Supporting Information

Optimization of 4,6-Disubstituted Pyrido[3,2-*d*]pyrimidines as Dual MNK/PIM Inhibitors to Inhibit Leukemia Cell Growth

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[#]Both authors contributed equally to this work.

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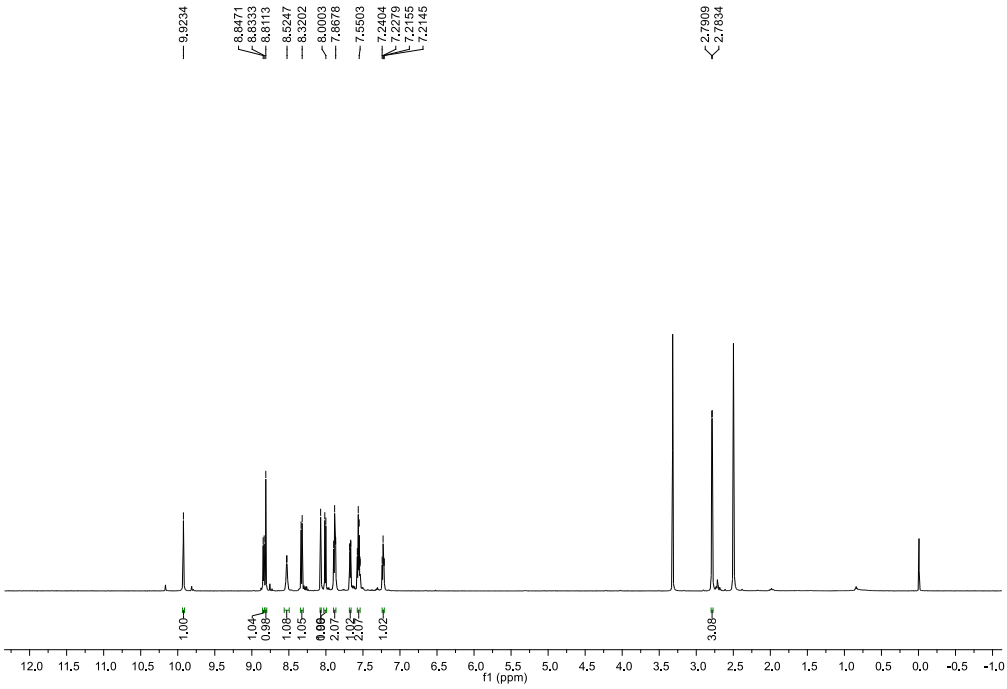
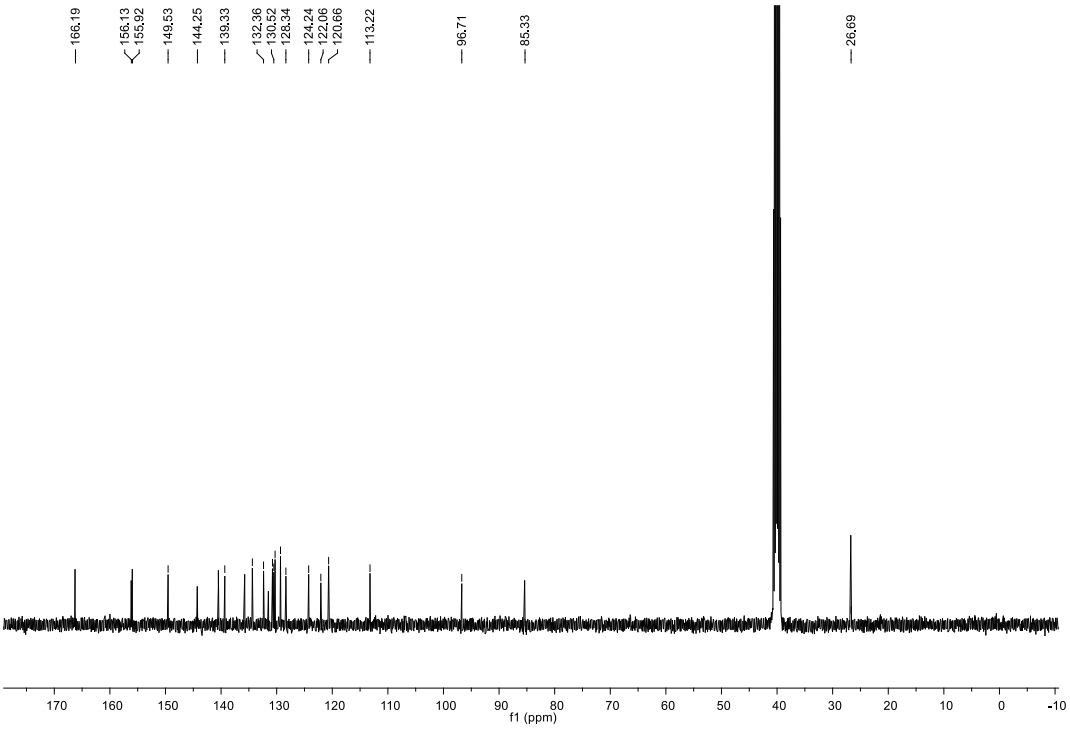
Content: ^{1}H NMR, ^{13}C NMR spectrum of target compounds; HPLC spectrum of representative compounds; Kinase selectivity of compound **21o** against 30 of kinases.

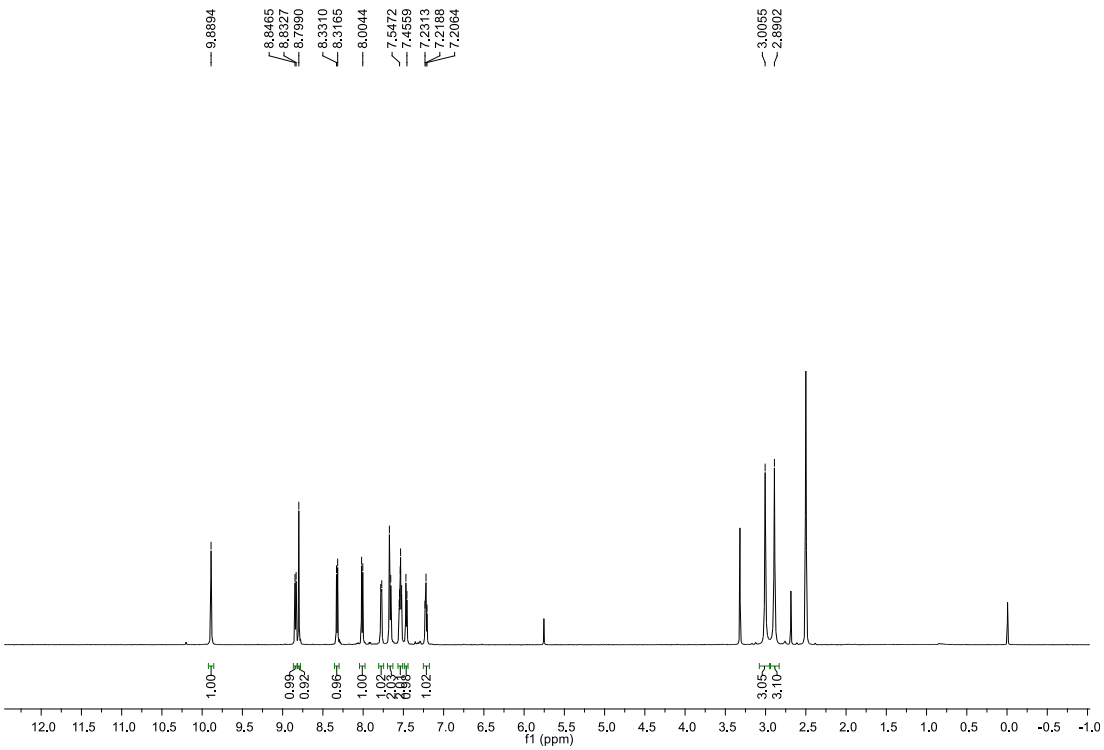
1. Spectra of target compounds



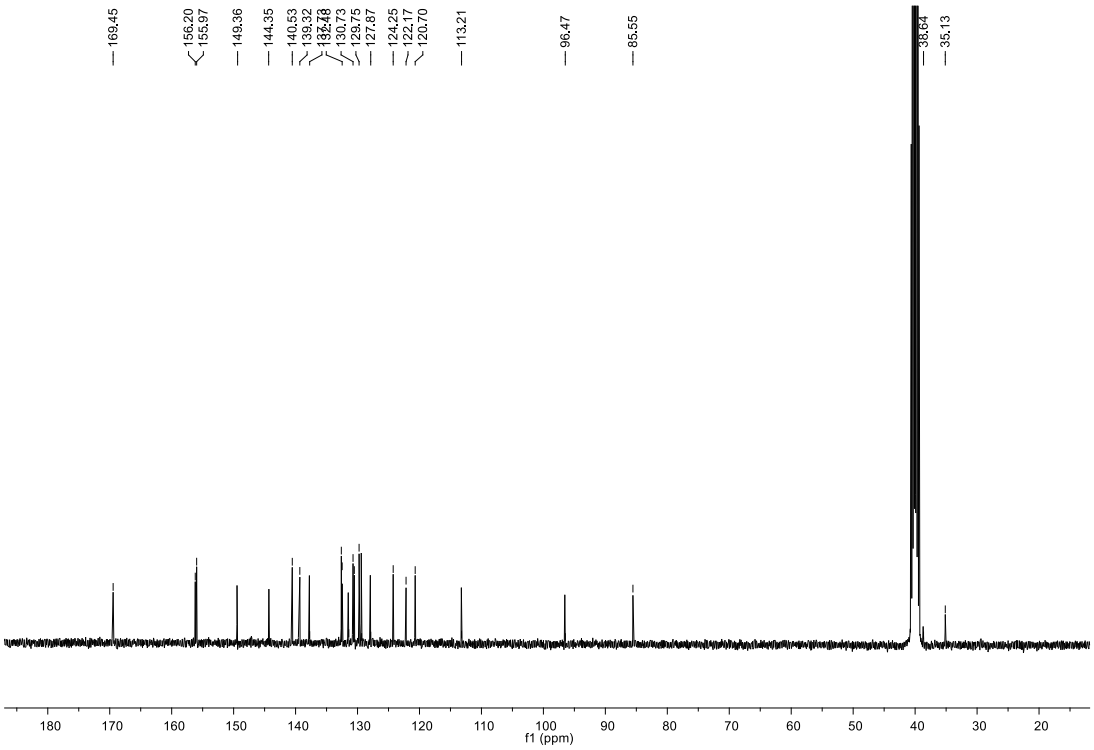
^{1}H-NMR spectra of 12a



^{13}C-NMR spectra of 12a



^{1}H-NMR spectra of 12b



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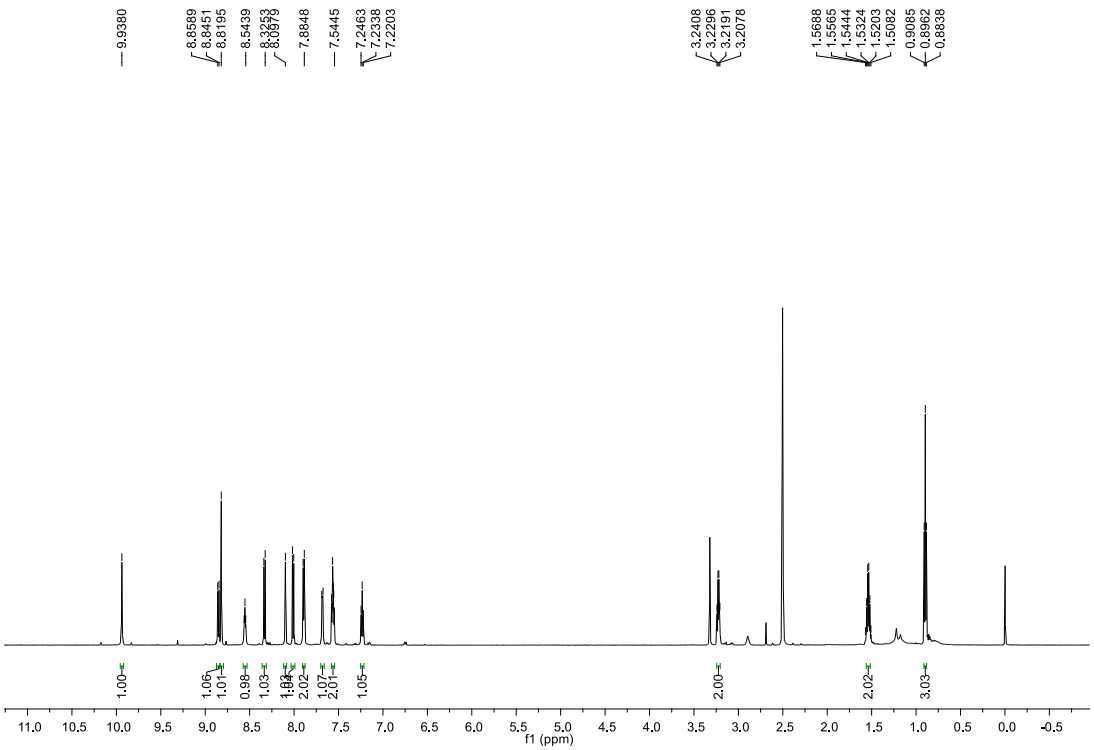
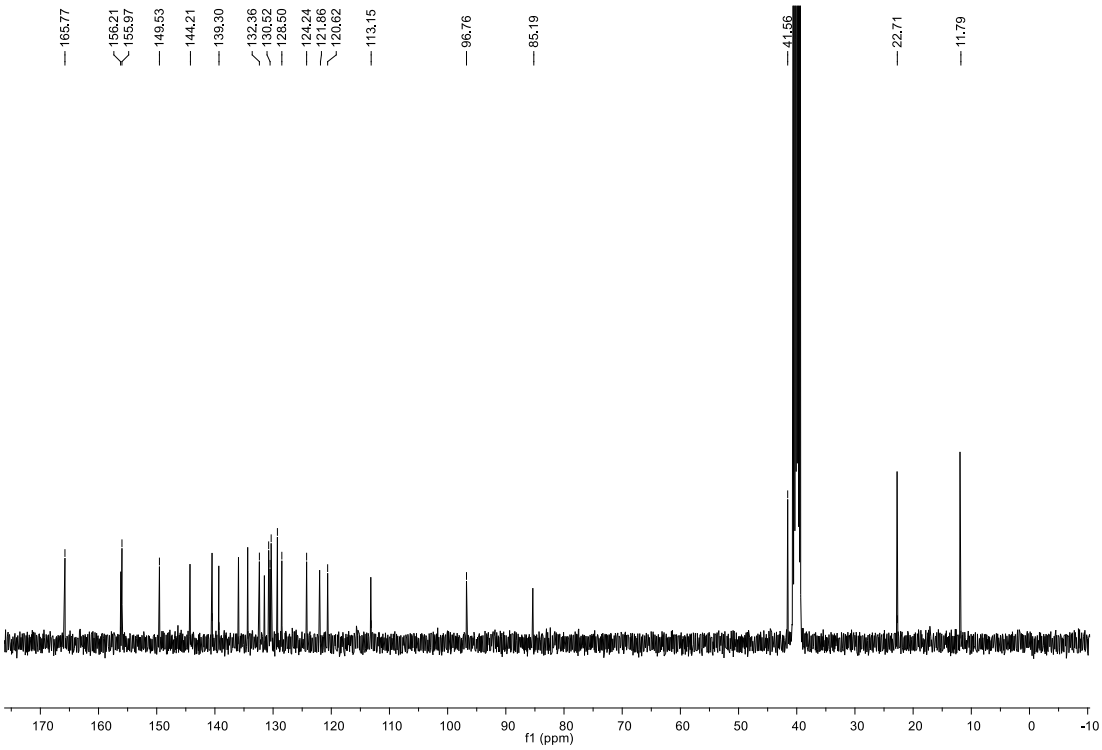


^{1}H-NMR spectra of 12c



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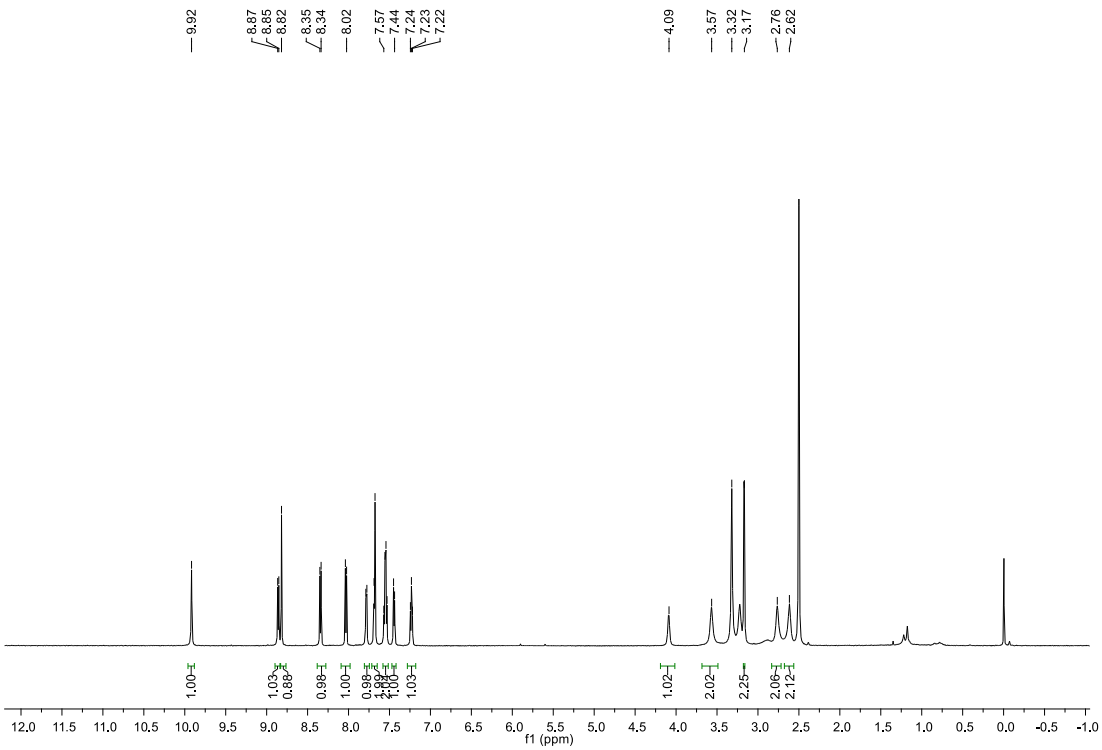
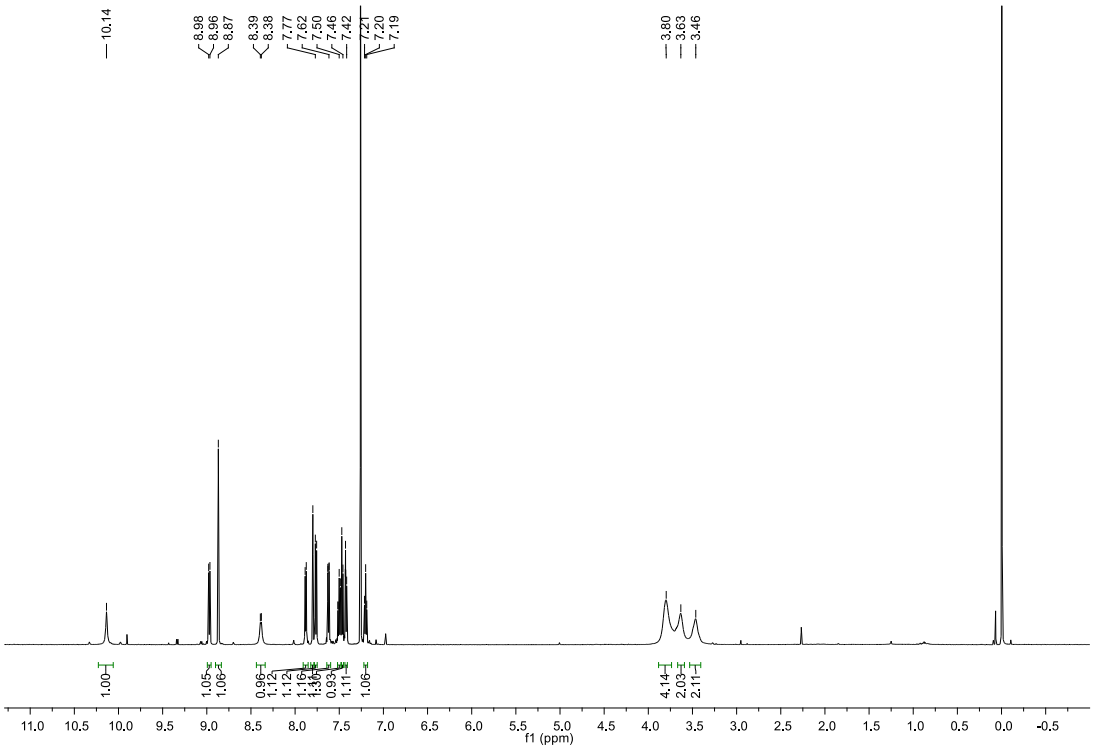
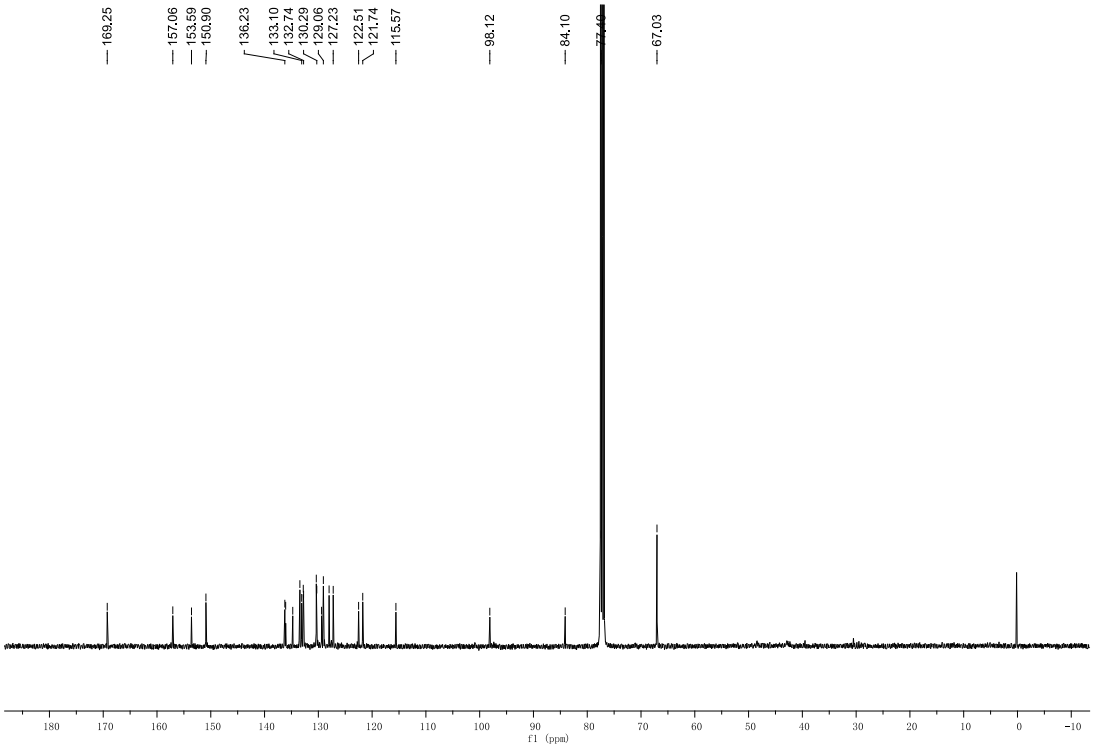


^{1}H-NMR spectra of 12d



^{1}H-NMR spectra of 12e



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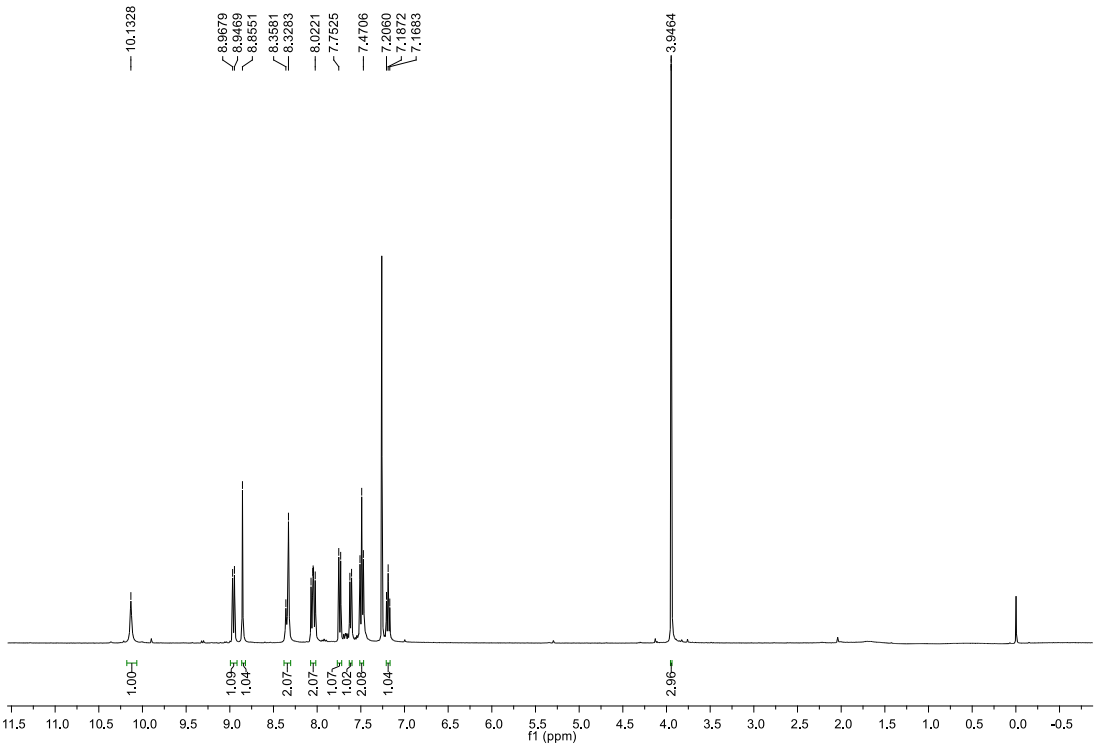
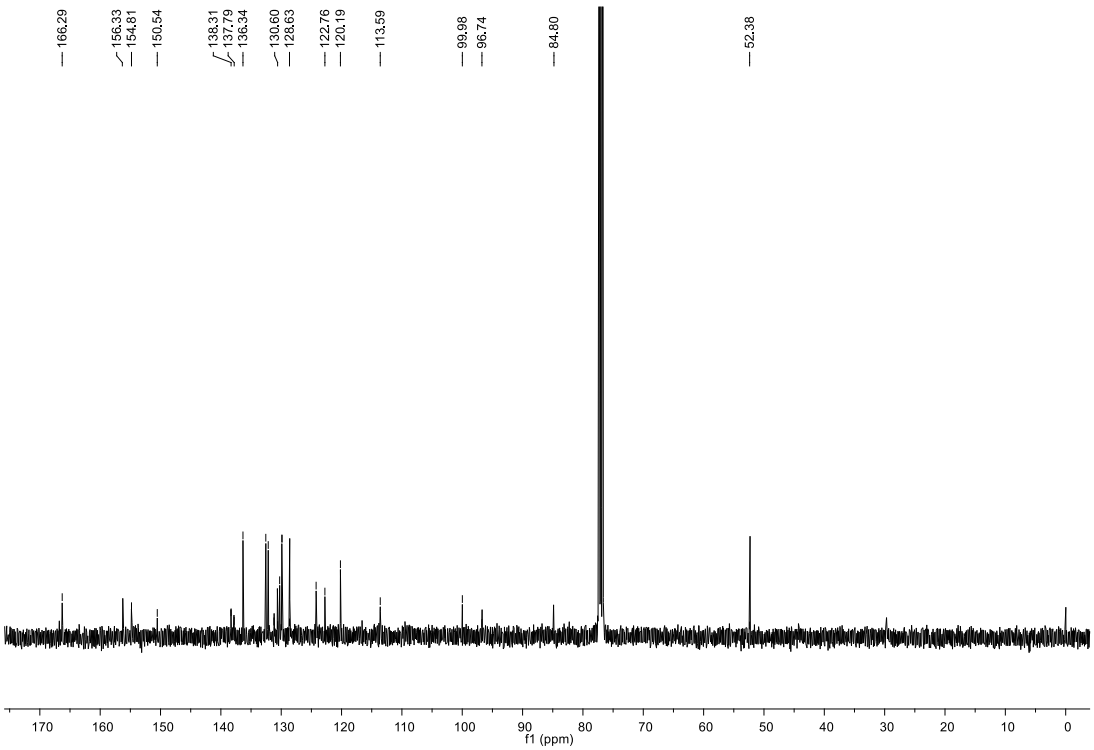


^{1}H-NMR spectra of 12f



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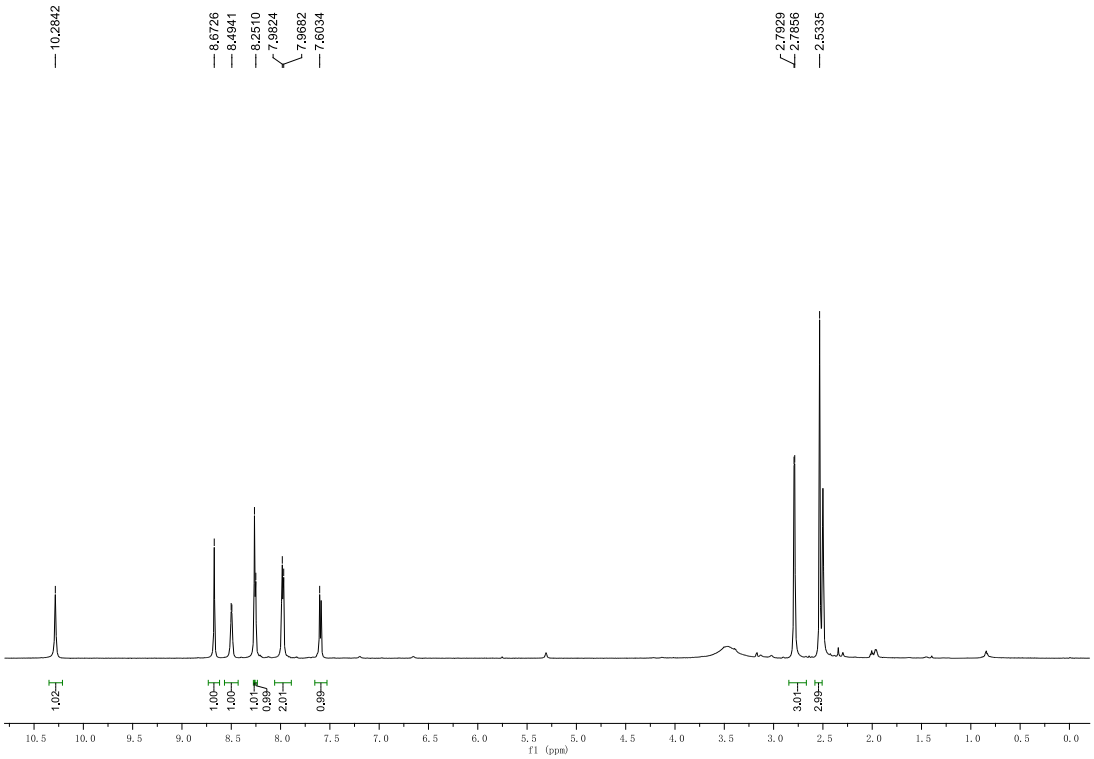
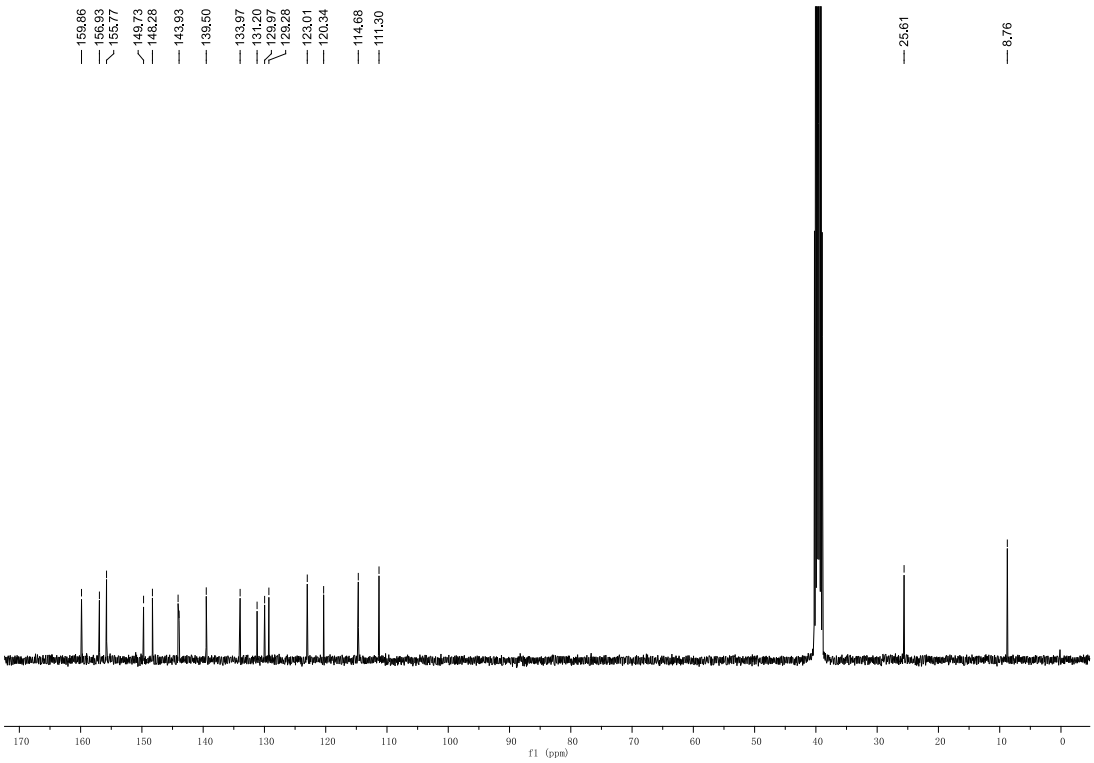
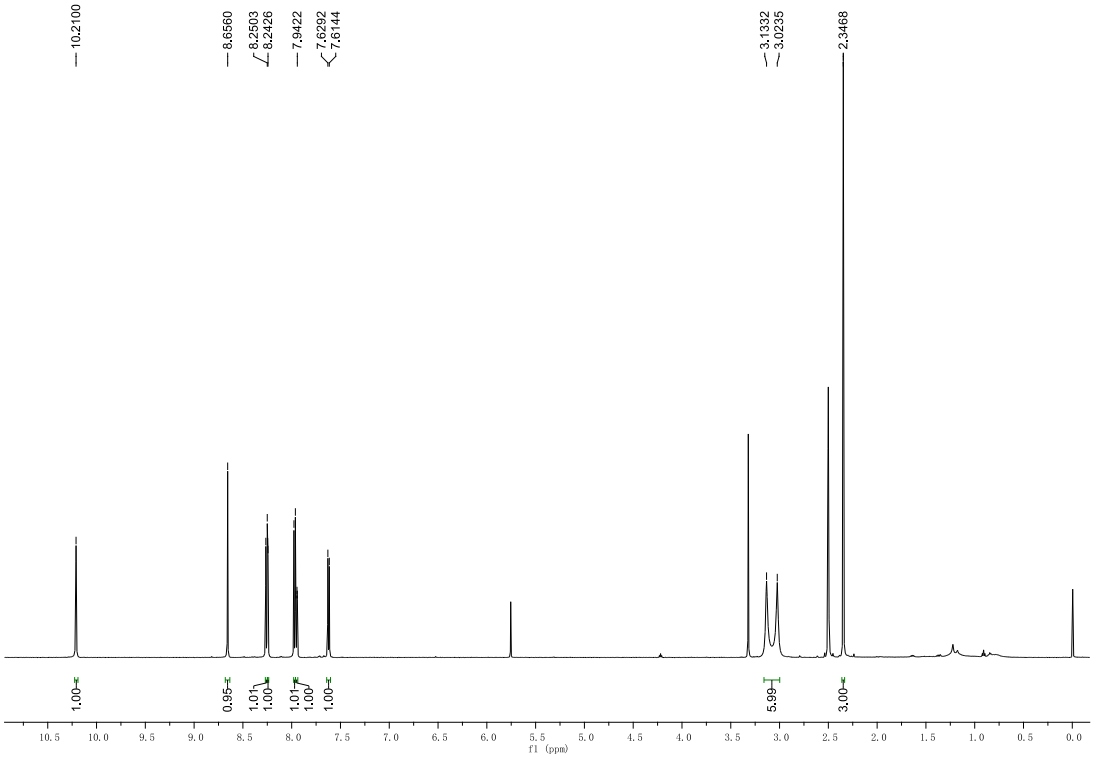


^{1}H-NMR spectra of 18a



^{13}C-NMR spectra of 18a



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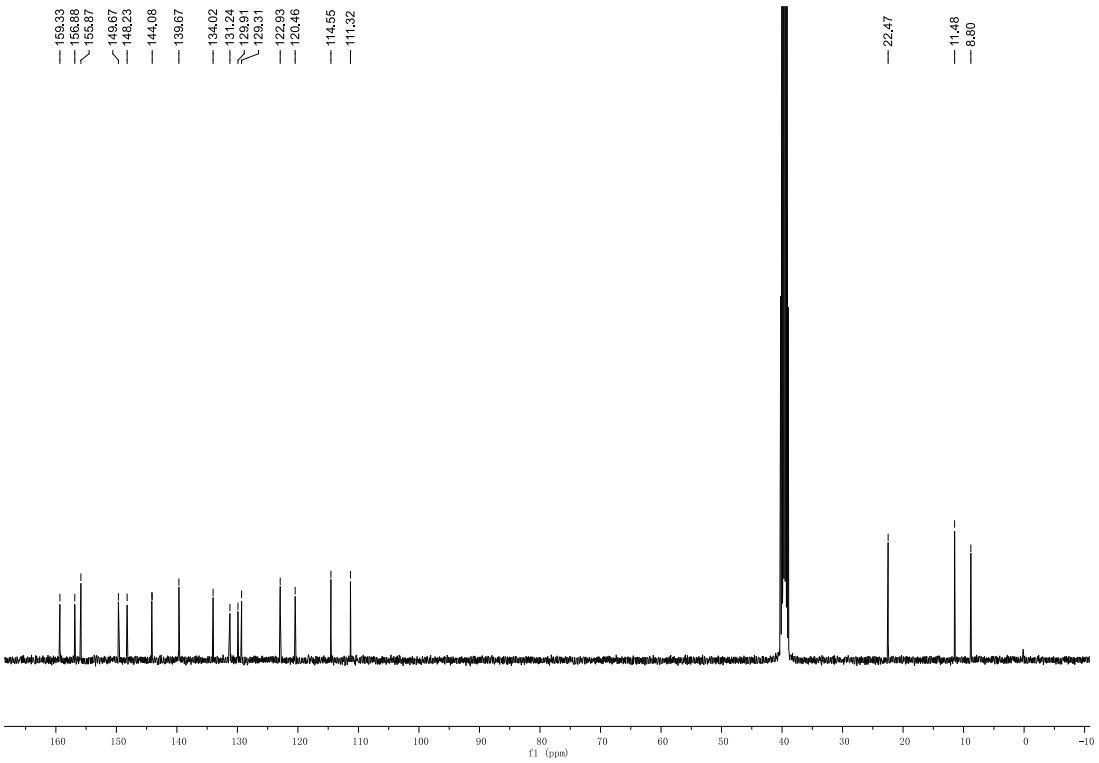

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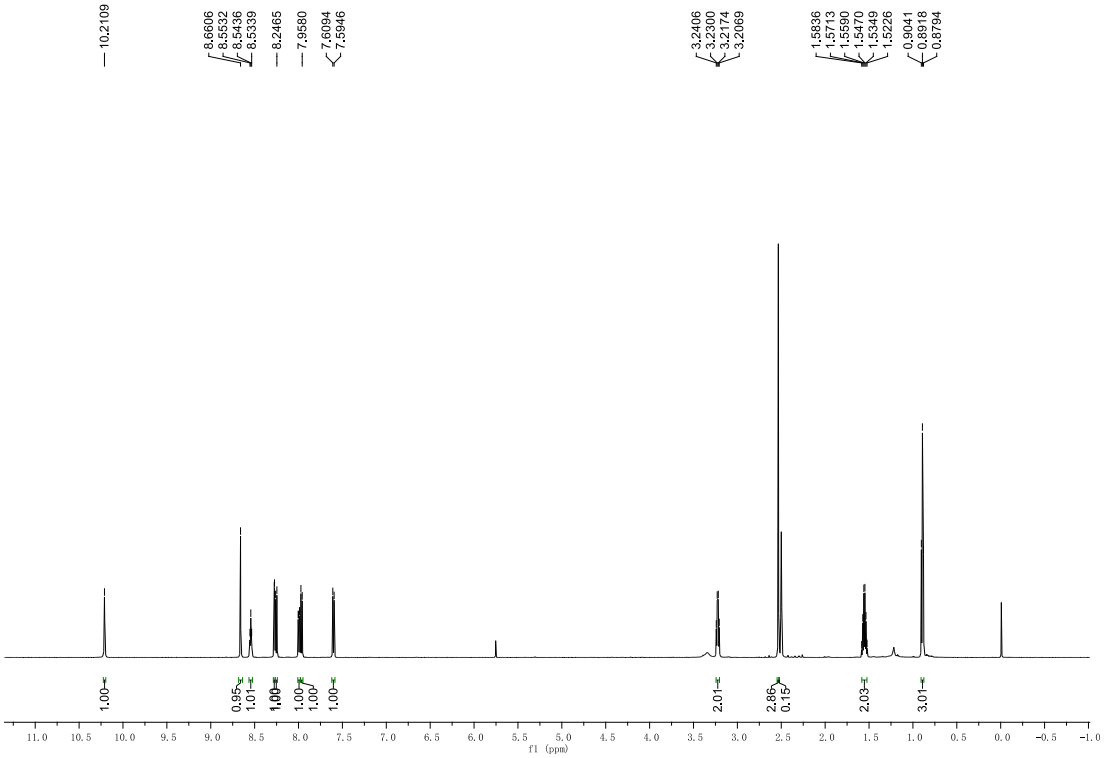

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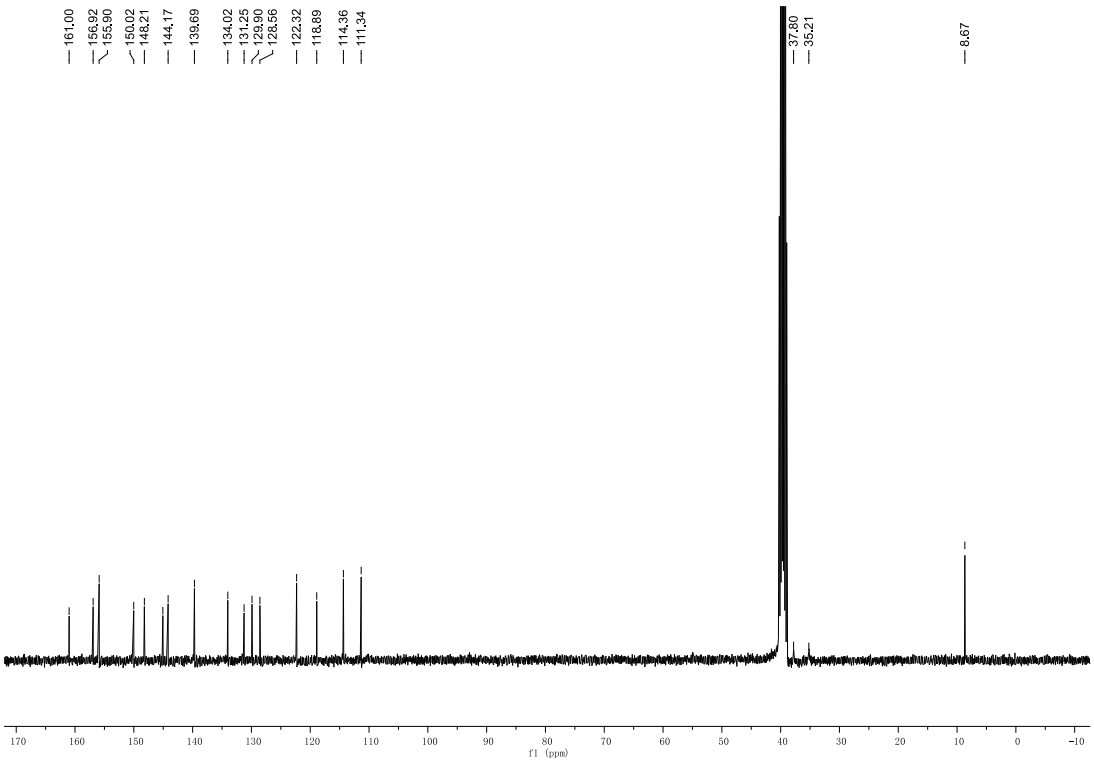

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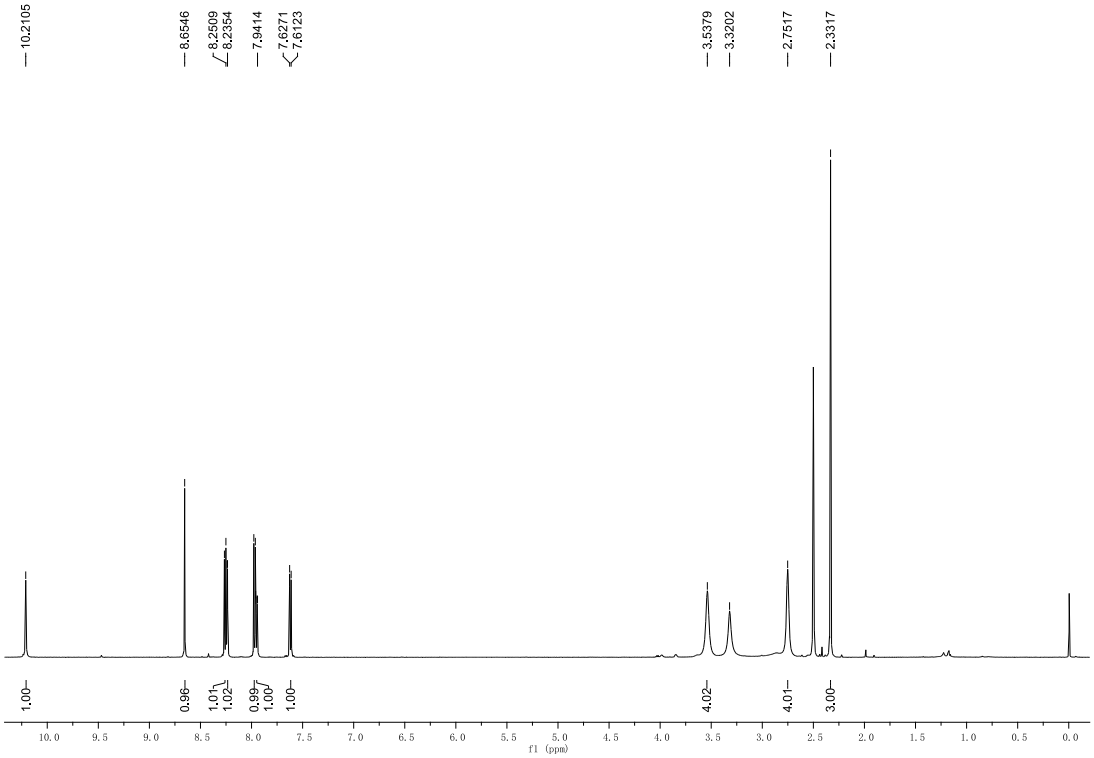

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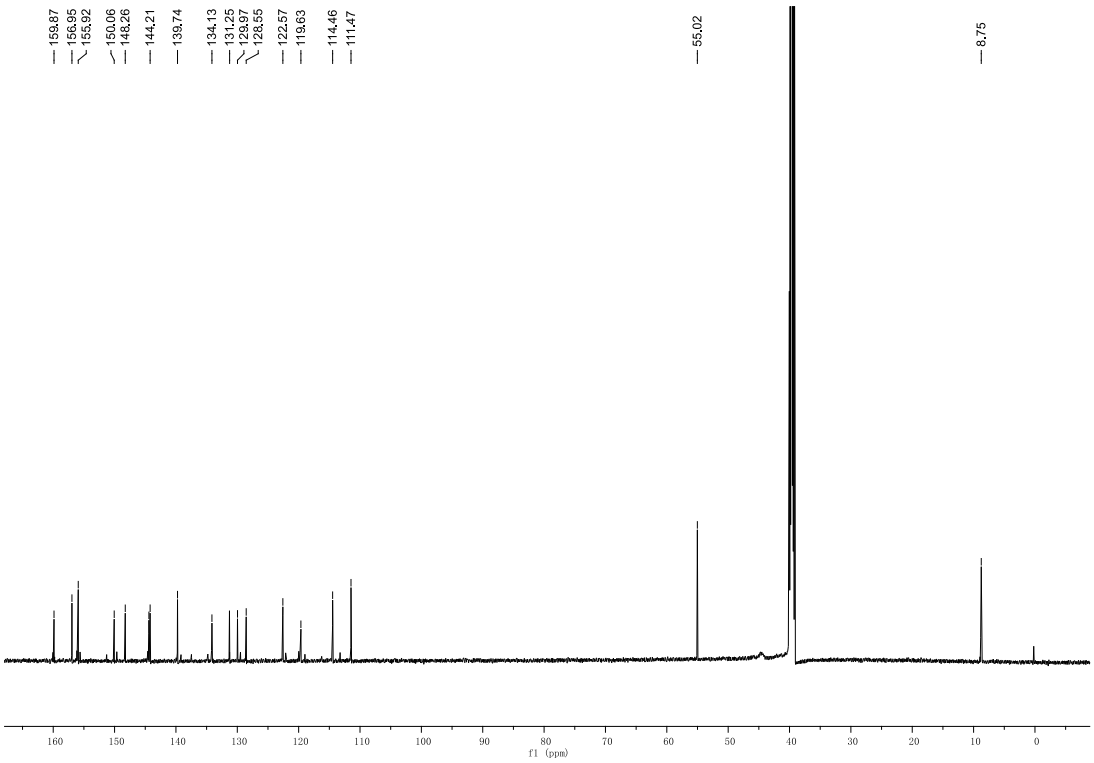

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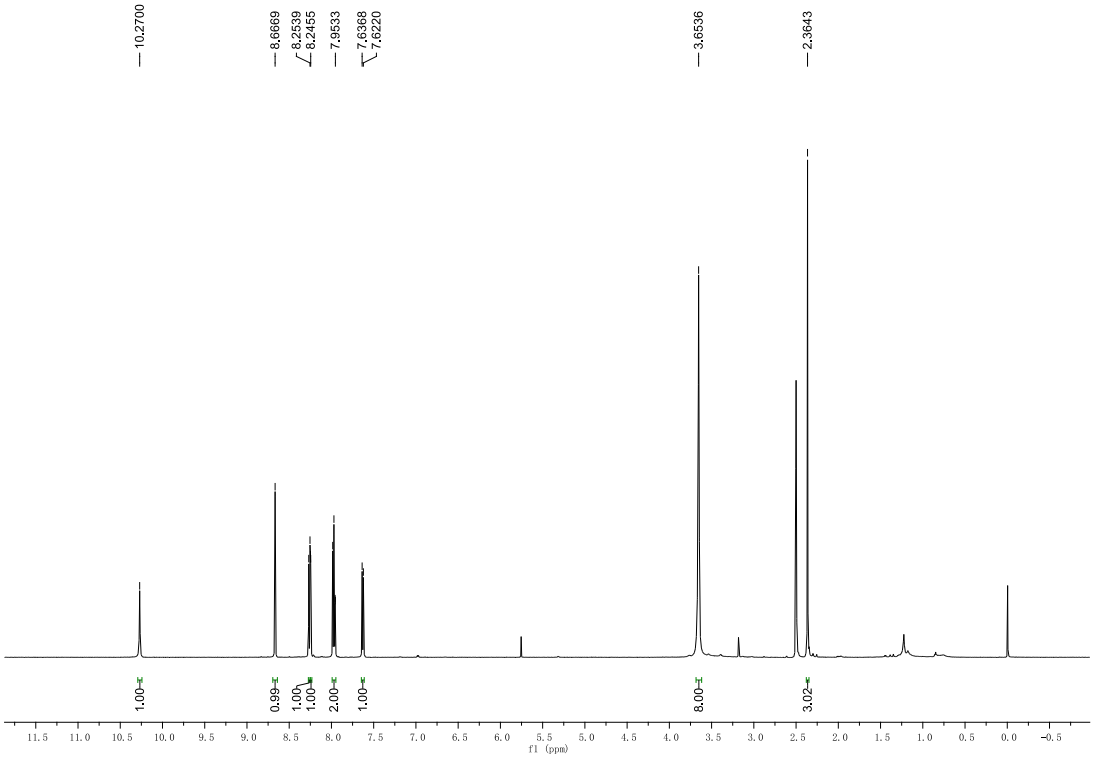

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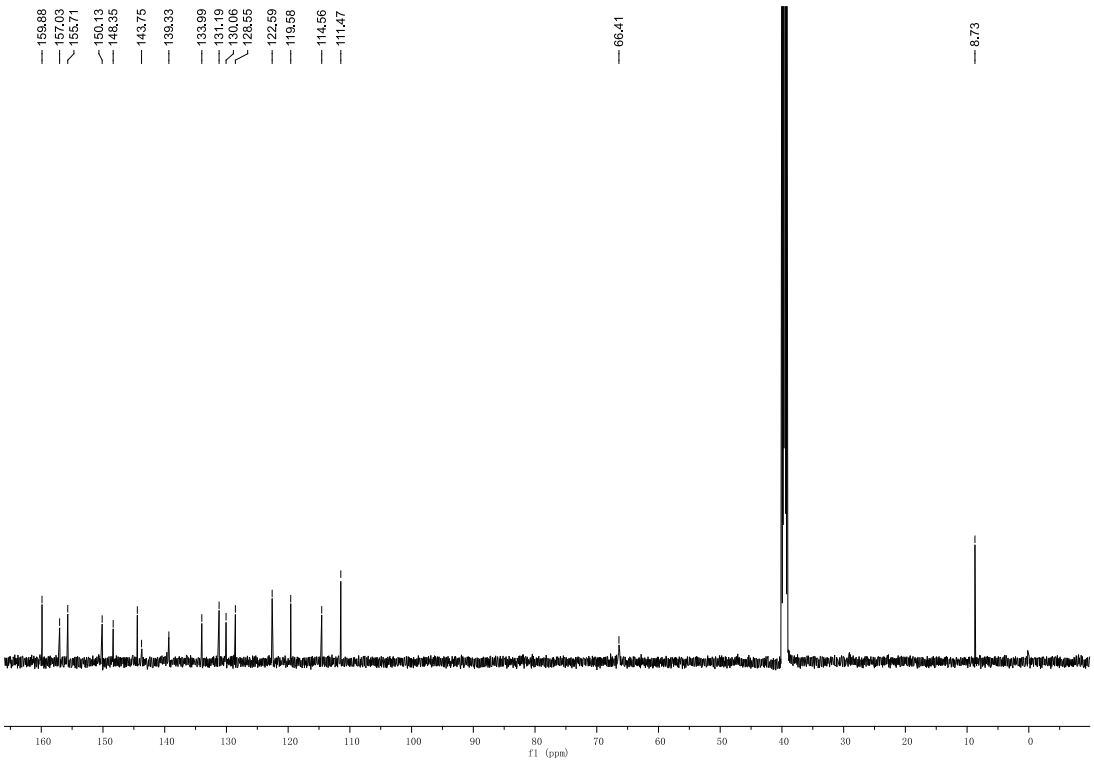

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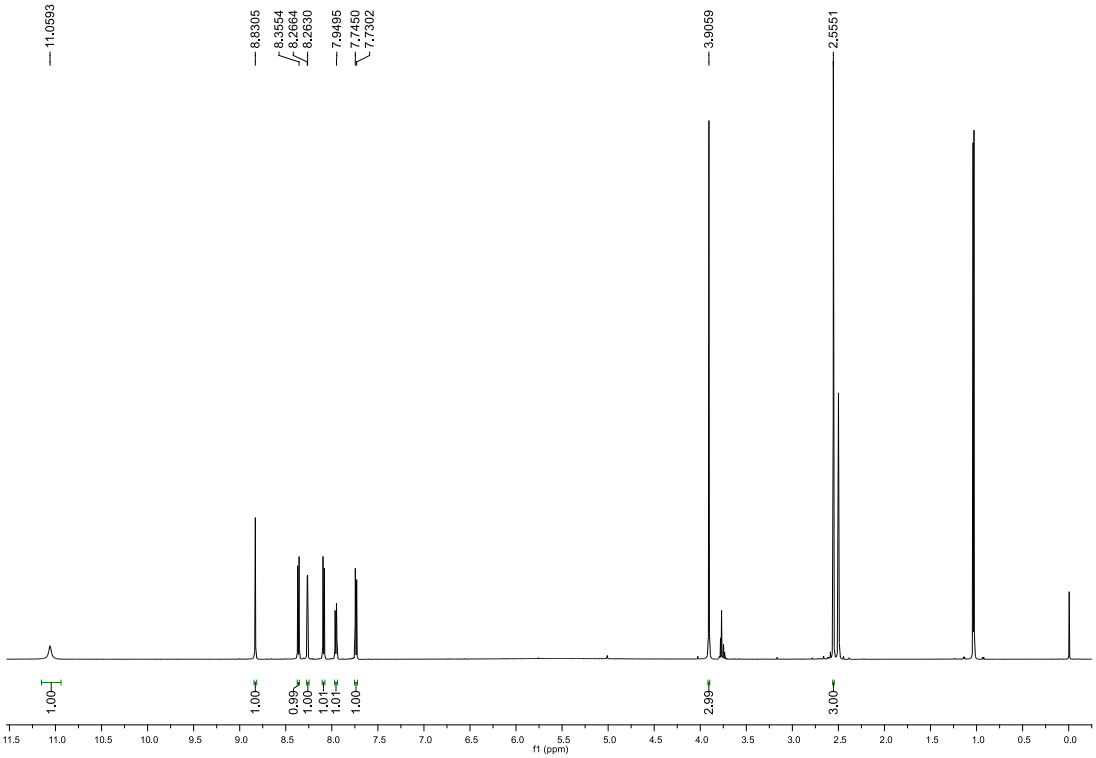
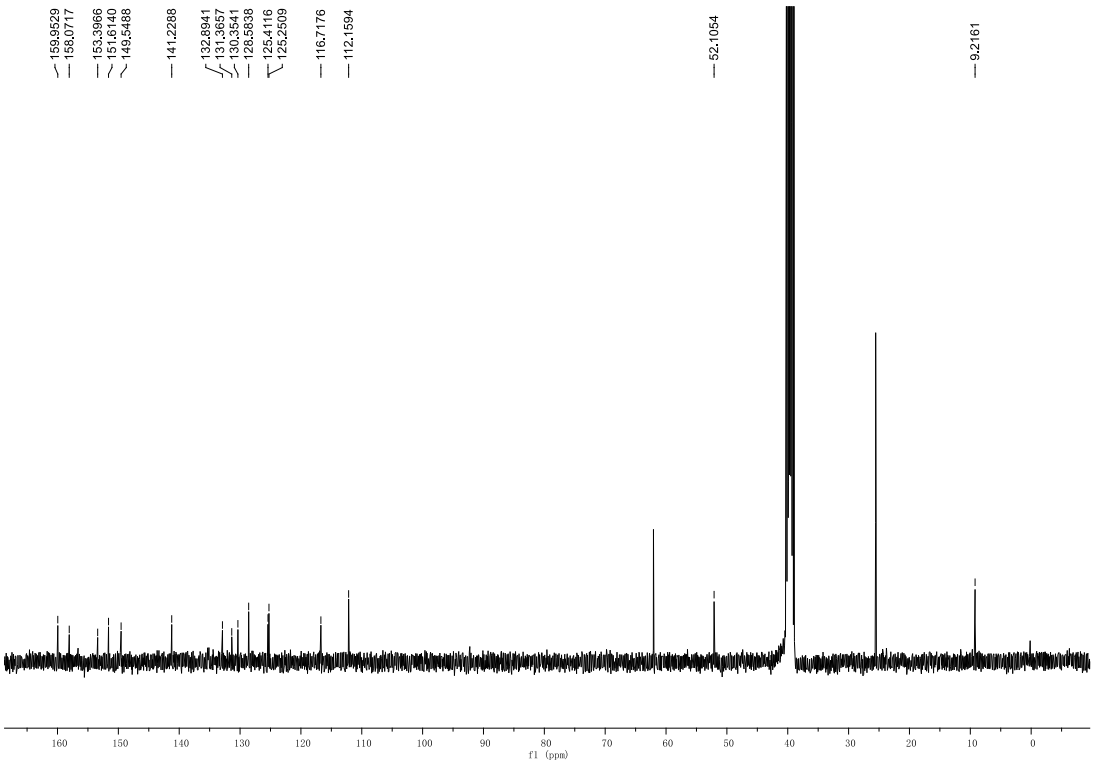


^{1}H-NMR spectra of 18f



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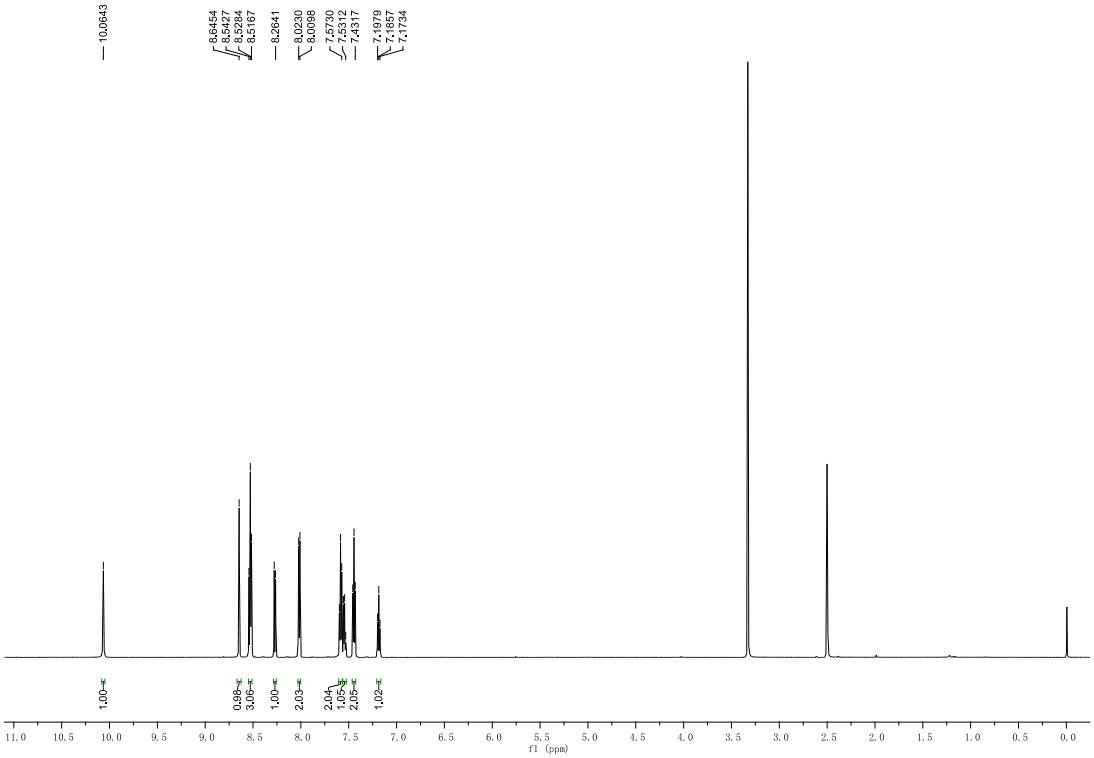

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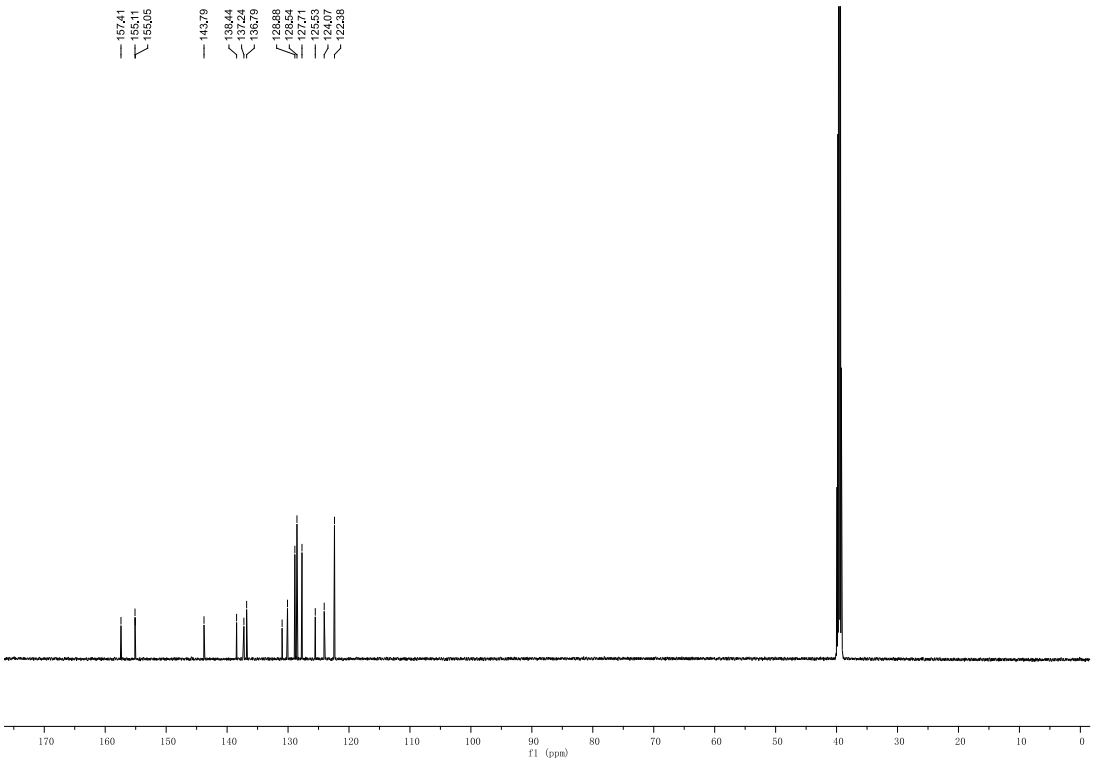

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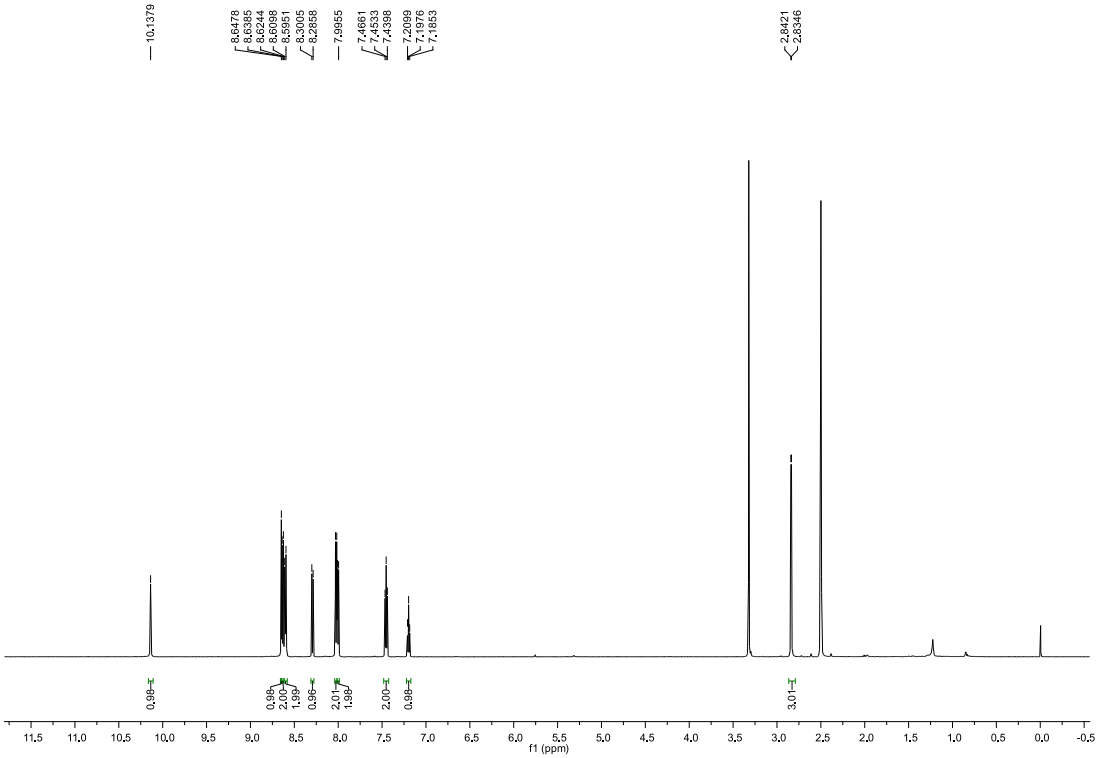
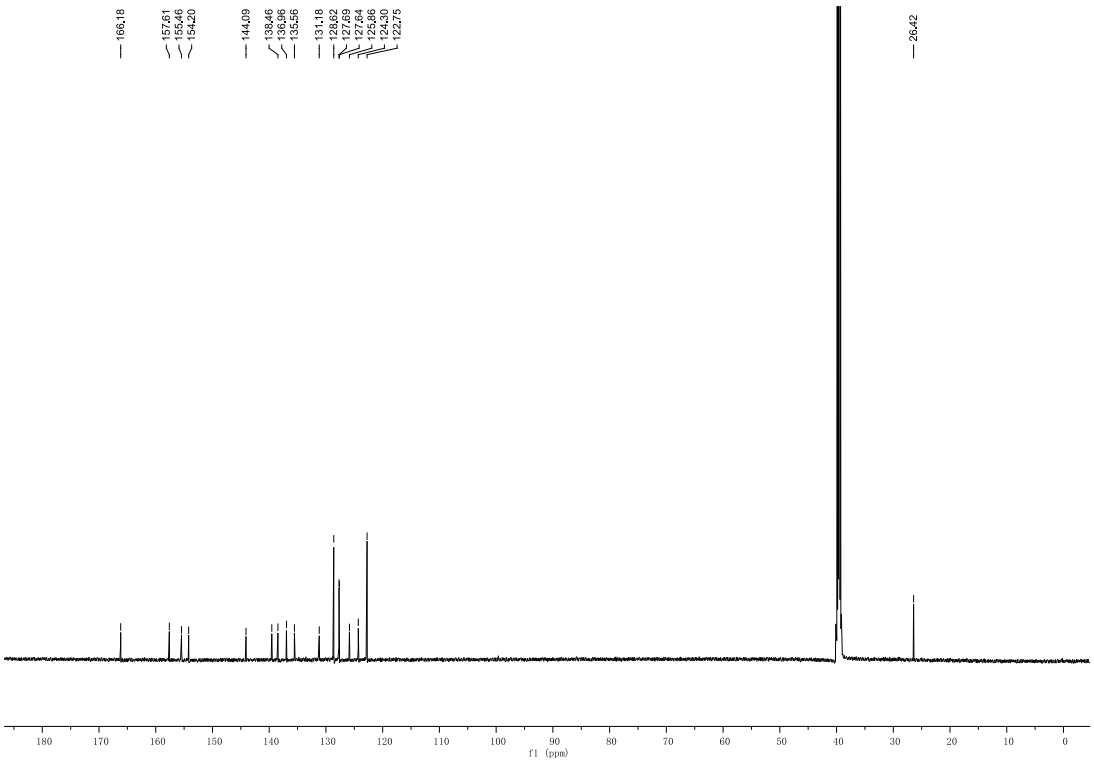


^{1}H-NMR spectra of 21a



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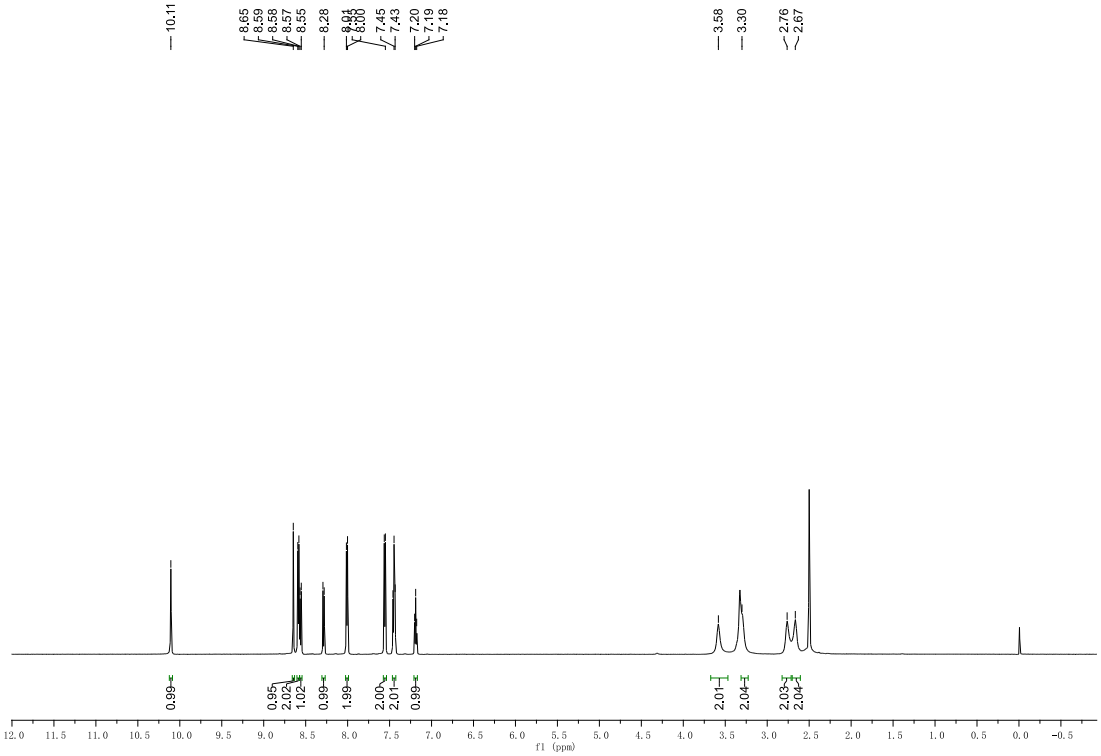
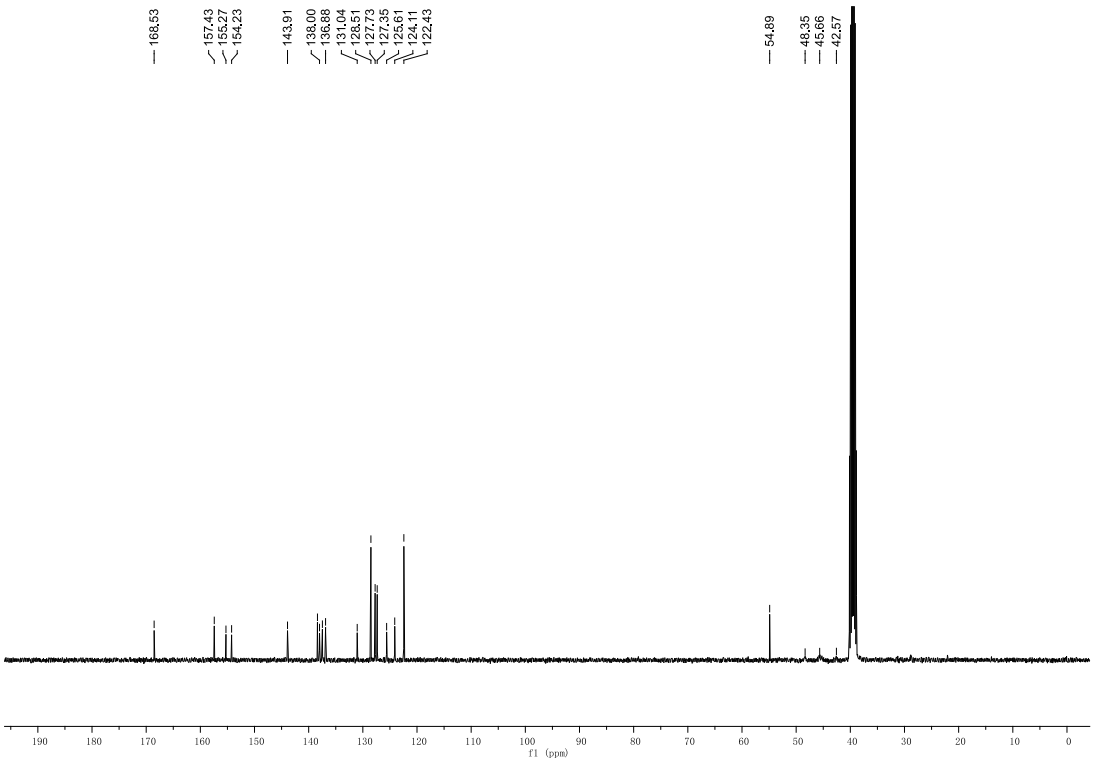


^{1}H-NMR spectra of 21b



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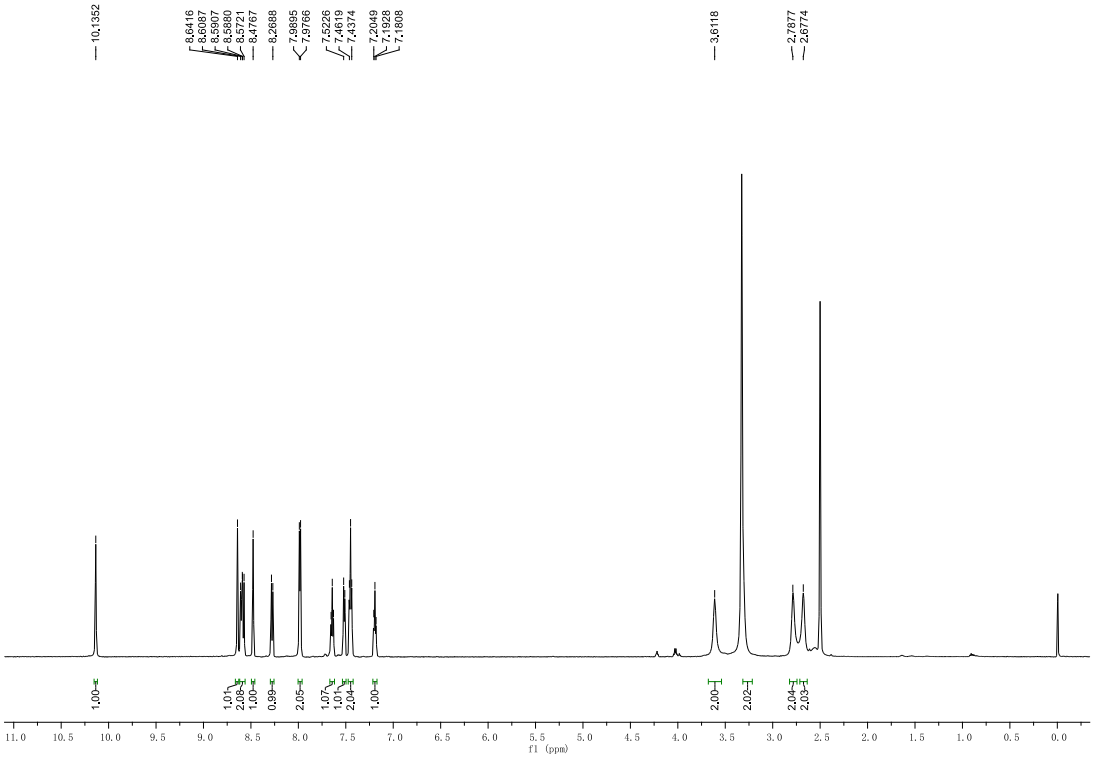

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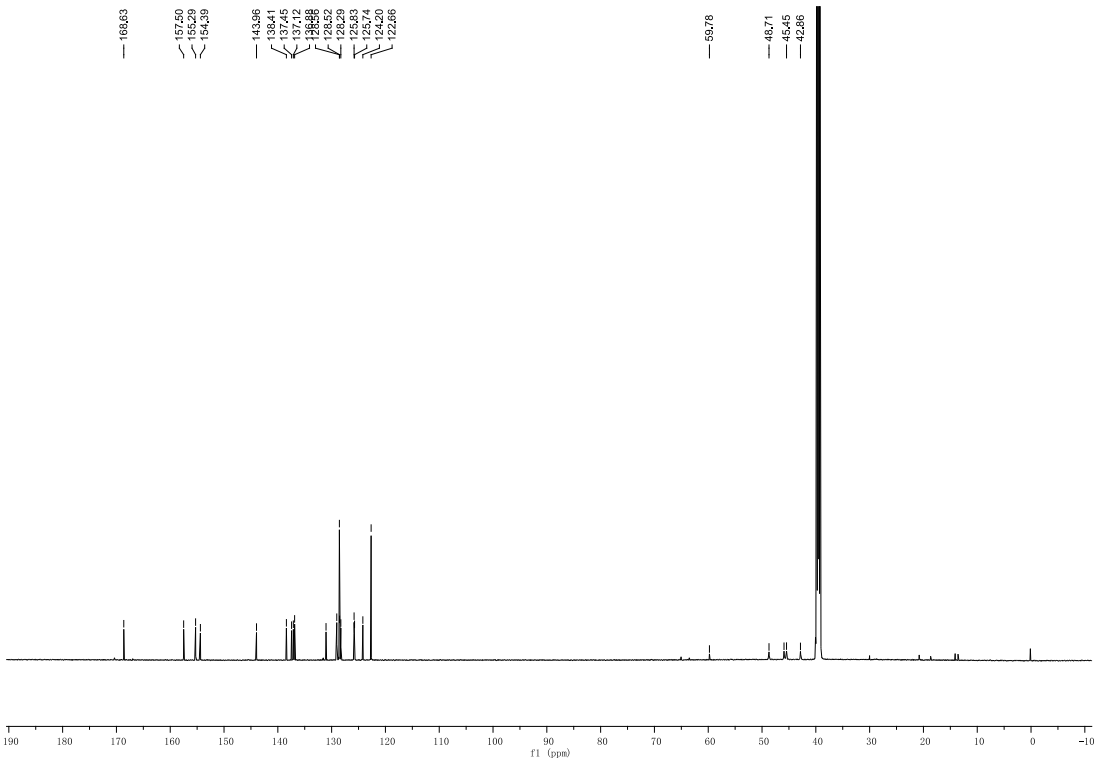

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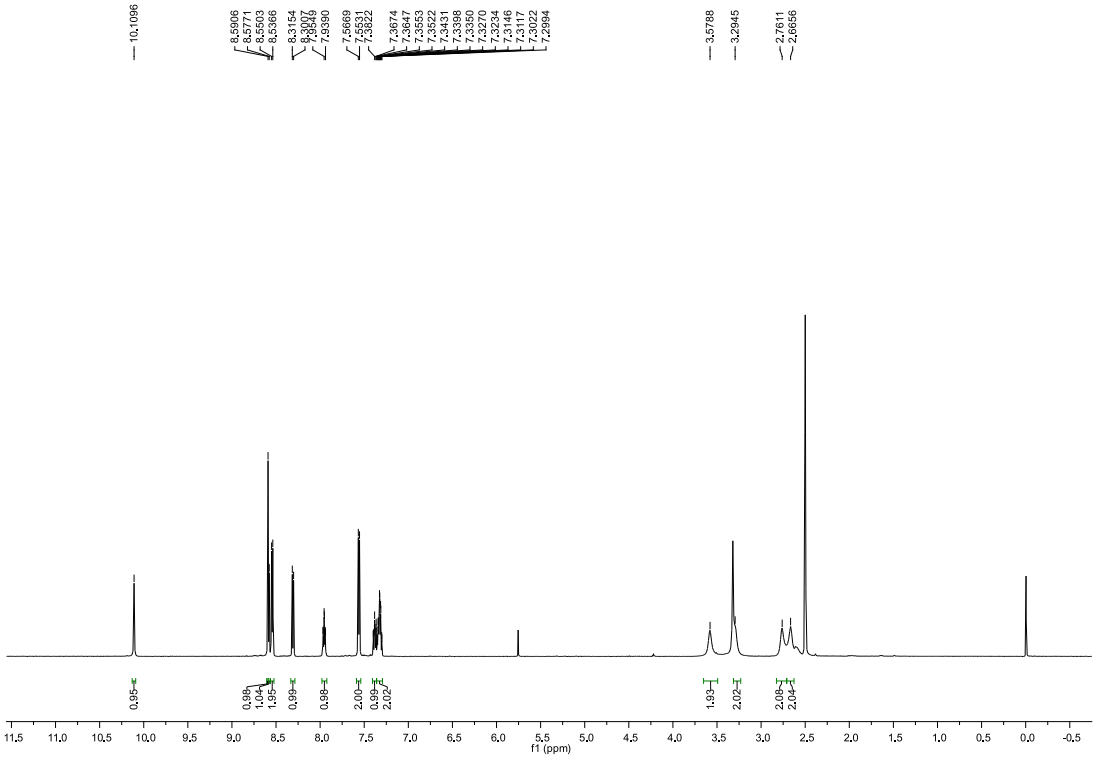
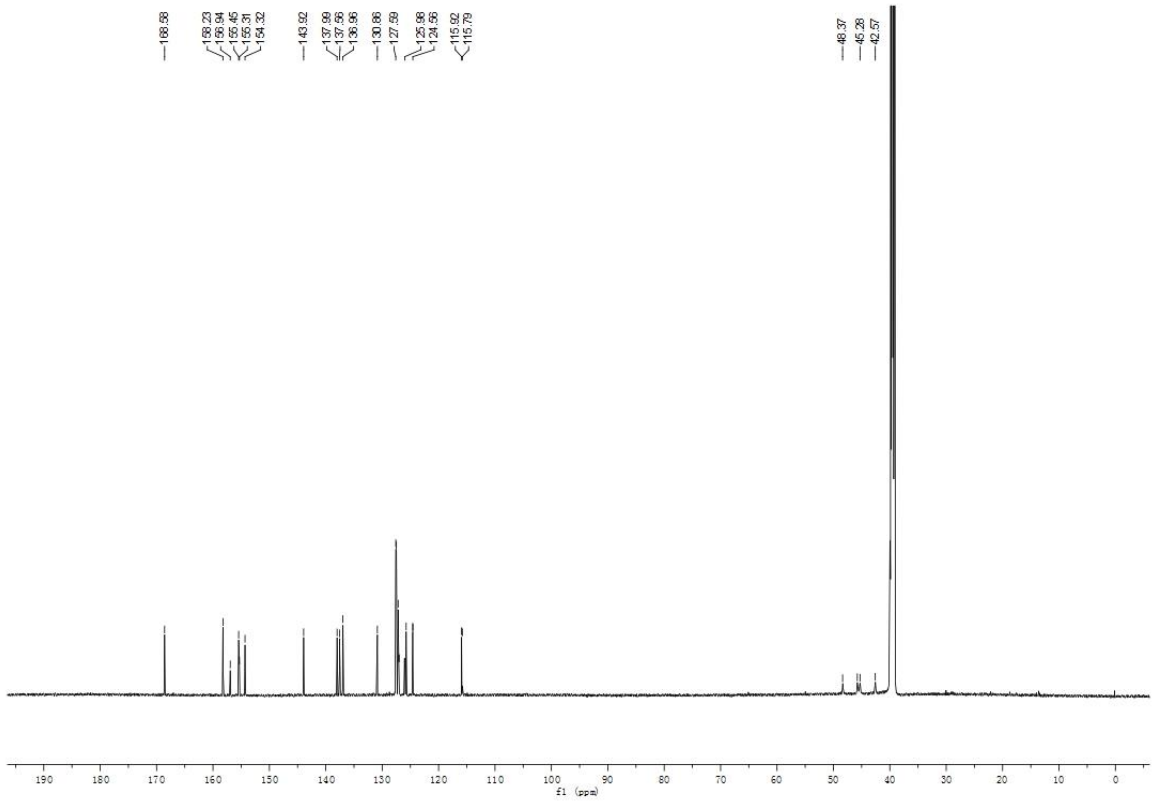


^{1}H-NMR spectra of 21d



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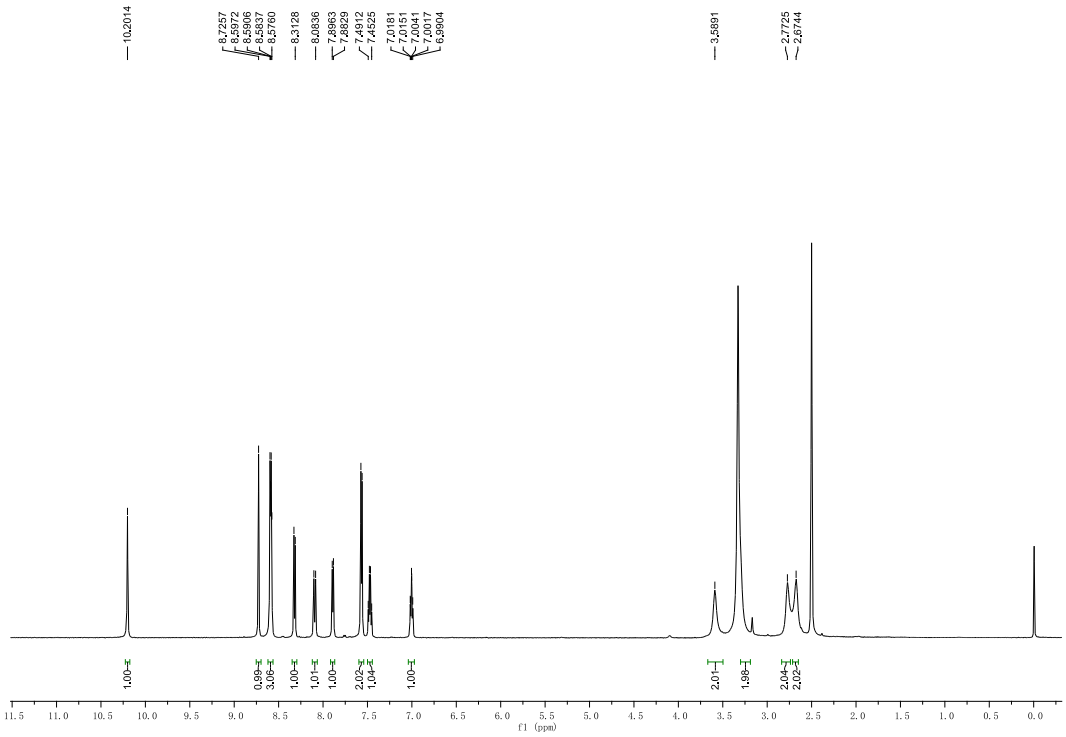

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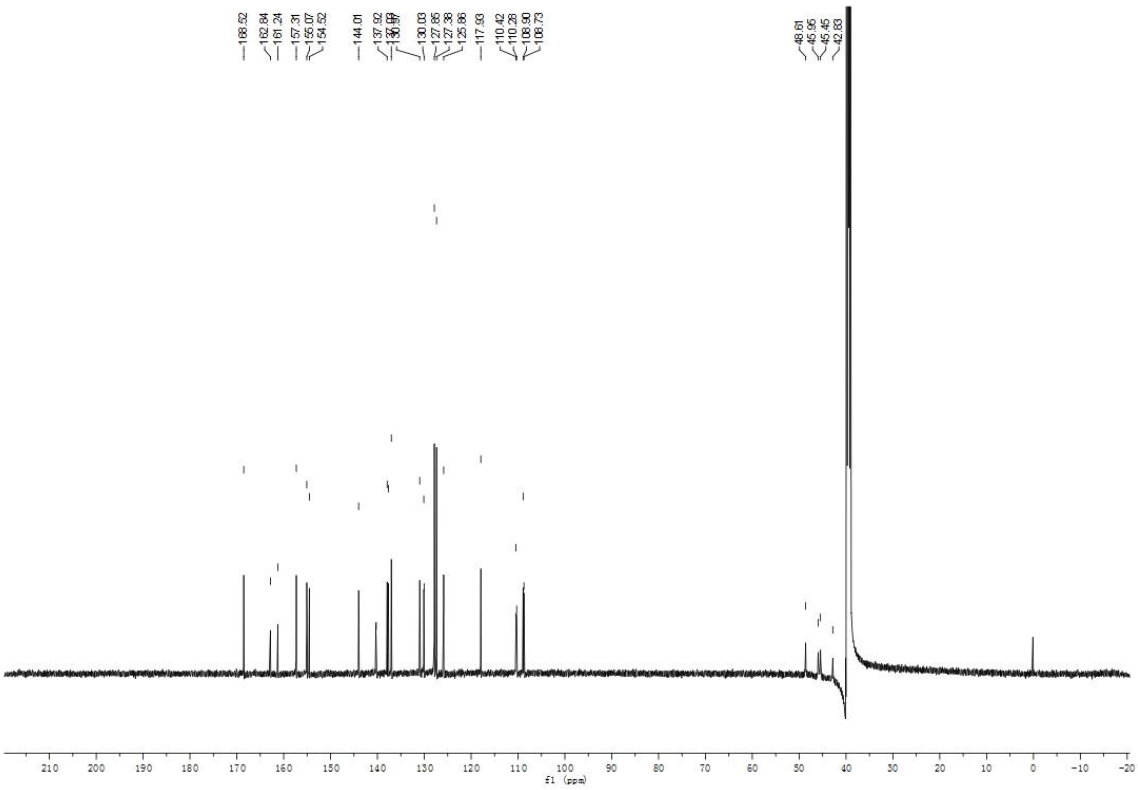

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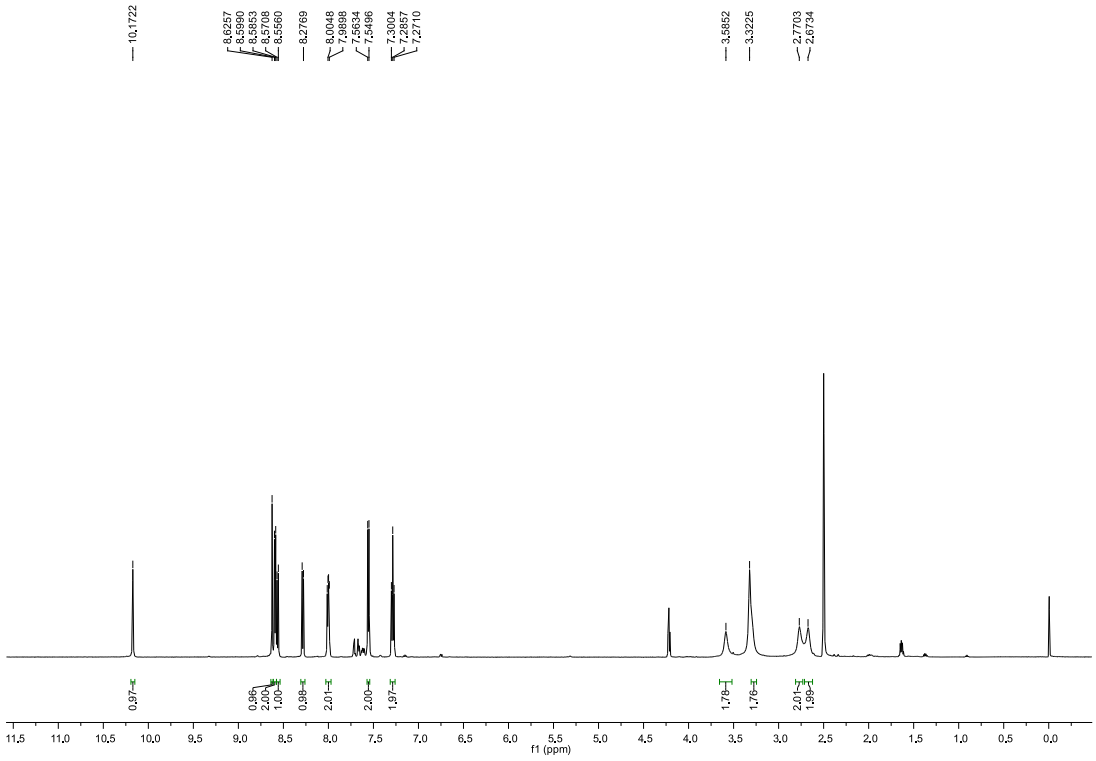

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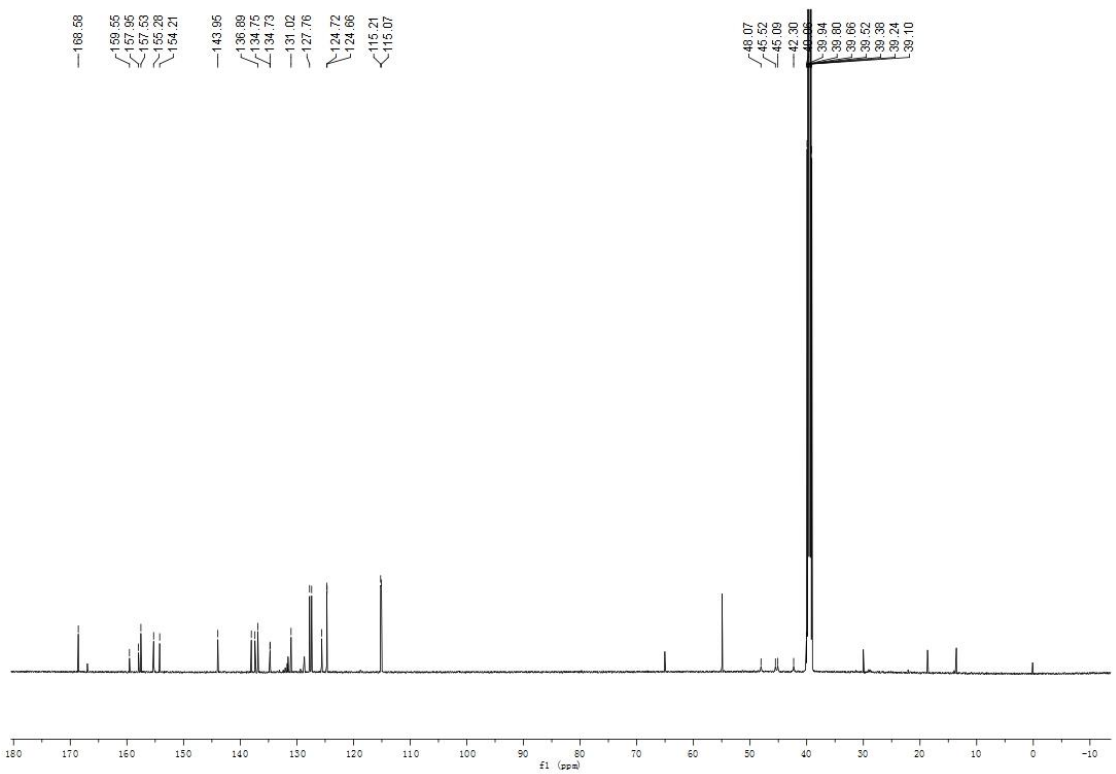

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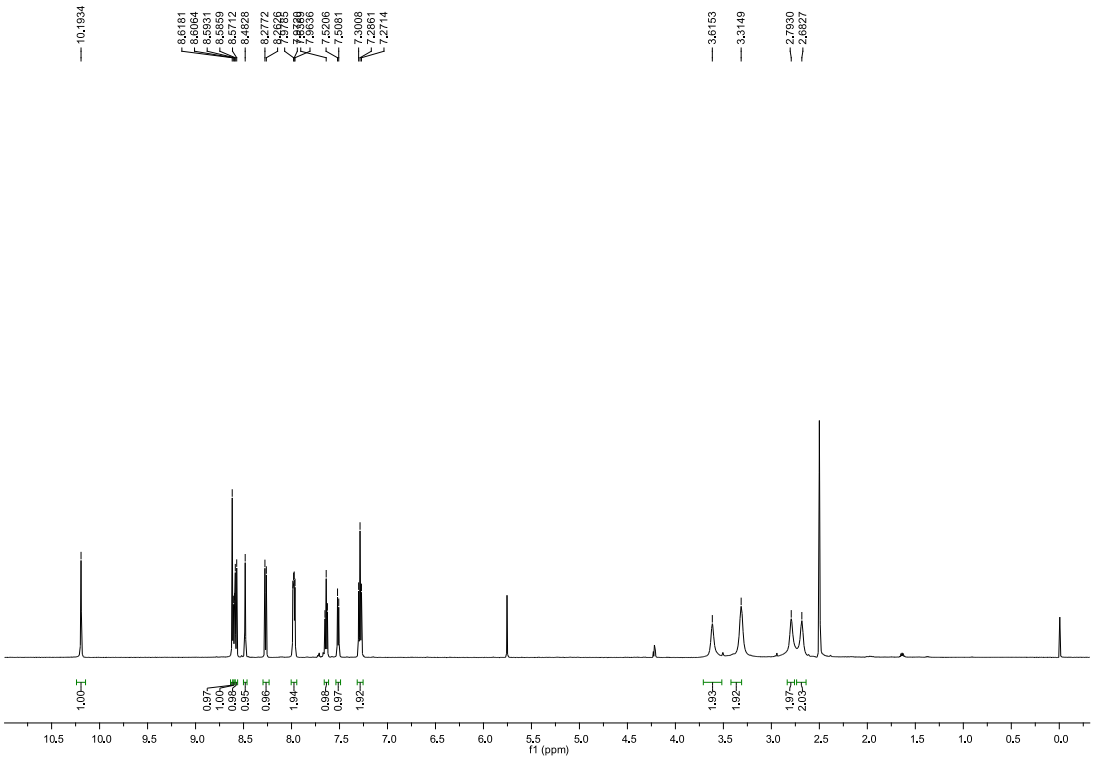

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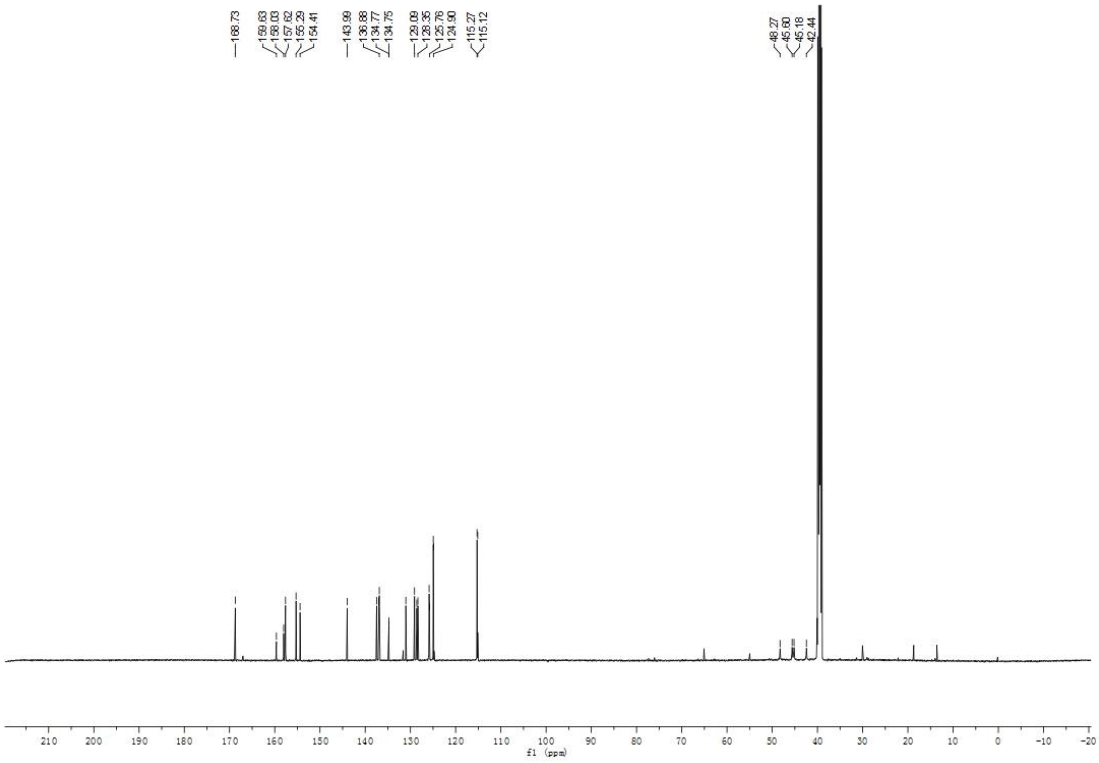
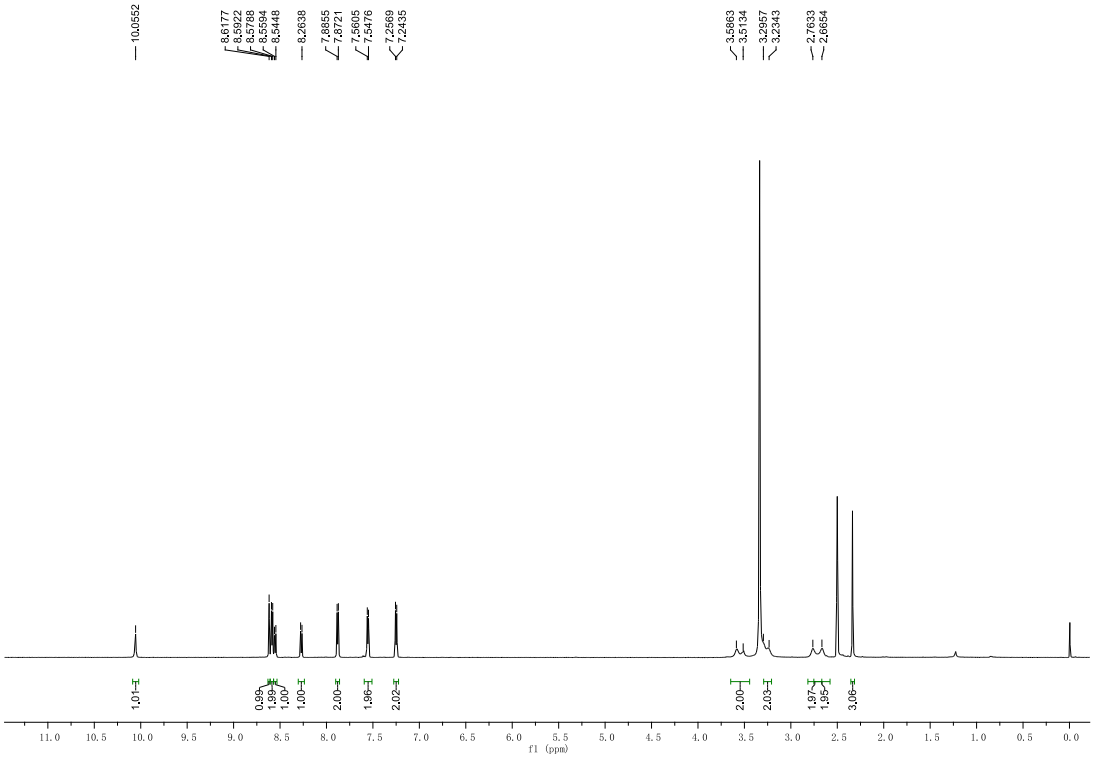


^{13}C-NMR spectra of 21g



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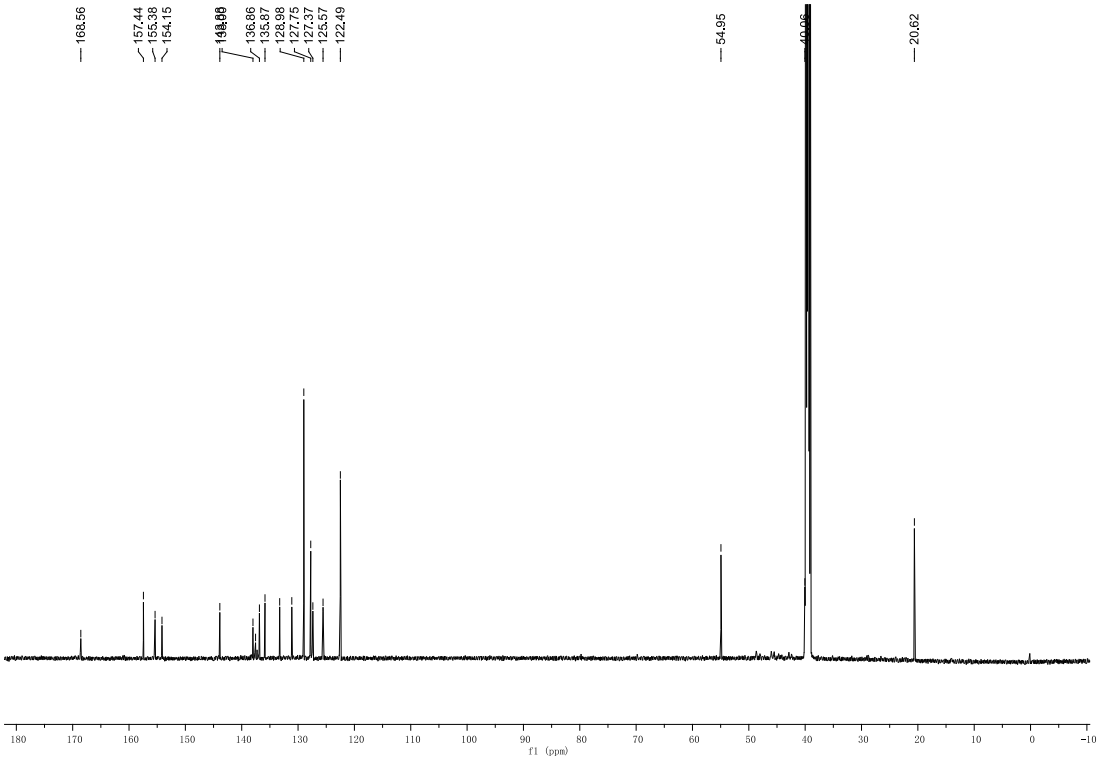

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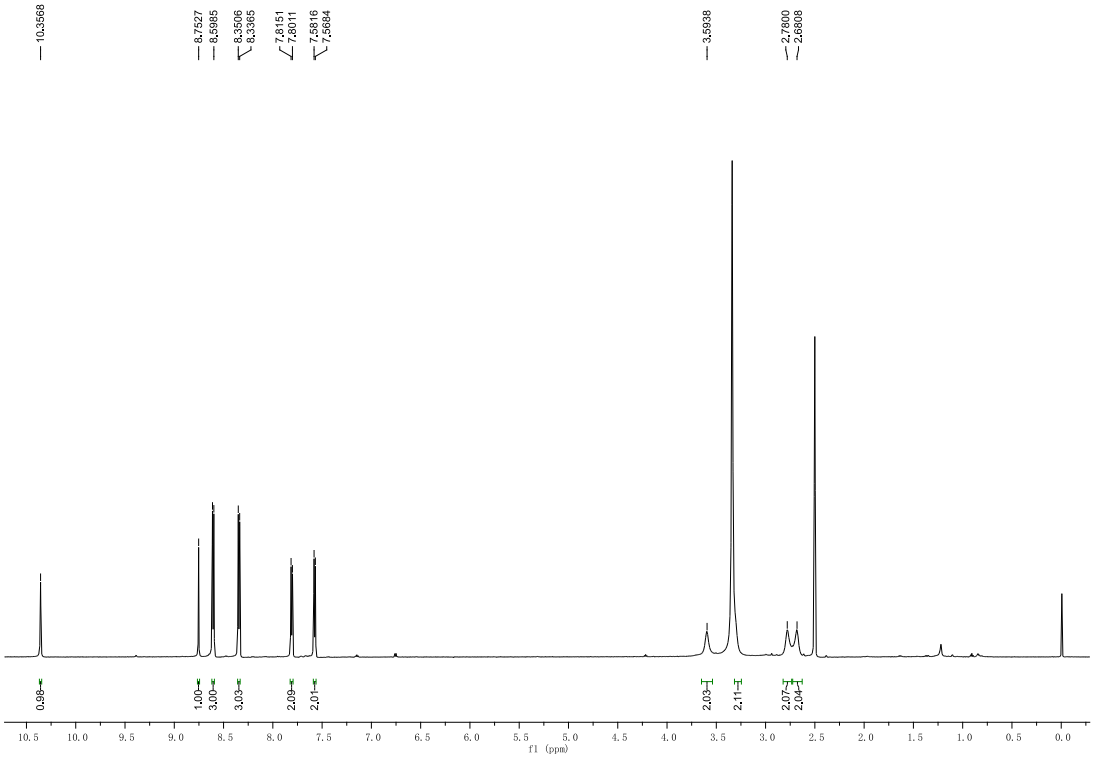
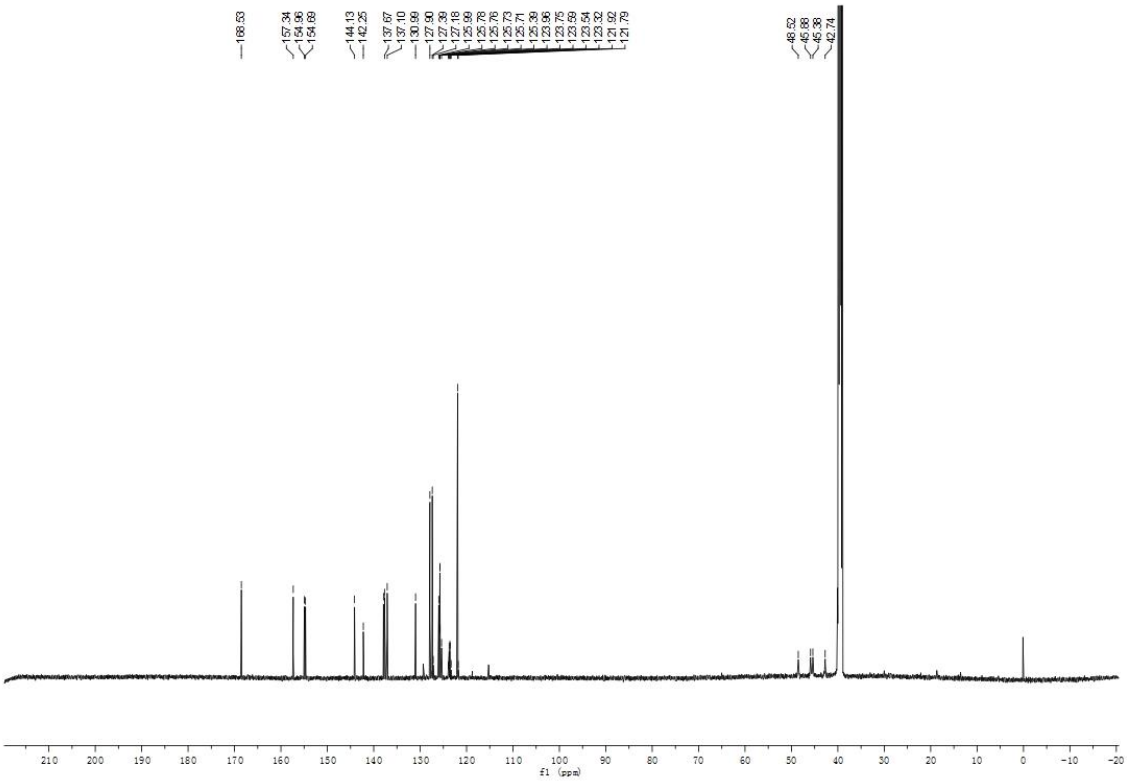


^{1}H-NMR spectra of 21i



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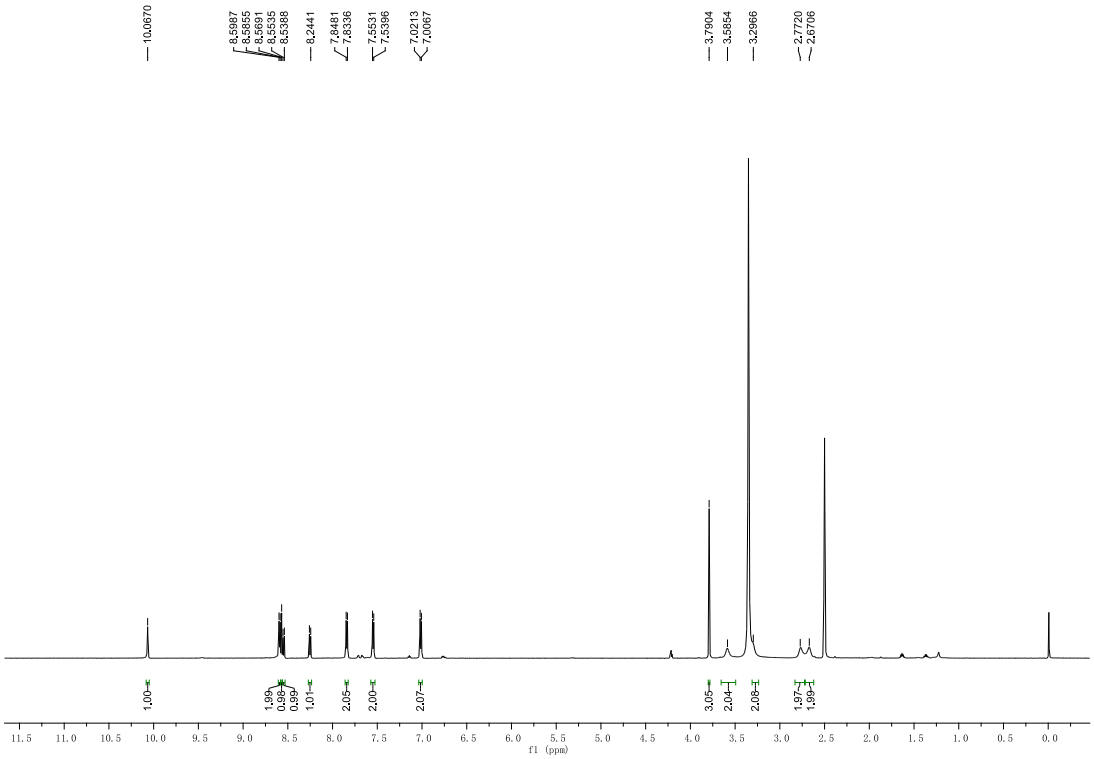

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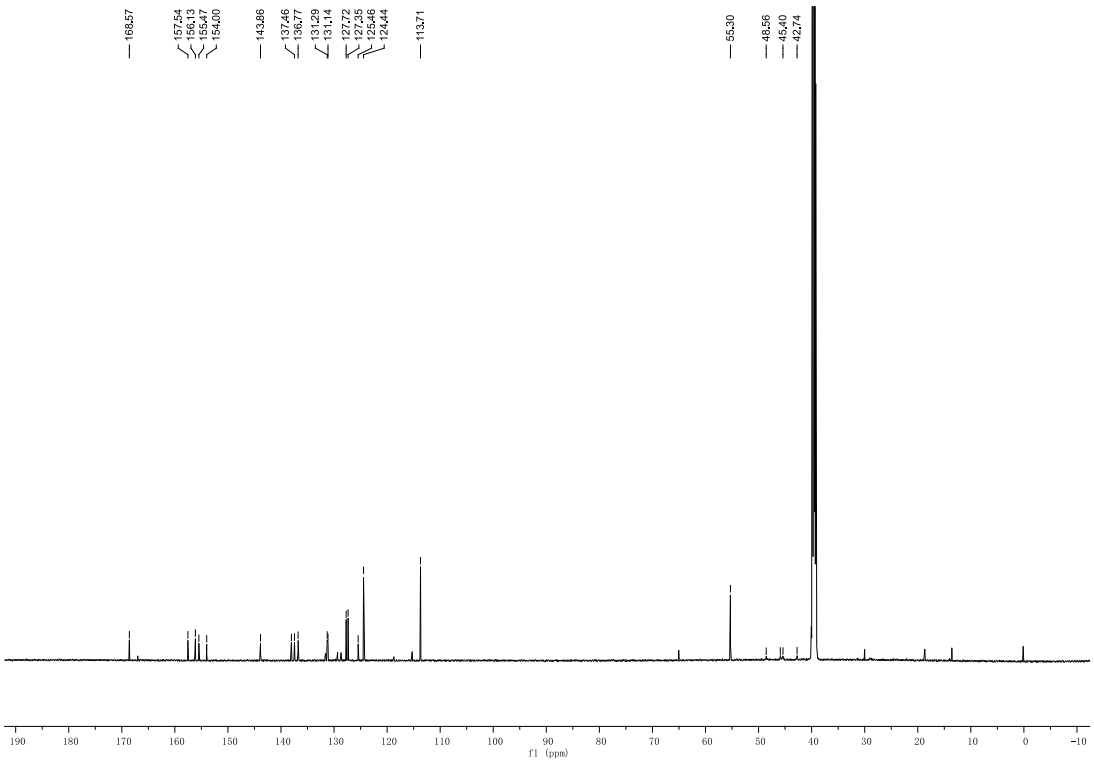

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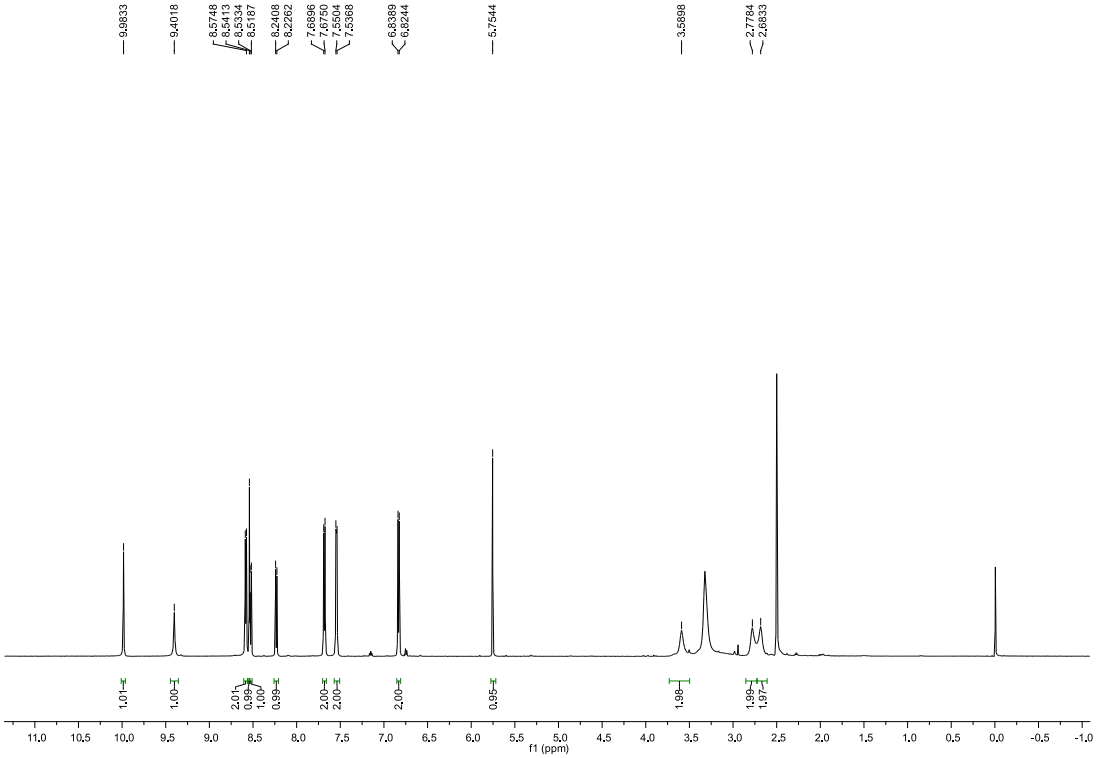
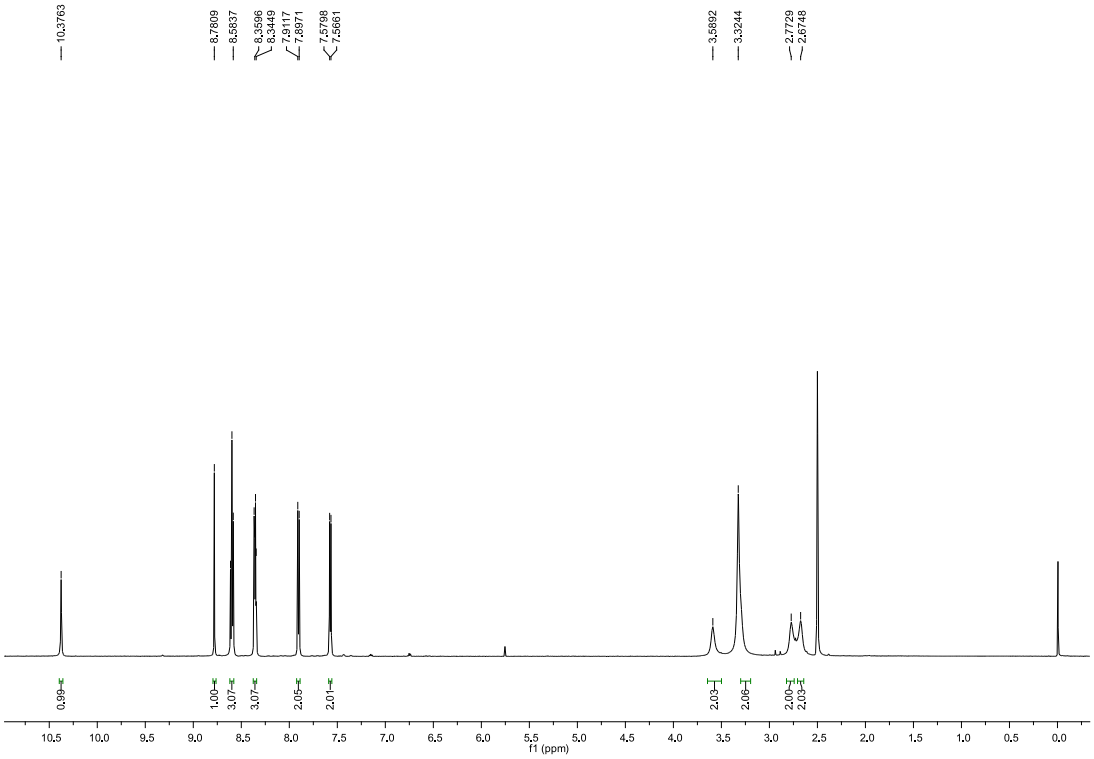
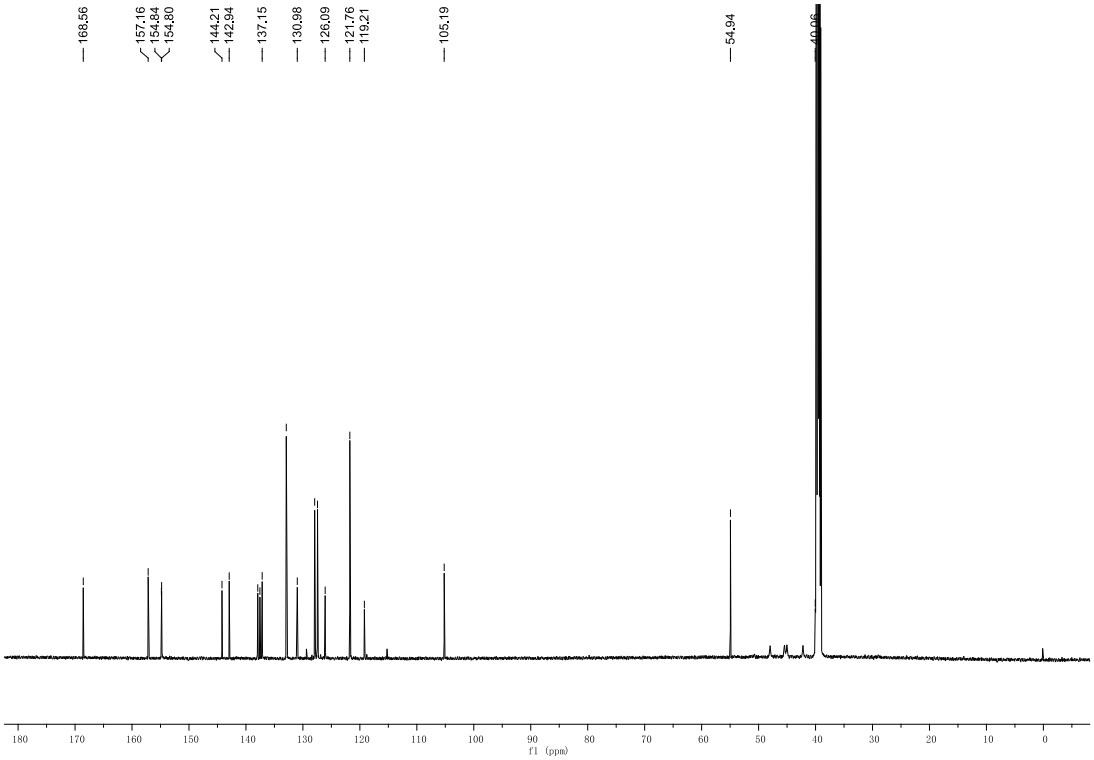


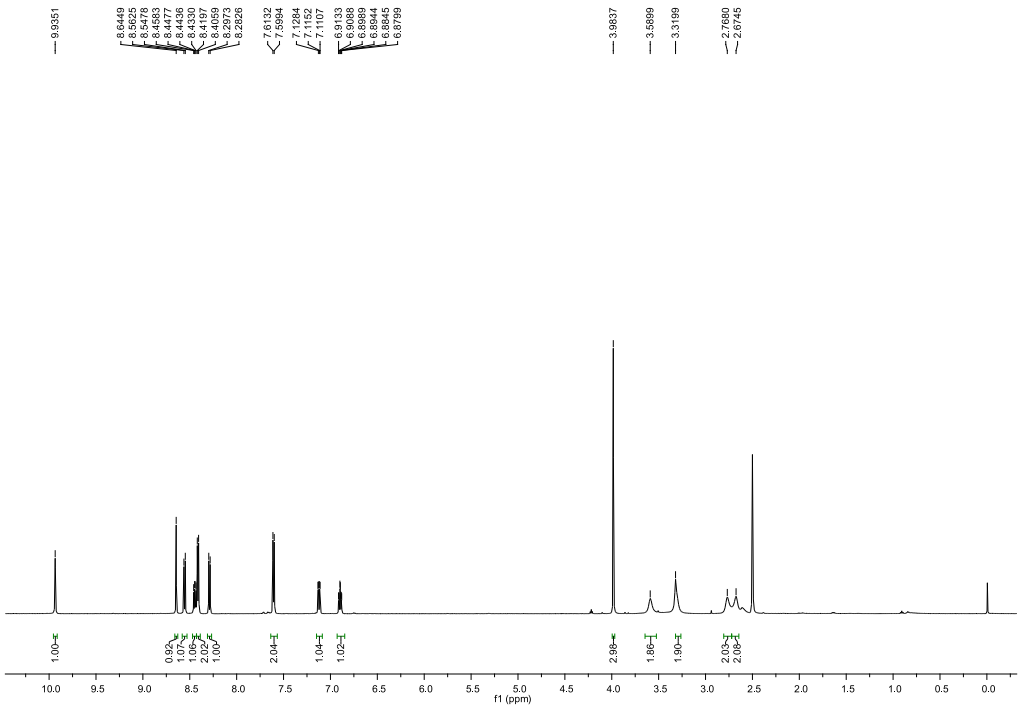
^{1}H-NMR spectra of 21k



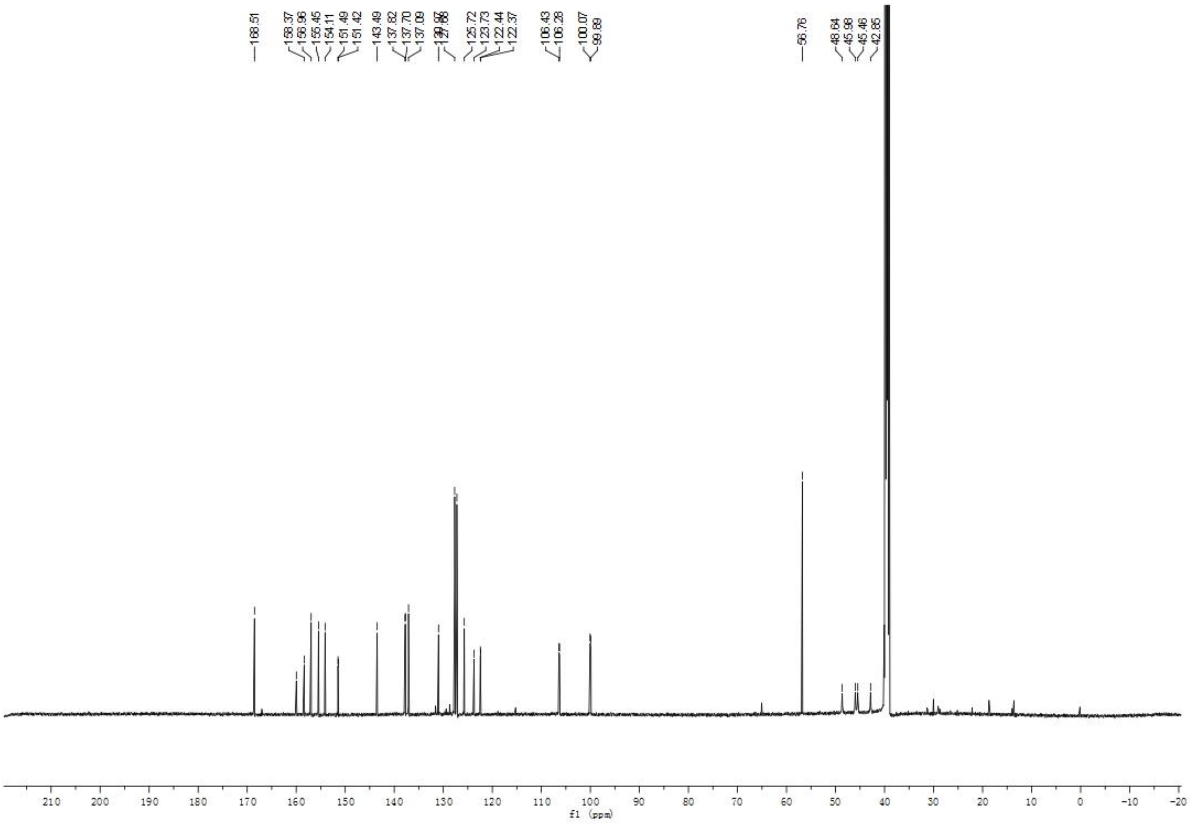
^{1}H-NMR spectra of 21l



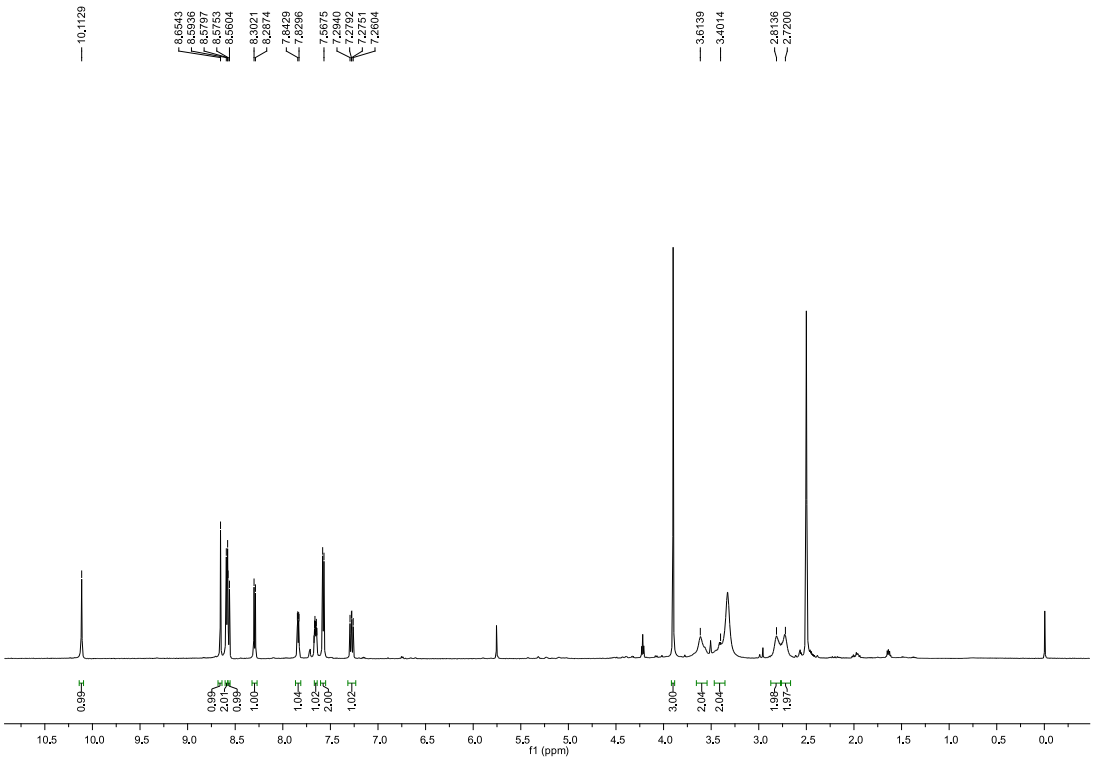
^{13}C-NMR spectra of 21l



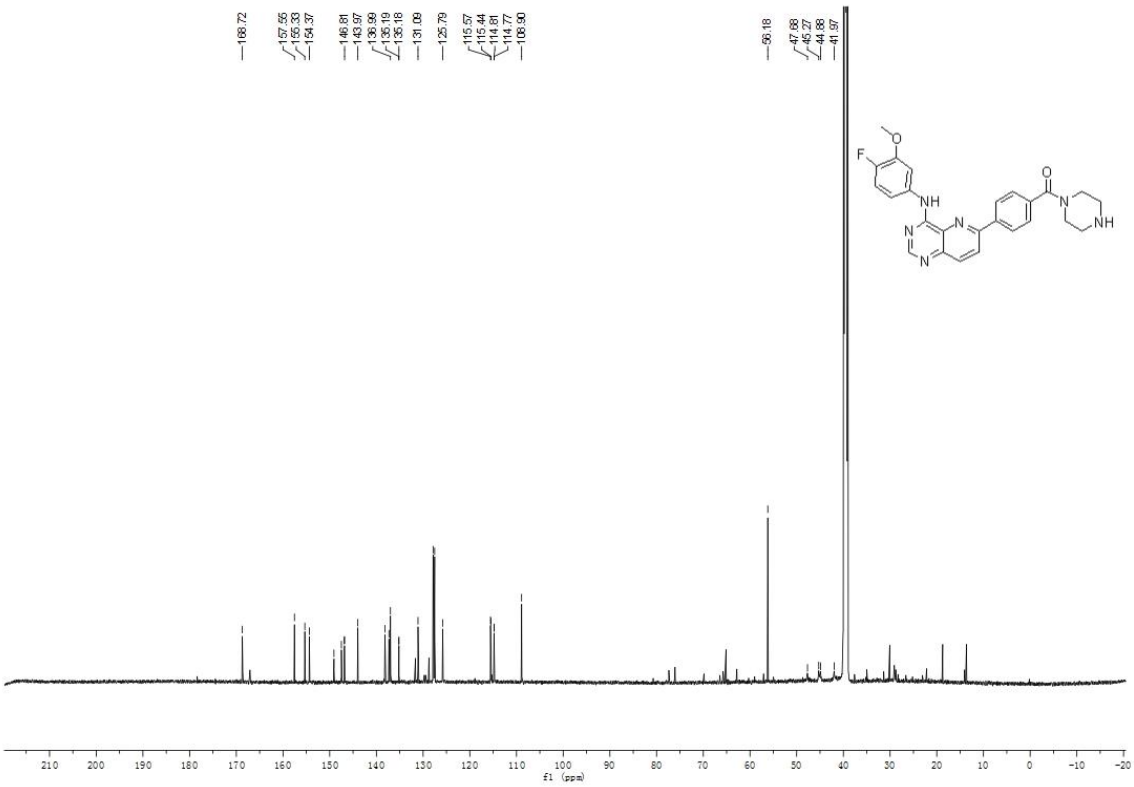
^{1}H-NMR spectra of 21m



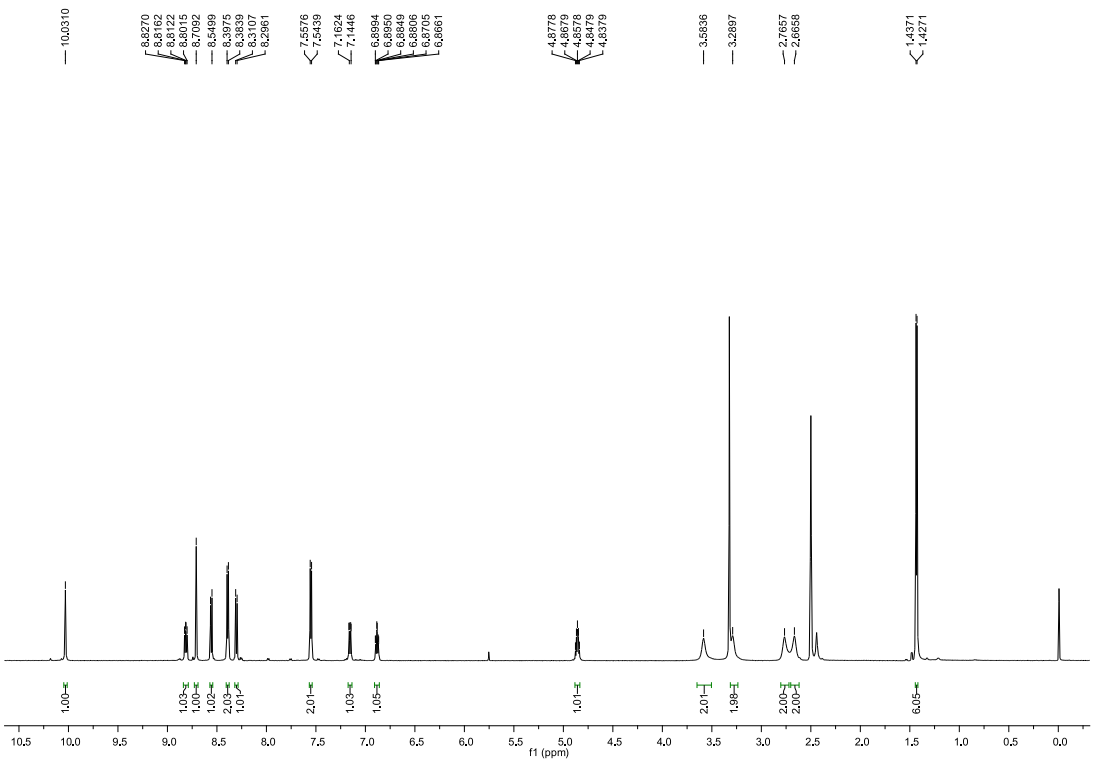
^{13}C-NMR spectra of 21m



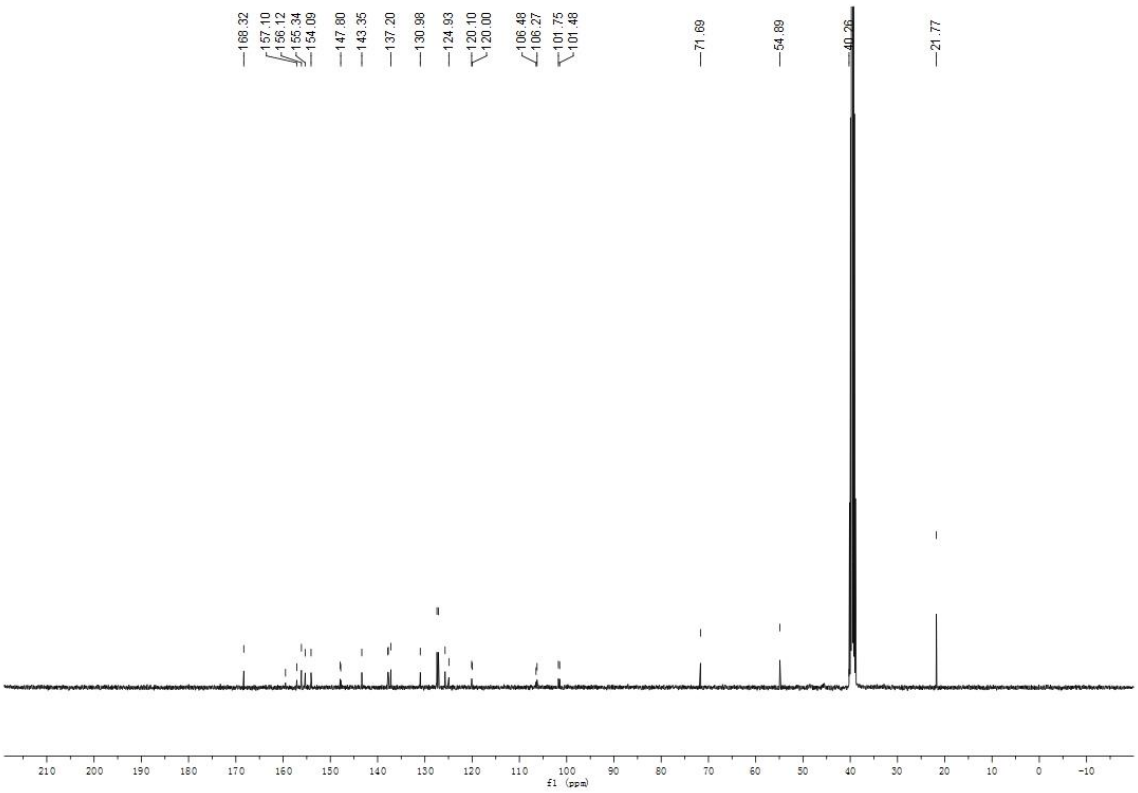
^{1}H-NMR spectra of 21n



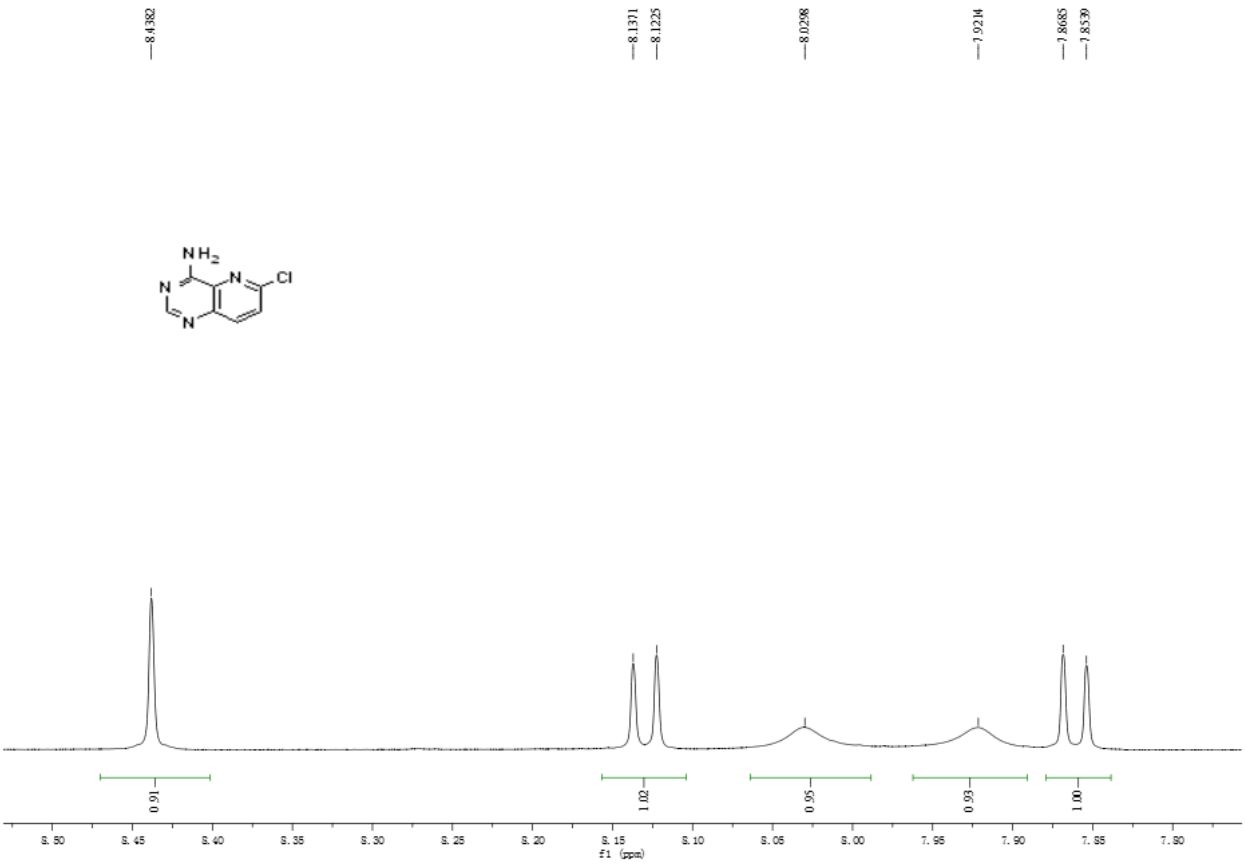
^{13}C-NMR spectra of 21n



^{1}H-NMR spectra of 21o

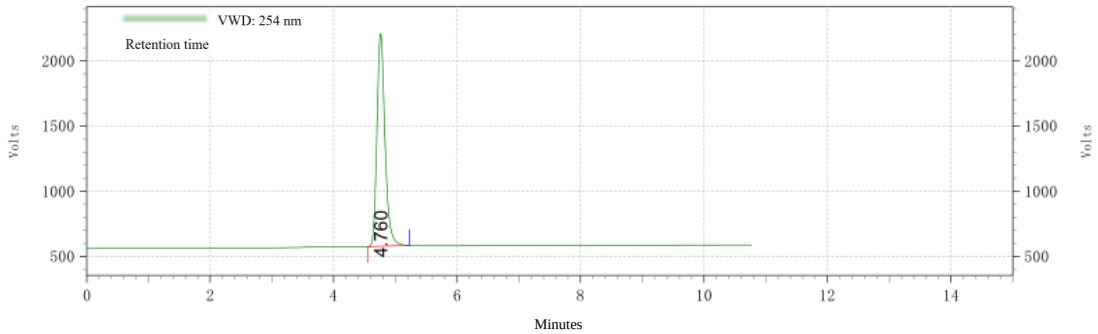


^{13}C-NMR spectra of 21o



^{1}H-NMR spectra of 23

2. HPLC spectrum of representative compounds

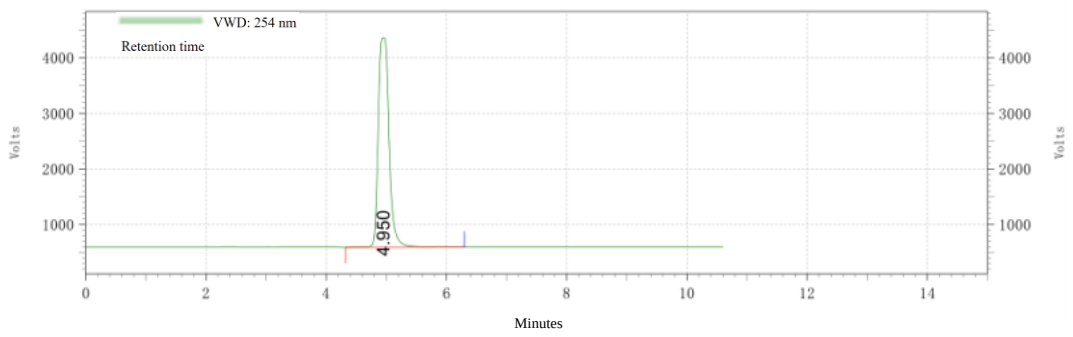


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
4.760	246368226	100.00	27340001	100.00

Sum	246368226	100.00	27340001	100.00

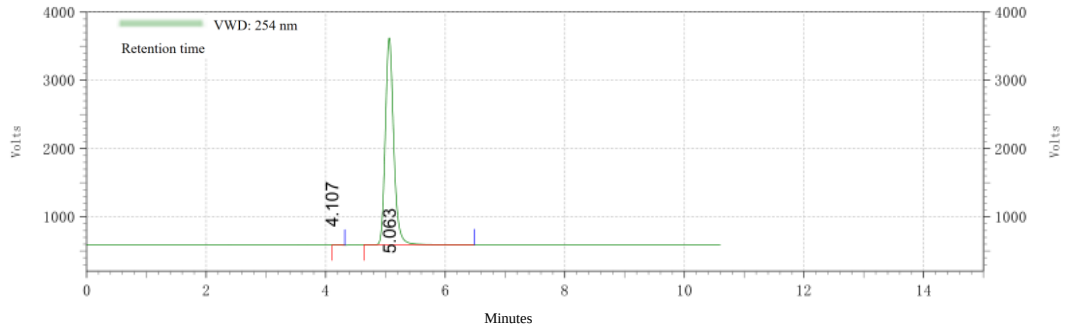
HPLC spectrum of 12a



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
4.950	790546950	100.00	63297815	100.00
Sum	790546950	100.00	63297815	100.00

HPLC spectrum of 12b

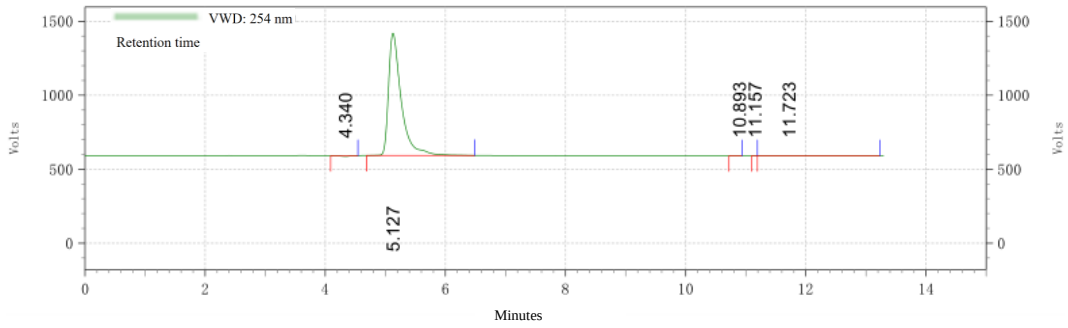


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
4.107	135332	0.03	0	0.00

5.063	496036902	99.97	50887123	100.00
Sum	496172234	100.00	50887123	100.00

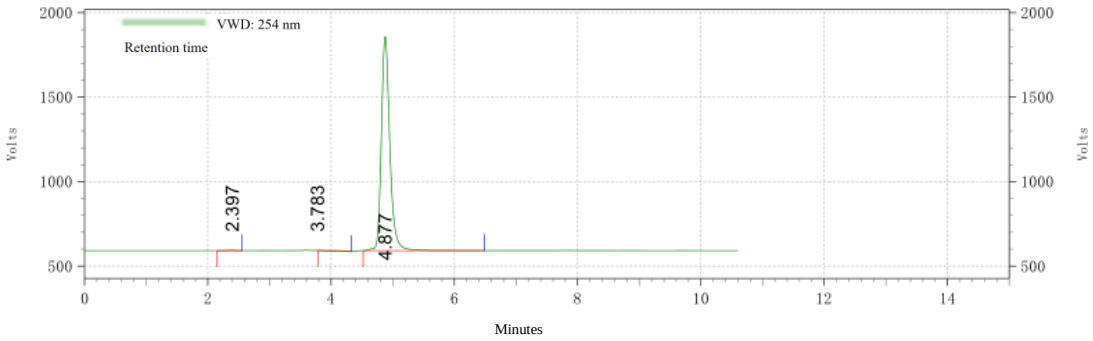
HPLC spectrum of 12c



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
4.340	1015076	0.50	94267	0.68
5.127	202817792	99.46	13858405	99.32
10.893	1084	0.00	111	0.00
11.157	290	0.00	87	0.00
11.723	77590	0.04	1044	0.01
Sum	203911832	100.00	13953914	100.00

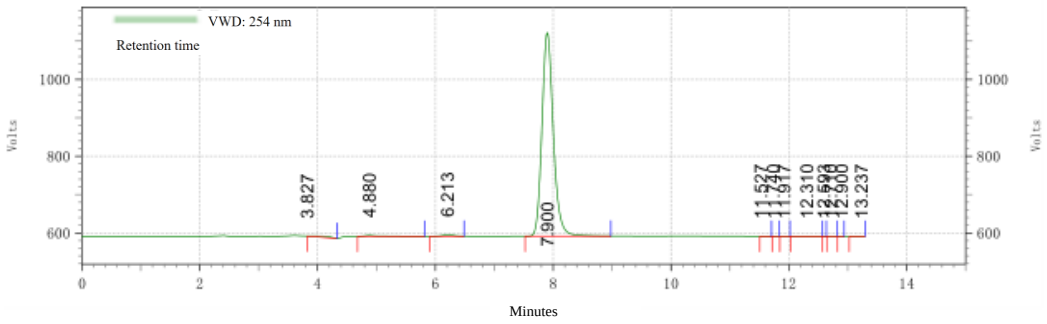
HPLC spectrum of 12d



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.397	231450	0.11	33847	0.16
3.783	957997	0.47	0	0.00
4.877	203272524	99.42	21284232	99.84
Sum	204461971	100.00	21318079	100.00

HPLC spectrum of 12e

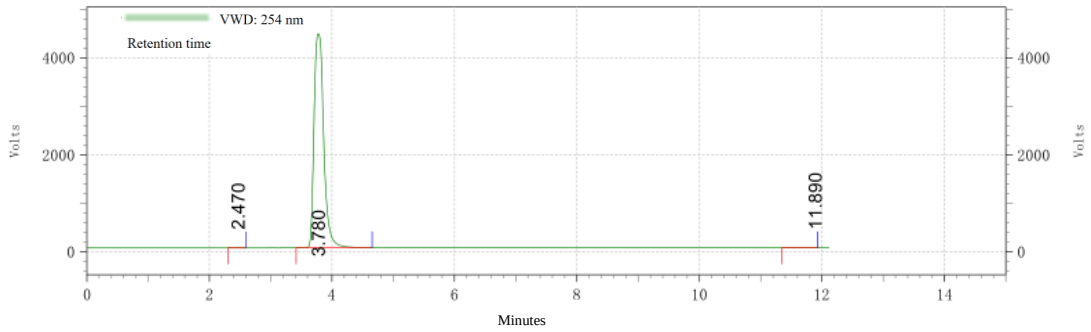


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
3.827	880421	0.73	0	0.00
4.880	427933	0.35	34461	0.38
6.213	739783	0.61	58339	0.65
7.900	118937944	98.30	8894207	98.96
11.527	224	0.00	43	0.00
11.740	125	0.00	41	0.00
11.917	480	0.00	101	0.00
12.310	4190	0.00	280	0.00
12.593	108	0.00	46	0.00
12.710	327	0.00	63	0.00
12.900	90	0.00	30	0.00

13.237	383	0.00	53	0.00
Sum	120992008	100.00	8987664	100.00

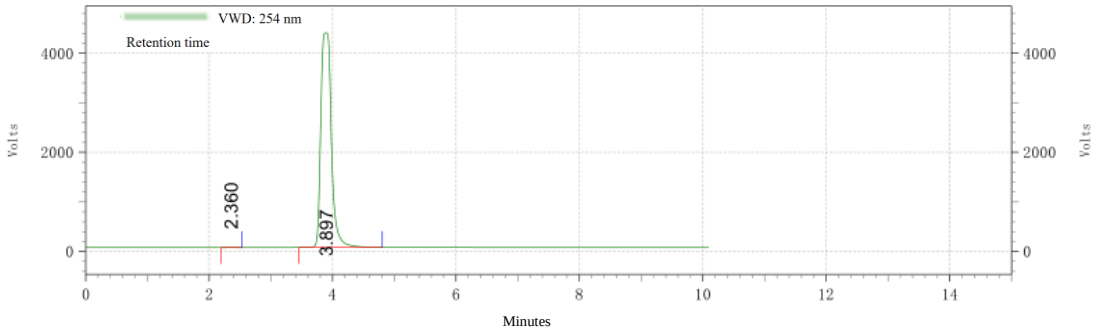
HPLC spectrum of 12f



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.470	132133	0.02	14497	0.02
3.780	811919825	99.98	74095464	99.98
11.890	2512	0.00	100	0.00
Sum	812054470	100.00	74110061	100.00

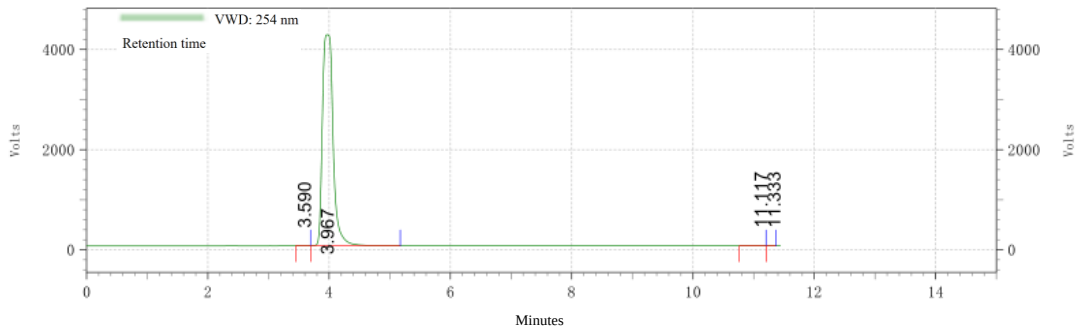
HPLC spectrum of 18a



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.360	183848	0.02	15815	0.02
3.897	864368524	99.98	72620531	99.98
Sum	864552372	100.00	72636346	100.00

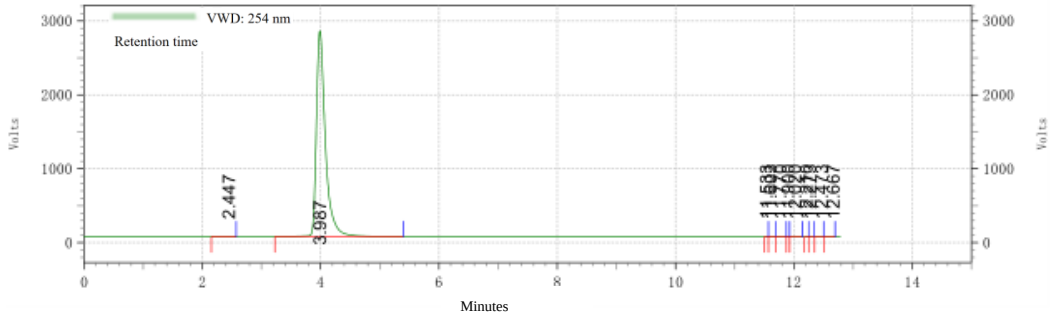
HPLC spectrum of 18b



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
3.590	297343	0.03	39335	0.06
3.967	867963905	99.97	70750088	99.94
11.117	3360	0.00	157	0.00
11.333	231	0.00	45	0.00
Sum	868264839	100.00	70789645	100.00

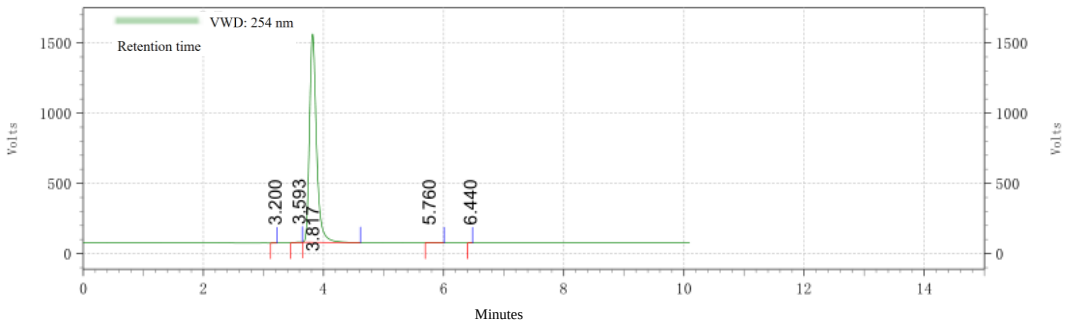
HPLC spectrum of 18c



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.447	165480	0.03	14586	0.03
3.987	497243495	99.97	46736767	99.97
11.533	81	0.00	38	0.00
11.603	254	0.00	44	0.00
11.770	411	0.00	84	0.00
11.900	40	0.00	23	0.00
12.020	286	0.00	57	0.00
12.210	71	0.00	32	0.00
12.273	84	0.00	30	0.00
12.473	106	0.00	25	0.00
12.667	447	0.00	62	0.00
Sum	497410755	100.00	46751748	100.00

HPLC spectrum of 18d

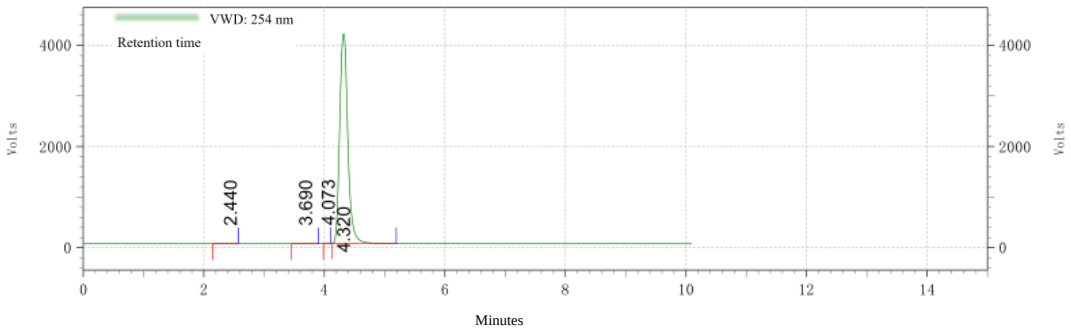


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
3.200	13979	0.01	3252	0.01
3.593	224481	0.11	33510	0.13

3.817	201230124	99.88	24878177	99.85
5.760	8057	0.00	651	0.00
6.440	175	0.00	77	0.00
Sum	201476816	100.00	24915667	100.00

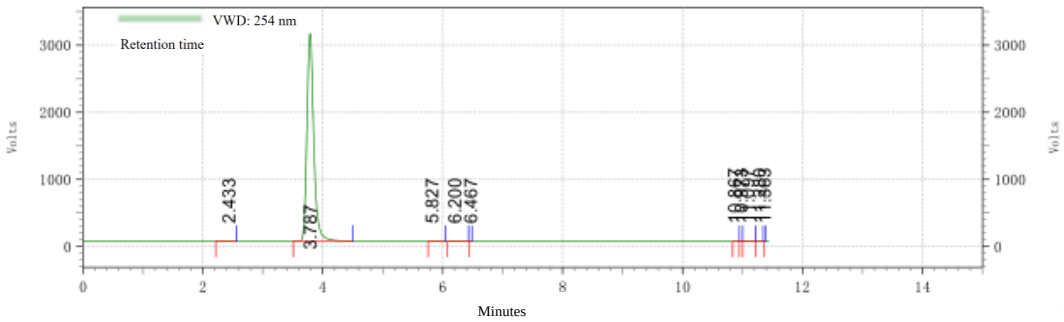
HPLC spectrum of 18e



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.440	165850	0.03	13248	0.02
3.690	494632	0.08	37532	0.05
4.073	260014	0.04	51072	0.07
4.320	648217659	99.86	69432356	99.85
Sum	649138155	100.00	69534208	100.00

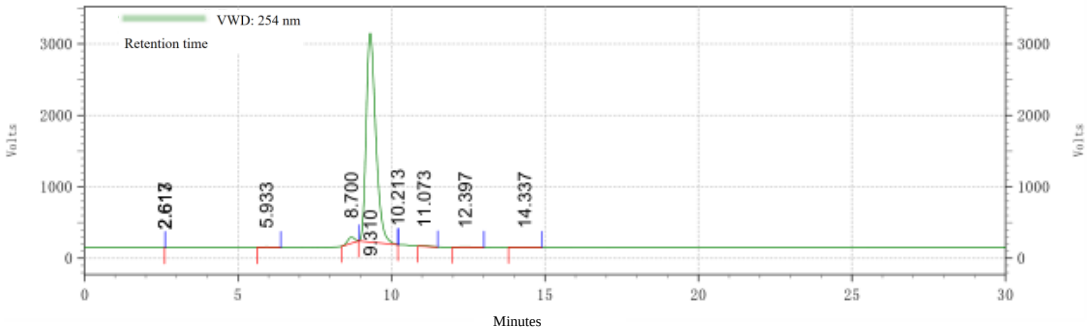
HPLC spectrum of 18f



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.433	193491	0.05	20384	0.04
3.787	411909729	99.95	51971961	99.96
5.827	3001	0.00	251	0.00
6.200	2263	0.00	215	0.00
6.467	41	0.00	25	0.00
10.867	219	0.00	50	0.00
10.973	77	0.00	47	0.00
11.097	331	0.00	61	0.00
11.280	188	0.00	51	0.00
11.363	2	0.00	0	0.00
Sum	412109342	100.00	51993045	100.00

HPLC spectrum of 21a

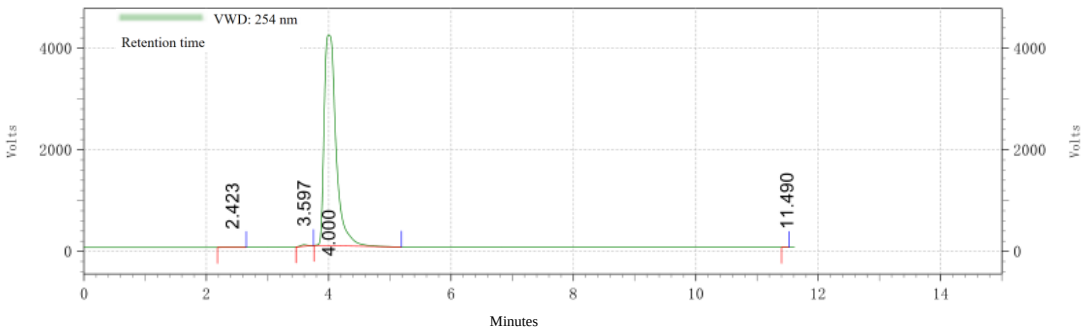


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.613	2	0.00	0	0.00
2.617	0	0.00	0	0.00
5.933	2642347	0.24	151352	0.30
8.700	22221974	2.04	1415505	2.79

9.310	1062454901	97.31	49028356	96.54
10.213	0	0.00	0	0.00
11.073	1875960	0.17	104794	0.21
12.397	1381195	0.13	47252	0.09
14.337	1254724	0.11	39148	0.08
Sum	1091831103	100.00	50786407	100.00

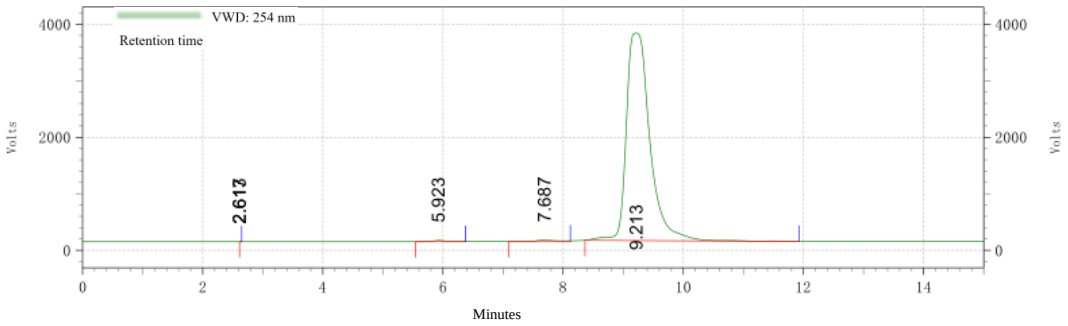
HPLC spectrum of 21c



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.423	425669	0.05	53237	0.08
3.597	3370368	0.36	463225	0.66
4.000	940276960	99.60	69594744	99.26
11.490	308	0.00	76	0.00
Sum	944073305	100.00	70111282	100.00

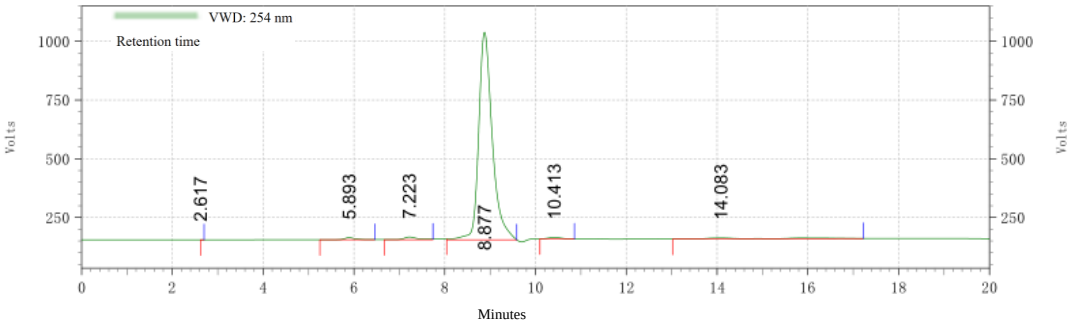
HPLC spectrum of 21d



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.613	8	0.00	0	0.00
2.617	0	0.00	0	0.00
5.923	5443028	0.32	378690	0.61
7.687	13436592	0.76	460808	0.74
9.213	1673815079	98.88	61626928	98.66
Sum	1692694707	100.00	62466426	100.00

HPLC spectrum of 21e

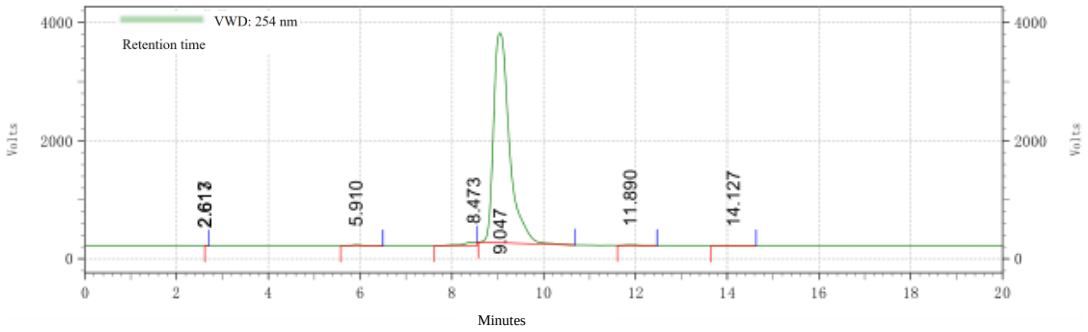


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.617	332	0.00	0	0.00
5.893	2482435	0.77	150253	0.98
7.223	4227995	1.31	191692	1.25

8.877	307509594	95.40	14818521	96.68
10.413	1810207	0.56	98533	0.64
14.083	6310257	1.96	68766	0.45
Sum	322340820	100.00	15327765	100.00

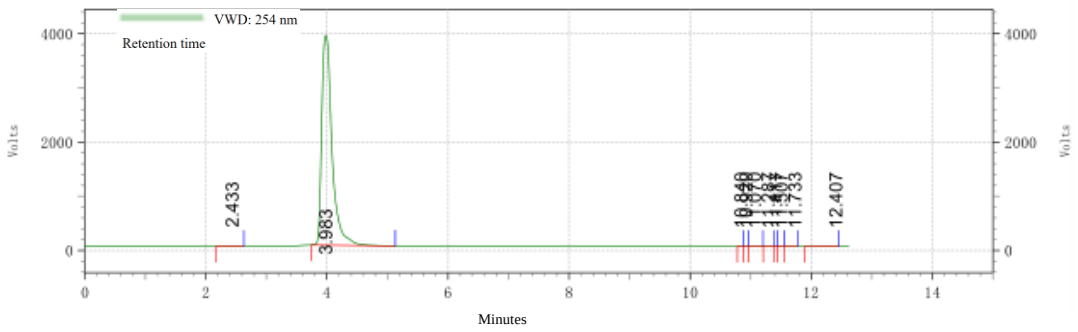
HPLC spectrum of 21f



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.613	106	0.00	0	0.00
2.617	0	0.00	0	0.00
5.910	6192611	0.42	339718	0.55
8.473	25782686	1.75	1104143	1.80
9.047	1435721838	97.46	59584269	97.23
11.890	3168241	0.22	180103	0.29
14.127	2218342	0.15	74452	0.12
Sum	1473083424	100.00	61282685	100.00

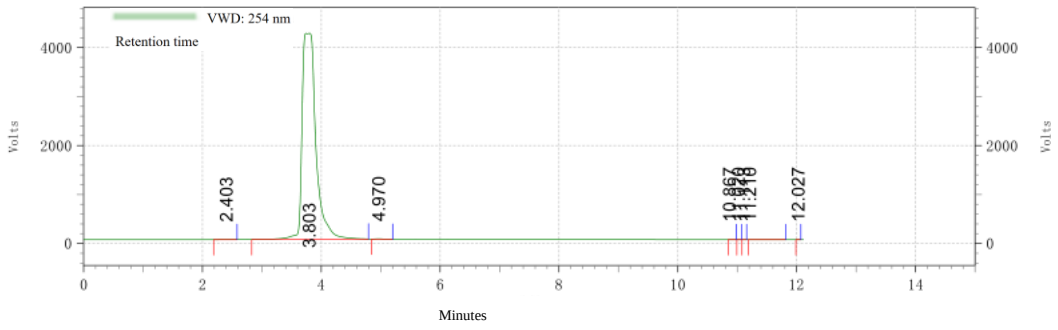
HPLC spectrum of 21g



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.433	828250	0.11	124651	0.19
3.983	767914878	99.89	64909273	99.81
10.840	251	0.00	80	0.00
10.920	145	0.00	61	0.00
11.070	566	0.00	78	0.00
11.287	311	0.00	67	0.00
11.417	47	0.00	26	0.00
11.507	85	0.00	23	0.00
11.733	386	0.00	47	0.00
12.407	2358	0.00	76	0.00
Sum	768747277	100.00	65034382	100.00

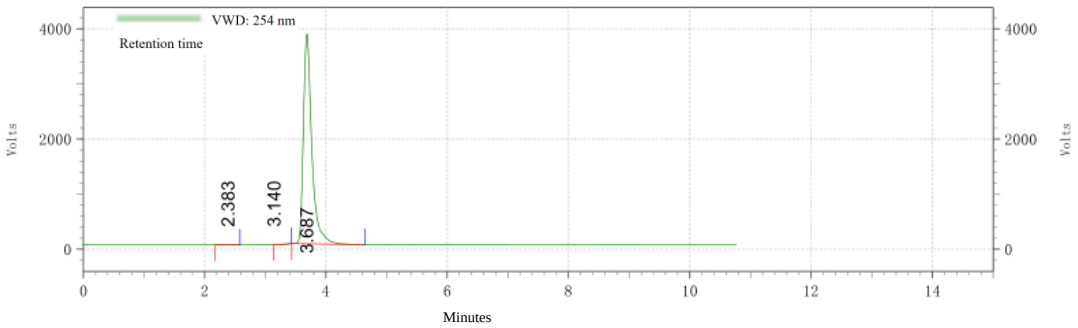
HPLC spectrum of 21h



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.403	403762	0.04	43320	0.06
3.803	1138457957	99.88	70578736	99.80
4.970	923384	0.08	96258	0.14
10.867	216	0.00	47	0.00
11.020	57	0.00	27	0.00
11.113	59	0.00	28	0.00
11.210	2166	0.00	44	0.00
12.027	73	0.00	31	0.00
Sum	1139787674	100.00	70718491	100.00

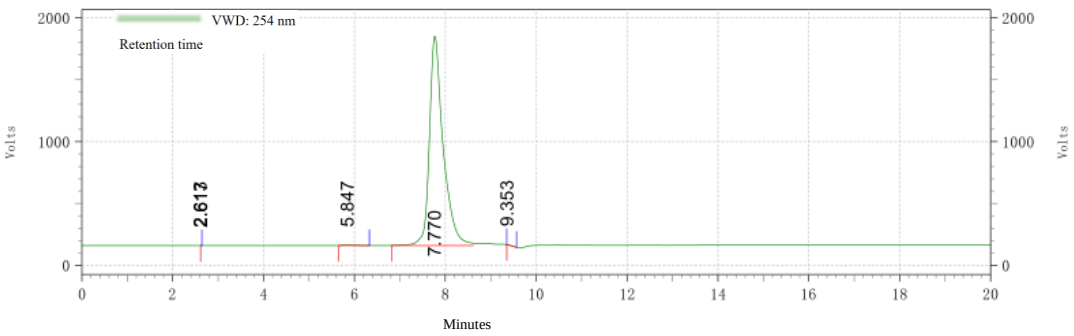
HPLC spectrum of 21i



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.383	321118	0.05	30432	0.05
3.140	1112009	0.18	0	0.00
3.687	615581101	99.77	63863984	99.95
Sum	617014228	100.00	63894416	100.00

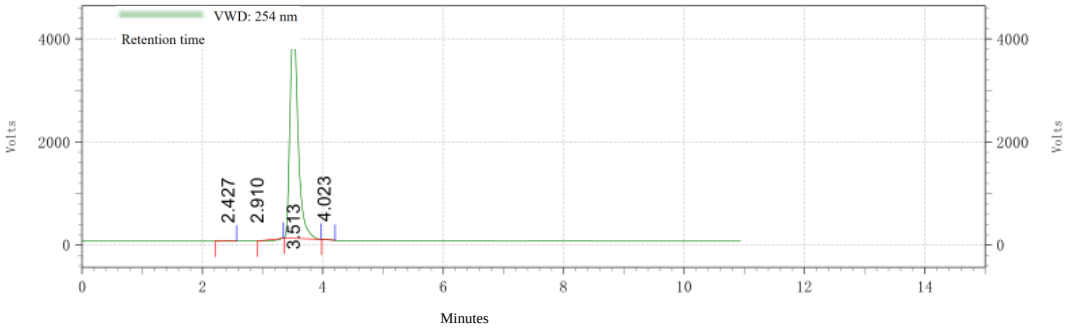
HPLC spectrum of 21j



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.613	4	0.00	0	0.00
2.617	0	0.00	0	0.00
5.847	1362376	0.22	81909	0.29
7.770	607603189	99.74	28392140	99.71
9.353	230045	0.04	0	0.00
Sum	609195614	100.00	28474049	100.00

HPLC spectrum of 21k

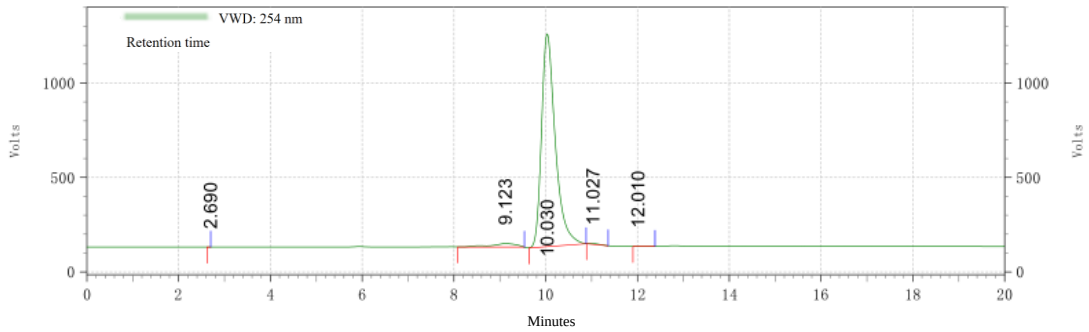


VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.427	269418	0.04	30208	0.04
2.910	5775909	0.89	0	0.00
3.513	644006784	98.97	67161171	99.83

4.023	651824	0.10	84276	0.13
Sum	650703935	100.00	67275655	100.00

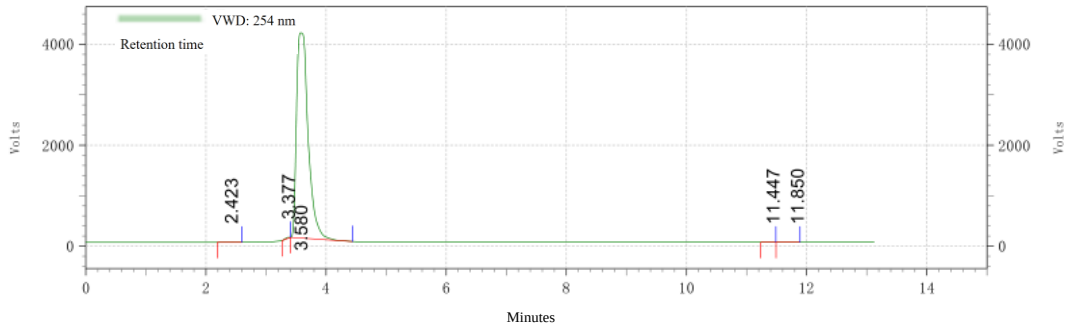
HPLC spectrum of 21l



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.690	11	0.00	24	0.00
9.123	12847501	3.16	315898	1.64
10.030	393095888	96.59	18884472	98.04
11.027	930697	0.23	57697	0.30
12.010	92910	0.02	4101	0.02
Sum	406967007	100.00	19262192	100.00

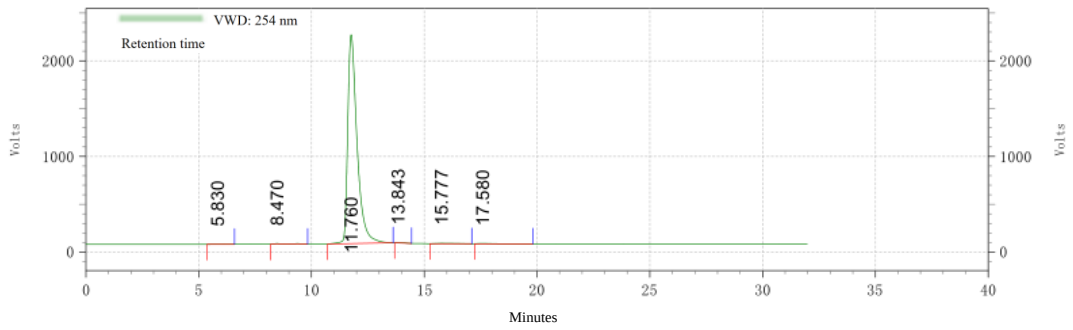
HPLC spectrum of 21m



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
2.423	1140065	0.12	186157	0.27
3.377	1427369	0.15	215839	0.31
3.580	922283675	99.72	68241034	99.41
11.447	860	0.00	60	0.00
11.850	1607	0.00	75	0.00
Sum	924853576	100.00	68643165	100.00

HPLC spectrum of 21n



VWD: 254 nM

Ret. Time	Area	Area%	Height	Height%
5.830	918072	0.09	41246	0.11
8.470	5613984	0.53	116120	0.31
11.760	1052337974	98.83	36615037	99.26
13.843	1036913	0.10	28571	0.08
15.777	3080200	0.29	52265	0.14
17.580	1770650	0.17	32994	0.09
Sum	1064757793	100.00	36886233	100.00

HPLC spectrum of 21o

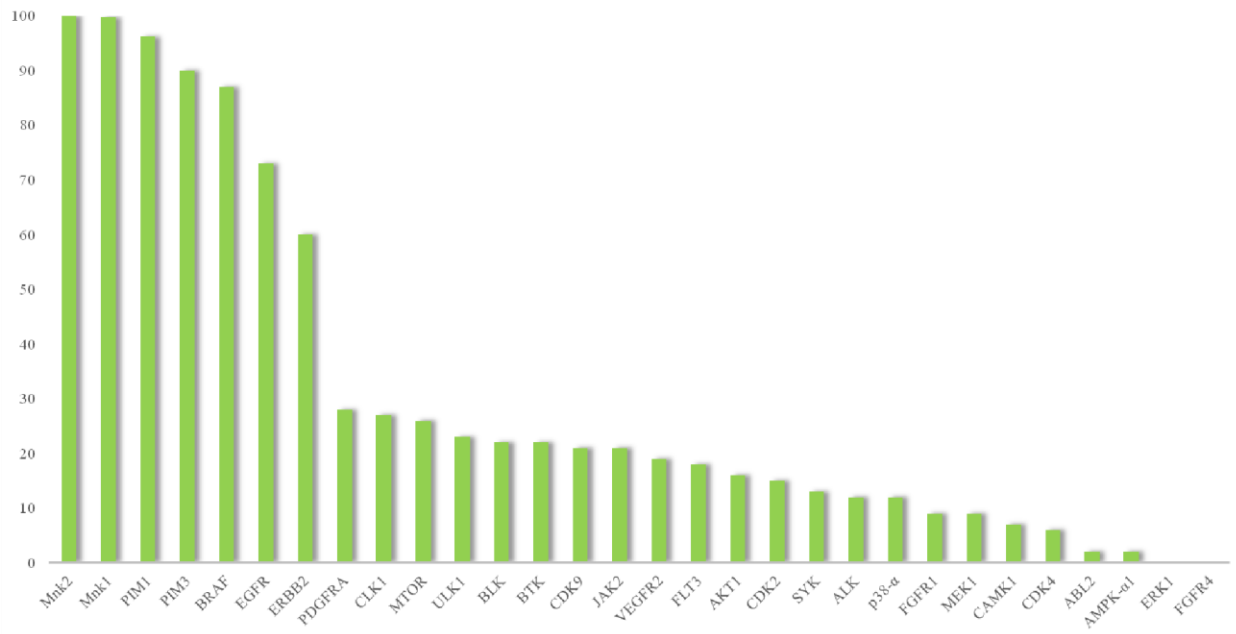


Figure S1. Kinase selectivity of compound **21o** against 30 kinases. The inhibition rates were measured using DiscoveryX KINOMEscan technology from Eurofins.