

Synthesis and Bio-evaluation of Aminoferrocene-Based Anticancer Prodrugs as Potent Ferroptosis Inducers

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Jing Wang,^[a] Shuang Yang,^[a] and Yong Wang,^{*[a]}

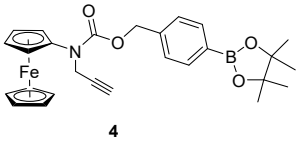
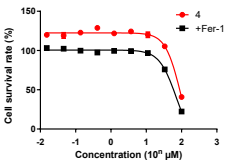
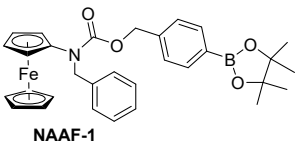
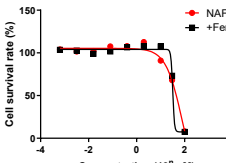
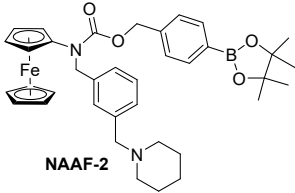
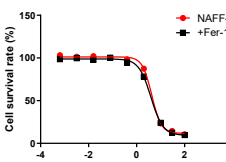
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Table S1. Antitumor activities of representative NAAF prodrugs against HT1080 cells.

Compound	HT1080 (IC ₅₀ μM) ^a			Curve
	-Fer 1 ^b	+Fer 1 ^c	SI ^d	
 <p>4</p>	93.92 ± 0.03	69.74 ± 0.05	0.74	
 <p>NAFF-1</p>	83.89 ± 0.04	-	-	
 <p>NAFF-2</p>	14.52 ± 0.03	12.87 ± 0.01	0.89	

^a All values are expressed as the mean ± SD from three independent experiments. ^b HT1080 and incubated with compounds alone. ^c HT1080 incubated with compounds and Fer-1 (1.5 μM). ^d + Fer-1 IC₅₀/- Fer-1 IC₅₀.

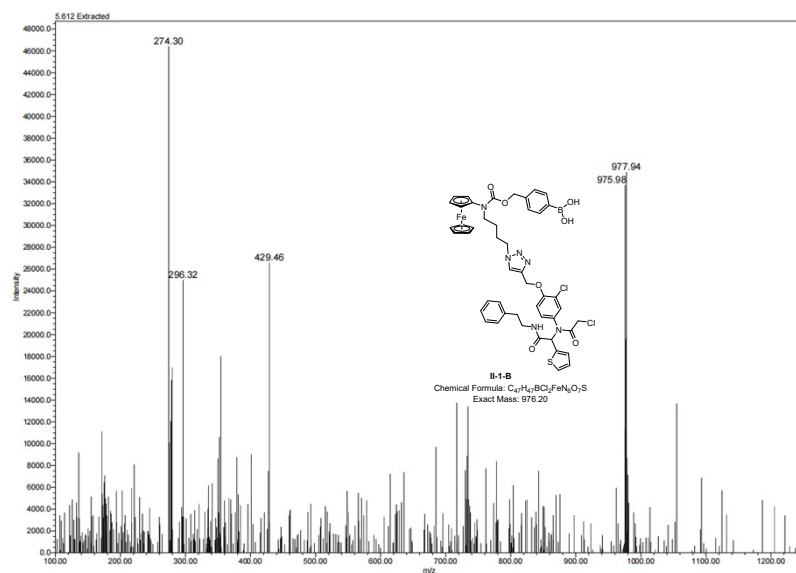
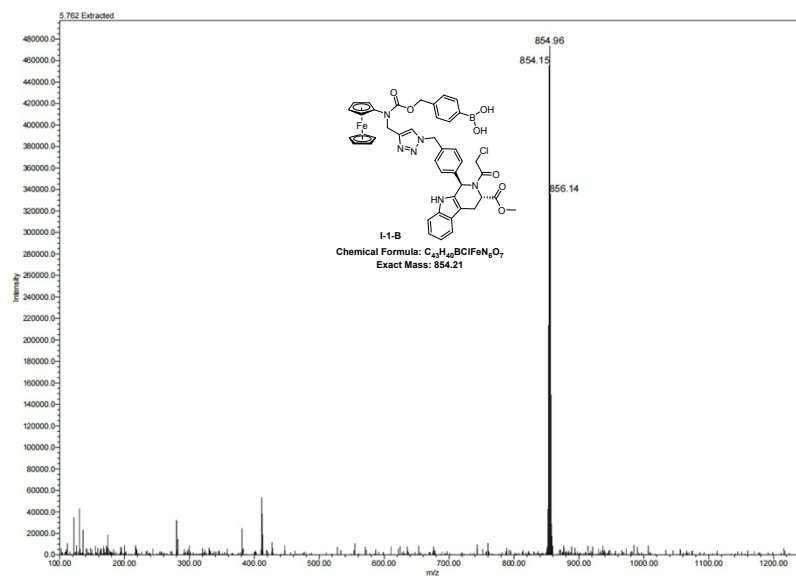
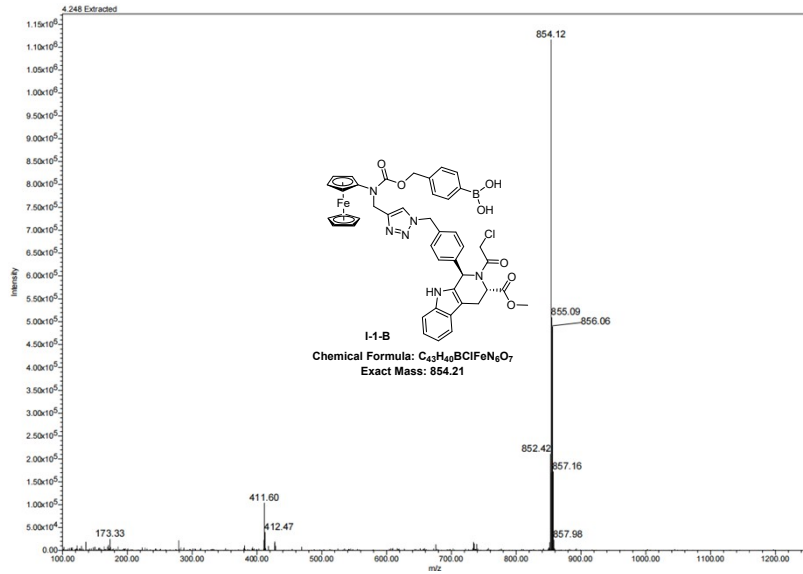
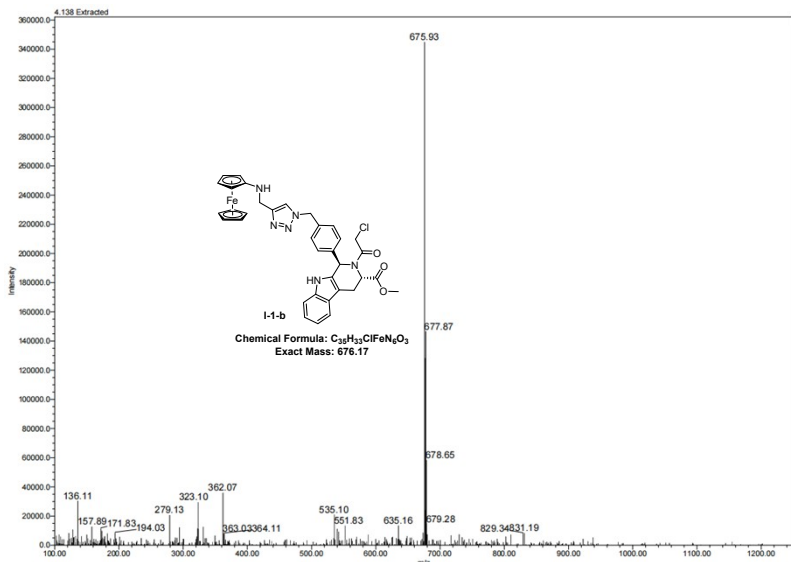
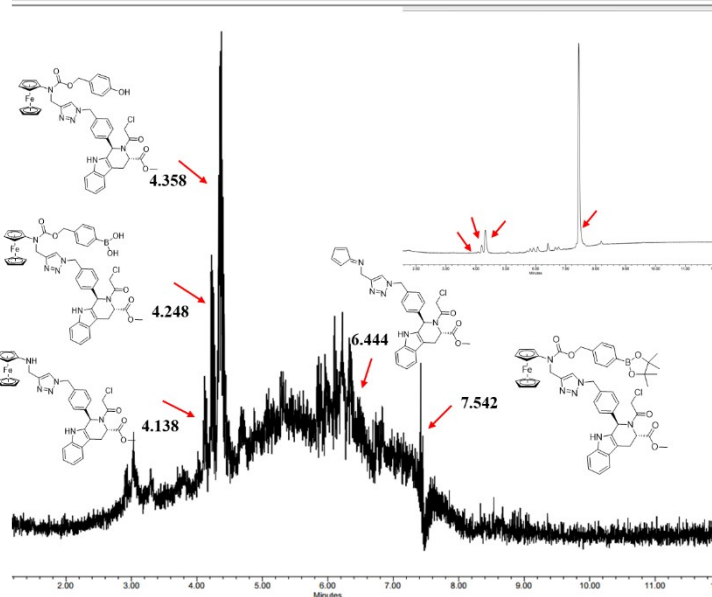


Fig. S1. Expanded regions of the spectra of **I-1** (top) and **II-1** (bottom) with the generation of boronic acid in the absence of H_2O_2 .



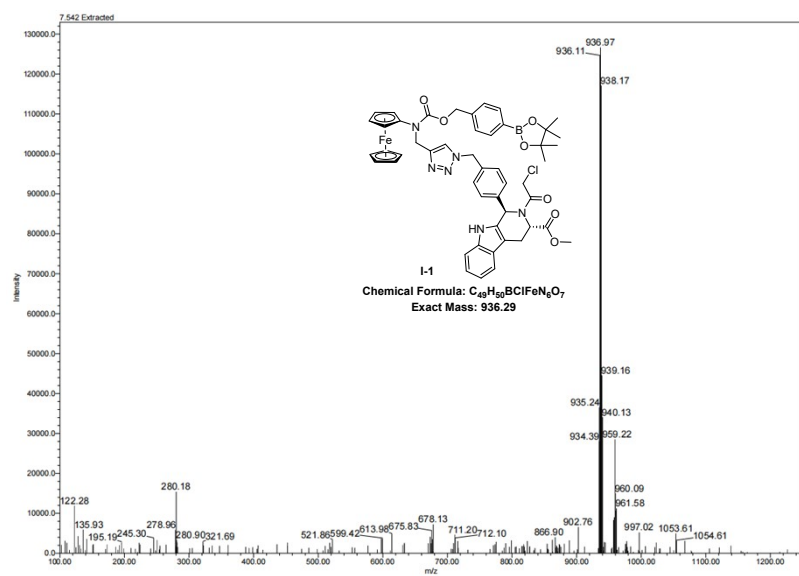
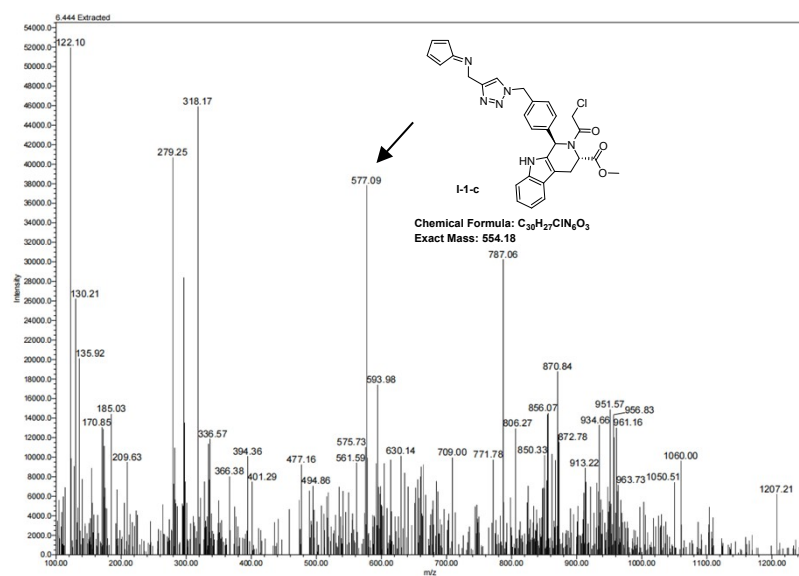
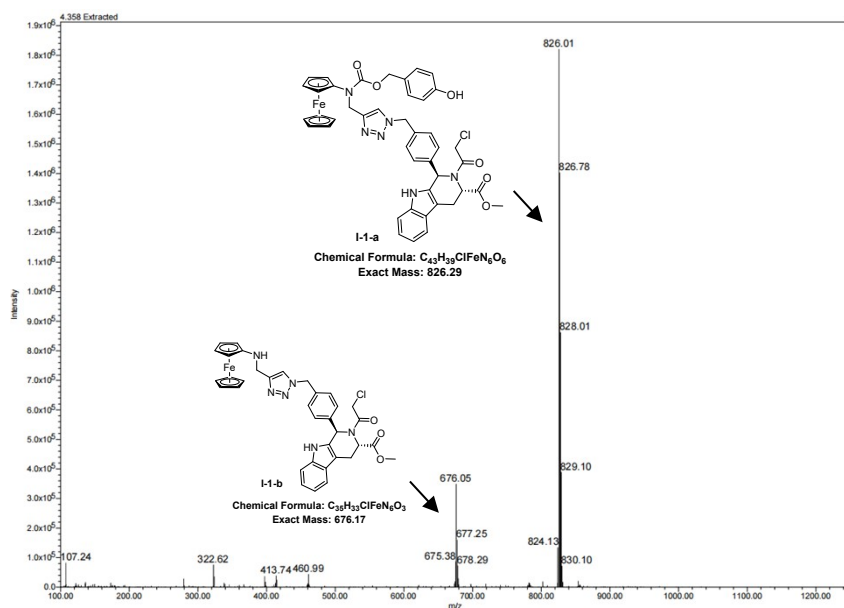


Fig. S2. Expanded regions of the spectra of I-1 hydrolysis in the presence of H_2O_2 .

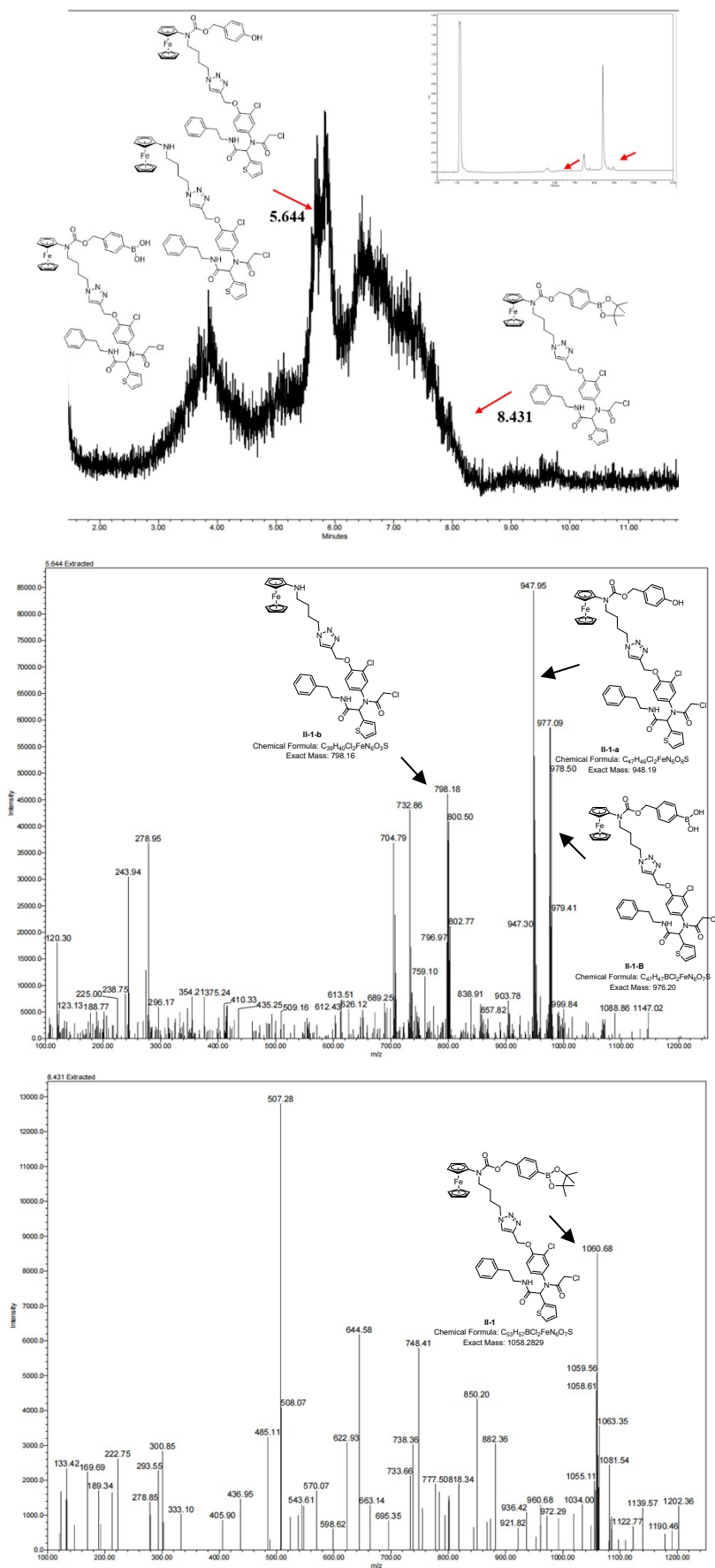


Fig. S3. Expanded regions of the spectra of **II-1** hydrolysis in the presence of H_2O_2 .

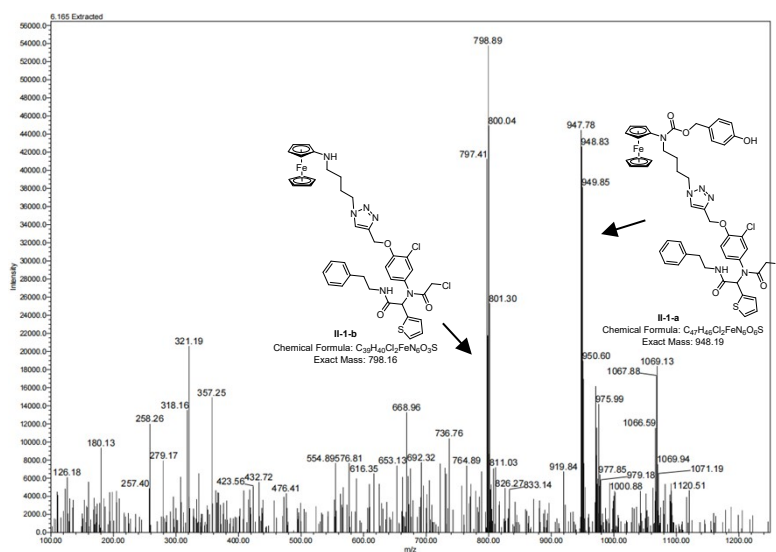
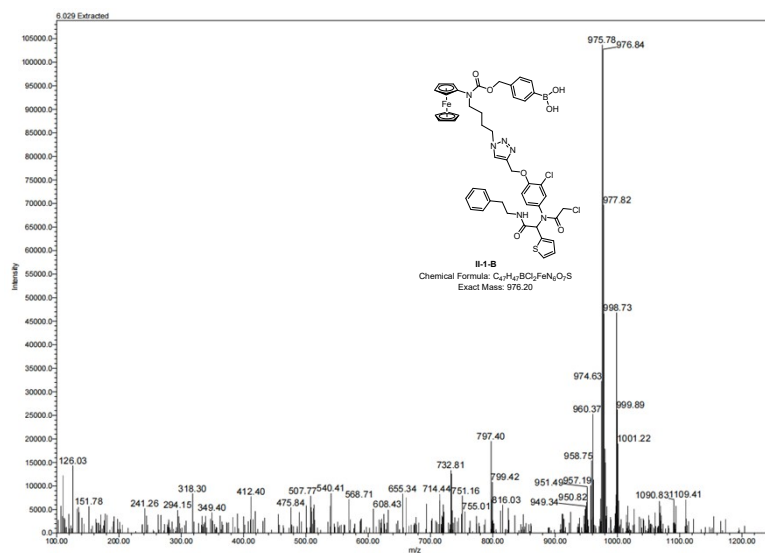
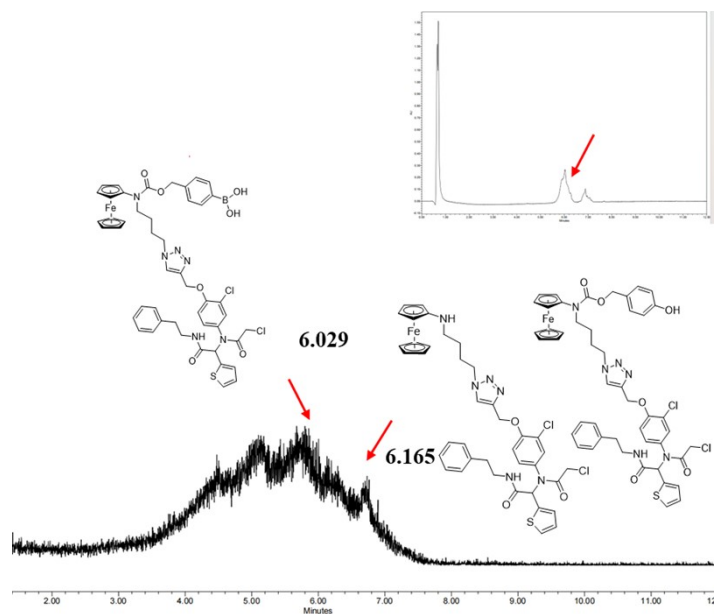
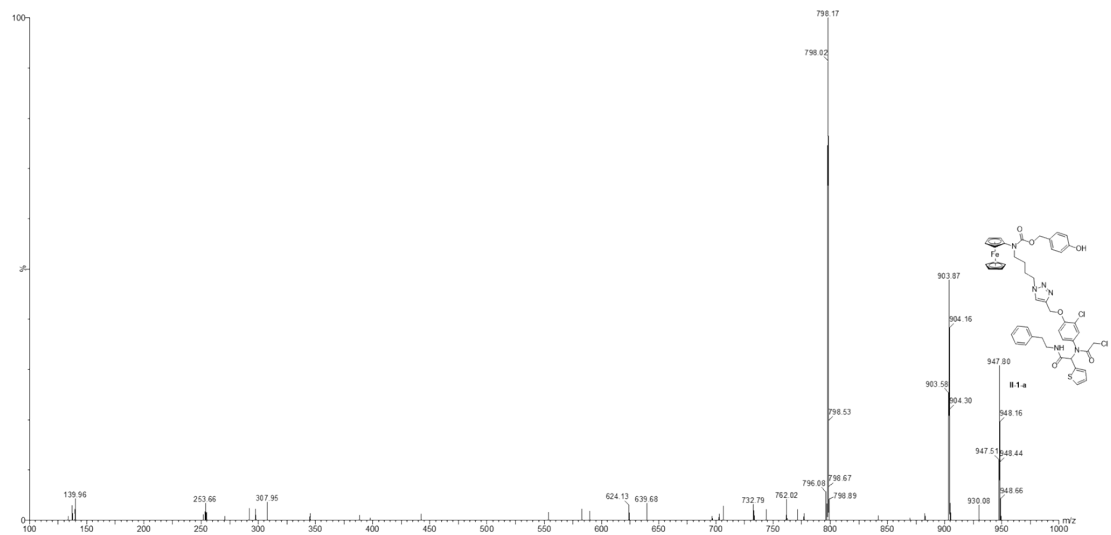
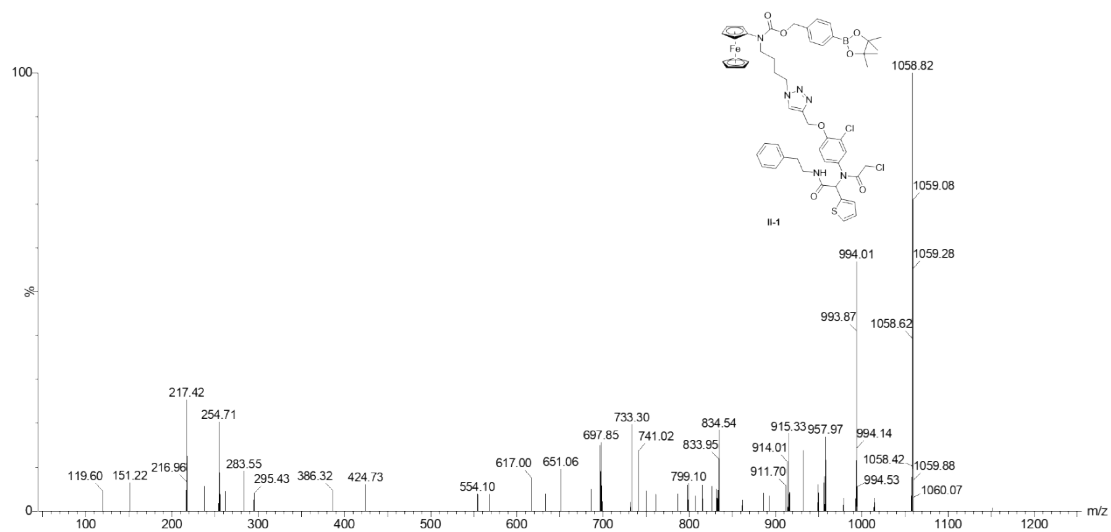
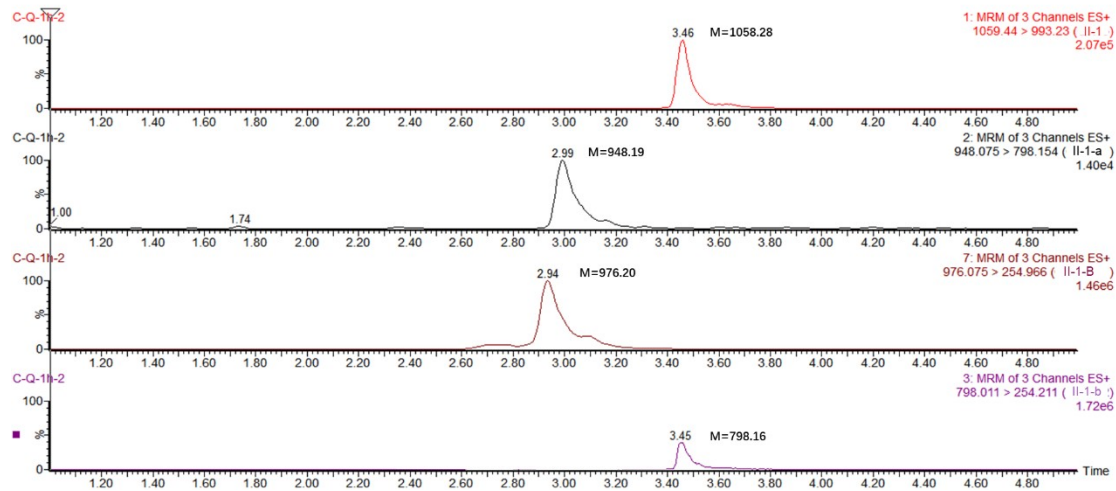


Fig. S4. Expanded regions of the spectra of II-1-b hydrolysis in the presence of H_2O_2 .



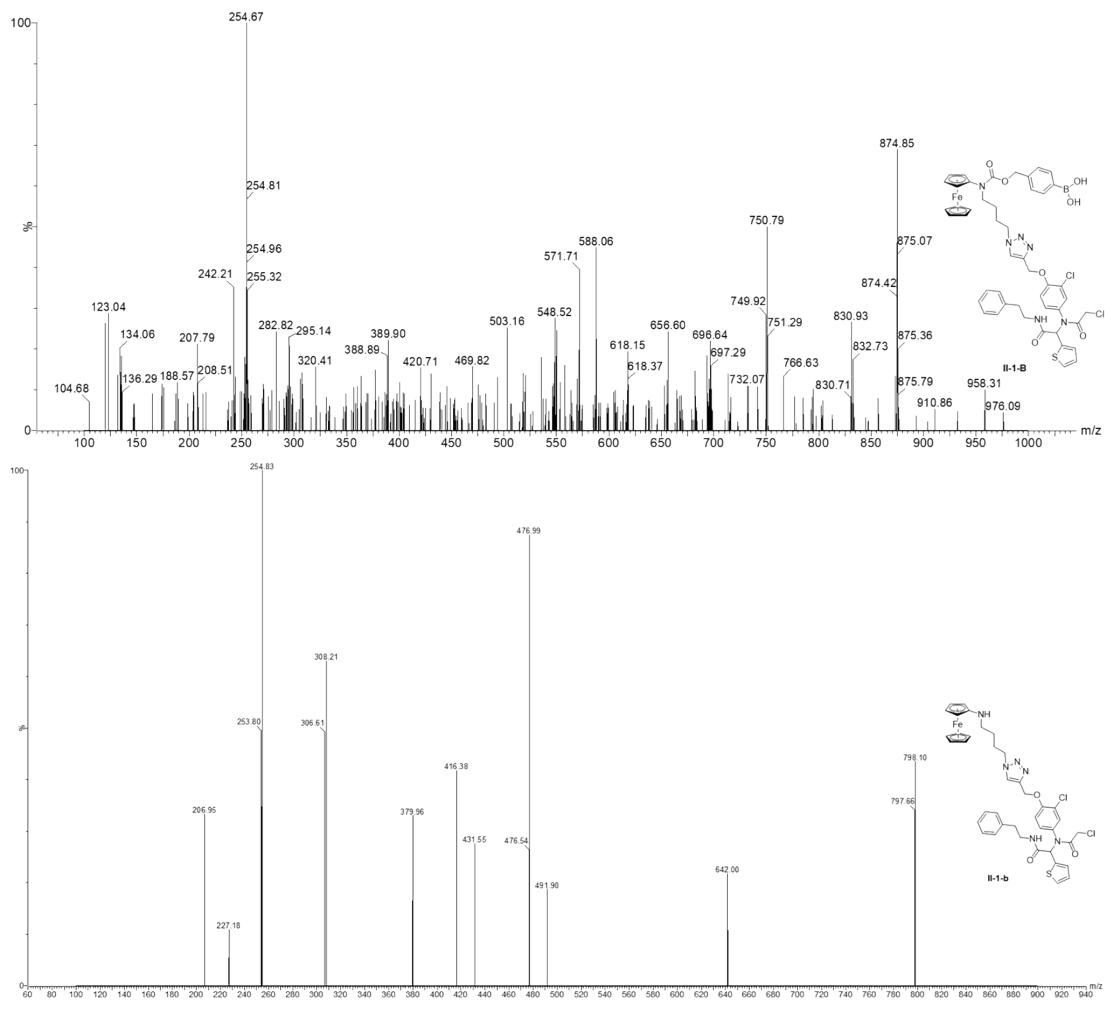
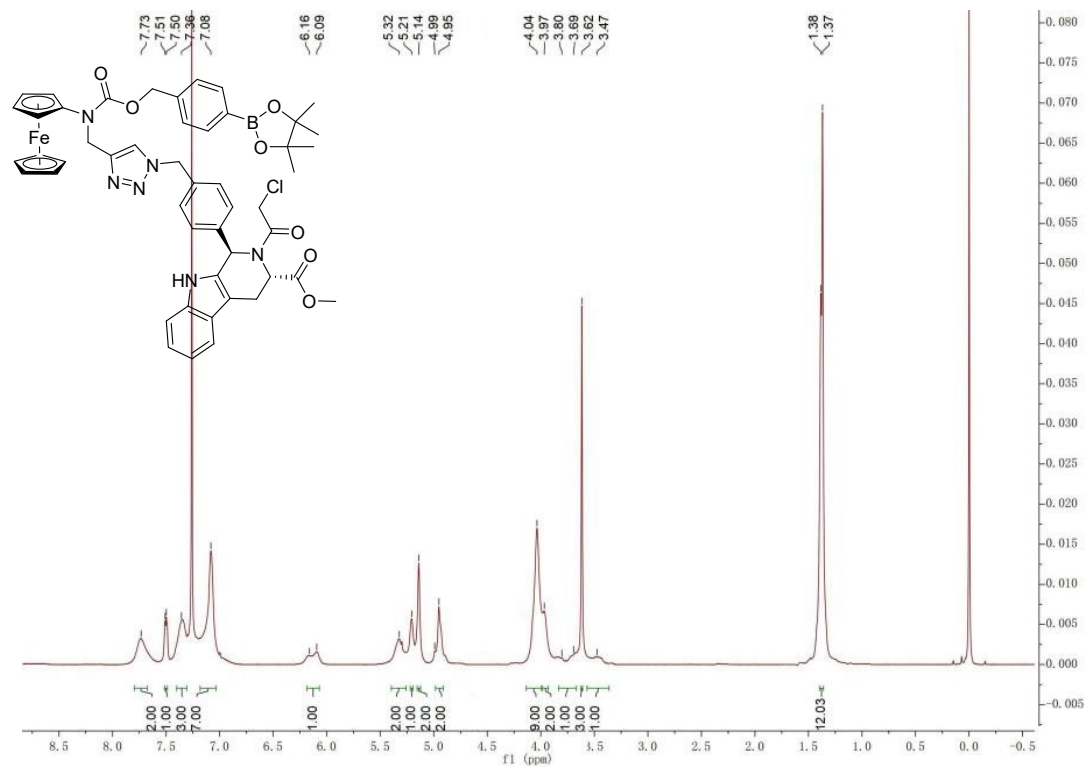


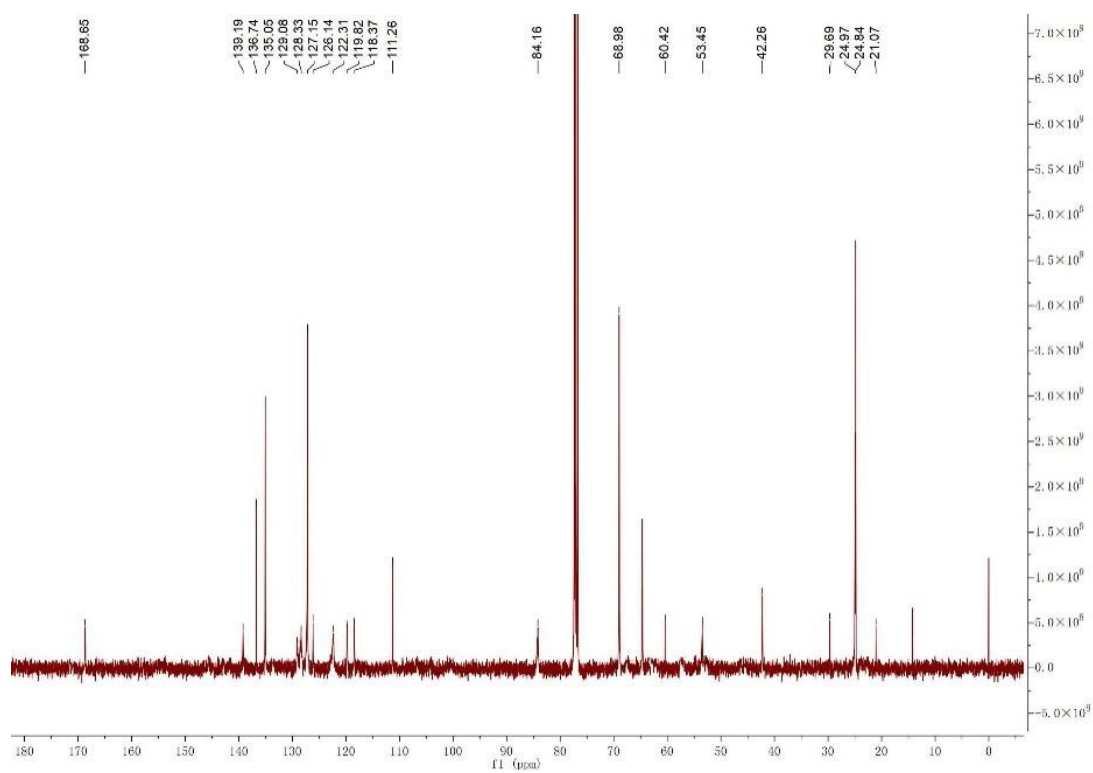
Fig. S5. Activation of II-1 in HT1080 cell verified by LC-MS/MS.

¹H, ¹³C NMR and HRMS spectra of compounds

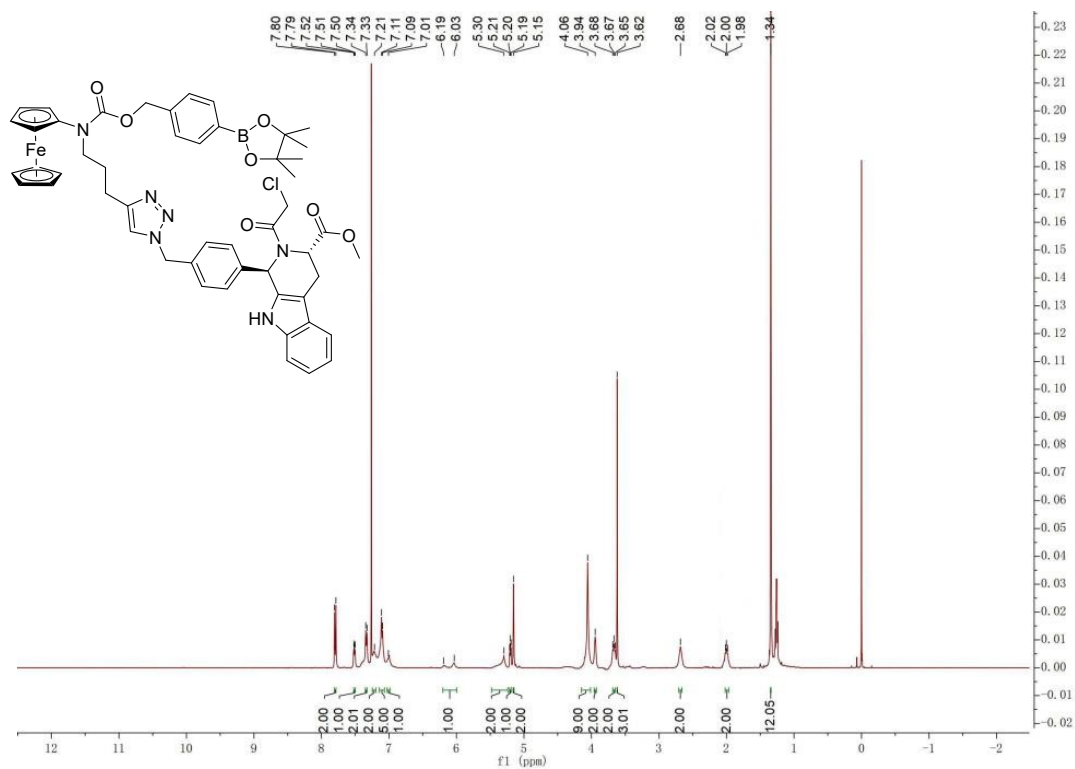
I-1 ¹H-NMR (Chloroform-*d*)



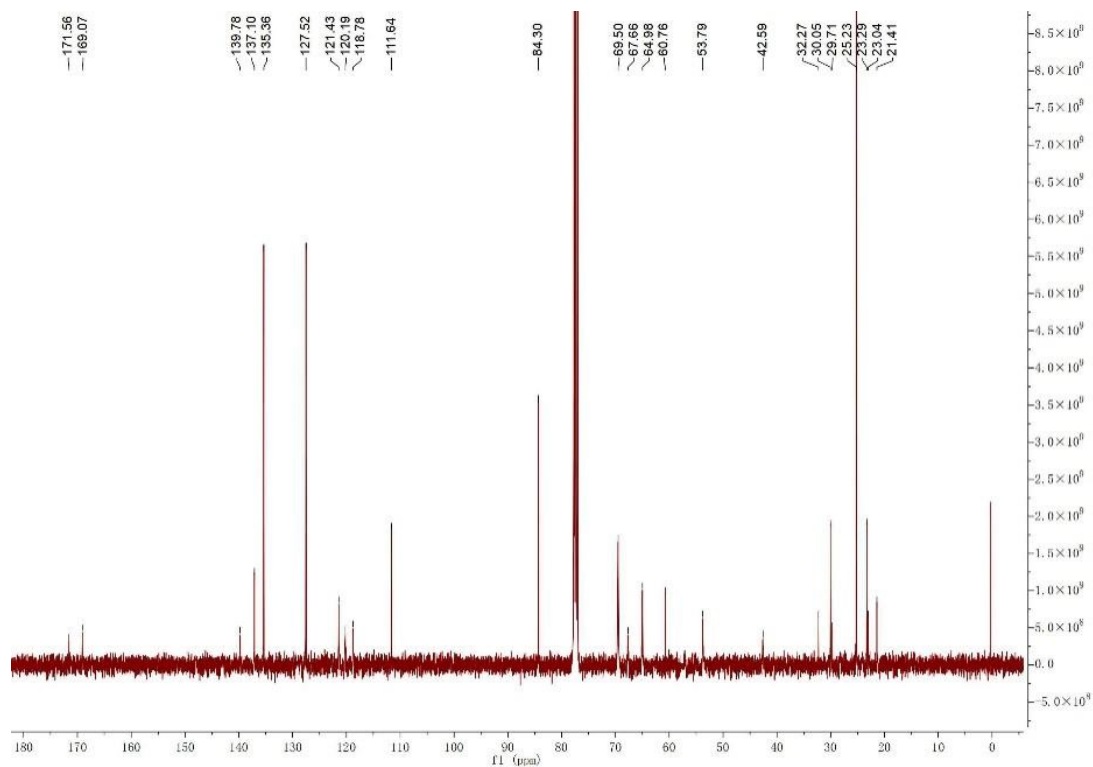
I-1 ¹³C-NMR (Chloroform-*d*)



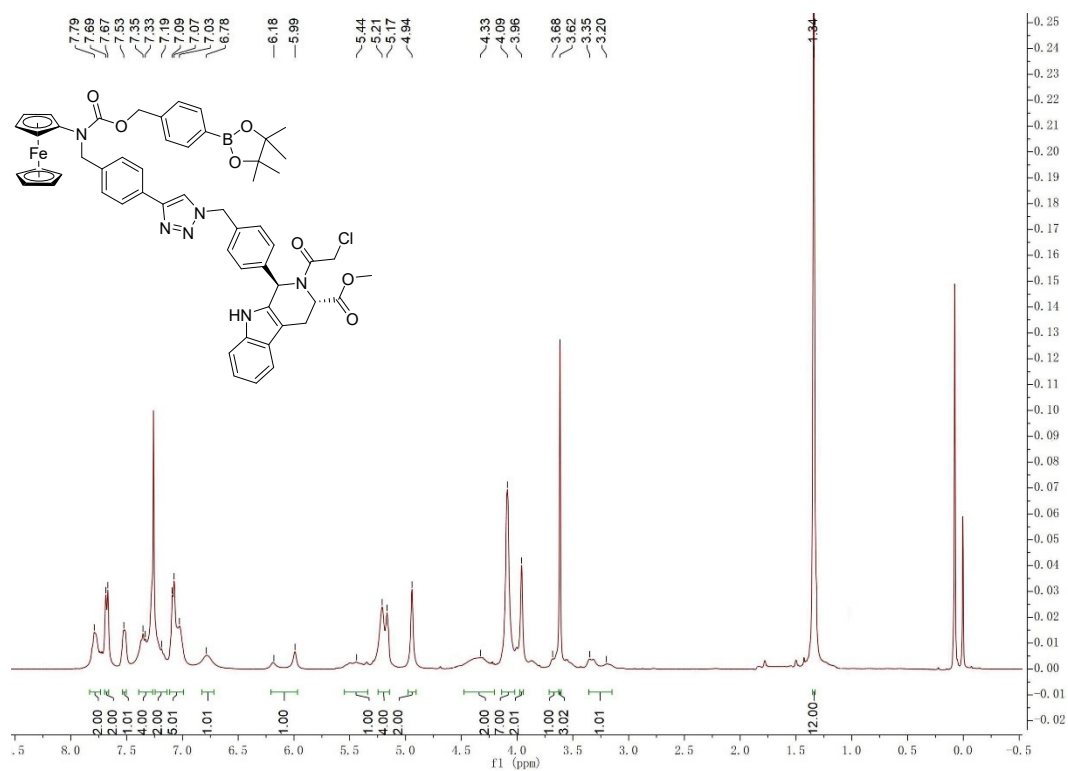
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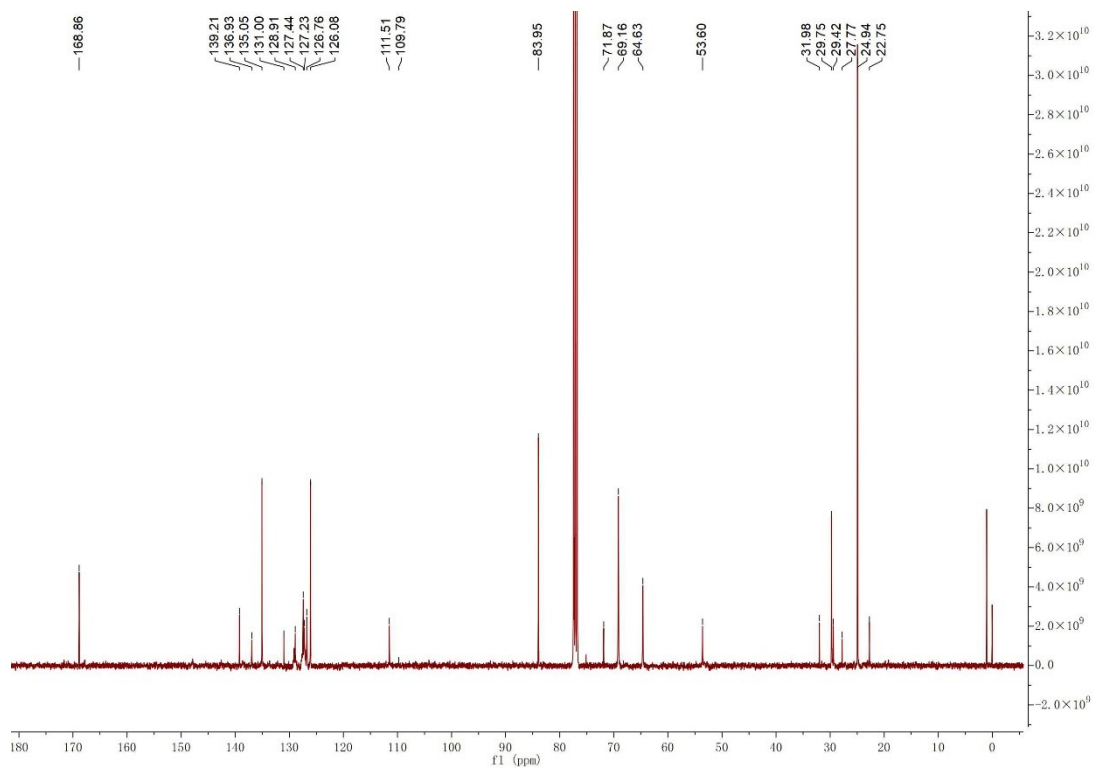
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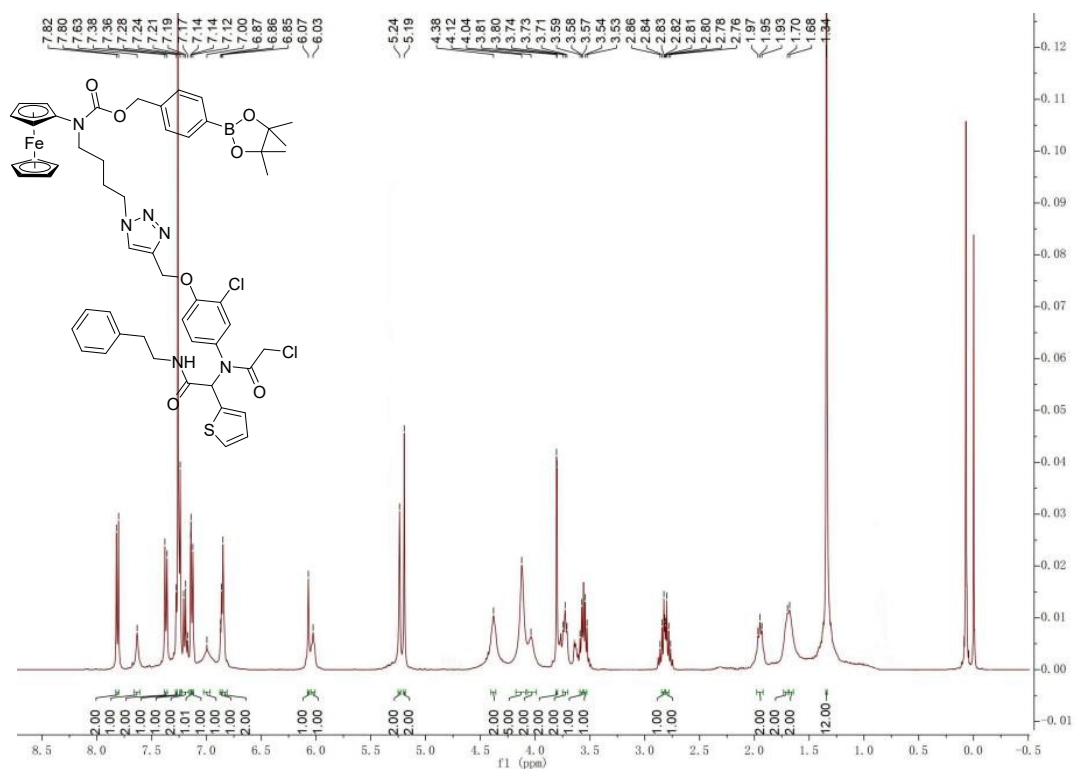
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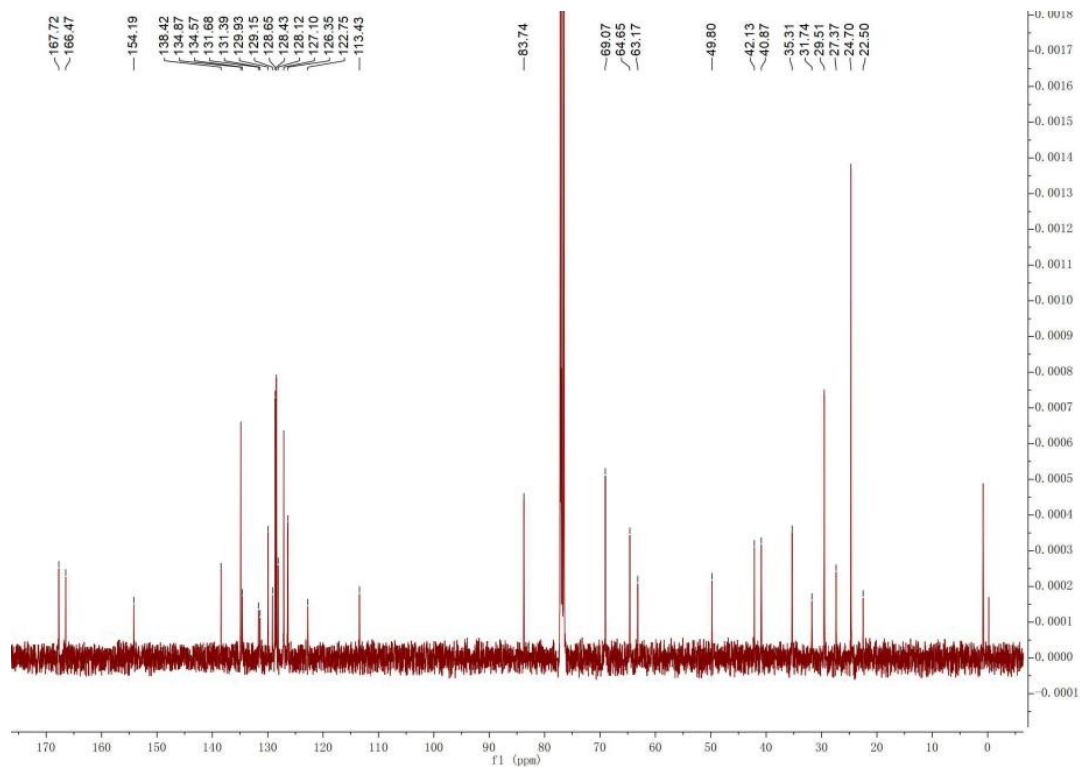
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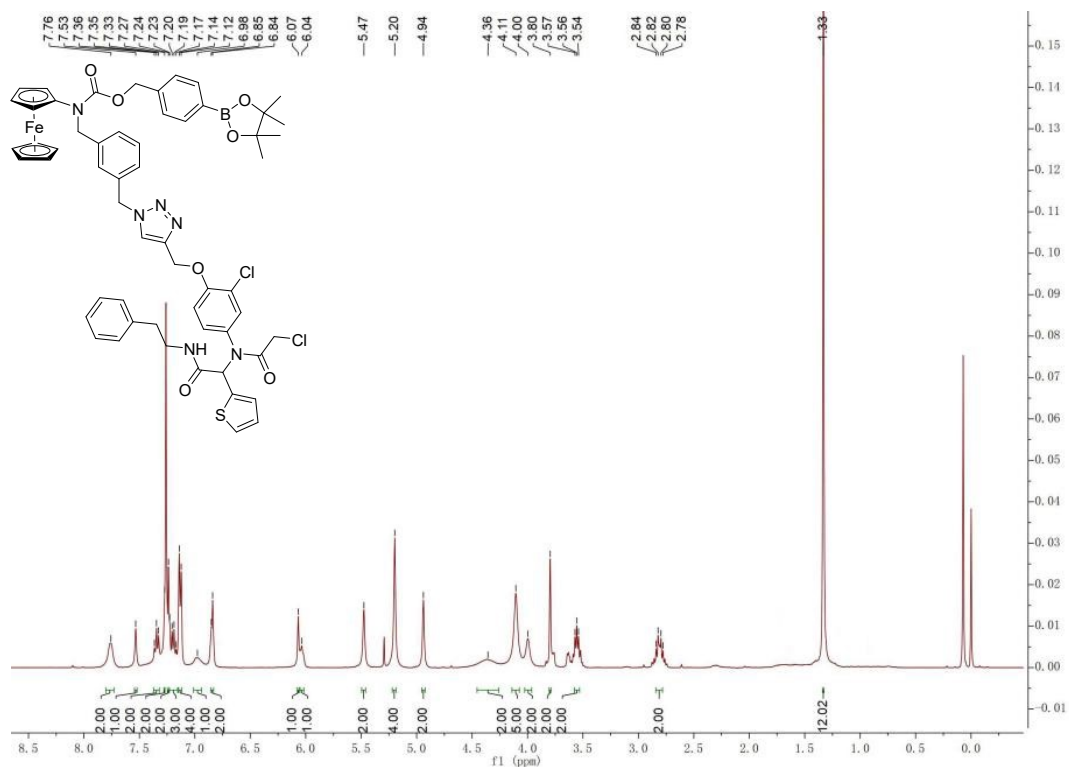
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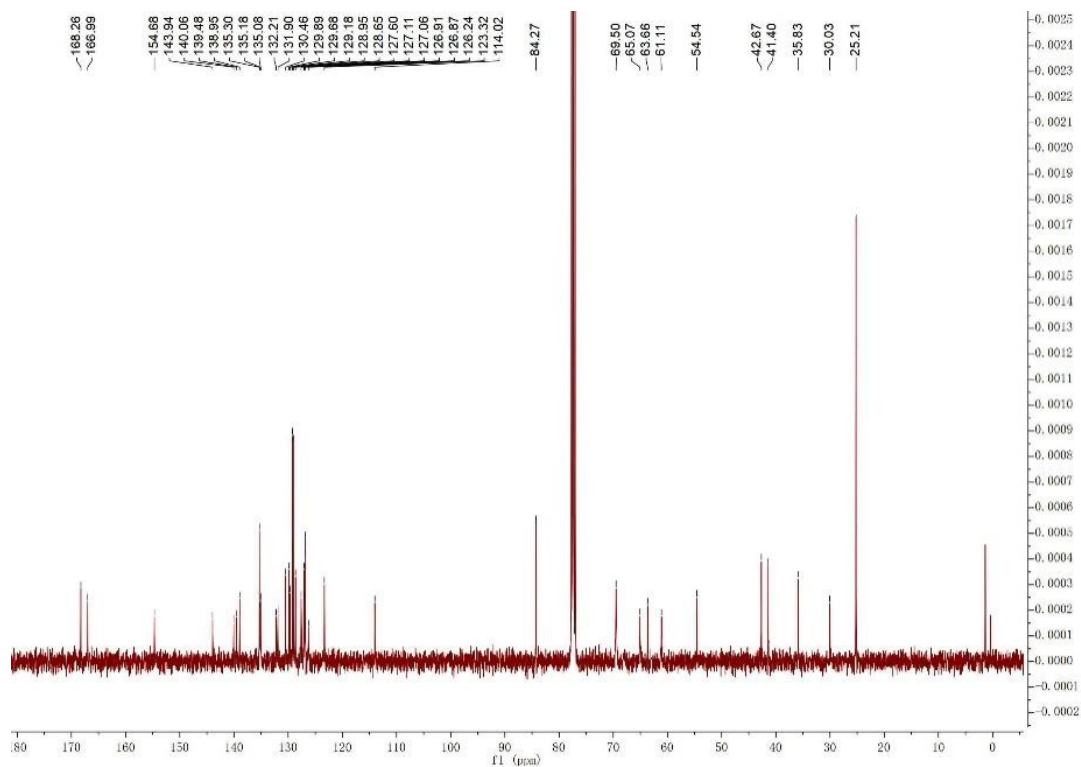
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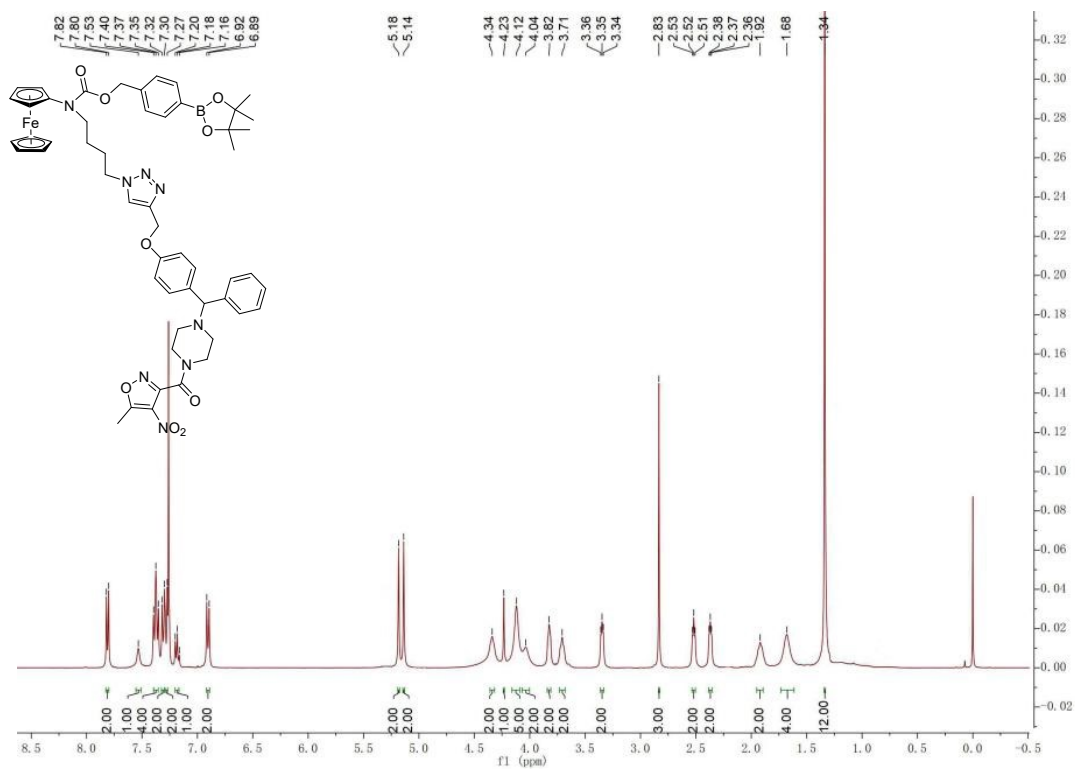
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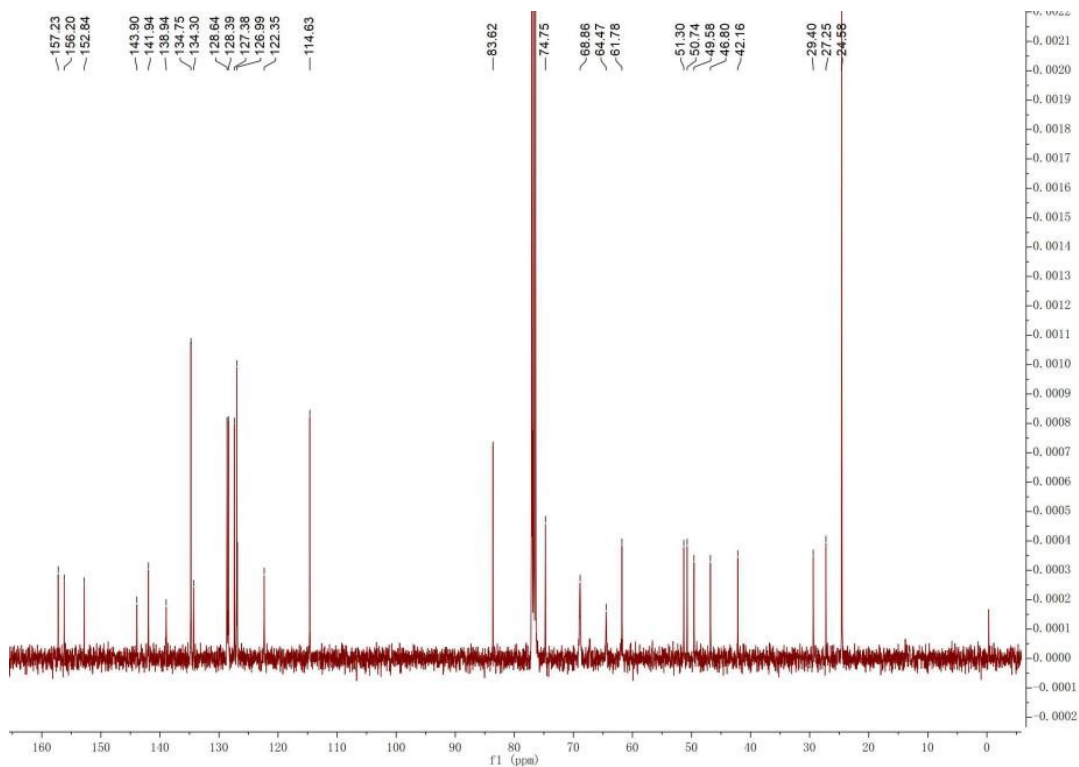
II-2 ¹³C-NMR (Chloroform-*d*)



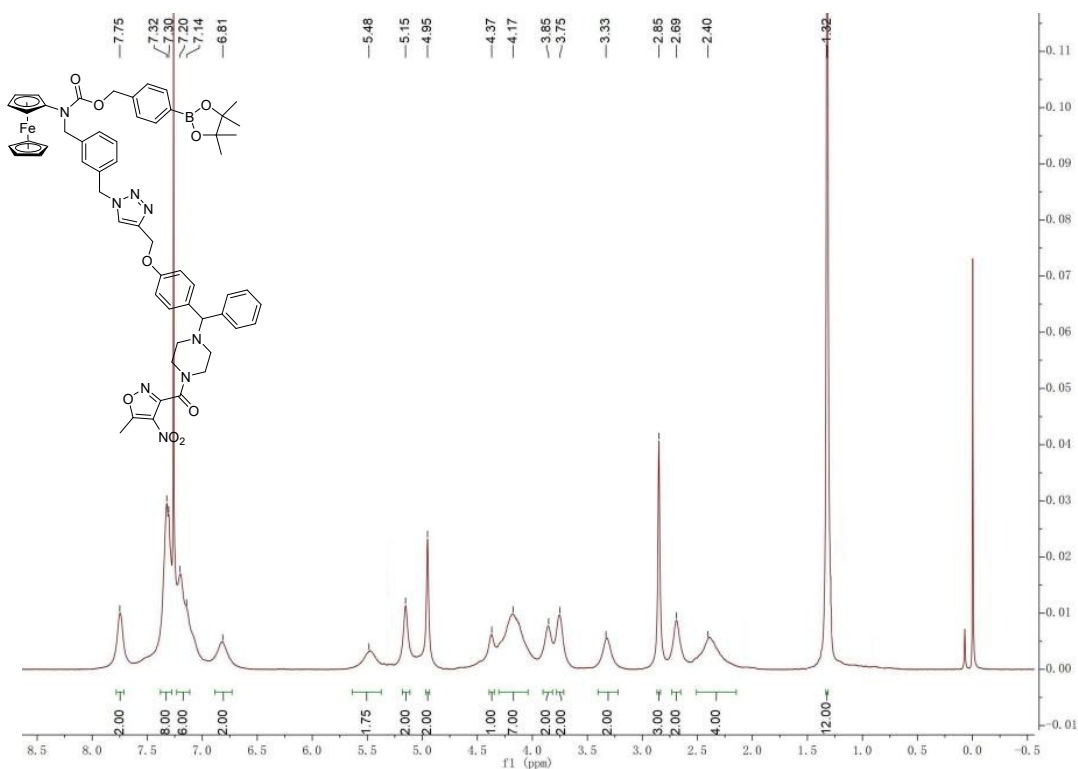
III-1 ¹H-NMR (Chloroform-*d*)



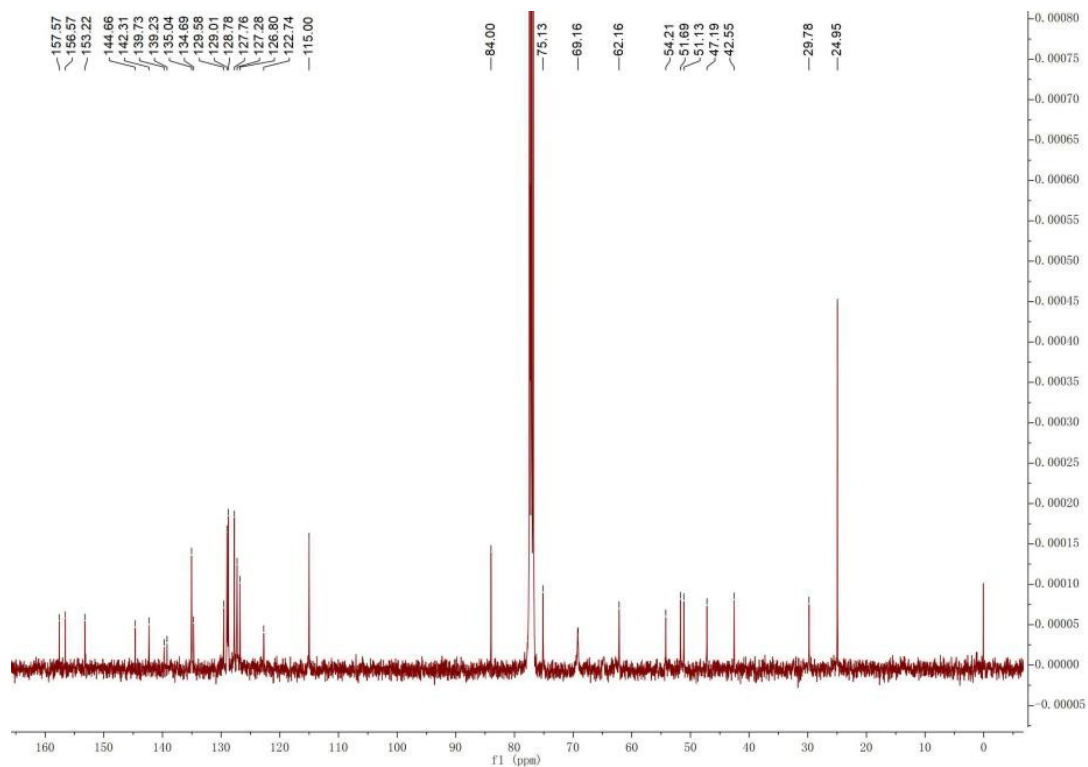
III-1 ¹³C-NMR (Chloroform-*d*)



III-2 ¹H-NMR (Chloroform-*d*)

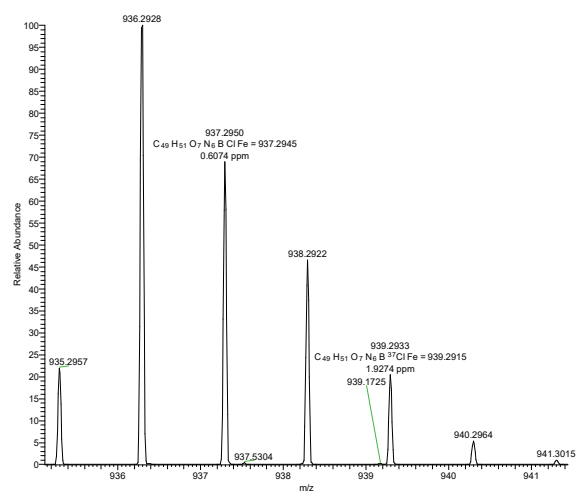


III-2 ¹³C-NMR (Chloroform-*d*)



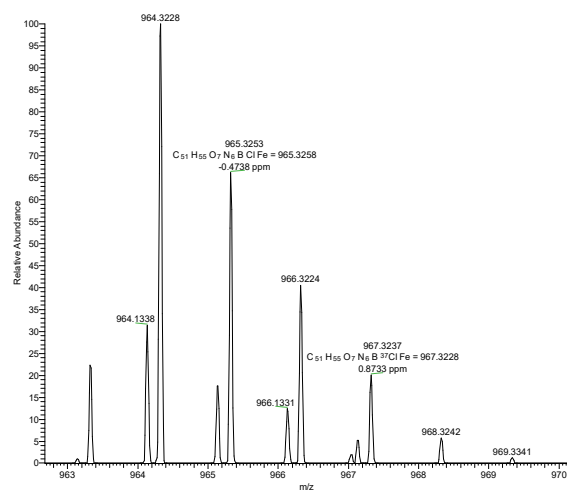
I-1 HRMS

20230821-QR-9_230822093119 #53 RT: 0.58 AV: 1 NL: 1.42E7
T: FTMS + p ESI Full ms [180.00-2000.00]



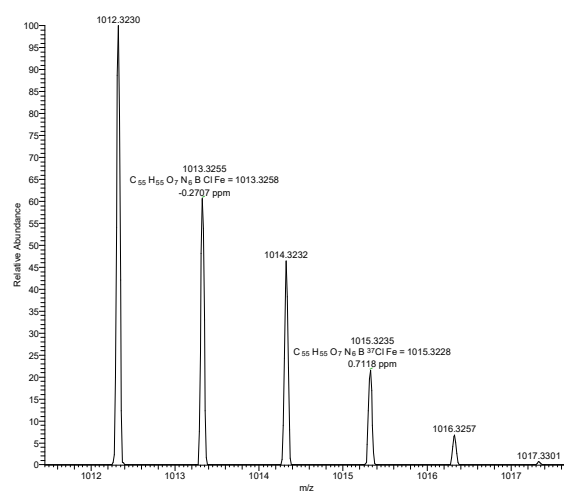
I-2 HRMS

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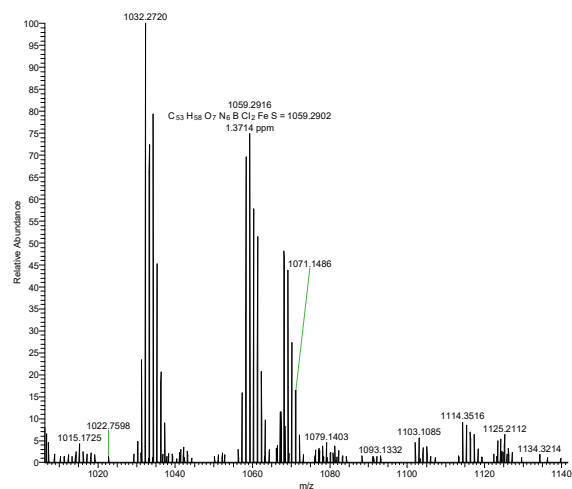
I-3 HRMS

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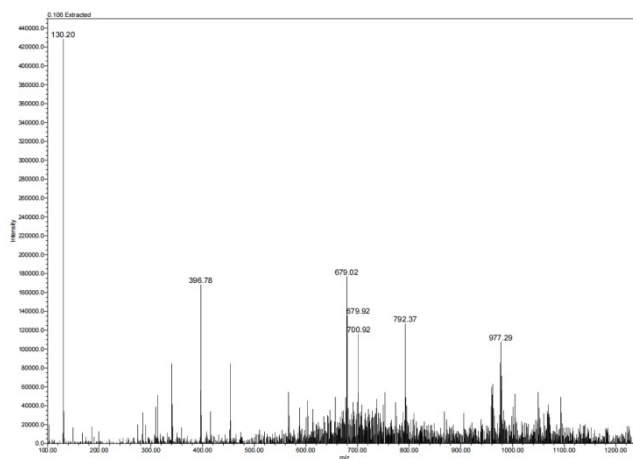


II-1 HRMS

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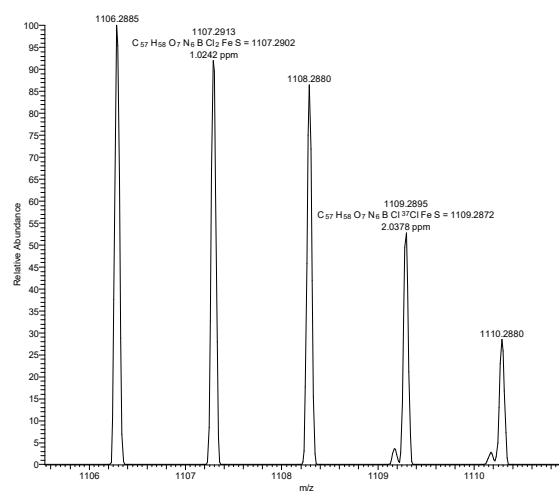


II-1-B LCMS



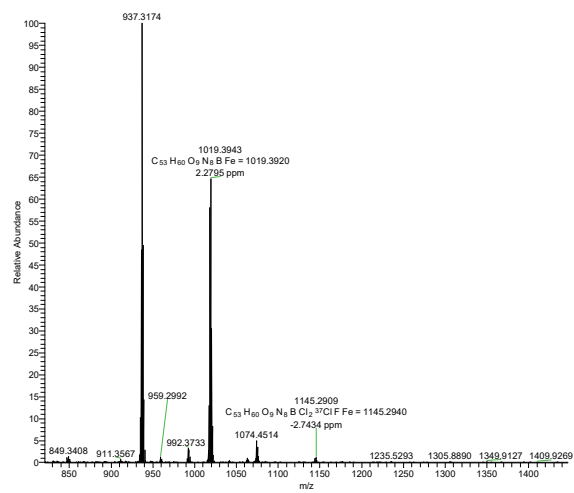
II-2 HRMS

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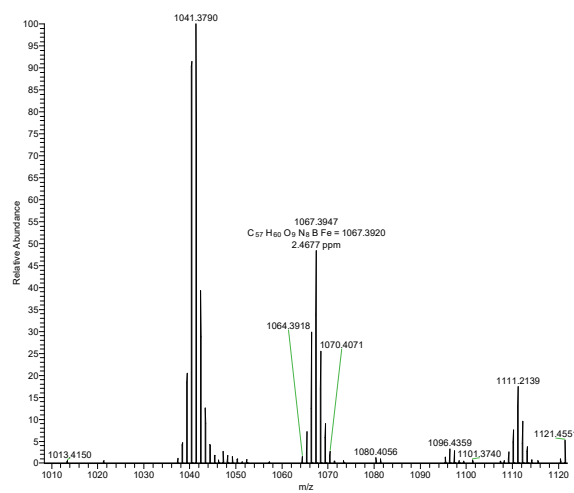
III-1 HRMS

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III-2 HRMS

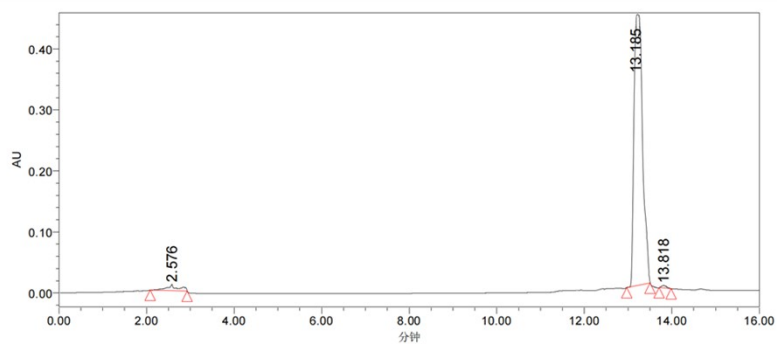
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HPLC analysis for compounds
Compound I-1

Result

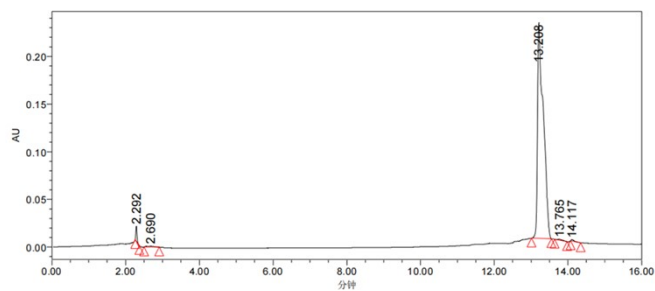
	Ret. Time	Area	Rel. Area (%)
1	2.576	176761	2.89
2	13.185	5900938	96.53
3	13.818	35208	0.58



Compound I-2

Result

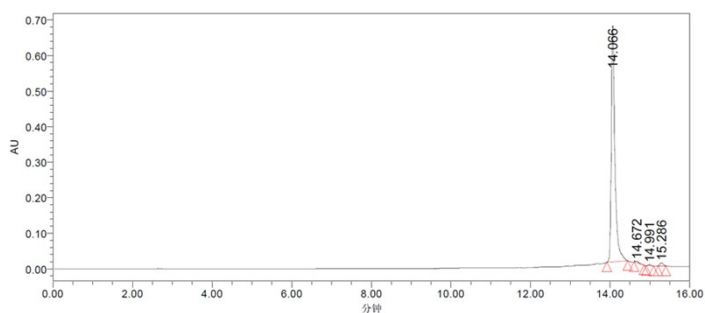
	Ret. Time	Area	Rel. Area (%)
1	2.292	33829	1.34
2	2.690	12662	0.50
3	13.208	2462095	97.60
4	13.765	7781	0.31
5	14.117	6287	0.25



Compound I-3

Result

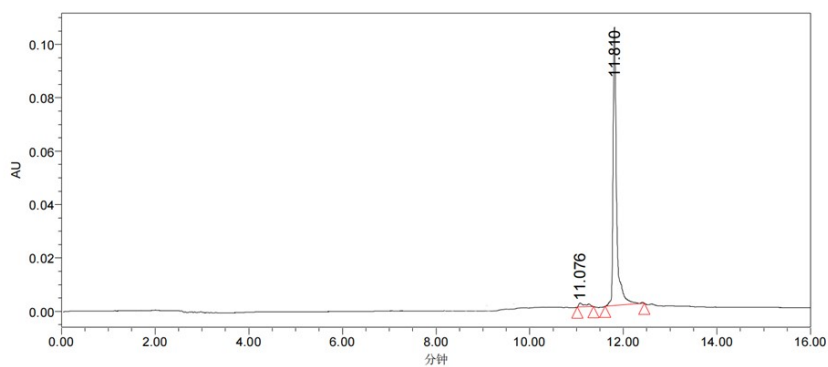
	Ret. Time	Area	Rel. Area (%)
1	14.066	4160493	97.59
2	14.672	32932	0.77
3	14.991	20228	0.47
4	15.286	49596	1.16



Compound II-1

Result

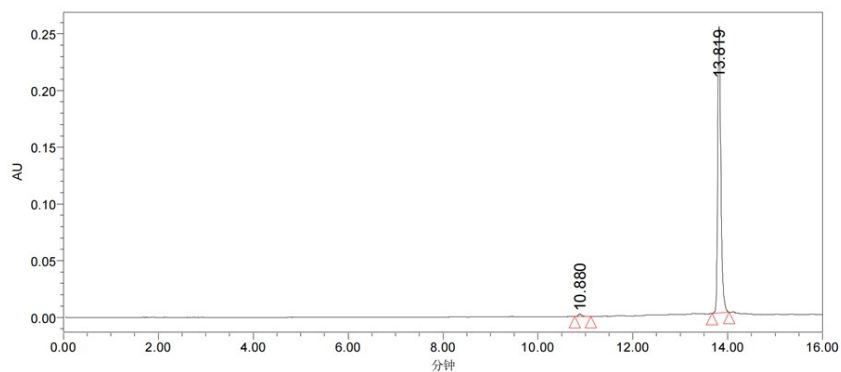
	Ret. Time	Area	Rel. Area (%)
1	11.076	14990	2.65
2	11.810	550991	97.35



Compound II-2

Result

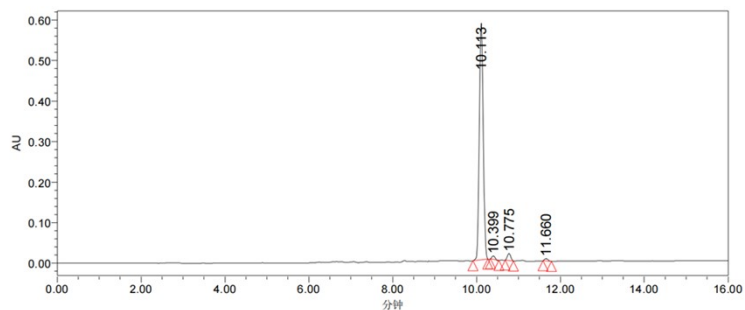
	Ret. Time	Area	Rel. Area (%)
1	10.880	10367	0.88
2	13.819	1170541	99.12



Compound III-1

Result

	Ret. Time	Area	Rel. Area (%)
1	10.113	3852405	95.65
2	10.399	41980	1.04
3	10.775	100230	2.49
4	11.660	33113	0.82



Compound III-2

Result

	Ret. Time	Area	Rel. Area (%)
1	13.981	3112944	98.36
2	14.482	51911	1.64

