

Supporting Information

Cu-Catalyzed Oxidative Denitrogenation of 3-Aminoindazoles for the Synthesis of Isoquinolinones

Yang Guo,[†] Peng-Fei Huang,[†] Bi-Quan Xiong, Jian-Hong Fan* and Yu Liu*

^a Department of Chemistry and Chemical Engineering, Hunan Institute of Science and Technology, Yueyang 414006, China

[†] These authors contributed equally to this work.

lyxtmj_613@163.com (Yu Liu) and 13548535911@163.com (Jian-Hong Fan)

List of Contents

1. General Information	S1
2. Experimental Section	S1
2.1. General Procedure for the Synthesis of Substrates	S1
2.2. Typical Experimental Procedure	S1
2.3. Control Experiments	S2
3. Reference	S5
4. ¹H and ¹³C spectra	S6

2. General Information

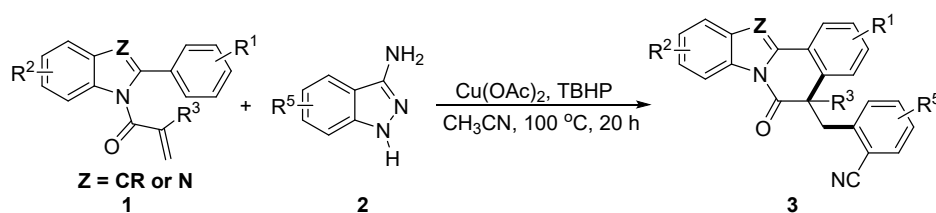
Unless otherwise stated, all commercial reagents were used as received. Propiophenone, aldehydes (Innochem, >98%), Phenylhydrazine hydrochloride and *o*-phenylenediamine were used without further treatment. All reagents and solvents were commercially available and used without any further purification unless specified. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (0.25mm, 300-400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25mm 300-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). All reactions were carried out with magnetic stirring and in dried glassware. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^1H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded in CDCl_3 on a Bruker DRX-400 spectrometer operating at 400 MHz, 282 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. The solvent peak was used as a reference value, for ^1H NMR: TMS = 0.00 ppm, for ^{13}C NMR: CDCl_3 = 77.00 ppm. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet, and br = broad. High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Experiment Section

2.1 General Procedure for the Synthesis of Substrates

All 2-aryl indoles **1**^[1] and 3-aminoindazoles **2**^[2] were synthesized according to the known methods.

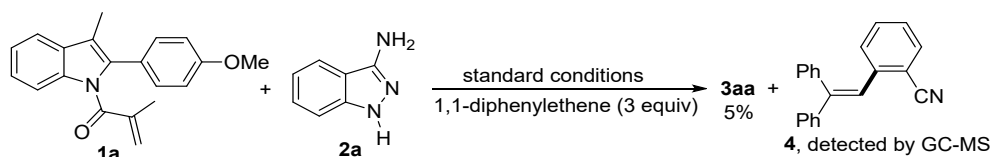
2.2 Typical Experimental Procedure



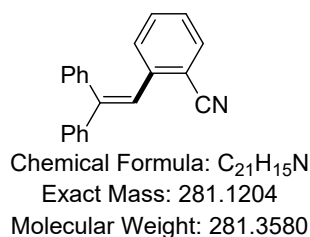
To a Schlenk tube were added **1** (0.2 mmol), **2** (0.4 mmol, 2 equiv.), Cu(OAc)₂ (20 mol%), aq. TBHP (*tert*-butyl hydroperoxide, 70% solution in water, 0.5 mmol, 2.5 equiv.), CH₃CN (2 mL). Then the mixture was stirred at 100 °C (oil bath temperature) in air atmosphere for 20 h until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 10 : 1 to 7 : 1) to afford the desired products **3**. An amplified experiment conducted in the presence of acrylamide **1a** (0.305 g, 1 mmol), 1*H*-indazol-3-amine **2a** (0.266 g, 2 mmol, 2 equiv.), Cu(OAc)₂ (0.2 mmol, 20 mol %), and aq. TBHP (2.5 mmol, 2.5 equiv.) and CH₃CN (10 mL) at 100 °C under air atmosphere for 96 h could deliver the target product **3aa** in 57% yield (231.4 mg).

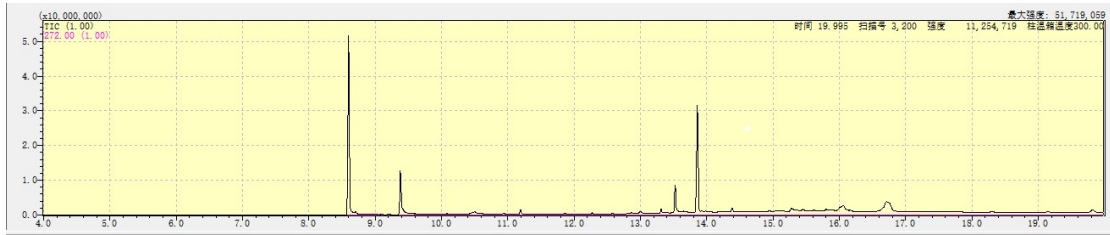
2.3 Control Experiments.

2.3.1 Using 1,1-diphenylethene as Radical Inhibitor

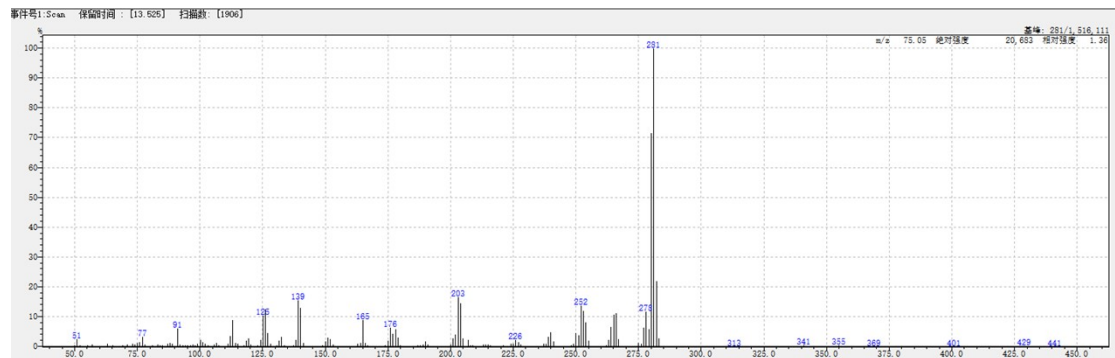


To a Schlenk tube were added **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv.), Cu(OAc)₂ (20 mol%), aq. TBHP (*tert*-butyl hydroperoxide, 70% solution in water, 0.5 mmol, 2.5 equiv.), 1,1-diphenylethene (3 equiv.), CH₃CN (2 mL). Then the mixture was stirred at 100 °C (oil bath temperature) in air atmosphere for 20 h. The GC-MS analysis of raw reaction mixture showed that only 5% yield of target product **3aa** was detected. The benzoyl-trapping products **4** could be detected by GC-MS analysis of raw reaction mixture. After the reaction was finished, the GC-MS analysis result of the raw reaction mixture was shown as following:





MS Spectra of the peak at 13.525 min



[MS Spectrum]	62.00	43860.29	85.10	96680.64
# of Peaks	400	63.00	17431 1.15	86.05 46260.31
Raw Spectrum 13.525 (scan : 1906)	64.05	31160.21	87.10	14884 0.98
	65.05	64640.43	88.05	20769 1.37
Background No	66.05	818 0.05	89.00	14119 0.93
Background Spectrum	67.00	34710.23	90.15	32630.22
Base Peak m/z 281.10 (Inten : 1,516,111)	68.05	17320.11	91.05	94515 6.23
	69.05	88320.58	92.10	99100.65
Event# 1	70.05	25290.17	93.05	96220.63
m/z Absolute Intensity	71.10	10839 0.71	94.05	68800.45
Relative Intensity	72.05	10400.07	95.05	76730.51
50.00	82340.54	73.05	14951 0.99	96.10 80070.53
51.00	37441 2.47	74.05	11633 0.77	97.10 10290 0.68
52.05	63960.42	75.05	20683 1.36	98.05 68310.45
52.95	20940.14	76.00	21913 1.45	99.05 17406 1.15
54.05	538 0.04	77.05	51804 3.42	100.05 33798 2.23
55.05	58890.39	78.05	10218 0.67	101.00 24977 1.65
56.10	24540.16	79.10	28790.19	102.05 15143 1.00
57.05	11722 0.77	80.05	930 0.06	103.10 81210.54
58.05	864 0.06	81.10	68070.45	104.55 19360.13
59.00	14410.10	82.10	43130.28	105.55 99670.66
60.05	678 0.04	83.10	10562 0.70	106.55 18413 1.21
61.00	10300.07	84.05	62220.41	107.45 58960.39

108.10	13110.09		153.05	11698	0.77	197.05	13300.09
109.10	44330.29		154.05	29660.20		198.00	28760.19
110.10	35590.23		155.20	25480.17		199.00	50840.34
111.15	16478	1.09	156.15	498	0.03	200.00	11692 0.77
112.15	55408	3.65	157.00	260	0.02	201.00	41860 2.76
113.05	136389	9.00	158.00	524	0.03	202.00	62852 4.15
114.05	19860	1.31	159.05	622	0.04	203.00	252591 16.66
115.00	14996	0.99	160.05	435	0.03	204.00	220873 14.57
116.35	26000.17		161.05	27460.18		205.00	43762 2.89
117.45	67770.45		162.05	40000.26		206.05	43990.29
118.45	29625	1.95	163.05	16884	1.11	207.00	36247 2.39
119.45	44223	2.92	164.05	20144	1.33	207.95	87190.58
120.35	13407	0.88	165.05	134210	8.85	209.00	58970.39
121.35	21350.14		166.05	19665	1.30	210.00	16070.11
122.10	31270.21		167.00	62940.42		211.00	45190.30
123.10	86820.57		168.05	10670.07		212.00	45270.30
124.15	33852	2.23	169.25	16410.11		213.05	11030 0.73
125.10	158636	10.46	170.10	548	0.04	214.00	11071 0.73
126.10	190937	12.59	171.05	508	0.03	215.05	10984 0.72
127.05	68832	4.54	172.00	478	0.03	216.00	79850.53
128.05	13852	0.91	173.00	24070.16		217.05	19310.13
129.05	24100.16		174.00	96550.64		218.05	337 0.02
130.65	65000.43		175.05	32021	2.11	218.90	10330.07
131.65	31479	2.08	176.05	95699	6.31	220.05	528 0.03
132.60	49745	3.28	177.05	67272	4.44	221.00	58580.39
133.55	77070.51		178.05	89194	5.88	222.05	49880.33
135.10	32380.21		179.05	47687	3.15	223.05	49390.33
136.15	20490.14		180.05	78810.52		224.00	14233 0.94
137.20	95350.63		181.10	13560.09		225.00	15511 1.02
138.25	33054	2.18	182.05	11680.08		226.05	34742 2.29
139.20	235404	15.53	183.20	16890.11		227.00	23340 1.54
140.15	199112	13.13	184.05	583	0.04	228.05	11691 0.77
141.15	21102	1.39	184.95	11140.07		229.05	45150.30
142.15	10130.07		186.00	15860.10		230.10	991 0.07
143.10	449	0.03	187.00	76410.50		231.15	621 0.04
144.05	302	0.02	188.00	69030.46		231.90	162 0.01
145.05	12810.08		189.00	10313	0.68	232.95	597 0.04
145.95	725	0.05	190.00	28465	1.88	234.05	583 0.04
147.05	50910.34		191.00	10750	0.71	235.05	23350.15
148.05	19590.13		192.05	24130.16		236.05	55550.37
149.05	86250.57		193.00	42010.28		237.05	15393 1.02
150.05	27353	1.80	194.05	881	0.06	238.05	16903 1.11
151.05	45127	2.98	195.15	939	0.06	239.05	49100 3.24
152.05	40115	2.65	196.05	474	0.03	240.05	72066 4.75

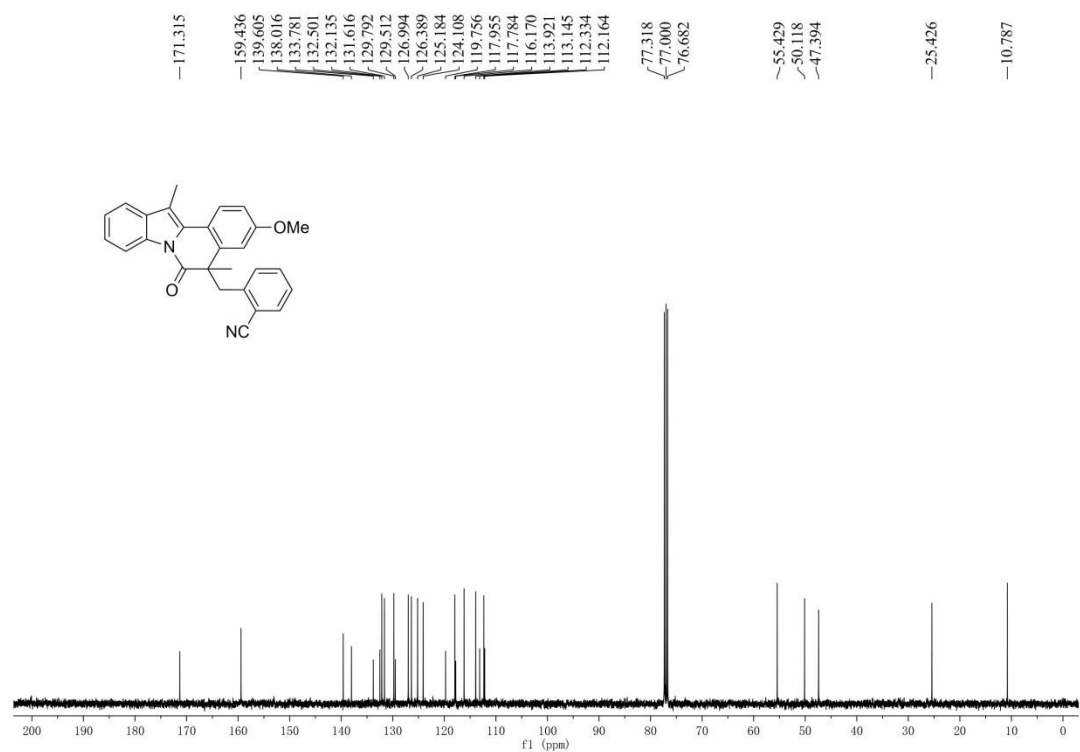
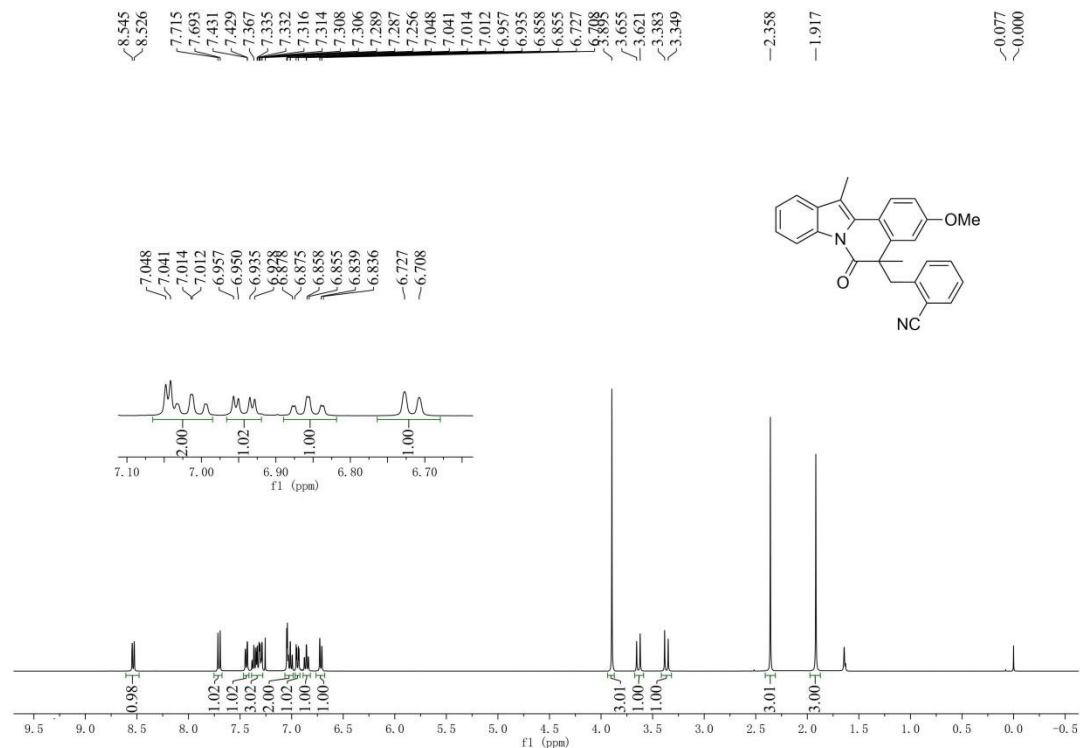
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242.00	46950.31		260.10	852	0.06	278.10	178287	11.76
243.10	622	0.04	261.05	22580.15		279.10	87766	5.79
244.10	242	0.02	262.10	60230.40		280.10	1088105	71.77
245.05	533	0.04	263.05	35474	2.34	281.10	1516111	100.00
246.05	14220.09		264.05	101365	6.69	282.10	334084	22.04
247.05	18380.12		265.05	161487	10.65	283.05	40960	2.70
248.05	89270.59		266.05	169949	11.21	284.05	42010.28	
249.05	14738	0.97	267.05	37140	2.45	285.15	12190.08	
250.00	68596	4.52	268.05	50400.33		286.10	294	0.02
251.05	56878	3.75	269.00	11530.08		287.10	276	0.02
252.05	207968	13.72	270.05	386	0.03	288.10	124	0.01
253.05	184232	12.15	271.05	413	0.03	289.00	150	0.01
254.05	124307	8.20	272.05	302	0.02	290.00	721	0.05
255.05	29330	1.93	273.00	16620.11		291.00	318	0.02
256.10	37610.25		274.05	22270.15		292.00	167	0.01
257.05	863	0.06	275.05	20904	1.38	293.0	407	0.03
258.10	271	0.02	276.05	17437	1.15			

3. References

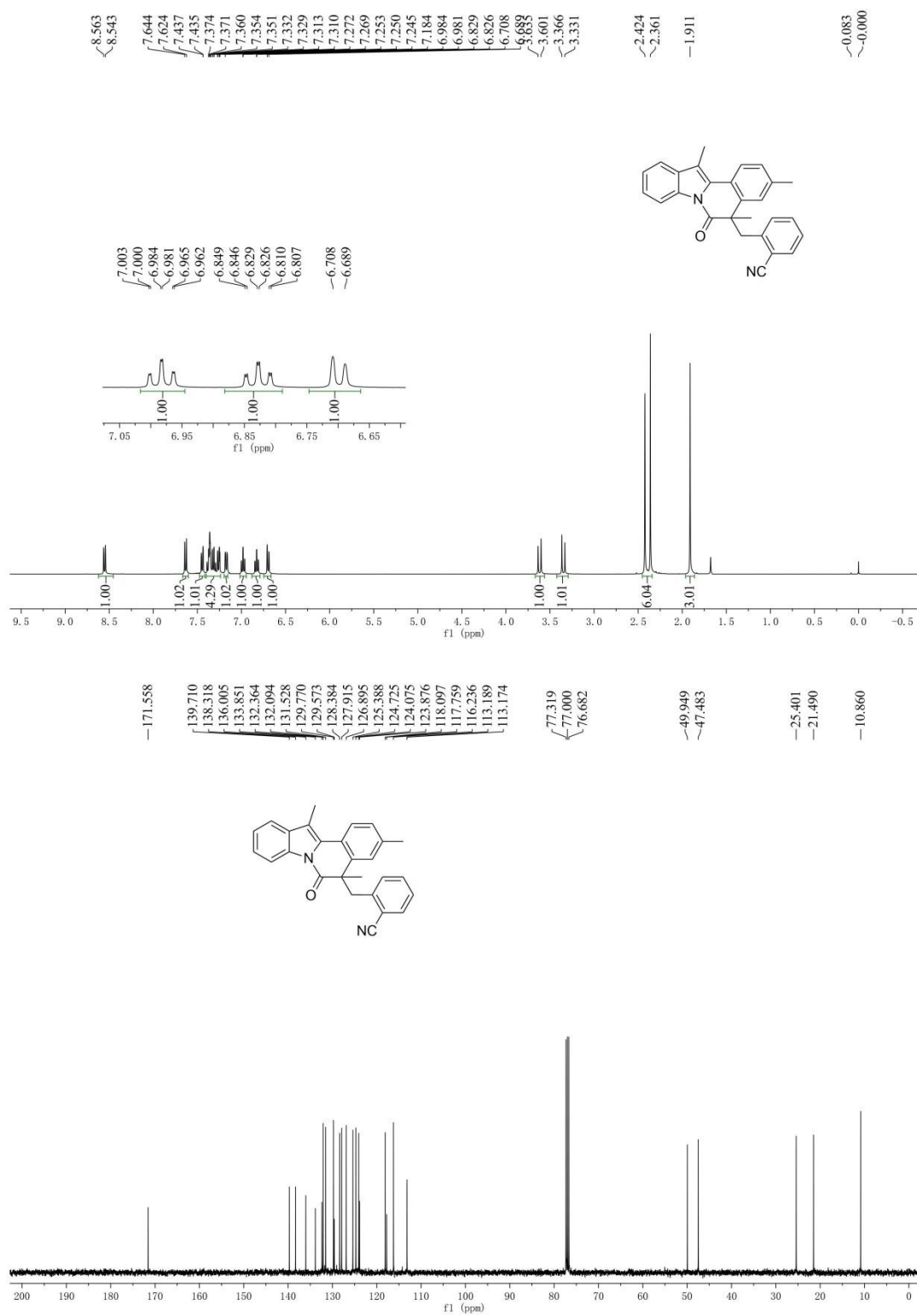
- [1] Y.-L. Wei, J.-Q. Chen, B. Sun, P.-F. Xu, *Chem. Commun.*, 2019, **55**, 5922.
- [2] W. Kong, Y. Zhou, Q. Song, *Adv. Synth. Catal.*, 2018, **360**, 1943.

4. Spectra

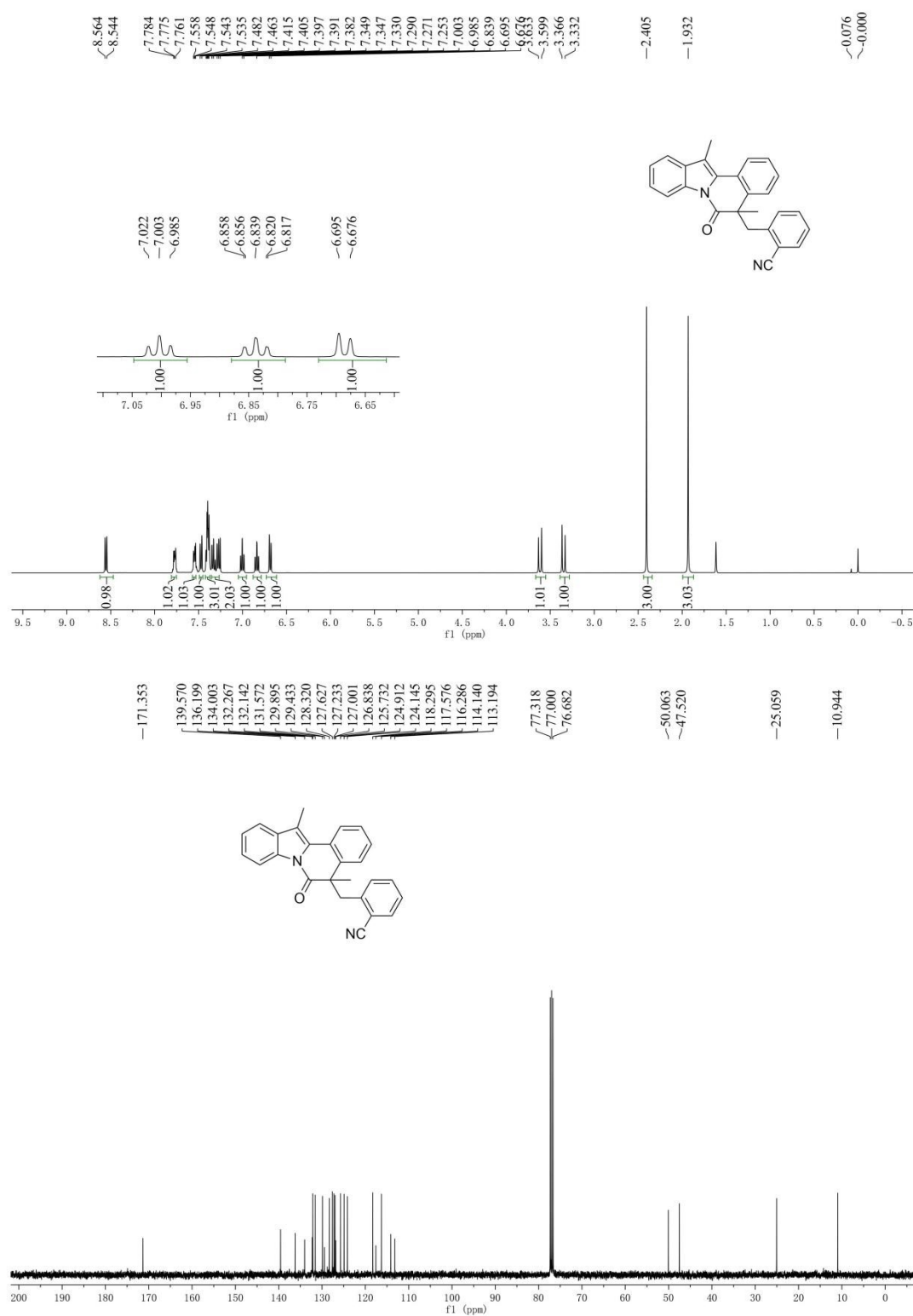
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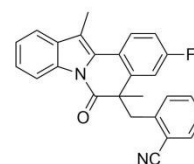
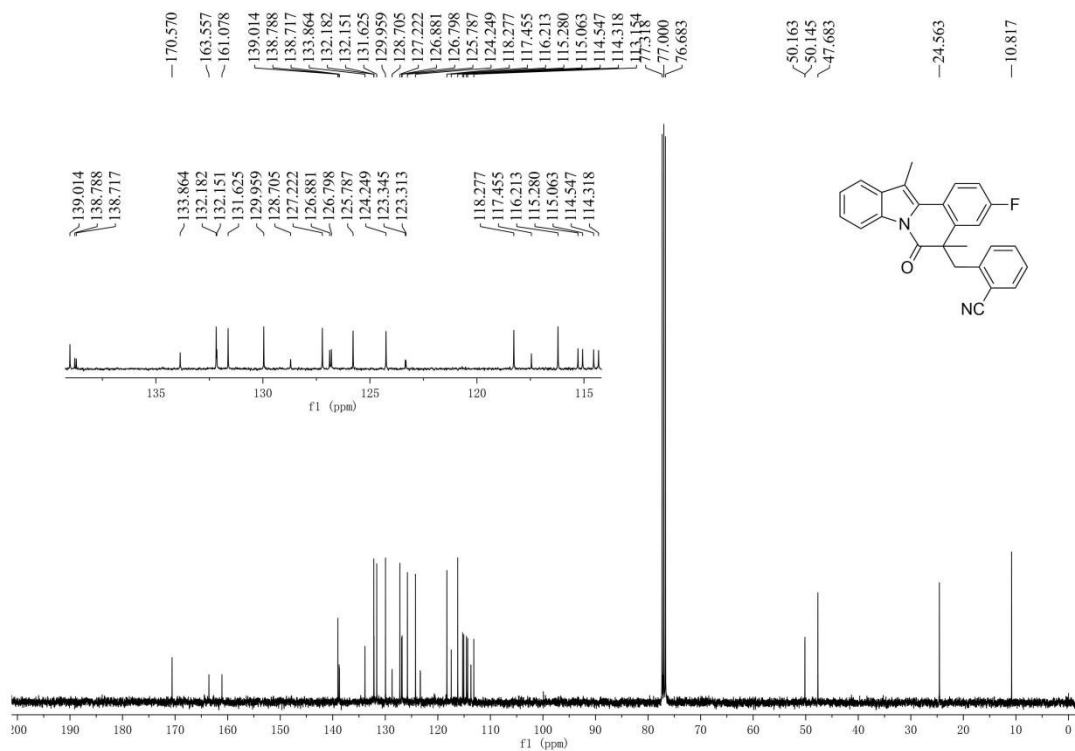
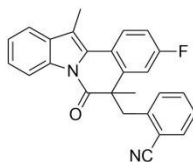
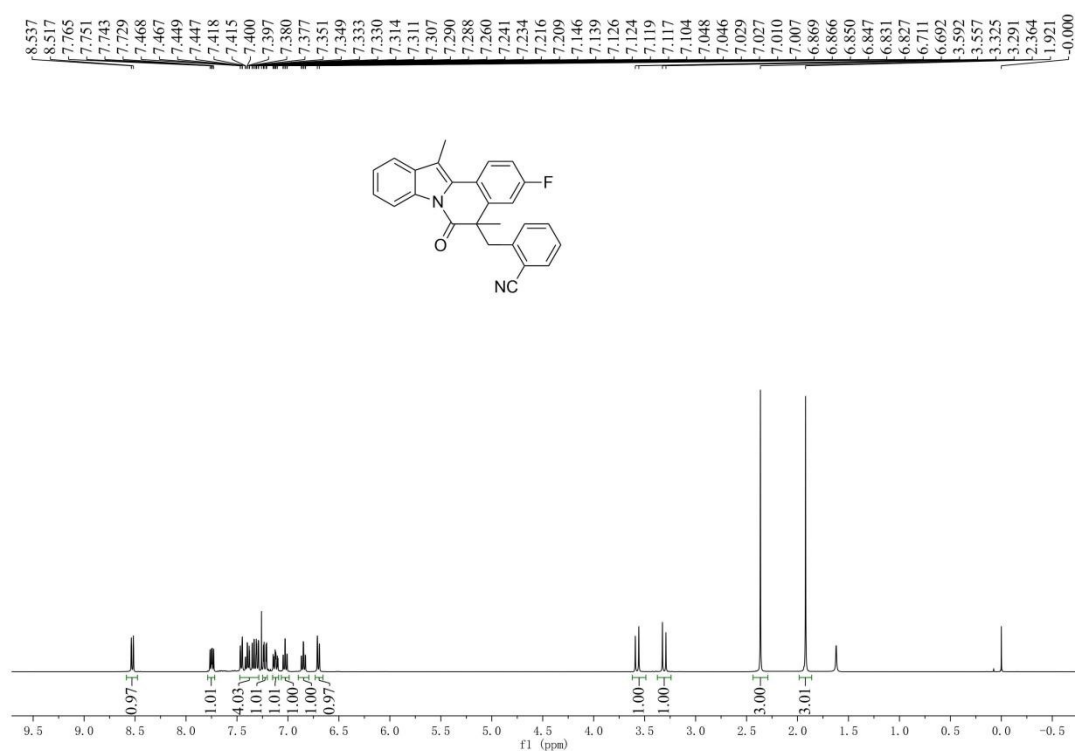
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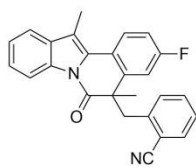


2-((5,12-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzotrile (3ca)

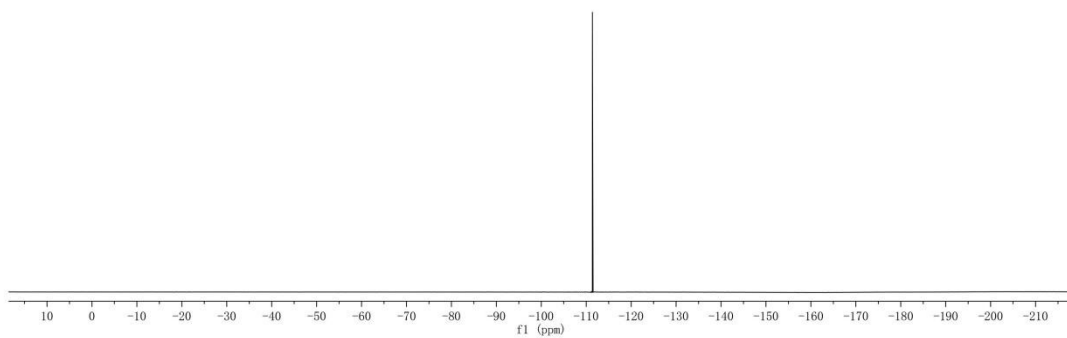


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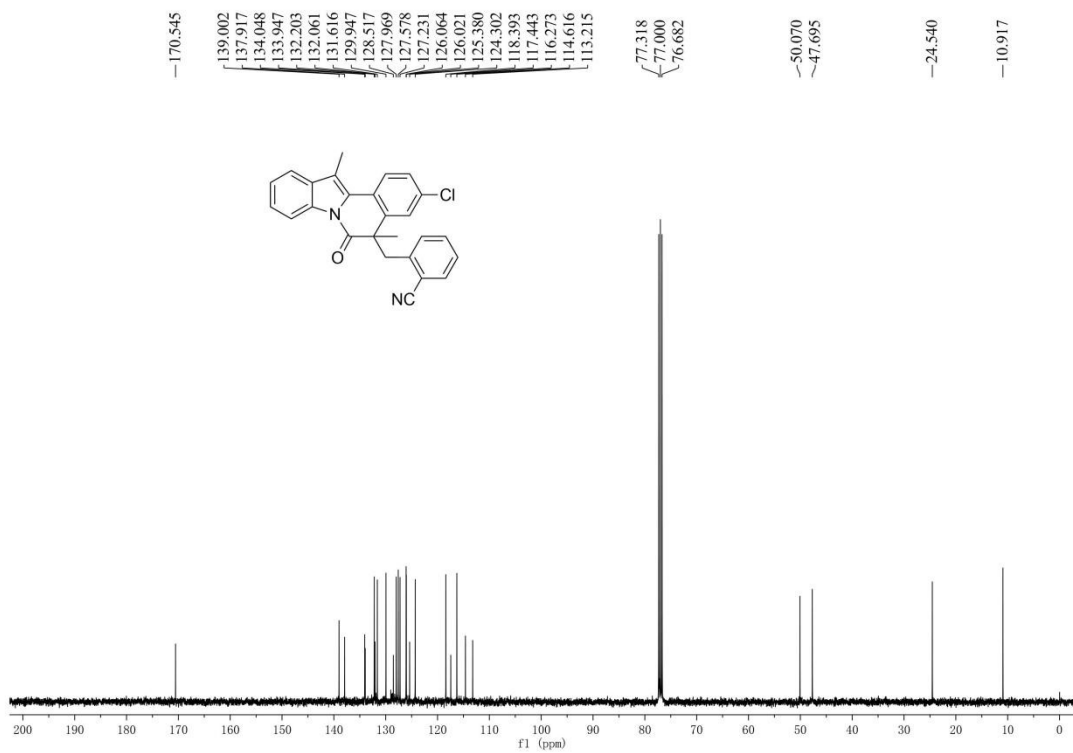
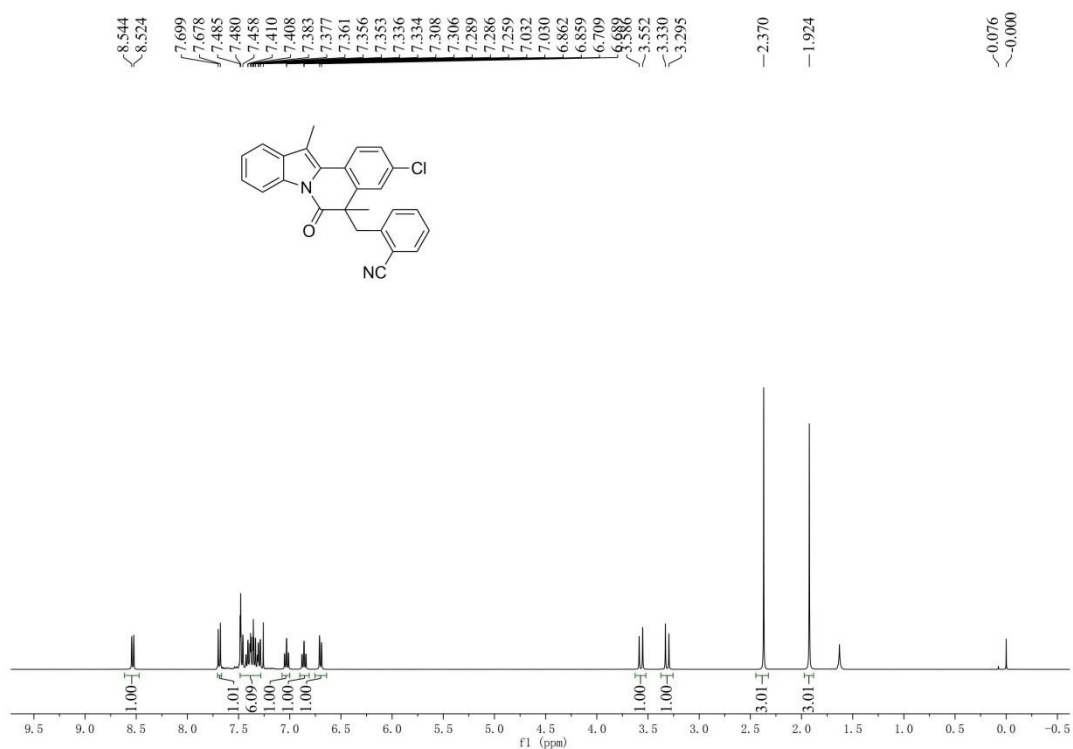




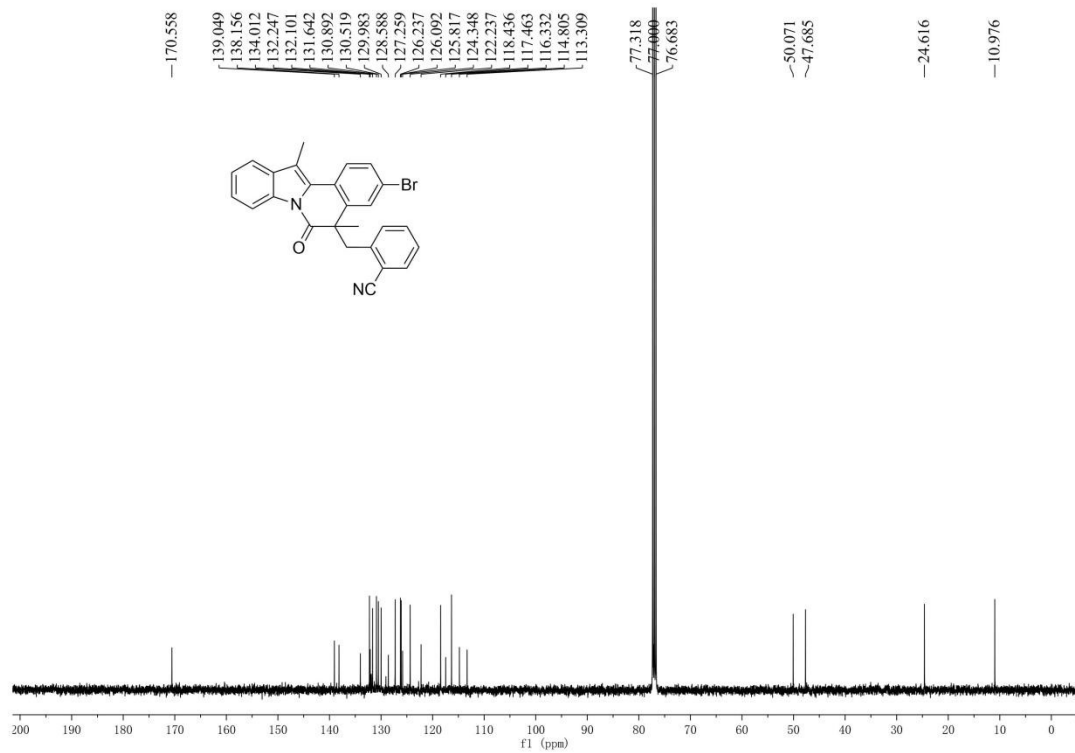
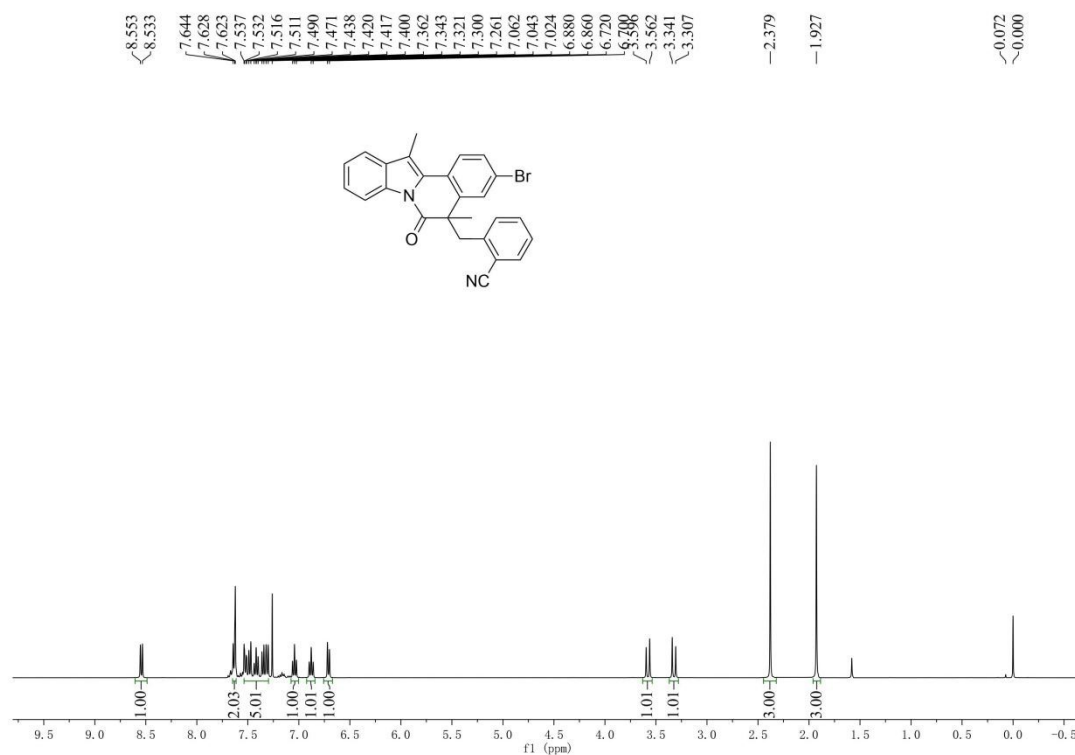
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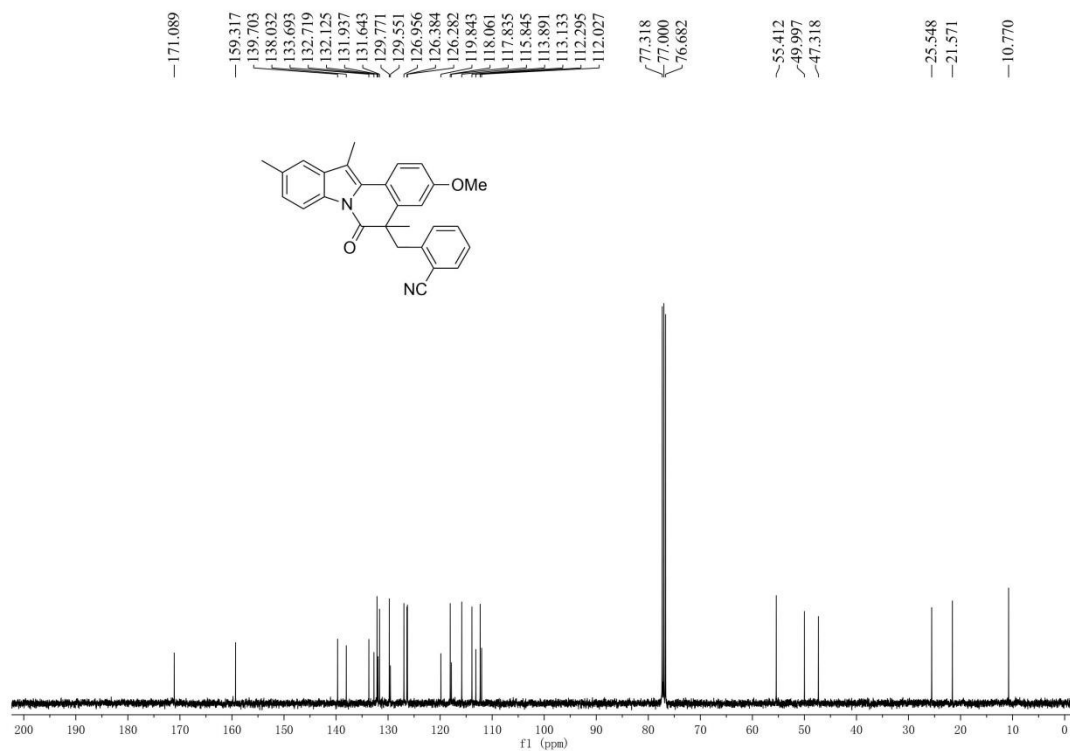
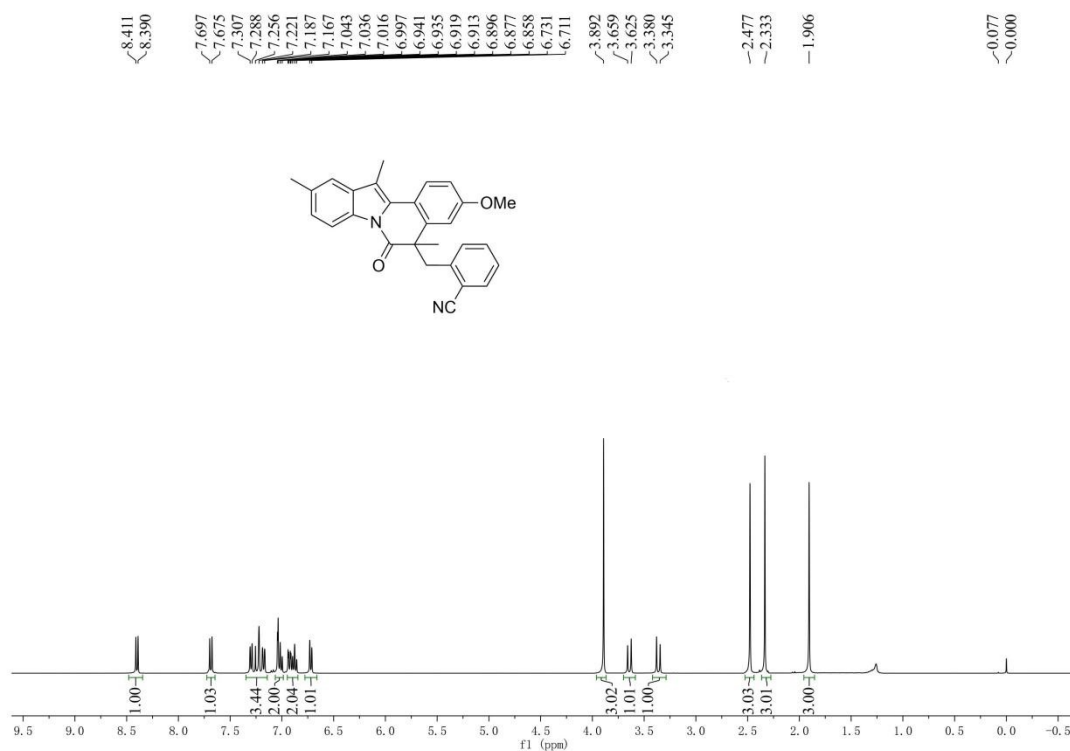
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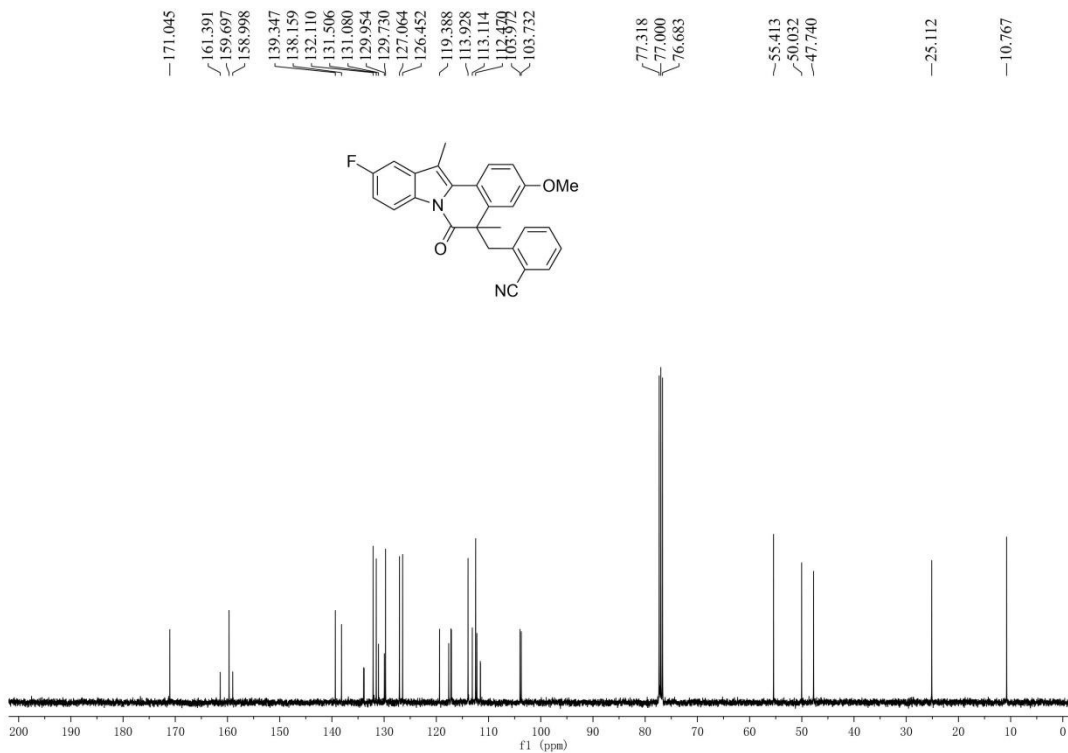
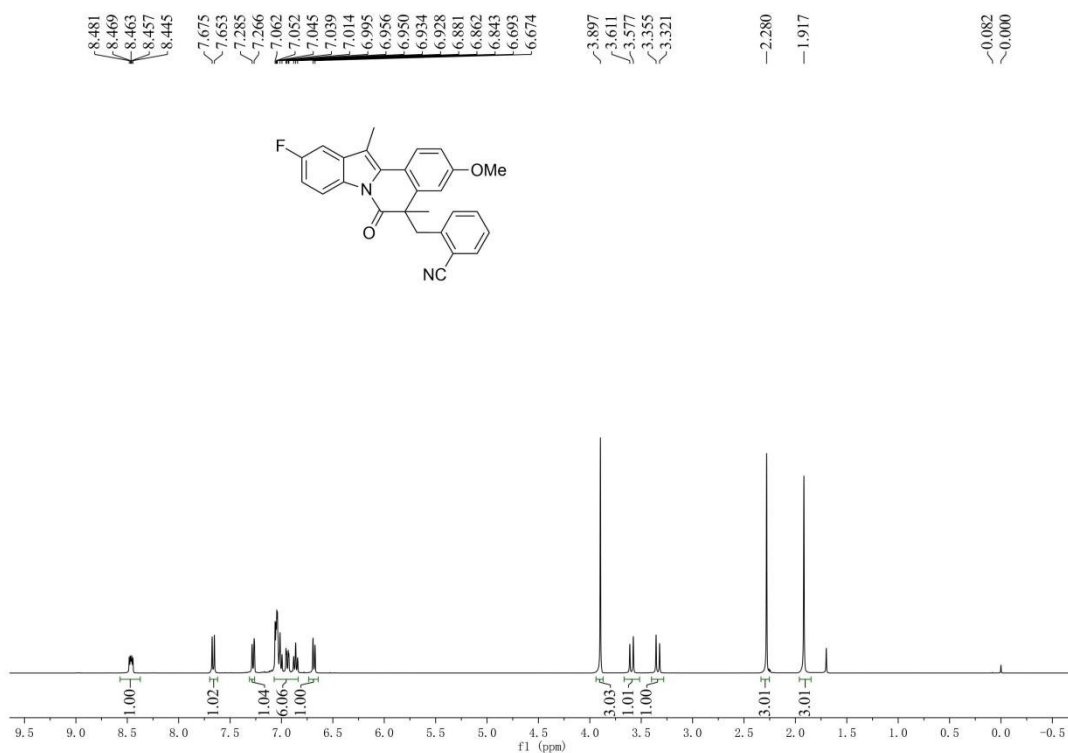
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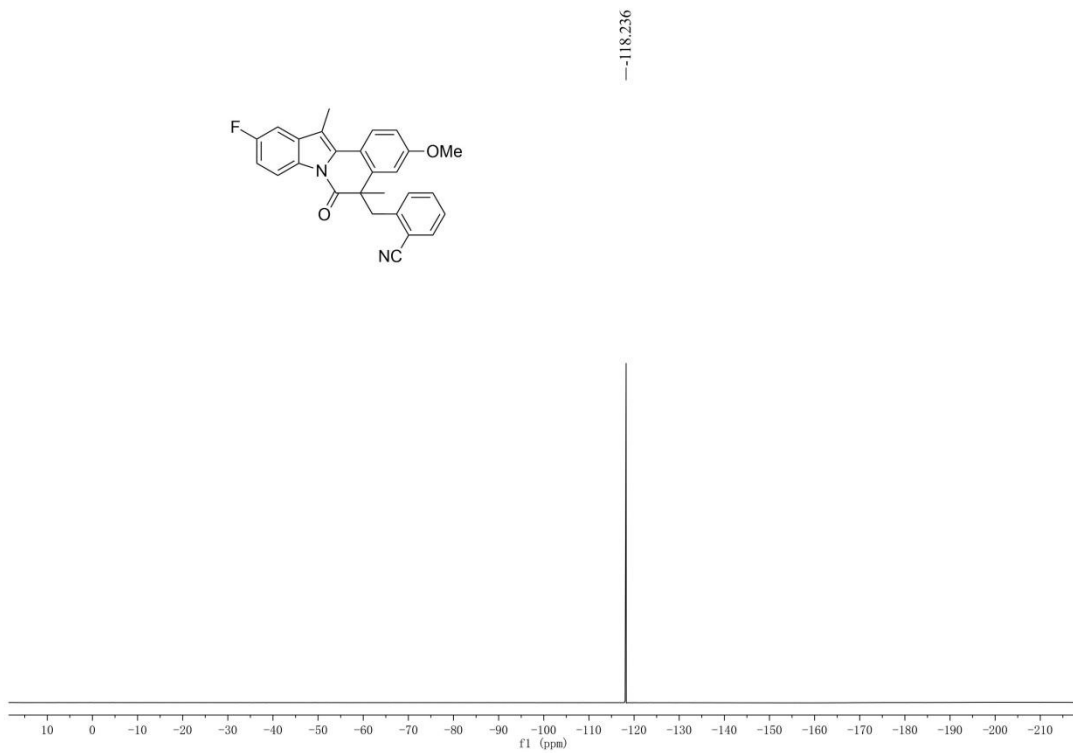


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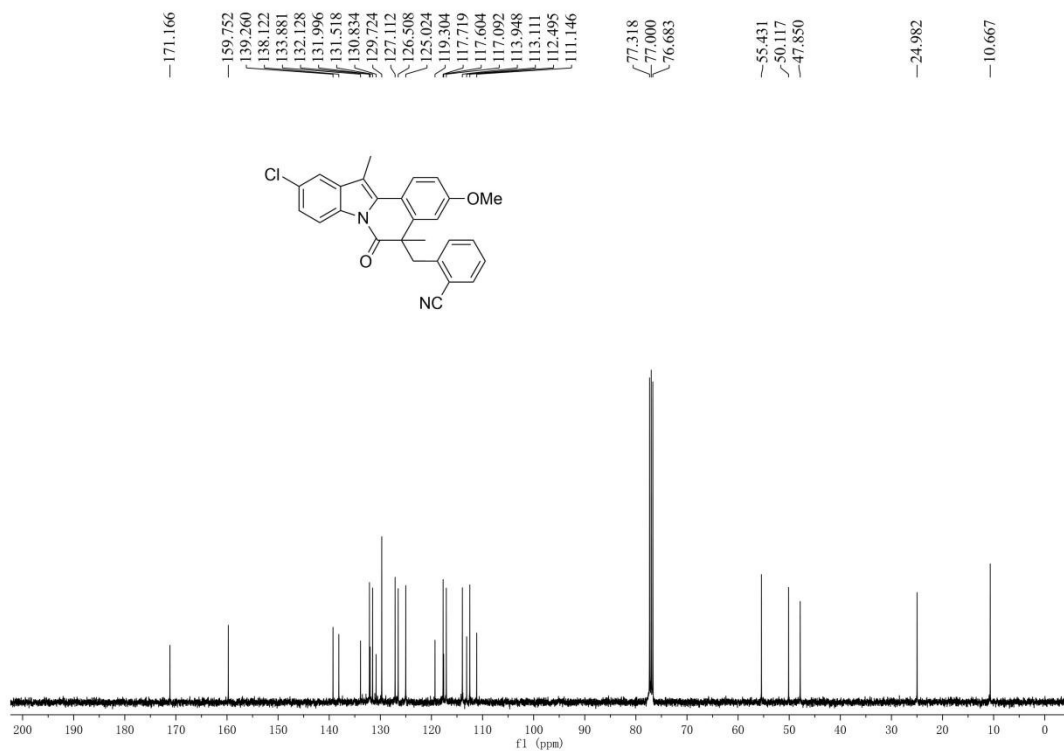
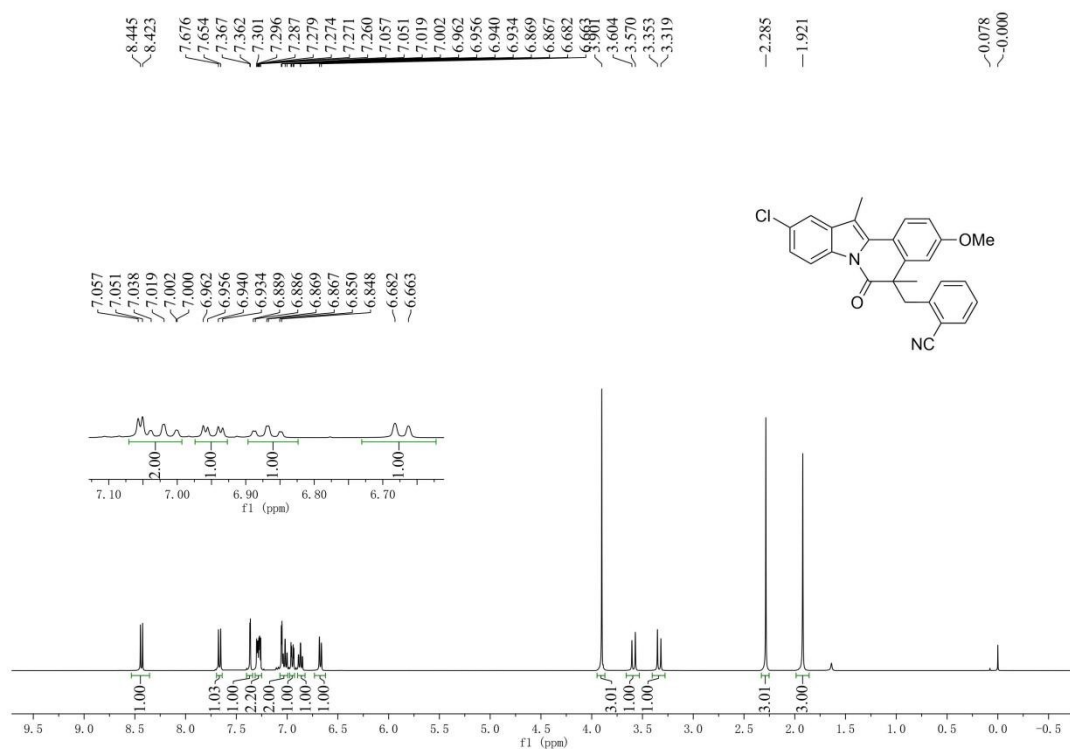


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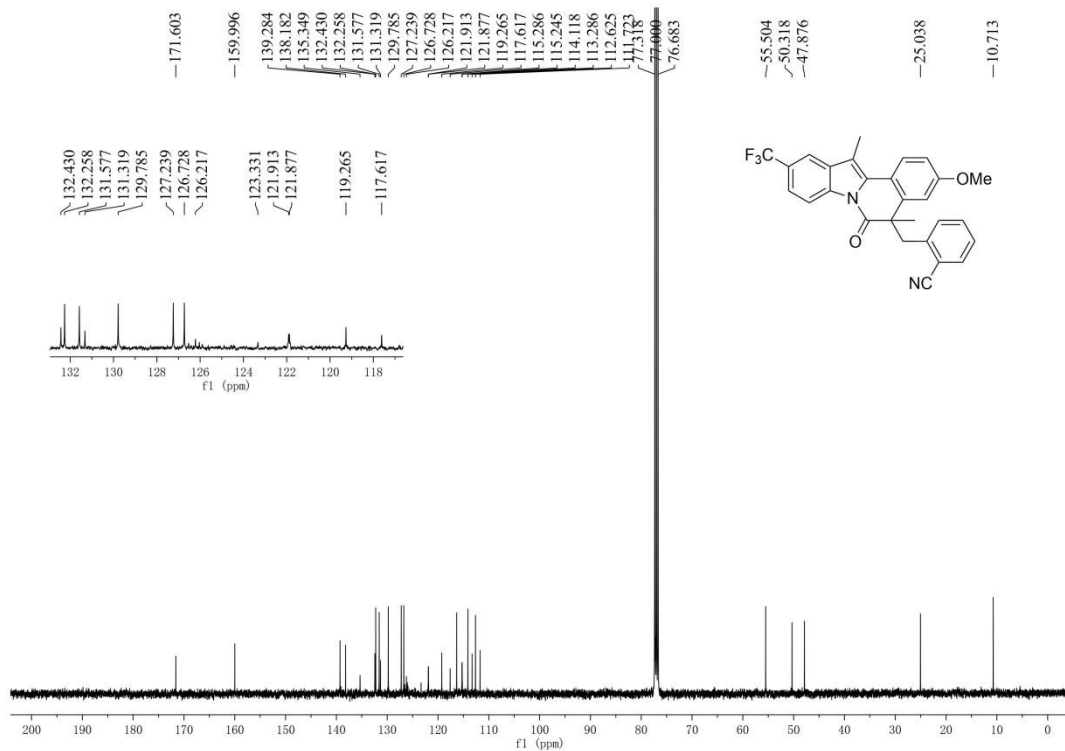
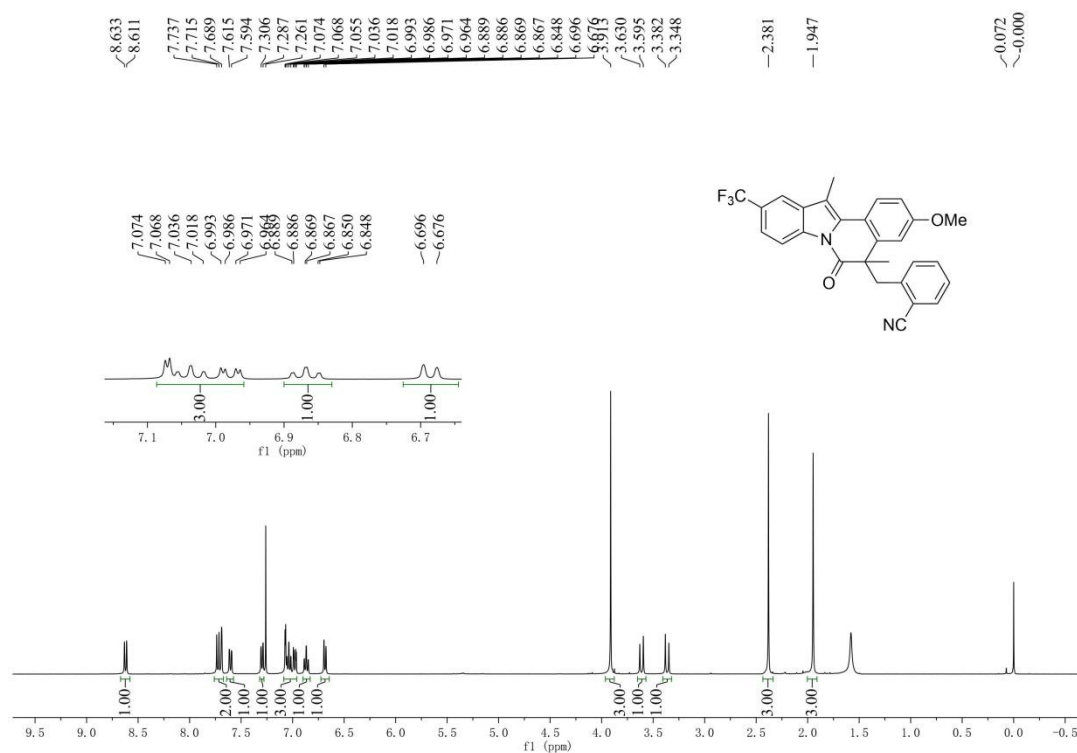


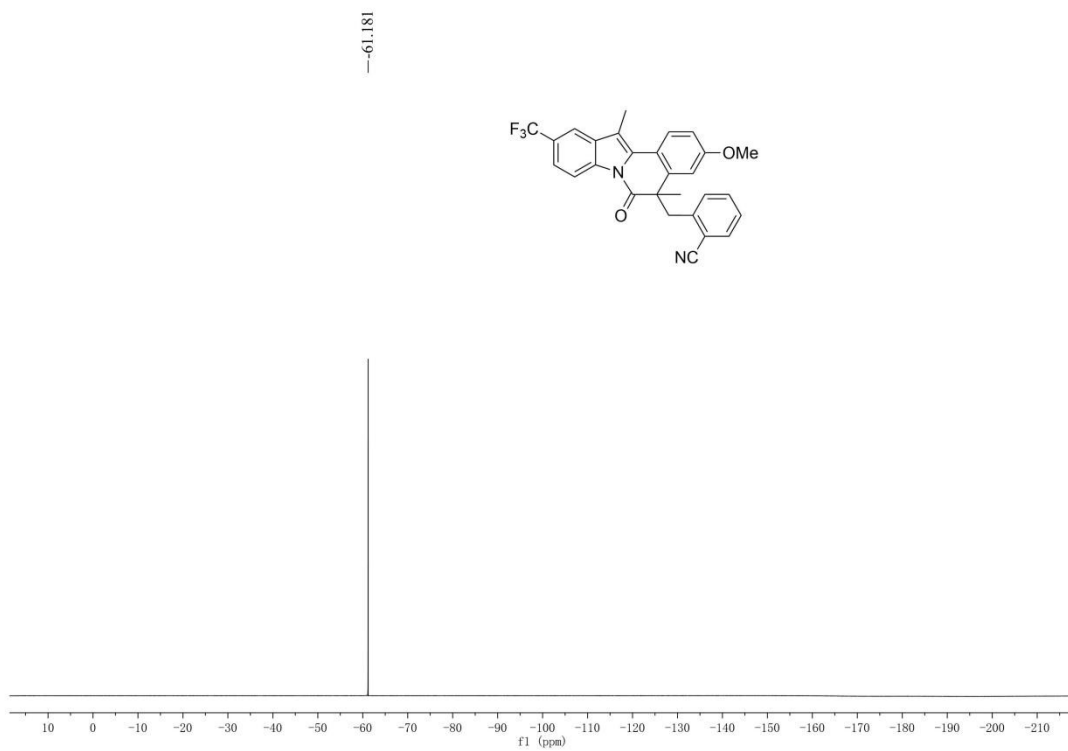


2-((10-Chloro-3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ia)

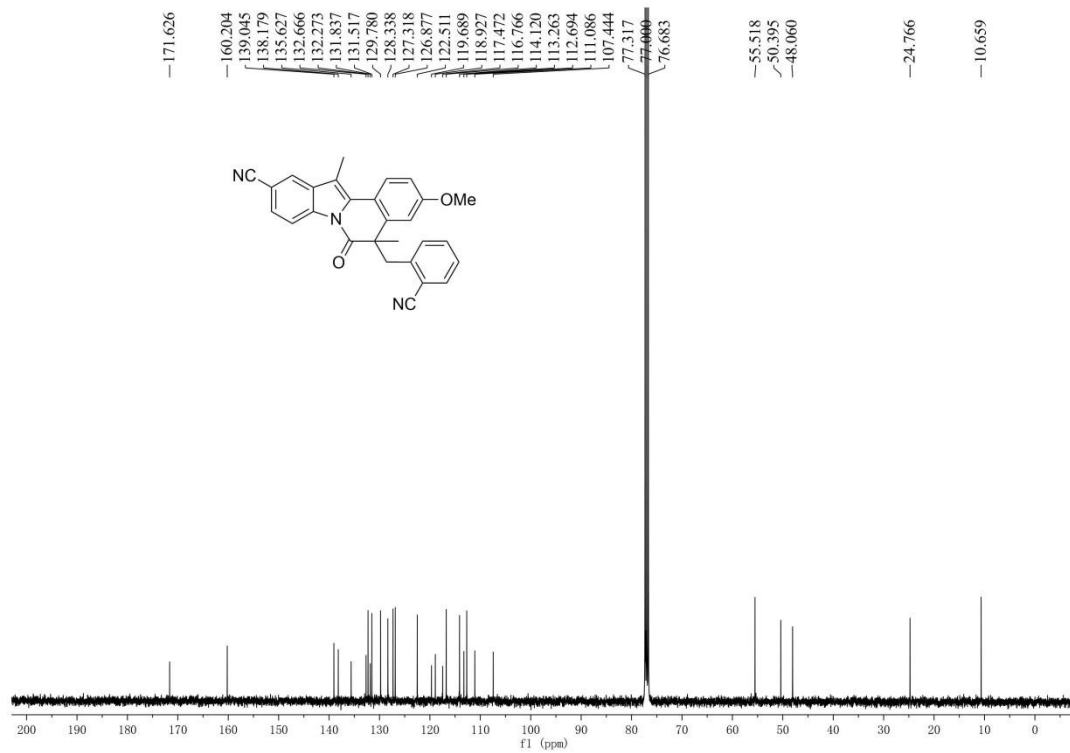
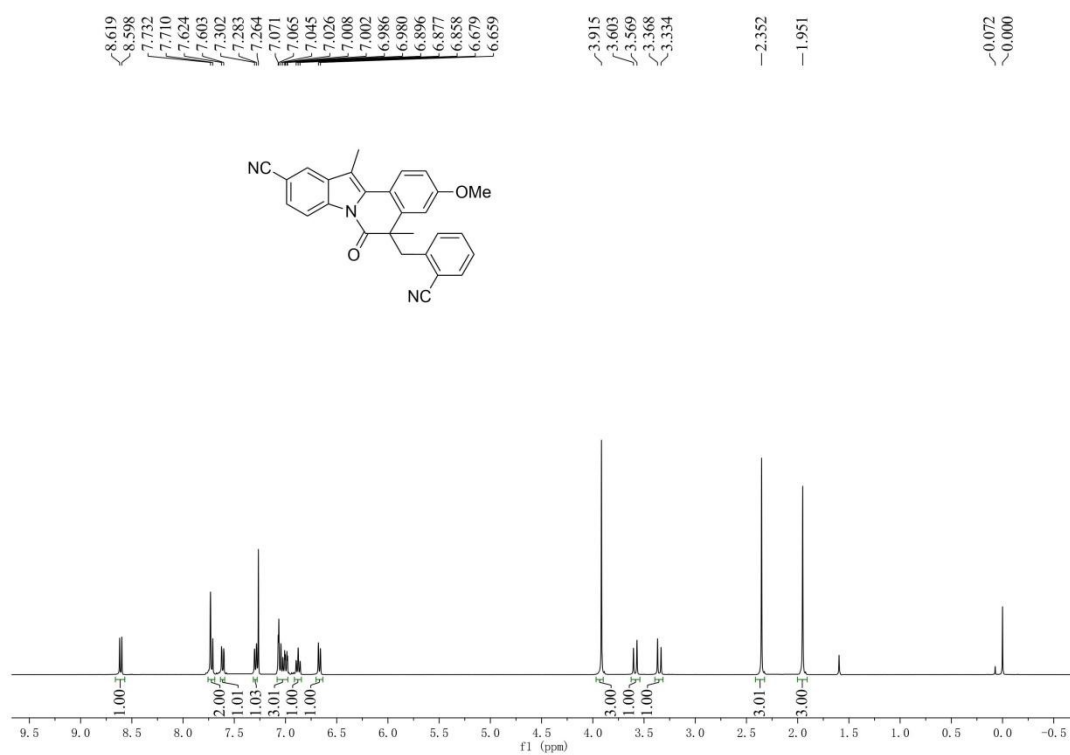


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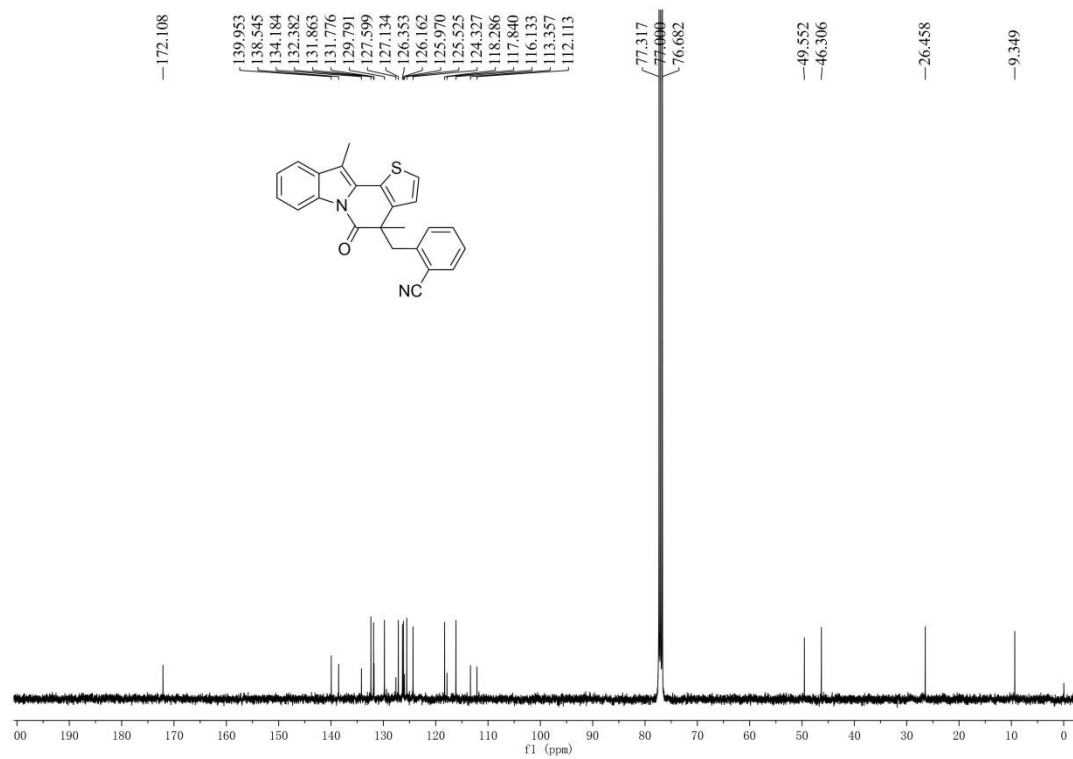
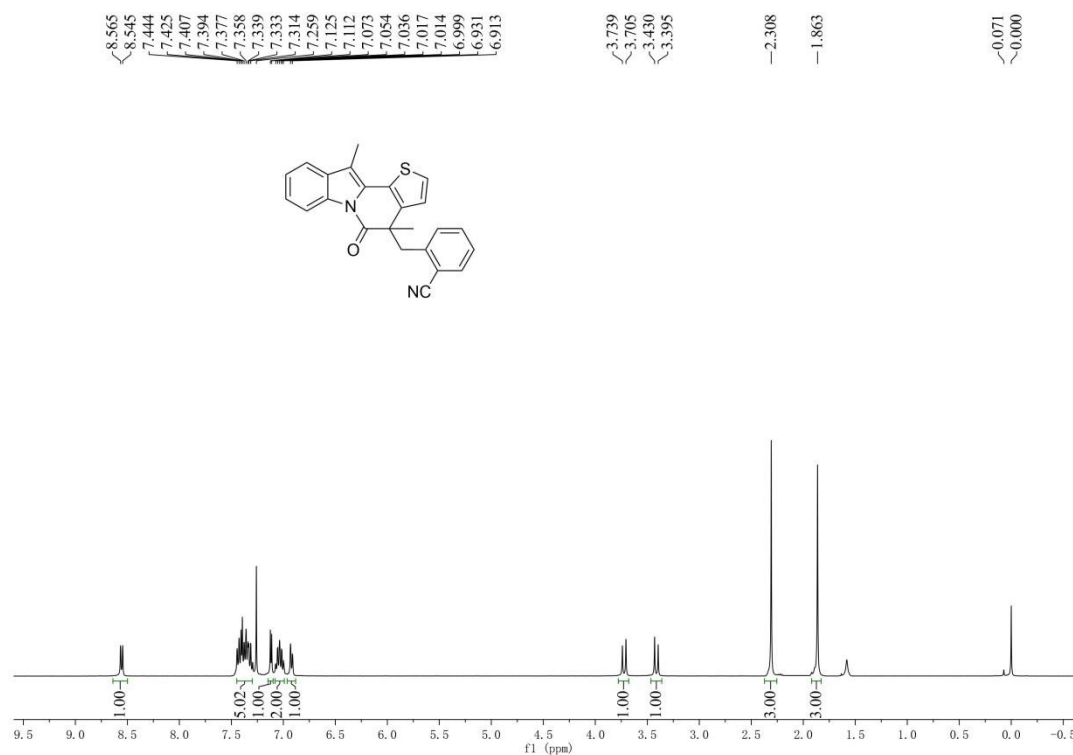




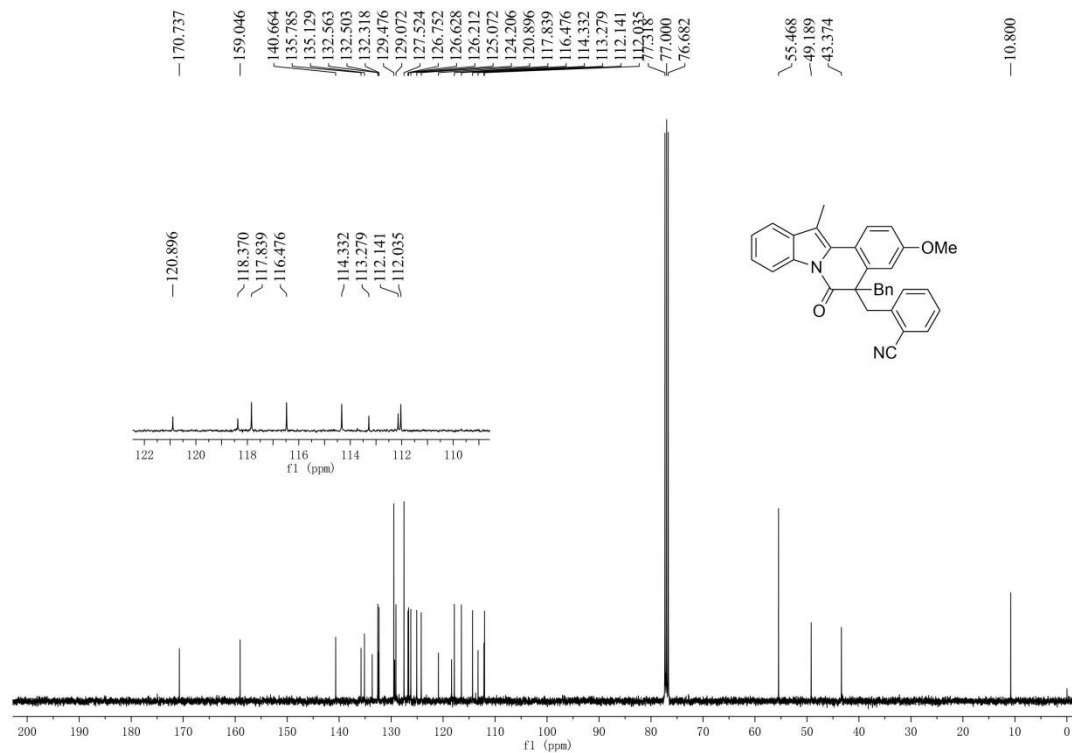
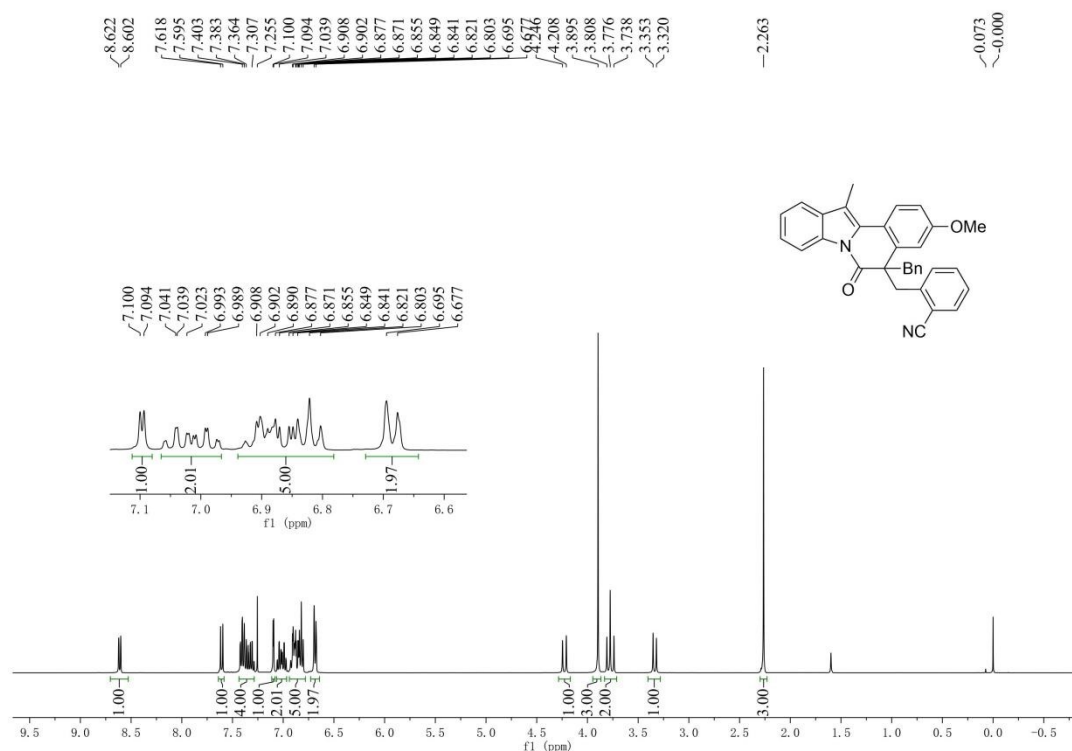
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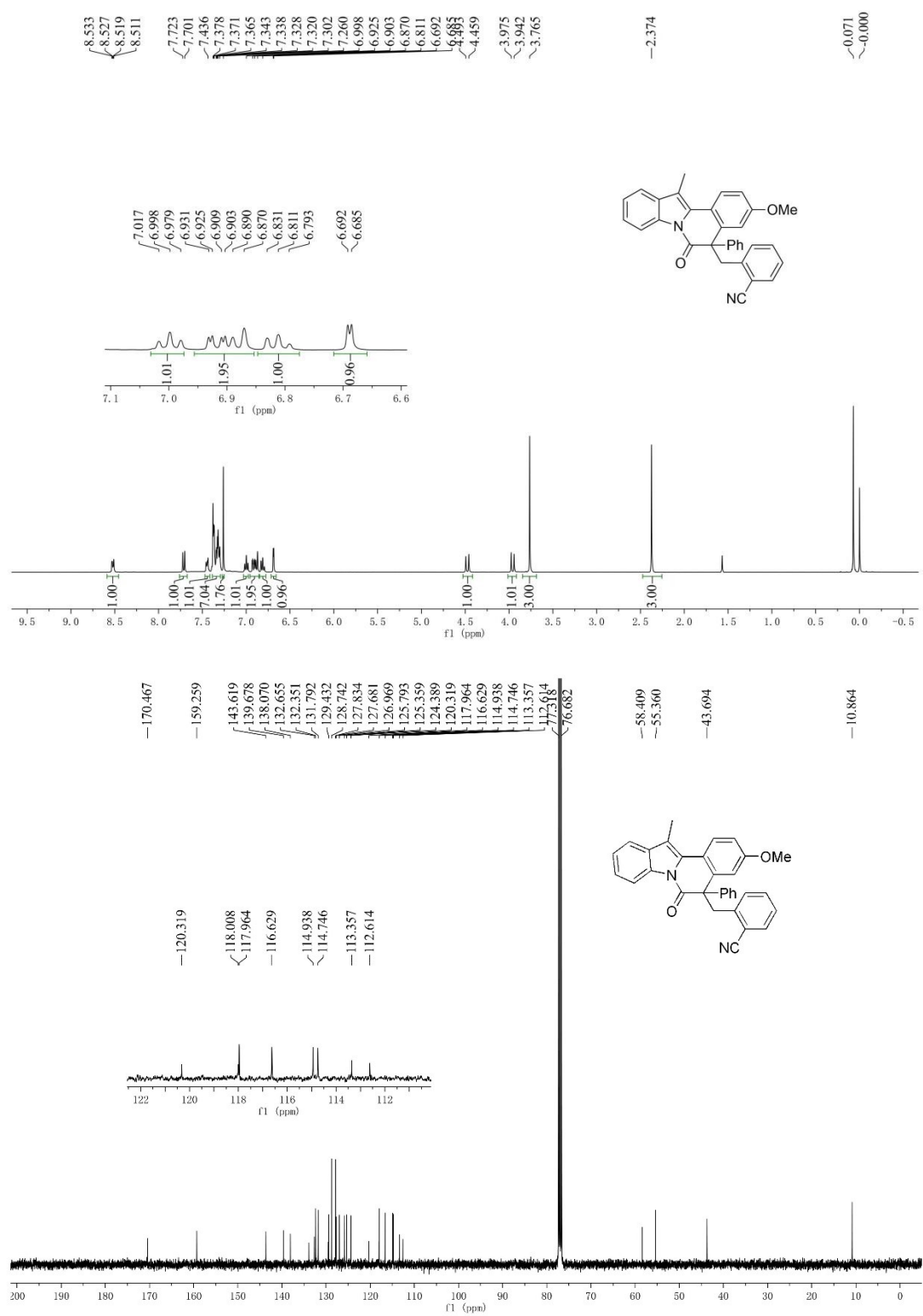
2-((4,11-Dimethyl-5-oxo-4,5-dihydrothieno[2',3':3,4]pyrido[1,2-*a*]indol-4-yl)methyl)benzonitrile (3la)



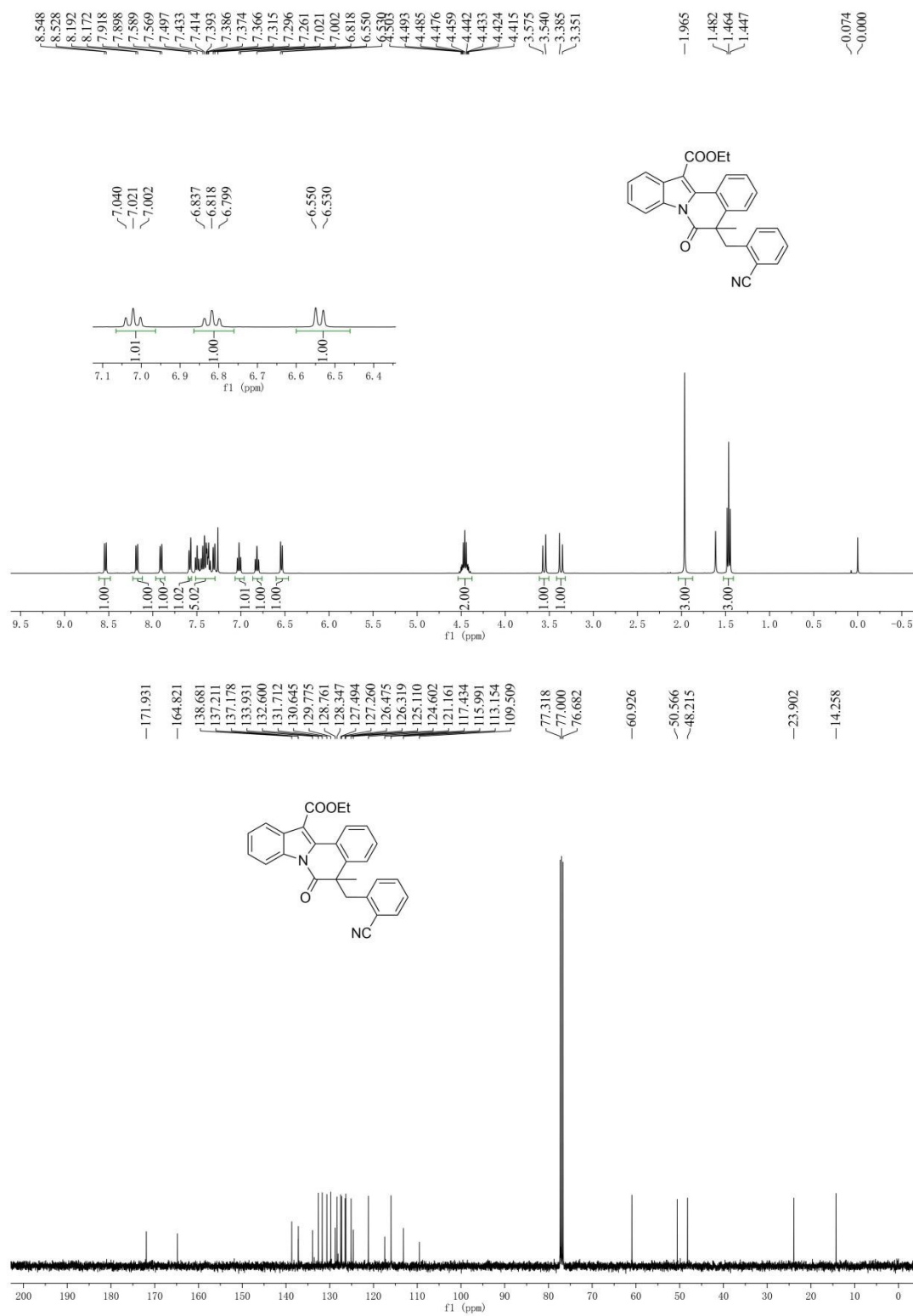
2-((5-Benzyl-3-methoxy-12-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ma)



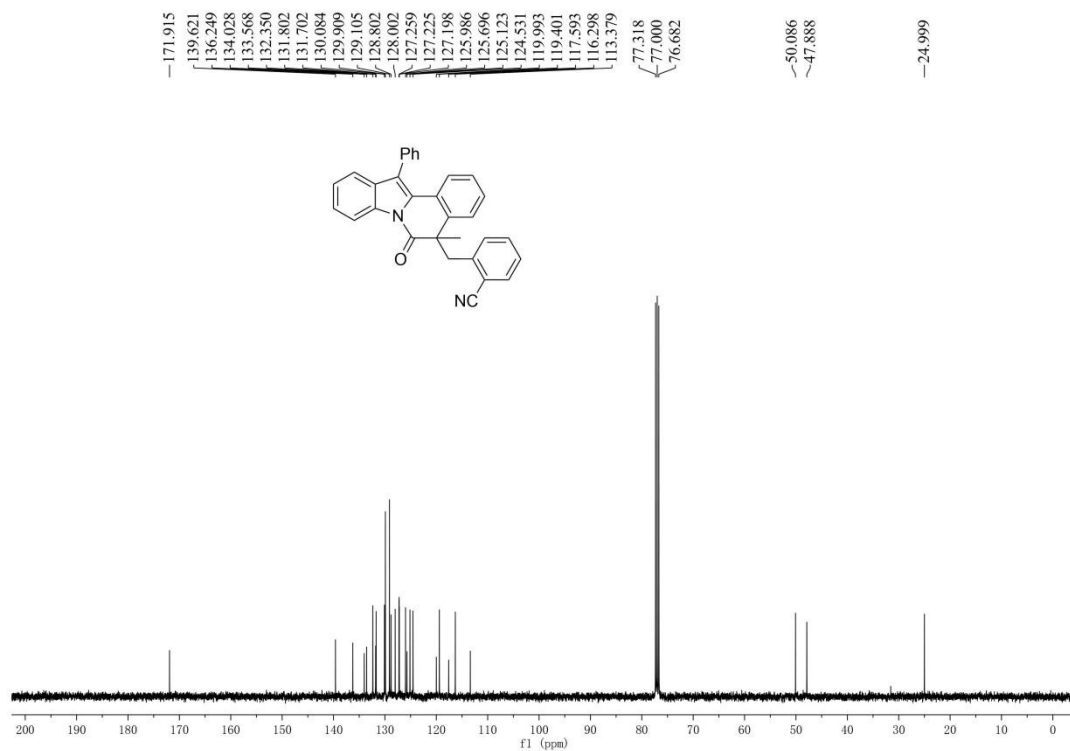
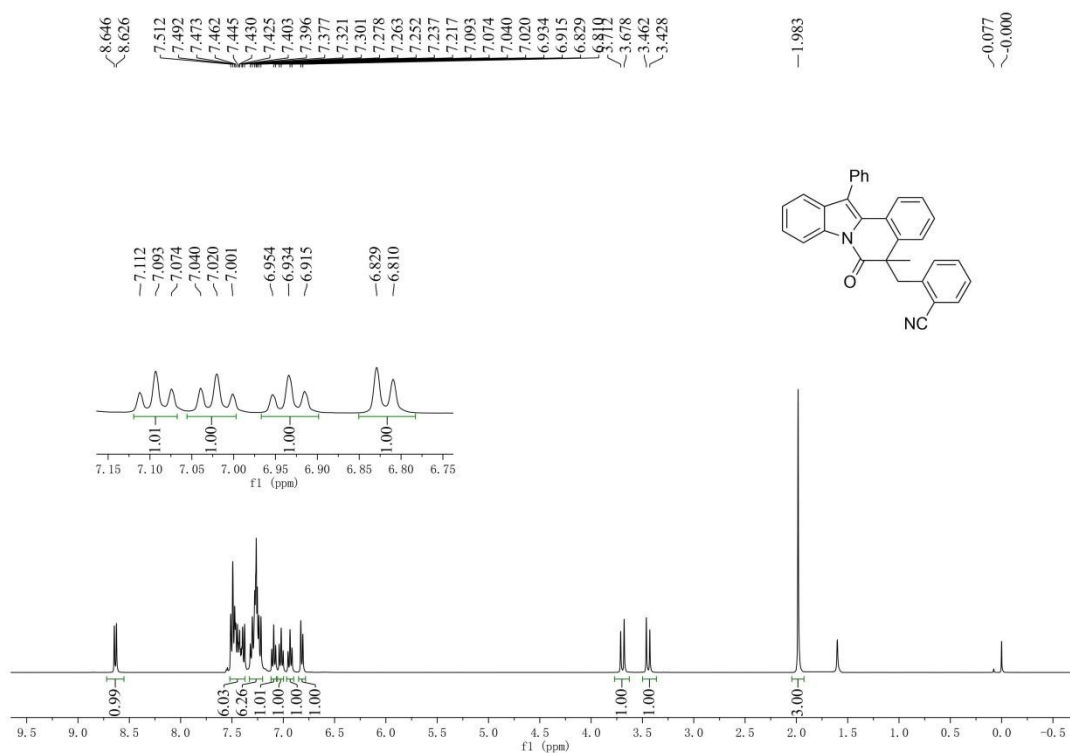
2-((3-Methoxy-12-methyl-6-oxo-5-phenyl-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)
 (D)methyl)benzonitrile (3na)



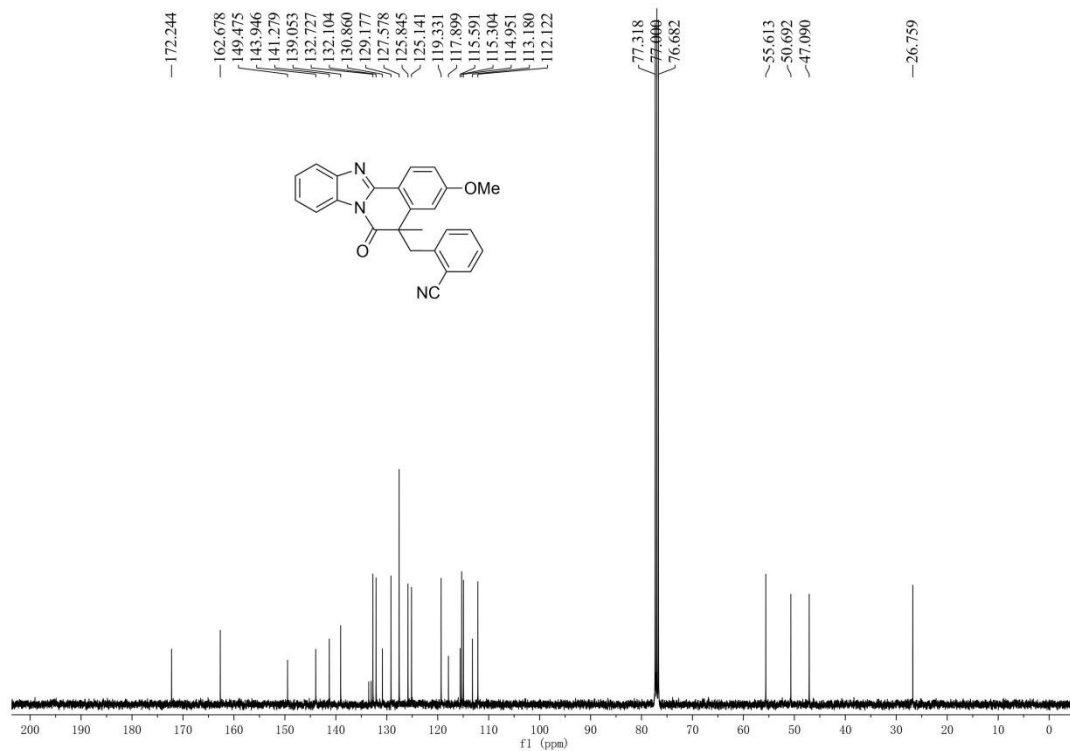
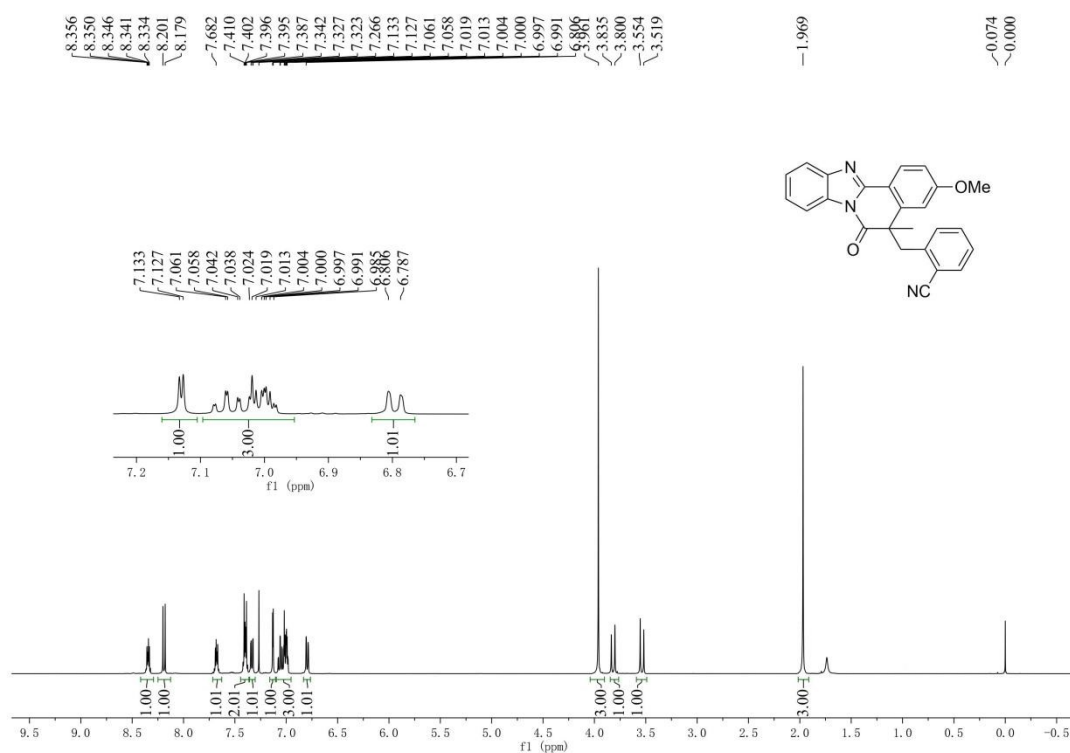
Ethyl 5-(2-cyanobenzyl)-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinoline-12-carboxylate (30a)



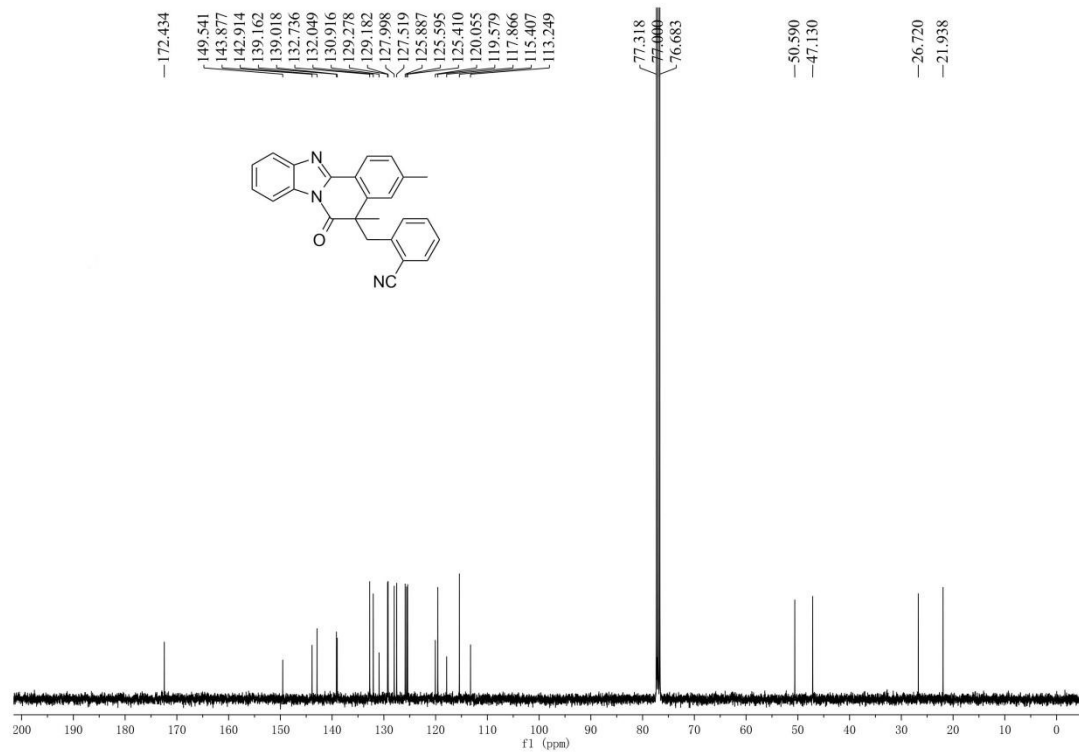
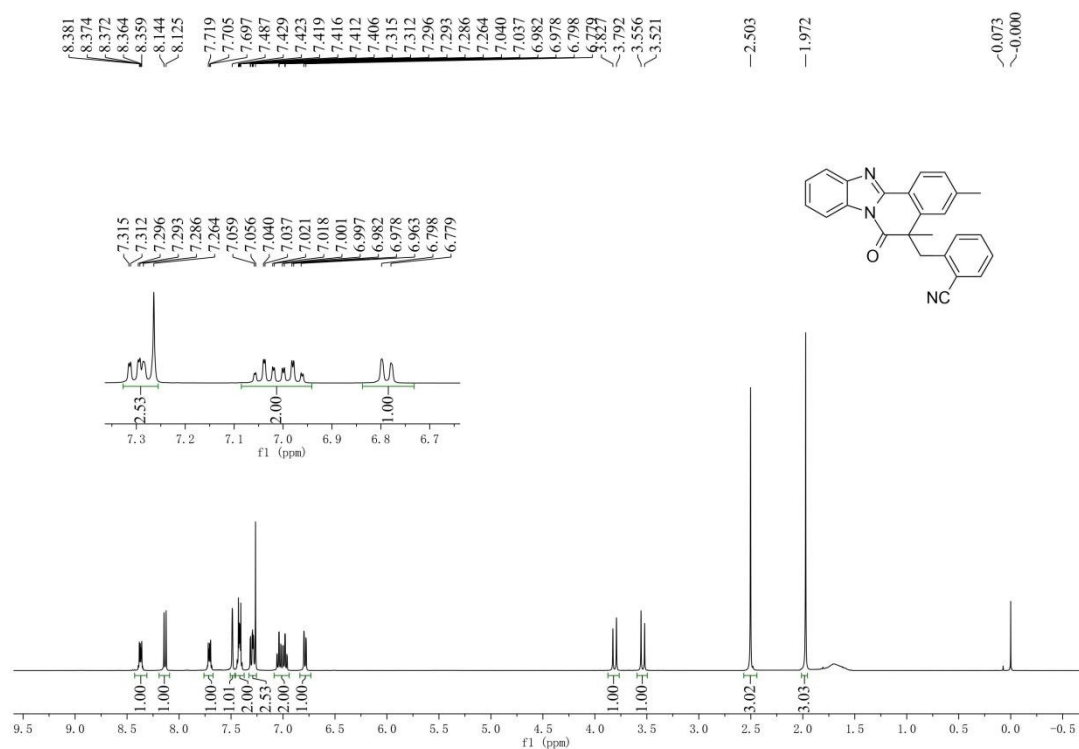
2-((5-Methyl-6-oxo-12-phenyl-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3pa)



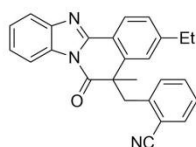
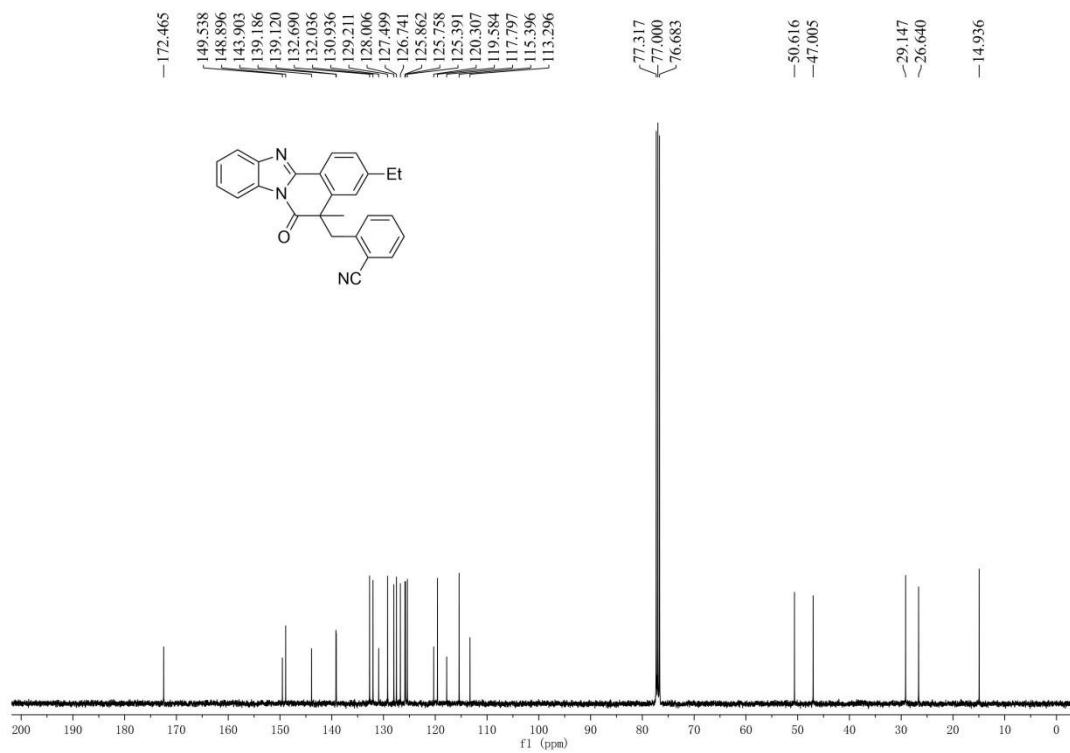
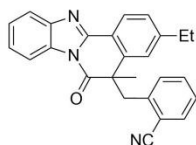
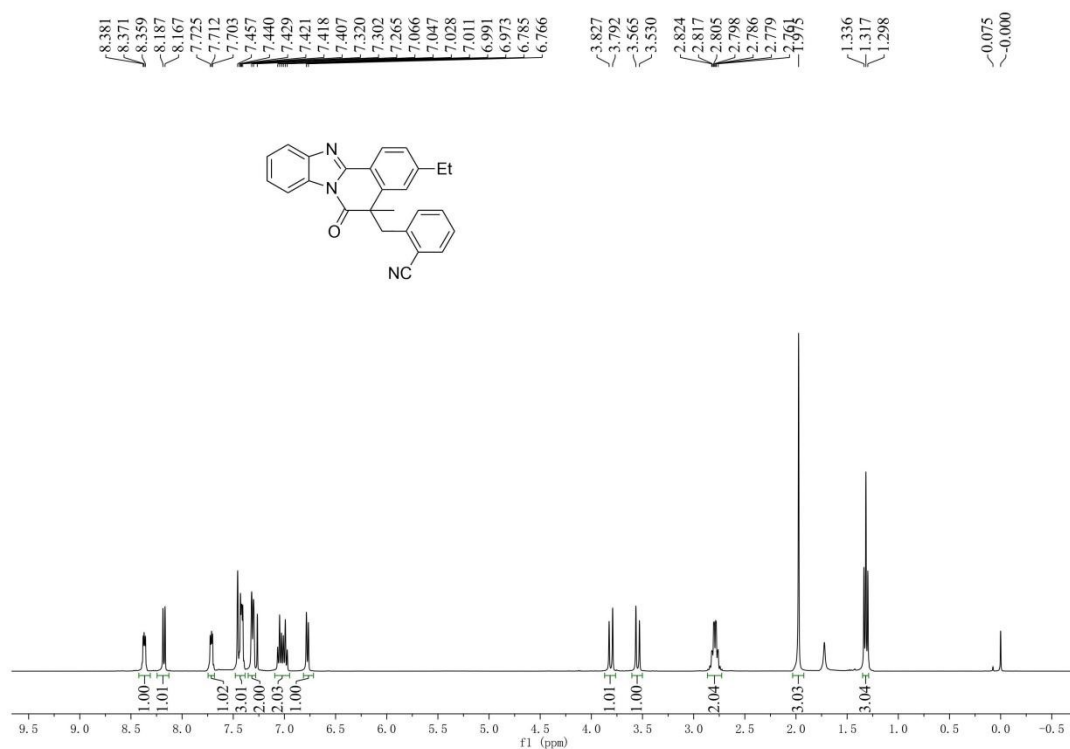
2-((3-Methoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3qa)



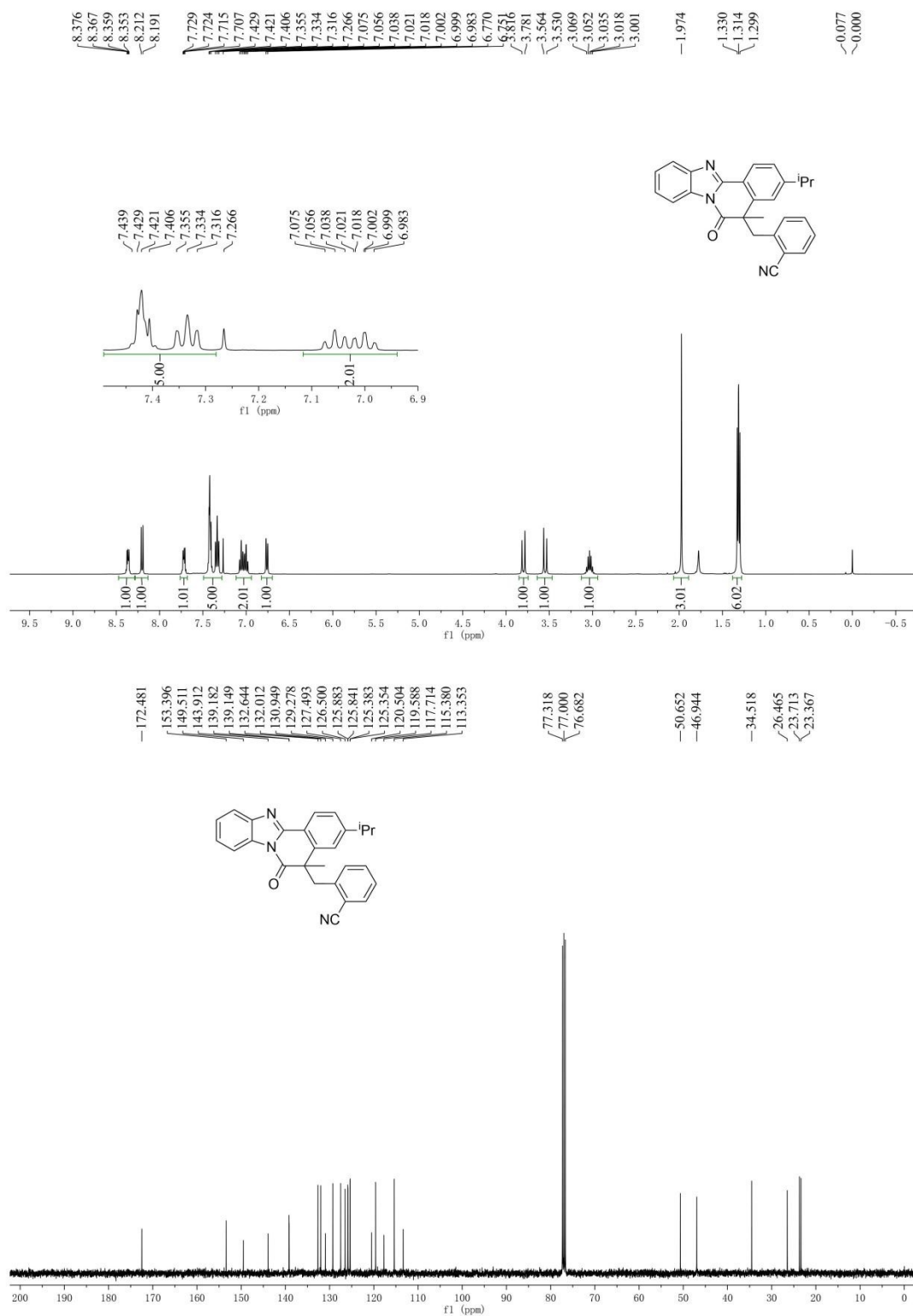
2-((3,5-Dimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ra)



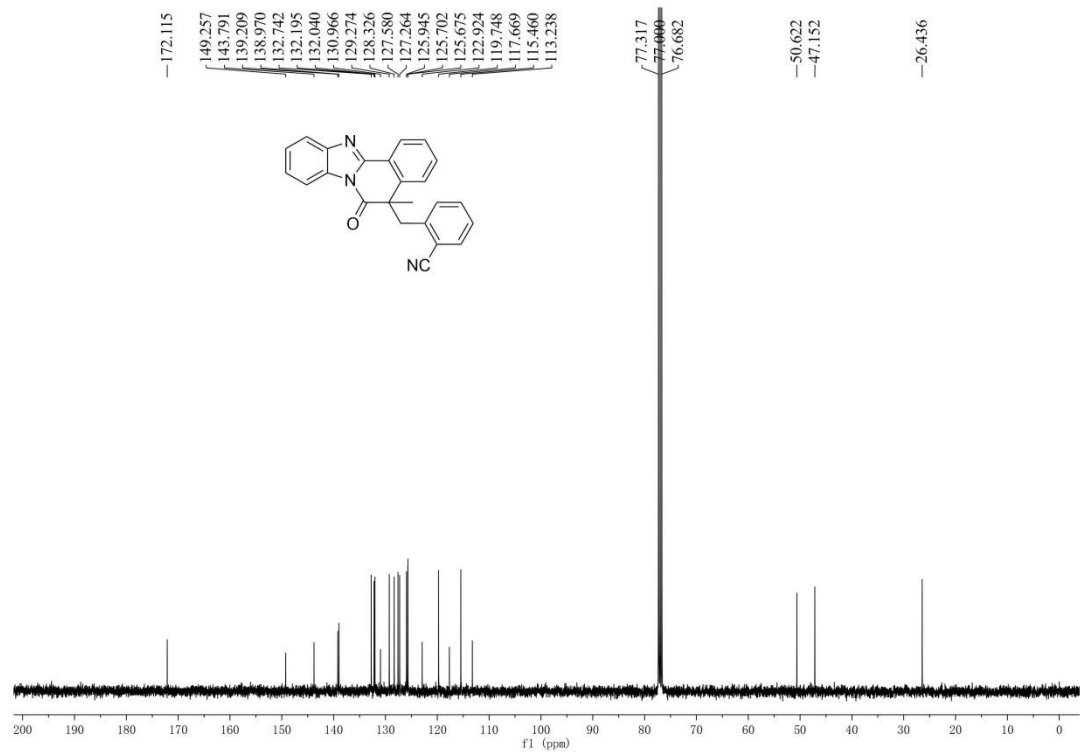
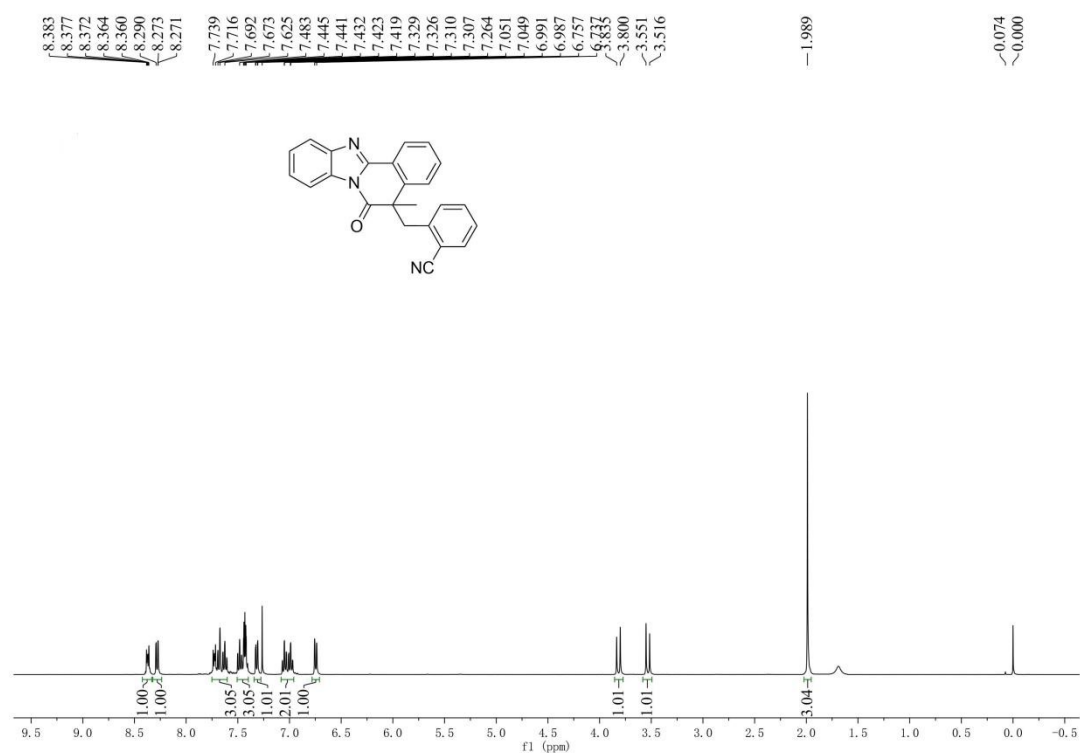
2-((3-Ethyl-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3sa)



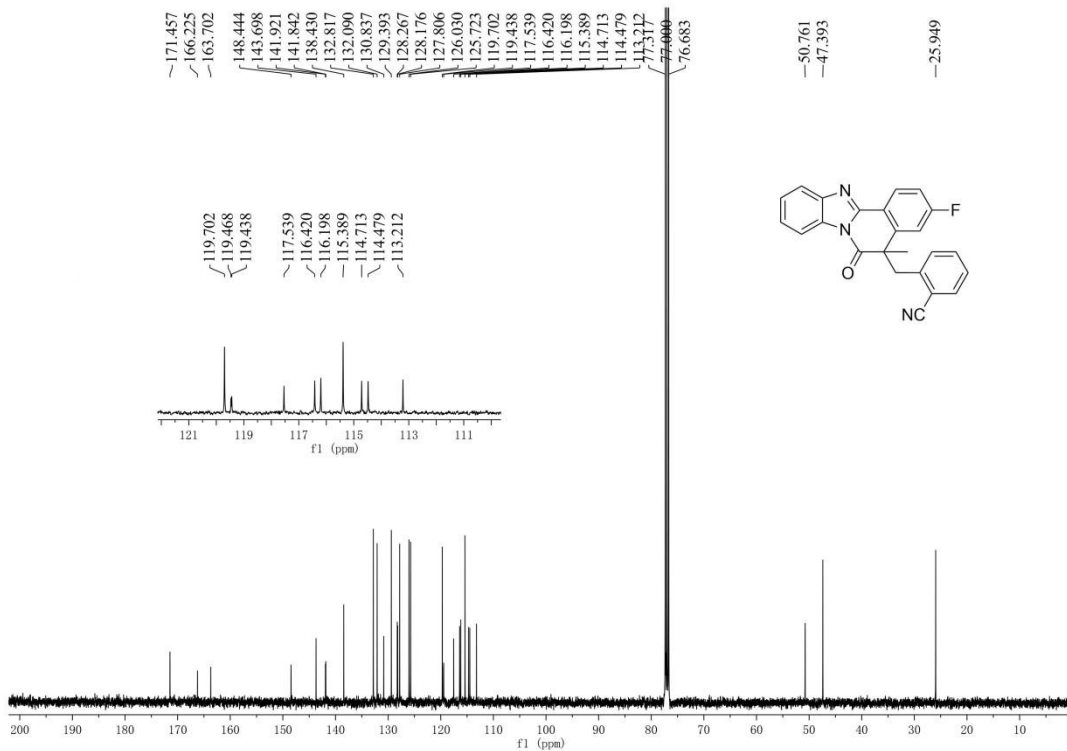
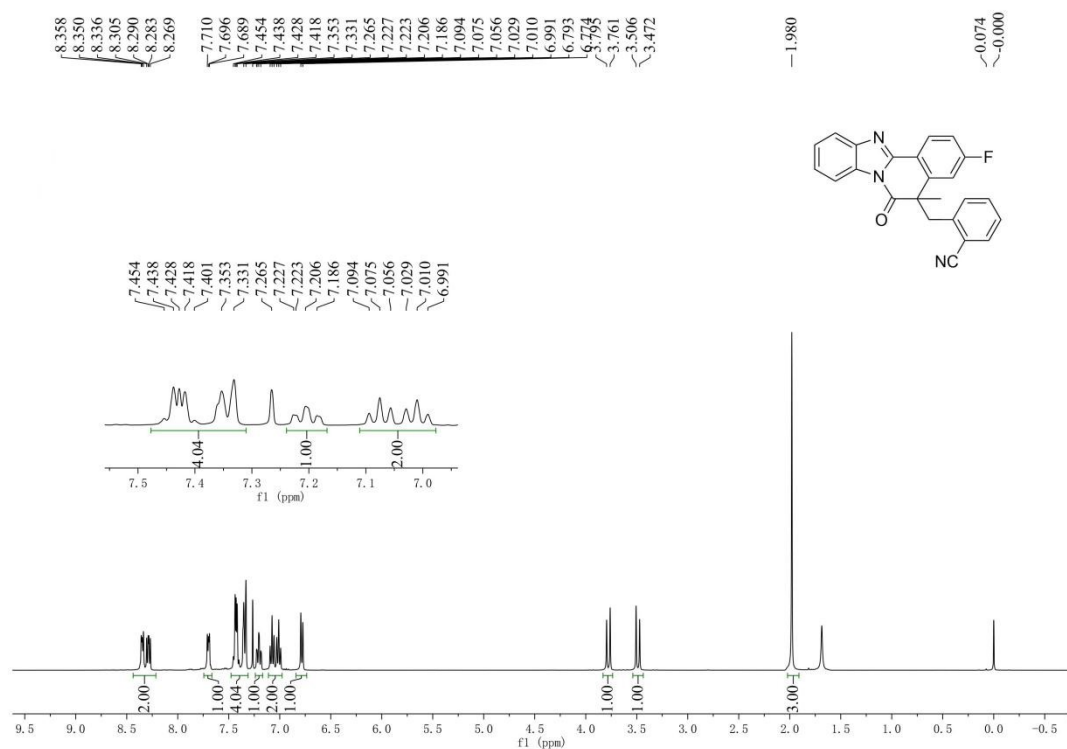
2-((3-Isopropyl-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ta)

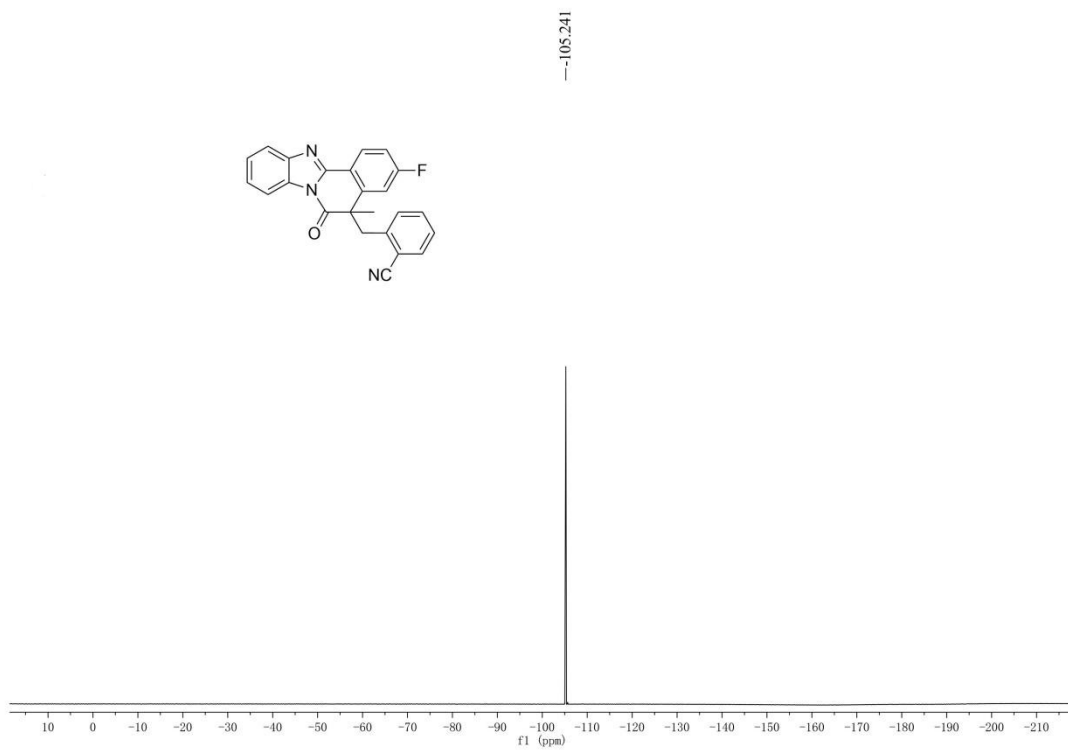


2-((5-Methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl) benzonitrile (3ua)

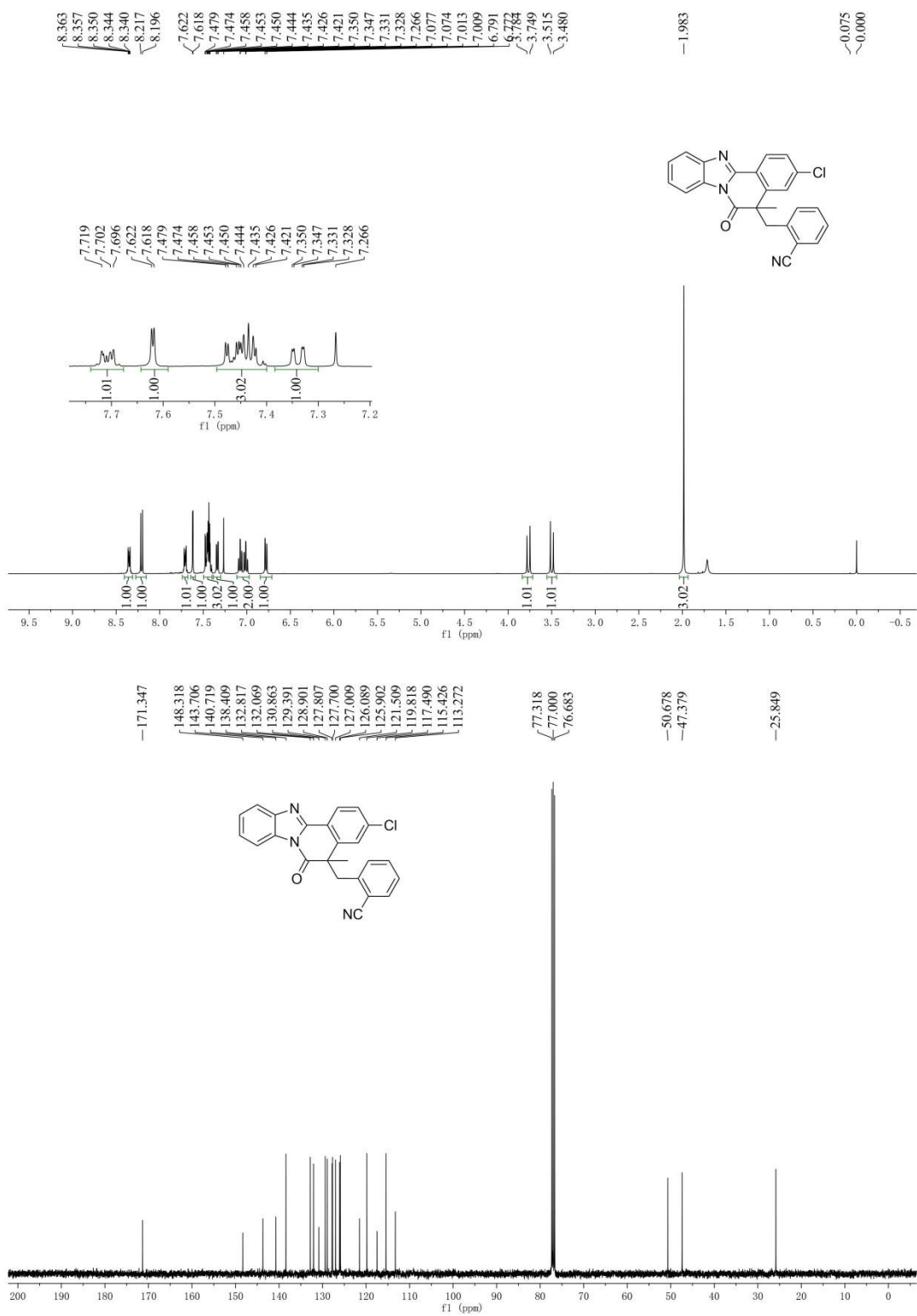


2-((3-Fluoro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3va)

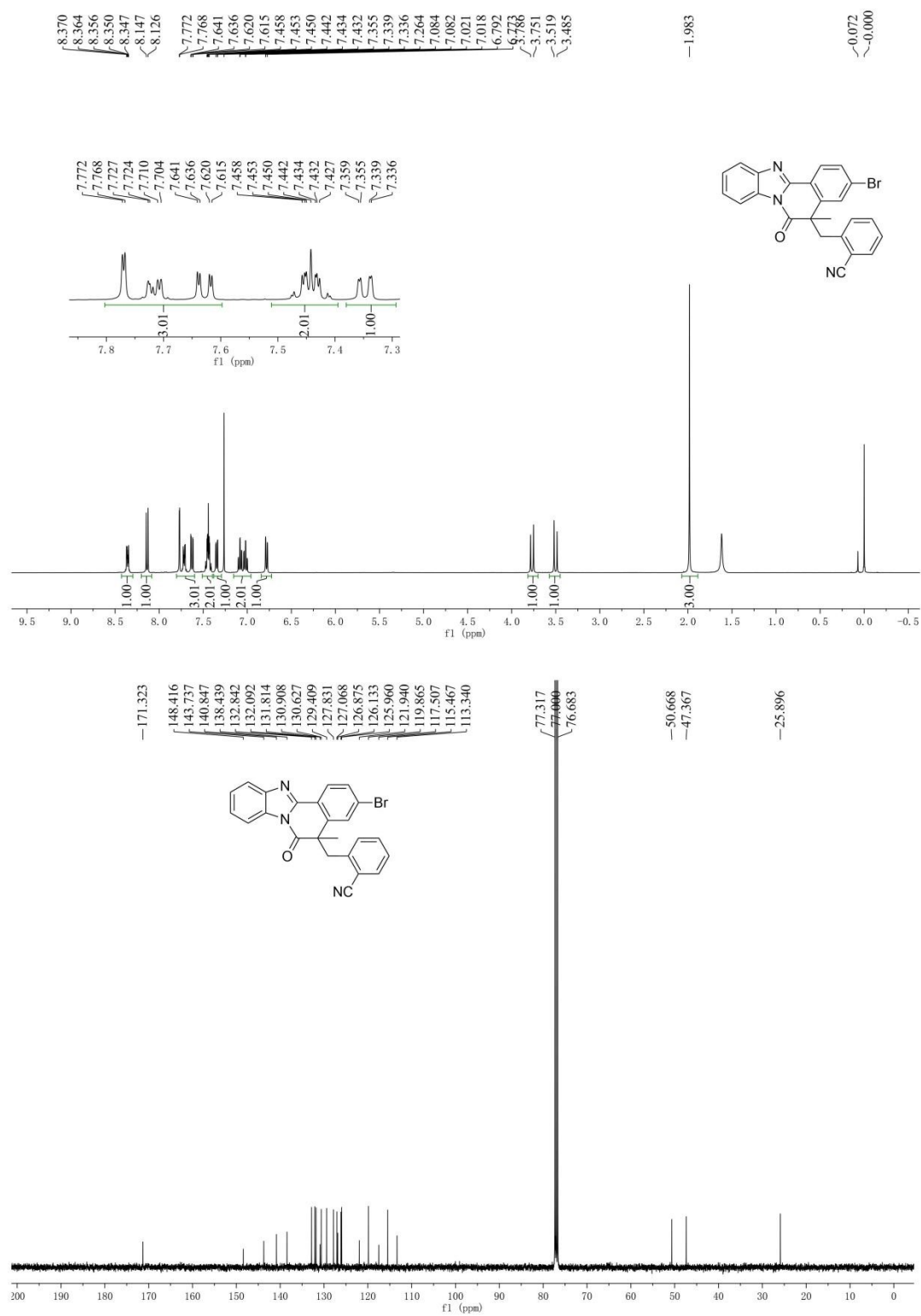




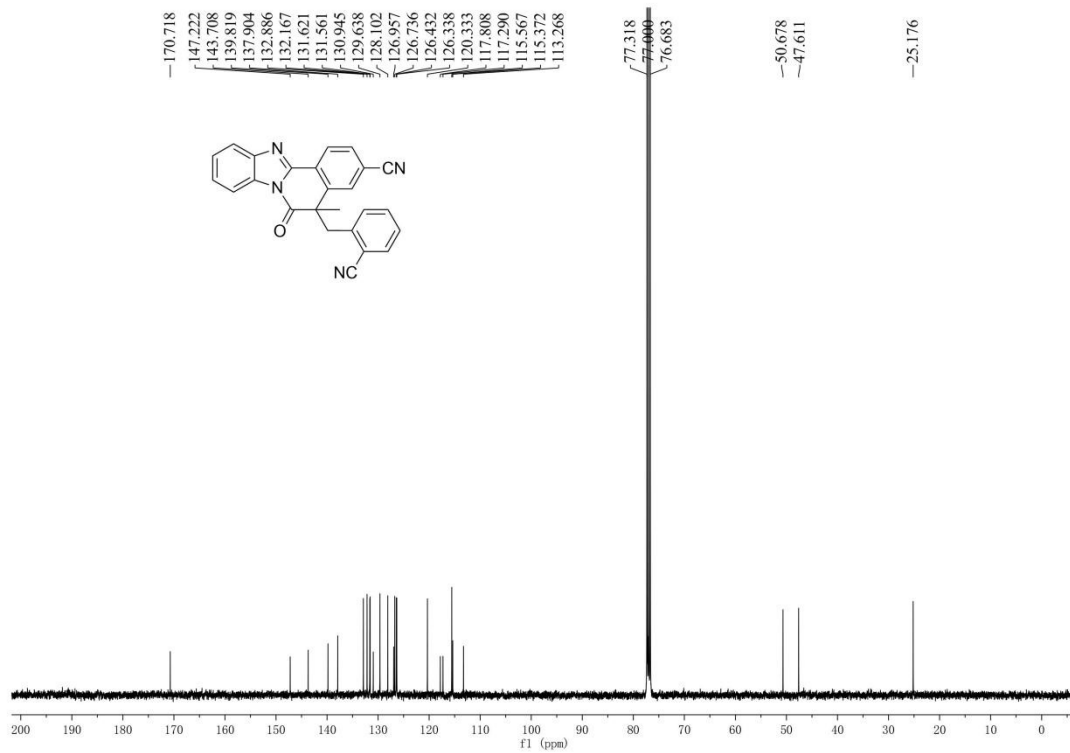
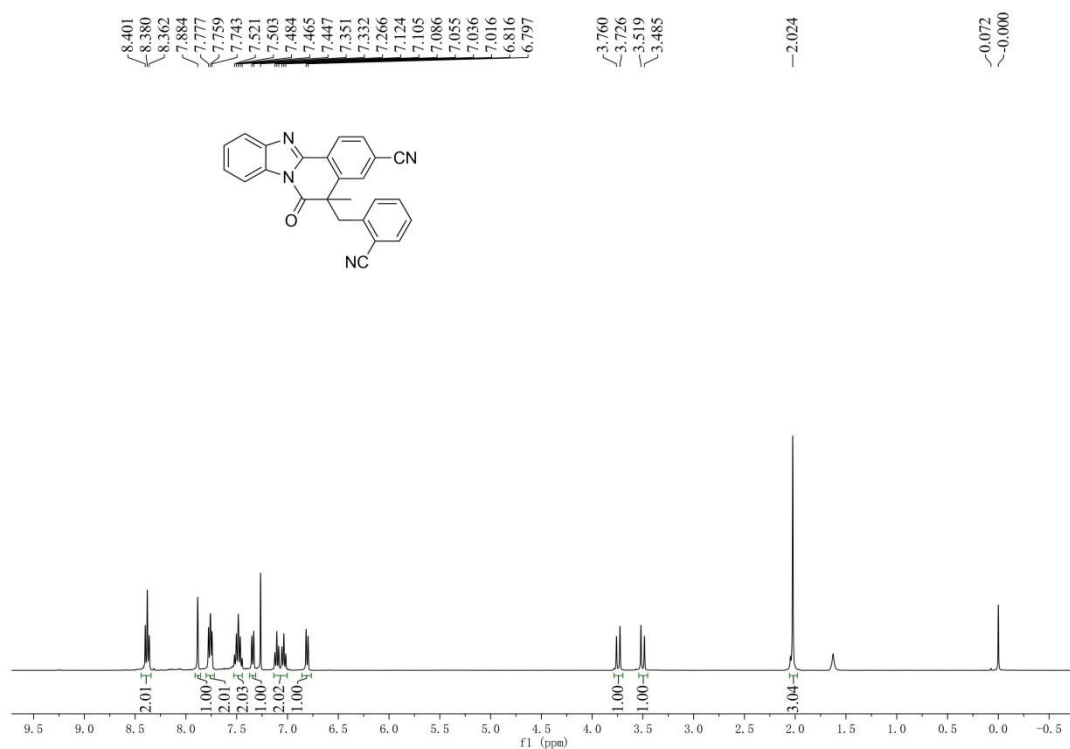
2-((3-Chloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3wa)



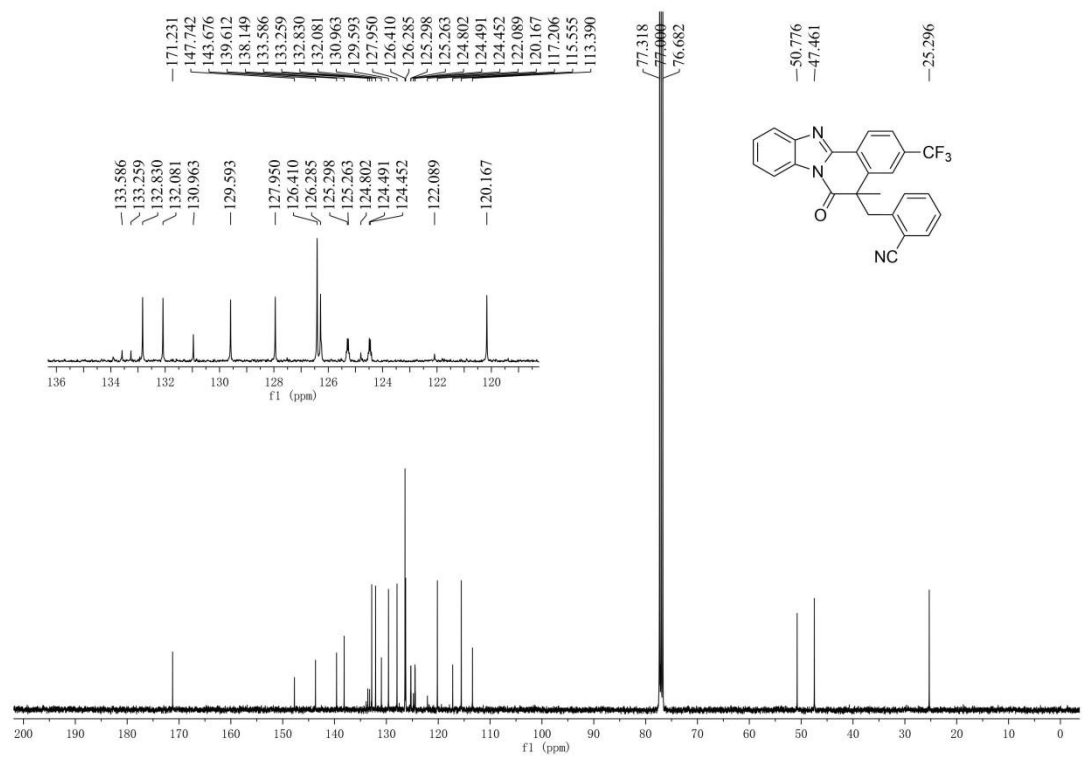
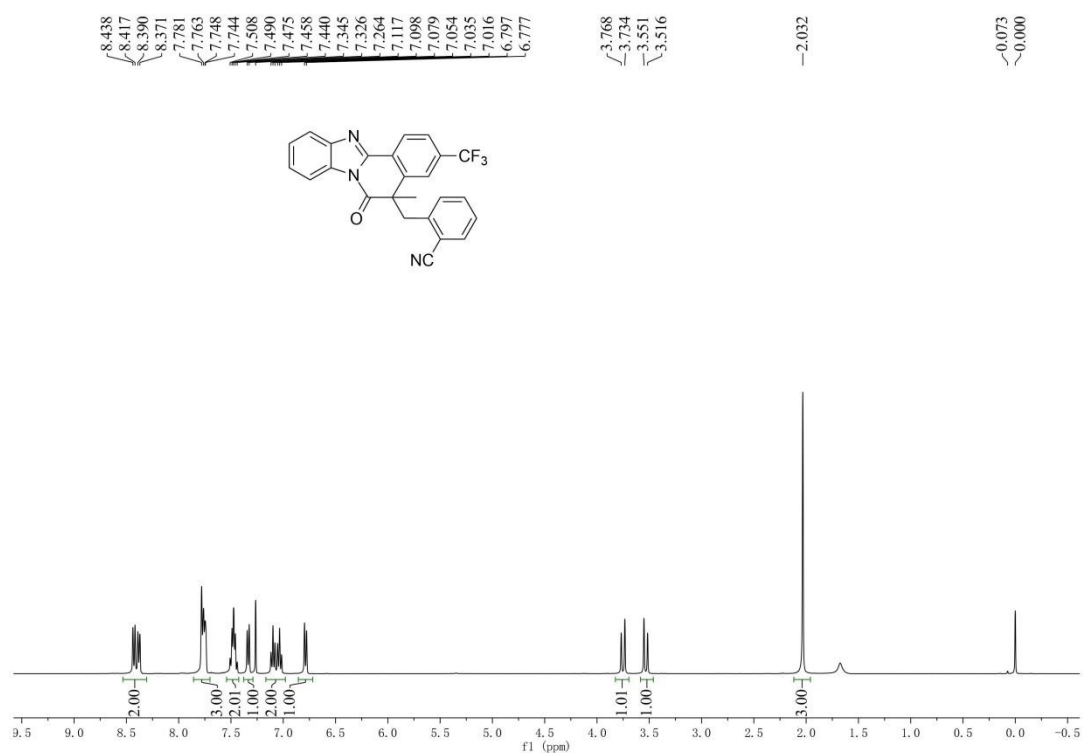
2-((3-Bromo-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3xa)



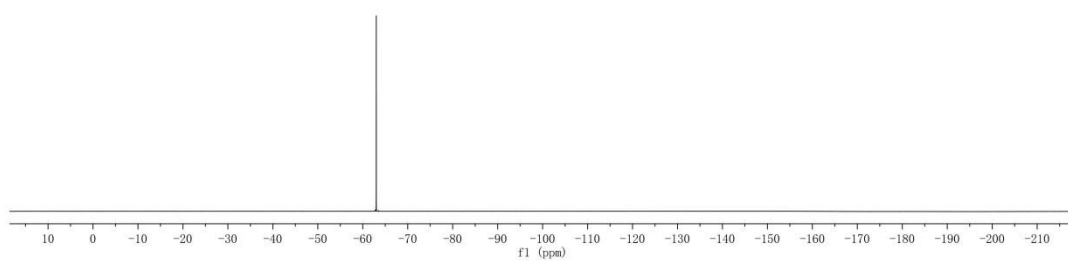
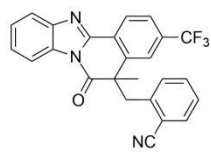
5-(2-Cyanobenzyl)-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline-3-carbonitrile (3ya)



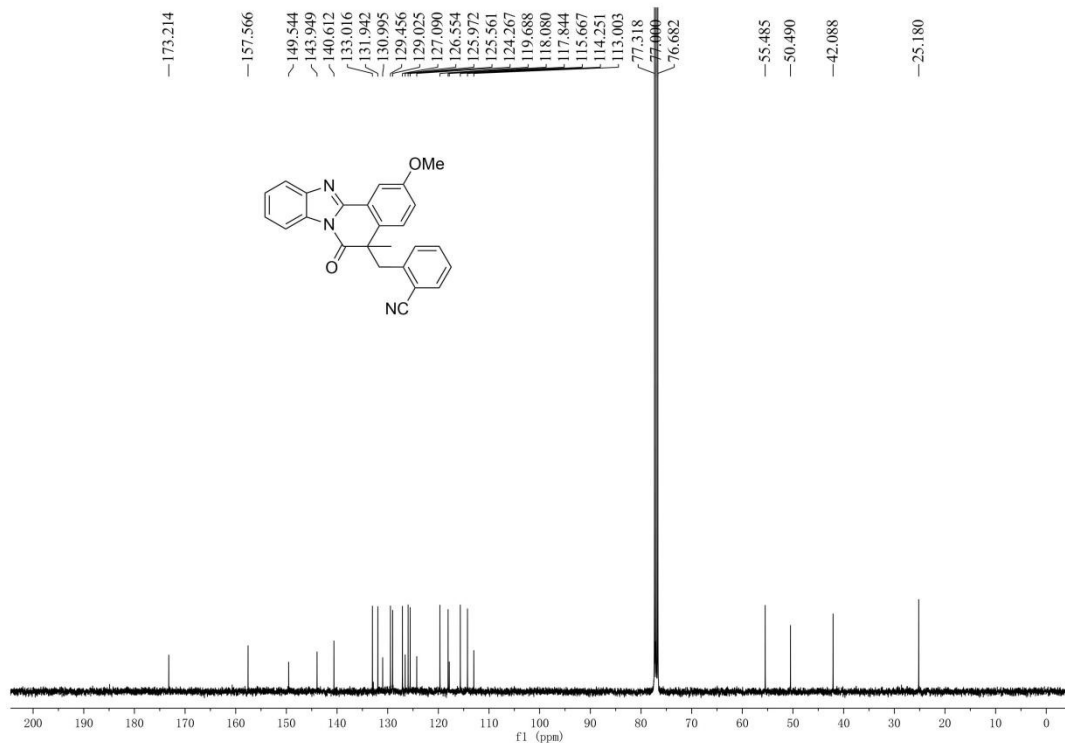
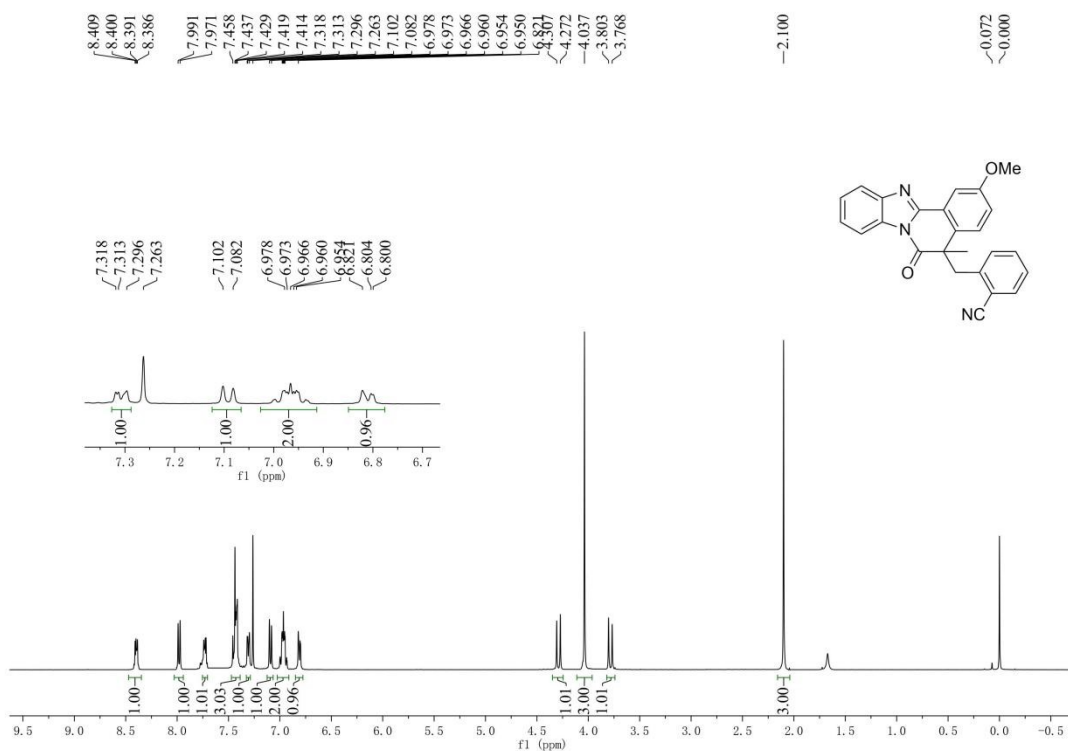
2-((5-Methyl-6-oxo-3-(trifluoromethyl)-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3za)



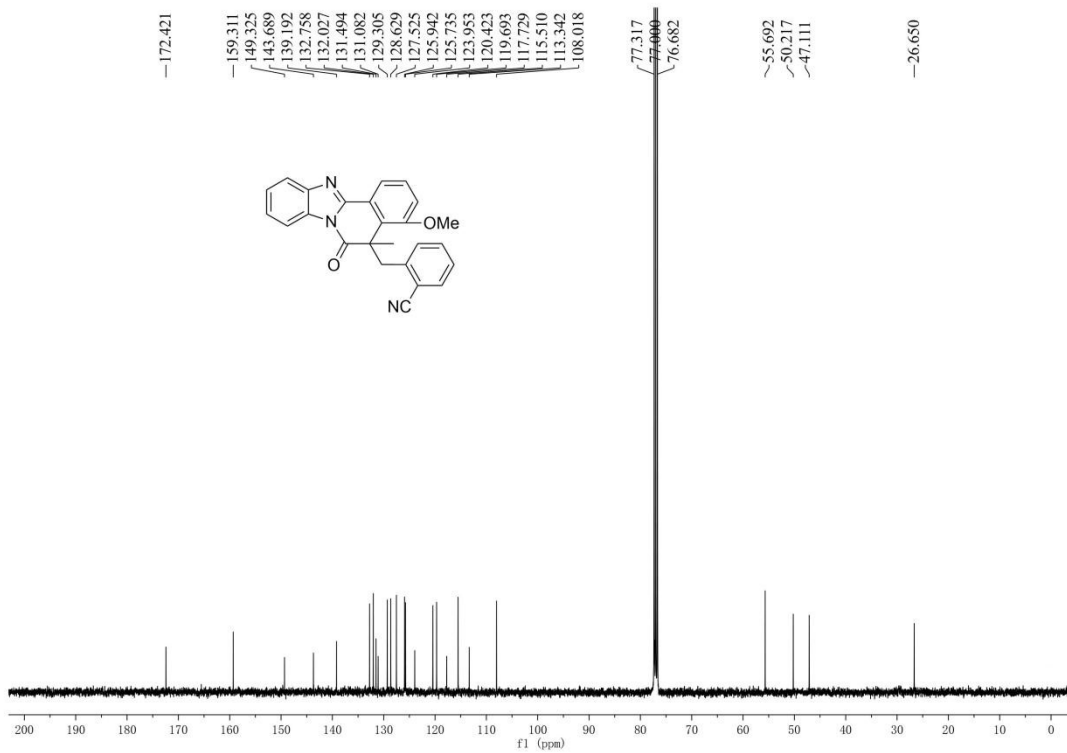
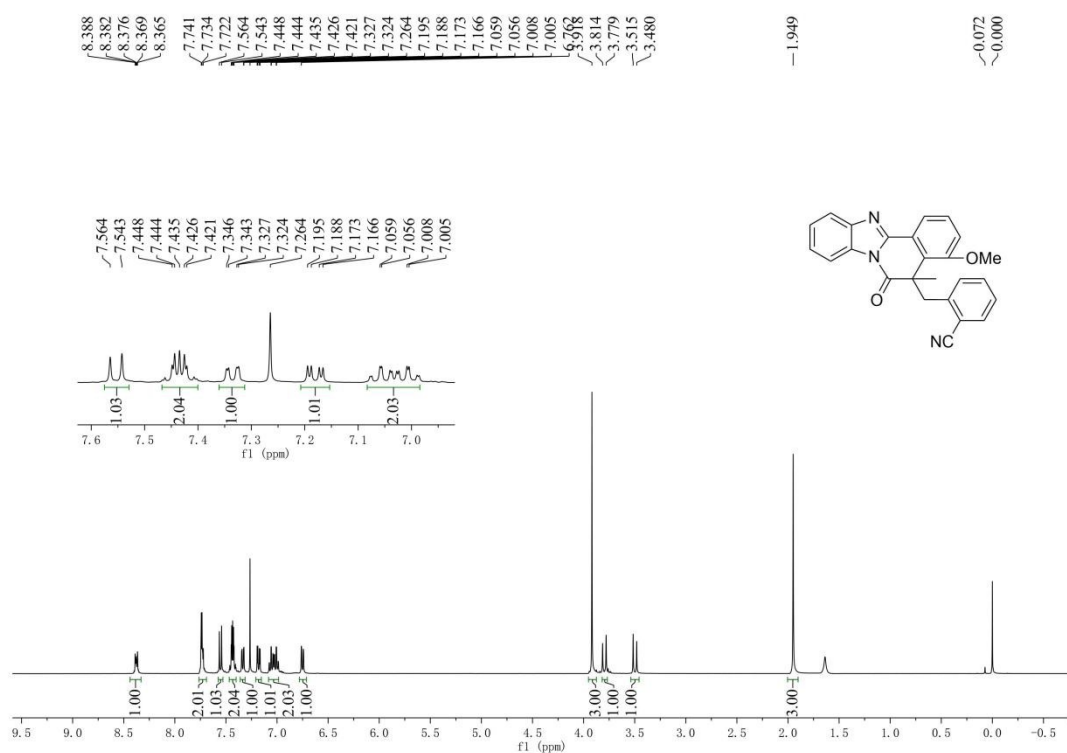
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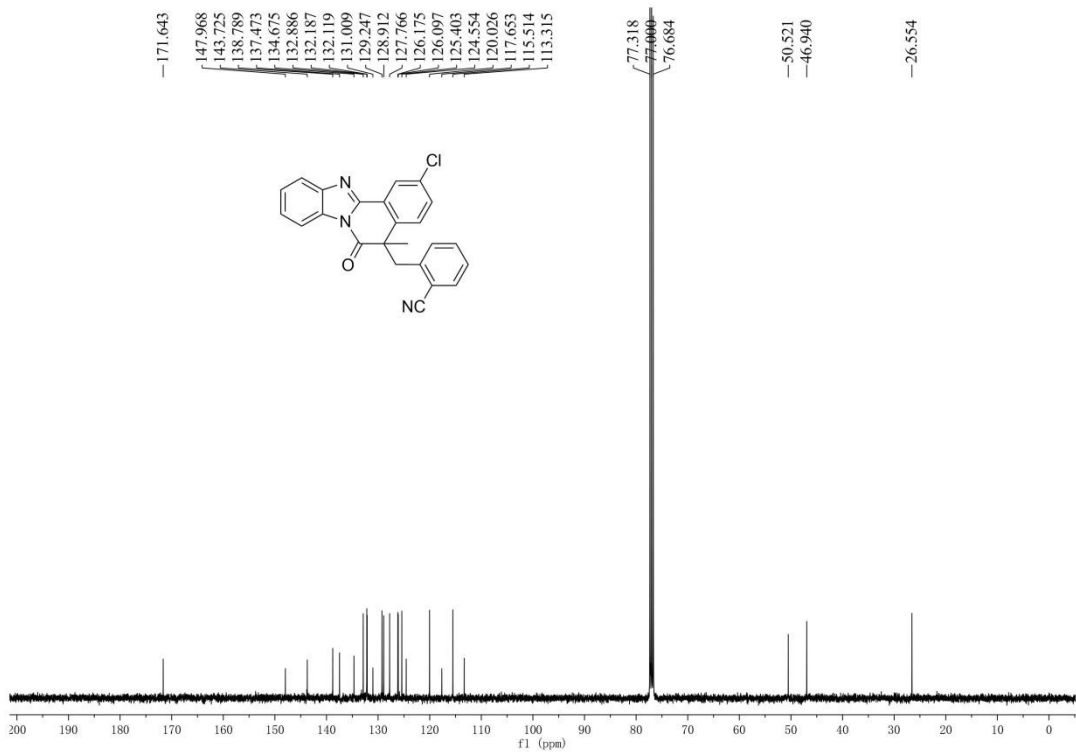
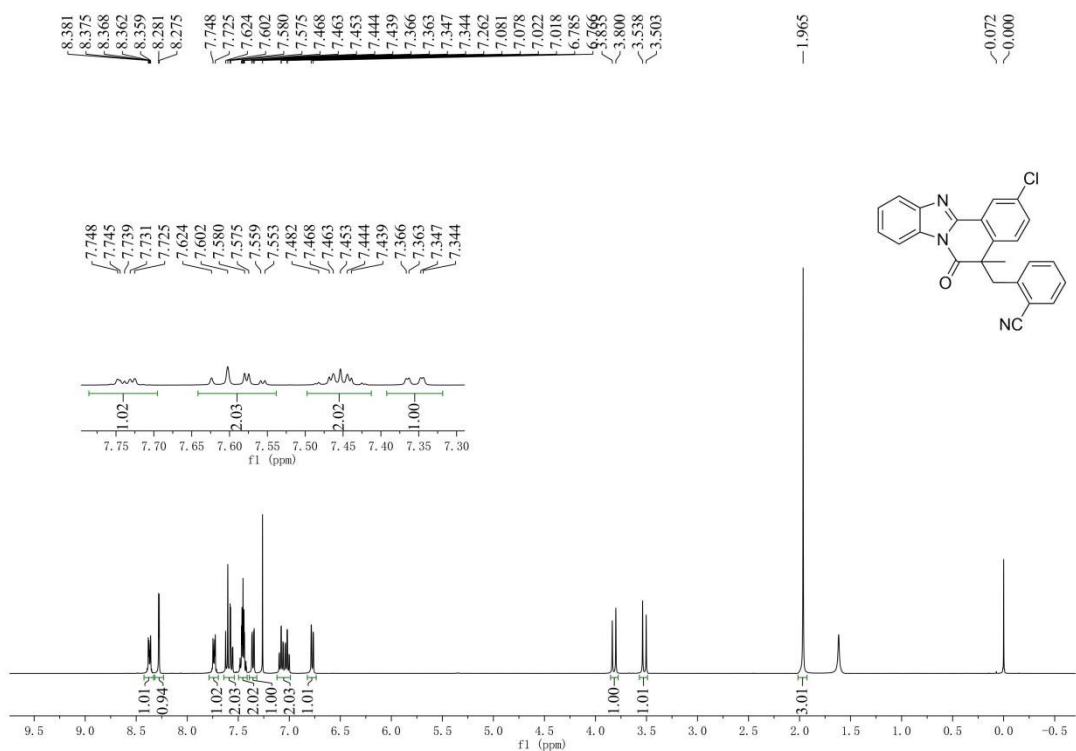
2-((2-Methoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolin-5-yl)methyl)benzonitrile (3aaa)



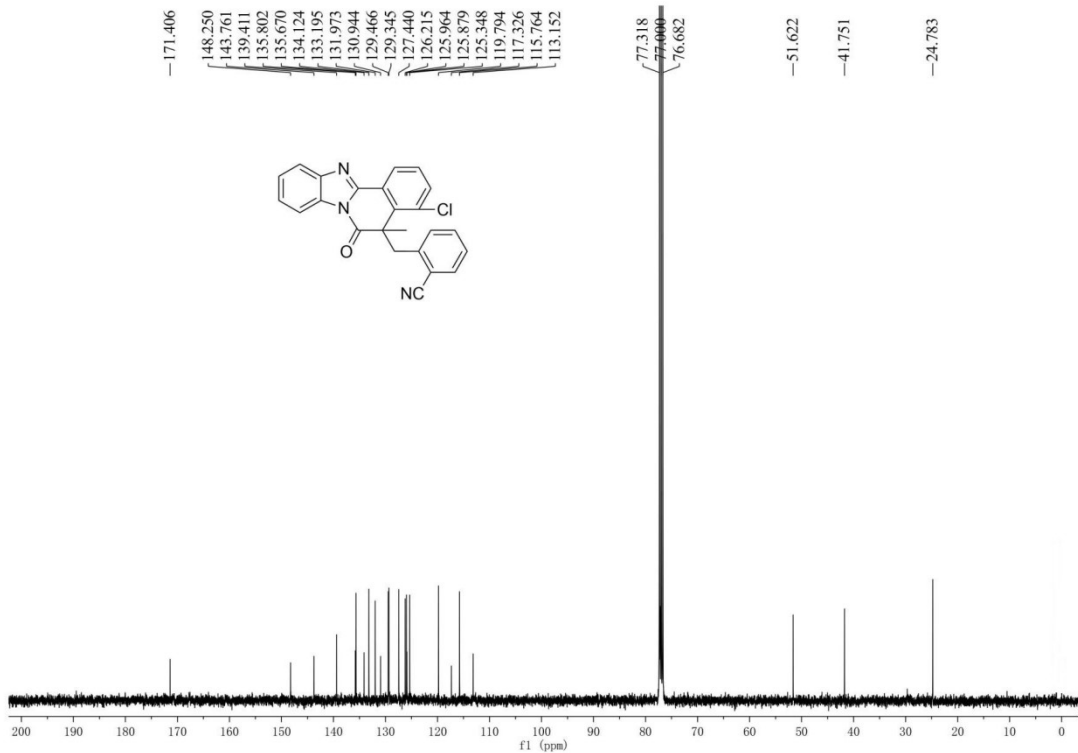
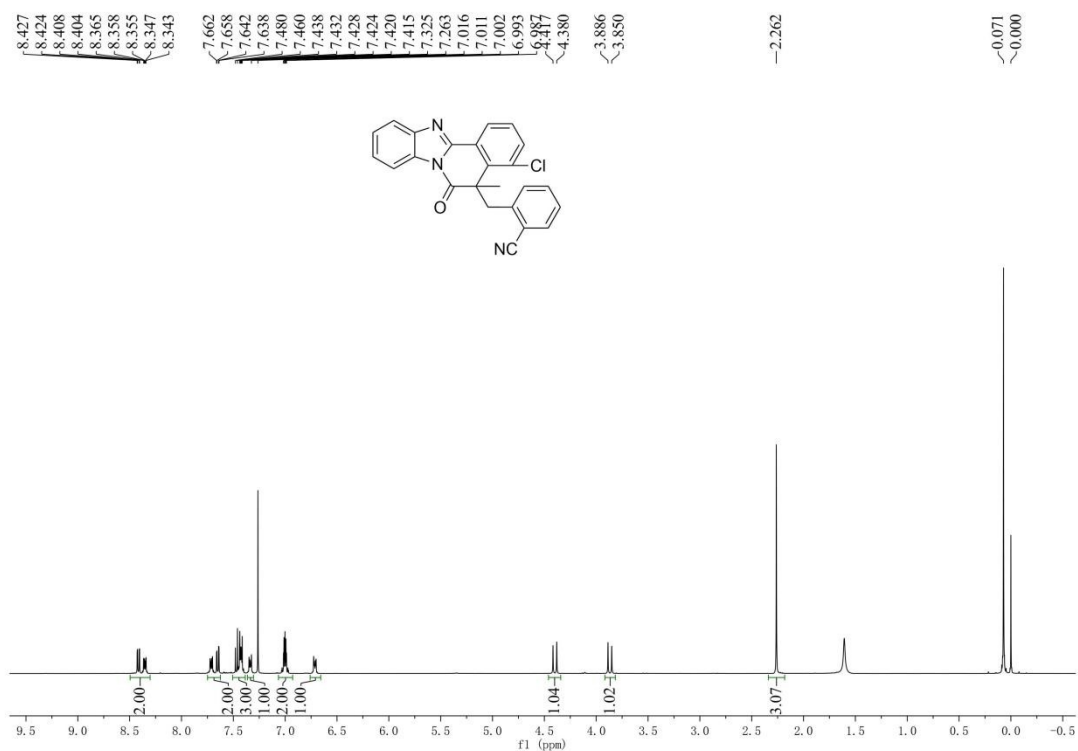
2-((4-Methoxy-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolin-5-yl)methyl)benzonitrile (3aaa')



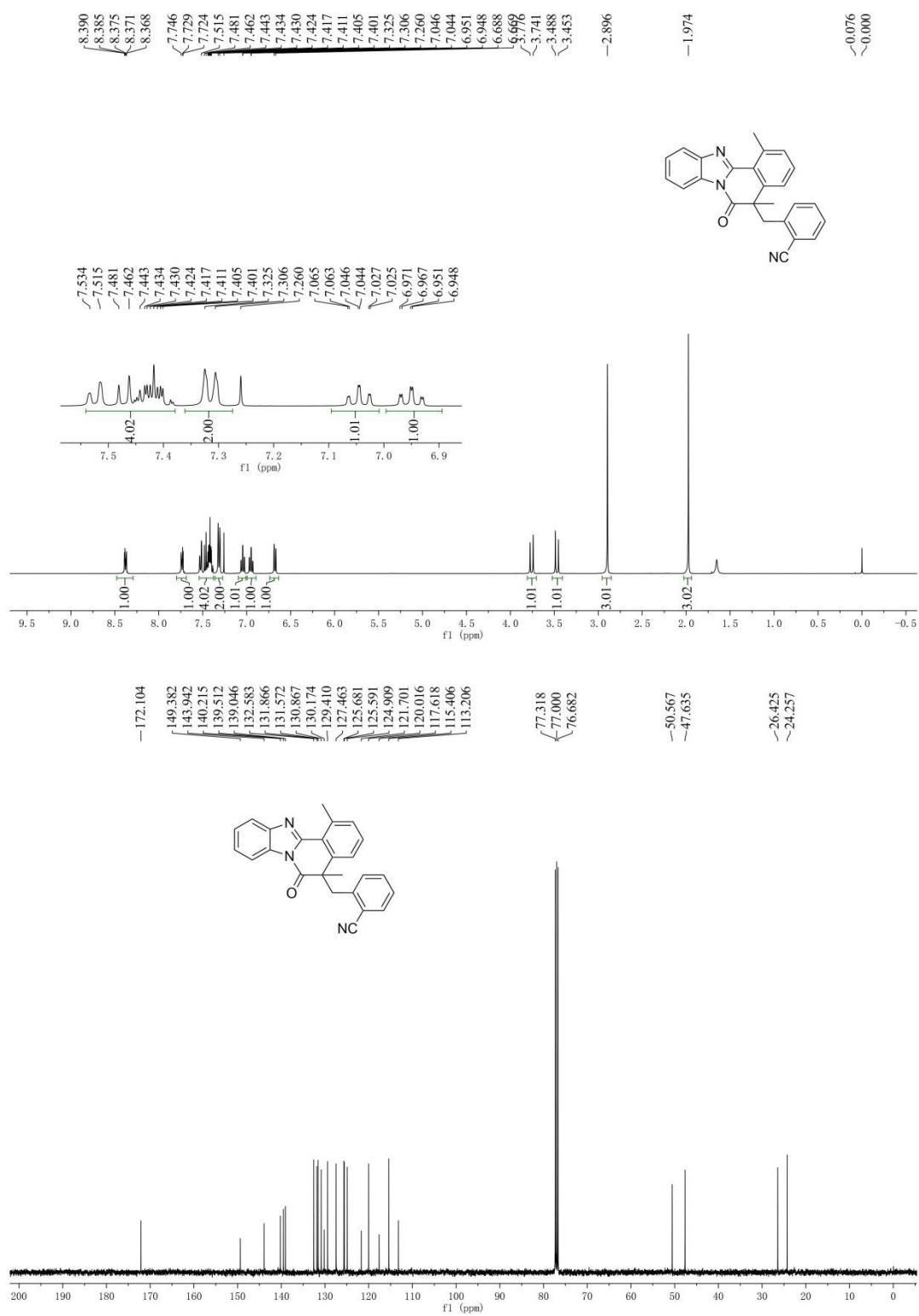
2-((2-Chloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ba)



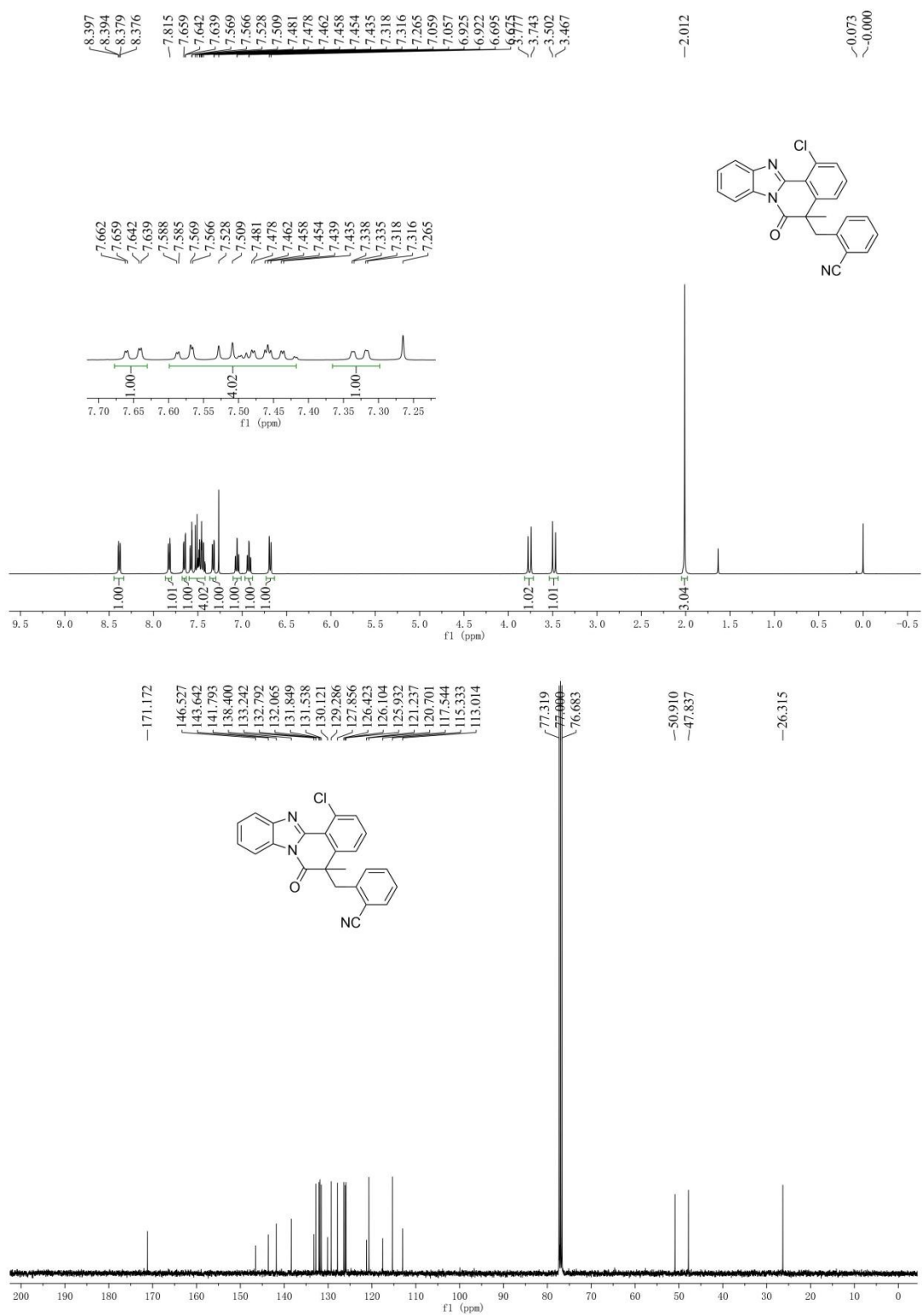
2-((4-Chloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3aba')



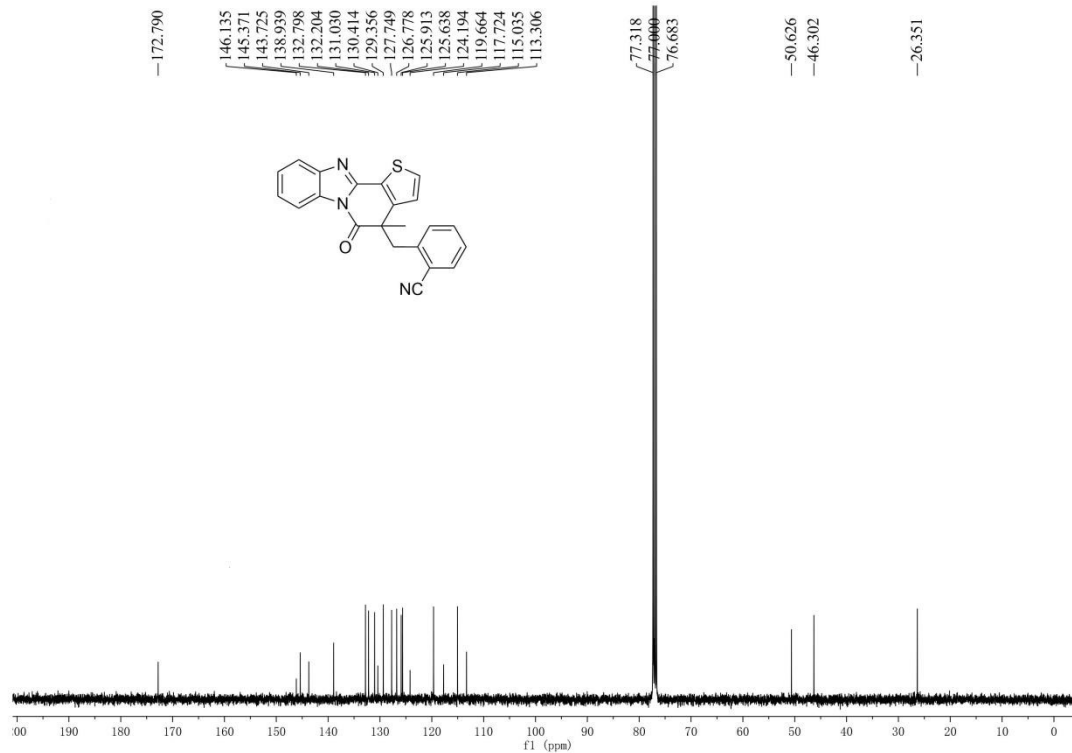
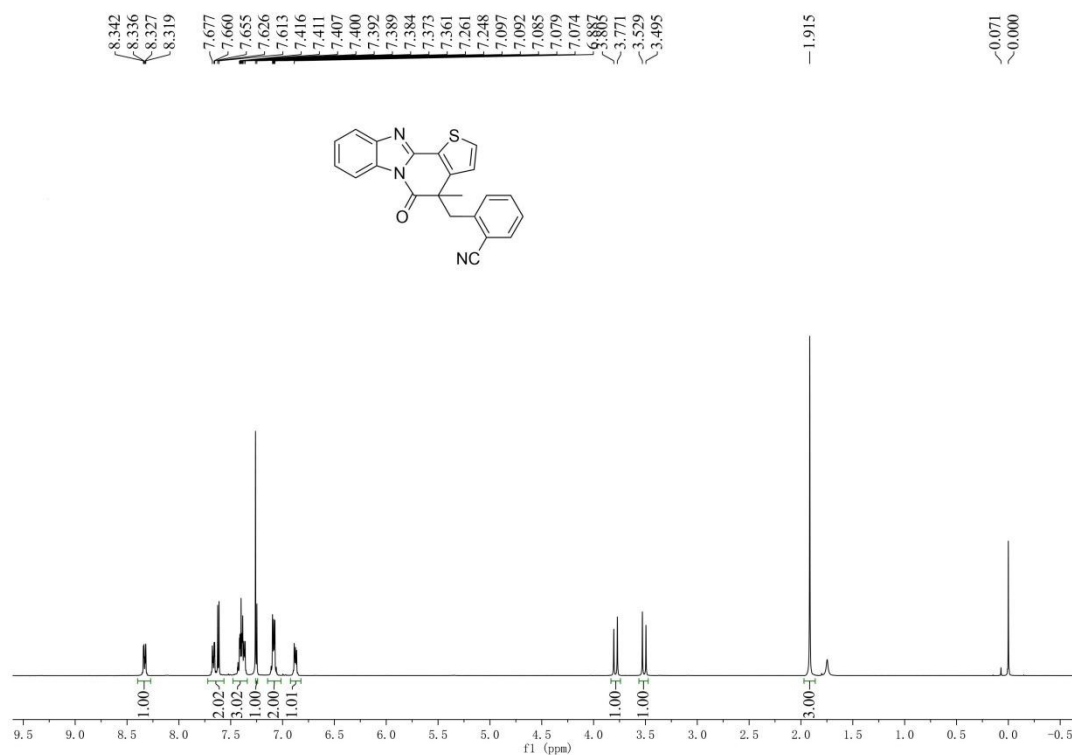
2-((1,5-Dimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3aca)



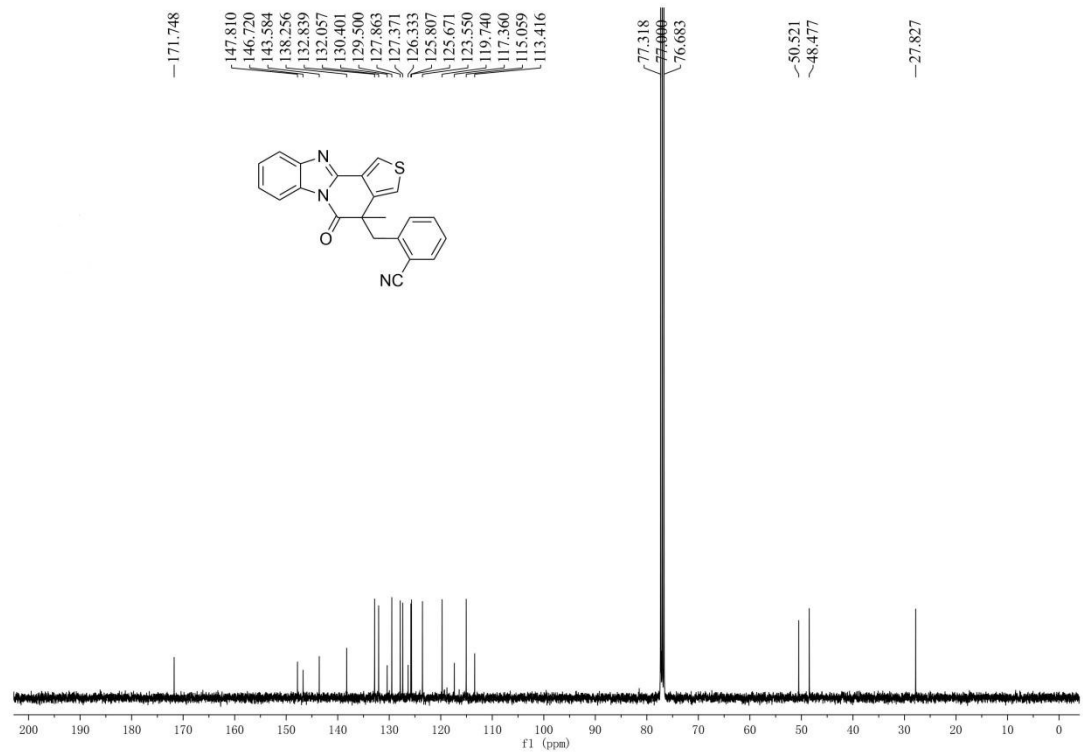
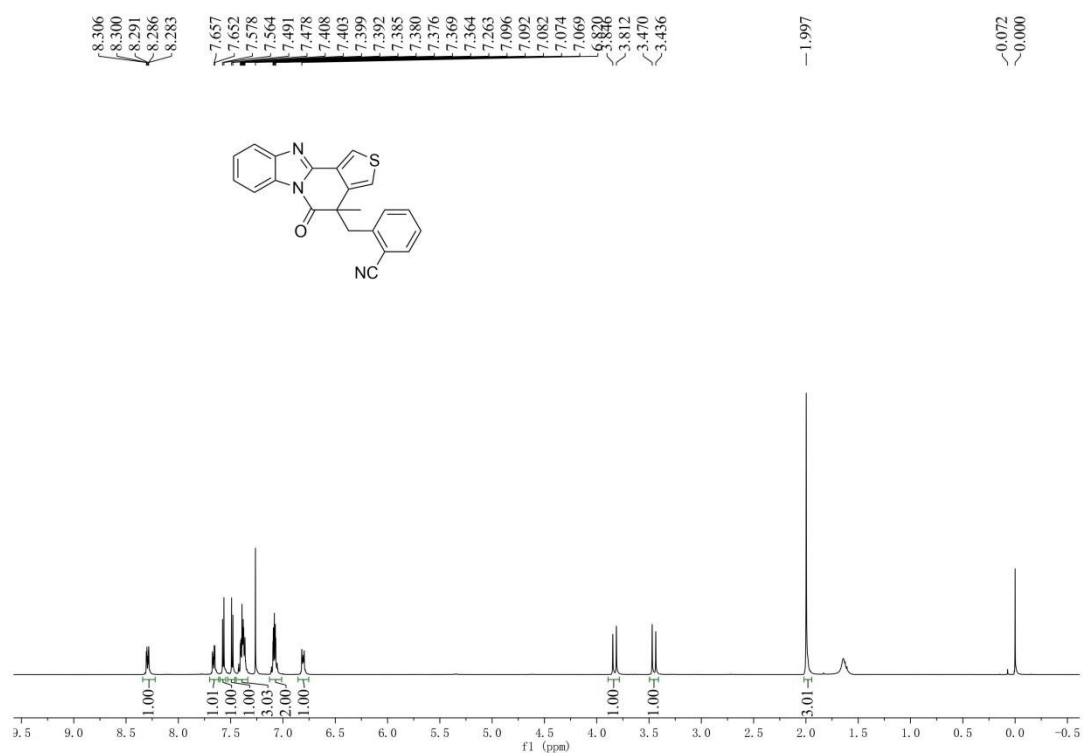
2-((1-Chloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ada)



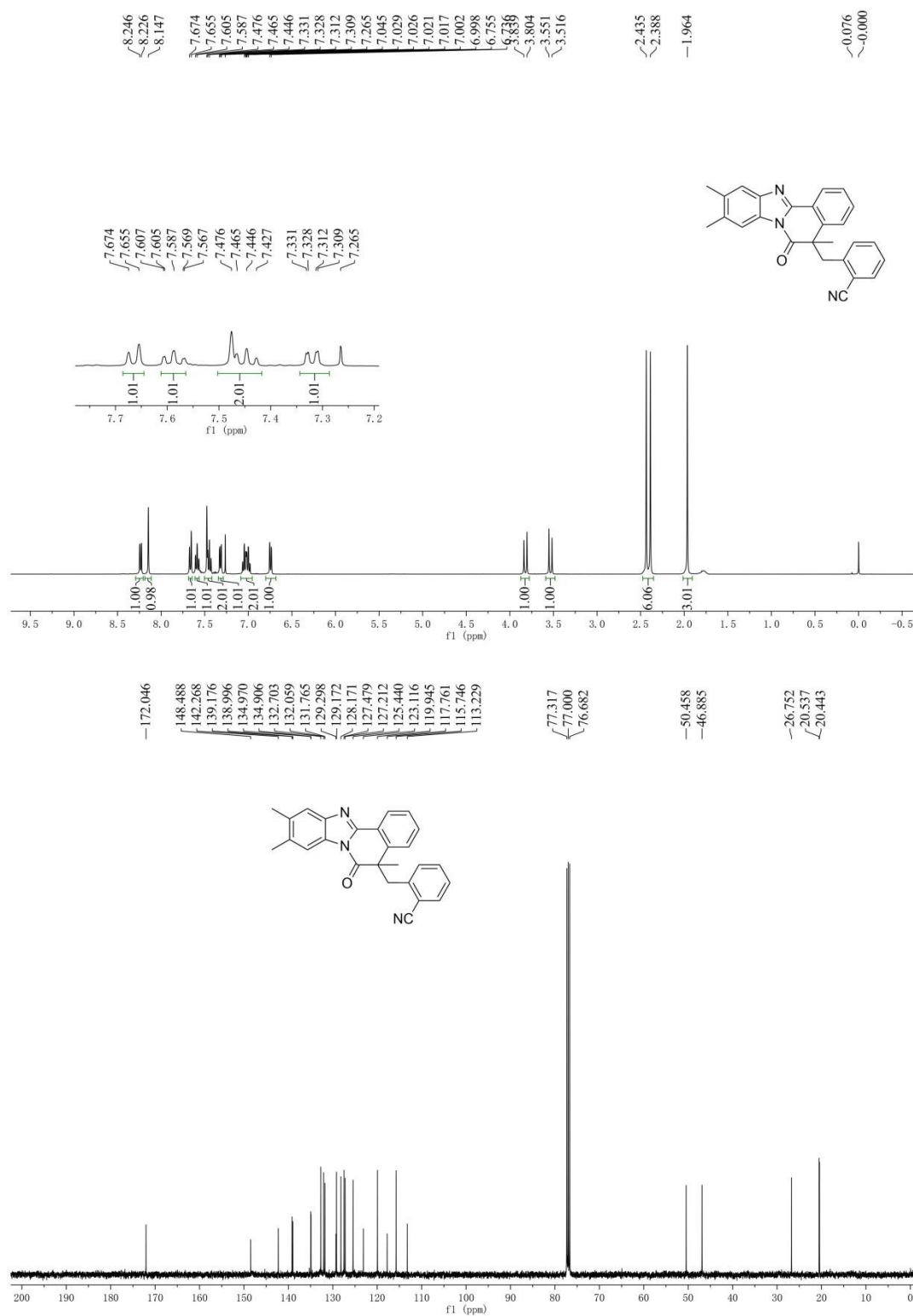
2-((4-Methyl-5-oxo-4,5-dihydrobenzo[4,5]imidazo[1,2-a]thieno[2,3-c]pyridin-4-yl)methyl)benzonitrile (3aea)



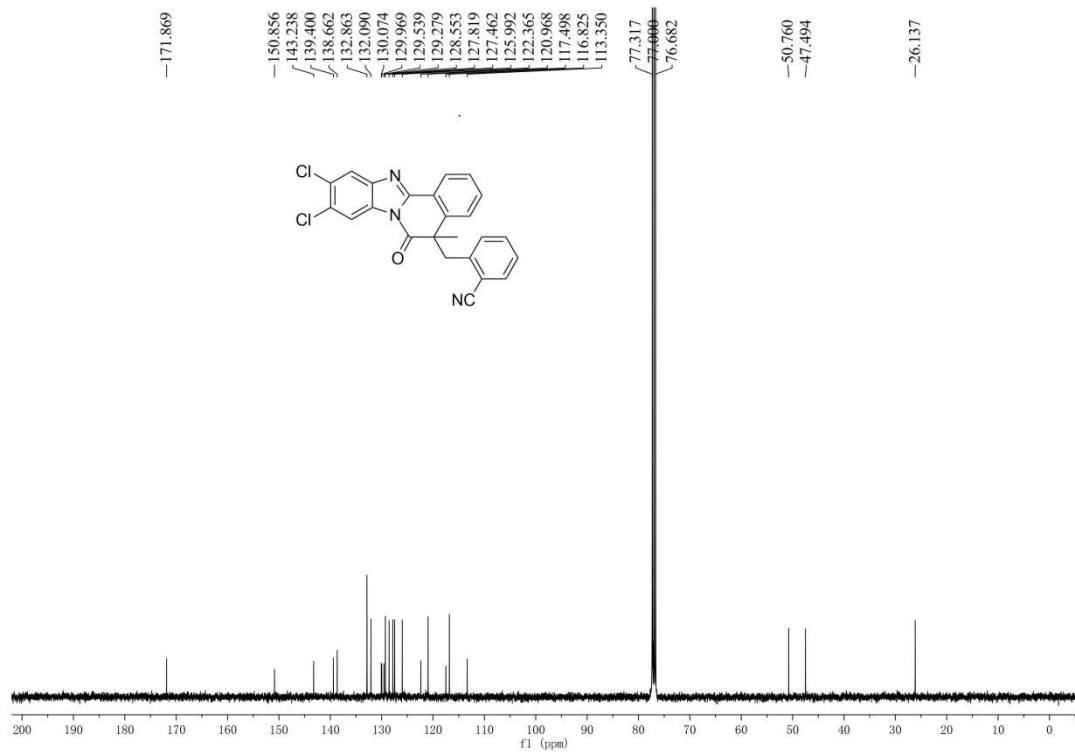
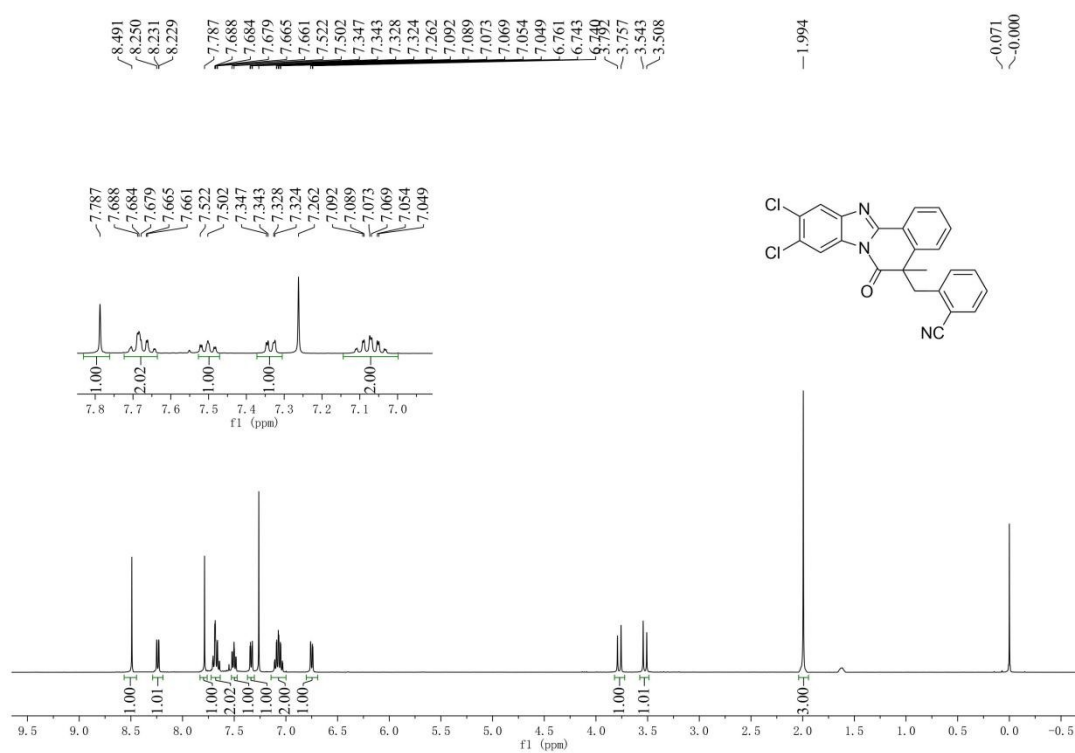
2-((4-Methyl-5-oxo-4,5-dihydrobenzo[4,5]imidazo[1,2-a]thieno[3,4-c]pyridin-4-yl)methyl)benzonitrile (3afa)



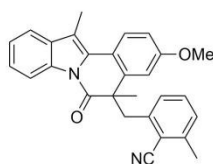
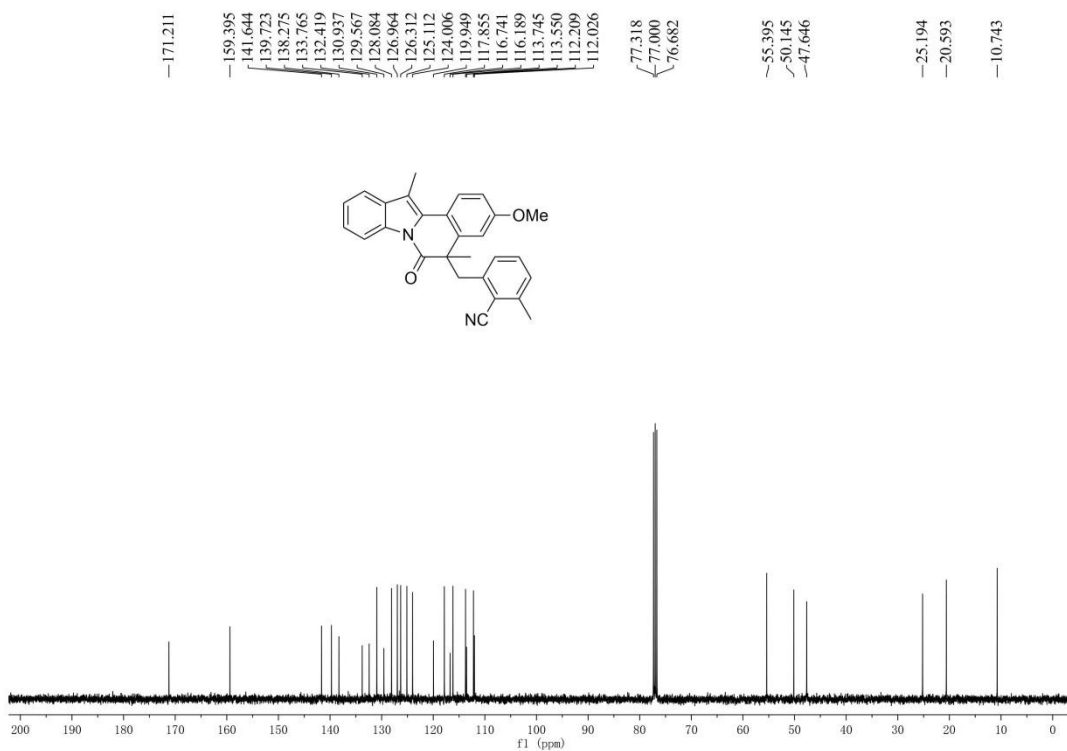
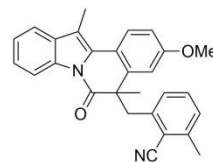
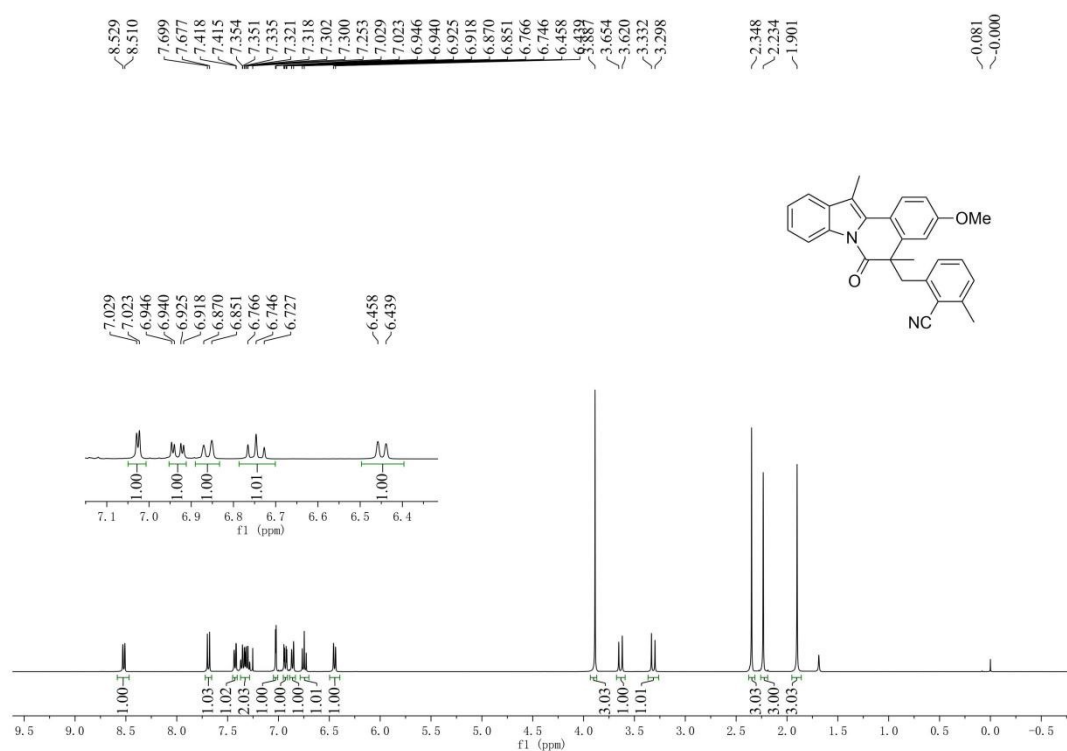
2-((5,9,10-Trimethyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3aga)



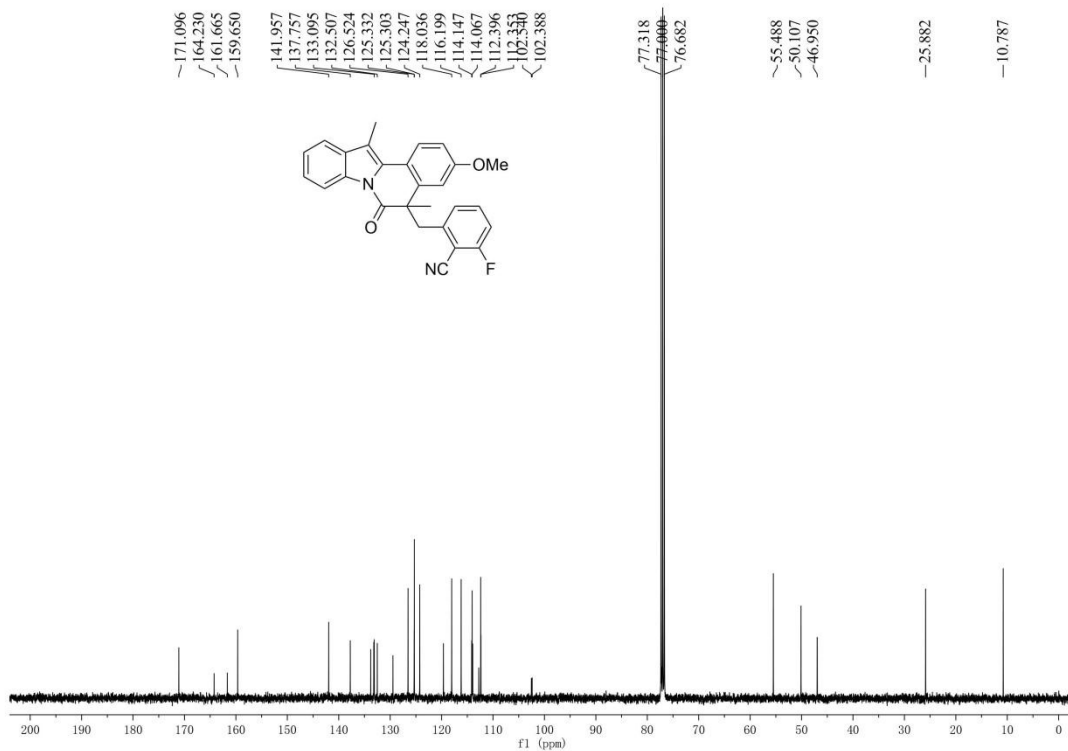
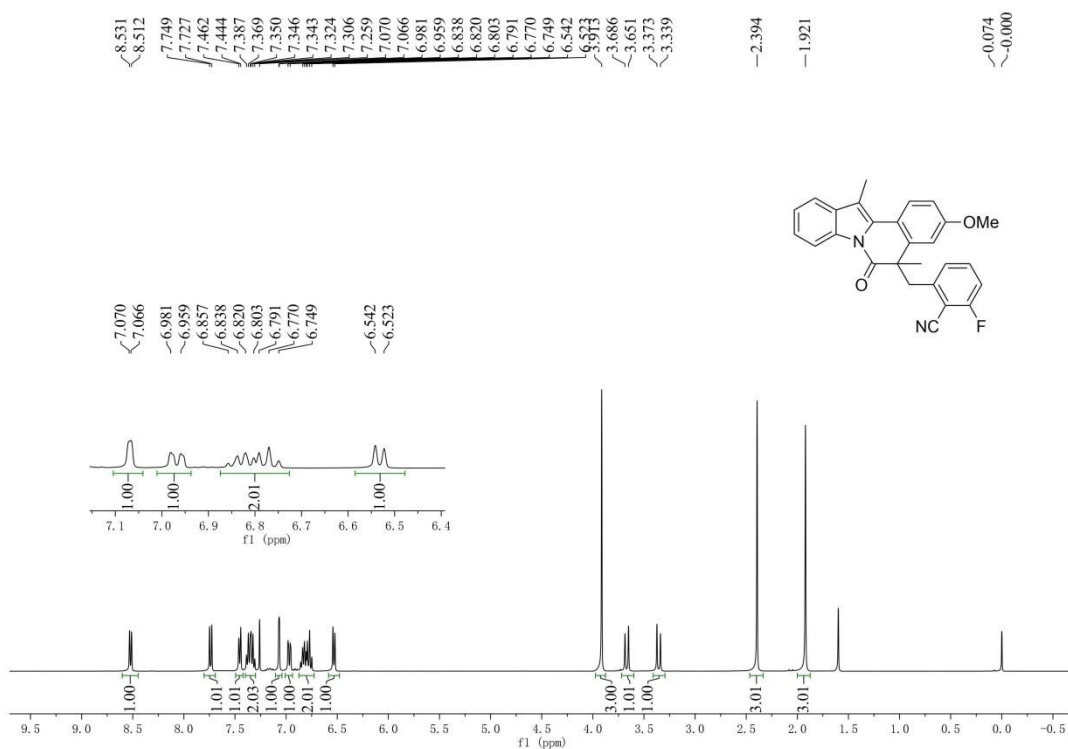
2-((9,10-Dichloro-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolin-5-yl)methyl)benzonitrile (3aha)

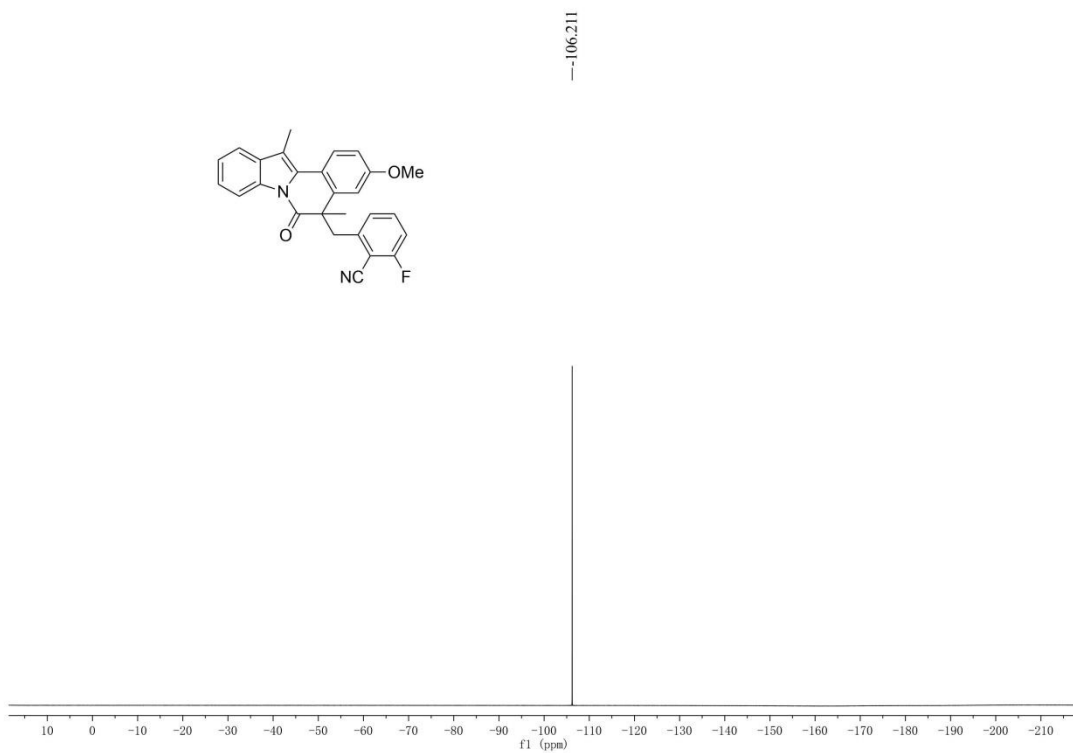


2-((3-Methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)-6-methylbenzonitrile (3ab)

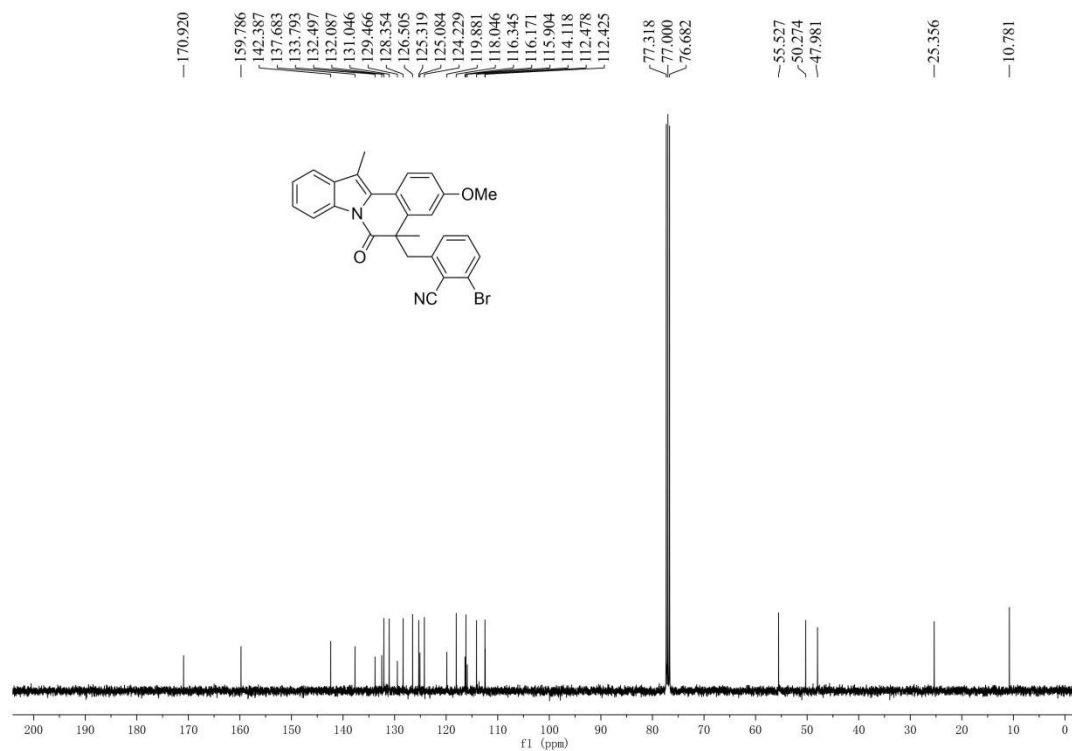
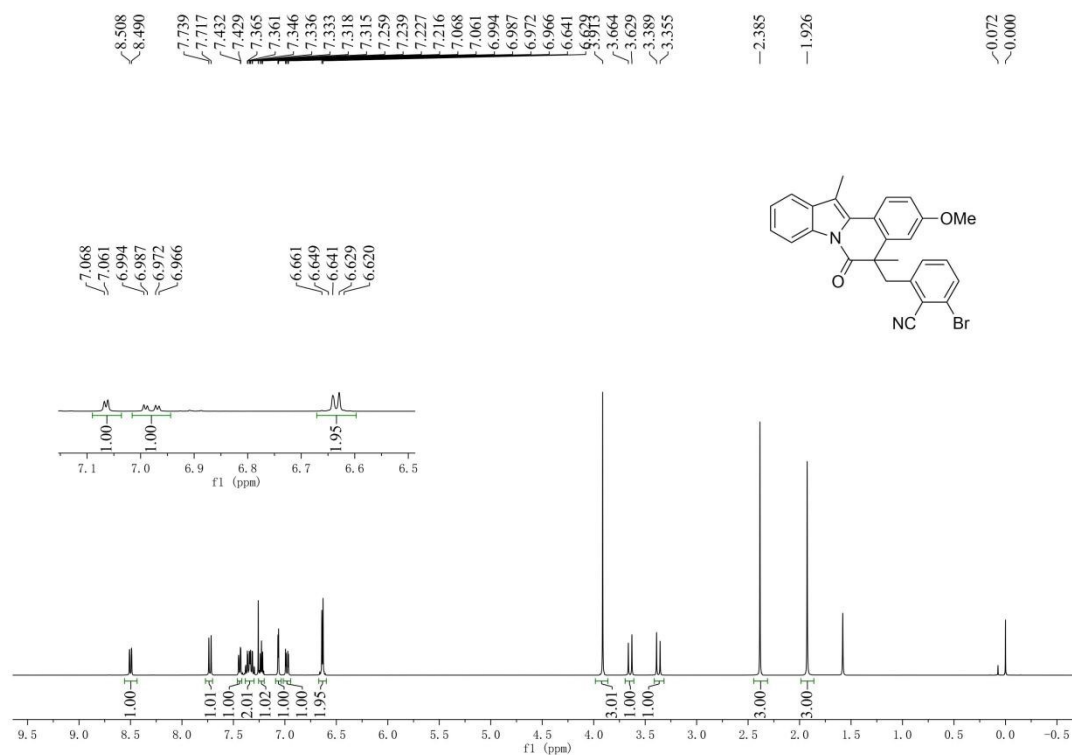


2-Fluoro-6-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ac)

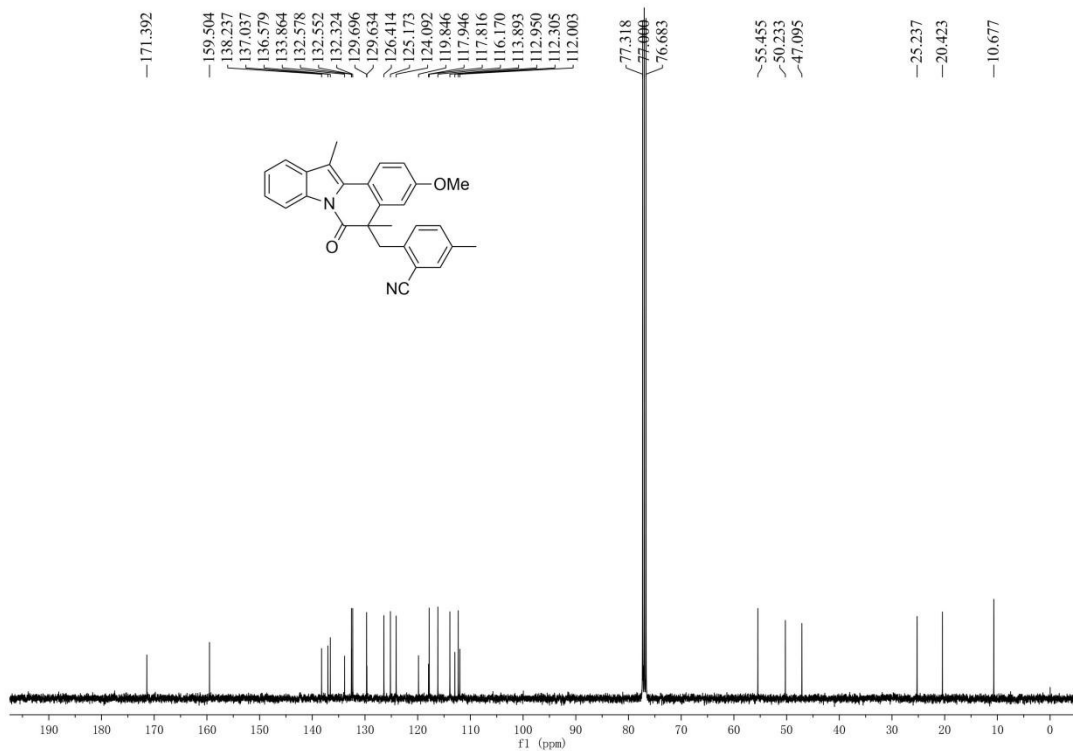
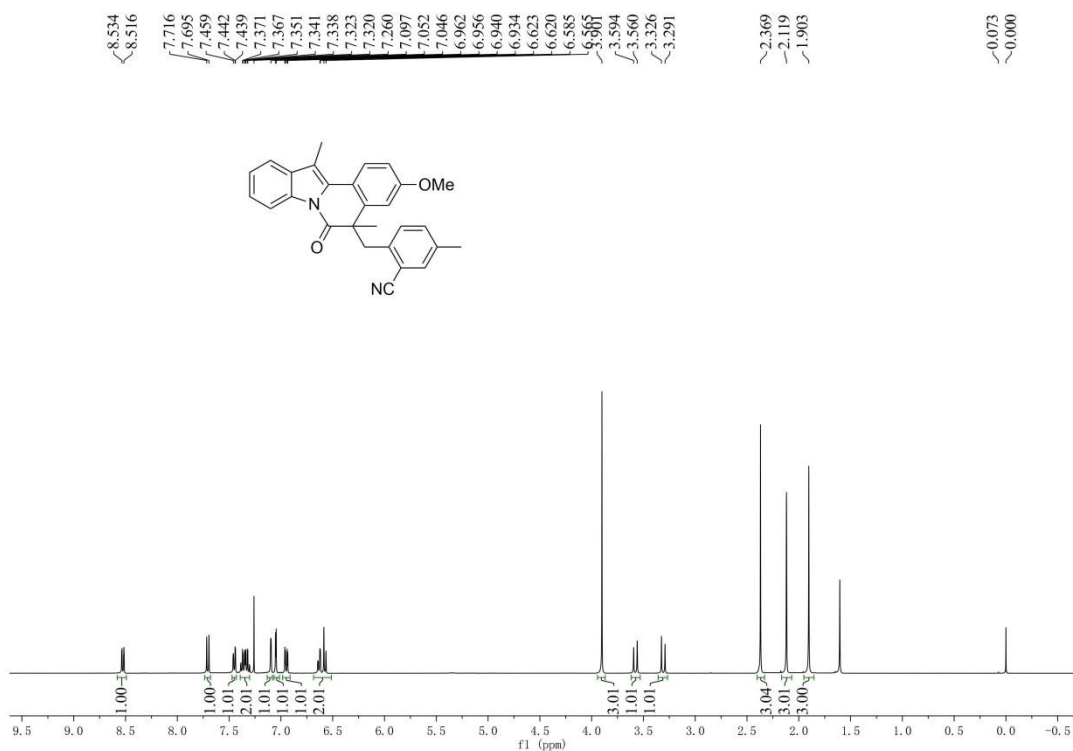




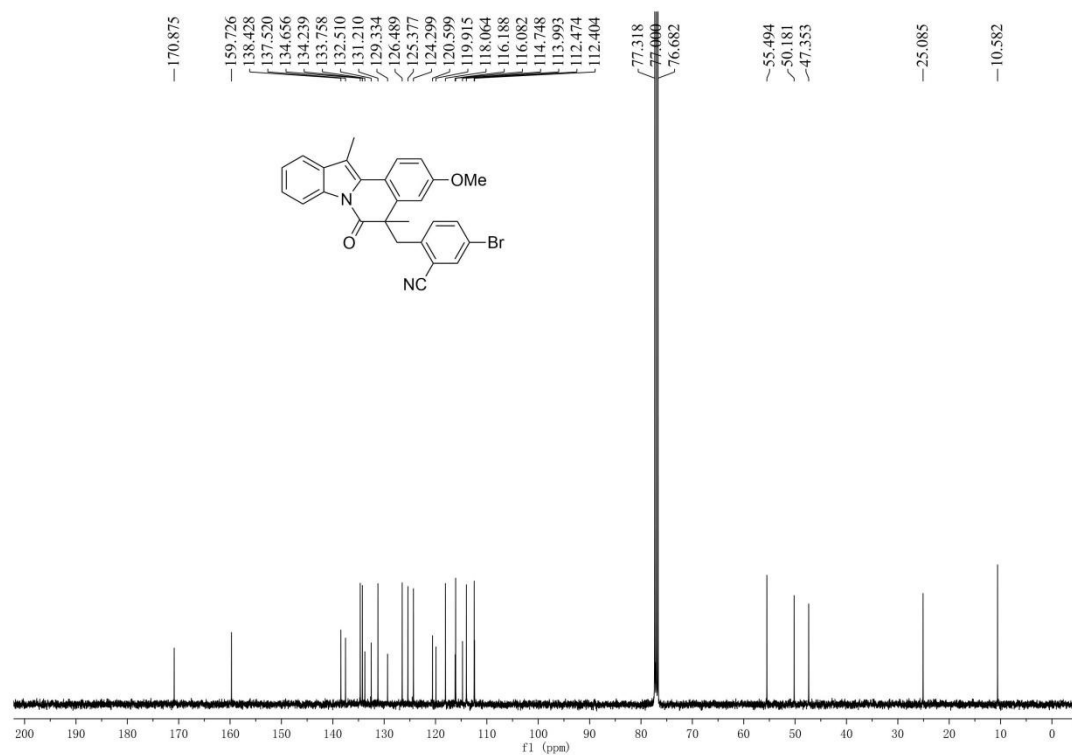
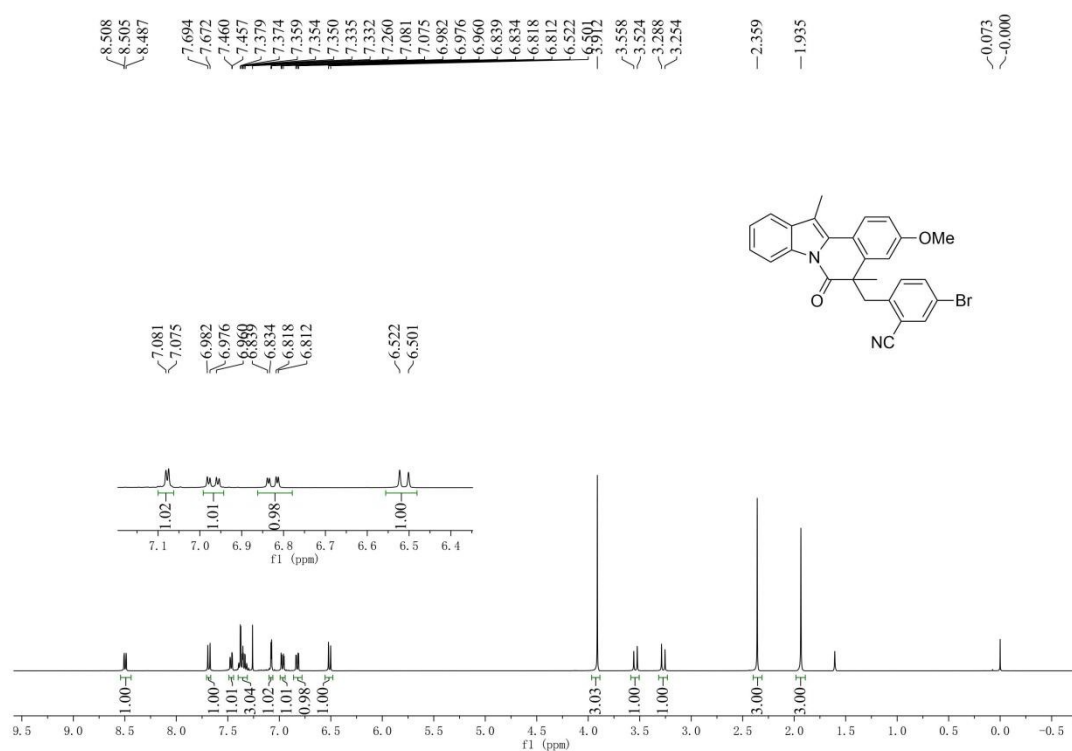
2-Bromo-6-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ad)



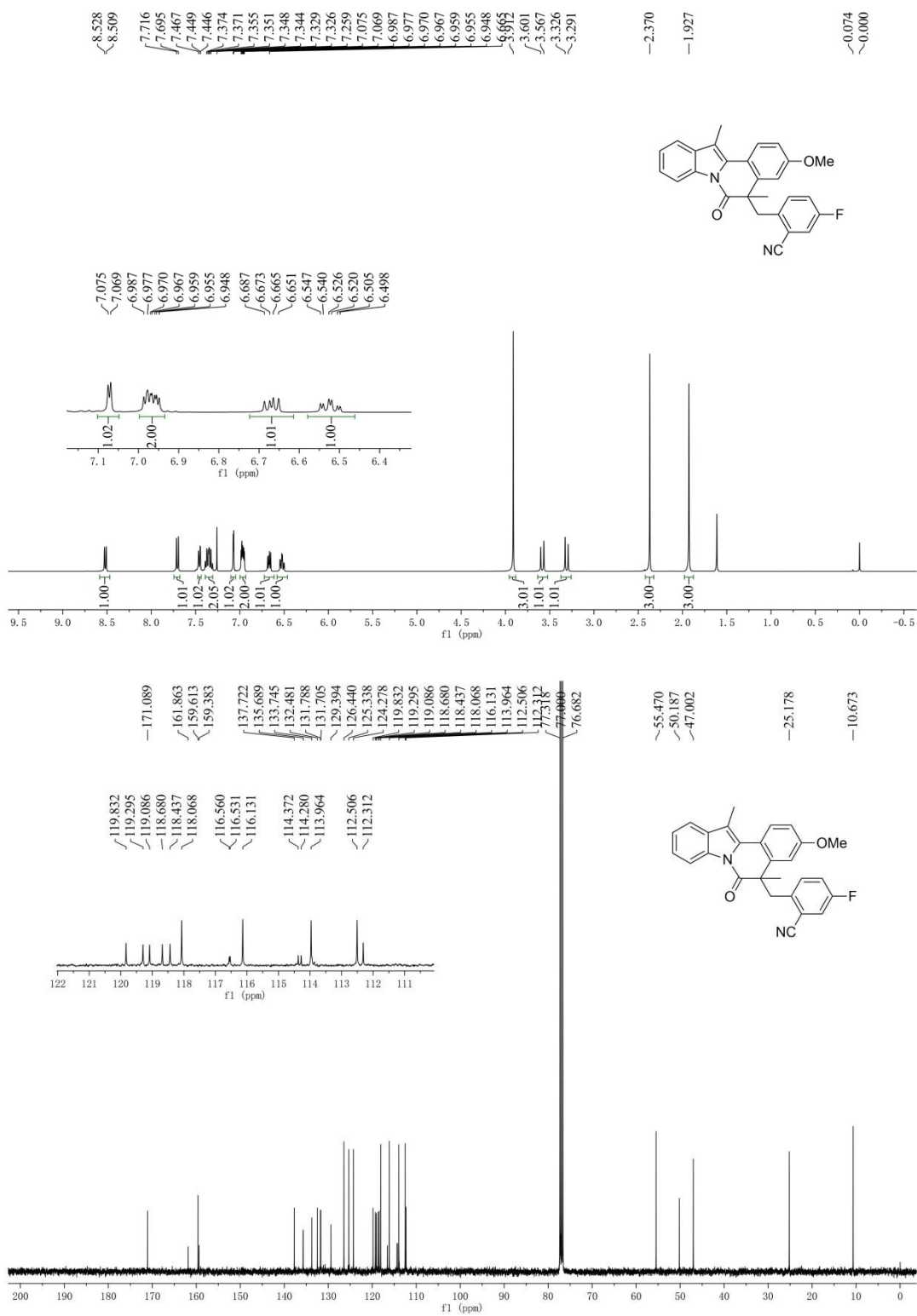
2-((3-Methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)-5-methylbenzonitrile (3ae)



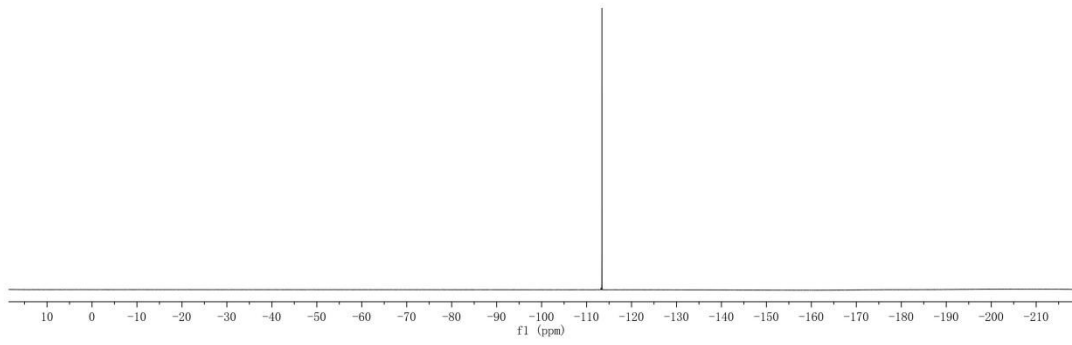
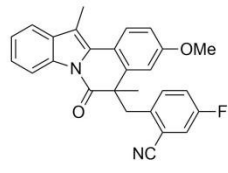
5-Bromo-2-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)methyl)benzonitrile (3af)



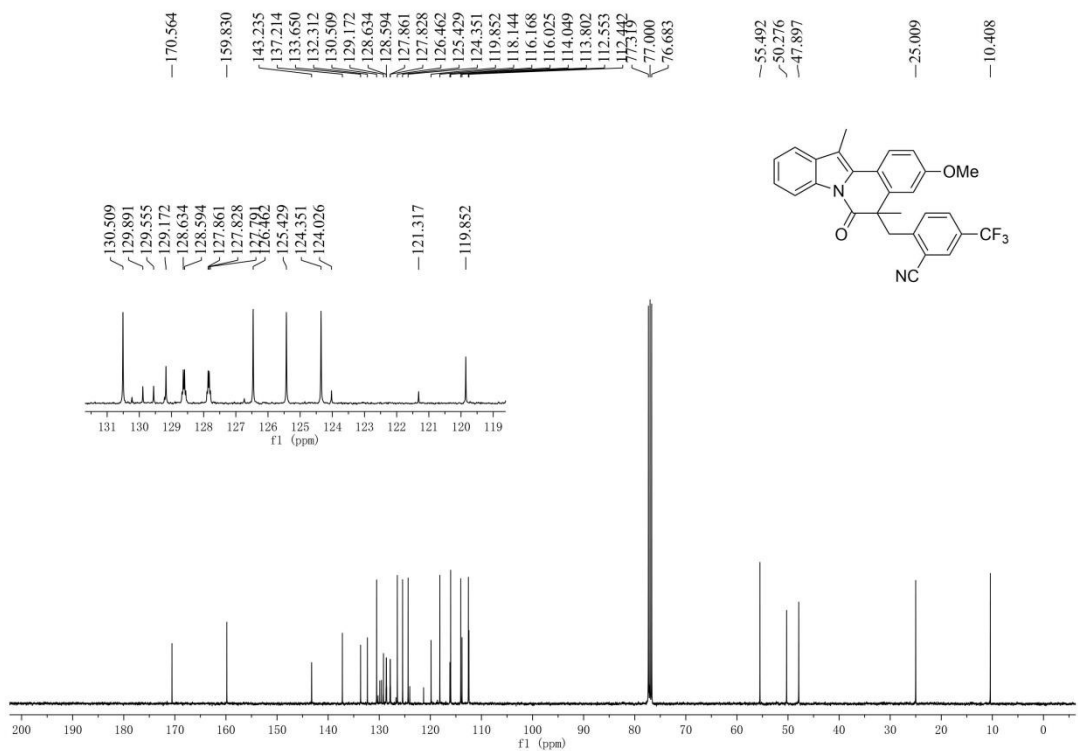
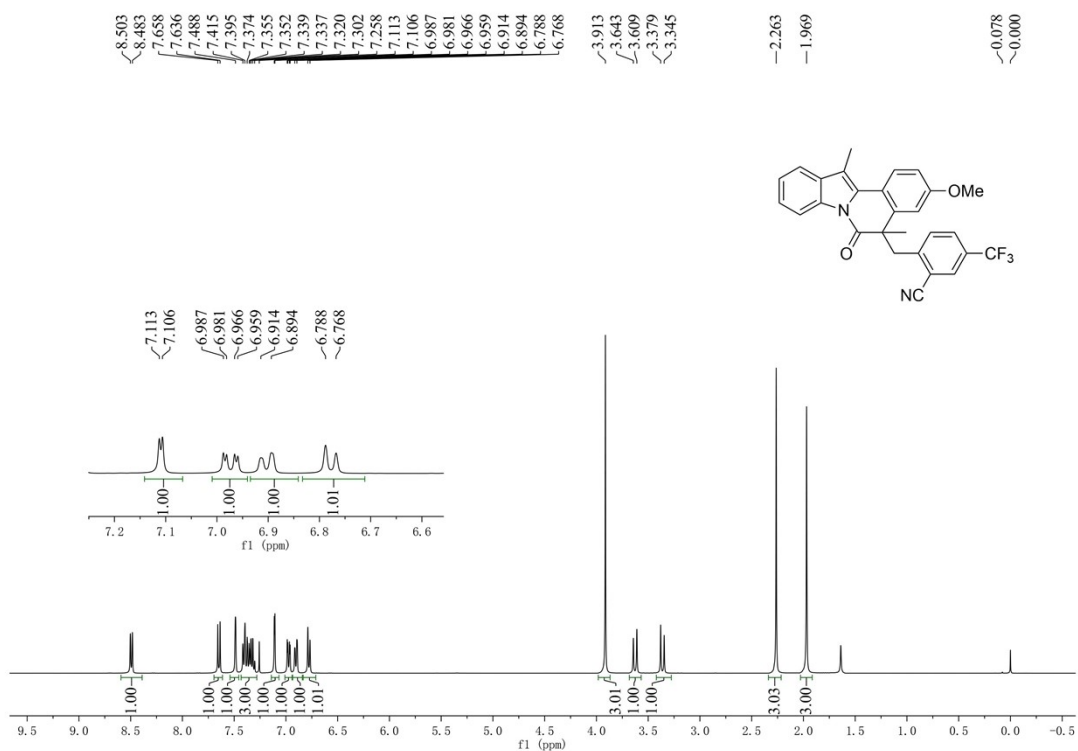
2-Fluoro-6-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ag)



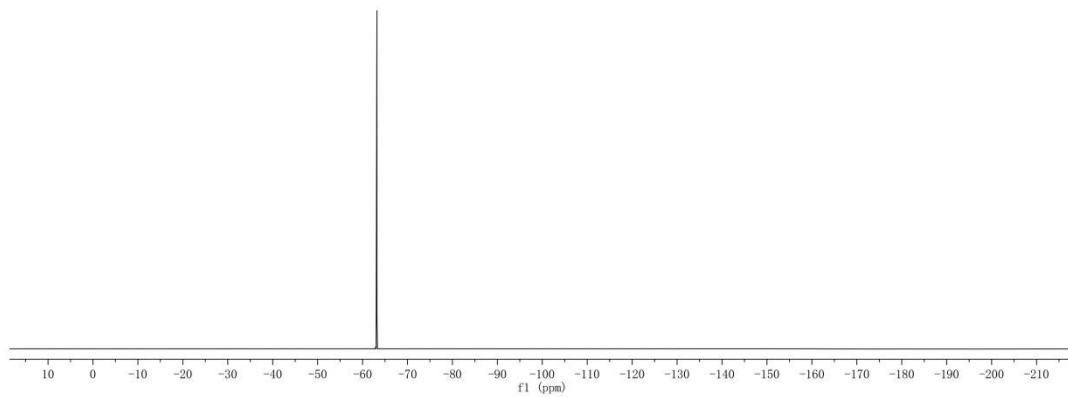
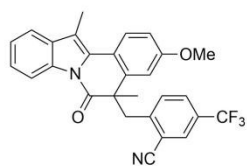
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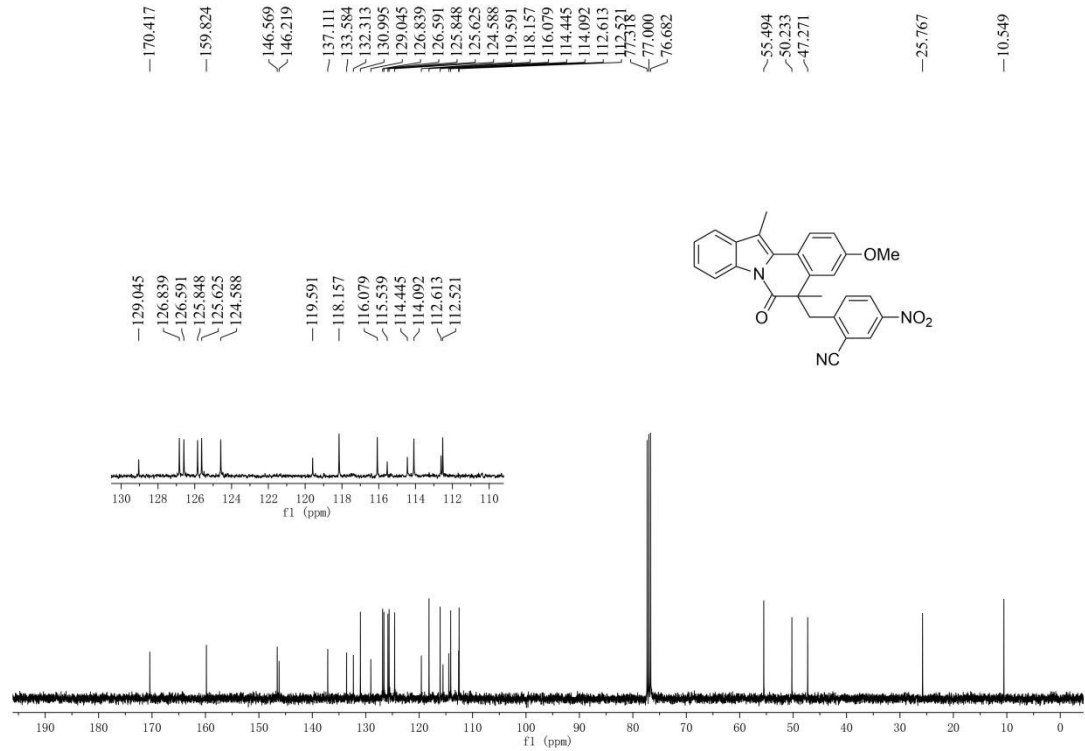
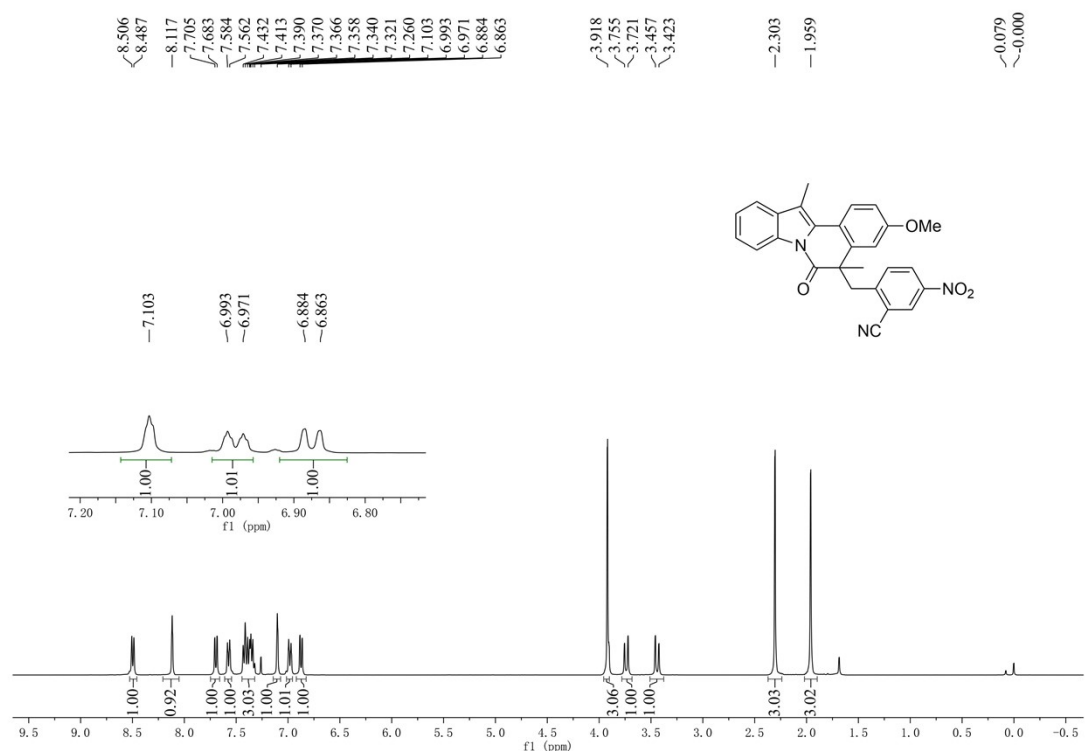
2-((3-Methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)-5-(trifluoromethyl)benzonitrile (3ah)



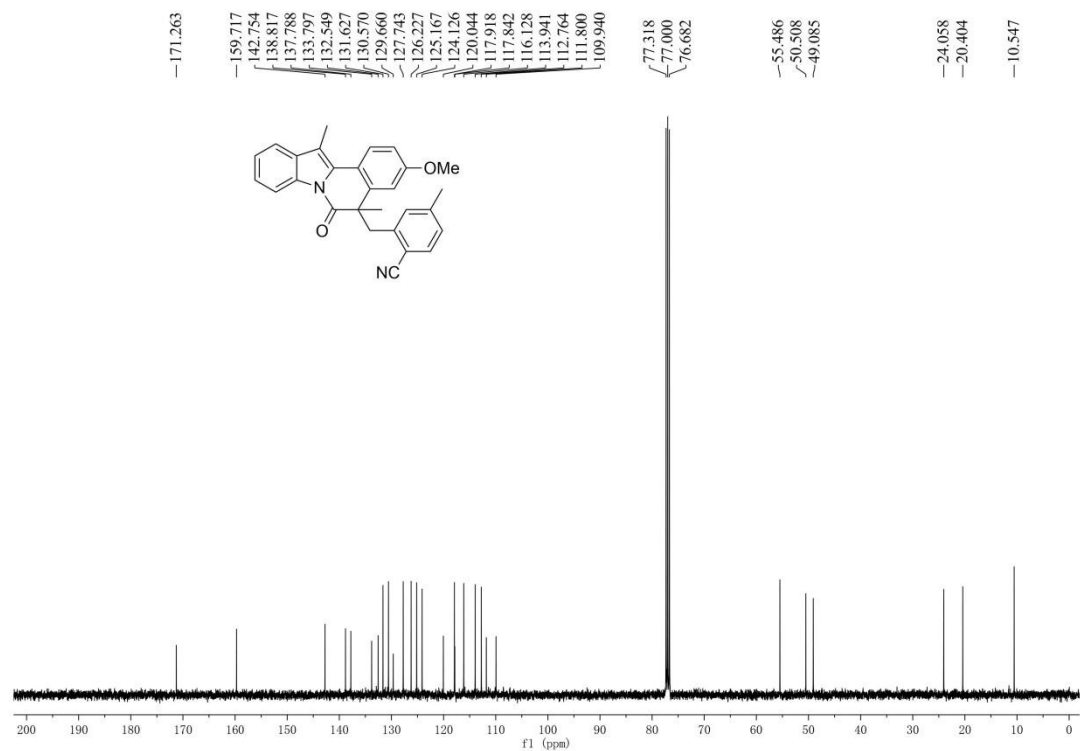
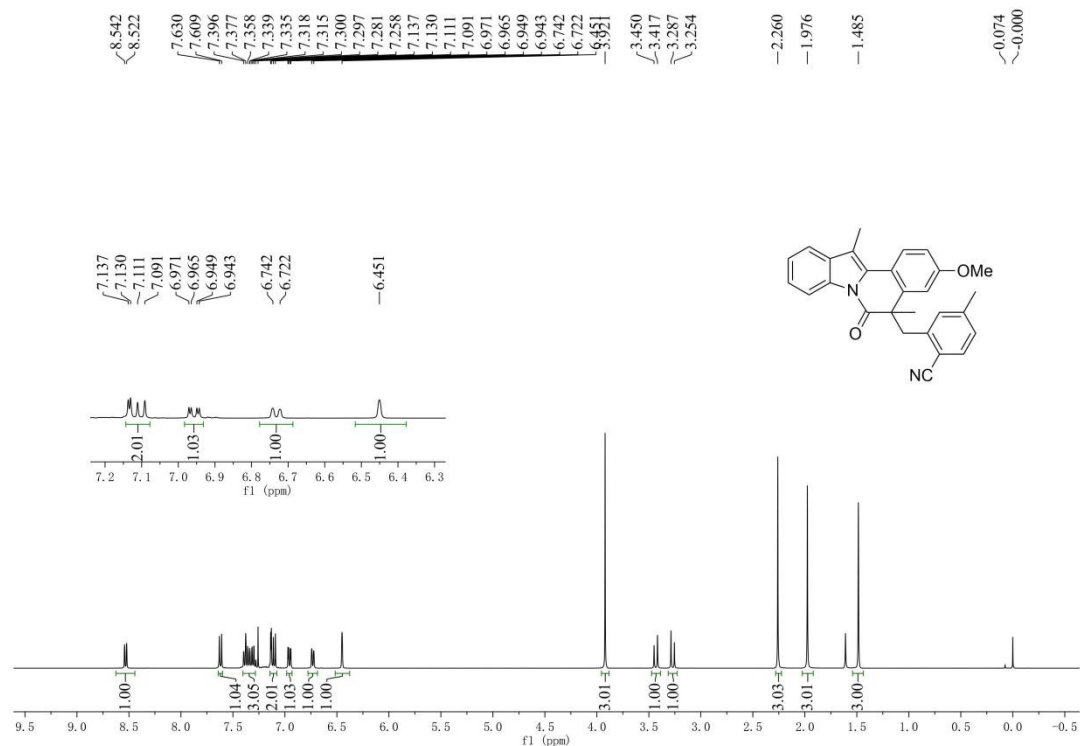
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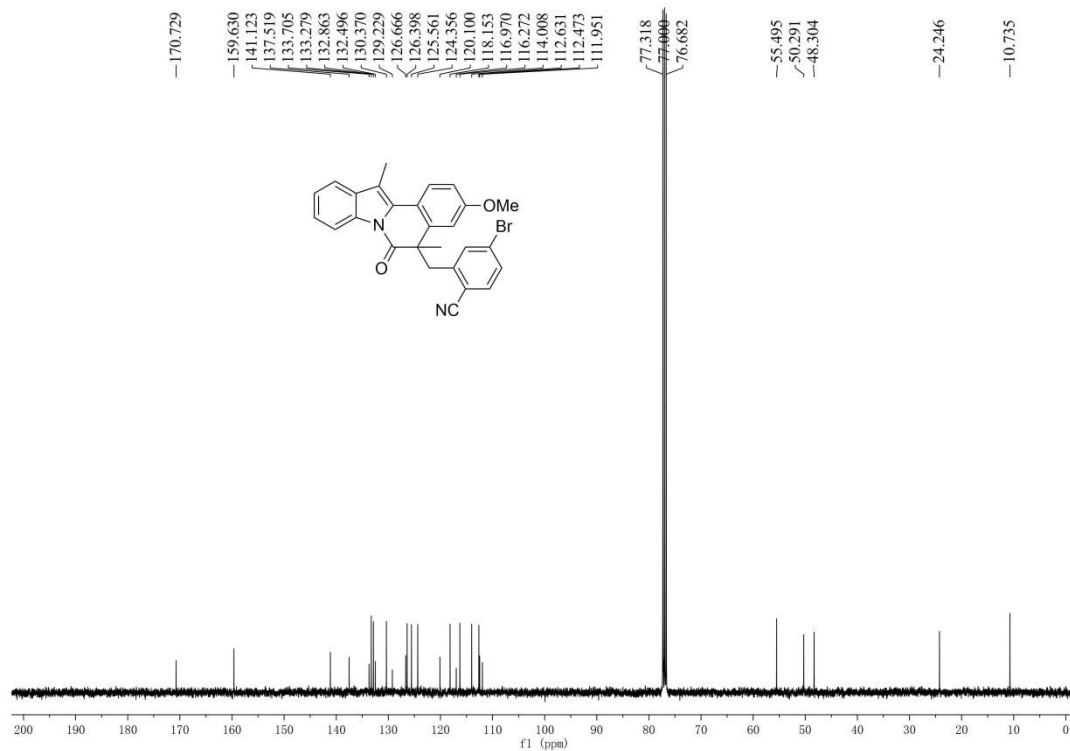
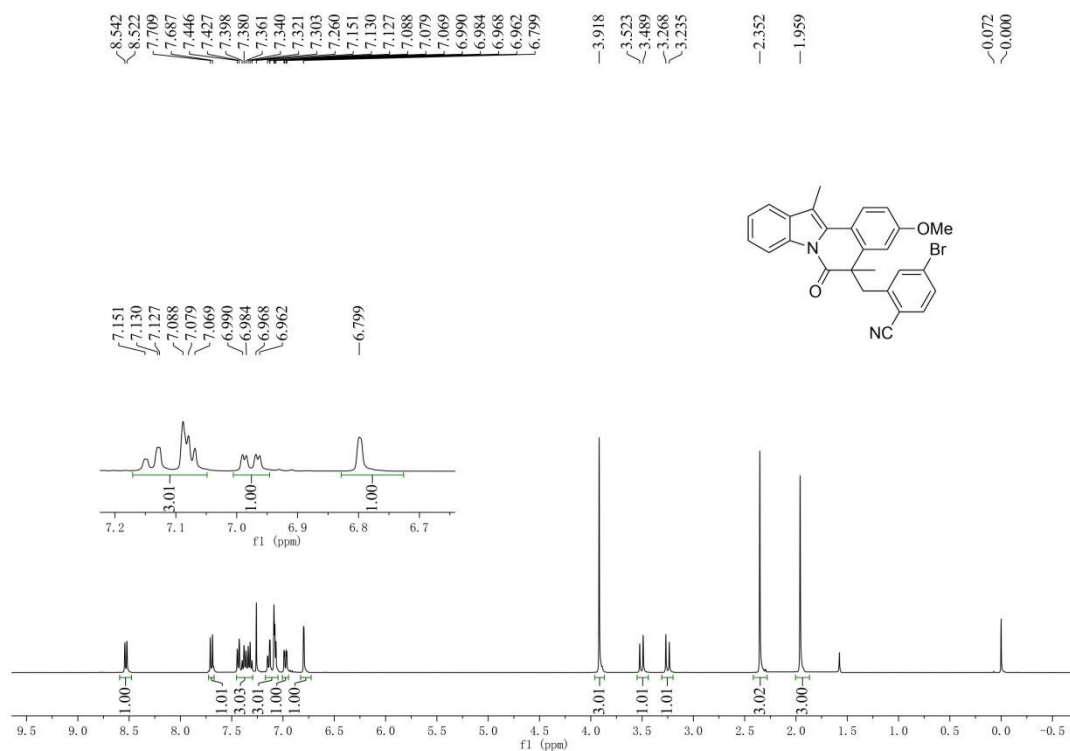
2-((3-Methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)-5-nitrobenzonitrile (3ai)



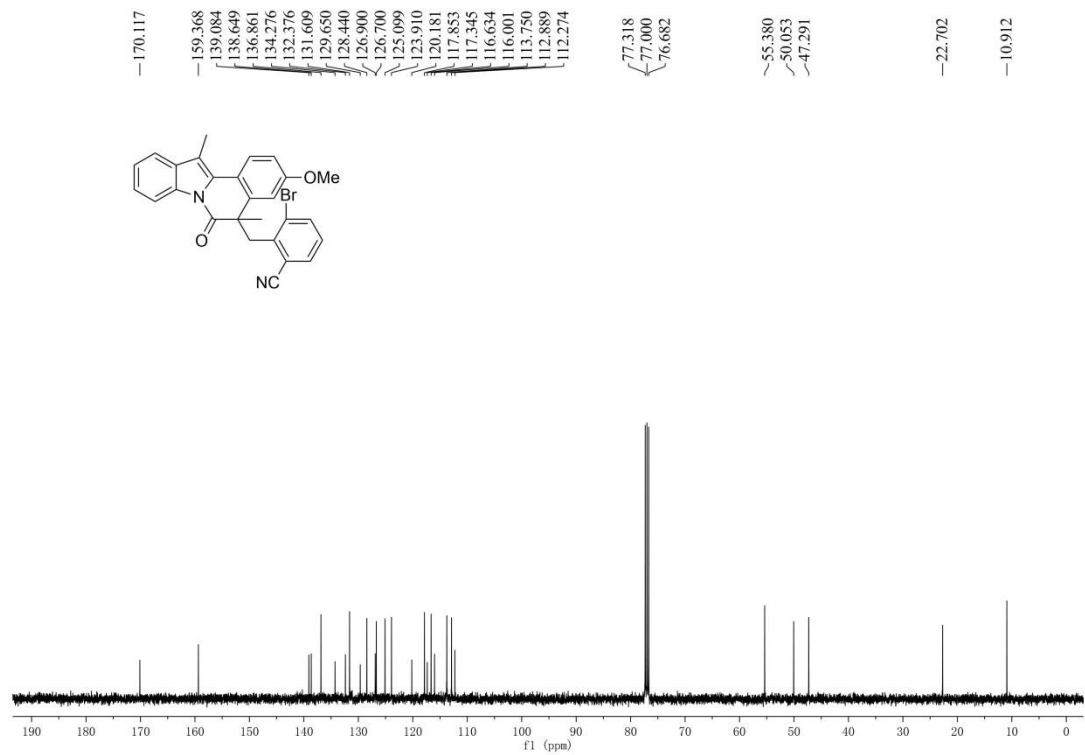
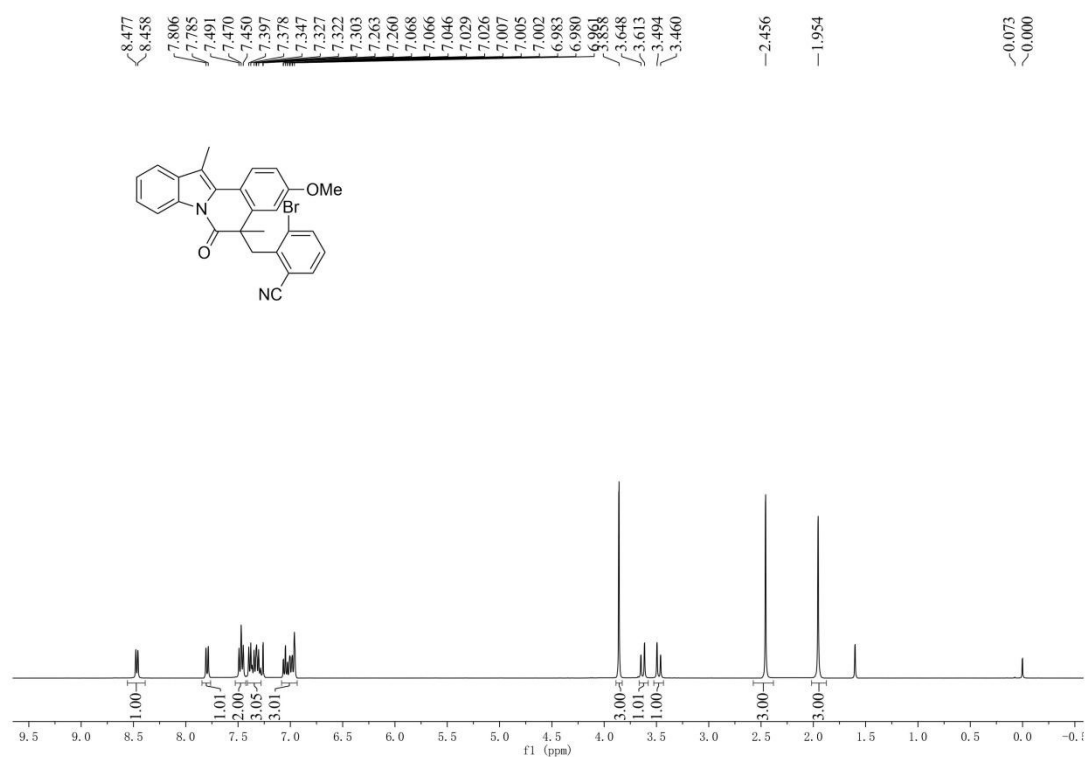
2-((3-Methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)-4-methylbenzonitrile (3aj)



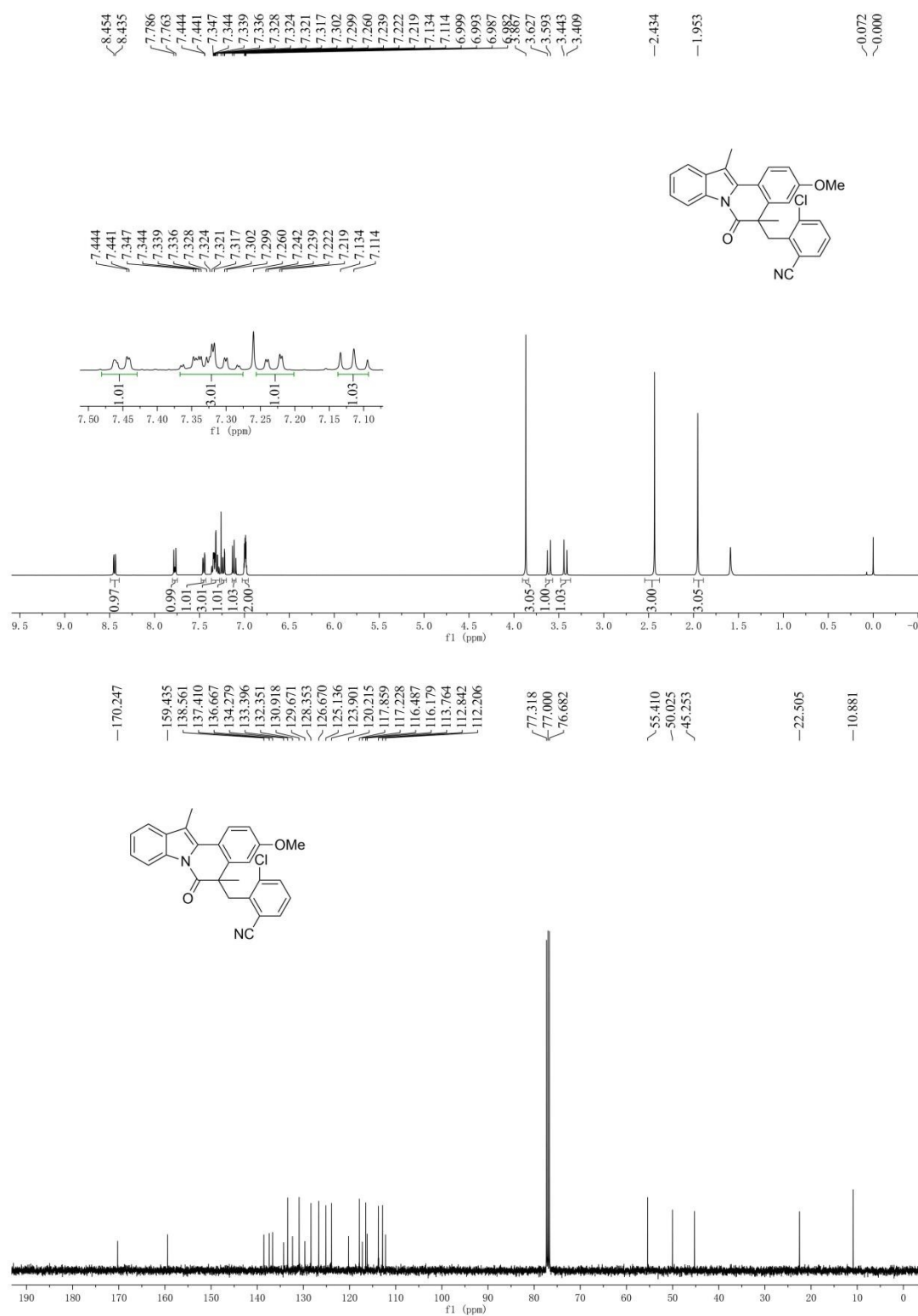
4-Bromo-2-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3ak)



3-Bromo-2-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)benzonitrile (3a)



3-Chloro-2-((3-methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)methyl)benzonitrile (3am)



2-((3-Methoxy-5,12-dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)nicotinitrile (3an)

