

Supporting Information

Synthesis and evaluation of new pirfenidone derivatives as anti-fibrosis agents

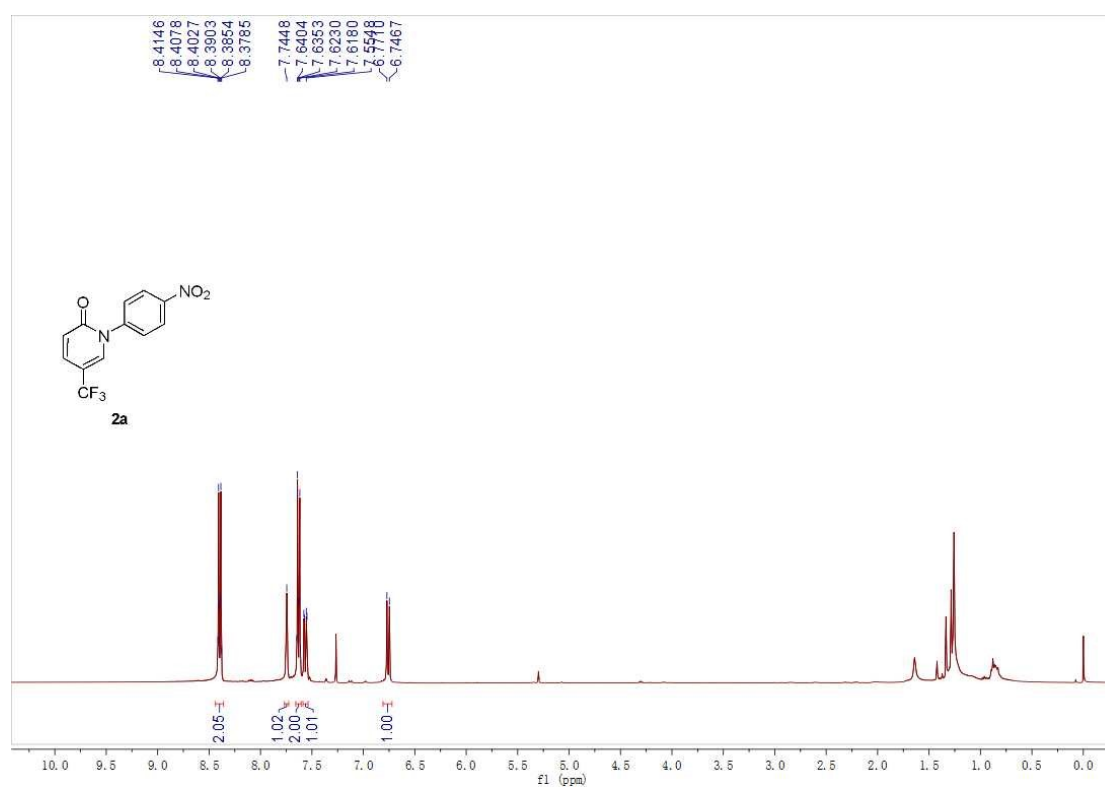
Chenxi Gu^a, Wei Li^a, Qing Ju^b, Han Yao^a, Lisheng Yang^a, Baijiao An^b, Wenhao Hu^{a*} and Xingshu Li^{a*}

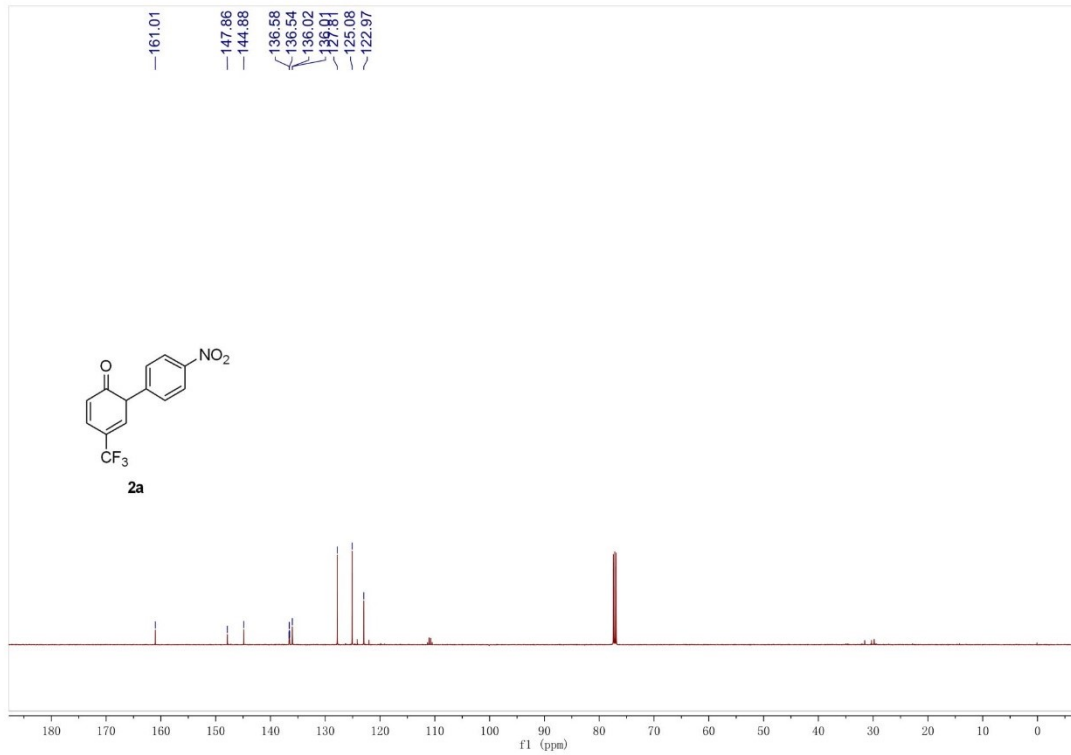
^aSchool of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, PR China.

^bMedicine and Pharmacy Research Center, Binzhou Medical University, Yantai, Shandong Province, 264003, PR China

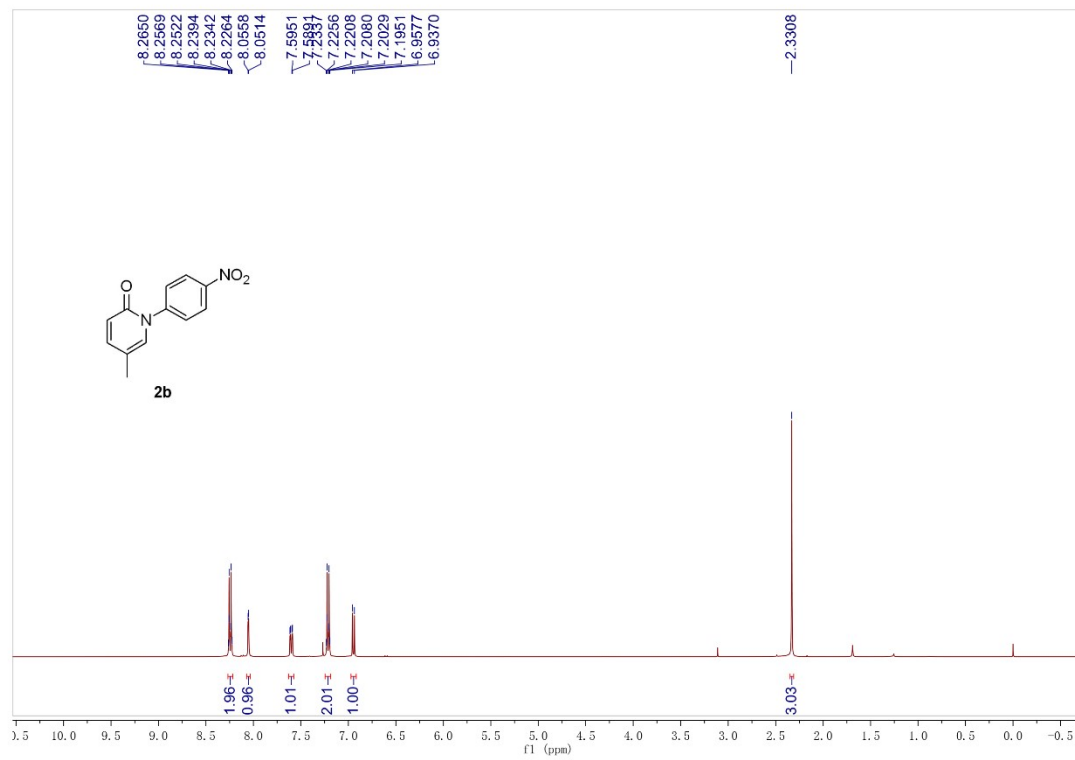
¹H NMR, ¹³C NMR, Mass and HPLC spectral data of compounds.

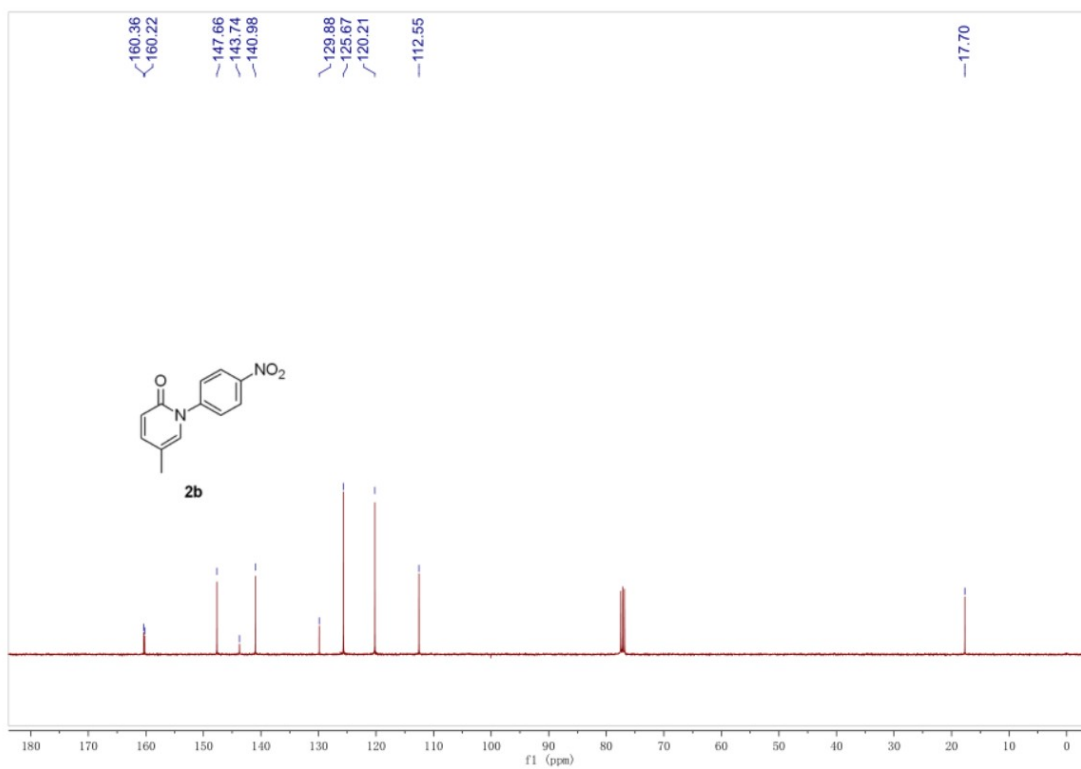
¹H NMR and ¹³C NMR of **2a**



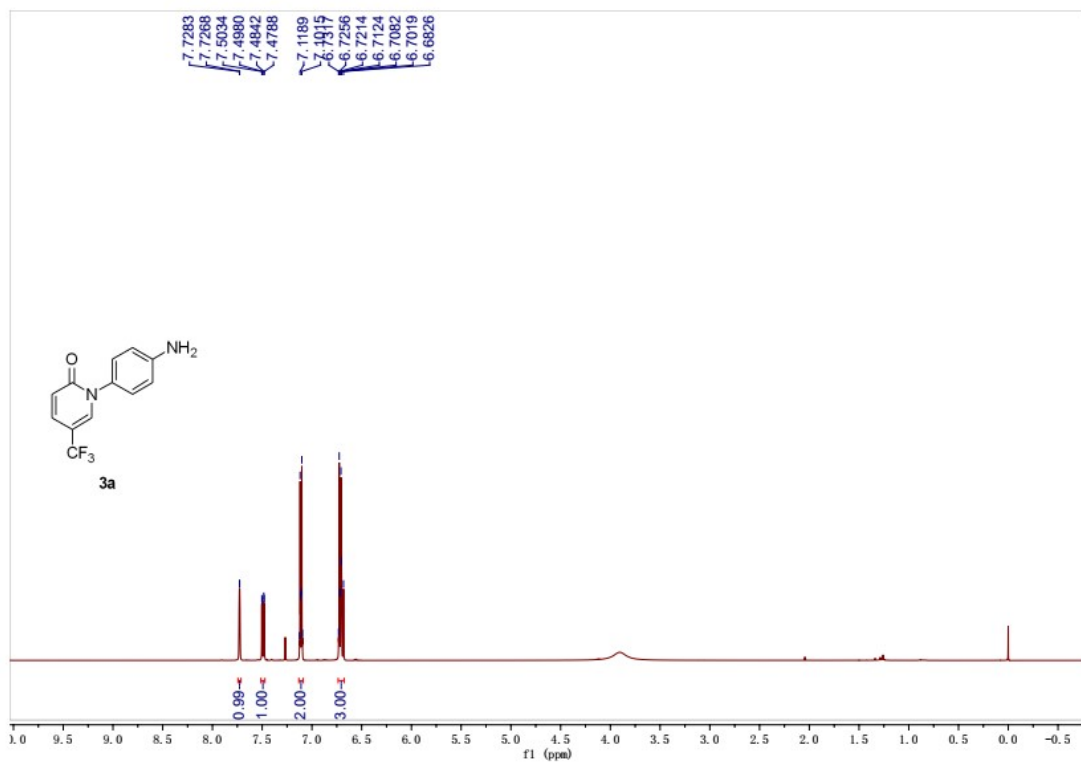


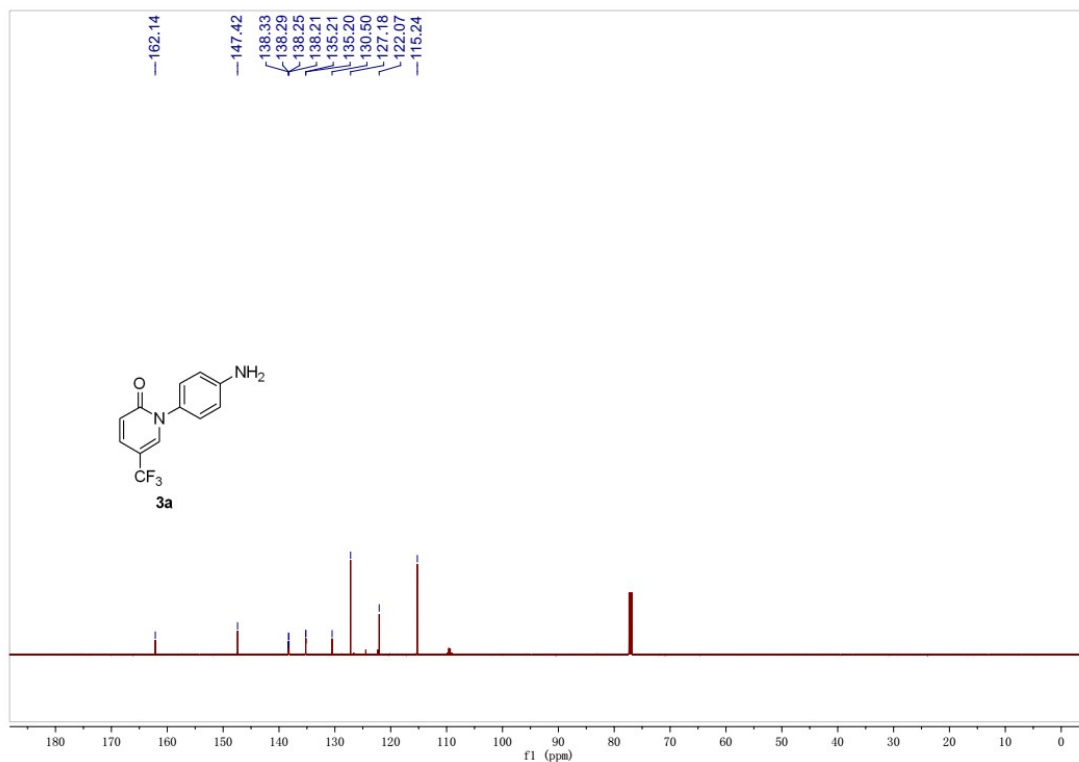
¹H NMR and ¹³C NMR of 2b



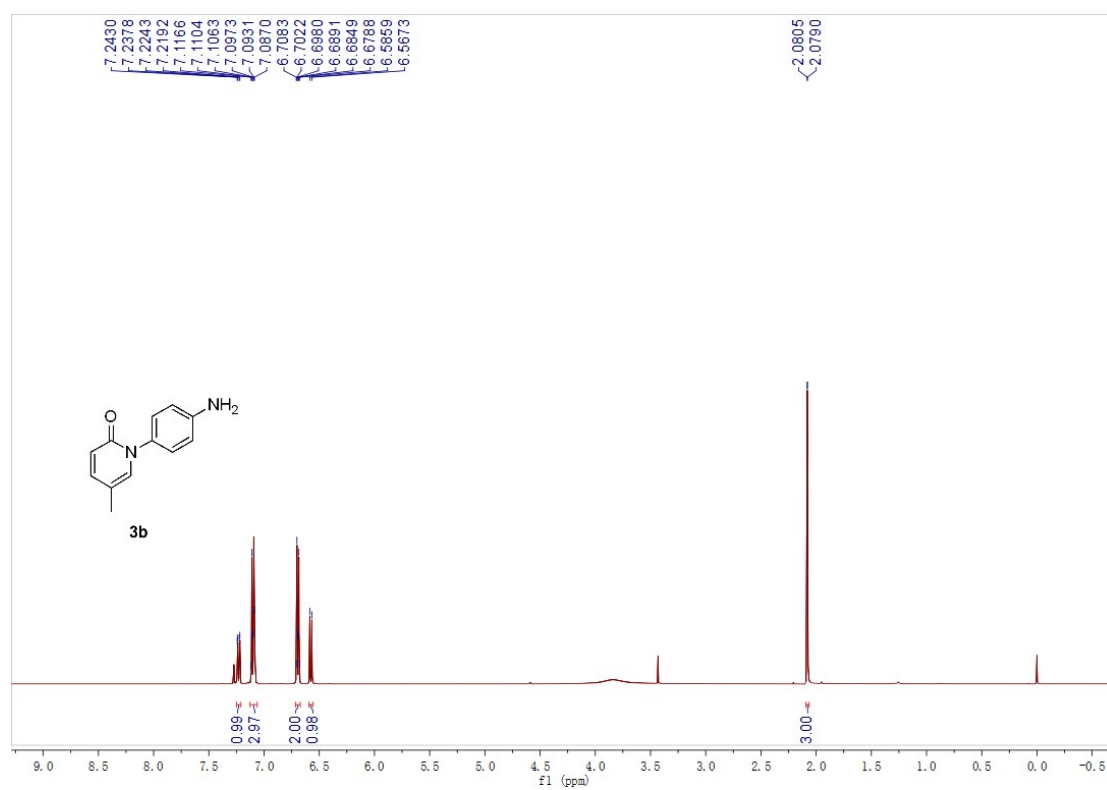


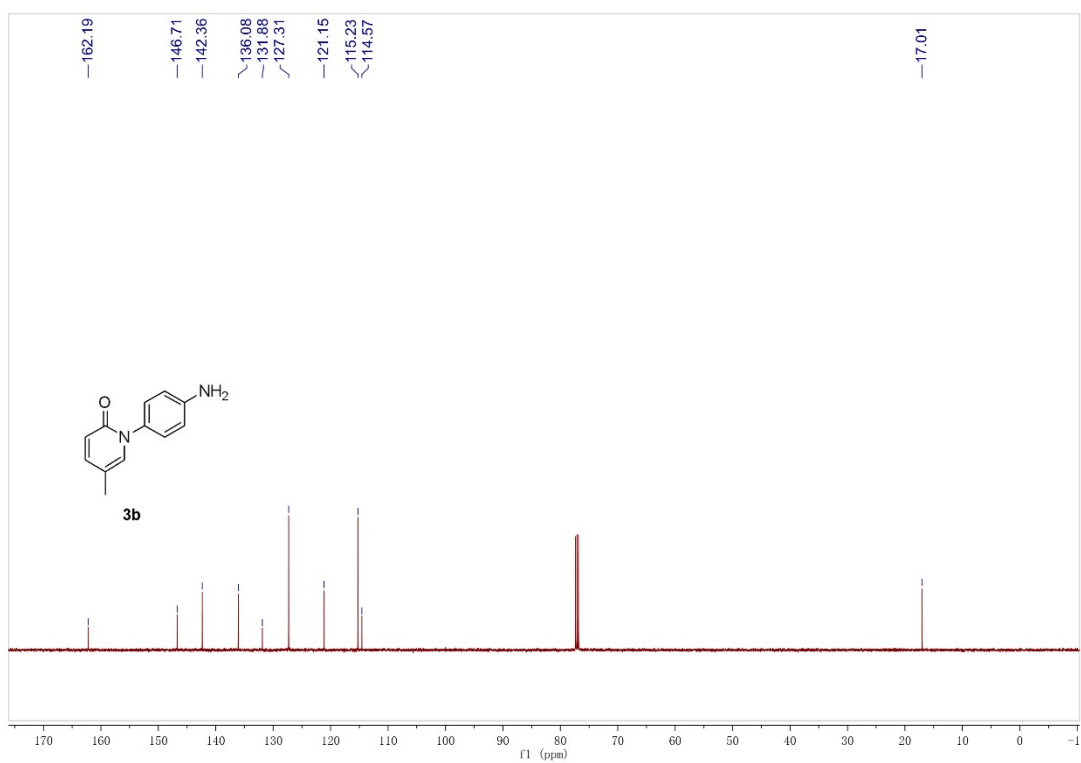
¹H NMR and ¹³C NMR of 3a



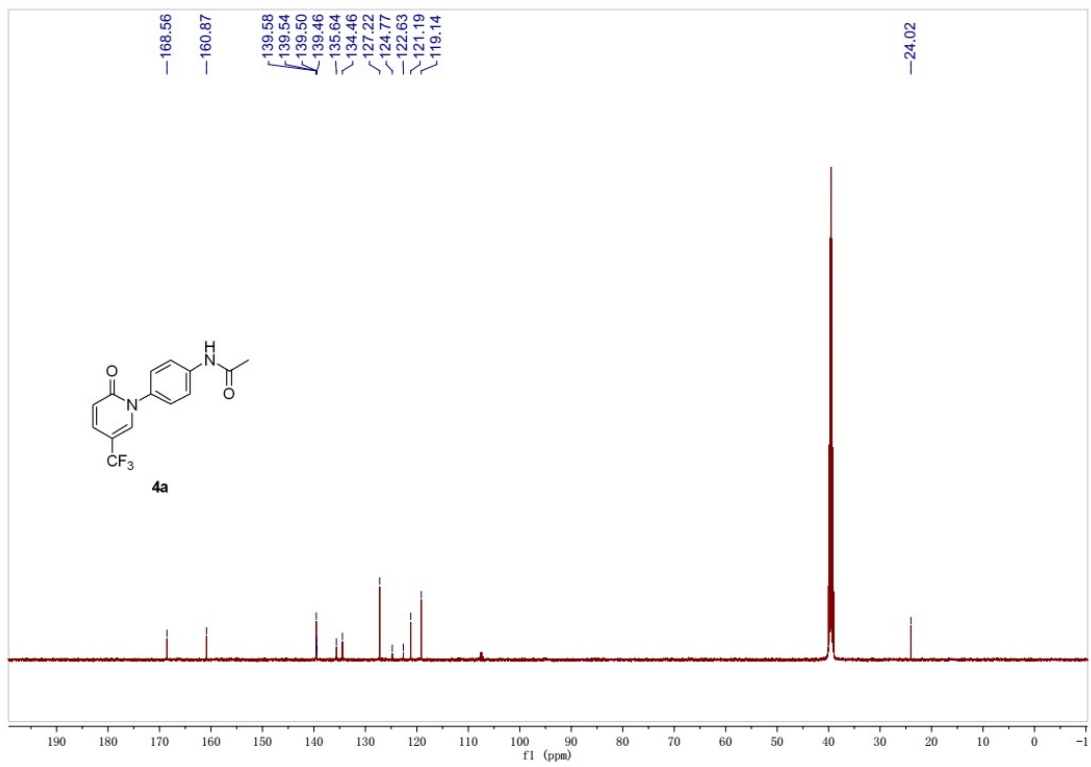
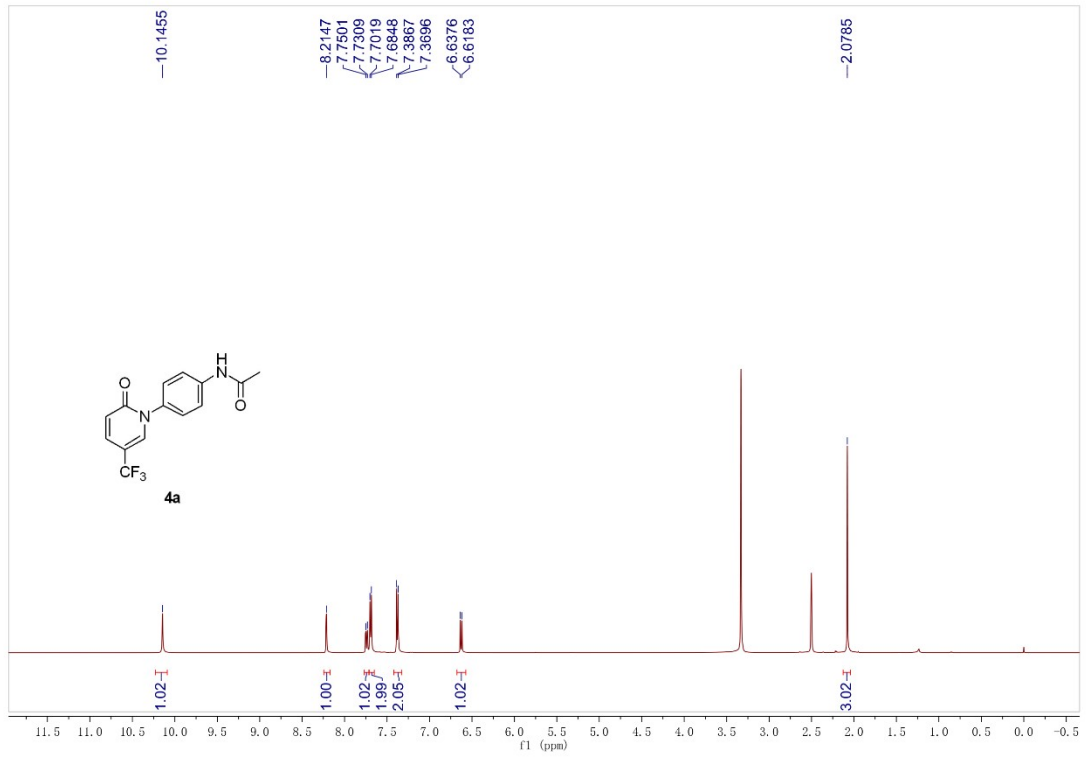


¹H NMR and ¹³C NMR of 3b



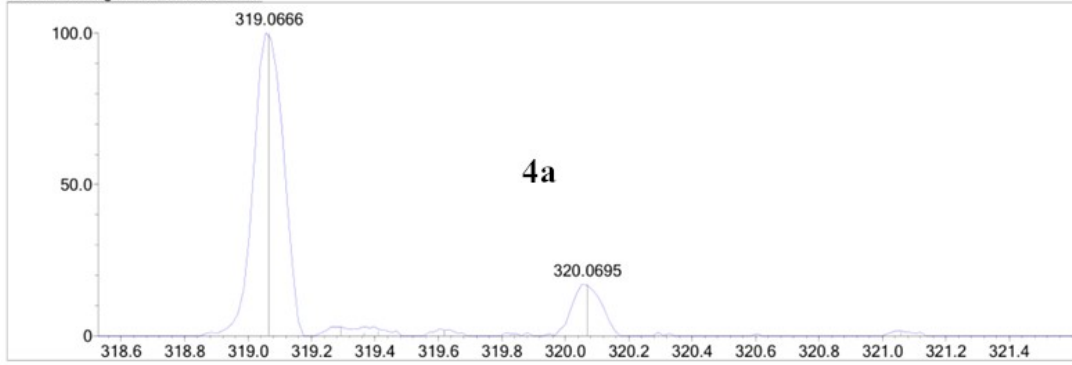


^1H NMR and ^{13}C NMR of **4a**



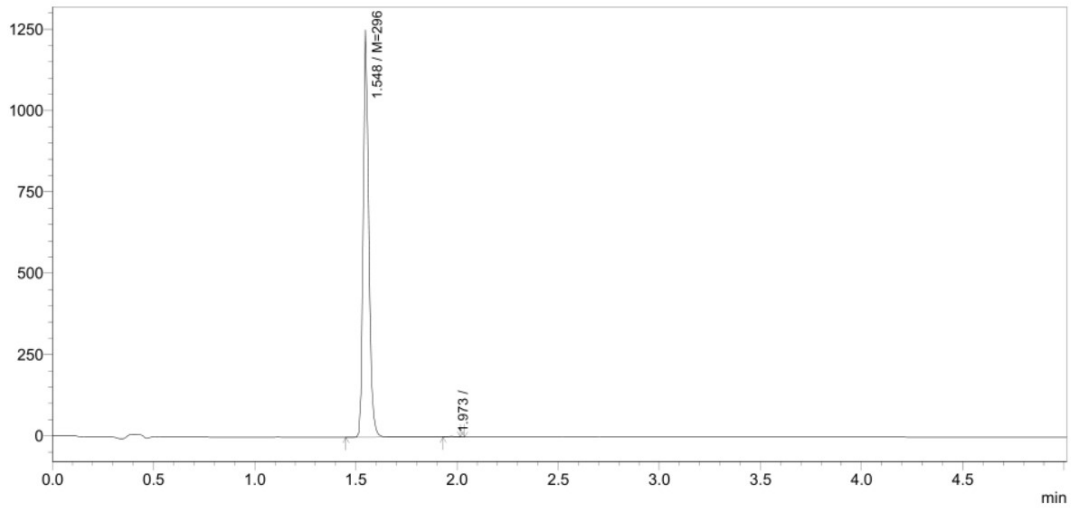
Mass of **4a**

Measured region for 319.0666 m/z



HPLC of 4a

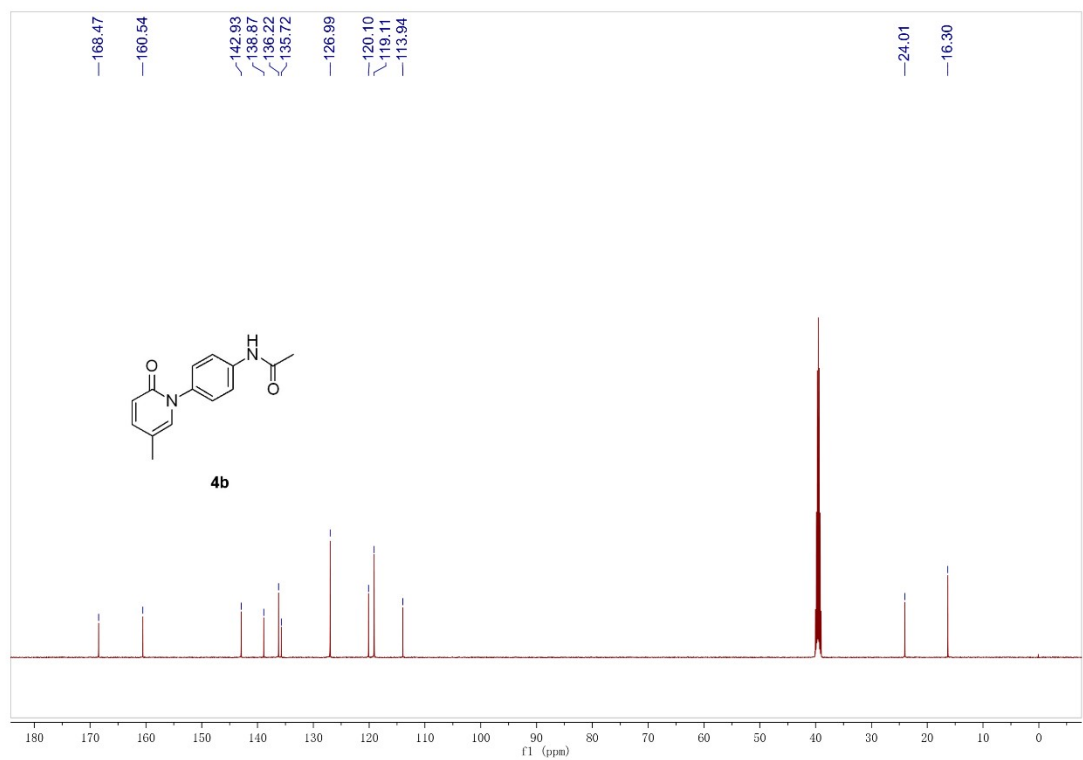
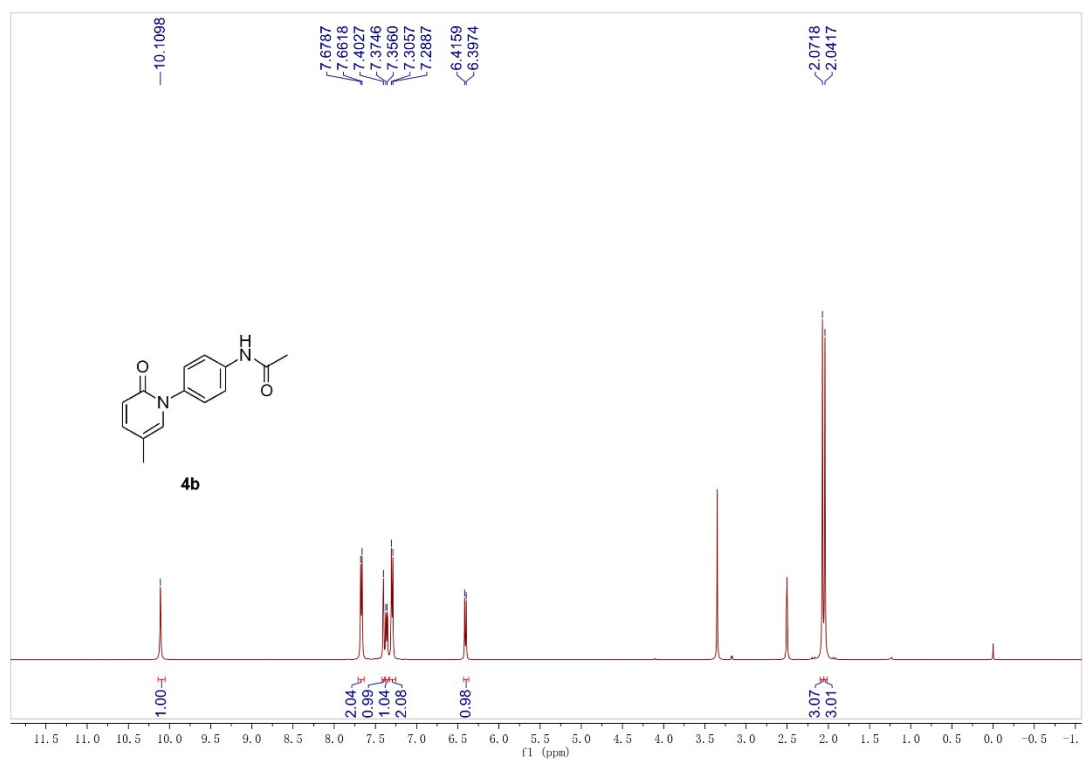
mAU



峰表

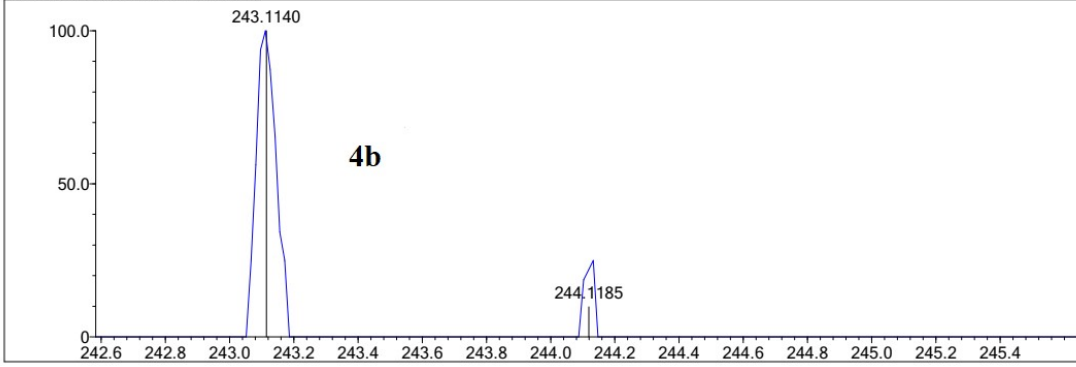
保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
1.548	M=296	0.029	1252978	2388386	99.788	10908	1.208	-
1.973		0.027	3007	5078	0.212	22598	1.158	7.597

^1H NMR and ^{13}C NMR of **4b**



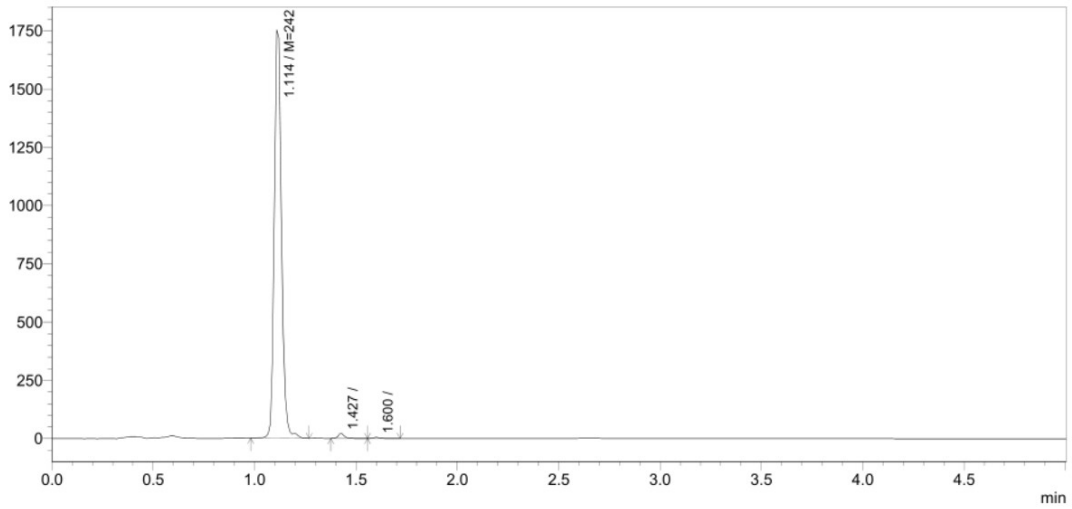
Mass of **4b**

Measured region for 243.1140 m/z



HPLC of 4b

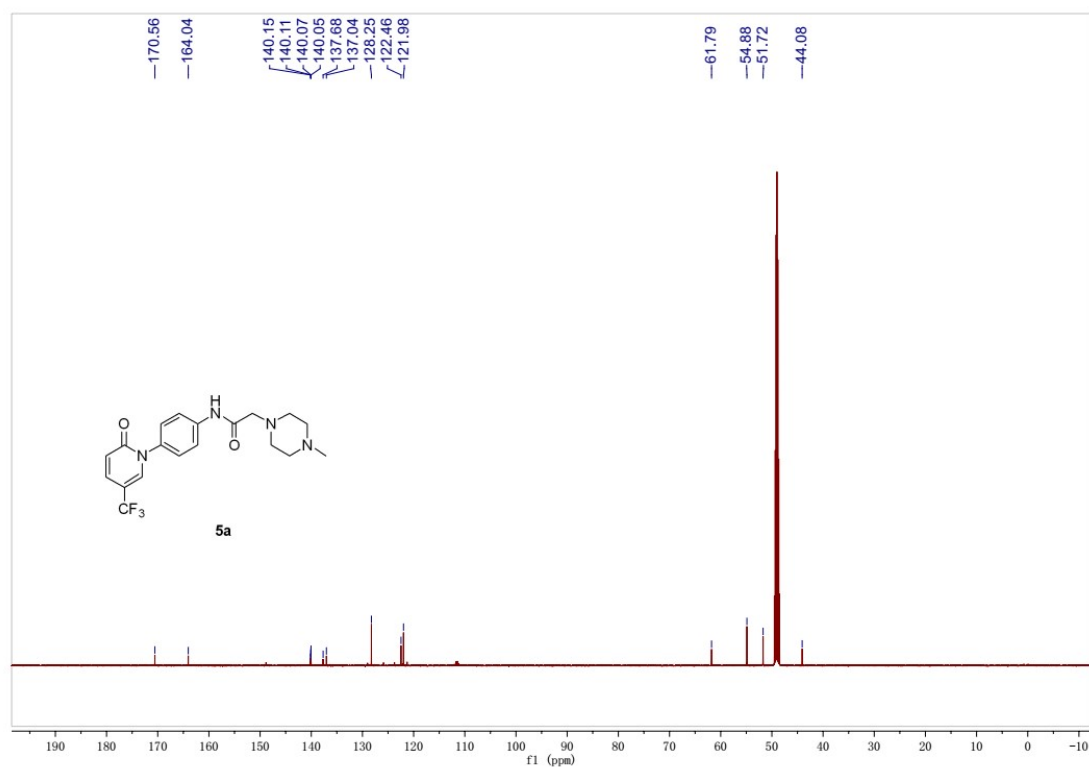
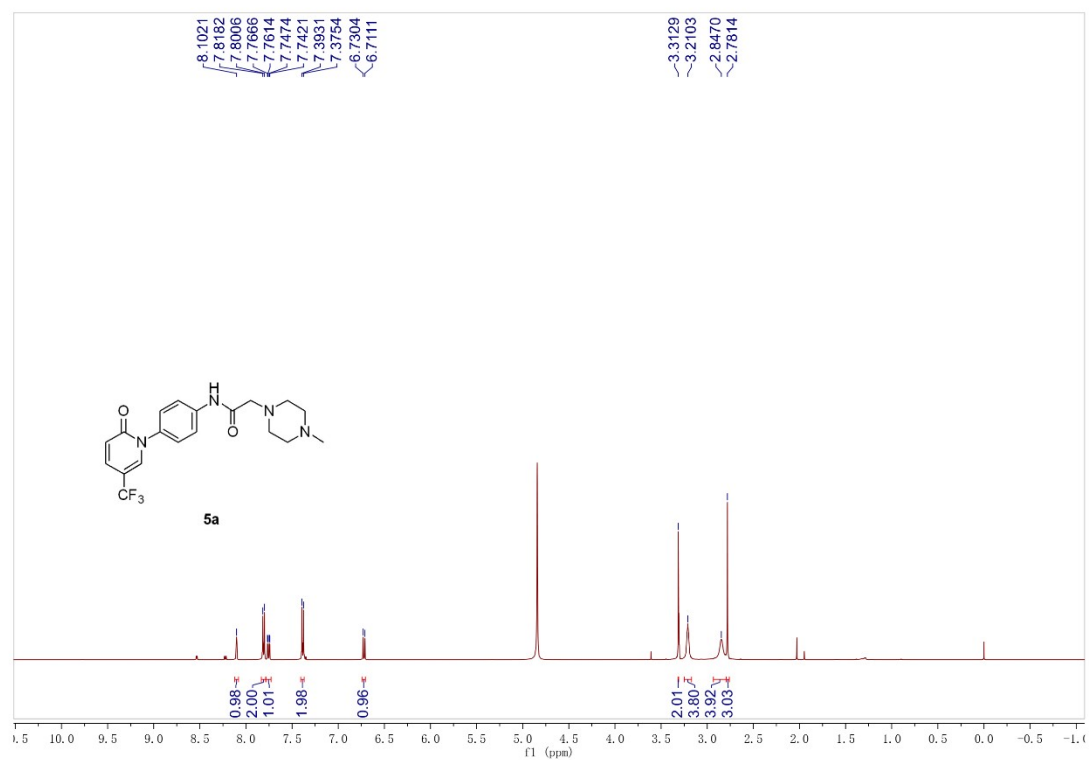
mAU



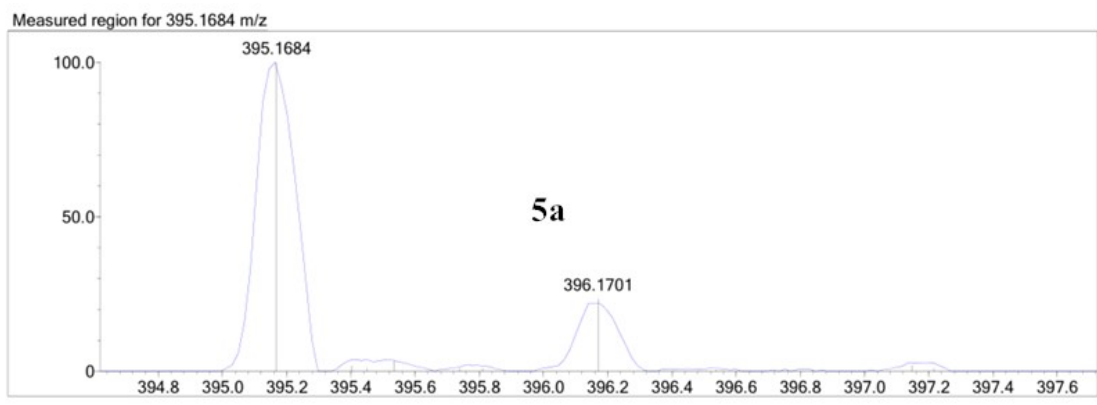
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
1.114	M=242	0.037	1753851	4319620	98.676	3789	1.153	—
1.427		0.030	22461	46482	1.062	8886	1.088	4.711
1.600		0.030	5587	11472	0.262	11584	1.508	2.871
			1781900	4377573	100.000			

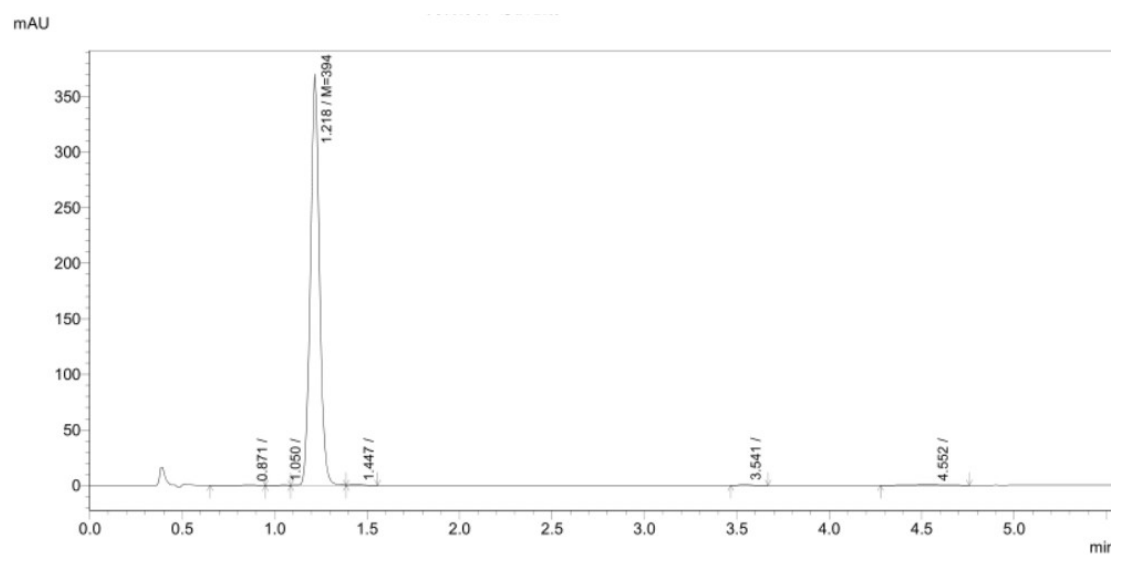
^1H NMR and ^{13}C NMR of **5a**



Mass of **5a**



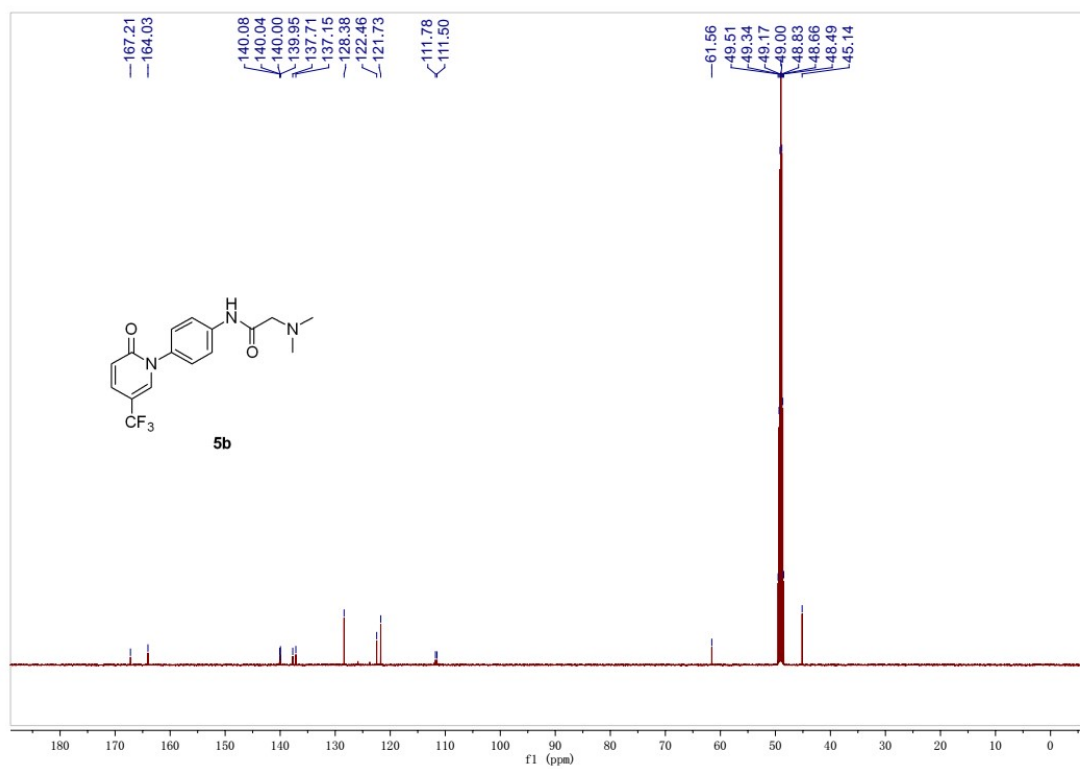
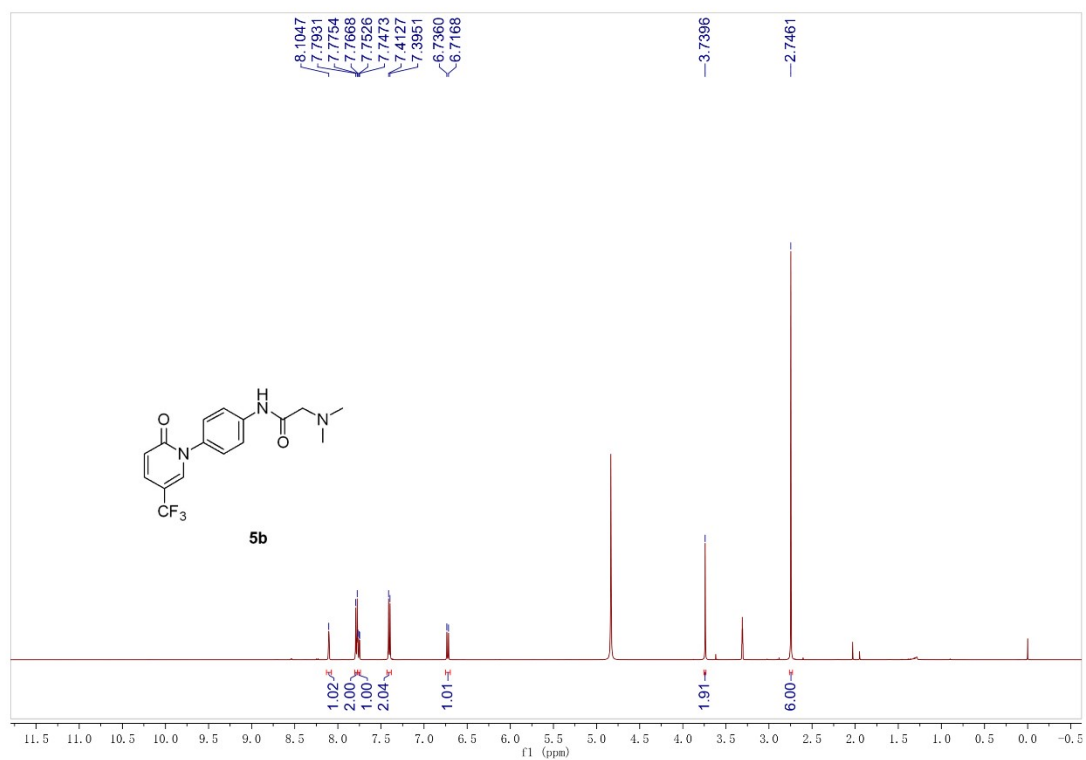
HPLC of 5a



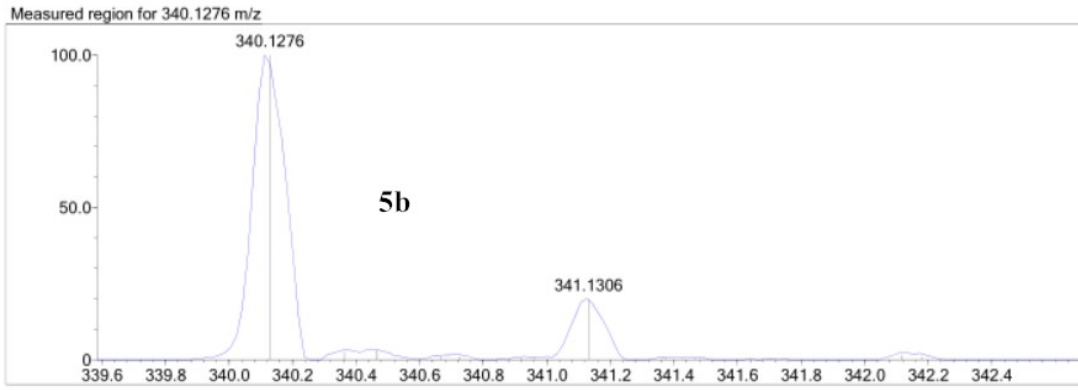
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
0.871		0.113	330	2574	0.200	289	0.657	—
1.050		—	365	1526	0.119	834	—	1.024
1.218	M=394	0.052	370957	1271273	98.740	2162	1.059	1.345
1.447		—	628	3638	0.283	479	—	1.239
3.541		0.048	991	3237	0.251	21832	1.507	11.615
4.552		0.255	338	5246	0.407	2259	0.858	4.222
			373608	1287493	100.000			

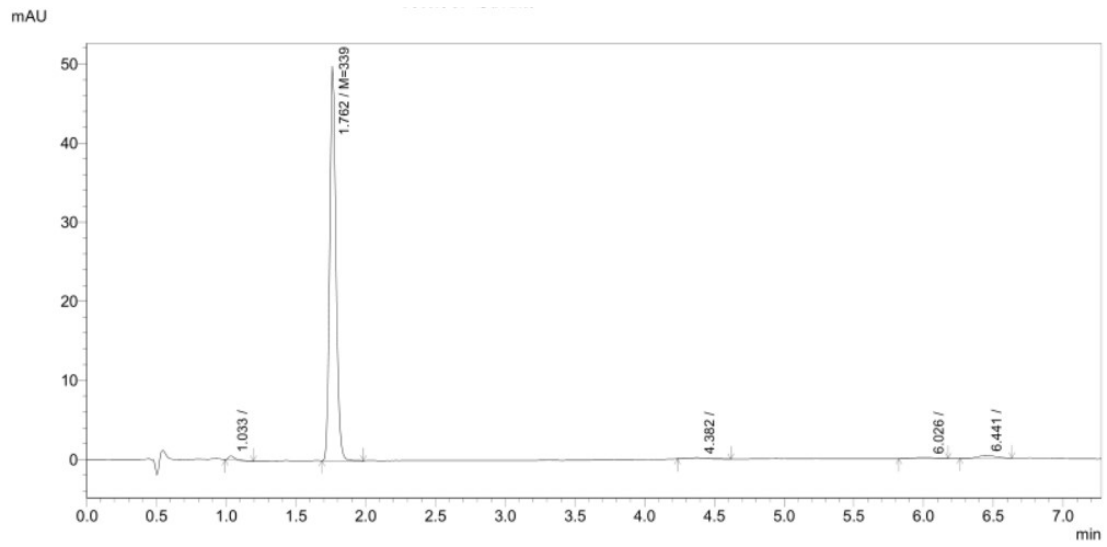
^1H NMR and ^{13}C NMR of **5b**



Mass of **5b**



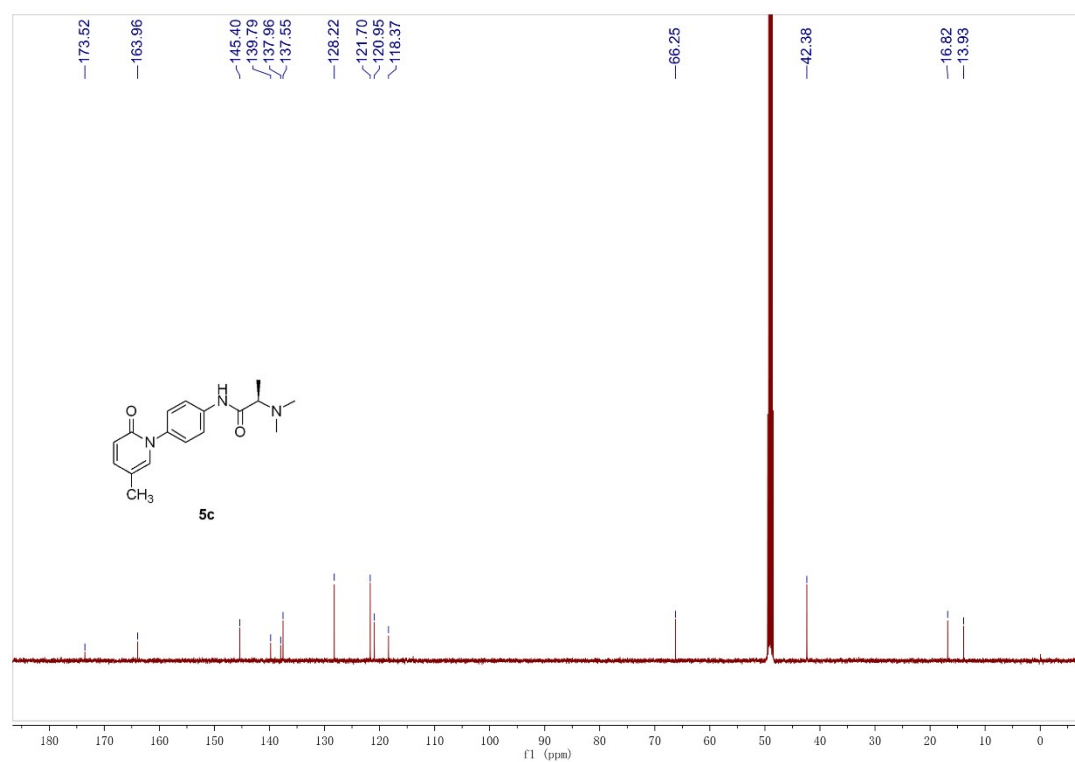
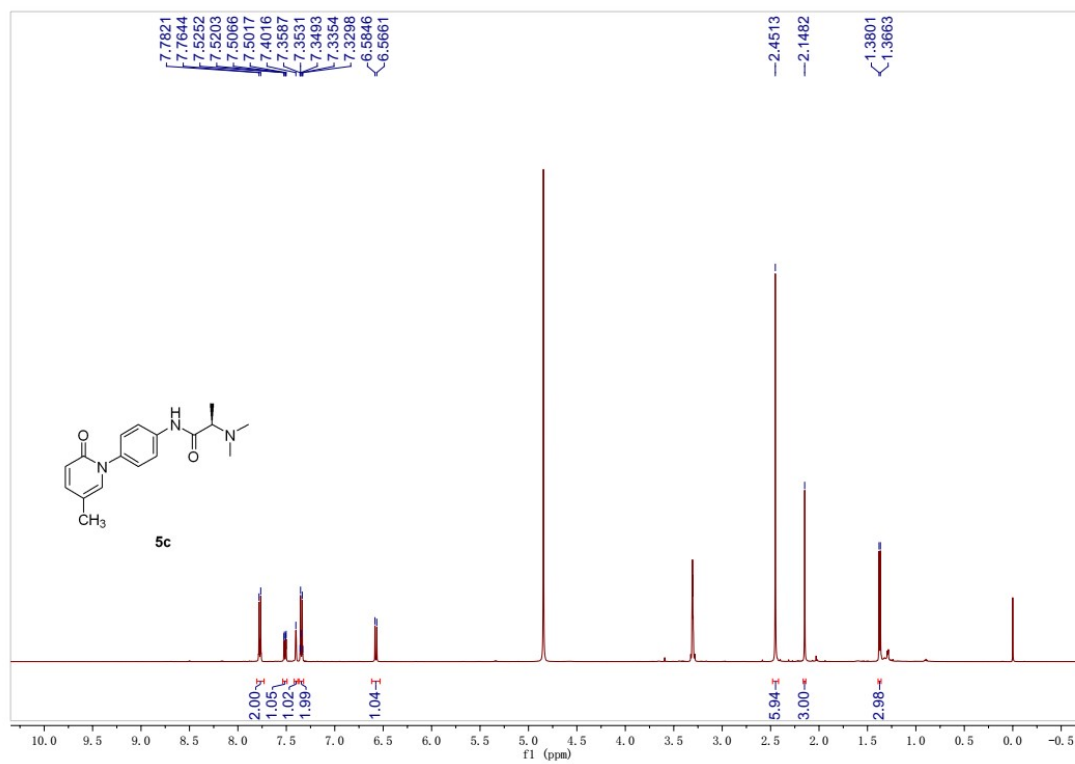
HPLC of 5b



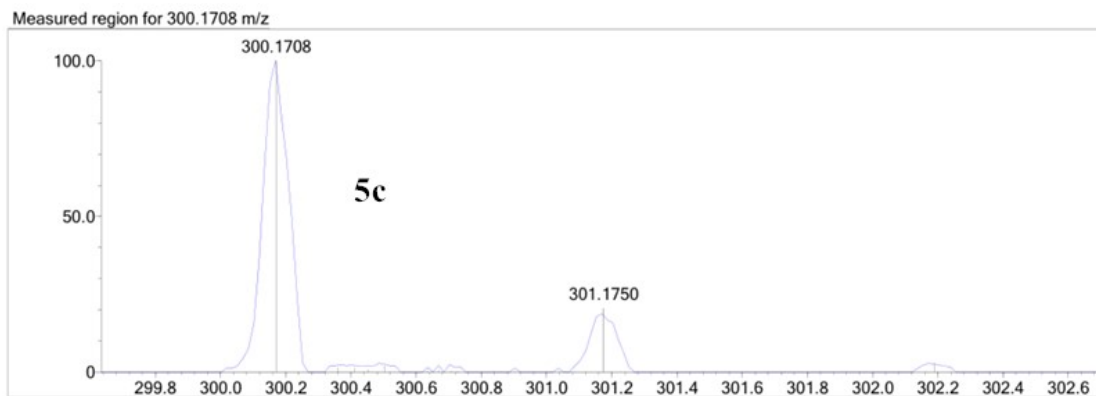
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
1.033		0.049	516	1609	1.000	1838	1.563	
1.762	M=339	0.047	49882	154007	95.716	5453	1.174	7.600
4.382		0.147	142	1354	0.842	4439	1.221	14.614
6.026		0.146	117	1155	0.718	9162	0.848	6.384
6.441		0.135	331	2774	1.724	11368	1.261	1.682
			50989	160899	100.000			

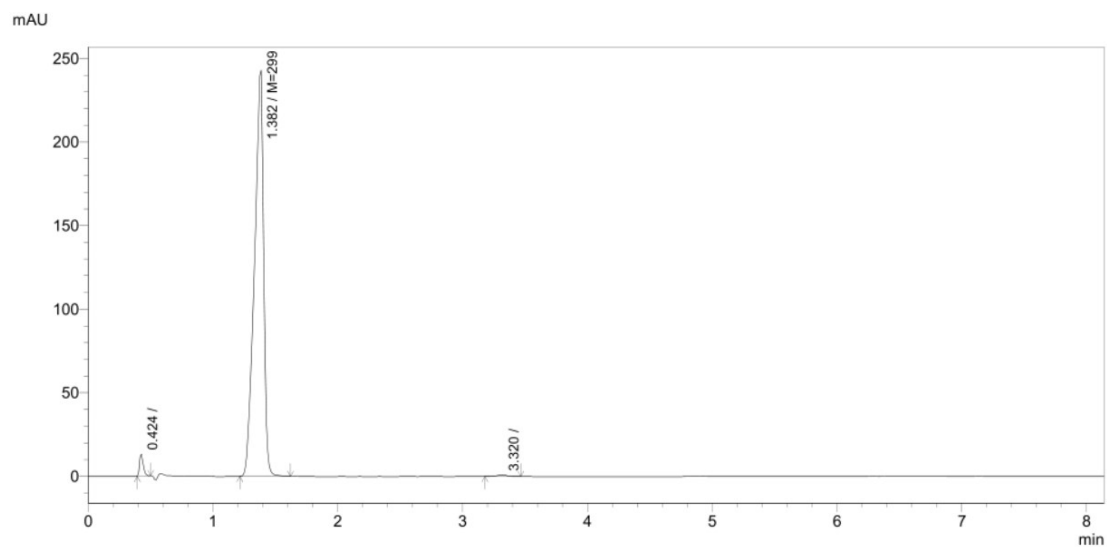
^1H NMR and ^{13}C NMR of **5c**



Mass of **5c**



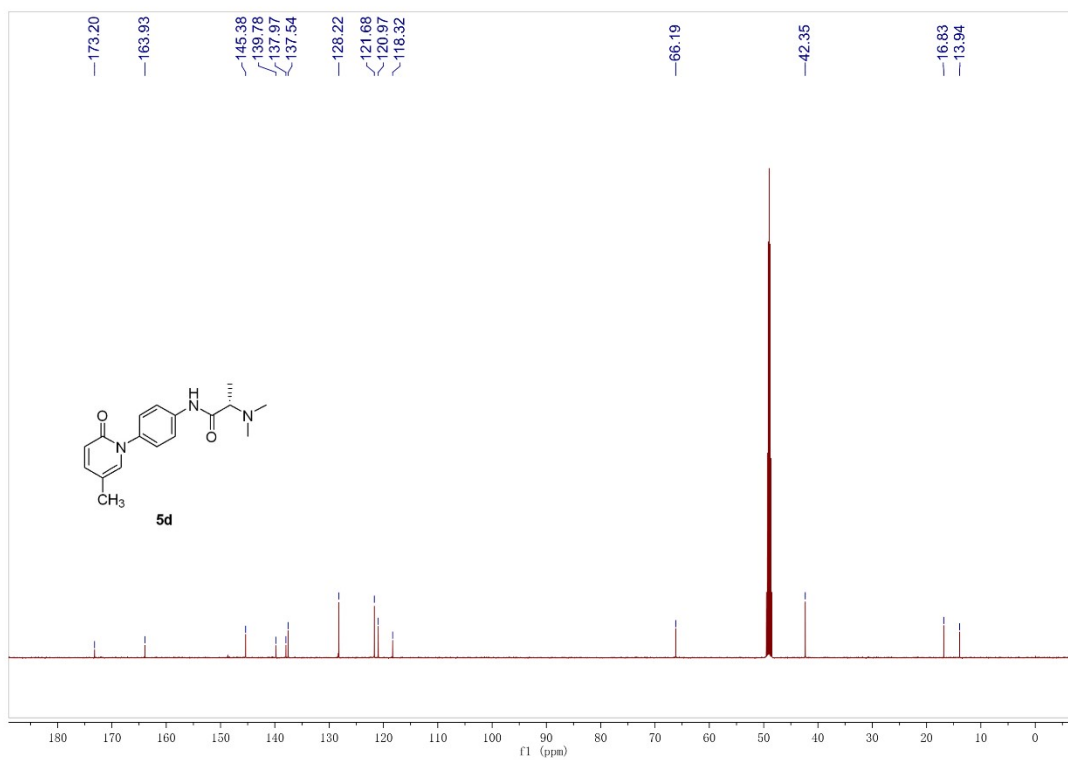
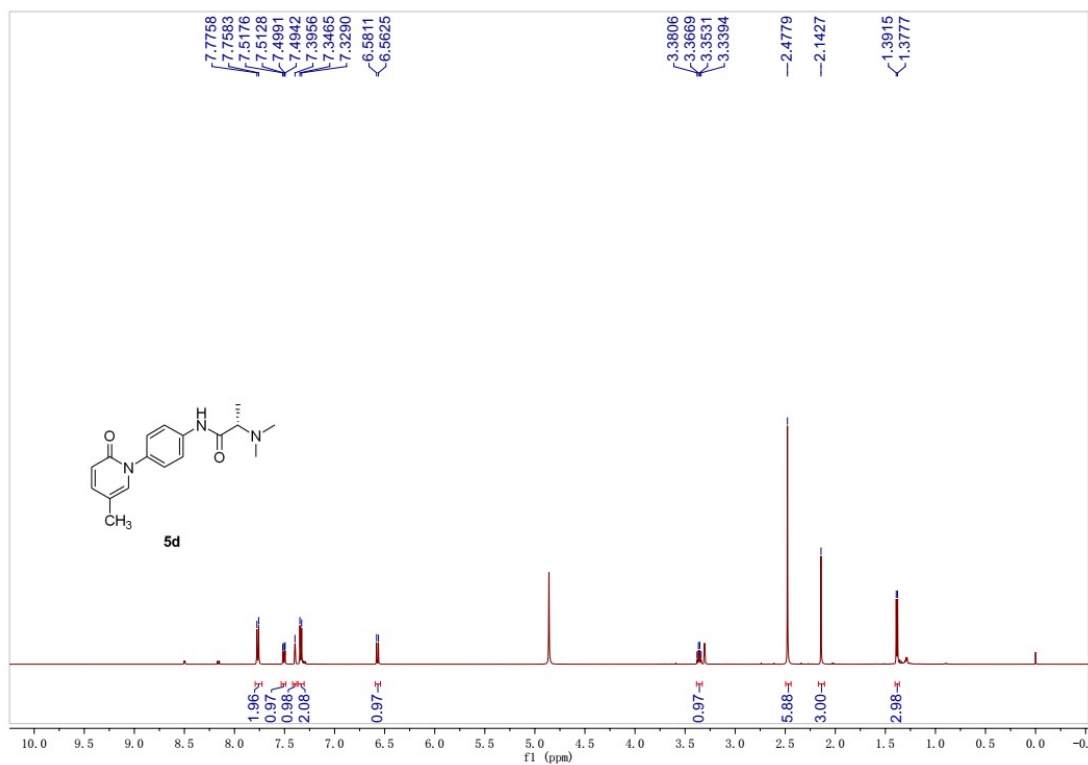
HPLC of 5c



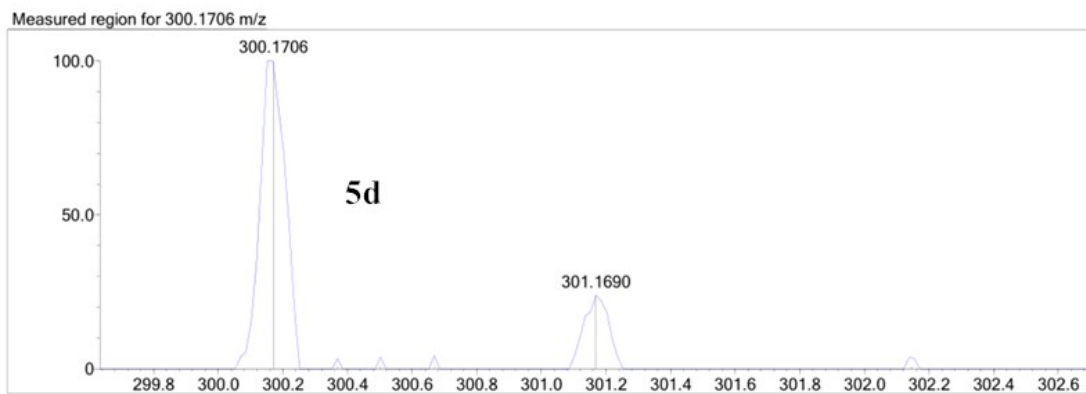
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
0.424		0.031	13256	26897	2.129	930	1.341	—
1.382	M=299	0.077	243123	1230946	97.424	1350	0.773	9.293
3.320		0.078	1055	5653	0.447	6938	1.047	12.511
			257435	1263497	100.000			

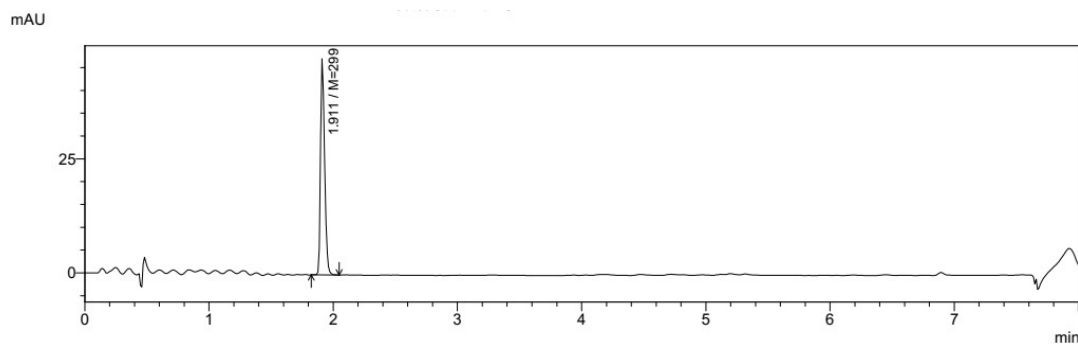
^1H NMR and ^{13}C NMR of **5d**



Mass of **5d**



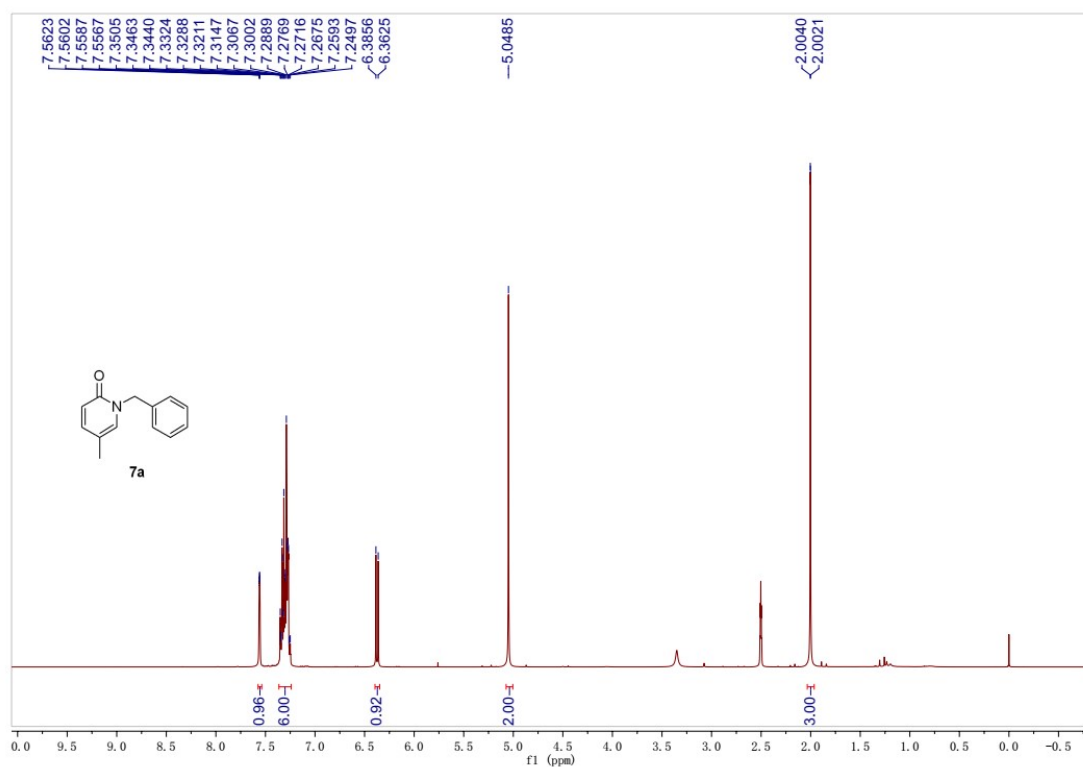
HPLC of 5d

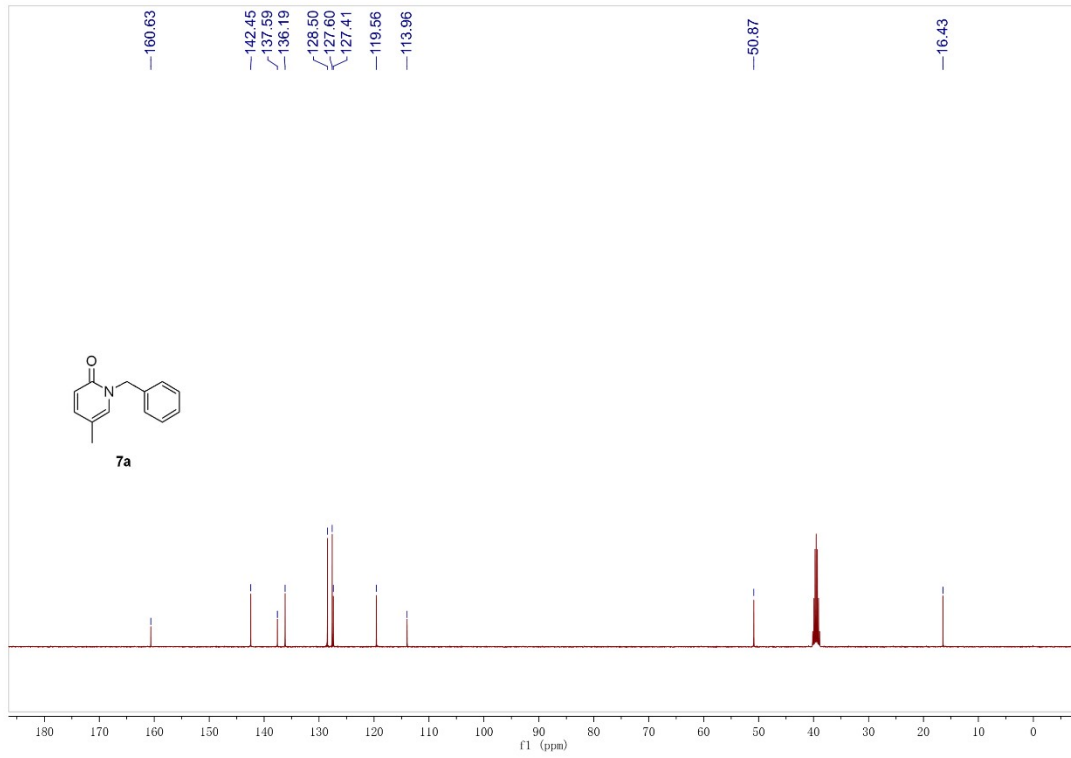


峰表

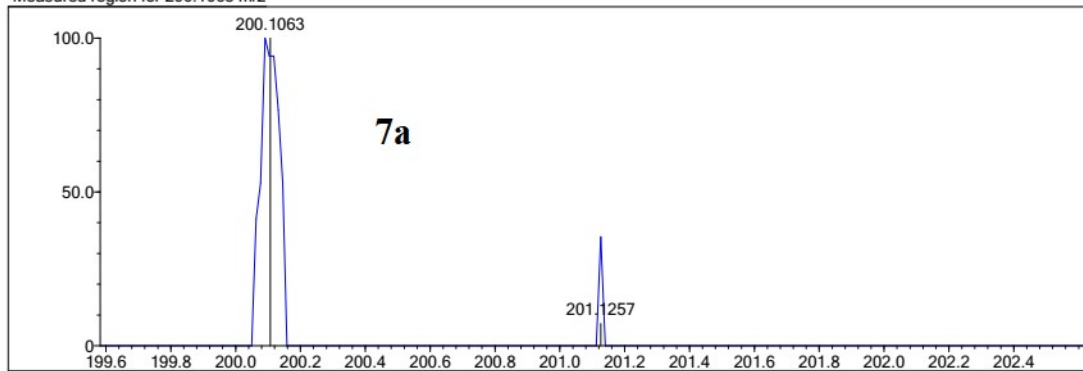
保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
1.911	M=299	0.035	47372	107621	100.000	11852	1.303	--
			47372	107621	100.000			

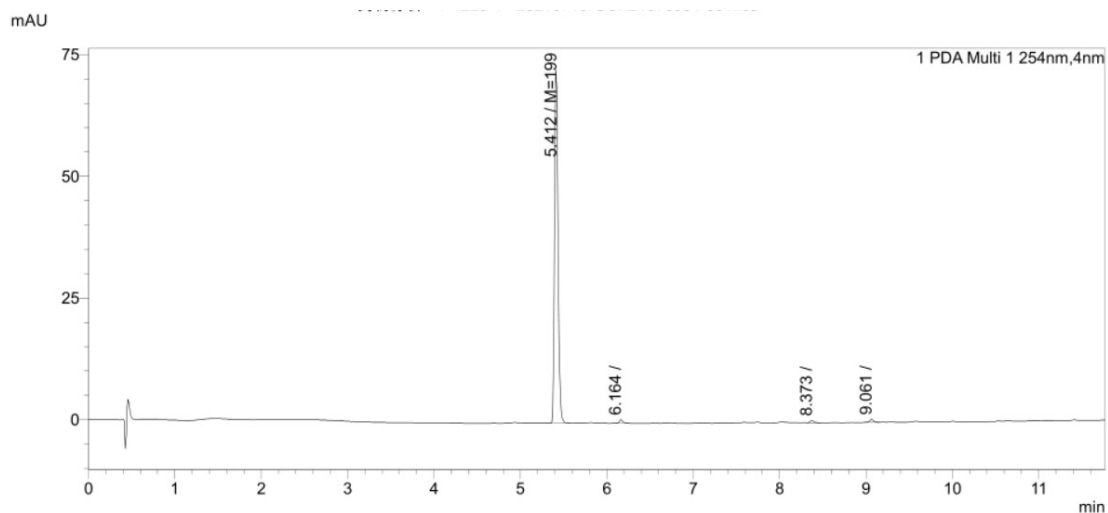
¹H NMR and ¹³C NMR of 7a





Measured region for 200.1063 m/z

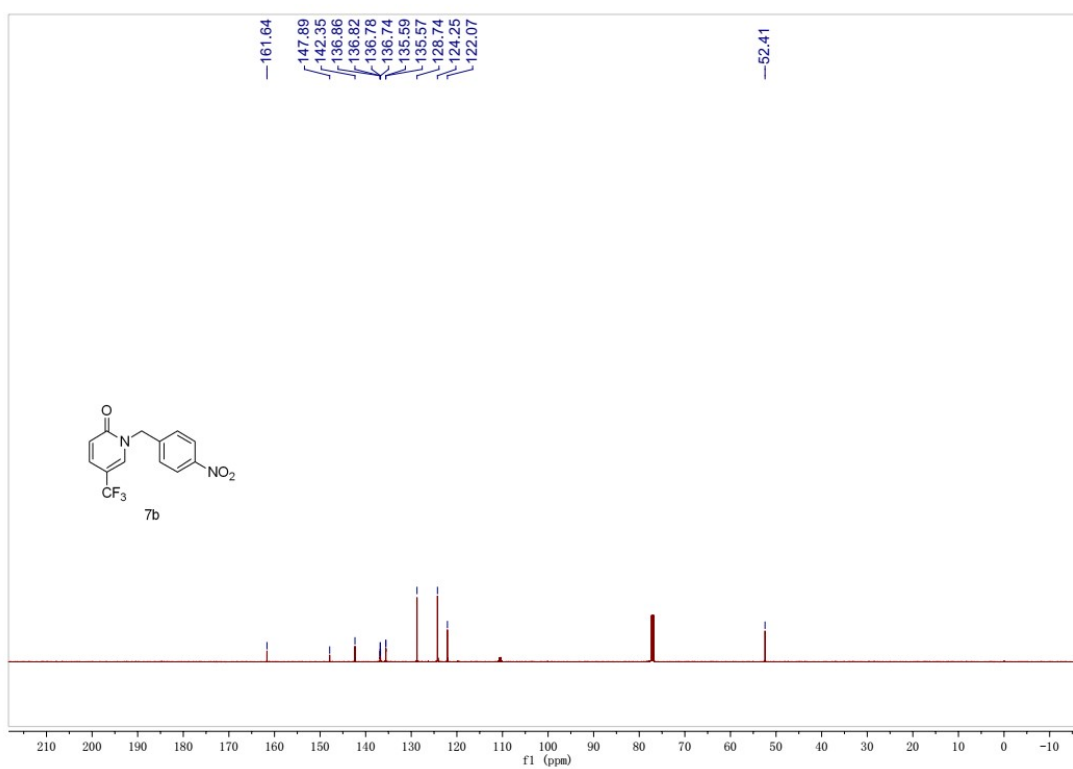
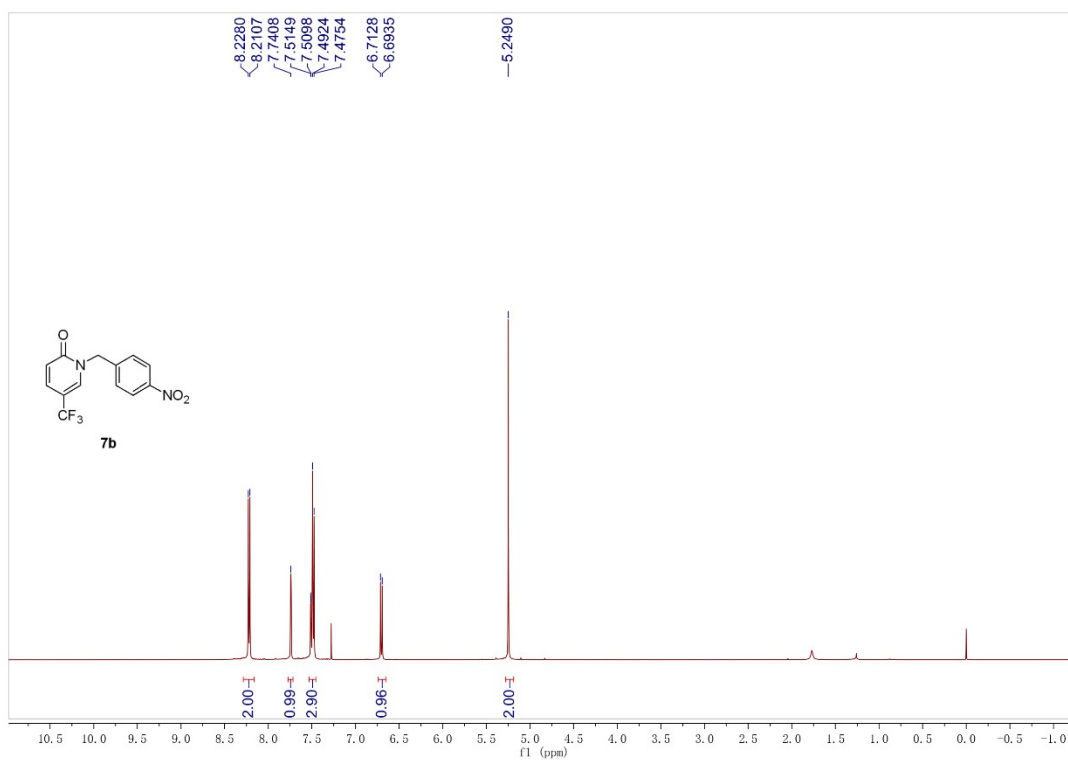




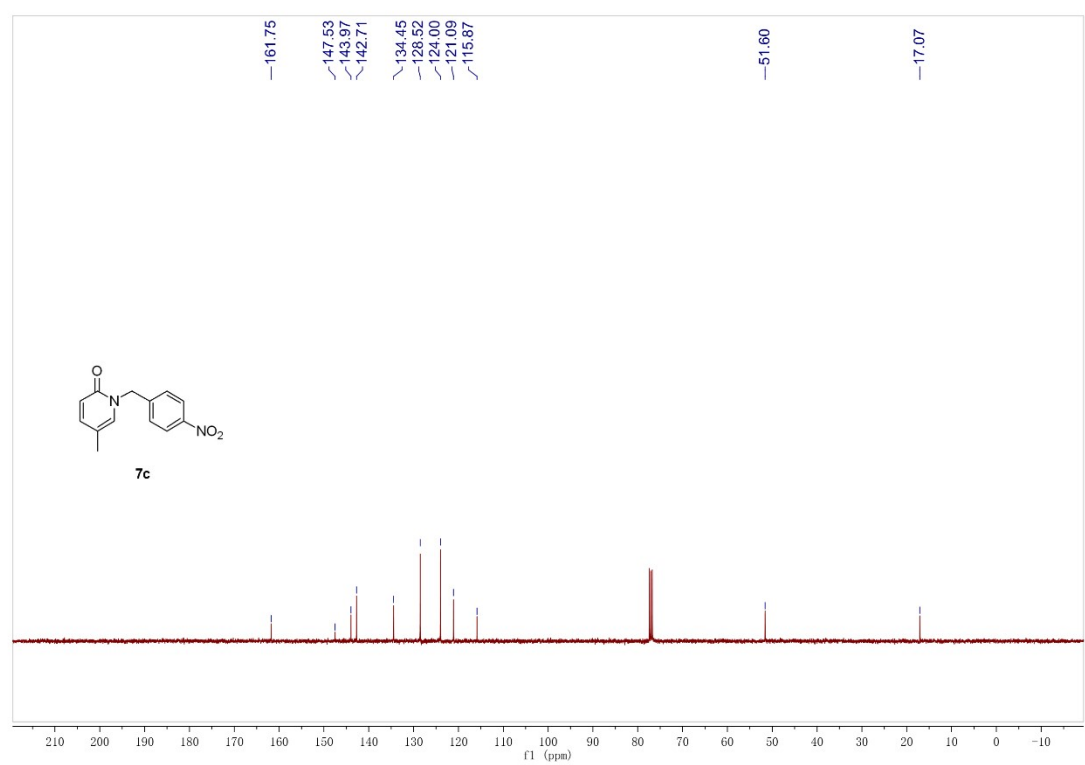
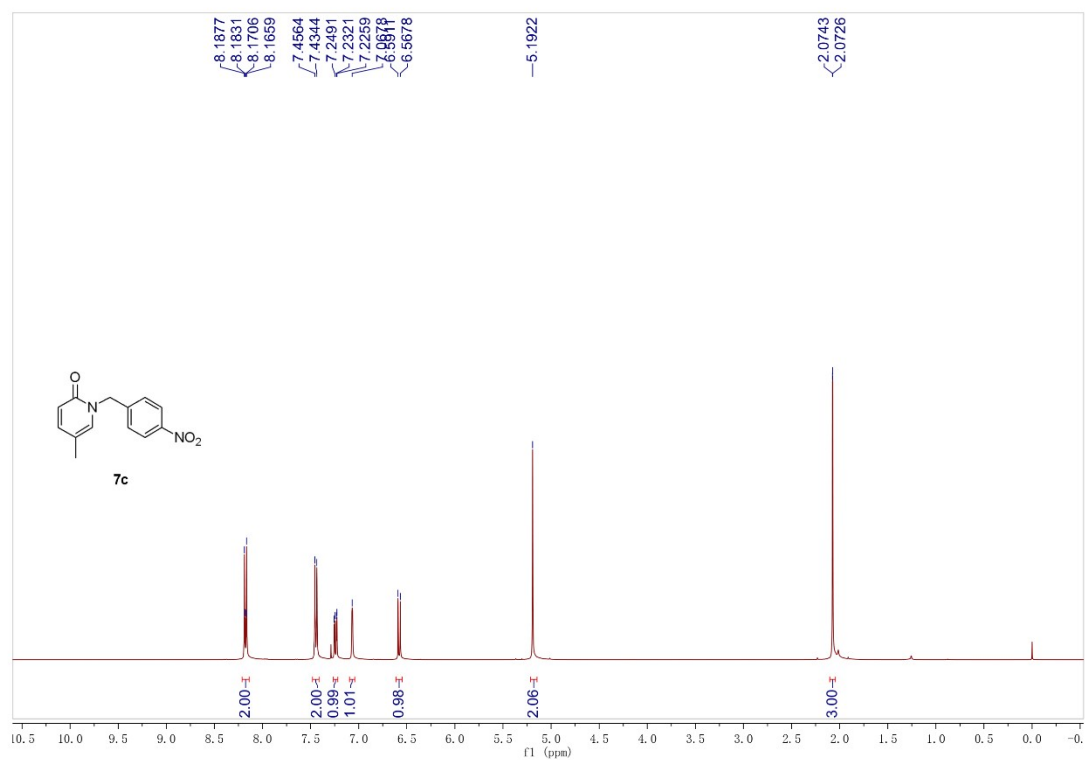
峰结果表 药物分析 - 1-1220-4 - 20210713-GCX21070901-001.kcd

峰号	保留时间	化合物名	半峰宽	高度 (mAU)	面积mAU*min	面积%	理论塔板数	分离度	拖尾因子	最小峰纯度指数
1	5.412	M=199	0.043	72627	201777	97.45	65218	N/A	1.30	2408
2	6.164		0.041	711	1945	0.94	88020	8.96	1.37	Cannot be calculated
3	8.373		0.049	449	1409	0.68	118694	24.51	1.31	Cannot be calculated
4	9.061		0.051	575	1923	0.93	126312	6.91	1.24	Cannot be calculated

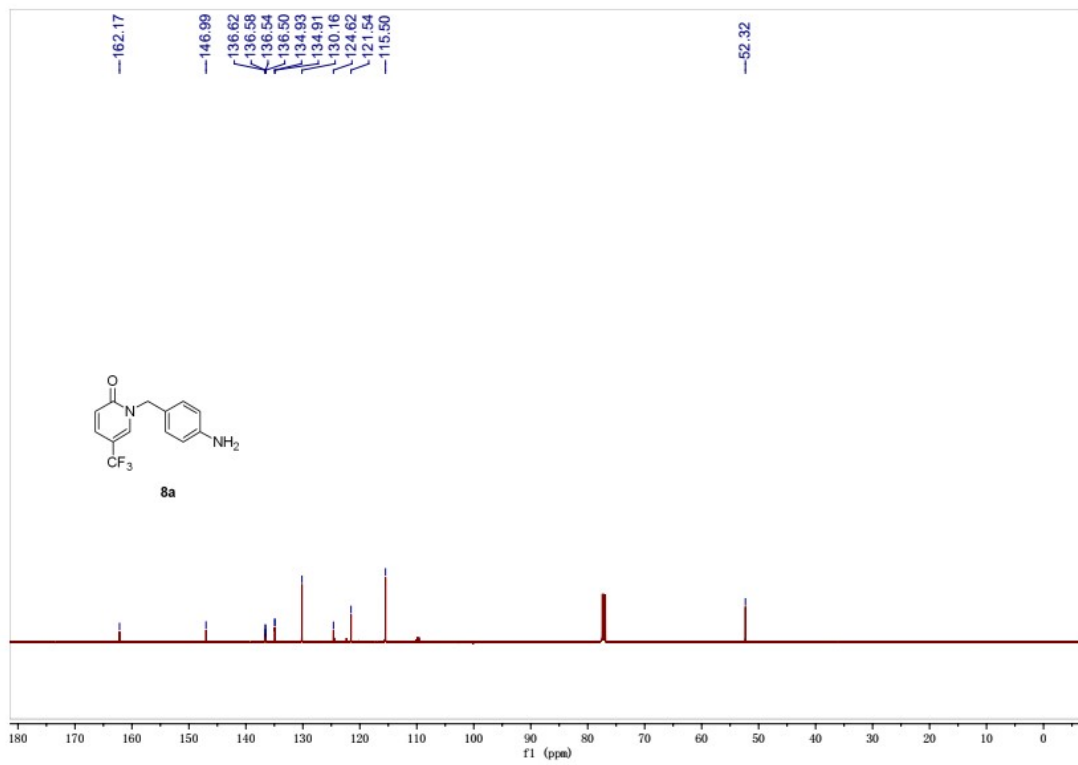
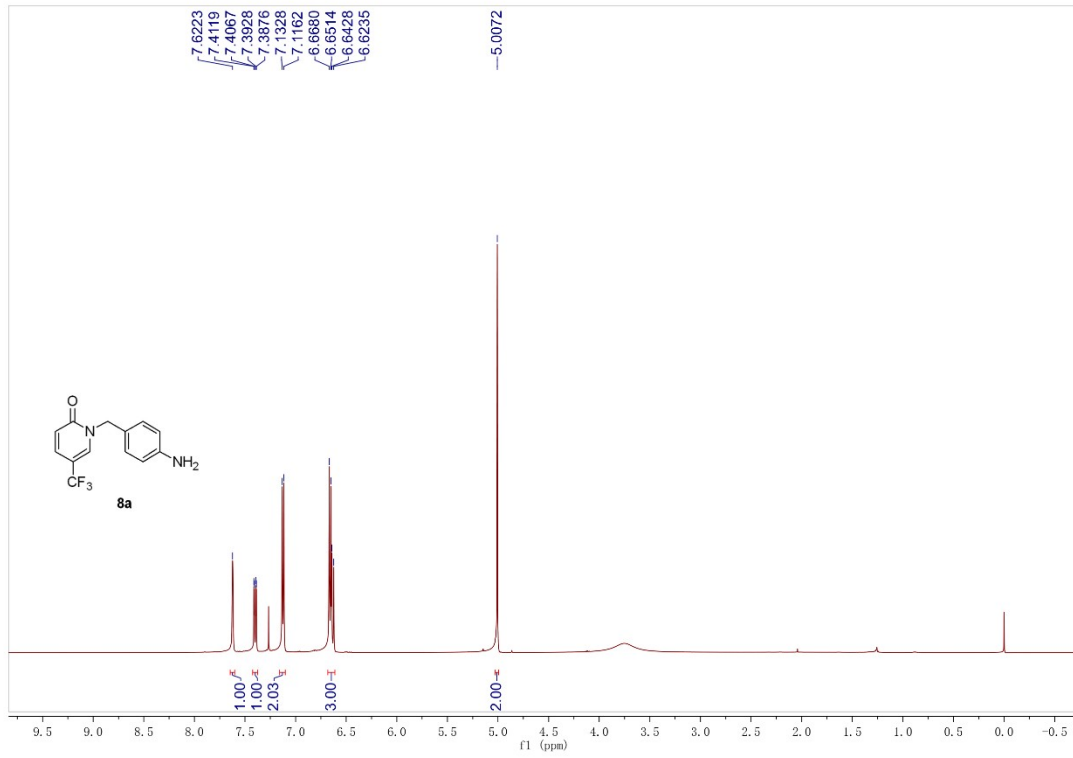
¹H NMR and ¹³C NMR of *7b*



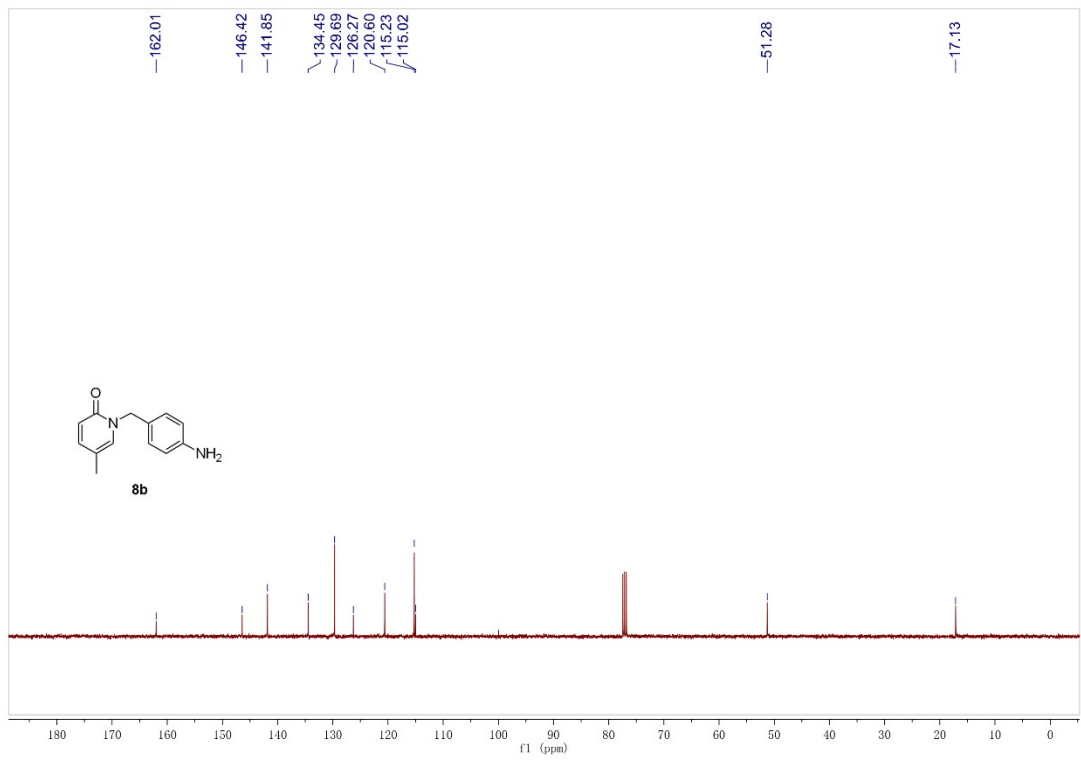
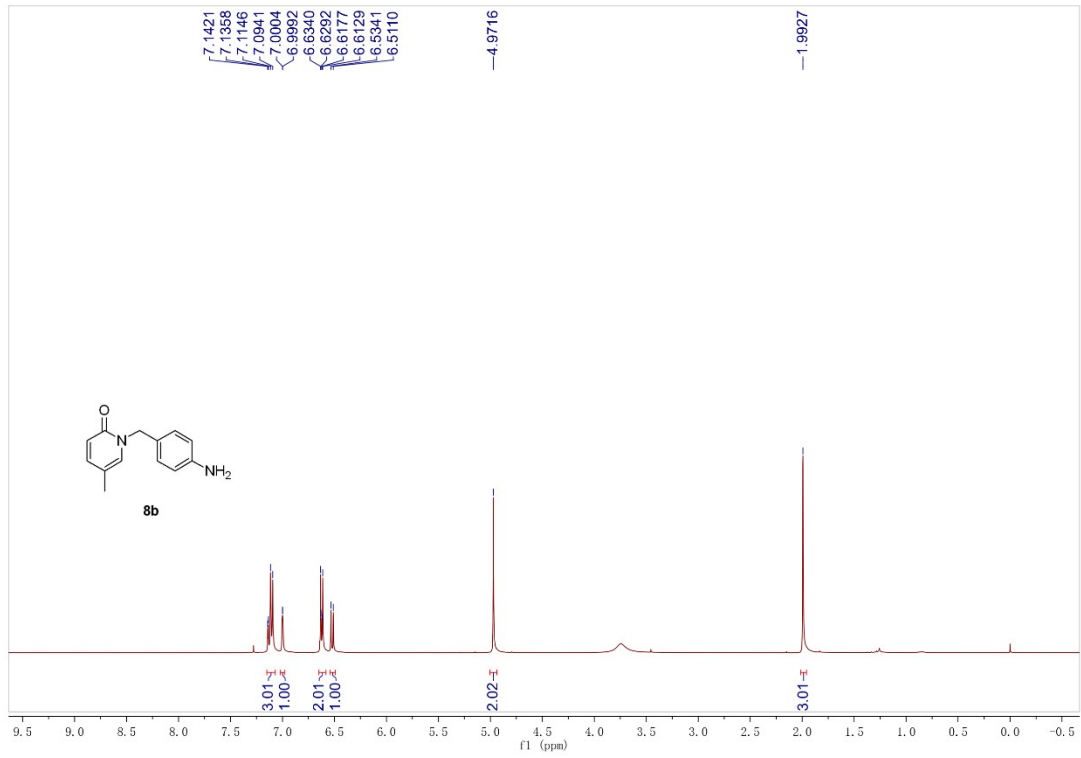
¹H NMR and ¹³C NMR of **7c**



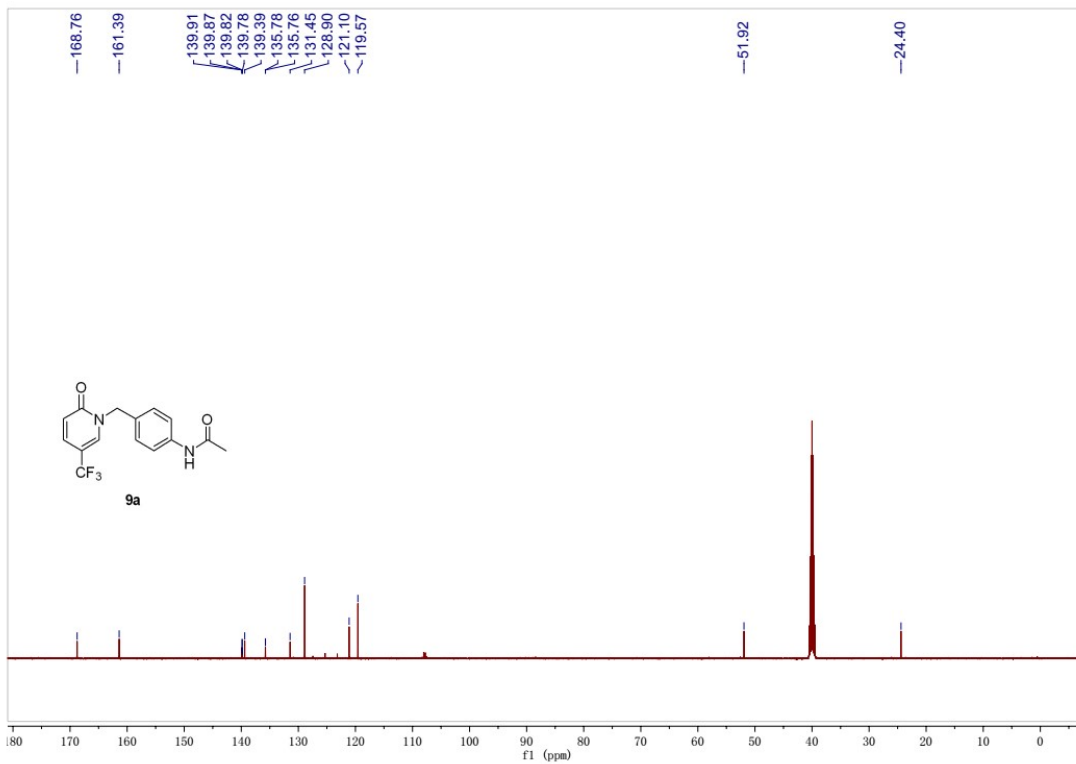
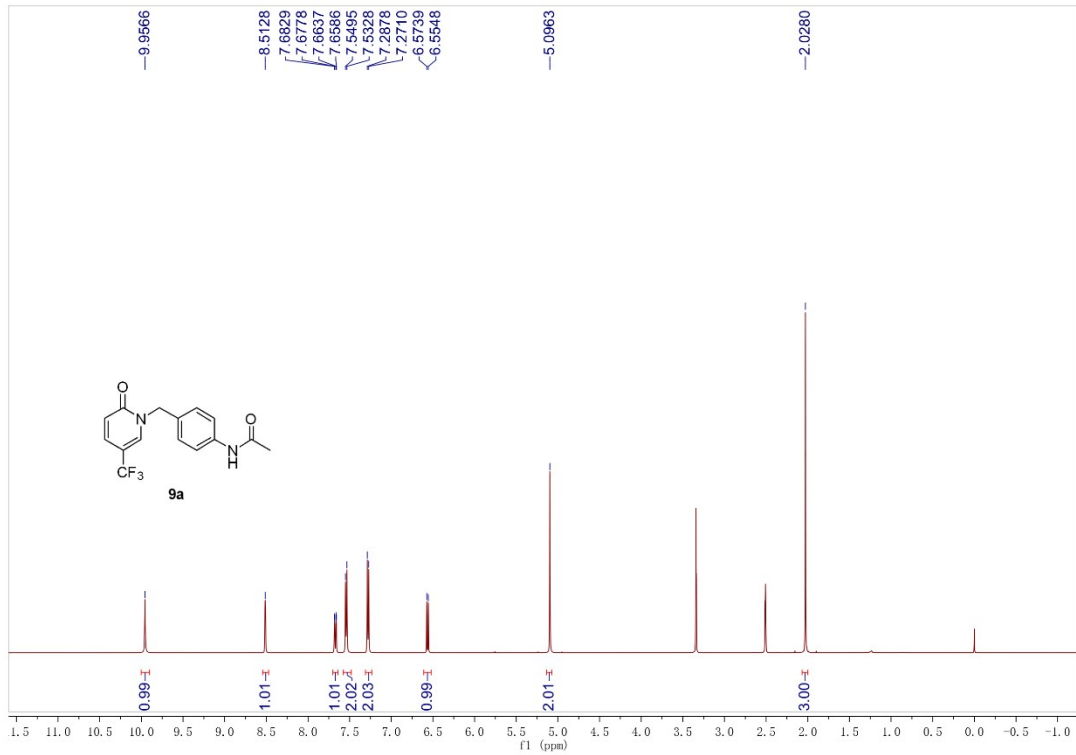
¹H NMR and ¹³C NMR of 8a



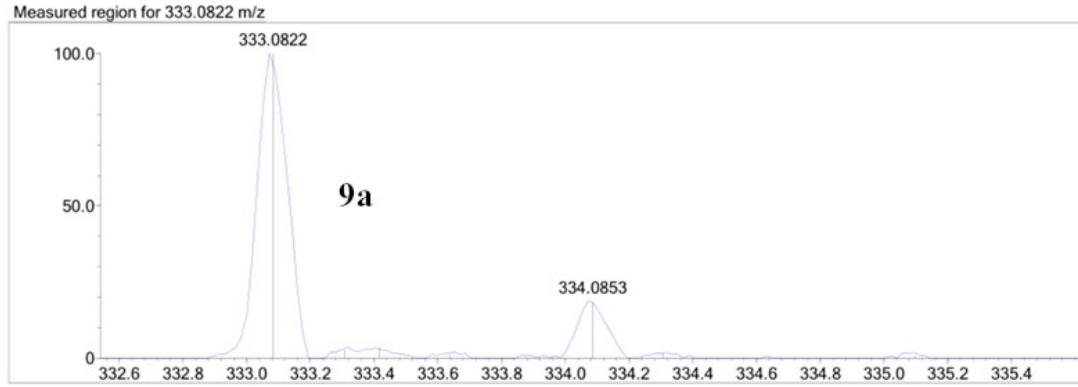
¹H NMR and ¹³C NMR of 8b



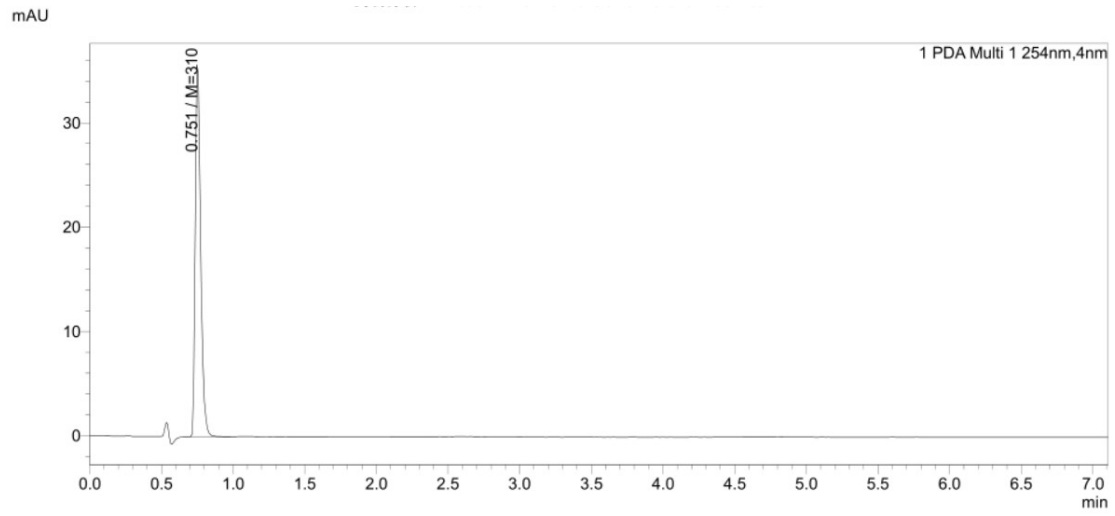
¹H NMR and ¹³C NMR of **9a**



Mass of **9a**



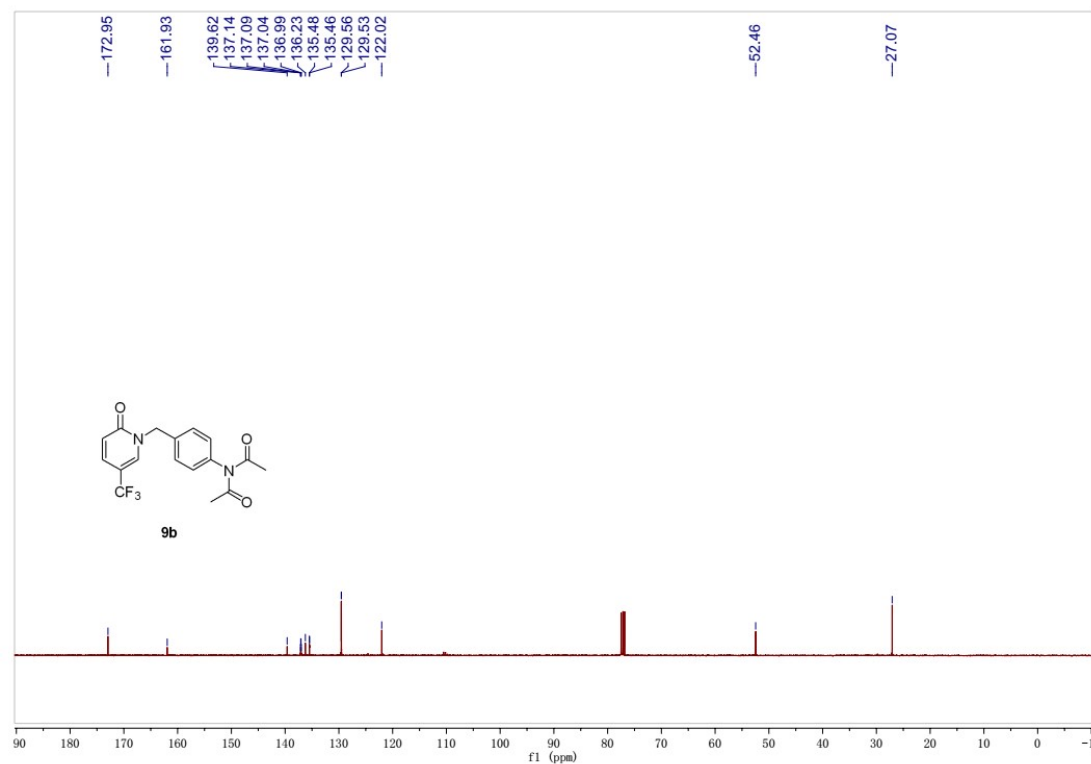
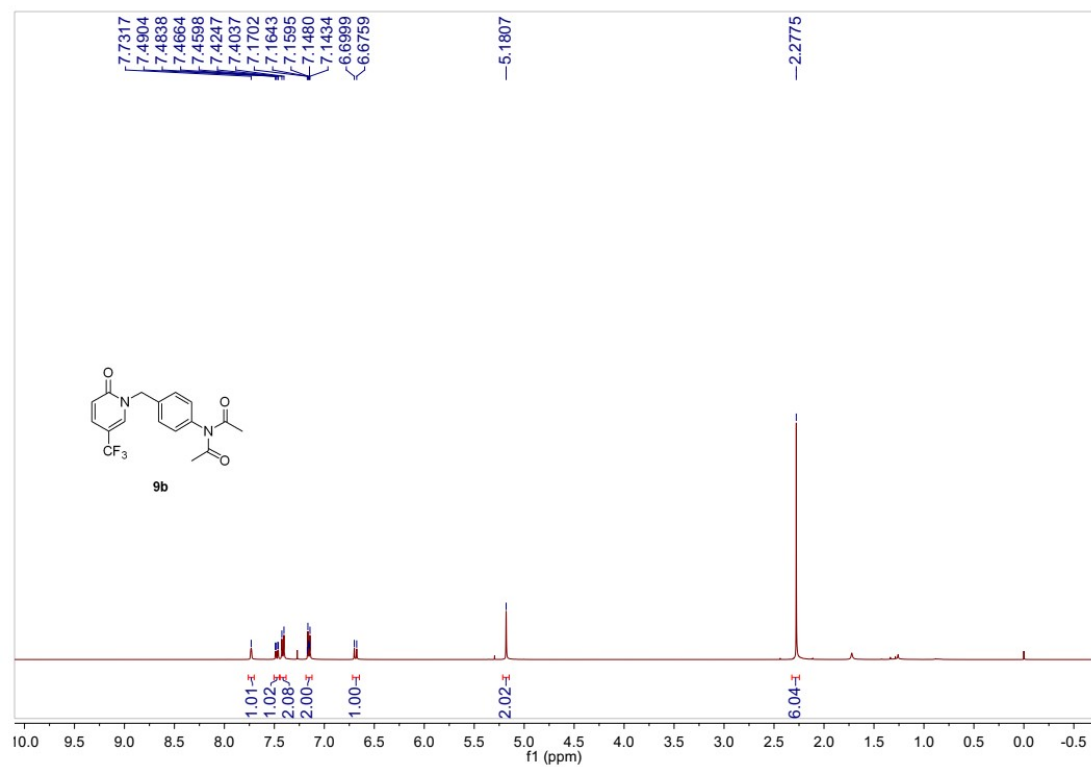
HPLC of 9a



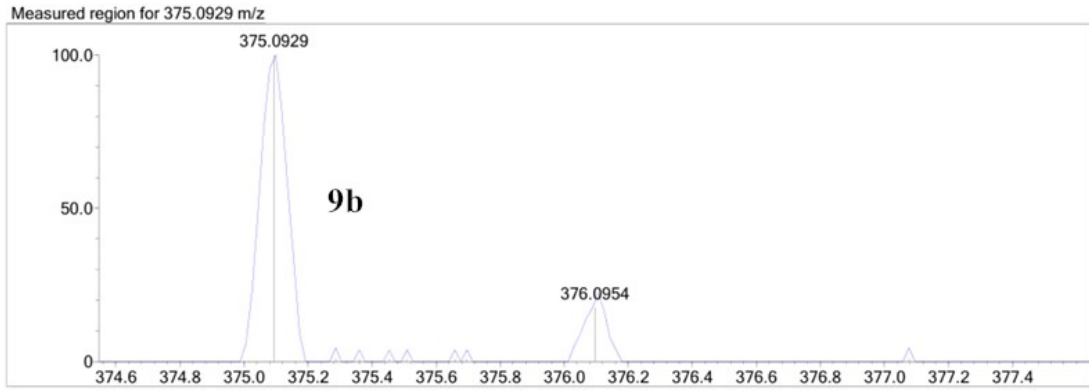
峰结果表 药物分析 - 1-1395-2 - 20210729-GCX0728-310-2-001.lcd

峰号	保留时间	化合物名	半峰宽	高度 (mAU)	面积mAU*min	面积%	理论塔板数	分离度	拖尾因子	最小峰纯度指数
1	0.751	M=310	0.040	35678	94773	100.00	1428	N/A	1.37	Not calculated

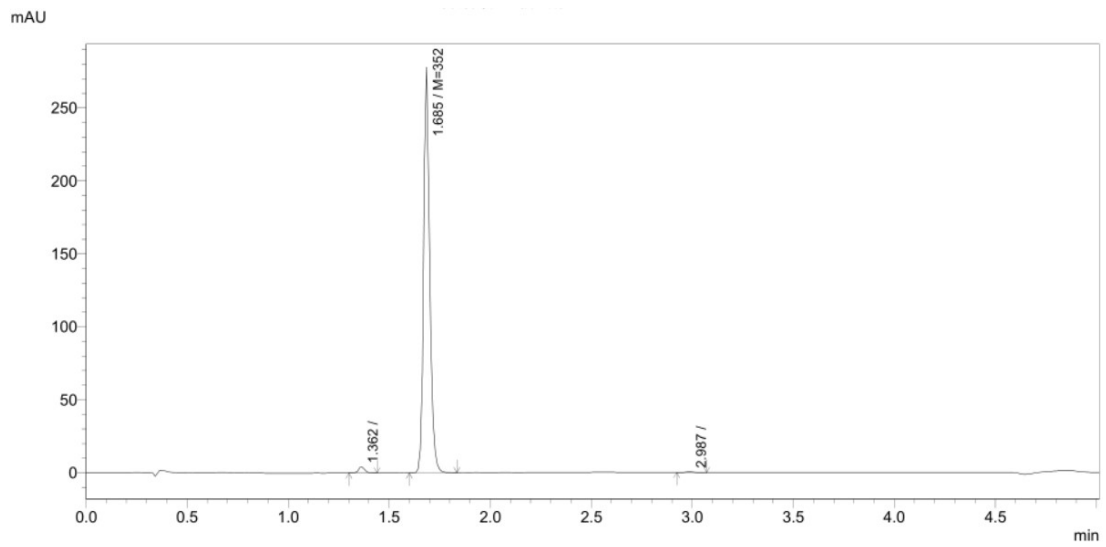
^1H NMR and ^{13}C NMR of **9b**



Mass of **9b**



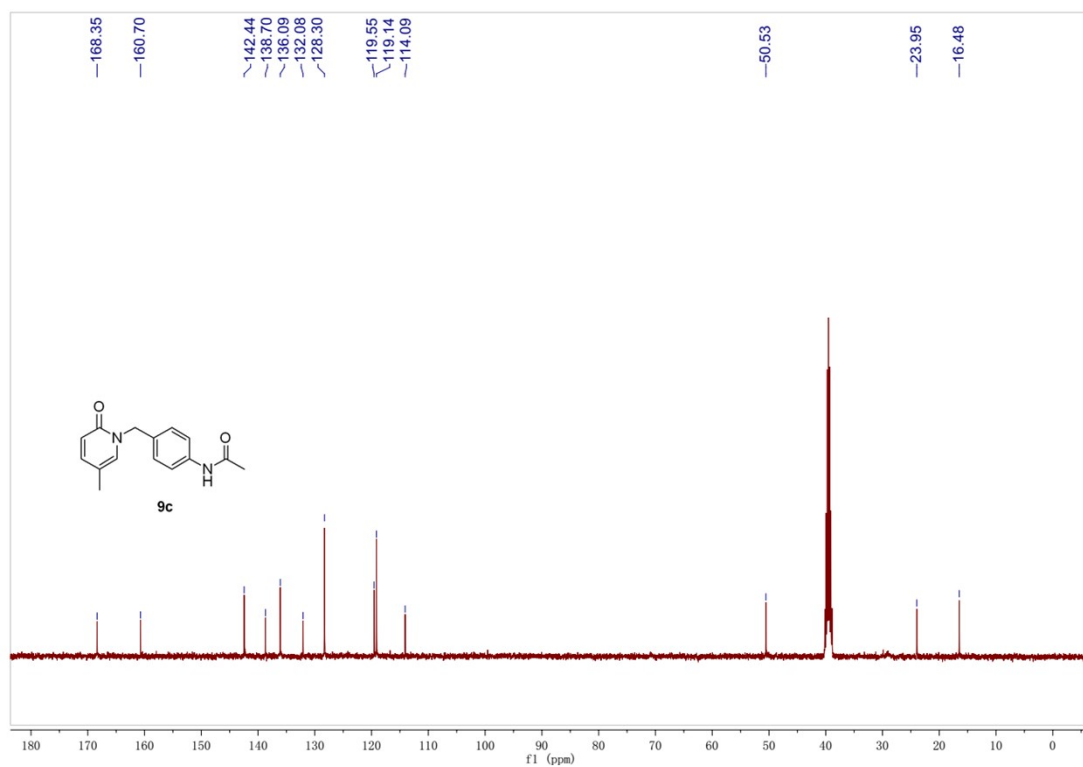
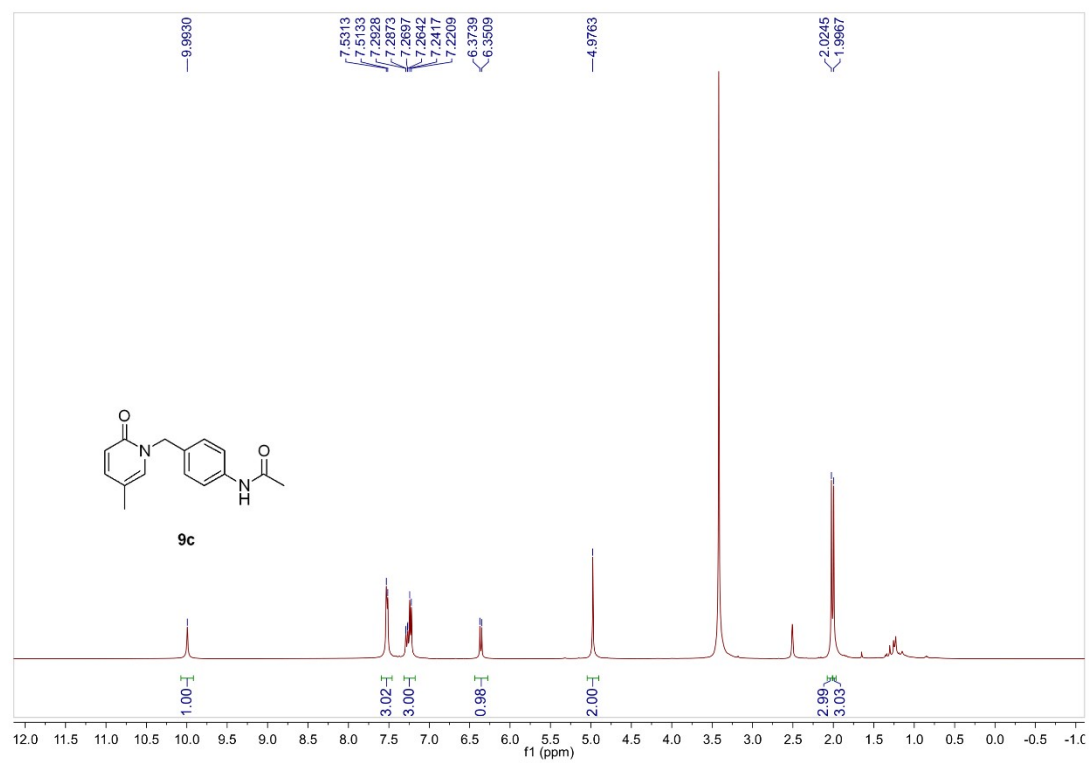
HPLC of 9b



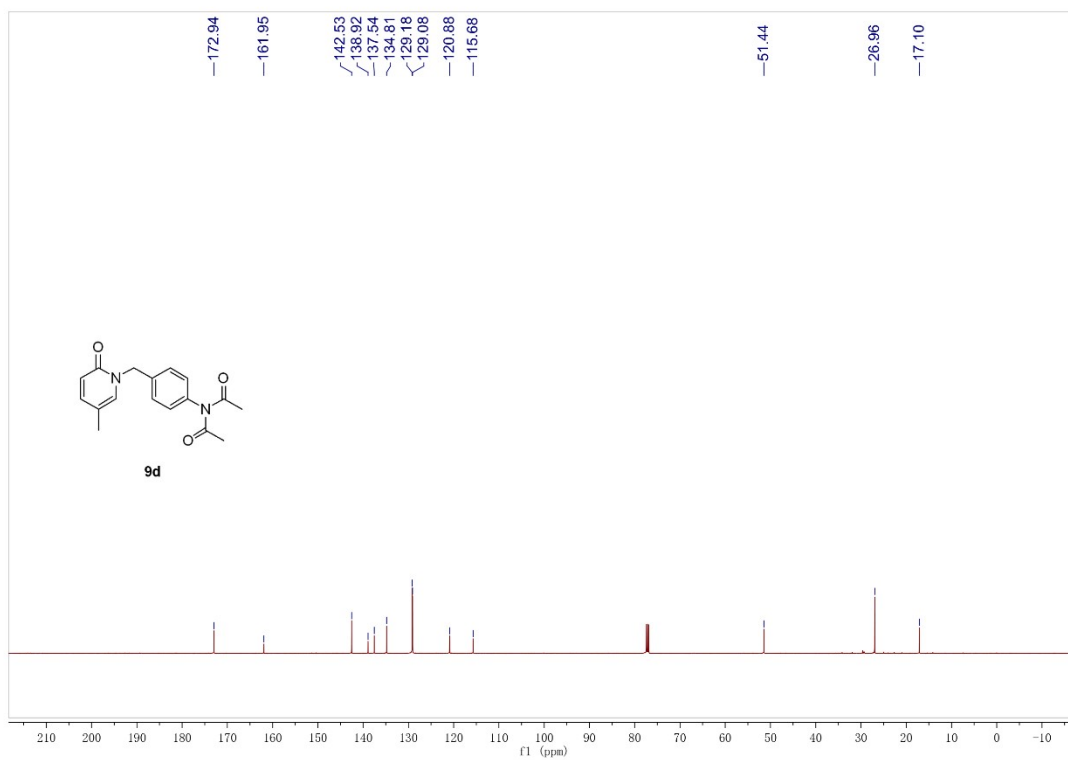
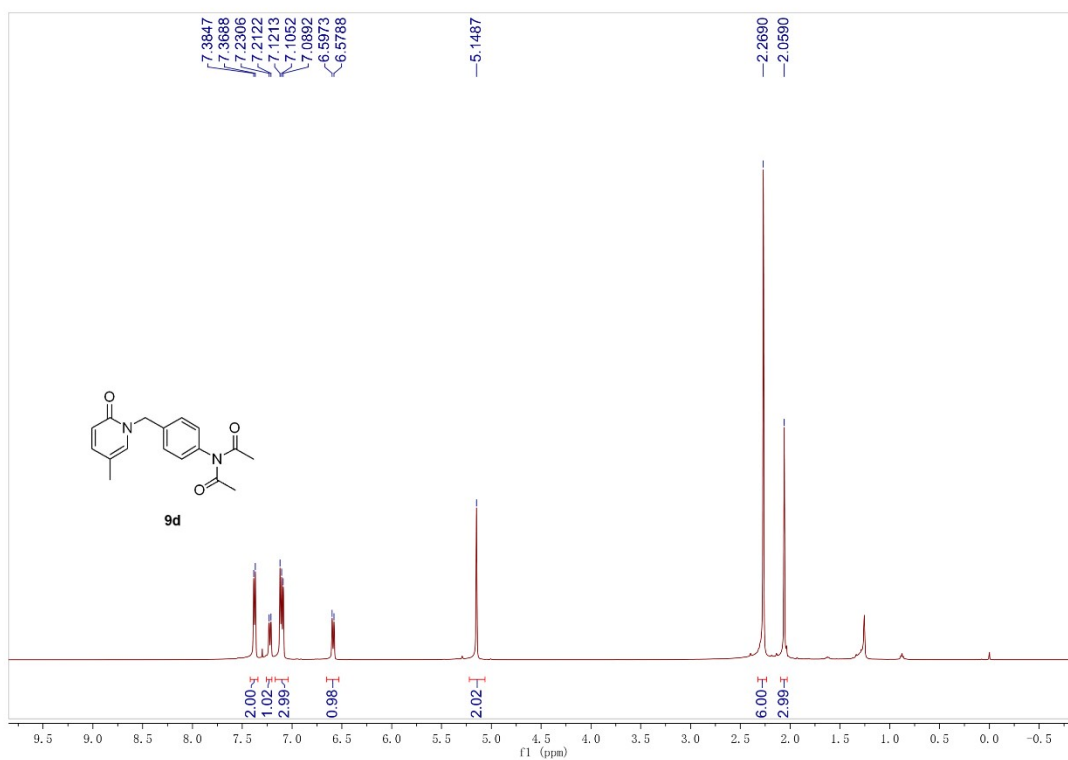
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
1.362		0.033	4218	9342	1.569	7339	1.166	--
1.685	M=352	0.032	278141	584975	98.245	11327	1.158	5.077
2.987		0.041	409	1105	0.186	20346	1.058	17.710
			282768	595422	100.000			

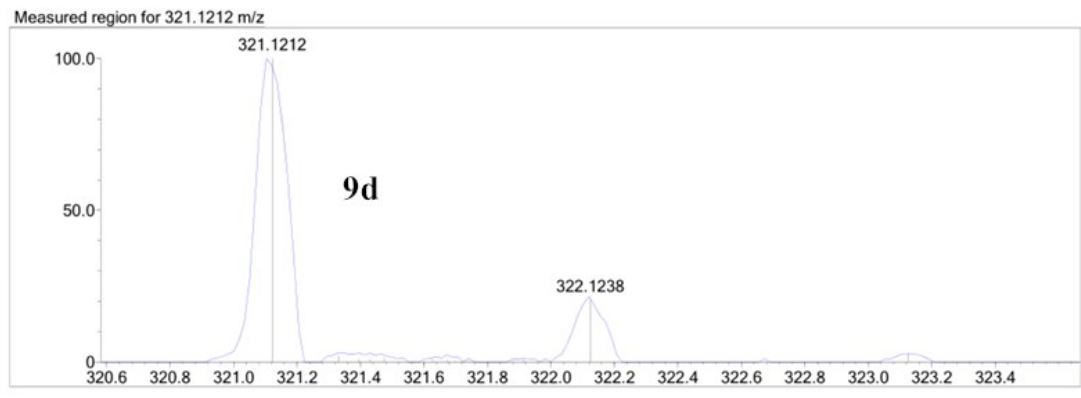
^1H NMR and ^{13}C NMR of **9c**



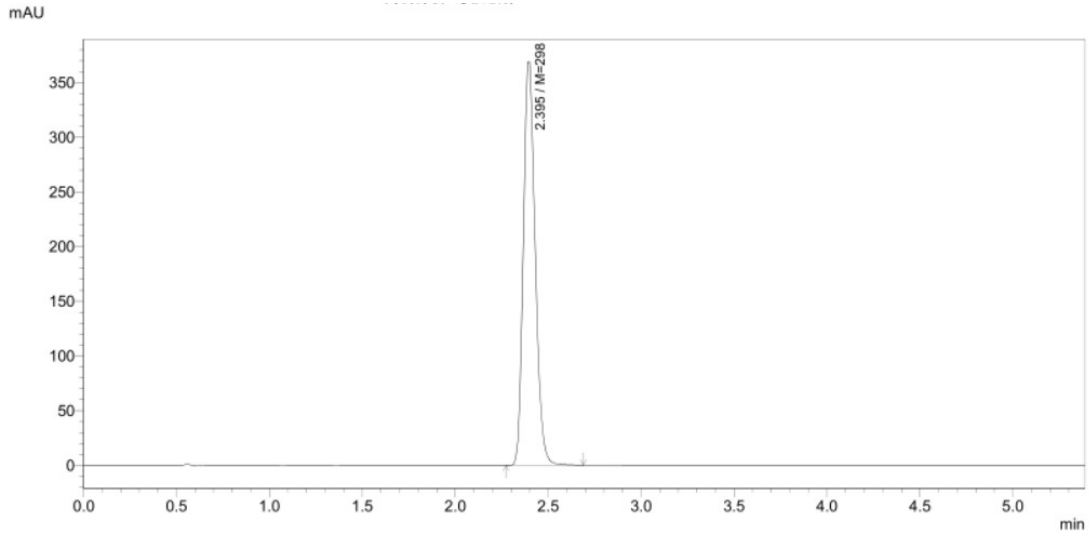
^1H NMR and ^{13}C NMR of **9d**



Mass of **9d**



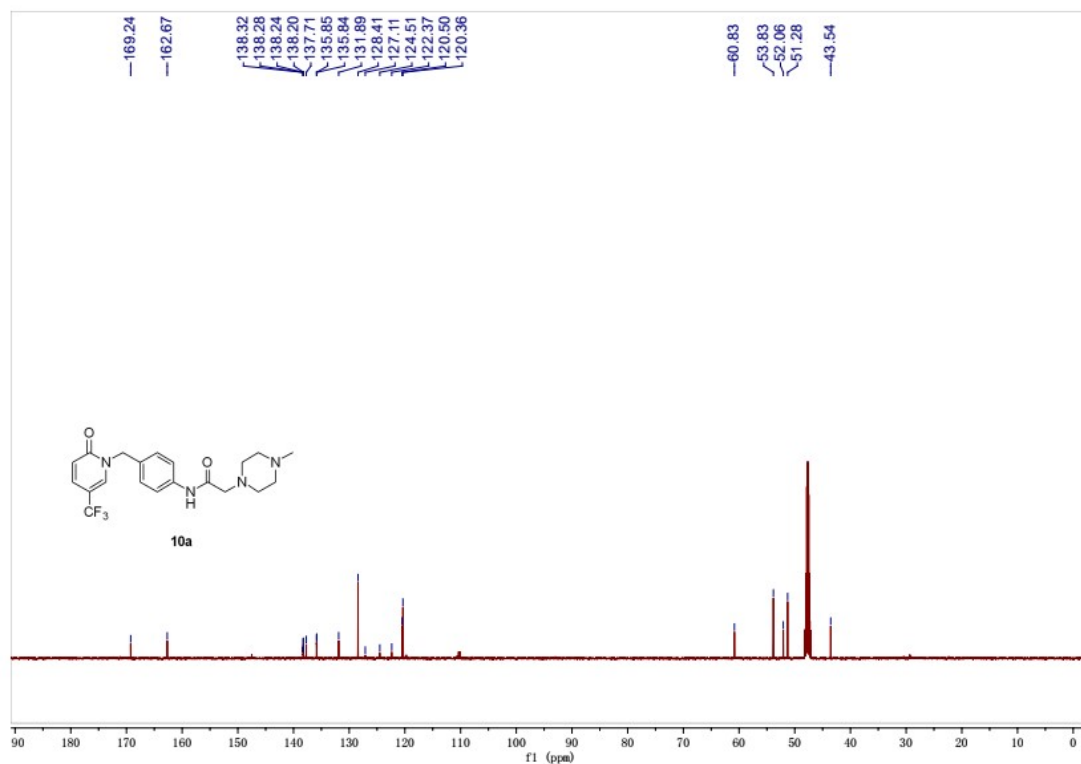
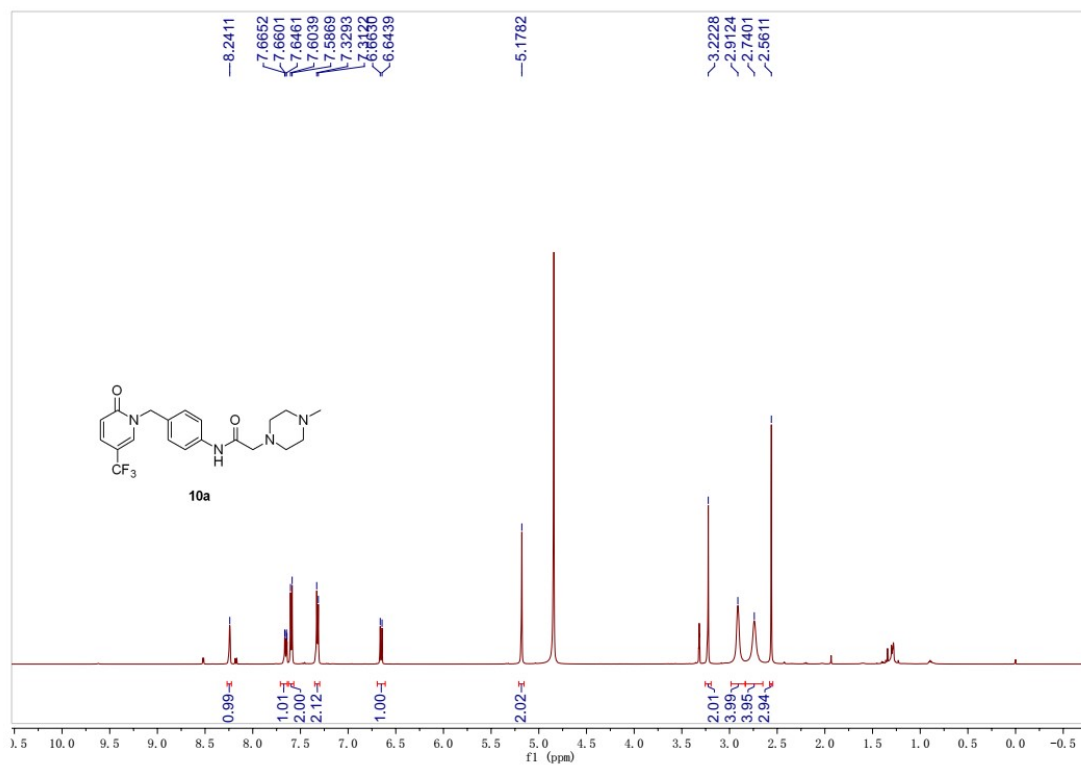
HPLC of 9d



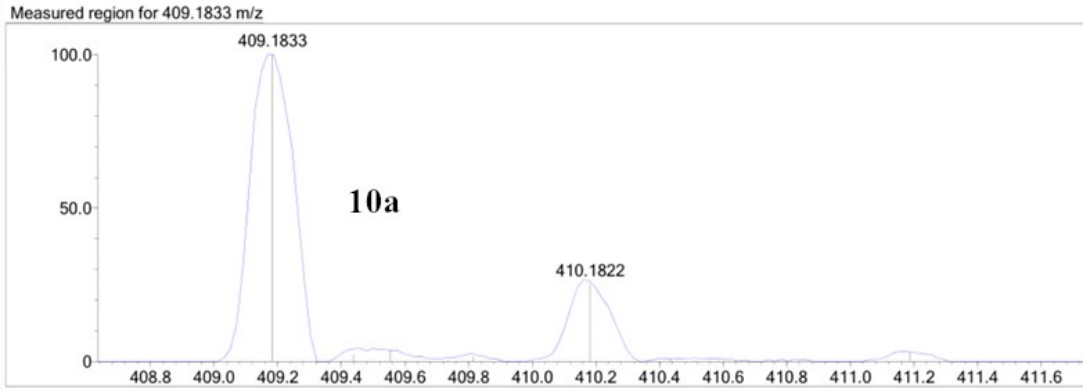
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
2.395	M=298	0.068	368902	1638048	100.000	5137	1.200	--
			368902	1638048	100.000			

^1H NMR and ^{13}C NMR of **10a**

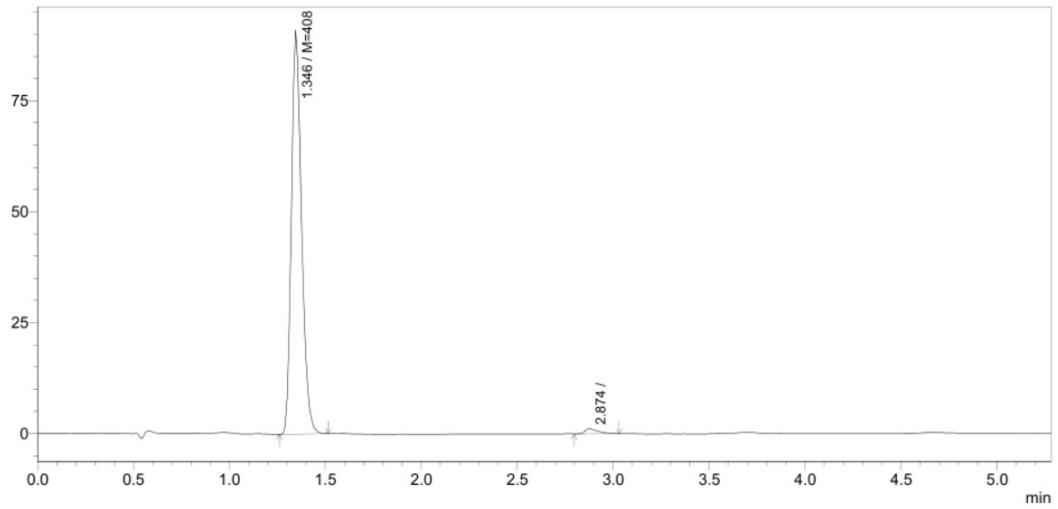


Mass of **10a**



HPLC of 10a

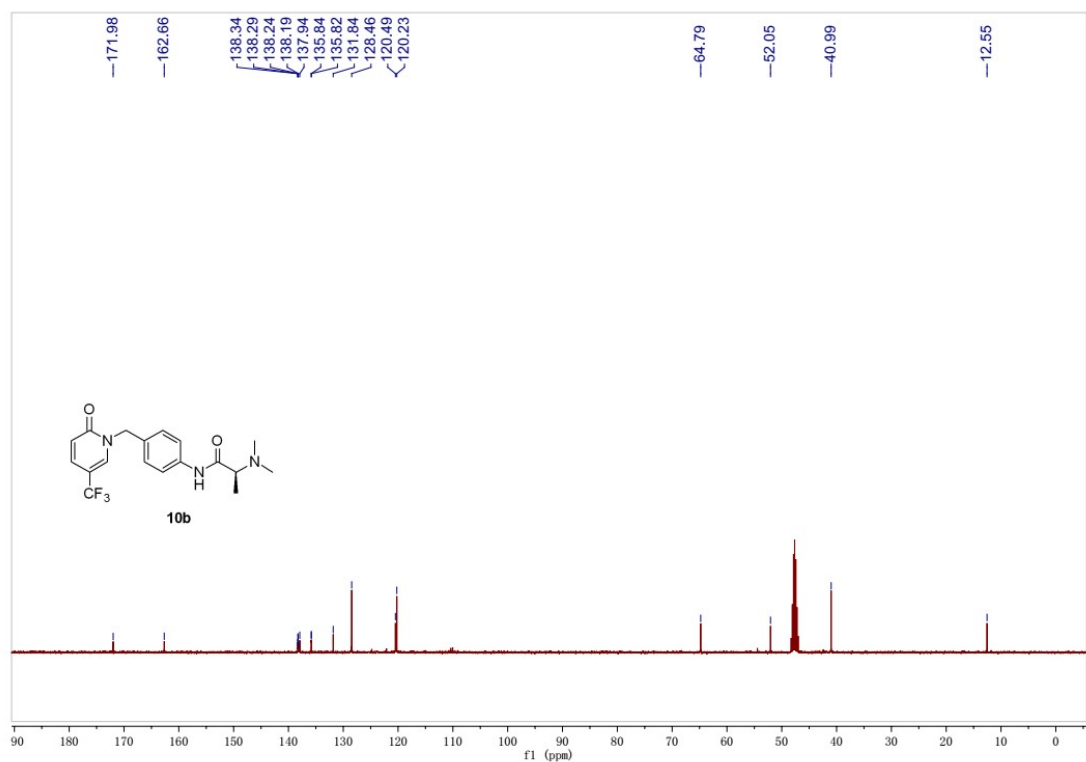
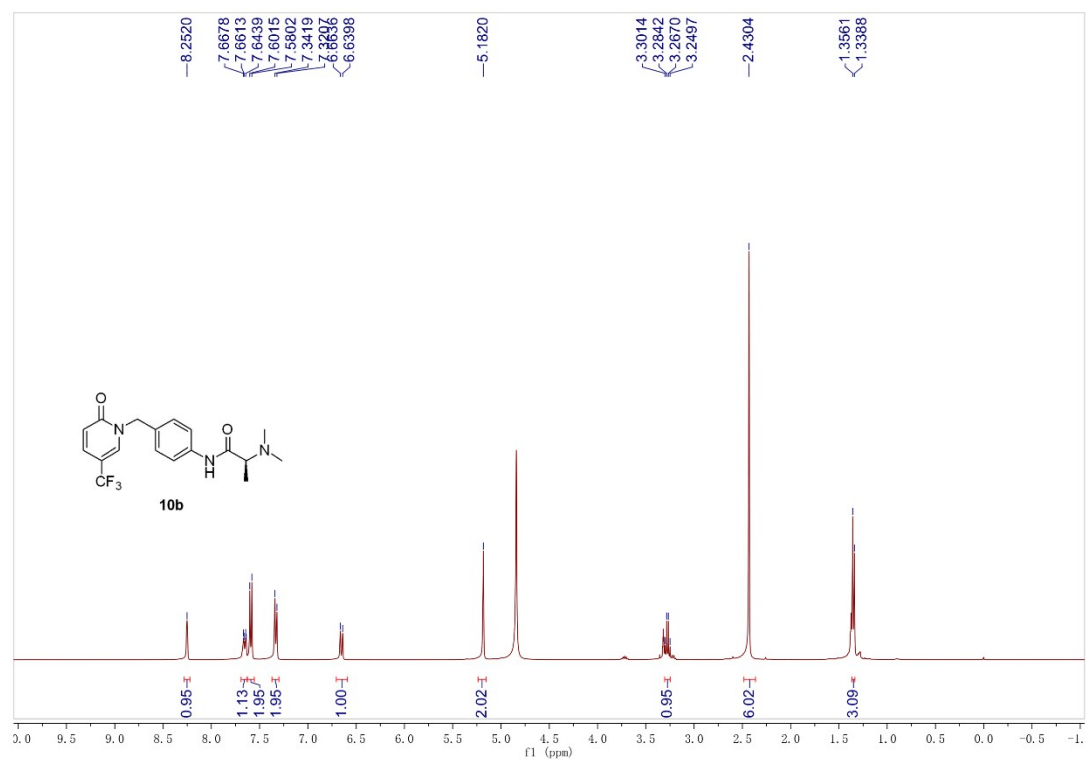
mAU



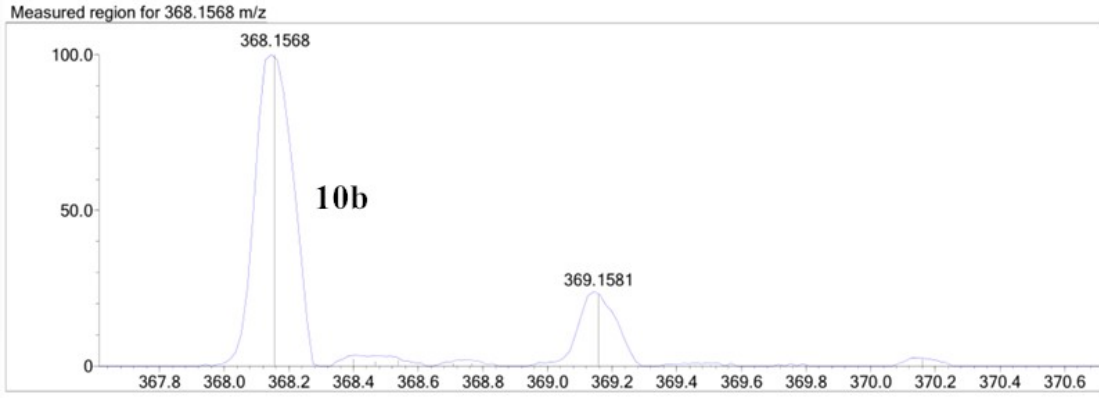
峰表

保留时间	化合物名	峰宽 (高度 50%)	高度	面积	面积%	理论塔板数 (USP)	拖尾因子	分离度 (USP)
1.346	M=408	0.056	91140	334346	98.385	2232	1.246	—
2.874		0.069	1178	5487	1.615	6836	1.842	12.082

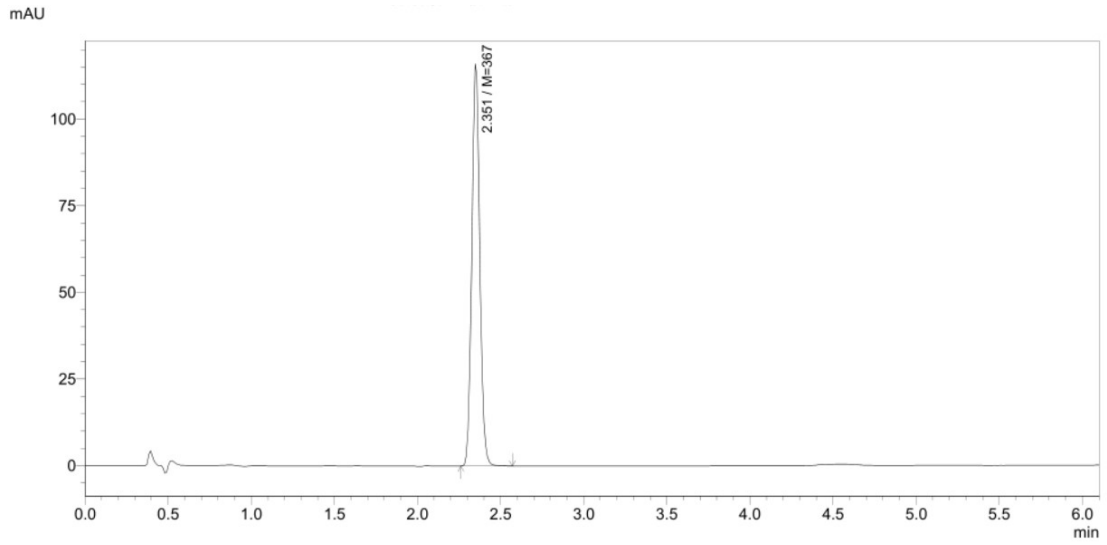
^1H NMR and ^{13}C NMR of **10b**



Mass of **10b**



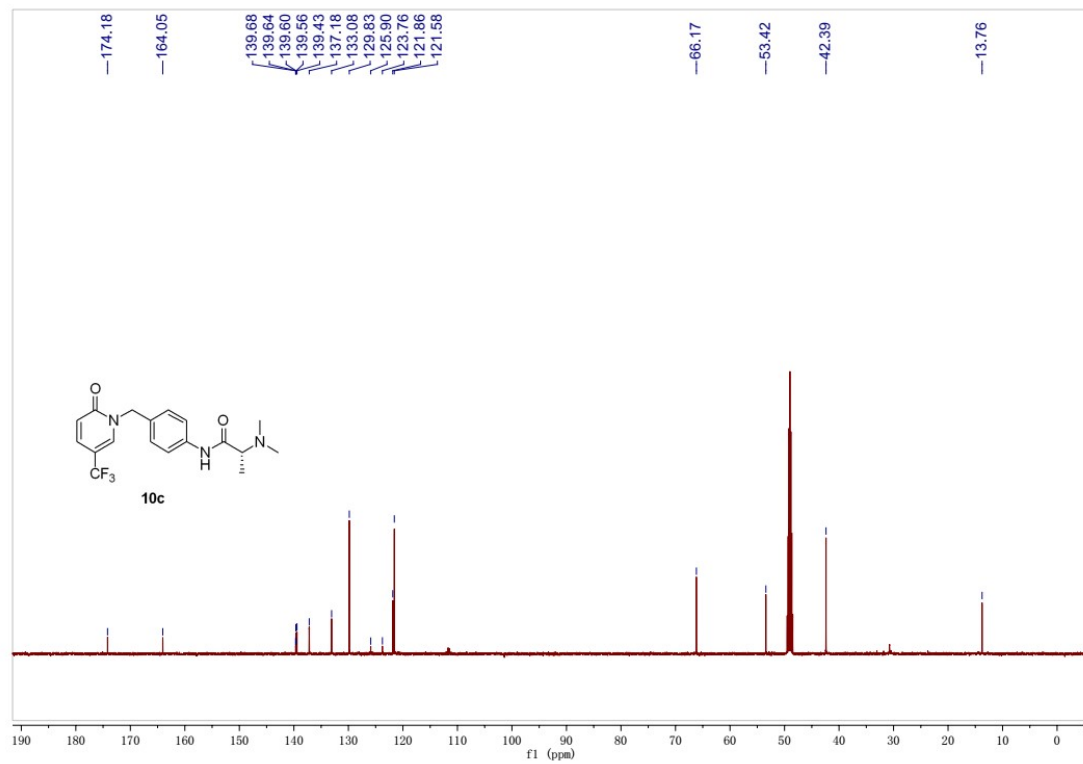
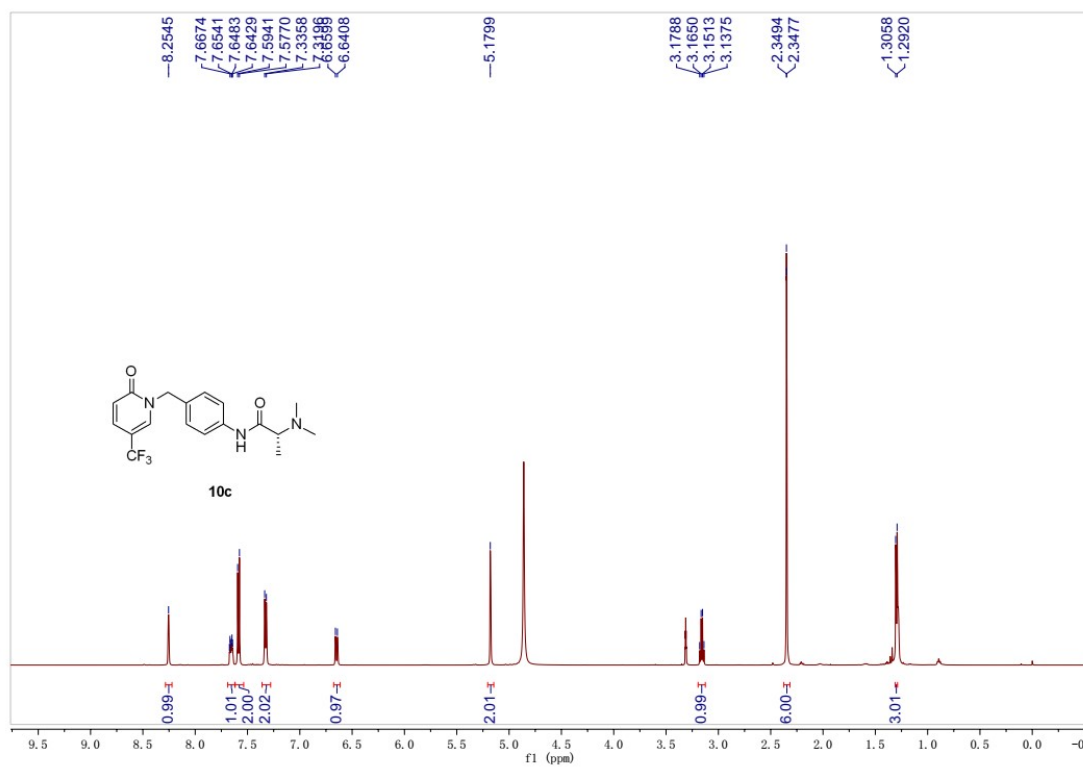
HPLC of 10b



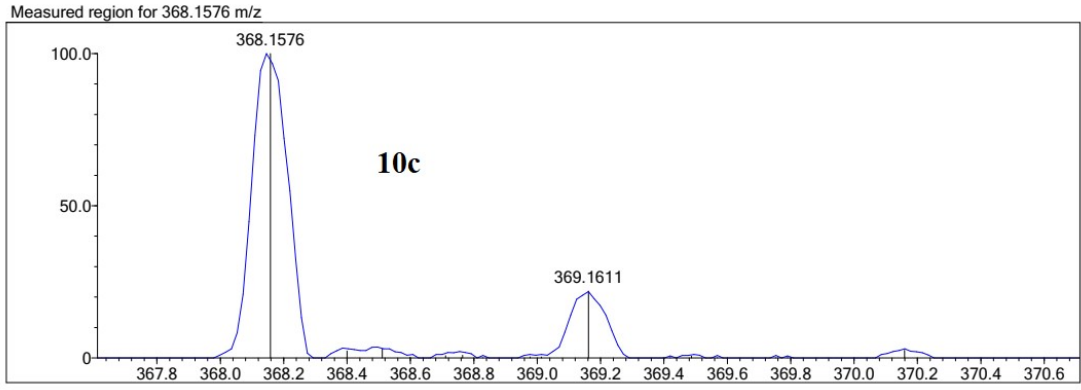
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
2.351	M=367	0.051	116138	386711	100.000	8656	1.063	—
			116138	386711	100.000			

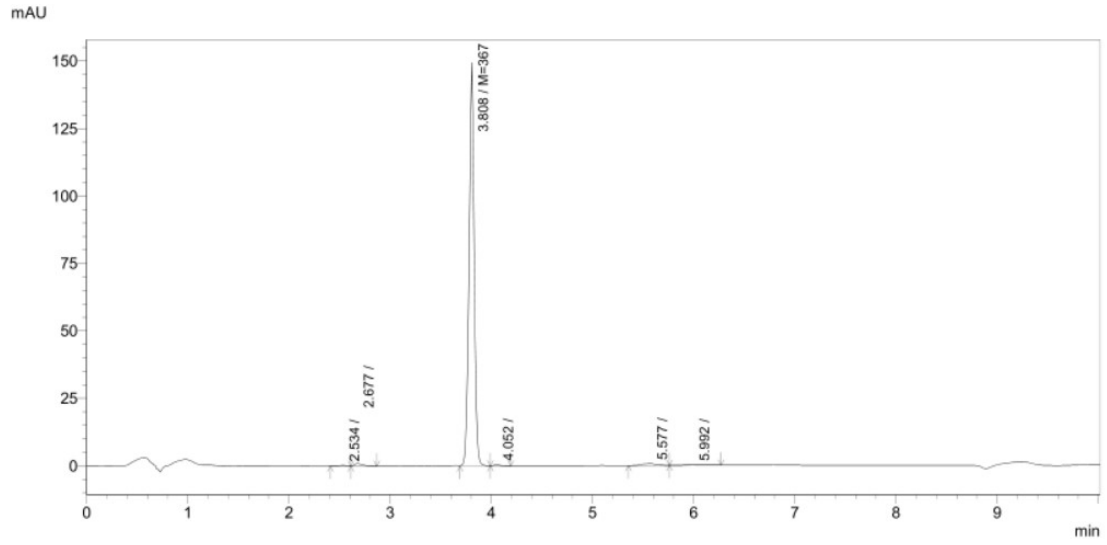
^1H NMR and ^{13}C NMR of **10c**



Mass of **10c**



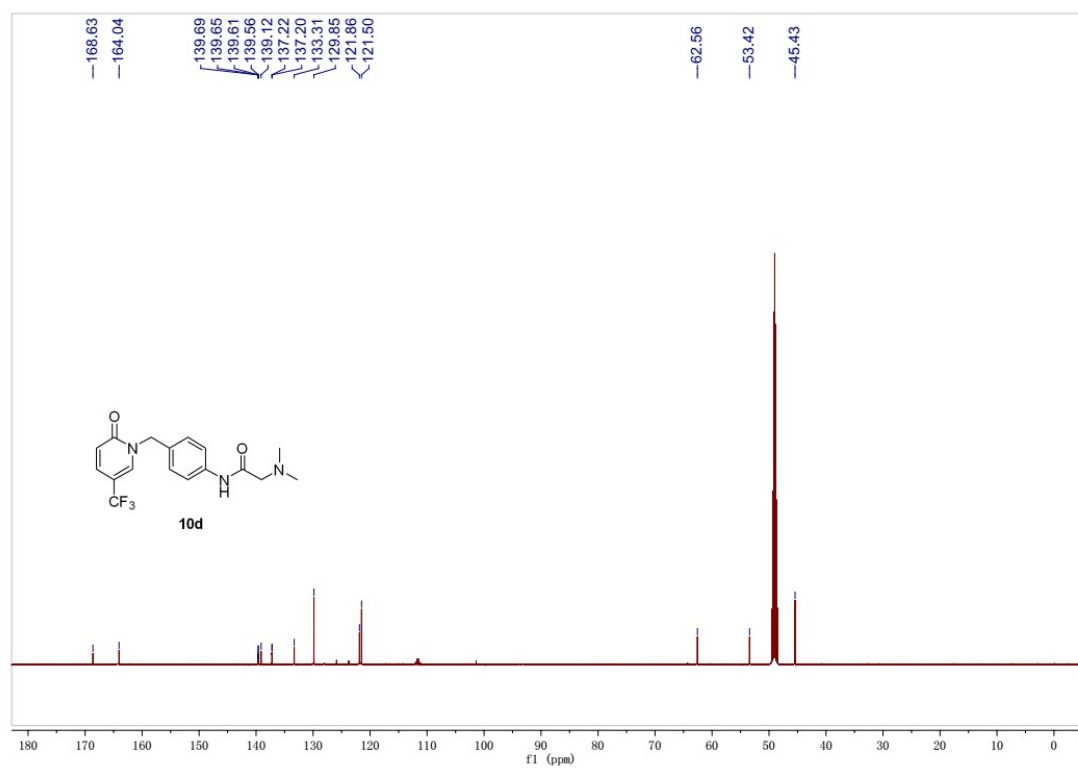
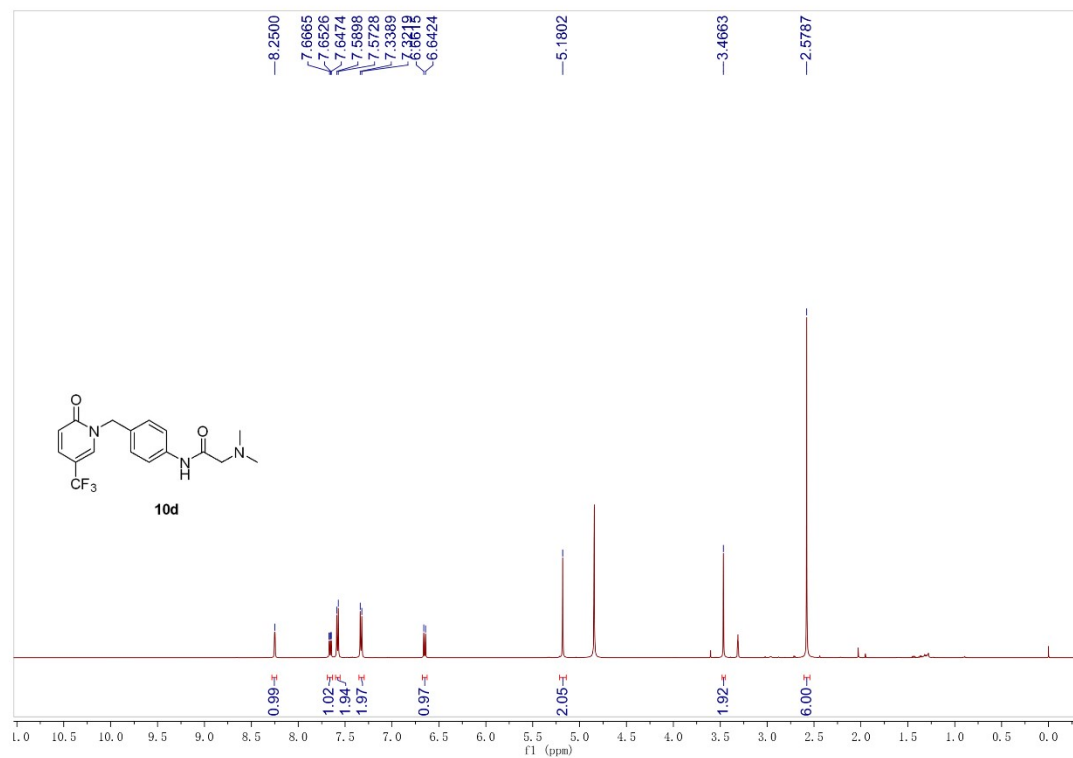
HPLC of 10c



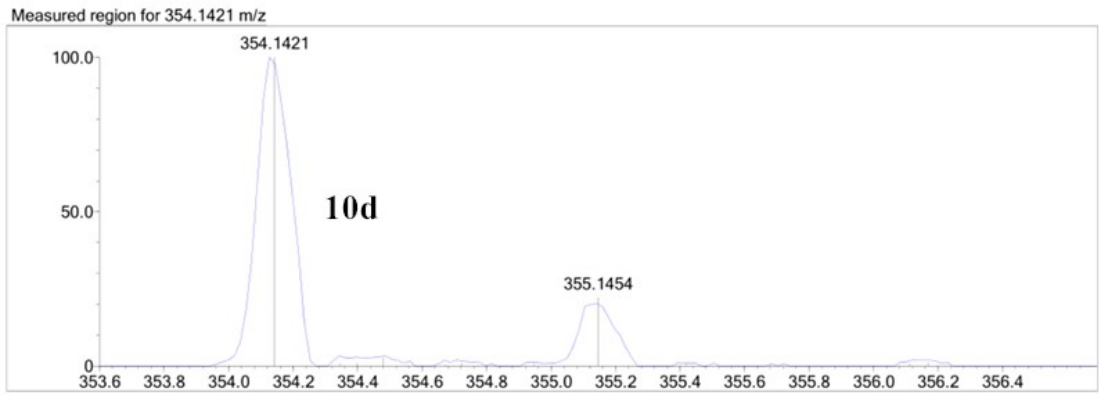
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
2.534		0.078	344	1746	0.315	4325	--	--
2.677		0.089	1010	5728	1.034	3906	--	0.879
3.808	M=367	0.054	149568	535555	96.687	18404	0.963	7.970
4.052		0.054	582	2267	0.409	20656	--	2.176
5.577		0.156	657	6677	1.205	7506	--	8.235
5.992		0.170	139	1934	0.349	5257	--	1.411
			152300	553906	100.000			

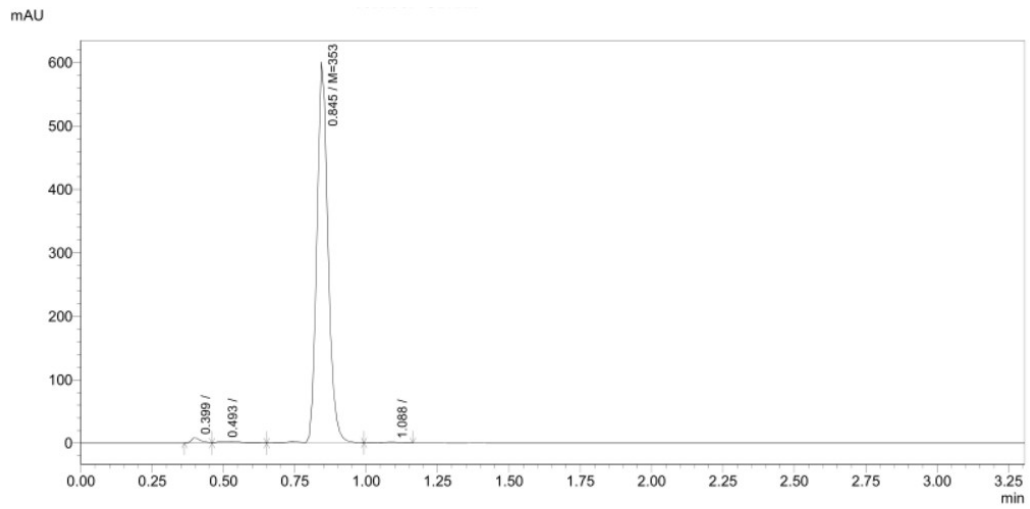
^1H NMR and ^{13}C NMR of **10d**



Mass of **10d**



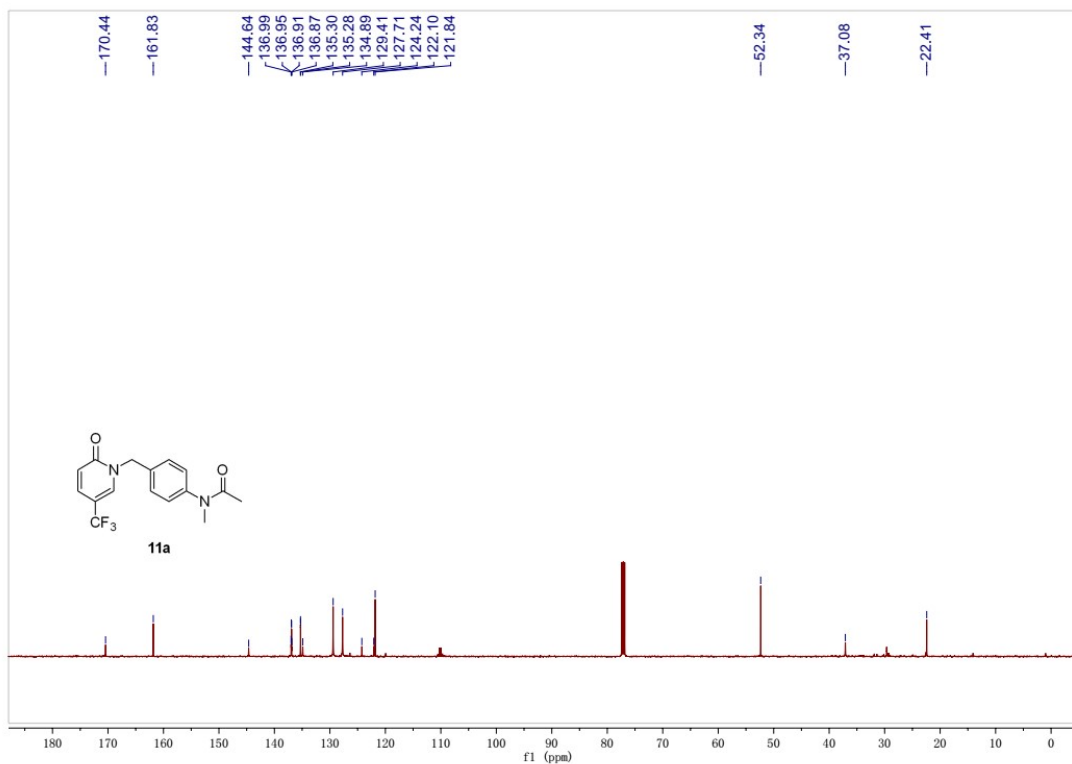
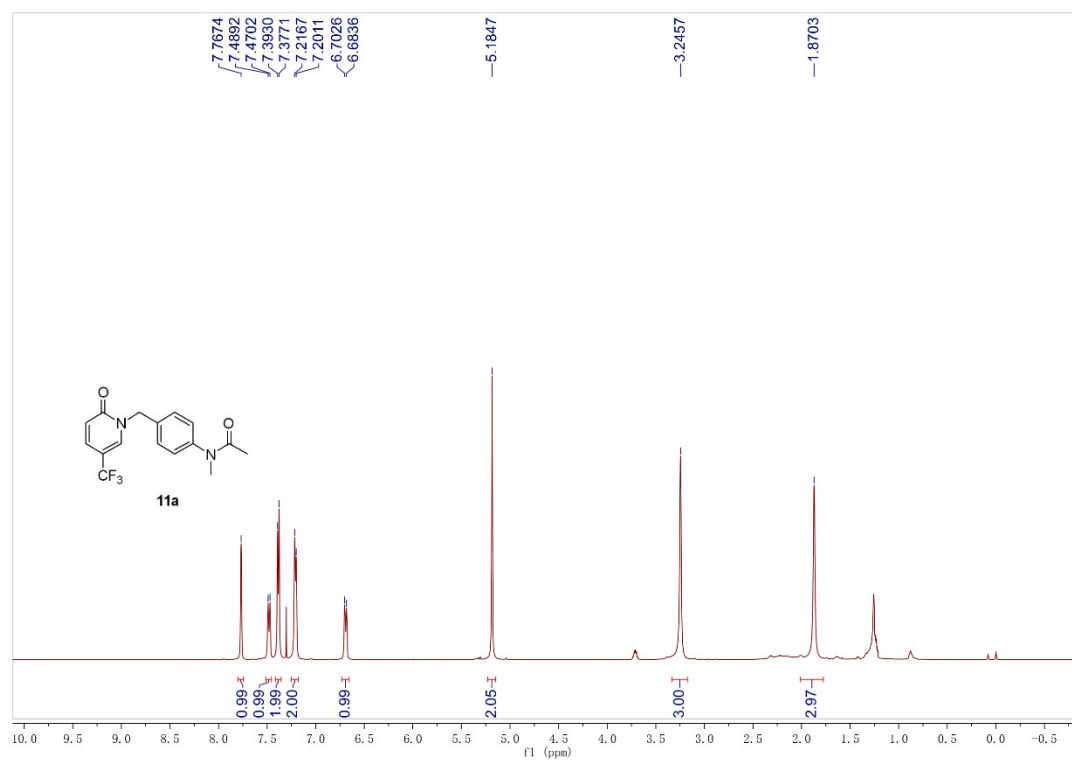
HPLC of 10d



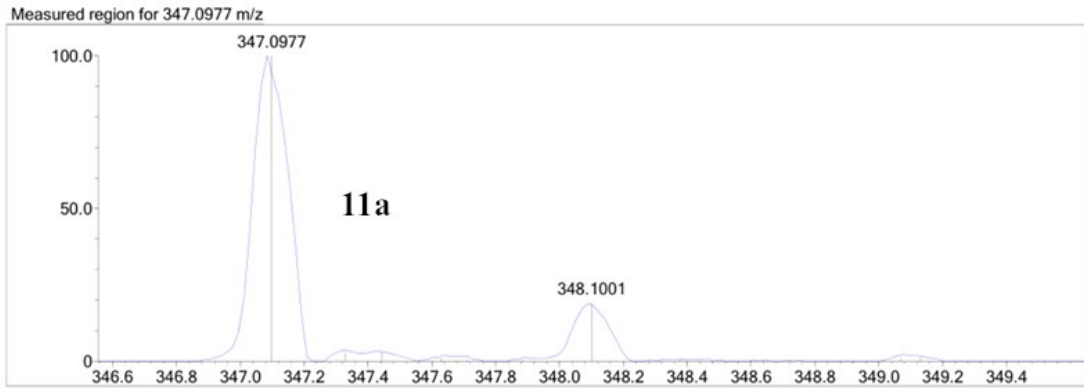
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
0.399		0.035	8136	20167	1.198	459	--	--
0.493		0.086	3170	19510	1.159	190	--	0.864
0.845	M=353	0.041	600939	1635676	97.170	1626	1.160	3.098
1.088		0.056	1486	7956	0.473	1224	--	2.333
			613732	1683308	100.000			

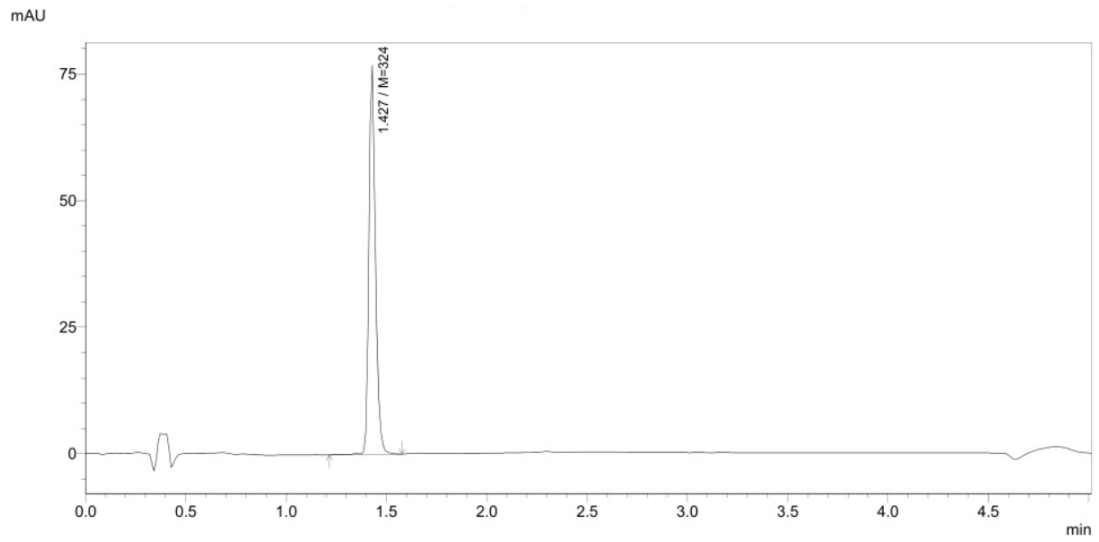
^1H NMR and ^{13}C NMR of *11a*



Mass of *11a*



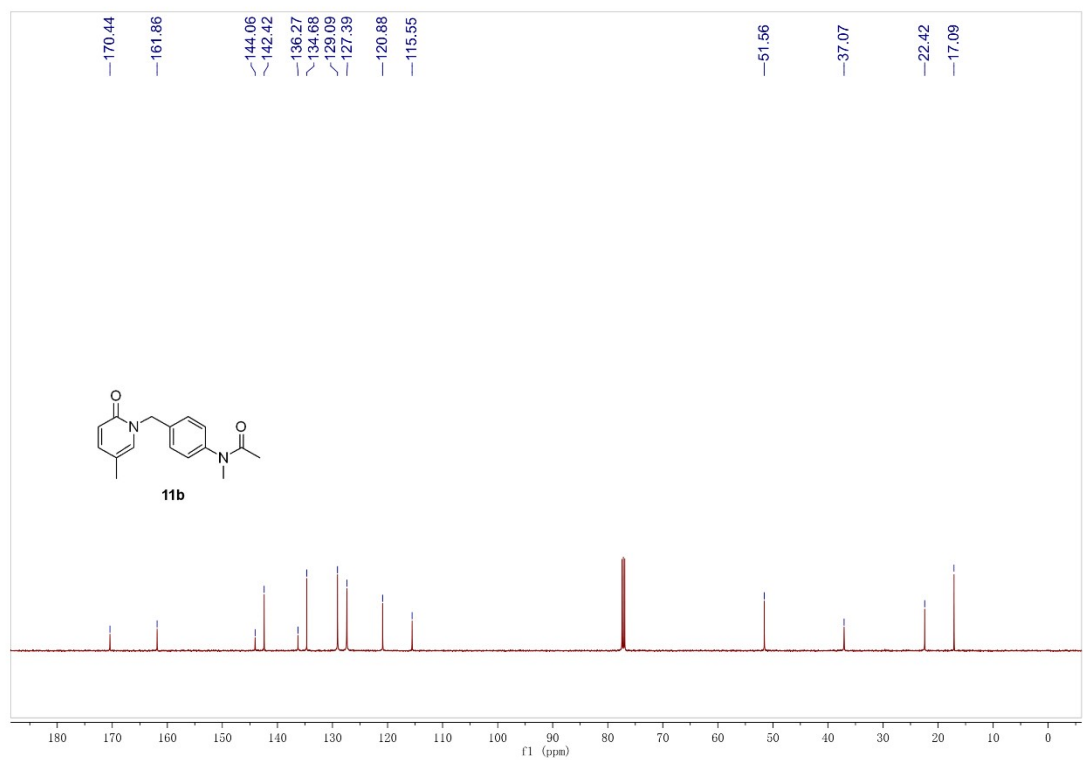
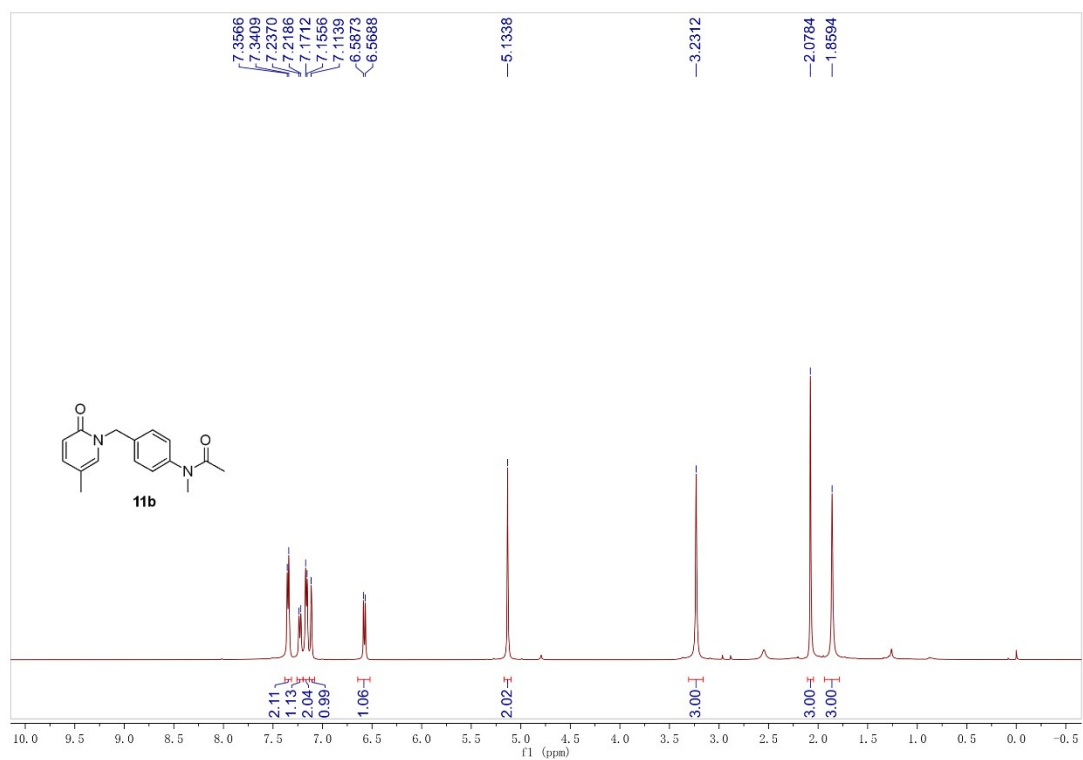
HPLC of 11a



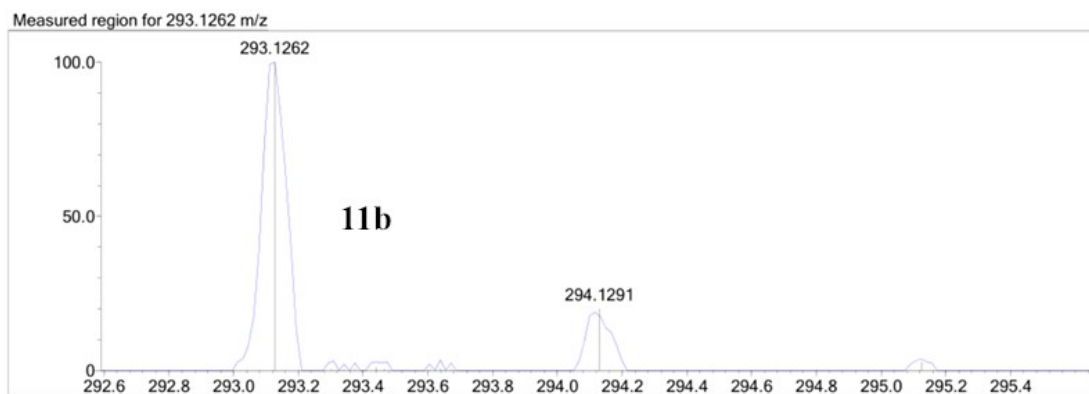
峰表

保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
1.427	M=324	0.034	76927	172646	100.000	7567	1.248	—
			76927	172646	100.000			

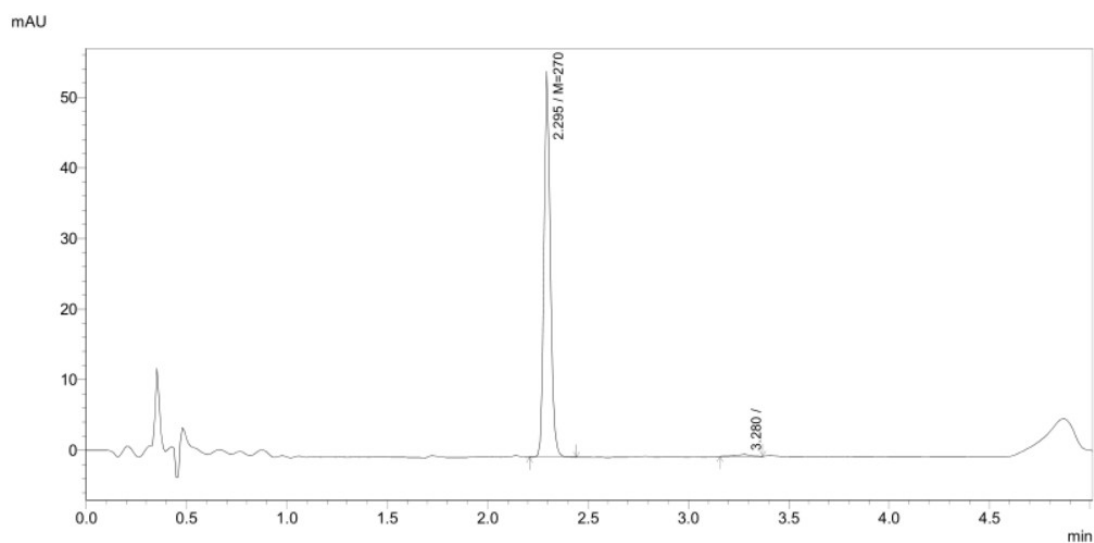
^1H NMR and ^{13}C NMR of **11b**



Mass of **11b**



HPLC of **11b**

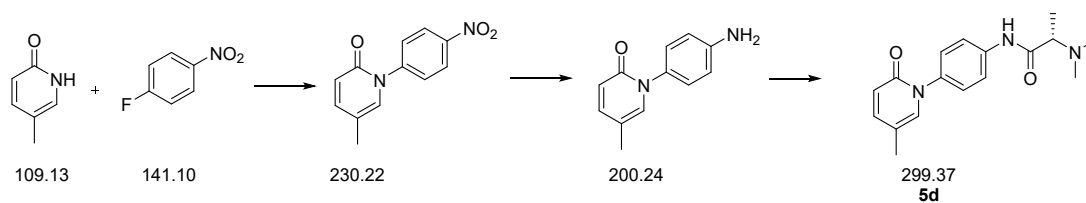


峰表

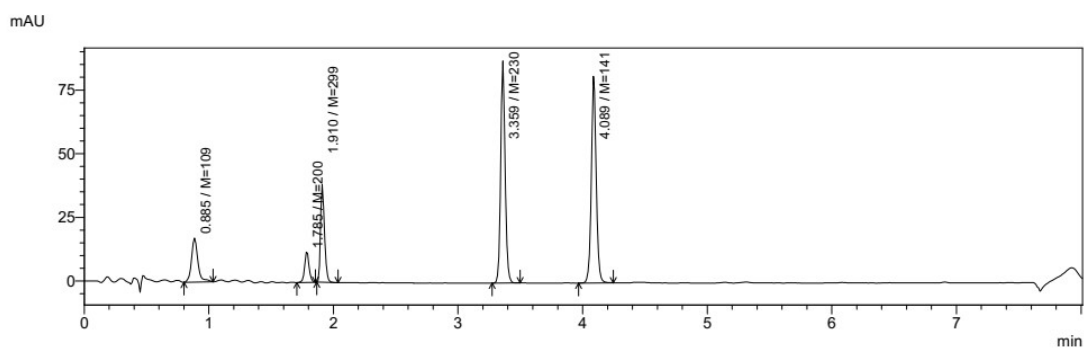
保留时间	化合物名	峰宽(高度 50%)	高度	面积	面积%	理论塔板数(USP)	拖尾因子	分离度(USP)
2.295	M=270	0.033	54667	119486	99.004	18556	1.202	---
3.280		0.058	277	1203	0.996	11936	0.733	10.514

Impurity analysis of **5d** and **9d**.

The synthetic route **5d**.



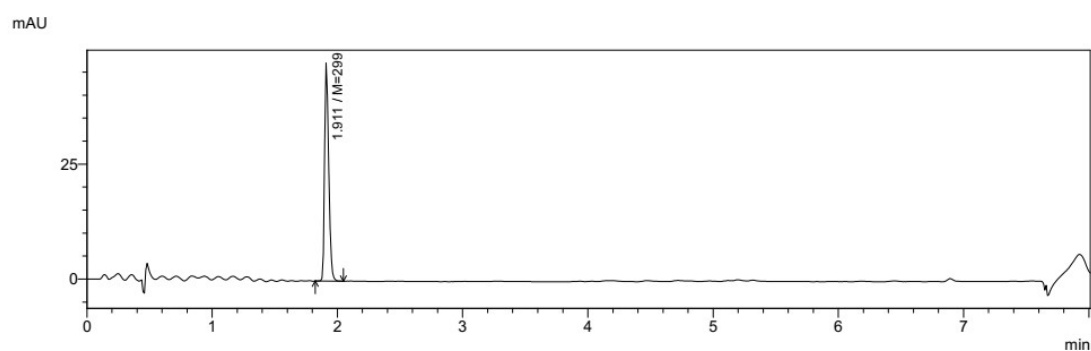
The LC-MS analysis of the mixed samples of the optimal compound **5d** and the substrates and intermediates



峰表

Ret. time	Name	width	height	Area	Area%	Theoretical Plate(USP)	Tailing Factor	Resolutin(UPS)
0.885	M=109	0.051	17385	61423	9.985	1149	1.344	--
1.785	M=200	0.039	11954	30727	4.995	8670	1.069	9.938
1.910	M=299	0.034	38333	83425	13.562	12313	1.283	1.710
3.359	M=230	0.037	87234	212533	34.550	32662	1.103	20.242
4.089	M=141	0.042	81113	227046	36.909	38026	1.057	9.219

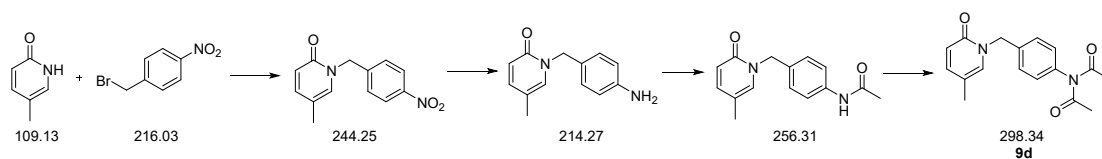
The LC-MS analysis of the optimal compound **5d**.



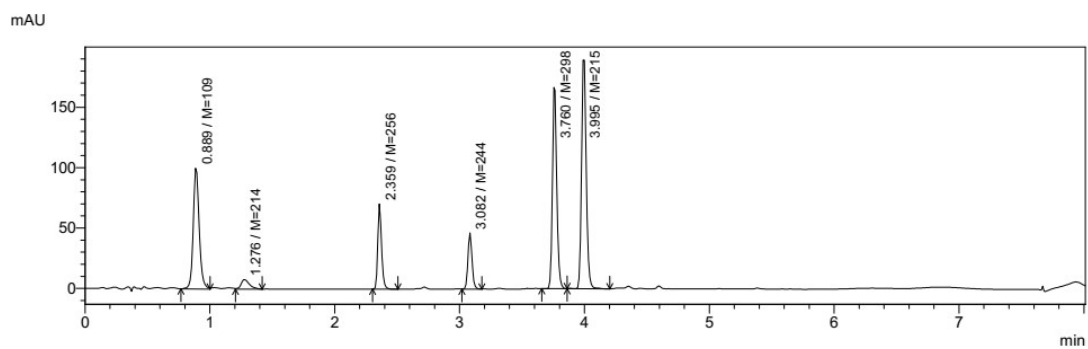
峰表

Ret. time	Name	width	height	Area	Area%	Theoretical Plate(USP)	Tailing Factor	Resolutin(UPS)
1.911	M=299	0.035	47372	107621	100.000	11852	1.303	--
			47372	107621	100.000			

The synthetic route **9d**.



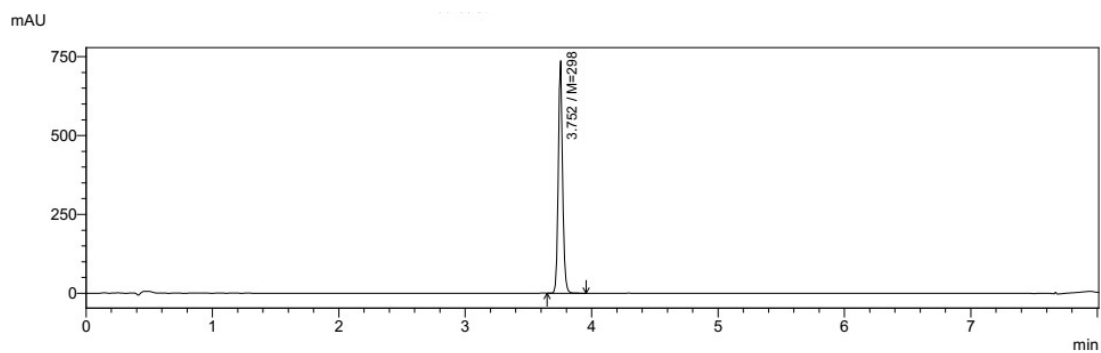
The LC-MS analysis of the mixed samples of the optimal compound **9d** and the substrates and intermediates



峰表

Ret. time	Name	width	height	Area	Area%	Theoretical Plate(USP)	Tailing Factor	Resolutin(UPS)
0.889	M=109	0.048	100003	329761	21.612	1313	1.138	--
1.276	M=214	0.070	7967	38144	2.500	1333	--	3.253
2.359	M=256	0.032	70666	146847	9.624	21474	1.213	10.603
3.082	M=244	0.035	46440	105863	6.938	31251	1.138	10.784
3.760	M=298	0.038	166673	414733	27.181	41318	1.164	9.432

The LC-MS analysis of the optimal compound **9d**.



峰表

Ret. time	Name	width	height	Area	Area%	Theoretical Plate(USP)	Tailing Factor	Resolutin(UPS)
3.752	M=298	0.037	736871	1793217	100.000	42471	1.104	--
			736871	1793217	100.000			