Supporting information

Cinchona Alkaloid Thiourea Catalyzed Asymmetric Synthesis and Anti-cancer Activity Assay of Tetrahydro-*β*-spirooxindoles

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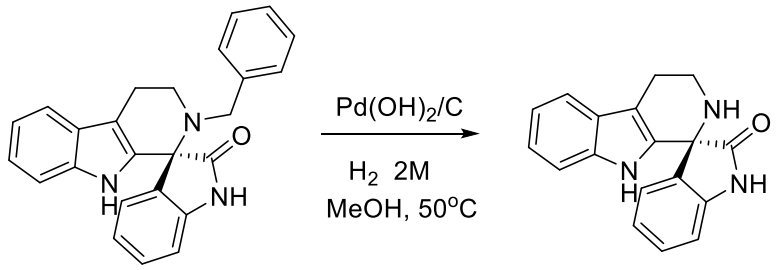
I. General Information and Procedure

1. General information

All reactions were carried out in oven-dried glassware with magnetic stirring under air unless otherwise mentioned. All other reagents were used without purification as commercially available. All reactions were monitored by thin layer chromatography. Purification of reaction products were carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. Solvents were purified and driedaccording to standard methods prior to use. Powdered 4Å molecular sieves were activated at 200 °C for 2 h. Catalysts C1-C8 were prepared according to the methods reported in the literature[1-2]. C9 were purchased from Energy Chemistry.

^{1}H NMR spectra were recorded on 500 MHz or 600 MHz spectrometer. The chemical shifts were reported relative to internal standard TMS (0) in $CDCl_3$. The following abbreviations may be used to describe peak patterns where appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{13}C NMR spectra were recorded on 125 MHz or 150 MHz spectrometer, referred to the internal solvent signals (77.0 for $CDCl_3$).Analytical HPLC was recorded on a HPLC machine equipped with Agilent 1100 series quaternary pump with a UV diode array detector. The chiral stationary phase was Daicel Chiralcel AD-H and OD-H column.



$[\alpha]_D^{25}$= -96.1(c=0.97, CH_2Cl_2)

$[\alpha]_D^{20}$= -83.0(c=0.5, MeCN)(ref.2)

Scheme 1 Debenzylation reaction[2a].

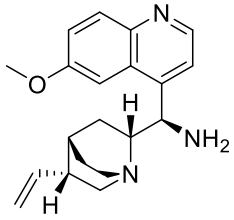
In order to determine the absolute configuration of the generated stereogenic center, the known compound *N*-debenzyl-**3o** was isolated and characterized. After three time of recrystallization (*ee*:94.5%), the specific rotation value was measured and compared with the reported data[2b], the absolute configuration of the known *N*-debenzyl-**3o** can be assigned as *S*.

2. General procedure for the reaction.

A mixture of *N*-protected tryptamine **1** (0.05 mmol), aldehyde**2**(0.06 mmol), catalyst **C2**(20% mol), 4 Å molecular sieves (0.1-0.2g, powdered) in 0.5 mL toluene and DCM was stirred at room temperature. The reaction was monitored with TLC. After the reaction was completed, the reaction mixture was directly purified by flash column chromatography (ethyl acetate / petroleum ether = 1/15 to 1/10, with 2% TEA) to give the desired product **3**.

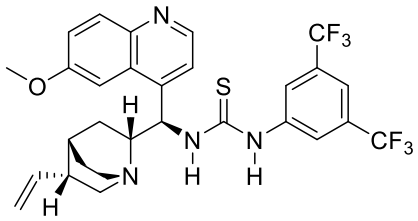
1.2 General procedure for the catalyst

9-Amino-(9-deoxy)-epi-quinine (S1)[3]



Quinine (2.0 g, 6.33 mmol) and Ph_3P (2.2 g, 8.43 mmol) was placed under vacuum and purged with N_2 three times, anhydrous THF (30 mL) was added and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (1.55 mL, 7.87 mmol) was added followed by the dropwise addition of a solution of diphenyl phosphoryl azide (1.65 mL, 7.66 mmol) in anhydrous THF (13 mL). The mixture was then allowed to warm to room temperature and stir for 16 h, at which point the mixture was heated at 50 °C for 2 h. Ph_3P (2.4 g, 8.96 mmol) was then added and mixture was stirred for a further 2 h at 50 °C. The solution was allowed to cool to room temperature before H_2O (0.7 mL) was added and then stirred for a further 3 h. The mixture was then concentrated in vacuo and the crude residue was dissolved in CH_2Cl_2 (30 mL) and diluted with 2 M HCl (30 mL) and the aqueous phase was washed with CH_2Cl_2 (2 x 30 mL). Excess concentrated aqueous ammonia was added to the aqueous phase followed by extraction with CH_2Cl_2 (3 x 30 mL), the combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography afforded amine **S1** as a white solid (1.9 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.76 (d,J=6Hz, 1H), 8.02-8.05(m, 1H), 7.28-7.67 (m, 5H), 5.86-5.92(m, 1H), 5.07-5.10(m, 2H), 4.70(br, 1H), 3.97 (s, 3H), 2.96-3.01(m, 4H), 2.29-2.32(m, 1H), 1.55-1.63(m, 3H), 1.13-1.17(m, 1H), 0.95-0.99(m, 1H), 0.88-0.90(m,1H).

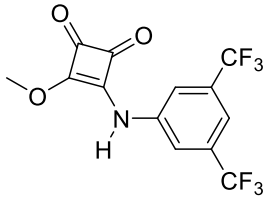
N-[3,5-Bis(trifluoromethyl)phenyl]-N′-[(8a,9S)-6′-methoxy-9-cinchonanyl]thiourea (S2)[4]



Amine **S1** (1.9 g, 5.89 mmol) was placed under vacuum and purged with N_2 three times, dissolved in anhydrous THF (20 mL). Solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.2 mL, 6.60 mmol) in

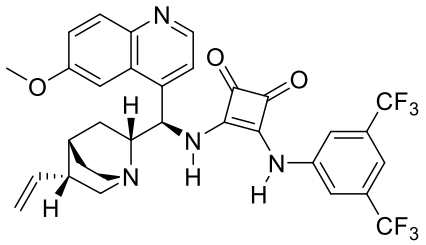
anhydrous THF (10 mL) was added dropwise at room temperature and the resulting mixture was stirred for 16 h. The reaction mixture was concentrated in vacuo and purified by column chromatography to afford thiourea **S2** as an off white solid (3.2 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.67 (d, *J*=4.7 Hz, 1H), 8.09 (s, 2H), 8.07 (br 1H), 7.93 (d, *J*=9.3 Hz,1H,), 7.59 (1H, br s), 7.56 (1H, d, *J*=4.8 Hz), 7.43 (d, *J*=9.3, 1H), 6.38 (br, 1H), 5.84-5.87 (m, 1H), 5.07-4.96 (m, 2H), 4.01 (s, 3H), 3.73-3.57 (m, 1H), 3.54-3.40 (m, 1H), 3.36-3.25 (m, 1H), 2.93-2.77 (m, 2H), 2.45-2.31 (m, 1H), 1.79-1.56 (m, 3H), 1.54-1.40 (m, 1H), 0.94-0.80 (m, 1H). Proton NMR were consistent with literature data.

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (S3) [5]



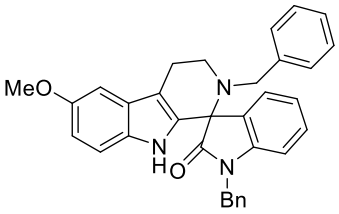
To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (2.00g, 14.1mmol) in MeOH (20ml) was added 3,5-bis(trifluoromethyl)aniline (2.40ml, 15.5mmol, 1.1equiv) at rt. The mixture was stirred at rt for 3 days. The reaction mixture was filtrate and washed with MeOH. Obtained yellow solid was dried in vacuo to give desired product 2a (4.59, 13.5mmol, 96%). ^{1}H NMR (600 MHz, DMSO) δ: 4.22(s, 3H), 7.78(s, 1H), 8.05(s, 2H), 11.19(s, 1H). Proton NMR were consistent with literature data.

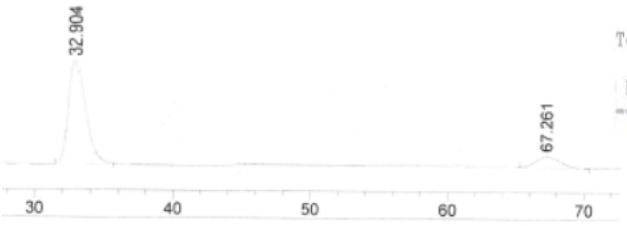
3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((R)-(6-methoxy-quinolin-4-yl)((1S, 2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-cyclobut-3-ene-1,2-dione. (S4) [6]



To a solution of 9-Amino-(9-deoxy)-epi-quinidine (1.0 mmol) in 5 mL CH_2Cl_2 was added **S3** (1.0 mmol). The reaction mixture was stirred for 48 h at room temperature. The desired product was obtained through filtration or by silica gel column chromatography. Yellow solid, 84% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.56 (s, 1H), 7.95 (d, *J*=12Hz, 1H), 7.70 (s, 1H), 7.41 (s, 1H), 7.31-7.35(m, 2H), 6.22 (br, 1H), 5.82-5.88 (m, 1H), 5.19 (d, *J*=18Hz, 1H), 5.12 (d, *J*=12Hz, 1H), 3.97 (s, 3H), 3.42 (br, 1H), 3.21 (br, 1H), 2.82-301 (m, 3H), 2.28 (br, 1H), 1.69 (s, 1H), 1.56 (br, 2H), 1.07-1.28 (m, 3H). Proton NMR were consistent with literature data.

II. HPLC Spectra

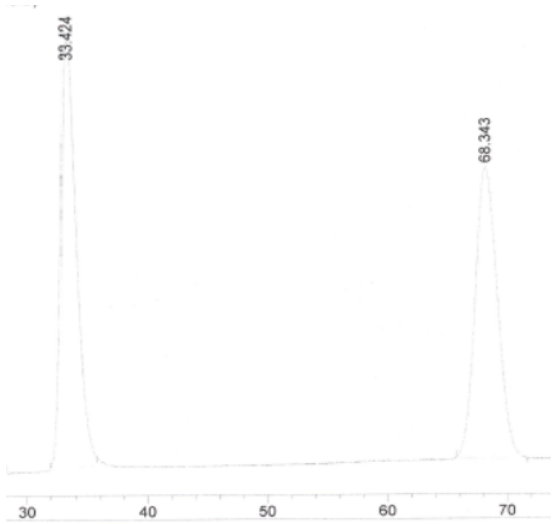




Signal 1: DAD1 A, Sig=225,4 Ref=360,100

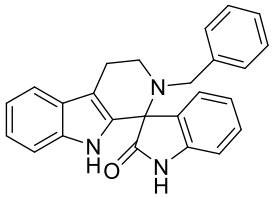
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.904	BB	1.2572	1.46092e4	178.81235	85.7
2	67.261	BP	1.6736	2429.95361	19.88605	14.2
Totals :				1.70391e4	198.69839	

Results obtained with enhanced integrator!



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.424	BB	1.2694	6455.65234	74.91471	49.4077
2	68.343	BB	2.0108	6610.44141	50.64411	50.5923
Totals :				1.30661e4	125.55882	

Results obtained with enhanced integrator!

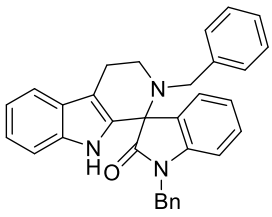


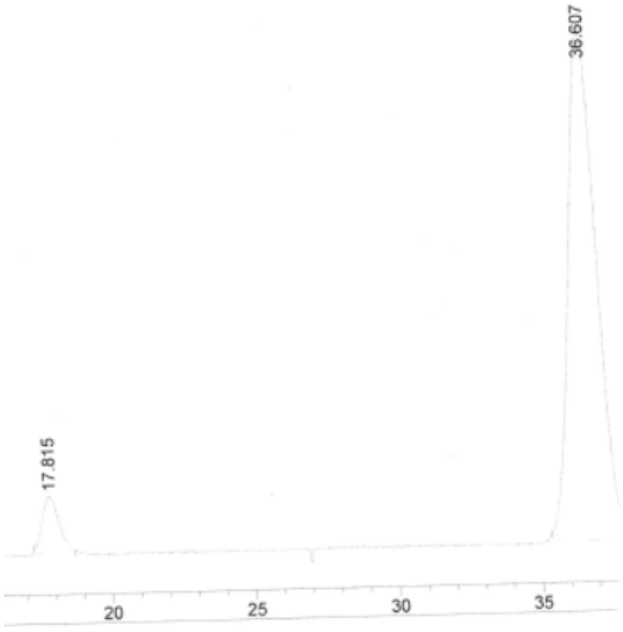
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.990	PB	0.2785	4541.79932	251.72536	61.0774
2	13.415	VB	0.3409	2894.34277	131.46277	38.9226
Totals :				7436.14209	383.18813	

Results obtained with enhanced integrator!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.995	PB	0.2735	9463.83691	532.09857	50.0460
2	13.421	BB	0.3457	9446.42773	424.38239	49.9540
Totals :				1.89103e4	956.48096	

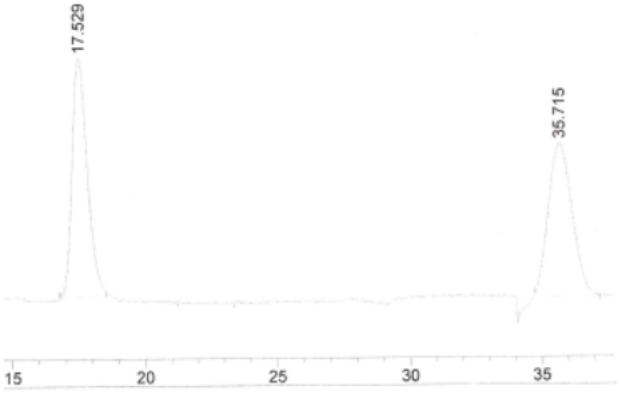
Results obtained with enhanced integrator!





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.815	BB	0.4902	161.17609	3.94878	6.2887
2	36.607	BB	0.9240	2401.77637	35.46756	93.7113
Totals :				2562.95245	39.41634	

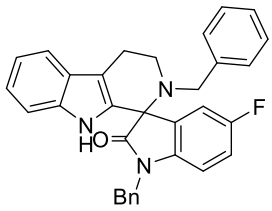
Results obtained with enhanced integrator!

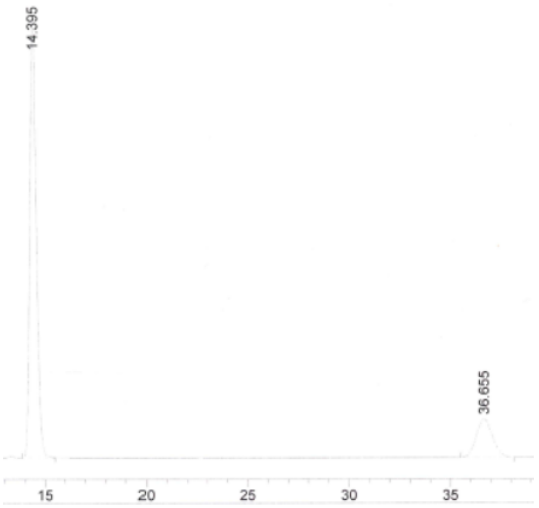


Signal 1: DAD1 B, Sig=225,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.529	BB	0.5505	458.52960	11.37098	50.0395
2	35.715	BB	0.7434	457.80637	7.28269	49.9605
Totals :				916.33597	18.65367	

Results obtained with enhanced integrator!

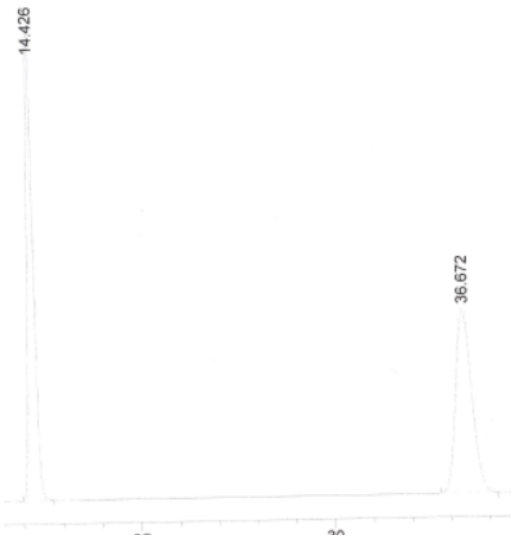




Signal 1: DAD1 A, Sig=225,4 Ref=360,100

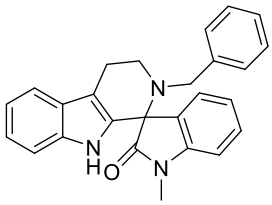
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.395	BB	0.3513	3.34385e4	1481.36841	81.5419
2	36.655	BB	0.8785	7569.26563	133.70119	18.4581
Totals :				4.10077e4	1615.06960	

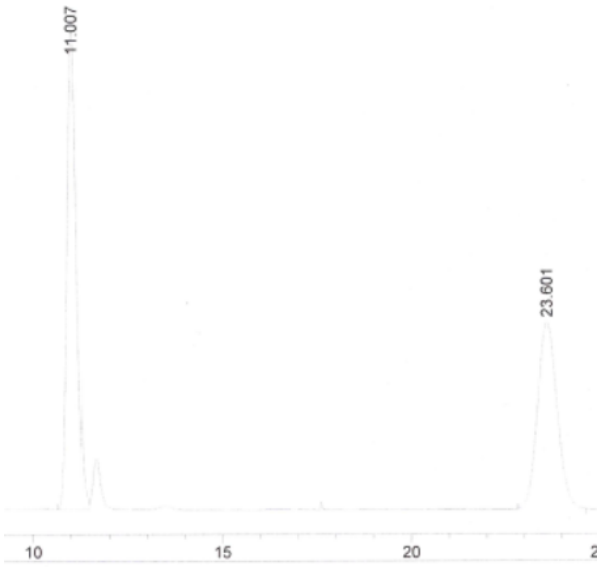
Results obtained with enhanced integrator!



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.426	BB	0.3468	2.37773e4	1063.70898	49.7904
2	36.672	BB	0.8900	2.39774e4	418.77780	50.2096
Totals :				4.77547e4	1482.48679	

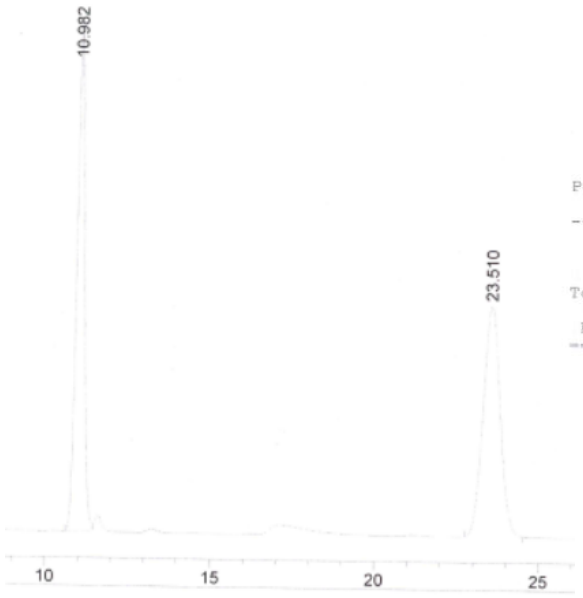
Results obtained with enhanced integrator!





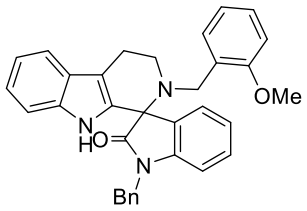
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.007	PV	0.2610	6548.04004	387.84021	54.2460
2	23.601	BB	0.5649	5522.97363	151.63686	45.7540
Totals :				1.20710e4	539.47707	

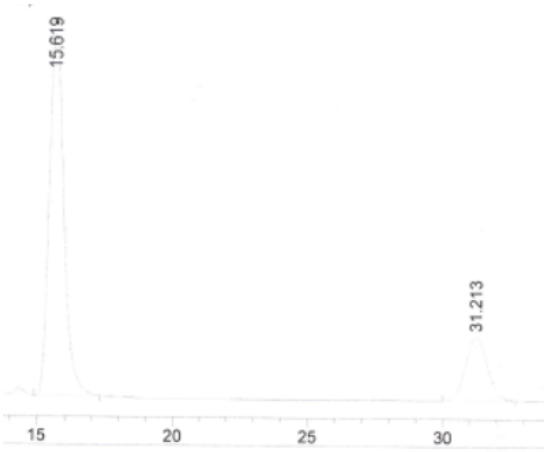
Results obtained with enhanced integrator!



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.982	BV	0.2594	4233.95703	252.78674	49.9882
2	23.510	BB	0.5650	4235.94873	116.84172	50.0118
Totals :				8469.90576	369.62846	

Results obtained with enhanced integrator!





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.619	VB	0.5254	1.88080e4	541.29285	77.5471
2	31.213	BB	0.7943	5445.64307	96.80287	22.4529
Totals :				2.42537e4	638.09572	

Results obtained with enhanced integrator!

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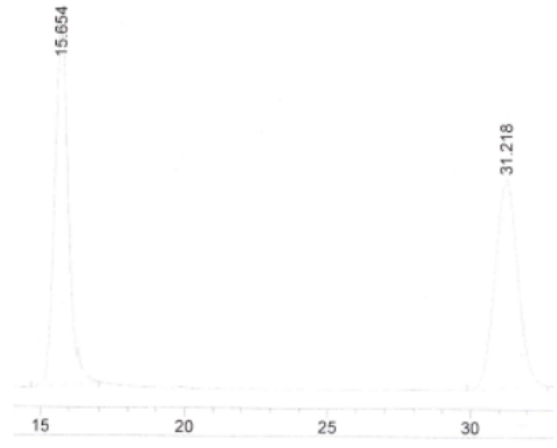

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.654	PB	0.5083	8438.17480	253.55478	50.612
2	31.218	PB	0.7824	8234.09473	146.35182	49.388
Totals :				1.66723e4	399.90660	

Results obtained with enhanced integrator!

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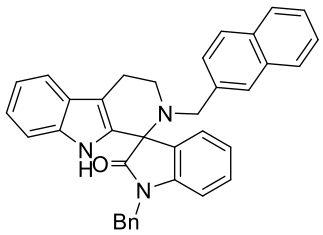
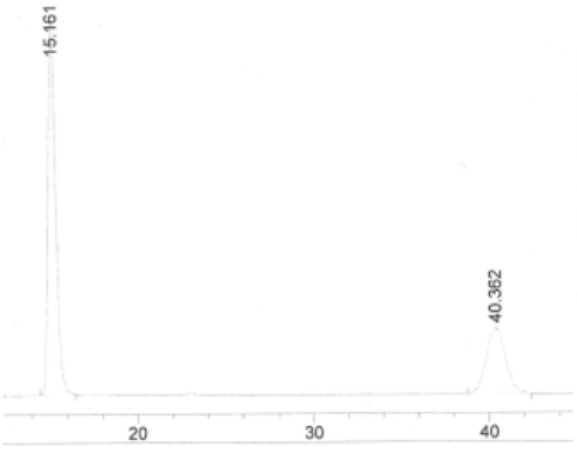
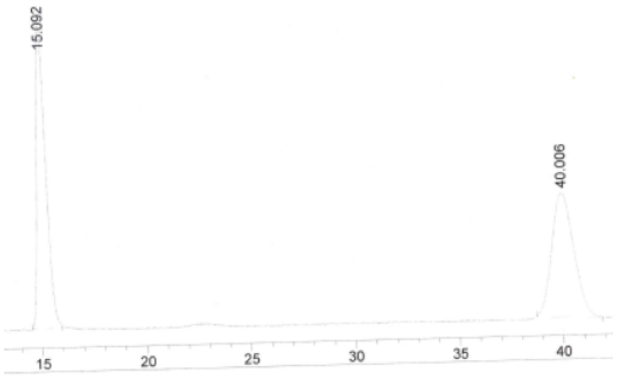




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.161	PB	0.4740	2.12867e4	697.59106	69.4825
2	40.362	BB	1.0424	9349.33203	123.32699	30.5175
Totals :				3.06360e4	820.91805	

Results obtained with enhanced integrator!

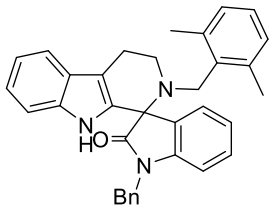
*** End of Report ***

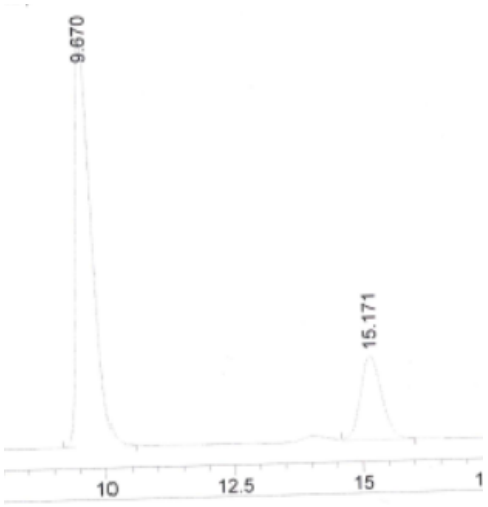


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.092	BB	0.4641	1807.96497	59.91433	50.2102
2	40.006	BB	0.8743	1792.82568	24.31420	49.7898
Totals :				3600.79065	84.22853	

Results obtained with enhanced integrator!

*** End of Report ***



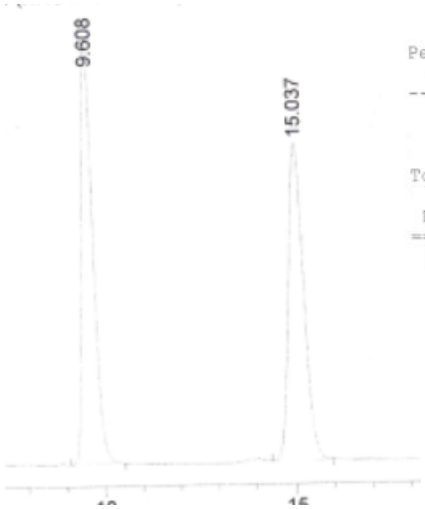


Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.670	BB	0.3245	9356.29102	442.77979	78.1941
2	15.171	VB	0.4306	2609.18481	90.98766	21.8059
Totals :				1.19655e4	533.76744	

Results obtained with enhanced integrator!

*** End of Report ***



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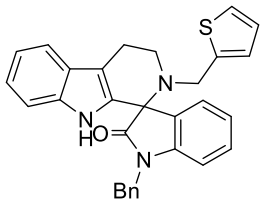
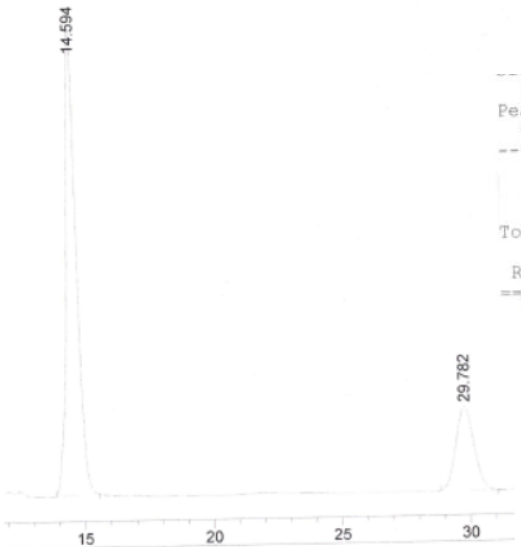
1	9.608	VB	0.3179	1.02894e4	500.41449	49.8389
2	15.037	VB	0.4301	1.03559e4	372.72714	50.1611
Totals :				2.06453e4	873.14163	

Results obtained with enhanced integrator!

*** End of Report ***





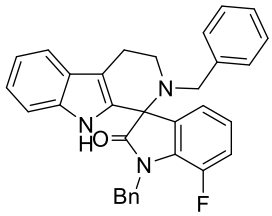
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.594	BB	0.4313	4690.99609	163.23322	76.4673
2	29.782	BB	0.7642	1443.64978	29.33085	23.5327
Totals :				6134.64587	192.56407	

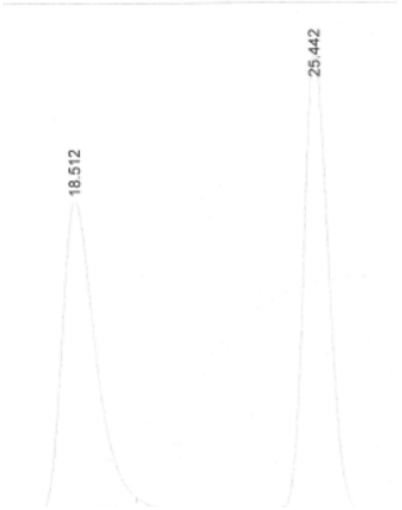
Results obtained with enhanced integrator!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.620	BB	0.4127	4316.62549	160.04659	50.1542
2	29.747	BB	0.7685	4290.08203	86.81378	49.8458
Totals :				8606.70752	246.86037	

Results obtained with enhanced integrator!

*** End of Report ***

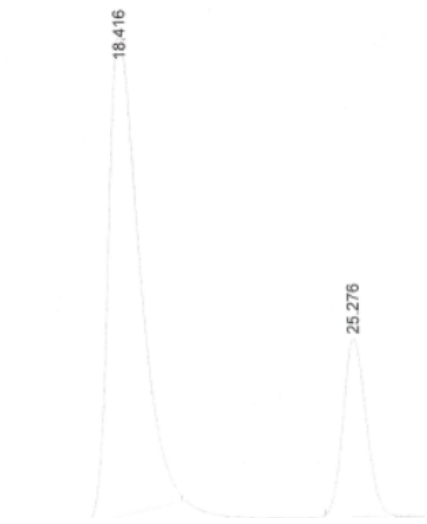




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.512	BB	0.9738	2716.42261	41.27829	47.0847
2	25.442	BB	0.7704	3052.80566	61.58144	52.9153
Totals :				5769.22827	102.85972	

Results obtained with enhanced integrator!

*** End of Report ***

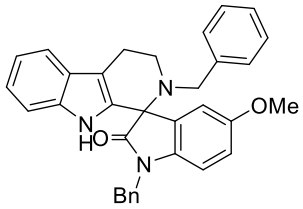


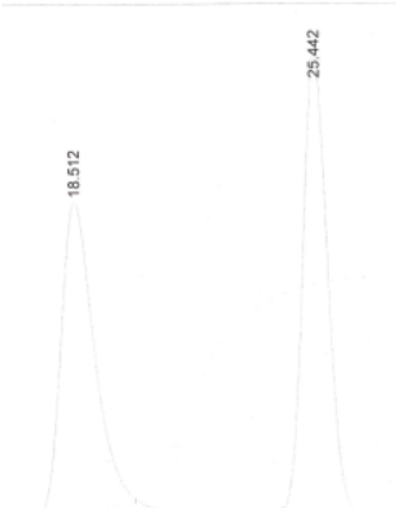
Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.416	BB	0.9494	3444.24536	53.61755	78.3978
2	25.276	BB	0.6868	949.04858	19.81527	21.6022
Totals :				4393.29395	73.43282	

Results obtained with enhanced integrator!

*** End of Report ***

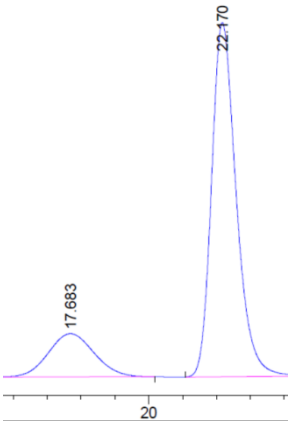




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.512	BB	0.9738	2716.42261	41.27829	47.0847
2	25.442	BB	0.7704	3052.80566	61.58144	52.9153
Totals :				5769.22827	102.85972	

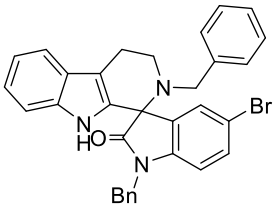
Results obtained with enhanced integrator!

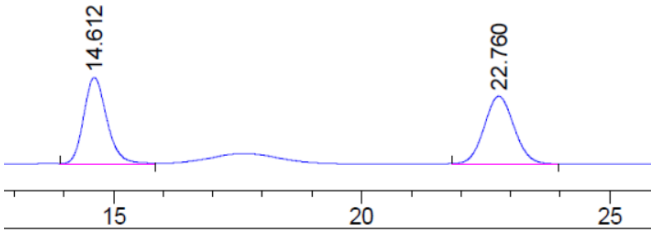
*** End of Report ***



Signal 1: VWD1 A, Wavelength=225 nm

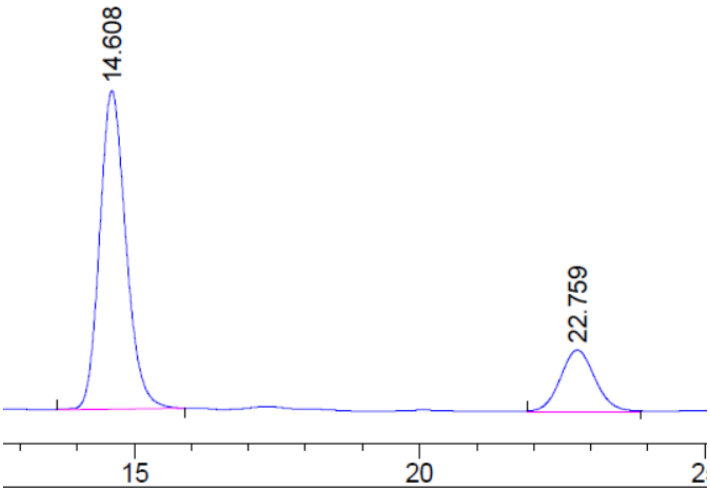
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.683	BB	1.4694	2400.83179	25.33875	18.5935
2	22.170	BB	0.7788	1.05114e4	207.52492	81.4065
Totals :				1.29122e4	232.86366	



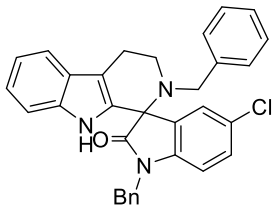


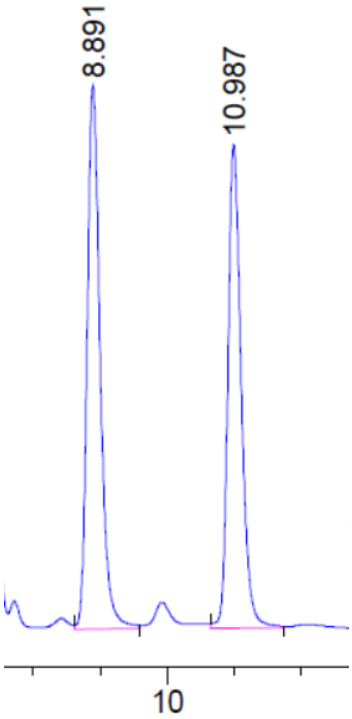
Signal 1: VWD1 A, Wavelength=225 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.612	VB	0.4982	2521.80469	77.95780	49.8519
2	22.760	BB	0.6502	2536.78833	60.93364	50.1481

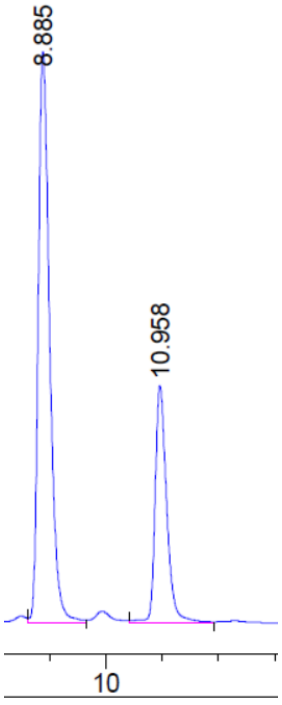


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.608	BB	0.4927	2981.40991	93.17503	79.9567
2	22.759	BB	0.6443	747.36963	17.90247	20.0433
Totals :				3728.77954	111.07750	

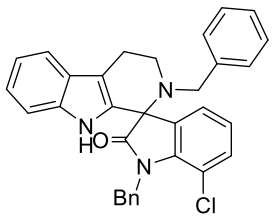


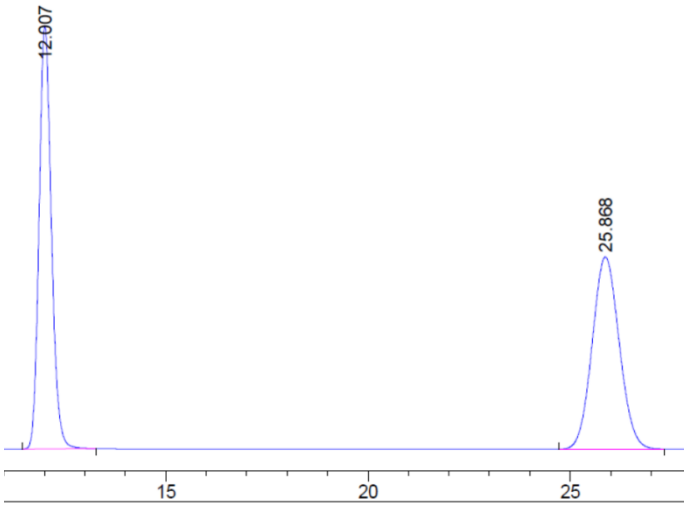


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.891	VB	0.2041	853.30280	63.78365	52.3471
2	10.987	BB	0.2106	776.78448	56.77229	47.6529
Totals :				1630.08728	120.55594	

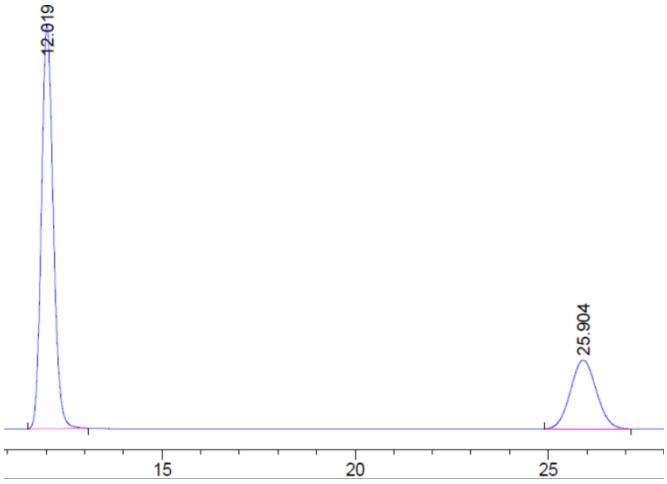


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.885	VV	0.2145	3781.88794	269.73950	70.0402
2	10.958	VB	0.2206	1617.70874	112.21205	29.9598
Totals :				5399.59668	381.95155	

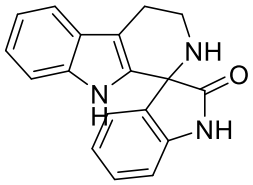




Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.007	BB	0.3275	8180.32178	385.70596	50.0541
2	25.868	BB	0.7253	8162.65088	175.28419	49.9459



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.019	BB	0.3274	3815.12549	179.95613	72.7790
2	25.904	BB	0.7283	1426.94470	30.63592	27.2210



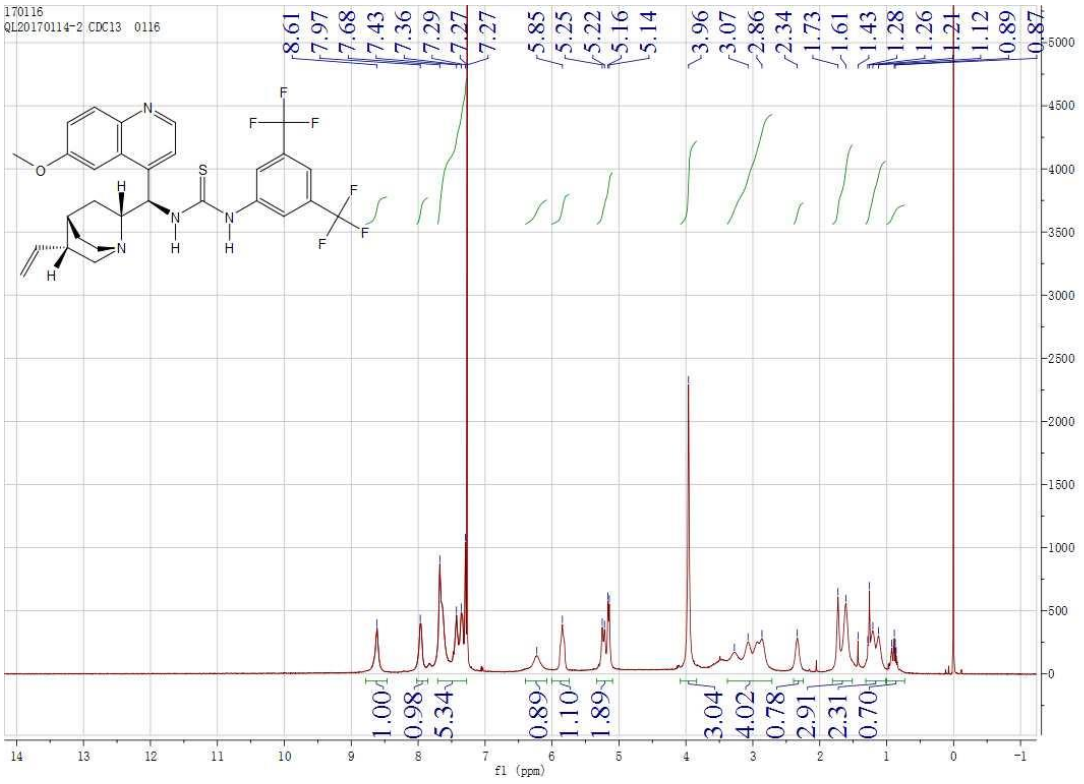
Signal 1: DAD1 A, Sig=210,4 Ref=360,100

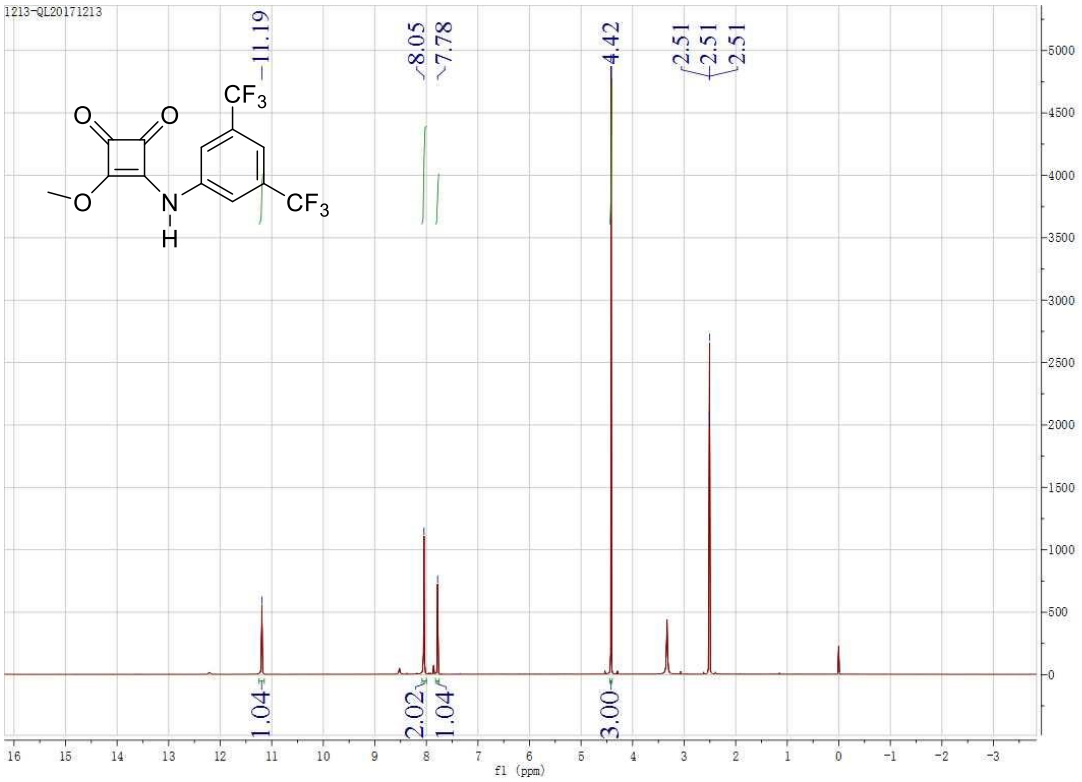
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.339	BB	0.4429	5318.84863	183.08112	50.1307
2	19.301	BB	0.4918	5291.10742	165.13316	49.8693
Totals :				1.06100e4	348.21428	

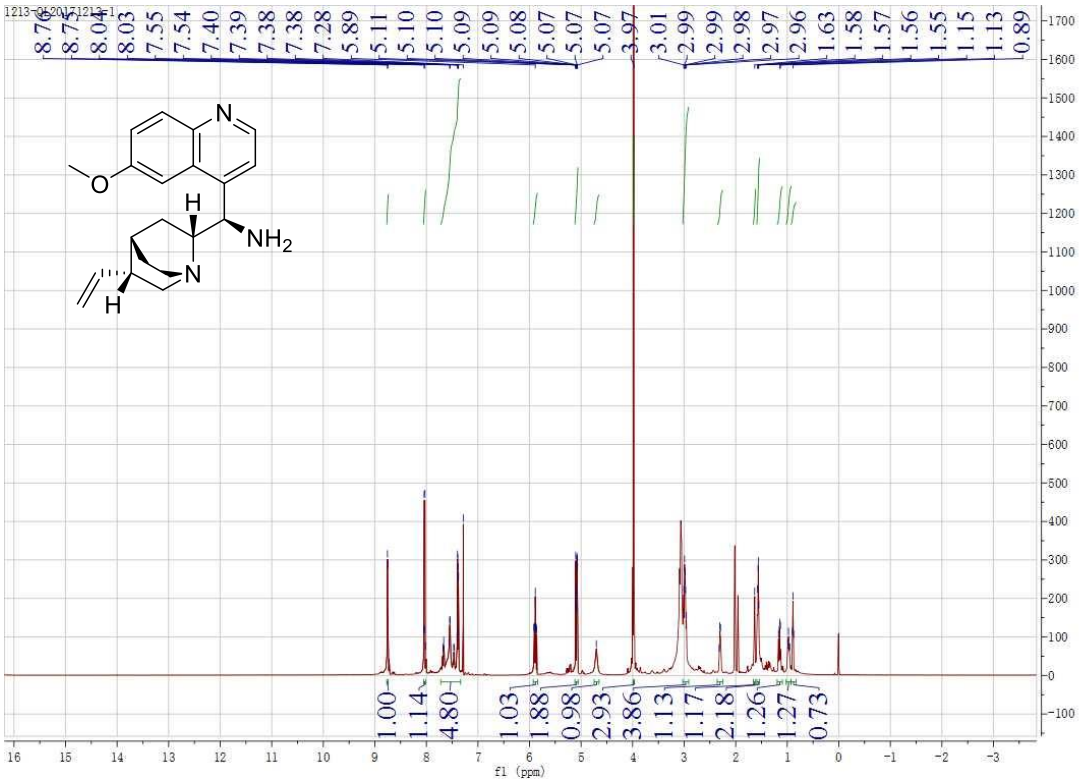
Signal 1: DAD1 A, Sig=210,4 Ref=360,100

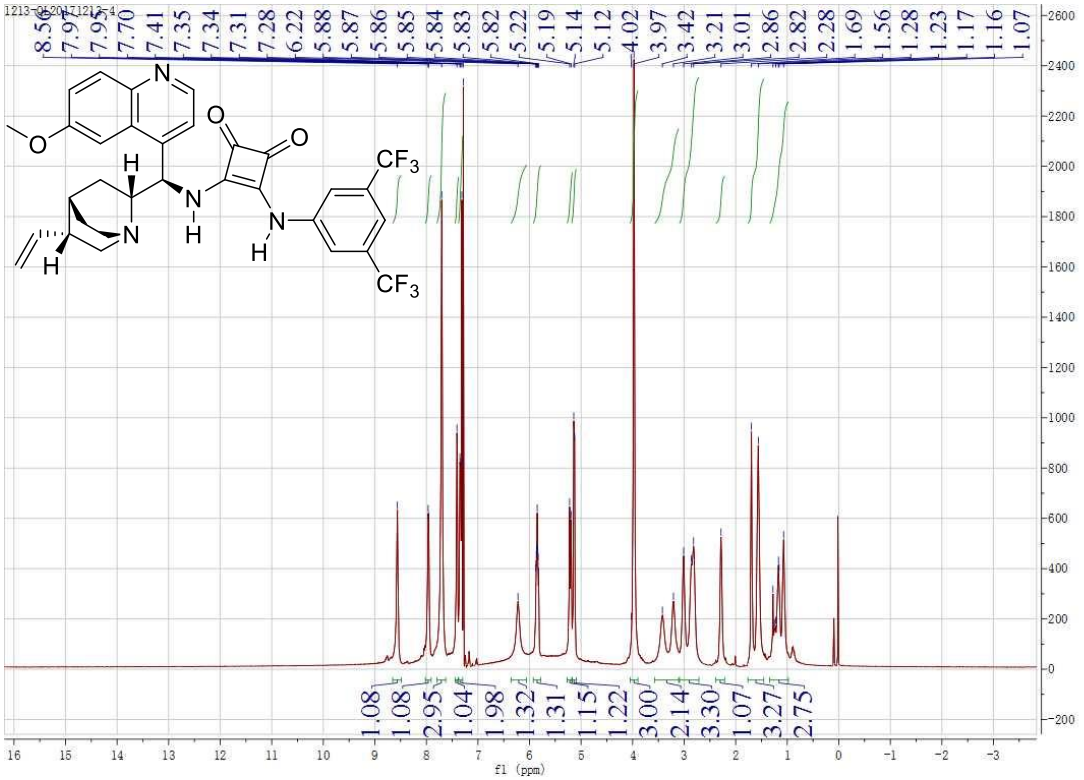
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.309	VB	0.7458	614.96411	12.86339	2.7342
2	20.105	BB	0.5331	2.18762e4	636.38330	97.2658
Totals :				2.24912e4	649.24669	

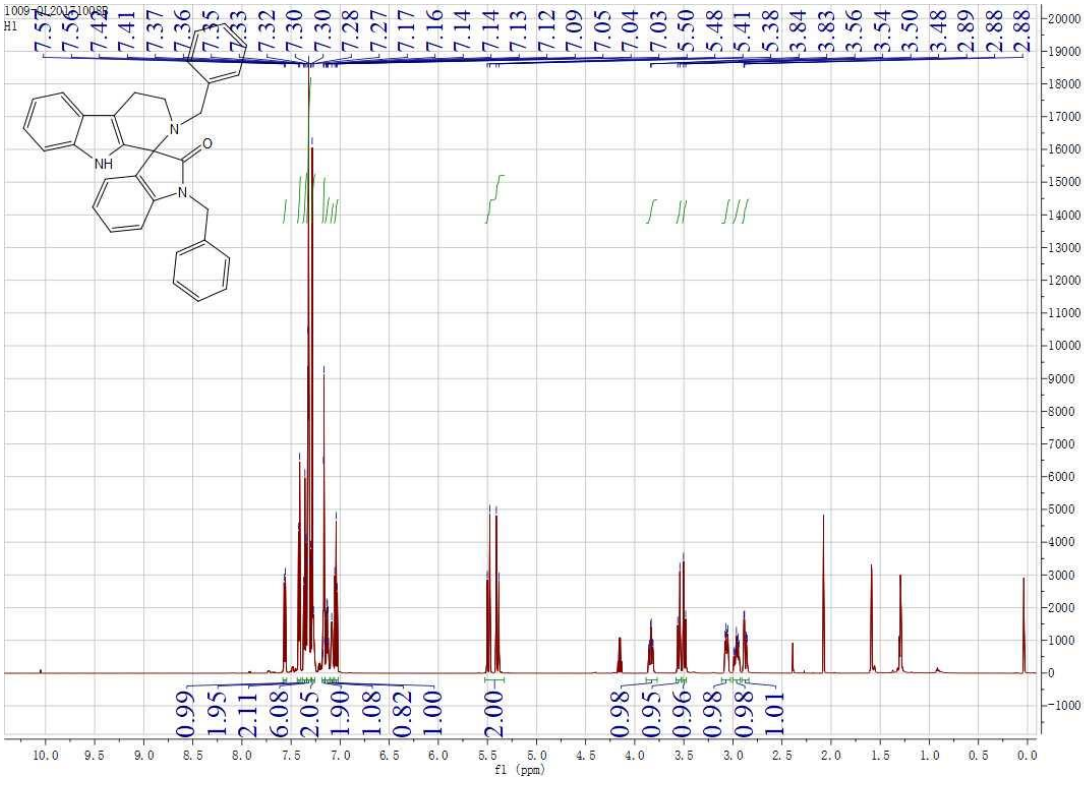
III. Copies of ^{1}H and ^{13}C NMR Spectra

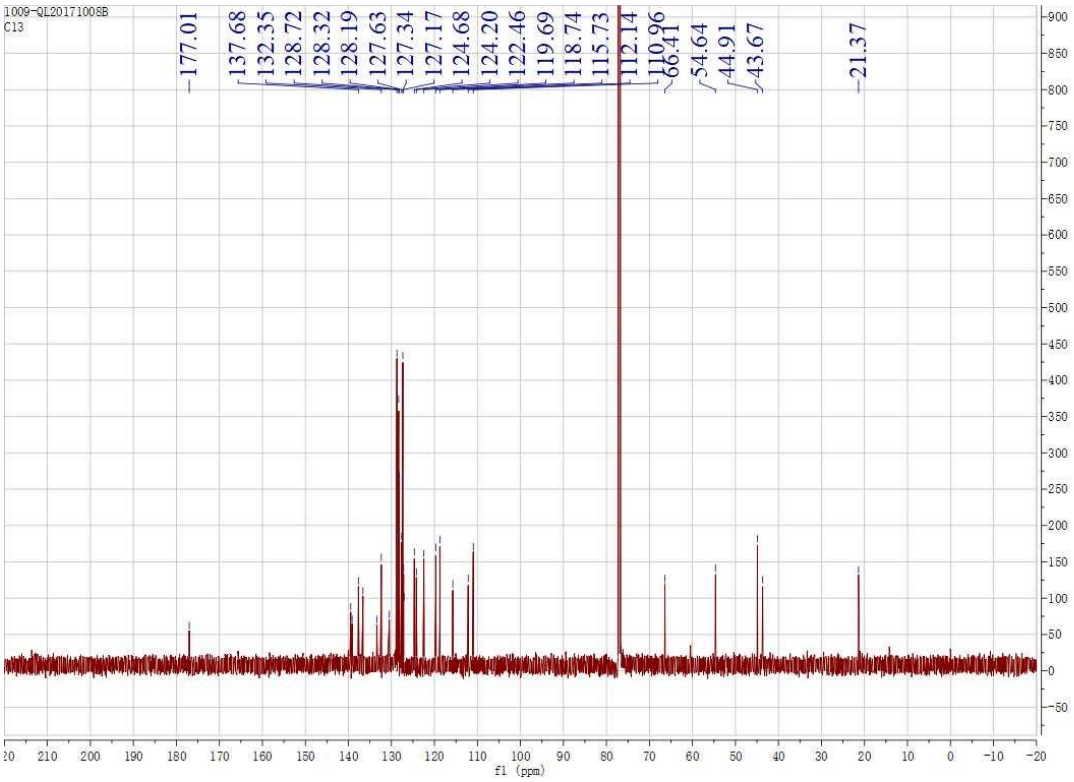


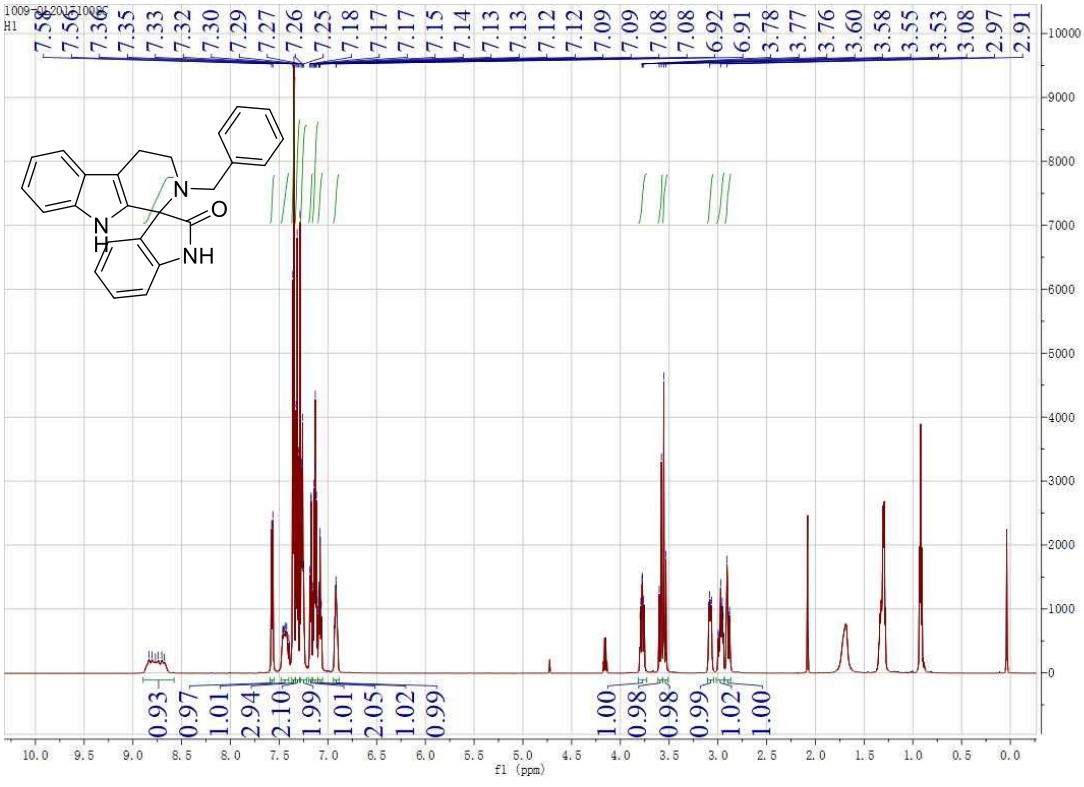

1213-QL20171213
11.19
8.05
7.78
4.42
2.51
2.51
2.51
CF3
CF3
O
O
O
N
H
1.04
2.02
1.04
3.00
f1 (ppm)

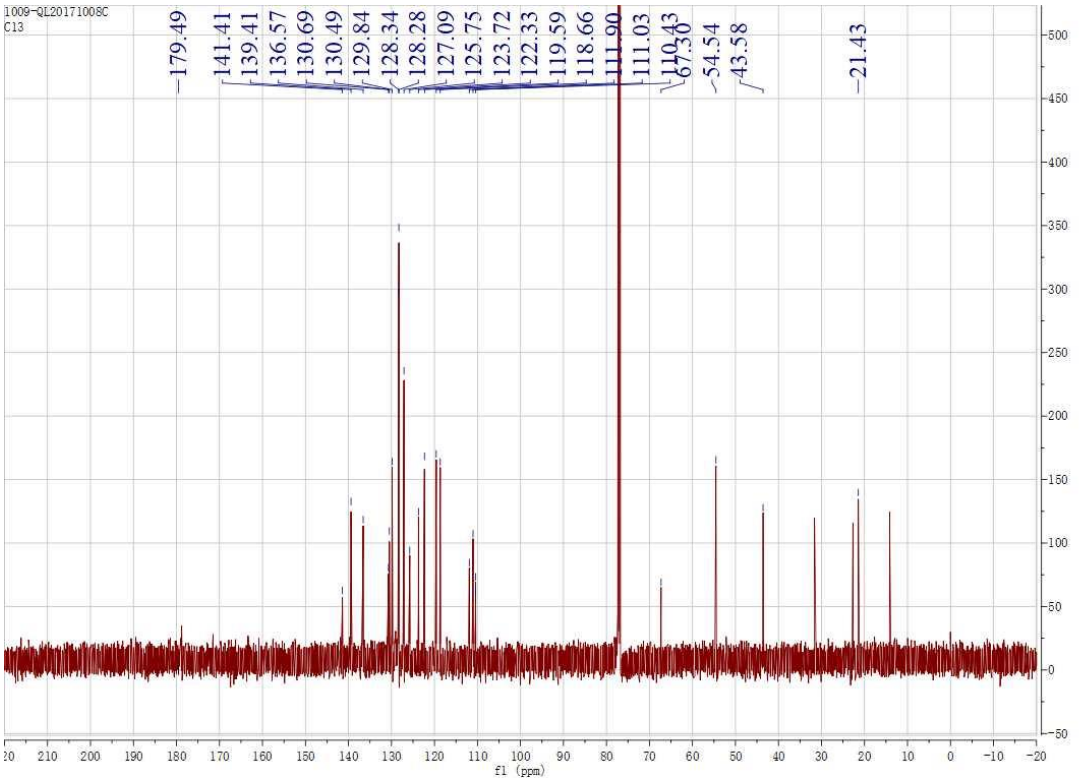

8.76
8.75
8.04
8.03
7.55
7.54
7.40
7.39
7.38
7.38
7.28
5.89
5.11
5.10
5.10
5.09
5.09
5.08
5.07
5.07
5.07
3.97
3.01
2.99
2.99
2.98
2.97
2.96
1.63
1.58
1.57
1.56
1.55
1.15
1.13
0.89
N
O
H
NH2
N
H
1.00
1.14
4.80
1.03
1.88
0.98
2.93
3.86
1.13
1.17
2.18
1.26
1.27
0.73
f1 (ppm)

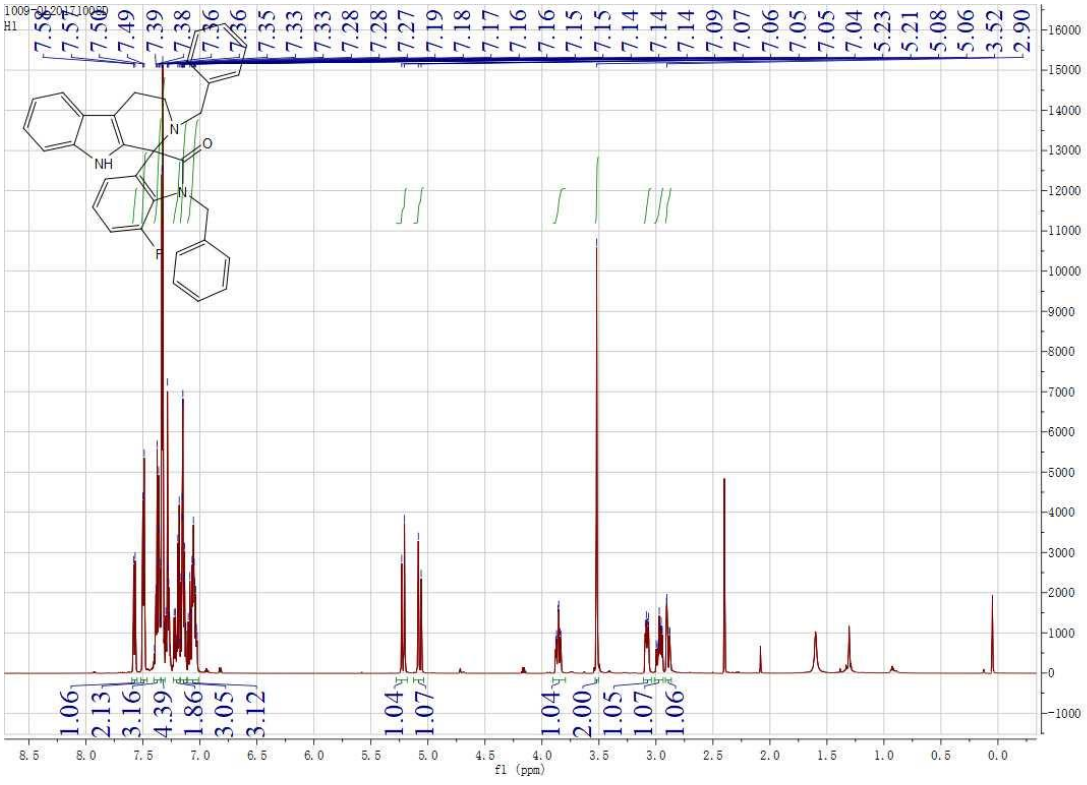

8.58 7.97 7.95 7.70 7.41 7.35 7.34 7.31 7.28 6.22 5.88 5.87 5.86 5.85 5.84 5.83 5.82 5.22 5.19 5.14 5.12 4.02 3.97 3.42 3.21 3.01 2.86 2.82 2.28 1.69 1.56 1.28 1.23 1.17 1.16 1.07
1.08 1.08 2.95 1.04 1.98 1.32 1.27 1.31 1.15 1.22 3.00 2.14 3.30 1.07 3.27 2.75
f1 (ppm)

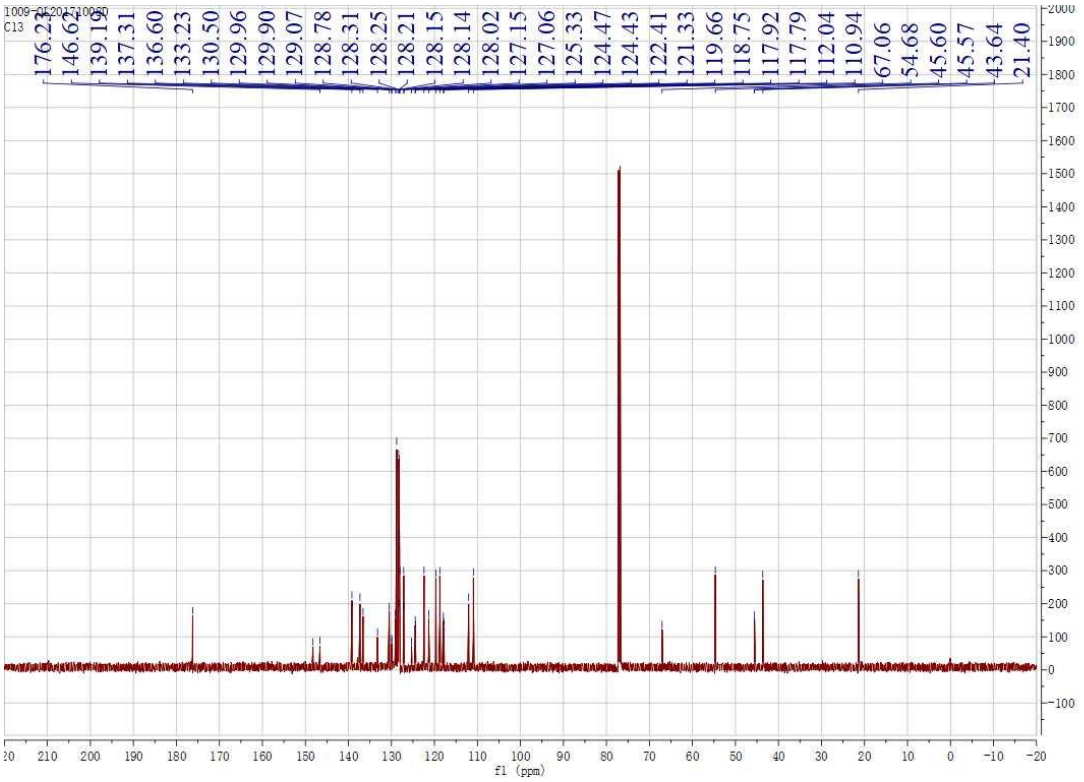

7.57 7.56 7.42 7.41 7.37 7.36 7.35 7.33 7.32 7.30 7.30 7.28 7.27 7.17 7.16 7.14 7.14 7.13 7.12 7.09 7.05 7.04 7.03 5.50 5.48 5.41 5.38 3.84 3.83 3.56 3.54 3.50 3.48 2.89 2.88 2.88
0.99 1.95 2.11 6.08 2.05 1.90 1.08 0.82 1.00 2.00 0.98 0.95 0.96 0.98 0.98 1.01
f1 (ppm)

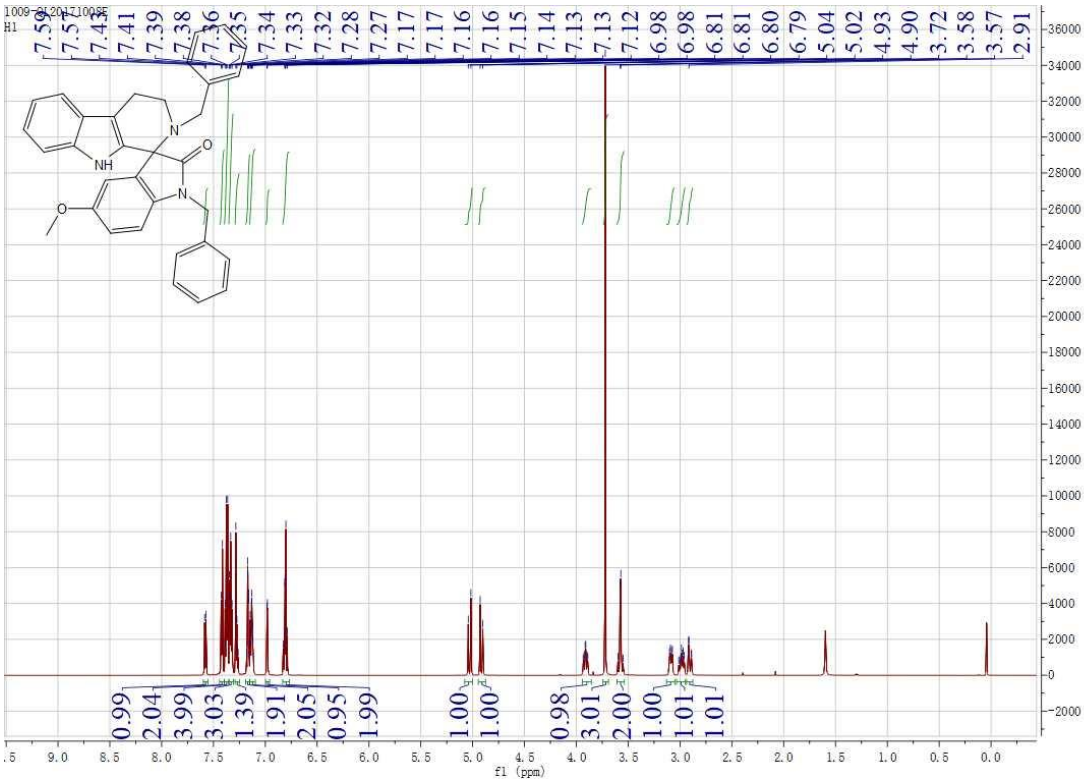

1009-QL20171008B
C13
177.01
137.68
132.35
128.72
128.32
128.19
127.63
127.34
127.17
124.68
124.20
122.46
119.69
118.74
115.73
112.14
110.96
66.41
54.64
44.91
43.67
21.37
f1 (ppm)

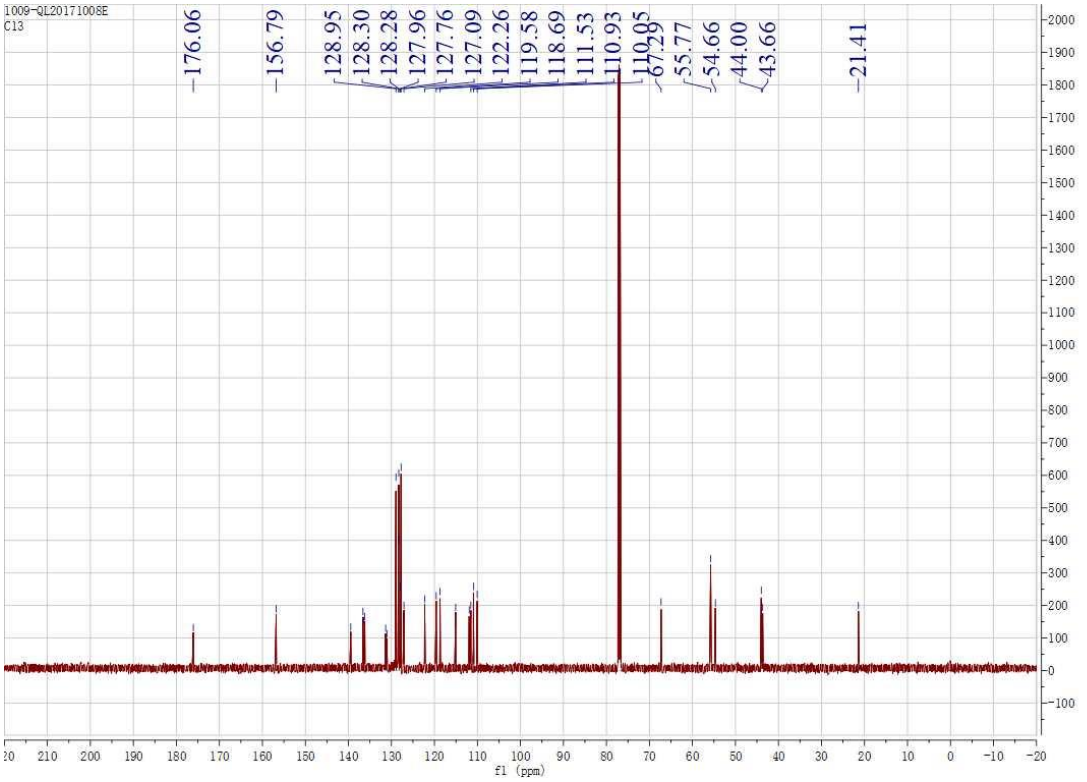

1009-QL20171008C
H1
7.58
7.56
7.35
7.33
7.32
7.30
7.29
7.27
7.26
7.25
7.18
7.17
7.17
7.15
7.14
7.13
7.13
7.12
7.12
7.09
7.09
7.08
7.08
6.92
6.91
3.78
3.77
3.76
3.60
3.58
3.55
3.53
3.08
2.97
2.91
0.93
0.97
1.01
2.94
2.10
1.99
1.01
2.05
1.02
0.99
1.00
0.98
0.98
0.99
1.02
1.00
N
O
N
H
NH
f1 (ppm)

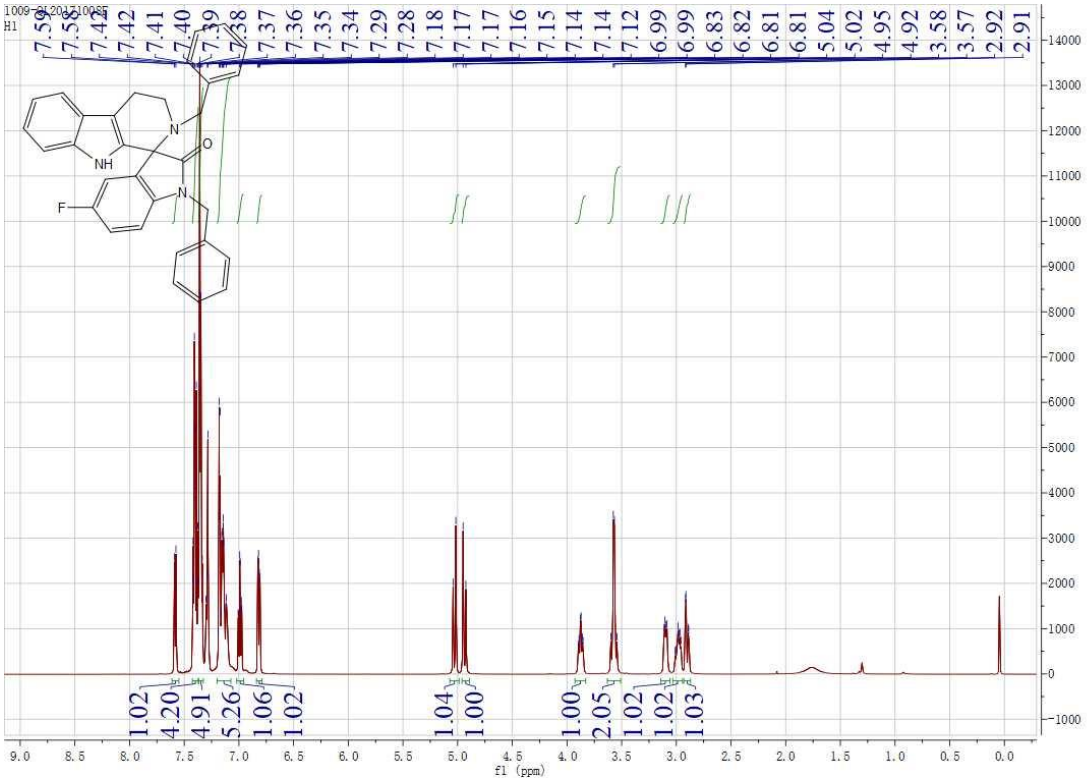

1009-QL20171008C
C13
179.49
141.41
139.41
136.57
130.69
130.49
129.84
128.34
128.28
127.09
125.75
123.72
122.33
119.59
118.66
111.90
111.03
110.43
67.30
54.54
43.58
21.43
f1 (ppm)

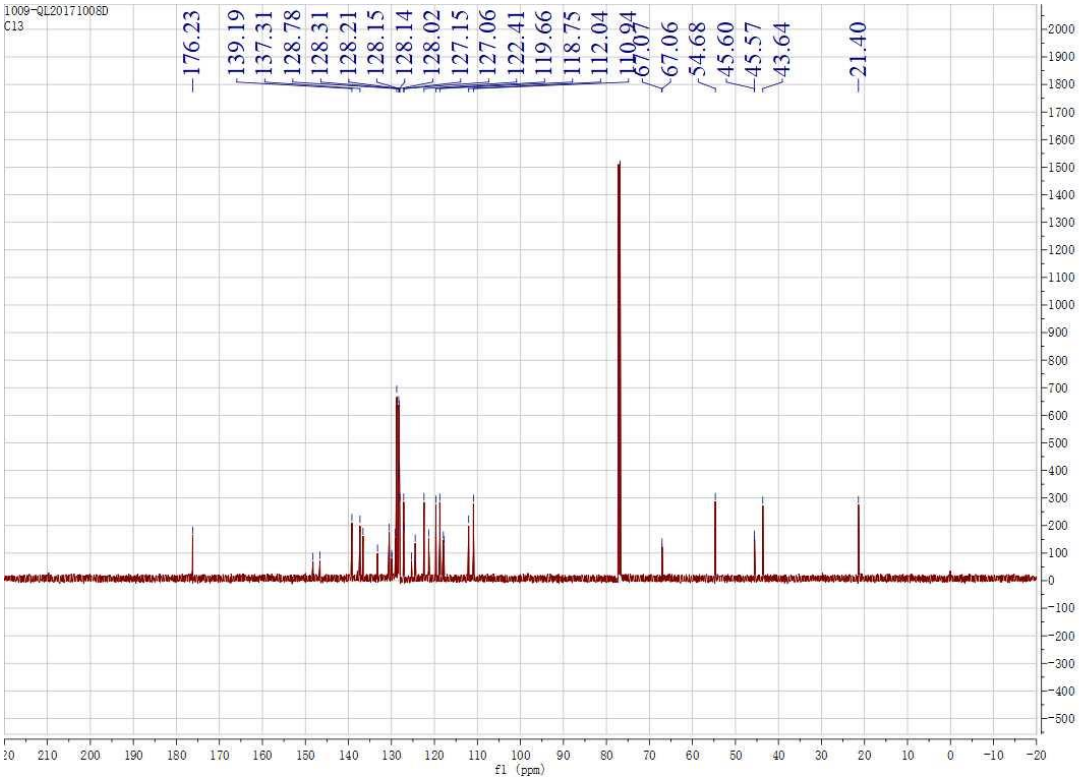

H1
7.58
7.57
7.50
7.49
7.39
7.38
7.36
7.35
7.33
7.33
7.28
7.28
7.27
7.19
7.18
7.17
7.16
7.16
7.15
7.15
7.14
7.14
7.14
7.09
7.07
7.06
7.05
7.05
7.04
5.23
5.21
5.08
5.06
3.52
2.90
NH
N
O
N
F
1.06
2.13
3.16
4.39
1.86
3.05
3.12
1.04
1.07
1.04
2.00
1.05
1.07
1.06
f1 (ppm)

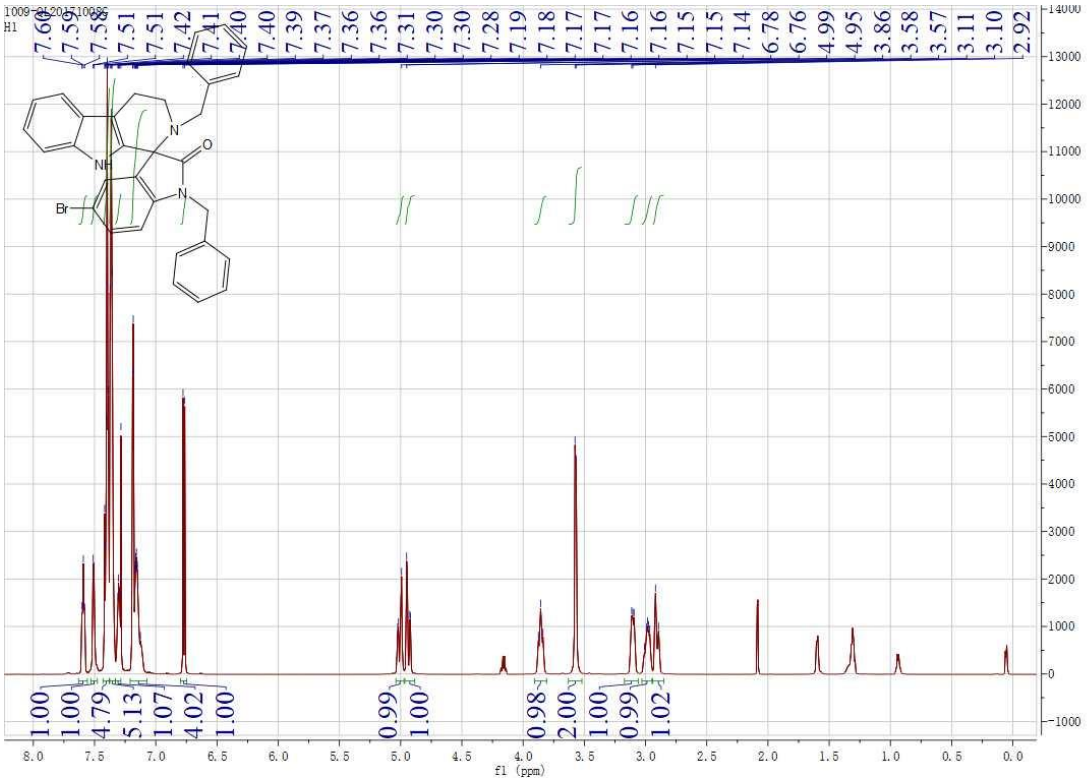

C13
176.23
146.62
139.19
137.31
136.60
133.23
130.50
129.96
129.90
129.07
128.78
128.31
128.25
128.21
128.15
128.14
128.02
127.15
127.06
125.33
124.47
124.43
122.41
121.33
119.66
118.75
117.92
117.79
112.04
110.94
67.06
54.68
45.60
45.57
43.64
21.40
f1 (ppm)

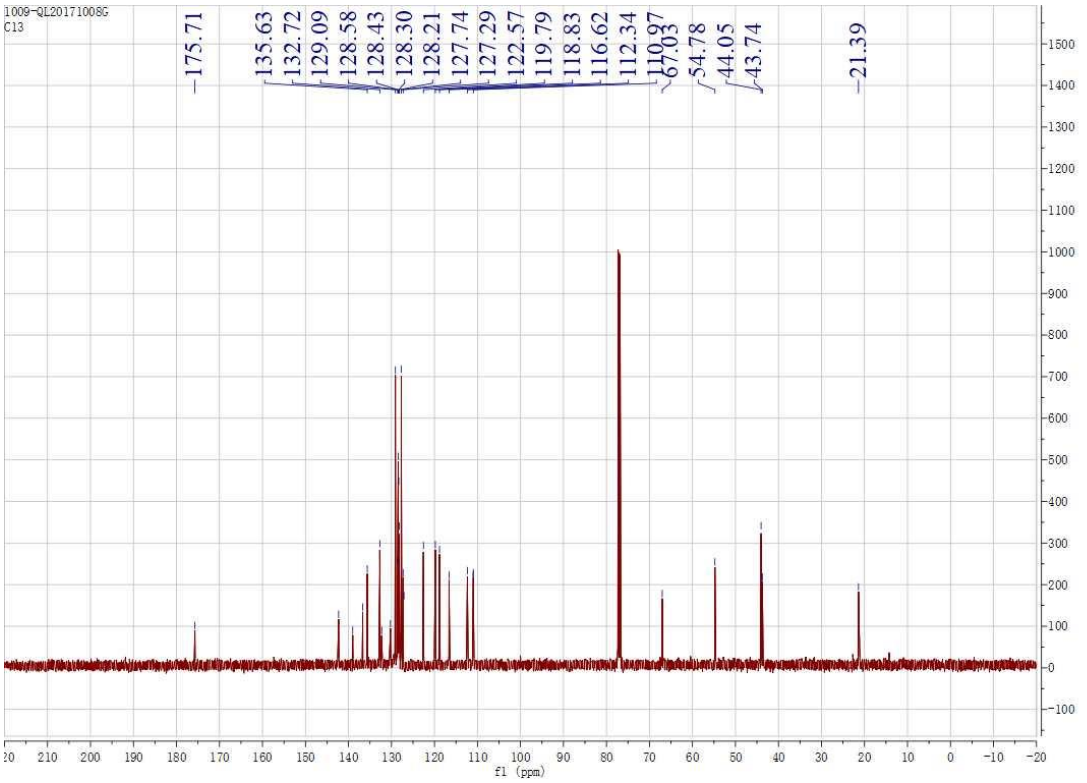

H1
7.59
7.54
7.43
7.41
7.39
7.38
7.36
7.35
7.34
7.33
7.32
7.28
7.27
7.17
7.17
7.16
7.16
7.15
7.14
7.13
7.13
7.12
6.98
6.98
6.81
6.81
6.80
6.79
5.04
5.02
4.93
4.90
3.72
3.58
3.57
2.91
NH
O
N
N
O
0.99
2.04
3.99
3.03
1.39
1.91
2.05
0.95
1.99
1.00
1.00
0.98
3.01
2.00
1.00
1.01
1.01
f1 (ppm)

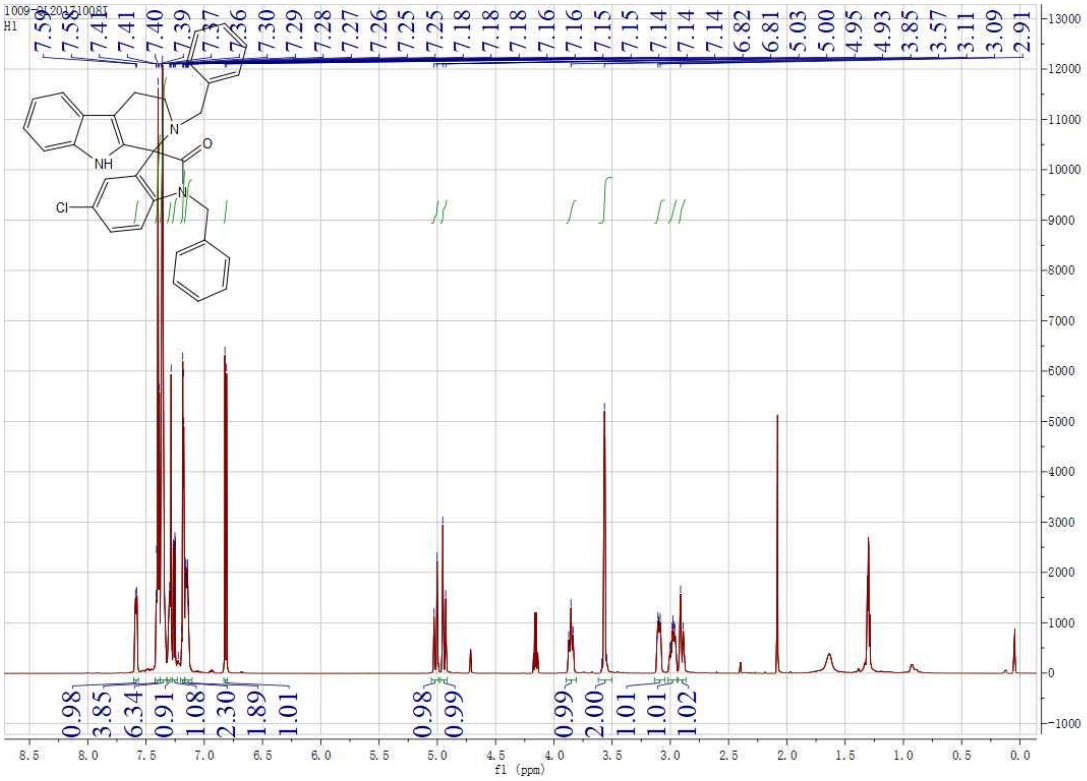

1009-QL20171008E
C13
176.06
156.79
128.95
128.30
128.28
127.96
127.76
127.09
122.26
119.58
118.69
111.53
110.93
110.05
67.29
55.77
54.66
44.00
43.66
21.41
f1 (ppm)

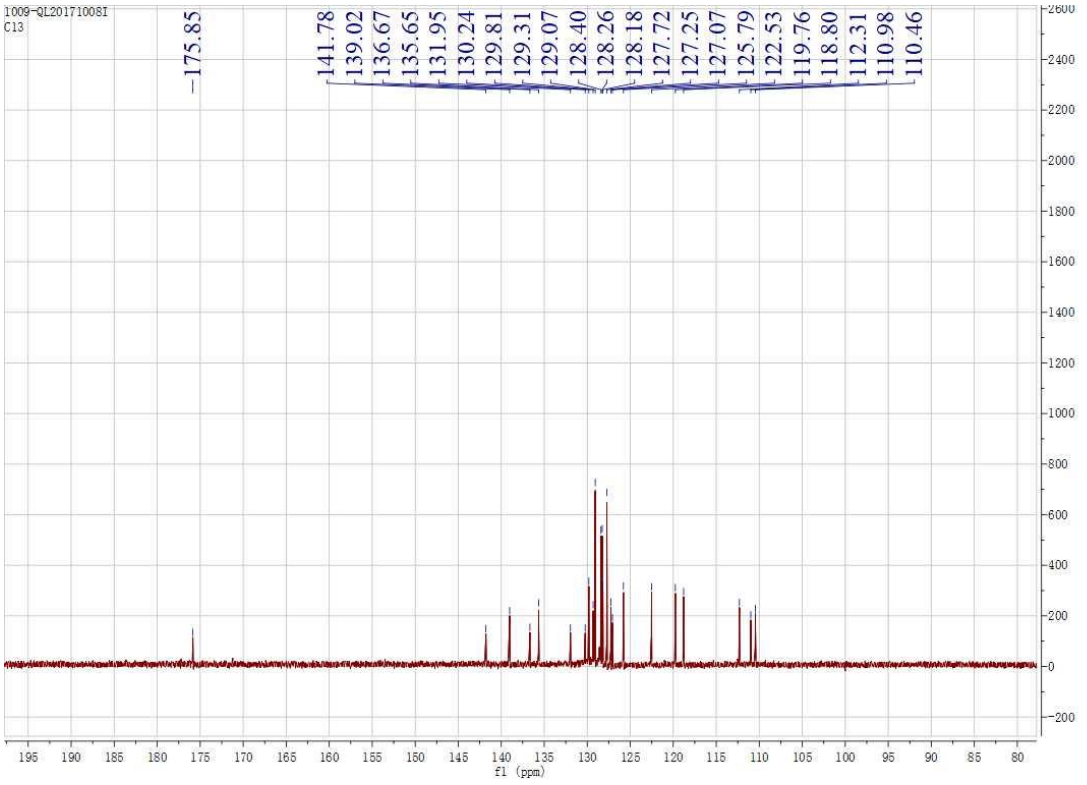

1009-QL20171008E
H1
7.59
7.52
7.42
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.35
7.34
7.29
7.28
7.18
7.17
7.17
7.16
7.15
7.14
7.14
7.12
6.99
6.99
6.83
6.82
6.81
6.81
5.04
5.02
4.95
4.92
3.58
3.57
2.92
2.91
N
O
NH
N
F
1.02
4.20
4.91
5.26
1.06
1.02
1.04
1.00
1.00
2.05
1.02
1.02
1.03
f1 (ppm)

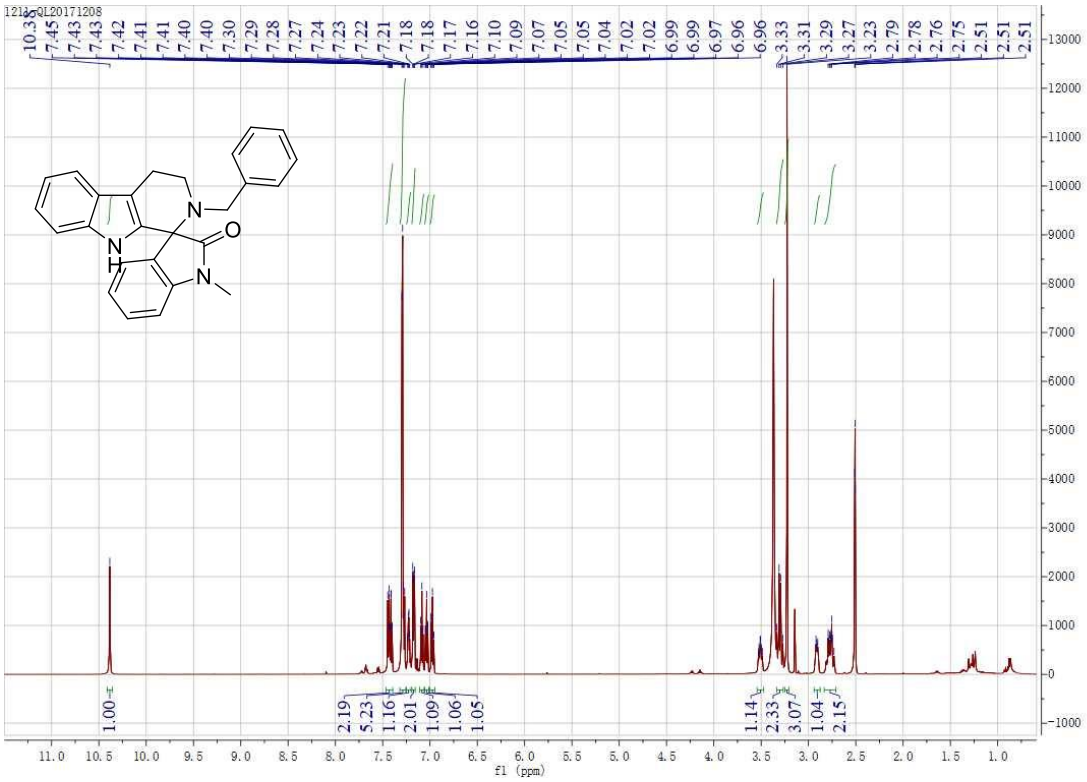

1009-QL20171008D
C13
176.23
139.19
137.31
128.78
128.31
128.21
128.15
128.14
128.02
127.15
127.06
122.41
119.66
118.75
112.04
110.94
67.07
67.06
54.68
45.60
45.57
43.64
21.40
f1 (ppm)

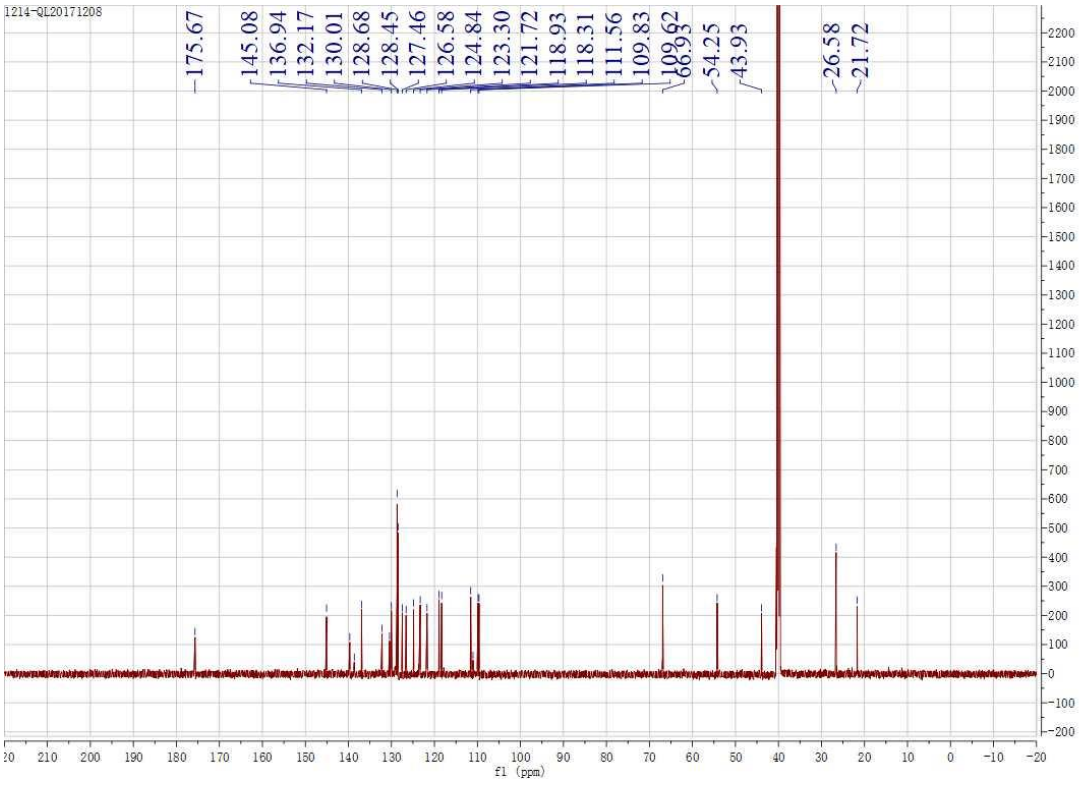

1009-QL20171008G
H1
7.60 7.59 7.58 7.51 7.51 7.42 7.41 7.40 7.40 7.39 7.37 7.36 7.36 7.31 7.30 7.30 7.28 7.19 7.18 7.17 7.17 7.16 7.16 7.15 7.15 7.14 6.78 6.76 4.99 4.95 3.86 3.58 3.57 3.11 3.10 2.92
1.00 1.00 4.79 5.13 1.07 4.02 1.00 0.99 1.00 0.98 2.00 1.00 0.99 1.02
f1 (ppm)

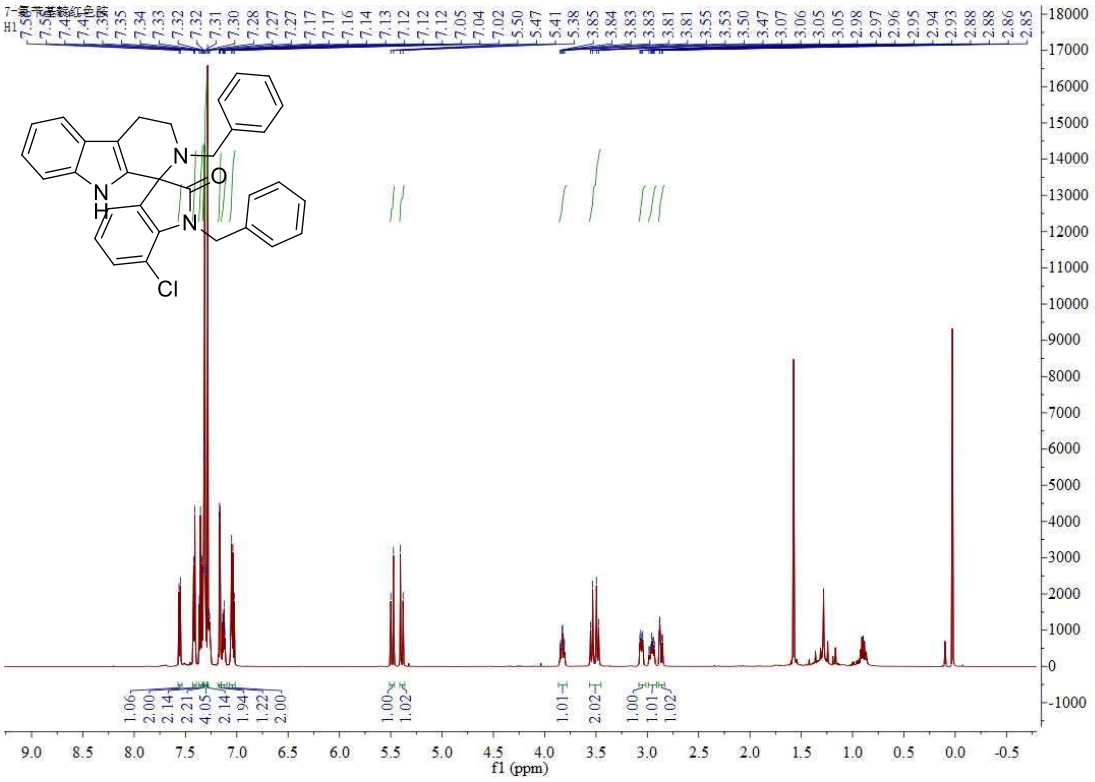

1009-QL20171008G
C13
175.71 135.63 132.72 129.09 128.58 128.43 128.30 128.21 127.74 127.29 122.57 119.79 118.83 116.62 112.34 110.97 67.03 54.78 44.05 43.74 21.39
f1 (ppm)

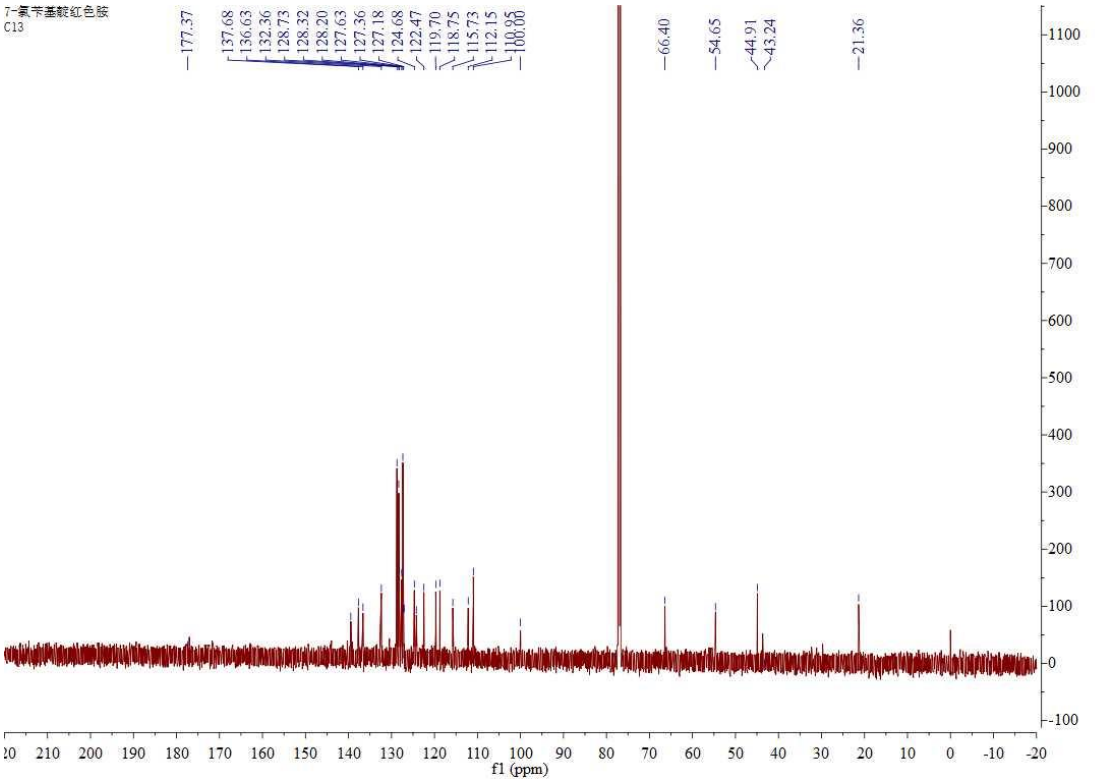

1009-QL20171008I
H1
7.59
7.58
7.41
7.41
7.40
7.39
7.37
7.36
7.30
7.29
7.28
7.27
7.26
7.25
7.25
7.18
7.18
7.18
7.16
7.16
7.15
7.15
7.14
7.14
7.14
6.82
6.81
5.03
5.00
4.95
4.93
3.85
3.57
3.11
3.09
2.91
N
O
NH
N
Cl
0.98
3.85
6.34
0.91
1.08
2.30
1.89
1.01
0.98
0.99
0.99
2.00
1.01
1.01
1.02
f1 (ppm)

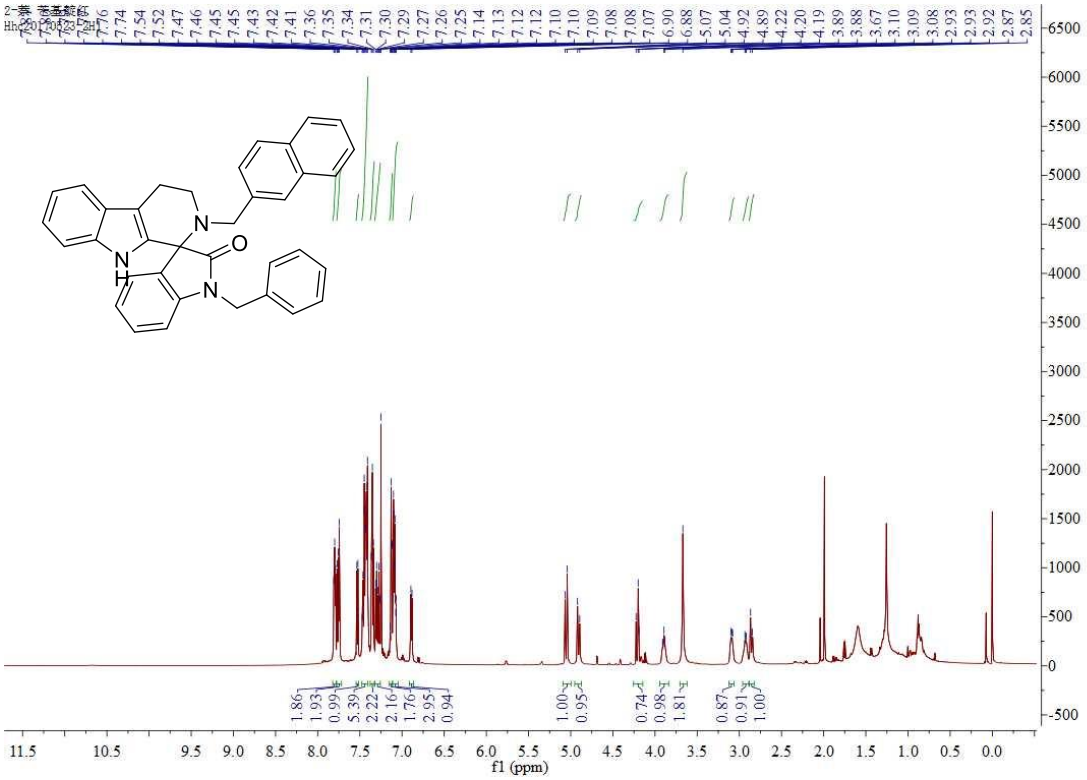

1009-QL20171008I
C13
175.85
141.78
139.02
136.67
135.65
131.95
130.24
129.81
129.31
129.07
128.40
128.26
128.18
127.72
127.25
127.07
125.79
122.53
119.76
118.80
112.31
110.98
110.46
f1 (ppm)

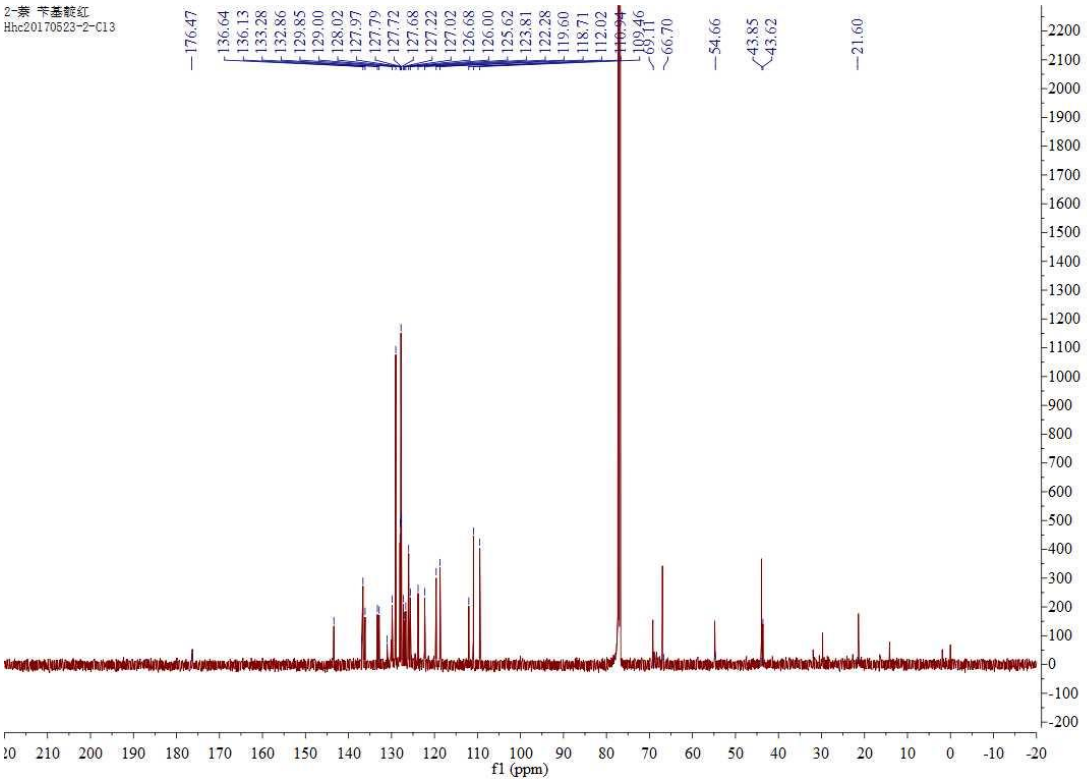

1214-QL20171208
10.35
7.45
7.43
7.43
7.42
7.41
7.41
7.40
7.40
7.30
7.29
7.28
7.27
7.24
7.23
7.22
7.21
7.18
7.18
7.17
7.16
7.10
7.09
7.07
7.05
7.05
7.04
7.02
7.02
6.99
6.99
6.97
6.96
6.96
3.33
3.31
3.29
3.27
3.23
2.79
2.78
2.76
2.75
2.51
2.51
2.51
1.00
2.19
5.23
1.16
2.01
1.09
1.06
1.05
1.14
2.33
3.07
1.04
2.15
f1 (ppm)

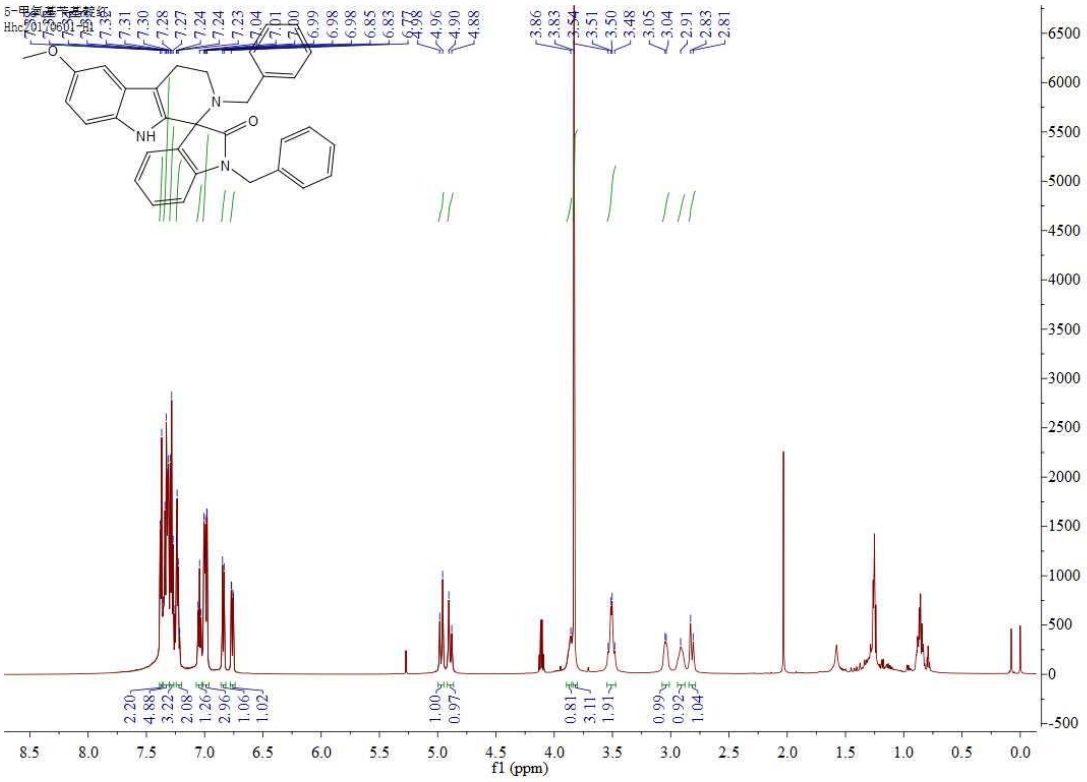

1214-QL20171208
175.67
145.08
136.94
132.17
130.01
128.68
128.45
127.46
126.58
124.84
123.30
121.72
118.93
118.31
111.56
109.83
109.62
68.93
54.25
43.93
26.58
21.72
f1 (ppm)

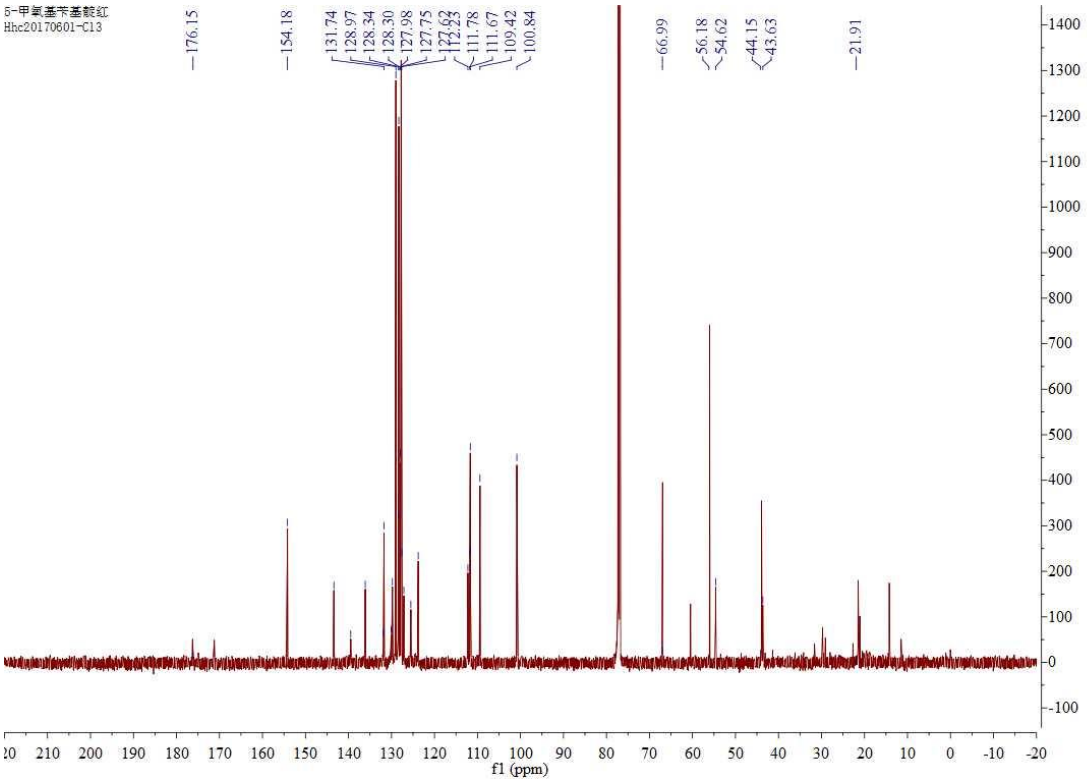

7-氯苄基靛红色胺
H1
f1 (ppm)

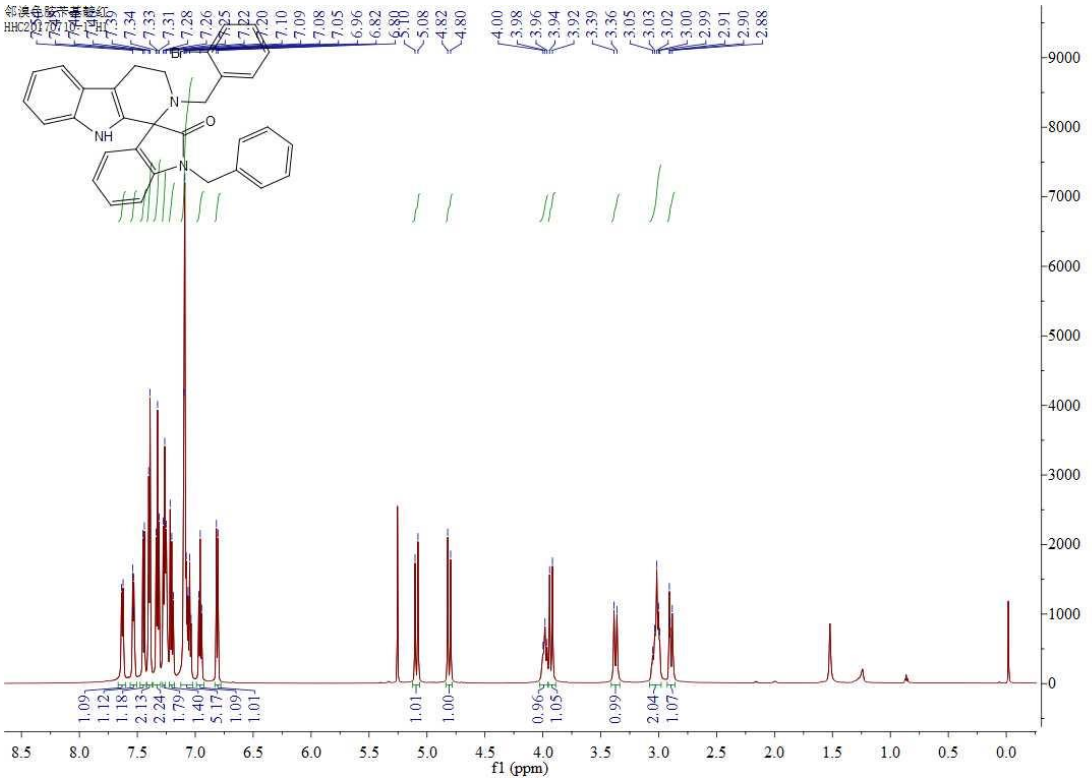

7-氯苄基靛红色胺
C13
177.37
137.68
136.63
132.36
128.73
128.32
128.20
127.63
127.36
127.18
124.68
122.47
119.70
118.75
115.73
112.15
100.05
100.00
66.40
54.65
44.91
43.24
21.36
f1 (ppm)

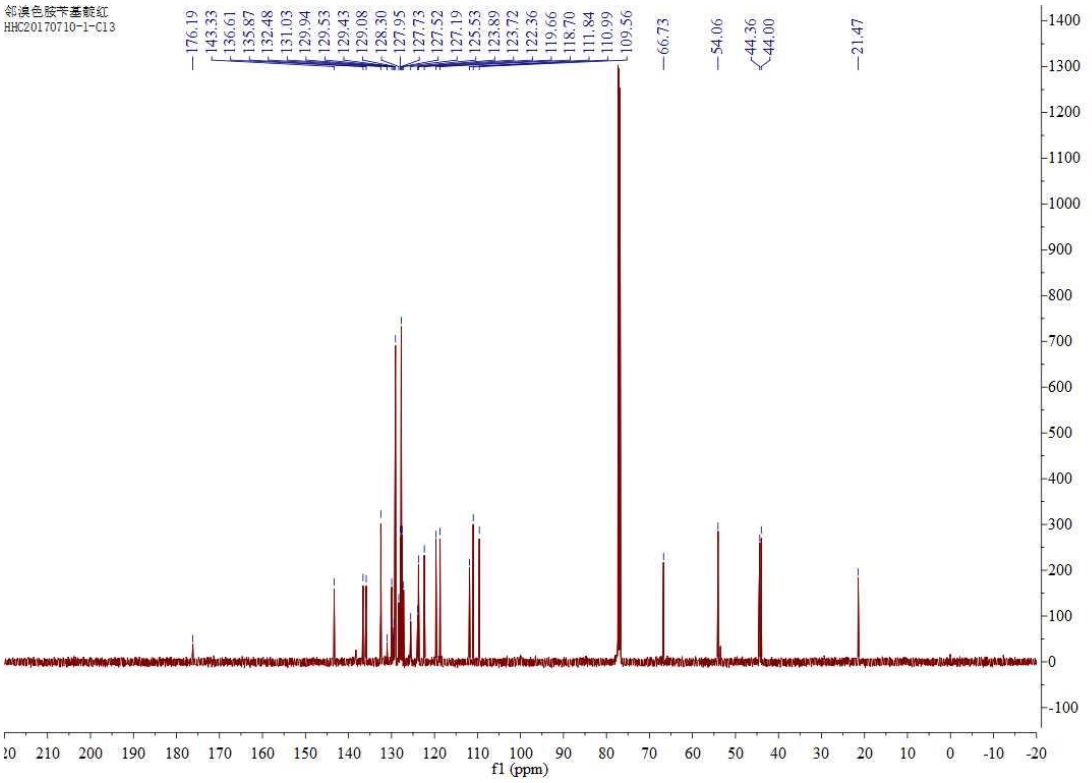

f1 (ppm)

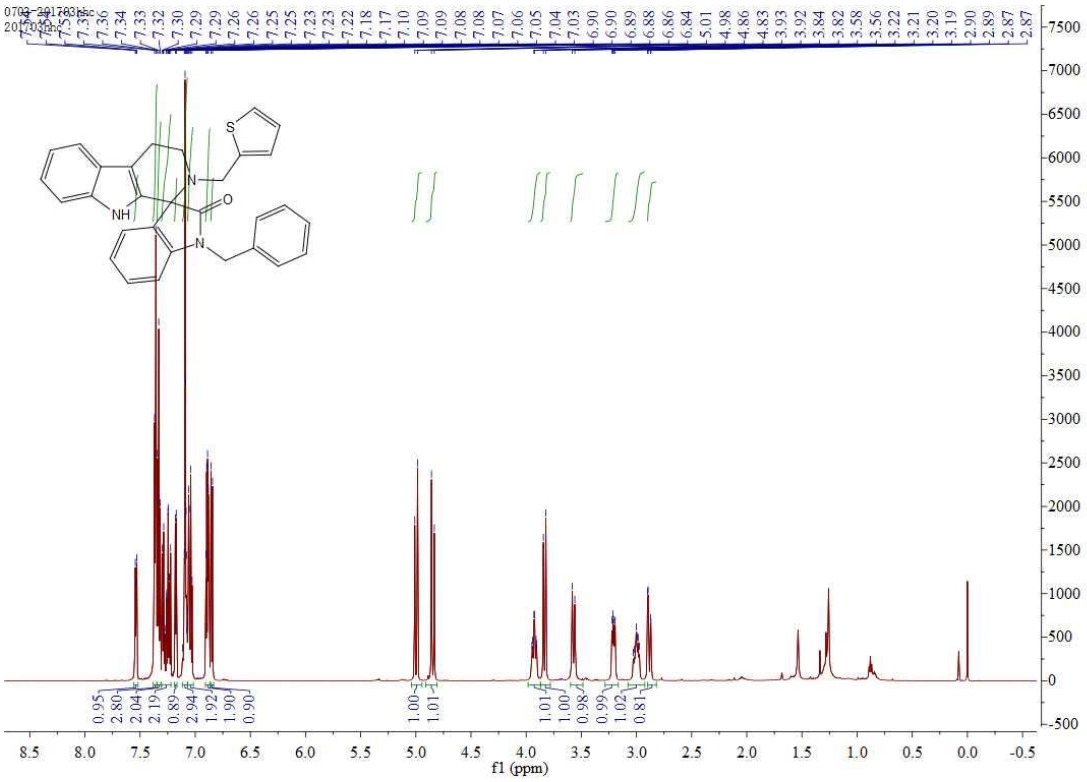

f1 (ppm)

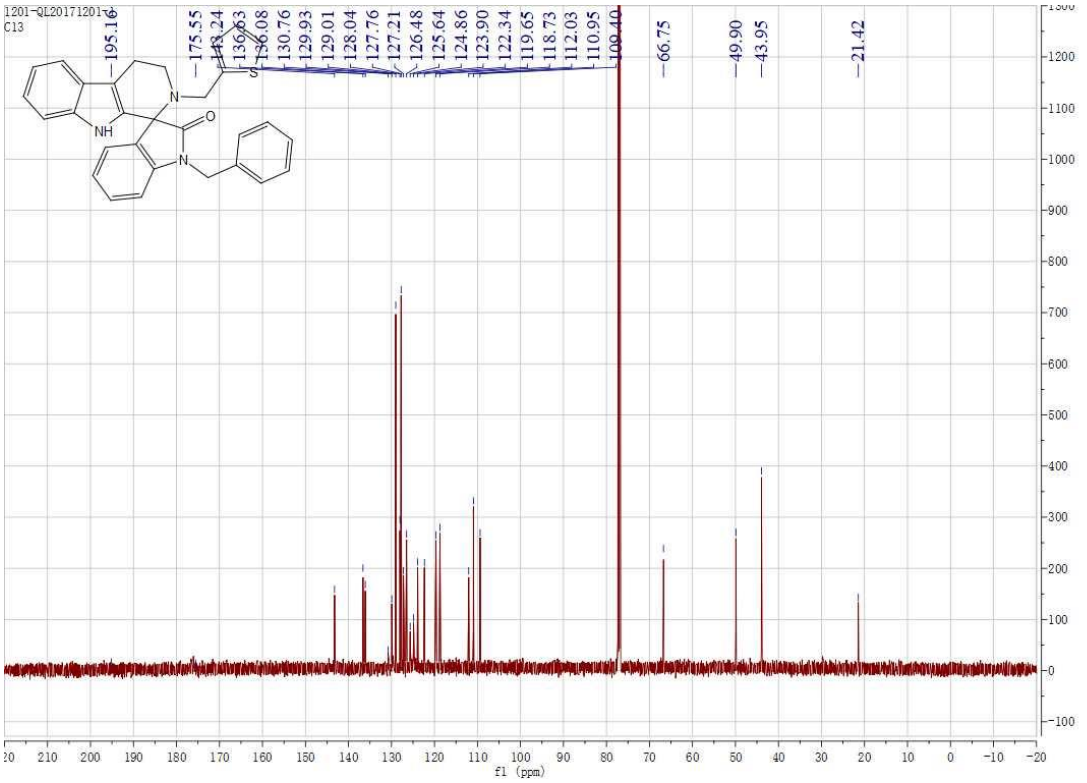

7.38
7.31
7.30
7.28
7.27
7.24
7.24
7.23
7.04
7.01
7.00
6.99
6.98
6.98
6.85
6.83
6.77
4.96
4.90
4.88
3.86
3.83
3.54
3.51
3.50
3.48
3.05
3.04
2.91
2.83
2.81
O
N
NH
O
N
2.20
4.88
3.22
2.08
1.26
2.96
1.06
1.02
1.00
0.97
0.81
3.11
1.91
0.99
0.92
1.04
f1 (ppm)

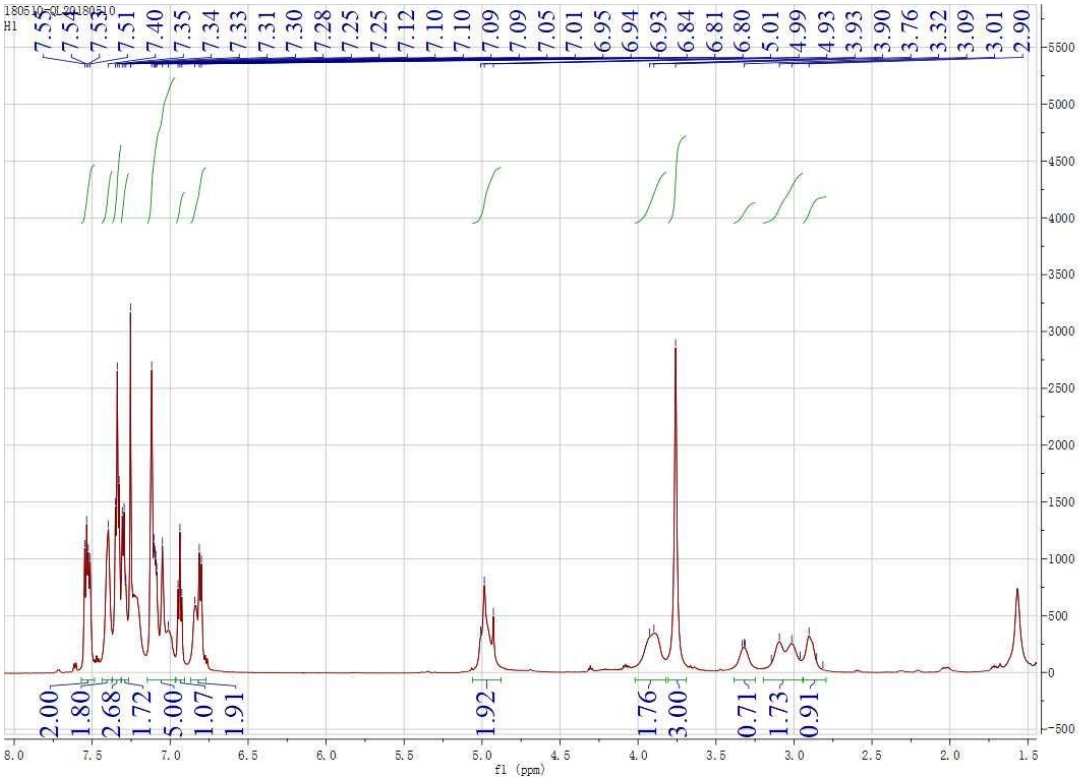

176.15
154.18
131.74
128.97
128.34
128.30
127.98
127.75
122.62
122.23
111.78
111.67
109.42
100.84
66.99
56.18
54.62
44.15
43.63
21.91
f1 (ppm)

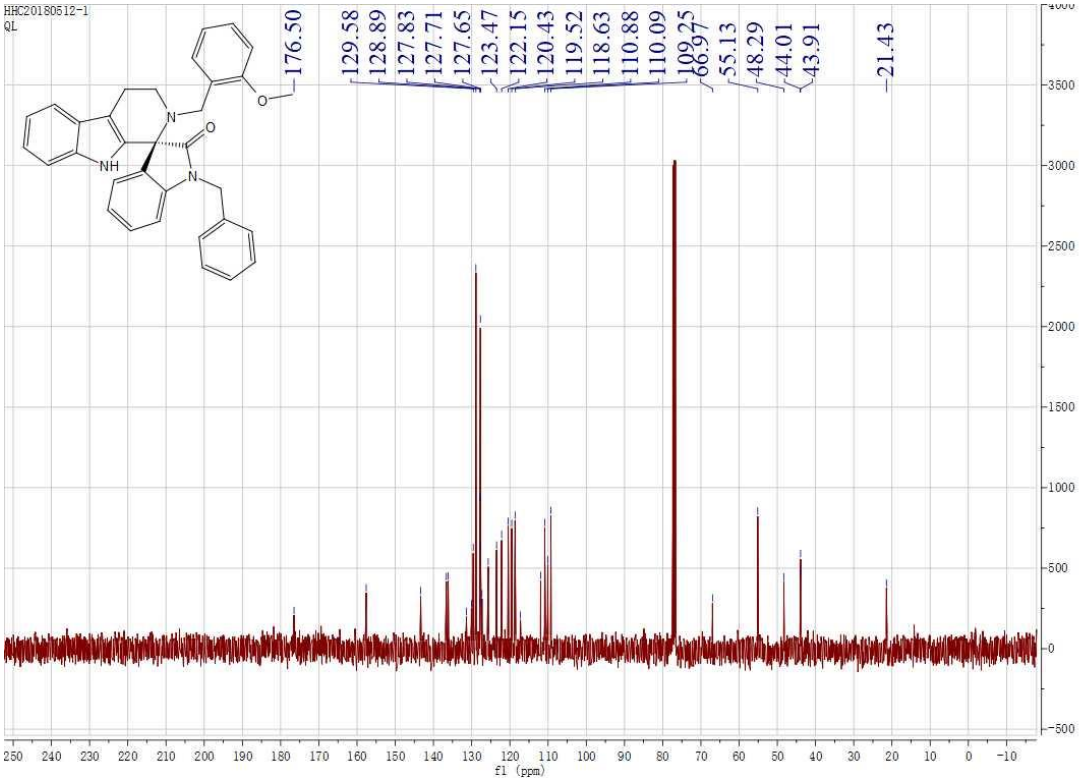

邻溴色胺苄基靛红
HHC20170710-1-H1
f1 (ppm)

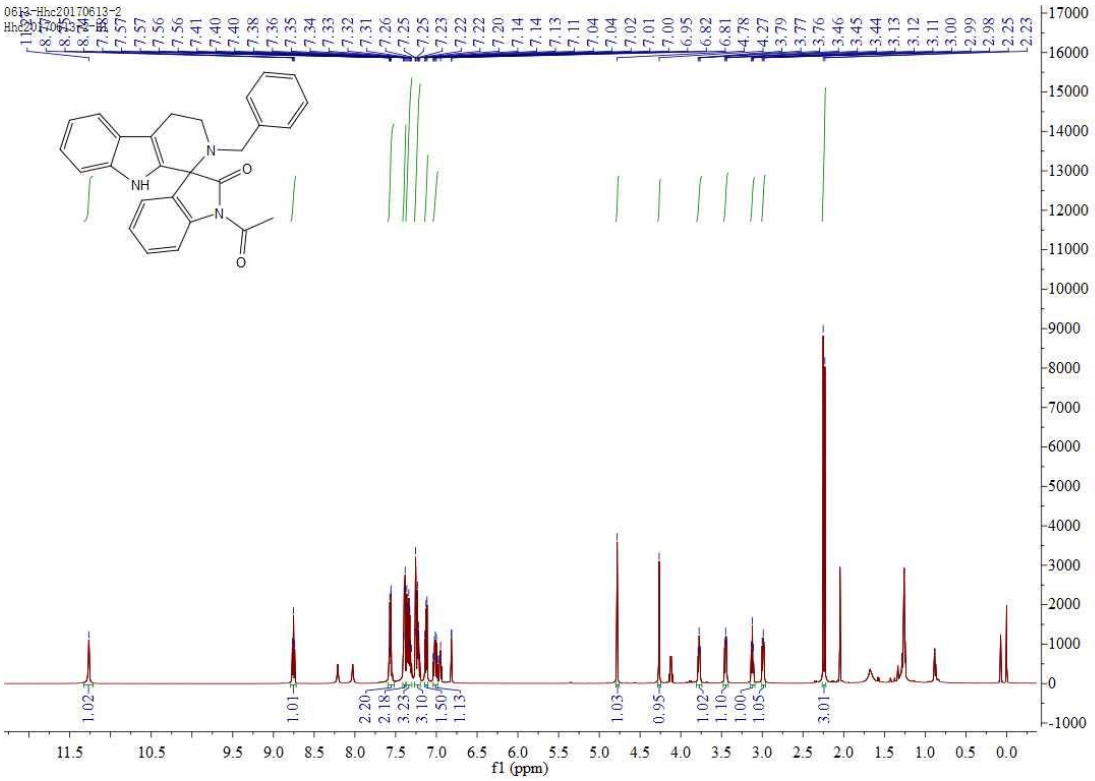

邻溴色胺苄基靛红
HHC20170710-1-C13
f1 (ppm)

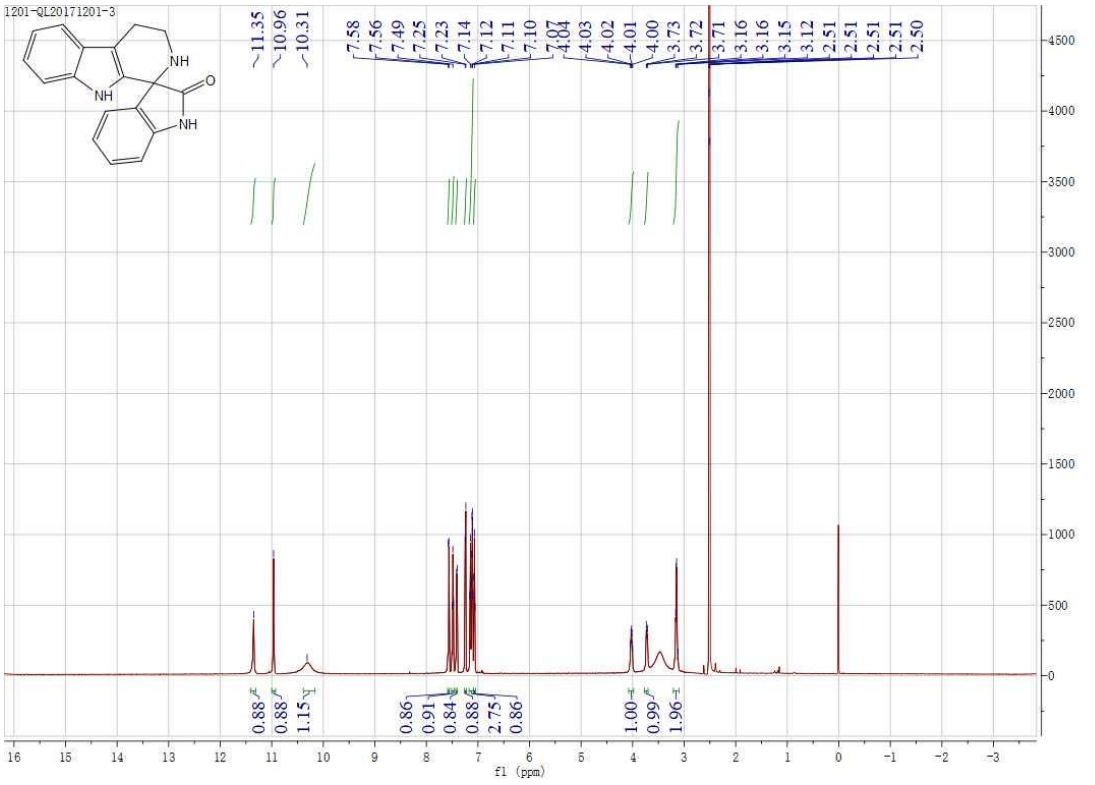

S
N
O
NH
N
f1 (ppm)


195.16
175.55
143.24
136.63
136.08
130.76
129.93
129.01
128.04
127.76
127.21
126.48
125.64
124.86
123.90
122.34
119.65
118.73
112.03
110.95
100.40
66.75
49.90
43.95
21.42
N
O
NH
N
f1 (ppm)


180510-QL-20180510
H1
7.55
7.54
7.53
7.51
7.40
7.35
7.34
7.33
7.31
7.30
7.28
7.25
7.25
7.12
7.10
7.10
7.09
7.09
7.05
7.01
6.95
6.94
6.93
6.84
6.81
6.80
5.01
4.99
4.93
3.93
3.90
3.76
3.32
3.09
3.01
2.90
2.00
1.80
2.68
1.72
5.00
1.07
1.91
1.92
1.76
3.00
0.71
1.73
0.91
f1 (ppm)


HHC20180512-1
QL
176.50
129.58
128.89
127.83
127.71
127.65
123.47
122.15
120.43
119.52
118.63
110.88
110.09
109.25
66.97
55.13
48.29
44.01
43.91
21.43
O
N
O
NH
N
f1 (ppm)


0613-Hhc20170613-2
NH
N
O
N
O
f1 (ppm)


1201-QL20171201-3
NH
NH
O
NH
f1 (ppm)

VI IC_{50} Values

Entry	IC_{50} values (A549 μM)	IC_{50} values (CHL μM)
3a	>100	N.D.
3b	>100	N.D.
3c	>100	N.D.
3d	>100	N.D.
3e	>100	N.D.
3g	85.55	19.37
3h	22.59	39.97
3i	28.86	31.28
3j	>100	N.D.
3k	>100	N.D.
3l	18.36	26.92
3m	5.90	118.20
3n	>100	N.D.
3o	17.89	16.45
3p	>100	N.D.
camptothecin	1.02	0.52

Anticancer activity

In vitro anticancer activity of all the synthesized compounds was studied by cell viability assay method. For evaluating the anticancer of the compounds, A549 (Human lung cancer) cell line was used. Cells were plated in 96-multiwell plates (104 cell/well) for 24 h. The compounds to be tested were dissolved in dimethyl sulphoxide. Solutions of different concentration of the compounds under test were added to the cell monolayer. After incubated for 72h, the viability of the cells was assessed by the MTT (3-(4,5- dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide) assay method. The anticancer potency of these compounds was indicated by IC_{50} (the concentration that causes a 50%reduction of the cell growth).

V. References

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