

# Supporting Information

## Ni-catalyzed Asymmetric Hetero-Diels–Alder Reactions of Conjugated Vinyl Azides: Synthesis of Chiral Azido Polycycles

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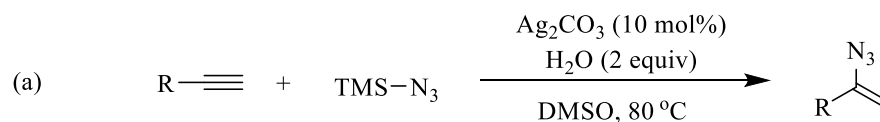
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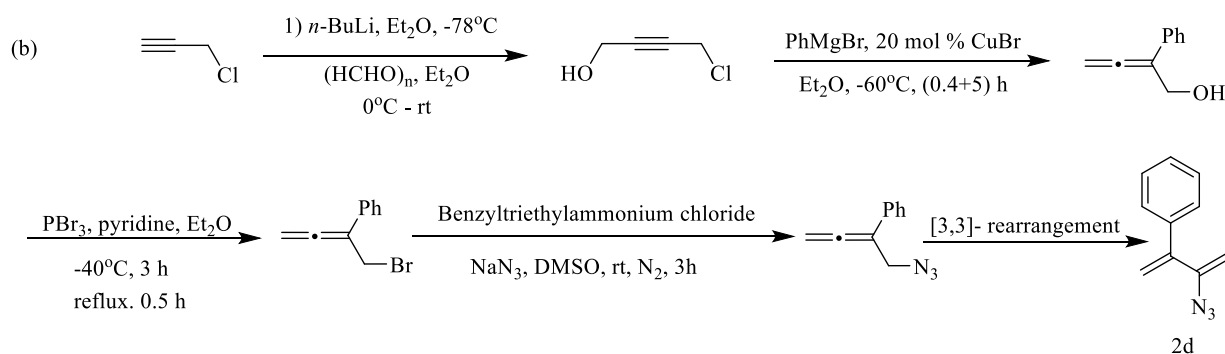
## 1. General Information

Unless otherwise noted, analytic grade solvents were used for the chromatography, and all the reagents were obtained commercially and used without further purification. All reactions were performed under nitrogen atmosphere and in a flame-dried or oven-dried glassware with magnetic stirring. Reactions were monitored by TLC. Solvents were dried with CaH<sub>2</sub>. All NMR spectra were recorded on Bruker-500 MHz spectrometer. The chemical shifts ( $\delta$ ) and coupling constants (J) were expressed in ppm and Hz respectively. HRMS were measured on the Q-TOF6510 instruments.

### General Procedure for the Synthesis of Vinyl Azides



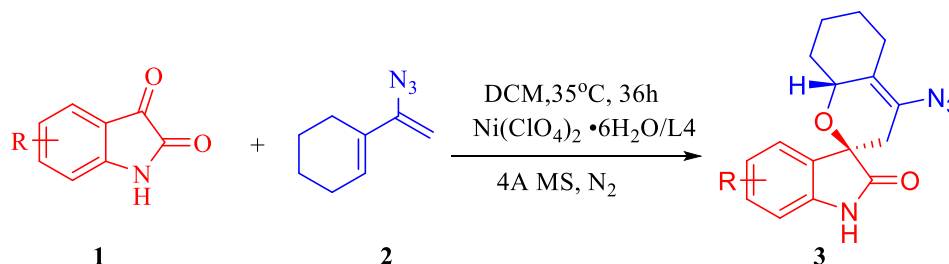
Vinyl Azides was prepared according to the reference.<sup>1</sup>



Vinyl Azides 2d was prepared according to the reference.<sup>2, 3, 4</sup>

$\alpha$ -keto esters were synthesized by reported methods,<sup>5</sup> and chiral N,N'-dioxide ligands were synthesized by reported methods.<sup>6</sup>

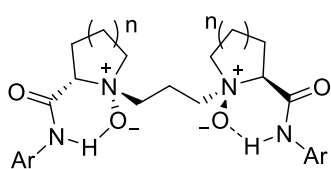
## 2. Standard Procedure for the HDA Reaction



To a mixture of Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (10 mol%), N,N'-dioxide ligand L4 (11 mol%), 1 (0.1 mmol), 4A MS (100 mg), 0.5 mL of DCM and 2 (1.2 eq) were added

under nitrogen atmosphere. The reaction mixture was stirred at 35 °C for 36h. After the reaction was completed, the reaction purified by column chromatography (silica gel, Petroleum ether/ EtOAc: 5/1 to 3/1) to afford the desired product **3**.

### 3. Optimization for the HDA reaction

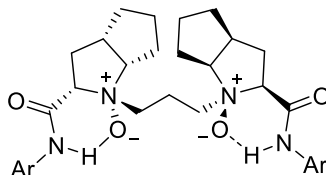


**L4:** Ar = 2,6-*i*-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, n = 2

**L5:** Ar = 2,6-*i*-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, n = 1

**L7:** Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>3</sub>, n = 2

**L8:** Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>3</sub>, n = 1



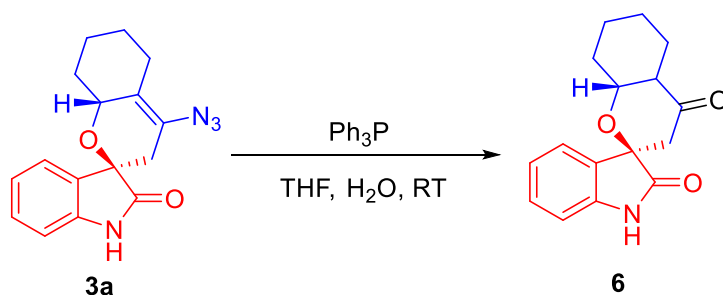
**L6:** Ar = 2,6-*i*-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

**L9:** Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>3</sub>

Entry	Catalyst	Ligand	Temperature/°C	Time/h	Yield/%	ee/%
1	Sc(OTf) <sub>3</sub>	L4	RT	15	81	61
2	Sc(OTf) <sub>3</sub>	L7	RT	15	61	38
3	Sc(OTf) <sub>3</sub>	L5	RT	15	86	50
4	Sc(OTf) <sub>3</sub>	L8	RT	15	26	24
5	Sc(OTf) <sub>3</sub>	L6	RT	15	75	72
6	Sc(OTf) <sub>3</sub>	L9	RT	15	85	62
7	Y(OTf) <sub>3</sub>	L4	RT	15	37	87
8	La(OTf) <sub>3</sub>	L4	RT	15	0	--
9	In(OTf) <sub>3</sub>	L6	RT	15	83	64
10	Yb(OTf) <sub>3</sub>	L6	RT	15	63	82
11	Zn(OTf) <sub>3</sub>	L6	RT	15	0	--
12	Ni(OTf) <sub>2</sub>	L4	35	40	0	--
<b>13</b>	<b>Y(OTf)<sub>3</sub></b>	<b>L4</b>	<b>35</b>	<b>40</b>	<b>56</b>	<b>91</b>

The reactions were carried out using isatin 1a (0.1mmol) and vinyl azide 2a (0.12 mmol), DCM (0.5 ml), Catalyst (0.01 mmol, 10 mol%), Ligand (0.011 mmol, 11 mmol%), 4A MS (100 mg).

## 4. Procedure of synthetic applications

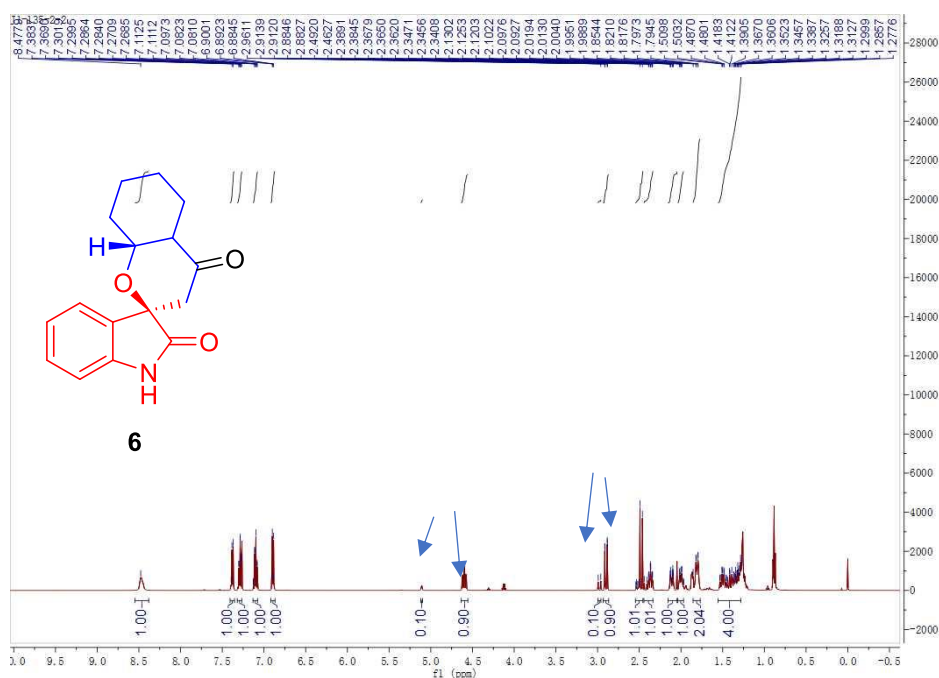


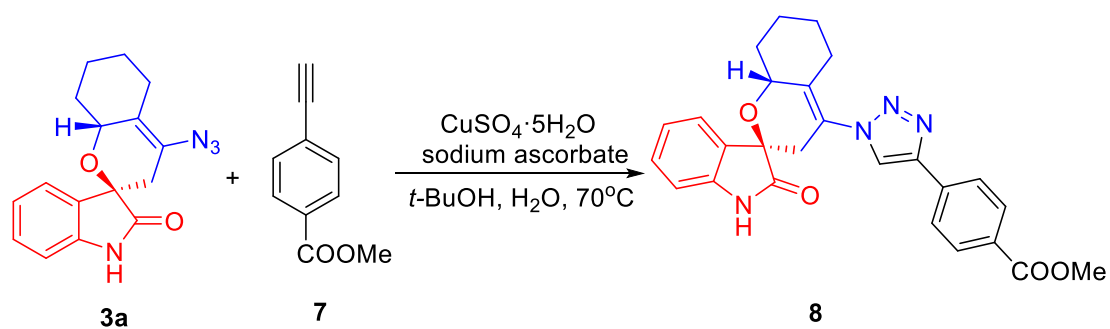
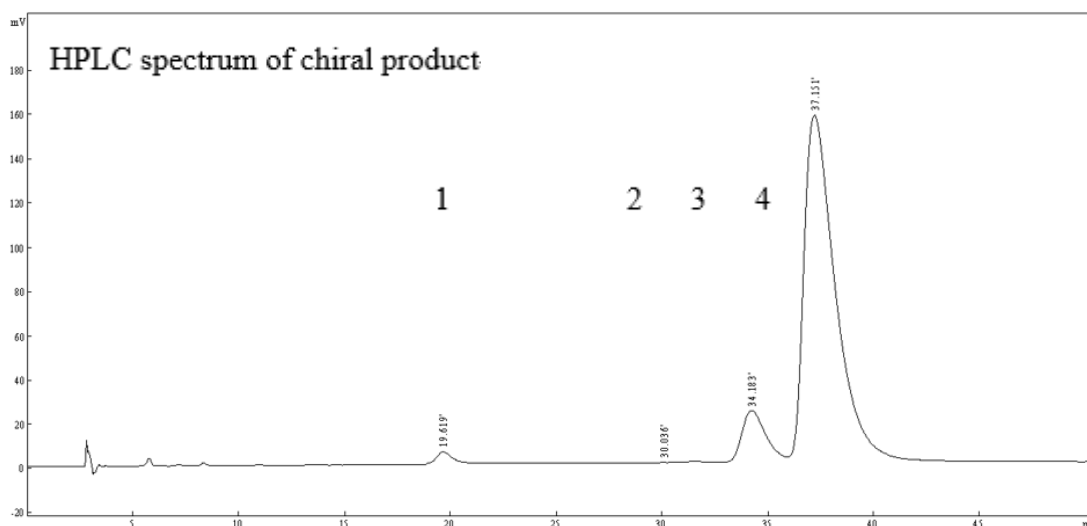
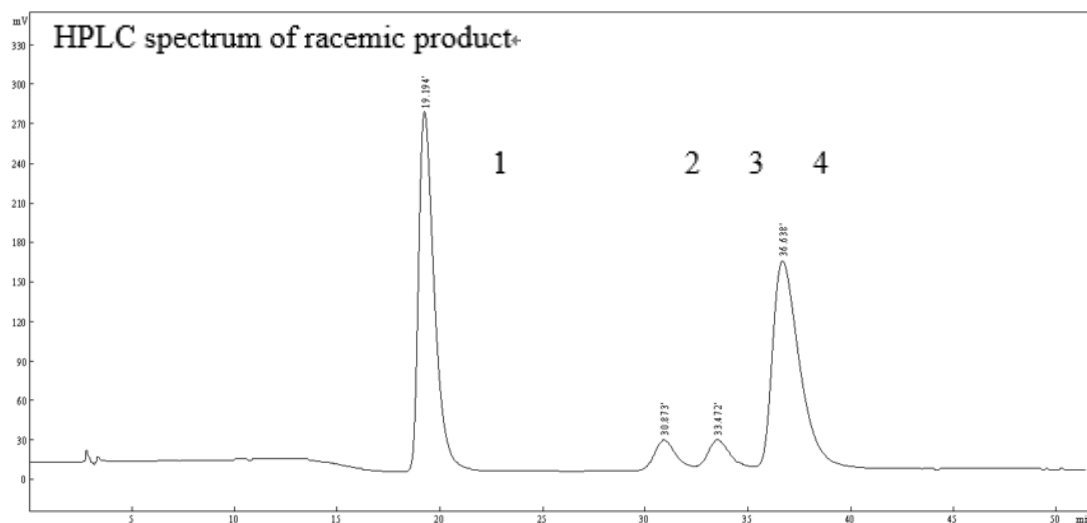
To the mixture of **3a** (59.2 mg, 0.2 mmol, 1 eq) and H<sub>2</sub>O (18.0 mg, 1 mmol, 5 eq) in 2 mL of THF, PPh<sub>3</sub> (131 mg, 0.5 mmol, 2.5 eq) was added at room temperature. After 12 hours of stirring (complete consumption of starting material, indicated by TLC analysis) the reaction mixture was filtration, concentrated under reduced pressure. Crude was purified by column chromatography (silica gel, Petroleum ether/ EtOAc: 5/1) to obtain the desired product **6** (43.9 mg, 81% yield, DR: 9:1) as a white solid.

### Diastereomer Ratio calculation

The Diastereomer Ratio was measured by <sup>1</sup>H NMR analysis and HPLC analysis.  
<sup>1</sup>H NMR analysis: DR = 9:1.

HPLC analysis: Peak 1 and Peak 4 are a pair of enantiomers, Peak 2 and Peak 3 are a pair of enantiomers. In the spectrum of chiral product, The area ratio between peak 4 and peak 3 =  $15650818 \div 1631873 \approx 9:1$ .

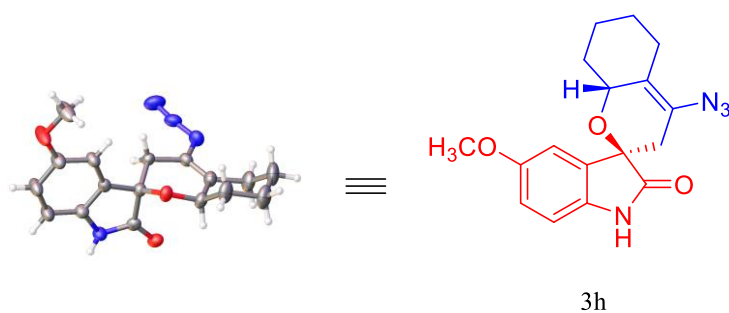




To the mixture of **3a** (59.2 mg, 0.2 mmol, 1 eq),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (9.9 mg, 0.04 mmol, 0.2 eq), and Sodium ascorbate (15.8 mg, 0.08 mmol, 0.4 eq) in 2 mL (*t*-BuOH+H<sub>2</sub>O, 1:1) alkyne (38.4 mg, 0.24 mmol, 1.2 eq) was added at room temperature. Then, the

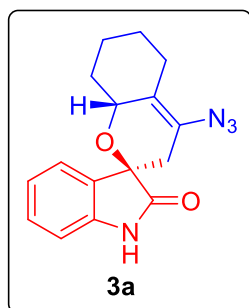
reaction mixture was stirred at 70 °C for 12 hours. After cool down to the room temperature, it was concentrated, diluted with 5 mL of water and extracted with ethyl acetate (3X10 mL). The combined organic layers were dried on Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, purified by column chromatography (silica gel, Petroleum ether/ EtOAc: 2/1) to get the desired product **8** (65.8 mg, 72% yield) as a light yellow solid.

## 5. X-ray Crystallography Data

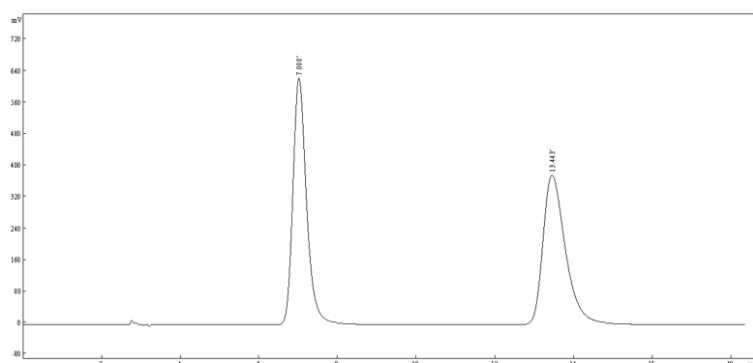


CCDC 2016806 (**3h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/ci](http://www.ccdc.cam.ac.uk/data_request/ci)

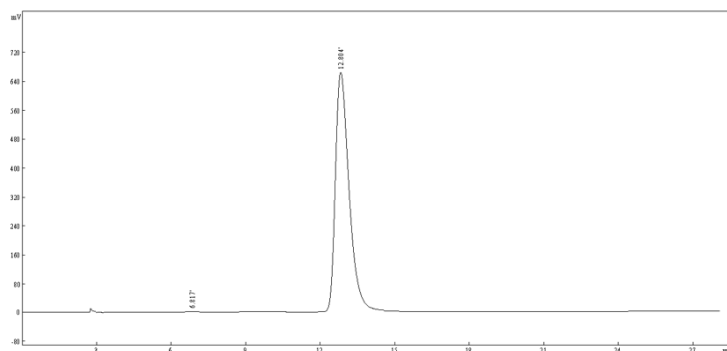
## 6. Characterization Data



Yellow solid. 95% yield. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.28 (td, *J* = 7.7, 1.2 Hz, 1H), 7.09 (td, *J* = 7.6, 0.9 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.72 – 4.60 (m, 1H), 2.98 – 2.91 (m, 1H), 2.88 (dt, *J* = 16.7, 2.8 Hz, 1H), 2.39 (dt, *J* = 16.7, 2.2 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.84 – 1.73 (m, 3H), 1.47 – 1.27 (m, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 176.35, 140.34, 130.22, 130.14, 125.78, 124.48, 123.29, 118.28, 110.10, 74.32, 72.54, 34.08, 30.27, 26.03, 25.70, 24.13. HRMS (ESI, *m/z*) calcd for C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub> [M-N<sub>2</sub>+H]<sup>+</sup> 269.12831, found 269.12845. [α]<sub>D</sub><sup>24</sup> = -127.1° (c 0.66, CHCl<sub>3</sub>); >99% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 6.8 min (minor), 12.8 min (major).



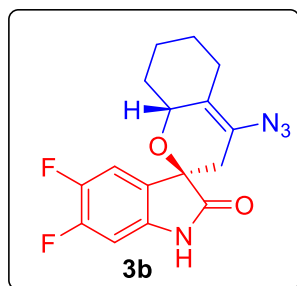
Peak#	Ret. Time	Area	Area%
1	7.008	15094874	50.03
2	13.443	15076251	49.97
Total		30171125	100



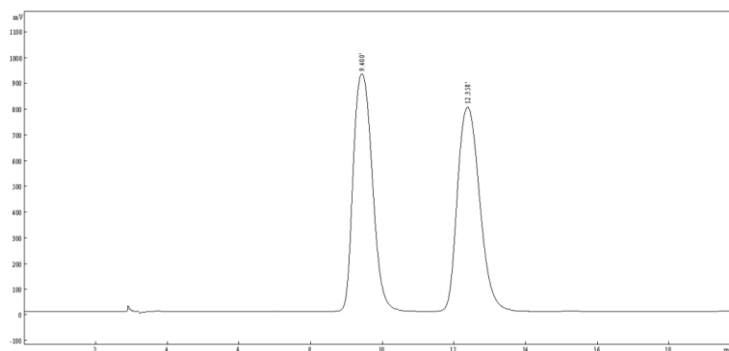
Peak#	Ret. Time	Area	Area%
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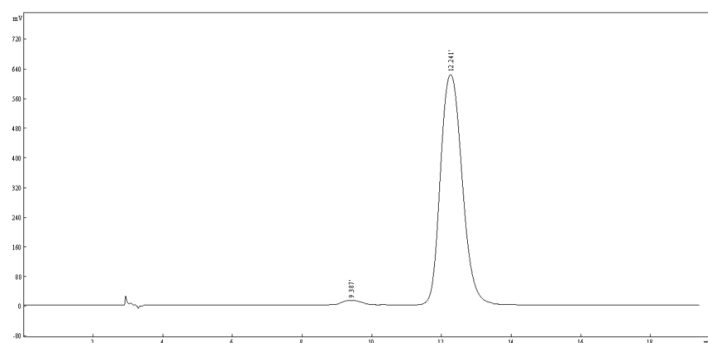
1	6.817	48072	0.189
2	12.804	25386542	99.81
Total		25434616	100



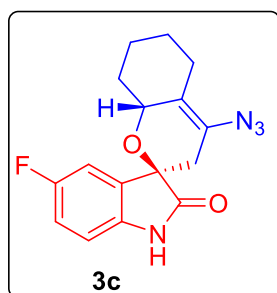
Brown solid. 95% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.34 (s, 1H), 7.12 (dd,  $J = 8.9, 7.7$  Hz, 1H), 6.66 (dd,  $J = 9.6, 6.3$  Hz, 1H), 4.60 – 4.49 (m, 1H), 2.91 – 2.83 (m, 1H), 2.74 (dt,  $J = 16.7, 2.8$  Hz, 1H), 2.31 (dt,  $J = 16.7, 2.1$  Hz, 1H), 2.01 – 1.98 (m, 1H), 1.79 – 1.67 (m, 3H), 1.41 – 1.20 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.35, 151.51 (dd,  $J = 250.8, 14.0$  Hz), 147.08 (dd,  $J = 245.1, 13.6$  Hz), 136.61 (d,  $J = 10.1$  Hz), 125.78, 125.55, 117.89, 114.38 (d,  $J = 20.4$  Hz), 100.43 (d,  $J = 23.0$  Hz), 74.26, 72.70, 34.04, 30.20, 25.96, 25.67, 24.07. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_4\text{O}_2$  [ $\text{M}-\text{N}_2+\text{H}$ ] $^+$  305.10961, found 305.10907.  $[\alpha]_D^{25} = -77.2^\circ$  (c 0.94,  $\text{CHCl}_3$ ); 97% ee; Chiral HPLC analysis of the product: Daicel Chiralpak AD-H 250X4.6 mm 5u column; hexane/2-propanol = 95/5, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 9.4 min (minor), 12.2 min (major).



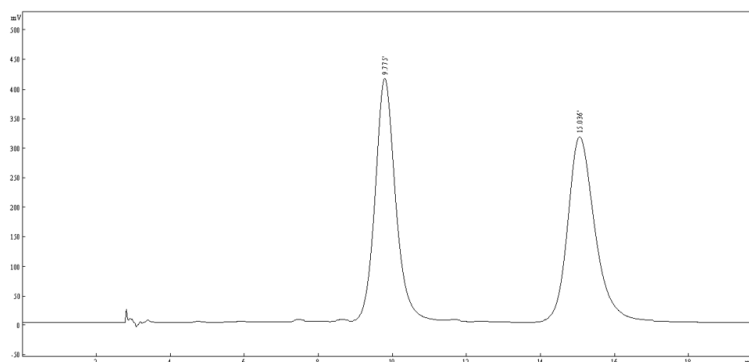
Peak#	Ret. Time	Area	Area%
1	9.400	34087715	49.89
2	12.358	34120032	50.02
Total		68207747	100



Peak#	Ret. Time	Area	Area%
1	9.387	425783	1.566
2	12.241	26763712	98.44
Total		27189495	100

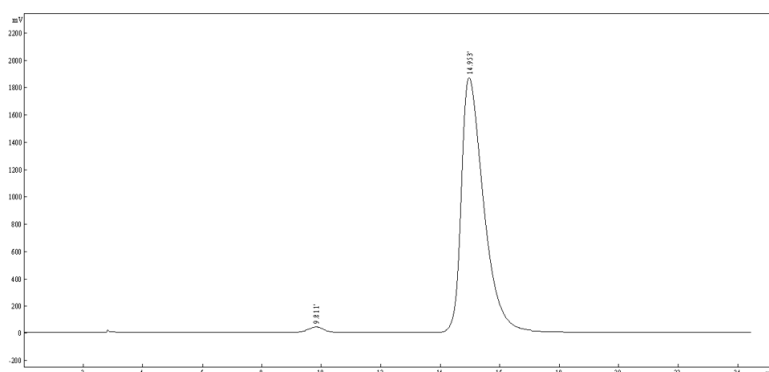


Brown solid. 98% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.36 (s, 1H), 7.02 (dd,  $J = 7.6$ , 2.6 Hz, 1H), 6.91 (td,  $J = 8.8$ , 2.6 Hz, 1H), 6.74 (dd,  $J = 8.5$ , 4.1 Hz, 1H), 4.64 – 4.46 (m, 1H), 2.95 – 2.81 (m, 1H), 2.76 (dt,  $J = 16.7$ , 2.8 Hz, 1H), 2.33 (dt,  $J = 16.7$ , 2.2 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.81 – 1.66 (m, 3H), 1.40 – 1.20 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.53, 159.44 (d,  $J = 242.6$  Hz), 136.24 (d,  $J = 2.2$  Hz), 131.60 (d,  $J = 7.7$  Hz), 125.78, 118.05, 116.59 (d,  $J = 23.6$  Hz), 112.55 (d,  $J = 24.9$  Hz), 110.94 (d,  $J = 7.8$  Hz), 74.64, 72.66, 34.05, 30.23, 25.99, 25.69, 24.10. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{15}\text{FN}_4\text{O}_2$   $[\text{M}-\text{N}_2+\text{H}]^+$  287.11903, found 287.11866.  $[\alpha]_D^{25} = -91.6^\circ$  (c 1.97,  $\text{CHCl}_3$ ); 97% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 95/5, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 9.8 min (minor), 15.0 min (major).

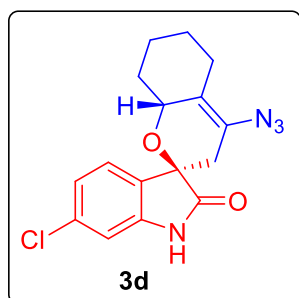


Peak#	Ret. Time	Area	Area%
1	9.777		
2	15.006		

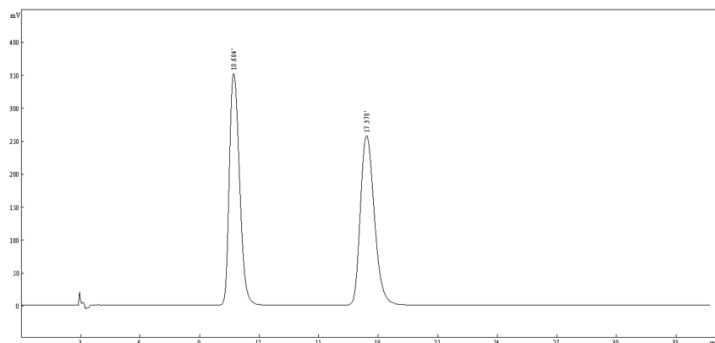
1	9.775	15637912	49.24
2	15.036	16120166	50.76
Total		31758078	100



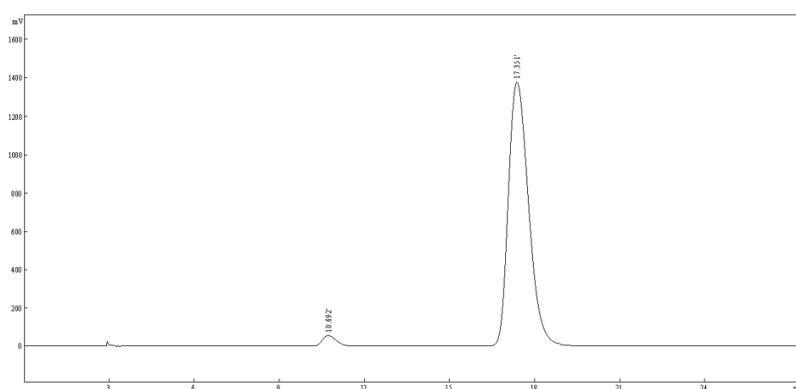
Peak#	Ret. Time	Area	Area%
1	9.811	1458863	1.472
2	14.953	97640243	98.53
Total		99099106	100



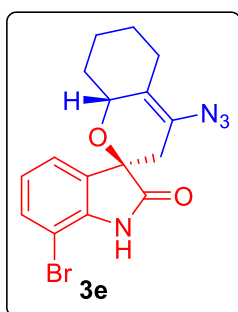
Brown solid. 92% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.36 (s, 1H), 7.19 (d,  $J = 2.3$  Hz, 1H), 7.00 (dd,  $J = 8.0, 1.8$  Hz, 1H), 6.81 (d,  $J = 1.7$  Hz, 1H), 4.61 – 4.49 (m, 1H), 2.91 – 2.83 (m, 1H), 2.77 (dt,  $J = 16.7, 2.8$  Hz, 1H), 2.31 (dt,  $J = 16.7, 2.1$  Hz, 1H), 2.05 – 1.94 (m, 1H), 1.80 – 1.65 (m, 3H), 1.41 – 1.21 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.34, 141.52, 135.98, 128.52, 125.80, 125.54, 123.28, 118.05, 110.80, 74.02, 72.64, 34.07, 30.13, 26.00, 25.70, 24.09. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{O}_2$   $[\text{M}-\text{N}_2+\text{H}]^+$  303.08948, found 303.08860.  $[\alpha]_D^{25} = -76.3^\circ$  (c 0.82,  $\text{CHCl}_3$ ); 95% ee; Chiral HPLC analysis of the product: Daicel Chiralpak AD-H 250X4.6 mm 5u column; hexane/2-propanol = 95/5, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 10.7 min (minor), 17.4 min (major).



Peak#	Ret. Time	Area	Area%
1	10.684	12518318	49.92
2	17.378	12558218	50.08
Total		25076536	100

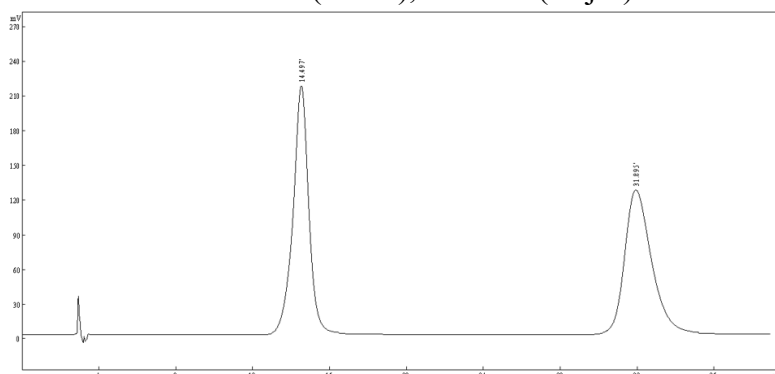


Peak#	Ret. Time	Area	Area%
1	10.692	1850228	2.65
2	17.351	67919072	97.35
Total		69769300	100

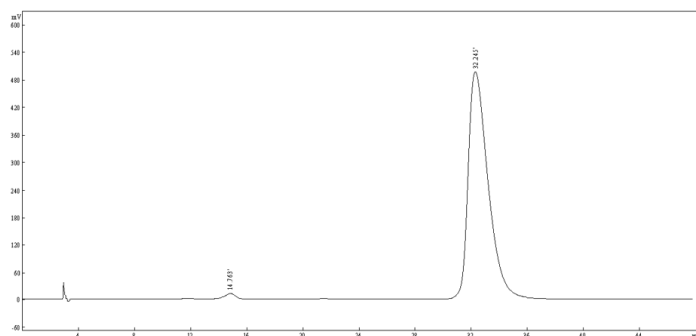


Brown solid. 99% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (s, 1H), 7.34 (dd,  $J = 8.2, 0.9$  Hz, 1H), 7.22 (d,  $J = 7.4$  Hz, 1H), 6.92 (dd,  $J = 8.1, 7.6$  Hz, 1H), 4.63 – 4.52 (m, 1H), 2.90 – 2.82 (m, 1H), 2.78 (dt,  $J = 16.7, 2.8$  Hz, 1H), 2.35 (dt,  $J = 16.7, 2.2$  Hz, 1H), 2.04 – 1.94 (m, 1H), 1.80 – 1.62 (m, 3H), 1.40 – 1.20 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  174.76, 139.81, 132.82, 131.35, 125.84, 124.52, 123.34, 117.91, 103.06, 75.46, 72.66, 34.03, 30.26, 26.00, 25.68, 24.11. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{15}\text{BrN}_4\text{O}_2$  [ $\text{M}-\text{N}_2+\text{H}$ ] $^+$  347.03897, found 347.03795.  $[\alpha]^{25}_{\text{D}} = -60.7^\circ$  (c 1.05,  $\text{CHCl}_3$ ); 97% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0

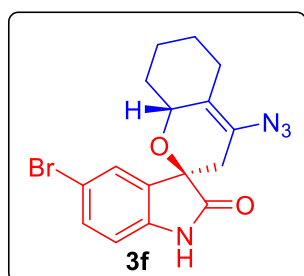
250X4.6 mm 5u column; hexane/2-propanol = 98/2, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 14.8 min (minor), 32.2 min (major).



Peak#	Ret. Time	Area	Area%
1	14.497	12162285	49.97
2	31.895	12175814	50.03
Total		24338099	100

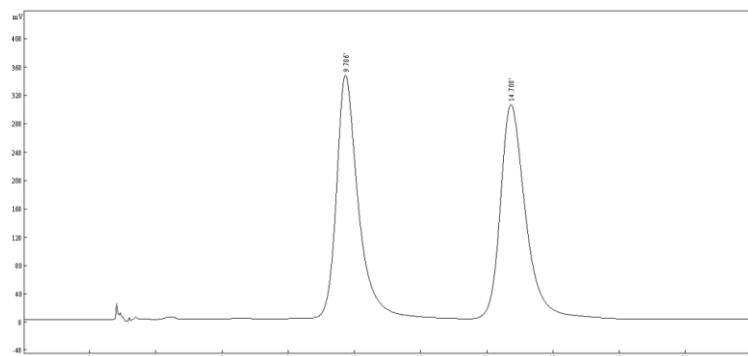


Peak#	Ret. Time	Area	Area%
1	14.763	625388	1.261
2	32.245	48976224	98.74
Total		49601612	100

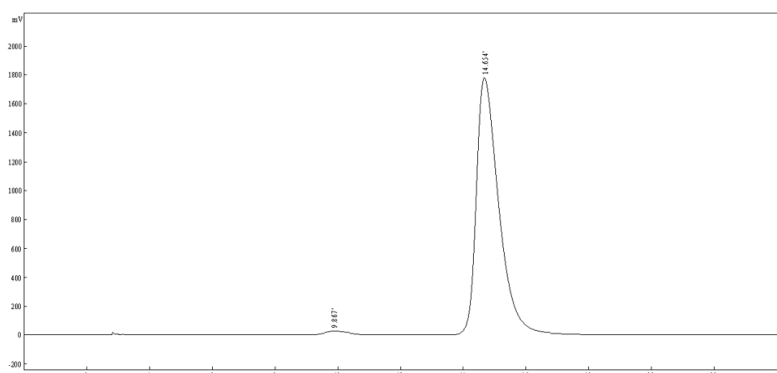


Brown solid. 95% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32 (s, 1H), 7.40 (d,  $J = 1.9$  Hz, 1H), 7.33 (dd,  $J = 8.3, 2.0$  Hz, 1H), 6.69 (d,  $J = 8.3$  Hz, 1H), 4.56 (dd,  $J = 7.0, 4.0$  Hz, 1H), 2.91 – 2.83 (m, 1H), 2.78 (dt,  $J = 16.7, 2.8$  Hz, 1H), 2.31 (dt,  $J = 16.7, 2.1$  Hz, 1H), 2.02 – 1.98 (m, 1H), 1.81 – 1.64 (m, 3H), 1.40 – 1.20 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  175.99, 139.35, 133.03, 132.05, 127.88, 125.75, 118.01, 115.85, 111.70, 74.39, 72.67, 34.06, 30.20, 25.99, 25.70, 24.10. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{15}\text{BrN}_4\text{O}_2$  [ $\text{M}-\text{N}_2+\text{H}$ ] $^+$  347.03897, found 347.03767.  $[\alpha]_D^{25} = -115.6^\circ$  (c 1.05,  $\text{CHCl}_3$ ); 97% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0

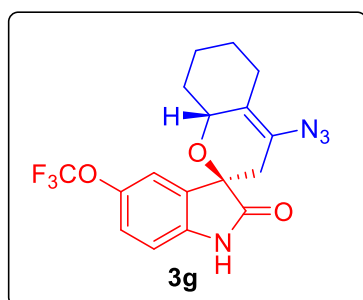
250X4.6 mm 5u column; hexane/2-propanol = 95/5, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 9.9 min (minor), 14.7 min (major).



Peak#	Ret. Time	Area	Area%
1	9.706	15775277	49.69
2	14.708	15974010	50.31
Total		31749287	100

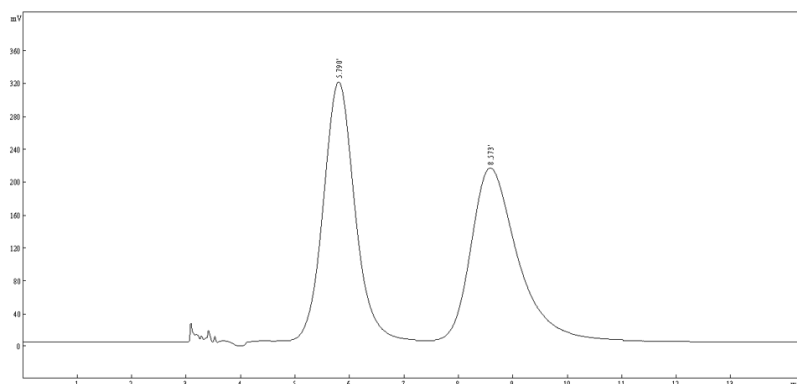


Peak#	Ret. Time	Area	Area%
1	9.867	1283076	1.429
2	14.654	88526726	98.57
Total		89809802	100

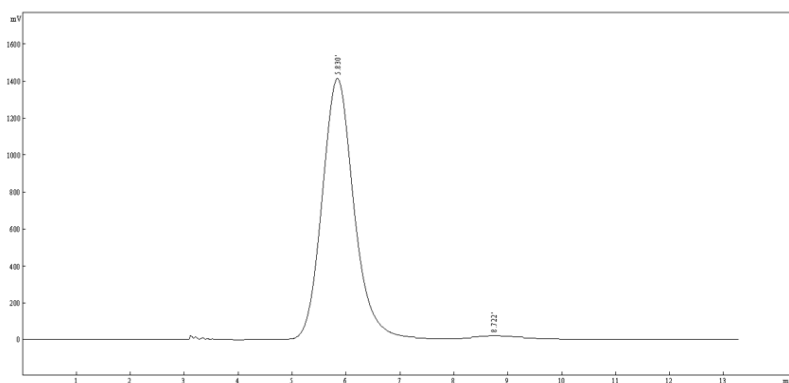


Brown solid. 99% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (s, 1H), 7.17 (d,  $J = 1.5$  Hz, 1H), 7.09 (dd,  $J = 8.4, 1.6$  Hz, 1H), 6.80 (d,  $J = 8.5$  Hz, 1H), 4.59 – 4.54 (m, 1H), 2.90 – 2.85 (m, 1H), 2.77 (dt,  $J = 16.7, 2.8$  Hz, 1H), 2.34 (dt,  $J = 16.7, 2.2$  Hz, 1H), 2.03 – 1.97 (m, 1H), 1.81 – 1.64 (m, 3H), 1.41 – 1.23 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.44, 145.14, 138.99, 131.58, 125.80, 123.33, 120.51 (q,  $J = 257.5$  Hz), 118.47, 117.96, 110.84, 74.50, 72.73, 34.04, 30.24, 25.98, 25.71, 24.09. HRMS (ESI,

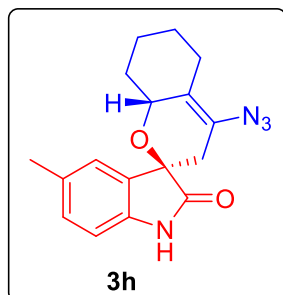
$m/z$ ) calcd for  $C_{17}H_{15}F_3N_4O_3$   $[M-N_2+H]^+$  353.11075, found 353.11040.  $[\alpha]_D^{25} = -70.5^\circ$  (c 1.09,  $CHCl_3$ ); 97% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 95/5, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 5.8 min (major), 8.7 min (minor).



Peak#	Ret. Time	Area	Area%
1	5.791	12593398	50.18
2	8.573	12501442	59.82
Total		25094840	100

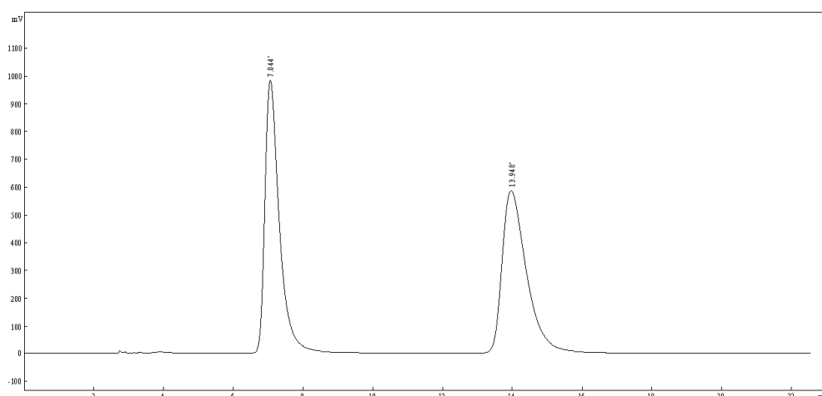


Peak#	Ret. Time	Area	Area%
1	5.830	57366746	98.38
2	8.722	941637	1.615
Total		58308383	100

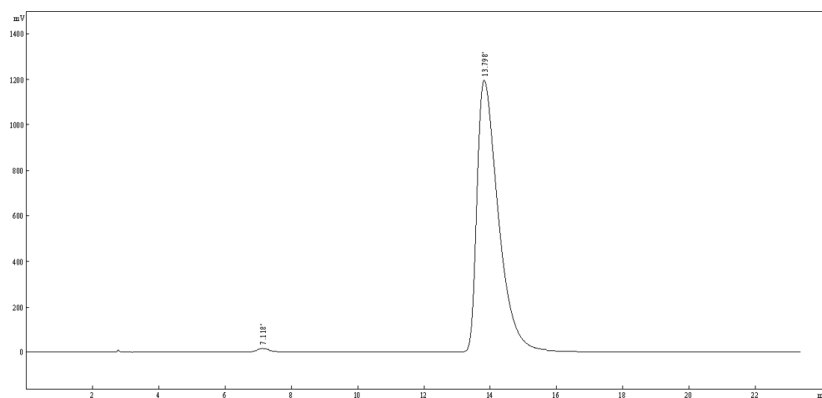


Brown solid. 96% yield.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.79 (s, 1H), 7.17 (s, 1H), 7.07 (dd,  $J = 7.9, 0.8$  Hz, 1H), 6.74 (d,  $J = 7.9$  Hz, 1H), 4.70 – 4.61 (m, 1H), 2.95 – 2.90 (m,

1H), 2.87 (dt,  $J = 16.7, 2.8$  Hz, 1H), 2.37 (dt,  $J = 16.7, 2.2$  Hz, 1H), 2.33 (s, 3H), 2.10 – 2.07 (m, 1H), 1.87 – 1.71 (m, 3H), 1.50 – 1.28 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.52, 137.87, 132.90, 130.49, 130.10, 125.75, 125.12, 118.36, 109.90, 74.46, 72.50, 34.11, 30.32, 26.04, 25.69, 24.14, 21.10. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_2$   $[\text{M}-\text{N}_2+\text{H}]^+$  283.14410, found 283.14325.  $[\alpha]_D^{25} = -38.3^\circ$  (c 2.1,  $\text{CHCl}_3$ ); 98% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 7.1 min (minor), 13.8 min (major).

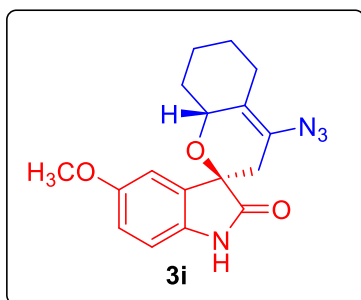


Peak#	Ret. Time	Area	Area%
1	7.044	28252115	49.83
2	13.948	28440138	50.17
Total		56692253	100

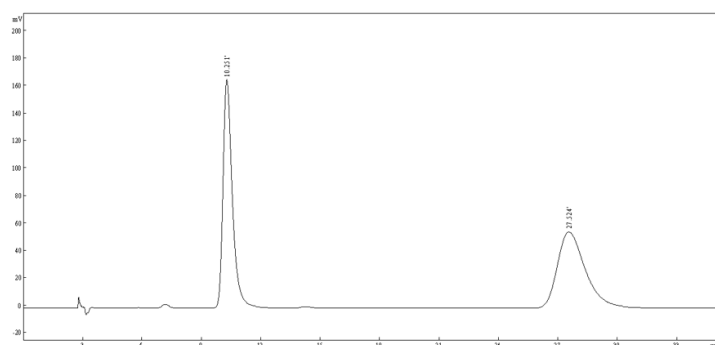


Peak#	Ret. Time	Area	Area%
1	7.118	437669	0.8124
2	13.798	53437635	99.19
Total		53875304	100

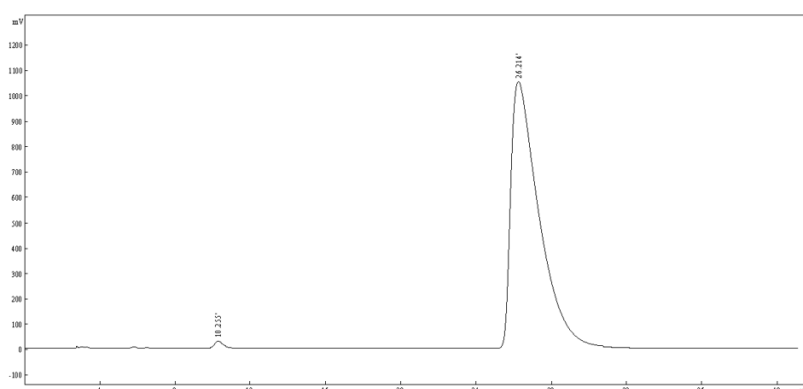




Brown solid. 95% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 – 7.96 (m, 1H), 6.87 (d,  $J$  = 2.4 Hz, 1H), 6.74 (dd,  $J$  = 8.5, 2.5 Hz, 1H), 6.70 (d,  $J$  = 8.5 Hz, 1H), 4.62 – 4.57 (m, 1H), 3.73 (s, 3H), 2.88 – 2.83 (m, 1H), 2.78 (dt,  $J$  = 16.7, 2.7 Hz, 1H), 2.32 (dt,  $J$  = 16.6, 2.1 Hz, 1H), 2.04 – 1.98 (m, 1H), 1.78 – 1.67 (m, 3H), 1.37 – 1.22 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.48, 156.40, 133.55, 131.23, 125.77, 118.29, 115.18, 111.12, 110.71, 74.75, 72.57, 55.87, 34.07, 30.41, 26.03, 25.69, 24.13. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  299.13902, found 299.13900.  $[\alpha]_D^{25} = -129.0^\circ$  (c 1.25,  $\text{CHCl}_3$ ); 98% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 10.3 min (minor), 26.2 min (major).

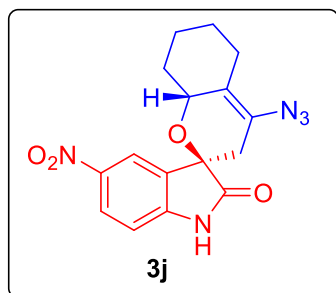


Peak#	Ret. Time	Area	Area%
1	10.251	4599696	50.11
2	27.524	4575933	49.89
Total		10975629	100

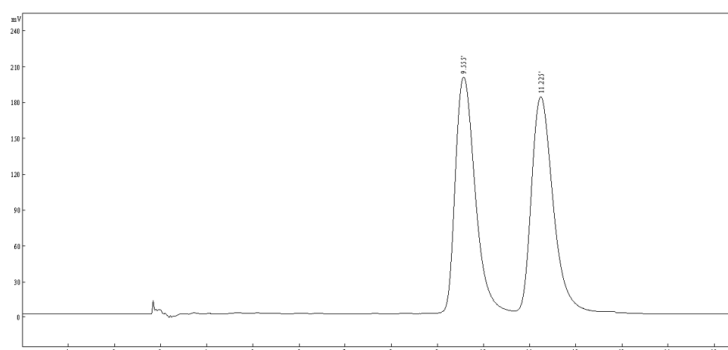


Peak#	Ret. Time	Area	Area%
1	10.255	943852	0.8507
2	26.214	110001293	99.15

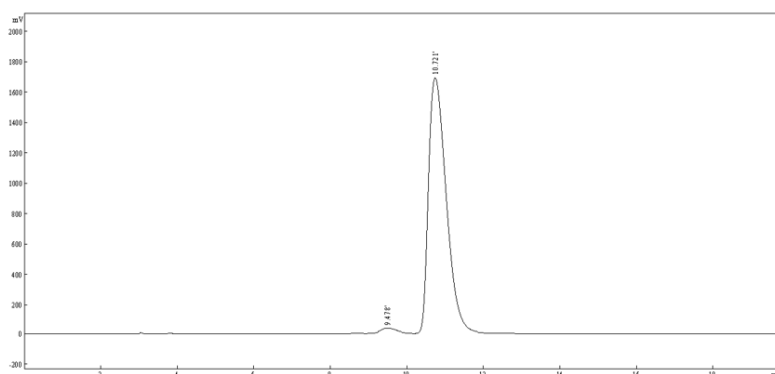
Total		110945145	100
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Brown solid. 98% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (td,  $J = 4.6, 2.3$  Hz, 2H), 8.24 (s, 1H), 7.02 – 6.98 (m, 1H), 4.66 – 4.59 (m, 1H), 2.98 – 2.91 (m, 2H), 2.42 (dt,  $J = 16.6, 2.1$  Hz, 1H), 2.10 – 2.05 (m, 1H), 1.86 – 1.75 (m, 3H), 1.47 – 1.29 (m, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  175.77, 146.03, 143.99, 130.99, 127.13, 125.85, 120.90 (s), 117.63, 109.92, 73.90, 72.90, 34.03, 30.02, 25.95, 25.71, 24.06. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}_4$   $[\text{M}-\text{N}_2+\text{H}]^+$  314.11353, found 314.11321.  $[\alpha]_D^{25} = -64.1^\circ$  (c 0.52,  $\text{CHCl}_3$ ); 96% ee; Chiral HPLC analysis of the product: Daicel Chiralpak AD-H 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 9.5 min (minor), 10.7 min (major).

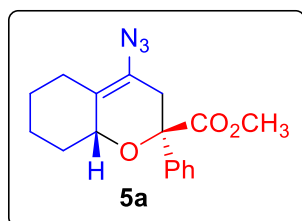


Peak#	Ret. Time	Area	Area%
1	9.555	5827759	50
2	11.225	5827820	50
Total		11655579	100

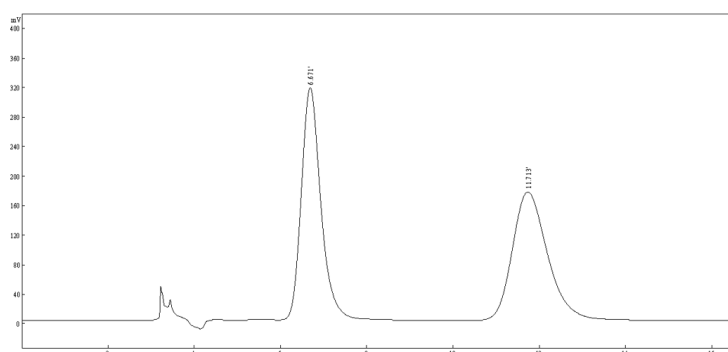


Peak#	Ret. Time	Area	Area%
1	9.478	1020133	1.874

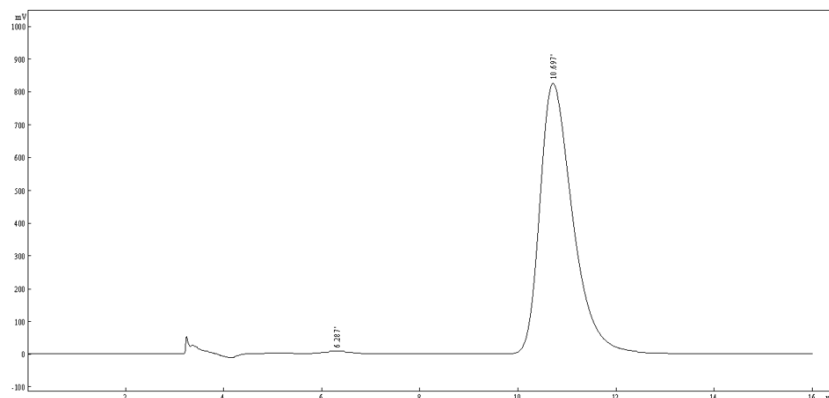
2	10.721	54215590	98.16
Total		55235723	100



Yellow solid. 97% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (dd,  $J = 5.2, 3.4$  Hz, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 4.30 – 4.19 (m, 1H), 3.64 (s, 3H), 3.27 (dt,  $J = 15.7, 2.0$  Hz, 1H), 2.80 – 2.71 (m, 1H), 2.48 (dt,  $J = 15.7, 3.0$  Hz, 1H), 2.25 – 2.22 (m, 1H), 1.79 – 1.72 (m, 1H), 1.69 – 1.64 (m, 1H), 1.49 (d,  $J = 16.8$  Hz, 1H), 1.38 – 1.26 (m, 2H), 1.12 – 1.06 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.01, 140.59, 128.56, 128.22, 125.14, 124.58, 121.07, 79.40, 73.51, 52.81, 34.71, 33.40, 26.33, 25.88, 24.14. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  286.14377, found 286.14321.  $[\alpha]_D^{25} = 265.4^\circ$  (c 0.7,  $\text{CHCl}_3$ ); 99% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 98/2, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 6.3 min (minor), 10.7 min (major).

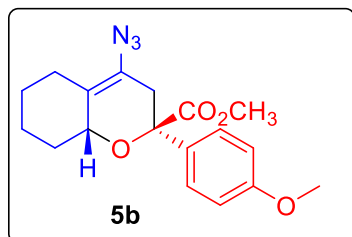


Peak#	Ret. Time	Area	Area%
1	6.671	9942223	50.1
2	11.713	9901781	49.9
Total		19844004	100

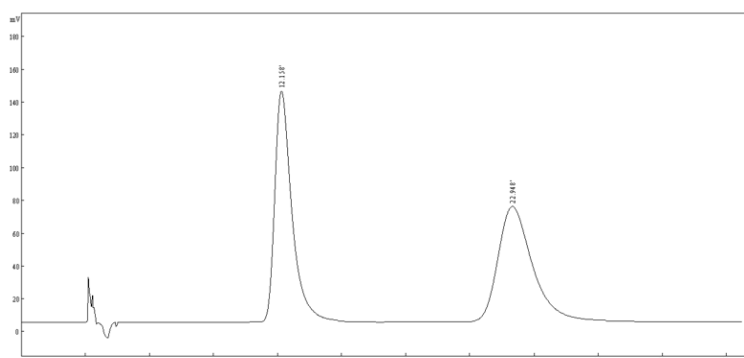


Peak#	Ret. Time	Area	Area%
1	6.287	257328	0.6688

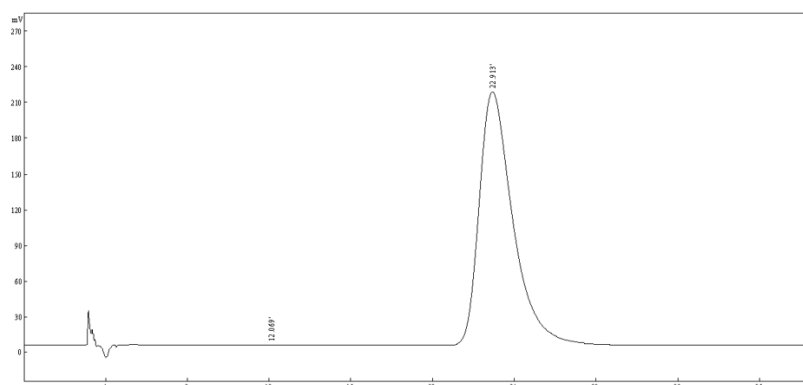
2	10.697	38218726	99.33
Total		38476054	100



Yellow solid. 78% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.39 (m, 2H), 6.85 – 6.80 (m, 2H), 4.23 (dd,  $J = 5.7, 2.7$  Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.25 (dt,  $J = 15.6, 2.0$  Hz, 1H), 2.80 – 2.70 (m, 1H), 2.47 (dt,  $J = 15.6, 3.0$  Hz, 1H), 2.26 – 2.18 (m, 1H), 1.78 – 1.72 (m, 1H), 1.66 (d,  $J = 12.7$  Hz, 1H), 1.47 (td,  $J = 13.8, 1.9$  Hz, 1H), 1.36 – 1.25 (m, 2H), 1.11 – 1.05 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  172.18, 159.48, 132.77, 125.96, 125.18, 121.04, 113.89, 79.06, 73.52, 55.31, 52.73, 34.74, 33.29, 26.34, 25.88, 24.14. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_4$   $[\text{M}-\text{N}_2+\text{H}]^+$  316.15433, found 316.15377.  $[\alpha]^{25}_{\text{D}} = 209.8^\circ$  (c 0.86,  $\text{CHCl}_3$ ); >99% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 97/3, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 12.1 min (minor), 22.9 min (major).

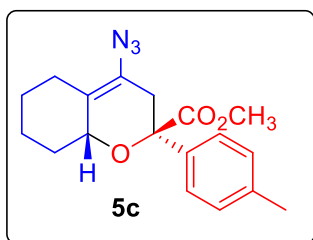


Peak#	Ret. Time	Area	Area%
1	12.158	7820976	49.99
2	22.948	7823703	50.01
Total		15644679	100

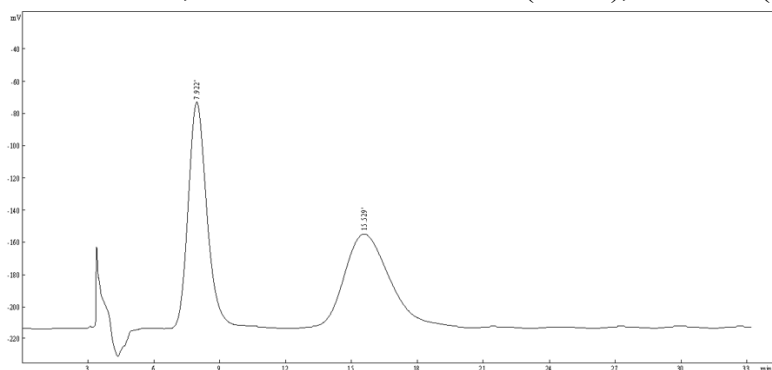


Peak#	Ret. Time	Area	Area%
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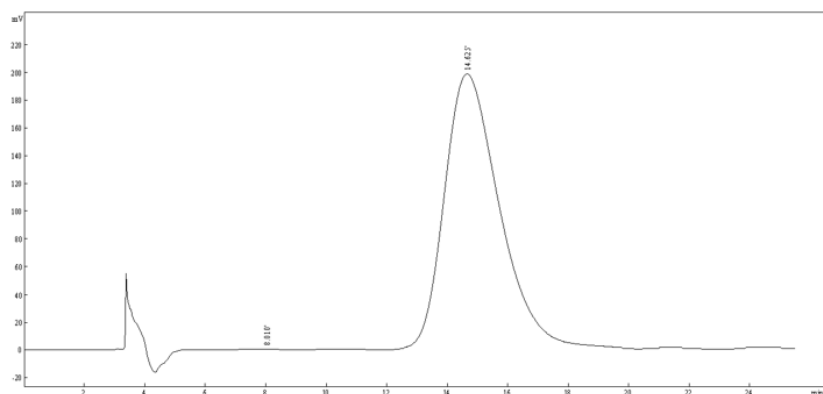
1	12.069	3843	0.01581
2	22.913	24305094	99.99
Total		24308937	100



Yellow solid. 86% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J = 8.3$  Hz, 2H), 7.10 (d,  $J = 8.0$  Hz, 2H), 4.25 – 4.19 (m, 1H), 3.64 (s, 3H), 3.25 (dt,  $J = 15.7, 2.1$  Hz, 1H), 2.75 (ddt,  $J = 14.0, 4.1, 2.1$  Hz, 1H), 2.46 (dt,  $J = 15.7, 3.0$  Hz, 1H), 2.27 (s, 3H), 2.24 – 2.16 (m, 1H), 1.79 – 1.71 (m, 1H), 1.66 (dd,  $J = 7.6, 5.1$  Hz, 1H), 1.39 – 1.22 (m, 3H), 1.12 – 1.05 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 136.96, 136.68, 128.19, 124.11, 123.47, 120.05, 78.27, 72.47, 51.73, 33.69, 32.33, 25.31, 24.84, 23.11, 20.06. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  300.15942, found 300.15901.  $[\alpha]_D^{25} = 214.1^\circ$  (c 0.66,  $\text{CHCl}_3$ ); >99% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 99/1, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 8.0 min (minor), 14.6 min (major).

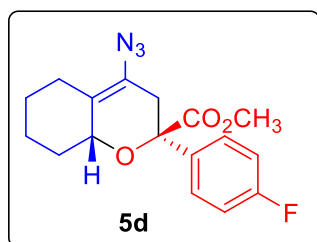


Peak#	Ret. Time	Area	Area%
1	7.922	8216995	49.14
2	15.529	8506046	50.86
Total		16723041	100

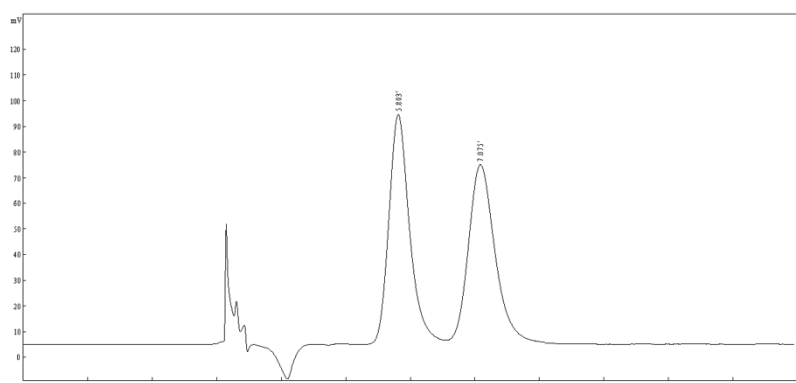


Peak#	Ret. Time	Area	Area%
1	14.627		

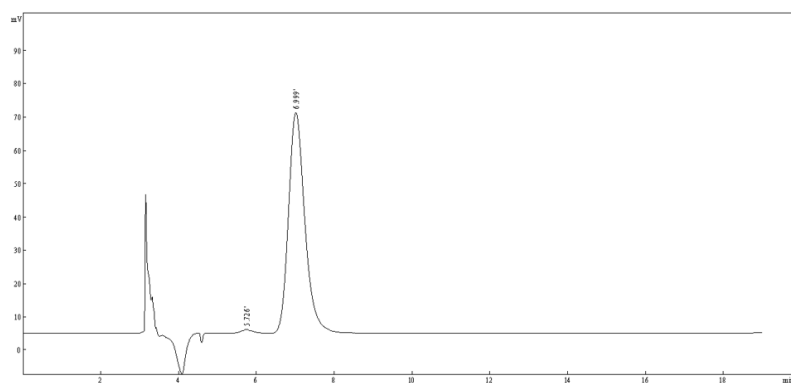
1	8.010	3635	0.01442
2	14.625	25208736	99.98
Total		25212371	100



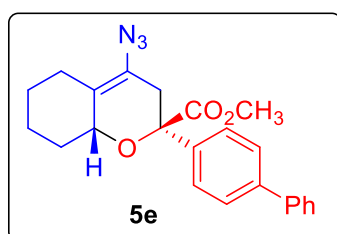
Yellow solid. 82% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 – 7.48 (m, 2H), 7.02 – 6.95 (m, 2H), 4.23 (dd,  $J = 6.3, 3.3$  Hz, 1H), 3.65 (s, 3H), 3.25 (dt,  $J = 15.6, 2.0$  Hz, 1H), 2.79 – 2.73 (m, 1H), 2.45 (dt,  $J = 15.6, 3.0$  Hz, 1H), 2.25 – 2.19 (m, 1H), 1.79 – 1.73 (m, 1H), 1.67 (d,  $J = 12.9$  Hz, 1H), 1.39 – 1.23 (m, 3H), 1.12 – 1.06 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.82, 161.54 (d,  $J = 247.5$  Hz), 135.36, 125.53 (d,  $J = 8.3$  Hz), 124.16, 119.84, 114.39 (d,  $J = 21.7$  Hz), 77.93, 72.54, 51.87, 33.67, 32.32, 25.28, 24.84, 23.08. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{18}\text{FN}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  304.13435, found 304.13347.  $[\alpha]_D^{21} = 293.9^\circ$  (c 0.64,  $\text{CHCl}_3$ ); 97% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 97/3, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 5.7 min (minor), 7.0 min (major).



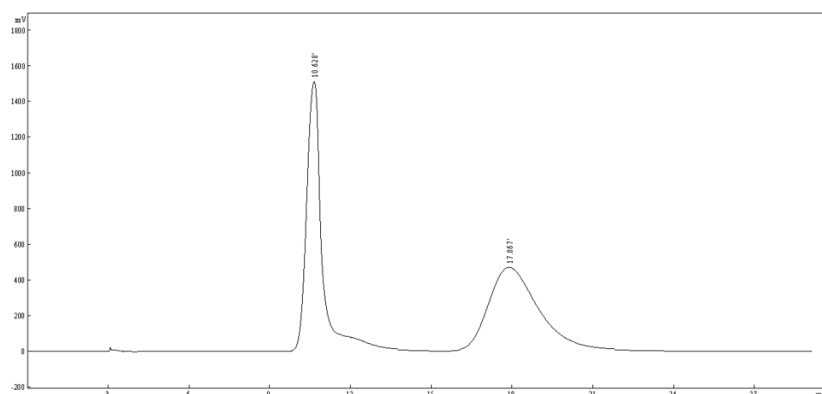
Peak#	Ret. Time	Area	Area%
1	5.803	1945218	50.14
2	7.075	1934662	49.86
Total		3879880	100



Peak#	Ret. Time	Area	Area%
1	5.726	27250	1.383
2	6.999	1942475	98.61
Total		1969725	100

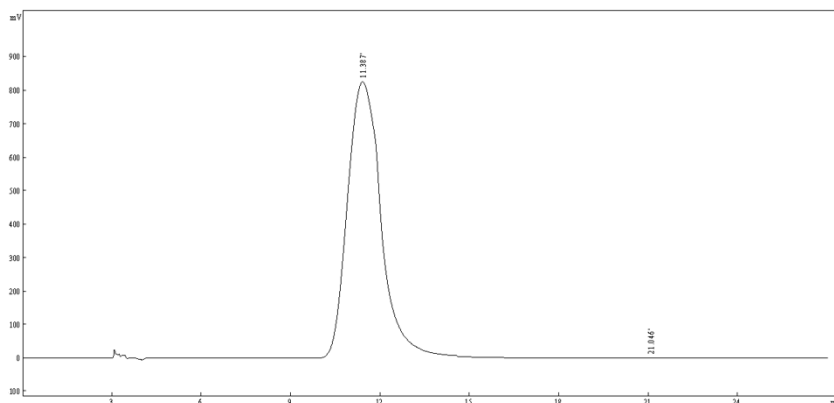


Yellow solid. 86% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (d,  $J = 8.4$  Hz, 2H), 7.54 – 7.48 (m, 4H), 7.37 (t,  $J = 7.6$  Hz, 2H), 7.28 (t,  $J = 7.4$  Hz, 1H), 4.26 (d,  $J = 8.4$  Hz, 1H), 3.67 (s, 3H), 3.31 (d,  $J = 15.6$  Hz, 1H), 2.77 (dd,  $J = 12.3, 1.8$  Hz, 1H), 2.53 (dt,  $J = 15.6, 3.0$  Hz, 1H), 2.25 (d,  $J = 10.1$  Hz, 1H), 1.80 – 1.74 (m, 1H), 1.67 (d,  $J = 12.7$  Hz, 1H), 1.41 – 1.25 (m, 3H), 1.12 – 1.06 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.96, 140.14, 139.55, 138.53, 127.77, 126.45, 126.27, 126.11, 124.18, 147.07, 119.99, 78.28, 72.54, 51.86, 33.71, 32.30, 25.31, 24.87, 23.11. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  362.17507, found 362.17491.  $[\alpha]_D^{25} = 139.4^\circ$  (c 0.32,  $\text{CHCl}_3$ ); >99% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 95/5, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 11.4 min (major), 21.0 min (minor).

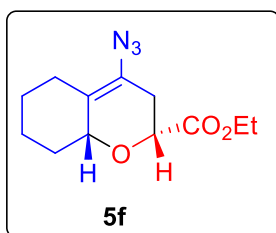


Peak#	Ret. Time	Area	Area%
1	10.628	61047123	49.92

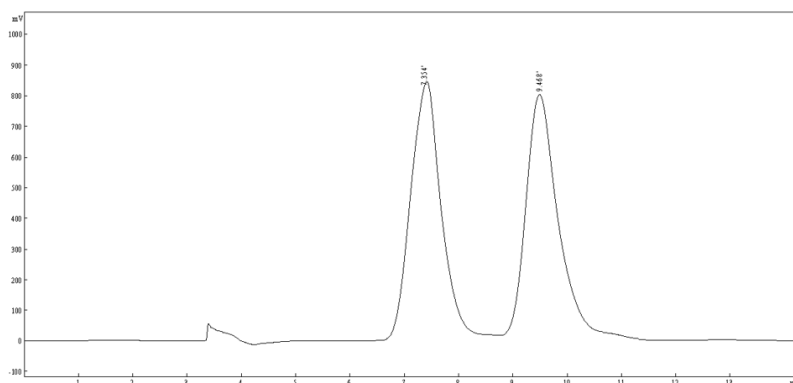
2	17.867	61235629	50.08
Total		122282752	100



Peak#	Ret. Time	Area	Area%
1	11.387	65051130	99.91
2	21.046	57484	0.08829
Total		65108614	100



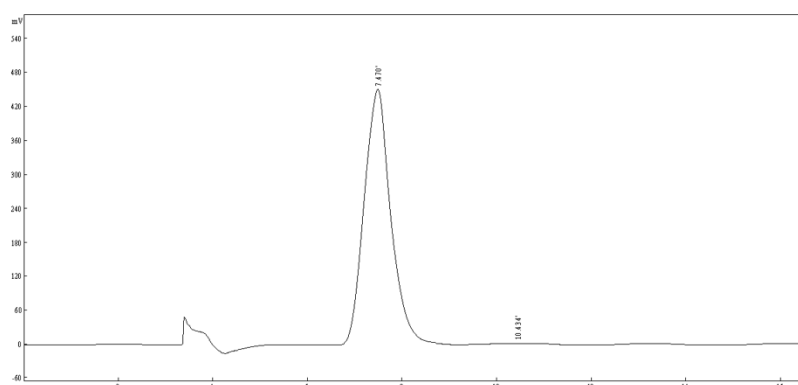
Yellow solid. 95% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.48 (t,  $J = 5.2$  Hz, 1H), 4.24 – 4.20 (m, 1H), 4.20 – 4.14 (m, 2H), 2.73 (ddt,  $J = 13.9, 4.2, 2.2$  Hz, 1H), 2.58 (td,  $J = 4.4, 2.1$  Hz, 2H), 2.03 – 1.96 (m, 1H), 1.79 – 1.72 (m, 1H), 1.65 (d,  $J = 12.9$  Hz, 1H), 1.50 – 1.43 (m, 1H), 1.35 – 1.28 (m, 2H), 1.24 (t,  $J = 7.1$  Hz, 3H), 1.11 – 1.02 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.87, 125.74, 120.49, 73.64, 69.67, 61.40, 33.82, 26.67, 26.42, 26.38, 24.38, 14.22. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  224.12812, found 224.12749.  $[\alpha]_D^{25} = 39.1^\circ$  (c 0.64,  $\text{CHCl}_3$ ); >99% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 99/1, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 7.5 min (major), 10.4 min (minor).



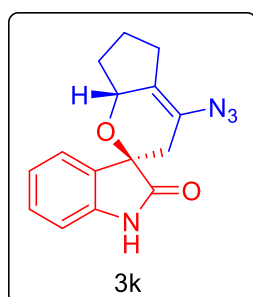
Peak#	Ret. Time	Area	Area%
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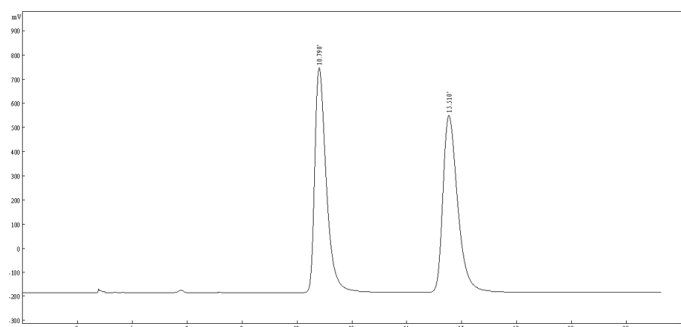
1	7.354	32085091	49.84
2	9.468	32286016	50.16
Total		64371107	100



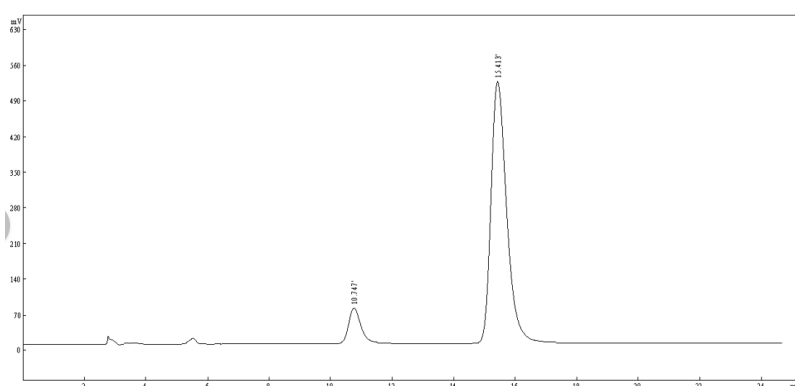
Peak#	Ret. Time	Area	Area%
1	7.470	17664293	99.83
2	10.434	30194	0.1706
Total		17694487	100



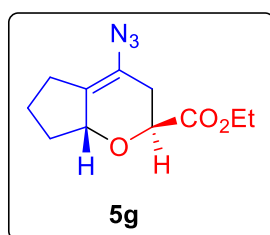
Red solid. 68% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 (s, 1H), 7.31 – 7.25 (m, 2H), 7.07 (td,  $J = 7.6, 0.9$  Hz, 1H), 6.87 (d,  $J = 7.8$  Hz, 1H), 5.06 – 4.99 (m, 1H), 2.67 – 2.60 (m, 1H), 2.59 – 2.49 (m, 2H), 2.47 – 2.39 (m, 1H), 2.15 – 2.08 (m, 1H), 1.92 – 1.84 (m, 1H), 1.75 – 1.70 (m, 1H), 1.58 – 1.50 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.92, 140.31, 130.57, 130.20, 128.74, 124.26, 123.42, 120.86, 110.21, 75.73, 32.51, 30.52, 29.71, 25.04, 20.69. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_2$   $[\text{M}-\text{N}_2+\text{H}]^+$  255.11280, found 255.11220.  $[\alpha]_D^{24} = -214.6^\circ$  (c 0.63,  $\text{CHCl}_3$ ); 81% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 10.7 min (minor), 15.4 min (major).



Peak#	Ret. Time	Area	Area%
1	10.790	27156714	49.92
2	15.510	27246829	50.08
Total		54403543	100

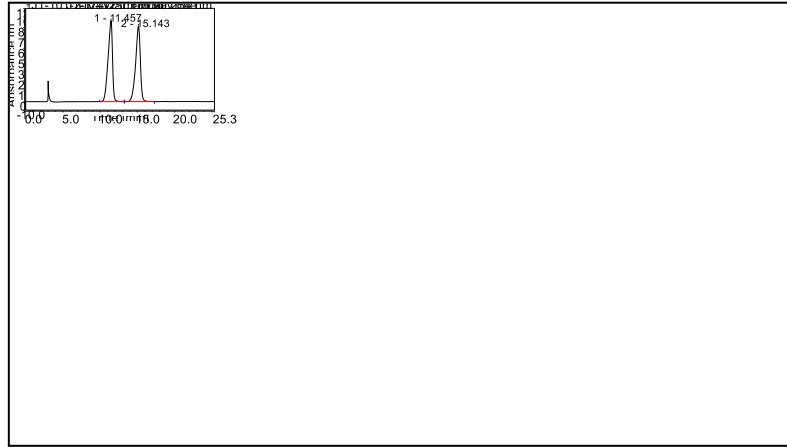


Peak#	Ret. Time	Area	Area%
1	10.747	1949070	9.662
2	15.413	18223733	90.34
Total		20172803	100

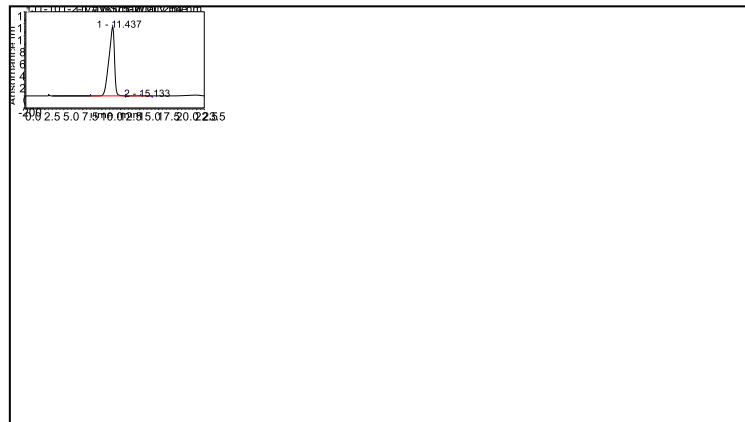


White solid. 78% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.67 (dd,  $J = 6.7, 3.0$  Hz, 1H), 4.51 – 4.40 (m, 1H), 4.30 – 4.22 (m, 2H), 2.70 – 2.60 (m, 2H), 2.49 – 2.39 (m, 1H), 2.25 – 2.12 (m, 2H), 1.83 – 1.75 (m, 1H), 1.67 – 1.59 (m, 1H), 1.44 (dt,  $J = 11.8, 3.4$  Hz, 1H), 1.32 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.20, 127.54, 121.48, 75.22, 72.02, 61.56, 31.99, 25.42, 24.39, 19.94, 14.24. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  210.1125, found 210.1119.  $[\alpha]_D^{22} = 45.5^\circ$  (c 1.18,  $\text{CHCl}_3$ ); >99% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0

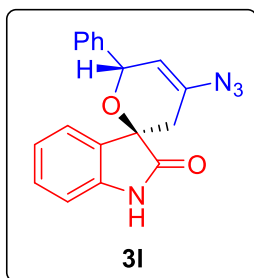
250X4.6 mm 5u column; hexane/2-propanol = 99/1, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 11.4 min (major), 15.1 min (minor).



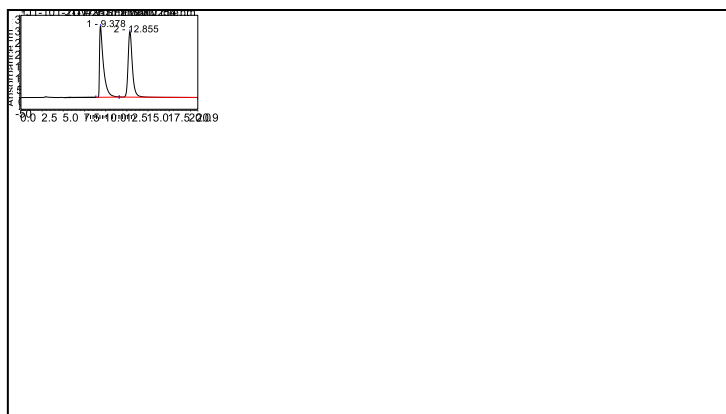
Integration Results					
No.	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1	11.457	65.999	95.639	49.92	51.76
2	15.143	66.203	89.128	50.08	48.24
<b>Total:</b>		<b>132.202</b>	<b>184.767</b>	<b>100.00</b>	<b>100.00</b>



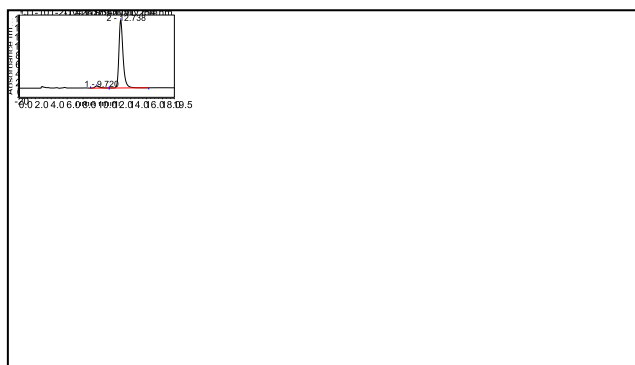
Integration Results					
No.	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1	11.437	975.551	1151.535	99.83	99.85
2	15.133	1.709	1.751	0.17	0.15
<b>Total:</b>		<b>977.259</b>	<b>1153.286</b>	<b>100.00</b>	<b>100.00</b>



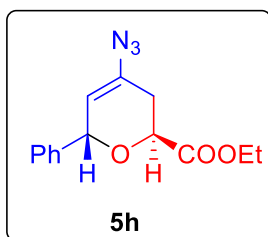
Yellow solid. 42% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (s, 1H), 7.41 – 7.33 (m, 5H), 7.31 – 7.25 (m, 2H), 7.06 (dd,  $J = 11.1, 4.0$  Hz, 1H), 6.86 (d,  $J = 7.8$  Hz, 1H), 5.97 (d,  $J = 2.4$  Hz, 1H), 5.62 (t,  $J = 1.8$  Hz, 1H), 2.87 – 2.80 (m, 1H), 2.28 (dd,  $J = 17.5, 2.2$  Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.34, 140.30, 130.47, 130.34, 129.88, 128.65, 128.33, 127.36, 124.53, 123.36, 113.36, 110.12, 75.61, 74.00, 31.37, 29.72. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_2$   $[\text{M}-\text{N}_2+\text{H}]^+$  291.1128, found 291.1138.  $[\alpha]_D^{22} = -16.4^\circ$  (c 0.61,  $\text{CHCl}_3$ ); 93% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 9.7 min (minor), 12.7 min (major).



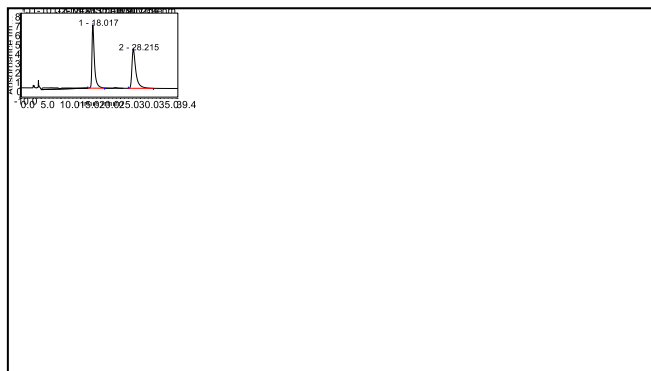
Integration Results					
No.	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1	9.378	161.411	303.259	50.07	51.99
2	12.855	160.980	280.056	49.93	48.01
<b>Total:</b>		<b>322.392</b>	<b>583.315</b>	<b>100.00</b>	<b>100.00</b>



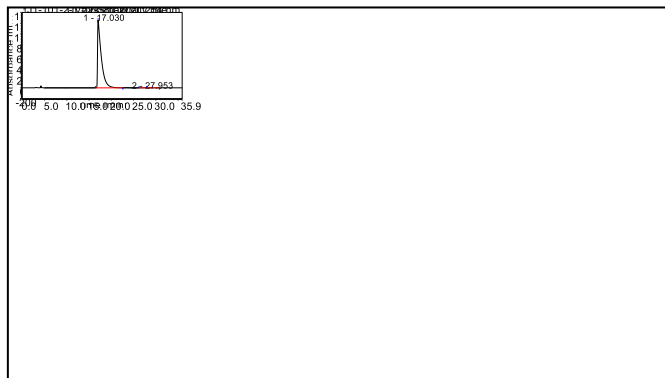
Integration Results					
No.	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1	9.720	3.199	4.523	3.47	2.95
2	12.738	89.096	148.611	96.53	97.05
<b>Total:</b>		<b>92.295</b>	<b>153.135</b>	<b>100.00</b>	<b>100.00</b>



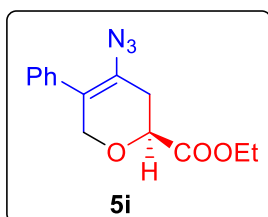
White solid. 82% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.35 (m, 4H), 7.35 – 7.29 (m, 1H), 5.61 – 5.59 (m, 1H), 5.59 – 5.56 (m, 1H), 4.40 (dd,  $J = 6.9, 5.6$  Hz, 1H), 4.27 – 4.21 (m, 2H), 2.58 – 2.50 (m, 2H), 1.29 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.57, 139.71, 133.62, 128.58, 128.40, 127.94, 111.47, 74.08, 68.50, 61.46, 28.39, 14.18. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  246.1125, found 246.1125.  $[\alpha]_D^{22} = -21.5^\circ$  (c 1.01,  $\text{CHCl}_3$ ); >99% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 17.0 min (major), 28.0 min (minor).



Integration Results					
No.	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1	18.017	49.156	67.754	50.55	61.92
2	28.215	48.077	41.661	49.45	38.08
<b>Total:</b>		<b>97.233</b>	<b>109.415</b>	<b>100.00</b>	<b>100.00</b>

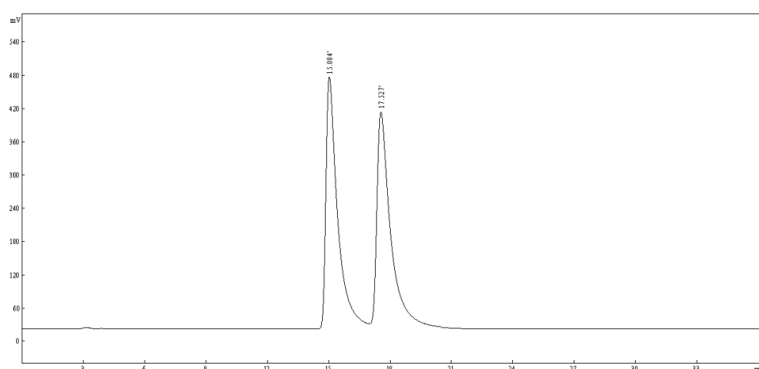


Integration Results					
No.	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %
1	17.030	1215.493	1261.838	99.79	99.84
2	27.953	2.573	2.004	0.21	0.16
<b>Total:</b>		<b>1218.066</b>	<b>1263.842</b>	<b>100.00</b>	<b>100.00</b>

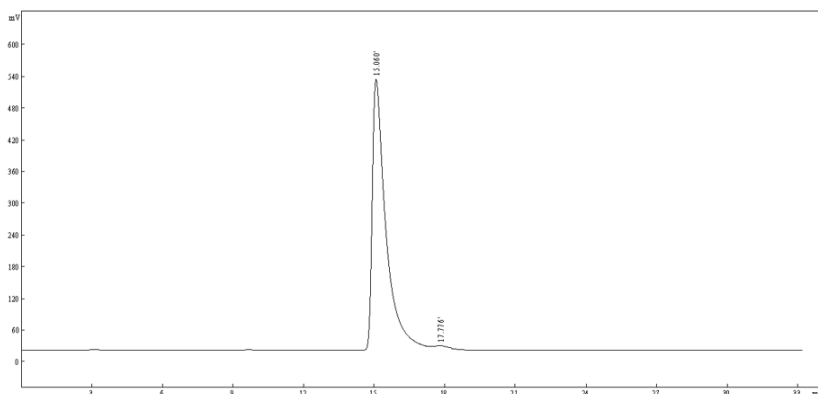


Yellow solid. 26% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 – 7.33 (m, 2H), 7.31 – 7.25 (m, 3H), 4.61 (dt,  $J = 16.0, 1.7$  Hz, 1H), 4.46 - 4.41 (m, 2H), 4.31 (qd,  $J = 7.1,$

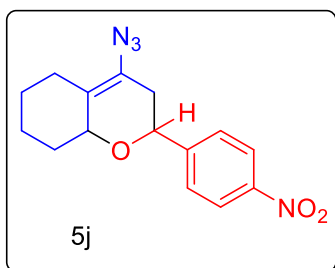
4.1 Hz, 2H), 2.80 – 2.68 (m, 2H), 1.35 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.07, 134.75, 128.40, 128.27, 127.93, 125.37, 122.46, 72.57, 68.41, 61.70, 27.76, 14.23. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  246.1125, found 246.1125.  $[\alpha]_D^{22} = -134.5^\circ$  (c 2.45,  $\text{CHCl}_3$ ); 98% ee; Chiral HPLC analysis of the product: Daicel Chiralpak OJ-H 250X4.6 mm 5u column; hexane/2-propanol = 80/20, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 15.1 min (major), 17.8 min (minor).



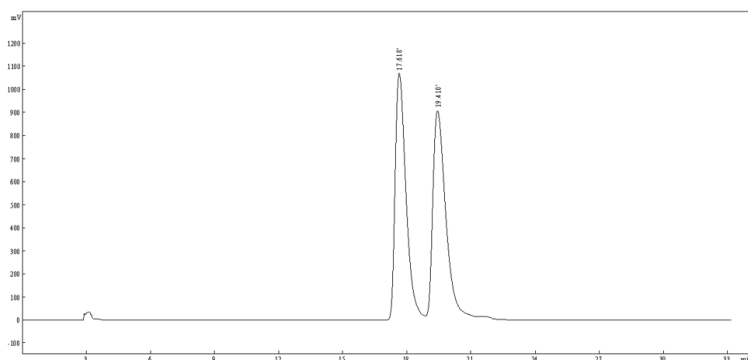
Peak#	Ret. Time	Area	Area%
1	15.004	17433181	50.19
2	17.527	17301514	59.81
Total		34734755	100



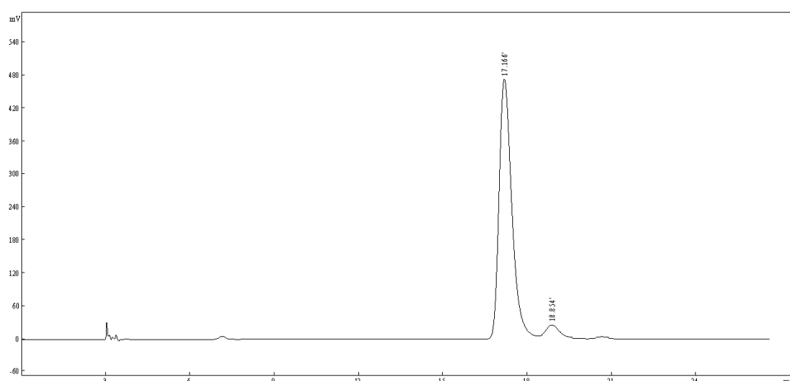
Peak#	Ret. Time	Area	Area%
1	15.060	20288210	99.42
2	17.776	118665	0.58
Total		20406929	100



Brown solid. 56% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 – 8.13 (m, 2H), 7.51 (d,  $J$  = 8.5 Hz, 2H), 4.72 – 4.64 (m, 1H), 4.09 (d,  $J$  = 25.6 Hz, 1H), 2.87 – 2.77 (m, 1H), 2.41 (dt,  $J$  = 6.9, 2.6 Hz, 2H), 2.18 – 2.09 (m, 1H), 1.82 – 1.74 (m, 1H), 1.72 – 1.66 (m, 1H), 1.58 – 1.51 (m, 1H), 1.36 – 1.27 (m, 2H), 1.16 – 1.10 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  148.77, 147.47, 126.61, 126.03, 123.77, 122.09, 76.24, 73.79, 34.09, 32.80, 25.97, 25.64, 24.00. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  273.1234, found 273.1209.  $[\alpha]^{22}_{\text{D}} = -14.6^\circ$  (c 0.72,  $\text{CHCl}_3$ ); 91% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 98/2, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 17.2 min (major), 18.9 min (minor).

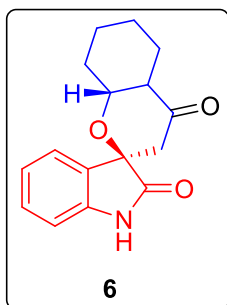


Peak#	Ret. Time	Area	Area%
1	17.618	36759840	50.24
2	19.410	36410966	49.76
Total		73170806	100

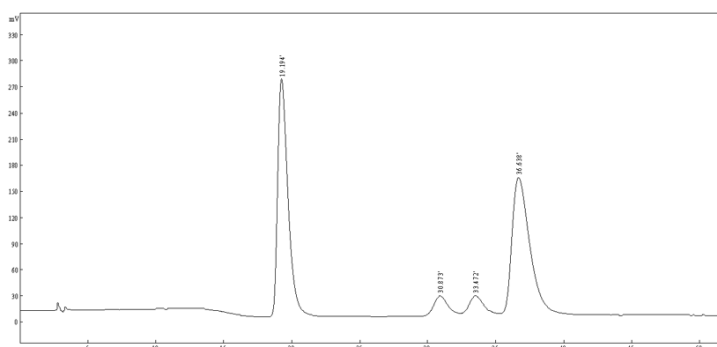


Peak#	Ret. Time	Area	Area%
1	17.166	14663638	95.5
2	18.854	690114	4.495
Total		15353752	100

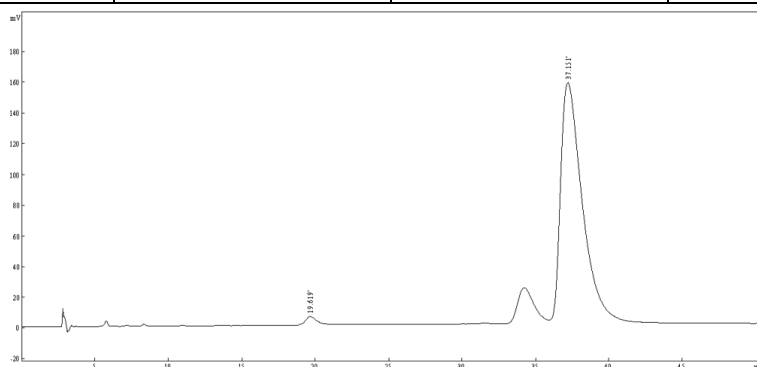




White solid. 81% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48 (s, 1H), 7.38 (t,  $J = 6.2$  Hz, 1H), 7.29 (td,  $J = 7.7, 1.2$  Hz, 1H), 7.13 – 7.08 (m, 1H), 6.90 (dd,  $J = 7.7, 3.8$  Hz, 1H), 4.60 (td,  $J = 10.7, 4.0$  Hz, 1H), 2.90 (dd,  $J = 14.6, 1.0$  Hz, 1H), 2.55 – 2.46 (m, 1H), 2.44 – 2.34 (m, 1H), 2.16 – 2.05 (m, 1H), 2.00 (dt,  $J = 15.9, 5.8$  Hz, 1H), 1.86 – 1.77 (m, 2H), 1.55 – 1.28 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  205.07, 177.07, 140.38, 130.44, 129.07, 124.25, 123.37, 110.63, 78.78, 75.86, 55.32, 45.73, 33.19, 24.81, 24.35, 23.06. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_3$   $[\text{M}+\text{H}]^+$  272.1281, found 272.1307.  $[\alpha]_D^{25} = 71.6^\circ$  (c 1.55,  $\text{CHCl}_3$ ); 96% ee; Chiral HPLC analysis of the product: Phenomenex 00G-4457-E0 250X4.6 mm 5u column; hexane/2-propanol = 90/10, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 19.6 min (minor), 37.2min (major).

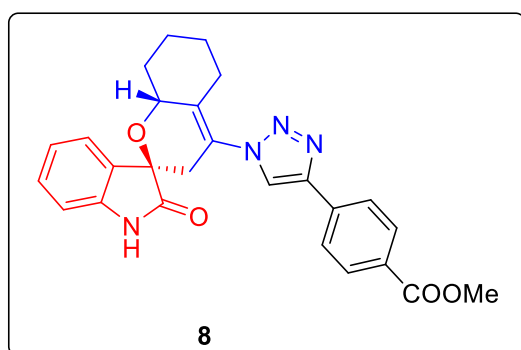


Peak#	Ret. Time	Area	Area%
1	19.194	14562179	50.34
4	36.638	14367328	49.66
Total		28929507	100

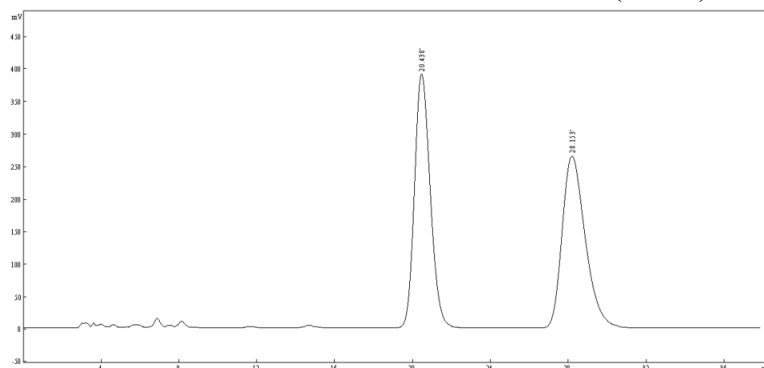


Peak#	Ret. Time	Area	Area%
1	19.619	291450	1.828

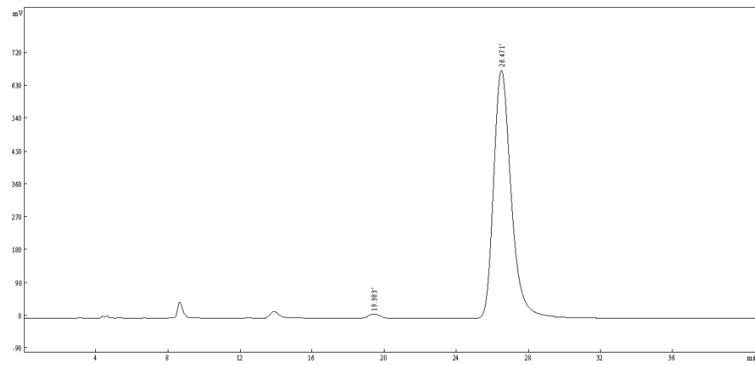
4	37.151	15650818	98.17
Total		15942268	100



Yellow solid. 72% yield.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 (d,  $J = 8.6$  Hz, 2H), 7.94 (s, 1H), 7.94 – 7.90 (m, 2H), 7.38 (d,  $J = 7.4$  Hz, 1H), 7.28 (d,  $J = 8.6$  Hz, 1H), 7.09 (td,  $J = 7.6, 0.9$  Hz, 1H), 6.87 (d,  $J = 7.8$  Hz, 1H), 4.89 – 4.84 (m, 1H), 3.93 (s, 3H), 3.30 (dt,  $J = 17.4, 2.8$  Hz, 1H), 2.51 (dt,  $J = 32.1, 8.4$  Hz, 2H), 2.26 – 2.20 (m, 1H), 1.90 (d,  $J = 10.3$  Hz, 3H), 1.63 – 1.51 (m, 2H), 1.50 – 1.32 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.25, 166.82, 146.20, 140.37, 137.35, 134.69, 130.33, 130.27, 129.65, 129.60, 125.53, 124.64, 123.38, 121.57, 120.70, 110.08, 74.15, 72.47, 52.19, 34.77, 33.80, 26.76, 26.25, 23.94. HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{26}\text{H}_{24}\text{N}_4\text{O}_4$   $[\text{M}+\text{H}]^+$  457.1870, found 457.2111.  $[\alpha]_D^{25} = -34.6^\circ$  (c 1.34,  $\text{CHCl}_3$ ); 98% ee; Chiral HPLC analysis of the product: Daicel Chiralpak AD-H 250X4.6 mm 5u column; hexane/2-propanol = 75/25, detected at 254 nm, Flow rate = 1 mL/min, Retention times: 19.4 min (minor), 26.5 min (major).

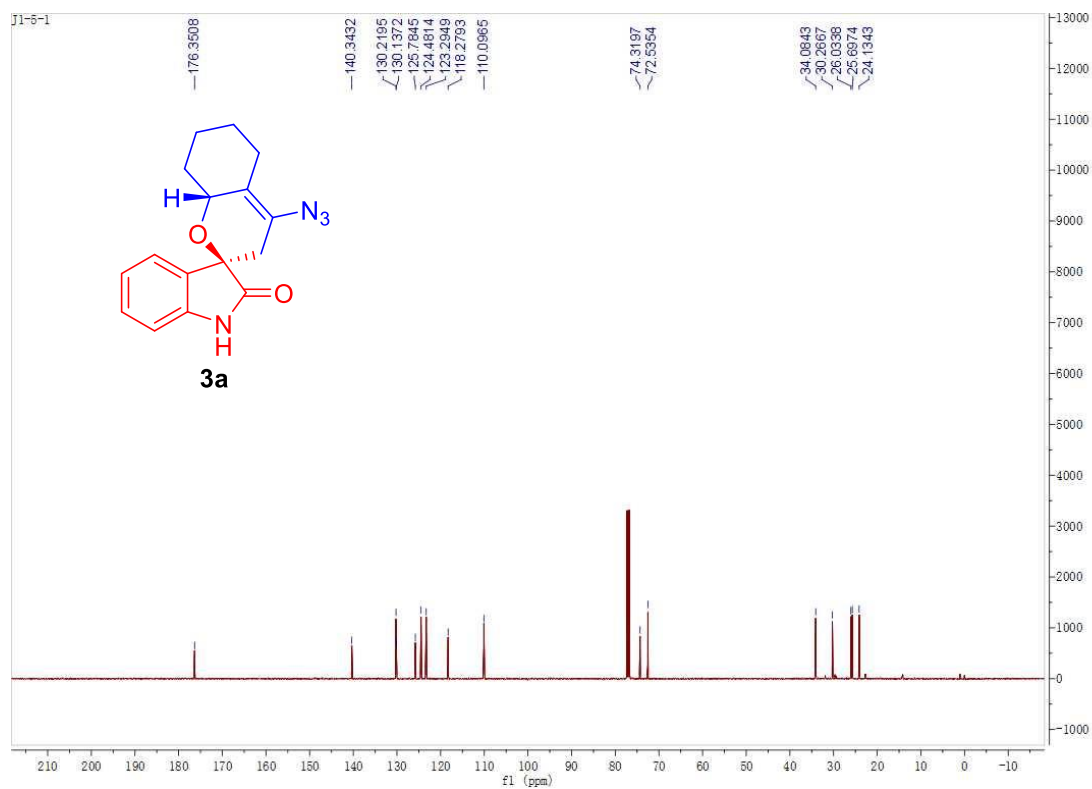
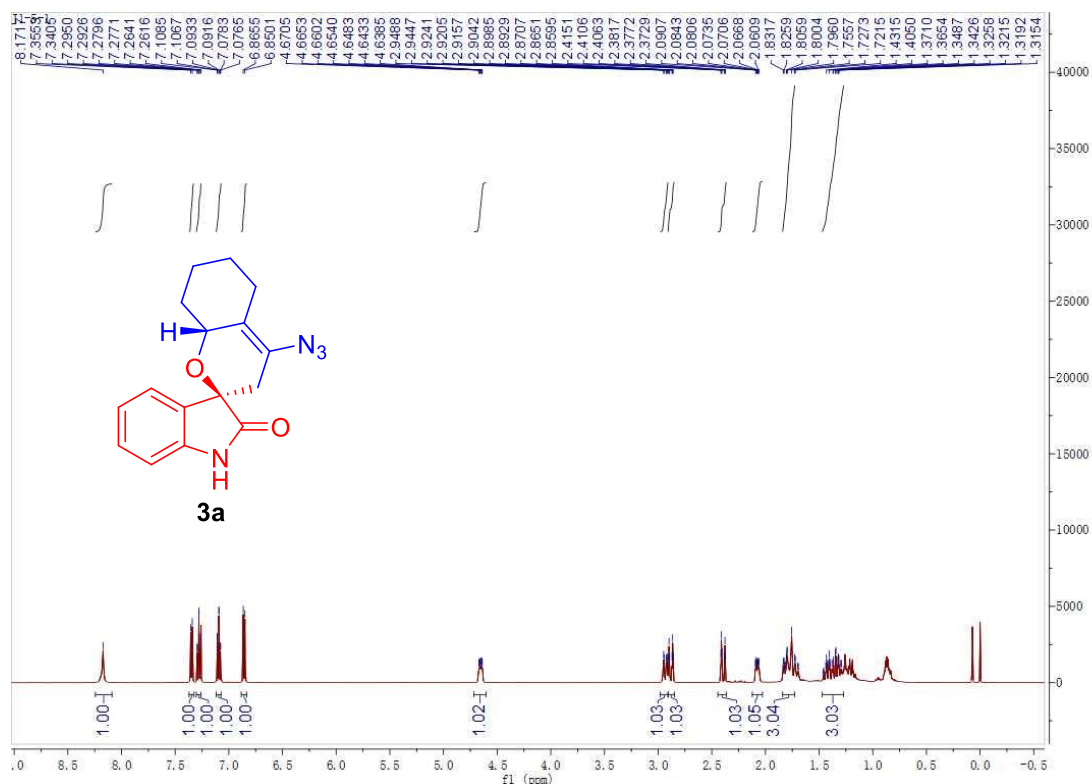


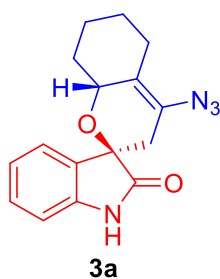
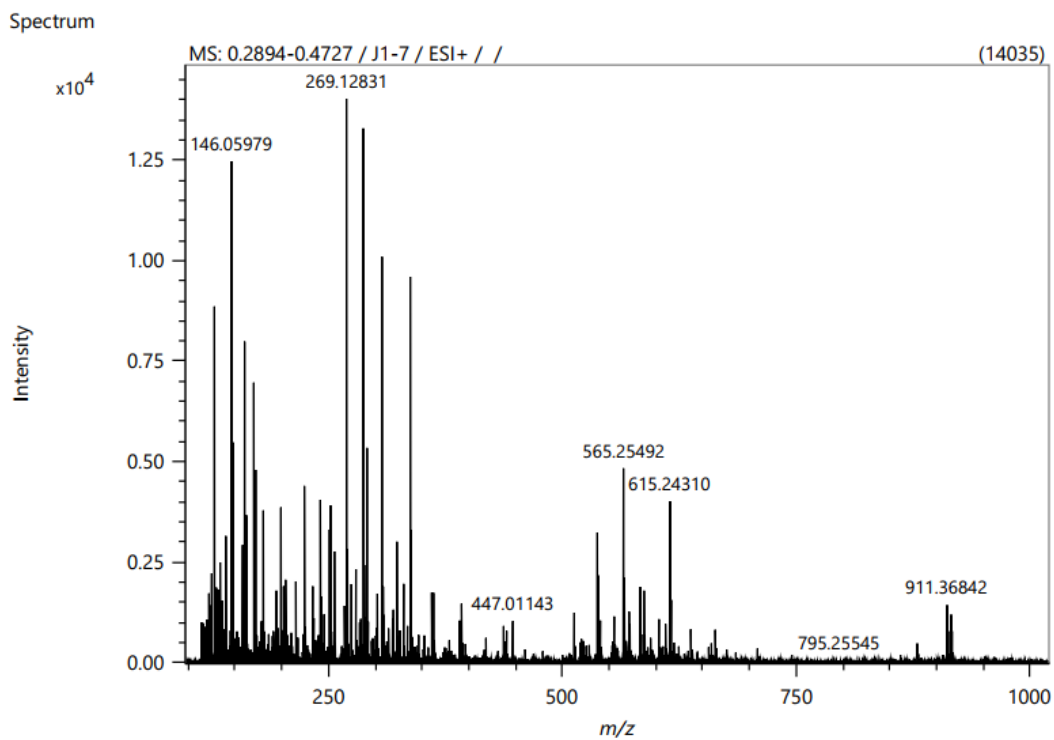
Peak#	Ret. Time	Area	Area%
1	20.438	22065830	50.11
2	28.153	21965450	49.89
Total		44031280	100



Peak#	Ret. Time	Area	Area%
1	19.383	550193	1.179
2	26.471	46104403	98.82
Total		46654596	100

## 7. Supplementary spectra





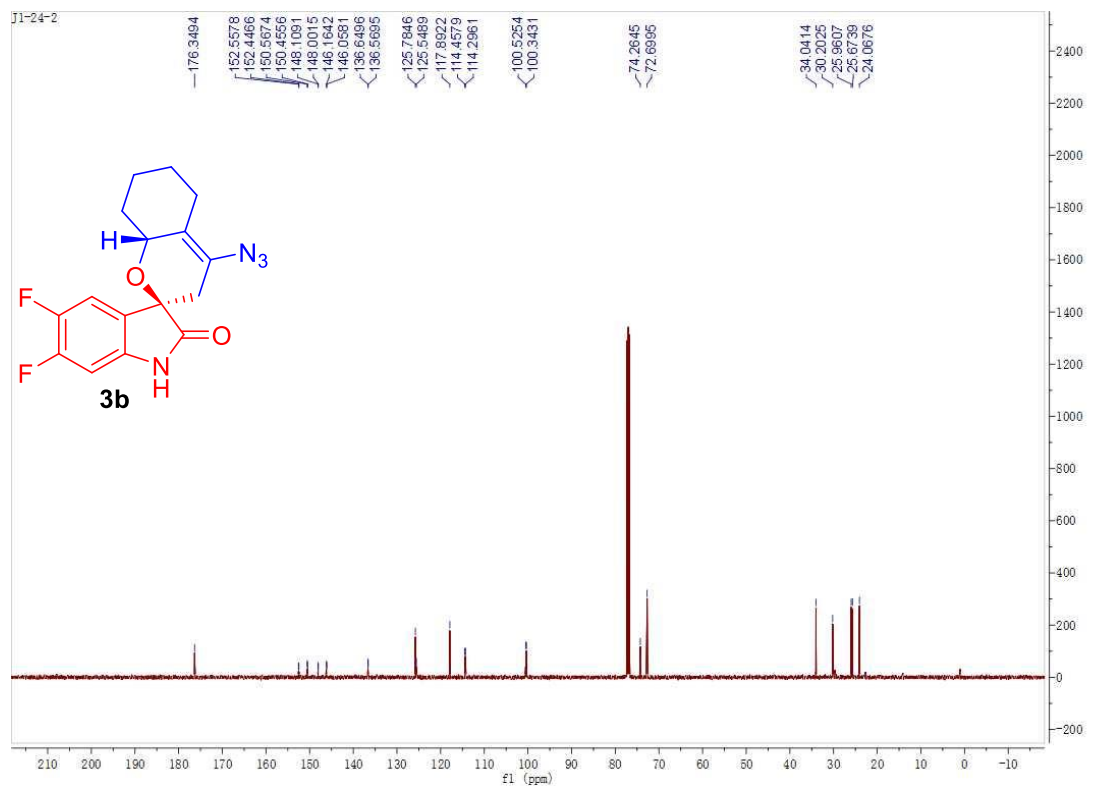
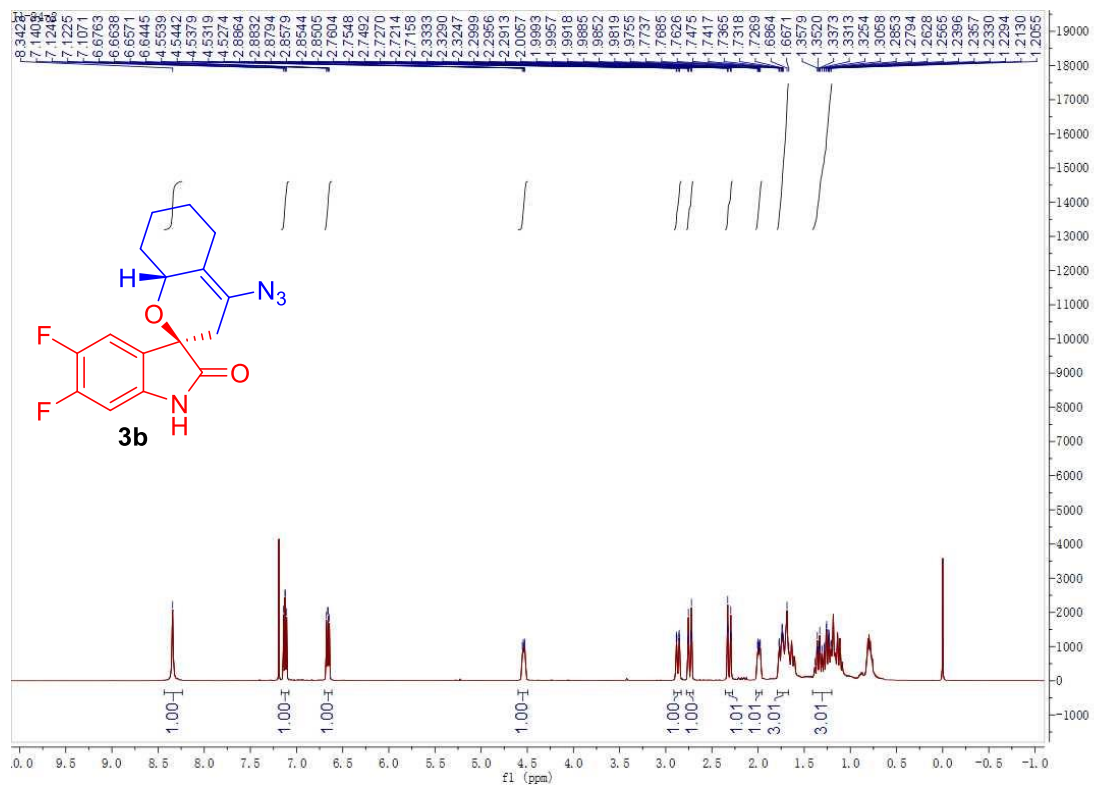
Exact Mass: 296.1273

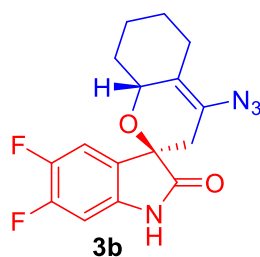
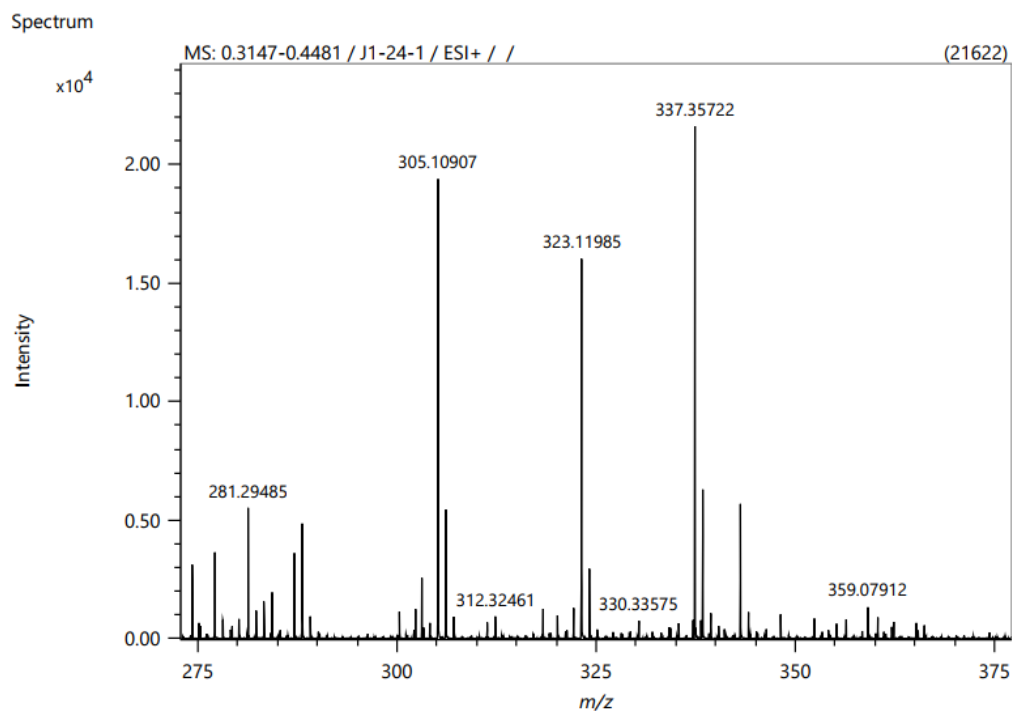
Molecular Weight: 296.3300

m/z: 296.1273 (100.0%), 297.1307 (17.3%), 297.1244 (1.5%), 298.1340 (1.4%)

Elemental Analysis: C, 64.85; H, 5.44; N, 18.91; O, 10.80

HRMS (ESI, m/z) calcd for  $C_{16}H_{16}N_4O_2$   $[M-N_2+H]^+$  269.12831, found 269.12845.





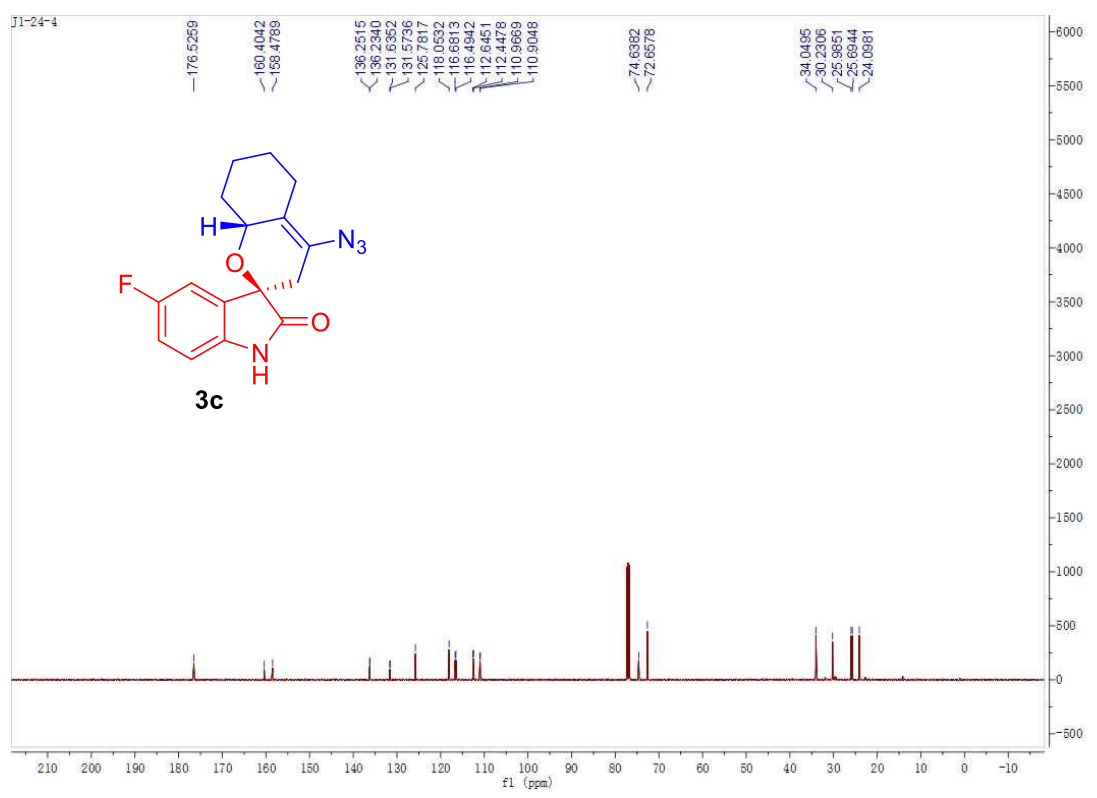
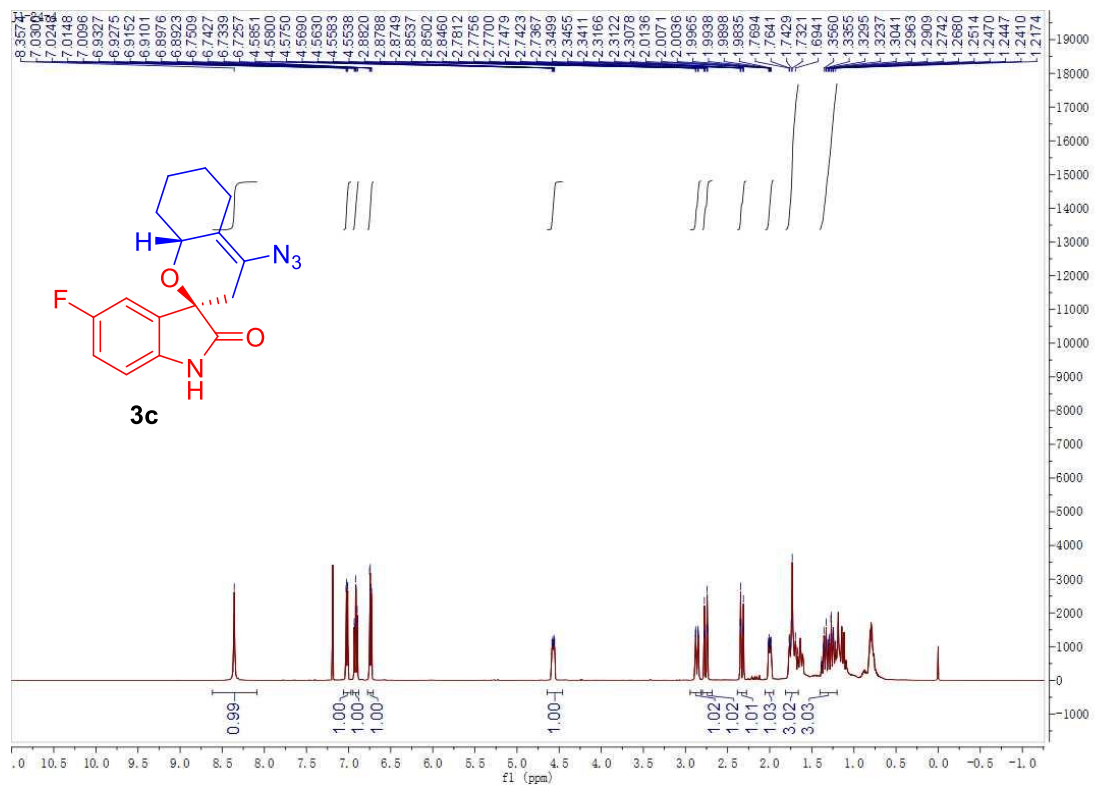
Exact Mass: 332.1085

Molecular Weight: 332.3108

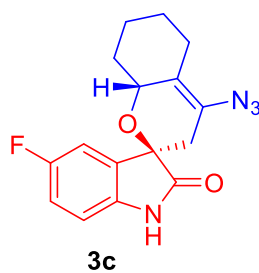
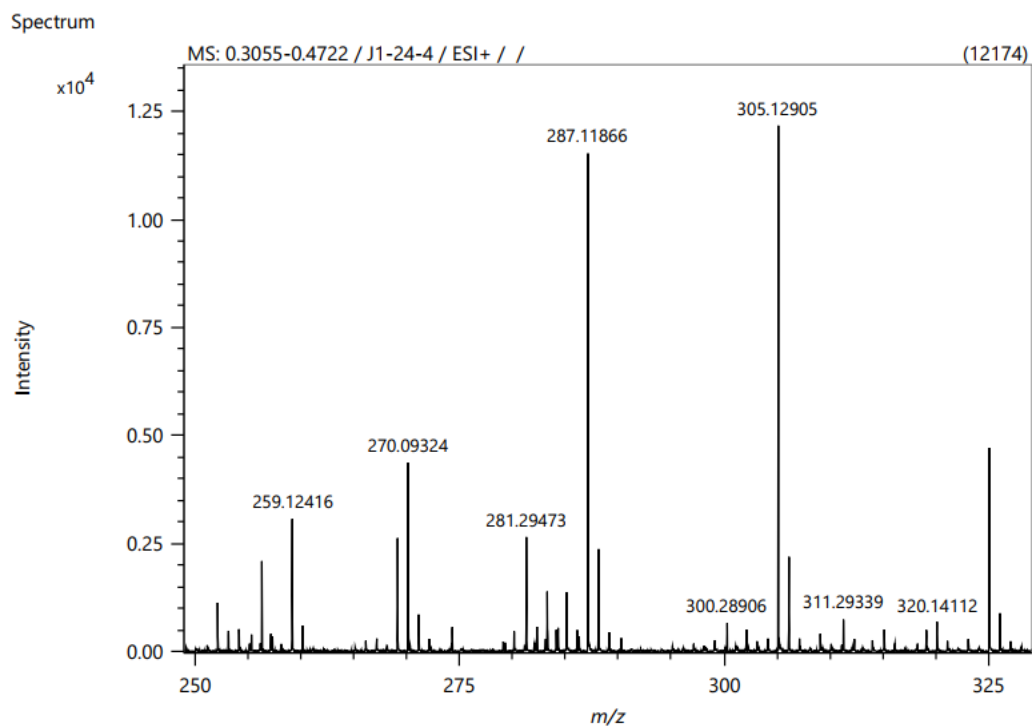
m/z: 332.1085 (100.0%), 333.1118 (17.3%), 333.1055 (1.5%), 334.1152 (1.4%)

Elemental Analysis: C, 57.83; H, 4.25; F, 11.43; N, 16.86; O, 9.63

HRMS (ESI, m/z) calcd for  $C_{16}H_{14}F_2N_4O_2 [M-N_2+H]^+$  305.10961, found 305.10907.







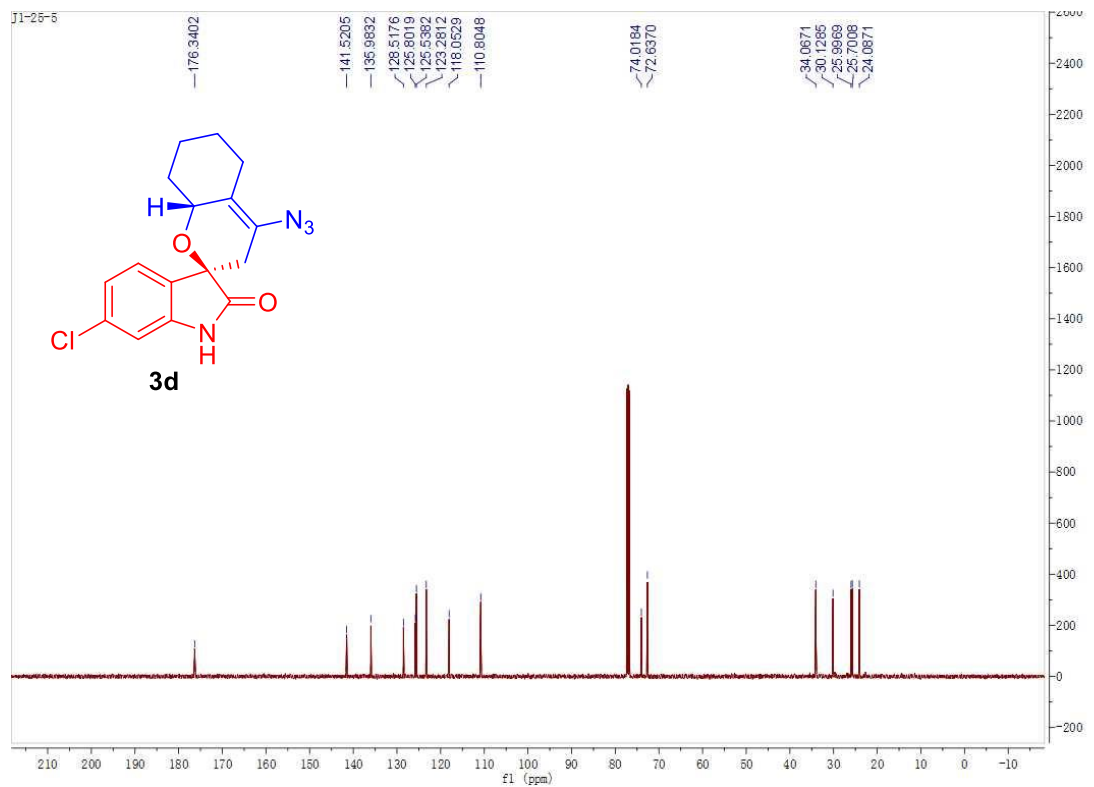
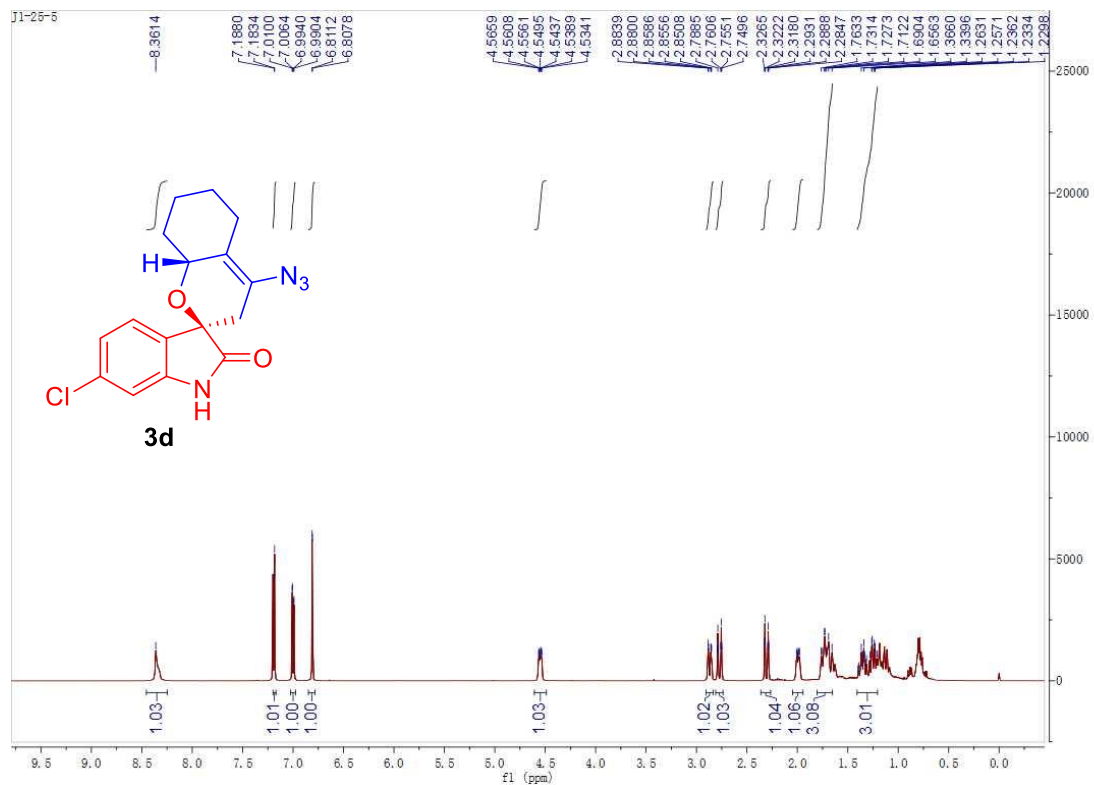
Exact Mass: 314.1179

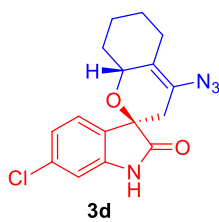
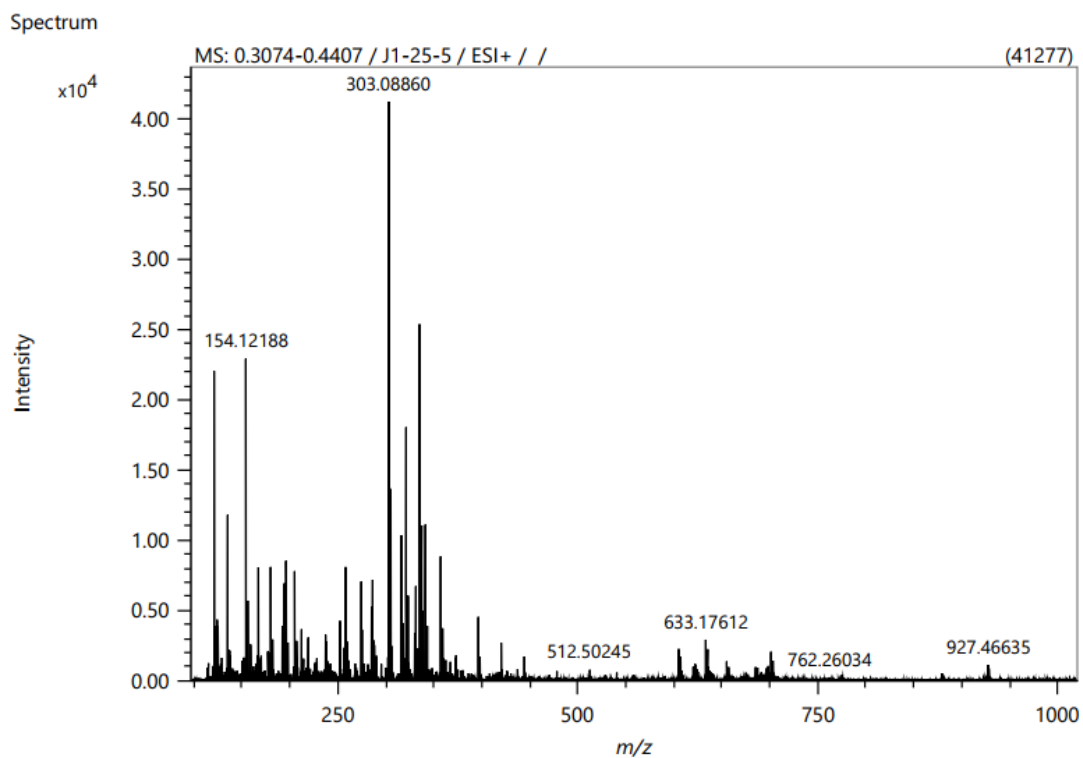
Molecular Weight: 314.3204

m/z: 314.1179 (100.0%), 315.1213 (17.3%), 315.1149 (1.5%), 316.1246 (1.4%)

Elemental Analysis: C, 61.14; H, 4.81; F, 6.04; N, 17.83; O, 10.18

HRMS (ESI, m/z) calcd for  $C_{16}H_{15}FN_4O_2$   $[M-N_2+H]^+$  287.11903, found 287.11866.





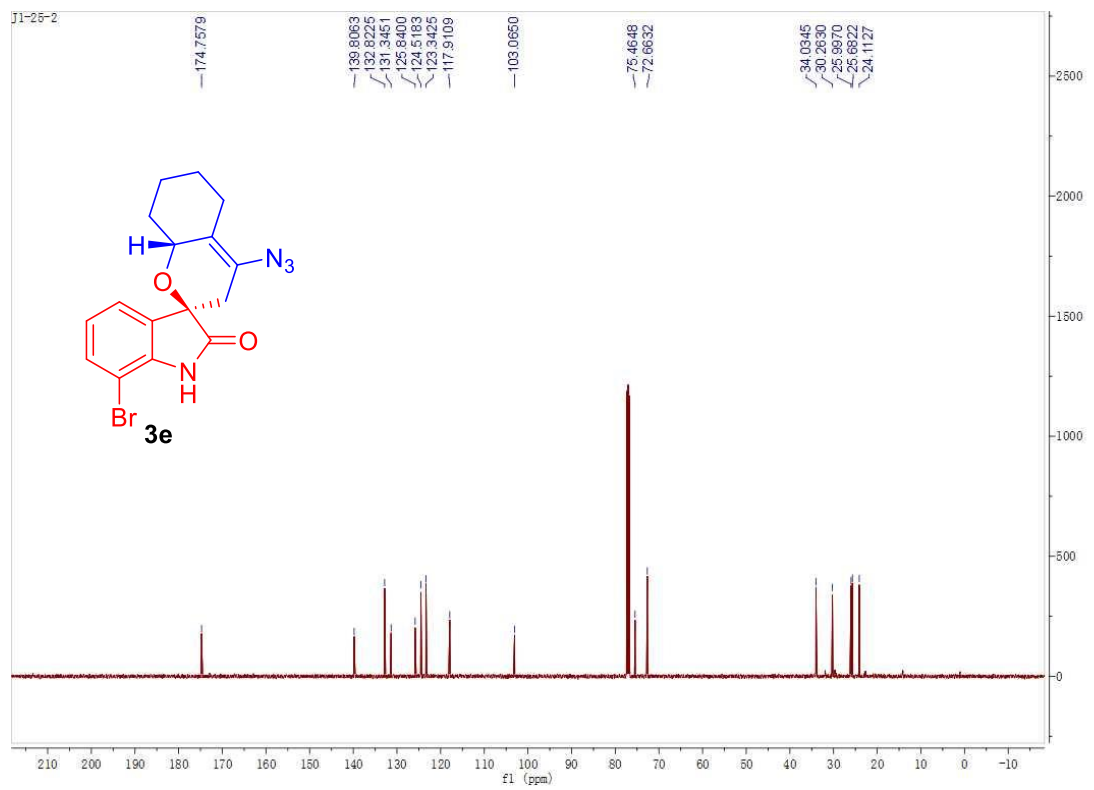
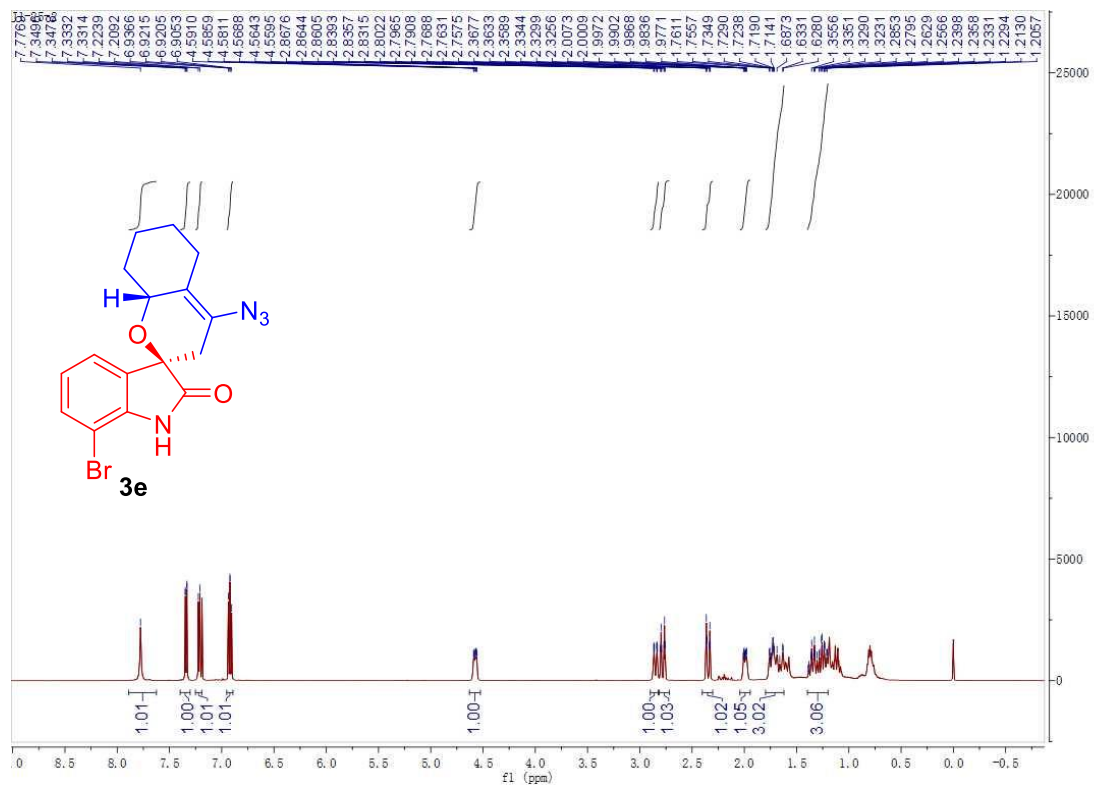
Exact Mass: 330.0884

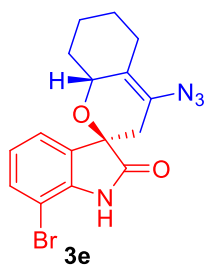
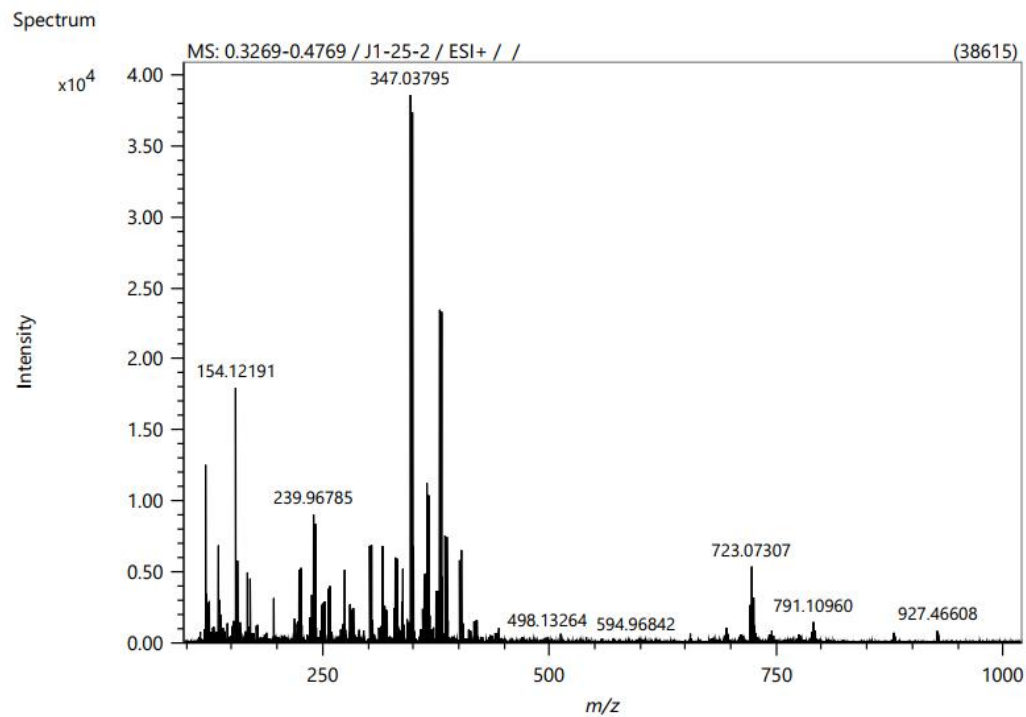
Molecular Weight: 330.7720

$m/z$ : 330.0884 (100.0%), 332.0854 (32.0%), 331.0917 (17.3%), 333.0888 (5.5%), 331.0854 (1.5%), 332.0951 (1.4%)

Elemental Analysis: C, 58.10; H, 4.57; Cl, 10.72; N, 16.94; O, 9.67

HRMS (ESI,  $m/z$ ) calcd for  $C_{16}H_{15}ClN_4O_2$   $[M-N_2+H]^+$  303.08948, found 303.08860.





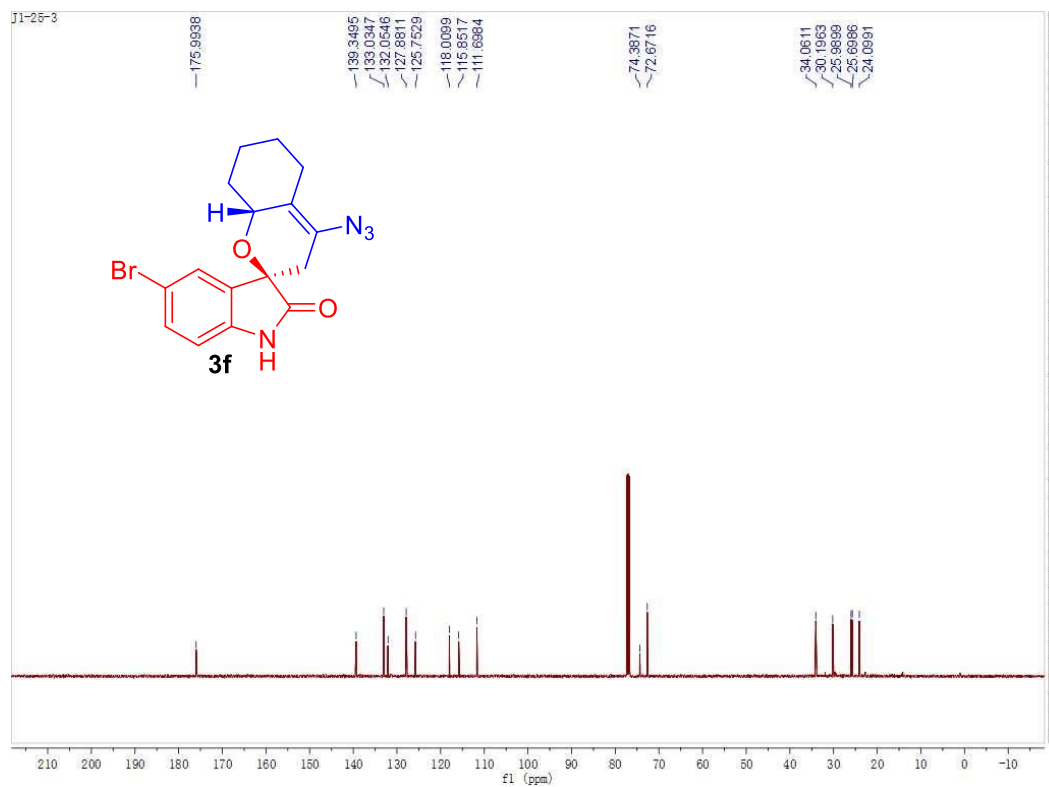
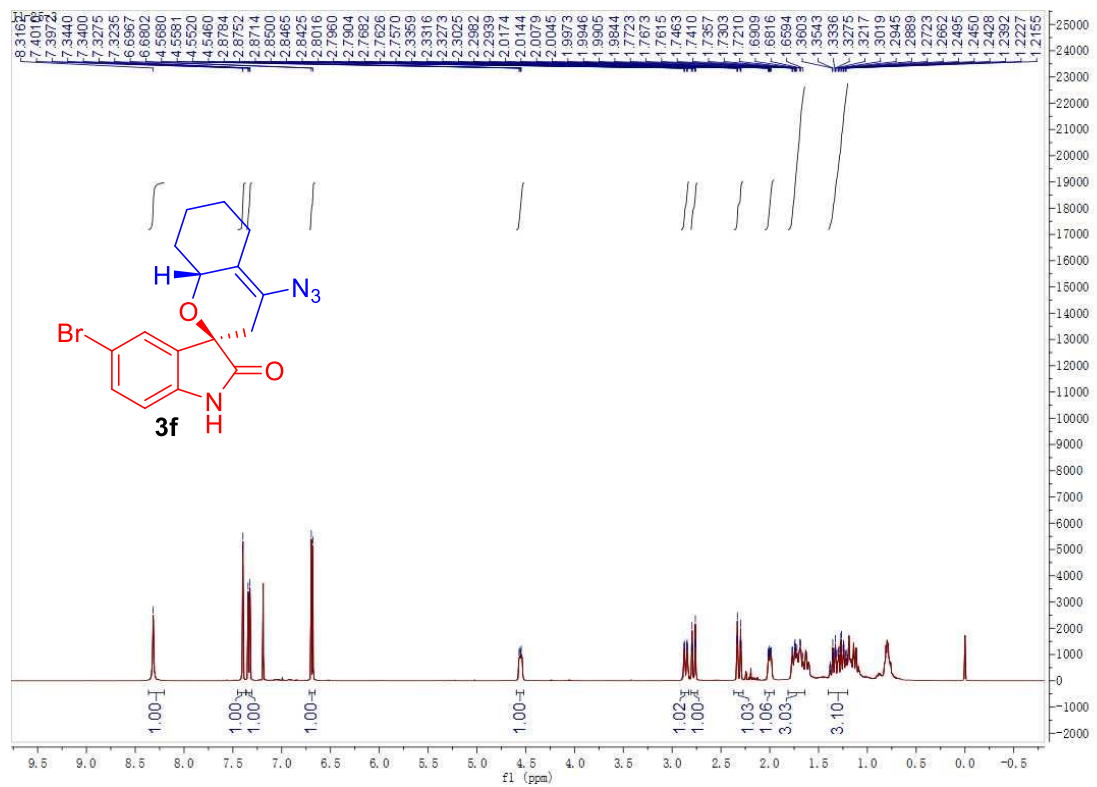
Exact Mass: 374.0378

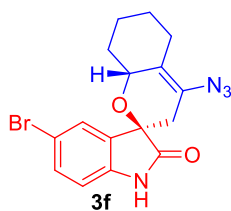
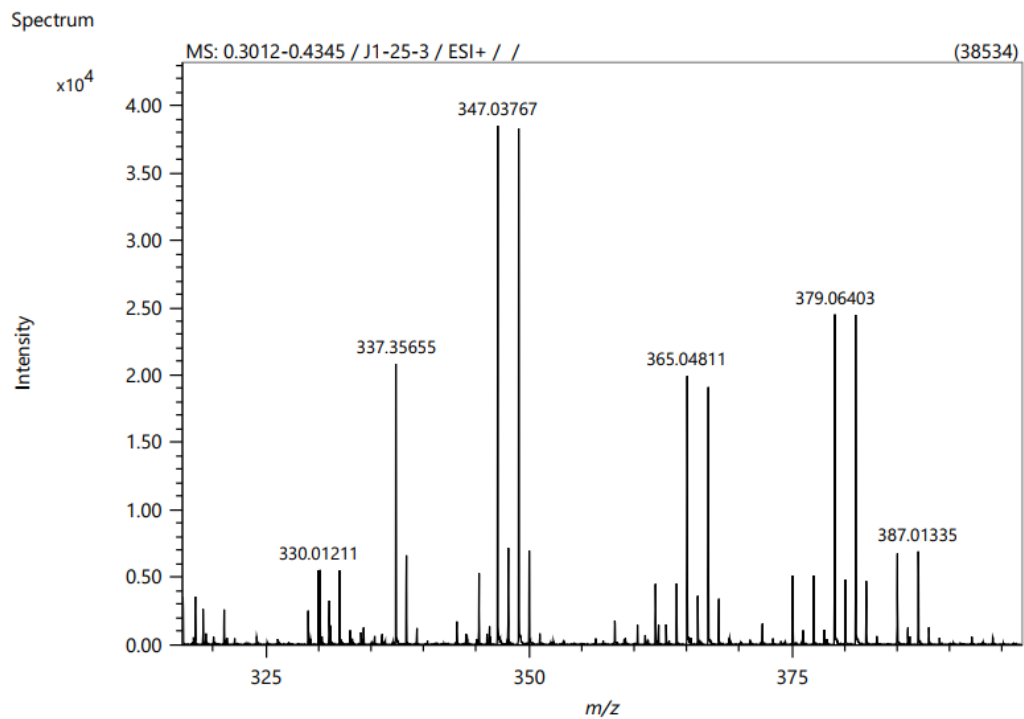
Molecular Weight: 375.2260

m/z: 374.0378 (100.0%), 376.0358 (97.3%), 377.0391 (16.8%), 375.0412 (16.2%), 375.0349 (1.5%), 377.0328 (1.4%), 378.0425 (1.2%), 375.0412 (1.1%), 376.0445 (1.1%)

Elemental Analysis: C, 51.22; H, 4.03; Br, 21.29; N, 14.93; O, 8.53

HRMS (ESI, m/z) calcd for  $C_{16}H_{15}BrN_4O_2$   $[M-N_2+H]^+$  347.03897, found 347.03795.





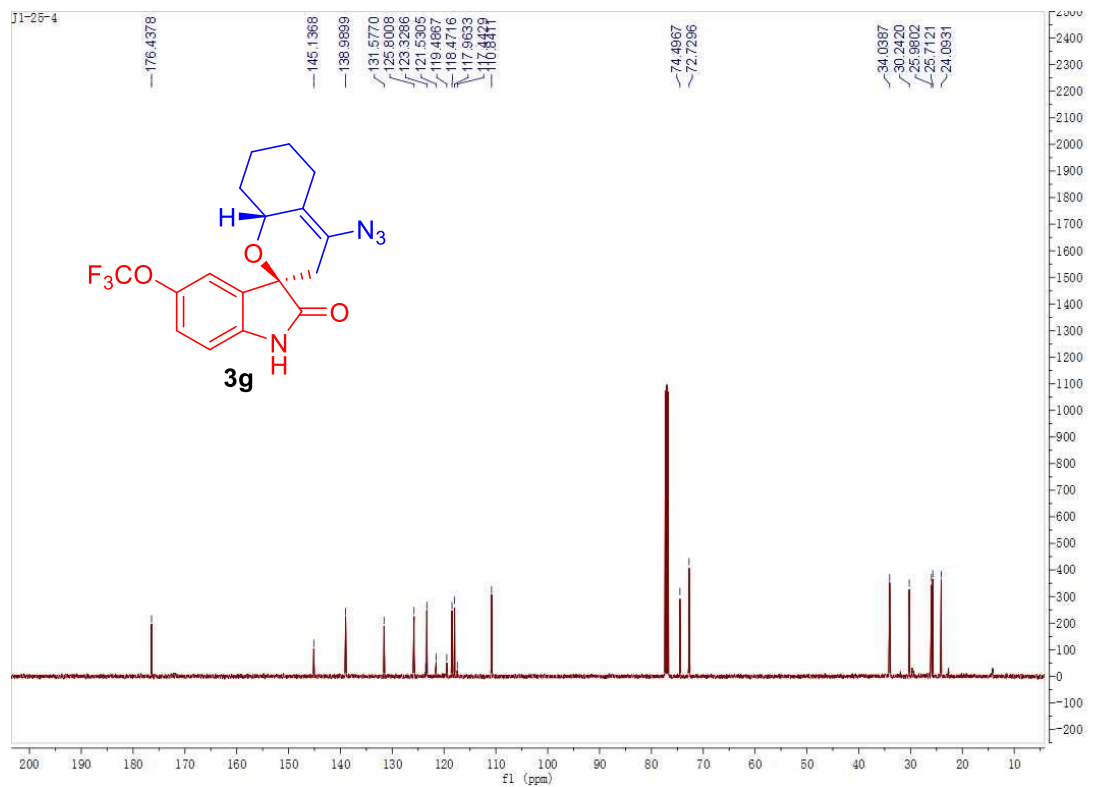
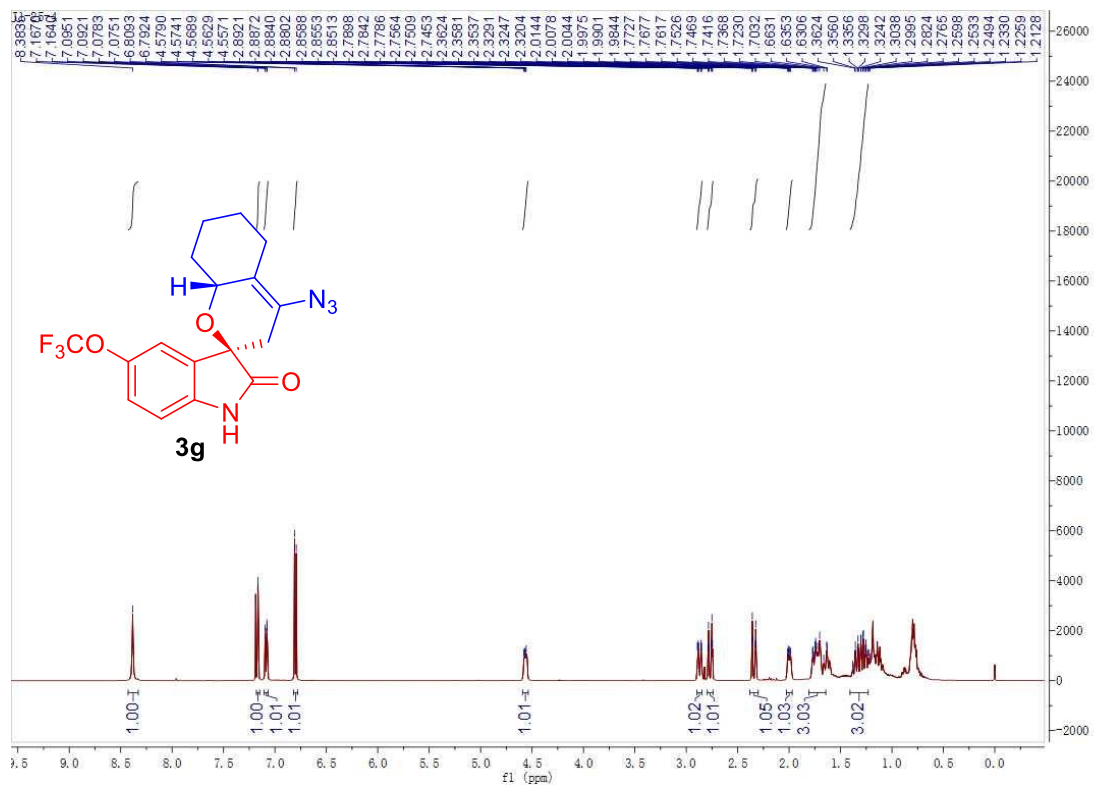
Exact Mass: 374.0378

Molecular Weight: 375.2260

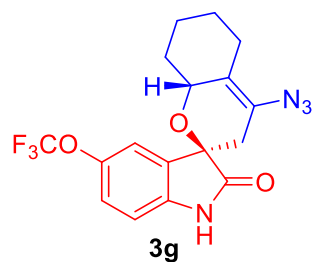
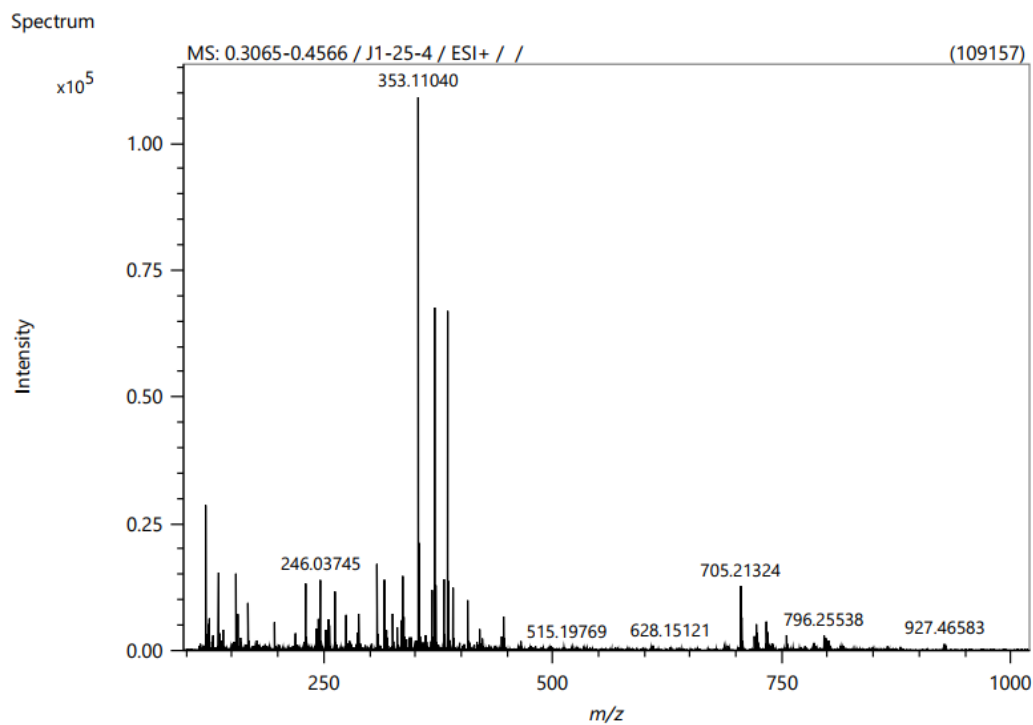
$m/z$ : 374.0378 (100.0%), 376.0358 (97.3%), 377.0391 (16.8%), 375.0412 (16.2%), 375.0349 (1.5%), 377.0328 (1.4%), 378.0425 (1.2%), 375.0412 (1.1%), 376.0445 (1.1%)

Elemental Analysis: C, 51.22; H, 4.03; Br, 21.29; N, 14.93; O, 8.53

HRMS (ESI,  $m/z$ ) calcd for  $C_{16}H_{15}BrN_4O_2 [M-N_2+H]^+$  347.03897, found 347.03767.







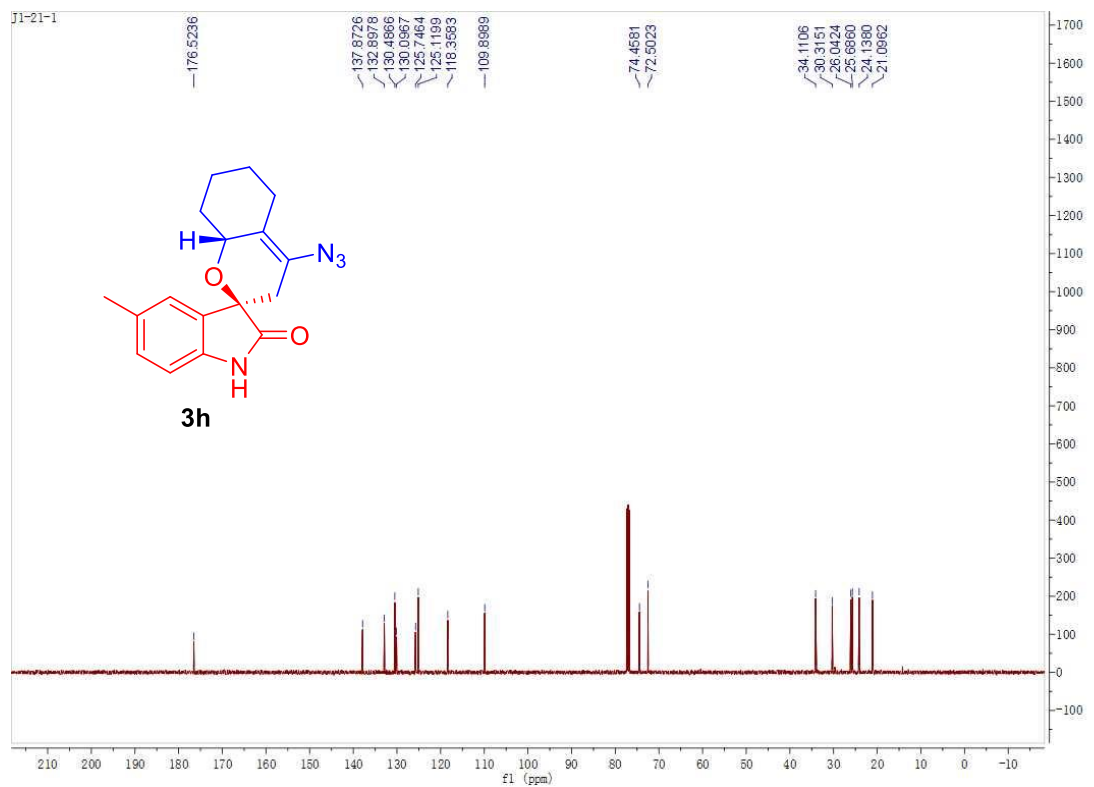
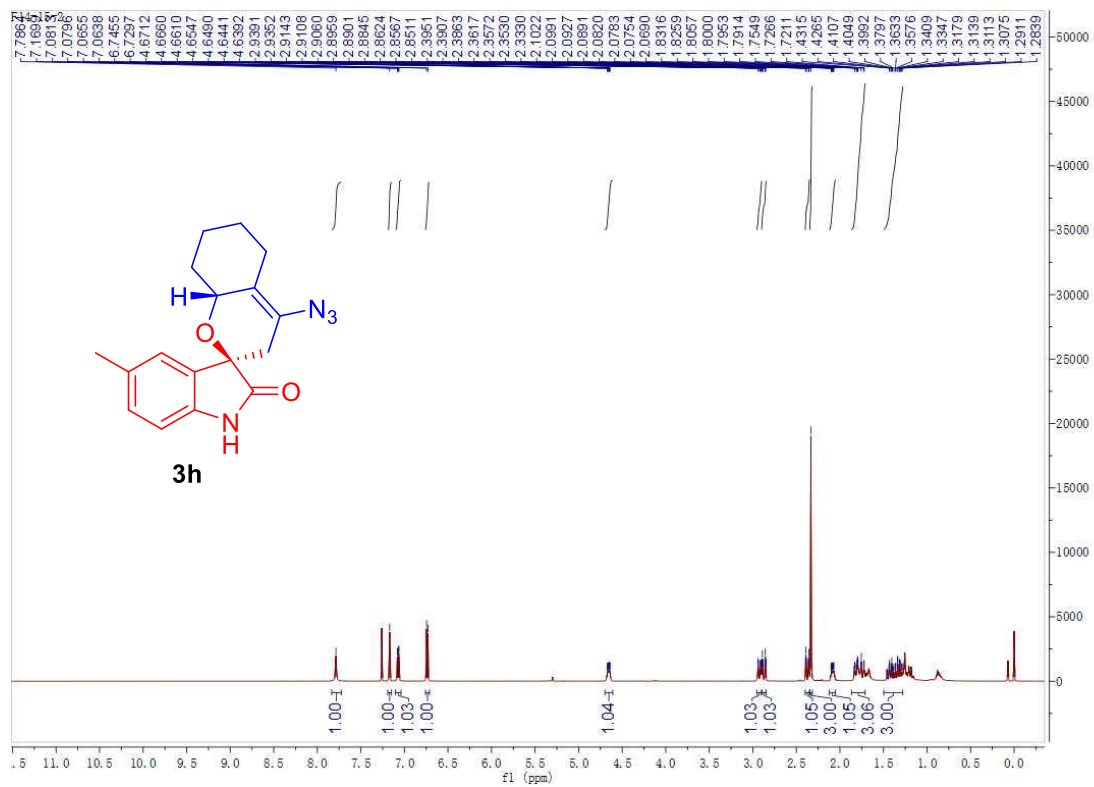
Exact Mass: 380.1096

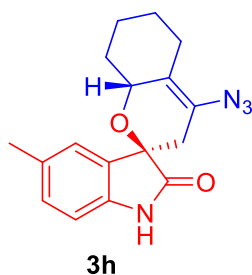
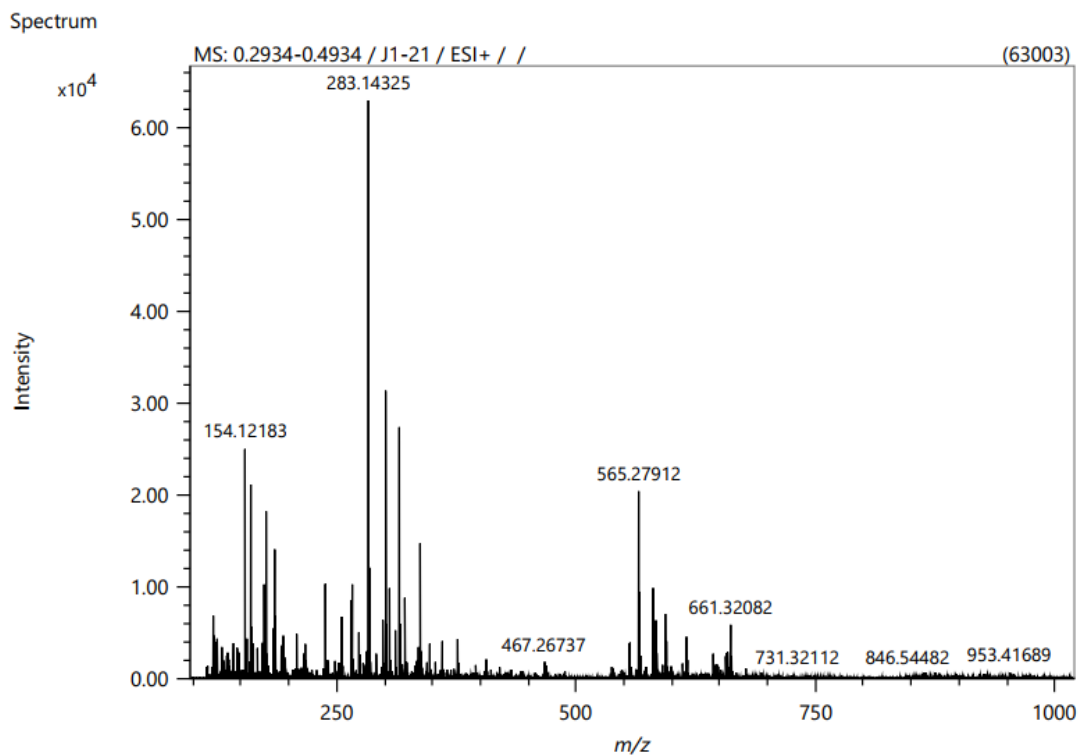
Molecular Weight: 380.3272

m/z: 380.1096 (100.0%), 381.1130 (18.4%), 382.1163 (1.6%), 381.1067 (1.5%)

Elemental Analysis: C, 53.69; H, 3.98; F, 14.99; N, 14.73; O, 12.62

HRMS (ESI, m/z) calcd for  $C_{17}H_{15}F_3N_4O_3$   $[M-N_2+H]^+$  353.11075, found 353.11040.





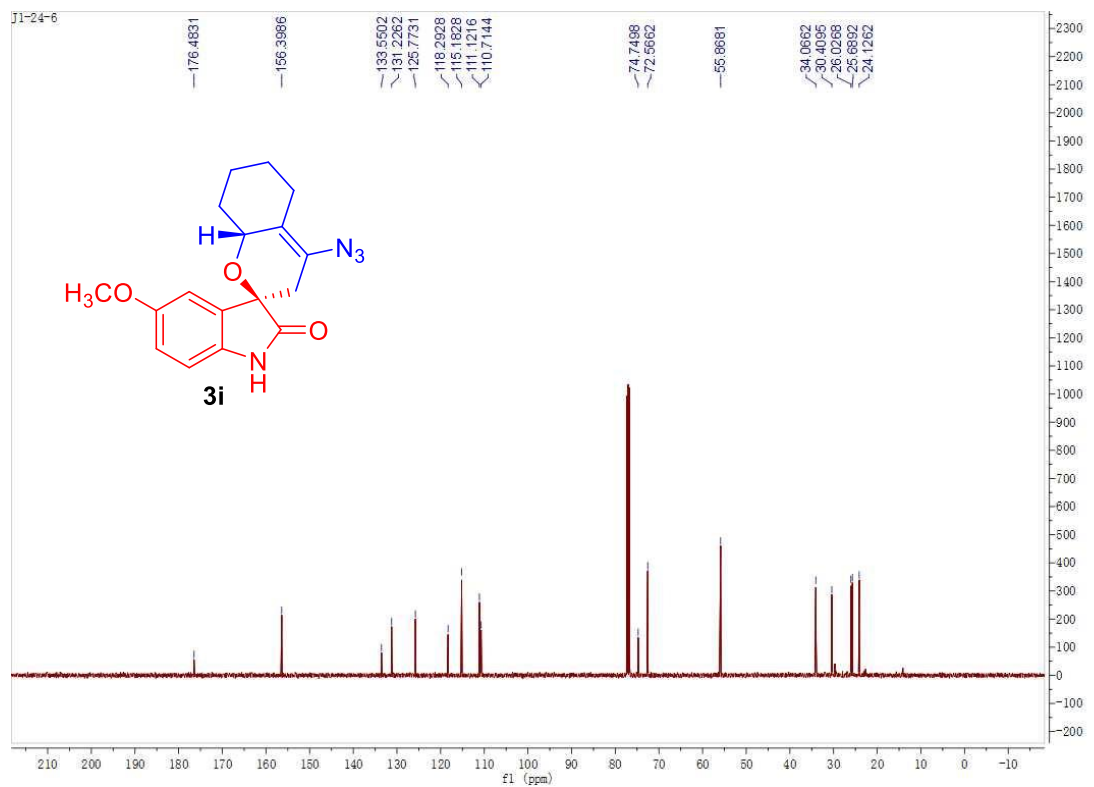
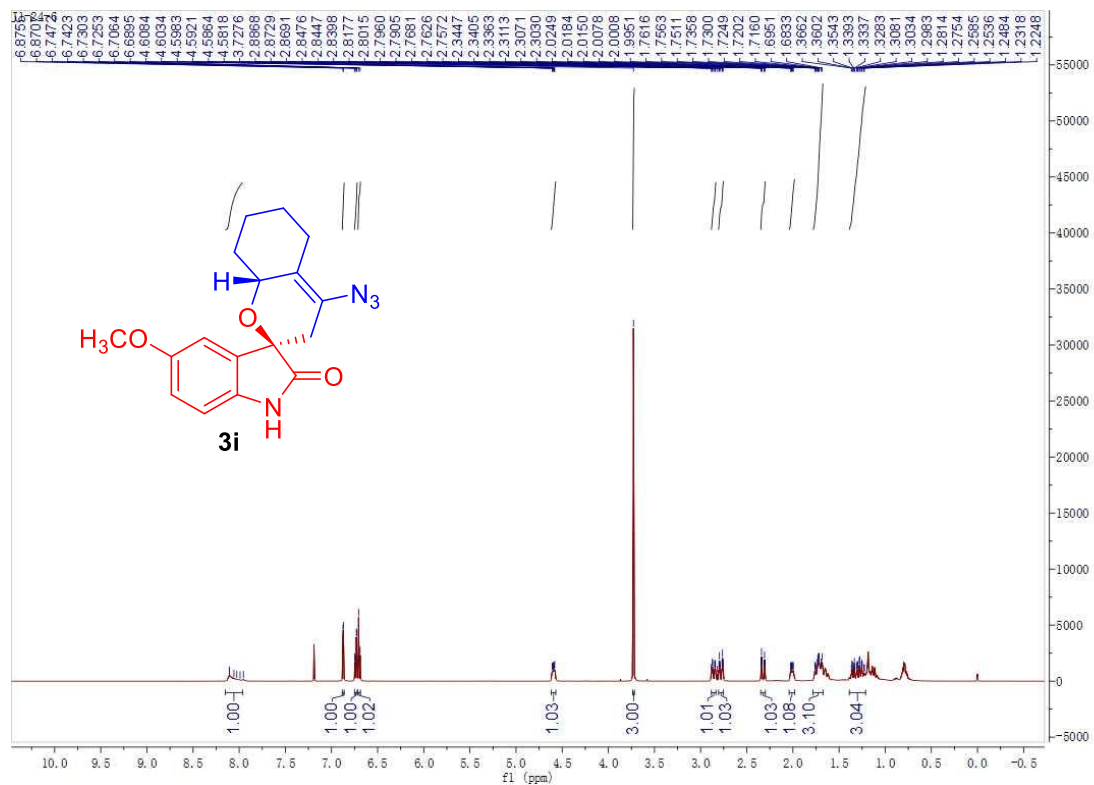
Exact Mass: 310.1430

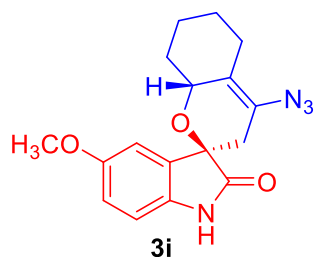
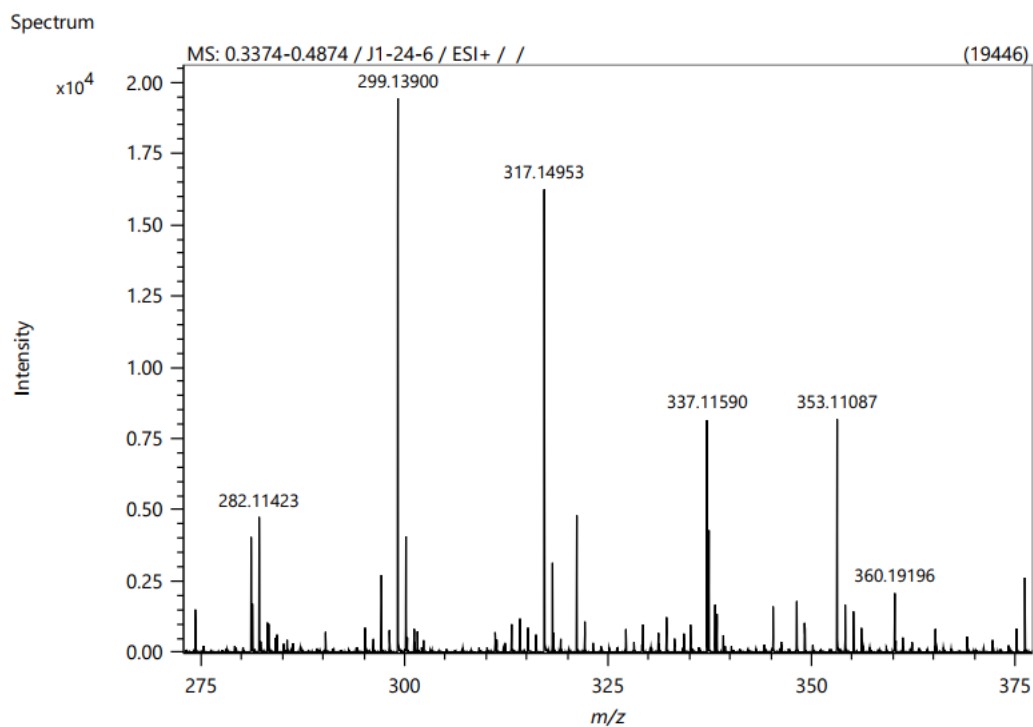
Molecular Weight: 310.3570

m/z: 310.1430 (100.0%), 311.1463 (18.4%), 312.1497 (1.6%), 311.1400 (1.5%)

Elemental Analysis: C, 65.79; H, 5.85; N, 18.05; O, 10.31

HRMS (ESI, m/z) calcd for  $C_{17}H_{18}N_4O_2 [M-N_2+H]^+$  283.14410, found 283.14325.





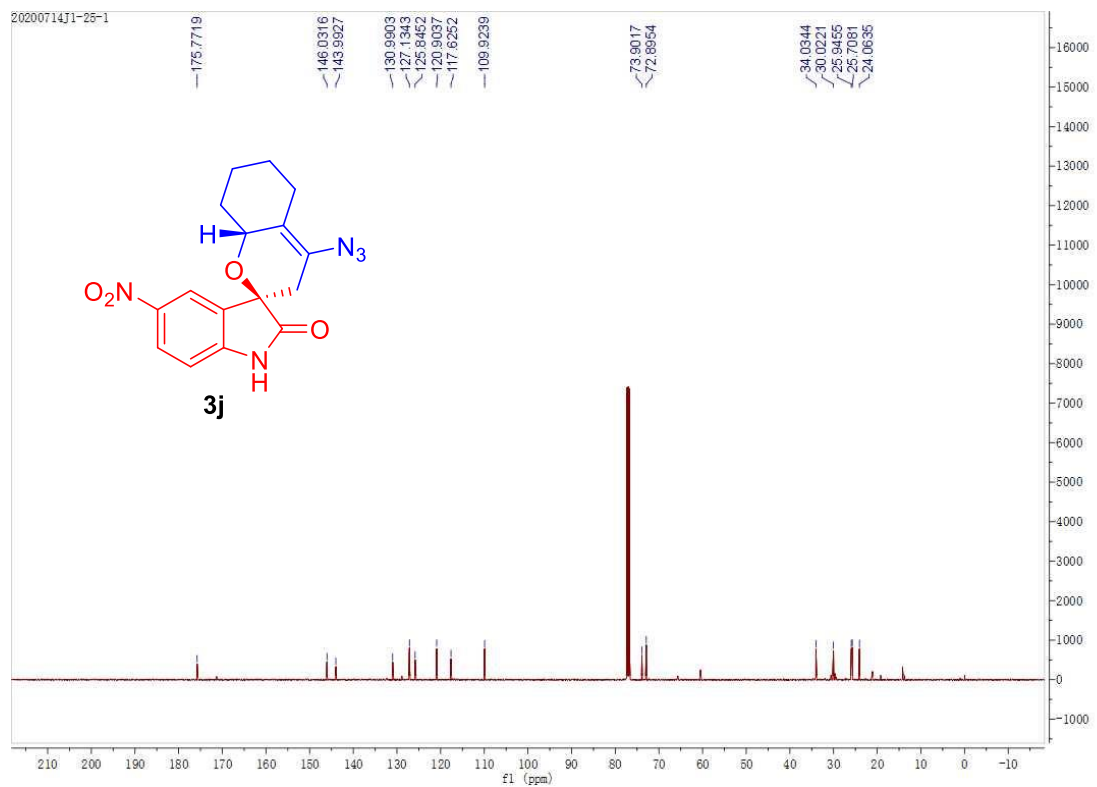
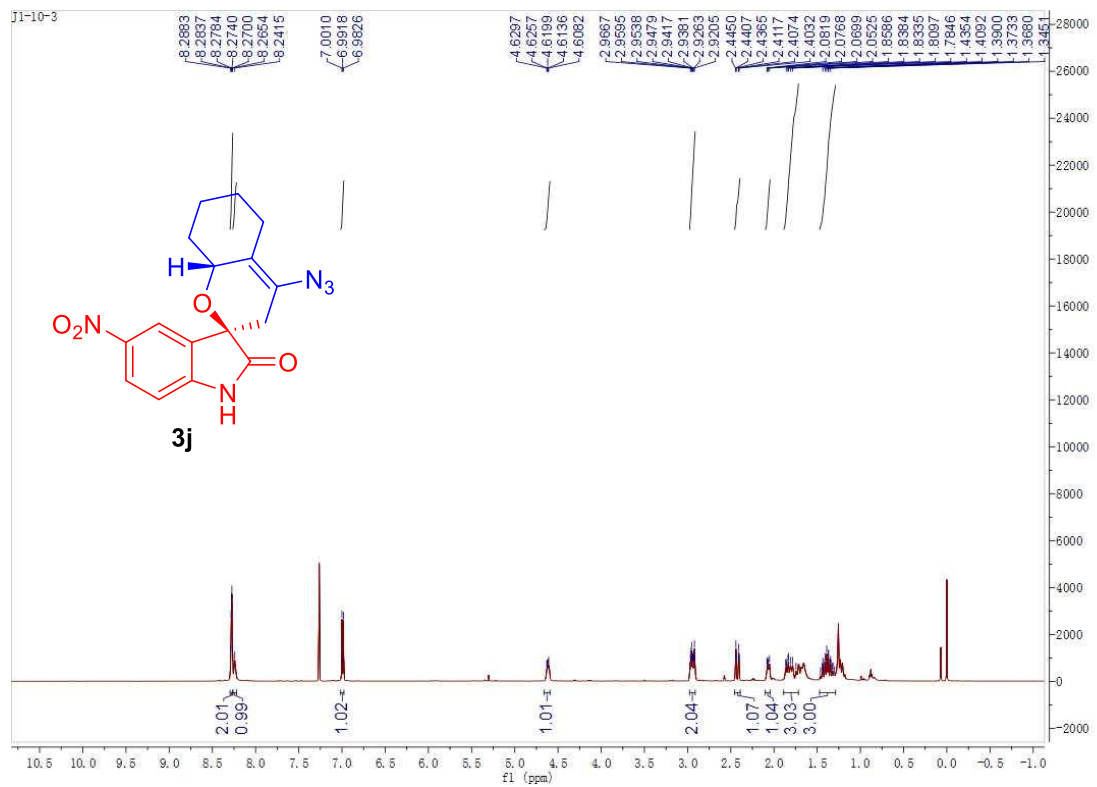
Exact Mass: 326.1379

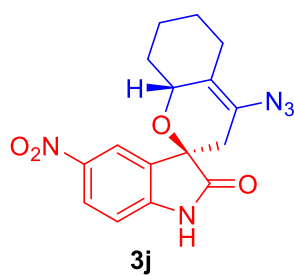
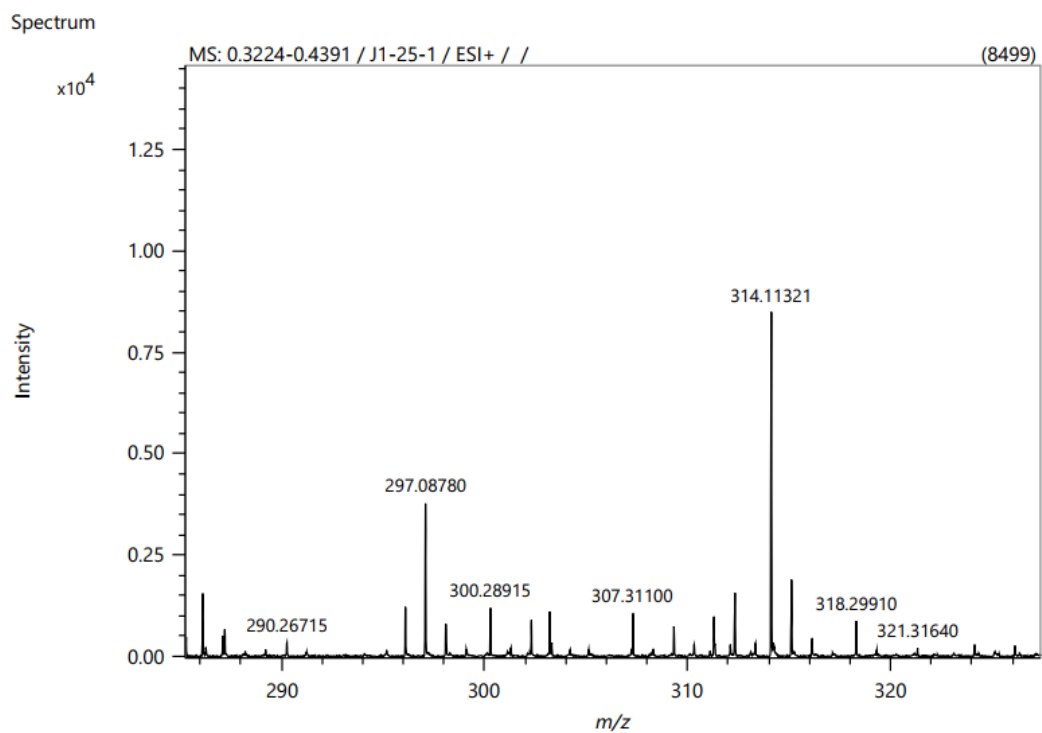
Molecular Weight: 326.3560

m/z: 326.1379 (100.0%), 327.1412 (18.4%), 328.1446 (1.6%), 327.1349 (1.5%)

Elemental Analysis: C, 62.57; H, 5.56; N, 17.17; O, 14.71

HRMS (ESI, m/z) calcd for  $C_{17}H_{18}N_4O_3 [M-N_2+H]^+$  299.13902, found 299.13900.





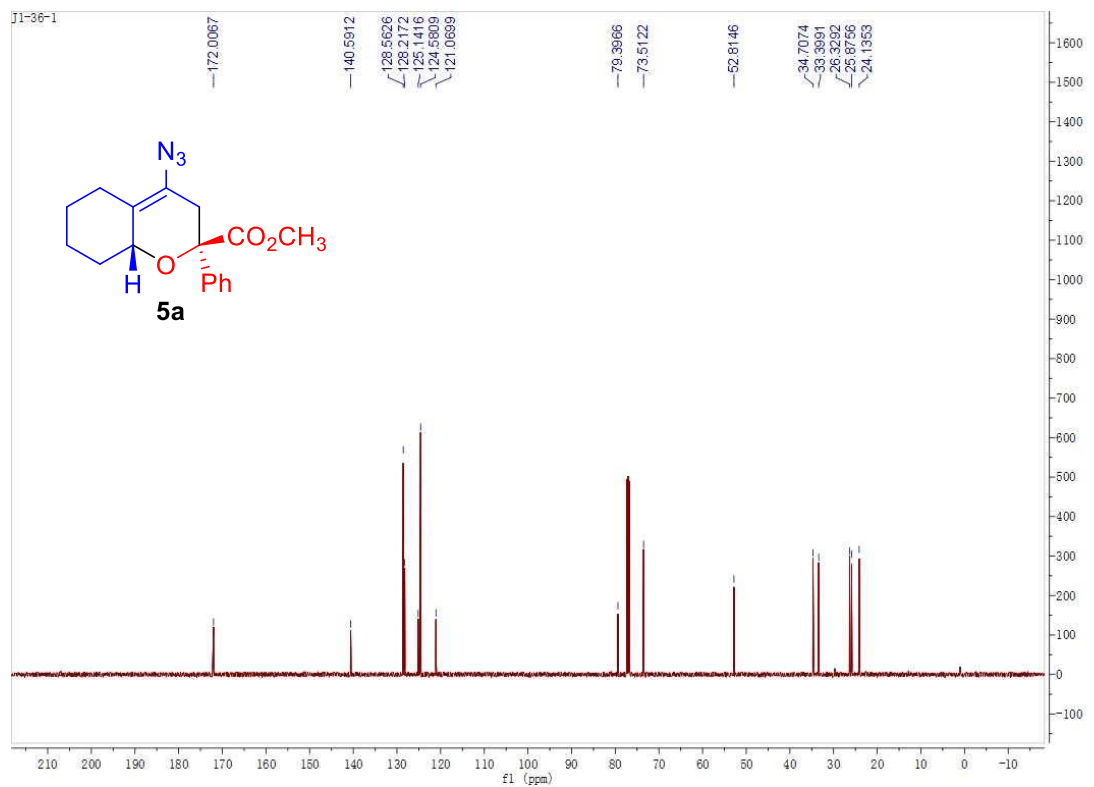
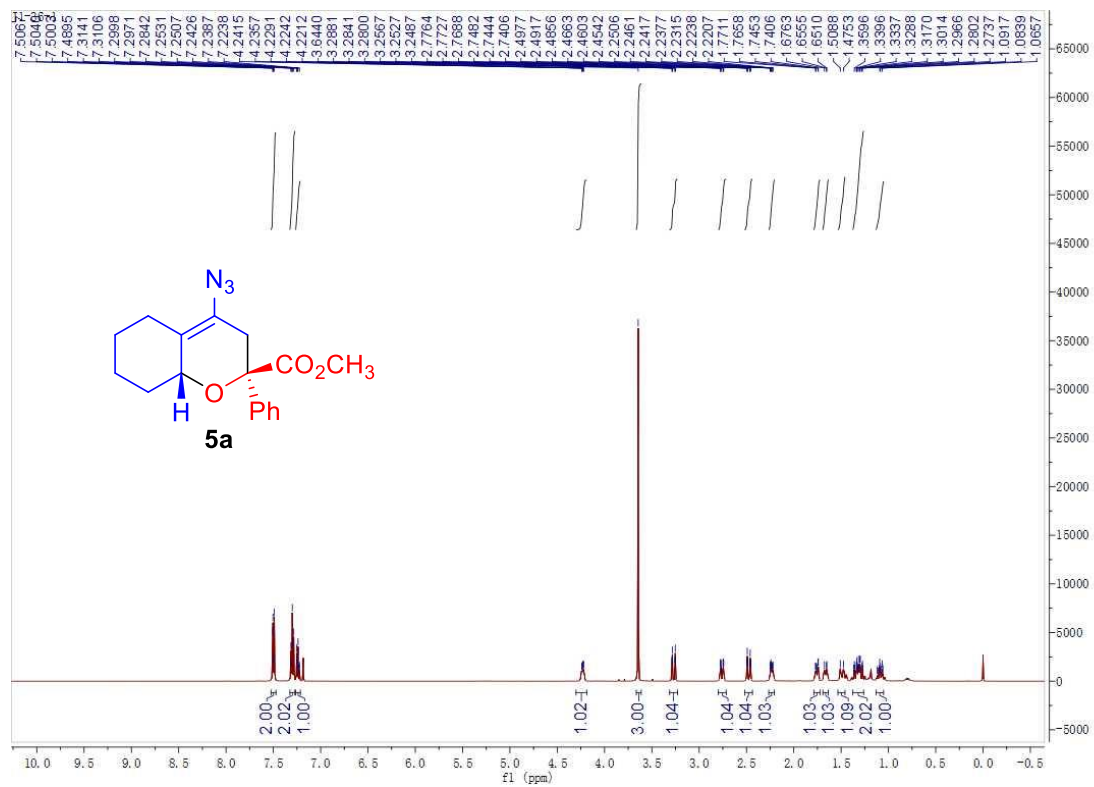
Exact Mass: 341.1124

Molecular Weight: 341.3270

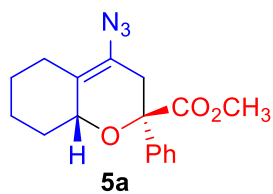
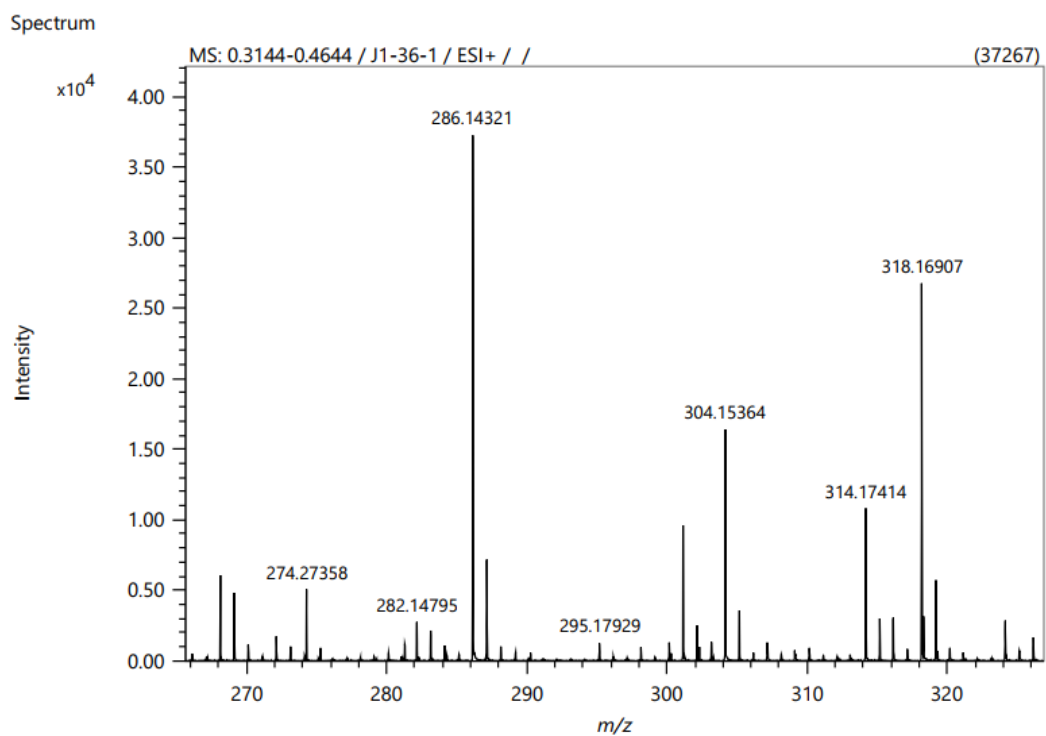
m/z: 341.1124 (100.0%), 342.1158 (17.3%), 342.1094 (1.8%), 343.1191 (1.4%)

Elemental Analysis: C, 56.30; H, 4.43; N, 20.52; O, 18.75

HRMS (ESI, m/z) calcd for  $C_{16}H_{15}N_5O_4$   $[M-N_2+H]^+$  314.11353, found 314.11321.







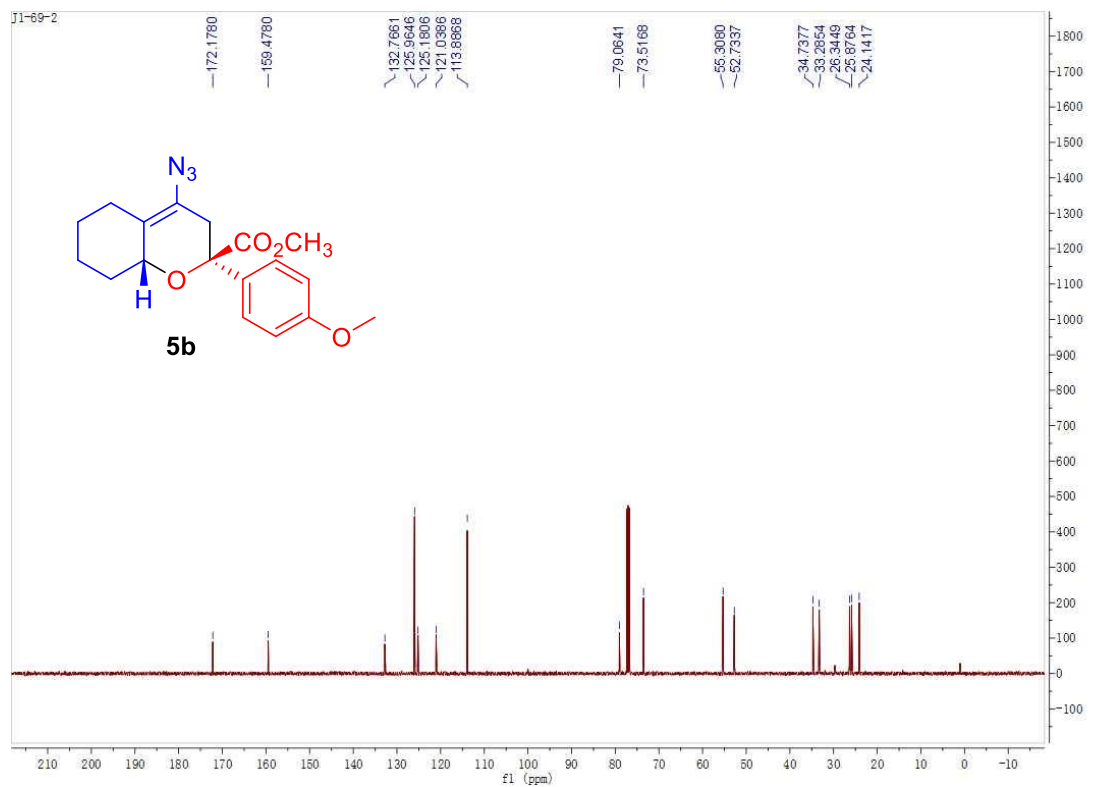
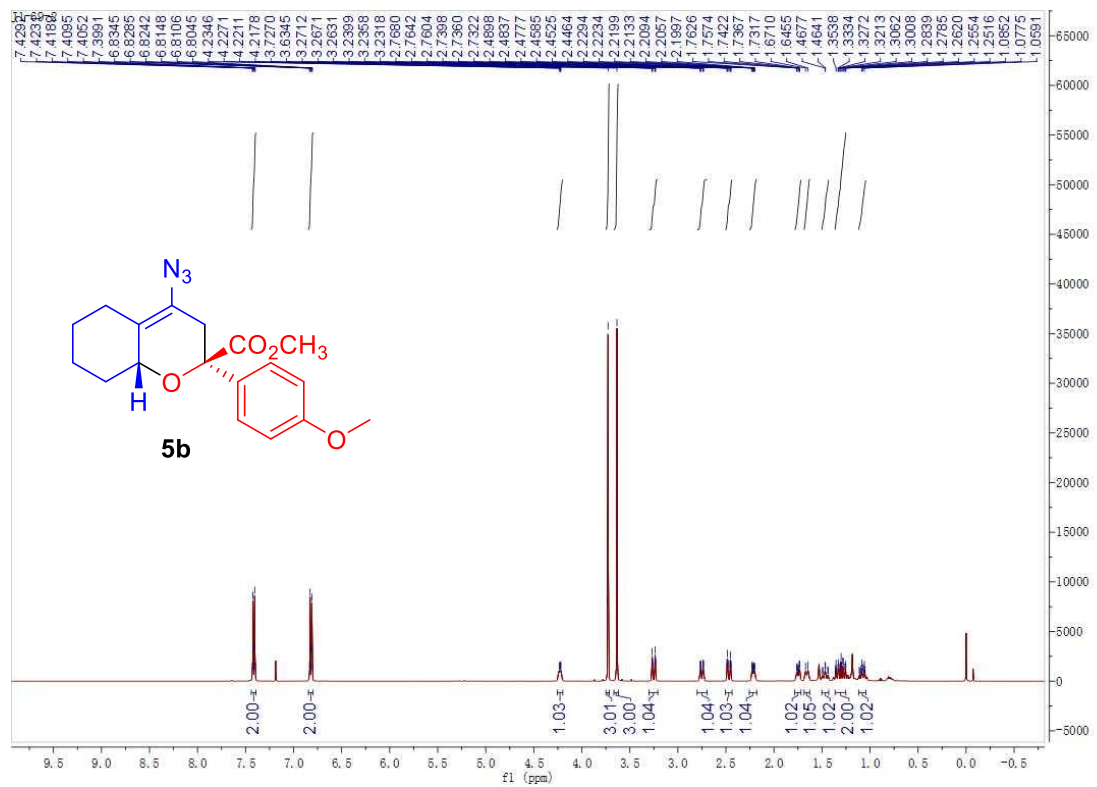
Exact Mass: 313.1426

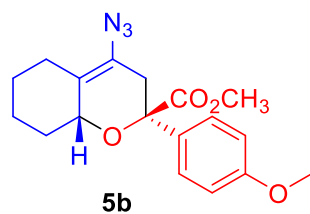
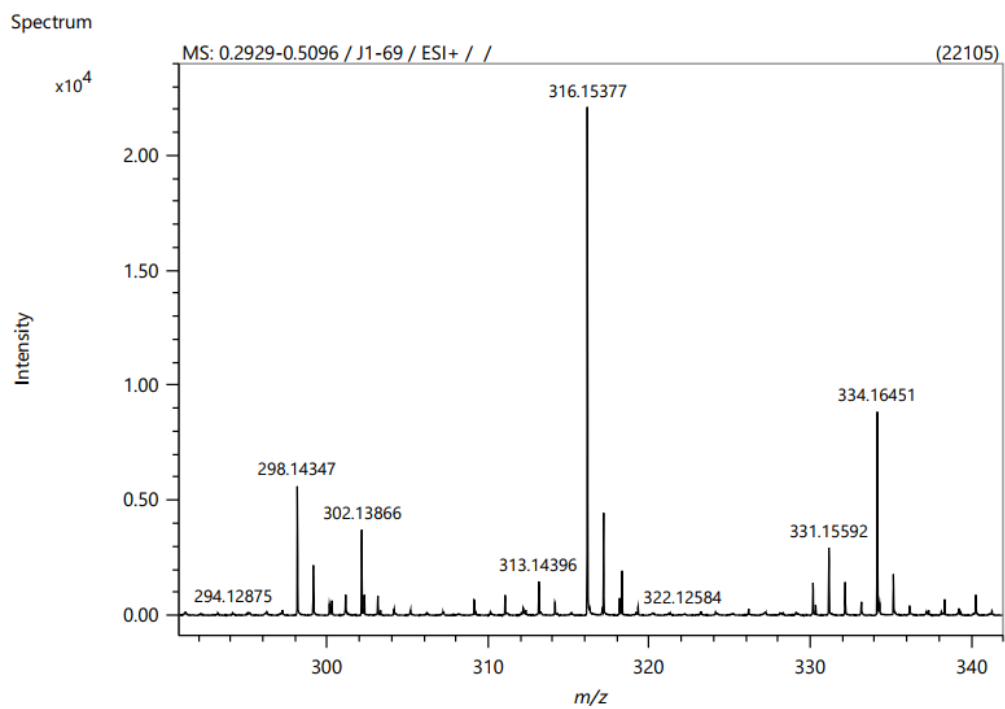
Molecular Weight: 313.3570

$m/z$ : 313.1426 (100.0%), 314.1460 (18.4%), 315.1494 (1.6%), 314.1397 (1.1%)

Elemental Analysis: C, 65.16; H, 6.11; N, 13.41; O, 15.32

HRMS (ESI,  $m/z$ ) calcd for  $C_{17}H_{19}N_3O_3$   $[M-N_2+H]^+$  286.14377, found 286.14321.





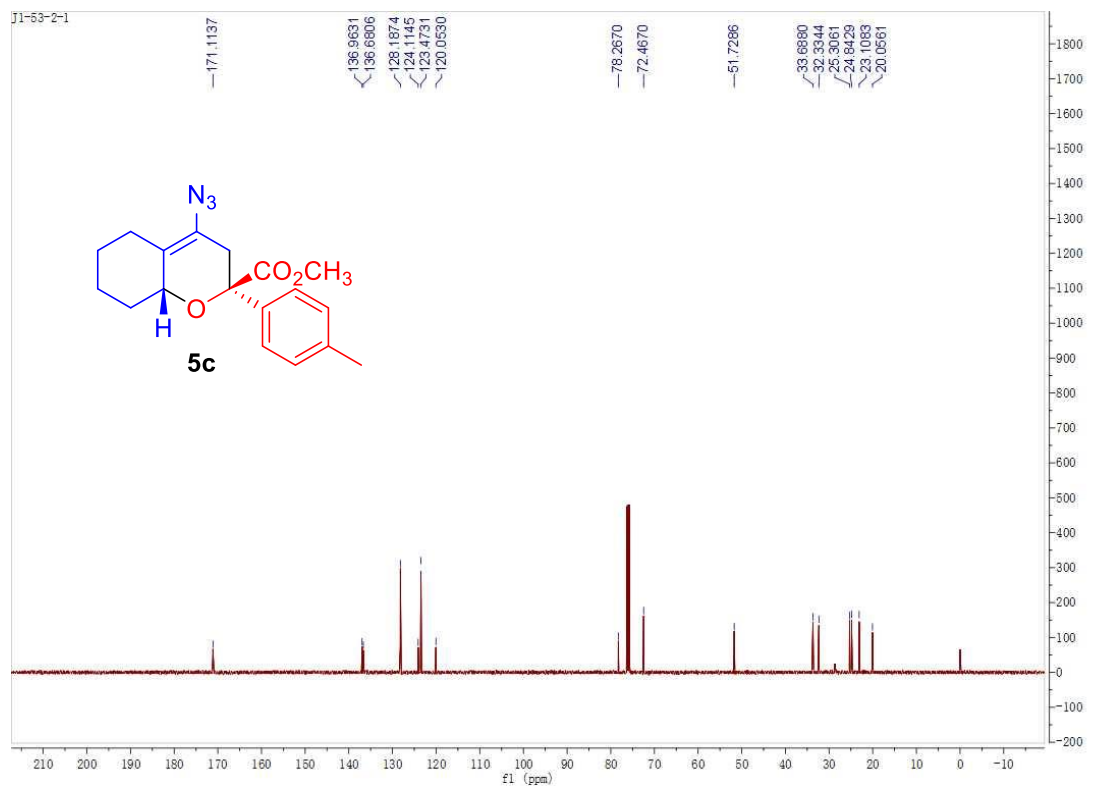
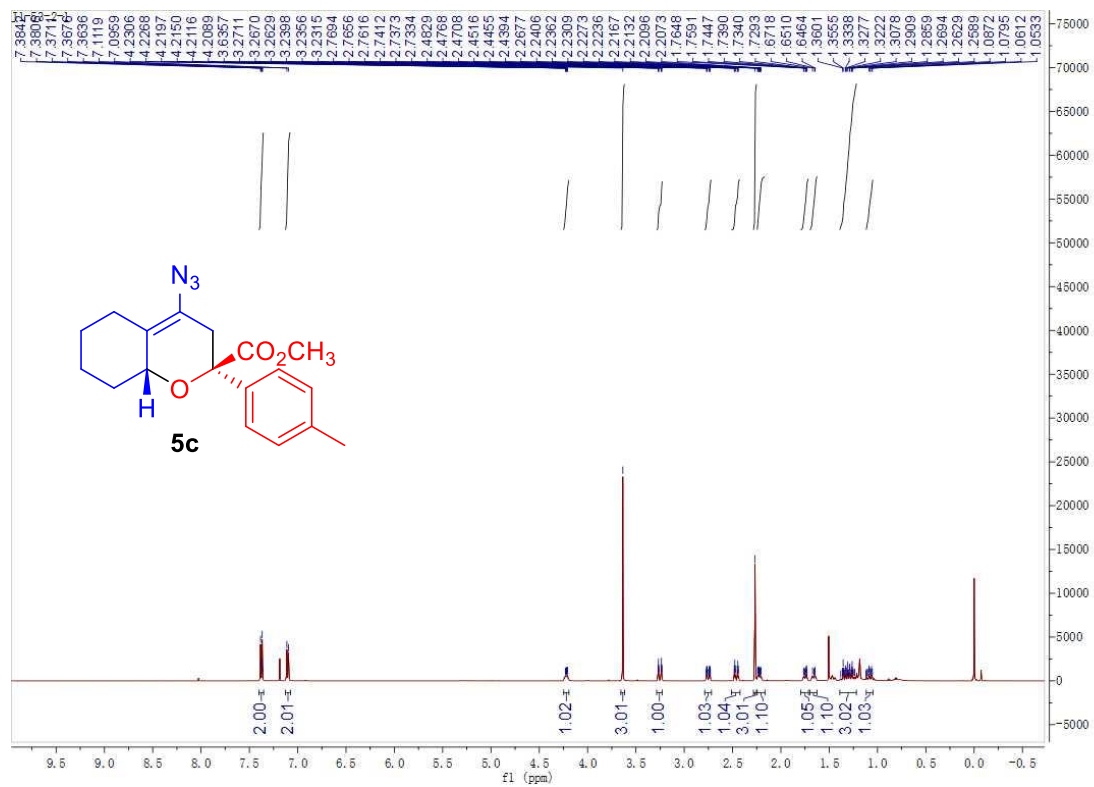
Exact Mass: 343.1532

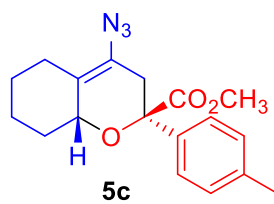
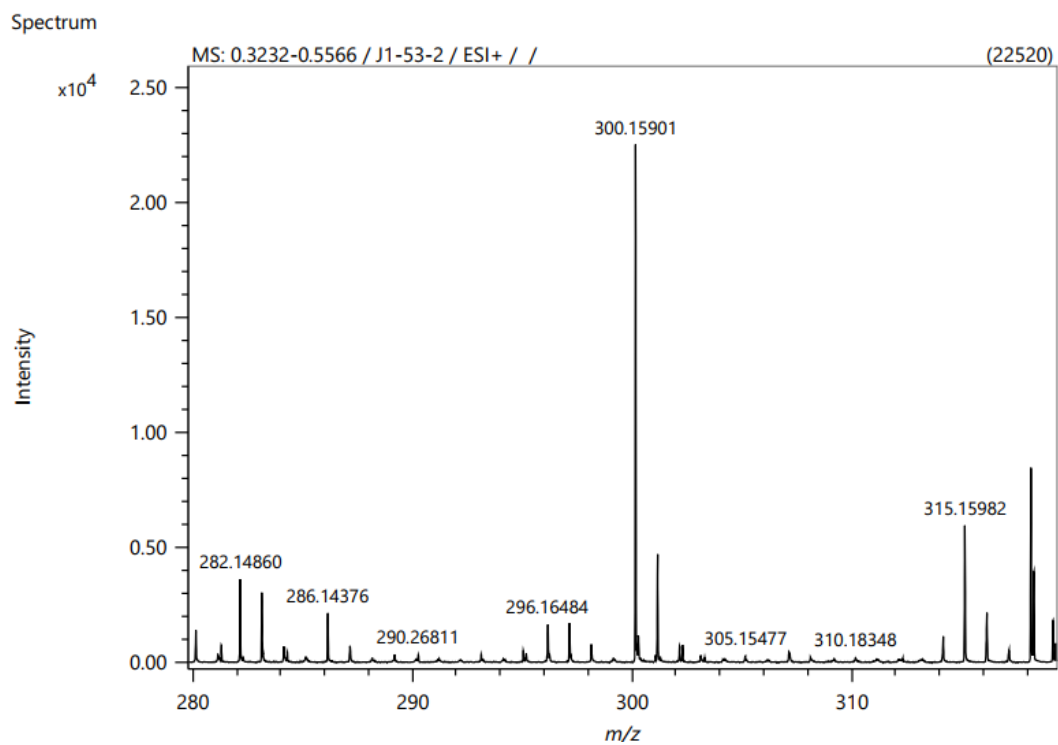
Molecular Weight: 343.3830

m/z: 343.1532 (100.0%), 344.1566 (19.5%), 345.1599 (1.8%), 344.1502 (1.1%)

Elemental Analysis: C, 62.96; H, 6.16; N, 12.24; O, 18.64

HRMS (ESI, m/z) calcd for  $C_{18}H_{21}N_3O_4$   $[M-N_2+H]^+$  316.15433, found 316.15377.





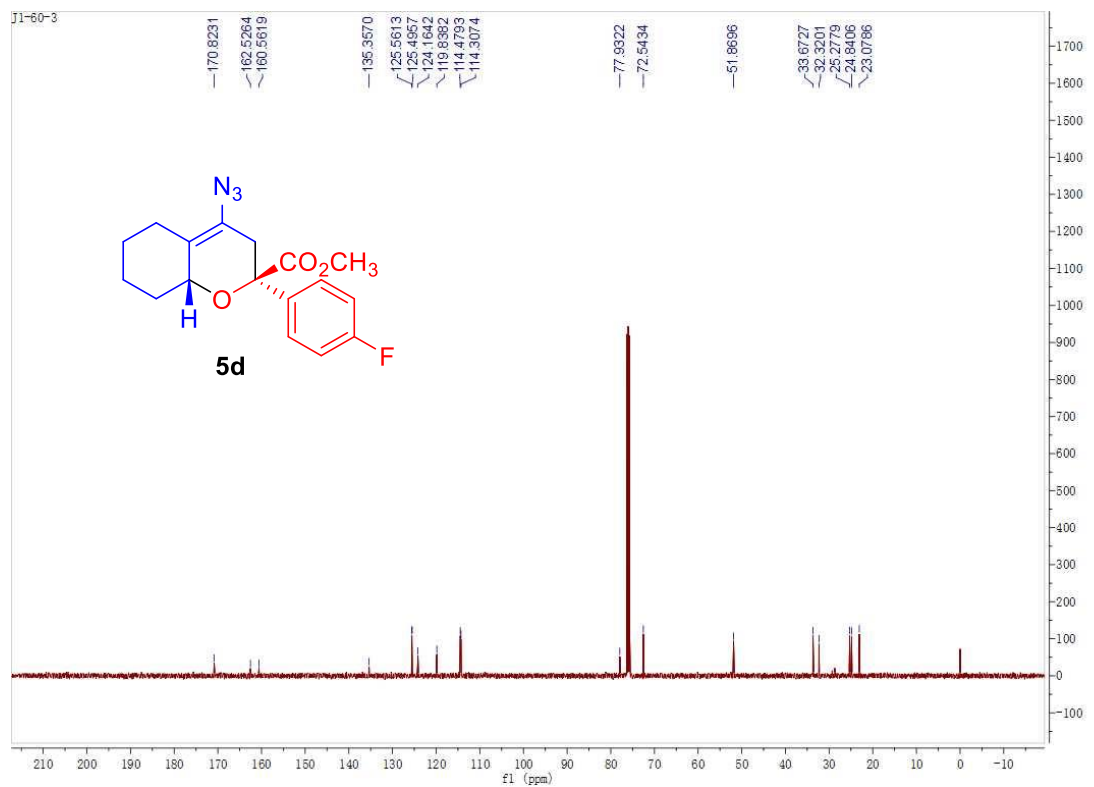
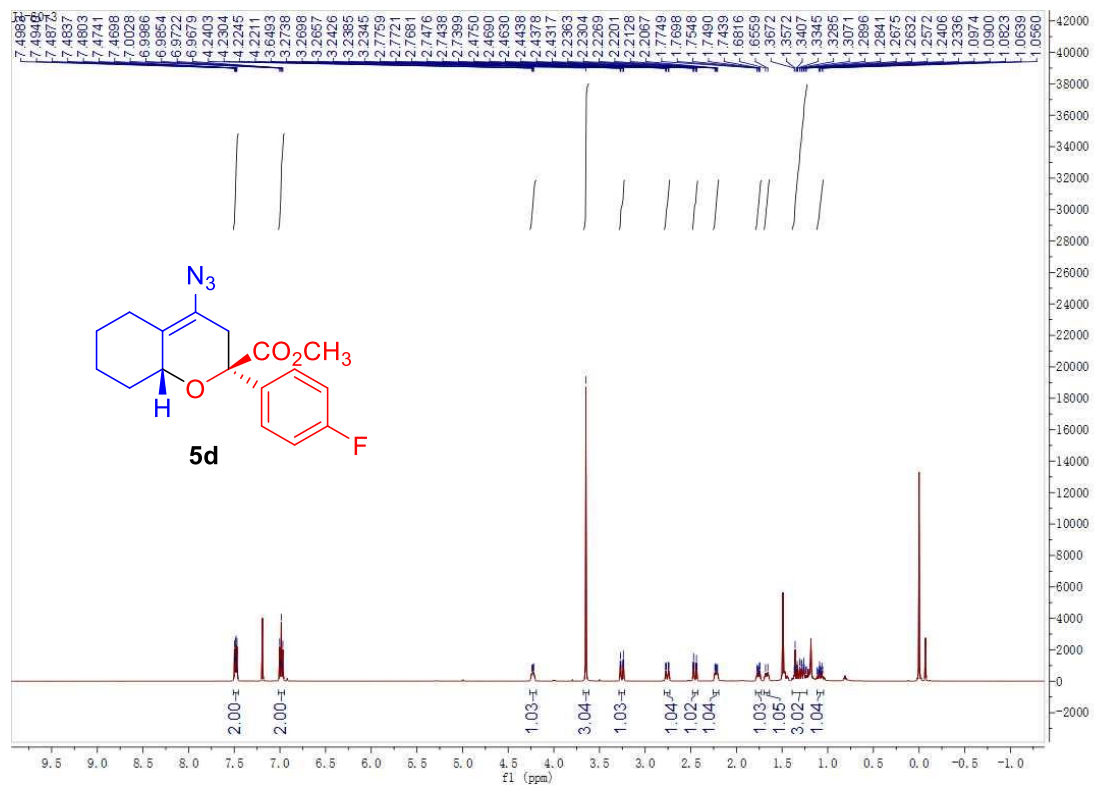
Exact Mass: 327.1583

Molecular Weight: 327.3840

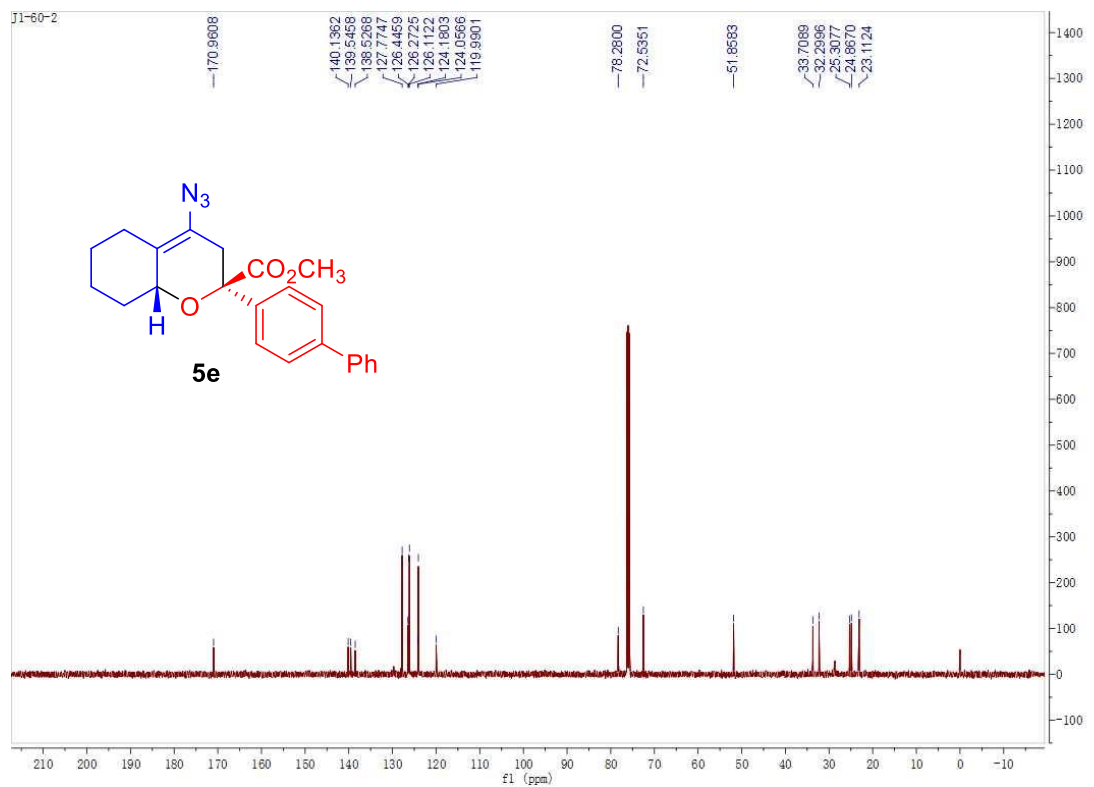
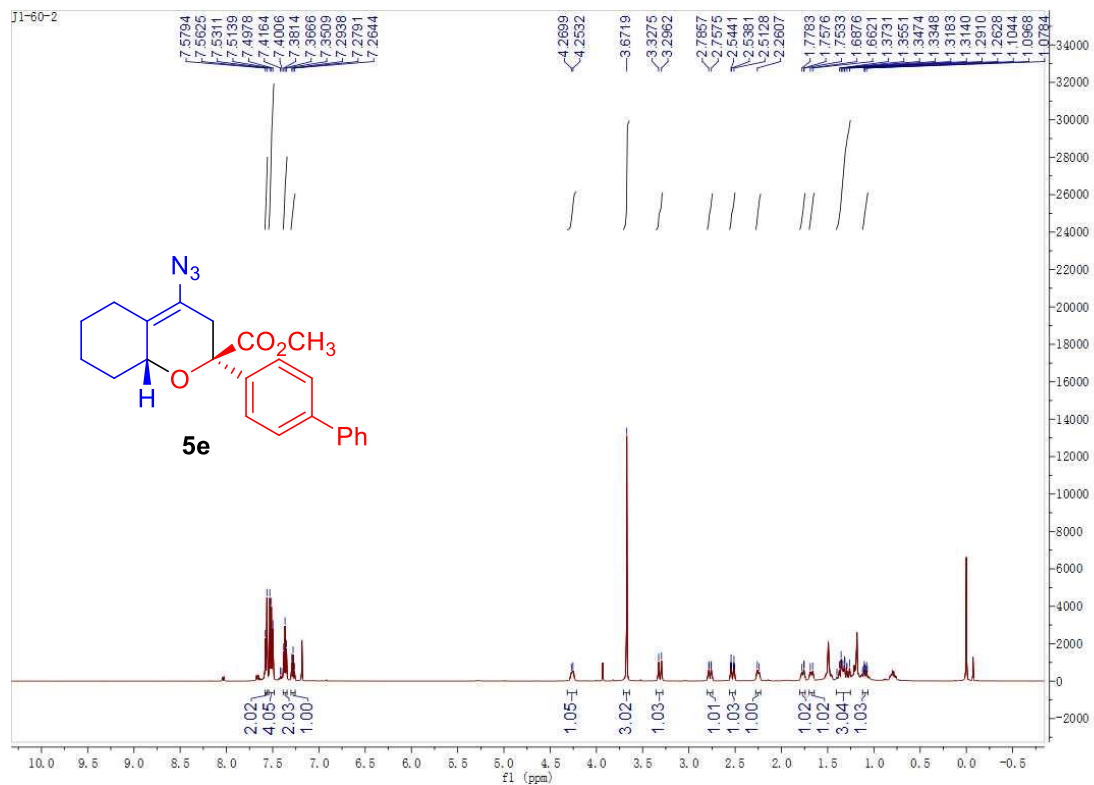
$m/z$ : 327.1583 (100.0%), 328.1616 (19.5%), 329.1650 (1.8%), 328.1553 (1.1%)

Elemental Analysis: C, 66.04; H, 6.47; N, 12.84; O, 14.66

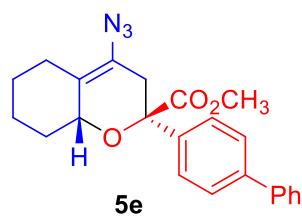
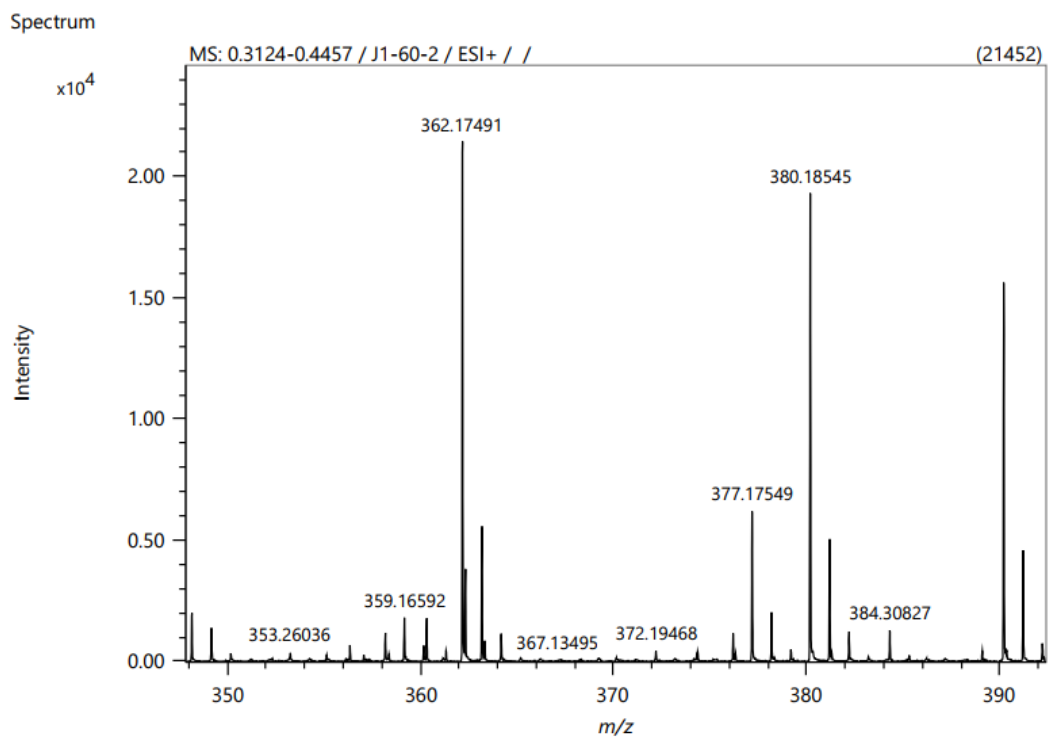
HRMS (ESI,  $m/z$ ) calcd for  $C_{18}H_{21}N_3O_3$   $[M-N_2+H]^+$  300.15942, found 300.15901.











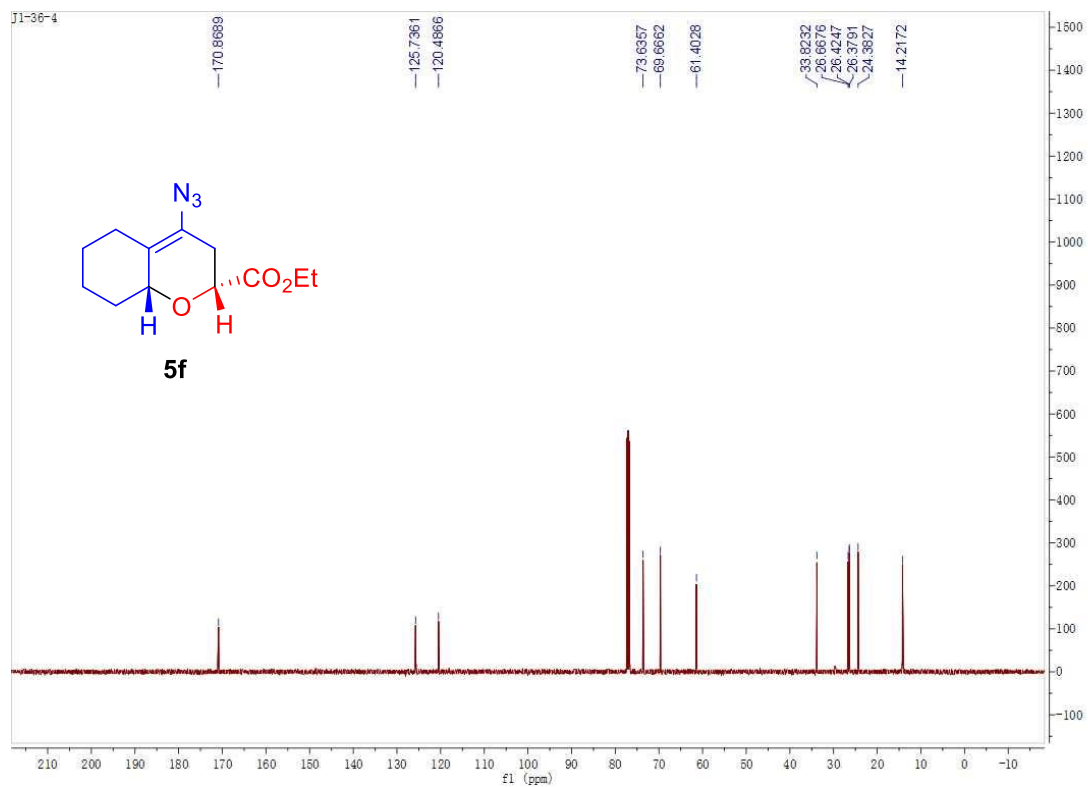
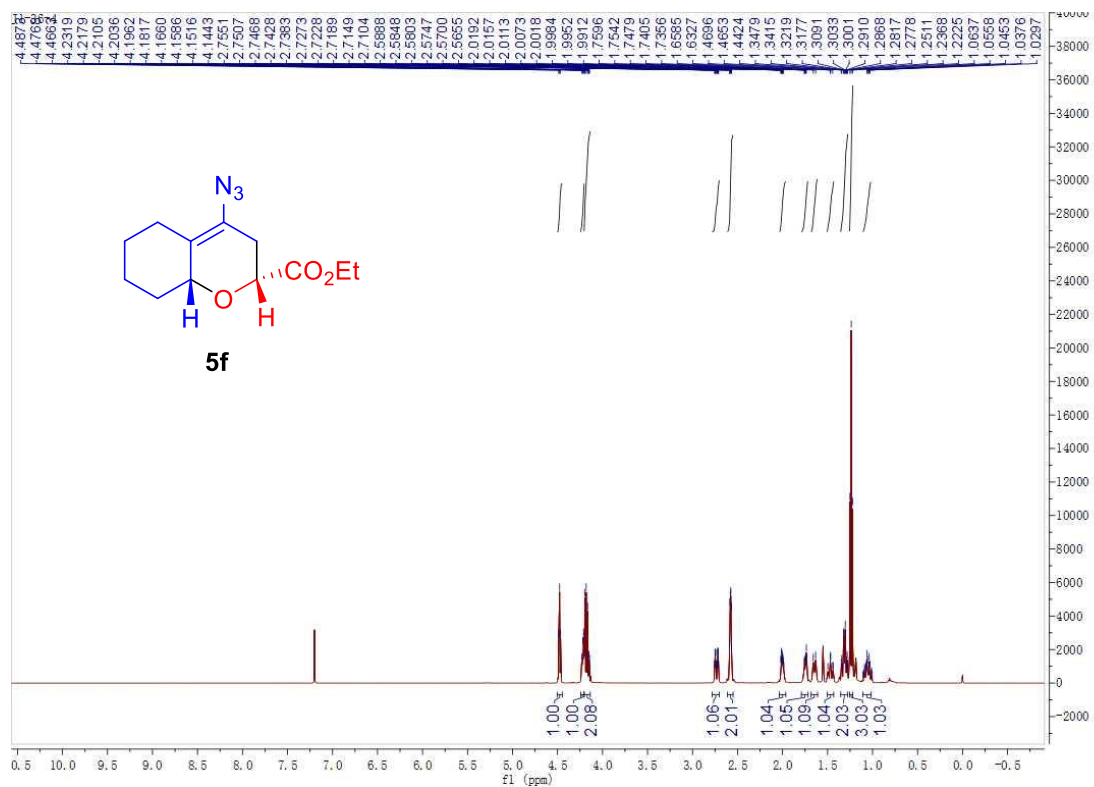
Exact Mass: 389.1739

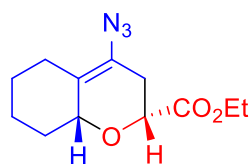
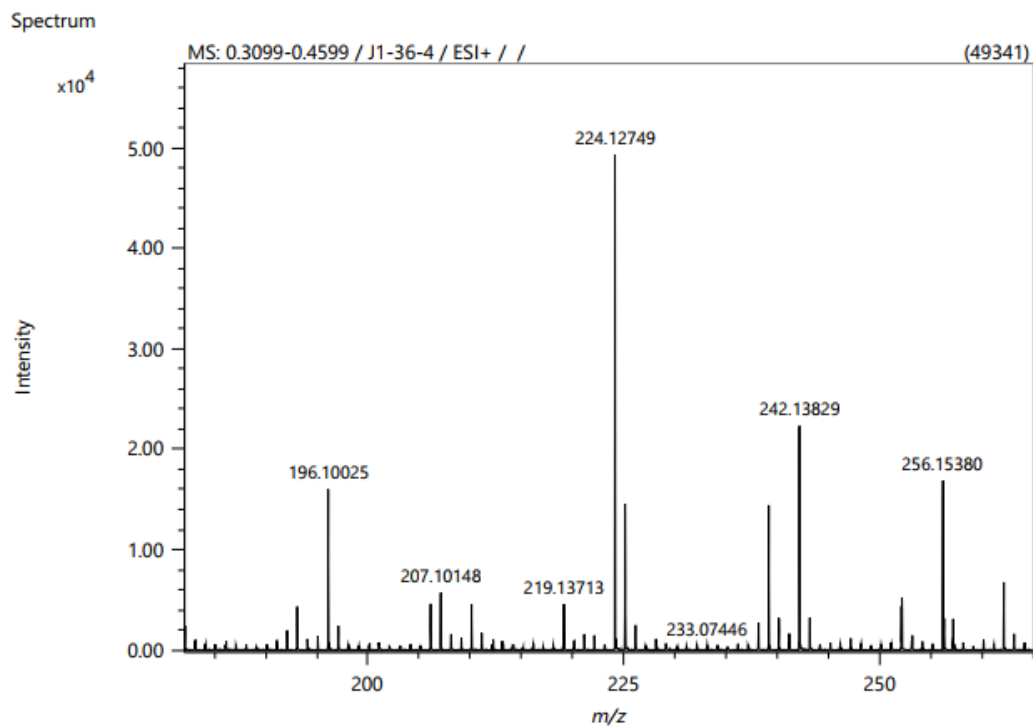
Molecular Weight: 389.4550

m/z: 389.1739 (100.0%), 390.1773 (24.9%), 391.1807 (2.7%), 390.1710 (1.1%)

Elemental Analysis: C, 70.93; H, 5.95; N, 10.79; O, 12.32

HRMS (ESI, m/z) calcd for  $C_{23}H_{23}N_3O_3$   $[M-N_2+H]^+$  362.17507, found 362.17491.





**5f**

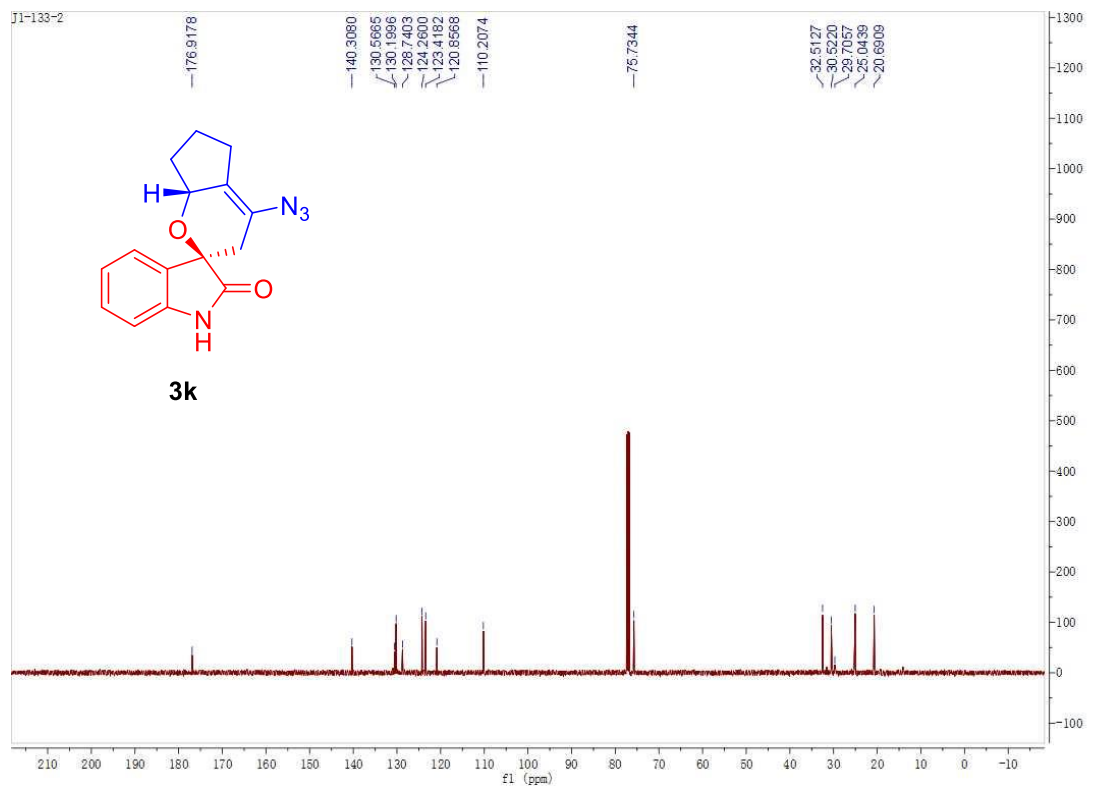
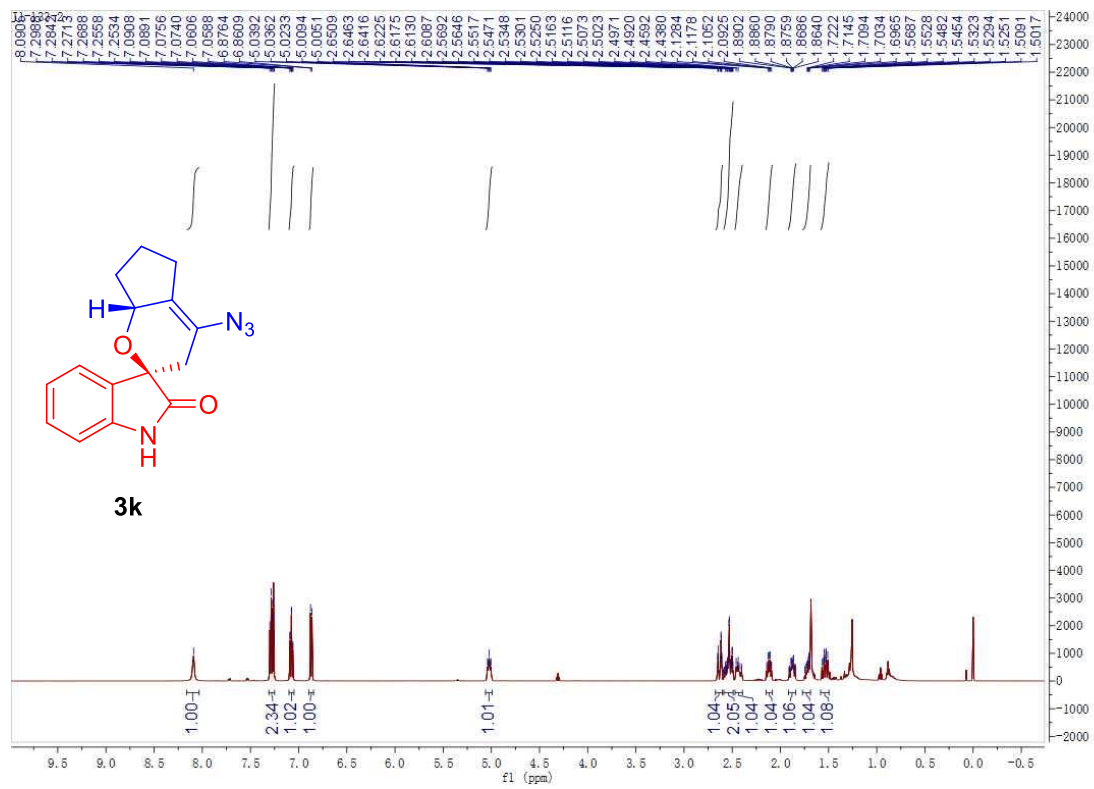
Exact Mass: 251.1270

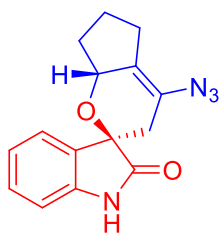
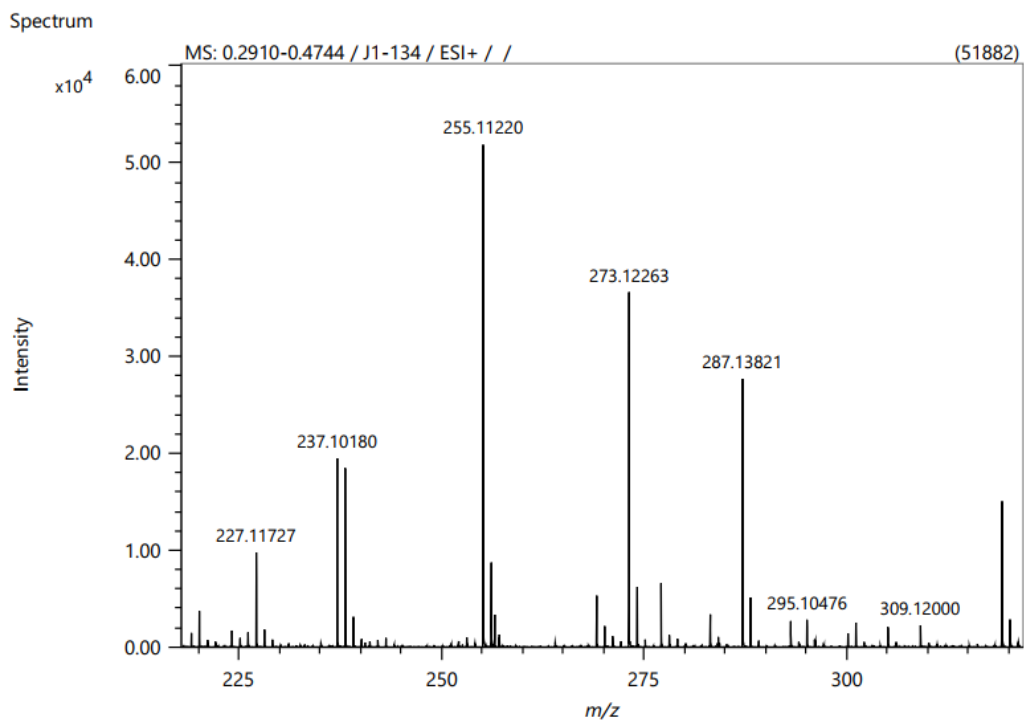
Molecular Weight: 251.2860

m/z: 251.1270 (100.0%), 252.1303 (13.0%), 252.1240 (1.1%)

Elemental Analysis: C, 57.36; H, 6.82; N, 16.72; O, 19.10

HRMS (ESI, m/z) calcd for  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3$   $[\text{M}-\text{N}_2+\text{H}]^+$  224.12812, found 224.12749.





**3k**

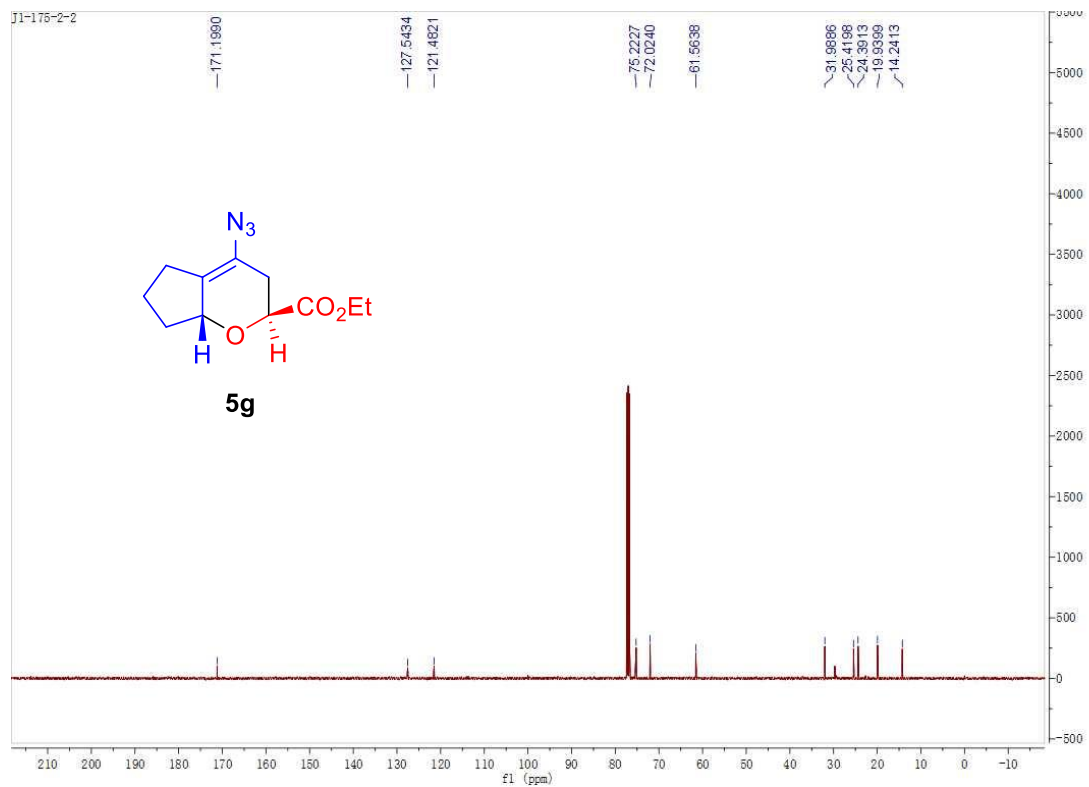
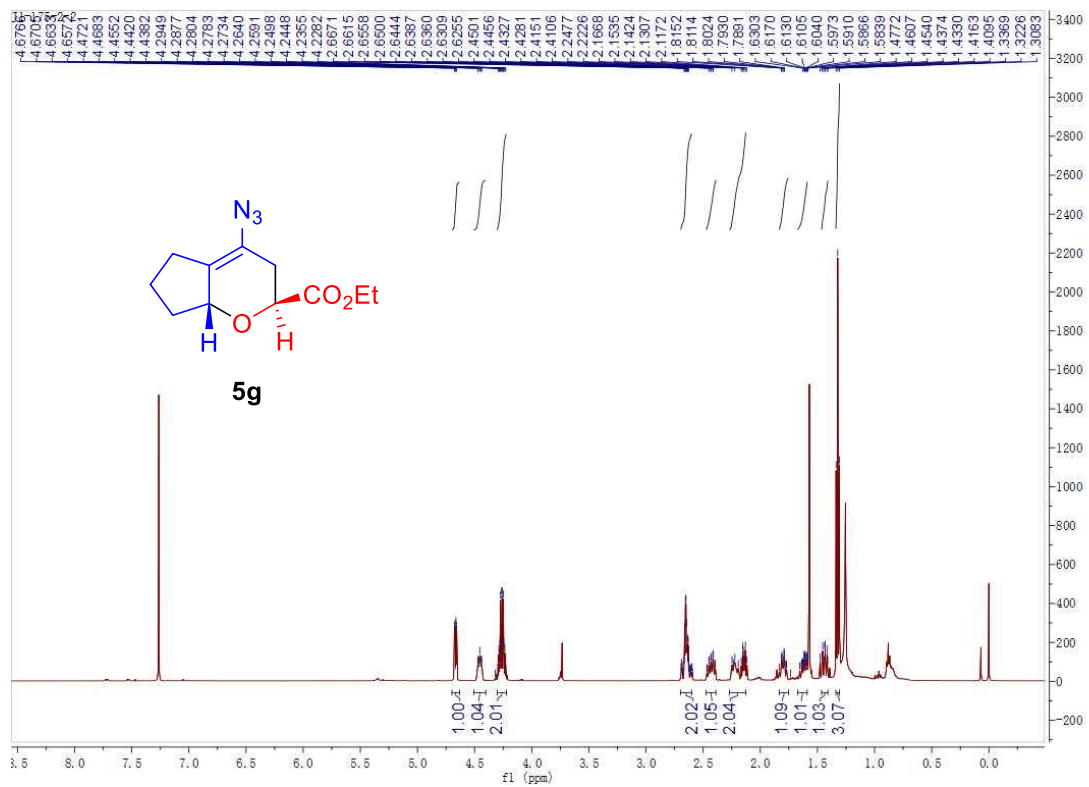
Exact Mass: 282.1117

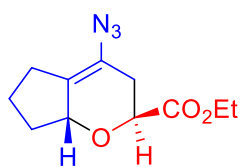
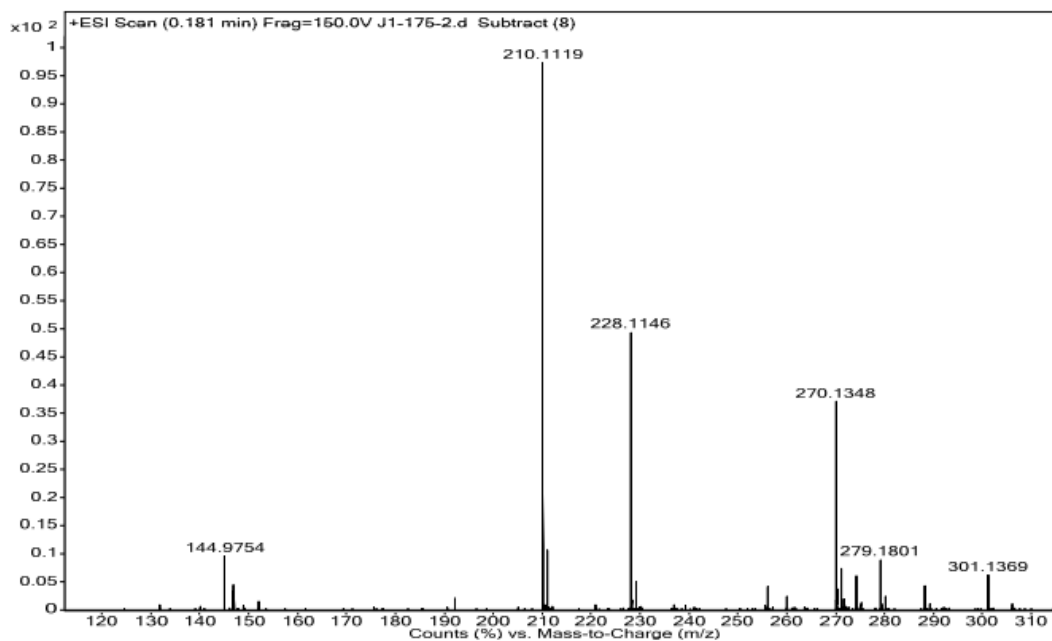
Molecular Weight: 282.3030

$m/z$ : 282.1117 (100.0%), 283.1150 (16.2%), 283.1087 (1.5%), 284.1184 (1.2%)

Elemental Analysis: C, 63.82; H, 5.00; N, 19.85; O, 11.33

HRMS (ESI,  $m/z$ ) calcd for  $C_{15}H_{14}N_4O_2$   $[M-N_2+H]^+$  255.11280, found 255.11220.





**5g**

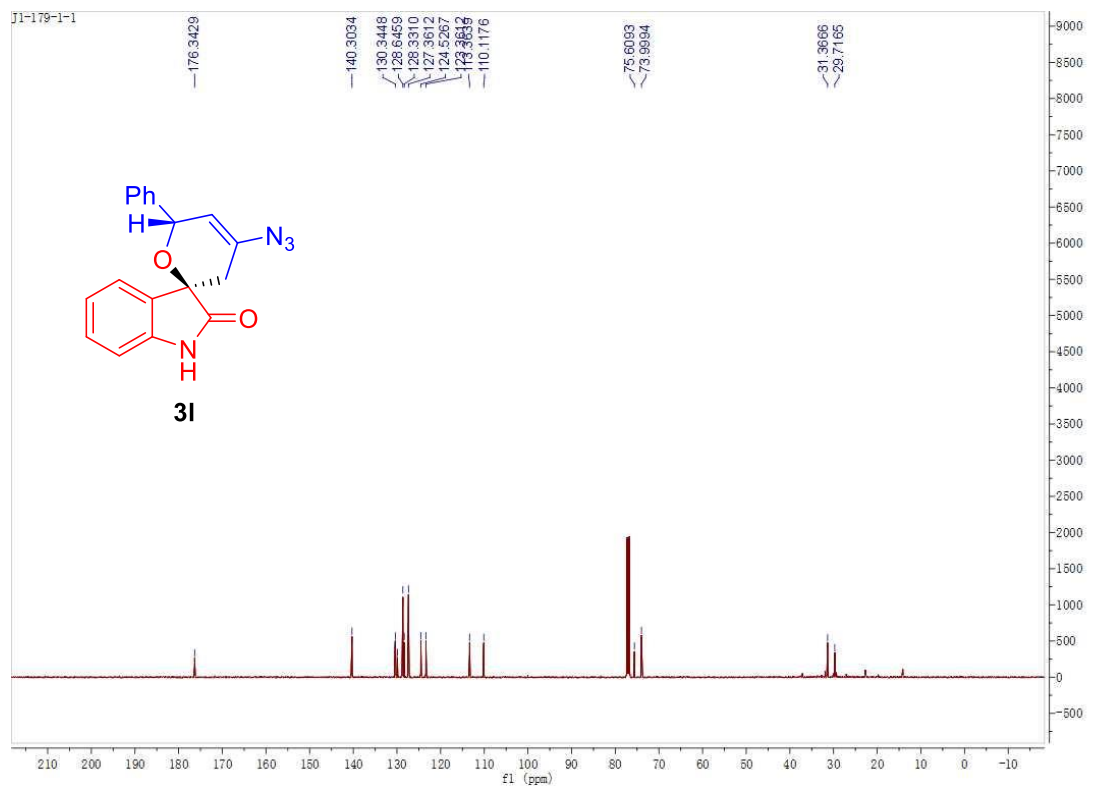
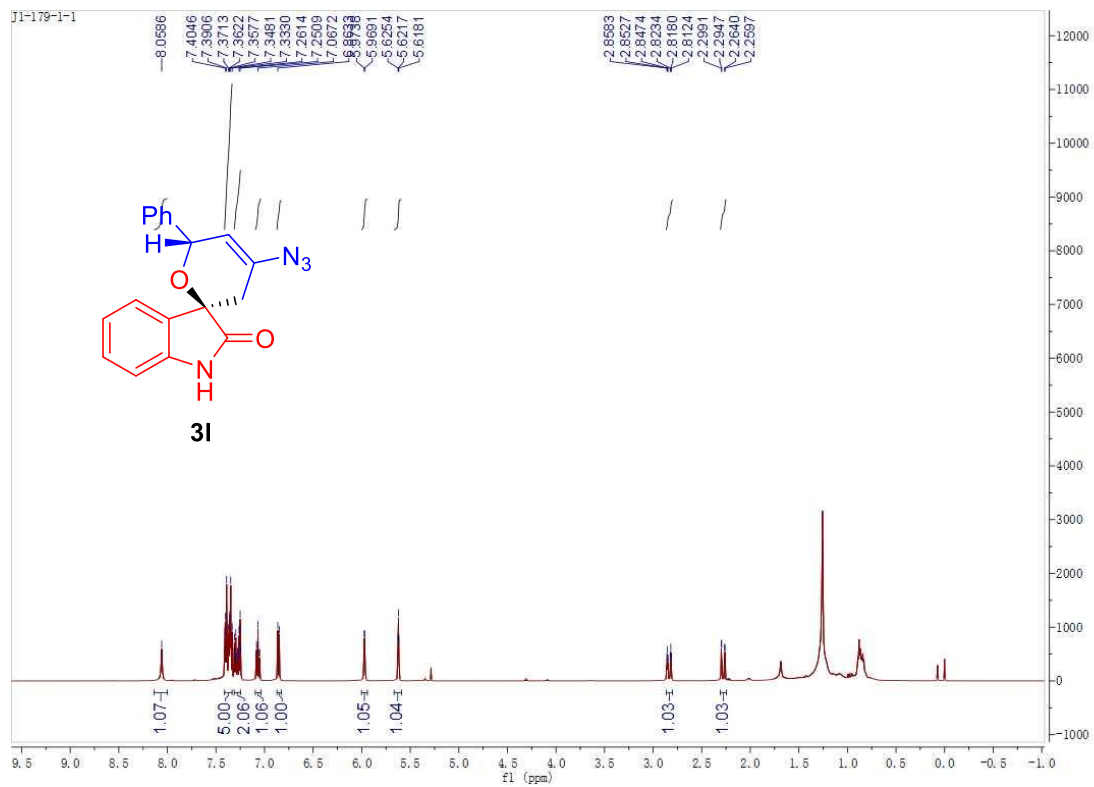
Exact Mass: 237.1113

Molecular Weight: 237.2590

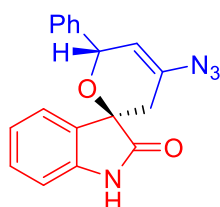
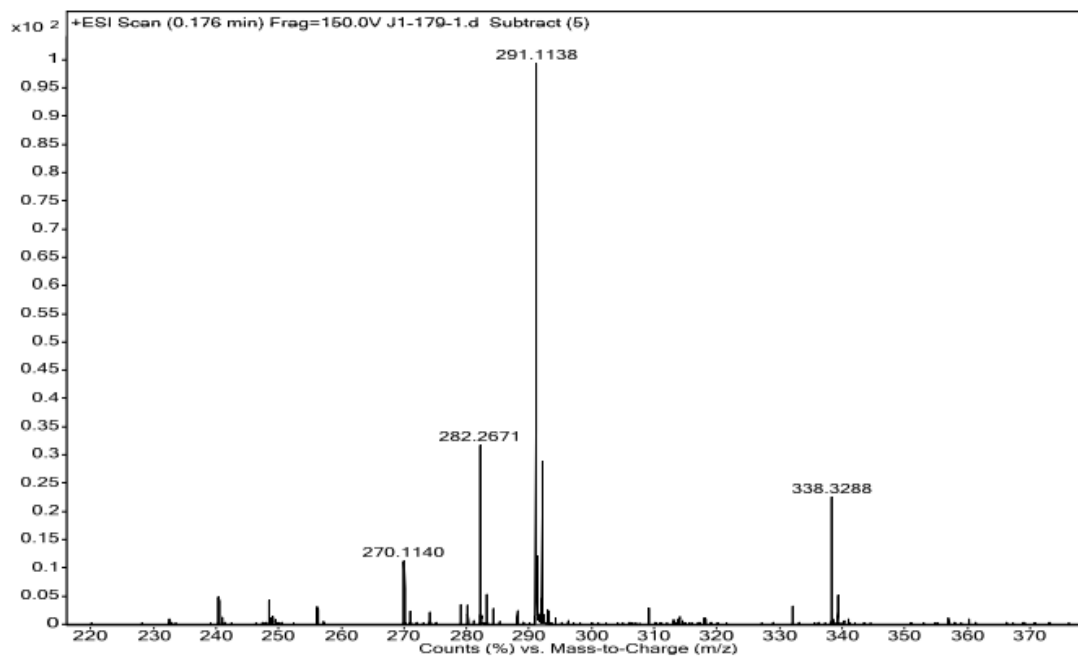
m/z: 237.1113 (100.0%), 238.1147 (11.9%), 238.1084 (1.1%)

Elemental Analysis: C, 55.69; H, 6.37; N, 17.71; O, 20.23

HRMS (ESI, m/z) calcd for  $C_{11}H_{15}N_3O_3$   $[M-N_2+H]^+$  210.1125, found 210.1119.







**3I**

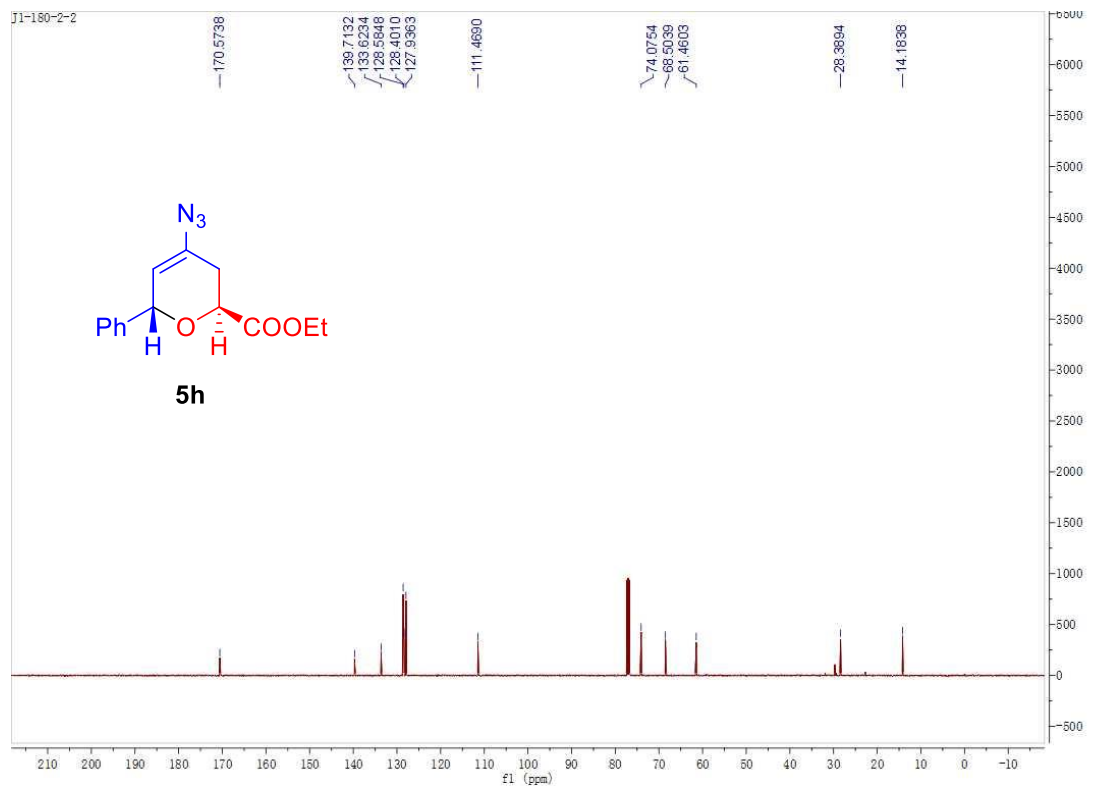
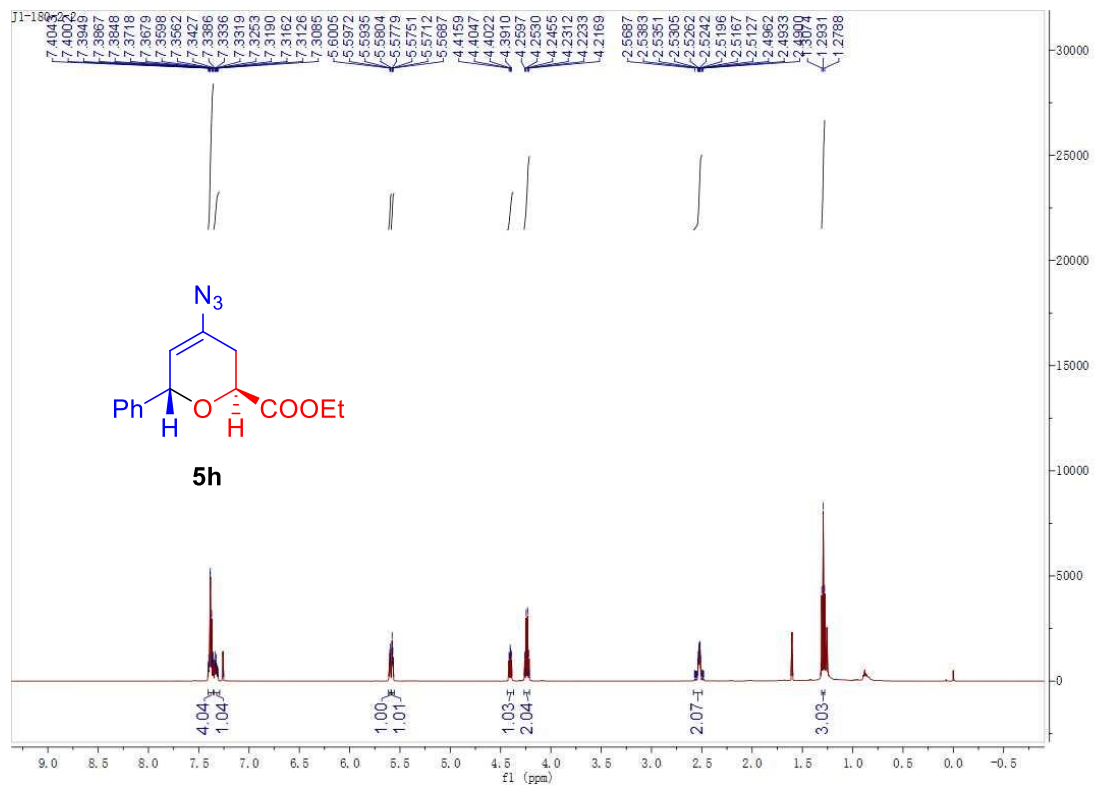
Exact Mass: 318.1117

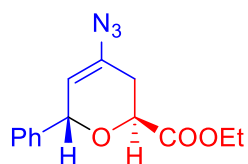
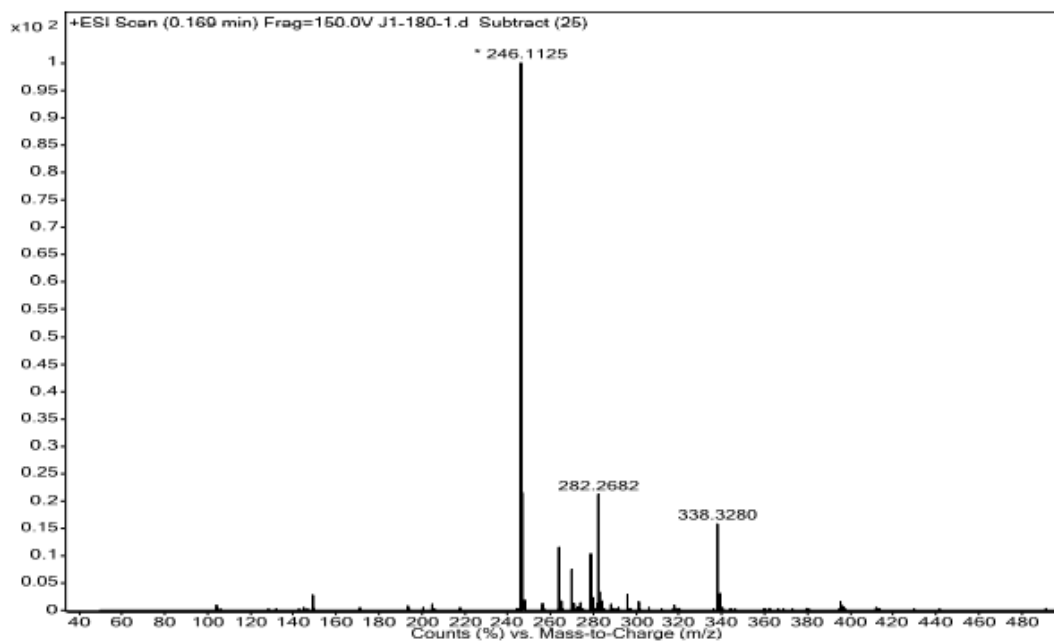
Molecular Weight: 318.3360

m/z: 318.1117 (100.0%), 319.1150 (19.5%), 320.1184 (1.8%), 319.1087 (1.5%)

Elemental Analysis: C, 67.92; H, 4.43; N, 17.60; O, 10.05

HRMS (ESI, m/z) calcd for C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub> [M-N<sub>2</sub>+H]<sup>+</sup> 291.1128, found 291.1138.





**5h**

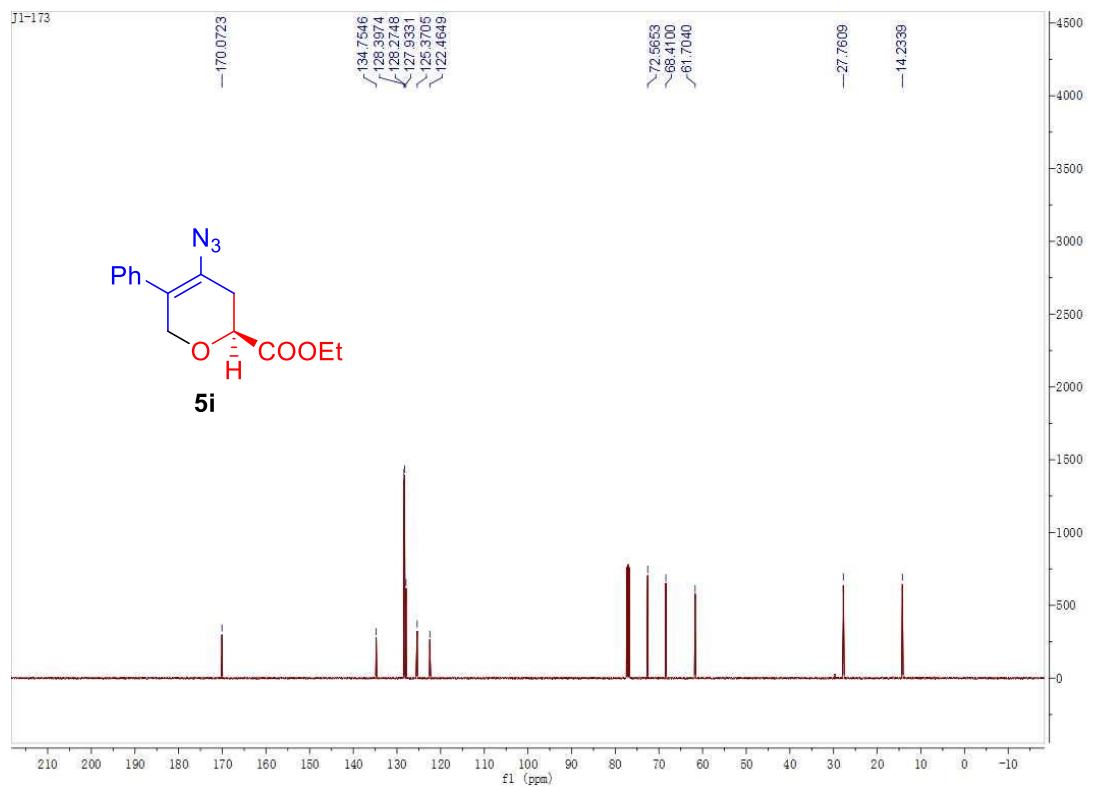
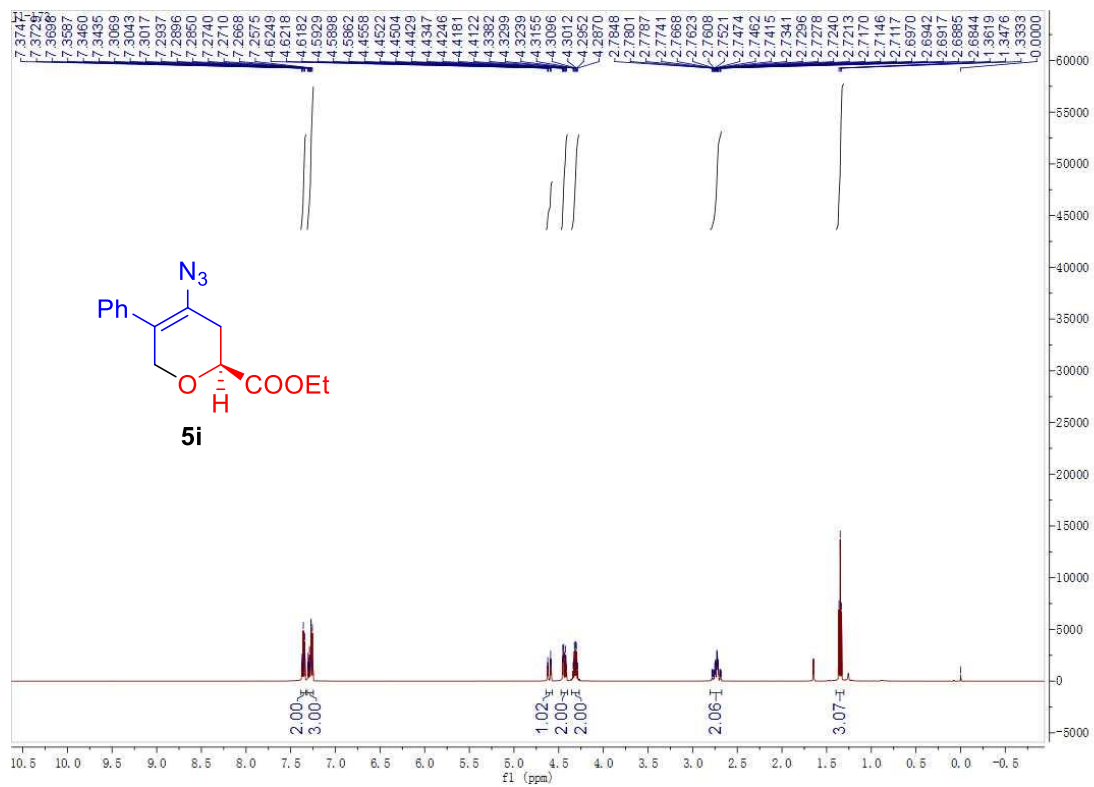
Exact Mass: 273.1113

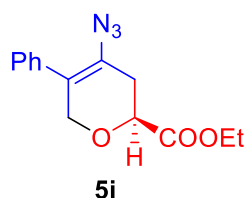
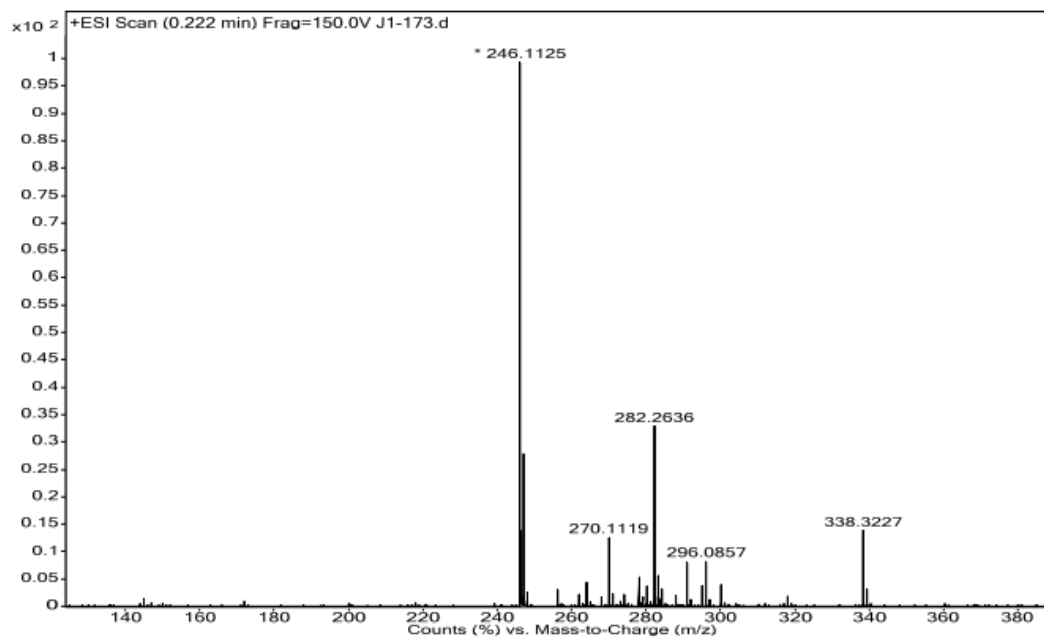
Molecular Weight: 273.2920

m/z: 273.1113 (100.0%), 274.1147 (15.1%), 274.1084 (1.1%), 275.1181 (1.1%)

Elemental Analysis: C, 61.53; H, 5.53; N, 15.38; O, 17.56

HRMS (ESI, m/z) calcd for  $C_{14}H_{15}N_3O_3$   $[M-N_2+H]^+$  246.1125, found 246.1125.





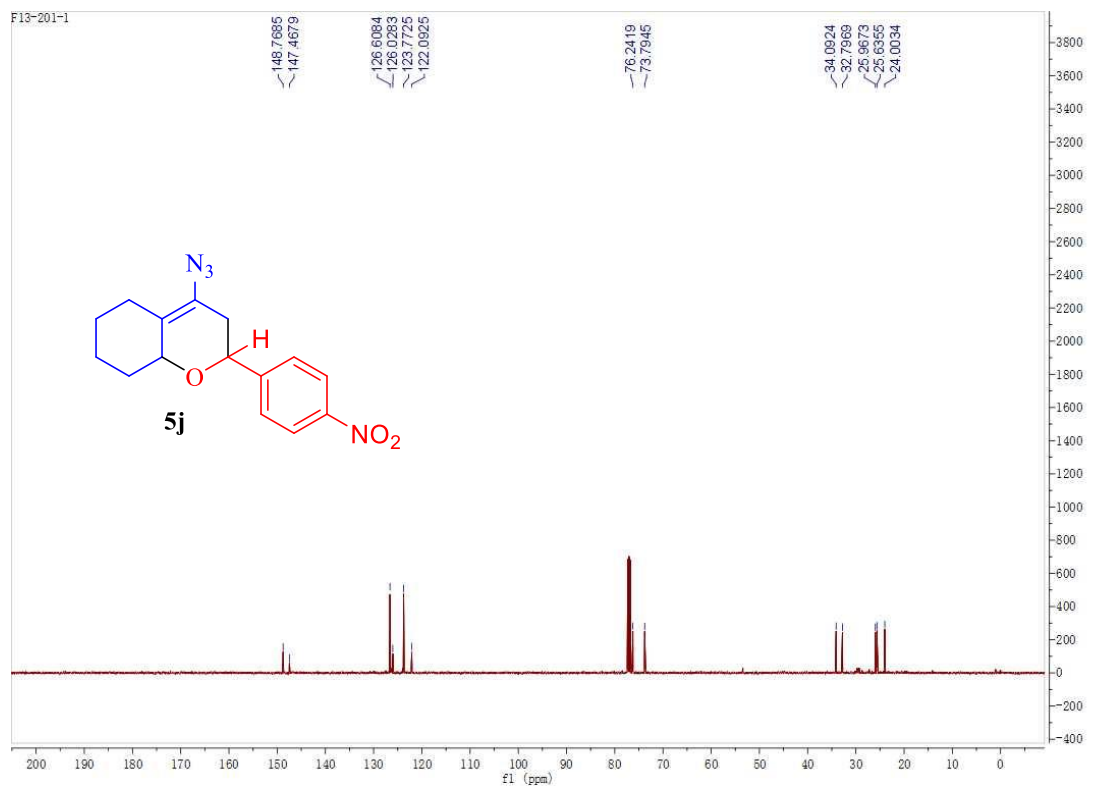
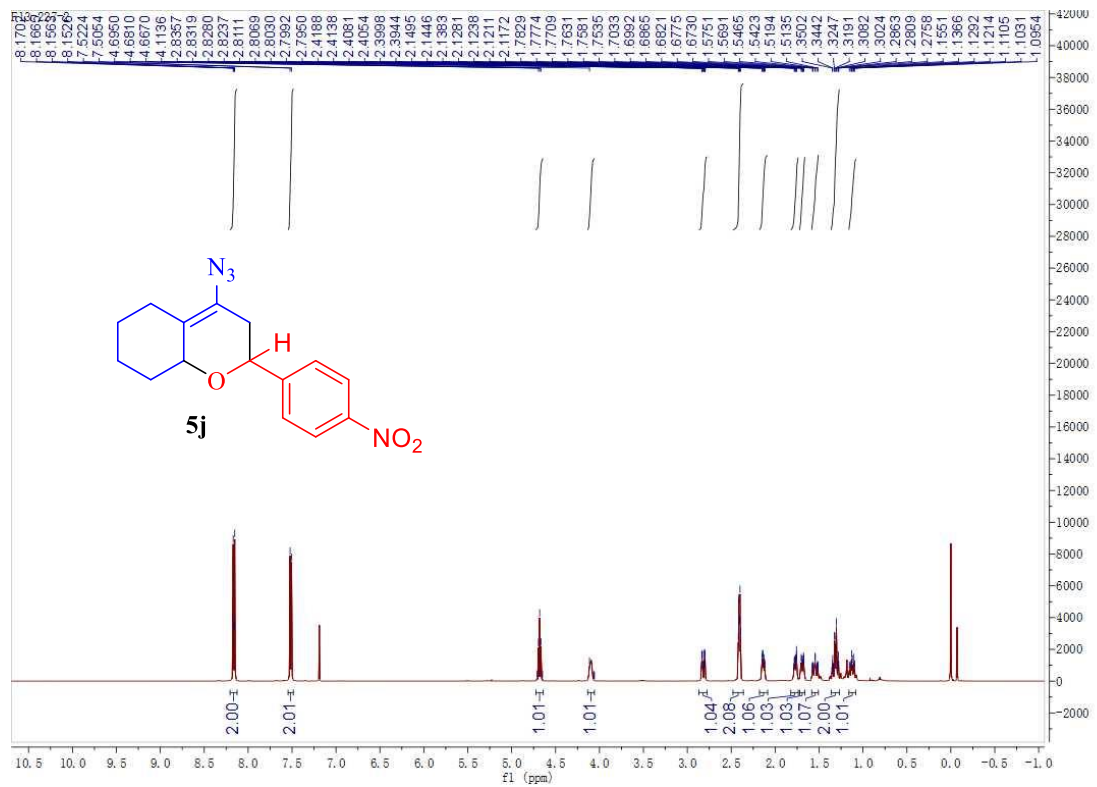
Exact Mass: 273.1113

Molecular Weight: 273.2920

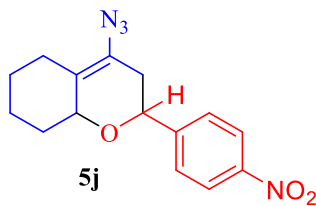
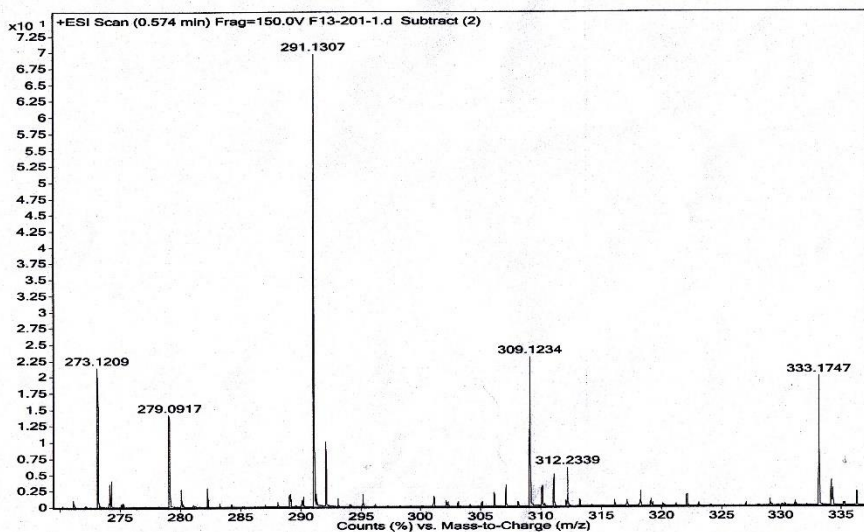
m/z: 273.1113 (100.0%), 274.1147 (15.1%), 274.1084 (1.1%), 275.1181 (1.1%)

Elemental Analysis: C, 61.53; H, 5.53; N, 15.38; O, 17.56

HRMS (ESI, m/z) calcd for  $C_{14}H_{15}N_3O_3$   $[M-N_2+H]^+$  246.1125, found 246.1125.



Sample Name	Position	Instrument Name	Instrument 1	User Name
F13-201-1	P1-C7		Instrument 1	
Inj Vol	InjPosition	SampleType	Sample	IRM Calibration Status
-1			Sample	Success
Data Filename	ACQ Method	Comment	Acquired Time	
F13-201-1.d	0103.m		7/20/2020 3:29:51 PM	



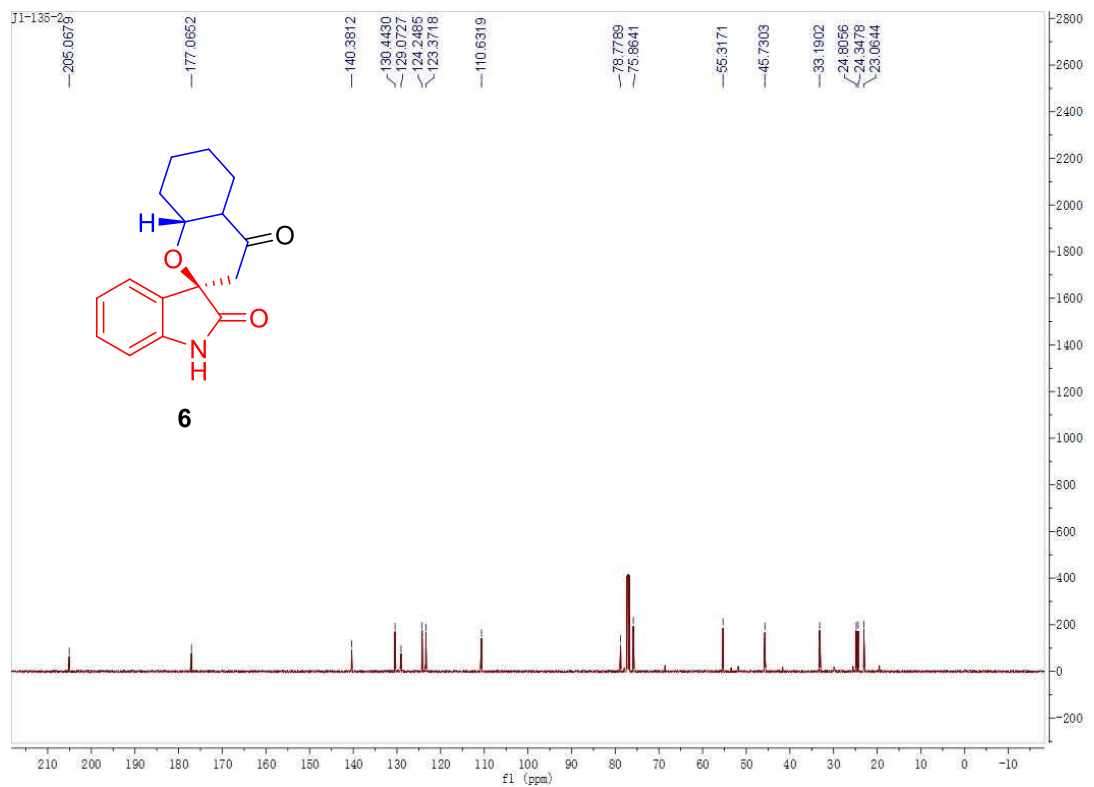
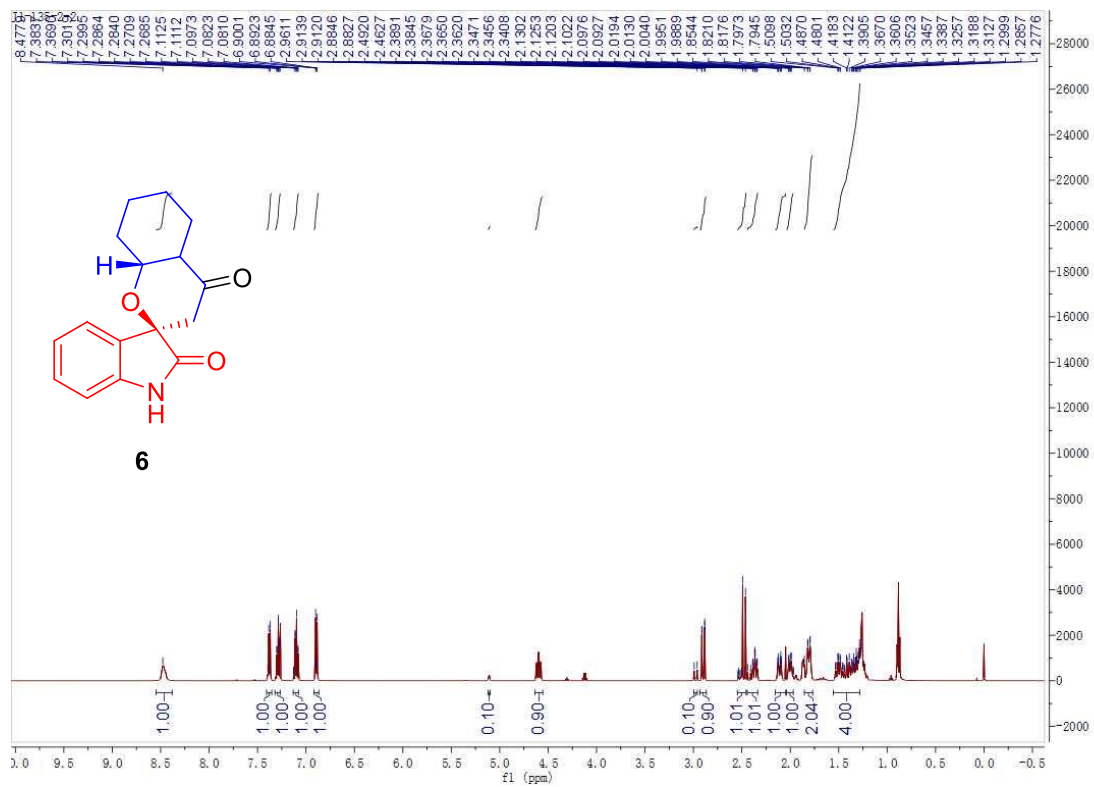
Exact Mass: 300.1222

Molecular Weight: 300.3180

m/z: 300.1222 (100.0%), 301.1256 (16.2%), 301.1193 (1.5%), 302.1290 (1.2%)

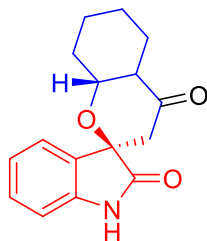
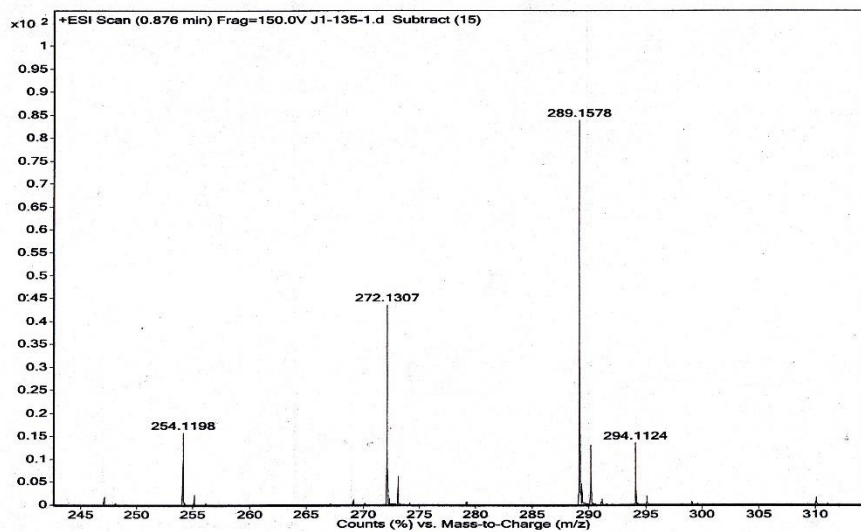
Elemental Analysis: C, 59.99; H, 5.37; N, 18.66; O, 15.98

HRMS (ESI, m/z) calcd for C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub> [M-N<sub>2</sub>+H]<sup>+</sup> 273.1234, found 273.1209.





Sample Name	Unavailable	Position	Unavailable	Instrument Name	Unavailable	User Name	Unavailable
Inj Vol	Unavailable	InjPosition	Unavailable	SampleType	Unavailable	IRM Calibration Status	Success
Data Filename	J1-135-1.d	ACQ Method	Unavailable	Comment	Sample information is unavailable	Acquired Time	Unavailable



6

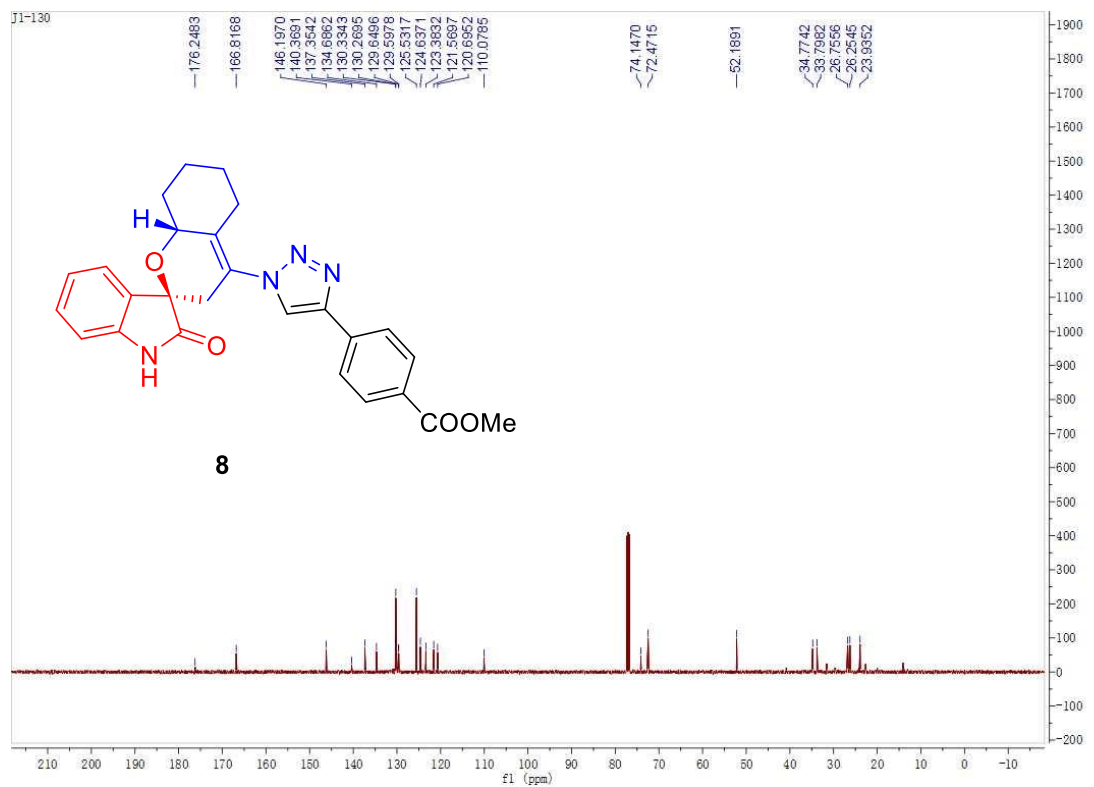
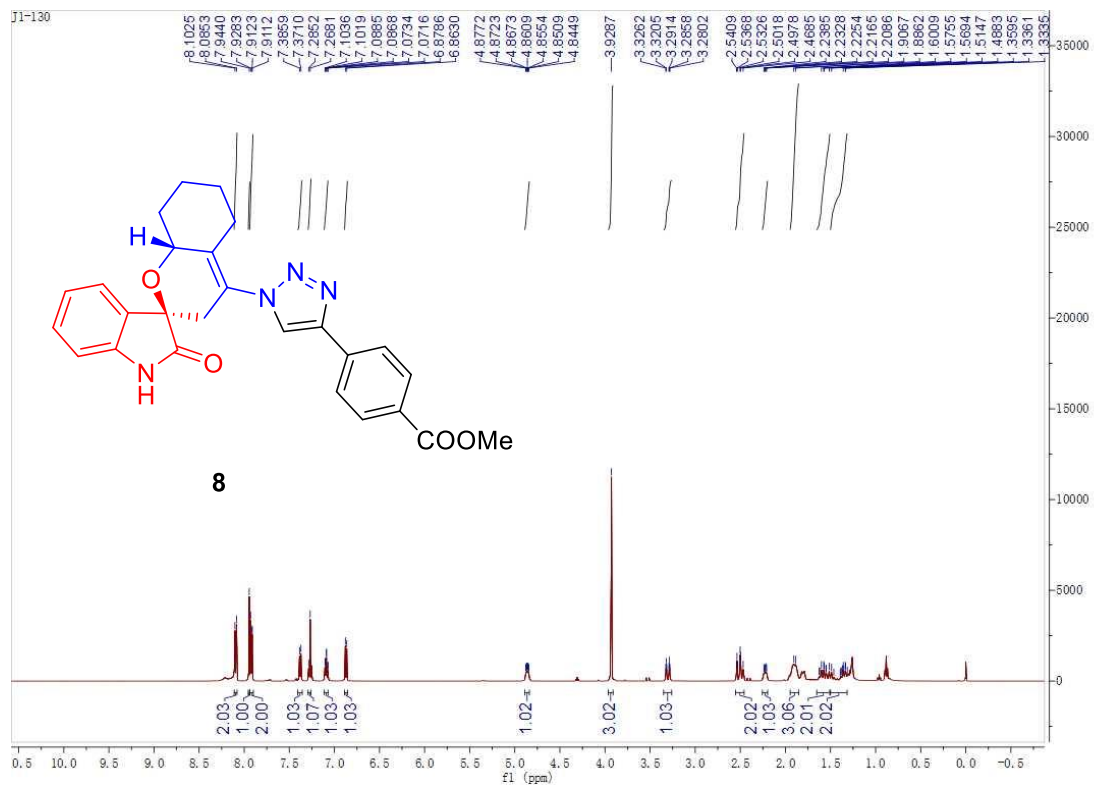
Exact Mass: 271.1208

Molecular Weight: 271.3160

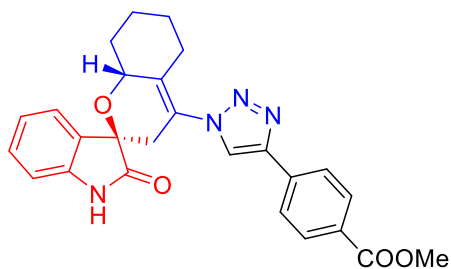
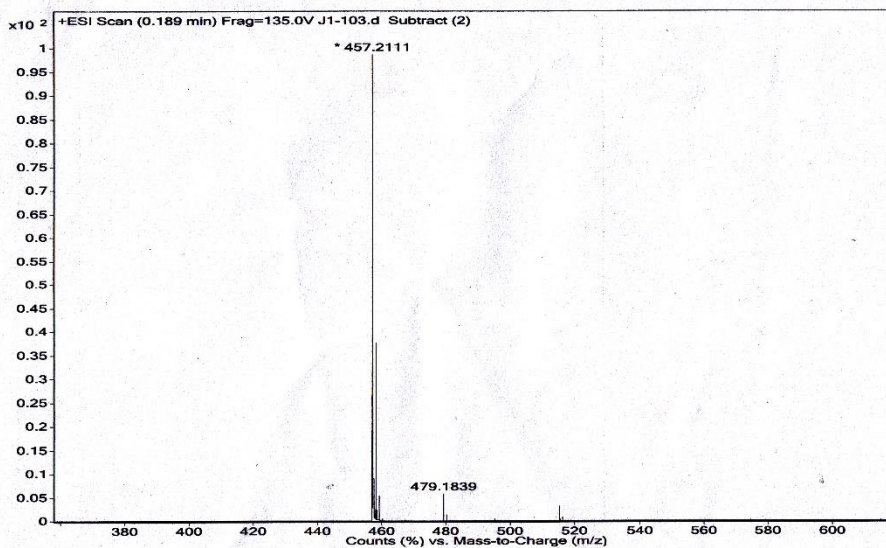
m/z: 271.1208 (100.0%), 272.1242 (17.3%), 273.1276 (1.4%)

Elemental Analysis: C, 70.83; H, 6.32; N, 5.16; O, 17.69

HRMS (ESI, m/z) calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 272.1281, found 272.1307.



Sample Name	Position	Instrument Name	Instrument 1	User Name
J1-103	P1-A4			
Inj Vol	InjPosition	SampleType	Sample	IRM Calibration Status
-1				Success
Data Filename	ACQ Method	Comment	Acquired Time	
J1-103.d	0103.m		11/7/2019 3:15:50 PM	



8

Exact Mass: 456.1798

Molecular Weight: 456.5020

m/z: 456.1798 (100.0%), 457.1831 (28.1%), 458.1865 (2.7%), 457.1768 (1.5%), 458.1865 (1.1%)

Elemental Analysis: C, 68.41; H, 5.30; N, 12.27; O, 14.02

HRMS (ESI, m/z) calcd for C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup> 457.1870, found 457.2111.

## 8. References

- [1] Z. Liu, P. Liao, X. Bi, *Org. Lett.* **2014**, *16*, 3668-3671.
- [2] B. Bennacer, M. Fujiwara, S – Y. Lee, L. Pjima, *J. AM. CHEM. SOC.* **2005**, *127*, 17756-17767.
- [3] J. Li, W. Kong, C. Fu, S. Ma, *J. Org. Chem.* **2009**, *74*, 5104–5106.
- [4] Q. Li, X. Jiang, C. Fu, S. Ma, *Org. Lett.* **2011**, *13*, 466-469.
- [5] S. Li, T. Xiao, D. Li, X. Zhang, *Org. Lett.* **2015**, *17*, 3782-3785.
- [6] Z. Yu, X. Liu, Z. Dong, M. Xie, X. Feng, *Angew. Chem. Int. Ed.* **2008**, *47*, 1308-1311.