

Enantioselective [3+2] annulation of 4-isothiocyanato pyrazolones and alkynyl ketones under organocatalysis

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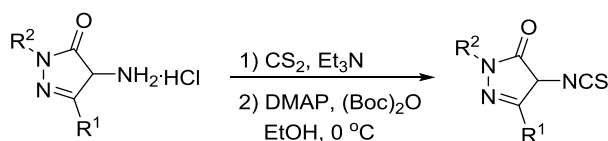
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1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (200~300 mesh). Enantiomeric excesses (ee) were determined by HPLC using corresponding commercial chiral columns as stated at 30 °C with UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]_D^{25}$ (c g/100 mL, solvent). All ^1H NMR and ^{19}F NMR spectra were recorded on a Bruker Avance II 400 MHz and Bruker Avance III 471 MHz respectively, ^{13}C NMR spectra were recorded on a Bruker Avance II 101 MHz or Bruker Avance III 126 MHz with chemical shifts reported as ppm (in CDCl_3 , TMS as an internal standard). Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, dd = double doublet, coupling constants in Hz, integration). HRMS (ESI) was obtained with a HRMS/MS instrument (LTQ Orbitrap XL TM). The absolute configuration of **4** was assigned by the X-ray analysis.

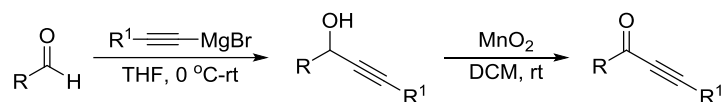
4-Isothiocyanato pyrazolones were prepared according to the literature.¹ Alkynyl ketones were prepared according to the literature.² Catalyst **Q5** was synthesized according to the literature procedure.³ The racemic products were synthesized using quinine/quinidine = 1:1 as the catalyst.

2. General procedure of 4-isothiocyanato pyrazolone **1**¹



To a suspension of 4-amino pyrazolone hydrochloride (4.0 mmol, 1.0 equiv) in EtOH (10 mL) were added CS_2 (3.05 g, 40.0 mmol, 10.0 equiv) and Et_3N (1.62 g, 16.0 mmol, 4.0 equiv), under argon. The reaction mixture was stirred for 45 min at room temperature and then cooled on an ice bath. Then a solution of Boc_2O (0.87 g, 4.0 mmol, 1.0 equiv) and DMAP (10 mol %) in 3 mL EtOH was added slowly. The reaction mixture was kept in the ice bath for 5 min, and then stirred for another 15 min at room temperature. Then the reaction mixture was quenched with 10% HCl aqueous (10 mL), and the mixture was extracted with DCM. The combined organic layers were dried over Na_2SO_4 , concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 6:1) or recrystallization (dichloromethane/hexane) to obtain the 4-isothiocyanato pyrazolone **1a-l** in 40-70% yields.

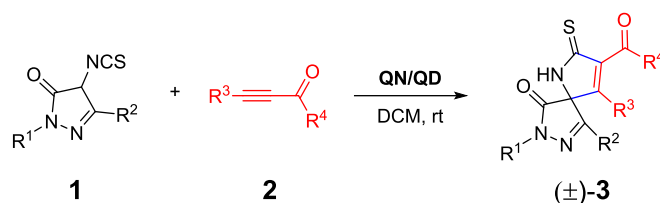
3. General procedure of ynones **2**^{2b}



Ethynylmagnesium bromide or 1-propynylmagnesium bromide solution (0.50 M solution in THF 12 mL, 1.2 equiv.) was added dropwise to a stirred solution of aldehyde (5.0 mmol, 1.0 equiv.) in anhydrous THF (10 mL) at 0 °C. The mixture was kept stirring at 0 °C for 20 minutes and warmed to room temperature for additional two hours. Then the reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with ethyl acetate for three times. The organic layers was combined and dried with anhydrous Na_2SO_4 . It was evaporated

under reduced pressure to give intermediate alcohol, which was used in next step directly. The crude alcohol **6** was dissolved in dichloromethane and treated with activated MnO_2 (10 equiv.). After completion of the reaction (monitored by TLC), the solid was removed by filtration of the reaction mixture through a pad of celite. Then it was extracted with ethyl acetate and dried with anhydrous Na_2SO_4 . Then the reaction mixture was concentrated under reduced pressure and purified by column chromatography to give the desired ynones **2**.

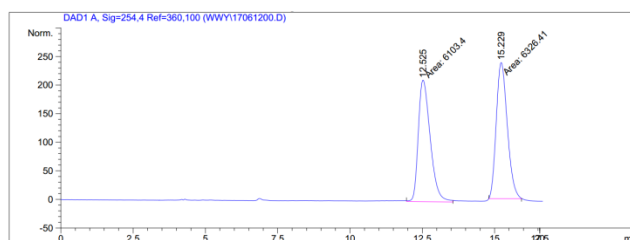
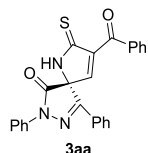
4. General procedure for the synthesis of racemic **3**



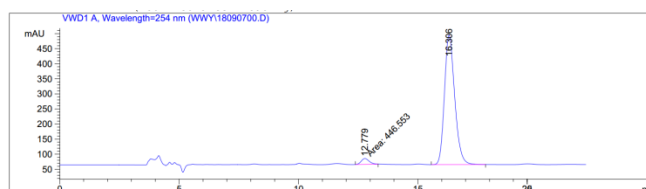
A tube equipped with a magnetic stir bar was charged with 4-isothiocyanato pyrazolone **1** (0.1 mmol), quinine/quinidine = 1:1 (0.01 mmol), and DCM (1 mL). After stirring for 5 min, alkynyl ketone **2** (0.11 mmol) was added in one portion. The reaction was detected by TLC. After 0.5-1 h, the mixture was purified by column chromatography on silica gel (unless otherwise noticed, petroleum ether/EtOAc = 8:1 was used as the eluent) directly to give the product racemic **3**.

5. Copies of HPLC chromatographs

Compound **3aa**

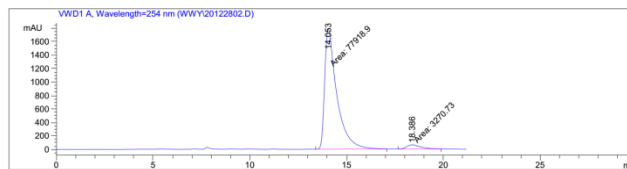
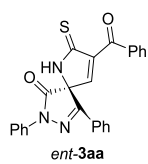


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.525	MM	0.4783	6103.39746	212.67453	49.1029
2	15.229	MM	0.4428	6326.41113	238.12169	50.8971



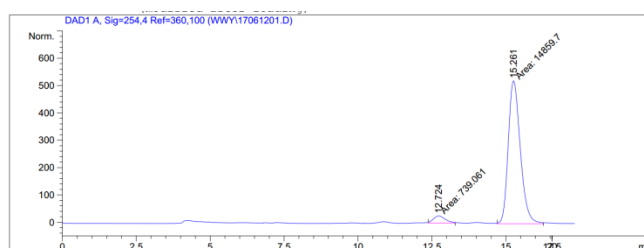
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	12.779	MM	0.382	446.553	3.369	
2	16.306	VB	0.457	12809.197	96.631	

Compound *ent*-3aa



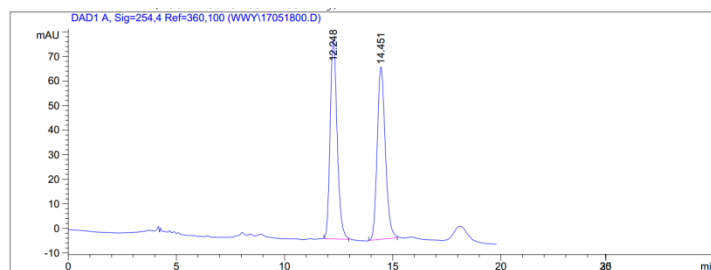
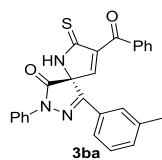
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.053	MM	0.7281	7.79189e4	1783.61633	95.9715
2	18.386	MM	0.8732	3270.72681	62.42479	4.0285

Gram-Scale Synthesis of 3aa

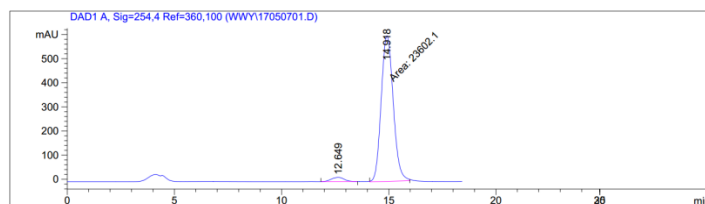


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1	12.724	MM	0.4651	739.06122	26.48324	4.7380
2	15.261	MM	0.4733	1.48597e4	523.23450	95.2620

Compound 3ba

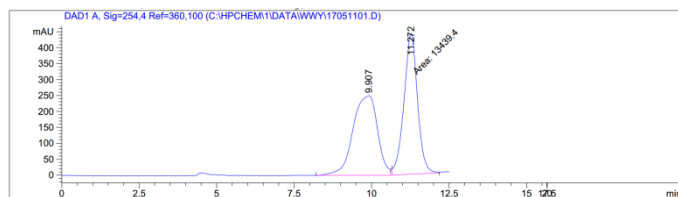
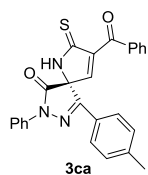


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1	12.248	BB	0.3466	1827.52051	81.18167	50.0699
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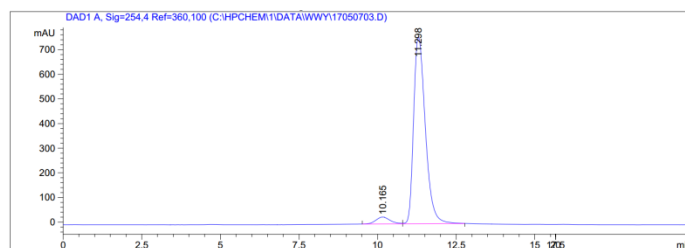


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1	12.649	BP	0.4957	722.19452	17.49250	2.9690
2	14.918	MM	0.6514	2.36021e4	603.91205	97.0310

Compound 3ca

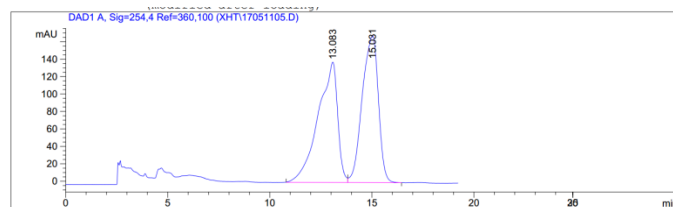
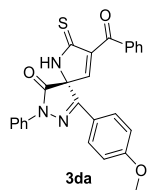


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1	9.907	MM	0.9061	1.33801e4	246.11040	50.1002
2	11.272	MM	0.5047	1.33265e4	440.09317	49.8998

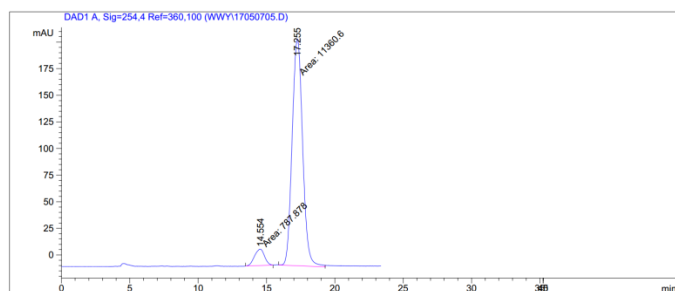


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1	10.165	MM	0.5020	812.64771	26.97836	3.9958
2	11.298	MM	0.4301	1.95249e4	756.57880	96.0042

Compound 3da

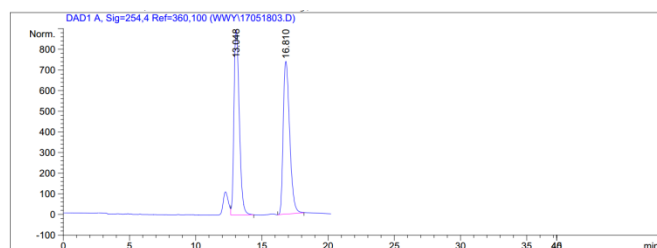
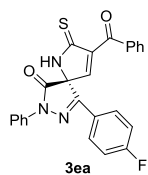


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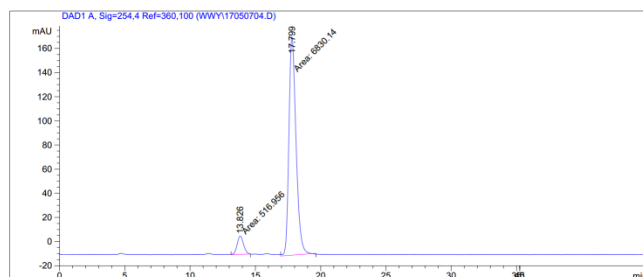


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1	14.554	MM	0.8506	787.87848	15.43762	6.4854
2	17.255	MM	0.8882	1.13606e4	213.18442	93.5146

Compound 3ea

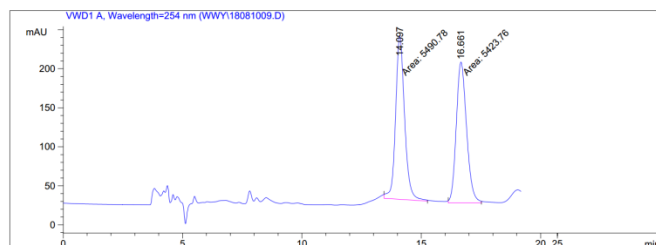
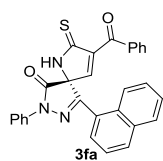


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2	16.810	VB	0.5145	2.50280e4	740.17712	50.0286

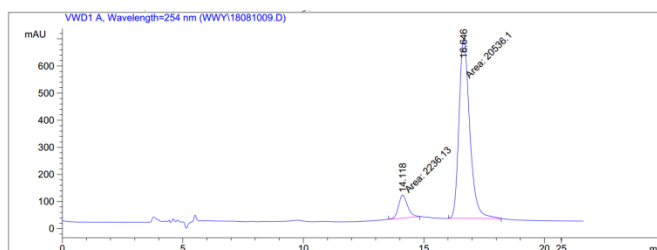


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1	13.826	MM	0.5676	516.95642	15.17873	7.0362
2	17.799	MM	0.6294	6830.13770	180.87192	92.9638

Compound 3fa

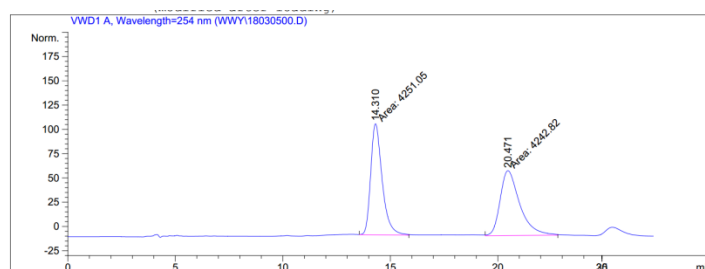
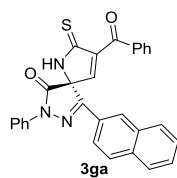


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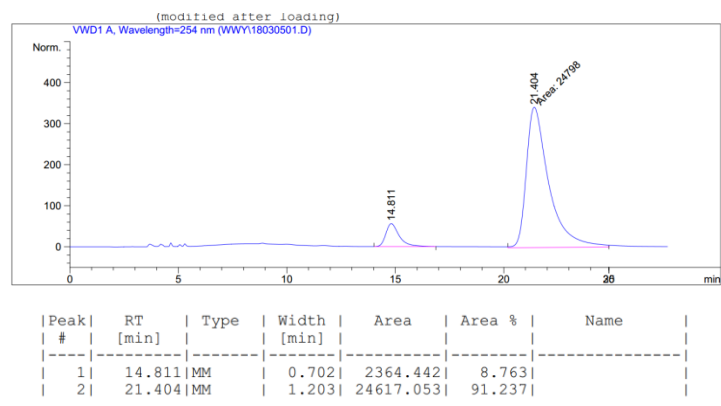


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1	14.118	MM	0.436	2236.127	9.820	
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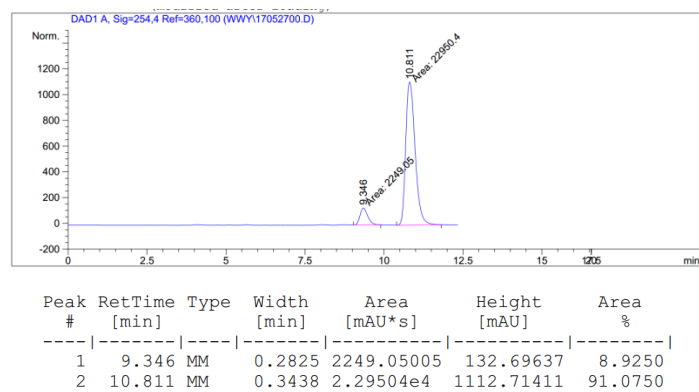
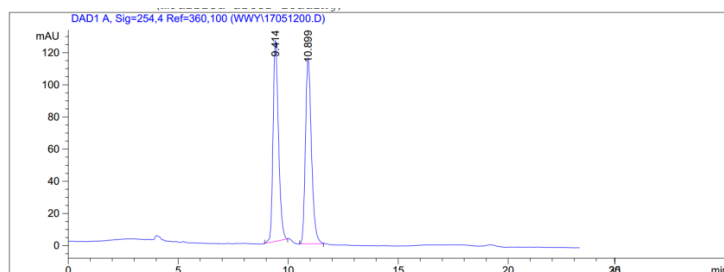
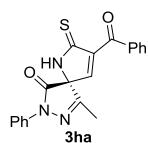
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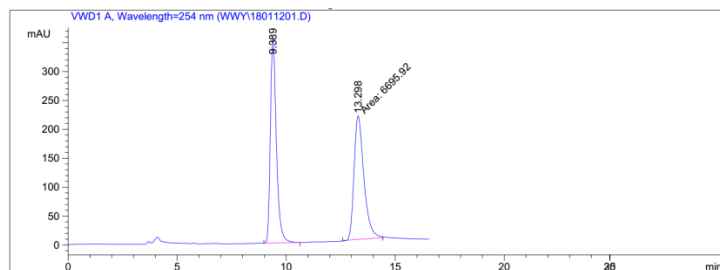
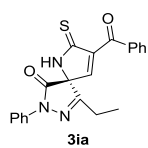
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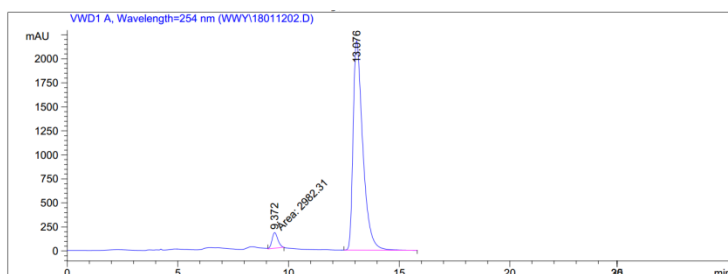
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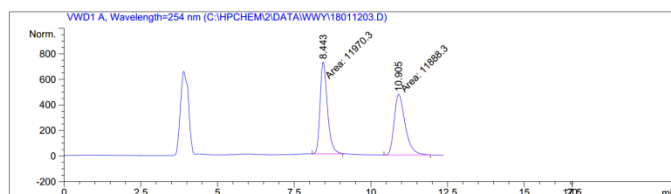
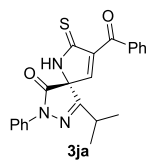


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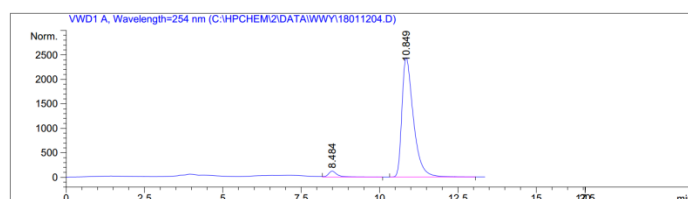


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Compound 3ja

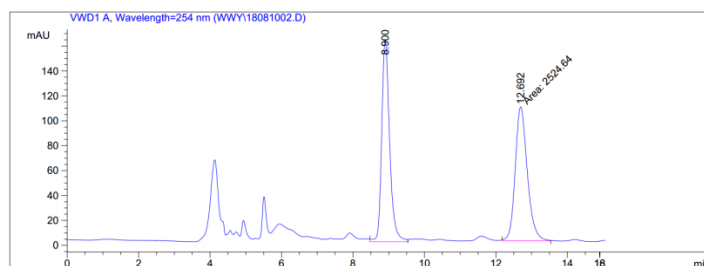
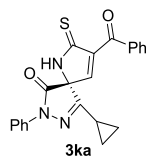


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1	8.443	MM	0.2770	1.19703e4	720.28613	1.204e3
2	10.905	MM	0.4165	1.18883e4	475.75409	1.196e3

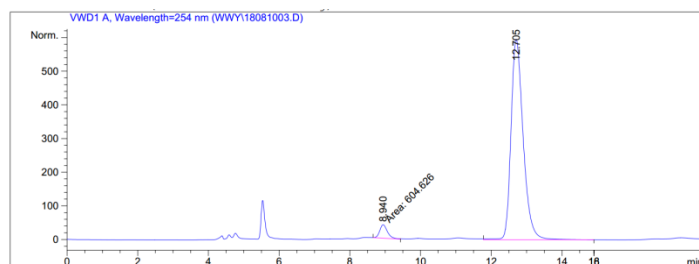


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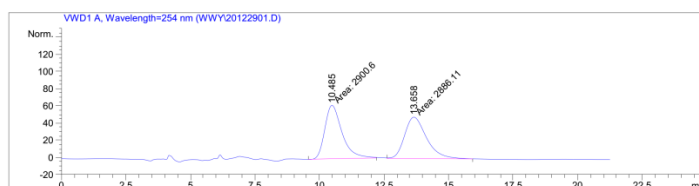
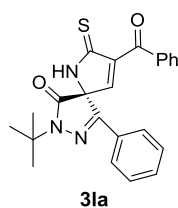


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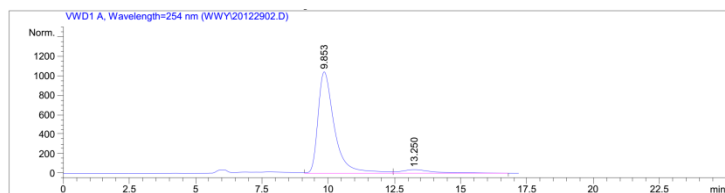


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1	8.940	MM	0.252	604.626	4.075	
2	12.705	VB	0.366	14231.077	95.925	

Compound 3la

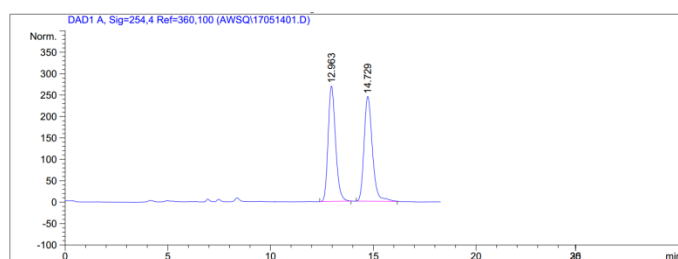
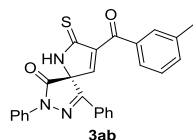


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1	10.485	MM	0.7765	2900.60352	62.25584	50.1252
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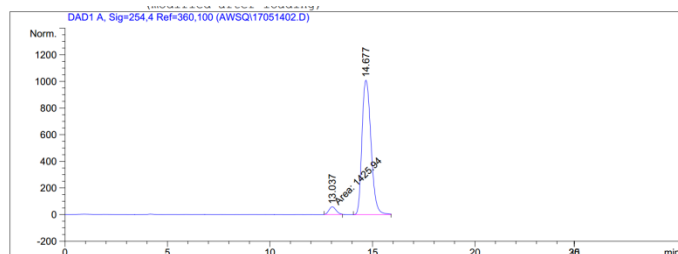


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1	9.853	VB	0.6462	4.49185e4	1040.88782	93.4091
2	13.250	BB	1.2042	3169.45190	36.96356	6.5909

Compound 3ab

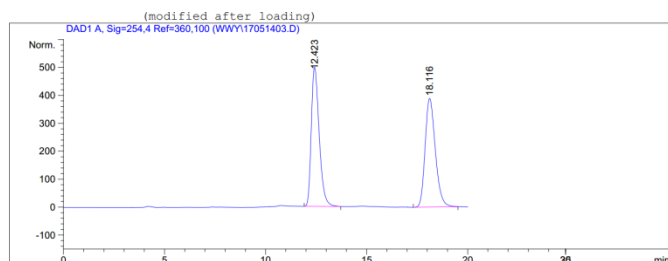
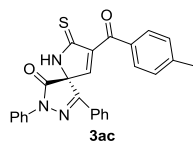


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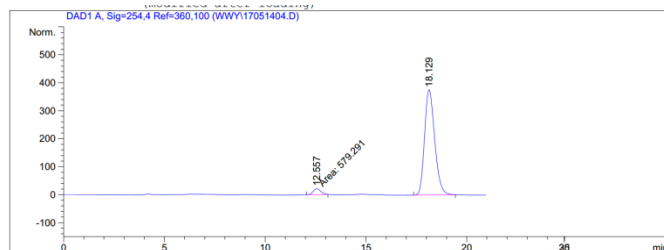


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1	13.037	MM	0.4091	1425.94238	58.08615	4.4106
2	14.677	BBA	0.4851	3.09042e4	1009.77924	95.5894

Compound 3ac

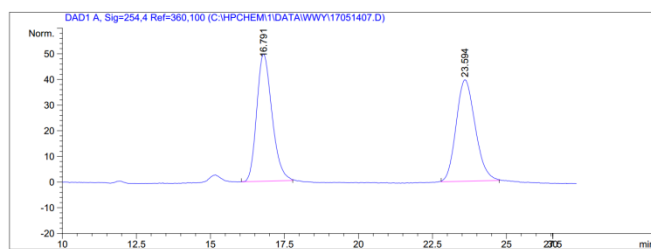
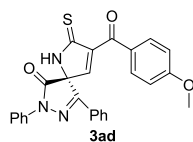


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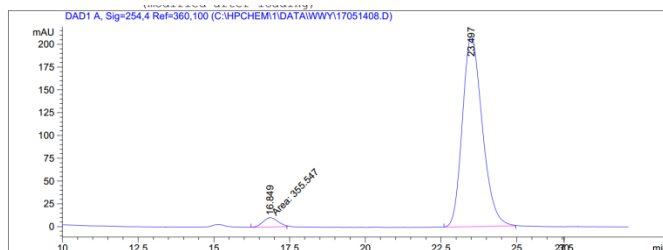


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1	12.557	MM	0.4442	579.29053	21.73561	4.2174
2	18.129	BB	0.5414	1.31565e4	376.73715	95.7826

Compound 3ad

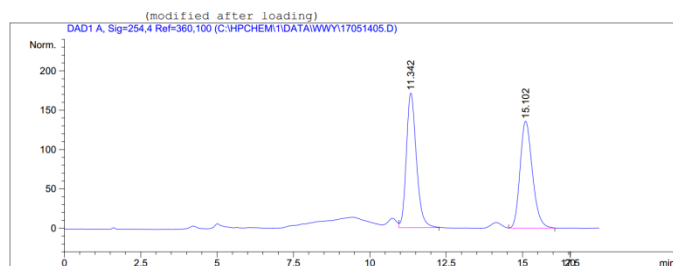
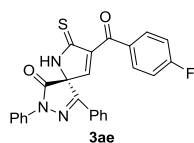


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1	16.791	BB	0.5449	1777.95374	49.51872	50.0369
2	23.594	BB	0.5902	1775.33350	39.51564	49.9631

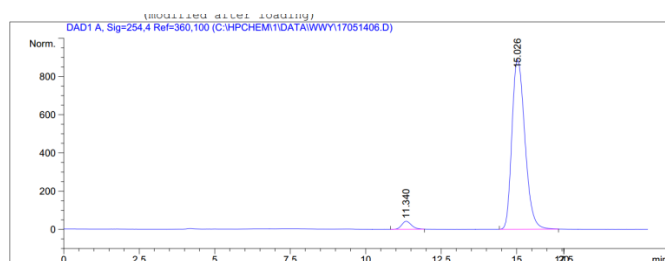


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.849	MM	0.5777	355.54651	10.25815	3.5922
2	23.497	BB	0.6894	9542.18555	208.69055	96.4078

Compound 3ae

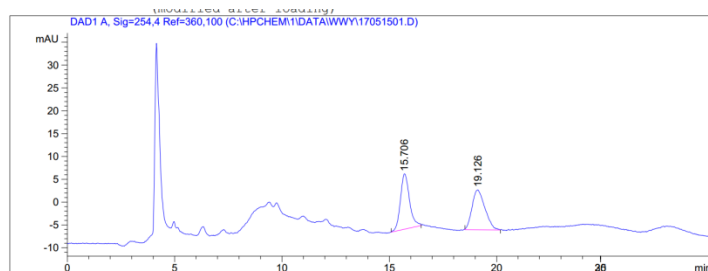
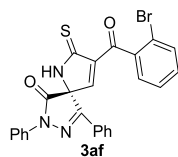


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.342	VB	0.3525	3909.26514	171.15196	50.5170
2	15.102	VB	0.4345	3829.25439	136.00378	49.4830

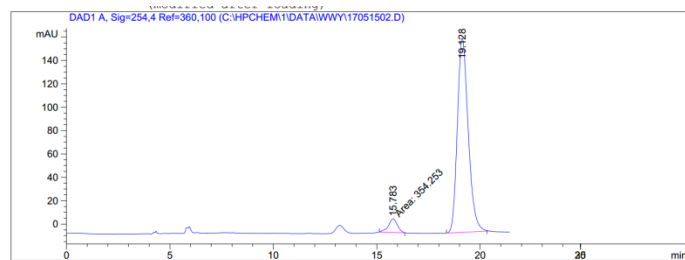


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.340	BB	0.3429	940.30994	42.04588	3.4184
2	15.026	BB	0.4701	2.65672e4	885.37549	96.5816

Compound 3af

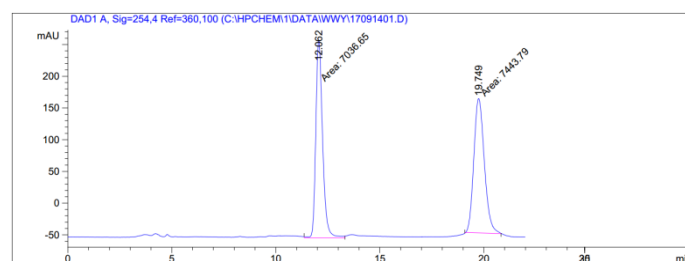
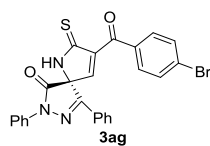


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.706	BB	0.4322	357.93979	12.13084	49.5879
2	19.126	BB	0.4922	363.88959	8.76781	50.4121

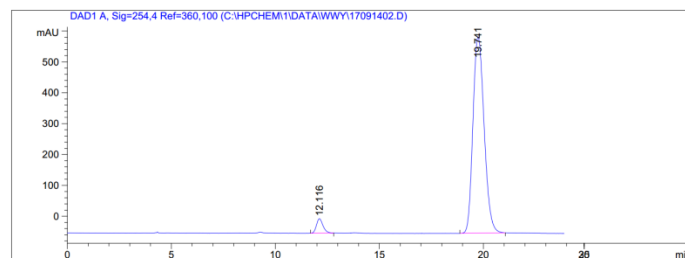


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.783	MM	0.5074	354.25250	11.63511	5.5343
2	19.128	BB	0.5486	6046.73193	166.13460	94.4657

Compound 3ag

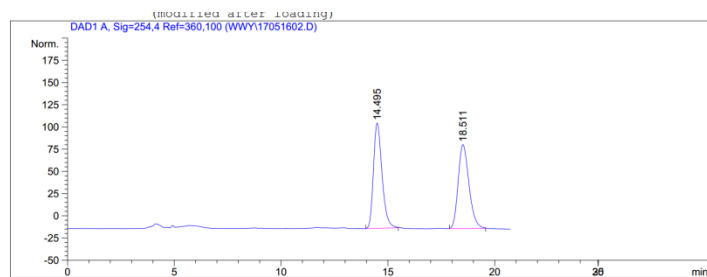
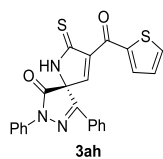


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.062	MM	0.3760	7036.64600	311.89212	48.5942
2	19.749	MM	0.5855	7443.79102	211.90860	51.4058

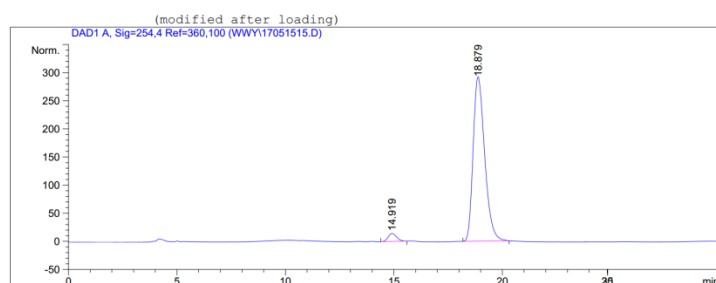


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.116	BB	0.3375	1041.18372	47.16986	4.1956
2	19.741	PB	0.5803	2.37749e4	635.74103	95.8044

Compound 3ah

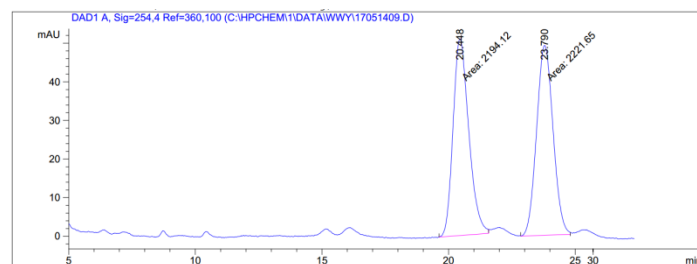
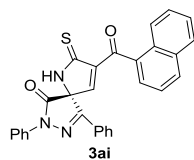


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.495	BB	0.4235	3303.89038	118.41063	49.9624
2	18.511	BB	0.5348	3308.86792	94.43951	50.0376

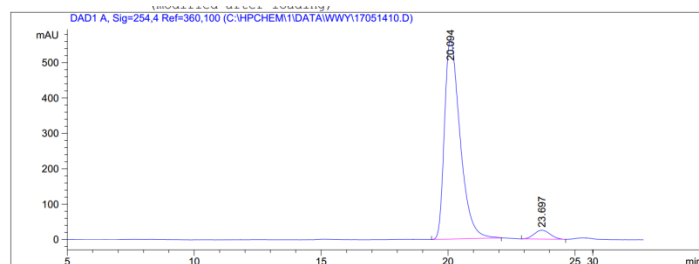


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.919	PV	0.3977	393.07764	14.34318	3.5016
2	18.879	BB	0.5662	1.08326e4	292.39658	96.4984

Compound 3ai

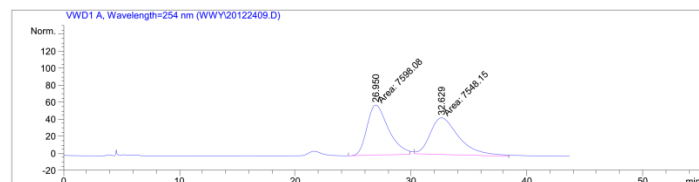
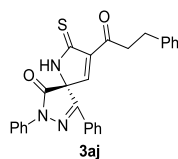


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.448	MM	0.7181	2194.11548	50.92534	49.6882
2	23.790	MM	0.7530	2221.65454	49.17273	50.3118

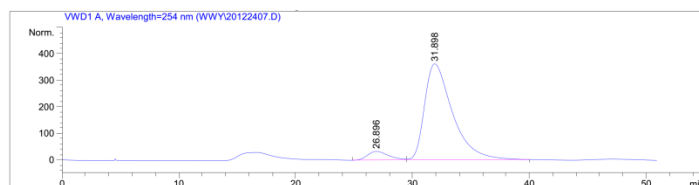


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.094	PB	0.6444	2.40948e4	564.01581	95.7046
2	23.697	PP	0.5272	1081.42822	24.97316	4.2954

Compound 3aj

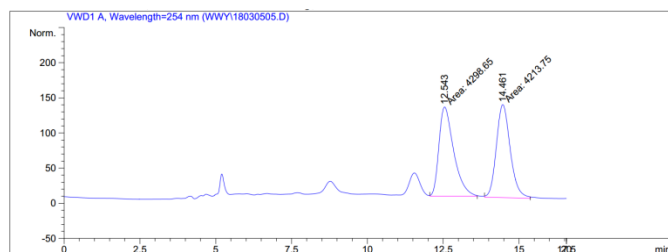
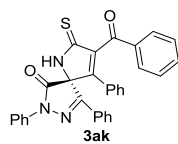


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.950	MM	2.1520	7598.07520	58.84440	50.1648
2	32.629	MM	2.9157	7548.15283	43.14595	49.8352

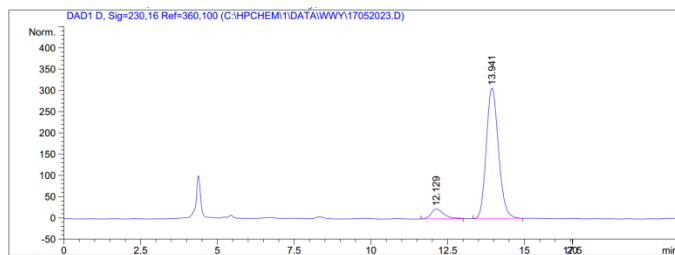


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.896	BV	1.6552	4137.22998	33.05692	6.4050
2	31.898	VB	2.4809	6.04565e4	362.06848	93.5950

Compound 3ak

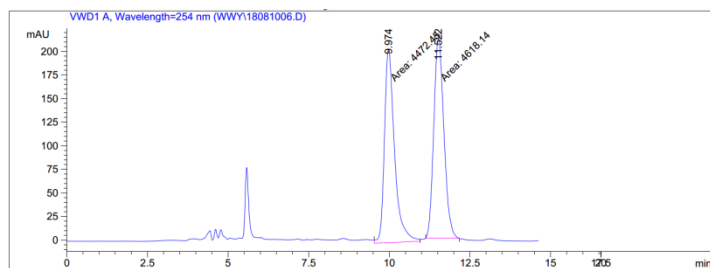
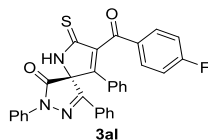


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.543	MM	0.5643	4298.64795	126.95582	1.212e3
2	14.461	MM	0.5304	4213.74902	132.39784	1.188e3

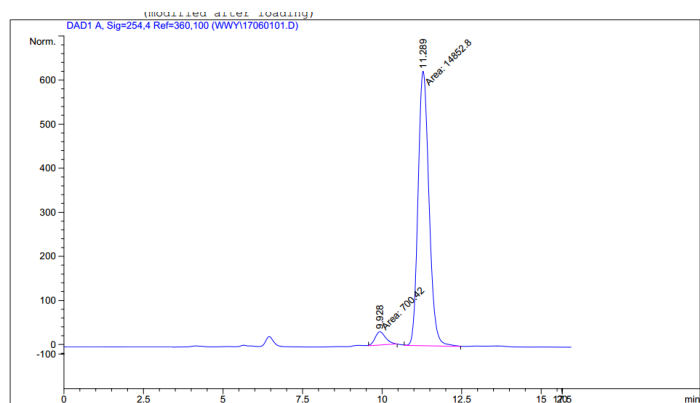


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.129	BB	0.4155	677.68359	23.42543	7.3944
2	13.941	BB	0.4302	8487.19434	307.27859	92.6056

Compound 3al

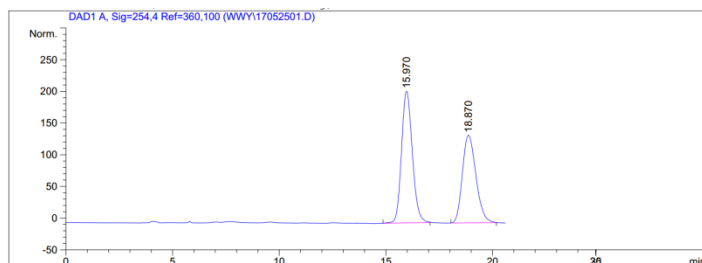
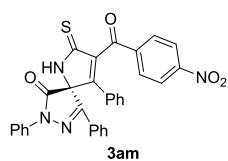


Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	9.974	MM	0.363	4472.455	49.199	
2	11.522	MM	0.364	4618.135	50.801	

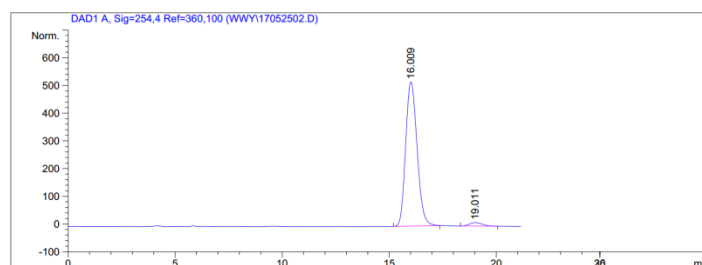


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.928	MM	0.3839	700.41986	30.40674	4.5034
2	11.289	MM	0.3973	1.48528e4	623.10040	95.4966

Compound 3am

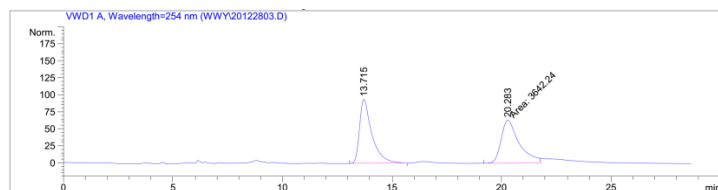
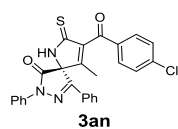


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.970	BB	0.5402	7309.07520	207.86688	54.4411
2	18.870	BB	0.6730	6116.58301	138.56688	45.5589

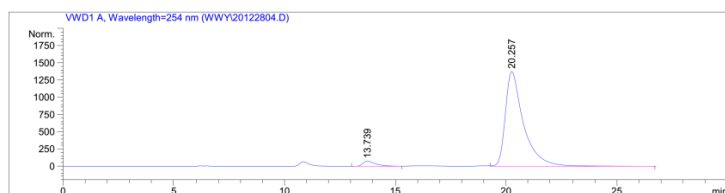


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.009	BB	0.5862	1.92937e4	520.83484	97.2973
2	19.011	BB	0.4943	535.94293	13.01842	2.7027

Compound 3an

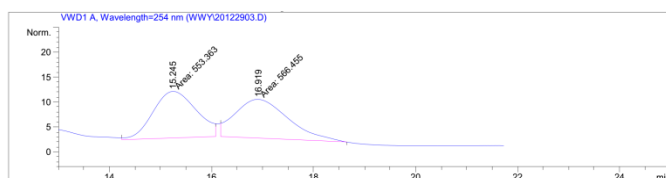
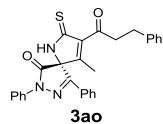


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.715	BB	0.5635	3664.30664	94.09260	50.1510
2	20.283	MM	0.9561	3642.24146	63.48817	49.8490

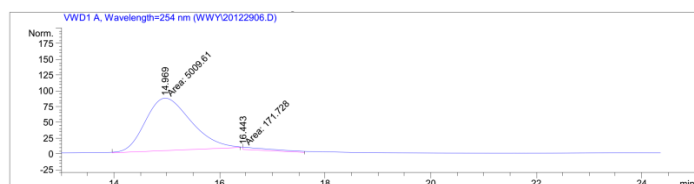


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.739	BB	0.5773	3092.67090	77.08334	3.7910
2	20.257	VB	0.8322	7.84857e4	1374.47986	96.2090

Compound 3ao

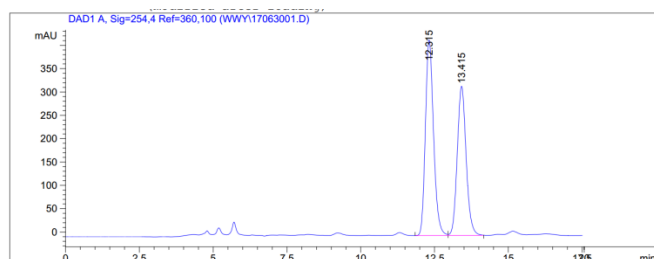
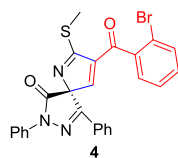


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.245	MM	0.9853	553.36255	9.36015	49.4154
2	16.919	MM	1.2132	566.45514	7.78208	50.5846

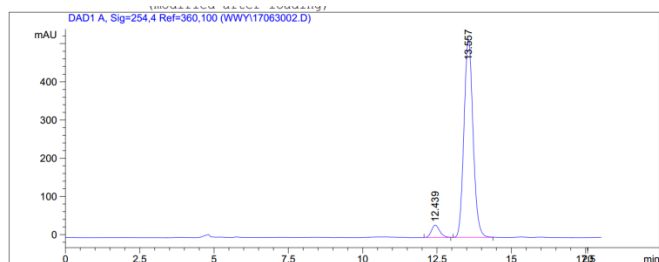


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.969	MM	1.0021	5009.60840	83.31757	96.6856
2	16.443	MM	0.7780	171.72791	3.67887	3.3144

Compound 4

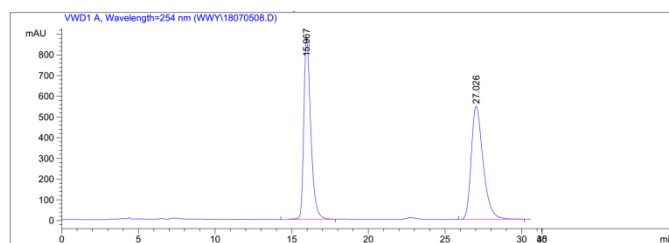
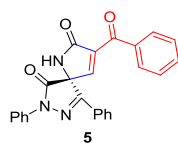


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.315	PV	0.2950	8009.60303	419.11423	54.5035
2	13.415	VB	0.3219	6685.96875	319.76541	45.4965

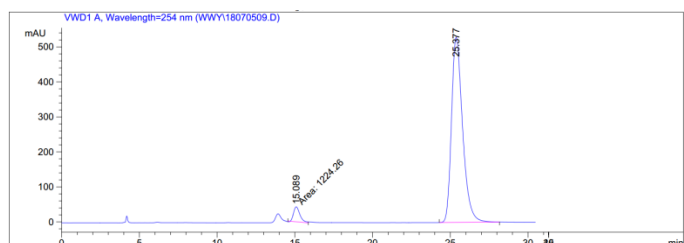


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.439	BB	0.2872	633.90479	32.83389	5.4319
2	13.557	BB	0.3300	1.10361e4	519.21307	94.5681

Compound 5



Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.967	BB	0.475	27656.131	48.568	
2	27.026	BB	0.809	29286.412	51.432	

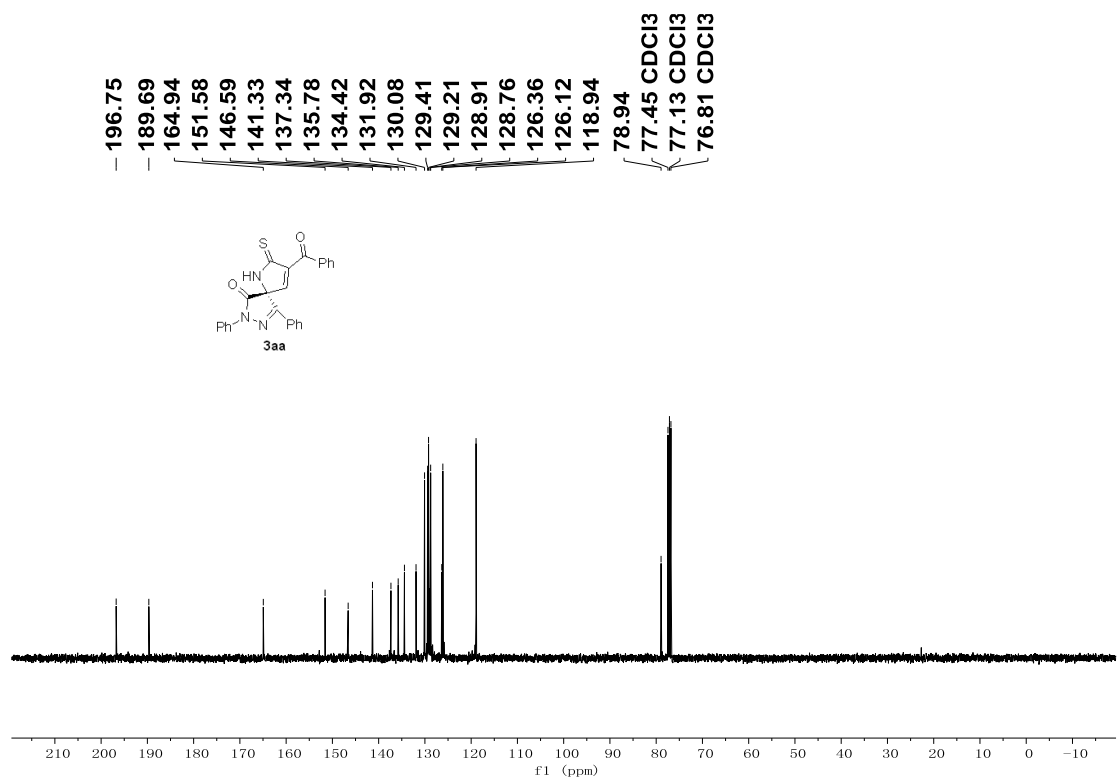
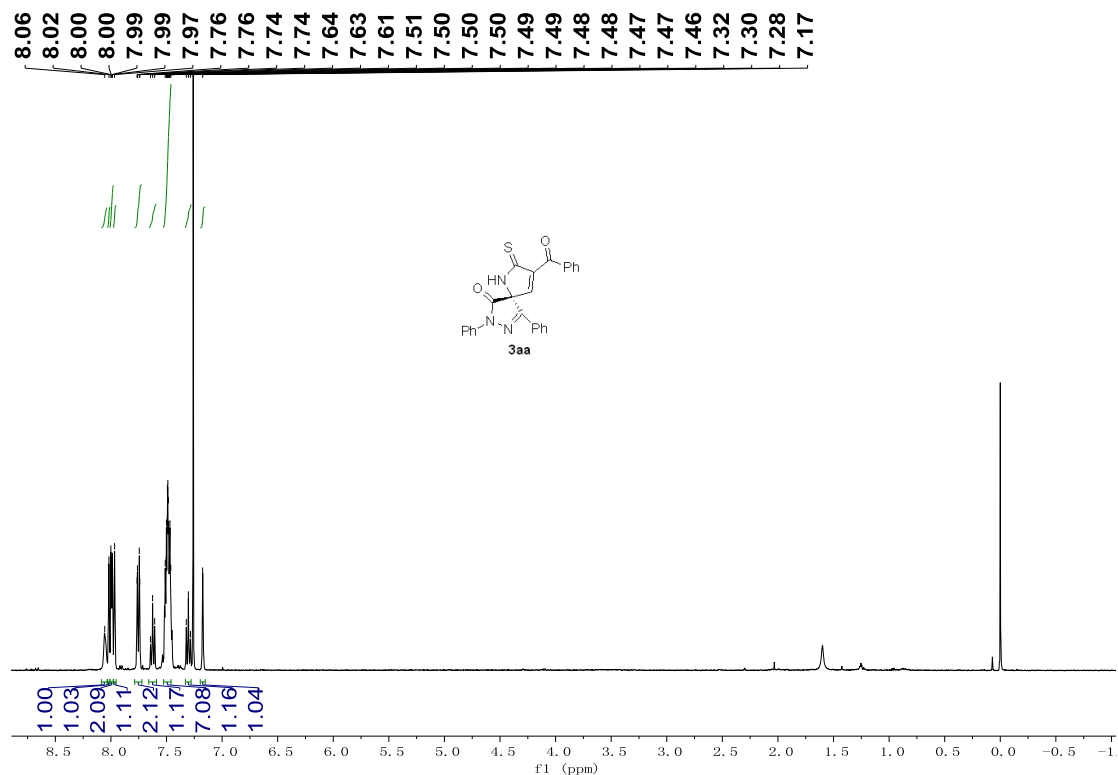


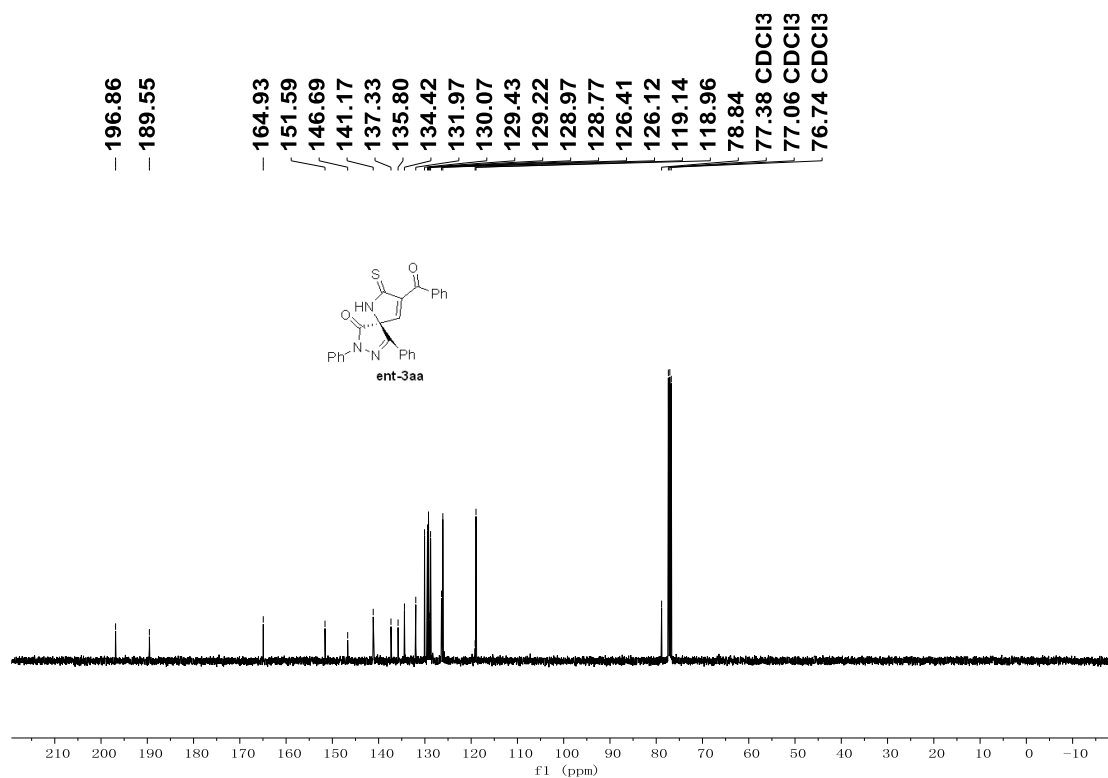
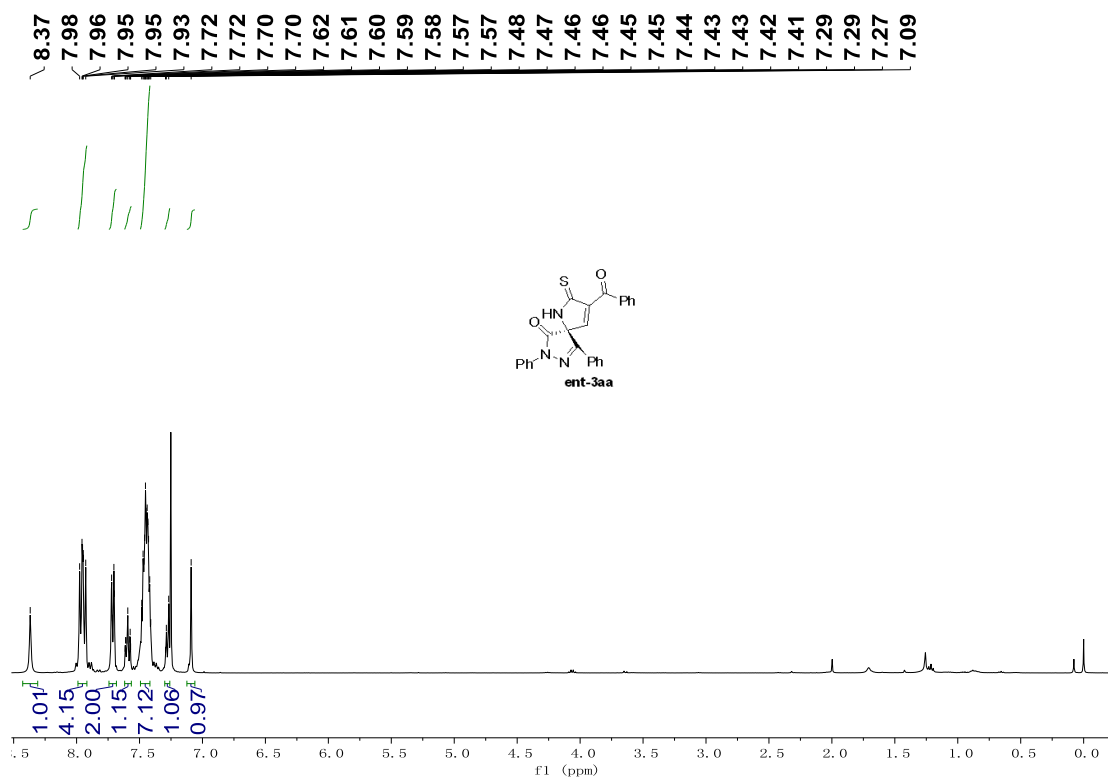
Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	15.088	MM	0.451	1155.021	4.217	
2	25.377	BB	0.756	26232.715	95.783	

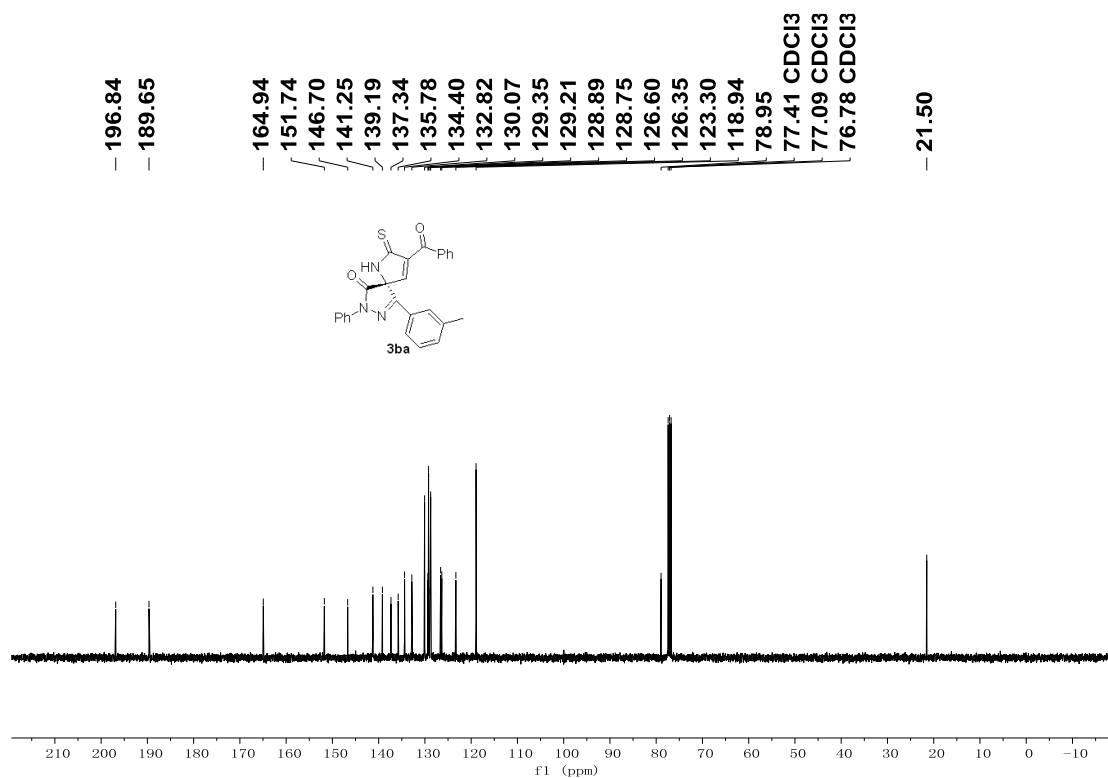
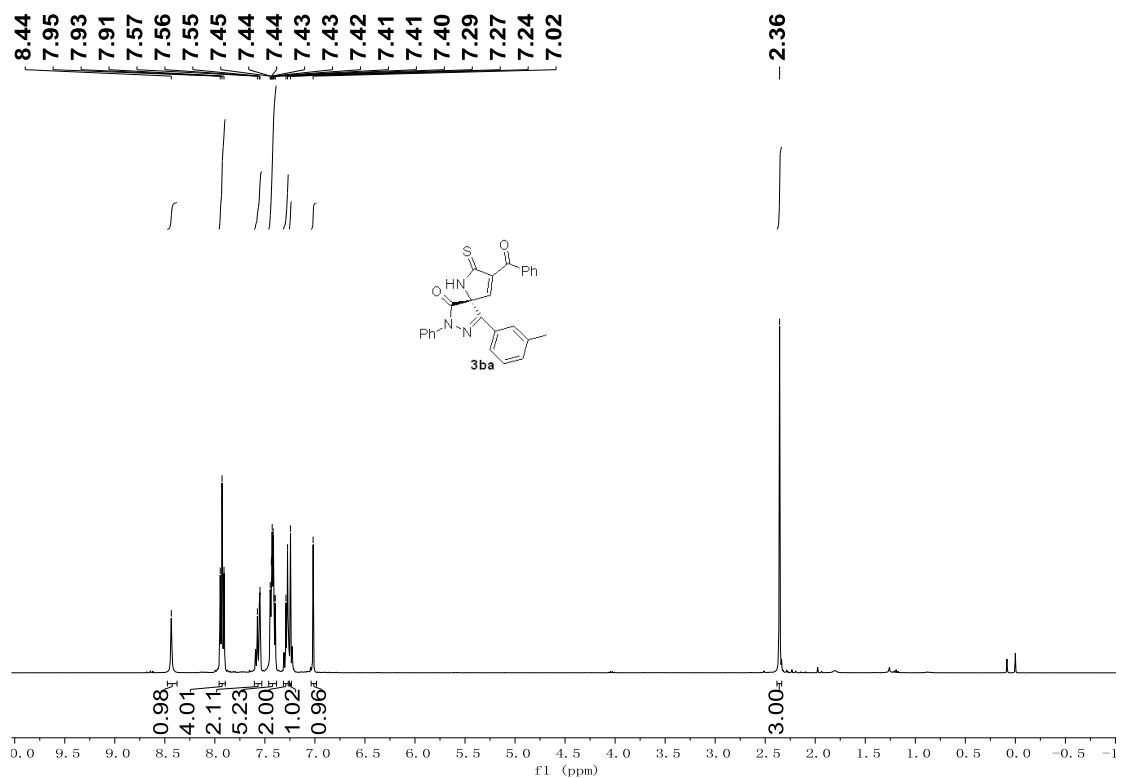
6. Reference

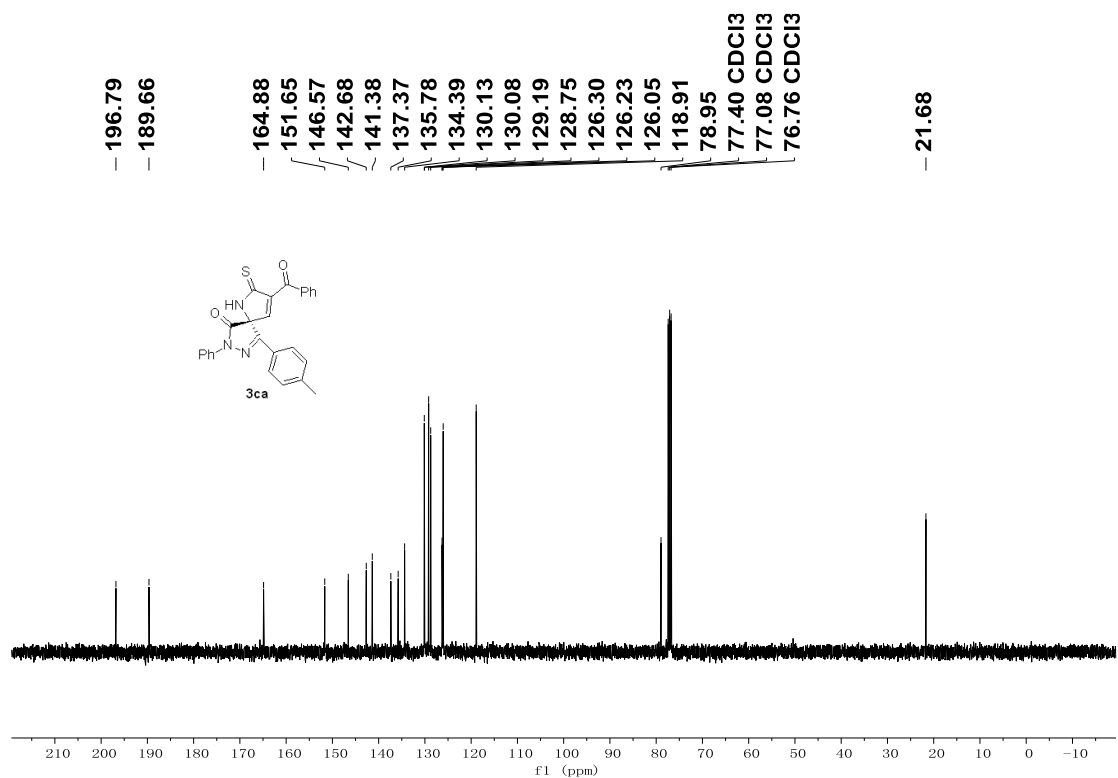
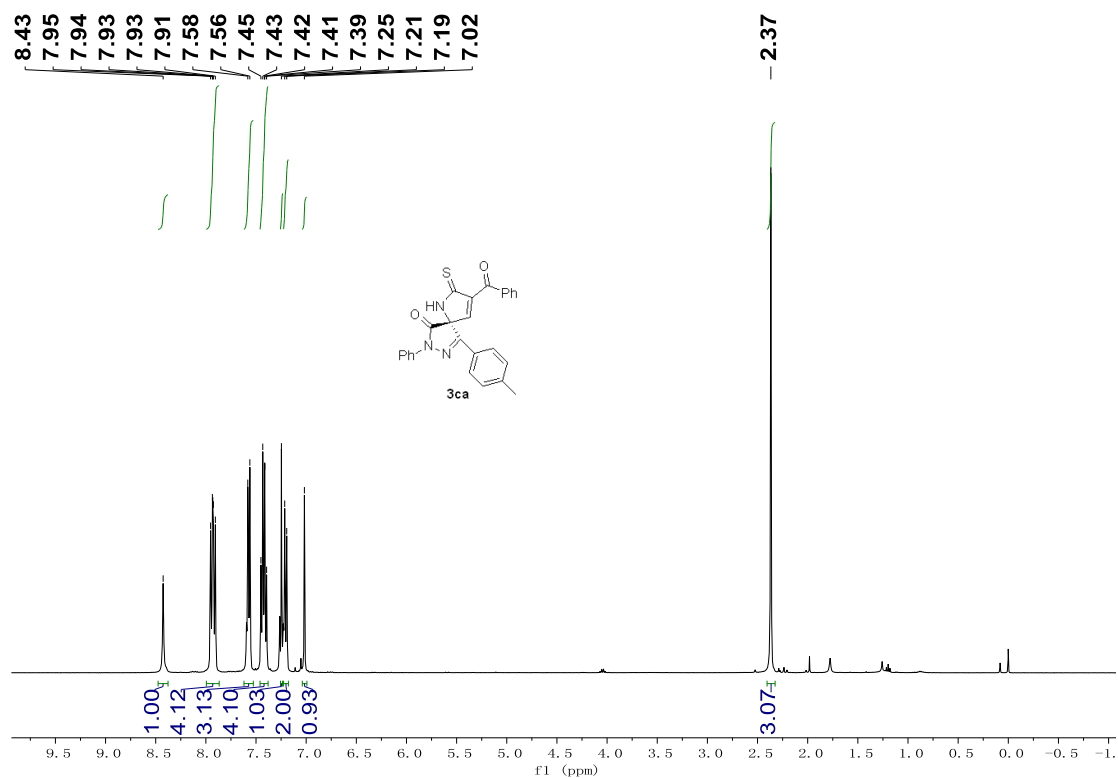
1. X. Bao, S. Wei, X. Qian, J. Qu, B. Wang, L. Zou and G. Ge, *Org. Lett.*, 2018, **20**, 3394-3398.
2. (a) F. Shi, S.-W. Luo, Z.-L. Tao, L. He, J. Yu, S.-J. Tu and L.-Z. Gong, *Org. Lett.*, 2011, **13**, 4680-4683; (b) J. Rong, H. Li, R. Fu, W. Sun, T.-P. Loh and Y. Jiang, *ACS Catal.*, 2020, **10**, 3664-3669.
3. W. Yang and D.-M. Du, *Org. Lett.* , 2010, **12**, 5450-5453.

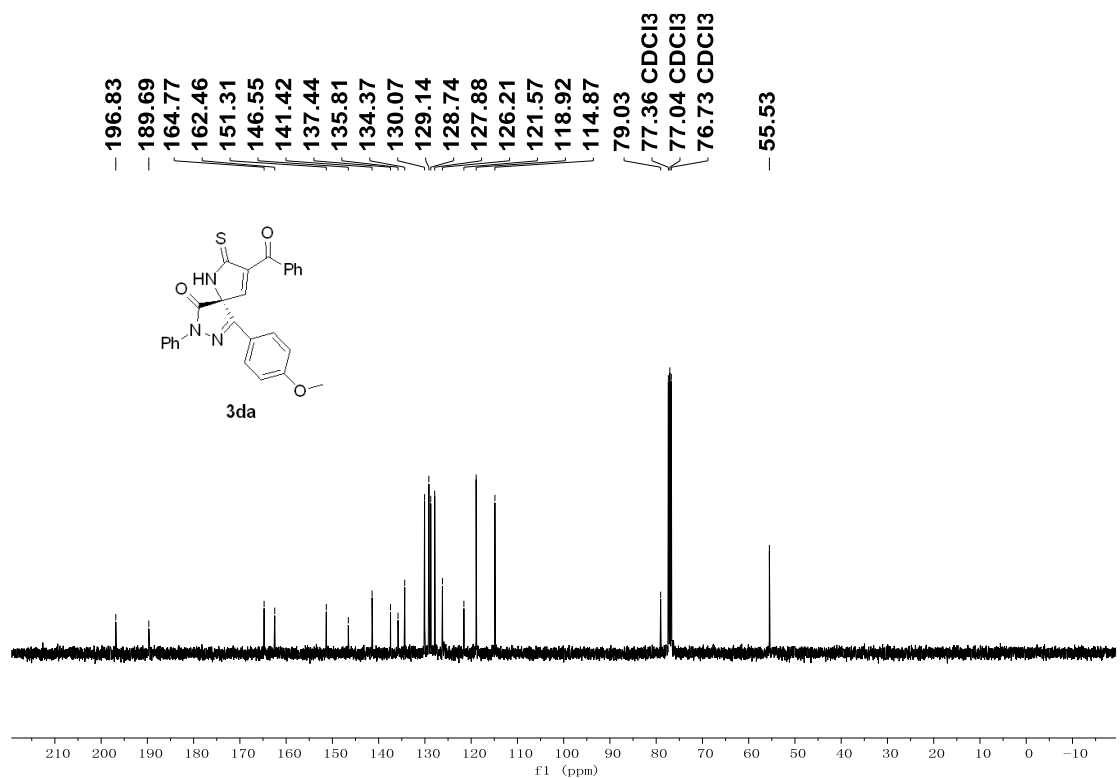
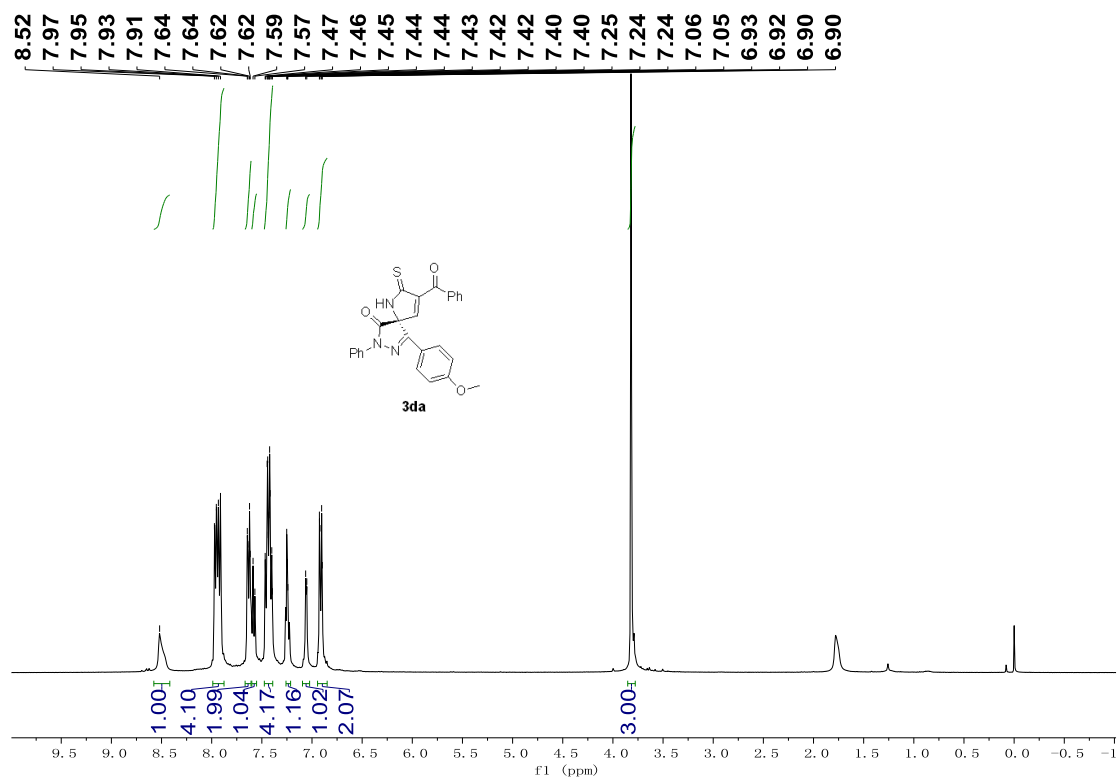
7. NMR spectra for compounds

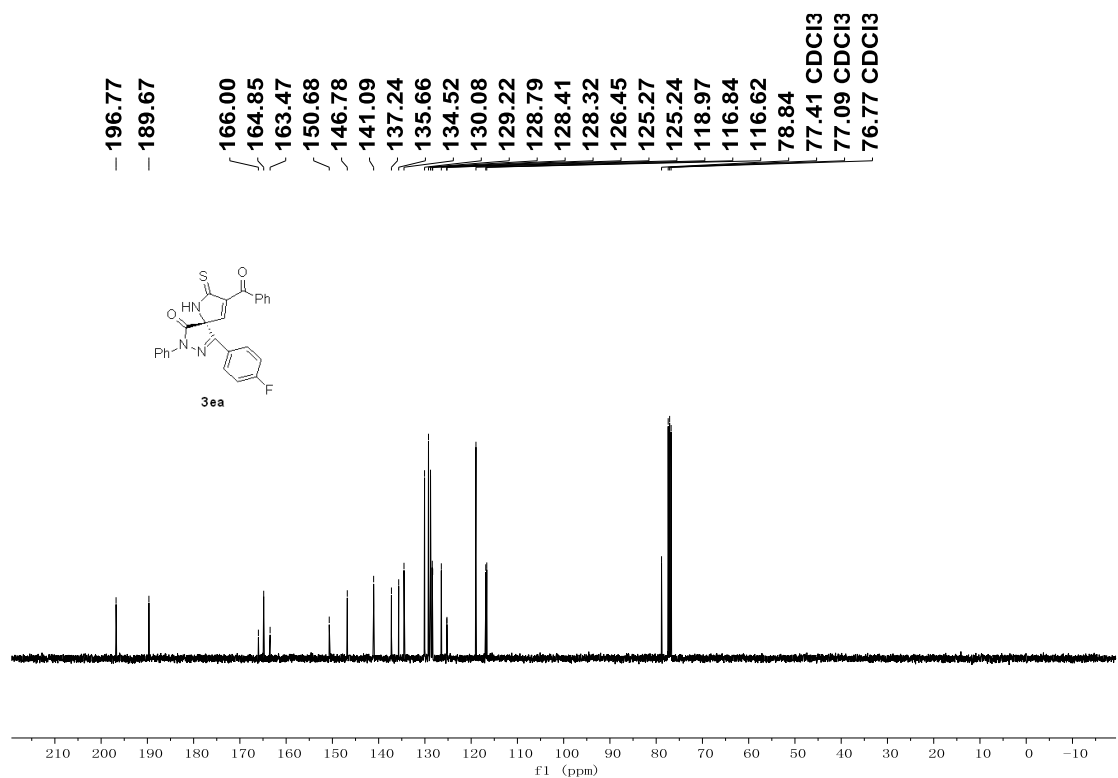
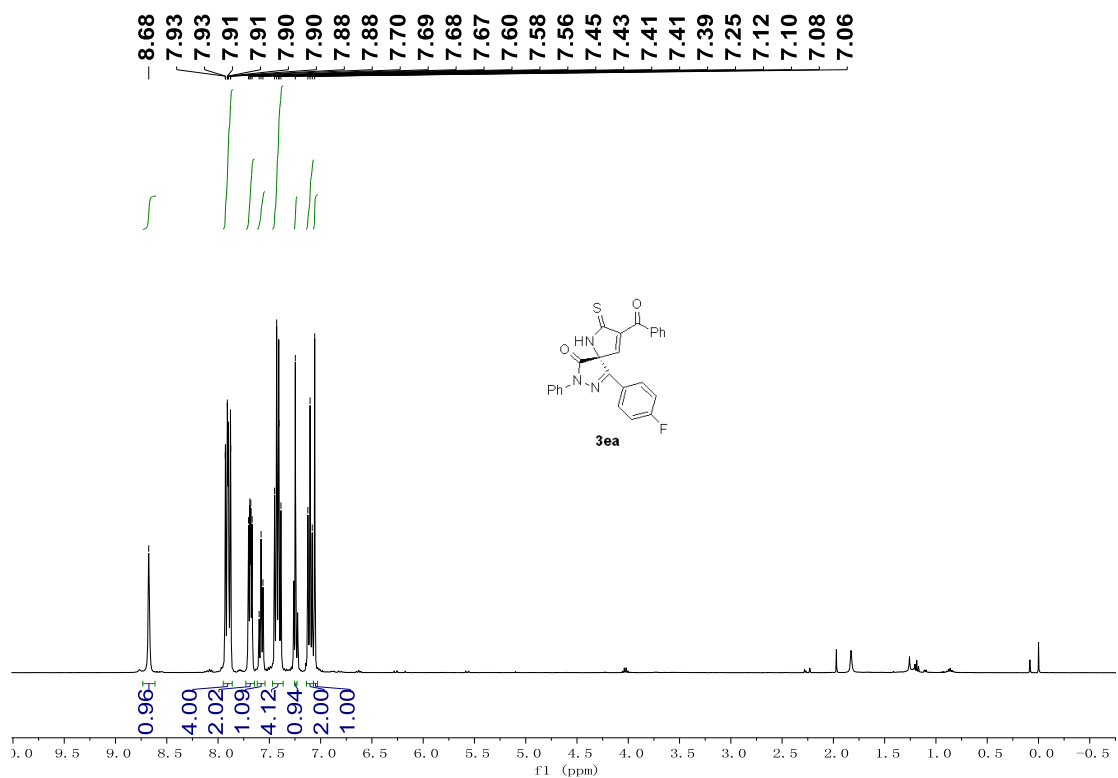


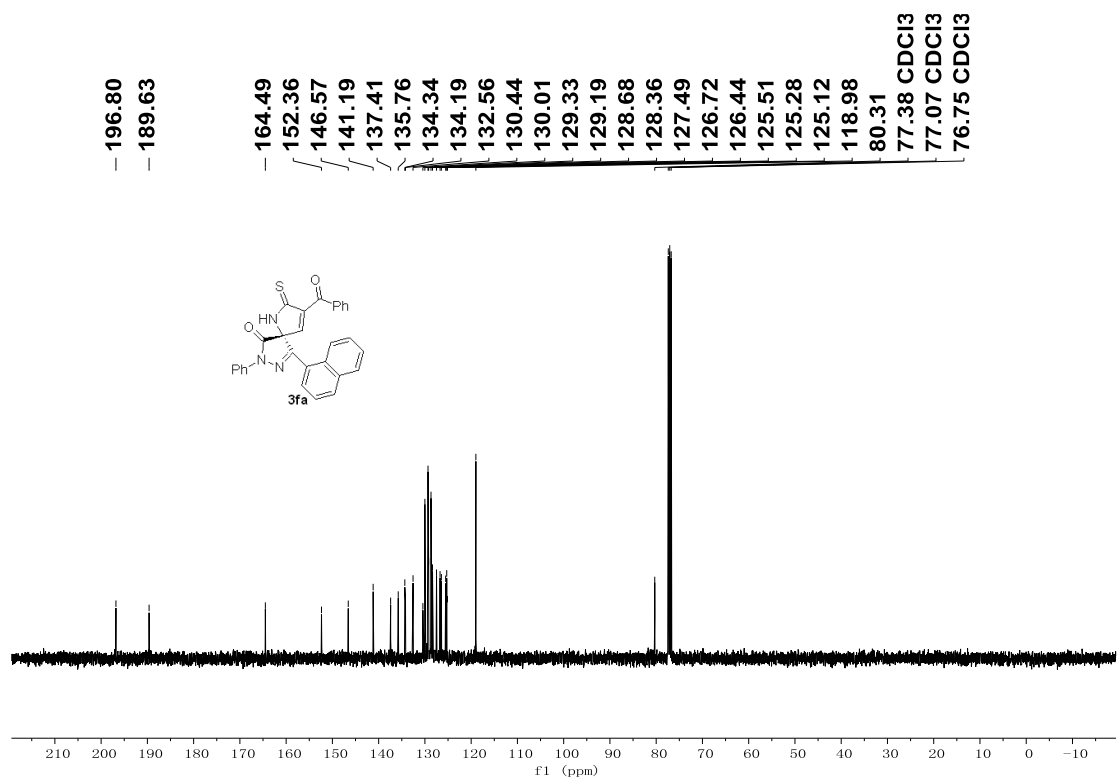
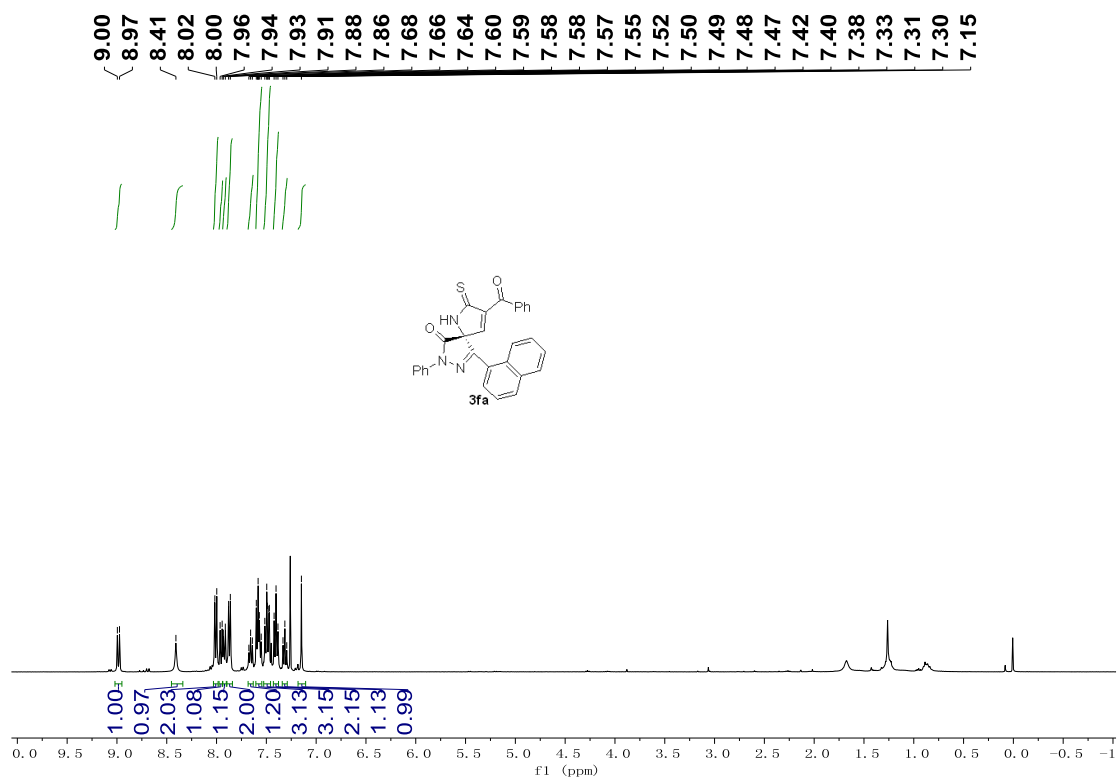


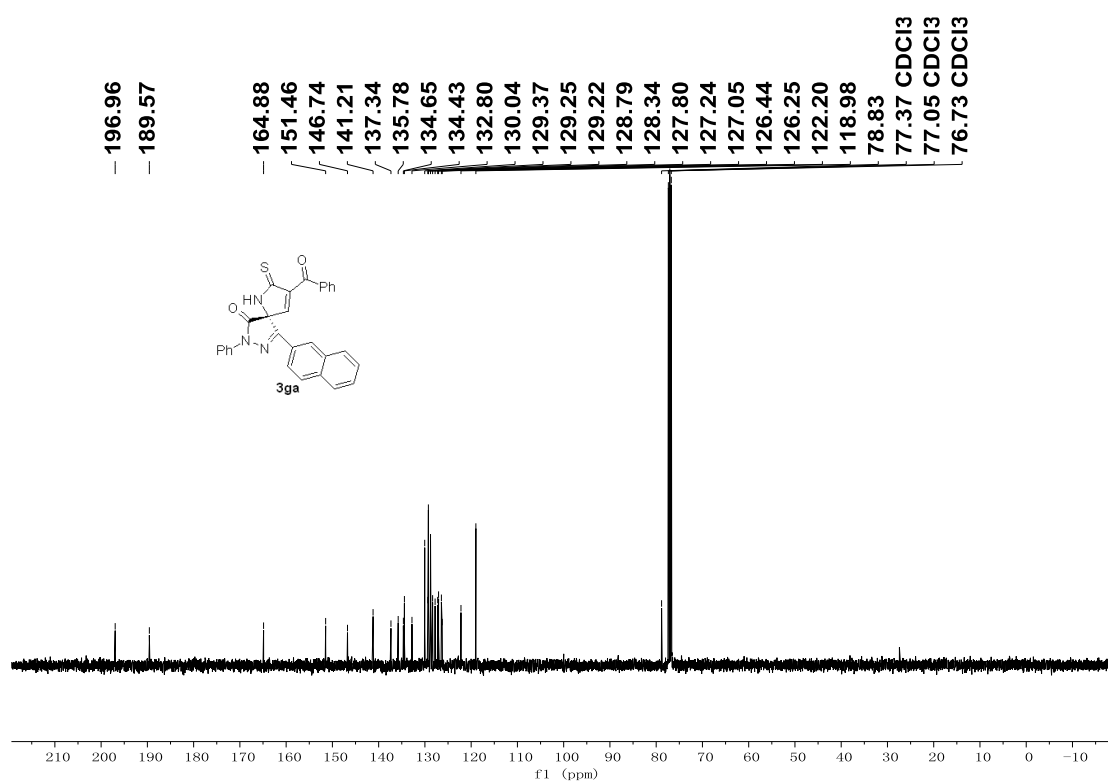
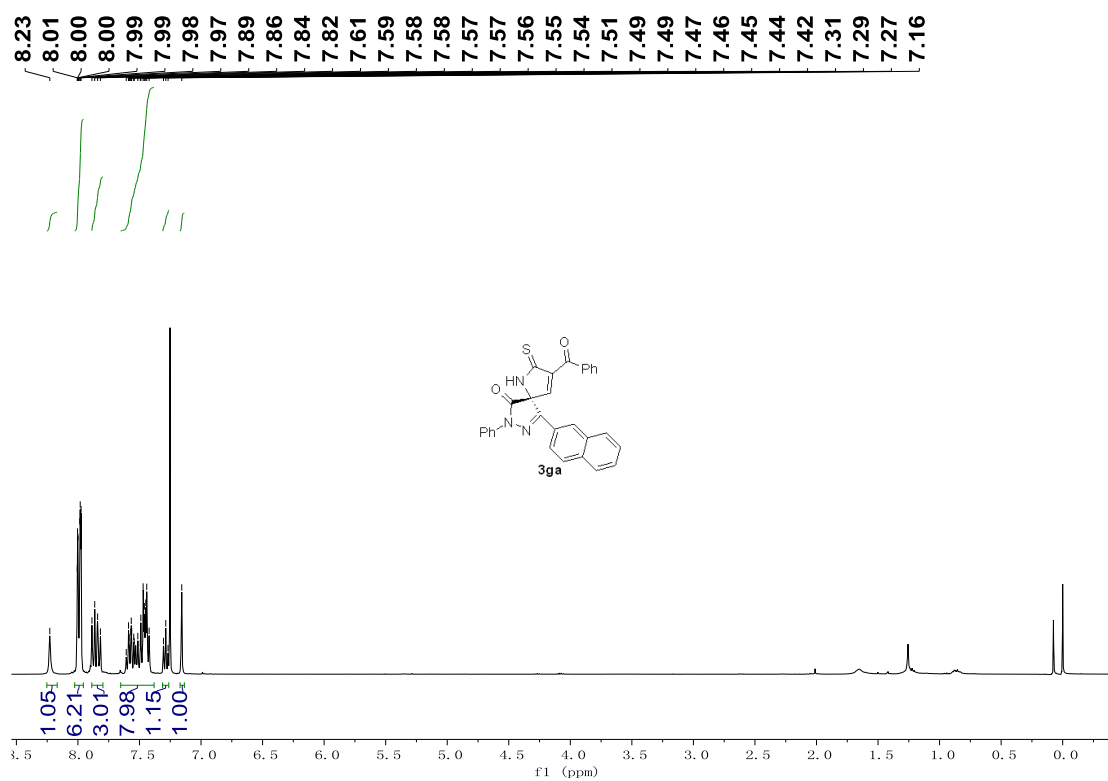


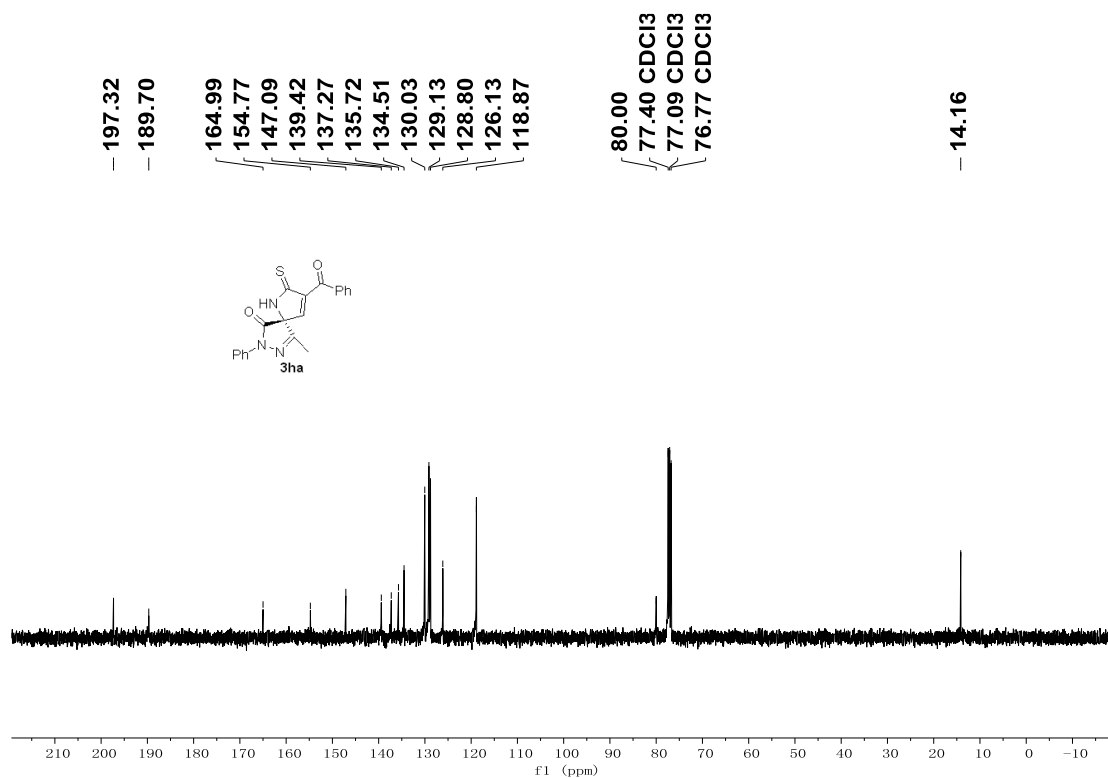
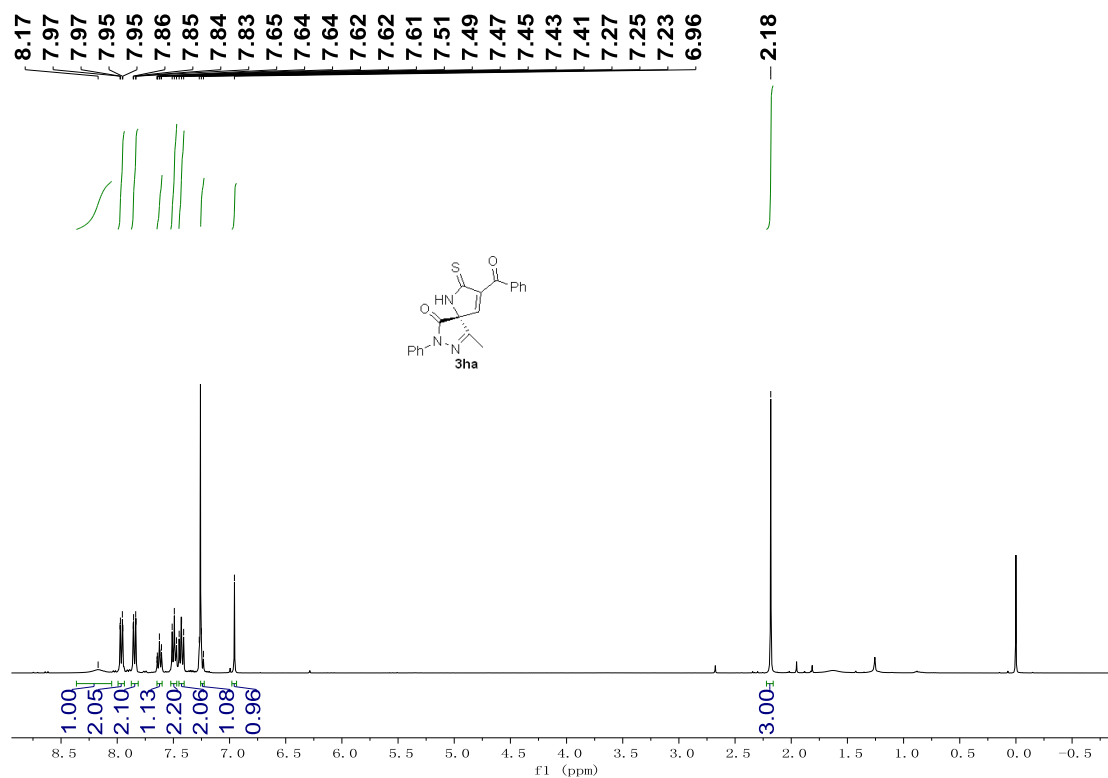


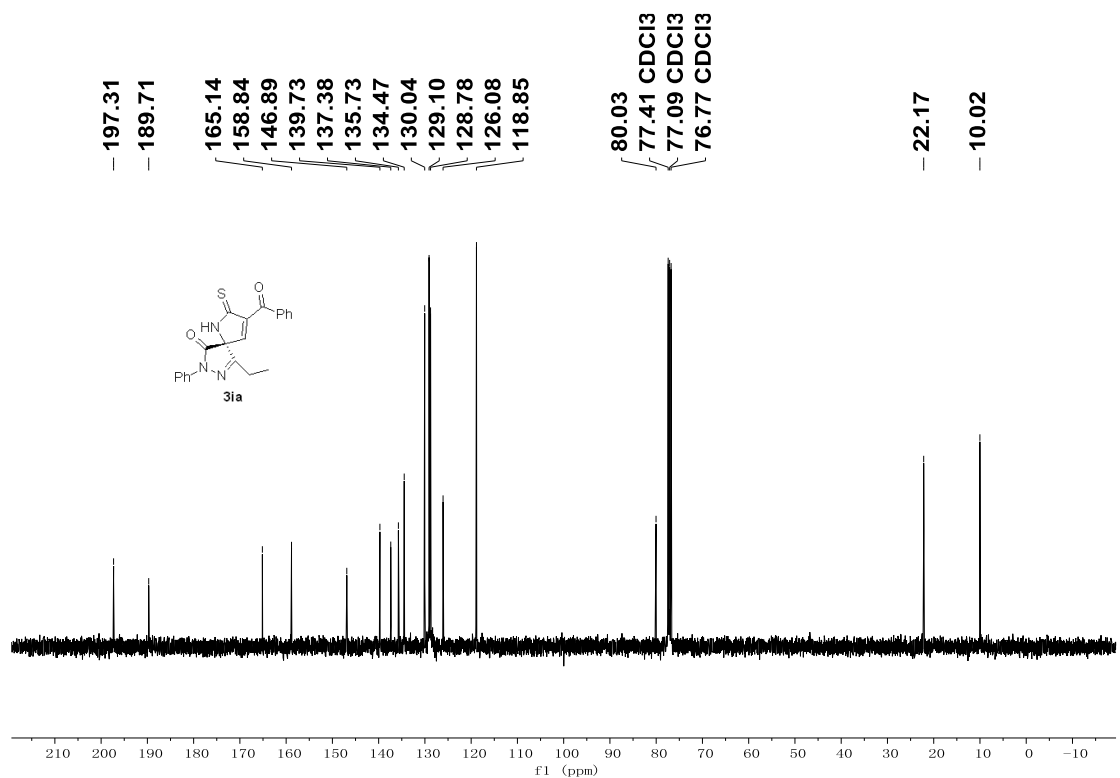
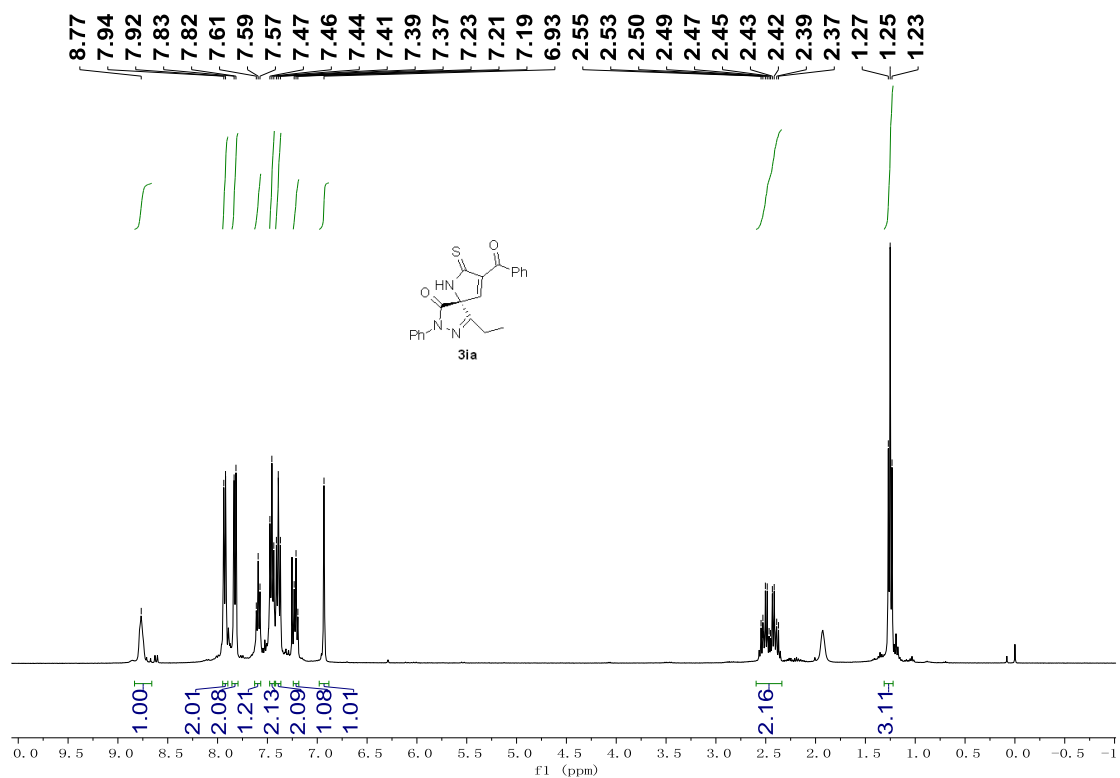


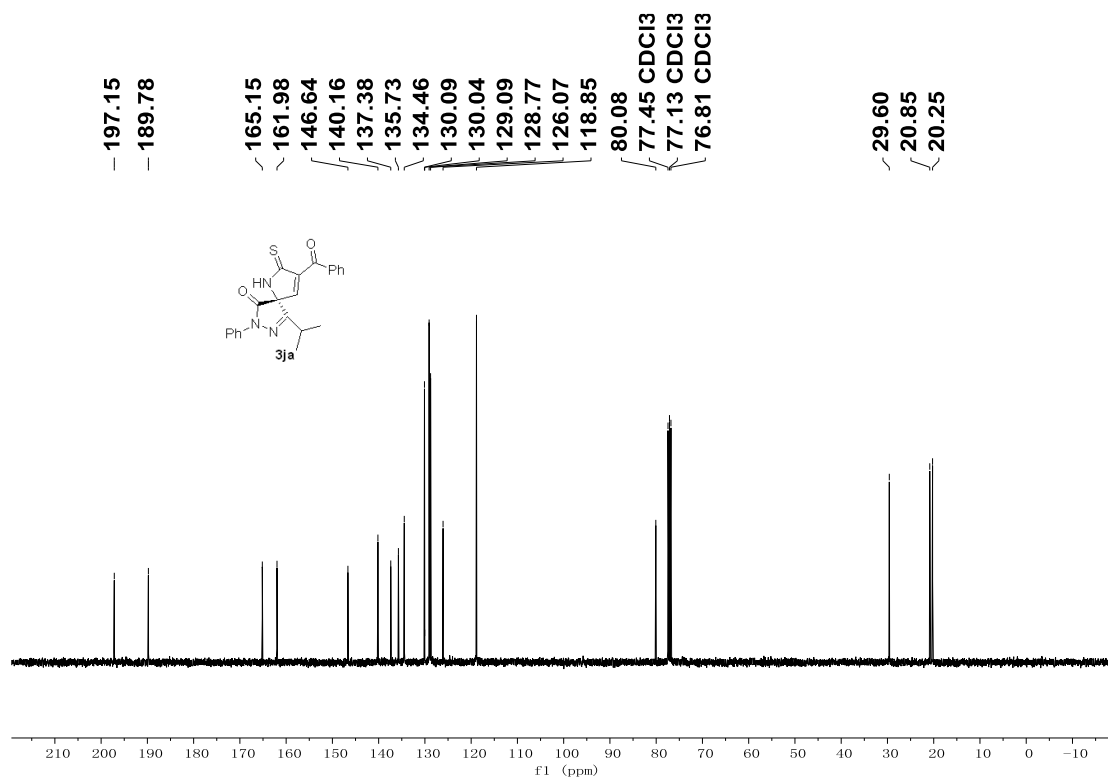
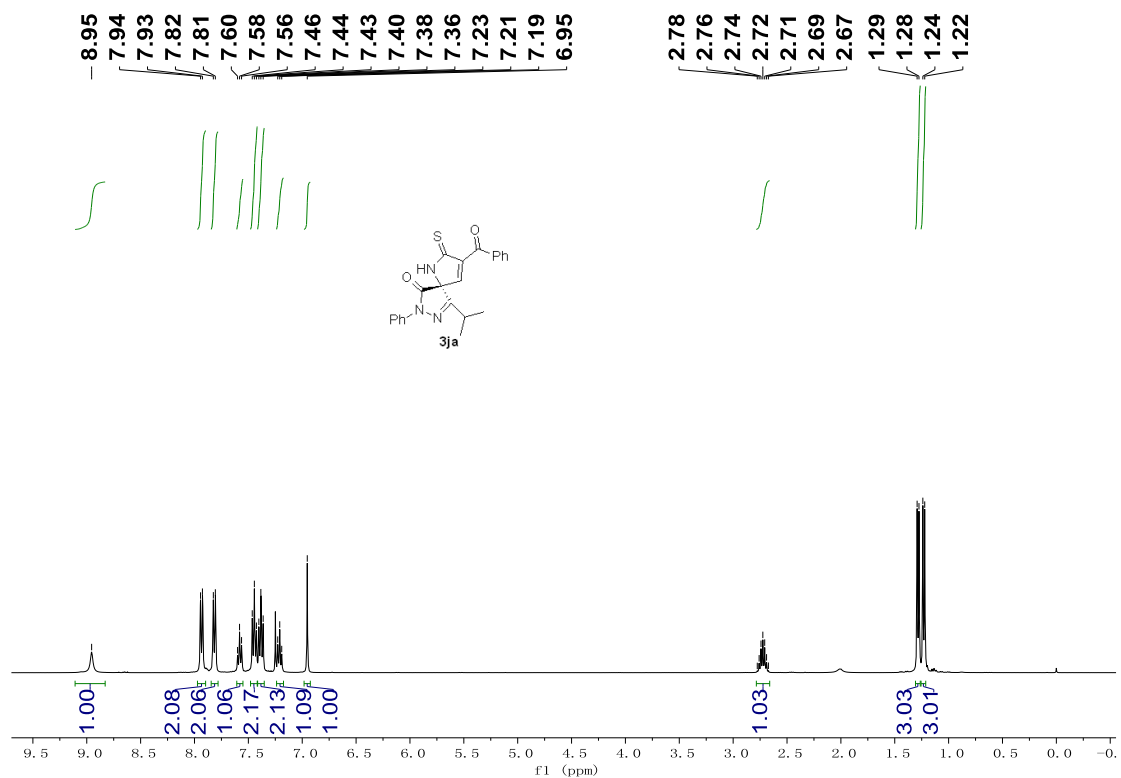


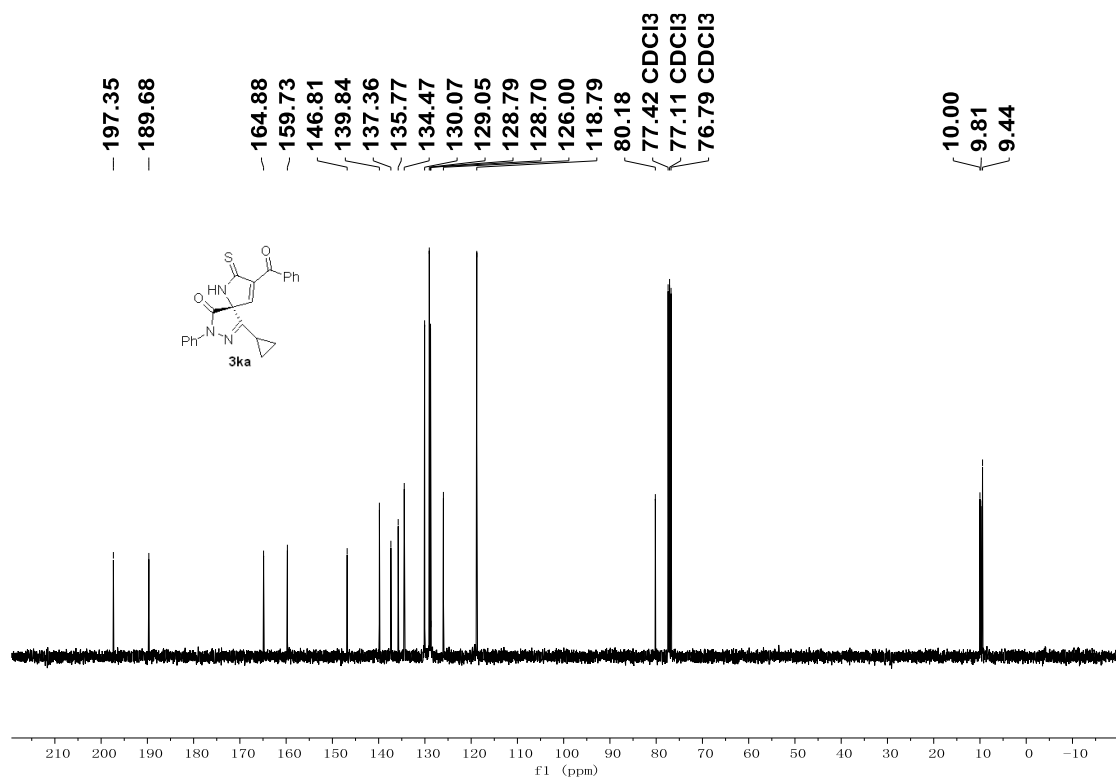
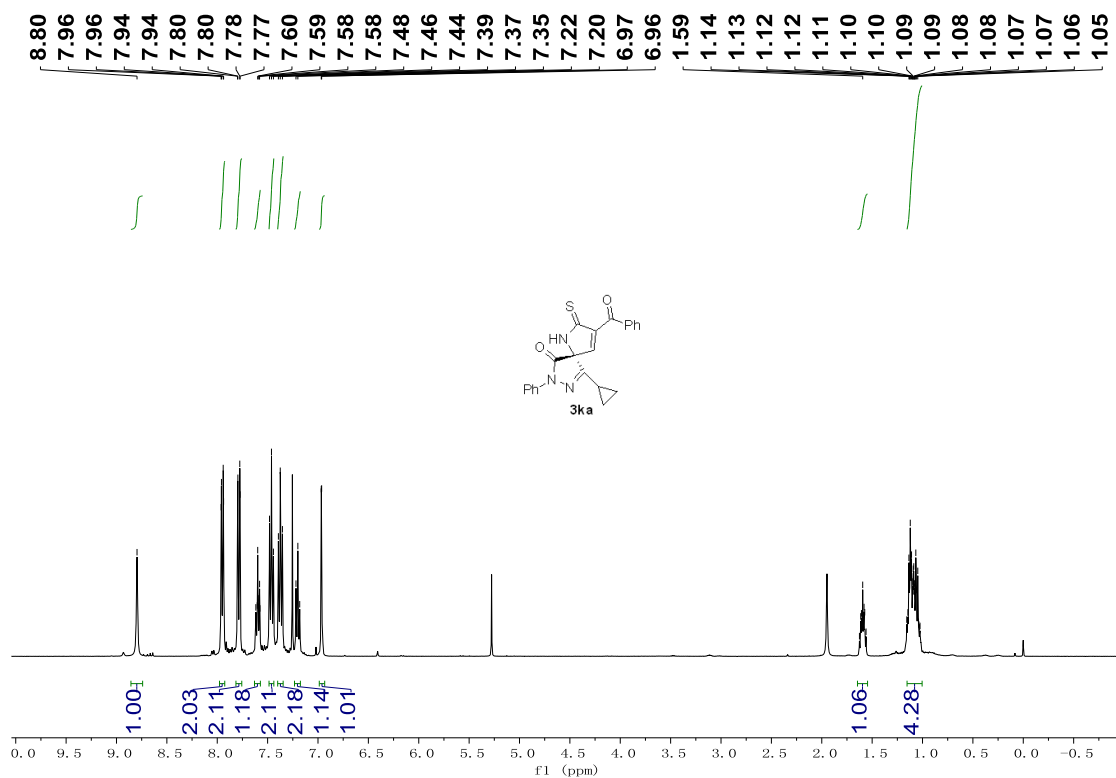


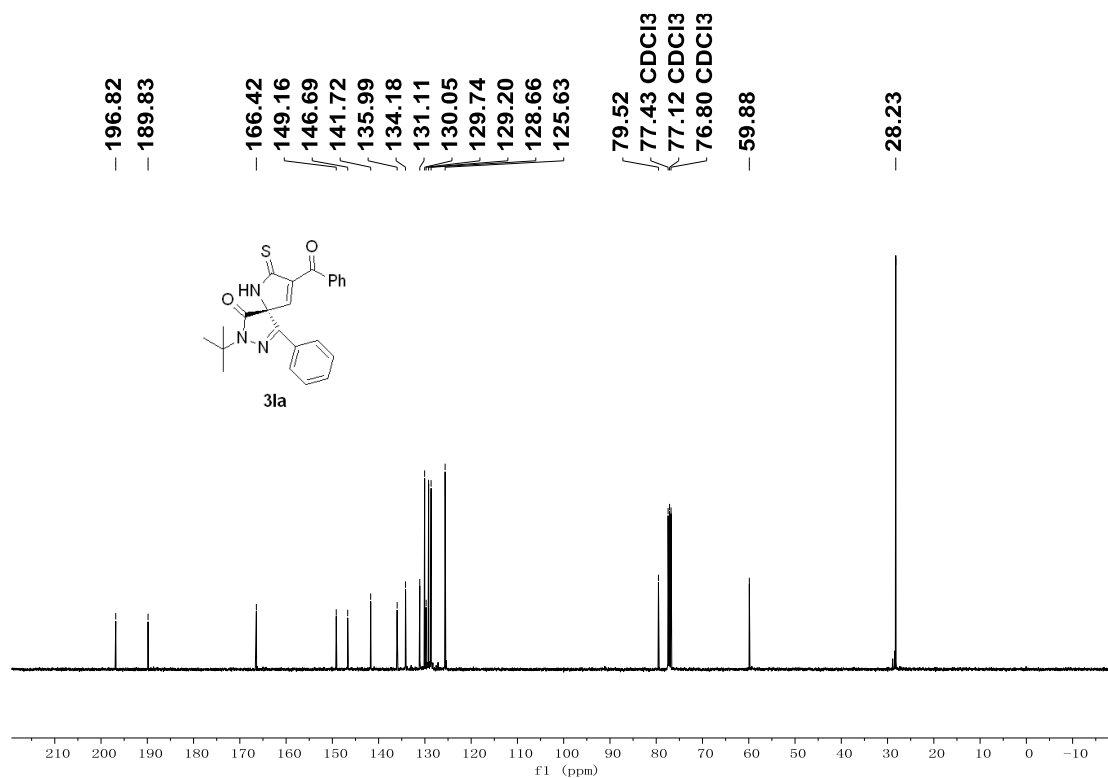
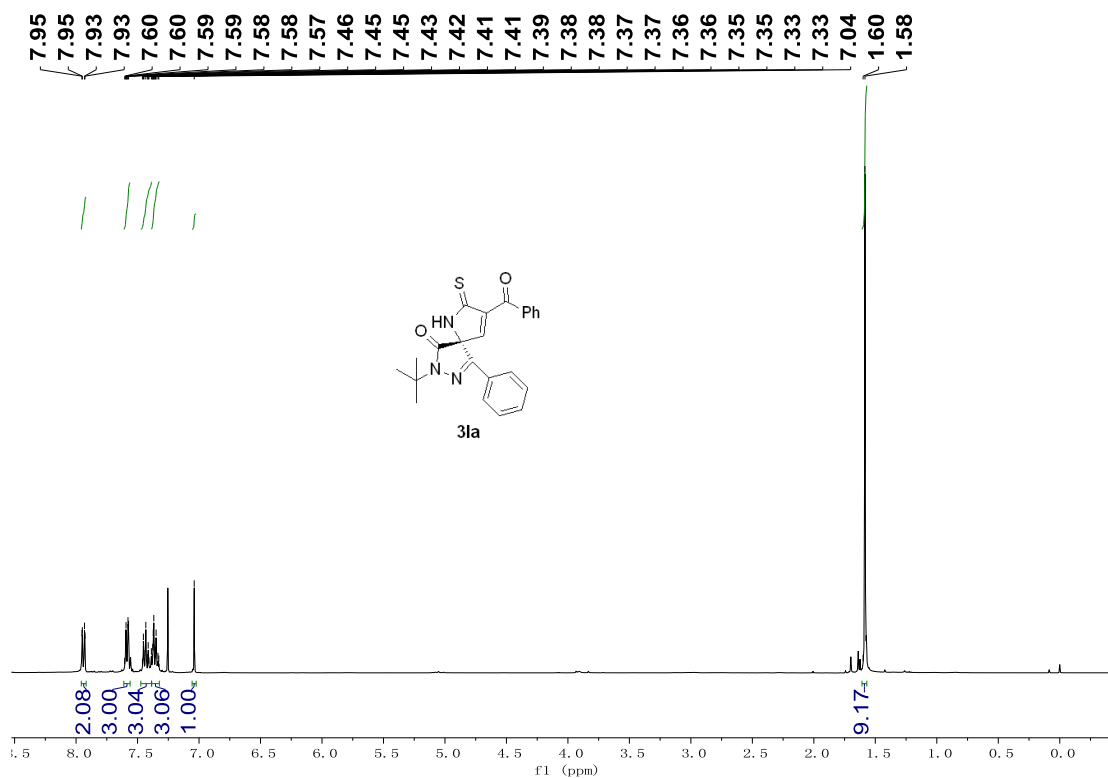


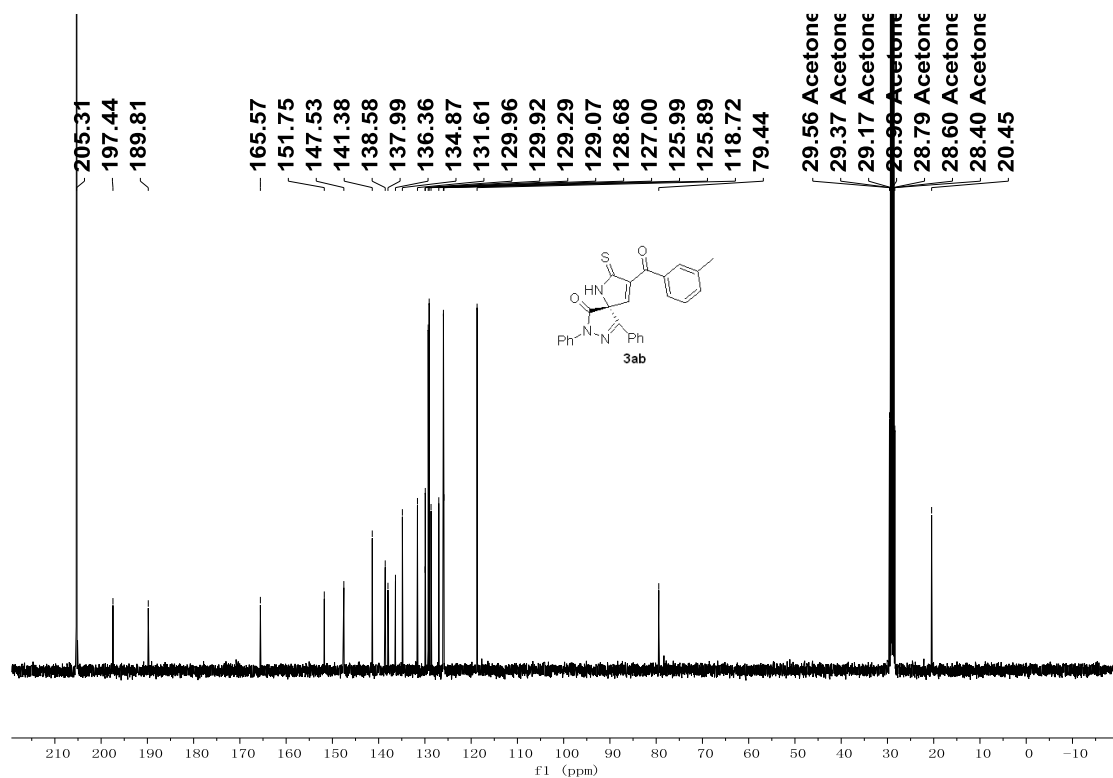
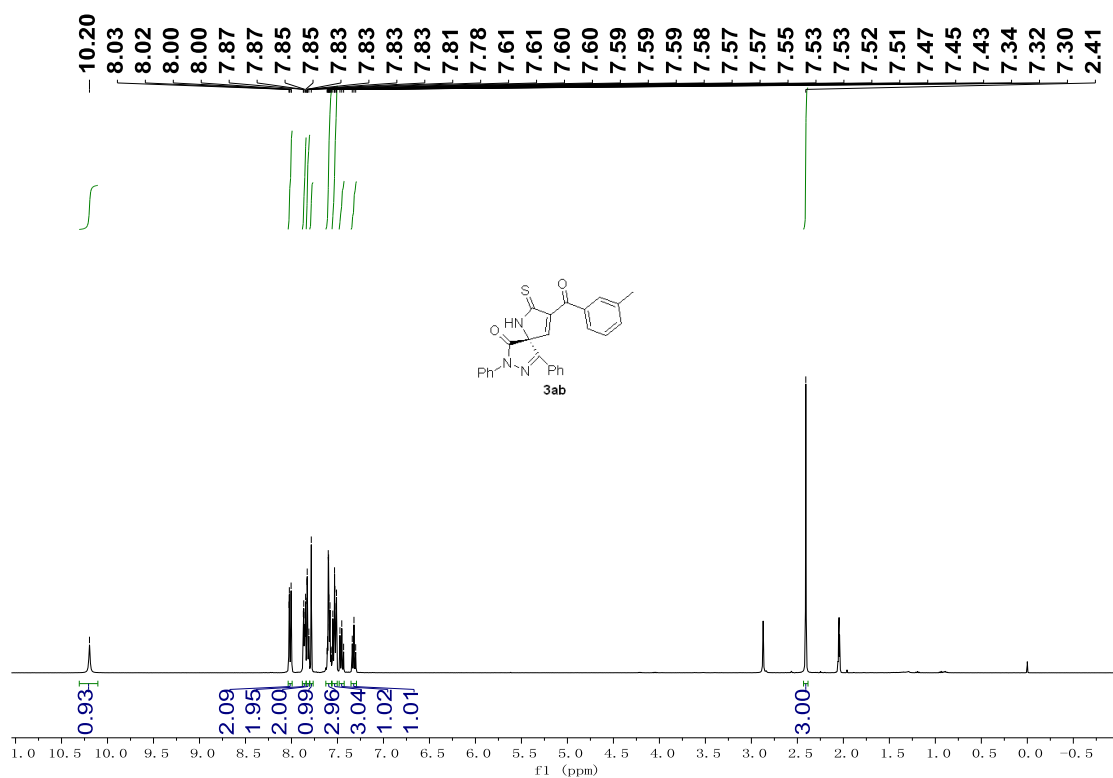


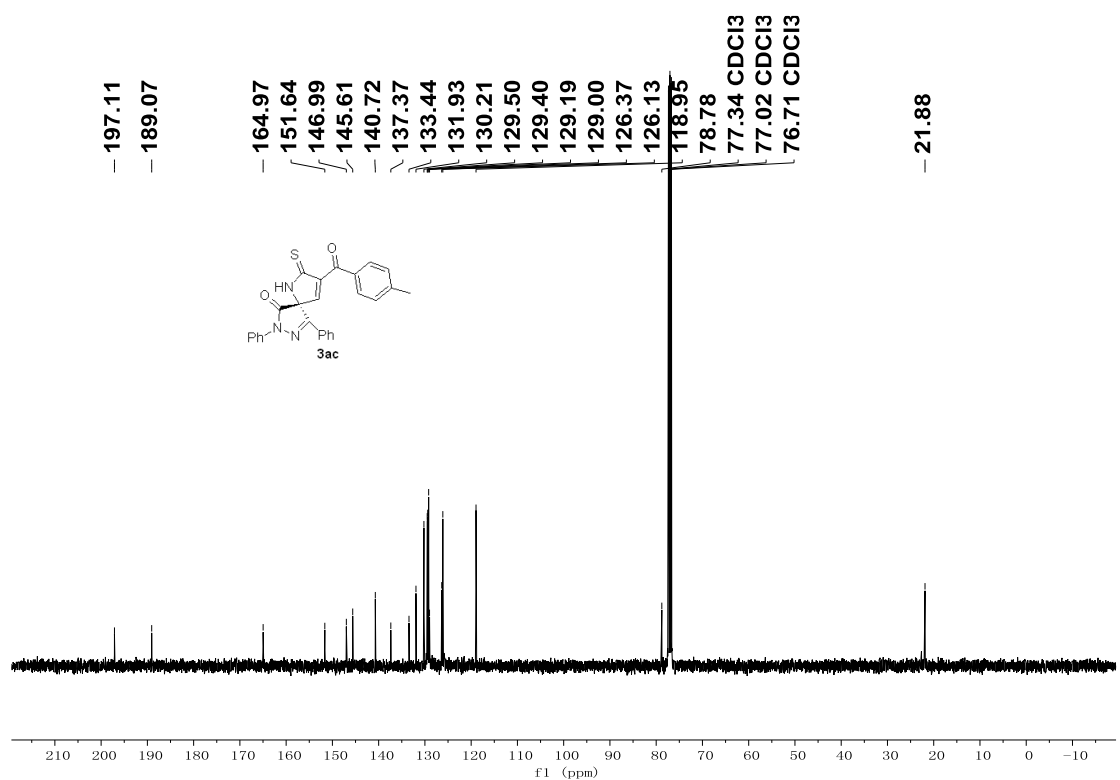
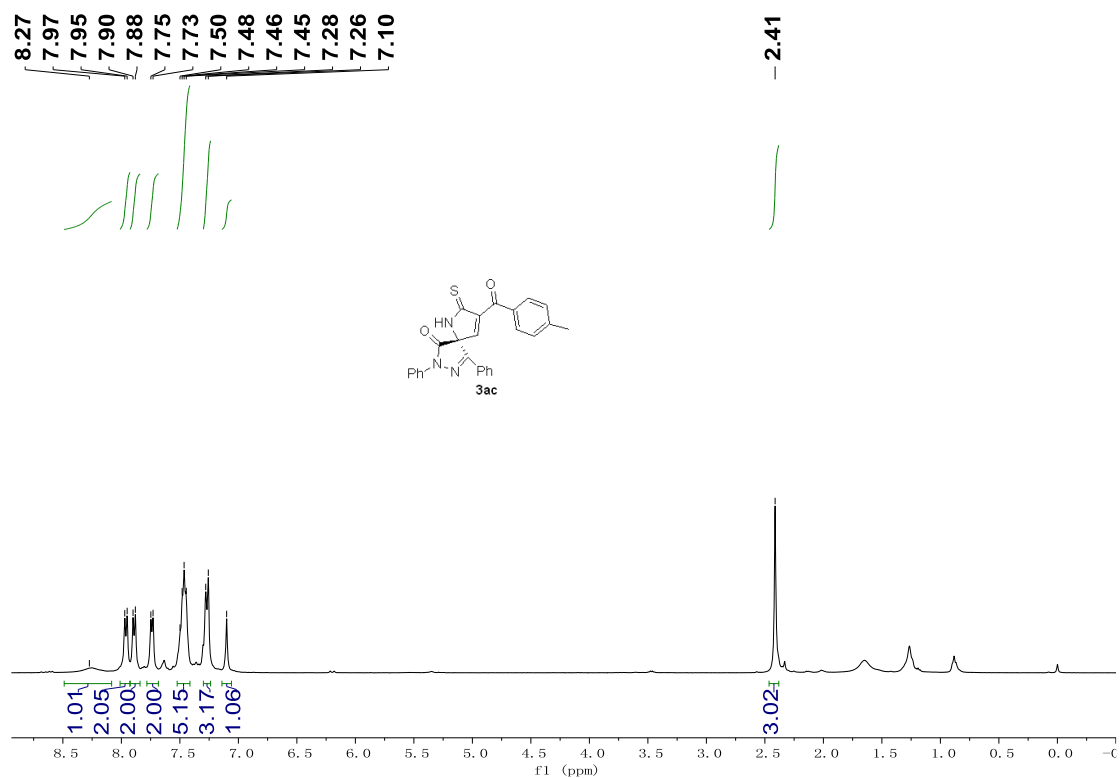


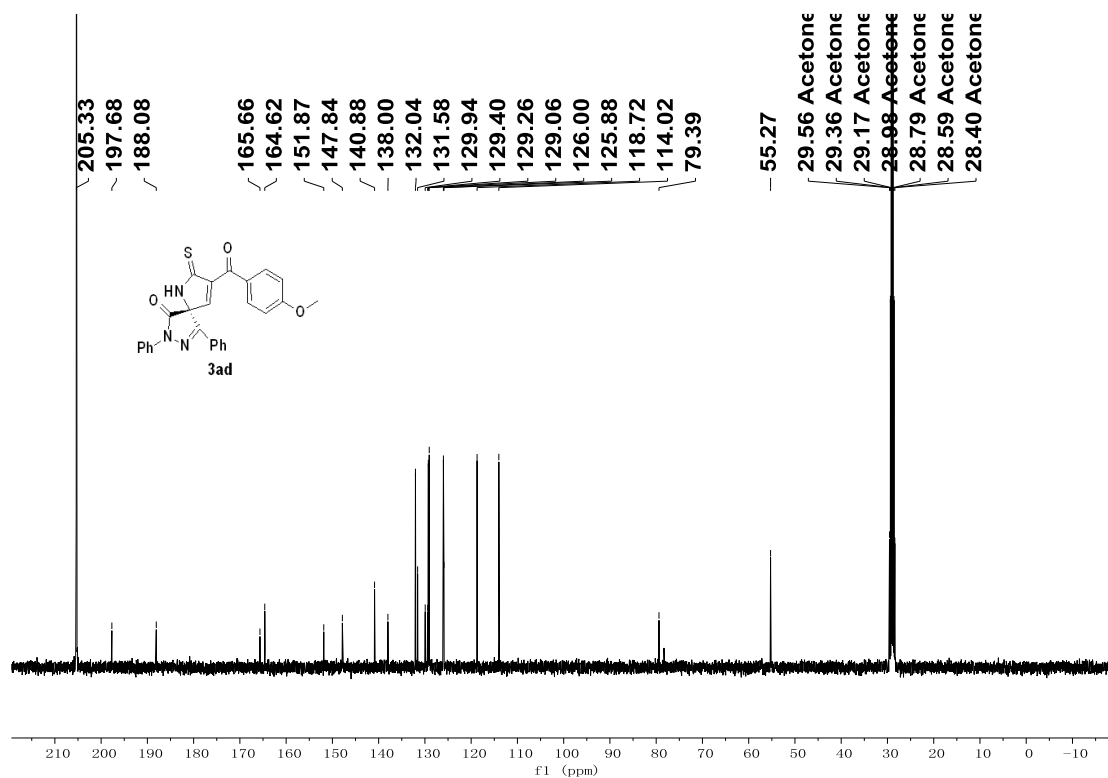
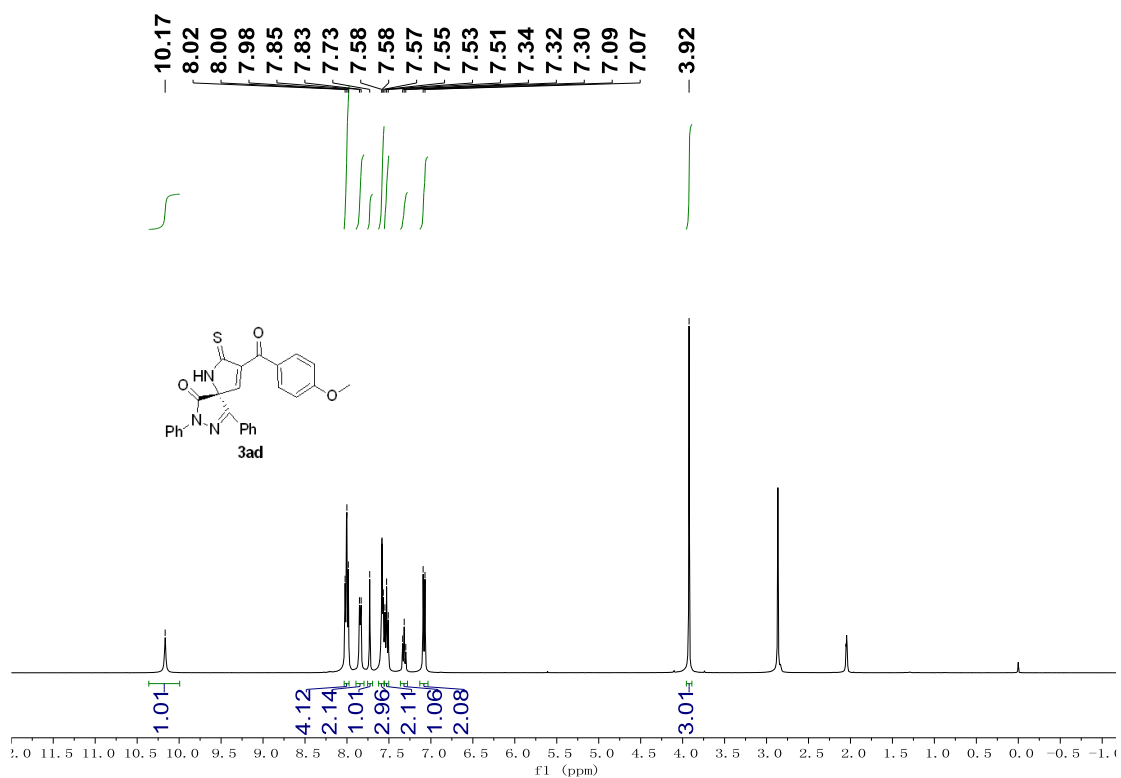


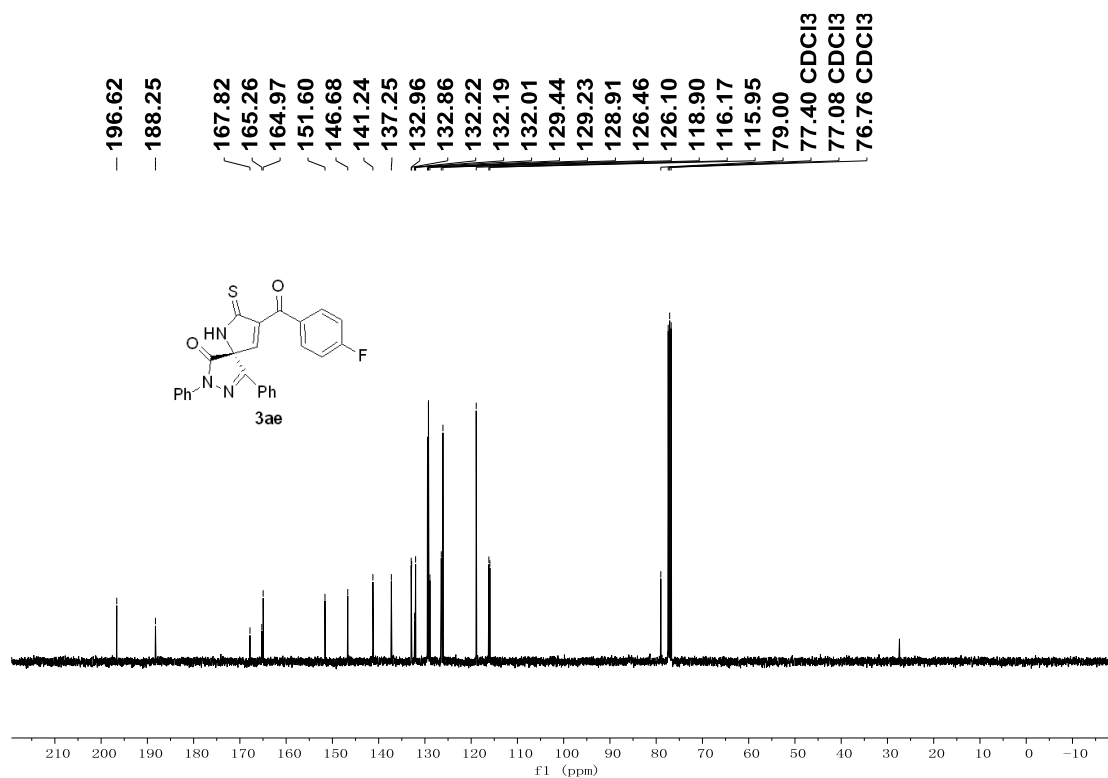
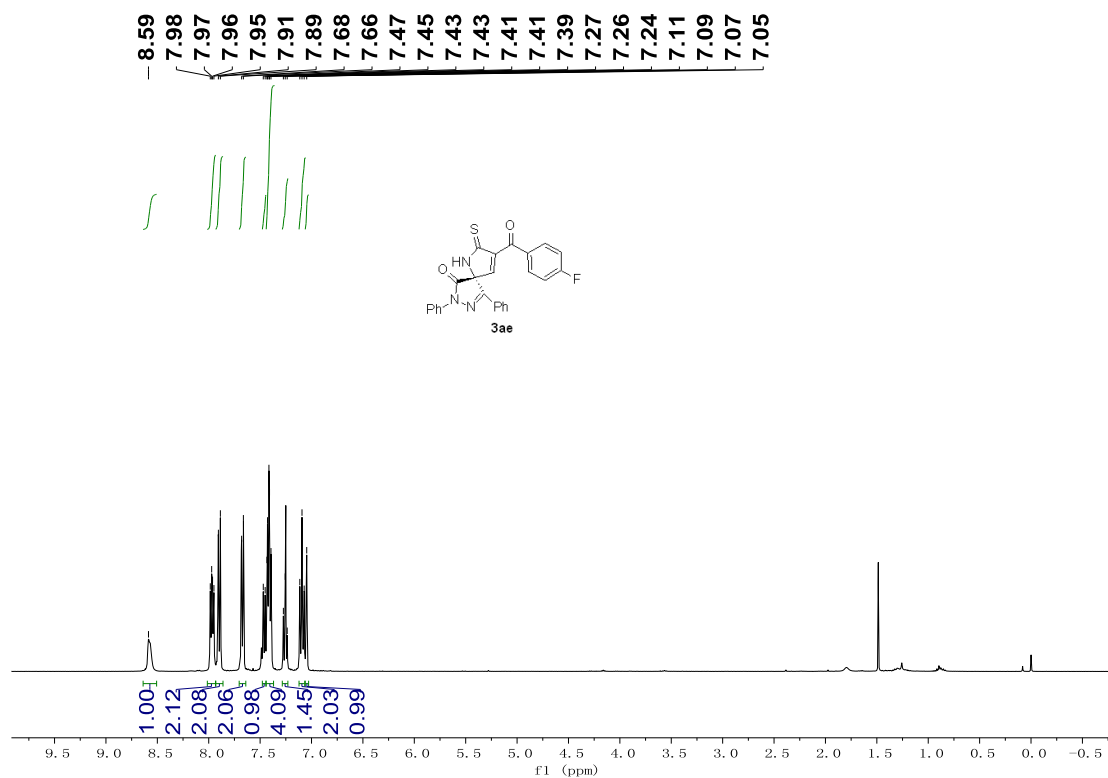


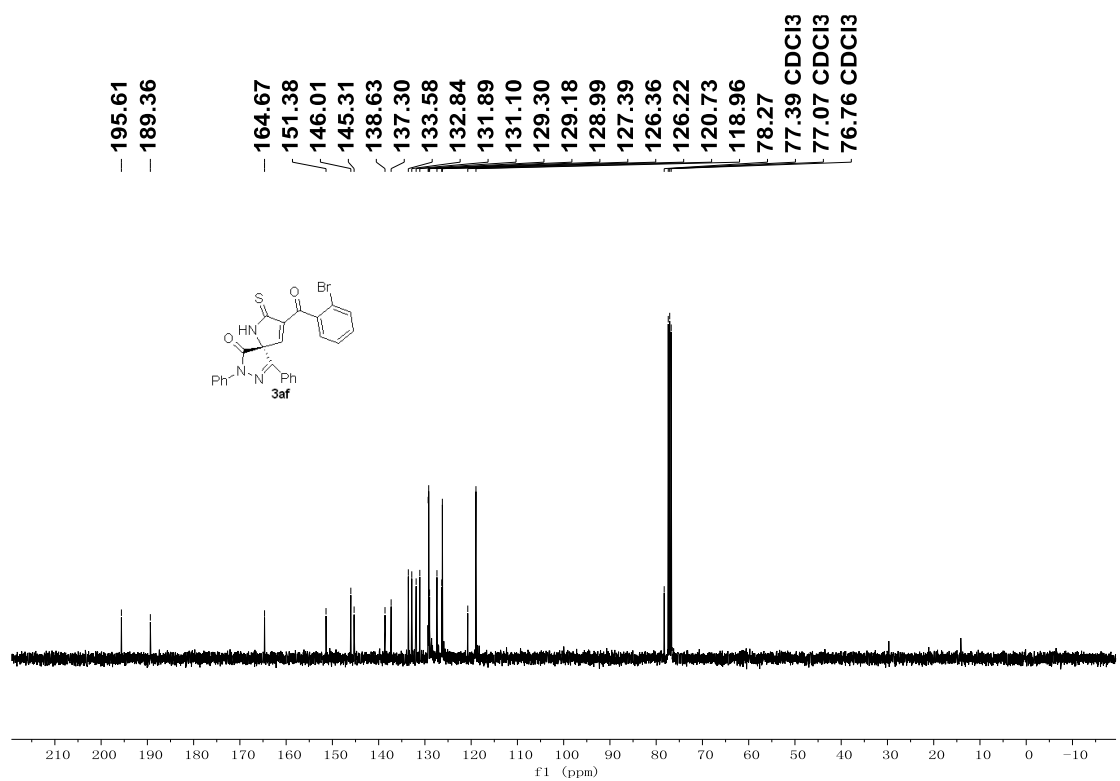
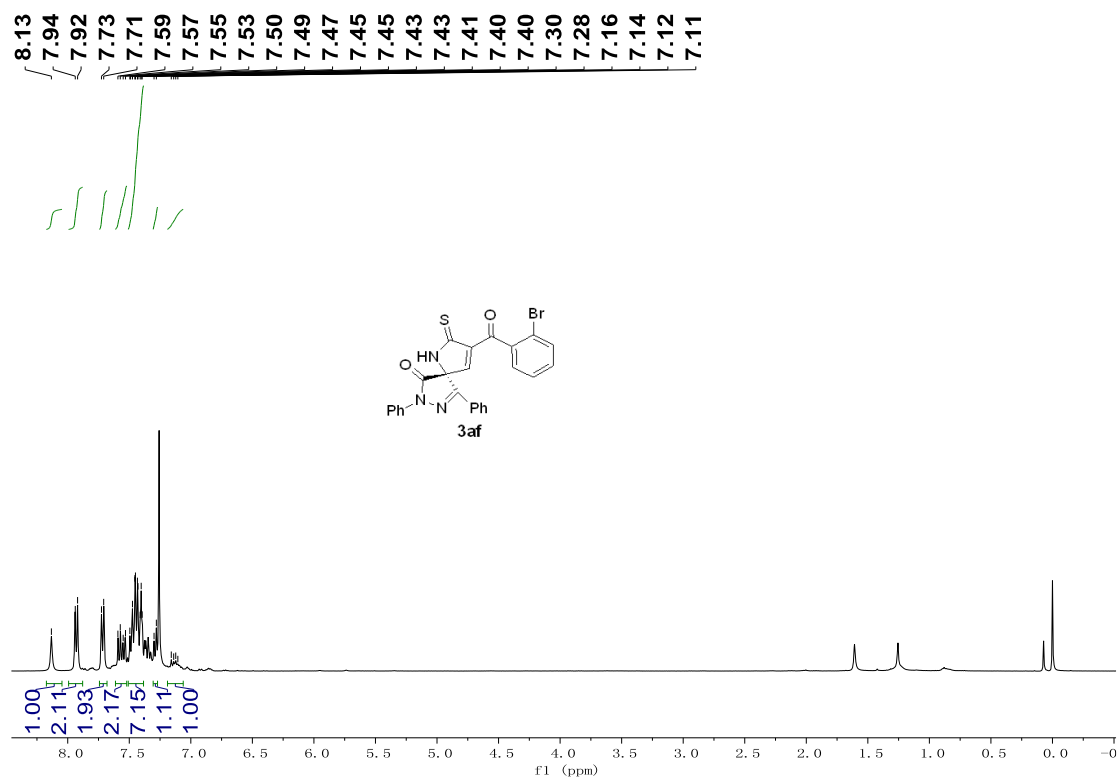


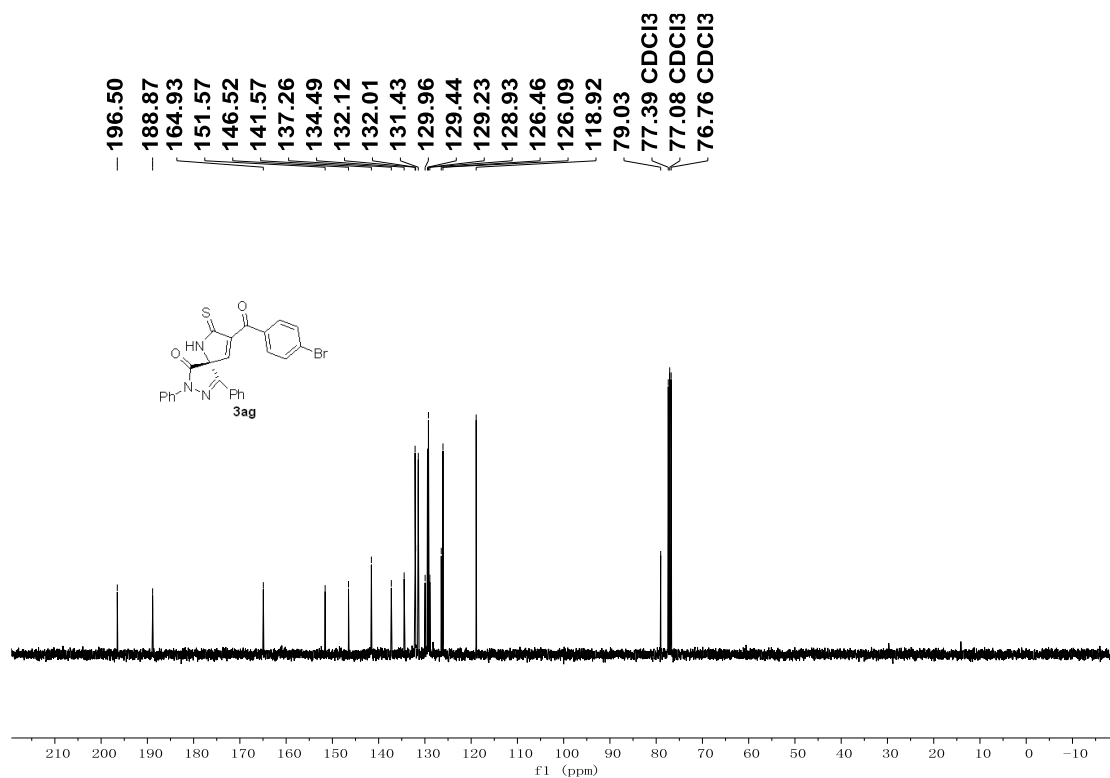
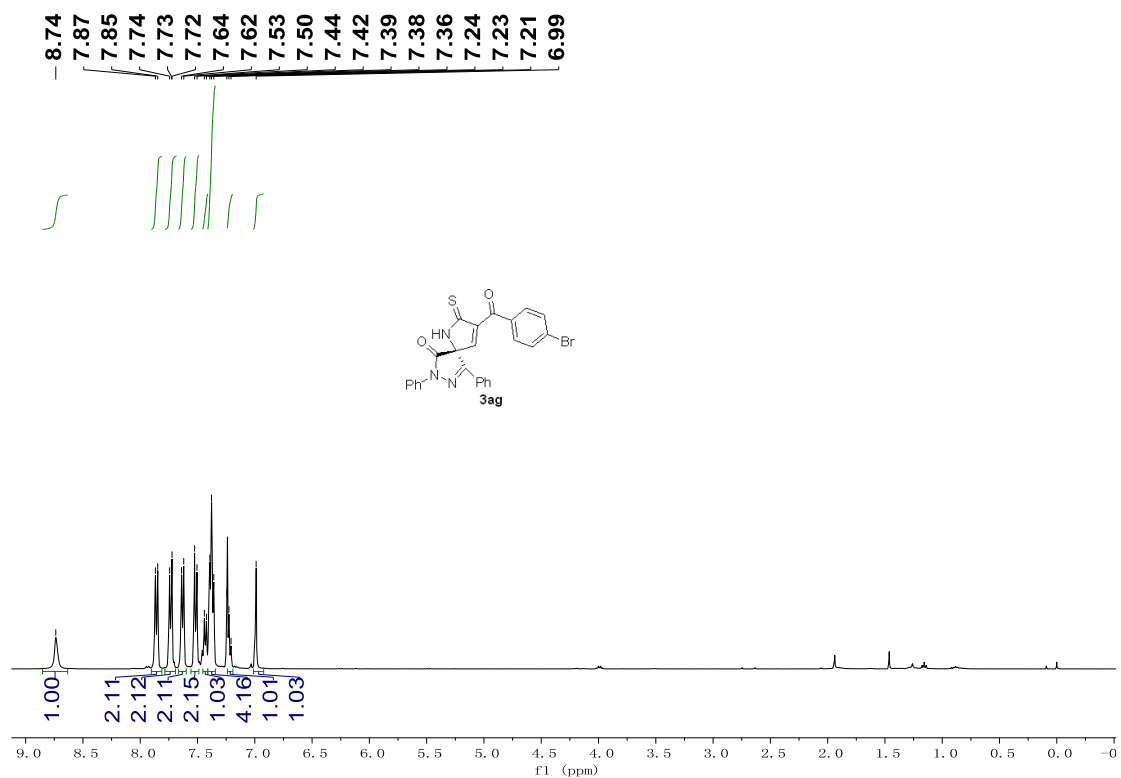


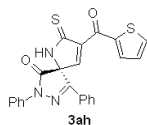
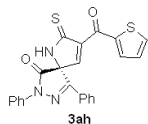


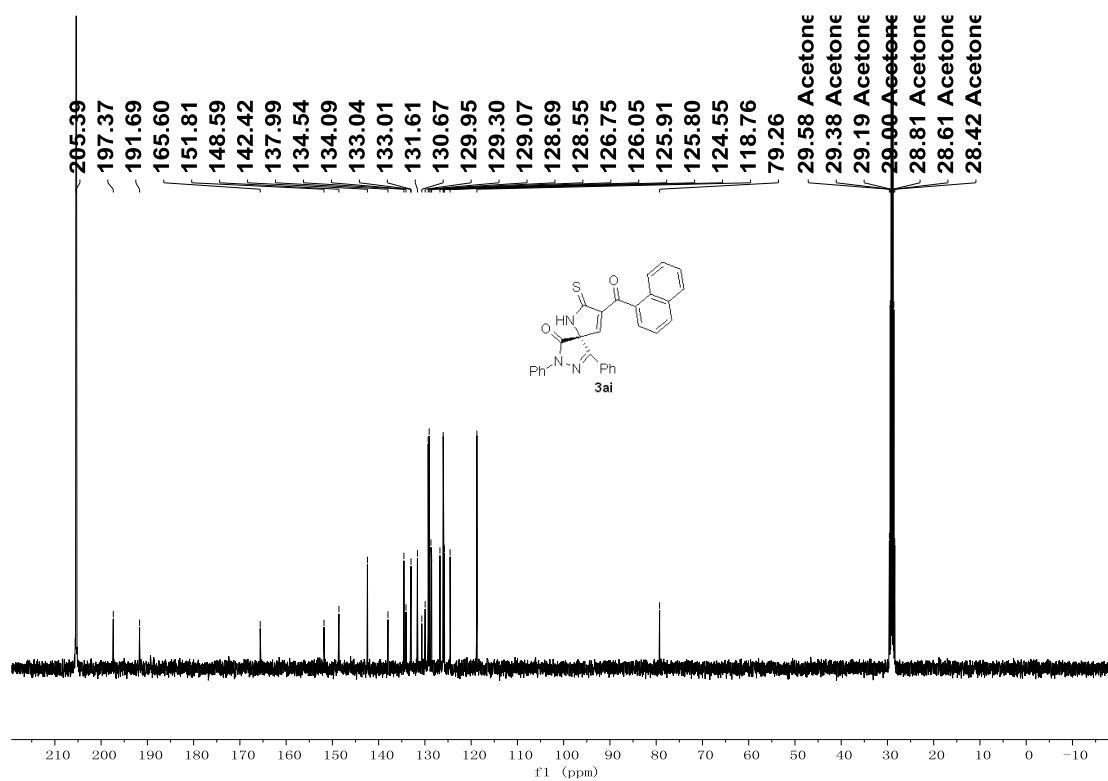
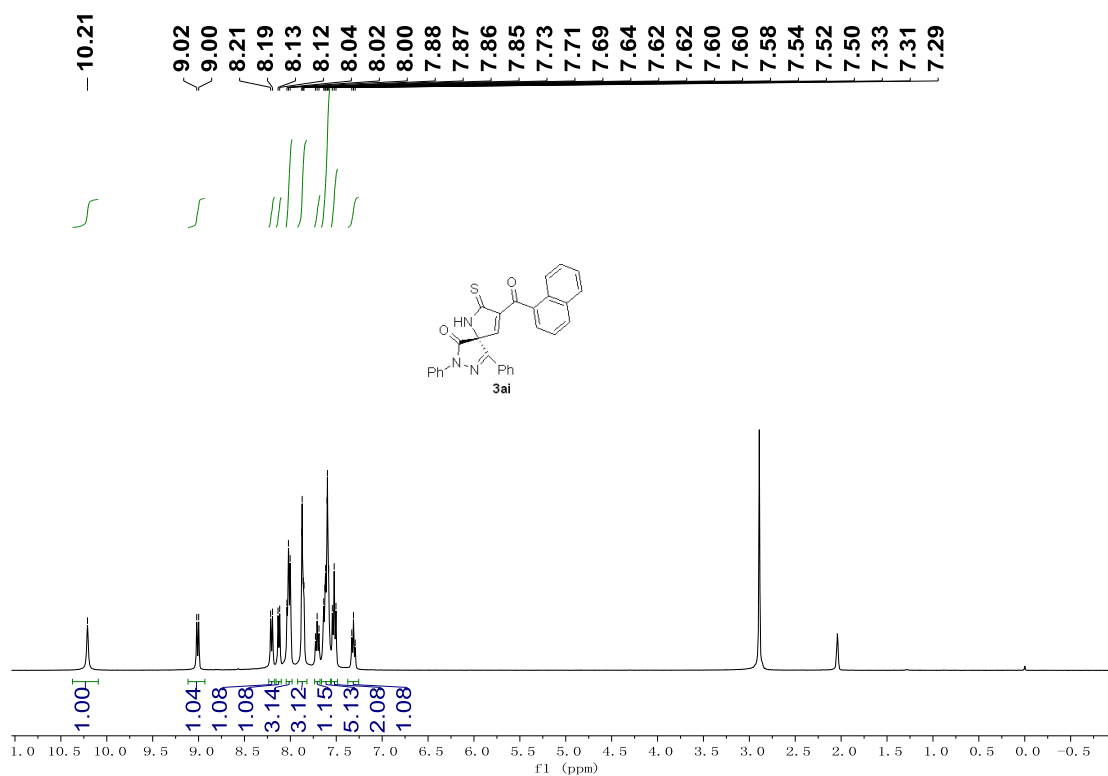




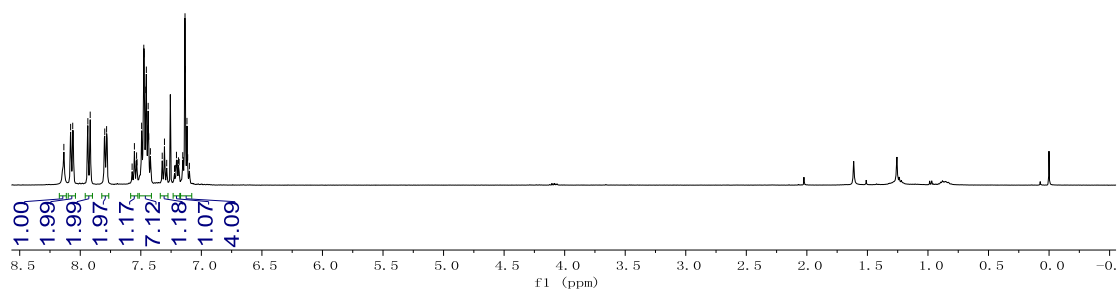
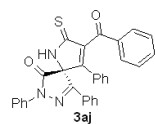








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