

Supplementary Information

Exploring the modulatory influence on the antimalarial activity of amodiaquine using scaffold hybridisation with ferrocene integration

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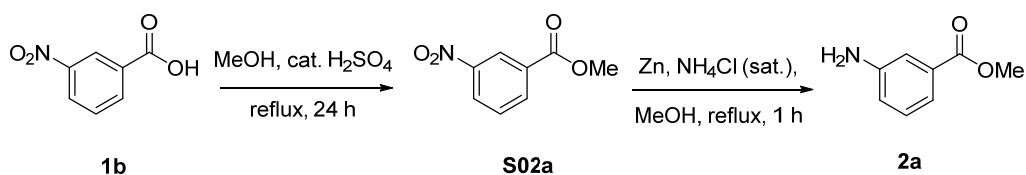
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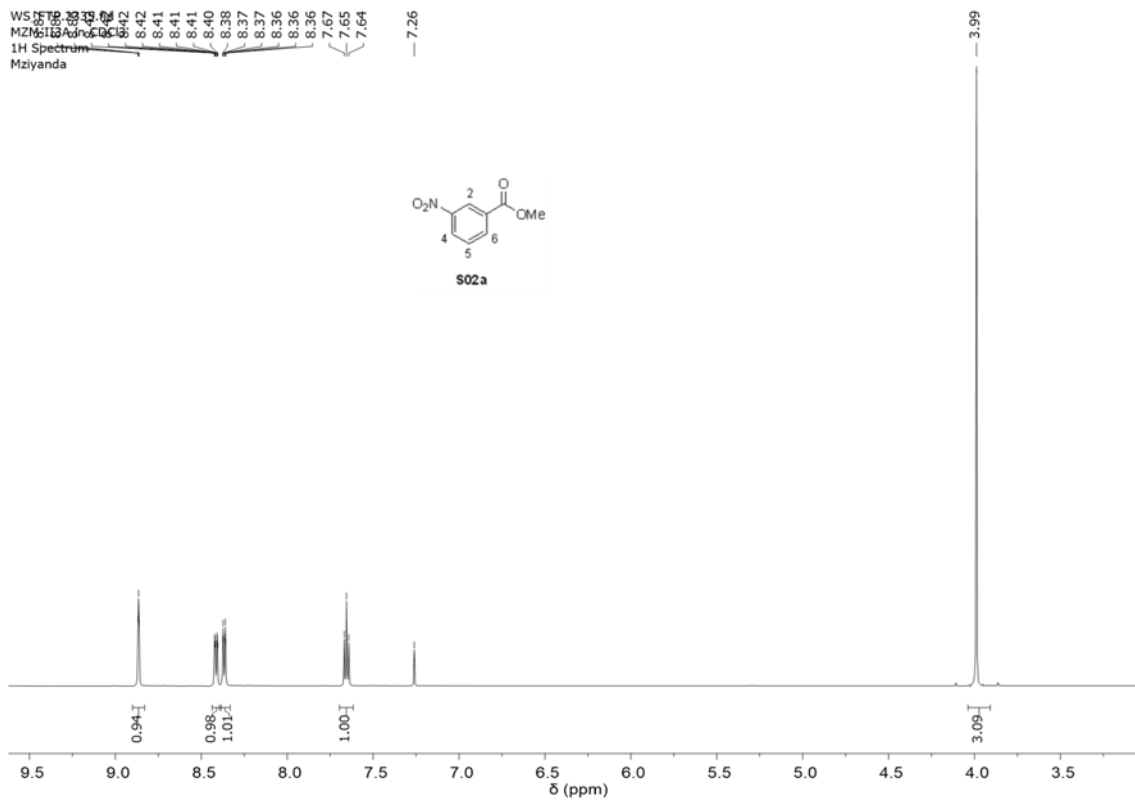
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Synthesis of aniline 2a

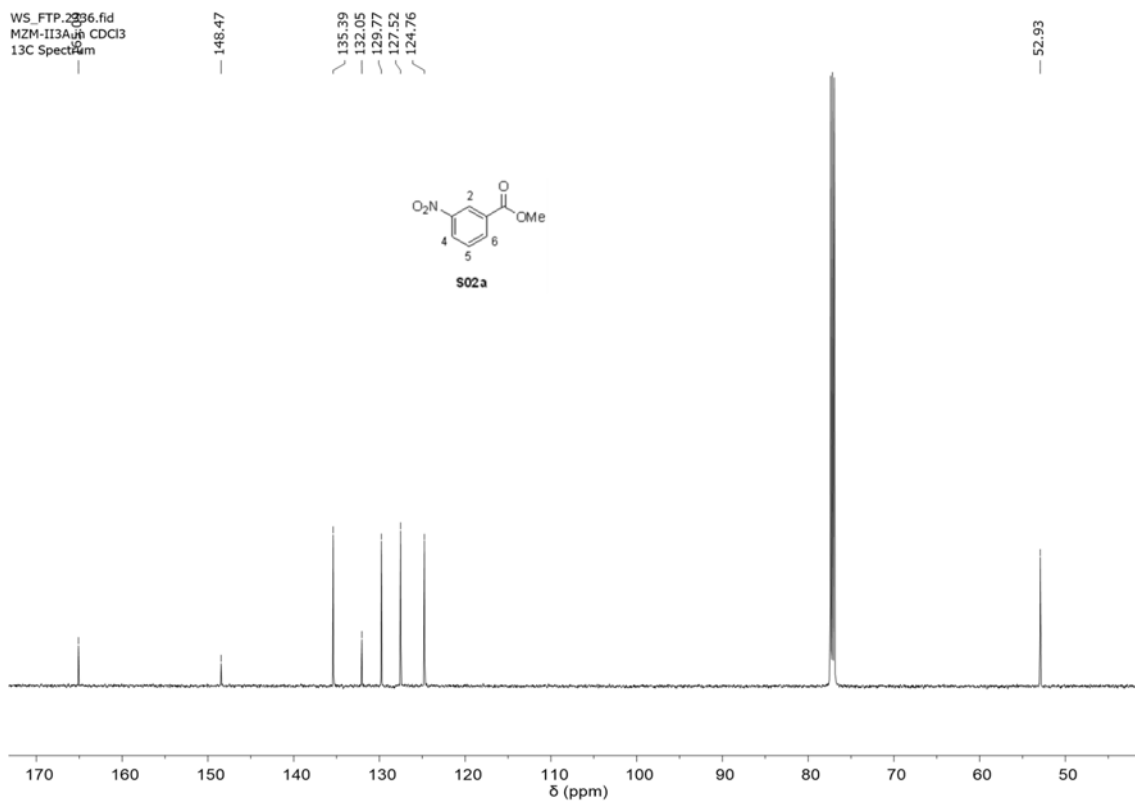


Methyl 3-nitrobenzoate (S02a). Two drops of sulfuric acid (100%) were added to a solution of 3-nitrobenzoic acid (2.00 g, 12.0 mmol) in MeOH (25 mL) and the resulting mixture refluxed for 24 h. After 24 h, the reaction mixture was diluted with distilled water (25 mL) and the product extracted with DCM (3 × 25 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to give an off-white solid. The crude product was purified by silica gel column chromatography (5% MeOH/DCM) to furnish the pure compound as a white solid. Yield: 1.78 g (82%). ¹H NMR (600 MHz, CDCl₃) δ 8.86 (t, *J* = 2.0 Hz, 1H, H₂), 8.41 (ddd, *J* = 8.3, 2.4, 1.2 Hz, 1H, H₄), 8.37 (dt, *J* = 7.8, 1.4 Hz, 1H, H₆), 7.65 (t, *J* = 8.0 Hz, 1H, H₅), 3.99 (s, 3H, OMe). ¹³C NMR (150 MHz, CDCl₃) δ 165.1, 148.5, 135.4, 132.1, 129.8, 127.5, 124.8, 52.9.

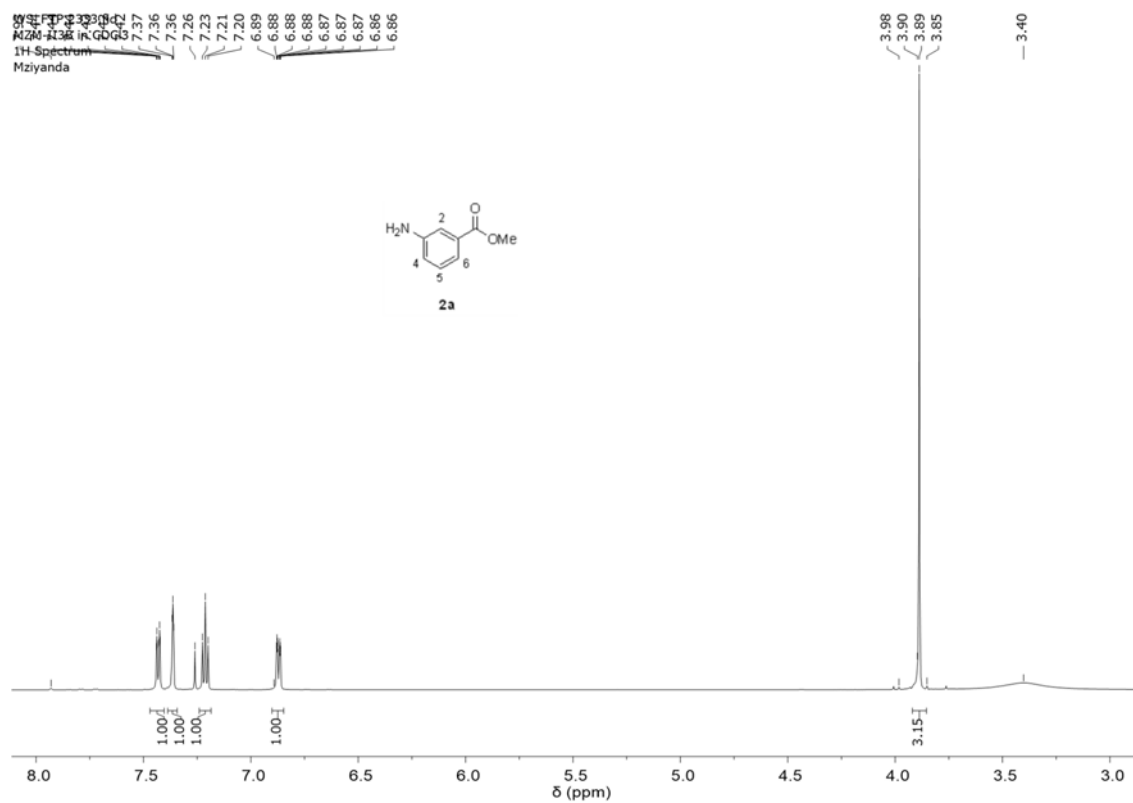
Methyl 3-aminobenzoate (2a). Saturated NH₄Cl solution (5 mL) was cautiously added to a suspension of S02a (1.75 g, 9.7 mmol) and Zn dust (3.81 g, 58.2 mmol), and the resulting mixture was refluxed for 1 h. The product was extracted with EtOAc (2 × 25 mL), dried over Na₂SO₄ and the solvent removed *in vacuo* to afford the pure product as a light-yellow oil. Yield: 1.30 g (88 %). ¹H NMR (600 MHz, CDCl₃) δ 7.43 (dt, *J* = 7.7, 1.3 Hz, 1H, H₆), 7.36 (t, *J* = 2.0 Hz, 1H, H₂), 7.21 (t, *J* = 7.8 Hz, 1H, H₅), 6.87 (ddd, *J* = 8.0, 2.5, 1.1 Hz, 1H, H₄), 3.89 (s, 3H, OMe). ¹³C NMR (150 MHz, CDCl₃) δ 167.4, 146.3, 131.3, 129.4, 120.1, 119.7, 116.1, 52.2.



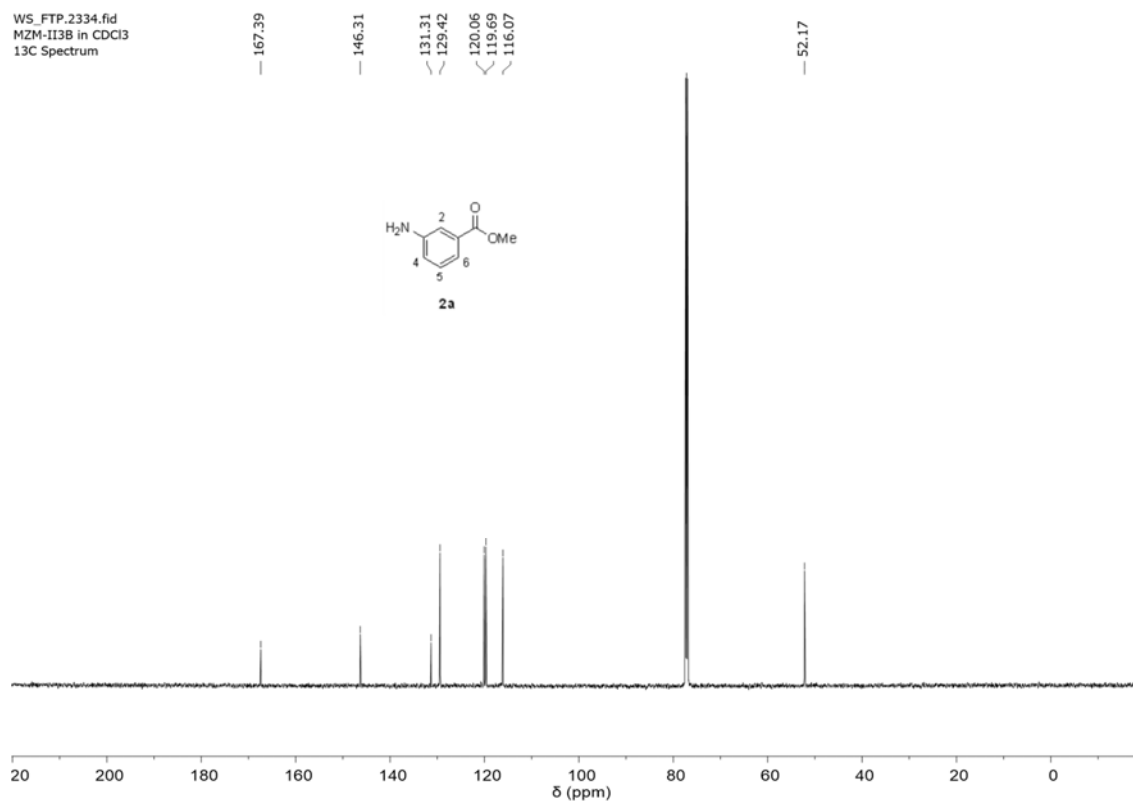
¹³C NMR spectrum of **S02a**



¹H NMR spectrum of **2a**

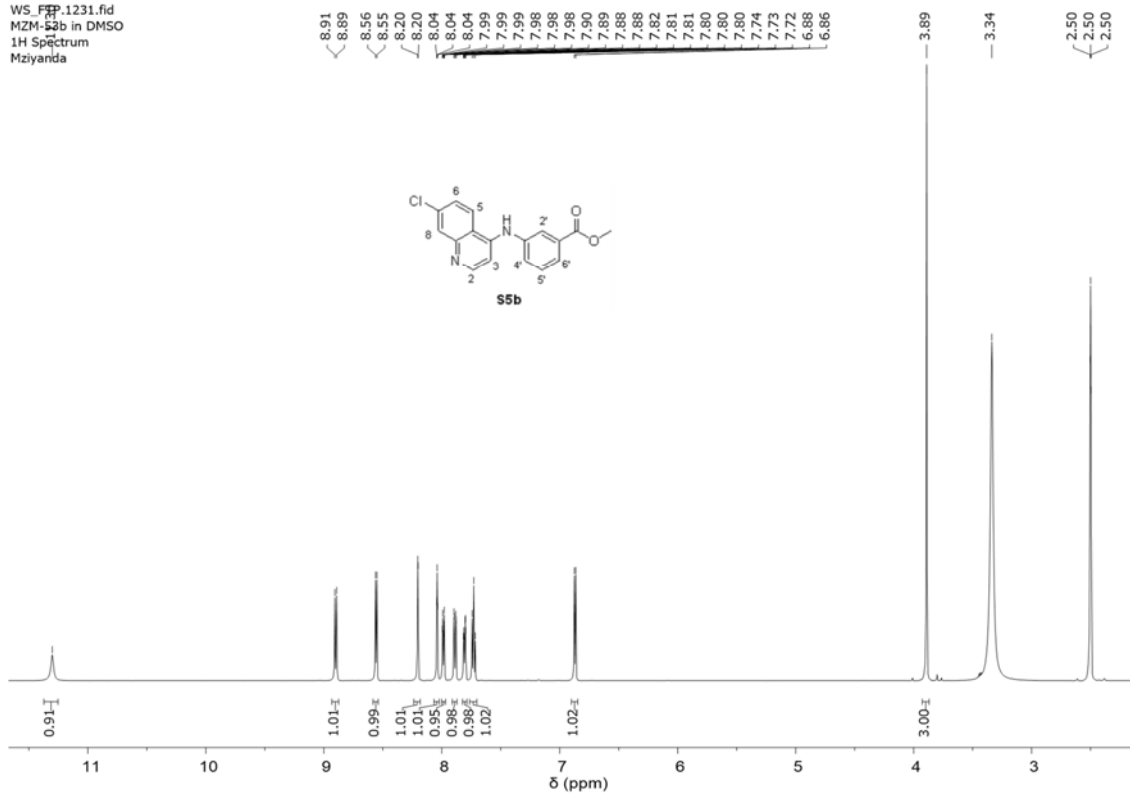


¹³C NMR spectrum of **2a**



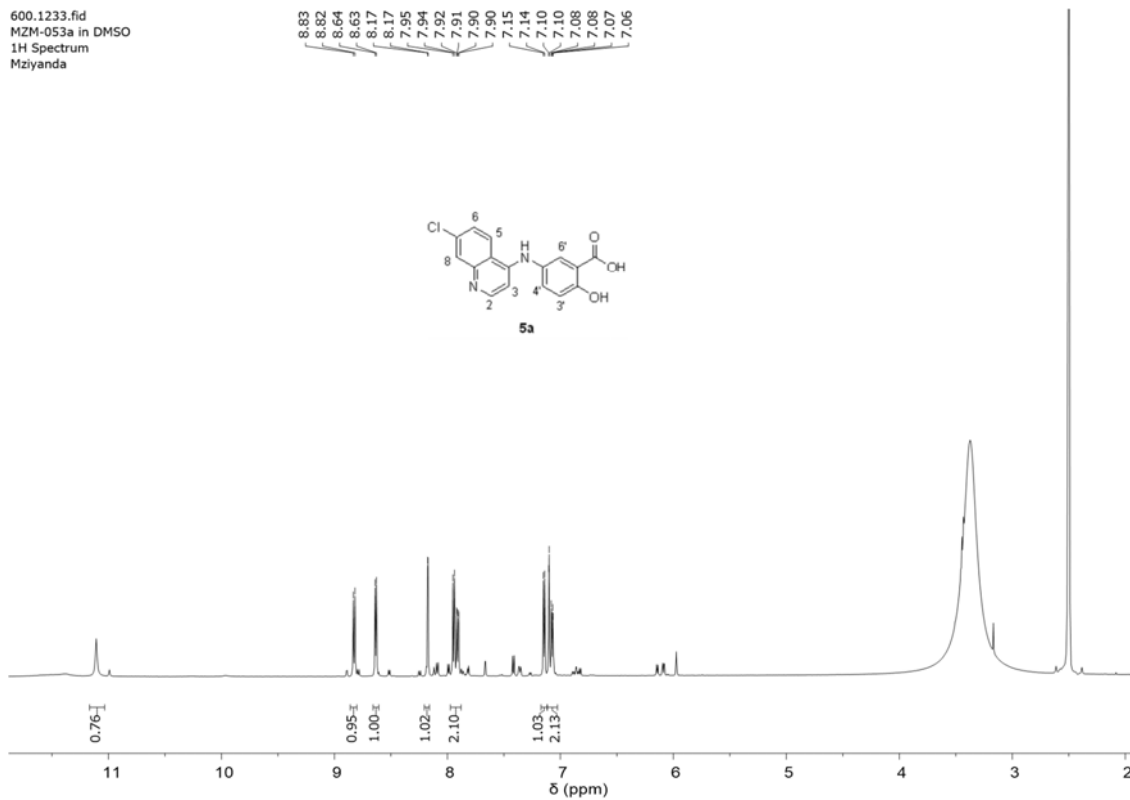
¹H NMR spectrum of **S5b**

WS_FPP_1231.fid
MZM-52b in DMSO
1H Spectrum
Mziyanda



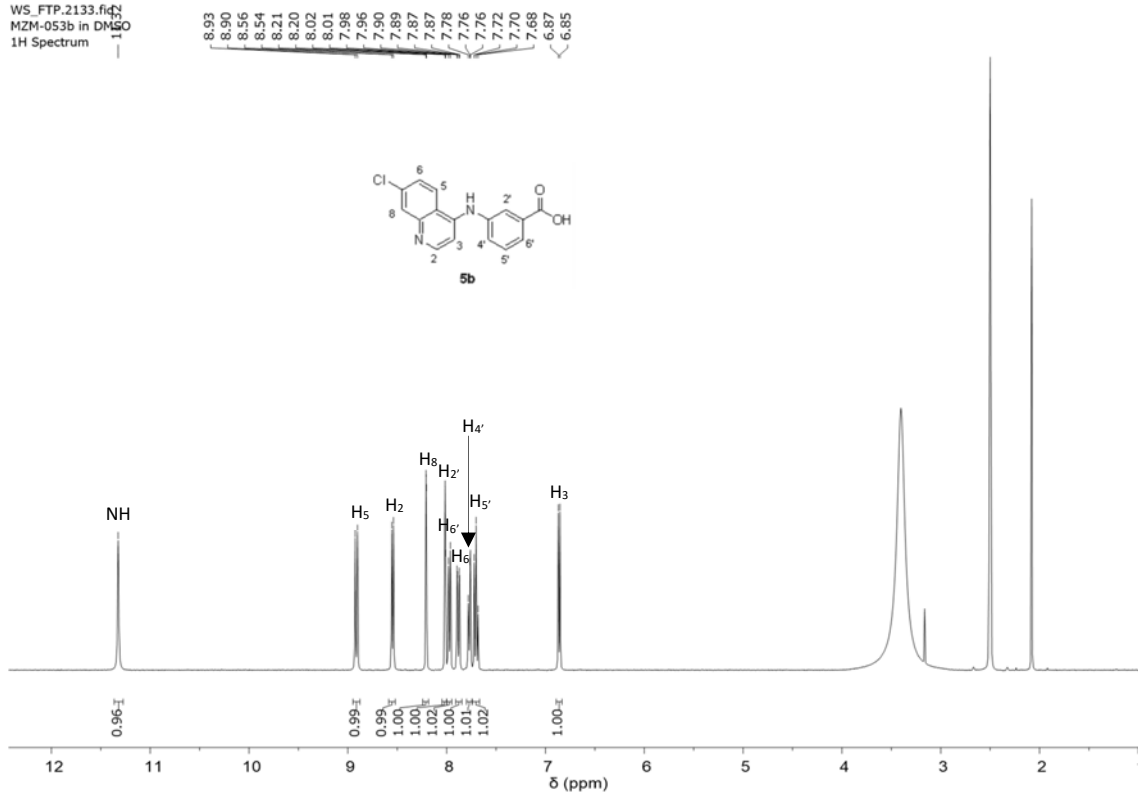
¹H NMR spectrum of **5a**

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MZM-053a in DMSO
1H Spectrum
Mziyanda



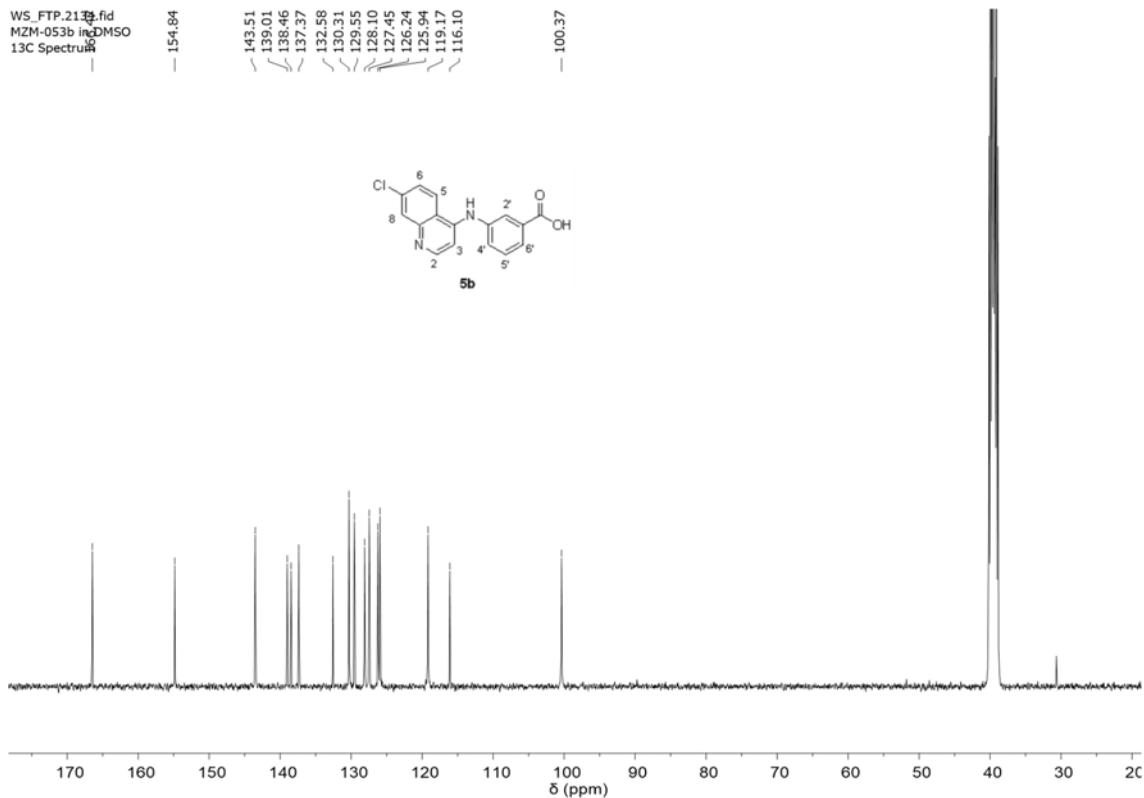
¹H NMR spectrum of **5b**

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MZM-053b in DMSO
1H Spectrum



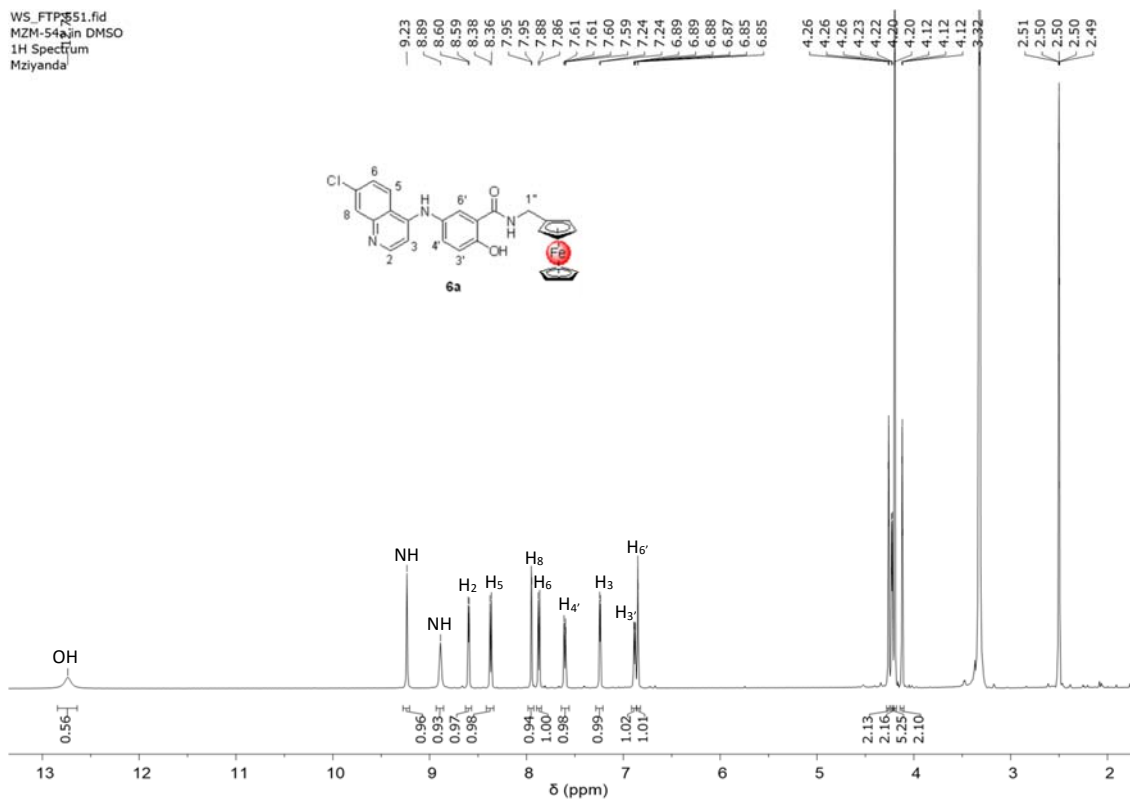
¹³C NMR spectrum of **5b**

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MZM-053b in DMSO
13C Spectrum



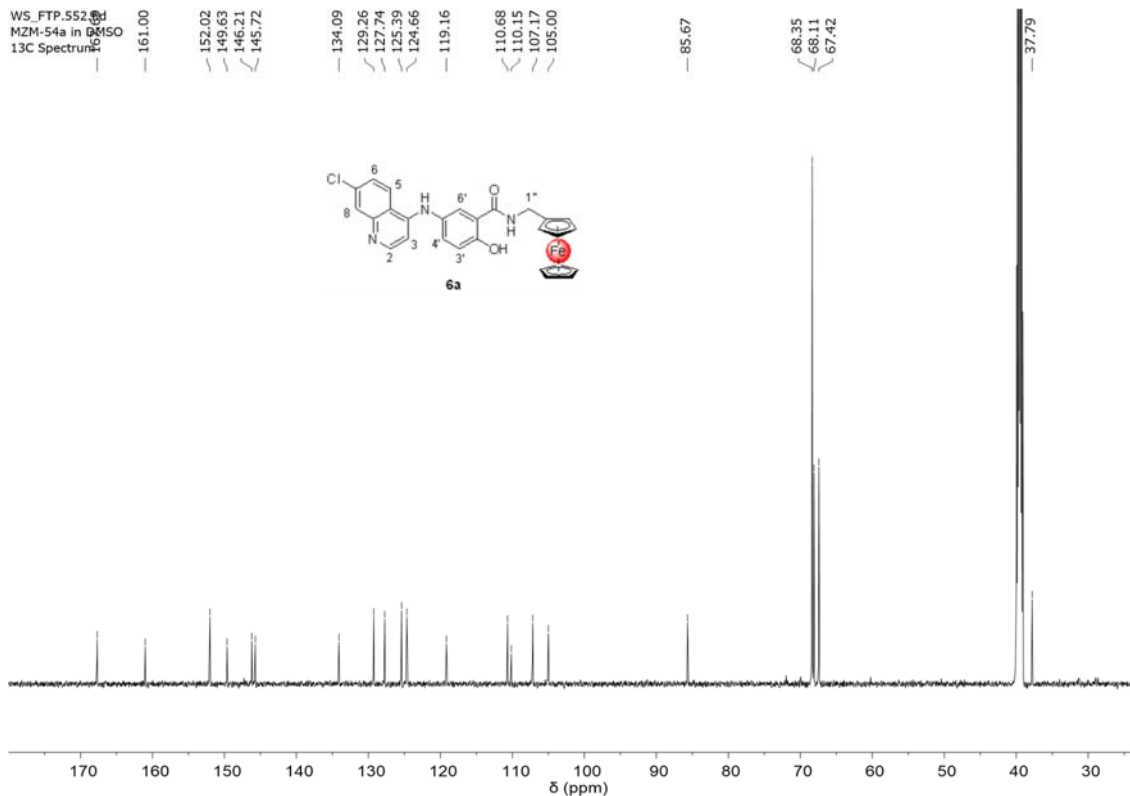
¹H NMR spectrum of 6a

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MZM-54a in DMSO
1H Spectrum
Mziyanda

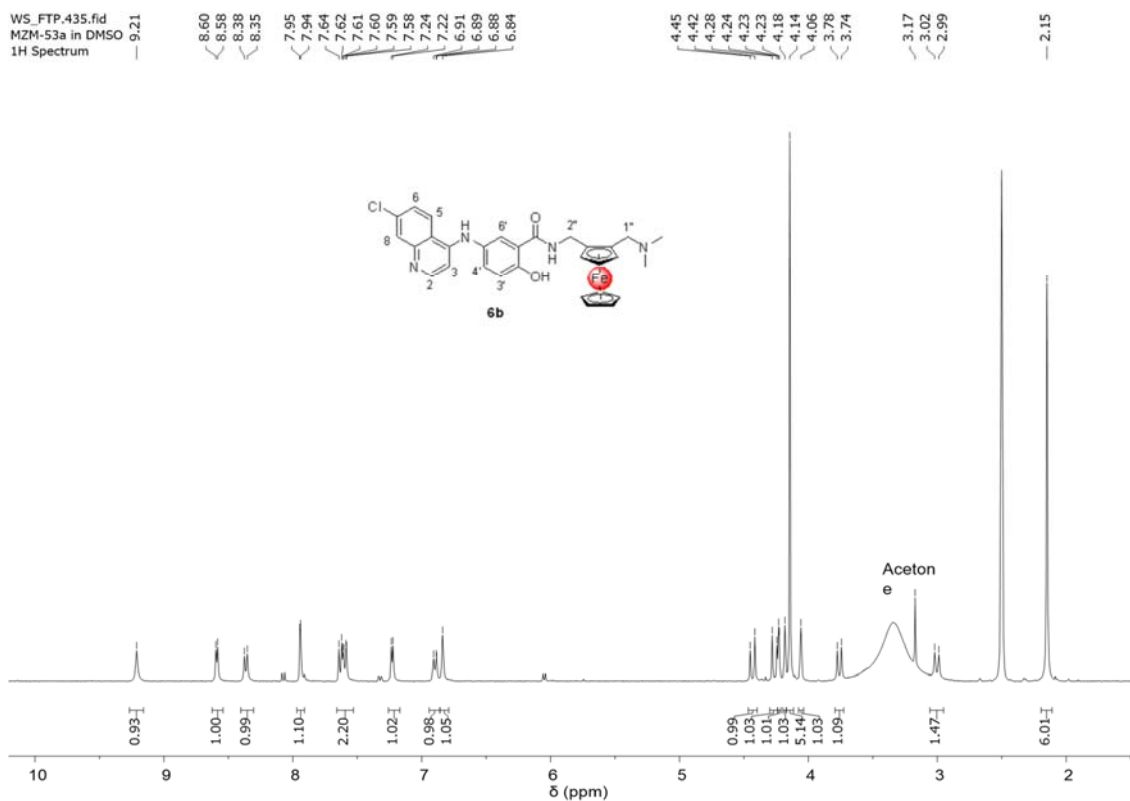


¹³C NMR spectrum of 6a

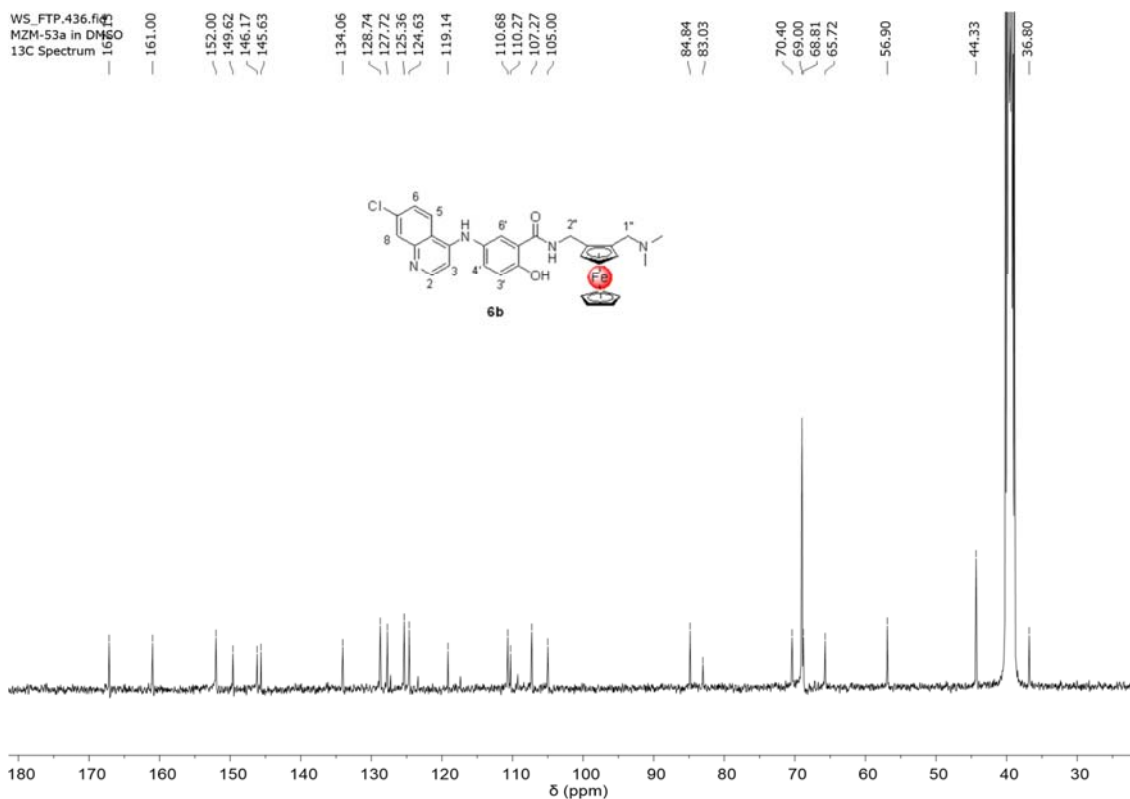
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MZM-54a in DMSO
13C Spectrum
Mziyanda



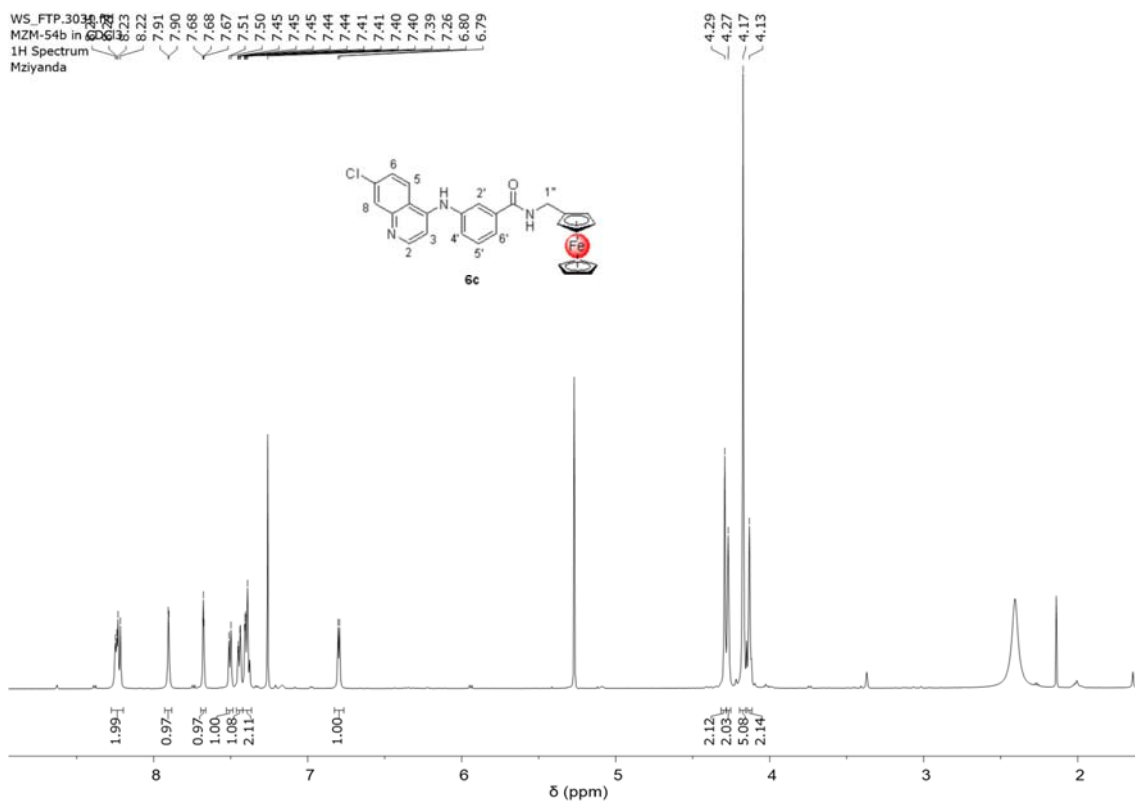
¹H NMR spectrum of **6b**



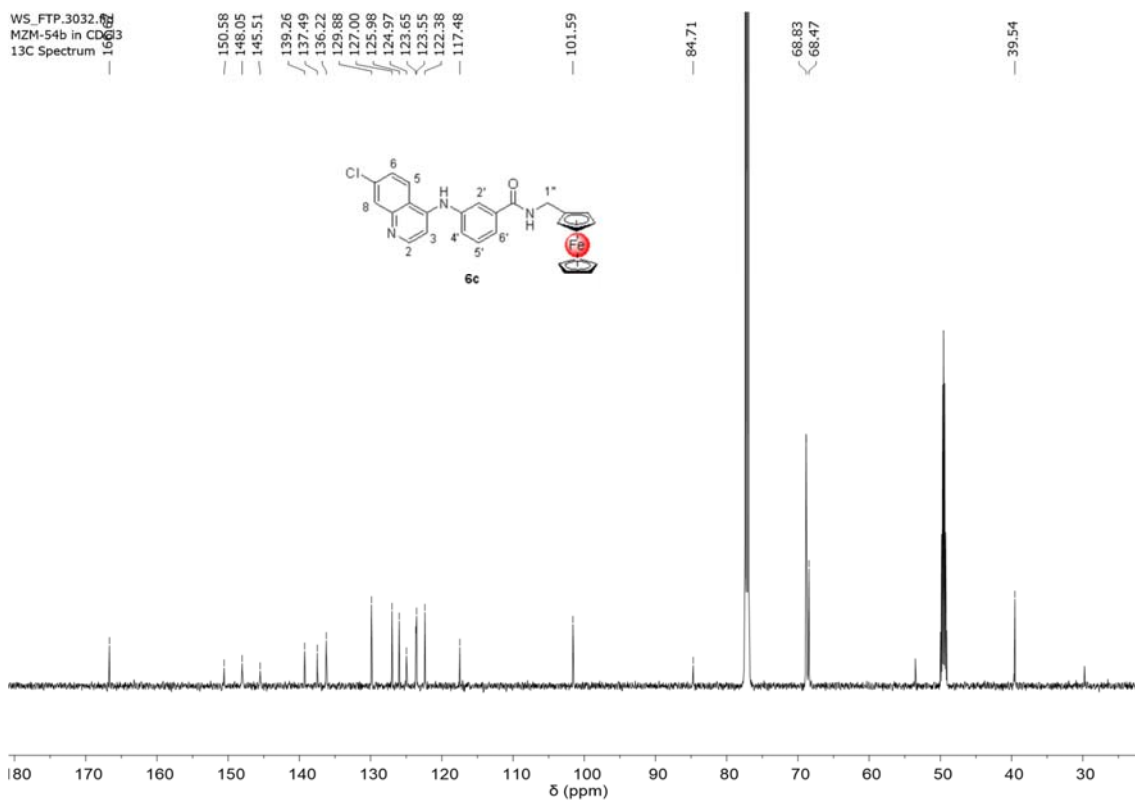
¹³C NMR spectrum of **6b**



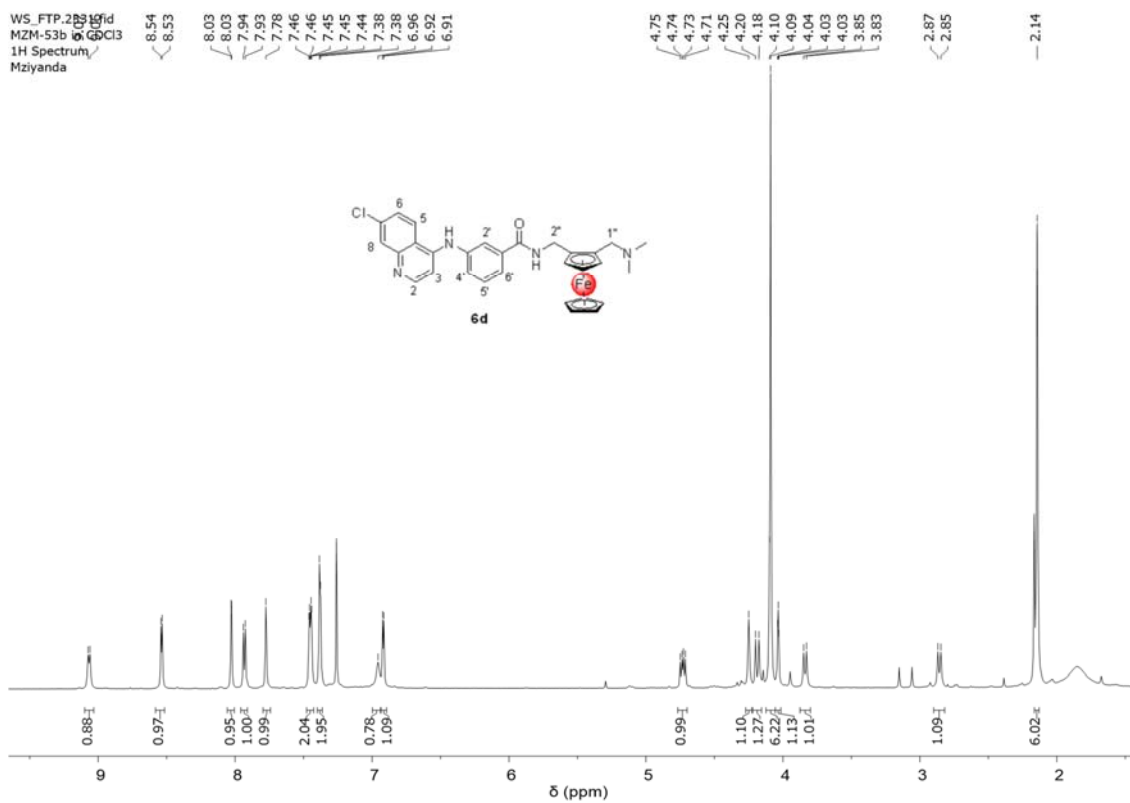
^1H NMR spectrum of **6c**



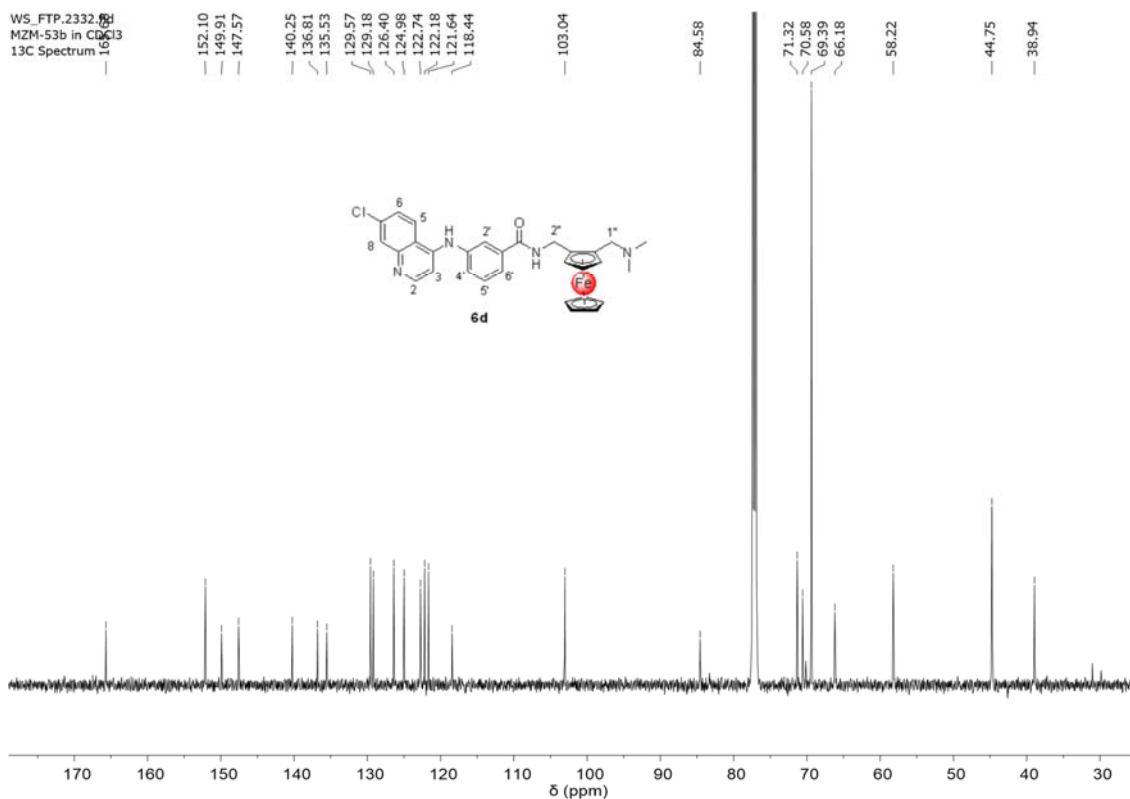
^{13}C NMR spectrum of **6c**



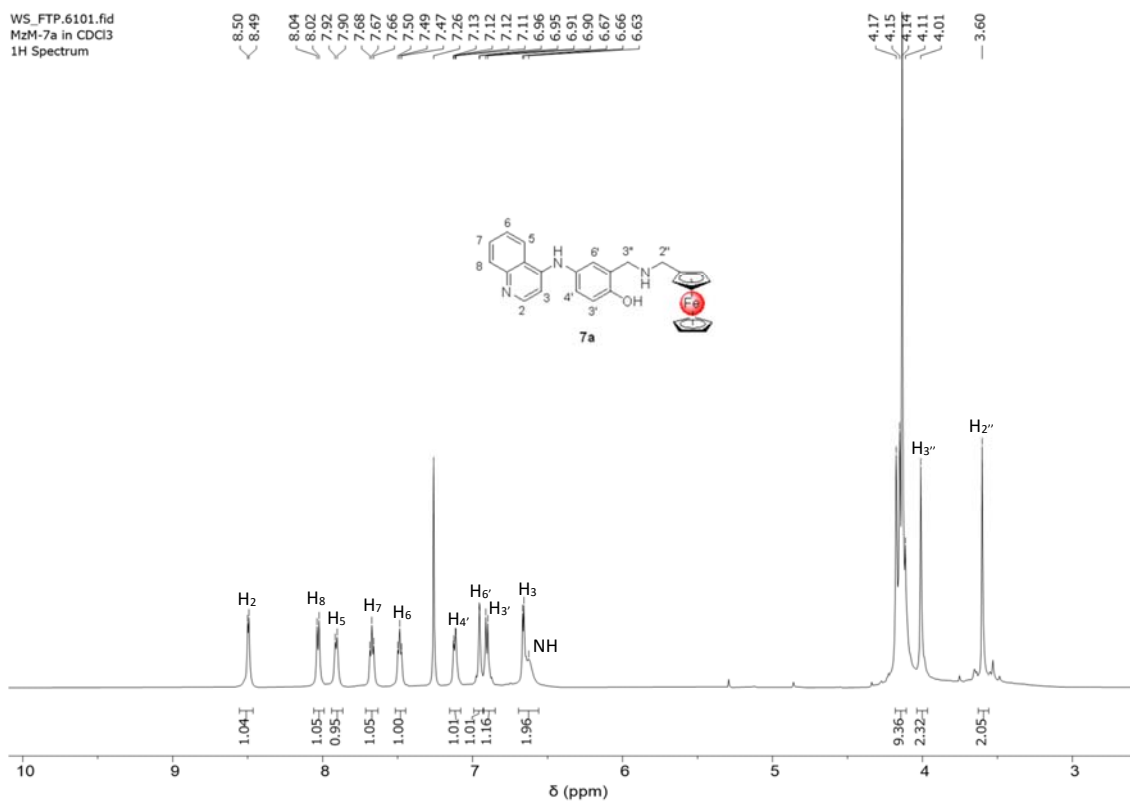
¹H NMR spectrum of **6d**



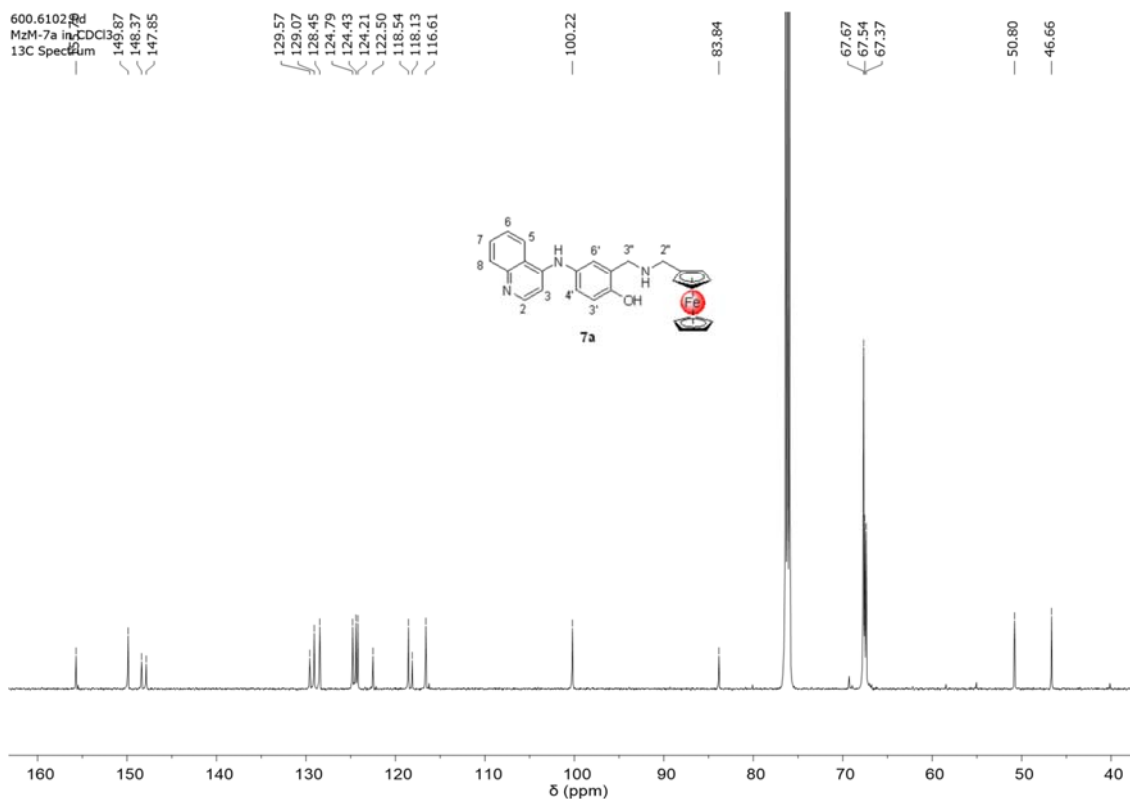
¹³C NMR spectrum of **6d**



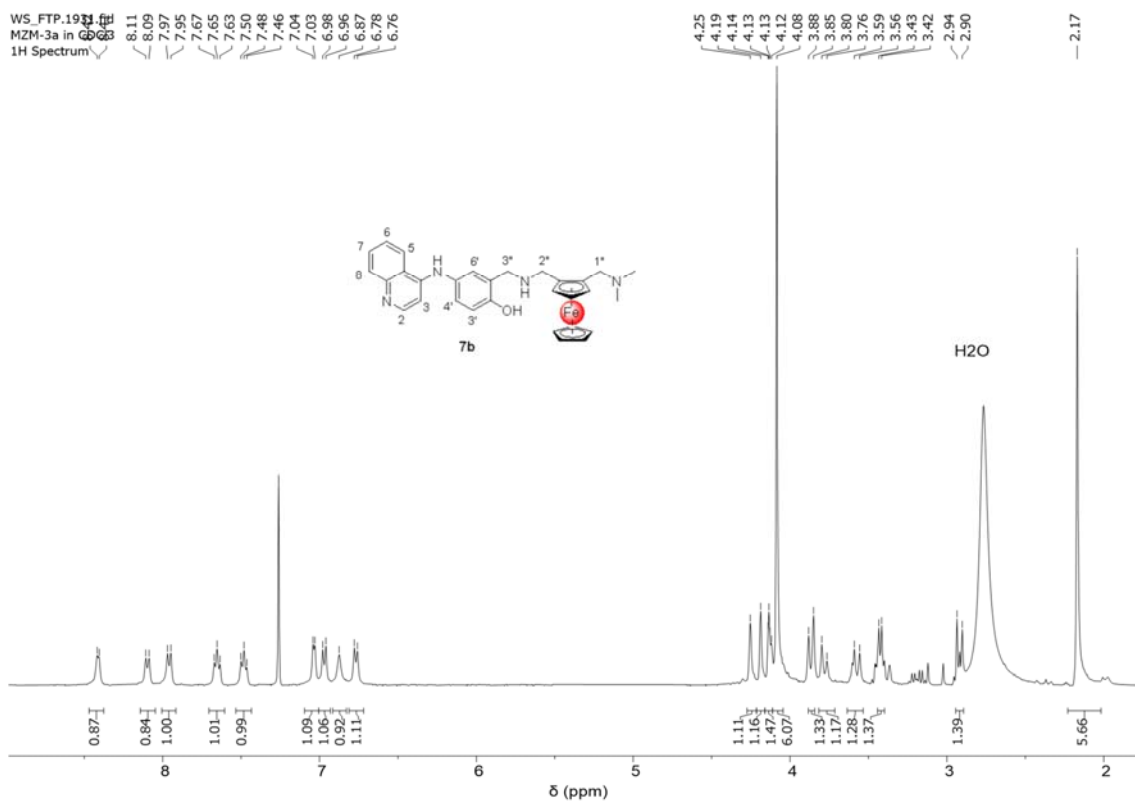
¹H NMR spectrum of **7a**



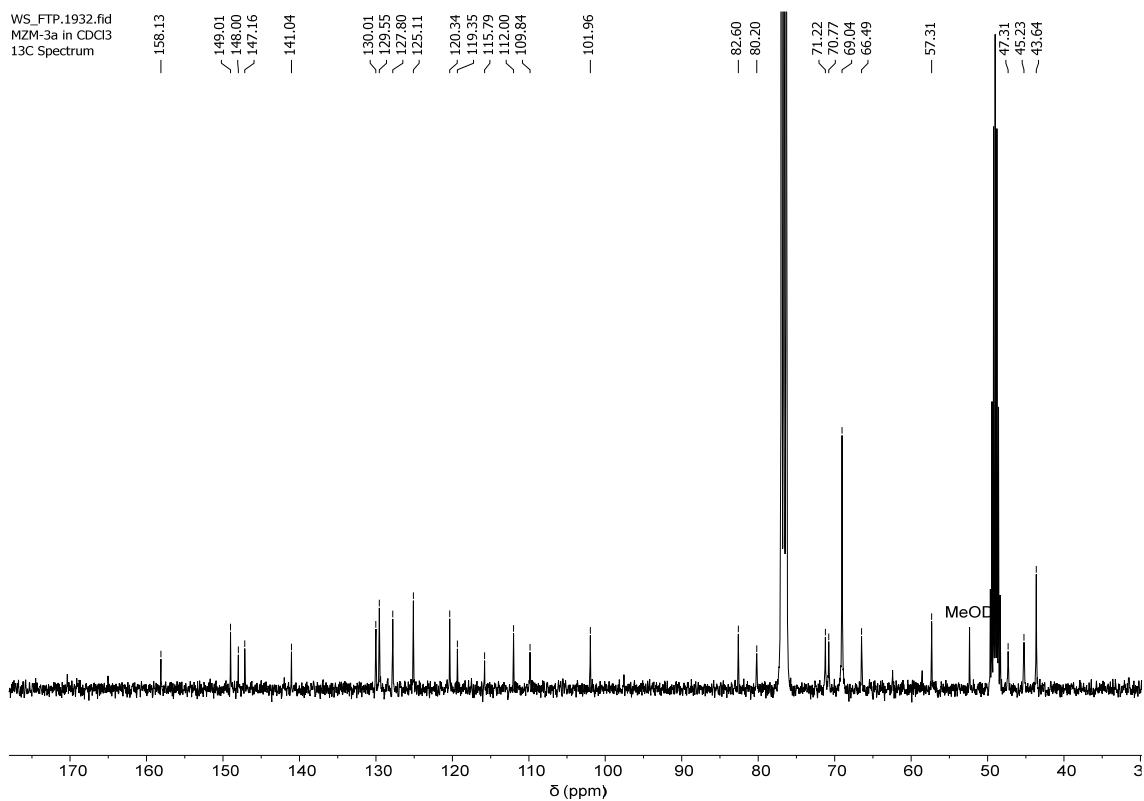
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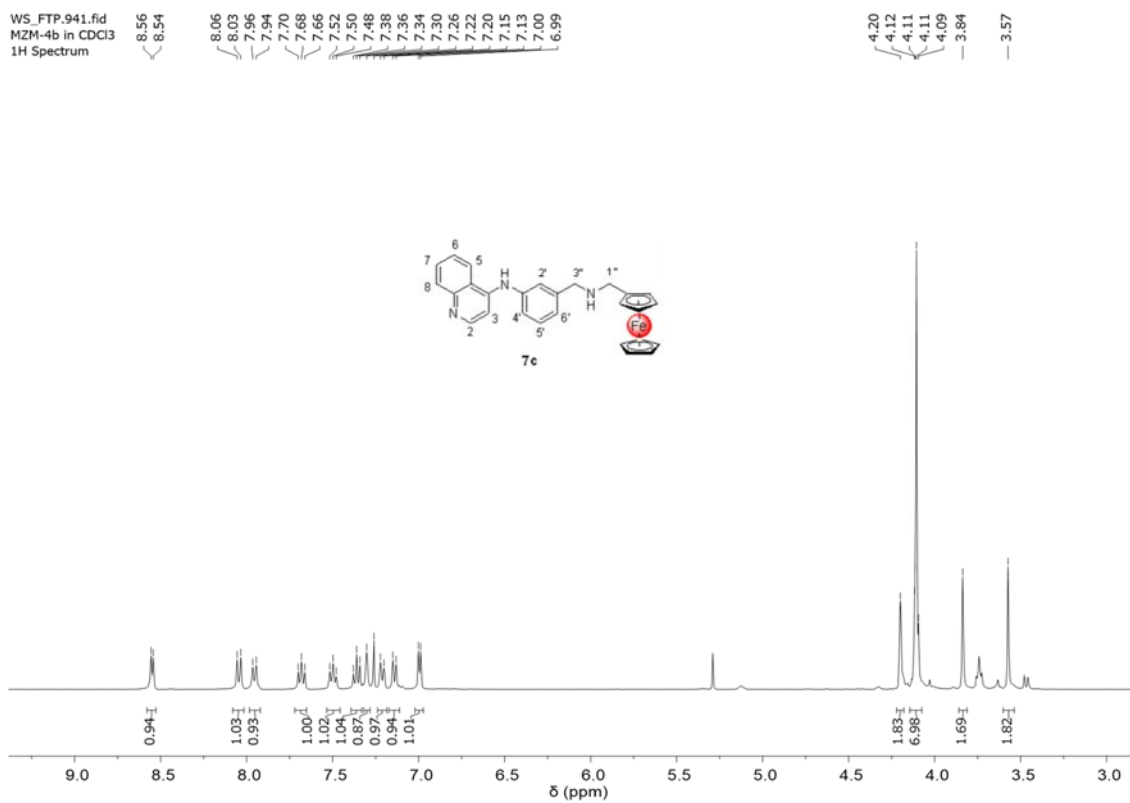
¹H NMR spectrum of **7b**



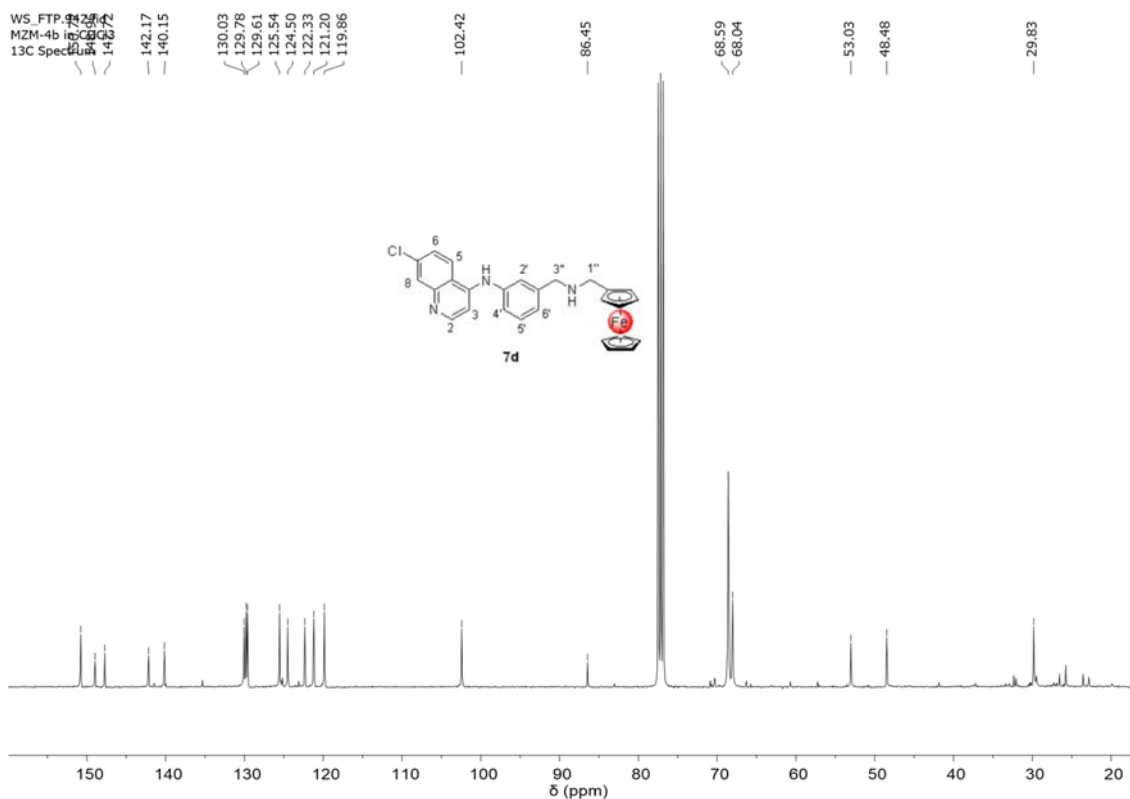
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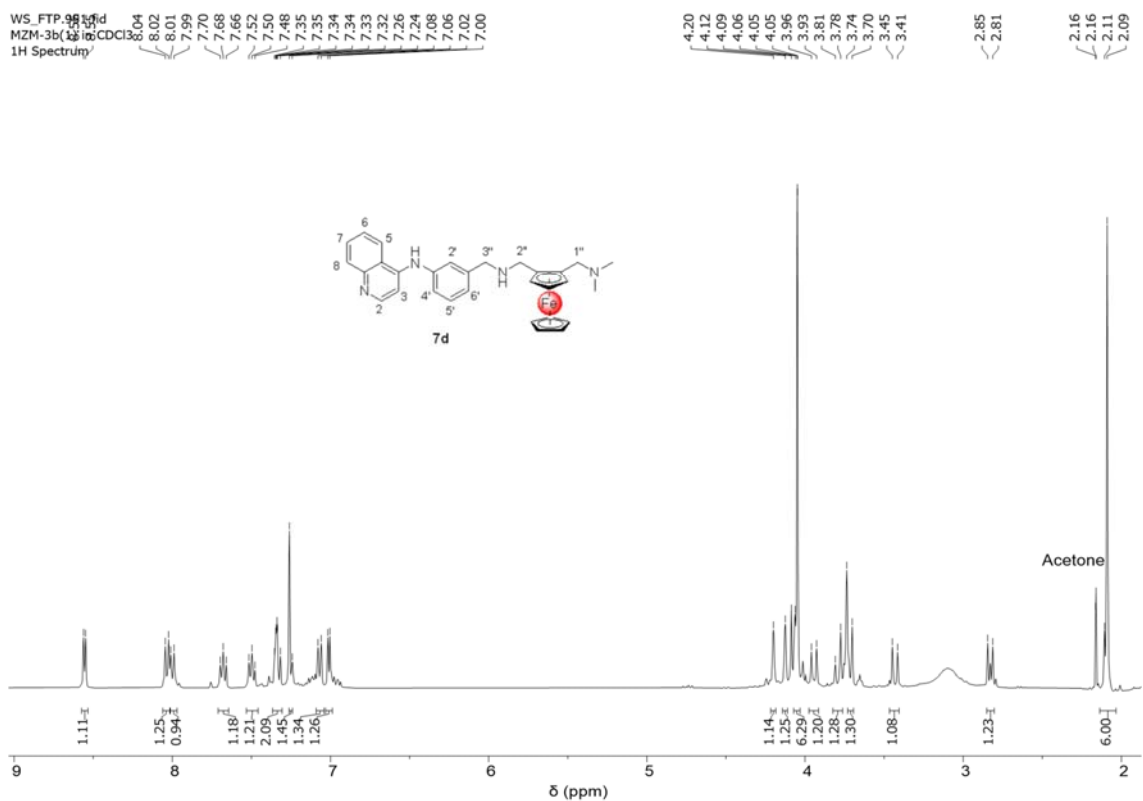
¹H NMR spectrum of **7c**



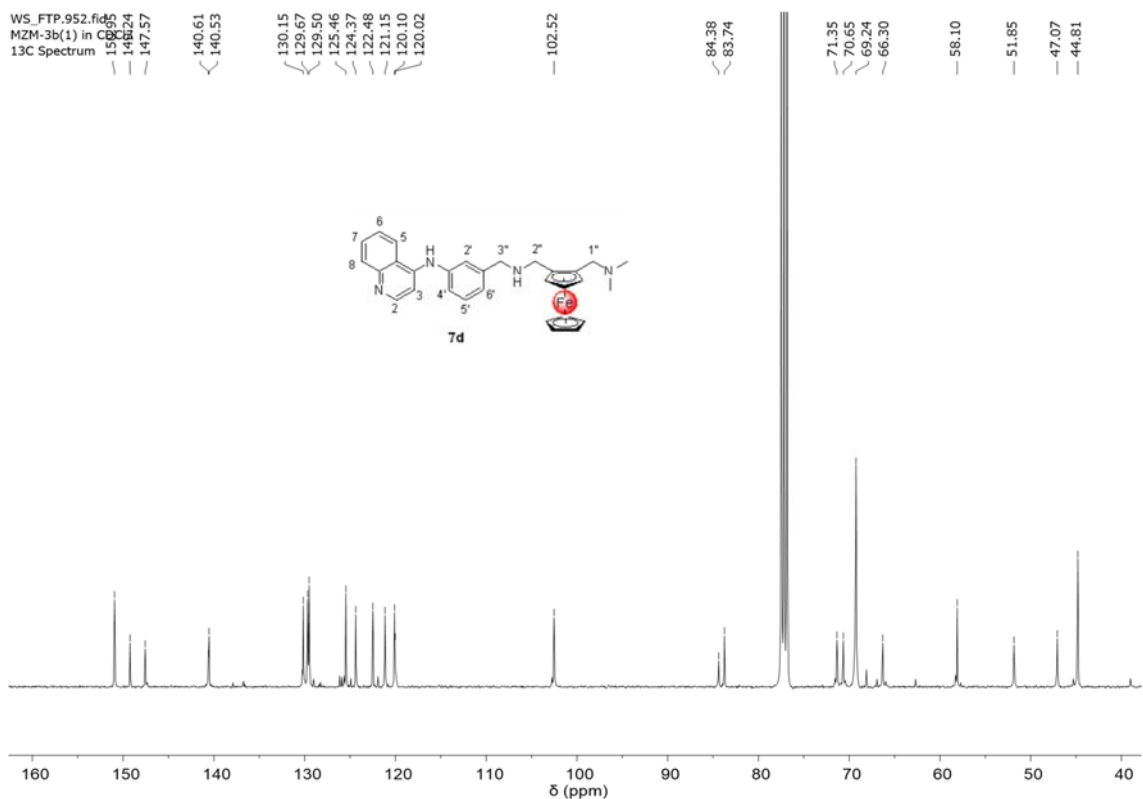
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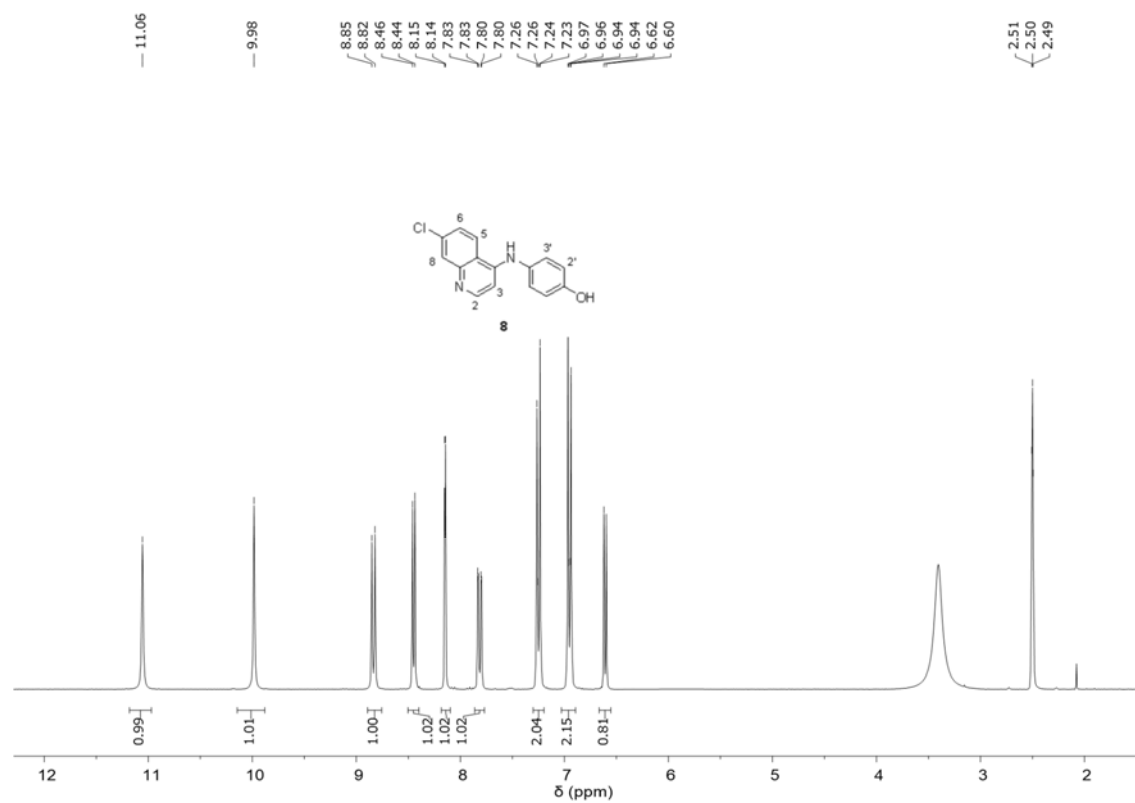
¹H NMR spectrum of **7d**



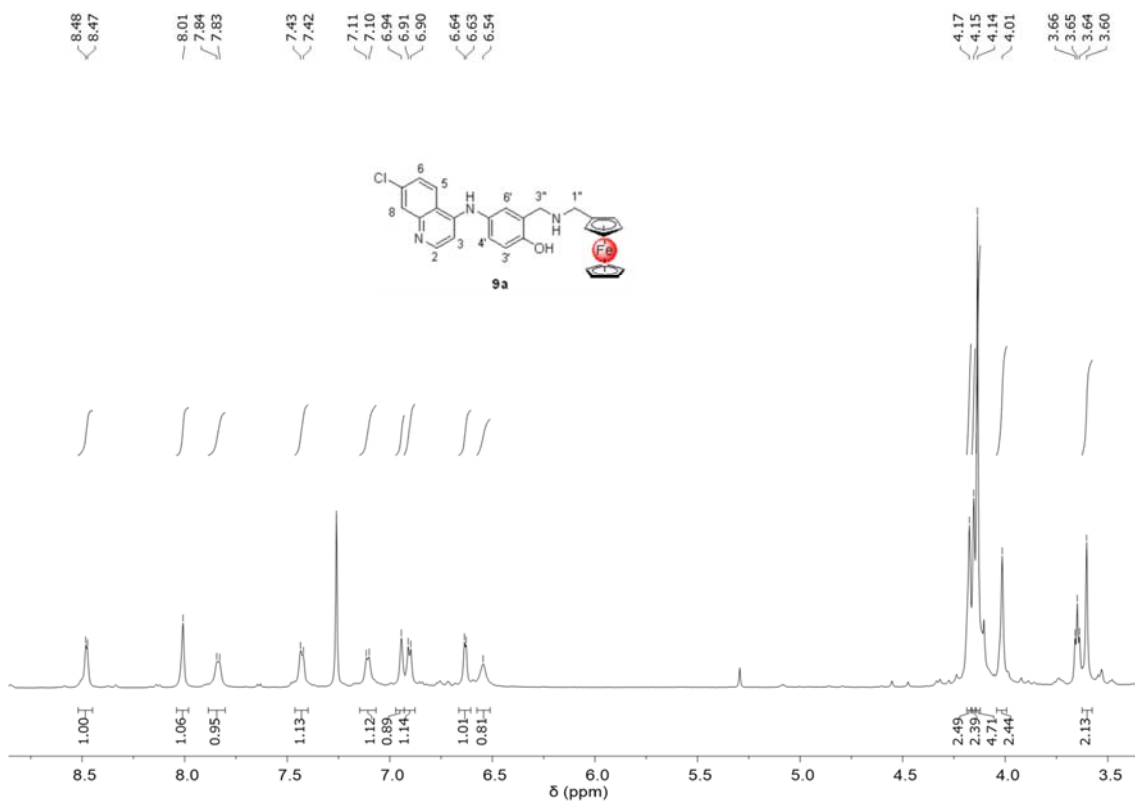
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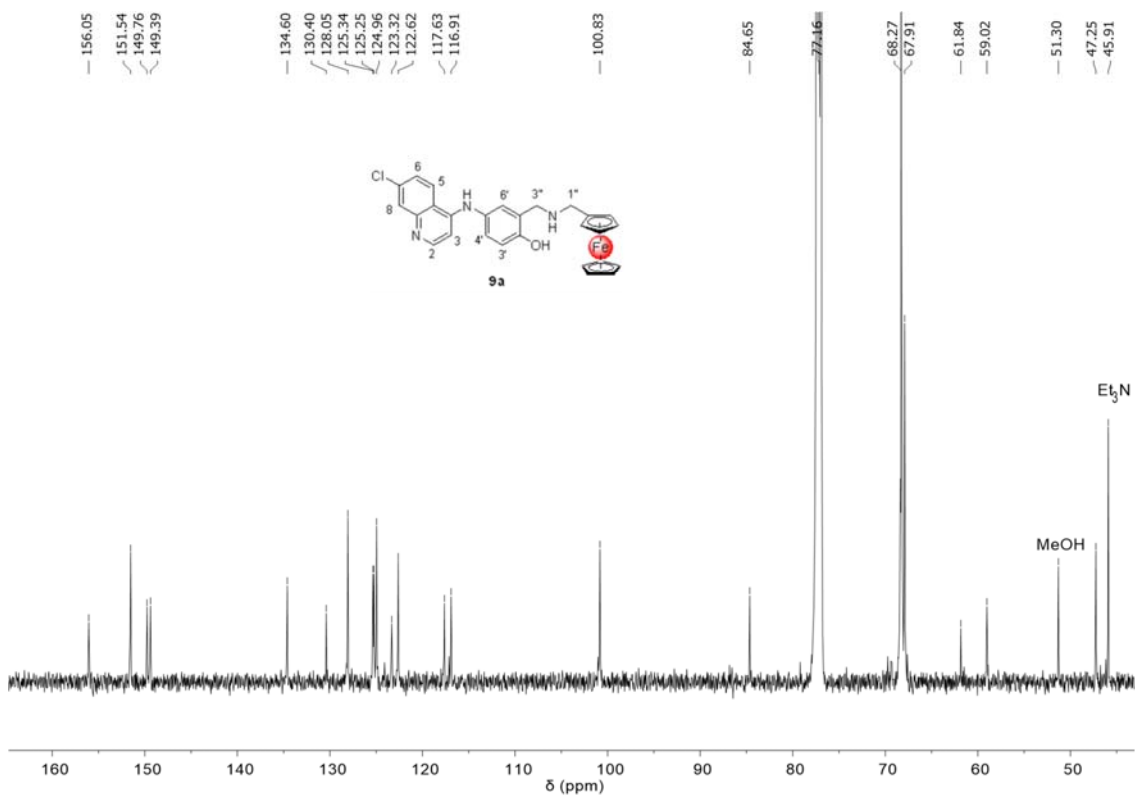
¹H NMR spectrum of **8**



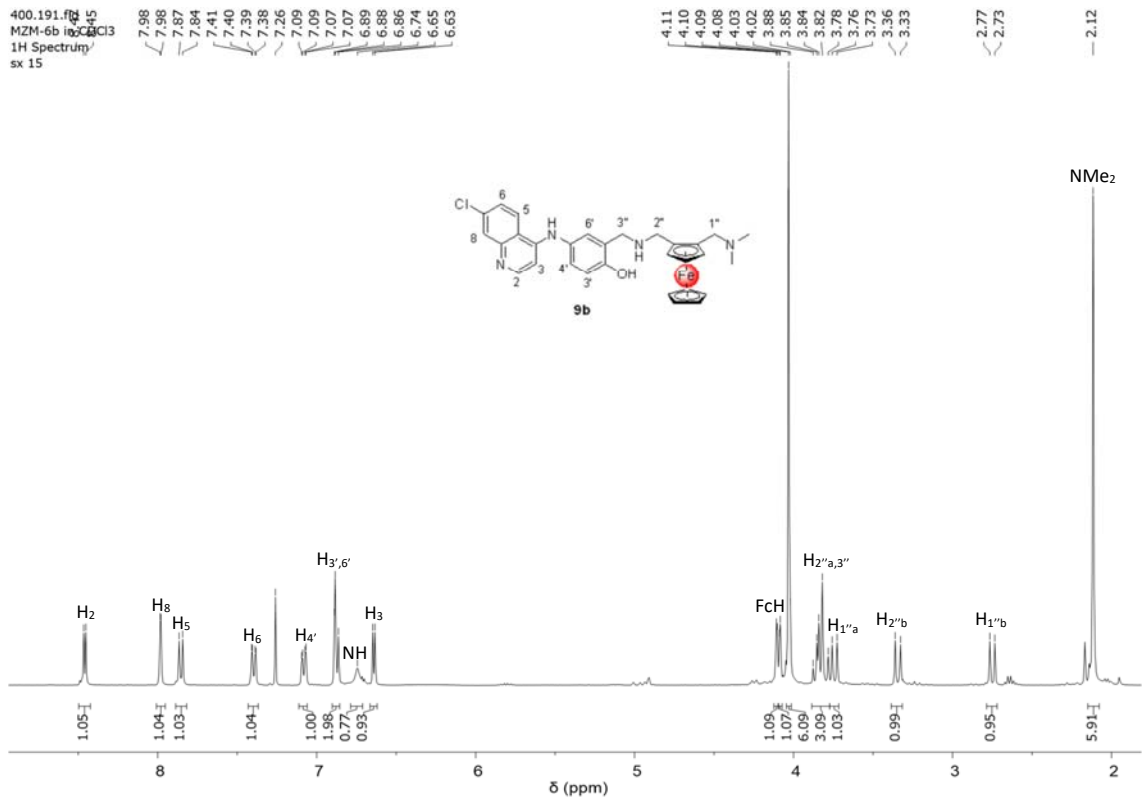
¹H NMR spectrum of **9a**



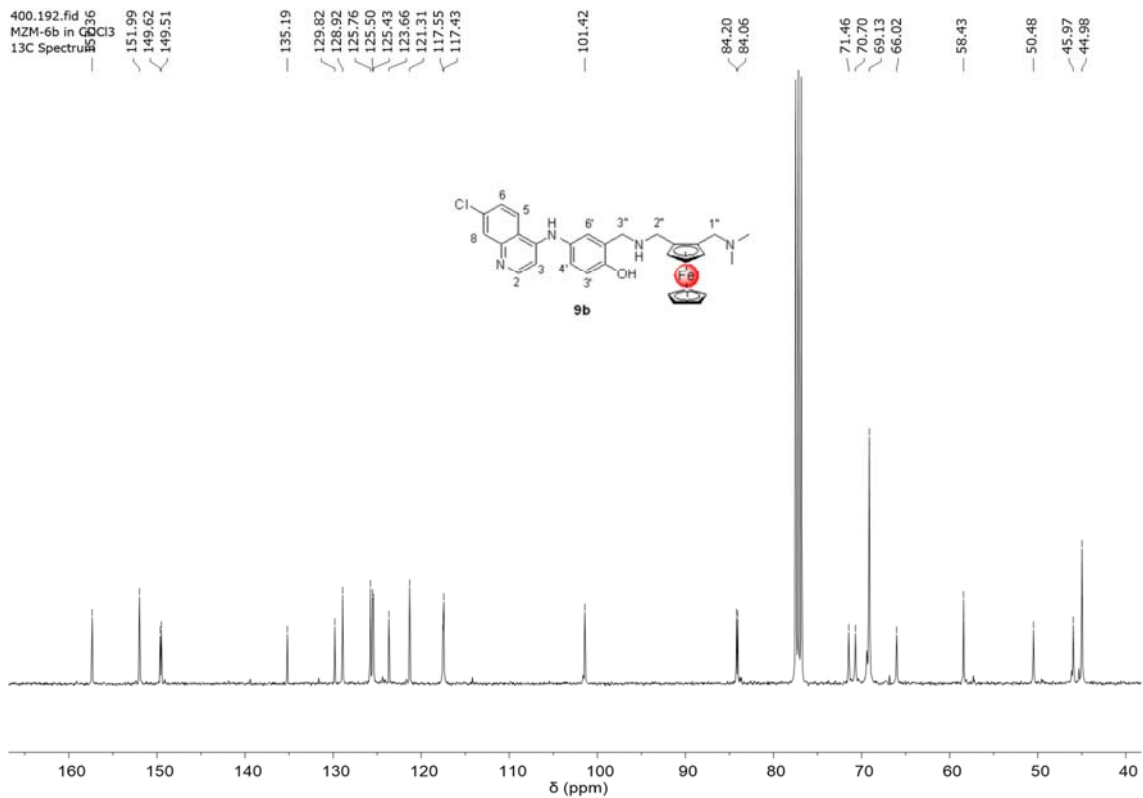
¹³C NMR spectrum of **9a**



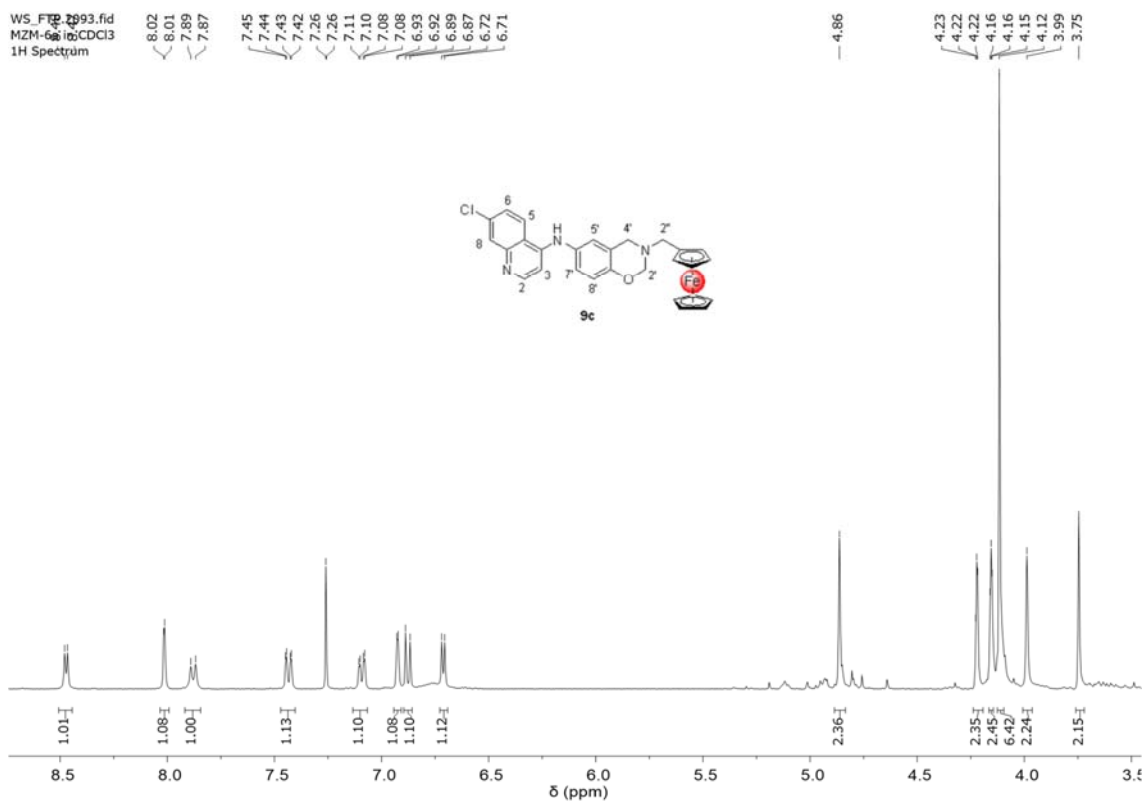
¹H NMR spectrum of **9b**



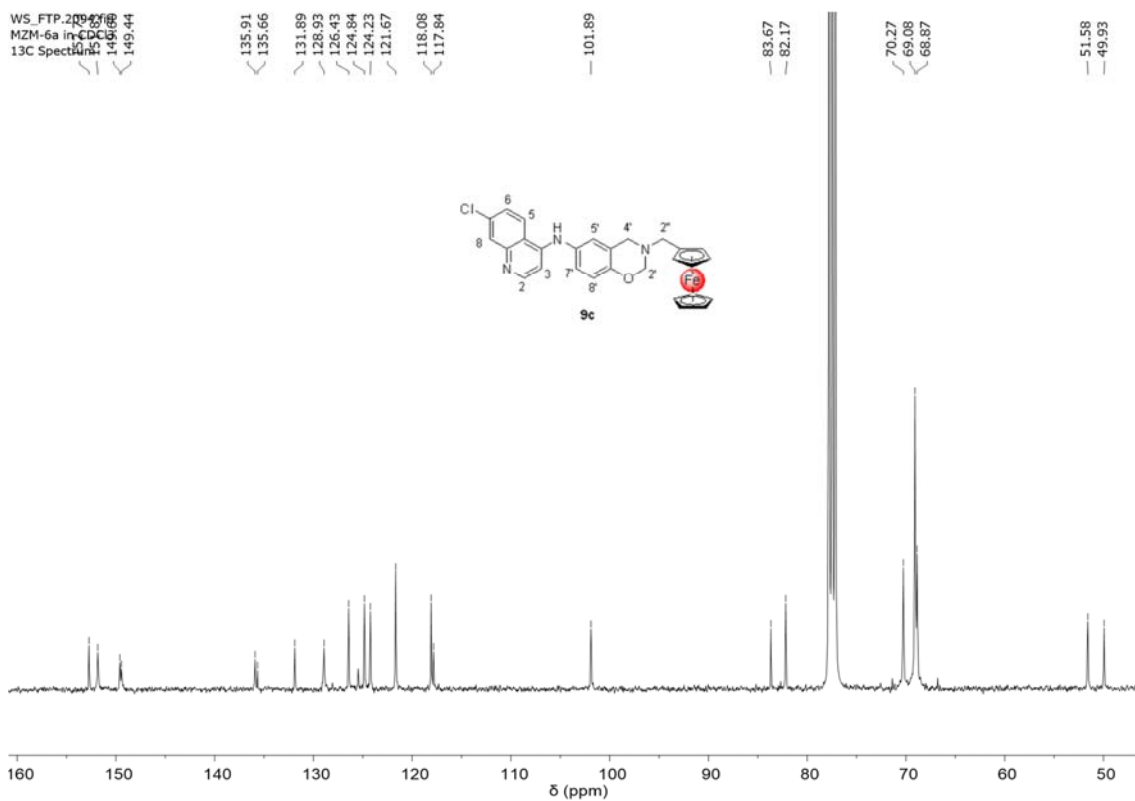
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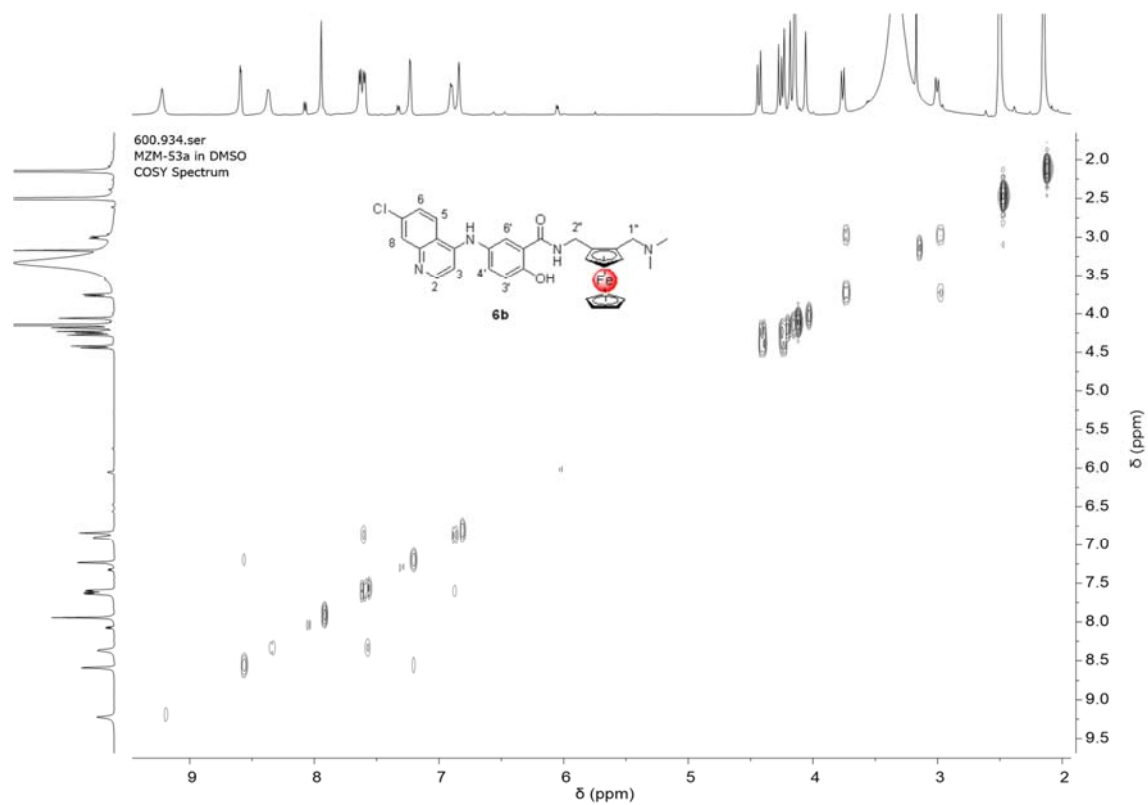
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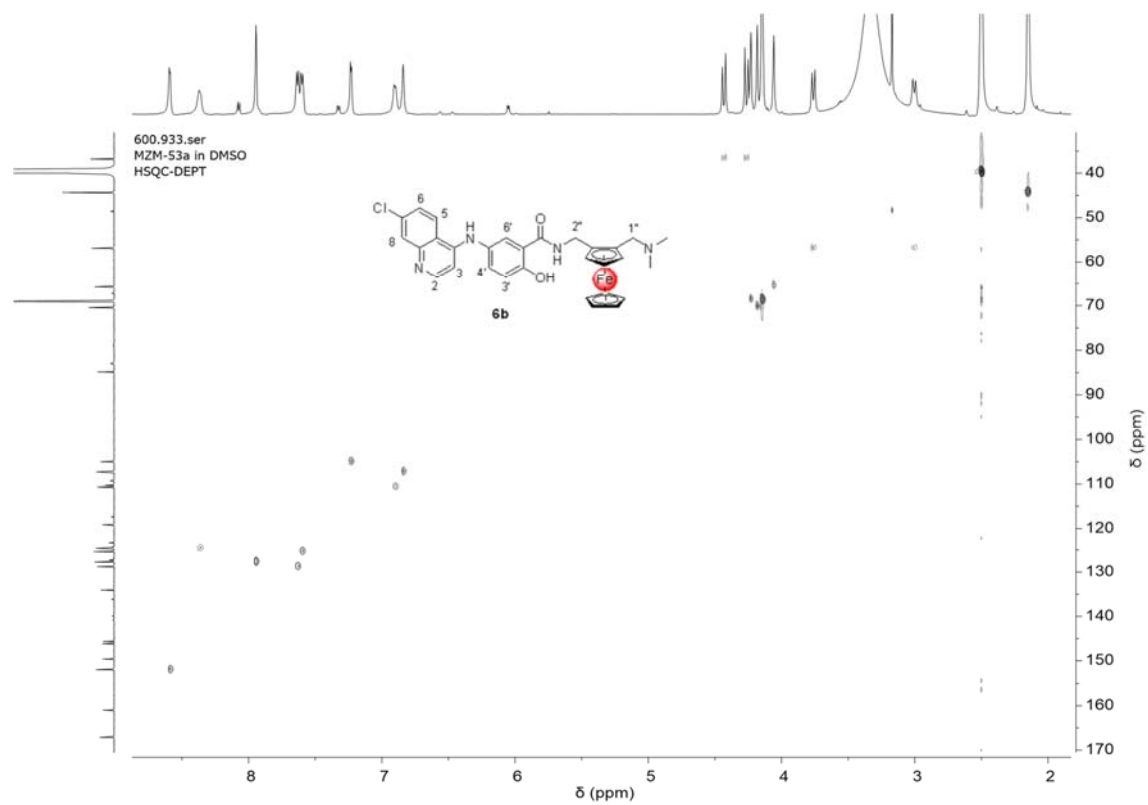
¹³C NMR spectrum of **9c**



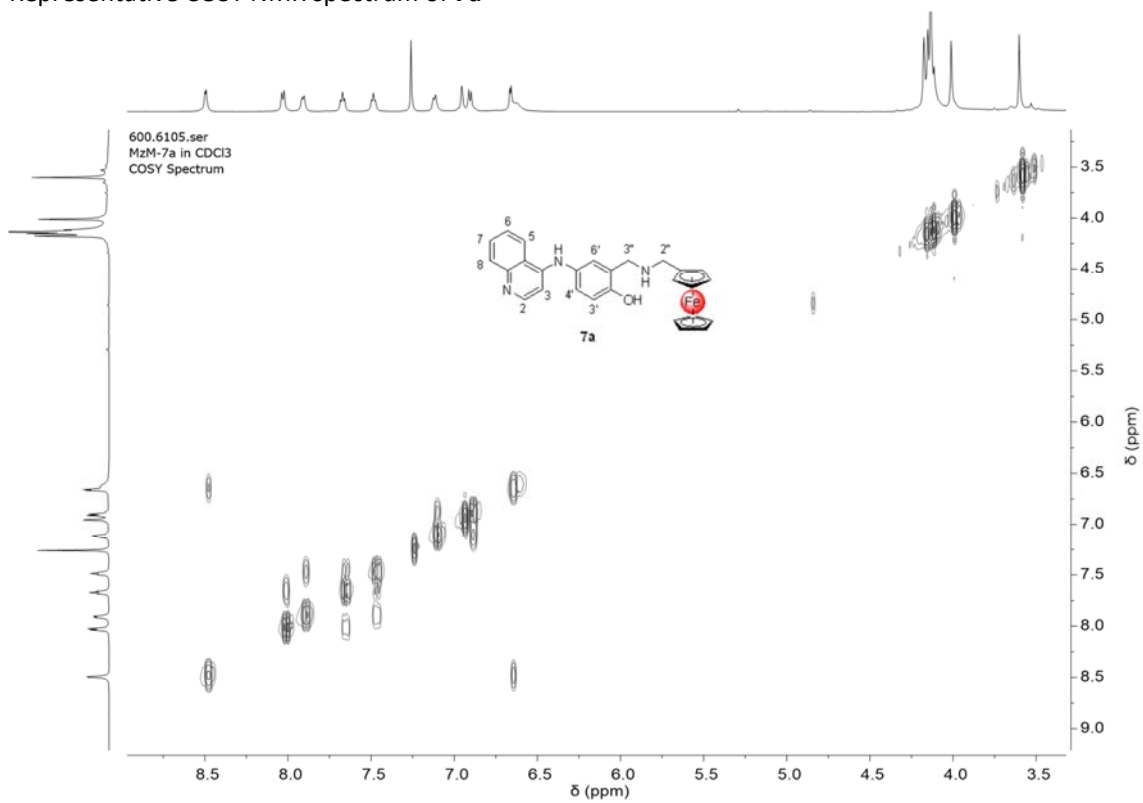
Representative COSY NMR spectrum of **6b**



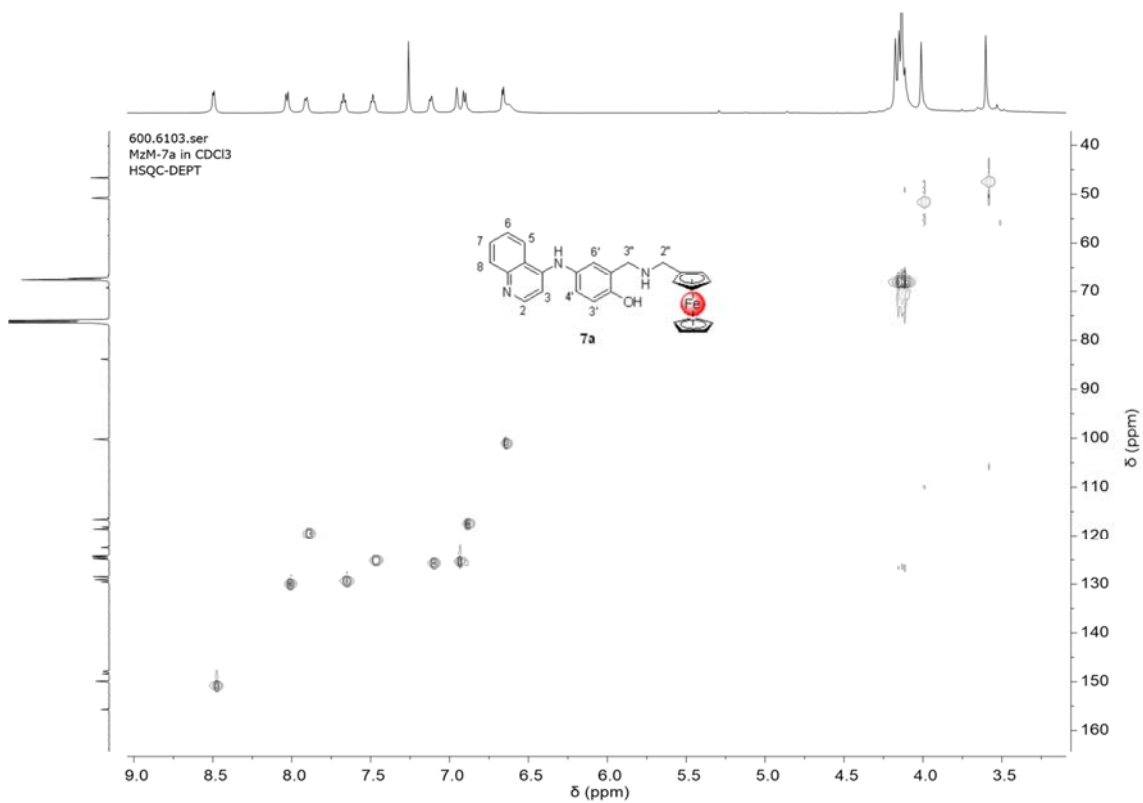
Representative HSQC NMR spectrum of **6b**



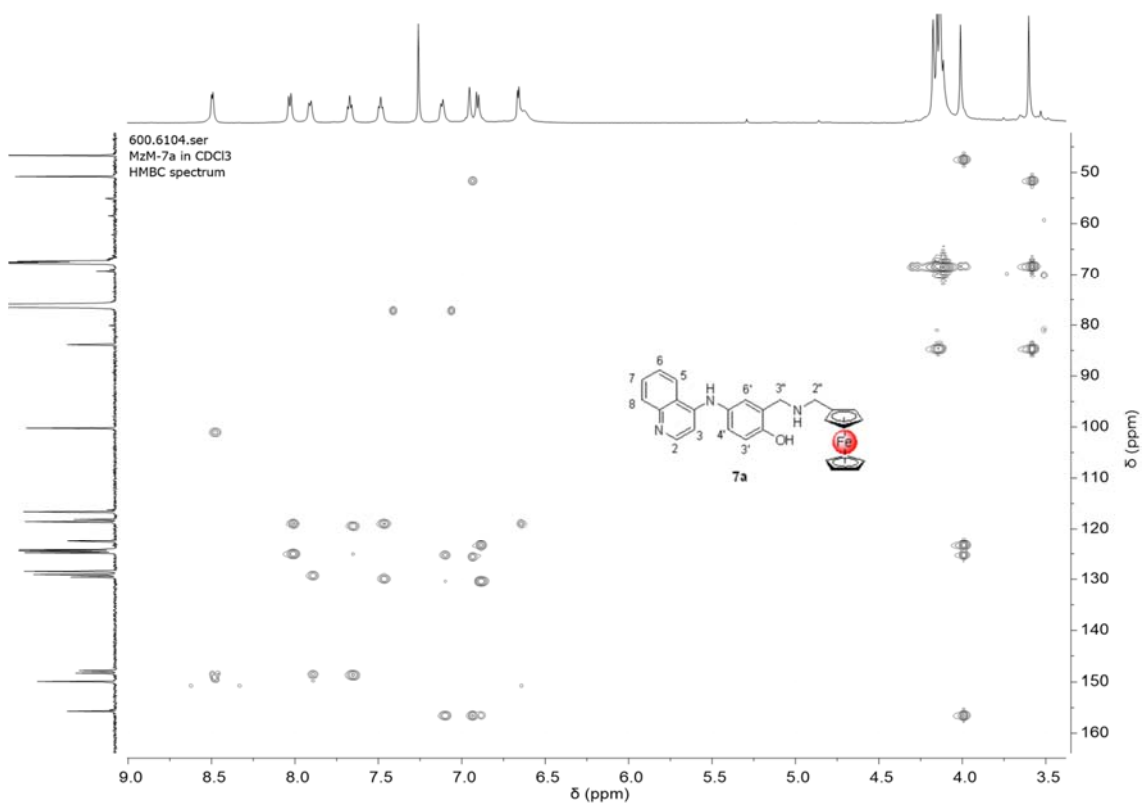
Representative COSY NMR spectrum of **7a**



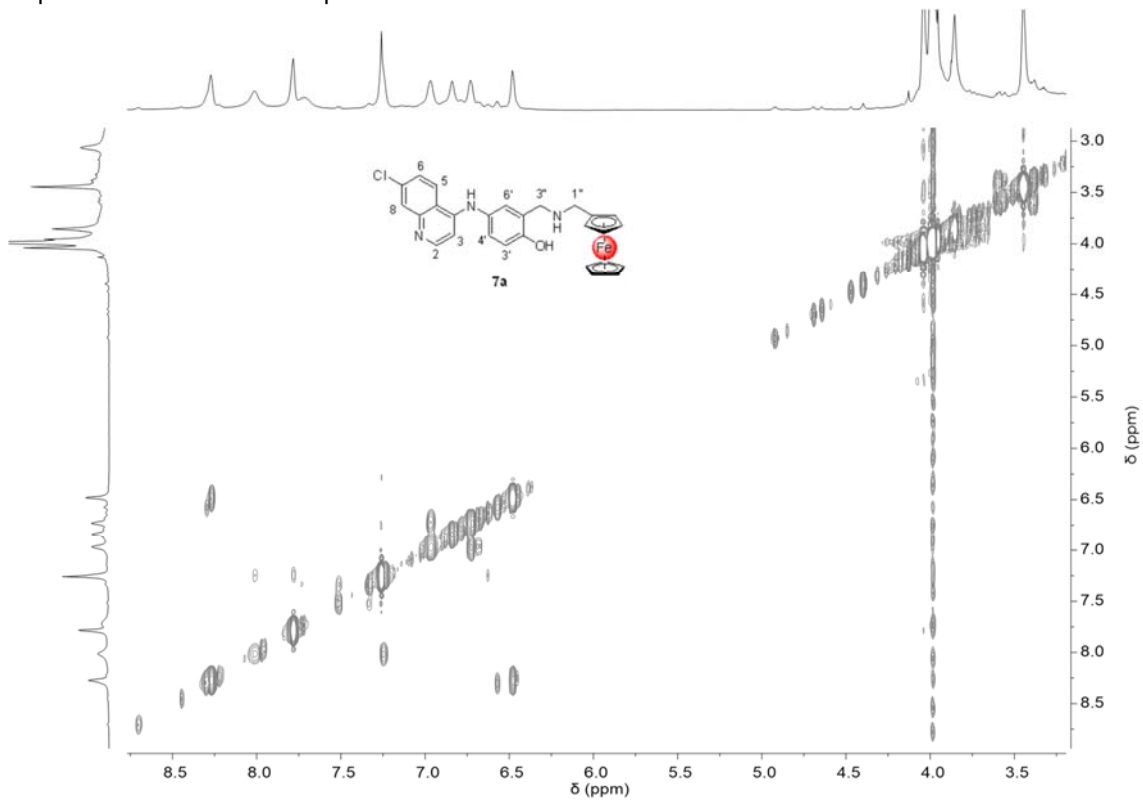
Representative HSQC spectrum of **7a**



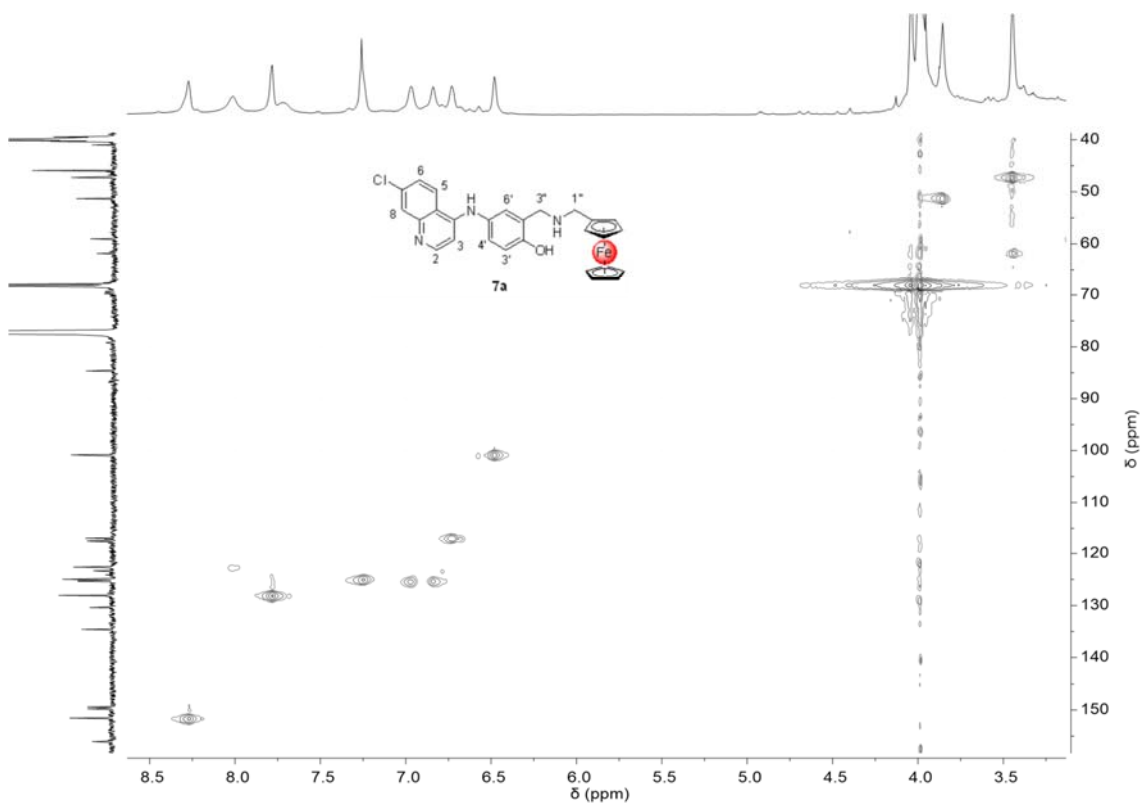
Representative HMBC spectrum of **7a**



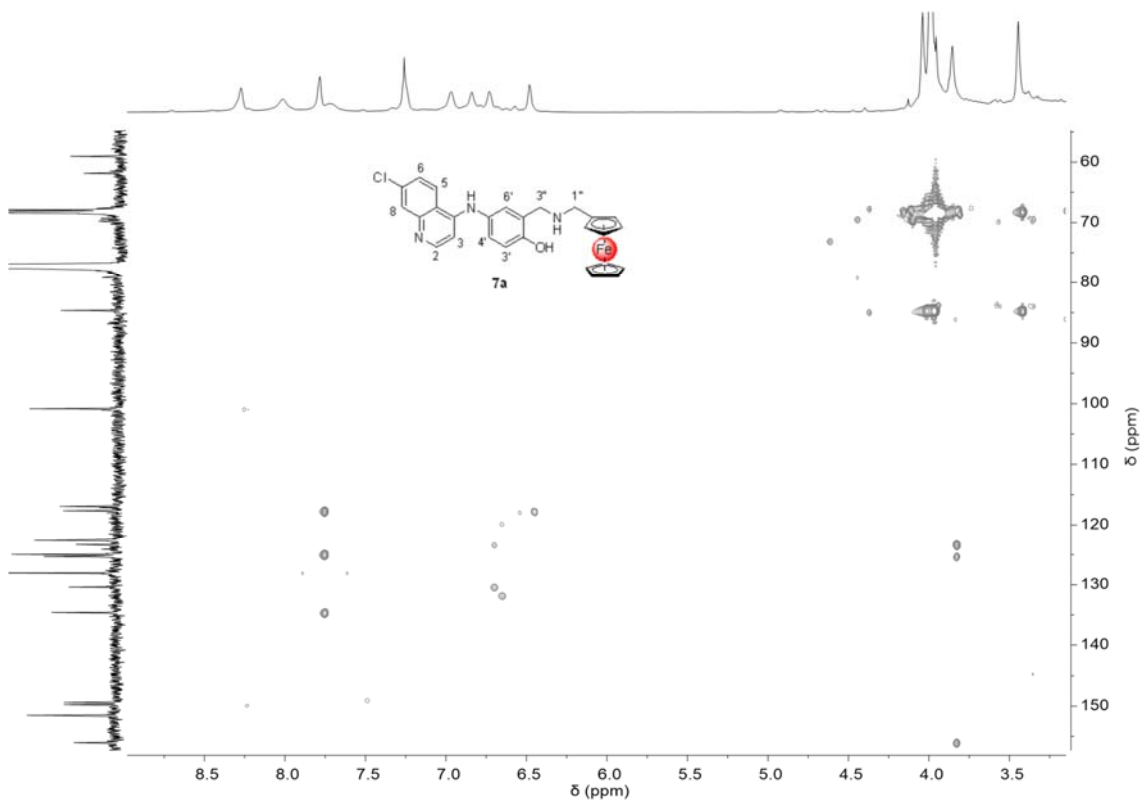
Representative COSY NMR spectrum of **7a**



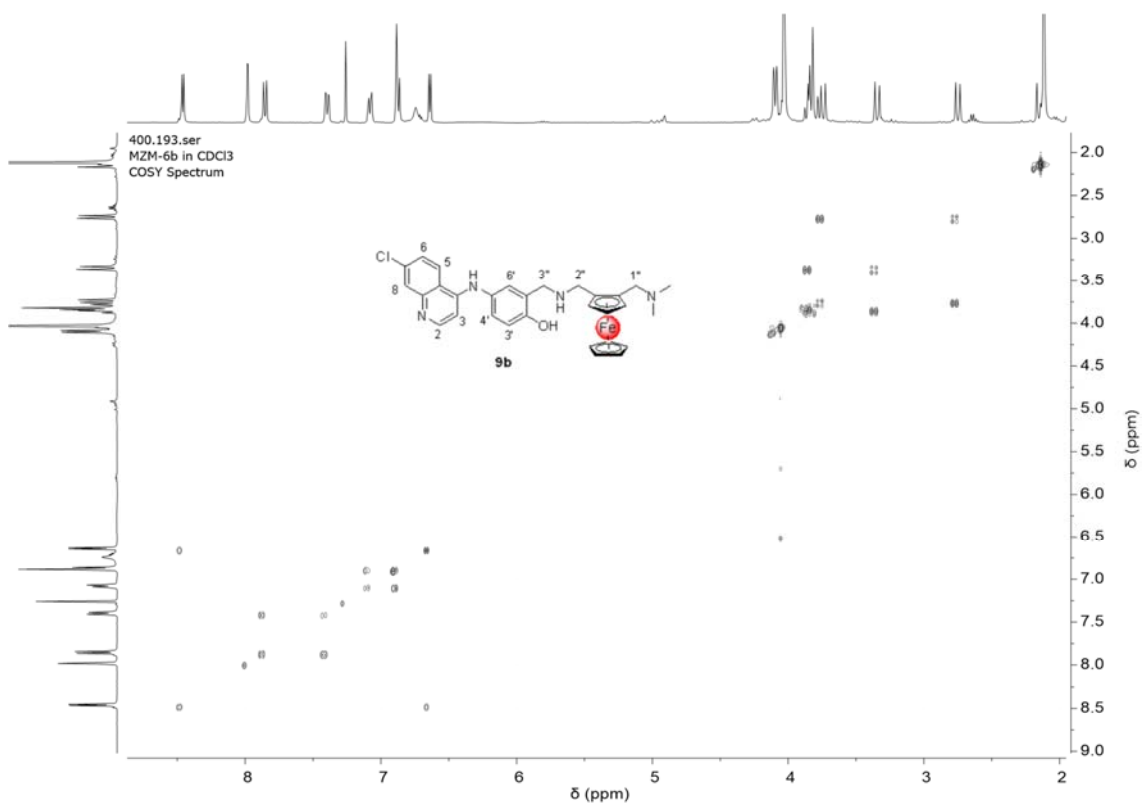
Representative HSQC spectrum of **7a**



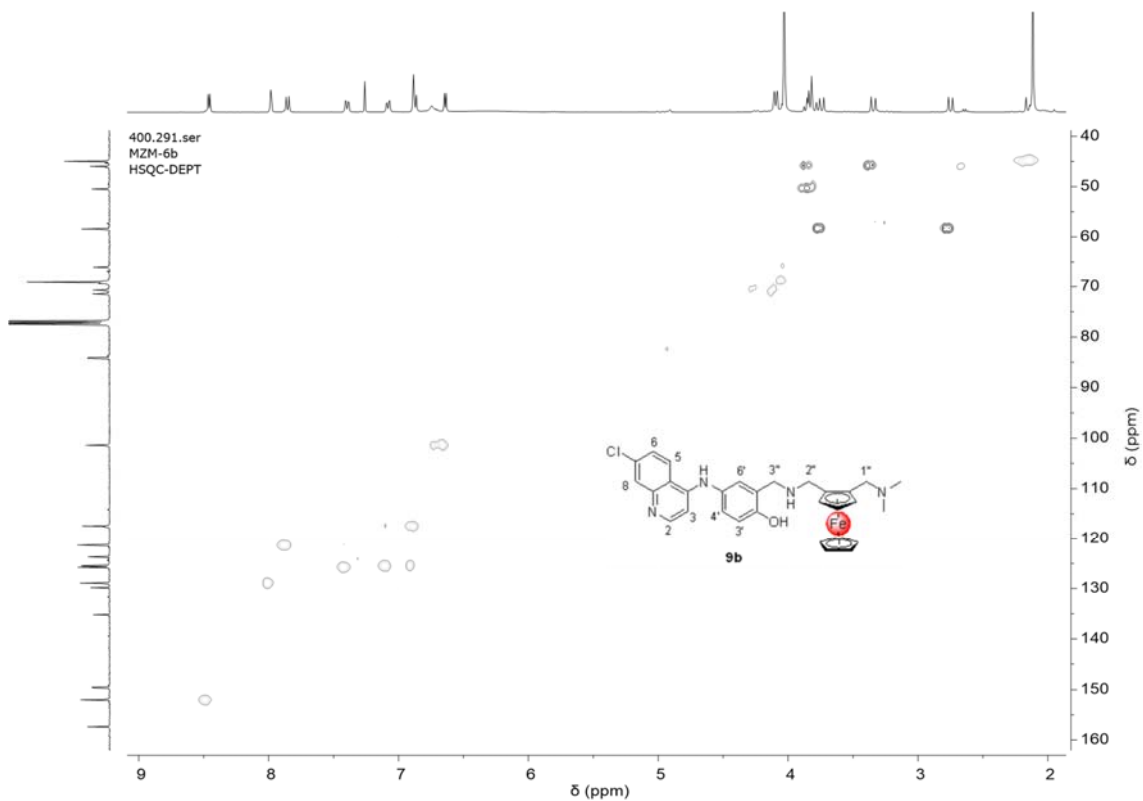
Representative HMBC spectrum of **7a**



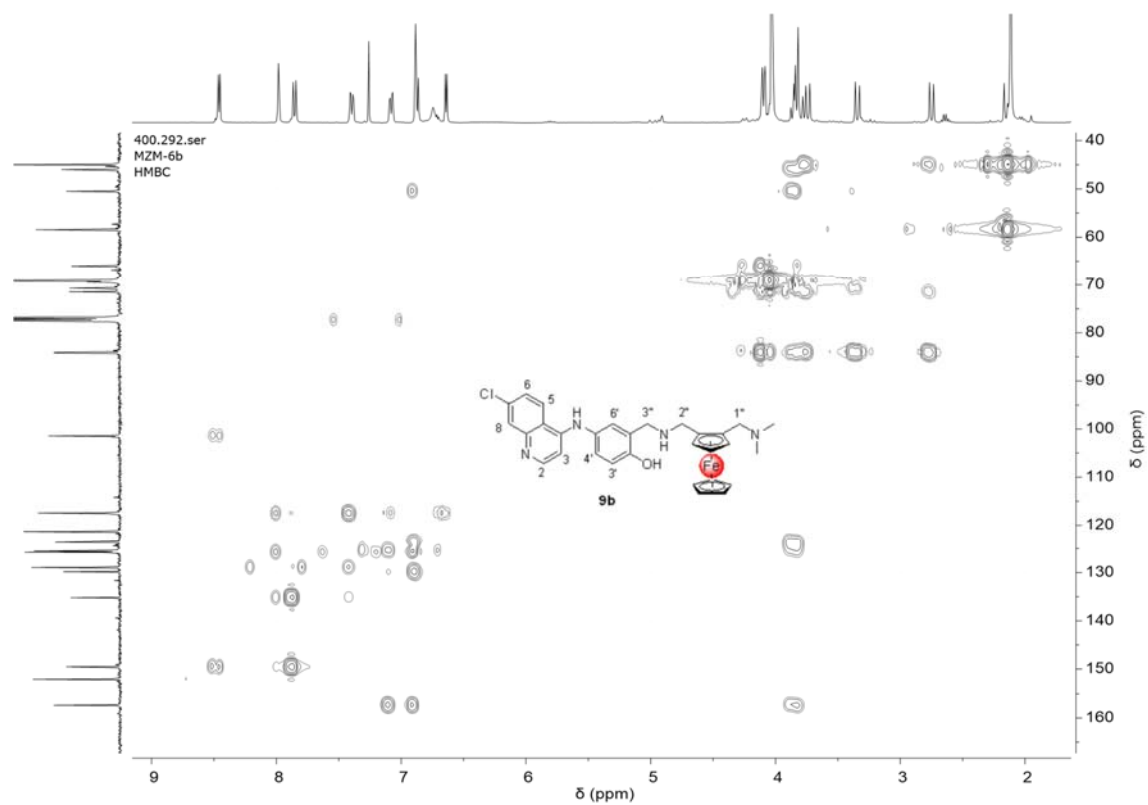
Representative COSY NMR spectrum of **9b**



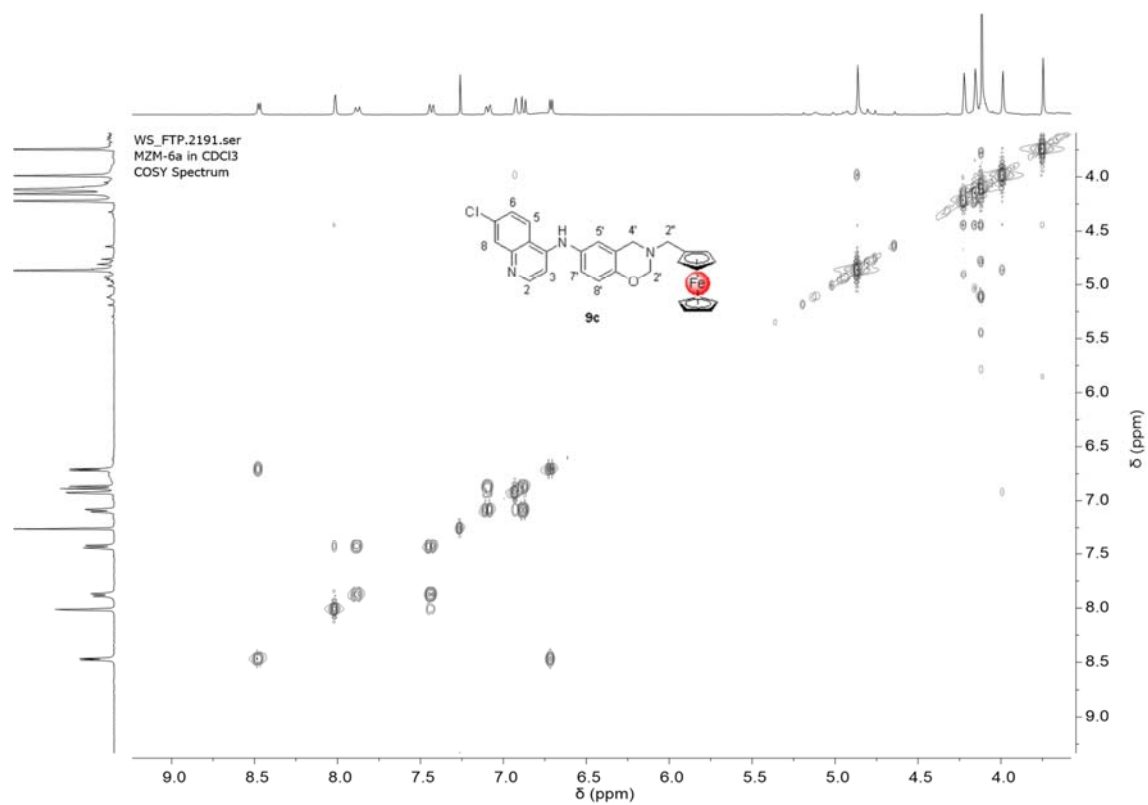
Representative HSQC NMR spectrum of **9b**



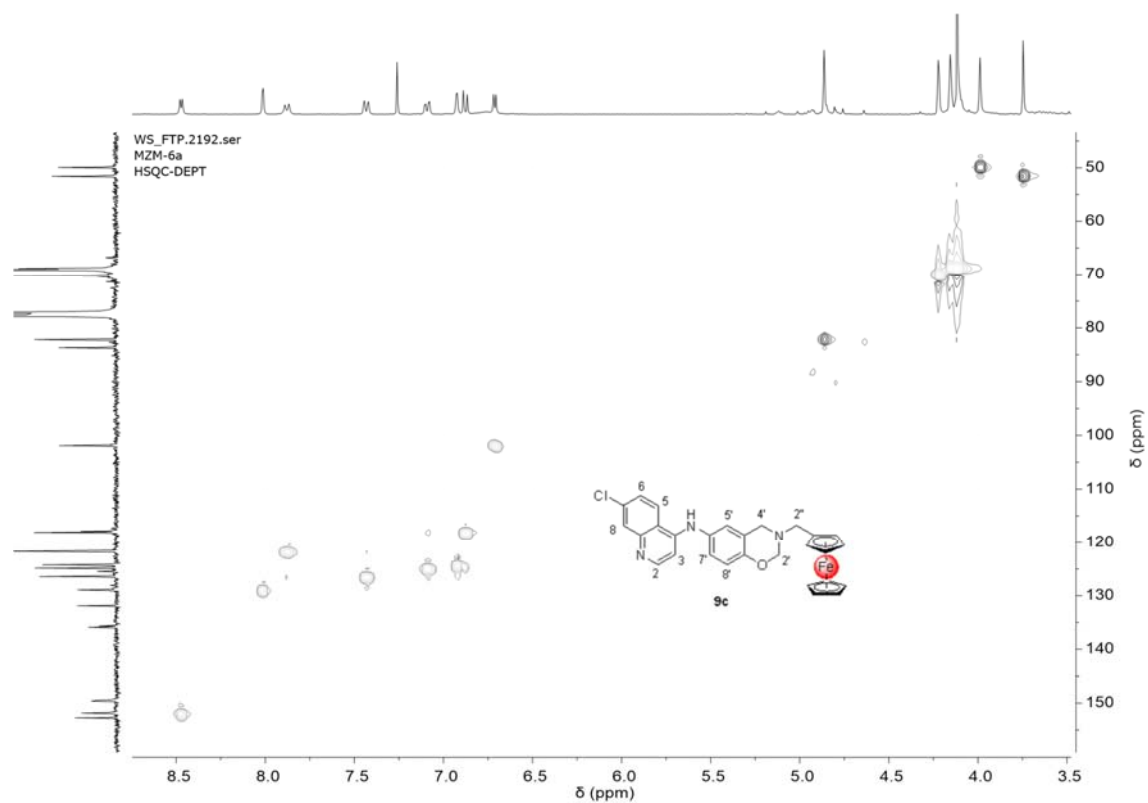
Representative HMBC spectrum of **9b**



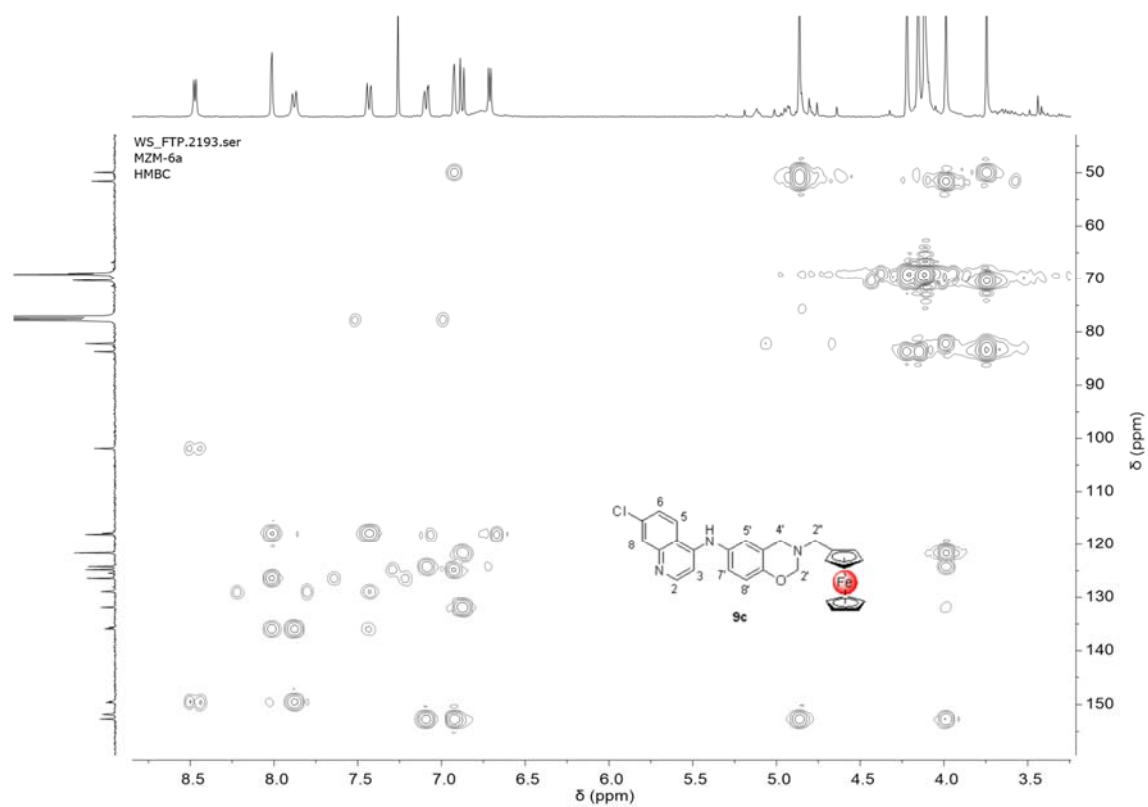
Representative COSY NMR spectrum of **9c**



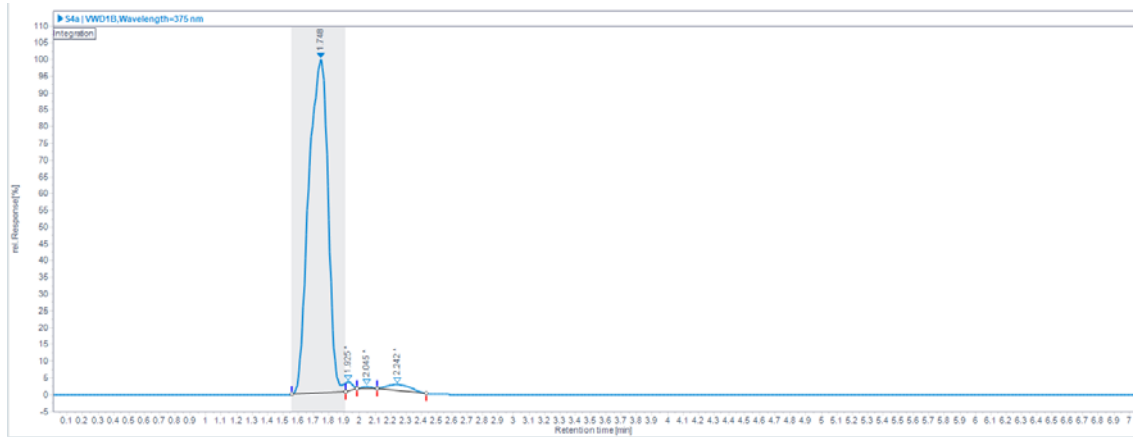
Representative HSQC spectrum of **9c**



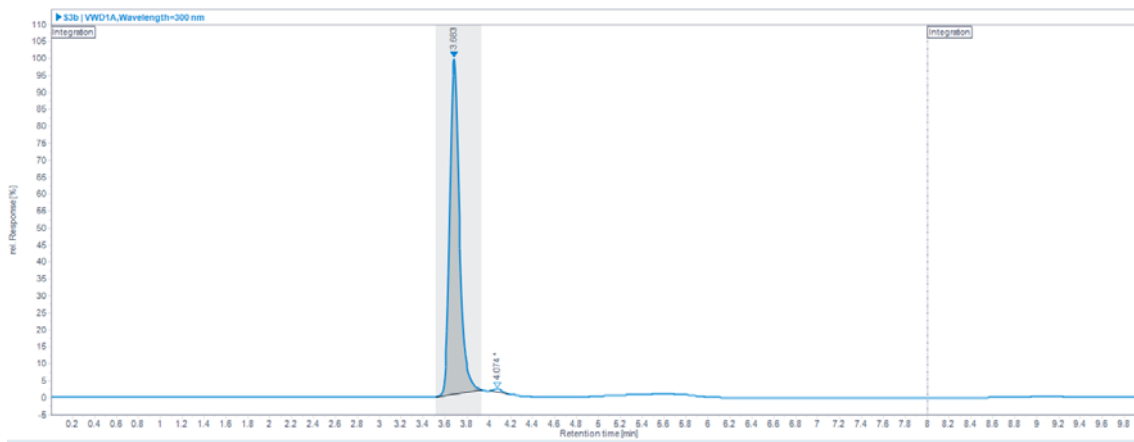
Representative HMBC spectrum of **9c**



HPLC trace of 6a



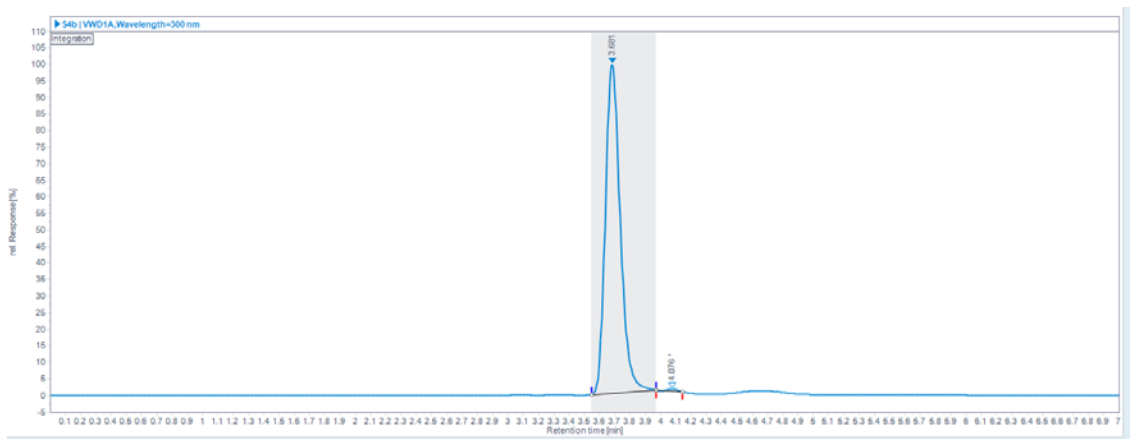
HPLC trace of 6b



Injection Results

PK#	Summary	RT (min)	Area	Area%	Height	Concentration	S/N	Tailing
1	VWD1A,Wavelength=300 nm	3.683	10400.824	99.167	1676.551			
2	VWD1A,Wavelength=300 nm	4.074	87.410	0.833	16.964			

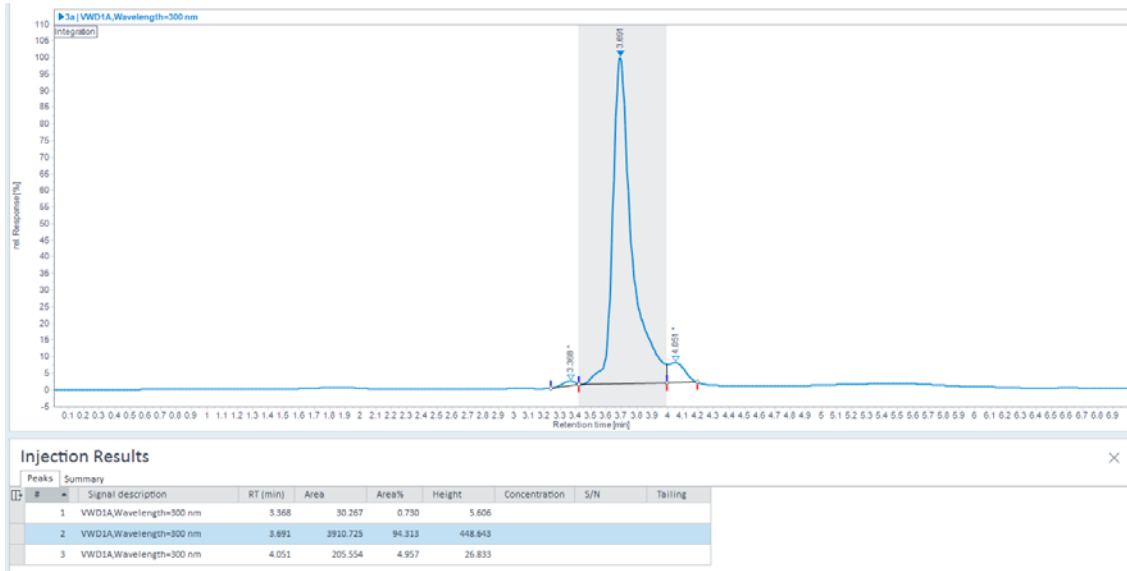
HPLC trace of 6c



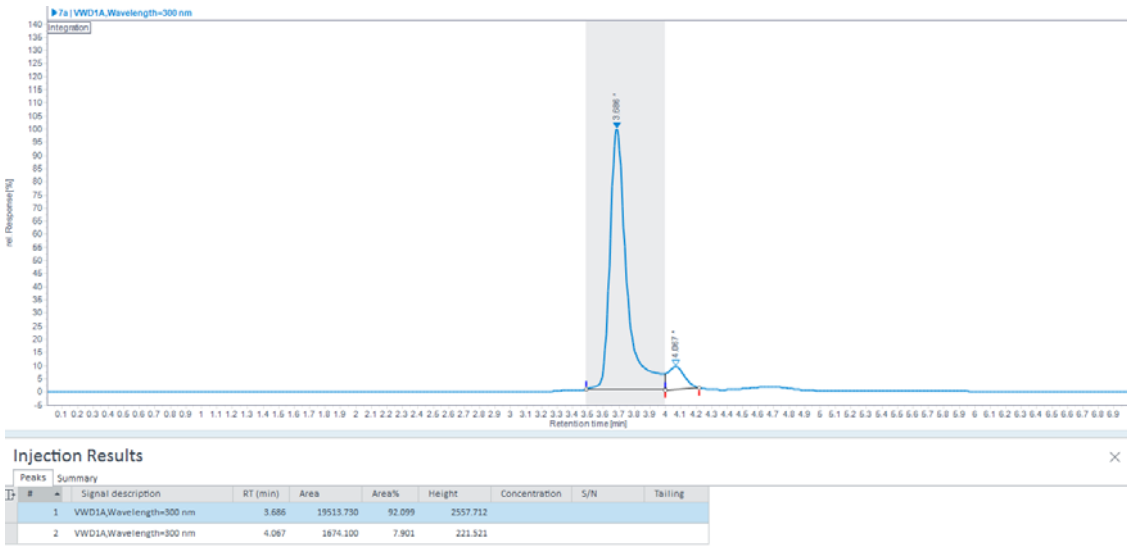
Injection Results

PK#	Summary	RT (min)	Area	Area%	Height	Concentration	S/N	Tailing
1	VWD1A,Wavelength=300 nm	3.881	18819.561	99.606	2477.335			
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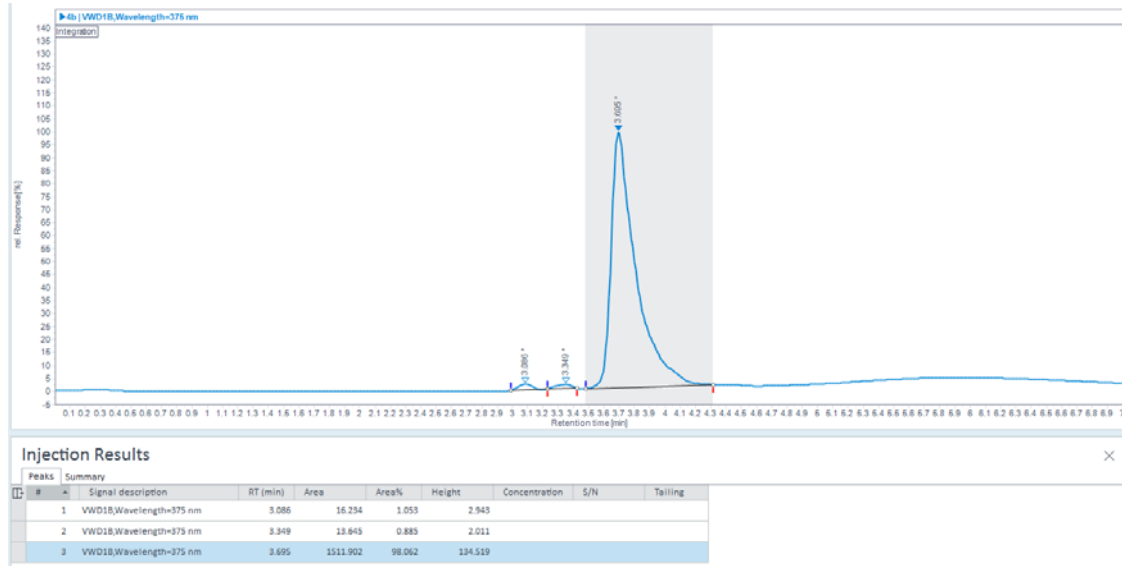
HPLC trace of 7a



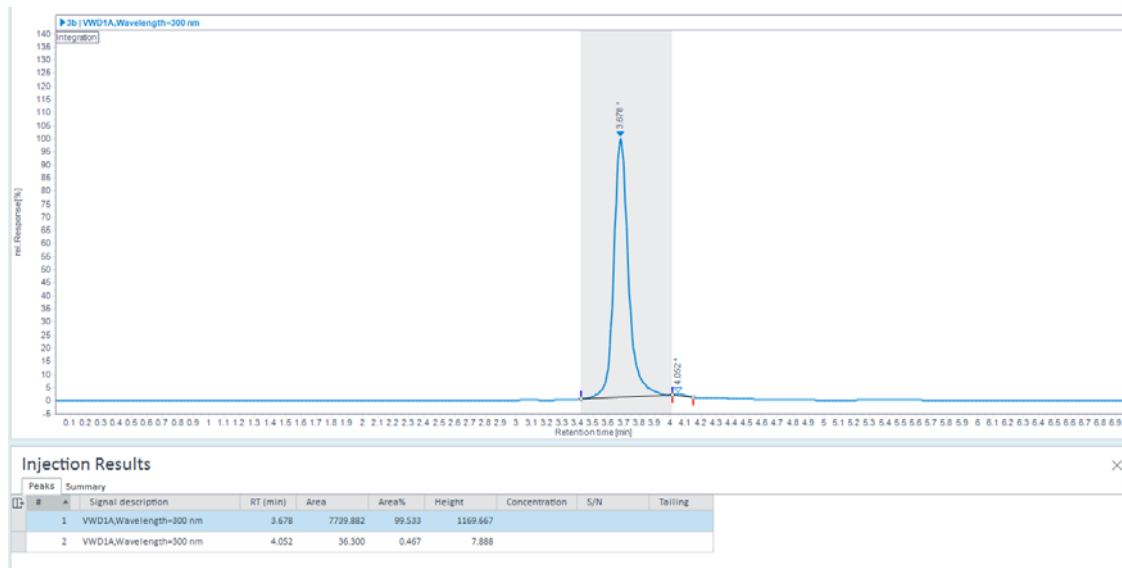
HPLC trace of 7b



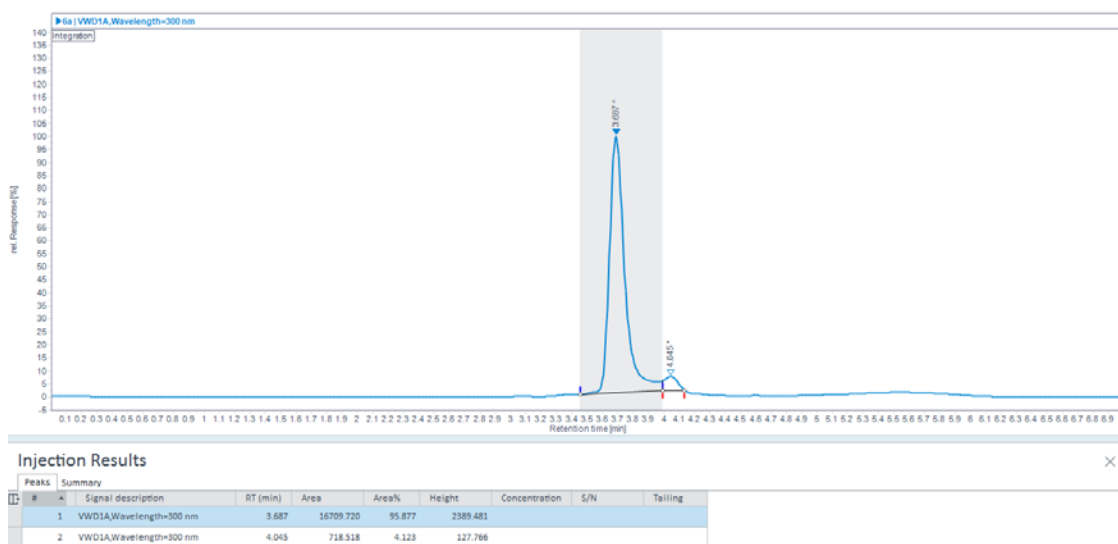
HPLC trace of **7c**



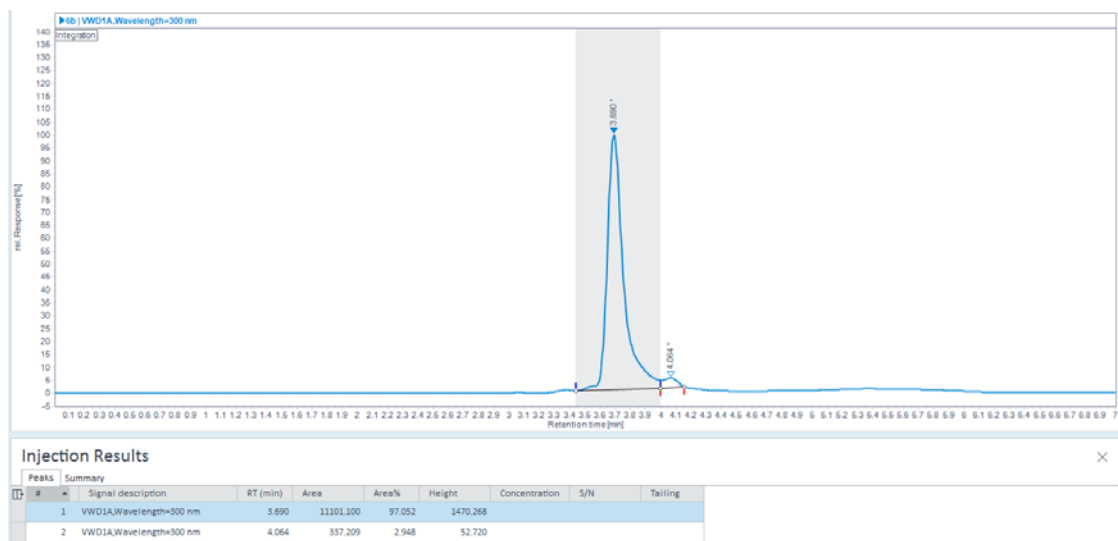
HPLC trace of **7d**



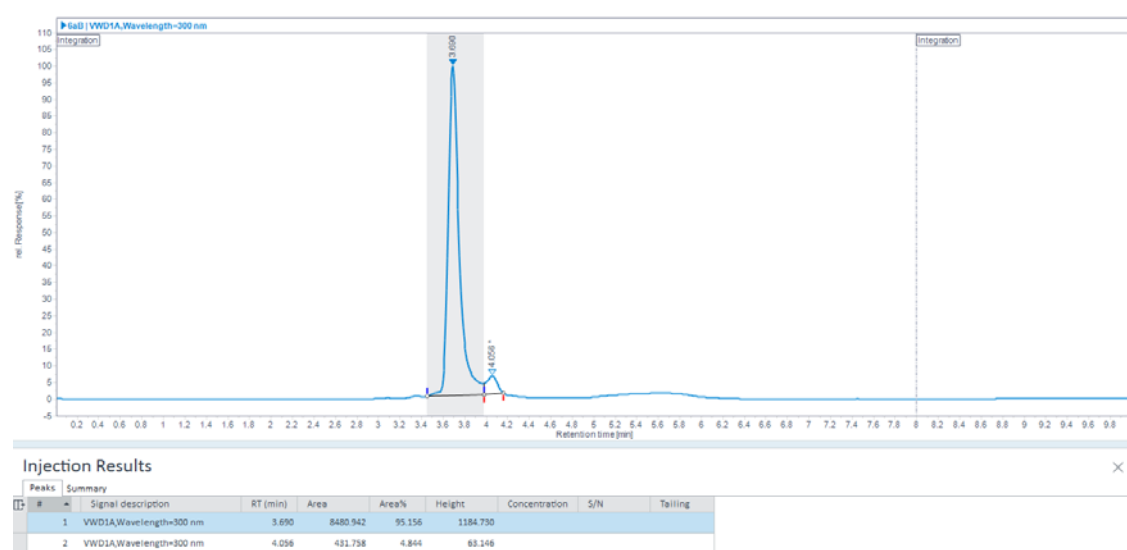
HPLC trace of 9a



HPLC trace of 9b



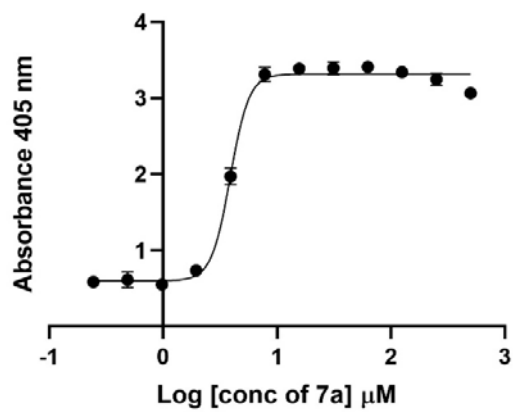
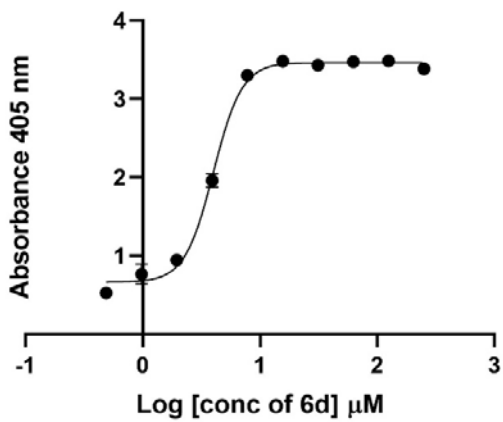
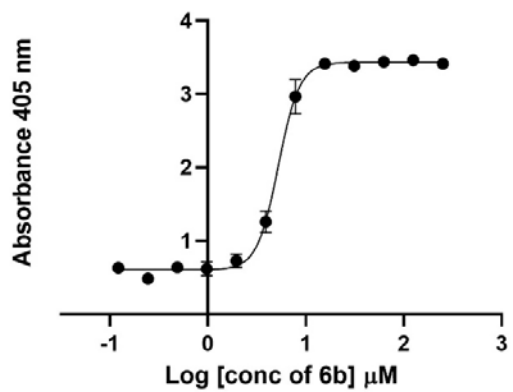
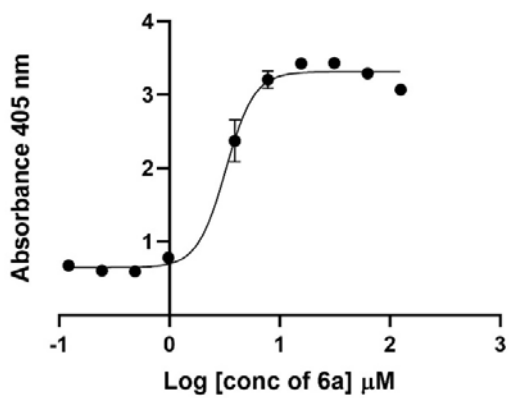
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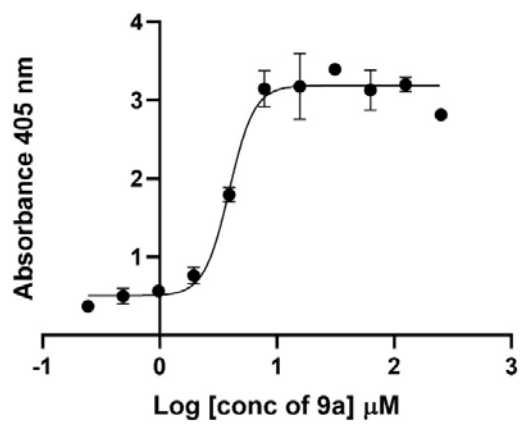
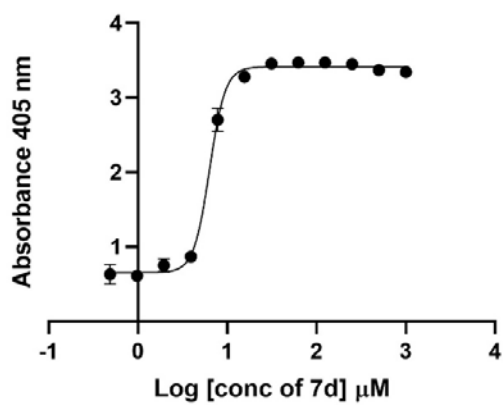
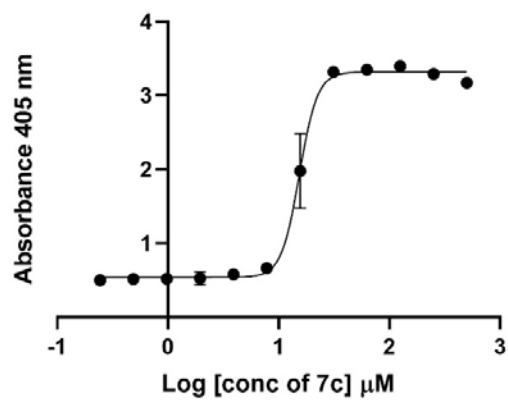
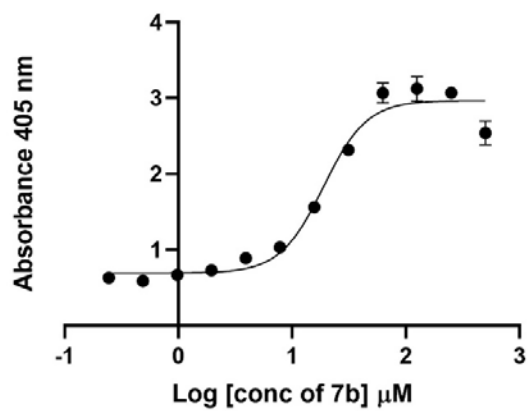
Injection Results

Peak #	Signal description	RT (min)	Area	Area%	Height	Concentration	S/N	Tailing
1	VWD1A.Wavelength=300 nm	3.690	8480.942	95.156	1184.730			
2	VWD1A.Wavelength=300 nm	4.096	431.758	4.844	63.246			

Representative graphs for β -hematin inhibition



Representative graphs for β -hematin inhibition



Representative graphs for β -hematin inhibition

