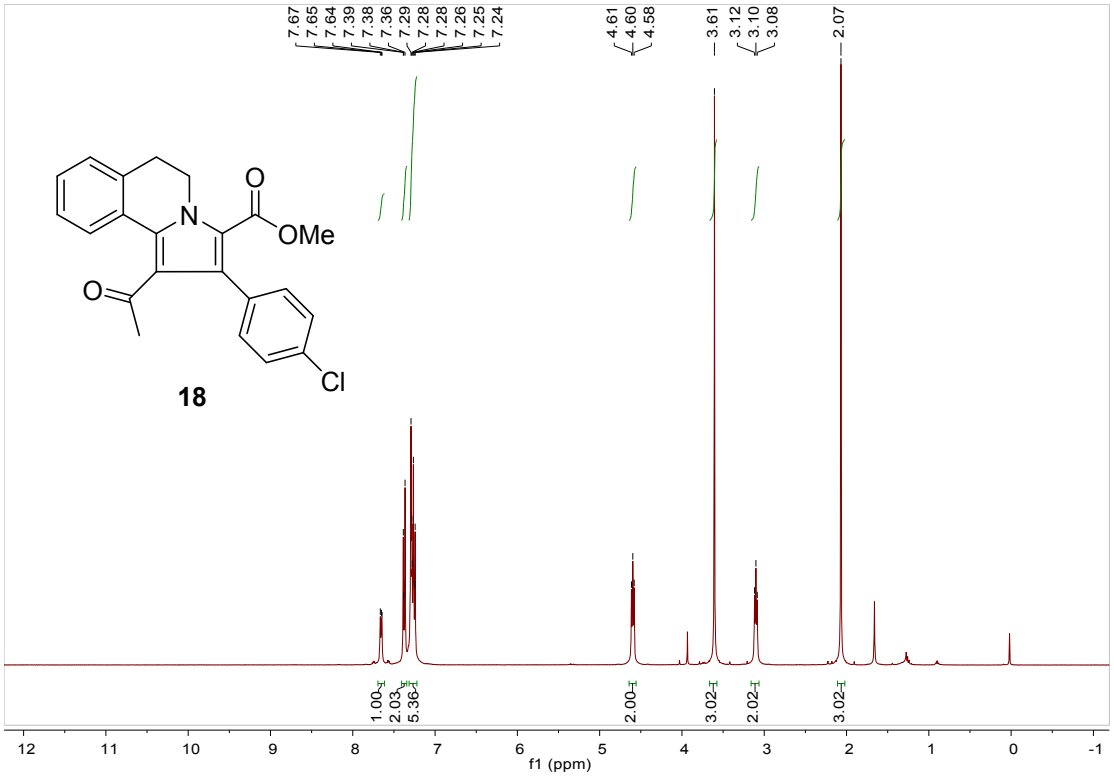
114.69
99.99
51.17
42.79
32.23
29.36
f1 (ppm)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7.25
7.24
4.61
4.60
4.58
3.61
3.12
3.10
3.08
2.07
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5.36
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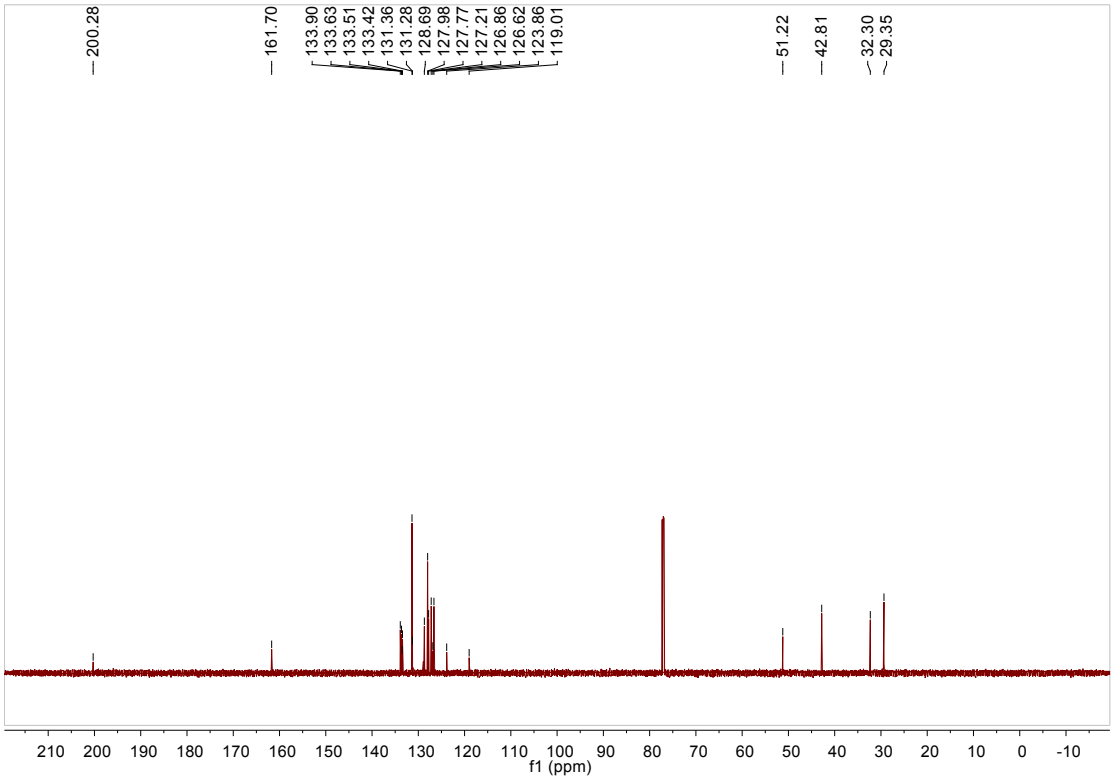
3.02
2.02
3.02
f1 (ppm)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42.81
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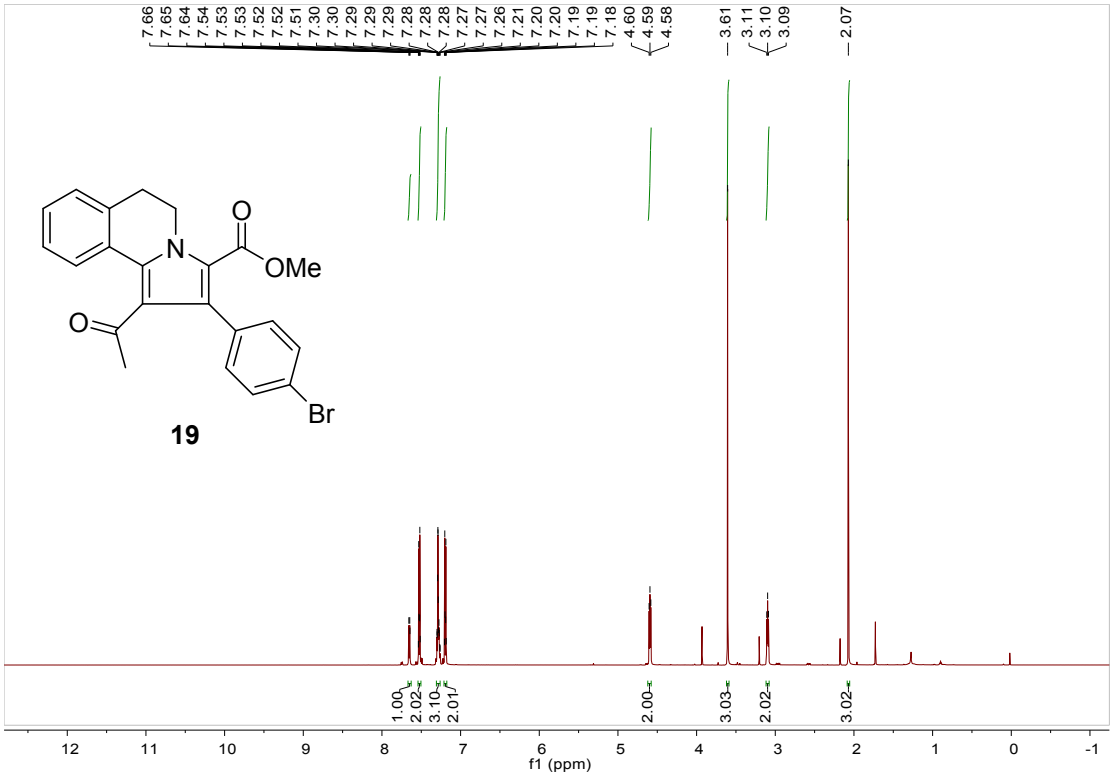
29.35
f1 (ppm)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7.26
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7.19
7.19
7.18
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4.59
4.58
3.61
3.11
3.10
3.09
2.07
O
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O
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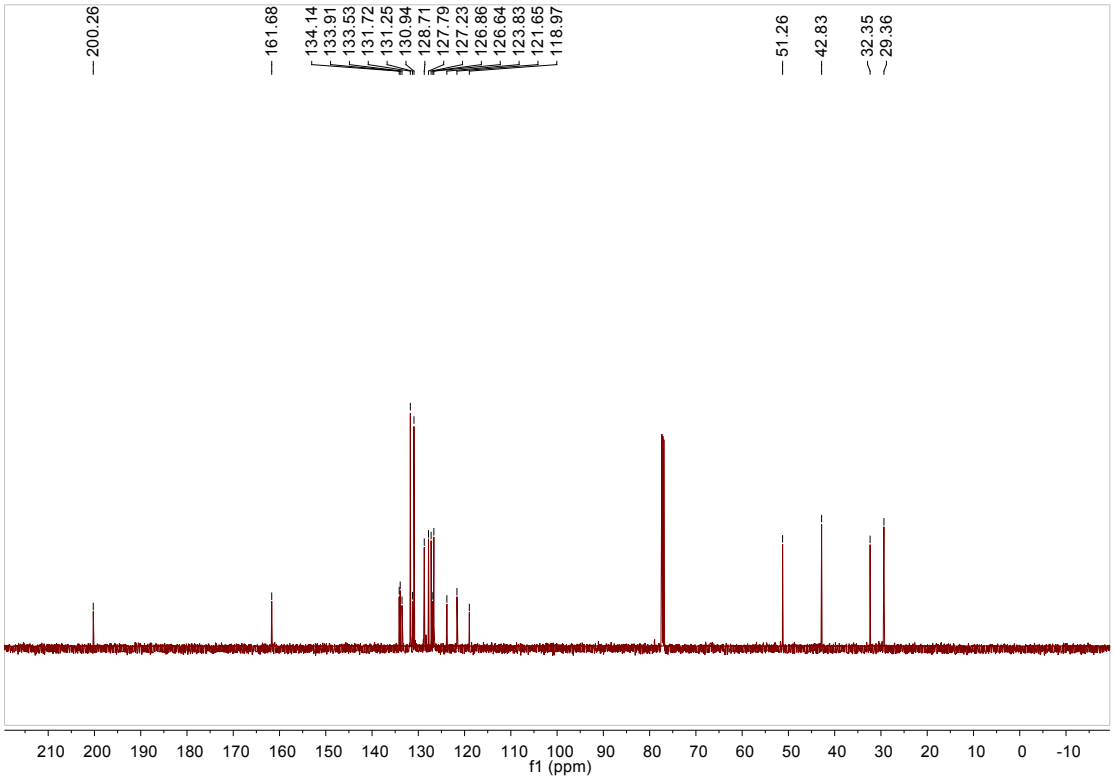
3.10
2.01
2.00
3.03
2.02
3.02
f1 (ppm)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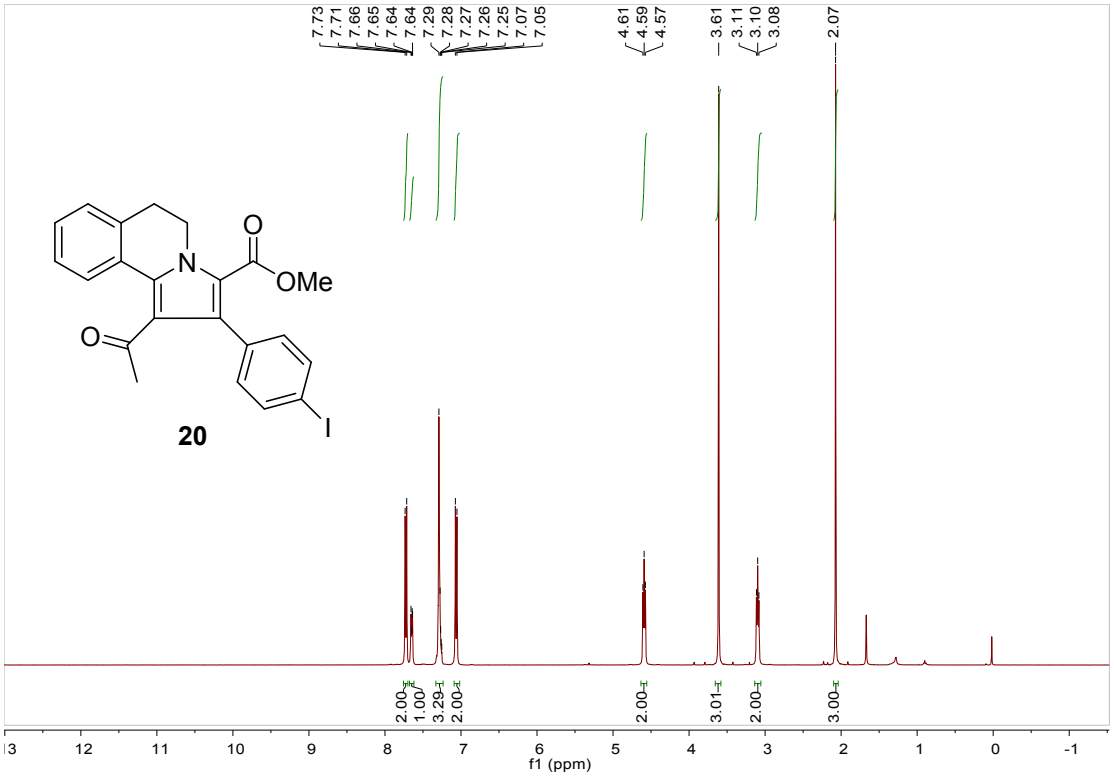
42.83
32.35
29.36
f1 (ppm)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7.26
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4.61
4.59
4.57
3.61
3.11
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3.08
2.07
O
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O
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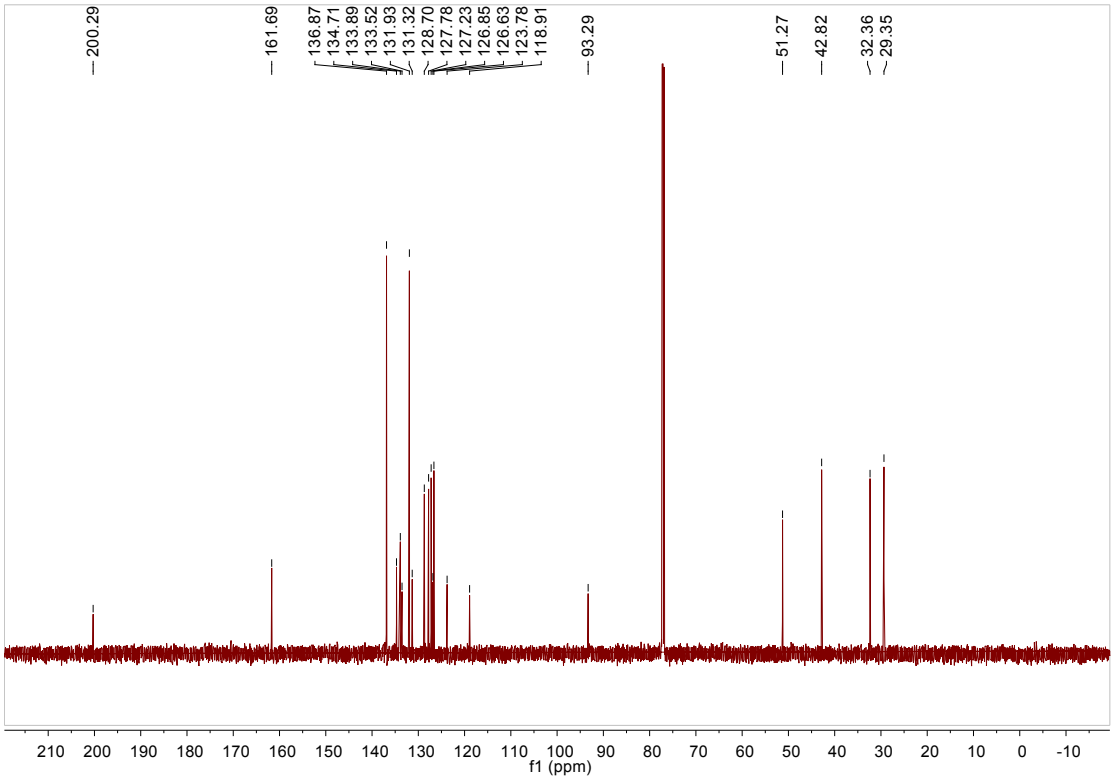
1.00
3.29
2.00
2.00
3.01
2.00
3.00
f1 (ppm)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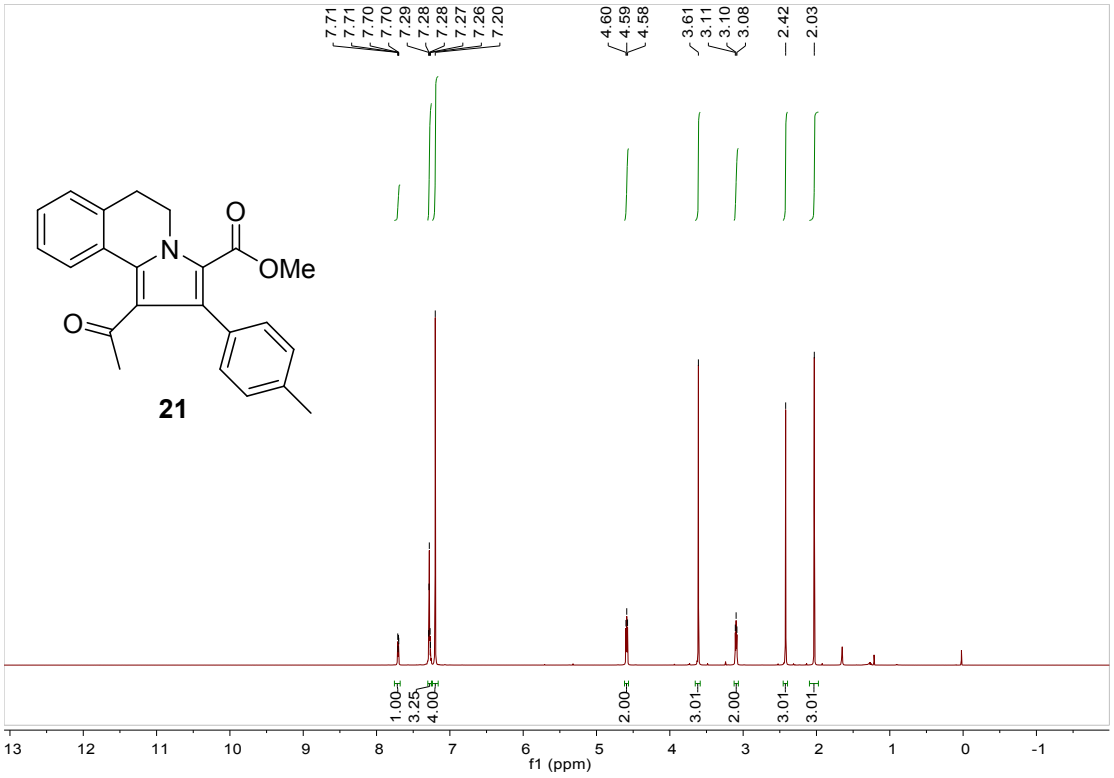
123.78
118.91
93.29
51.27
42.82
32.36
29.35
f1 (ppm)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3.08
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2.03
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f1 (ppm)

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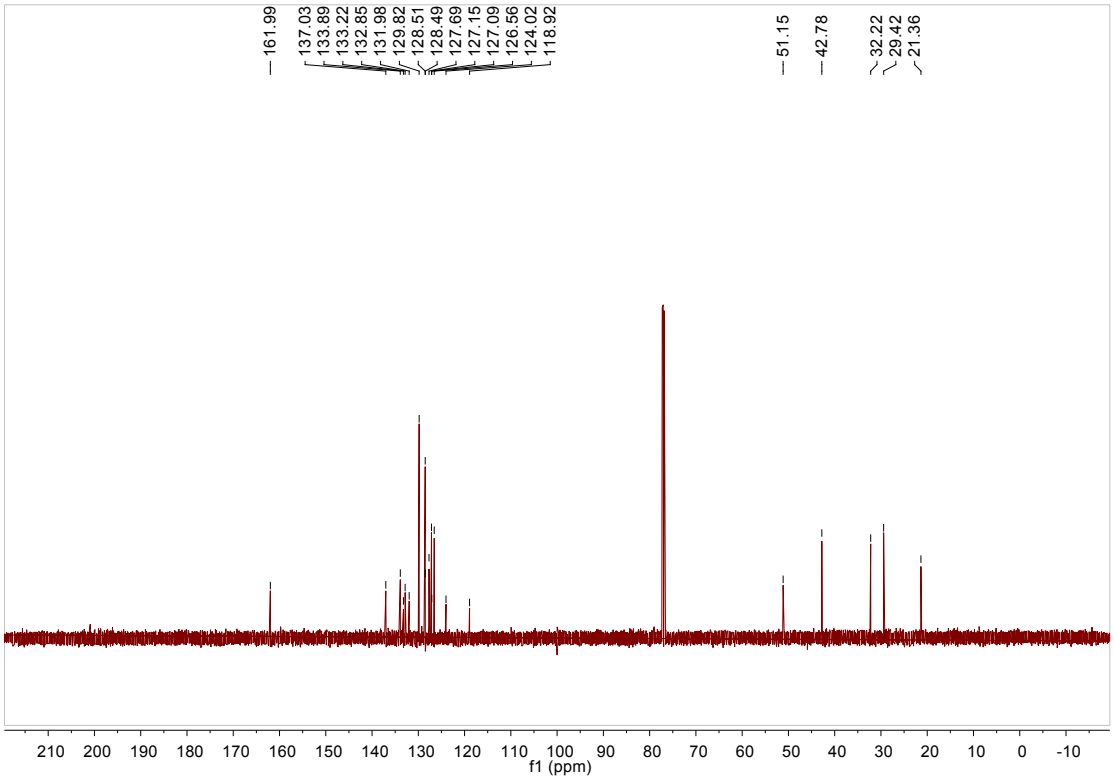
OMe
O

21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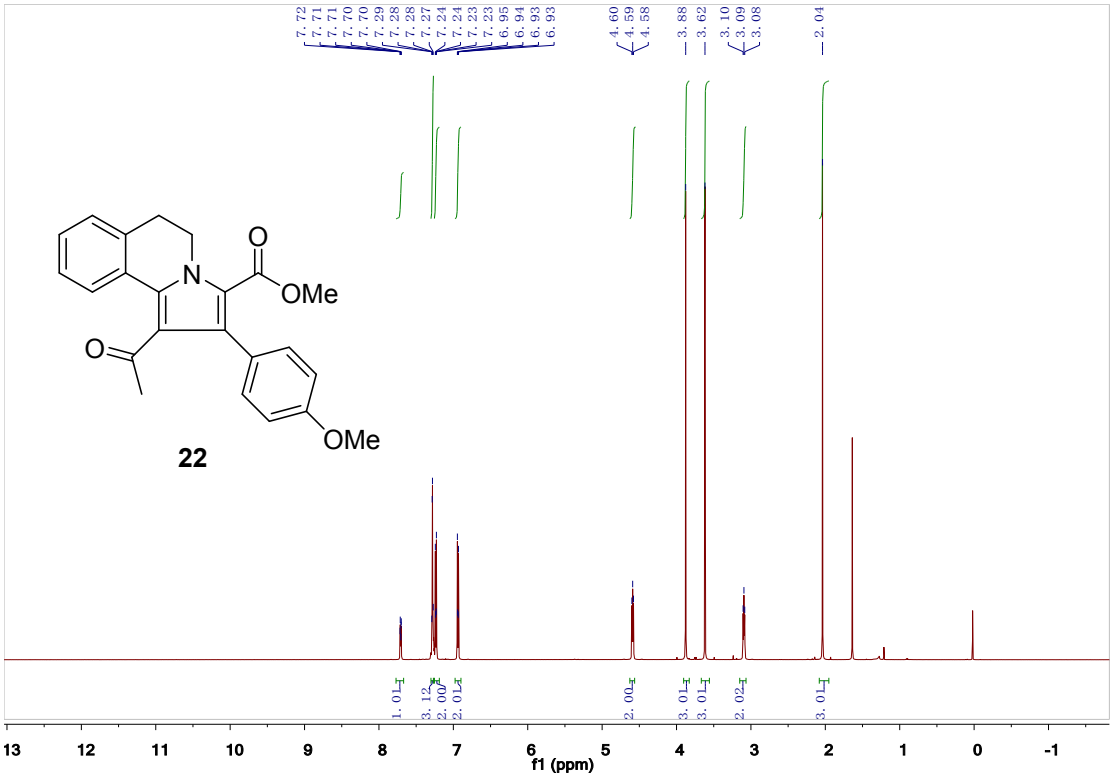
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6.93
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4.58
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3.62
3.10
3.09
3.08
2.04
O
N
OMe
O
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2.01
2.00
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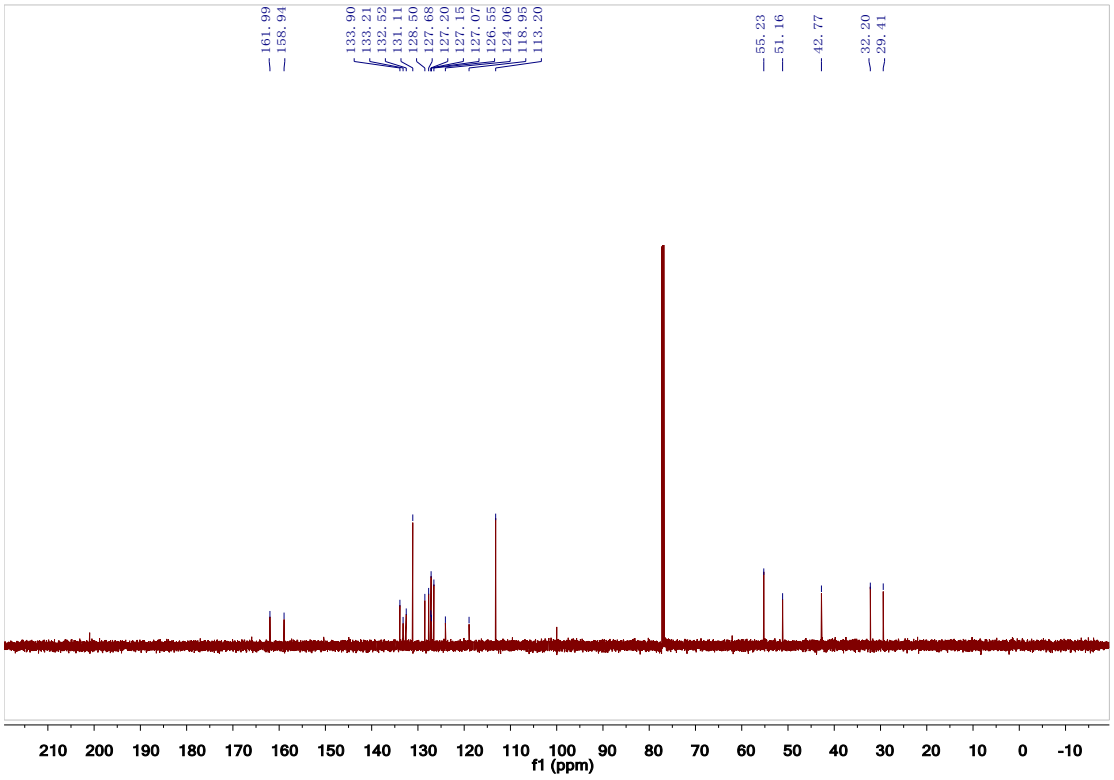
3.01
2.02
3.01
f1 (ppm)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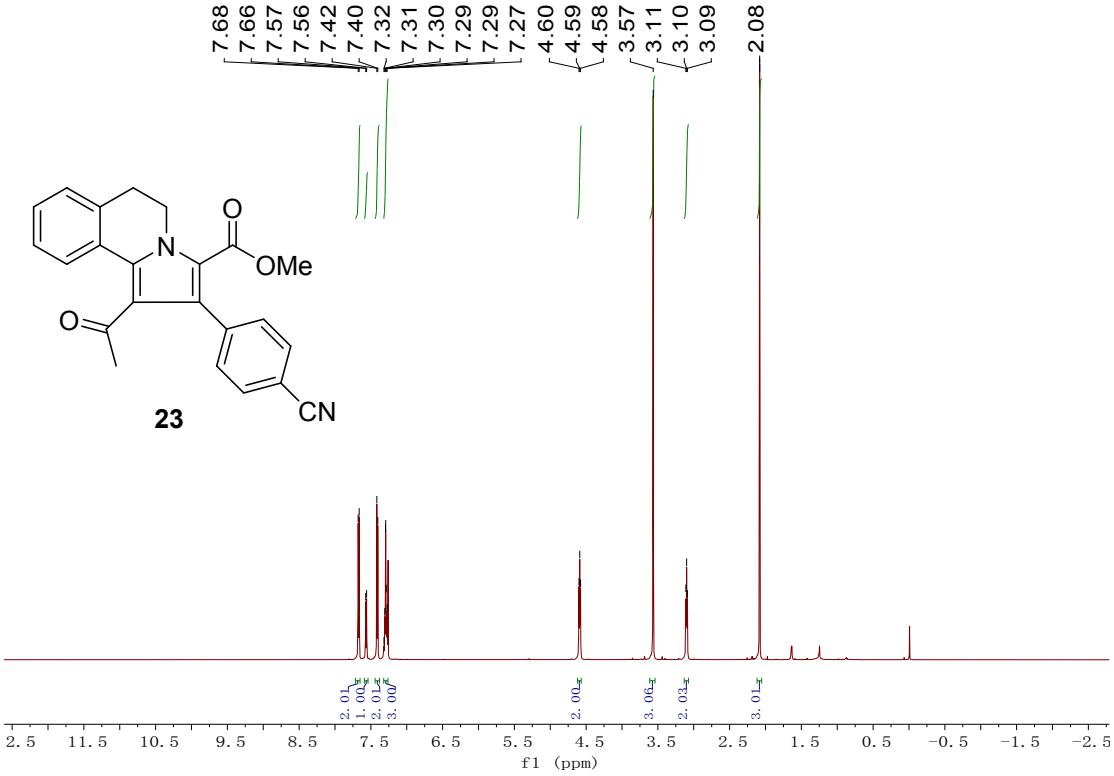
42.77
32.20
29.41
f1 (ppm)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3.09
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N
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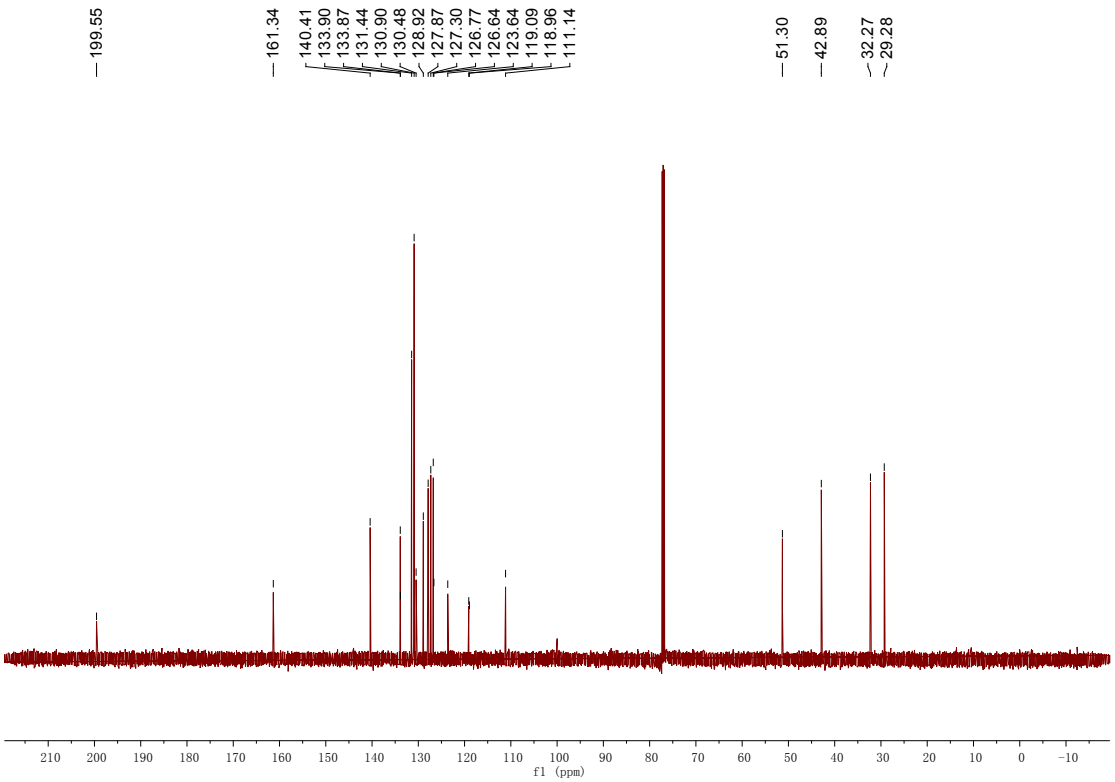
O
CN
23
f1 (ppm)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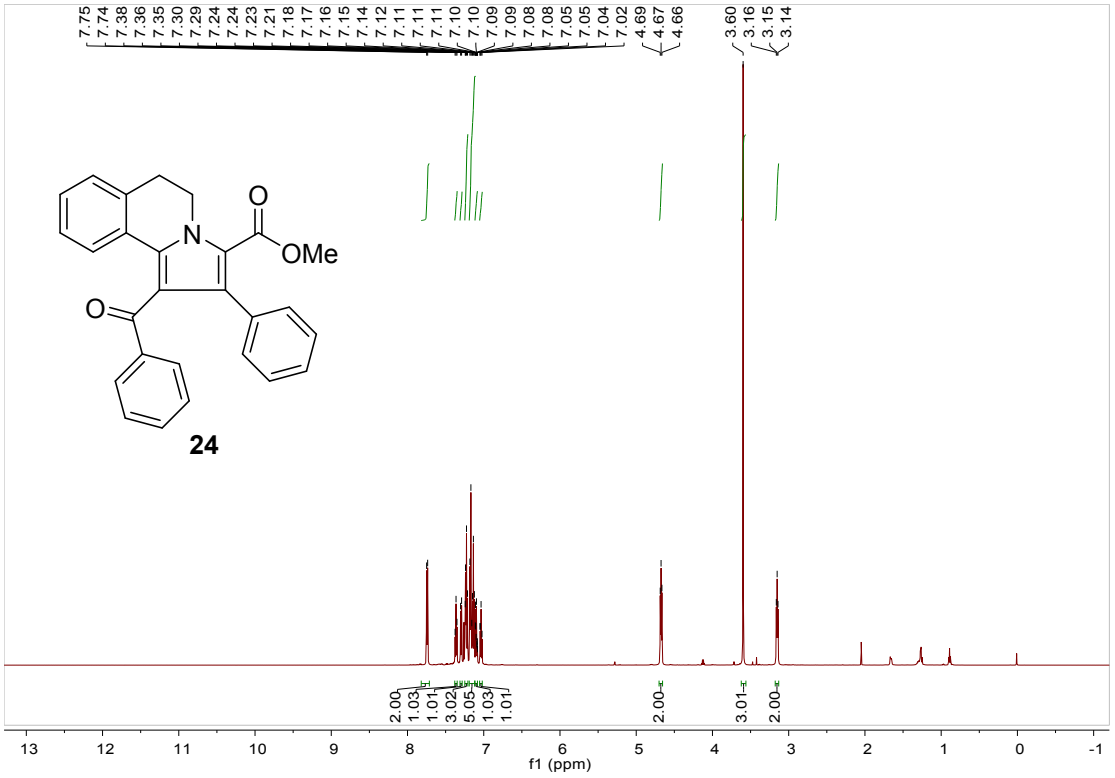
f1 (ppm)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7.17
7.16
7.15
7.14
7.12
7.11
7.11
7.11
7.10
7.10
7.09
7.09
7.08
7.08
7.05
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7.04
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3.14
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OMe
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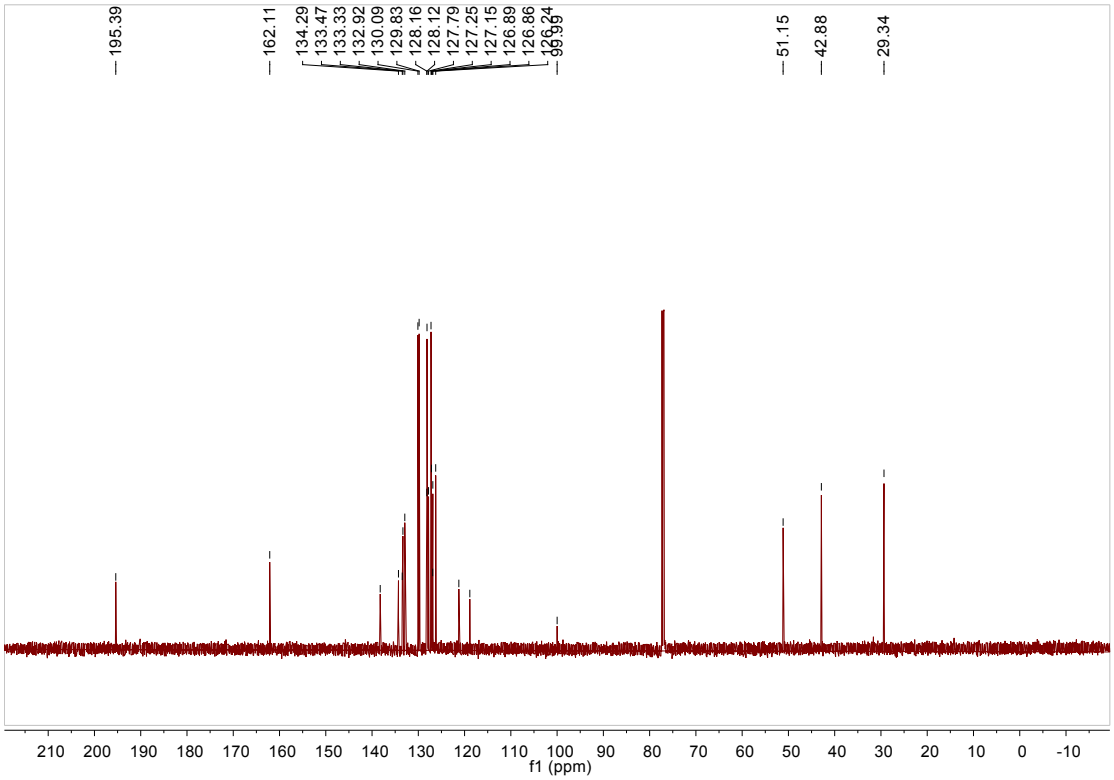
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126.86
126.24
99.99
51.15
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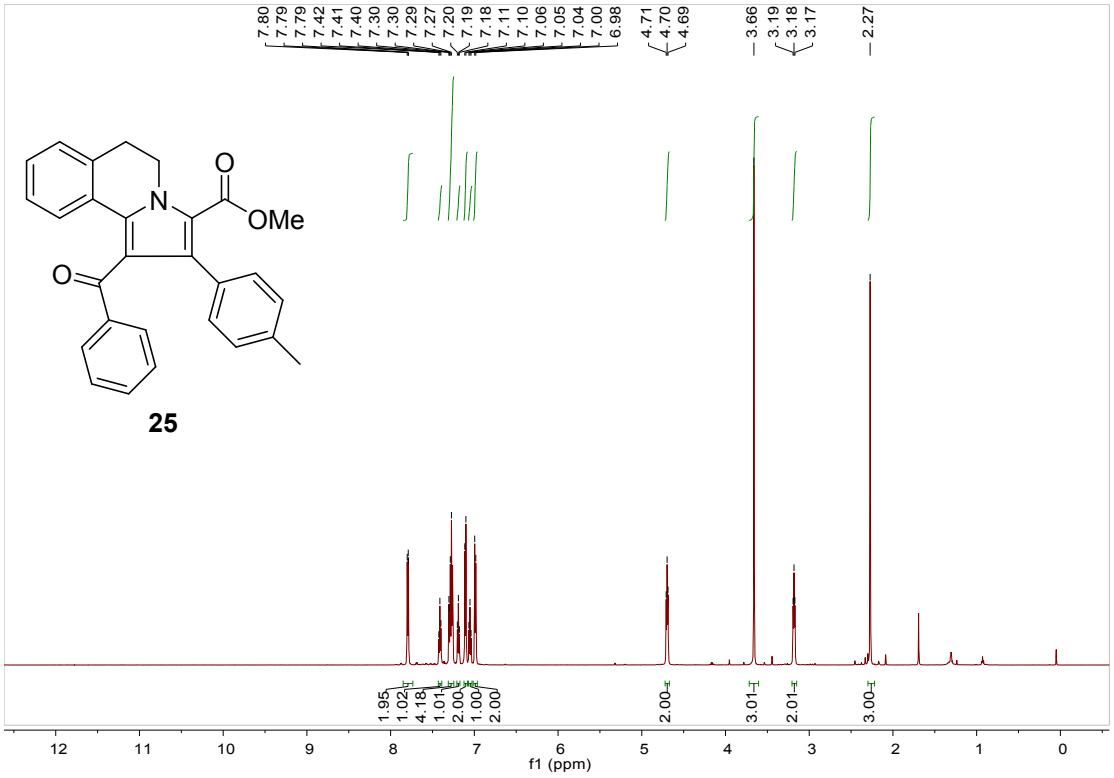
29.34
f1 (ppm)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7.18
7.11
7.10
7.06
7.05
7.04
7.00
6.98
4.71
4.70
4.69
3.66
3.19
3.18
3.17
2.27
O
N
OMe
O
25
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1.00
2.00
2.00
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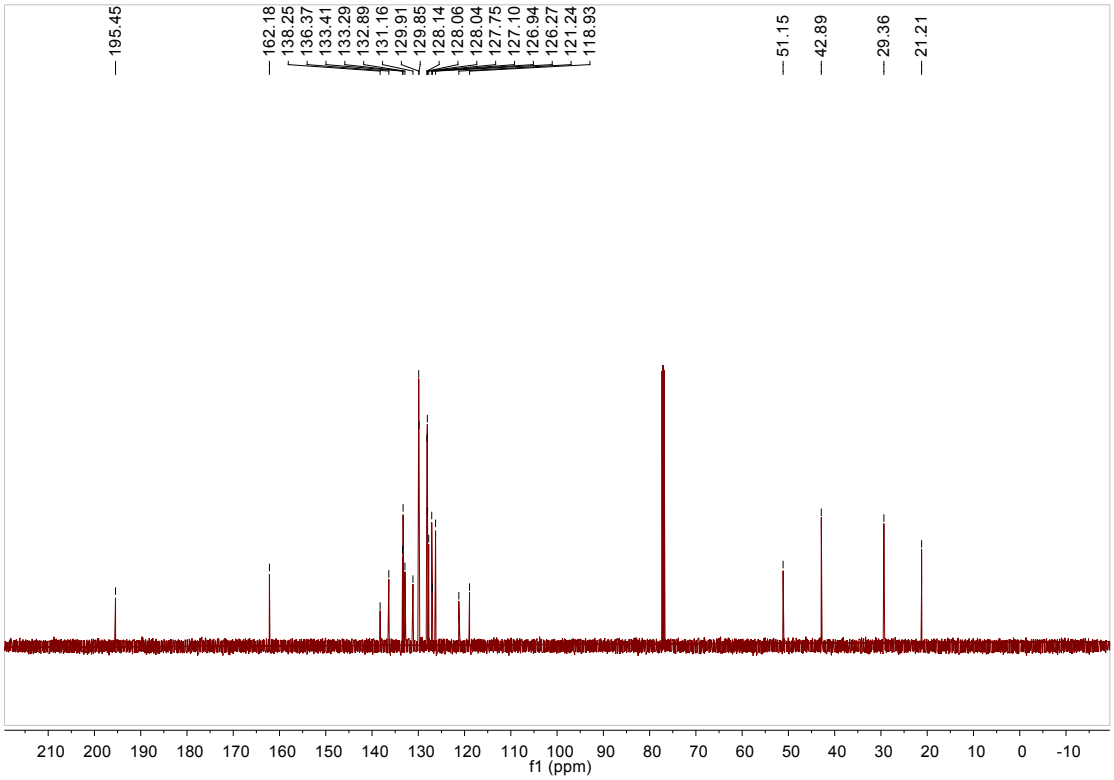
2.01
3.00
f1 (ppm)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126.27
121.24
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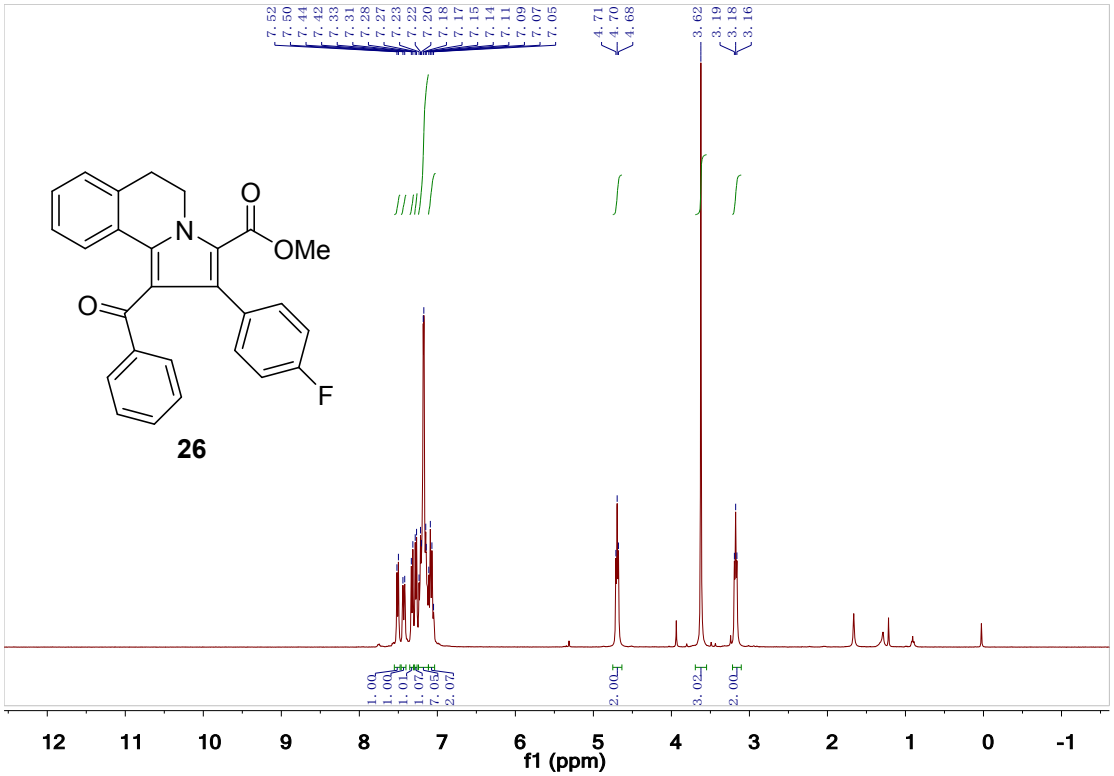
f1 (ppm)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7.14
7.11
7.09
7.07
7.05
4.71
4.70
4.68
3.62
3.19
3.18
3.16
O
N
OMe
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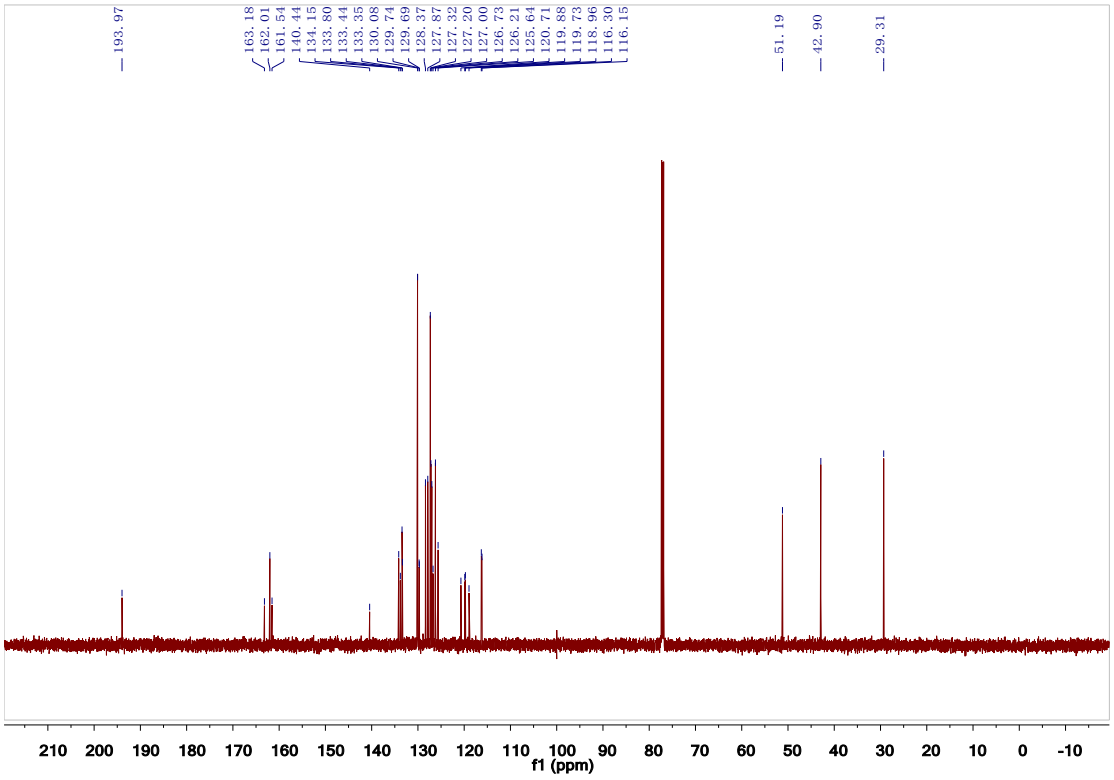
2.00
3.02
2.00
f1 (ppm)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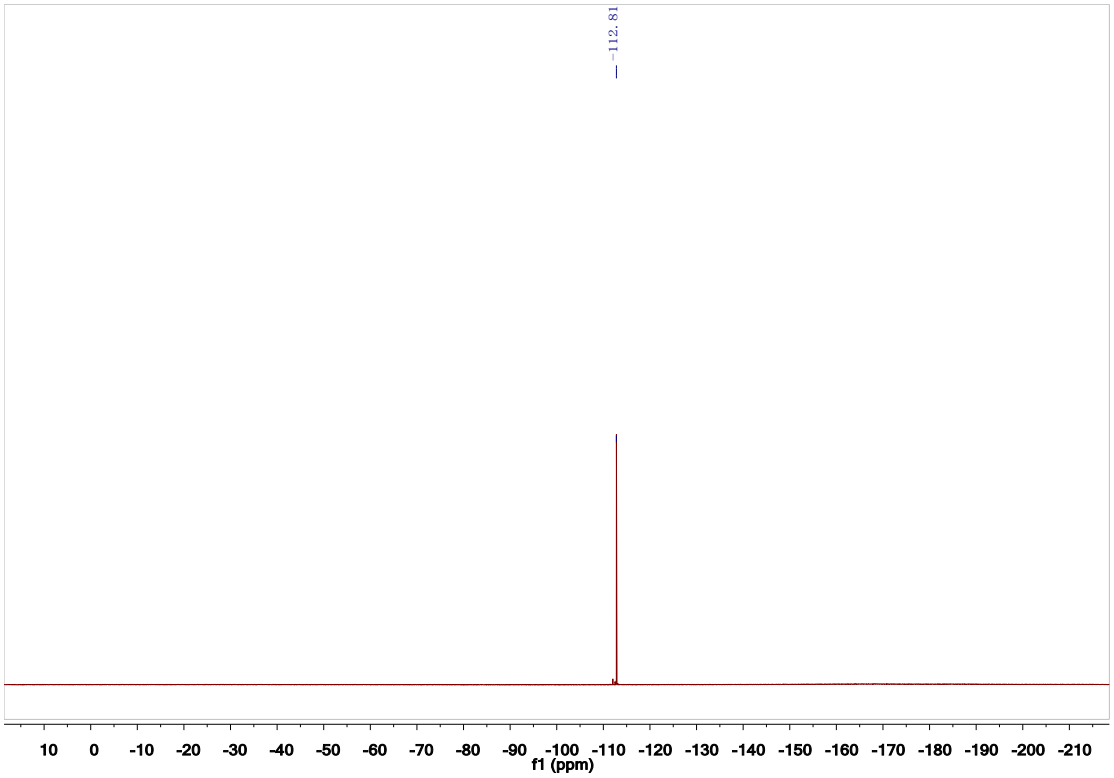
128.37
127.87
127.32
127.20
127.00
126.73
126.21
125.64
120.71
119.88
119.73
118.96
116.30
116.15
51.19
42.90
29.31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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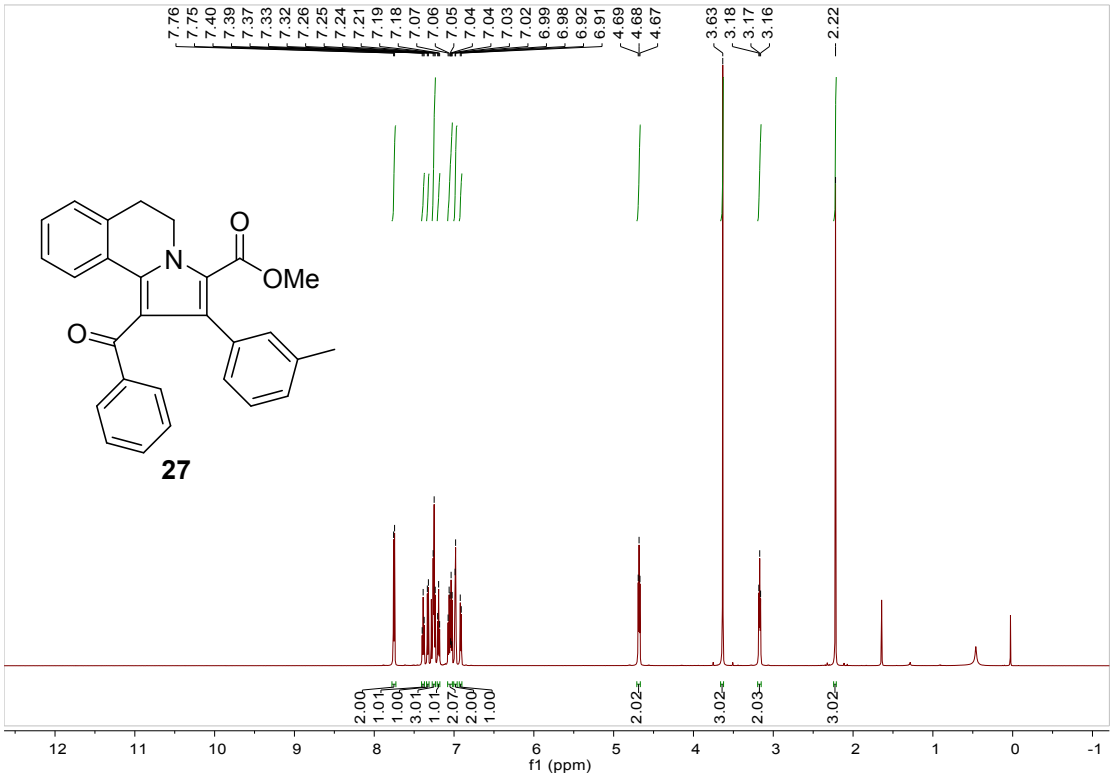
f1 (ppm)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4.67
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3.17
3.16
2.22
O
N
OMe
O
27
2.00
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3.02
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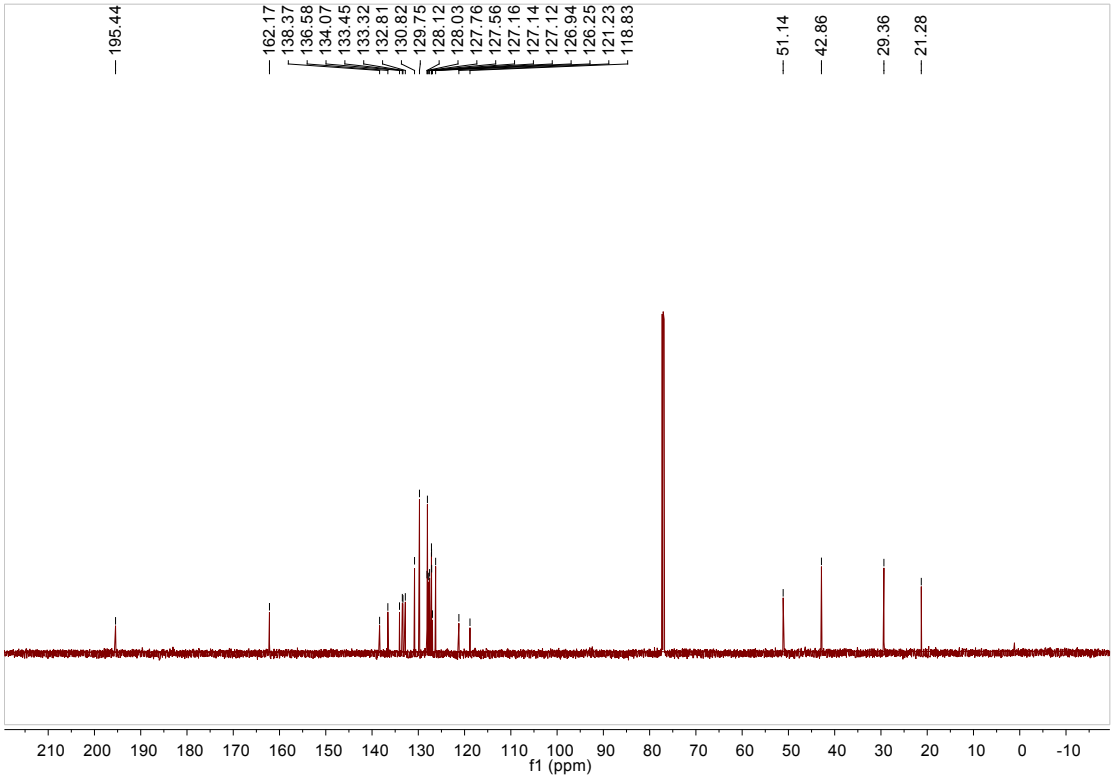
3.02
f1 (ppm)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128.12
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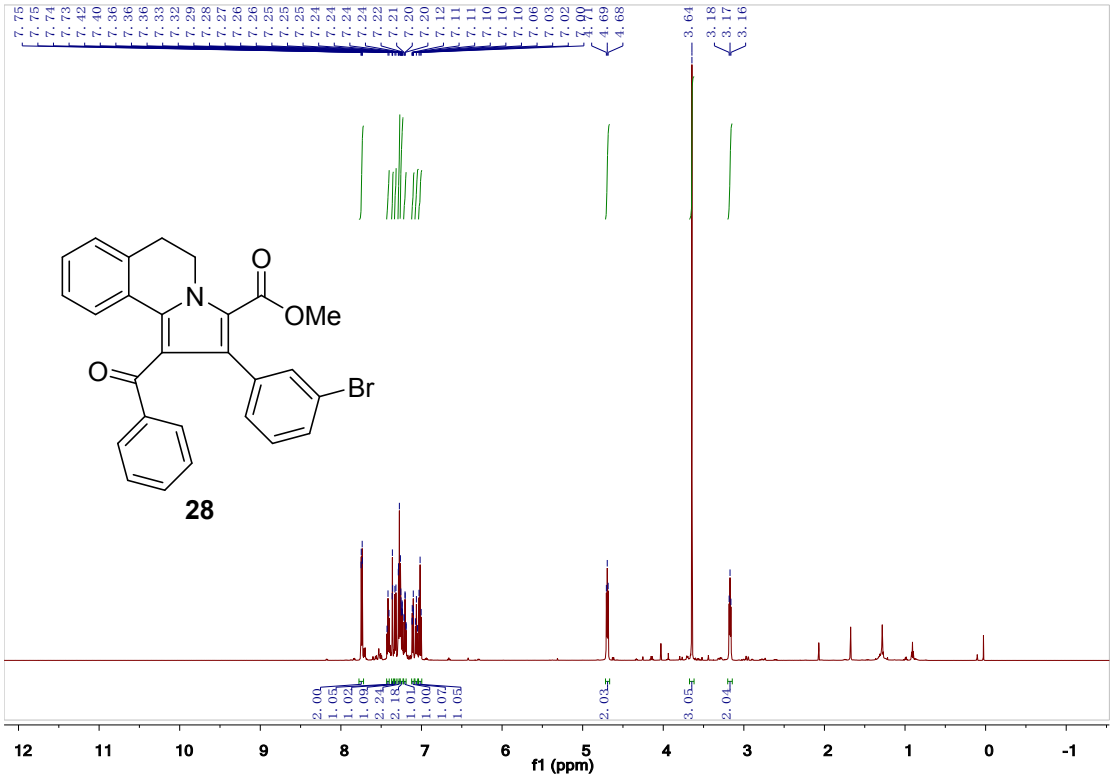
126.94
126.25
121.23
118.83
51.14
42.86
29.36
21.28
f1 (ppm)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O
Br
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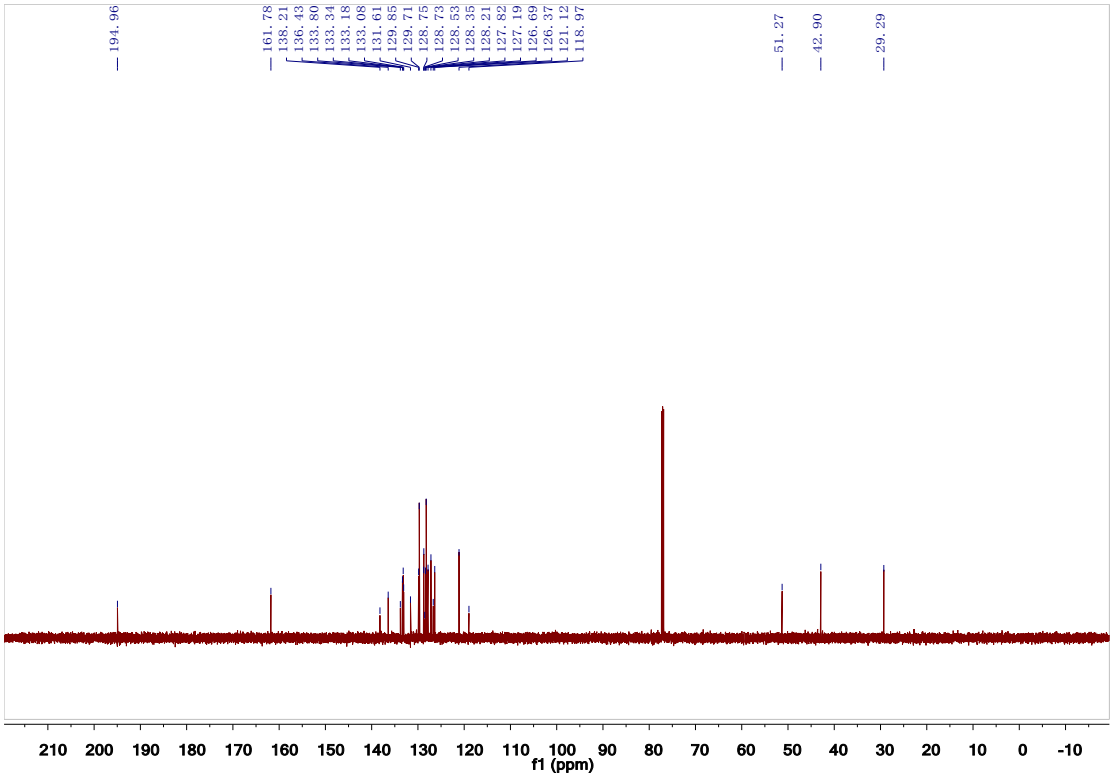
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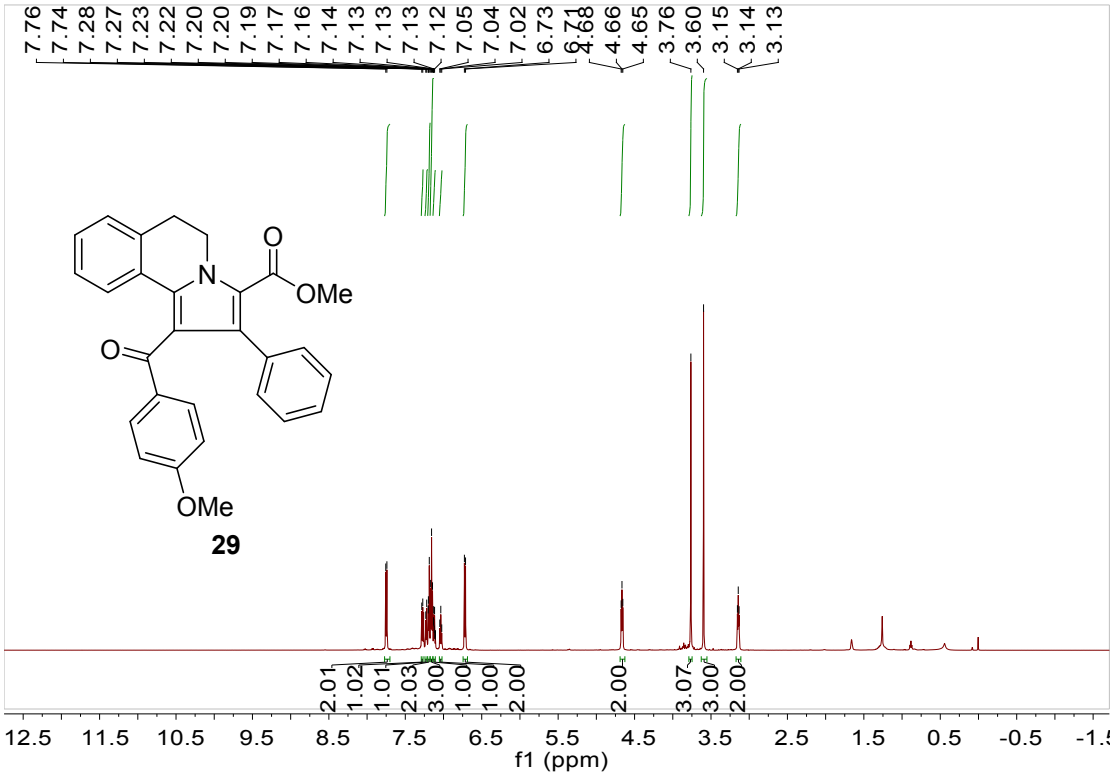
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7.13
7.13
7.12
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6.71
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4.65
3.76
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3.15
3.14
3.13
O
N
OMe
O
OMe
29
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1.02
1.01
2.03
3.00
1.00
1.00
2.00
2.00
3.07
3.00
2.00
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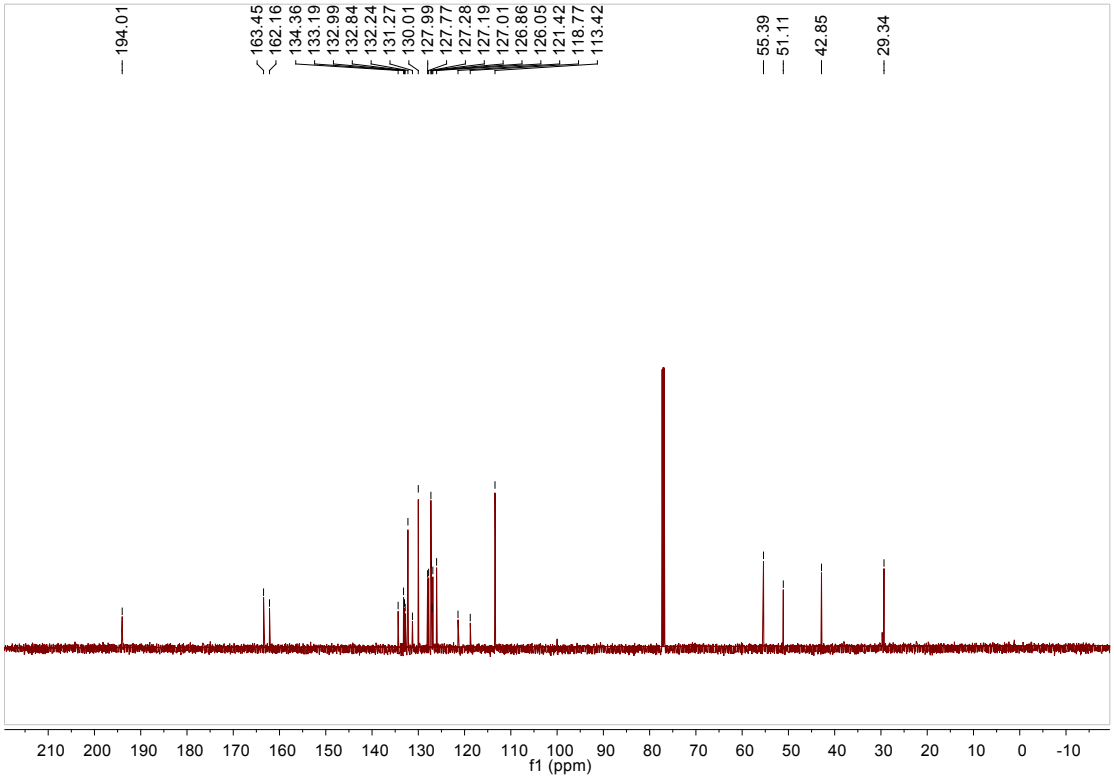
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126.05
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51.11
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100
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80
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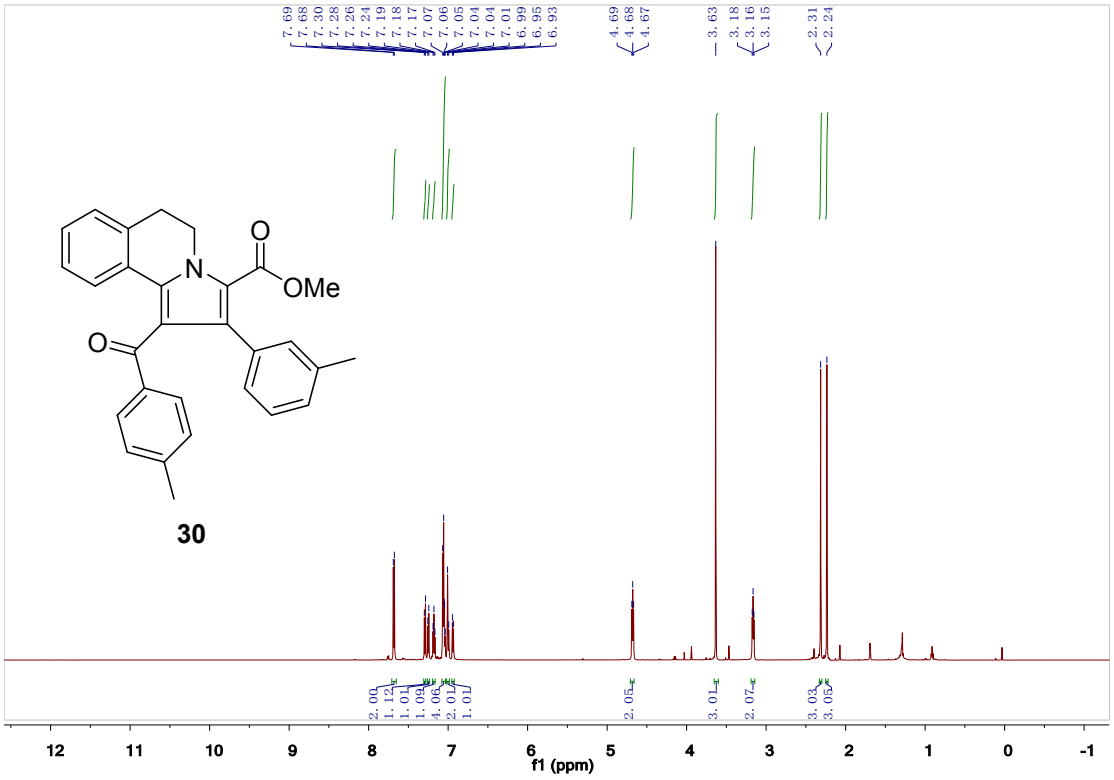
-10
f1 (ppm)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6.93
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4.68
4.67
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3.18
3.16
3.15
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2.24
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OMe
O
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1.01
2.05
3.01
2.07
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0
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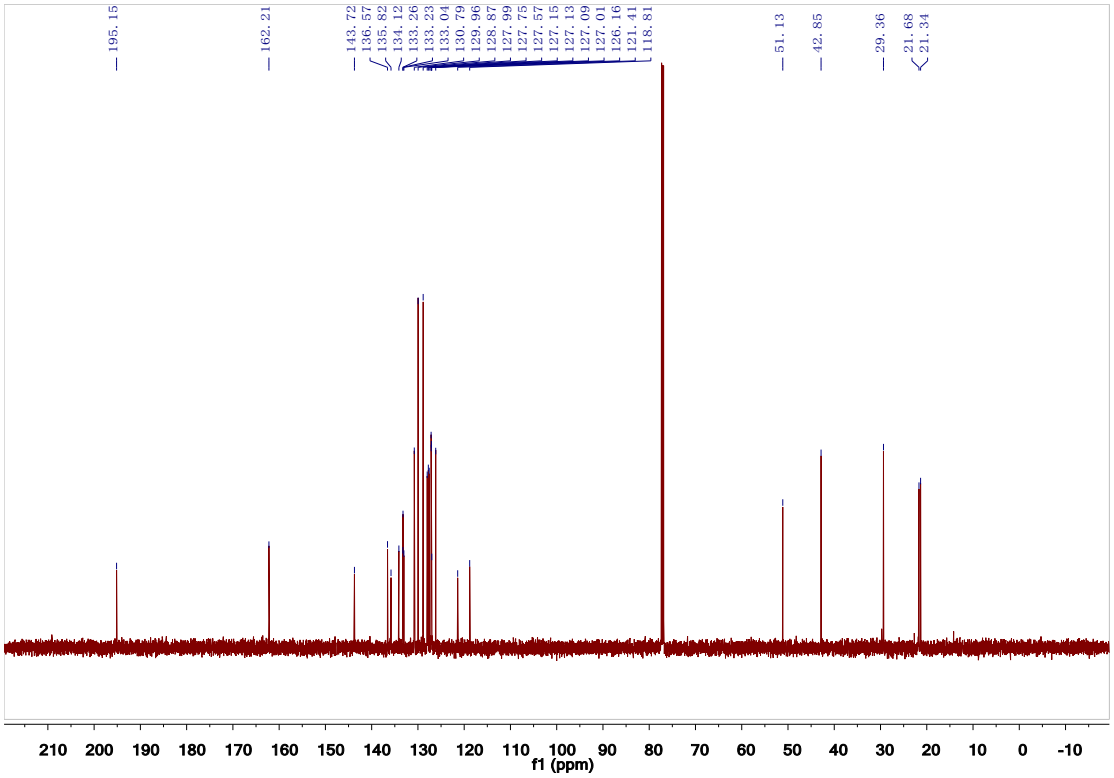
f1 (ppm)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127.13
127.09
127.01
126.16
121.41
118.81
51.13
42.85
29.36
21.68
21.34
210
200
190
180
170
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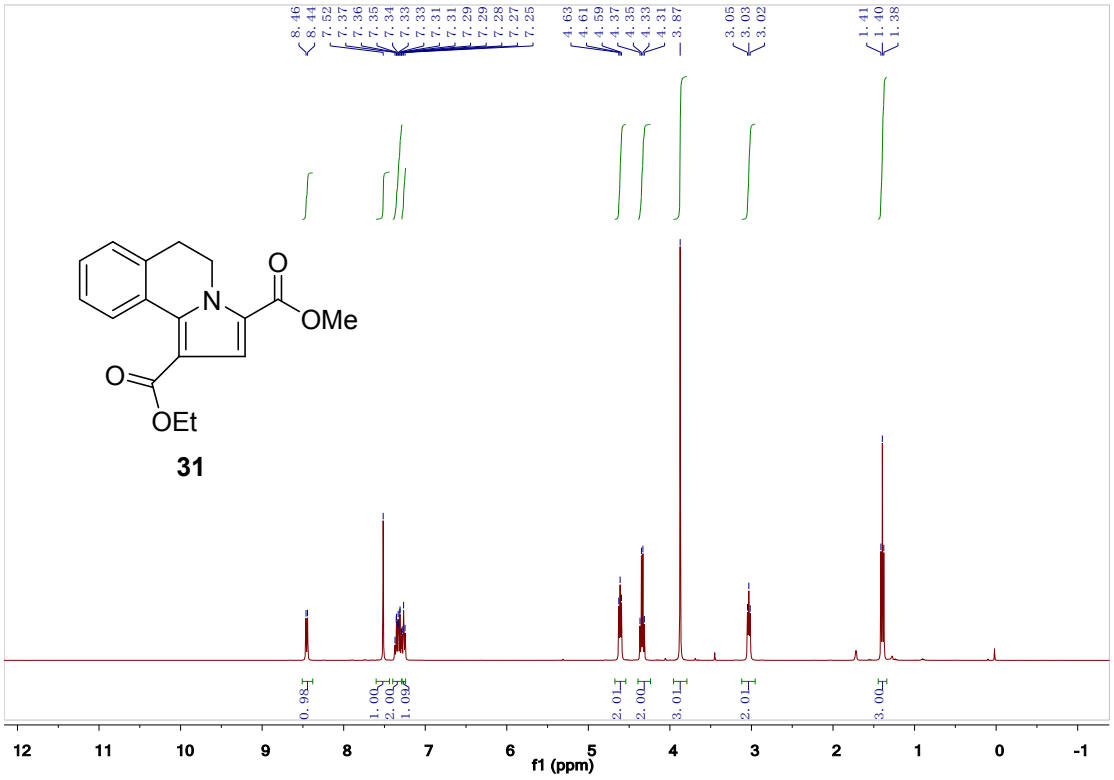
f1 (ppm)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7.27
7.25
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4.61
4.59
4.37
4.35
4.33
4.31
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3.05
3.03
3.02
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1.40
1.38
O
N
OMe
O
OEt
31
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2.00
1.09
2.01
2.00
3.01
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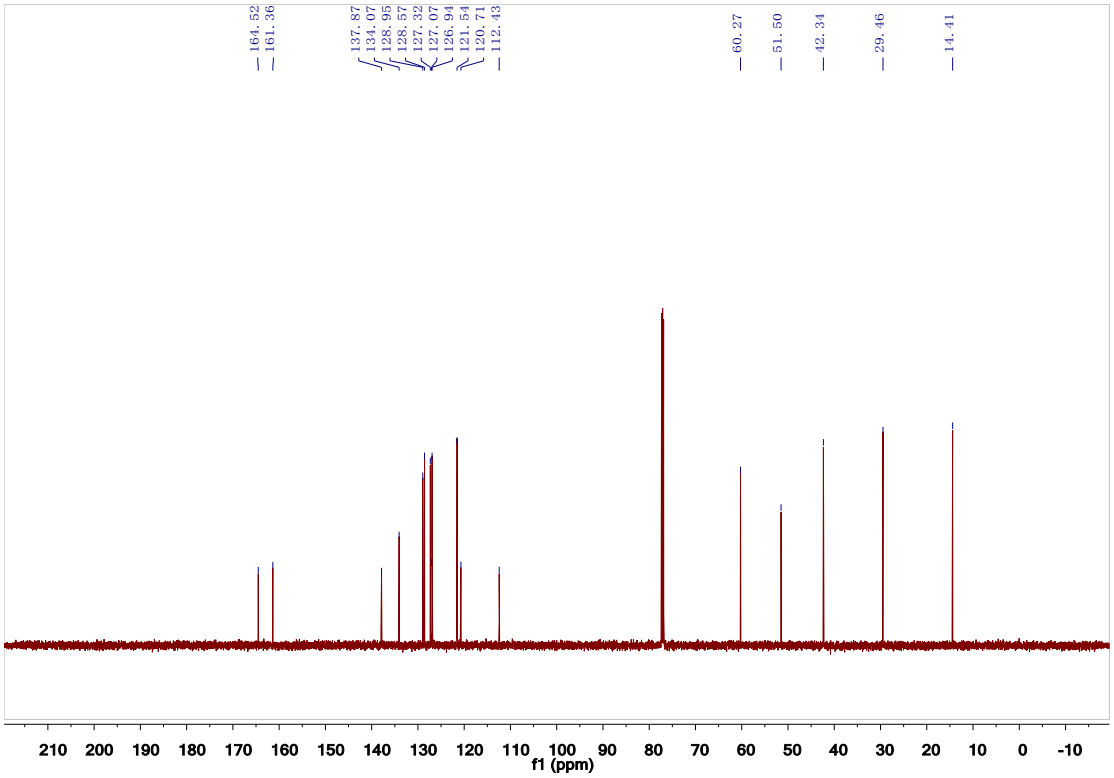
f1 (ppm)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29.46
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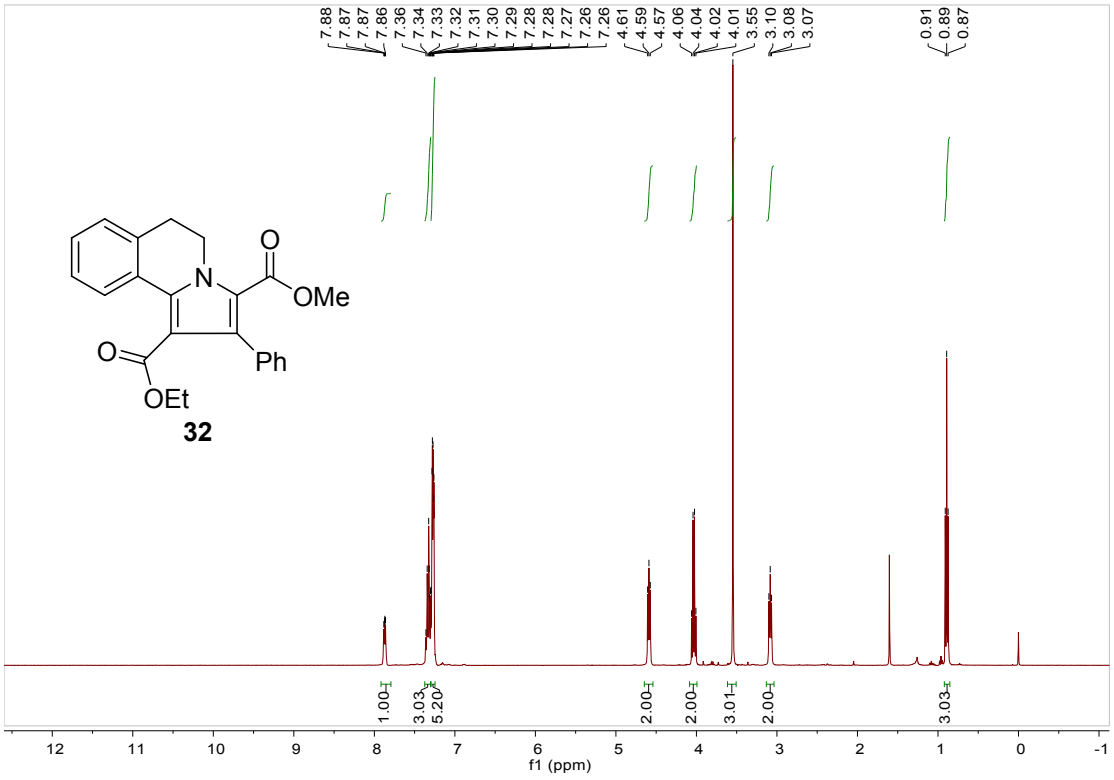
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4.02
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0.87
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O
Ph
OEt
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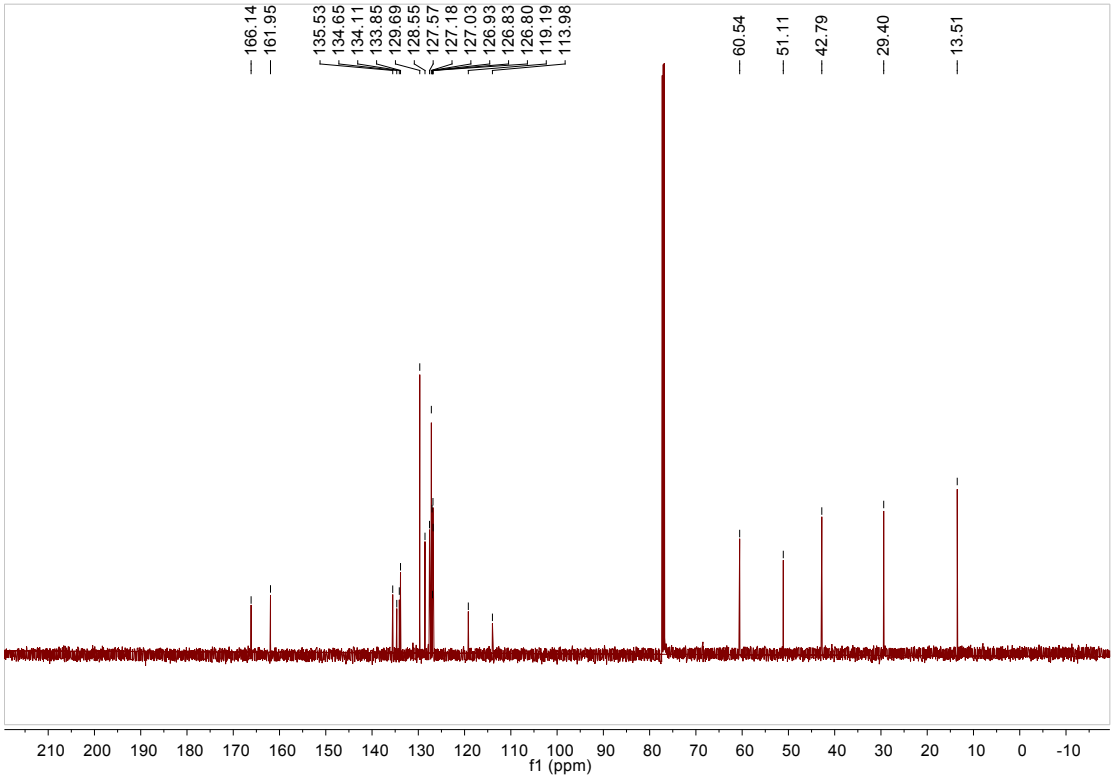
f1 (ppm)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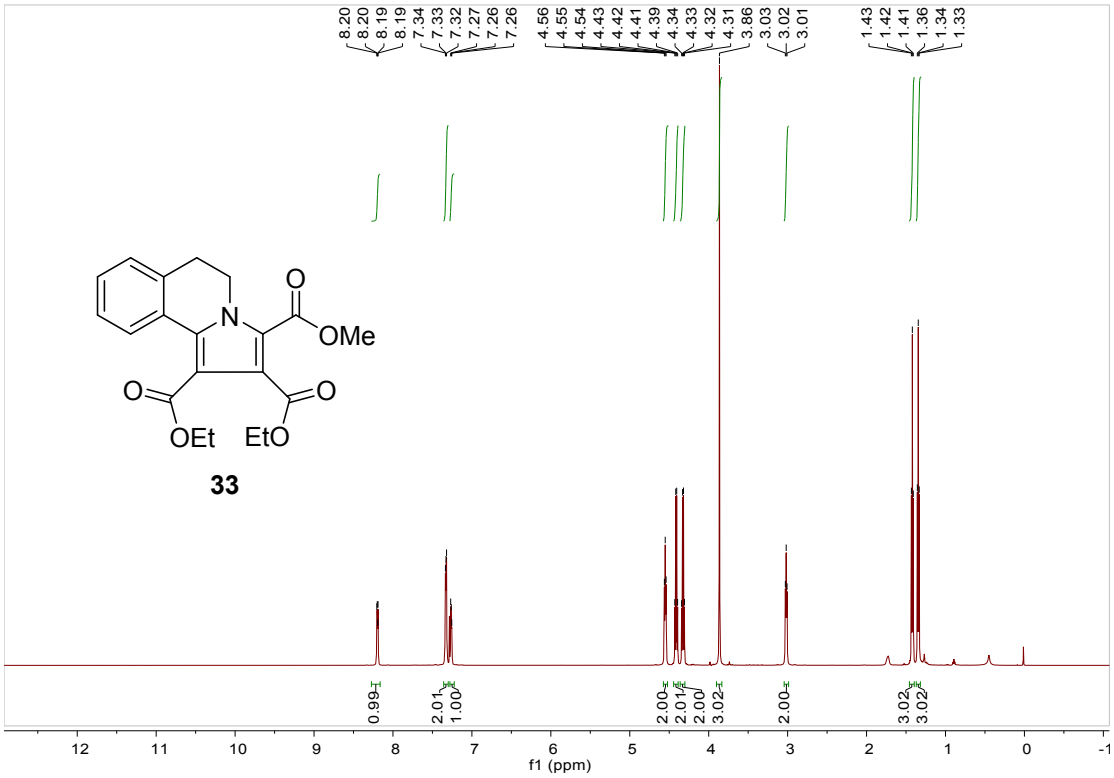
f1 (ppm)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4.33
4.32
4.31
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3.02
3.01
1.43
1.42
1.41
1.36
1.34
1.33
O
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OMe
O
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EtO
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0.99
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1.00
2.00
2.01
2.00
3.02
2.00
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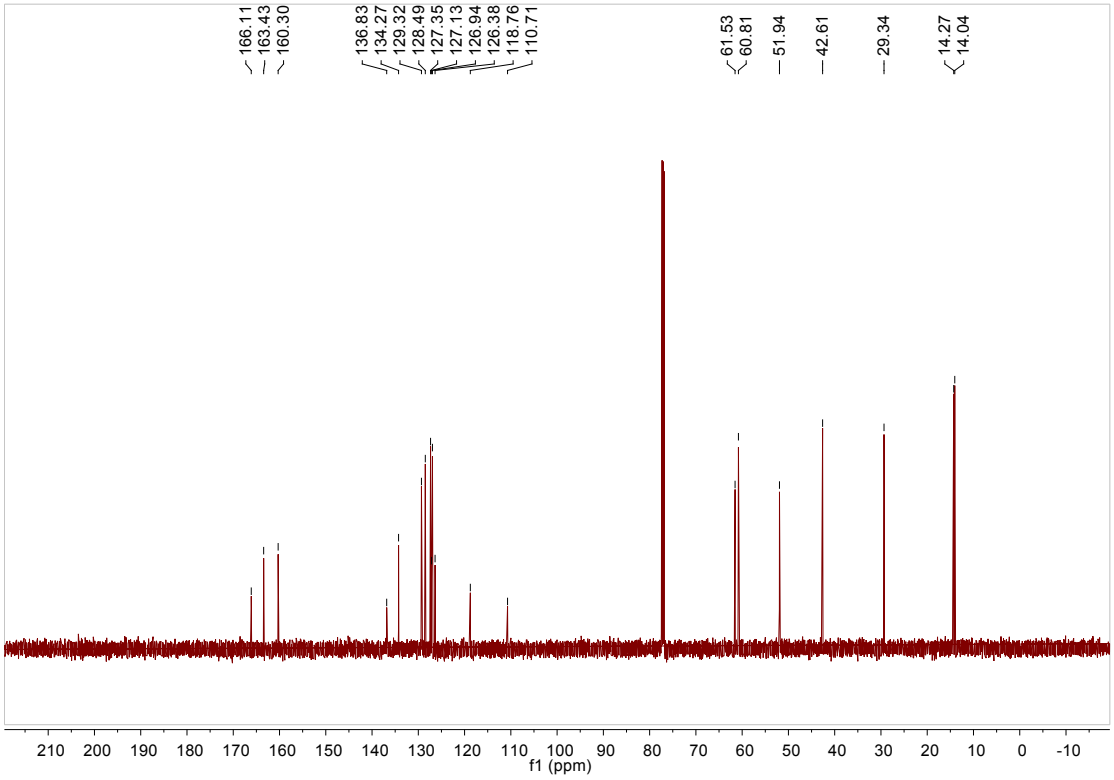
f1 (ppm)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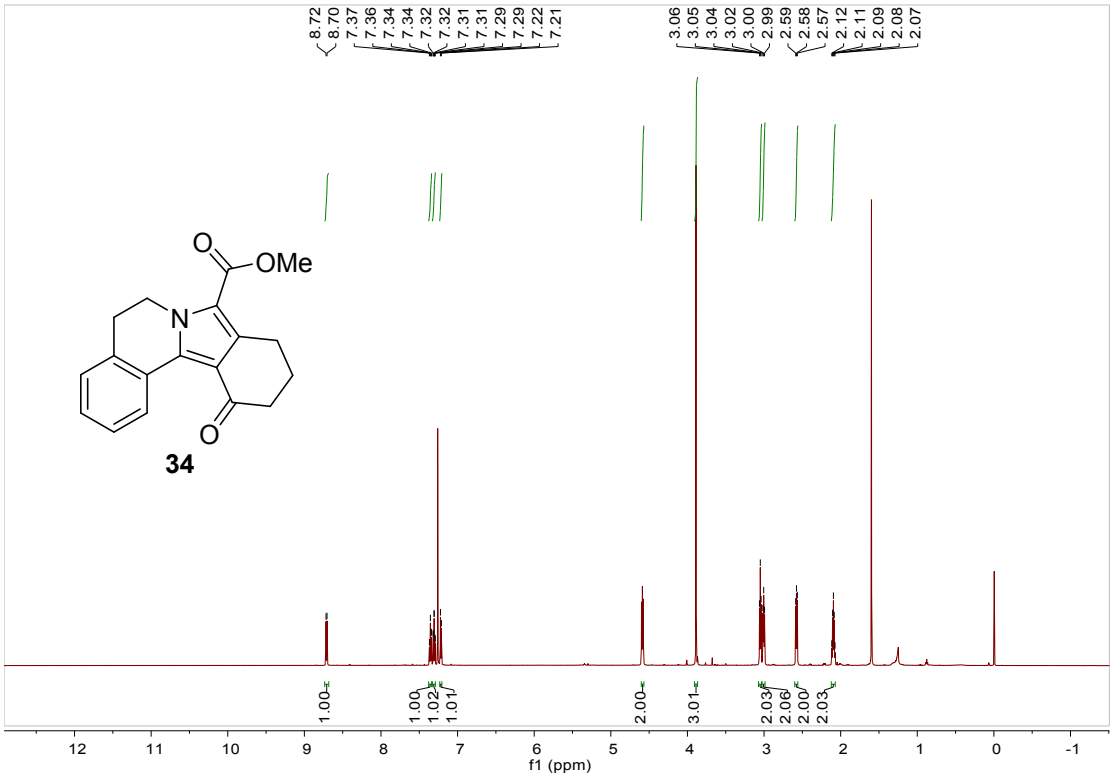
f1 (ppm)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3.05
3.04
3.02
3.00
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2.59
2.58
2.57
2.12
2.11
2.09
2.08
2.07
O
OMe
N
O
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1.00
1.02
1.01
2.00
3.01
2.03
2.06
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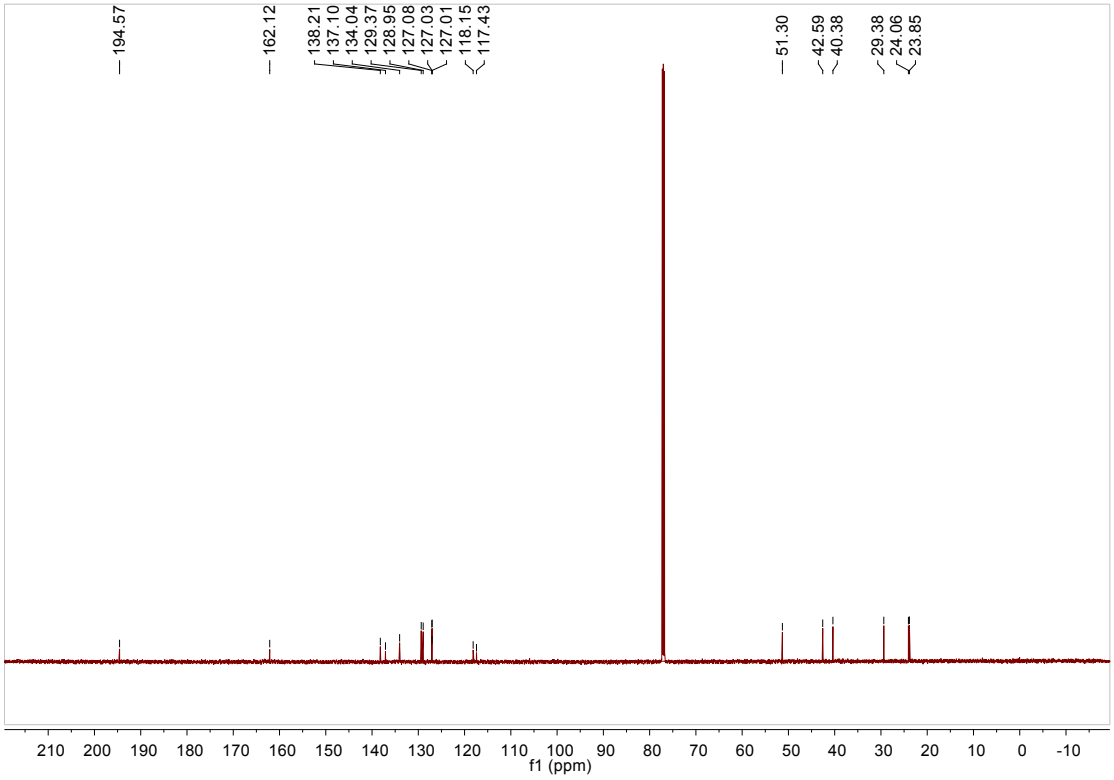
-1
f1 (ppm)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29.38
24.06
23.85
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200
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180
170
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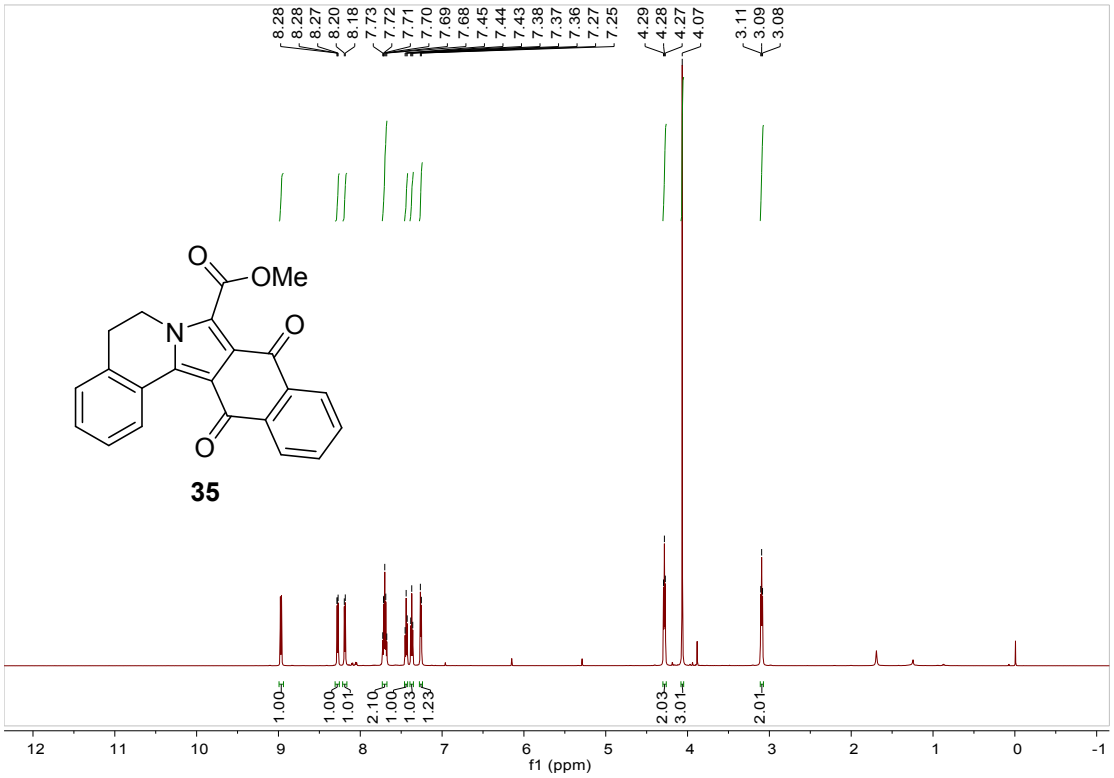
-10
f1 (ppm)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7.44
7.43
7.38
7.37
7.36
7.27
7.25
4.29
4.28
4.27
4.07
3.11
3.09
3.08
O
OMe
N
O
O
35
1.00
1.00
1.01
2.10
1.00
1.03
1.23
2.03
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8
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3
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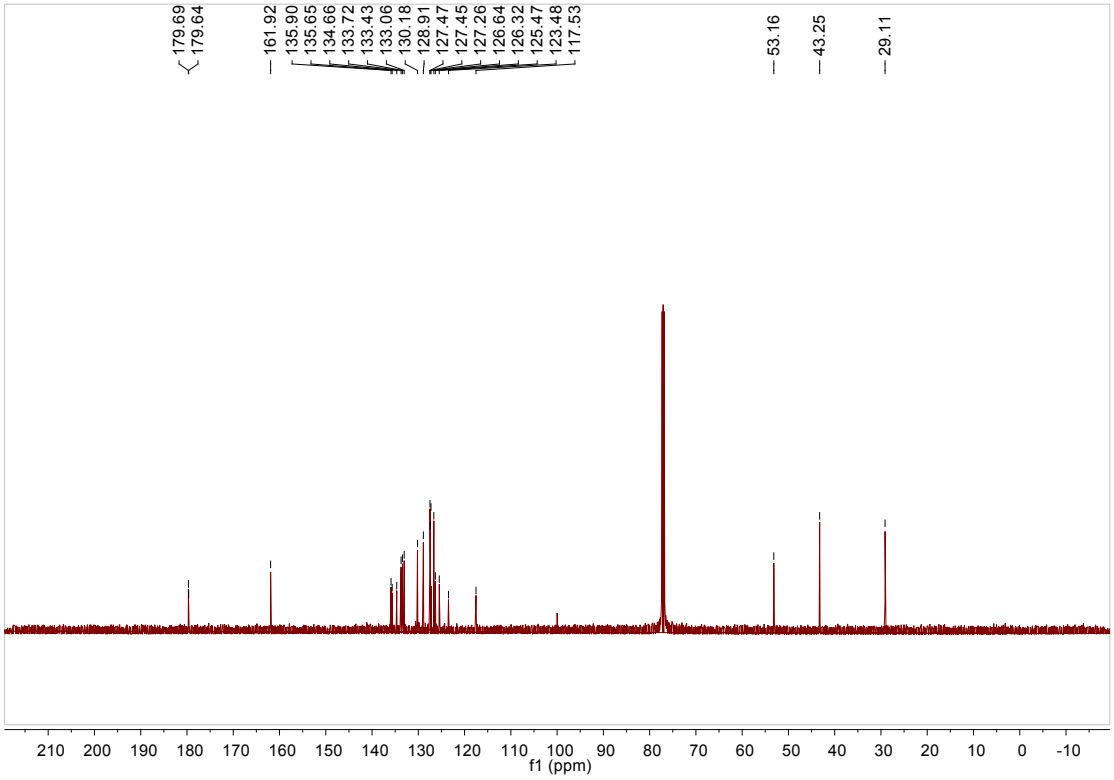
f1 (ppm)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134.66
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133.43
133.06
130.18
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127.45
127.26
126.64
126.32
125.47
123.48
117.53
53.16
43.25
29.11
210
200
190
180
170
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30
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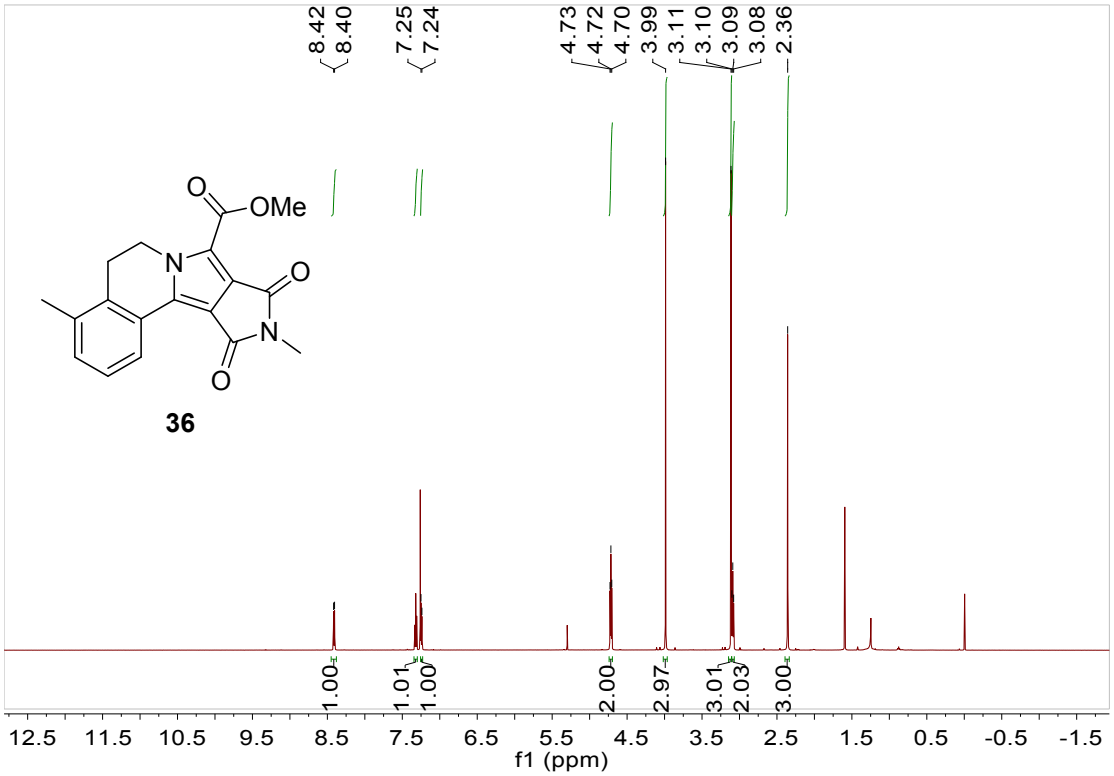
0
-10
f1 (ppm)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7.24
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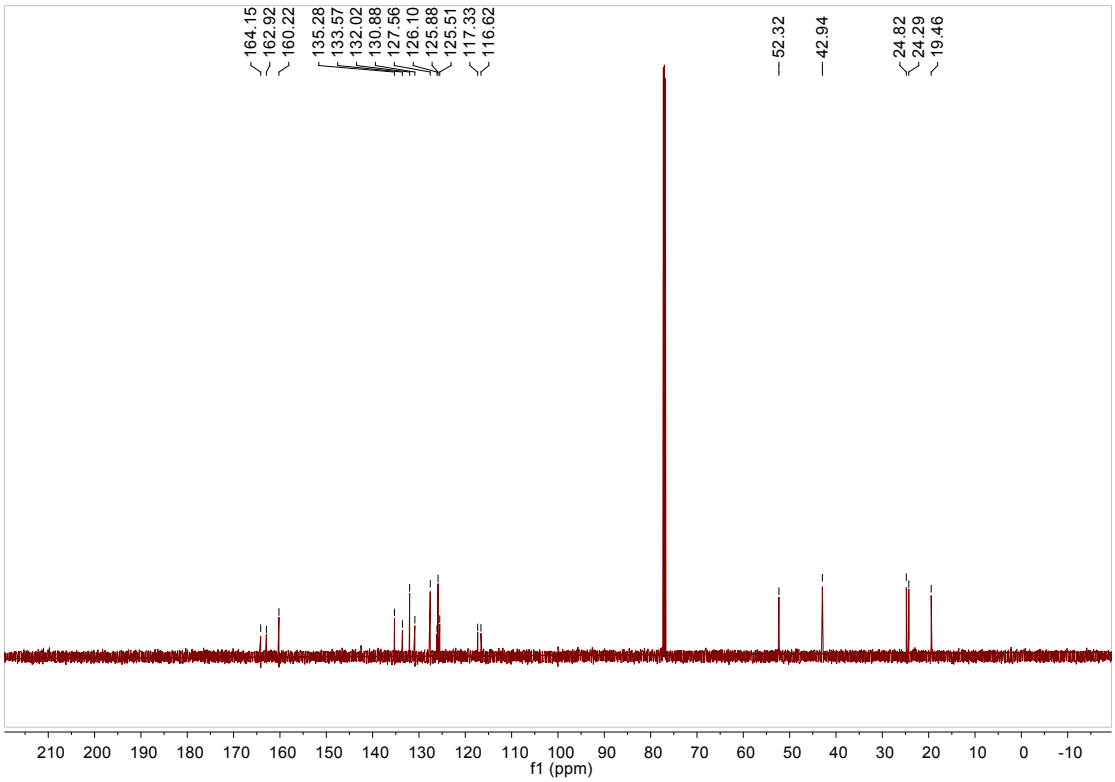
4.72
4.70
3.99
3.11
3.10
3.09
3.08
2.36
O
OMe
N
O
N
O
1.00
1.01
1.00
2.00
2.97
3.01
2.03
3.00
12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
f1 (ppm)

36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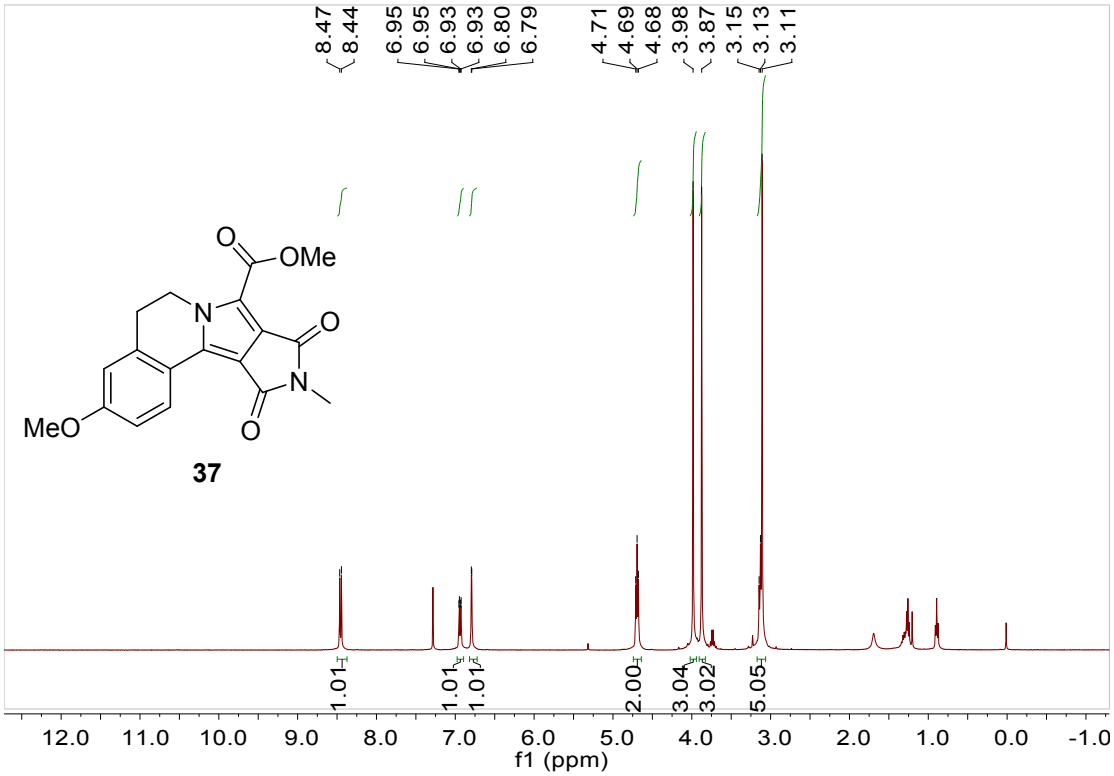
24.29
19.46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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4.69
4.68
3.98
3.87
3.15
3.13
3.11
O
OMe
N
O
N
MeO
O
37
1.01
1.01
1.01
2.00
3.04
3.02
5.05
12.0
11.0
10.0
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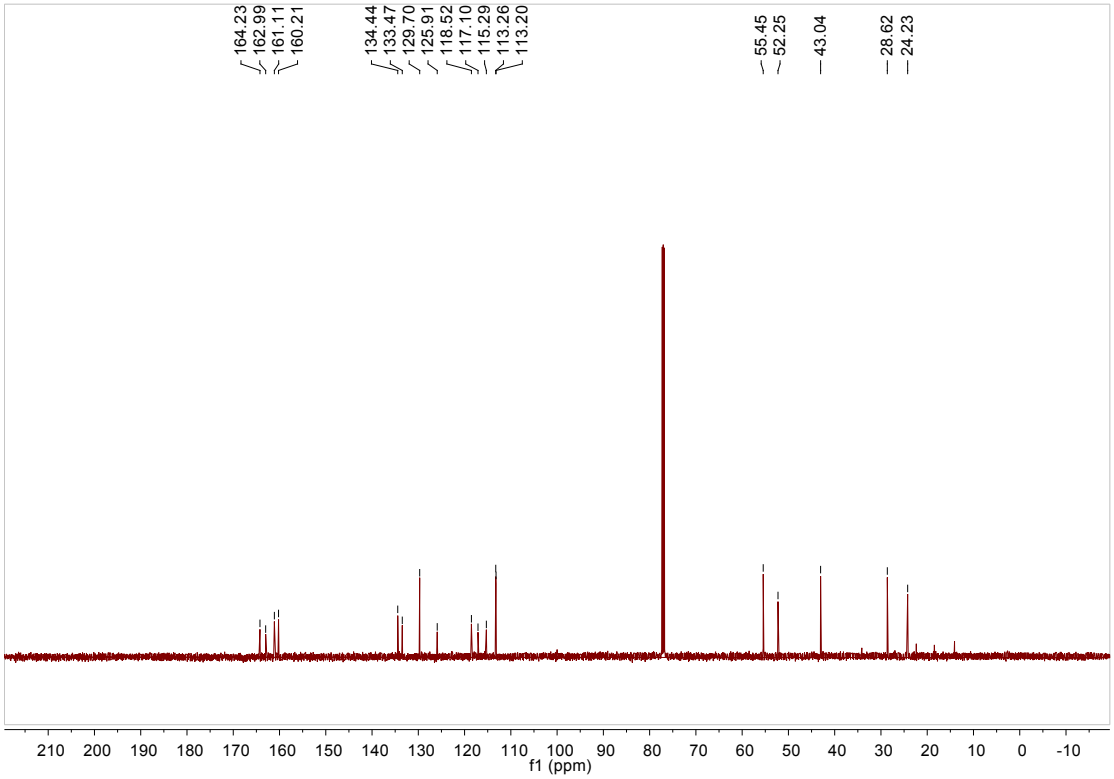
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)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117.10
115.29
113.26
113.20
55.45
52.25
43.04
28.62
24.23
210
200
190
180
170
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140
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120
110
100
90
80
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60
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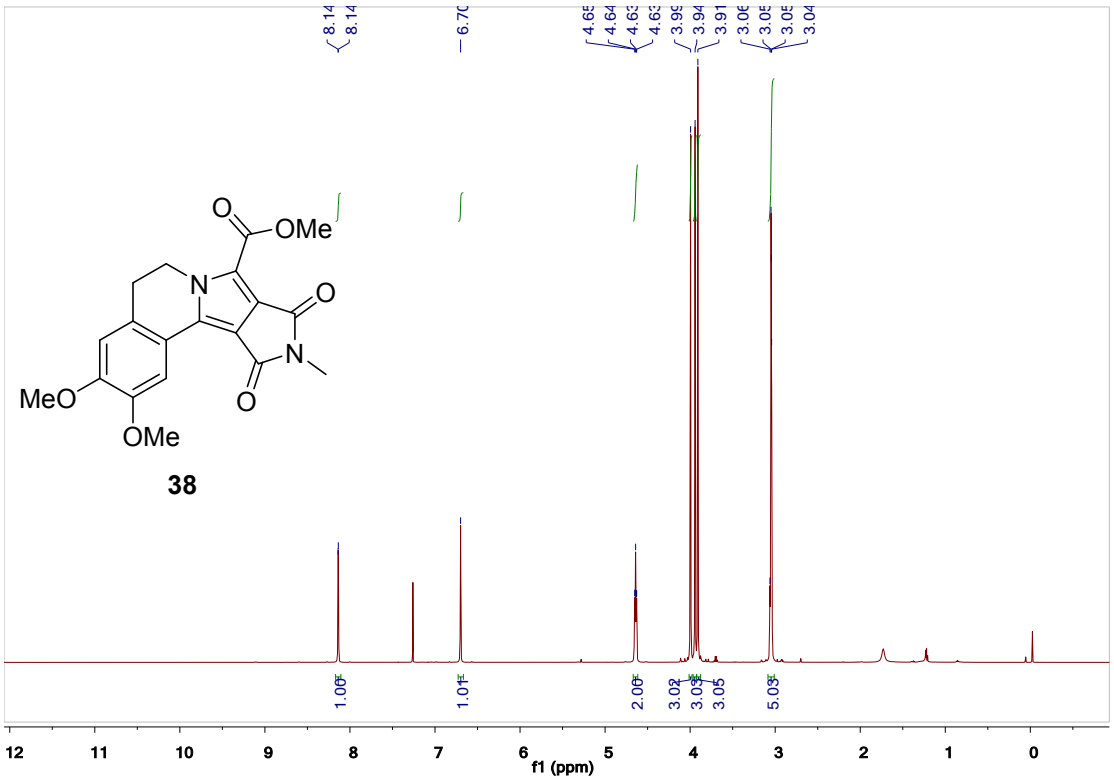
40
30
20
10
0
-10
f1 (ppm)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3.99
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3.91
3.06
3.05
3.05
3.04
O
OMe
N
O
N
O
MeO
OMe
1.00
1.01
2.00
3.02
3.03
3.05
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10
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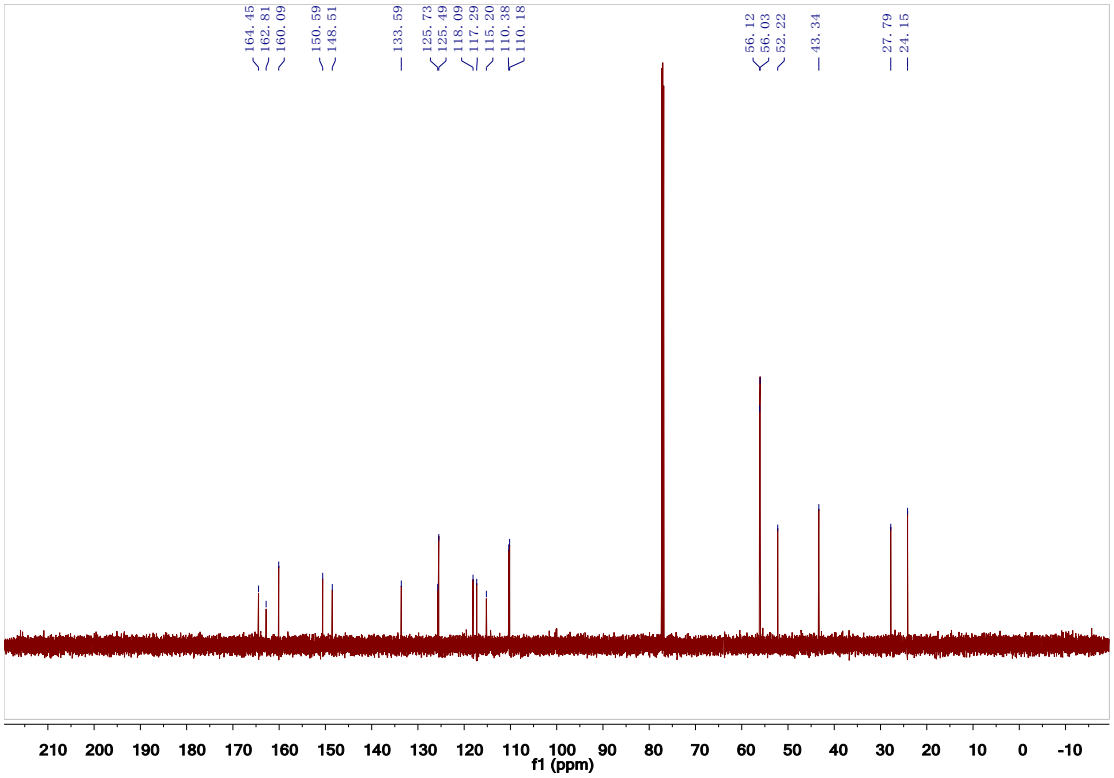
8
7
6
5
4
3
2
1
0
f1 (ppm)

38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125.49
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110.18
56.12
56.03
52.22
43.34
27.79
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210
200
190
180
170
160
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120
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100
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80
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30
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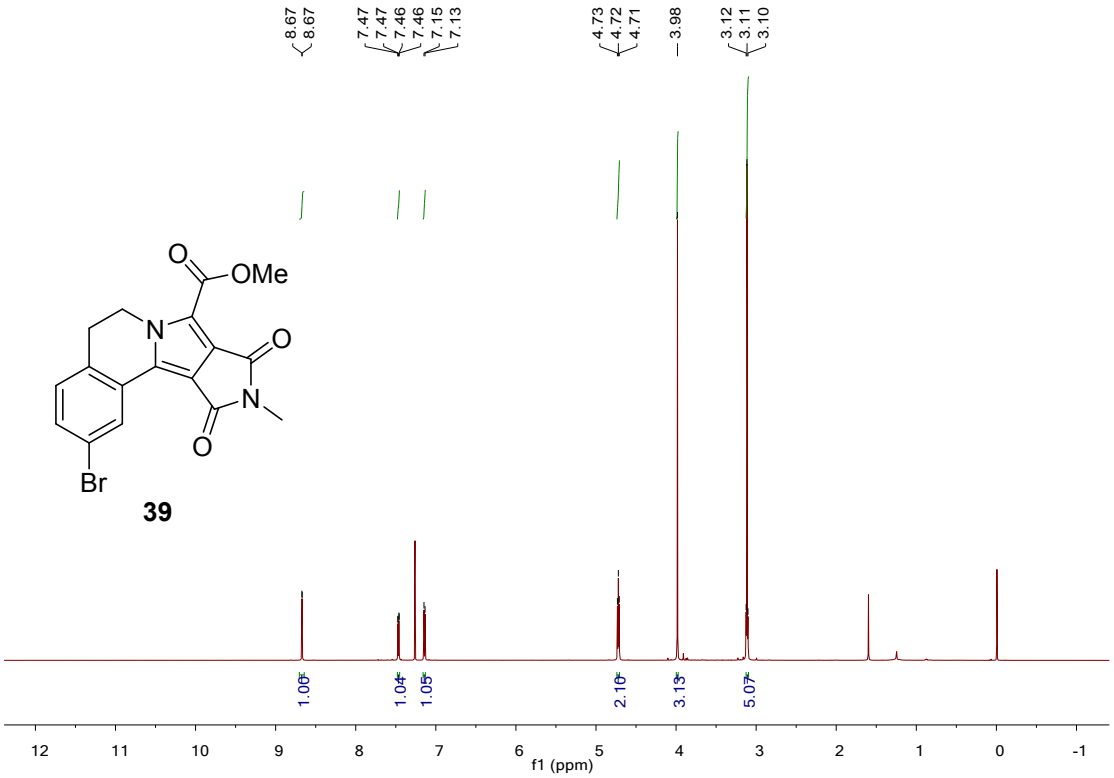
0
-10
f1 (ppm)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4.71
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3.12
3.11
3.10
O
OMe
N
O
N
O
Br
1.00
1.04
1.05
2.10
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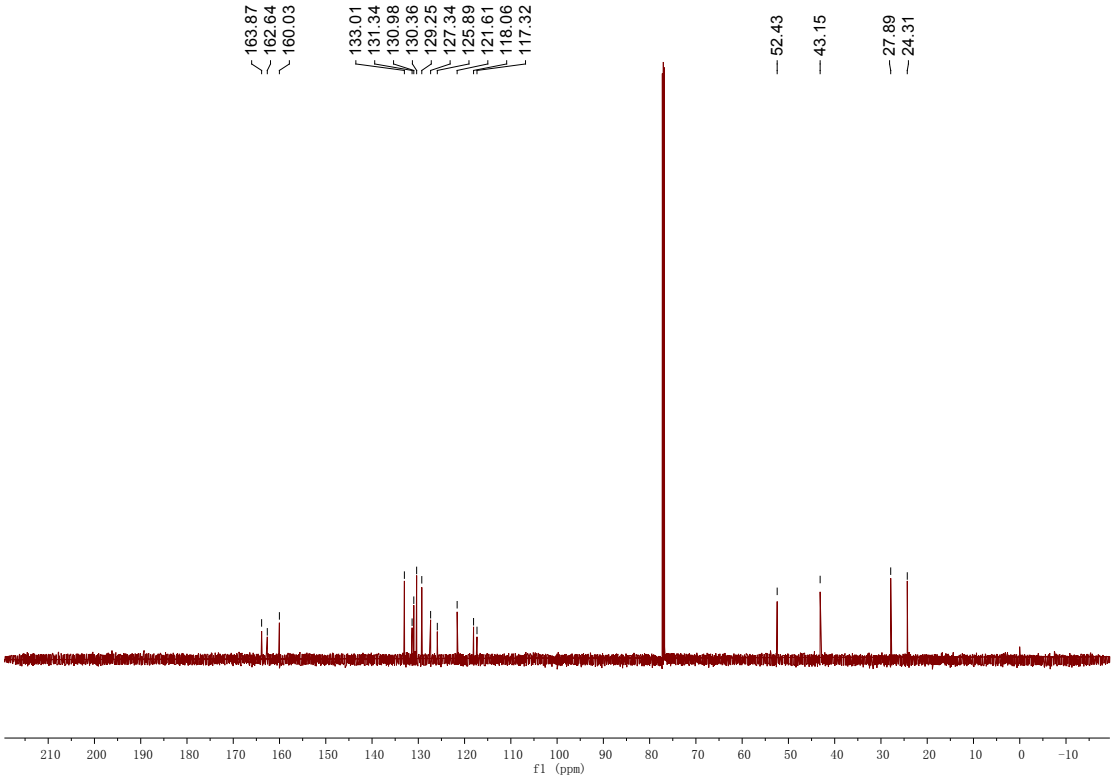
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

39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129.25
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125.89
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118.06
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52.43
43.15
27.89
24.31
210
200
190
180
170
160
150
140
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120
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100
90
80
70
60
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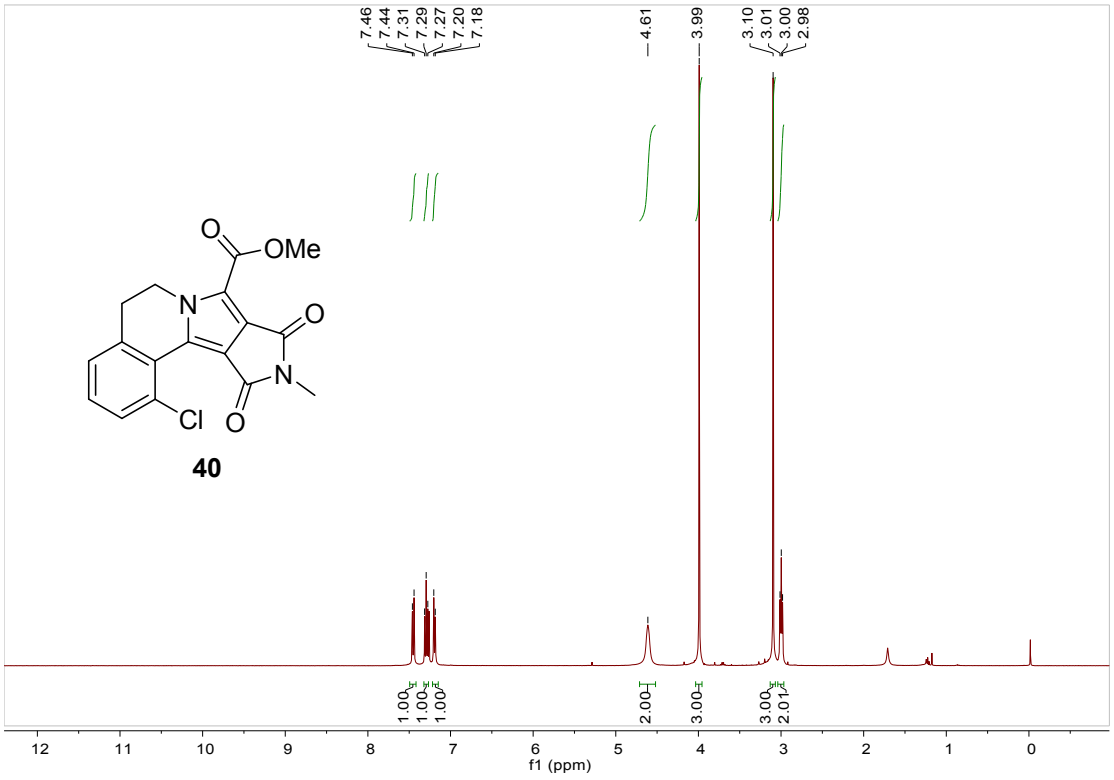
40
30
20
10
0
-10
f1 (ppm)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4.61
3.99
3.10
3.01
3.00
2.98
O
OMe
N
O
N
Cl
O
1.00
1.00
1.00
2.00
3.00
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12
11
10
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8
7
6
5
4
3
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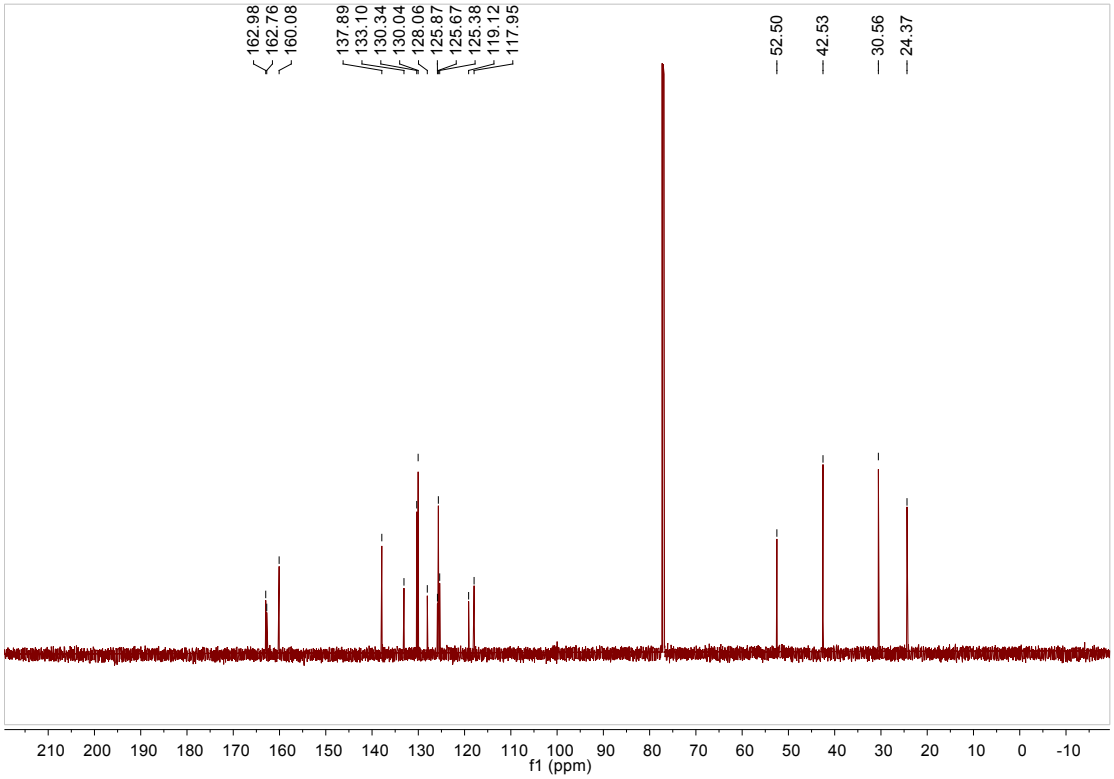
1
0
f1 (ppm)

40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125.38
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200
190
180
170
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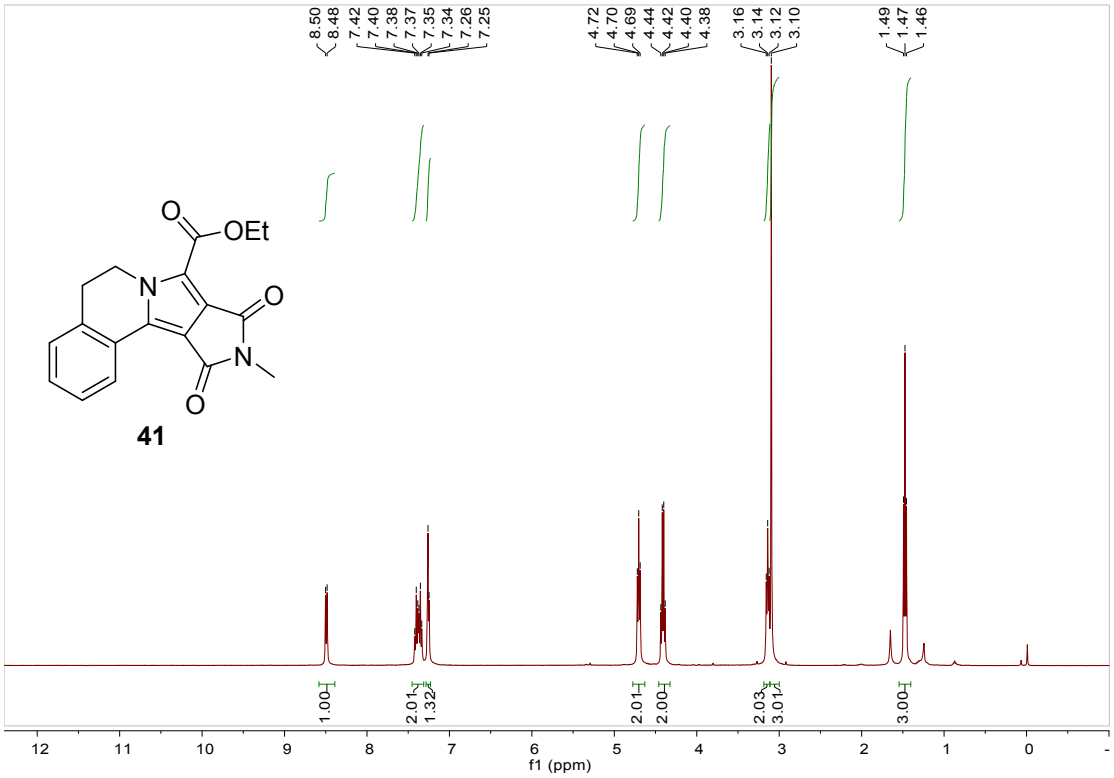
f1 (ppm)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4.69
4.44
4.42
4.40
4.38
3.16
3.14
3.12
3.10
1.49
1.47
1.46
O
OEt
N
O
N
O
41
1.00
2.01
1.32
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2.00
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9
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5
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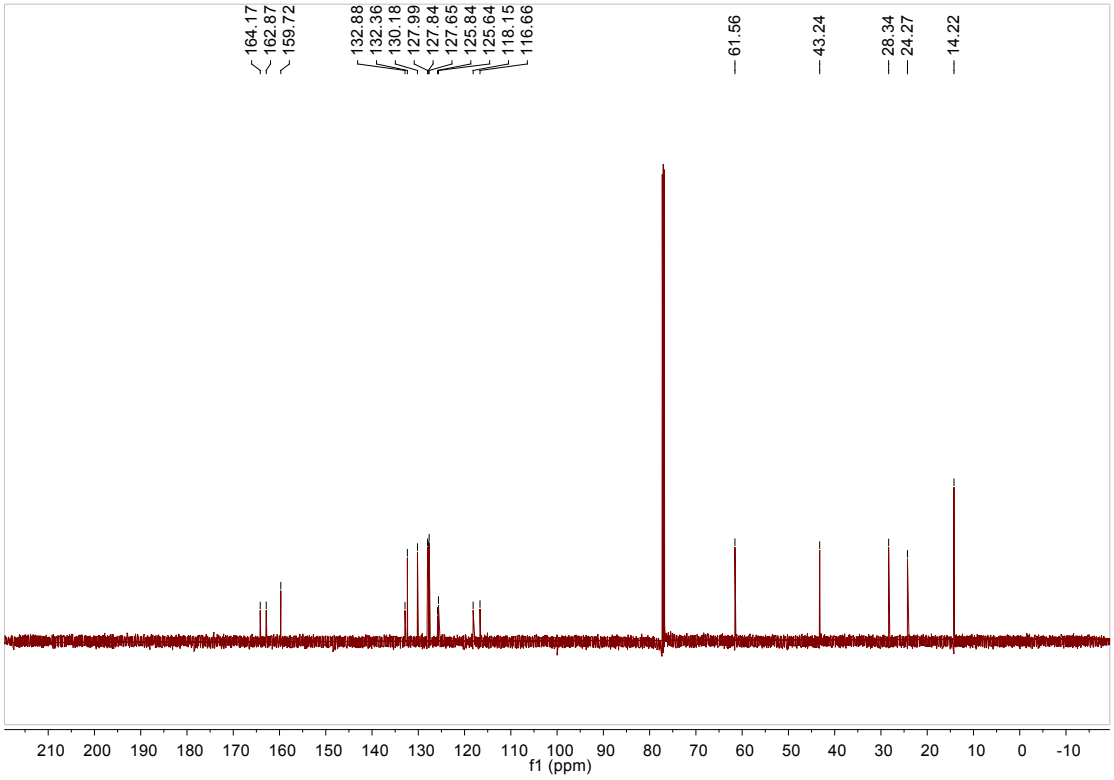
f1 (ppm)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127.65
125.84
125.64
118.15
116.66
61.56
43.24
28.34
24.27
14.22
210
200
190
180
170
160
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140
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120
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100
90
80
70
60
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40
30
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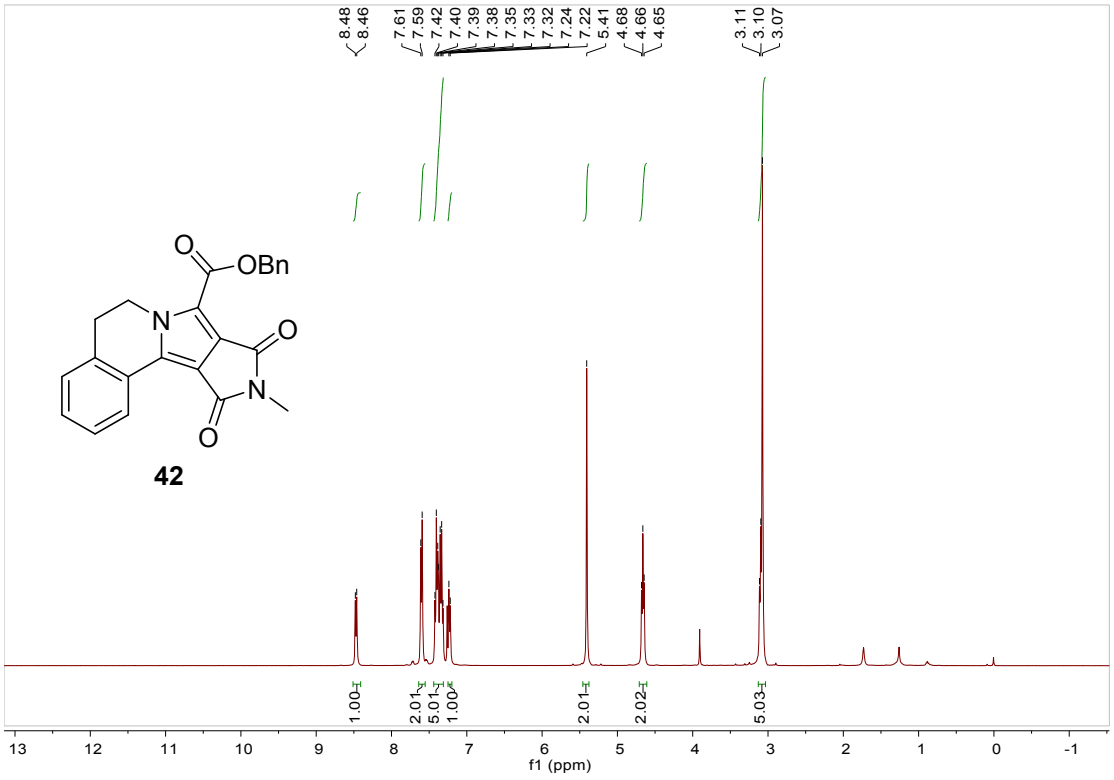
0
-10
f1 (ppm)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7.32
7.24
7.22
5.41
4.68
4.66
4.65
3.11
3.10
3.07
O
OBn
N
O
N
O
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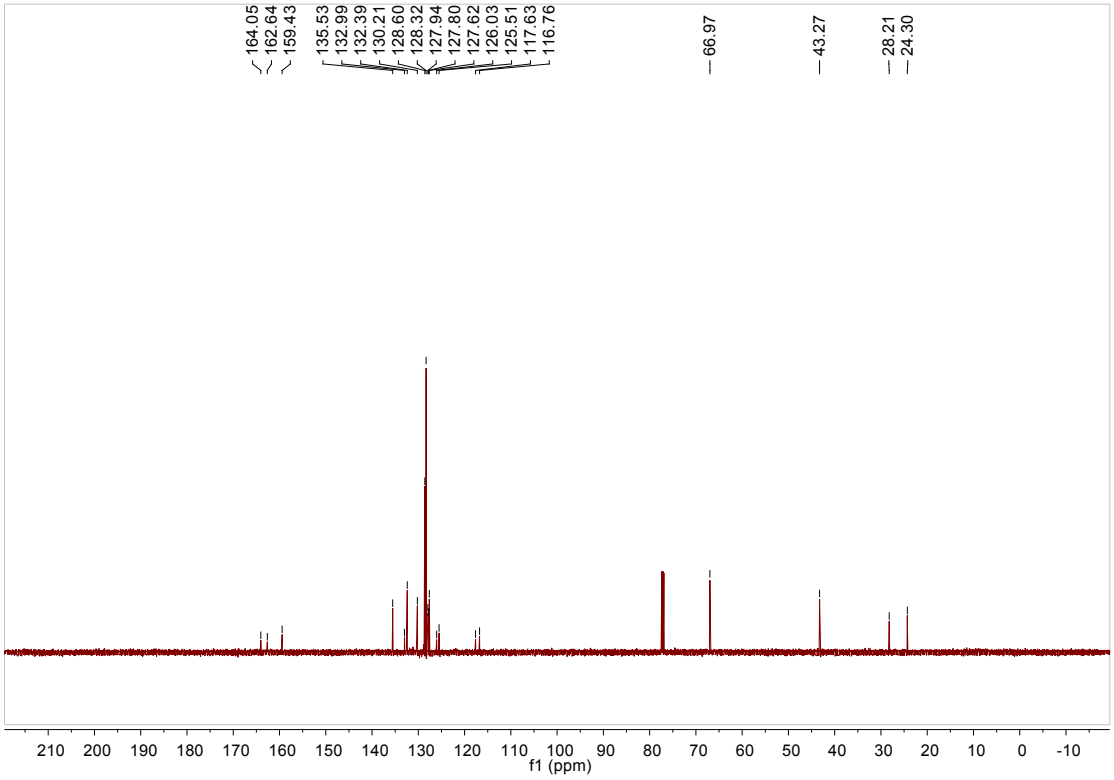
2.01
5.01
1.00
2.01
2.02
5.03
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

42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127.94
127.80
127.62
126.03
125.51
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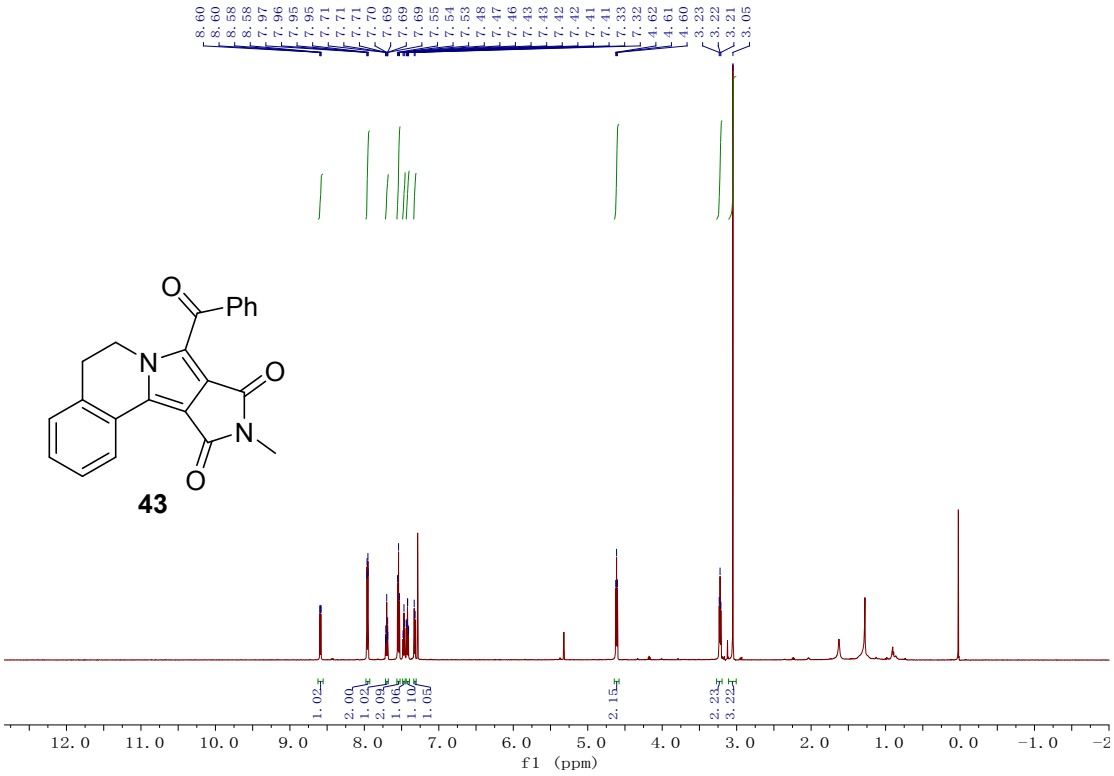
43.27
28.21
24.30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.69
7.69
7.69
7.55
7.54
7.53
7.48
7.47
7.46
7.43
7.43
7.42
7.42
7.41
7.41
7.33
7.32
4.62
4.61
4.60
3.23
3.22
3.21
3.05
O
Ph
N
O
N
O
43
1.02
2.00
1.02
2.02
1.06
1.10
1.05
2.15
2.23
3.22
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10.0
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6.0
5.0
4.0
3.0
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1.0
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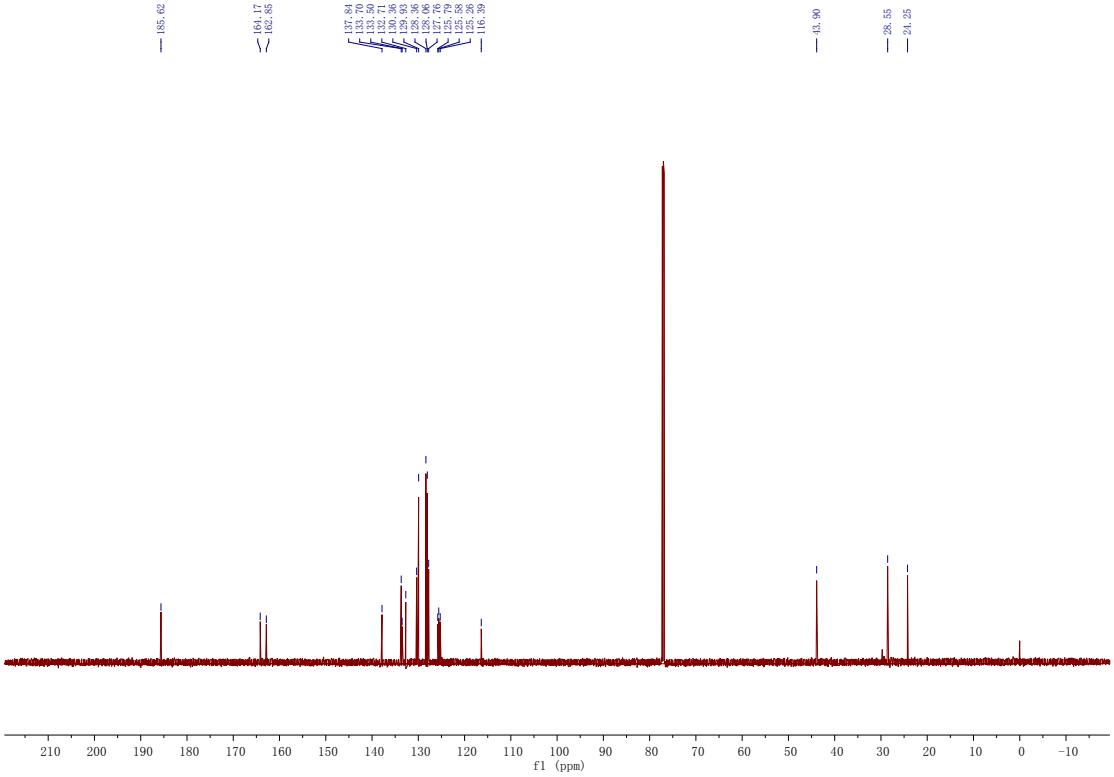
−1.0
f1 (ppm)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130.36
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128.36
128.06
127.76
125.79
125.58
125.26
116.39
43.90
28.55
24.25
210
200
190
180
170
160
150
140
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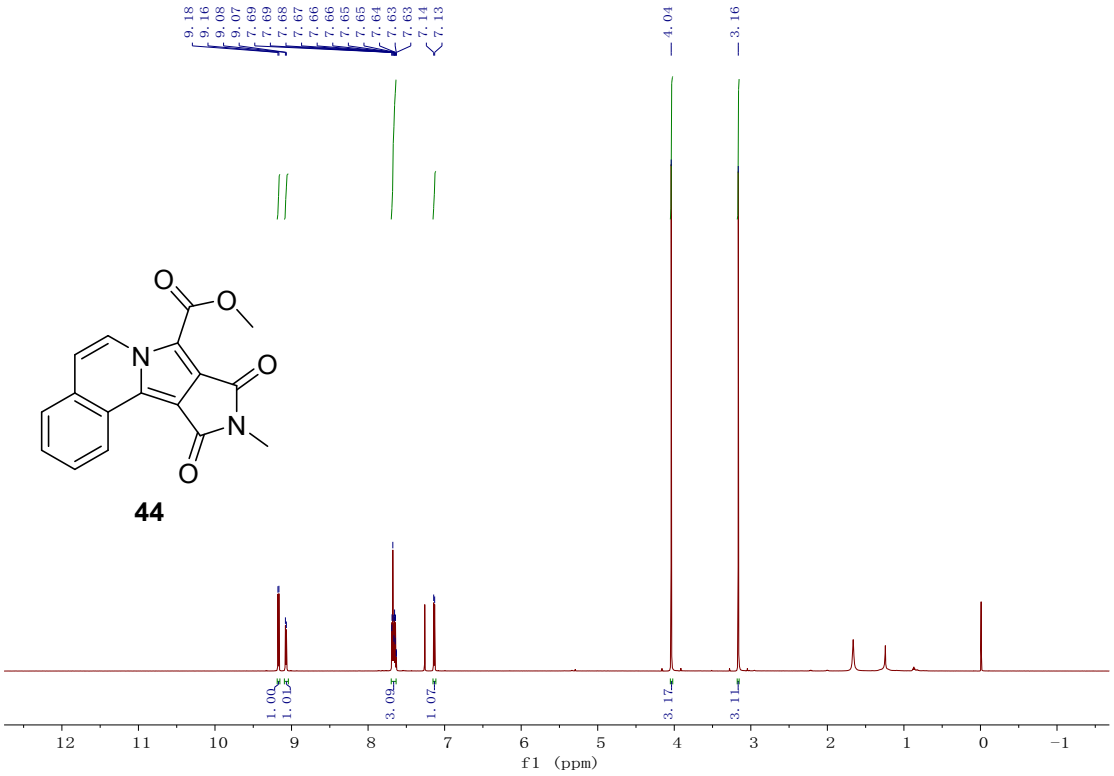
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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7.66
7.65
7.65
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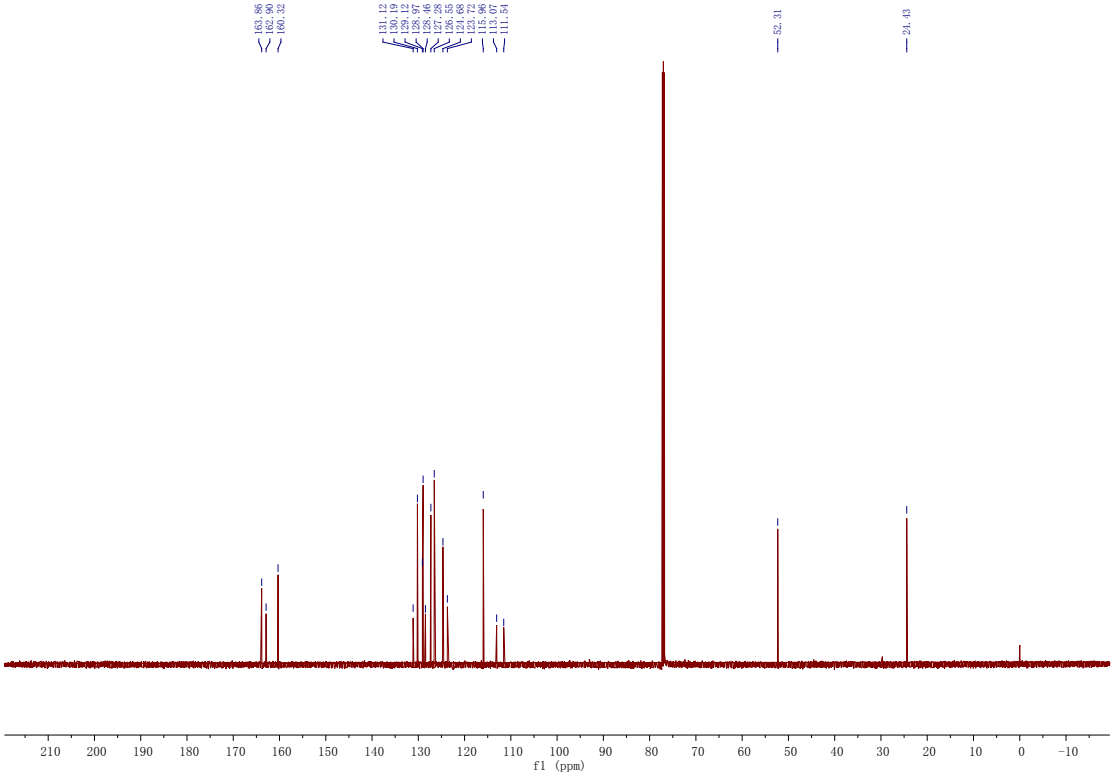
7.63
7.63
7.14
7.13
4.04
3.16
O
O
N
O
N
O
1.00
1.01
3.09
1.07
3.17
3.11
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)

44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128.97
128.46
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124.68
123.72
115.96
113.07
111.84
52.31
24.43
210
200
190
180
170
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110
100
90
80
70
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50
40
30
20
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0
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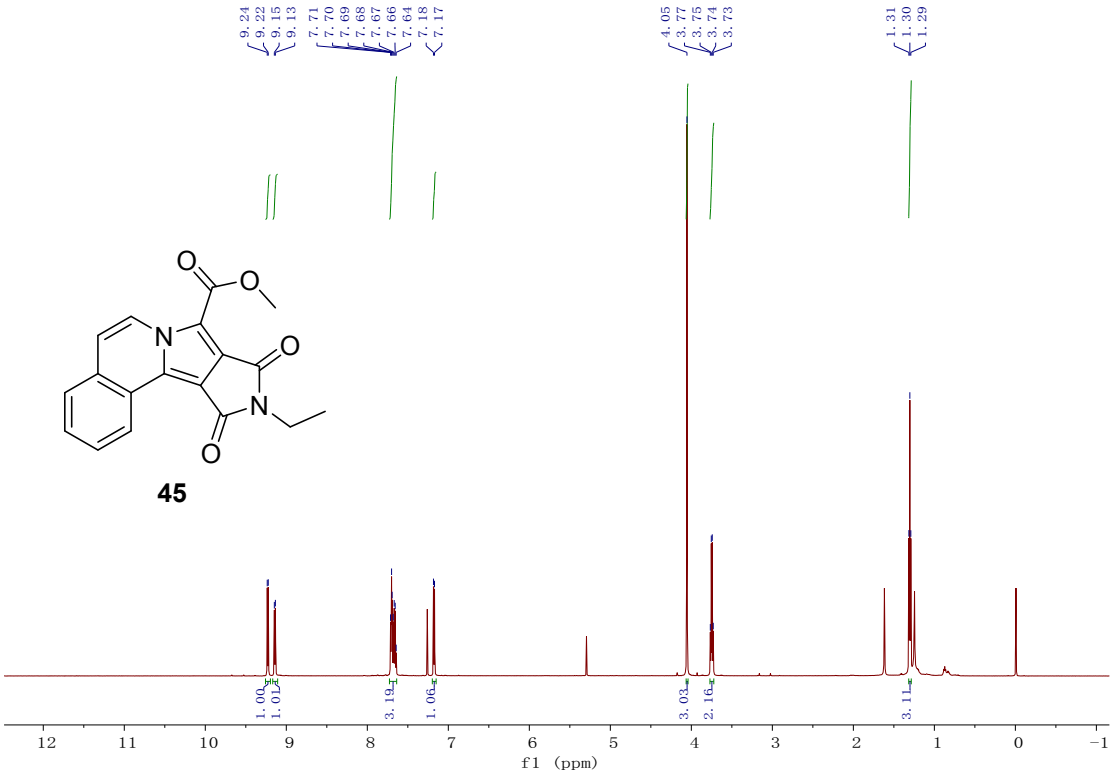
f1 (ppm)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7.68
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7.64
7.18
7.17
4.05
3.77
3.75
3.74
3.73
1.31
1.30
1.29
O
O
N
O
N
O
45
1.00
1.01
3.19
1.06
3.03
2.16
3.11
12
11
10
9
8
7
6
5
4
3
2
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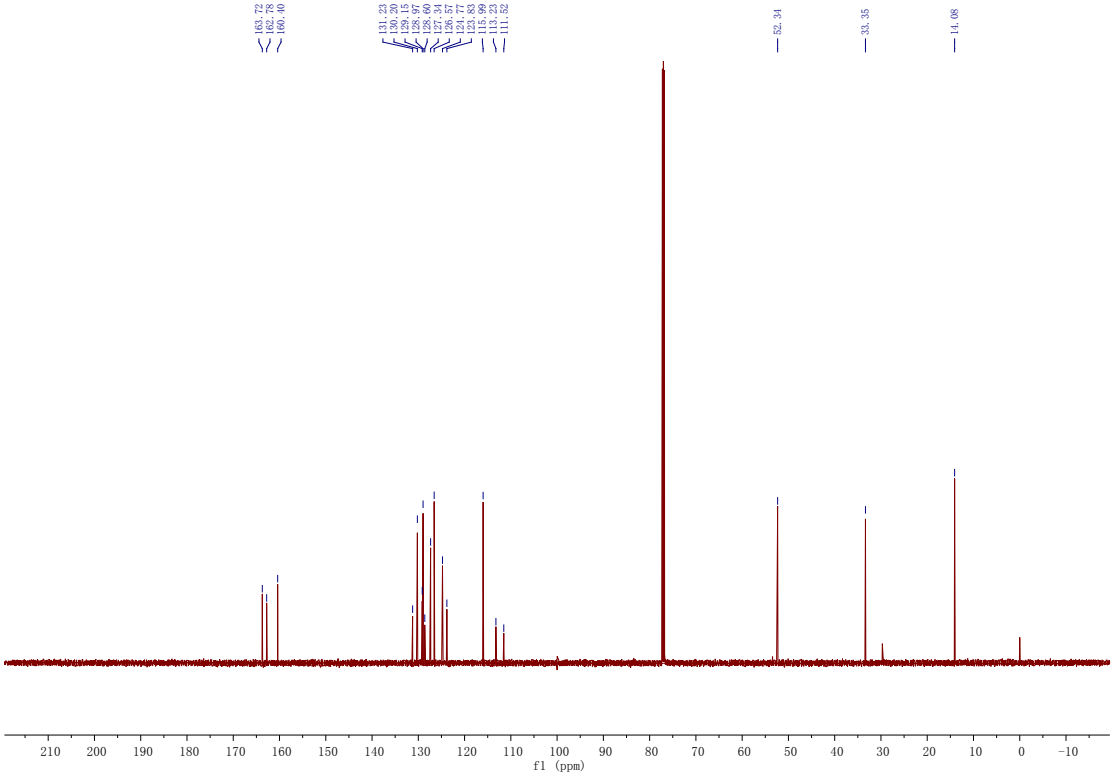
0
−1
f1 (ppm)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115.99
113.23
111.52
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33.35
14.08
210
200
190
180
170
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120
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100
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80
70
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40
30
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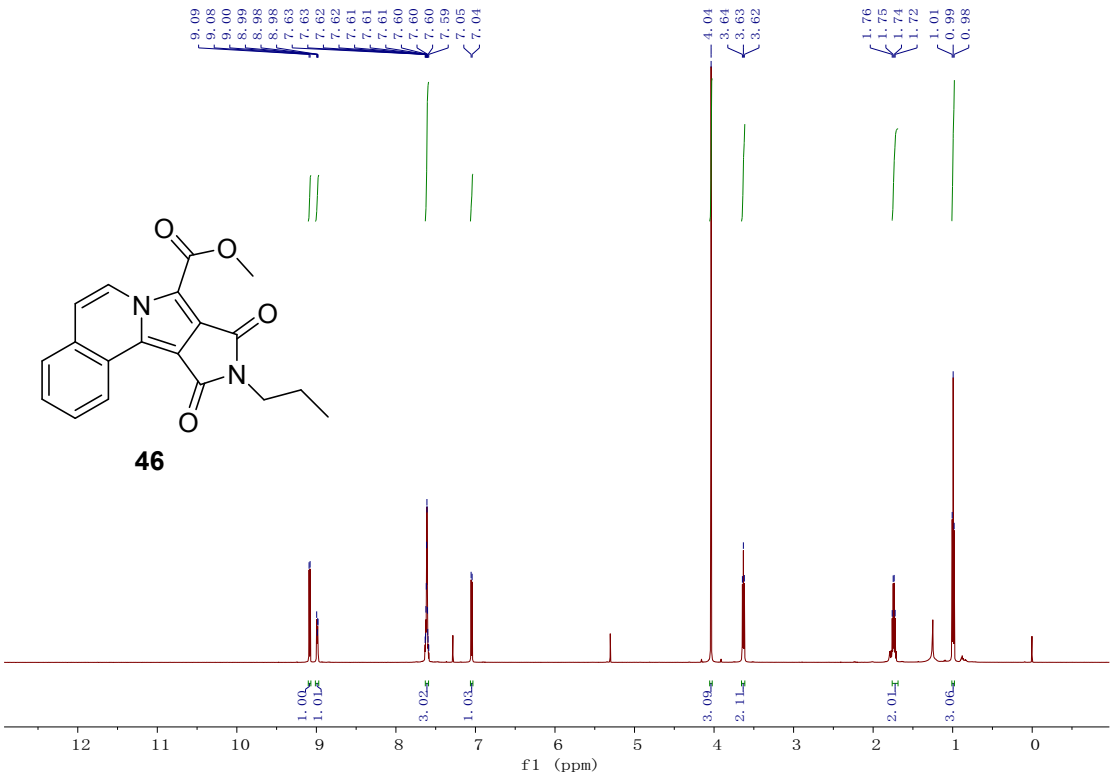
0
−10
f1 (ppm)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7.59
7.05
7.04
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3.63
3.62
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1.75
1.74
1.72
1.01
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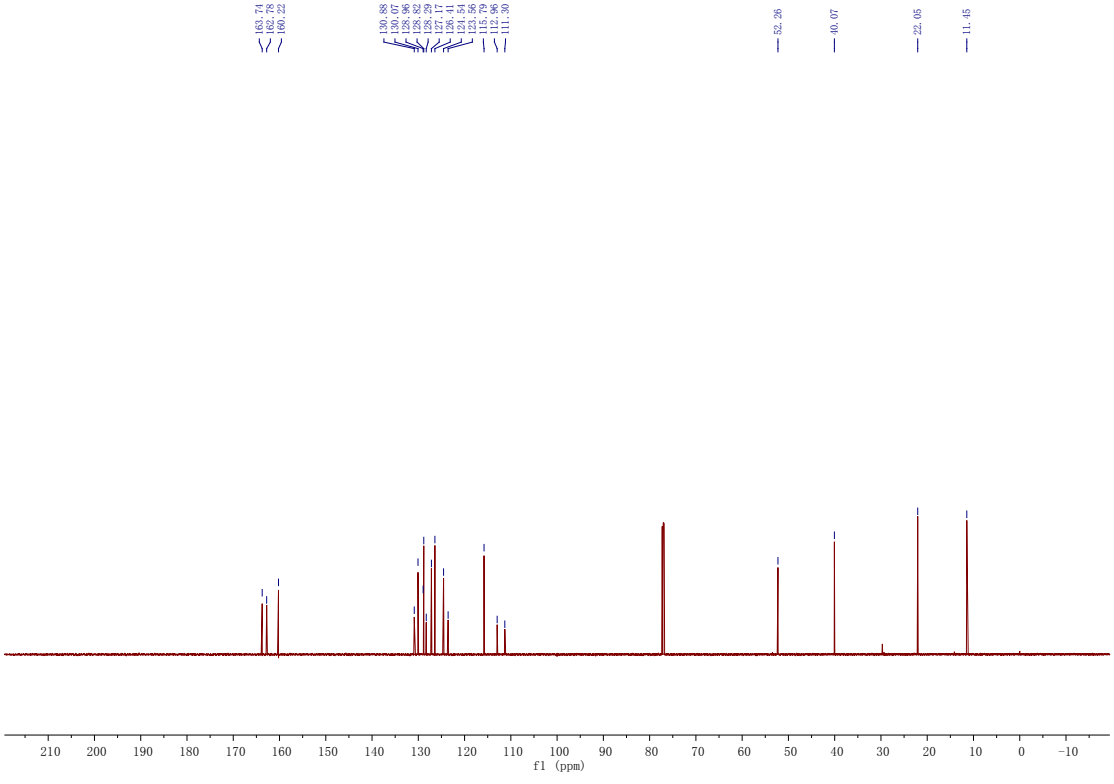
0.98
O
O
N
O
N
O
46
1.00
1.01
3.02
1.03
3.09
2.11
2.01
3.06
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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129.96
128.82
128.29
127.17
126.41
124.54
123.56
115.79
112.96
111.30
52.26
40.07
22.05
11.45
210
200
190
180
170
160
150
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120
110
100
90
80
70
60
50
40
30
20
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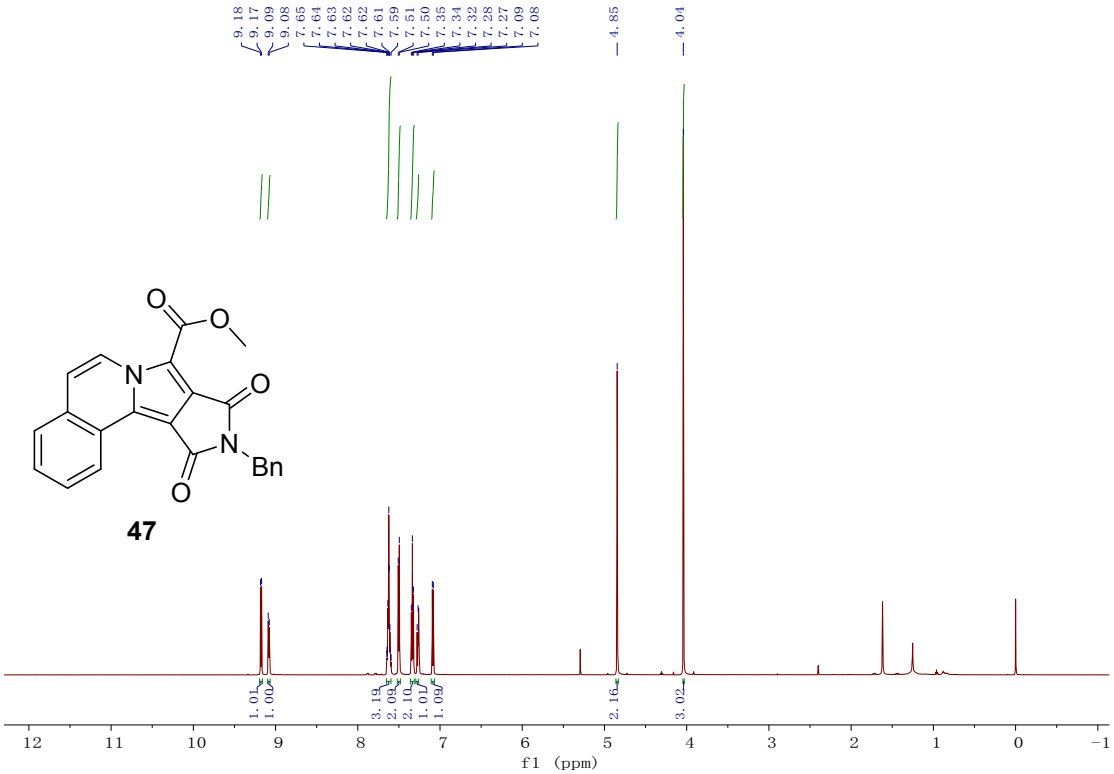
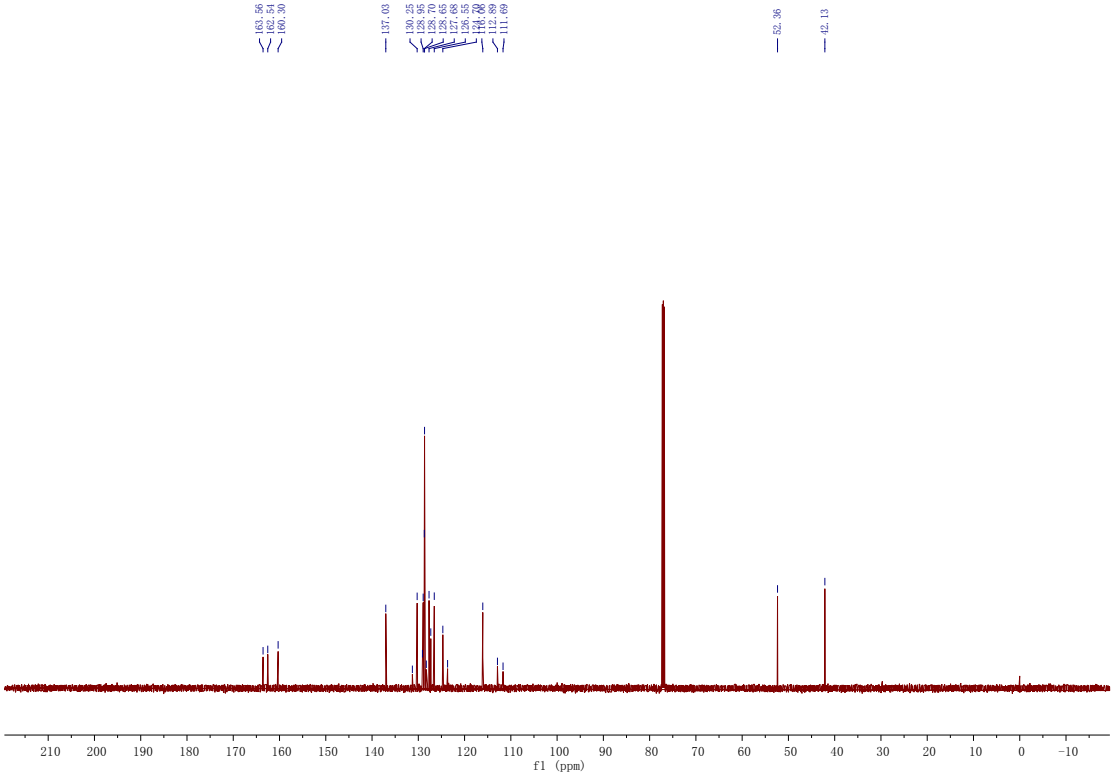
0
−10
f1 (ppm)


9.18
9.17
9.09
9.08
7.65
7.64
7.63
7.62
7.62
7.61
7.59
7.51
7.50
7.35
7.34
7.32
7.28
7.27
7.09
7.08
4.85
4.04
O
O
N
O
N
Bn
O
1.01
1.00
3.19
2.09
2.10
1.01
1.09
2.16
3.02
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)

47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162.54
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137.03
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129.95
128.70
128.65
127.68
126.55
52.36
42.13
210
200
190
180
170
160
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120
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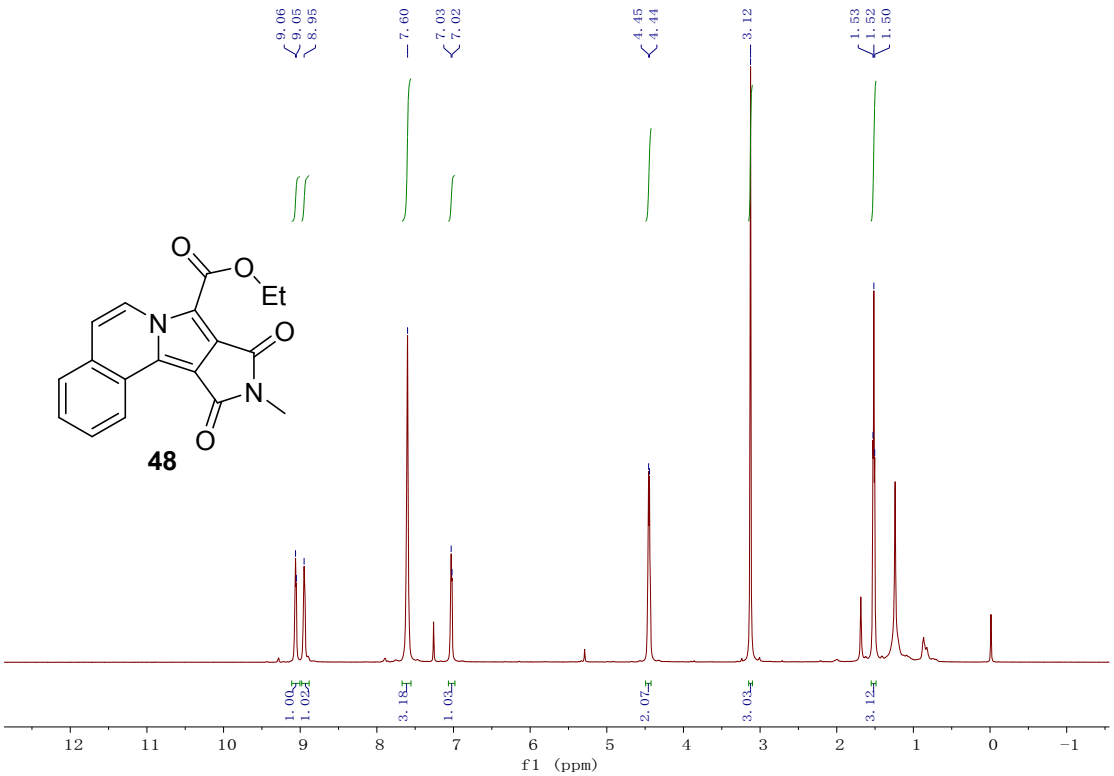
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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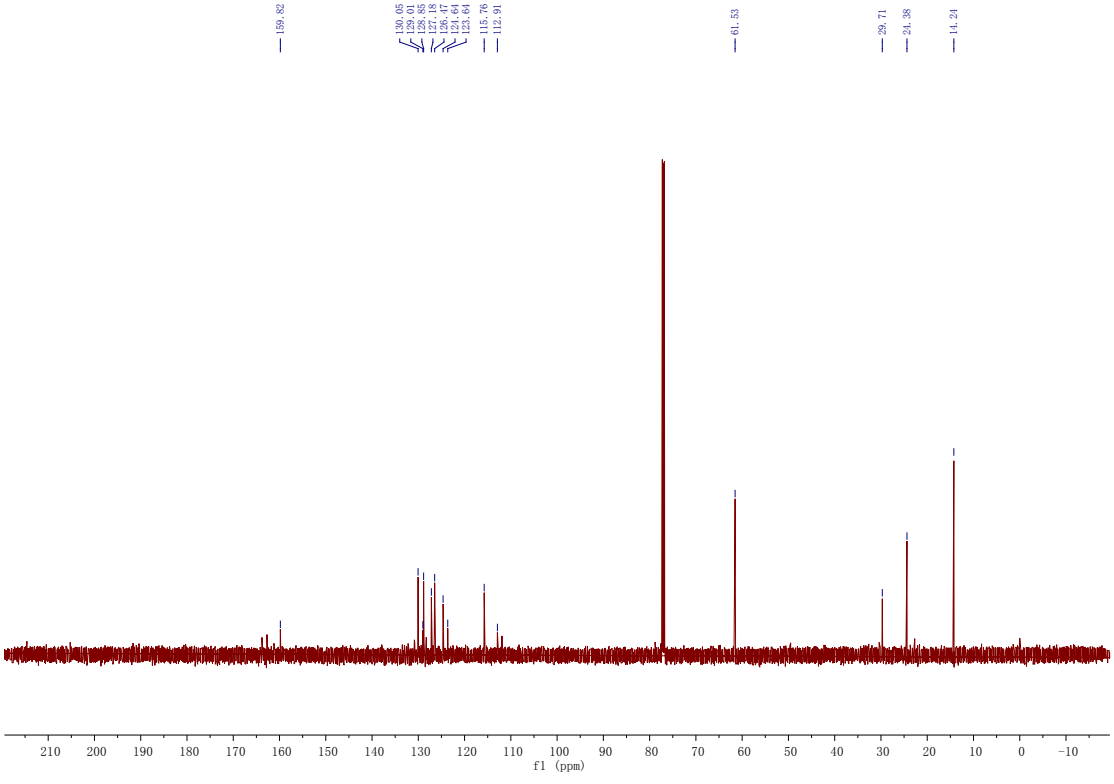
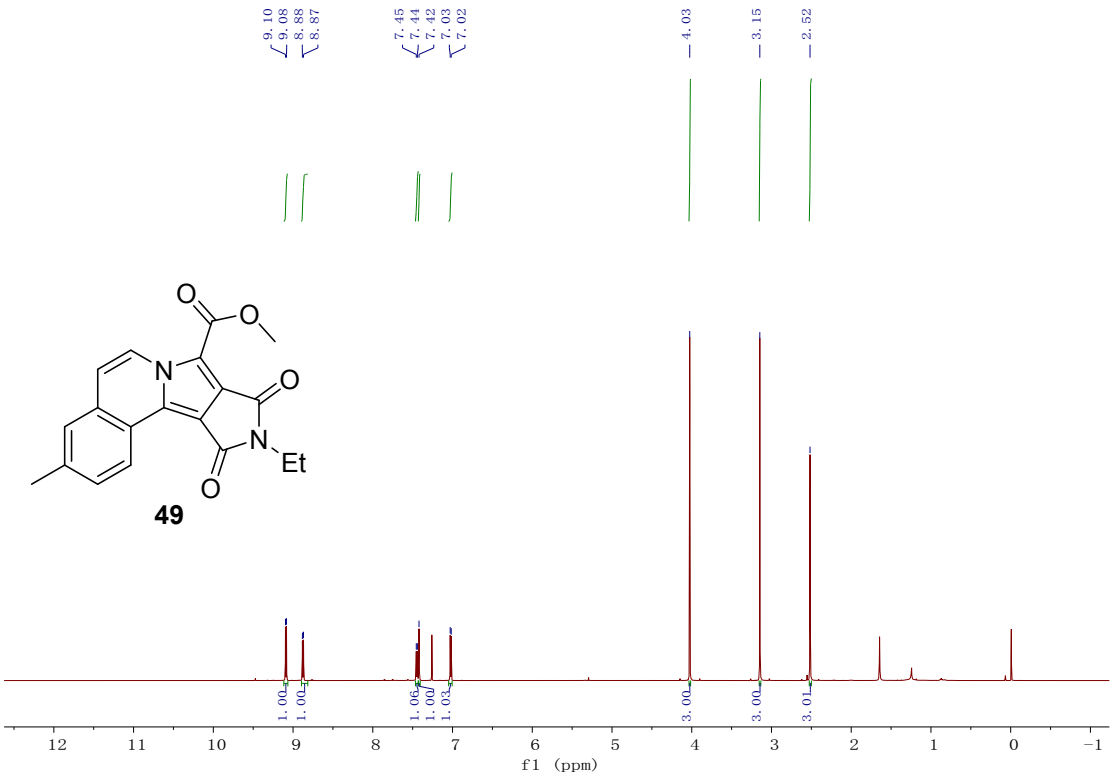
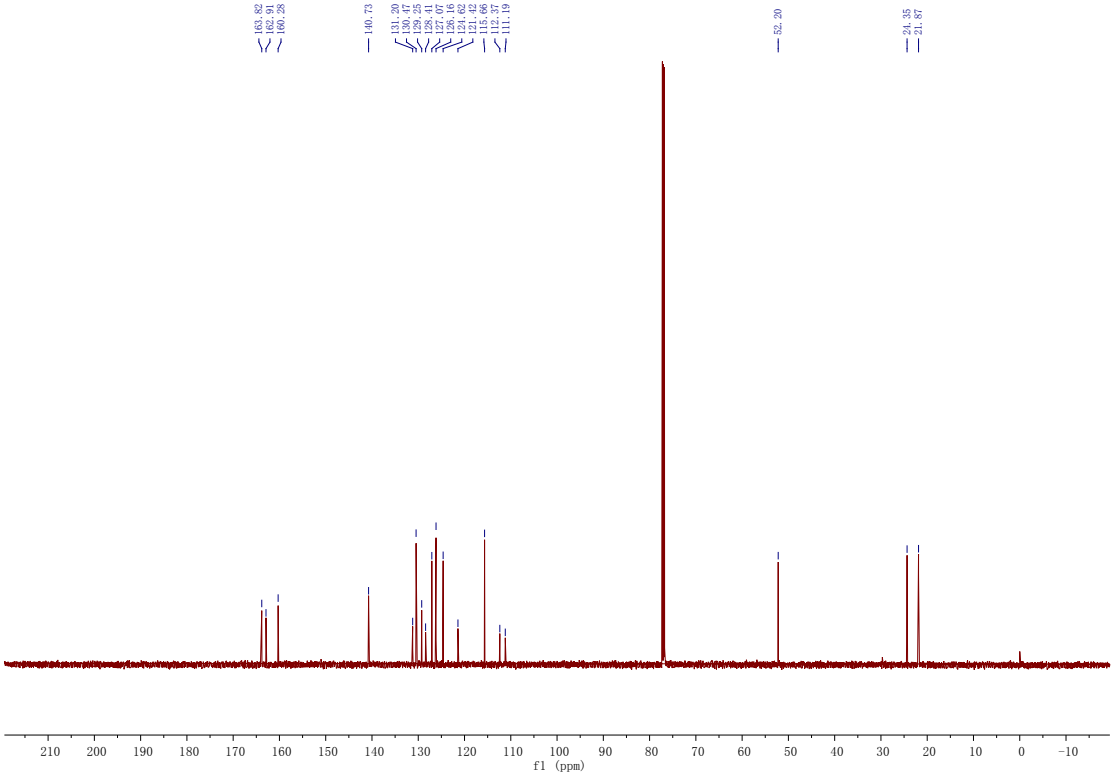
9.05
8.95
7.60
7.03
7.02
4.45
4.44
3.12
1.53
1.52
1.50
O
O
Et
N
O
N
O
48
1.00
1.02
3.18
1.03
2.07
3.03
3.12
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)


159.82
130.05
129.01
128.55
127.18
126.47
124.64
123.64
115.76
112.91
61.53
29.71
24.38
14.24
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)


9.10
9.08
8.88
8.87
7.45
7.44
7.42
7.03
7.02
4.03
3.15
2.52
O
O
N
O
N
Et
O
1.00
1.00
1.06
1.00
1.03
3.00
3.00
3.01
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)

49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162.91
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131.20
130.47
129.25
128.41
127.07
126.16
125.62
121.42
115.66
112.37
111.19
52.20
24.35
21.87
210
200
190
180
170
160
150
140
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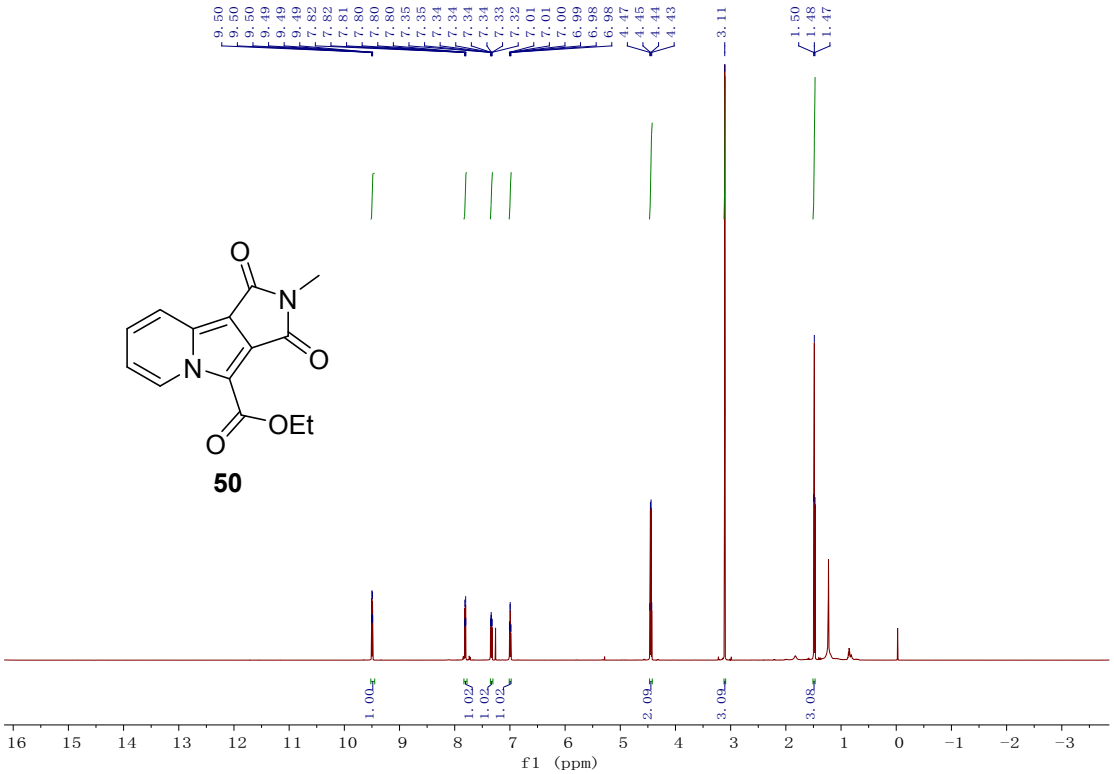
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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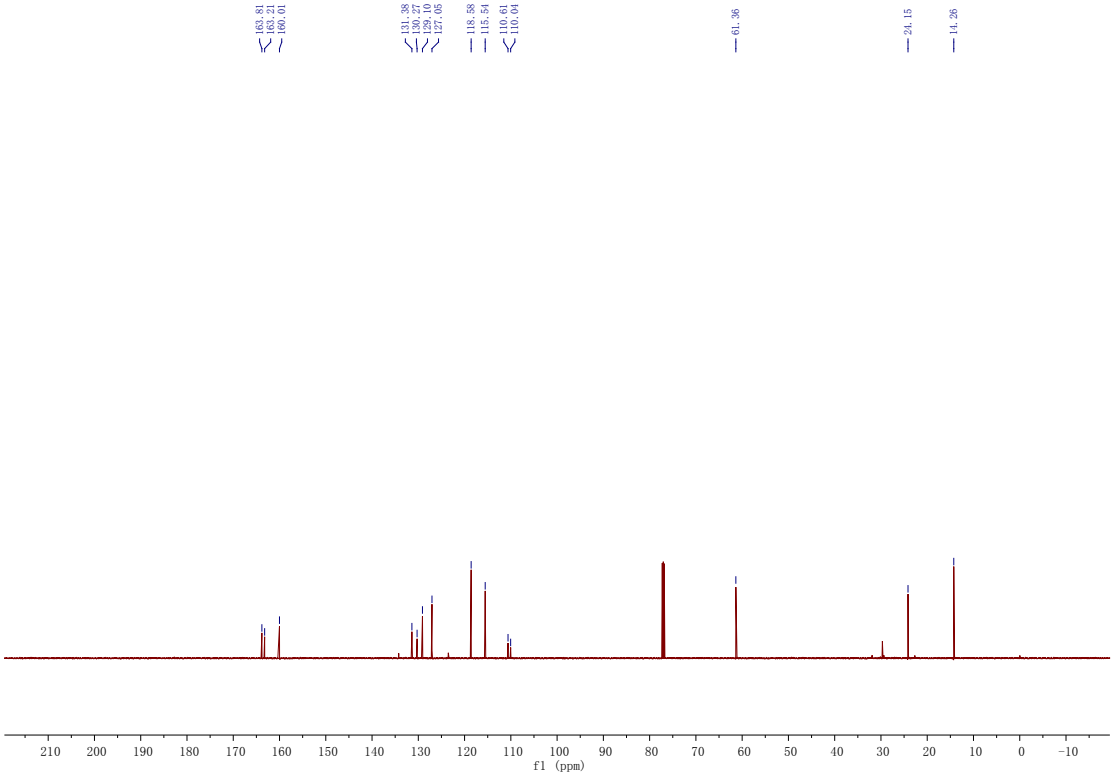
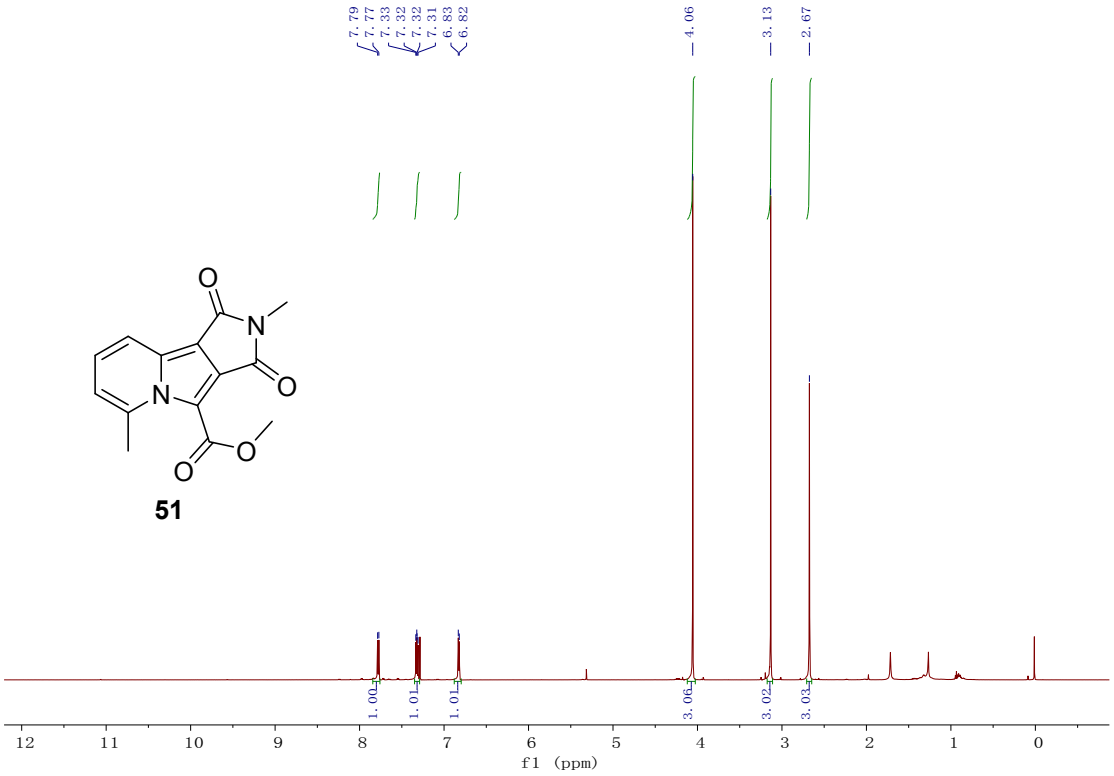
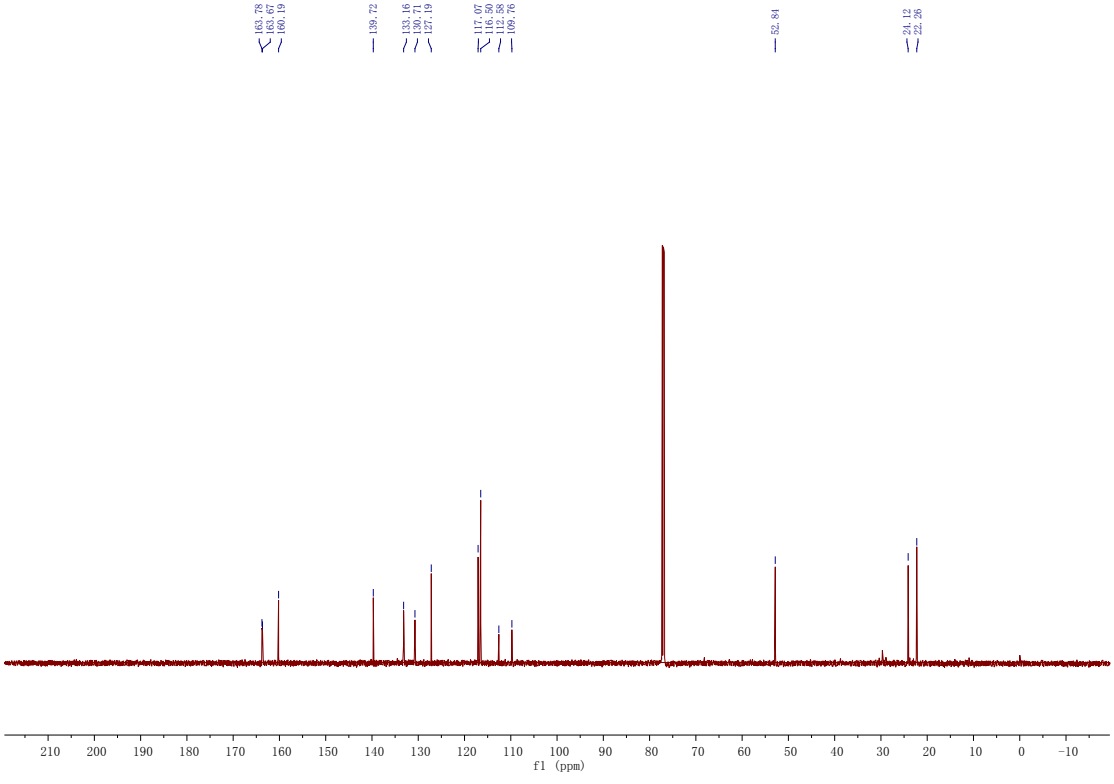
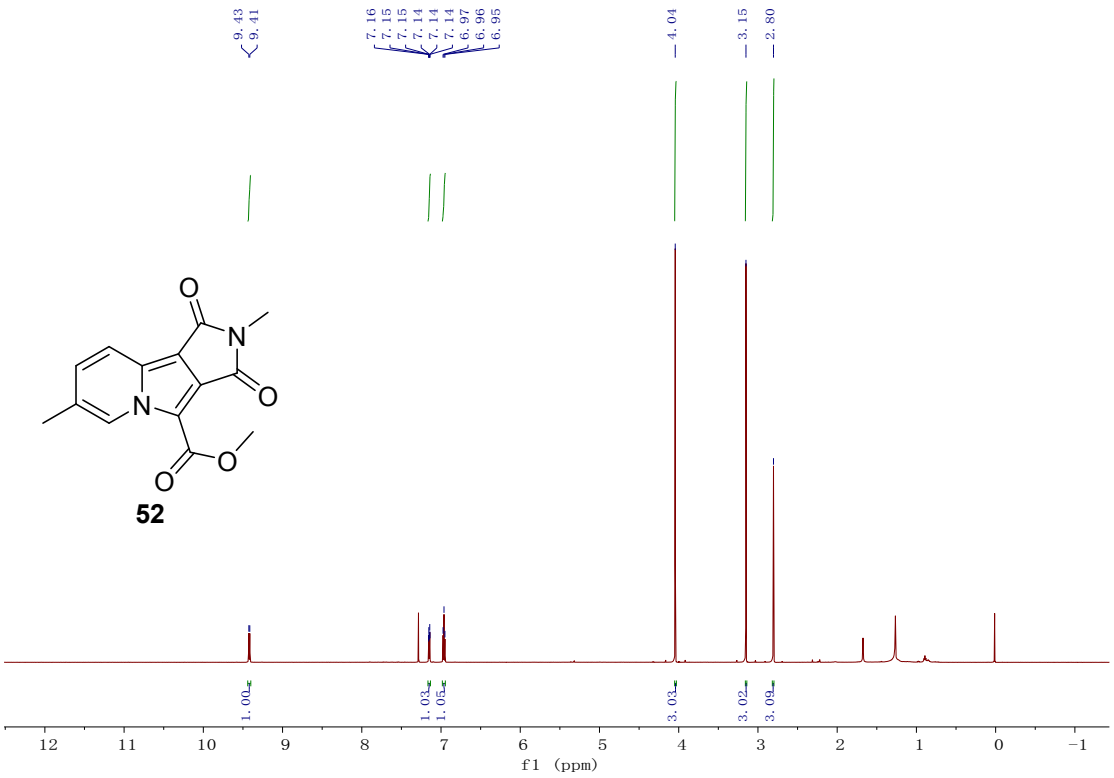
9.50
9.50
9.49
9.49
9.49
7.82
7.82
7.81
7.80
7.80
7.80
7.80
7.35
7.35
7.34
7.34
7.34
7.34
7.33
7.32
7.01
7.01
7.00
6.99
6.98
6.98
4.47
4.45
4.44
4.43
3.11
1.50
1.48
1.47
O
N
O
N
O
OEt
O
50
1.00
1.02
1.02
1.02
2.09
3.09
3.08
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
f1 (ppm)


163.81
163.21
160.01
131.38
130.27
129.10
127.05
118.58
115.54
110.61
110.04
61.36
24.15
14.26
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)


7.79
7.77
7.33
7.32
7.32
7.31
6.83
6.82
4.06
3.13
2.67
O
N
O
N
O
O
1.00
1.01
1.01
3.06
3.02
3.03
12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

51


163.78
163.67
160.19
139.72
133.16
130.71
127.19
117.07
116.50
112.58
109.76
52.84
24.12
22.26
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)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9.41
7.16
7.15
7.15
7.14
7.14
7.14
6.97
6.96
6.95
4.04
3.15
2.80
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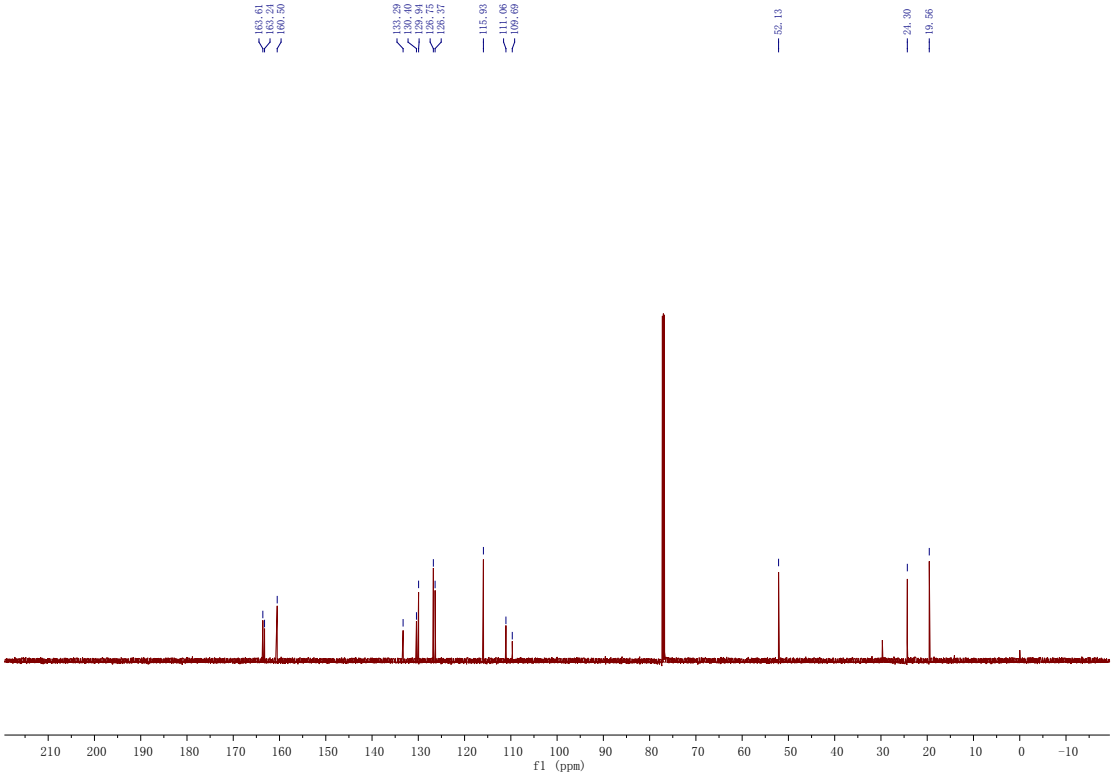
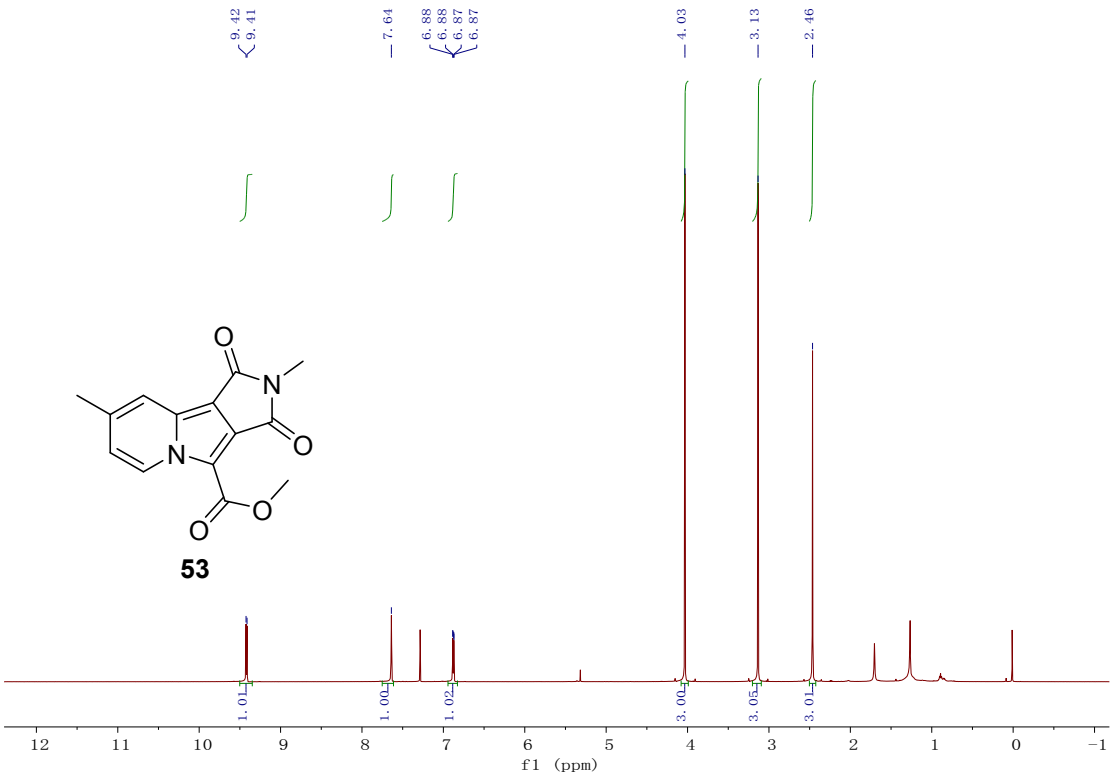
O
N
O
O
O
52
1.00
1.03
1.05
3.03
3.02
3.09
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)


163.61
163.24
160.59
133.29
130.40
129.94
126.75
126.37
115.93
111.06
109.69
52.13
24.30
19.56
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)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9.41
7.64
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6.88
6.87
6.87
4.03
3.13
2.46
O
N
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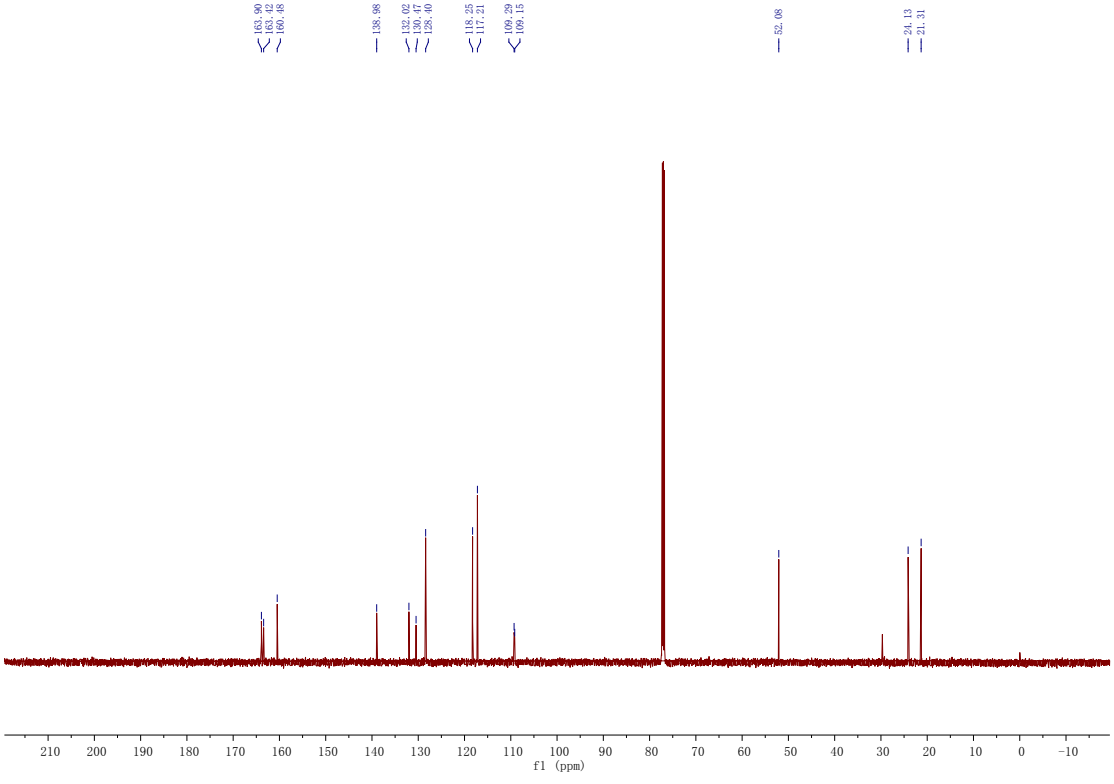
N
O
O
O
53
1.01
1.00
1.02
3.00
3.05
3.01
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)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163.42
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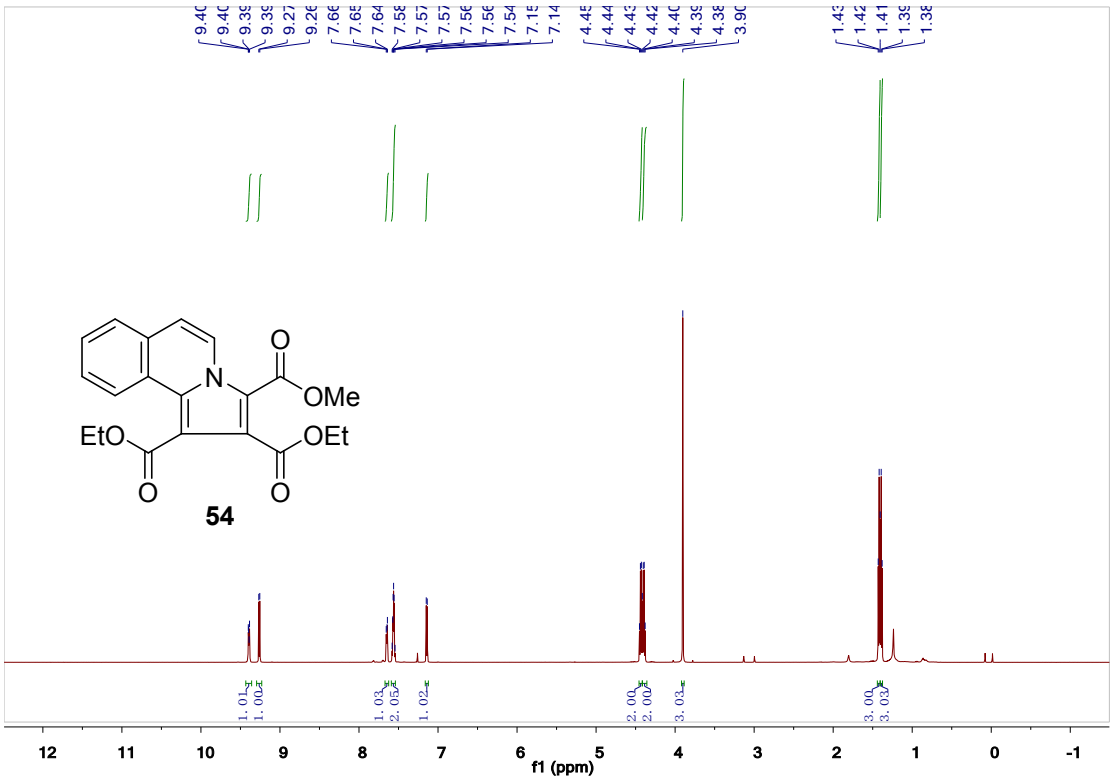
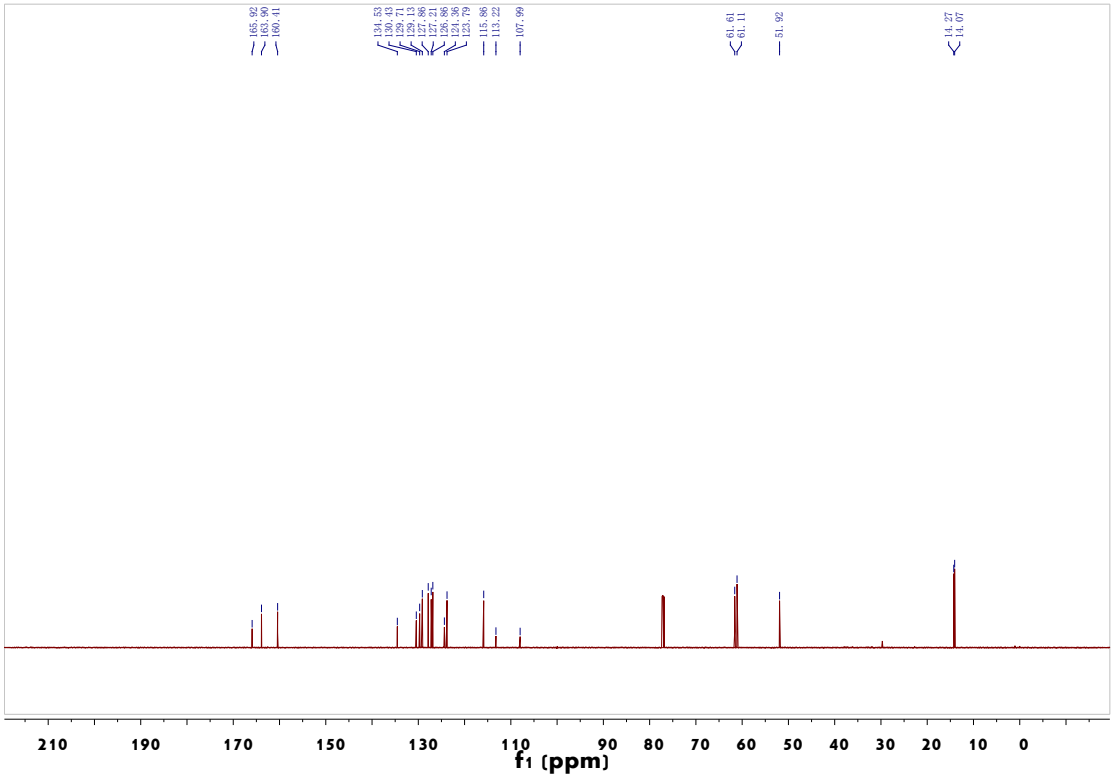
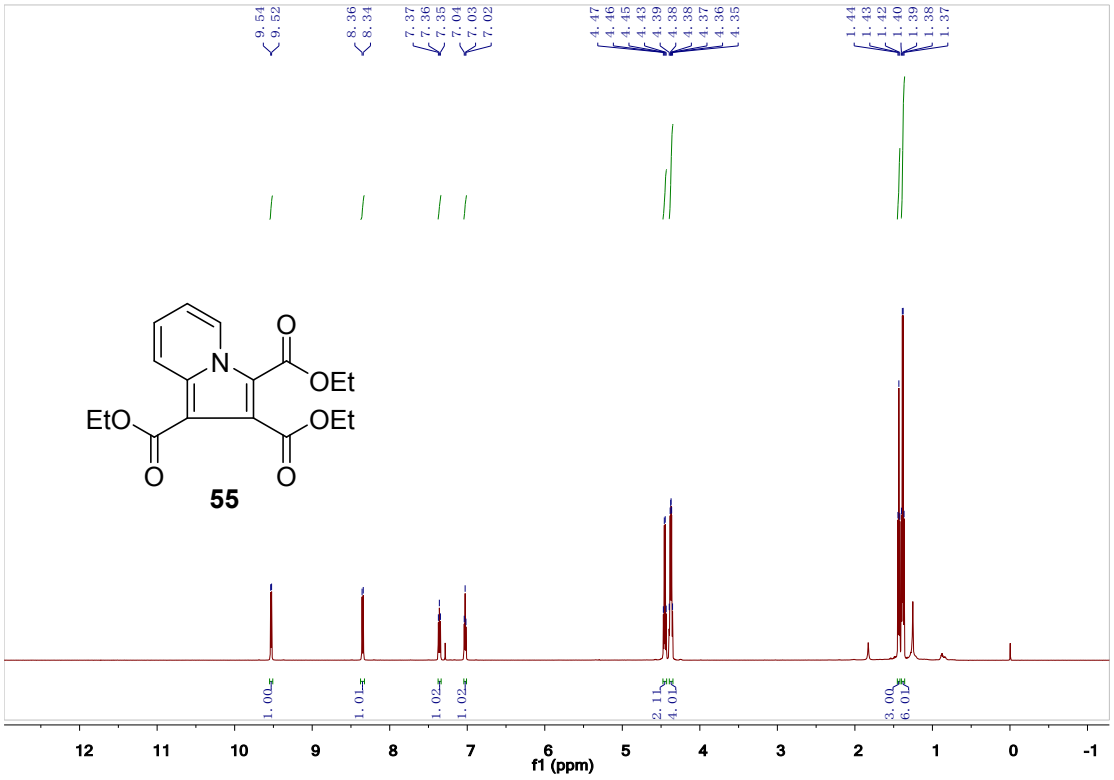
138.98
132.02
130.47
128.40
118.25
117.21
109.29
109.15
52.08
24.13
21.31
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


N
O
OMe
EtO
OEt
O
O
O
54
f1 (ppm)


f1 (ppm)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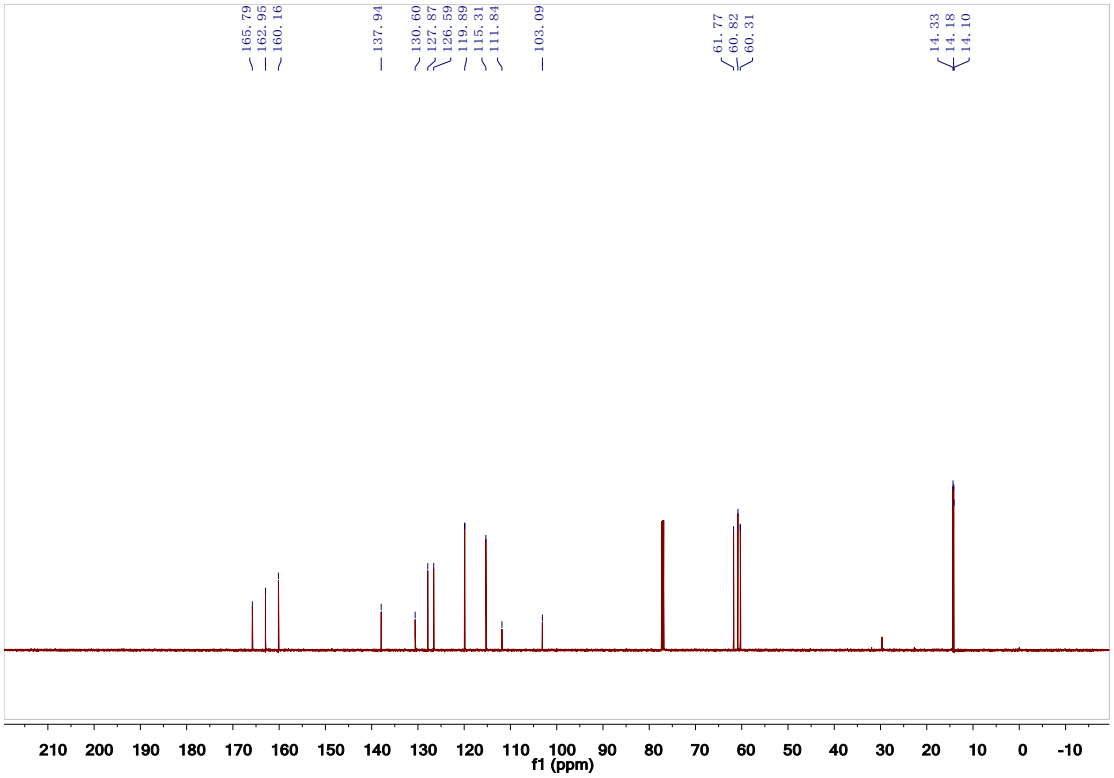
7.36
7.35
7.04
7.03
7.02
4.47
4.46
4.45
4.43
4.39
4.38
4.38
4.37
4.36
4.35
1.44
1.43
1.42
1.40
1.39
1.38
1.37
O
N
OEt
EtO
OEt
O
O
O
55
1.00
1.01
1.02
1.02
2.11
4.01
3.00
6.01
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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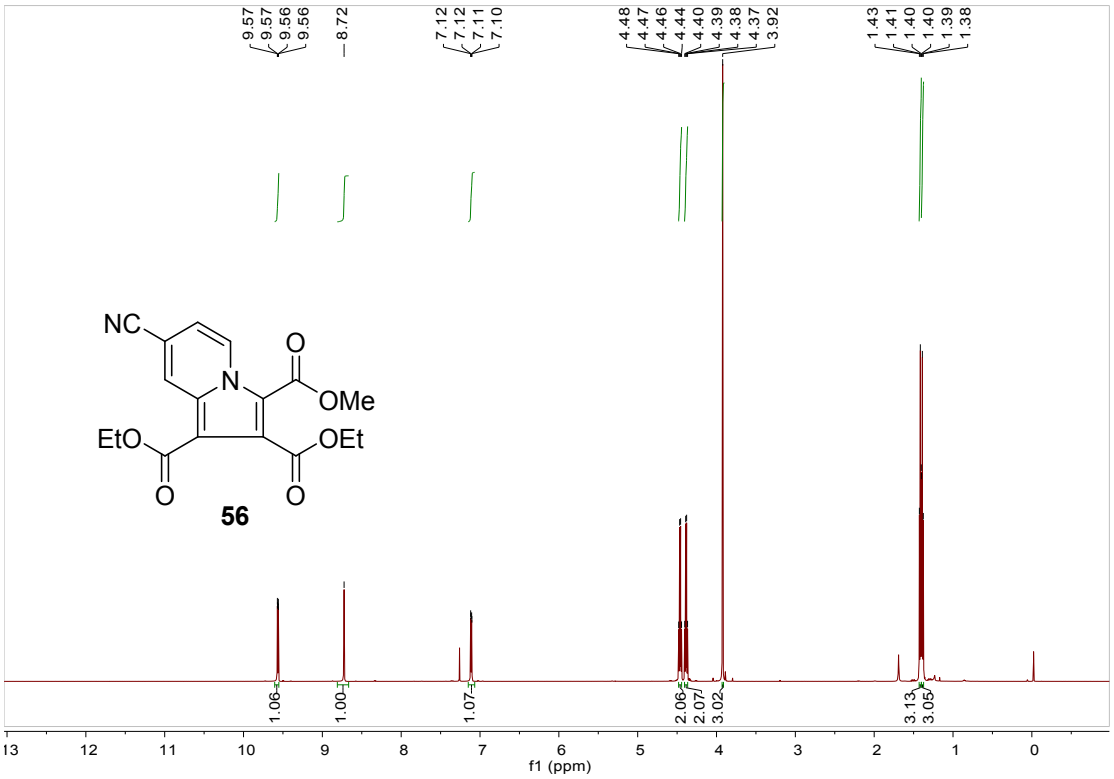
137.94
130.60
127.87
126.59
119.89
115.31
111.84
103.09
61.77
60.82
60.31
14.33
14.18
14.10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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9.57
9.56
9.56
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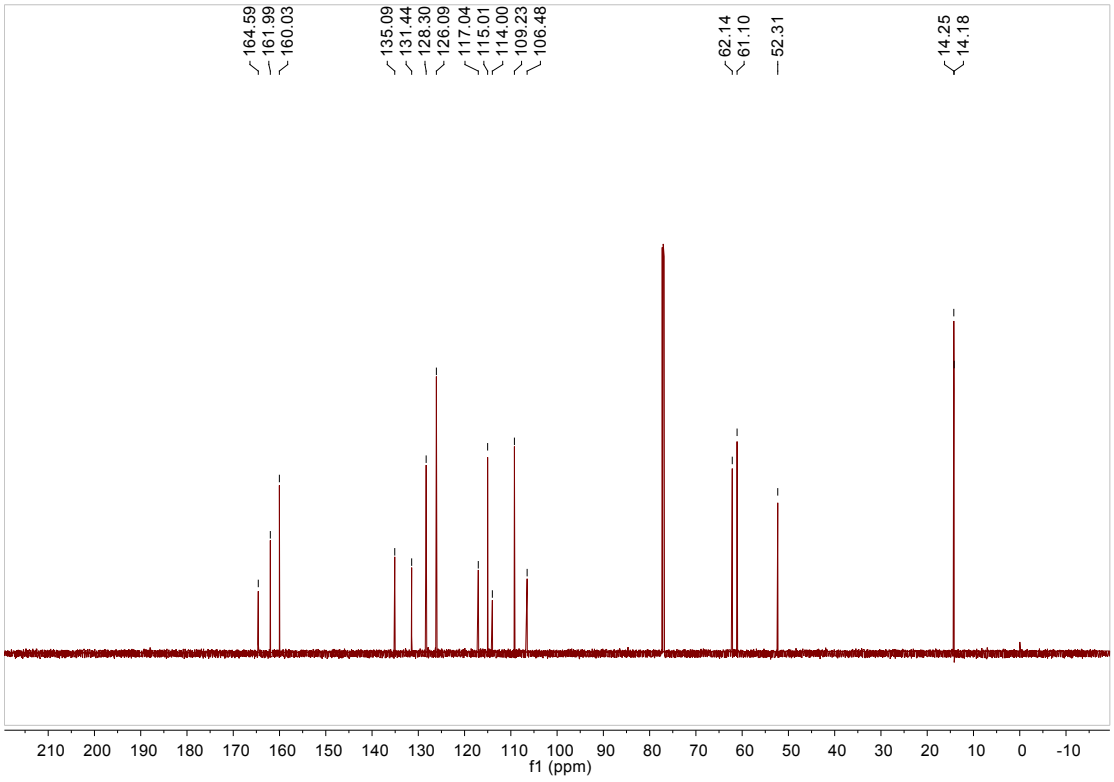
7.12
7.11
7.10
4.48
4.47
4.46
4.44
4.40
4.39
4.38
4.37
3.92
1.43
1.41
1.40
1.40
1.39
1.38
NC
N
O
OMe
EtO
OEt
O
O
O
56
1.06
1.00
1.07
2.06
2.07
3.02
3.13
3.05
f1 (ppm)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131.44
128.30
126.09
117.04
115.01
114.00
109.23
106.48
62.14
61.10
52.31
14.25
14.18
f1 (ppm)