Supporting Information

Binding Free Energy Calculation Based on the Fragment Molecular Orbital Method and Its Application in Designing Novel SHP-2 Allosteric Inhibitors

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Table S1. Results for ranking with different affinity prediction methods in Schrödinger FEP+ benchmark set.

	FMO					FMOScore					FEP+				
Protein	N	R	ρ	τ	RMSE	N	R	ρ	τ	RMSE	N	R	ρ	τ	RMSE
CDK8	32	$0.78^{0.71}_{0.85}$	$0.82^{0.73}_{0.89}$	$0.64^{0.52}_{0.73}$	$0.93^{0.64}_{1.26}$	32	$0.81^{0.72}_{0.88}$	$0.84^{0.75}_{0.92}$	$0.67^{0.56}_{0.78}$	$0.88^{0.63}_{1.15}$	32	$0.64^{0.44}_{0.81}$	$0.67^{0.46}_{0.84}$	$0.53^{0.36}_{0.69}$	$1.11^{0.66}_{1.55}$
c-Met	24	$0.83^{0.72}_{0.91}$	$0.79^{0.60}_{0.92}$	$0.65^{0.47}_{0.80}$	$1.04^{0.71}_{1.37}$	24	$0.90^{0.82}_{0.96}$	$0.90^{0.79}_{0.97}$	$0.77^{0.64}_{0.88}$	$0.78^{0.43}_{1.09}$	24	$0.91^{0.85}_{0.95}$	$0.88^{0.77}_{0.95}$	$0.75^{0.63}_{0.85}$	$0.76^{0.57}_{0.97}$
Eg5	28	$0.68^{0.48}_{0.83}$	$0.59^{0.31}_{0.81}$	$0.56^{0.22}_{0.65}$	$0.69^{0.47}_{0.91}$	28	$0.79^{0.66}_{0.88}$	$0.74^{0.54}_{0.89}$	$0.60^{0.41}_{0.76}$	$0.58^{0.41}_{0.76}$	28	$0.73^{0.57}_{0.86}$	$0.71^{0.52}_{0.86}$	$0.57^{0.40}_{0.73}$	$0.68^{0.47}_{0.92}$
HIF-2α	42	$0.31^{0.05}_{0.54}$	$0.23^{-0.05}_{0.49}$	$0.16^{-0.03}_{0.36}$	$1.12^{0.78}_{1.46}$	42	$0.43^{0.13}_{0.67}$	$0.28^{0.01}_{0.53}$	$0.21^{0.01}_{0.40}$	$1.07^{0.77}_{1.38}$	42	$0.57^{0.23}_{0.80}$	$0.54^{0.29}_{0.74}$	$0.41^{0.22}_{0.58}$	$0.98^{0.62}_{1.34}$
PFKFB3	40	$0.86^{0.80}_{0.91}$	$0.84^{0.75}_{0.90}$	$0.77^{0.56}_{0.76}$	$0.56^{0.42}_{0.69}$	40	$0.90^{0.85}_{0.93}$	$0.89^{0.81}_{0.94}$	$0.73^{0.63}_{0.81}$	$0.49^{0.37}_{0.63}$	40	$0.81^{0.73}_{0.88}$	$0.81^{0.71}_{0.89}$	$0.64^{0.53}_{0.74}$	$0.64^{0.47}_{0.80}$
SHP-2	26	$0.57^{0.34}_{0.74}$	$0.59^{0.33}_{0.79}$	$0.45^{0.26}_{0.63}$	$1.05^{0.76}_{1.39}$	26	$0.80^{0.70}_{0.88}$	$0.75^{0.56}_{0.88}$	$0.56^{0.39}_{0.70}$	$0.76^{0.50}_{1.02}$	26	$0.73^{0.58}_{0.85}$	$0.71^{0.50}_{0.87}$	$0.57^{0.39}_{0.73}$	$0.88^{0.64}_{1.15}$
SYK	39	$0.43^{0.27}_{0.57}$	$0.43^{0.21}_{0.63}$	$0.31^{0.15}_{0.27}$	$0.77^{0.57}_{0.96}$	39	$0.76^{0.62}_{0.87}$	$0.76^{0.61}_{0.88}$	$0.61^{0.46}_{0.74}$	$0.54^{0.37}_{0.72}$	39	$0.47^{0.18}_{0.70}$	$0.40^{0.16}_{0.60}$	$0.28^{0.11}_{0.43}$	$0.75^{0.56}_{0.94}$
TNKS2	27	$0.36^{0.05}_{0.58}$	$0.21^{-0.19}_{0.54}$	$0.10^{-0.19}_{0.37}$	$1.02^{0.65}_{1.35}$	27	$0.62^{0.29}_{0.85}$	$0.50^{0.17}_{0.77}$	$0.39^{0.12}_{0.63}$	$0.86^{0.51}_{1.19}$	27	$0.46^{0.16}_{0.70}$	$0.43^{0.10}_{0.69}$	$0.32^{0.07}_{0.54}$	$0.98^{0.66}_{1.29}$
Total	258	$0.62^{0.55}_{0.68}$	$0.64^{0.57}_{0.70}$	$0.47^{0.41}_{0.52}$	$1.14^{1.02}_{1.26}$	258	$0.87^{0.84}_{0.89}$	$0.87^{0.84}_{0.89}$	$0.69^{0.65}_{0.72}$	$0.71^{0.62}_{0.80}$	258	$0.78^{0.74}_{0.83}$	$0.77^{0.71}_{0.81}$	$0.58^{0.53}_{0.63}$	$0.89^{0.77}_{1.00}$

	MM/GBSA					MM/PBSA					Vina				
Protein	N	R	ρ	τ	RMSE	N	R	ρ	τ	RMSE	N	R	ρ	τ	RMSE
CDK8	32	$0.30^{0.03}_{0.68}$	$0.45^{0.16}_{0.71}$	$0.33^{0.11}_{0.53}$	$1.42^{0.93}_{2.09}$	32	$0.02^{-0.34}_{0.38}$	$-0.04^{-0.34}_{0.38}$	$-0.02^{-0.27}_{0.24}$	$1.50^{1.02}_{2.03}$	32	$0.58^{0.35}_{0.79}$	$0.61^{0.36}_{0.80}$	$0.48^{0.27}_{0.66}$	$1.17^{0.73}_{1.70}$
c-Met	24	$0.68^{0.48}_{0.83}$	$0.72^{0.47}_{0.89}$	$0.59^{0.39}_{0.77}$	$1.43^{0.89}_{2.02}$	24	$0.23^{-0.16}_{0.56}$	$0.15^{-0.25}_{0.51}$	$0.10^{-0.19}_{0.39}$	$1.83^{1.26}_{2.46}$	24	$-0.31^{-0.56}_{-0.05}$	$-0.37^{-0.62}_{-0.07}$	$-0.22^{-0.44}_{0}$	$1.80^{1.26}_{2.32}$
Eg5	28	$0.43^{0.11}_{0.69}$	$0.41^{0.08}_{0.70}$	$0.30^{0.04}_{0.53}$	$0.88^{0.61}_{1.17}$	28	$0.02^{-0.27}_{0.31}$	$0.10^{-0.25}_{0.43}$	$0.05^{-0.20}_{0.29}$	$0.96^{0.65}_{1.27}$	28	$-0.44^{-0.65}_{-0.22}$	$-0.47^{-0.69}_{-0.20}$	$-0.31^{-0.50}_{-0.10}$	$0.84^{0.51}_{1.15}$
HIF-2α	42	$0.19^{-0.03}_{0.43}$	$0.23^{0.0003}_{0.45}$	$0.15^{-0.005}_{0.30}$	$1.15^{0.82}_{1.52}$	42	$0.26^{0.001}_{0.51}$	$0.20^{-0.06}_{0.45}$	$0.15^{-0.04}_{0.33}$	$1.14^{0.80}_{1.49}$	42	$0.28^{0.003}_{0.54}$	$0.50^{0.26}_{0.70}$	$0.39^{0.21}_{0.56}$	$1.13^{0.76}_{1.50}$
PFKFB3	40	$0.48^{0.23}_{0.70}$	$0.45^{0.19}_{0.69}$	$0.33^{0.14}_{0.51}$	$0.99^{0.73}_{1.28}$	40	$0.26^{0.01}_{0.49}$	$0.28^{0.005}_{0.54}$	$0.21^{0.01}_{0.41}$	$1.10^{0.87}_{1.34}$	40	$0.35^{0.13}_{0.54}$	$0.33^{0.10}_{0.54}$	$0.22^{0.05}_{0.38}$	$1.06^{0.84}_{1.28}$
SHP-2	26	$0.34^{0.08}_{0.64}$	$0.35^{0.02}_{0.67}$	$0.31^{0.08}_{0.55}$	$1.24^{0.82}_{1.75}$	26	$0.50^{0.19}_{0.77}$	$0.48^{0.18}_{0.74}$	$0.38^{0.15}_{0.59}$	$1.19^{0.70}_{1.73}$	26	$0.37^{0.04}_{0.67}$	$0.35^{0.04}_{0.64}$	$0.35^{0.01}_{0.48}$	$1.17^{0.72}_{1.61}$
SYK	39	$0.50^{0.29}_{0.69}$	$0.47^{0.24}_{0.68}$	$0.36^{0.19}_{0.52}$	$0.74^{0.55}_{0.93}$	39	$0.18^{-0.12}_{0.43}$	$0.06^{-0.23}_{0.34}$	$0.04^{-0.16}_{0.24}$	$0.84^{0.61}_{1.06}$	39	$0.39^{0.21}_{0.56}$	$0.35^{0.14}_{0.54}$	$0.34^{0.09}_{0.37}$	$0.77^{0.55}_{0.99}$
TNKS2	27	$0.47^{0.19}_{0.69}$	$0.41^{0.13}_{0.65}$	$0.28^{0.07}_{0.48}$	$0.96^{0.63}_{1.27}$	27	$-0.21^{-0.48}_{0.07}$	$-0.11^{-0.43}_{0.20}$	$-0.09^{-0.31}_{0.12}$	$1.06^{0.68}_{0.36}$	27	$-0.06^{-0.35}_{0.25}$	$0.11^{-0.22}_{0.44}$	$0.09^{-0.14}_{0.33}$	$1.10^{0.70}_{1.44}$
Total	258	$0.27^{0.18}_{0.36}$	$0.27^{0.17}_{0.26}$	$0.18^{0.12}_{0.25}$	$1.39^{1.25}_{1.54}$	258	$0.13^{0.03}_{0.23}$	$0.09^{-0.01}_{0.19}$	$0.06^{-0.01}_{0.19}$	$1.44^{1.30}_{1.57}$	258	$0.09^{0.008}_{0.18}$	$0.09^{0.00}_{0.18}$	$0.06^{0.00}_{0.12}$	$1.44^{1.30}_{1.57}$

Table S2. Linear coefficients of FMOScore of 8 targets in Schrödinger FEP+ benchmark.

Target	ΔE^{int}	ΔG^{sol}	ΔE_{lig}^{def}	constant
CDK8	0.05066	-0.04087	0.02395	-3.05111
c-Met	0.04297	0.03001	0.04486	-3.85653
EG5	0.04591	-0.00677	0.01301	-6.73679
HIF-2α	0.02229	0.01377	0.07526	-8.75932
PFKFB3	0.05389	-0.00547	0.03022	-3.05507
SHP2	0.02002	-0.02125	0.04421	-2.78159
SYK	0.01577	-0.0056	0.04735	-9.47309
TNKS2	0.08894	-0.03104	0.05194	-1.31775

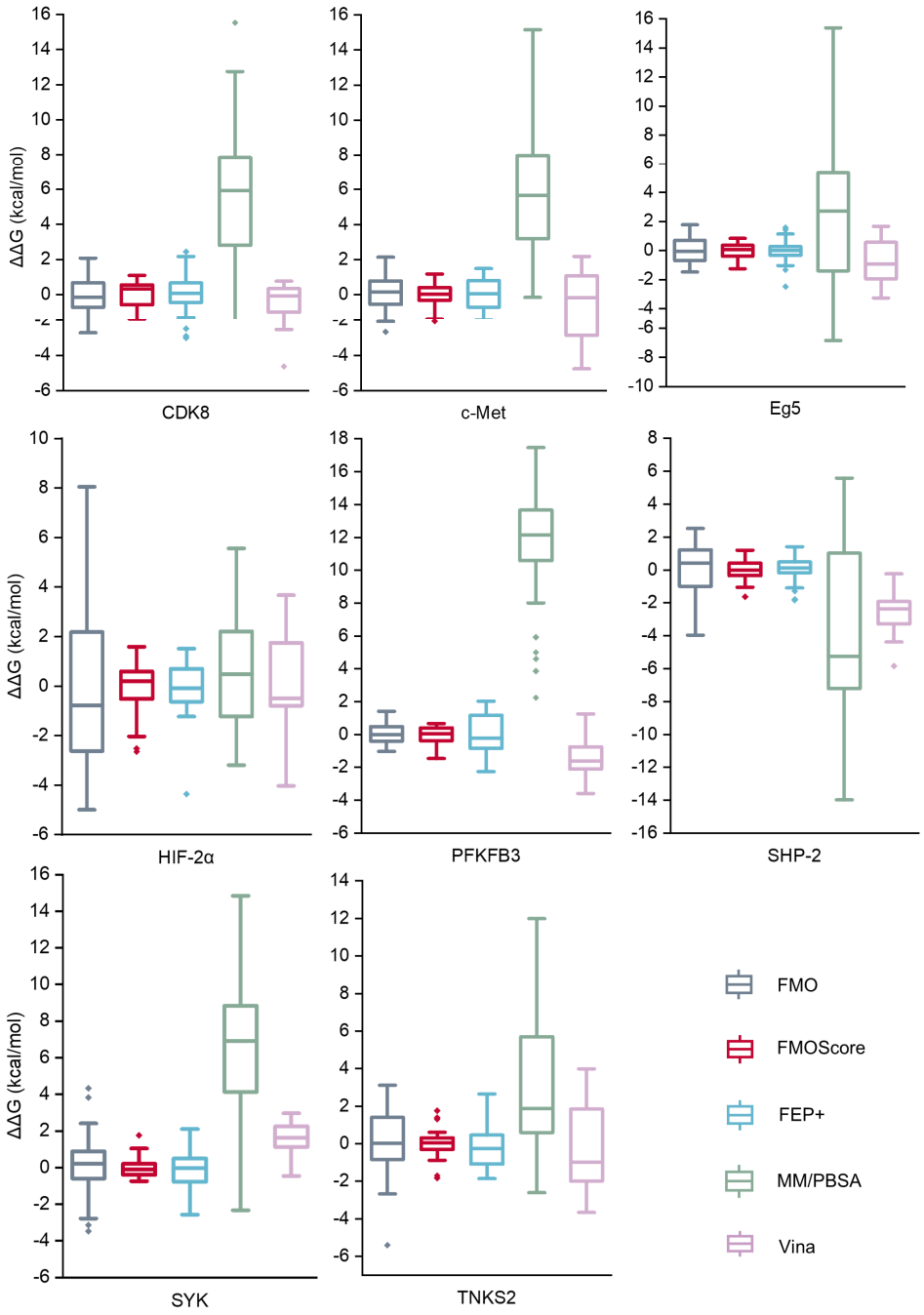
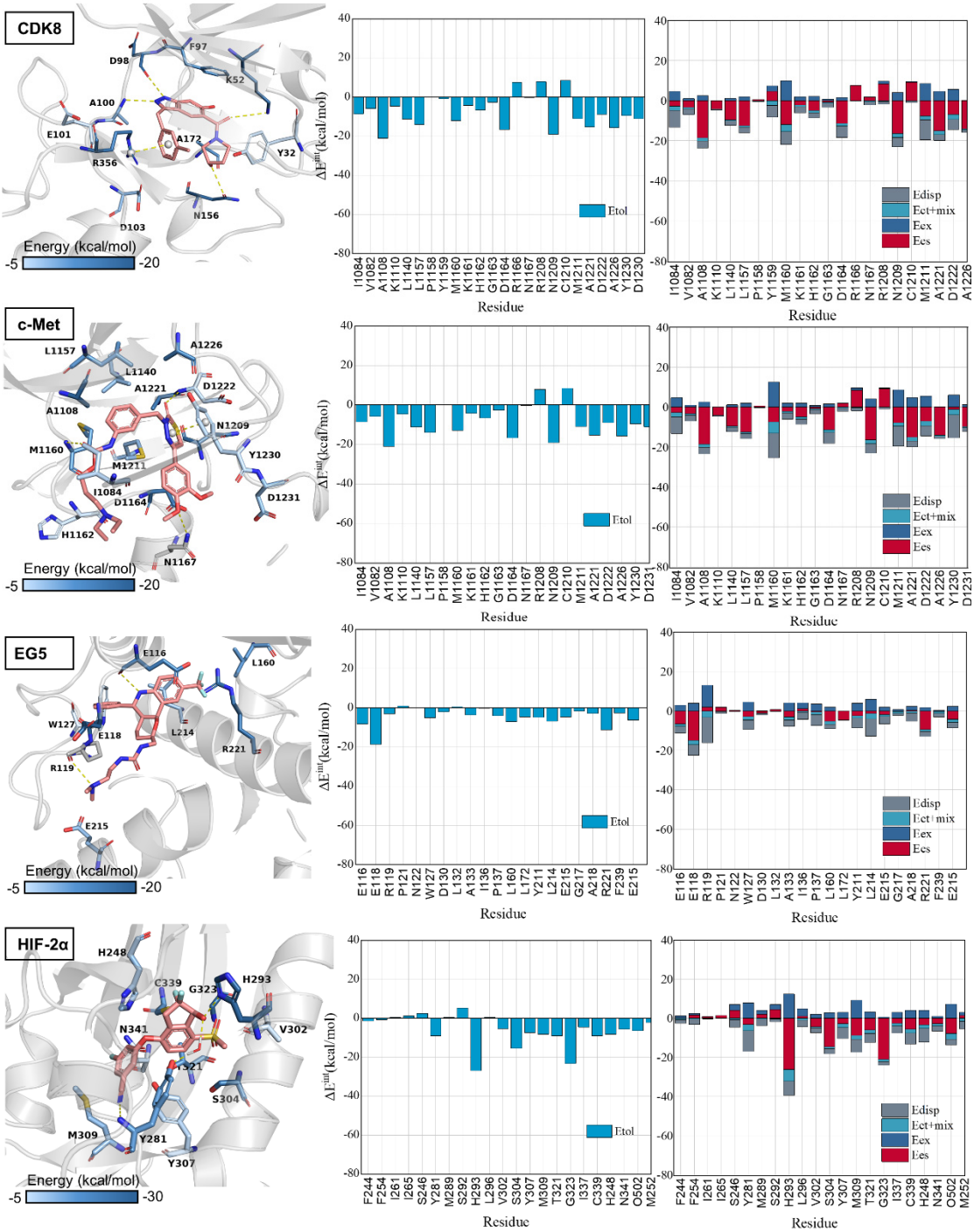


Figure S1. Box-plot diagrams of the error for pairwise relative affinities $|\Delta G_{pred} - \Delta G_{exp}|$.

Table S3. Results of different energy term contributions for eight targets with the FMOScore method on a literature curated benchmark set.

Protein	PDB ID [a]	ΔG_{exp} [b]	ΔG_{pred} [c]	ΔE^{int}					ΔG^{sol}	ΔE_{lig}^{def}
				Total [d]	ΔE_{es}	ΔE_{ex}	ΔE_{ct+mix}	ΔE_{disp}		
CDK8	5HNB	-11.22	-11.86	-129.11	-93.83	61.14	-26.82	-69.60	61.73	12.63
c-Met	4R1Y	-8.73	-10.79	-174.79	-121.22	62.26	-28.53	-87.30	-30.36	32.47
Eg5	3L9H	-11.05	-11.04	-91.23	-43.25	58.82	-25.41	-81.39	119.70	44.91
HIF-2α	5TBM	-11.01	-10.54	-135.58	-92.19	76.45	-32.98	-86.86	43.36	7.74
PFKFB3	6HV1	-10.3	-10.15	-134.46	-87.75	72.19	-28.62	-90.27	53.92	10.37
SHP-2	5EHR	-9.75	-9.76	-141.73	-131.02	98.16	-30.97	-77.90	196.22	7.55
SYK	4PV0	-11.42	-10.75	-132.67	-94.44	62.87	-24.57	-76.53	69.14	26.54
TNKS2	4UI5	-10.05	-10.93	-106.69	-68.45	69.01	-27.56	-79.69	46.88	14.78

[a]The structures of the lead compounds in each target in the FEP+ benchmark have been selected for presentation, which are usually the starting points for structural modifications. [b]Experimental affinities were converted to ΔG_{exp} values using the equation $\Delta G_{exp} \approx k_B T \log IC_{50}$. [c]Predicted binding free energy ΔG_{prep} was fitted to the three types of energies calculated by the FMOScore method, consisting of binding affinities in vacuo (ΔE^{int}), solvation free energy (ΔG^{sol}), and deformation energy into the isolated form (ΔE_{lig}^{def}). [d]The total fragment pair interaction energy (ΔE^{int}) was decomposed into the electrostatic term (ΔE_{es}), exchange-repulsion term (ΔE_{ex}), charge transfer terms (ΔE_{ct+mix}), and dispersion term (ΔE_{disp}). All calculated values are in kcal/mol.


CDK8
F97
D98
K52
A100
E101
A172
Y32
R356
N156
D103
Energy (kcal/mol)
-5
-20
ΔE^int(kcal/mol)
Etol
Edisp
Eet+mix
Eex
Ees
Residue
c-Met
L1157
A1226
L1140
A1221
D1222
A1108
N1209
M1160
Y1230
M1211
I1084
D1164
D1231
H1162
N1167
EG5
E116
L160
W127
E118
L214
R221
R119
E215
HIF-2α
H248
C339
G323
H293
N341
V302
T321
S304
M309
Y281
Y307

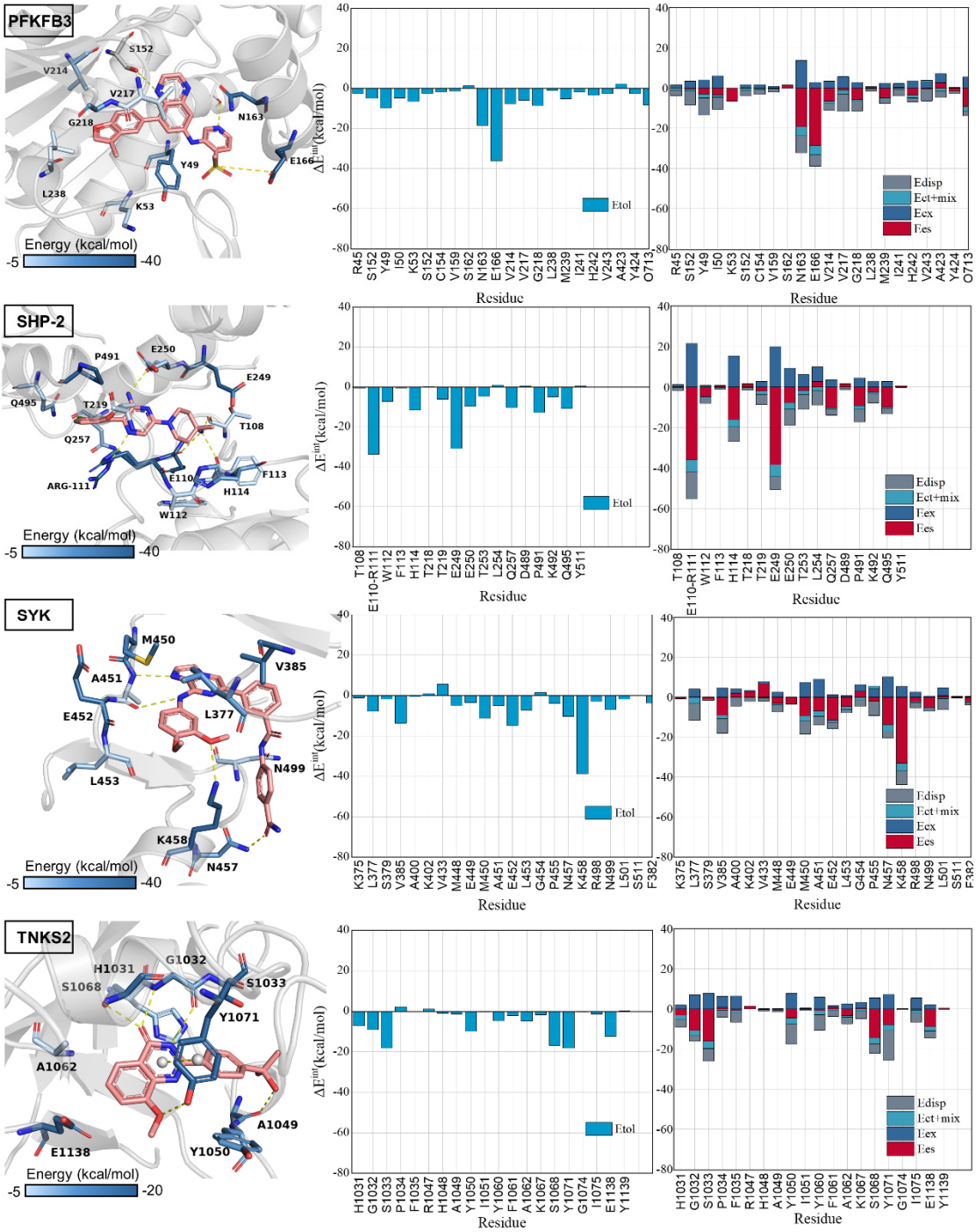


Figure S2. FMO results of eight targets: CDK8 (PDB: 5HNB), c-Met (PDB: 4R1Y), EG5 (PDB: 3I9H), HIF-2α (PDB: 5TBM), PFKFB3 (PDB: 6HVJ), SHP-2 (PDB: 5EHR), SYK (PDB: 4PV0), TNKS2 (PDB: 4UI5). The key interactions according to FMO calculations are marked as yellow dashed lines, and key residues are shown in dark blue sticks. The left-hand bar plots describe PIE between the residues at the active site and ligands, and the right-hand plots show the PIEDA of these key interactions.

The electrostatics, charge-transfer, dispersion, and exchange-repulsion PIE terms are represented in red, blue, gray, and dark blue, respectively.

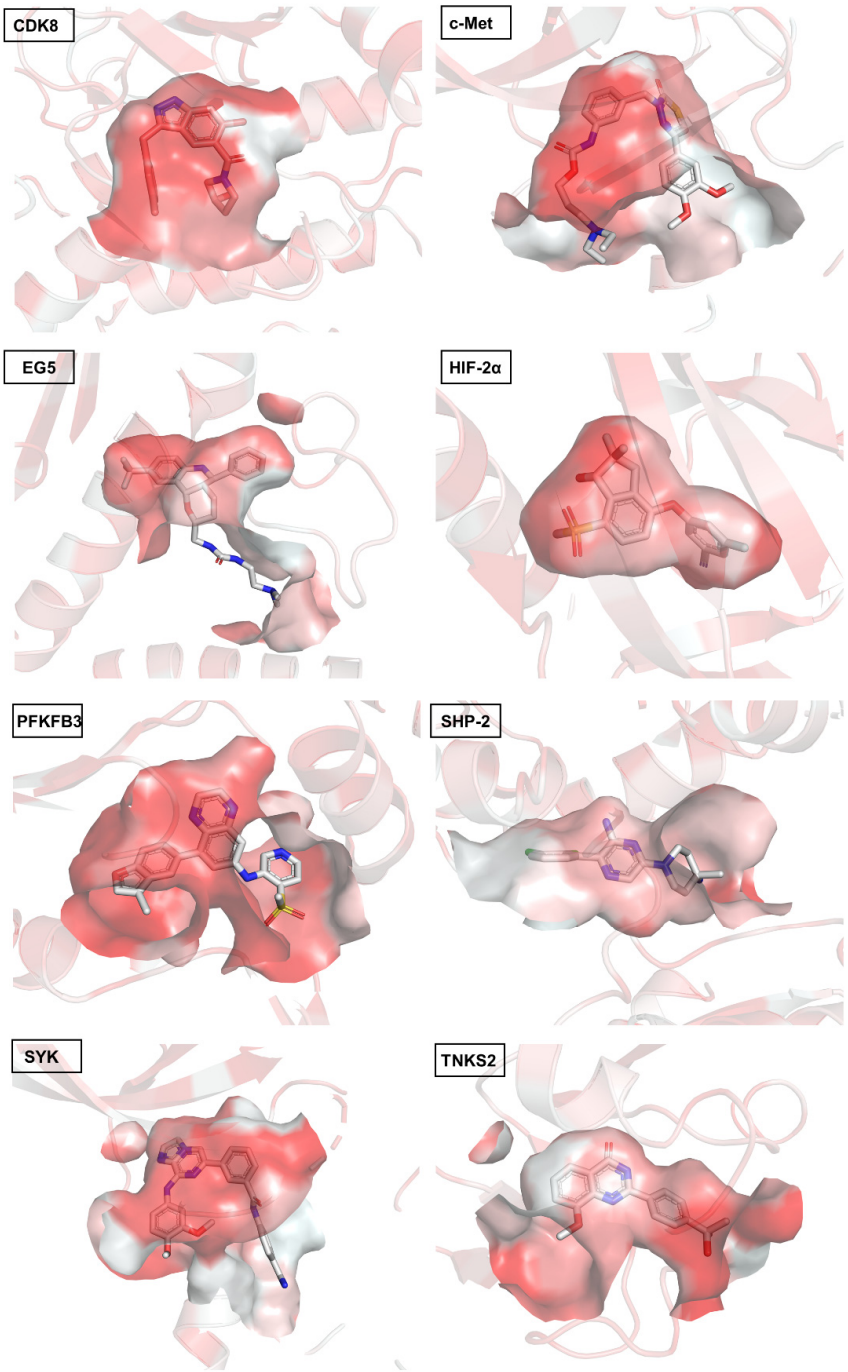


Figure S3. Pocket shapes and hydrophobic surfaces were rendered with PyMOL (version 2.3.0) for the eight targets: CDK8 (PDB: 5HNB), c-Met (PDB: 4R1Y), EG5 (PDB: 3I9H), HIF-2α (PDB: 5TBM), PFKFB3 (PDB: 6HVJ), SHP-2 (PDB: 5EHR), SYK (PDB: 4PV0), TNKS2 (PDB: 4UI5). The redder color indicates a stronger hydrophobic surface.

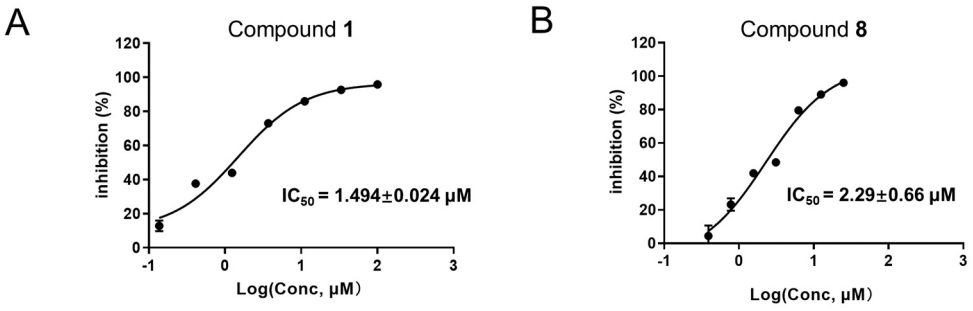
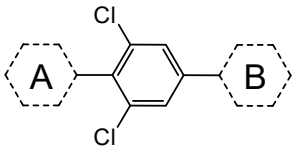
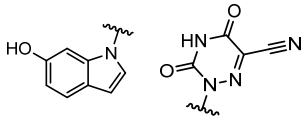
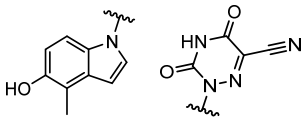
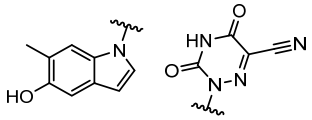
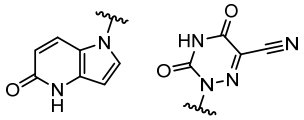
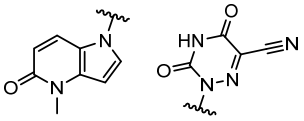
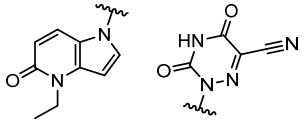
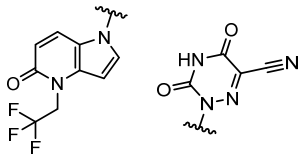
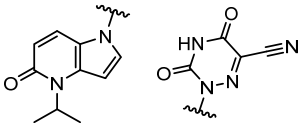
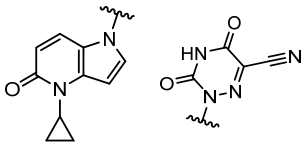
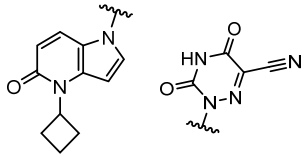
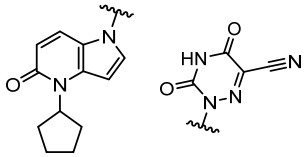


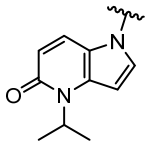
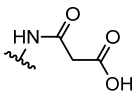
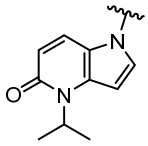
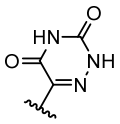
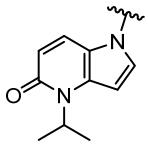
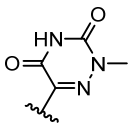
Figure S4. Identification of SHP-2 inhibitors through biochemical screening. (A-B) Compound **1** and **8** exhibited potent inhibitory activity against SHP-2. Phosphatase assays were conducted using the artificial substrate DIFMUP, and data represent mean ± SD (n = 3).

Table S4. Structure activity relationship study of THR-β inhibition activities.



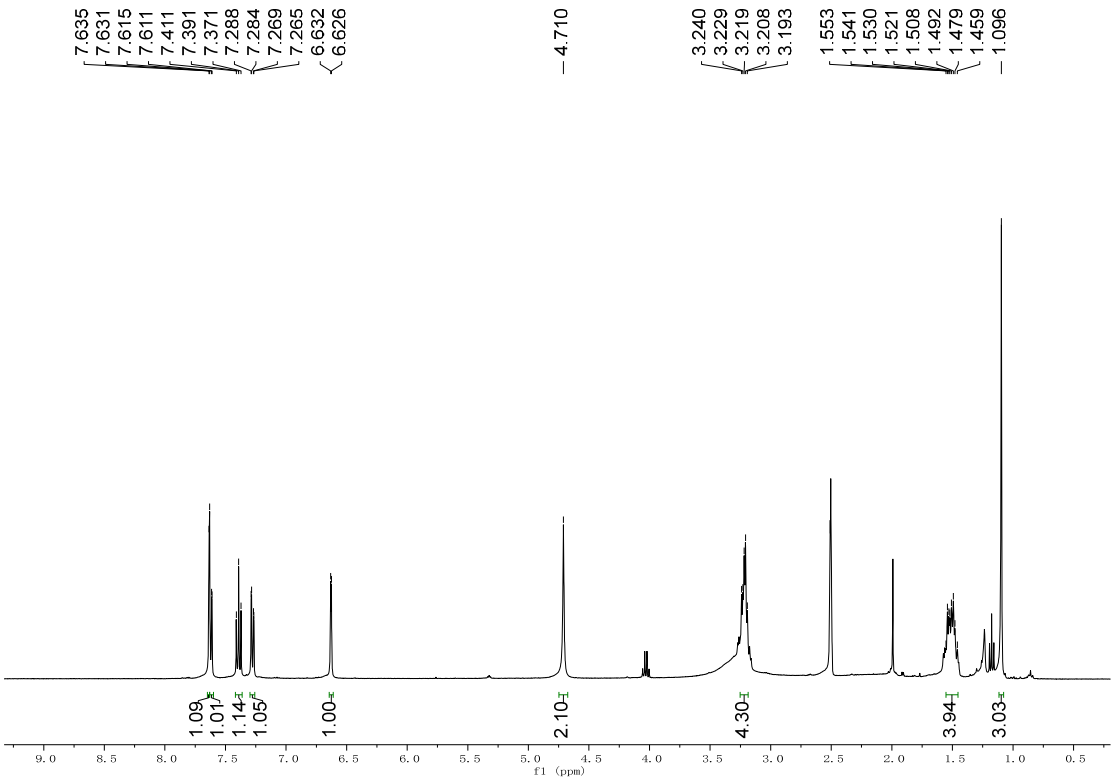
Ligand	Part A	Part B	THR-β IC_{50} (μM) [a]	ΔG_{exp} [b]	FMOScore (kcal/mol)			
					ΔG_{pred} [c]	ΔE^{int}	ΔE_{lig}^{def}	ΔG^{sol}
1			0.99±0.08	-8.186	-9.629	-101.46	27.19	245.55
2			>33	-6.110	-6.318	-80.016	24.10	224.18
3			0.65±0.07	-8.435	-8.475	-105.35	18.56	236.24
4			>100	-5.453	-5.925	-84.49	16.06	224.85

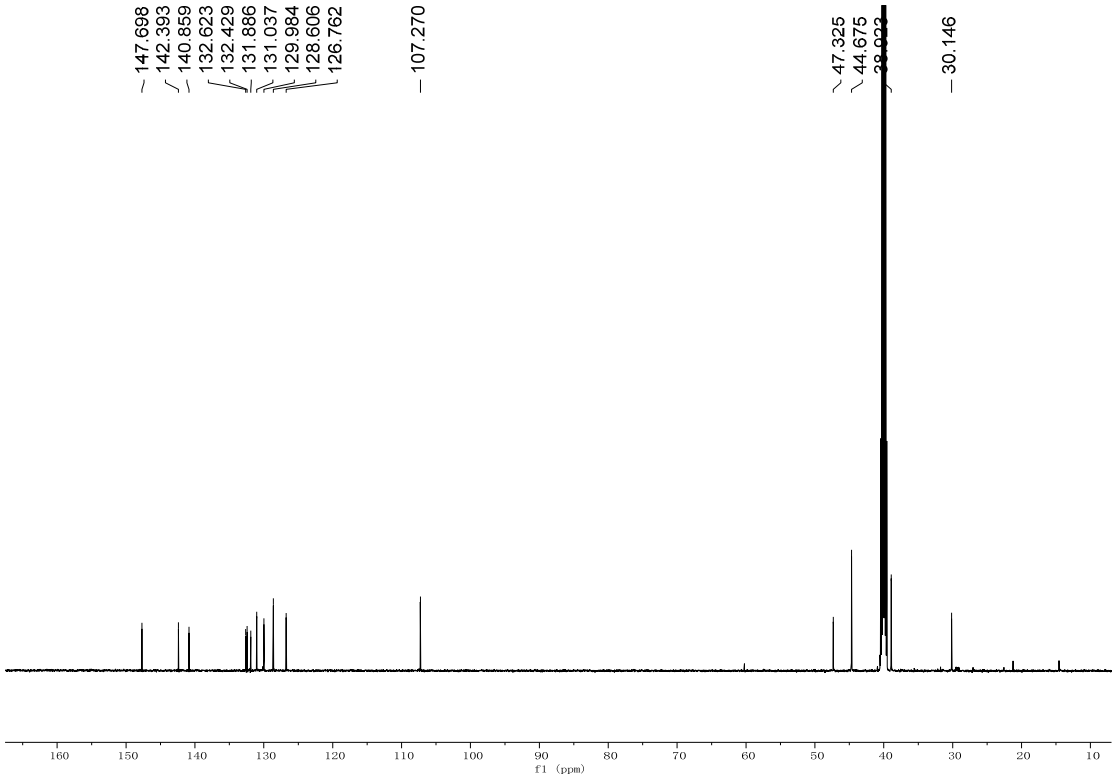
5		>100	-5.453	-6.624	-78.58	19.95	236.48
6		0.03±0.01	-10.257	-9.177	-112.88	22.27	232.94
7		>3.7	-7.406	-7.832	-95.74	22.45	231.71
8		>1.2	-8.072	-7.740	-91.58	20.76	237.49
9		0.20±0.05	-9.133	-9.539	-107.01	21.70	245.91
10		0.02±0.001	-10.497	-9.468	-101.48	25.28	245.88
11		0.07±0.01	-9.755	-9.921	-106.95	26.54	244.73
12		0.03±0.01	-10.257	-10.135	-107.75	27.03	246.33
13		0.03±0.007	-10.257	-9.983	-110.78	27.52	239.90
14		0.02±0.006	-10.497	-10.126	-100.10	32.65	246.69
15		0.04±0.01	-10.086	-10.282	-106.87	35.74	236.90

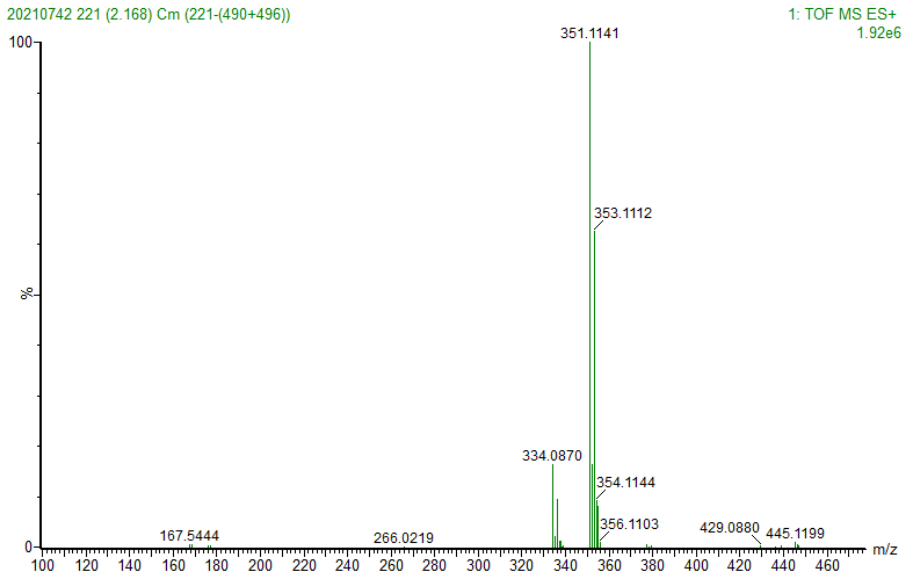
16			0.21±0.06	-9.105	-10.820	-99.17	30.21	261.81
17			0.04±0.007	-10.086	-7.824	-75.72	24.64	251.07
18			0.009±0.003	-10.970	-10.192	-108.04	28.32	245.01
	R^2		-	-	0.71	0.46	0.40	0.37

The spectra of ^{1}H NMR, ^{13}C NMR and HRMS (ESI) of all final compounds

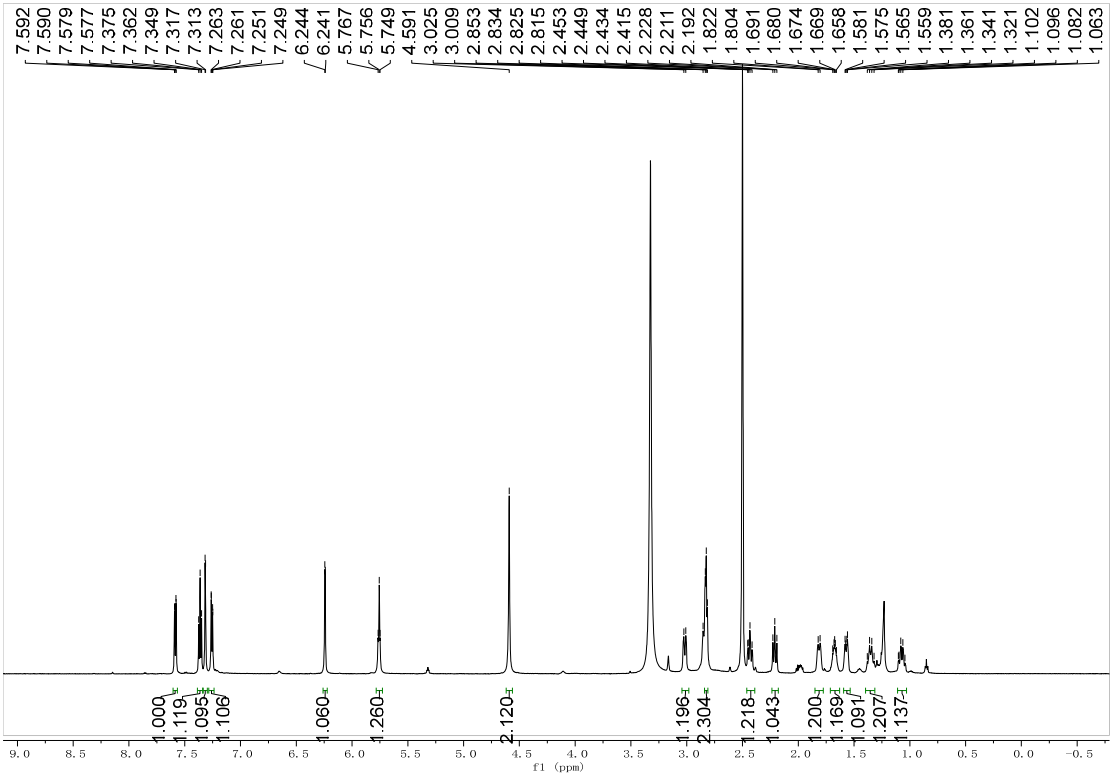
Compound 1

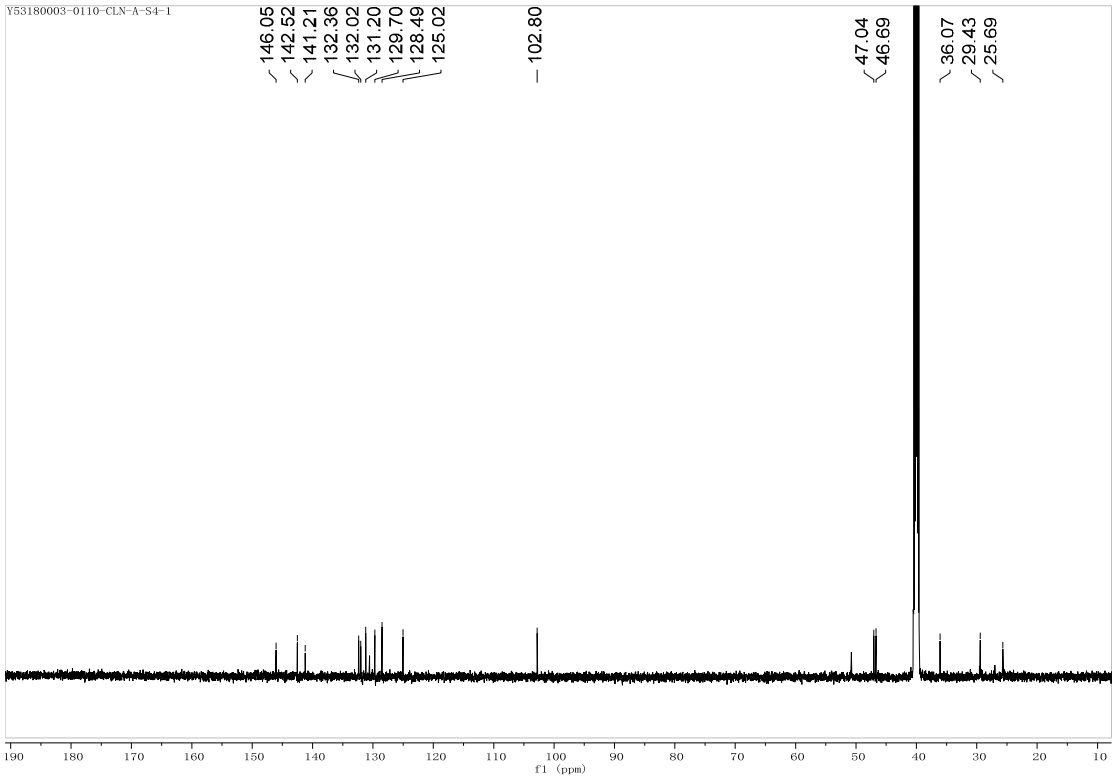


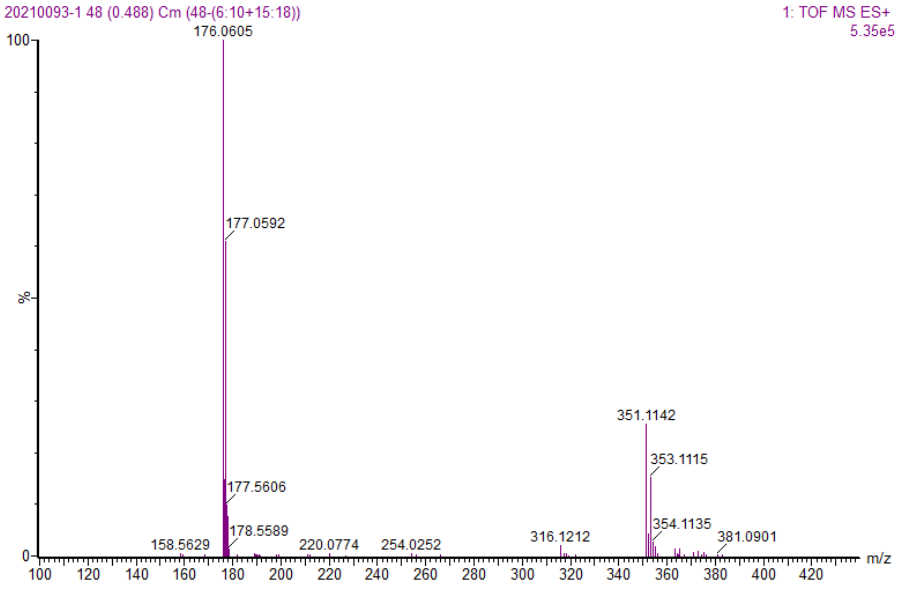



20210742 221 (2.168) Cm (221-(490+496))
1: TOF MS ES+
1.92e6
351.1141
353.1112
334.0870
354.1144
356.1103
167.5444
266.0219
429.0880
445.1199
m/z

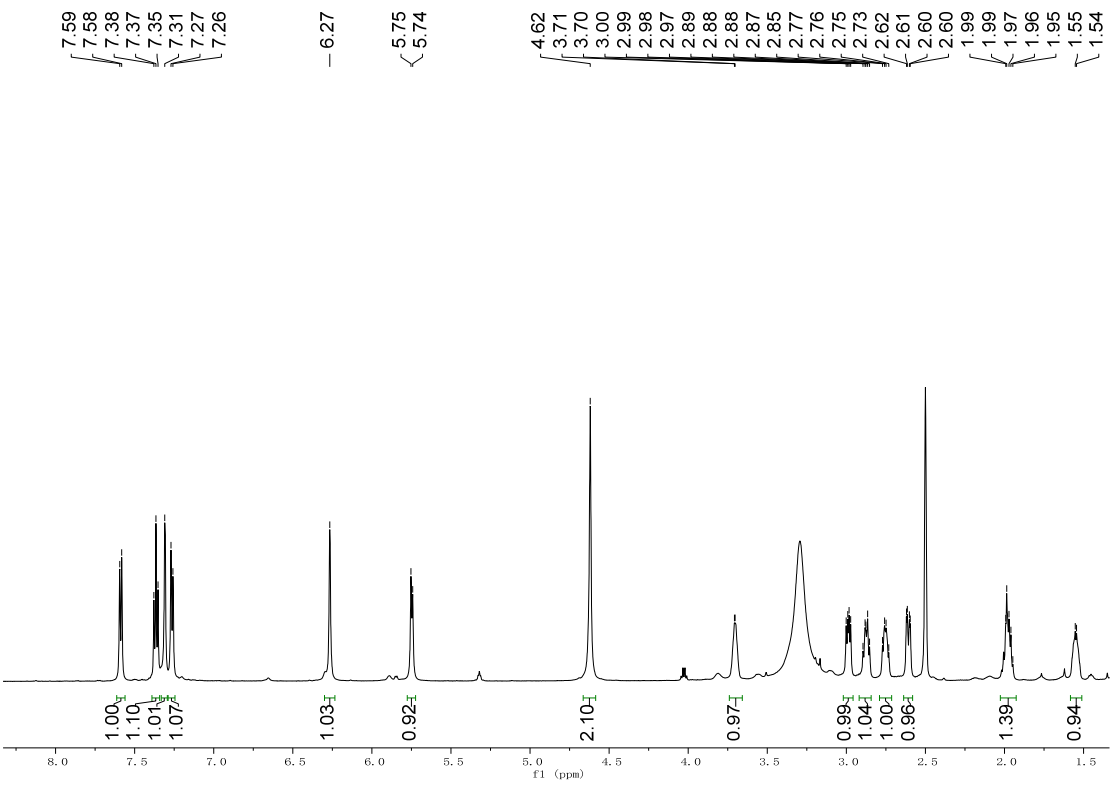
Compound 2

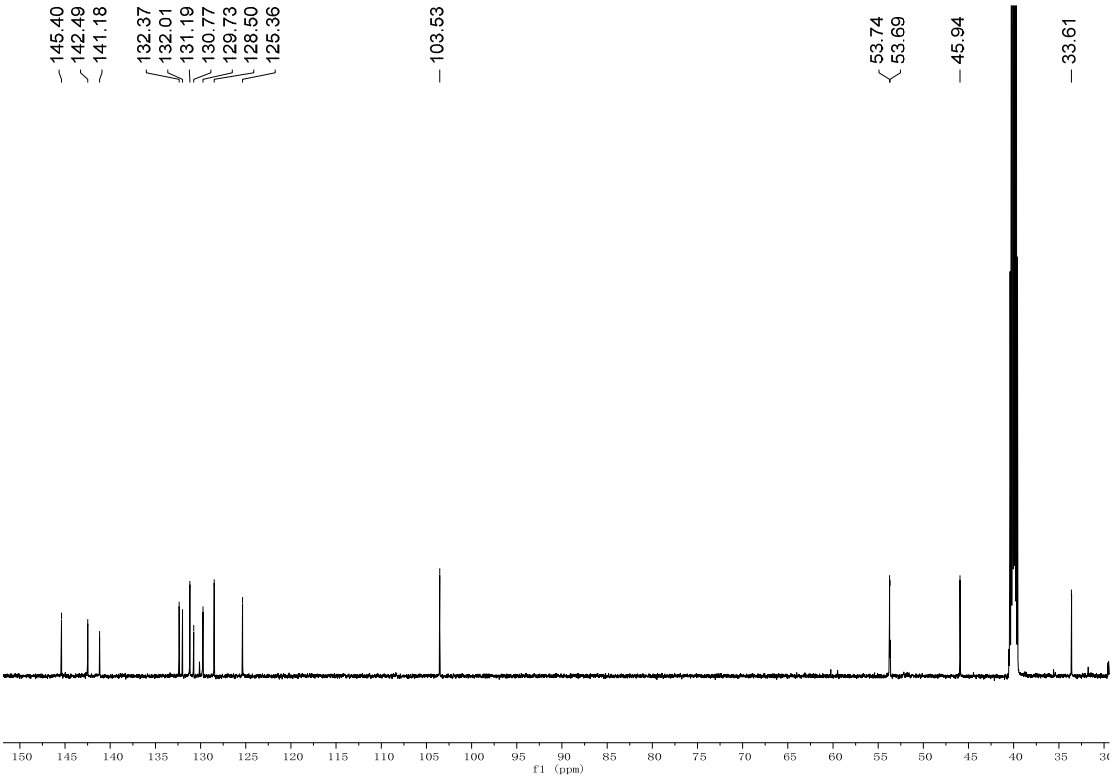

f1 (ppm)

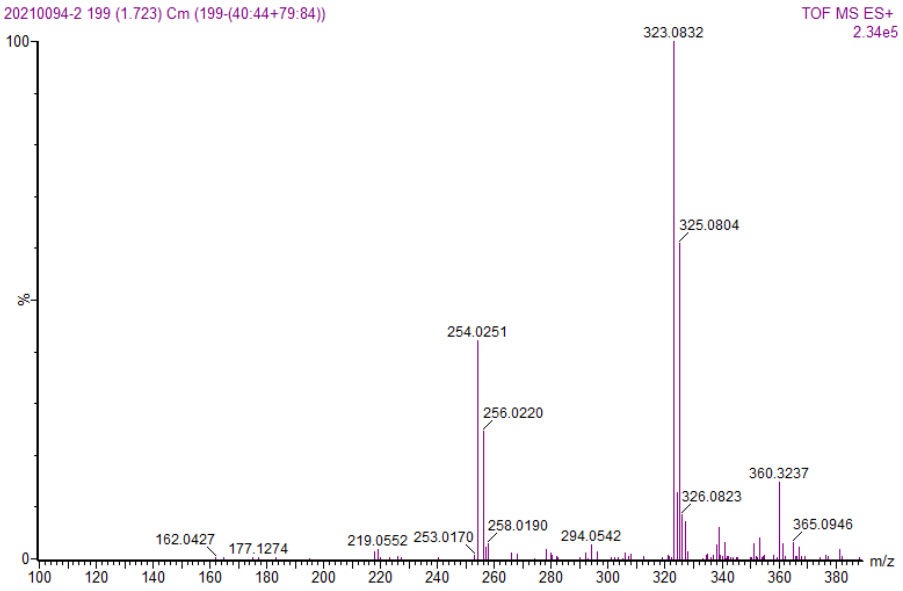

Y53180003-0110-CLN-A-S4-1
146.05
142.52
141.21
132.36
132.02
131.20
129.70
128.49
125.02
102.80
47.04
46.69
36.07
29.43
25.69
f1 (ppm)


20210093-1 48 (0.488) Cm (48-(6:10+15:18))
1: TOF MS ES+
5.35e5
176.0605
177.0592
177.5606
178.5589
158.5629
220.0774
254.0252
316.1212
351.1142
353.1115
354.1135
381.0901
%
m/z

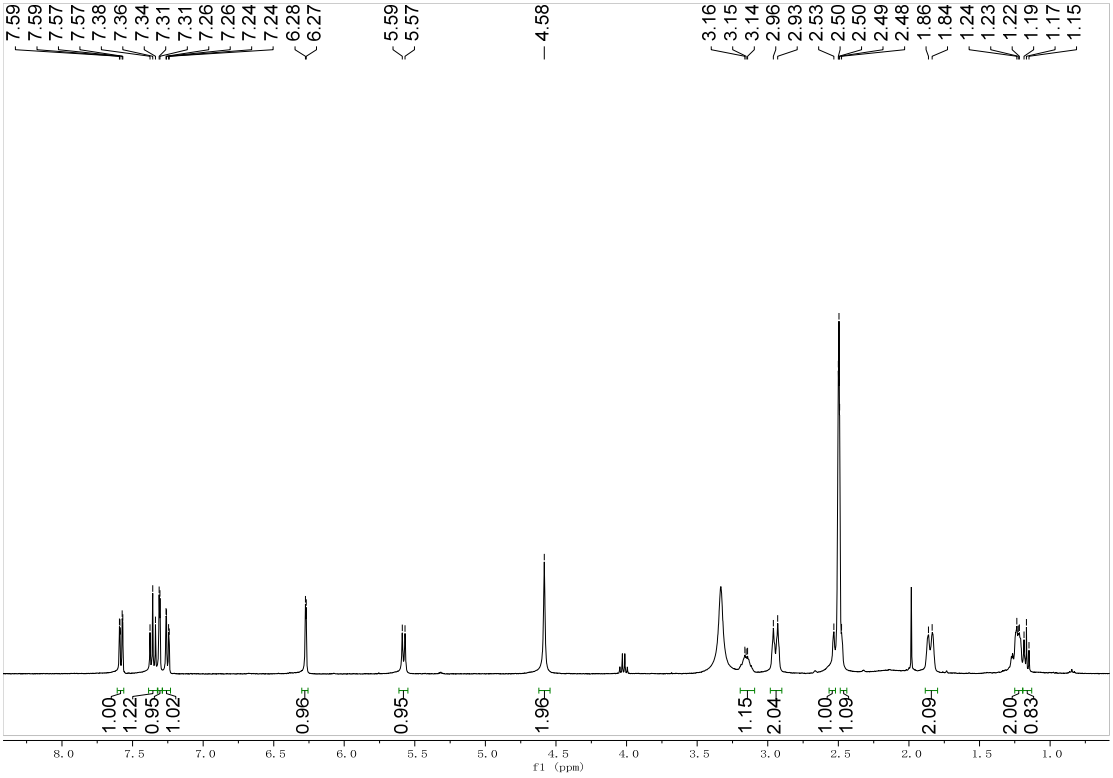
Compound 3

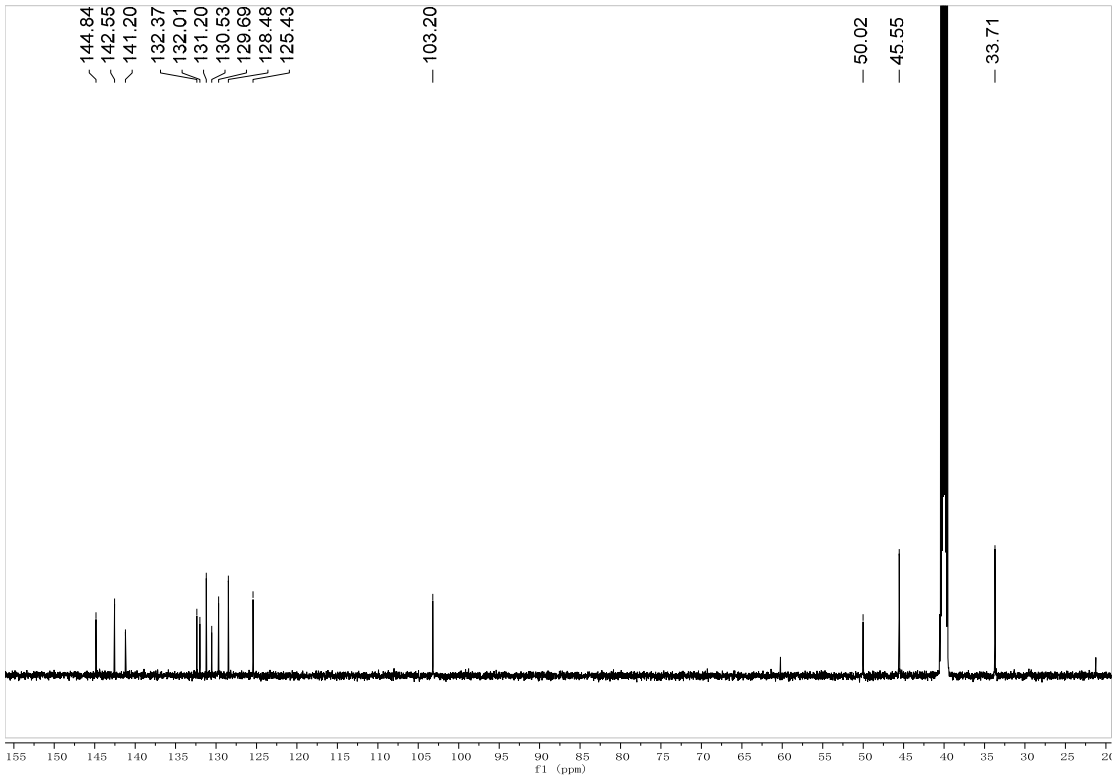

7.59
7.58
7.38
7.37
7.35
7.31
7.27
7.26
6.27
5.75
5.74
4.62
3.71
3.70
3.00
2.99
2.98
2.97
2.89
2.88
2.88
2.87
2.85
2.77
2.76
2.75
2.73
2.62
2.61
2.60
2.60
1.99
1.99
1.97
1.96
1.95
1.55
1.54
1.00
1.10
1.01
1.07
1.03
0.92
2.10
0.97
0.99
1.04
1.00
0.96
1.39
0.94
f1 (ppm)

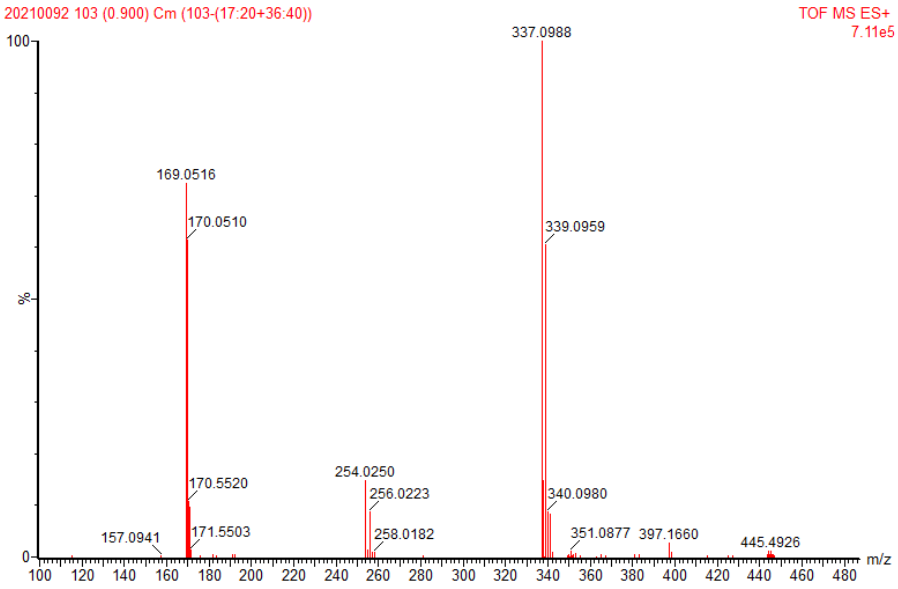

145.40
142.49
141.18
132.37
132.01
131.19
130.77
129.73
128.50
125.36
103.53
53.74
53.69
45.94
33.61
f1 (ppm)


20210094-2 199 (1.723) Cm (199-(40:44+79:84))
TOF MS ES+
2.34e5
323.0832
325.0804
254.0251
256.0220
360.3237
326.0823
365.0946
258.0190
162.0427
177.1274
219.0552
253.0170
294.0542
%
m/z

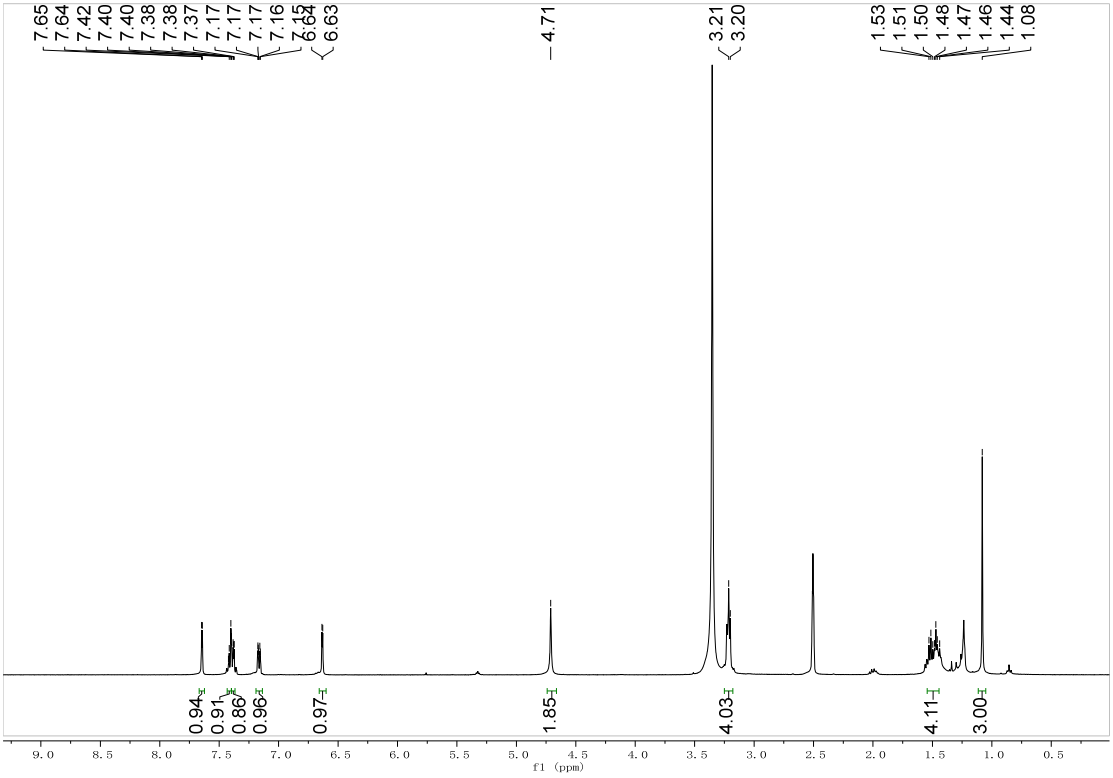
Compound：4

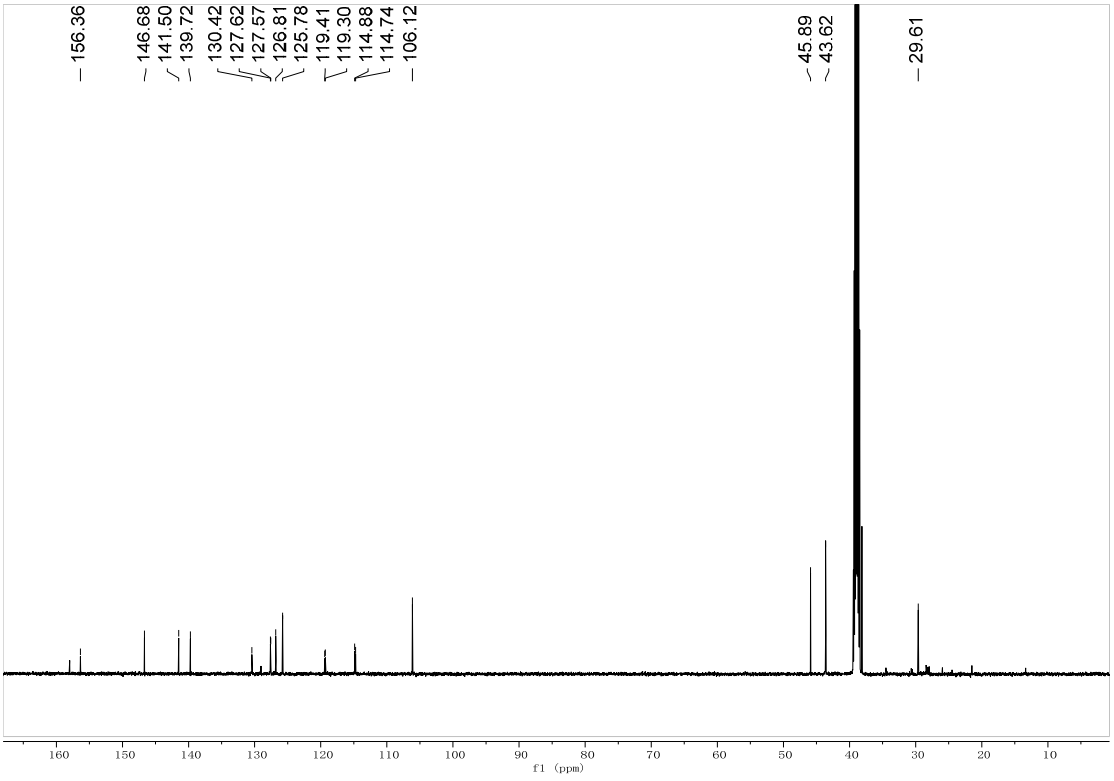

7.59
7.59
7.57
7.57
7.38
7.36
7.34
7.31
7.31
7.26
7.26
7.24
7.24
6.28
6.27
5.59
5.57
4.58
3.16
3.15
3.14
2.96
2.93
2.53
2.50
2.50
2.49
2.48
1.86
1.84
1.24
1.23
1.22
1.19
1.17
1.15
1.00
1.22
0.95
1.02
0.96
0.95
1.96
1.15
2.04
1.00
1.09
2.09
2.00
0.83
f1 (ppm)

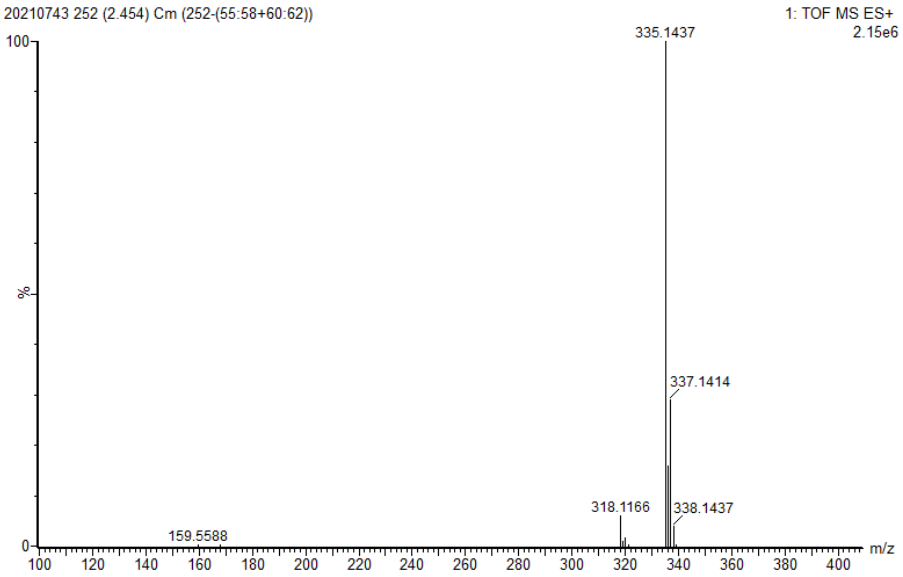

144.84
142.55
141.20
132.37
132.01
131.20
130.53
129.69
128.48
125.43
103.20
50.02
45.55
33.71
f1 (ppm)


20210092 103 (0.900) Cm (103-(17:20+36:40))
TOF MS ES+
7.11e5
337.0988
169.0516
170.0510
339.0959
170.5520
254.0250
256.0223
340.0980
157.0941
171.5503
258.0182
351.0877
397.1660
445.4926
%
m/z

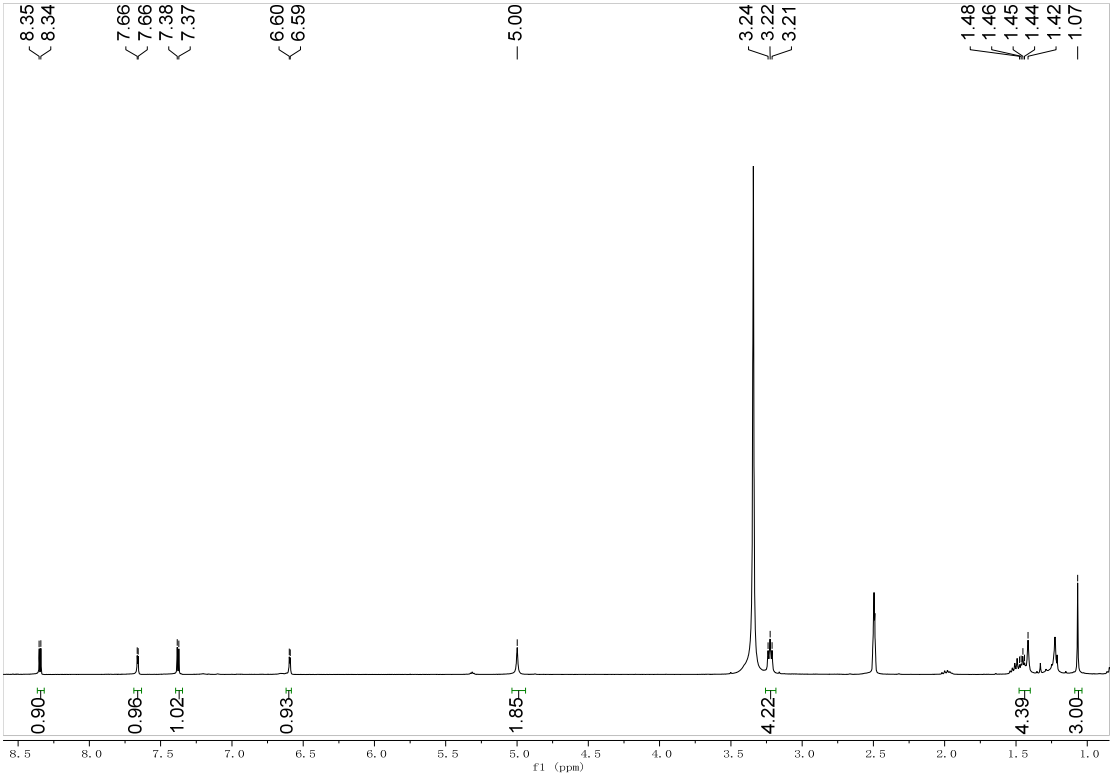
Compound：5

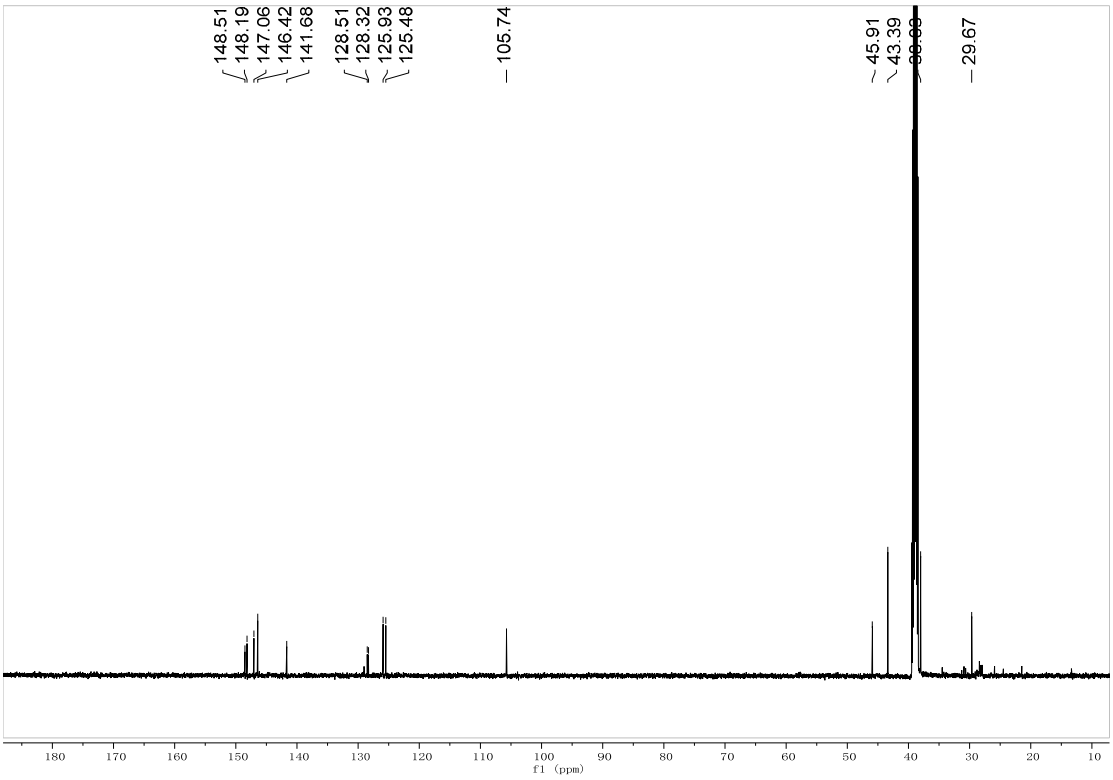

7.65
7.64
7.42
7.40
7.40
7.38
7.38
7.37
7.17
7.17
7.17
7.16
7.15
6.64
6.63
4.71
3.21
3.20
1.53
1.51
1.50
1.48
1.47
1.46
1.44
1.08
0.94
0.91
0.86
0.96
0.97
1.85
4.03
4.11
3.00
f1 (ppm)

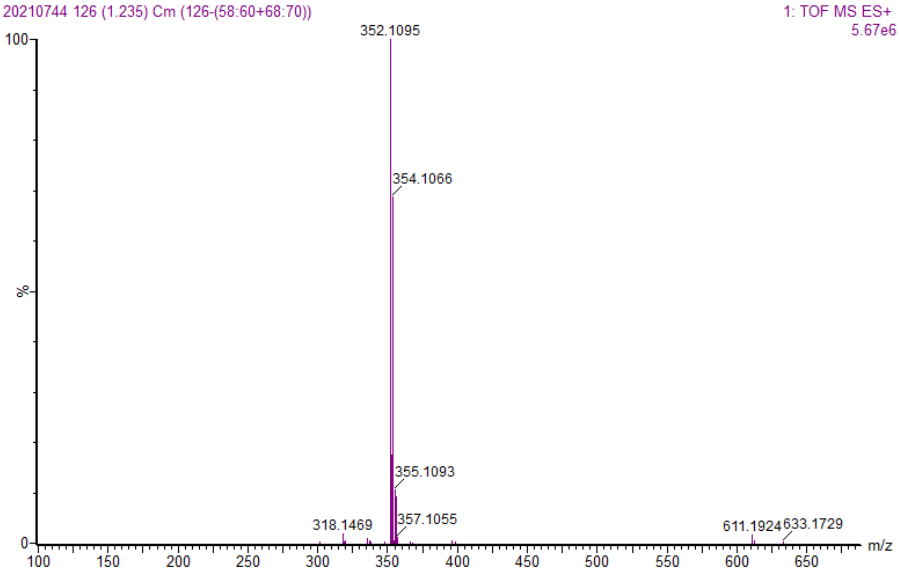

156.36
146.68
141.50
139.72
130.42
127.62
127.57
126.81
125.78
119.41
119.30
114.88
114.74
106.12
45.89
43.62
29.61
f1 (ppm)


20210743 252 (2.454) Cm (252-(55:58+60:62))
1: TOF MS ES+
2.15e6
335.1437
337.1414
318.1166
338.1437
159.5588
%
m/z

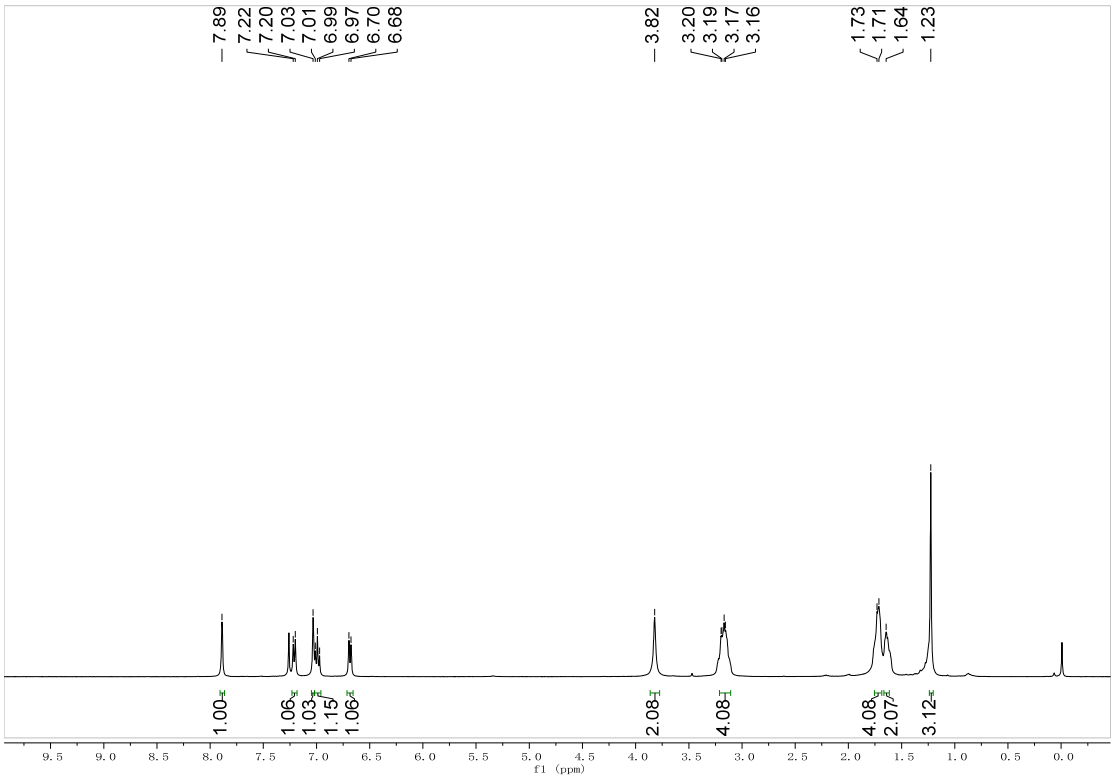
Compound：6

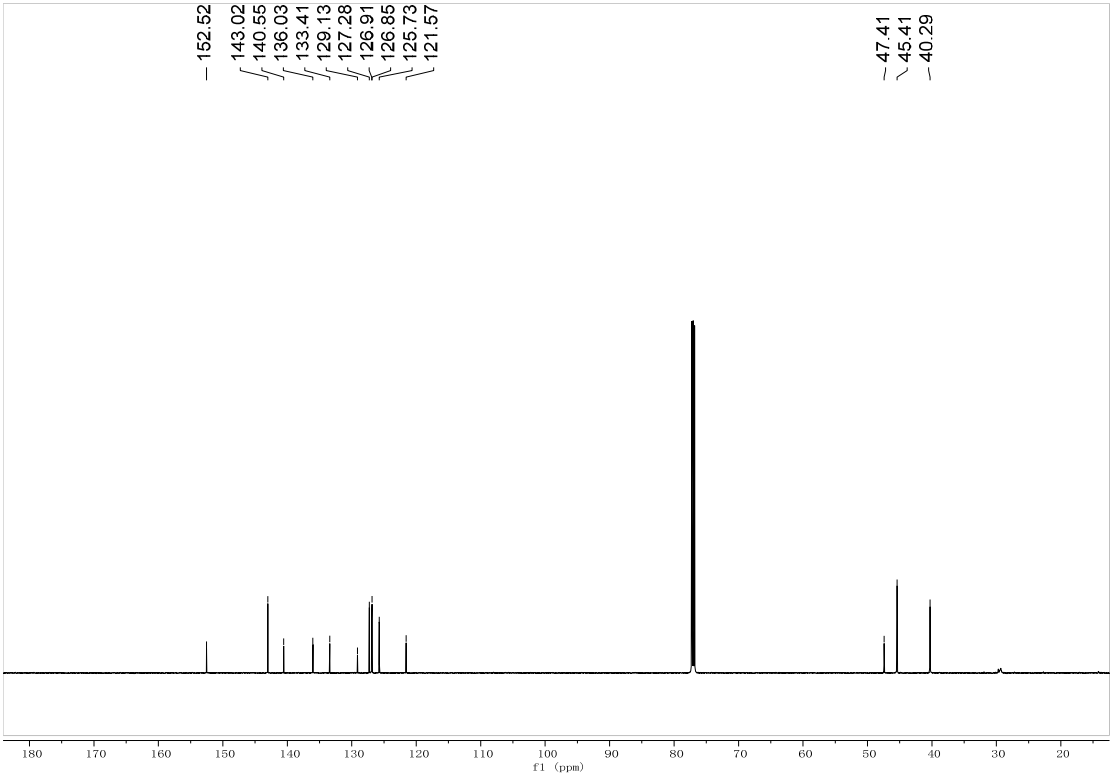

8.35
8.34
7.66
7.66
7.38
7.37
6.60
6.59
5.00
3.24
3.22
3.21
1.48
1.46
1.45
1.44
1.42
1.07
0.90
0.96
1.02
0.93
1.85
4.22
4.39
3.00
f1 (ppm)

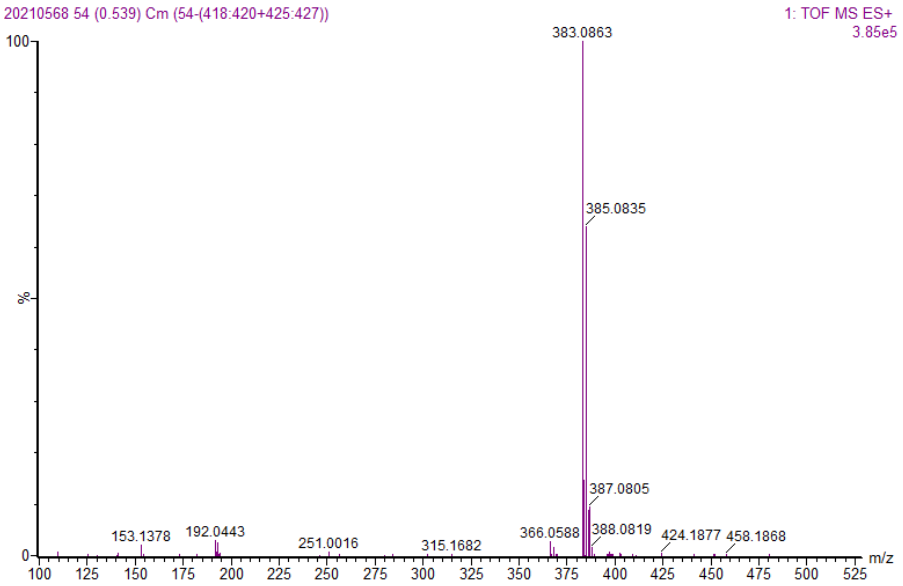

148.51
148.19
147.06
146.42
141.68
128.51
128.32
125.93
125.48
105.74
45.91
43.39
29.67
f1 (ppm)


20210744 126 (1.235) Cm (126-(58:60+68:70))
1: TOF MS ES+
5.67e6
352.1095
354.1066
355.1093
357.1055
318.1469
611.1924
633.1729
%
m/z

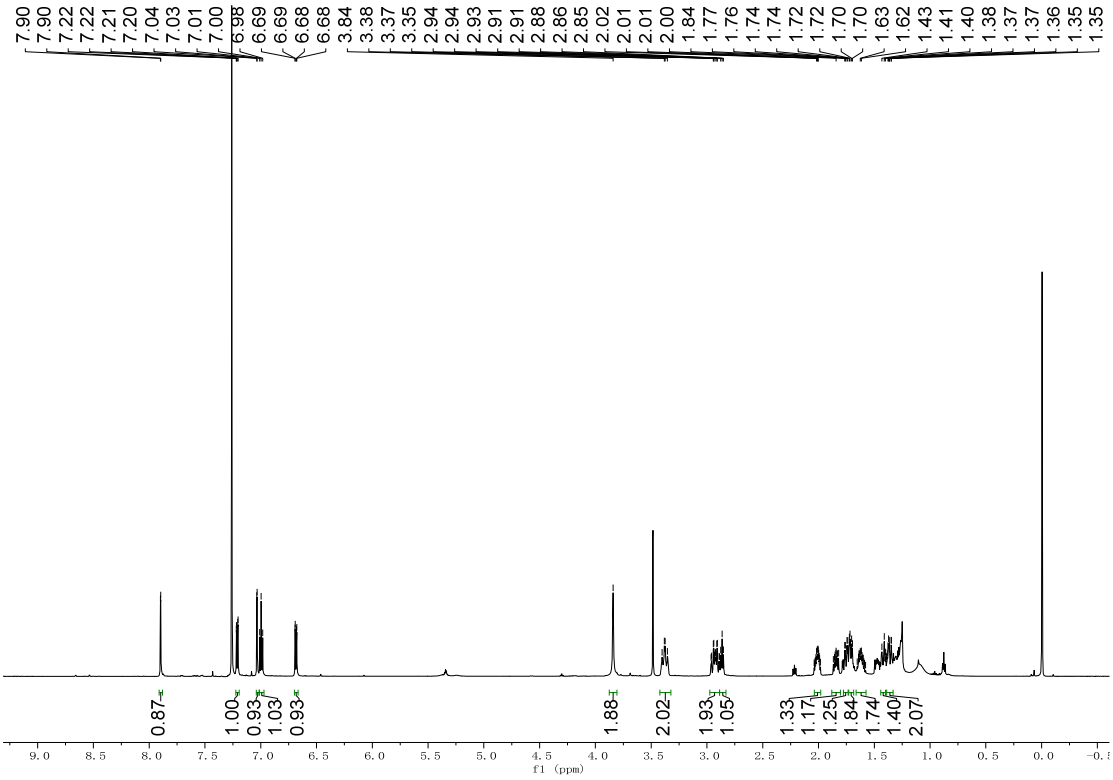
Compound：7

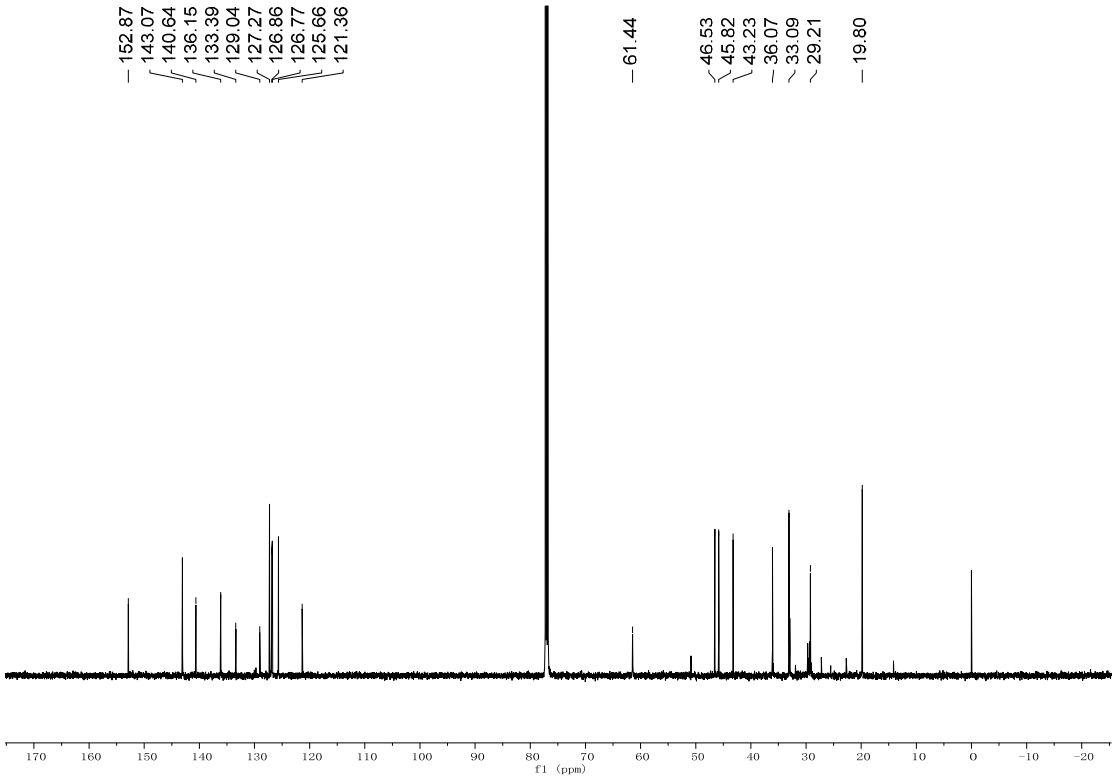

7.89
7.22
7.20
7.03
7.01
6.99
6.97
6.70
6.68
3.82
3.20
3.19
3.17
3.16
1.73
1.71
1.64
1.23
1.00
1.06
1.03
1.15
1.06
2.08
4.08
4.08
2.07
3.12
f1 (ppm)

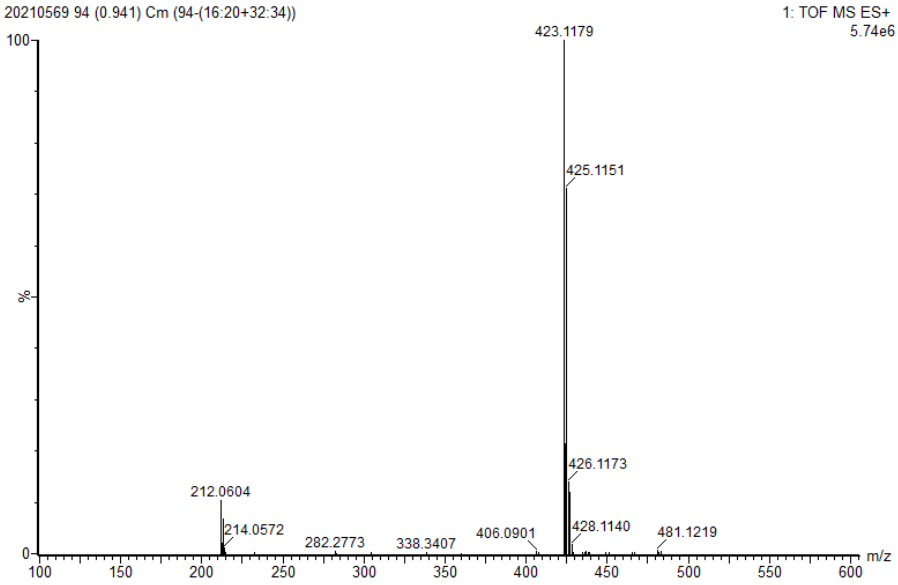

152.52
143.02
140.55
136.03
133.41
129.13
127.28
126.91
126.85
125.73
121.57
47.41
45.41
40.29
f1 (ppm)


20210568 54 (0.539) Cm (54-(418:420+425:427))
1: TOF MS ES+
3.85e5
383.0863
385.0835
387.0805
388.0819
153.1378
192.0443
251.0016
315.1682
366.0588
424.1877
458.1868
%
m/z

Compound 8


7.90 7.90 7.22 7.22 7.21 7.20 7.04 7.03 7.01 7.00 6.98 6.69 6.69 6.68 6.68 3.84 3.38 3.37 3.35 2.94 2.94 2.93 2.91 2.88 2.86 2.85 2.02 2.01 2.01 2.00 1.84 1.77 1.76 1.74 1.74 1.72 1.72 1.70 1.70 1.63 1.62 1.43 1.41 1.40 1.38 1.37 1.37 1.36 1.35 1.35
0.87 1.00 0.93 1.03 0.93 1.88 2.02 1.93 1.05 1.33 1.17 1.25 1.84 1.74 1.40 2.07
f1 (ppm)


152.87
143.07
140.64
136.15
133.39
129.04
127.27
126.86
126.77
125.66
121.36
61.44
46.53
45.82
43.23
36.07
33.09
29.21
19.80
f1 (ppm)


20210569 94 (0.941) Cm (94-(16:20+32:34))
1: TOF MS ES+
5.74e6
423.1179
425.1151
426.1173
212.0604
214.0572
282.2773
338.3407
406.0901
428.1140
481.1219
%
m/z