Supporting Information for

Original article

Discovery of novel covalent selective estrogen receptor degraders against endocrine-resistant breast cancer

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PART I. The synthesis and characterization of intermediate compounds

General Procedure for intermediate compounds 13a-f.

To a solution of 4-aminophenyl ethenesulfonate **11** (5 mmol) in 10 mL DCM were added Et_3N (6 mmol) and corresponding acyl chloride (5.5 mmol). The mixture was stirred at room temperature for 12 h. The mixture was diluted with saturated aqueous solution of sodium hydrogen carbonate (20 mL) and extracted with DCM (3 × 30 mL). The organic layer was dried (Na_2SO_4), after filtration, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether and ethyl acetate, 10:1~1:1).

4-Acrylamidophenyl ethenesulfonate (13a). Compound **13a** was synthesized according to above general procedure as yellow solid, 80% yield. ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.62 (s, 1H), 8.02 -7.69 (m, 2H), 7.42 - 7.17 (m, 2H), 7.08 - 6.94 (m, 1H), 6.58 - 6.21 (m, 4H), 5.75 (dt, J = 9.7, 2.4 Hz, 1H).

(*E*)-4-(But-2-enamido)phenyl ethenesulfonate (13b). Compound **13b** was synthesized according to above general procedure as white solid, 71% yield. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 - 7.60 (m, 2H), 7.32 - 7.16 (m, 2H), 7.01 - 6.87 (m, 2H), 6.36 - 6.20 (m, 2H), 6.16 - 6.08 (m, 1H), 1.94 (dd, J = 6.9, 1.7 Hz, 3H).

4-(3-Methylbut-2-enamido)phenyl ethenesulfonate (13c). Compound **13c** was synthesized according to above general procedure as yellow solid, 77% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.73 - 6.58 (m, 1H), 6.34 (d, J = 16.6 Hz, 1H), 6.18 (d, J = 9.9 Hz, 1H), 5.74 (s, 1H), 2.21 (s, 3H), 1.88 (s, 3H).

4-Propiolamidophenyl ethenesulfonate (13d). Compound **13d** was synthesized according to above general procedure as yellow solid, 72% yield.^{1}H NMR (400 MHz, Acetone-d_6) δ 7.86 - 7.69 (m, 2H), 7.41 - 7.20 (m, 2H), 7.07 - 6.98 (m, 1H), 6.43 -6.24 (m, 2H), 3.79 (s, 1H).

4-(2-Chloroacetamido)phenyl ethenesulfonate (13e). Compound **13e** was synthesized according to above general procedure as yellow solid, 67% yield. ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.60 (s, 1H), 7.88 - 7.70 (m, 2H), 7.37 - 7.21 (m, 2H), 7.06 - 6.97 (m, 1H), 6.43 - 6.23 (m, 2H), 4.26 (s, 2H).

4-(2-Bromoacetamido)phenyl ethenesulfonate (13f). Compound **13f** was synthesized according to above general procedure as yellow solid, 43% yield. ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.90 - 7.68 (m, 2H), 7.41 - 7.25 (m, 2H), 7.05 - 6.94 (m, 1H), 6.47 - 6.20 (m, 2H), 4.07 (s, 2H).

General Procedure for intermediate compounds **24a-e**

To a solution of 4-(4-(4-aminophenyl)furan-3-yl)phenol **23** (5 mmol) in 10 mL DCM were added Et_3N (6 mmol) and corresponding acyl chloride (5.5 mmol). The mixture was stirred at 0 °C for 12 h. The mixture was diluted with saturated aqueous solution of sodium hydrogen carbonate (20 mL) and extracted with DCM (3 × 30 mL). The organic layer was dried (Na_2SO_4), after filtration, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether and ethyl acetate, 10:1~5:1).

***N*-(4-(4-(4-Hydroxyphenyl)furan-3-yl)phenyl)acrylamide (24a).** Compound **24a** was synthesized according to above general procedure as yellow solid, 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.25 (s, 1H), 7.93 - 7.71 (m, 4H), 7.30 - 7.22 (m, 2H), 7.20 - 7.14 (m, 2H), 7.01 - 6.94 (m, 2H), 6.20 - 6.12 (m, 1H), 5.82 - 5.70 (m, 1H).

(*E*)-*N*-(4-(4-(4-Hydroxyphenyl)furan-3-yl)phenyl)but-2-enamide (24b). Compound **24b** was synthesized according to above general procedure as yellow solid, 42% yield. ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.27 (s, 1H), 8.50 (s, 1H), 7.82 - 7.61 (m, 4H), 7.25 - 7.17 (m, 2H), 7.14 - 7.08 (m, 2H), 6.96 - 6.86 (m, 1H), 6.84 - 6.79 (m, 2H), 6.18 - 6.11 (m, 1H), 1.87 (dd, J = 6.9, 1.7 Hz, 3H).

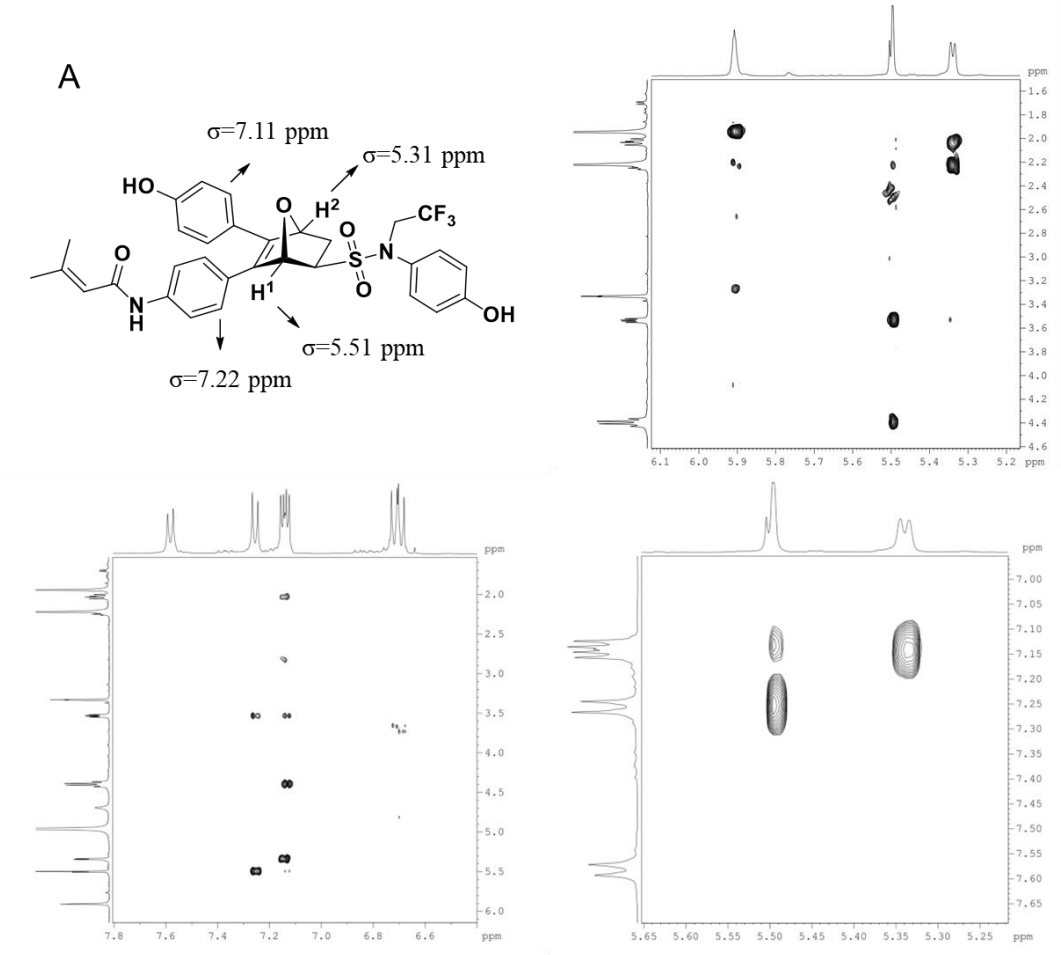
***N*-(4-(4-(4-Hydroxyphenyl)furan-3-yl)phenyl)-3-methylbut-2-enamide (24c).** Compound **24c** was synthesized according to above general procedure as yellow solid, 45% yield. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.65 - 7.42 (m, 4H), 7.23 - 7.12 (m, 2H), 7.10 - 7.00 (m, 2H), 6.77 - 6.64 (m, 2H), 5.92 - 5.82 (m, 1H), 2.19 (s, 3H), 1.91 (s, 3H).

2-Chloro-*N*-(4-(4-(4-hydroxyphenyl)furan-3-yl)phenyl)acetamide (24d). Compound **24d** was synthesized according to above general procedure as yellow solid, 39% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.24 (s, 1H), 7.63 - 7.58 (m, 2H),

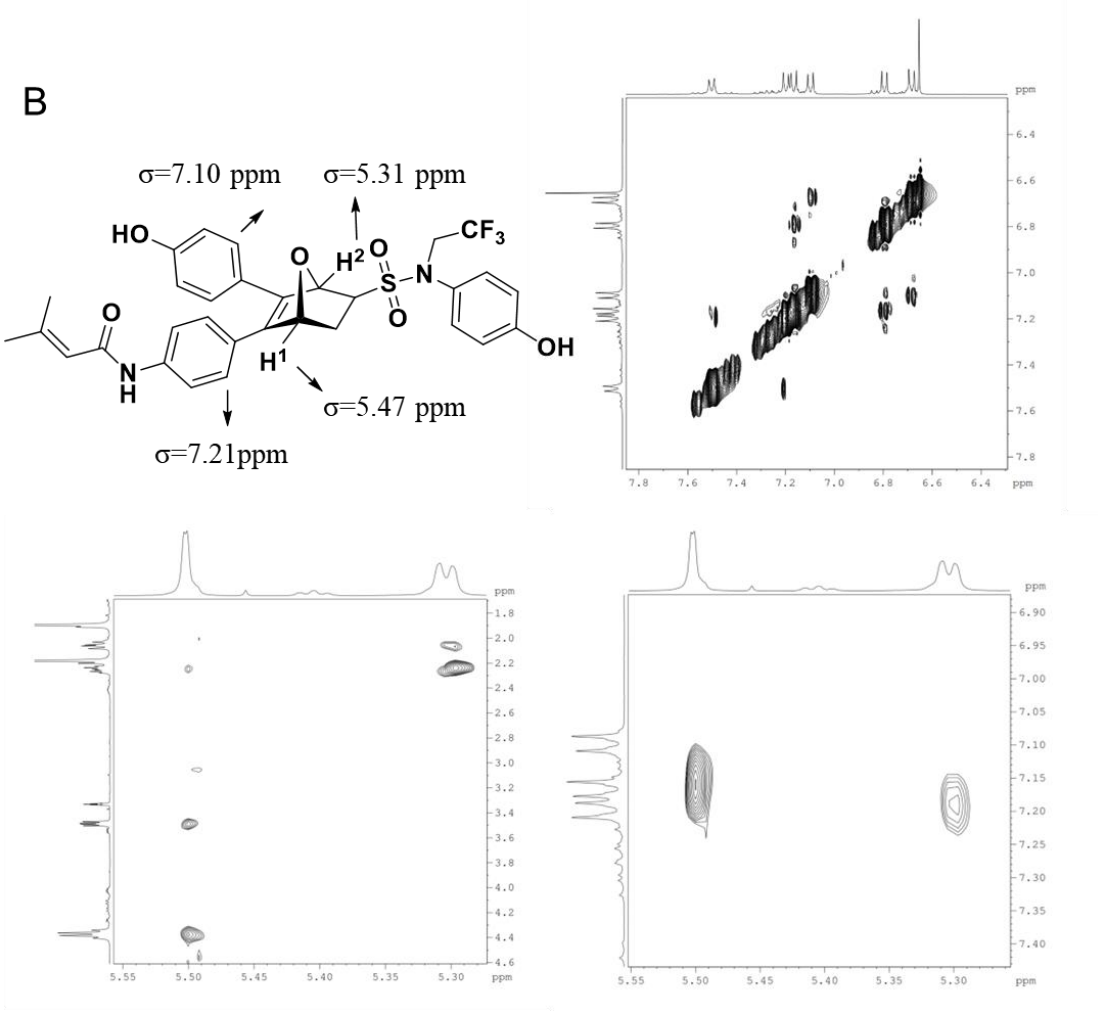
7.55 - 7.49 (m, 2H), 7.34 - 7.22 (m, 4H), 7.13 - 7.08 (m, 2H), 4.14 (s, 2H).

2-Bromo-*N*-(4-(4-(4-hydroxyphenyl)furan-3-yl)phenyl)acetamide (24e). Compound **24e** was synthesized according to above general procedure as yellow solid, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.22 (s, 1H), 7.60 - 7.55 (s, 2H), 7.52 - 7.47 (m, 2H), 7.32 - 7.19 (m, 4H), 7.11 - 7.05 (m, 2H), 4.04 (s, 2H).

The NOESY-NMR of regioisomer 29c and 29c'.



The peaks at δ 5.51 and δ 5.31 are the hydrogen atoms on the bridgehead carbons (H^1 and H^2), it is evident that the H^1 interacts with the aniline moiety, and H^2 interacts with the phenol.

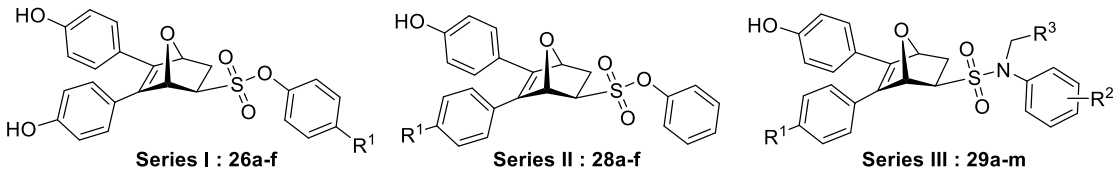


The peaks at δ 5.47 and δ 5.31 are the hydrogen atoms on the bridgehead carbons (H^1 and H^2), it is evident that the H^1 interacts with the moiety, and H^2 interacts with the phenol.

Figure S1. The characterization of the regioisomers **29c** and **29c'**. (A) NOESY-NMR of compound **29c**; (B) NOESY-NMR of compound **29c'**.

PART II. The cell viability of the target compounds and the transcriptional curves of selected compounds for ERα antagonist activity

Table S1. The cell viability of the target compounds on MCF-10A cells (IC_{50}, μM)[a].



Entry	Cmpd.	R^1	R^2	R^3	MCF-10A cells (IC_{50}, μM)	TI[b]
1	**26a**		/	/	19.97 ± 3.61	2.59
2	**26b**		/	/	27.31 ± 2.94	2.97
3	**26c**		/	/	43.77 ± 2.85	13.85
4	**26d**		/	/	39.21 ± 2.67	21.91
5	**26e**		/	/	15.31 ± 1.93	4.48
6	**26f**		/	/	5.16 ± 0.88	7.37
7[c]	**28a**		/	/	15.86 ± 2.20	3.13
8[c]	**28b**		/	/	20.88 ± 1.82	47.45
9[c]	**28c**		/	/	11.25 ± 0.15	32.14
10[c]	**28d**		/	/	9.02 ± 0.27	13.67
11[c]	**28e**		/	/	8.08 ± 0.22	7.35
12[c]	**28f**		4-OH	/	13.59 ± 0.35	14.61
13	**29a**		4-OH	CF_3	20.73 ± 0.88	24.69
14	**29b**		4-OH	CF_3	19.21 ± 3.89	53.36
15	**29c**		4-OH	CF_3	8.16 ± 0.15	145.71
16[d]	**29c'**		4-OH	CF_3	38.97 ± 2.27	41.02
17	**29d**		4-Me	CF_3	23.41 ± 1.89	31.21
18	**29e**		H	CF_3	>50	>75.75
19	**29f**		4-OMe	CF_3	5.16 ± 0.15	54.89

20	**29g**		4-F	CF_3	>50	>78.12
21	**29h**		3-OH	CF_3	17.99 ± 1.48	18.36
22	**29i**		4-OH	CH_3	8.72 ± 0.45	122.82
23	**29j**		4-OMe	CH_3	20.11± 1.06	69.34
24	**29k**		4-OH	CF_3	21.16 ± 0.89	19.96
25	**29l**	NH_2	4-OH	CF_3	32.32 ± 0.66	10.20
26	**29m**	OH		CF_3	29.20 ± 1.70	182.50
27[d]	**6a**				21.38 ± 1.29	85.52
28	**4-OHT**				21.50 ± 2.74	32.09
29	**Ful**				>50	>357.1

[a]The data are expressed as mean ± SD of at least three independent determinations; [b]TI is therapeutic index, TI = $IC_{50}^{MCF\text{-}10A}$ /$IC_{50}^{MCF\text{-}7}$. [c]Series II compounds were mixtures of regioisomers. [d]Compound **29c'** was regioisomer of **29c**. [d]**6a** was a derivative of OBHSA, X = NCH_2CF_3, R = 4-OH.

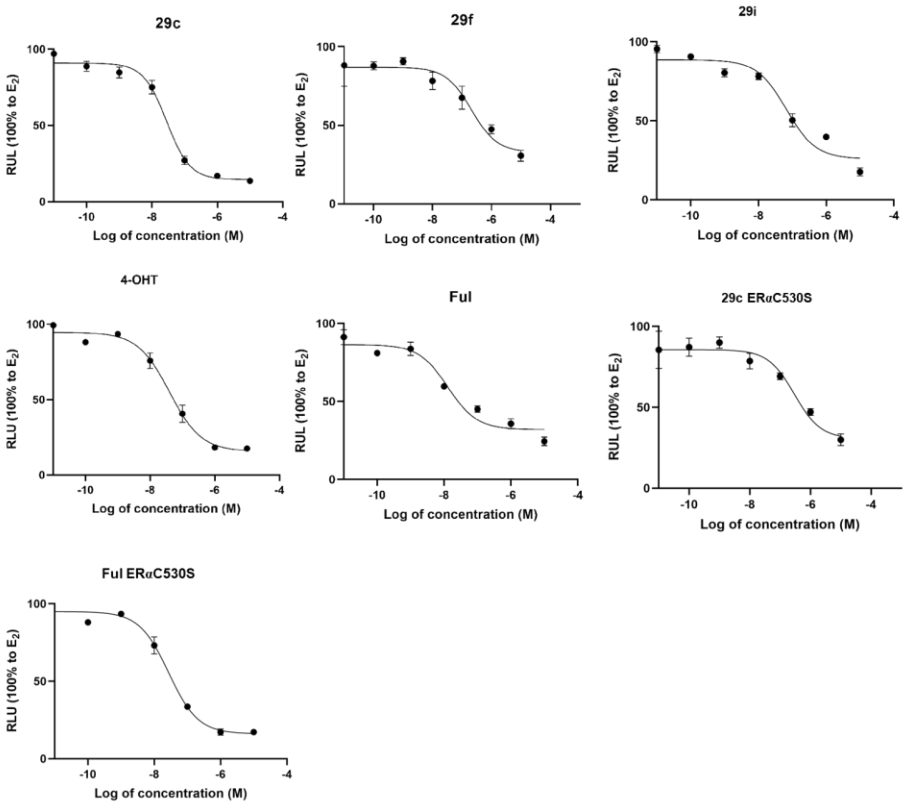


Figure S2. The transcriptional curves of selected compounds for ERα Antagonist activity.

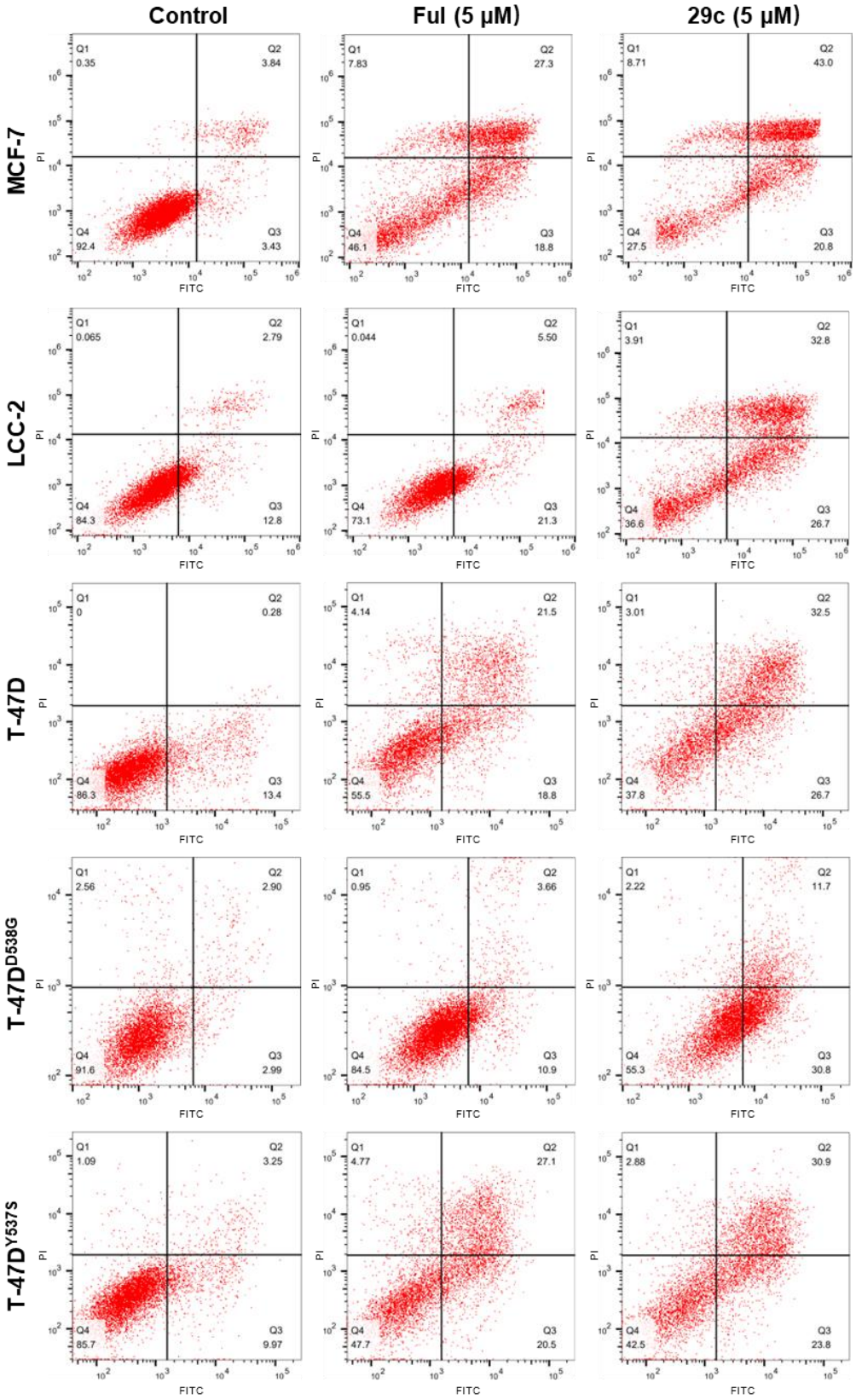


Figure S3. Cell lines (MCF-7, LCC-2, T-47D, T-47D^{Y537S}, T-47D^{D538G}) undergoing apoptosis were detected by flow cytometry. Cells were treated with or without 5 μM **29c** in multi-well X6 culture plates for 48 h, and 5 μM fulvestrant severed as positive control.

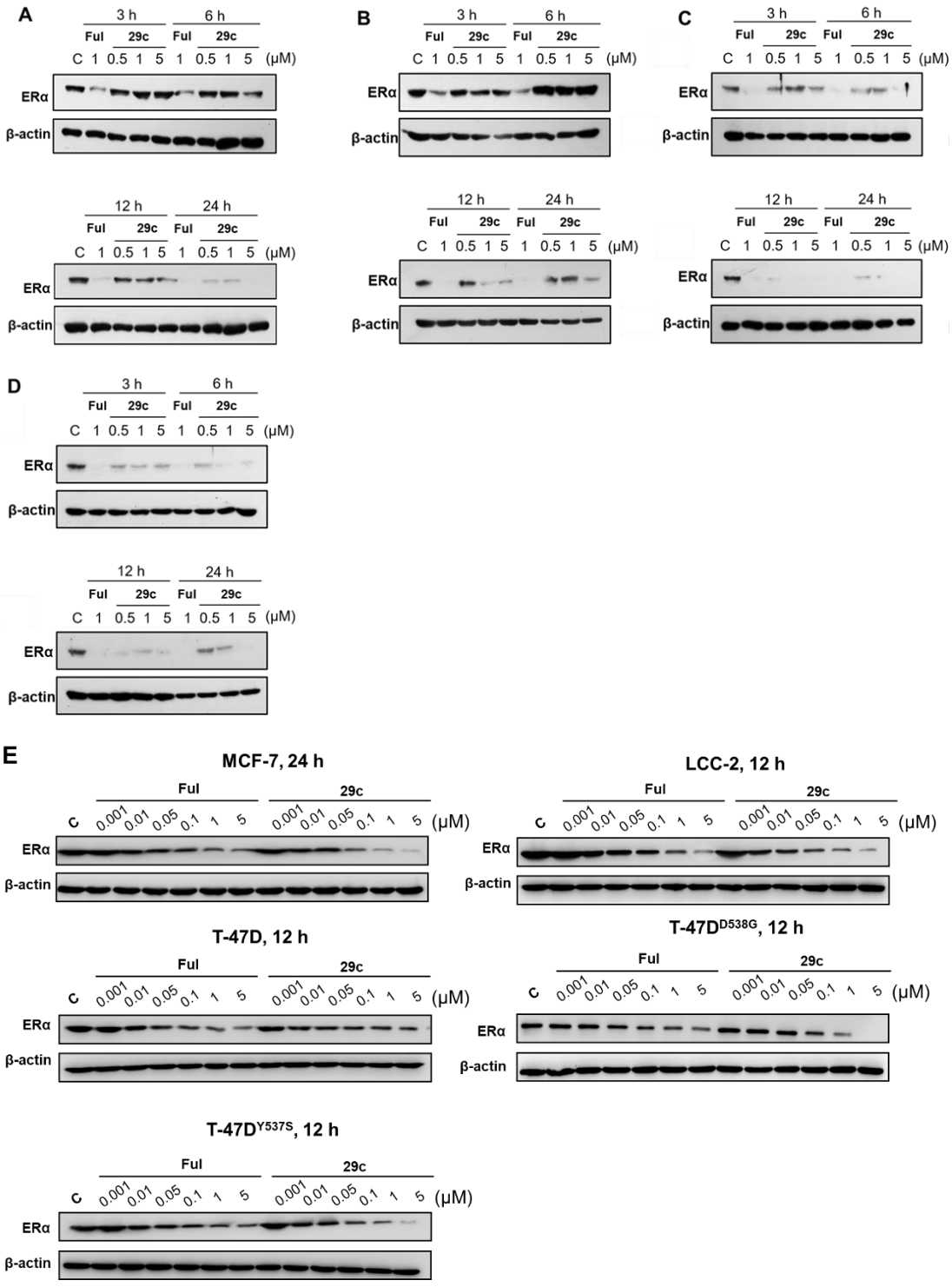


Figure S4. (A) Immunoblot analysis of ERα protein treated with **29c** at 0.5, 1, and 5 μM and time course of ERα degradation in (A) MCF-7cells, (B) LCC-2 cells, (C) T-47D^{D538G} cells and (D) T-47D^{Y537S} cells. (D) Immunoblot analysis of ERα protein treated with gradient concentrations Ful or **29c** in the indicated BC cell lines. DC_{50} and D_{max} values were quantified from two independent experiments. All Immunoblot was treated with β-actin as the loading control.

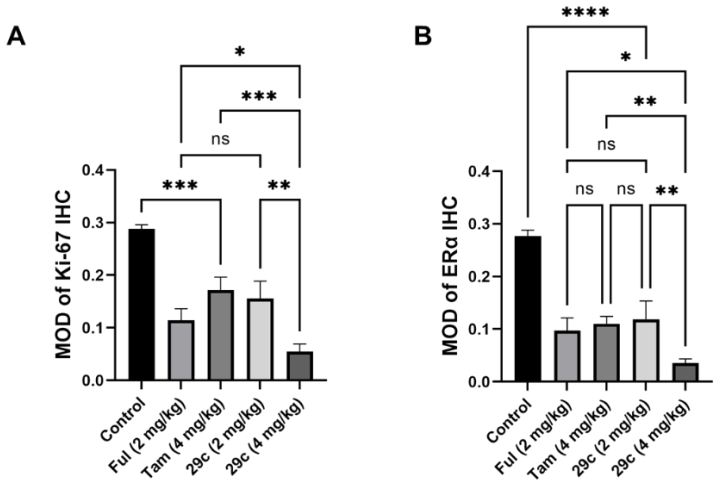


Figure S5. Statistical IHC analysis of Ki-67 and ERα in dissected tumor tissues of each treatment group. ****P value <0.0001, ***P value <0.001, **P value <0.01 and *P value <0.05. ns = not statistically significant.

PART III. LC/MS analysis of mutant ER and compound 29c covalent profile

A

ERα mutant Y537S:

ERMKCKNVVPLSDLLLEMLDA

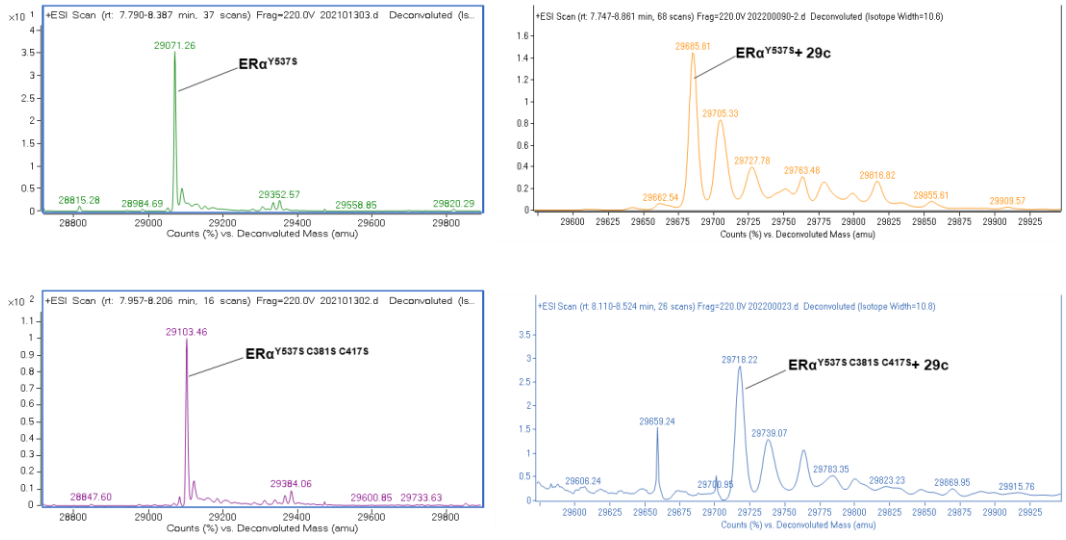
ERα mutant Y537S C381S C417S ：

LTLHDQVHLLESAWLEILMI

DRNQGKSVEGMVEIFDMLLA

YSMKCKNVVPLSDLLLEMLD

B



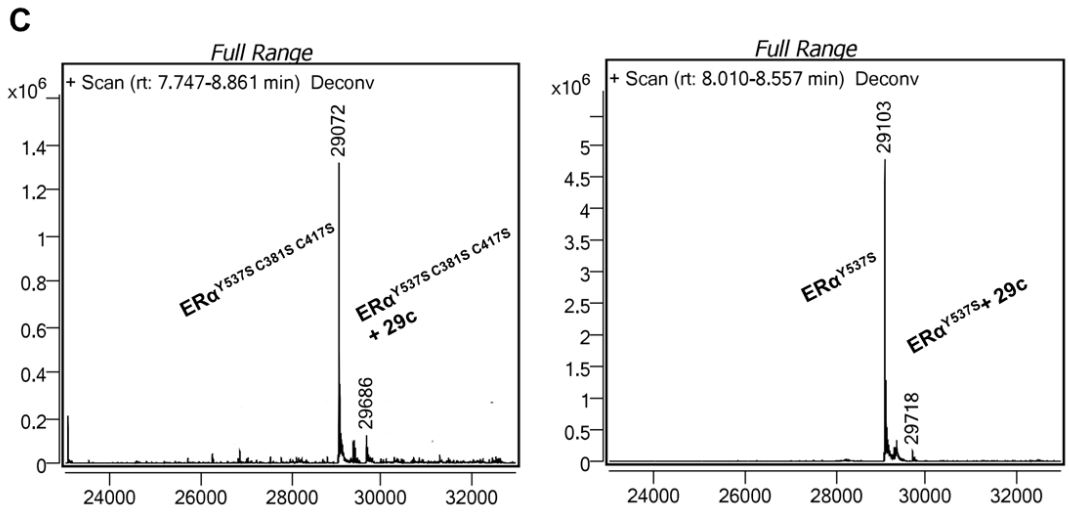


Figure S6. (A) ERα mutant sequence alignment highlighting position (shown in red) and (B, C) LC-MS analysis of **29c** covalent targeting ERα^{Y537S} and ERα$^{Y537S\ C381S\ C417S}$.

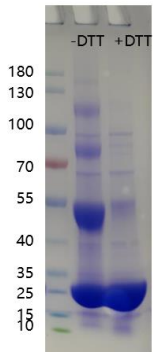
PART IV. ERα protein purification and crystallography

Protein Expression and Purification

Escherichia coli codon-optimized genes encoding the LBDs of the receptors, His-TEV-ERα-Y537S (305-554), and His-TEV-ERα C381S-C417S-Y537S (305-554) were synthesized and cloned into pET46 EK/LIC (Genecreate). Proteins were expressed in BL21 (DE3) Escherichia coli overnight at 16 °C after induction with 0.2 mM IPTG at an OD600 of ~0.8. Soluble protein was purified by immobilized metal affinity chromatography using a Ni^{2+} column twice followed by dialysis. For mass spectrometry and crystallography, the His-tag was removed by TEV protease digest.[45]

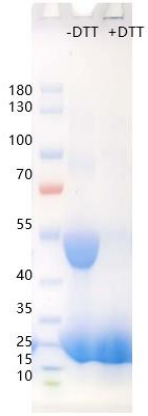
Protein sequences of ERα LBD Y537S (305-554)

SLALSLTADQMVSALLDAEPPILYSEYDPTRPFSEASMMGLLTNLADRELVHMI
NWAKRVPGFVDLTLHDQVHLLECAWLEILMIGLVWRSMEHPGKLLFAPNLLL
DRNQGKCVEGMVEIFDMLLATSSRFRMMNLQGEEFVCLKSIILLNSGVYTFLS
STLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQLLLILSHIRHM
SNKGMEHLYSMKCKNVVPLSDLLLEMLDAHRLHAPTS



Protein sequences of ERα LBD Y537S C381S C417S (305-554)

SLALSLTADQMVSALLDAEPPILYSEYDPTRPFSEASMMGLLTNLADRELVHMI
NWAKRVPGFVDLTLHDQVHLLESAWLEILMIGLVWRSMEHPGKLLFAPNLLL
DRNQGKSVEGMVEIFDMLLATSSRFRMMNLQGEEFVCLKSIILLNSGVYTFLS
STLKSLEEKDHIHRVLDKITDTLIHLMAKAGLTLQQQHQRLAQLLLILSHIRHM
SNKGMEHLYSMKCKNVVPLSDLLLEMLDAHRLHAPTS



Macromolecular X-ray Crystallography

The ERα C381S-C417S-Y537S LBD was co-crystallized with compound **29c** through sitting drop vapor diffusion method using trial gradients of 16 to 18% (weight/ volume) PEG 3350, 0.25 M Ammonium sulfate, and 0.1 M HEPES pH 7.5. The X-ray diffraction datasets were collected on the in-house Bruker D8 Venture coupled with a CMOS-PHOTON II detector in Hubei university. Proteum 3 (Bruker AXS GmbH) was used to process the X-ray diffraction datasets. The structures were solved by molecular replacement of the starting model, Protein Data Bank (PDB) entry 5DI7, and then rebuilt and refined using the Refmac5[1] and COOT[2]. Prior to structure refinement, 5%

randomly selected reflections were set aside for calculating R_{free} as a monitor of model quality. All graphics for the protein structures were prepared by using the PyMOL program (http://pymol.sourceforge.net/). The PDB identification code for ER complex with compound **29c** is 7YMK.

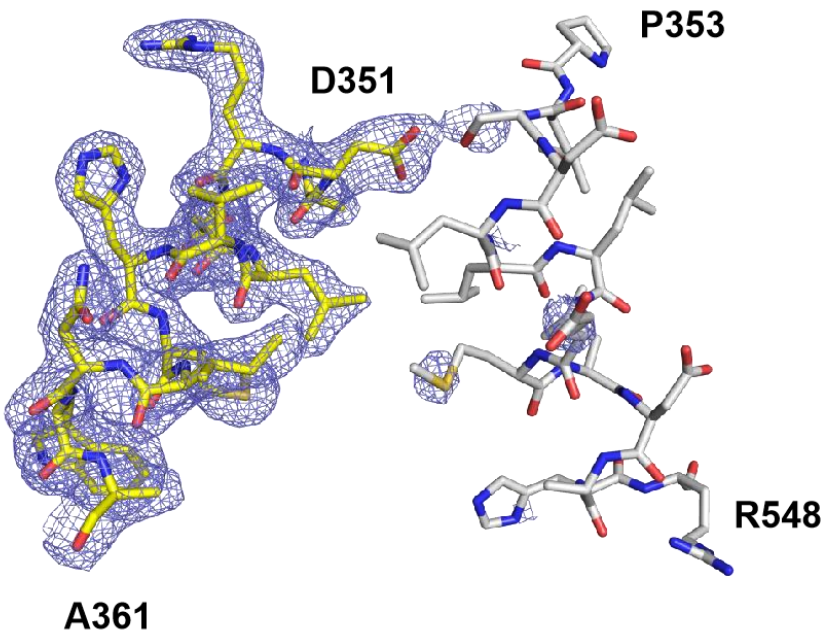


Figure S7. Structure of the ER LBD with **29c** shows that H12 could not be modeled in two of four subunits due to poor electron density. The A chain of H3 (yellow) is shown with the B chain superimposed (gray) to show the expected location of H12, which was not modeled. The 2Fo-Fc electron density map is contoured at 1.0 σ.

Table S2. Data collection and refinement statistics for crystal structures

	ERα LBD C381S C417S Y537S / **29c**
PDB code	7YMK
Data collection	
Wavelength	1.34138
Space group	$C222_1$
Unit cell	
a, b, c (Å)	52.4, 101.4, 195.8
α, β, γ (°)	90, 90, 90

Resolution (Å)[a]	33.76-2.25 (2.28-2.25)
No. of observed reflections	25394 (1020)
Redundancy	10.1 (6.4)
Completeness (%)	99.8 (98.7)
Average I/σ (I)	12.2 (2.2)
R_{merge} (%)[b]	8.7 (51.0)
Refinement[c]	
R_{work} (%)	19.4
R_{free} (%)	25.3
r.m.s.d. bonds (Å)[d]	0.009
r.m.s.d. angles (°)	1.58
Ramachandran statistics[e]	
Most favored (%)	98.7
Allowed (%)	1.3
Outliers (%)	0
Average B-factor (Å^2) /atoms	
Protein	47.7/3757
Water	44.0/153
Ligand	60.9/55

[a] Values in parentheses are for the highest resolution shell.

[b] $R_{merge} = \Sigma_{hkl}\Sigma_i |I_i(hkl) - \langle I(hkl)\rangle| / \Sigma_{hkl}\Sigma_i I_i(hkl)$, in which the sum is over all the *i* measured reflections with equivalent miller indices *hkl*; $\langle I(hkl)\rangle$ is the averaged intensity of these *i* reflections, and the grand sum is over all measured reflections in the data set.

[c] All positive reflections were used in the refinement.

[d] According to Engh and Huber [3].

[e] Calculated by using MolProbity [4].

PART V. Proteomics experiments

Tandem Mass Tag (TMT)-based quantitative proteomic approach was applied to measure the protein fold changes after 12 hours of treatment with 5 μM **29c** or DMSO in MCF-7 cells. A total of 2 μg of simple peptides were separated and analyzed using a nano-UPLC (Thermo Fisher Scientific). The separation was achieved using a reversed-phase column (100 μm ID × 15 cm, Reprosil-Pur 120 C18-AQ, 1.9 μm, Dr. Maisch). Mobile phases consisted of H_2O with 0.1% FA, 2% ACN (phase A) and 80% ACN, 0.1% FA (phase B). The sample separation was performed with a 90-minute gradient at a flow rate of 300 nL/min. Mass spectrometry files were analyzed using Proteome Discoverer software (Version 2.4.0.305) with the built-in Sequest HT search engine. The false discovery rate (FDR) was set to 0.01 for both peptide-spectrum matches (PSMs).

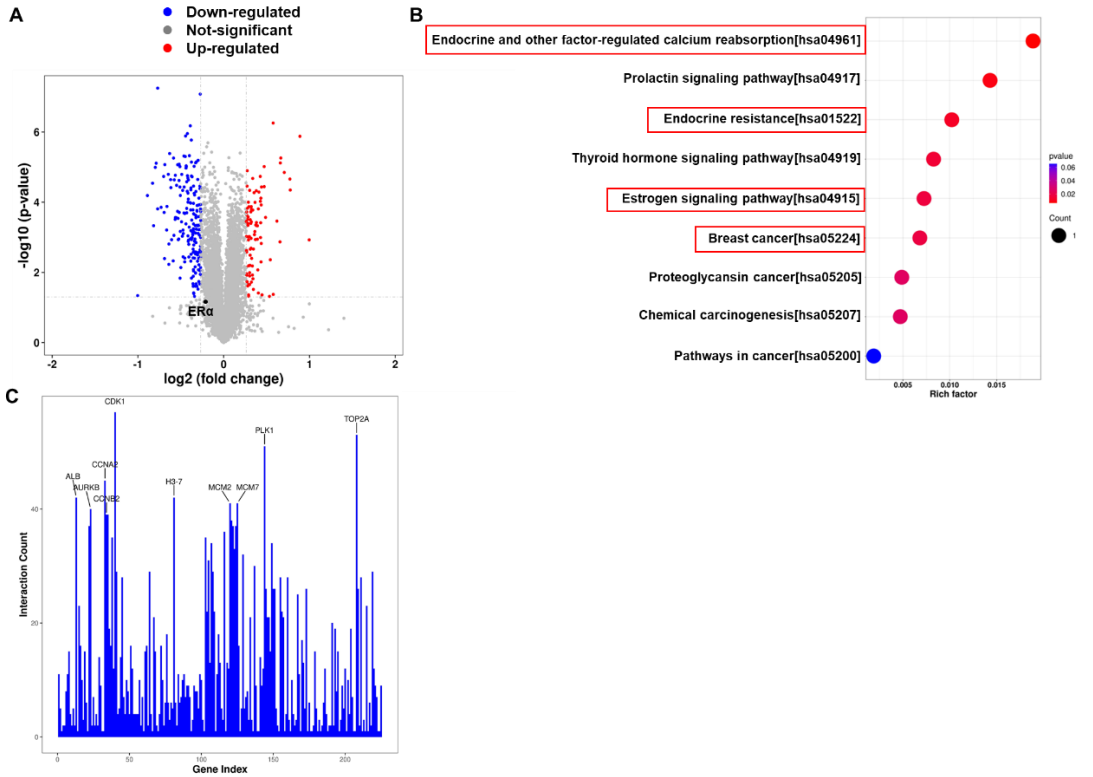


Figure S8. Tandem Mass Tag (TMT)-based quantitative proteomic approach was applied to measure the protein fold changes. (A) Proteomic analysis was performed to compare the protein level change between **29c** treated group and the control group. (B) Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathway enrichment analysis of differentially expressed proteins. The color of the circle indicates the size of the p-value, with deeper red shades being correlated with smaller p-values. (C) Significant regulation of protein-involved interactions.

References

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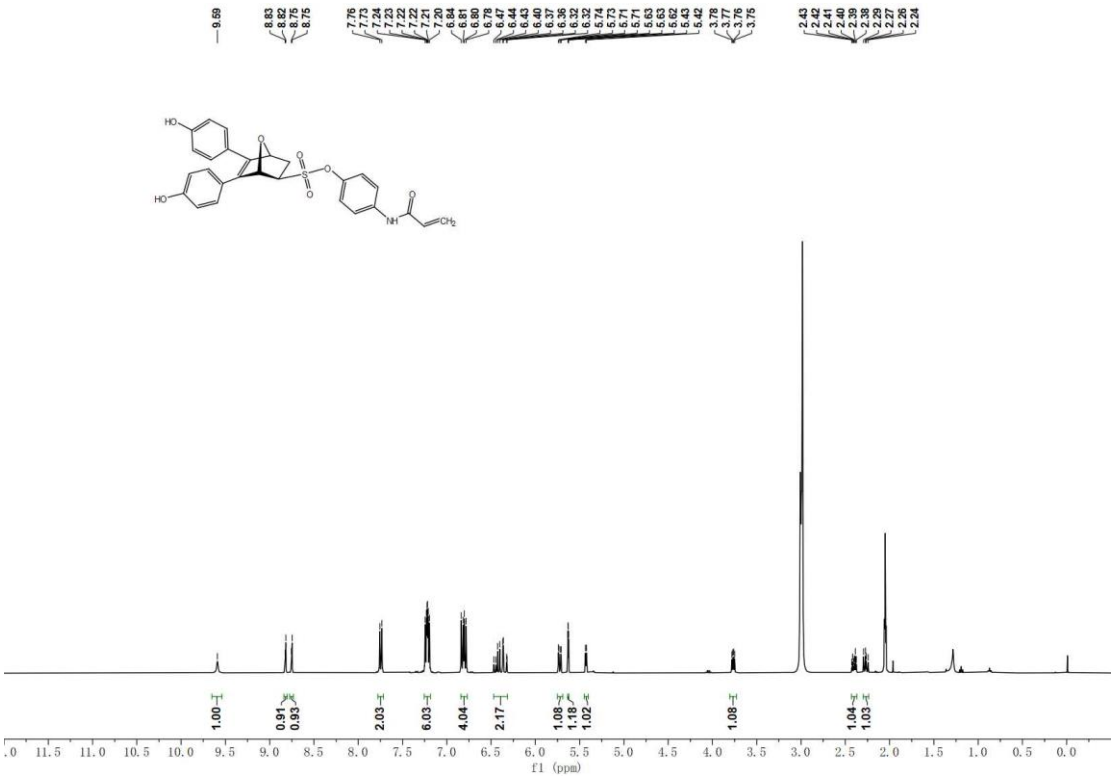
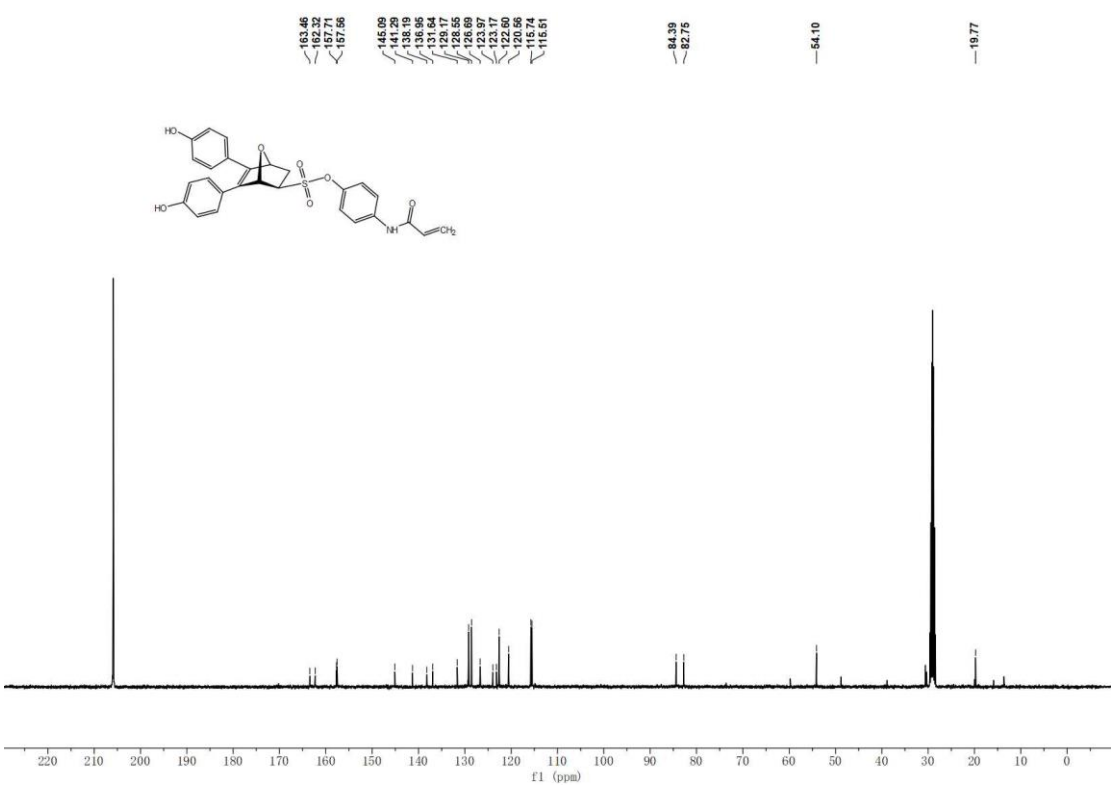
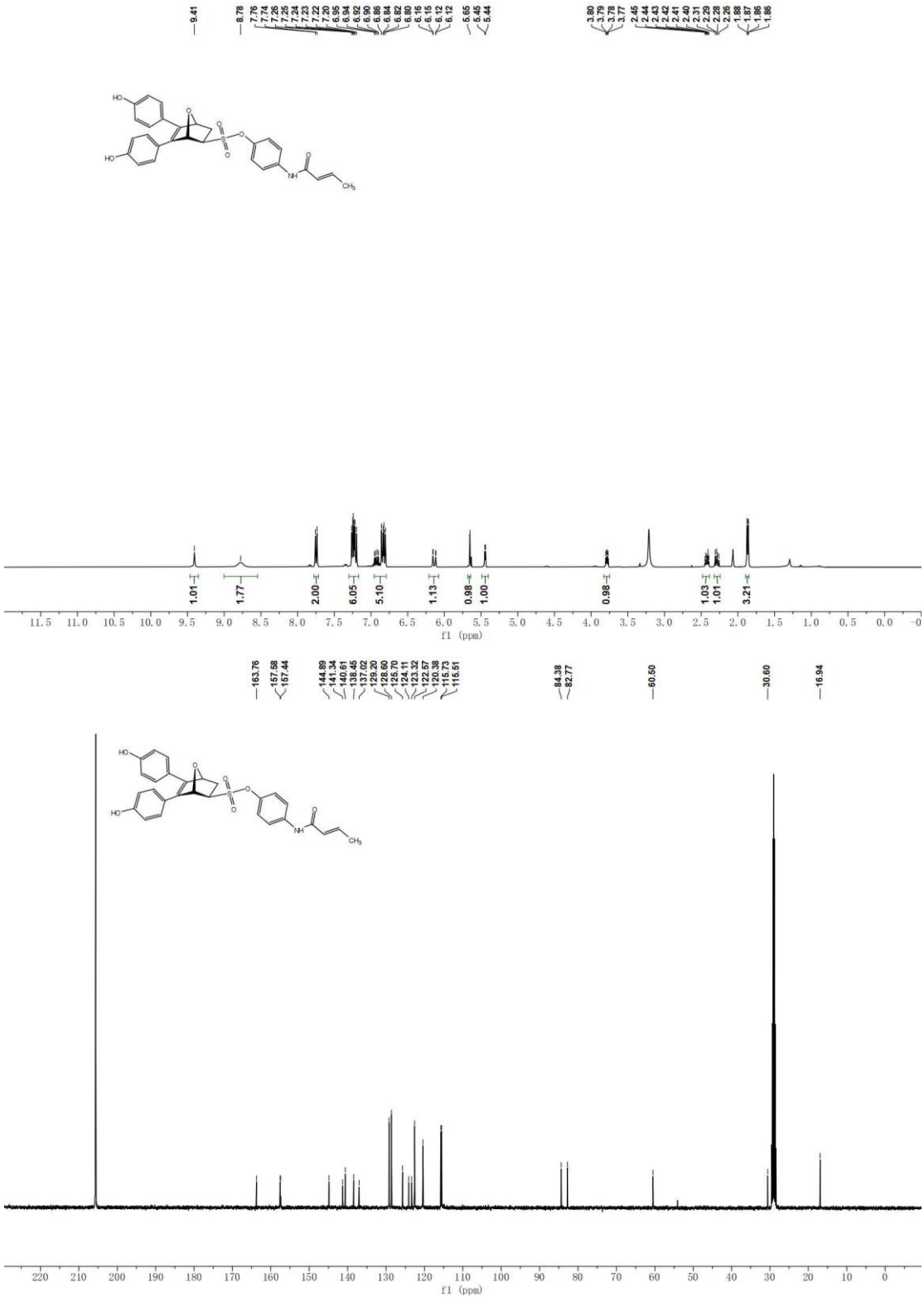
PART VI. ^{1}H NMR and ^{13}C NMR spectra of final compounds



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6.92
6.90
6.86
6.84
6.82
6.80
6.16
6.15
6.12
6.12
5.65
5.45
5.44
3.80
3.79
3.78
3.77
2.45
2.44
2.43
2.42
2.41
2.40
2.31
2.29
2.28
2.26
1.88
1.87
1.86
1.85
HO
HO
O
O
S
O
O
NH
CH3
1.01
1.77
2.00
6.05
5.10
1.13
0.98
1.00
0.98
1.03
1.01
3.21
11.5 11.0 10.5 10.0 9.5 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
f1 (ppm)
163.76
157.58
157.44
144.89
141.34
140.61
138.45
137.02
129.30
128.60
125.70
124.11
123.32
122.57
120.38
115.73
115.51
84.38
82.77
60.50
30.60
16.94
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HO
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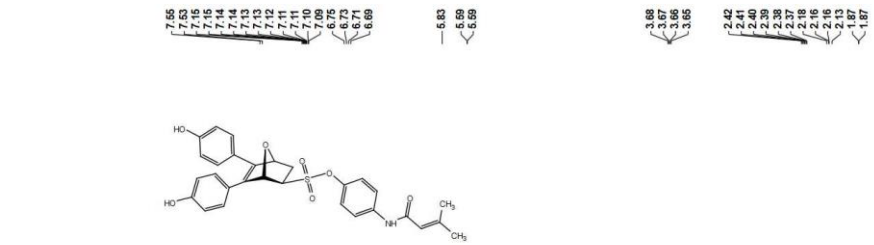
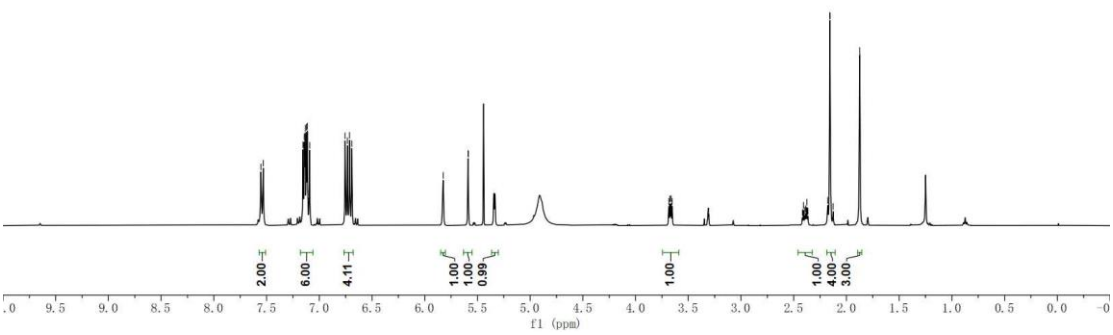
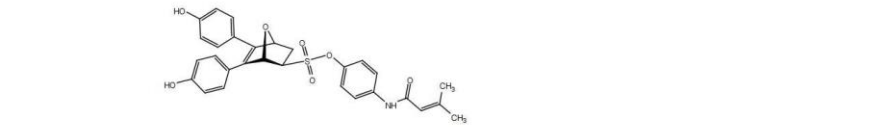
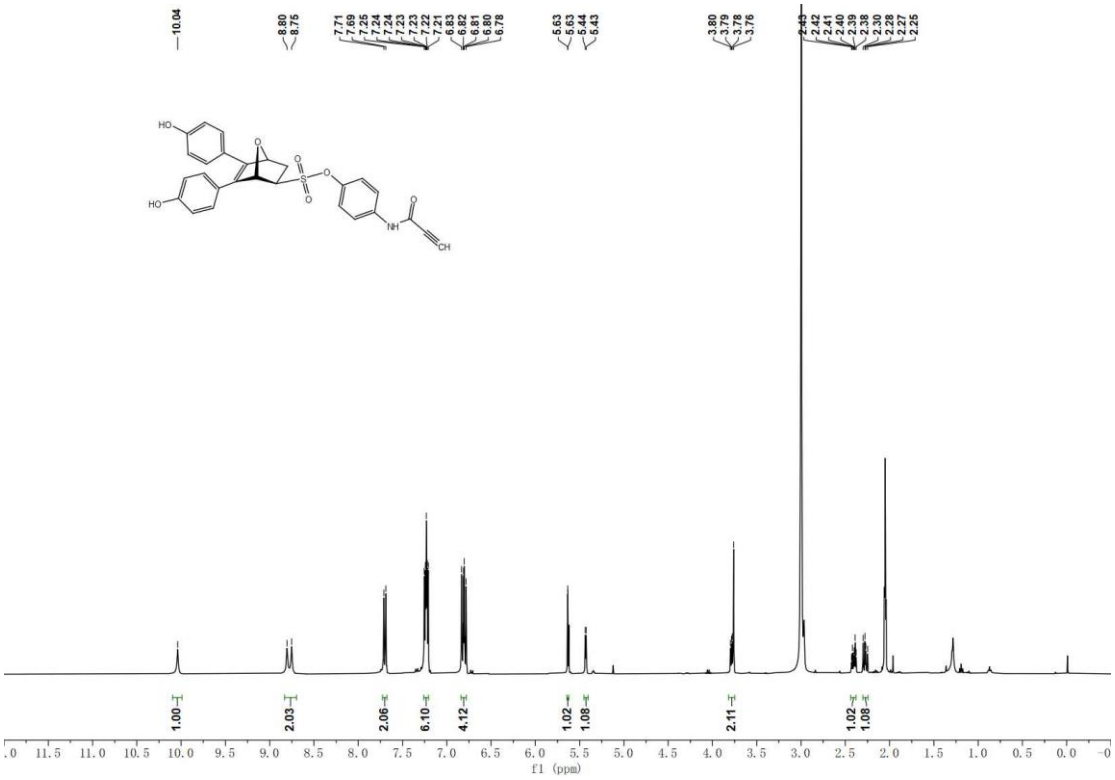
O
S
O
O
NH
CH3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)





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7.23
7.22
7.21
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6.82
6.81
6.80
6.78
5.63
5.63
5.44
5.43
3.80
3.79
3.78
3.76
2.43
2.42
2.41
2.40
2.39
2.38
2.30
2.28
2.27
2.25
HO
HO
O
O
S
O
O
NH
CH
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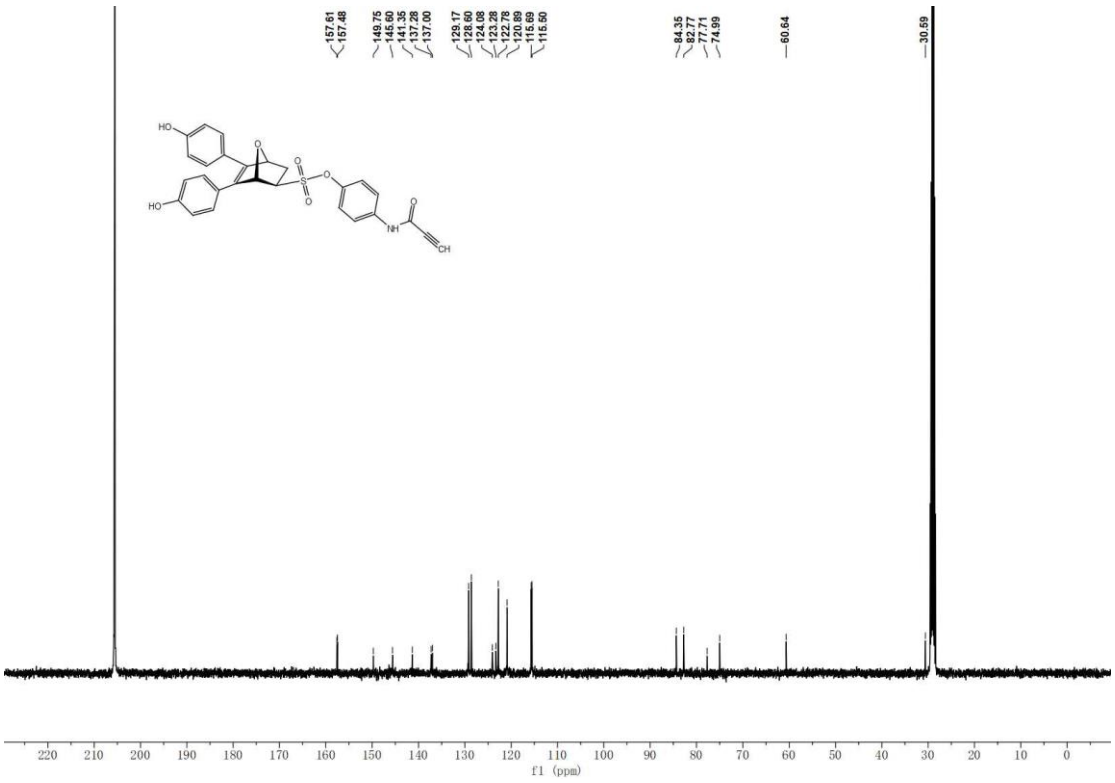
1.08
2.11
1.02
1.08
f1 (ppm)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129.17
128.60
124.08
123.28
123.78
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115.69
115.50
84.35
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30.59
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HO
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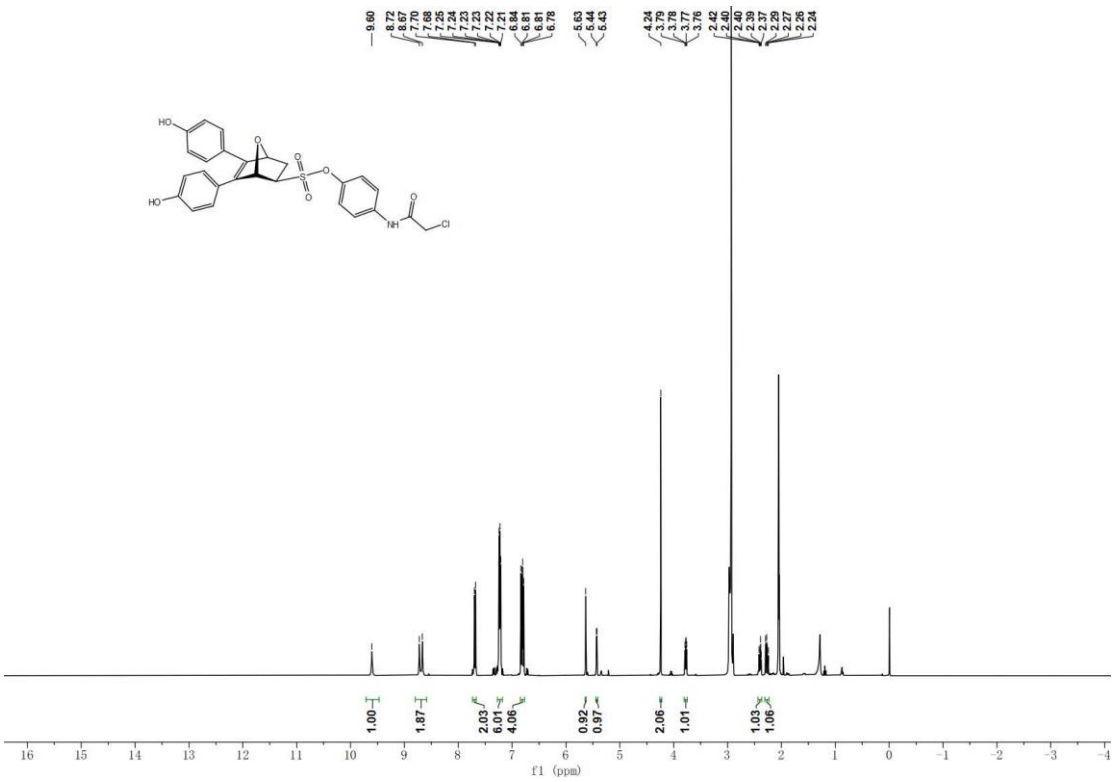
O
S
O
O
NH
CH
f1 (ppm)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7.24
7.23
7.23
7.22
7.21
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6.81
6.81
6.78
5.63
5.44
5.43
4.24
3.79
3.78
3.77
3.76
2.42
2.40
2.40
2.39
2.37
2.29
2.27
2.26
2.24
HO
HO
O
O
S
O
O
NH
O
Cl
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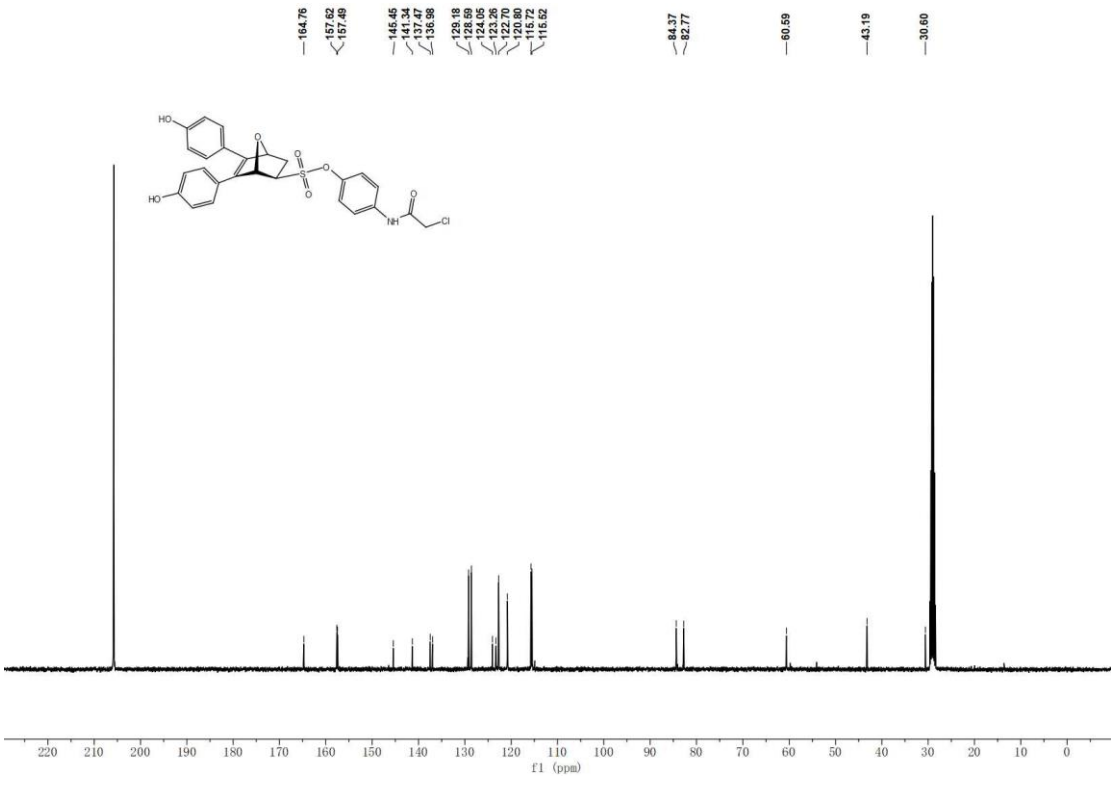
6.01
4.06
0.92
0.97
2.06
1.01
1.03
1.06
f1 (ppm)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129.18
128.59
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123.26
123.20
120.80
115.72
115.52
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82.77
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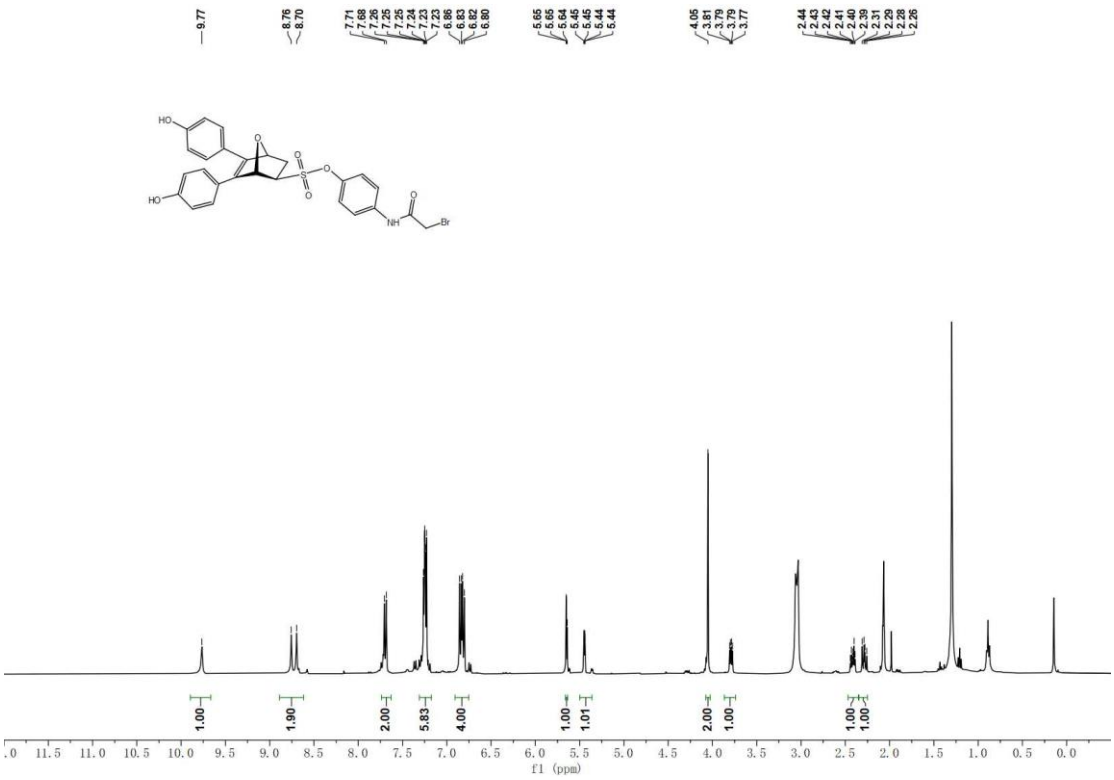
43.19
30.60
HO
HO
O
O
S
O
O
NH
O
Cl
f1 (ppm)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7.23
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6.80
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5.64
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5.45
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2.41
2.40
2.39
2.31
2.29
2.28
2.26
HO
HO
O
O
S
O
O
NH
O
Br
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1.00
1.01
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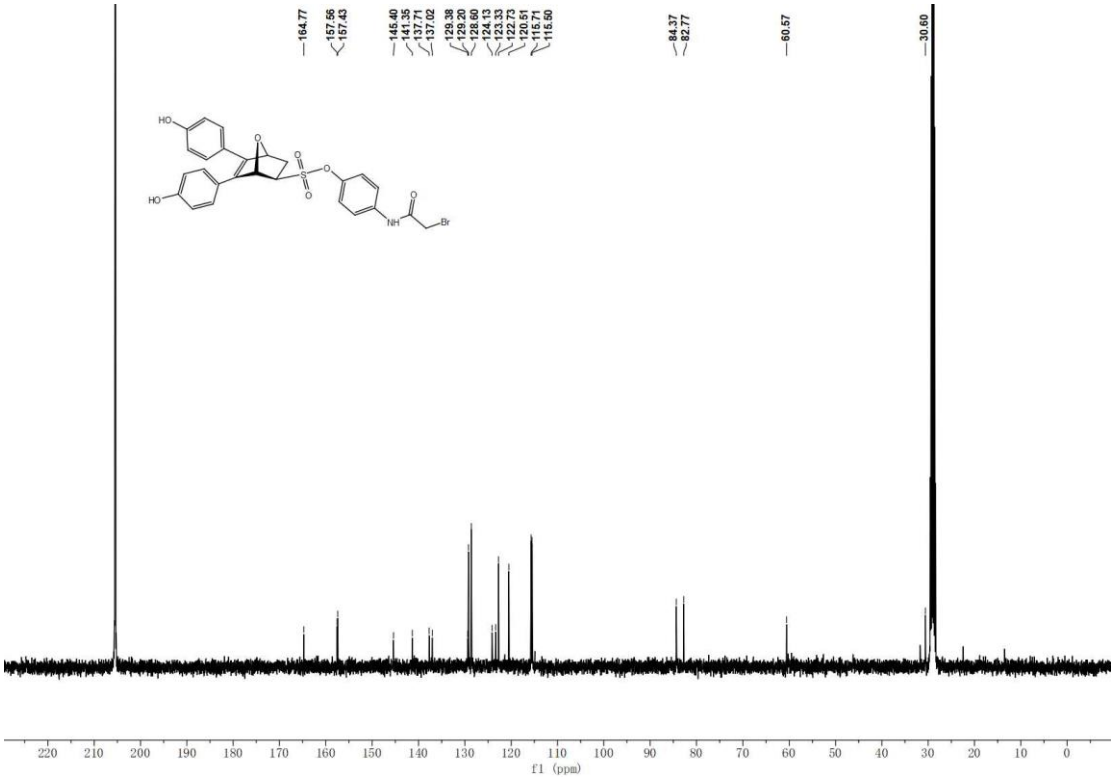
1.00
1.00
1.00
f1 (ppm)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157.43
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137.71
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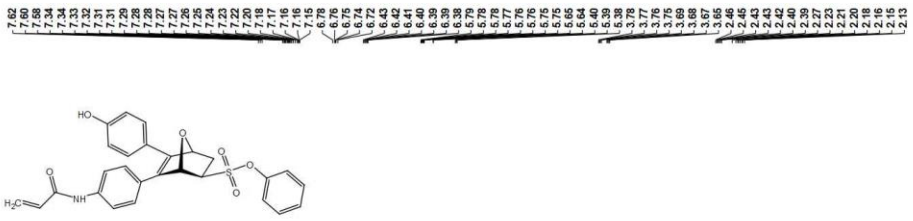
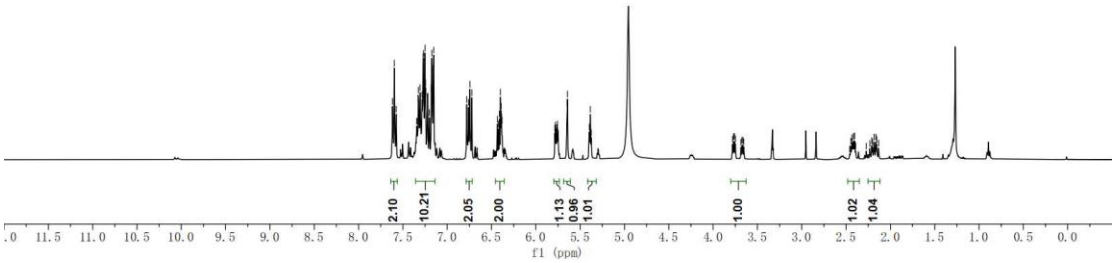
129.38
129.20
128.60
124.13
123.33
122.73
120.51
115.71
115.60
84.37
82.77
60.57
30.60
HO
HO
O
O
S
O
O
NH
O
Br
f1 (ppm)

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0.96
1.01
1.00
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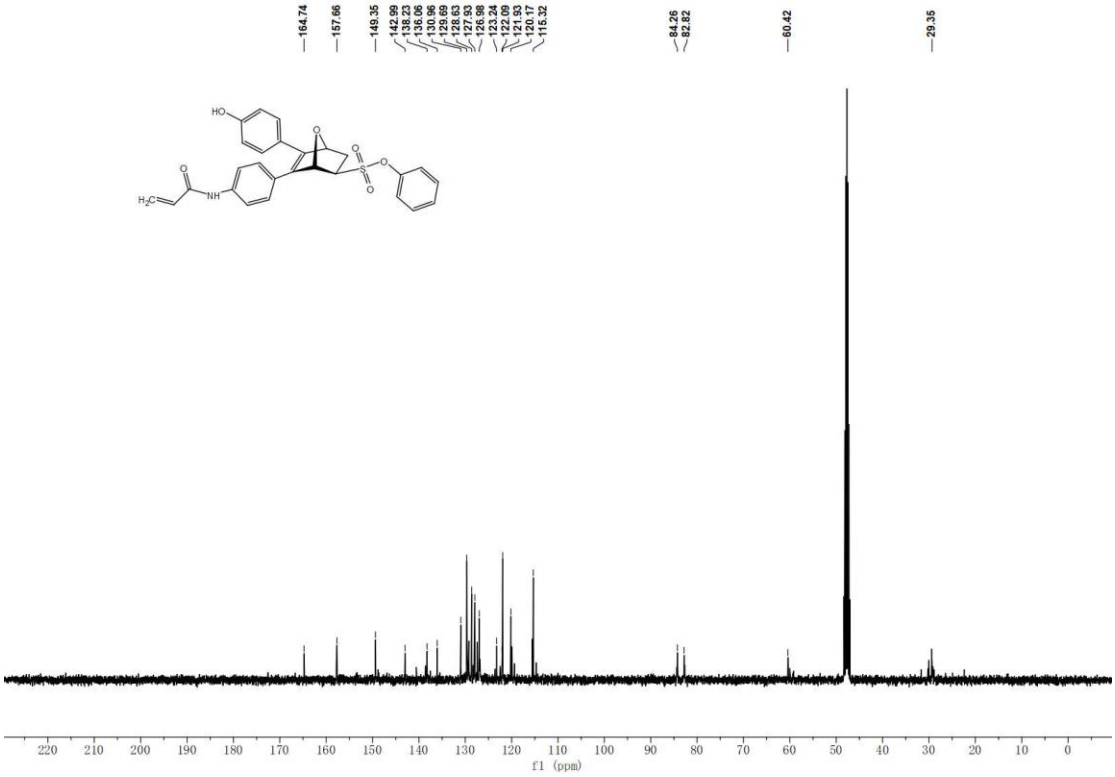
1.04
f1 (ppm)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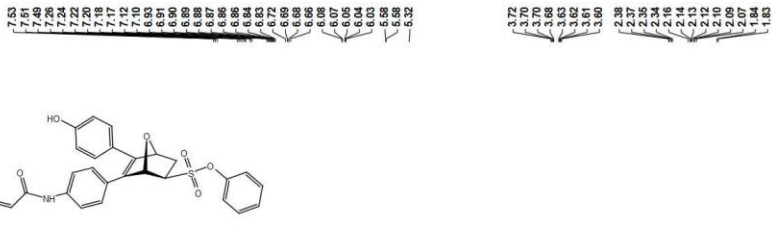
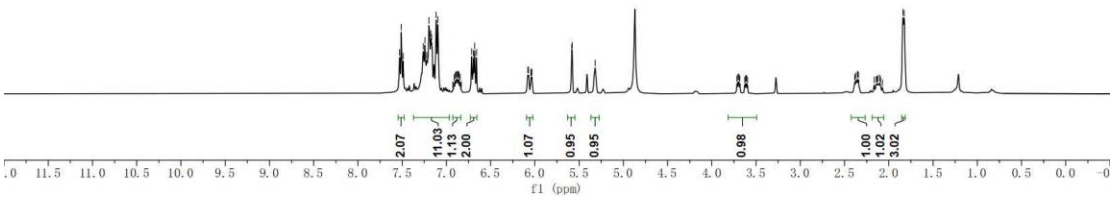
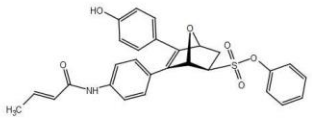
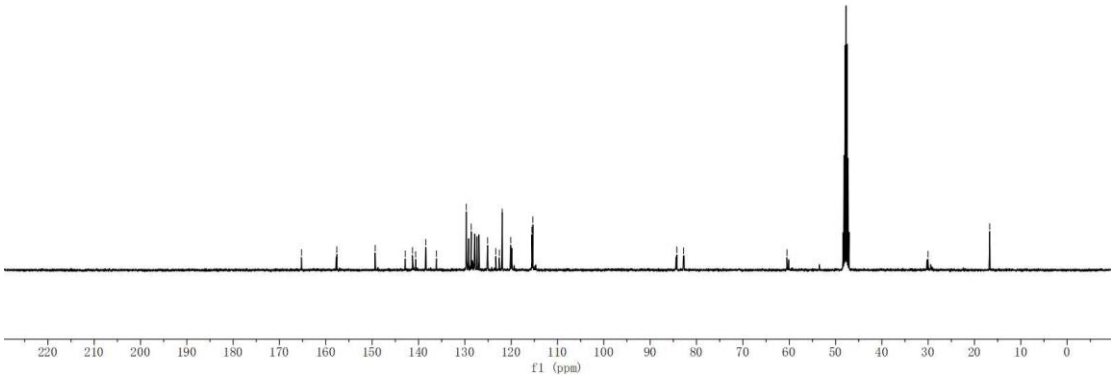
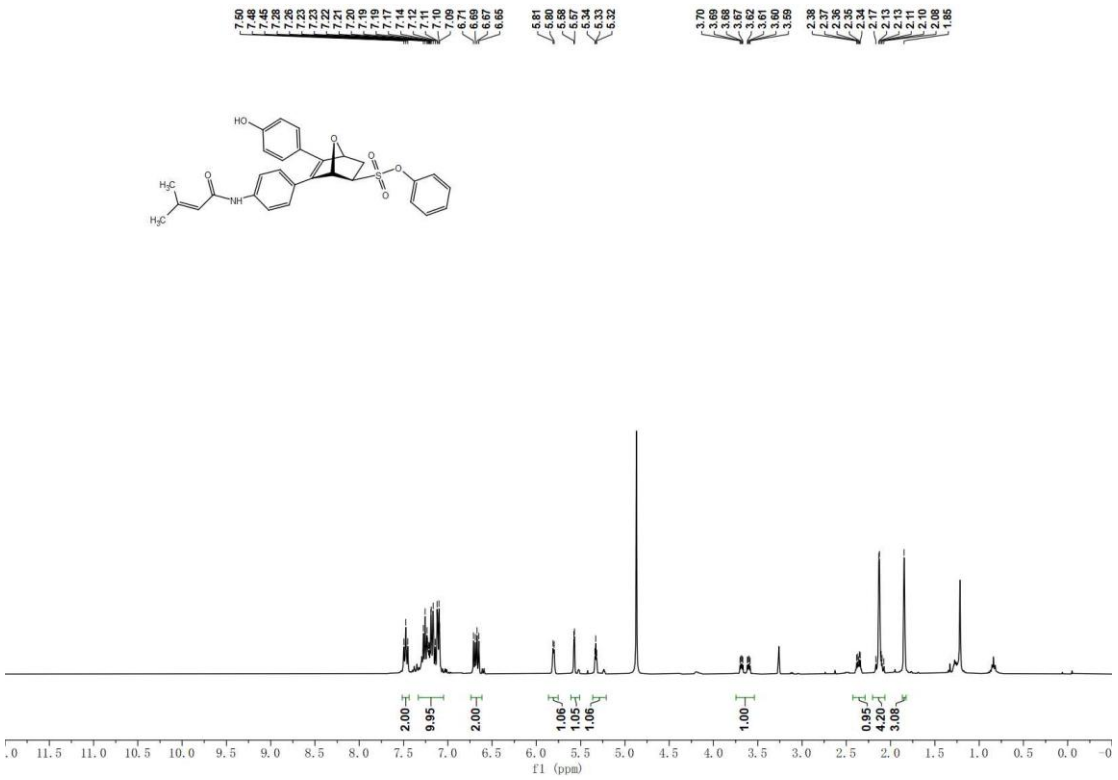
82.82
60.42
29.35
f1 (ppm)

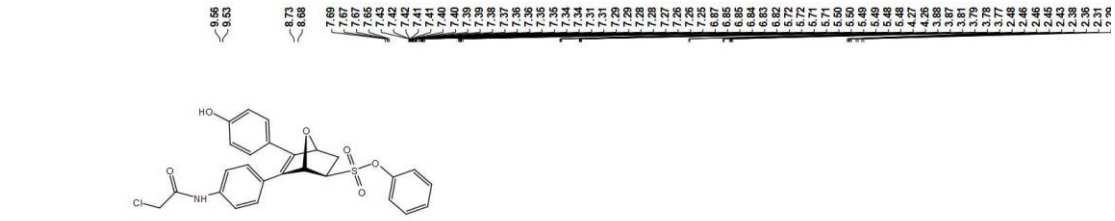


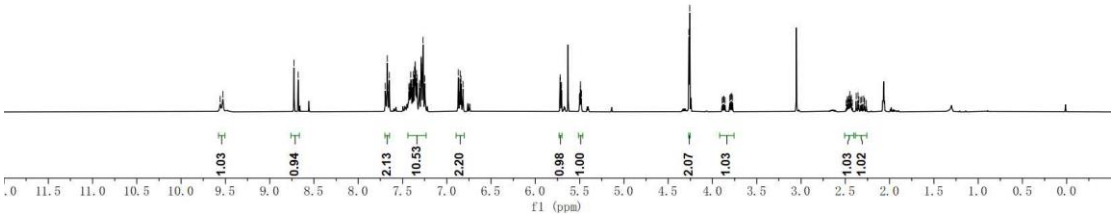


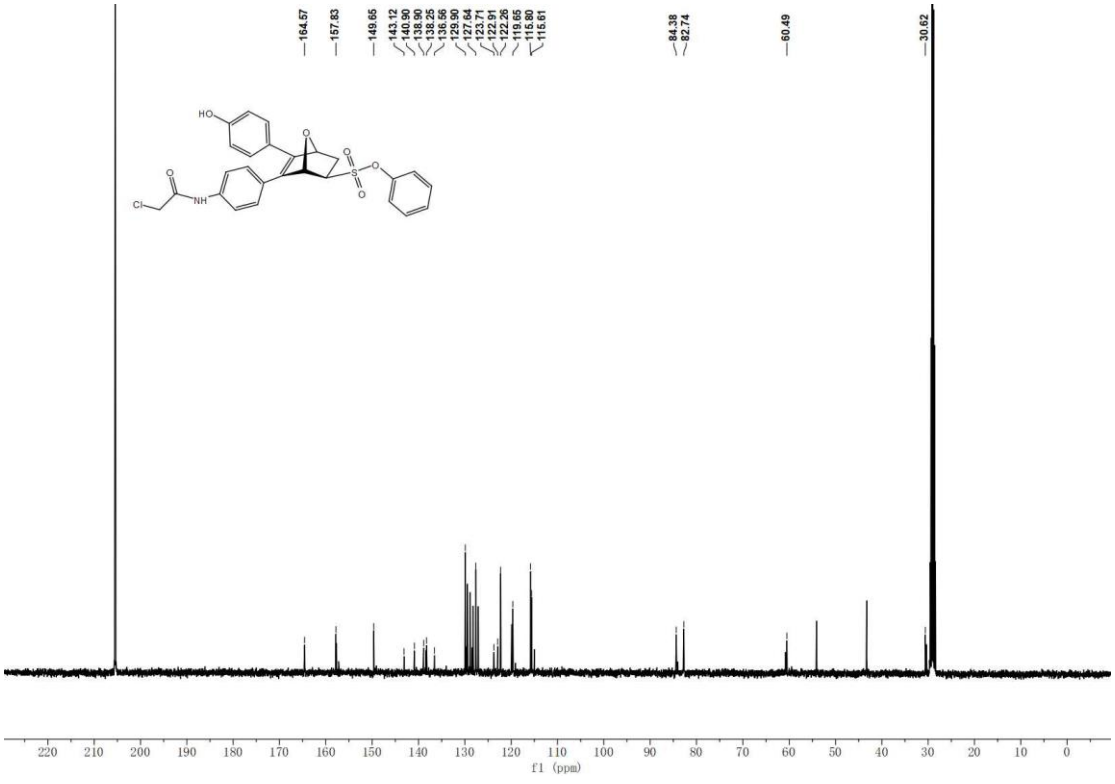


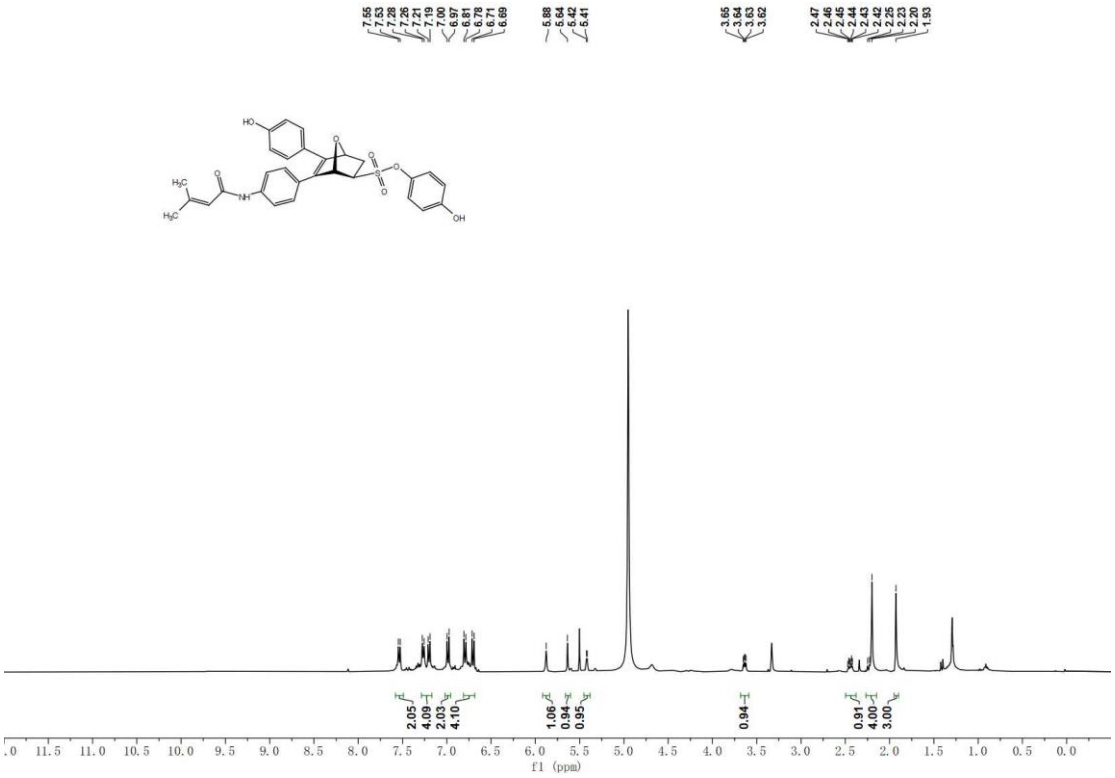








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6.71
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5.88
5.84
5.42
5.41
3.65
3.64
3.63
3.62
2.47
2.46
2.45
2.44
2.43
2.42
2.25
2.23
2.20
1.93
HO
O
O
S
O
O
NH
H3C
H3C
OH
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4.10
1.06
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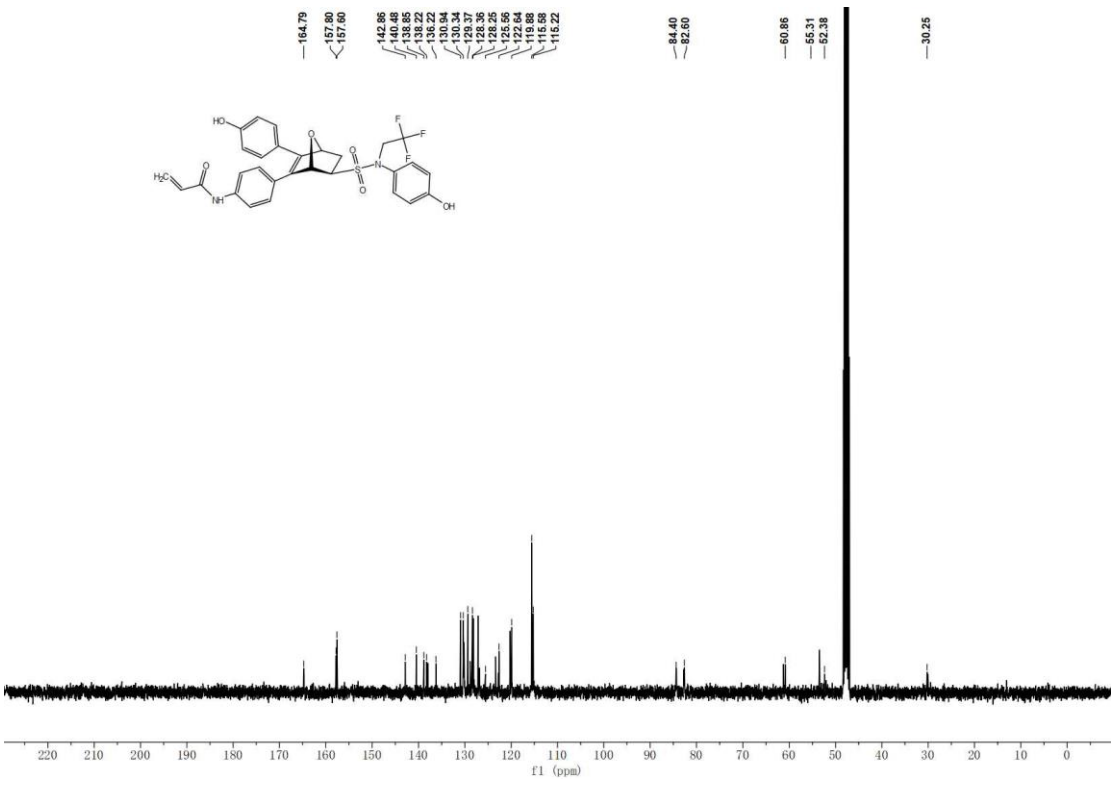
0.95
0.94
0.91
4.00
3.00
f1 (ppm)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128.25
125.55
122.64
119.88
115.58
115.22
84.40
82.60
60.86
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O
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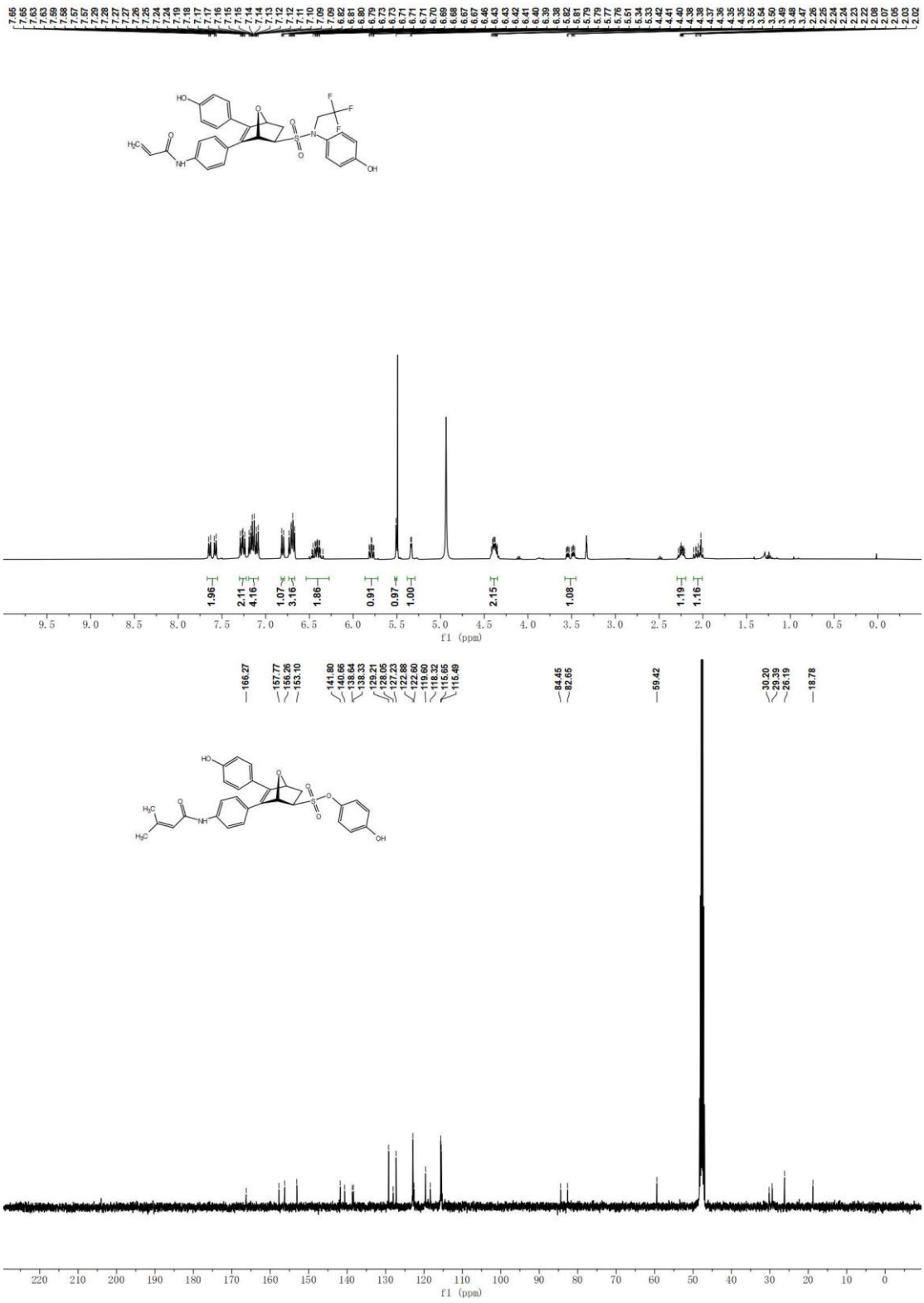
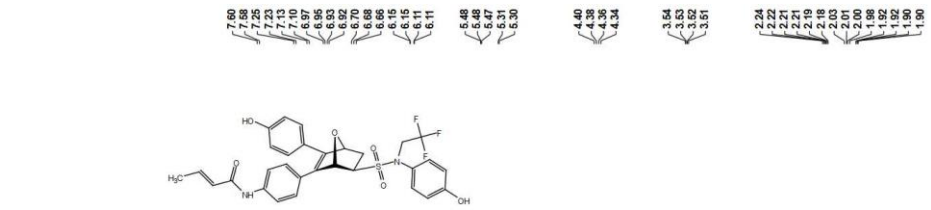
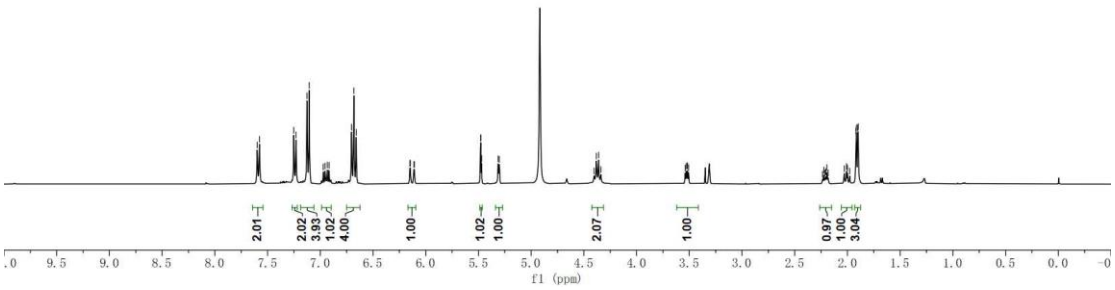
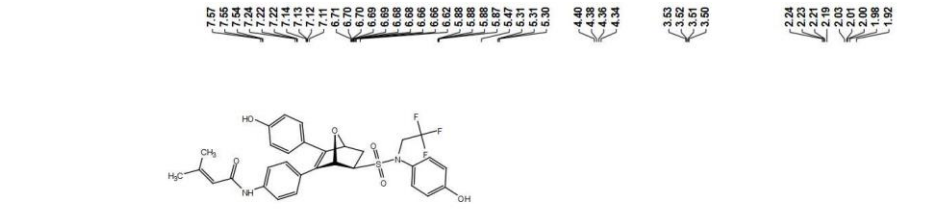
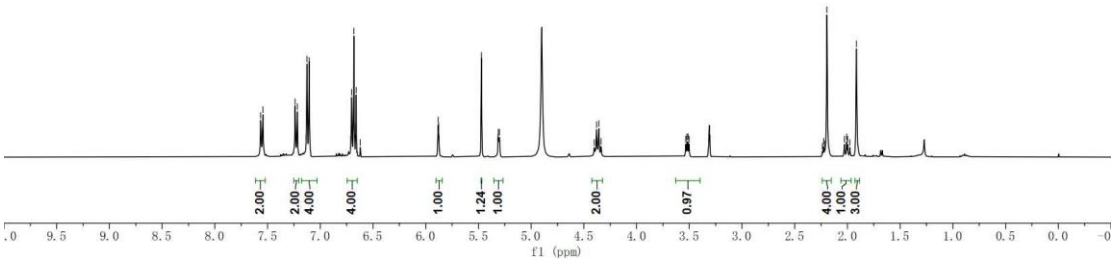
N
F
F
F
H2C
NH
OH
f1 (ppm)

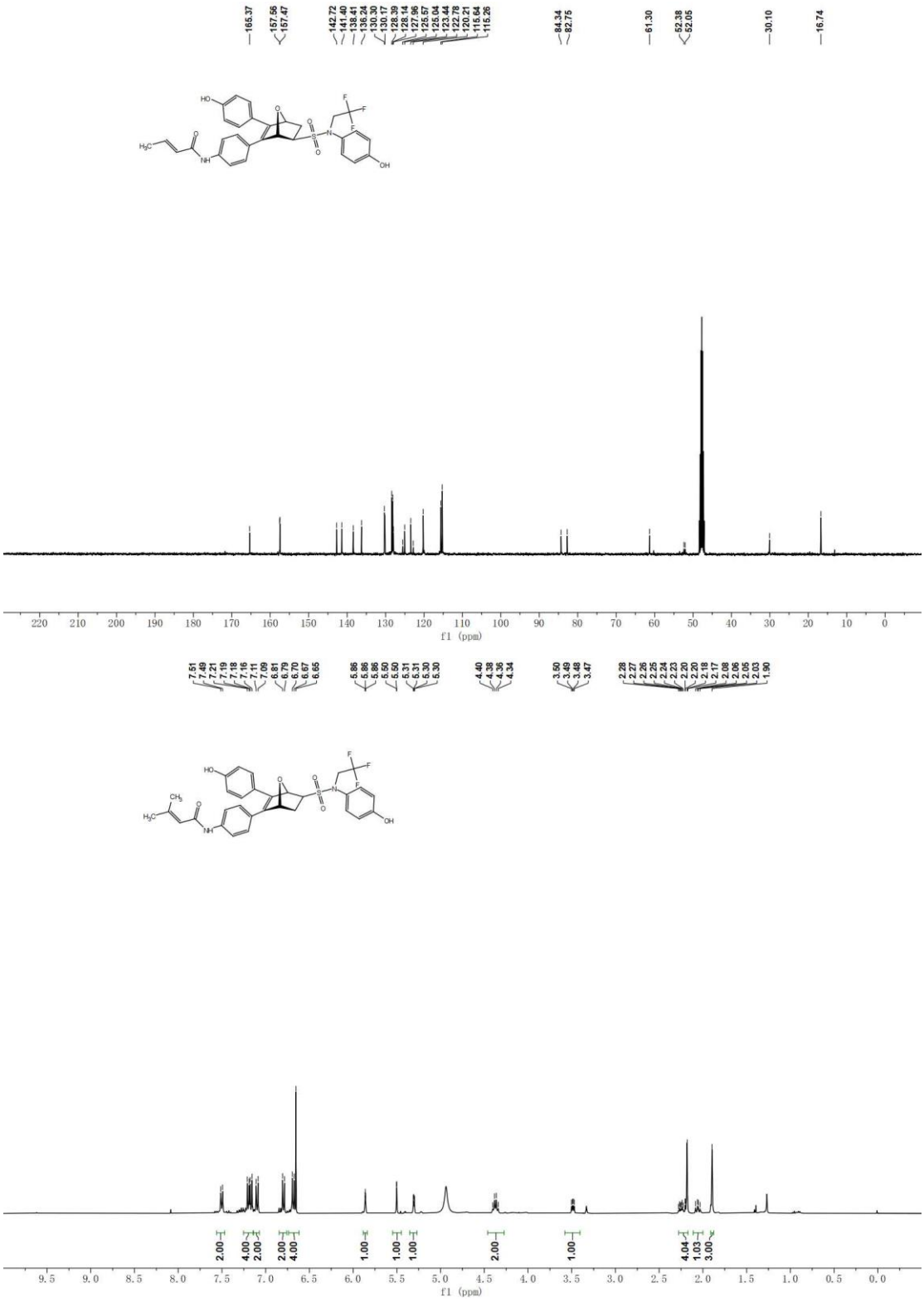








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127.96
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125.04
123.44
122.78
120.71
115.64
115.26
84.34
82.75
61.30
52.38
52.05
30.10
16.74
f1 (ppm)
7.51
7.49
7.21
7.19
7.18
7.16
7.11
7.09
6.81
6.79
6.70
6.67
6.65
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5.86
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5.30
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4.36
4.34
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3.49
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3.47
2.28
2.27
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2.25
2.24
2.23
2.20
2.20
2.18
2.17
2.08
2.06
2.05
2.03
1.90
2.00
4.00
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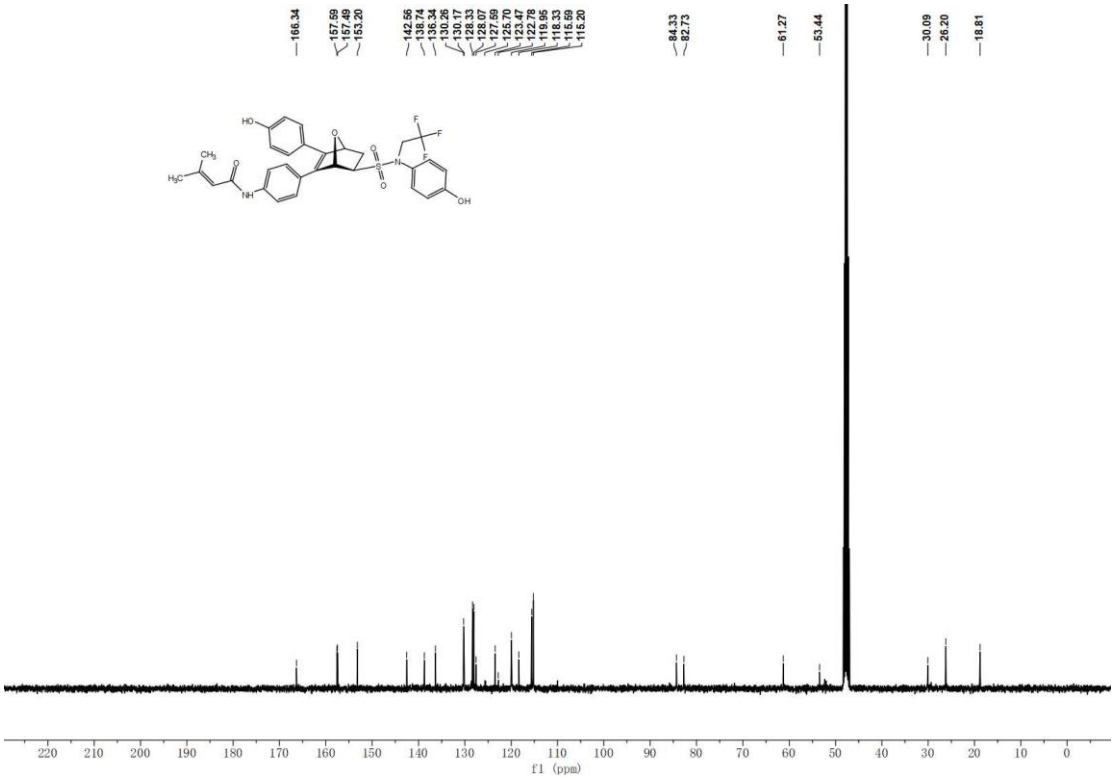
4.04
1.03
3.00
f1 (ppm)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128.07
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122.47
122.78
119.95
118.33
116.69
115.20
84.33
82.73
61.27
53.44
30.09
26.20
18.81
HO
O
O
S
O
N
F
F
F
OH
CH3
H3C
O
NH
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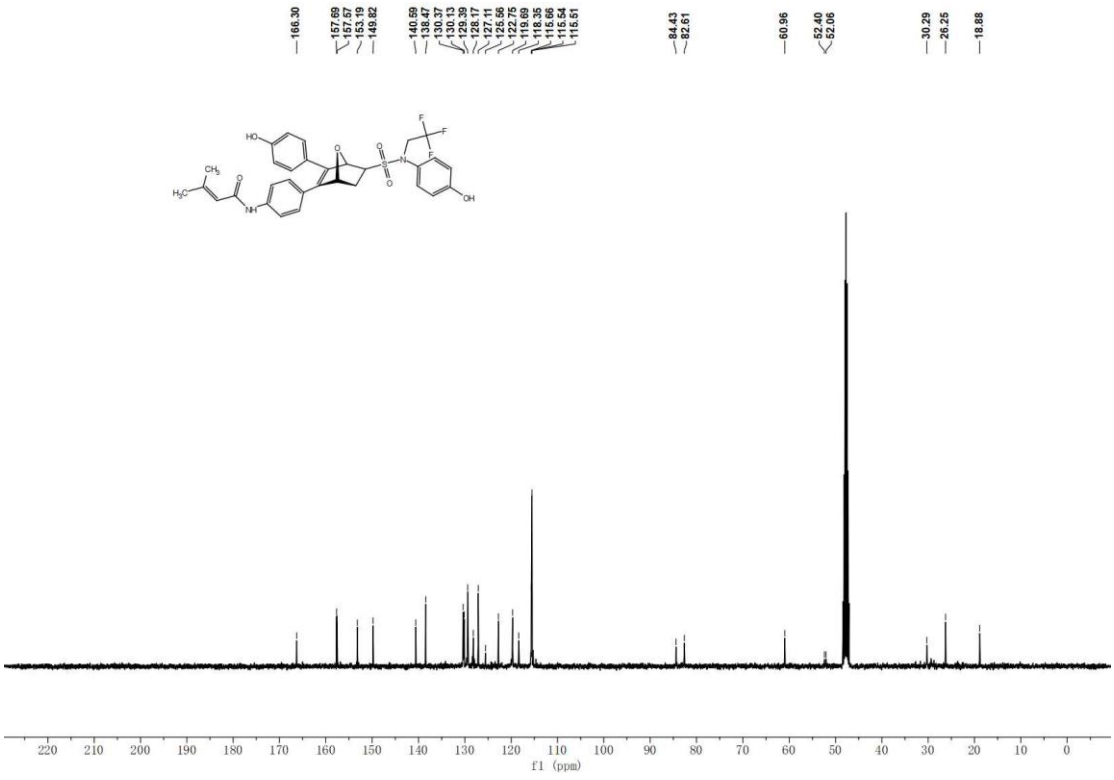
f1 (ppm)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130.37
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128.17
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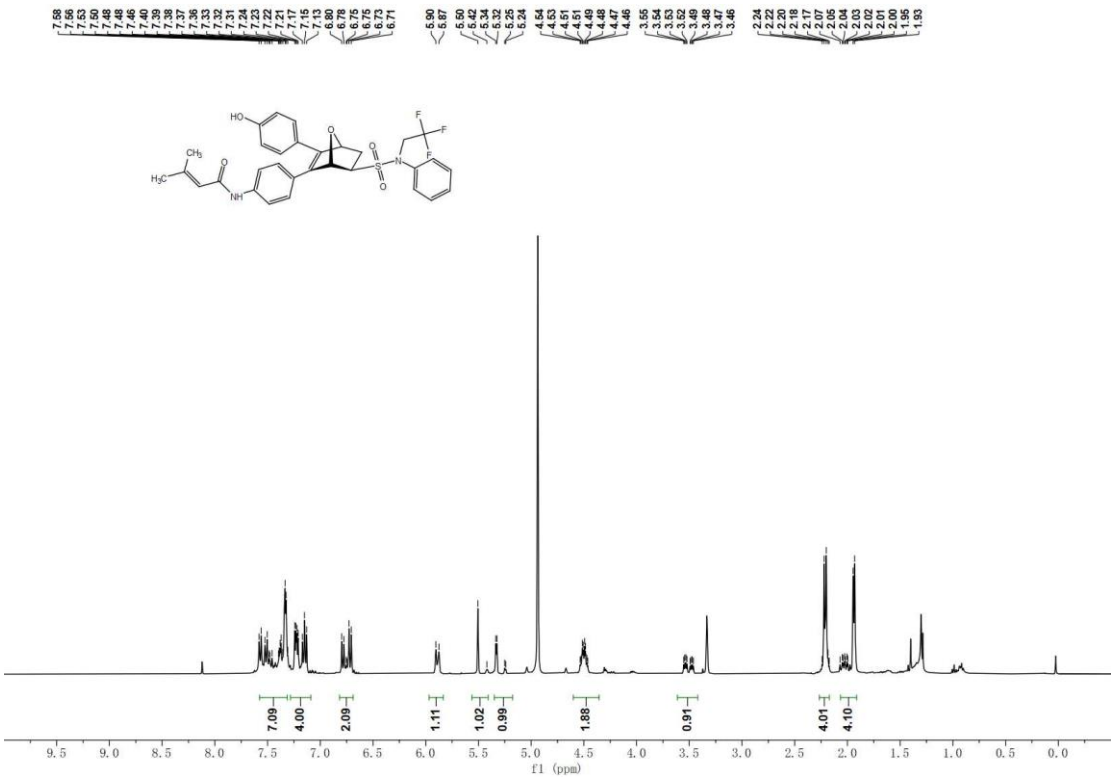
118.35
116.66
115.54
116.61
84.43
82.61
60.96
52.40
52.06
30.29
26.25
18.88
HO
O
O
S
O
N
F
F
F
OH
CH3
H3C
O
NH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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4.00
2.09
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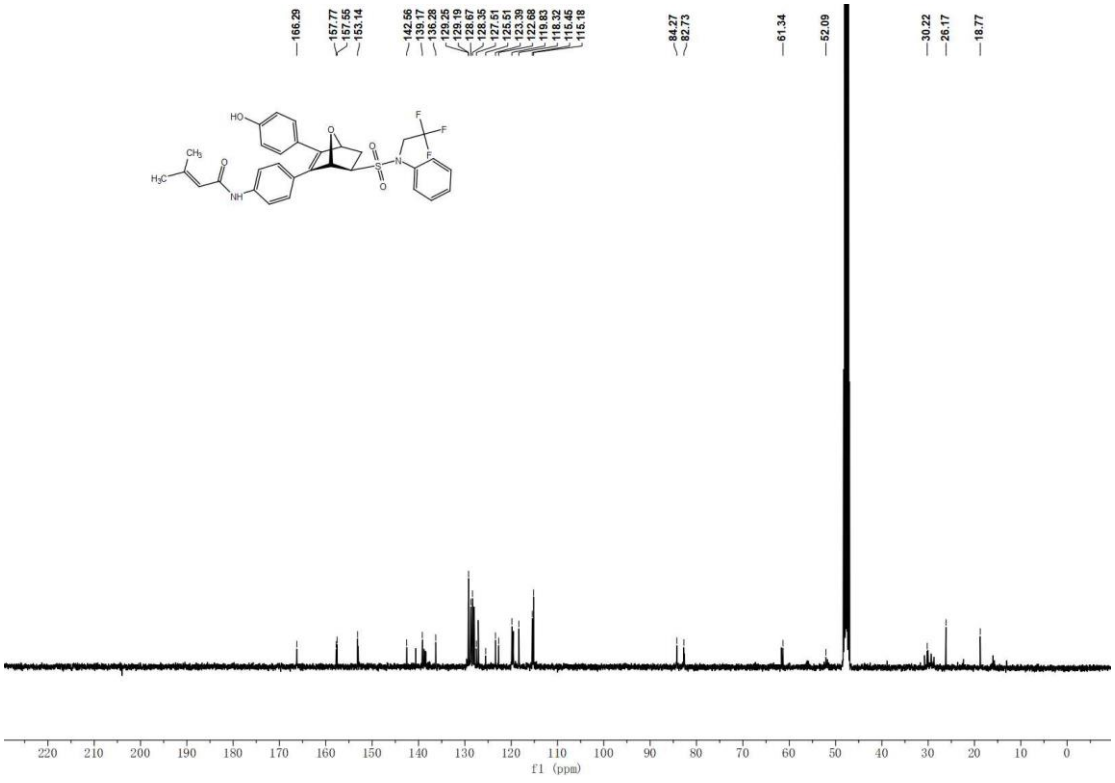
1.02
0.99
1.88
0.91
4.01
4.10
f1 (ppm)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123.39
122.68
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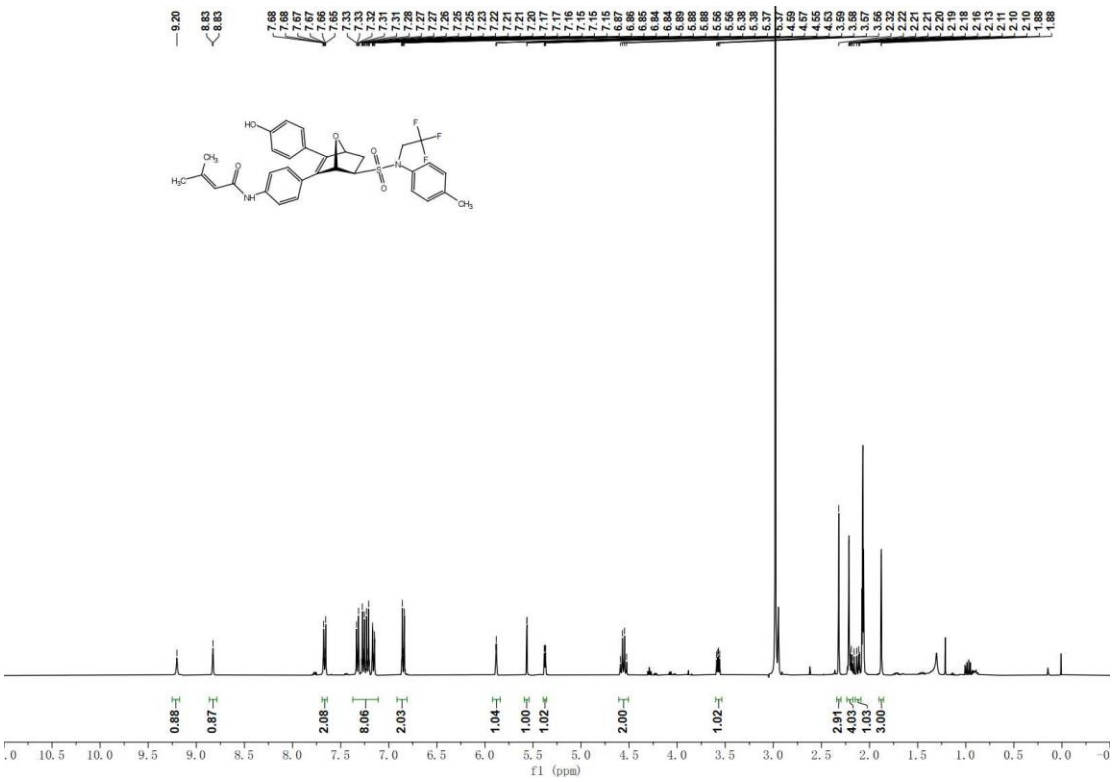
f1 (ppm)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7.17
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7.15
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6.85
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6.84
5.89
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5.88
5.56
5.56
5.38
5.38
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4.65
4.63
3.58
3.58
3.57
3.56
2.32
2.22
2.21
2.21
2.20
2.19
2.18
2.16
2.13
2.11
2.10
2.10
1.89
1.88
HO
O
O
S
O
N
F
F
F
CH3
H3C
O
NH
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0.87
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2.00
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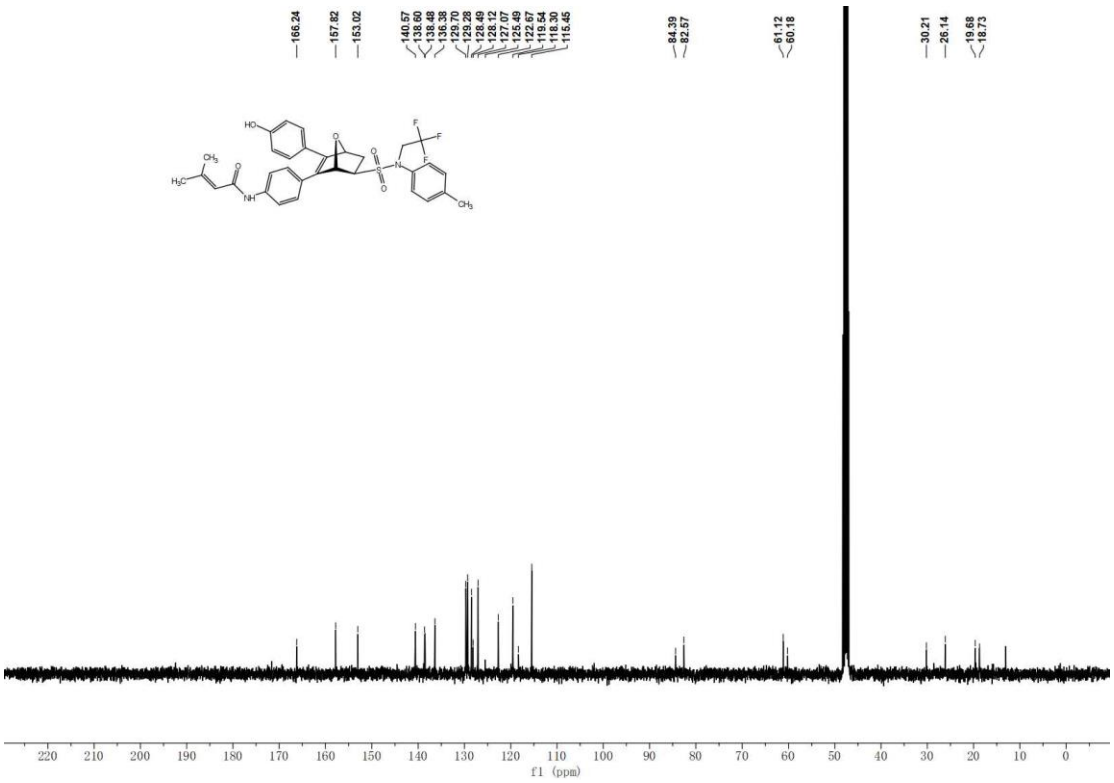
f1 (ppm)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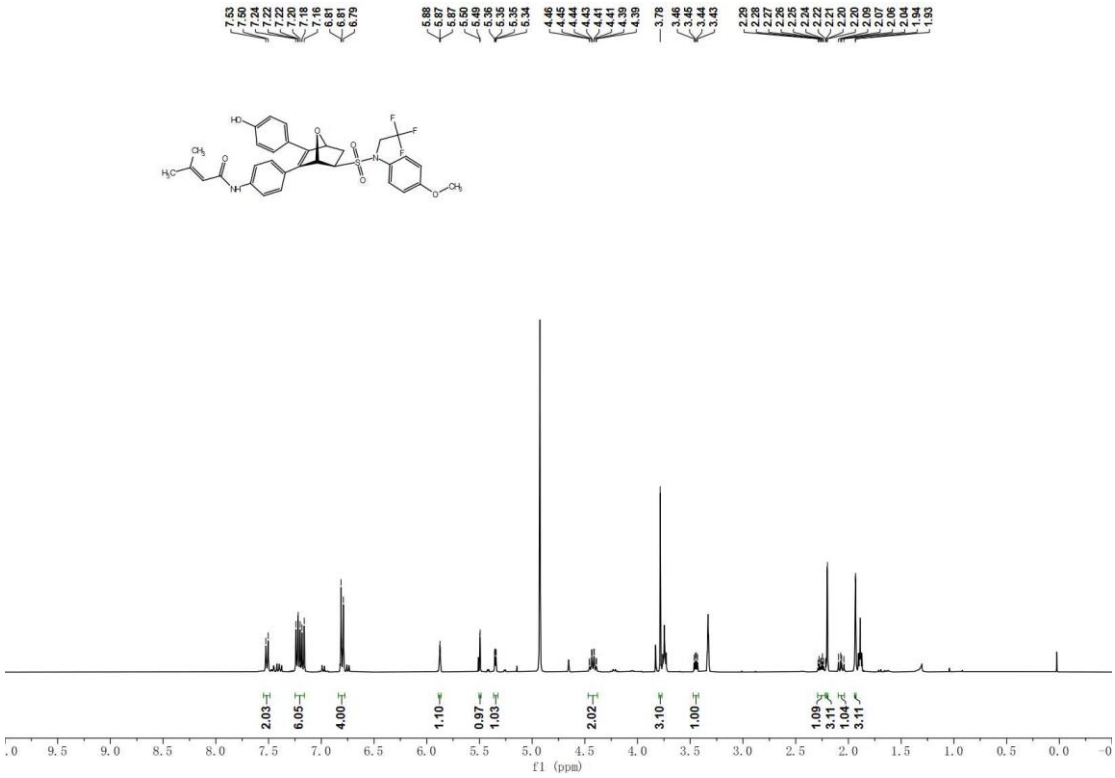
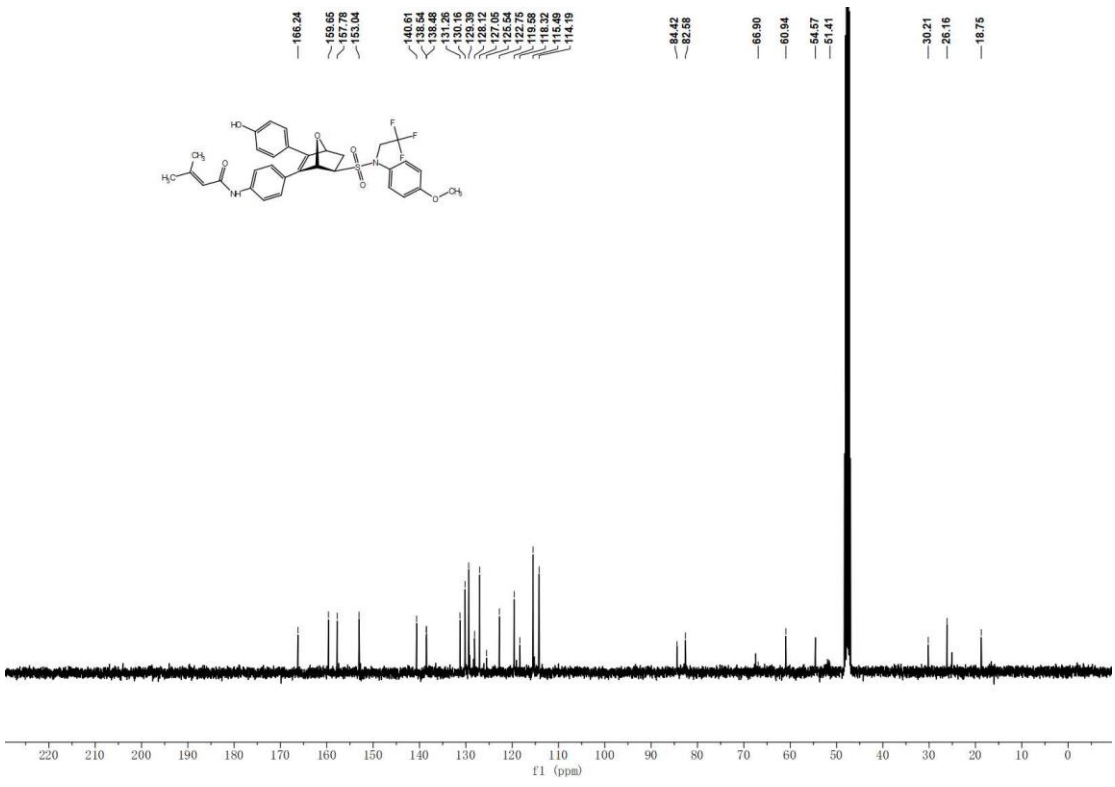
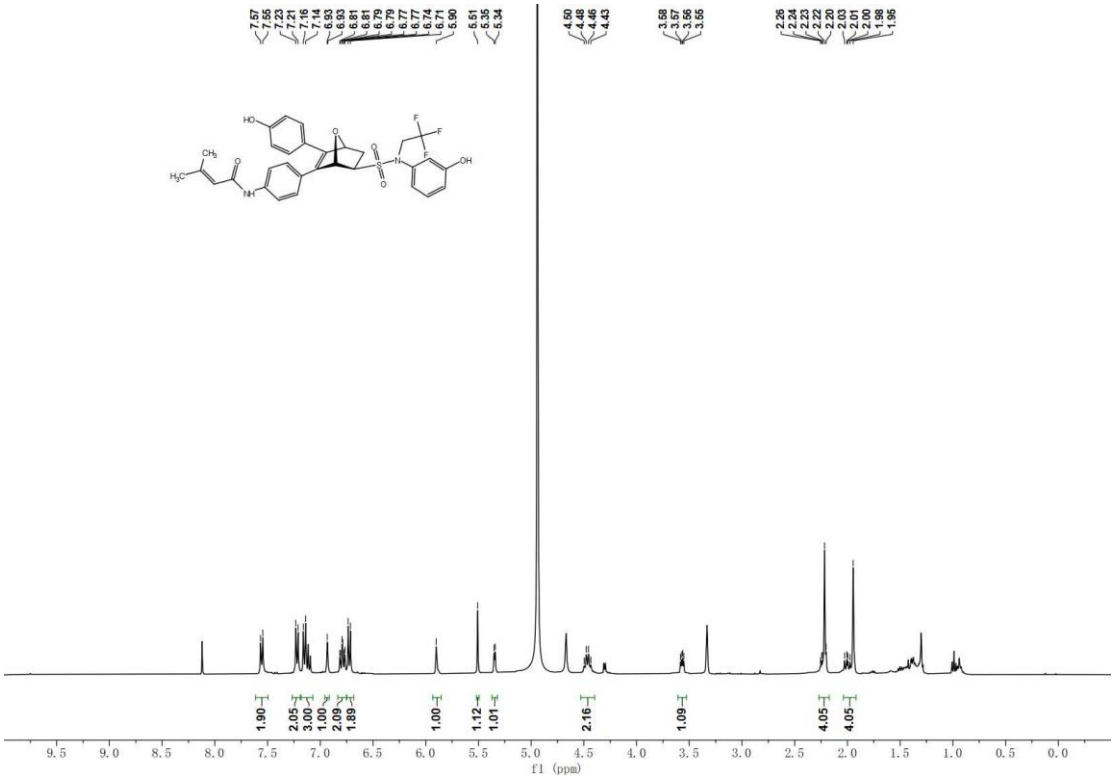
CH3
H3C
O
NH
f1 (ppm)



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4.46
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3.58
3.57
3.56
3.55
2.26
2.24
2.23
2.22
2.20
2.03
2.01
2.00
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1.95
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S
O
N
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CH3
H3C
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NH
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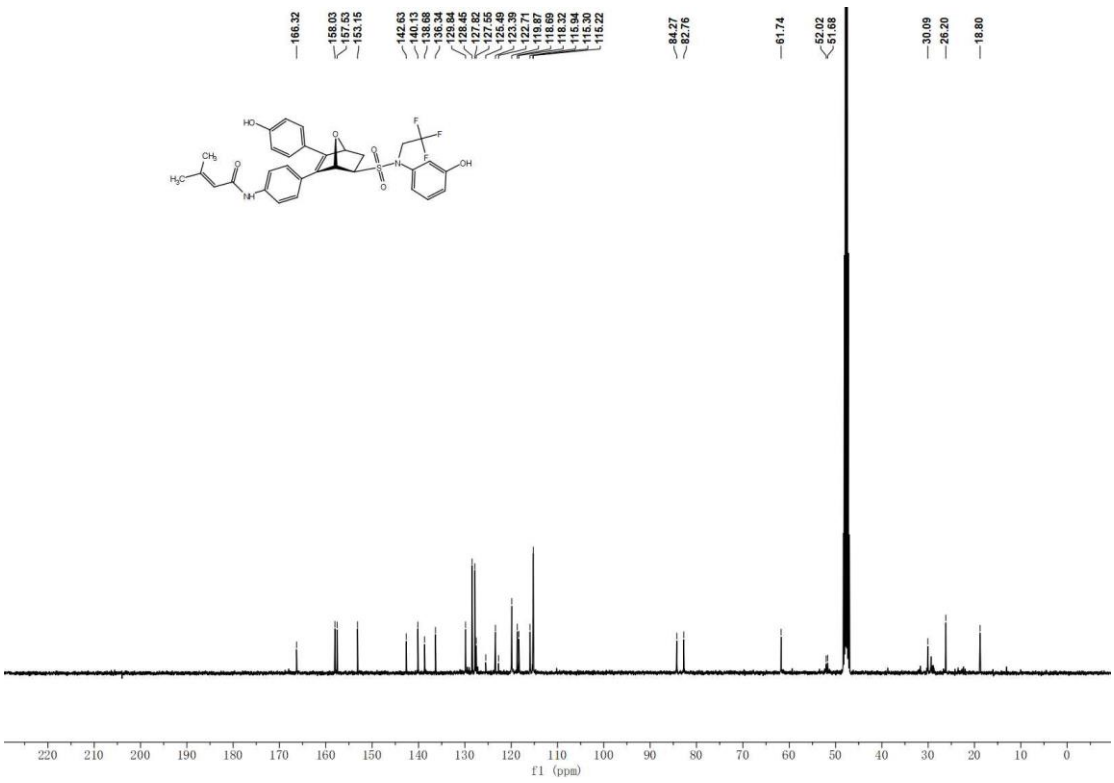
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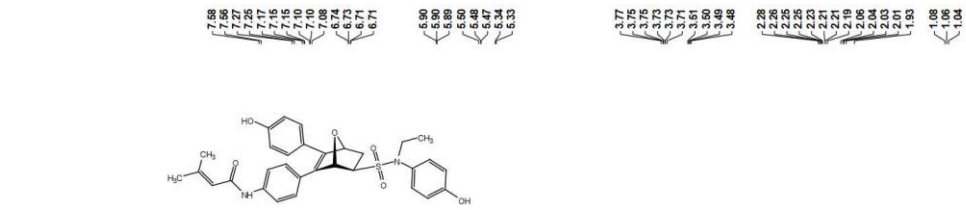
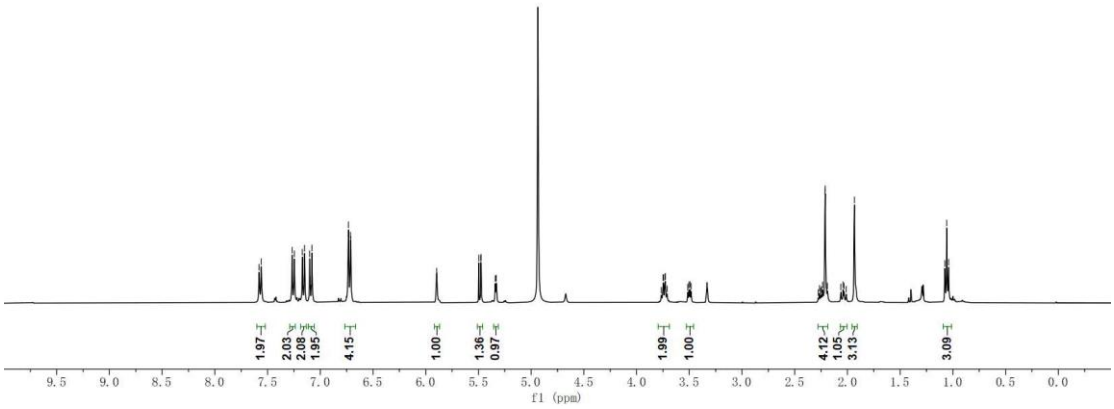
OH
CH3
H3C
O
NH
f1 (ppm)

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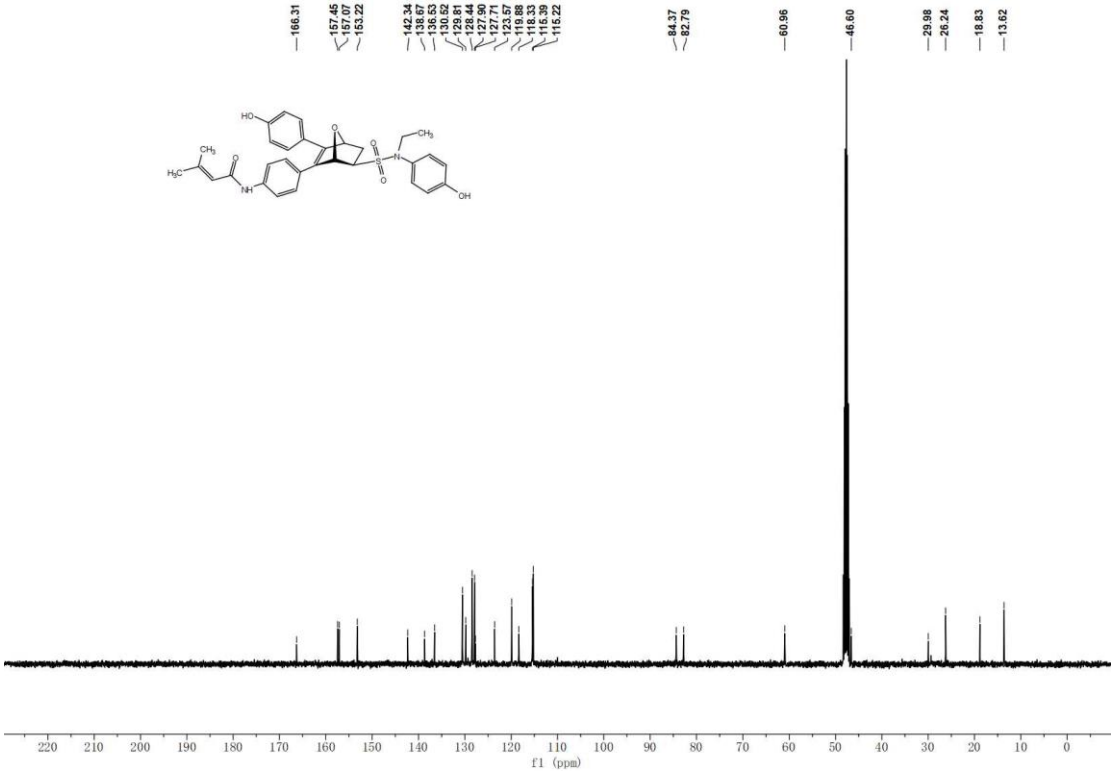
f1 (ppm)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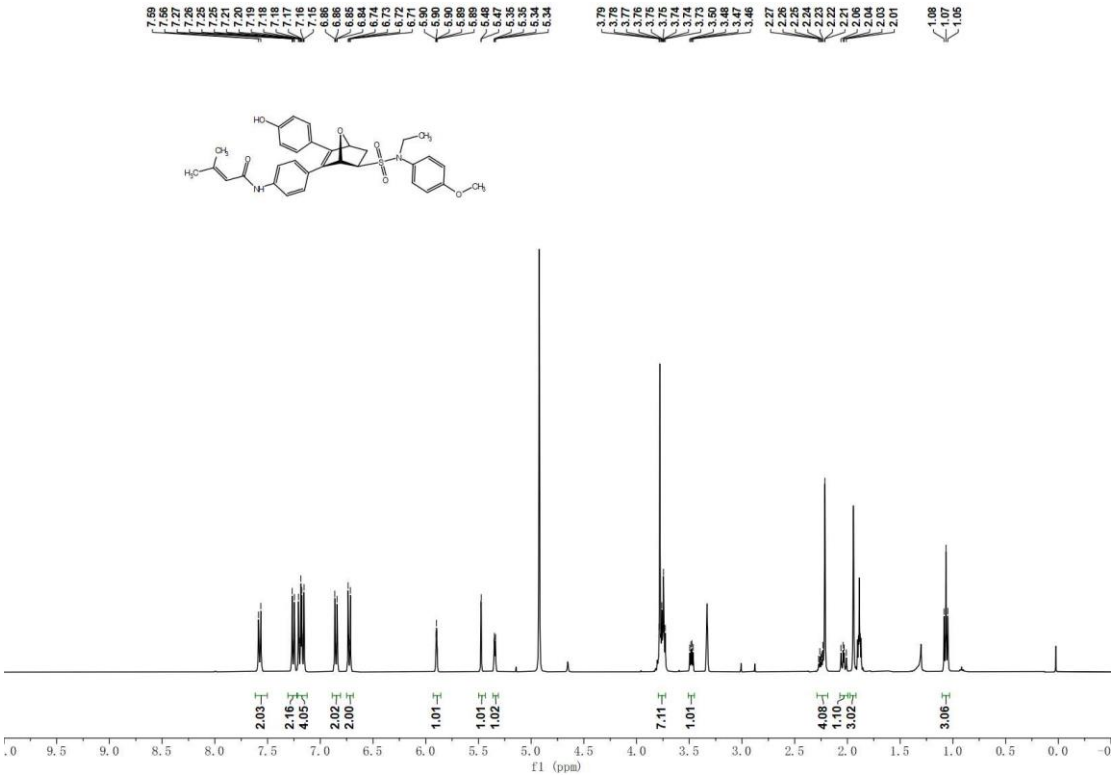
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2.03
2.01
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1.07
1.05
HO
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CH3
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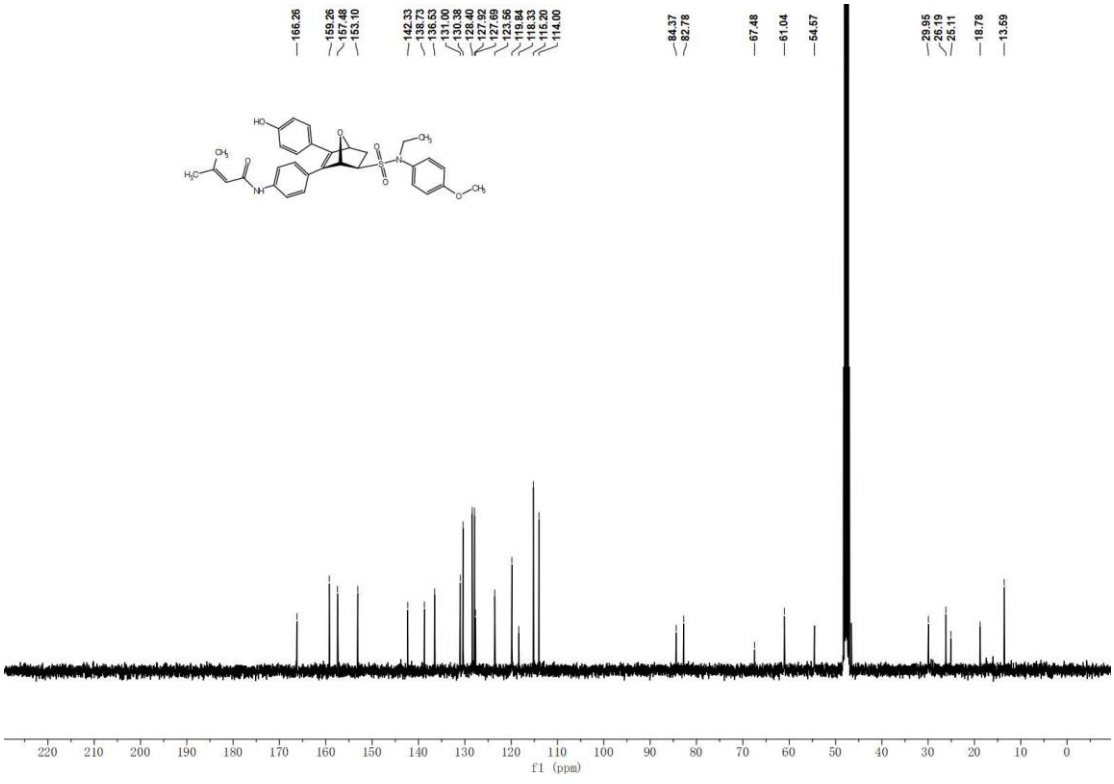
f1 (ppm)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118.33
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114.00
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67.48
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29.95
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25.11
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13.59
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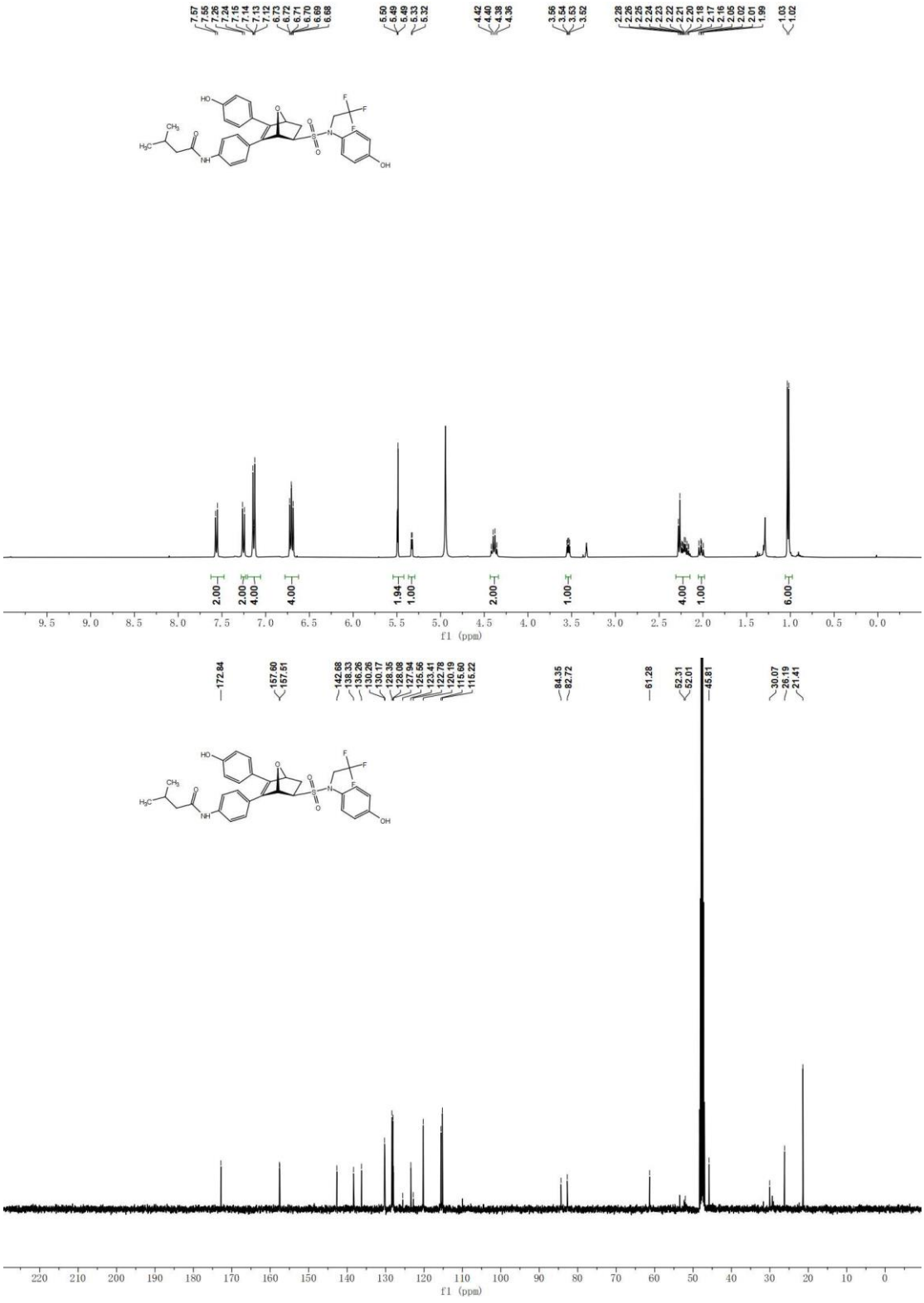
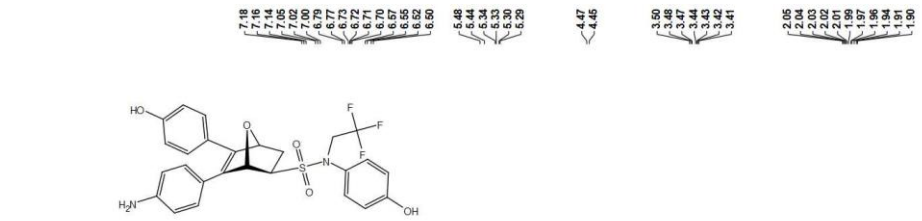
N
O
CH3
H3C
NH
O
CH3
f1 (ppm)

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3.48
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2.04
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F
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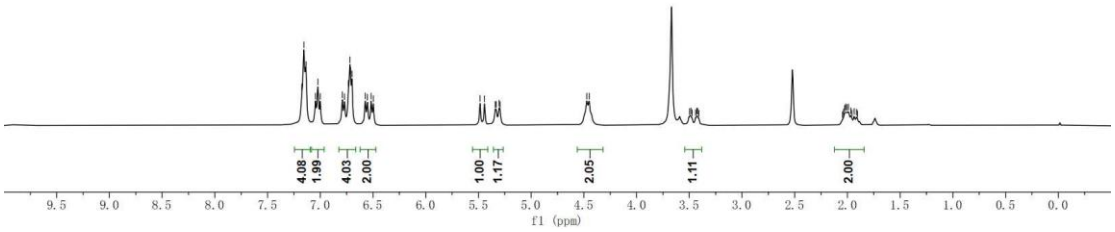
S
O
N
H2N
OH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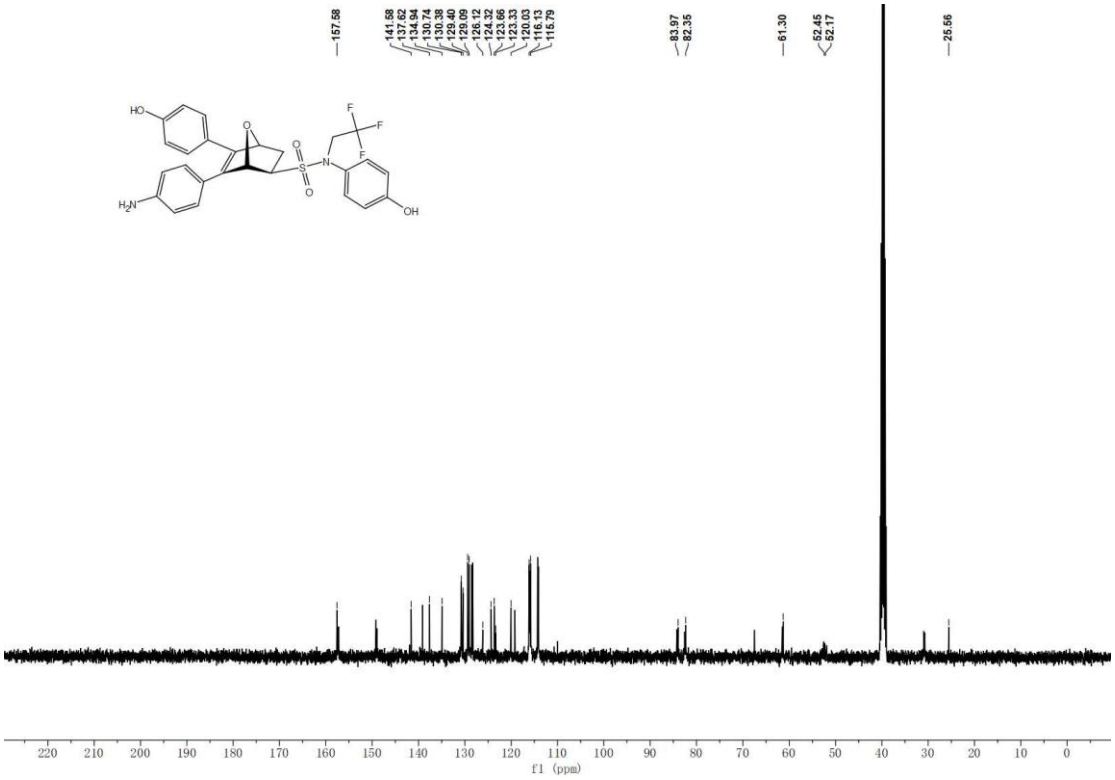
2.05
1.11
2.00
f1 (ppm)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83.97
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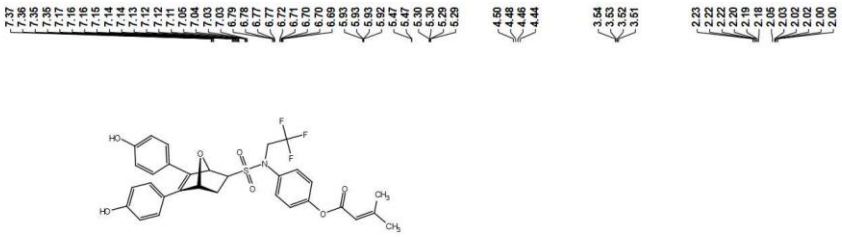
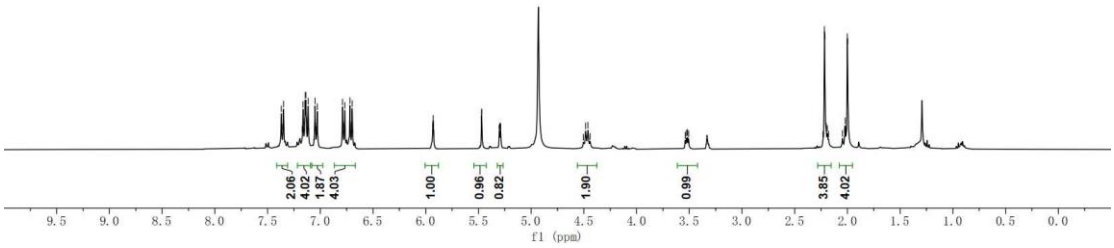
F
O
S
O
N
H2N
OH
f1 (ppm)

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4.03
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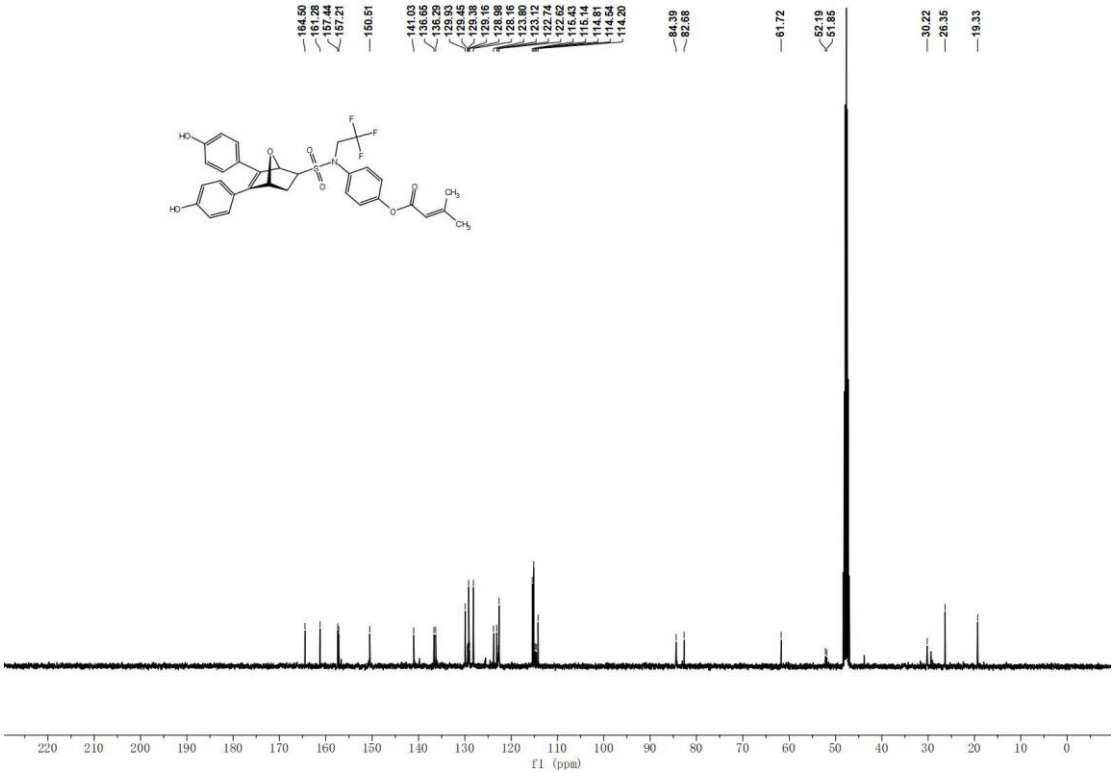
0.96
0.82
1.90
0.99
3.85
4.02
f1 (ppm)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128.98
128.16
123.80
123.12
122.74
122.62
115.43
115.14
114.81
114.54
114.20
84.39
82.68
61.72
52.19
51.85
30.22
26.35
19.33
f1 (ppm)

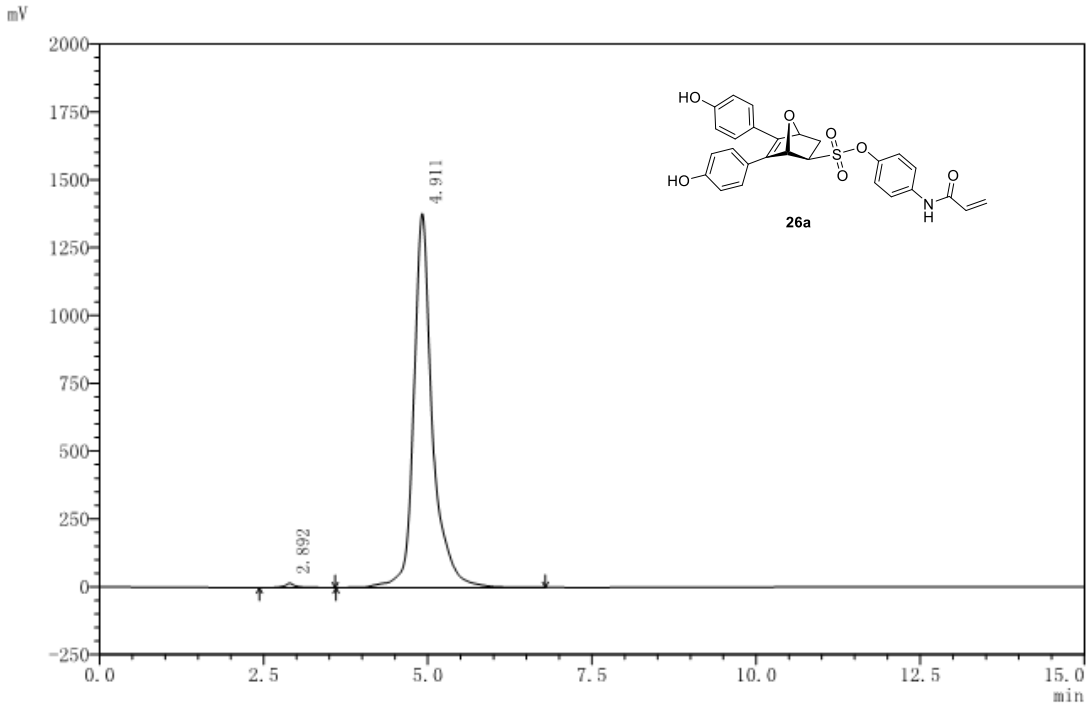
PART VII. HPLC and HMRS spectra of final compounds

All the HPLC were conducted on Shimadzu LabSolutions LC and all the results were obtained under the condition of UV 254 nm.

Table S3. Ascertainment of purity by HPLC.

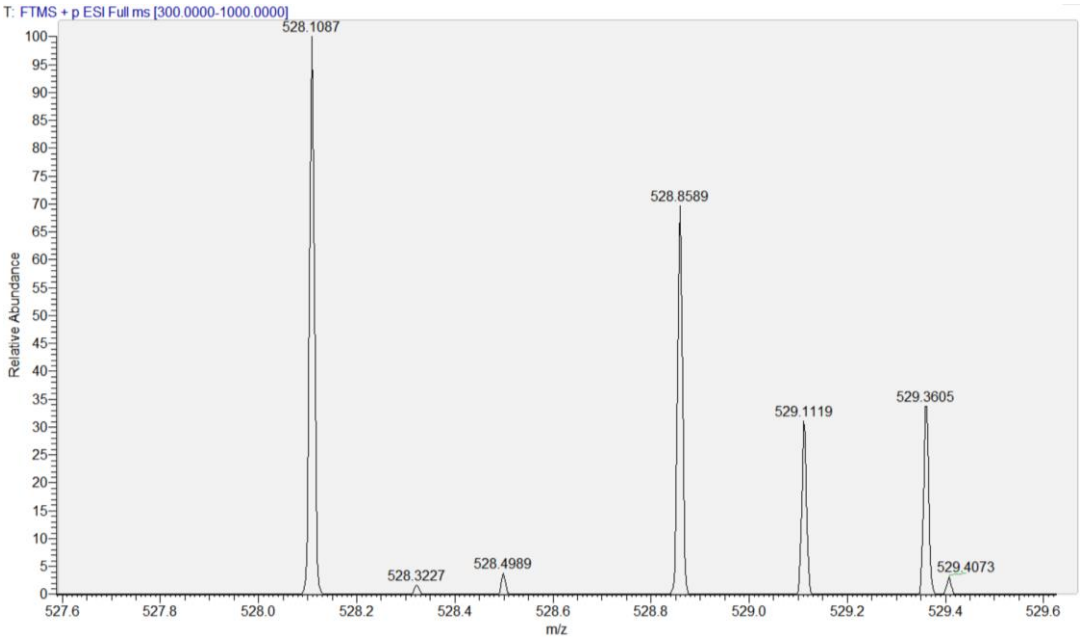
Cmpd.	Reverse Phase	Ret. Time	Purity %	Cmpd.	Reverse Phase	Ret. Time	Purity %
26a	90:10 MeOH: H2O	4.91	99.21	**29b**	90:10 MeOH: H2O	4.86	99.94
26b	90:10 MeOH: H2O	5.45	96.68	**29c**	90:10 MeOH: H2O	4.66	99.91
26c	90:10 MeOH: H2O	4.61	99.56	**29c'**	90:10 MeOH: H2O	4.59	100
26d	90:10 MeOH: H_2O	4.13	98.71	**29d**	90:10 MeOH: H2O	5.29	99.89
26e	90:10 MeOH: H_2O	4.63	99.80	**29e**	90:10 MeOH: H2O	5.03	98.64
26f	90:10 MeOH: H_2O	4.66	100	**29f**	90:10 MeOH: H2O	5.03	99.73
28a	80:20 MeOH: H_2O	11.91	98.01	**29g**	90:10 MeOH: H2O	5.13	98.09
28b	80:20 MeOH: H_2O	9.00	99.15	**29h**	90:10 MeOH: H2O	4.64	99.88
28c	80:20 MeOH: H_2O	11.27	99.44	**29i**	90:10 MeOH: H2O	4.71	99.56
28d	80:20 MeOH: H_2O	13.84	100	**29j**	90:10 MeOH: H2O	5.22	100
28e	80:20 MeOH: H_2O	15.76	95.32	**29k**	90:10 MeOH: H2O	4.73	99.87
28f	80:20 MeOH: H_2O	11.70	99.28	**29l**	90:10 MeOH: H2O	4.59	98.96
29a	80:20 MeOH: H_2O	5.13	99.87	**29m**	90:10 MeOH: H2O	4.99	98.42

HPLC chromatogram of **26a.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

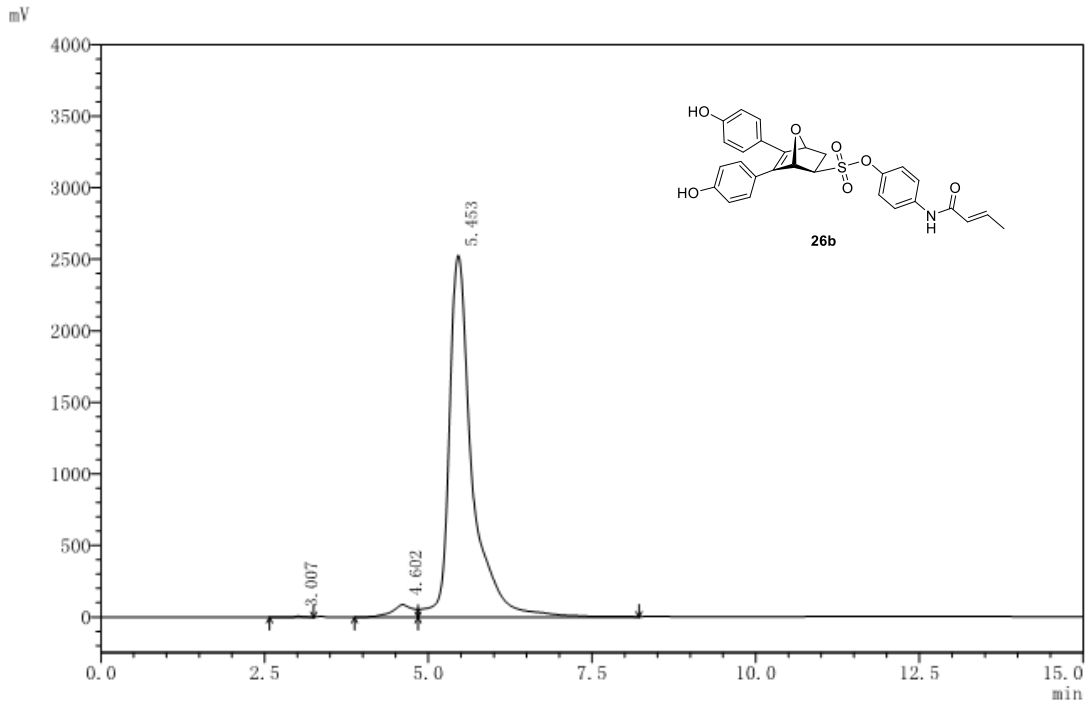


NO.	Retention Time	Area	Percent
1	2.892	217701	0.786
2	4.911	27466493	99.214
Total			100.000

HRMS (ESI) calcd for $C_{27}H_{23}NO_7S$ $[M + Na]^+$ 528.1087, found 528.1087.



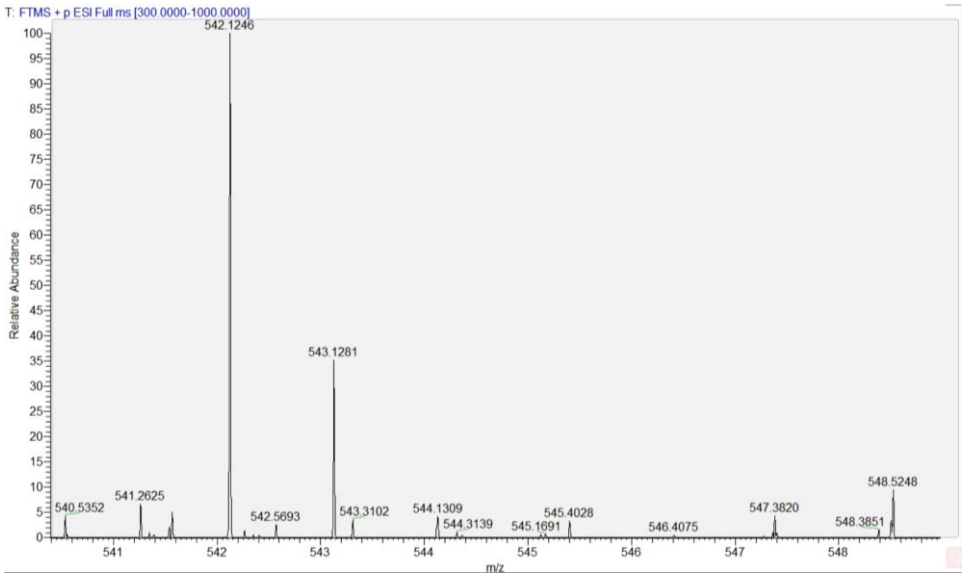
HPLC chromatogram of **26b.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



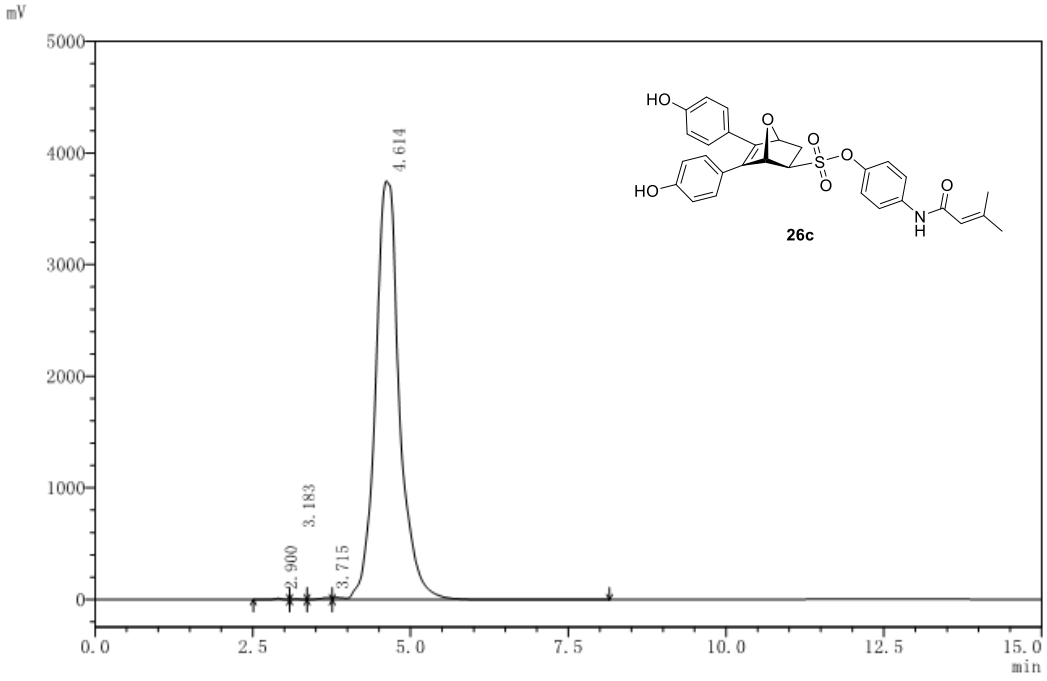
NO.	Retention Time	Area	Percent
1	3.007	110787	0.173
2	4.602	2021108	3.152

3	5.453	61998968	96.676
Total			100.000

HRMS (ESI) calcd for $C_{28}H_{25}NO_7S$ $[M + Na]^+$ 542.1244, found 542.1246.



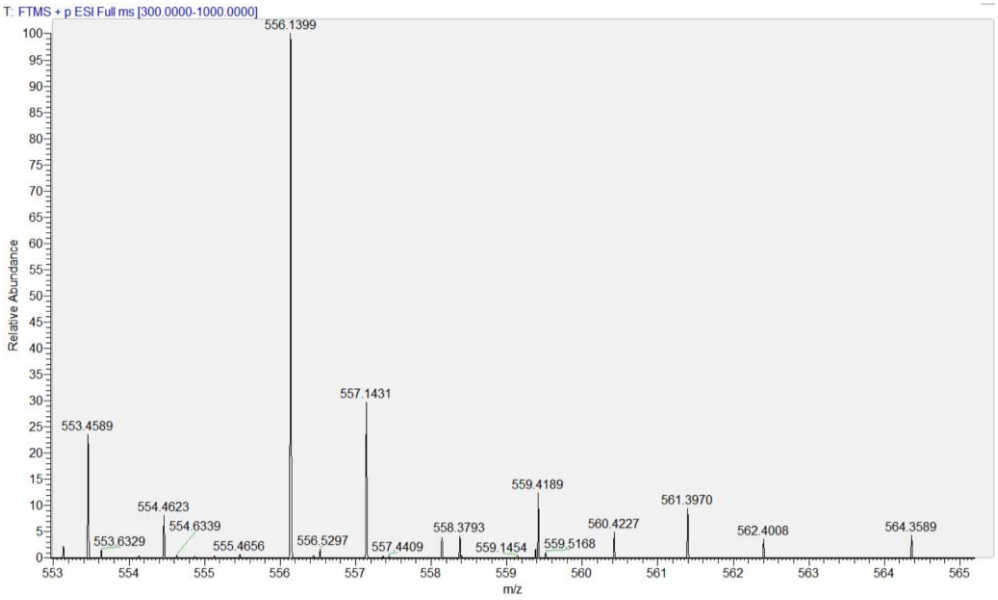
HPLC chromatogram of **26c.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



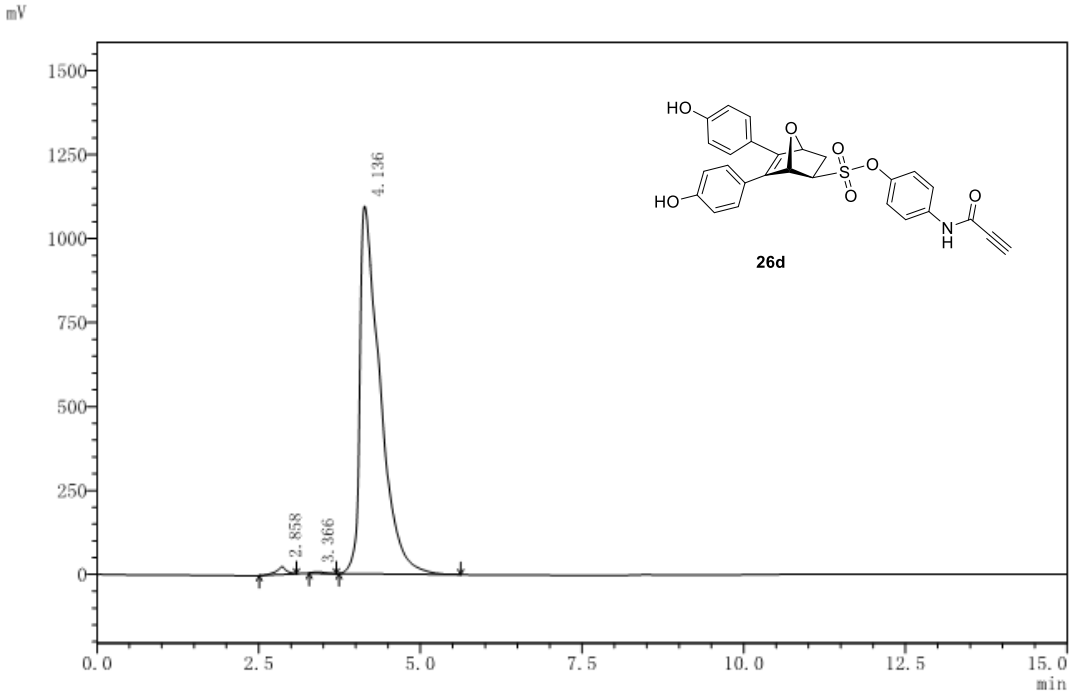
No.	Retention Time	Area	Percent
1	2.900	136768	0.137
2	3.183	64467	0.064

3	3.715	234892	0.235
4	4.614	99640073	99.564
Total			100.000

HRMS (ESI) calcd for $C_{29}H_{27}NO_7S$ $[M + Na]^+$ 556.1400, found 556.1399.



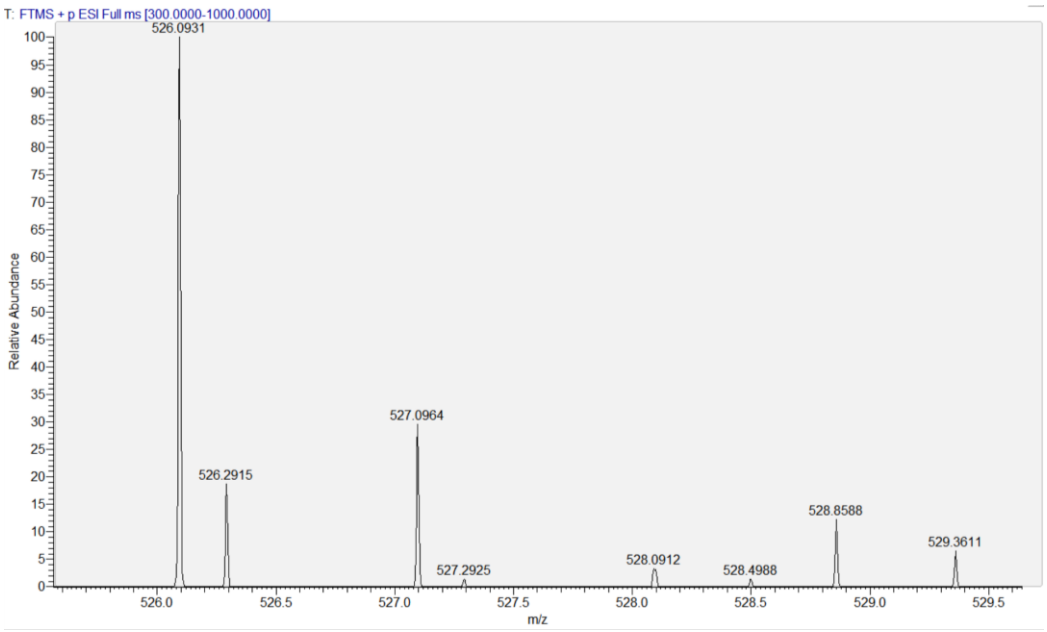
HPLC chromatogram of **26d.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



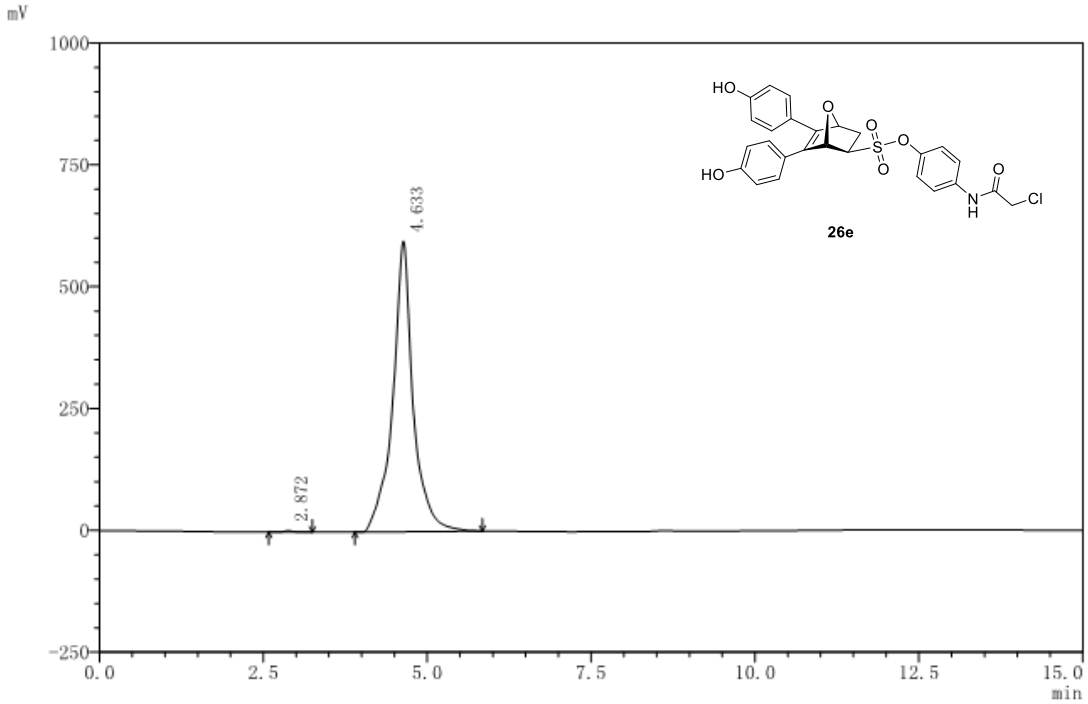
NO.	Retention Time	Area	Percent

1	2.858	256624	1.068
2	3.366	53802	0.224
3	4.136	23727744	98.709
Total			100.000

HRMS (ESI) calcd for $C_{27}H_{21}NO_7S$ $[M + Na]^+$ 526.0931, found 526.0931.

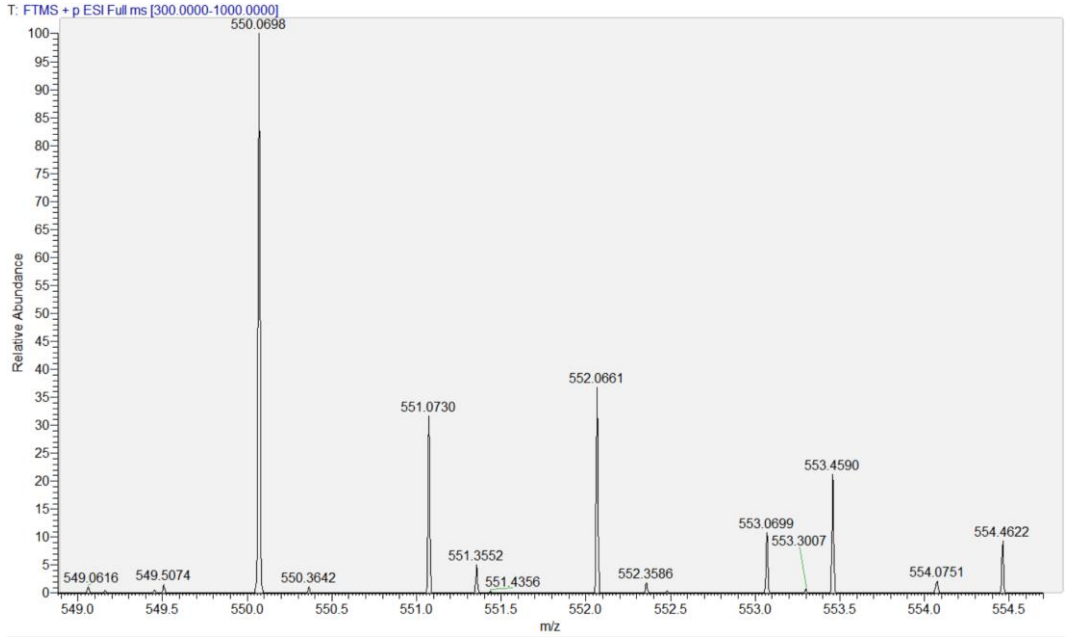


HPLC chromatogram of **26e.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

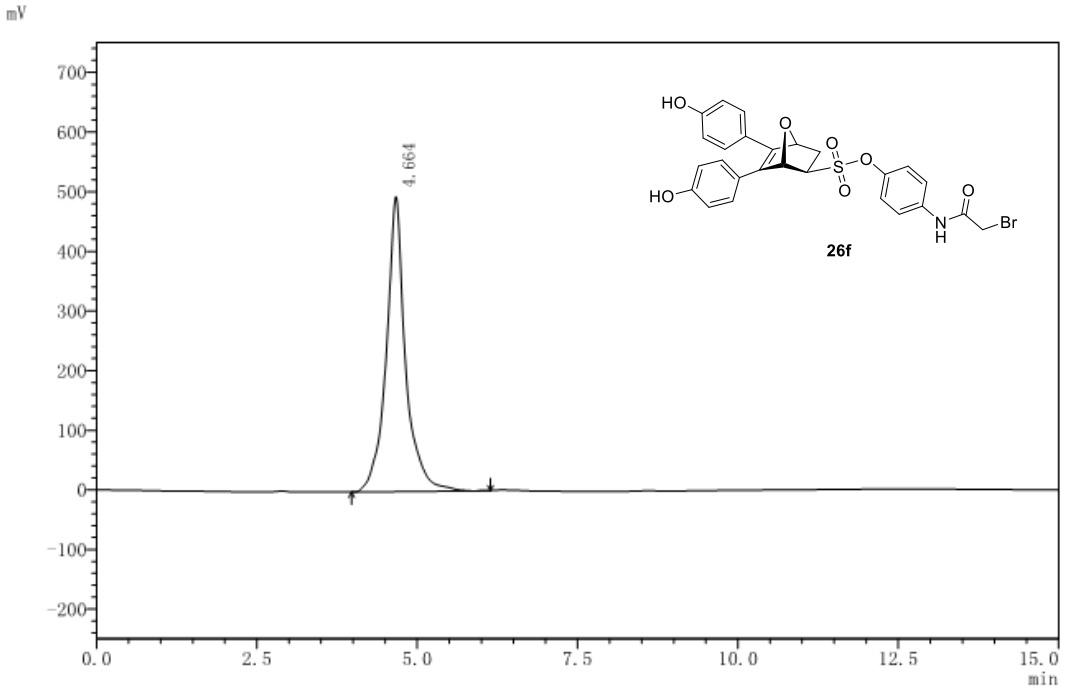


NO.	Retention Time	Area	Percent
1	2.872	25408	0.196
2	4.633	12963539	99.804
Total			100.000

HRMS (ESI) calcd for $C_{26}H_{22}ClNO_7S$ $[M + Na]^+$ 550.0698, found 550.0698.

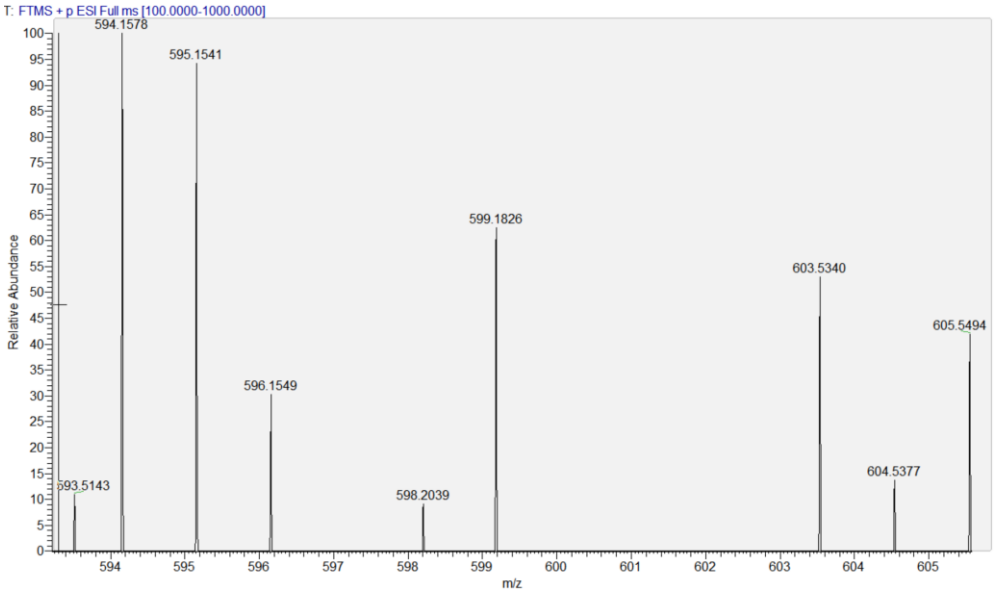


HPLC chromatogram of **26f.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

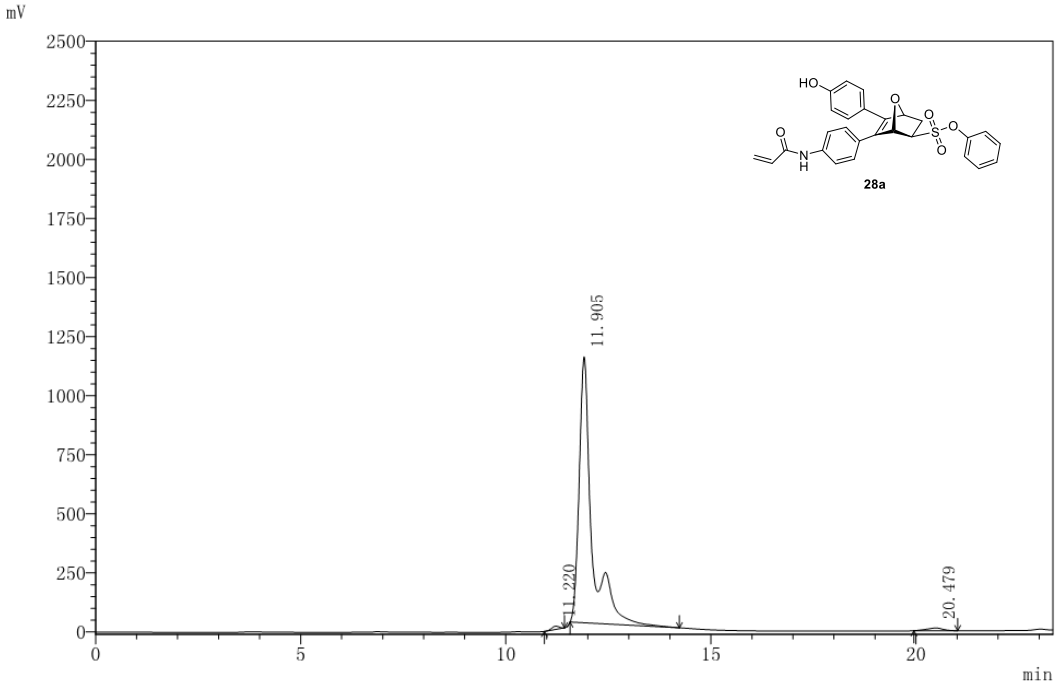


NO.	Retention Time	Area	Percent
1	4.664	10376805	100.000
Total			100.000

HRMS (ESI) calcd for $C_{26}H_{22}BrNO_7S$ $[M + Na]^+$ 594.1573, found 594.1578.

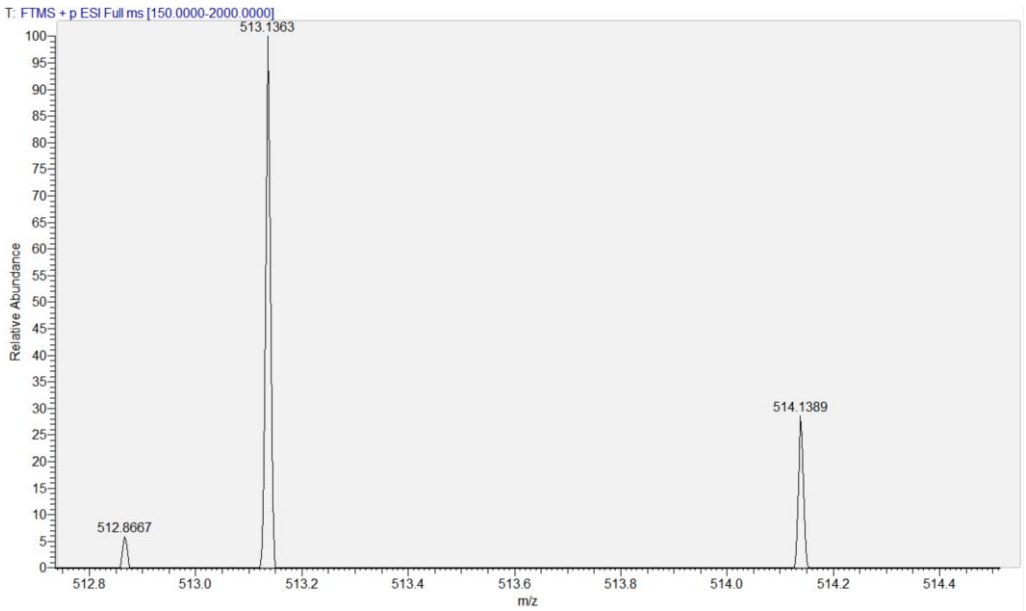


HPLC chromatogram of **28a.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).

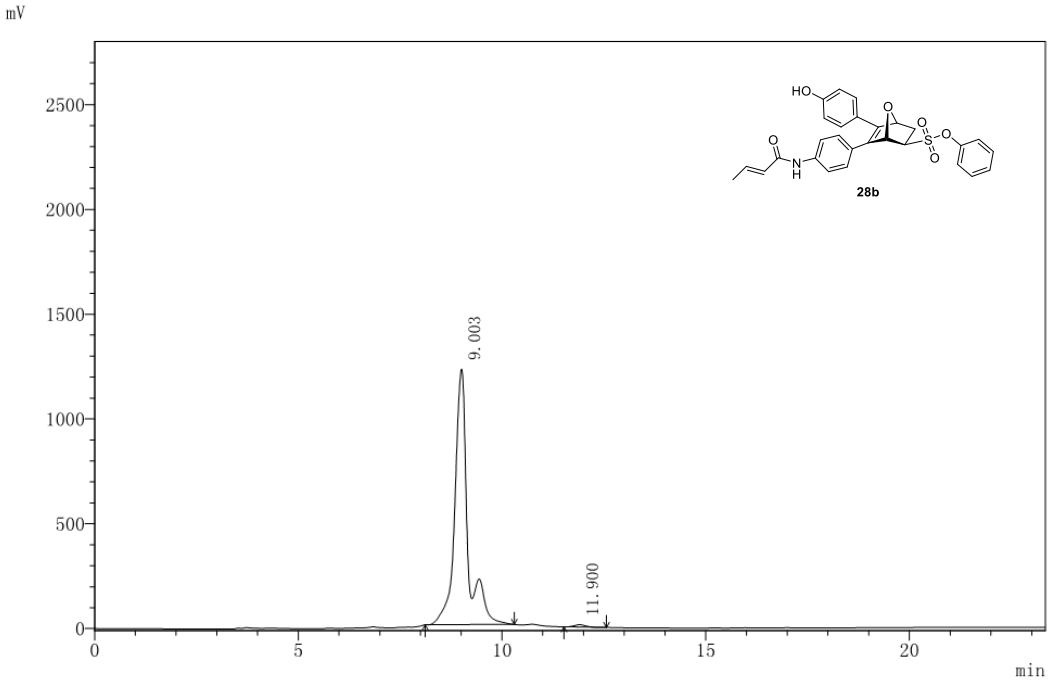


NO.	Retention Time	Area	Percent
1	10.220	178559	0.716
2	11.905	24447747	98.077
3	20.479	300792	1.207
Total			100.000

HRMS (ESI) calcd for $C_{27}H_{23}NO_6S$ $[M + Na]^+$ 513.1367, found 513.1363.

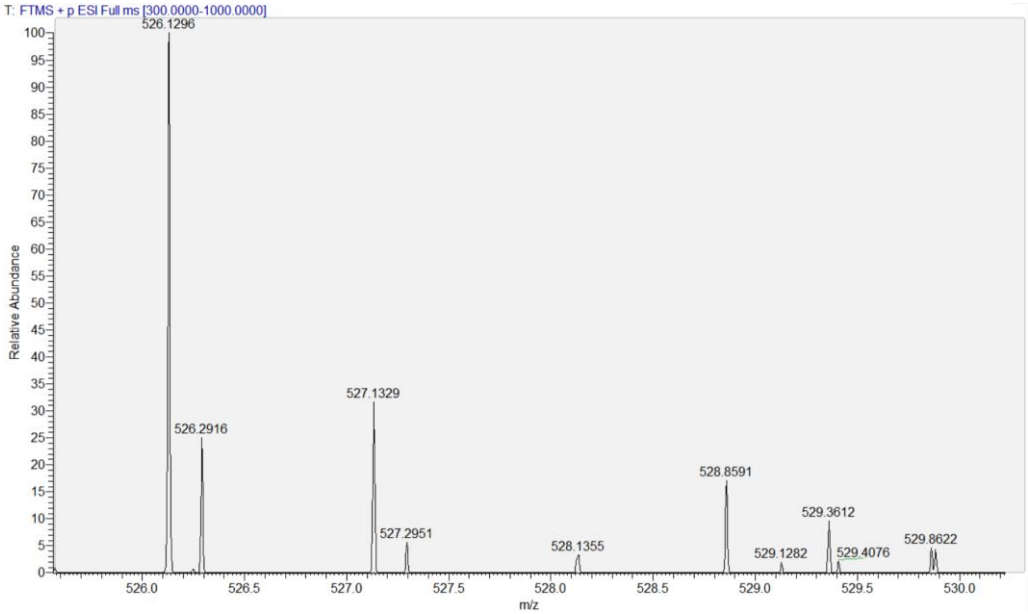


HPLC chromatogram of **28b.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).

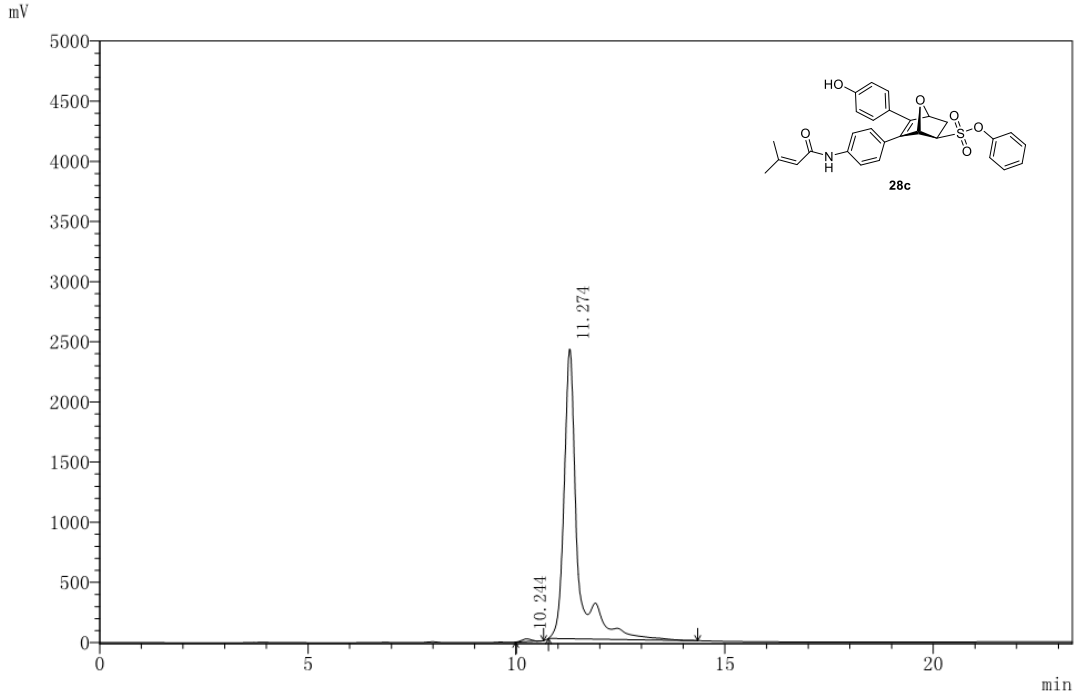


NO.	Retention Time	Area	Percent
1	9.003	26905238	99.154
2	11.900	229425	0.846
Total			100.000

HRMS (ESI) calcd for $C_{28}H_{25}NO_6S$ $[M + Na]^+$ 526.1294, found 526.1296.

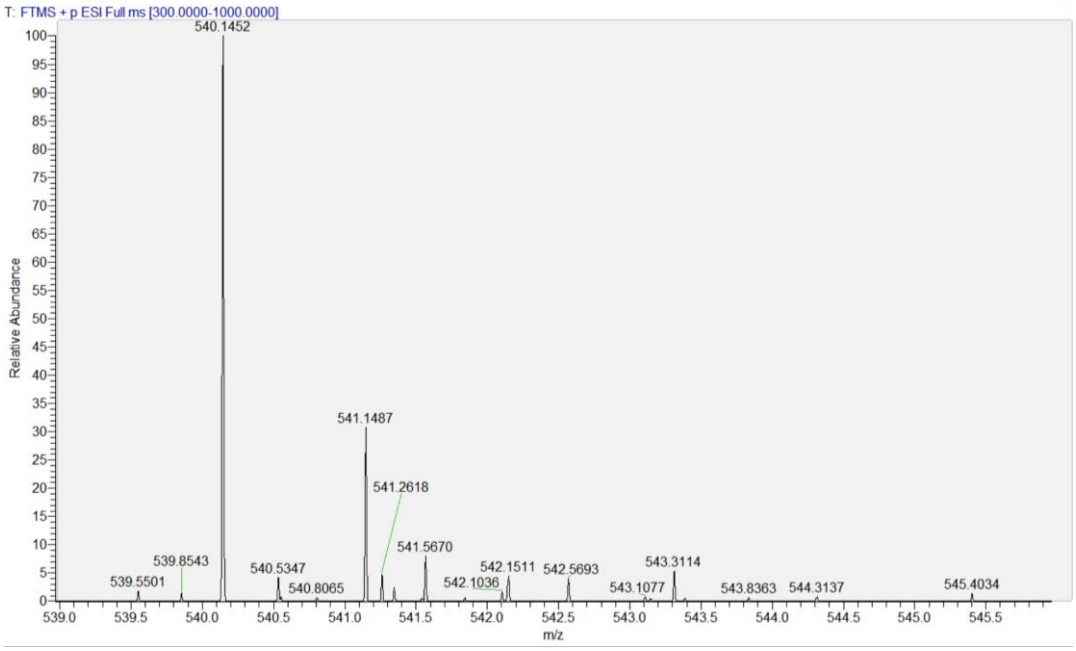


HPLC chromatogram of **28c.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).

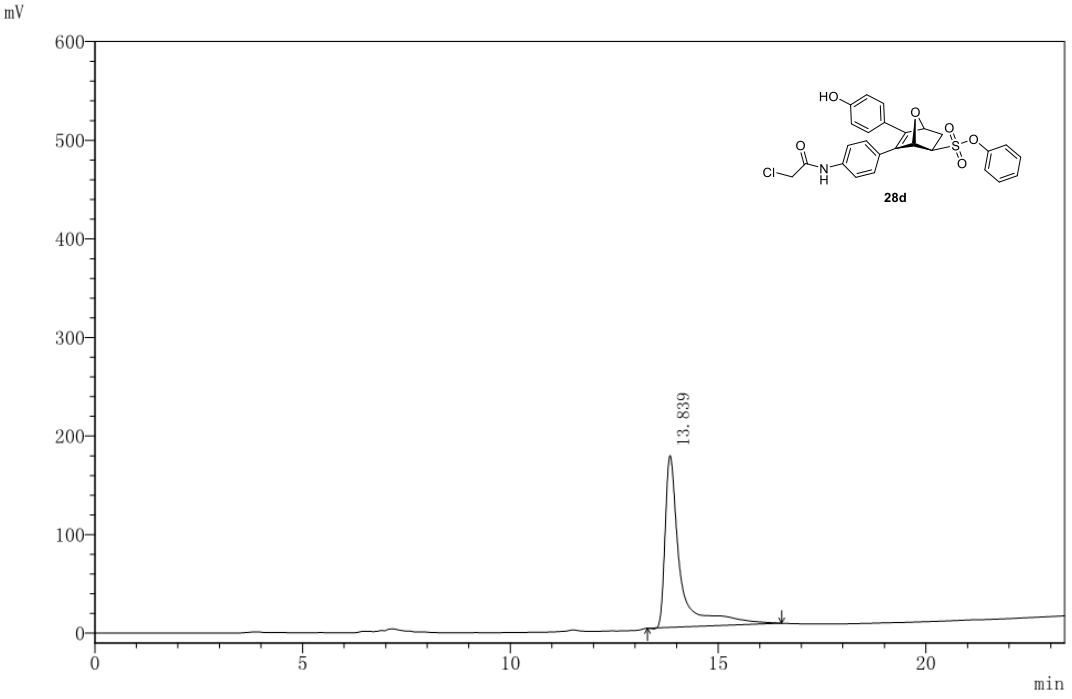


NO.	Retention Time	Area	Percent
1	10.244	307021	0.557
2	11.274	54819112	99.443
Total			100.000

HRMS (ESI) calcd for $C_{29}H_{27}NO_6S$ $[M + Na]^+$ 540.1451, found 540.1452.

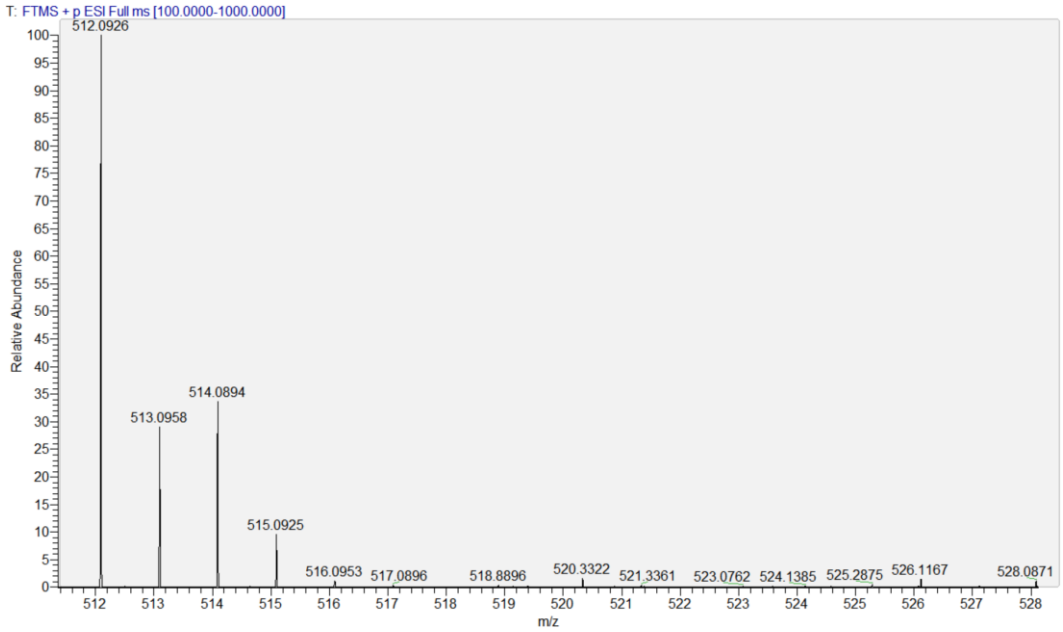


HPLC chromatogram of **28d.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).

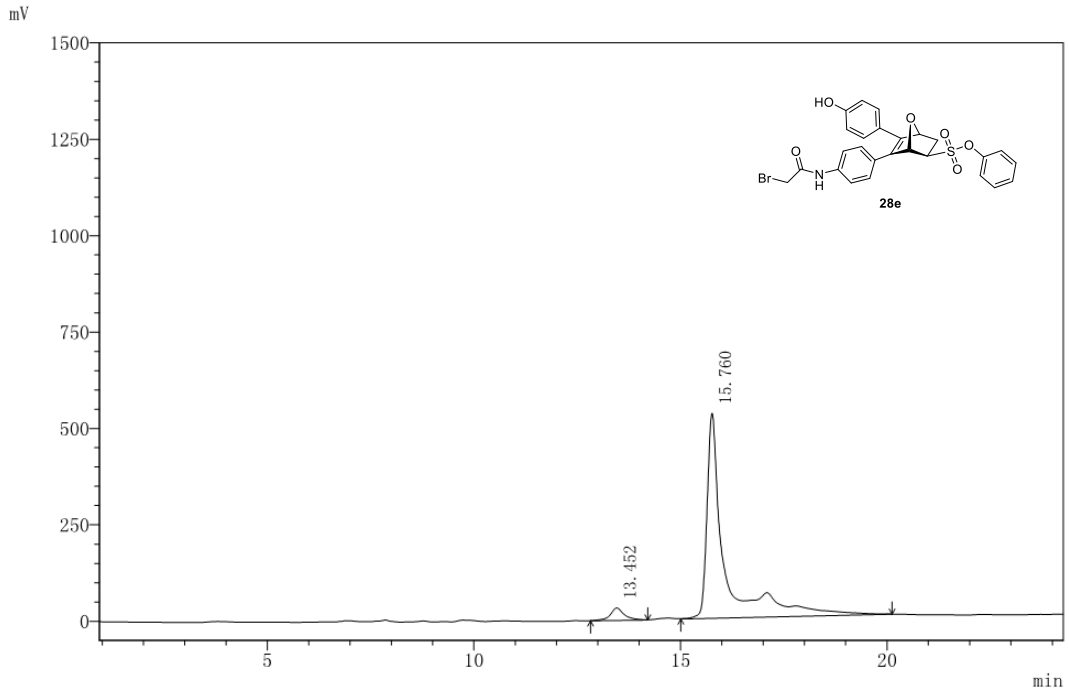


NO.	Retention Time	Area	Percent
1	13.839	4431856	100.000
Total			100.000

HRMS (ESI) calcd for $C_{26}H_{22}ClNO_6S$ $[M + H]^+$ 512.0923, found 512.0926.

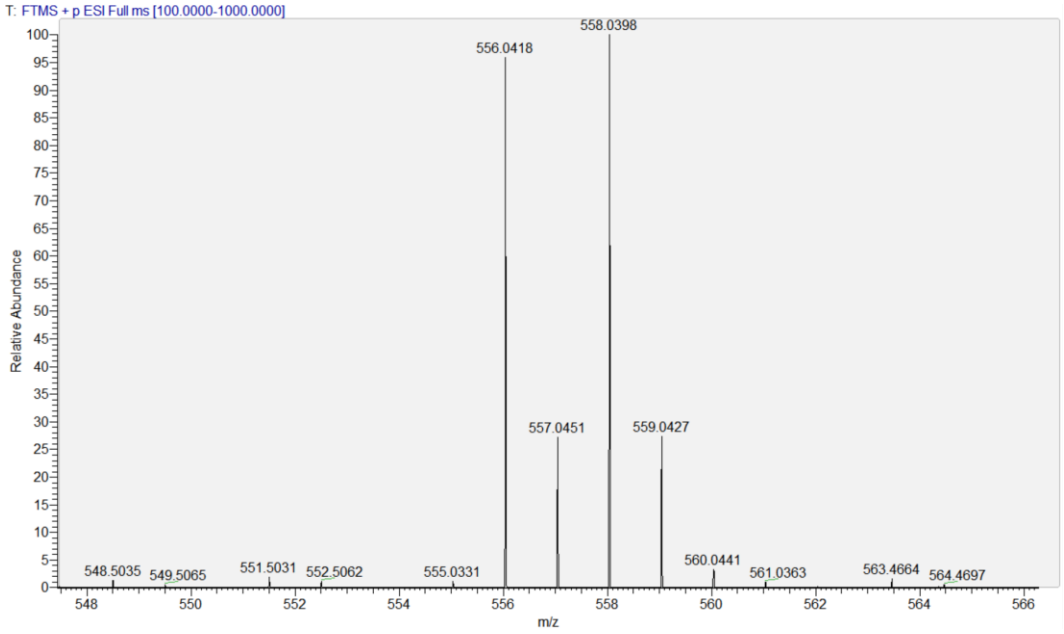


HPLC chromatogram of **28e.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).

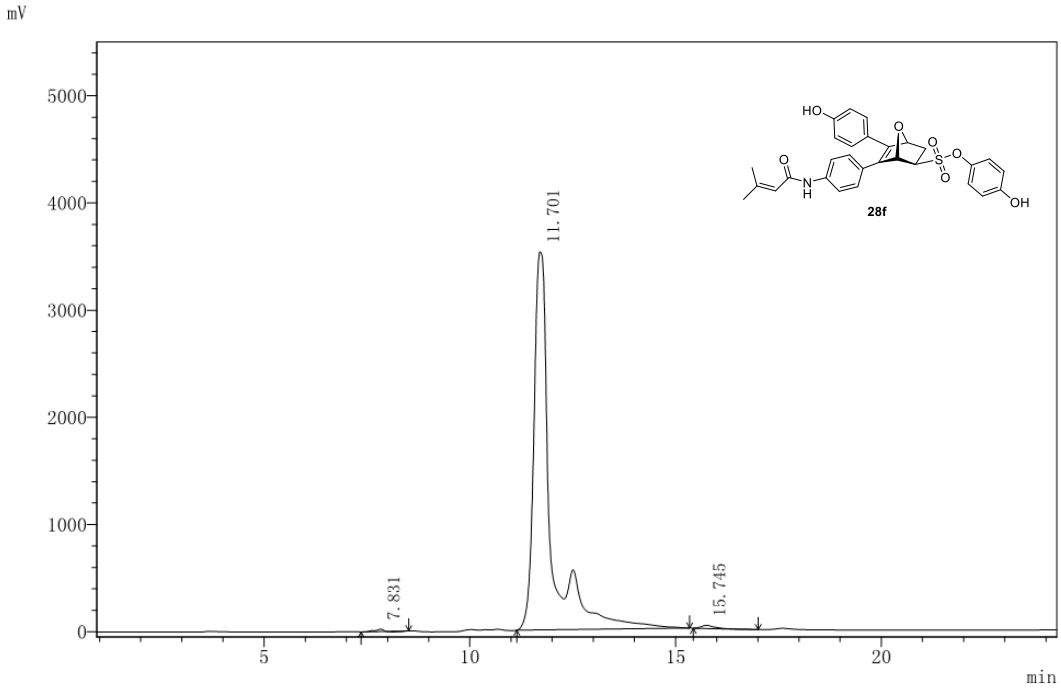


NO.	Retention Time	Area	Percent
1	13.452	790490	4.677
2	15.760	16111732	95.323
Total			100.000

HRMS (ESI) calcd for $C_{26}H_{22}BrNO_6S$ $[M + H]^+$ 556.0423, found 556.0418.



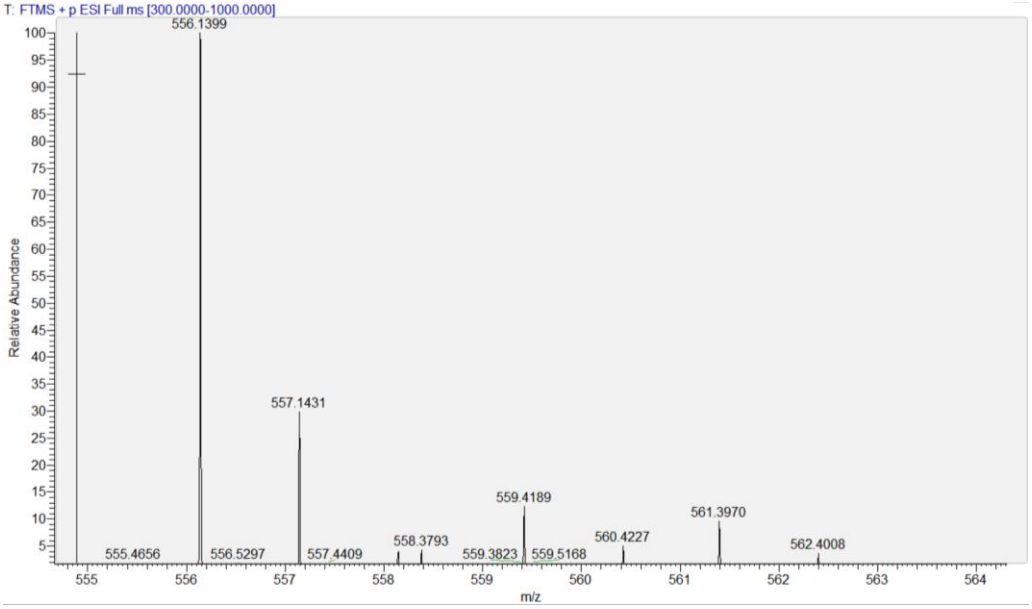
HPLC chromatogram of **28f.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).



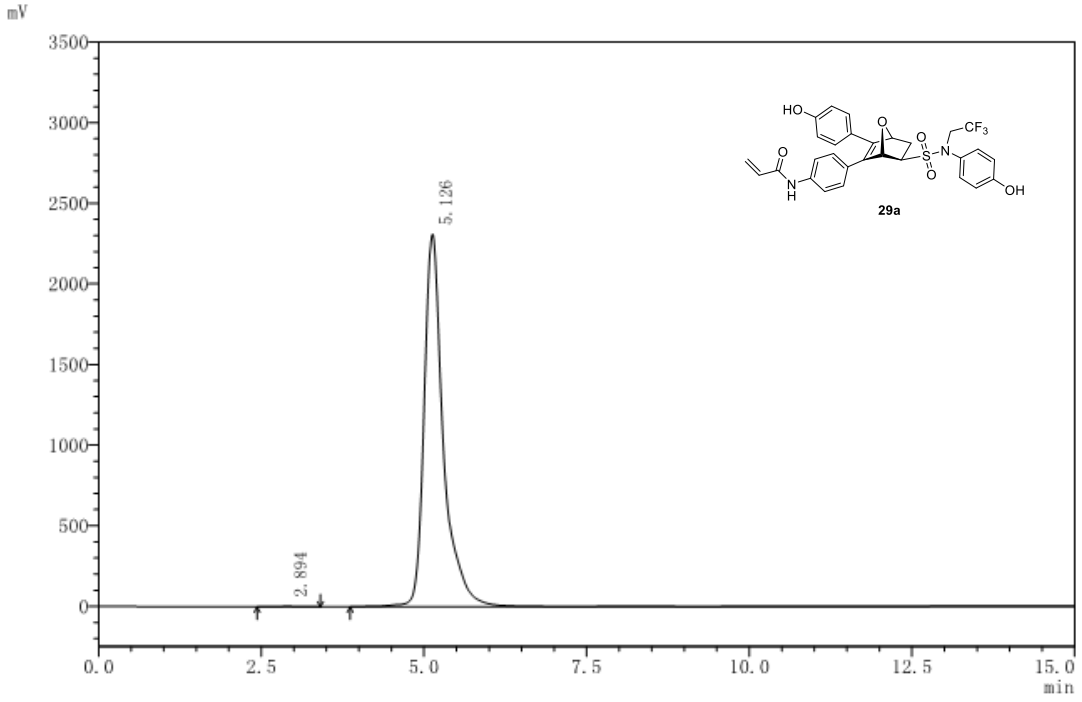
NO.	Retention Time	Area	Percent
1	7.831	153399	0.151
2	11.701	101000162	99.286
3	15.745	573141	0.563

Total	100.000

HRMS (ESI) calcd for $C_{29}H_{27}NO_7S$ $[M + Na]^+$ 556.1400, found 556.1399.



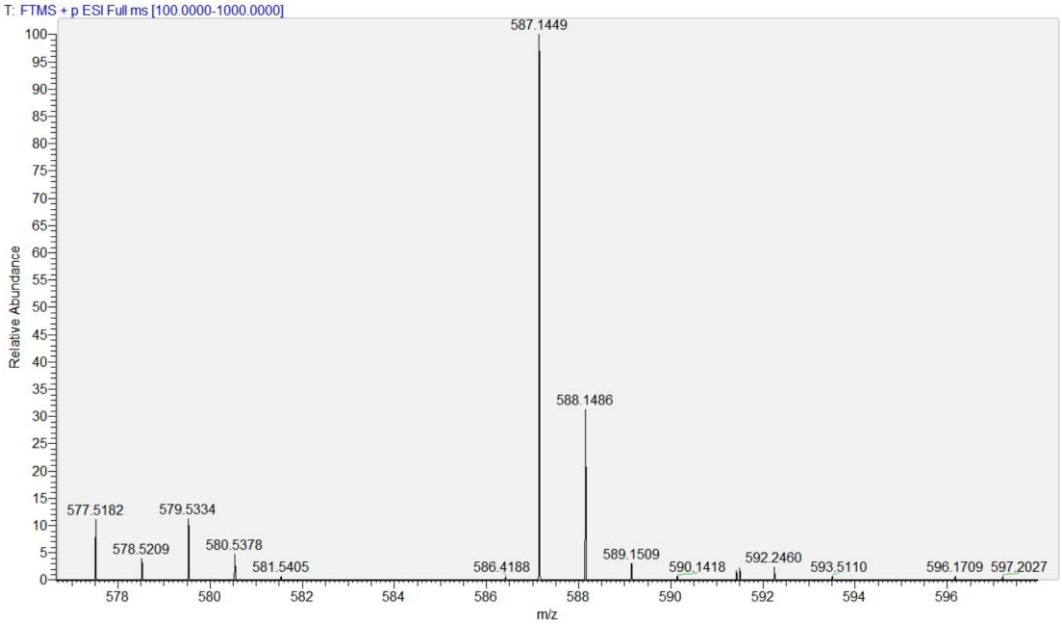
HPLC chromatogram of **29a.** Reverse Phase (Method 80:20 CH_3OH: H_2O, Flow rate 1.0 mL/min).



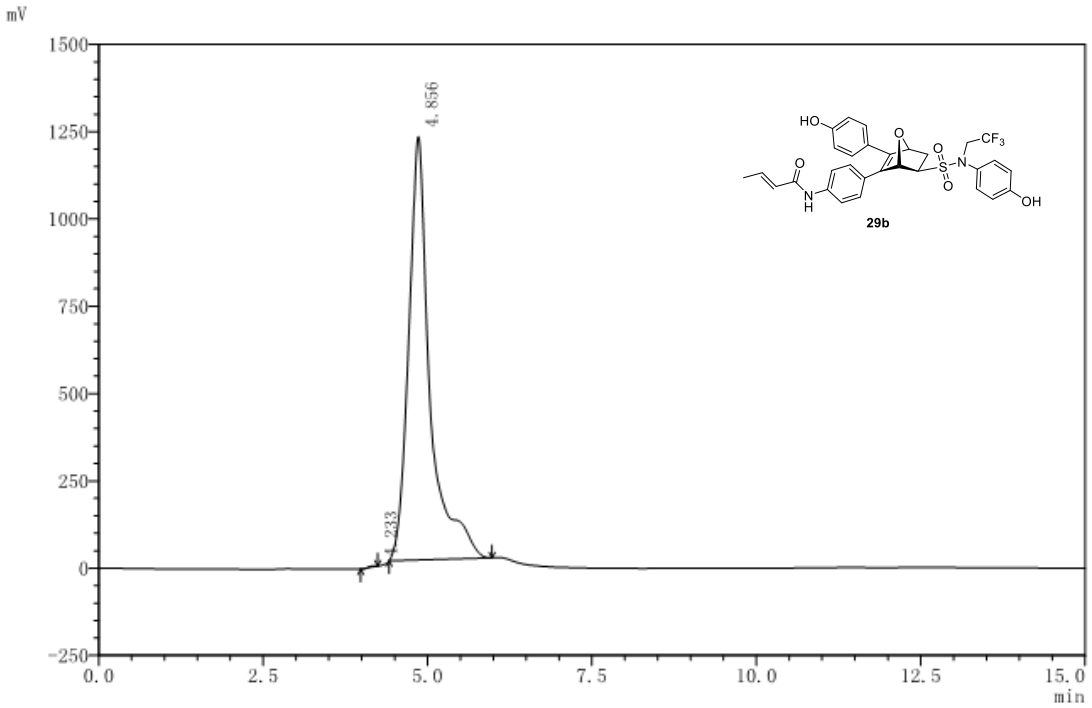
NO.	Retention Time	Area	Percent
1	2.894	63743	0.131
2	5.126	48538224	99.869

Total	100.000

HRMS (ESI) calcd for $C_{29}H_{25}F_3N_2O_6S$ $[M + H]^+$ 587.1458, found 587.1449.



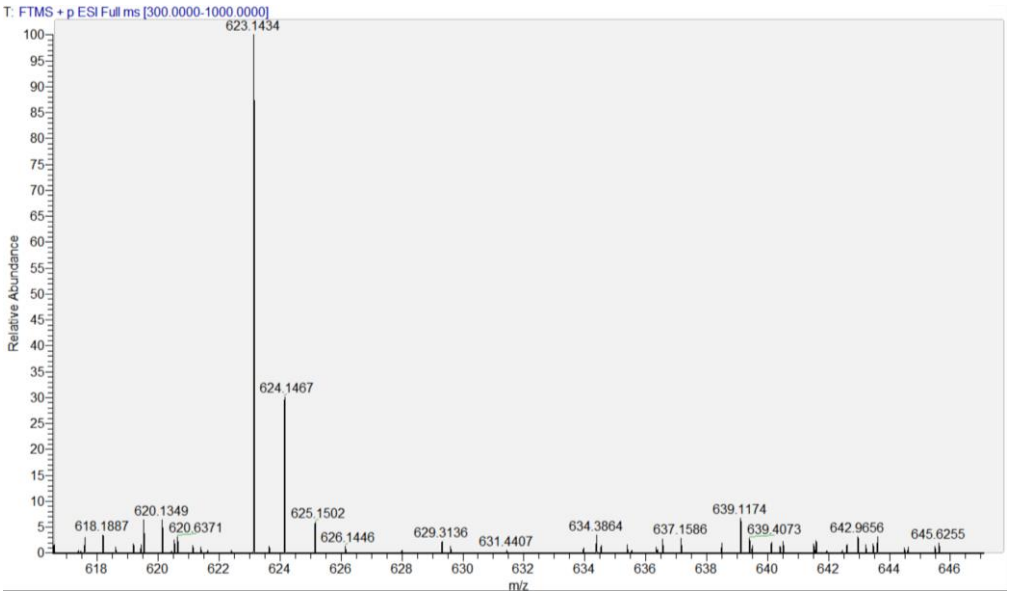
HPLC chromatogram of **29b.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



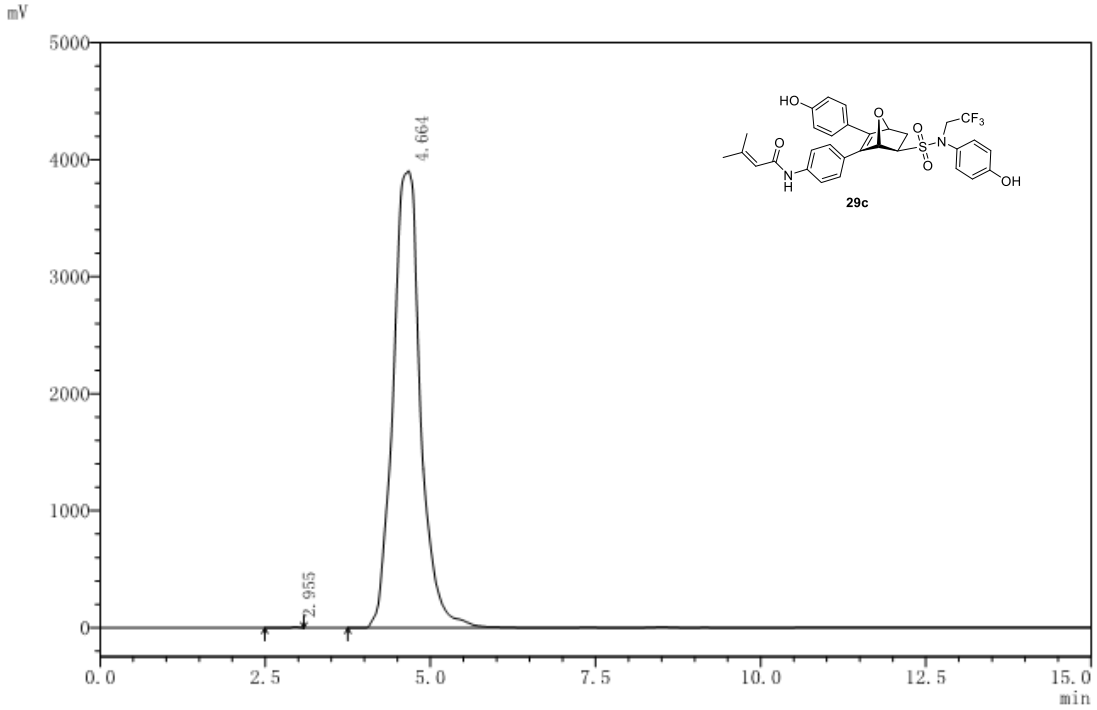
NO.	Retention Time	Area	Percent
1	4.233	15455	0.056

2	4.856	27366362	99.944
Total			100.000

HRMS (ESI) calcd for $C_{30}H_{27}F_3N_2O_6S$ $[M + Na]^+$ 623.1431, found 623.1434.



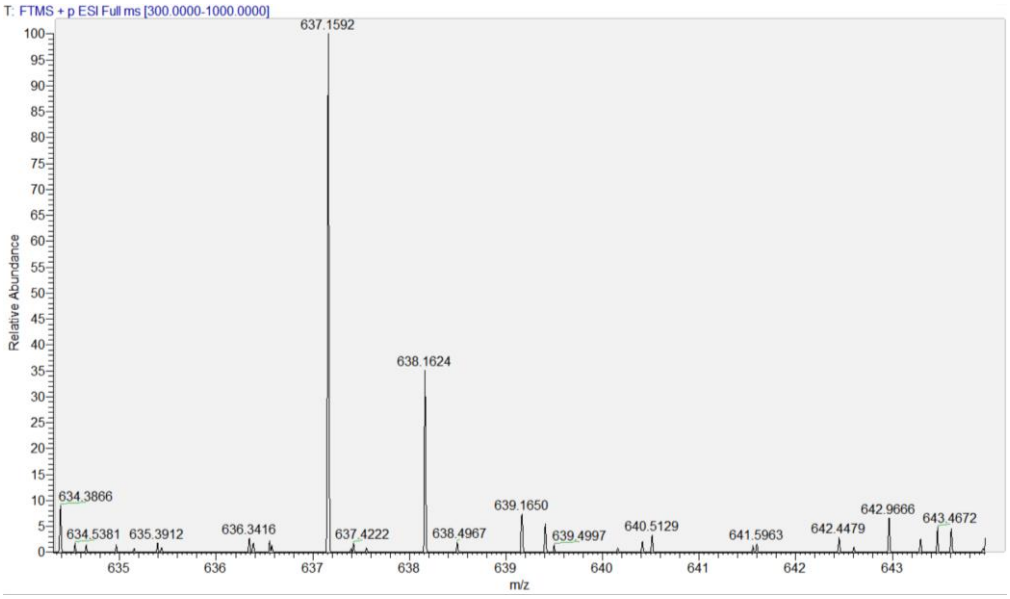
HPLC chromatogram of **29c.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



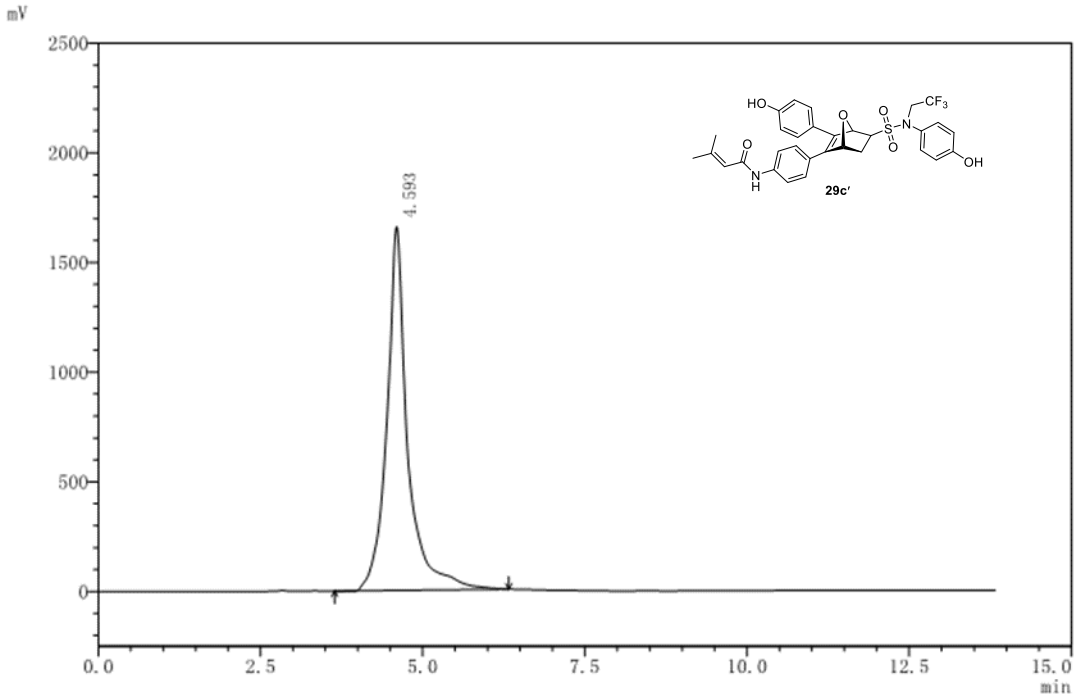
NO.	Retention Time	Area	Percent

1	2.955	97216	0.085
2	4.664	114591504	99.915
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{29}F_3N_2O_6S$ $[M + Na]^+$ 637.1590, found 637.1592.

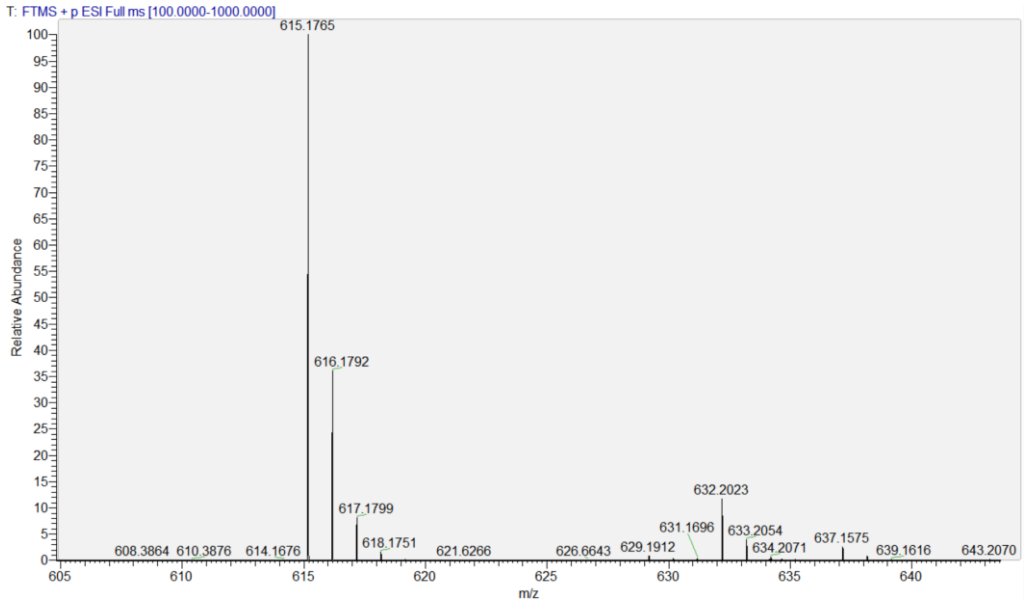


HPLC chromatogram of **29c'.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

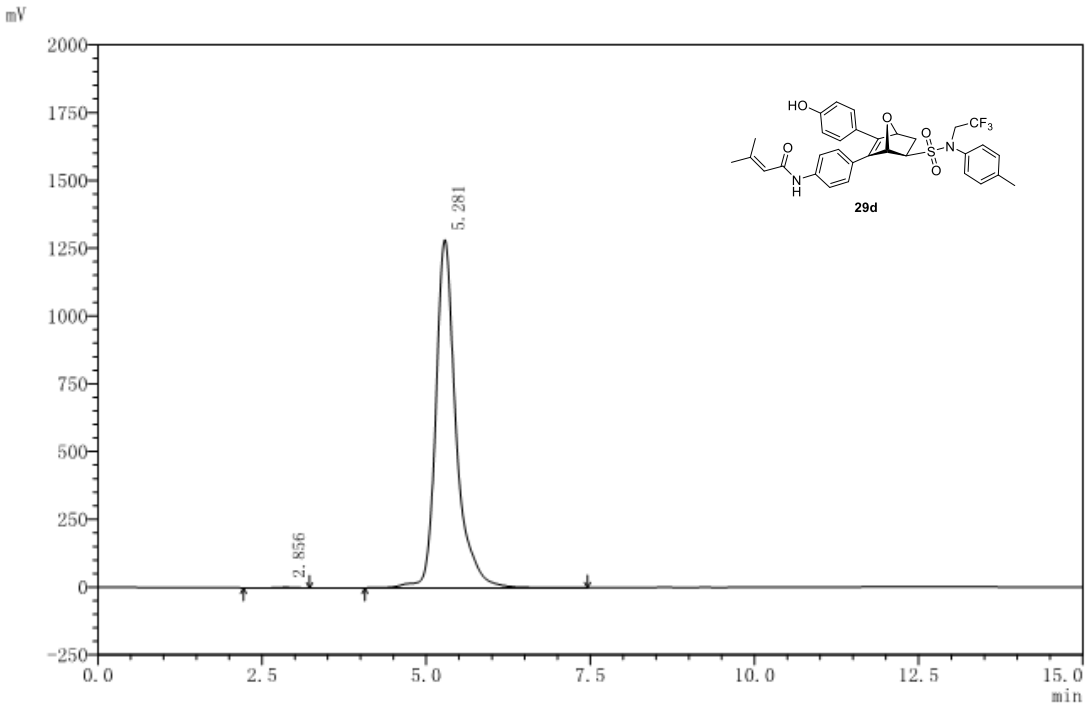


NO.	Retention Time	Area	Percent
1	4.593	37073514	100.000
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{29}F_3N_2O_6S$ $[M + H]^+$ 615.1771, found 615.1765.

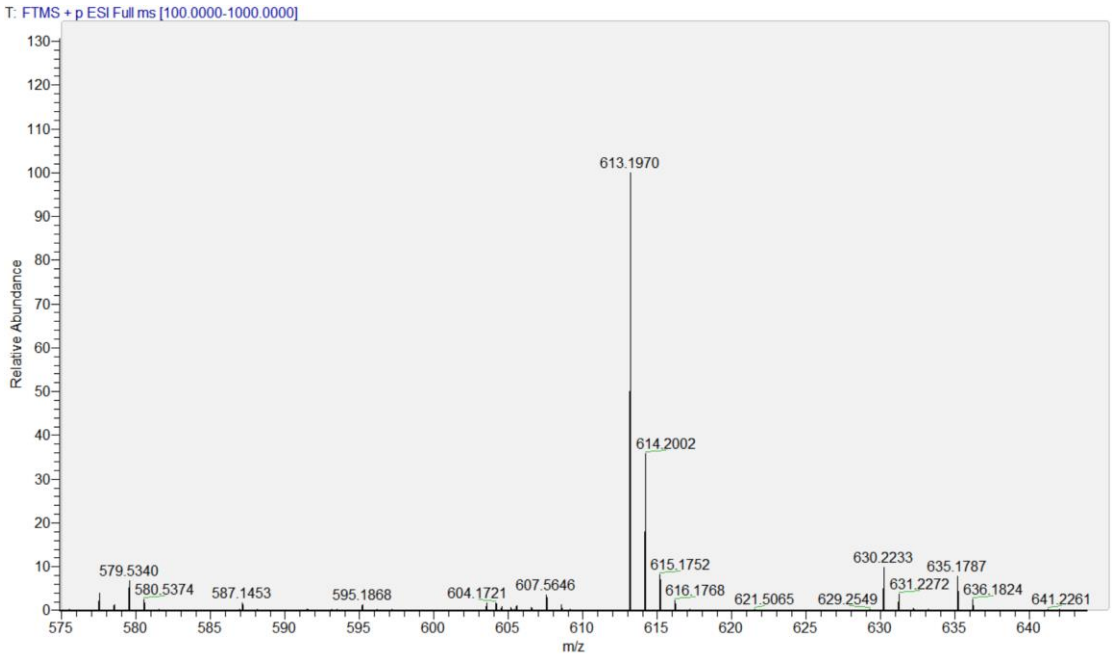


HPLC chromatogram of **29d.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

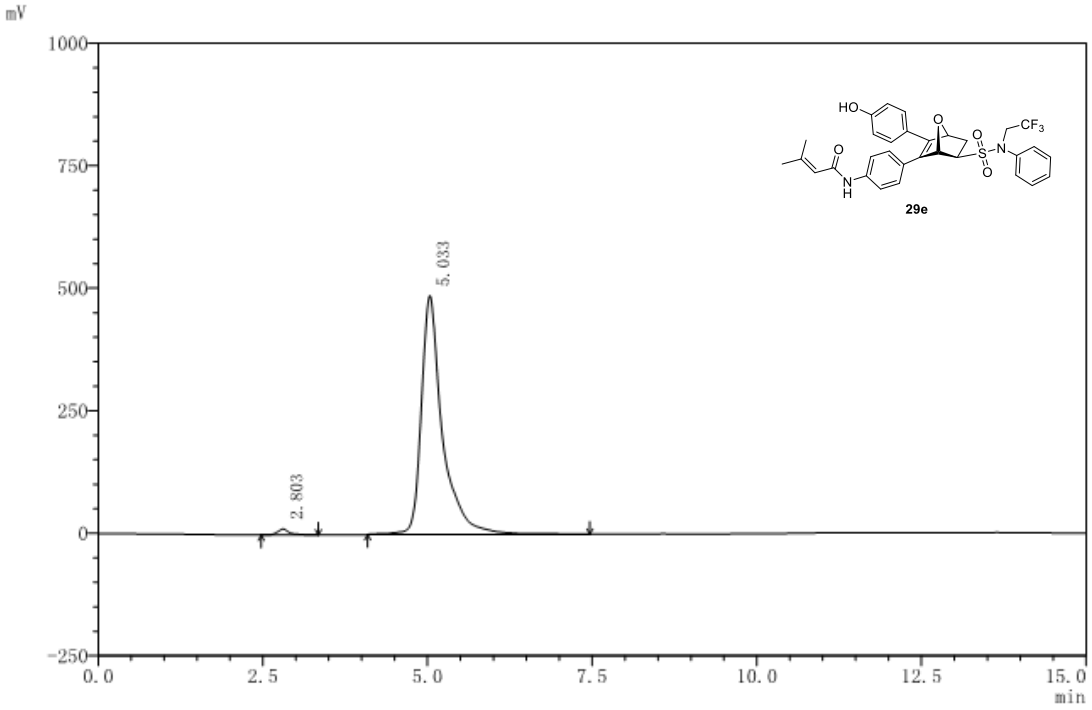


NO.	Retention Time	Area	Percent
1	2.856	31066	0.112
2	5.281	27693128	99.888
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{29}F_3N_2O_6S$ $[M + H]^+$ 613.1978, found 613.1970.

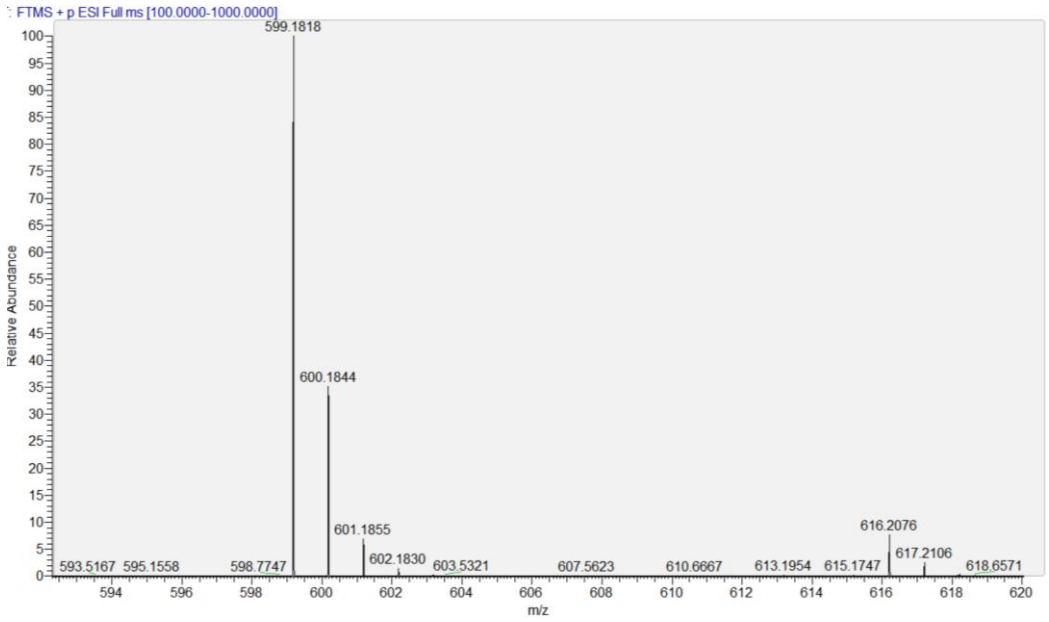


HPLC chromatogram of **29e.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



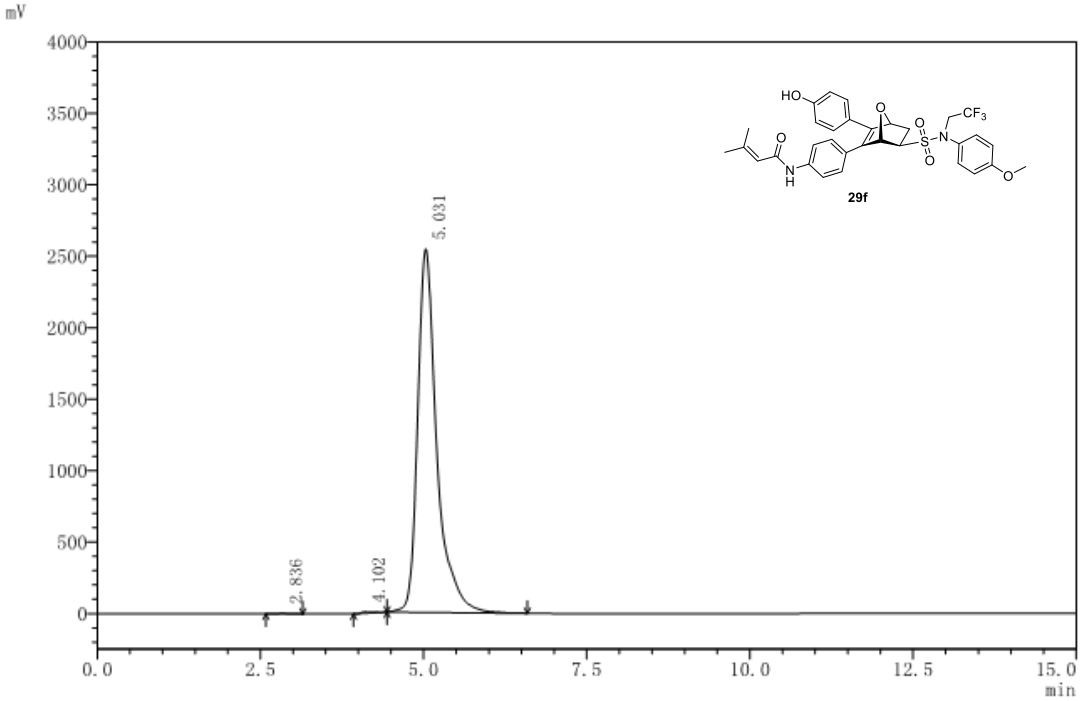
NO.	Retention Time	Area	Percent
1	2.803	150928	1.365
2	5.033	10904719	98.635
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{29}F_3N_2O_5S$ $[M + H]^+$ 599.1822, found 599.1818.



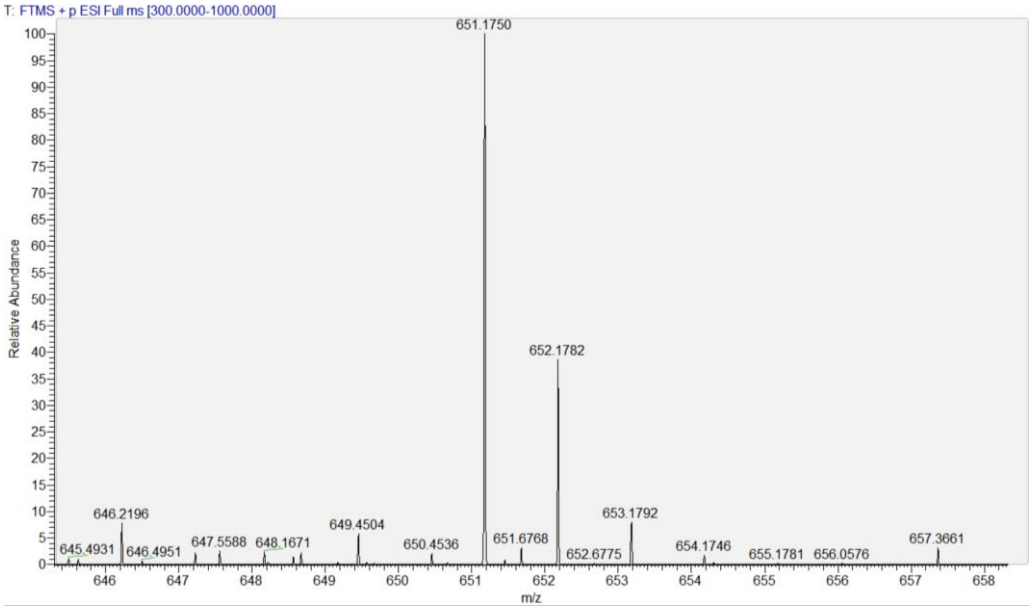
HPLC chromatogram of **29f.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate

0.7 mL/min).

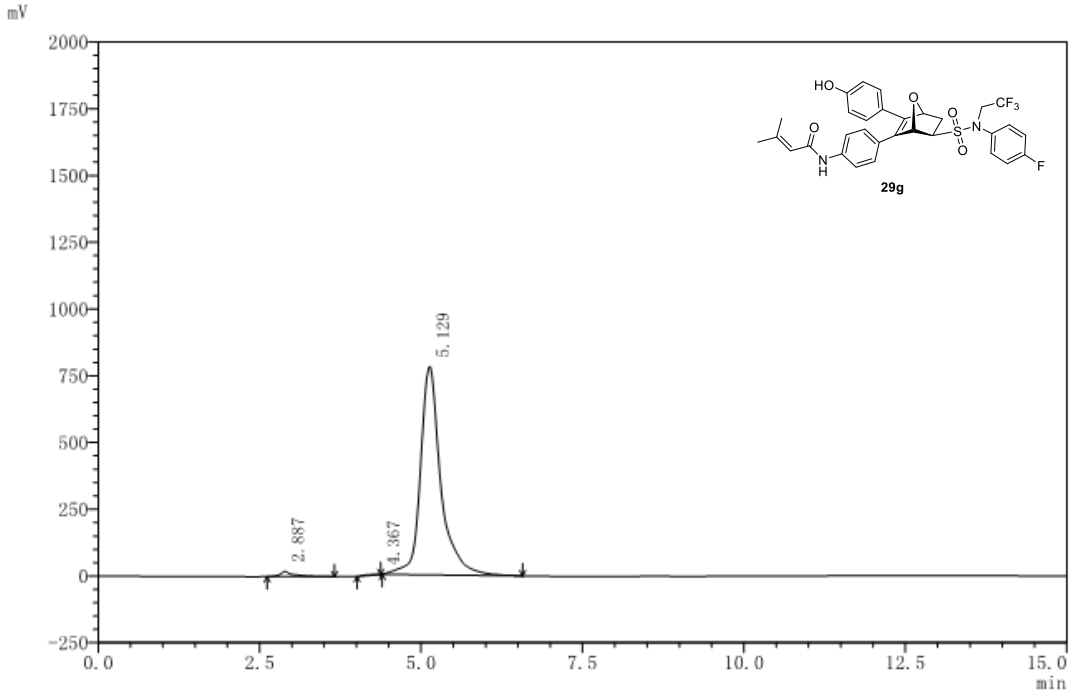


NO.	Retention Time	Area	Percent
1	2.836	48419	0.093
2	4.102	93117	0.179
3	5.031	51943923	99.728
Total			100.000

HRMS (ESI) calcd for $C_{32}H_{31}F_3N_2O_6S$ $[M + Na]^+$ 651.1747, found 651.1750.

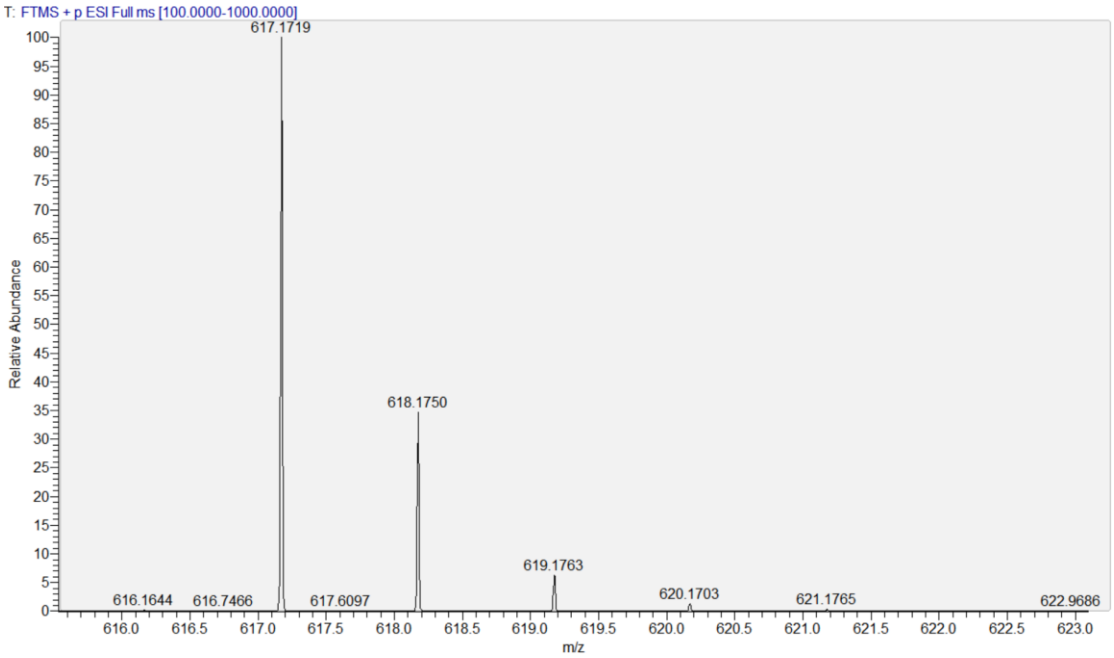


HPLC chromatogram of **29g.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

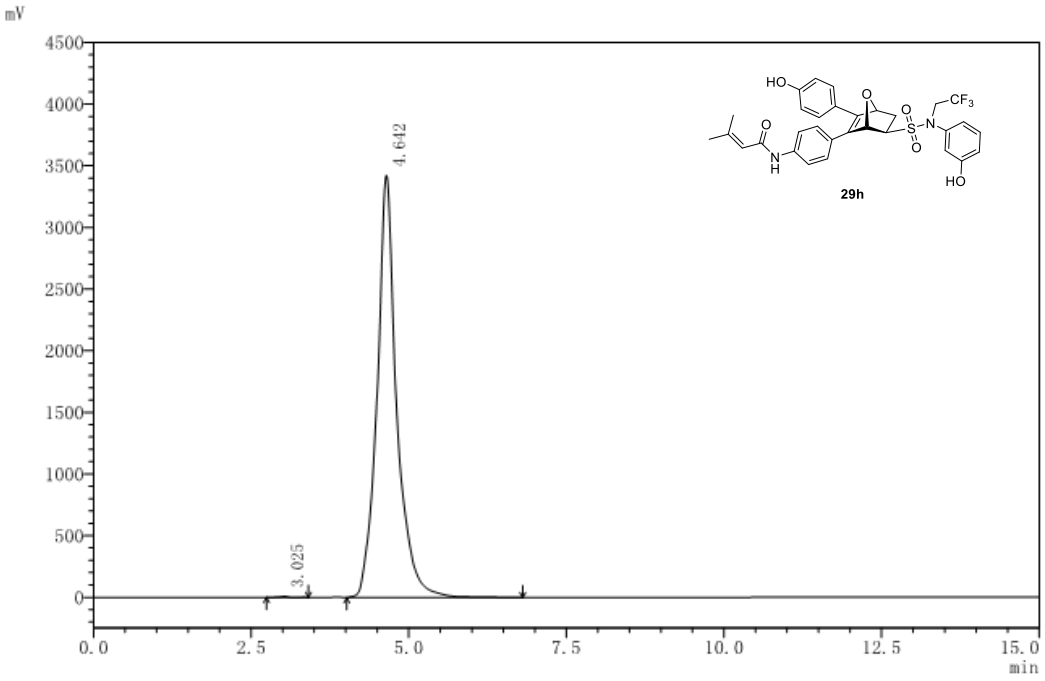


NO.	Retention Time	Area	Percent
1	2.887	294732	1.688
2	4.367	39266	0.225
3	5.129	17124094	98.087
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{28}F_4N_2O_5S$ $[M + H]^+$ 617.1727, found 617.1719.

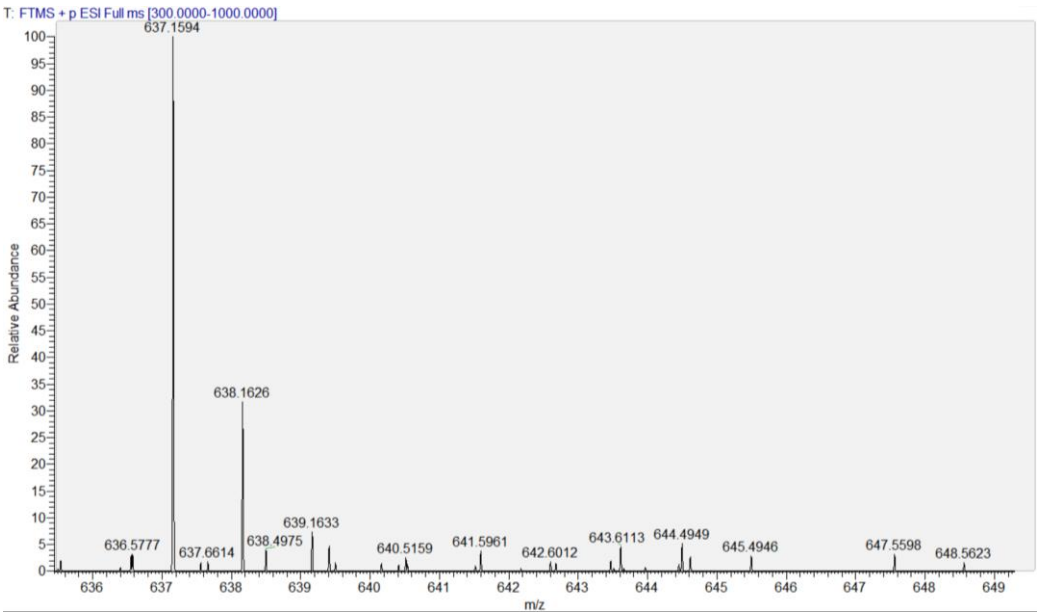


HPLC chromatogram of **29h.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

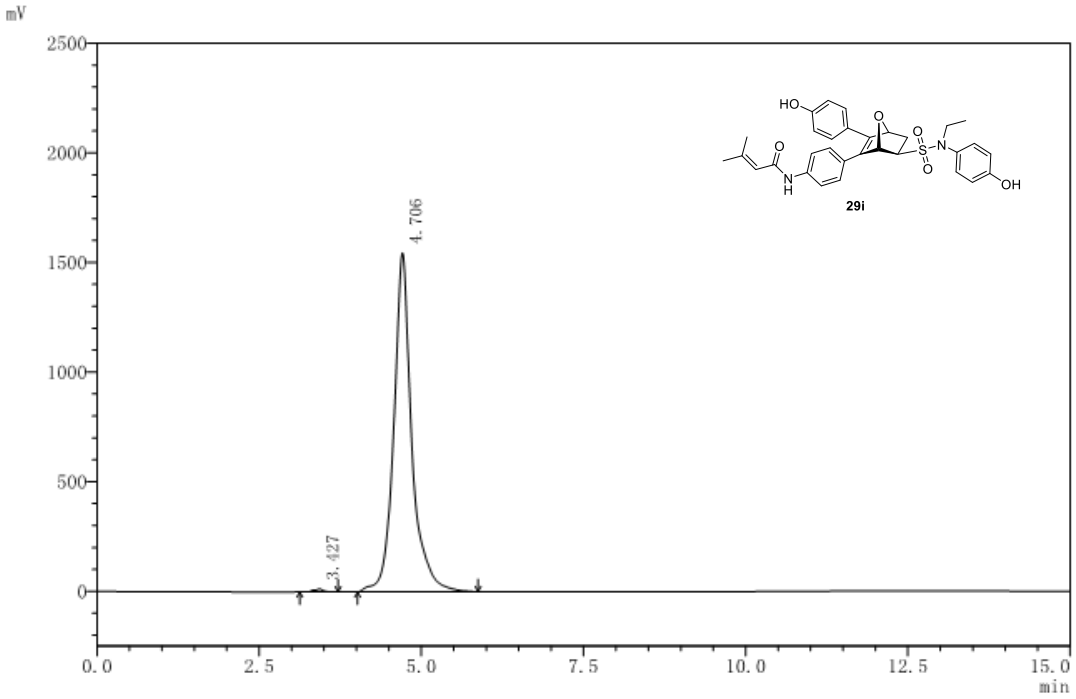


NO.	Retention Time	Area	Percent
1	3.025	93384	0.125
2	4.642	74556580	99.875
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{29}F_3N_2O_6S$ $[M + Na]^+$ 637.1590, found 637.1594.

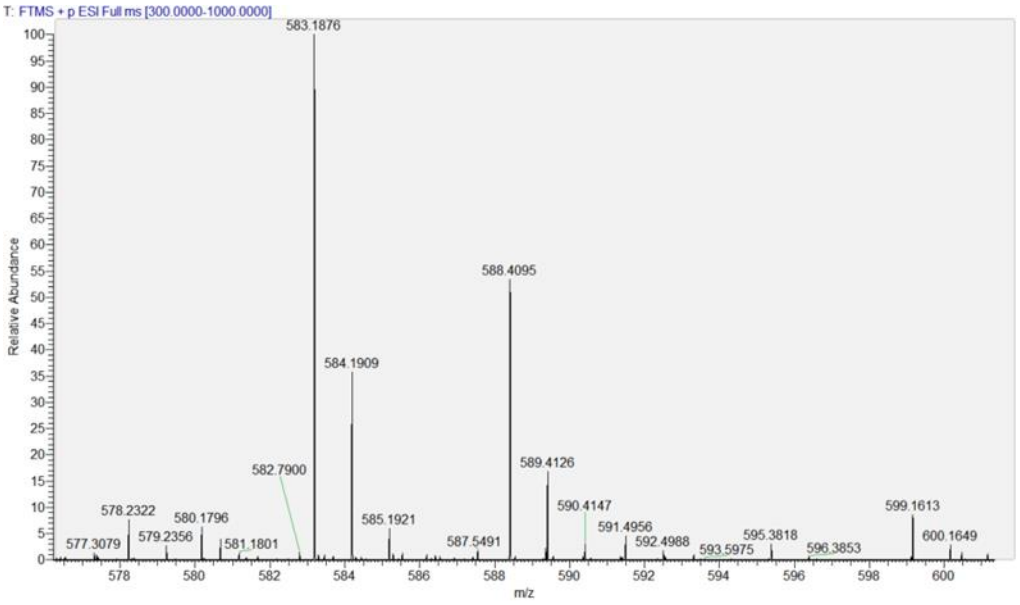


HPLC chromatogram of **29i.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

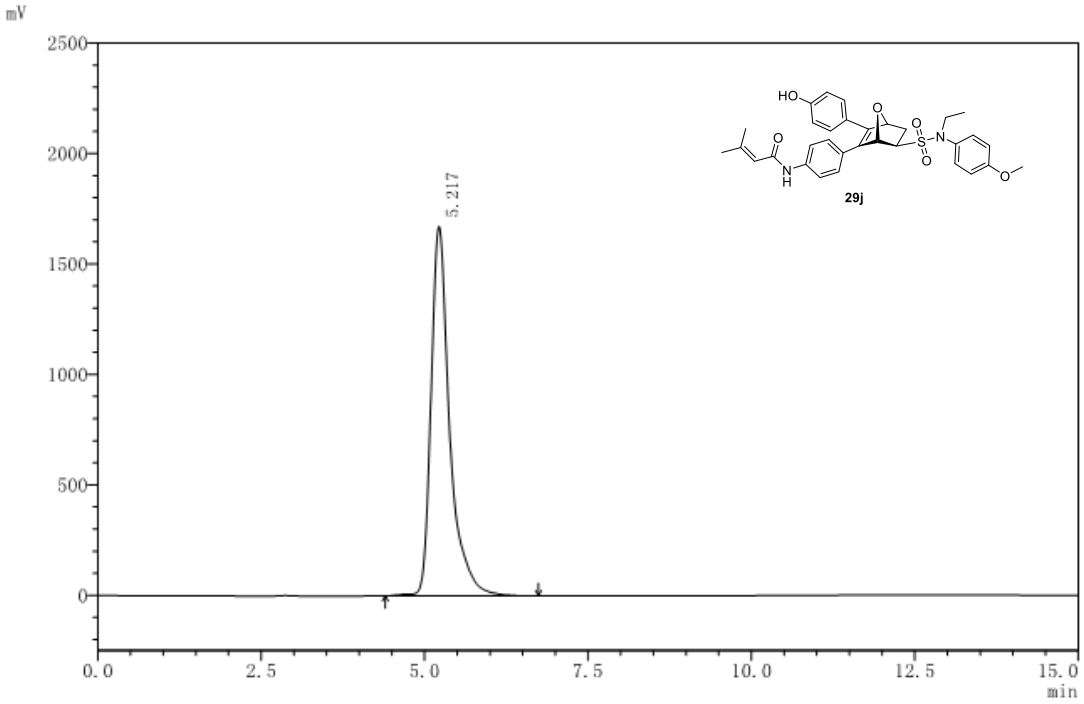


NO.	Retention Time	Area	Percent
1	3.427	132319	0.441
2	4.706	29880432	99.559
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{32}N_2O_6S$ $[M + Na]^+$ 583.1873, found 583.1876.

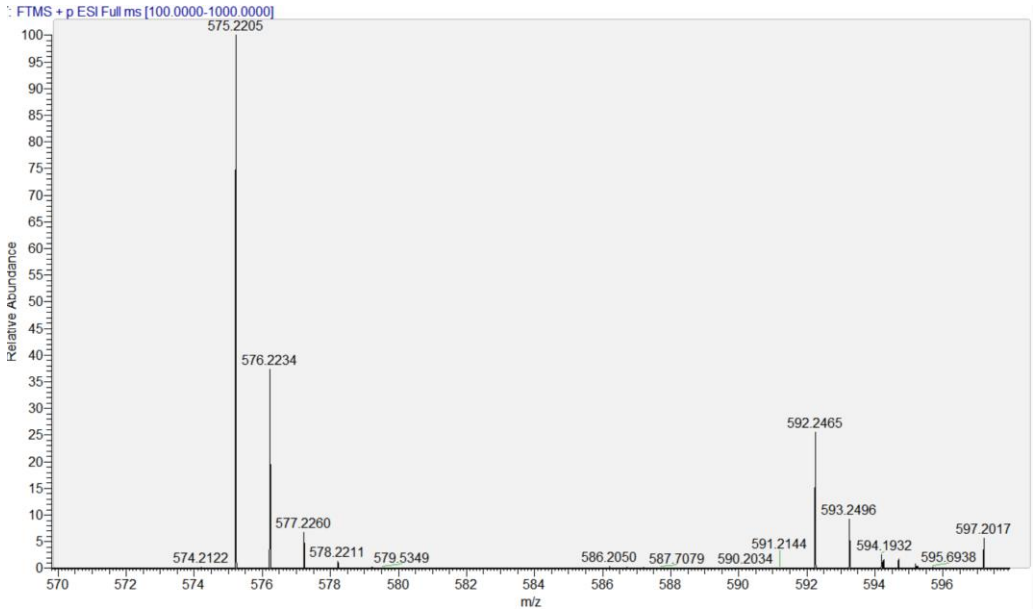


HPLC chromatogram of **29j.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).

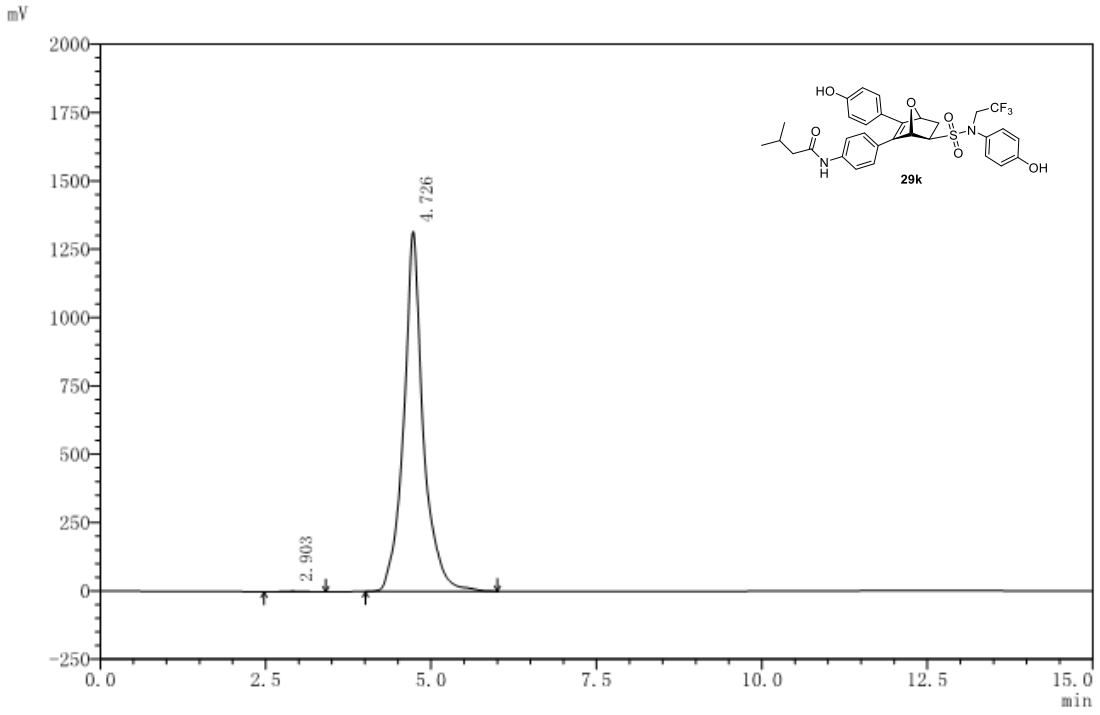


NO.	Retention Time	Area	Percent
1	5.217	33141916	100.000
Total			100.000

HRMS (ESI) calcd for $C_{32}H_{34}N_2O_6S$ $[M + H]^+$ 575.2210, found 575.2205.



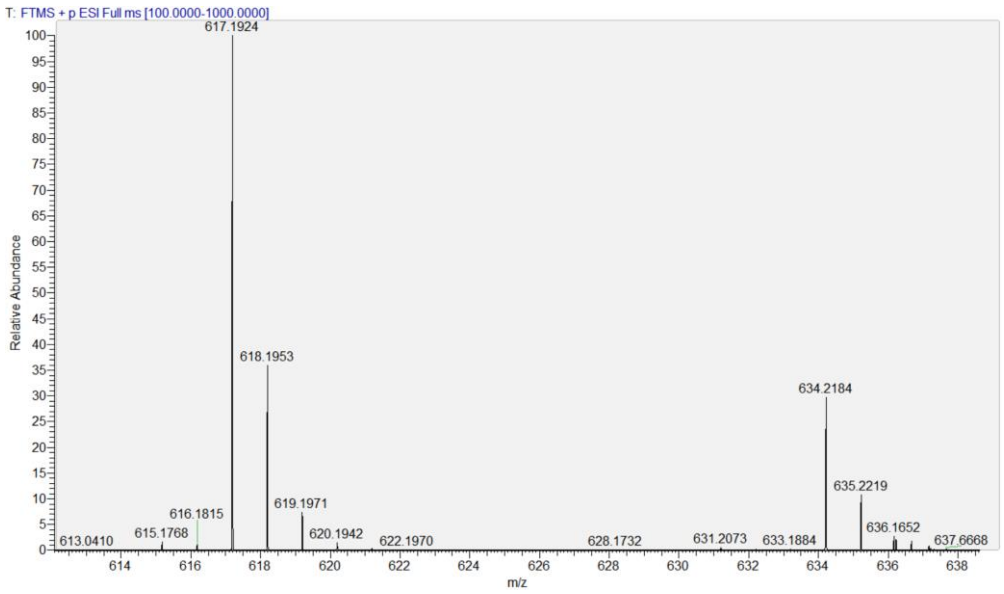
HPLC chromatogram of **29k.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



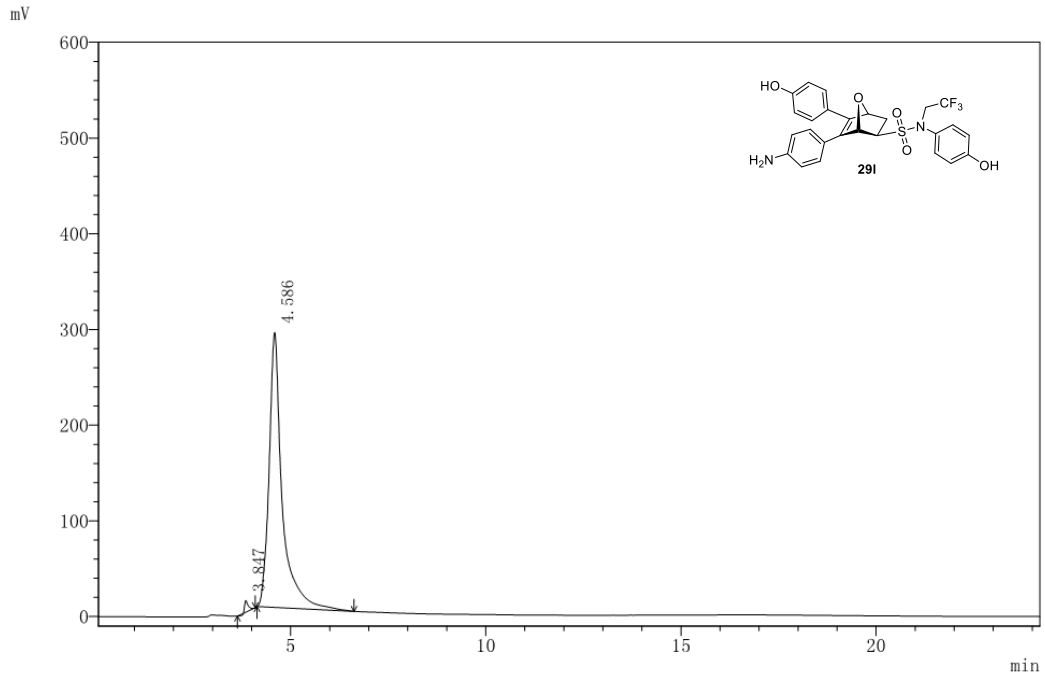
NO.	Retention Time	Area	Percent
1	2.903	35249	0.129
2	4.726	27201662	99.871

Total	100.000

HRMS (ESI) calcd for $C_{31}H_{31}F_3N_2O_6S$ $[M + H]^+$ 617.1927, found 617.1924.



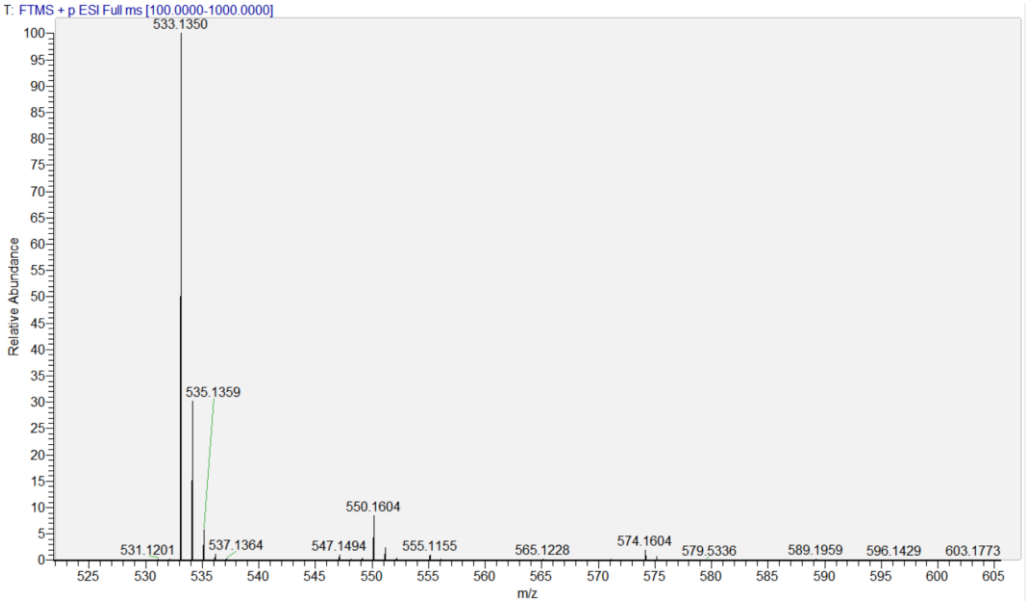
HPLC chromatogram of **29l.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



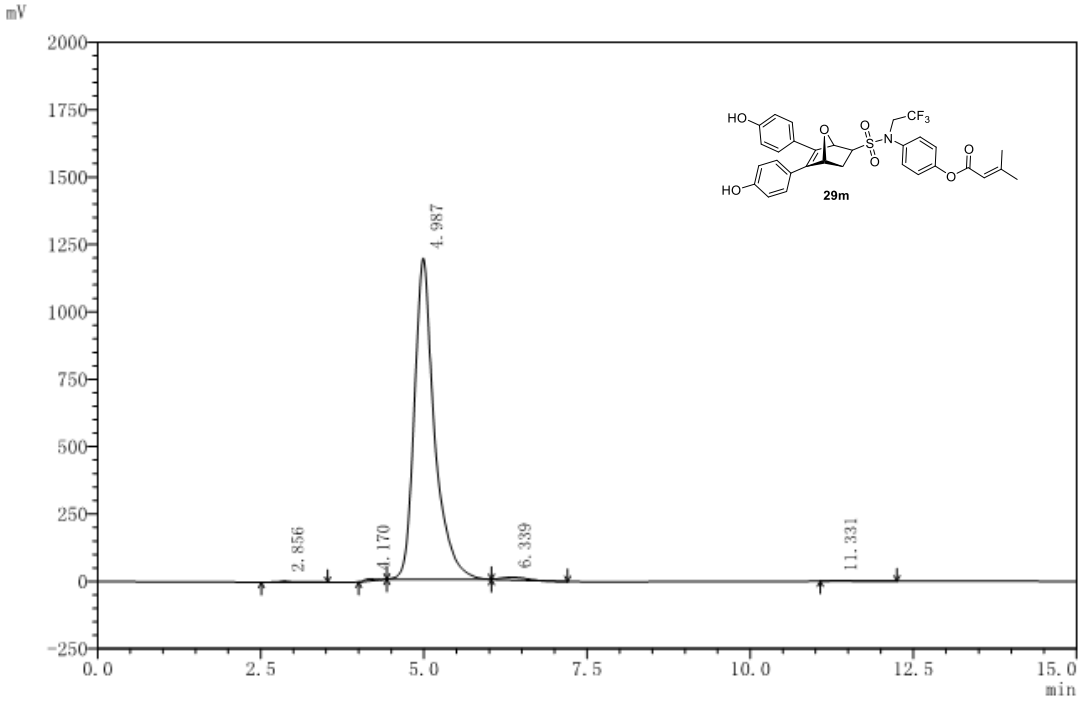
NO.	Retention Time	Area	Percent
1	3.847	70290	1.036

2	4.586	6713454	98.964
Total			100.000

HRMS (ESI) calcd for $C_{26}H_{23}F_3N_2O_5S$ $[M + Na]^+$ 533.1352, found 533.1350.



HPLC chromatogram of **29m.** Reverse Phase (Method 90:10 CH_3OH: H_2O, Flow rate 0.7 mL/min).



NO.	Retention Time	Area	Percent

1	2.856	80189	0.328
2	4.170	85196	0.327
3	4.987	25605793	98.417
4	6.339	246285	0.927
Total			100.000

HRMS (ESI) calcd for $C_{31}H_{28}F_3NO_7S$ $[M + Na]^+$ 638.1430, found 638.1436.