

## ***Supporting Information***

### **Enantioselective synthesis of novel pyrano[3,2-*c*]chromene derivatives as AChE inhibitors via an organocatalytic domino reaction**

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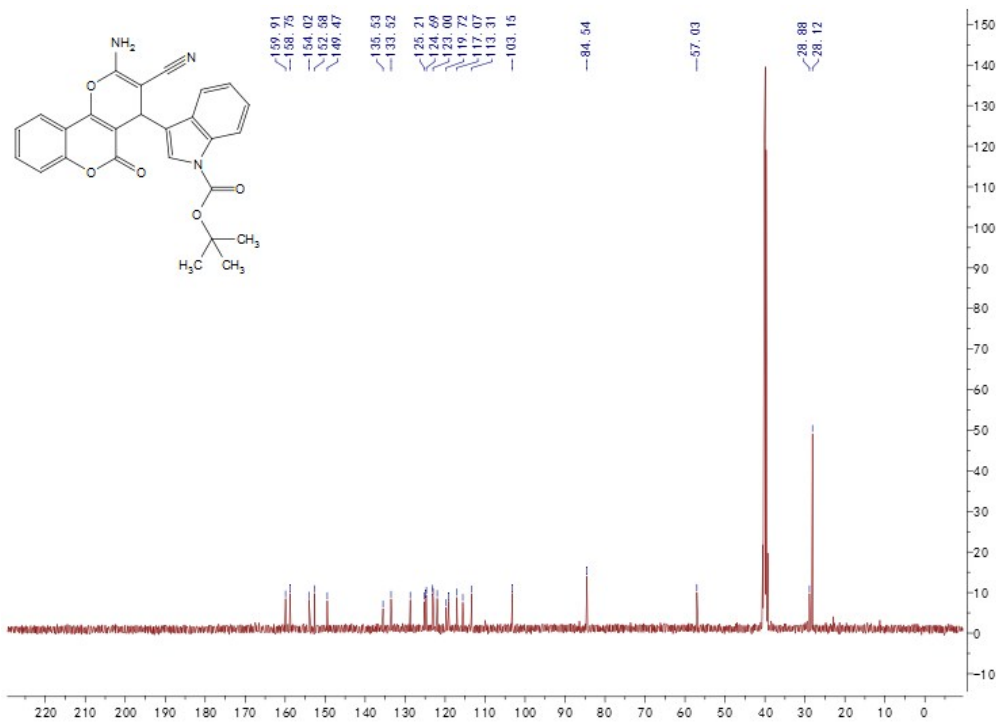
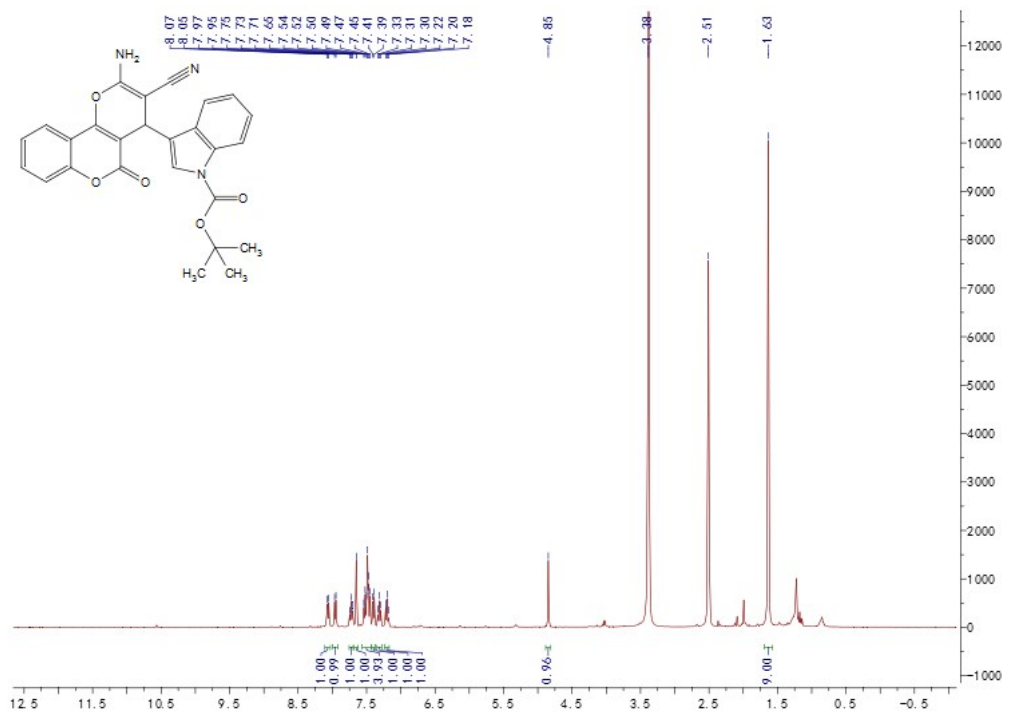
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\*Corresponding author, *E-mail address:* [zhouhb@whu.edu.cn](mailto:zhouhb@whu.edu.cn), Tel: 027-68759586

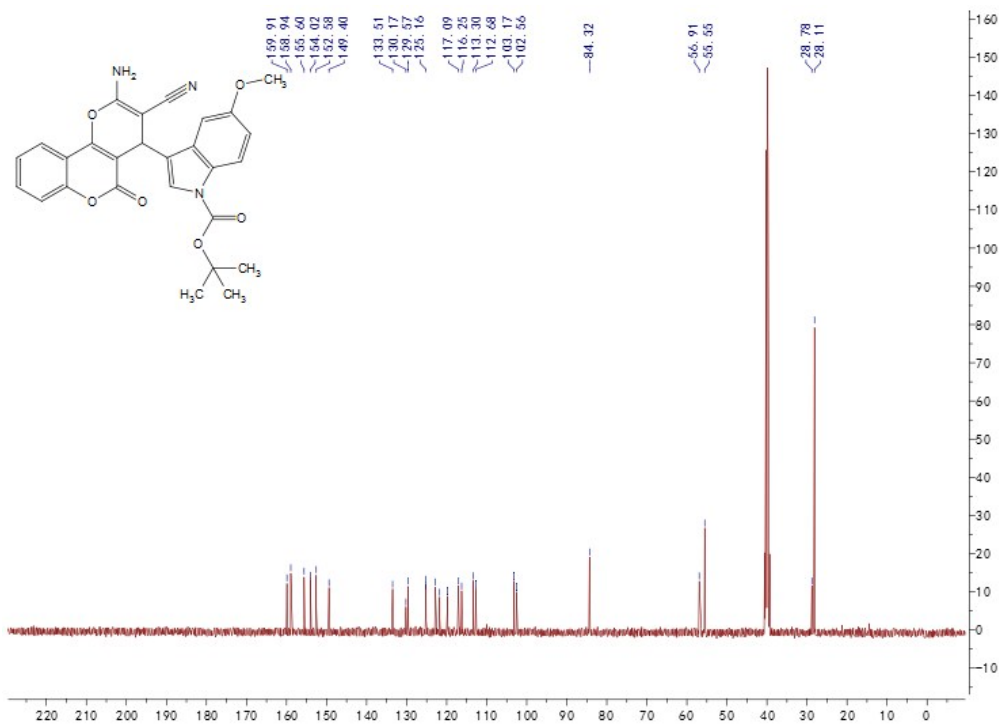
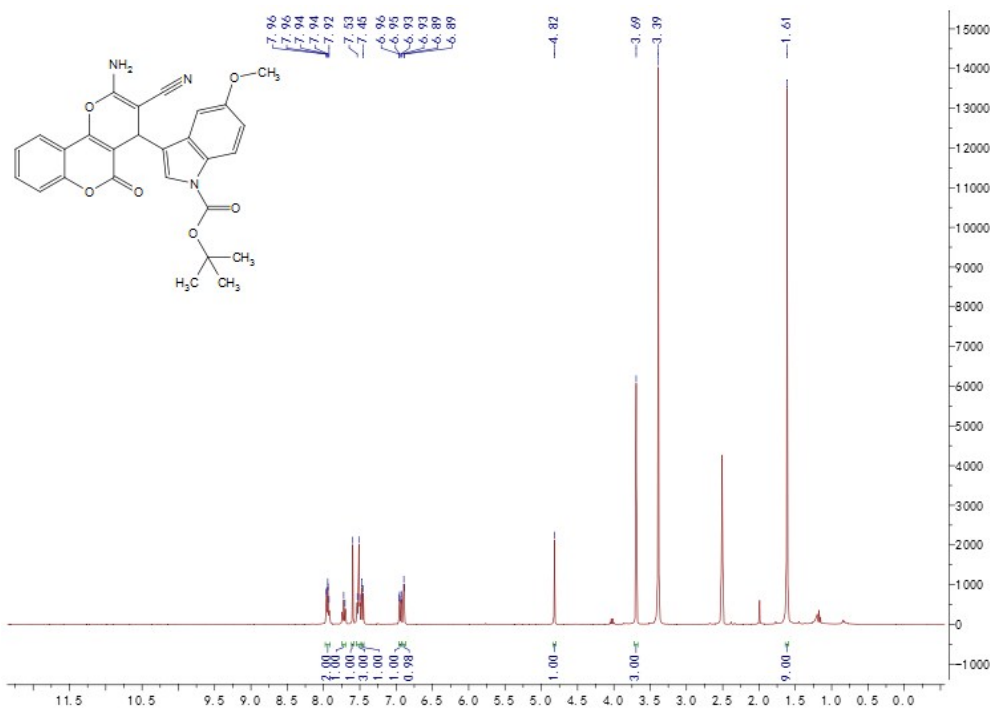
\*Corresponding author, *E-mail address:* [cdong@whu.edu.cn](mailto:cdong@whu.edu.cn), Tel: 027-68759586

# I Representative NMR spectra of compounds 4 and 1

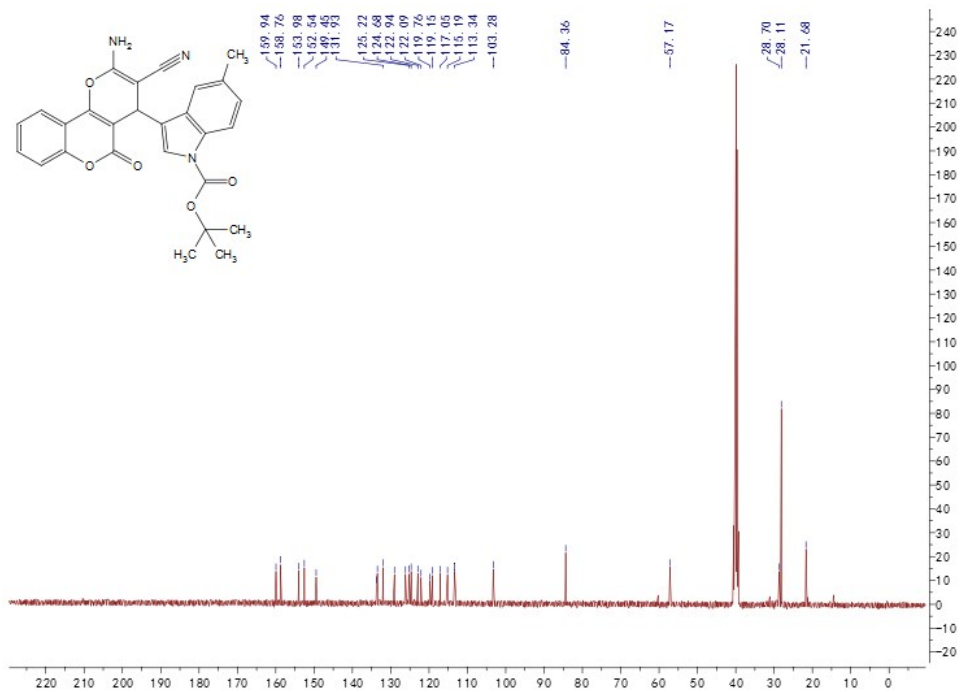
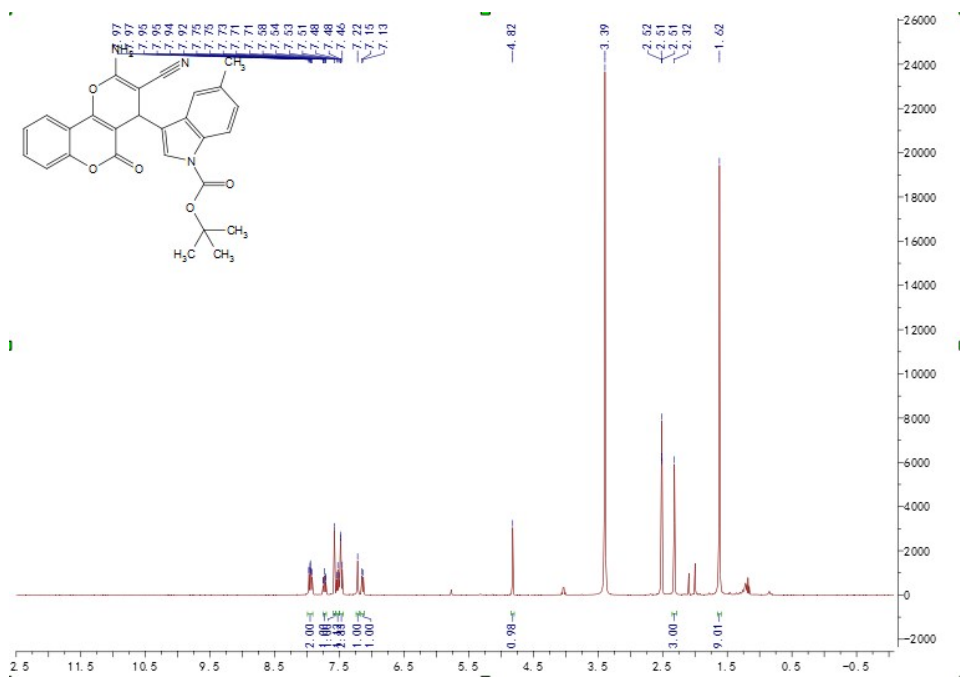
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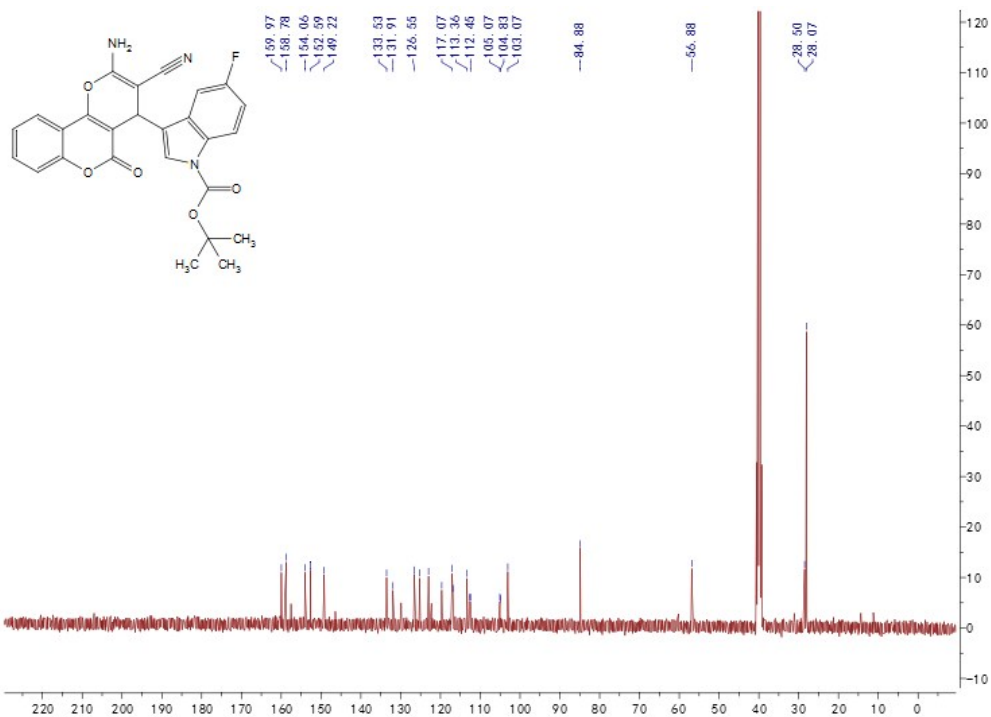
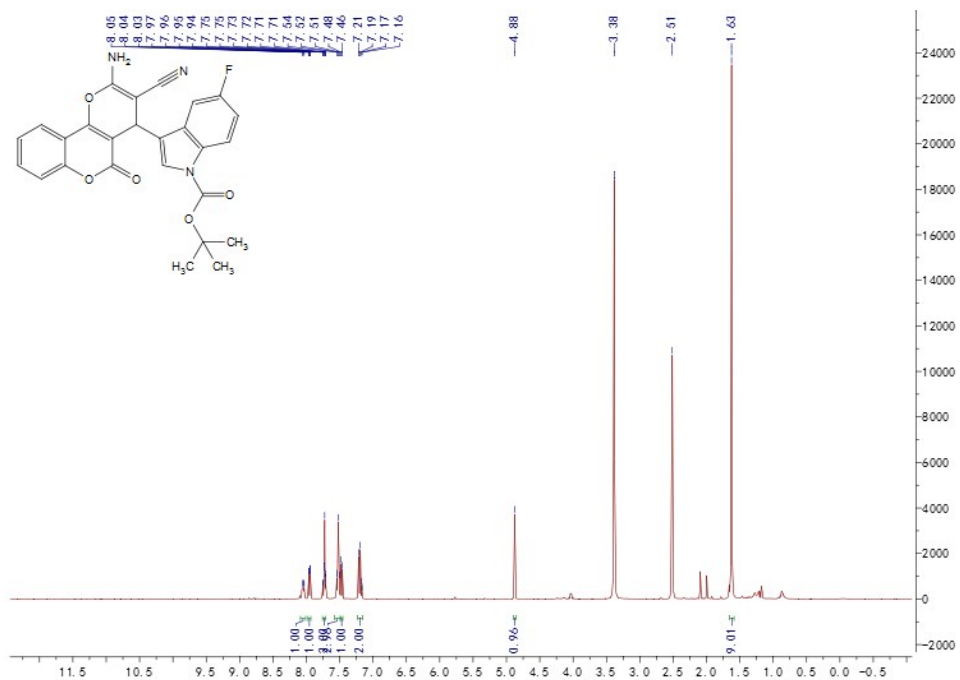
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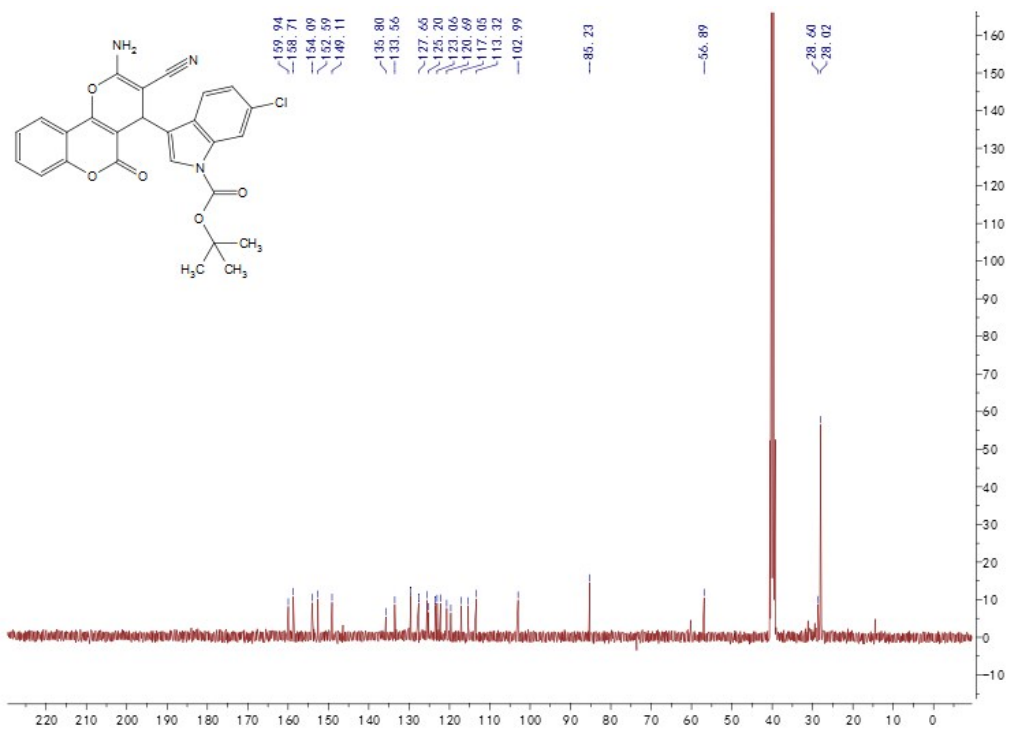
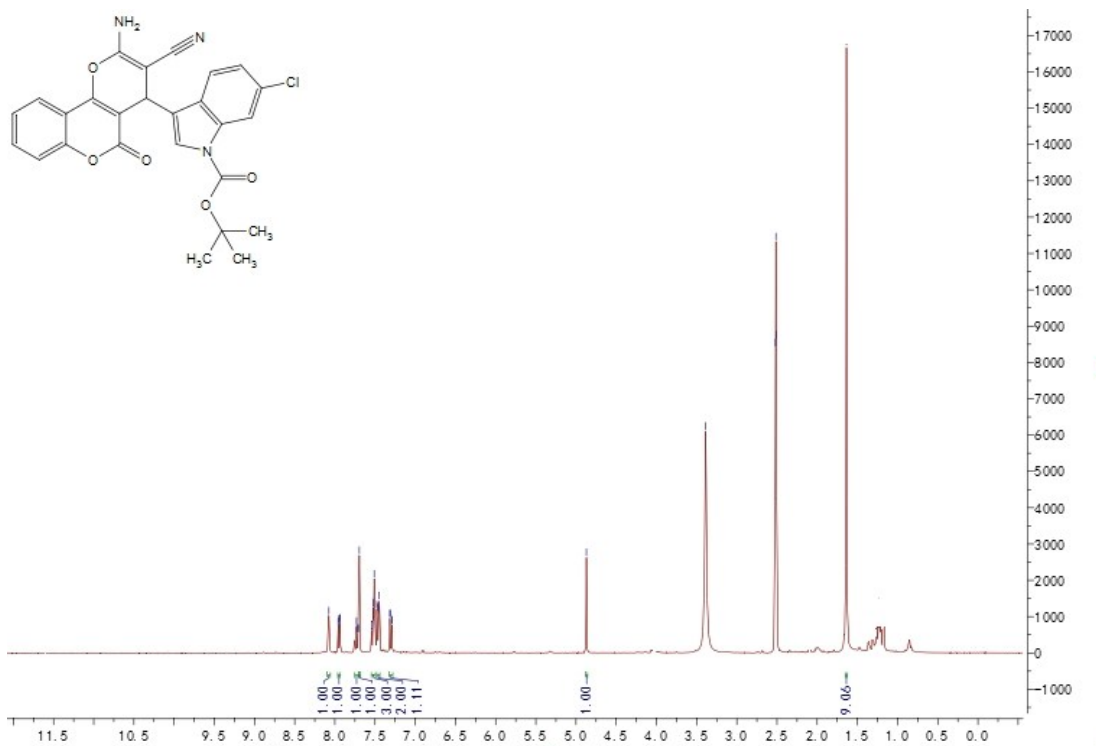
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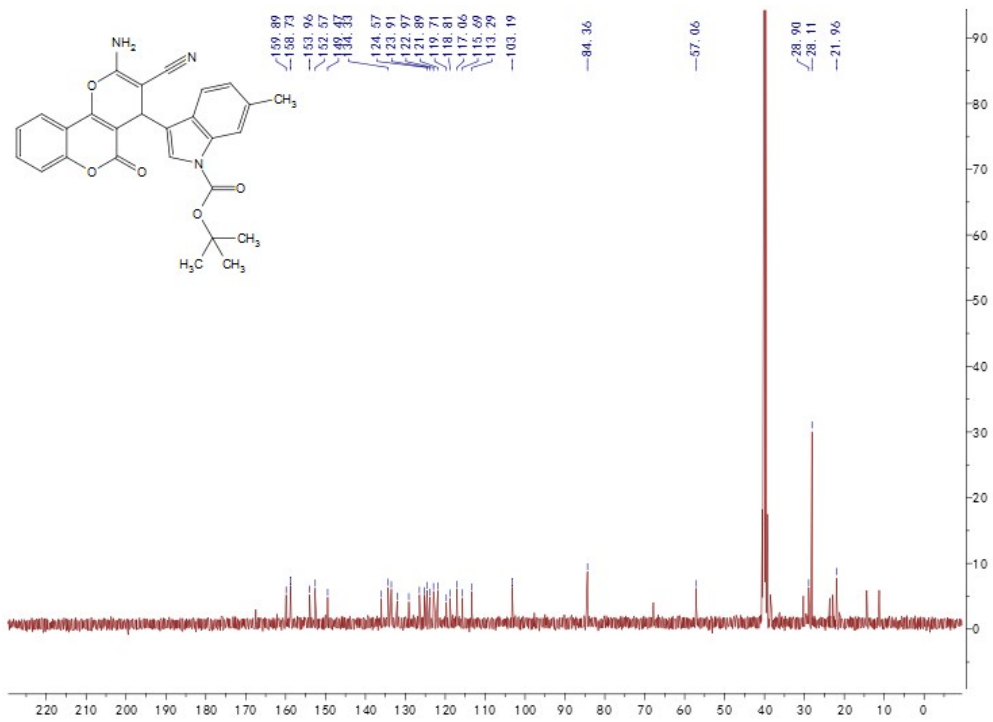
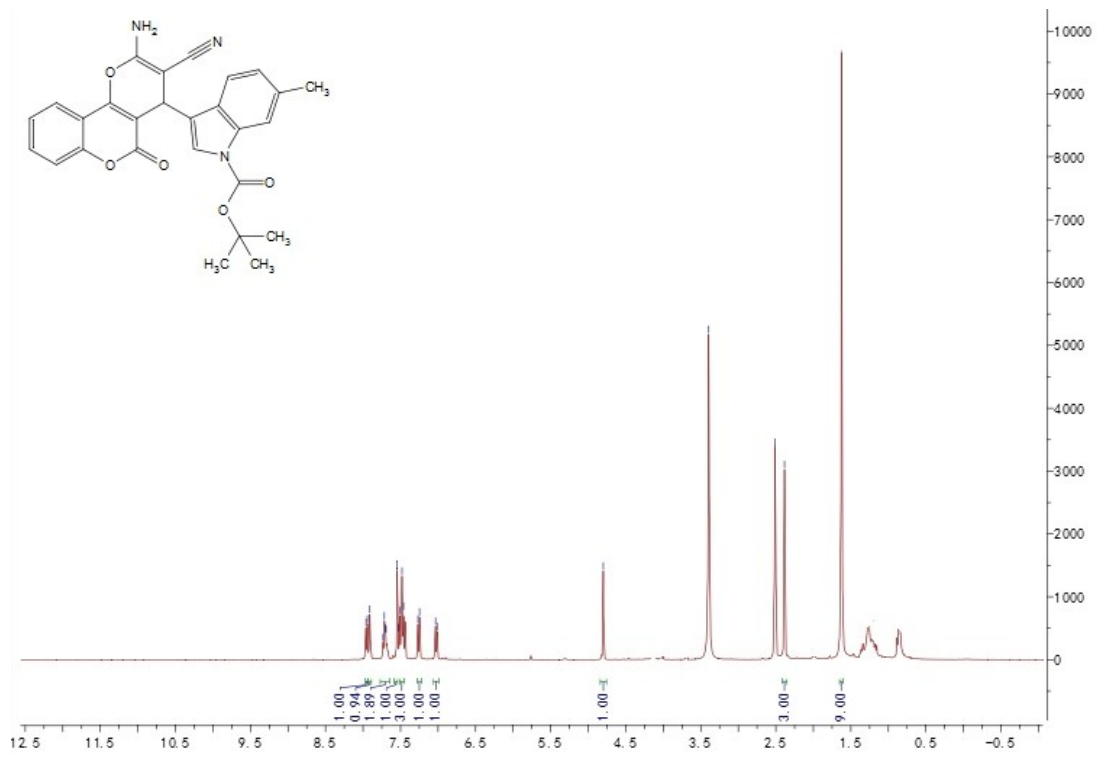
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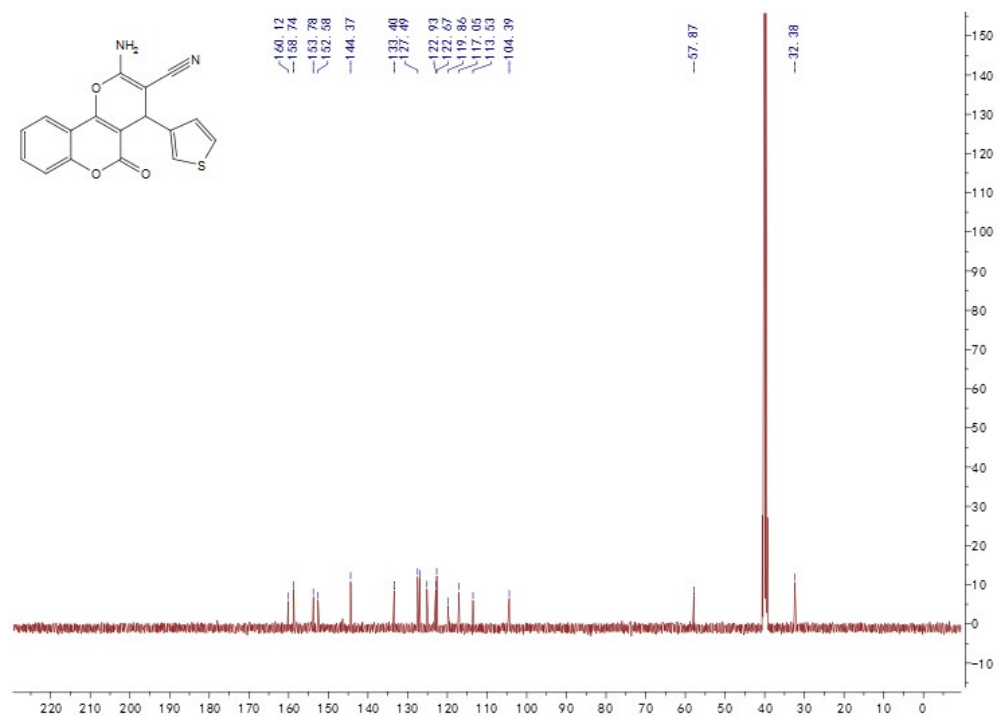
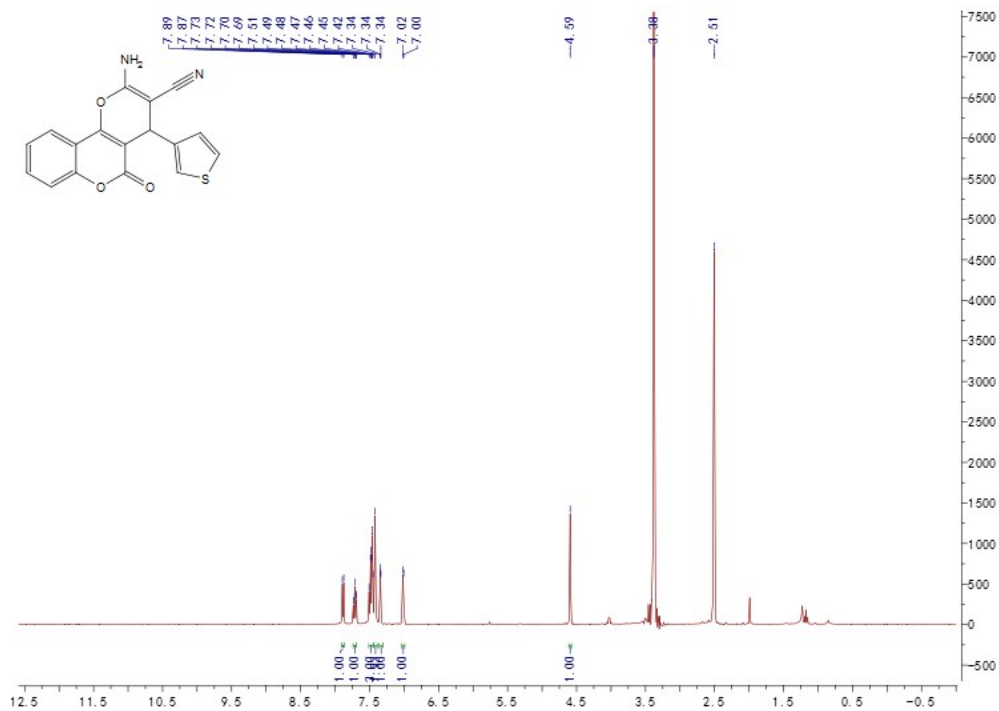
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4f

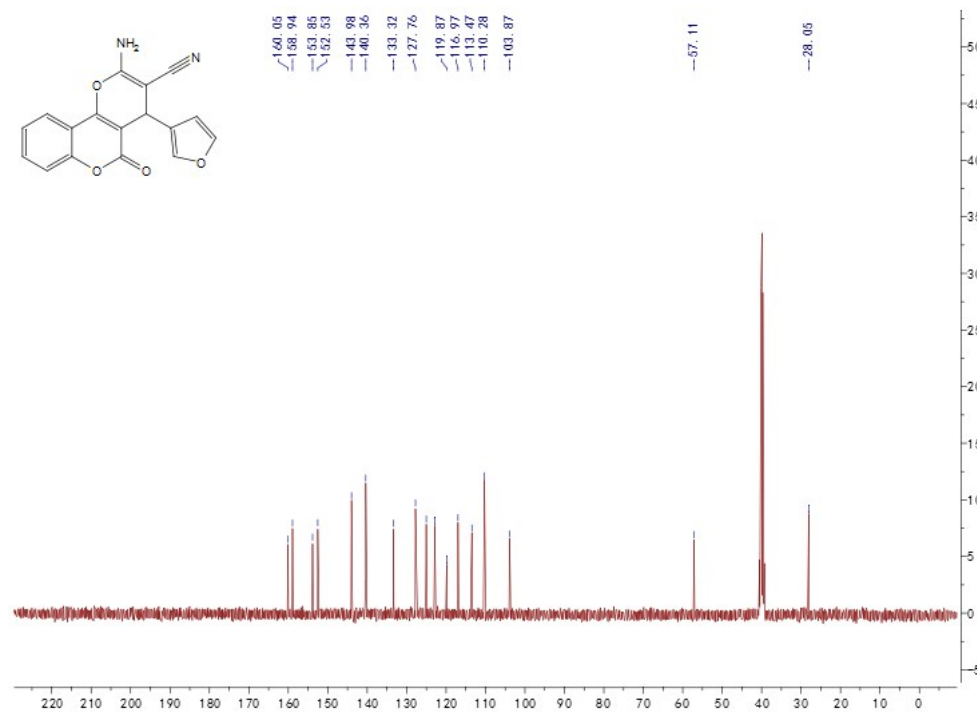
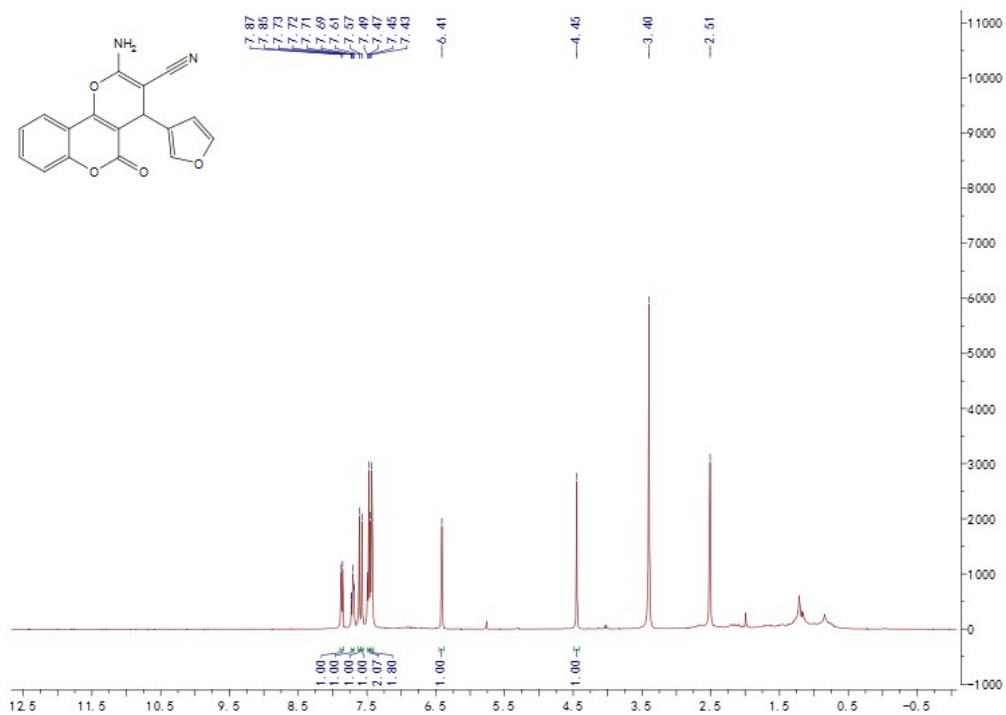


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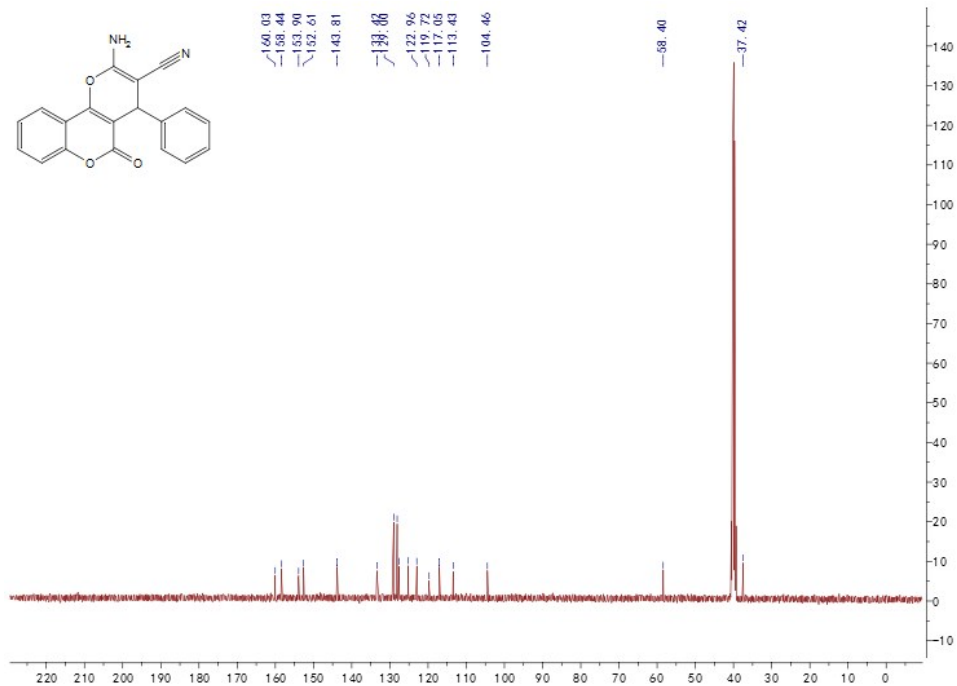
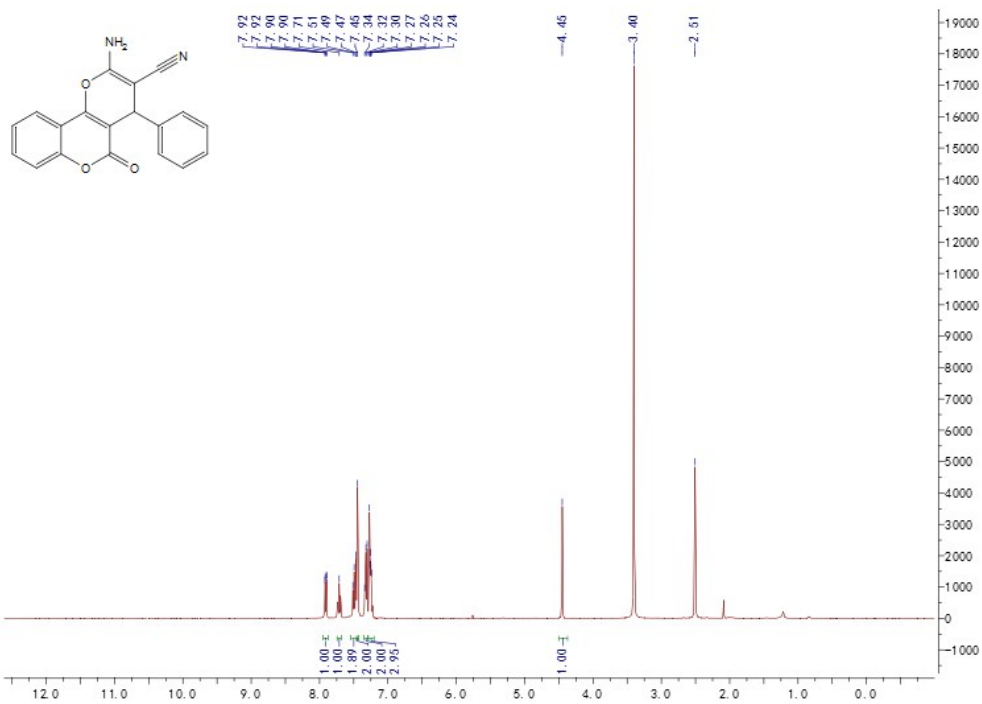




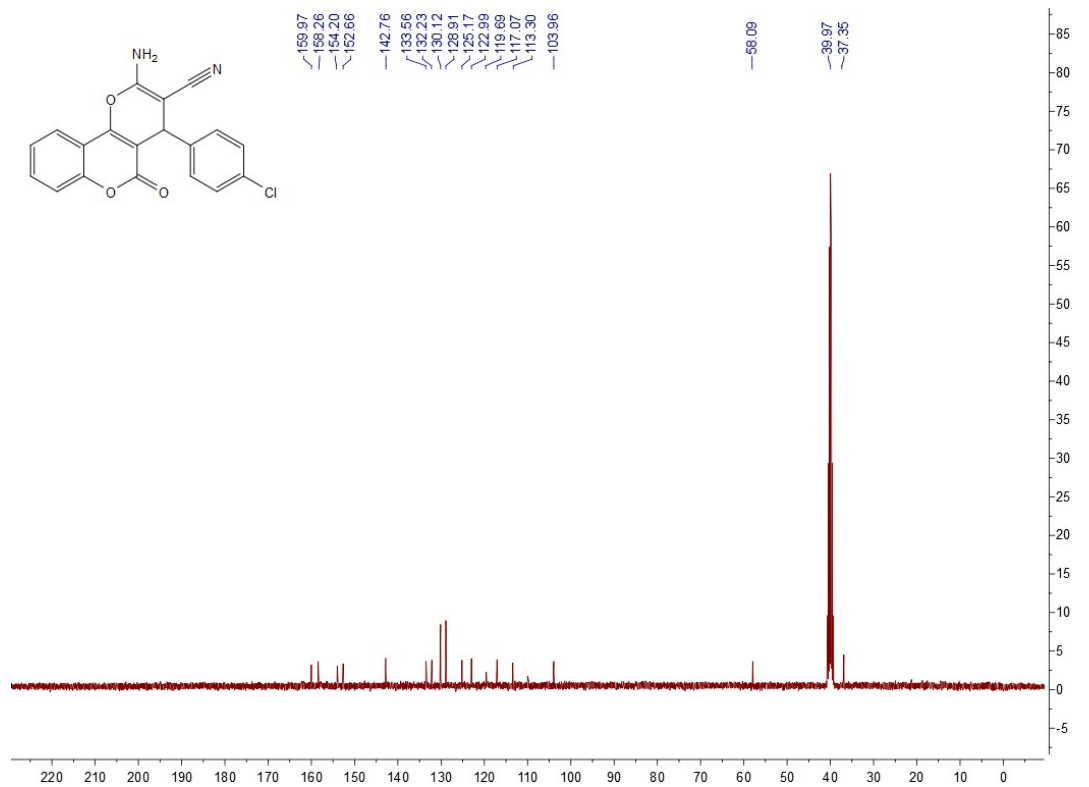
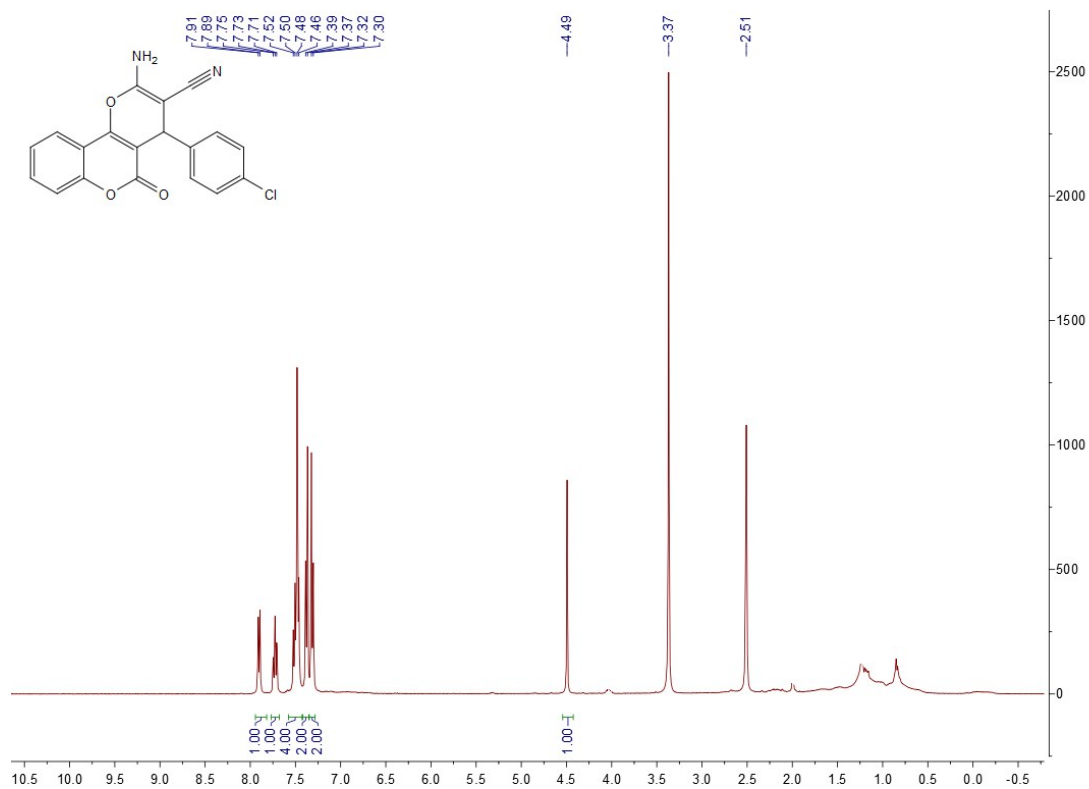
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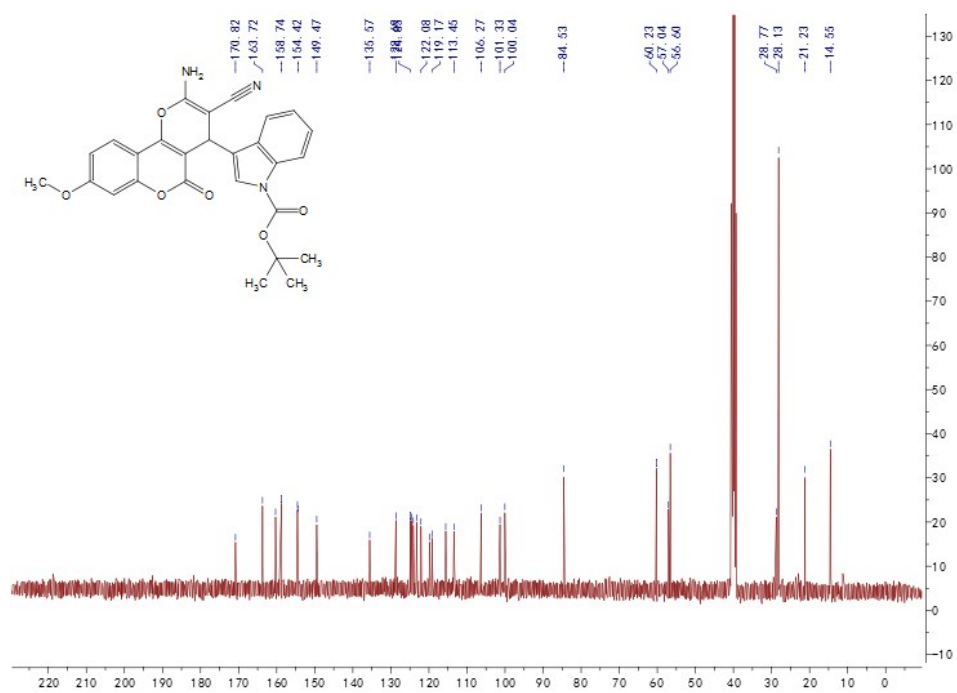
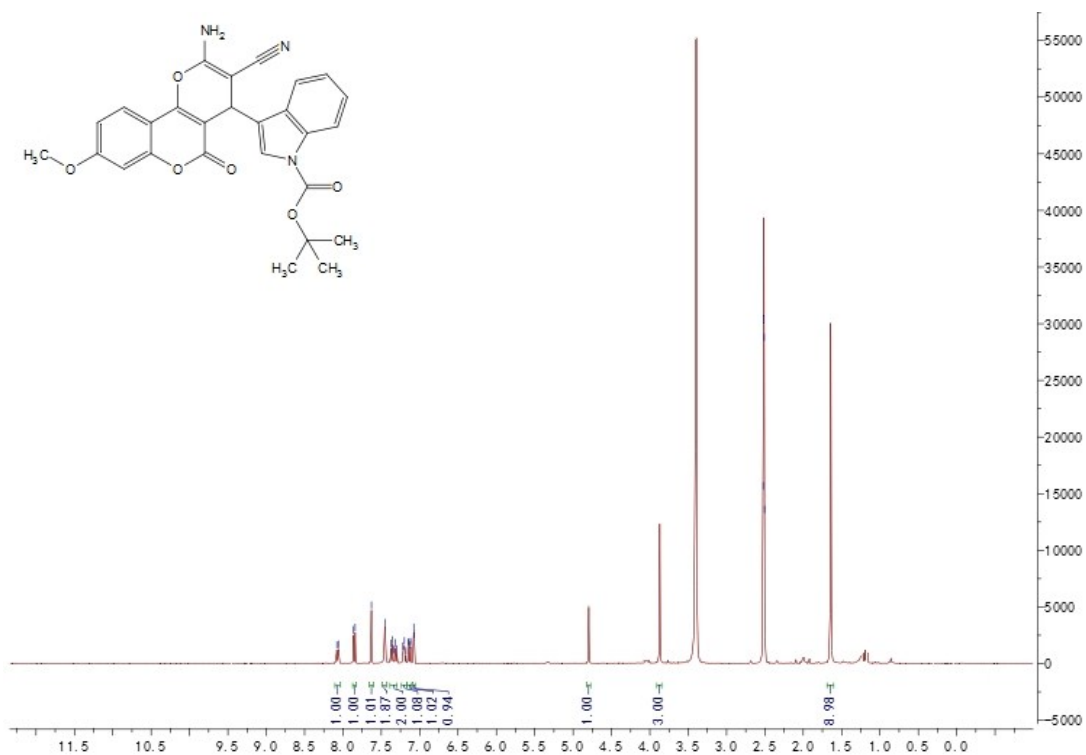
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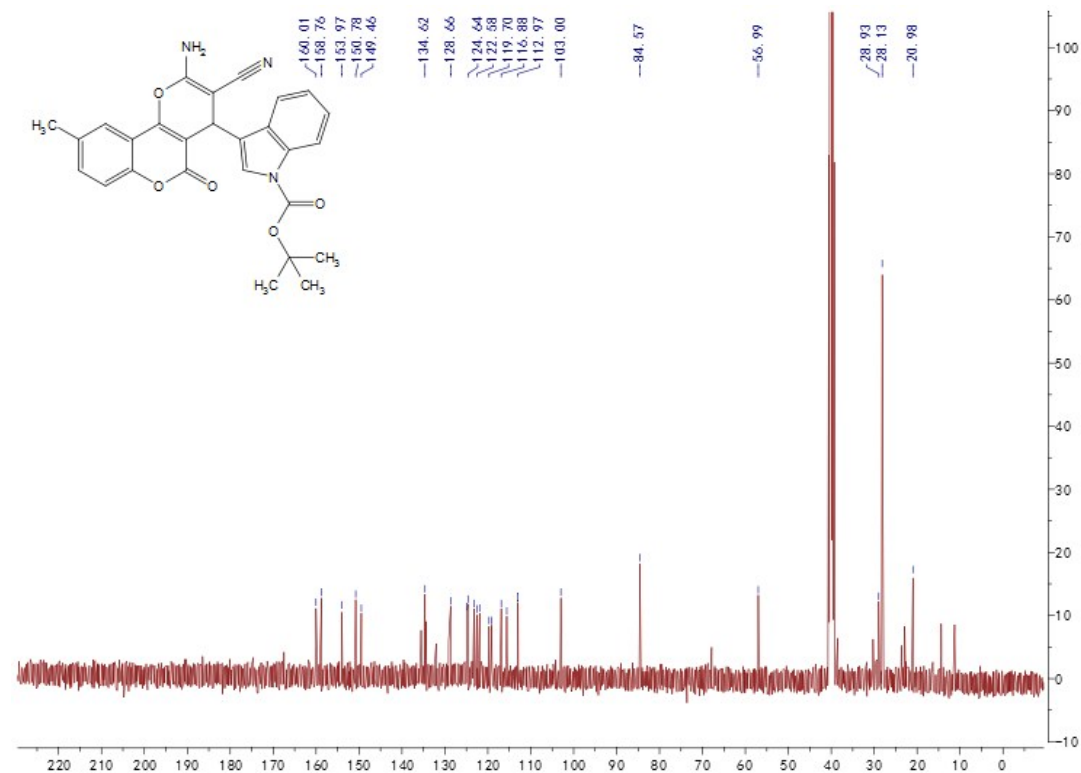
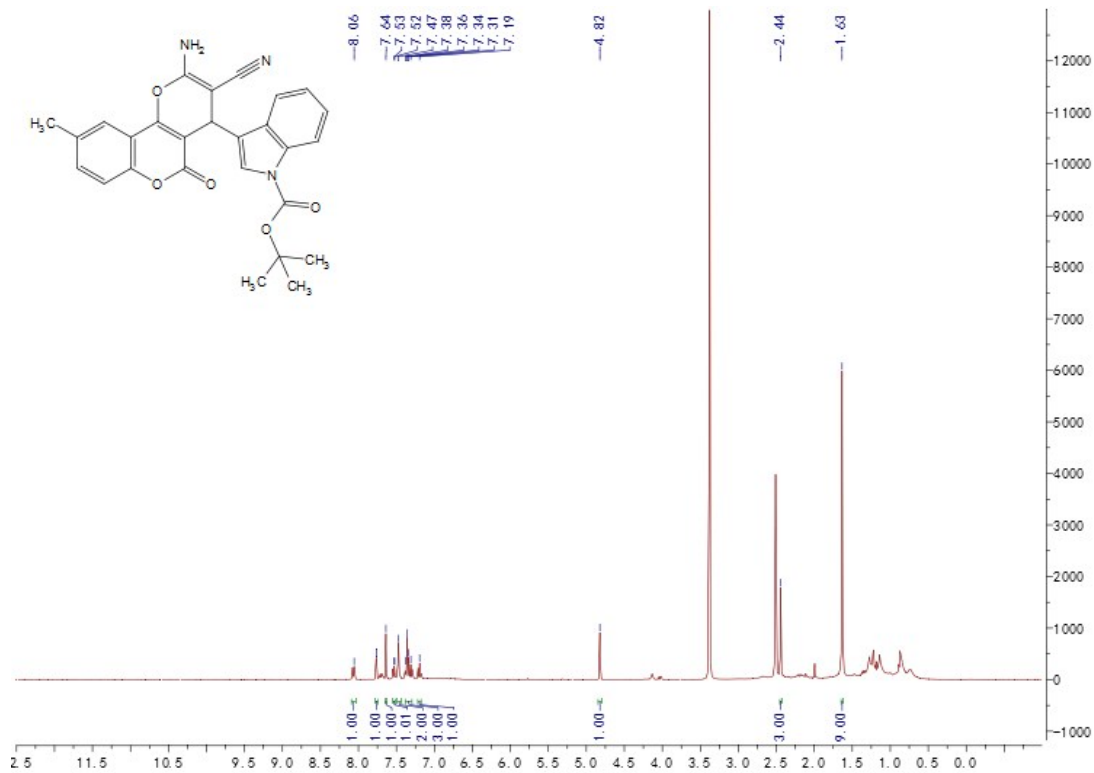
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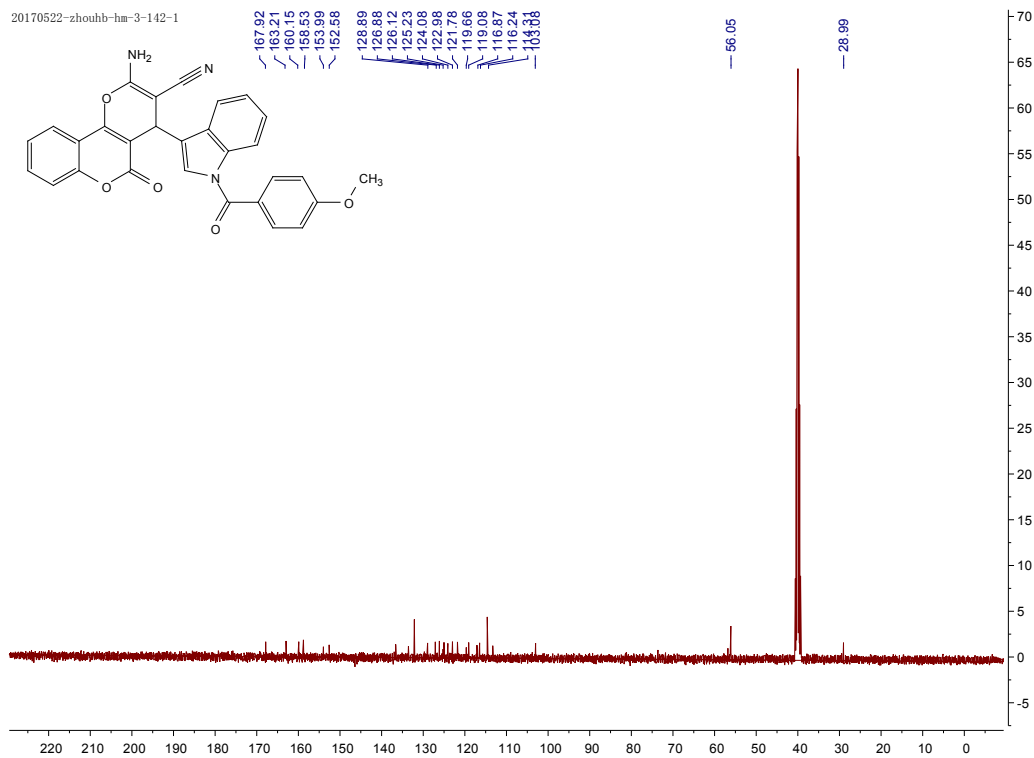
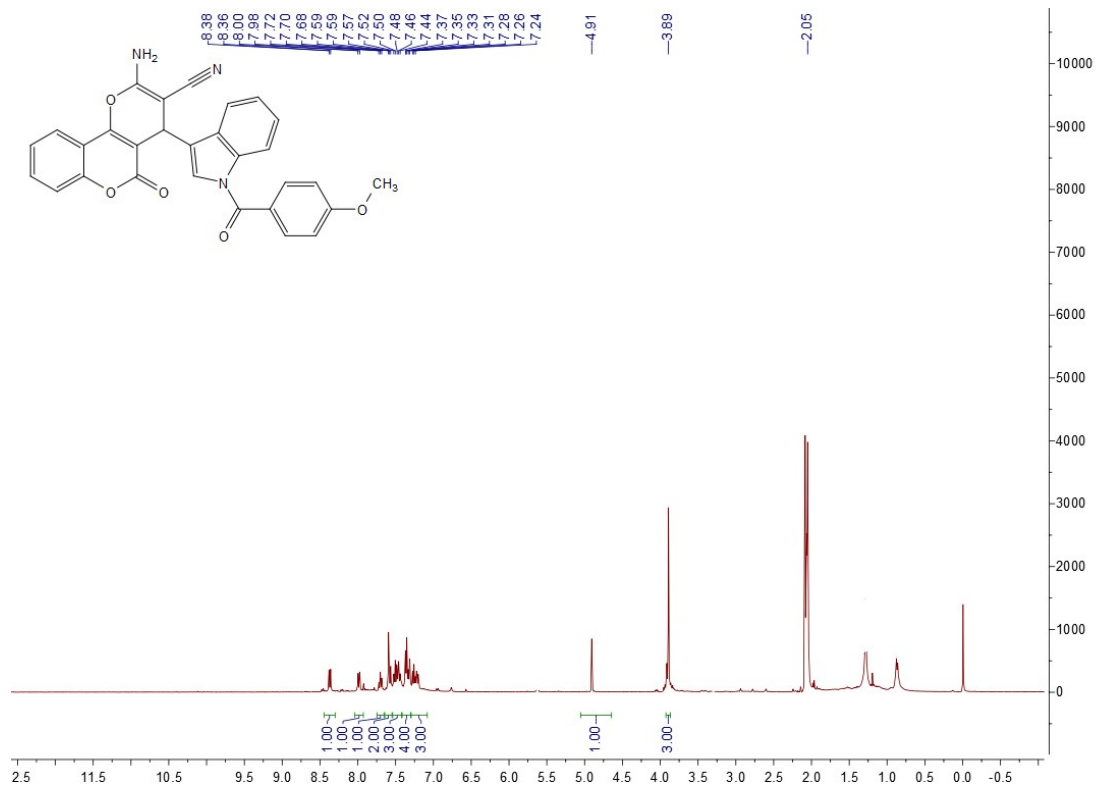
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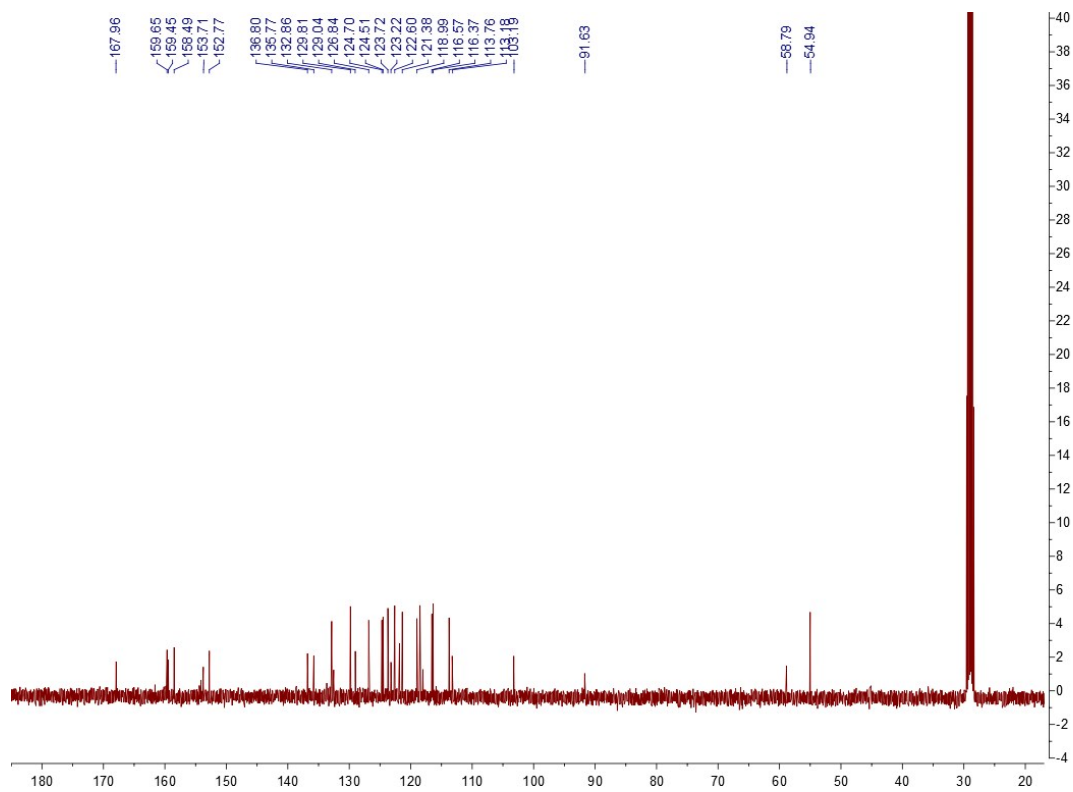
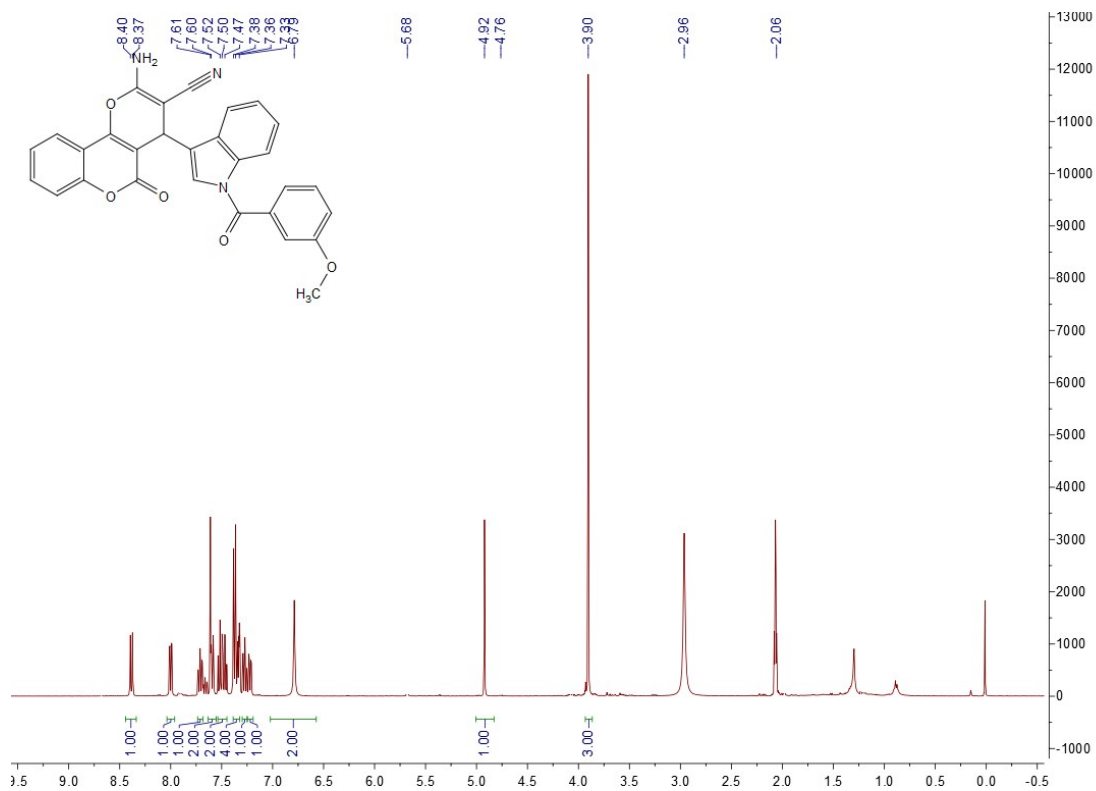
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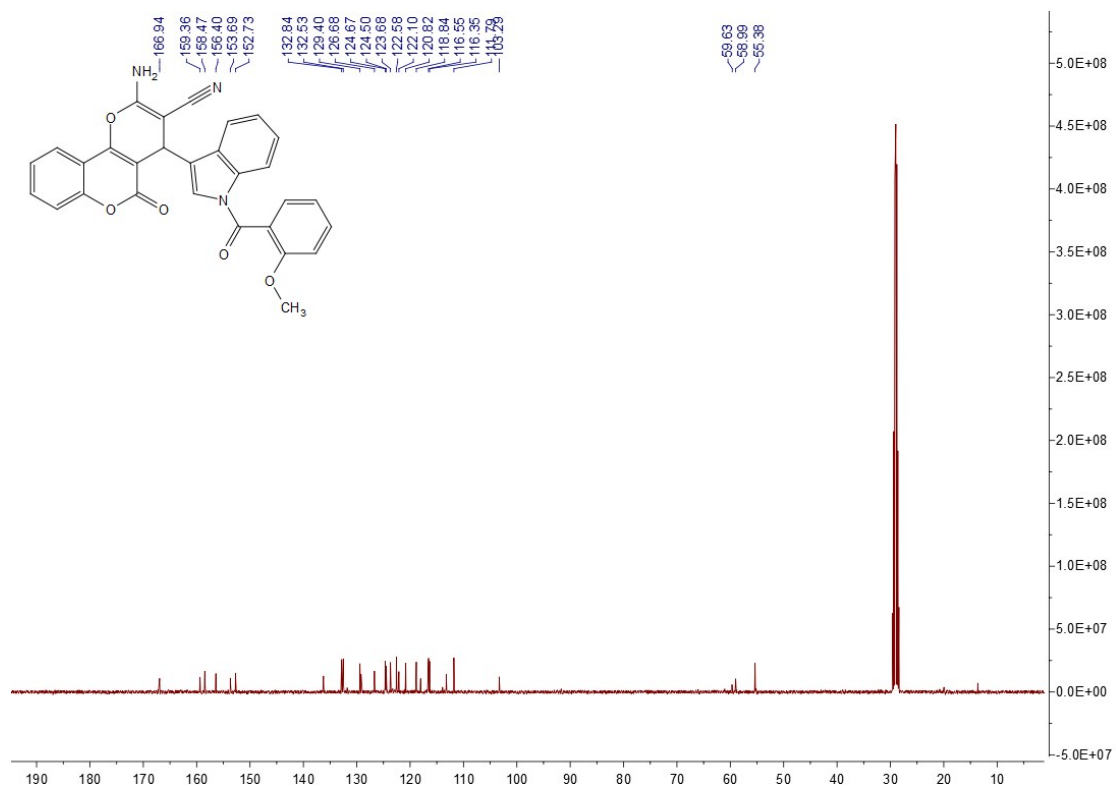
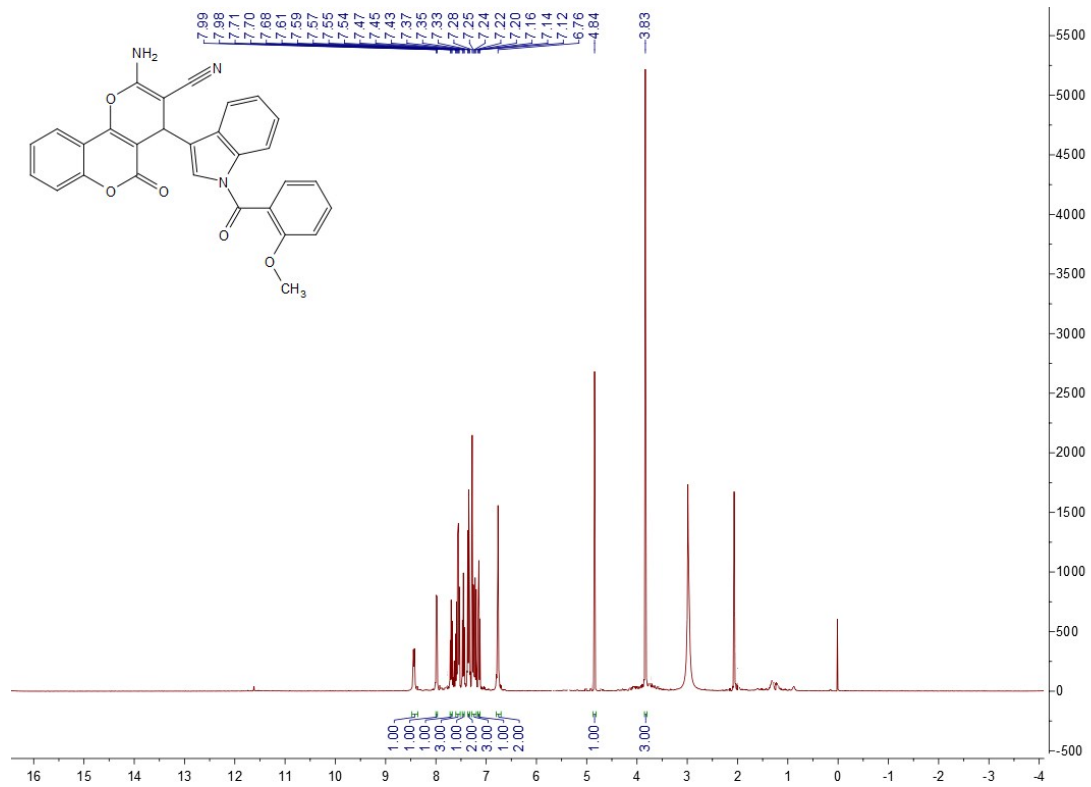
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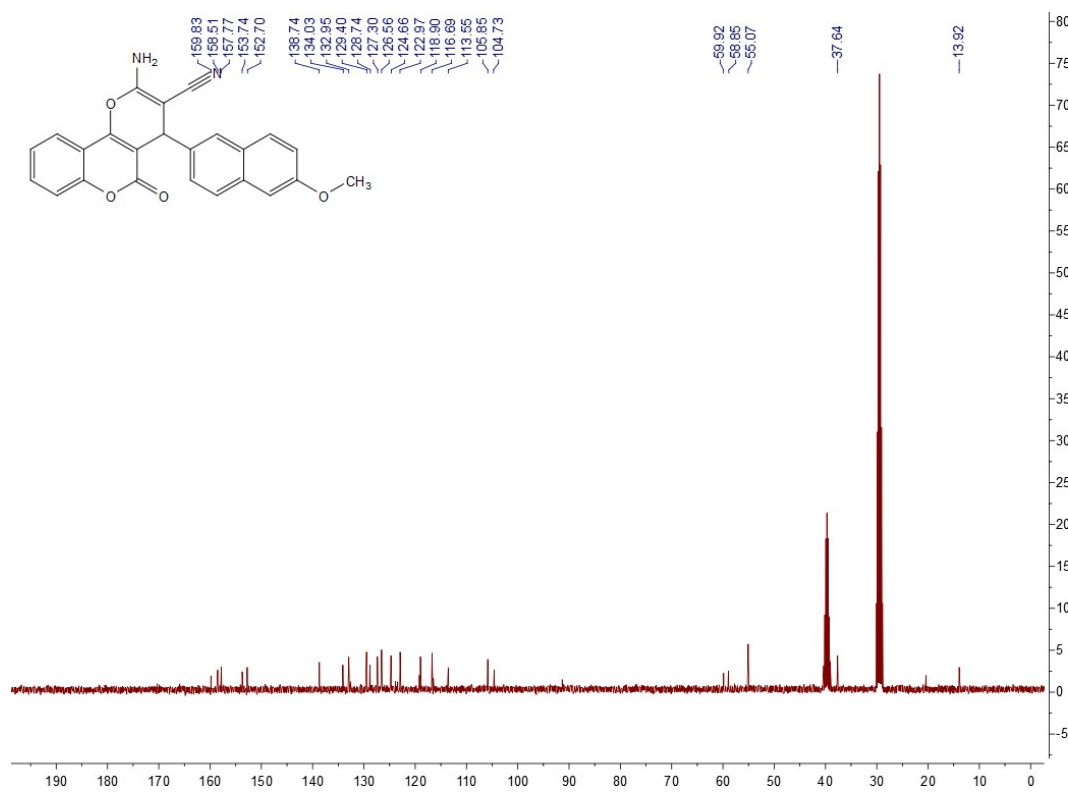
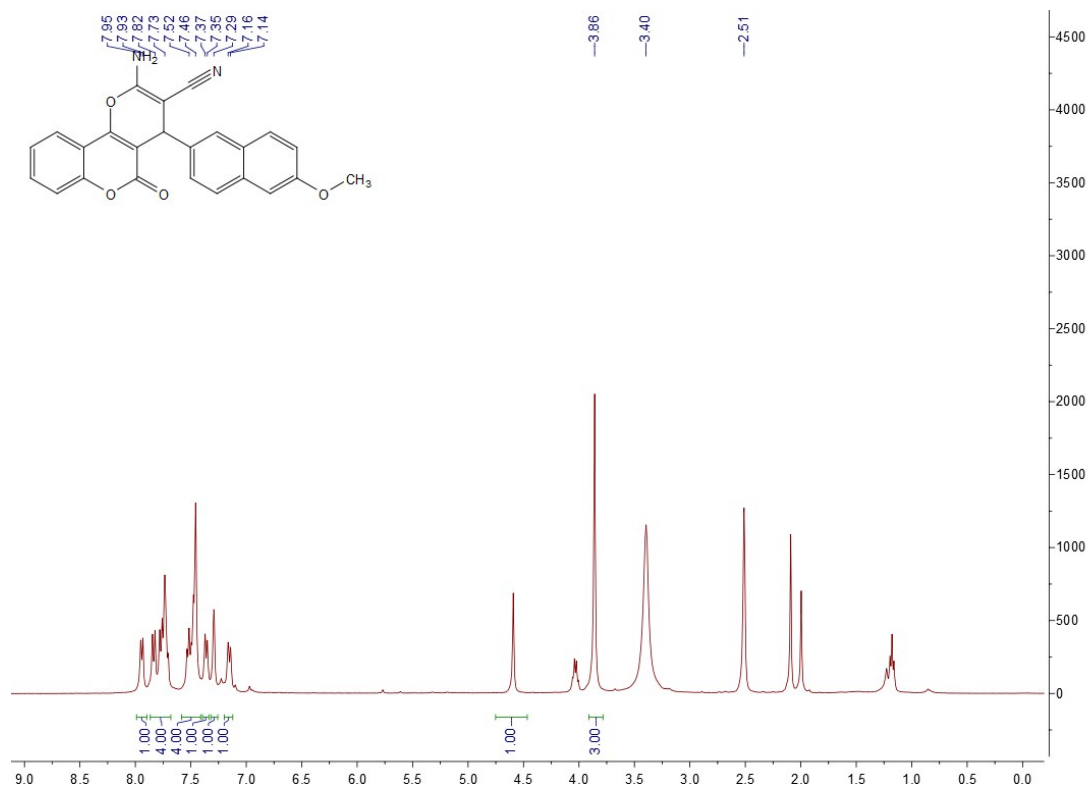


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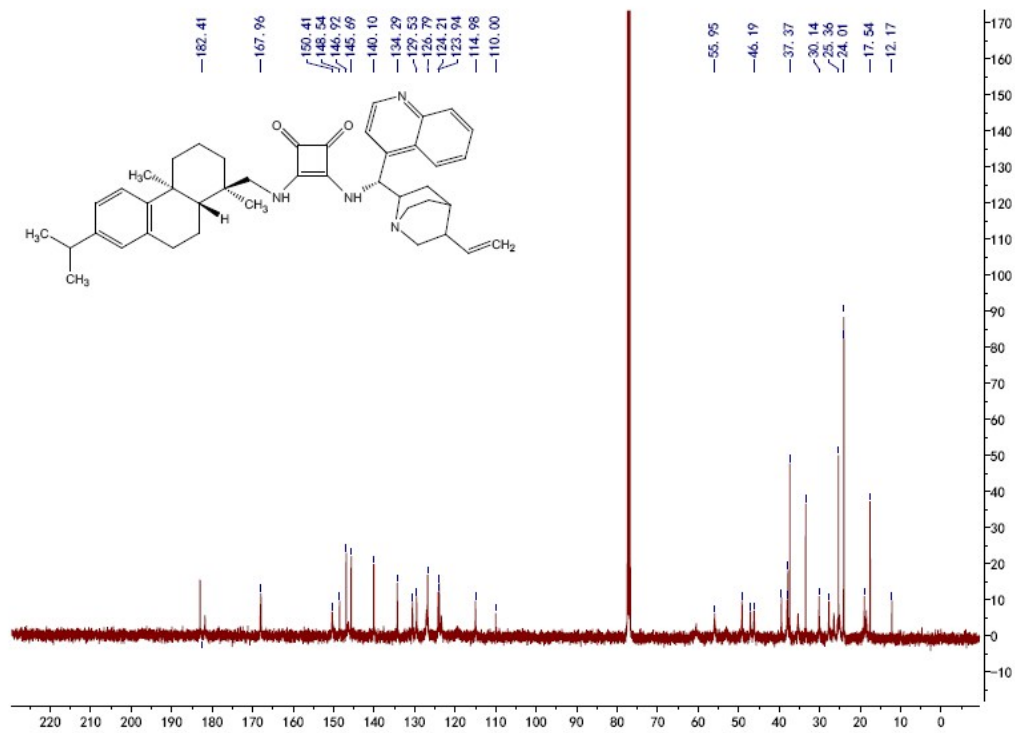
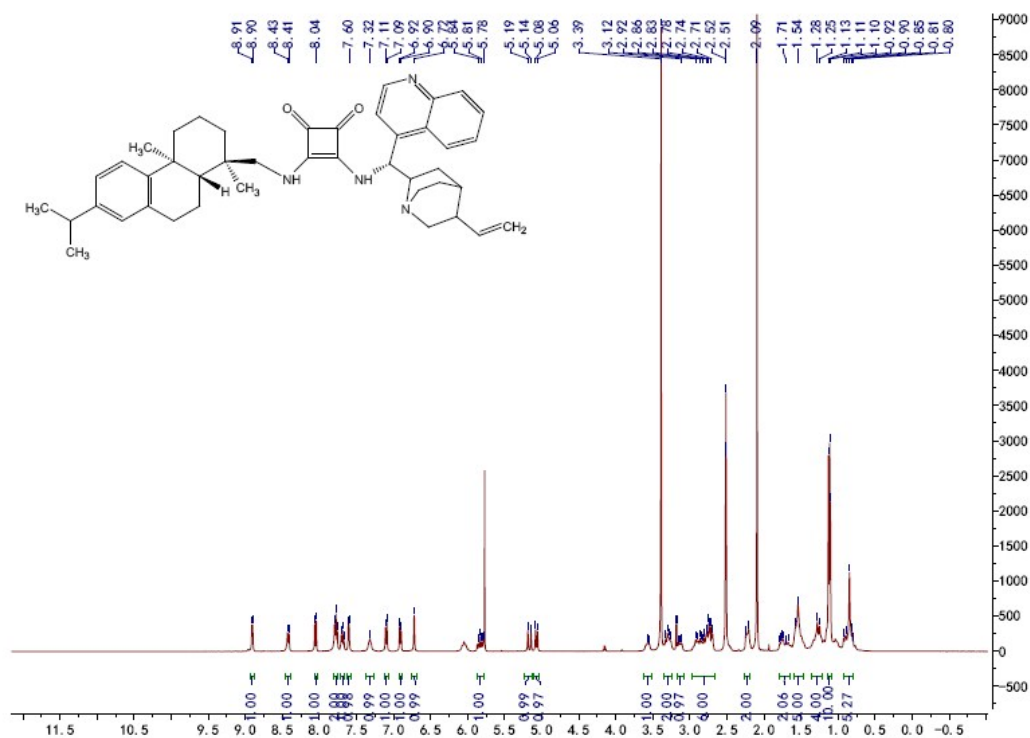




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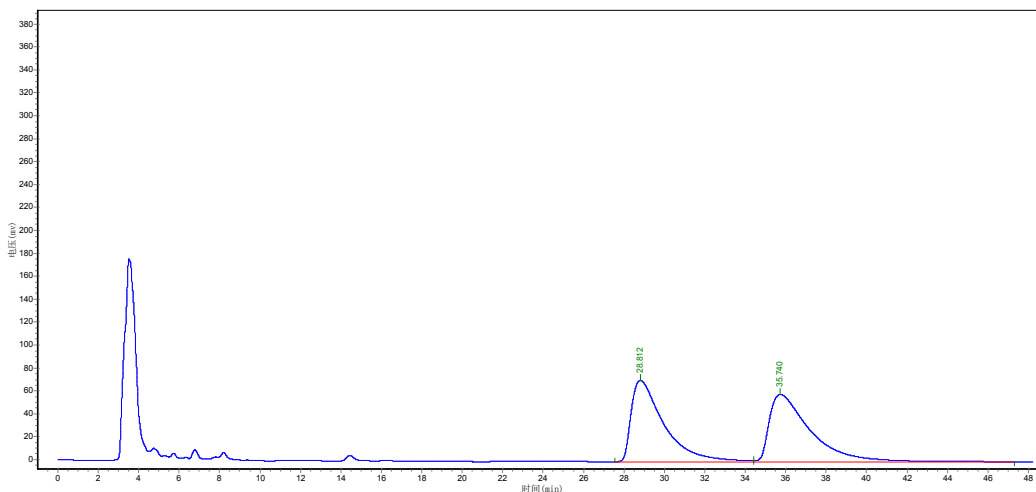


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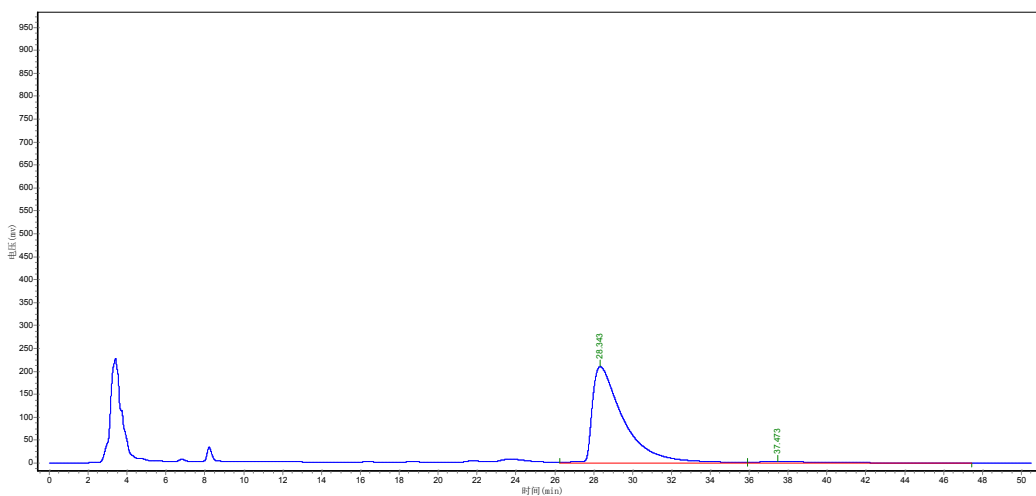


## II HPLC spectra of compound 4

4a

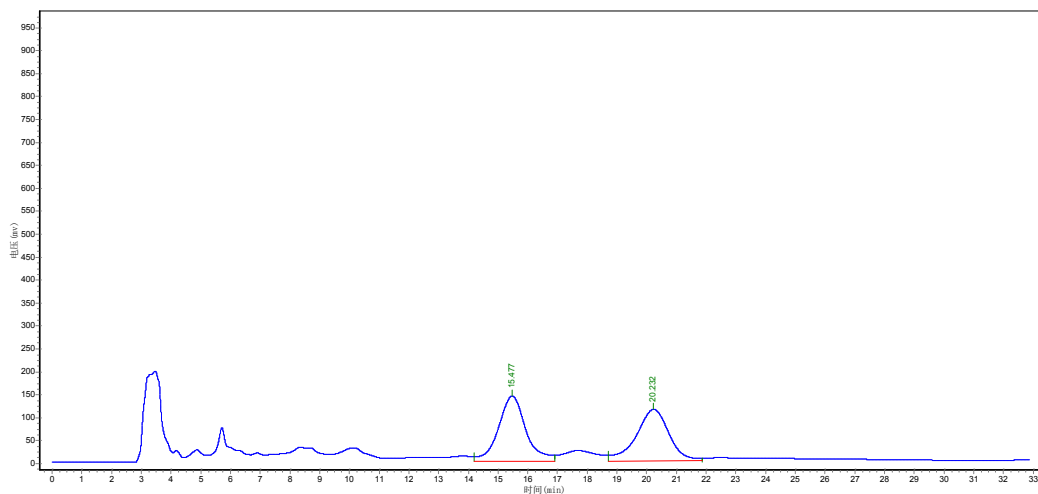


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	28.812	71039.188	7980246.500	48.9686
2	35.740	58684.453	8316418.500	51.0314

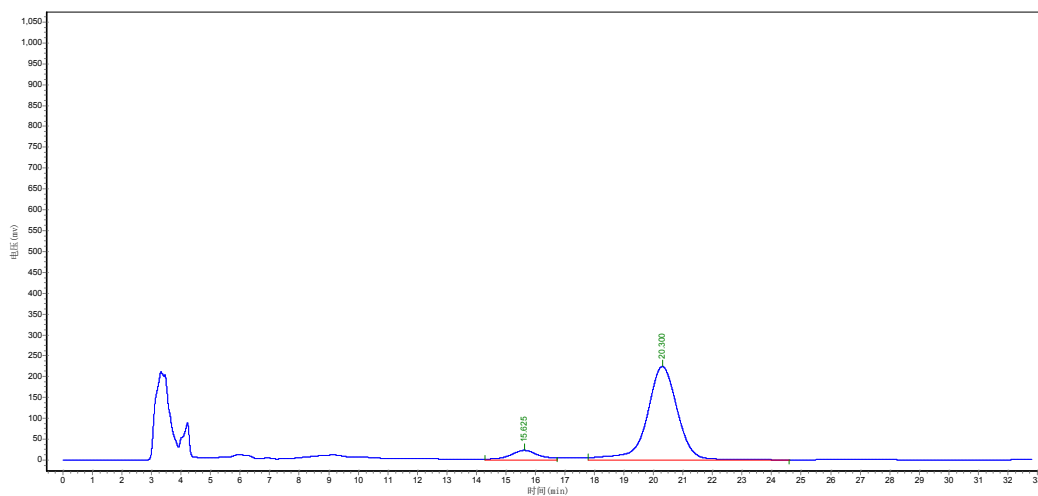


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	28.343	210171.875	23484714.000	96.5412
2	37.473	3963.806	841380.313	3.4588

4b

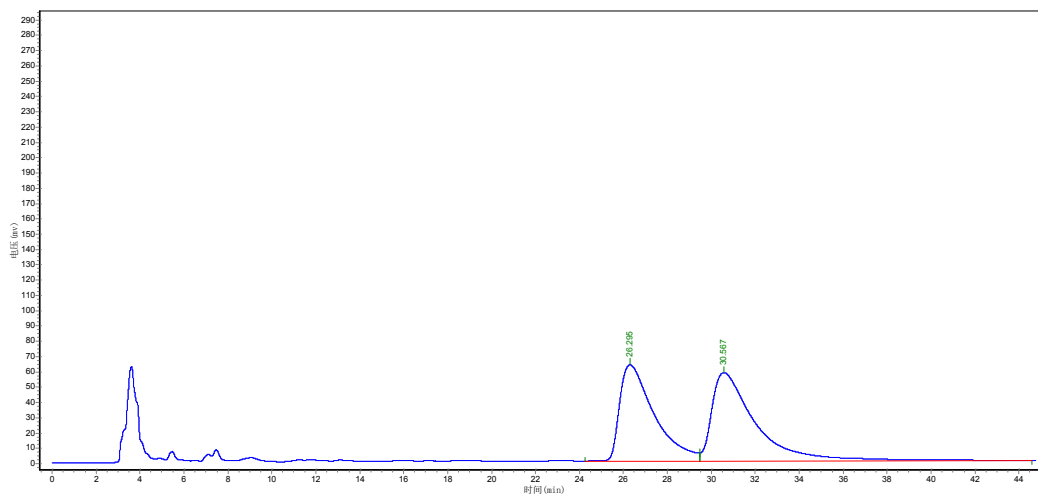


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	15.477	141912.031	9127446.000	51.3975
2	20.232	112483.563	8631091.000	48.6025

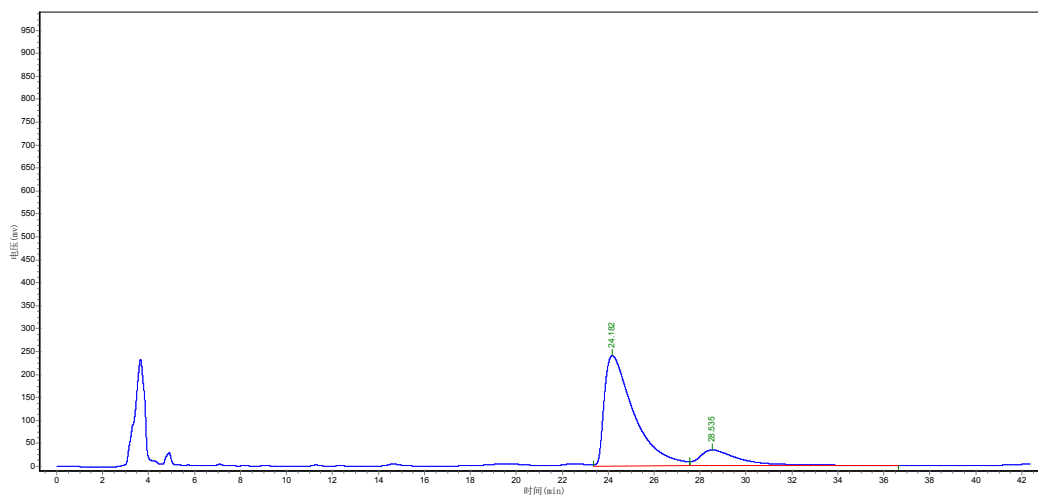


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	15.625	23654.666	1669433.500	9.2695
2	20.300	224616.406	16340494.000	90.7305

4c

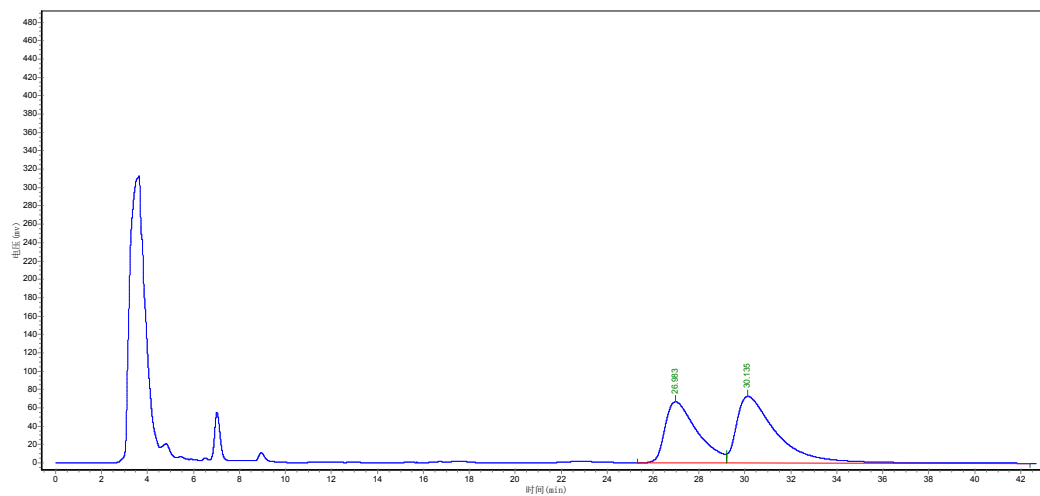


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	26.295	63106.055	6889177.500	46.3057
2	30.567	57792.109	7988438.000	53.6943

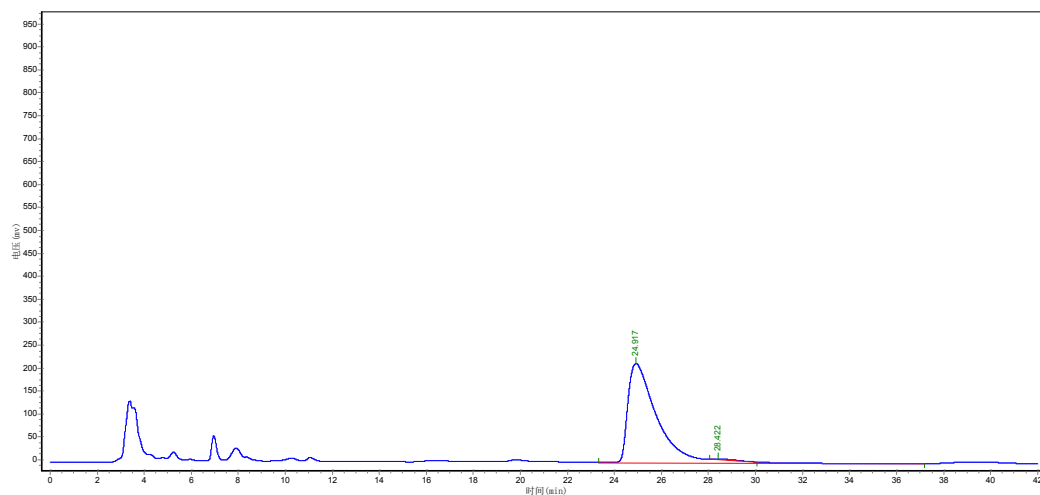


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
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2	28.535	34416.328	4246342.500	16.4658

4d

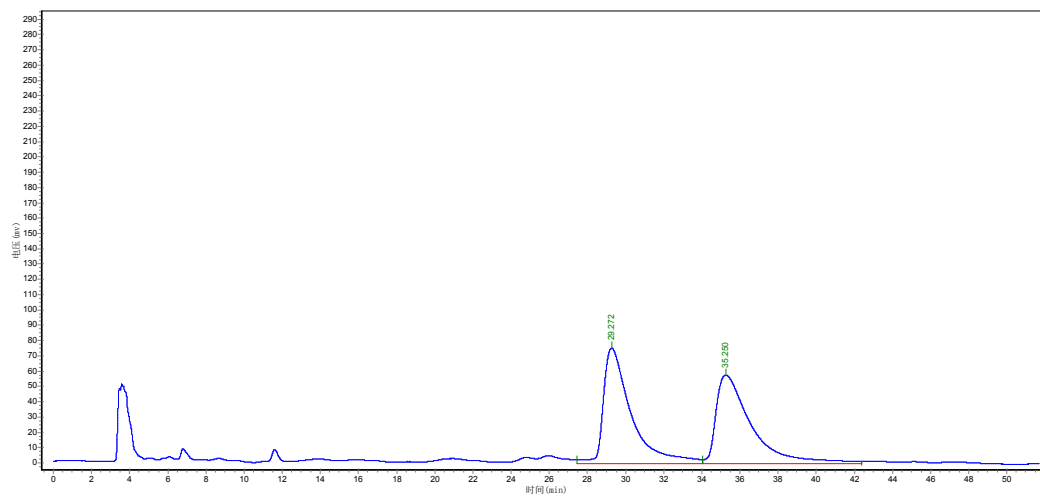


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	26.983	66652.930	7479100.000	47.4786
2	30.135	72554.813	8373524.000	52.5214

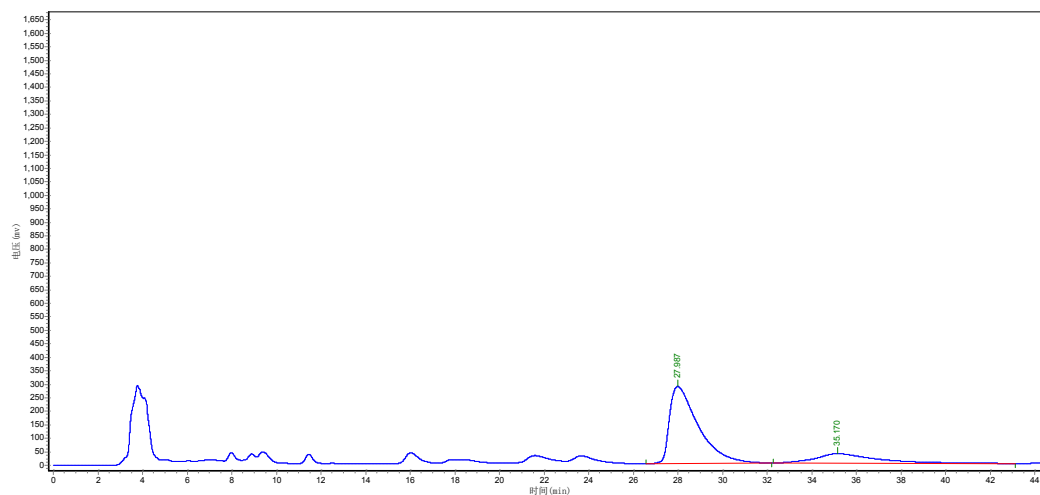


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	24.917	217011.078	19372962.000	99.4600
2	28.422	1419.900	105174.344	0.5400

4e

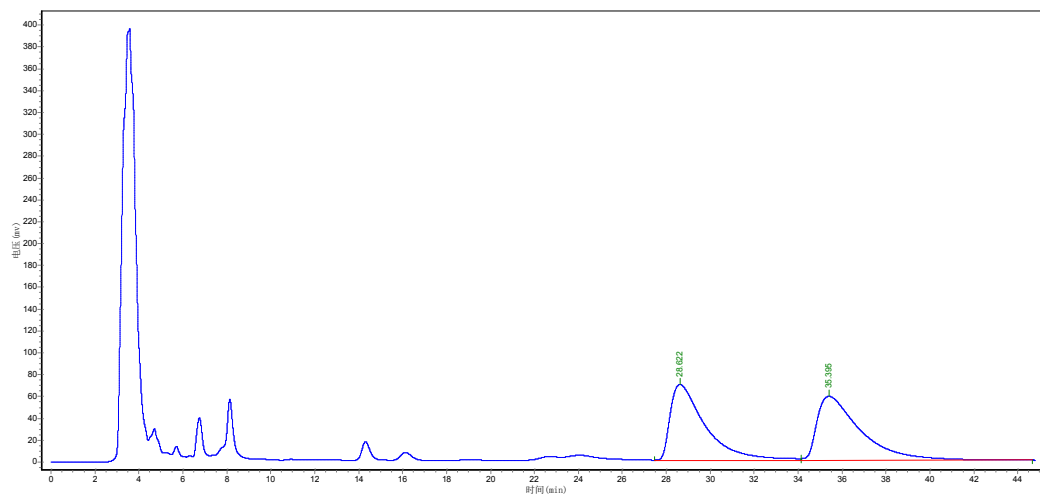


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	29.272	75297.383	7630465.000	50.6193
2	35.250	57836.449	7443767.000	49.3807

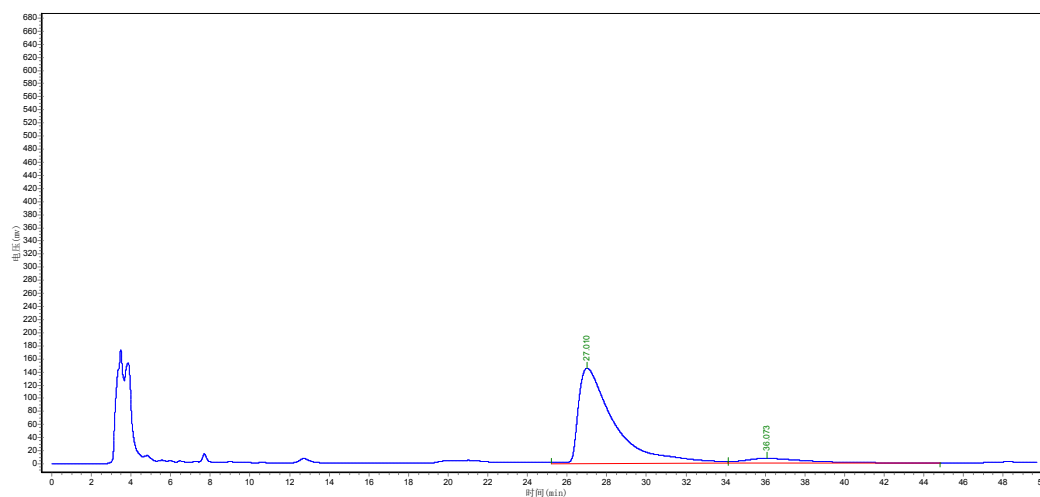


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	27.987	286119.906	25666466.000	79.4000
2	35.170	34988.988	6659070.000	20.6000

4f



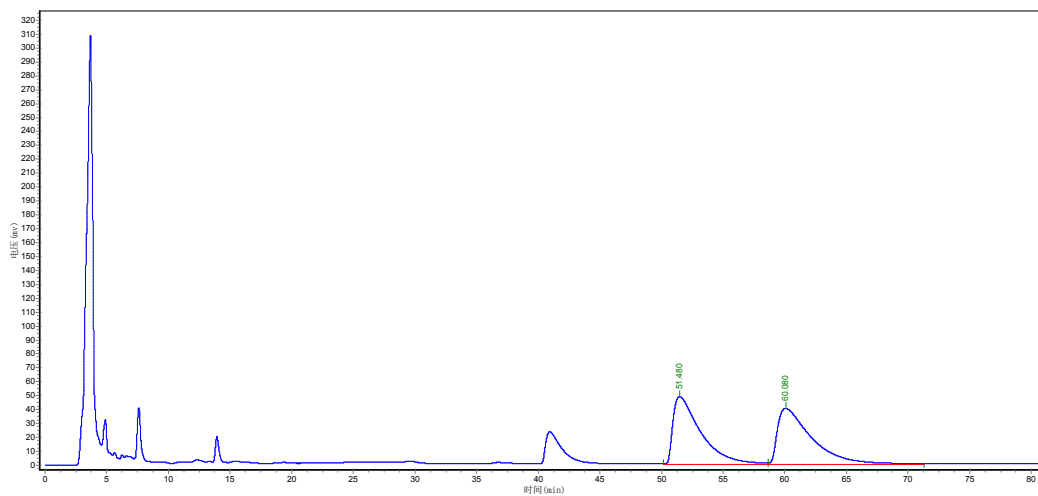
Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	28.622	69826.406	7853365.000	49.1447
2	35.395	58796.098	8126707.500	50.8553



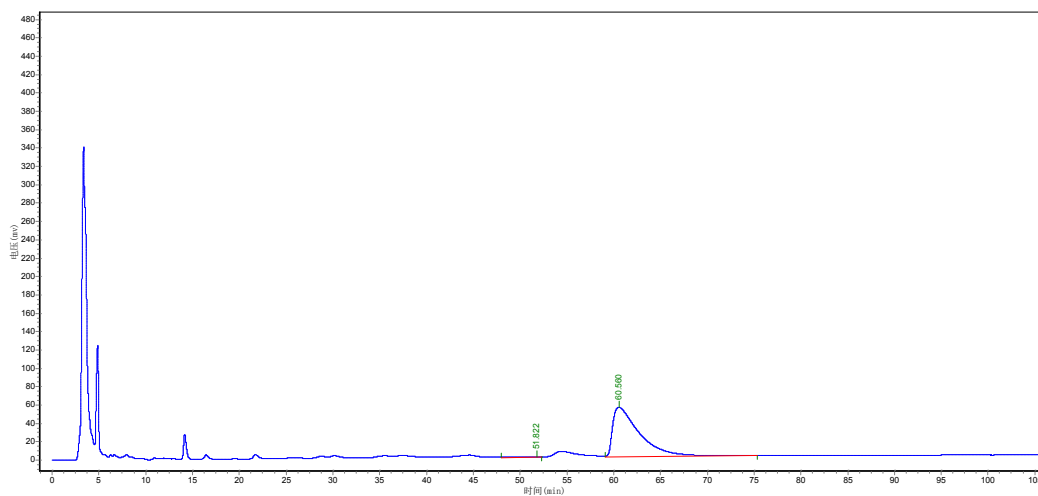
Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	27.010	145306.922	18264700.000	91.2157
2	36.073	7464.083	1758932.875	8.7843



4g

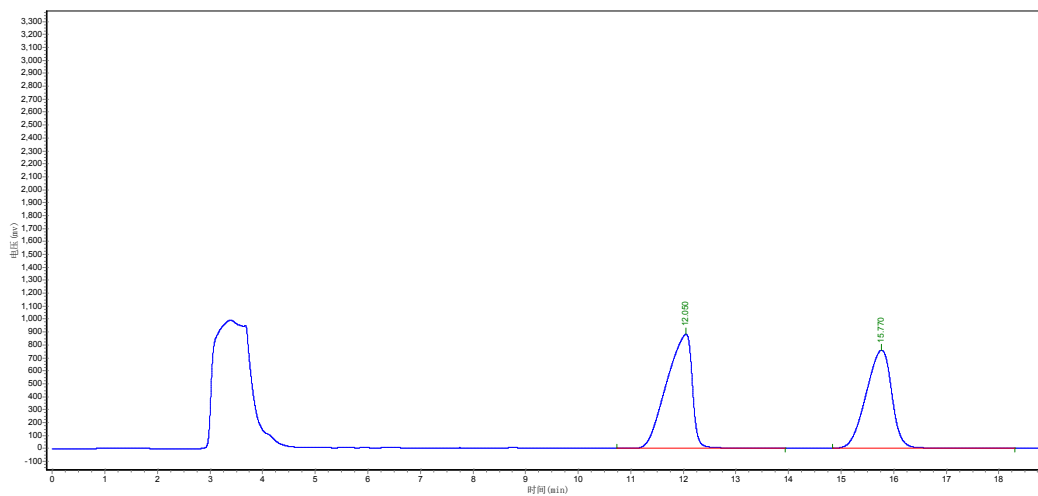


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
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2	60.080	40171.672	7723521.000	50.3563

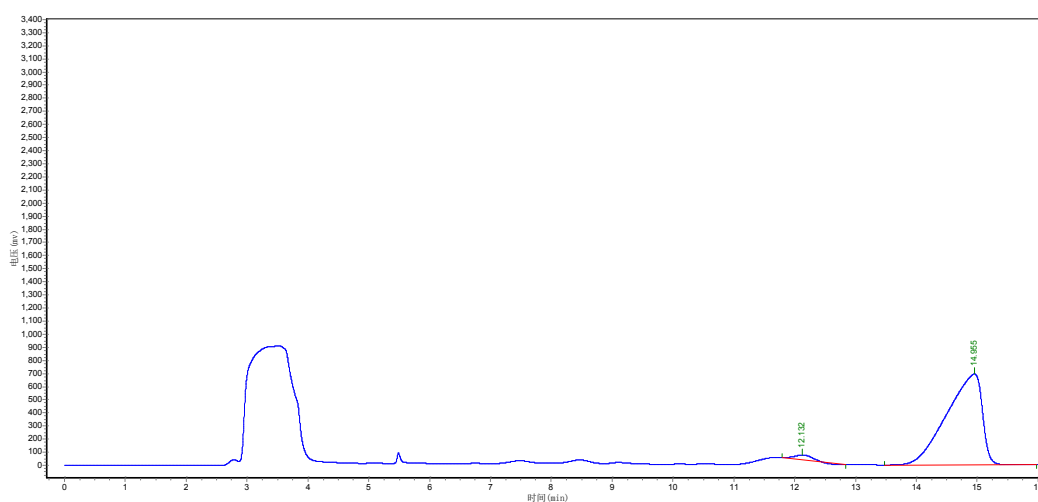


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
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2	60.560	53854.043	10757606.000	98.5738

4h

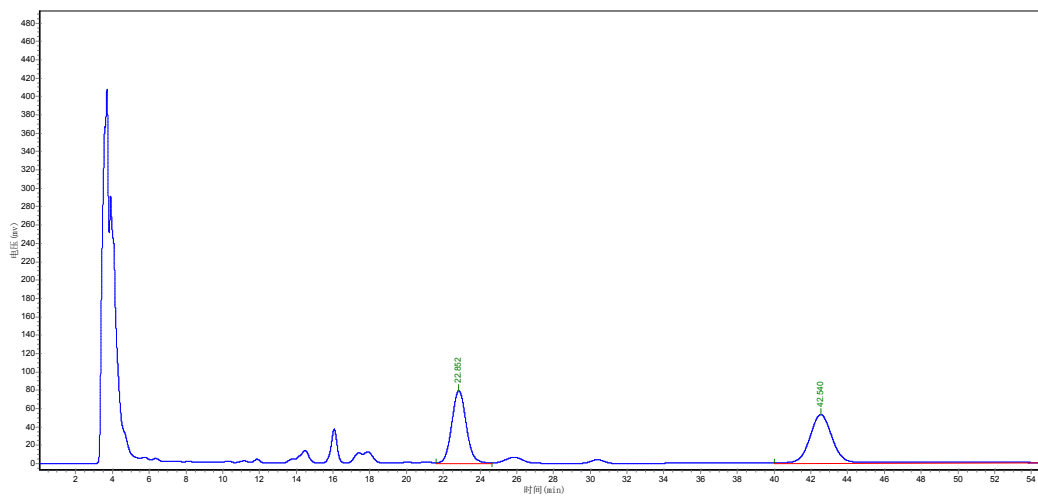


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
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2	15.770	760365.688	25959944.000	46.4315

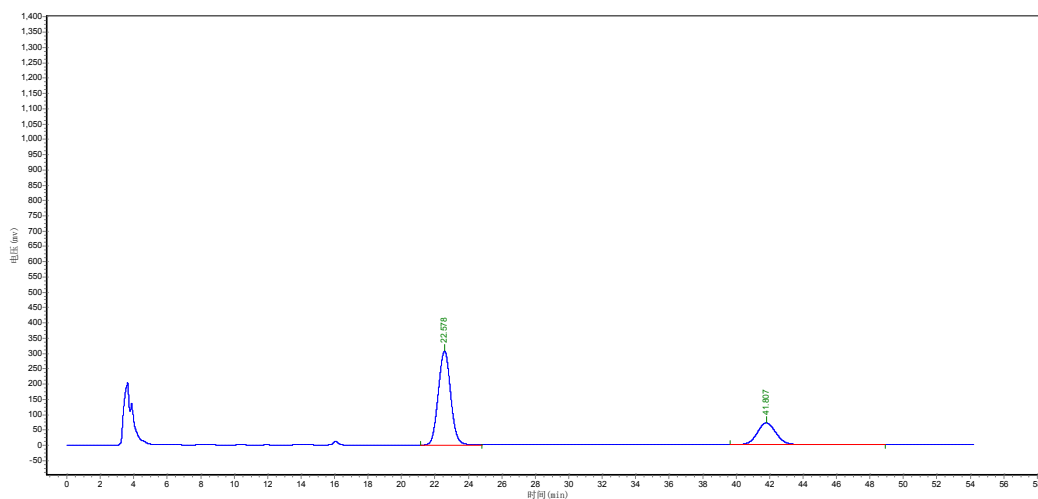


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
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2	14.955	693413.250	28035680.000	97.5994

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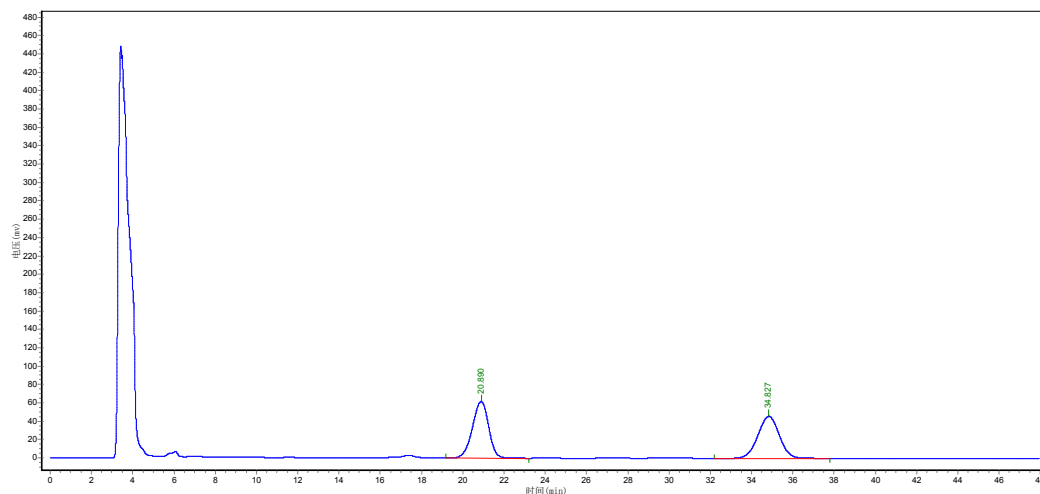


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	22.852	79522.016	4368077.000	44.7510
2	42.540	53134.879	5392761.500	55.2490

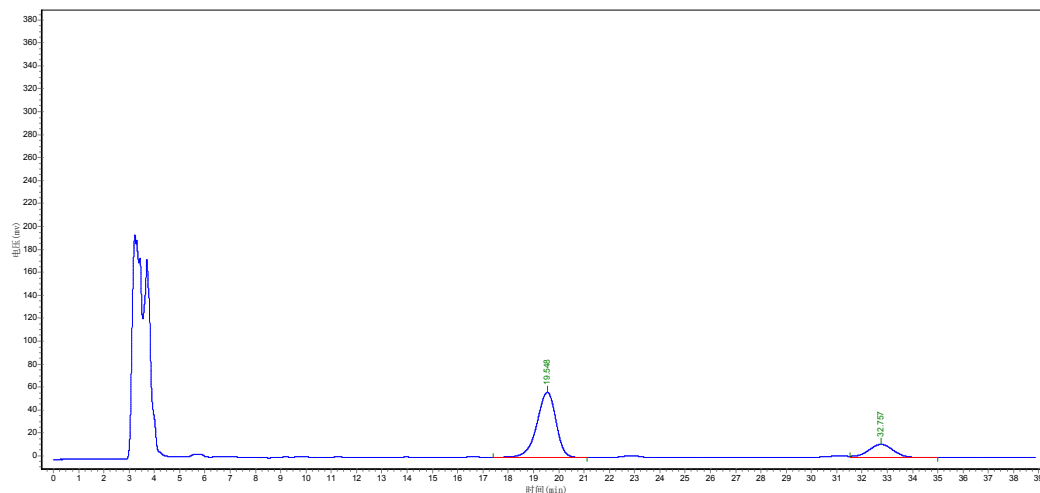


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	22.578	307270.719	15851232.000	73.9101
2	41.807	71141.859	5595420.500	26.0899

4j

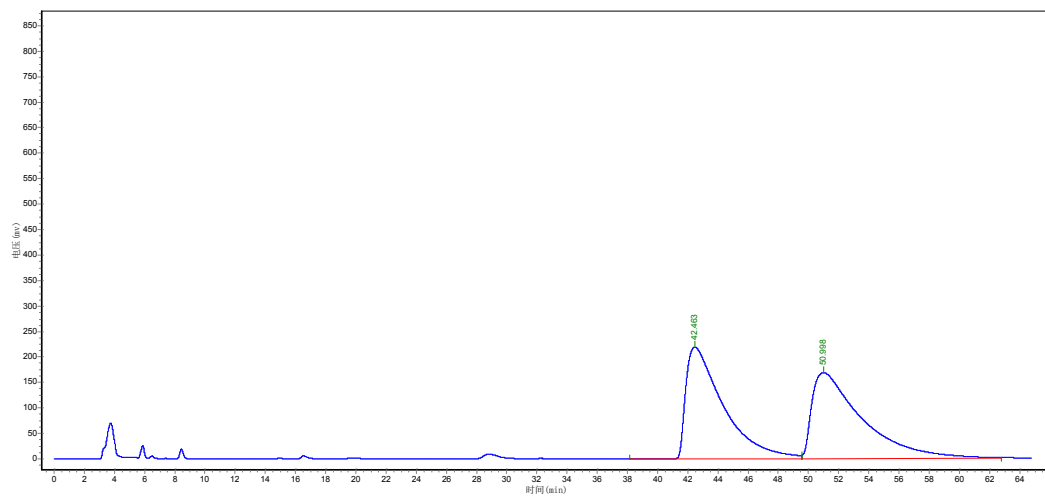


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	20.890	61871.836	3392466.750	50.7355
2	34.827	45762.941	3294107.500	49.2645

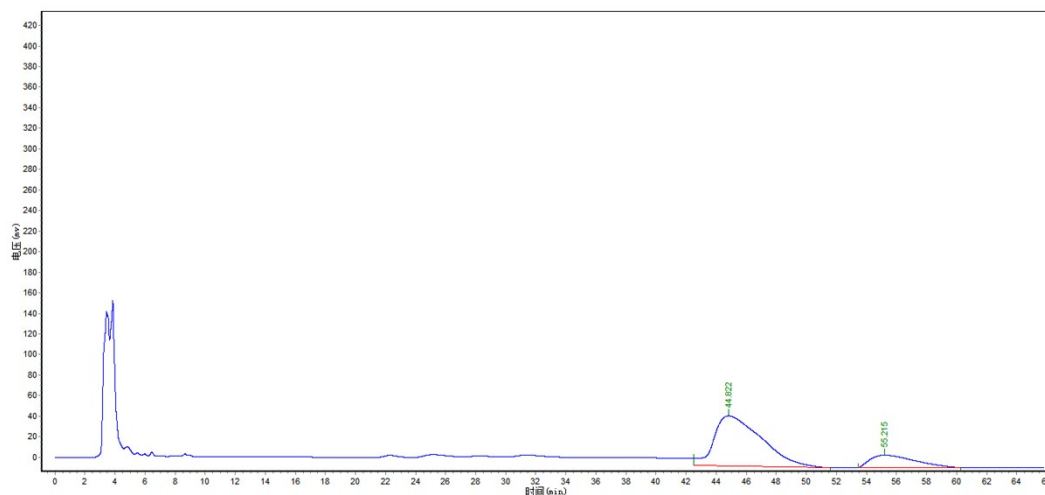


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	19.548	56674.211	2962628.250	81.5396
2	32.757	10660.020	670731.188	18.4604

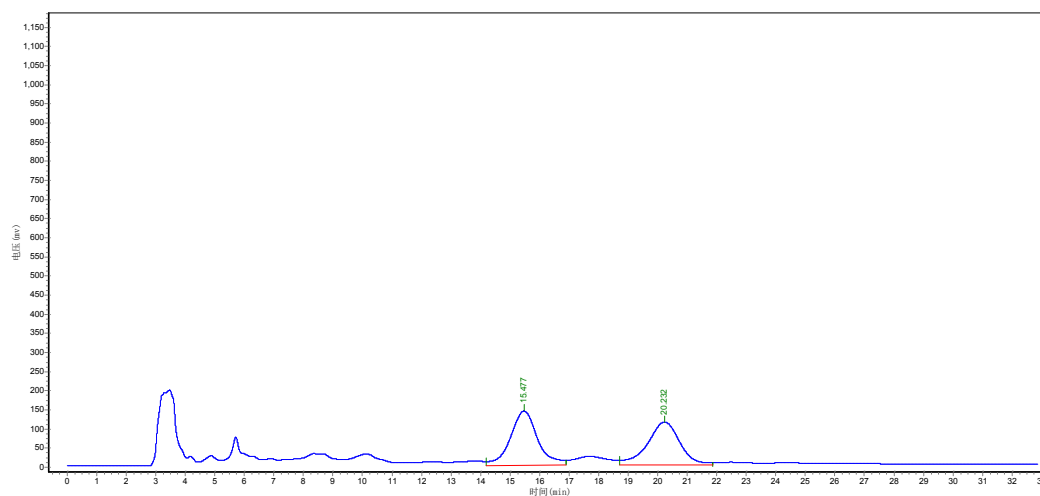
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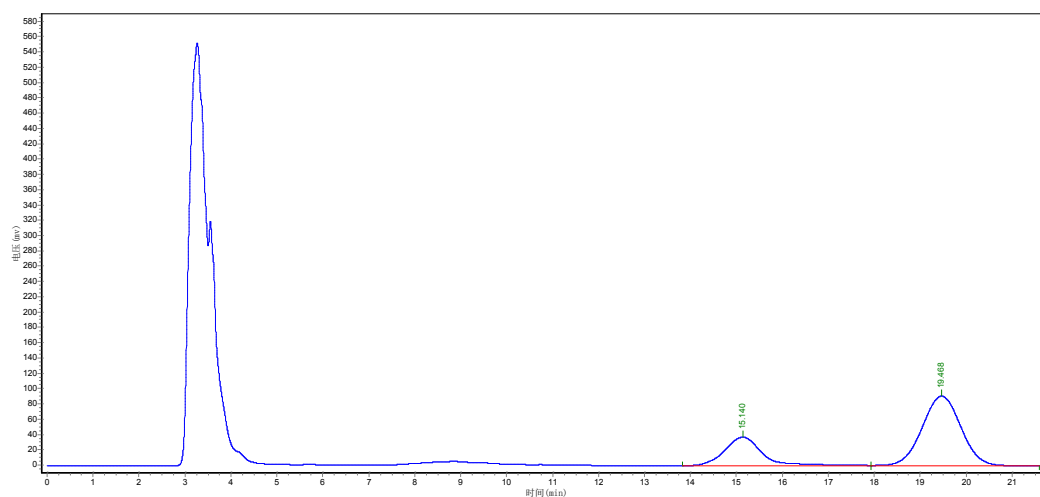
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1	42.463	219074.344	37800836.000	49.2964
2	50.998	168771.781	38879836.000	50.7036



Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	44.822	48549.945	10658692.000	81.0854
2	55.215	12051.740	2486324.750	18.9146

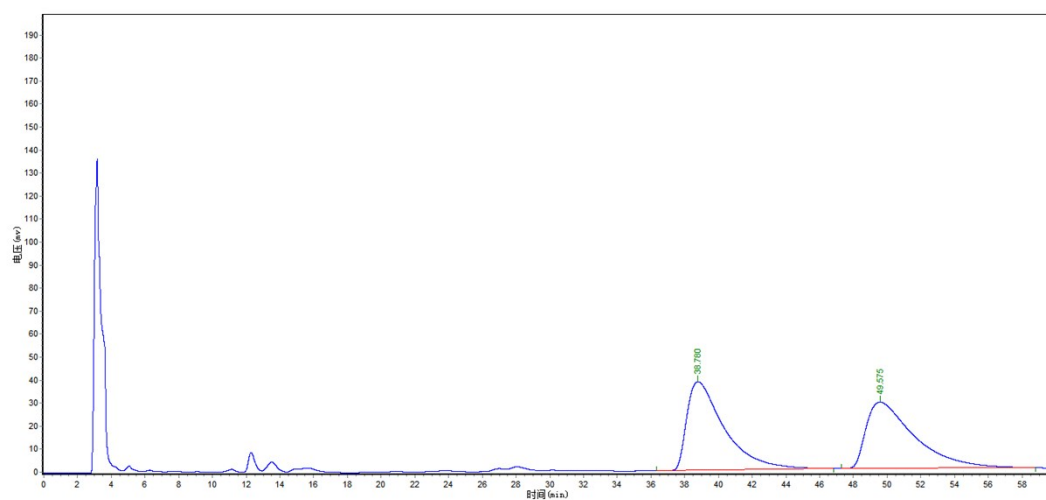


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	15.477	141912.031	9127446.000	51.3975
2	20.232	112483.563	8631091.000	48.6025

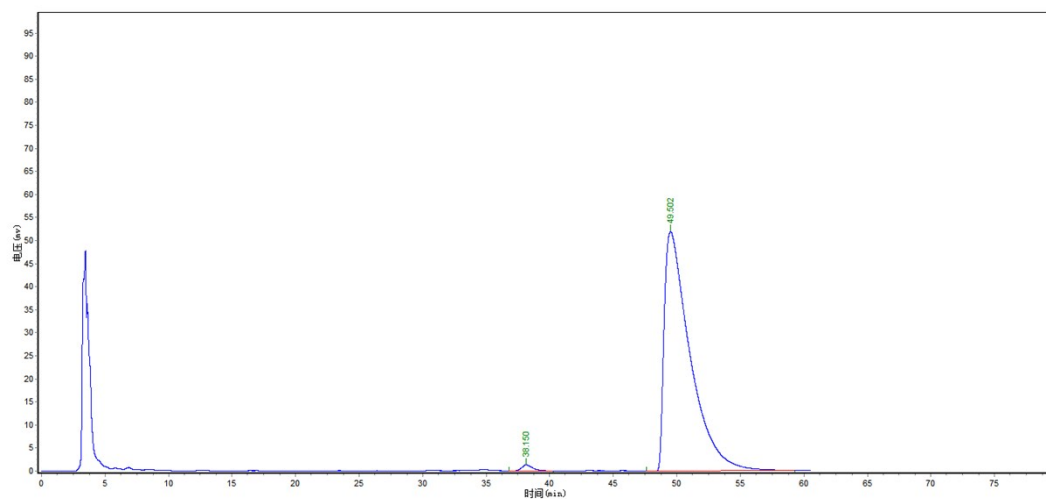


Peak	Ret Time (min)	Height (mAU)	Area (Mau *s)	Area (%)
1	15.140	37607.488	2207534.000	29.0857
2	19.468	91352.102	5382235.000	70.9143

# 4m

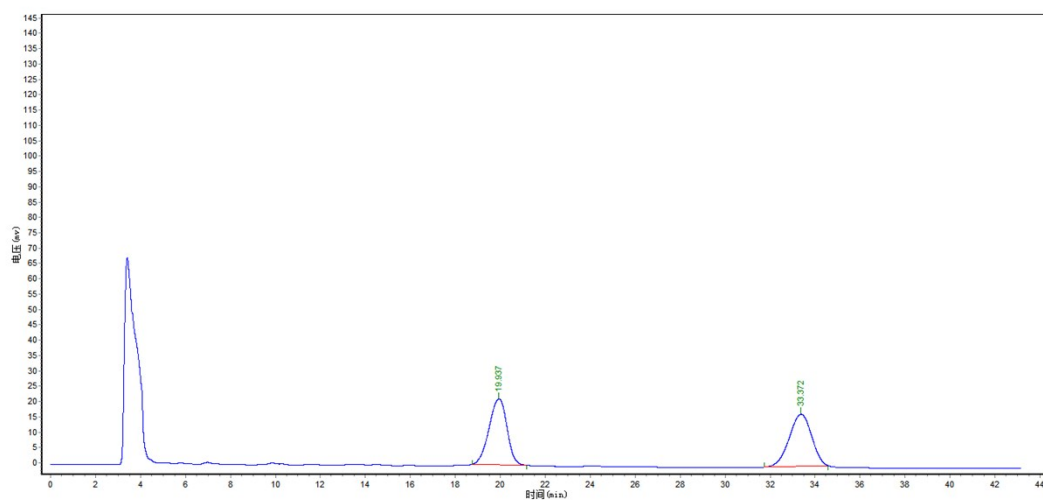


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1	38.780	38547.676	5943547.500	50.8863	
2	49.575	28758.545	5736512.000	49.1137	

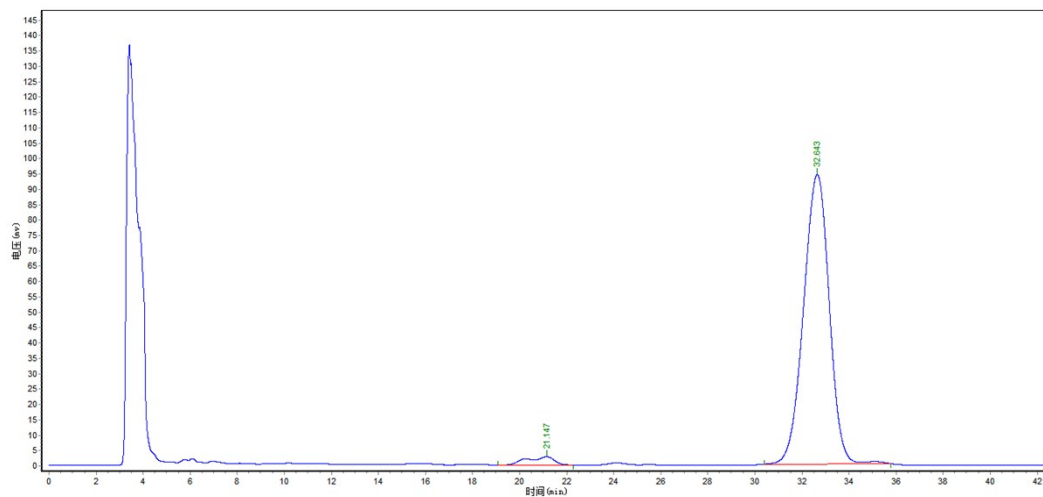


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4n



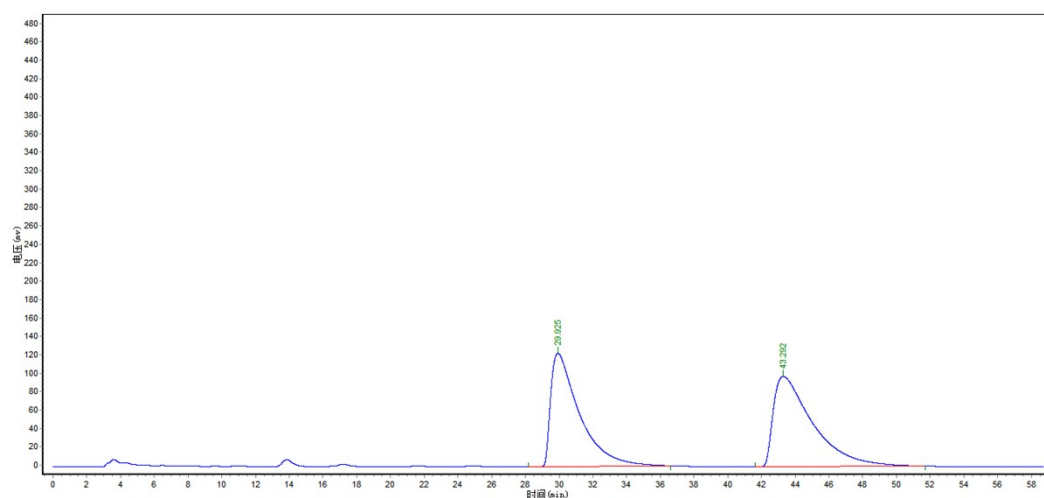
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1	19.937	21540.975	1190426.500	50.3381	
2	33.372	16985.869	1174435.875	49.6619	



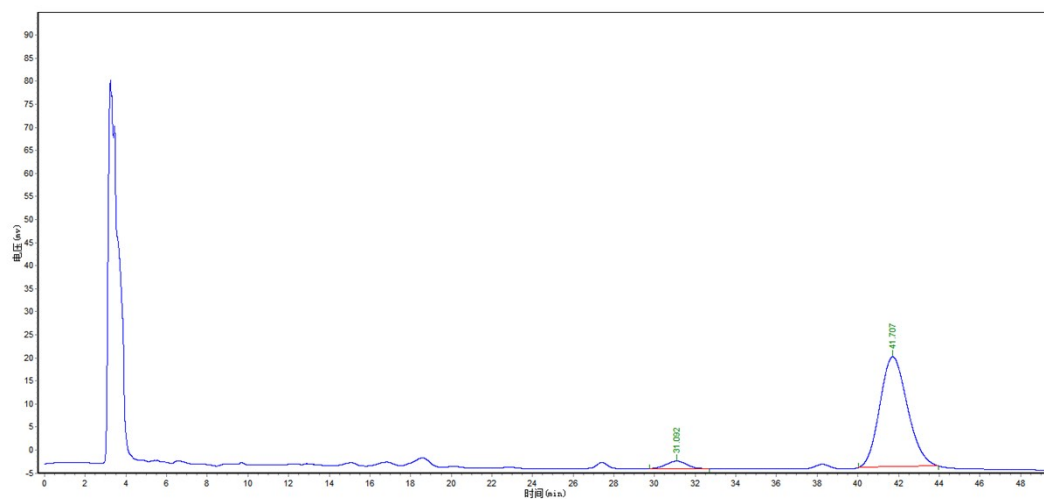
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1	21.147	2710.160	218931.000	2.9754	
2	32.643	94169.586	7138996.000	97.0246	



# 40

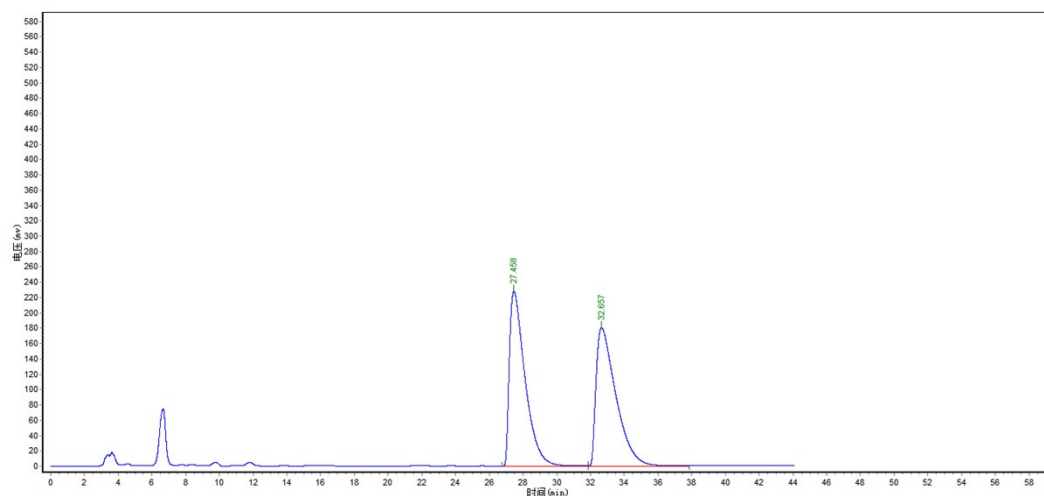


峰号	峰名	保留时间	峰高	峰面积	含量
1	29.925	123226.719	14560932.000	47.7959	
2	43.292	97991.828	15903866.000	52.2041	

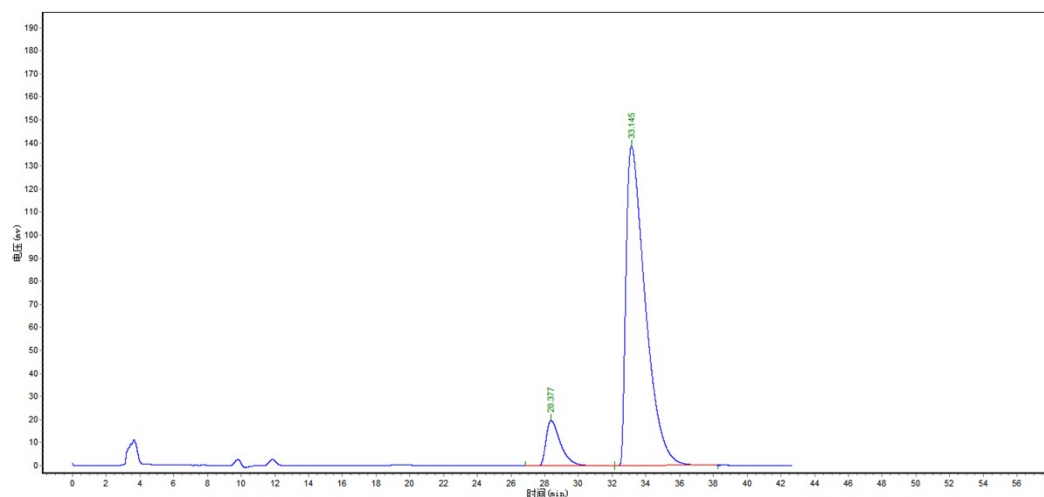


峰号	峰名	保留时间	峰高	峰面积	含量
1	31.092	1611.734	110761.609	4.6939	
2	41.707	23854.264	2248931.750	95.3061	

4p

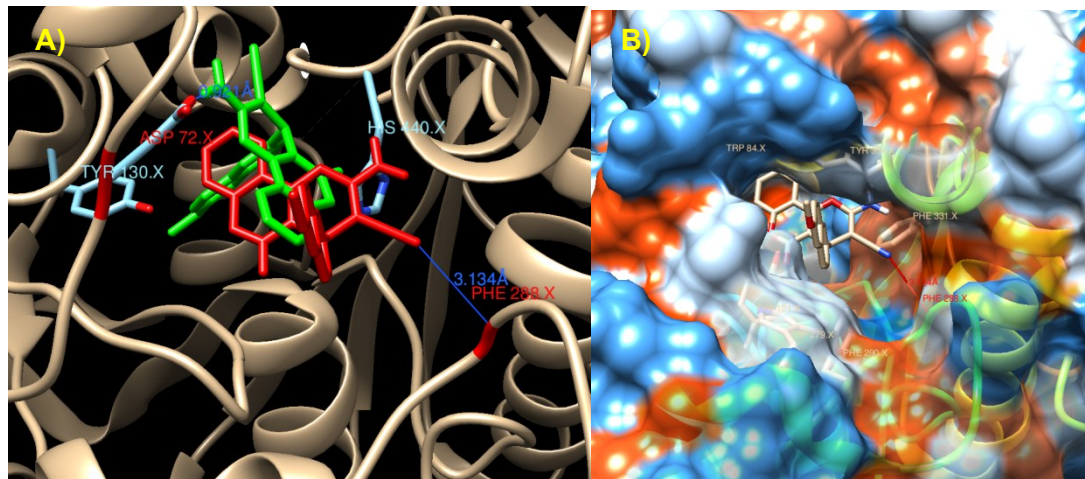


峰号	峰名	保留时间	峰高	峰面积	含量
1	27.458	227601.266	14699840.000	49.9897	
2	32.657	180455.266	14705889.000	50.0103	



峰号	峰名	保留时间	峰高	峰面积	含量
1	28.377	19714.949	1170667.875	9.6604	
2	33.145	138696.375	10947515.000	90.3396	

### III Computer modeling of the complex structures of AChE protein with (*S*)-**4p** and (*R*)-**4p**



**Fig. S1.** (A) Computer modeling of the complex structures of AChE protein with (*S*)-**4p** (green) and (*R*)-**4p** (red). (B) The surface type between (*S*)-**4a** with AchE protein.

For compound **4p**, both enantiomers showed the similar  $IC_{50}$  values for AChE. In the proposed structures of **4p**-protein (**Fig. S1**), (*R*)- and (*S*)-conformers fitted well in the pocket, and can form hydrogen bonds with the protein (pdb: 2w6c). For (*S*)-**4p**, the amino group forms hydrogen bond with ASP 72 and the length is 0.921 Å; for (*R*)-**4p**, the cyano group forms hydrogen bond with PHE 288 and the length is 3.134 Å. In addition, the naphthalenyl moiety, the chiral determinant of the compounds was docked outside, at least to some extent, partially buried in the hydrophobic pocket. As such, both (*R*)- and (*S*)-**4p** had a very similar activity range. But for (*S*)-conformer, the hydrogen bonds are significantly stronger than the (*R*)-one, so a slightly lower  $IC_{50}$  value for (*S*)-**4p** was observed than that of (*R*)-**4p**.