

Supporting Information for

Catalytic Asymmetric Substitution of *ortho*-Hydroxybenzyl Alcohols with Tetric Acid-Derived Enamines: Enantioselective Synthesis of Tetric Acid-Derived Diarylmethanes

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Nanjing, 210029, China*

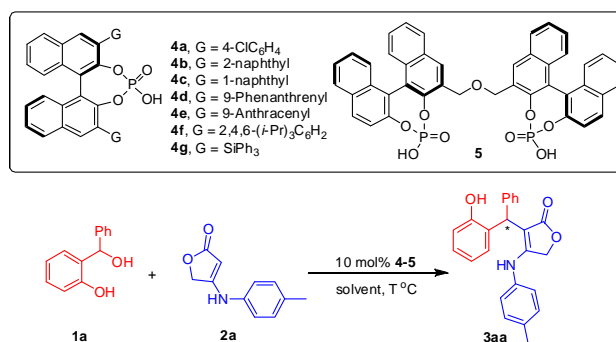
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1. Screening of catalysts and optimization of reaction conditions

Table 1. Screening of Catalysts and optimization of reaction conditions^[a]

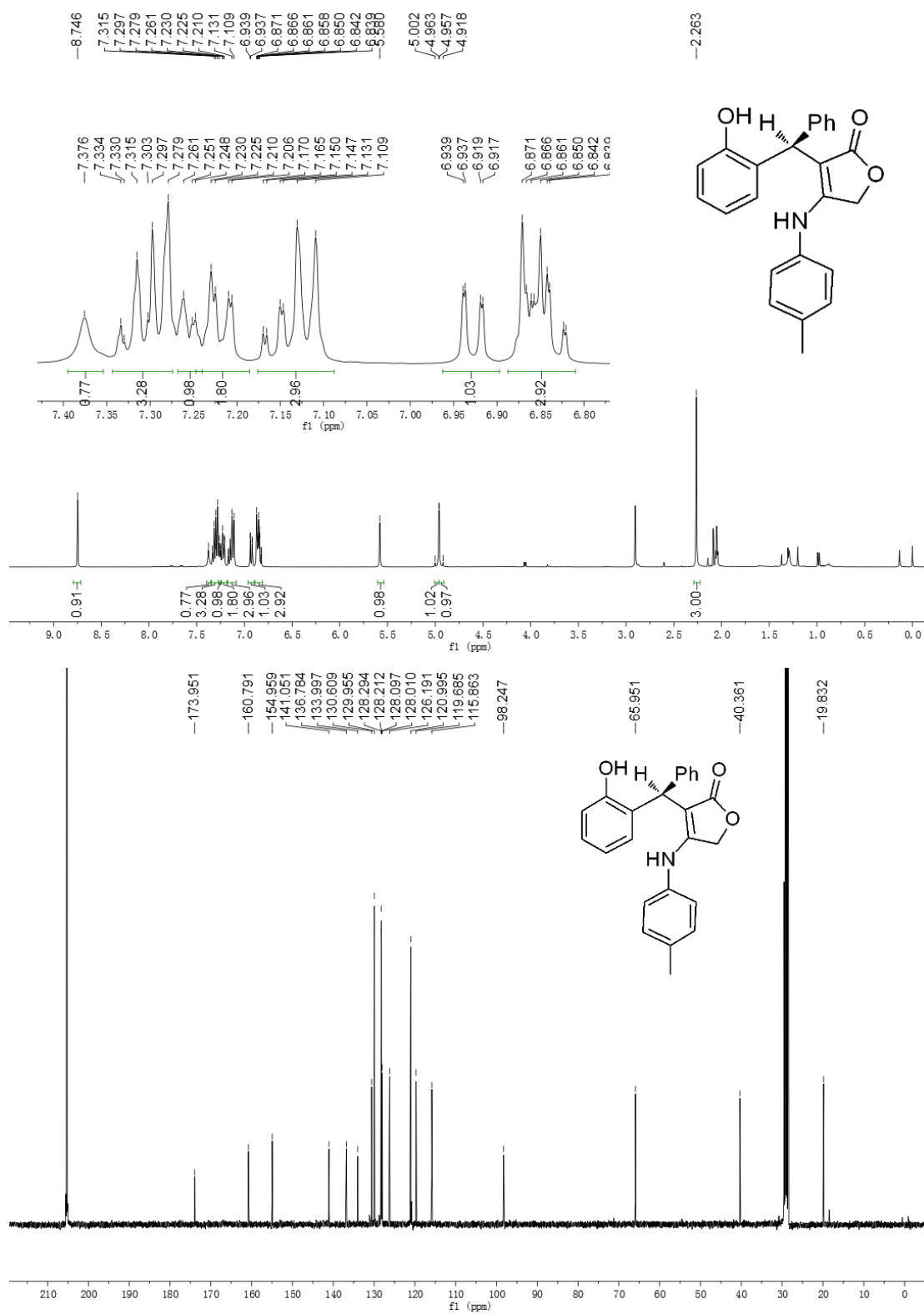


entry	Cat.	solvent	T (°C)	1a:2a	additives	yield (%) ^[b]	er ^[c]
1	4a	CHCl ₃ (1mL)	50	4:1	-	26	51:49
2	4b	CHCl ₃ (1mL)	50	4:1	-	18	63:37
3	4c	CHCl ₃ (1mL)	50	4:1	-	26	65:35
4	4d	CHCl ₃ (1mL)	50	4:1	-	11	69:31
5	4e	CHCl ₃ (1mL)	50	4:1	-	24	78:22
6	4f	CHCl ₃ (1mL)	50	4:1	-	14	90:10
7	4g	CHCl ₃ (1mL)	50	4:1	-	19	70:30
8	5	CHCl ₃ (1mL)	50	4:1	-	46	53:47
9	4f	toluene (1mL)	50	4:1	-	trace	-
10	4f	EtOAc (1mL)	50	4:1	-	87	93:7
11	4f	CH ₃ CN (1mL)	50	4:1	-	99	90:10
12	4f	1,4-dioxane (1mL)	50	4:1	-	trace	-
13	4f	acetone (1mL)	50	4:1	-	40	93:7
14	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	-	63	93:7
15	4f	<i>n</i> -propyl acetate (1mL)	50	4:1	-	75	91:9
16	4f	ethyl propionate (1mL)	50	4:1	-	75	91:9
17	4f	<i>s</i> -butyl acetate (1mL)	50	4:1	-	80	93:7
18	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	-	80	95:5
19	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	3 Å	trace	-
20	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	4 Å	trace	-
21	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	5 Å	46	90:10
22	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	Na ₂ SO ₄	76	91:9
23	4f	<i>i</i> -butyl acetate (1mL)	50	4:1	MgSO ₄	64	91:9
24	4f	<i>i</i> -butyl acetate (1mL)	50	2:1	-	36	95:5
25	4f	<i>i</i> -butyl acetate (1mL)	50	1:1	-	trace	-
26	4f	<i>i</i> -butyl acetate (1mL)	r.t.	4:1	-	trace	-
27	4f	<i>i</i> -butyl acetate (1mL)	80	4:1	-	76	90:10
28	4f	<i>i</i> -butyl acetate (0.5mL)	50	4:1	-	96	90:10
29	4f	<i>i</i> -butyl acetate (2mL)	50	4:1	-	36	90:10
30	4f	<i>i</i> -butyl acetate (4mL)	50	4:1	-	trace	-

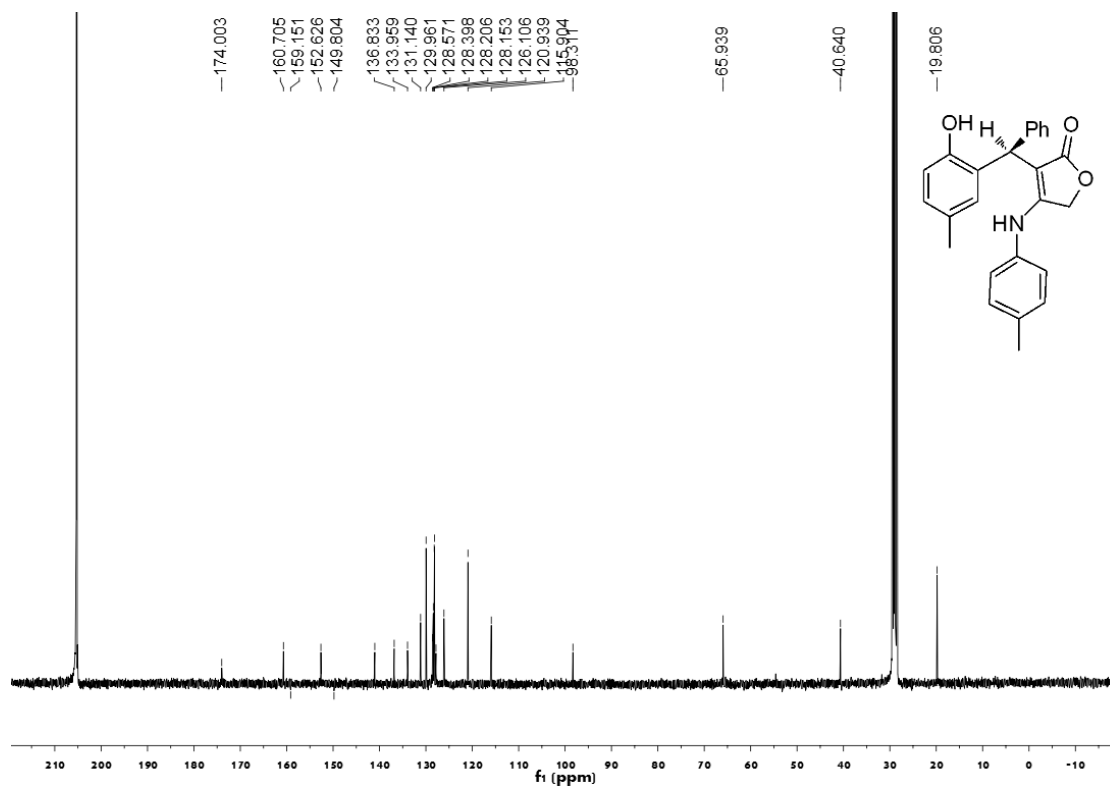
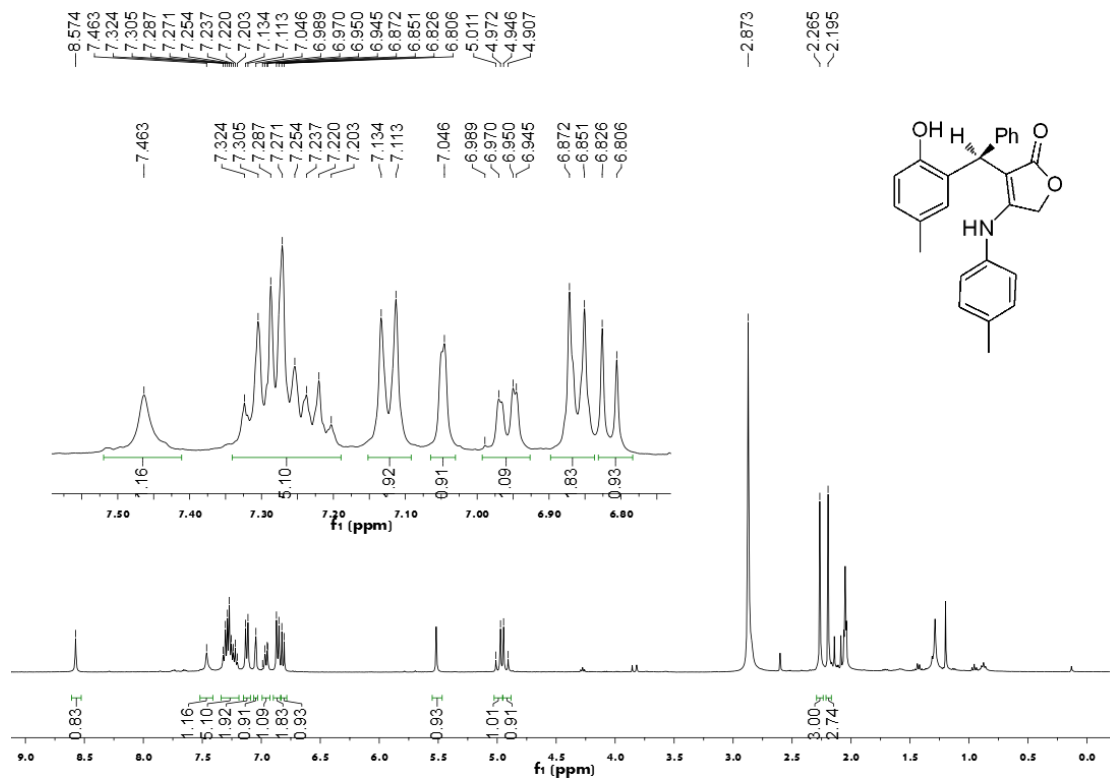
[a] Unless otherwise indicated, the reaction was carried out at the 0.1 mmol scale and catalyzed by 10 mol% **4-5** in a solvent for 12 h. [b] Isolated yield. [c] The *er* value was determined by HPLC.

2. NMR spectra of all products 3

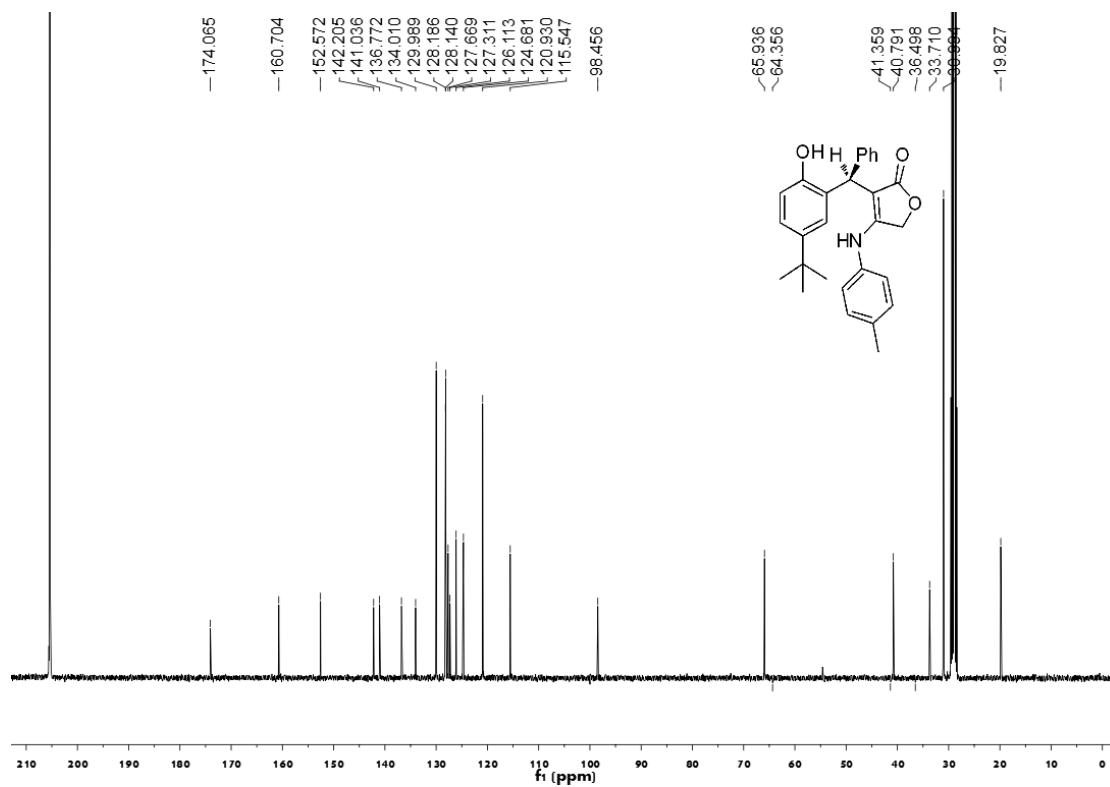
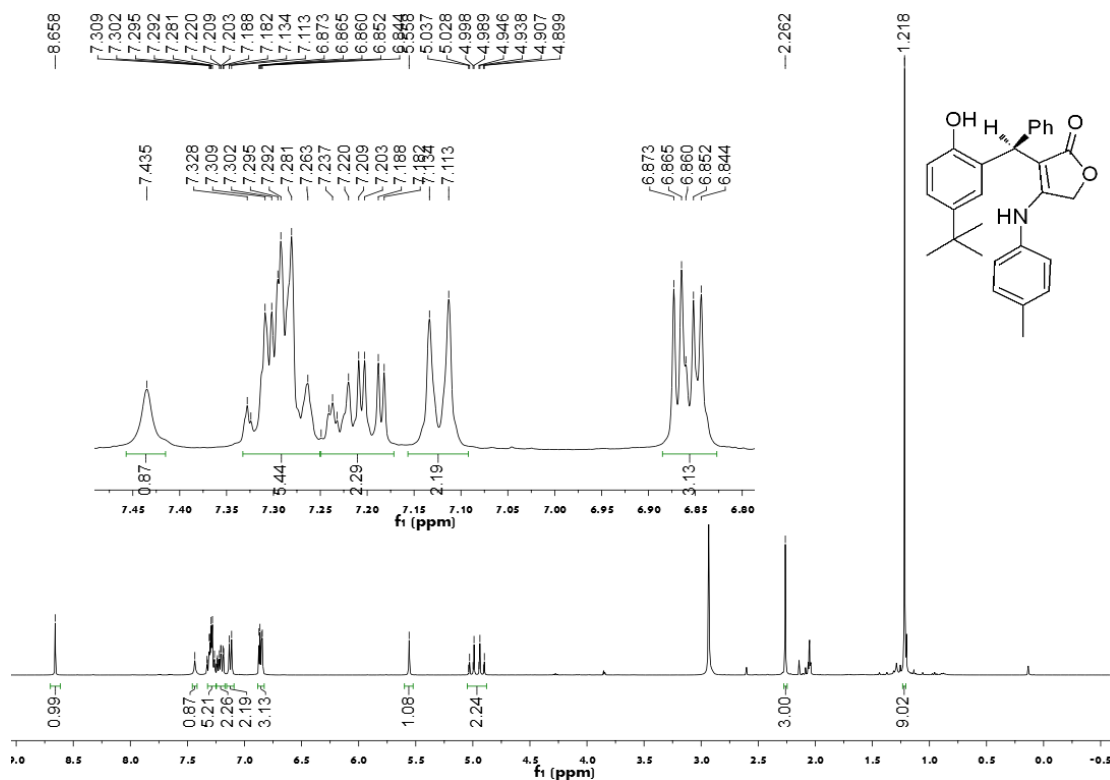
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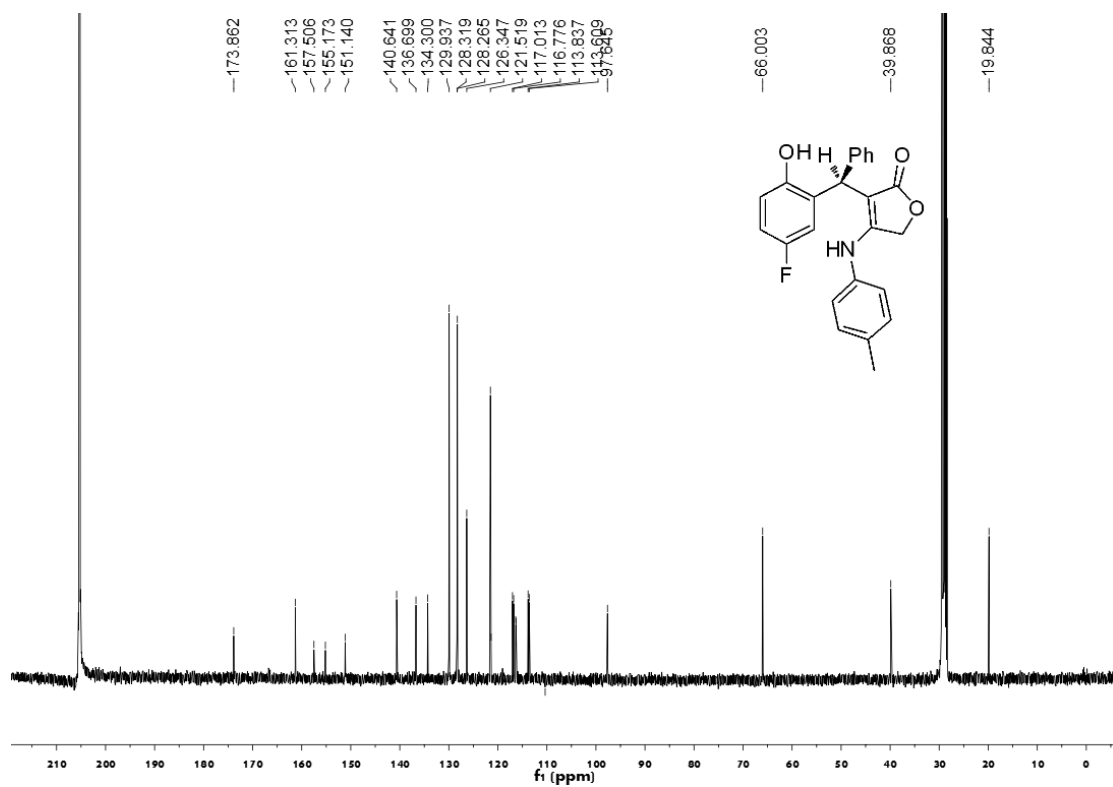
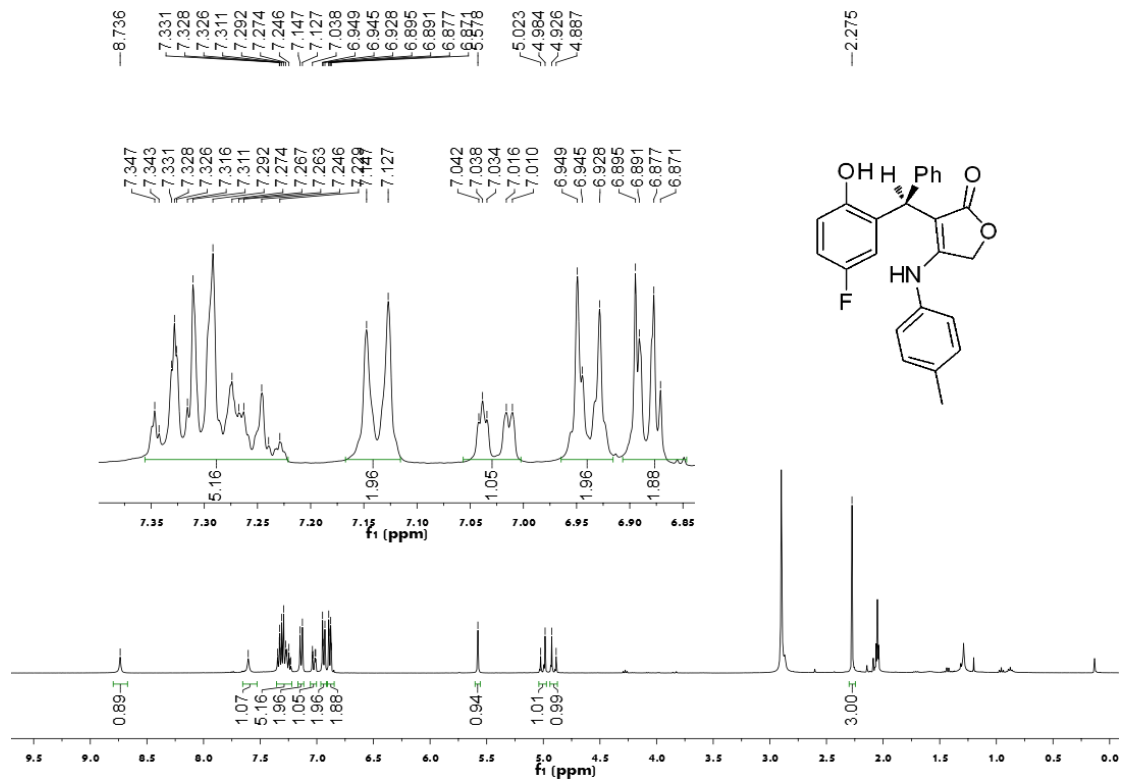
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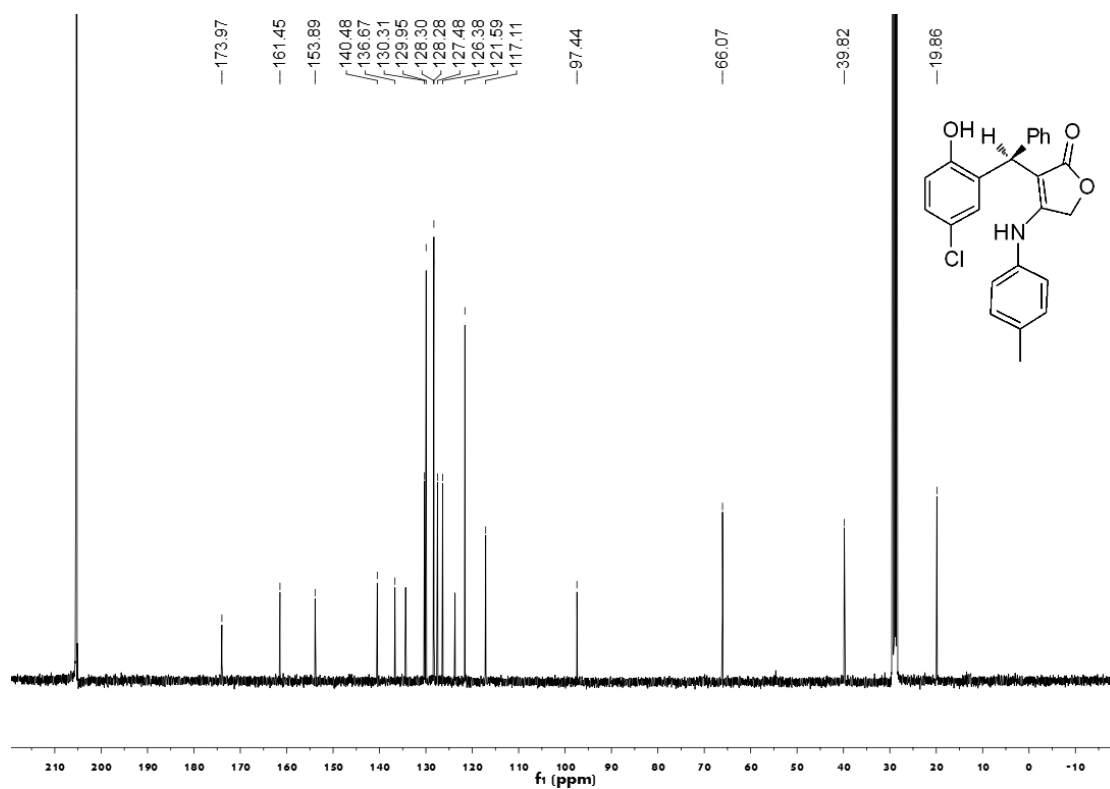
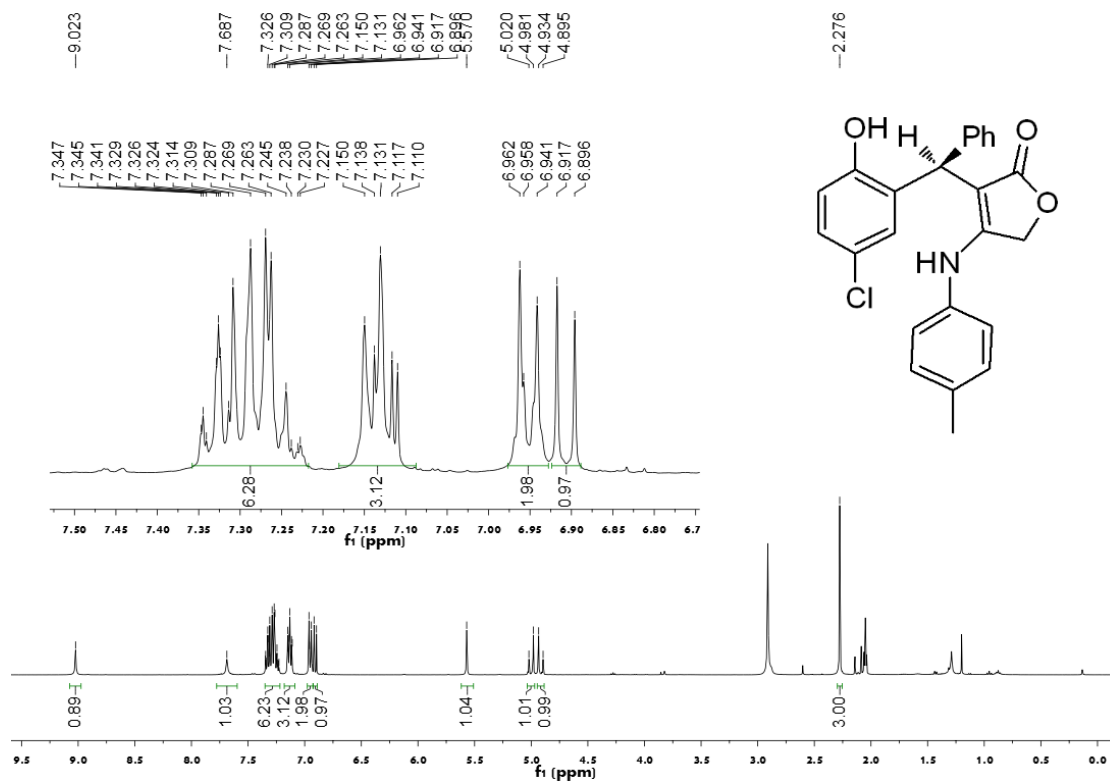
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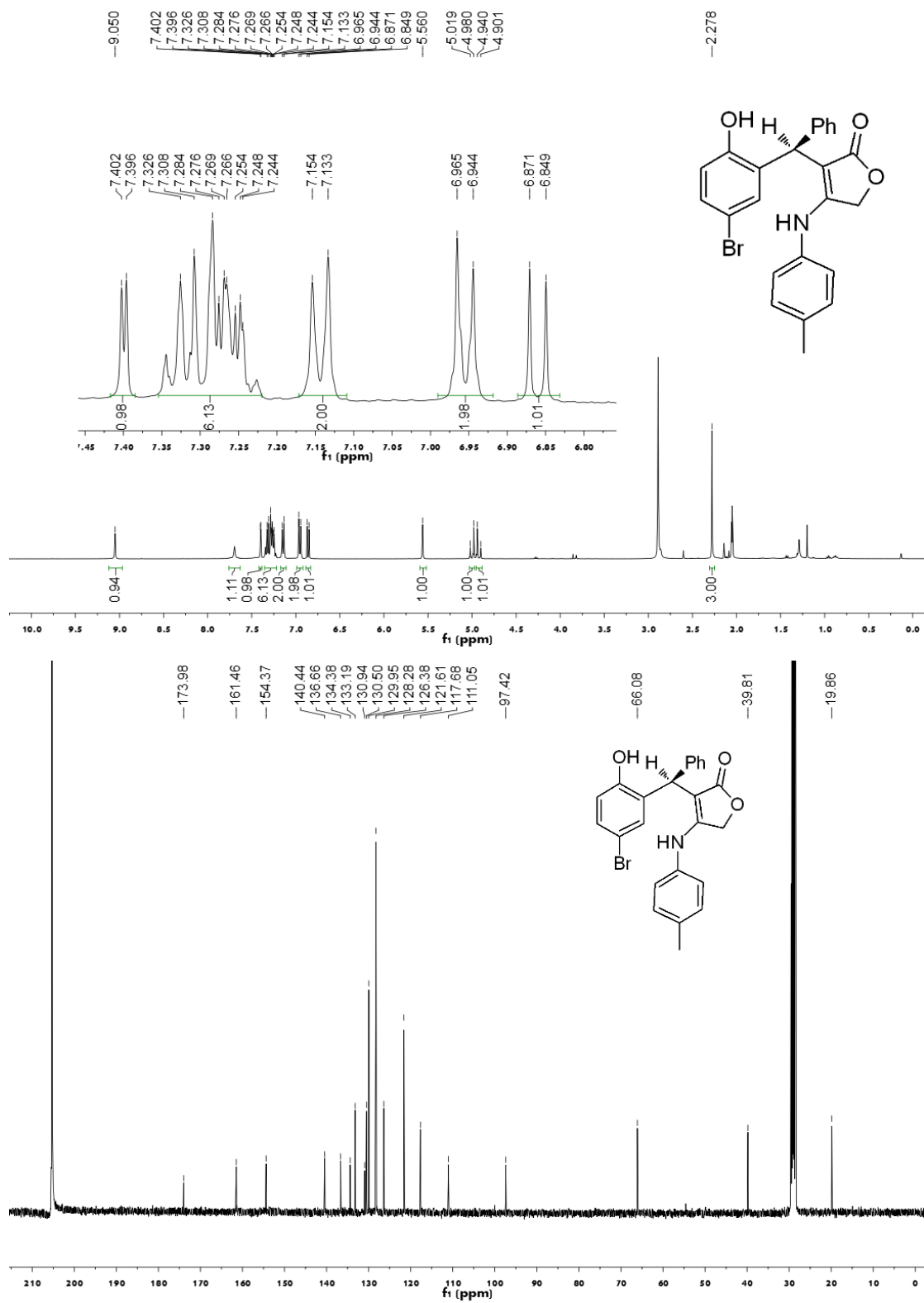
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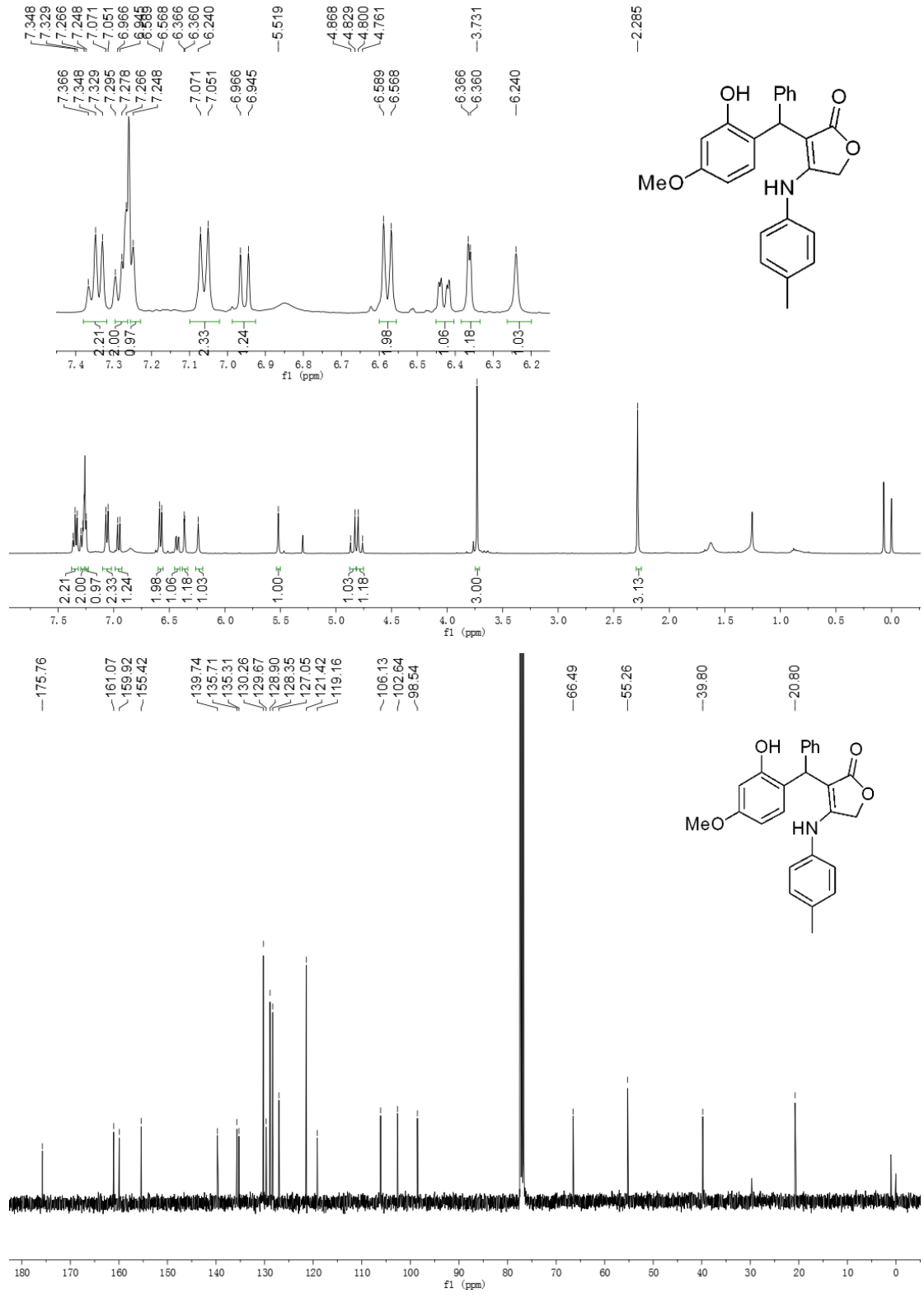
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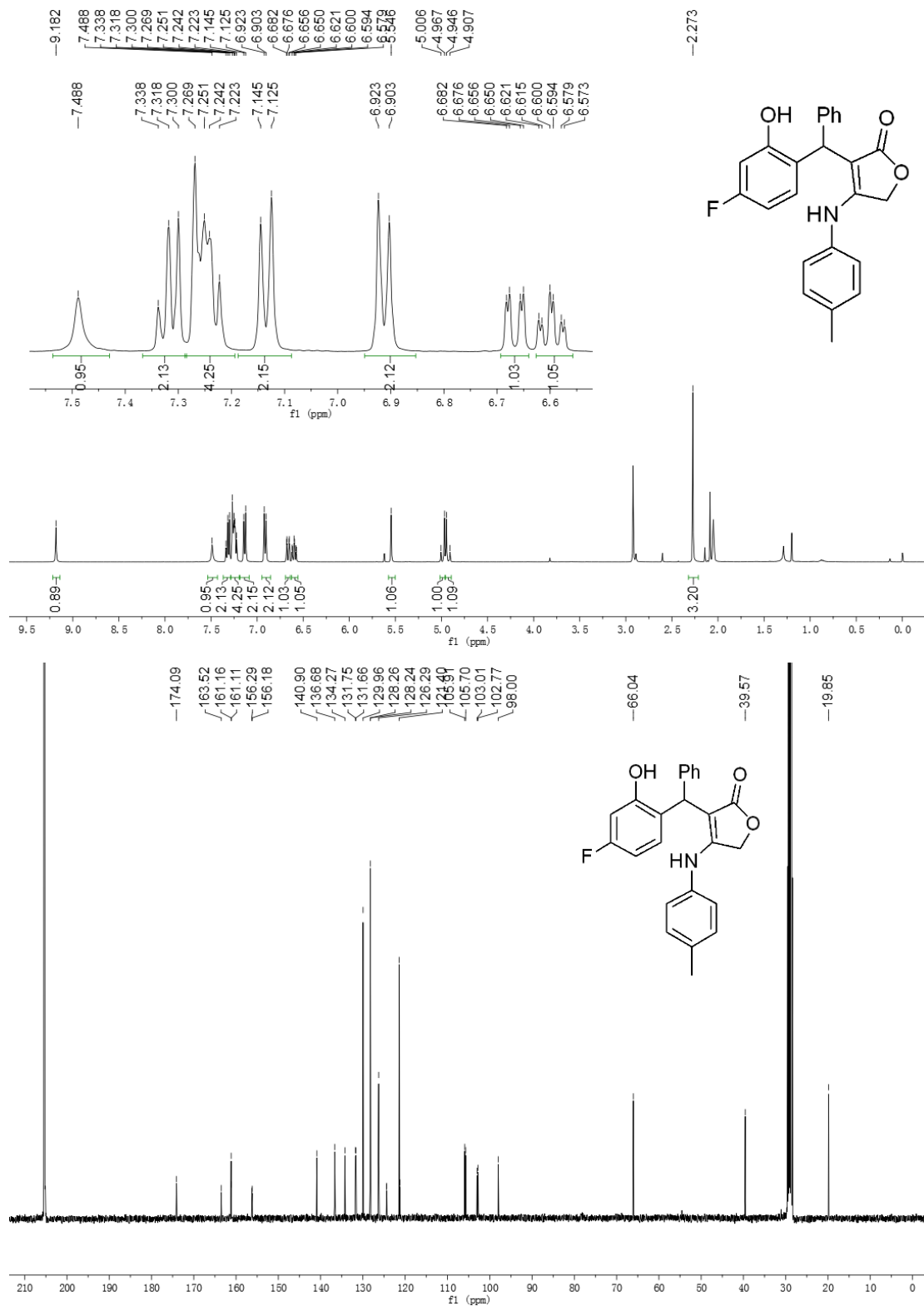
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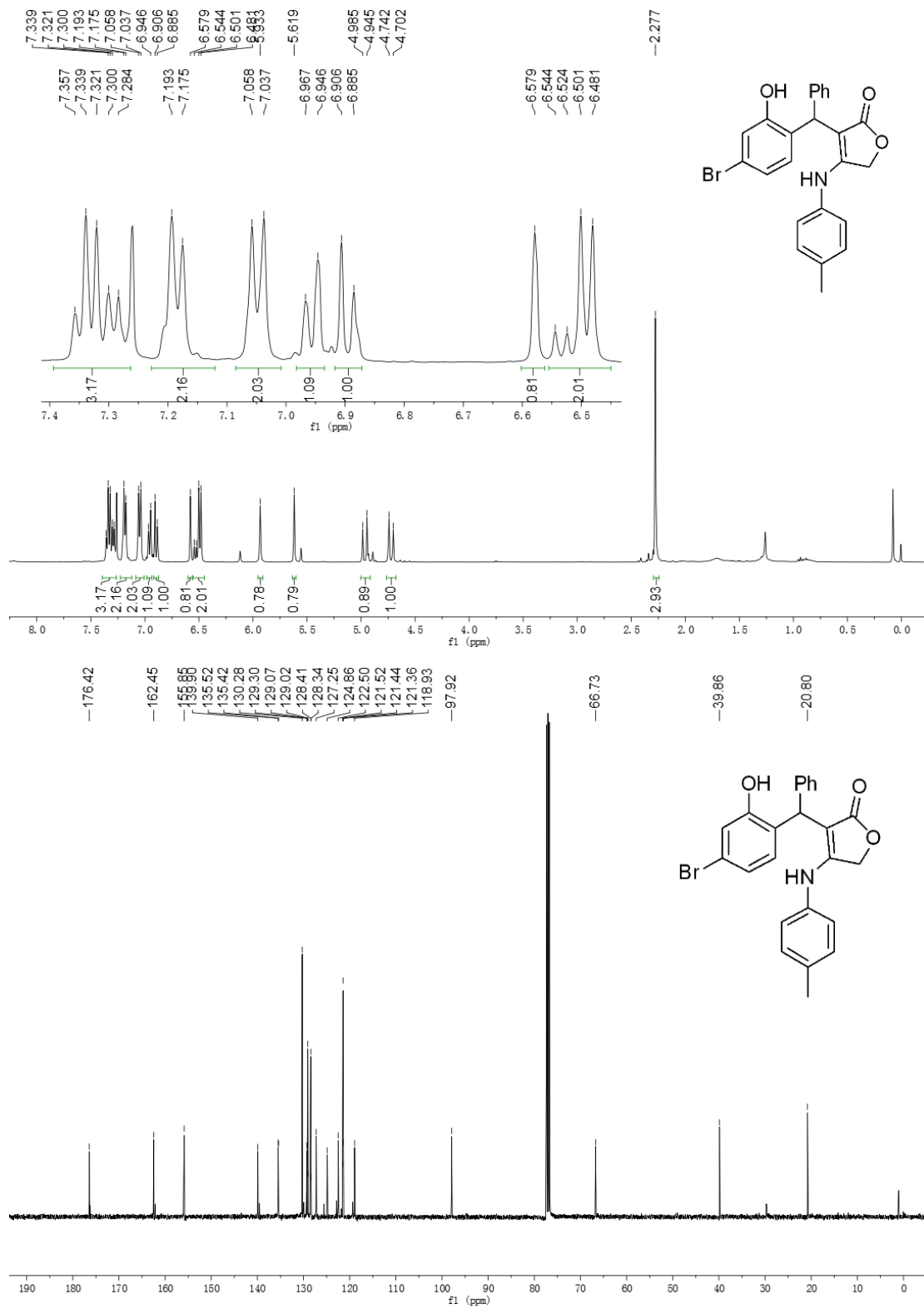
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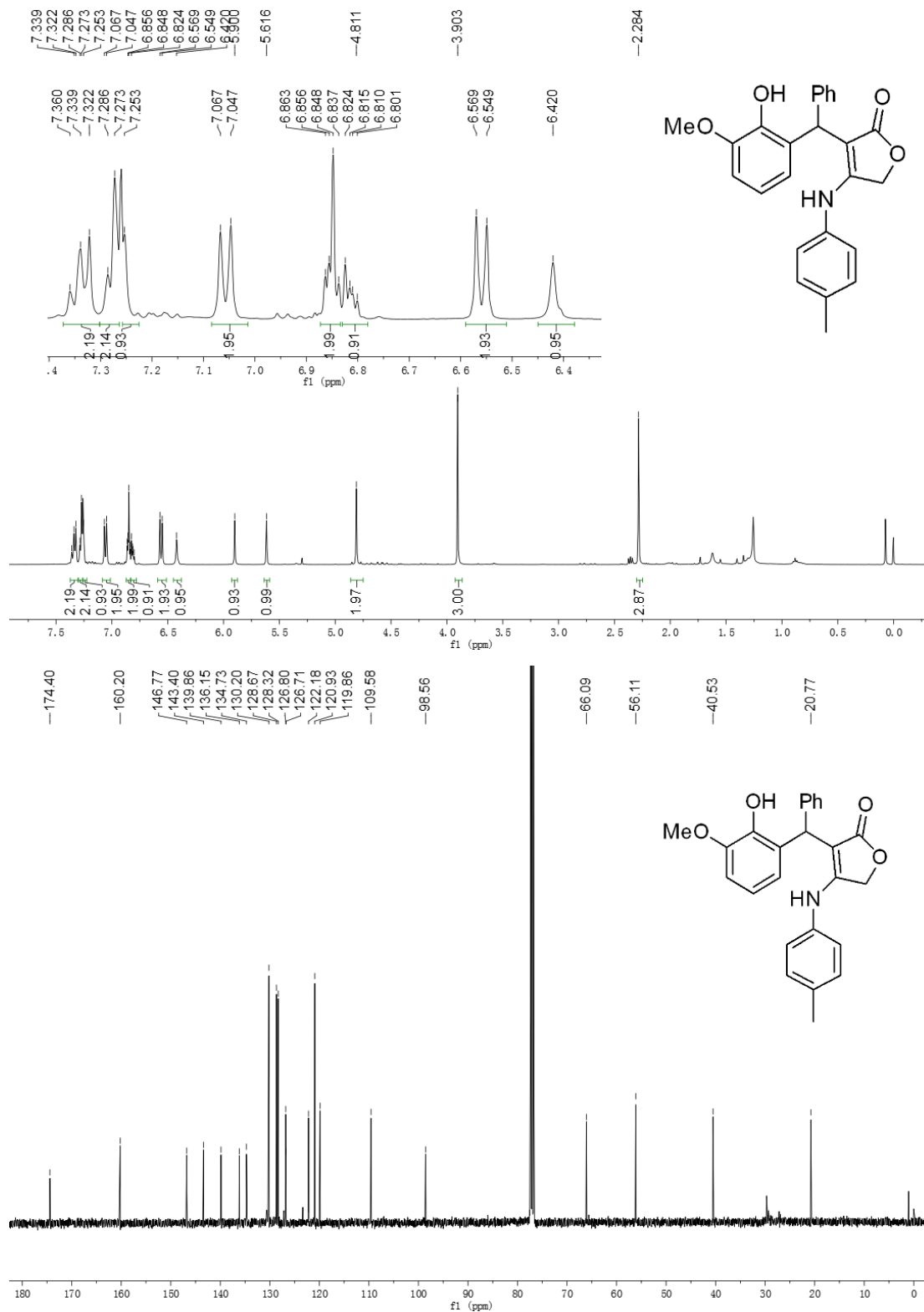
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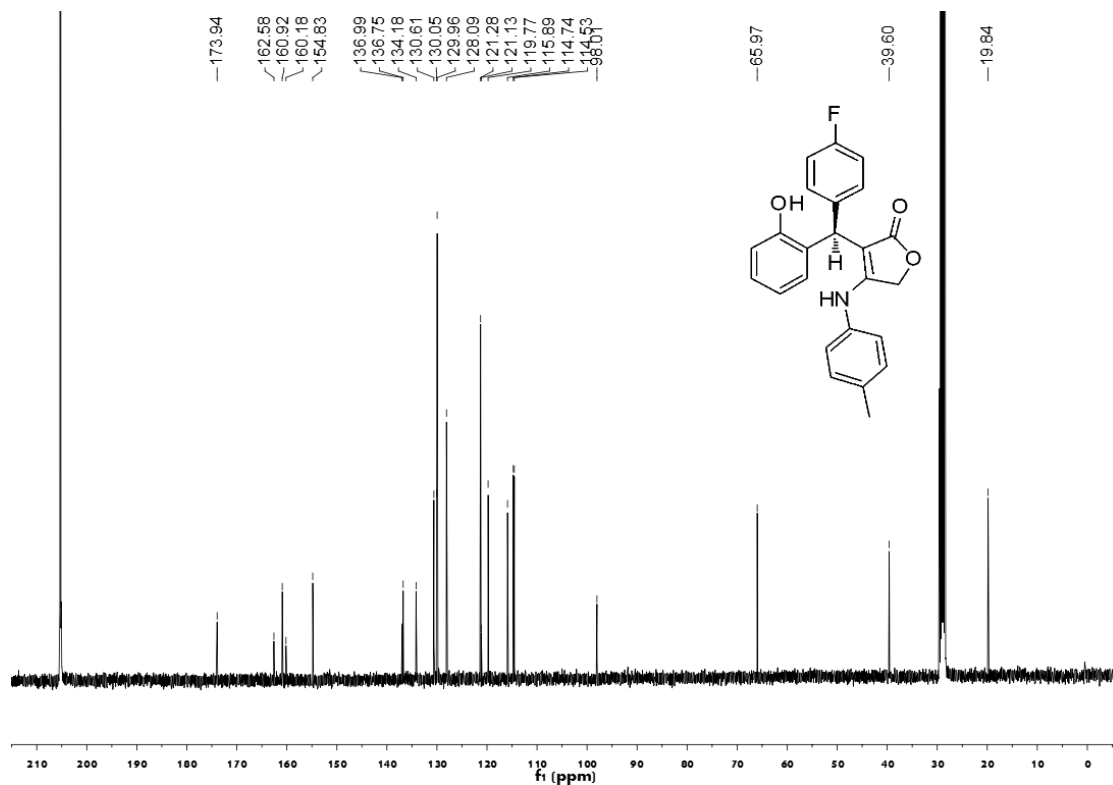
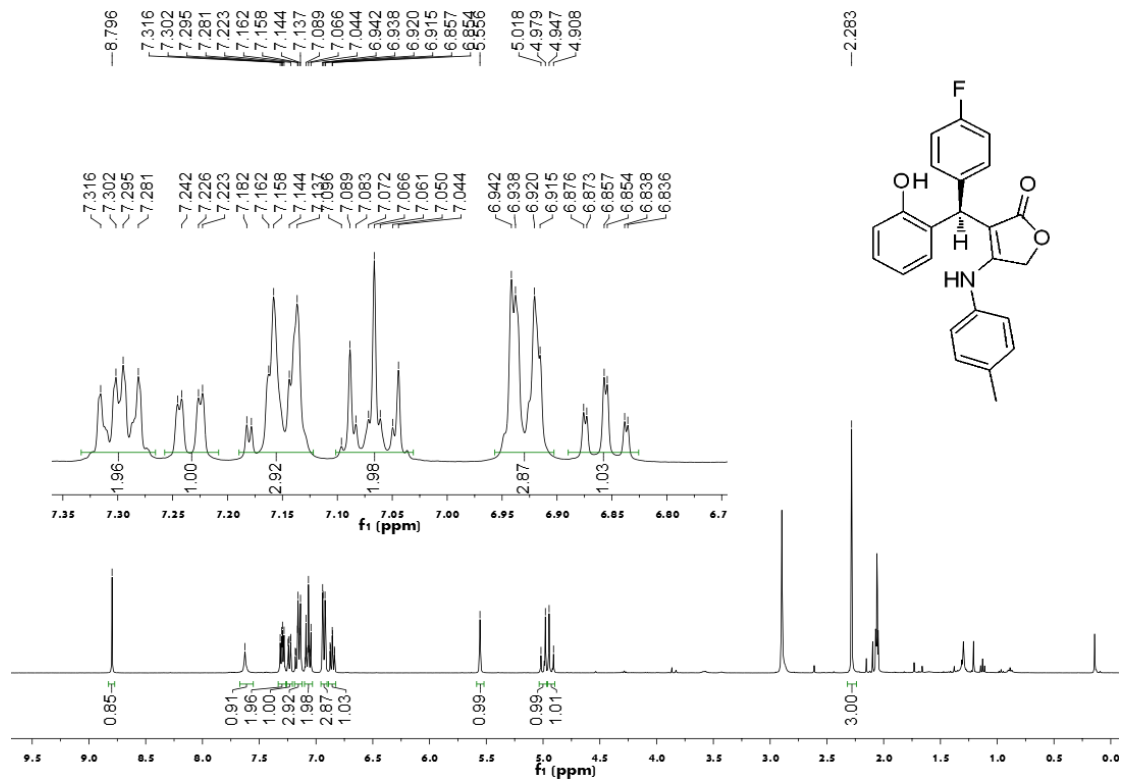
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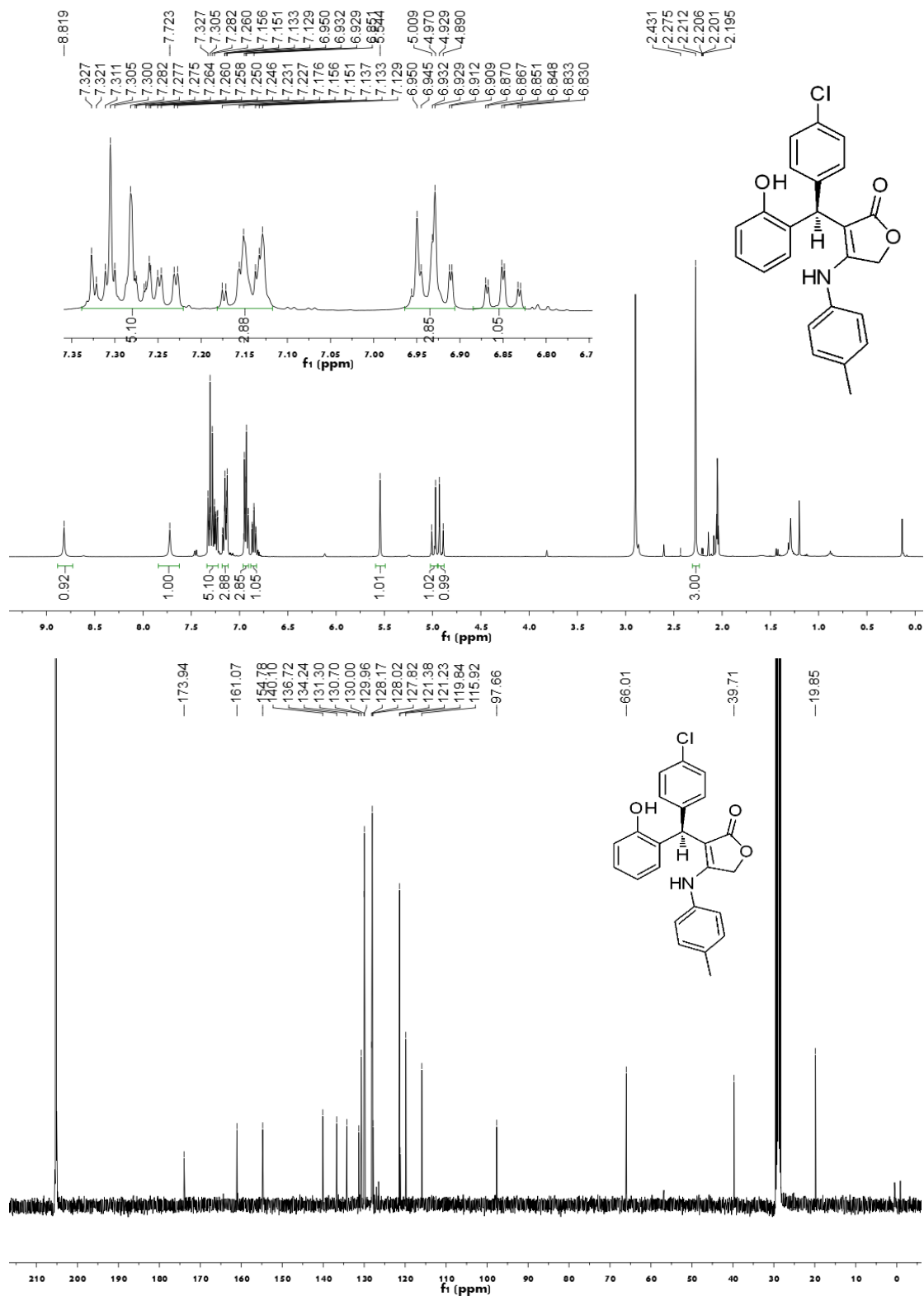
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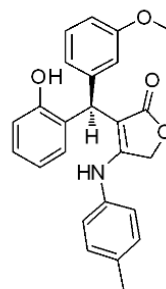
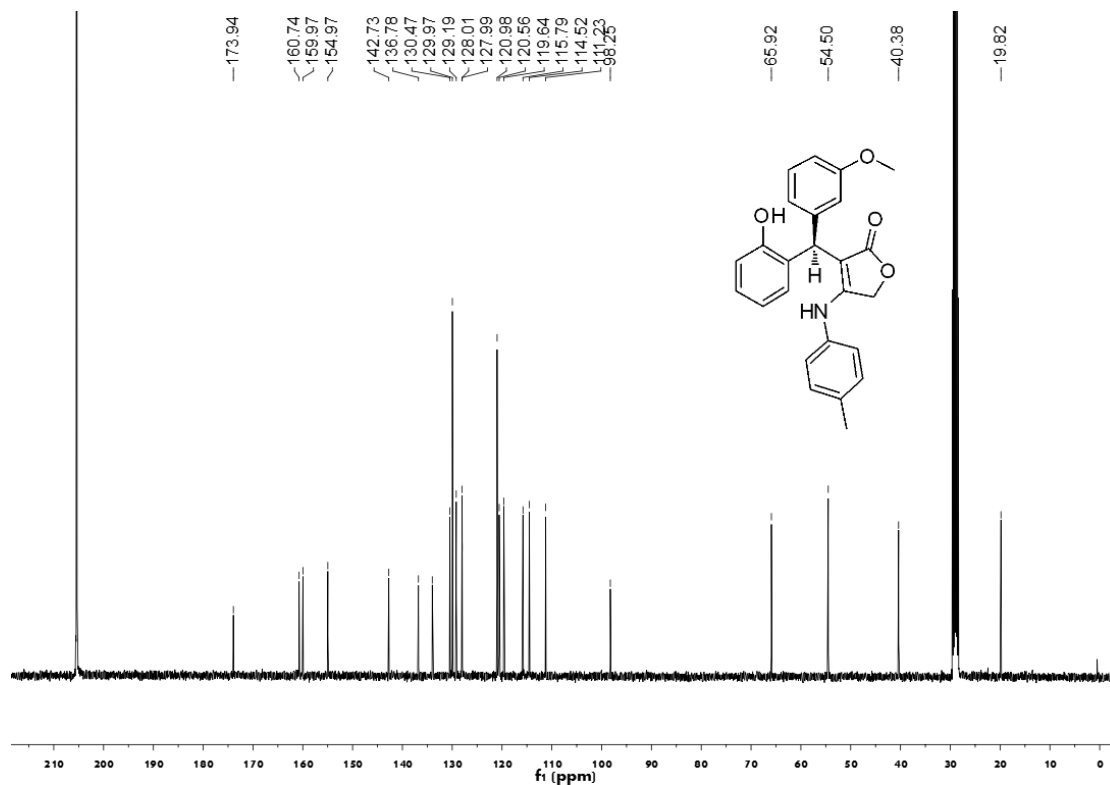
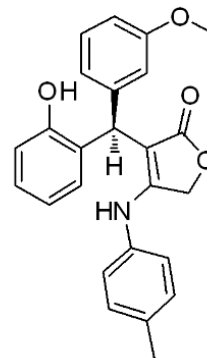
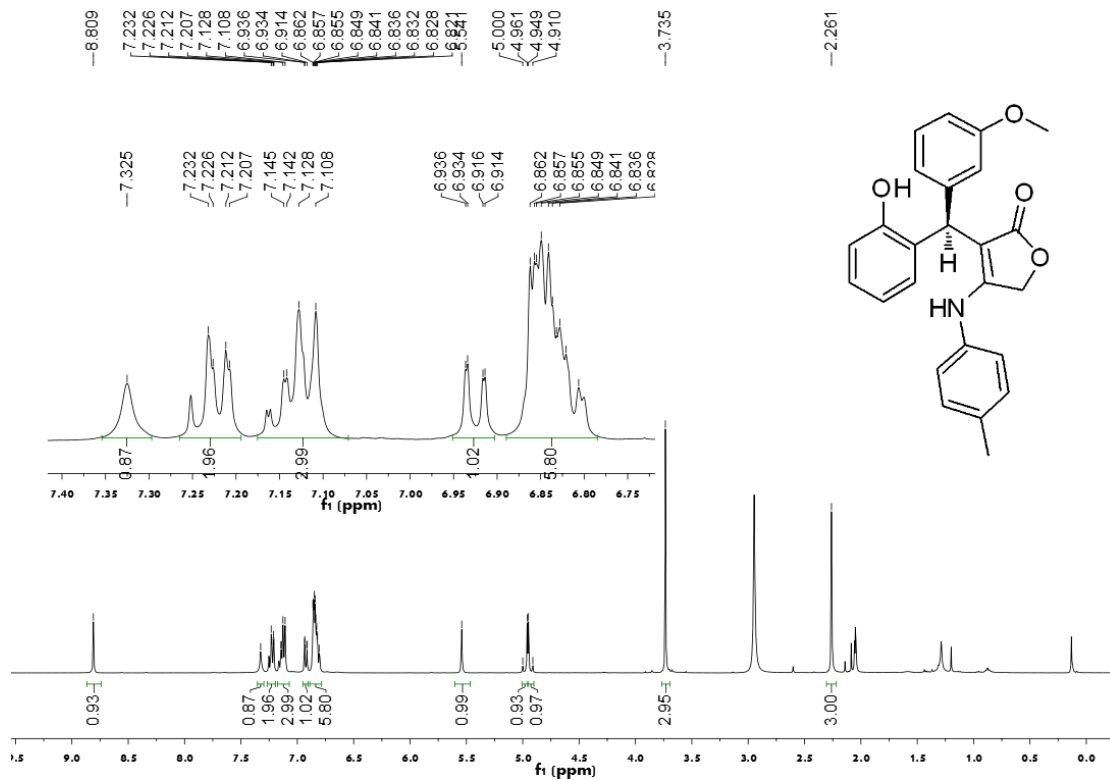
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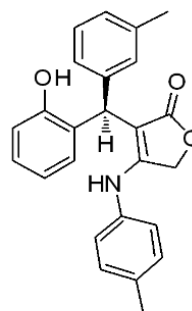
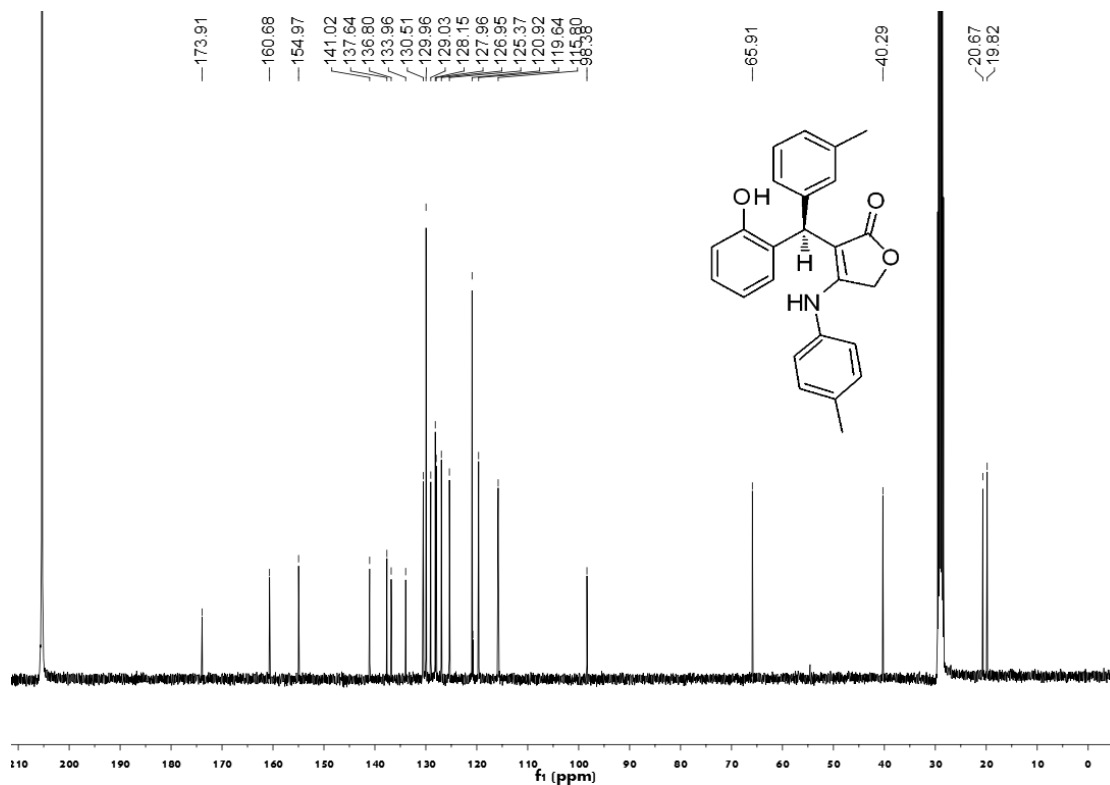
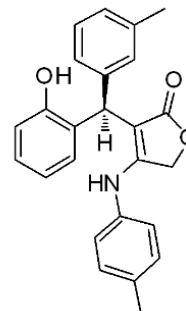
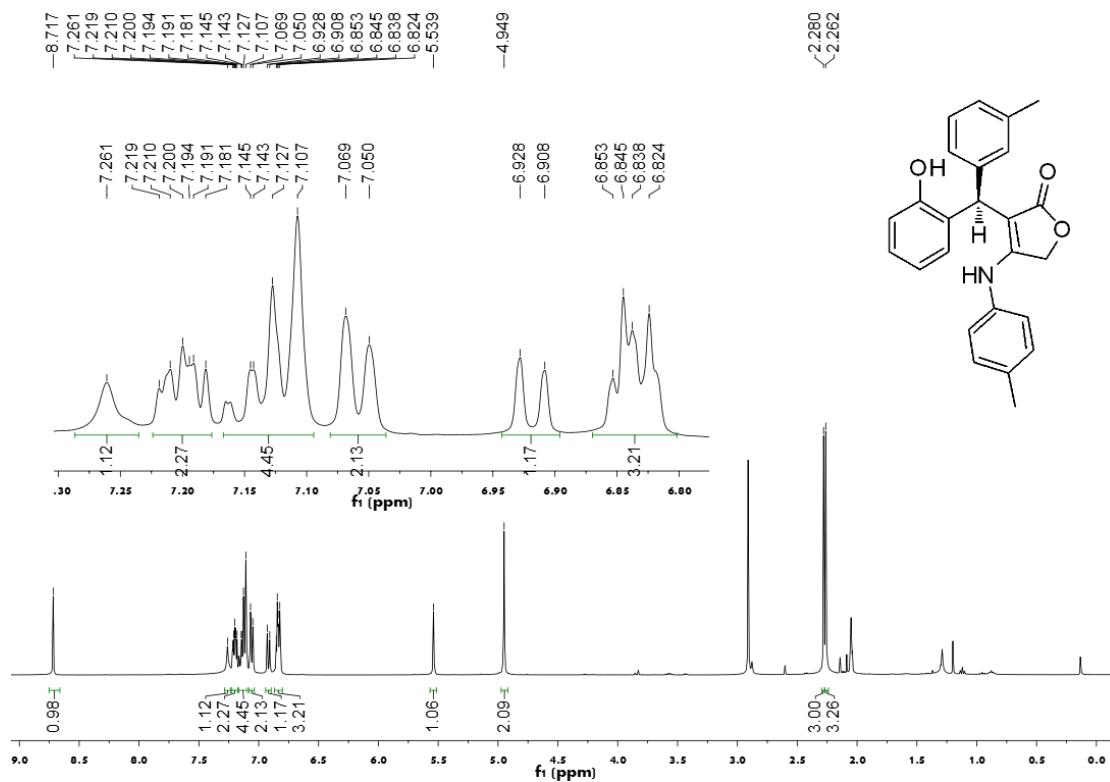
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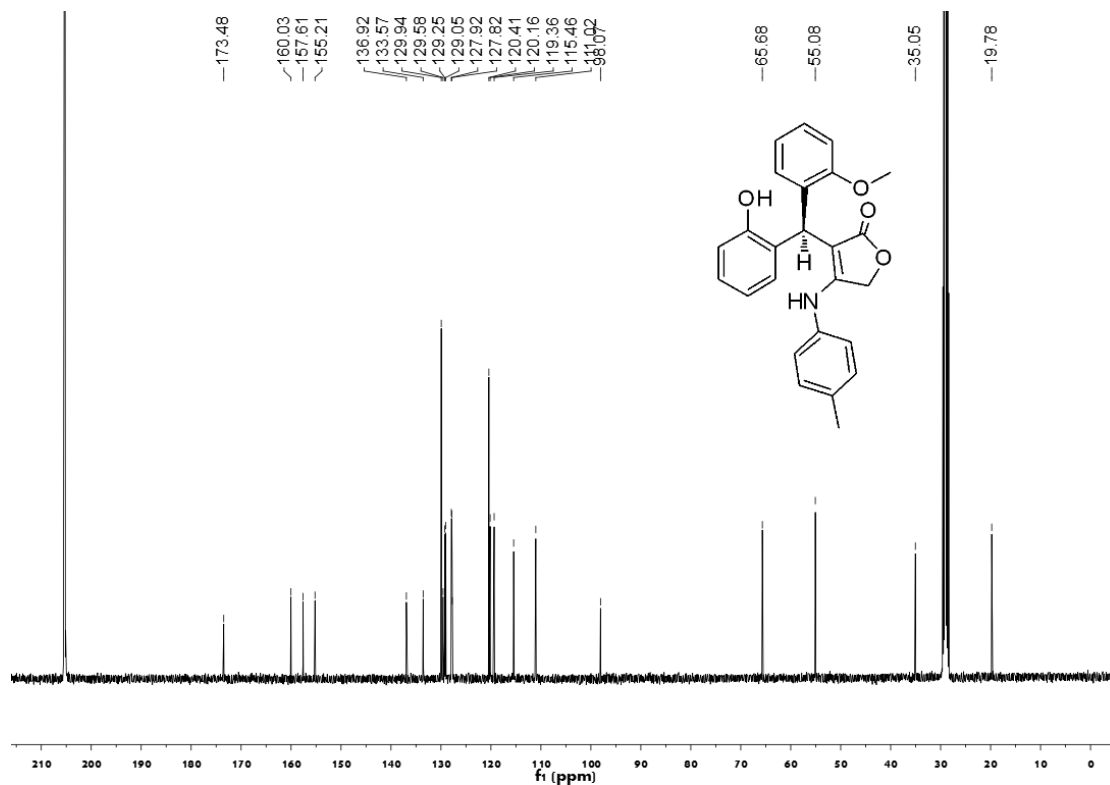
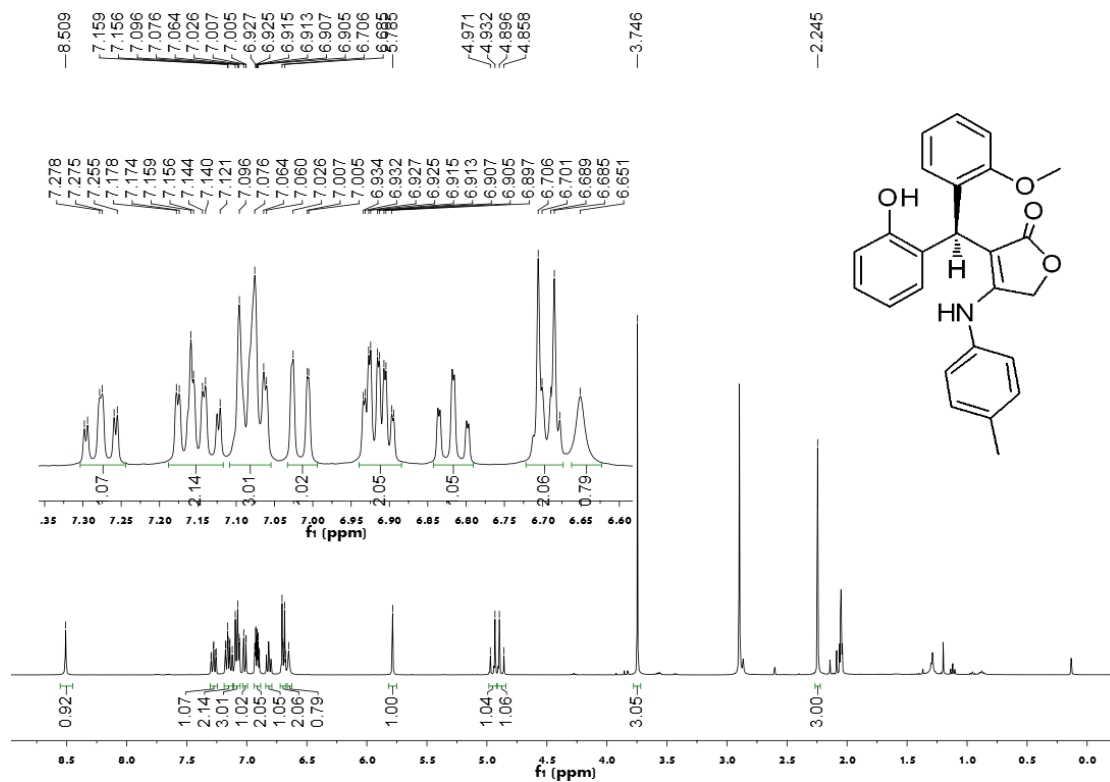
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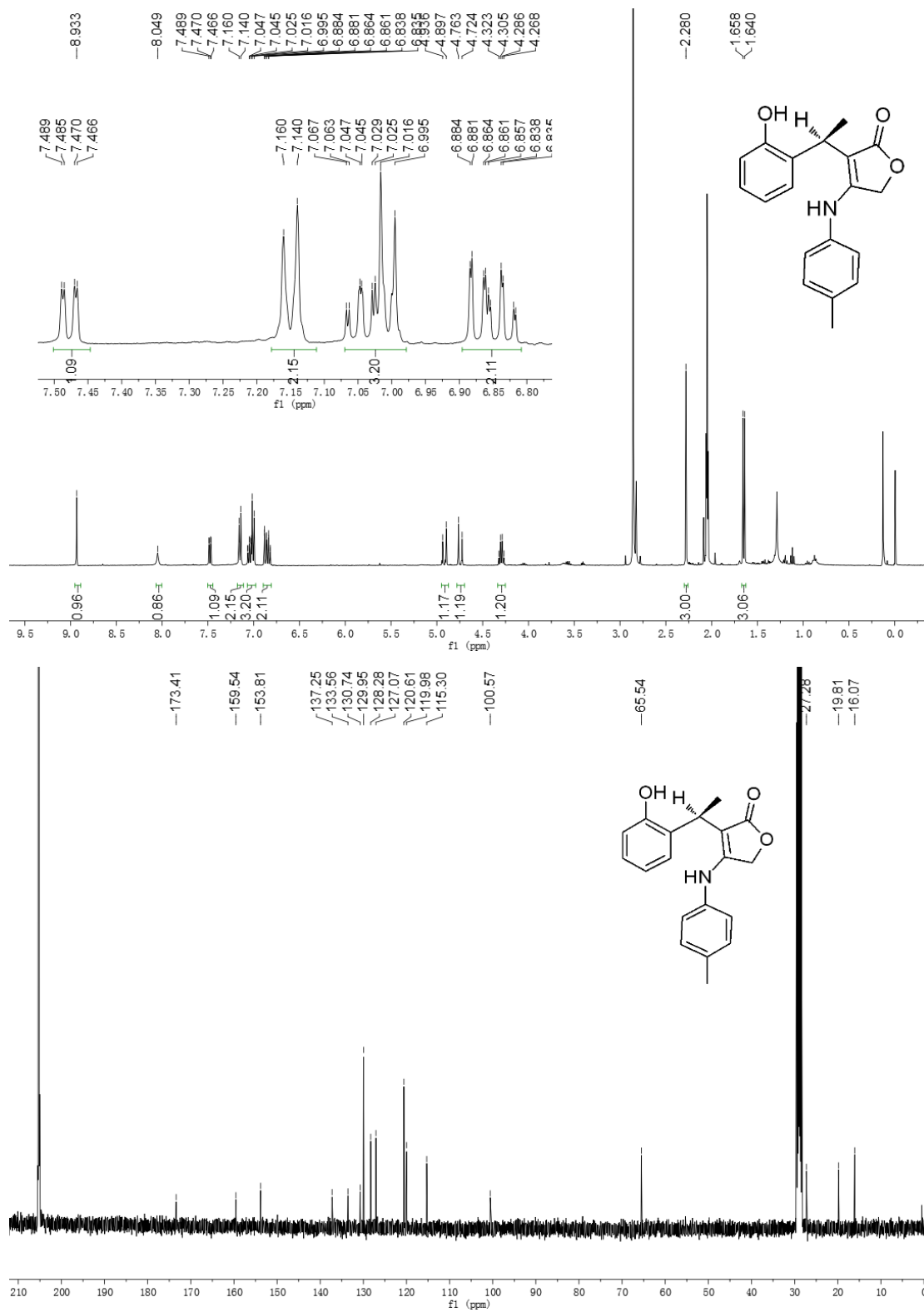
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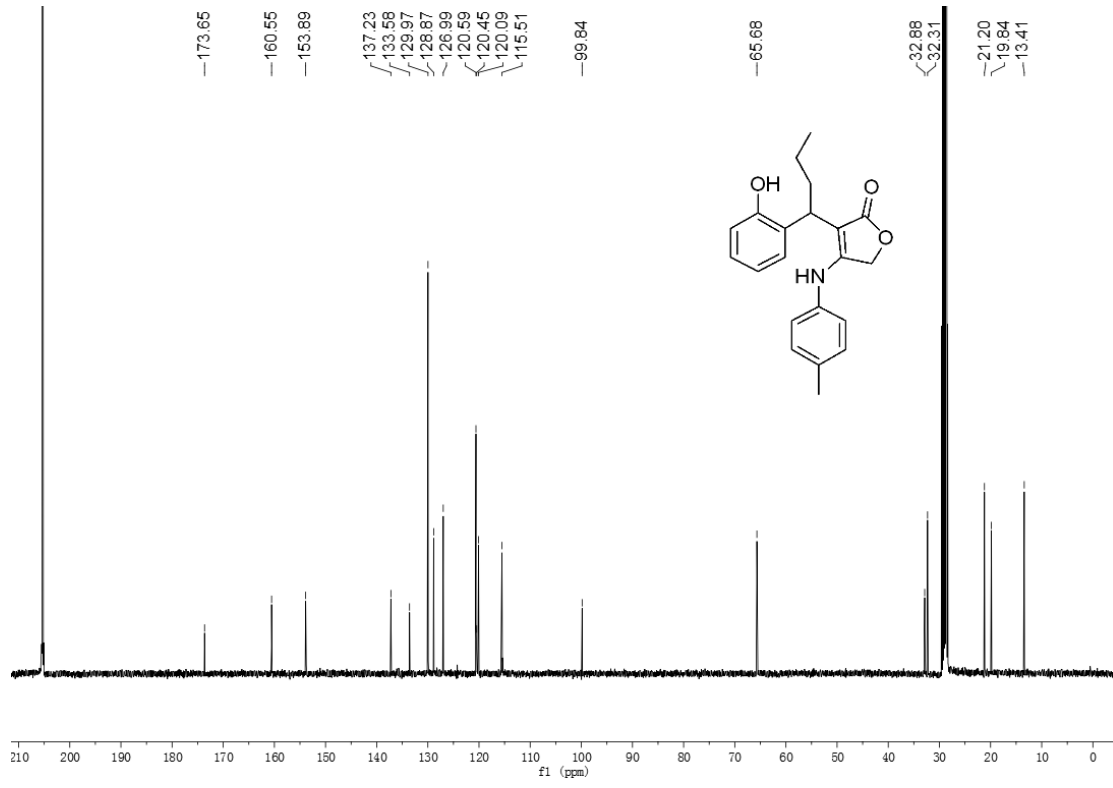
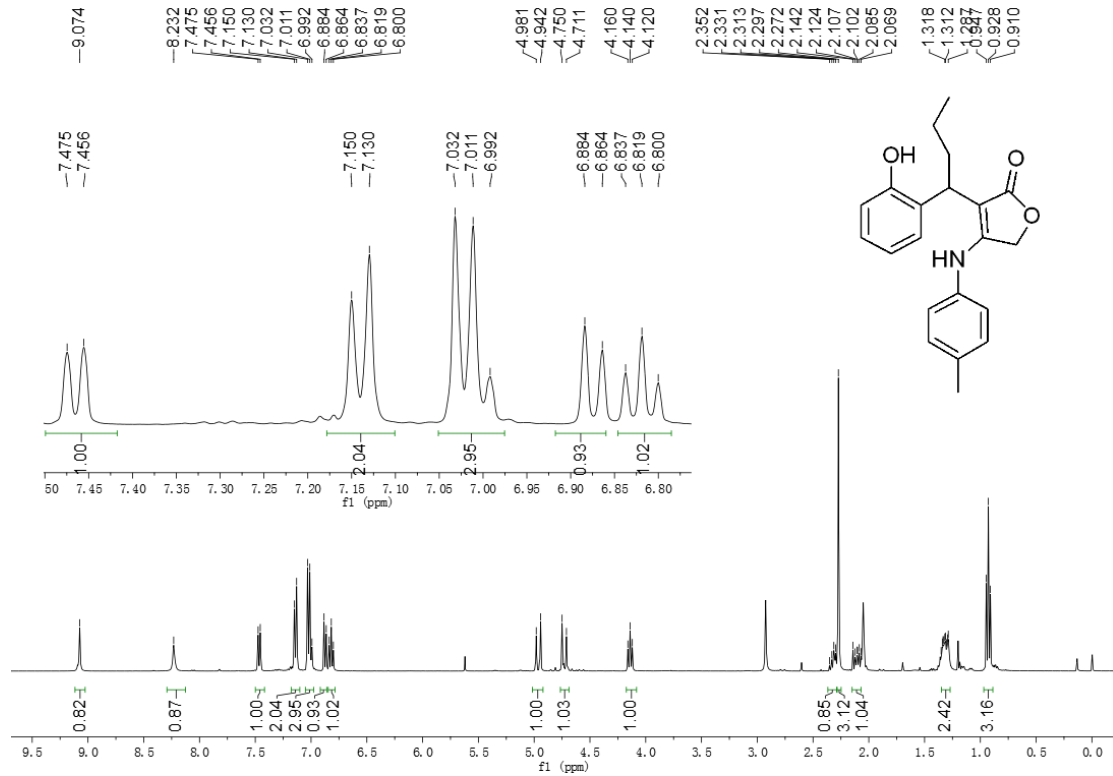
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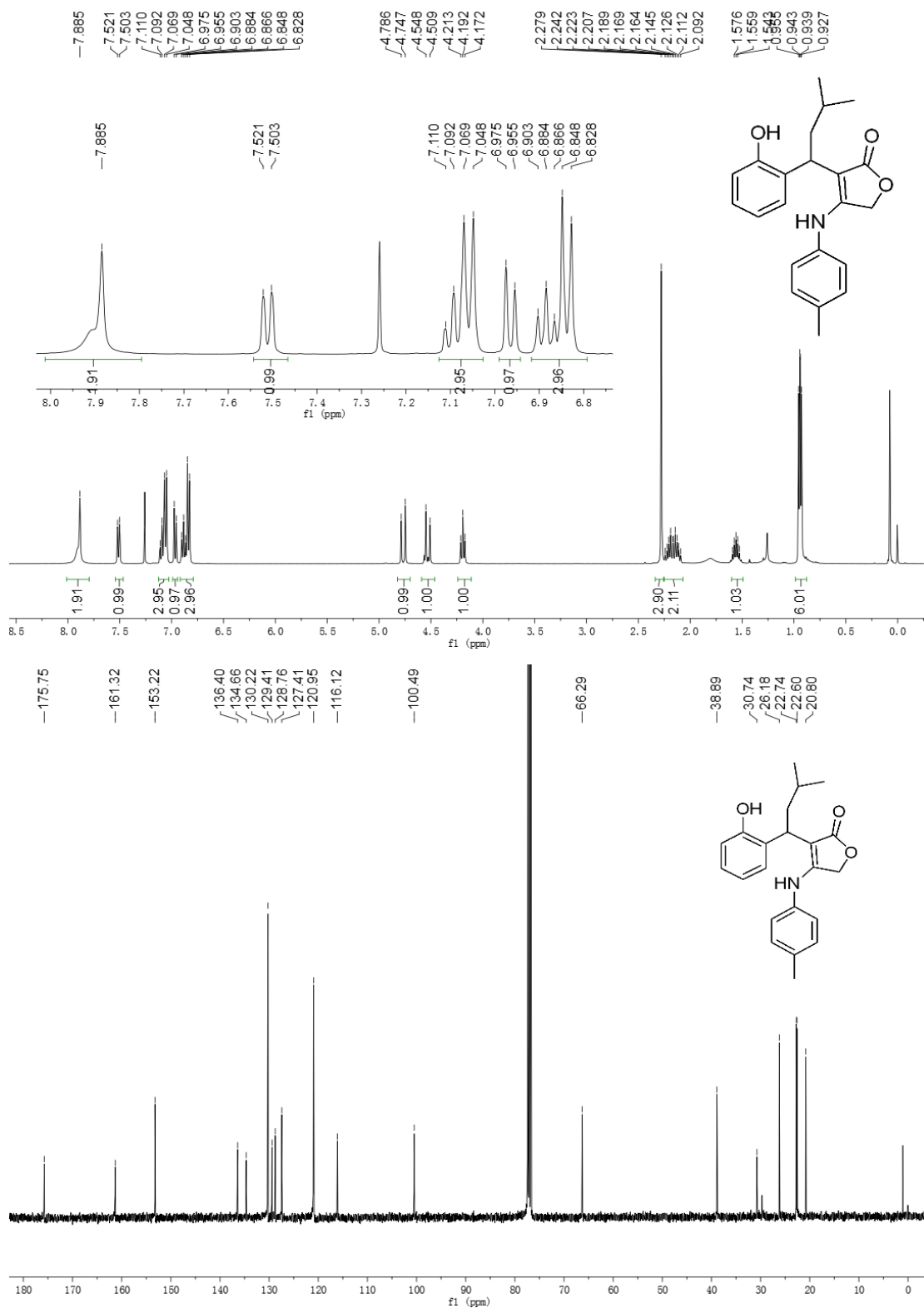
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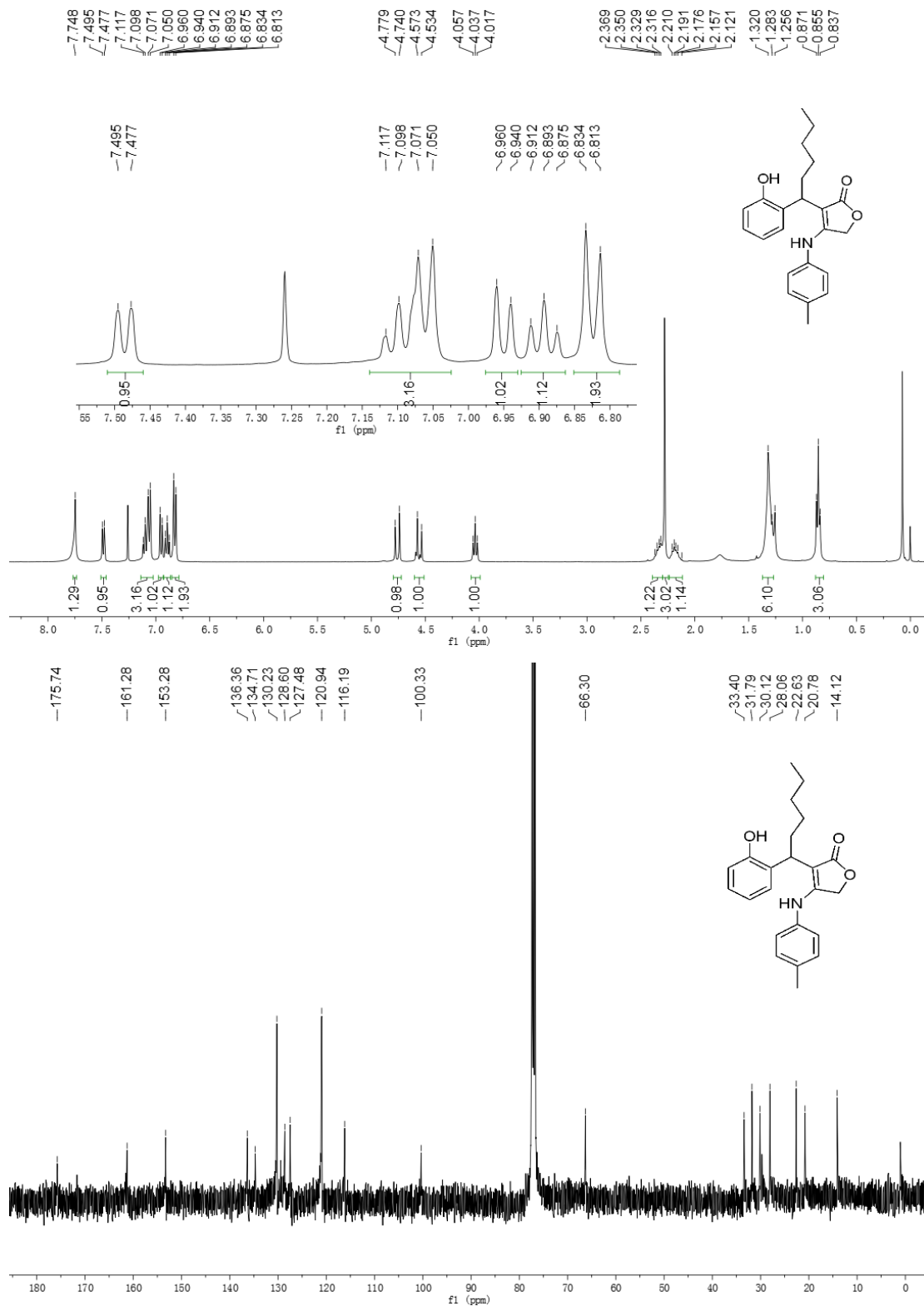
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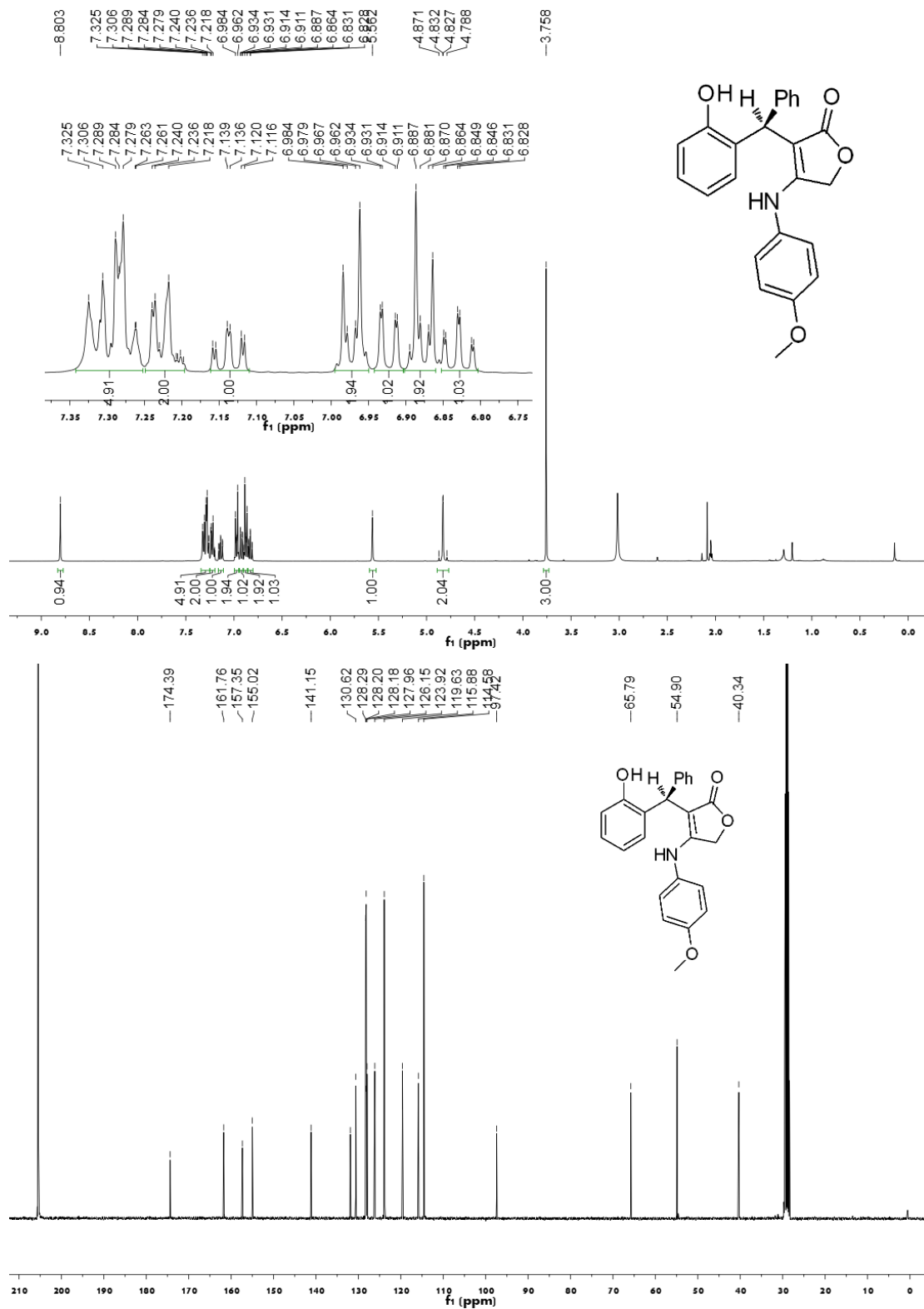
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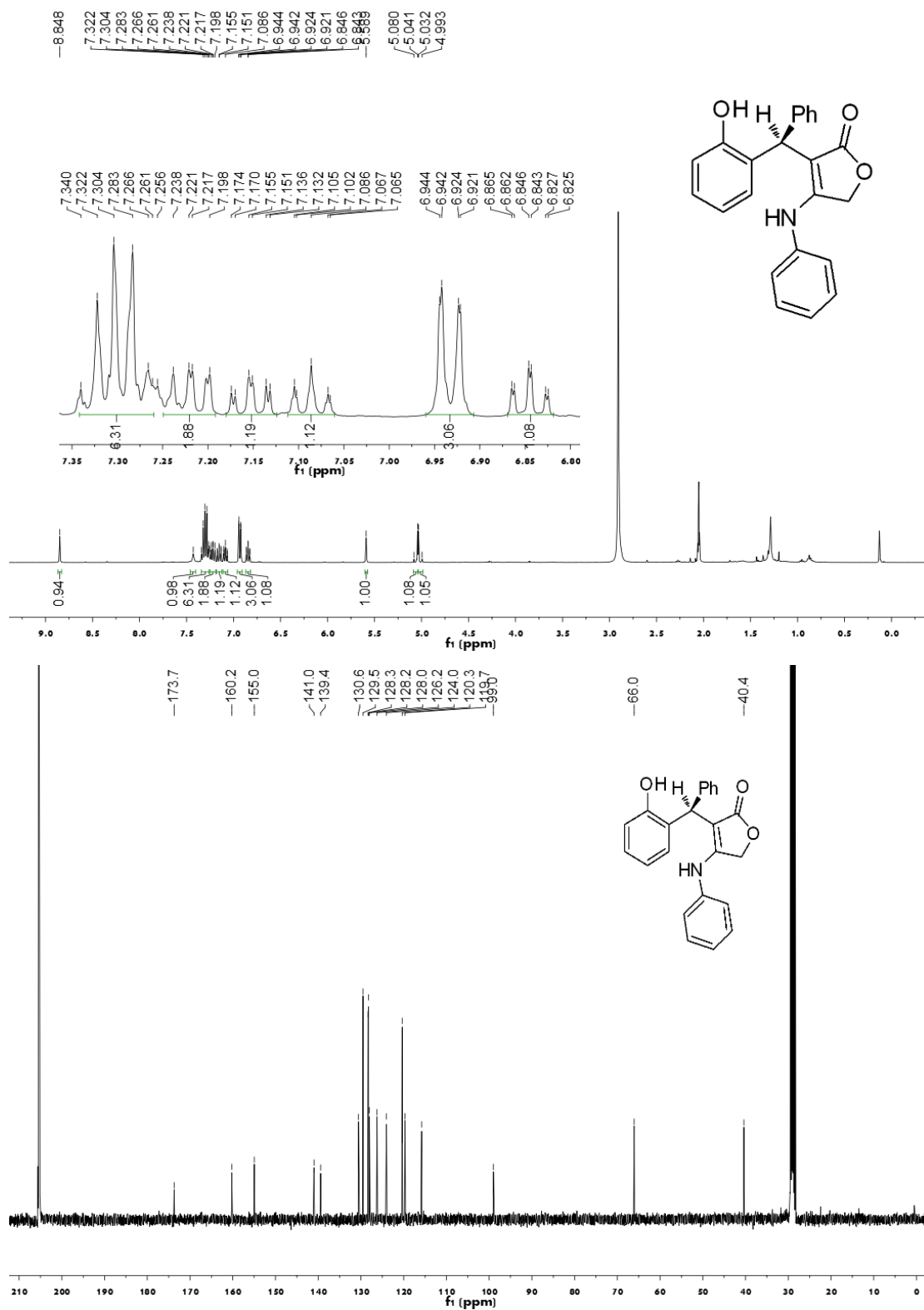
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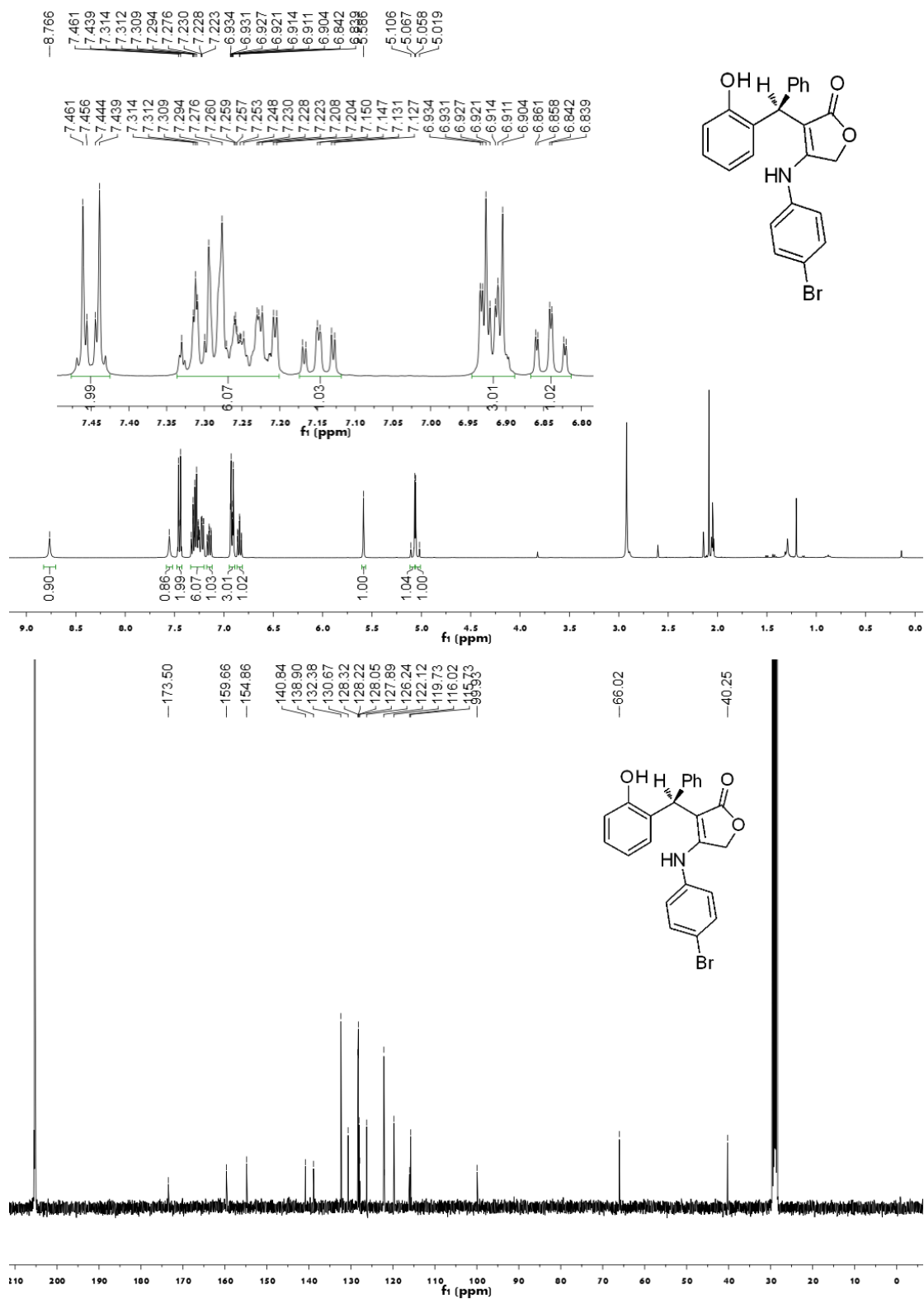
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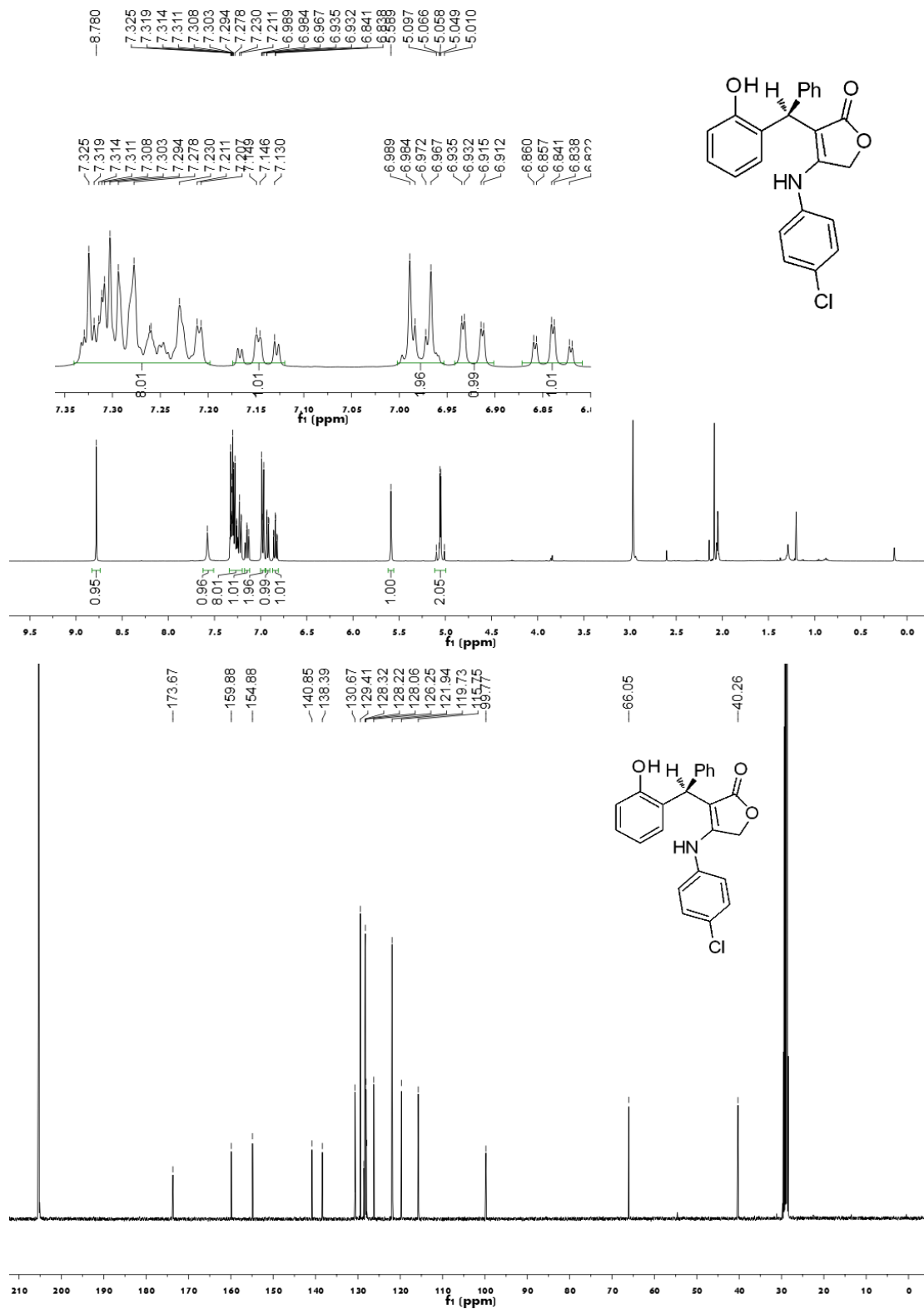
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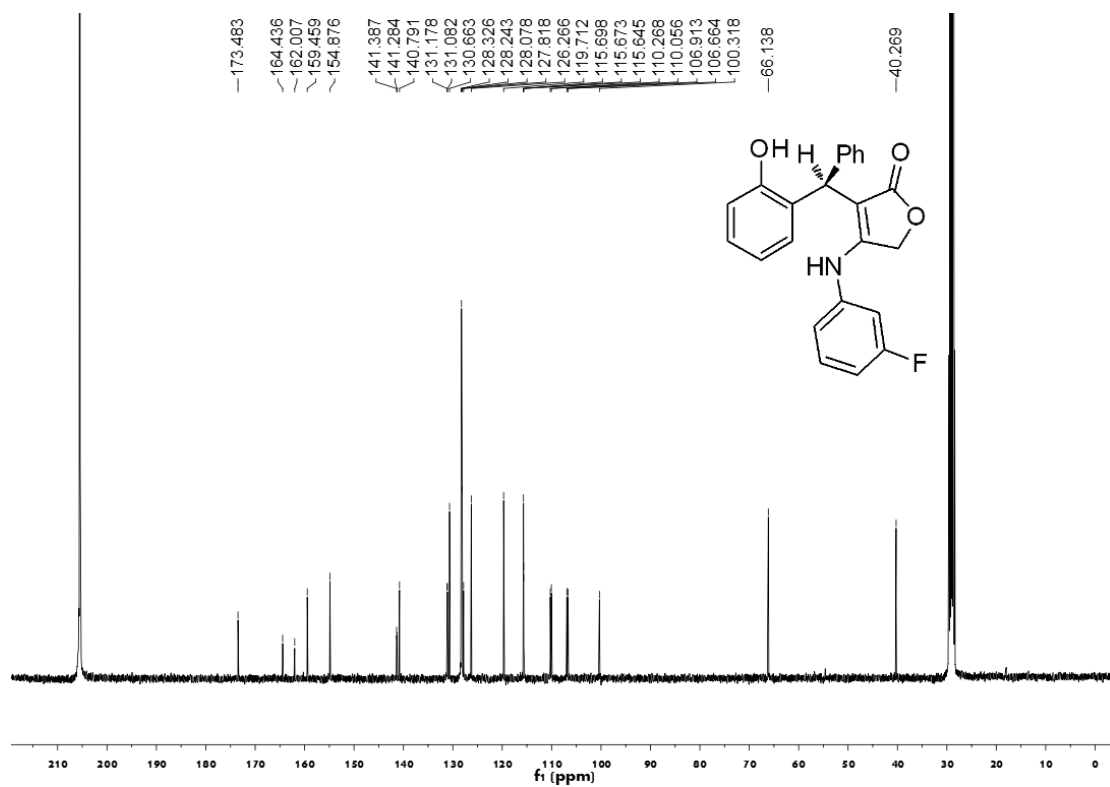
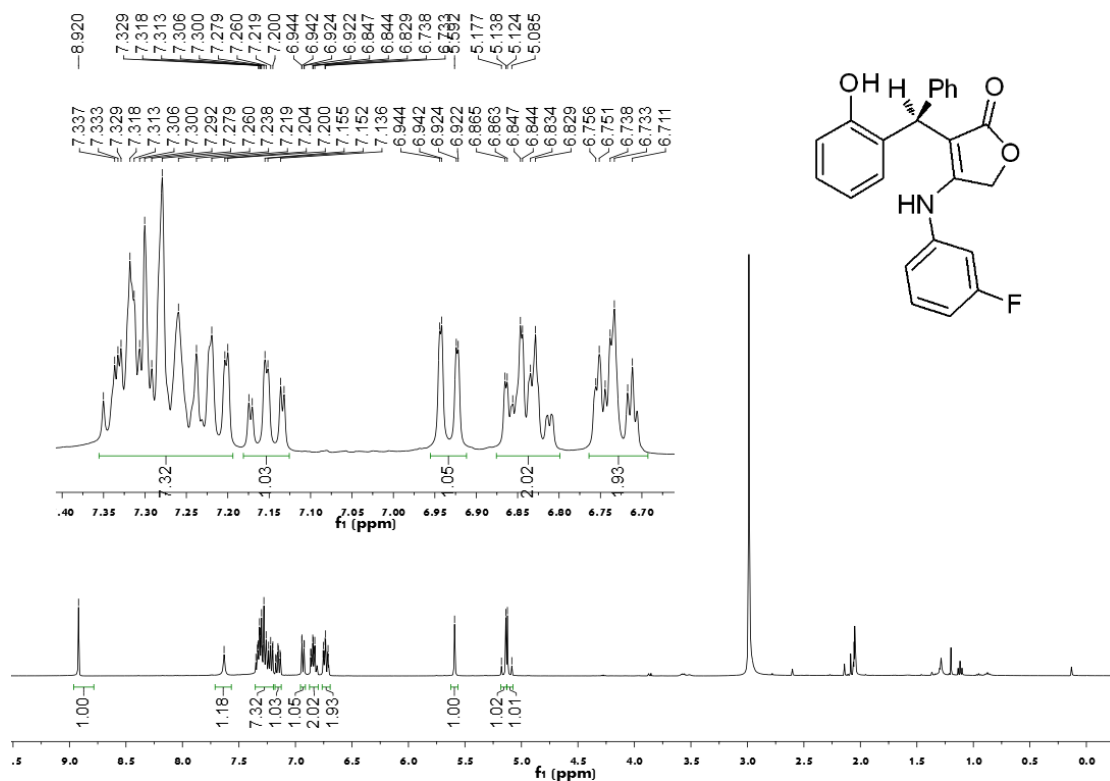
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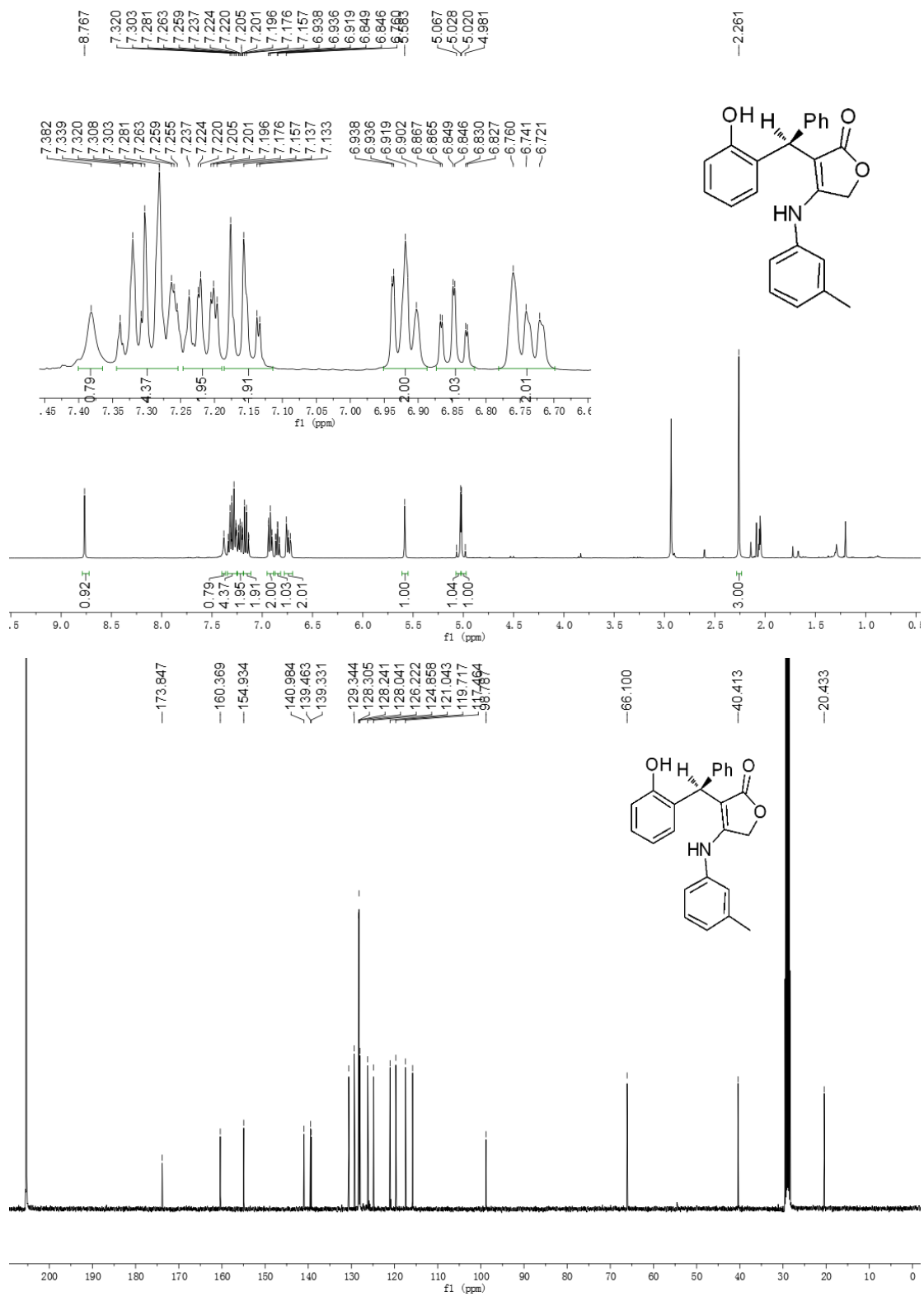
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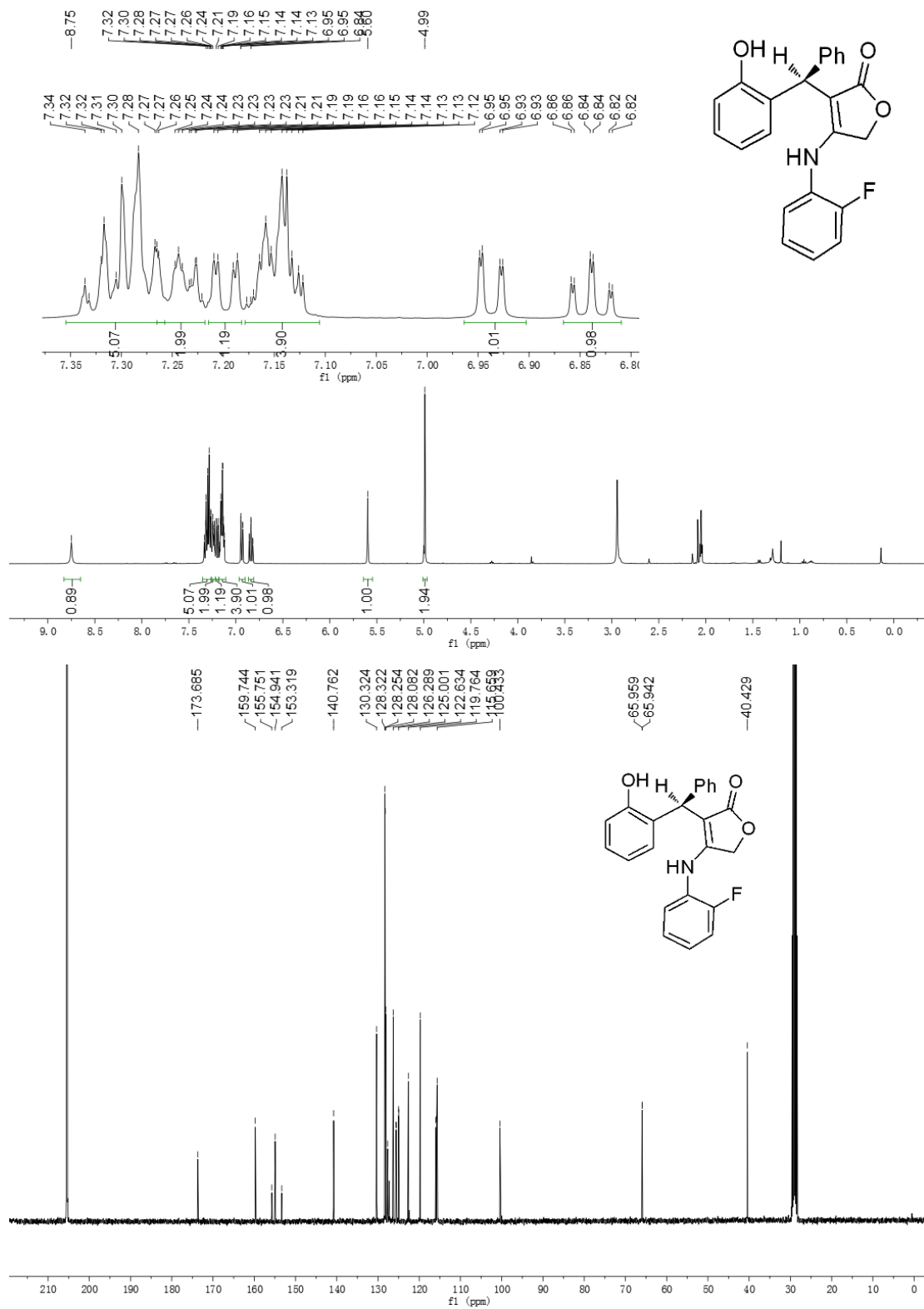
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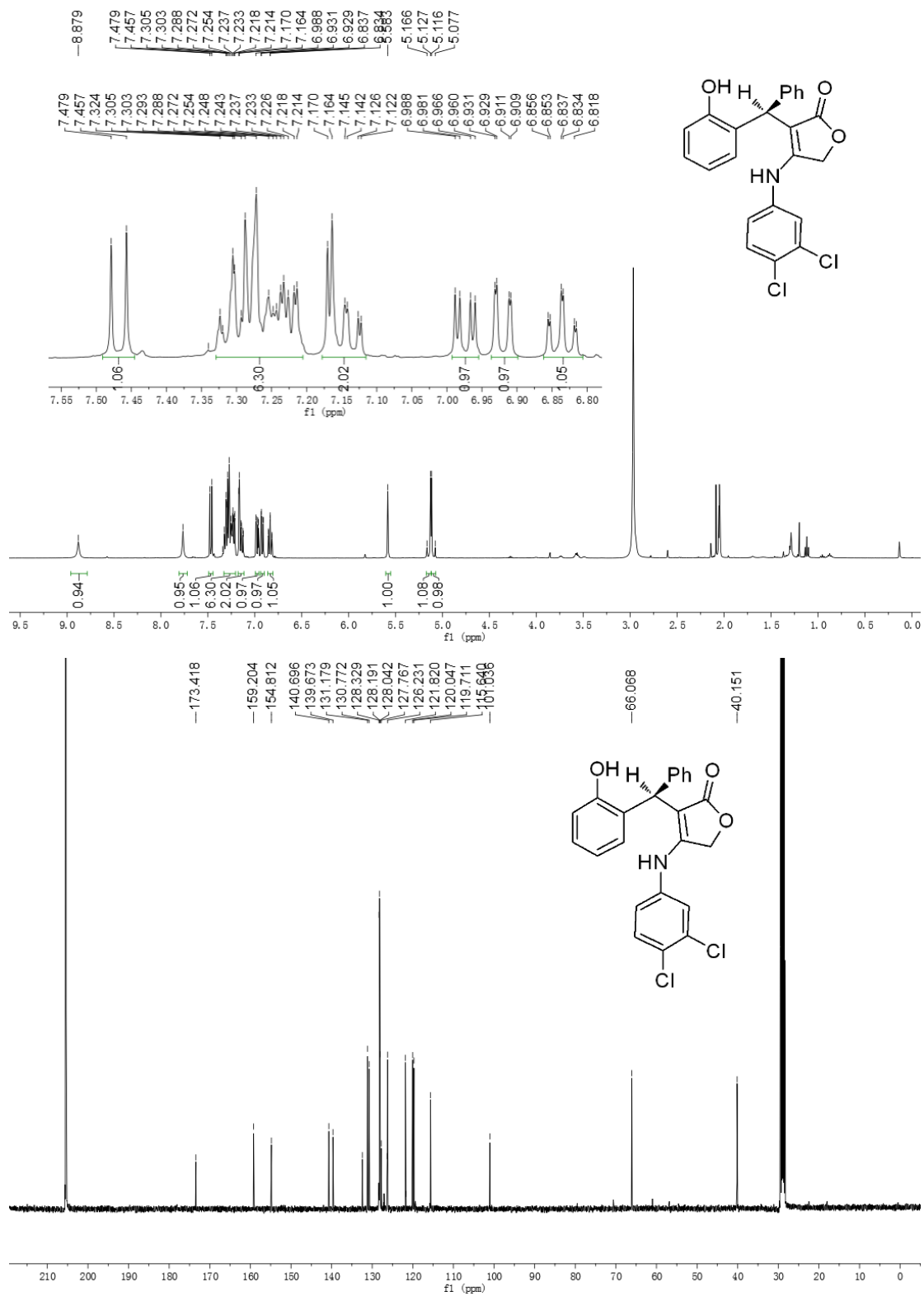
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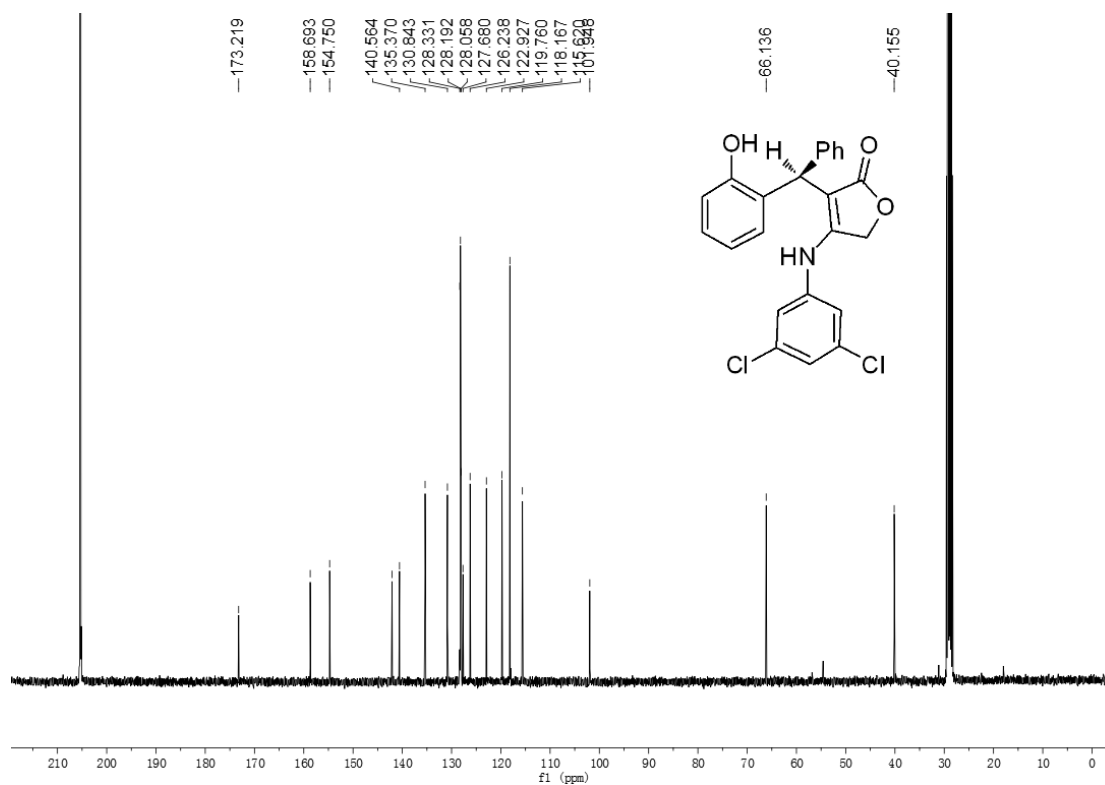
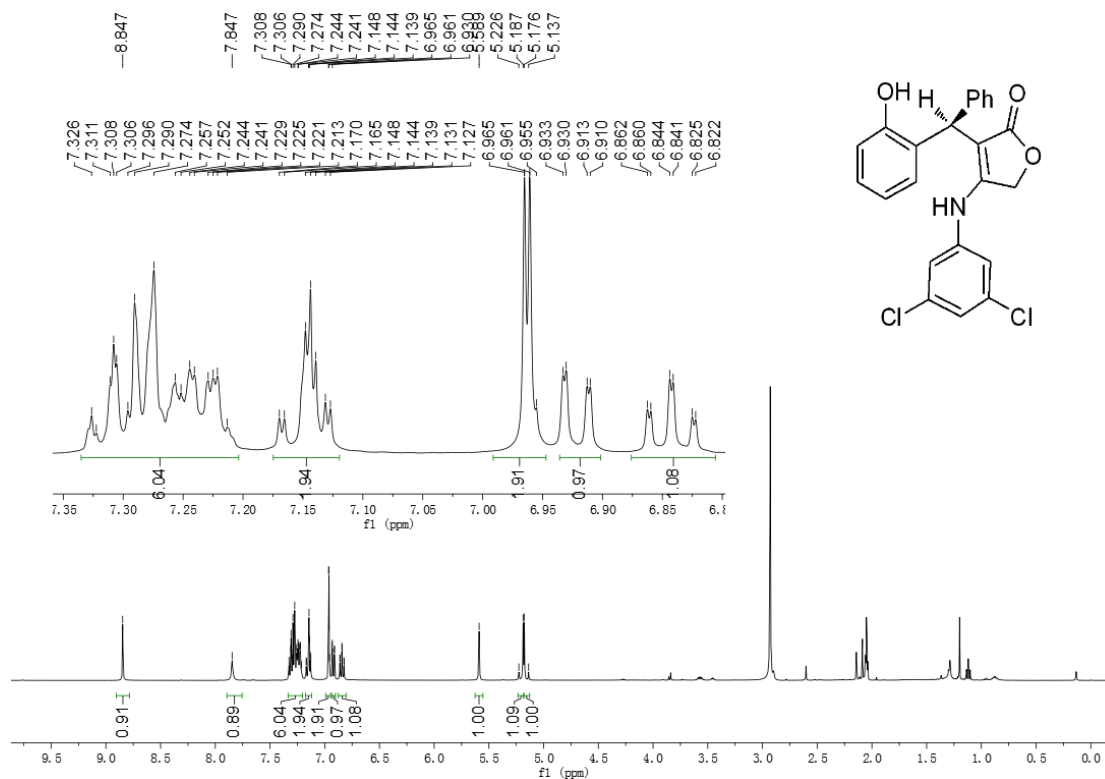
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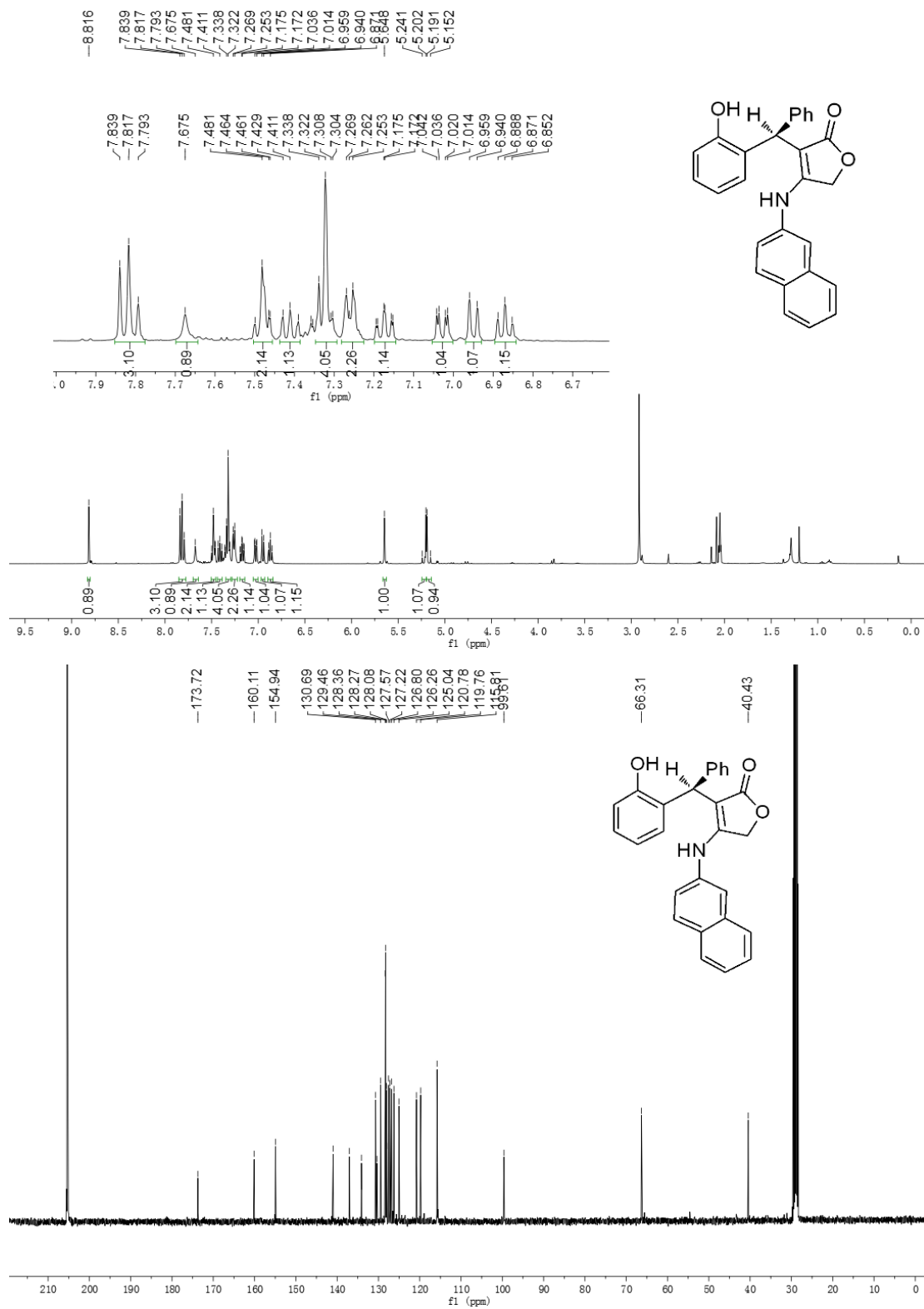
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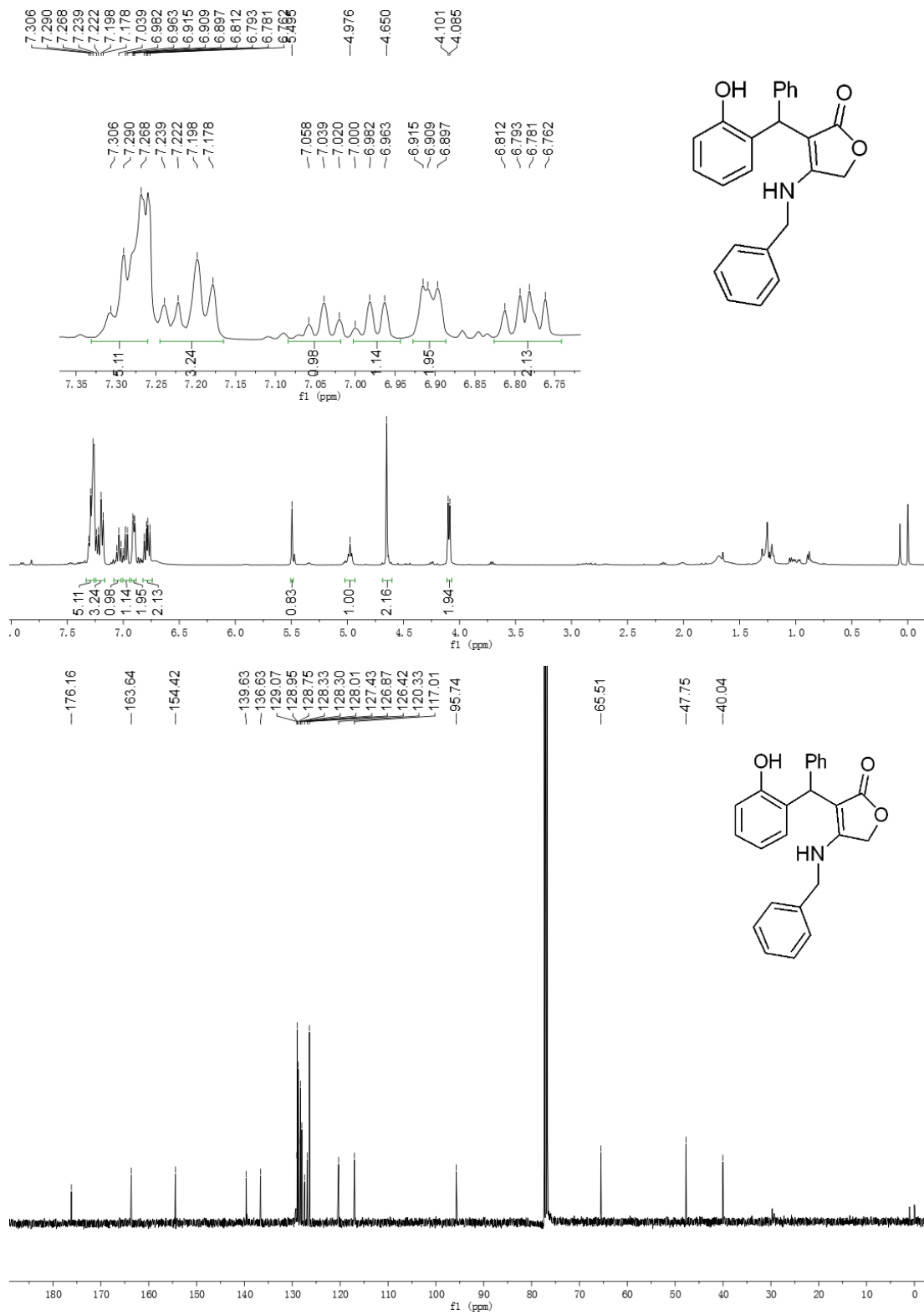
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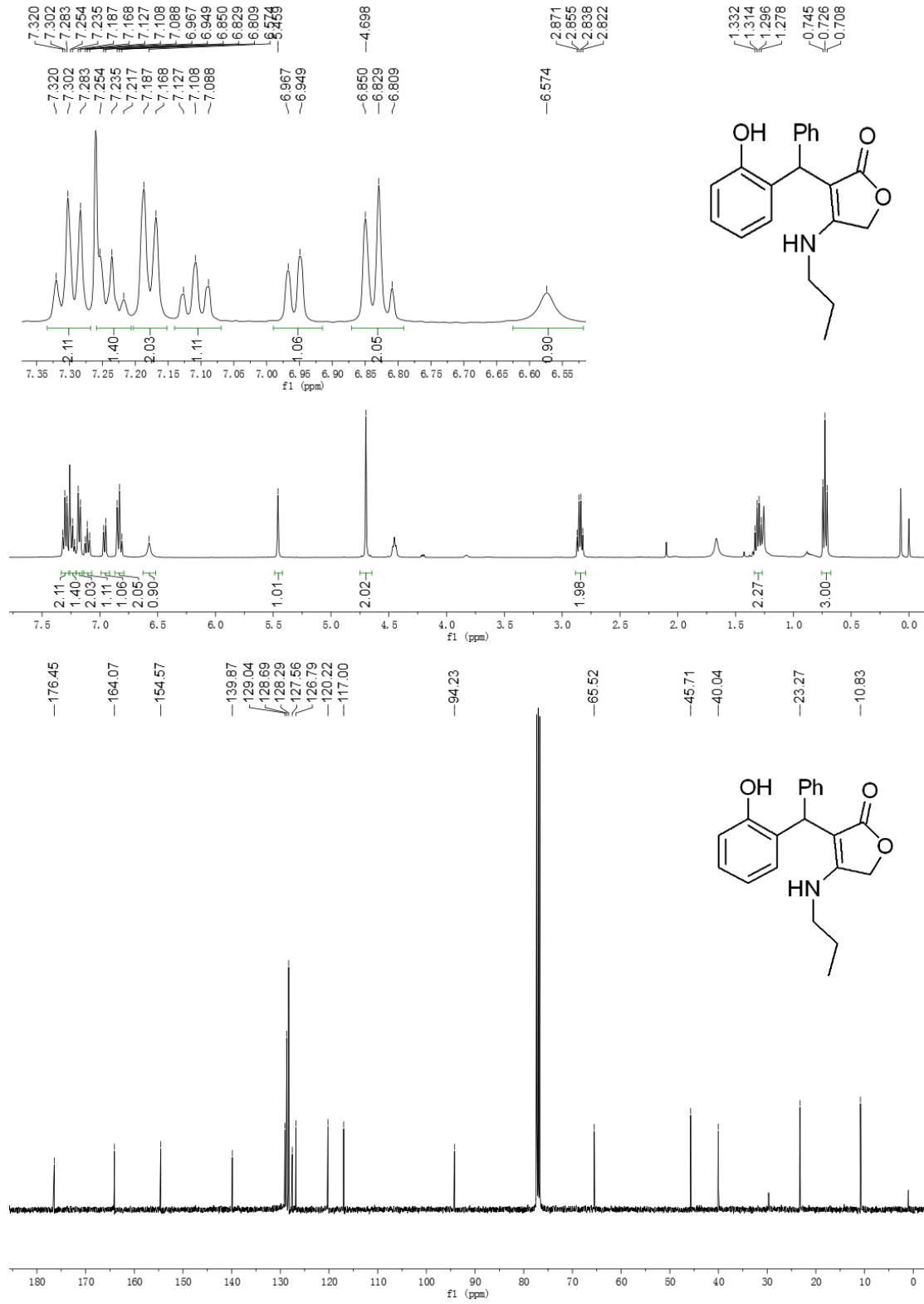
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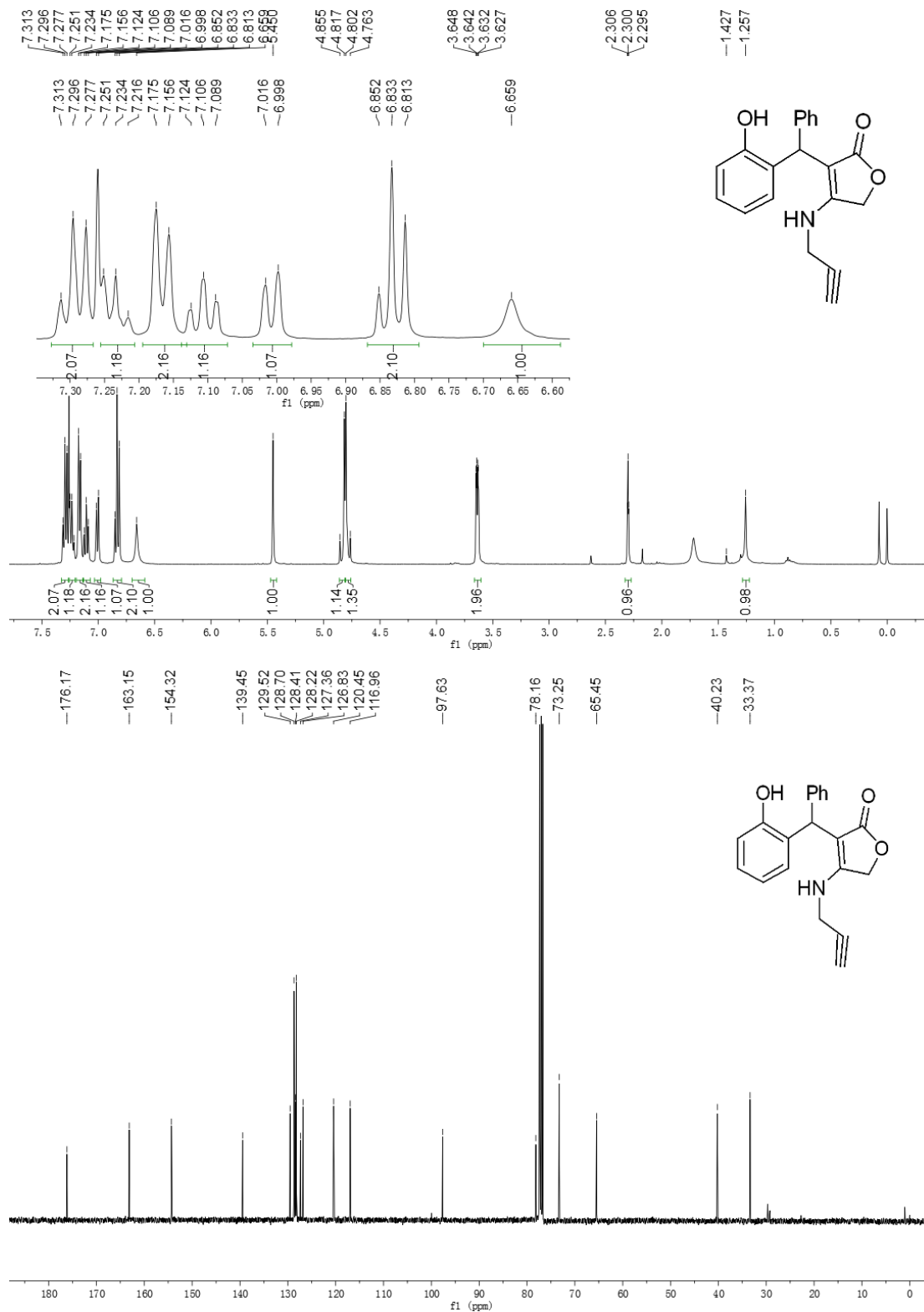
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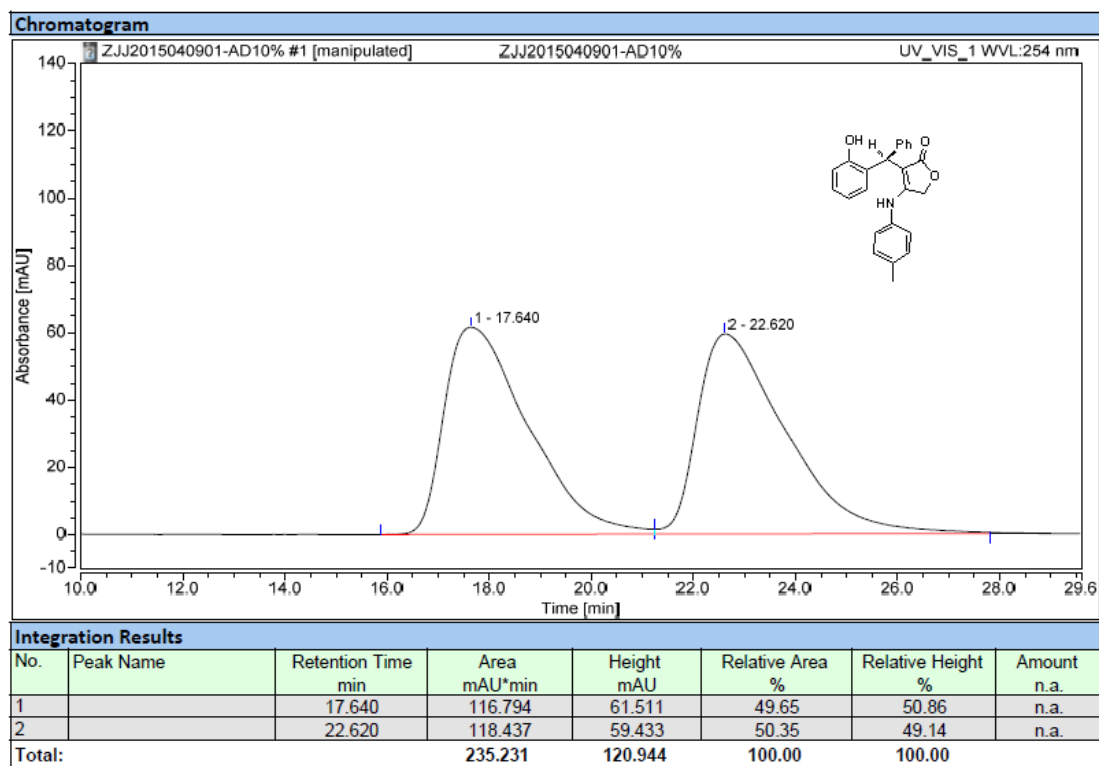
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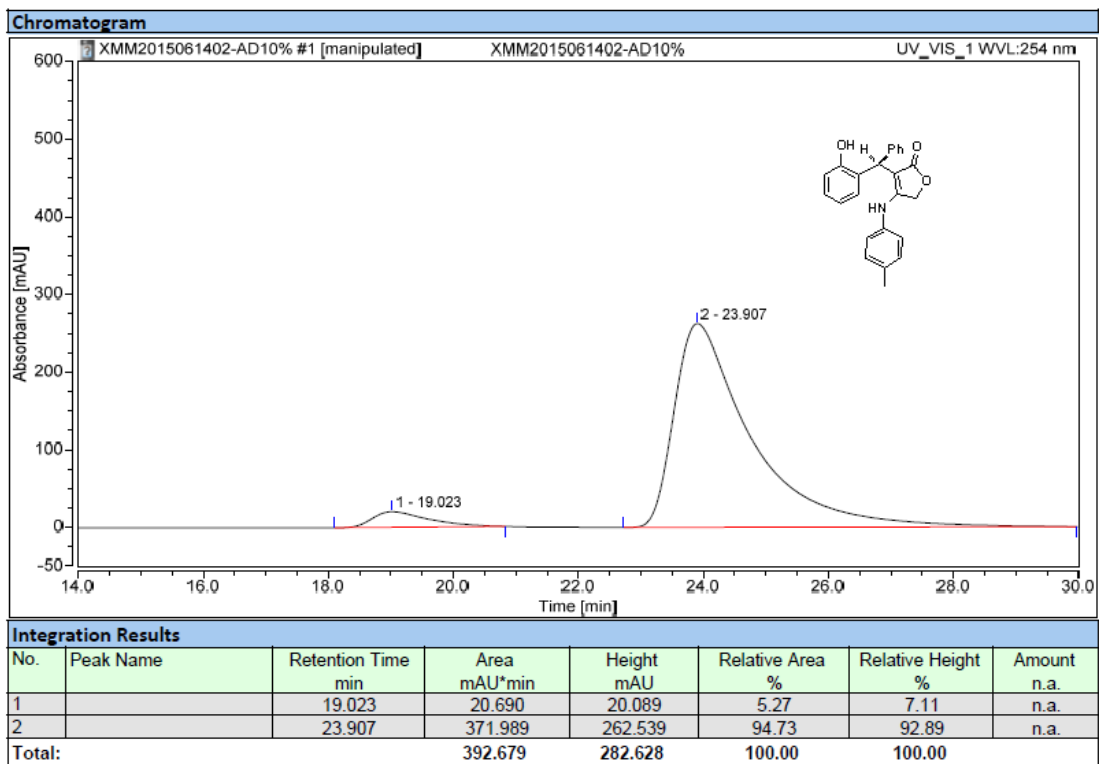
3. HPLC spectra of all products 3

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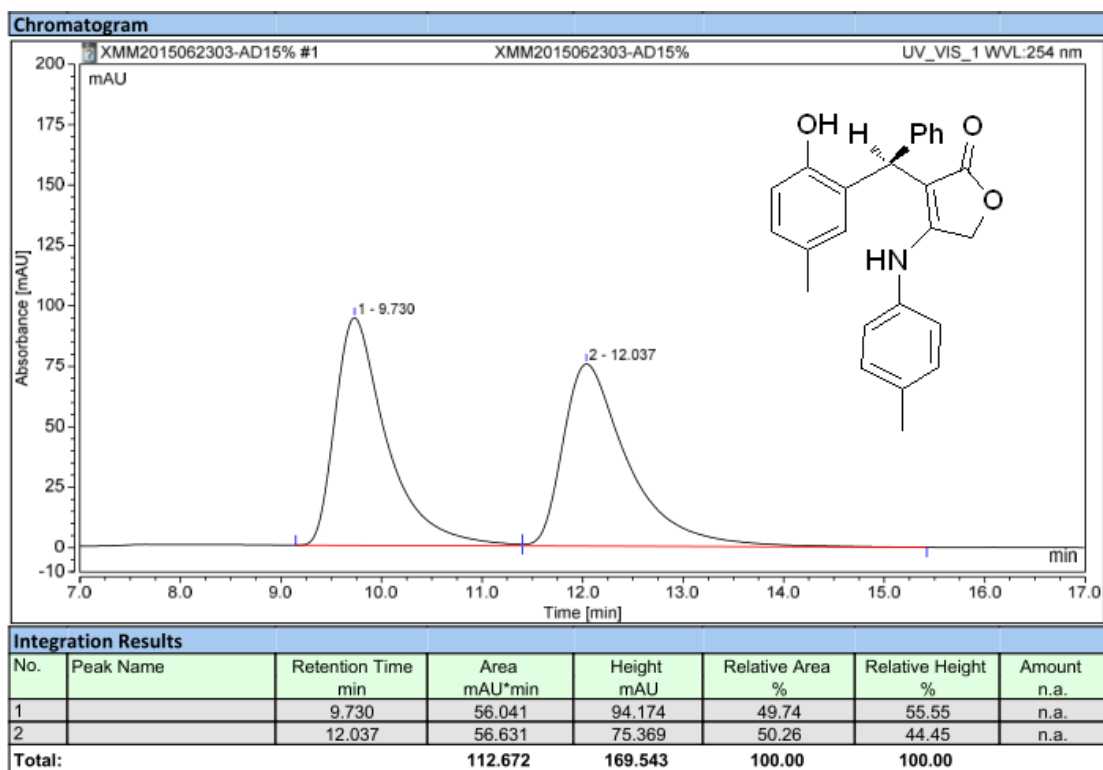


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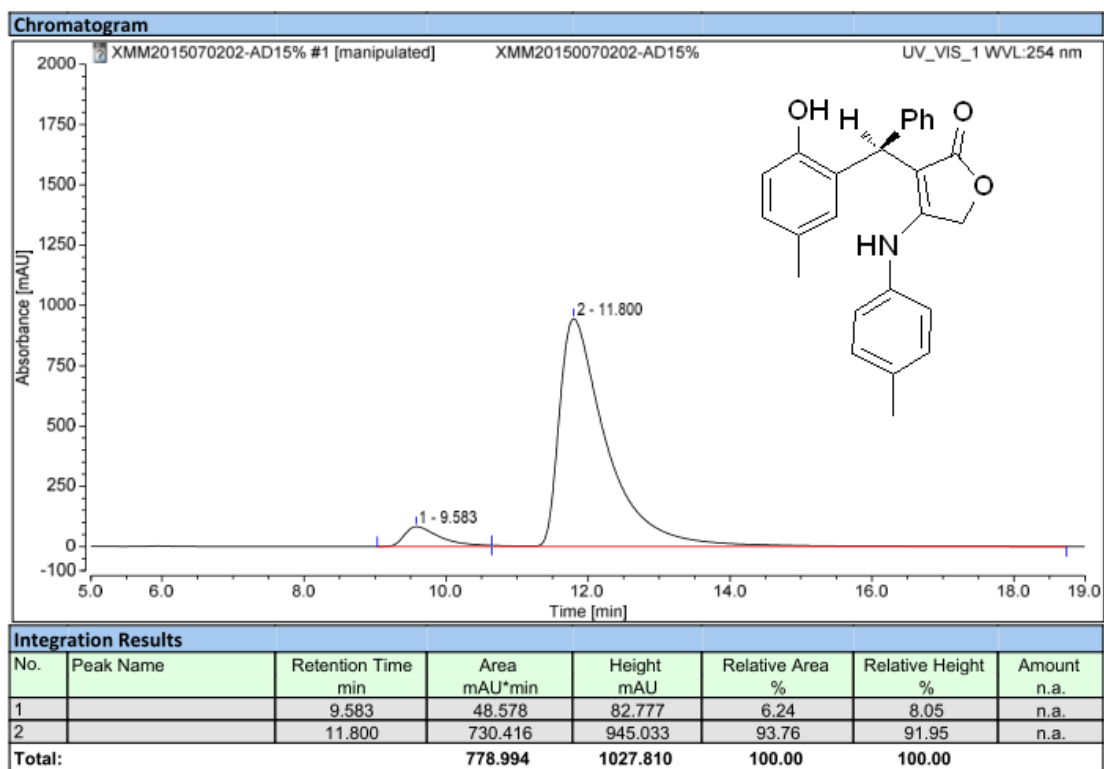


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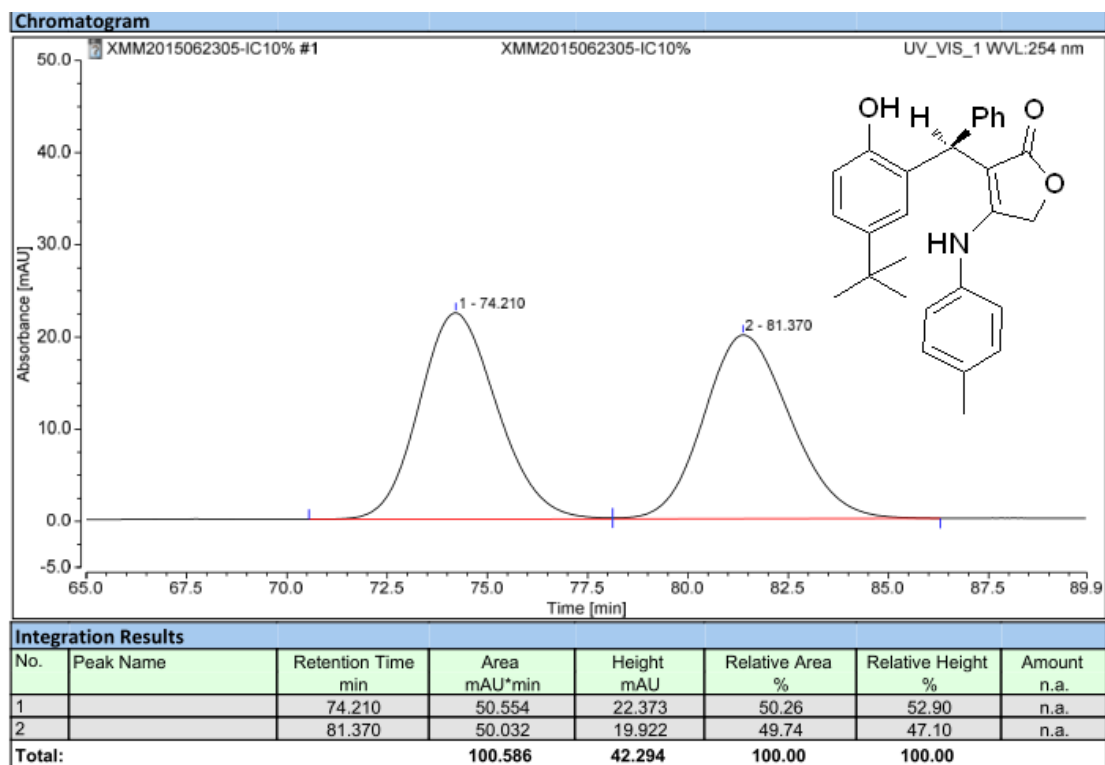


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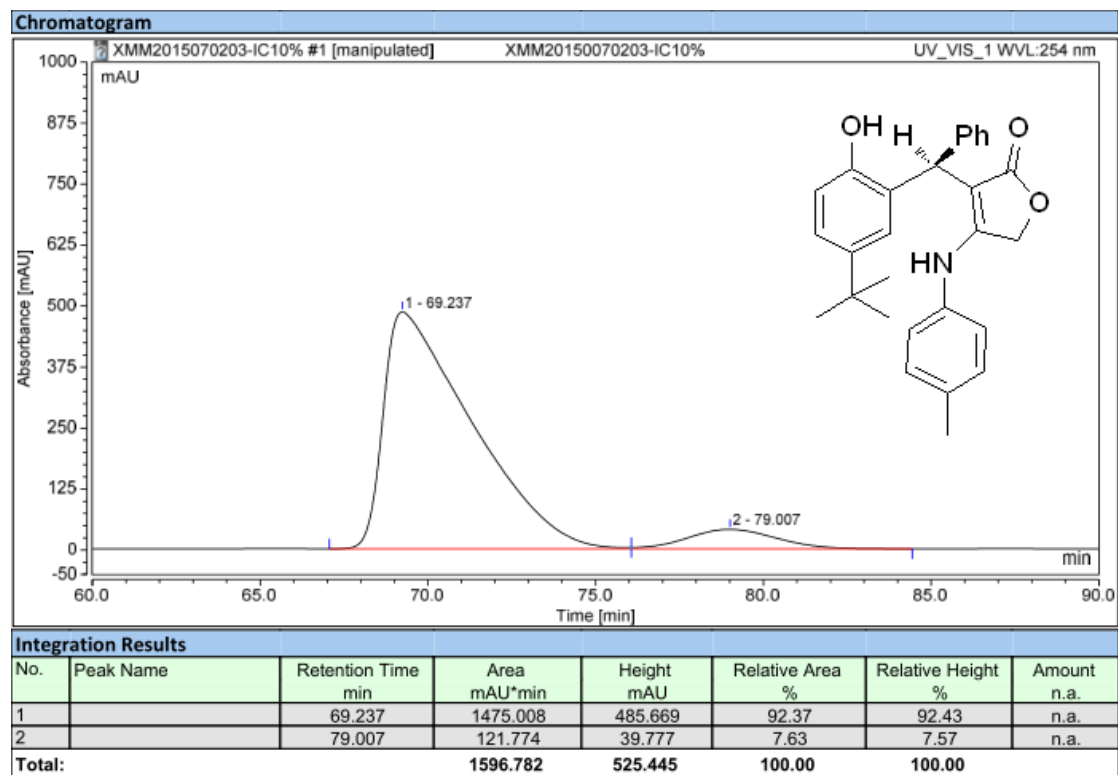


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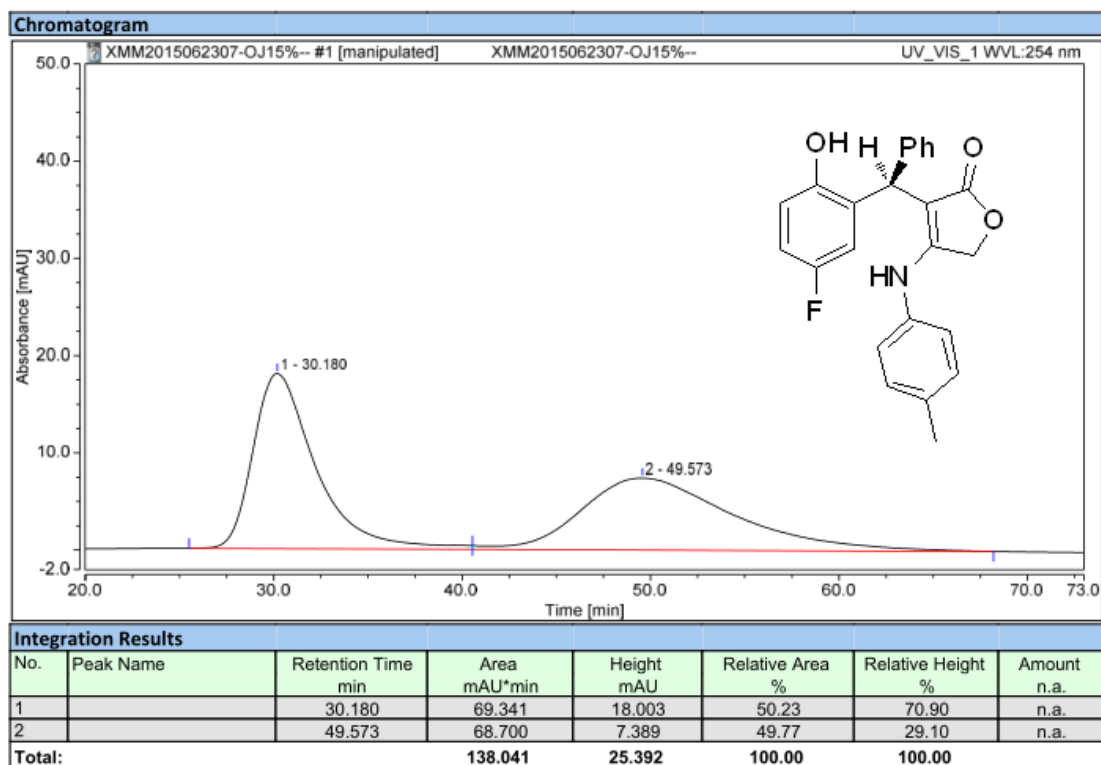


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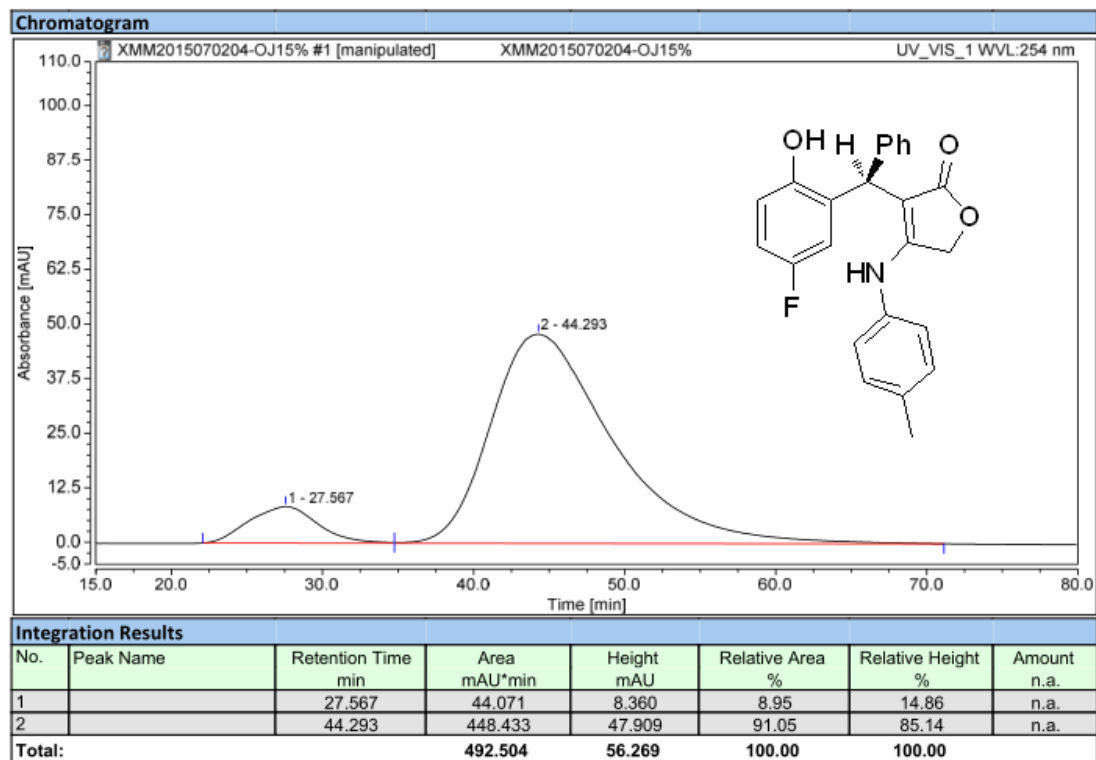


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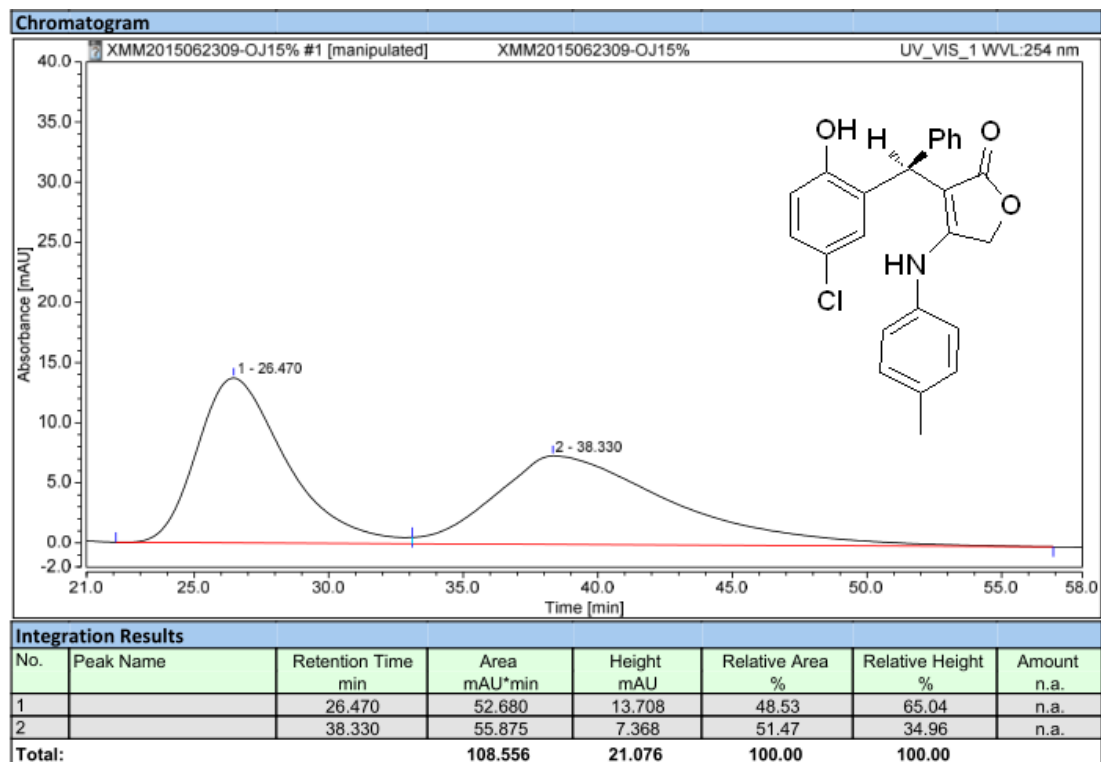


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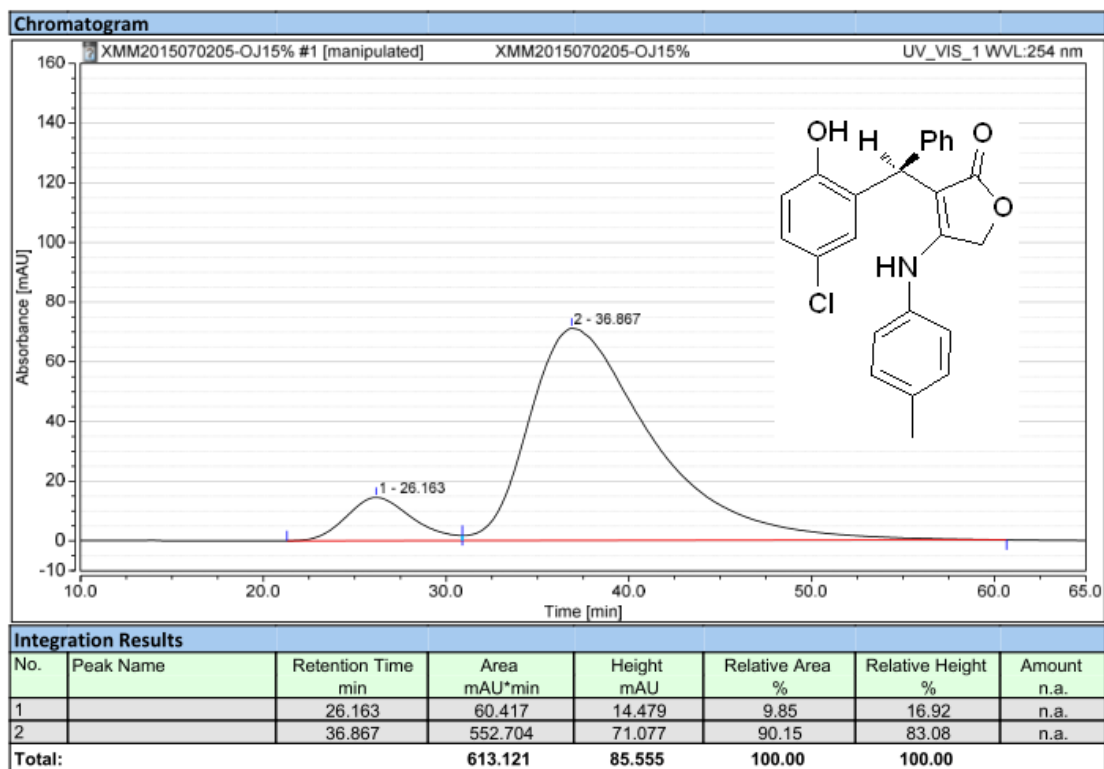


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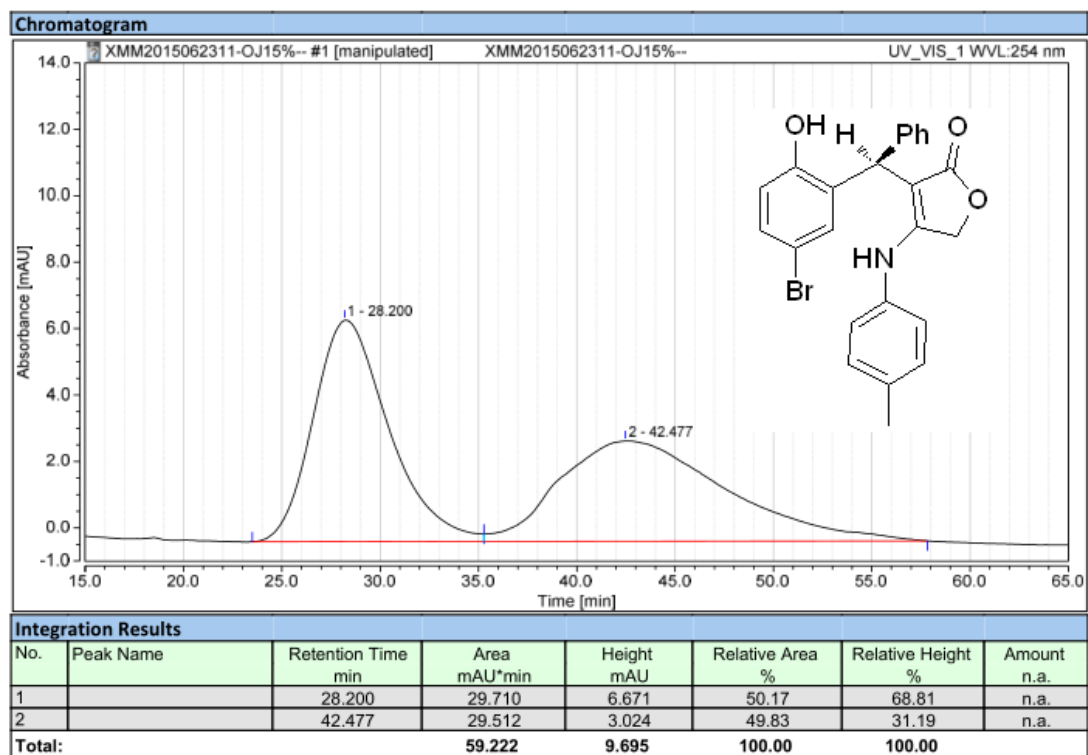


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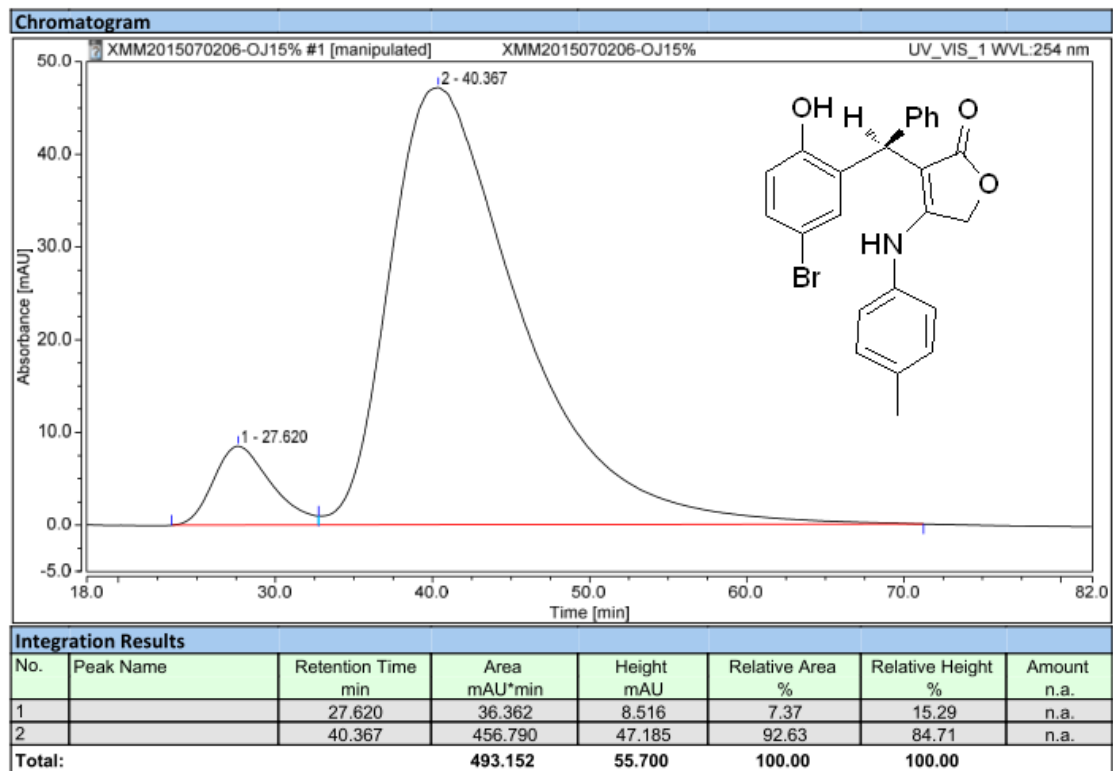


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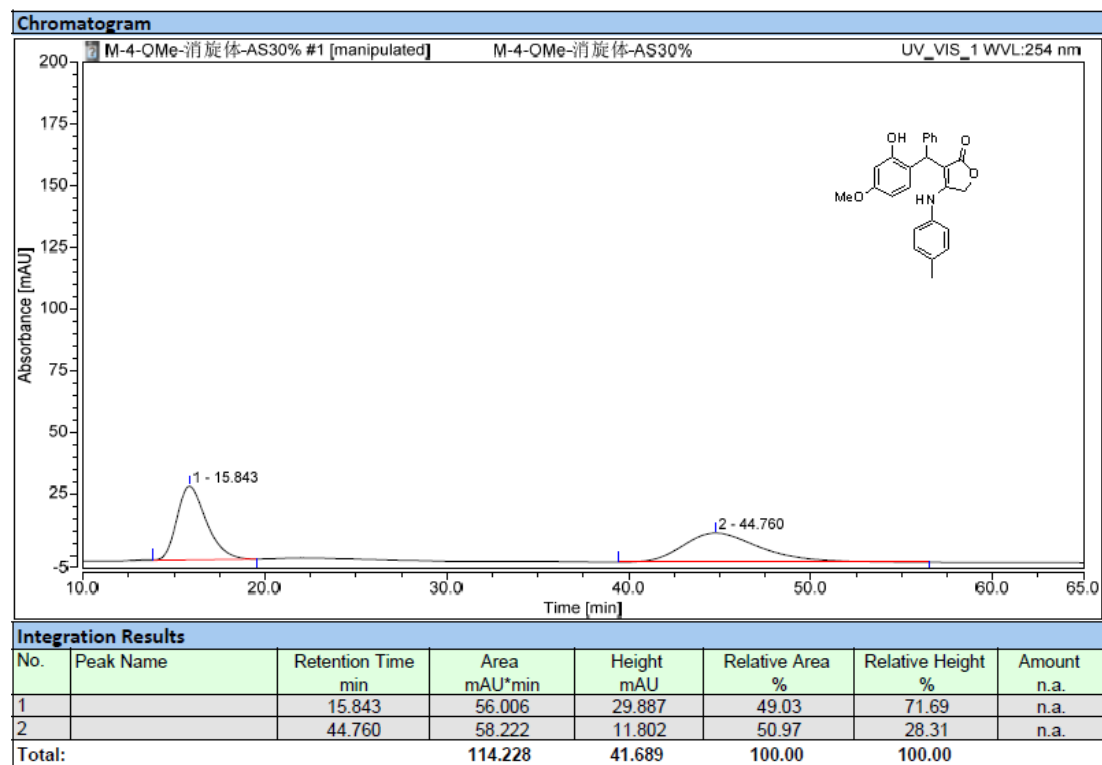


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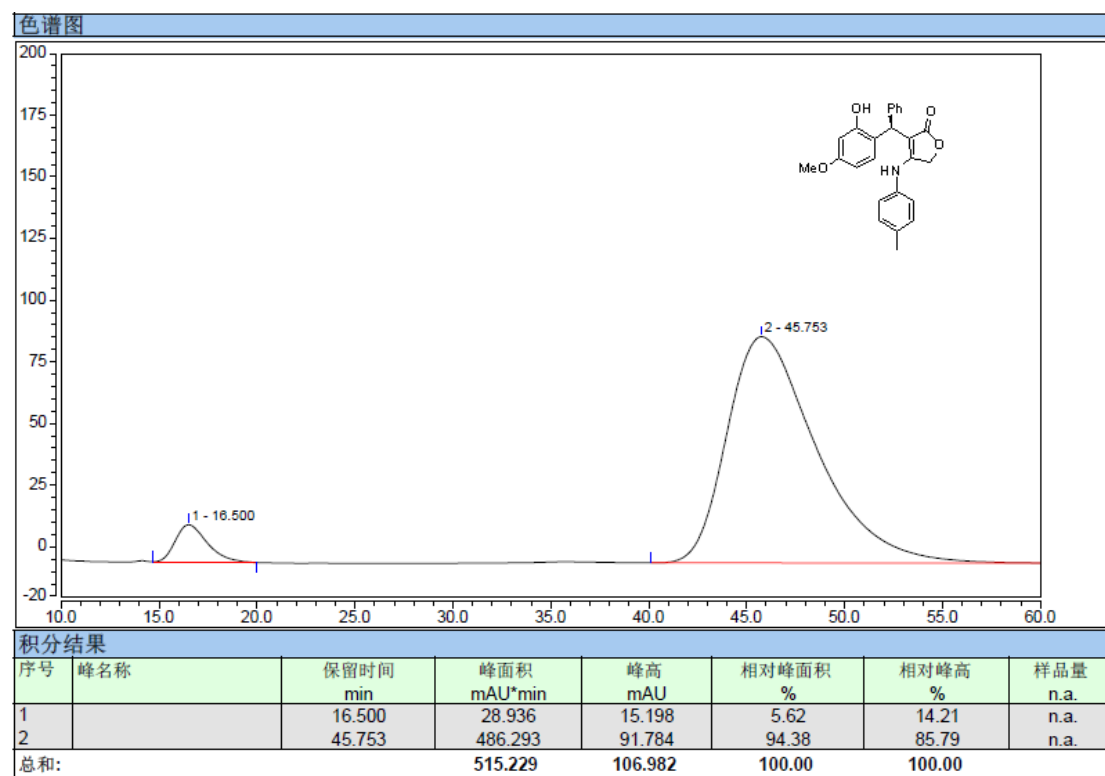


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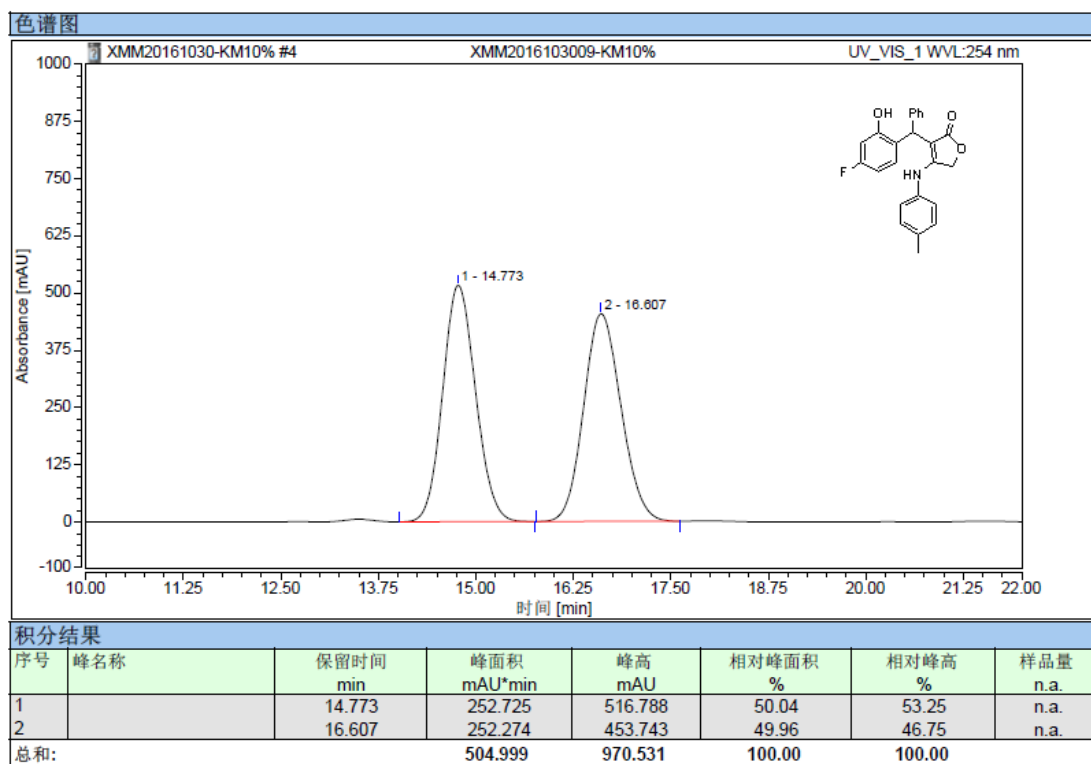


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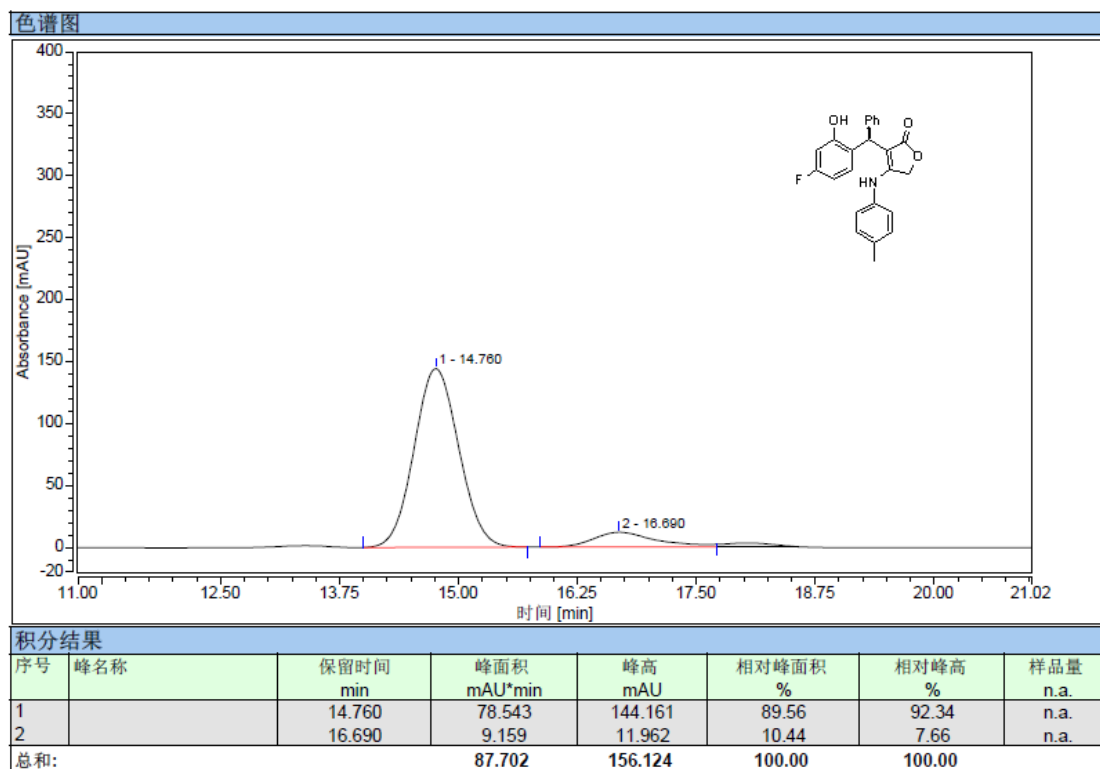


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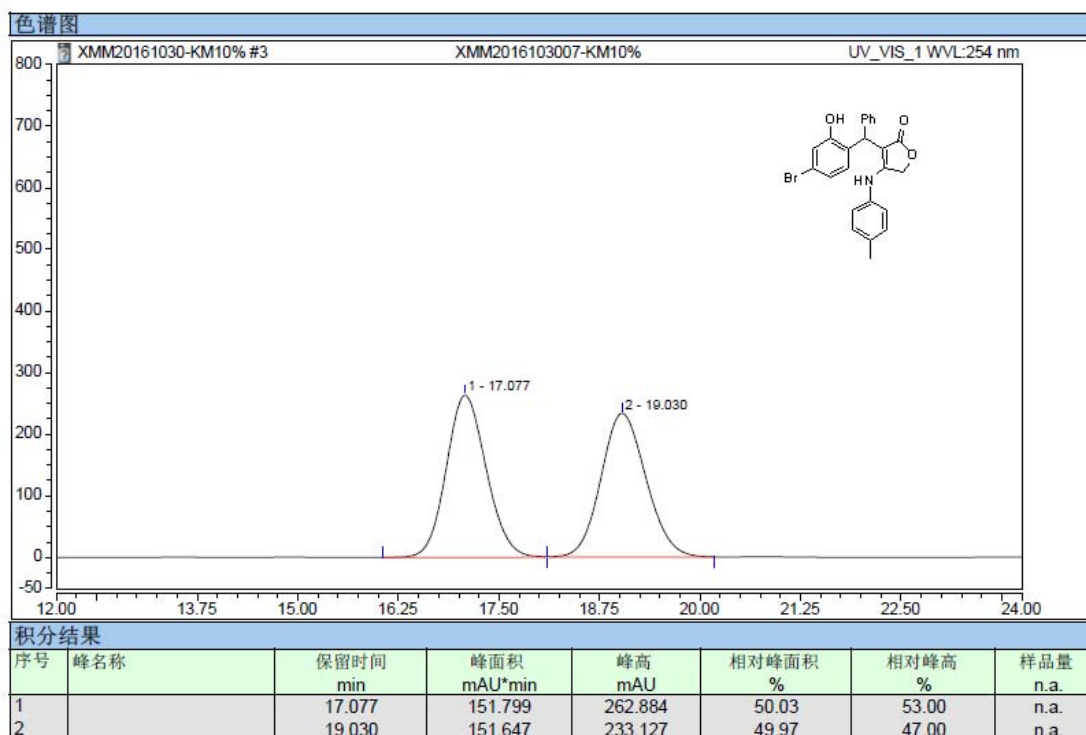
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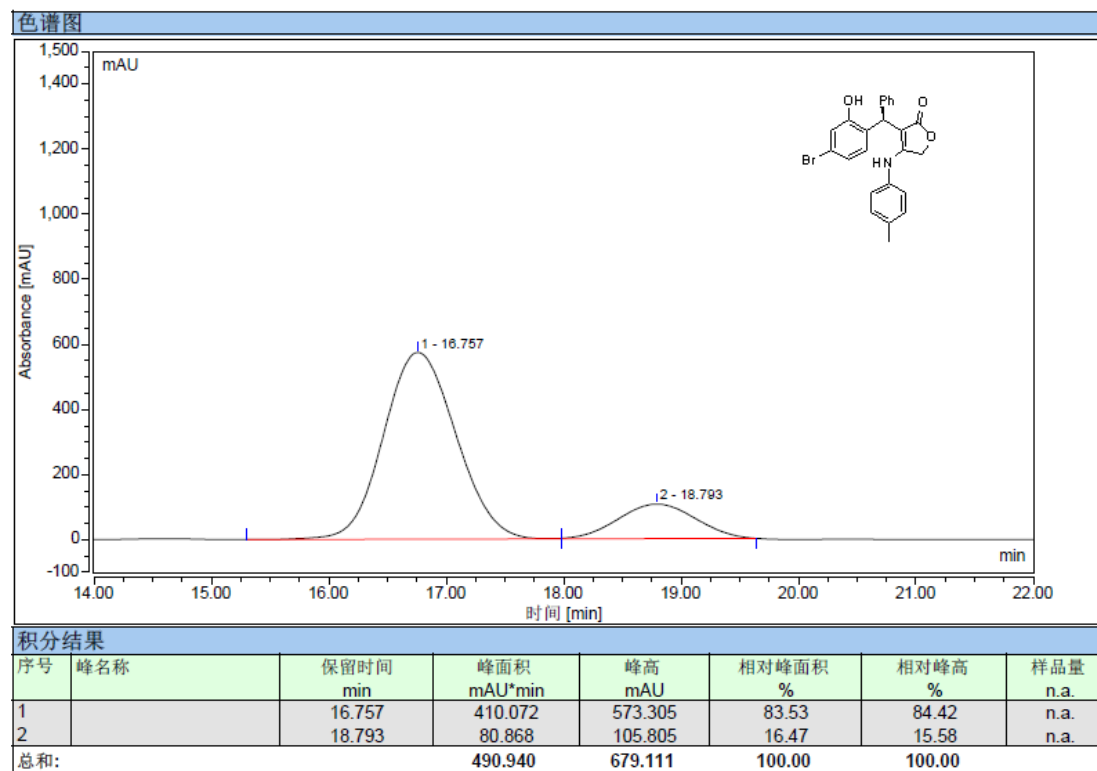
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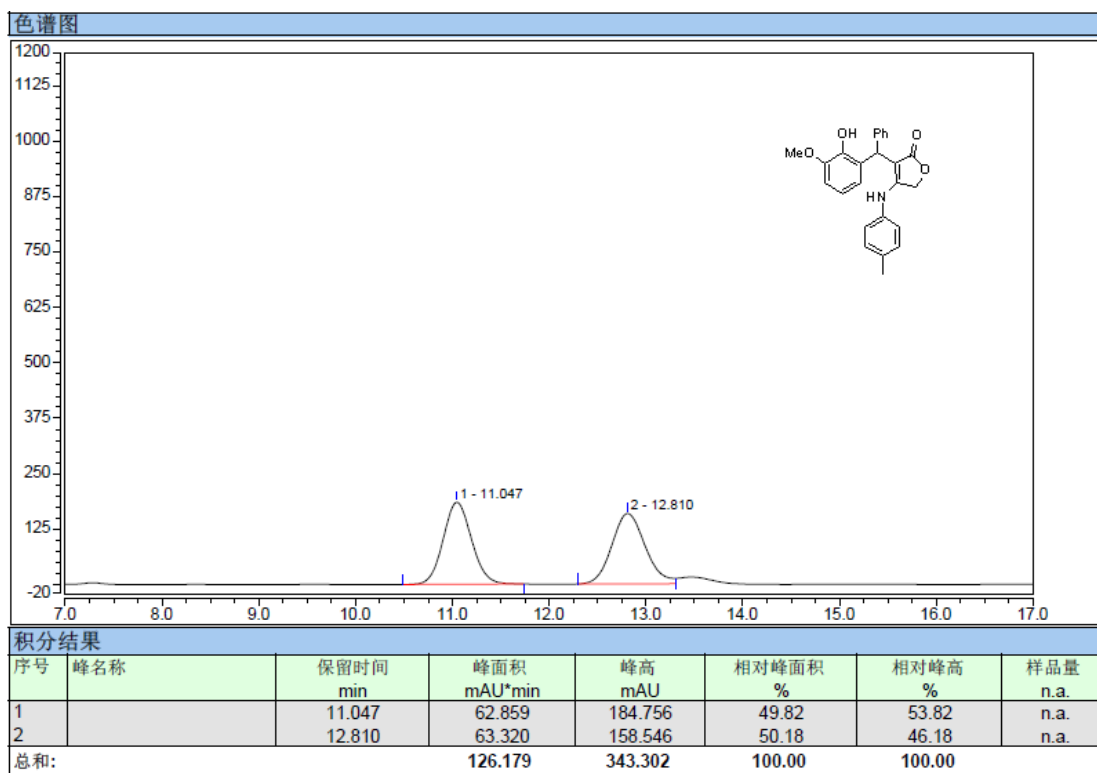


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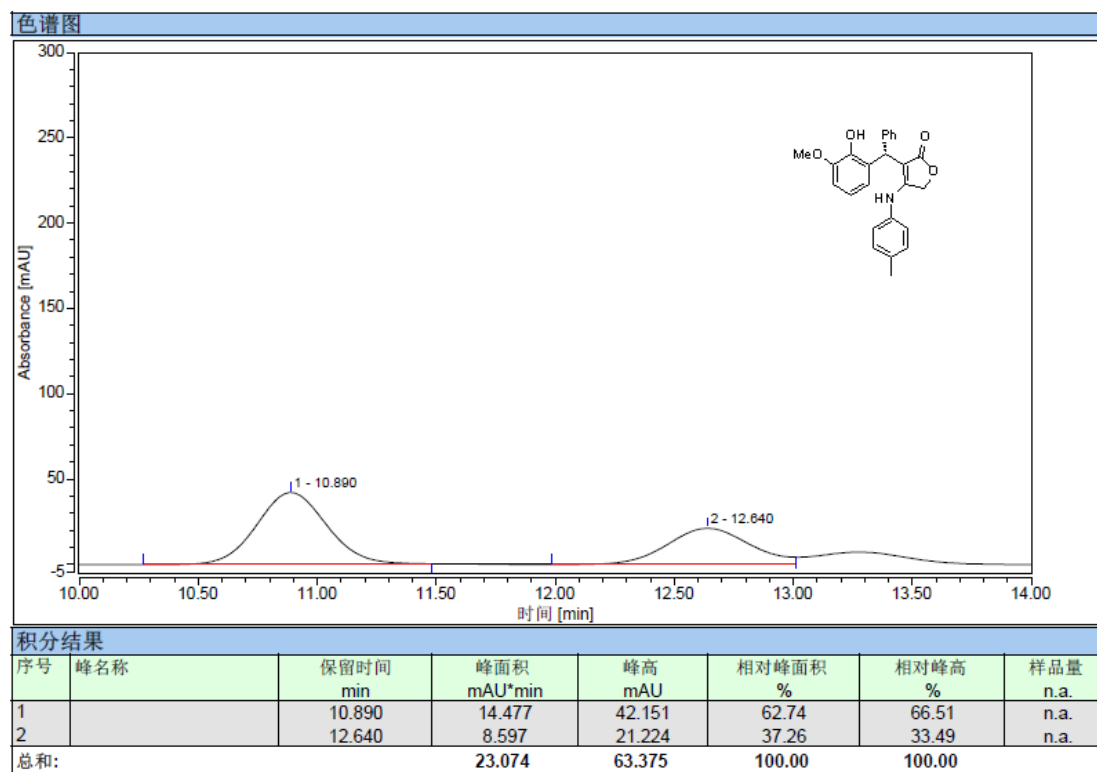


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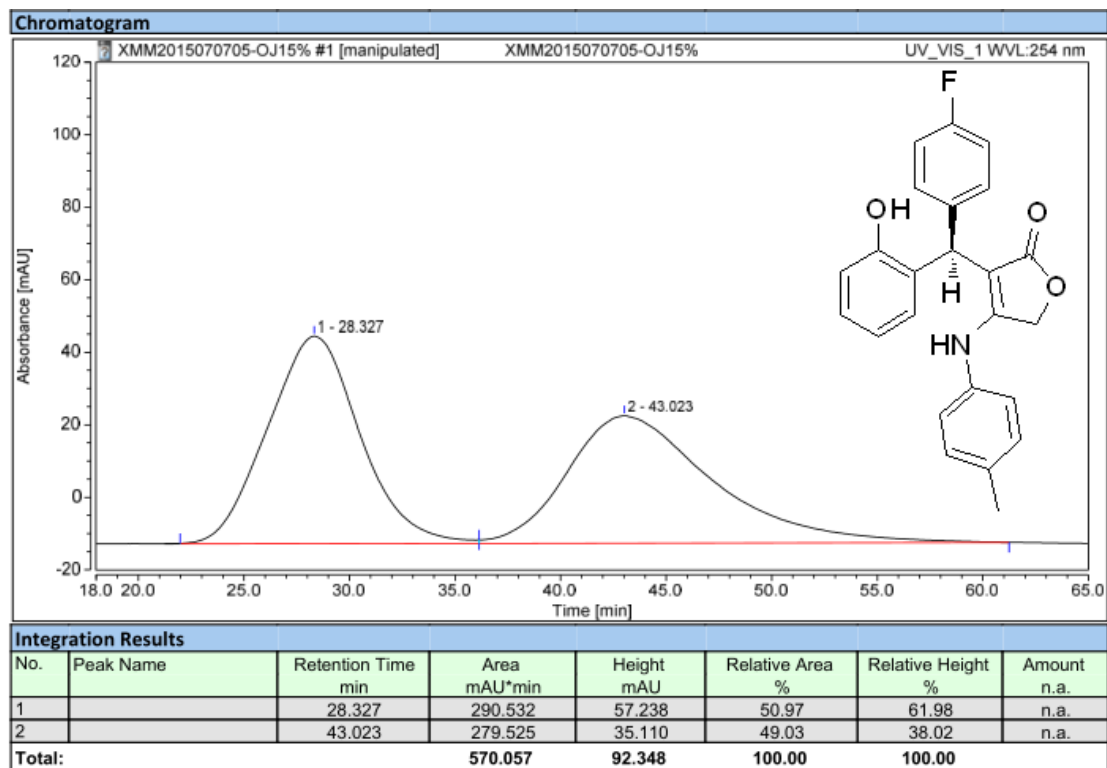


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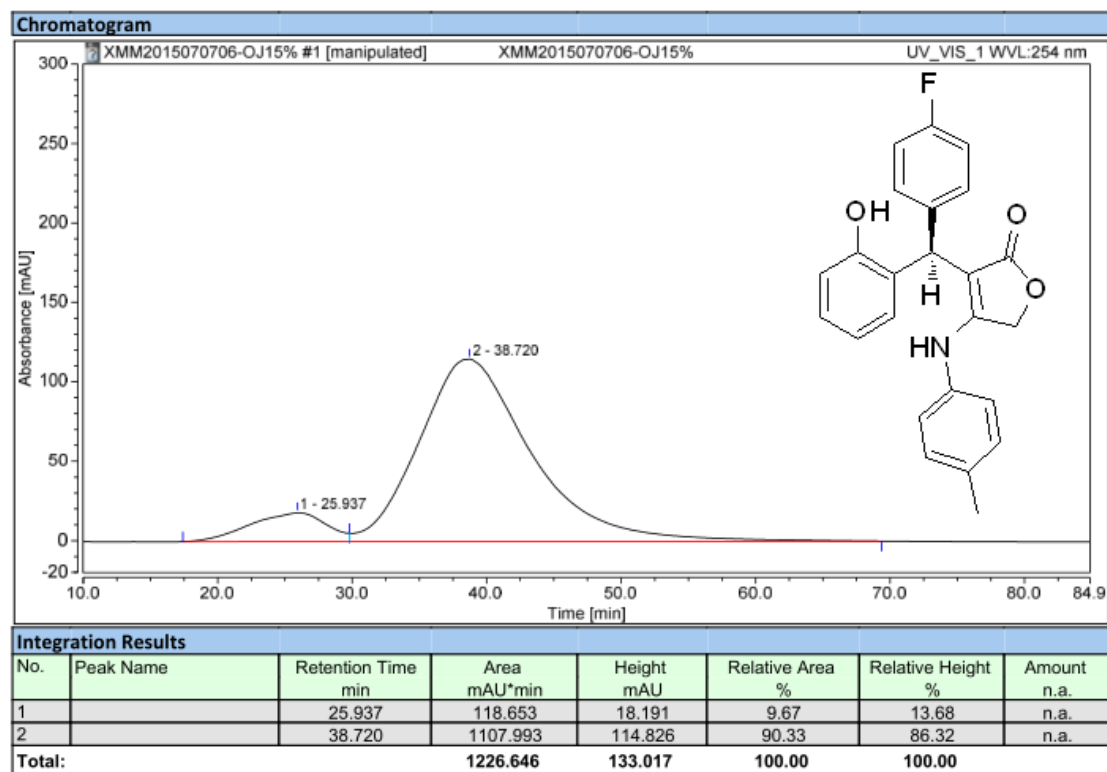


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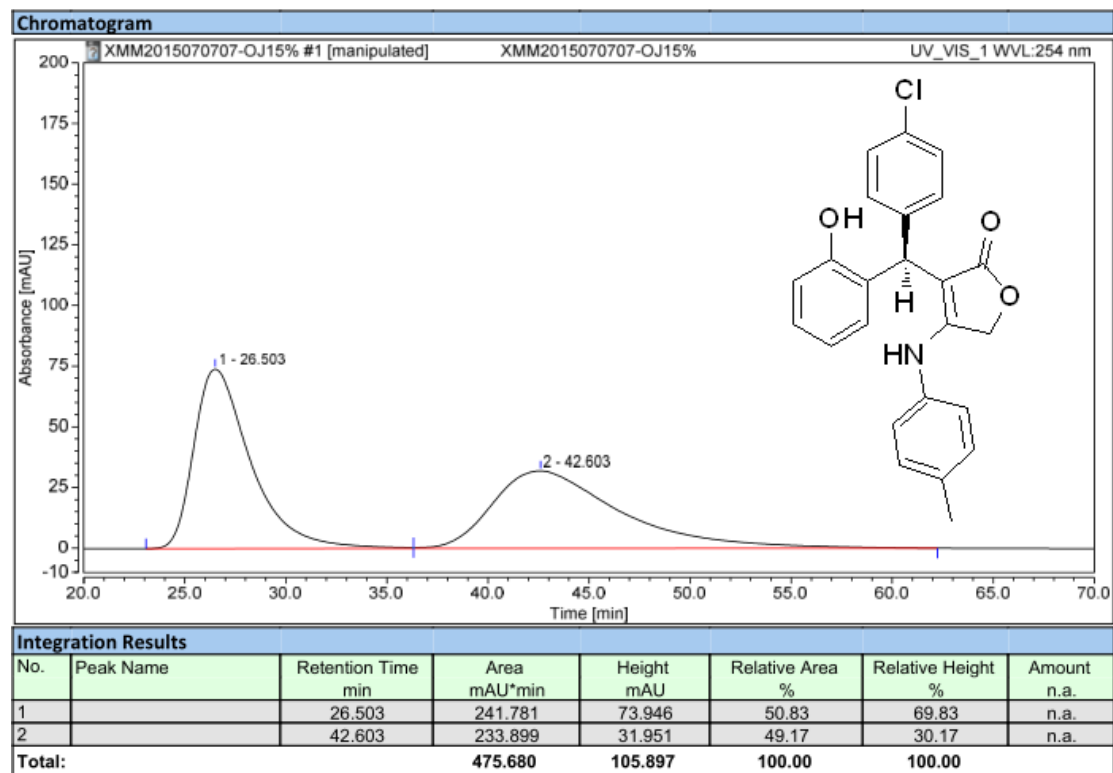


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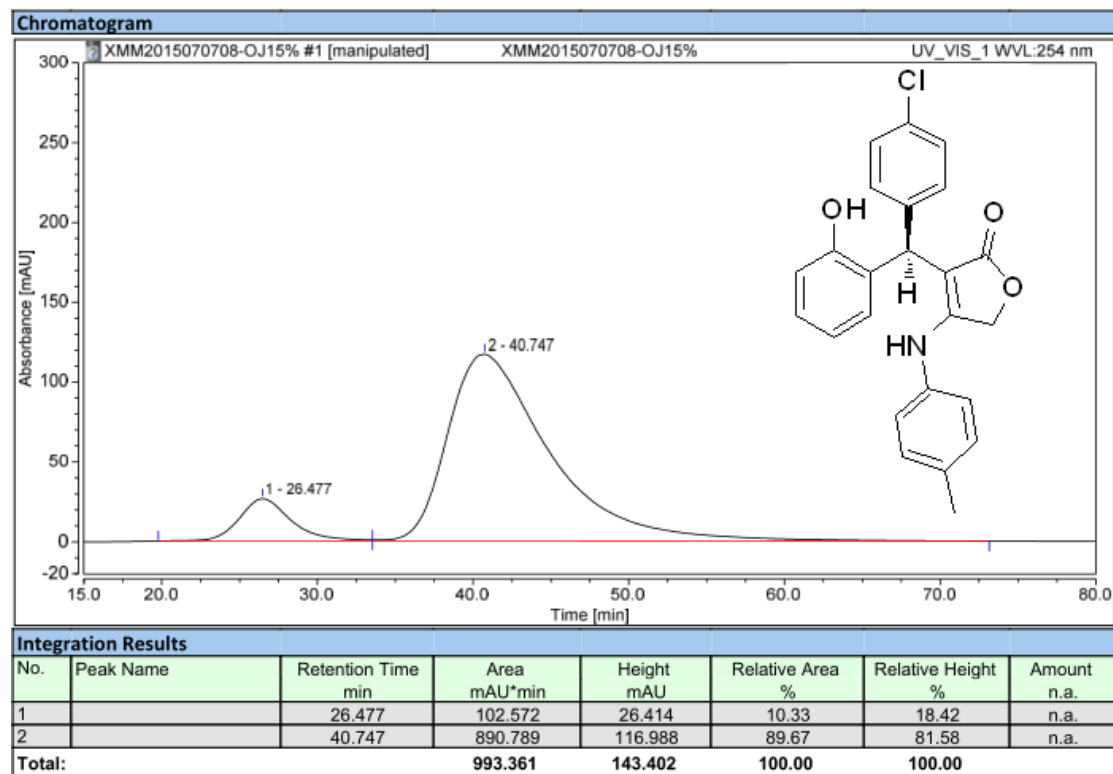


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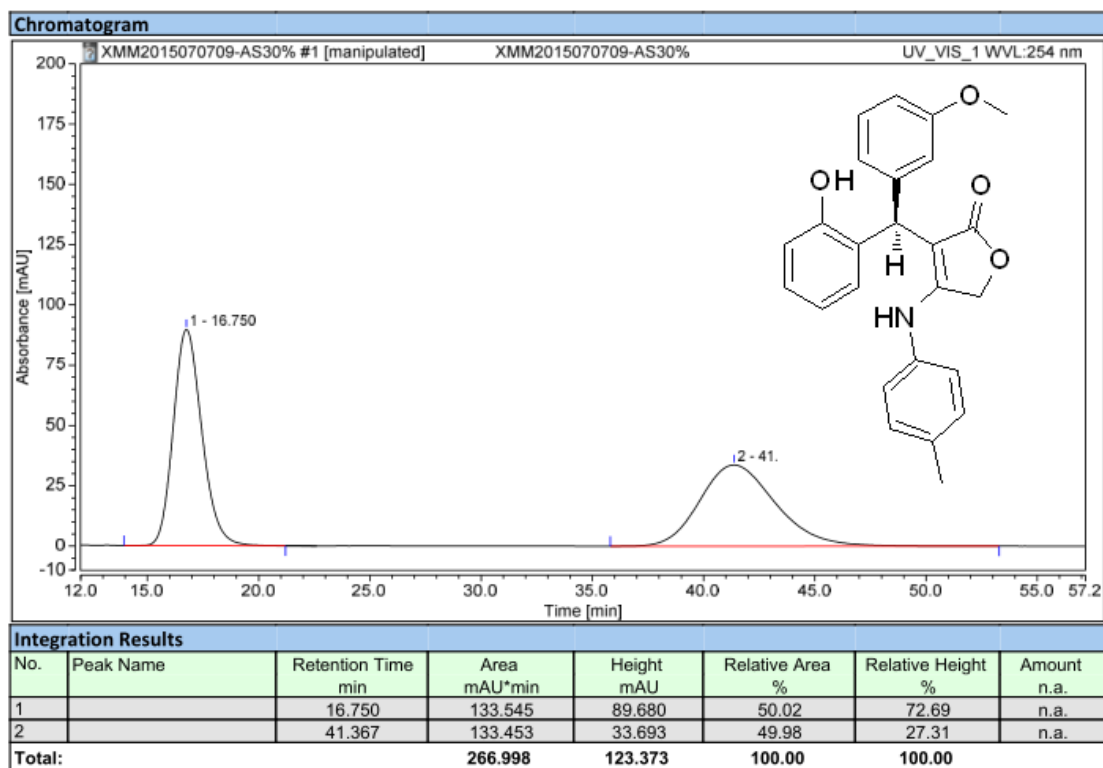


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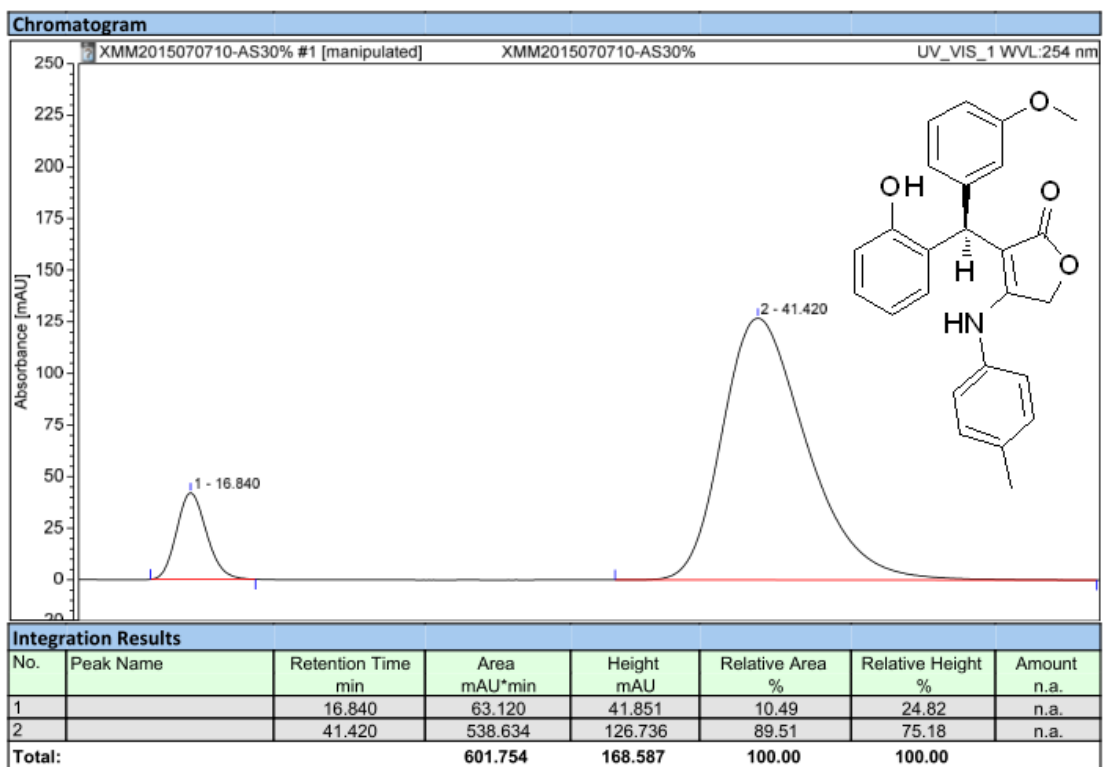


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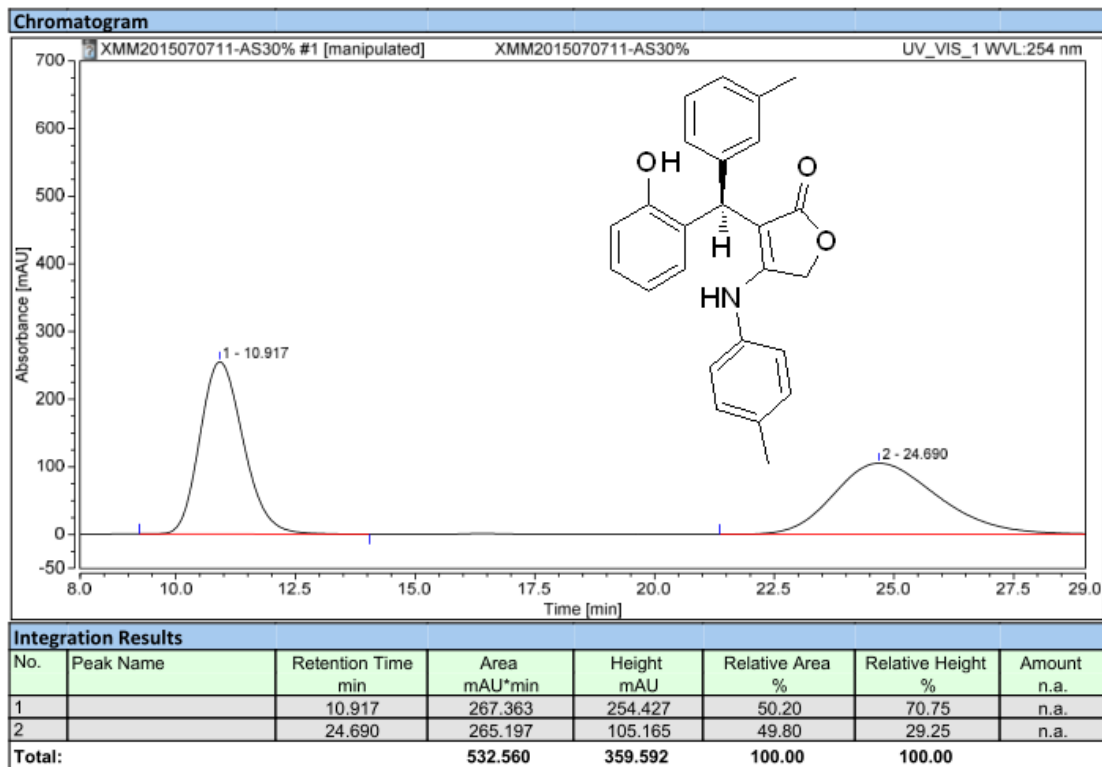


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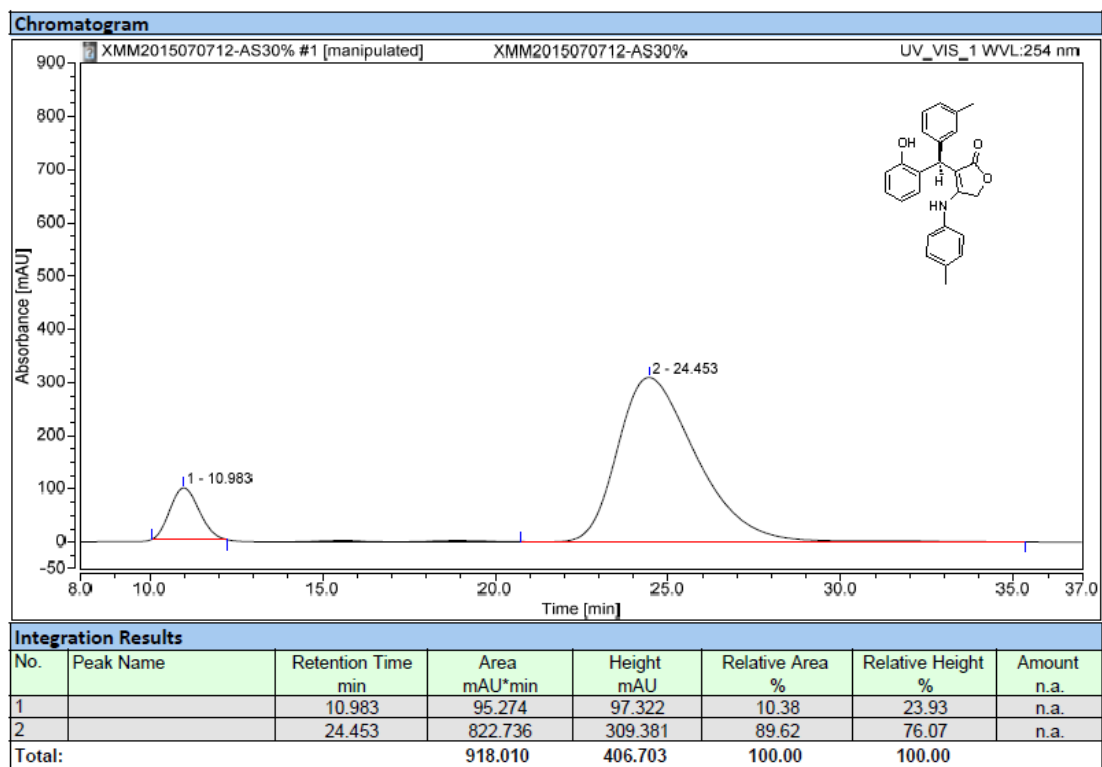


3na

Racemic:

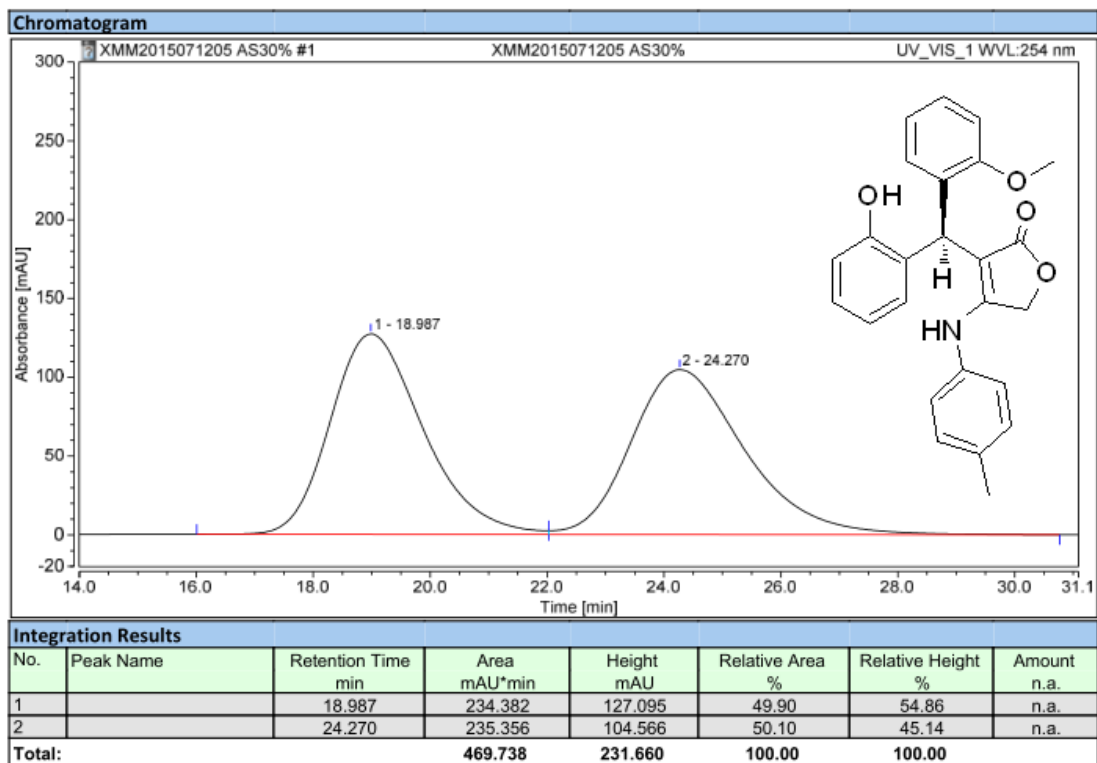


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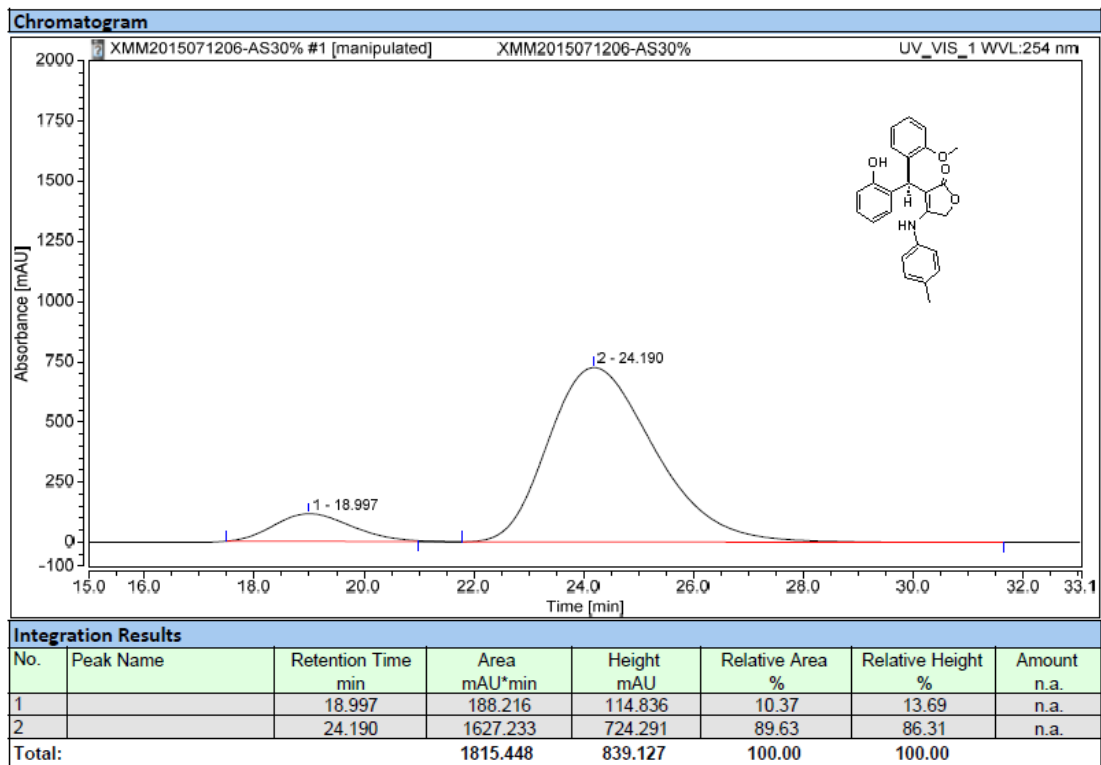


30a

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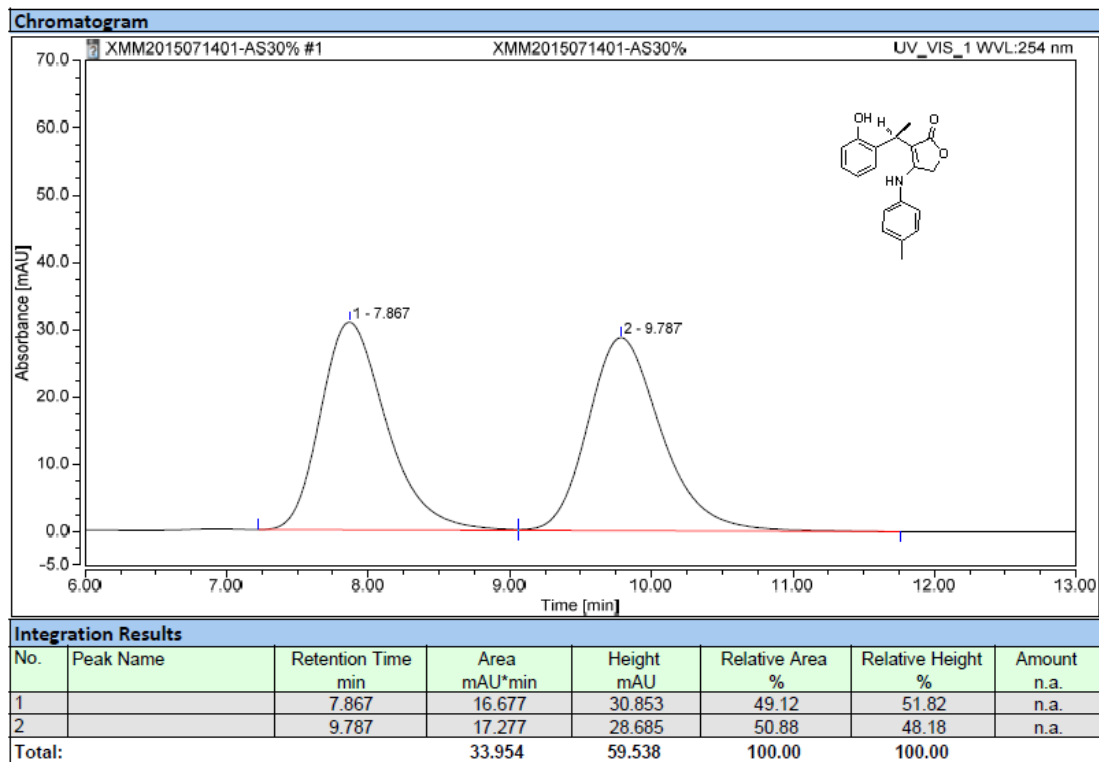


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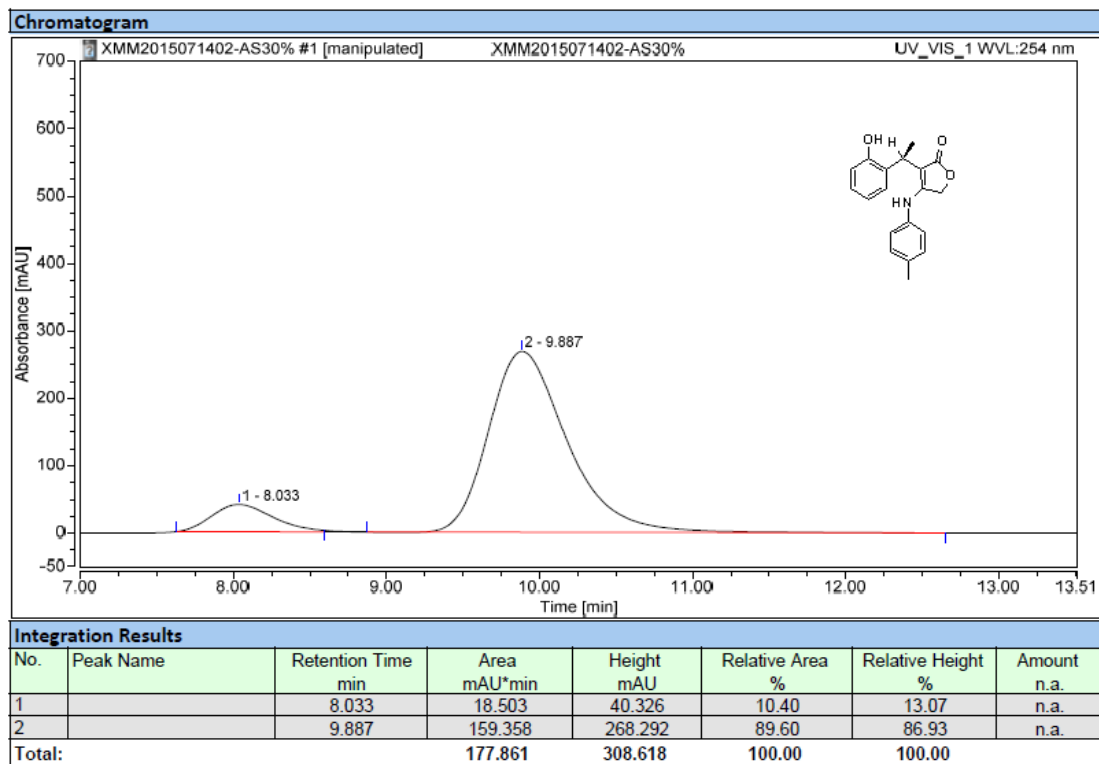


3pa

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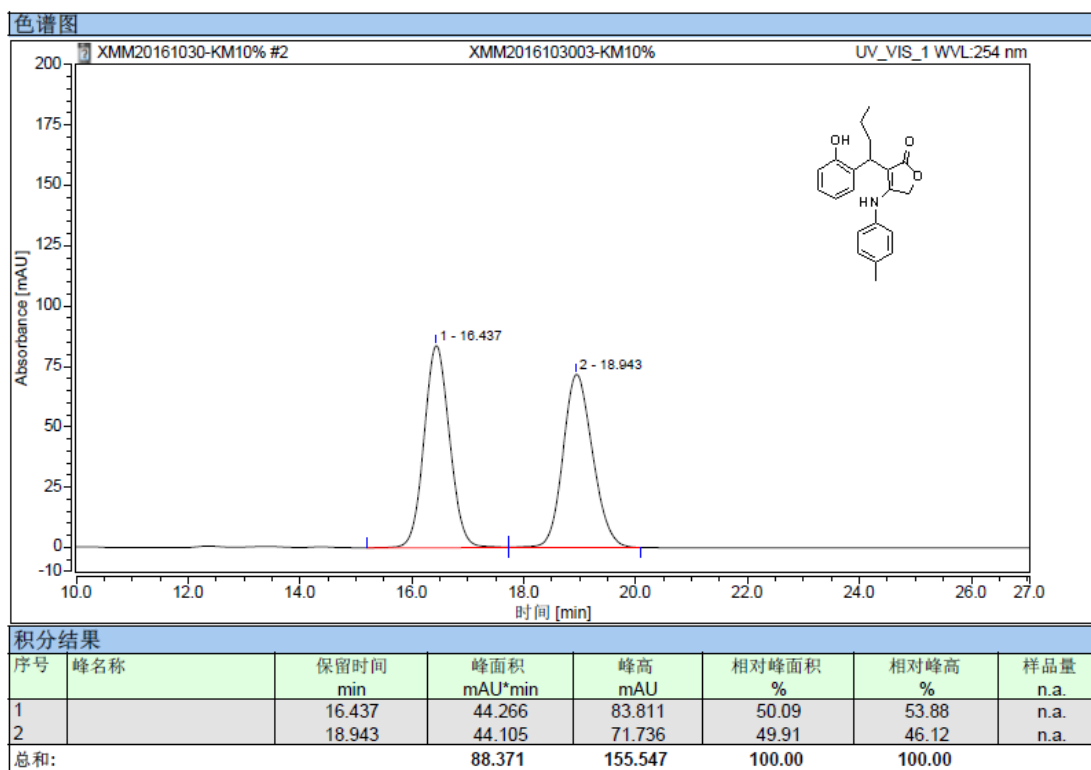


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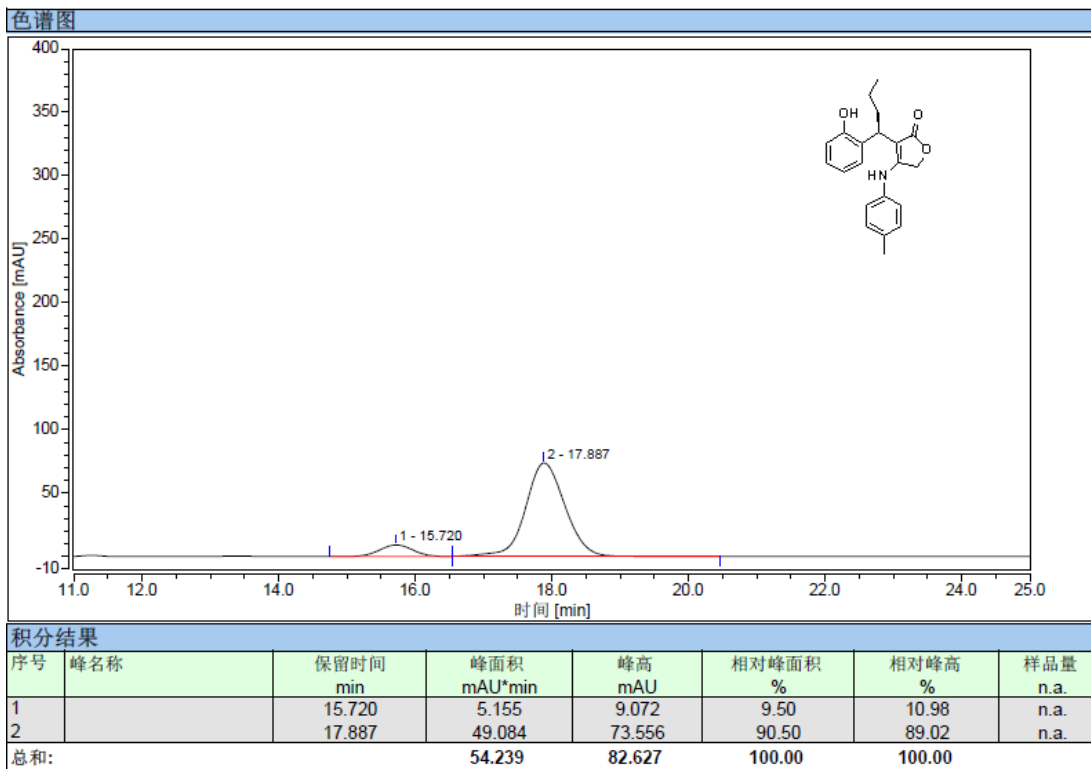


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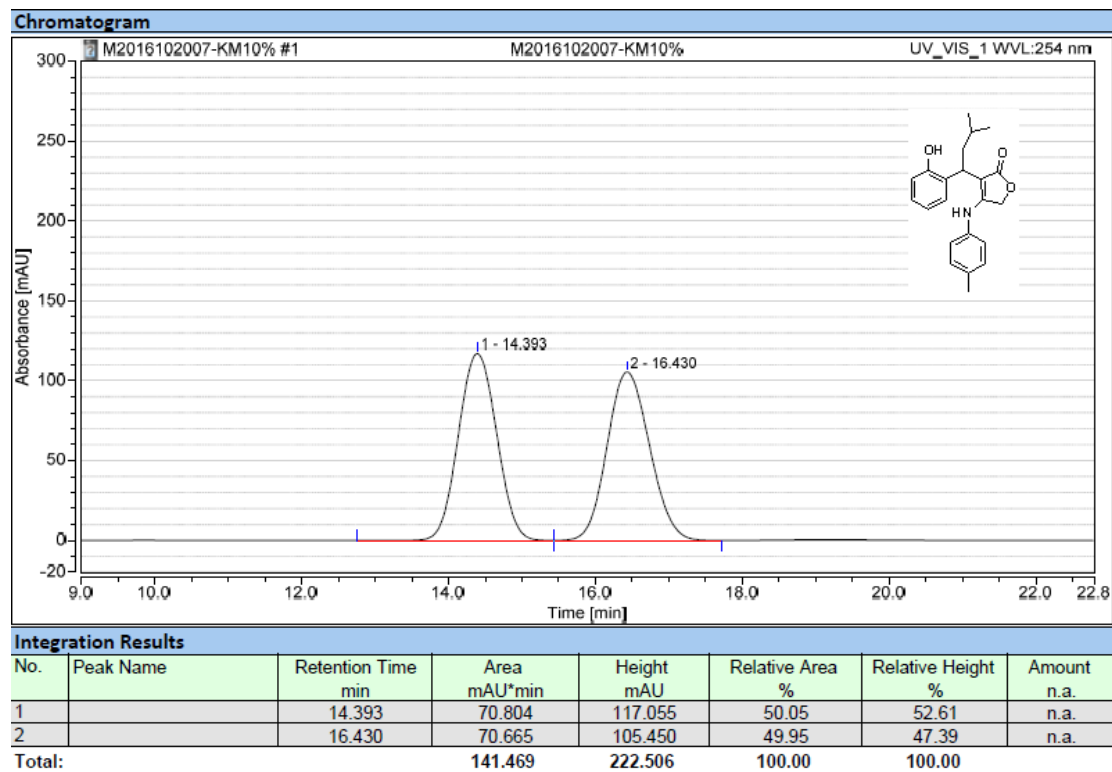


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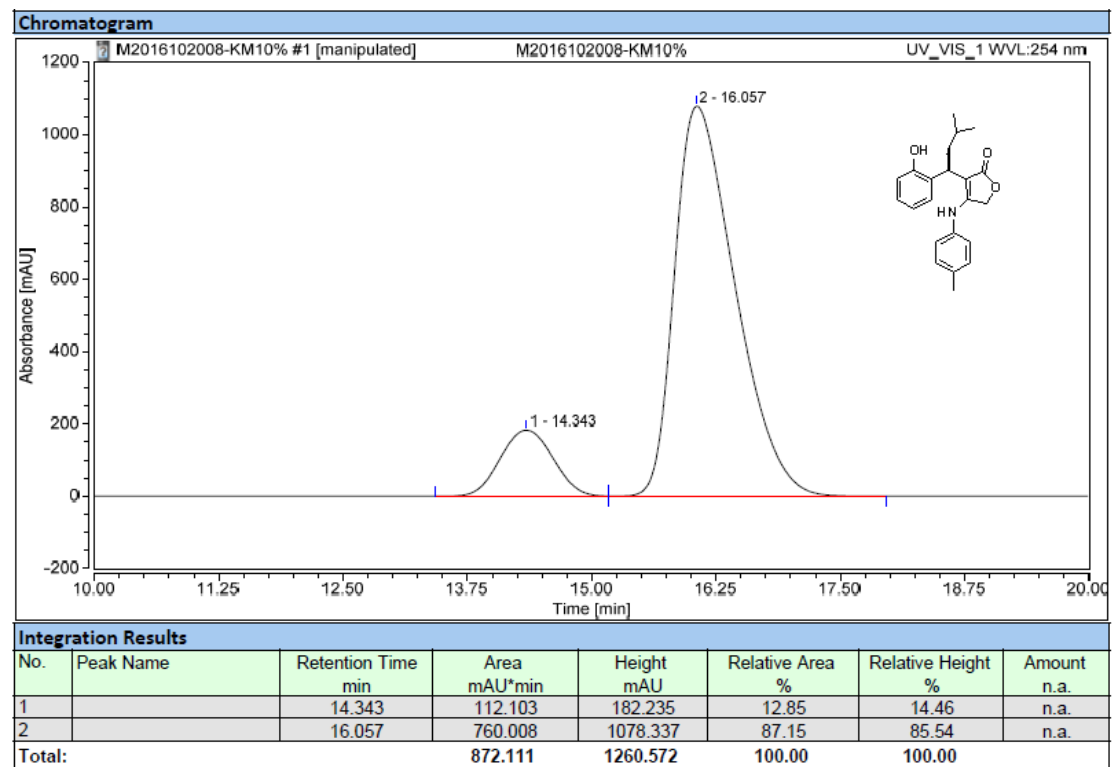


3ra

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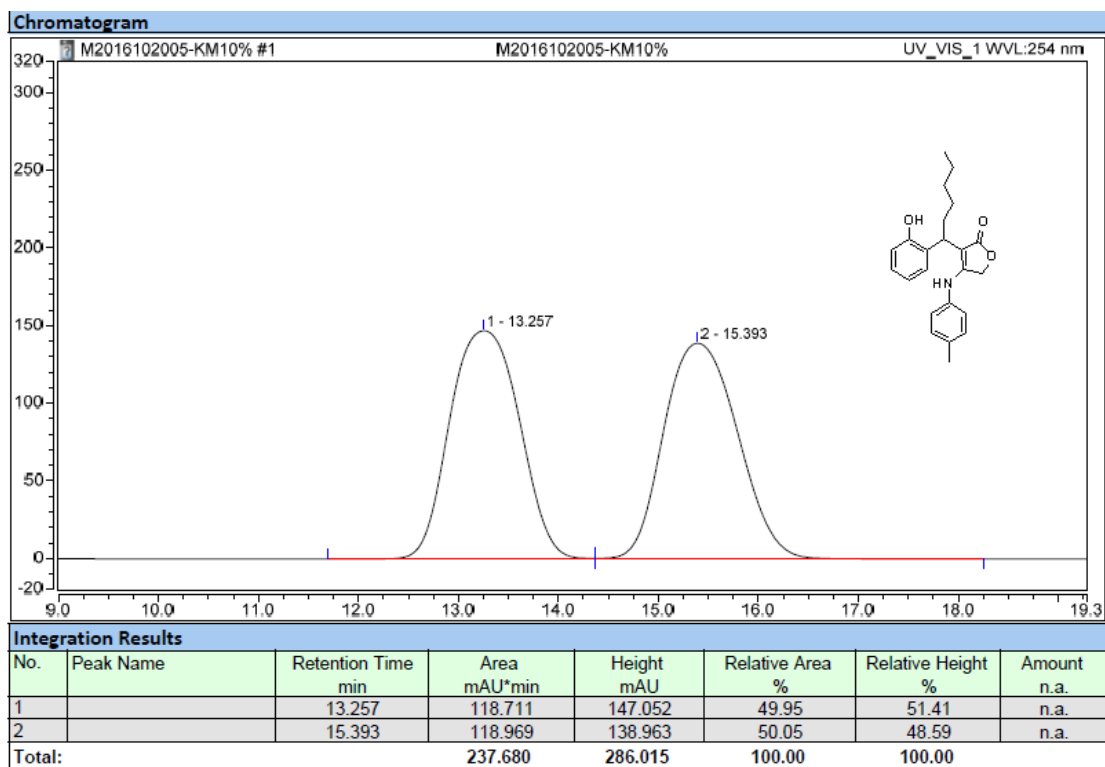


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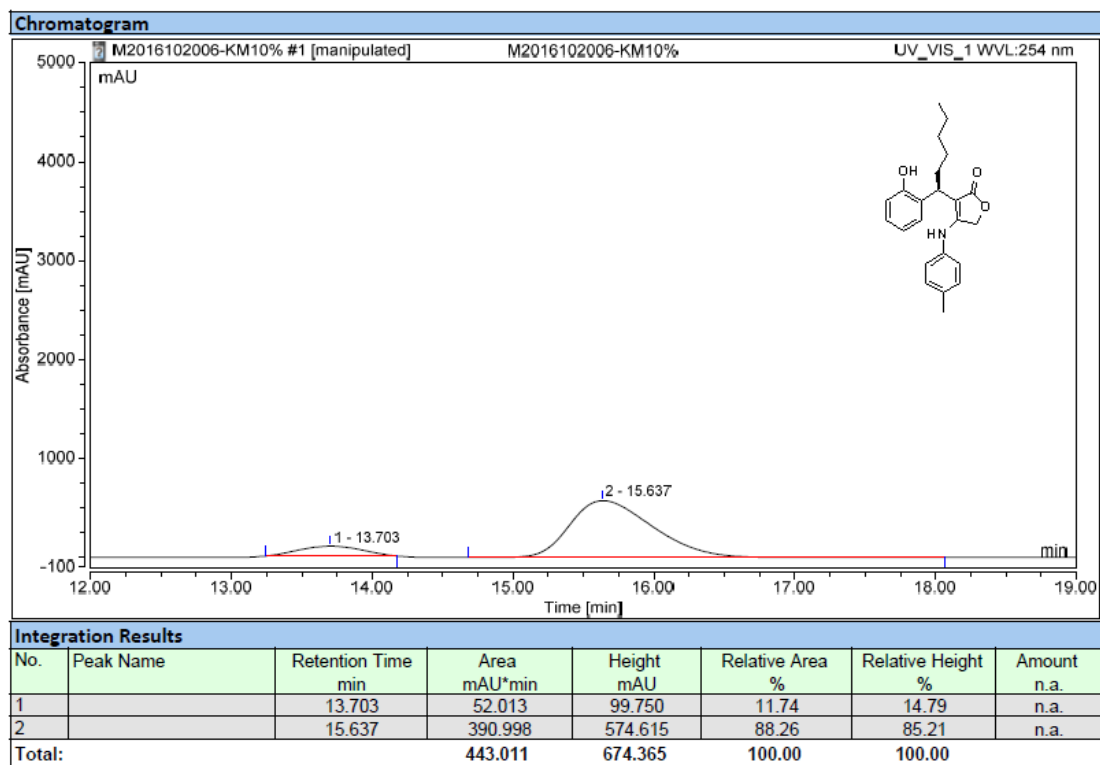


3sa

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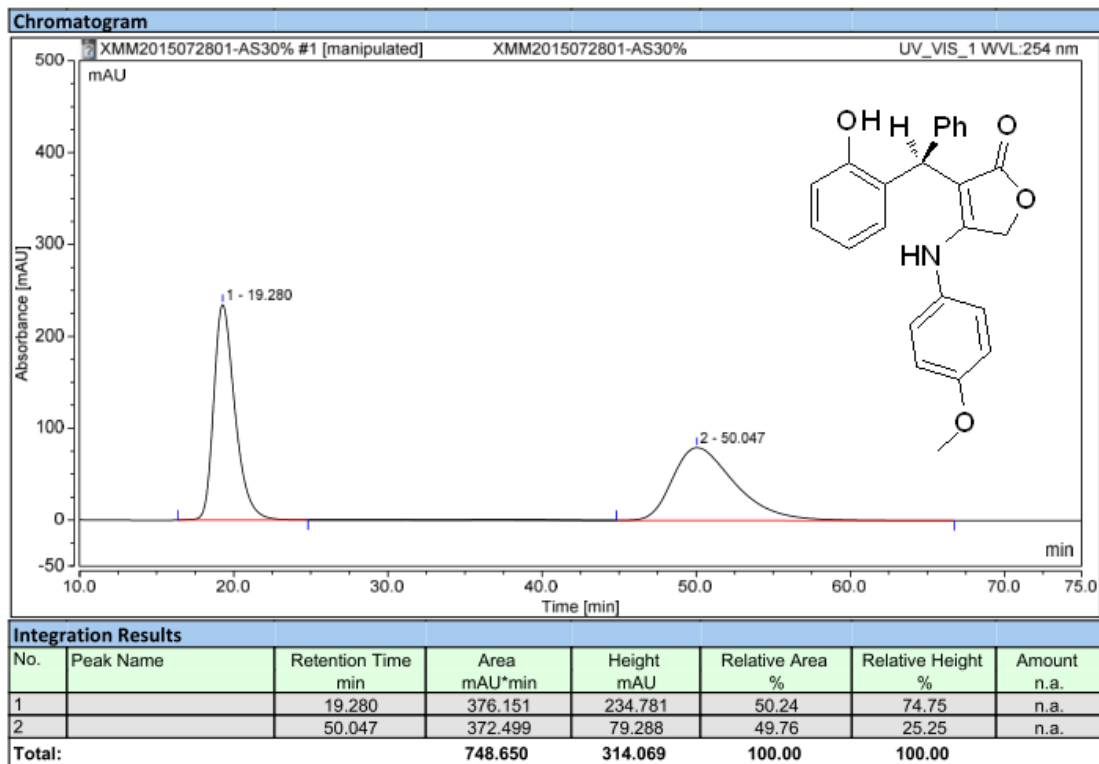


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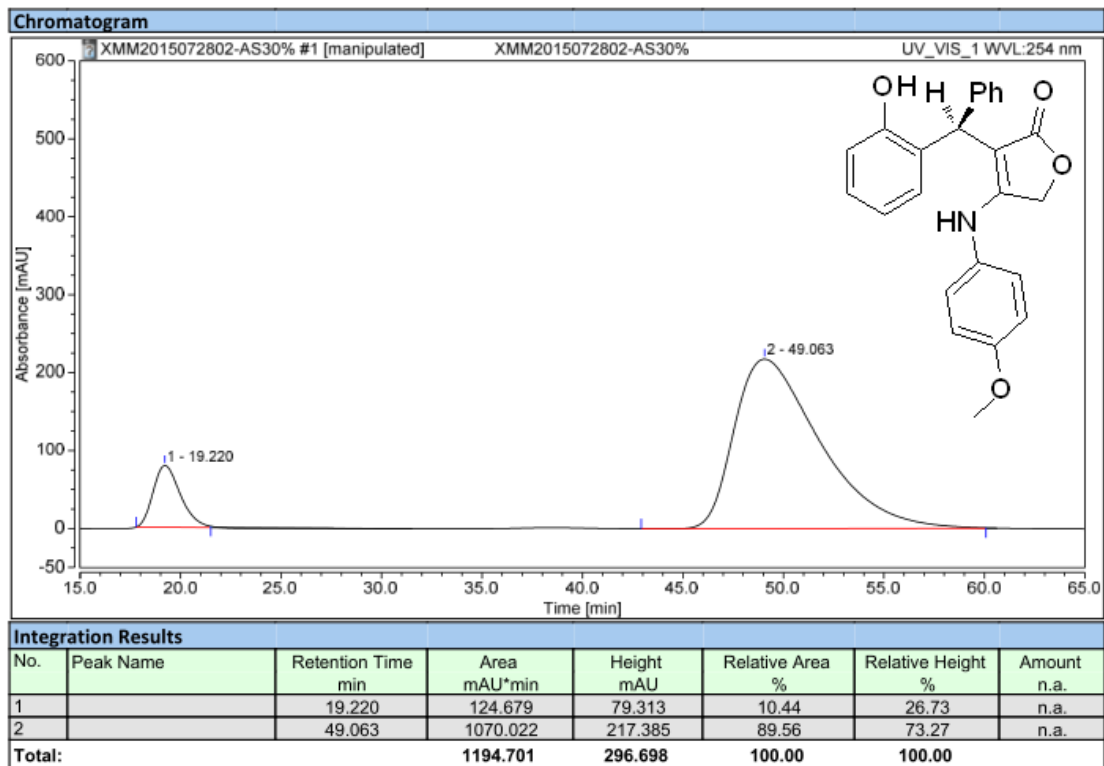


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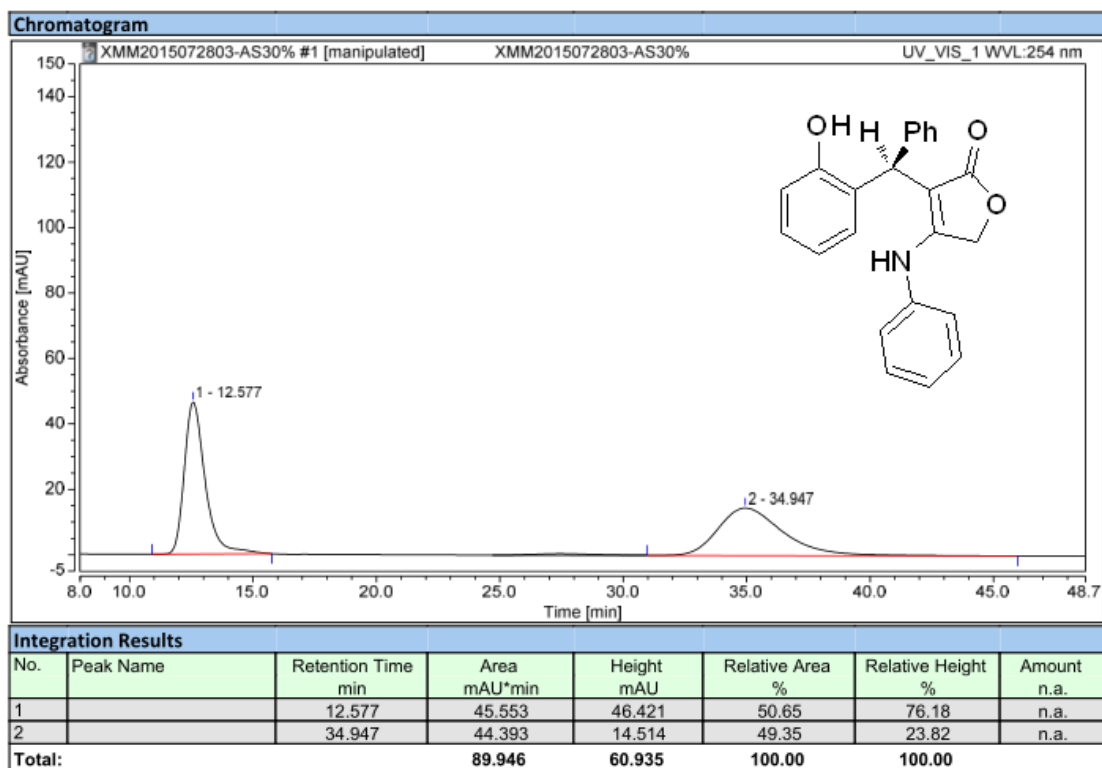


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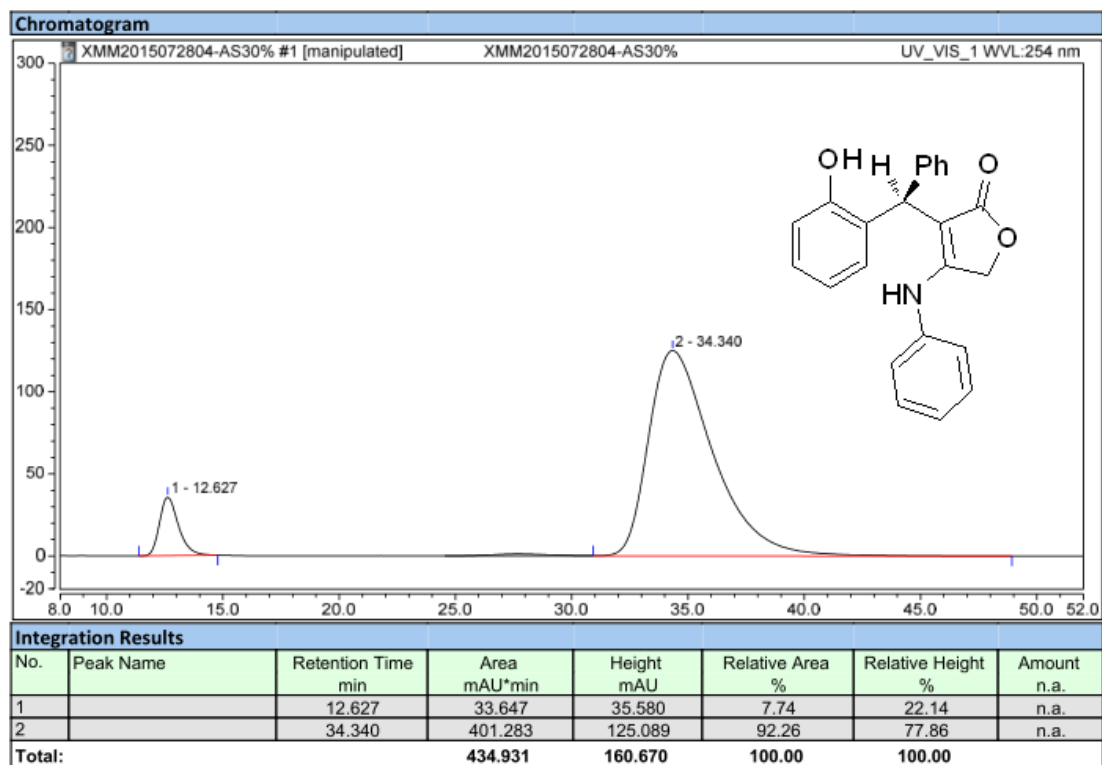


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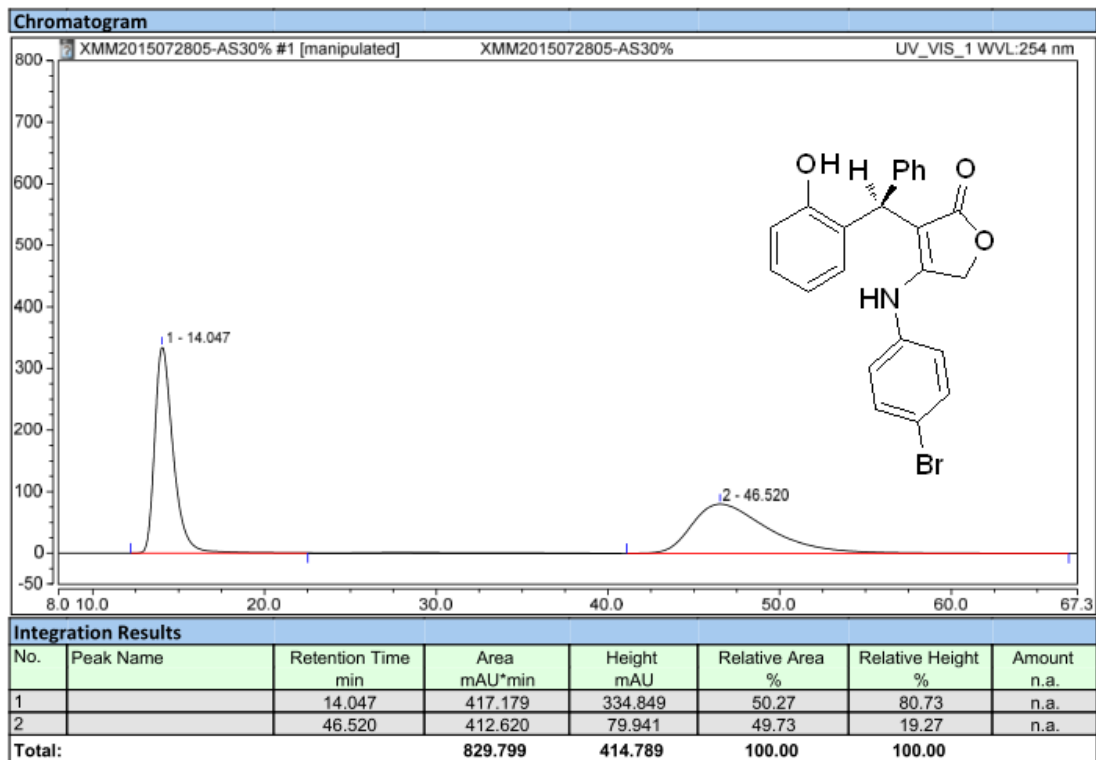


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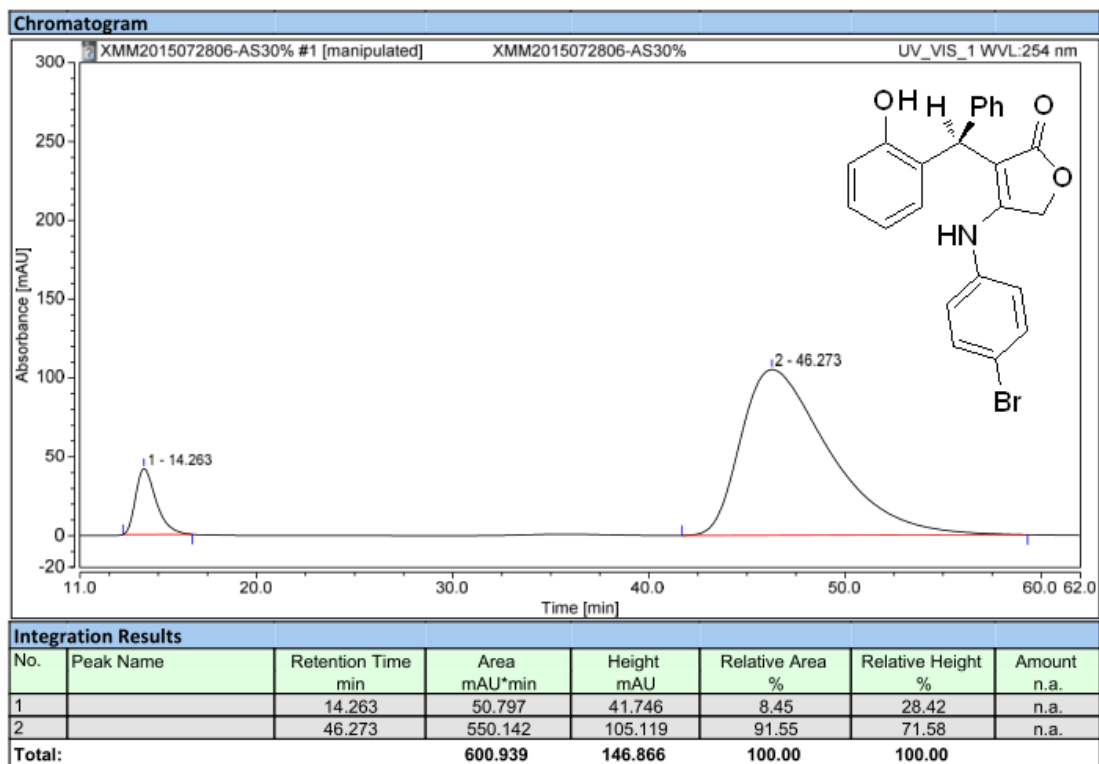


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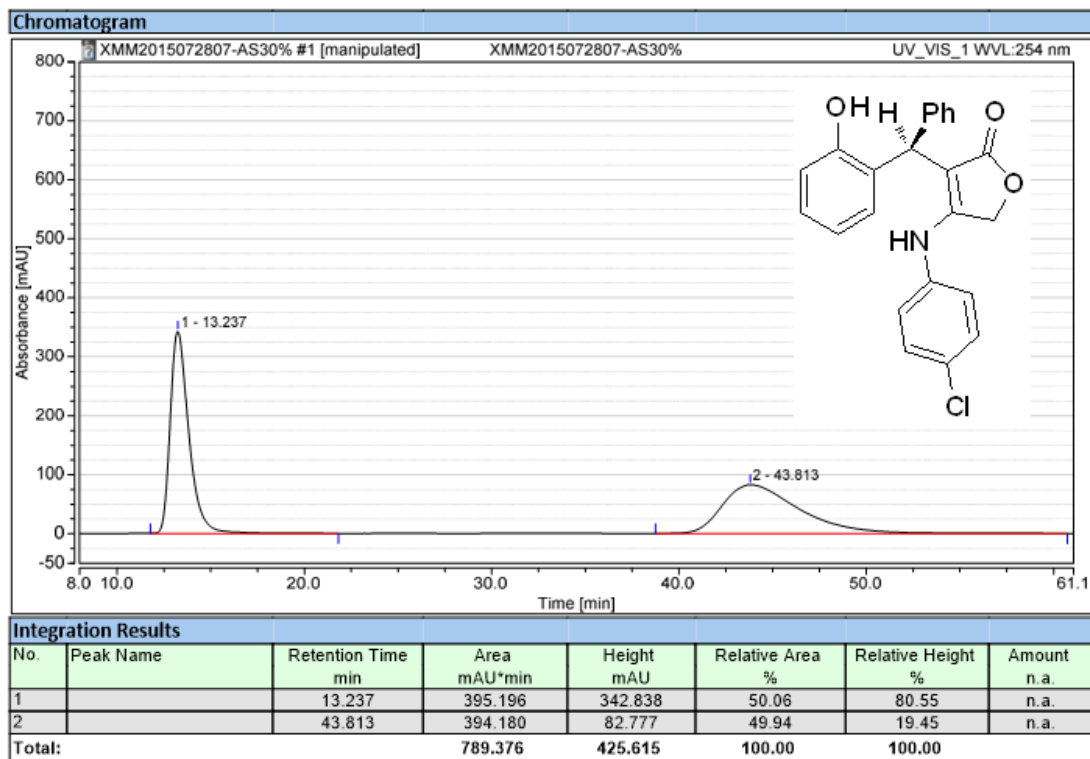


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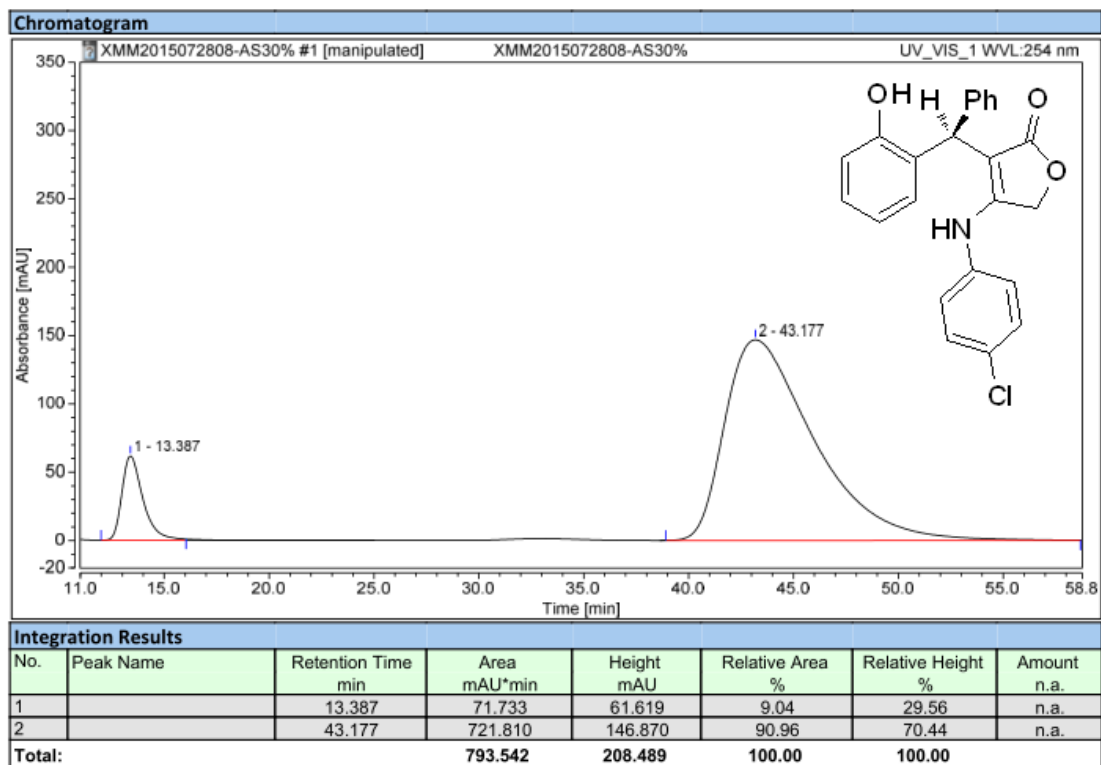


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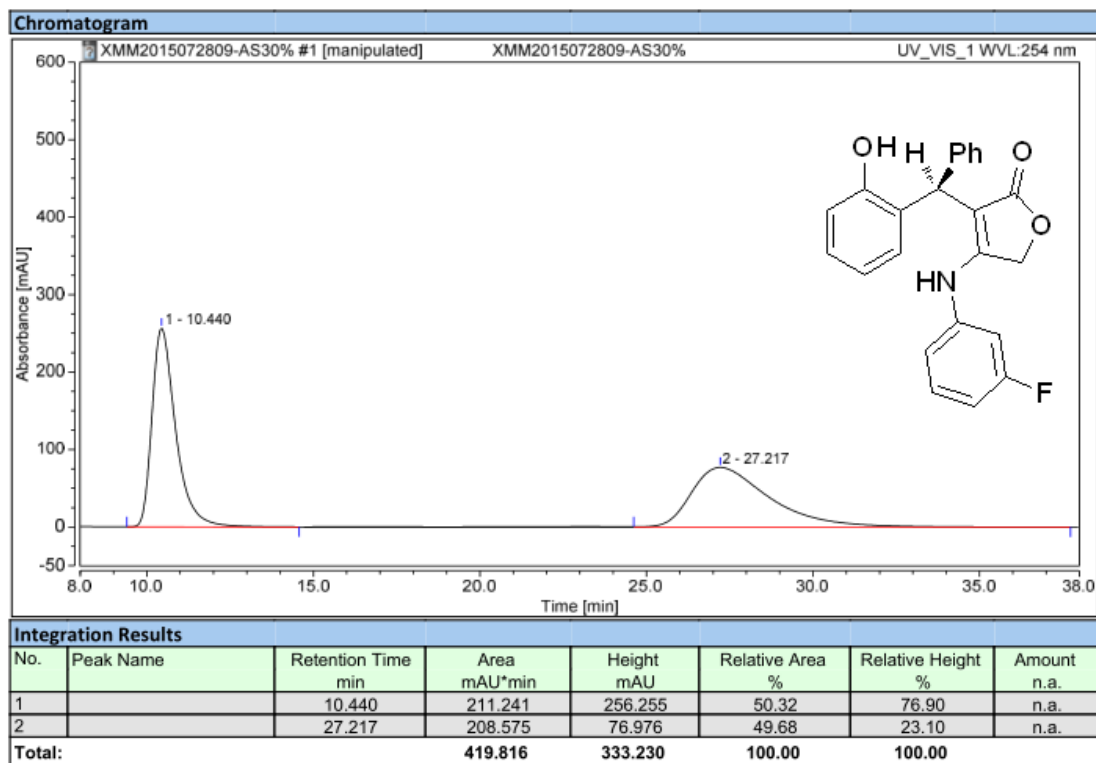


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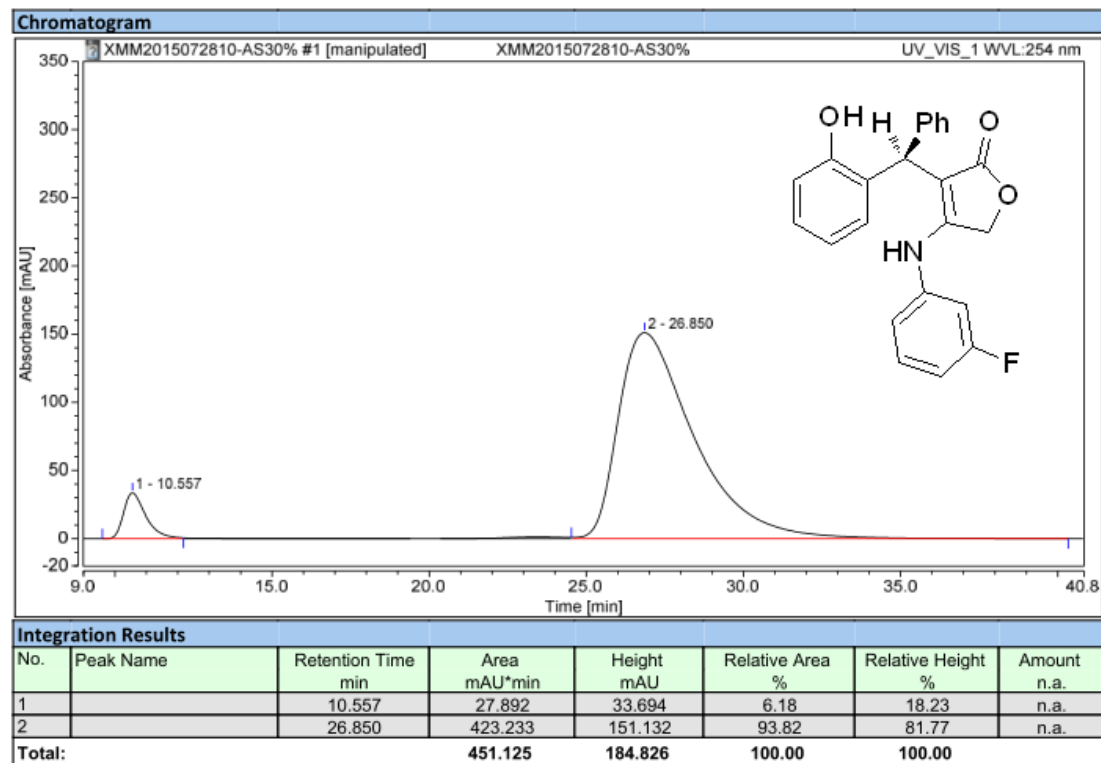


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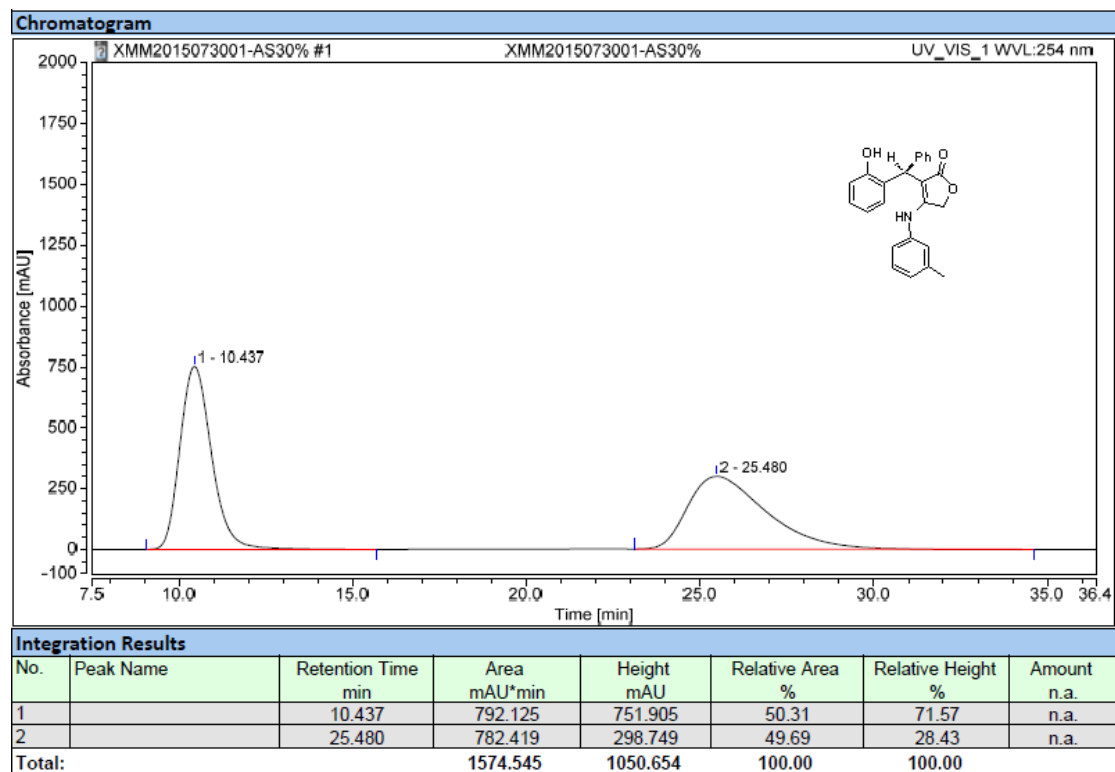


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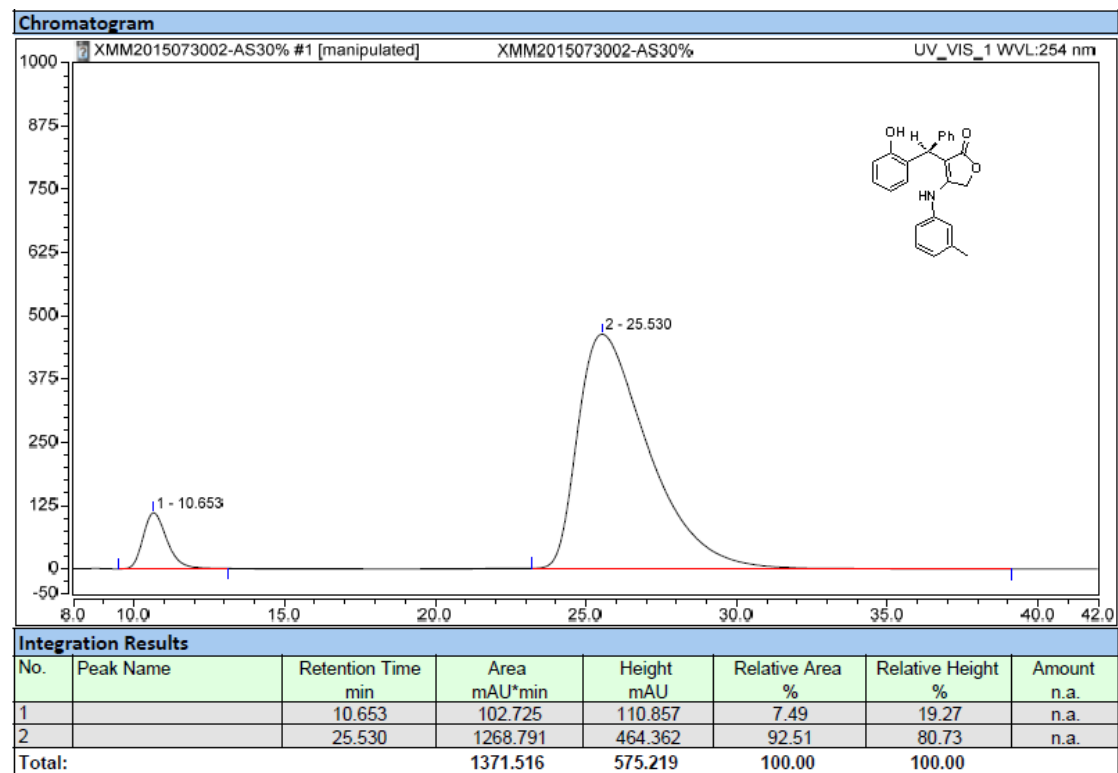


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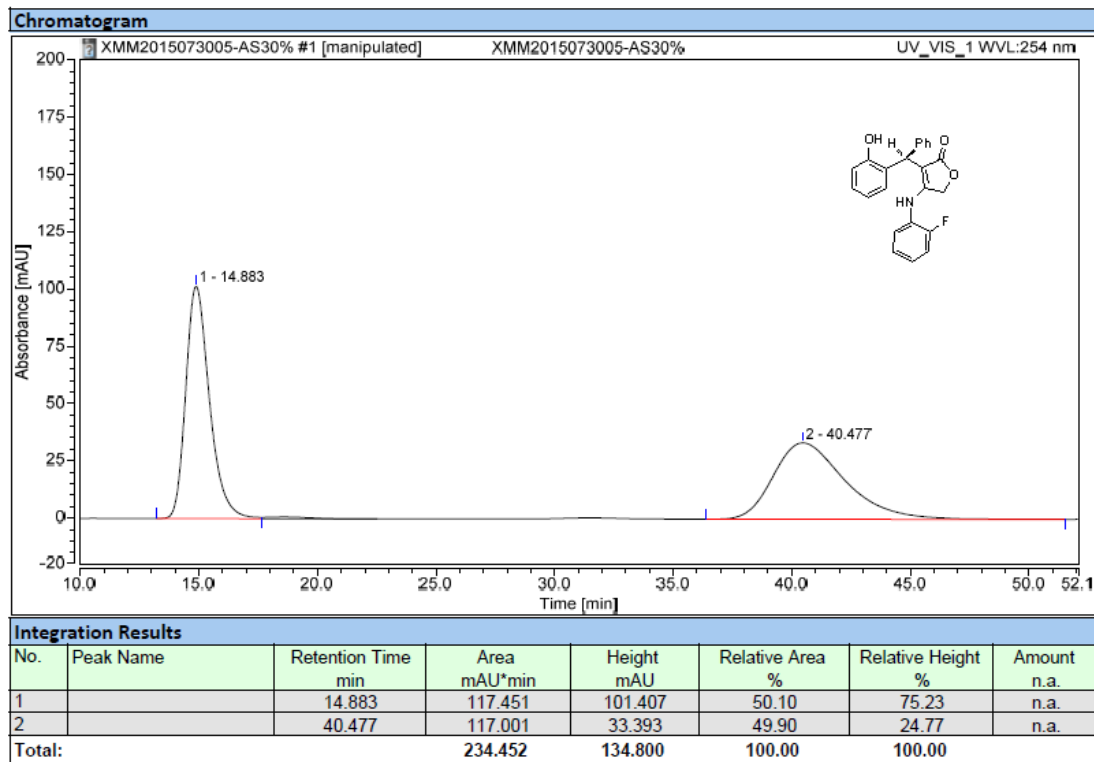


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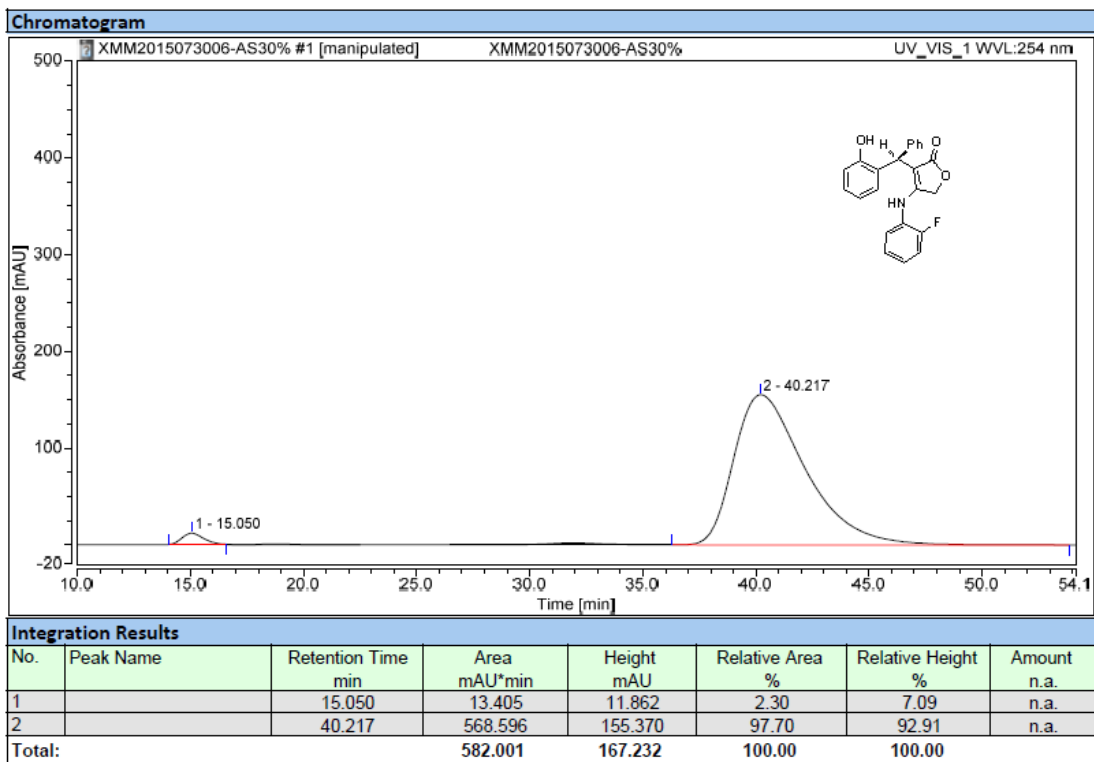


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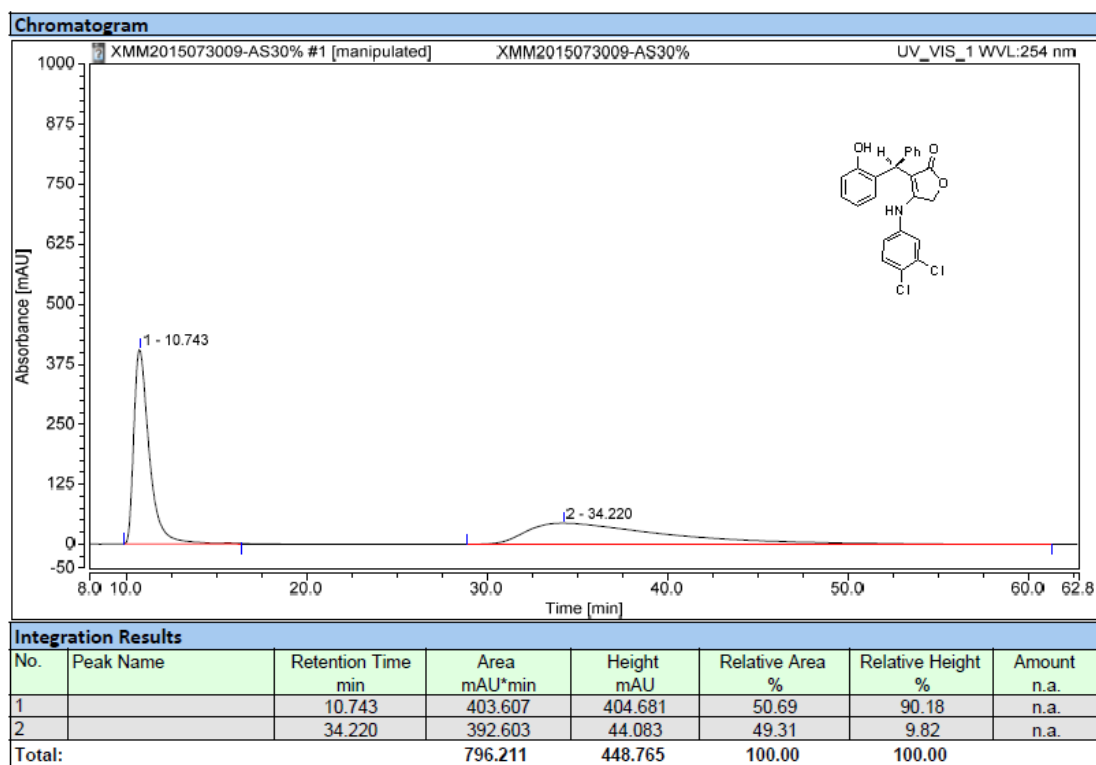


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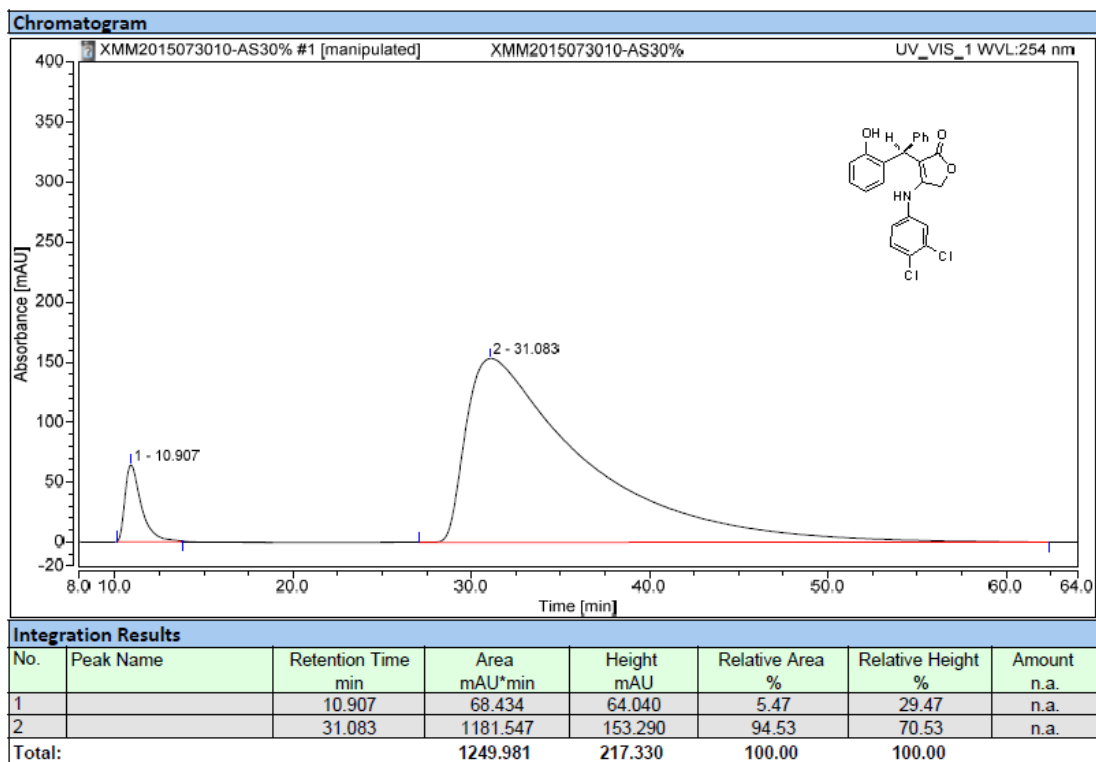


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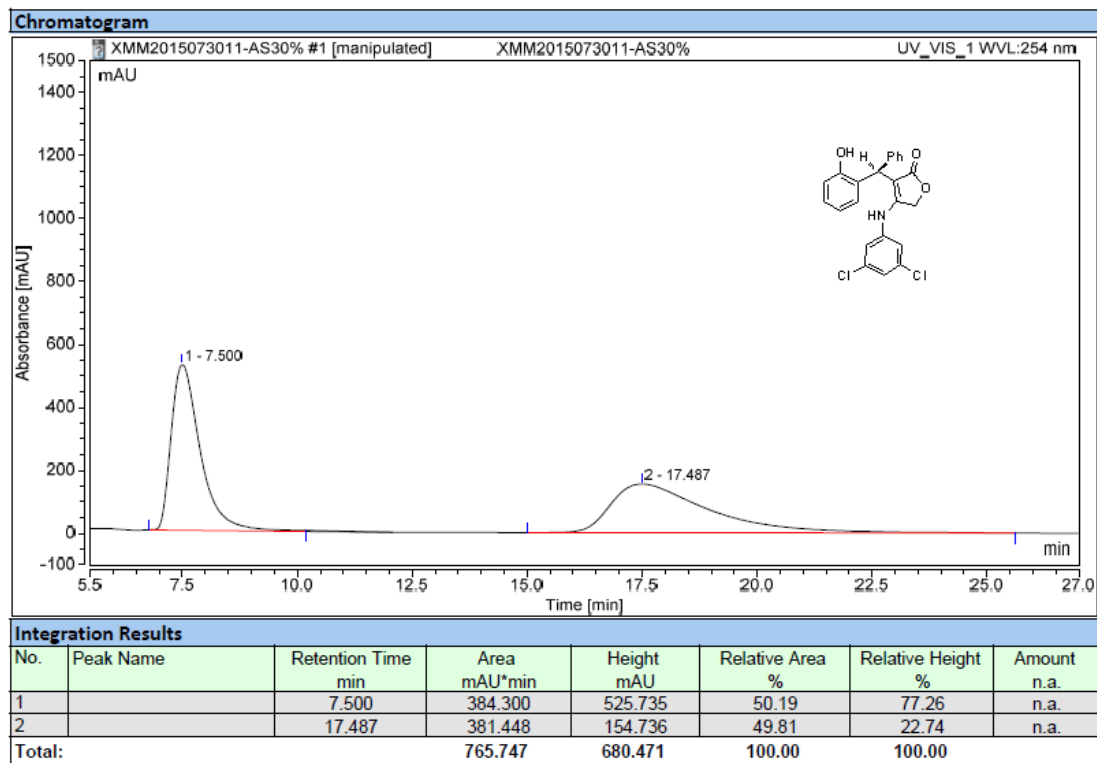


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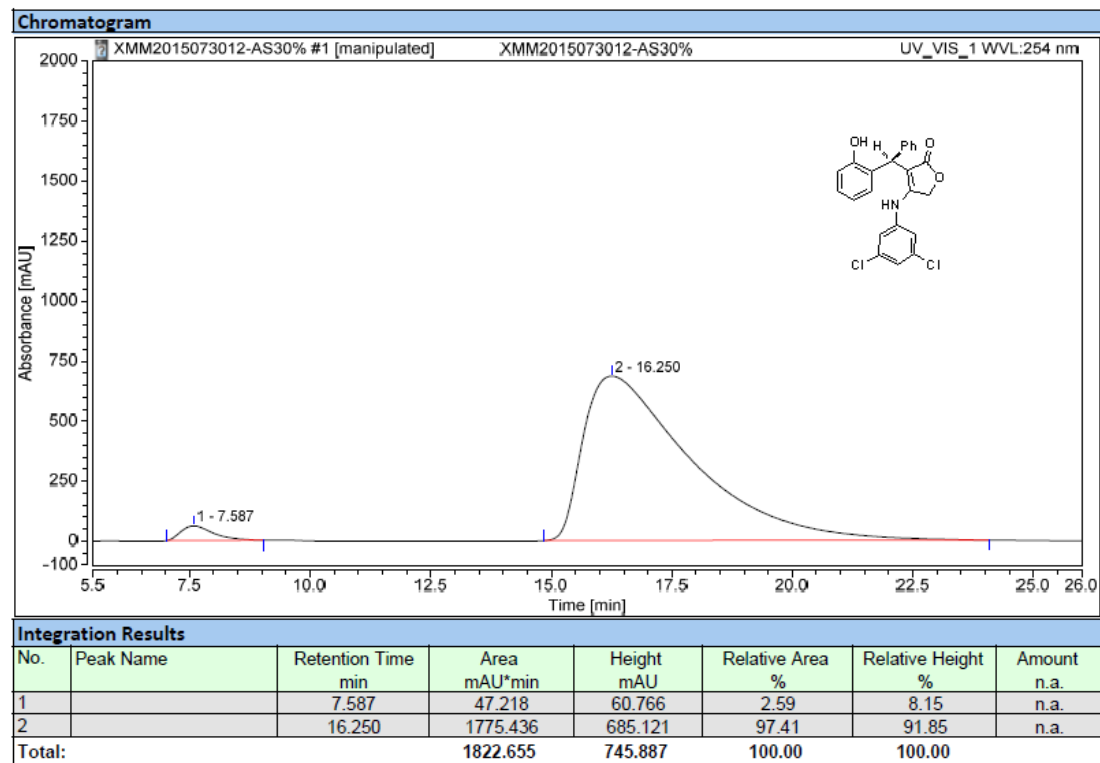


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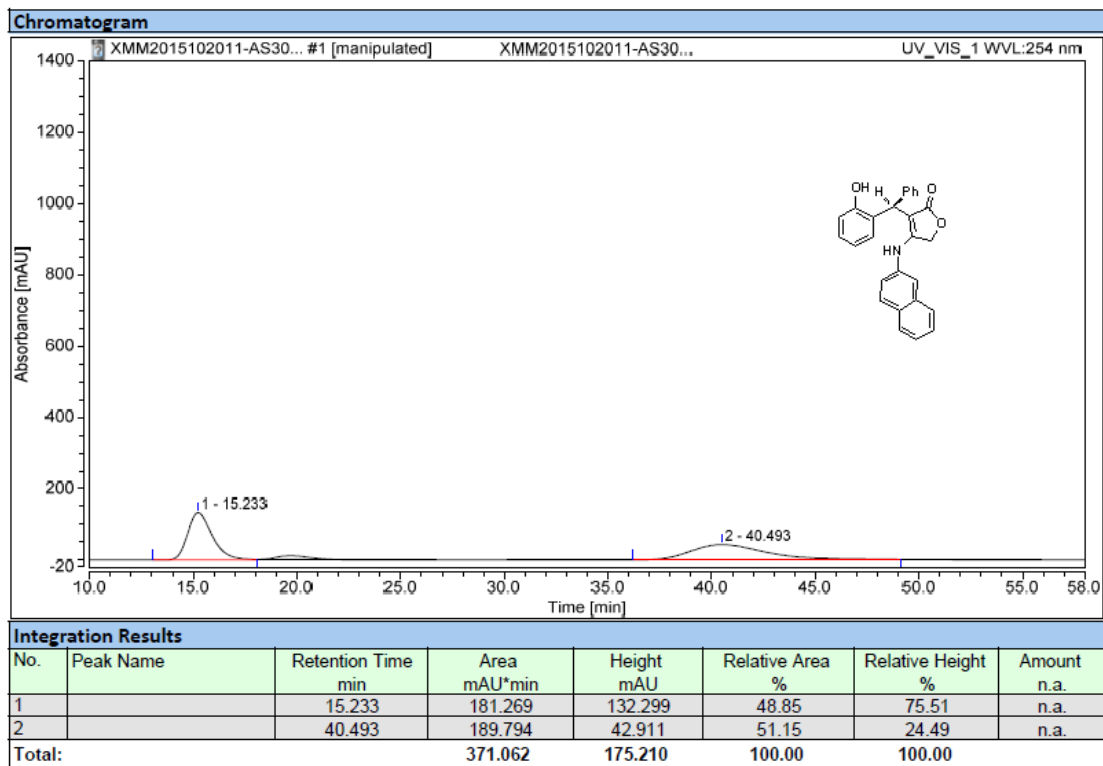


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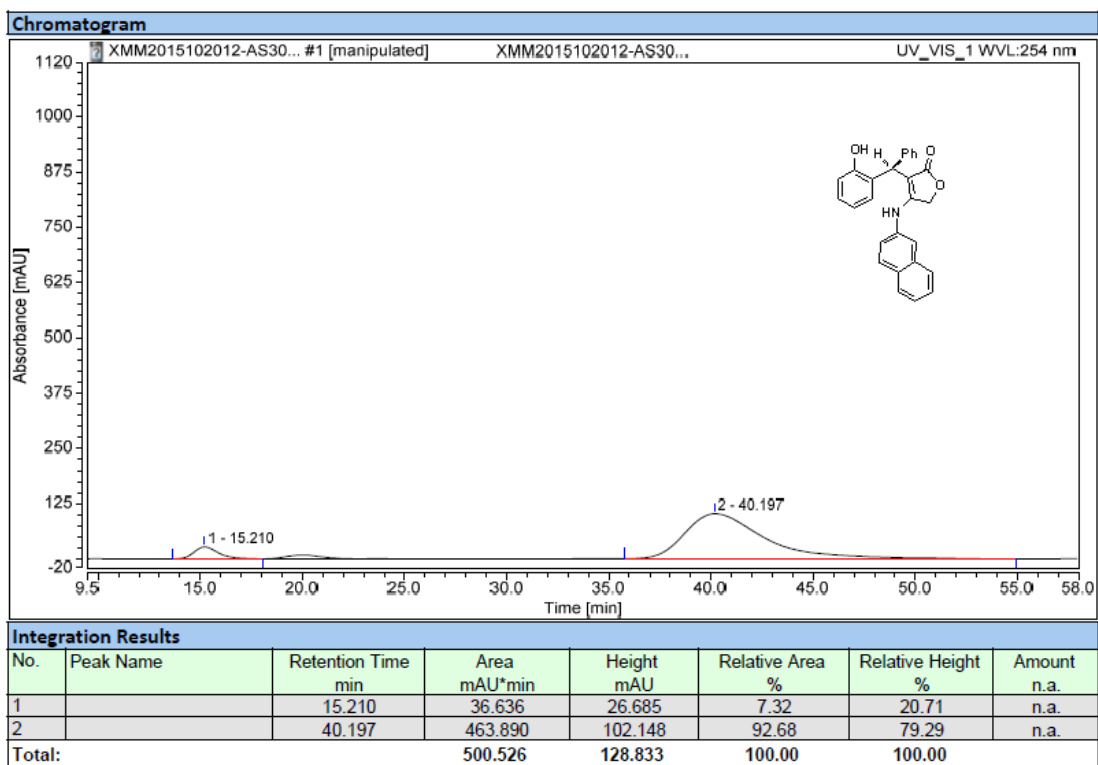


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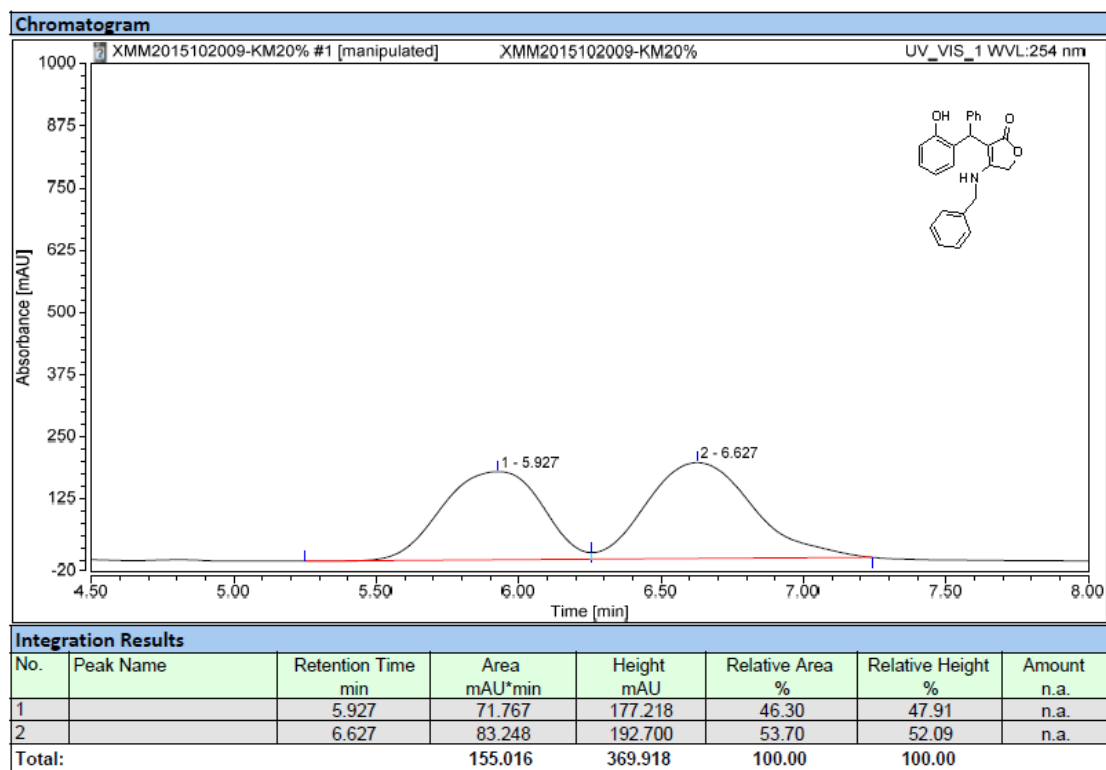


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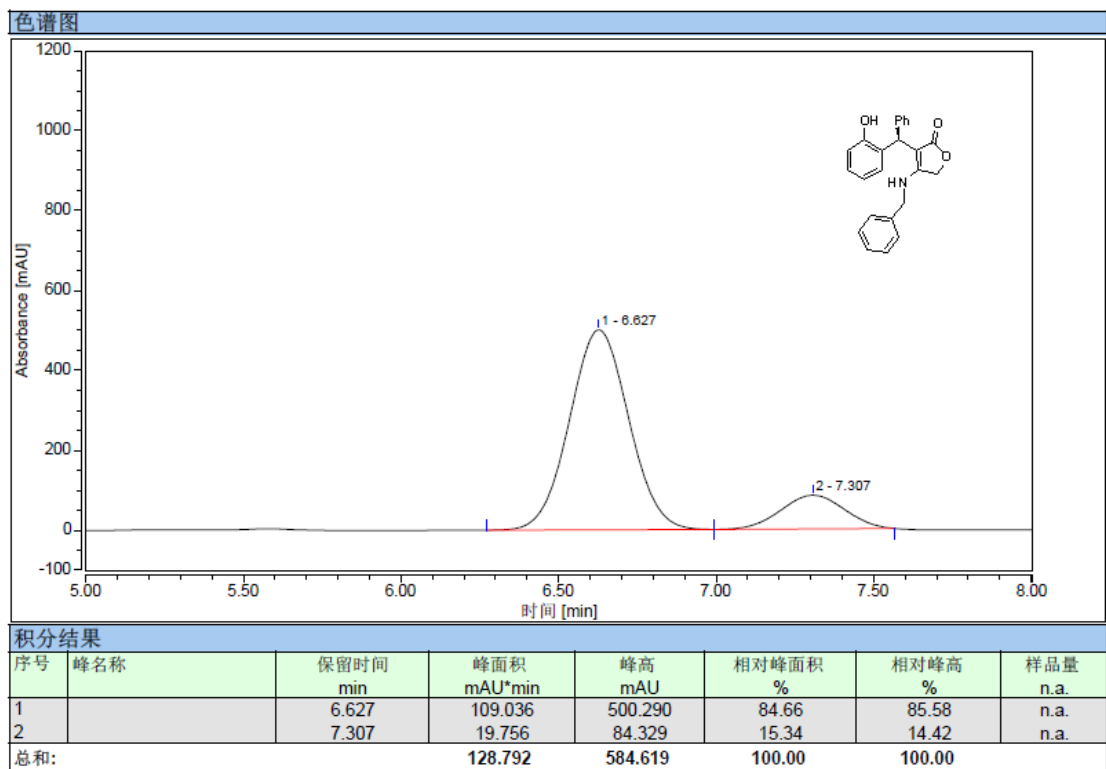


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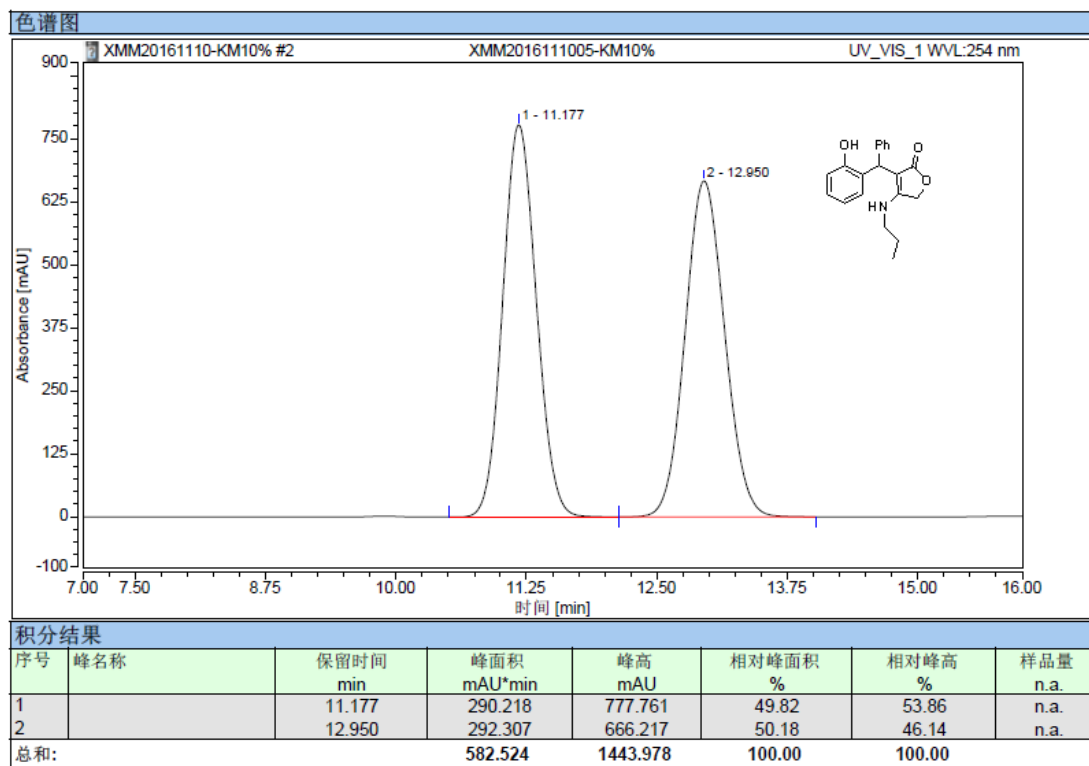


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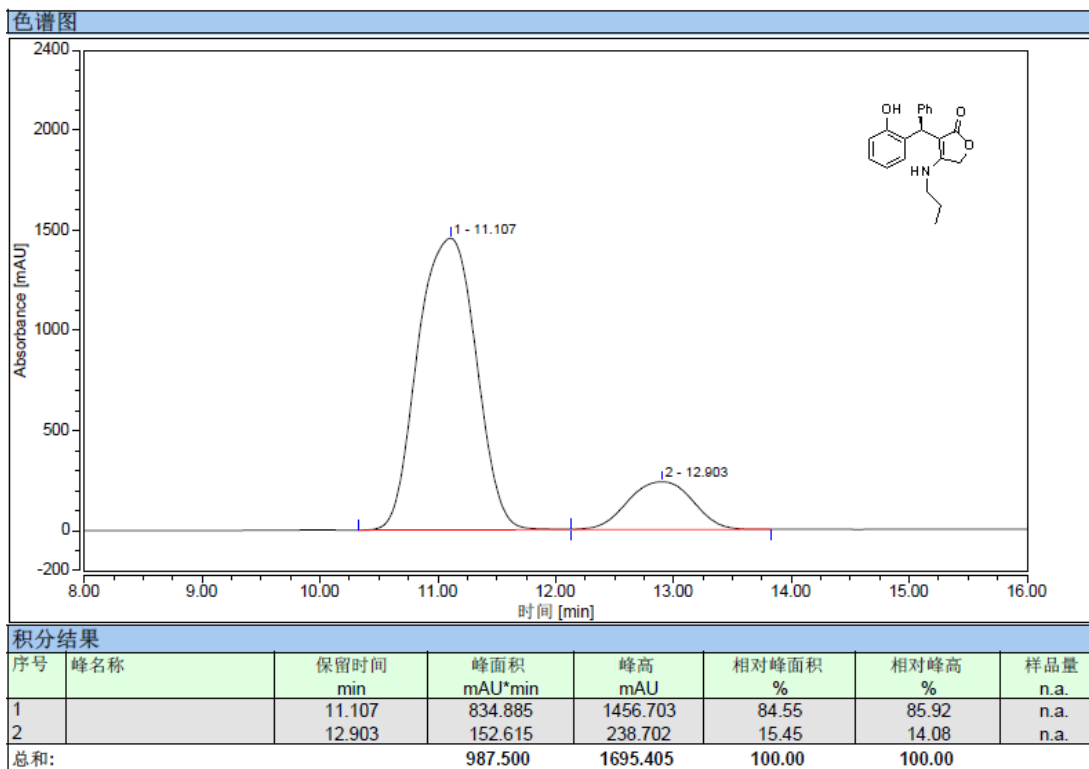


3am

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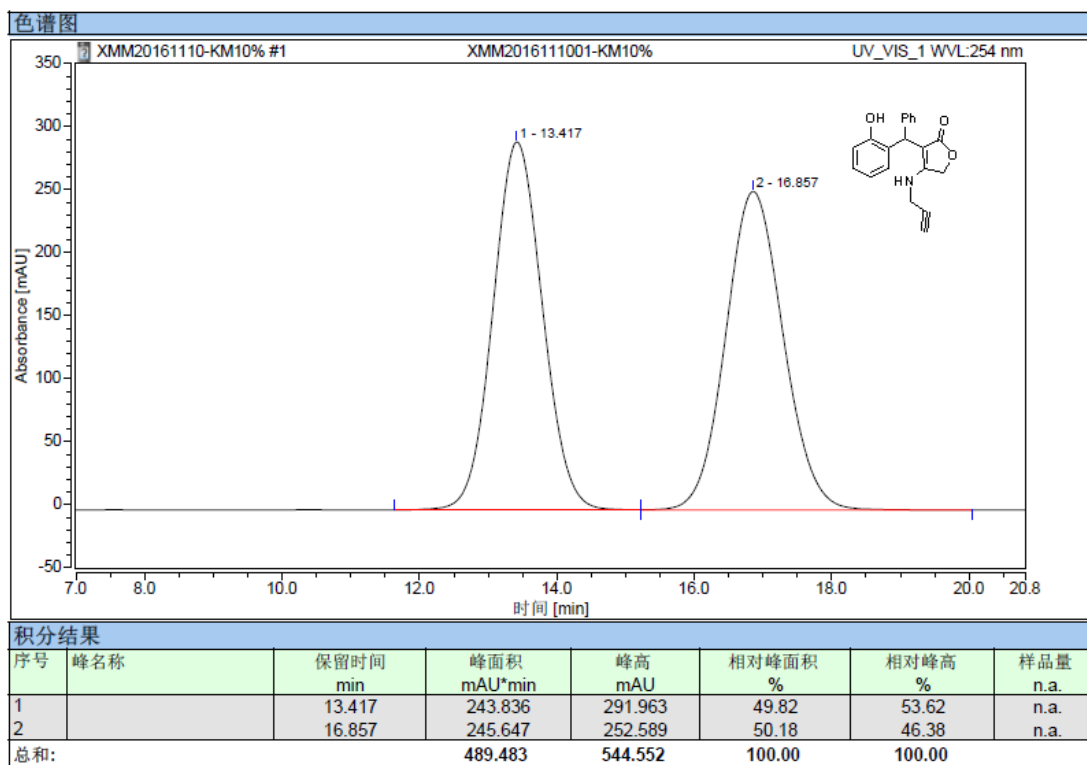


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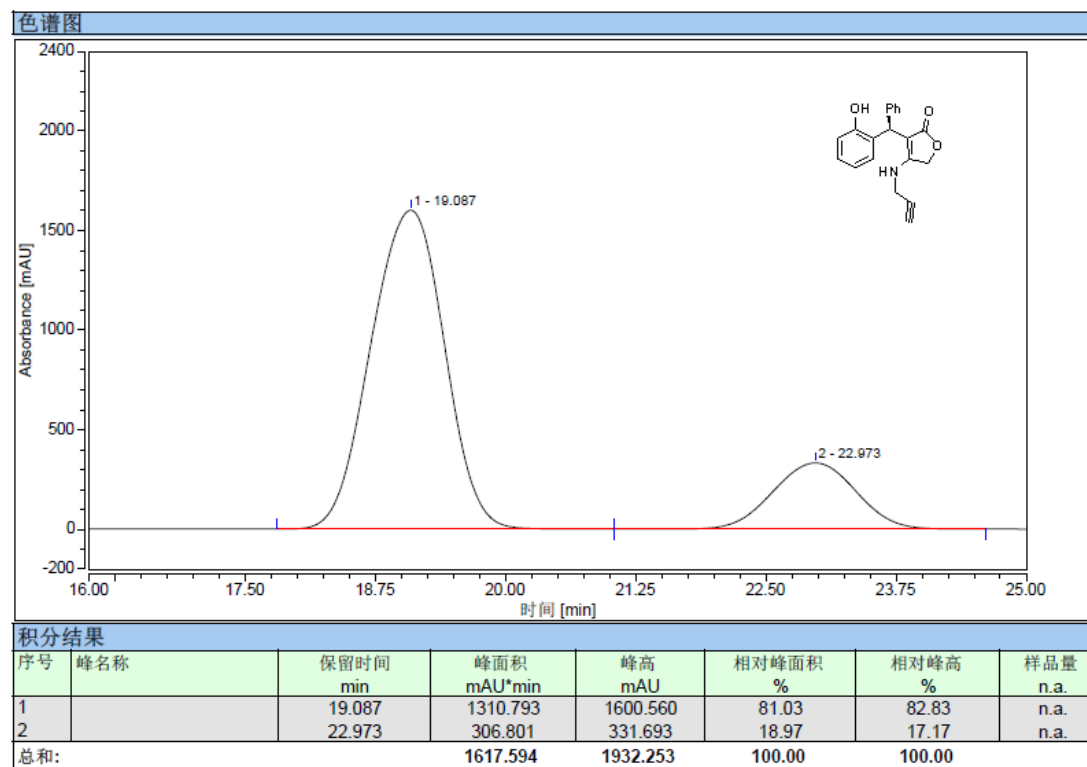


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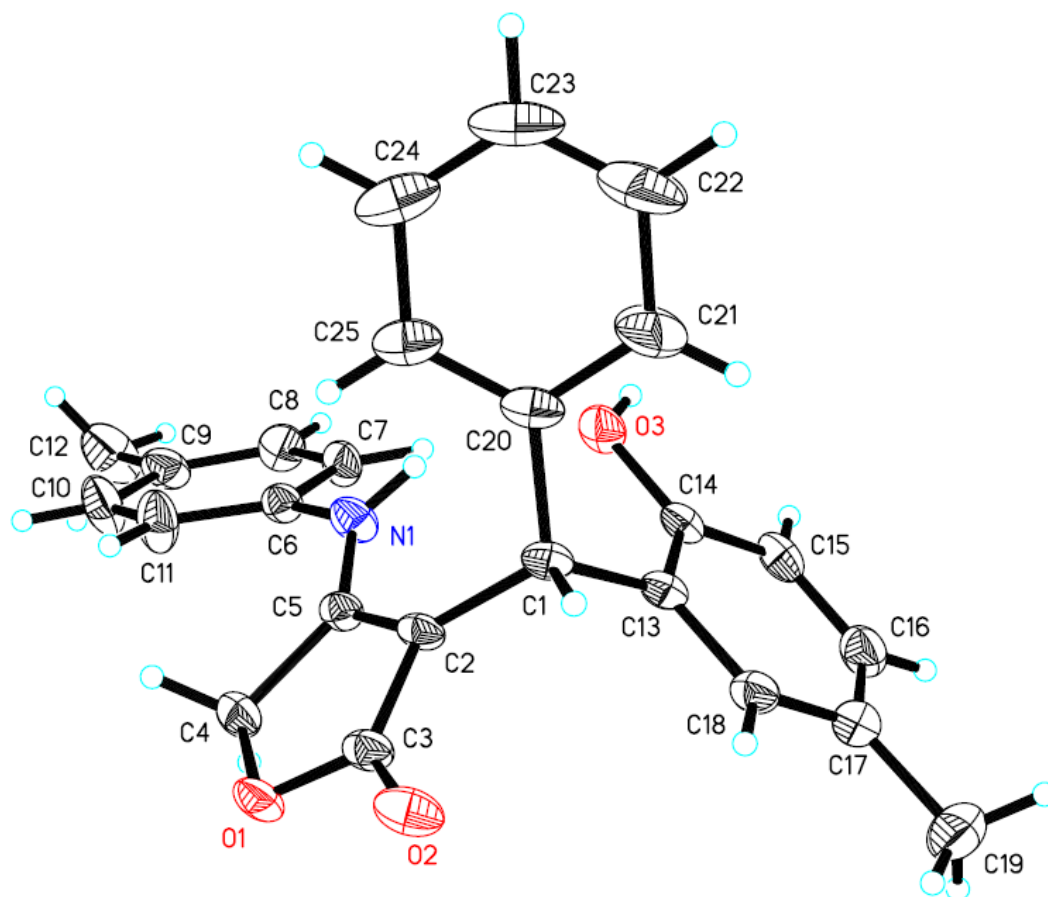
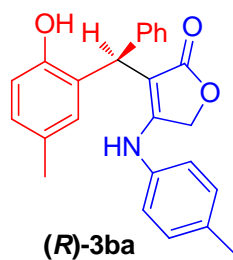
Racemic:



Enantioselective:



4. X-ray single crystal data for compound 3ba



The thermal ellipsoid was drawn at the 30% probability level.

Empirical formula	C ₂₅ H ₂₃ N O ₃	
Formula weight	385.44	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Tetragonal	
Space group	P 41	
Unit cell dimensions	a = 8.40910(10) Å	α = 90°.
	b = 8.40910(10) Å	β = 90°.
	c = 29.3175(6) Å	γ = 90°.

Volume	2073.13(7) Å ³
Z	4
Density (calculated)	1.235 Mg/m ³
Absorption coefficient	0.646 mm ⁻¹
F(000)	816
Crystal size	0.2 x 0.15 x 0.05 mm ³
Theta range for data collection	5.260 to 69.576°.
Index ranges	-9<=h<=10, -9<=k<=10, -35<=l<=35
Reflections collected	15374
Independent reflections	3807 [R(int) = 0.0707]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9643 and 0.8673
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3807 / 1 / 265
Goodness-of-fit on F ²	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0574, wR2 = 0.1527
R indices (all data)	R1 = 0.0591, wR2 = 0.1550
Absolute structure parameter	0.13(14)
Extinction coefficient	n/a
Largest diff. peak and hole	0.201 and -0.268 e.Å ⁻³

5. Evaluation on the cytotoxicity of selected compounds 3

Table 1. Cytotoxicity to colorectal cancer line HT-29

Compound	Survival rate on HT-29 (%) ^a				IC ₅₀ to HT-29 (μg/mL) ^b
	0.01μg/mL	0.1μg/mL	1μg/mL	5μg/mL	
3aa	93.97± 2.68	86.00± 4.56	75.70± 6.01	11.29± 10.61	1.773
3da	72.48±6.91	65.72± 8.50	59.96± 5.81	6.76± 3.01	0.3991
3ea	89.00± 8.20	82.55± 9.09	51.74± 5.21	1.25± 0.76	0.7839
3ba	83.67± 7.89	70.81± 9.51	4.03± 11.94	8.13± 3.32	0.7259
3ah	82.80± 7.58	72.19± 9.13	60.93± 9.53	49.11± 12.53	4.787
3aj	76.11± 6.38	64.19± 5.89	64.60± 6.48	0.69± 0.07	0.4295

^aThe viability rate was represented as mean±S.D.

^bThe IC₅₀ value corresponded to the compound concentration causing 50% mortality in cancer cells.

Table 2. Cytotoxicity to breast cancer cell line MCF-7

Compound	Survival rate on MCF-7(%) ^a				IC ₅₀ to MCF-7 (μg/mL) ^b
	0.01μg/mL	0.1μg/mL	1μg/mL	5μg/mL	
3aa	91.82±5.62	87.25± 7.21	84.43± 7.75	22.61± 2.49	2.52
3da	91.43±5.97	88.19± 4.53	81.21± 5.50	26.75± 3.37	2.564
3ea	89.98± 3.22	84.04± 3.24	71.04±4.41	9.72± 5.78	1.591
3ba	89.57± 8.17	80.05± 8.38	69.31±8.03	20.97± 4.52	1.535
3ah	90.05±8.24	84.19± 5.53	78.53±4.79	49.90± 16.97	7.439
3aj	87.17± 9.58	84.82±7.87	73.30±10.77	14.82± 7.86	1.788

^aThe viability rate was represented as mean±S.D.

^bThe IC₅₀ value corresponded to the compound concentration causing 50% mortality in cancer cells.

Table 3. Cytotoxicity to human esophageal squamous cell line TE-13

Compound	Survival rate on TE-13 (%) ^a				IC ₅₀ to TE-13 (μg/mL) ^b
	0.01μg/mL	0.1μg/mL	1μg/mL	5μg/mL	
3aa	98.89± 0.33	93.15± 3.97	86.44± 4.08	63.03± 3.00	11.29
3da	95.93±1.16	89.59± 4.60	84.09± 6.17	50.23± 6.71	3.901
3ea	94.44± 4.93	93.44± 5.35	83.40± 9.30	1.78± 1.28	1.59
3ba	98.41± 0.93	92.34± 3.09	80.05± 3.63	4.45± 2.01	1.655
3ah	99.13± 0.19	96.60± 2.11	84.39± 4.15	67.36± 1.92	15.69
3aj	100.09±1.44	91.49± 1.39	85.32± 2.73	40.54± 6.61	3.739

^aThe viability rate was represented as mean±S.D.

^bThe IC₅₀ value corresponded to the compound concentration causing 50% mortality in cancer cells.