Highly Enantioselective α-alkylation of 2-Oxindoles with (3-Indolyl)methanols by Cooperative Catalysis of Lewis Acid and Organocatalyst

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[b] *University of Chinese Academy of Sciences, Beijing 100049,China*

[c] *School of Chemistry and Chemical Engineering, Institute of Theoretical and Computational Chemistry, Key Laboratory of Mesoscopic Chemistry of MOE, Nanjing University, Nanjing, Jiangsu, 210093, China.*

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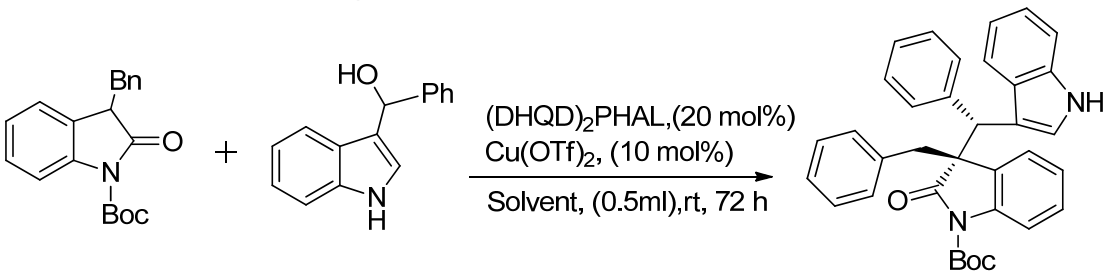
1. Experimental section

1.1 Solvent screening

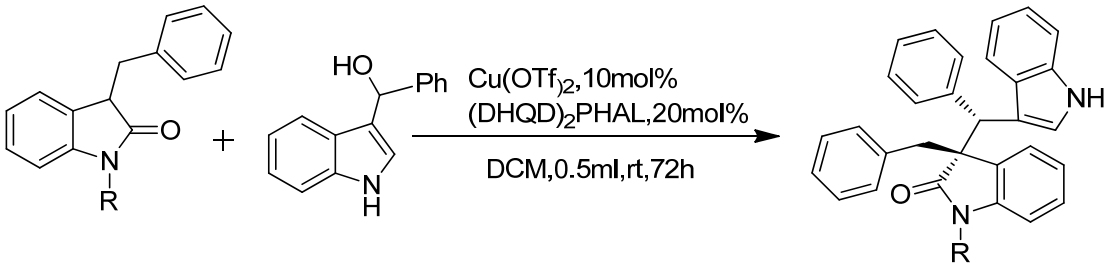


1a **2a** **3a**

Entry	Solvent	dr[b]	Yield(%)[c]	Ee[d](%) Syn-3a
1	EtOAc	N.D.	57	62
2	DMSO	1:1	70	4
3	Toluene	2:1	72	57
4	CH_3NO_2	5:1	70	85
5	$CHCl_3$	3:1	80	82
6	1,1,2-trichloroethene	2:1	55	73
7	1,1,2,2-tetrachloroethane	3:1	80	75
8	1,1,2-trichloroethane	2:1	65	71
9	CH_2Cl_2	3:1	74	80

[a] Reaction conditions: **1a** (0.2mmol), **2a** (0.1mmol). [b] Determined by ^{1}H NMR. [c] Isolated yield of the combined products. [d] Major diastereoisomer's ee determined by chiral HPLC.

1.2 Effect of N-Substituent of oxindoles



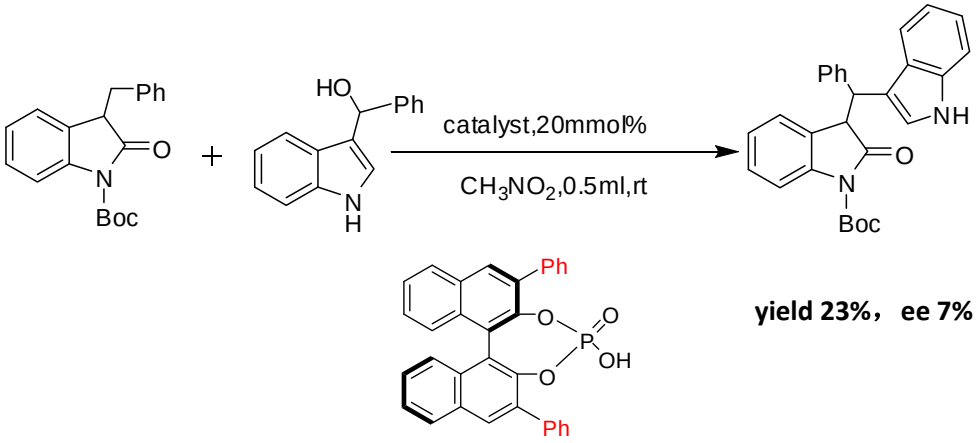
R=Boc, yield 74%, dr 3:1, ee 80%

R=Ac, yield 62%, dr 3:1, ee rac

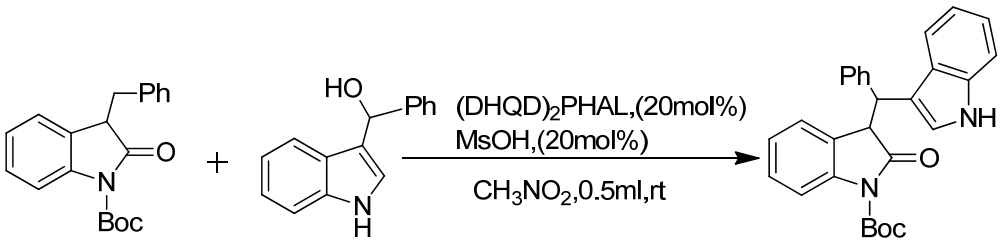
R=H, trace

R=Bn, trace

1.3 Screening catalyst

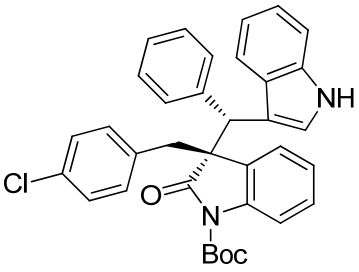


yield 23%， ee 7%



yield 15%　ee 20%

2. Determination of absolute configuration of syn-3f



2.1 Experimental

About 11 mg of sample was dissolved in 150μl $CDCl_3$ and placed in a BaF_2 cell with a path-length of 75μm. IR and VCD spectra were recorded on a Chiral IR-2X FT-VCD spectrometer (BioTools, Inc.) equipped with single photoelastic modulation, with 4 cm^{-1} resolution, 9h collection for both the chiral sample.

2.2 Theoretical Calculation

Since there are two chiral centers in 3g , we investigated the geometry of all the possible conformations, i.e., RR, RS, SR and SS. The IR and VCD spectra were calculated for all of them. We find that the calculated IR and VCD spectra of the RR configuration agree best with the experiment, as shown in Fig.2. Therefore the absolute configuration of 3g is assigned as (RR).

Geometry optimization, frequency, and IR and VCD intensity calculations were carried out at the B3LYP/6-31G(d,p) level of theory. Polarized continuum model (PCM) was adopted to consider solvent (chloroform) effects in the calculation of IR and VCD spectra. The IR and VCD intensities were converted to Lorentzian bands with 8 cm-1 half-width for comparison to experiment. All calculations were performed with the Gaussian 09 program suite.

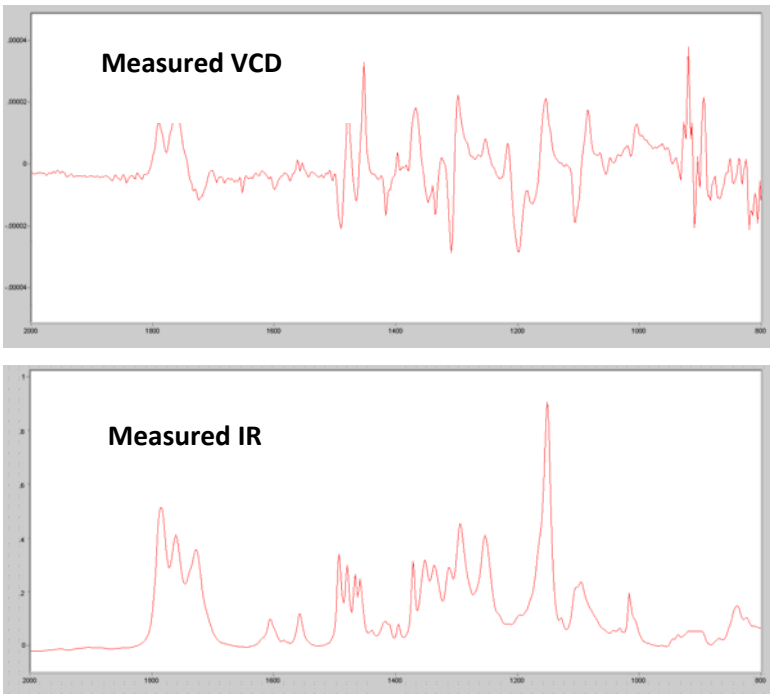


Fig.1 VCD and IR spectra of 3g in $CDCl_3$(11mg/0.15ml)

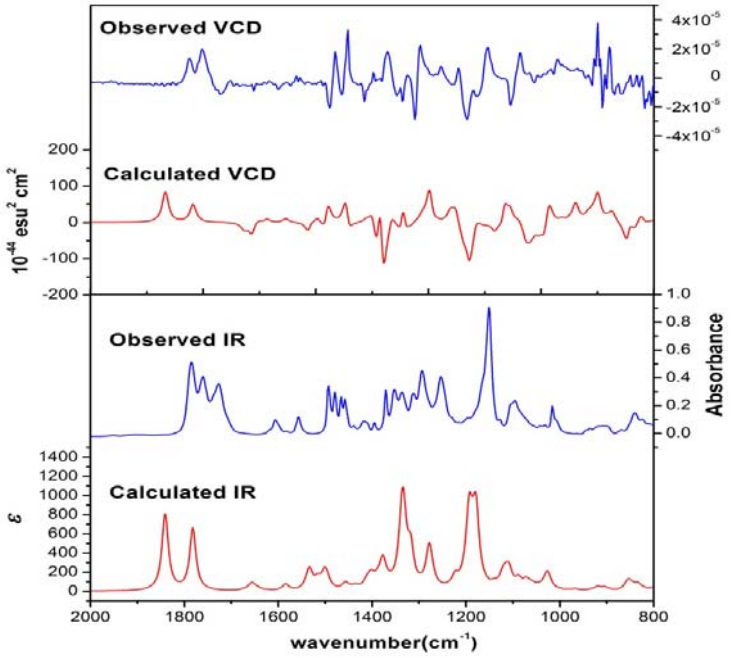
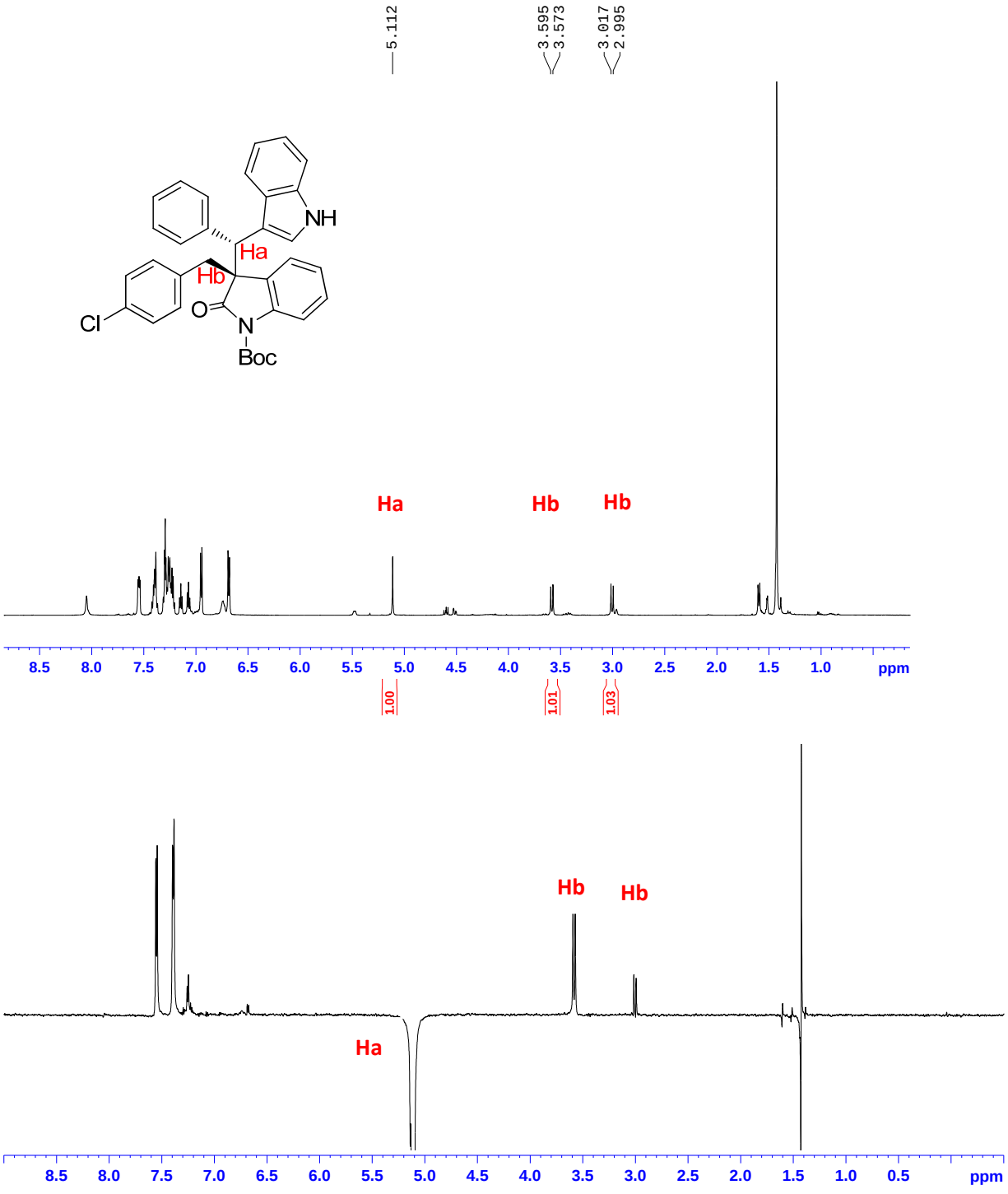
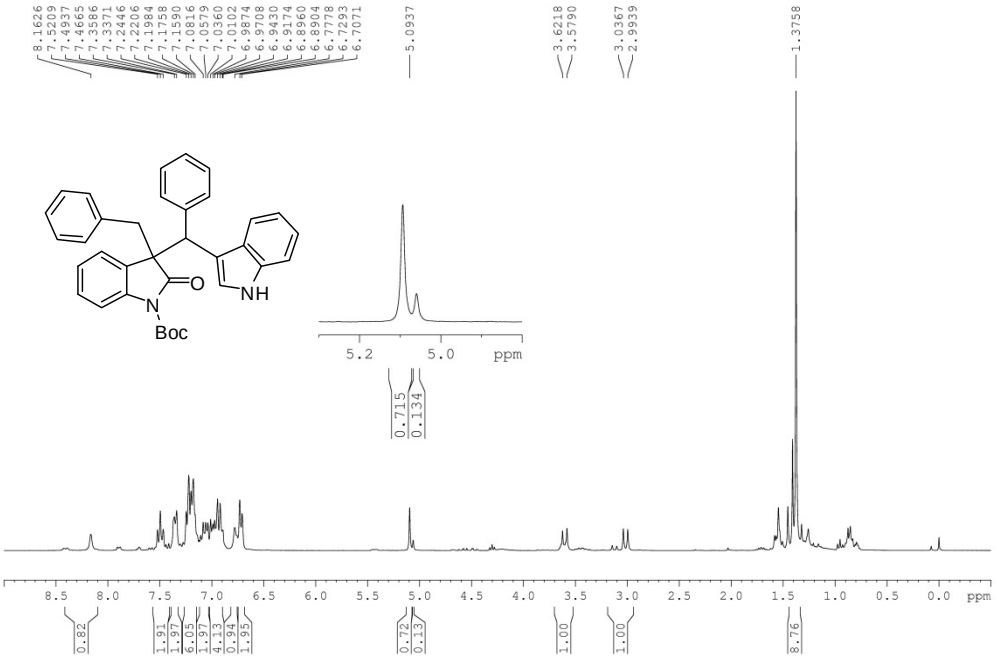


Fig.2 VCD and IR spectra observed for syn-3f compared with calculated spectra

2.3 1D NOE of 3f



3. NMR Spectrum and HPLC Chromatograms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7.1590
7.0816
7.0579
7.0360
7.0102
6.9974
6.9708
6.9430
6.9174
6.8960
6.8904
6.7778
6.7293
6.7071
5.0937
3.6218
3.5790
3.0367
2.9939
1.3758
O
NH
N
Boc
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5.0
ppm
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0.134
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
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0.13
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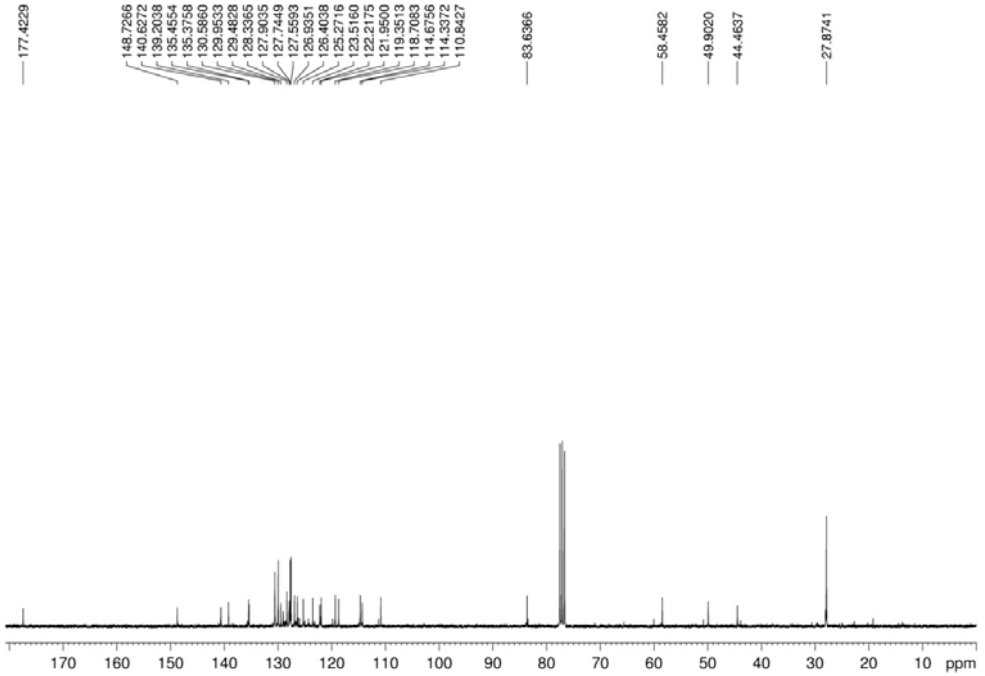
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140.6272
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135.4554
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130.5860
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127.9035
127.7449
127.5593
126.9351
126.4038
125.2716
123.5160
122.2175
121.9500
119.3513
118.7083
114.6756
114.3372
110.8427
83.6366
58.4582
49.9020
44.4637
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140
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70
60
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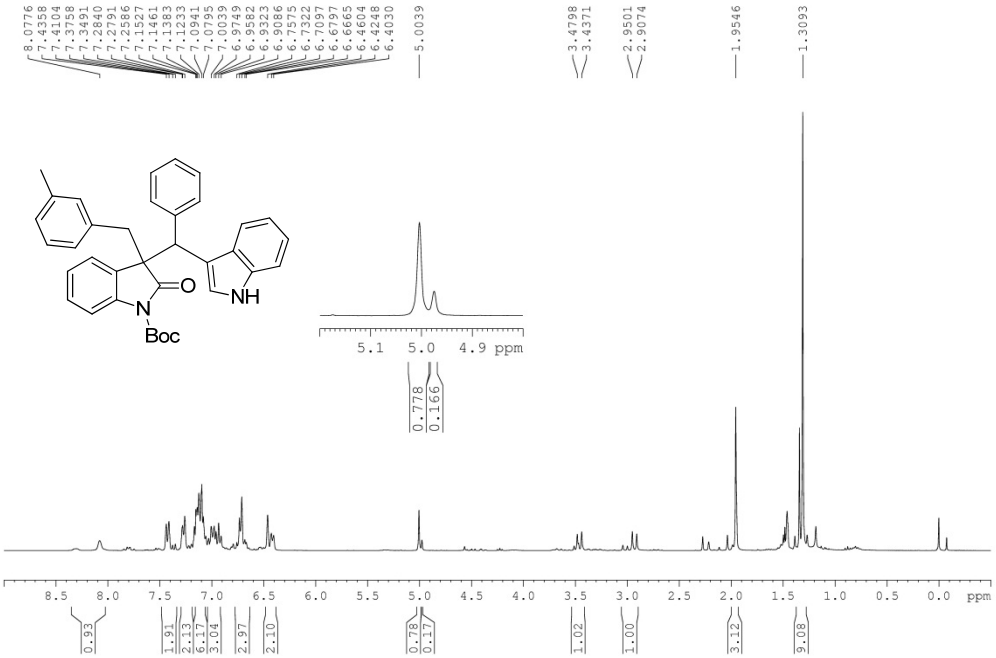
10
ppm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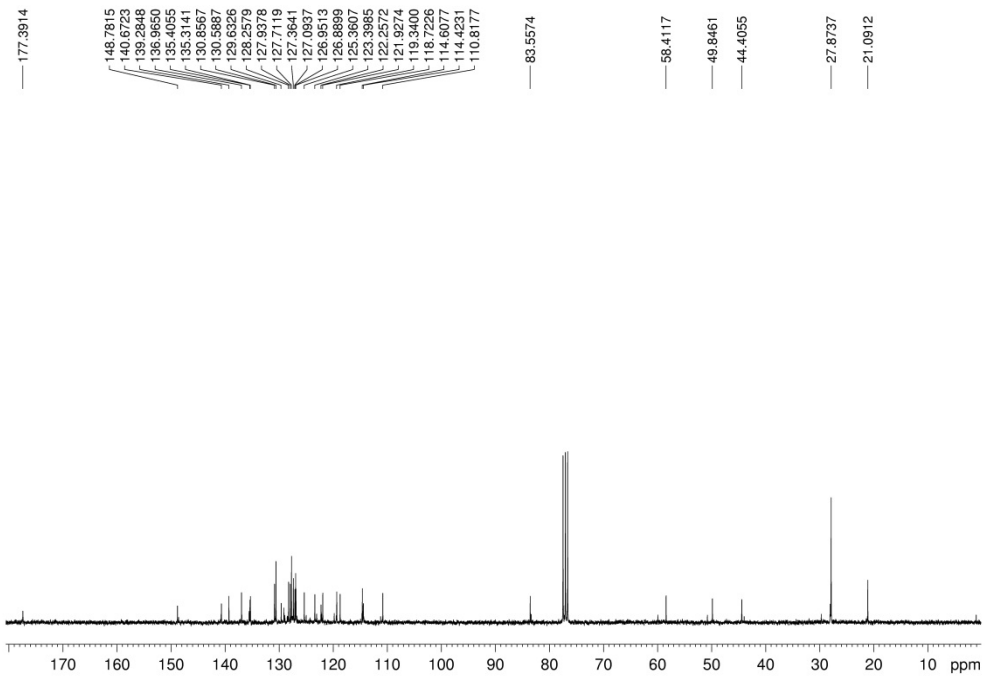
7.0941
7.0795
7.0039
6.9749
6.9582
6.9323
6.9086
6.7575
6.7322
6.7097
6.6797
6.6665
6.4604
6.4248
6.4030
5.0039
3.4798
3.4371
2.9501
2.9074
1.9546
1.3093
O
NH
N
Boc
5.1 5.0 4.9 ppm
0.778
0.166
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.93
1.91
2.13
6.17
3.04
2.97
2.10
0.78
0.17
1.02
1.00
3.12
9.08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127.7119
127.3641
127.0937
126.9513
126.8899
125.3807
123.3985
122.2572
121.9274
119.3400
118.7226
114.6077
114.4231
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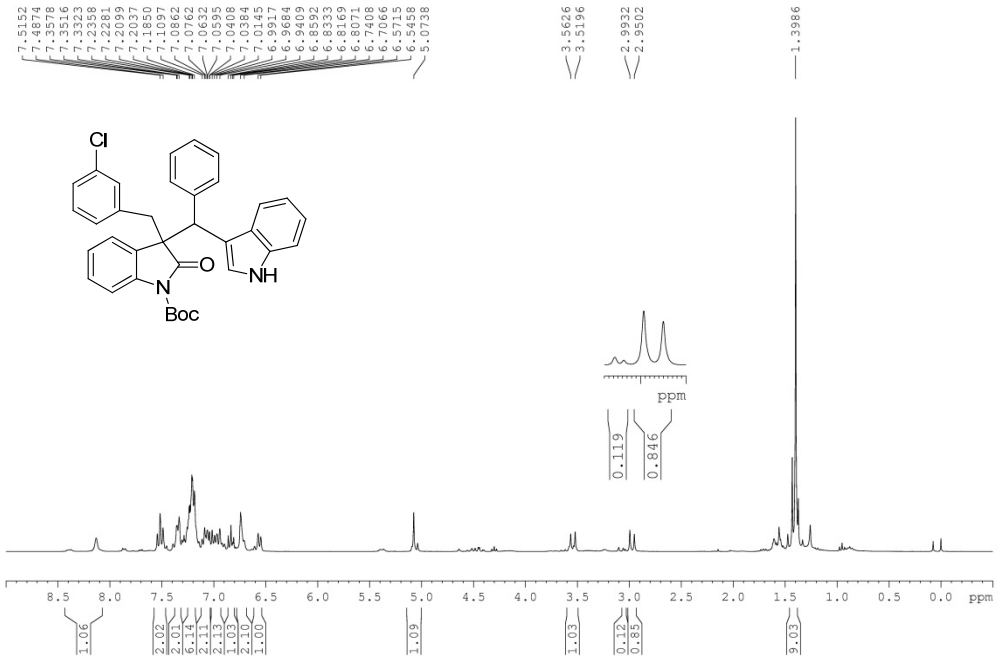
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N
Boc
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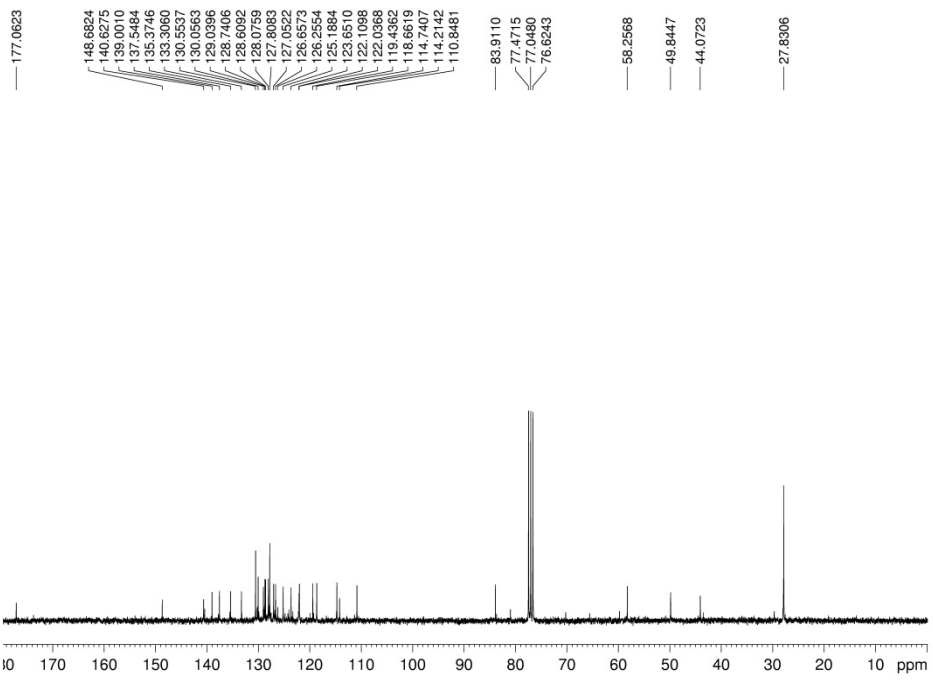
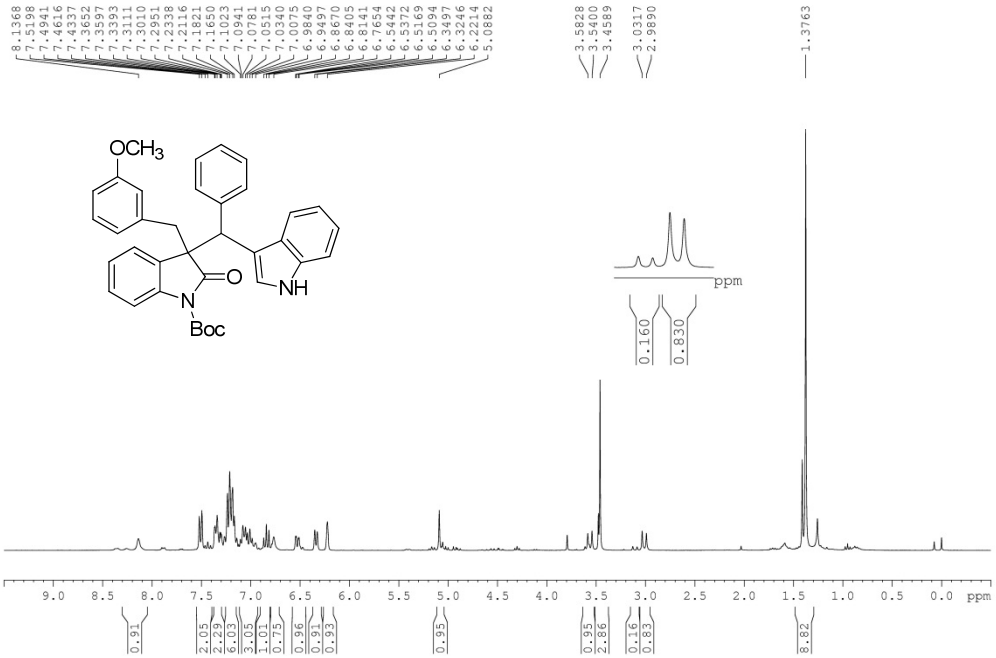
9.03

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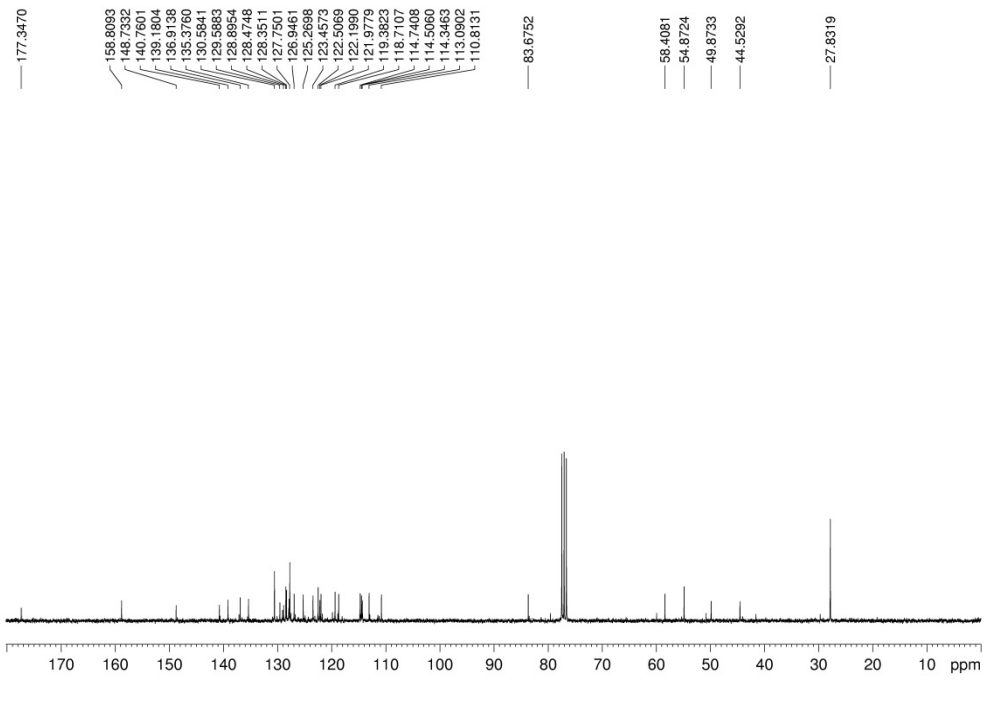

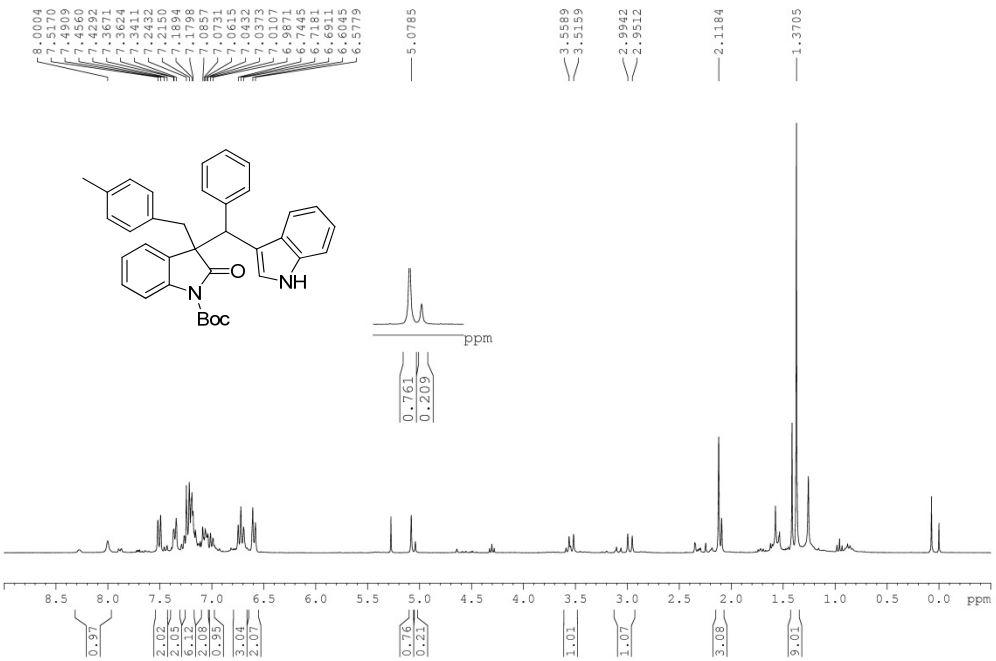
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7.1198
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7.0631
7.0615
7.0432
7.0373
7.0107
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6.7445
6.7181
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2.1184
1.3705
O
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N
Boc
ppm
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0.97
2.02
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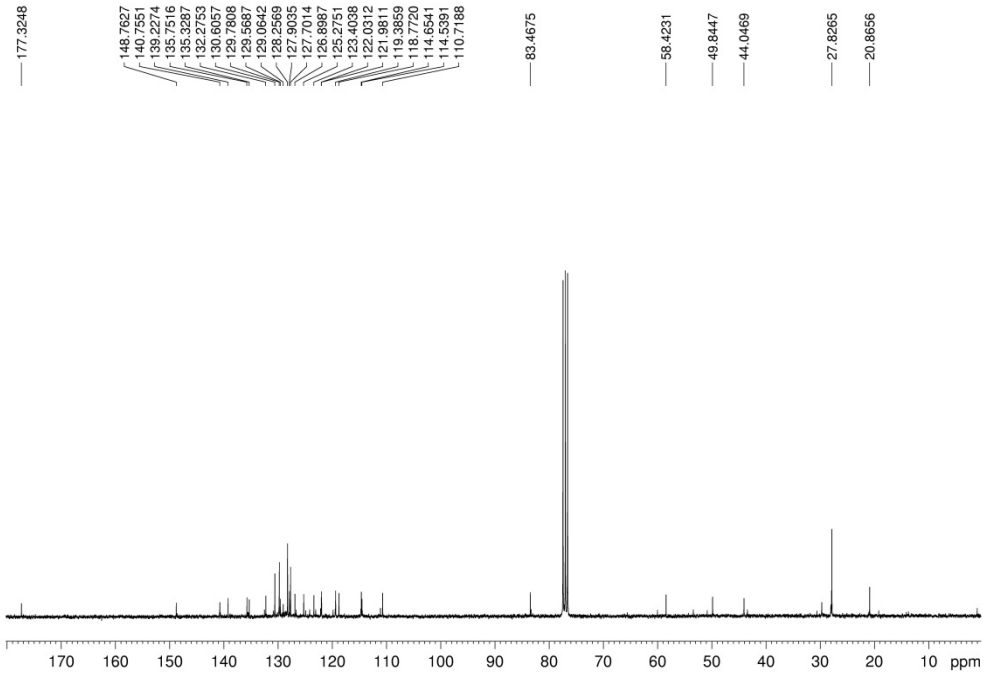
3.08
9.01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126.8987
125.2751
123.4038
122.0312
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119.3859
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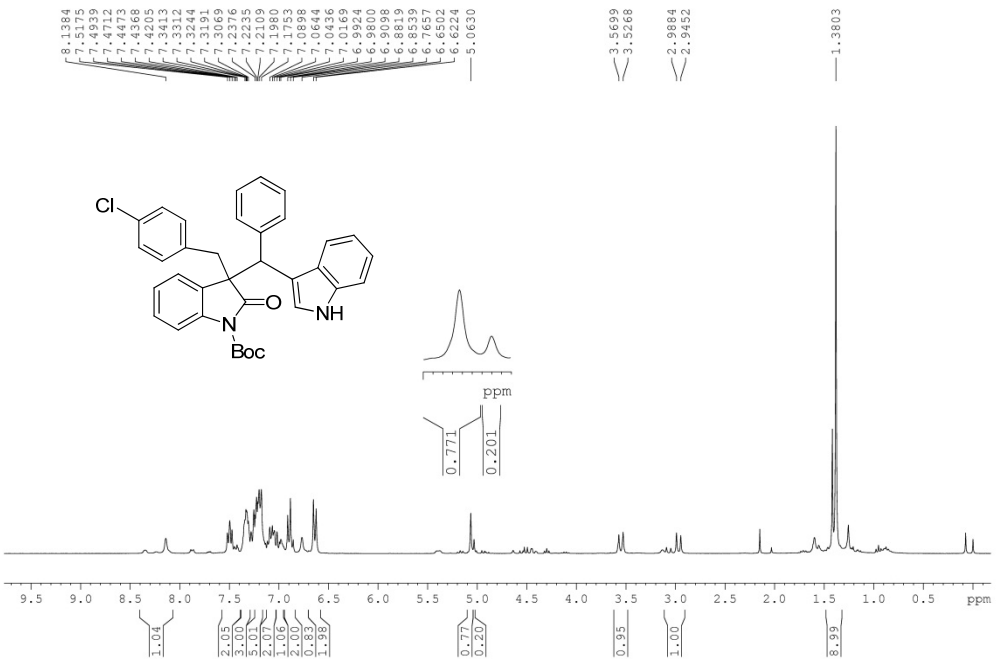
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Boc
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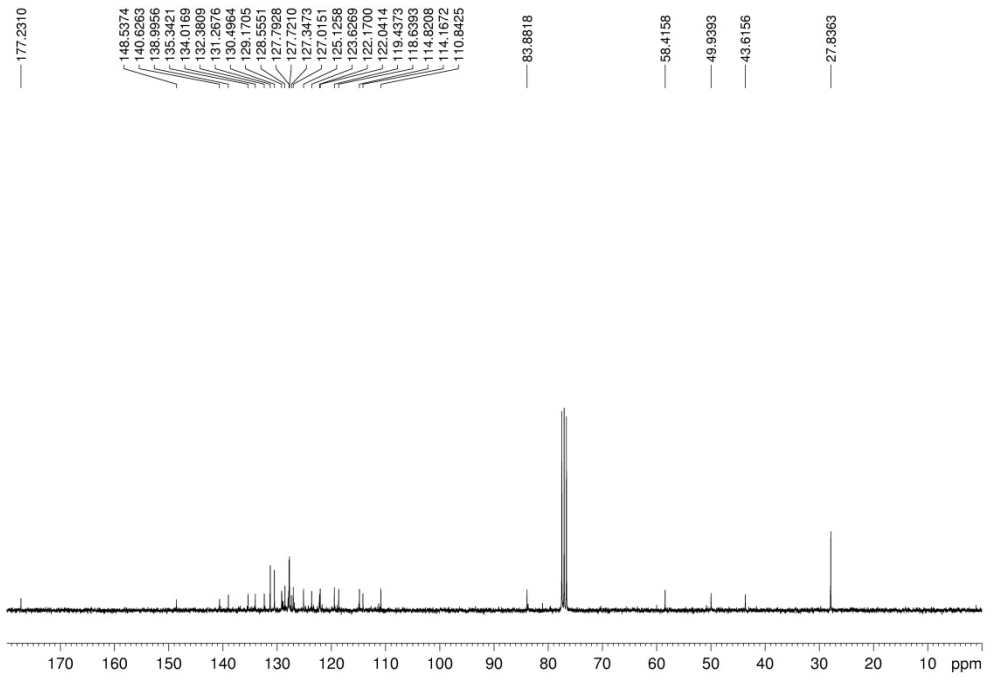
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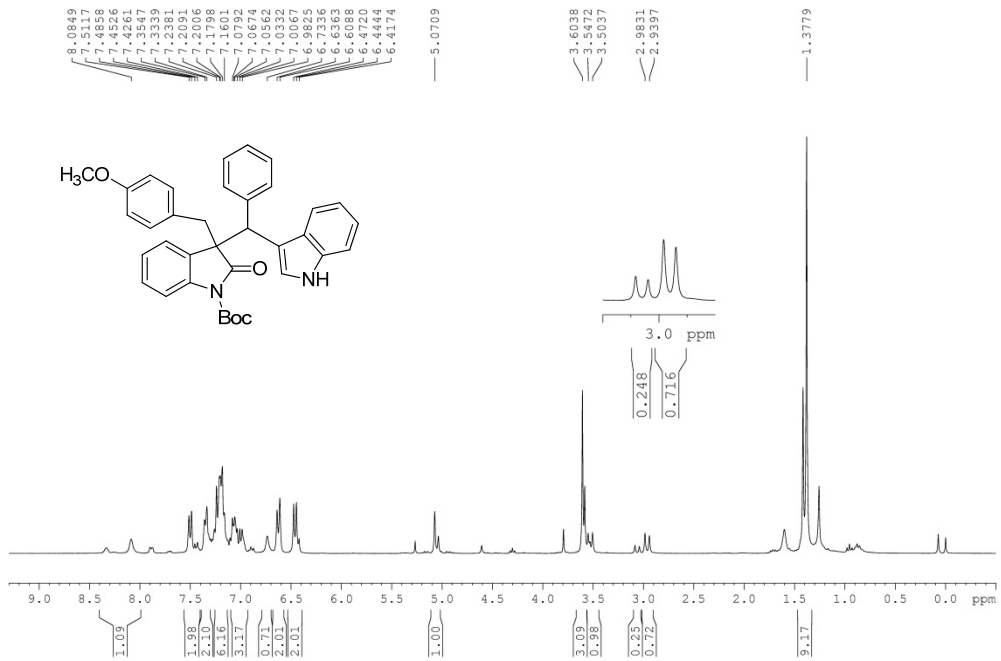
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5.0709
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3.5037
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1.3779
H3CO
O
N
Boc
NH
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1.98
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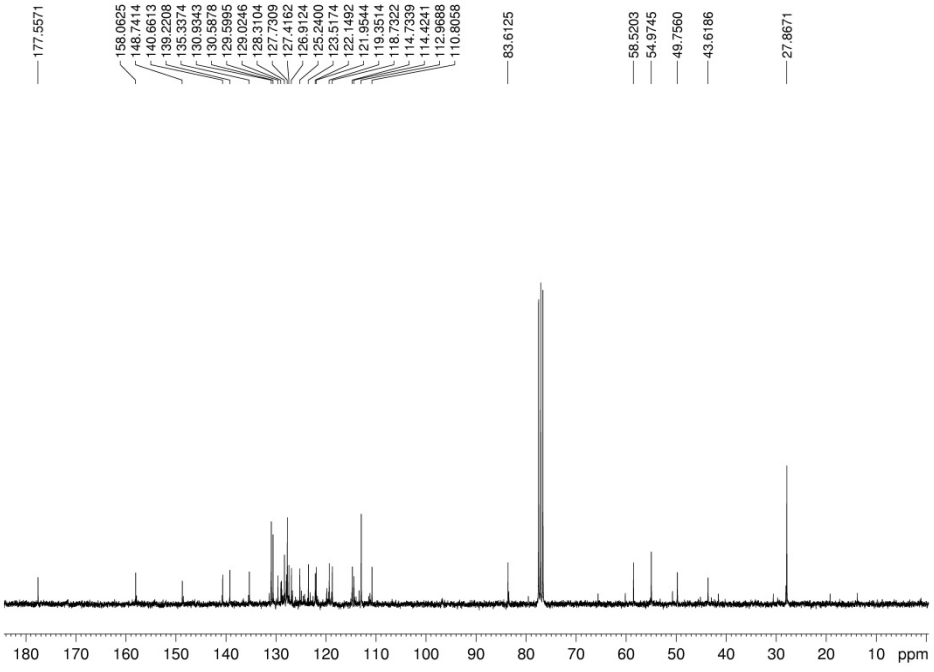
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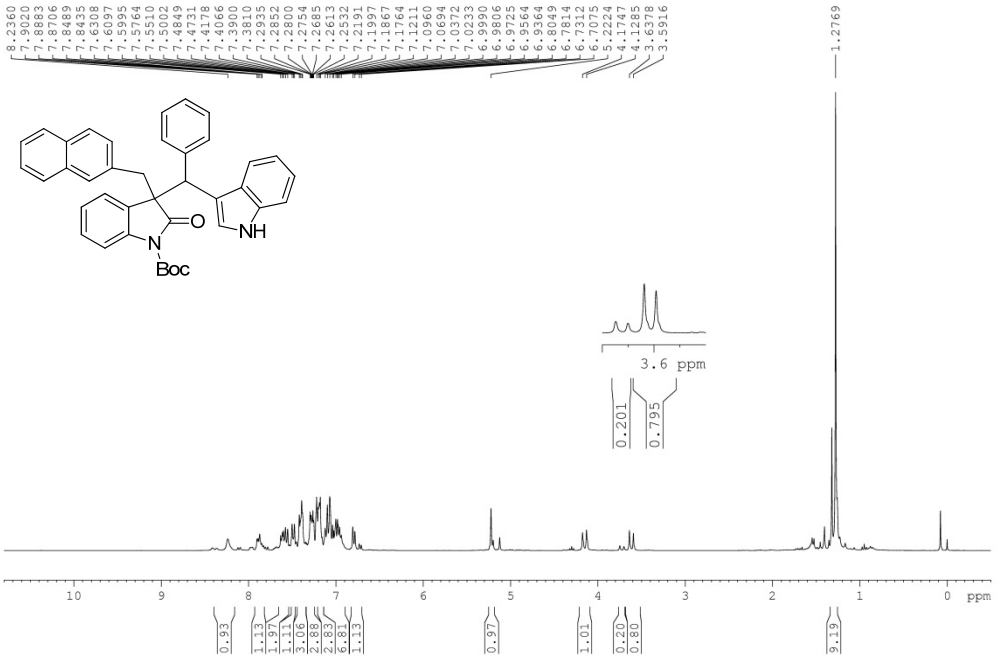
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7.0694
7.0372
7.0233
6.9990
6.9806
6.9725
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6.9364
6.8049
6.7814
6.7312
6.7075
5.2224
4.1747
4.1285
3.6378
3.5916
1.2769
O
NH
N
Boc
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10
9
8
7
6
5
4
3
2
1
0
ppm
0.93
1.13
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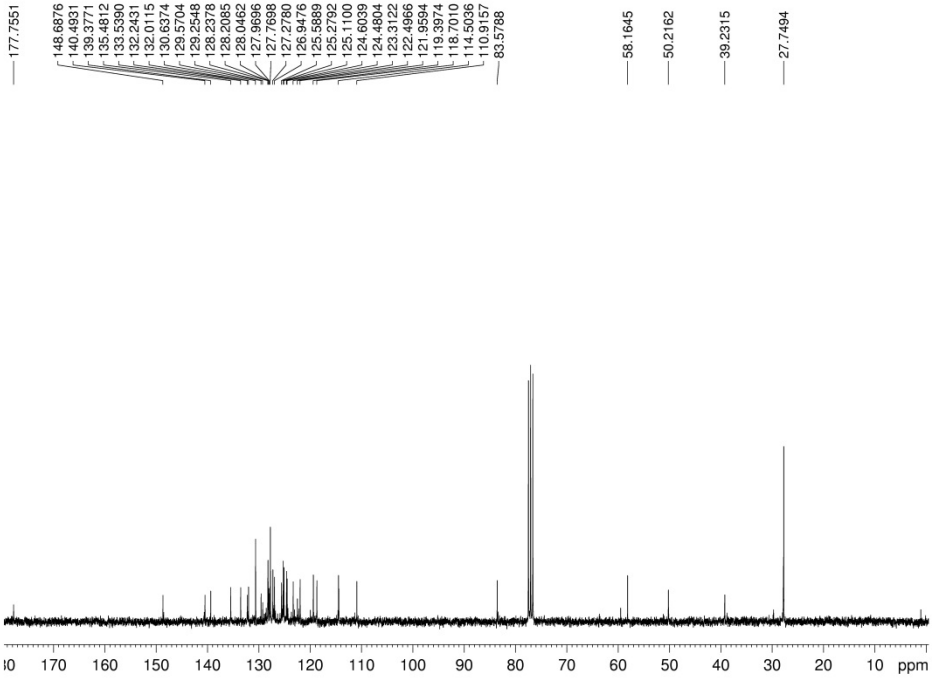
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126.9476
125.5889
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124.6039
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114.5036
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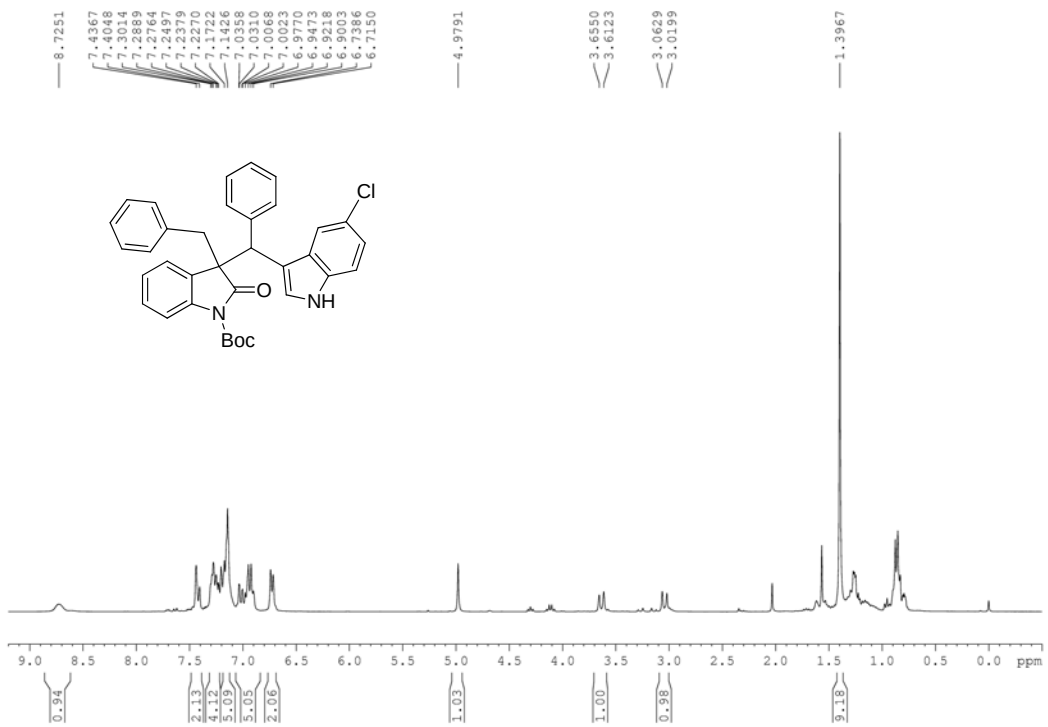
ppm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7.0068
7.0023
6.9770
6.9473
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4.9791
3.6550
3.6123
3.0629
3.0199
1.3967
Cl
O
NH
N
Boc
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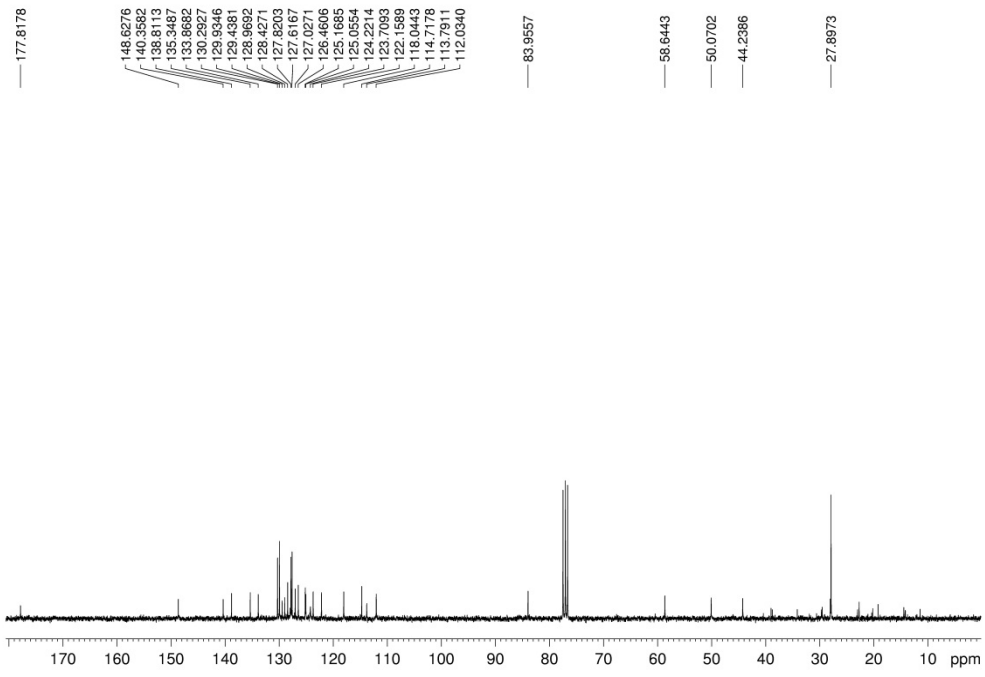
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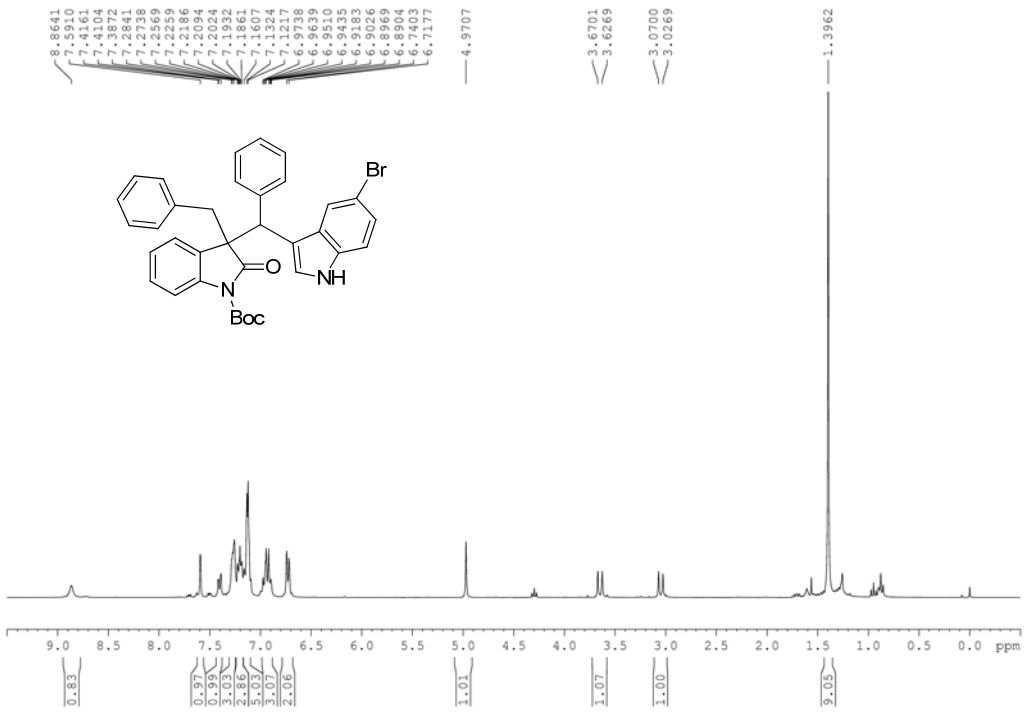
127.0271
126.4606
125.1685
125.0554
124.2214
123.7093
122.1589
118.0443
114.7178
113.7911
112.0340
83.9557
58.6443
50.0702
44.2386
27.8973
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.4161
7.4104
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7.2259
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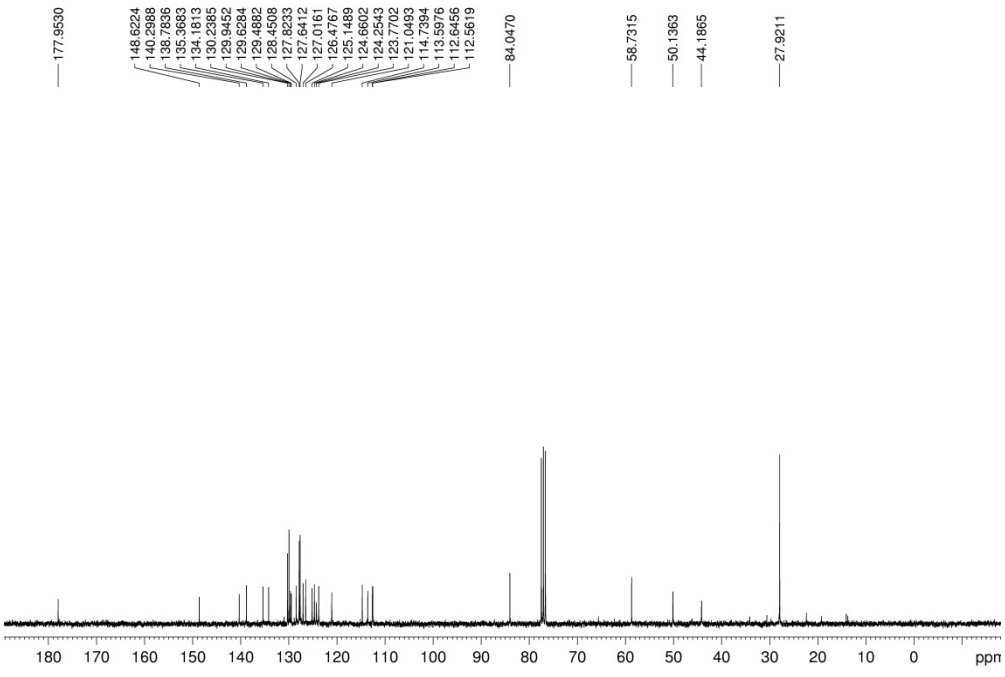
7.2094
7.2024
7.1932
7.1861
7.1607
7.1324
7.1217
6.9738
6.9639
6.9510
6.9435
6.9183
6.9026
6.8969
6.8904
6.7403
6.7177
4.9707
3.6701
3.6269
3.0700
3.0269
1.3962
Br
O
N
Boc
NH
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.83
0.97
0.99
3.03
2.86
5.03
3.07
2.06
1.01
1.07
1.00
9.05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140.2988
138.7836
135.3683
134.1813
130.2385
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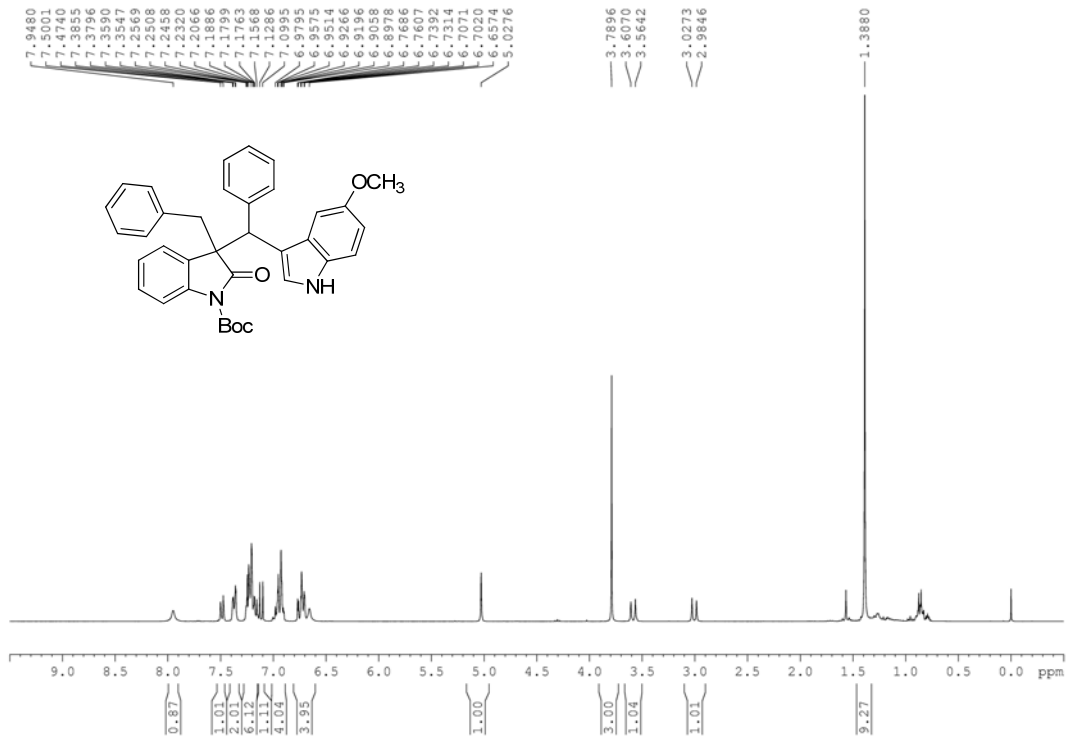
129.4882
128.4508
127.8233
127.6412
127.0161
126.4767
125.1489
124.6602
124.2543
123.7702
121.0493
114.7394
113.5976
112.6456
112.5619
84.0470
58.7315
50.1363
44.1865
27.9211
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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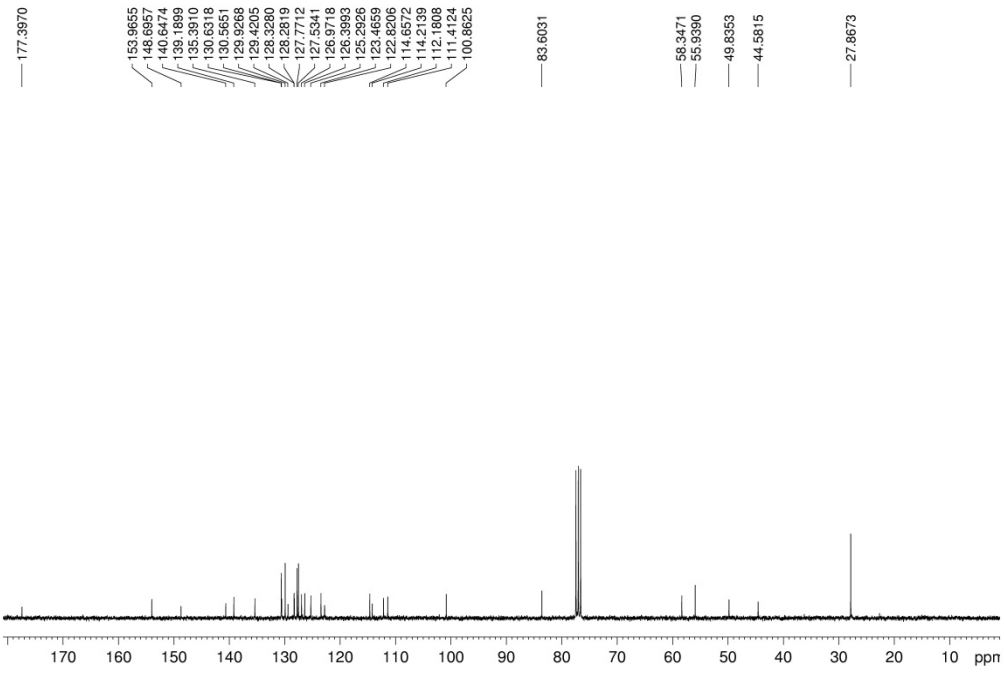
7.2508
7.2458
7.2320
7.2066
7.1886
7.1799
7.1763
7.1568
7.1286
7.0995
6.9795
6.9575
6.9514
6.9266
6.9196
6.9058
6.8978
6.7686
6.7607
6.7392
6.7314
6.7071
6.7020
6.6574
5.0276
3.7896
3.6070
3.5642
3.0273
2.9846
1.3880
OCH3
O
N
Boc
NH
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.87
1.01
2.01
6.12
1.11
4.04
3.95
1.00
3.00
1.04
1.01
9.27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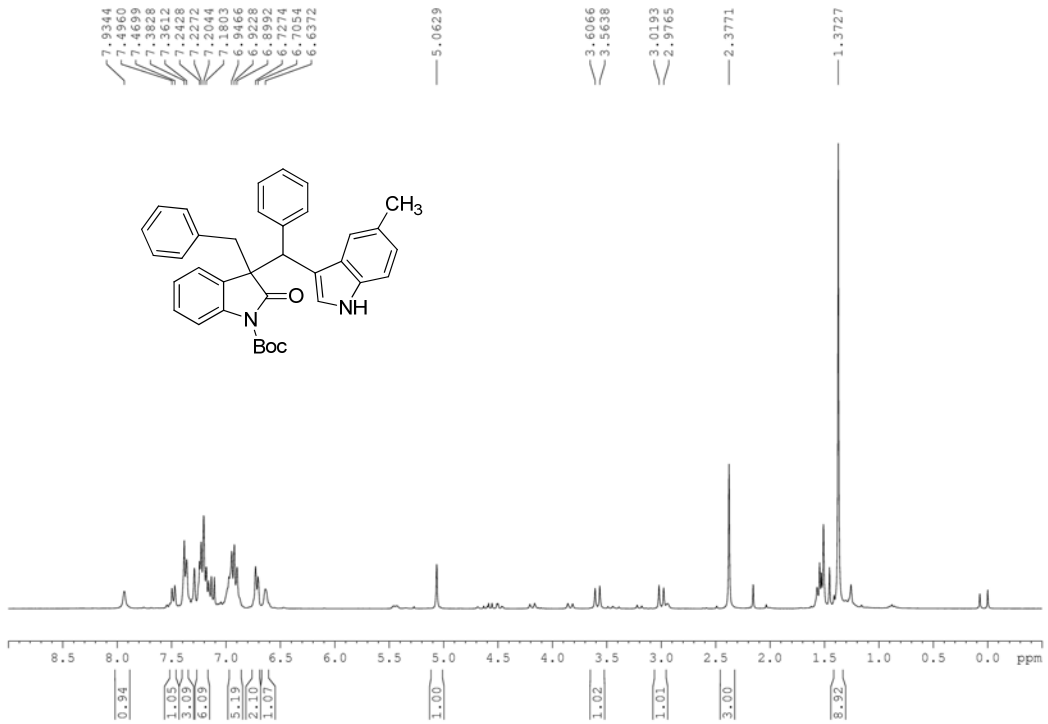
125.2926
123.4659
122.8206
114.6572
114.2139
112.1808
111.4124
100.8625
83.6031
58.3471
55.9390
49.8353
44.5815
27.8673
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.2428
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7.1803
6.9466
6.9228
6.8992
6.7274
6.7054
6.6372
5.0629
3.6066
3.5638
3.0193
2.9765
2.3771
1.3727
CH3
O
N
Boc
NH
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.94
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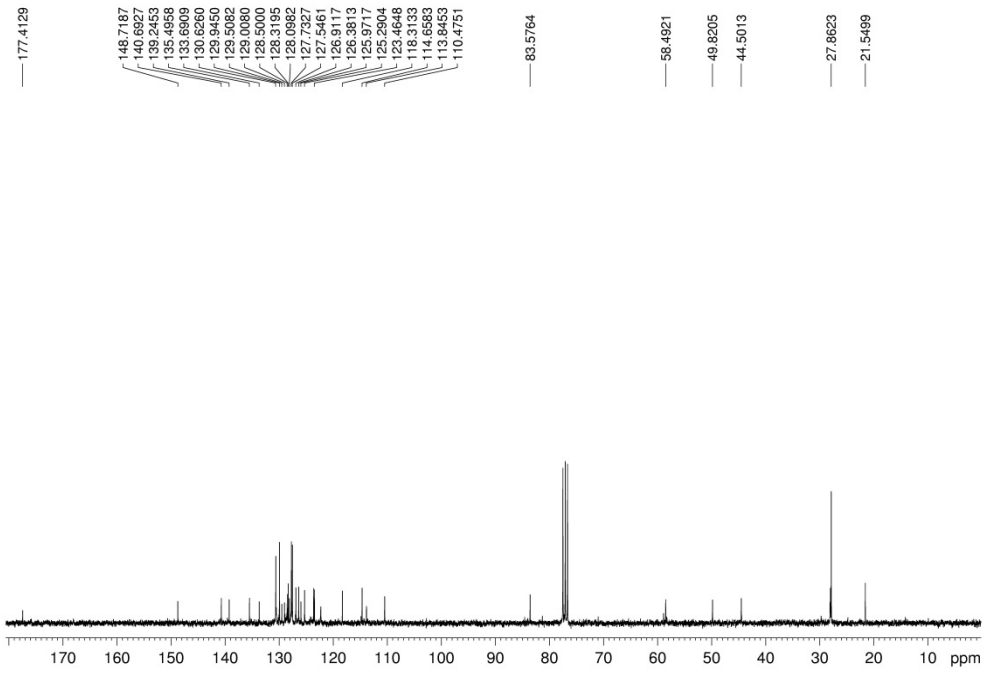
3.09
6.09
5.19
2.10
1.07
1.00
1.02
1.01
3.00
8.92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139.2453
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128.5000
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128.0982
127.7327
127.5461
126.9117
126.3813
125.9717
125.2904
123.4648
118.3133
114.6583
113.8453
110.4751
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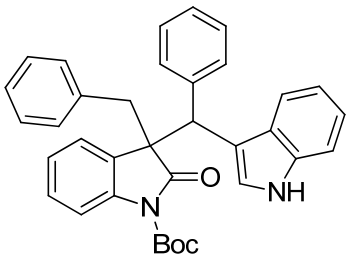
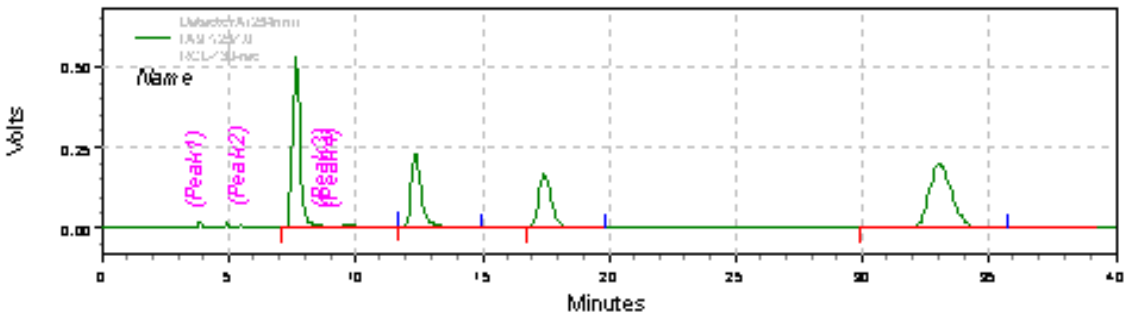
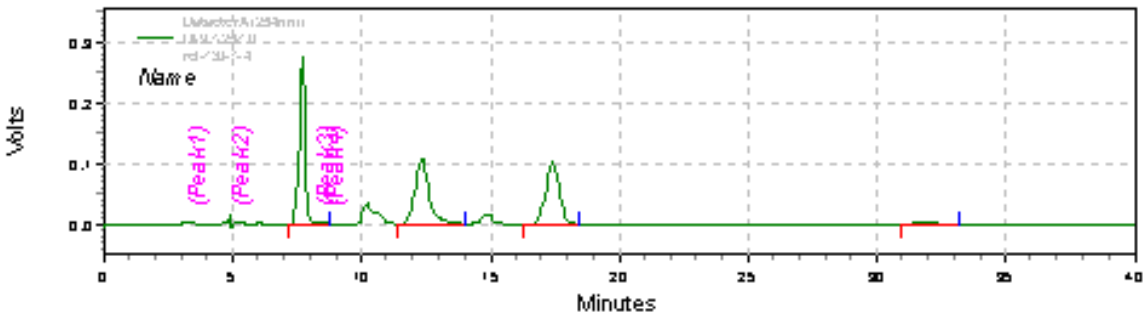
58.4921
49.8205
44.5013
27.8623
21.5499
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm





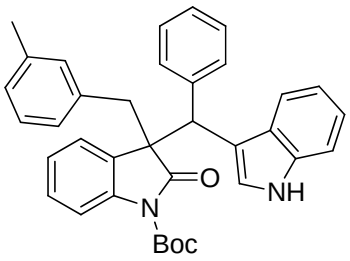
DetectorA (254nm)

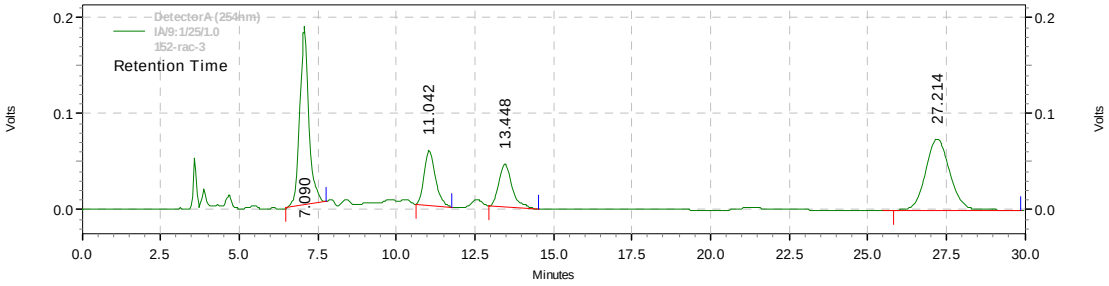
Pk #	Retention Time	Area	Area %
1	7.662	11820771	32.158
2	12.374	6494285	17.667
3	17.463	6043375	16.441
4	33.048	12400196	33.734



DetectorA (254nm)

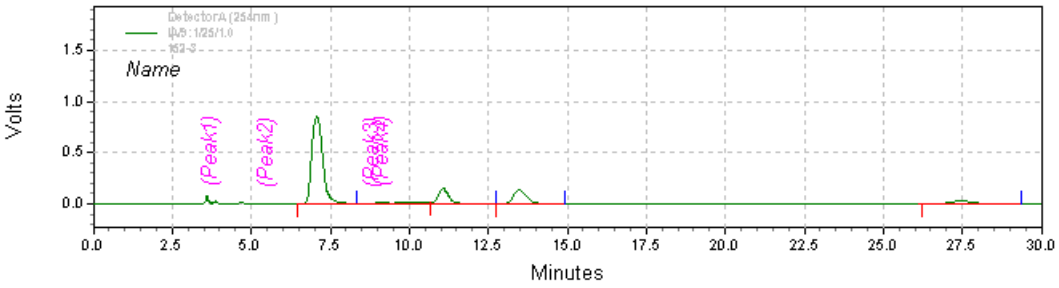
Pk #	Retention Time	Area	Area %
1	7.719	4532143	36.189
2	12.368	4040827	32.266
3	17.434	3751099	29.953
4	31.902	199401	1.592





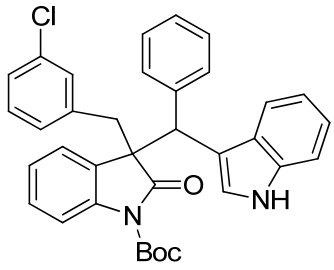
DetectorA (254nm)

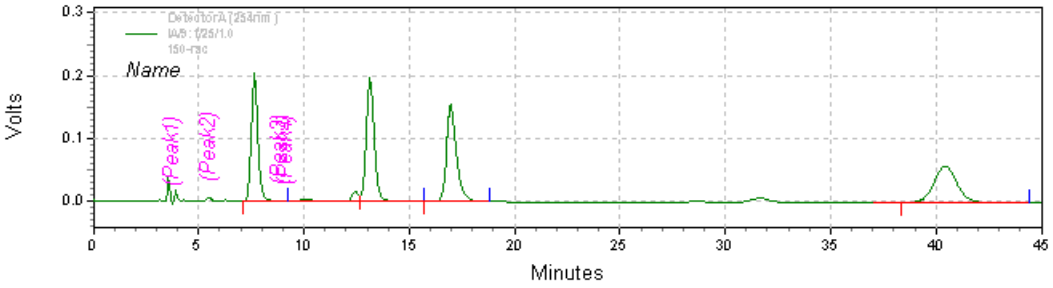
Pk #	Retention Time	Area	Area %
1	7.090	3854419	37.163
2	11.042	1383426	13.338
3	13.448	1288795	12.426
4	27.214	3845100	37.073



DetectorA (254nm)

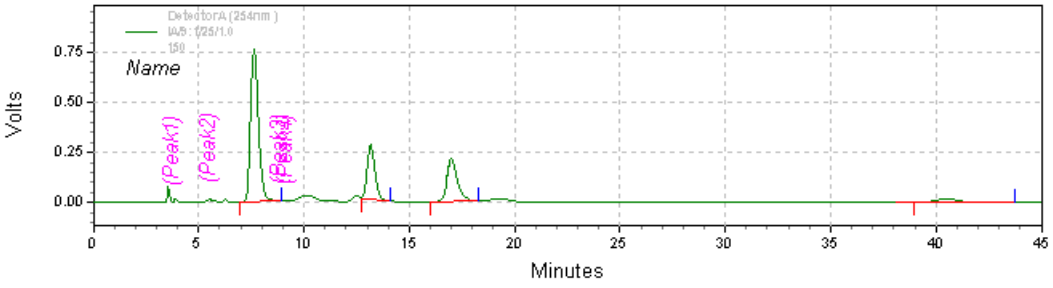
Pk #	Retention Time	Area	Area %
1	7.059	20825203	70.552
2	11.054	3754924	12.721
3	13.481	3907798	13.239
4	27.480	1029557	3.488





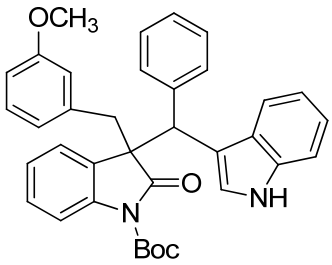
DetectorA (254nm)

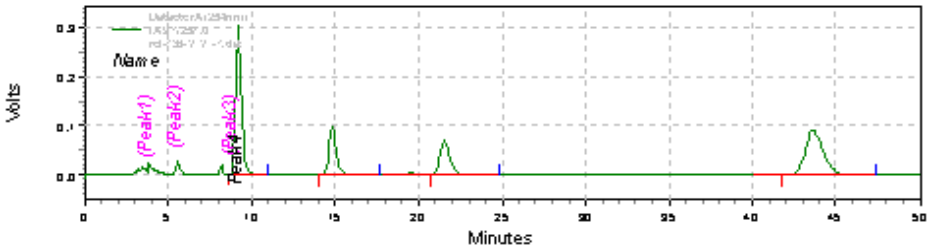
Pk #	Retention Time	Area	Area %
1	7.670	4392566	22.718
2	13.146	5173683	26.758
3	16.984	5466442	28.272
4	40.474	4302224	22.251



DetectorA (254nm)

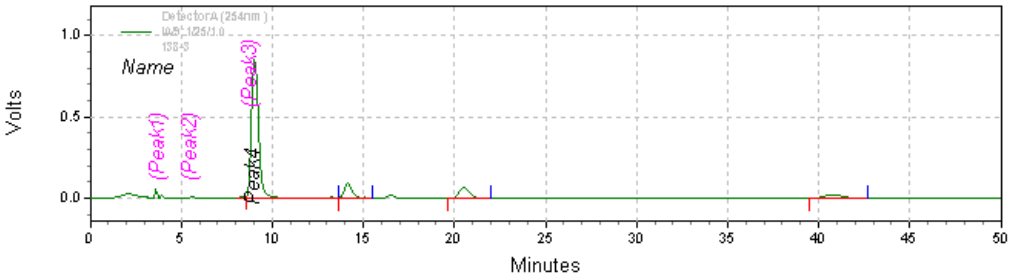
Pk #	Retention Time	Area	Area %
1	7.650	19783269	55.028
2	13.179	6853713	19.064
3	17.014	8011486	22.284
4	40.549	1302736	3.624





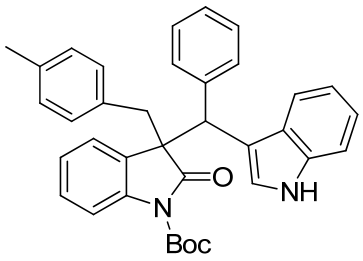
DetectorA (254nm)

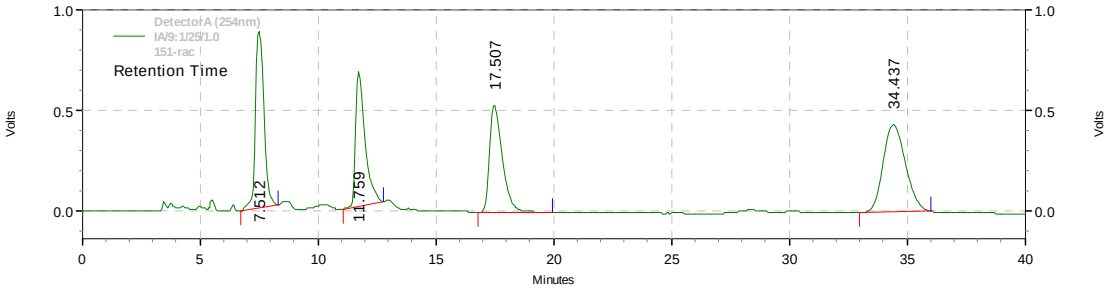
Pk #	Retention Time	Area	Area %
1	9.199	6971075	34.402
2	14.829	2917085	14.396
3	21.559	2950015	14.558
4	43.646	7425350	36.644



DetectorA (254nm)

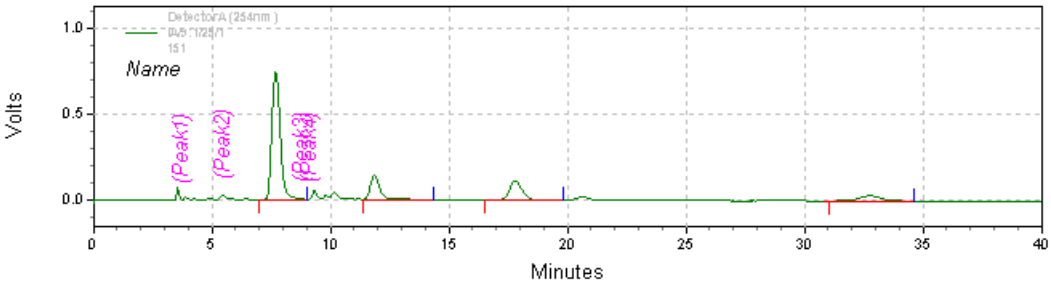
Pk #	Retention Time	Area	Area %
1	9.034	23285138	78.884
2	14.173	2642428	8.952
3	20.532	2459236	8.331
4	40.770	1131506	3.833





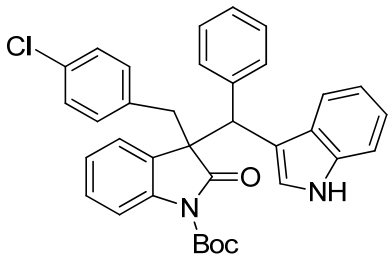
DetectorA (254nm)

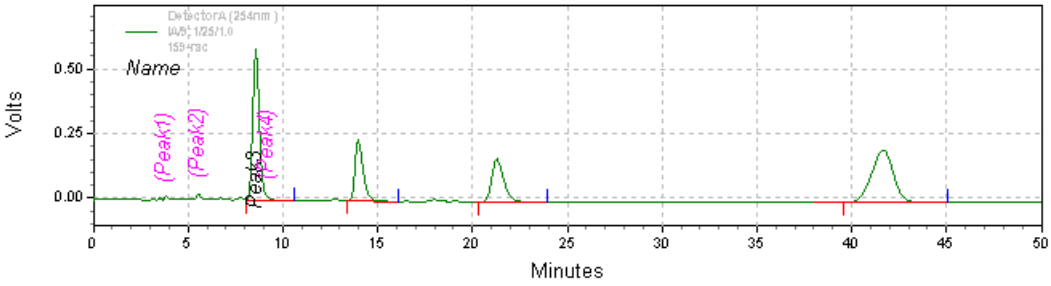
Pk #	Retention Time	Area	Area %
1	7.512	22234716	26.509
2	11.759	18421165	21.962
3	17.507	20050896	23.905
4	34.437	23170422	27.624



DetectorA (254nm)

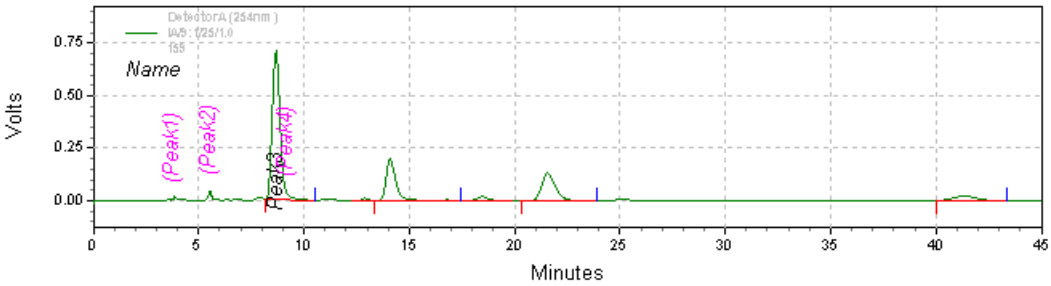
Pk #	Retention Time	Area	Area %
1	7.702	18365583	65.512
2	11.867	4042758	14.421
3	17.808	4376417	15.611
4	32.755	1249243	4.456





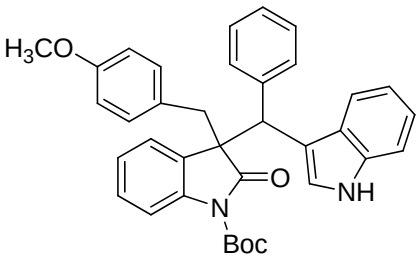
DetectorA (254nm)

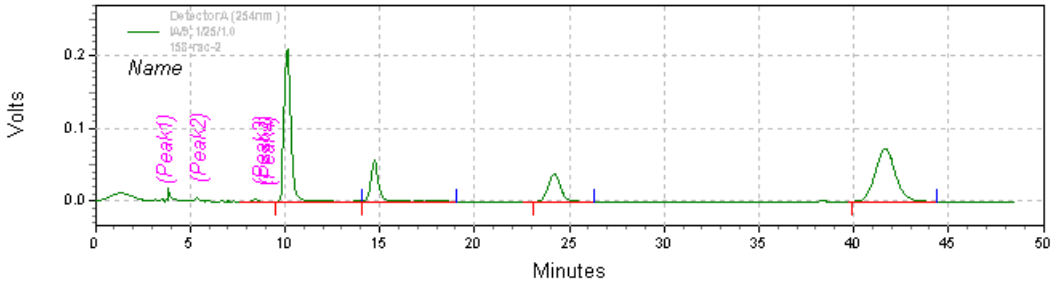
Pk #	Retention Time	Area	Area %
1	8.586	12739624	29.720
2	13.989	8334034	19.442
3	21.292	8546406	19.938
4	41.667	13245046	30.899



DetectorA (254nm)

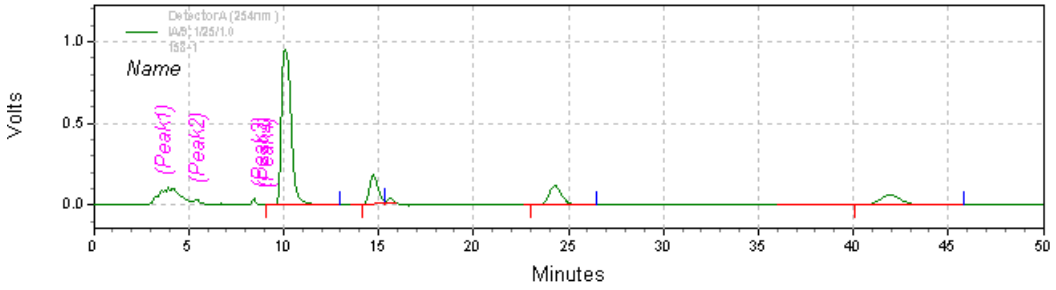
Pk #	Retention Time	Area	Area %
1	8.667	18355905	57.857
2	14.083	6185249	19.496
3	21.547	5795118	18.266
4	41.327	1389986	4.381





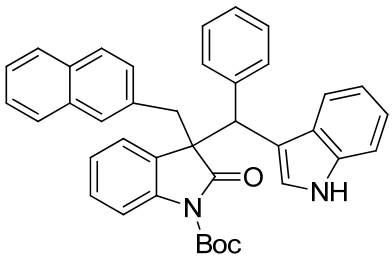
DetectorA (254nm)

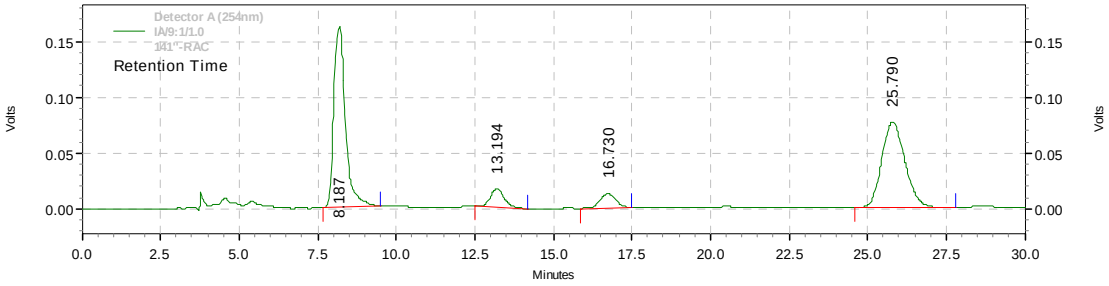
Pk #	Retention Time	Area	Area %
1	10.159	5327327	37.179
2	14.711	1776974	12.401
3	24.173	1731936	12.087
4	41.647	5492464	38.332



DetectorA (254nm)

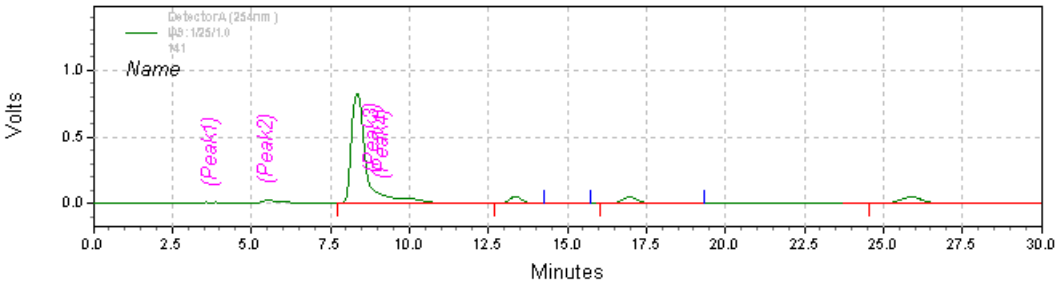
Pk #	Retention Time	Area	Area %
1	10.080	33374189	69.657
2	14.740	5470676	11.418
3	24.261	5462729	11.401
4	41.900	3604900	7.524





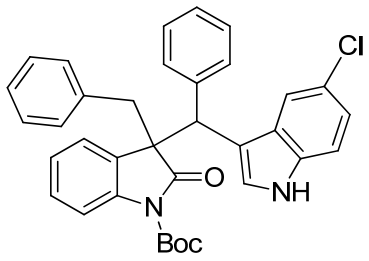
Detector A (254nm)

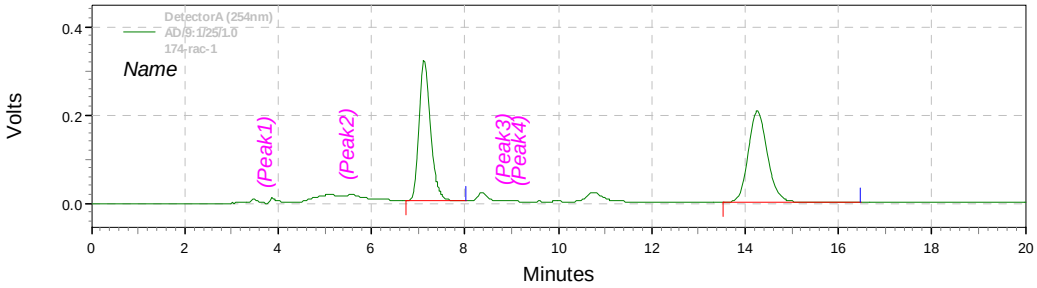
Pk #	Retention Time	Area	Area %
1	8.187	4058081	45.112
2	13.194	512538	5.698
3	16.730	449860	5.001
4	25.790	3975054	44.189



DetectorA (254nm)

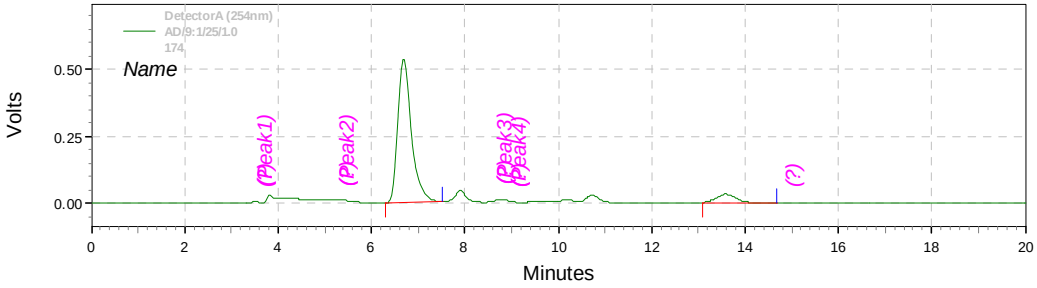
Pk #	Retention Time	Area	Area %
1	8.374	27277537	82.388
2	13.353	1477853	4.464
3	16.978	1749911	5.285
4	25.879	2603354	7.863





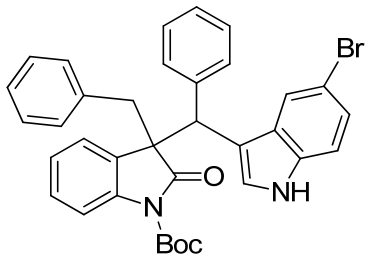
DetectorA (254nm)

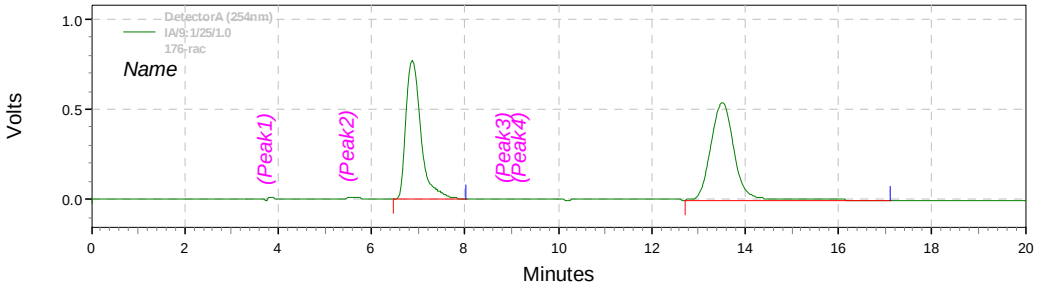
Pk #	Retention Time	Area	Area %
1	7.117	5503602	48.725
2	14.255	5791645	51.275



DetectorA (254nm)

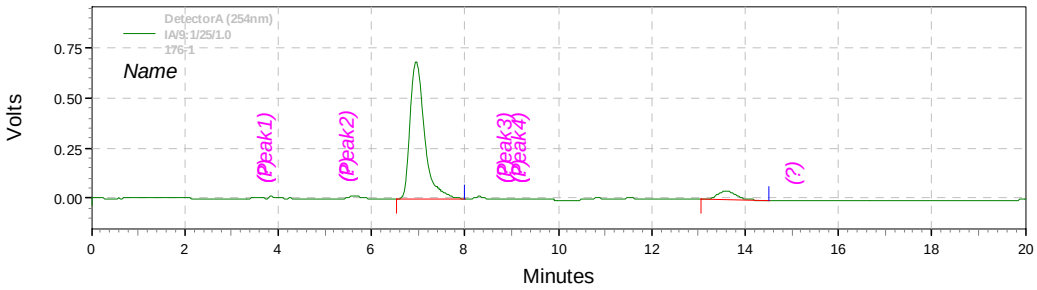
Pk #	Retention Time	Area	Area %
1	6.685	10682026	92.066
2	13.595	920605	7.934





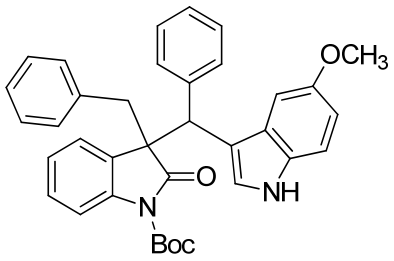
DetectorA (254nm)

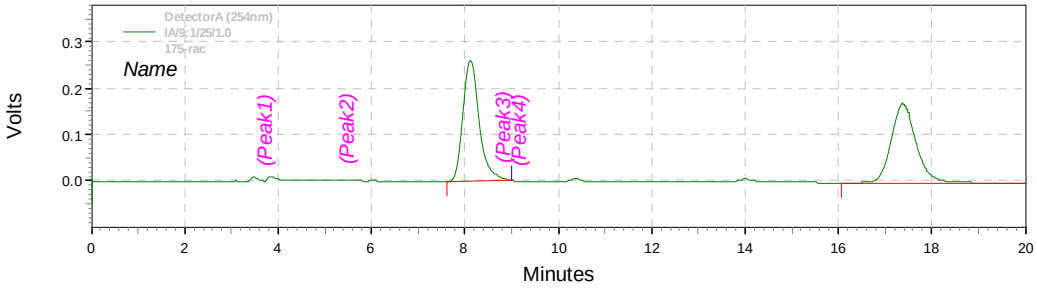
Pk #	Retention Time	Area	Area %
1	6.863	17157025	48.408
2	13.518	18285702	51.592



DetectorA (254nm)

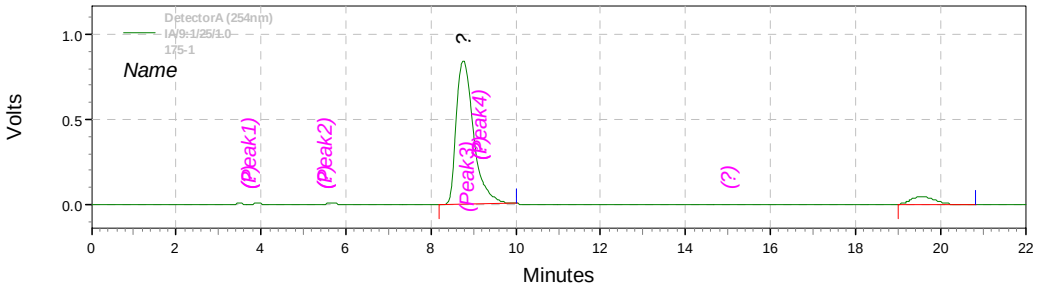
Pk #	Retention Time	Area	Area %
1	6.947	14683610	91.892
2	13.600	1295509	8.108





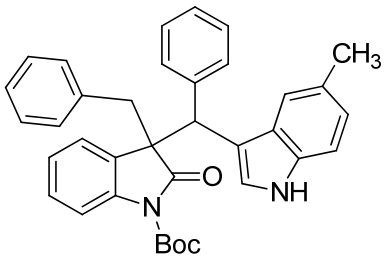
DetectorA (254nm)

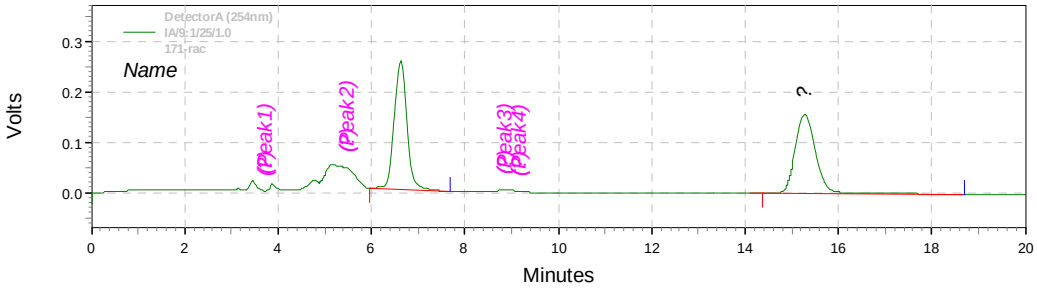
Pk #	Retention Time	Area	Area %
1	8.128	6304699	48.788
2	17.374	6618073	51.212



DetectorA (254nm)

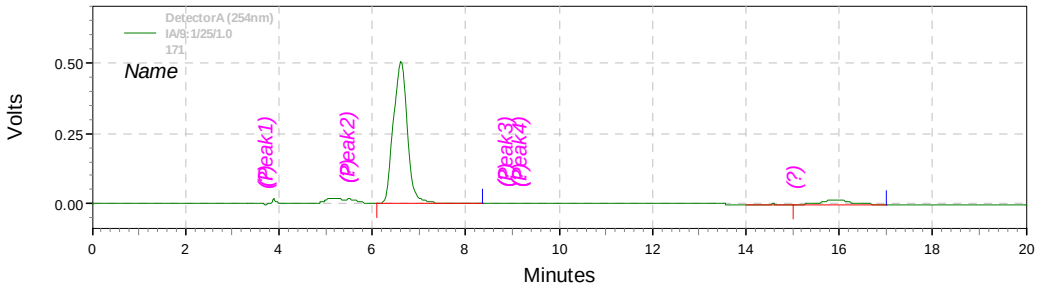
Pk #	Retention Time	Area	Area %
1	8.774	23766794	93.268
2	19.578	1715526	6.732





DetectorA (254nm)

Pk #	Retention Time	Area	Area %
1	6.624	4796188	49.416
2	15.289	4909648	50.584



DetectorA (254nm)

Pk #	Retention Time	Area	Area %
1	6.611	10394244	94.883
2	15.927	560576	5.117