

TiCl₄/DMAP Mediated Z-Selective Knoevenagel Condensation of Isatins with Nitroacetates and Related Compounds

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Table of contents

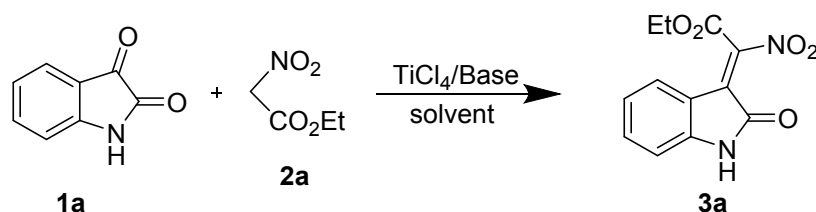
I. General information:	S2
II. Optimization of reaction conditions:.....	S3
III. Control experiments:	S4
IV. NMR spectra of products	S6

I. General information: Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate.

Flash column chromatography was performed using Merck aluminium oxide 90 active neutral with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

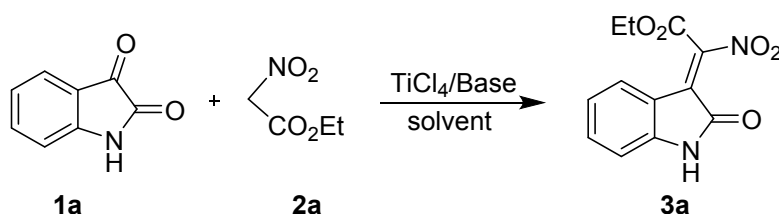
Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on Bruker AMX 400 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (0.0) and relative to the signal of chloroform-d (7.26, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (0.0) and relative to the signal of chloroform-d (77.0, triplet). Mass spectra (EI-MS) were acquired on an Agilent 5975 spectrometer. Analytical thin layer chromatography (TLC) was performed on Merckprecoated TLC (silica gel 60 F254) plates.

II. Optimization of reaction conditions:



To a stirred solution of isatin (**1a**, 0.5 mmol, 1.0 equiv) in anhydrous THF, TiCl_4 (0.75 mmol, 1.5 equiv) and ethyl nitroacetate (**2a**, 0.5 mmol, 1.0 equiv) were added slowly at 0 °C, then DMAP (1.5 mmol, 3.0 equiv) was added, the resulting mixture was stirred at rt. After the reaction was complete, (monitored by TLC), DCM (10 mL) was added and the mixture was filtered through a pad of celite. The celite was washed by DCM (5.0 mL each time) for two times, and the combined organic layers were dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **3a**.

Table 1 Reaction condition optimization.[a]



Entry	Base	solvent	time [h]	Yield [%] ^[b]	Z/E ^[c]
1	Et_3N (3.0)	THF	8	65	2:1
2	<i>n</i> - Bu_3N (3.0)	THF	8	55	2:1
3	DBU (3.0)	THF	8	67	1.5:1
4	DIEPA (3.0)	THF	8	88	1.5:1
5	NMM ^[d] (3.0)	THF	8	85	2:1
6	Pyridine (3.0)	THF	8	68	6:1
7	DMAP (3.0)	THF	8	88	8:1
8	CsCO_3 (3.0)	THF	24	- ^[e]	-
9	Na_2CO_3 (3.0)	THF	24	-	-
10	DMAP (3.0)	DCM	24	trace	-
11	DMAP (3.0)	Et_2O	24	32	2:1
12	DMAP (3.0)	toluene	24	trace	-

[a] All reactions were carried out with 1.0 equiv (0.5 mmol) of **1a**, 1.0 equiv (0.5 mmol) of

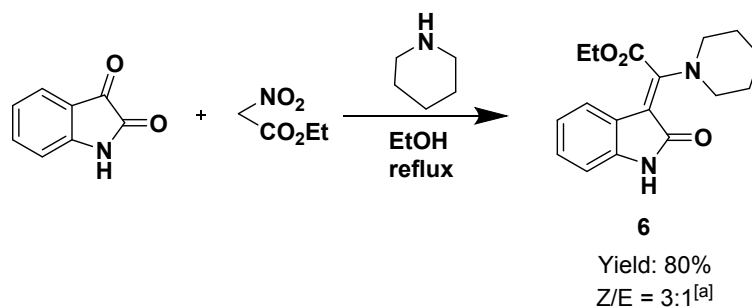
2a, TiCl₄ and base at room temperature. [b] Yields of isolated product after column chromatography. [c] Determined by ¹HNMR analysis. [d] NMM = N-Methylmorpholine. [e] No reaction.

Table 2 Reaction condition optimization[a]

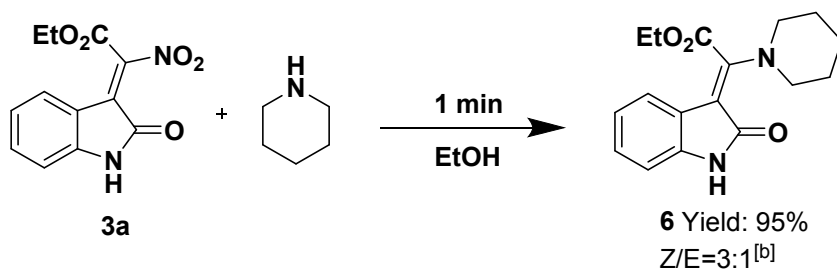
Entry	DMAP (equiv)	TiCl ₄ (equiv)	Time	Yield [%] ^[e]	trans/cis ^[f]
1	-	1.5	24	-	-
2	3.0	-	24	-	-
3	<1.5	1.5	24	-	-
4	2.0	1.5	24	90	9:1
5	2.5	1.5	8	72	9:1
6	3.0	1.5	8	90	9:1
7	4.0	1.5	8	78	9:1
8	3.0	1.0	24	43	2:1
9	3.0	2.0	8	82	6:1
10	3.0	3.0	24	61	3:1

[a] All reactions were carried out with 1 equiv (0.5 mmol) of **1a**, 1 equiv (0.5 mmol) of **2a**, different equiv TiCl₄ and DMAP at room temperature. [e] Isolated yields after column chromatography. [f] Determined by ¹HNMR analysis.

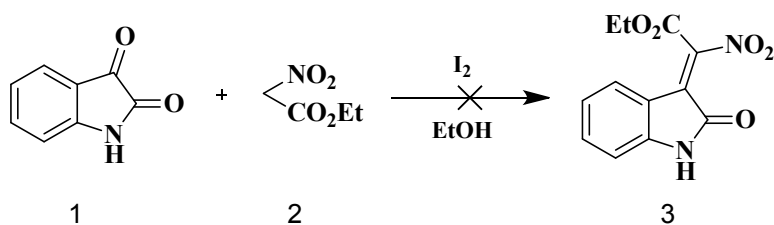
III. Control experiments:



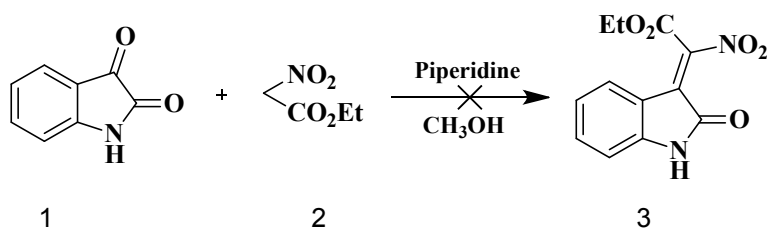
Ethyl Nitroacetate (0.5 mmol, 1.0 equiv) was added to a solution of isatin (0.5 mmol, 1.0 equiv.) in ethanol, followed by addition of Piperidine (1.5 mmol, 3 equiv.), the resulting reaction mixture was stirred under 80°C. After the reaction was complete (monitored by TLC), the reaction was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **6** in high yield.



[b] Piperidine (1.5mmol, 3equiv.) was added to a solution of (Z)-ethyl 2-nitro-2-(2-oxoindolin-3-ylidene)acetate(3f, 0.5mmol, 1.0equiv.) inEthanol, the resulting reaction mixture was stirred under air 1 mintue. After the reaction was complete, (monitored by TLC) concentrated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane) to provide **6**.

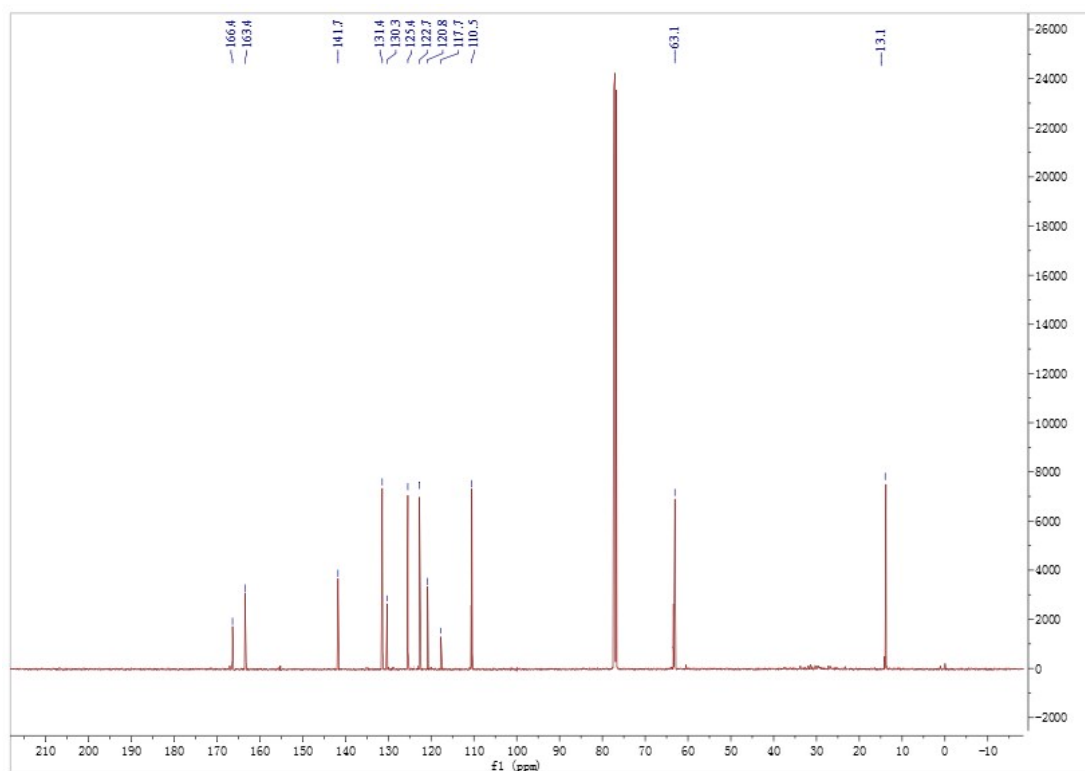
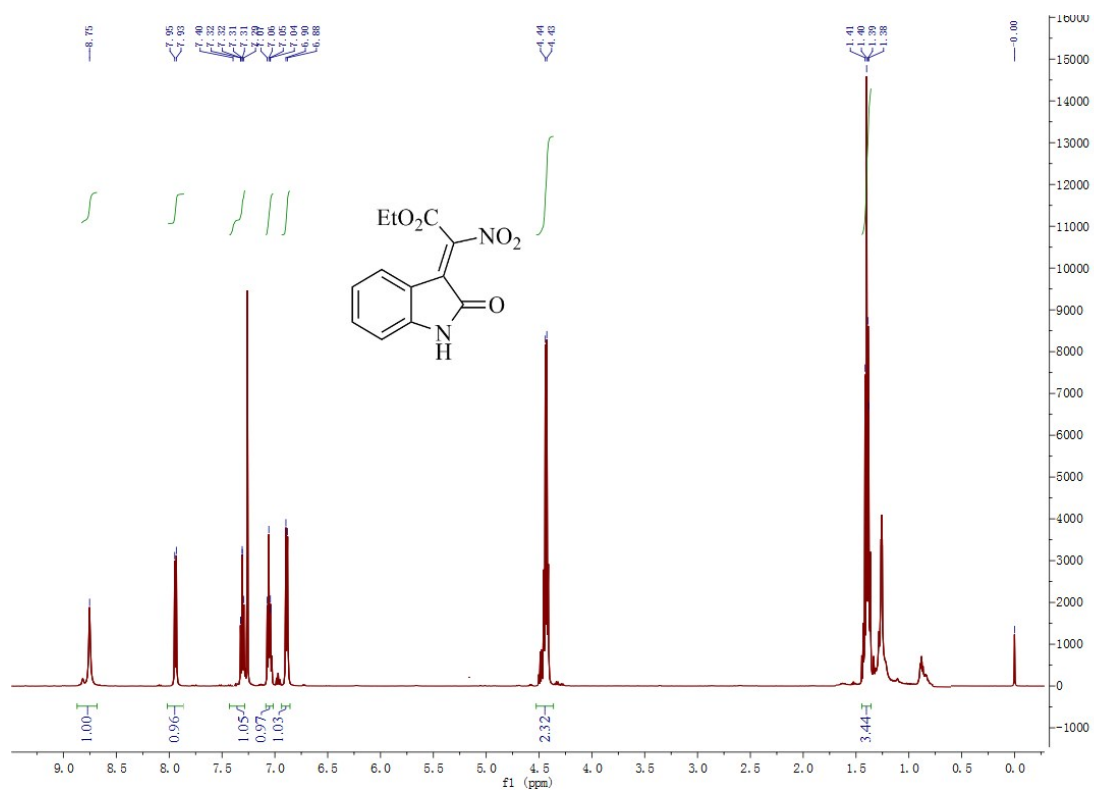


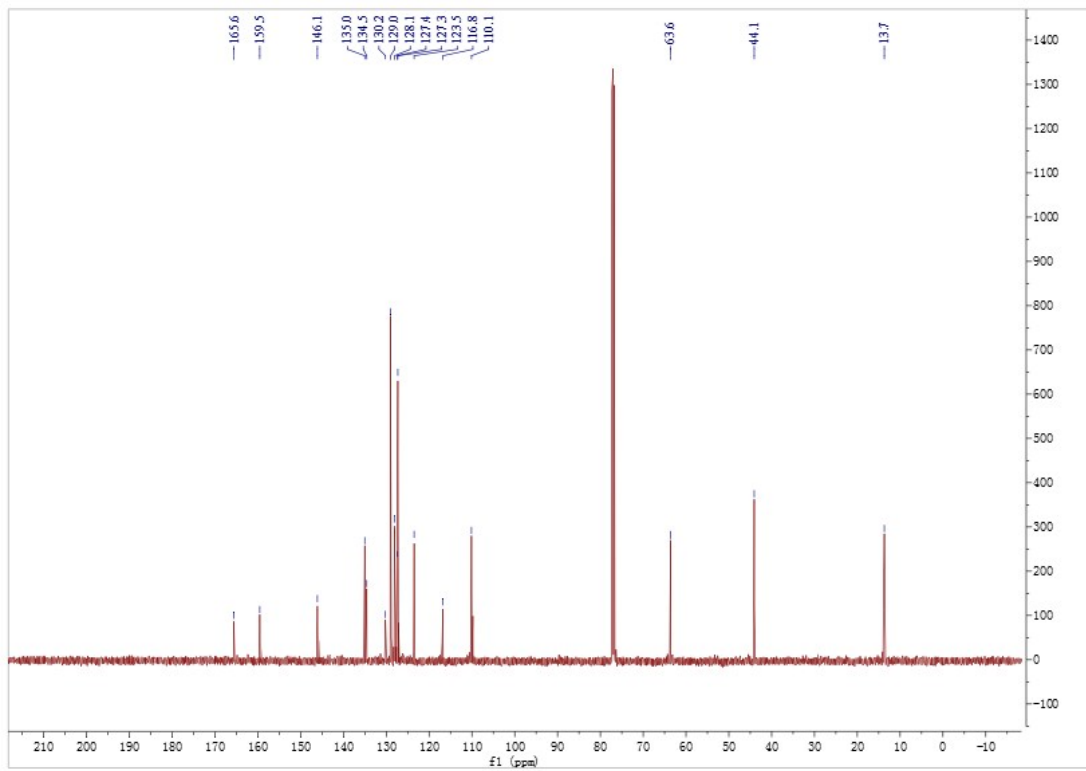
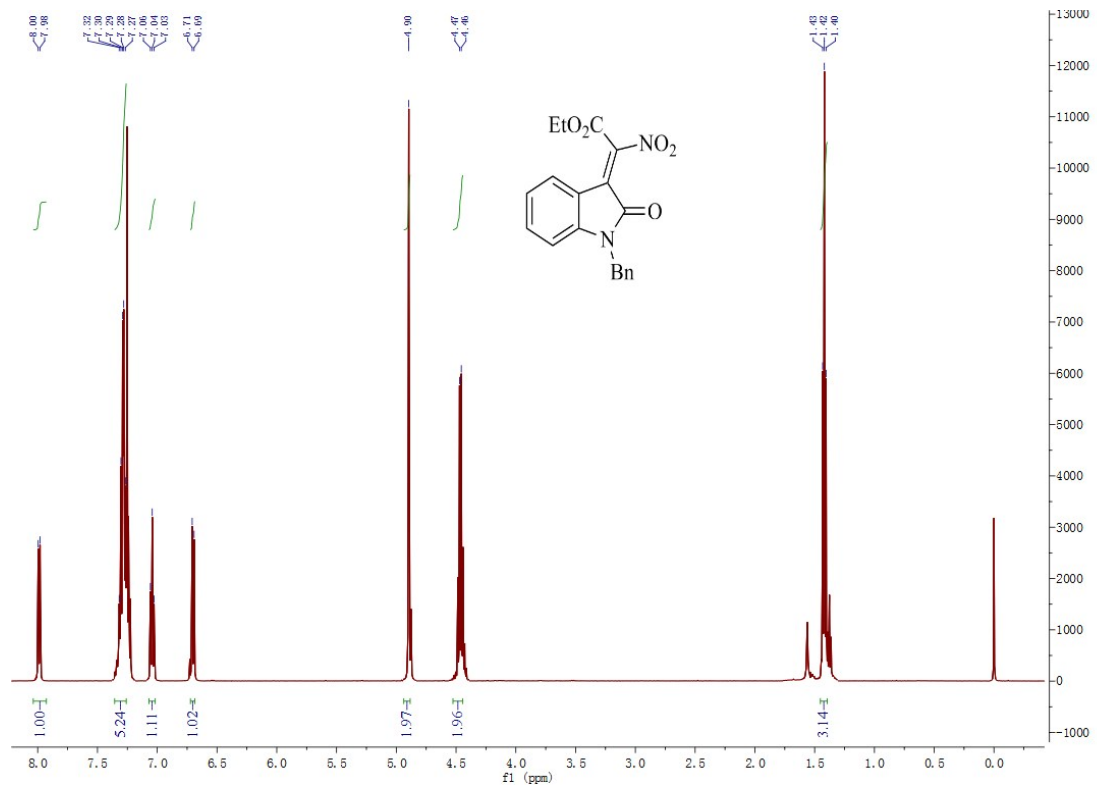
Ethyl Nitroacetate (**1**, 0.5mmol, 1.0 equiv.) was added to a solution of Isatin(**2**, 0.5mmol, 1.0equiv.) inEthanol, followed by addition of I_2 (1.5mmol, 3equiv.), the resulting reaction mixture was stirred under air at rt for 24 hours.

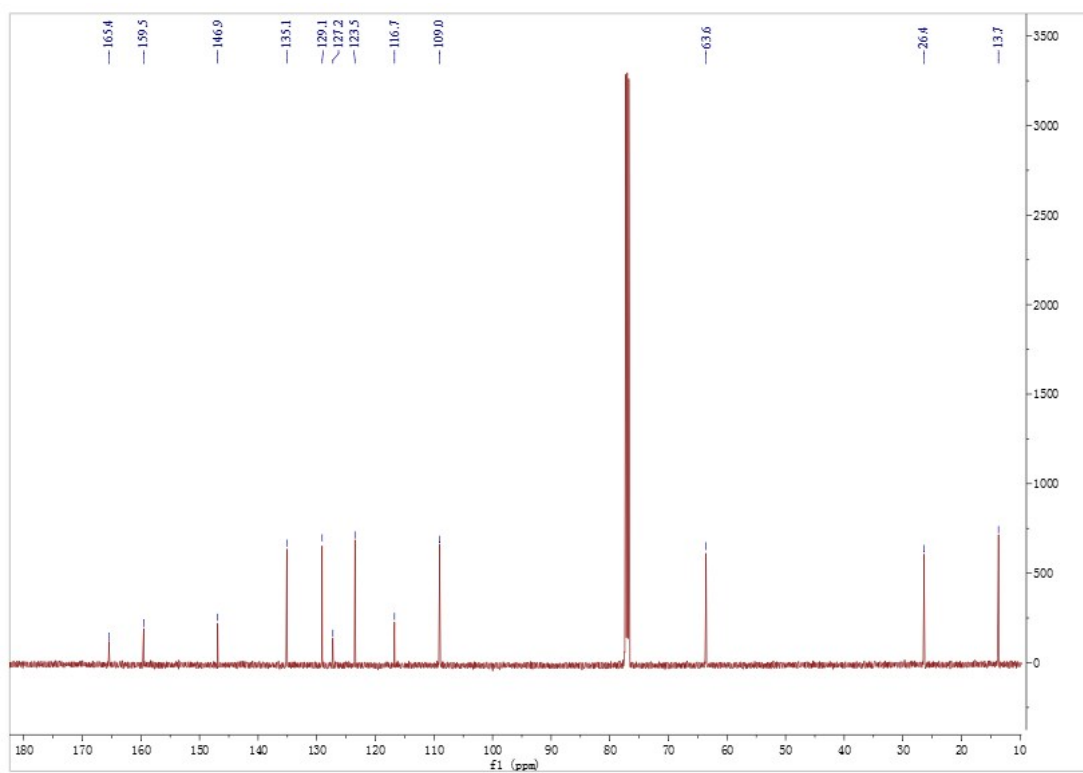
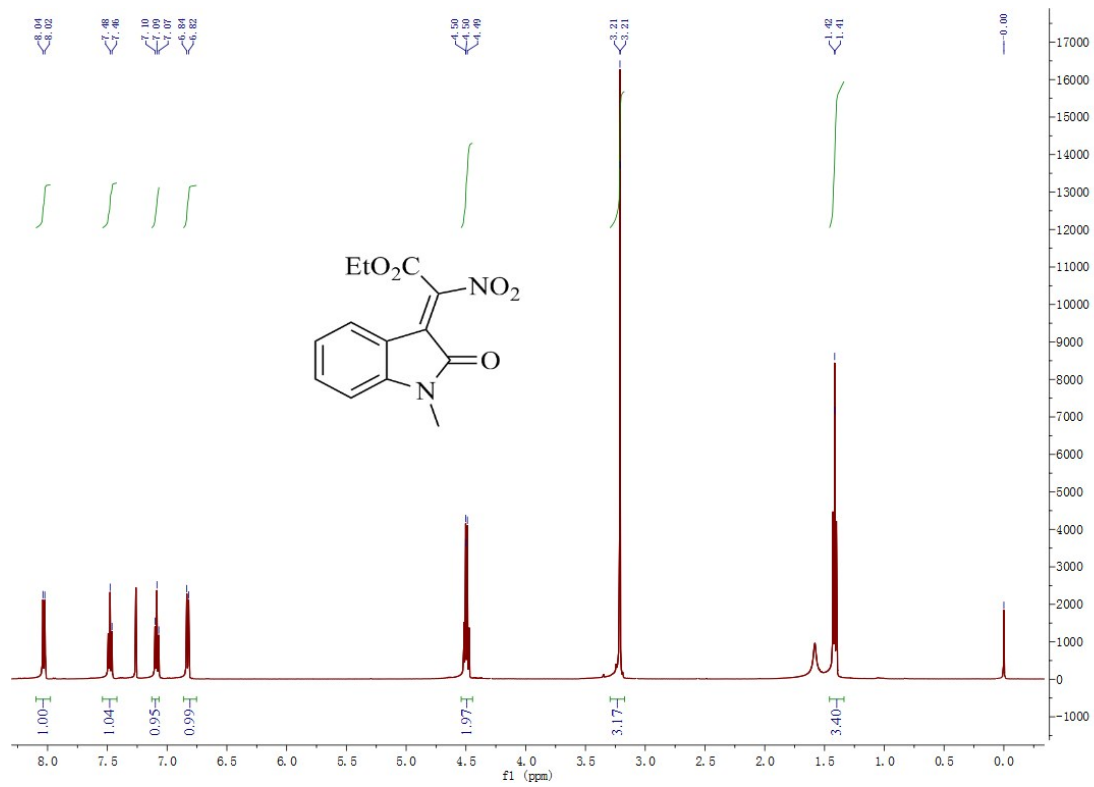


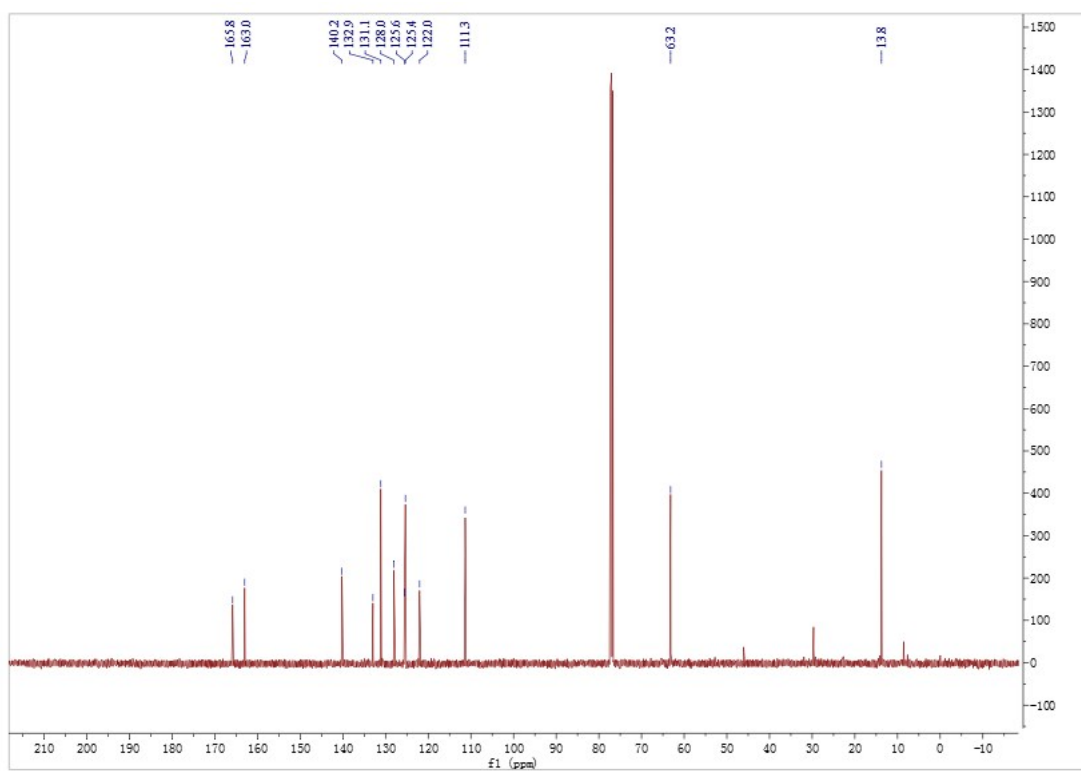
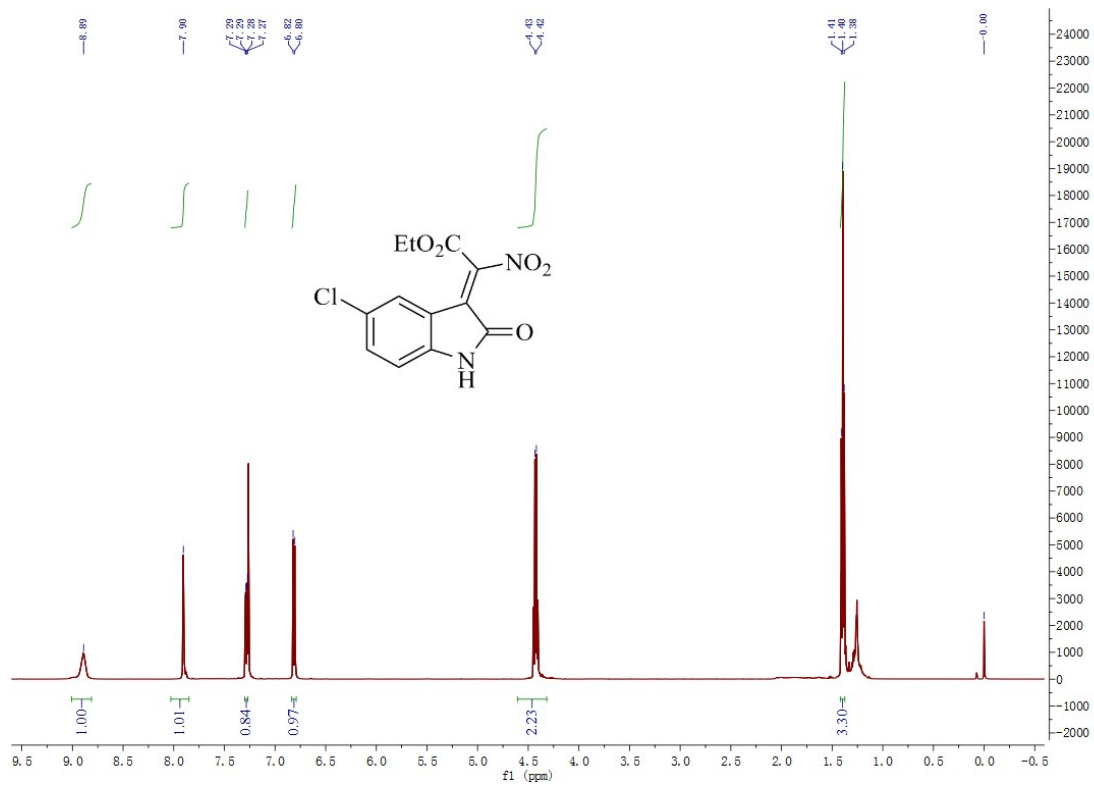
Ethyl Nitroacetate (**1**, 0.5mmol, 1.0 equiv.) was added to a solution of Isatin (**2**, 0.5mmol, 1.0 equiv.) in Methanol, followed by addition of Piperidine (1.5 mmol, 3 equiv.), the resulting reaction mixture was stirred under air at rt for 24 hours.

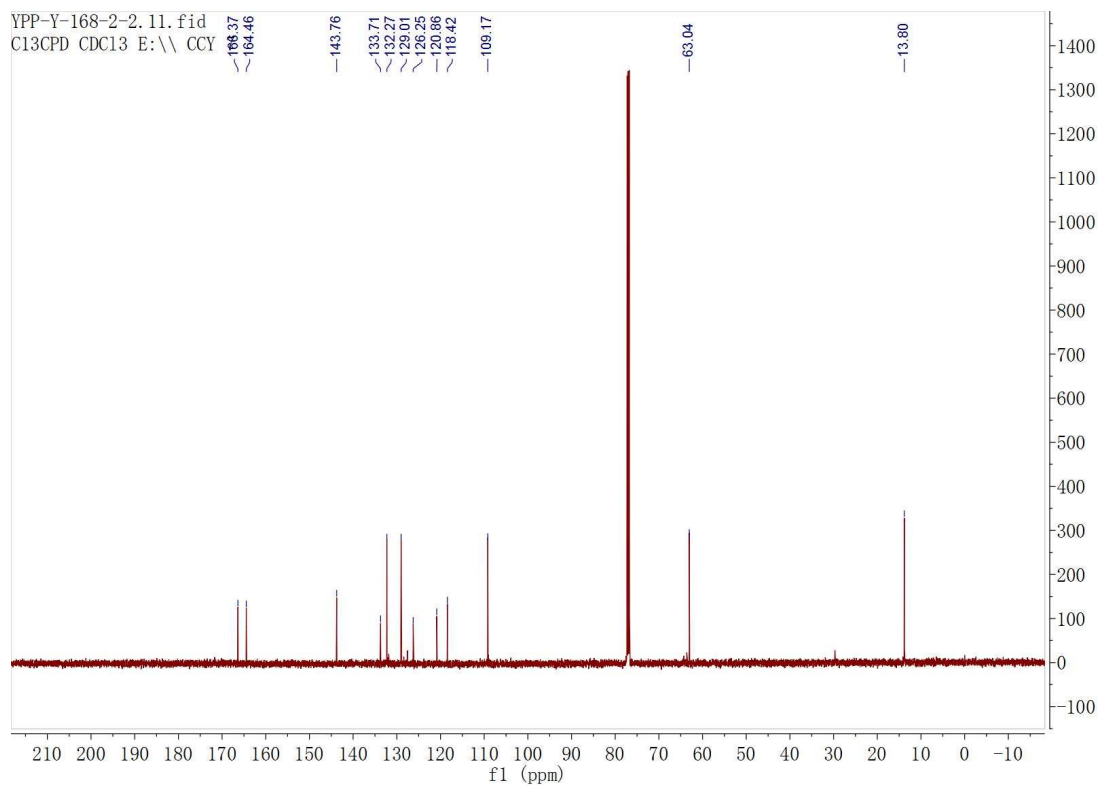
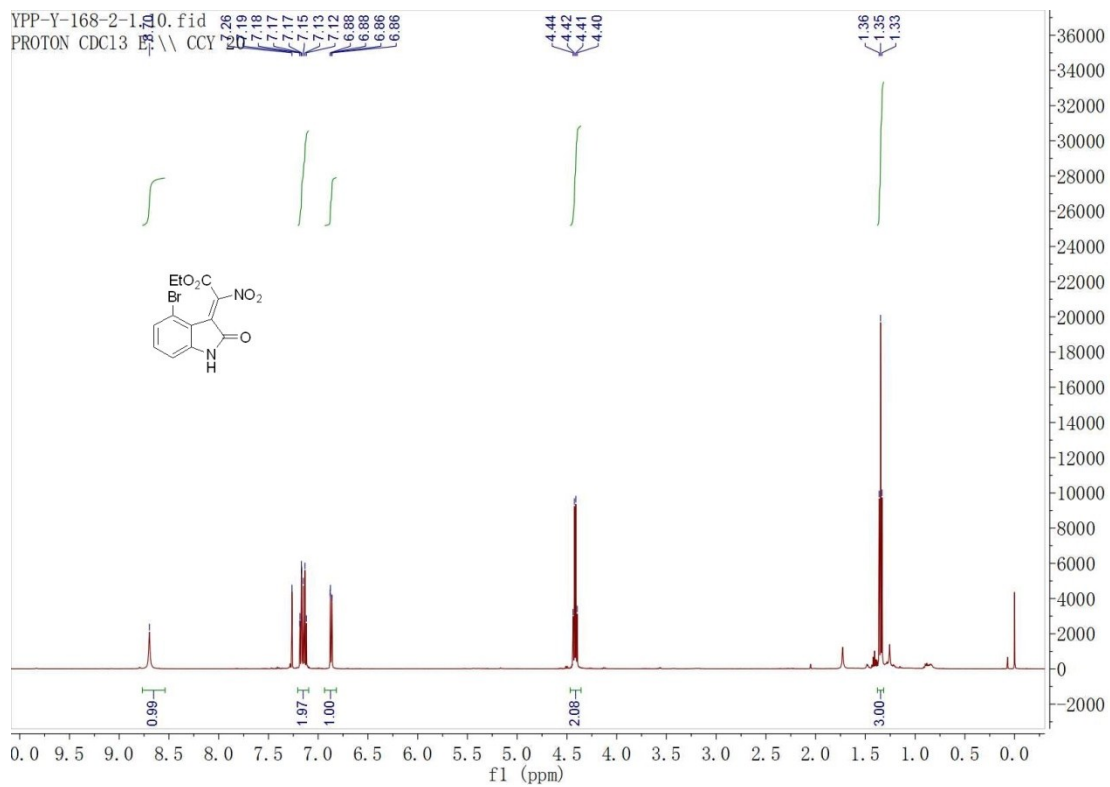
IV. NMR spectra of products

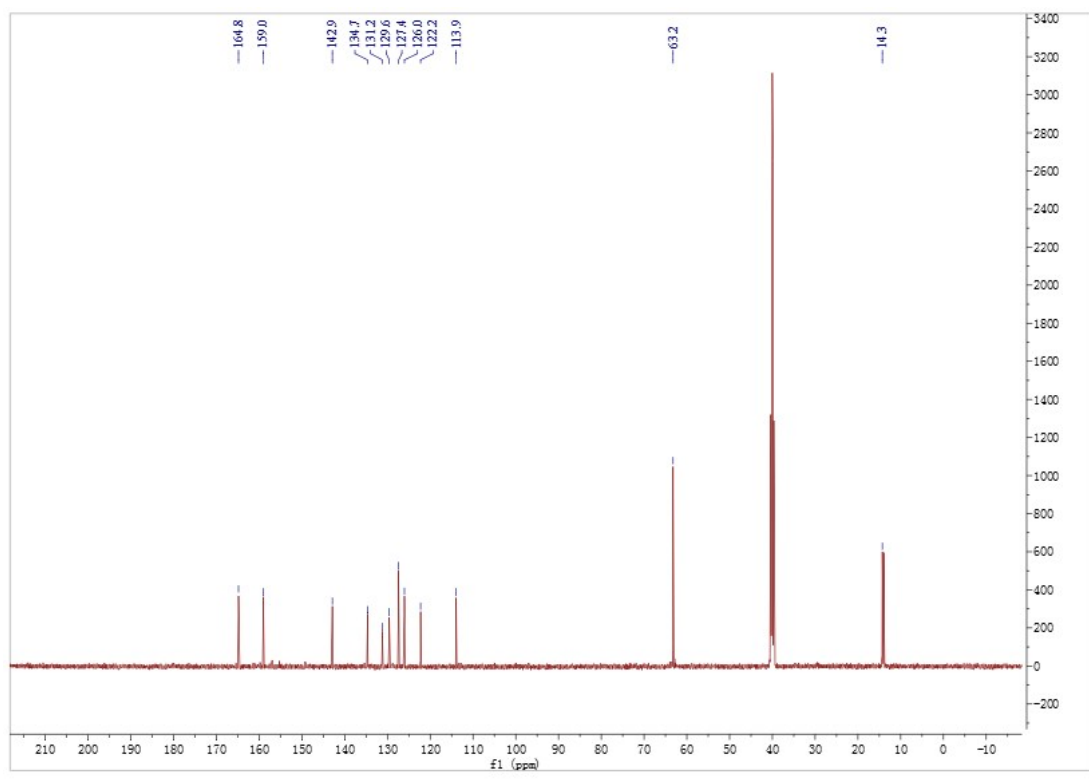
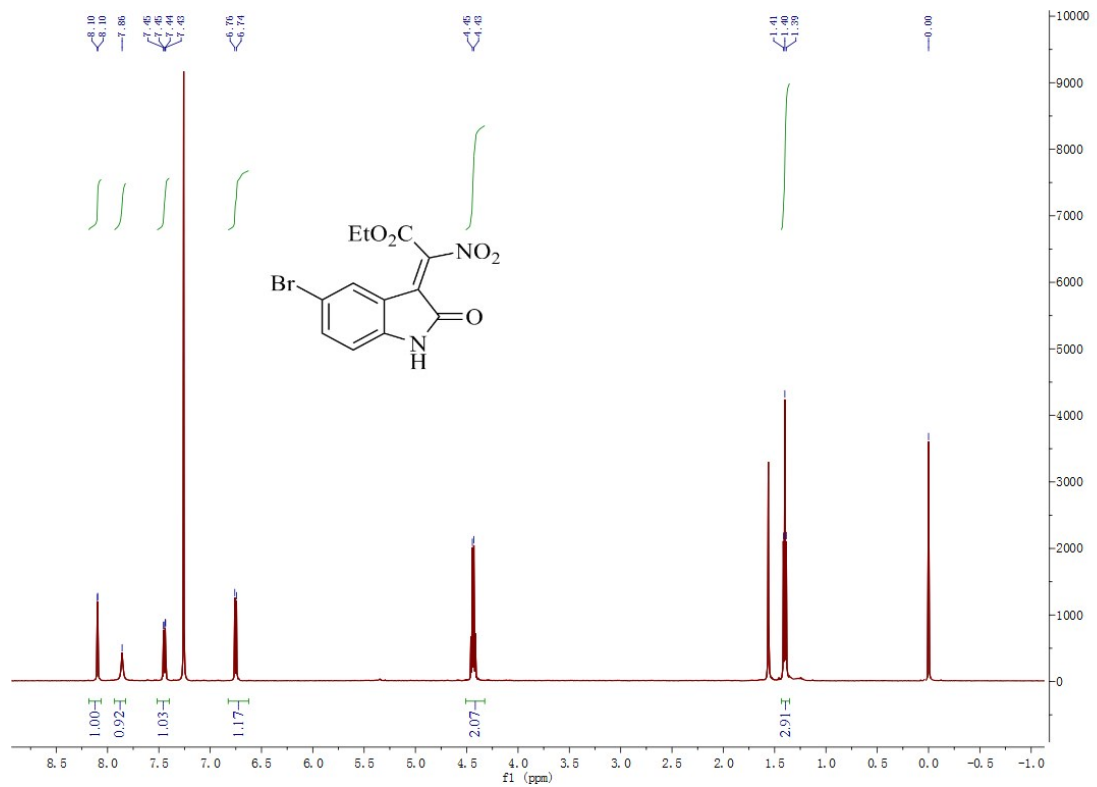


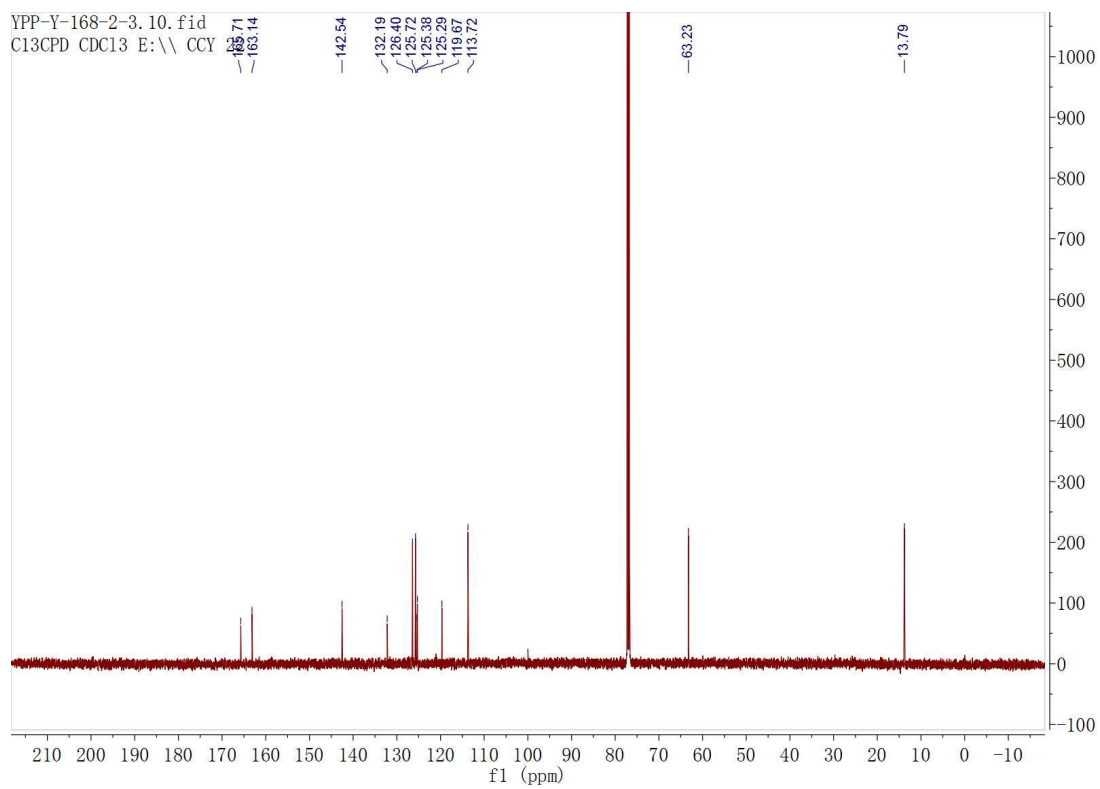
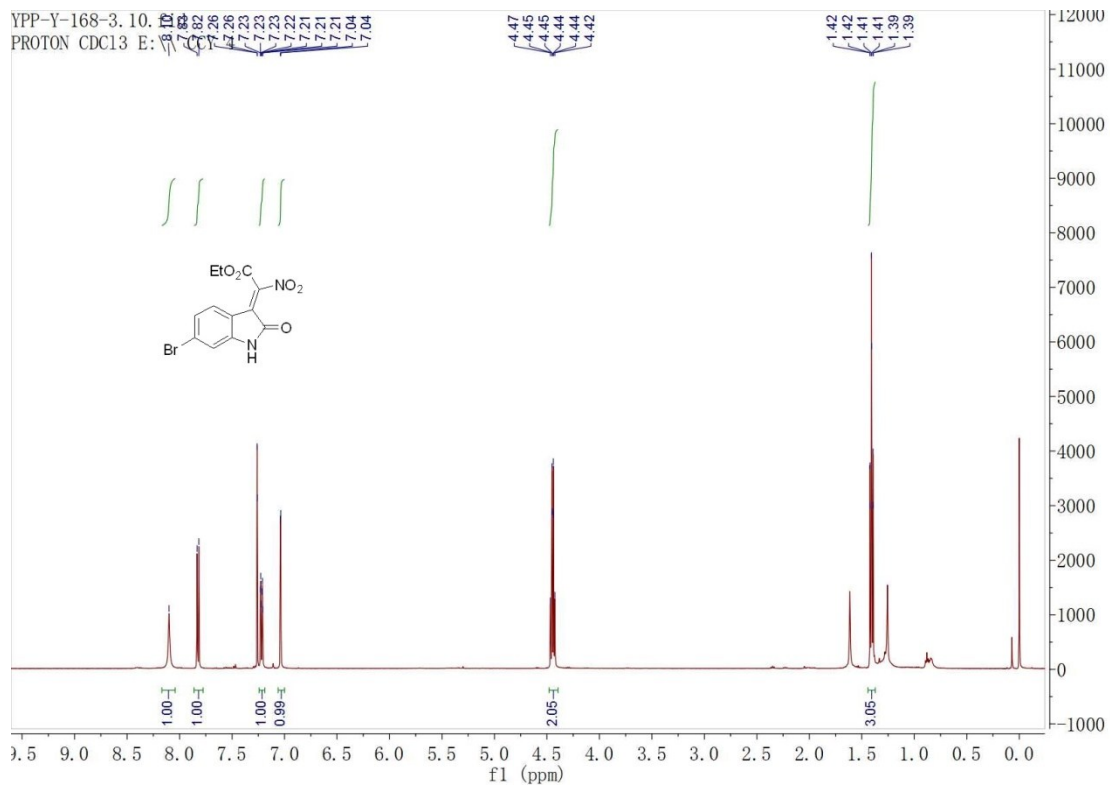


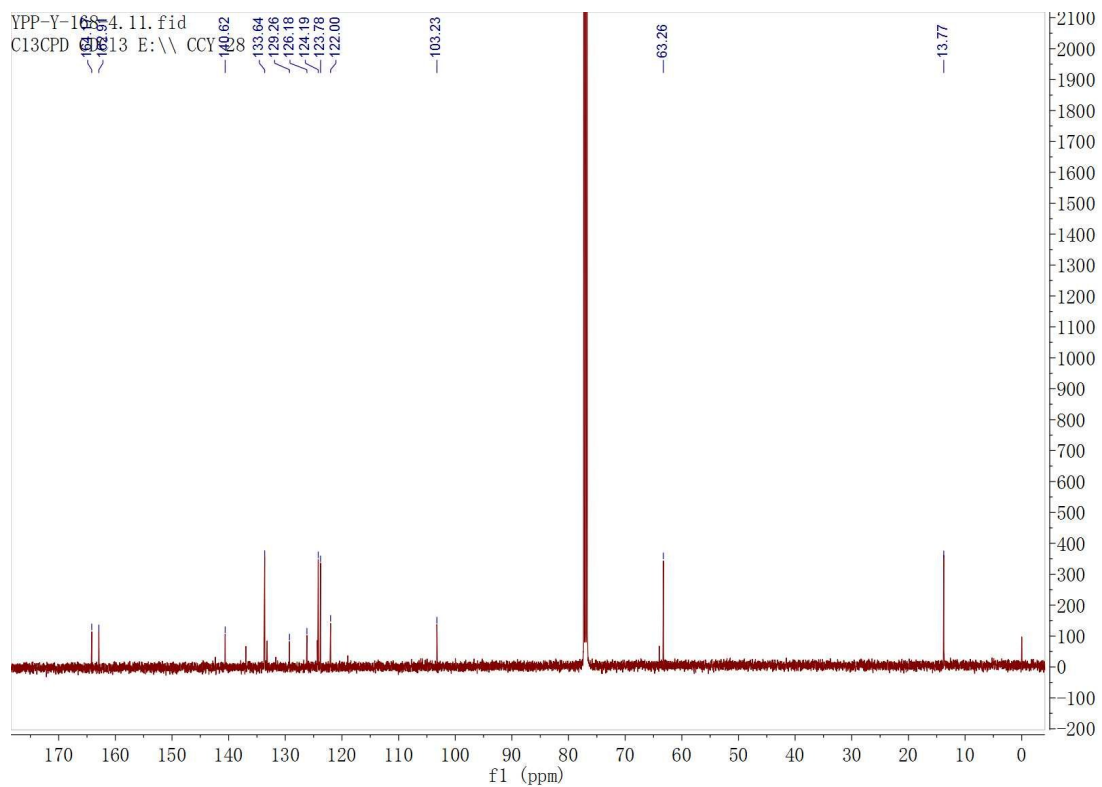
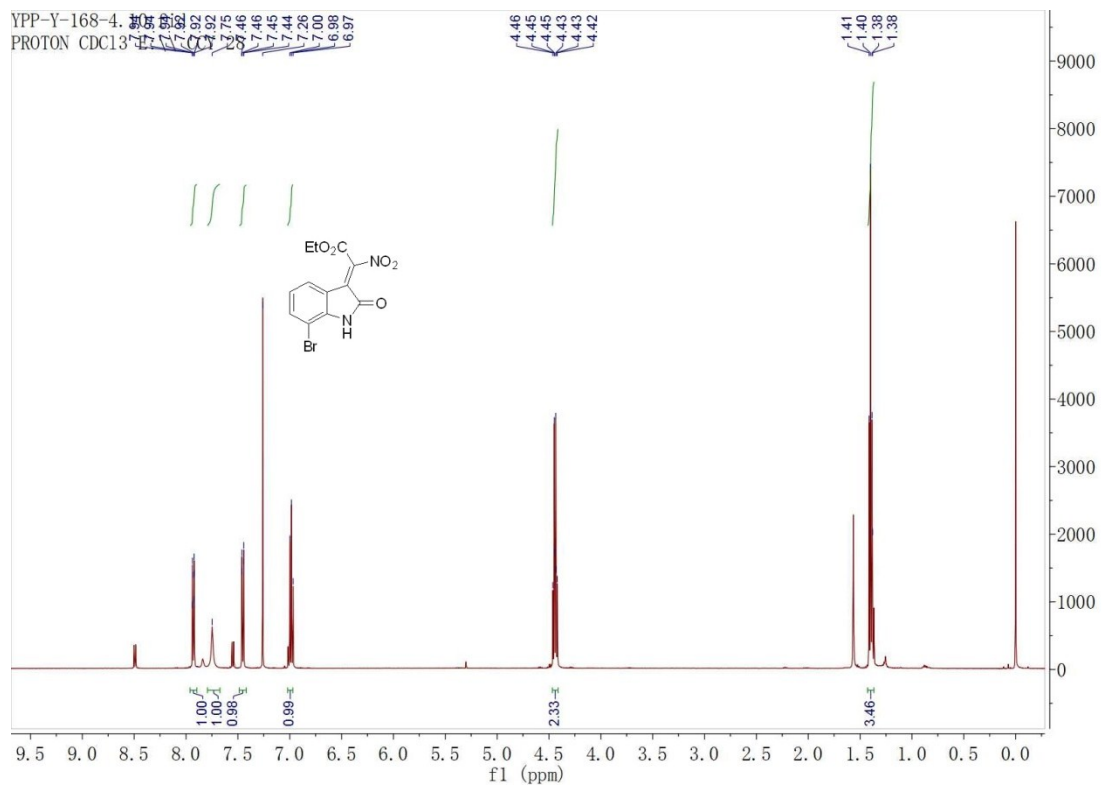


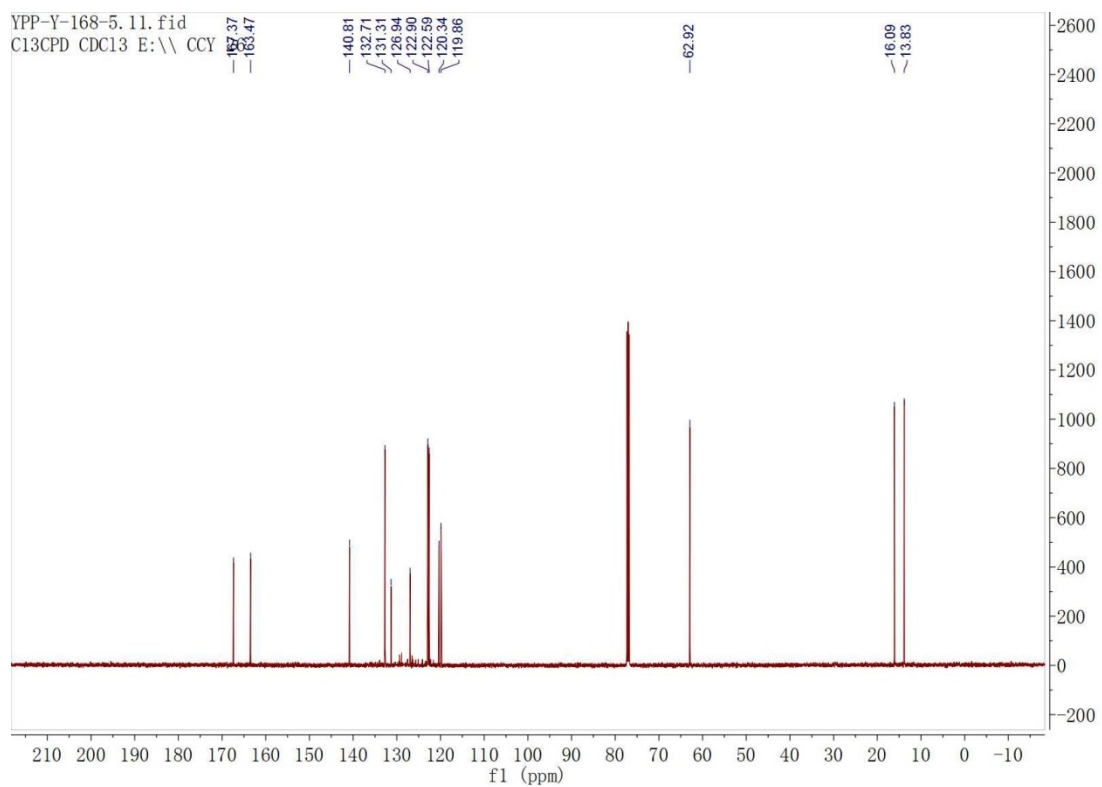
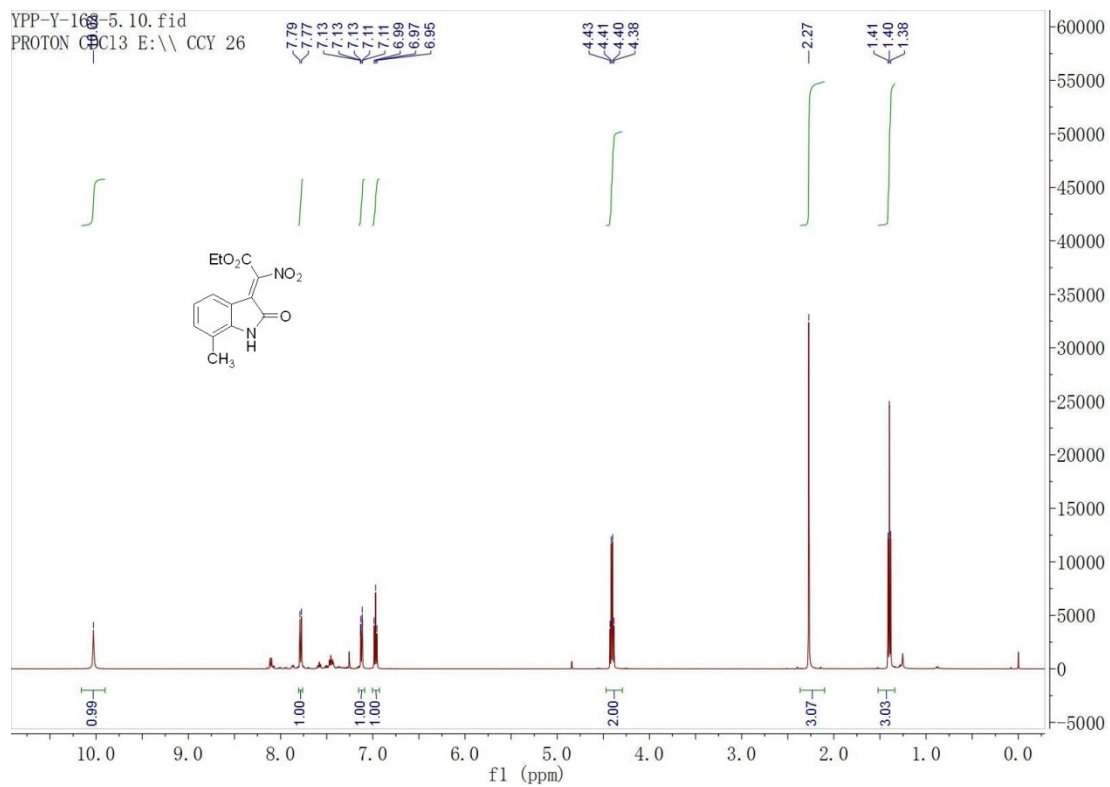


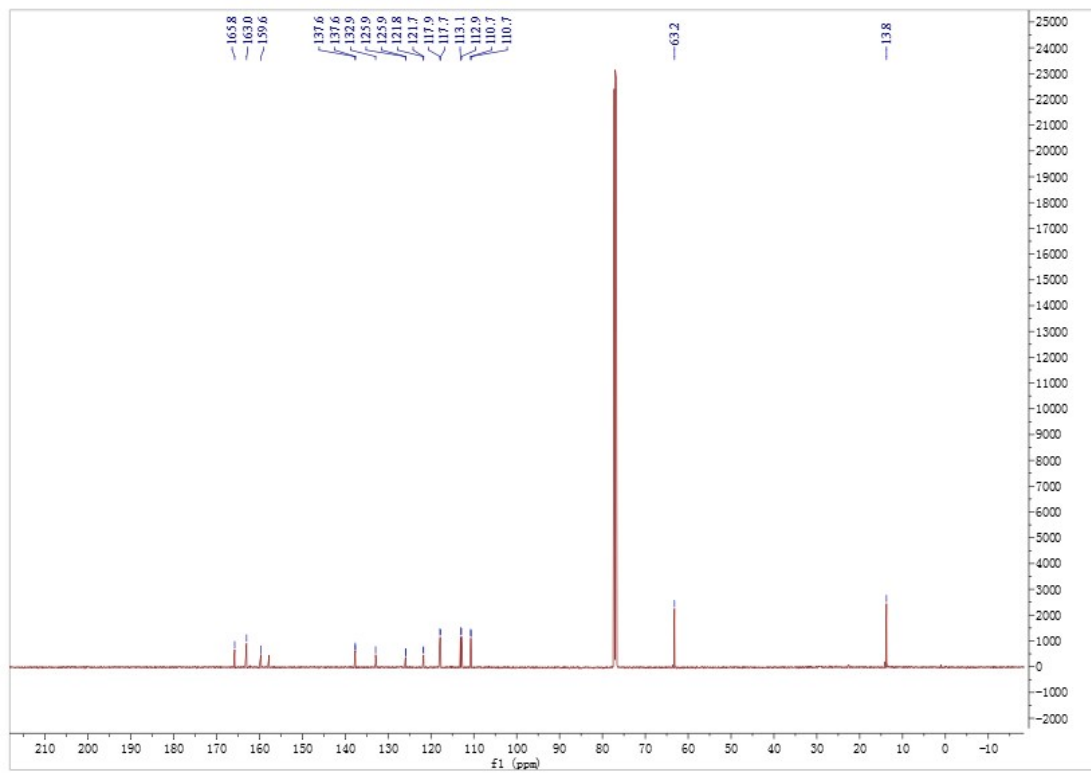
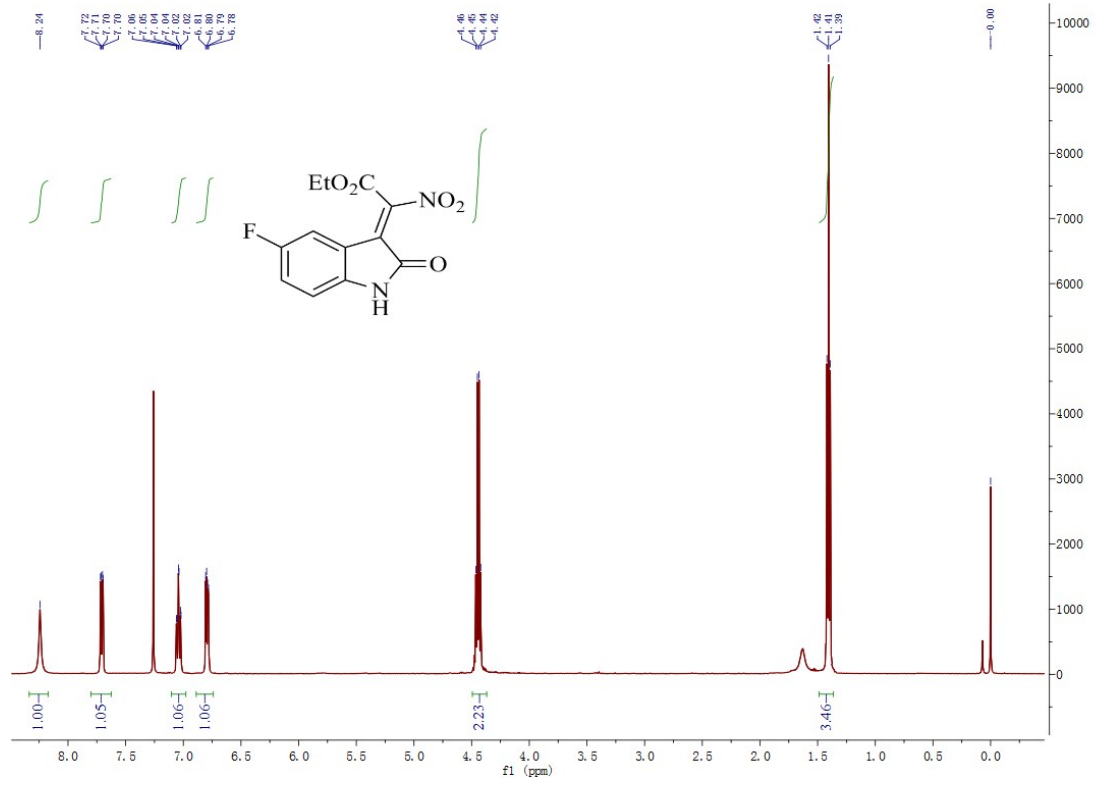


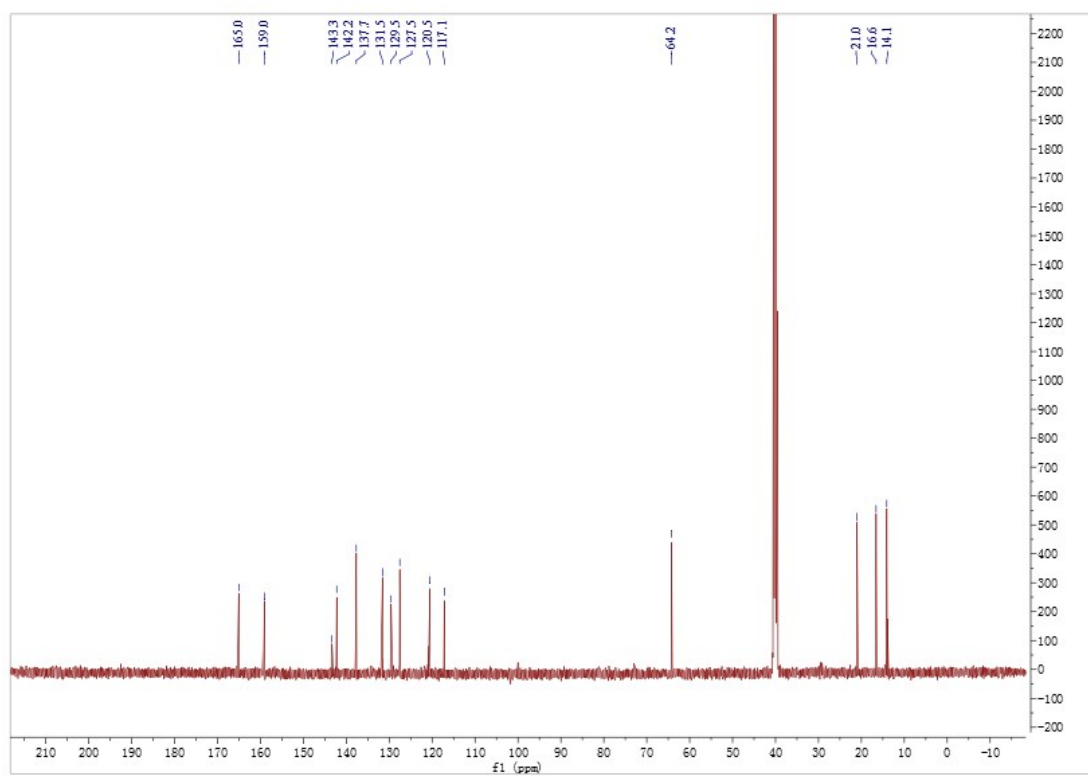
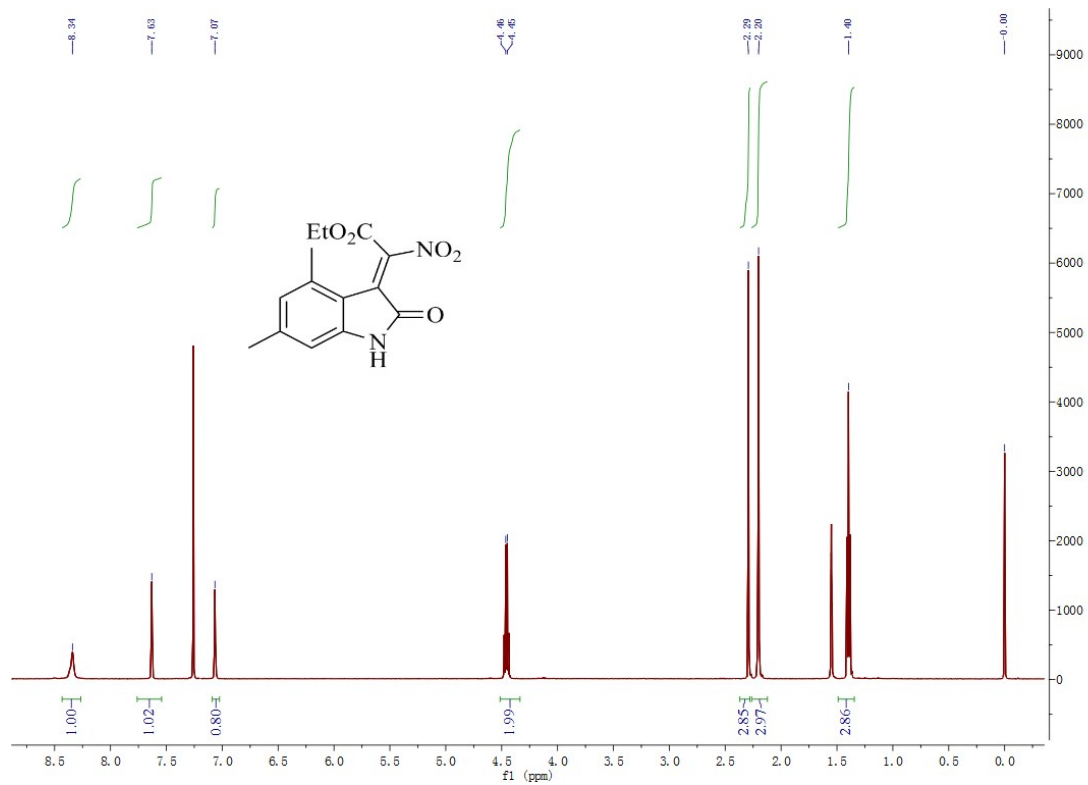


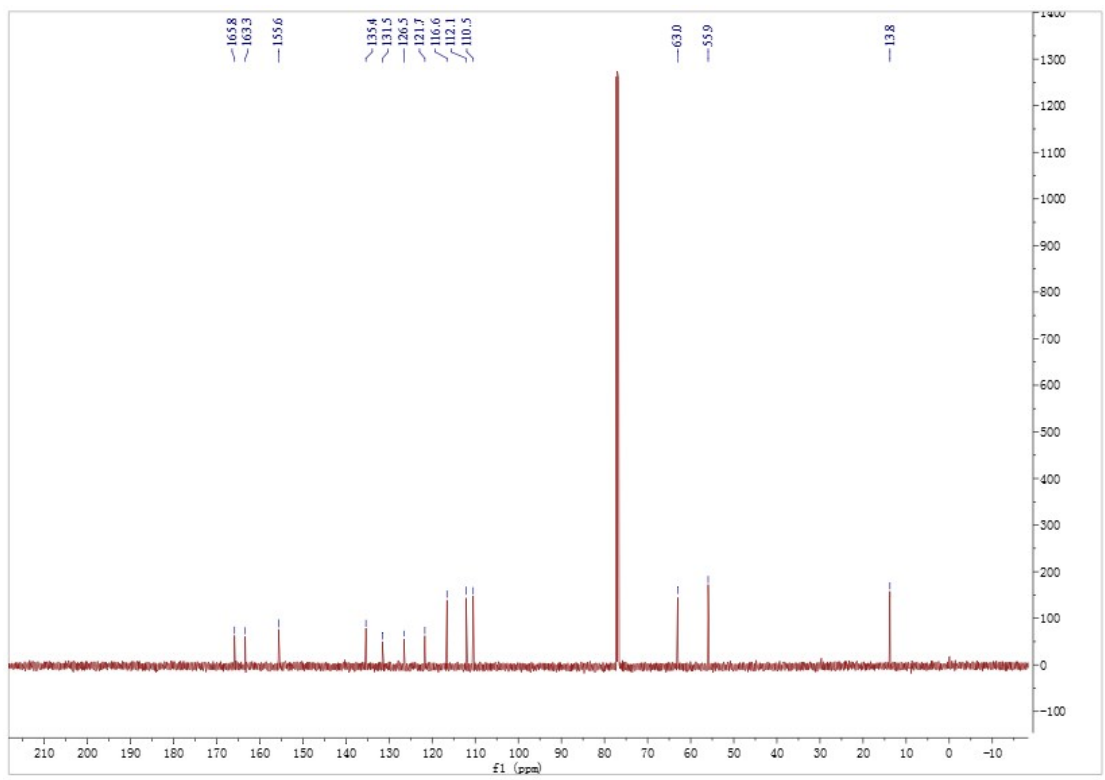
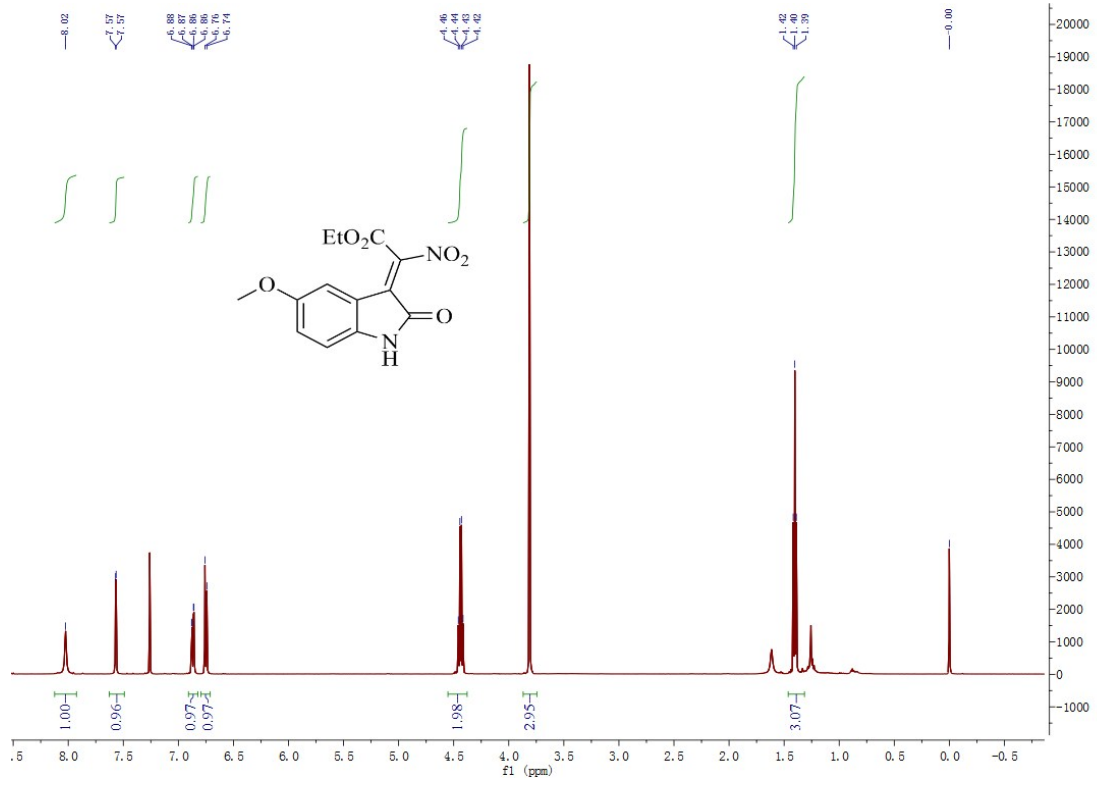


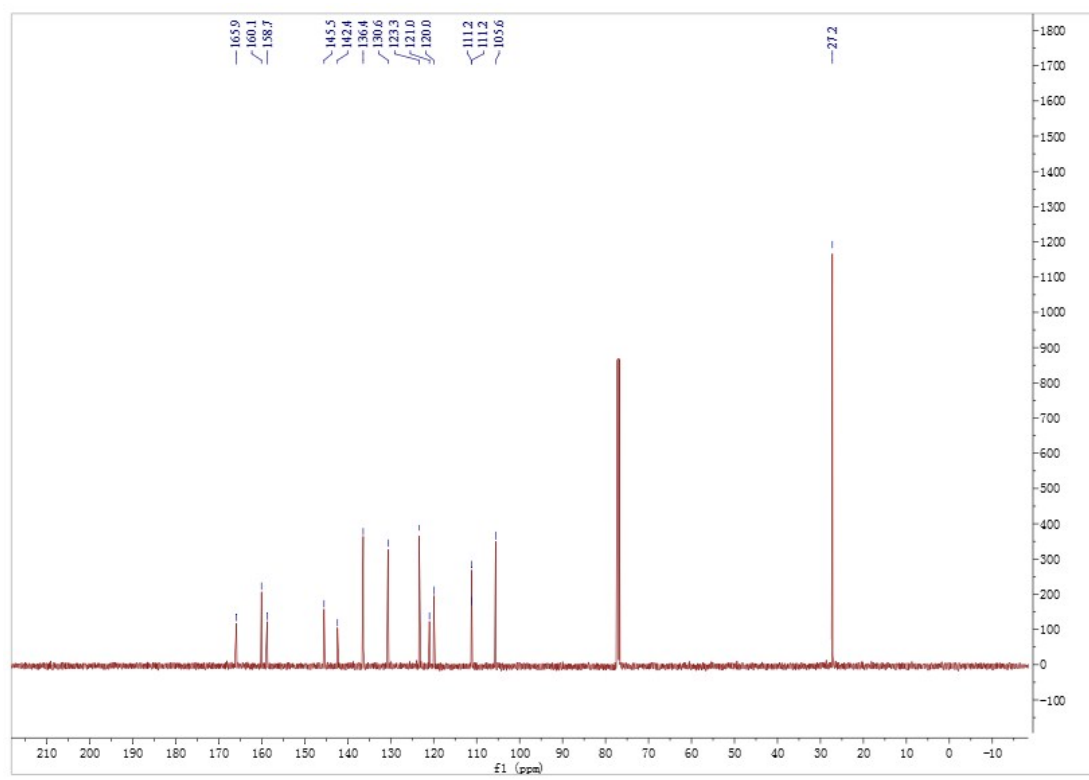
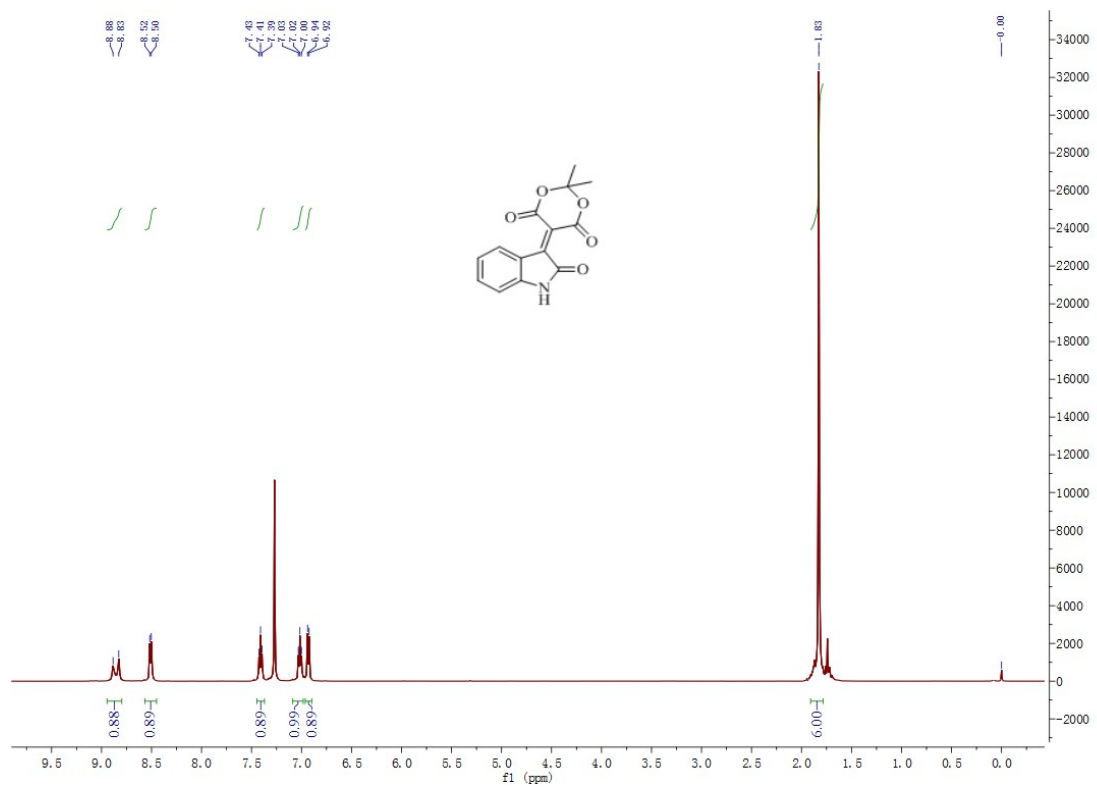


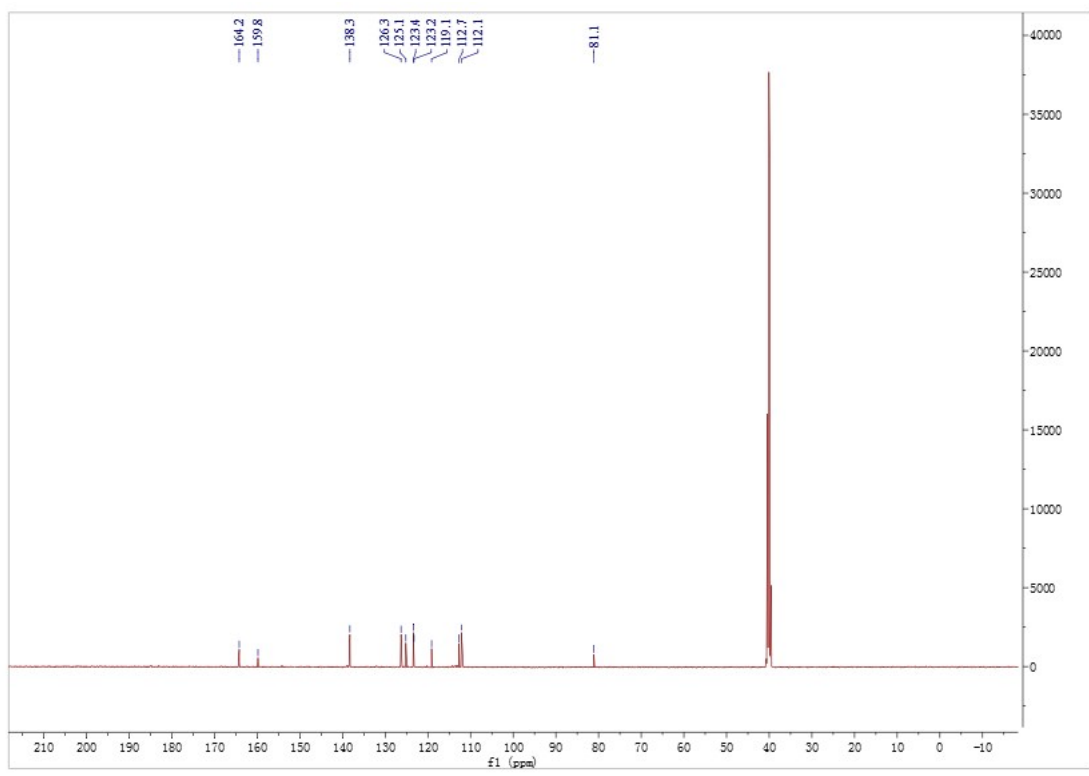
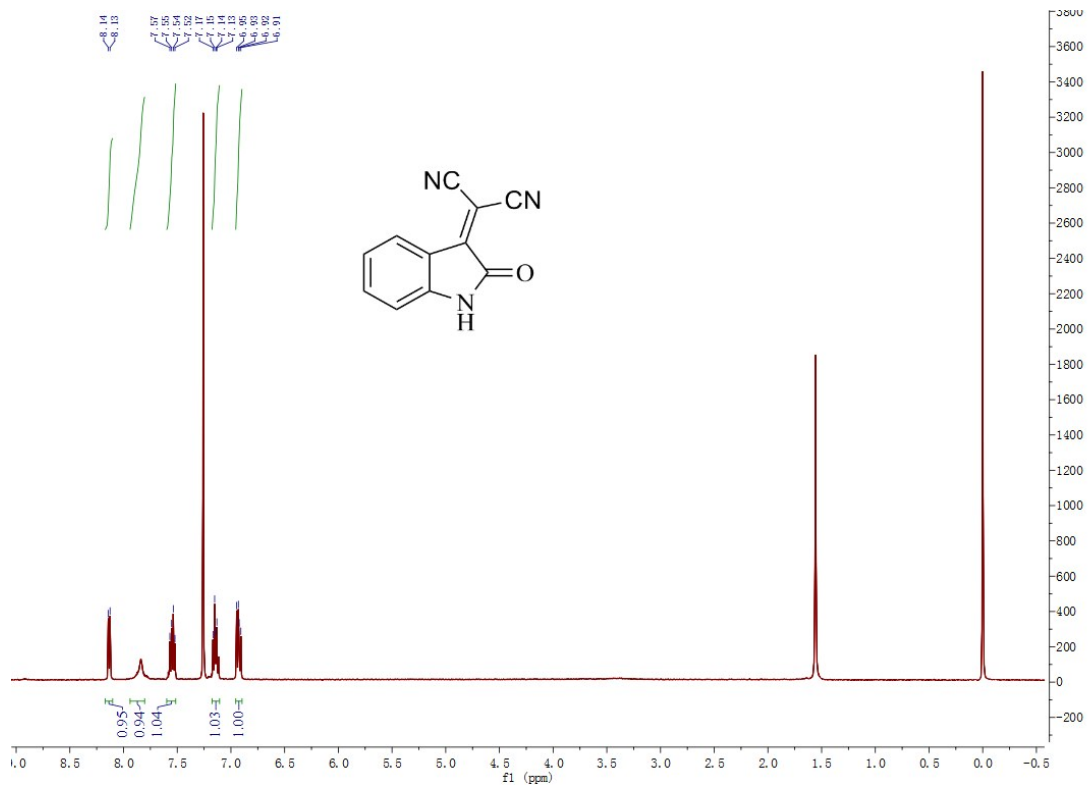


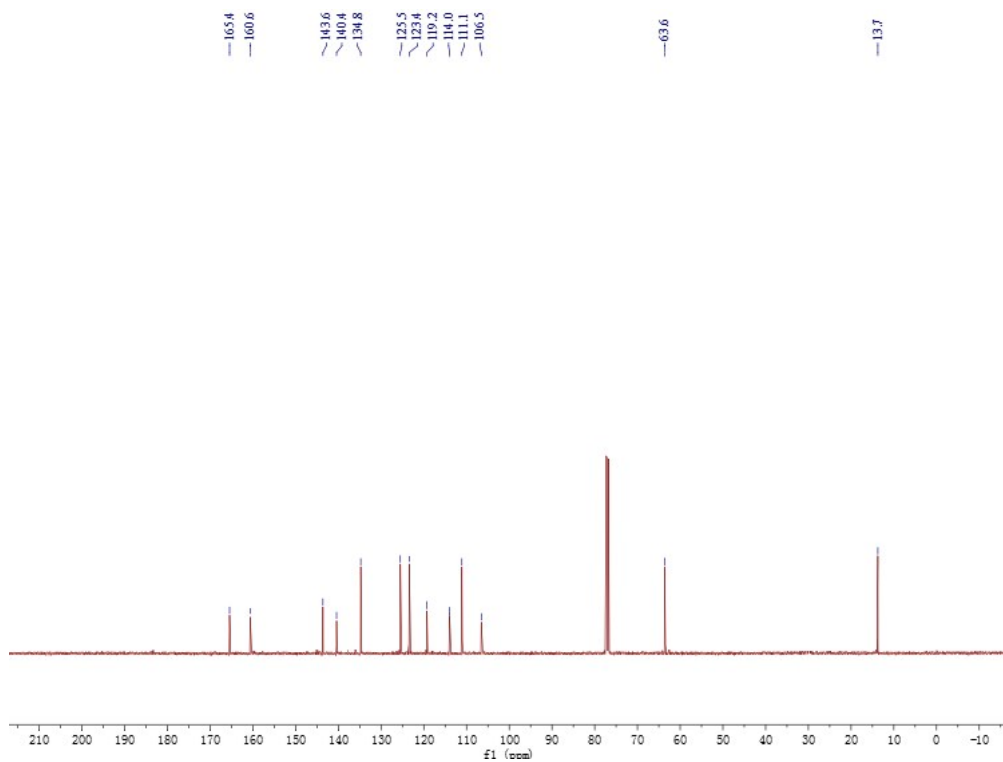
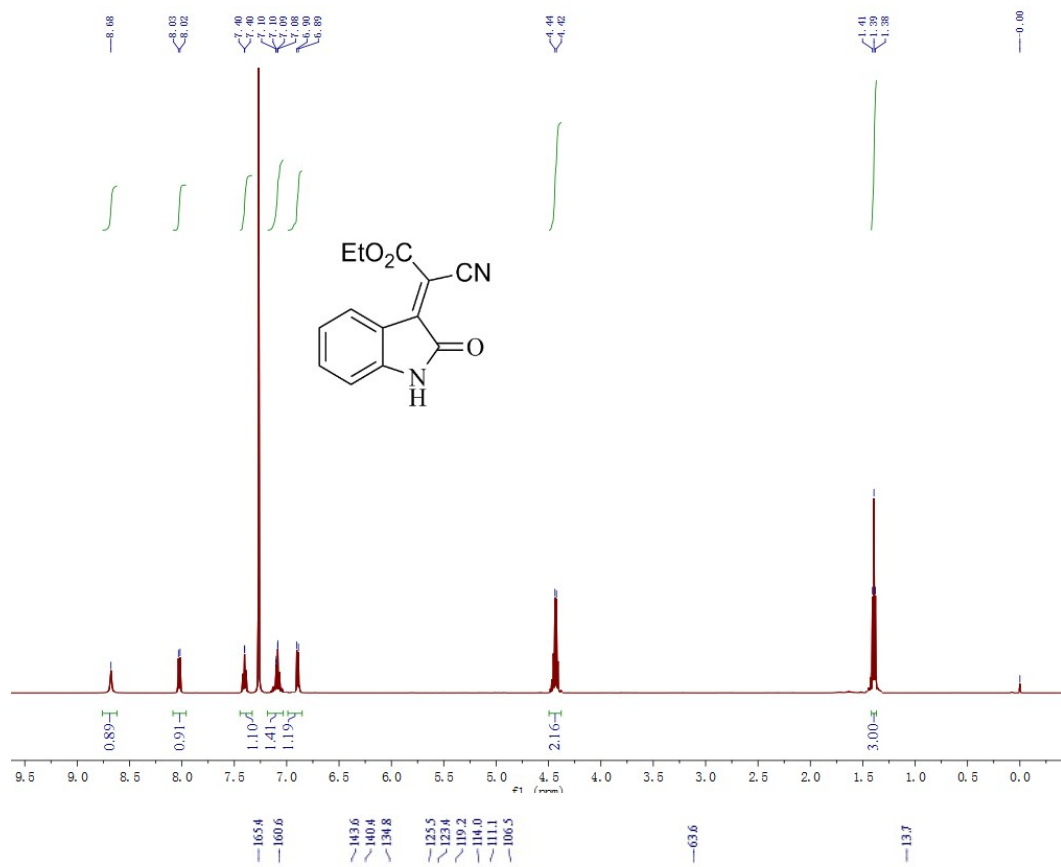


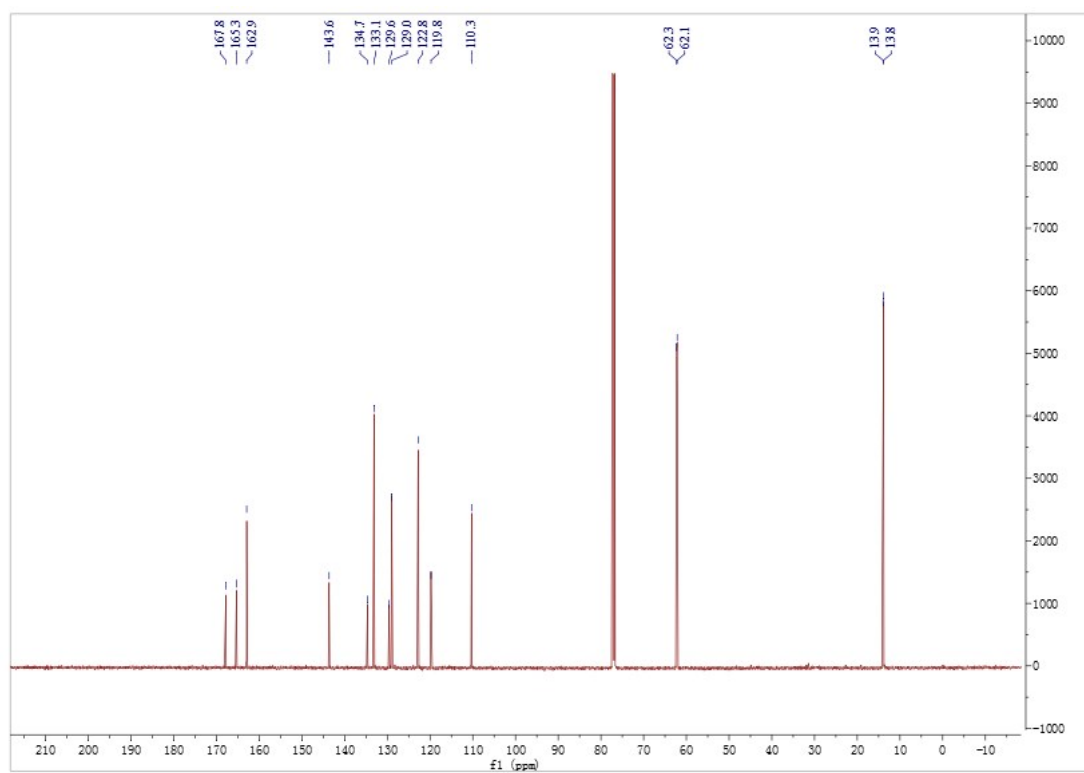
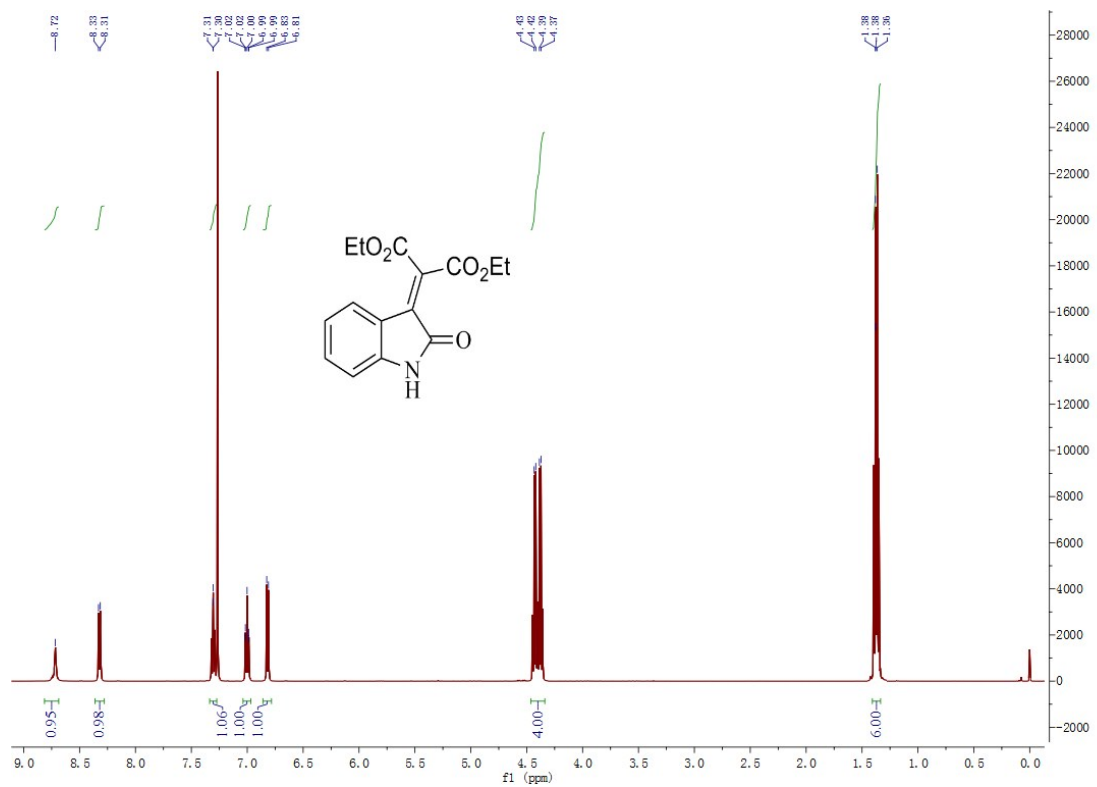


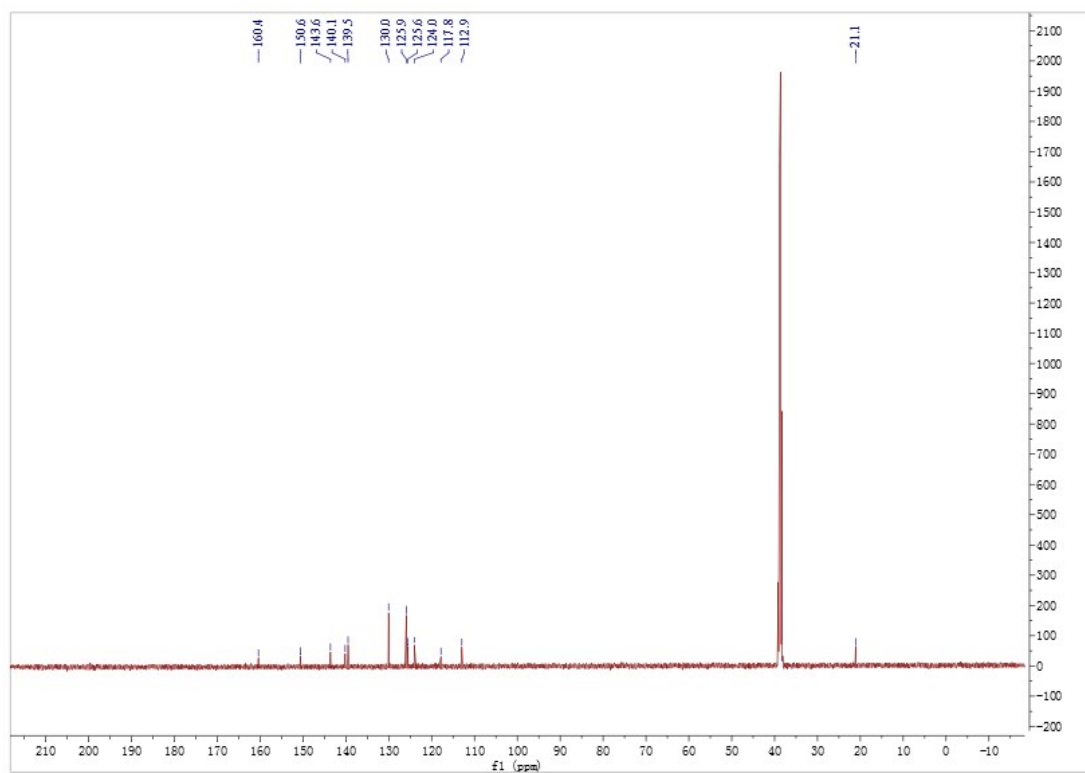
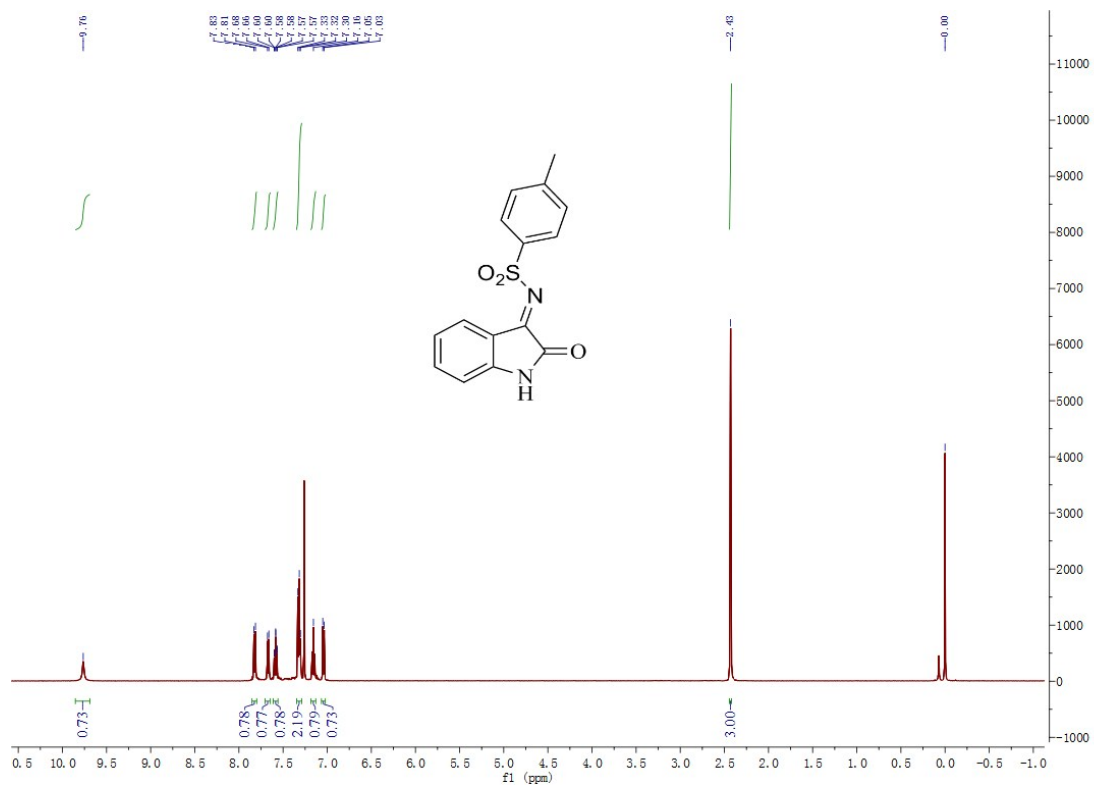


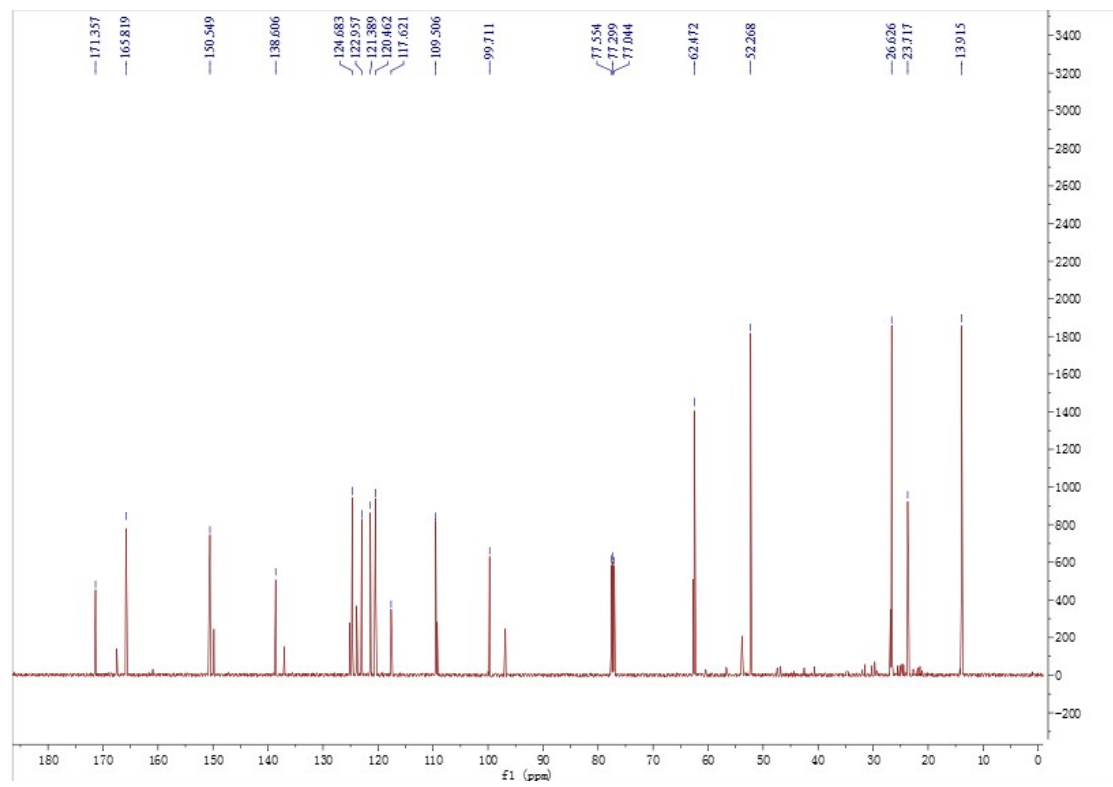
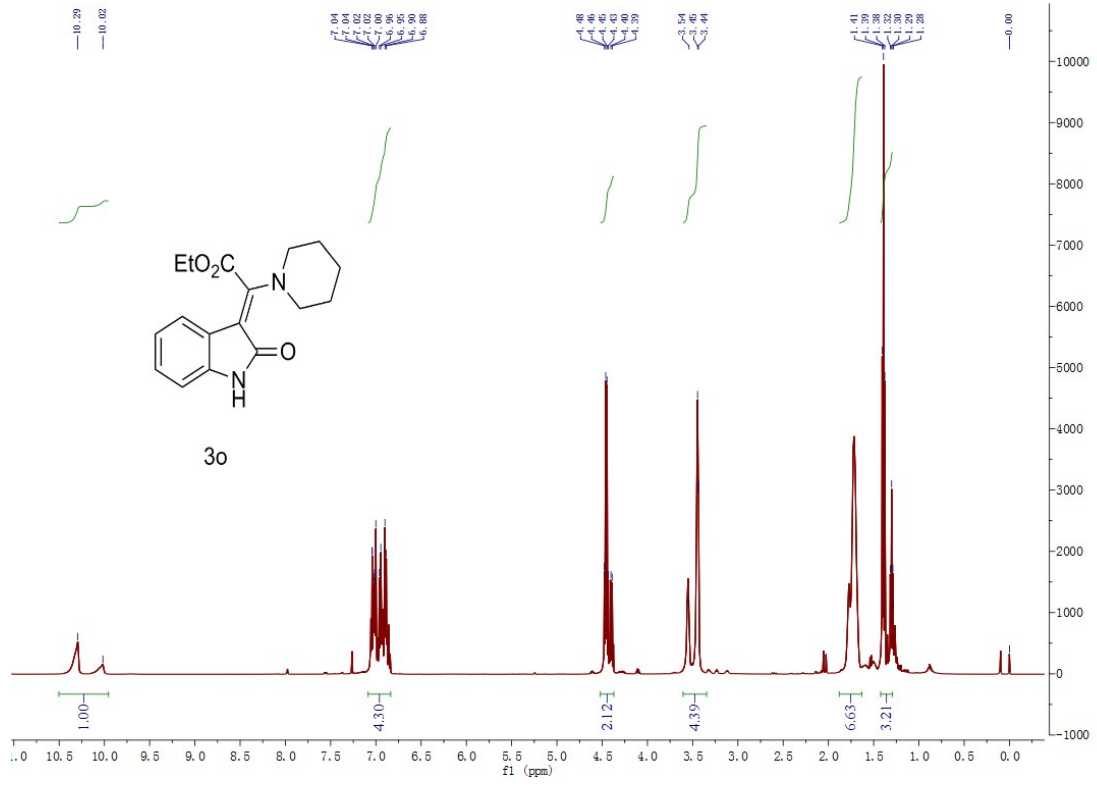


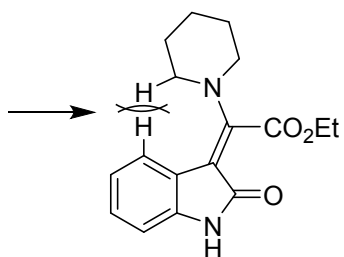












NOE interaction

An obvious NOE interaction between 4-position H atom and CH₂ of piperidine could be seen from the spectrum below, which means that the C=C double bond of the main product of **7** should be E configuration, the *E/Z* ratio is 3:1.

