

Supporting Information

Biocatalytic one-pot three-component synthesis of 3,3'-disubstituted oxindoles and spirooxindole pyrans using α -amylase from hog pancreas

Tao He, Qing-Qing Zeng, Da-Cheng Yang, Yan-Hong He*, Zhi Guan*

Key Laboratory of Applied Chemistry of Chongqing Municipality, School of Chemistry and Chemical Engineering,

Southwest University, Chongqing, 400715, P. R. China

Fax: +86-23-68254091; e-mails: heyh@swu.edu.cn (for Yan-Hong He); guanzhi@swu.edu.cn (for Zhi Guan)

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1 General information

Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (GF254 silica gel plates) from Haiyang chemical industry Co Ltd, Qingdao, China. Flash column chromatography was performed using silica gel (100–200 mesh) from Haiyang chemical industry Co Ltd, Qingdao, China. Melting points were taken on a YuHua X-4 apparatus and were uncorrected. Organic solutions were concentrated under reduced pressure on rotary evaporator. ^1H (600 and 300 MHz) NMR, as well as ^{13}C (150 and 75 MHz) NMR spectra were recorded in d_6 -DMSO on Bruker-AM 300 (300 MHz) or Bruker Ascend 600 (600 MHz) (Bruker BioSpin AG Ltd., Beijing, China). Chemical shifts were reported in ppm from TMS with the solvent resonance as the internal standard and coupling constants (J) in Hz. HRMS were recorded on a Varian 7.0T FTICR-MS spectrometer. X-ray crystal structures were tested in Agilent SuperNova X-ray single-crystal diffractometer. Purity of new products is measured by Shimadzu LC-20AT HPLC with Daicel AD-H chiral column or ELITE Hypersil NH_2 column.

2 Materials

α -Amylase from hog pancreas, EC Number 3.2.1.1, CAS number: 9000-90-2, powder, ~50 U/mg, product number: 10080, 1 U will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C), was purchased from Sigma-Aldrich.

α -Amylase from *Aspergillus oryzae*, EC Number 3.2.1.1, CAS number: 9001-19-8, powder, ~30 U/mg, Product number: 10065-10G, 1 U will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C), was purchased from Sigma-Aldrich.

α -Amylase from *Bacillus Subtilis*, EC Number 3.2.1.1, powder, ~4 U/mg, 1 U will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 °C), was purchased from Shanghai kayon Biological Technology Co., Ltd, China.

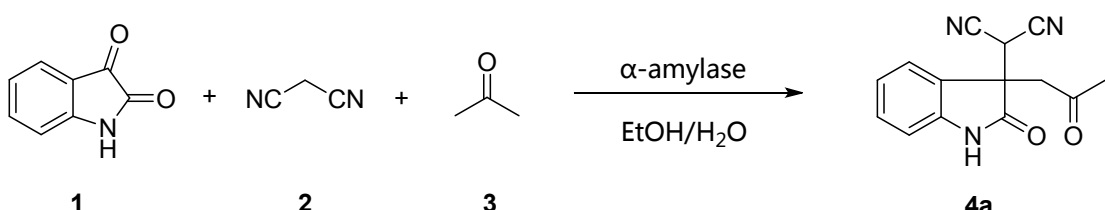
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification.

3 Comparison of different forms of α -amylase for the catalysis on the three-component reaction

In our initial study, to find out an enzyme for the reaction, we have screened several enzymes

which included three α -amylases (α -amylase from hog pancreas, α -amylase from *Aspergillus oryzae*, and α -amylase from *Bacillus Subtilis*). Only the reaction with α -amylase from hog pancreas gave the product in a good yield of 55%. The other two α -amylases gave low yields of 7% and 2%. Thus, α -amylase from hog pancreas was selected as the catalyst for the investigation in this study. The results were represented in **S-Table 1**.

S-Table 1. Comparison of different forms of α -amylase for the catalysis on the three-component reaction ^a

			
Entry	α -amylase	Time [d]	Yield [%] ^b
1	α -amylase from hog pancreas	2	55
2	α -amylase from <i>Aspergillus oryzae</i>	3	7
3	α -amylase from <i>Bacillus Subtilis</i>	3	2

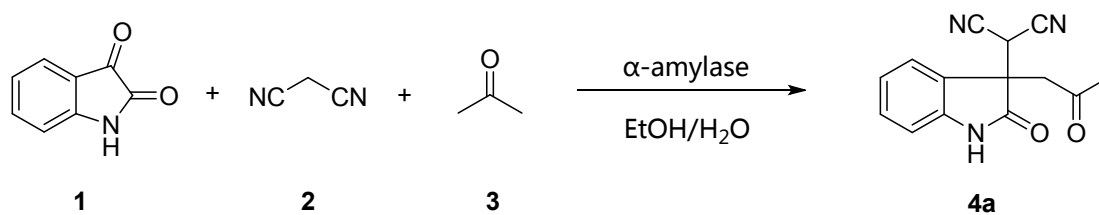
^a Reaction conditions: isatin (0.25 mmol), malononitrile (0.25 mmol), acetone (2.5 mmol), α -amylase (30 mg), ethanol (0.90 mL), and deionized water (0.10 mL) at 25 °C.

^b Yield of the isolated product.

4 Optimization of reaction conditions

The influence of the amounts of acetone on the yield of α -amylase-catalyzed reaction was investigated (**S-Table 2**). Initially the yield of the product increased with increasing the amount of acetone (**S-Table 2**, entries 1-6). After acetone reached 30 equivalents (the molar ratio of isatin/malononitrile/acetone = 1:1:30), continuous increase in the amount of acetone did not have an obvious effect on the yield (**S-Table 2**, entries 7 and 8). Thus, we choose 30 equivalents of acetone as the best molar ratio of substrates for the further studies.

S-Table 2 Influence of the amounts of acetone on the α -amylase-catalyzed three-component reaction^a

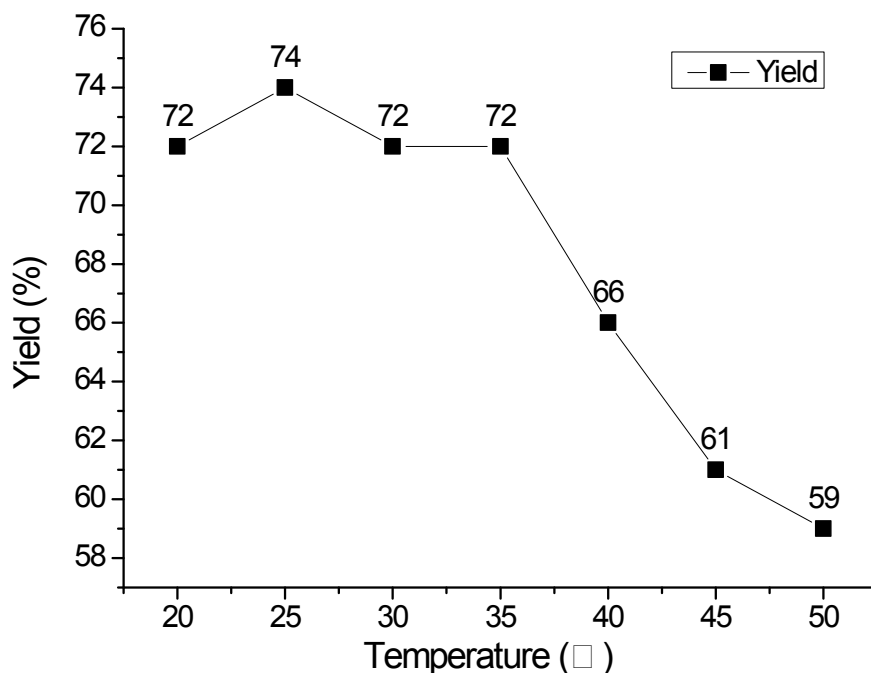


Entry	Molar ratio of 1/2/3	Yield [%] ^b
1	1:1:5	48
2	1:1:10	58
3	1:1:15	65
4	1:1:20	67
5	1:1:25	67
6	1:1:30	73
7	1:1:35	74
8	1:1:40	73

^a Reaction conditions: isatin (0.25 mmol), malononitrile (0.25 mmol), acetone, α -amylase (738 U), ethanol (0.90 mL), and deionized water (0.10 mL) at 25 °C for 2 d.

^b Yield of the isolated product.

Temperature has a significant effect on enzyme stability and activity. It is crucial to confirm the optimal temperature for this α -amylase catalyzed reaction. Thus, the effect of temperature on the product yield was investigated (**S- Figure 1**). The reaction proceeded faster at higher temperatures than at room temperature but afforded lower yield, due to the formation of some side products. So 25 °C was selected as the optimal temperature for the reaction.



S-Figure 1 Influence of temperature on the α -amylase-catalyzed reaction

The reactions were carried out with isatin (0.25 mmol), malononitrile (0.25 mmol) and acetone (7.5 mmol) in the presence of α -amylase (738 U) in ethanol (0.90 mL) and deionized water (0.10 mL) for 2 d. Yield of the isolated product.

The influence of enzyme loading on the α -amylase catalyzed three-component reaction was also surveyed (**S-Table 3**). When 49 U of α -amylase was used, the model reaction only gave the product in a low yield of 25% (**S-Table 3**, entry 1). Increasing the enzyme loading from 49 U to 246 U led to an obvious increase in yield (**S-Table 3**, entries 1-5). Further increasing the enzyme loading hardly improved the results. Thus we chose 246 U as the optimal enzyme loading for the three-component reaction.

S-Table 3 Effect of enzyme loading on the α -amylase-catalyzed three-component reaction ^a

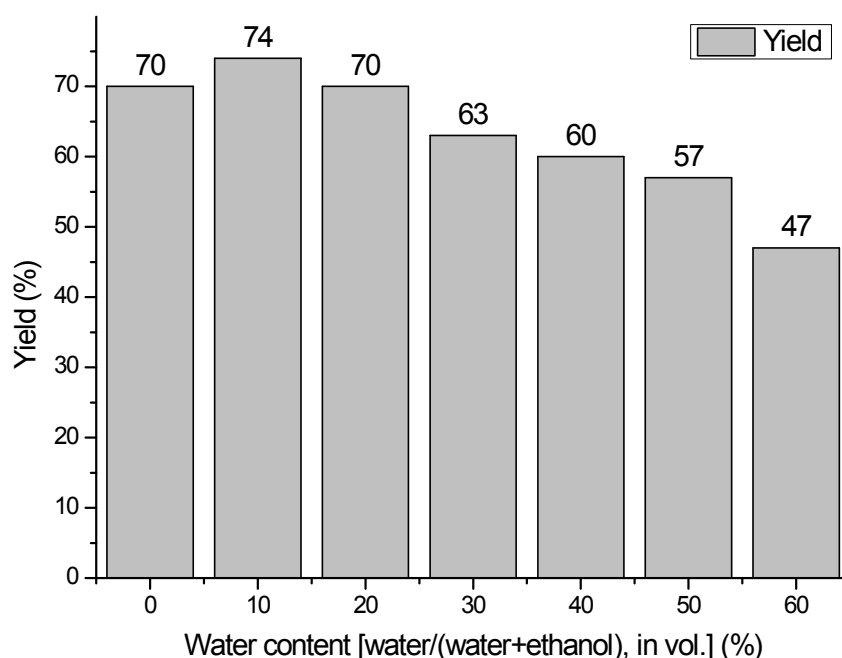
1	2	3
4a		
Entry	Enzyme loading (U)	Yield [%] ^b

1	49	25
2	98	43
3	148	53
4	197	68
5	246	75
6	492	72
7	738	74

^a Reaction conditions: isatin (0.25 mmol), malononitrile (0.25 mmol), acetone (7.5 mmol), ethanol (0.90 mL), and deionized water (0.10 mL) at 25 °C for 2 d.

^b Yield of the isolated product.

The effect of water content in the system on the reaction yield was also investigated (**S-Figure 2**). The water content [water/(water+ethanol), in vol.] (%) has been screened from 0 to 60%. The increase of water content from 0 to 10% led to a slight rise in the yield (from 70% to 74%). However, further increasing the water content caused a decrease in yield. Thus we chose a water content of 10% as the optimal condition for the next investigation.

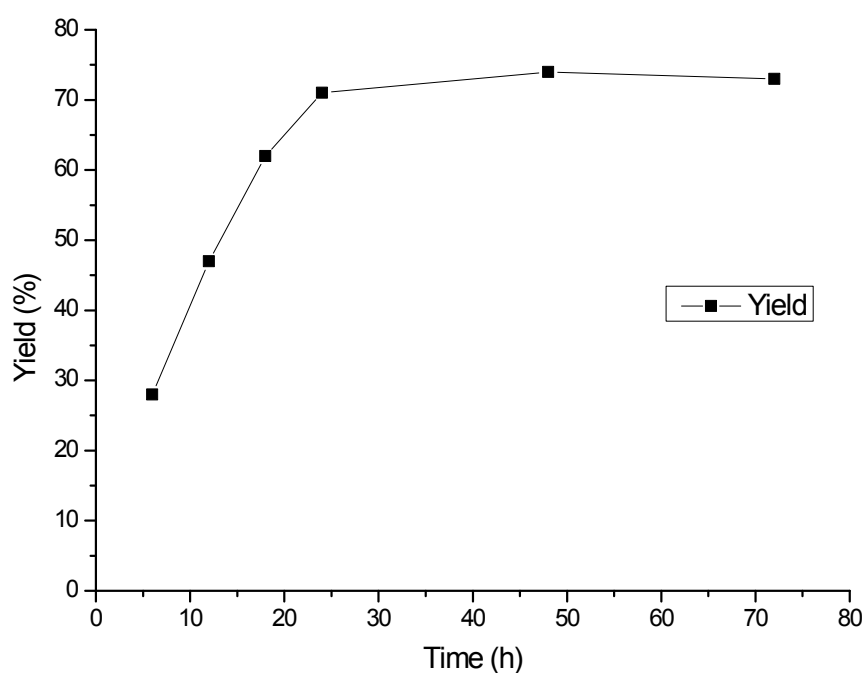


S-Figure 2 Influence of water content on the α -amylase-catalyzed three-component reaction.

The reactions were carried out with isatin (0.25 mmol), malononitrile (0.25 mmol) and acetone (7.5 mmol) in the presence of α -amylase (246 U) in ethanol and deionized water (ethanol + deionized water = 1.0 mL) at 25 °C for 2

d. Yield of the isolated product.

In order to investigate the relationship between time and yield, we tested the time course of the α -amylase-catalyzed model three-component reaction (**S-Figure 3**). The product yield increased obviously within the first 24 hours, and after that the yield almost kept constant.



S-Figure 3 Time course of the α -amylase-catalyzed three-component reaction.

The reactions were carried out with isatin (0.25 mmol), malononitrile (0.25 mmol) and acetone (7.5 mmol) in the presence of α -amylase (246 U) in ethanol (0.90 mL) and deionized water (0.10 mL) at 25 °C for 6-72 h. Yield of the isolated product.

5 Crystallographic data

X-ray crystal structure analysis of 6d

Crystal	6d
Empirical formula	C ₁₃ H ₁₀ N ₄ O ₃
Formula weight	270.25
Temperature/K	288.91(10)
Crystal system	monoclinic

Space group	P2 ₁ /c
a/Å	9.21681(17)
b/Å	7.14117(12)
c/Å	19.9378(3)
α /°	90
β /°	92.7636(15)
γ /°	90
Volume/Å ³	1310.76(4)
Z	4
ρ_{calc} /cm ³	1.369
μ /mm ⁻¹	0.848
F(000)	560.0
Crystal size/mm ³	0.06 × 0.05 × 0.05
Radiation	CuK α (λ = 1.54184)
2 Θ range for data collection/°	9.608 to 142.806
Index ranges	-11 ≤ h ≤ 7, -8 ≤ k ≤ 8, -24 ≤ l ≤ 24
Reflections collected	9919
Independent reflections	2514 [R_{int} = 0.0241, R_{sigma} = 0.0169]
Data/restraints/parameters	2514/0/182
Goodness-of-fit on F ²	1.019
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0448, wR_2 = 0.1217
Final R indexes [all data]	R_1 = 0.0462, wR_2 = 0.1231
Largest diff. peak/hole / e Å ⁻³	0.30/-0.33

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC: 1053771. Copy of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

X-ray crystal structure analysis of 11b

Crystal	11b
Empirical formula	C ₃₄ H ₃₀ N ₆ O ₆
Formula weight	614.61
Temperature/K	288.02(10)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	8.82662(14)
b/Å	27.6395(4)
c/Å	13.1668(2)

$\alpha/^\circ$	90
$\beta/^\circ$	105.9160(17)
$\gamma/^\circ$	90
Volume/ $\text{\AA}^3$	3089.08(9)
Z	4
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.322
μ/mm^{-1}	0.769
F(000)	1280.0
Crystal size/ mm^3	$0.13 \times 0.12 \times 0.11$
Radiation	CuK α ($\lambda = 1.54184$)
2 Θ range for data collection/ $^\circ$	9.474 to 142.996
Index ranges	$-10 \leq h \leq 10$, $-33 \leq k \leq 33$, $-16 \leq l \leq 13$
Reflections collected	22707
Independent reflections	5944 [$R_{\text{int}} = 0.0351$, $R_{\text{sigma}} = 0.0237$]
Data/restraints/parameters	5944/0/437
Goodness-of-fit on F^2	1.158
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0639$, $wR_2 = 0.1699$
Final R indexes [all data]	$R_1 = 0.0663$, $wR_2 = 0.1714$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.60/-0.22

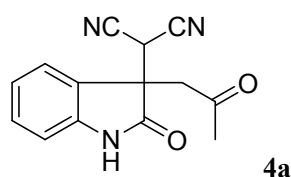
Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC: 1053772. Copy of the data can be obtained free of charge on application to The Director, 'CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

6 Enzymatic assay of α -amylase

Unit definition (U mg^{-1}), One unit will liberate 1.0 mg of maltose from starch in 3 minutes at pH 6.9 at 20 $^\circ\text{C}$.

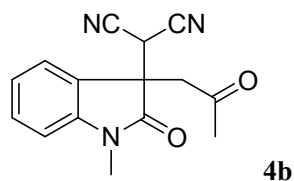
The enzymatic assay was conducted according to the literature¹.

7 Characterization data of the products



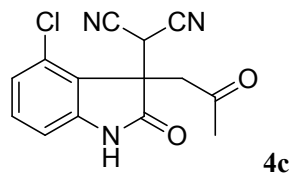
2-(2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

Mp 198-199 °C (lit. **2** 199-200 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.02 (s, 1H), 7.51 – 7.18 (m, 2H), 7.14 – 6.75 (m, 2H), 5.54 (s, 1H), 3.62 (d, J = 18.0 Hz, 1H), 3.29 (d, J = 18.0 Hz, 1H), 2.05 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.01, 175.77, 143.42, 130.31, 126.93, 123.77, 122.37, 112.00, 111.64, 110.52, 48.60, 46.04, 30.44, 30.23.



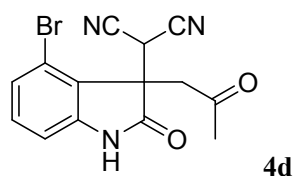
2-(1-methyl-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

Mp 210-211 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 7.47 – 7.38 (m, 2H), 7.18 – 7.11 (m, 2H), 5.58 (s, 1H), 3.69 (d, J = 18.1 Hz, 1H), 3.32 (s, 1H), 3.21 (s, 3H), 3.15 (d, J = 6.0 Hz, 1H), 2.04 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 203.97, 174.17, 144.85, 130.46, 126.19, 123.48, 123.08, 111.87, 111.55, 109.55, 48.22, 46.17, 30.42, 30.15, 26.89.



2-(4-chloro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

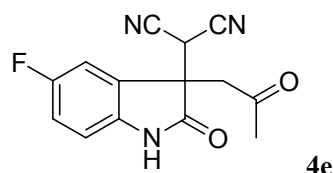
Mp 206-207 °C (lit. **2** 205-206 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.31 (s, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 5.53 (s, 1H), 3.91 (d, J = 18.1 Hz, 1H), 3.30 (d, J = 18.1 Hz, 1H), 2.08 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 203.81, 174.63, 146.09, 132.55, 126.20, 124.57, 117.92, 111.28, 110.91, 110.14, 50.35, 44.69, 29.93, 28.76.



2-(4-bromo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

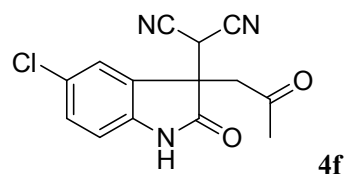
Mp 197-199 °C (lit. **2** 200-201 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.32 (s, 1H), 7.32 (t, J =

8.0 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 5.56 (s, 1H), 3.84 (d, J = 18.1 Hz, 1H), 3.33 (d, J = 18.2 Hz, 1H), 2.07 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 203.89, 174.70, 145.80, 132.34, 129.62, 123.06, 122.94, 111.37, 111.02, 109.70, 49.70, 44.72, 29.93, 28.84.



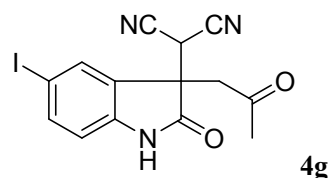
2-(5-fluoro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

Mp 204-206 °C (lit. **2** 205-206 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.03 (s, 1H), 7.27 (m, 1H), 7.13 (m, 1H), 6.92 (m, 1H), 5.55 (s, 1H), 3.66 (d, J = 18.2 Hz, 1H), 3.30 (d, J = 18.2 Hz, 1H), 2.05 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.04, 175.72, 159.74, 156.59, 139.74, 128.61, 128.49, 116.79, 116.49, 112.16, 111.83, 111.74, 111.41, 111.32, 48.99, 45.99, 30.26, 30.06.



2-(5-chloro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

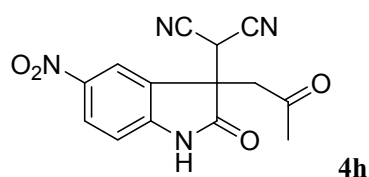
Mp 210-211 °C (lit. **2** 209-210 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.14 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 5.56 (s, 1H), 3.69 (d, J = 18.3 Hz, 1H), 3.31 (d, J = 18.3 Hz, 1H), 2.05 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.13, 175.53, 142.47, 130.18, 129.00, 126.21, 124.23, 111.91, 111.72, 111.39, 48.73, 46.04, 30.23, 30.01.



2-(5-iodo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile³

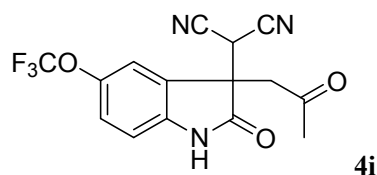
Mp 218-220 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.21 (s, 1H), 7.44 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 5.58 (s, 1H), 3.72 (d, J = 18.2 Hz, 1H), 3.32 (d, J = 18.2 Hz, 1H), 2.04 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.19, 175.80, 143.43, 142.69, 128.56, 123.57,

118.02, 111.62, 111.35, 48.81, 45.92, 30.16, 30.02.



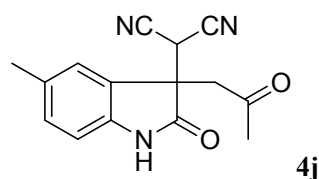
2-(5-nitro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile²

Mp 233-234 °C (lit. **2** 233-234 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.75 (s, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.27 (dd, J = 8.7, 2.2 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 5.71 (s, 1H), 3.88 (d, J = 18.4 Hz, 1H), 3.41 (d, J = 18.5 Hz, 1H), 2.06 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.34, 176.32, 150.00, 142.65, 127.98, 127.57, 120.21, 111.48, 111.18, 110.62, 48.53, 46.28, 29.94, 29.82.



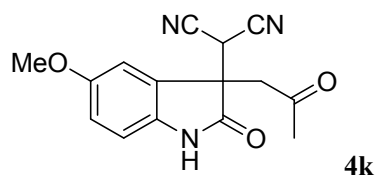
2-(2-oxo-3-(2-oxopropyl)-5-(trifluoromethoxy)indolin-3-yl)malononitrile³

Mp 147-149 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.13 (s, 1H), 7.70 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.54 (s, 1H), 3.68 (d, J = 18.3 Hz, 1H), 3.29 (d, J = 18.3 Hz, 1H), 2.05 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.17, 175.26, 143.29, 138.80, 132.22, 129.63, 112.86, 111.75, 111.42, 85.13, 48.45, 46.06, 30.26, 30.04.



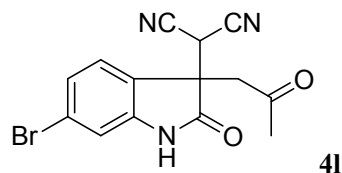
2-(5-methyl-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

Mp 207-208 °C (lit. **2** 206-207 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.89 (s, 1H), 7.18 (s, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 5.49 (s, 1H), 3.57 (d, J = 18.0 Hz, 1H), 3.25 (d, J = 18.1 Hz, 1H), 2.24 (s, 3H), 2.03 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 203.97, 175.72, 140.97, 131.25, 130.56, 127.02, 124.31, 112.04, 111.66, 110.29, 48.65, 46.07, 30.49, 30.23, 21.15.



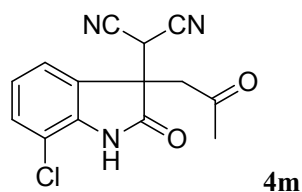
2-(5-methoxy-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile^{2,3}

Mp 203-204 °C (lit. 202-203 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.81 (s, 1H), 7.01 (s, 1H), 6.84 (s, 2H), 5.50 (s, 1H), 3.69 (s, 3H), 3.60 (d, J = 18.1 Hz, 1H), 3.24 (d, J = 18.1 Hz, 1H), 2.03 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 203.98, 175.57, 155.22, 136.54, 128.18, 114.33, 111.97, 111.62, 111.22, 110.88, 55.76, 48.94, 46.00, 30.46, 30.22.



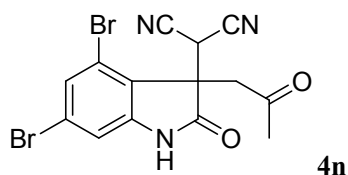
2-(6-bromo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile³

Mp 202-204 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.17 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 5.55 (s, 1H), 3.64 (d, J = 18.2 Hz, 1H), 3.31 (d, J = 18.2 Hz, 1H), 2.04 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.10, 175.67, 145.12, 126.35, 125.70, 125.05, 123.11, 113.32, 111.77, 111.42, 48.40, 46.03, 30.12, 30.08.



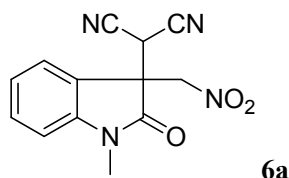
2-(7-chloro-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile²

Mp 197-199 °C (lit. **2** 200-201 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.47 (s, 1H), 7.36 (t, J = 8.4 Hz, 2H), 7.04 (t, J = 7.9 Hz, 1H), 5.58 (s, 1H), 3.67 (d, J = 18.2 Hz, 1H), 3.35 (d, J = 18.2 Hz, 1H), 2.04 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 204.12, 175.75, 141.24, 130.38, 128.81, 123.70, 122.47, 114.71, 111.72, 111.41, 49.31, 46.23, 30.34, 30.07.



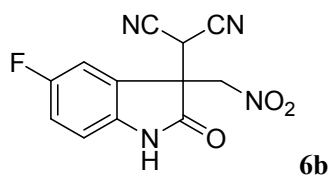
2-(4,6-dibromo-2-oxo-3-(2-oxopropyl)indolin-3-yl)malononitrile³

Mp 207-209 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.50 (s, 1H), 7.45 (d, J = 1.1 Hz, 1H), 7.12 (d, J = 1.1 Hz, 1H), 5.55 (s, 1H), 3.84 (d, J = 22.0 Hz, 1H), 3.33 (d, J = 18.3 Hz, 1H), 2.09 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 203.98, 174.61, 147.19, 127.98, 124.25, 118.81, 113.01, 111.17, 110.68, 50.20, 44.74, 29.83, 28.54.



2-(1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

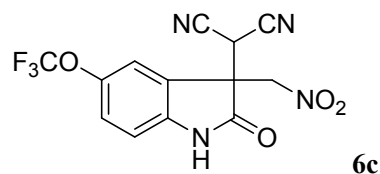
Mp 162-164 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 7.56 (d, J = 7.3 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.27 – 7.15 (m, 2H), 5.78 (s, 1H), 5.49 (q, J = 14.1 Hz, 2H), 3.24 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 171.80, 144.65, 131.80, 124.33, 123.83, 122.59, 111.11, 110.70, 110.36, 75.73, 49.69, 28.79, 27.17. HRMS (QFT-ESI): calcd for C₁₃H₉N₄O₃ [M-H]⁺ : 369.0680, found 369.0677. The purity was determined by HPLC on Daicel AD-H chiral column with *i*-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t₁ = 12.877 min; t₂ = 16.696 min



2-(5-fluoro-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

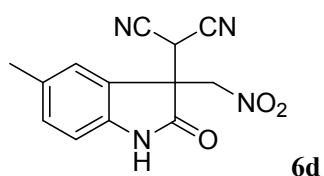
Mp 154-156 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.39 (s, 1H), 7.45 (dd, J = 8.1, 2.4 Hz, 1H), 7.25 (td, J = 9.2, 2.5 Hz, 1H), 7.01 (dd, J = 8.6, 4.3 Hz, 1H), 5.74 (s, 1H), 5.48 (dd, J = 39.5, 14.3 Hz, 2H). ¹³C NMR (151 MHz, DMSO-d₆) δ 173.43, 159.23, 157.65, 139.80, 124.99, 118.37, 118.22, 112.88, 112.71, 112.50, 112.44, 111.04, 110.57, 75.63, 50.49, 28.71. HRMS (QFT-ESI): calcd for C₁₂H₆FN₄O₃ [M-H]⁺ : 273.0430, found 273.0427. The purity was determined by HPLC

on Daicel AD-H chiral column with *i*-PrOH /Hexane (8:92) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t_1 = 48.874 min; t_2 = 55.111 min



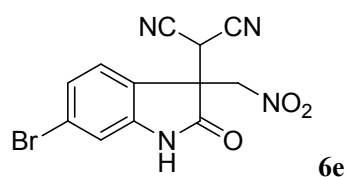
2-(3-(nitromethyl)-2-oxo-5-(trifluoromethoxy)indolin-3-yl)malononitrile

Mp 130-132 °C, ^1H NMR (300 MHz, DMSO- d_6) δ 11.56 (s, 1H), 7.63 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 5.78 (s, 1H), 5.52 (dd, J = 46.7, 14.3 Hz, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 173.51, 143.88, 142.69, 125.05, 121.43, 119.73, 118.80, 112.42, 110.94, 110.50, 75.58, 50.33, 28.61. HRMS (QFT-ESI): calcd for $\text{C}_{13}\text{H}_6\text{F}_3\text{N}_4\text{O}_4$ $[\text{M}-\text{H}]^-$: 339.0347, found 339.0345. The purity was determined by HPLC on Daicel AD-H chiral column with *i*-PrOH /Hexane (10:90) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t_1 = 14.710 min; t_2 = 16.237 min



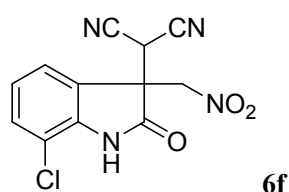
2-(5-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

Mp 185-187 °C, ^1H NMR (300 MHz, DMSO- d_6) δ 11.24 (s, 1H), 7.32 (s, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 5.70 (s, 1H), 5.50 – 5.33 (m, 2H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 173.38, 140.88, 132.16, 131.95, 124.95, 123.39, 111.25, 111.04, 110.79, 75.82, 50.11, 28.78, 21.08. HRMS (QFT-ESI): calcd for $\text{C}_{13}\text{H}_9\text{N}_4\text{O}_3$ $[\text{M}-\text{H}]^-$: 269.0680, found 269.0678. The purity was determined by HPLC on Daicel AD-H chiral column with *i*-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t_1 = 6.061 min; t_2 = 7.630 min



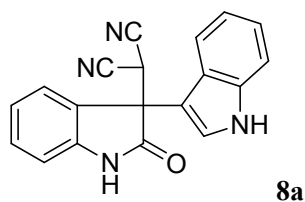
2-(6-bromo-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

Mp 47-49 °C, ^1H NMR (300 MHz, DMSO- d_6) δ 11.52 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.1, 1.7 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 5.75 (s, 1H), 5.47 (dd, J = 30.6, 14.2 Hz, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 173.36, 144.94, 126.55, 125.93, 124.56, 122.74, 114.12, 111.05, 110.54, 75.54, 49.86, 28.49. The purity was determined by HPLC on Daicel AD-H chiral column with *i*-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t_1 = 26.809 min; t_2 = 31.815 min



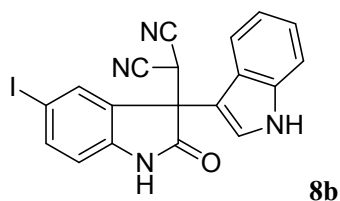
2-(7-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)malononitrile

Mp 153-155 °C, ^1H NMR (300 MHz, DMSO- d_6) δ 11.84 (s, 1H), 7.49 (dd, J = 7.2, 5.9 Hz, 2H), 7.15 (t, J = 7.9 Hz, 1H), 5.78 (s, 1H), 5.51 (q, J = 14.3 Hz, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 173.49, 141.18, 131.72, 125.22, 124.50, 123.35, 115.40, 111.00, 110.53, 75.69, 50.73, 28.72. HRMS (QFT-ESI): calcd for $\text{C}_{12}\text{H}_6\text{ClN}_4\text{O}_3$ $[\text{M}-\text{H}]^-$: 289.0134, found 289.0135. The purity was determined by HPLC on Daicel AD-H chiral column with *i*-PrOH /Hexane (20:80) as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t_1 = 14.154 min; t_2 = 24.643 min



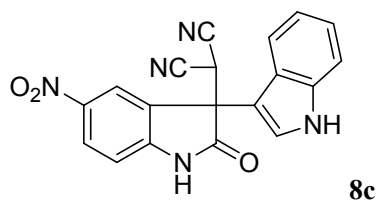
2-(3-(1H-indol-3-yl)-2-oxoindolin-3-yl)malononitrile

Brown oil, ^1H NMR (300 MHz, DMSO- d_6) δ 11.45 (s, 1H), 11.24 (s, 1H), 7.43 (t, J = 8.1 Hz, 4H), 7.10 (ddd, J = 22.8, 15.4, 8.0 Hz, 4H), 6.89 (t, J = 7.5 Hz, 1H), 6.30 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 175.08, 142.65, 137.20, 130.91, 128.01, 125.63, 125.08, 124.62, 123.15, 122.28, 119.80, 119.54, 113.01, 112.56, 112.29, 111.15, 108.29, 60.17, 52.86, 30.17, 21.14, 14.46. HRMS (QFT-ESI): calcd for $\text{C}_{19}\text{H}_{11}\text{N}_4\text{O}$ $[\text{M}-\text{H}]^-$: 311.0938, found 311.0935. The purity was determined by HPLC on Elite Hypersil NH_2 column with methanol as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t = 6.784 min.



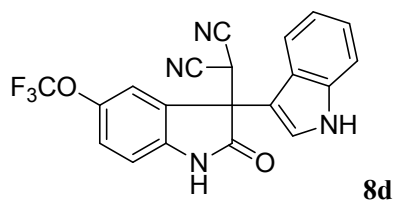
2-(3-(1H-indol-3-yl)-5-iodo-2-oxoindolin-3-yl)malononitrile

Brown oil, ^1H NMR (300 MHz, DMSO- d_6) δ 11.47 (s, 1H), 11.41 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.63 (s, 1H), 7.44 (dd, J = 11.5, 5.3 Hz, 2H), 7.15 – 7.01 (m, 2H), 6.93 (dd, J = 12.8, 7.8 Hz, 2H), 6.35 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 174.47, 142.29, 139.46, 137.12, 133.07, 130.63, 125.55, 124.37, 122.42, 120.01, 119.06, 113.60, 112.72, 112.04, 107.75, 85.90, 52.49, 29.81. HRMS (QFT-ESI): calcd for $\text{C}_{19}\text{H}_{10}\text{IN}_4\text{O}$ $[\text{M}-\text{H}]^-$: 436.9905, found 436.9901. The purity was determined by HPLC on Elite Hypersil NH_2 column with methanol as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t = 19.035 min.



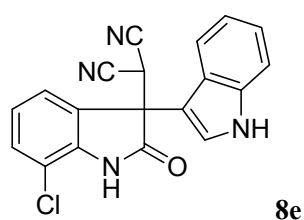
2-(3-(1H-indol-3-yl)-5-nitro-2-oxoindolin-3-yl)malononitrile

Brown oil, ^1H NMR (300 MHz, DMSO- d_6) δ 12.03 (s, 1H), 11.56 (s, 1H), 8.39 (dd, J = 8.7, 2.2 Hz, 1H), 8.31 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.37 – 7.25 (m, 2H), 7.13 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.53 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 175.44, 148.68, 143.23, 137.30, 128.78, 127.99, 126.14, 124.21, 122.54, 120.70, 120.18, 119.27, 112.82, 112.48, 111.88, 111.60, 106.93, 52.70, 29.72. HRMS (QFT-ESI): calcd for $\text{C}_{19}\text{H}_{10}\text{N}_5\text{O}_3$ $[\text{M}-\text{H}]^-$: 356.0789, found 356.0785. The purity was determined by HPLC on Elite Hypersil NH_2 column with methanol as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t = 51.267 min.



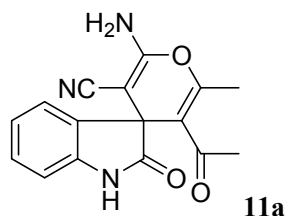
2-(3-(1H-indol-3-yl)-2-oxo-5-(trifluoromethoxy)indolin-3-yl)malononitrile

Brown oil, ^1H NMR (300 MHz, DMSO- d_6) δ 11.51 (s, 2H), 7.55 – 7.36 (m, 4H), 7.23 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 14.9, 7.5 Hz, 2H), 6.93 (t, J = 7.5 Hz, 1H), 6.41 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 175.05, 143.93, 143.90, 141.86, 137.19, 129.48, 125.75, 124.40, 124.33, 122.42, 119.96, 119.18, 118.67, 112.71, 112.66, 112.37, 111.98, 107.41, 53.01, 29.94. HRMS (QFT-ESI): calcd for $\text{C}_{20}\text{H}_{10}\text{F}_3\text{N}_4\text{O}_2$ $[\text{M}-\text{H}]^-$: 395.0761, found 395.0758. The purity was determined by HPLC on Elite Hypersil NH_2 column with methanol as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t = 18.902 min.



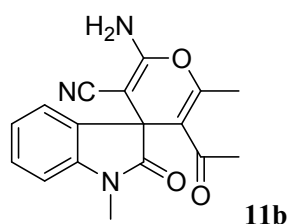
2-(7-chloro-3-(1H-indol-3-yl)-2-oxoindolin-3-yl)malononitrile

Brown oil, ^1H NMR (300 MHz, DMSO- d_6) δ 11.74 (s, 1H), 11.50 (d, J = 1.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 6.6, 3.4 Hz, 3H), 7.14 (dt, J = 19.8, 6.8 Hz, 3H), 6.94 (t, J = 7.5 Hz, 1H), 6.38 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 175.04, 140.37, 137.22, 130.95, 129.67, 125.79, 124.58, 128.41, 123.75, 122.41, 120.00, 119.37, 115.39, 112.70, 112.09, 107.61, 60.17, 53.63, 30.10. HRMS (QFT-ESI): calcd for $\text{C}_{19}\text{H}_{10}\text{ClN}_4\text{O}$ $[\text{M}-\text{H}]^-$: 345.0548, found 345.0544. The purity was determined by HPLC on Elite Hypersil NH_2 column with methanol as the eluent. Flow: 1.0 mL/min; λ = 254 nm: t = 14.718 min.



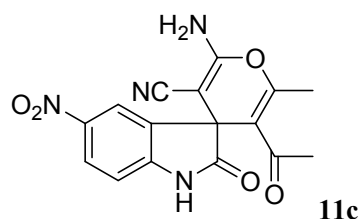
3'-acetyl-6'-amino-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp 243-244 °C (lit. **4** 240 °C), ^1H NMR (300 MHz, DMSO- d_6) δ 10.38 (s, 1H), 7.19 – 7.07 (m, 3H), 7.02 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 2.27 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 197.89, 178.92, 159.60, 156.61, 142.34, 134.49, 128.89, 123.72, 122.26, 117.96, 115.22, 109.81, 57.02, 49.76, 31.73, 19.76.



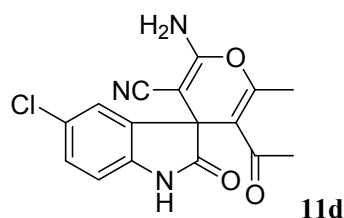
3'-acetyl-6'-amino-1,2'-dimethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp 248-250 °C (lit. **4** 250-252 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 7.24 (t, J = 7.6 Hz, 1H), 7.17 (s, 2H), 7.08 (d, J = 7.0 Hz, 1H), 6.98 (t, J = 7.9 Hz, 2H), 3.11 (s, 3H), 2.30 (s, 3H), 2.07 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 197.15, 176.95, 159.16, 156.81, 143.37, 133.39, 128.57, 122.91, 122.48, 117.36, 114.76, 108.28, 56.27, 48.91, 31.31, 26.33, 19.47.



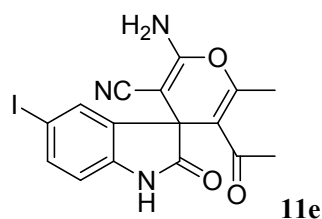
3'-acetyl-6'-amino-2'-methyl-5-nitro-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp >300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.11 (s, 1H), 8.12 (dd, J = 8.6, 2.2 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.33 (s, 2H), 6.98 (d, J = 8.6 Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 197.34, 179.58, 160.12, 159.44, 148.97, 142.68, 136.44, 126.14, 119.00, 117.58, 114.60, 109.78, 55.93, 49.93, 32.00, 20.57.



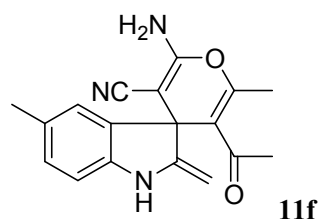
3'-acetyl-6'-amino-5-chloro-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp 276 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.80 (s, 1H), 7.20 (d, J = 10.7 Hz, 3H), 7.00 (d, J = 7.0 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 197.65, 178.94, 159.47, 157.96, 140.17, 136.63, 128.80, 123.47, 122.21, 117.77, 115.10, 113.93, 56.60, 50.66, 31.93, 20.08.



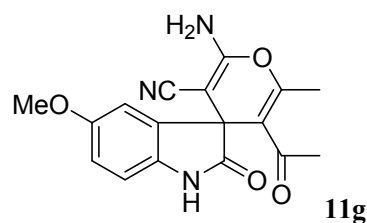
3'-acetyl-6'-amino-5-iodo-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp >300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.49 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.32 (s, 1H), 7.19 (s, 2H), 6.63 (d, J = 8.1 Hz, 1H), 2.33 (s, 3H), 2.17 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 197.42, 178.44, 159.39, 158.58, 142.14, 137.79, 137.26, 131.68, 117.82, 114.86, 112.24, 84.91, 56.69, 49.82, 31.98, 20.27.



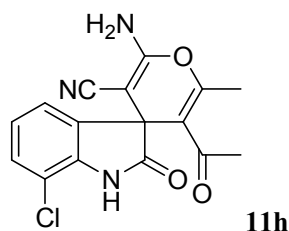
3'-acetyl-6'-amino-2',5-dimethyl-2-methylenespiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp 280-281 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.29 (s, 1H), 7.10 (s, 2H), 6.94 (d, J = 7.7 Hz, 1H), 6.83 (s, 1H), 6.66 (d, J = 7.8 Hz, 1H), 2.27 (s, 3H), 2.20 (s, 3H), 2.07 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 197.75, 178.90, 159.52, 156.69, 139.82, 134.70, 131.11, 129.17, 124.26, 118.01, 115.23, 109.58, 57.28, 49.82, 31.70, 21.04, 19.79.



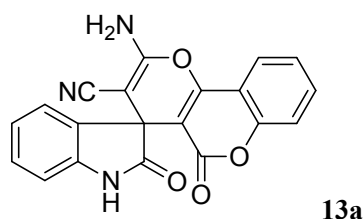
3'-acetyl-6'-amino-5-methoxy-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp 275-277 °C, ¹H NMR (600 MHz, DMSO-d₆) δ 10.22 (s, 1H), 7.11 (s, 2H), 6.74 (dt, J = 17.9, 5.4 Hz, 2H), 6.68 (d, J = 2.5 Hz, 1H), 3.68 (s, 3H), 2.29 (s, 3H), 2.11 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 197.95, 178.88, 159.67, 156.57, 155.55, 135.82, 135.73, 118.04, 115.20, 113.55, 110.71, 110.31, 57.27, 55.87, 50.35, 31.75, 19.80.



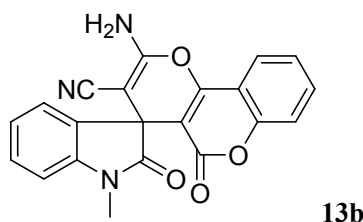
3'-acetyl-6'-amino-7-chloro-2'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carbonitrile⁴

Mp 276-277 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.80 (s, 1H), 7.20 (d, J = 9.4 Hz, 3H), 7.00 (d, J = 7.0 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 197.66, 178.95, 159.47, 157.98, 140.16, 136.63, 128.80, 123.48, 122.21, 117.78, 115.09, 113.93, 56.59, 50.66, 31.93, 20.08.



2'-amino-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile^{5,6}

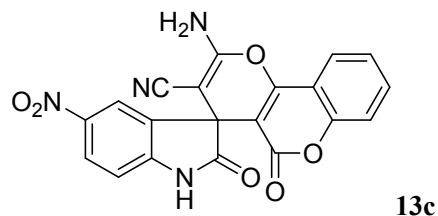
Mp >300 °C (lit. **6** >300 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.69 (s, 1H), 7.92 (dd, J = 7.8, 1.1 Hz, 1H), 7.80 – 7.71 (m, 1H), 7.68 (s, 2H), 7.57 – 7.43 (m, 2H), 7.20 (dt, J = 7.4, 3.6 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ 177.58, 158.84, 158.69, 155.48, 152.43, 142.57, 134.08, 133.45, 129.34, 125.42, 124.54, 123.07, 122.47, 117.41, 117.07, 112.85, 109.92, 101.80, 57.37, 48.00.



2'-amino-1-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitril⁶

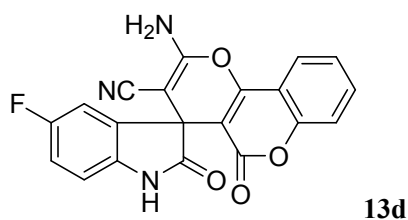
Mp 227-229 °C (lit. **6** 225 °C), ¹H NMR (600 MHz, DMSO-d₆) δ 7.96 (d, J = 7.8 Hz, 1H), 7.74 (s, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 3.23 (s, 3H). ¹³C NMR (151 MHz, DMSO-

d6) δ 176.16, 159.07, 158.76, 155.65, 152.52, 144.14, 134.17, 132.71, 129.62, 125.46, 124.34, 123.32, 123.19, 117.36, 117.12, 112.89, 108.97, 101.77, 57.18, 56.55, 47.74, 27.03.



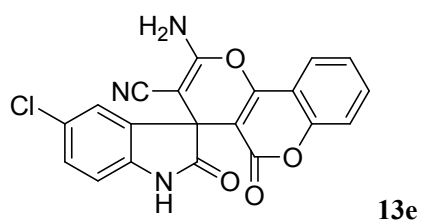
2'-amino-5-nitro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile⁶

Mp 200-202 °C (lit. **6** 198 °C), ¹H NMR (600 MHz, DMSO-d₆) δ 11.46 (s, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 8.7, 2.1 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.87 (s, 2H), 7.77 (t, J = 7.8 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H). ¹³C NMR (151 MHz, DMSO-d₆) δ 178.41, 159.30, 159.19, 156.31, 152.61, 149.10, 143.25, 134.48, 134.22, 126.79, 125.47, 123.29, 121.01, 117.32, 117.14, 113.13, 110.20, 100.71, 56.54, 56.14, 48.28.



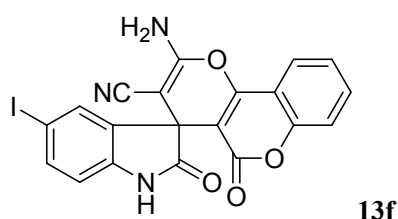
2'-amino-5-fluoro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile⁶

Mp >300 °C (lit. **6** >300 °C), ¹H NMR (600 MHz, DMSO-d₆) δ 10.73 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.73 (s, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 8.7 Hz, 1H), 6.88 (dd, J = 8.1, 3.9 Hz, 1H). ¹³C NMR (151 MHz, DMSO-d₆) δ 177.74, 159.64, 159.04, 158.88, 158.06, 155.82, 152.58, 138.90, 135.20, 135.15, 134.16, 125.45, 123.21, 117.35, 117.12, 115.75, 113.01, 112.71, 112.54, 110.74, 110.69, 101.41, 57.13, 48.61.



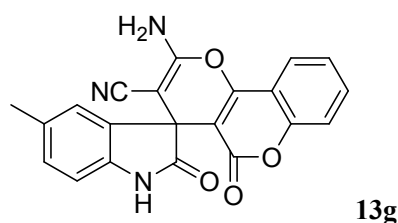
2'-amino-5-chloro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile^{5, 6}

Mp 277-279 °C (lit. **6** 275 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.85 (s, 1H), 7.97 – 7.87 (m, 1H), 7.81 – 7.69 (m, 3H), 7.56 – 7.39 (m, 3H), 7.26 (dd, J = 8.3, 2.1 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ 177.48, 158.98, 158.91, 155.84, 152.48, 141.50, 135.44, 134.07, 129.23, 126.53, 125.36, 125.00, 123.13, 117.37, 117.04, 112.96, 111.31, 101.15, 56.74, 48.28.



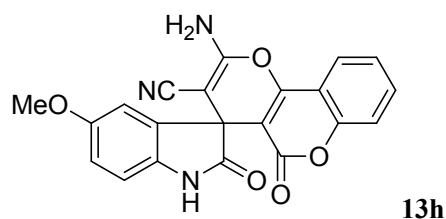
2'-amino-5-iodo-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile⁶

Mp >300 °C, ¹H NMR (600 MHz, DMSO-d₆) δ 10.85 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.75 (s, 2H), 7.67 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H). ¹³C NMR (151 MHz, DMSO-d₆) δ 177.24, 159.06, 159.00, 155.92, 152.55, 142.48, 137.97, 136.11, 134.10, 133.08, 125.42, 123.23, 117.48, 117.10, 113.08, 112.48, 101.31, 85.49, 56.99, 56.59, 48.12.



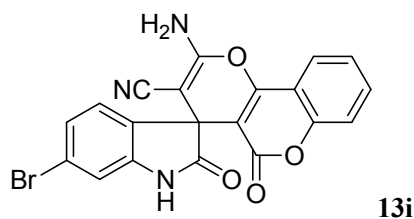
2'-amino-5-methyl-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile⁷

Mp >300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.59 (s, 1H), 7.96 – 7.88 (m, 1H), 7.78 – 7.70 (m, 1H), 7.66 (s, 2H), 7.49 (dd, J = 18.9, 8.0 Hz, 2H), 7.01 (d, J = 10.0 Hz, 2H), 6.74 (d, J = 7.7 Hz, 1H), 2.18 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 177.55, 158.81, 158.70, 155.42, 152.41, 140.10, 134.03, 133.57, 131.41, 129.59, 125.40, 125.07, 123.05, 117.48, 117.04, 112.86, 109.66, 101.92, 57.57, 48.03, 20.98.



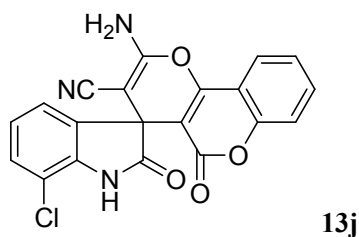
2'-amino-5-methoxy-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile⁶

Mp 271-273 °C (lit. **6** 269 °C), ¹H NMR (600 MHz, DMSO-d₆) δ 10.53 (s, 1H), 7.95 (dd, J = 7.9, 1.4 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.67 (s, 2H), 7.52 (dd, J = 11.4, 4.1 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.94 (s, 1H), 6.80 (d, J = 1.4 Hz, 2H), 3.67 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 177.62, 158.92, 158.82, 155.78, 155.61, 152.53, 135.93, 134.79, 134.03, 125.38, 123.16, 117.55, 117.08, 114.26, 113.04, 111.40, 110.40, 101.89, 57.71, 55.89, 48.61



2'-amino-6-bromo-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile⁷

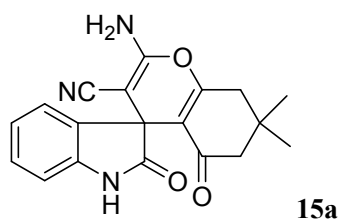
Mp >300 °C, ¹H NMR (600 MHz, DMSO-d₆) δ 10.88 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.75 (s, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.04 (s, 1H). ¹³C NMR (151 MHz, DMSO-d₆) δ 177.59, 159.02, 158.89, 155.80, 152.54, 144.34, 134.23, 132.81, 126.60, 125.51, 125.22, 123.19, 122.02, 117.37, 117.16, 112.91, 112.81, 101.30, 56.78, 56.53, 47.92.



2'-amino-7-chloro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-

carbonitrile⁶

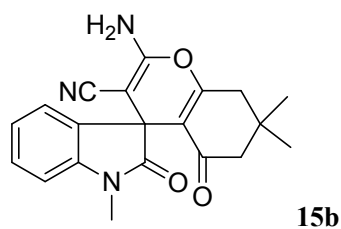
Mp >300 °C (lit. **6** >300 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.00 – 7.88 (m, 1H), 7.78 (s, 2H), 7.76 – 7.70 (m, 1H), 7.50 (dd, J = 16.7, 8.1 Hz, 2H), 7.25 (dd, J = 16.2, 7.7 Hz, 2H), 6.96 (t, J = 7.8 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ 177.67, 158.92, 158.84, 155.68, 152.45, 140.34, 135.15, 134.21, 129.43, 125.46, 123.82, 123.35, 123.14, 117.29, 117.10, 114.14, 112.78, 101.29, 56.80, 56.45, 48.87, 18.93.



2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-

carbonitrile^{5, 8-10}

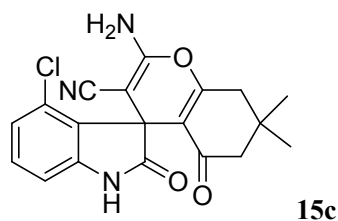
Mp >300 °C (lit. **10** >300 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.41 (s, 1H), 7.23 (s, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.59 – 2.47 (m, 2H), 2.12 (q, J = 16.0 Hz, 2H), 0.99 (d, J = 9.8 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.34, 178.48, 164.58, 159.17, 142.42, 134.81, 128.59, 123.41, 122.12, 117.78, 111.16, 109.67, 57.84, 50.38, 47.20, 32.34, 28.01, 27.40, 18.96.



2-amino-1',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-

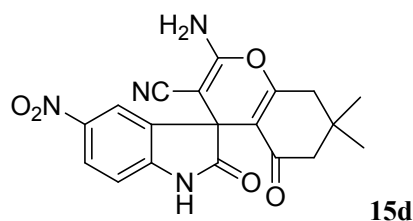
carbonitrile⁹

Mp 237-239 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 7.34 – 7.19 (m, 3H), 7.03 (d, J = 7.0 Hz, 1H), 6.96 (t, J = 7.5 Hz, 2H), 3.12 (s, 3H), 2.52 (d, J = 19.8 Hz, 2H), 2.10 (q, J = 16.0 Hz, 2H), 0.99 (d, J = 10.1 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.35, 176.97, 164.69, 159.28, 143.93, 133.93, 128.82, 123.17, 122.87, 117.64, 111.10, 108.60, 57.37, 50.31, 46.84, 32.38, 27.93, 27.44, 26.77.



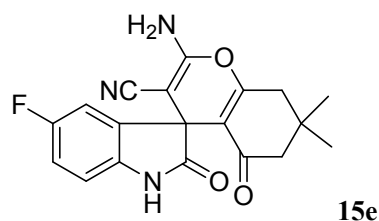
2-amino-4'-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile⁸

Mp >300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.70 (s, 1H), 7.36 (s, 2H), 7.18 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.64 – 2.38 (m, 2H), 2.15 (dd, J = 51.2, 16.1 Hz, 2H), 1.01 (d, J = 11.7 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.52, 177.67, 165.53, 160.23, 144.40, 130.47, 129.49, 129.38, 122.51, 117.56, 109.73, 108.82, 54.79, 50.25 47.68, 32.16, 28.55, 26.96, 18.97.



2-amino-7,7-dimethyl-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile^{8,9}

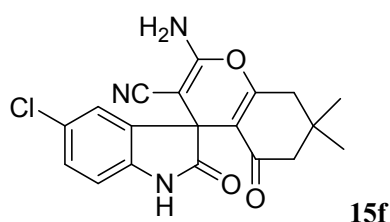
Mp >300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 11.20 (s, 1H), 8.14 (dd, J = 8.6, 2.2 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.47 (s, 2H), 7.01 (d, J = 8.6 Hz, 1H), 2.57 (dd, J = 43.3, 17.5 Hz, 2H), 2.23 – 2.06 (m, 2H), 1.02 (d, J = 10.7 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.81, 179.05, 165.63, 159.49, 149.04, 142.80, 135.76, 126.21, 119.27, 117.50, 110.14, 109.85, 56.44, 56.22, 50.17, 47.35, 32.45, 28.05, 27.38, 18.93.



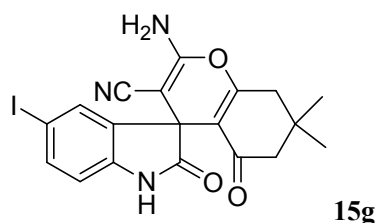
2-amino-5'-fluoro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile^{8,9}

3-carbonitrile^{8,9}

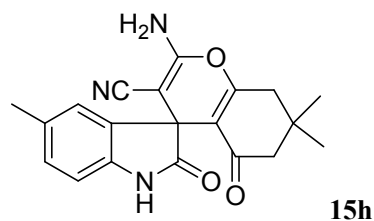
Mp 300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.44 (s, 1H), 7.30 (s, 2H), 6.95 (t, J = 7.5 Hz, 2H), 6.84 – 6.70 (m, 1H), 2.53 (s, 2H), 2.13 (s, 2H), 1.02 (d, J = 11.6 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.44, 195.41, 178.51, 164.88, 160.16, 159.28, 157.03, 138.69, 138.67, 136.53, 136.43, 117.62, 114.94, 114.64, 111.48, 111.15, 110.72, 110.36, 110.26, 57.36, 56.46, 50.37, 47.76, 47.74, 32.32, 27.77, 27.72, 18.93.

**2-amino-5'-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile^{5, 8-10}**

Mp 289-291 °C (lit. **10** 286-288 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.56 (s, 1H), 7.32 (s, 2H), 7.18 (dd, J = 8.2, 1.6 Hz, 1H), 7.09 (s, 1H), 6.80 (d, J = 8.2 Hz, 1H), 2.63 – 2.47 (m, 2H), 2.13 (s, 2H), 1.02 (d, J = 13.3 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.55, 177.90, 165.01, 159.24, 142.30, 137.44, 137.17, 131.77, 117.68, 112.19, 110.61, 84.89, 57.16, 56.47, 50.33, 47.22, 32.41, 27.91, 27.59, 18.98.

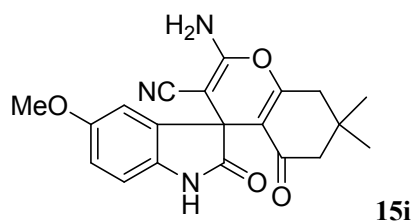
**2-amino-5'-iodo-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile⁹**

Mp 298-300 °C, ¹H NMR (300 MHz, DMSO-d₆) δ 10.54 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 3.1 Hz, 3H), 6.65 (d, J = 8.1 Hz, 1H), 2.53 (q, J = 17.5 Hz, 2H), 2.14 (s, 2H), 1.02 (d, J = 14.1 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.55, 177.90, 165.01, 159.24, 142.30, 137.44, 137.17, 131.77, 117.68, 112.19, 110.61, 84.89, 57.16, 56.47, 50.33, 47.22, 32.41, 27.91, 27.59, 18.98.



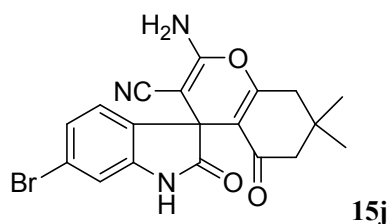
2-amino-5',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile⁹⁻¹¹

Mp 279-281 °C (lit. **11** 279-280 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.29 (s, 1H), 7.20 (s, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.77 (s, 1H), 6.66 (d, J = 7.8 Hz, 1H), 2.54 (s, 2H), 2.15 (d, J = 18.9 Hz, 5H), 1.00 (d, J = 6.0 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.32, 178.43, 164.47, 159.11, 139.99, 134.91, 130.87, 128.85, 124.00, 117.82, 111.22, 109.40, 58.03, 50.41, 47.23, 32.36, 27.86, 27.60, 21.07.



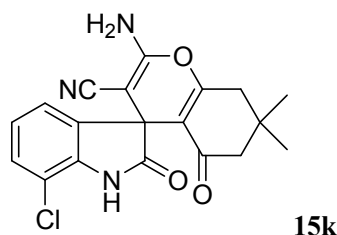
2-amino-5'-methoxy-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile⁸

Mp 289-291 °C (lit. **8** 287-289 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.23 (s, 1H), 7.23 (s, 2H), 6.69 (s, 2H), 6.59 (s, 1H), 3.63 (s, 3H), 2.53 (s, 2H), 2.21 – 2.03 (m, 2H), 1.00 (d, J = 5.3 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.34, 178.36, 164.56, 159.14, 155.35, 136.13, 135.75, 117.81, 112.91, 111.09, 110.48, 109.96, 57.89, 55.69, 50.40, 47.65, 32.34, 27.95, 27.49.



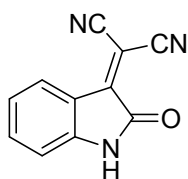
2-amino-6'-bromo-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile^{7, 11}

Mp >300 °C, (lit. **11** >300 °C) ¹H NMR (300 MHz, DMSO-d₆) δ 10.58 (s, 1H), 7.32 (s, 2H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.94 (dd, *J* = 10.0, 4.5 Hz, 2H), 2.51 (d, *J* = 15.1 Hz, 2H), 2.12 (q, *J* = 16.1 Hz, 2H), 0.99 (d, *J* = 8.1 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.50, 178.33, 164.92, 159.23, 144.15, 134.09, 125.36, 124.75, 121.15, 117.63, 112.41, 110.67, 57.00, 56.45, 50.28, 47.00, 32.37, 27.87, 27.52, 18.96.



2-amino-7'-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile⁹⁻¹¹

Mp >300 °C, (lit. **11** >300 °C), ¹H NMR (300 MHz, DMSO-d₆) δ 10.86 (s, 1H), 7.34 (s, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 6.9 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 2.51 (d, *J* = 18.4 Hz, 2H), 2.13 (q, *J* = 16.0 Hz, 2H), 0.99 (d, *J* = 10.1 Hz, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 195.51, 178.46, 164.90, 159.23, 140.17, 136.50, 128.69, 123.47, 122.19, 117.62, 113.91, 110.81, 57.17, 56.45, 50.25, 48.07, 32.38, 27.90, 27.44, 18.95.

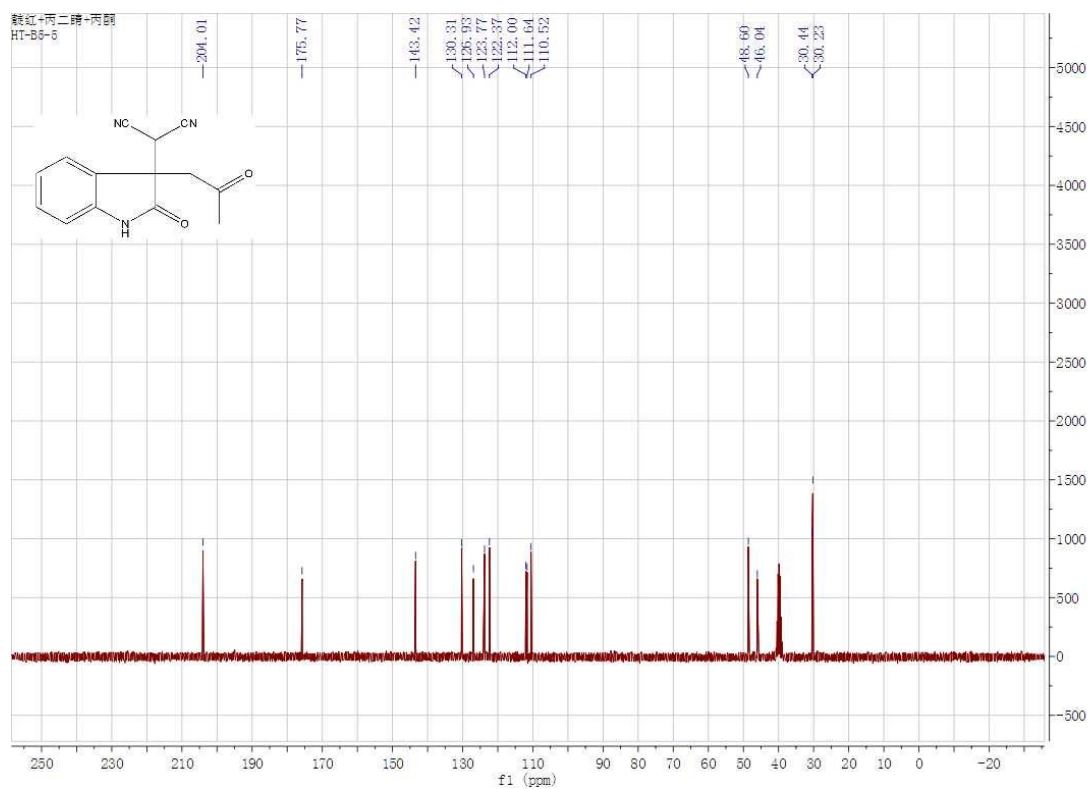
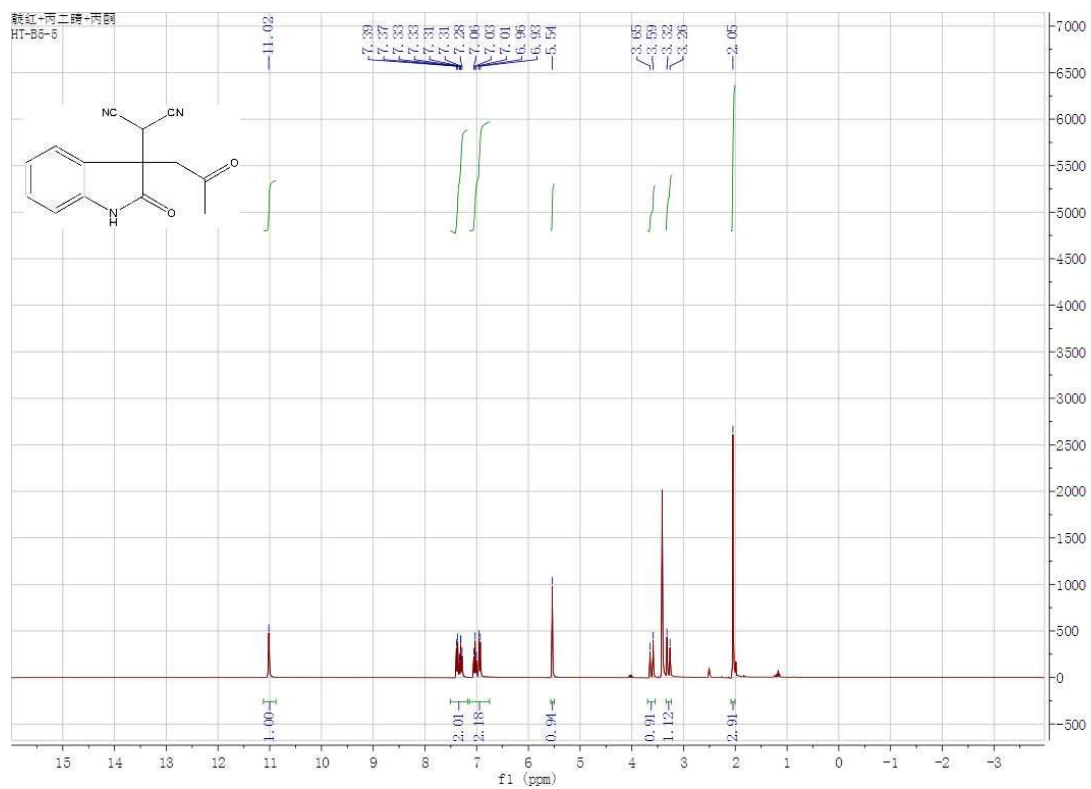


2-(2-oxoindolin-3-ylidene)malononitrile¹²

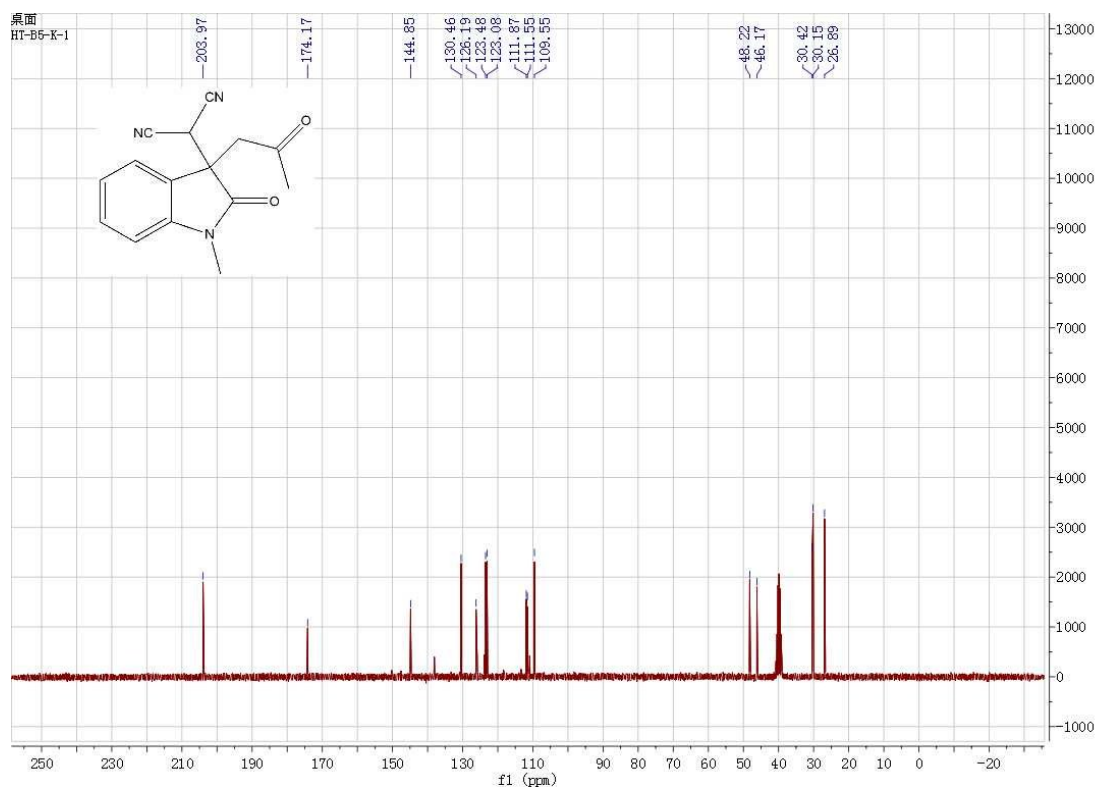
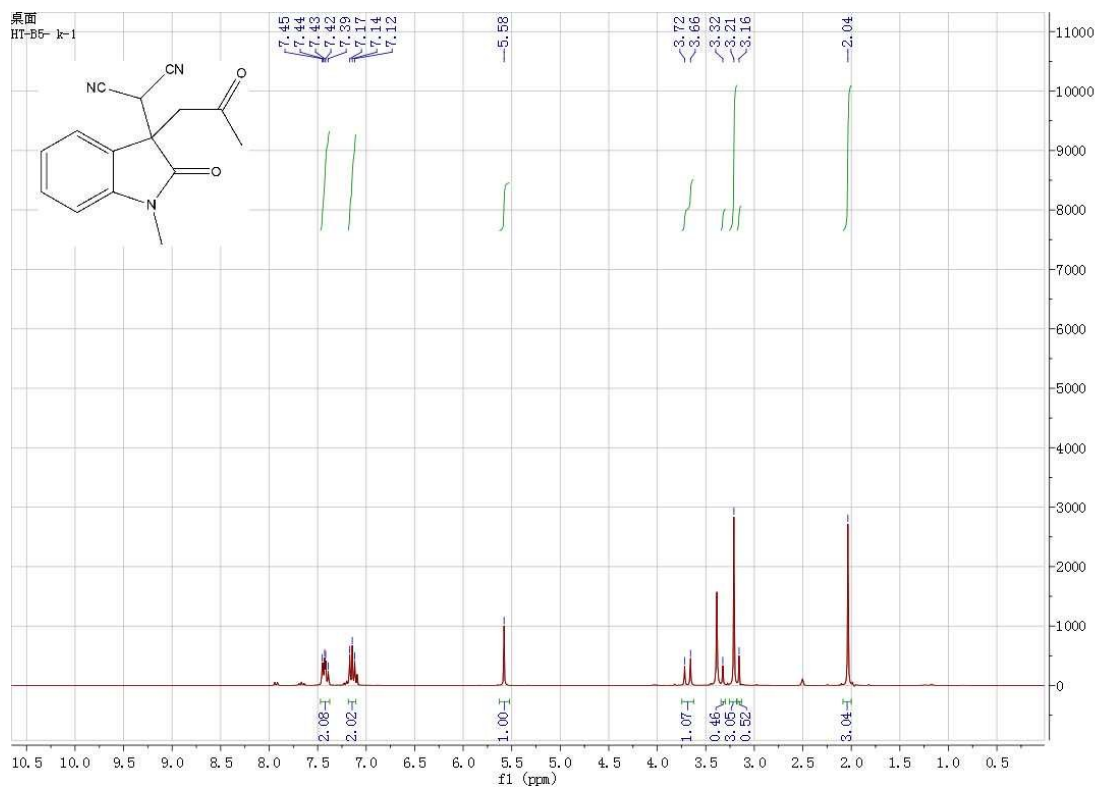
Mp 234-235 °C (lit. 232-233 °C), ¹H NMR (600 MHz, DMSO-d₆) δ 11.20 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.9, 0.9 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H).

8 ^1H NMR, ^{13}C NMR, HRMS Spectra Copies and HPLC traces of the products

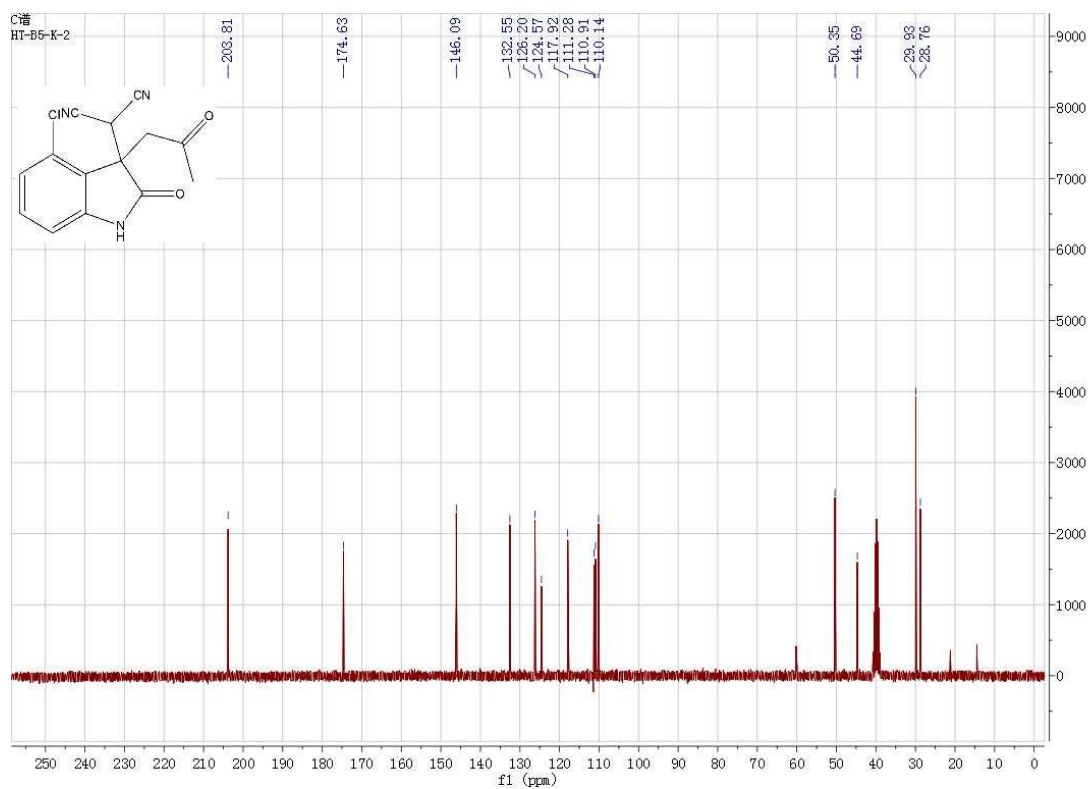
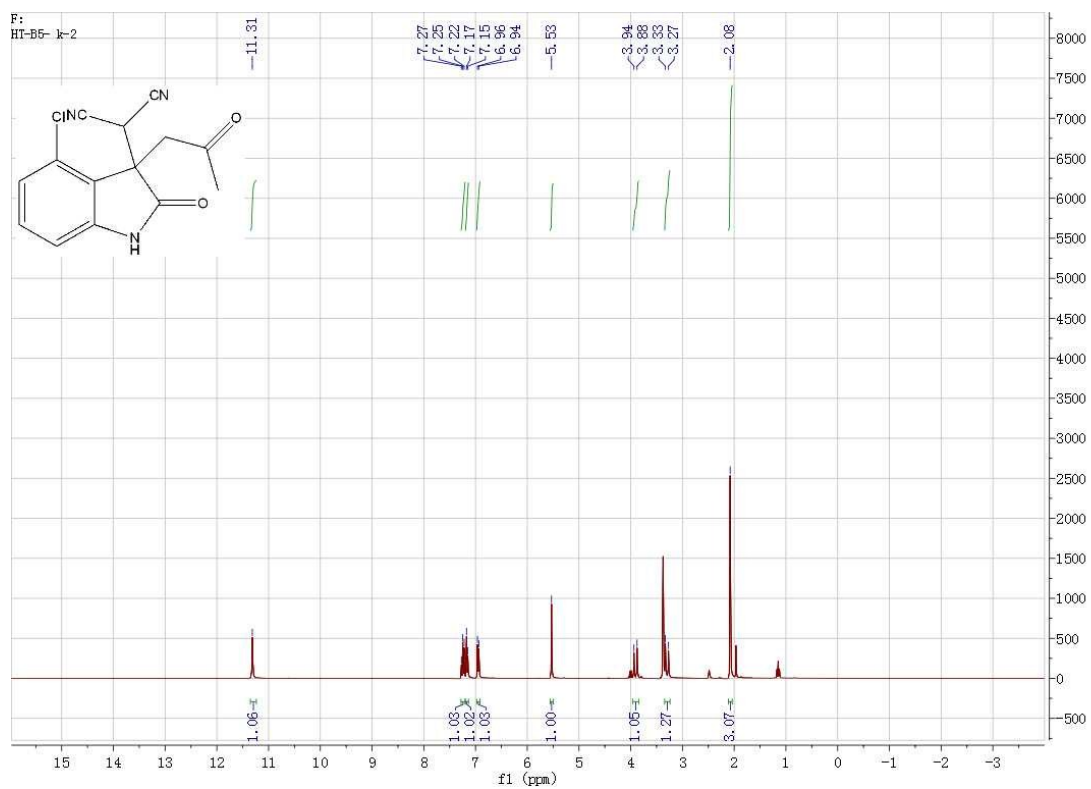
4a



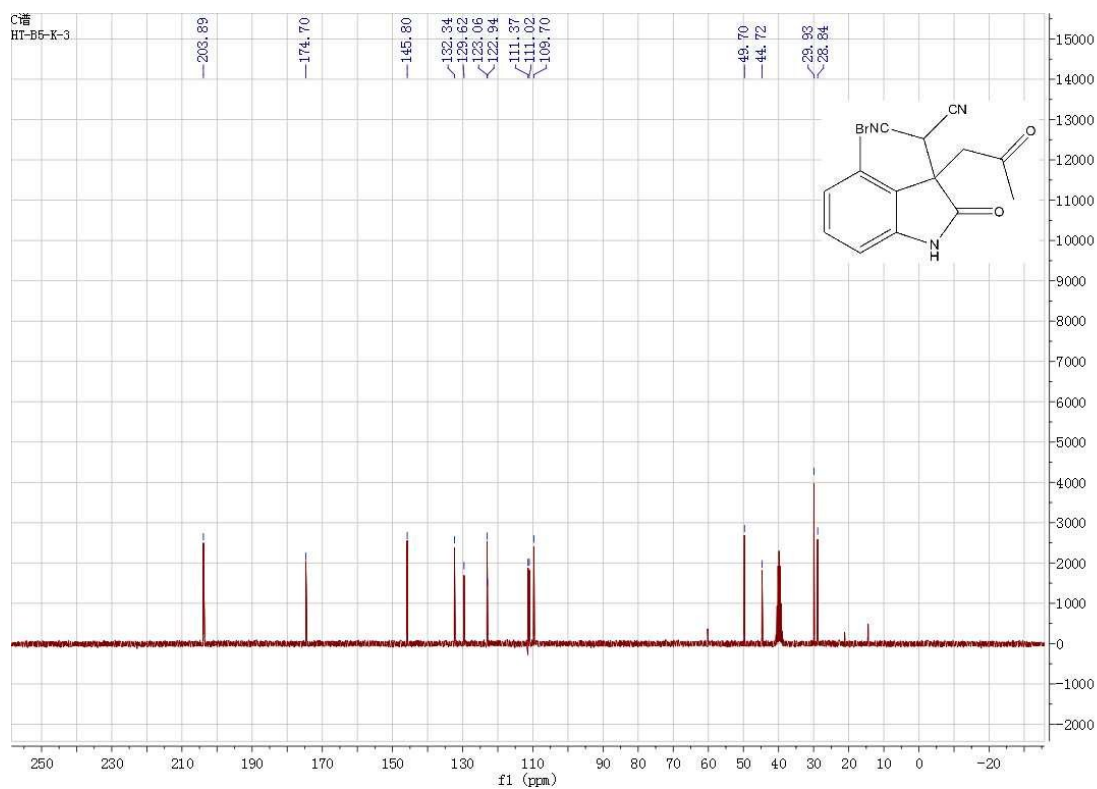
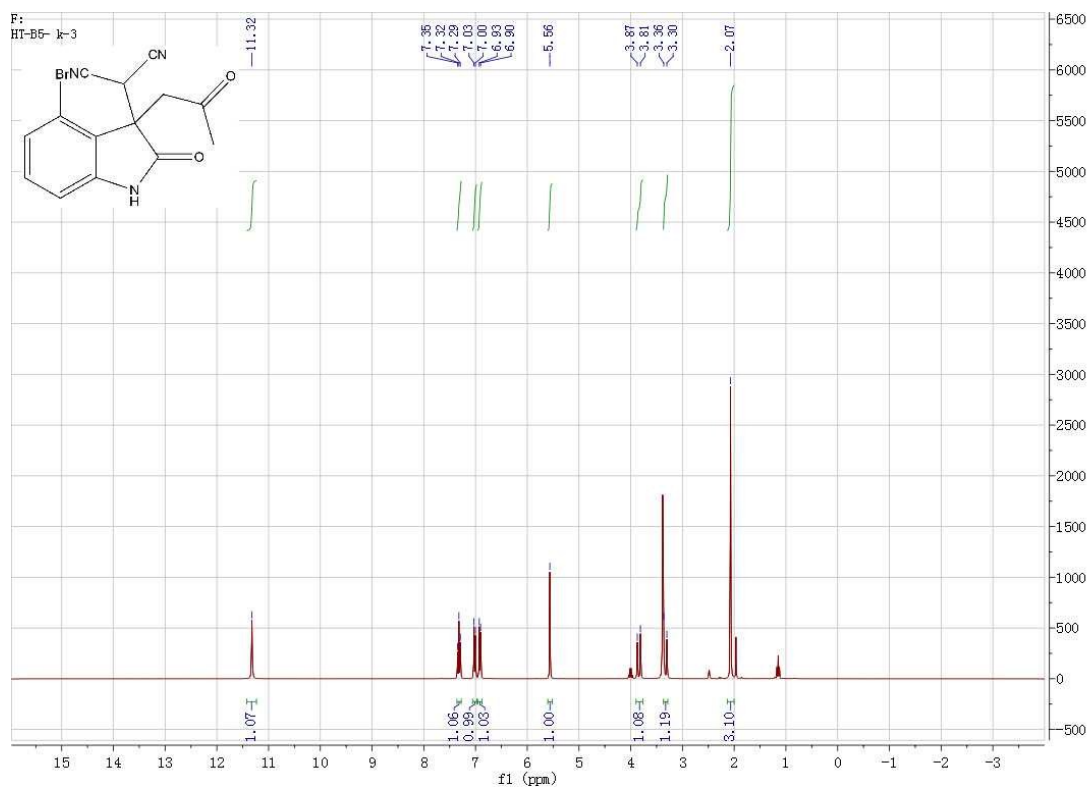
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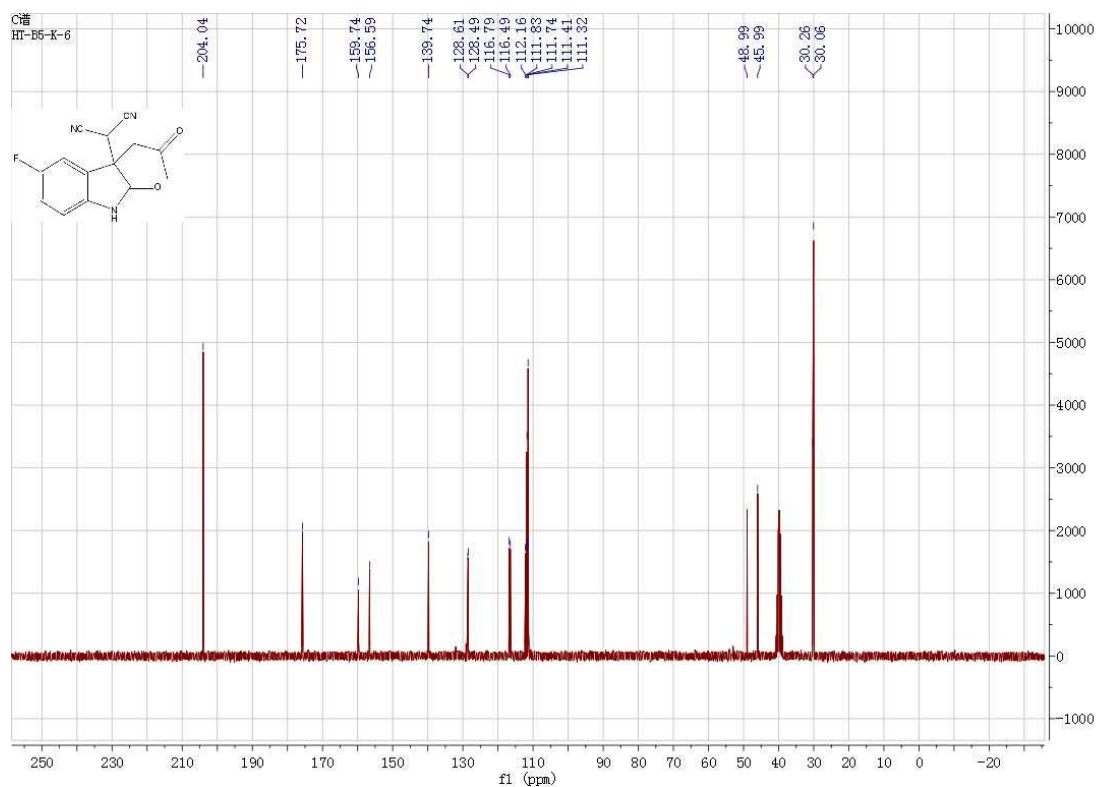
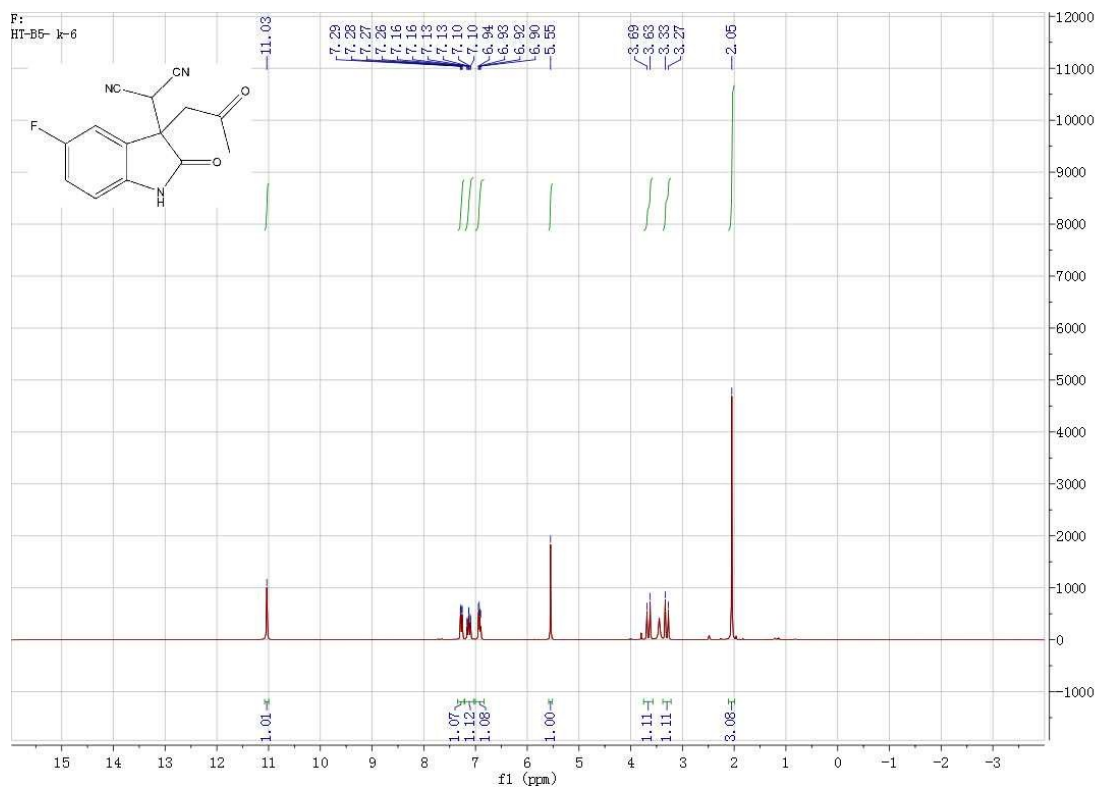


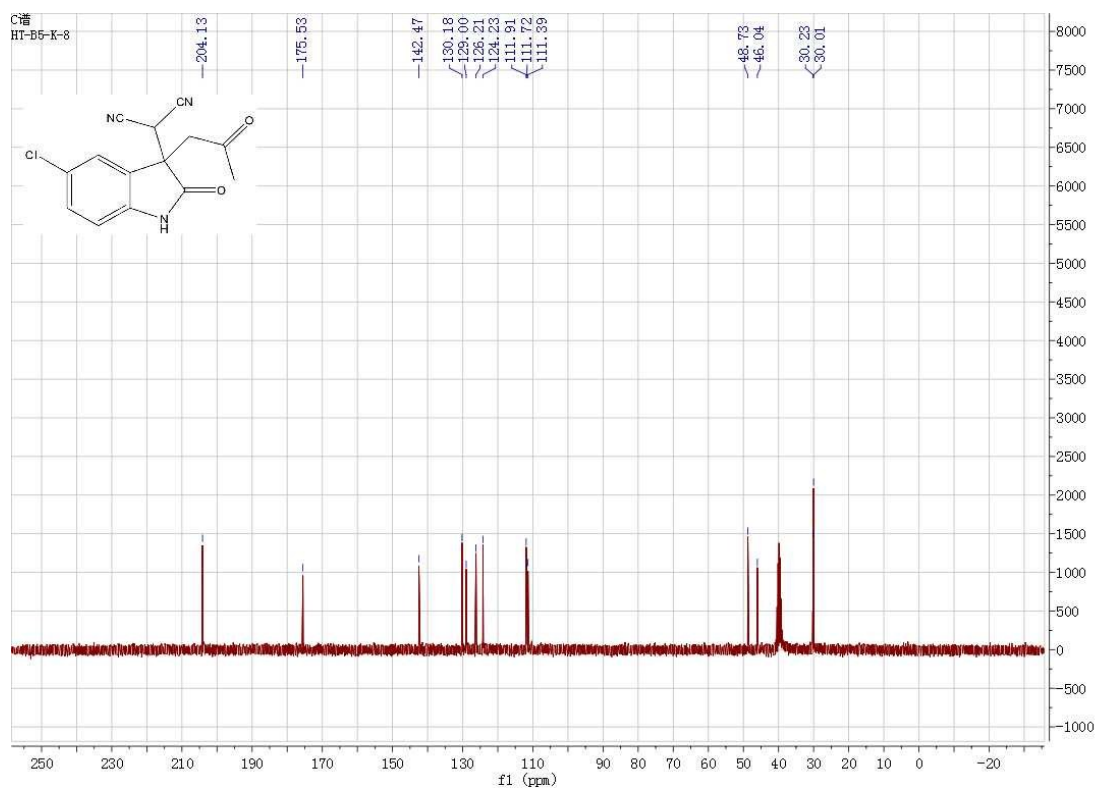
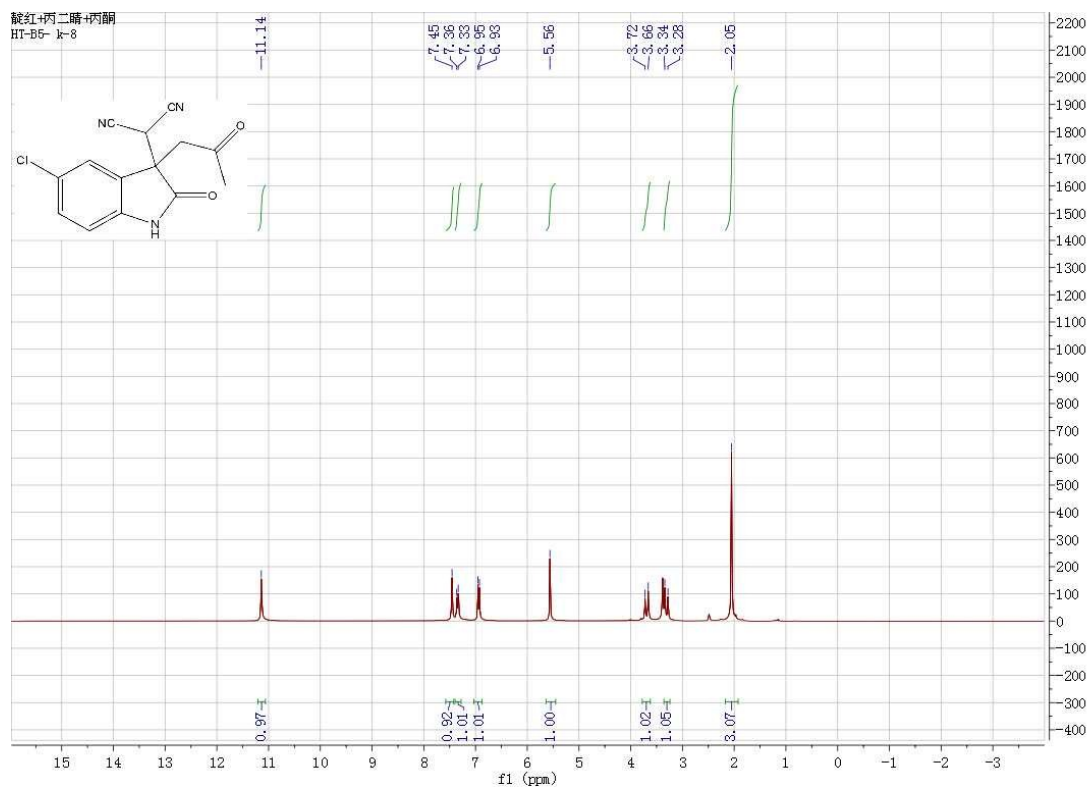
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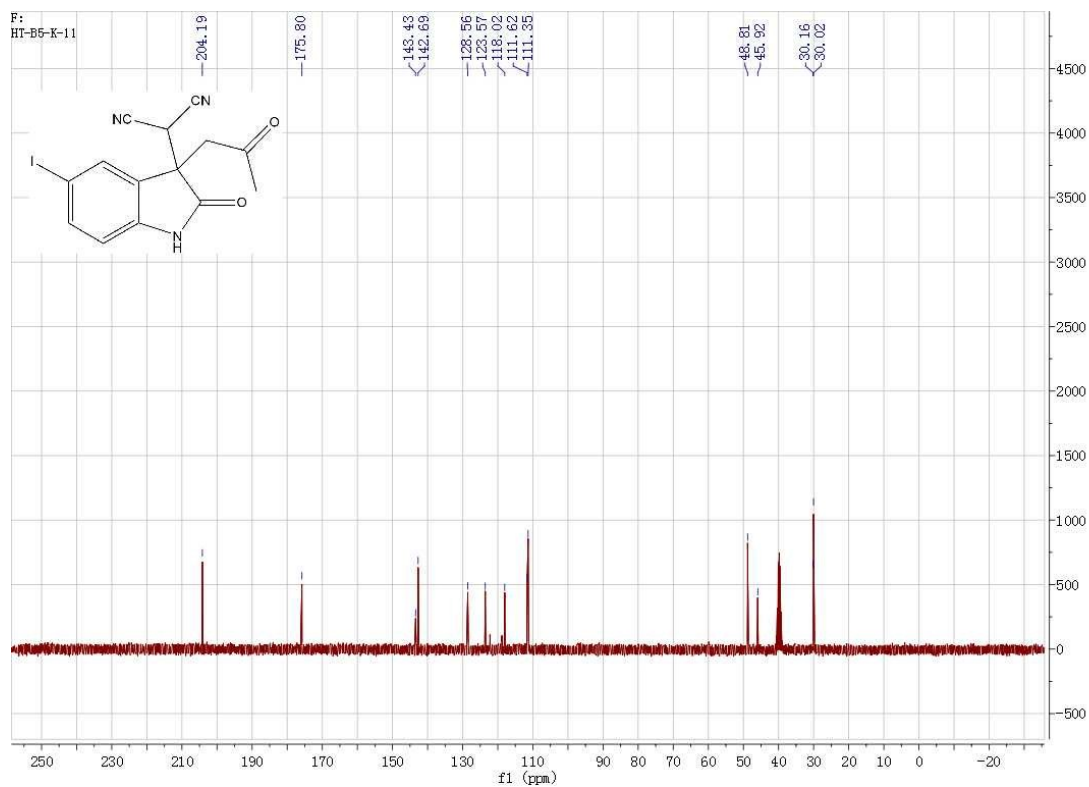
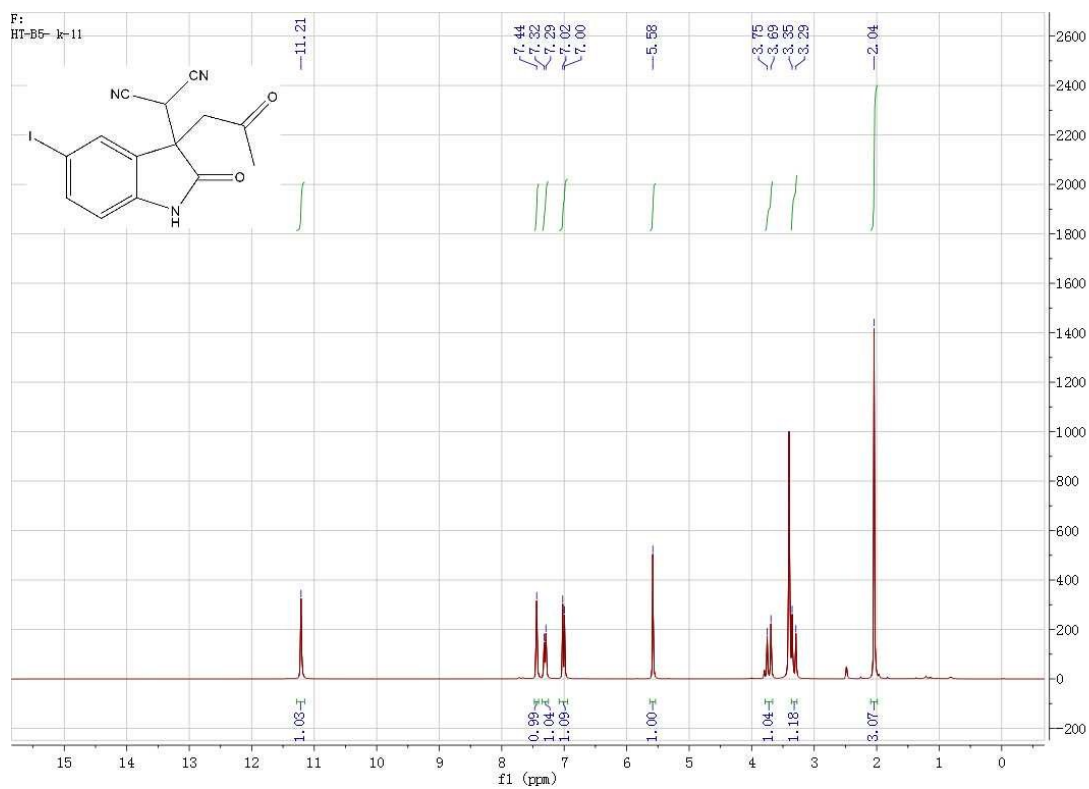
4d



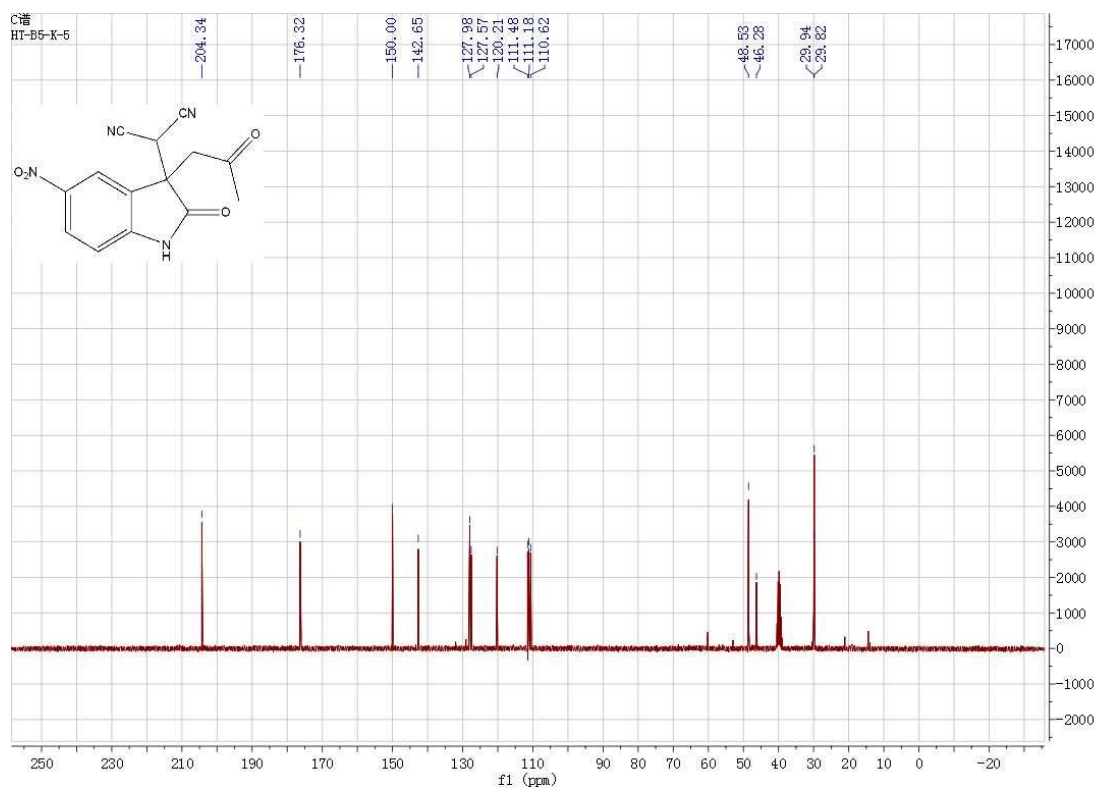
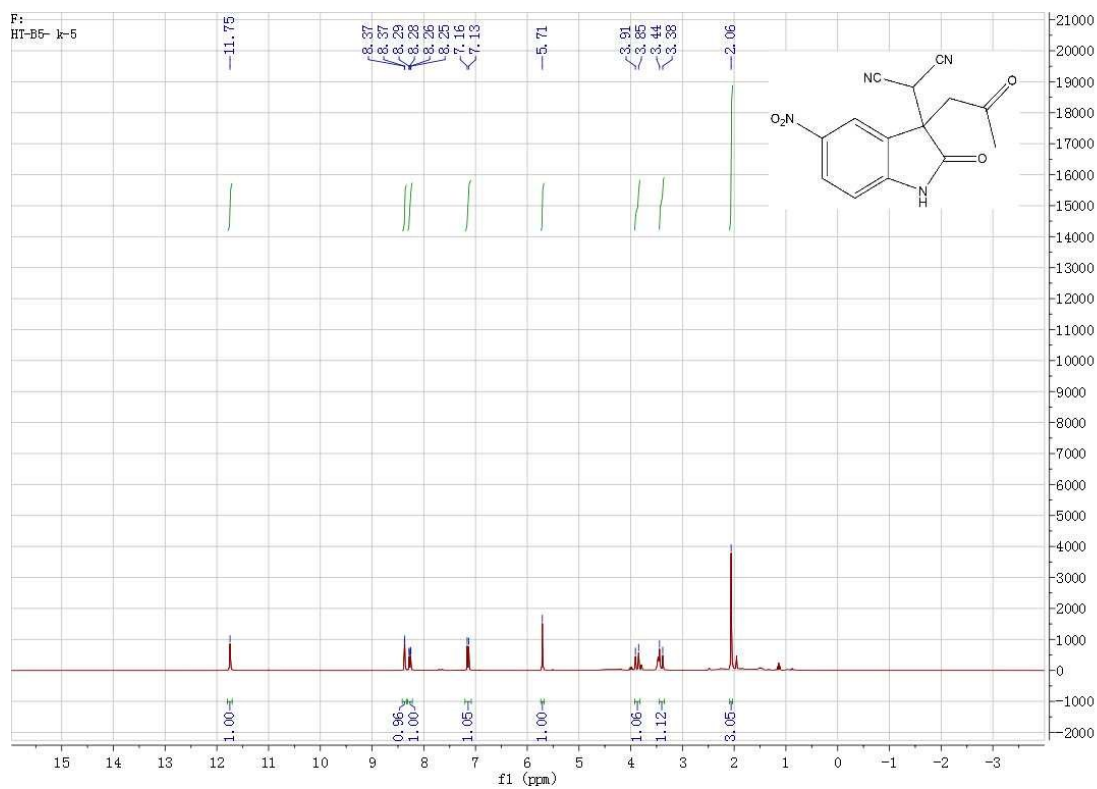


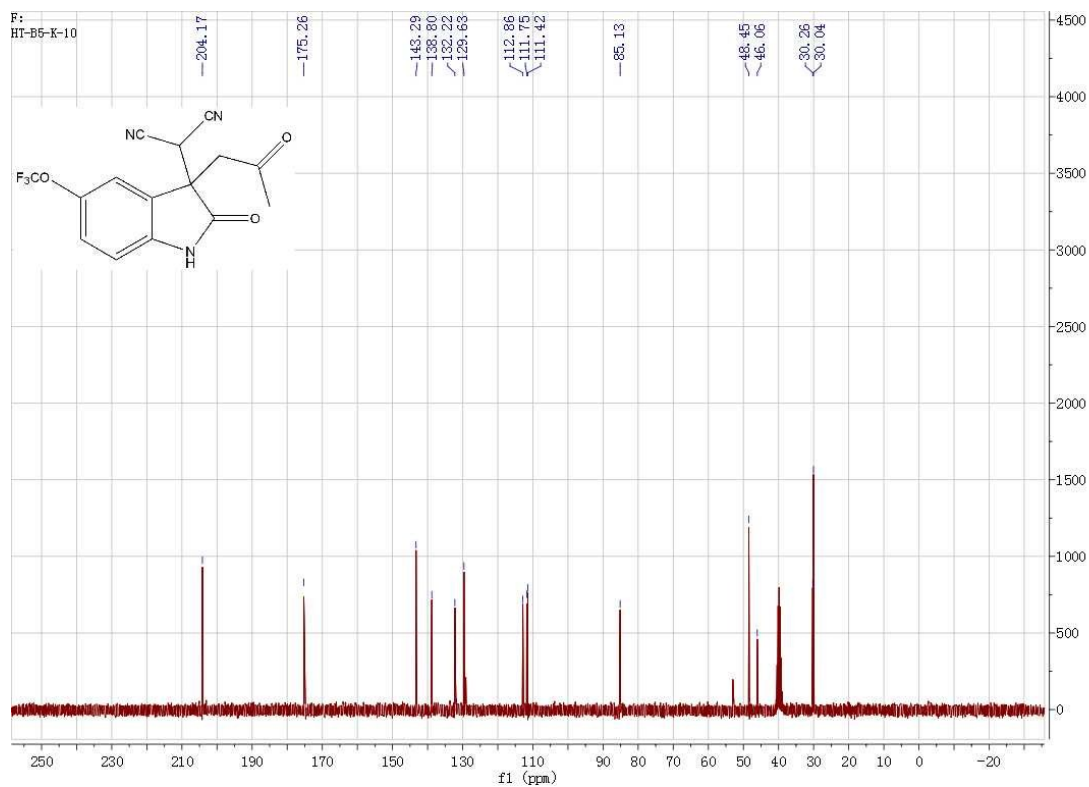
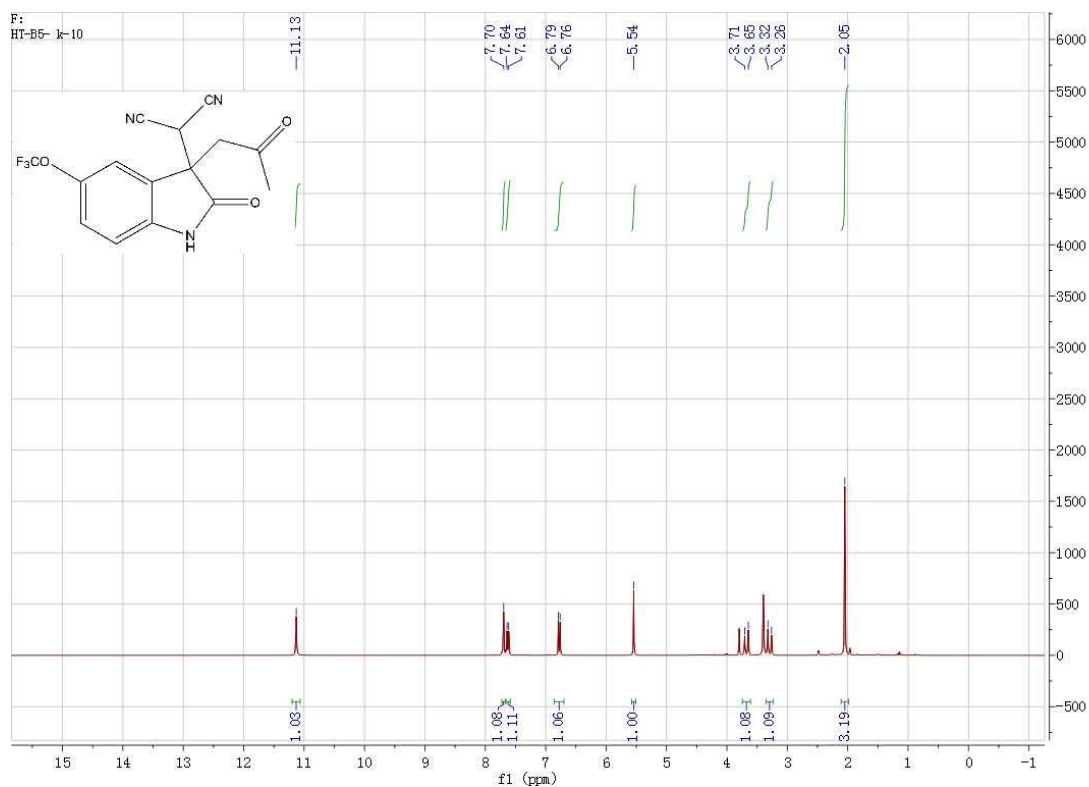


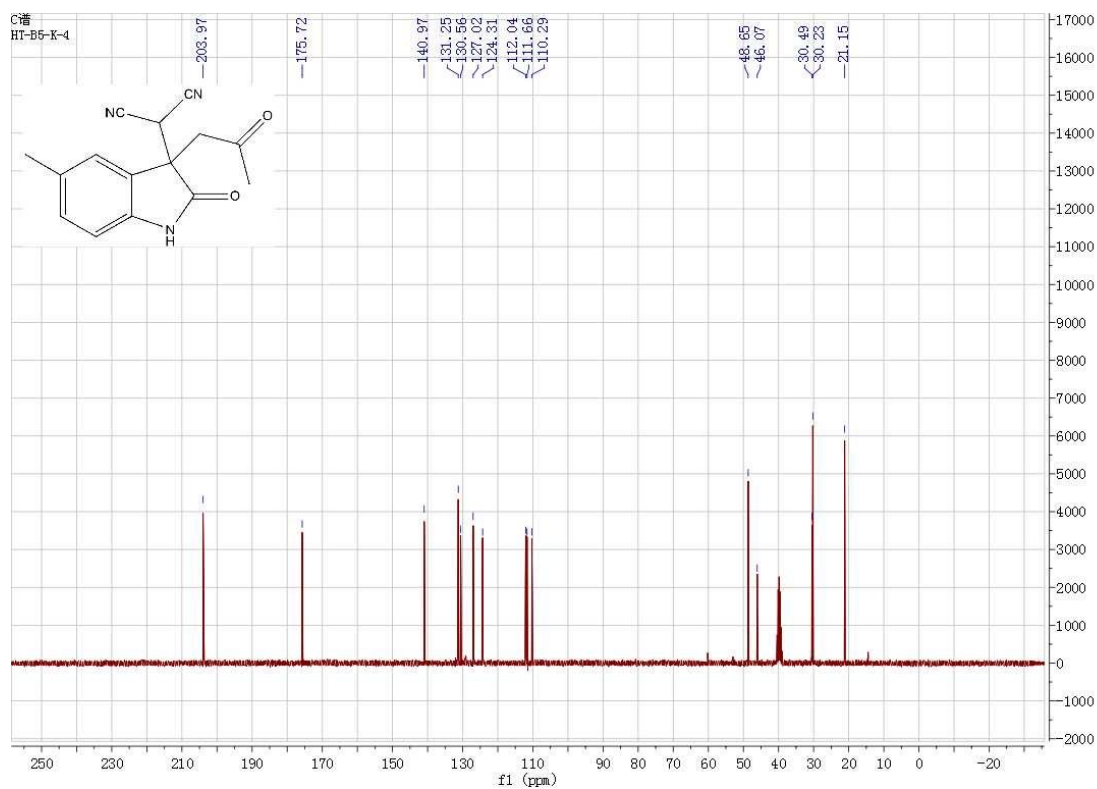
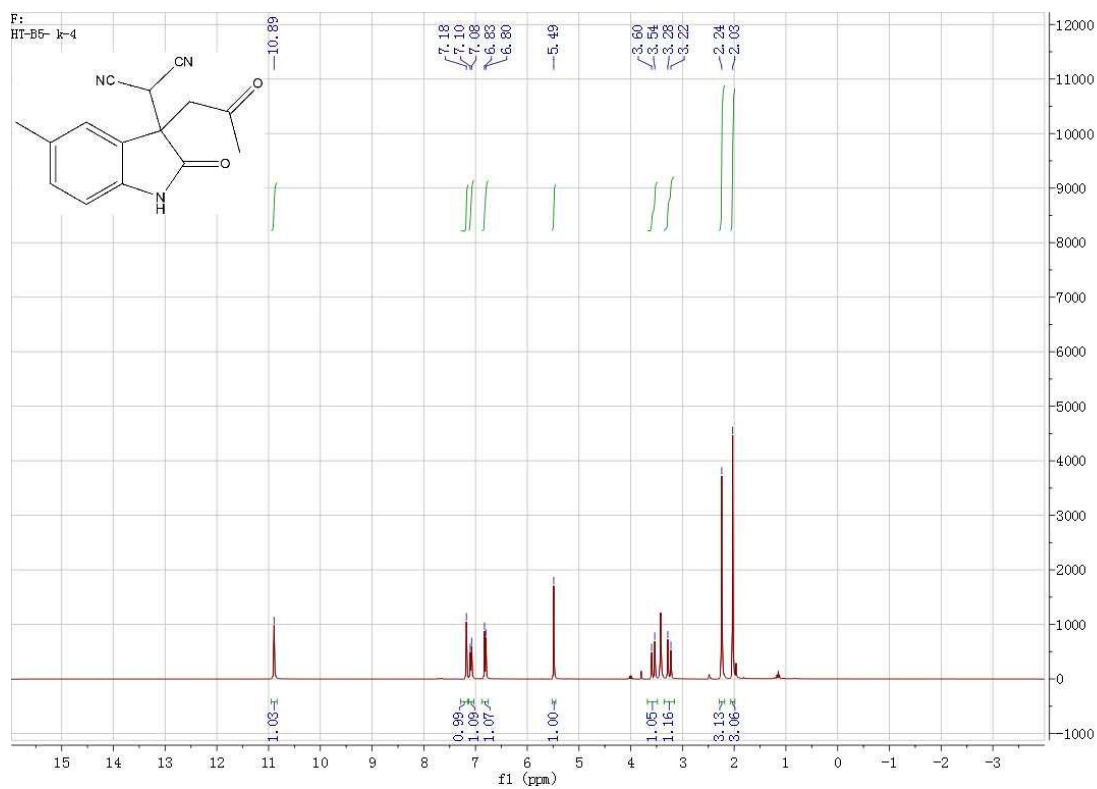
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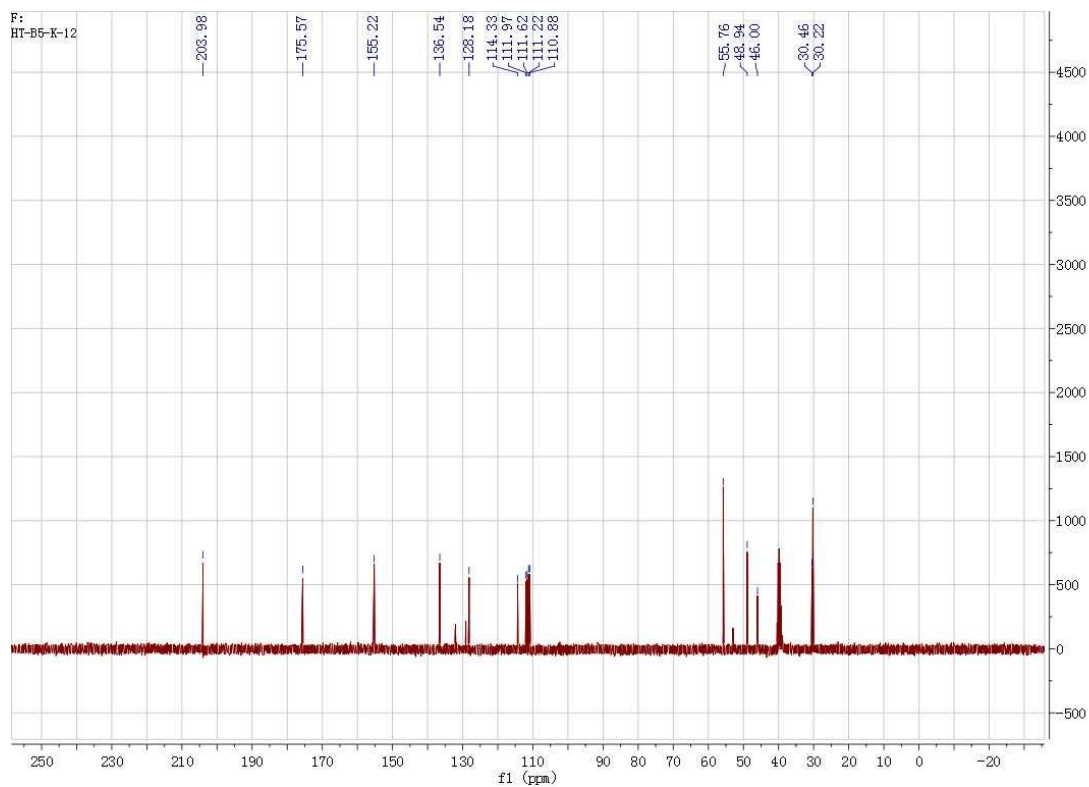
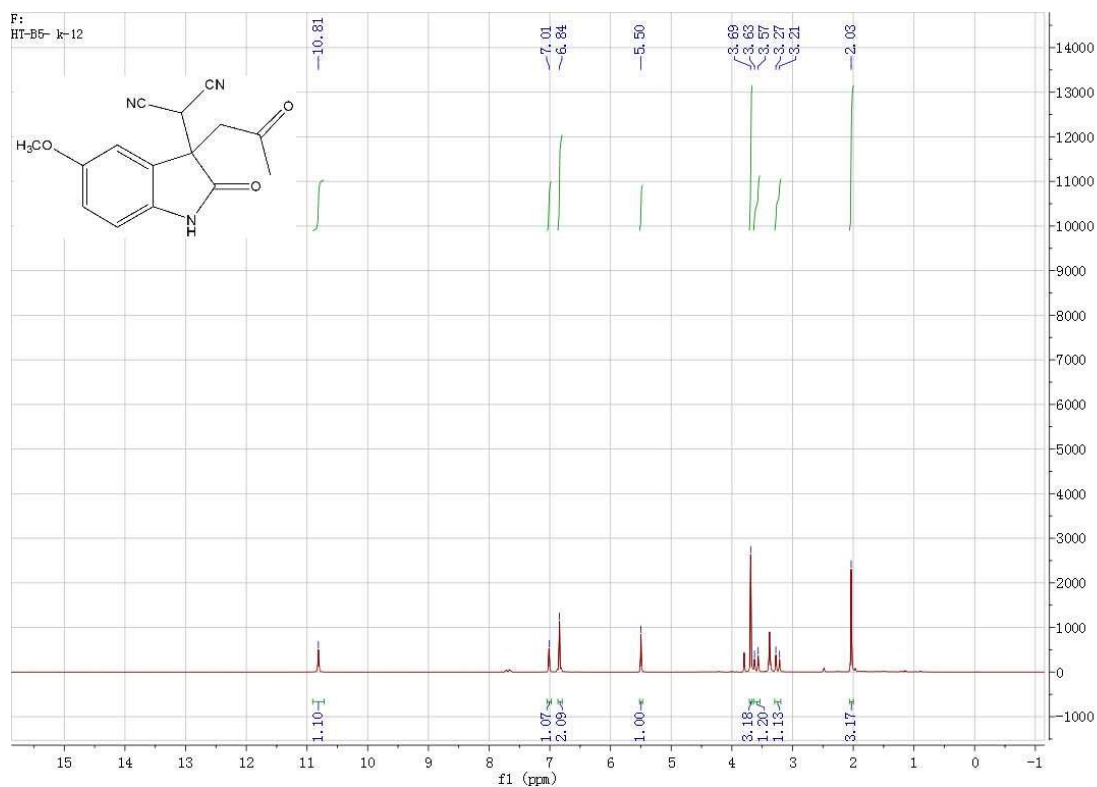


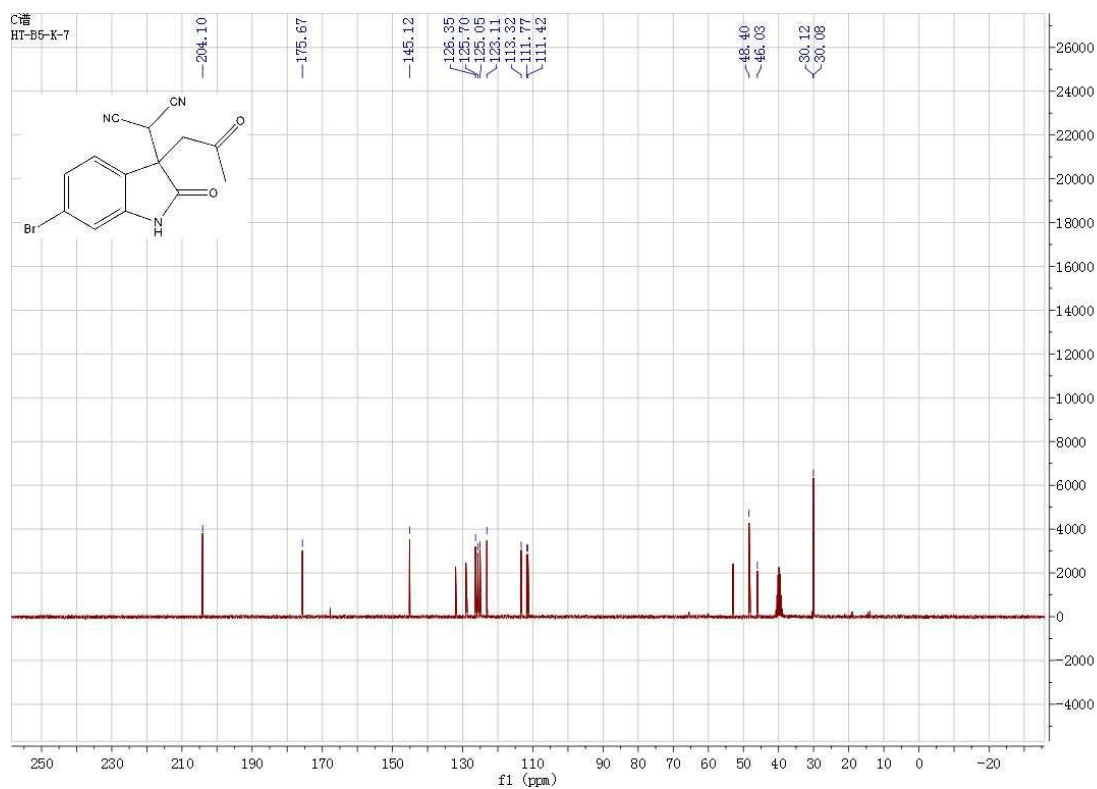
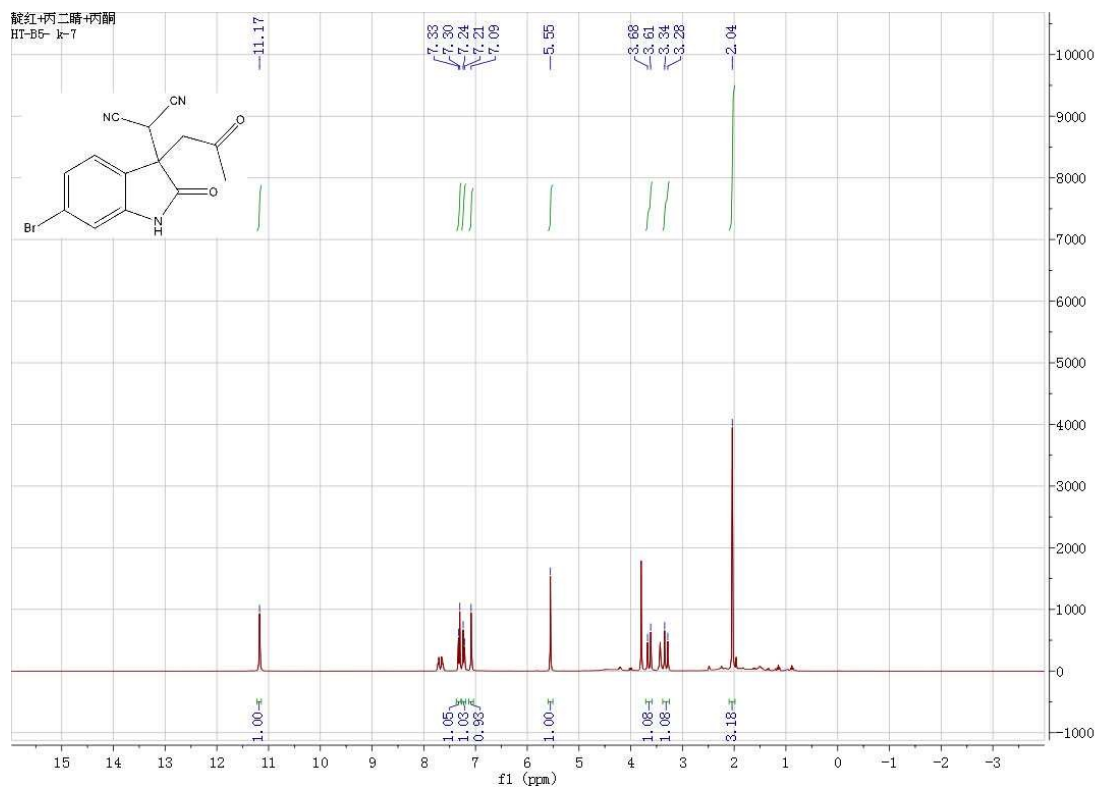
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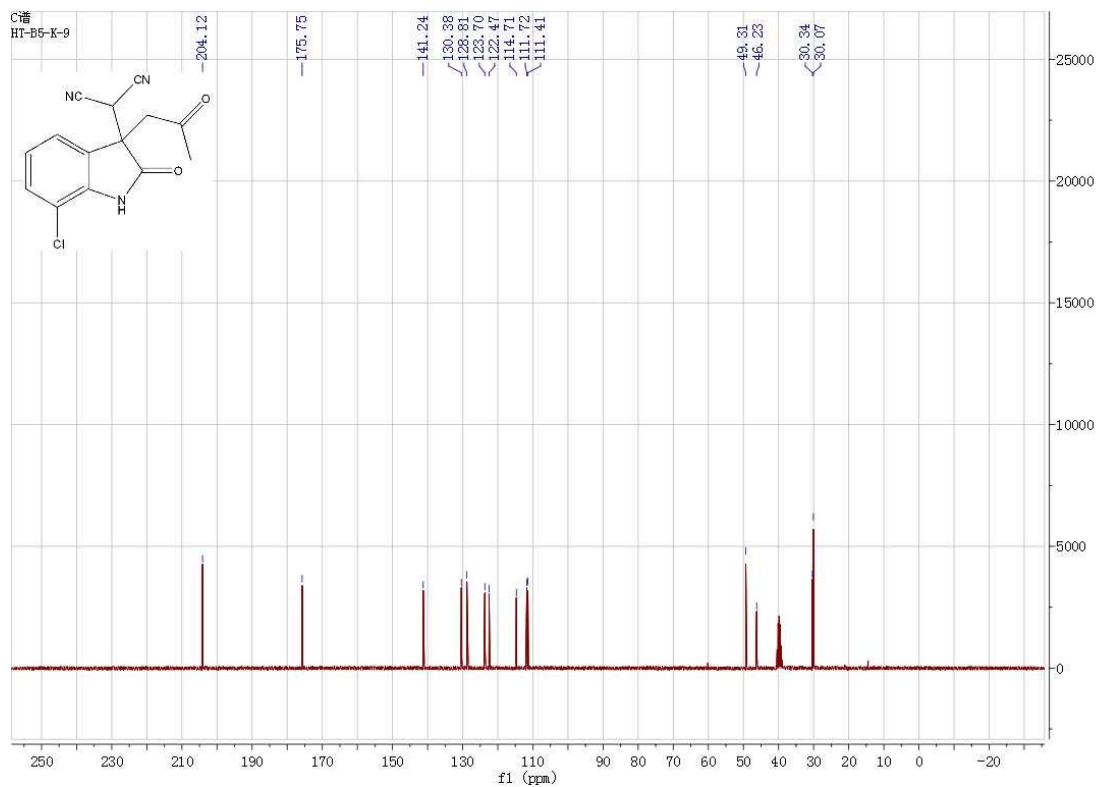
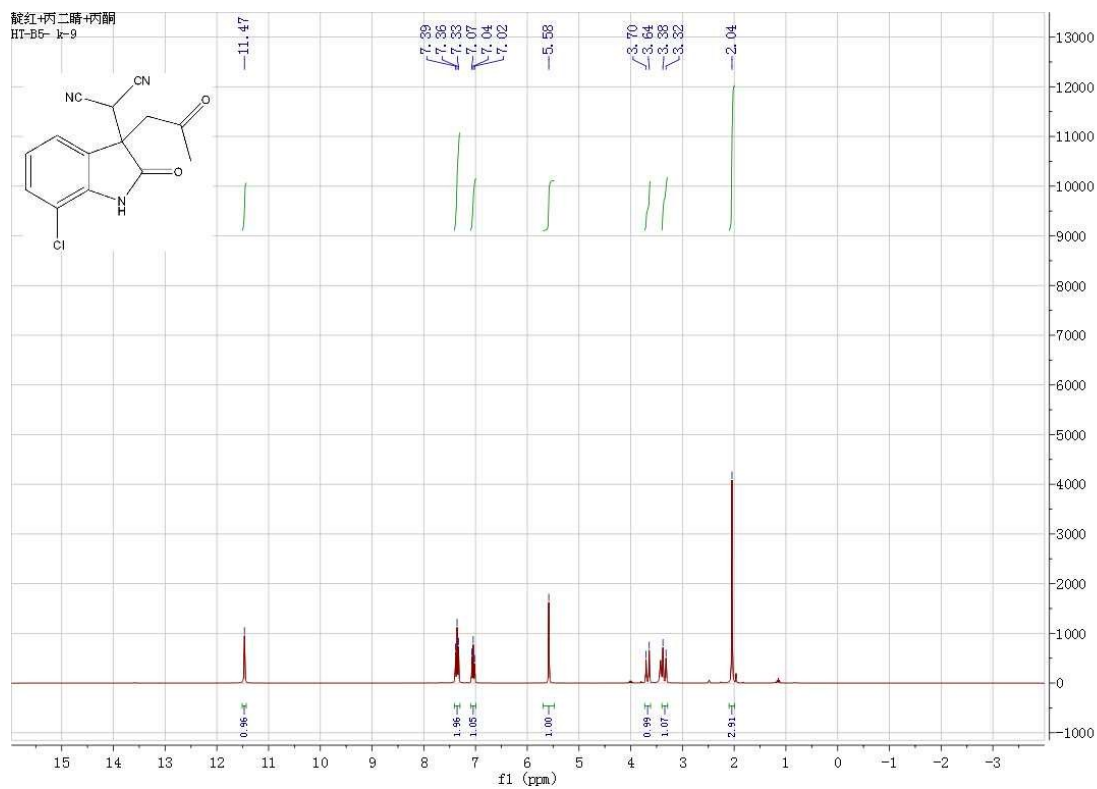




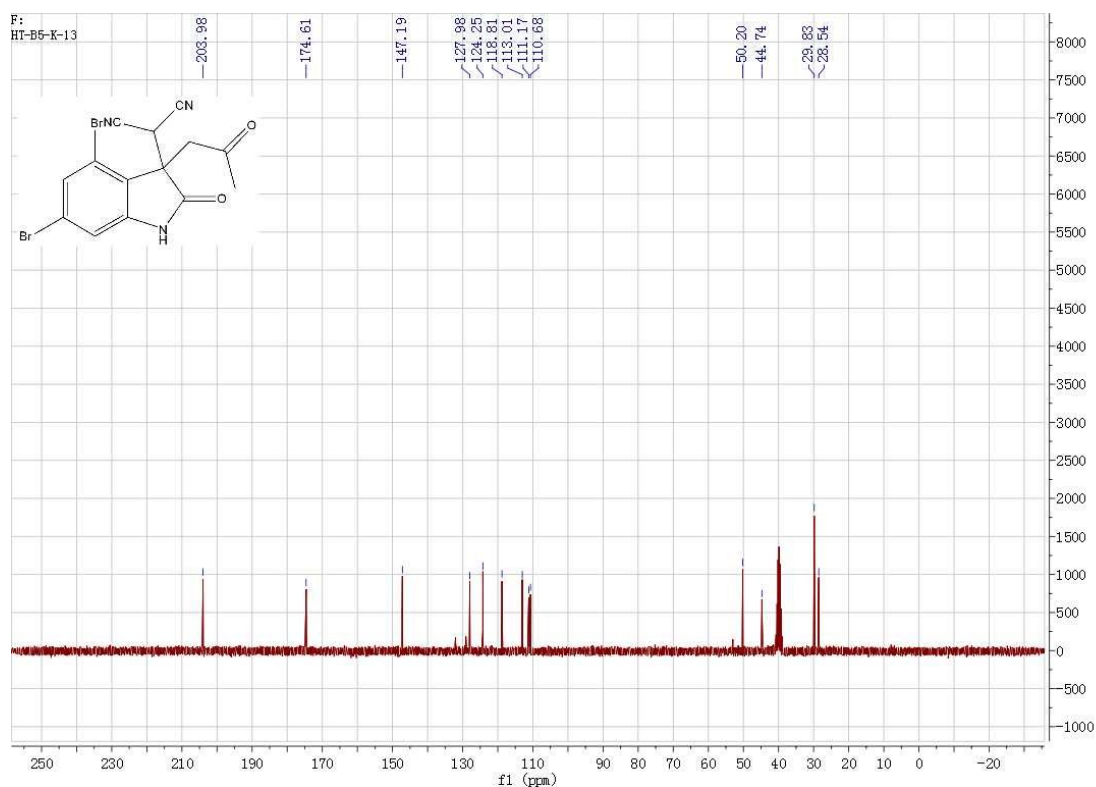
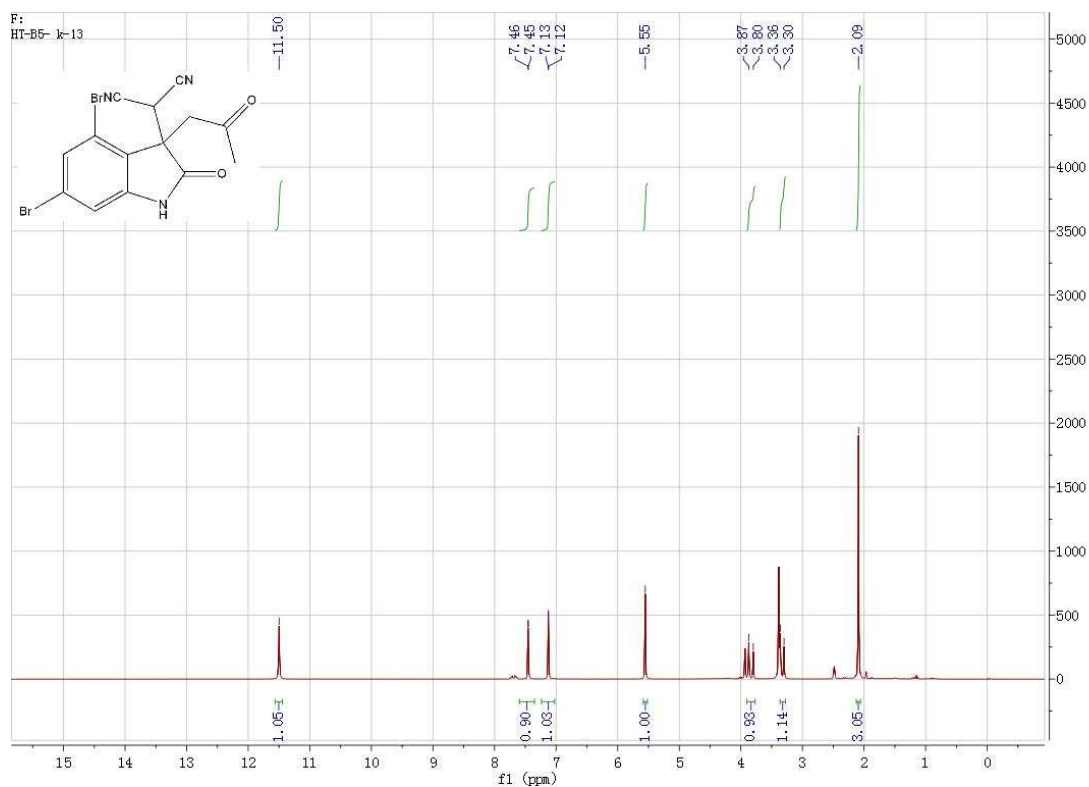




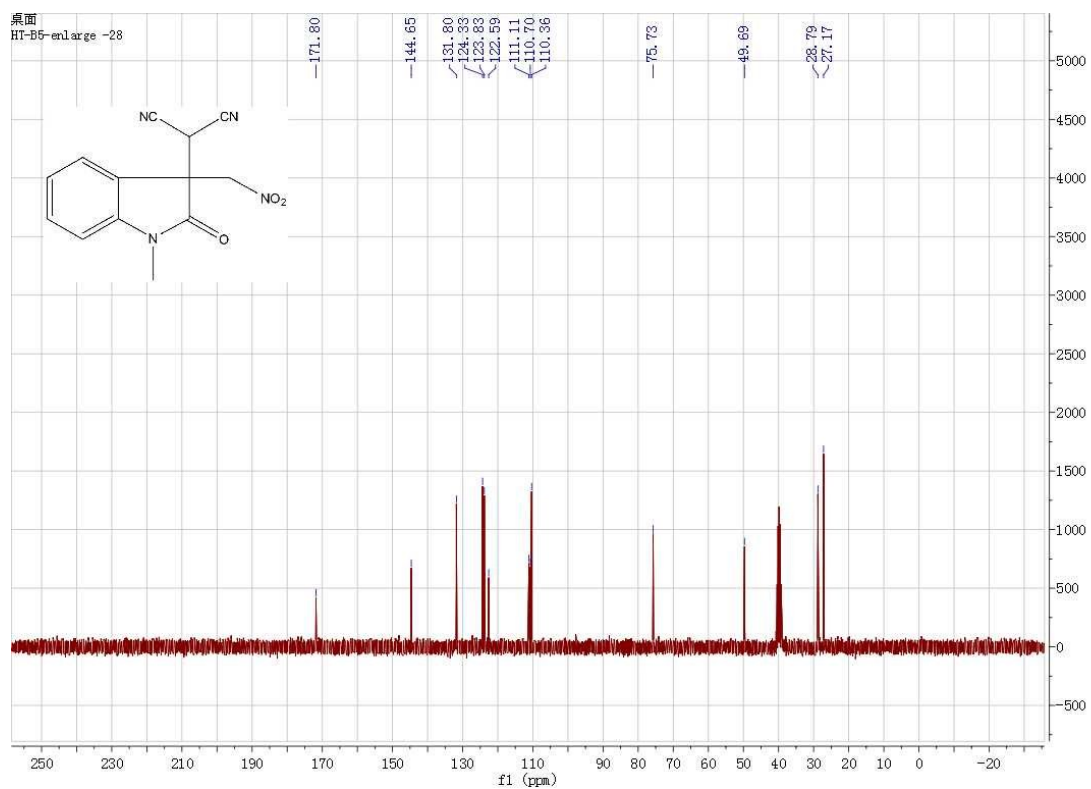
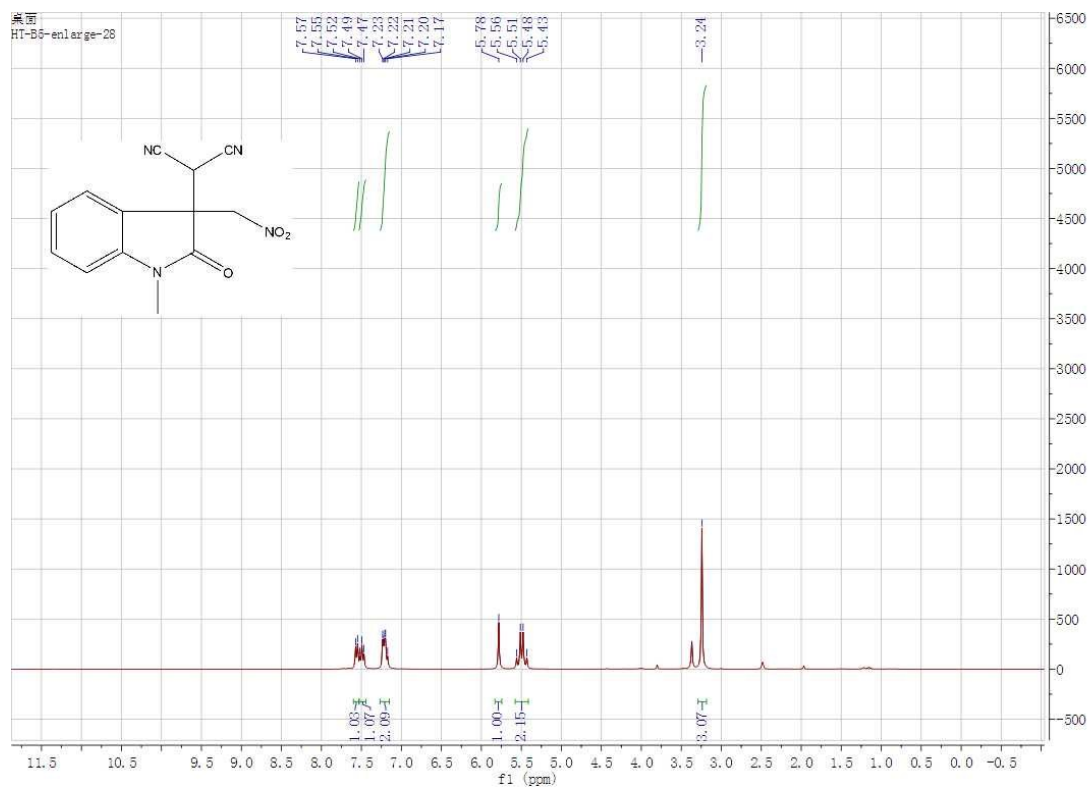
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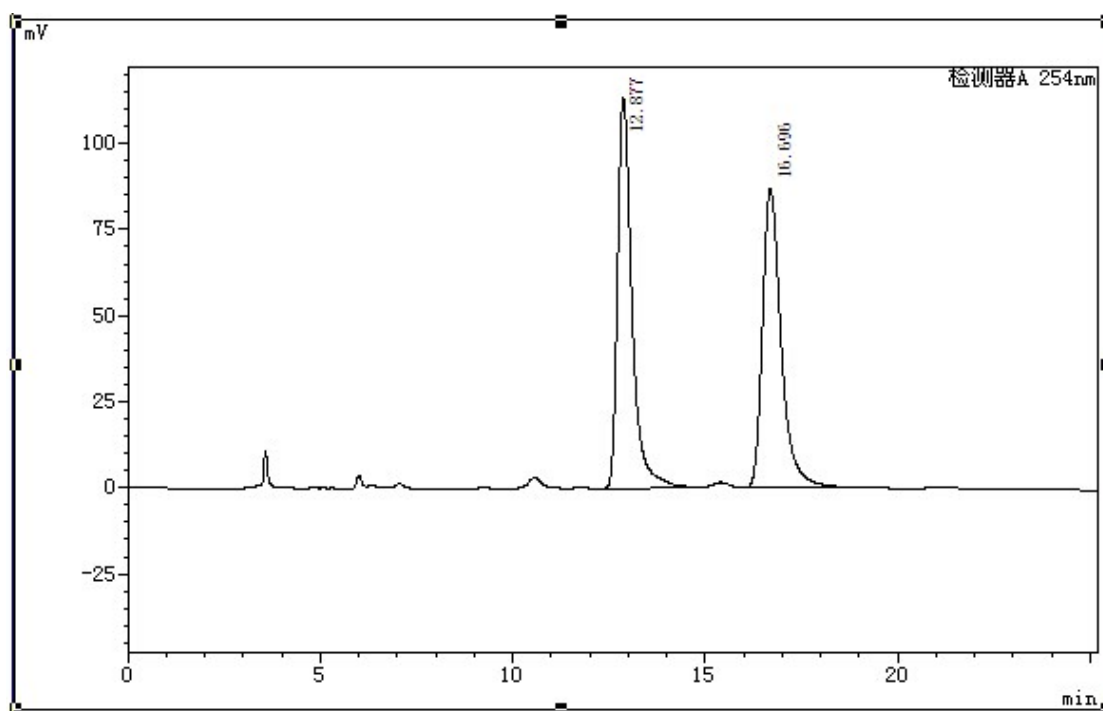
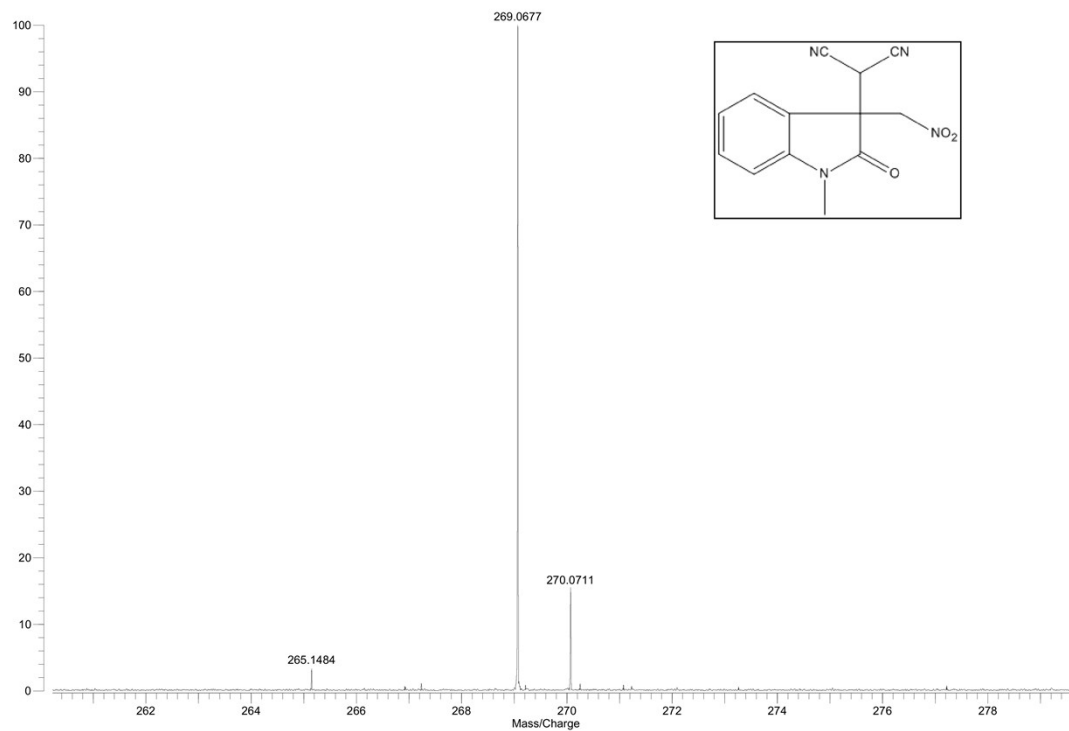


4n



6a



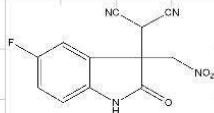
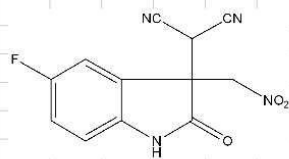


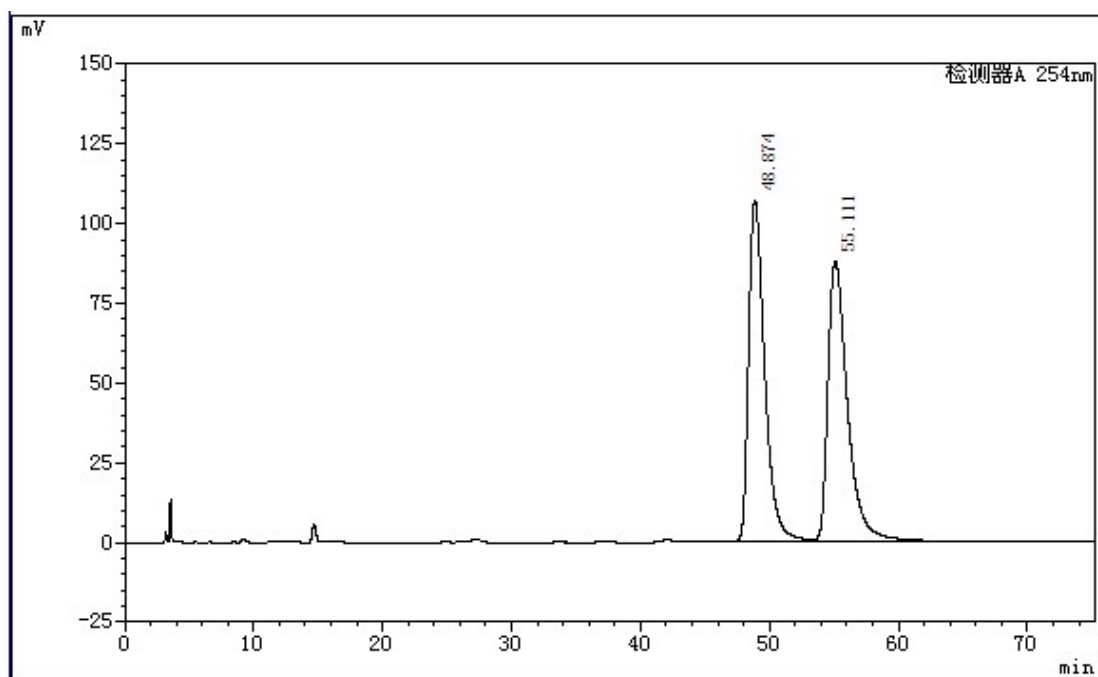
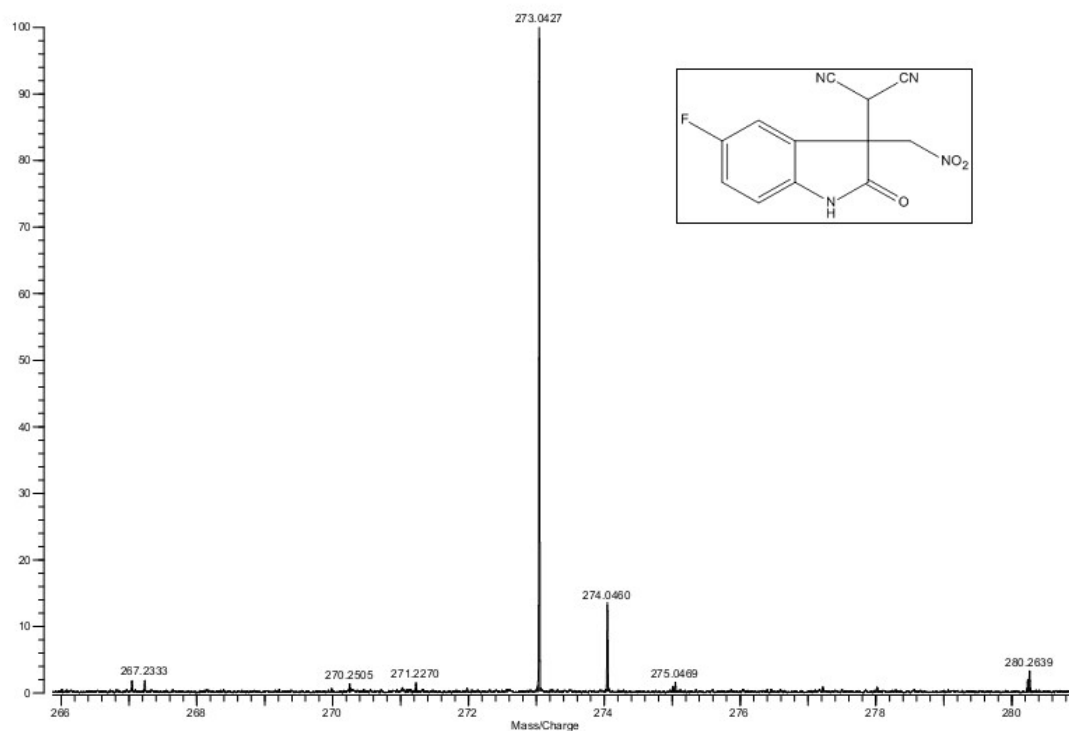
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检测器A 254nm

峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	12.877	2946519	113571	50.319			
2	16.696	2909107	86813	49.681			

靛紅+丙二晴+丙酮
HT-B5-K-50





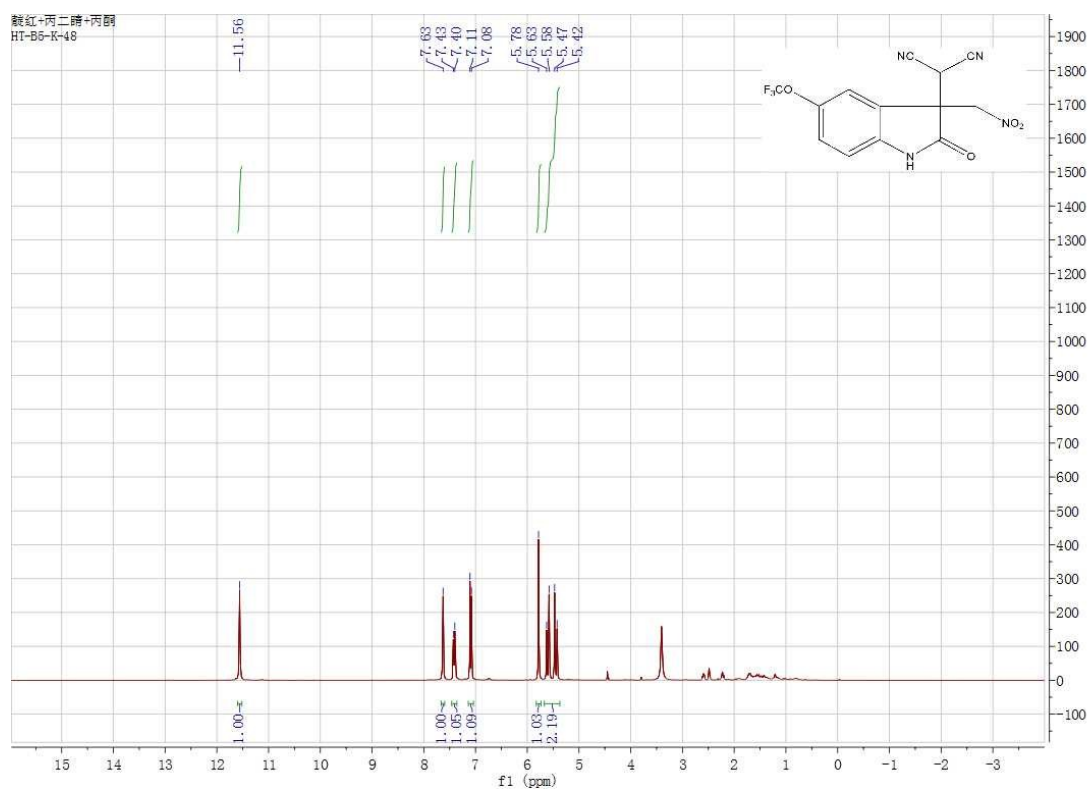
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检测器A 254nm

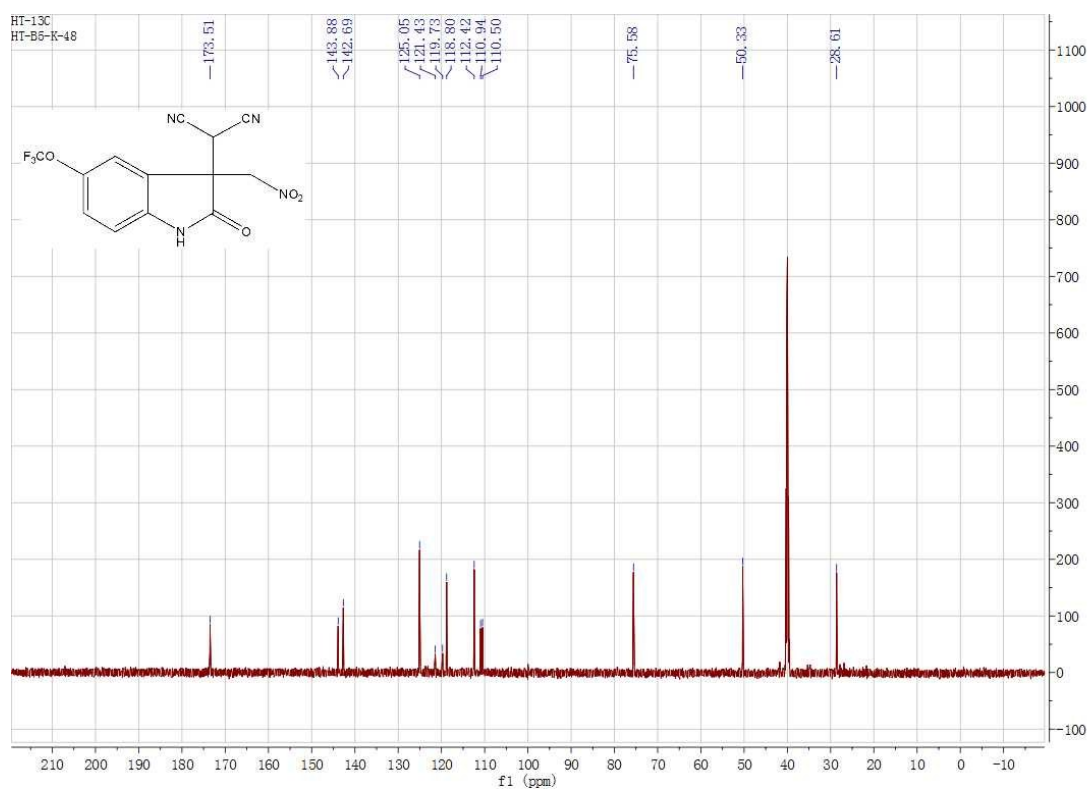
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1	48.874	9297974	107180	50.132			
2	55.111	9248883	88035	49.868		SV	

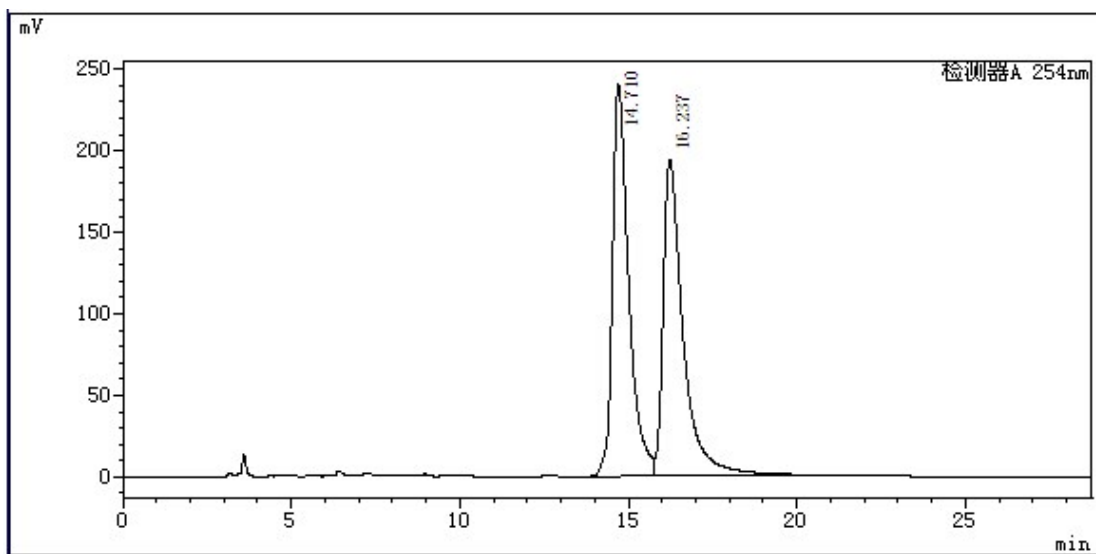
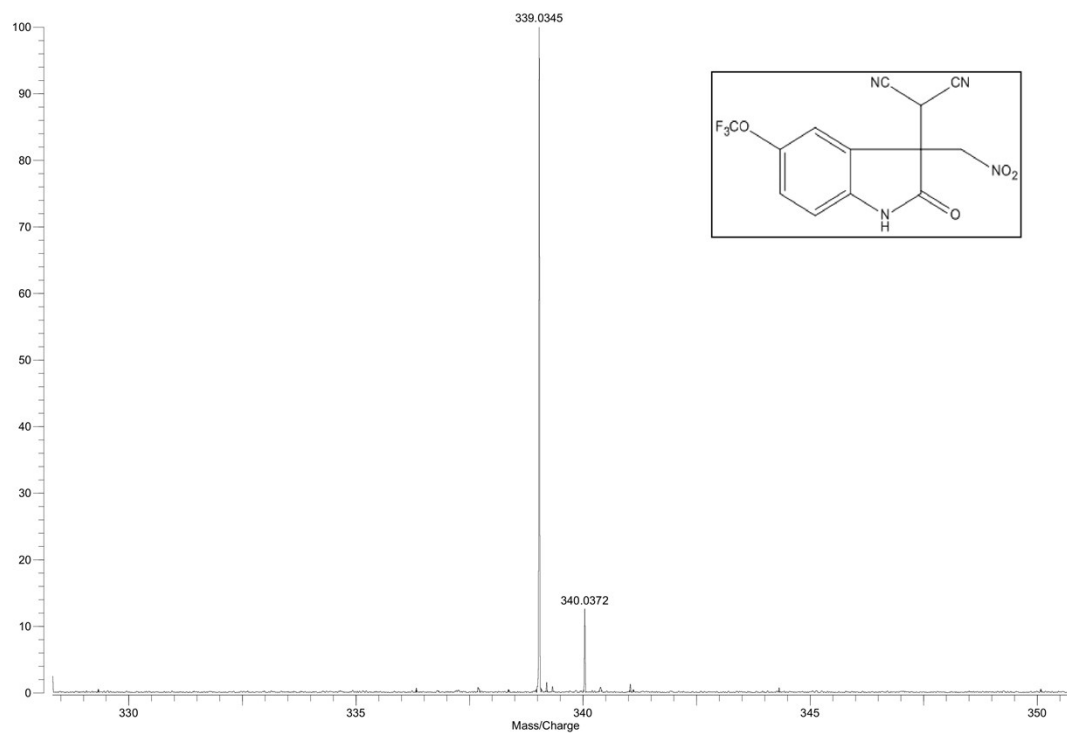
6c

靛红-丙二腈-丙酮
HT-B5-K-48



HT-13C
HT-B5-K-48





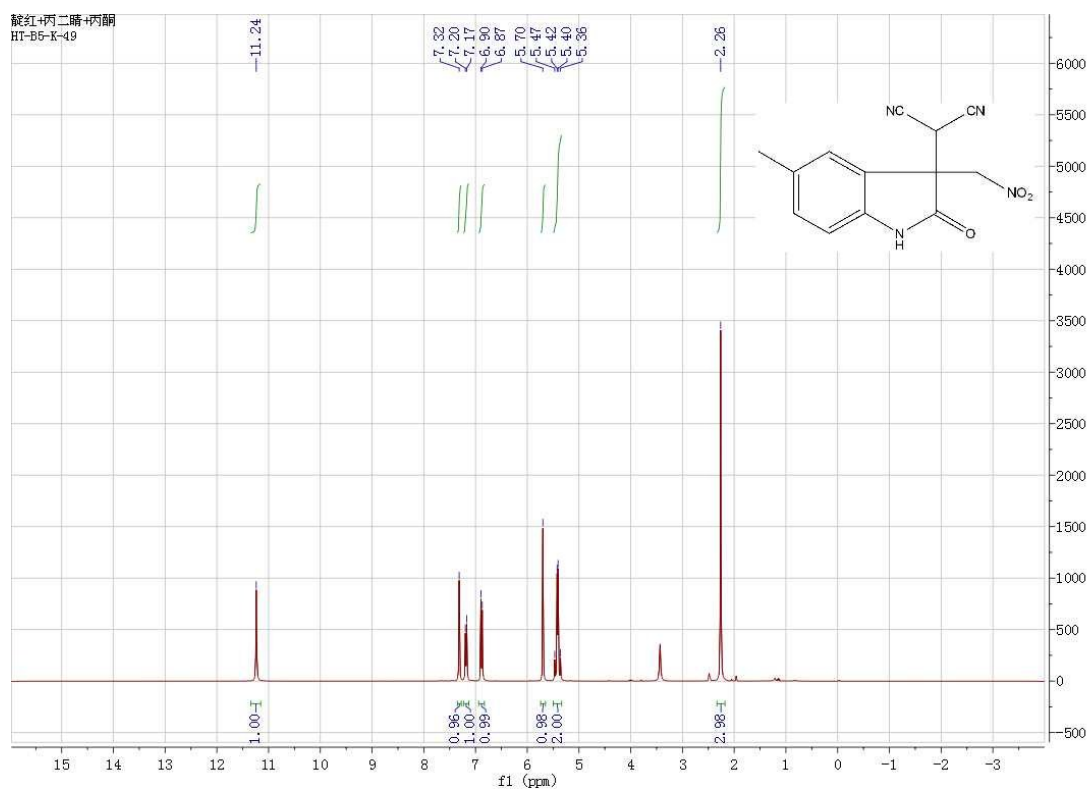
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检测器A 254nm

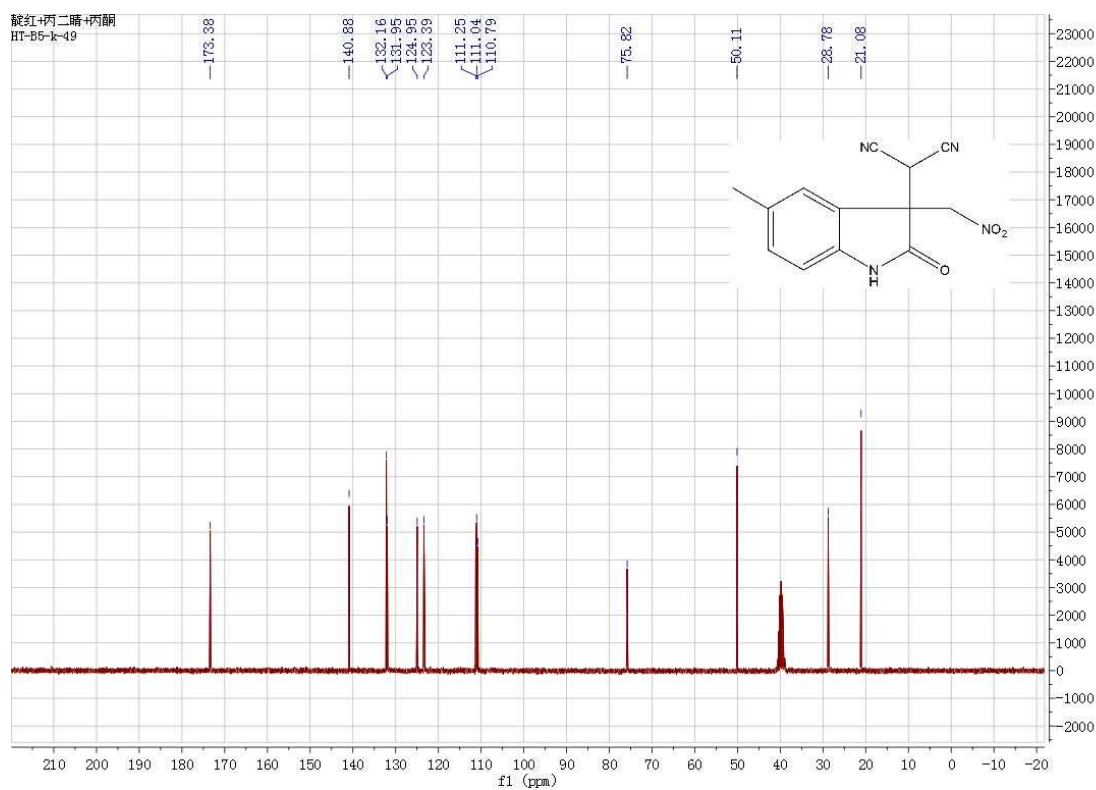
峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	14.710	8069258	240723	49.774			
2	16.237	8142433	193626	50.226		V	

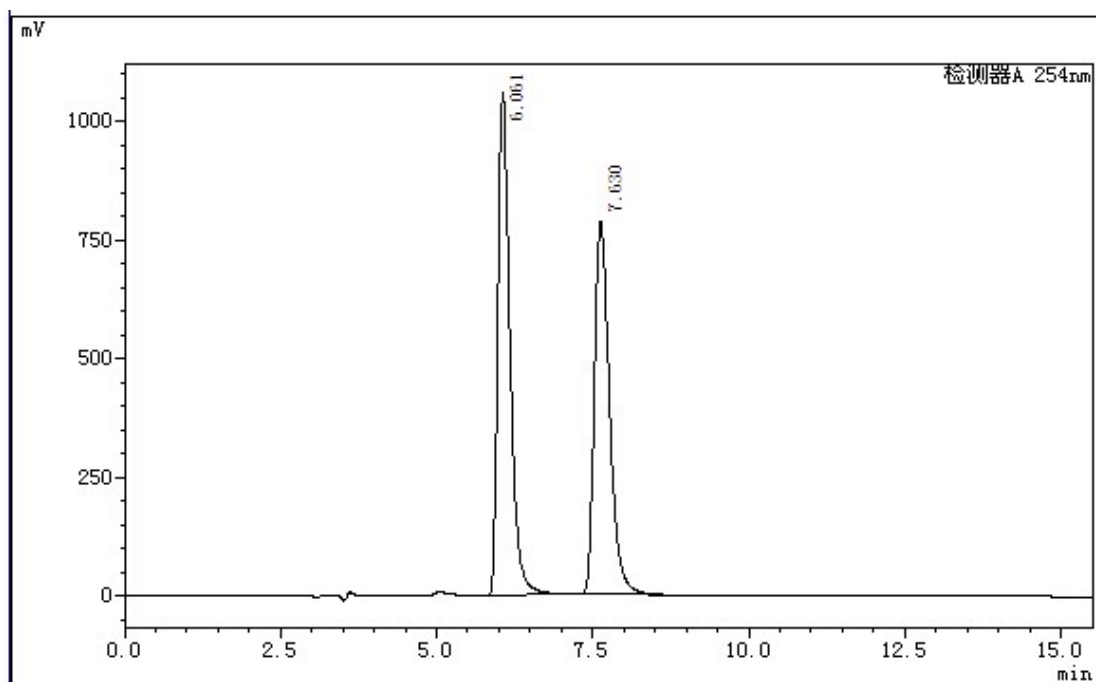
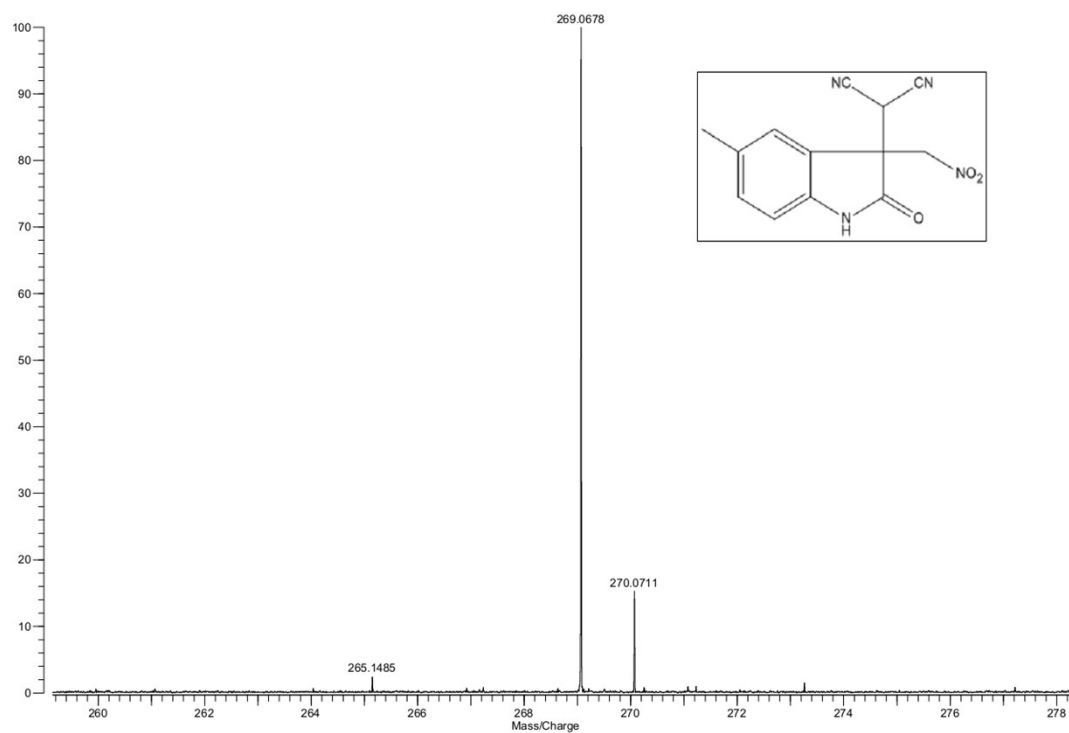
6d

靛红+丙二腈+丙酮
HT-B5-K-49



靛红+丙二腈+丙酮
HT-B5-K-49



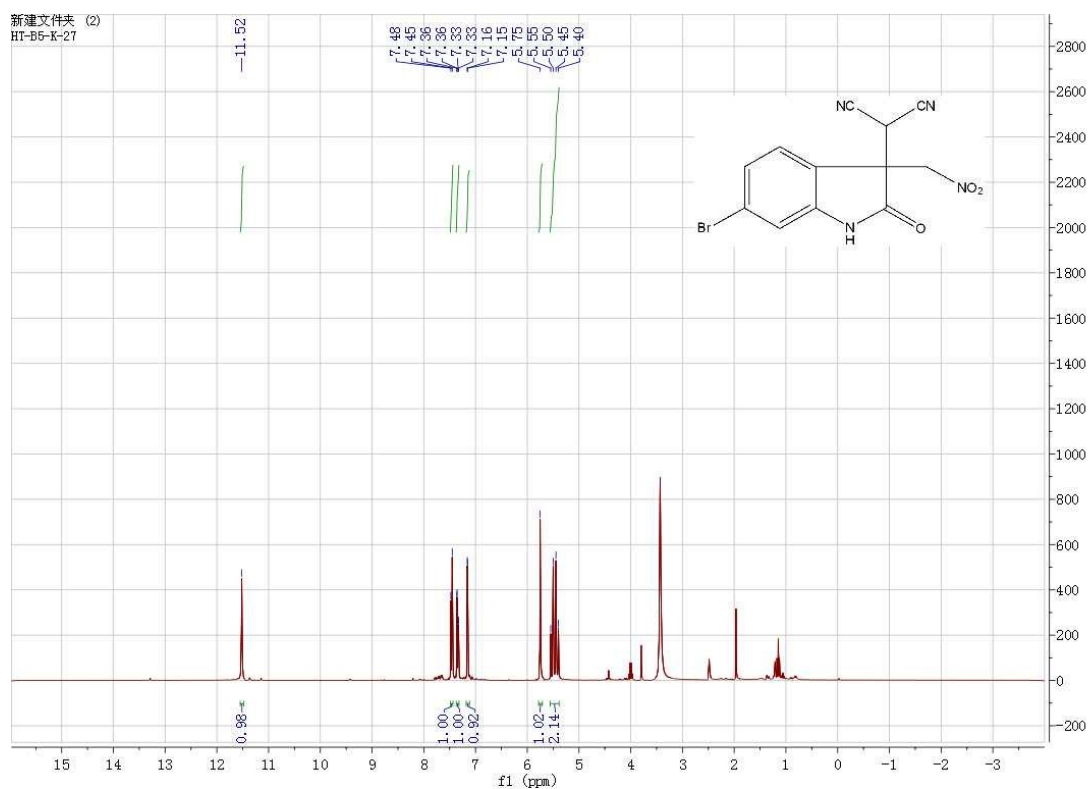
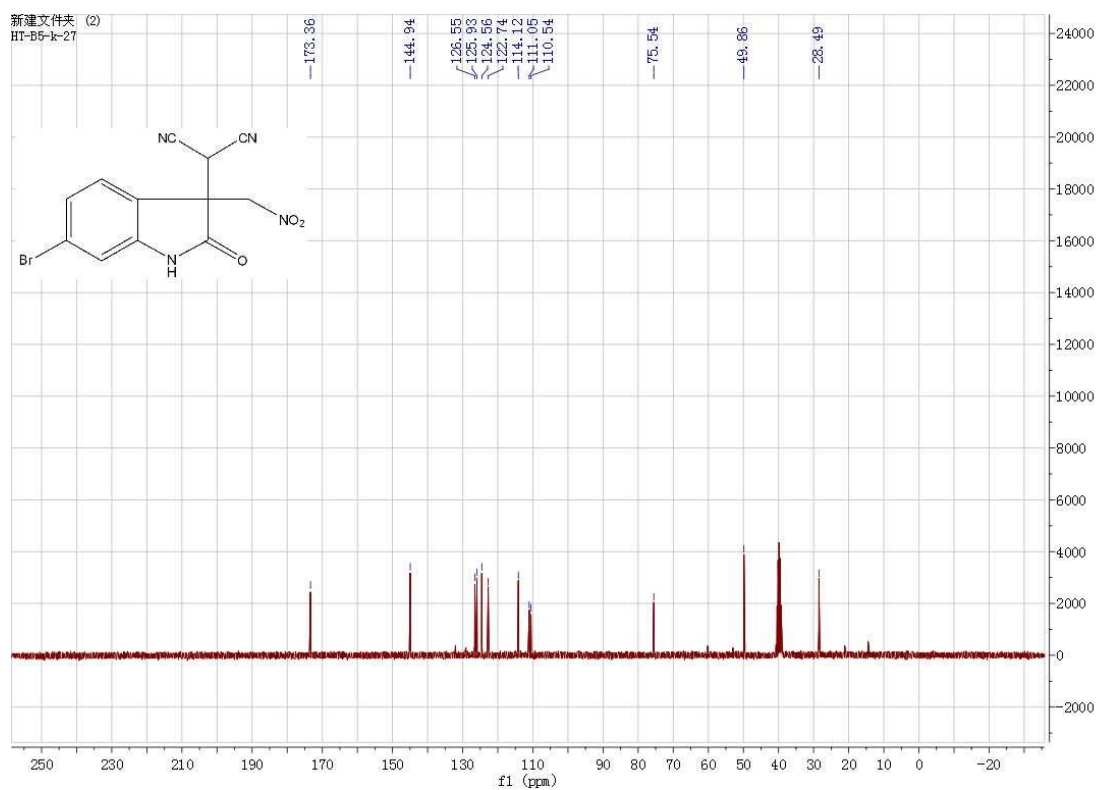


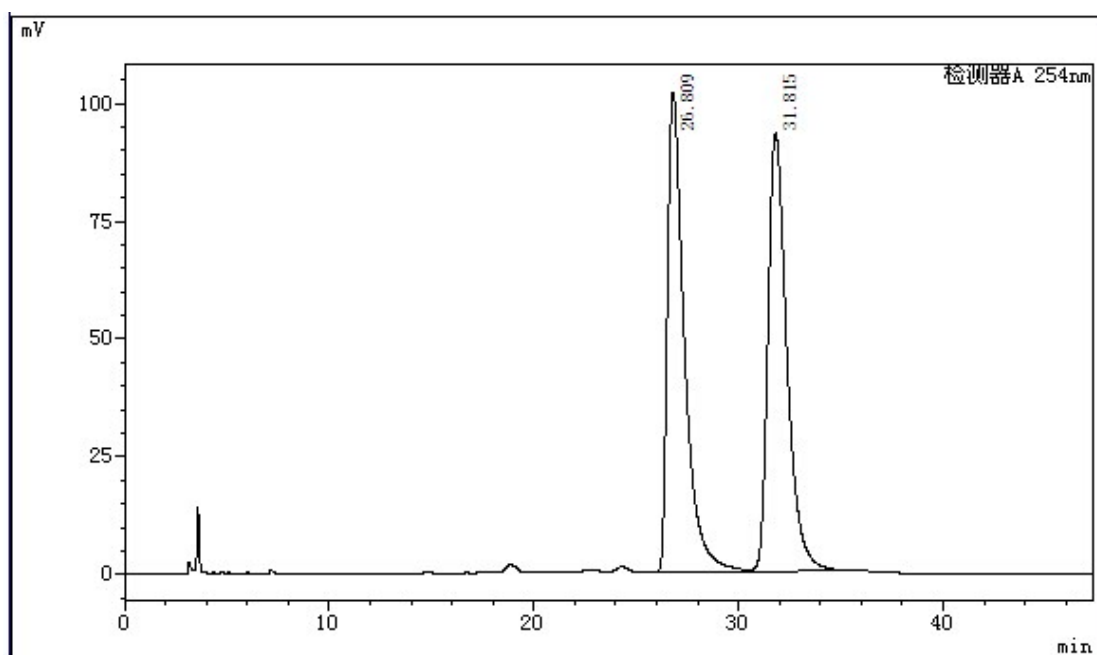
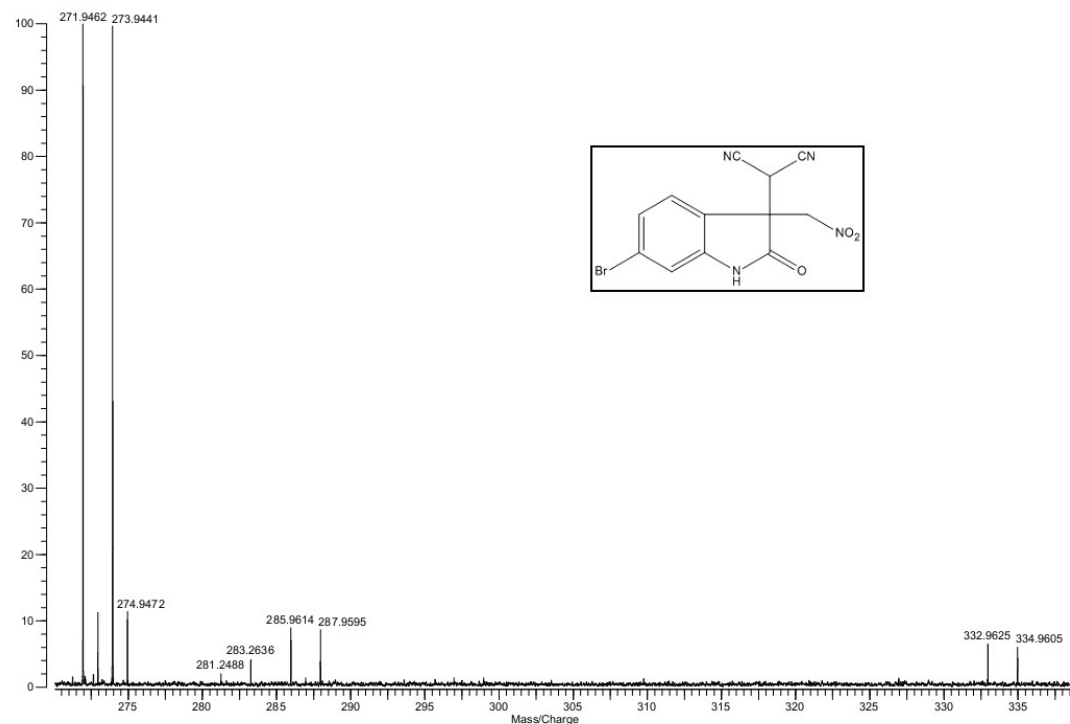
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检测器A 254nm

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1	6.061	14362973	1056548	51.872			
2	7.630	13326056	786422	48.128			

6e

新建文件夹 (2)
HT-B5-K-27新建文件夹 (2)
HT-B5-K-27



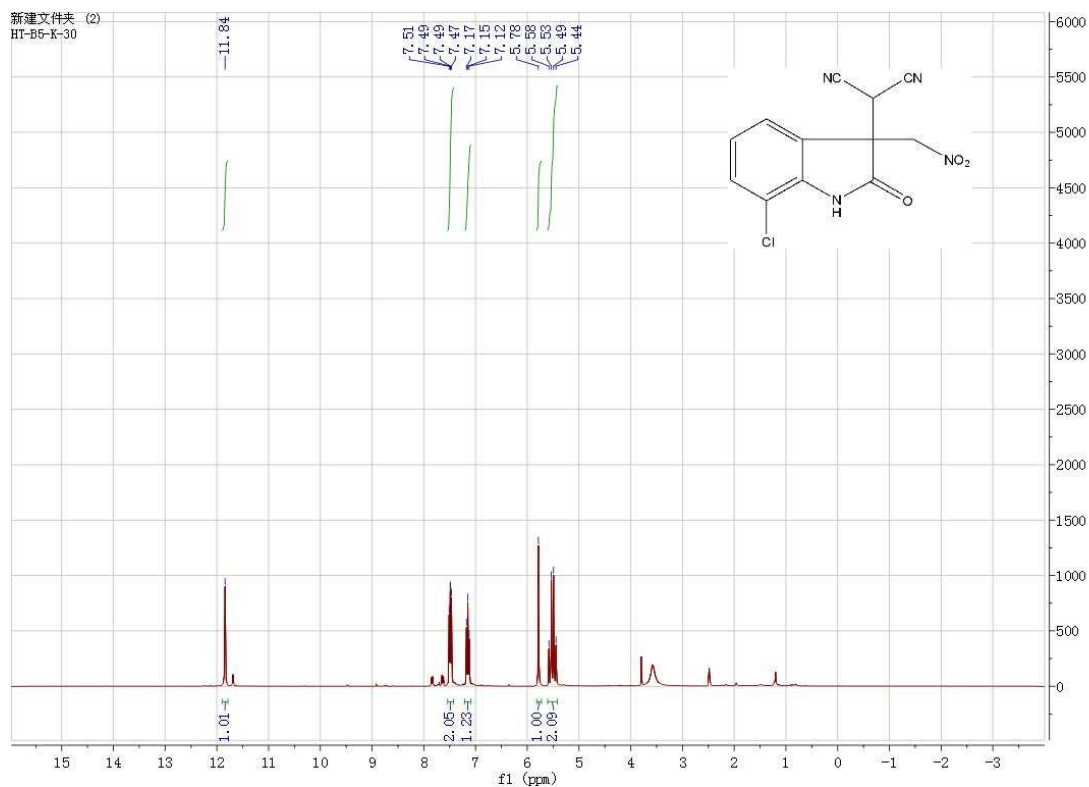
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检测器A 254nm

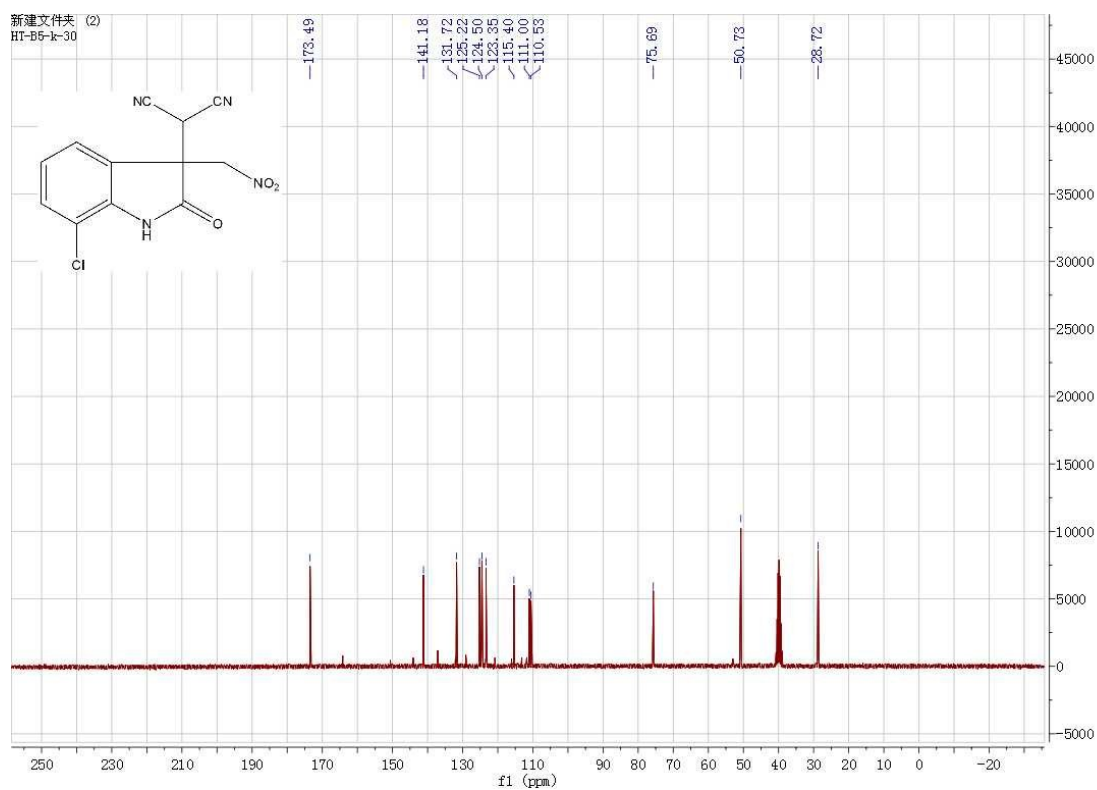
峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	26.809	5896937	101970	49.653			
2	31.815	5979364	93013	50.347		V	

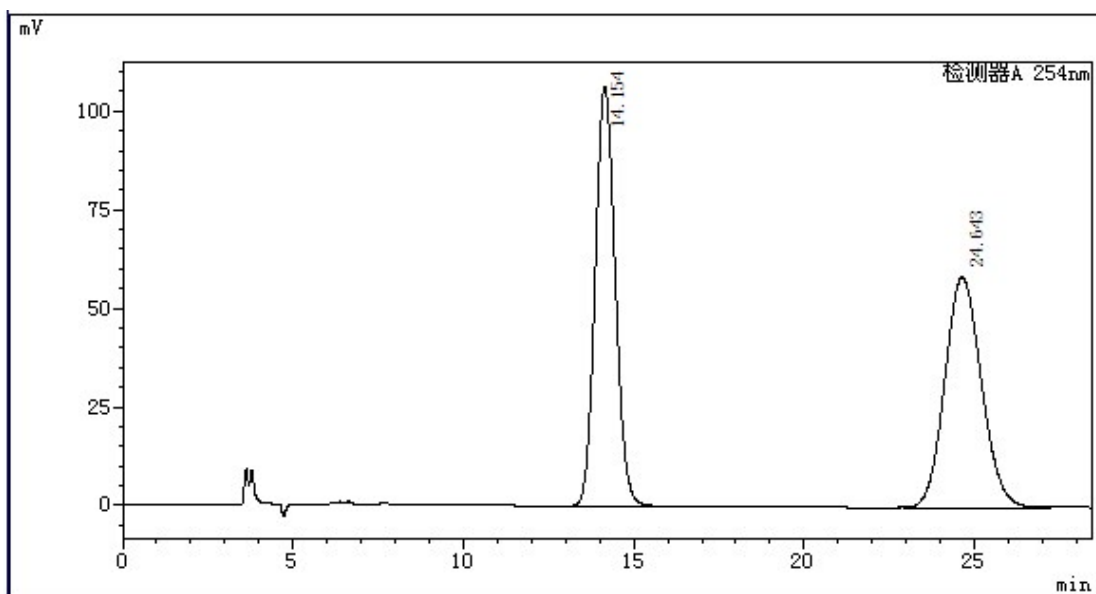
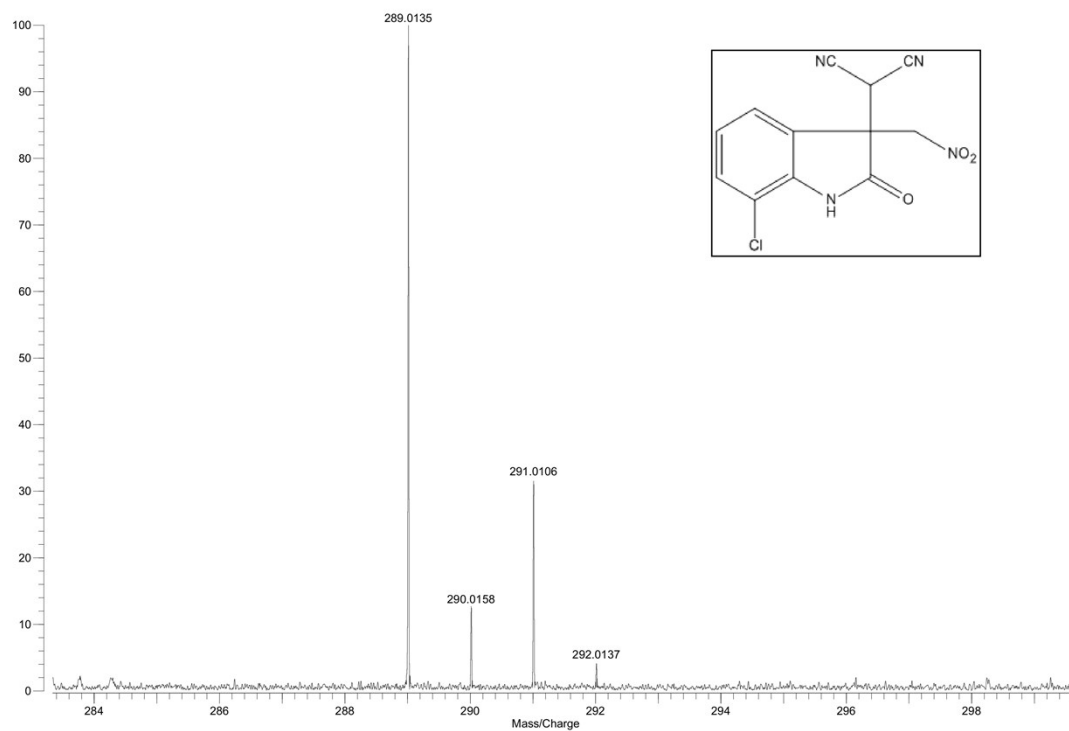
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新建文件夹 (2)
HT-B5-K-30



新建文件夹 (2)
HT-B5-K-30



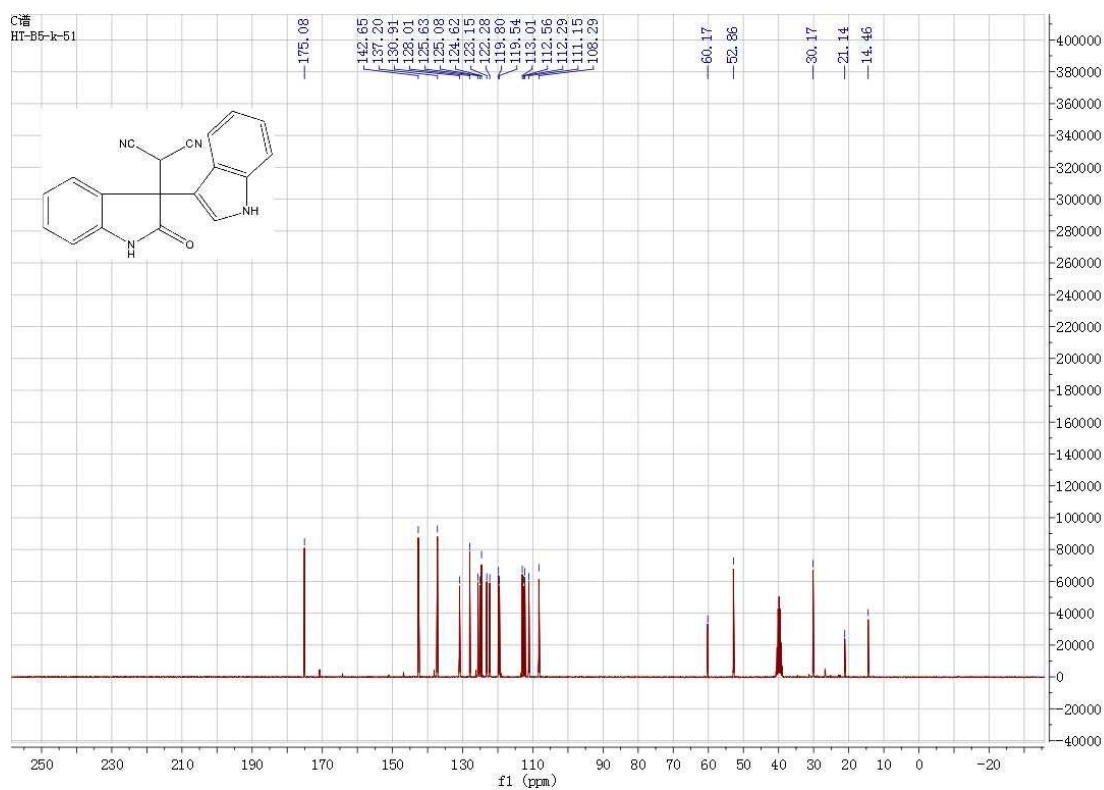
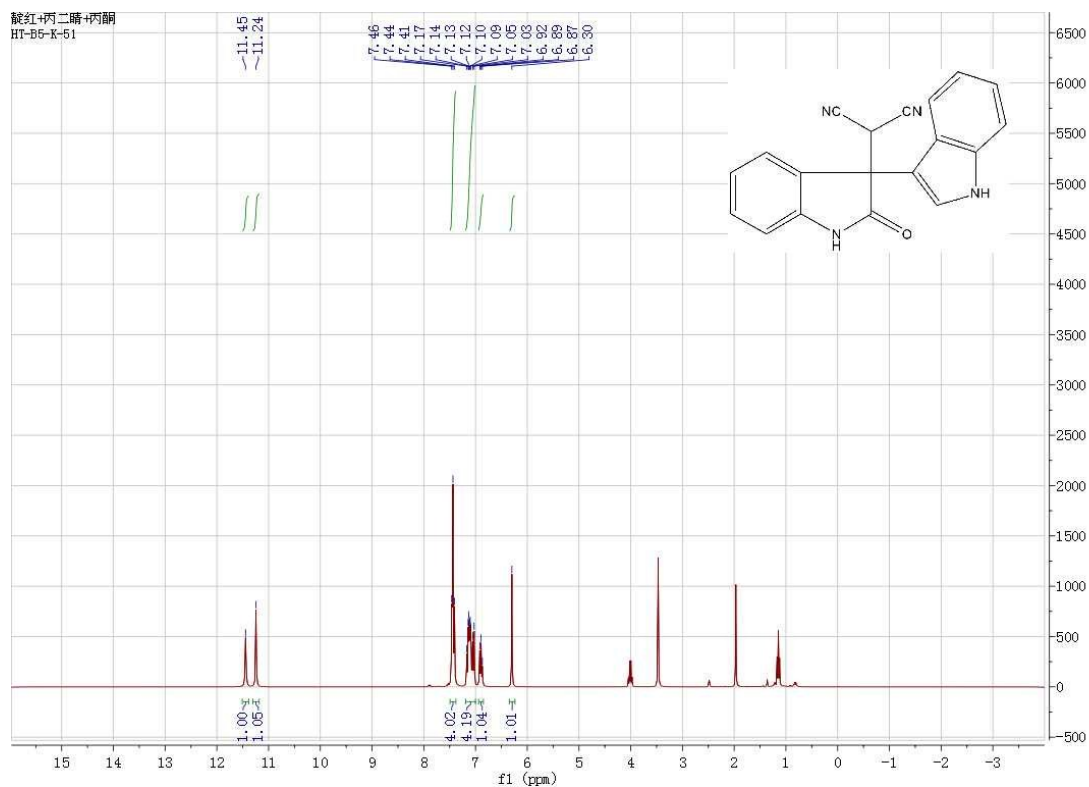


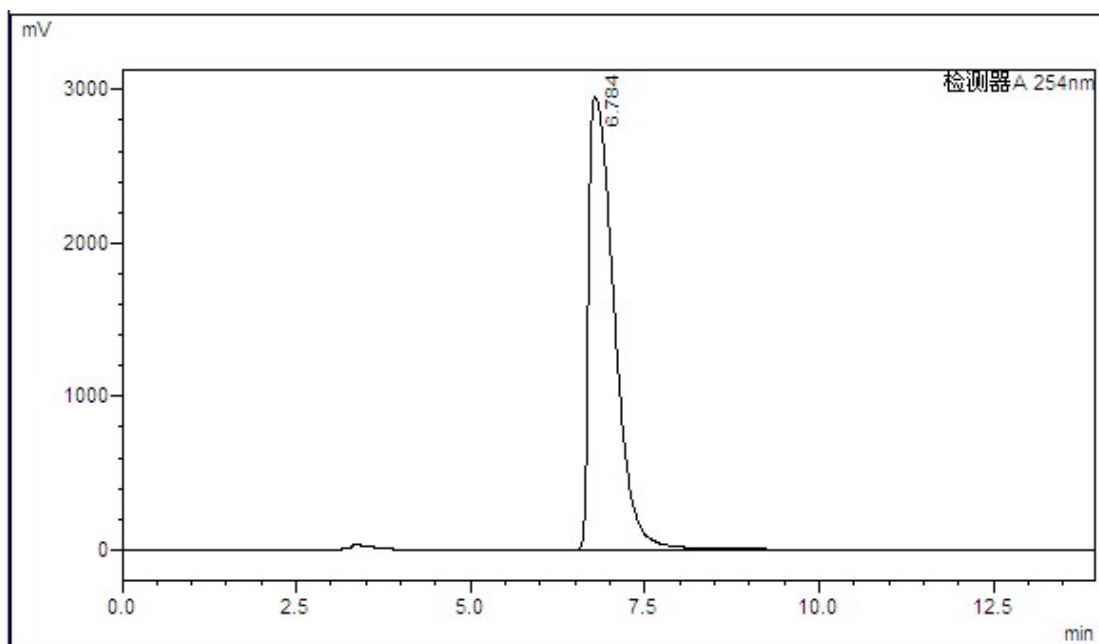
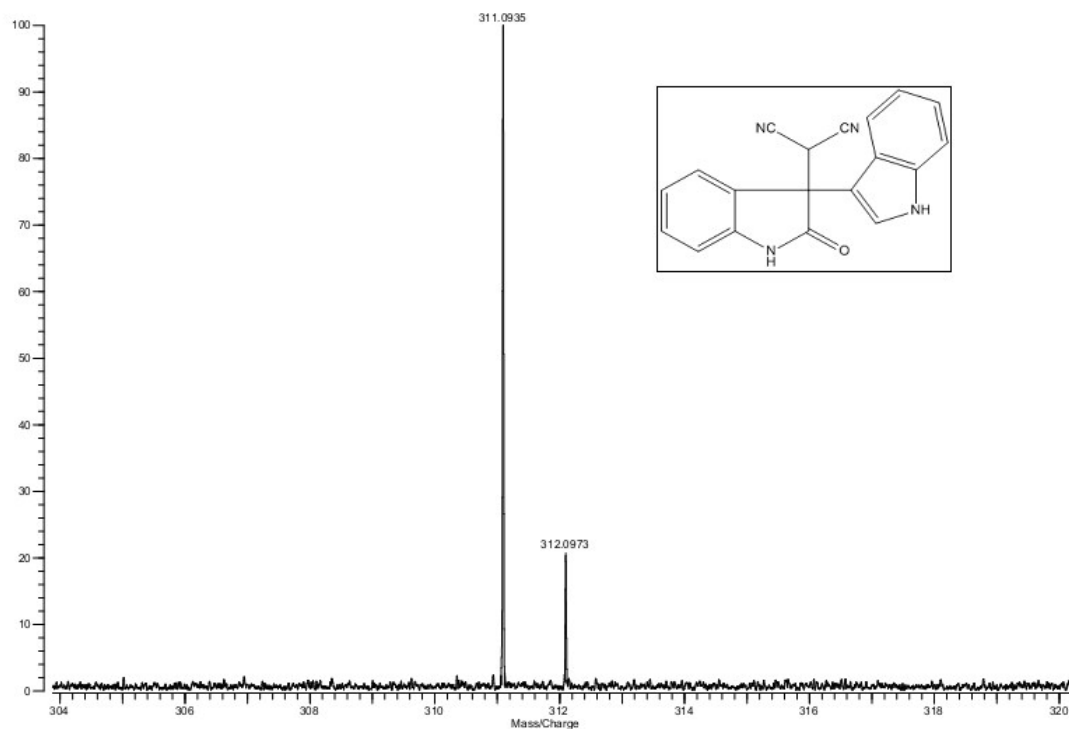
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检测器A 254nm

峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	14.154	4348130	106309	49.903			
2	24.643	4365045	58507	50.097		V	

靛红+丙二晴+丙酮
HT-B5-K-51





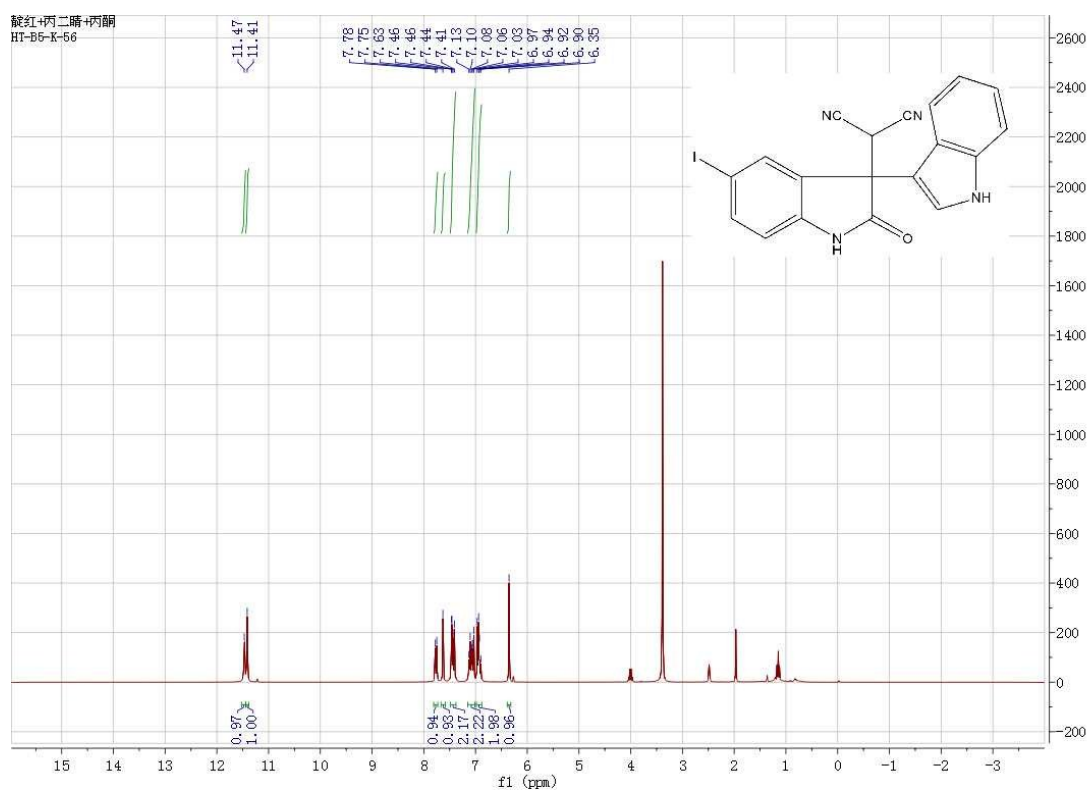
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检测器A 254nm

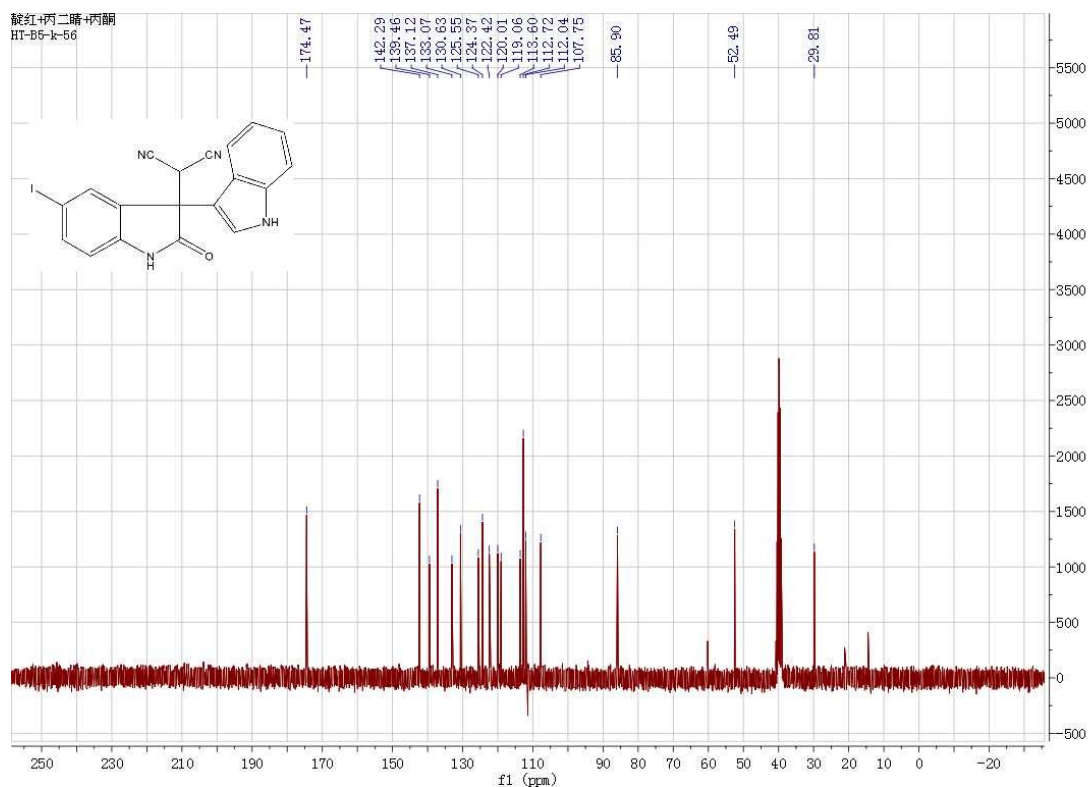
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1	6.784	75072110	2954915	100.000		S	
总计		75072110	2954915				

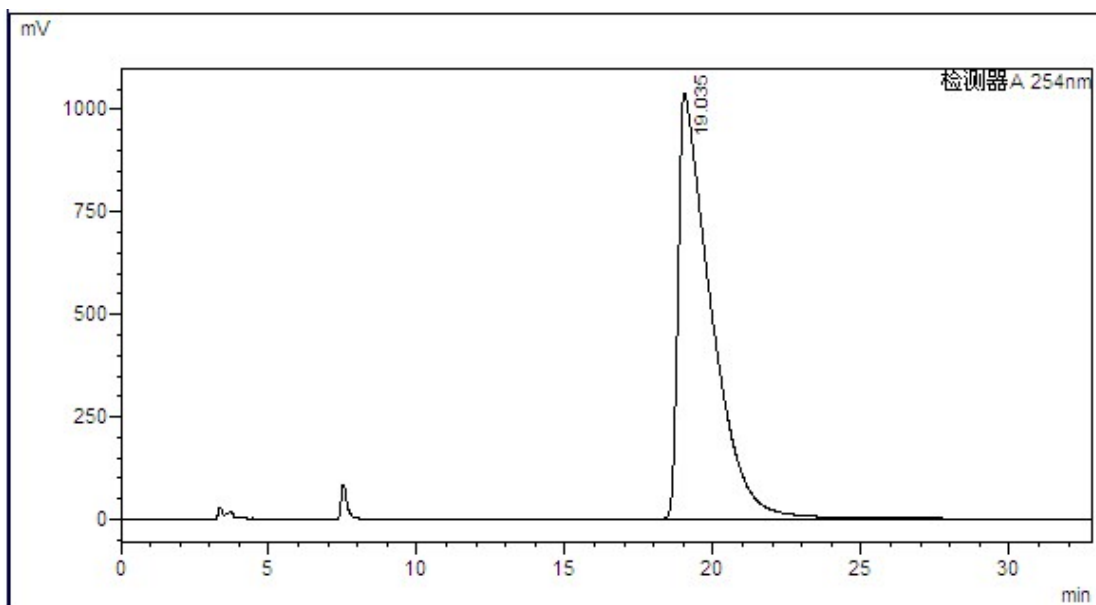
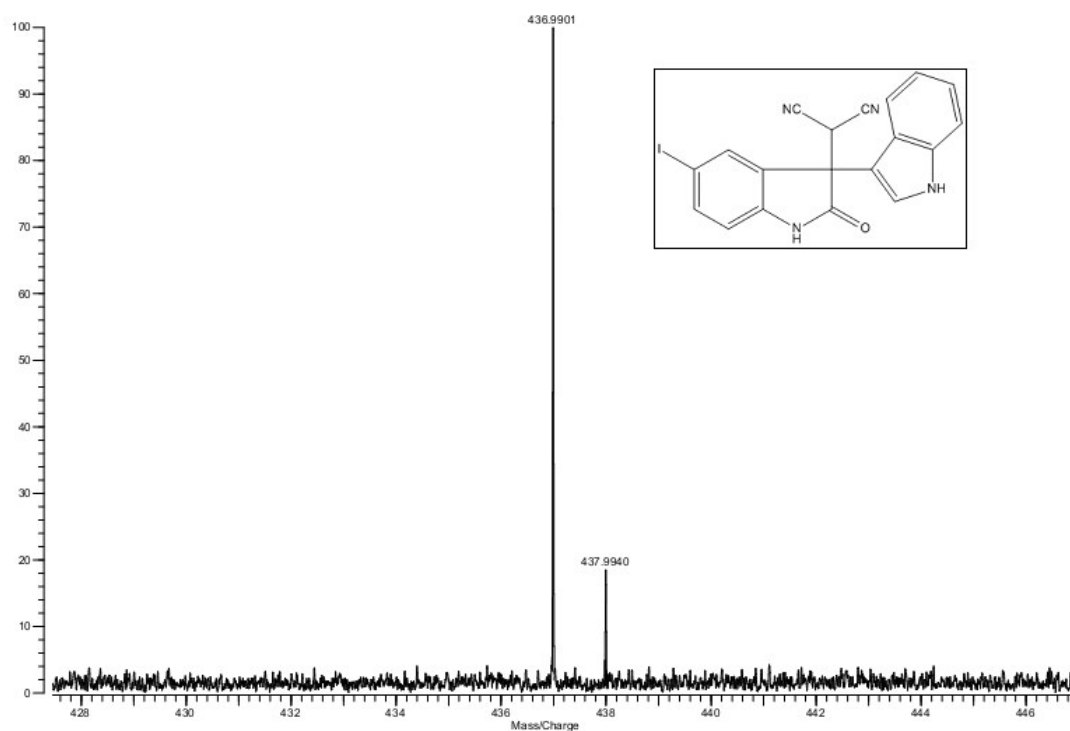
8b

靛红+丙二腈+丙酮
HT-B5-K-56



靛红+丙二腈+丙酮
HT-B5-K-56





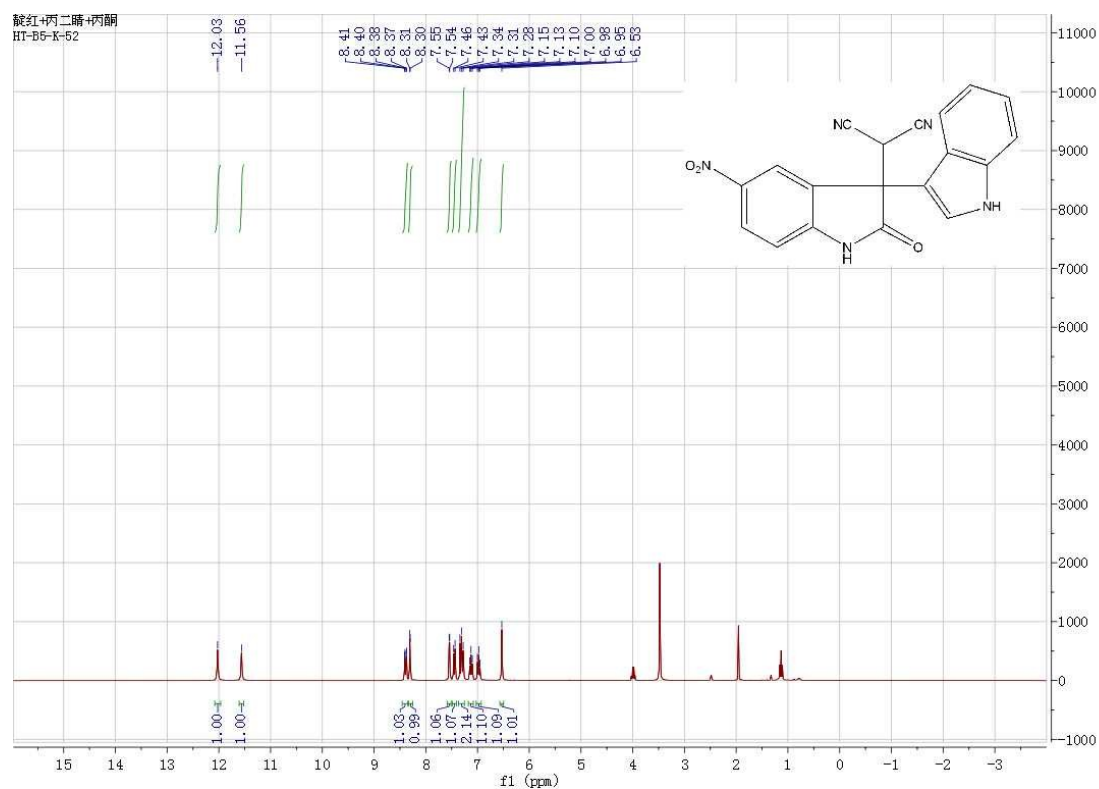
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检测器A 254nm

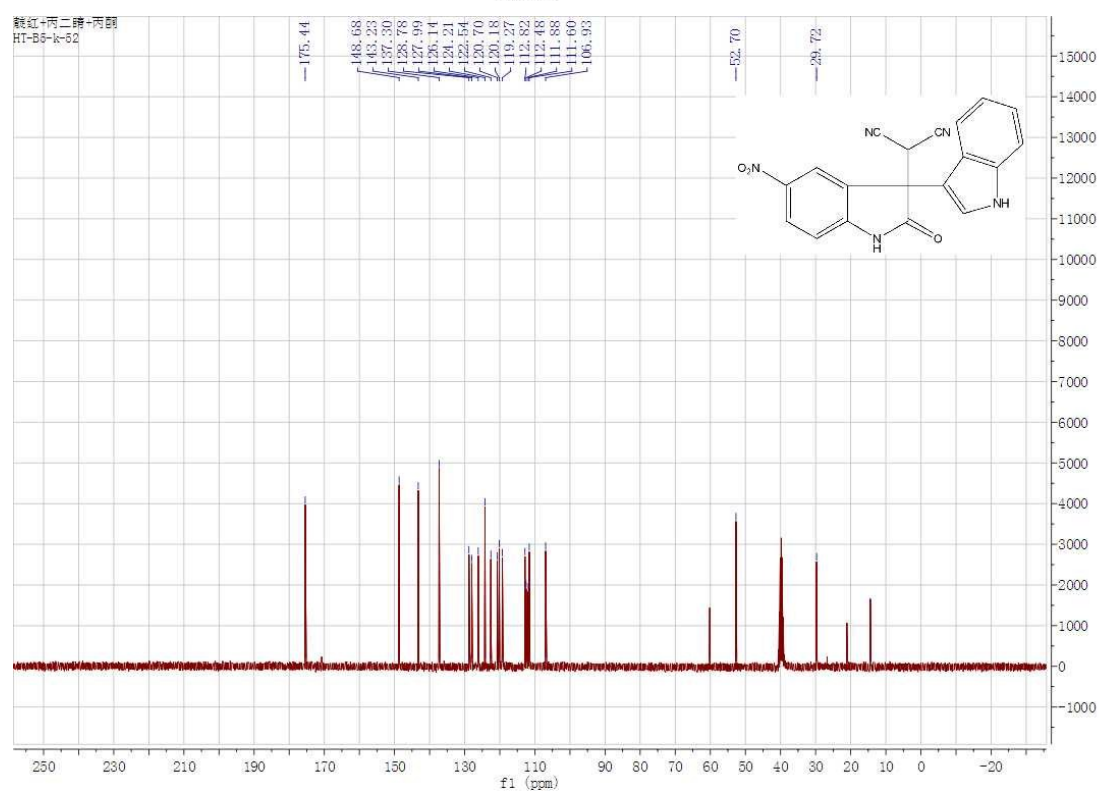
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	19.035	79926726	1037207	100.000		S	
总计		79926726	1037207				

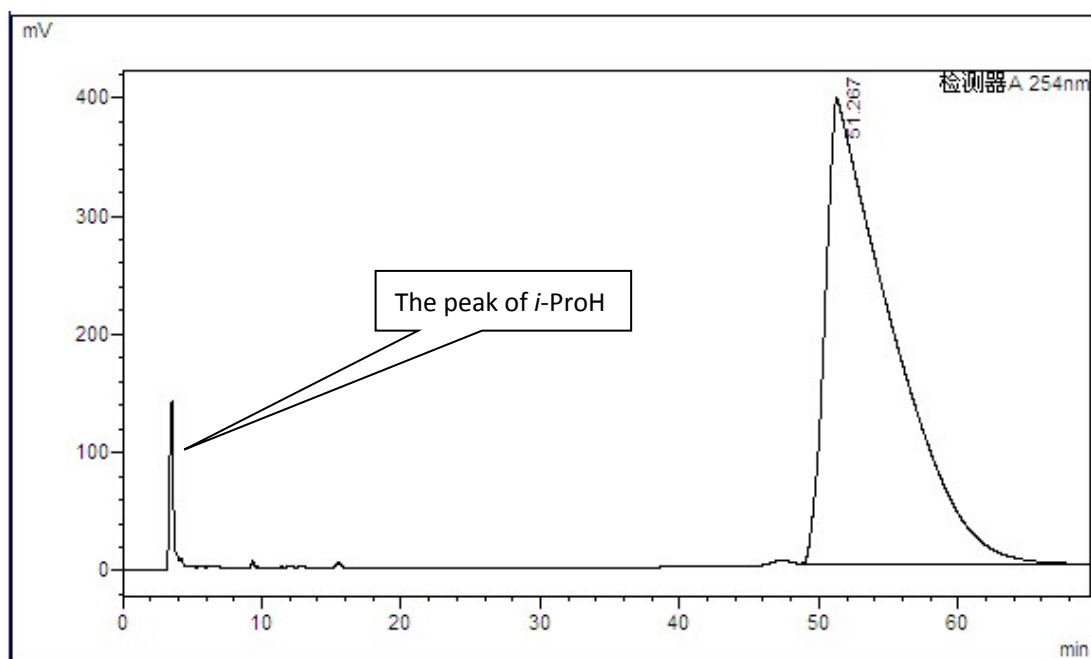
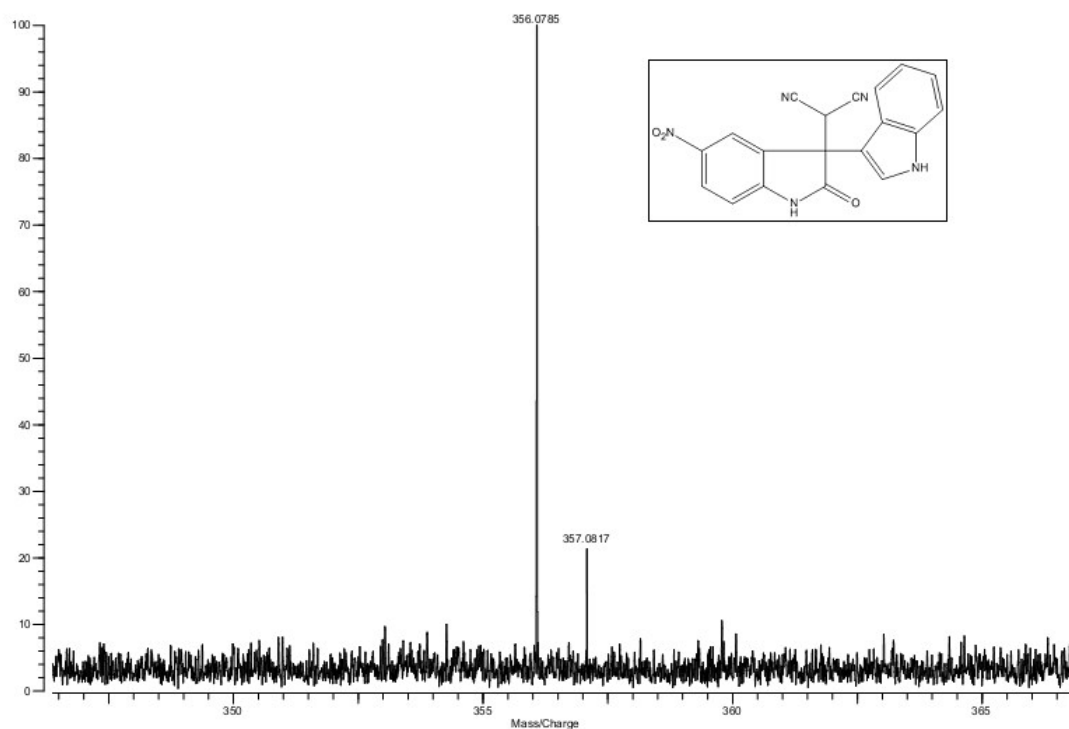
8c

靛红+丙二腈+丙酮
HT-B5-K-52



靛红+丙二腈+丙酮
HT-B5-K-52



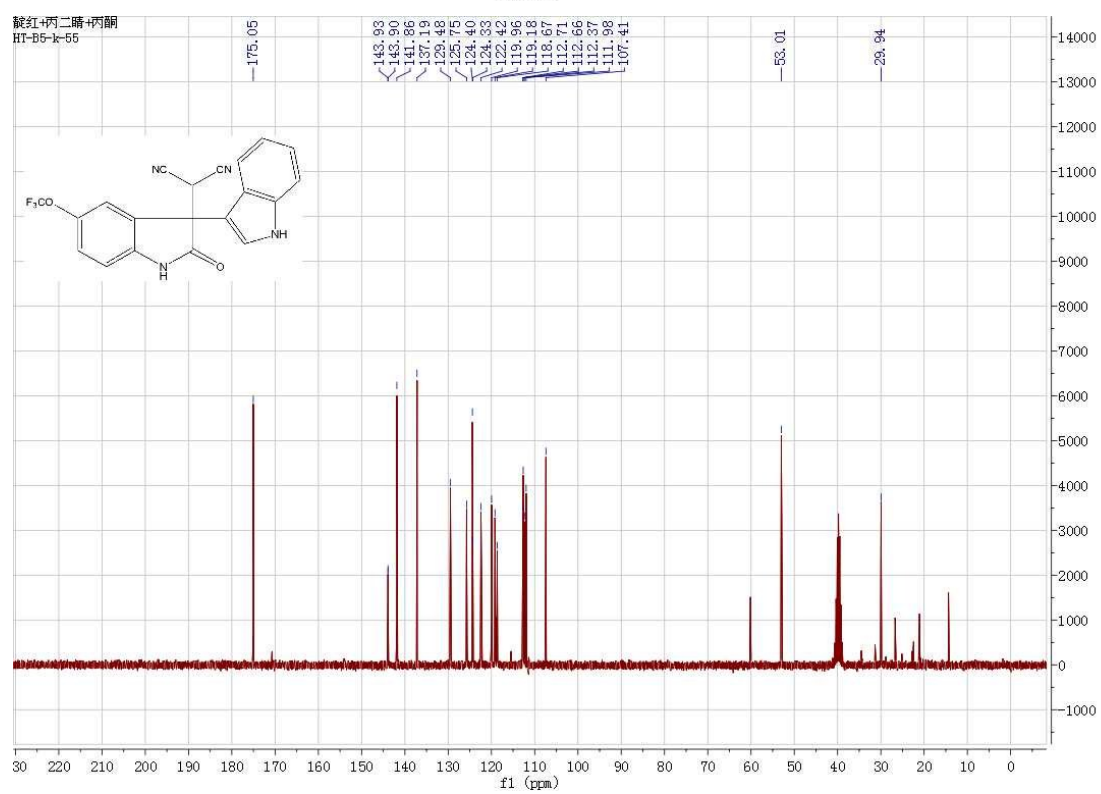
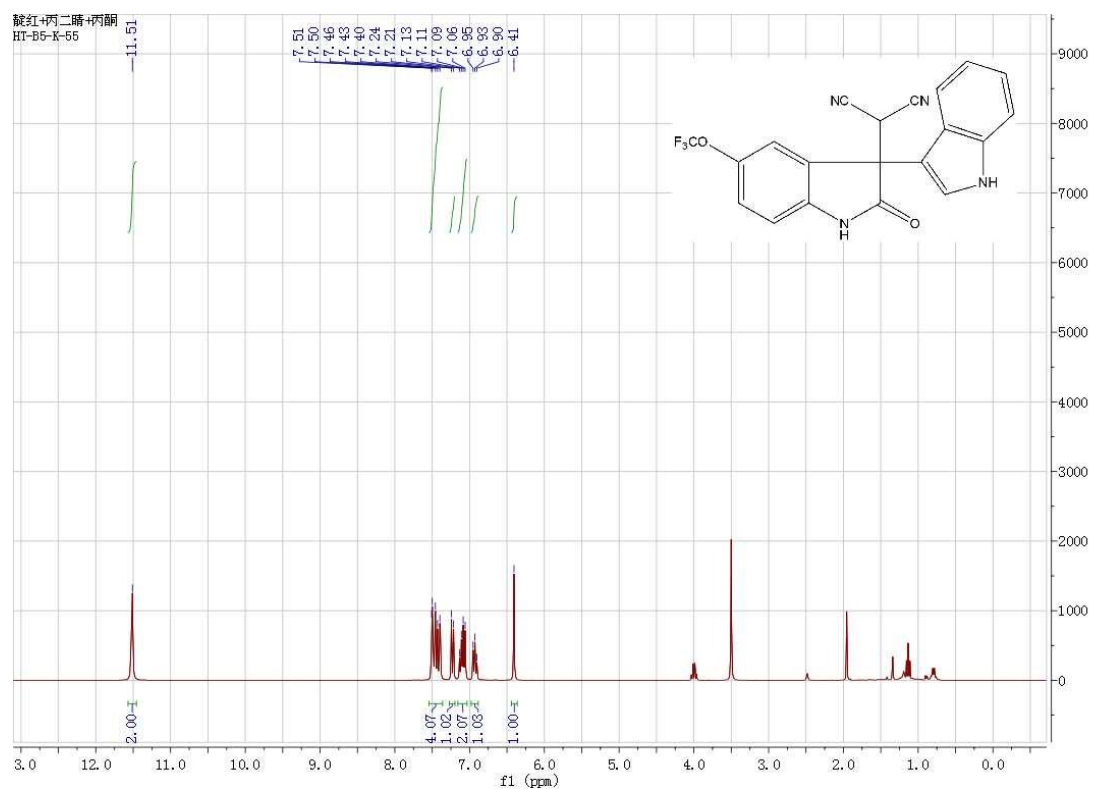


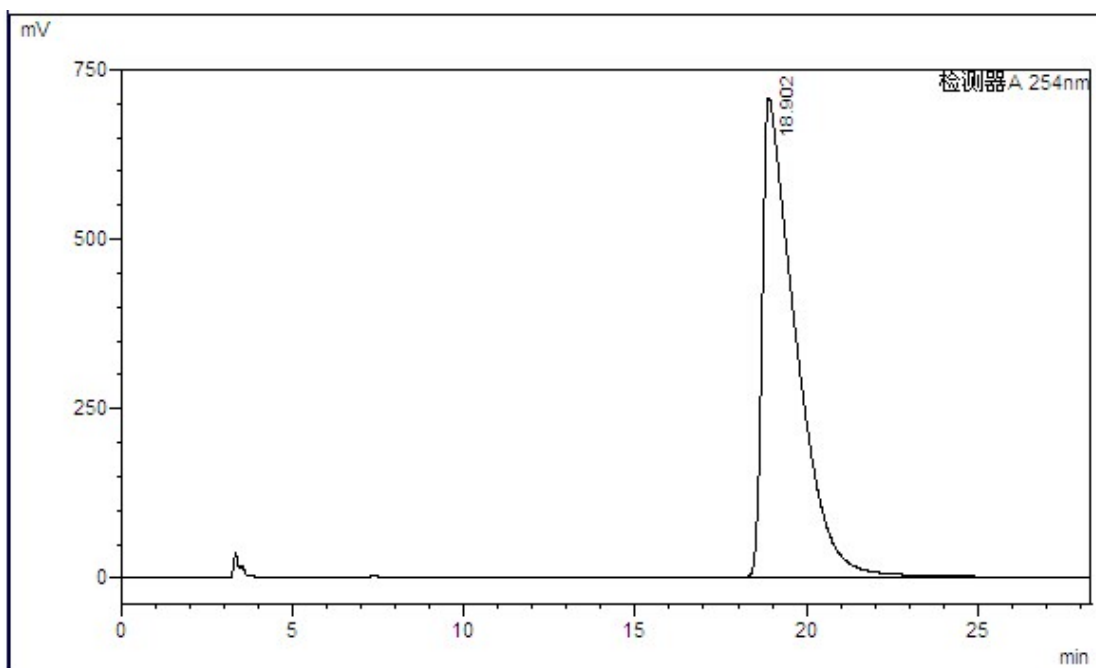
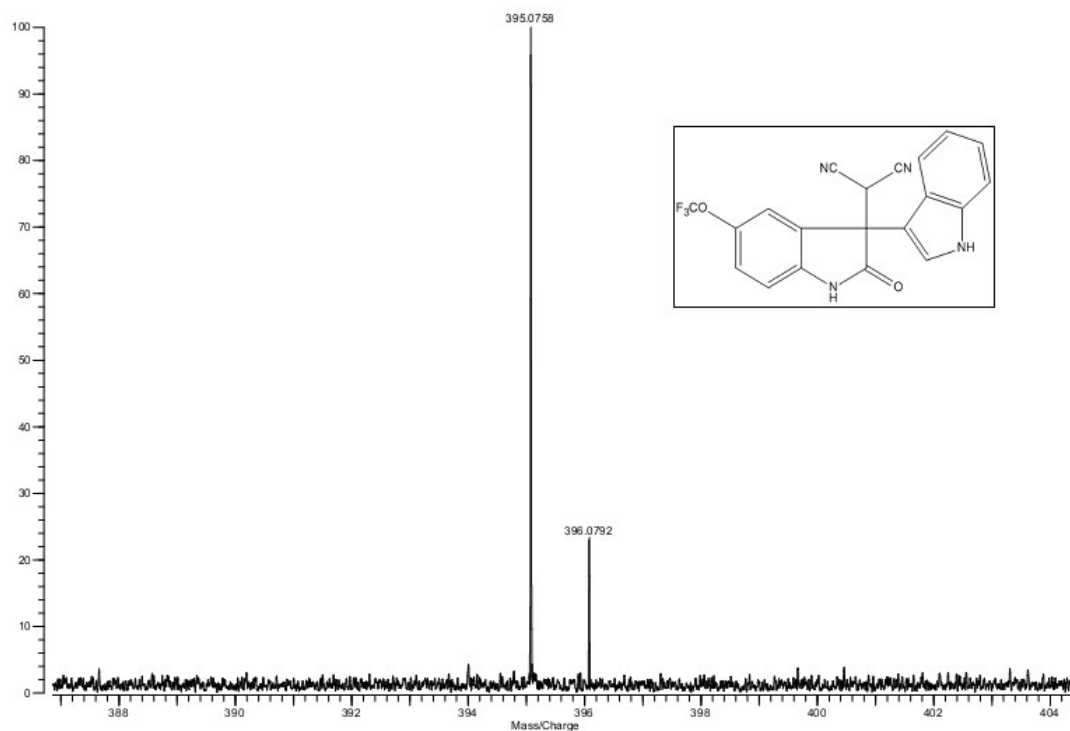
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检测器A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	51.267	130218331	393928	100.000		S	
总计		130218331	393928				

8d





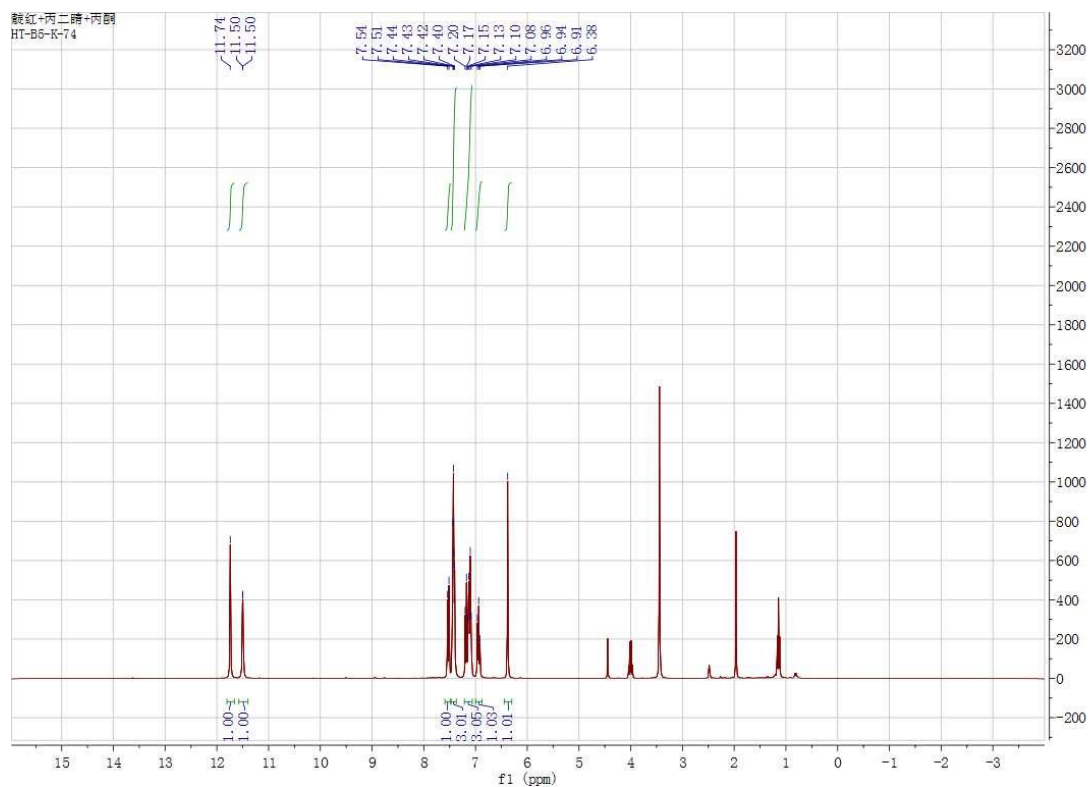
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检测器A 254nm

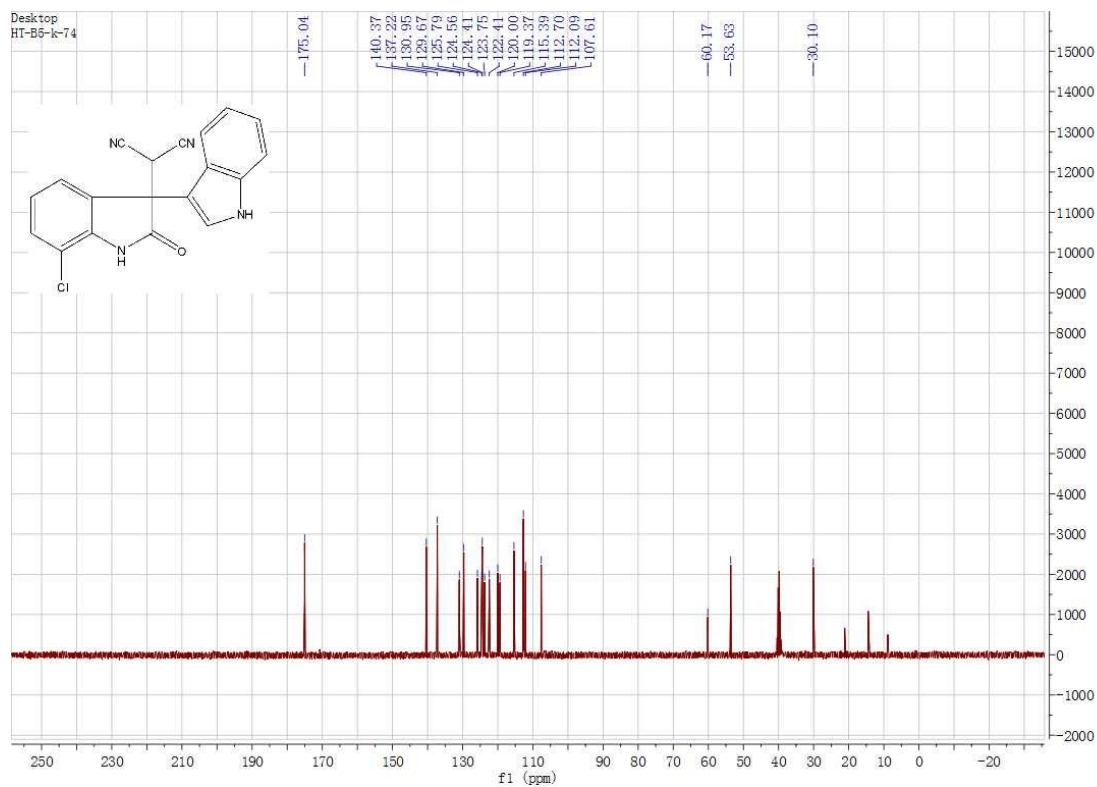
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1	18.902	48159609	707701	100.000			
总计		48159609	707701				

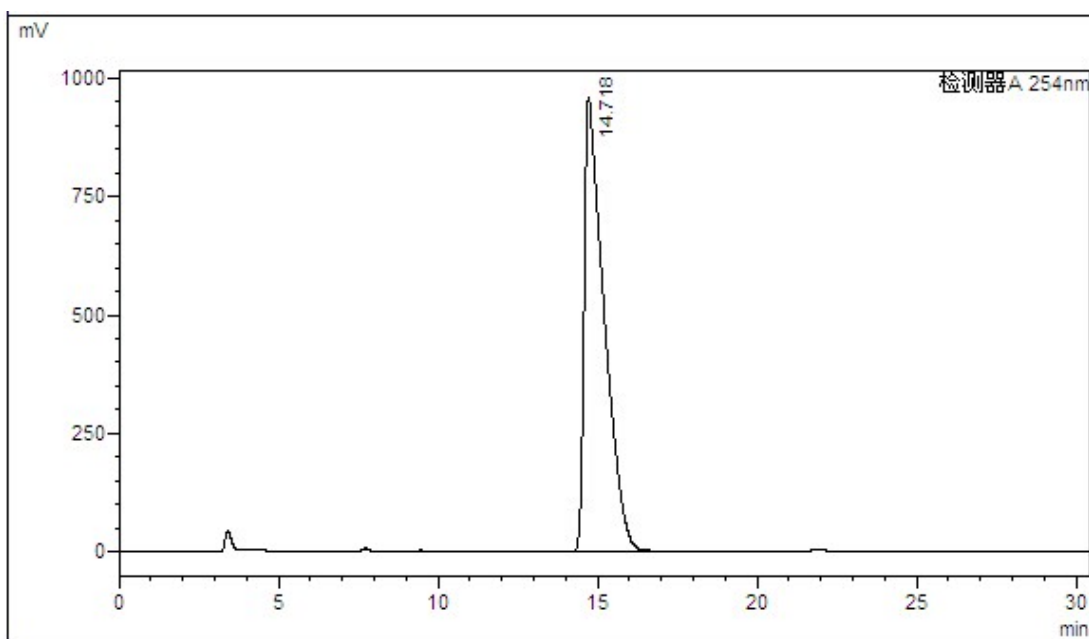
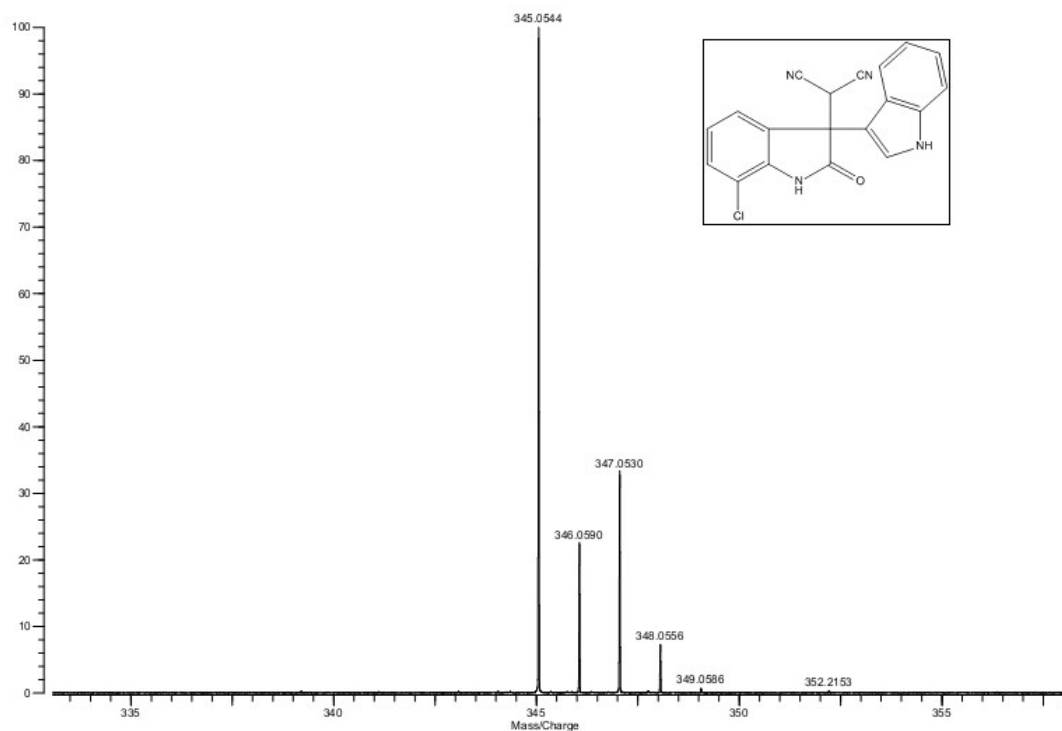
8e

靛红-丙二腈-丙酮
HT-B5-K-74



Desktop
HT-B5-k-74



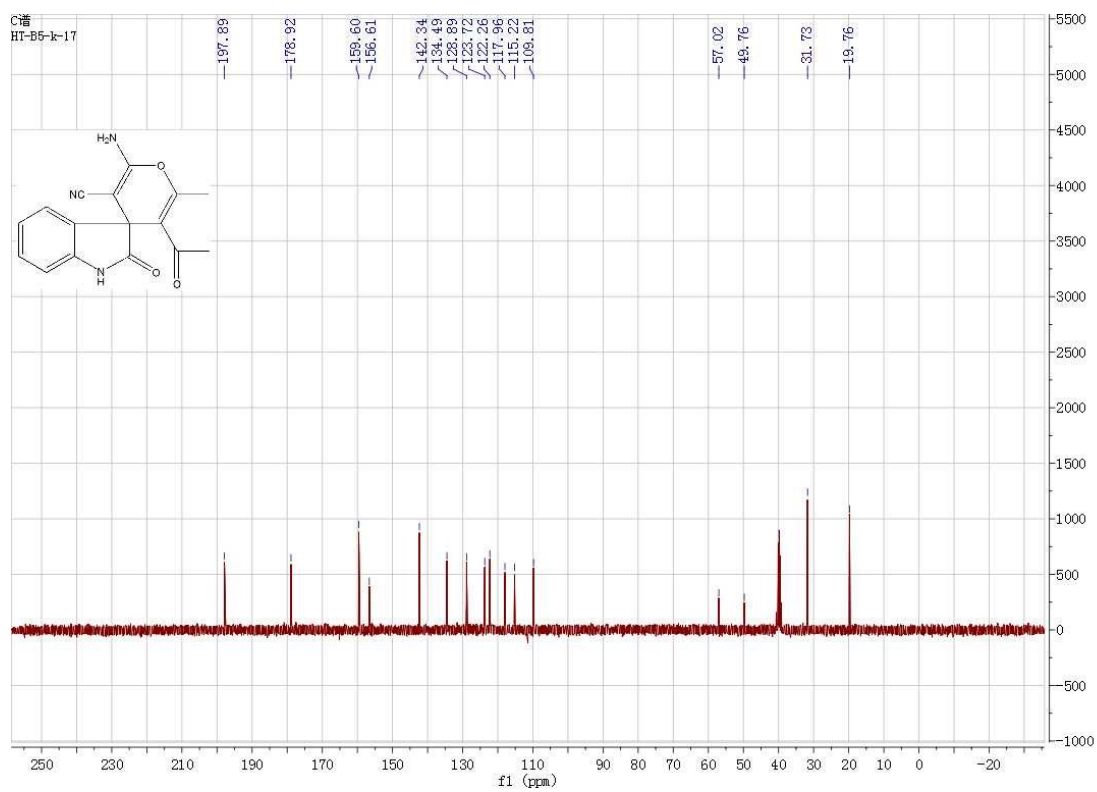
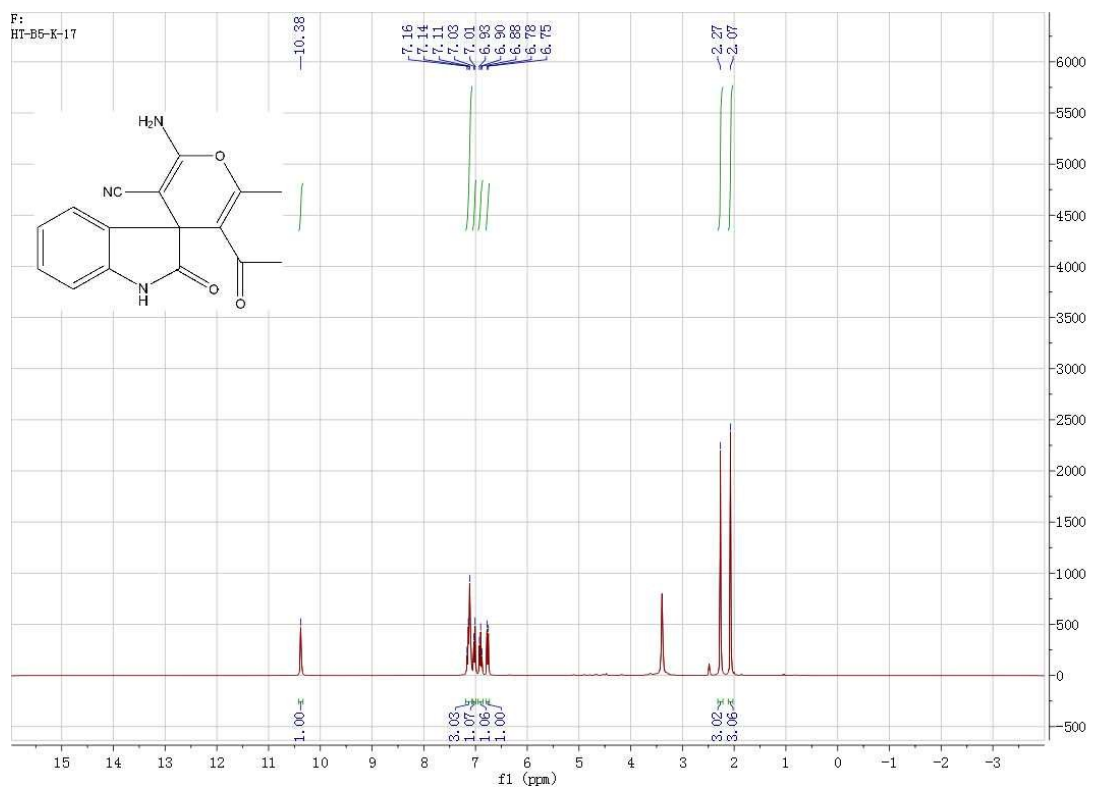


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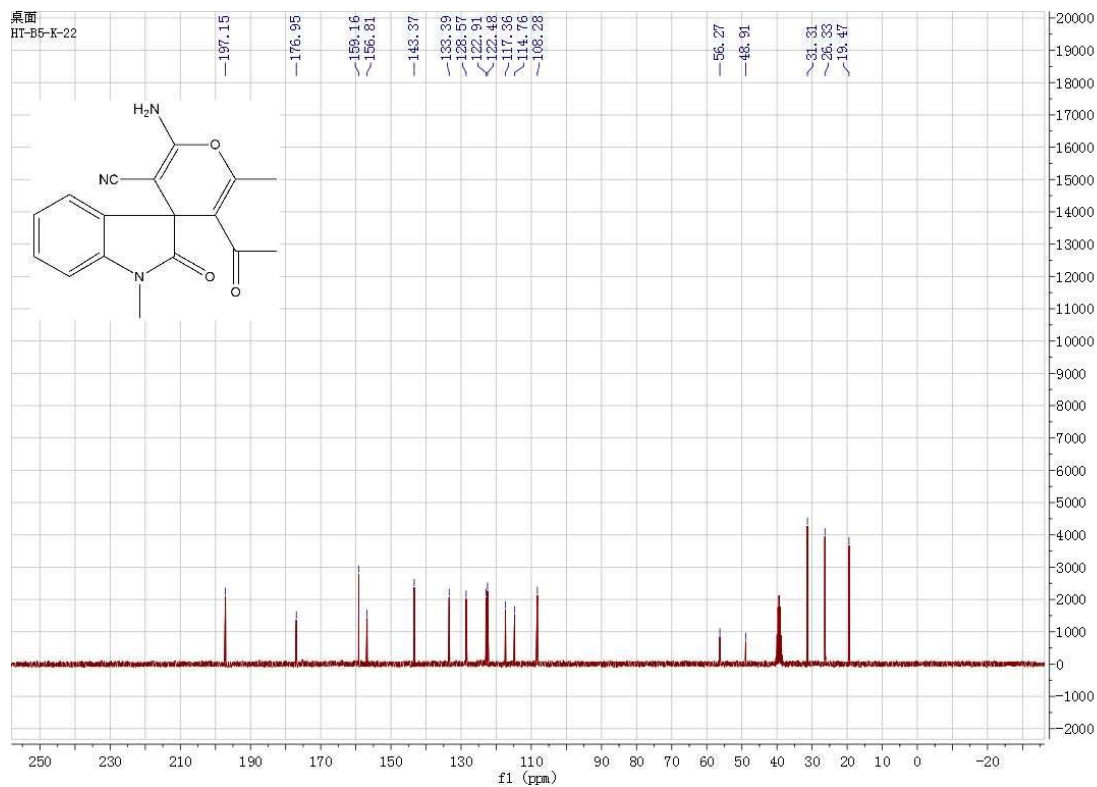
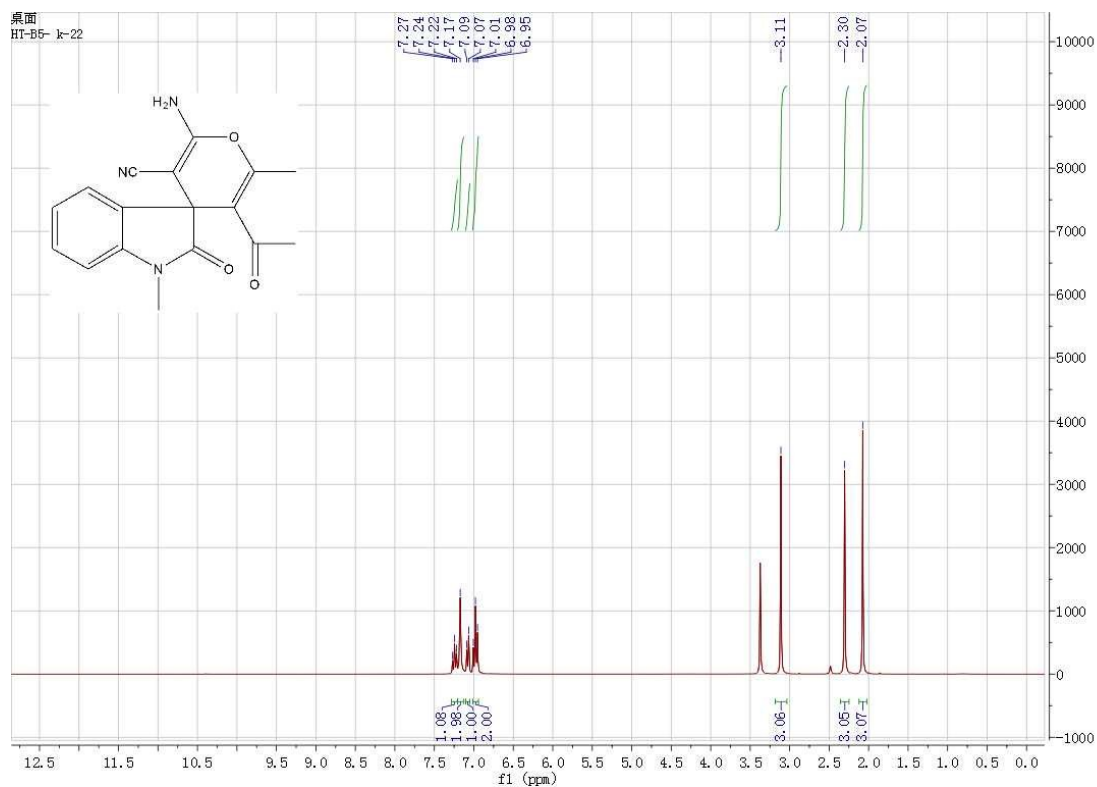
检测器A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.718	41676932	959960	100.000		S	
总计		41676932	959960				

11a

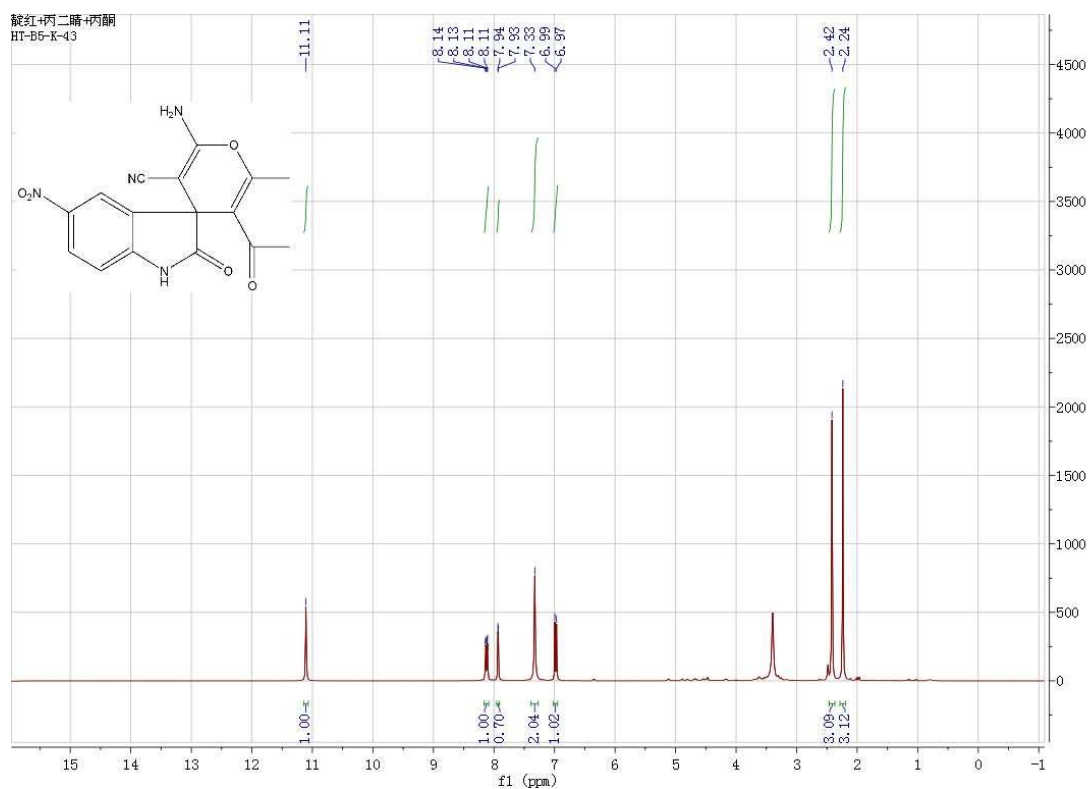


11b

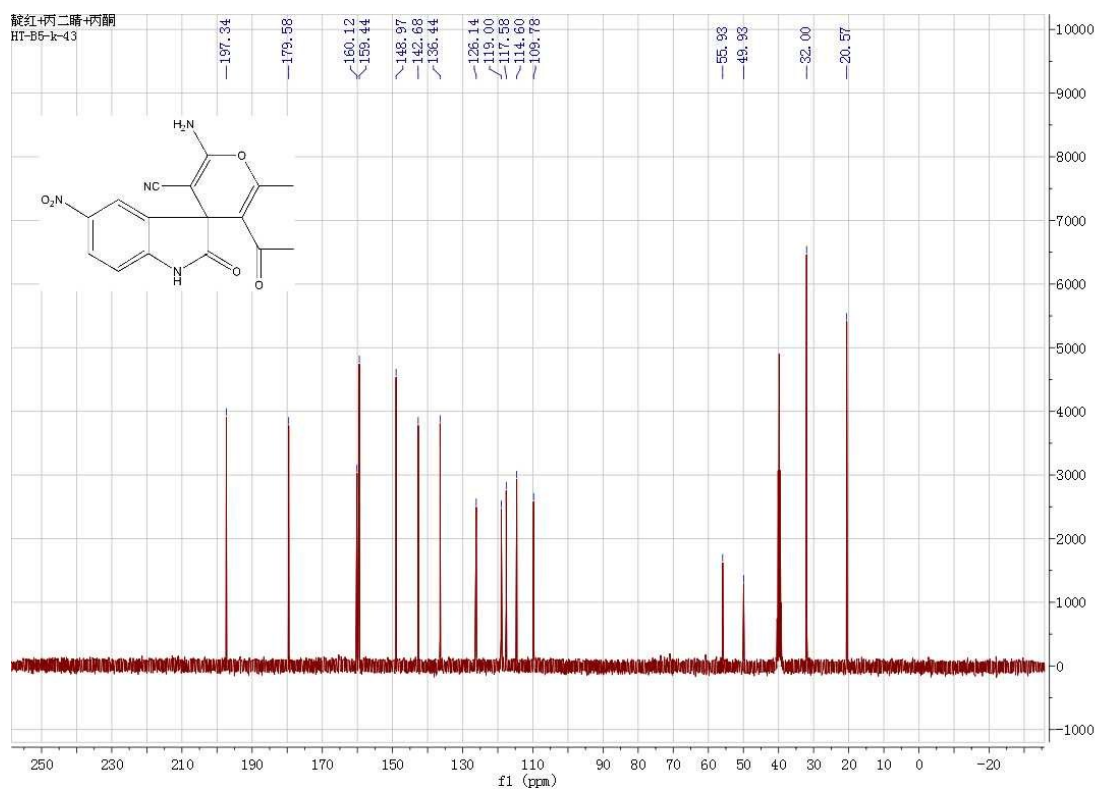


11c

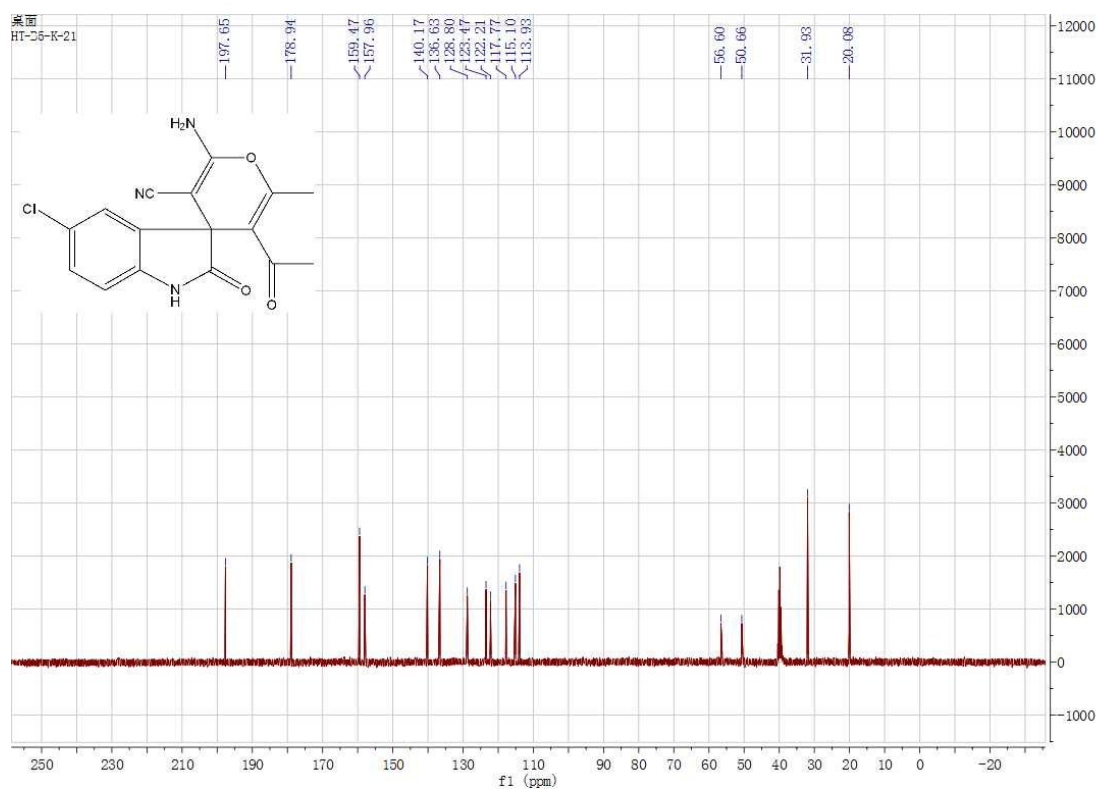
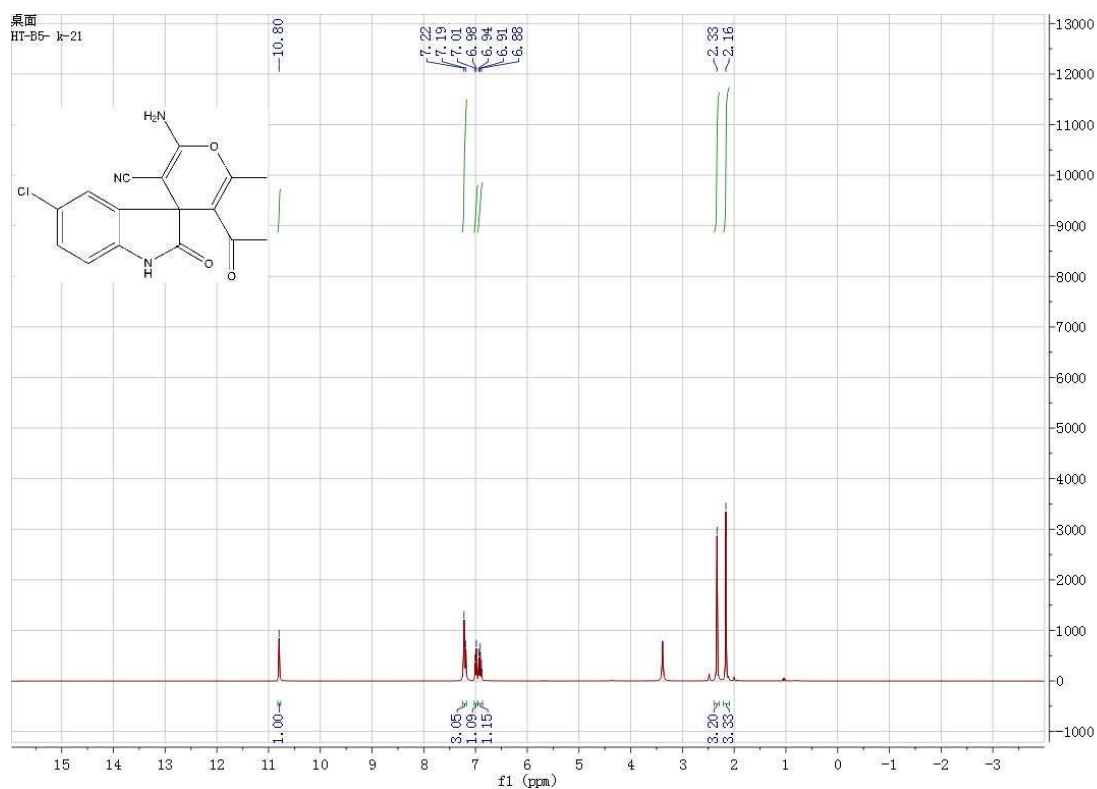
靛红+丙二腈+丙酮
HT-B5-K-43



靛红+丙二腈+丙酮
HT-B5-K-43

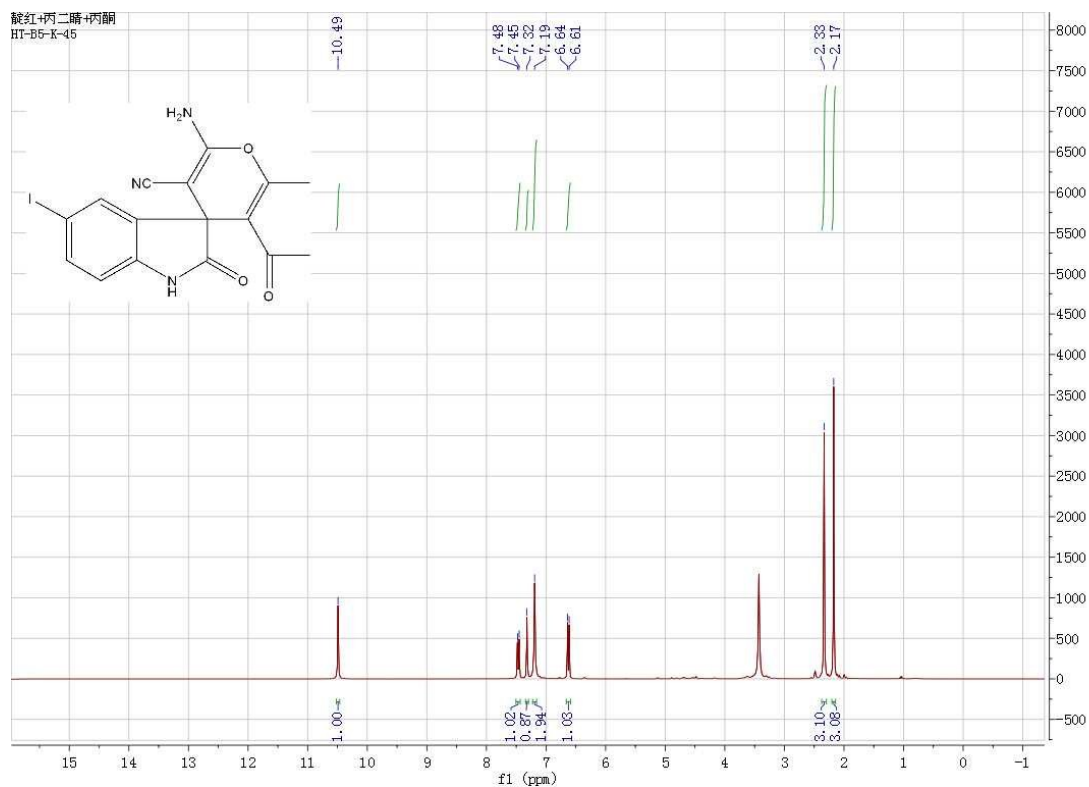


11d

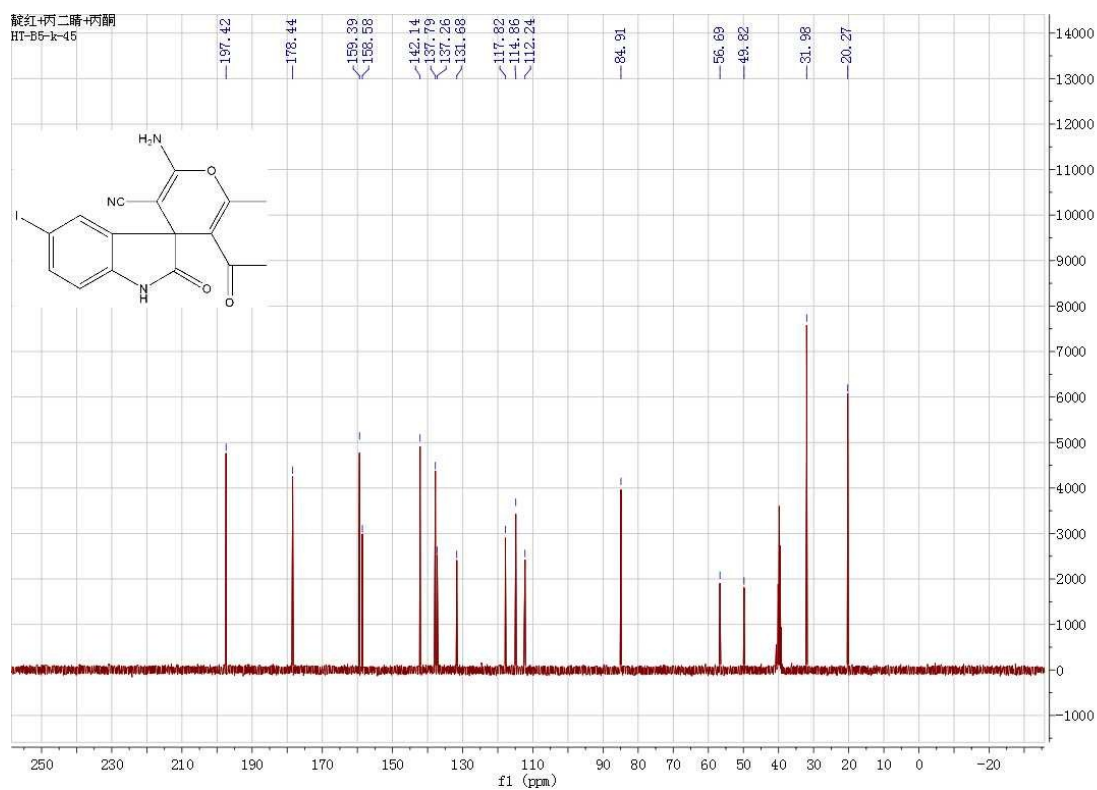


11e

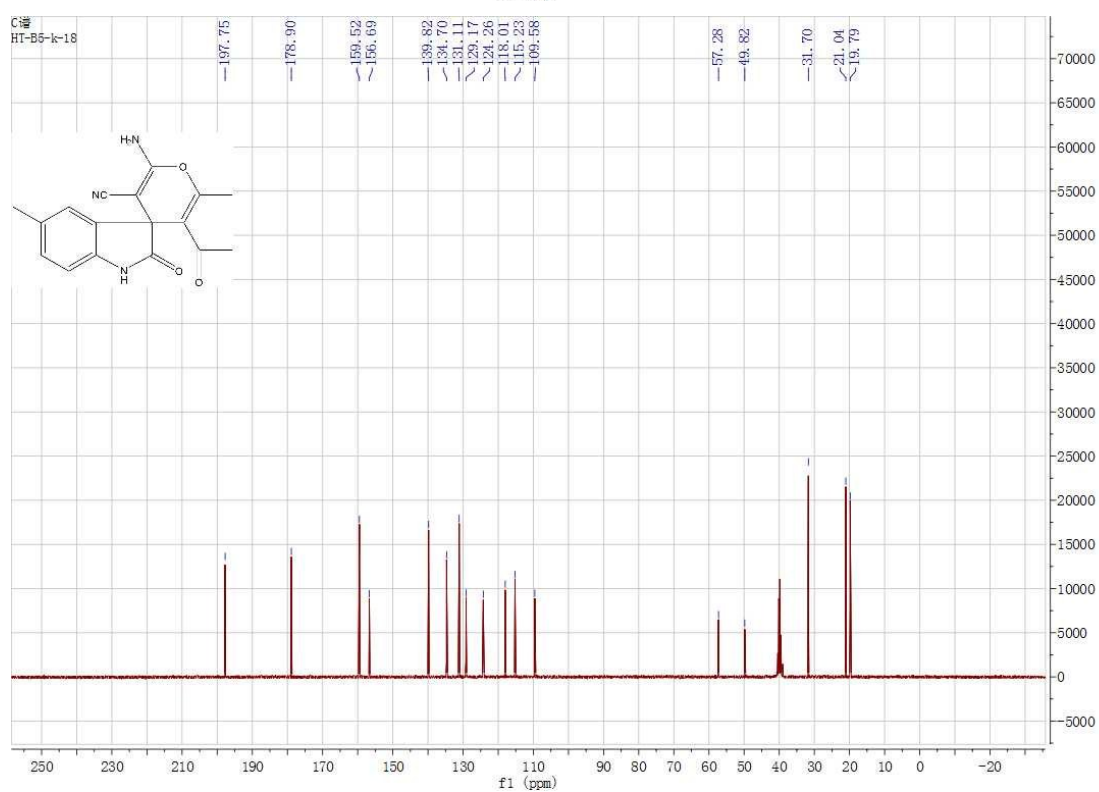
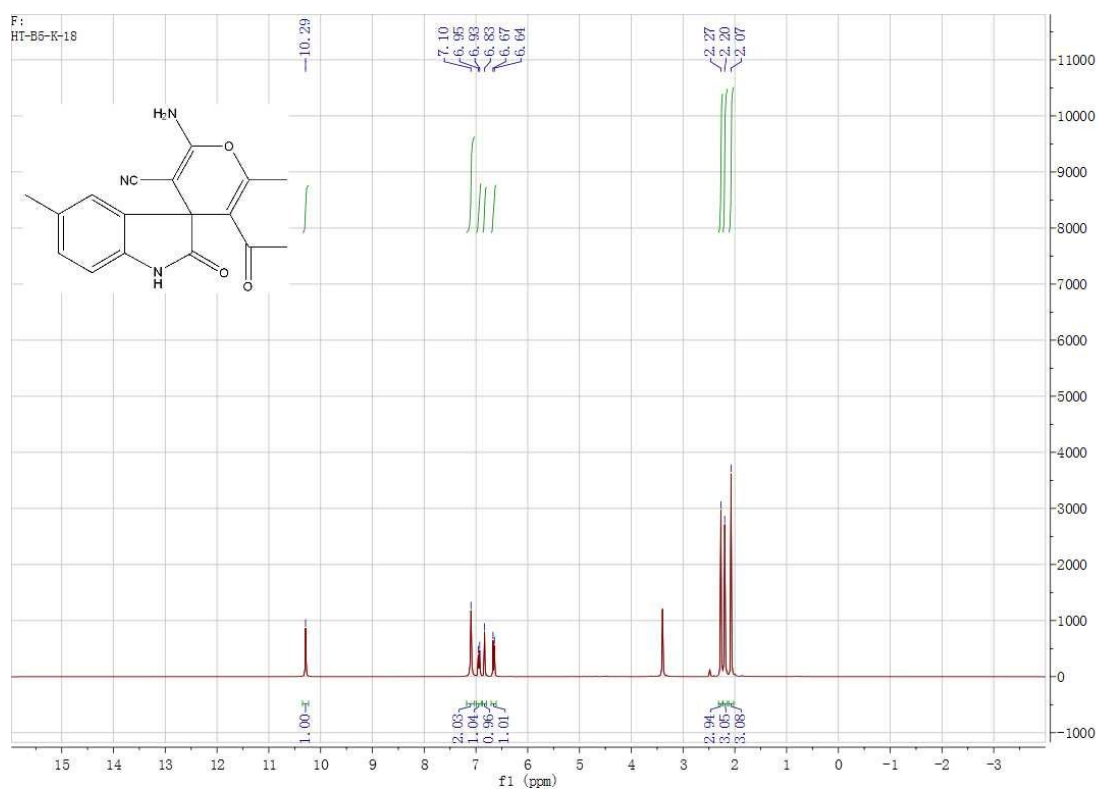
靛红+丙二腈+丙酮
HT-B5-K-45



靛红+丙二腈+丙酮
HT-B5-K-45

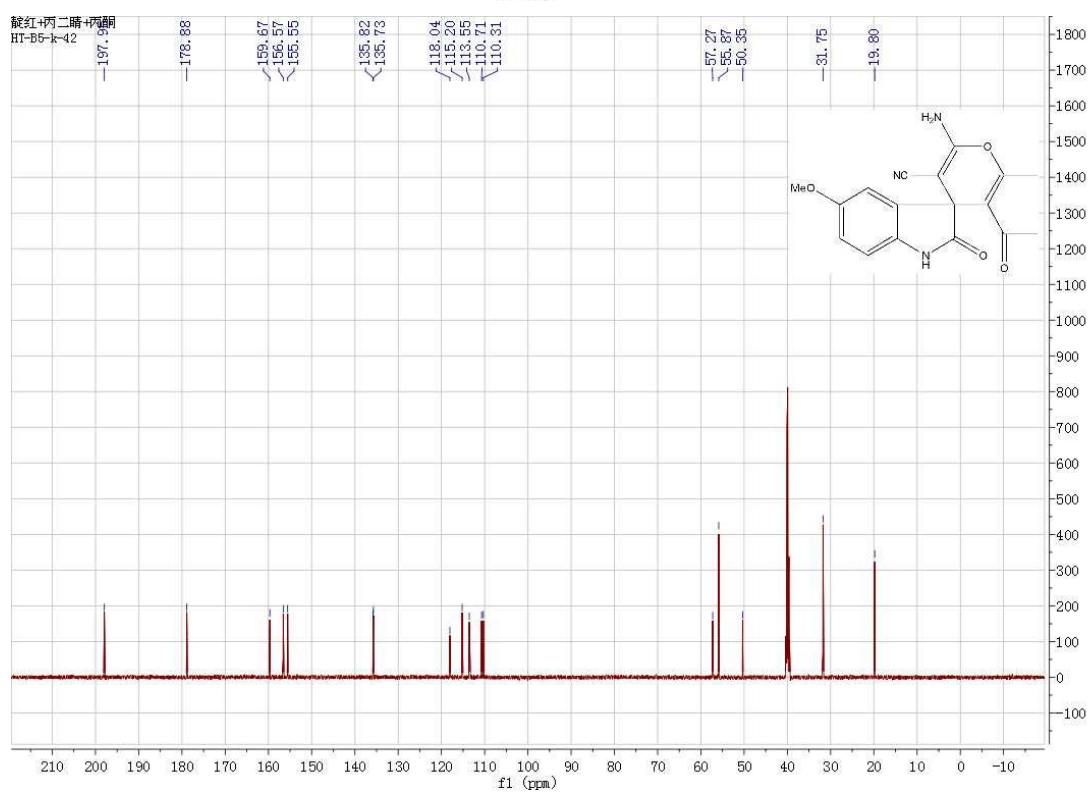
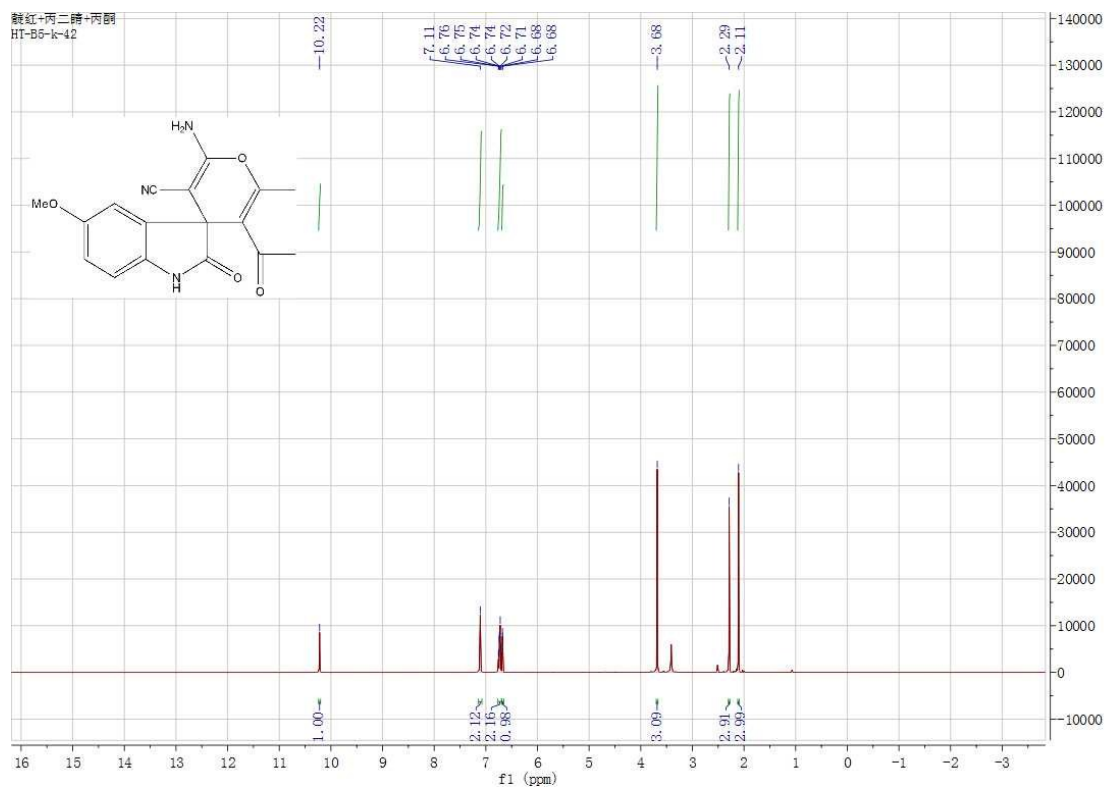


11f

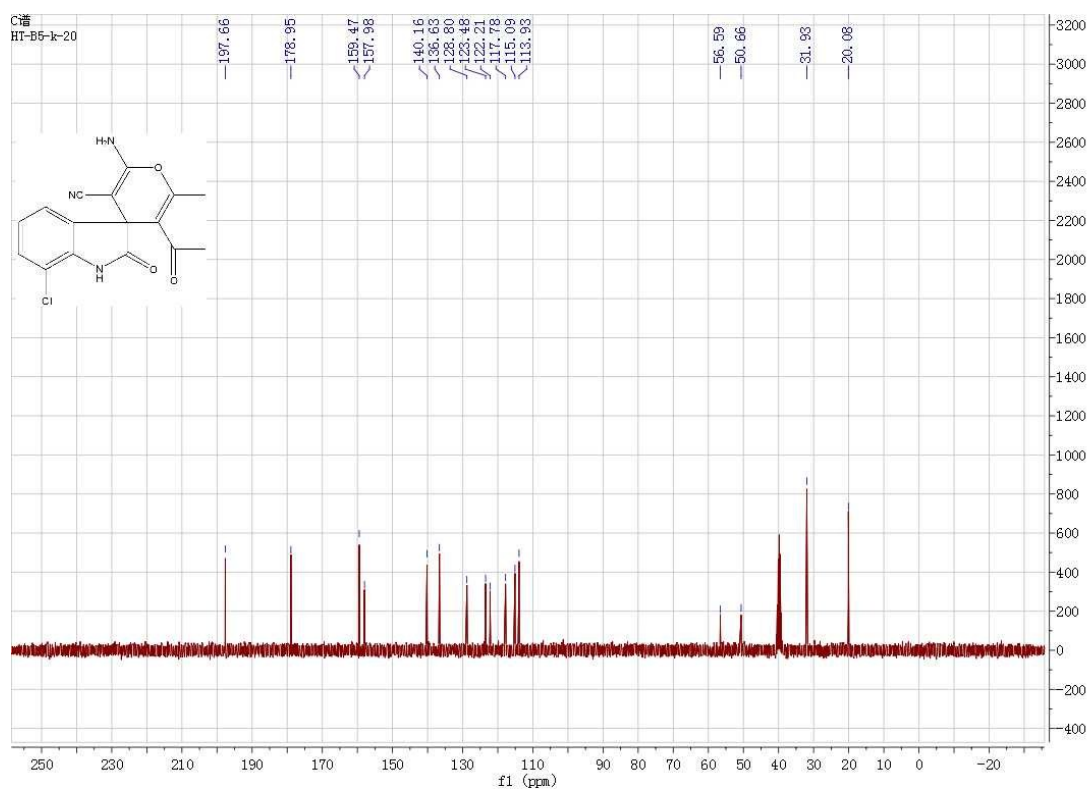
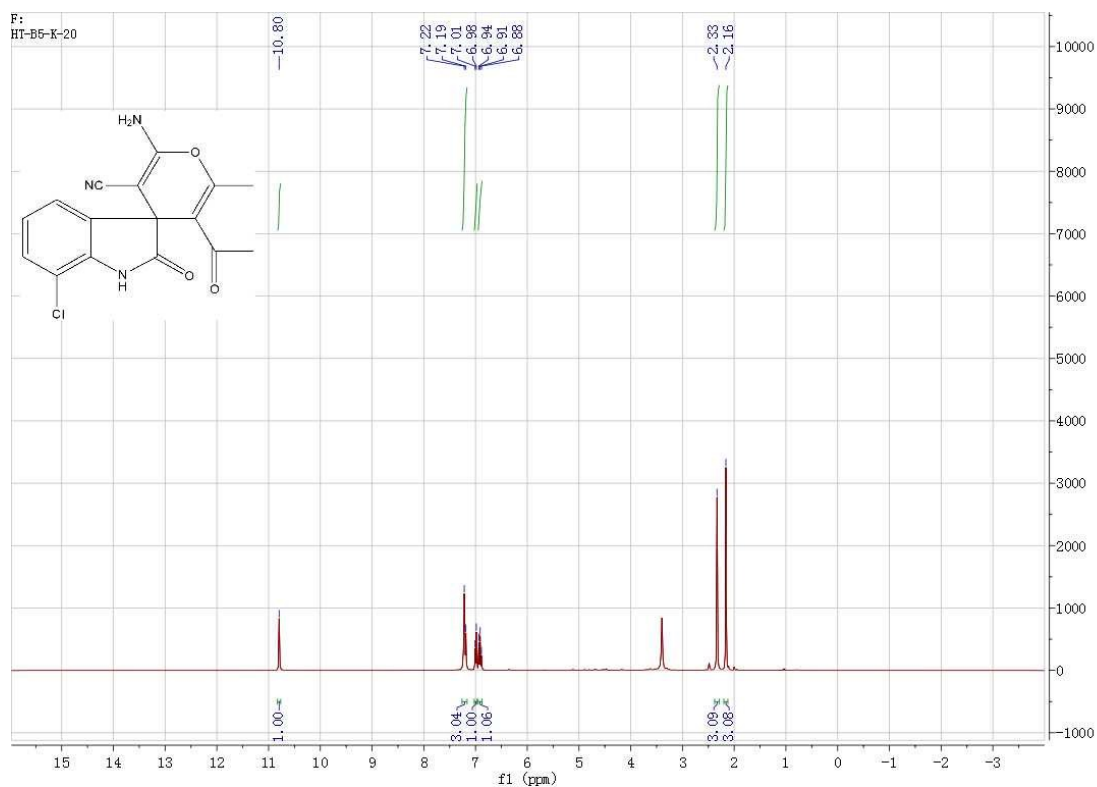


11g

靛红+丙二腈+丙酮
HT-B5-k-42

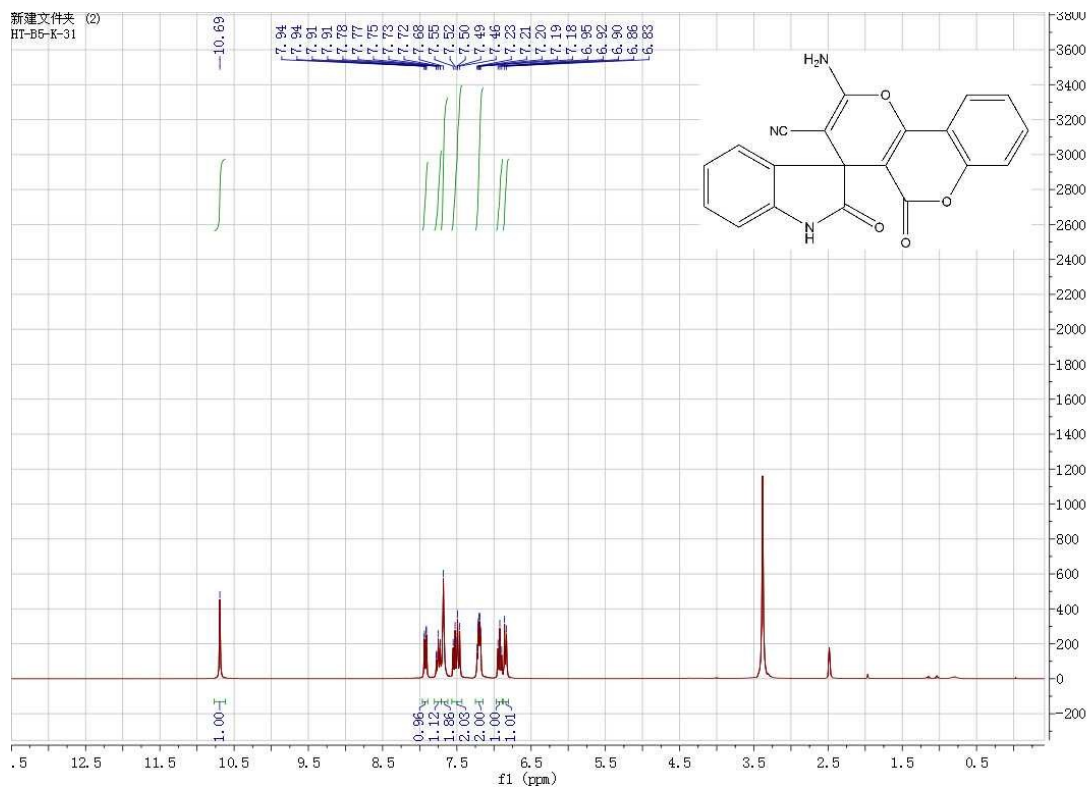


11h

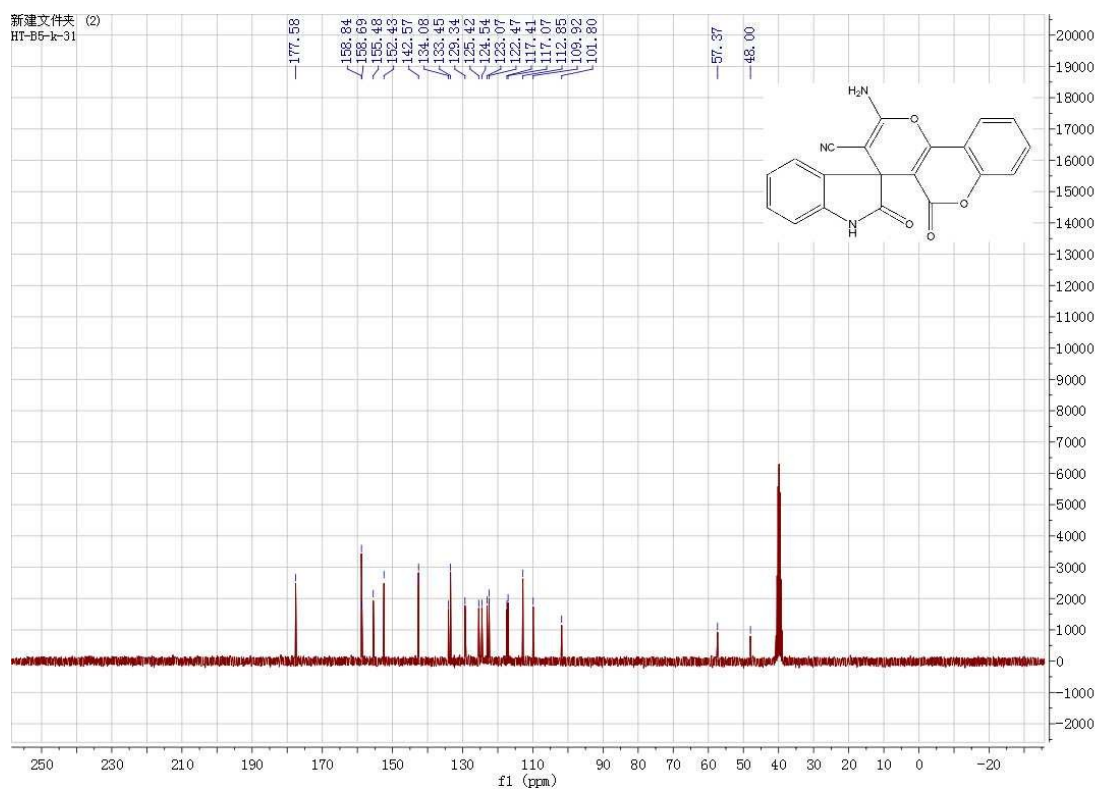


13a

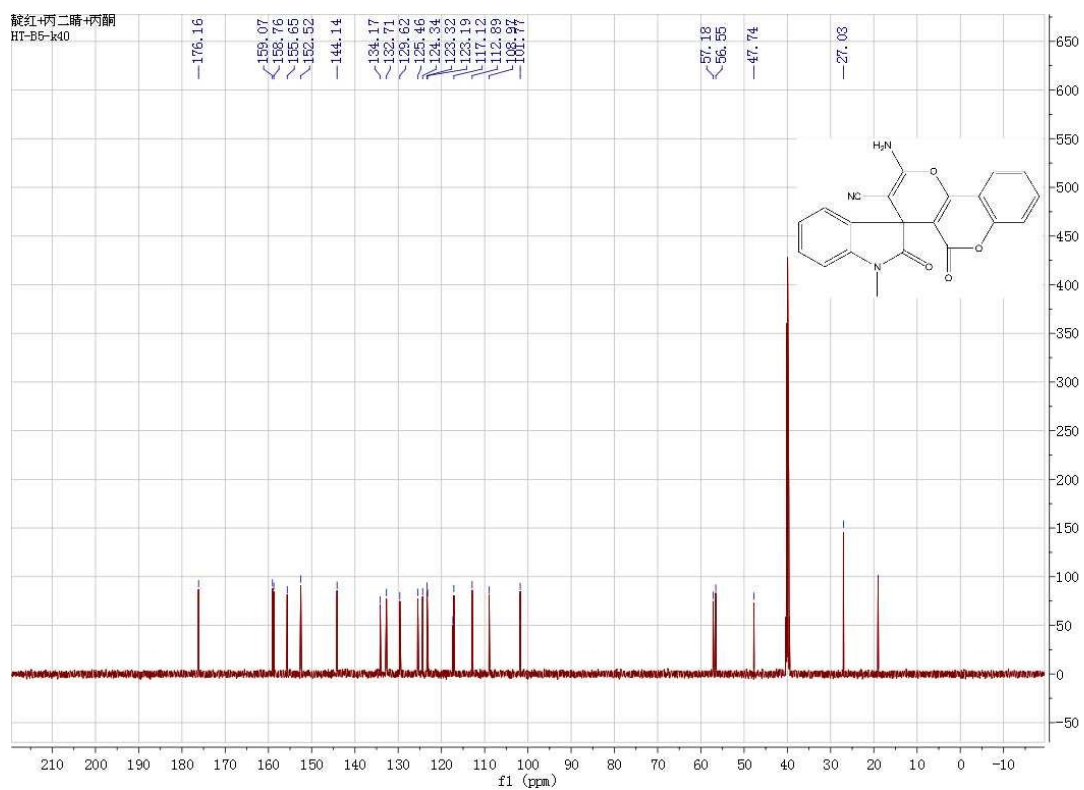
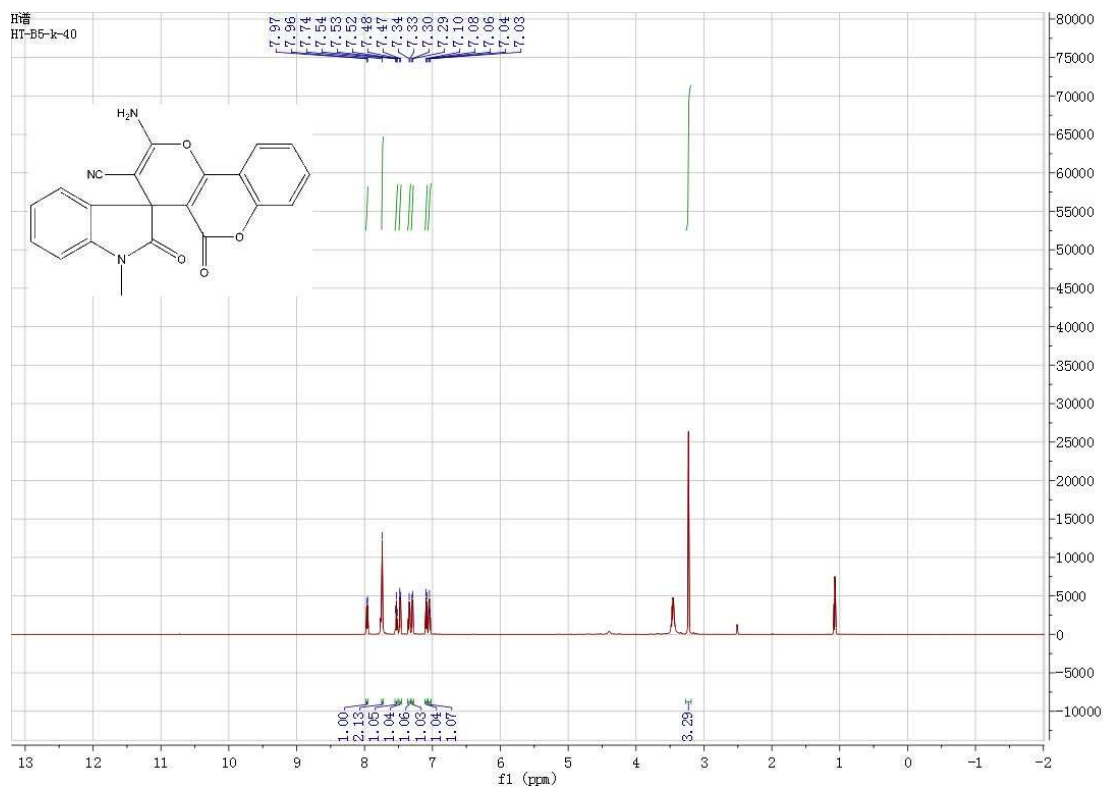
新建文件夹 (2)
HT-B5-K-31



新建文件夹 (2)
HT-B5-K-31

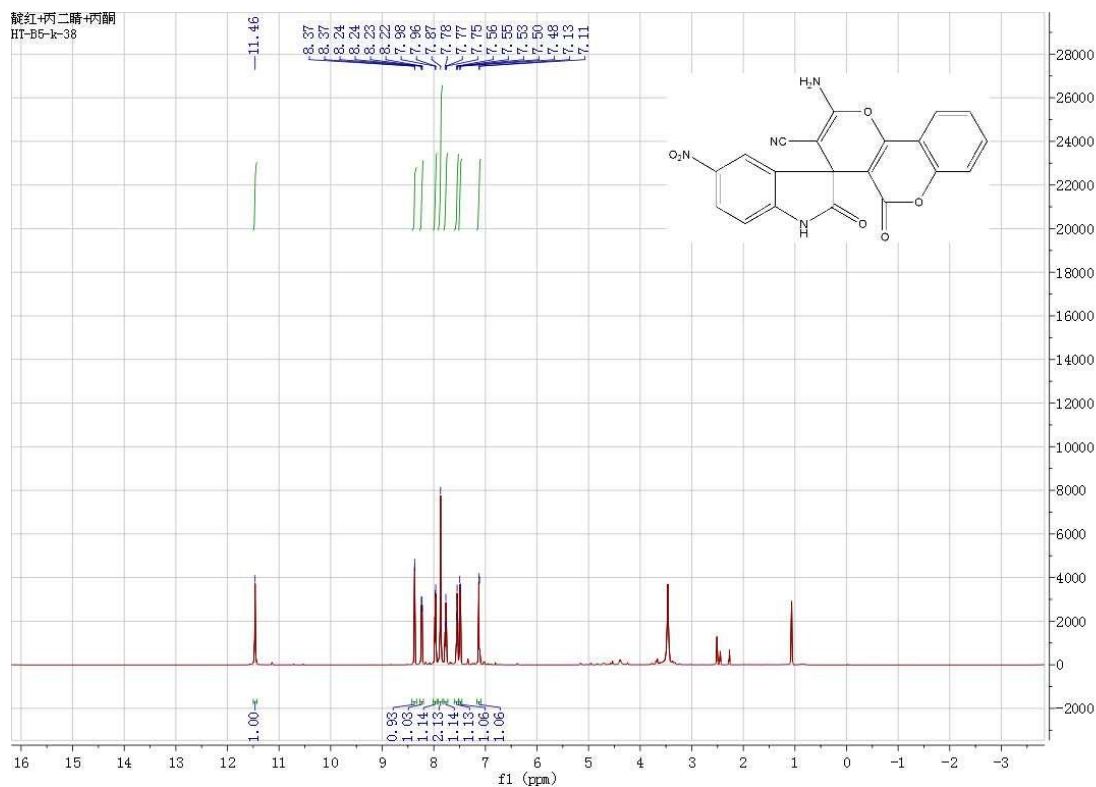


13b

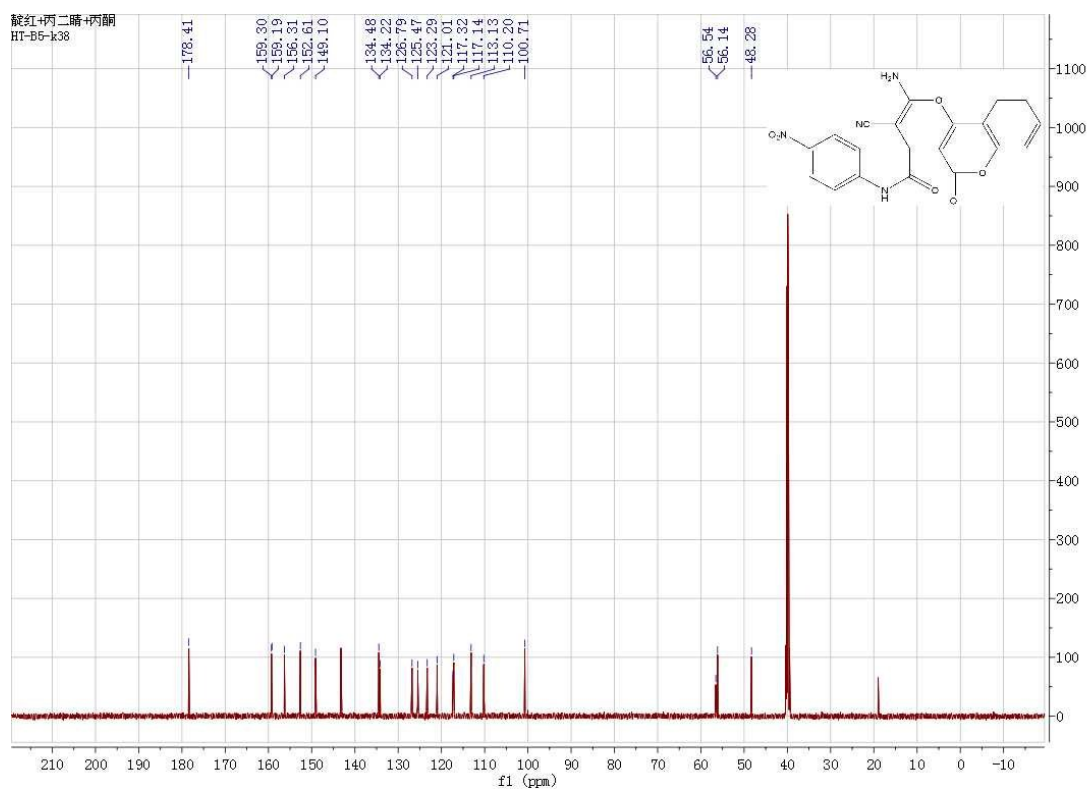


13c

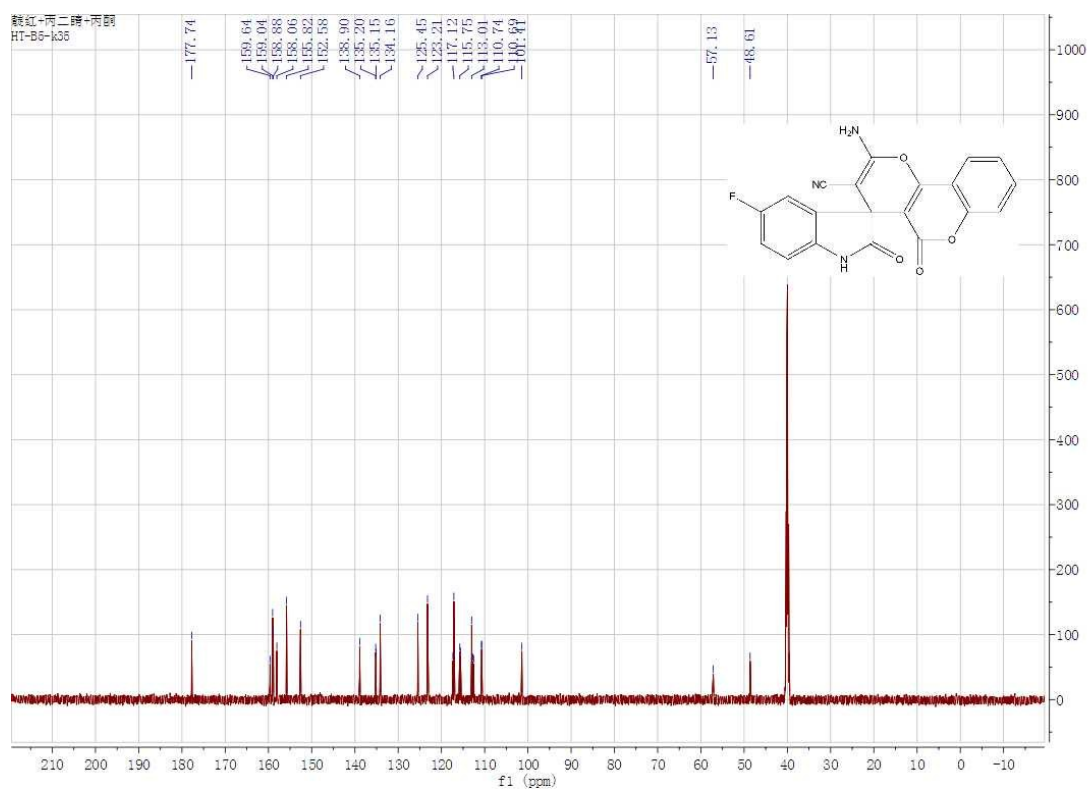
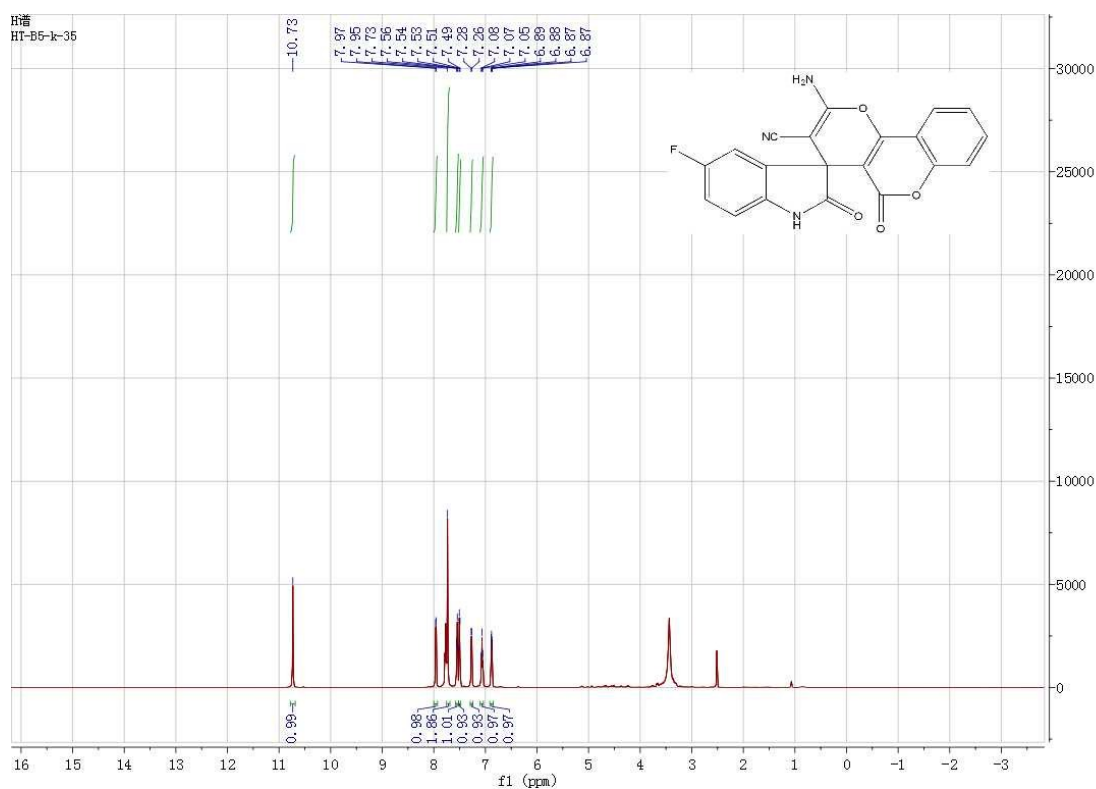
靛红+丙二腈+丙酮
HT-B5-k-38



靛红+丙二腈+丙酮
HT-B5-k-38

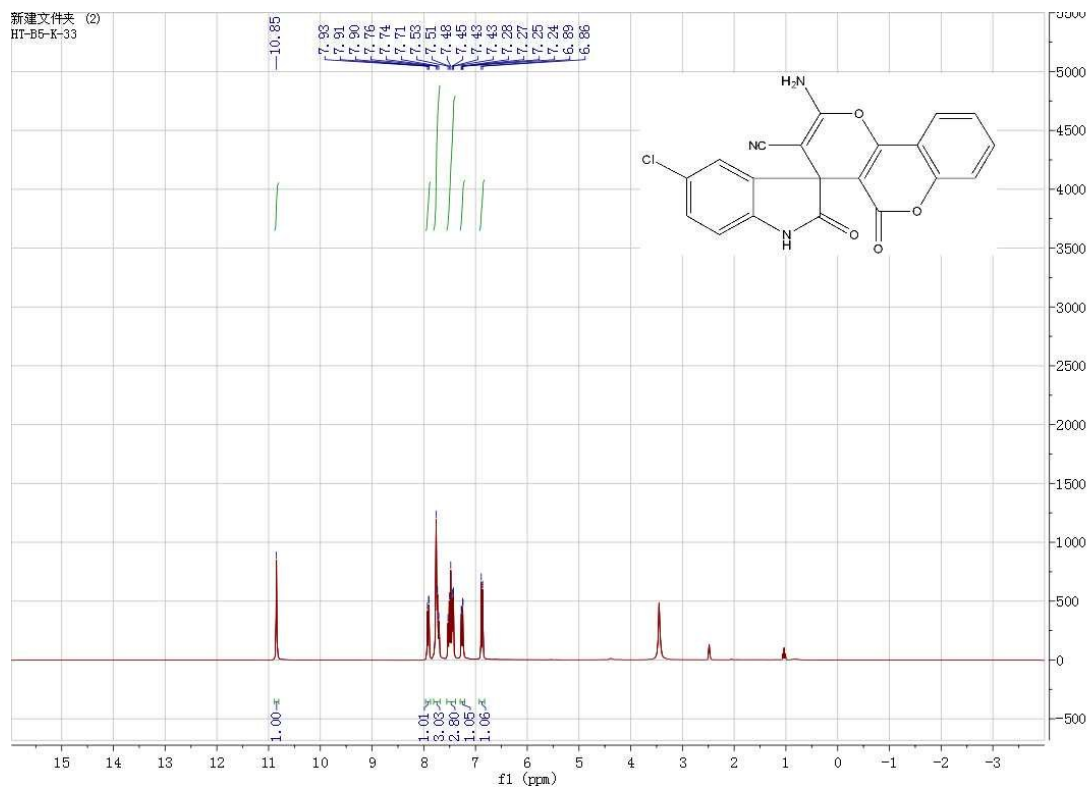


13d

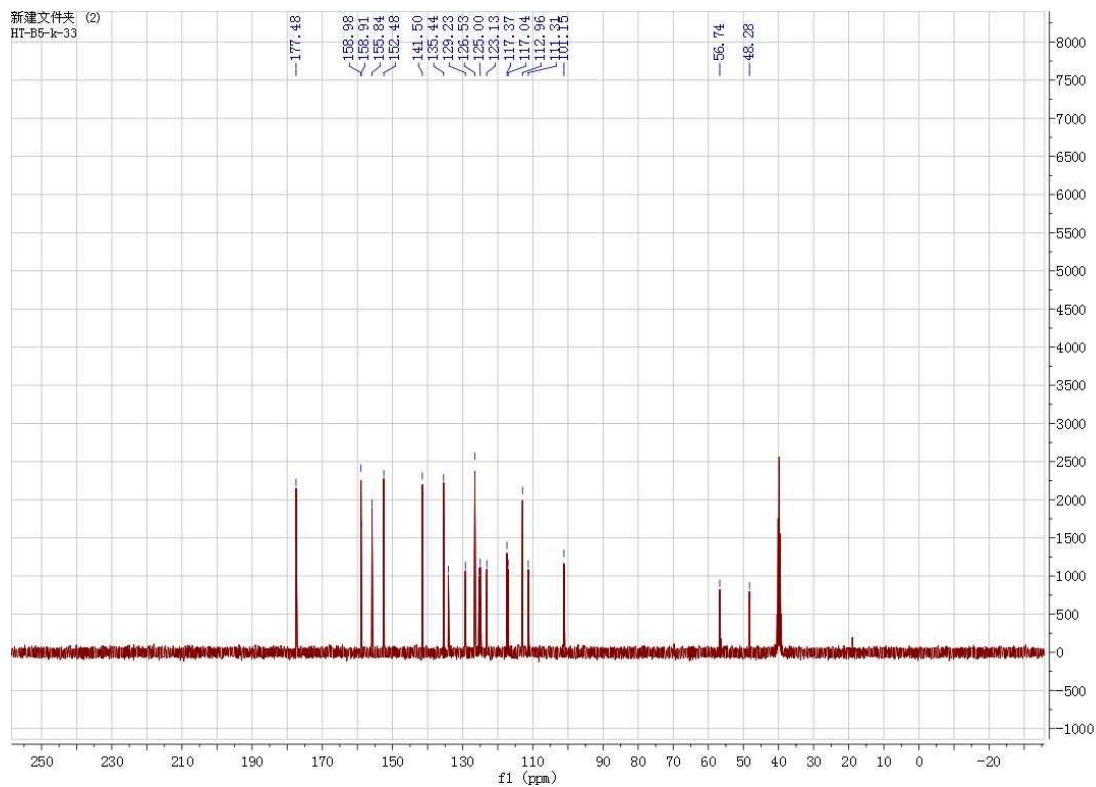


13e

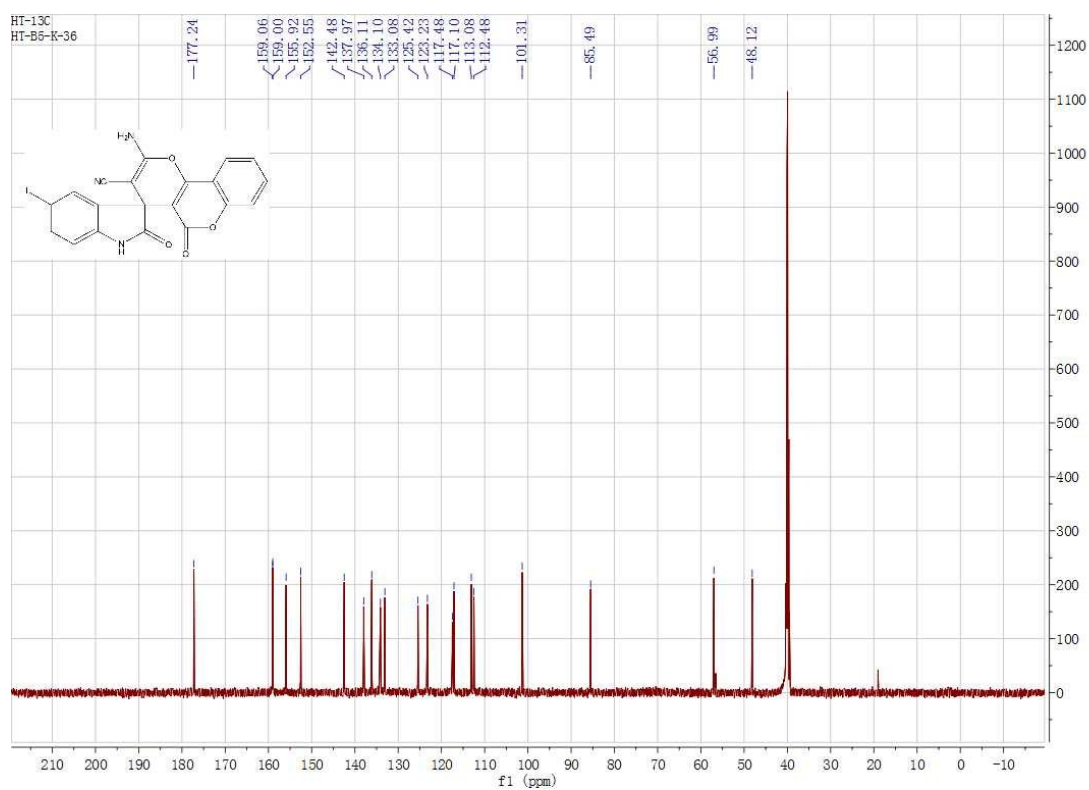
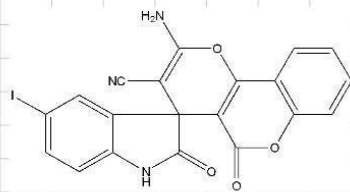
新建文件夹 (2)
HT-B5-K-33



新建文件夹 (2)
HT-B5-K-33

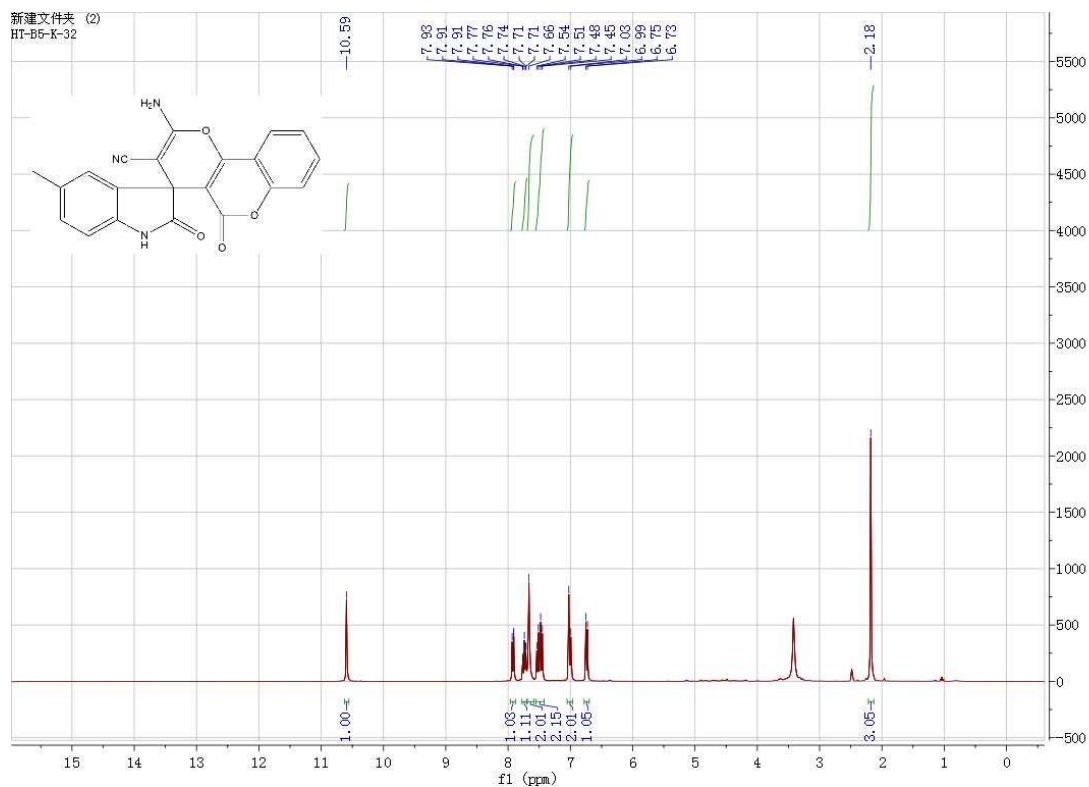


HT-1H	
HT-B5-K-36	

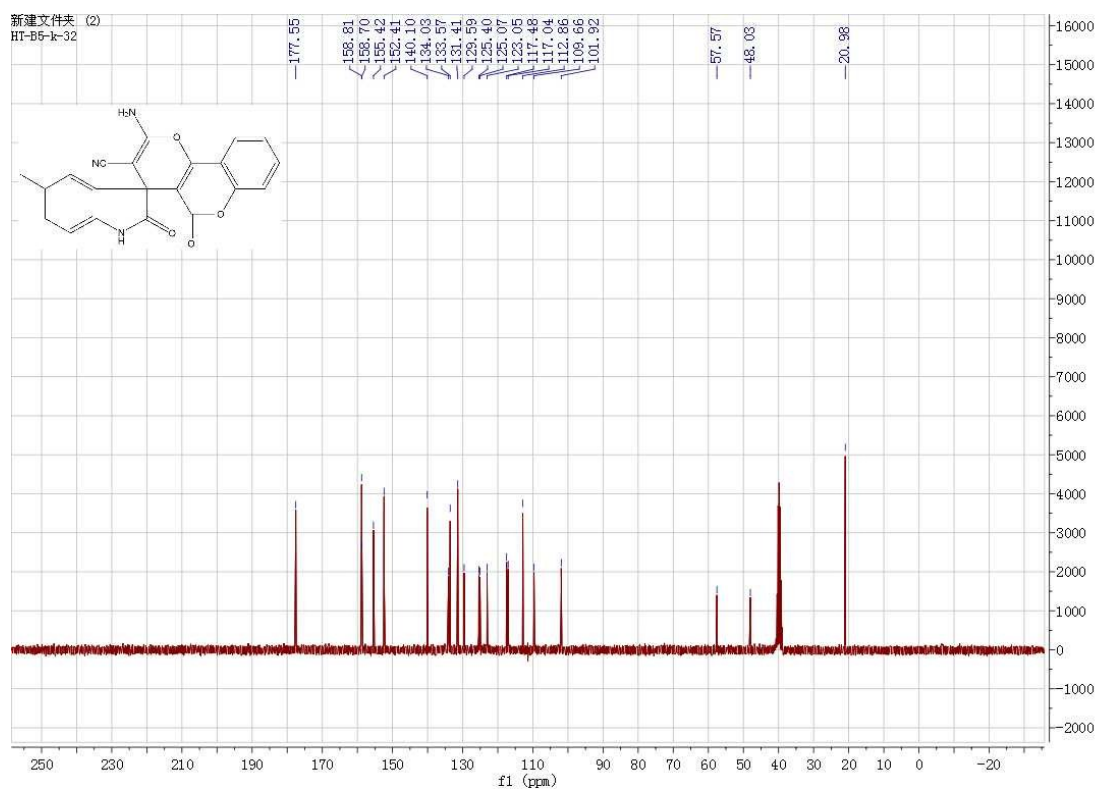


13g

新建文件夹 (2)
HT-B5-X-32

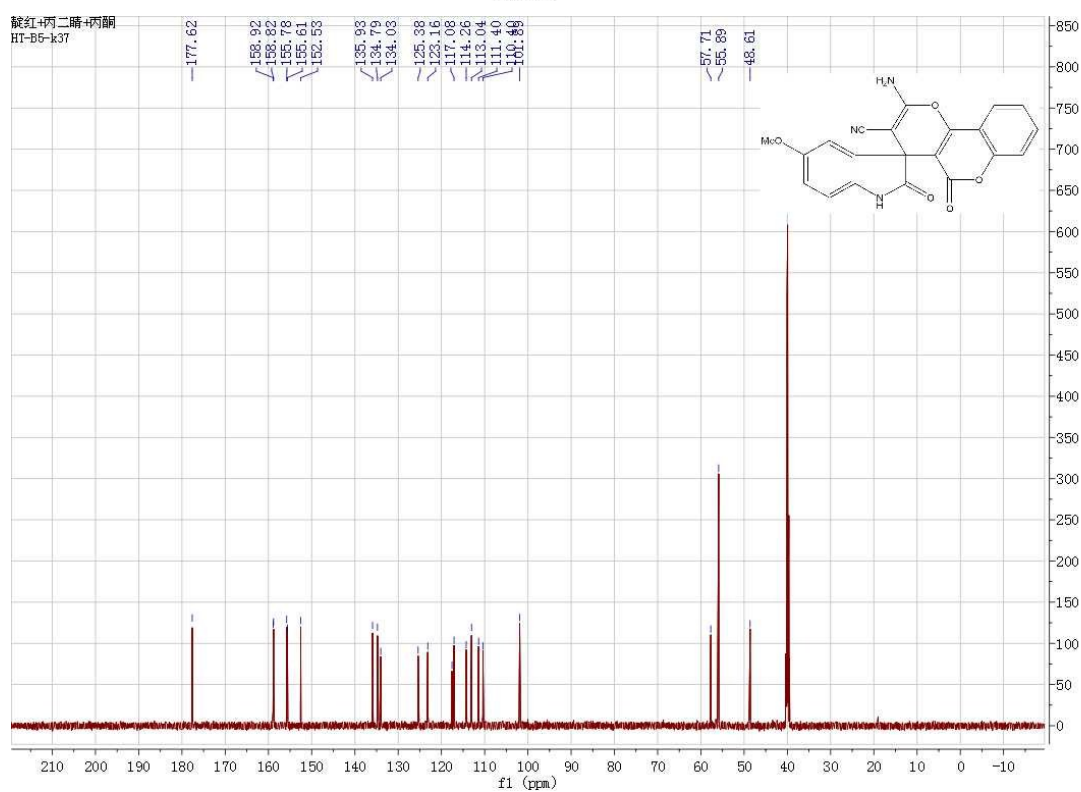
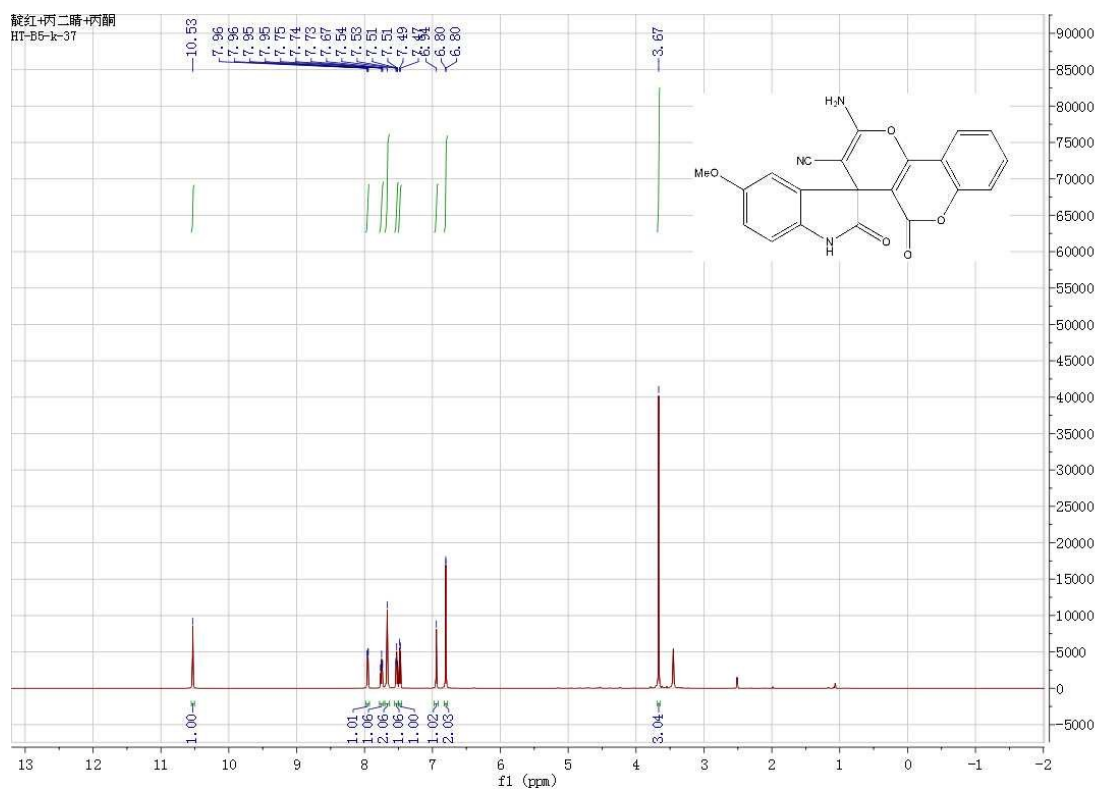


新建文件夹 (2)
HT-B5-X-32

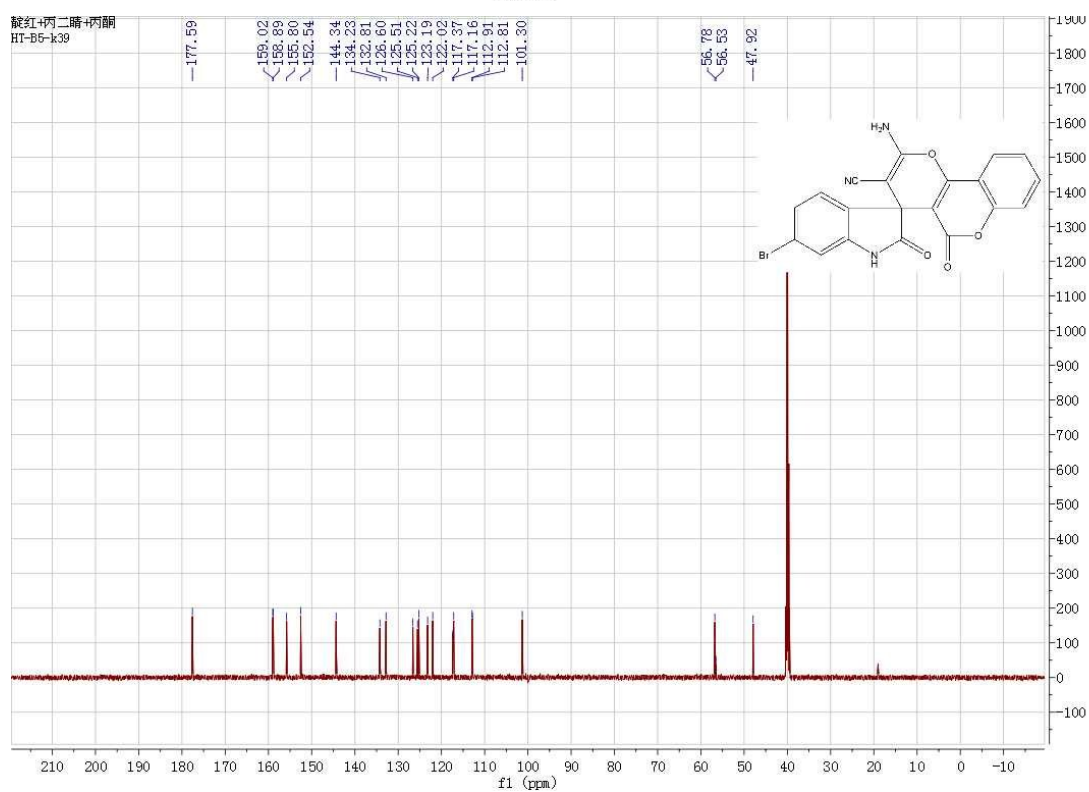
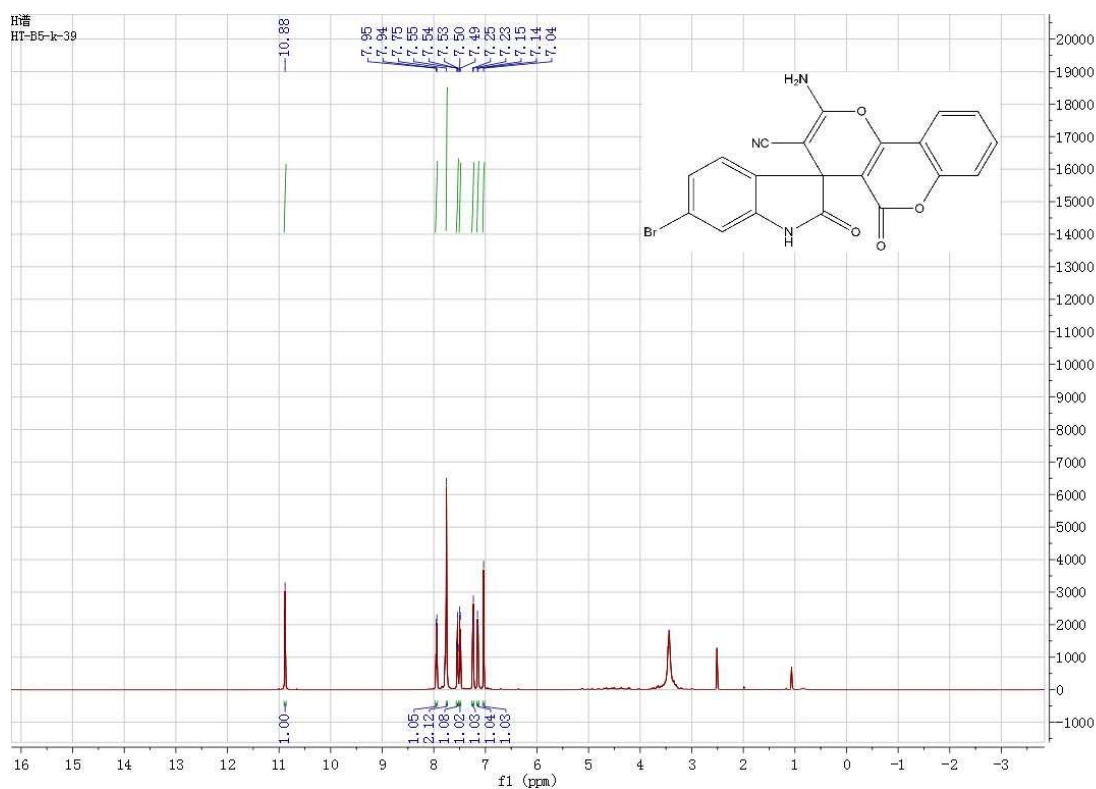


13h

靛红+丙二腈+丙酮
HT-B5-k-37

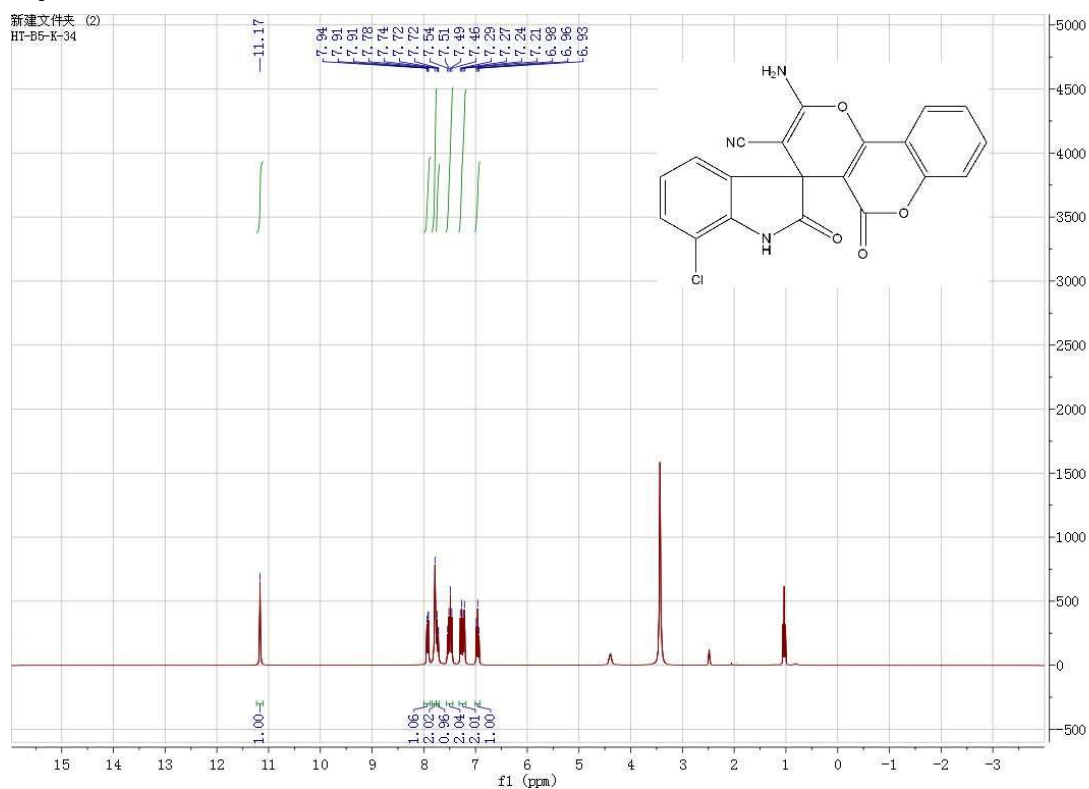


13i

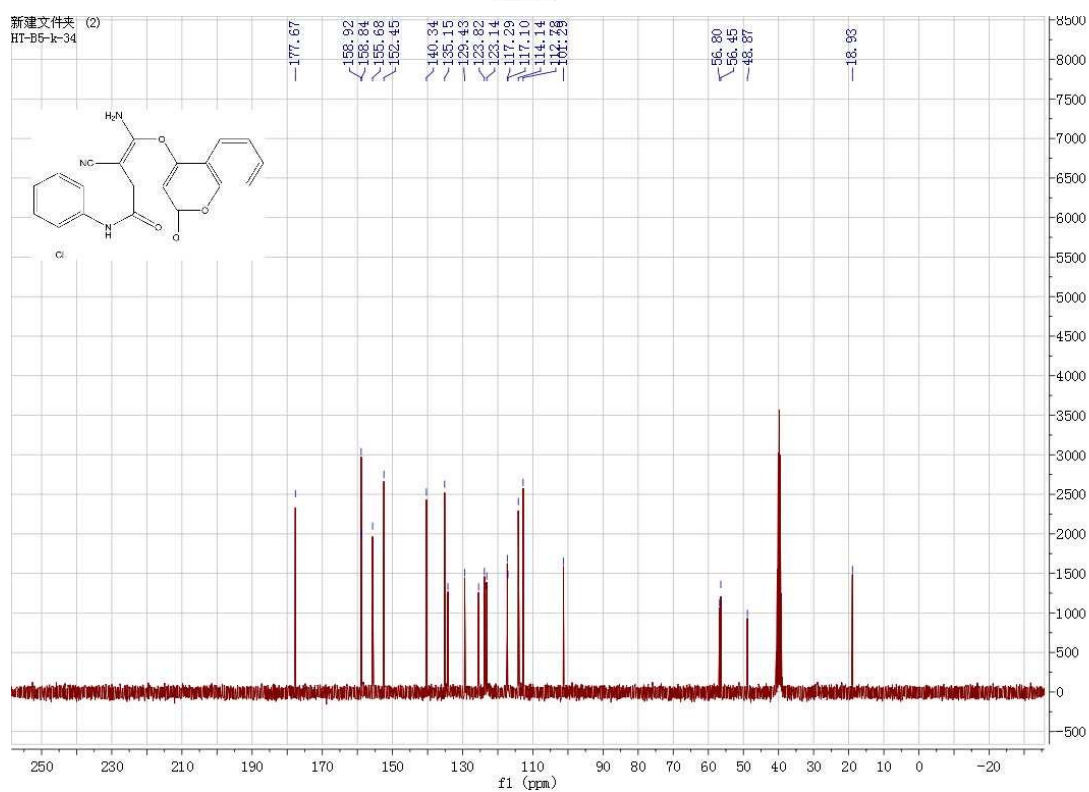


13j

新建文件夹 (2)
HT-B5-K-34

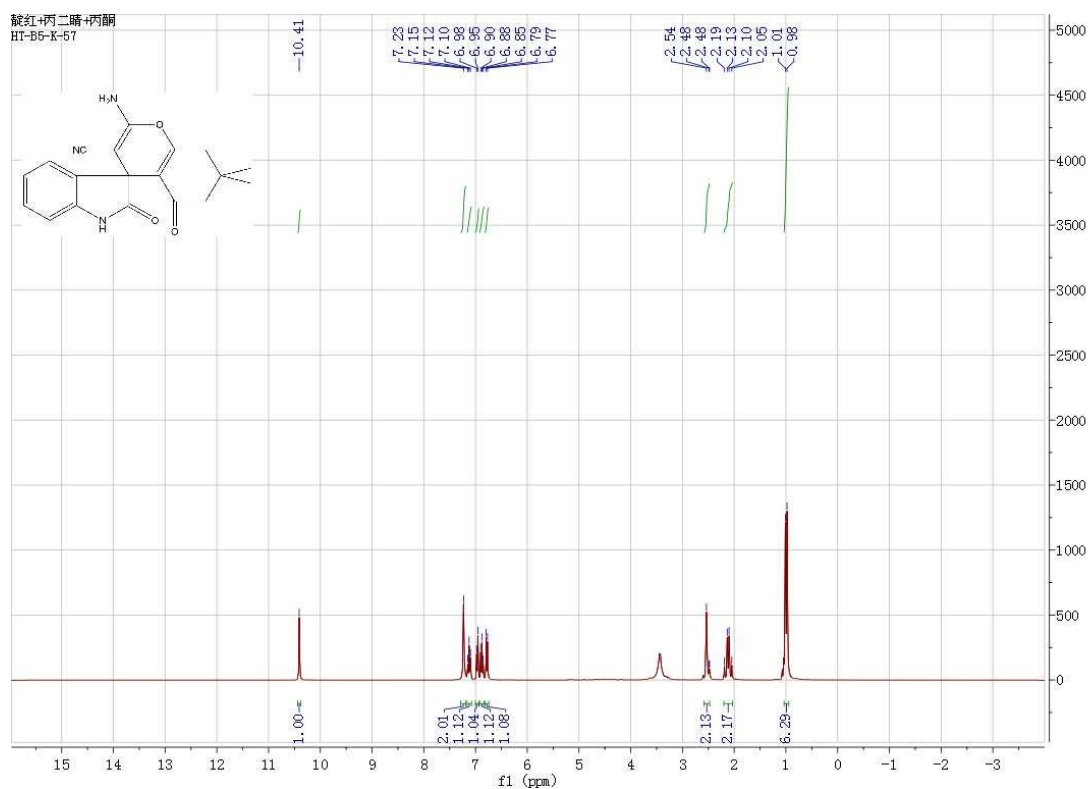


新建文件夹 (2)
HT-B5-K-34

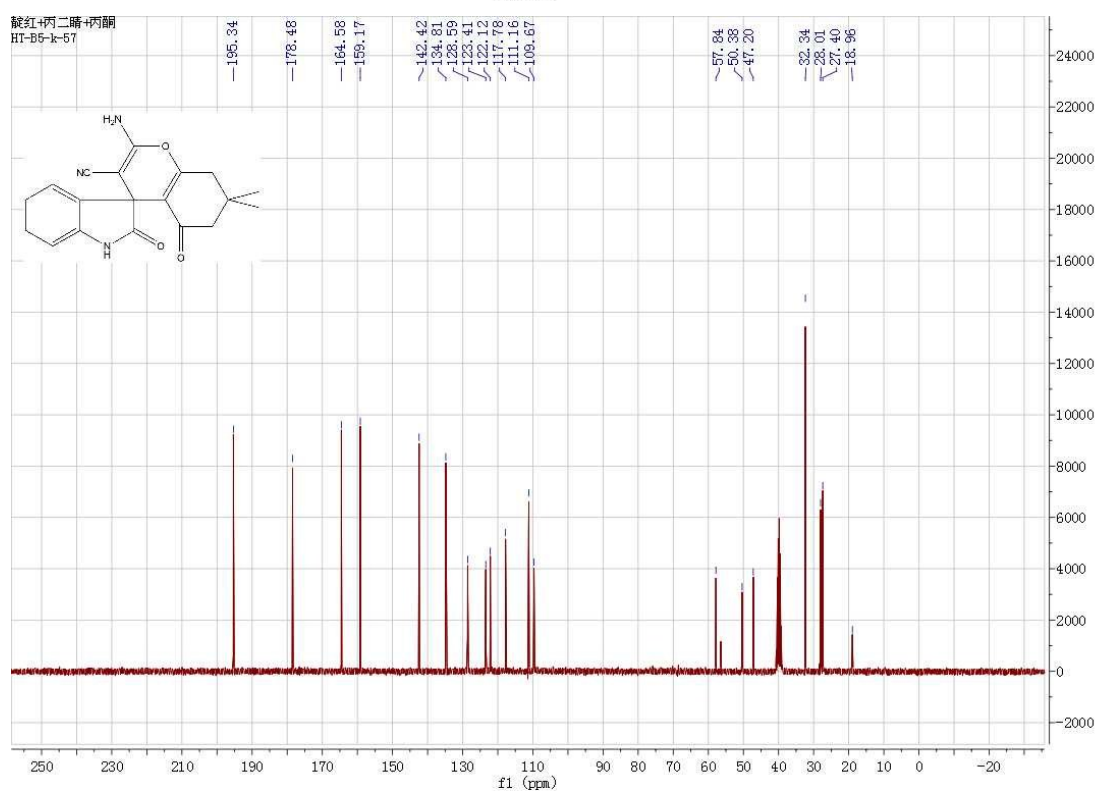


15a

靛红+丙二腈+丙酮
HT-B5-X-57

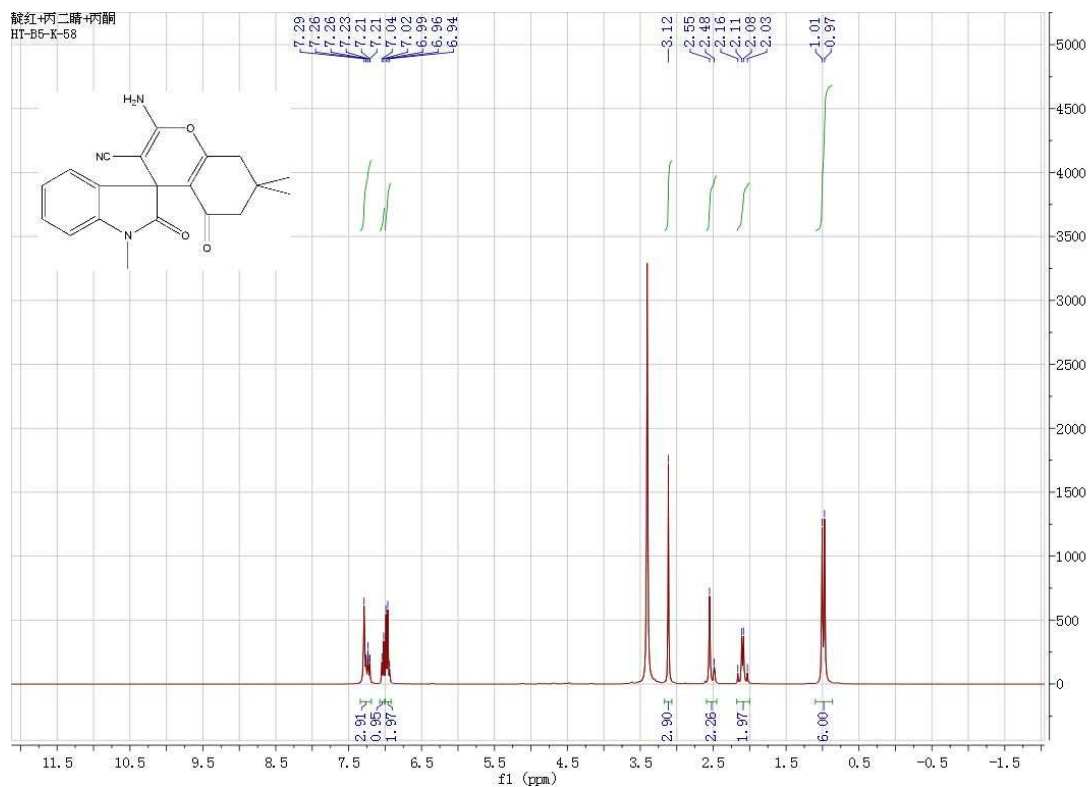


靛红+丙二腈+丙酮
HT-B5-k-57

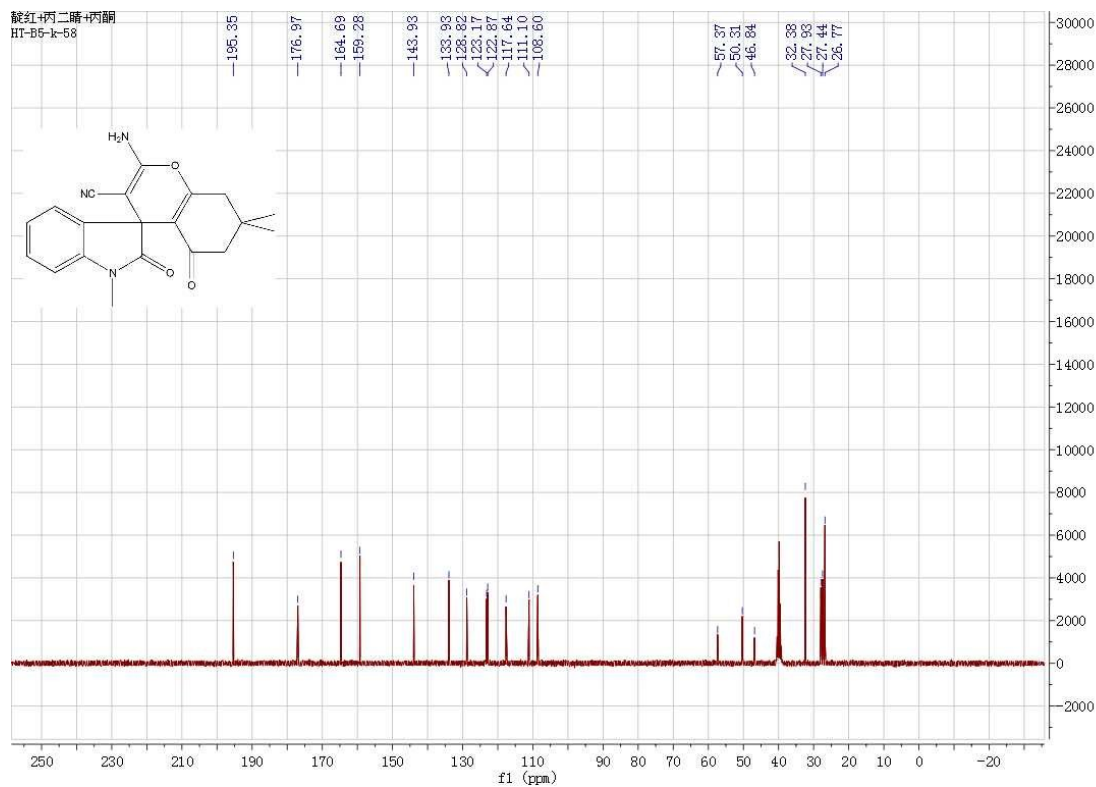


15b

靛红+丙二腈+丙酮
HT-B5-X-58

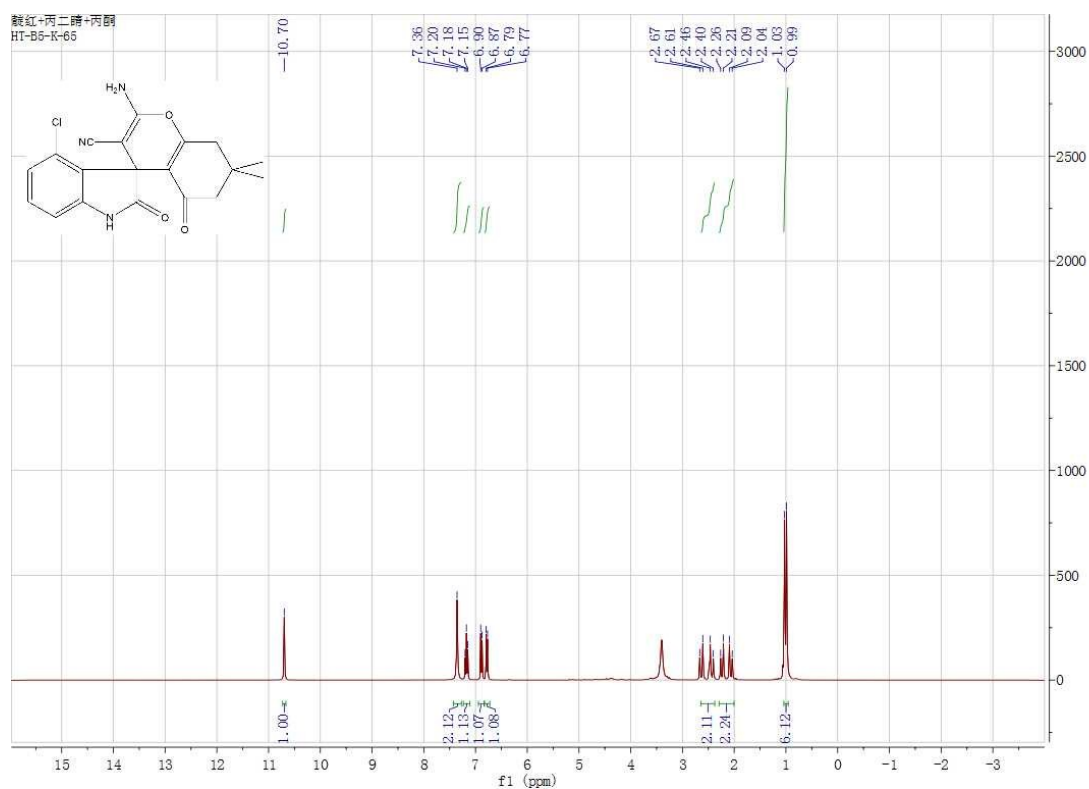


靛红+丙二腈+丙酮
HT-B5-X-58

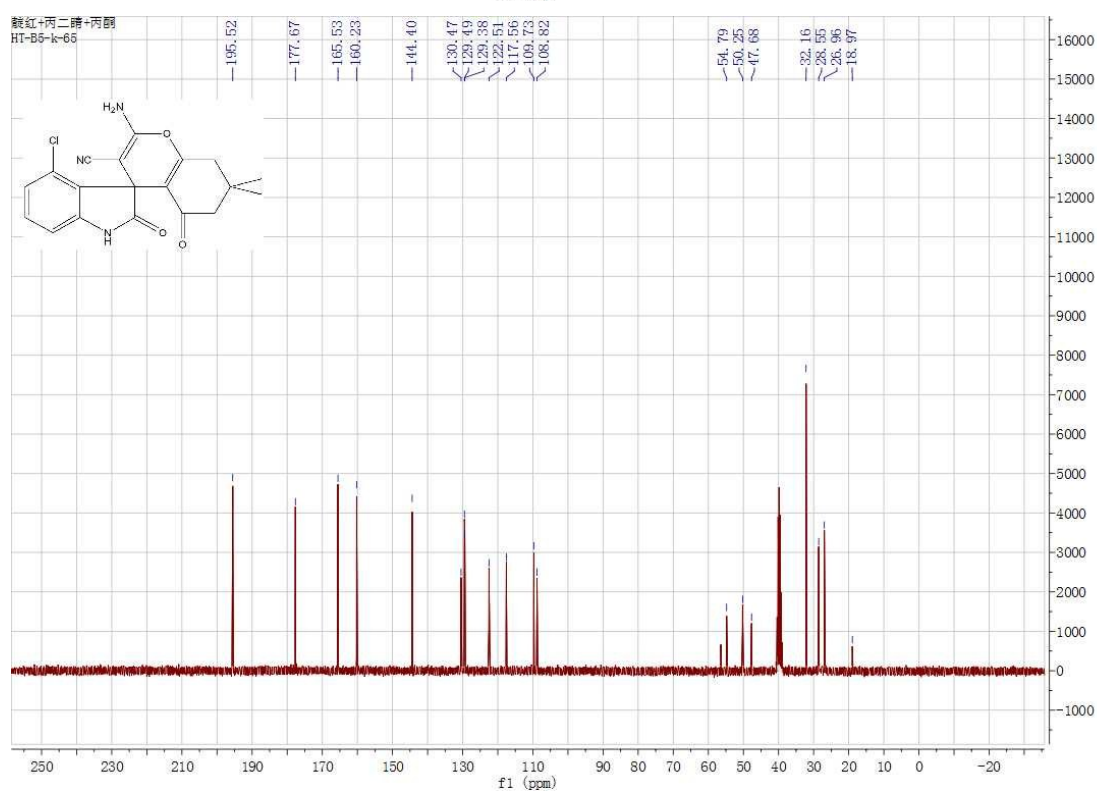


15c

靛紅+丙二腈+丙酮
HT-B5-K-65

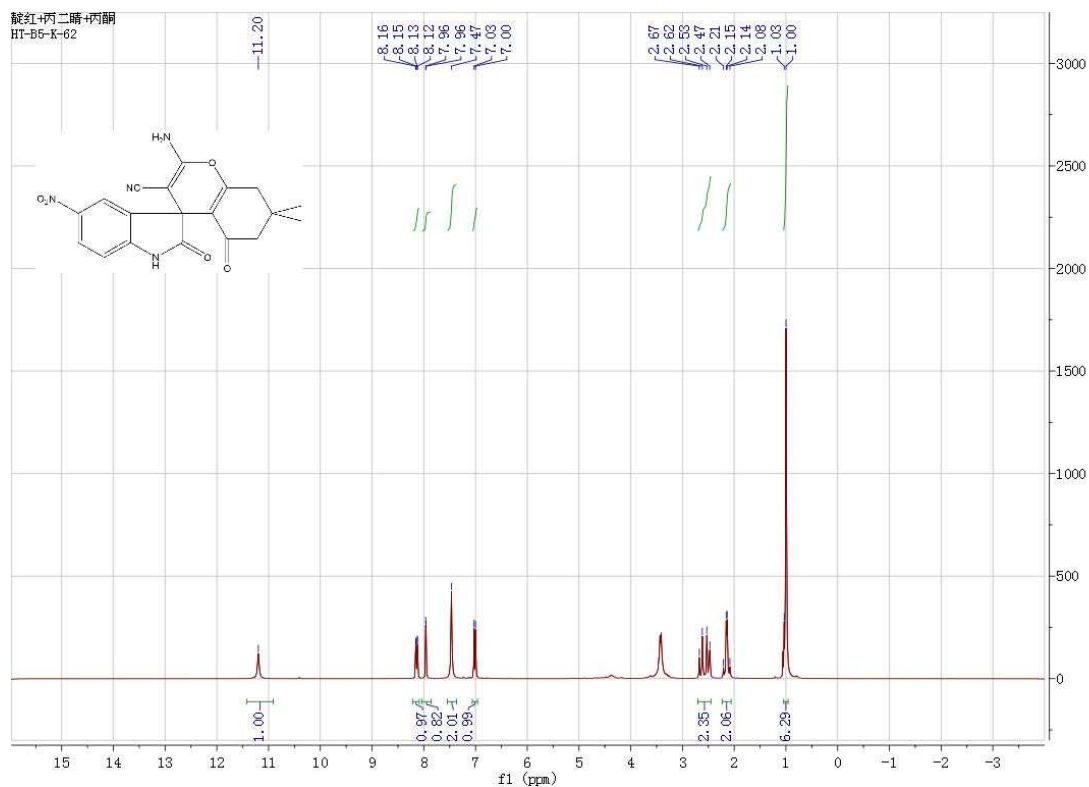


靛紅+丙二腈+丙酮
HT-B5-K-65

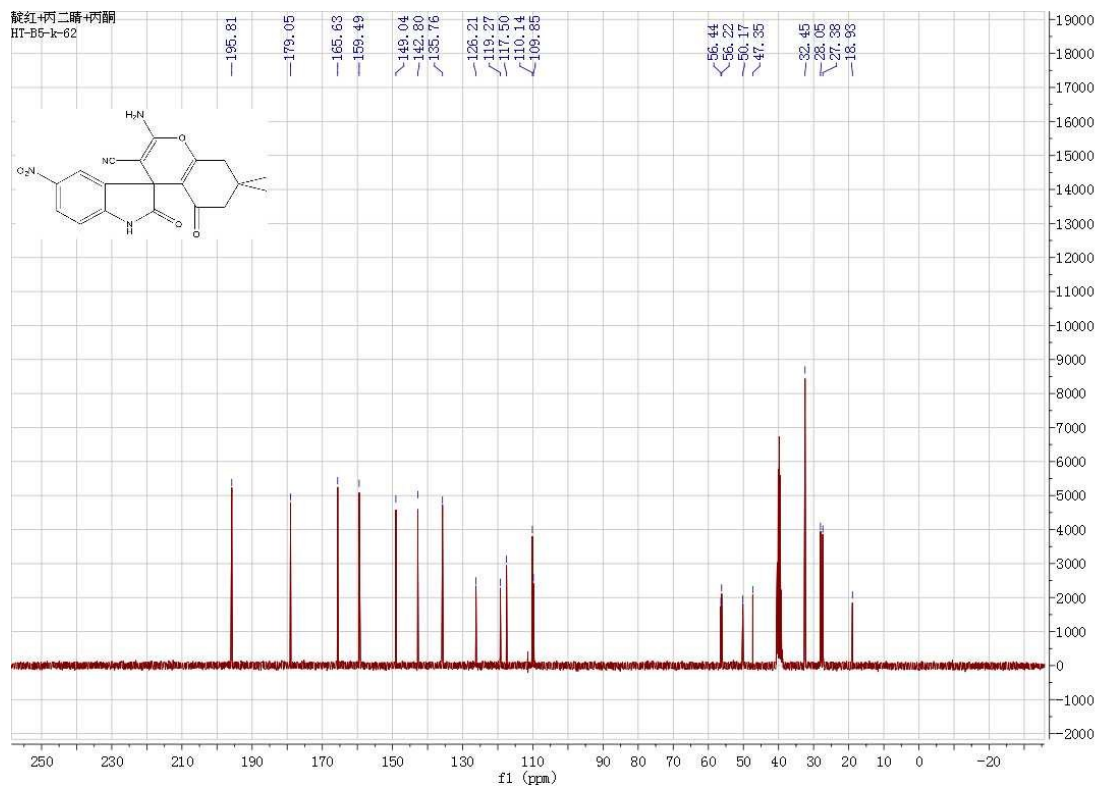


15d

靛红+丙二腈+丙酮
HT-B5-K-62

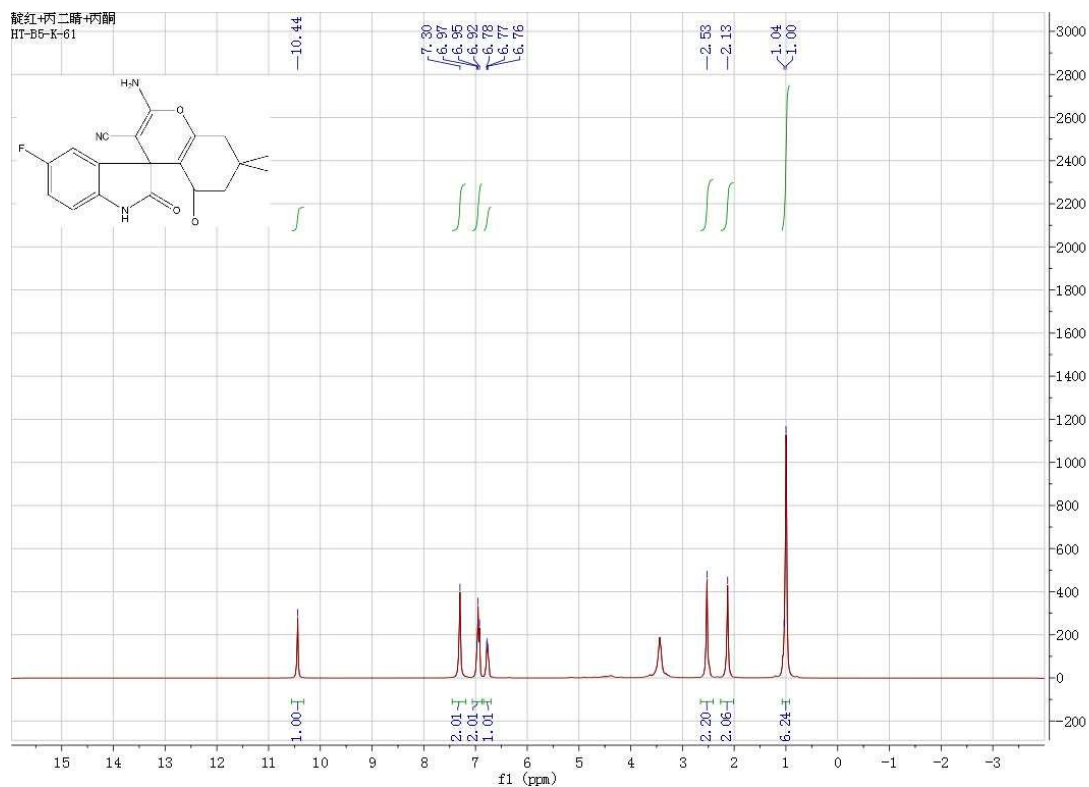


靛红+丙二腈+丙酮
HT-B5-K-62

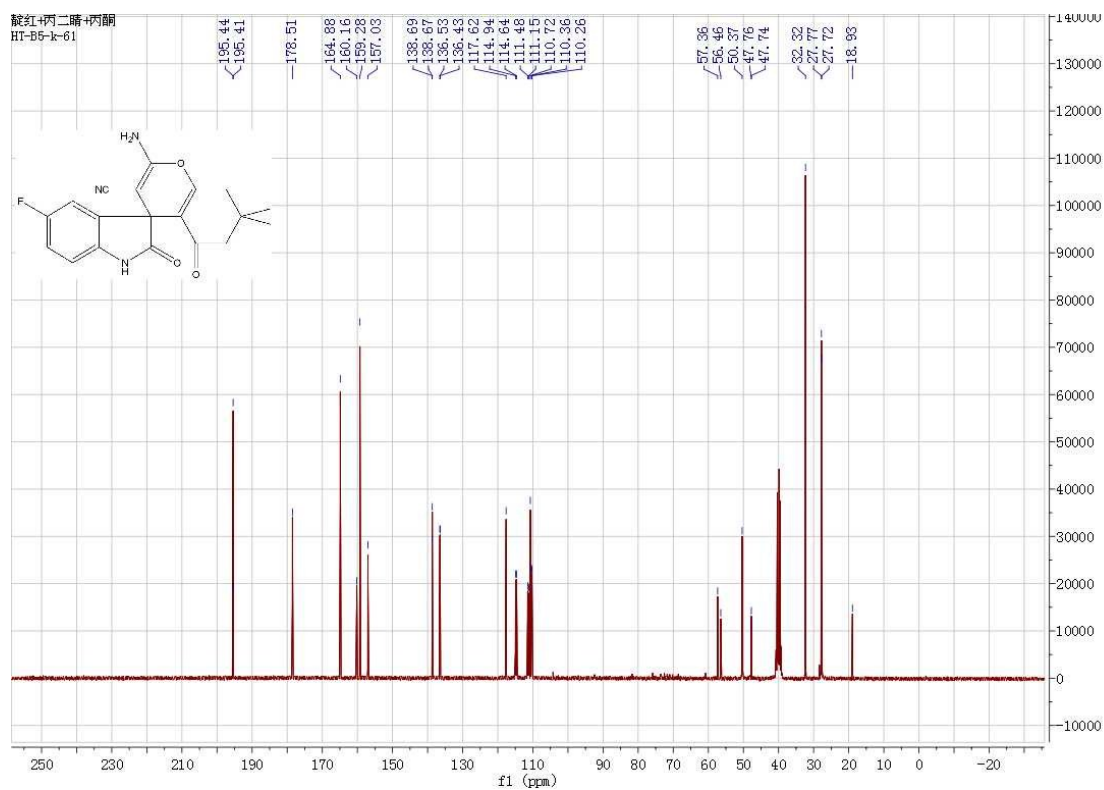


15e

靛红+丙二腈+丙酮
HT-B5-K-61

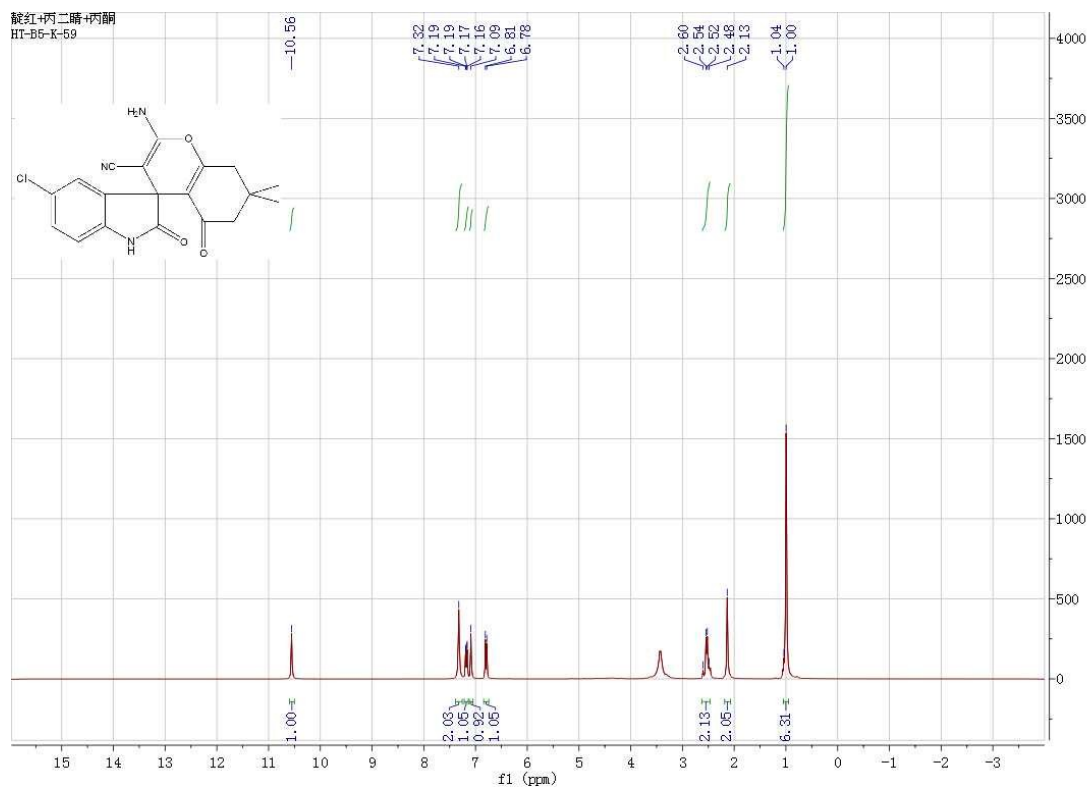


靛红+丙二腈+丙酮
HT-B5-K-61

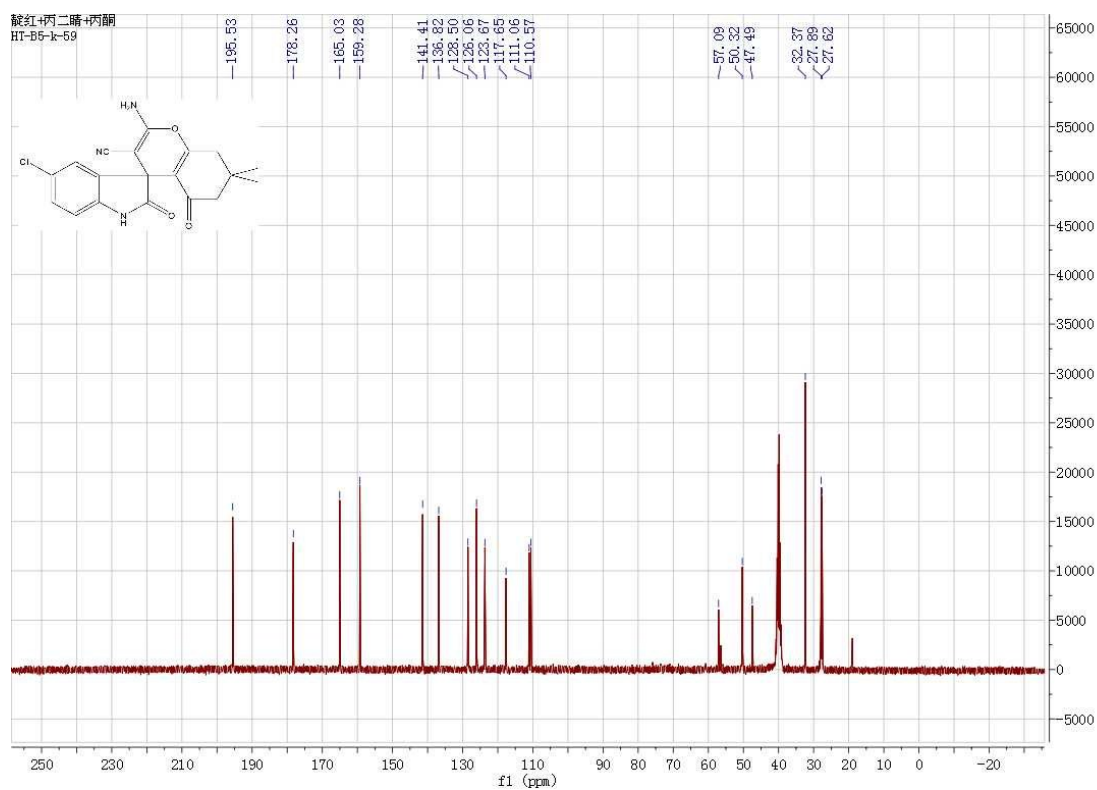


15f

靛红+丙二腈+丙酮
HT-B5-K-59

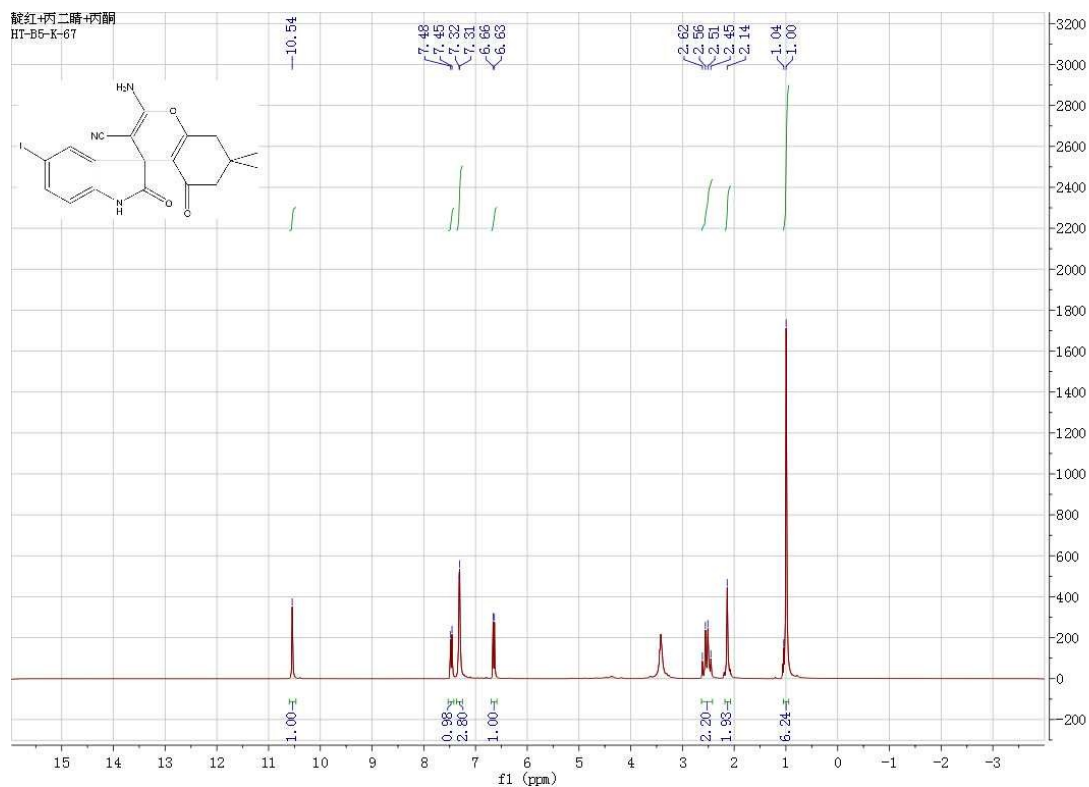


靛红+丙二腈+丙酮
HT-B5-K-59

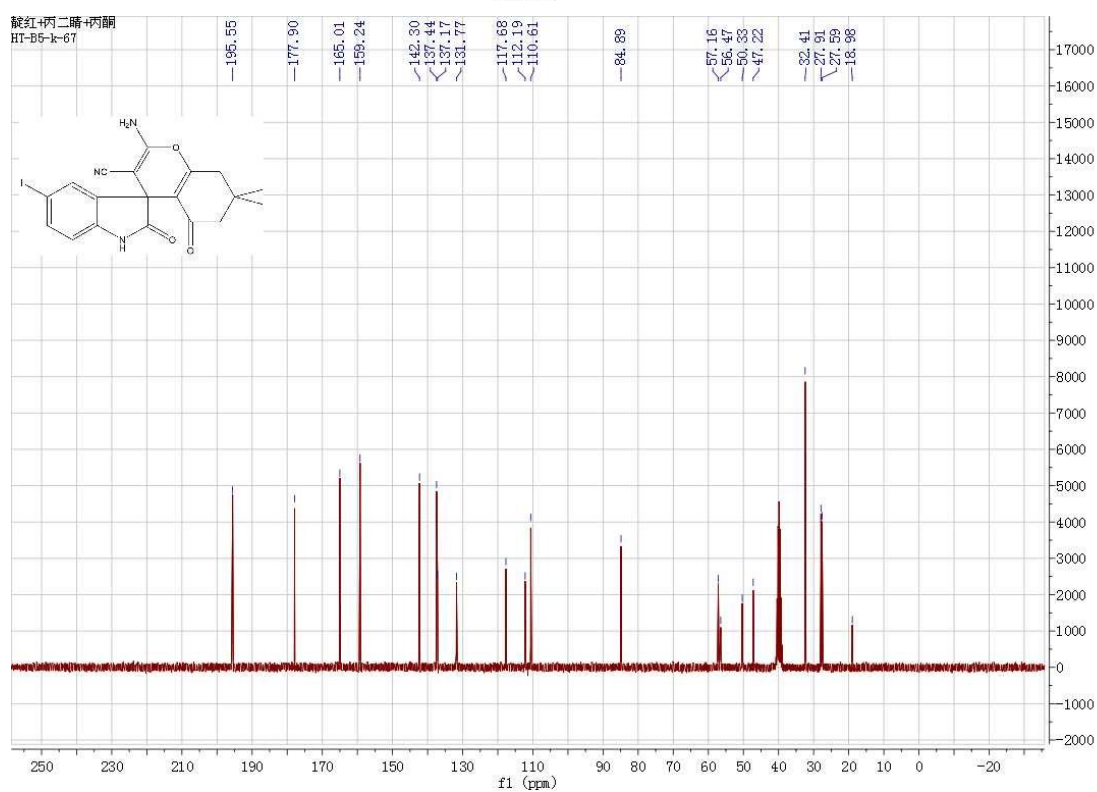


15g

靛红+丙二腈+丙酮
HT-B5-K-67

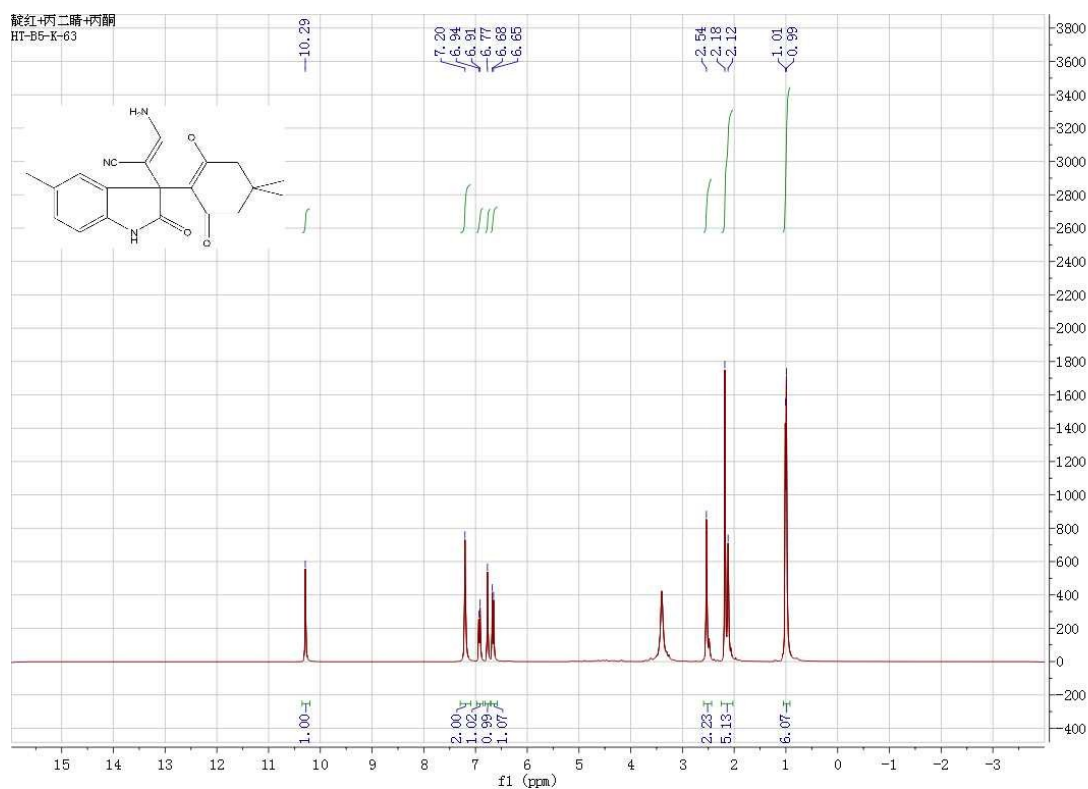


靛红+丙二腈+丙酮
HT-B5-K-67

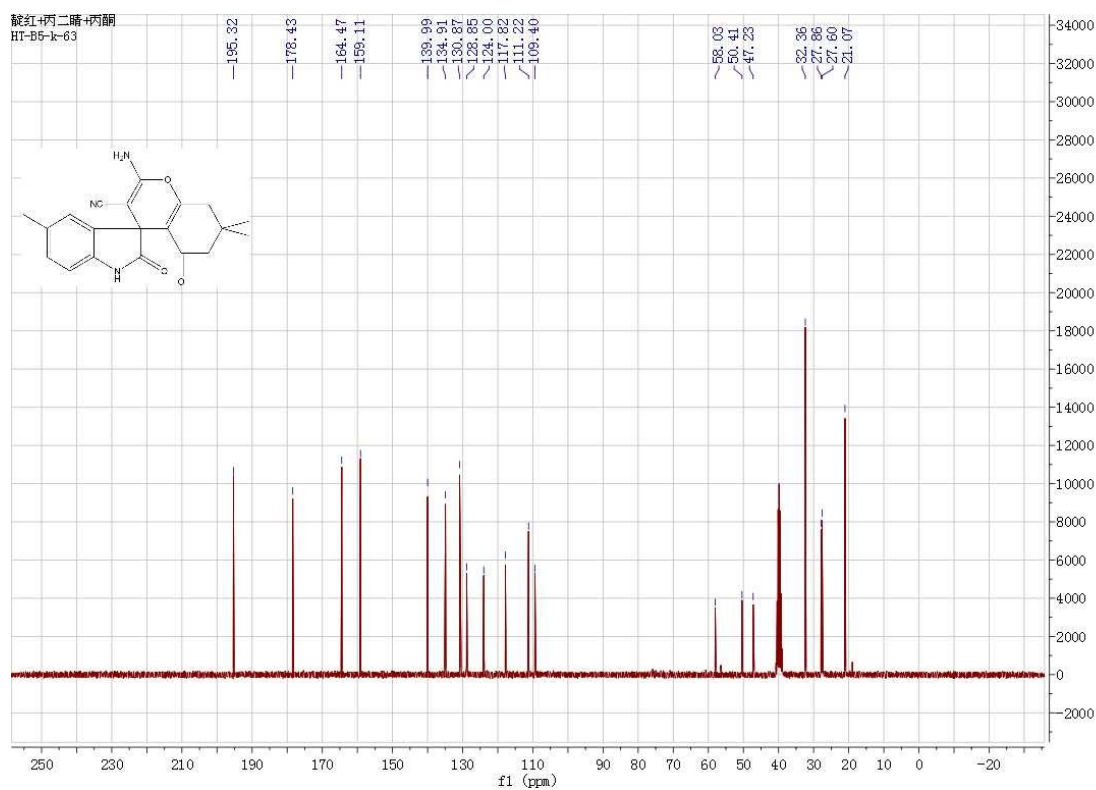


15h

靛红+丙二腈+丙酮
HT-B5-K-63

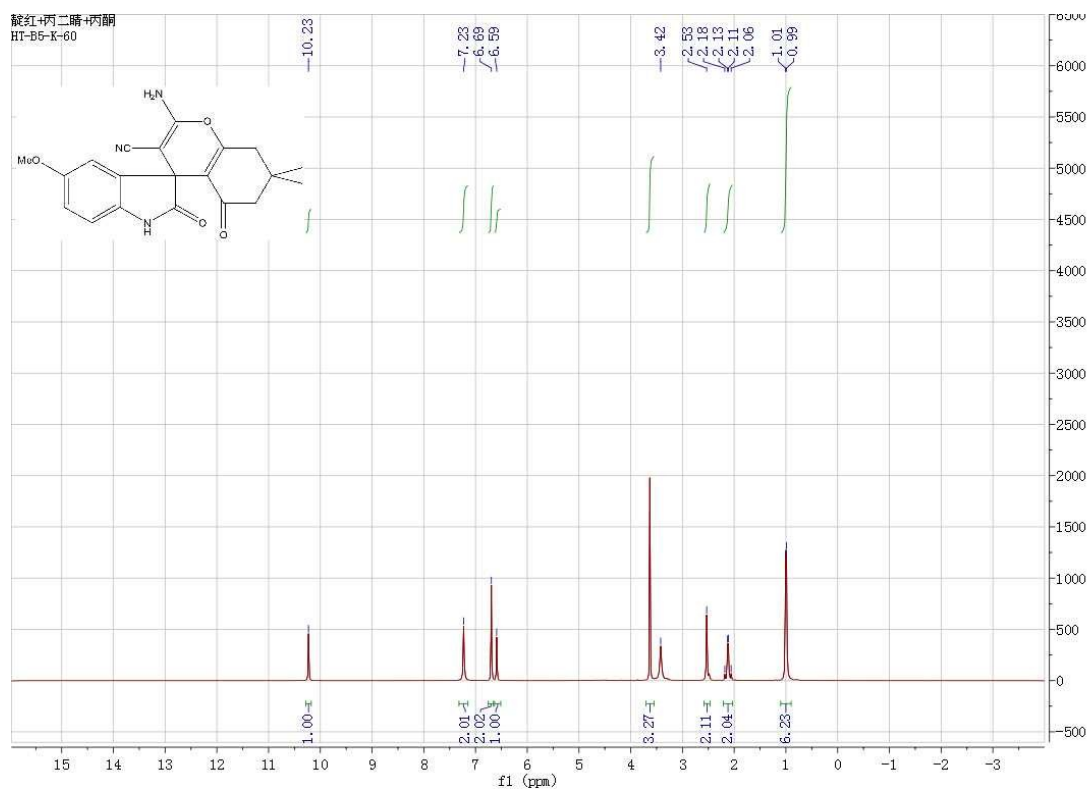


靛红+丙二腈+丙酮
HT-B5-K-63

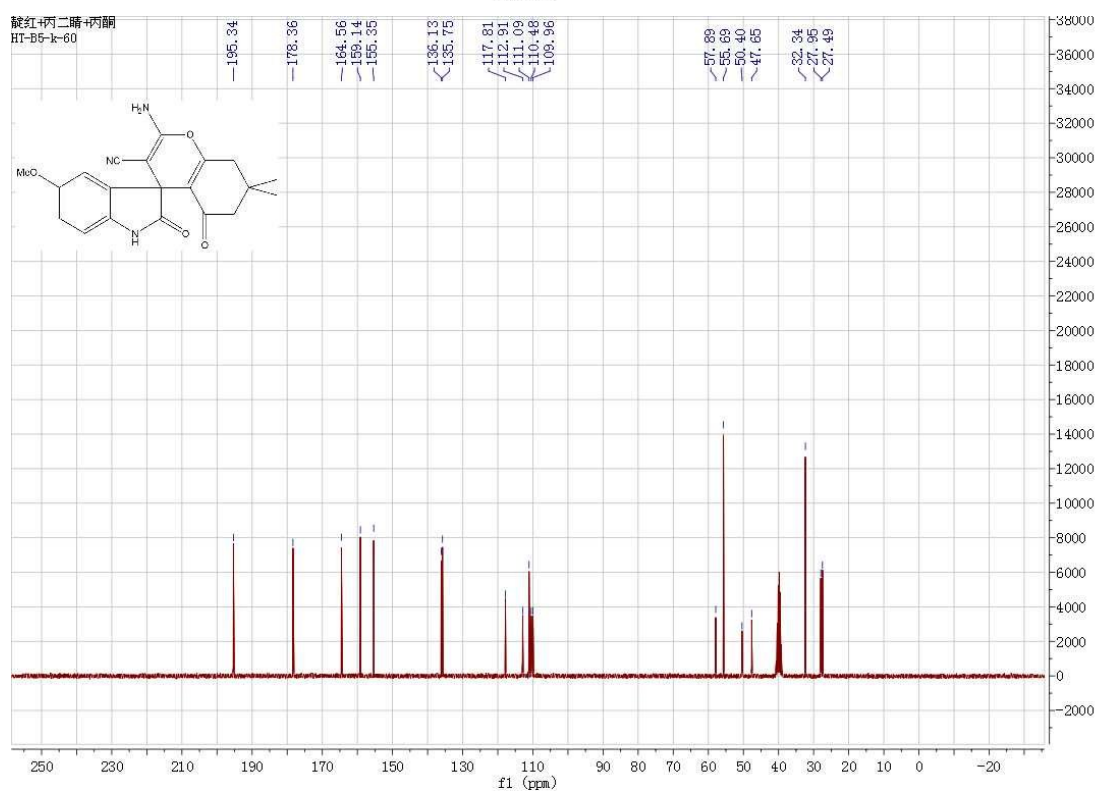


15i

靛红+丙二腈+丙酮
HT-B5-K-60

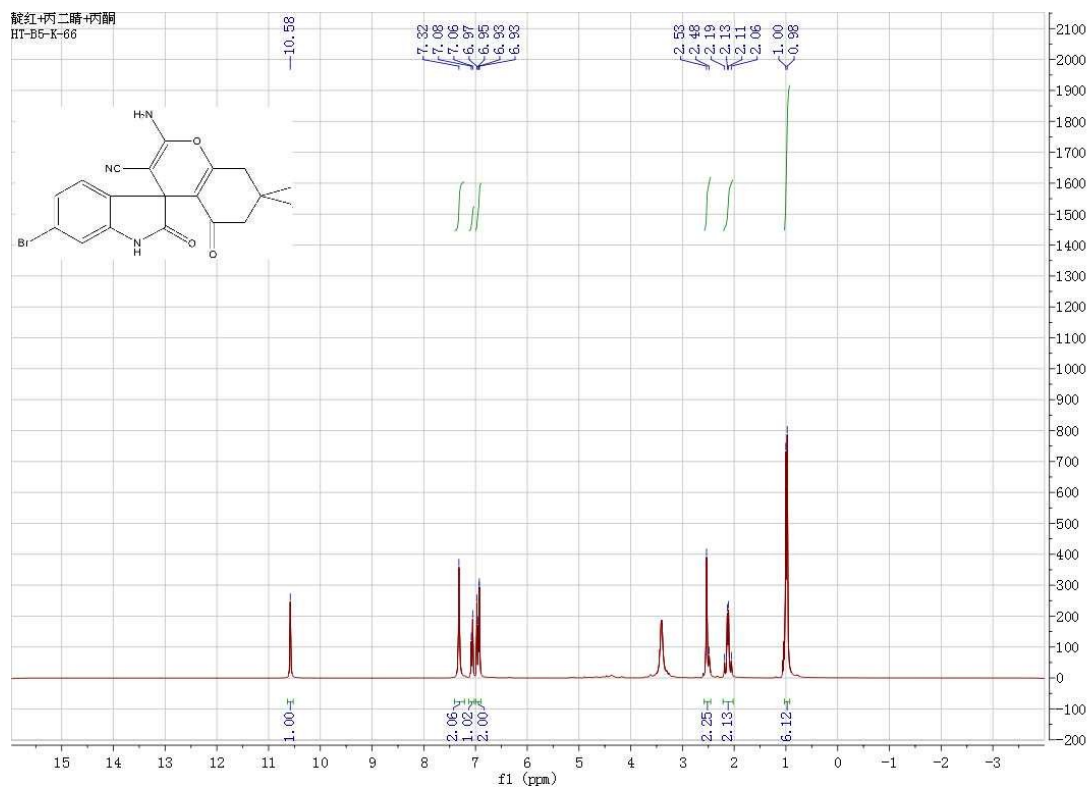


靛红+丙二腈+丙酮
HT-B5-K-60

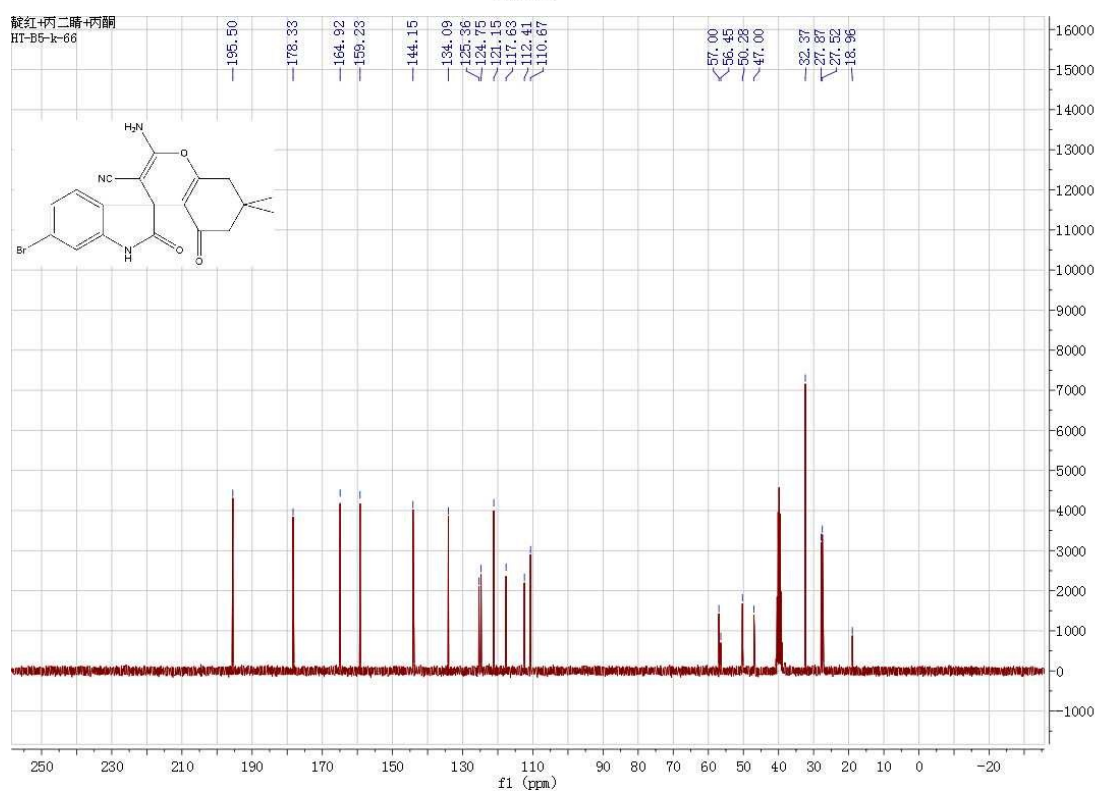


15j

靛红+丙二腈+丙酮
HT-B5-K-66

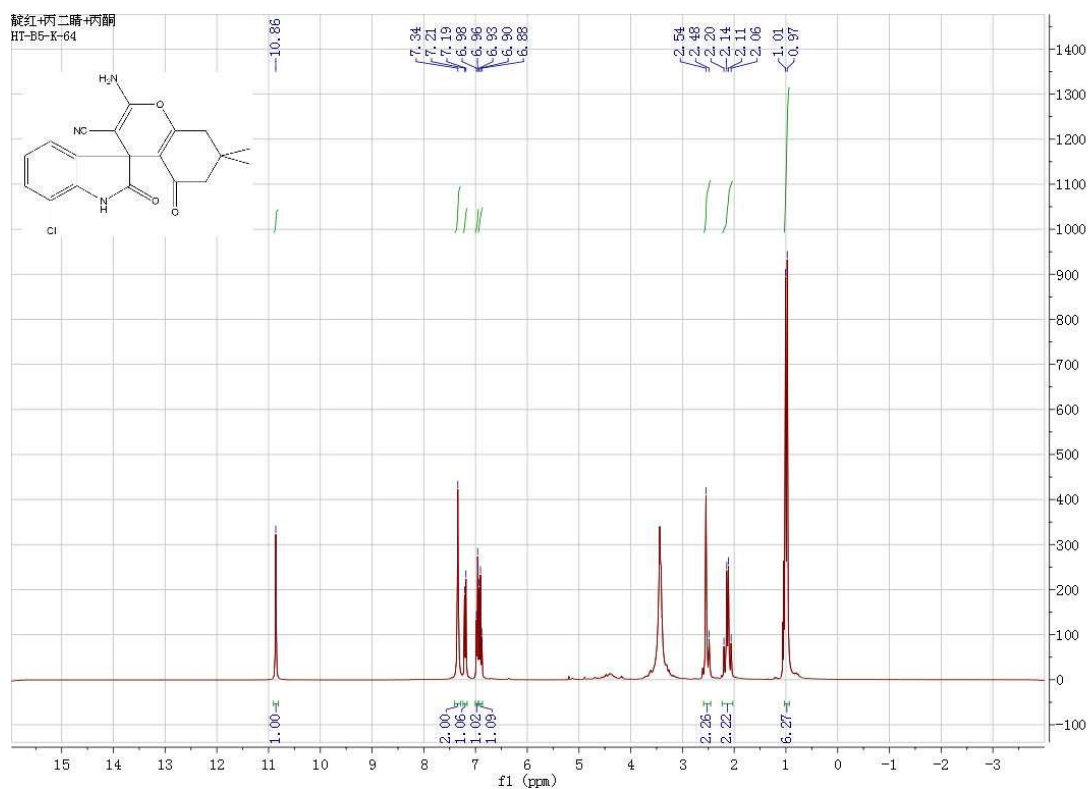


靛红+丙二腈+丙酮
HT-B5-K-66

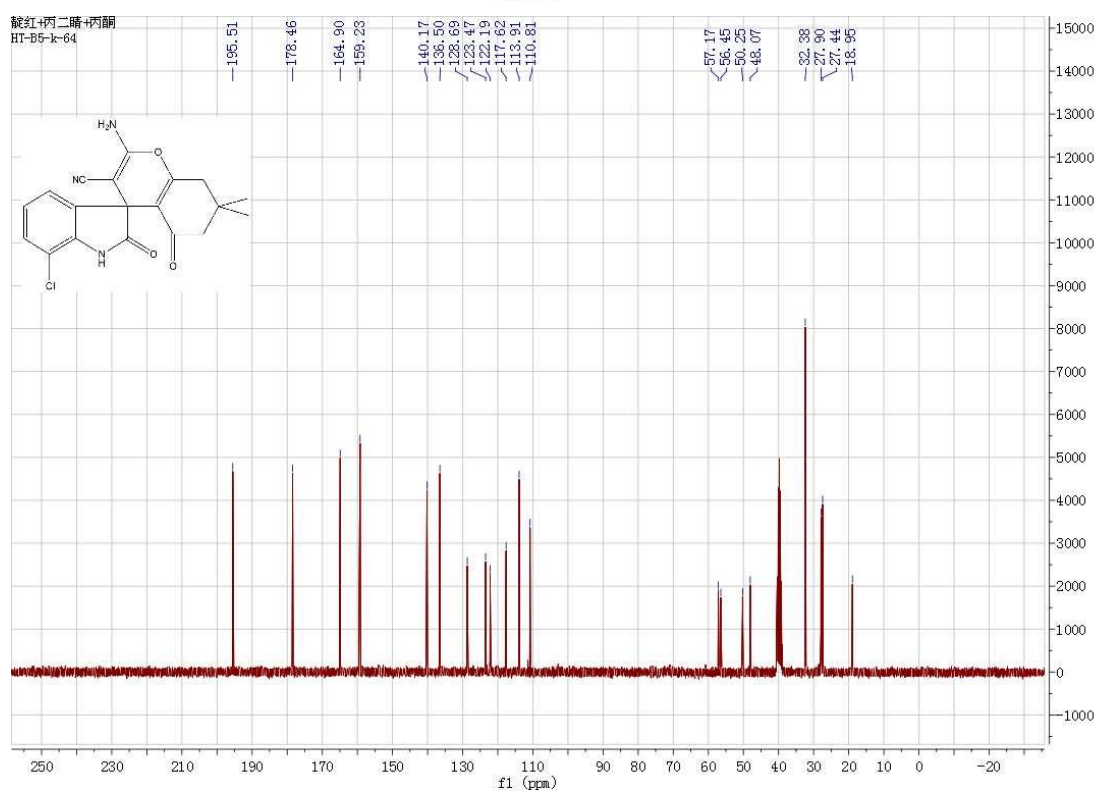


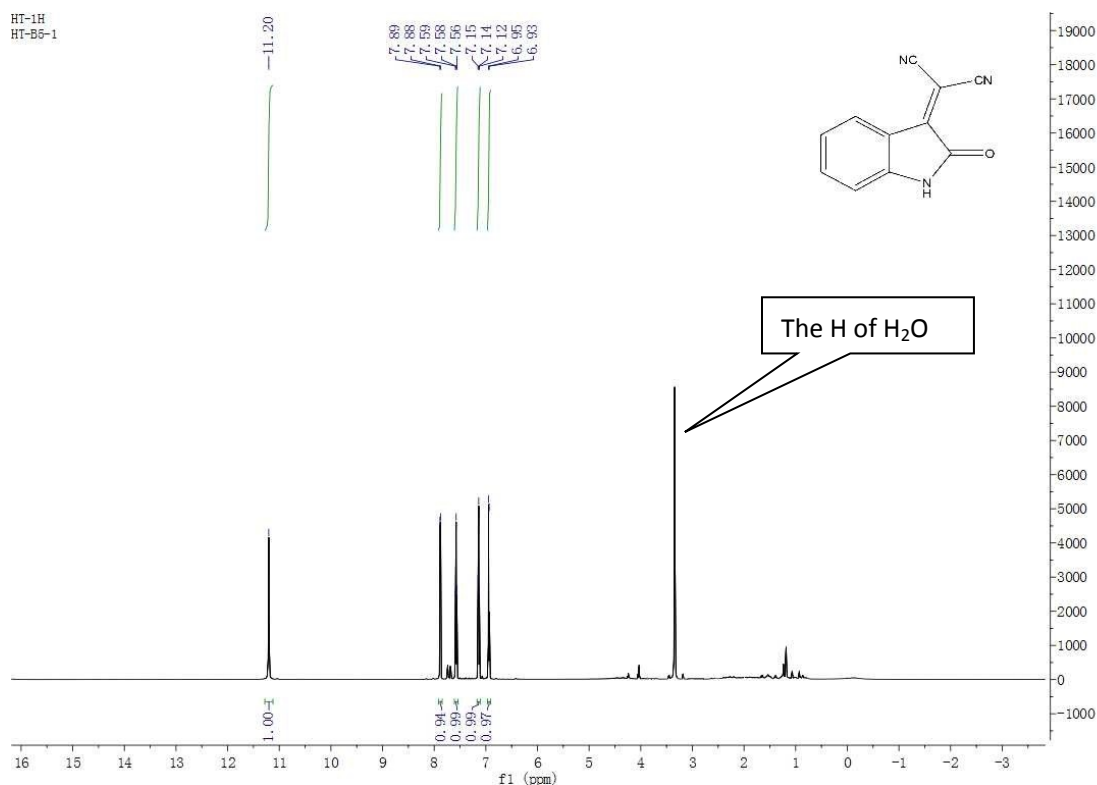
15k

靛红+丙二腈+丙酮
HT-B5-K-64



靛红+丙二腈+丙酮
HT-B5-K-64





9 References

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