

Supporting Information

Design, synthesis, and biological evaluation of substituted oxopyridine derivatives as selective FXIa inhibitors

Yanshi Wang ^{a, b}, Sida Yan ^{a, b}, Jianglin Yuan ^{a, b}, Xiaoyan Meng ^{a, b}, Peng Liu ^{a, b}, Shijun Zhang ^{a, b}, Fancui Meng ^{a, b},
Wei Liu ^{a, b}, Shuhao Zhang ^{a, b}, Changjiang Huang ^{a, b, *} and Qunchao Wei ^{a, b, *}

^a State Key Laboratory of Druggability Evaluation and Systematic Translational Medicine, Puchuang Pharmaceutical Technology (Tianjin) Co., Ltd., Tianjin Institute of Pharmaceutical Research, 306 Huiren Road, Tianjin 300301, P. R. China

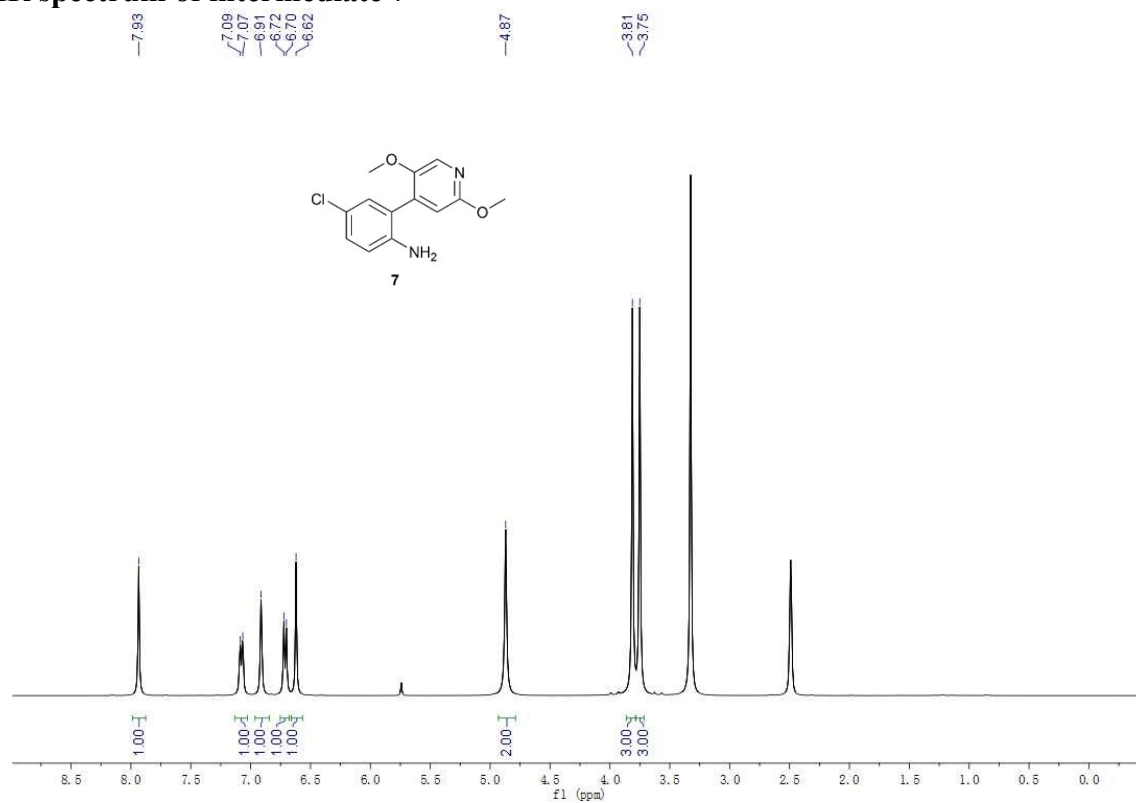
^b Tianjin Key Laboratory of Molecular Design and Drug Discovery, Puchuang Pharmaceutical Technology (Tianjin) Co., Ltd., Tianjin Institute of Pharmaceutical Research, 306 Huiren Road, Tianjin 300301, P. R. China

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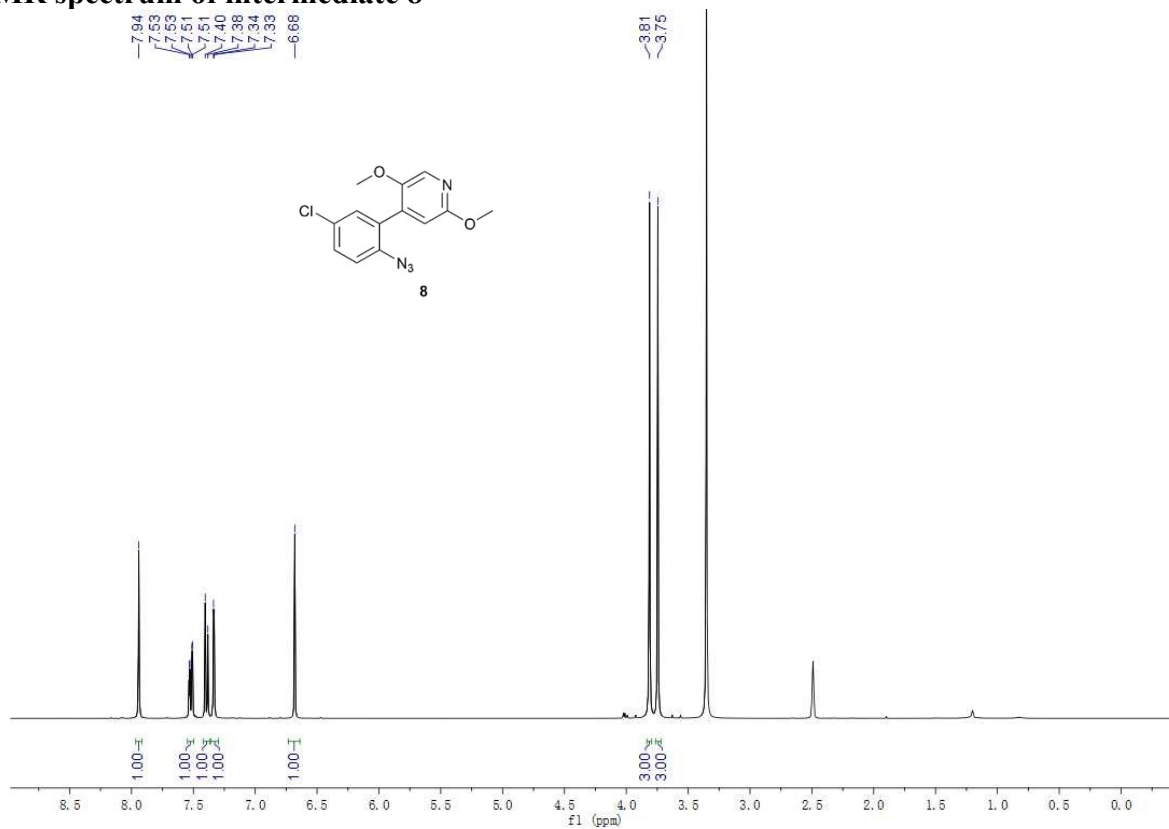
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^1H -NMR and ^{13}C -NMR spectra for intermediates and tested compounds

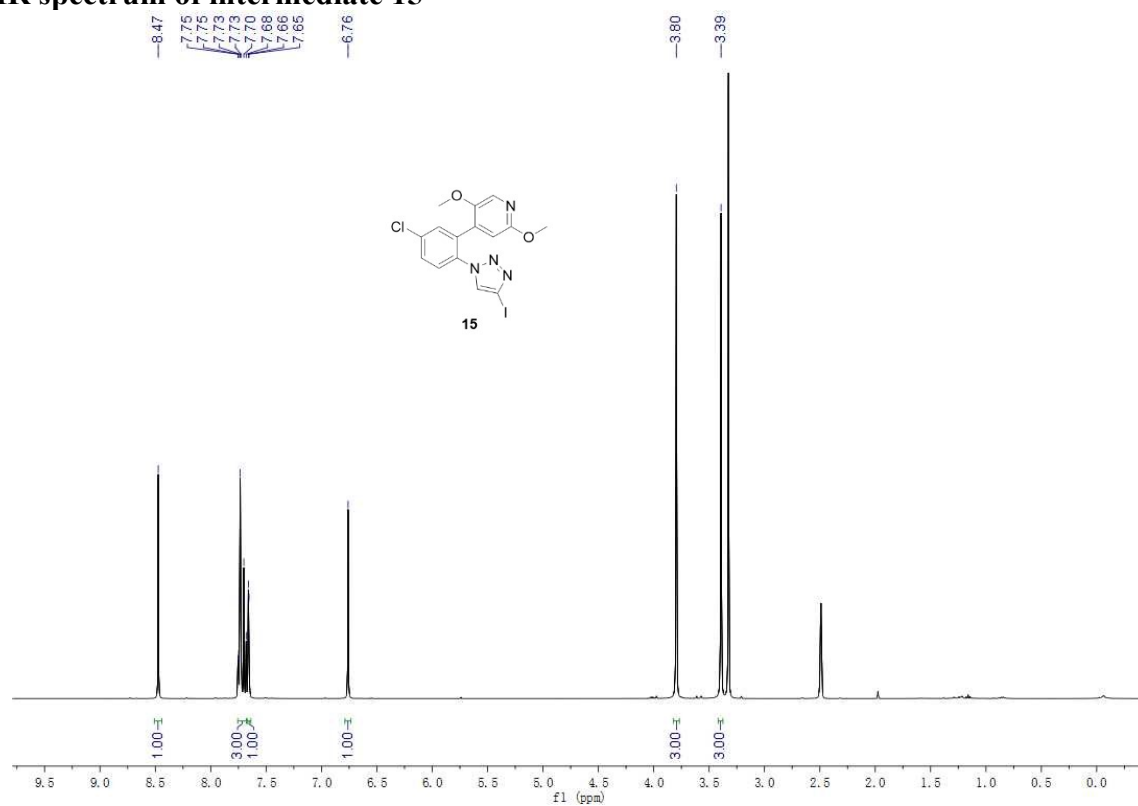
^1H -NMR spectrum of intermediate 7



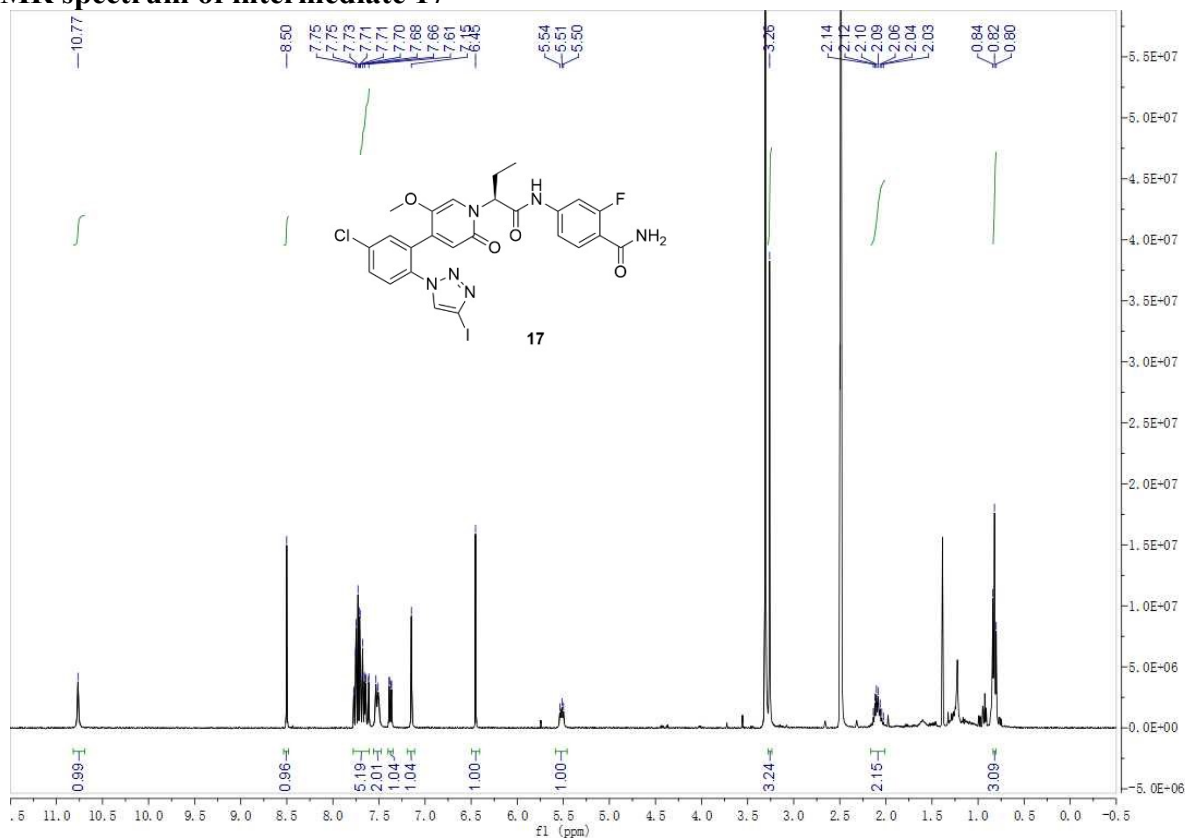
^1H -NMR spectrum of intermediate 8



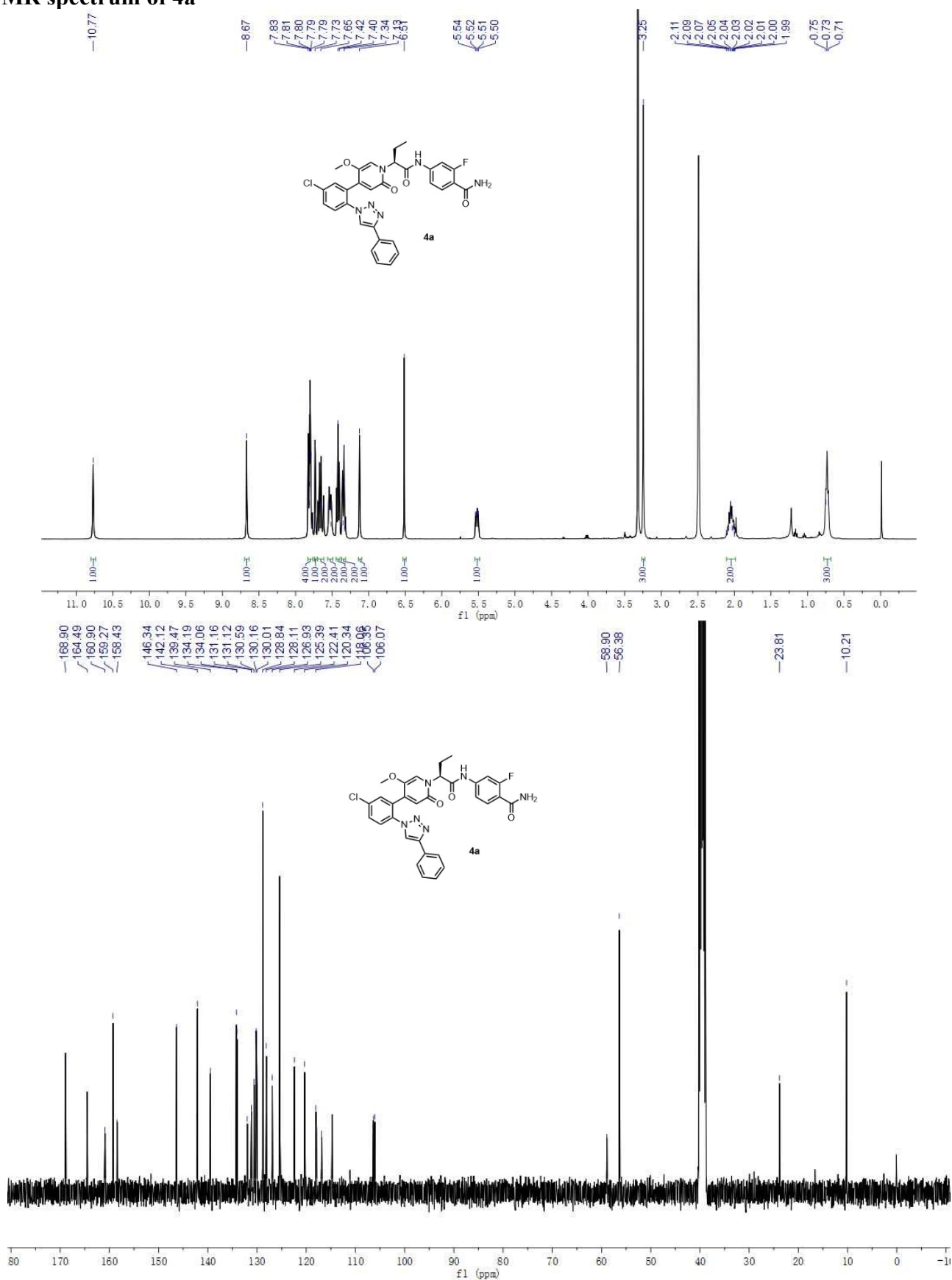
¹H-NMR spectrum of intermediate 15



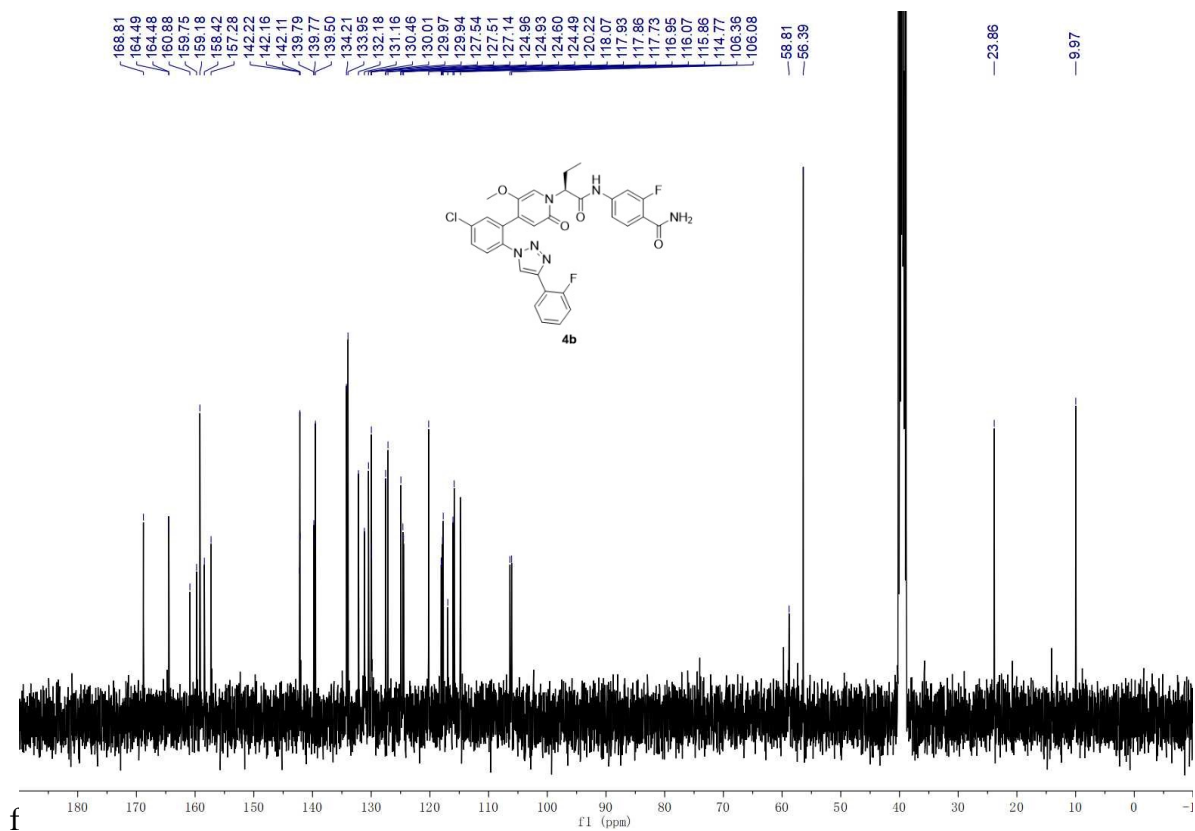
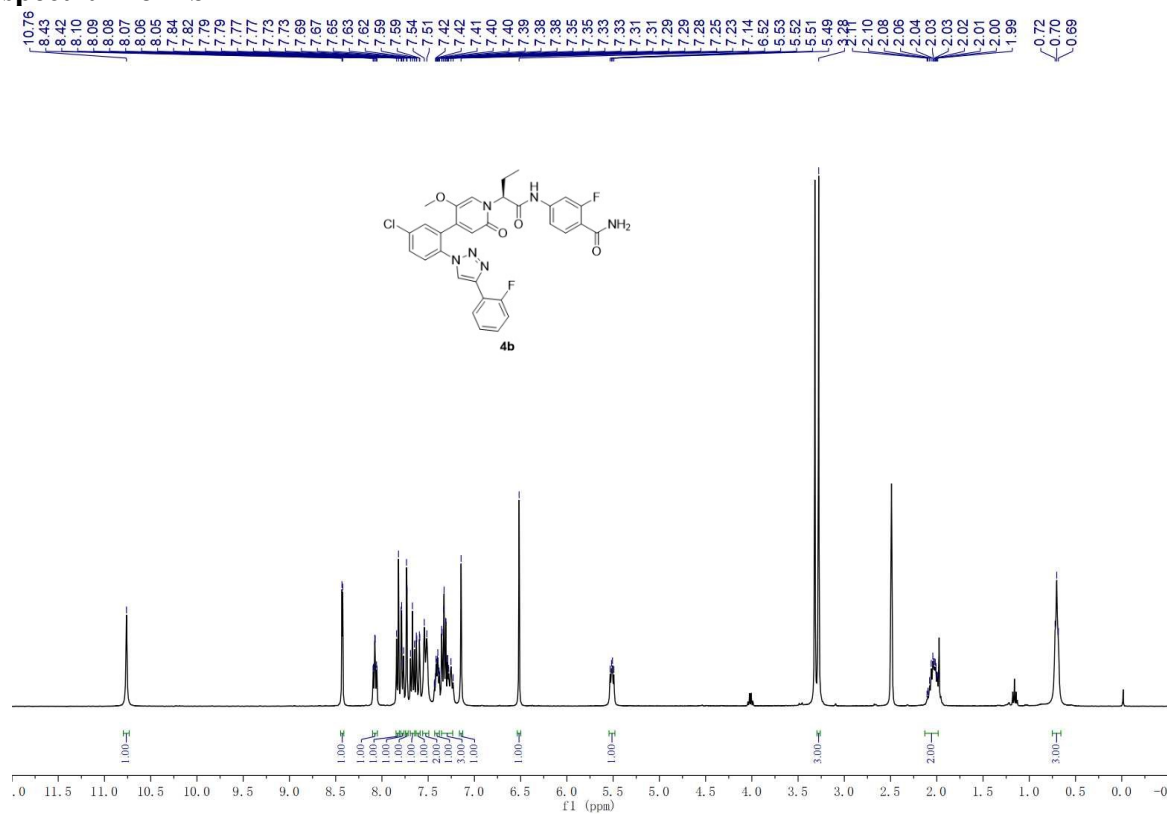
¹H-NMR spectrum of intermediate 17



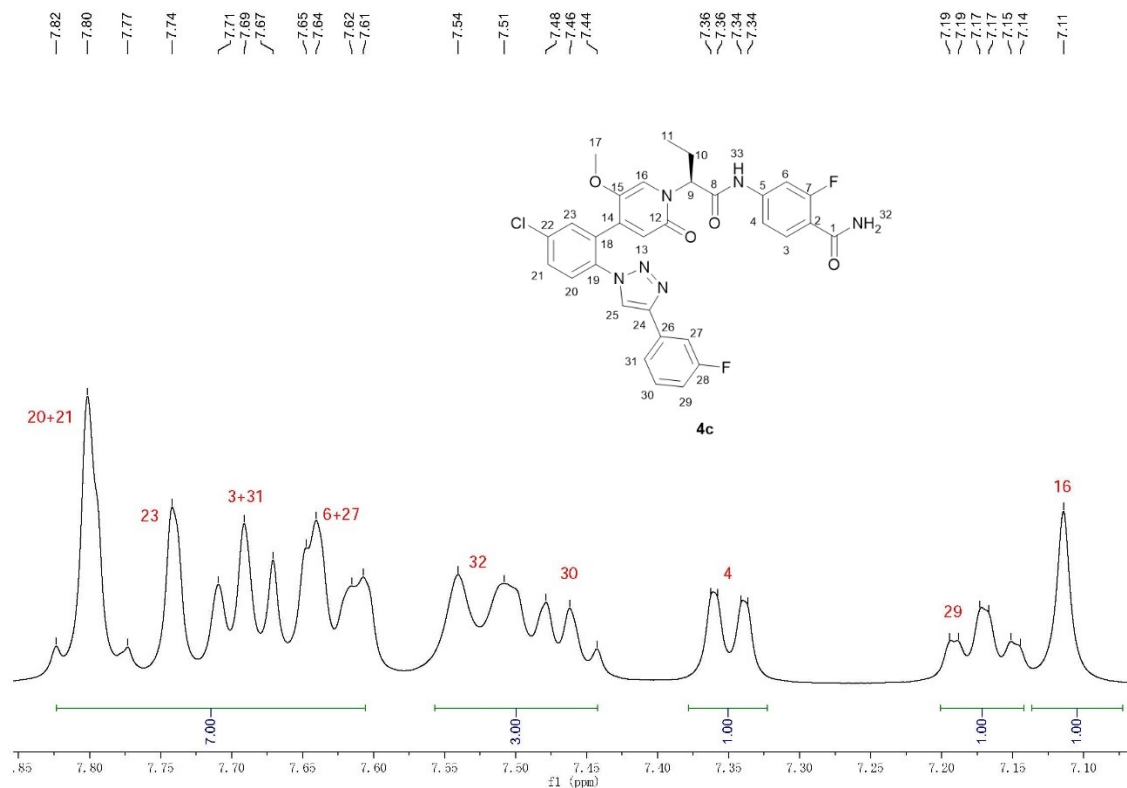
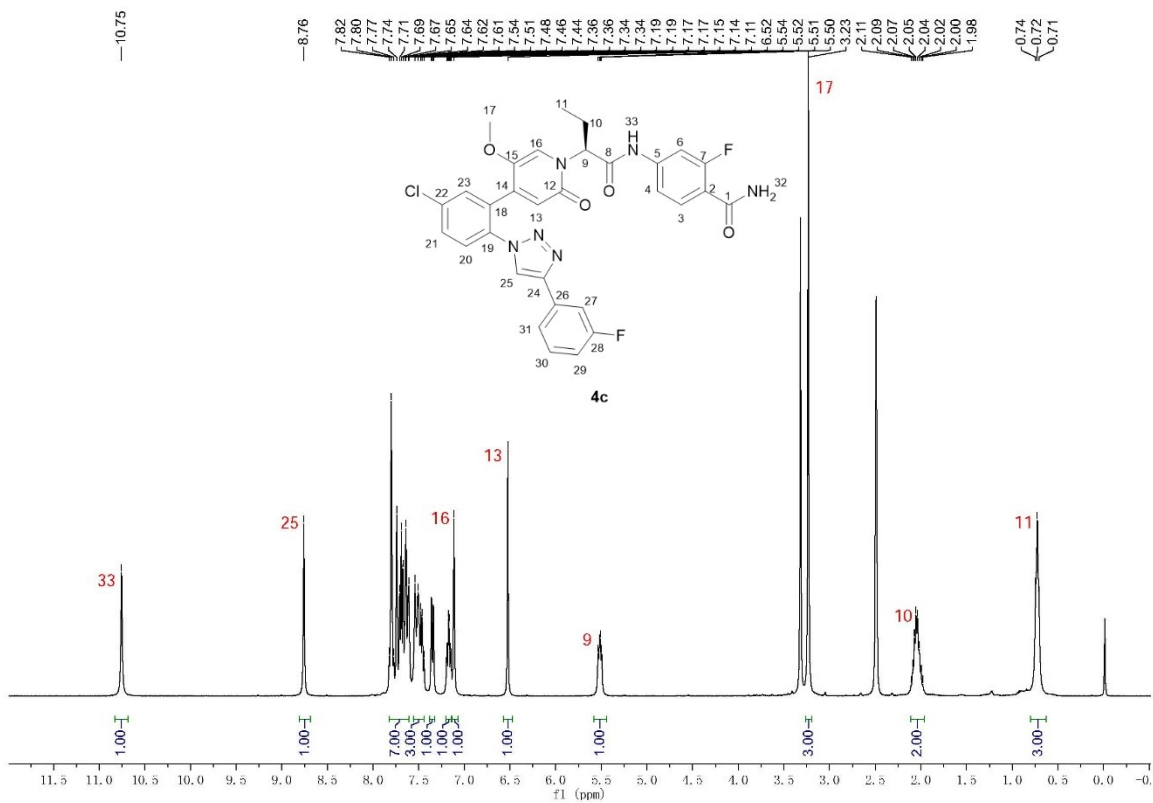
NMR spectrum of 4a



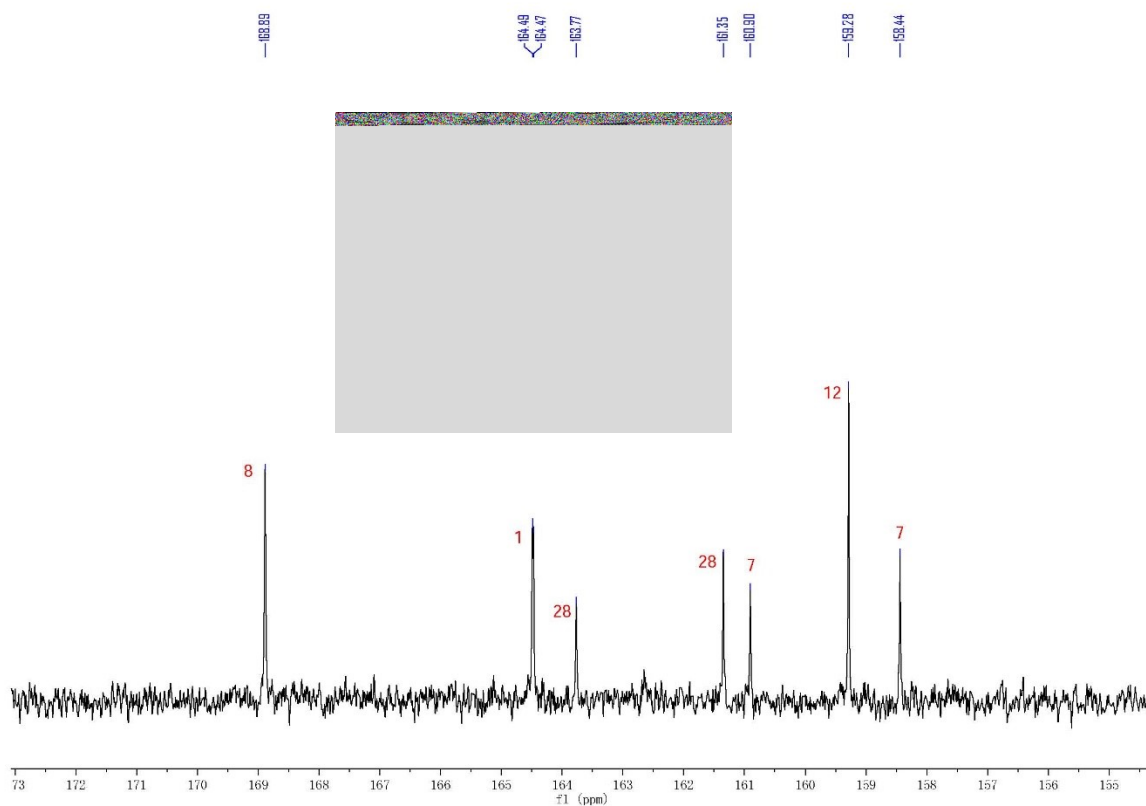
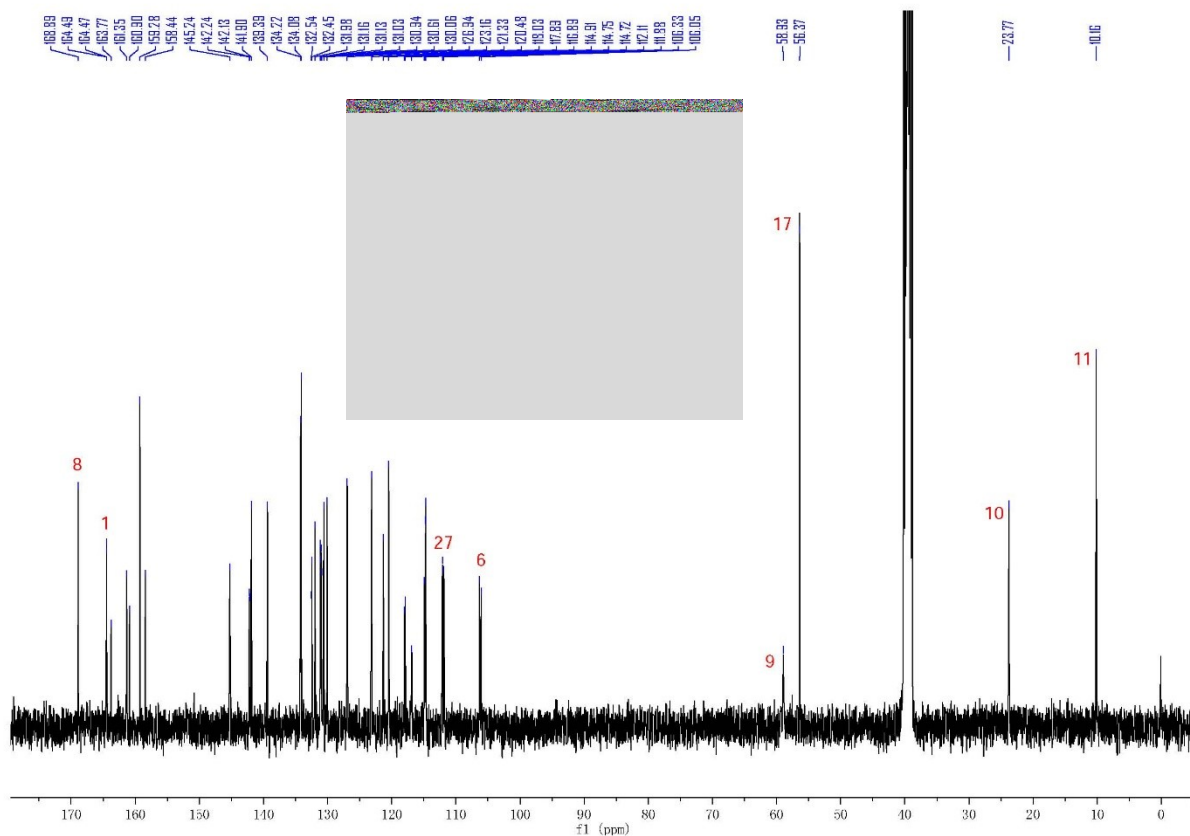
NMR spectrum of 4b

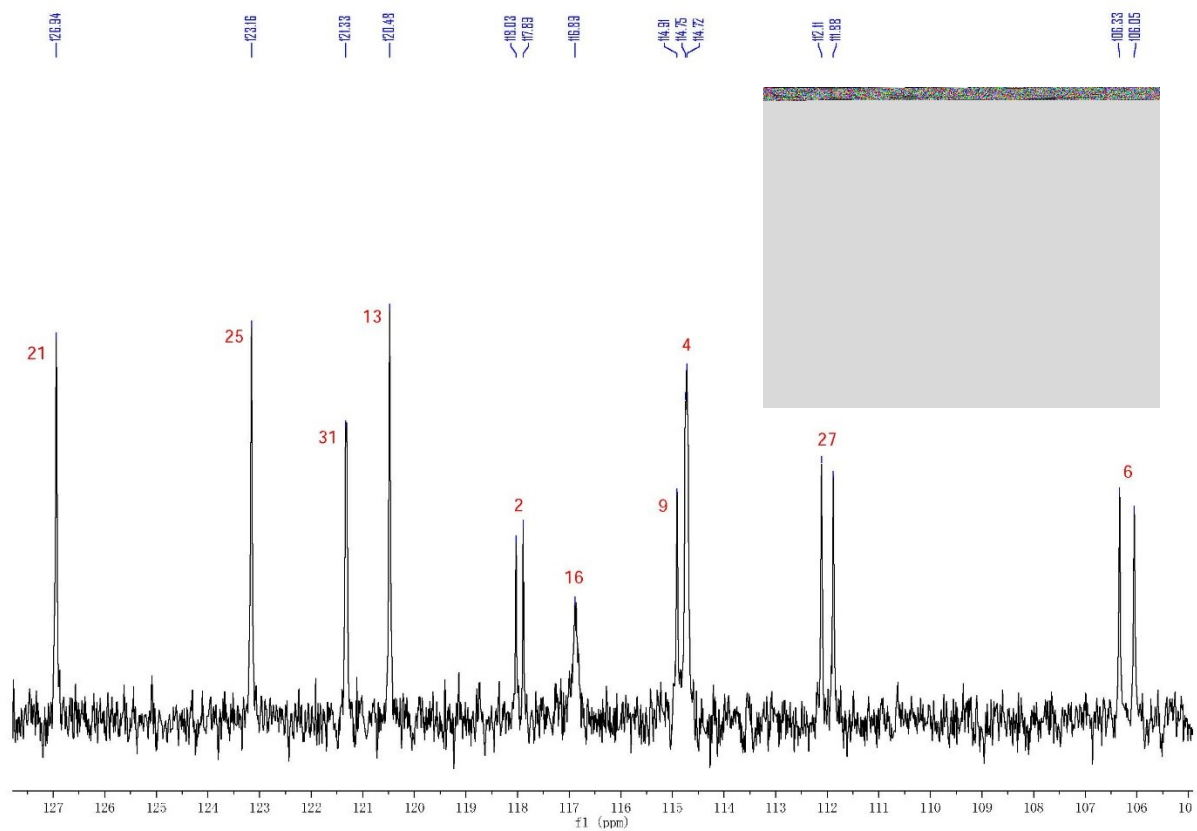
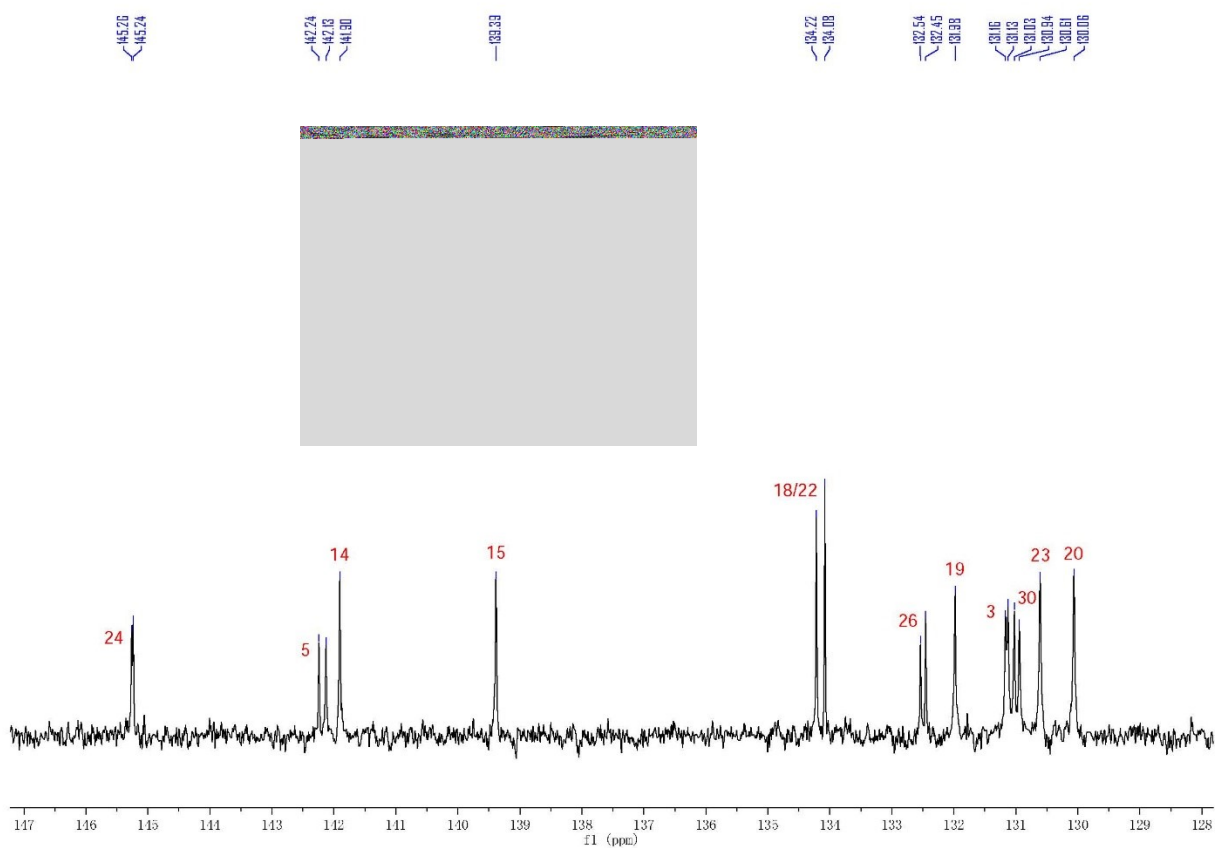


¹H-NMR spectrum of 4c

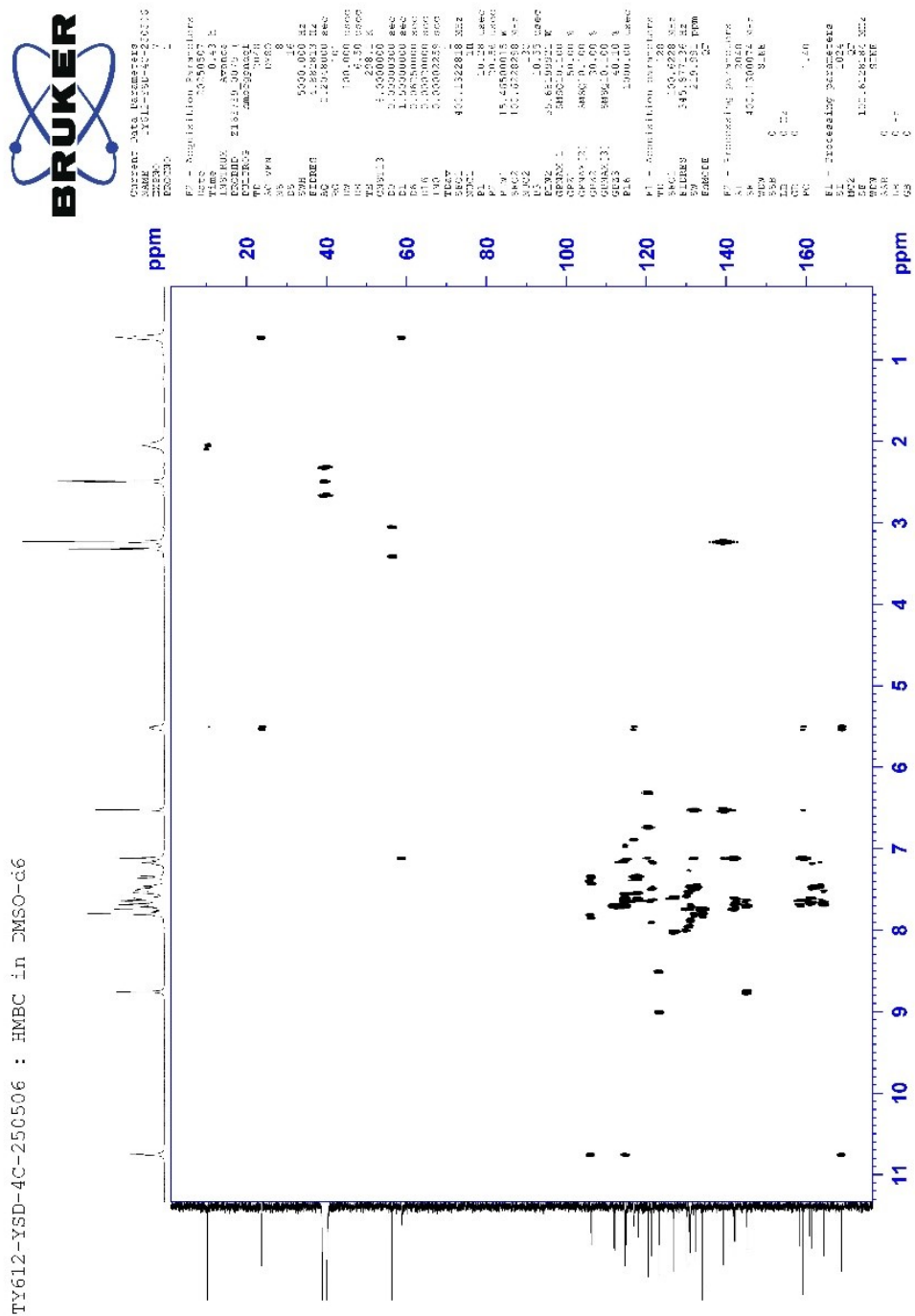


^{13}C -NMR spectrum of 4c

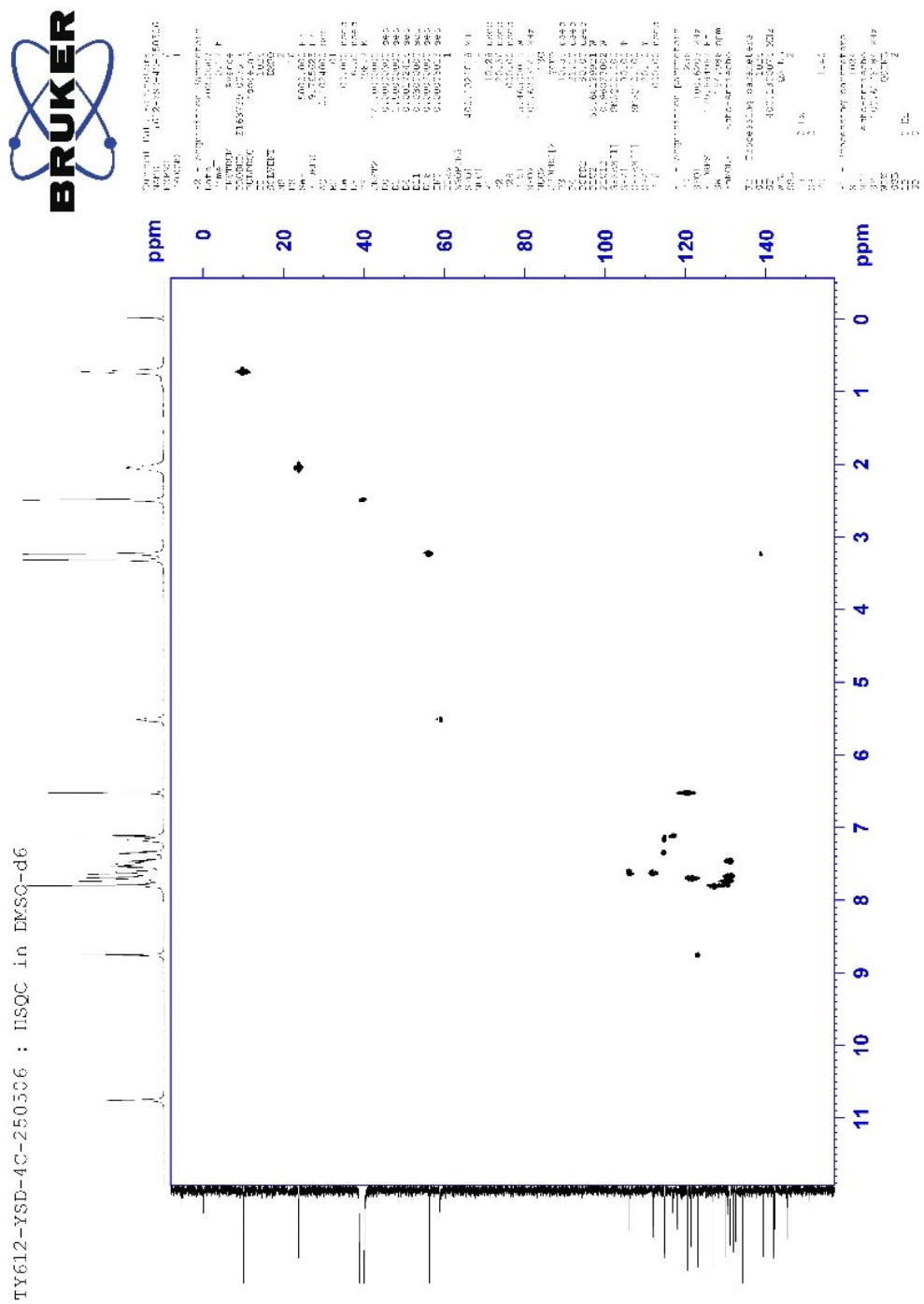




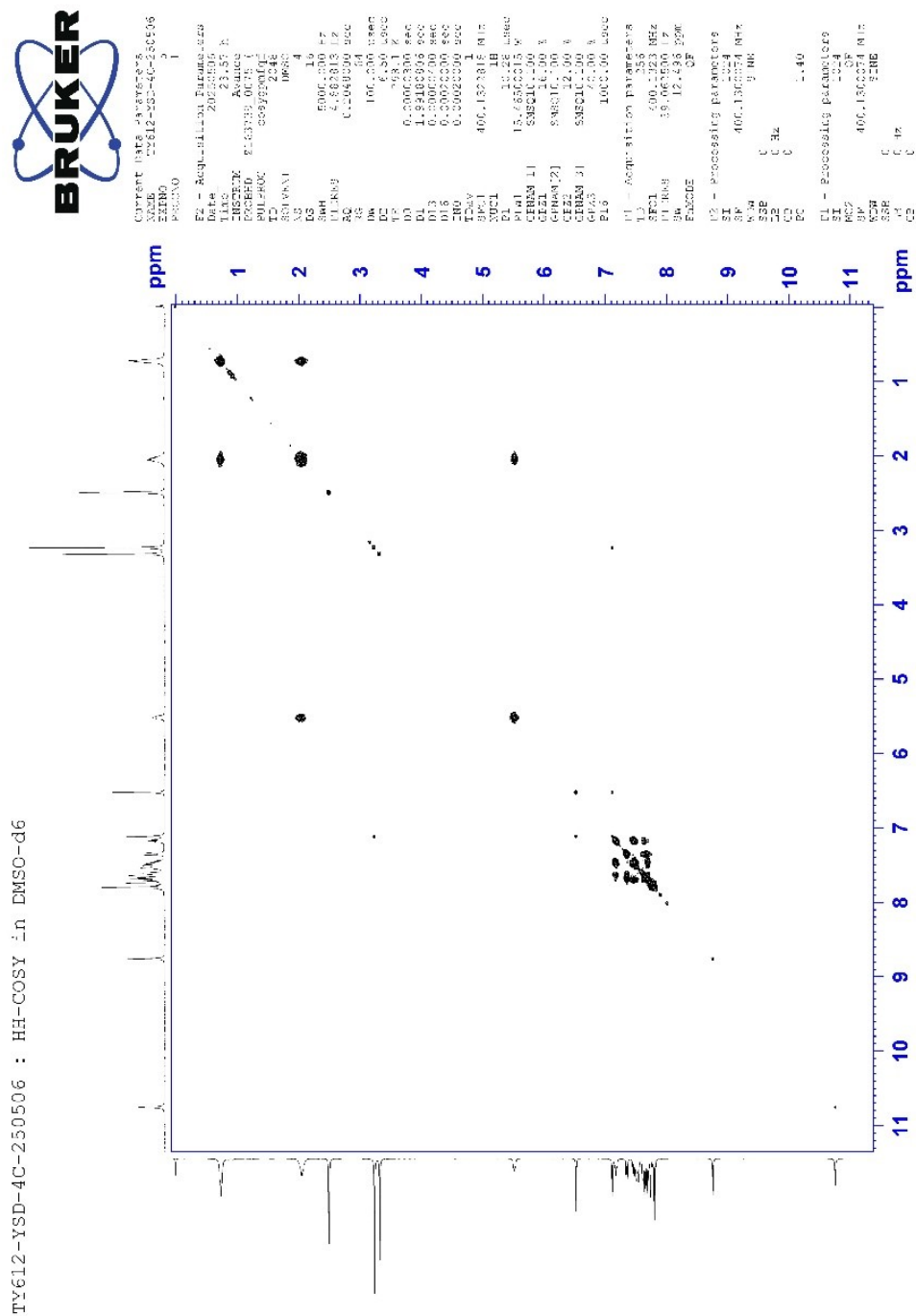
HMBC of 4c



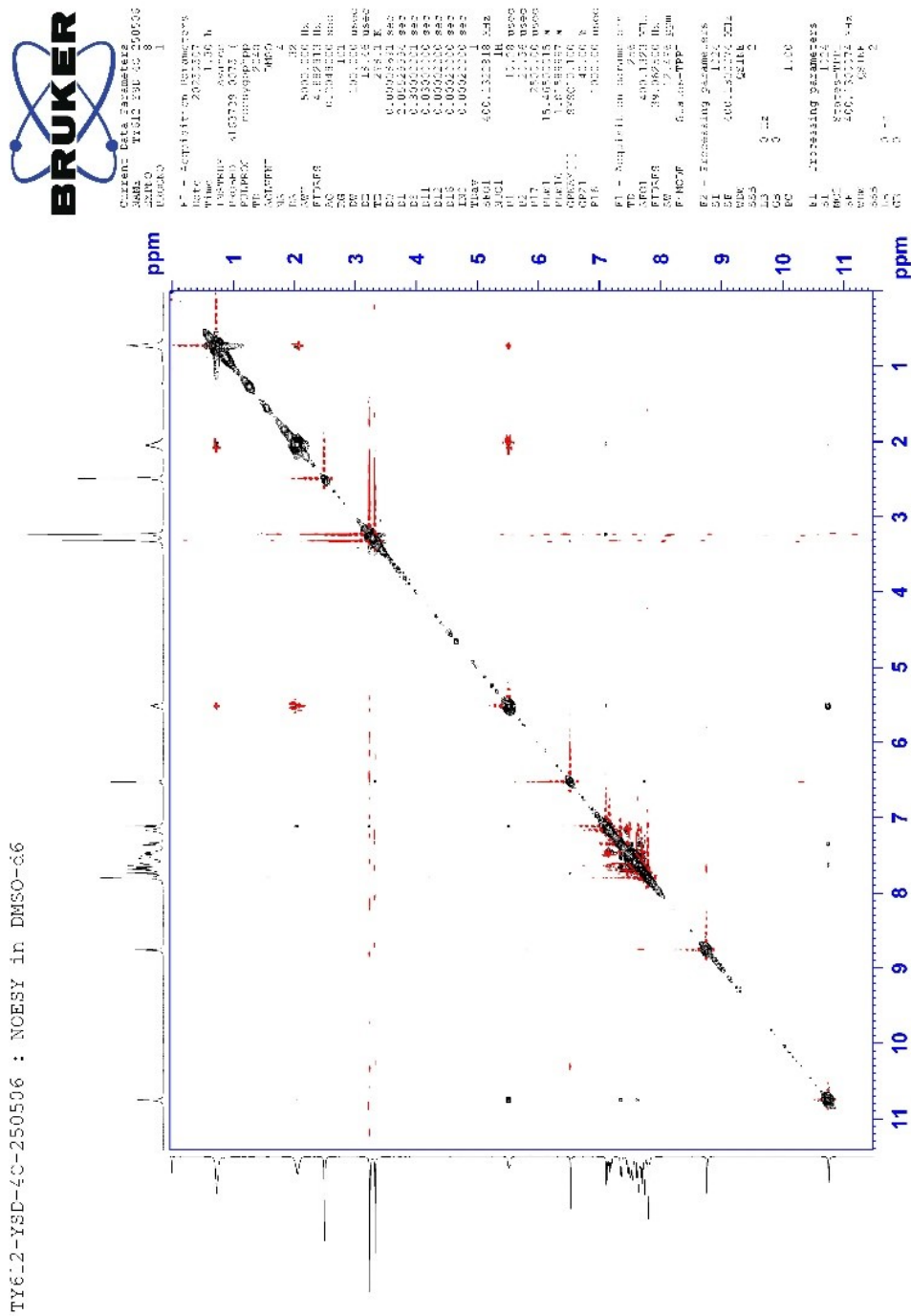
HSQC of 4c



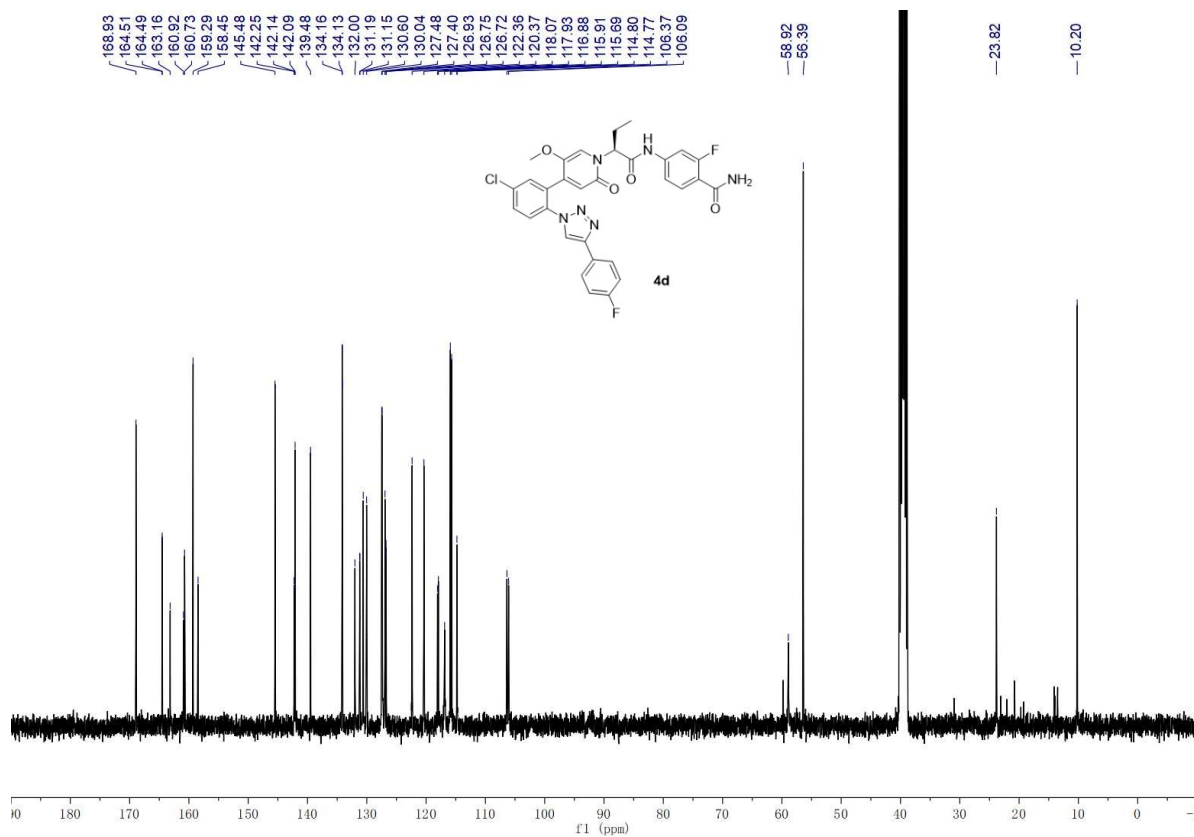
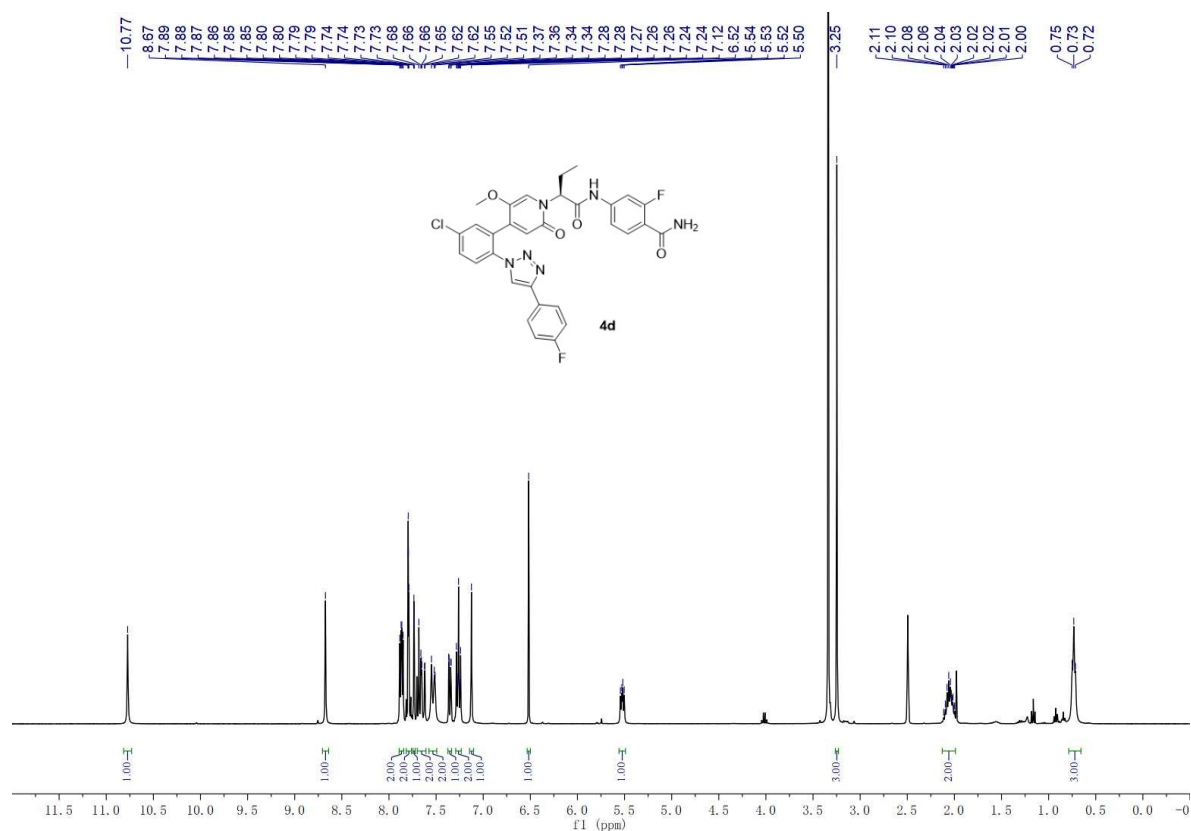
H-H COSY of 4c



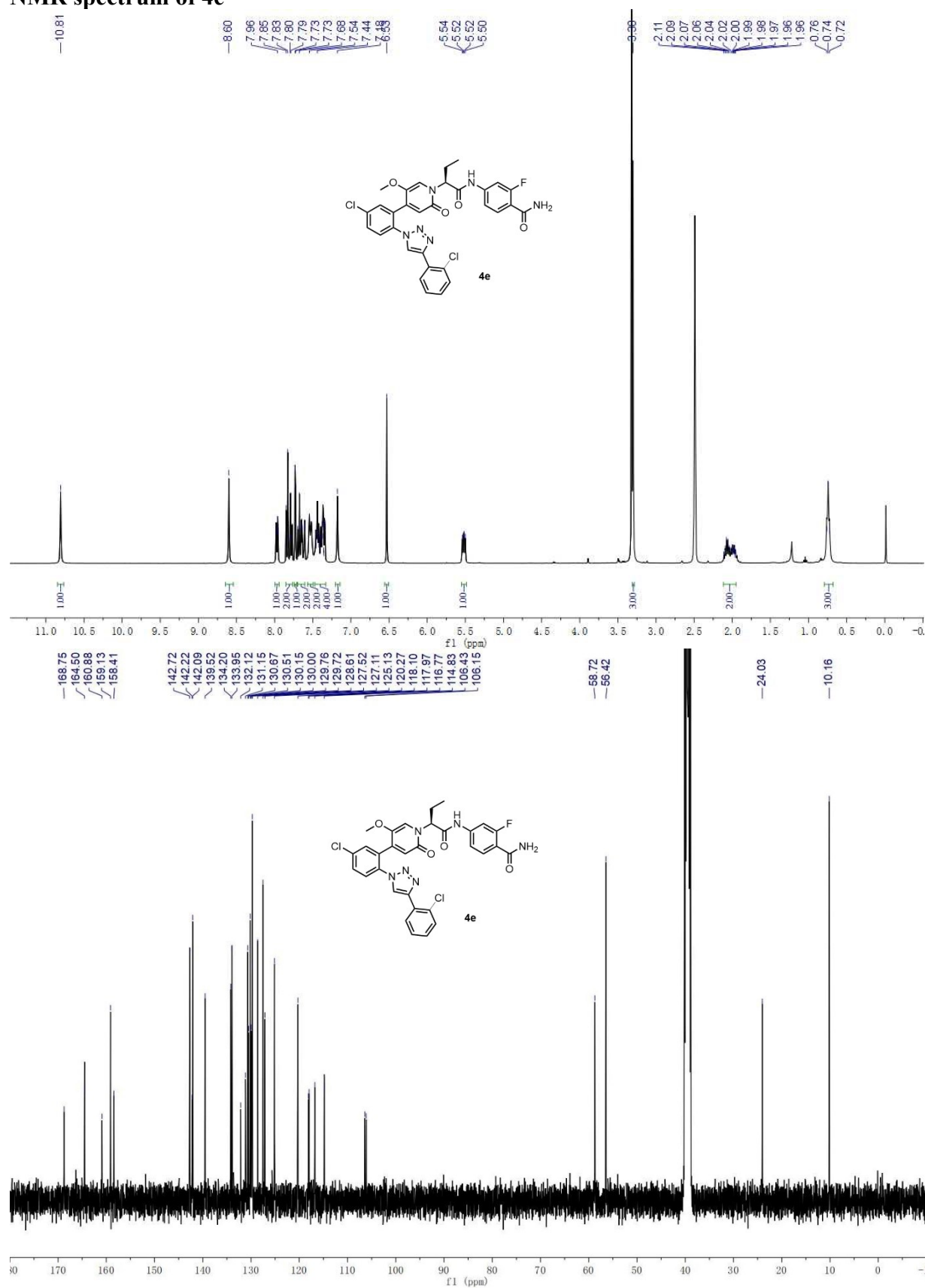
NOESY of 4c



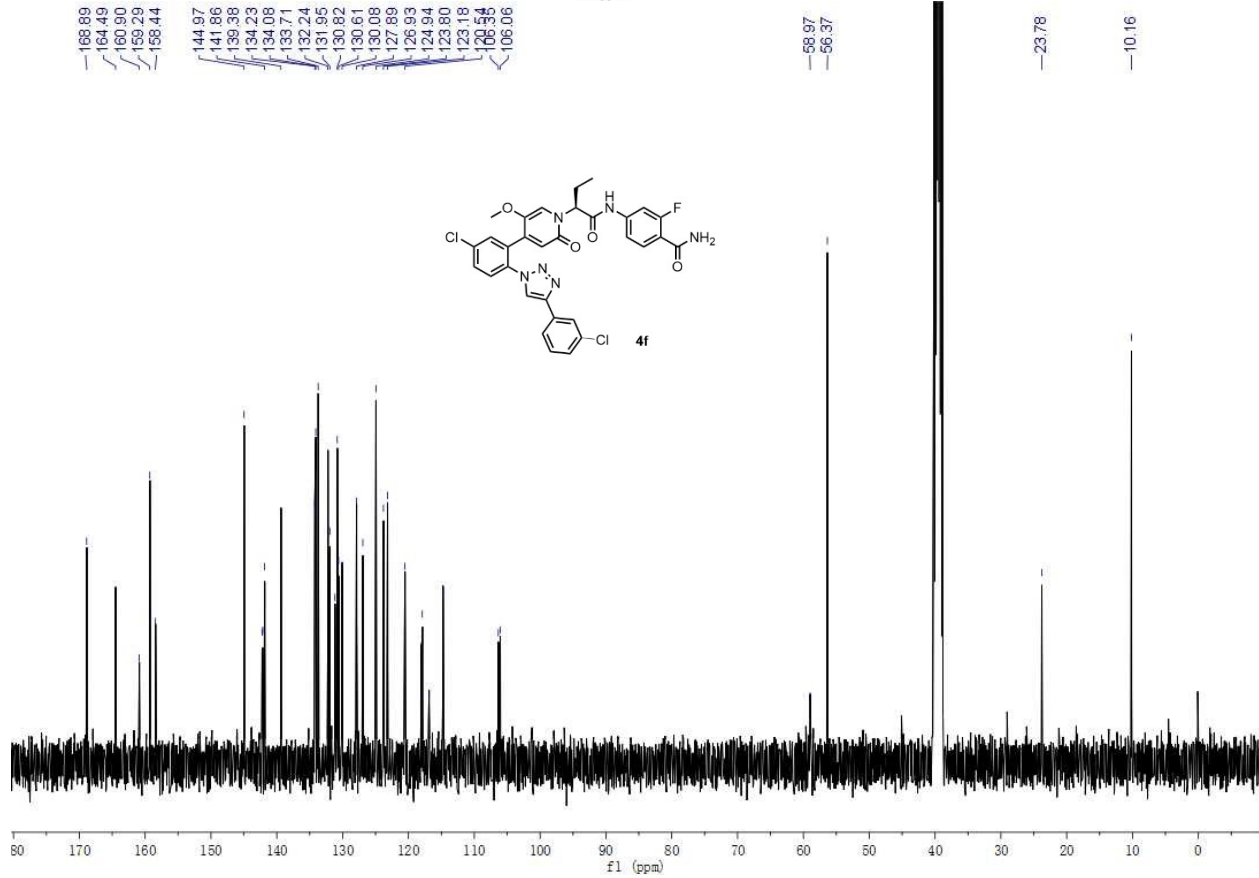
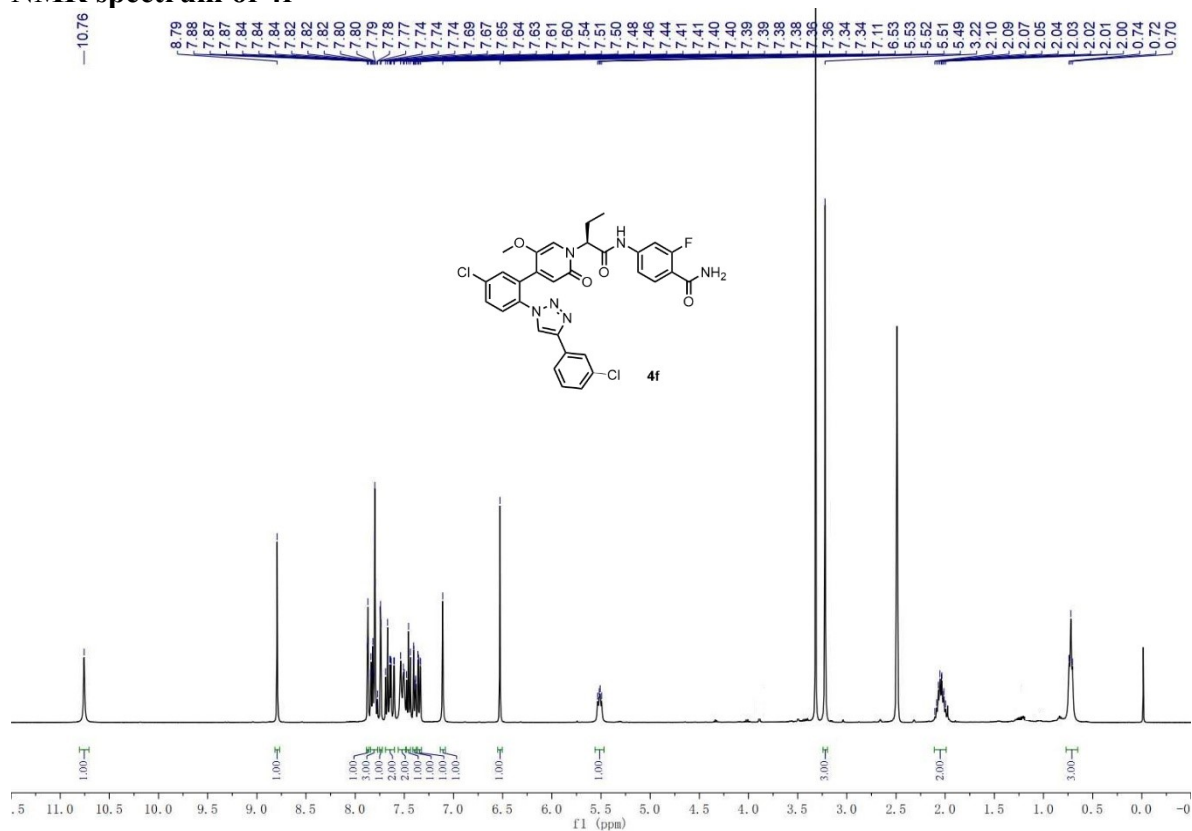
NMR spectrum of 4d



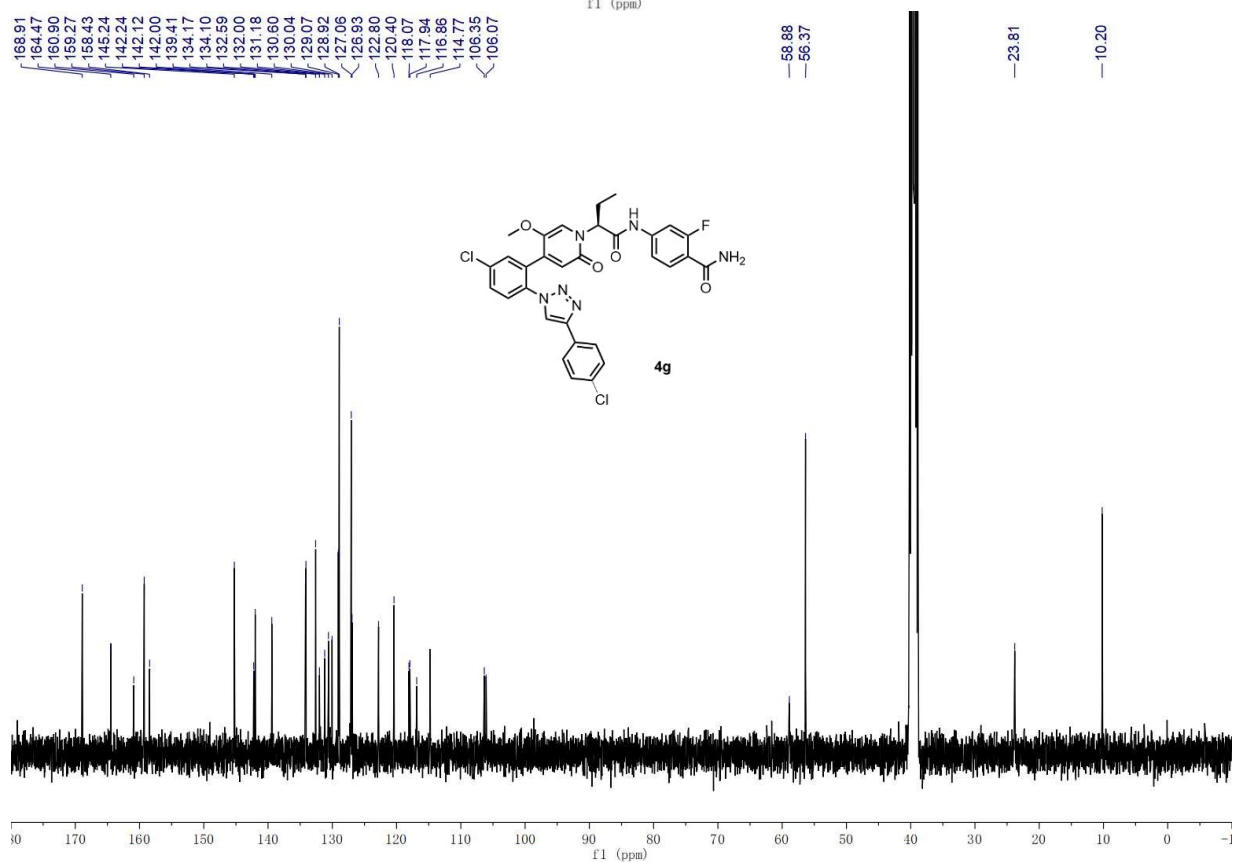
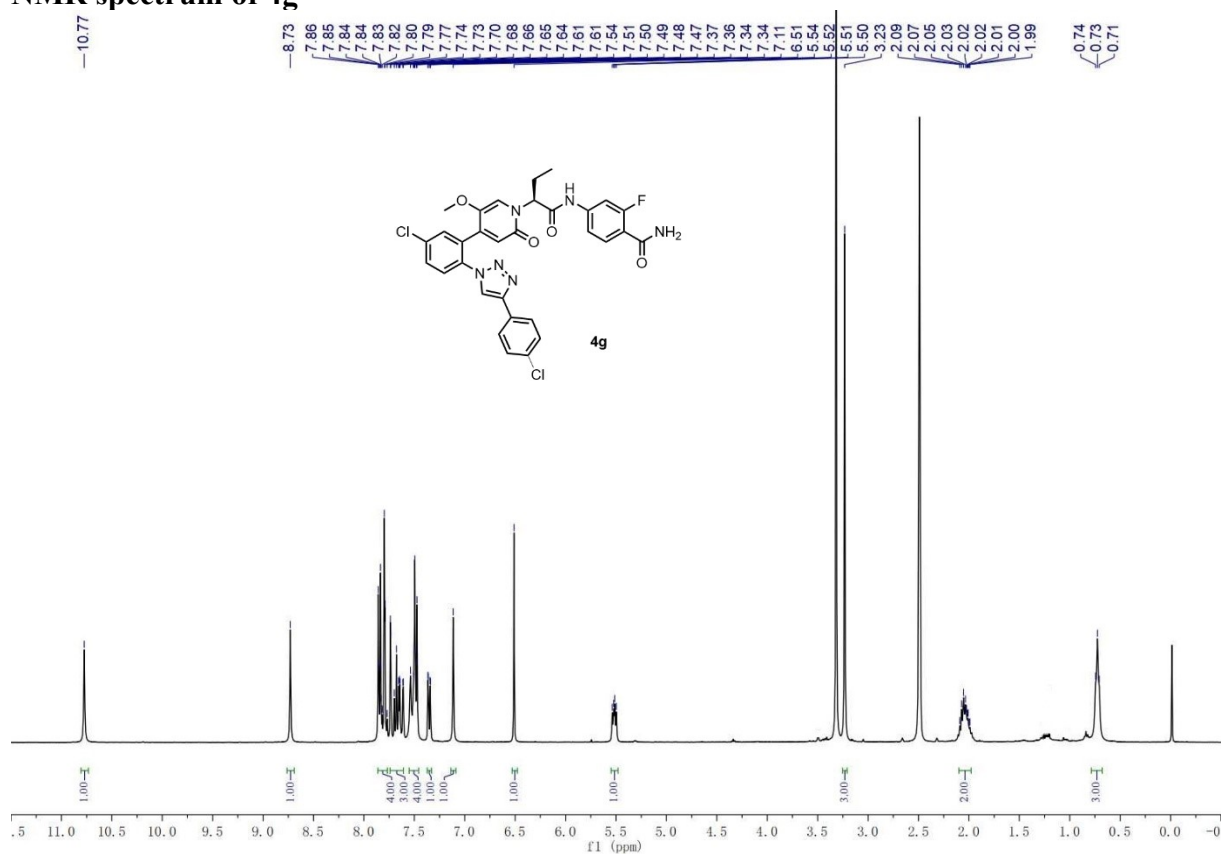
NMR spectrum of 4e



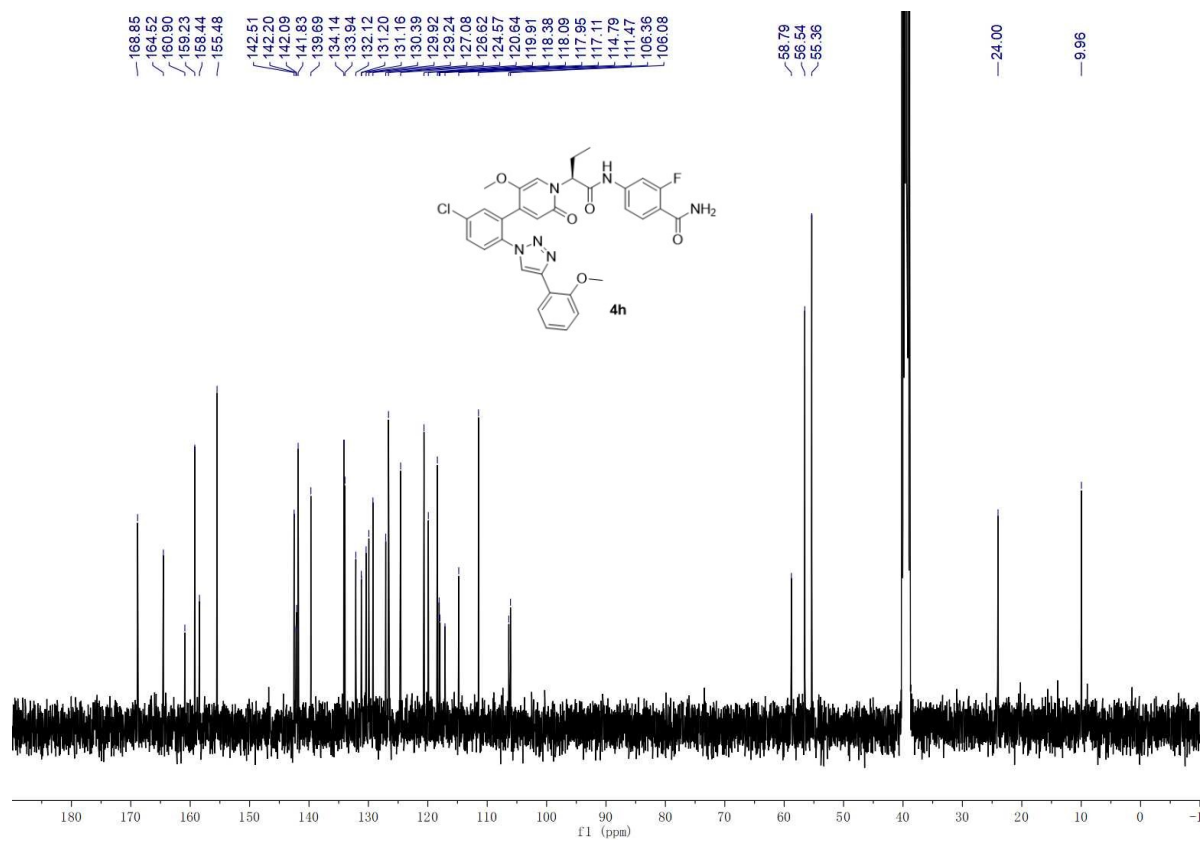
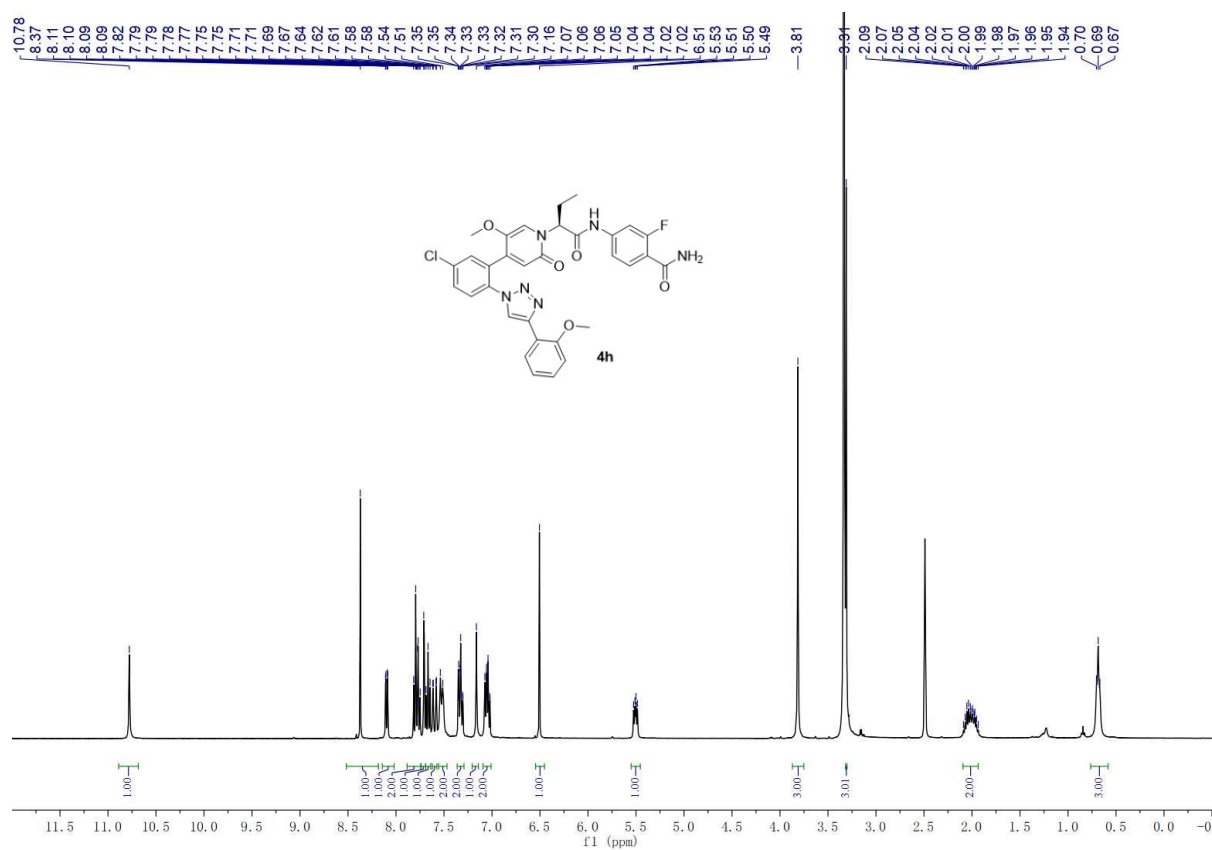
NMR spectrum of 4f



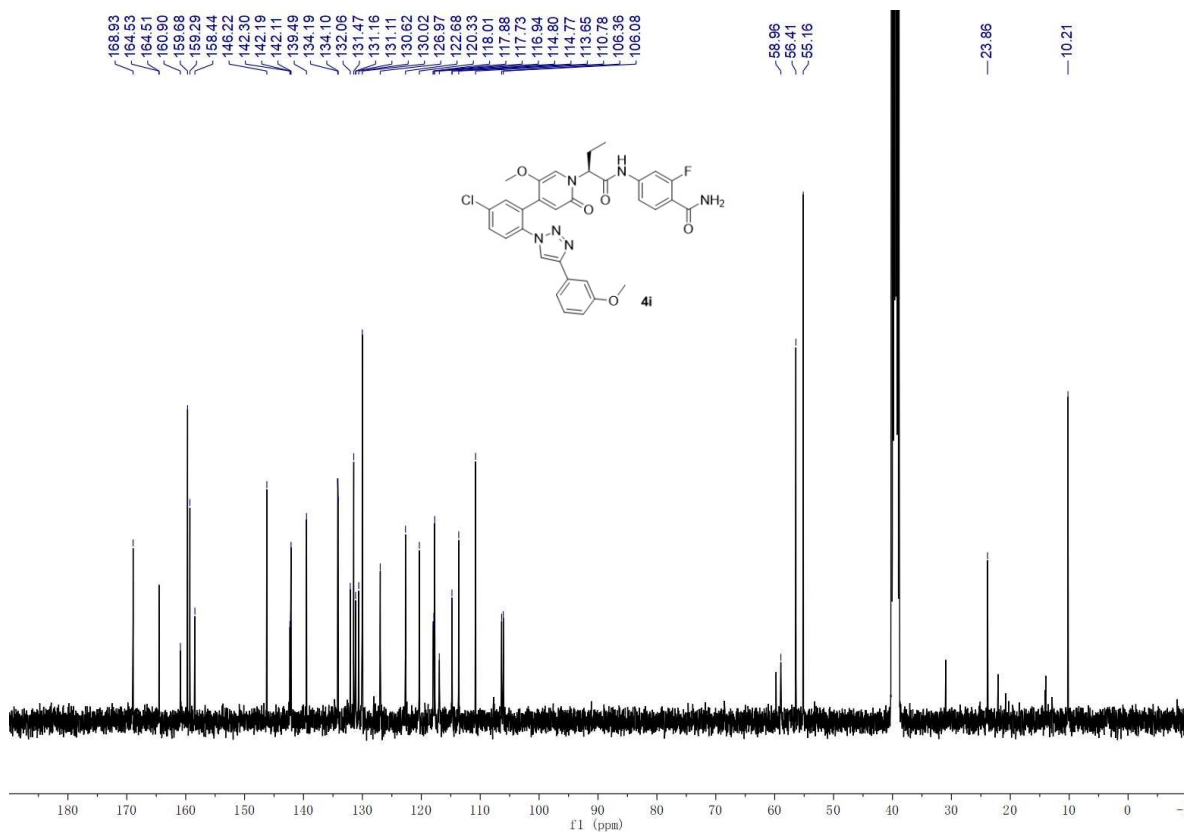
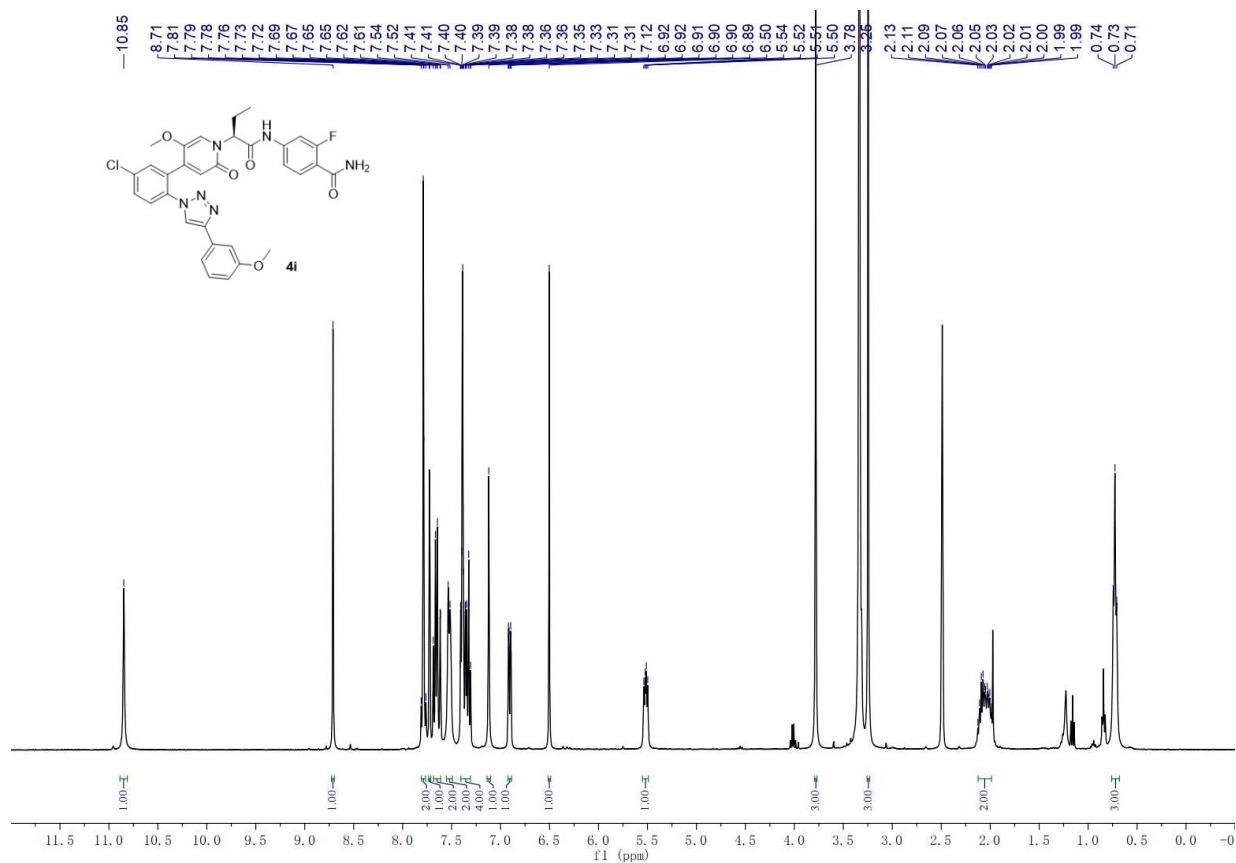
NMR spectrum of 4g



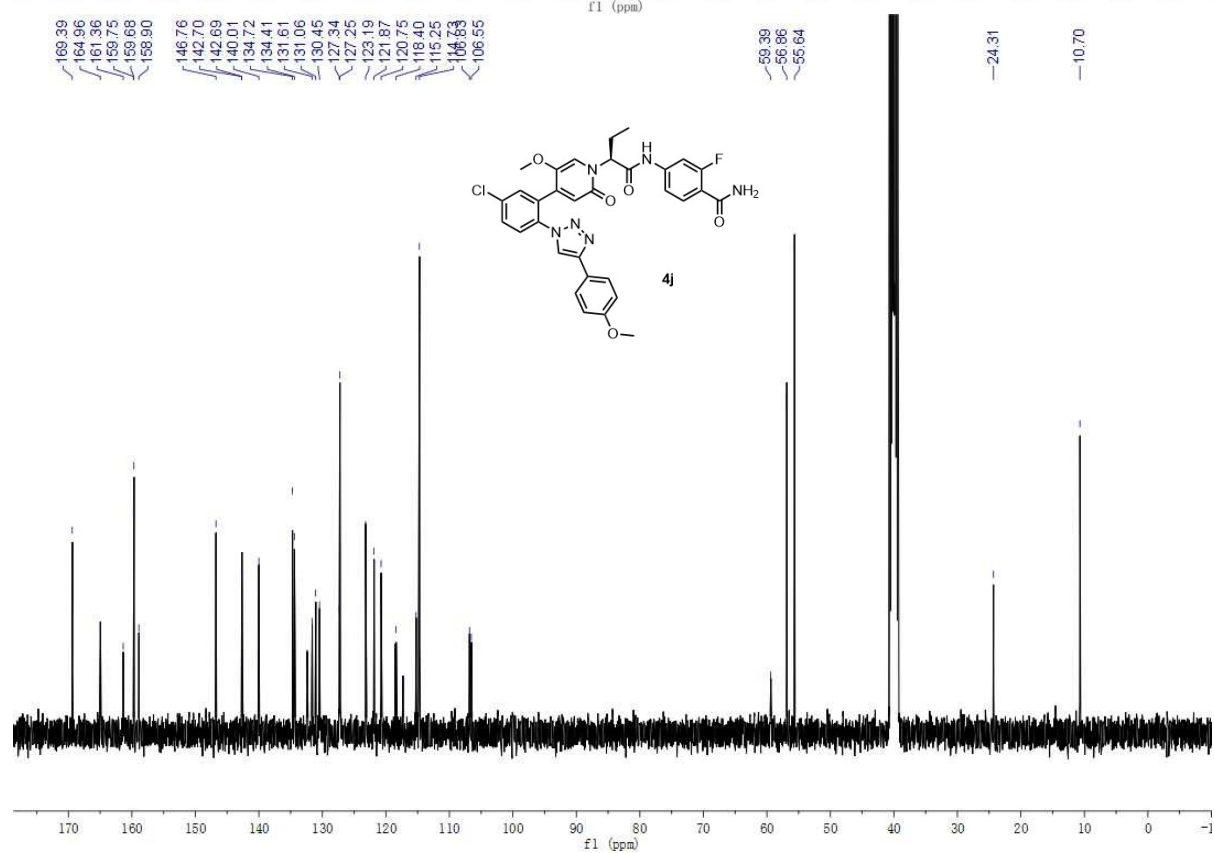
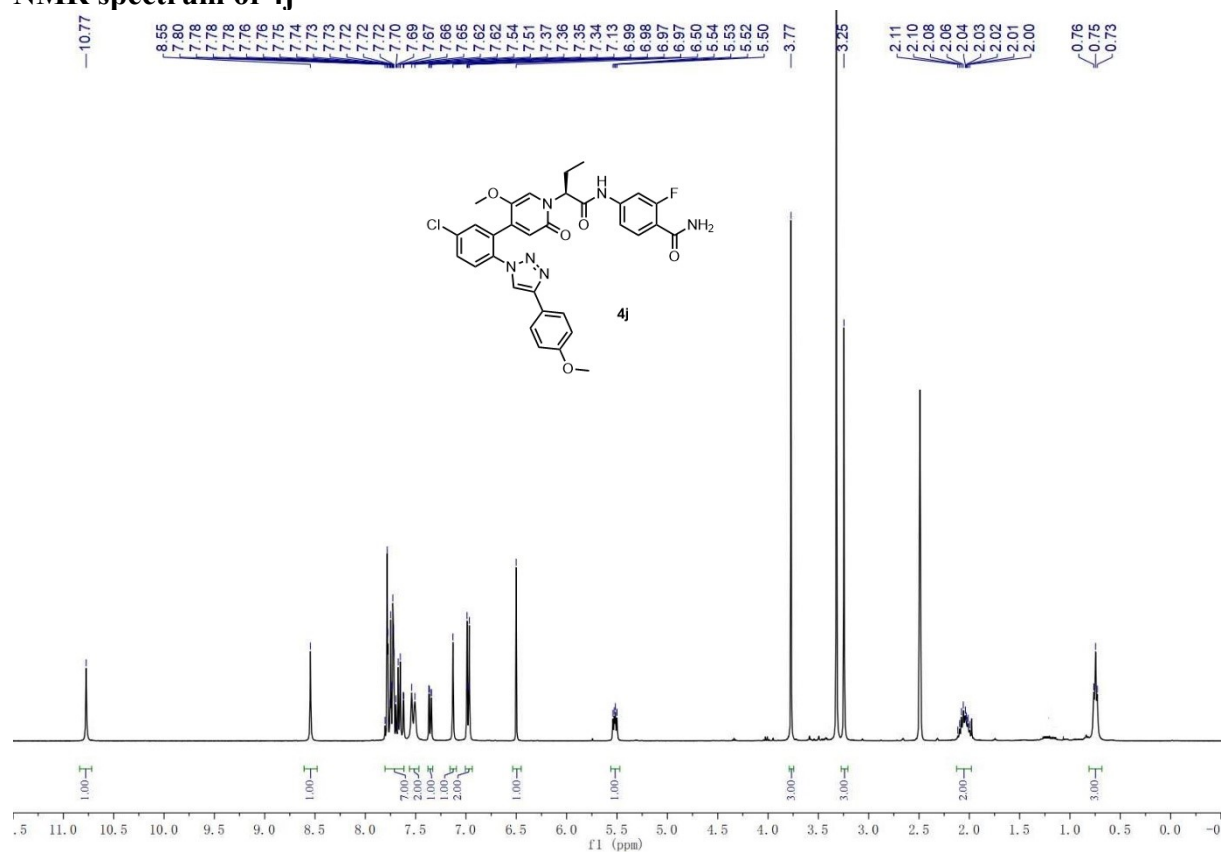
NMR spectrum of 4h



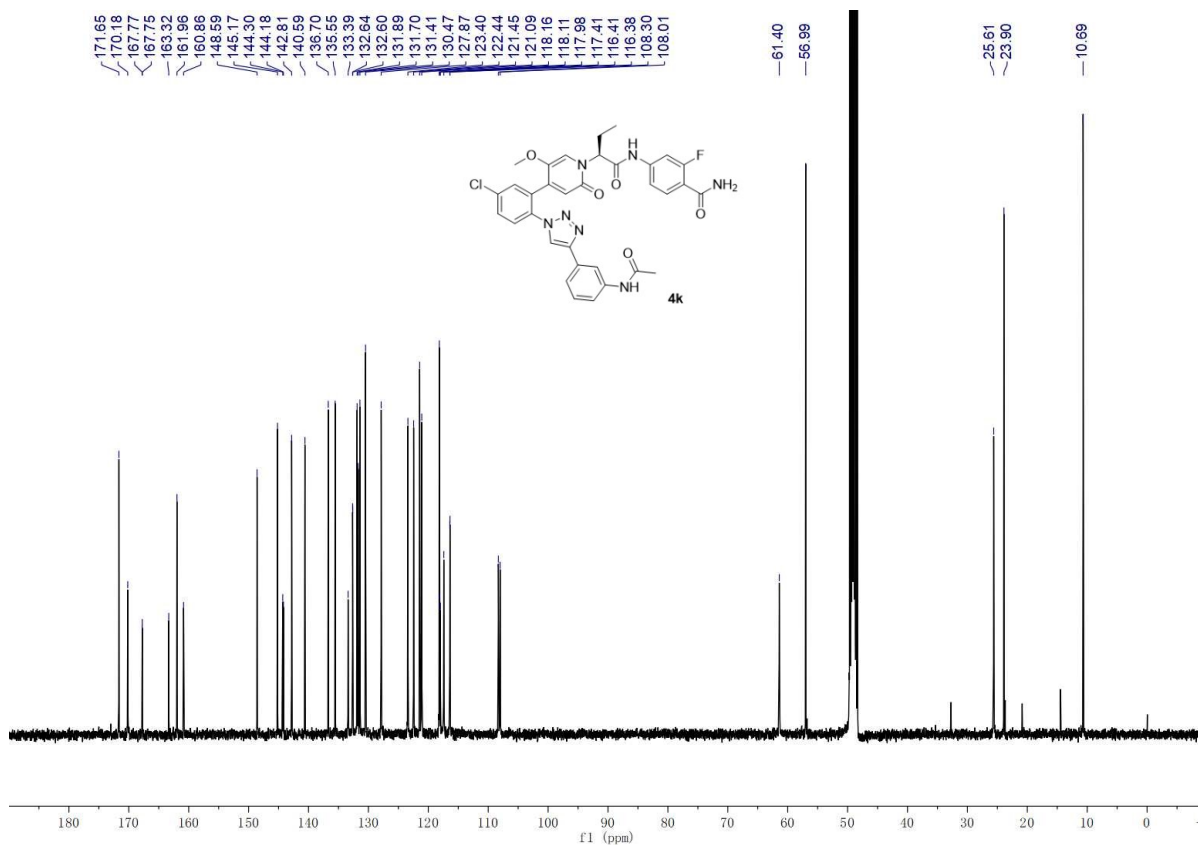
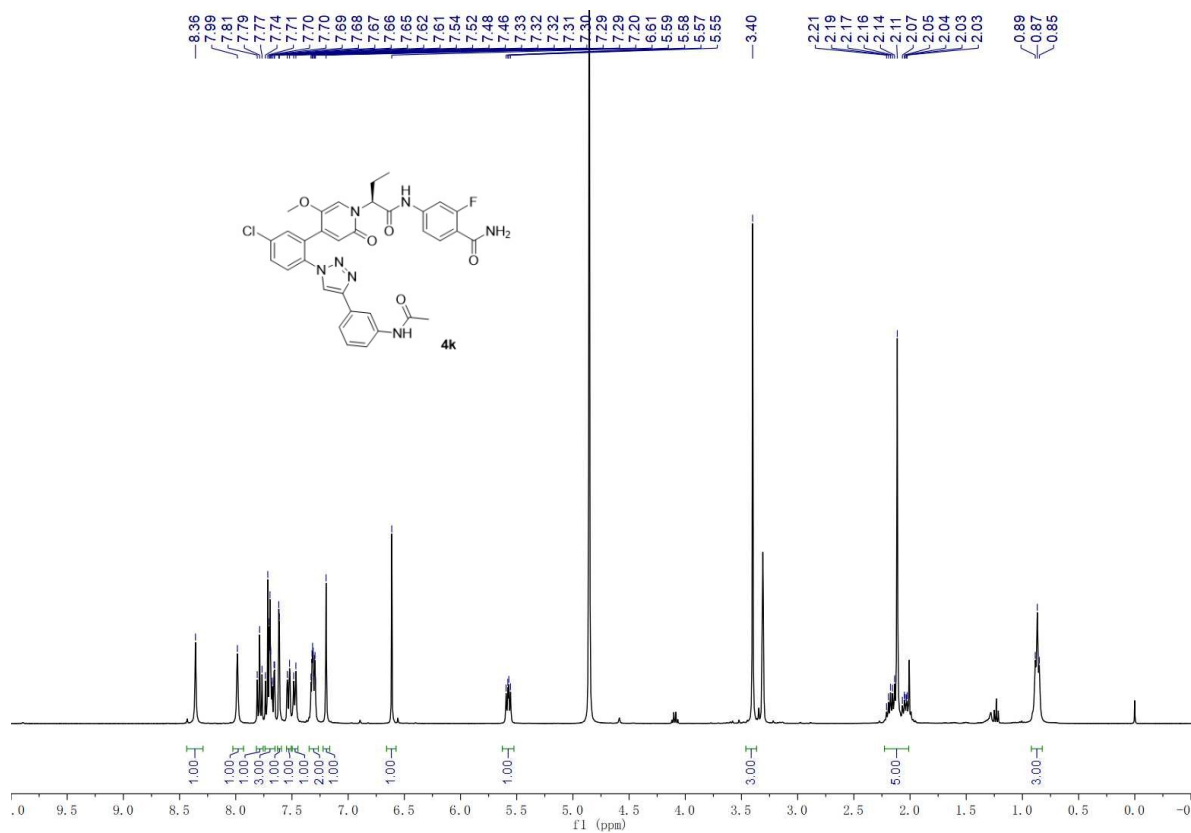
NMR spectrum of 4i



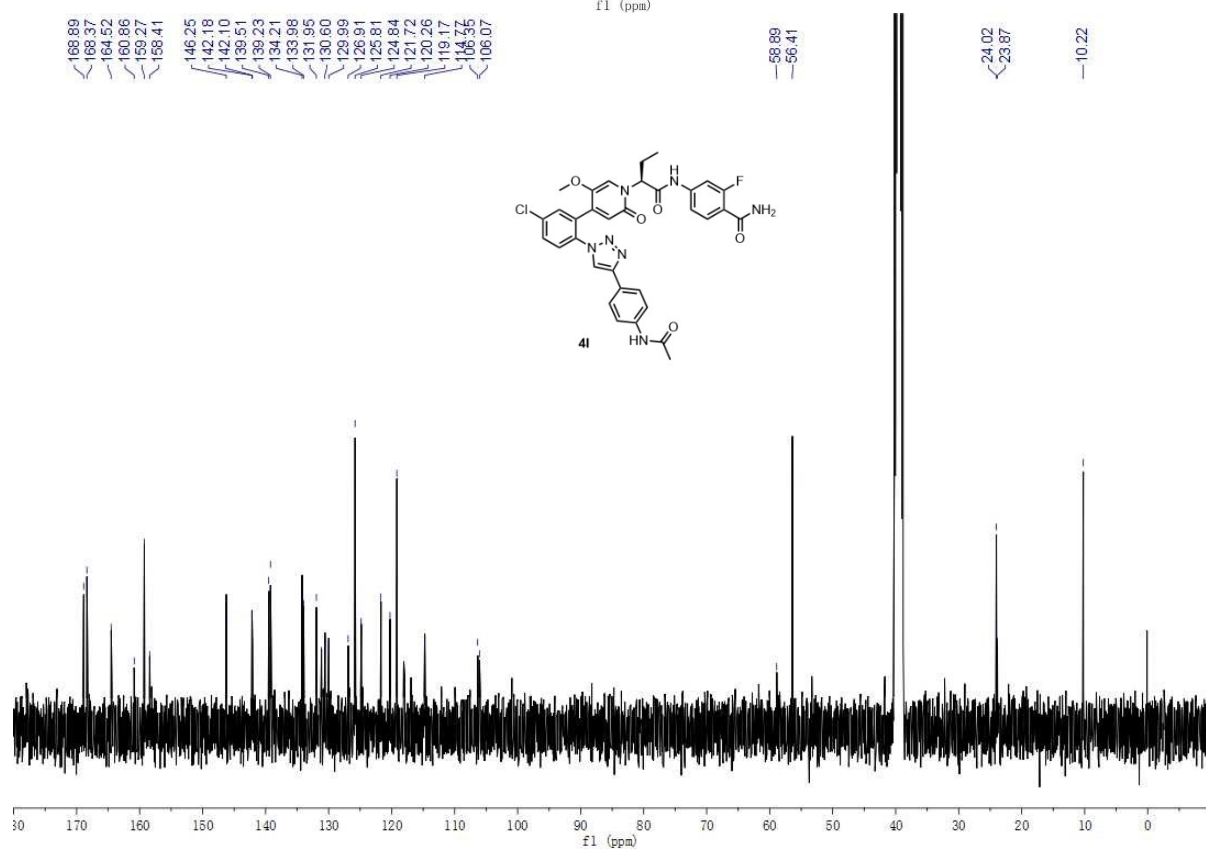
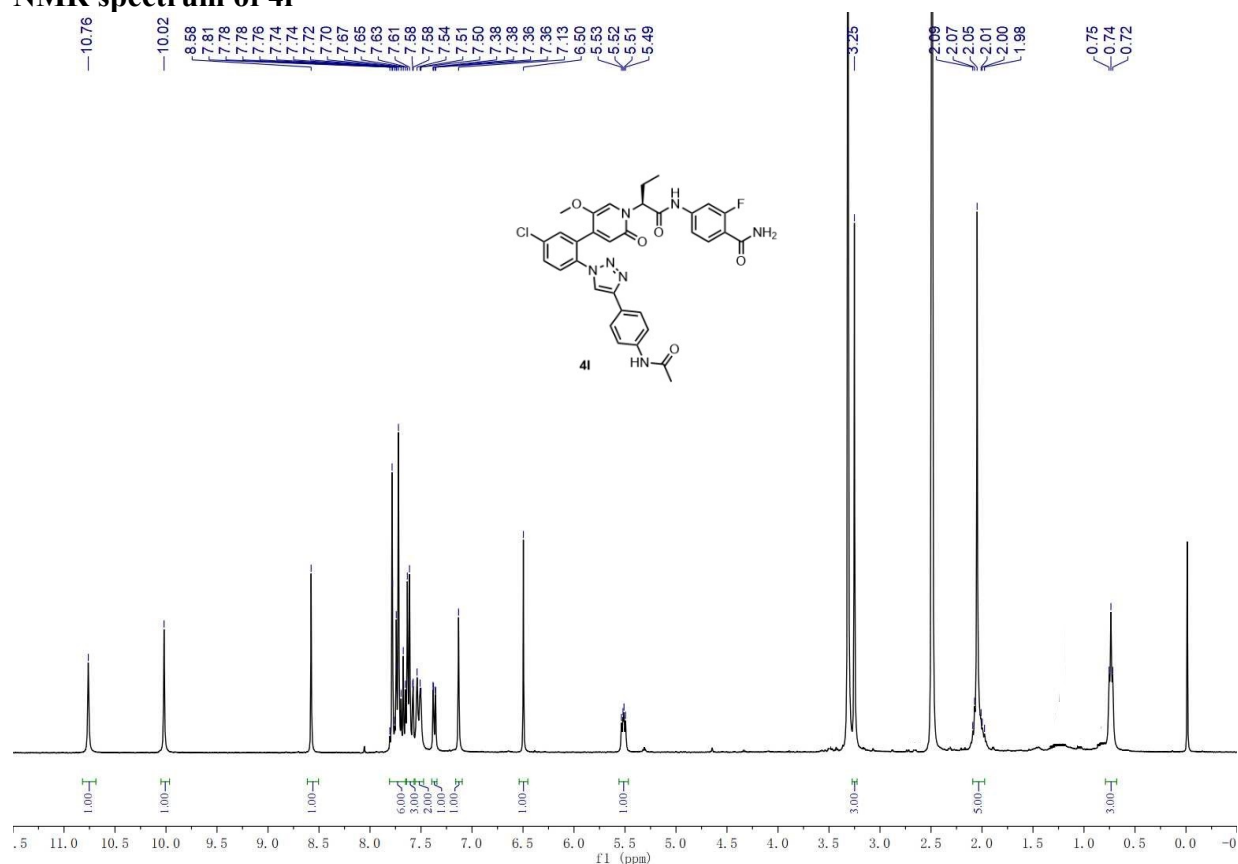
NMR spectrum of 4j



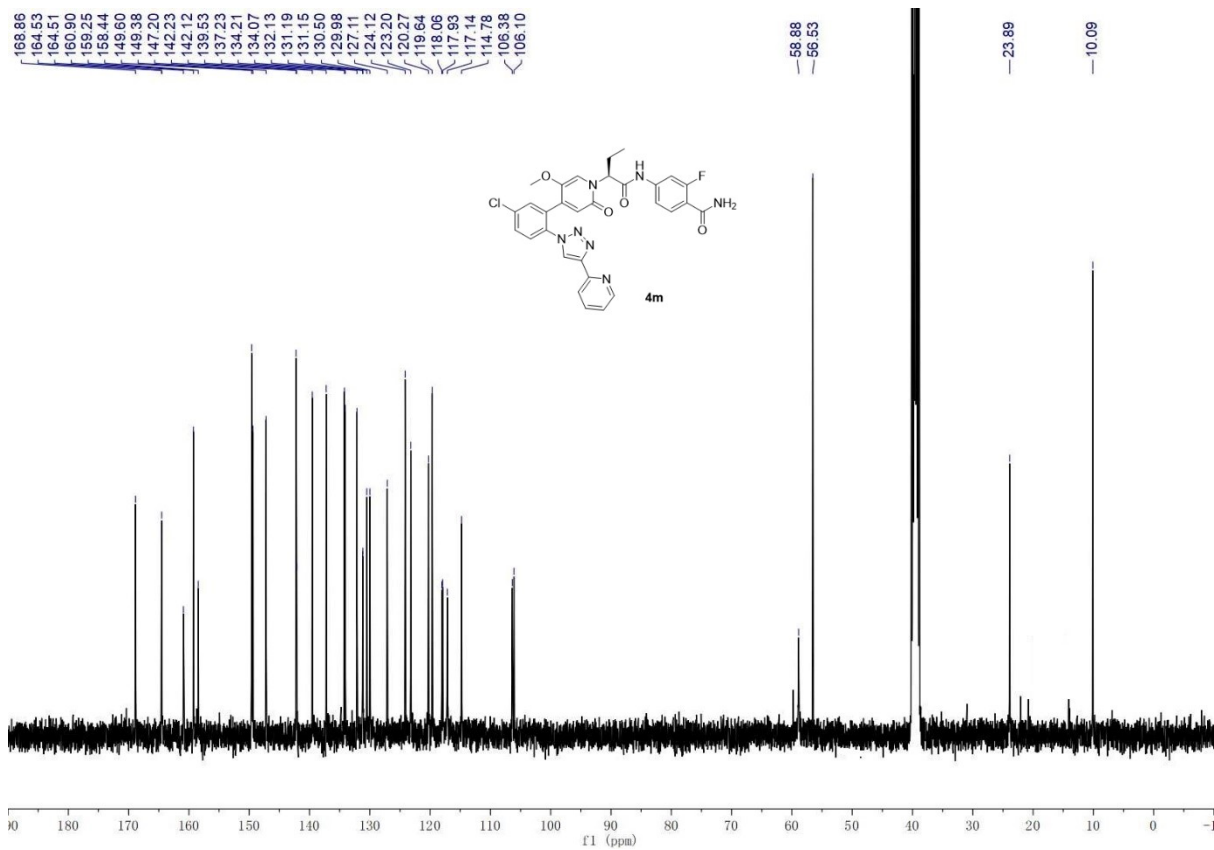
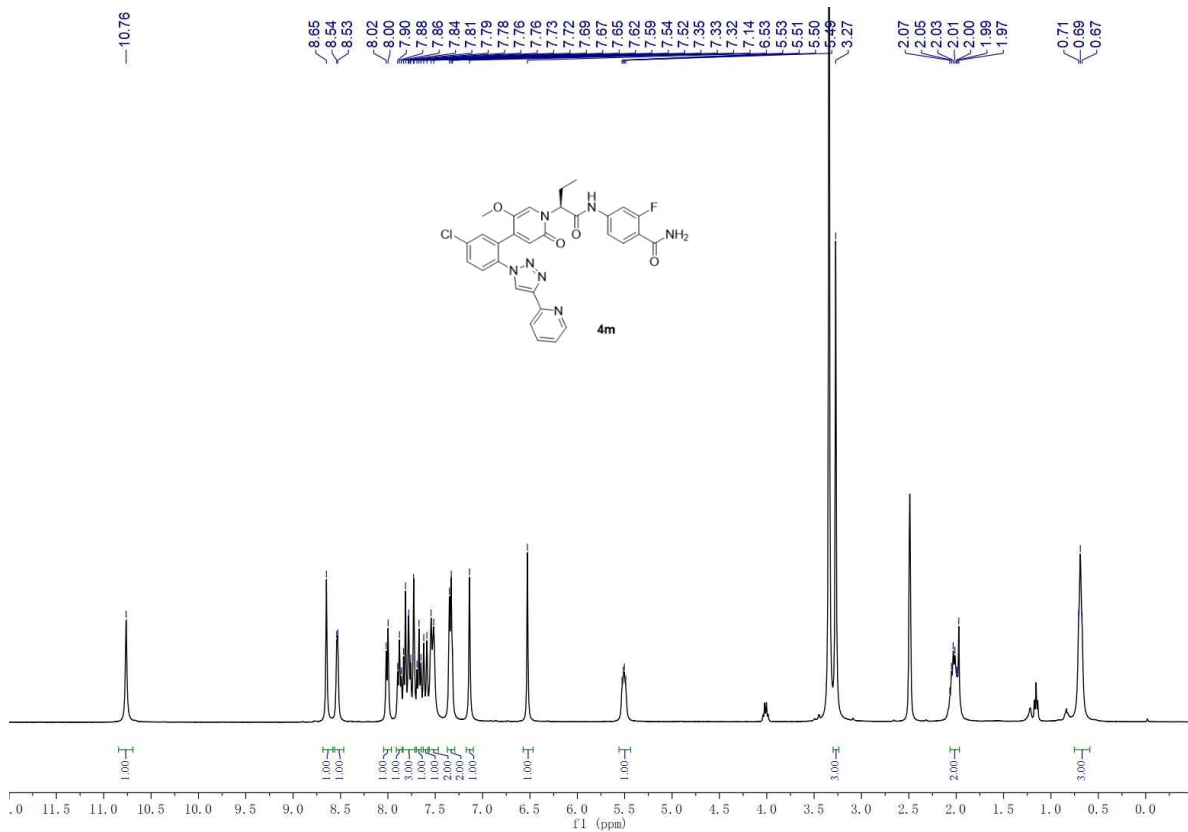
NMR spectrum of 4k



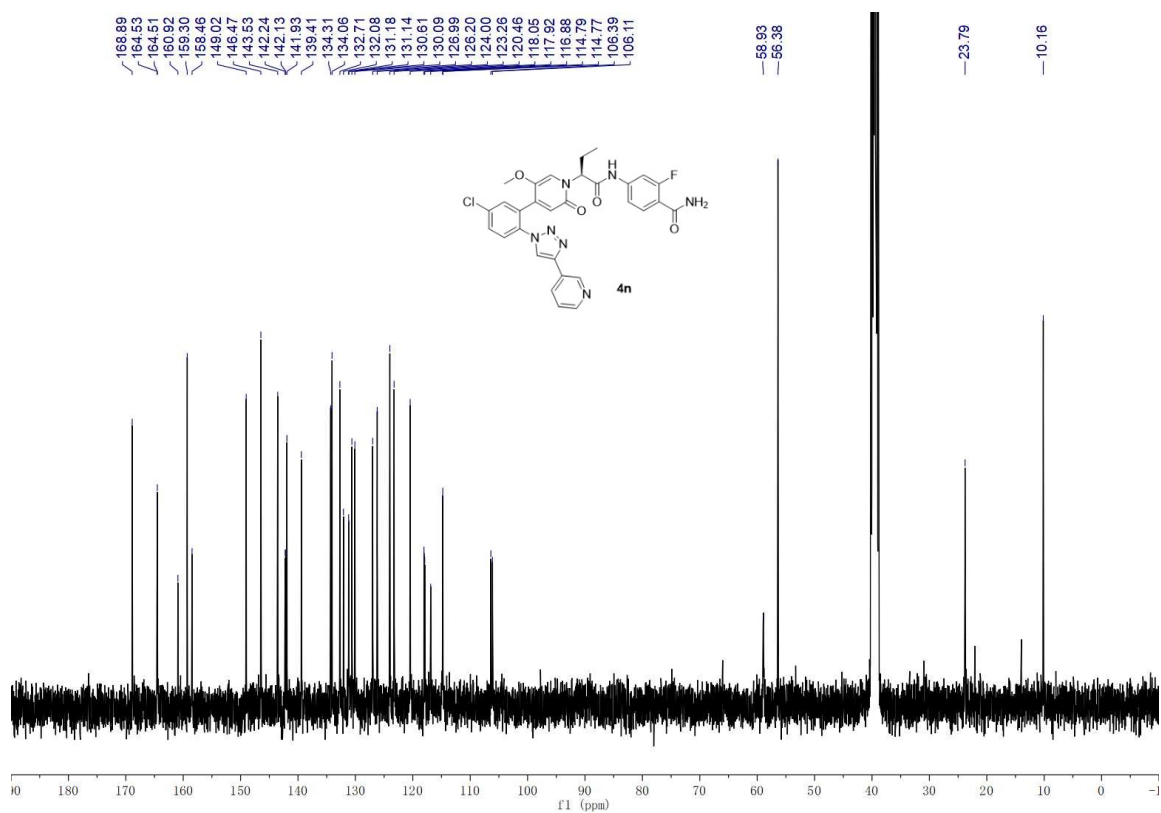
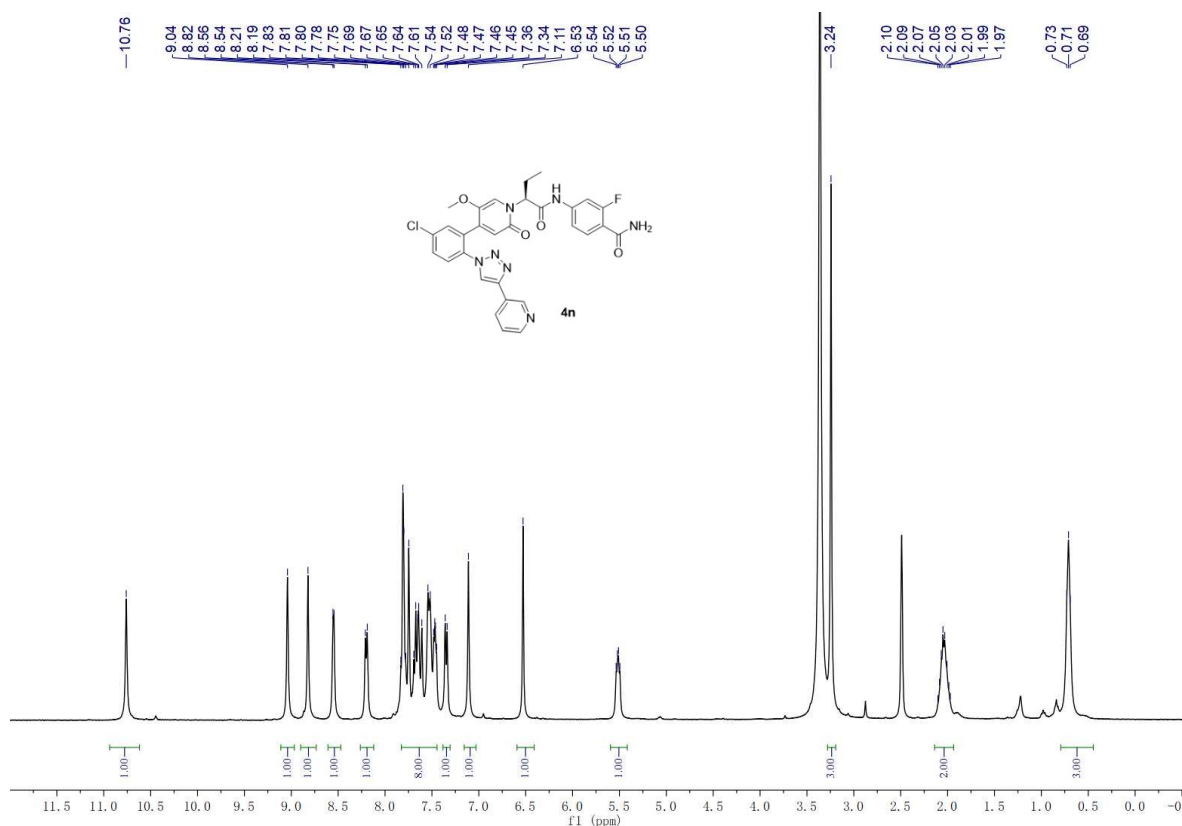
NMR spectrum of 4l



NMR spectrum of 4m



NMR spectrum of 4n



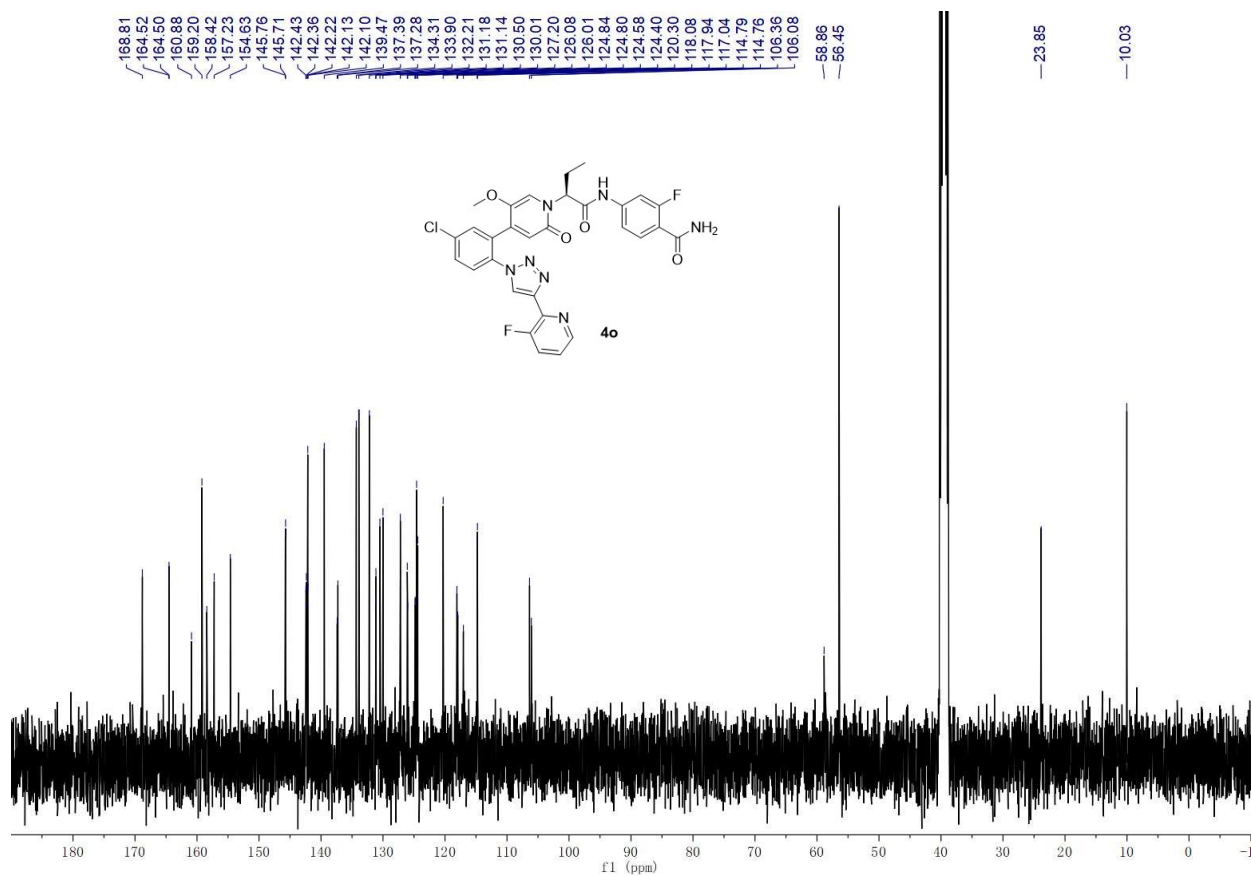
Spectrum of 4o

Chemical structure of **4o** is shown above the spectrum.

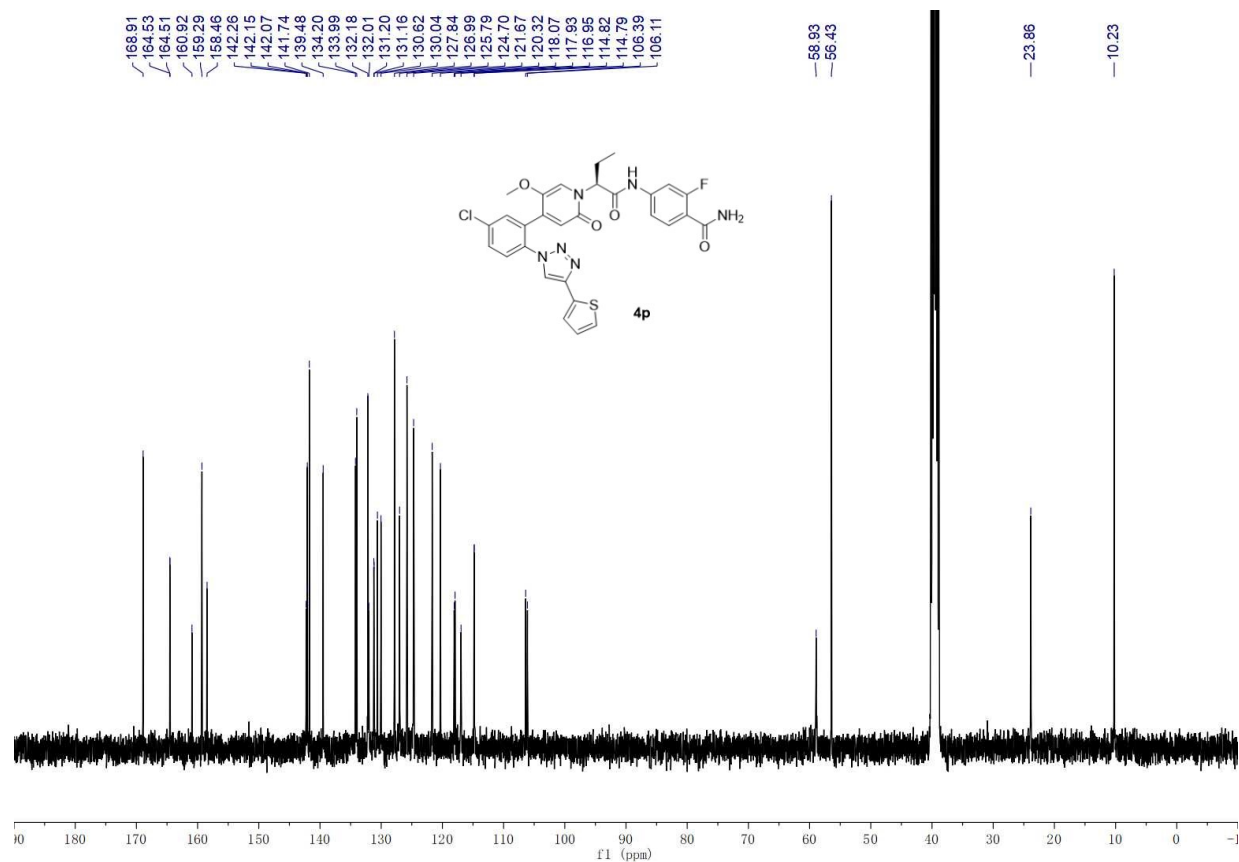
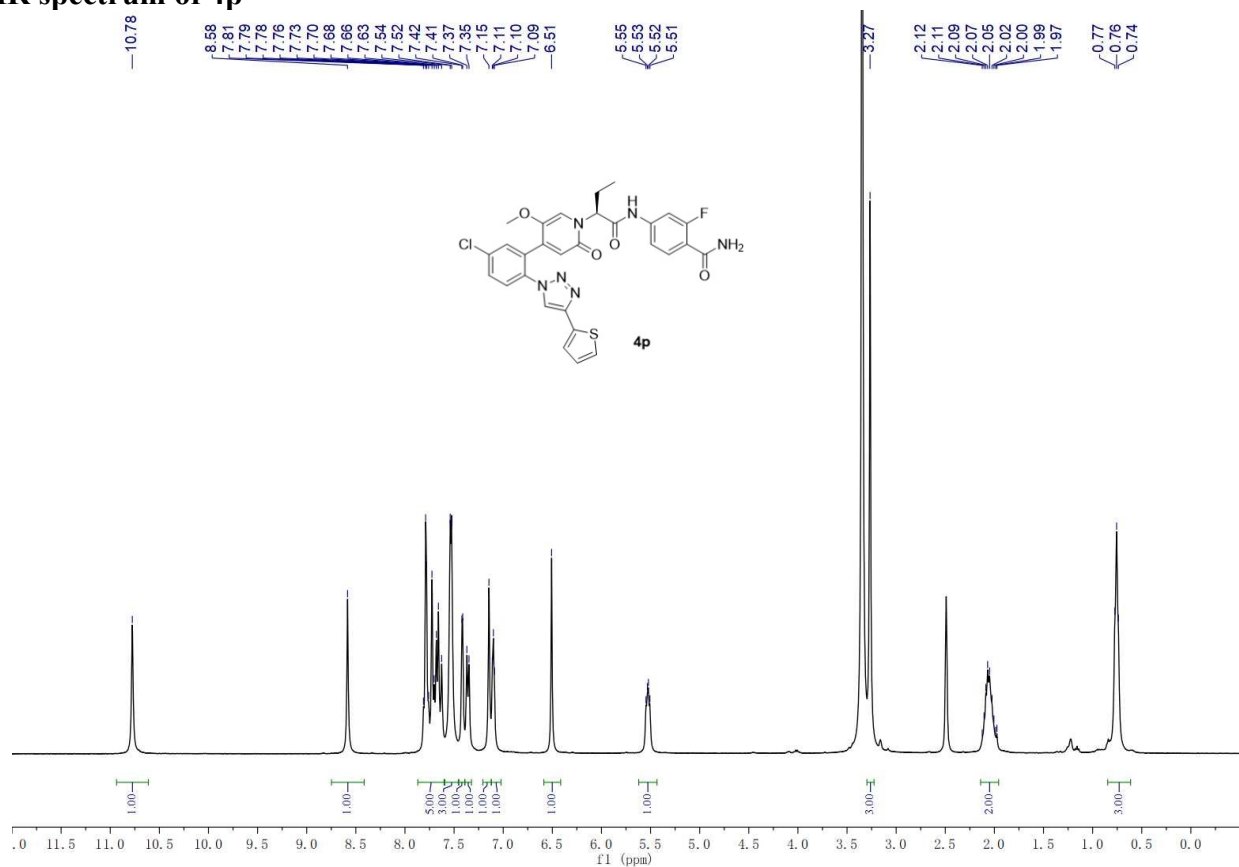
¹H NMR spectrum (CDCl₃) of **4o** is displayed below the structure. The x-axis represents the chemical shift in ppm, ranging from 0.0 to 11.5. The spectrum shows several peaks, with the following chemical shifts (ppm) labeled above the peaks:

8.64, 8.63, 8.48, 8.48, 8.48, 8.47, 8.47, 8.46, 8.46, 7.85, 7.83, 7.80, 7.79, 7.78, 7.77, 7.77, 7.73, 7.68, 7.66, 7.64, 7.61, 7.60, 7.57, 7.57, 7.54, 7.51, 7.49, 7.48, 7.47, 7.46, 7.45, 7.34, 7.34, 7.32, 7.32, 7.14, 7.14, 6.53, 5.52, 5.51, 5.51, 5.50, 5.48, 5.27, 2.69, 2.07, 2.05, 2.03, 2.01, 2.00, 2.00, 1.99, 1.98, 1.95, 0.71, 0.69, 0.67.

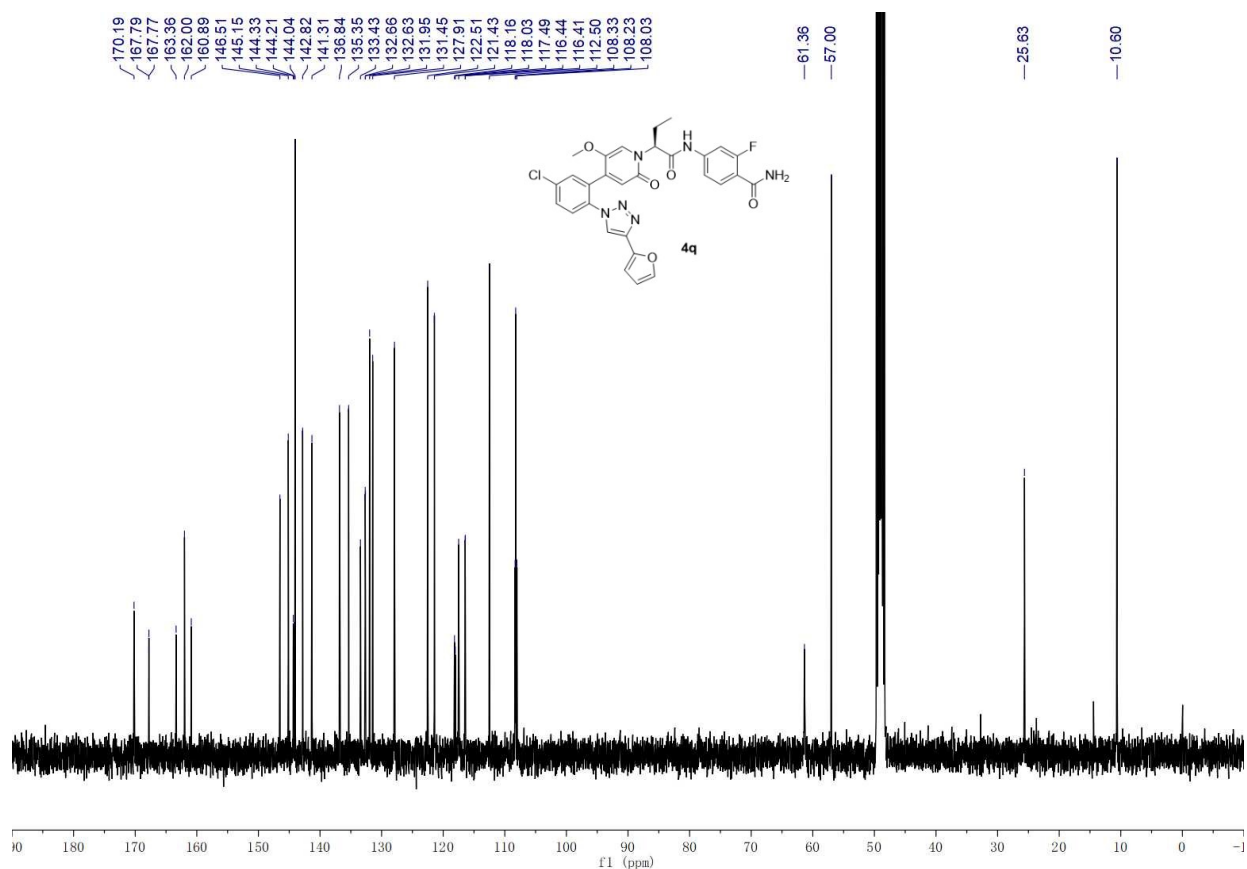
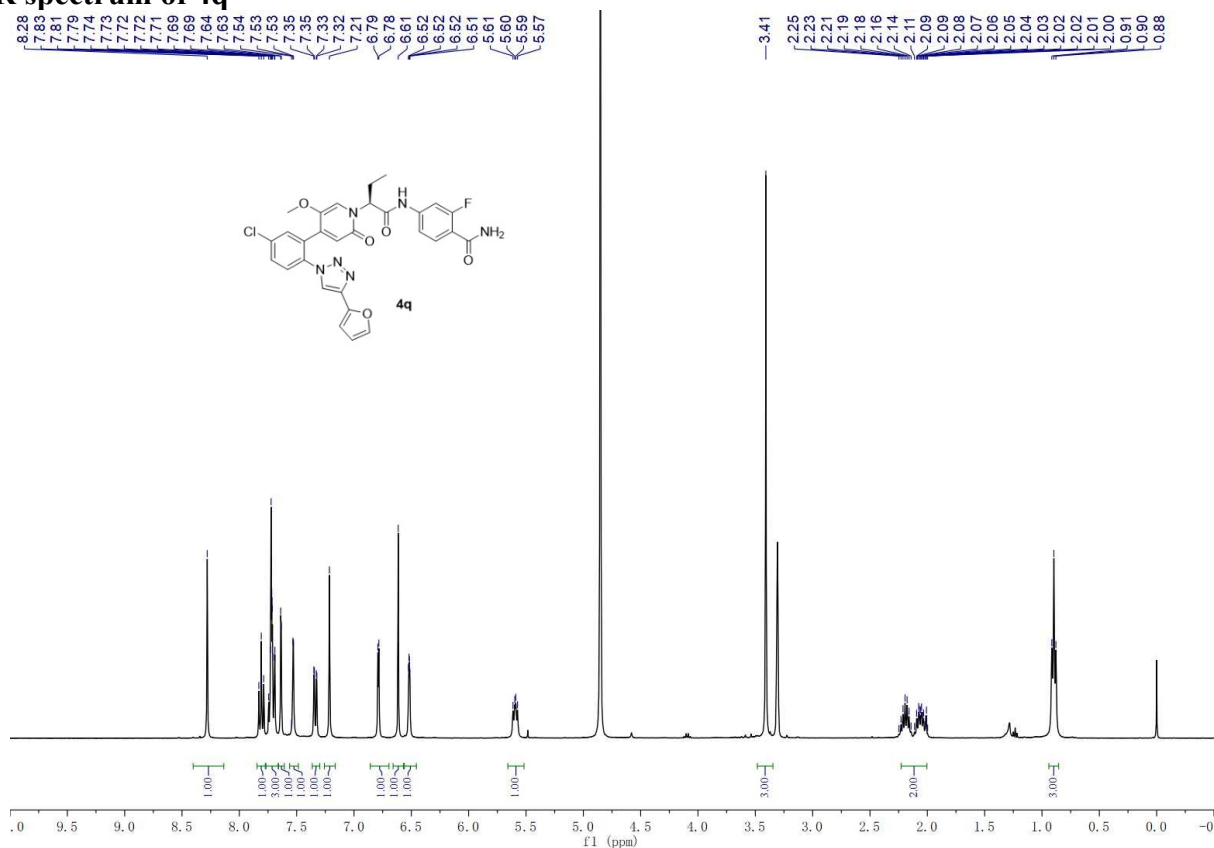
Integration values are shown below the baseline: 1.00, 1.00, 3.00, 1.00, 1.00, 2.00, 1.00, 1.00, 1.00, 1.00, 3.00, 2.00, 3.00.



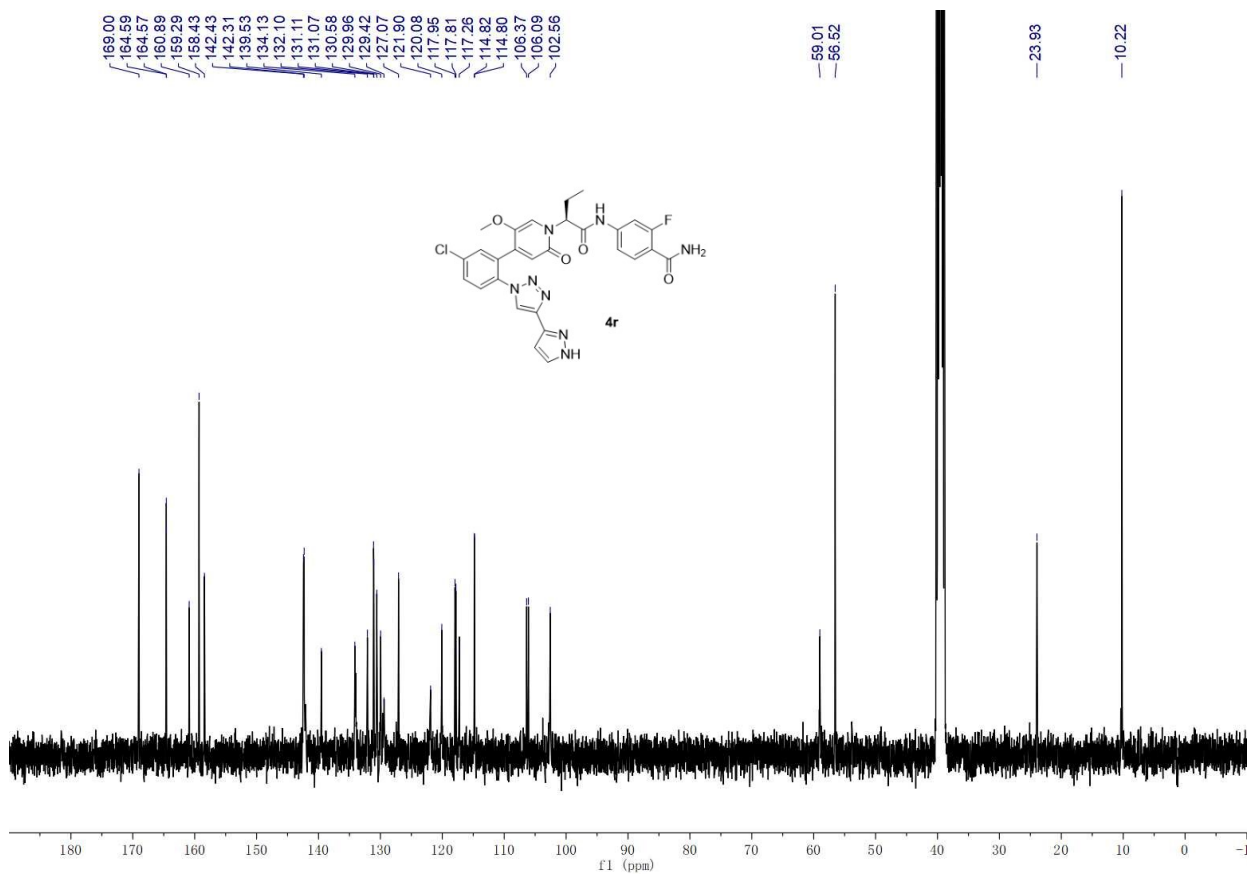
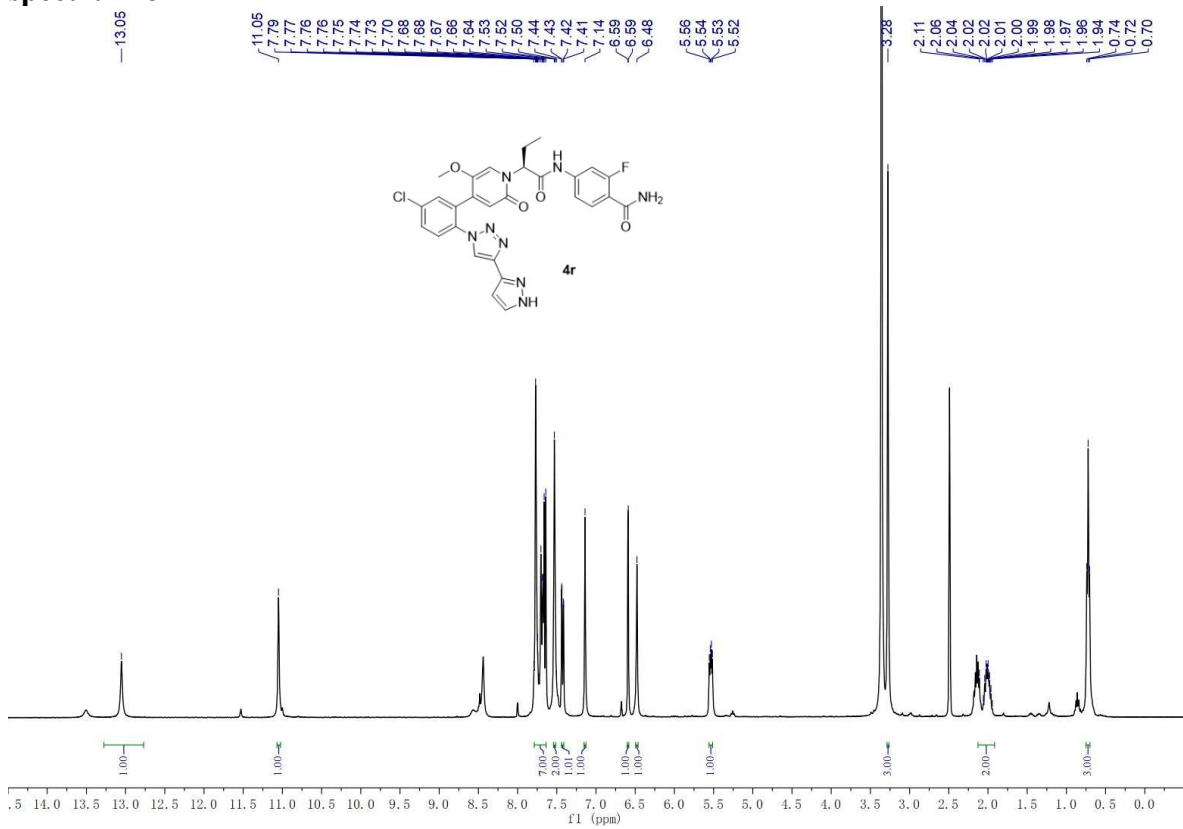
NMR spectrum of 4p



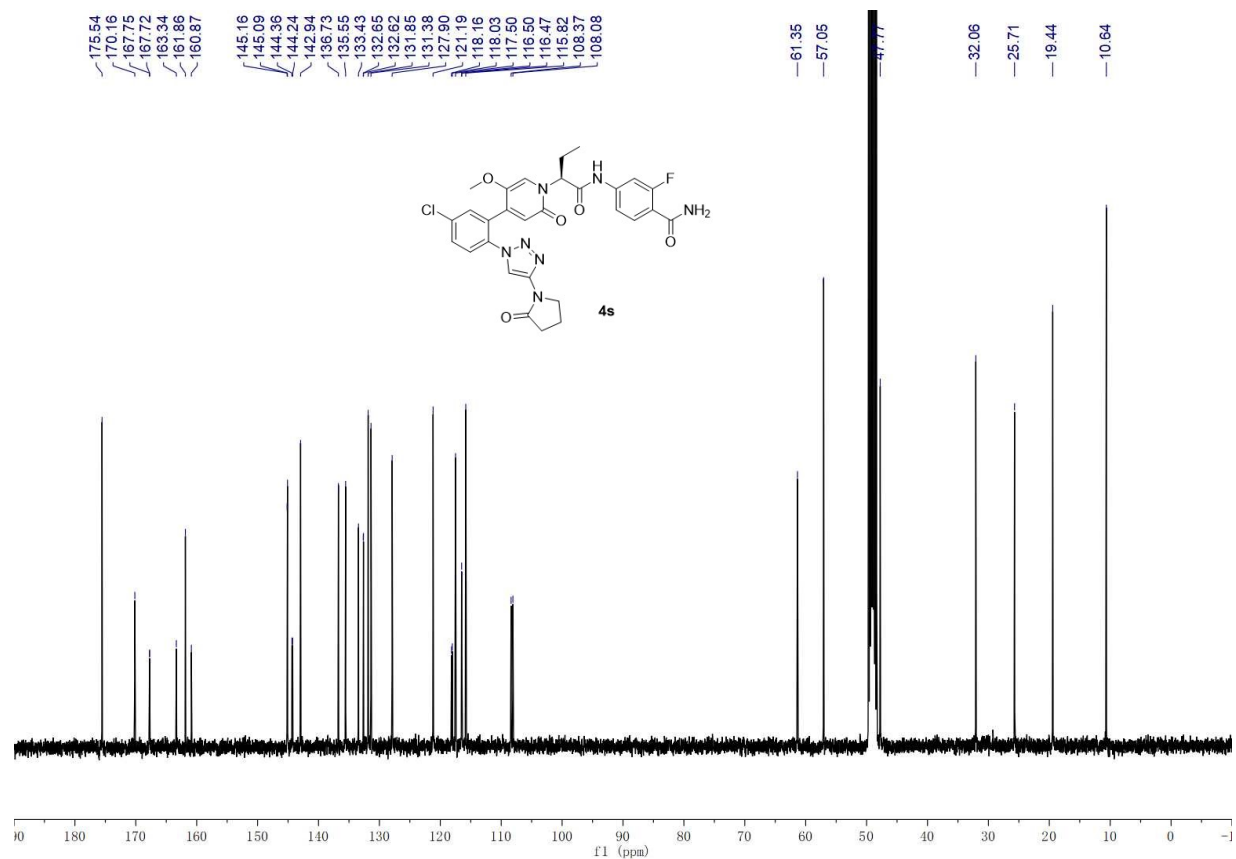
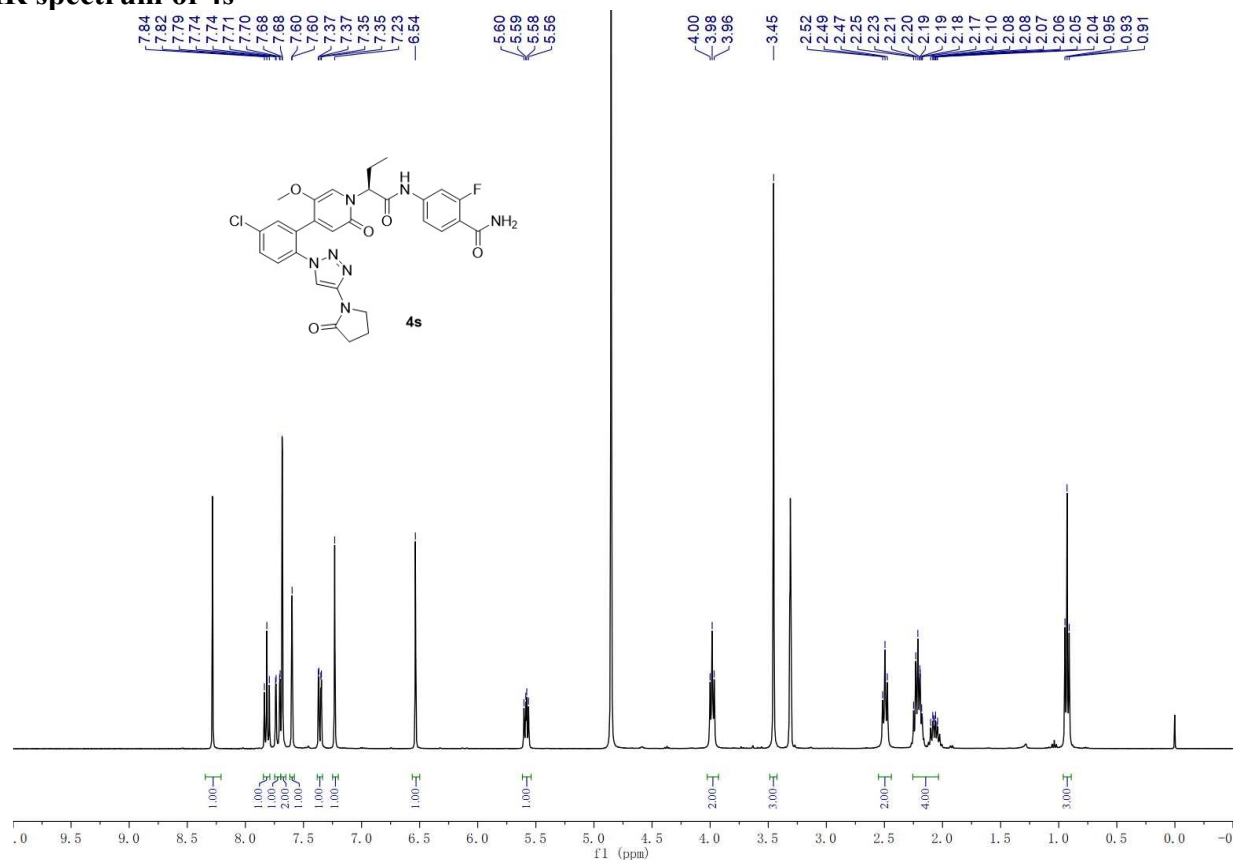
NMR spectrum of 4q



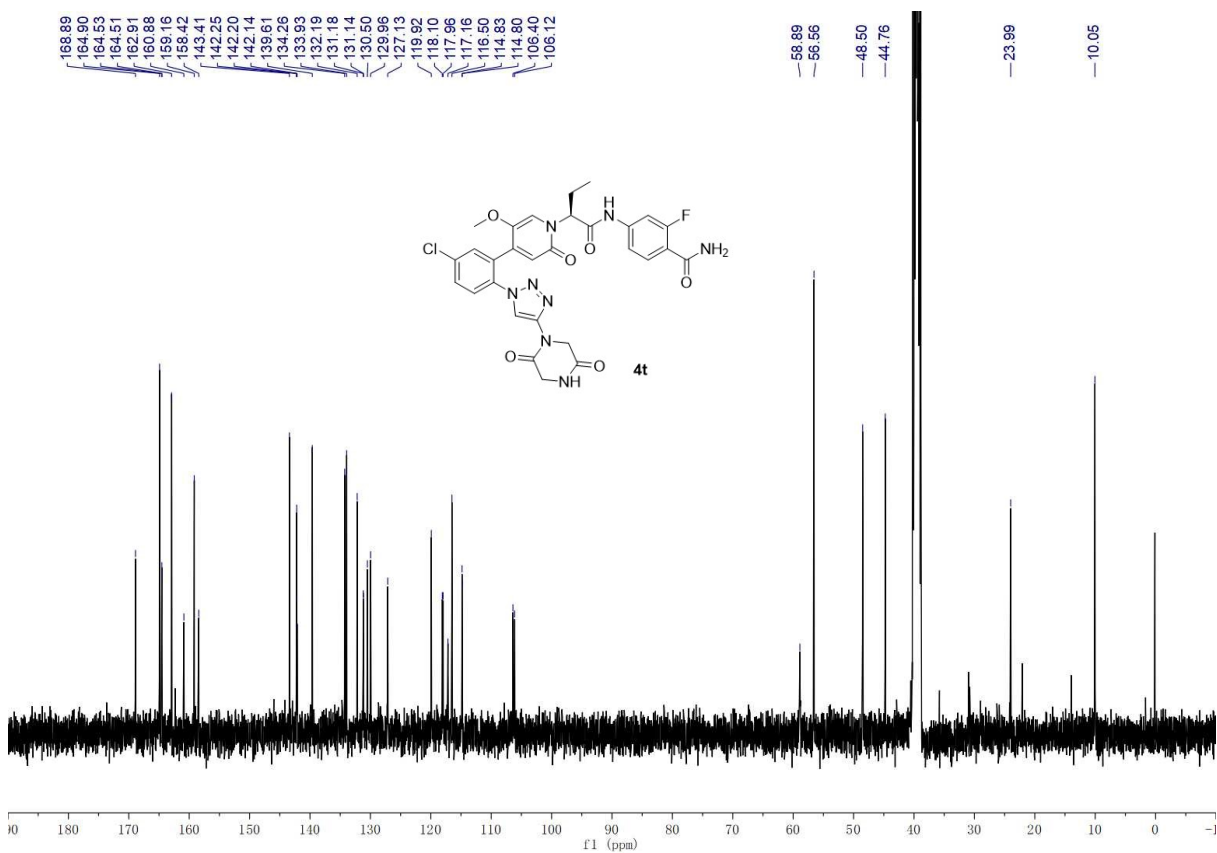
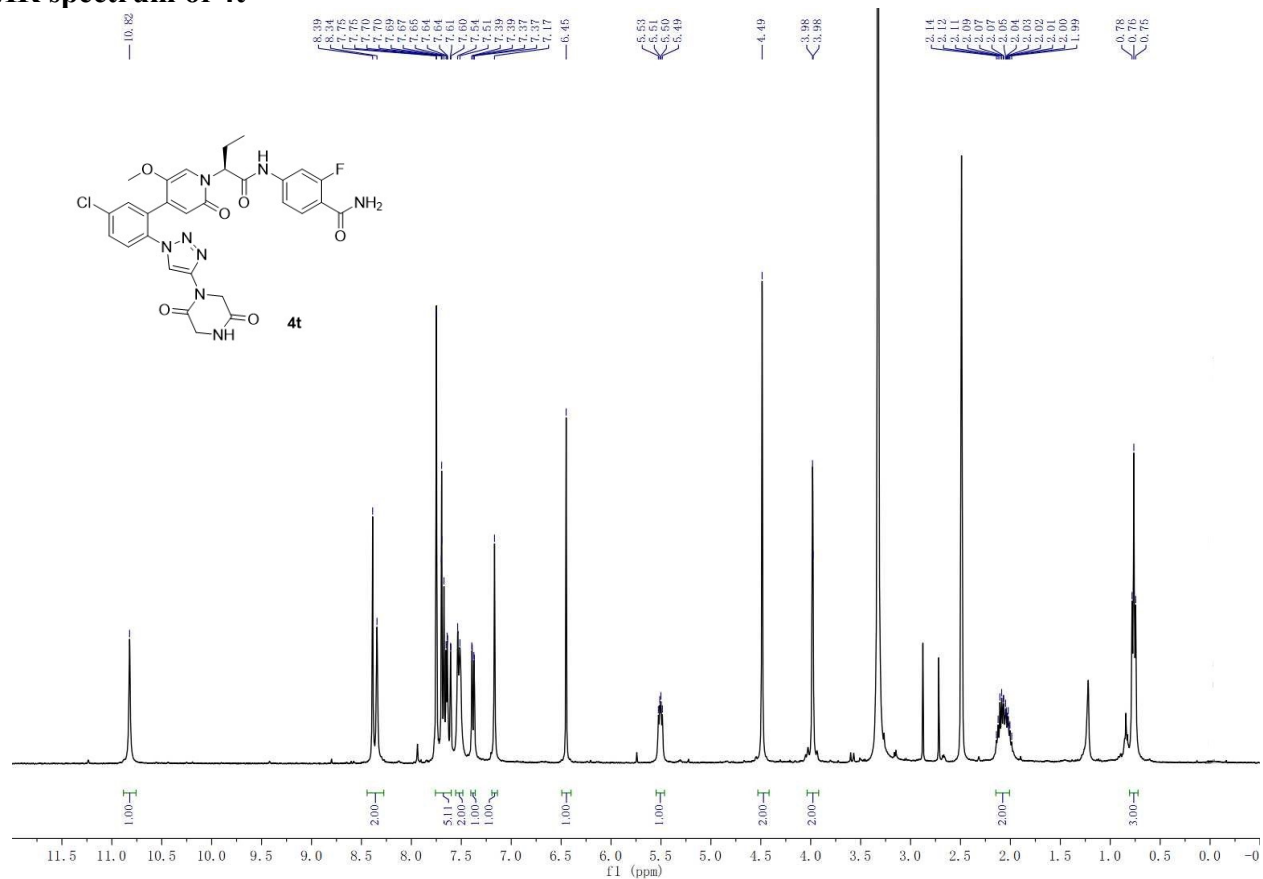
NMR spectrum of 4r



NMR spectrum of 4s



NMR spectrum of 4t



Purity data of tested compounds

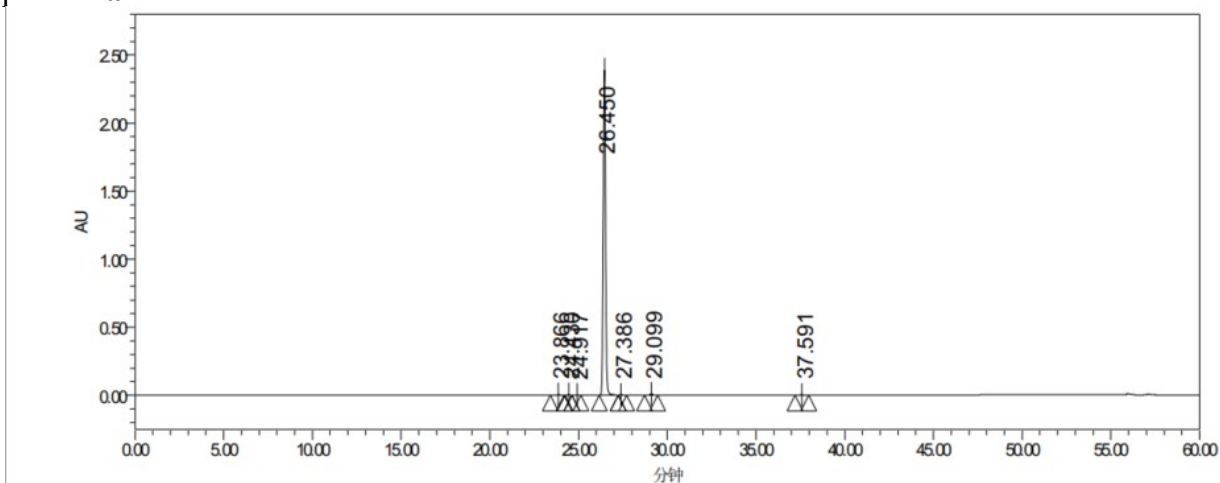
The general purity of the compounds was determined by HPLC using the following methods. HPLC analyses were conducted on a Waters e2695 system equipped with a 2998 PDA detector. A Kromasil C18 Column (5 μ m, 4.6*150 mm) was used at 35 °C. The other tested compounds were dissolved in CH₃CN. The volume of each injection was 10 μ L. The detection wavelength was 220 nm.

Flow rate: 1ml/min Eluent A: CH₃CN Eluent B: 10mM NH₄H₂PO₄(pH=3.0)

Gradient elution method is as follows:

t/min	0	40	50	51	60
A%	15	80	80	15	15
B%	85	20	20	85	85

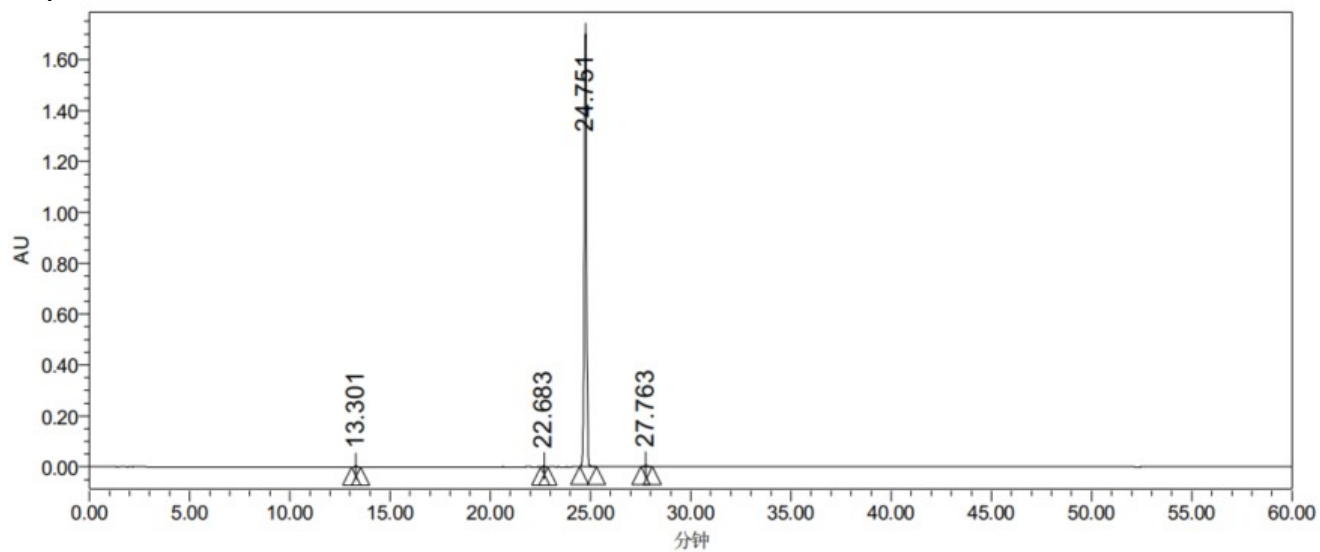
Compound 4a



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	高度 (微伏)	%面积	USP 理论塔板数	USP 分离度	USP 拖尾
1	23.866	51827	5433	0.233	162292		1.03
2	24.430	45373	5431	0.204	191194	2.41	0.99
3	24.917	36145	2556	0.163	22738	1.55	0.80
4	26.450	21928508	2389379	98.686	200218	4.79	1.04
5	27.386	26098	2462	0.117	203513	3.75	1.69
6	29.099	106676	9307	0.476	202511	6.52	1.02
7	37.591	28827	2252	0.121	231473	29.15	1.01
Sum		22220453					

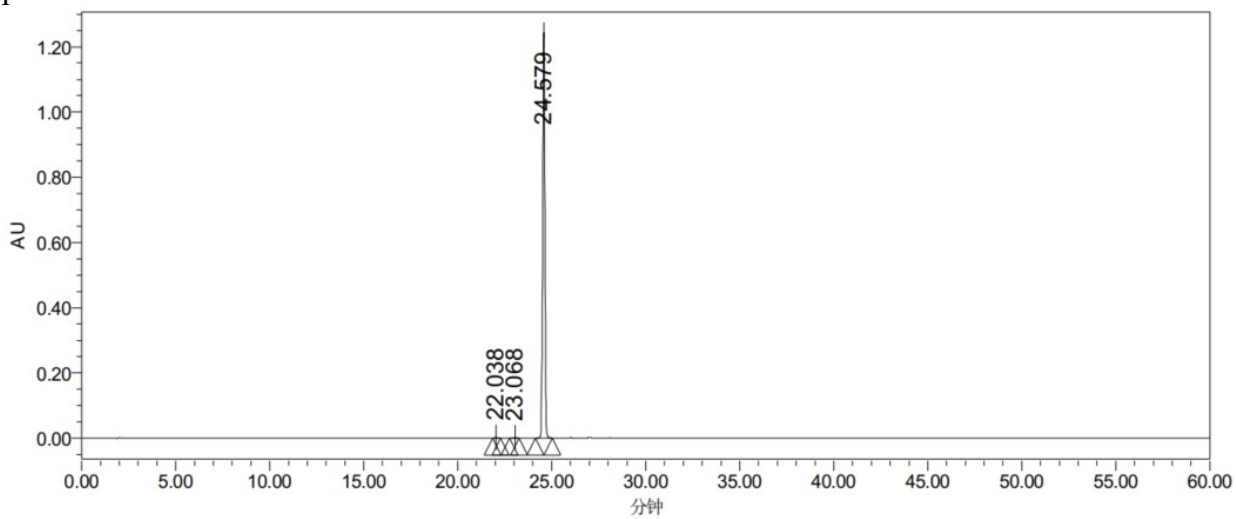
Compound 4b



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	13.301	17903	0.132	2359		69787	0.97
2	22.683	27603	0.203	3702	46.10	206597	1.00
3	24.751	13504592	99.269	1701032	9.97	223118	0.95
4	27.763	53880	0.396	5685	12.82	198315	0.90
Sum		13603977					

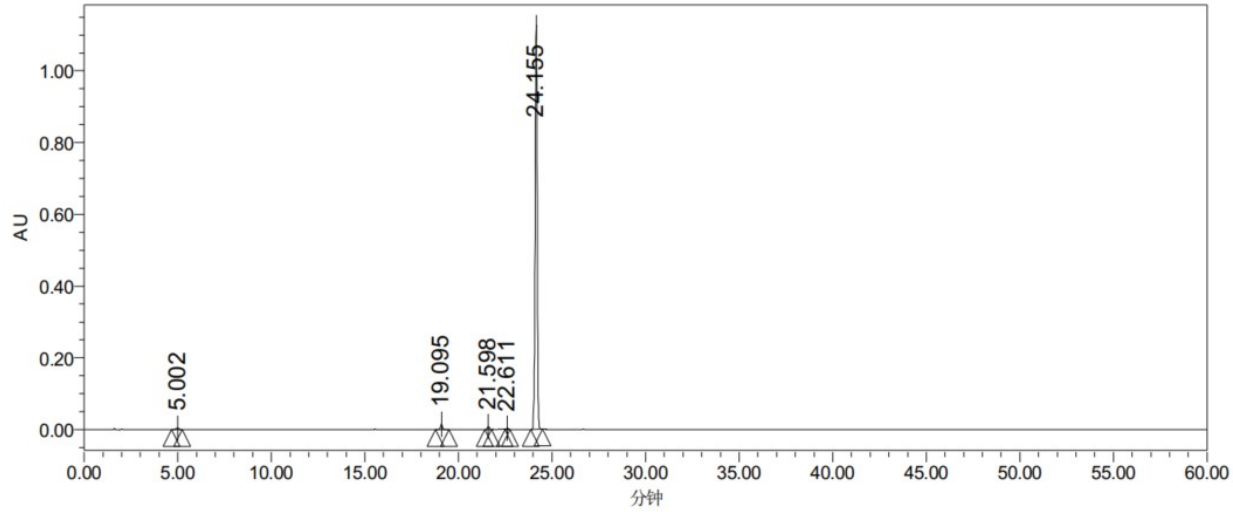
Compound 4c



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	22.038	21175	0.215	2796		192217	1.01
2	23.068	18837	0.191	2039	4.65	154397	0.81
3	24.579	9799540	99.593	1246848	6.73	226316	0.96
Sum		9839552					

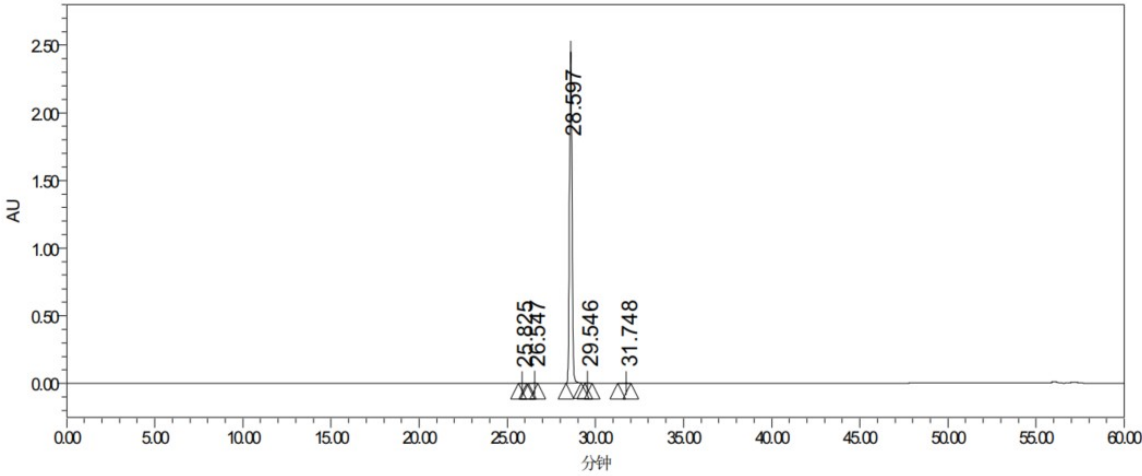
Compound 4d



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	5.002	47585	0.530	4316		4106	0.77
2	19.095	116018	1.292	15471	56.57	153432	0.99
3	21.598	61704	0.687	8359	12.54	190612	0.95
4	22.611	21391	0.238	2878	4.98	198569	1.03
5	24.155	8731672	97.252	1129287	7.47	224235	0.96
Sum		8978370					

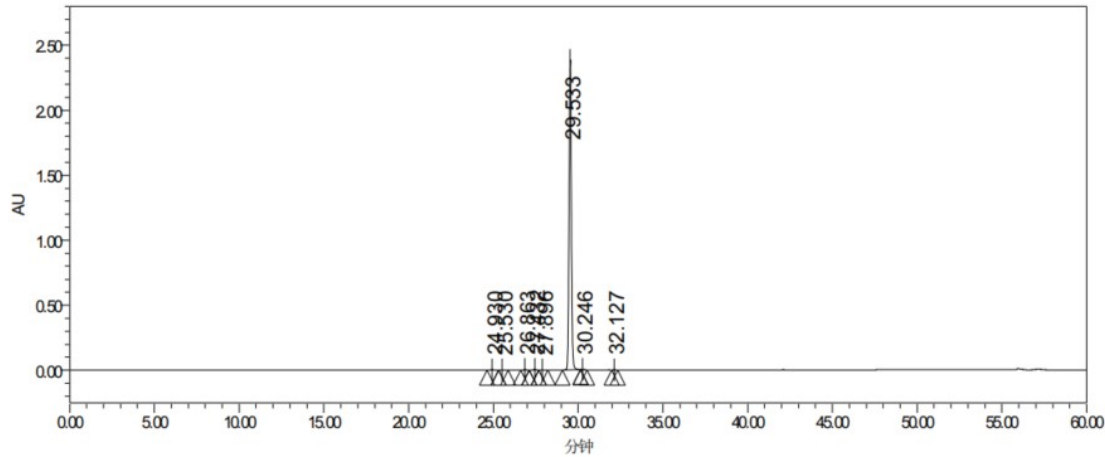
Compound 4e



峰结果

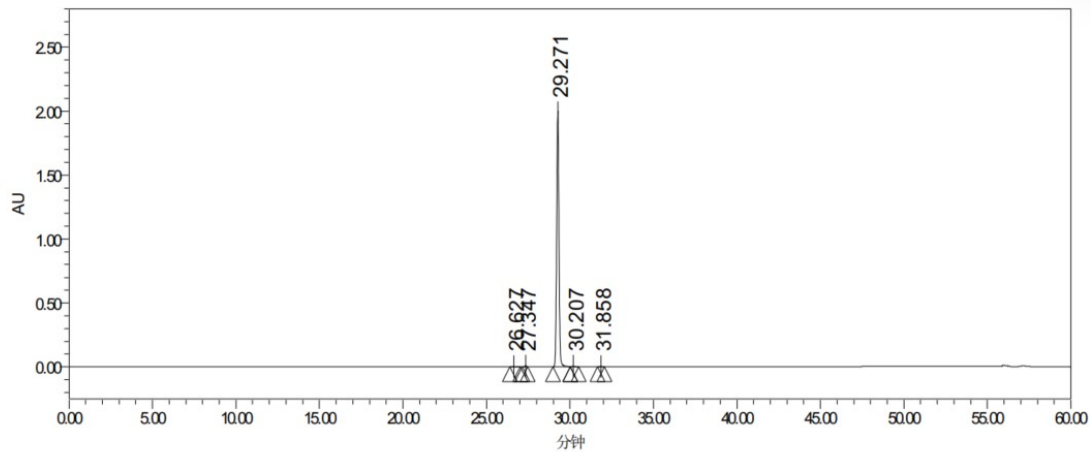
	保留时间 (分钟)	面积 (微伏*秒)	高度 (微伏)	%面积	USP 理论塔板数	USP 分离度	USP 拖尾
1	25.825	21583	2408	0.089	190271		1.08
2	26.547	53178	5538	0.220	178655	2.91	0.80
3	28.597	23986096	2450581	99.383	208560	8.04	1.03
4	29.546	33552	2799	0.139	113714	3.22	1.61
5	31.748	40546	3399	0.168	191205	6.95	0.75
Sum		24135056					

Compound 4f



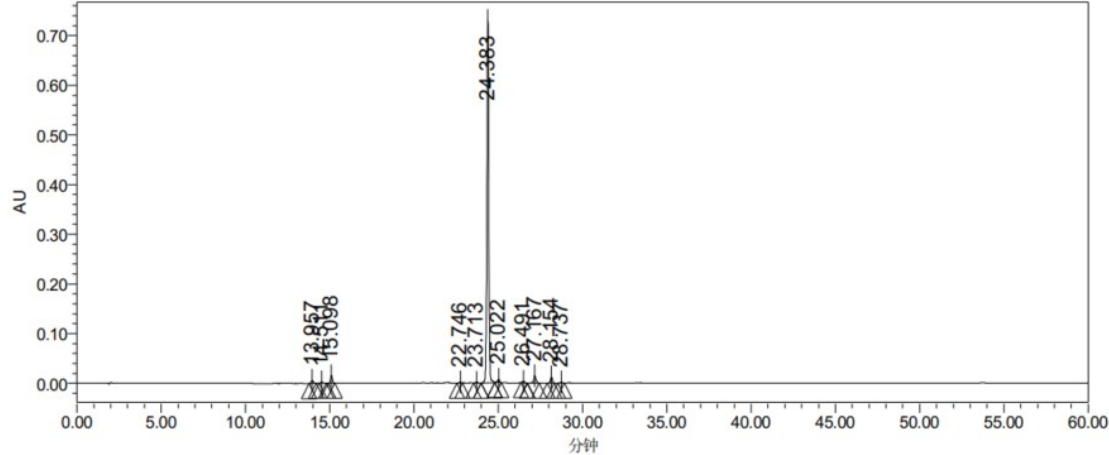
峰结果							
	保留时间 (分钟)	面积 (微伏*秒)	高度 (微伏)	%面积	USP 理论塔板数	USP 分离度	USP 拖尾
1	24.930	54212	4124	0.231	83835		1.11
2	25.530	27278	2553	0.116	177884	2.02	0.98
3	26.863	54873	5487	0.234	163818	5.15	0.97
4	27.432	68327	6914	0.291	187609	2.14	1.05
5	27.896	33105	2212	0.141	66870	1.35	1.15
6	29.533	23175706	2385623	98.788	222593	4.80	1.04
7	30.246	22665	2024	0.097	134799	2.04	1.83
8	32.127	23984	2610	0.102	262430	5.39	1.05
Sum		23460150					

Compound 4g



峰结果							
	保留时间 (分钟)	面积 (微伏*秒)	高度 (微伏)	%面积	USP 理论塔板数	USP 分离度	USP 拖尾
1	26.627	35803	3552	0.185	181142		1.40
2	27.347	47851	5867	0.247	244072	3.01	0.88
3	29.271	19209049	2005259	99.249	222377	8.11	1.04
4	30.207	36887	3556	0.191	186100	3.50	1.34
5	31.858	24865	2389	0.129	201343	5.80	0.96
Sum		19354476					

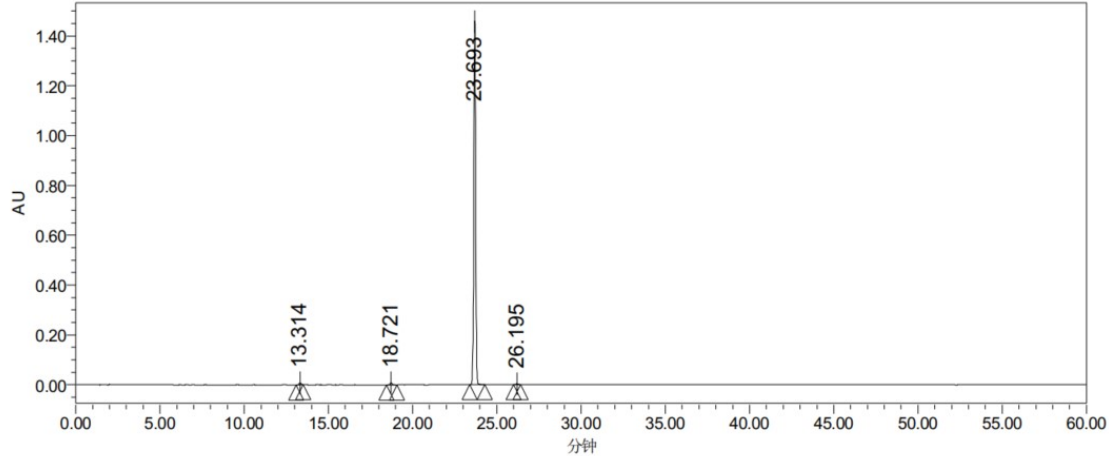
Compound 4h



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	13.957	45610	0.717	5853		74242	1.08
2	14.511	22326	0.351	3044	2.73	90028	1.19
3	15.098	119316	1.875	15521	2.90	86958	1.06
4	22.746	16685	0.262	2248	37.26	209423	0.83
5	23.713	18459	0.290	1840	4.18	138088	1.29
6	24.383	5803875	91.196	729655	2.85	220190	0.97
7	25.022	55849	0.878	7044	3.04	236507	0.90
8	26.491	26669	0.419	3280	6.82	239043	1.28
9	27.167	134371	2.111	14104	2.90	210960	0.96
10	28.154	101063	1.588	12487	4.26	273069	0.95
11	28.737	19985	0.314	2435	2.64	275259	0.93
Sum		6364208					

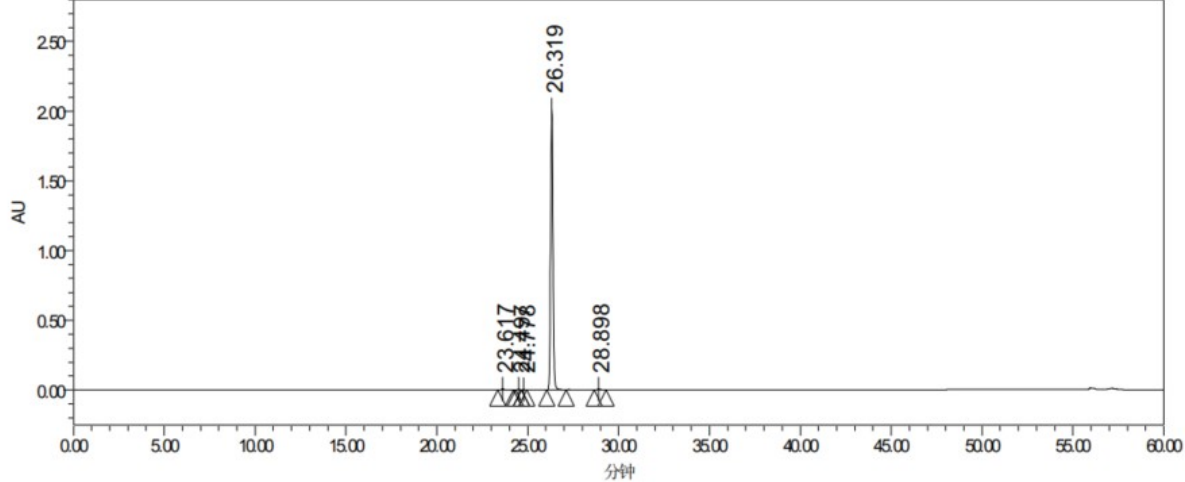
Compound 4i



峰结果

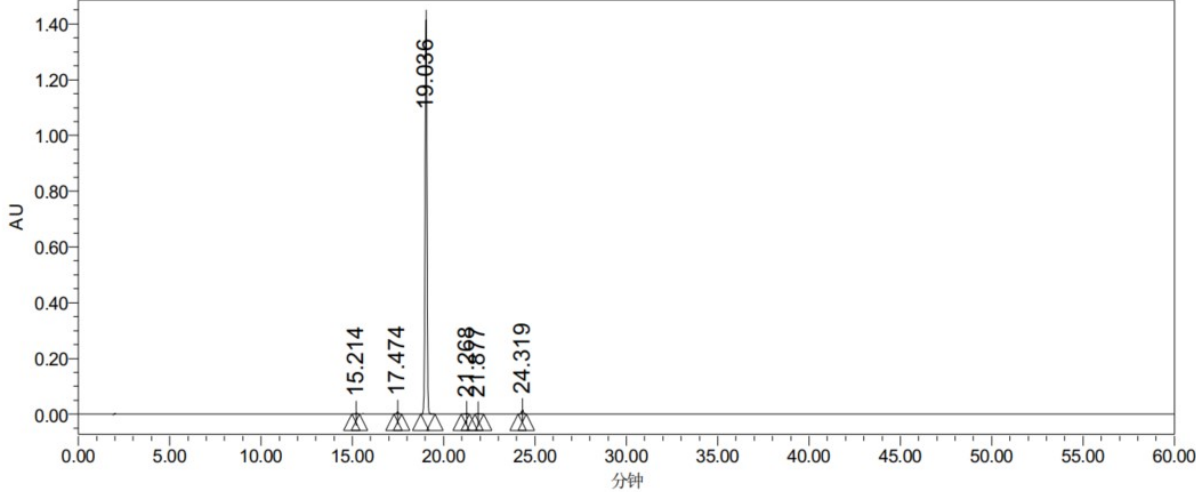
	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	13.314	59209	0.517	7808		69841	0.96
2	18.721	61914	0.540	8353	26.88	148422	0.98
3	23.693	11303520	98.673	1460390	24.55	214882	0.96
4	26.195	30920	0.270	3445	10.97	189126	1.10
Sum		11455563					

Compound 4j



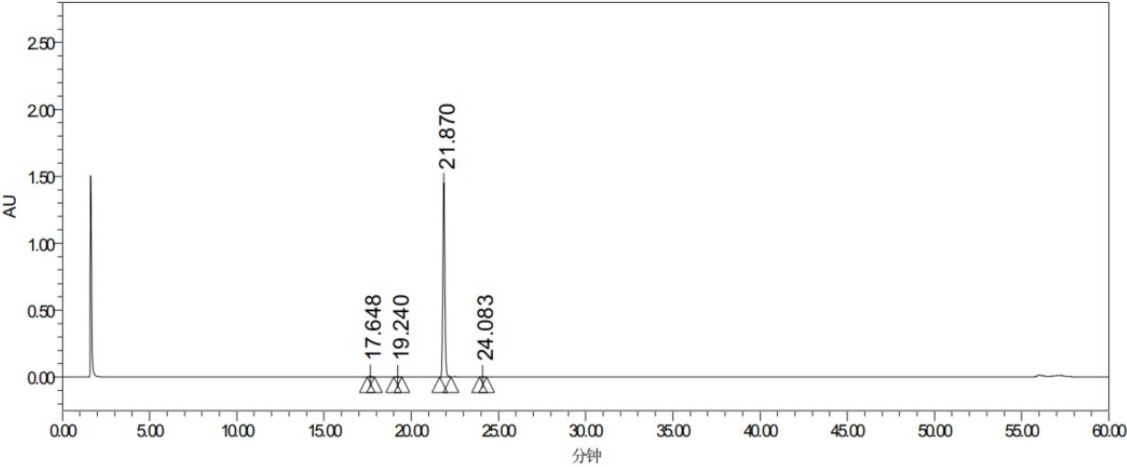
峰结果							
	保留时间 (分钟)	面积 (微伏*秒)	高度 (微伏)	%面积	USP 理论塔板数	USP 分离度	USP 拖尾
1	23.617	94467	8810	0.514	151941		1.47
2	24.497	49171	5586	0.268	164325	3.52	0.99
3	24.778	20557	2576	0.112	207605	1.22	1.20
4	26.319	1812708	2019847	98.686	204660	6.79	1.04
5	28.898	75362	5868	0.410	111187	8.78	1.33
Sum		18366655					

Compound 4k



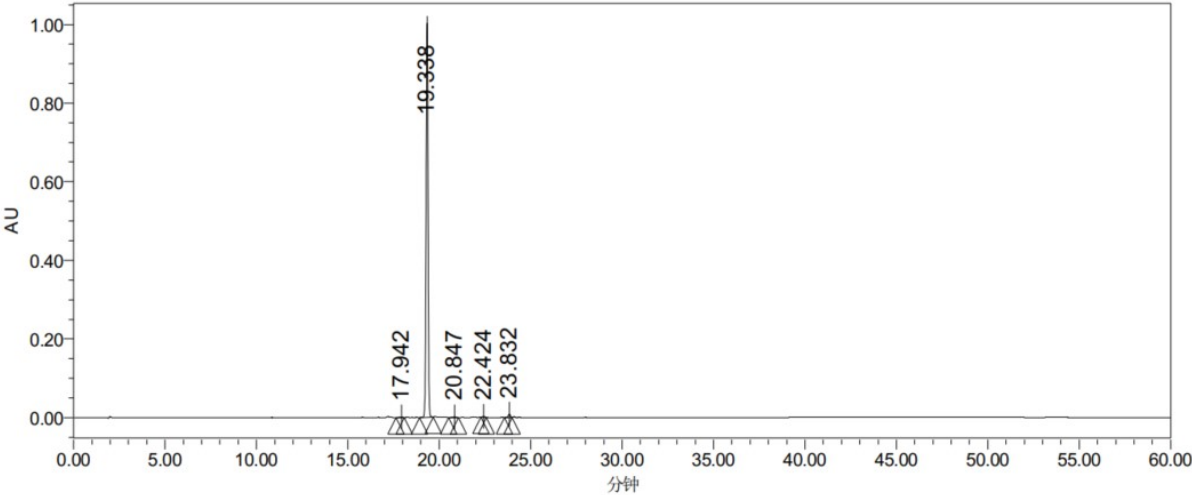
峰结果							
	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	15.214	26216	0.258	3831		113694	0.96
2	17.474	50797	0.501	7449	12.45	155630	0.96
3	19.036	9913608	97.744	1417150	8.50	169839	0.97
4	21.268	22262	0.219	3018	11.58	190765	0.89
5	21.877	20182	0.199	2675	3.06	196521	1.07
6	24.319	109325	1.078	14115	11.91	223638	0.98
Sum		10142390					

Compound 4l



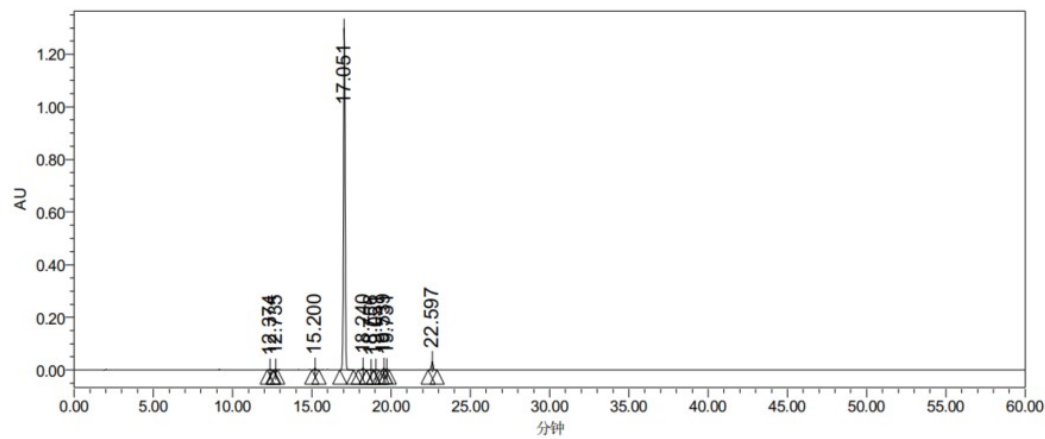
峰结果							
	保留时间 (分钟)	面积 (微伏*秒)	高度 (微伏)	%面积	USP 理论塔板数	USP 分离度	USP 拖尾
1	17.648	61608	8045	0.527	119722		1.11
2	19.240	34459	4208	0.295	130576	7.50	0.98
3	21.870	11553269	1454618	98.918	177192	12.25	1.06
4	24.083	30309	3476	0.260	180432	9.96	1.26
Sum		11679644					

Compound 4m



峰结果							
	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	17.942	15673	0.210	1504		79842	0.74
2	19.338	7330111	98.451	1004833	5.99	161074	0.97
3	20.847	17033	0.229	1516	6.00	71242	0.86
4	22.424	20705	0.278	2834	6.22	203261	1.02
5	23.832	61940	0.832	8063	6.99	229274	0.83
Sum		7445462					

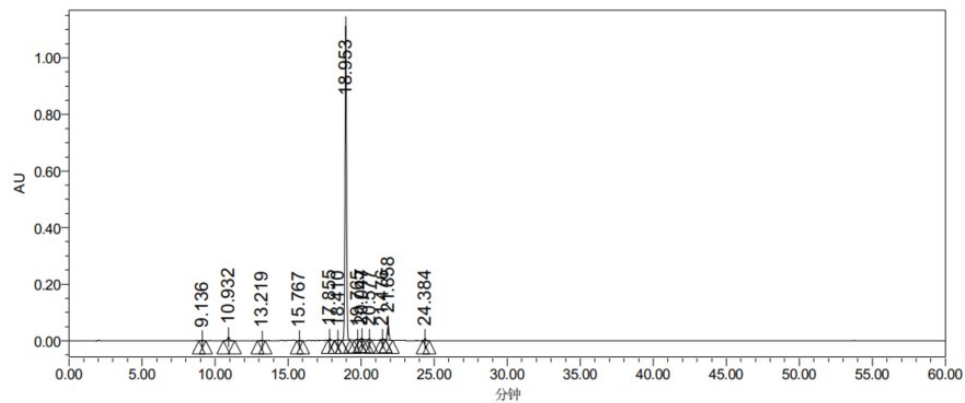
Compound 4n



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	12.374	18767	0.196	2459		58565	0.96
2	12.735	17364	0.181	3014	1.98	105289	0.91
3	15.200	43101	0.450	5845	14.01	101764	1.13
4	17.051	9109218	95.122	1298707	9.69	136541	0.96
5	18.240	51525	0.538	6978	6.18	141632	0.97
6	18.756	17879	0.187	1914	2.17	74631	0.80
7	19.051	15932	0.166	2157	1.25	158652	1.13
8	19.539	34050	0.356	5488	2.68	210643	0.92
9	19.731	22242	0.232	3660	1.14	226077	1.24
10	22.597	246321	2.572	31446	15.21	190867	0.98
Sum		9576399					

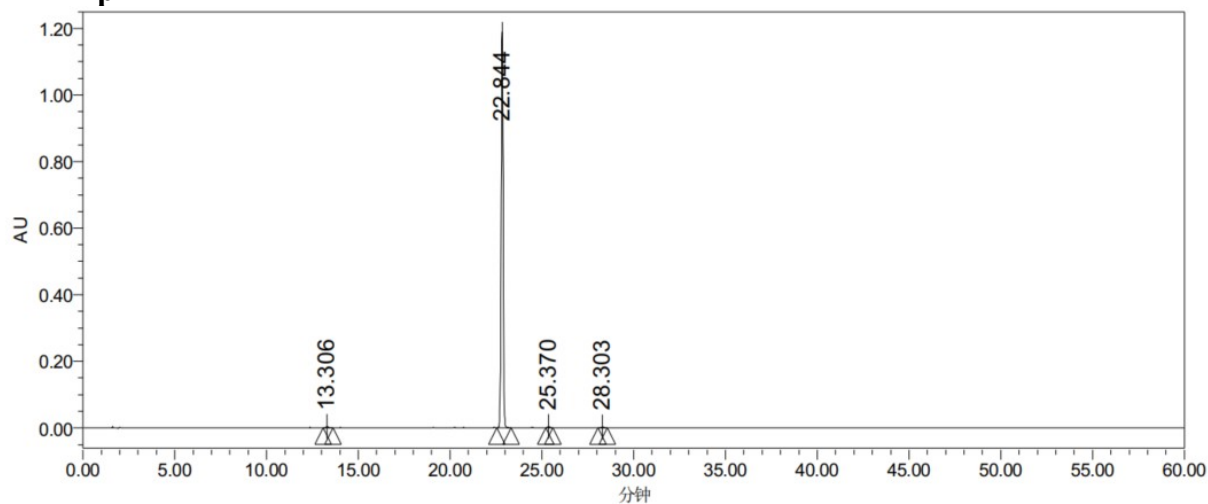
Compound 4o



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	9.136	15804	0.176	1809		27052	0.94
2	10.932	134407	1.497	13324	7.25	30623	0.82
3	13.219	16213	0.181	1564	8.01	36628	0.74
4	15.767	15562	0.173	1810	10.01	99409	1.47
5	17.855	55727	0.621	6151	9.71	107323	1.63
6	18.410	25861	0.288	2199	2.11	63453	1.16
7	18.953	8105869	90.295	1113271	2.20	155787	0.98
8	19.765	22618	0.252	1952	3.18	61745	0.81
9	20.047	42685	0.475	6519	1.14	203265	1.02
10	20.577	41154	0.458	5676	2.84	182827	0.99
11	21.476	45626	0.508	4073	3.63	75758	1.23
12	21.858	401356	4.471	50847	1.49	175126	1.03
13	24.384	54190	0.604	6770	12.03	225799	1.39
Sum		8977072					

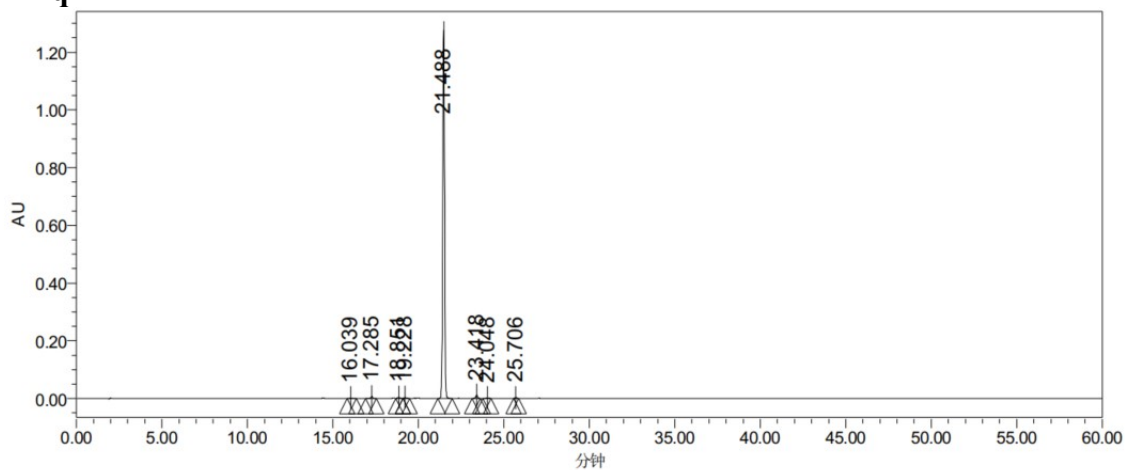
Compound 4p



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	13.306	34500	0.376	4483		69378	0.97
2	22.844	9081165	99.040	1191019	46.53	206141	0.96
3	25.370	30304	0.330	3871	12.09	232786	1.02
4	28.303	23242	0.253	2768	13.37	261187	0.99
Sum		9169211					

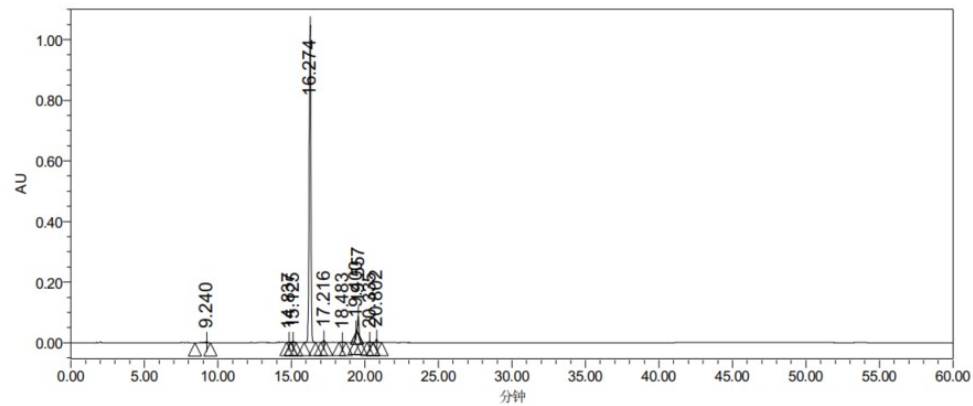
Compound 4q



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	16.039	18026	0.184	2270		110884	1.32
2	17.285	57423	0.586	6840	6.03	110095	0.89
3	18.851	35982	0.367	4199	7.17	121636	1.31
4	19.228	30282	0.309	3632	1.70	137866	1.42
5	21.488	9532728	97.222	1280028	10.80	191359	0.97
6	23.418	87413	0.892	10674	9.23	191994	0.91
7	24.048	22205	0.226	1926	2.49	112678	0.88
8	25.706	21064	0.215	2902	6.81	272976	1.08
Sum		9805123					

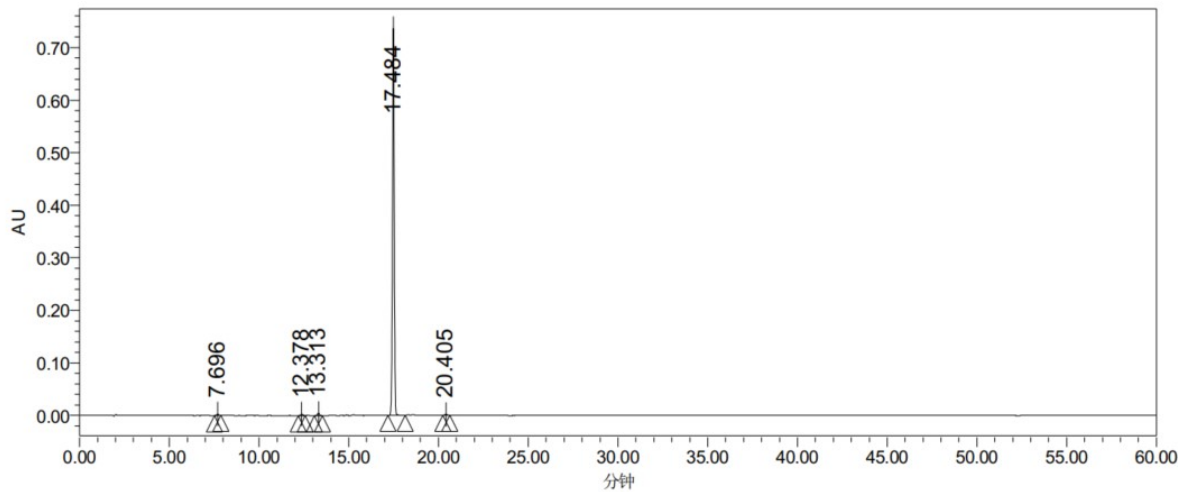
Compound 4r



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	9.240	55006	0.593	3623		18357	0.66
2	14.837	15870	0.171	1848	20.64	64220	0.83
3	15.125	29943	0.323	2725	1.09	40601	1.06
4	16.274	8533368	92.063	1046997	4.46	90402	0.90
5	17.216	54336	0.586	6952	4.35	107191	0.87
6	18.483	19452	0.210	1339	4.00	15780	1.03
7	19.400	76431	0.825	16292	3.33	363625	0.85
8	19.557	383783	4.140	64233	1.07	231594	1.19
9	20.335	24424	0.264	3033	4.13	150895	0.98
10	20.802	76417	0.824	10223	2.25	177392	0.98
Sum		9269032					

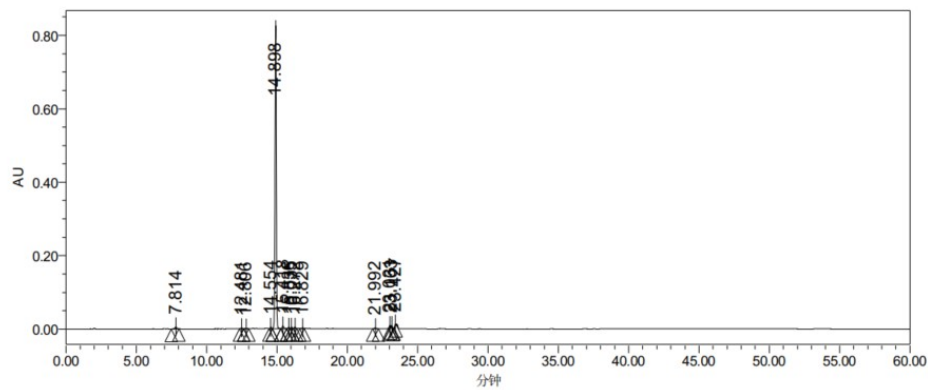
Compound 4s



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	7.696	20089	0.385	2789		25440	0.96
2	12.378	20191	0.387	2683	23.50	61188	0.98
3	13.313	34432	0.659	4558	4.60	71006	0.98
4	17.484	5126951	98.177	736694	21.42	145880	0.97
5	20.405	20470	0.392	2061	12.39	76735	1.15
Sum		5222134					

Compound 4t



峰结果

	保留时间 (分钟)	面积 (微伏*秒)	% 面积	高度 (微伏)	USP 分离度	USP 理论塔板数	USP 拖尾
1	7.814	45820	0.819	5276		21379	0.74
2	12.481	19750	0.353	2900	22.73	73936	0.97
3	12.806	15999	0.286	1643	1.26	24375	1.07
4	14.554	25579	0.457	4272	7.07	127190	0.93
5	14.898	5244070	93.743	826062	2.06	126633	0.98
6	15.418	55805	0.998	7235	2.84	102829	1.37
7	15.836	21324	0.381	3296	2.23	128695	0.89
8	16.035	17766	0.318	3086	1.18	163589	1.07
9	16.272	26326	0.471	3620	1.33	106354	1.03
10	16.829	20456	0.366	2832	2.95	149219	0.76
11	21.992	23099	0.413	3096	27.41	204960	1.05
12	23.031	22219	0.397	4262	6.18	440262	0.76
13	23.163	27449	0.491	4919	0.91	382027	1.35
14	23.427	28451	0.509	5510	1.87	490999	0.75
Sum		5594113					