Synthesis and evaluation of biological properties of ferrocenyl-podophyllotoxin conjugates

Anna Wieczorek[a], Andrzej Błauż[b], Anna Makal[c], Błażej Rychlik*[b], Damian Plażuk*[a]

[a] *Department of Organic Chemistry, Faculty of Chemistry, University of Łódź, Tamka 12, 91-403 Łódź, Poland. Fax: (+48)42 6786583; Tel: (+48)42 6355760;*

[b] *Cytometry Lab, Department of Molecular Biophysics, Faculty of Biology and Environmental Protection, University of Łódź, 141/143 Pomorska St. 90-236 Łódź, Poland*

[c] *University of Warsaw, Biological and Chemical, Research Centre, ul. Żwirki i Wigury 101, 02-096 Warsaw, Poland*

*Corresponding authors: *e-mail: damplaz@uni.lodz.pl (D.P.), * brychlik@biol.uni.lodz.pl (B.R.)*

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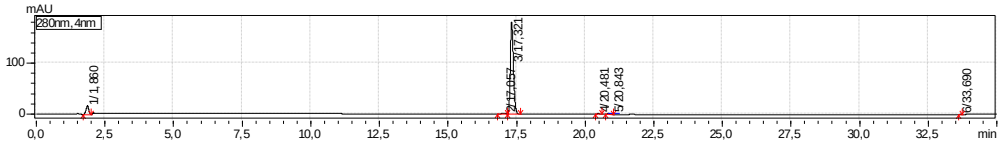
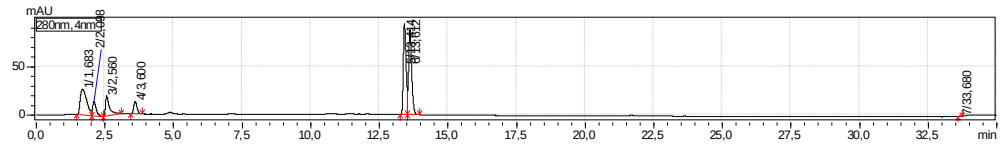
a)

HPLC chromatogram of Oregon-Green diacetate – reference



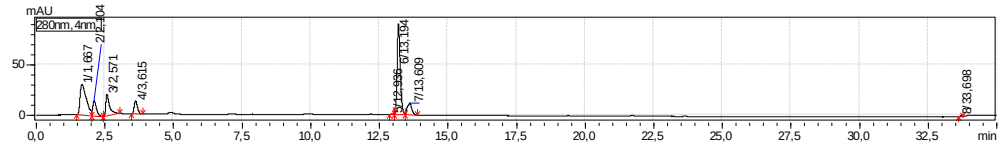
b)

HPLC chromatogram of Oregon-Green diacetate – after 1h – complete hydrolysis



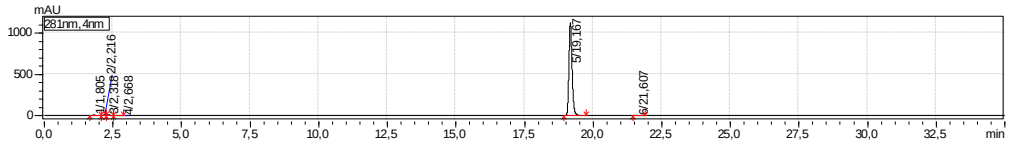
c)

HPLC chromatogram of PPT – reference



d)

HPLC chromatogram of **17** – reference



e)

HPLC chromatogram of **17** – after 2h

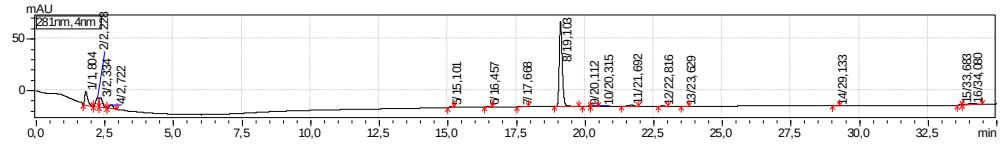


Figure S1. HPLC chromatograms: a) Oregon Green diacetate (positive standard); b) Oregon Green diacetate (positive standard) after 2h; c) podophyllotoxin (PPT); d) compound **17** – control sample; e) compound **17** after 2h

X-ray experimental

A specimen of **33**, approximate dimensions 0.050 mm x 0.100 mm x 0.300 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured were measured on BRUKER KAPPA APEX-II Ultra diffractometer, with molybdenum rotating anode as X-ray source and multi-layer focusing mirrors. The total exposure time was 6.59 hours. The data were collected with Bruker APEX-II software[1], integrated using, and were corrected for absorption effects using the multi-scan method (SADABS[7]).

The integration of the data with the Bruker SAINT software package[2], using a triclinic unit cell and a narrow-frame algorithm, yielded a total of 103731 reflections to a maximum θ angle of 33.62° (0.64 Å resolution), of which 18596 were independent (average redundancy 5.578, completeness = 99.7%, R_{int} = 3.60%) and 17703 (95.20%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.0851(5) Å, b = 10.8685(5) Å, c = 15.5678(8) Å, α = 91.650(2)°, β = 92.190(2)°, γ = 111.5072(19)°, volume = 1584.73(16) $Å^3$, are based upon the refinement of the XYZ-centroids of 9893 reflections above 20 σ(I) with 4.347° < 2θ < 64.32°. Data were corrected for absorption effects using the multi-scan method (SADABS[3]). The ratio of minimum to maximum apparent transmission was 0.928. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9424 and 1.0000.

The structure was solved by direct methods using SXELXS[4] and refined by full-matrix least squares procedure with SHELXL[4] within OLEX2[5] graphical interface. Figures were produced with Ortep3v2[6] and Mercury_3.5[7] software. Flack parameter was estimated using [(I+)-(I-)]/[(I+)+(I-)] quotients[8].

All H atoms were visible in the residual density map, but were added geometrically and refined in riding approximation. No strong H-bonds, requiring more specific H atom treatment, were present in the analyzed crystal structure.

Detailed information about the data processing, structure solution and refinement is presented in Table S1.

Table S1.

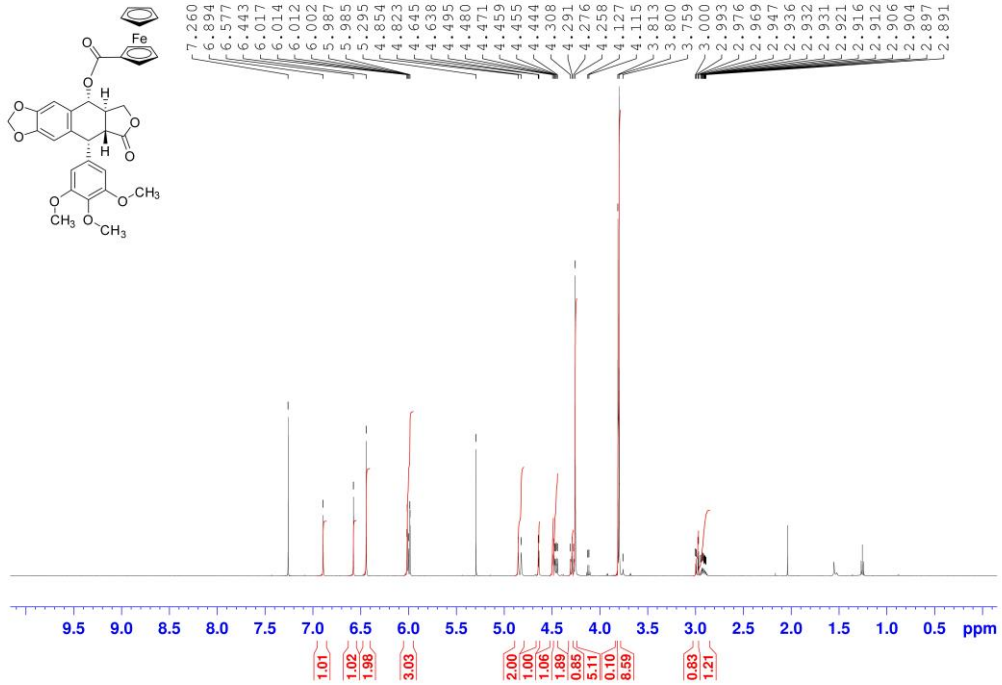
Identification code	**33**	
Chemical formula	$C_{34}H_{31}FeN_3O_7$, CH_2Cl_2	
Formula weight	734.39	
Wavelength	0.71073 Å	
Crystal size	0.050 x 0.100 x 0.300 mm	
Crystal system	triclinic	
Unit cell dimensions	a = 10.0851(5) Å	α = 91.650(2)°
	b = 10.8685(5) Å	β = 92.190(2)°
	c = 15.5678(8) Å	γ = 111.507(3)°
Volume	1584.73(16) $Å^3$	
Z	2	
Density (calculated)	1.539 g/cm^3	
Absorption coefficient	0.701 mm^{-1}	

F(000)	760

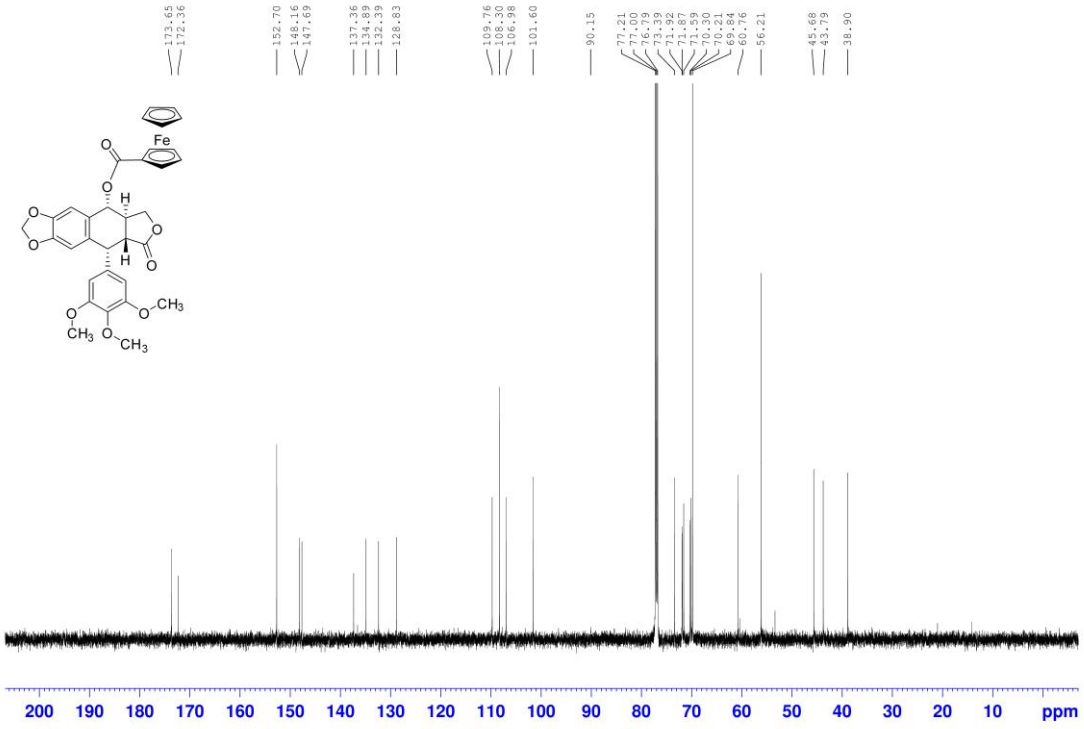
Theta range for data collection	1.31 to 33.62°
Index ranges	-14<=h<=14, -15<=k<=15, -21<=l<=21
Reflections collected	103731
Independent reflections	18596 [R(int) = 0.0360]
Coverage of independent reflections	99.6%
Absorption correction	multi-scan
Max. and min. transmission	1.0000 and 0.9424
Structure solution technique	direct methods
Structure solution program	SHELXS, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	18596 / 3 / 871
Goodness-of-fit on F^2	1.036
Δ/σ_{max}	0.001
Final R indices	17703 data; I>2σ(I) R1 = 0.0249, wR2 = 0.0614 all data R1 = 0.0272, wR2 = 0.0624
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0369P)^2+(0.0198P)]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.006(0)
Largest diff. peak and hole	0.447 and -0.220 eÅ^{-3}
R.M.S. deviation from mean	0.048 eÅ^{-3}

NMR spectra

^{1}H NMR spectra of **17**



^{13}C{^{1}H} NMR spectra of **17**



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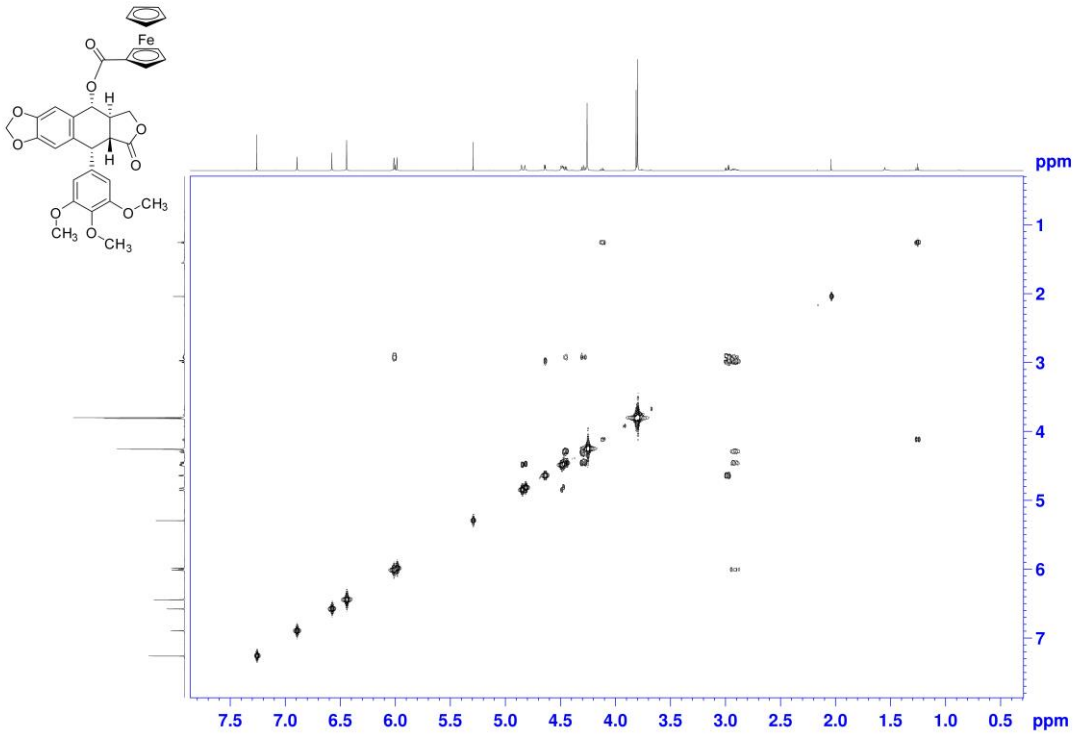
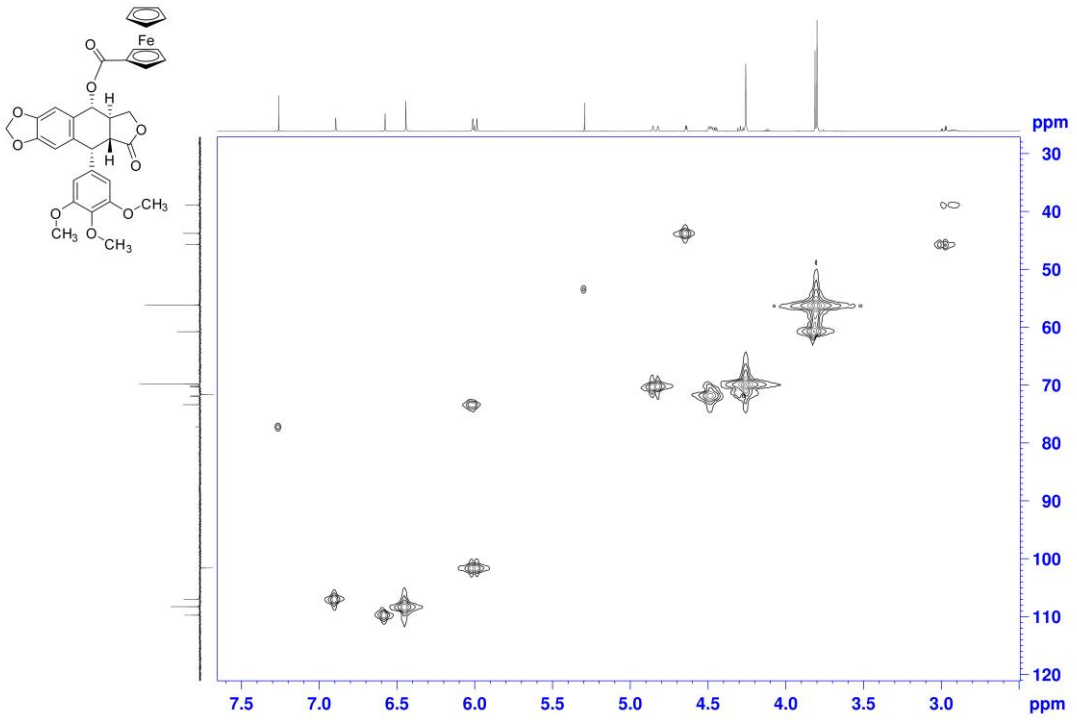


^{1}H-^{13}C HMQC spectra of **17**



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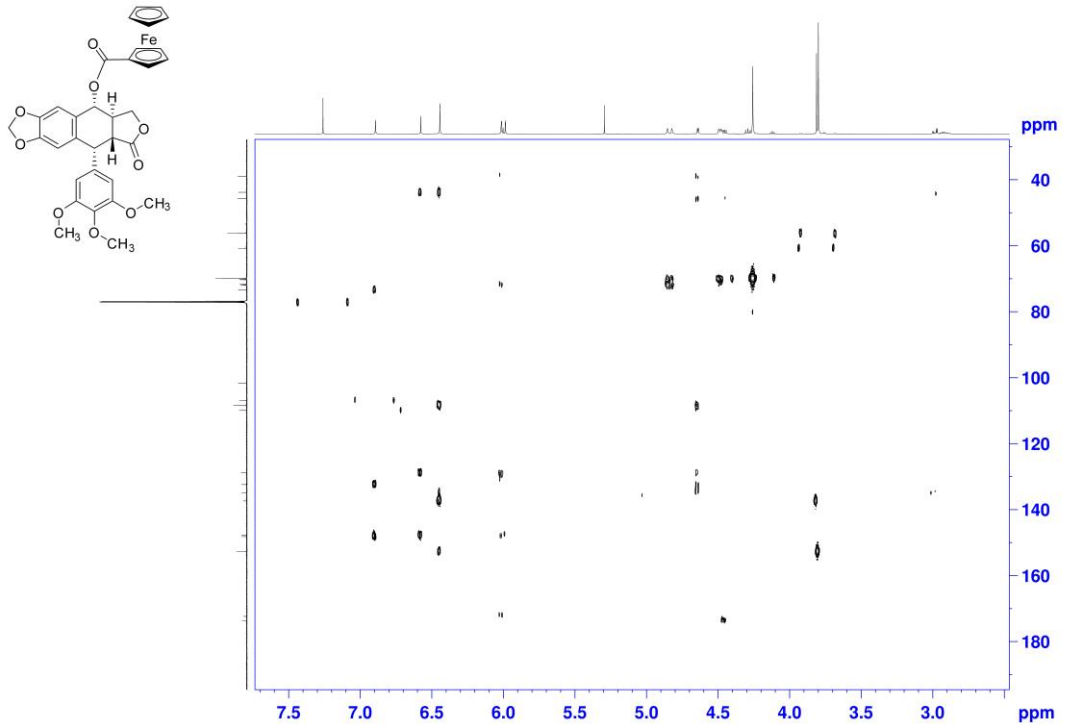

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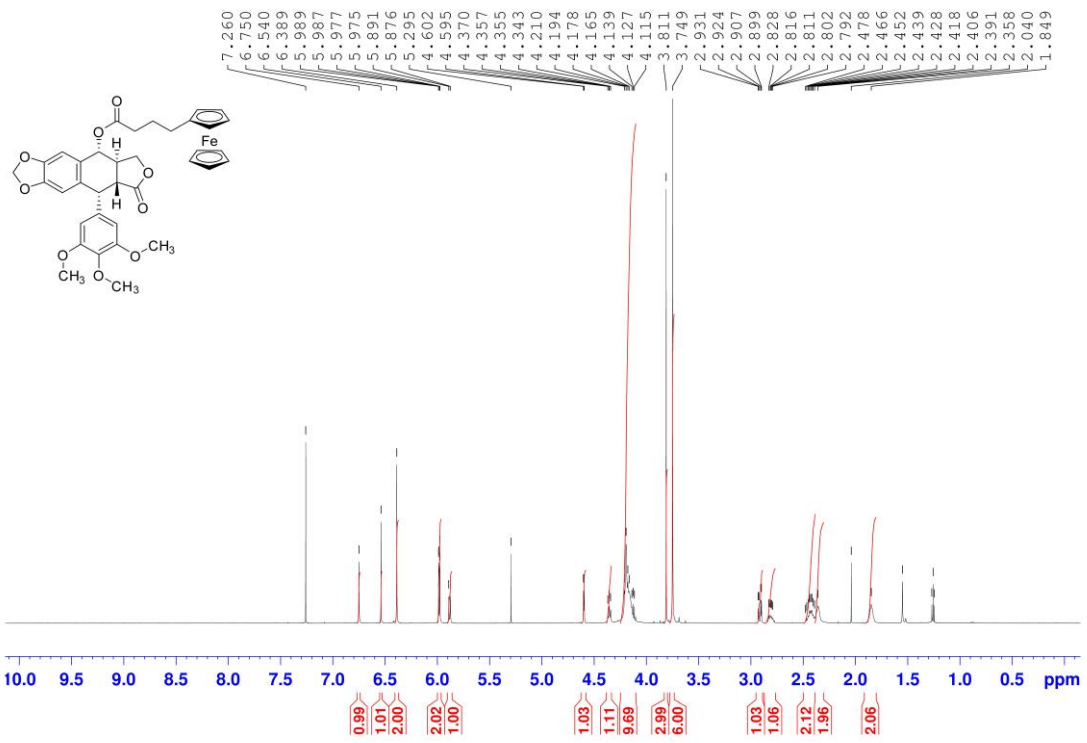
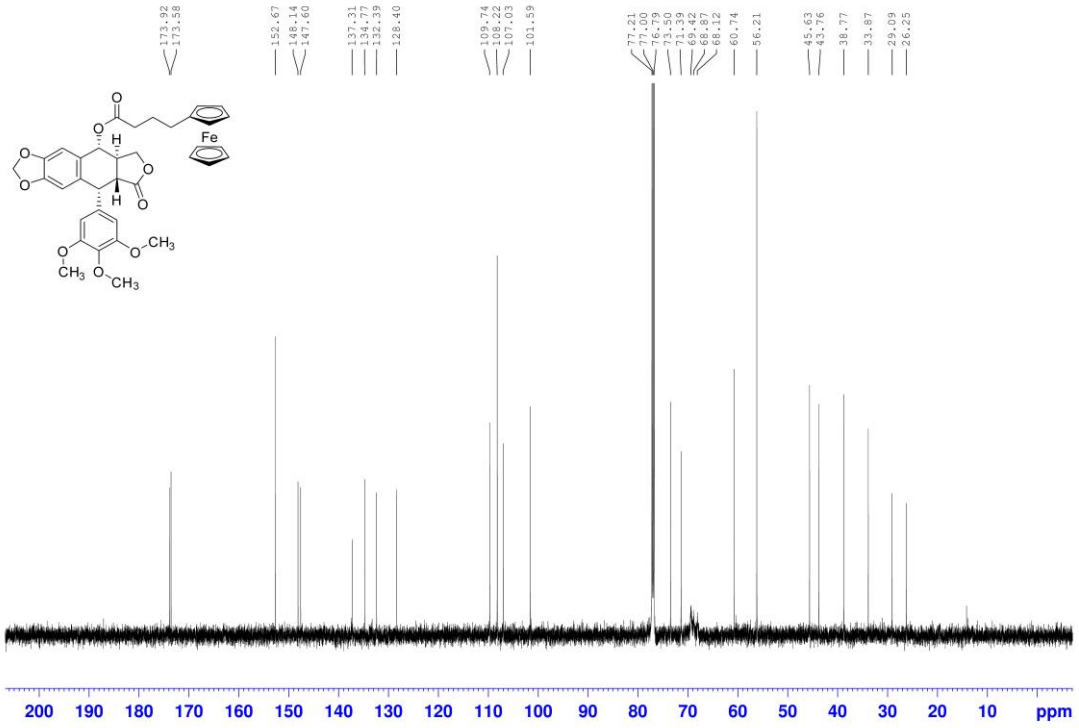


$^{13}C\{^{1}H\}$ NMR spectra of **18**



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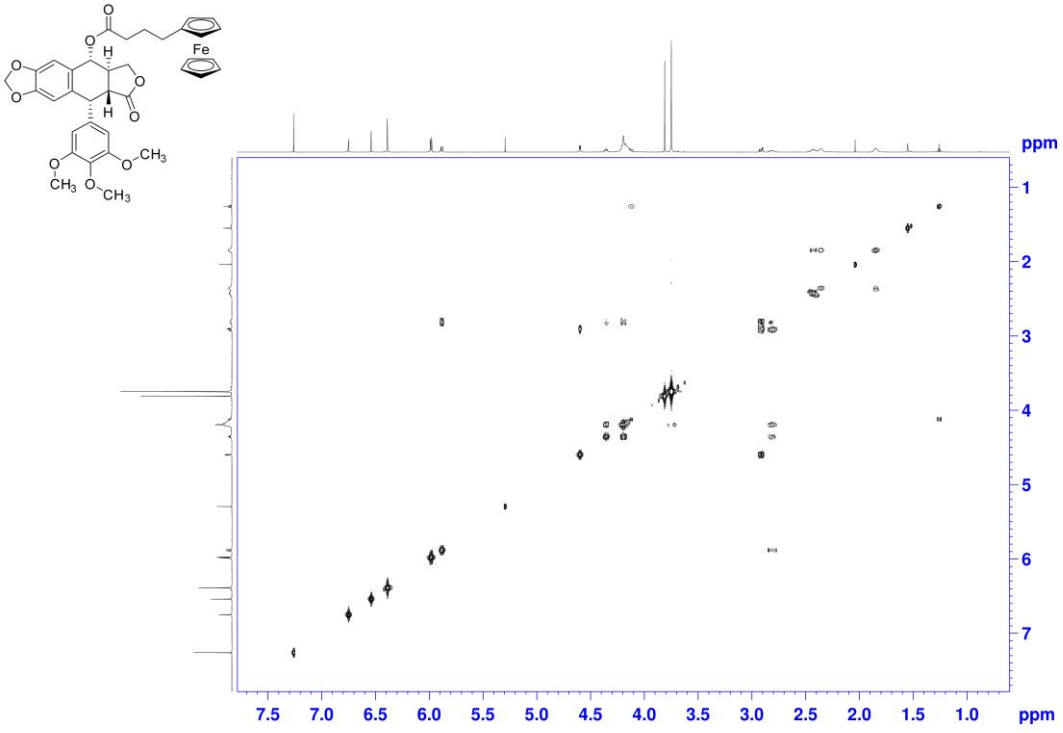

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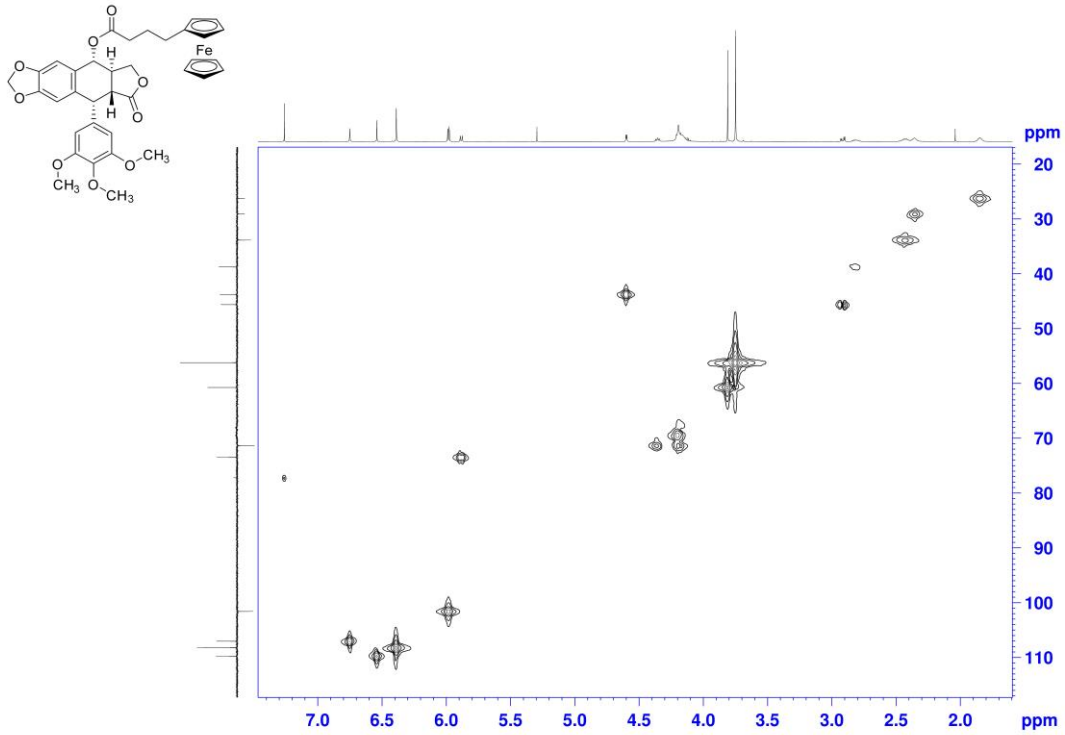

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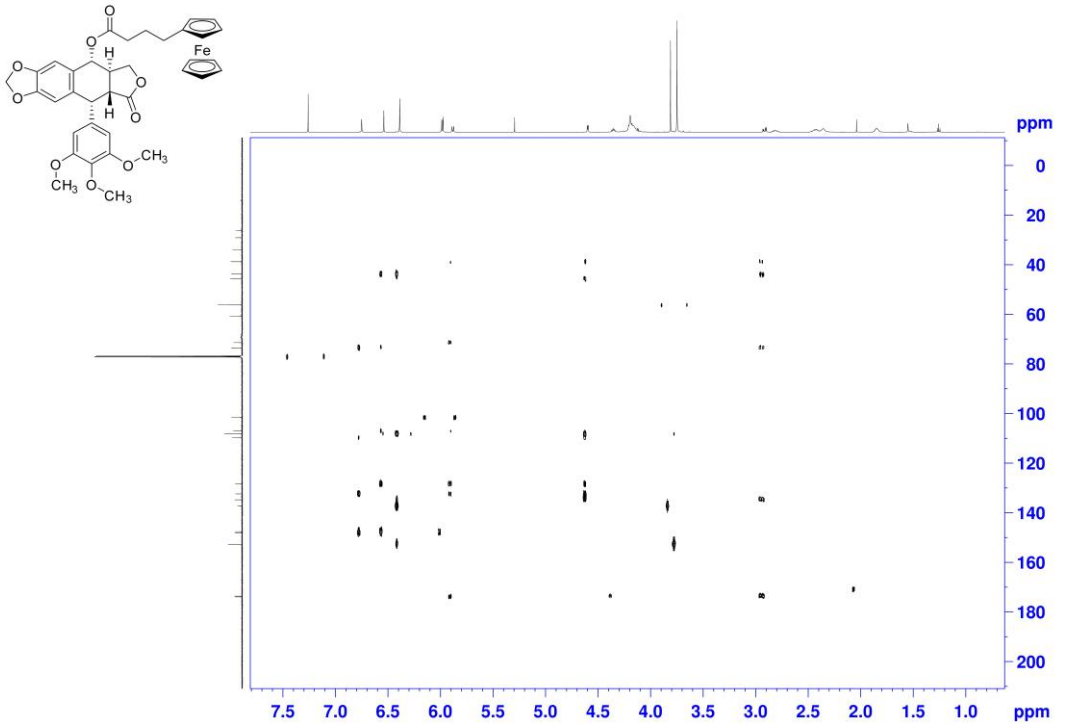
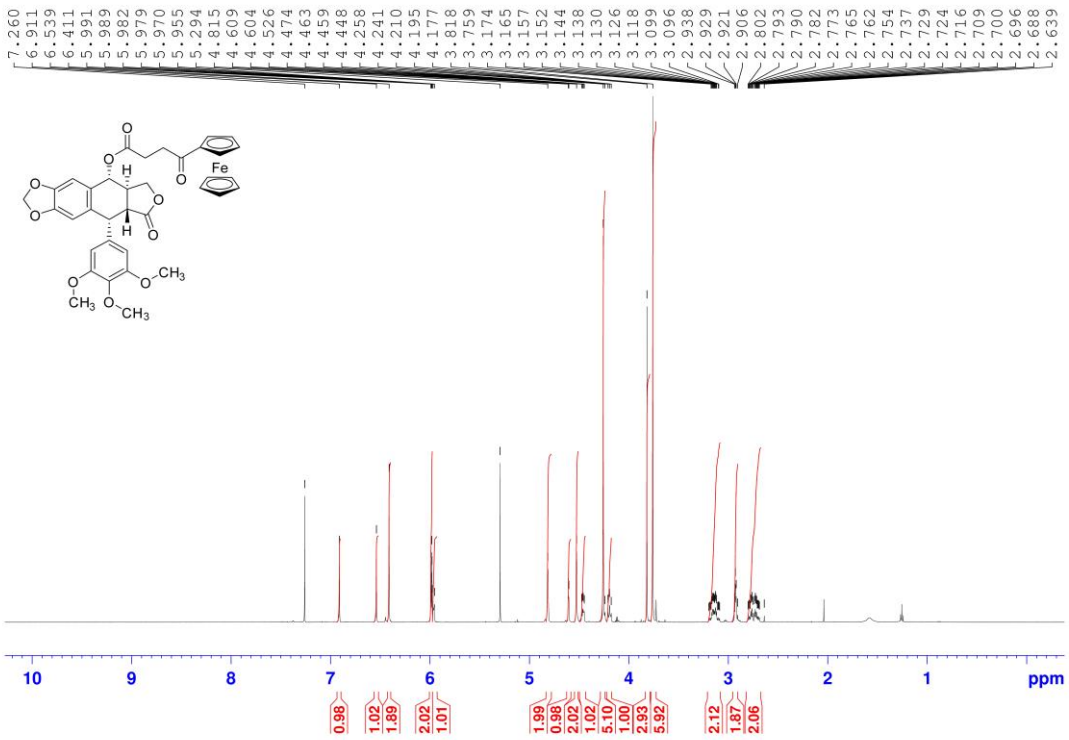


^{1}H NMR spectra of **19**



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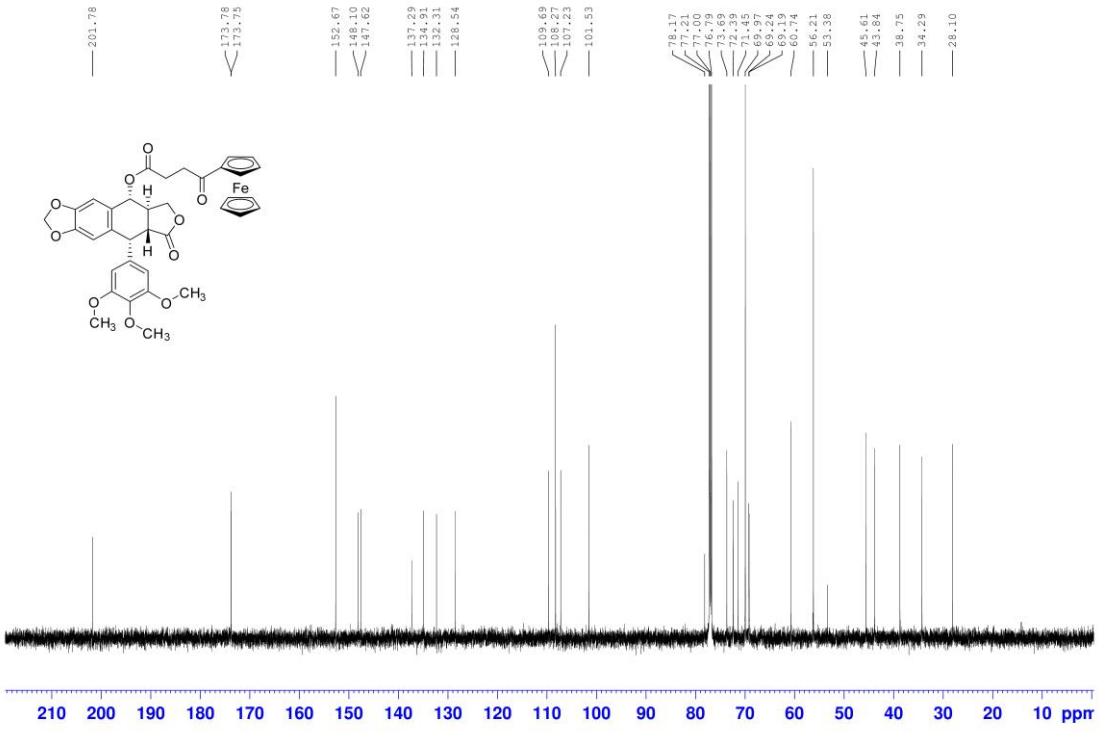

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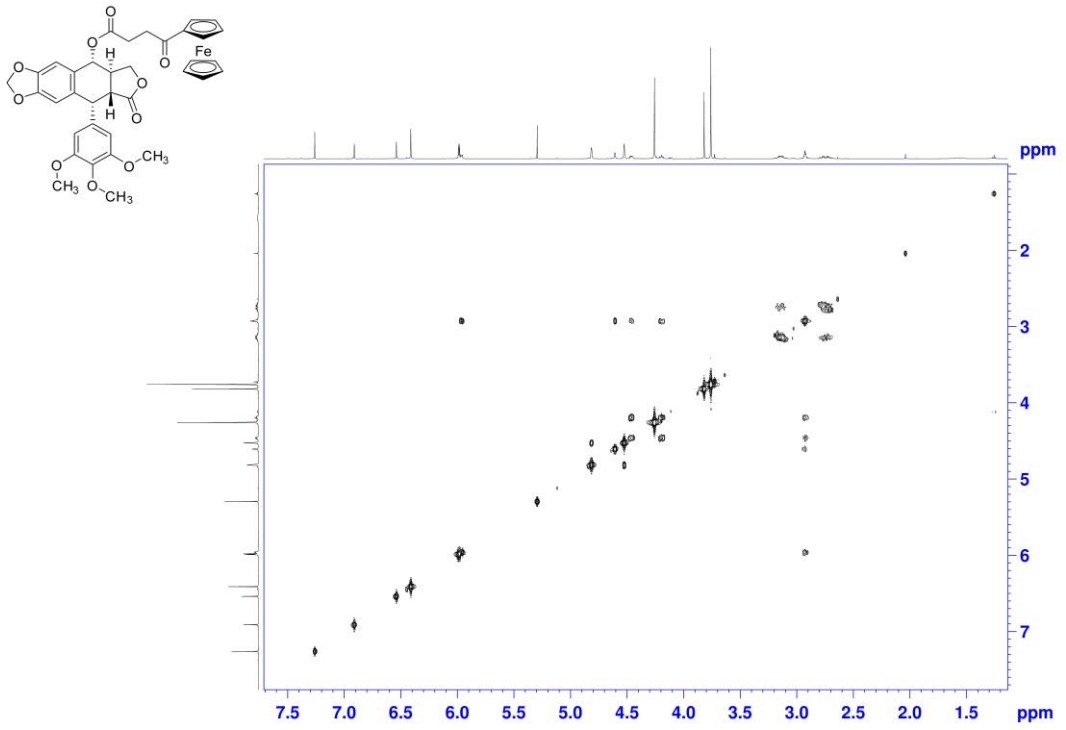

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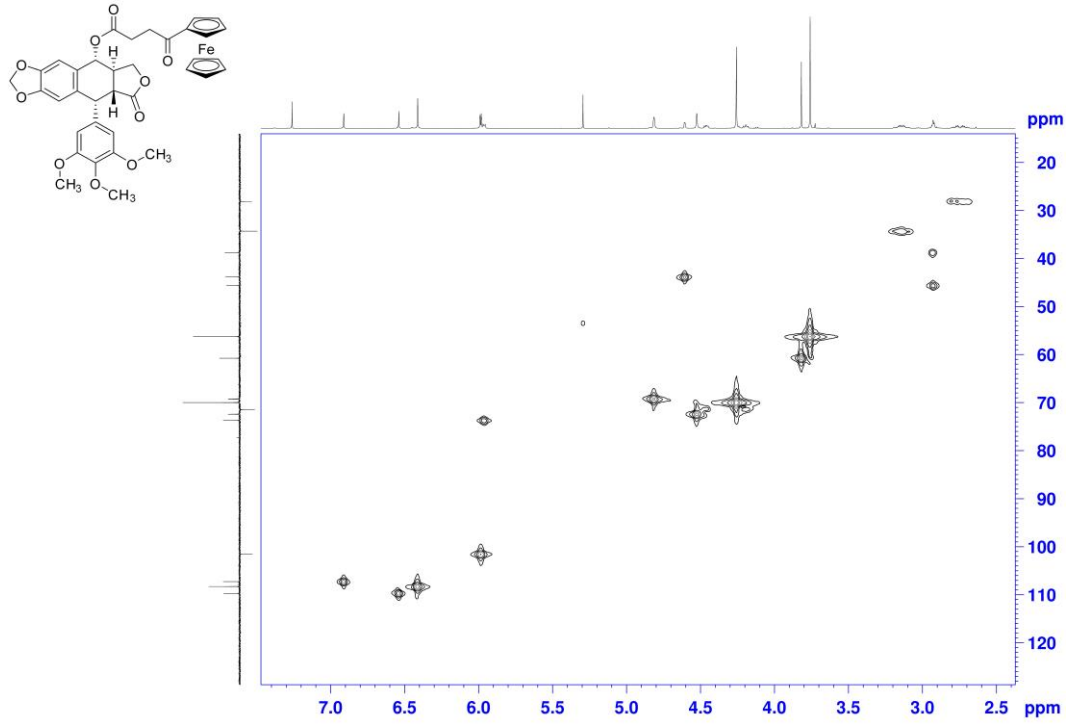

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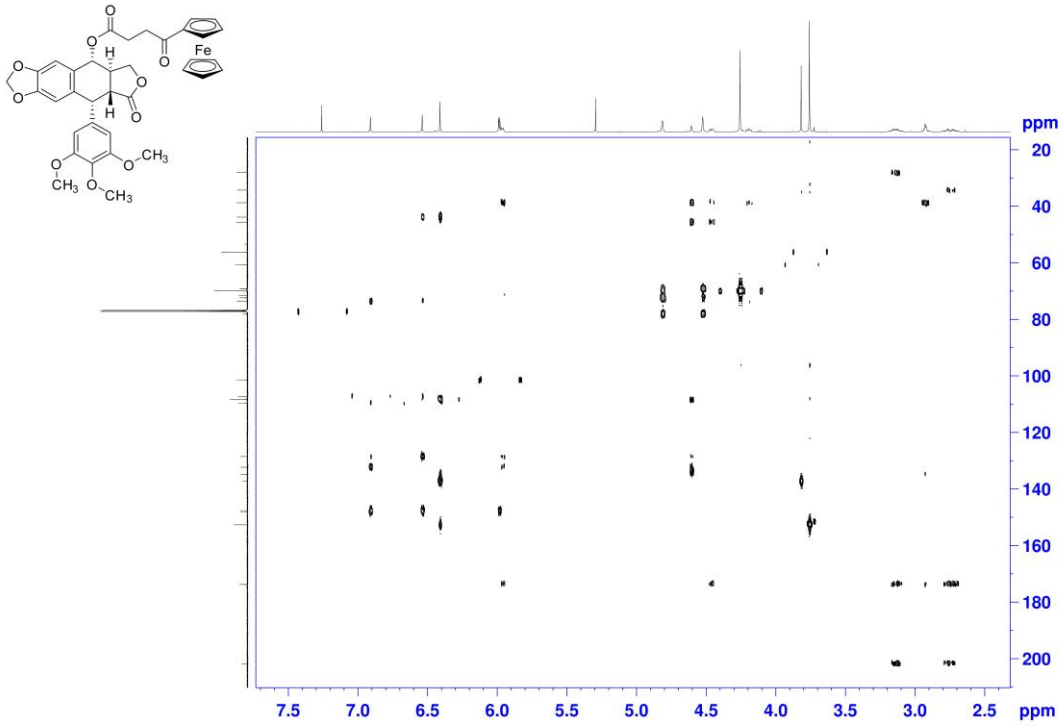

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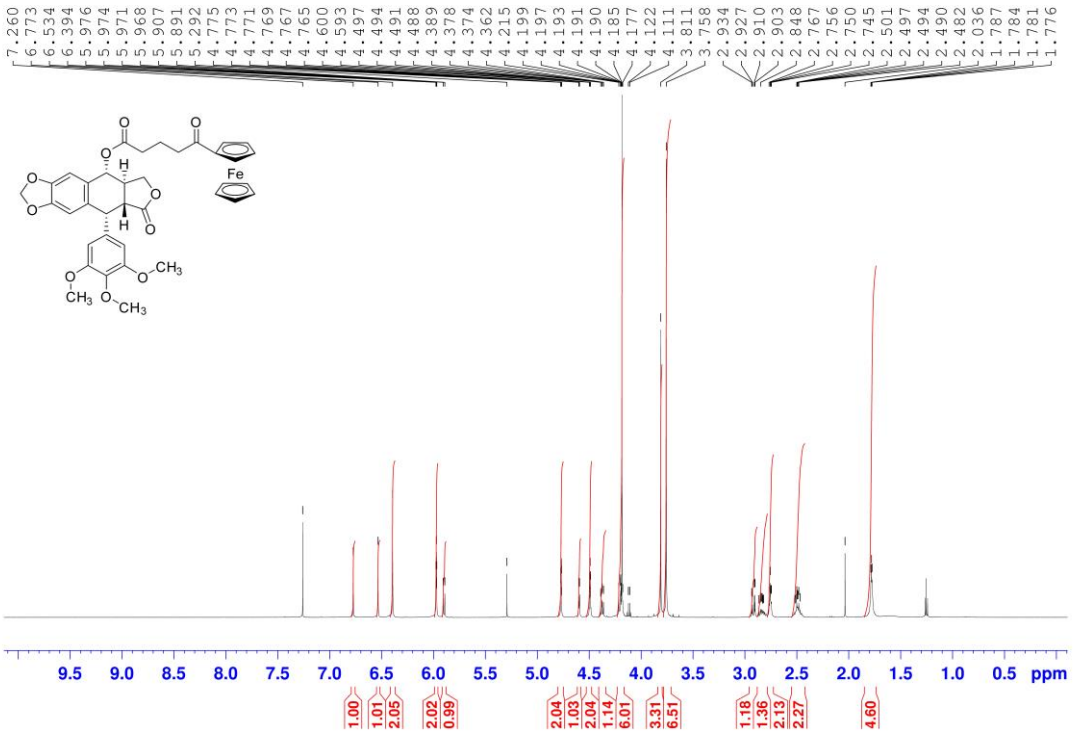

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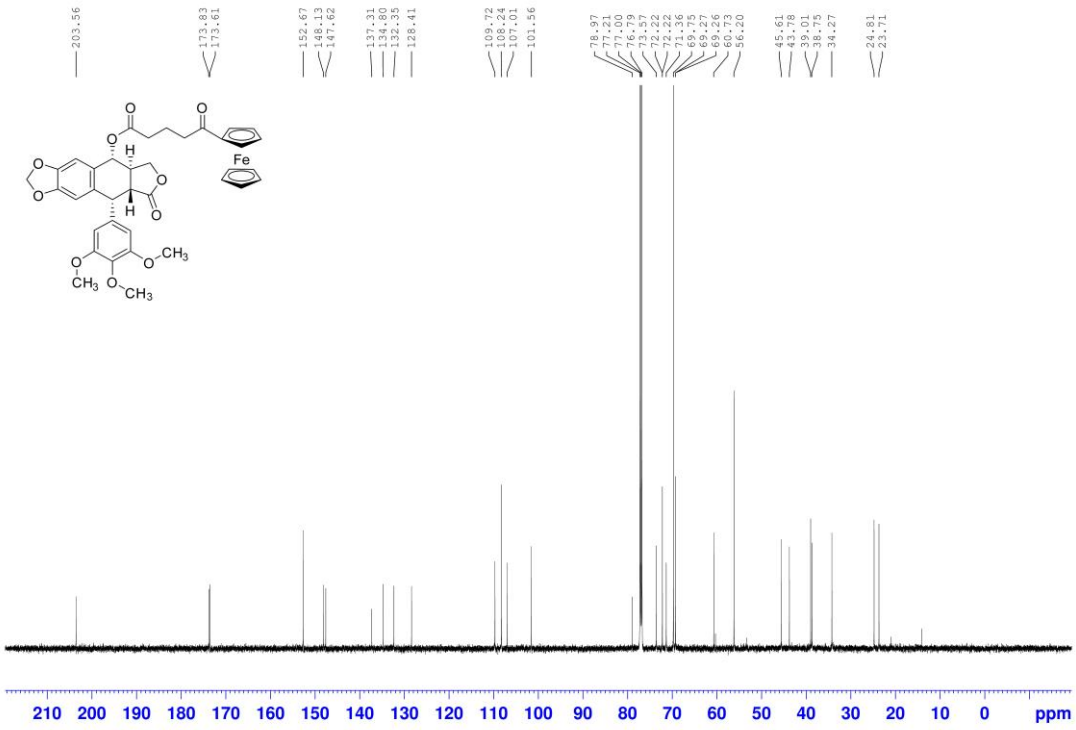

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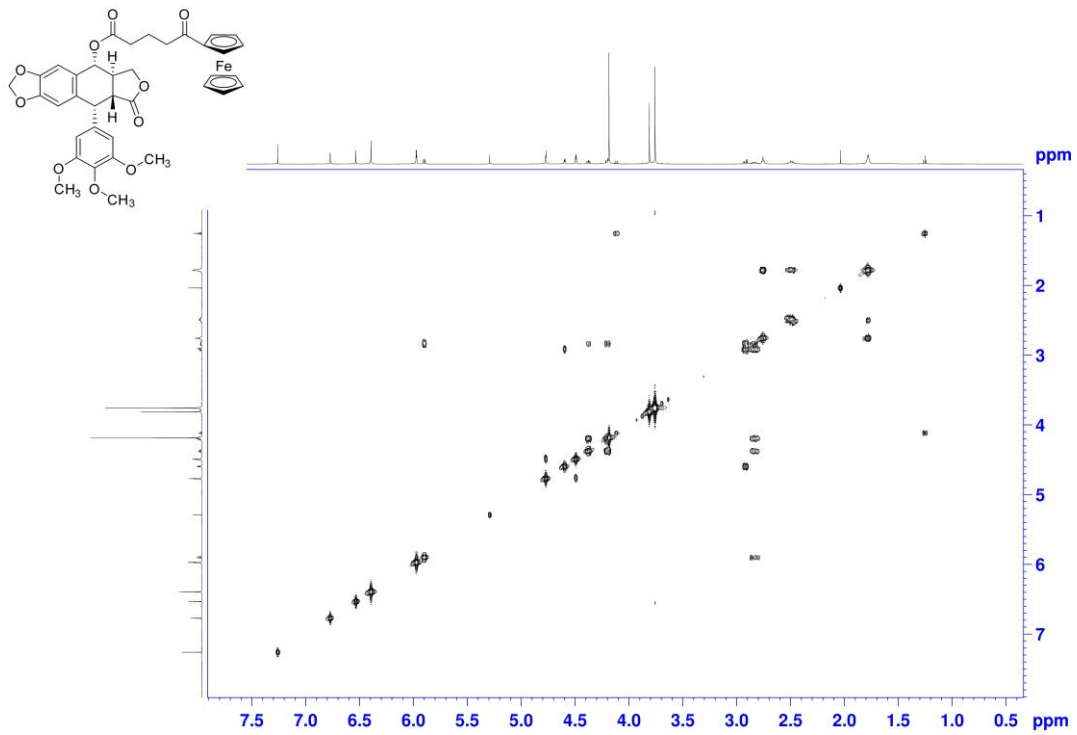

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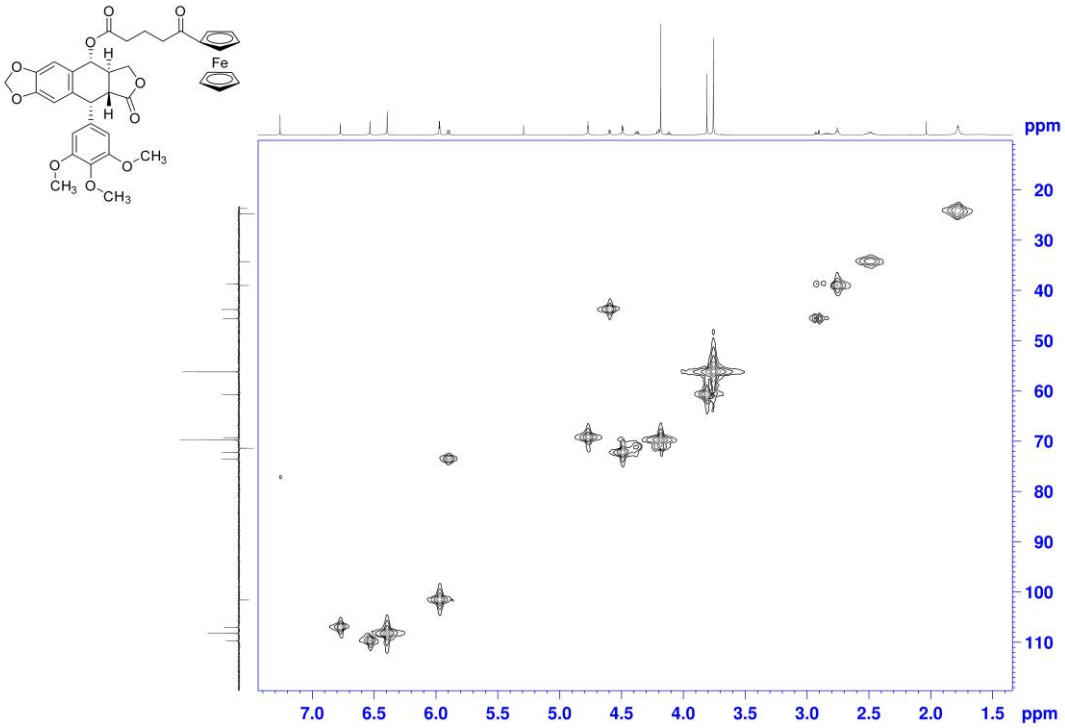

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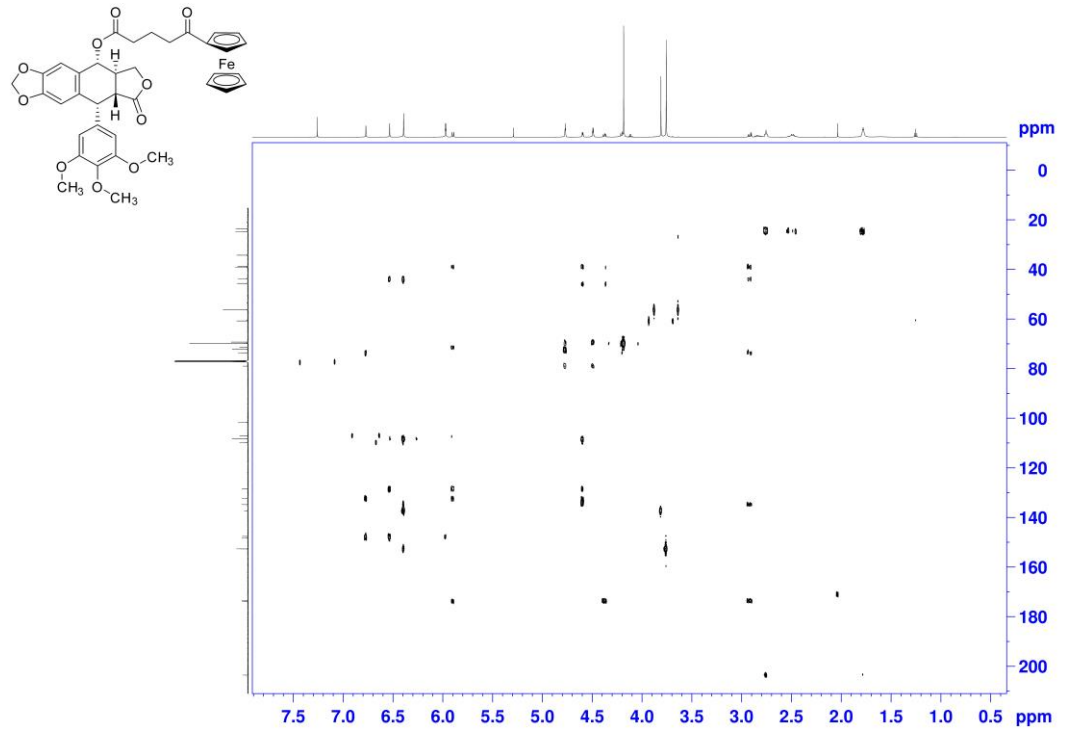

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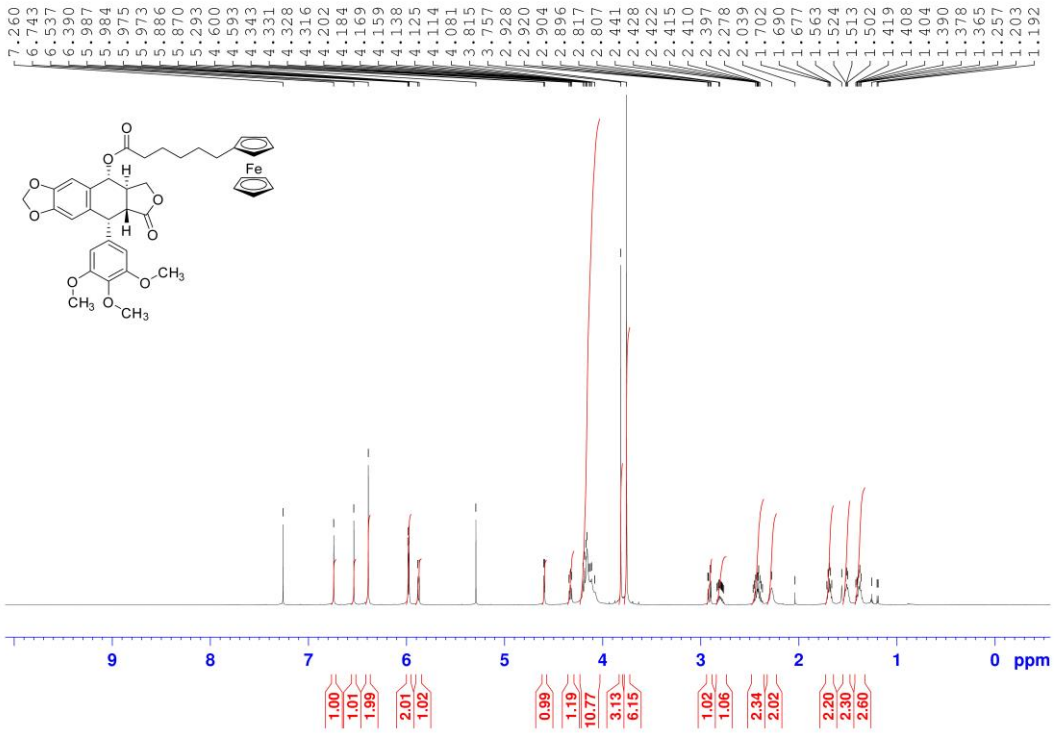

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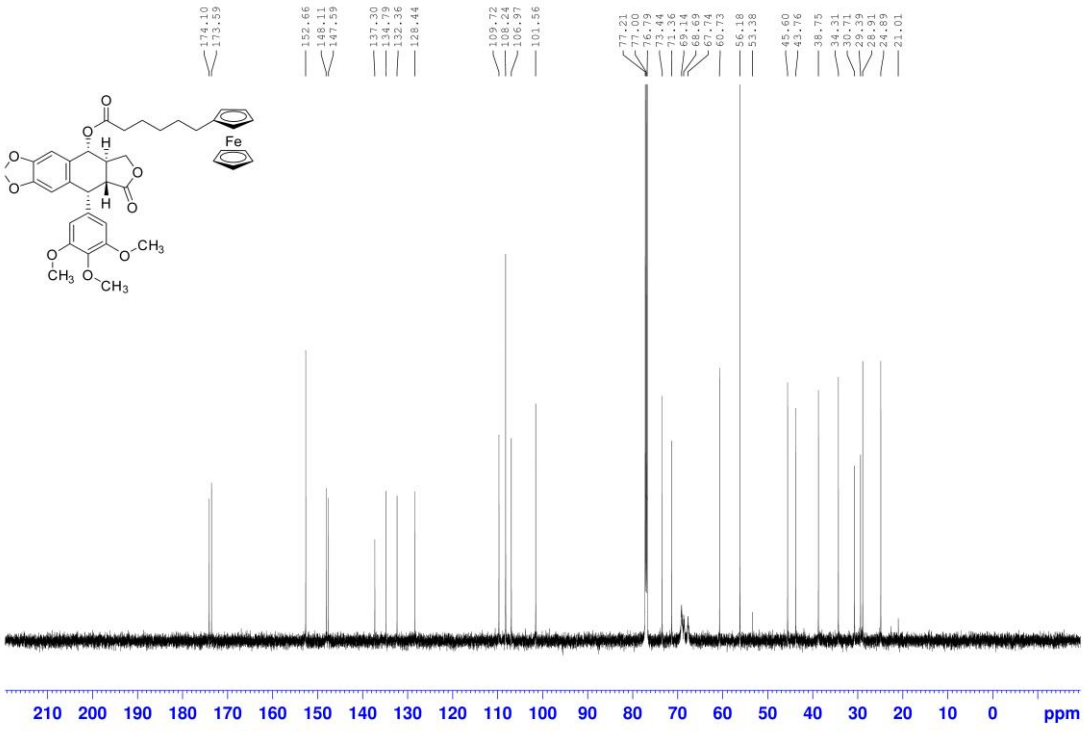

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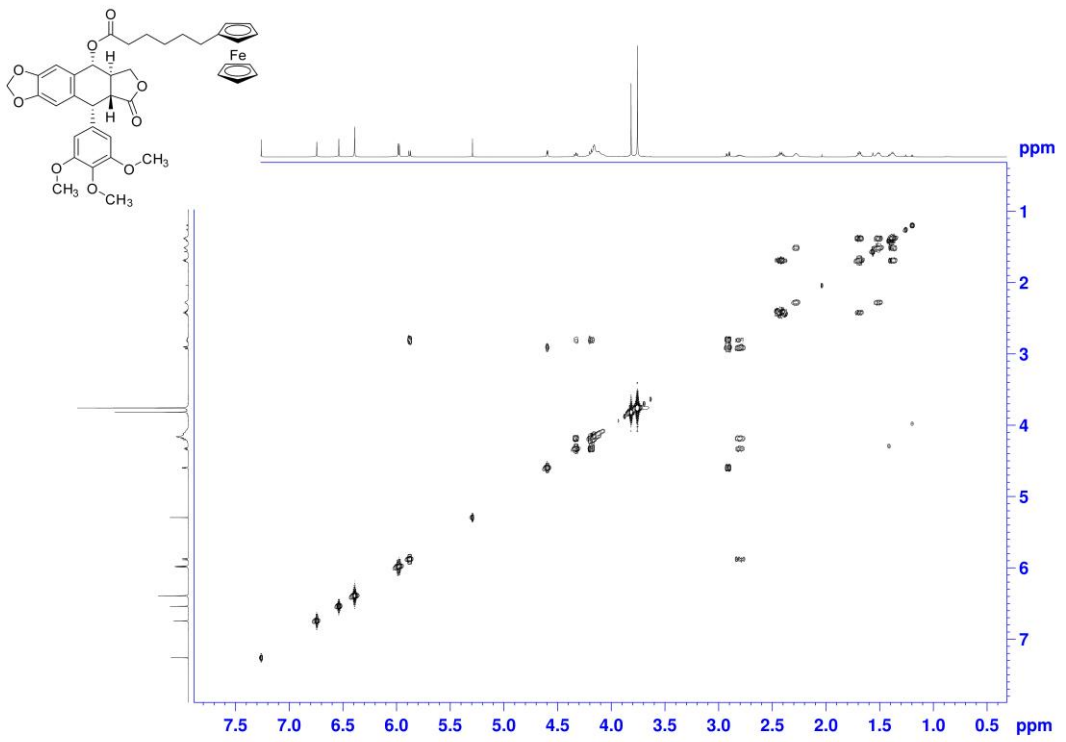

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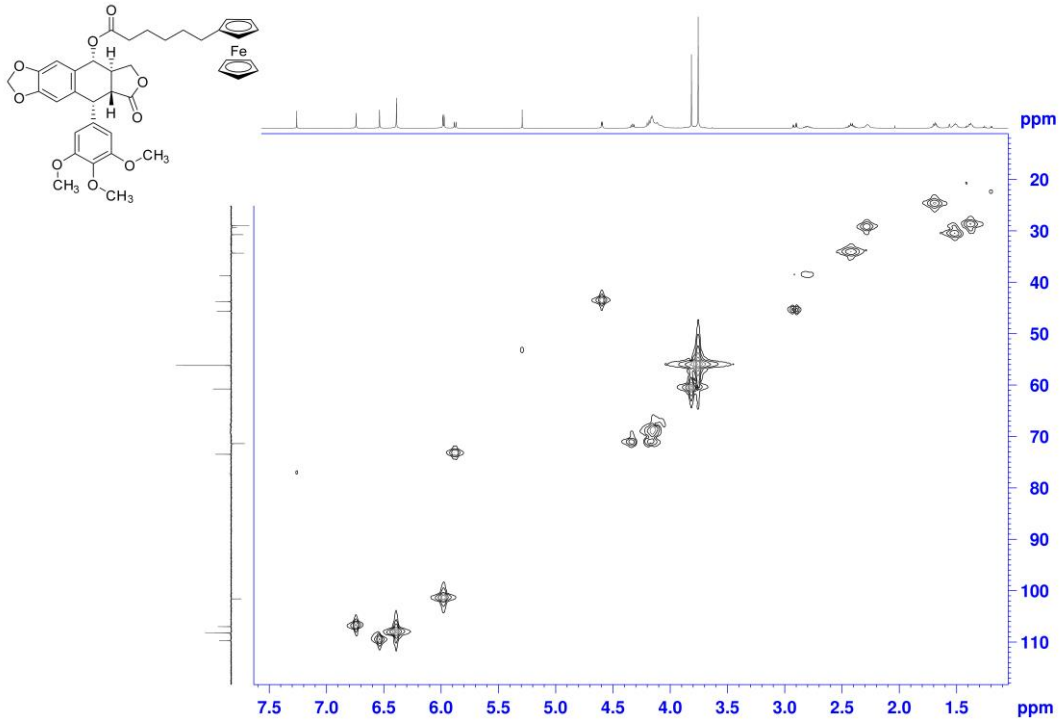

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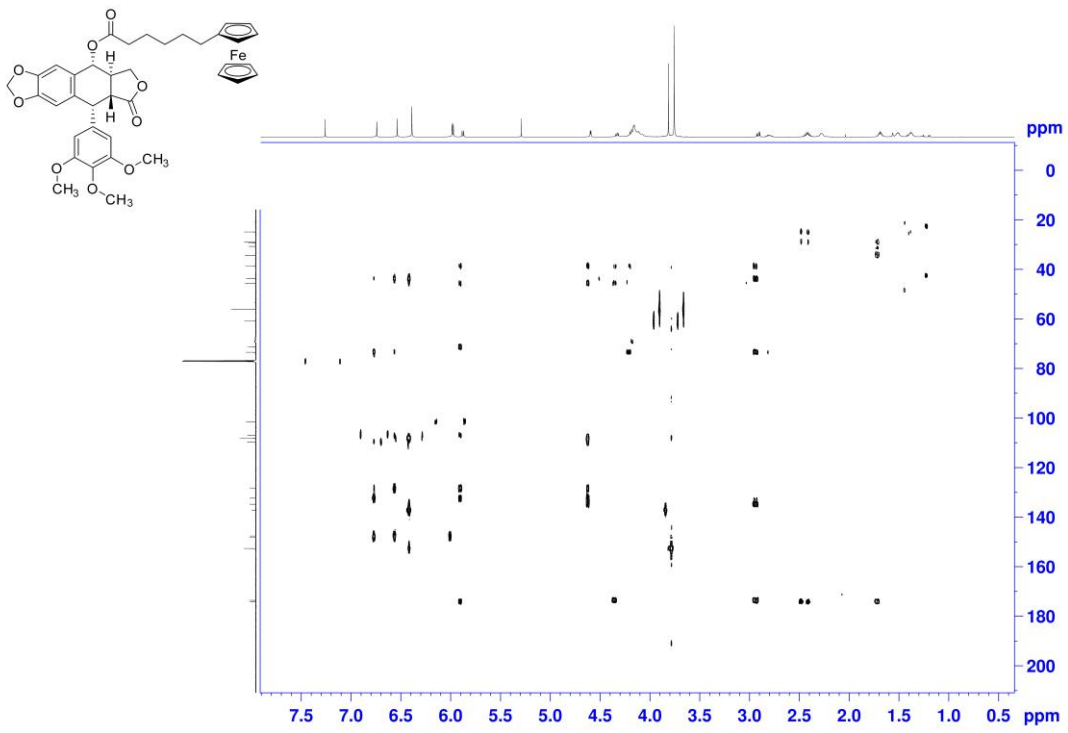

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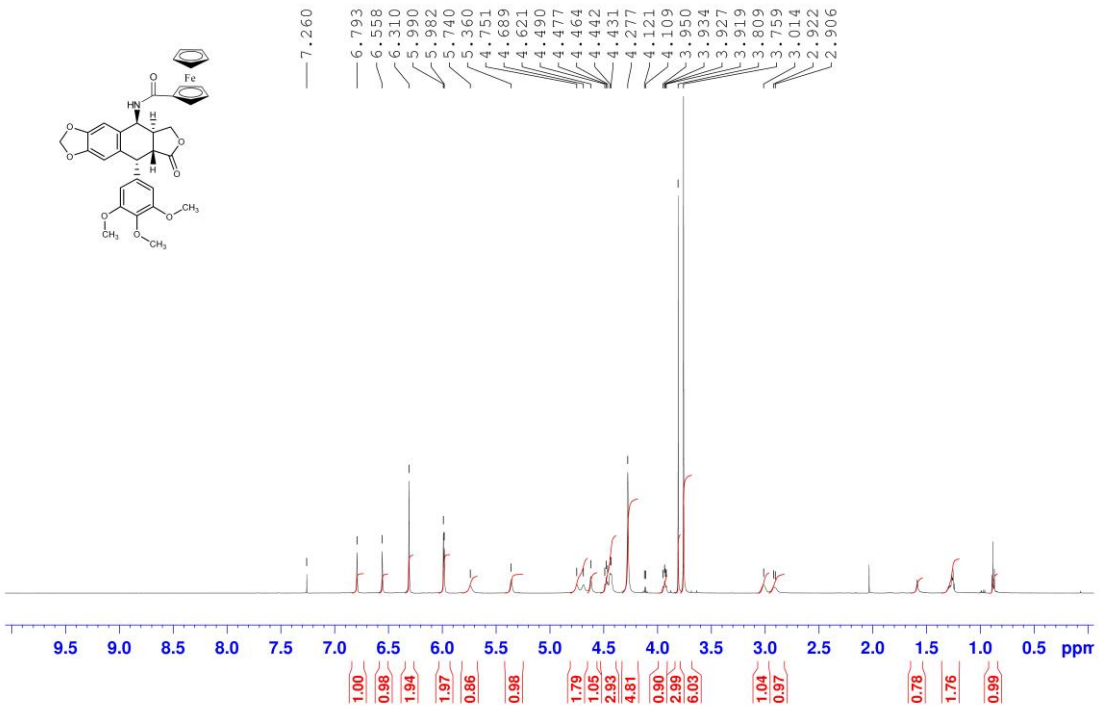

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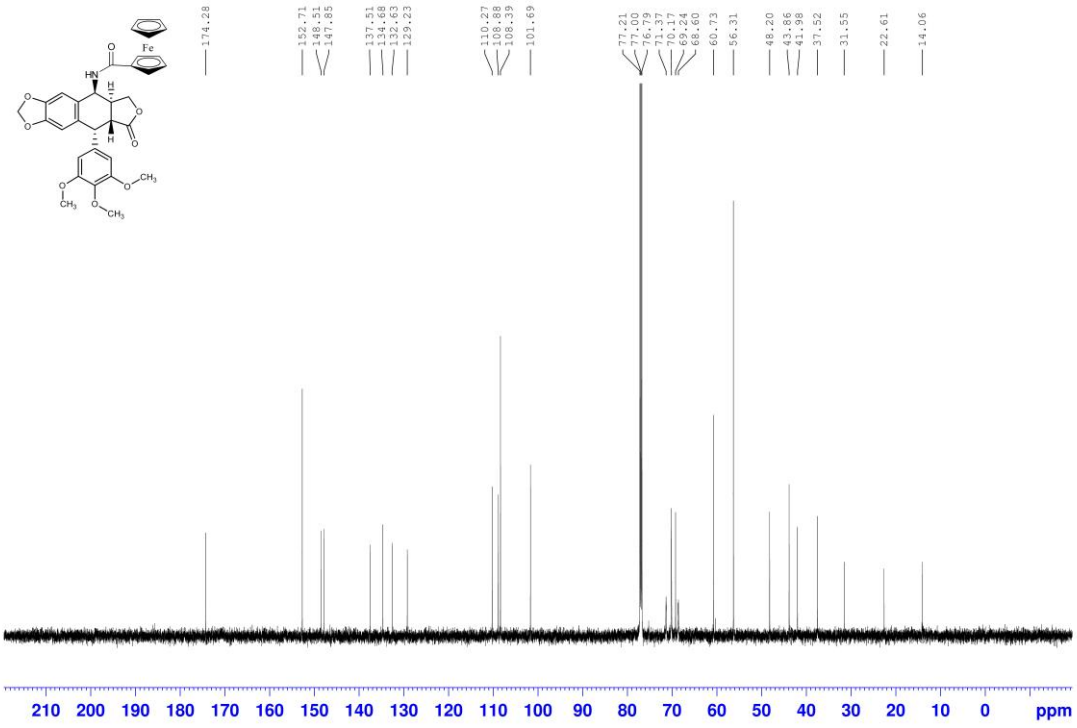

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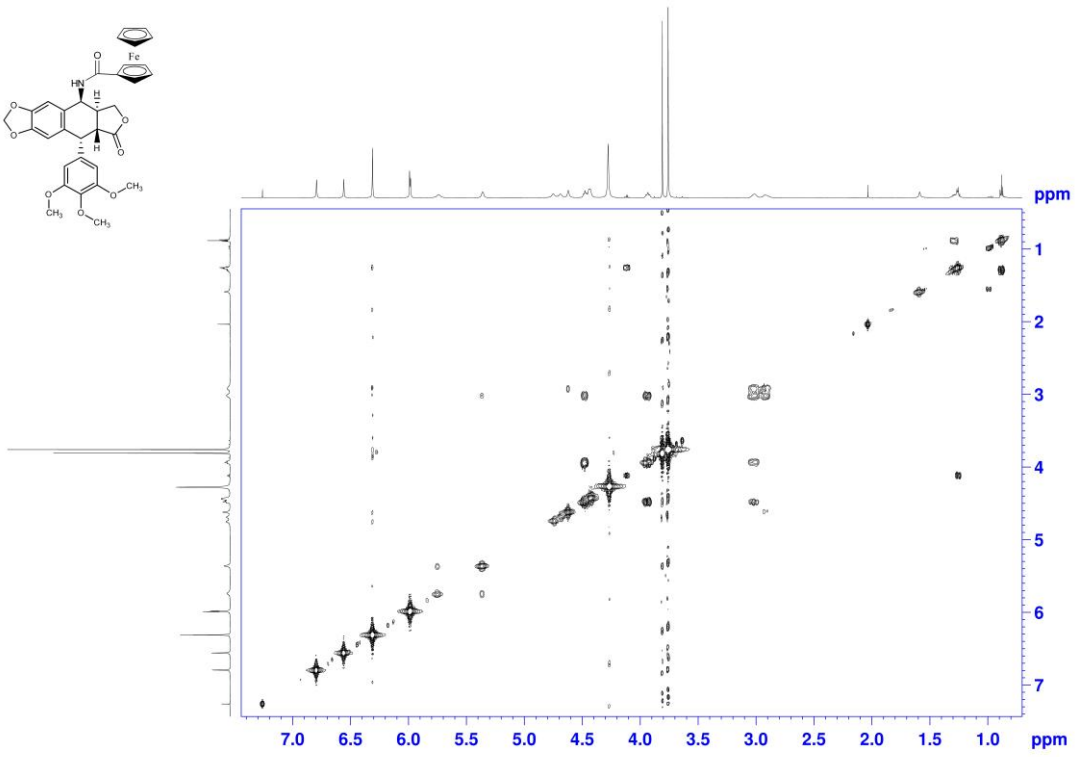

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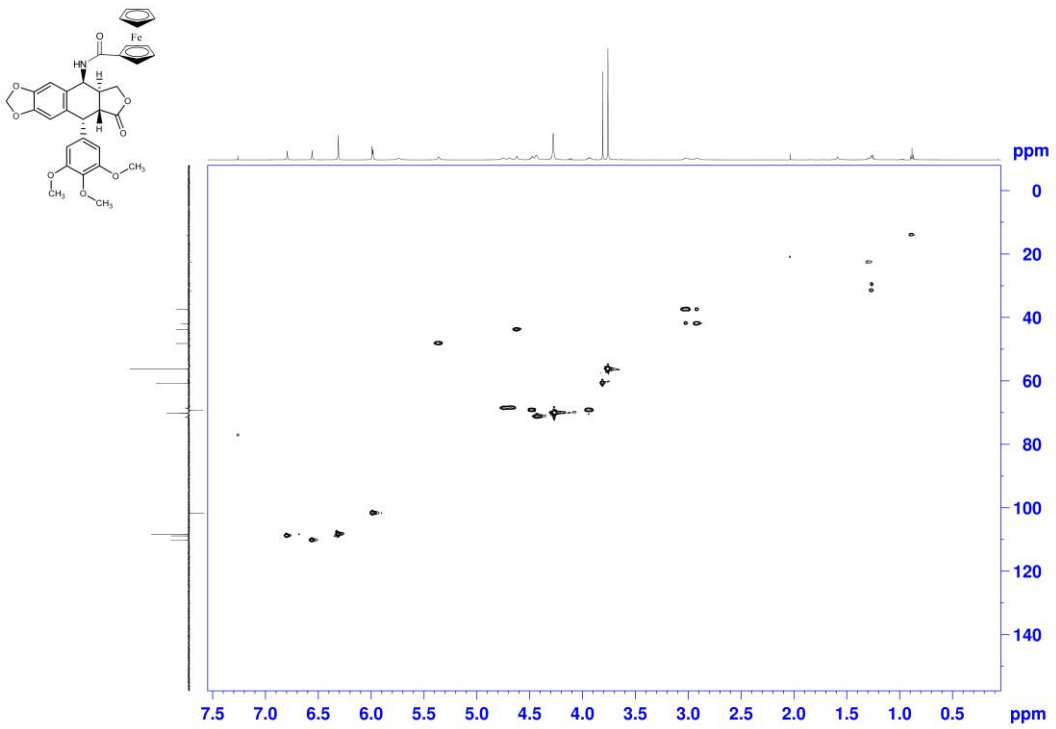

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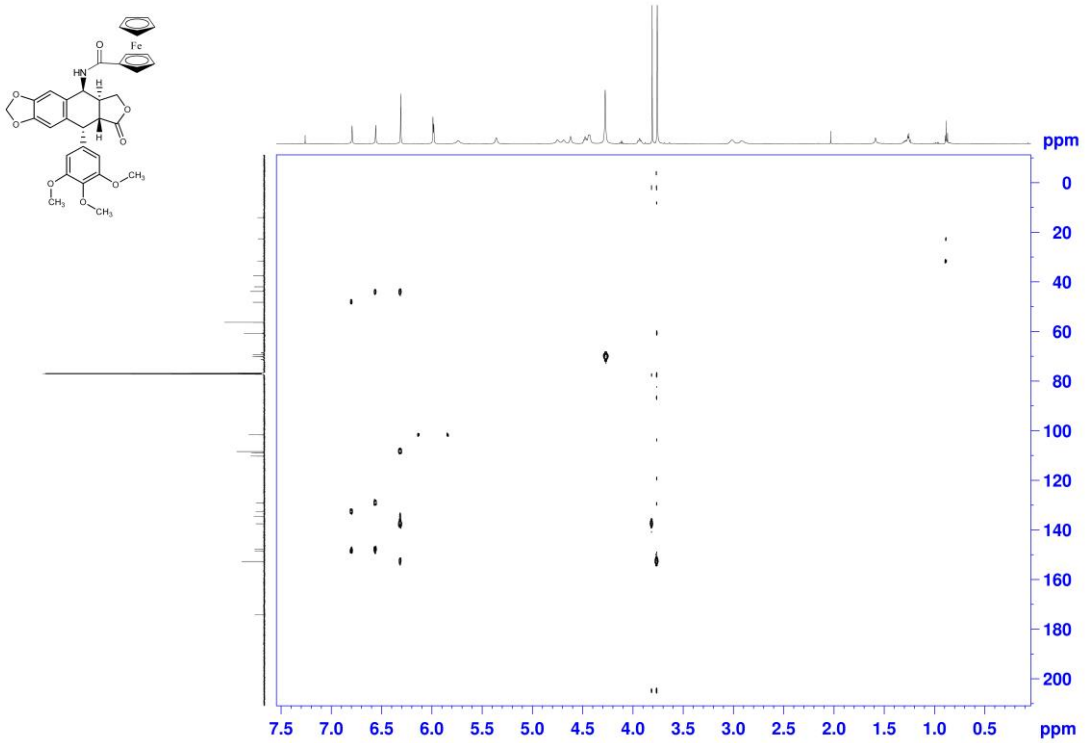

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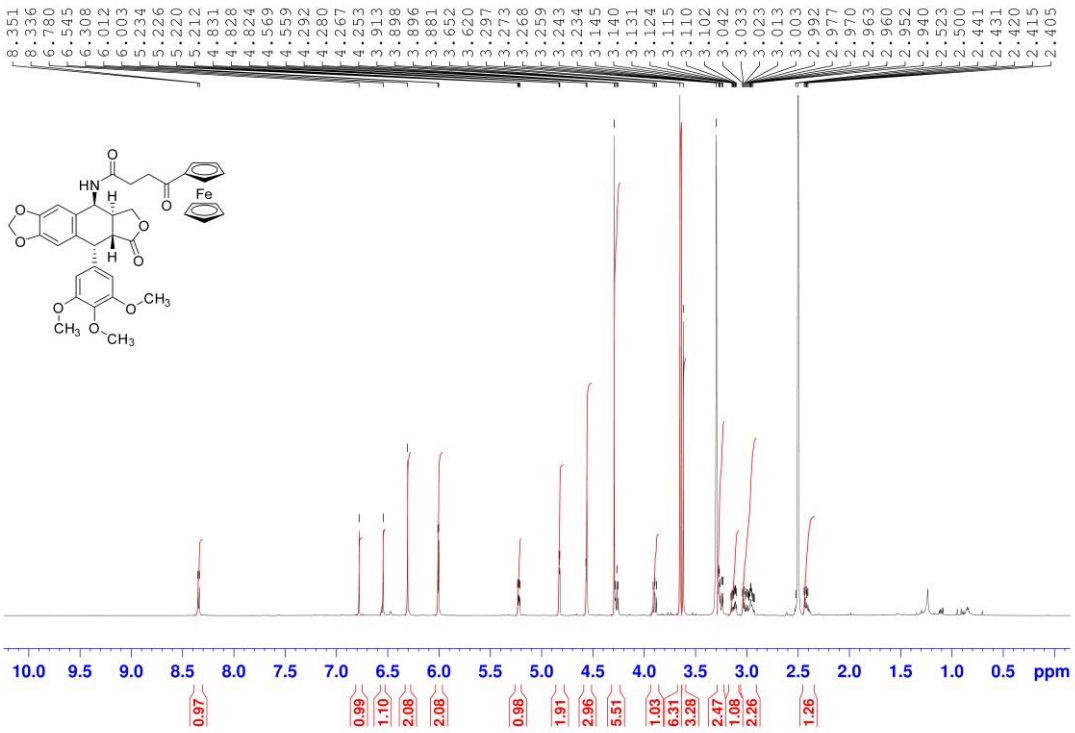

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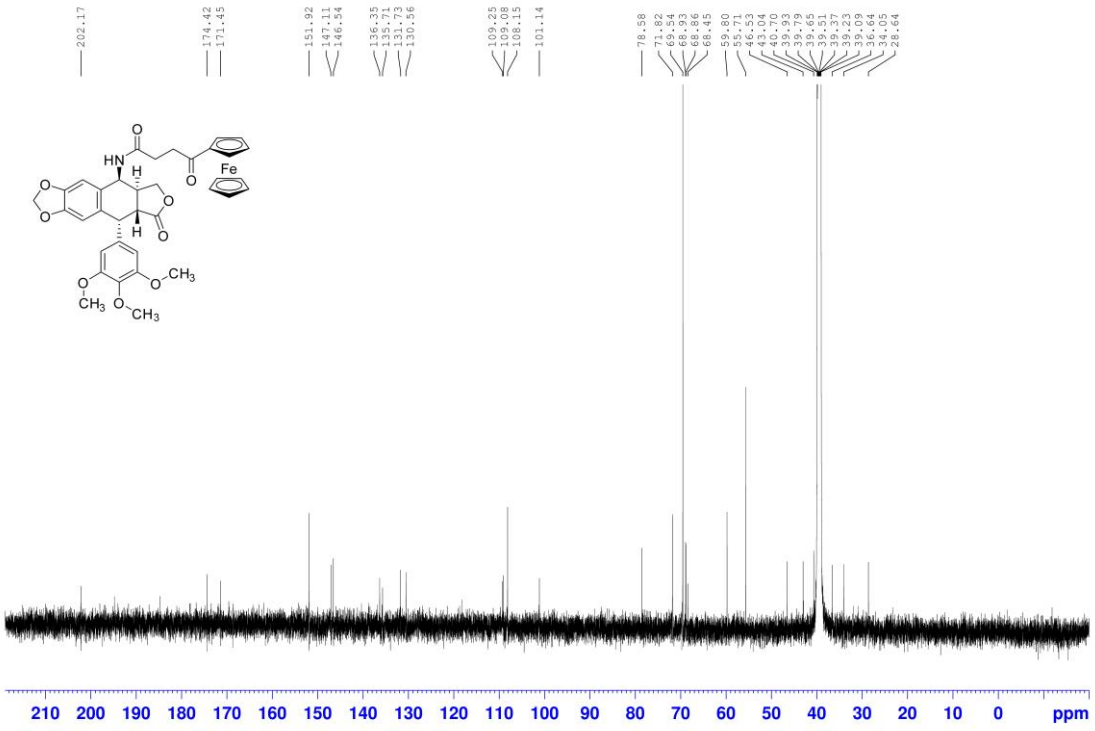

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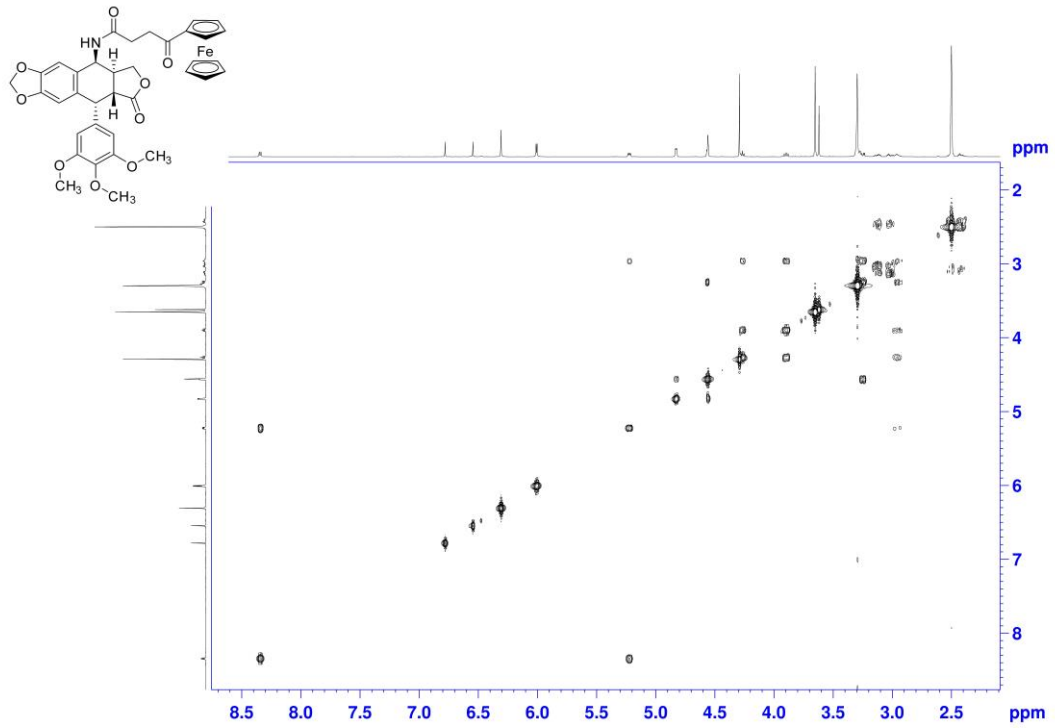

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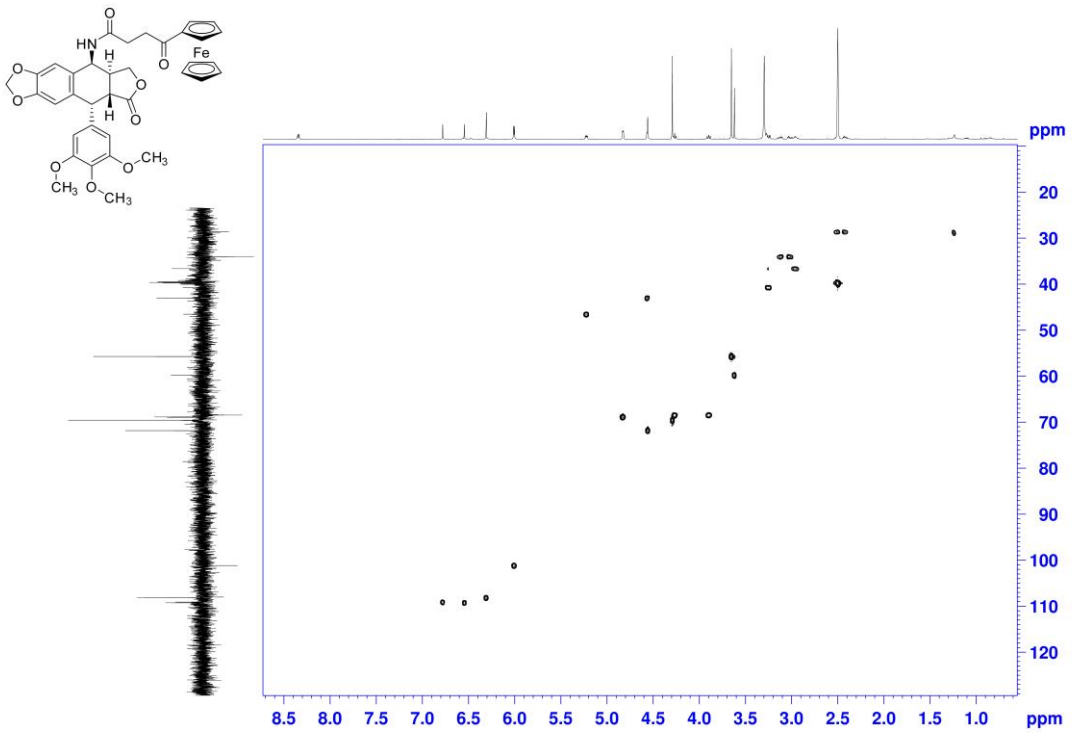

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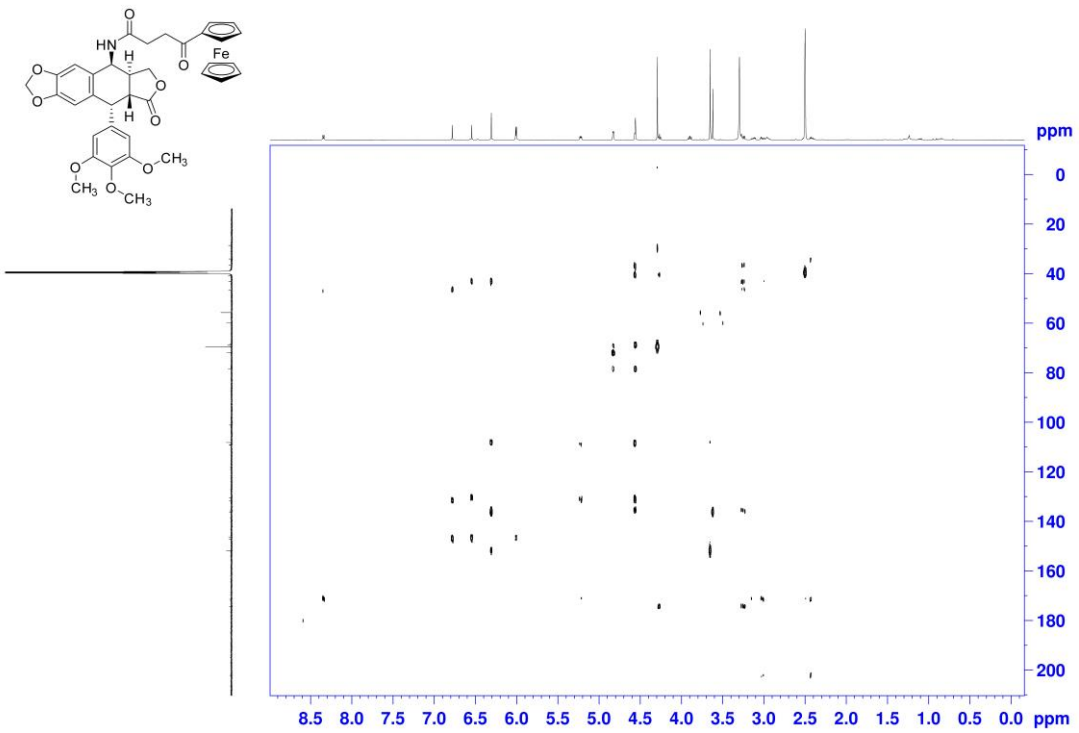

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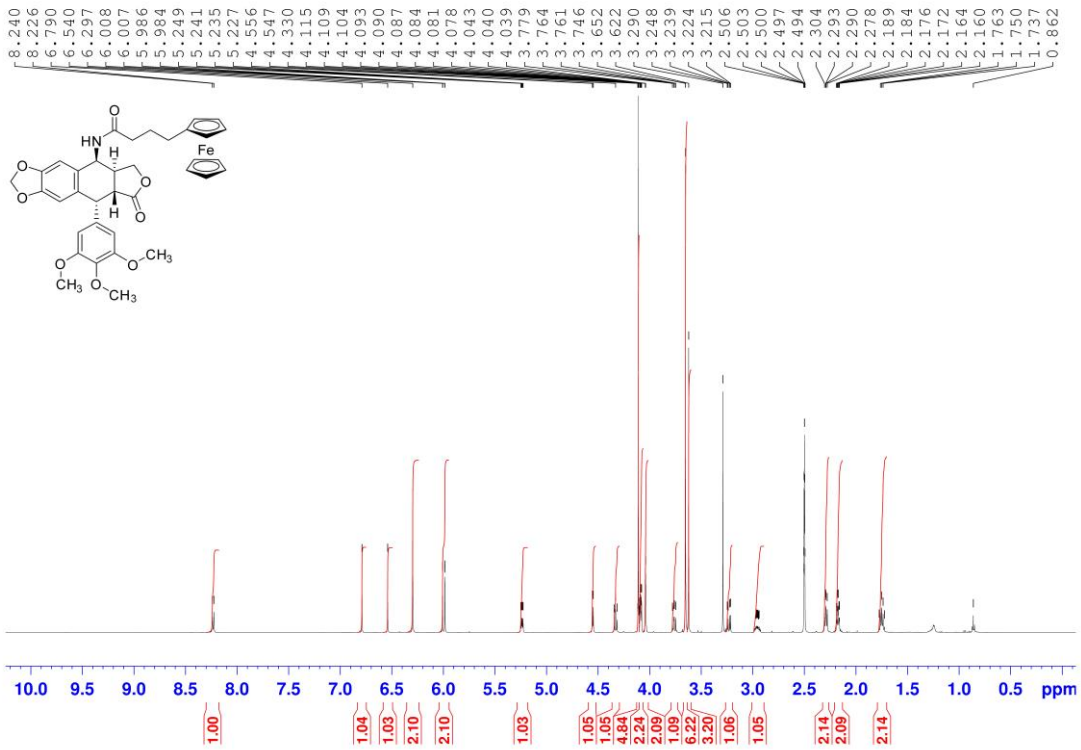

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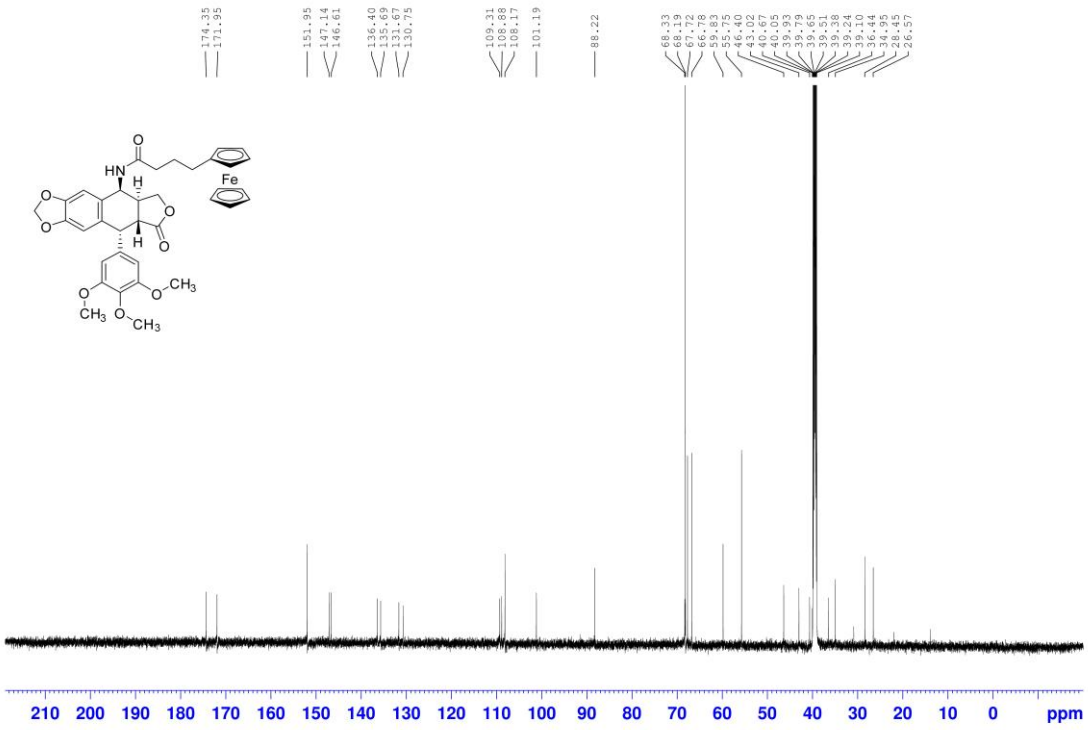

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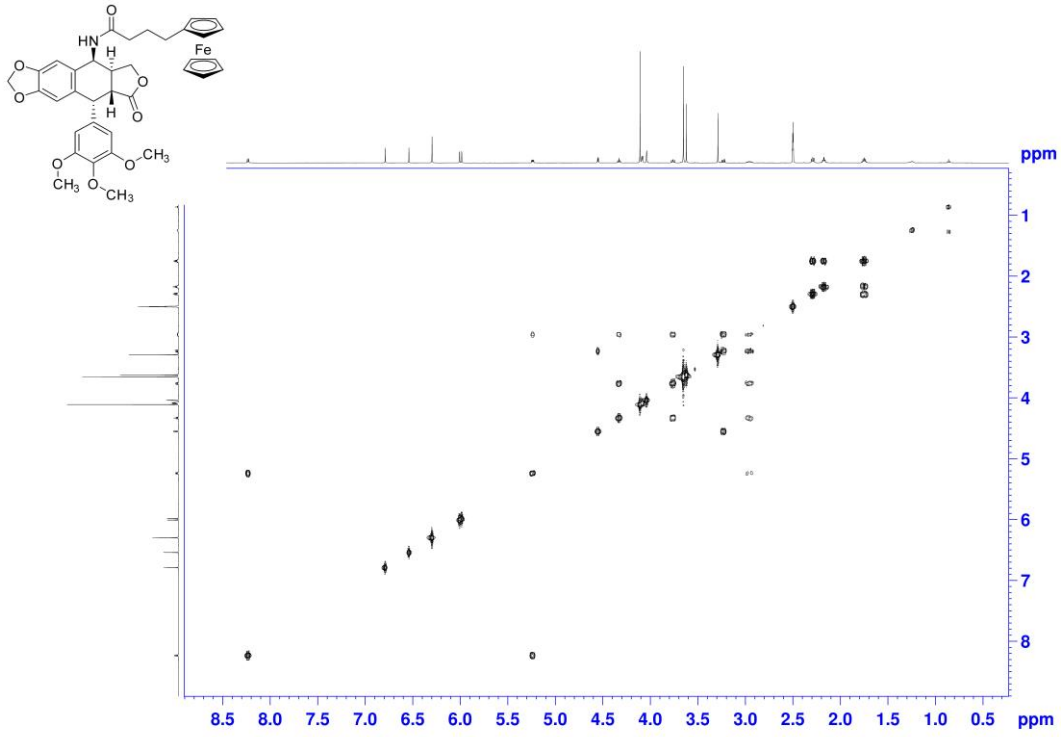

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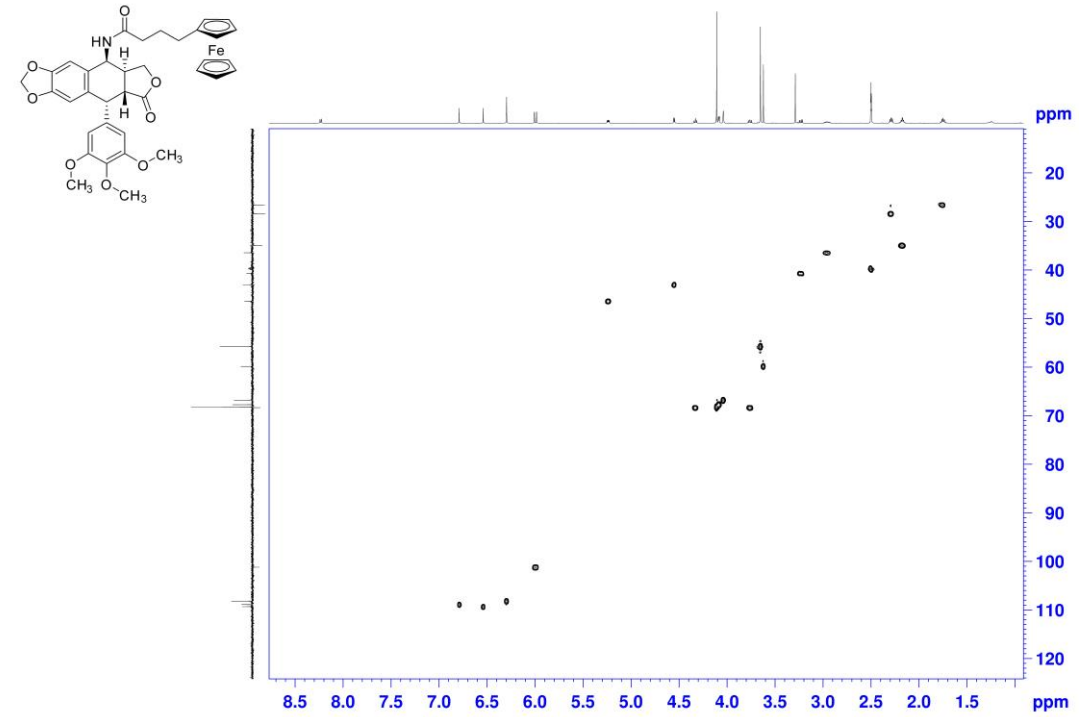
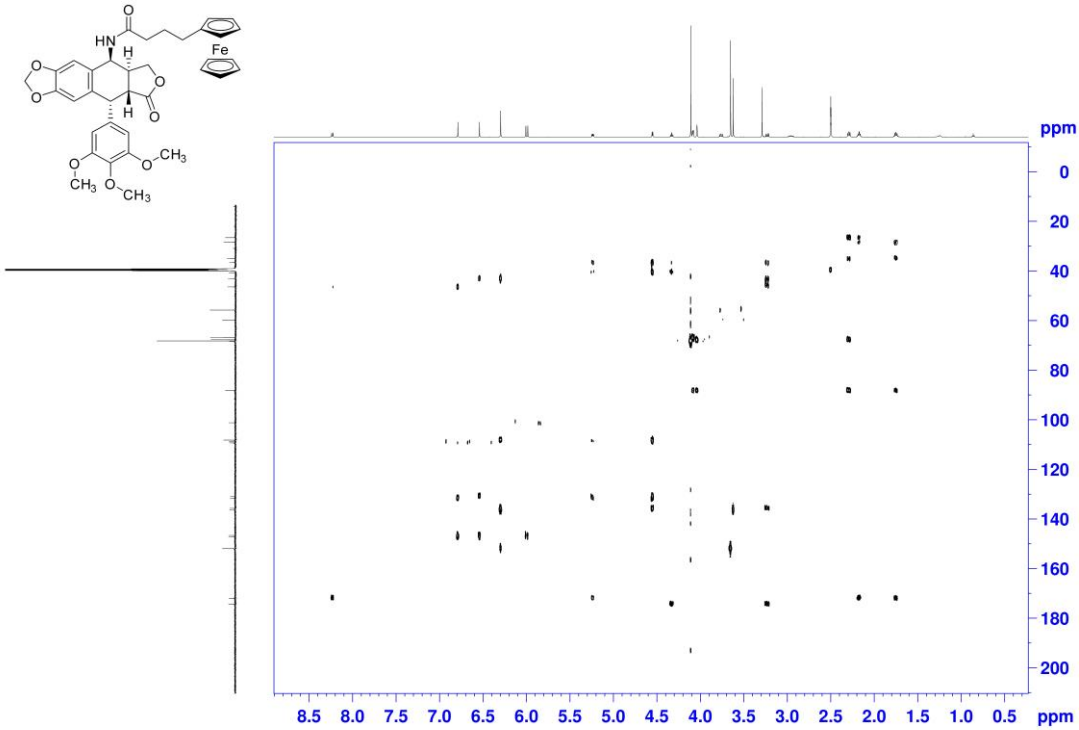
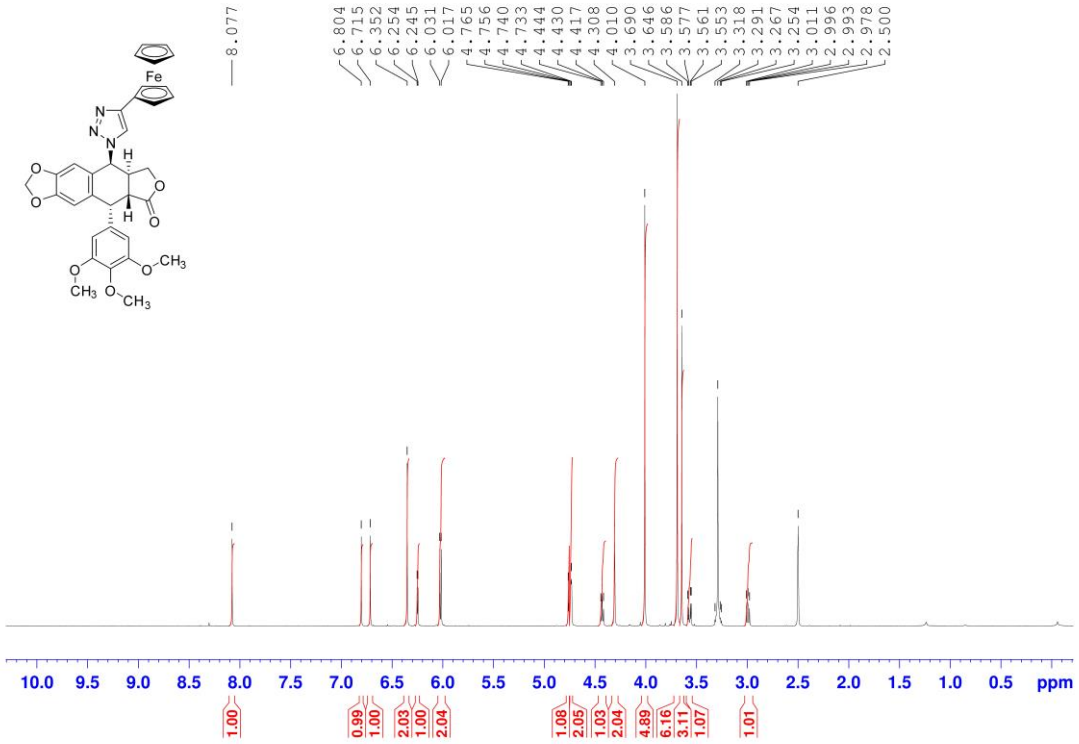


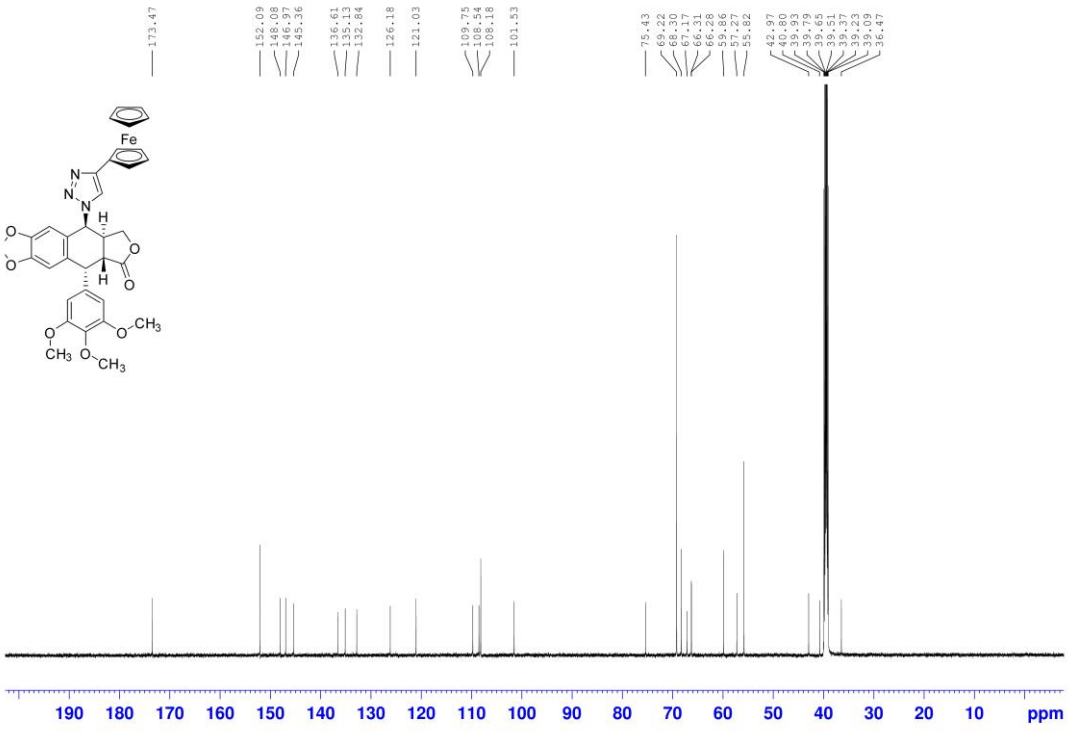
^{1}H-^{13}C HMBC spectra of **24**



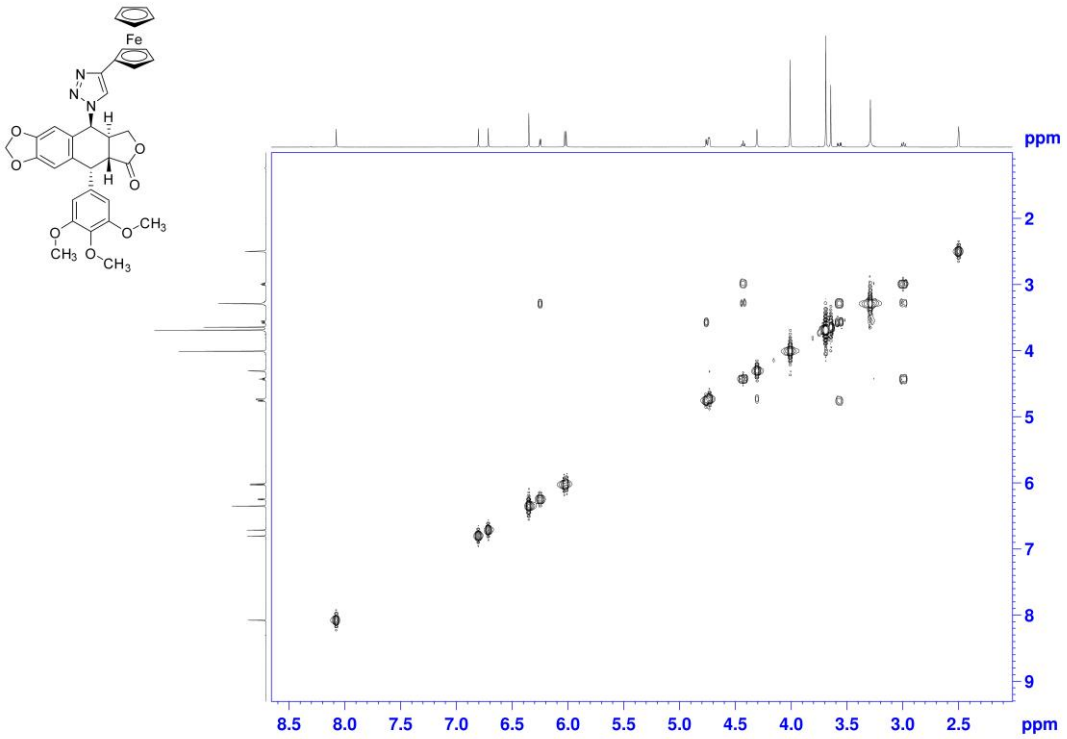
^{1}H NMR spectra of **33**



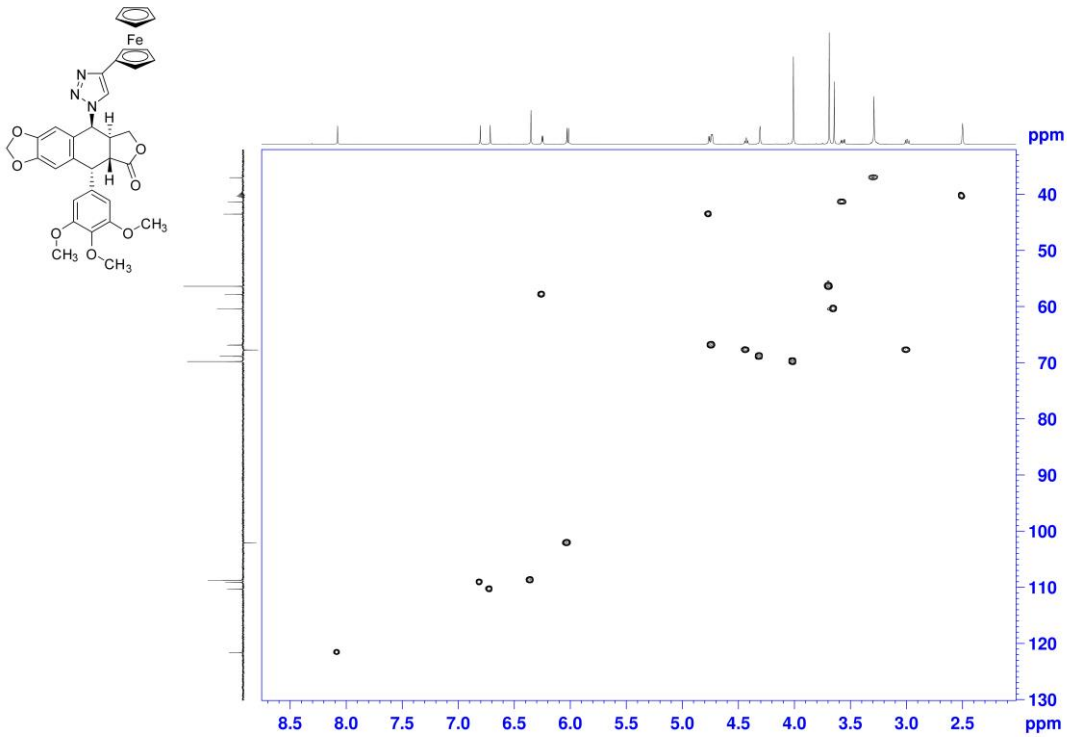
^{13}C{^{1}H} NMR spectra of **33**



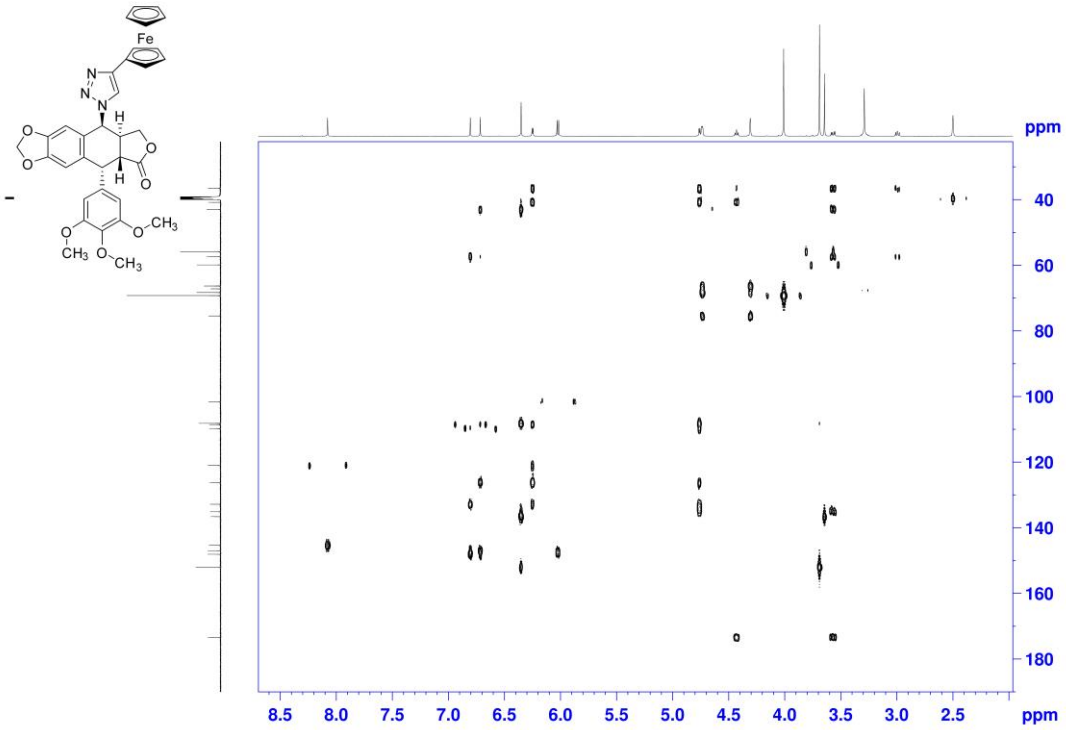
^{1}H-^{1}H COSY spectra of **33**



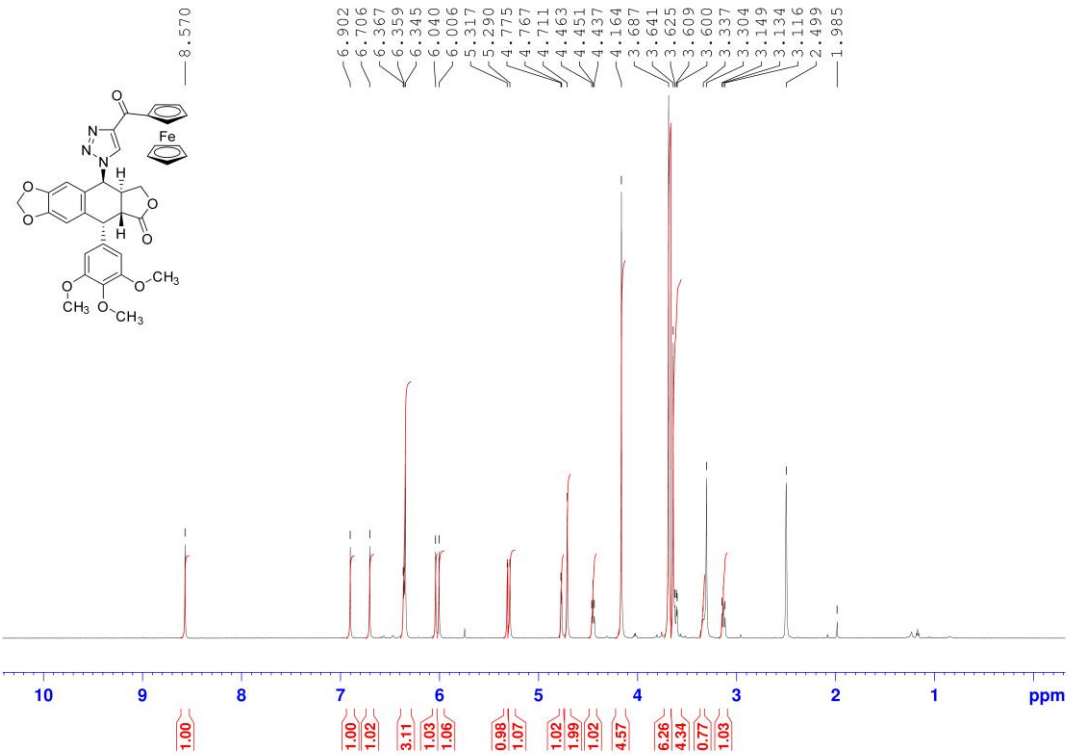
^{1}H-^{13}C HSQC spectra of **33**



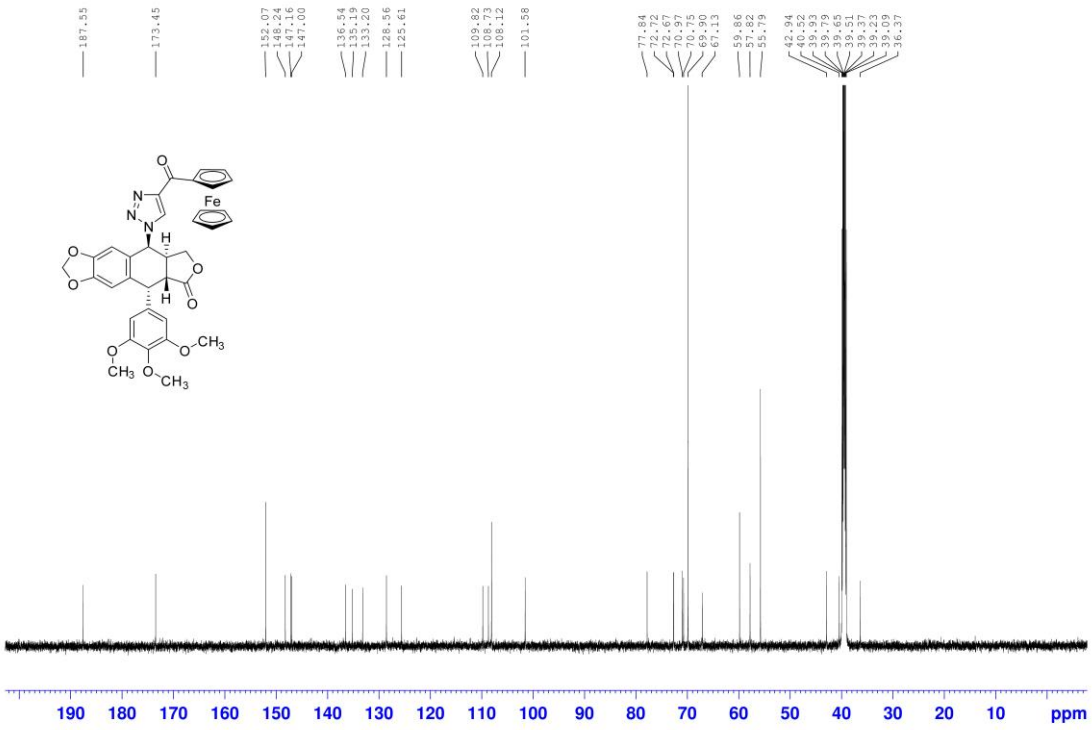
^{1}H-^{13}C HMBC spectra of **33**



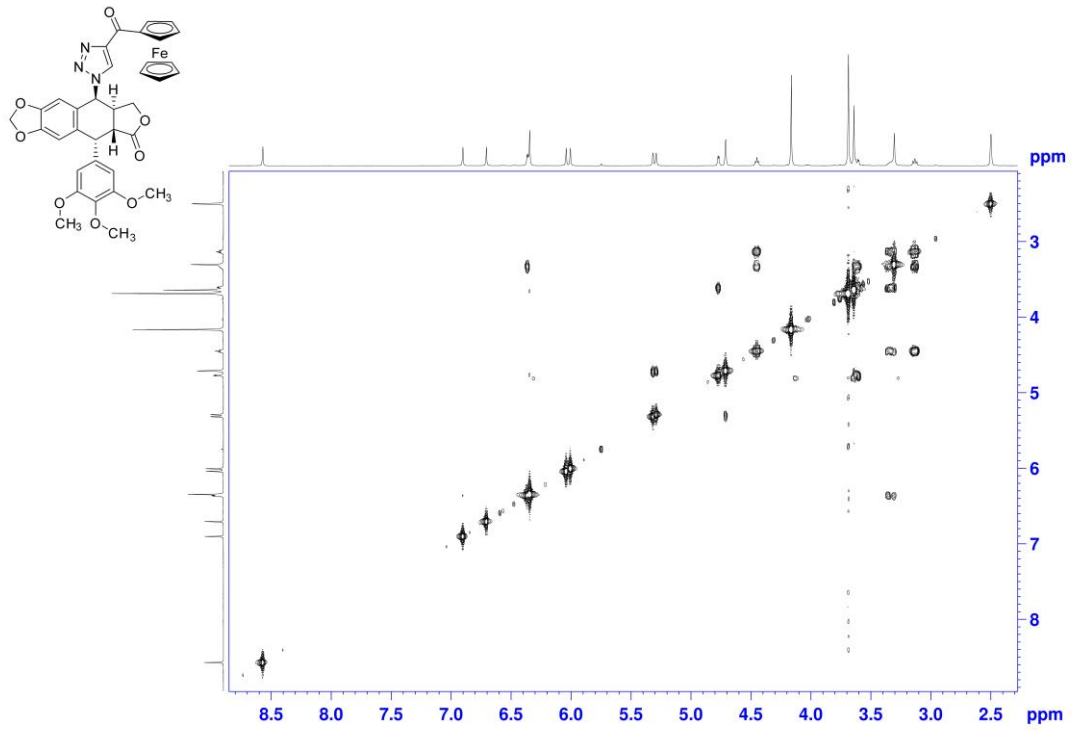
^{1}H NMR spectra of **34**



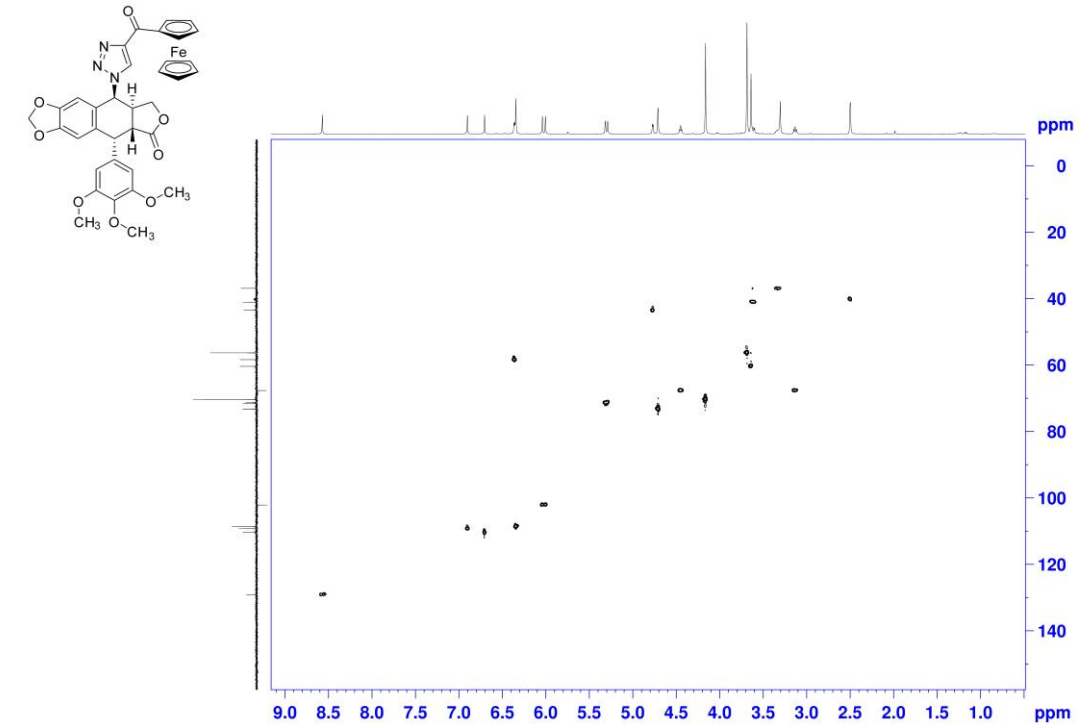
$^{13}C\{^{1}H\}$ NMR spectra of **34**



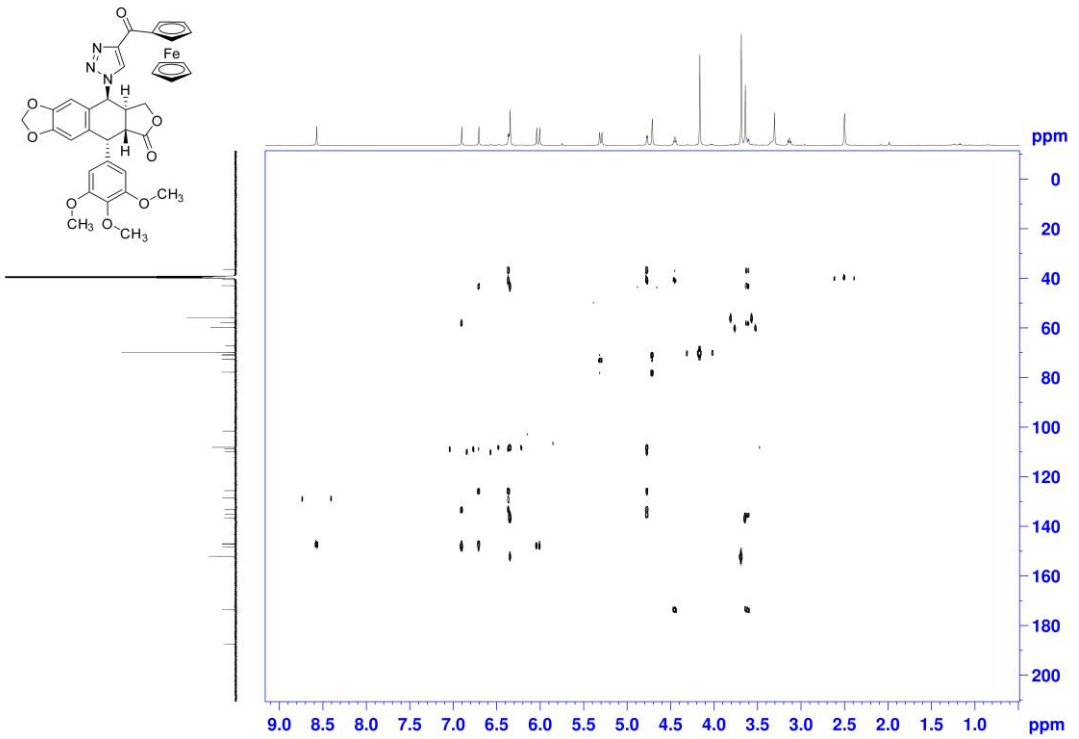
^{1}H-^{1}H COSY spectra of **34**



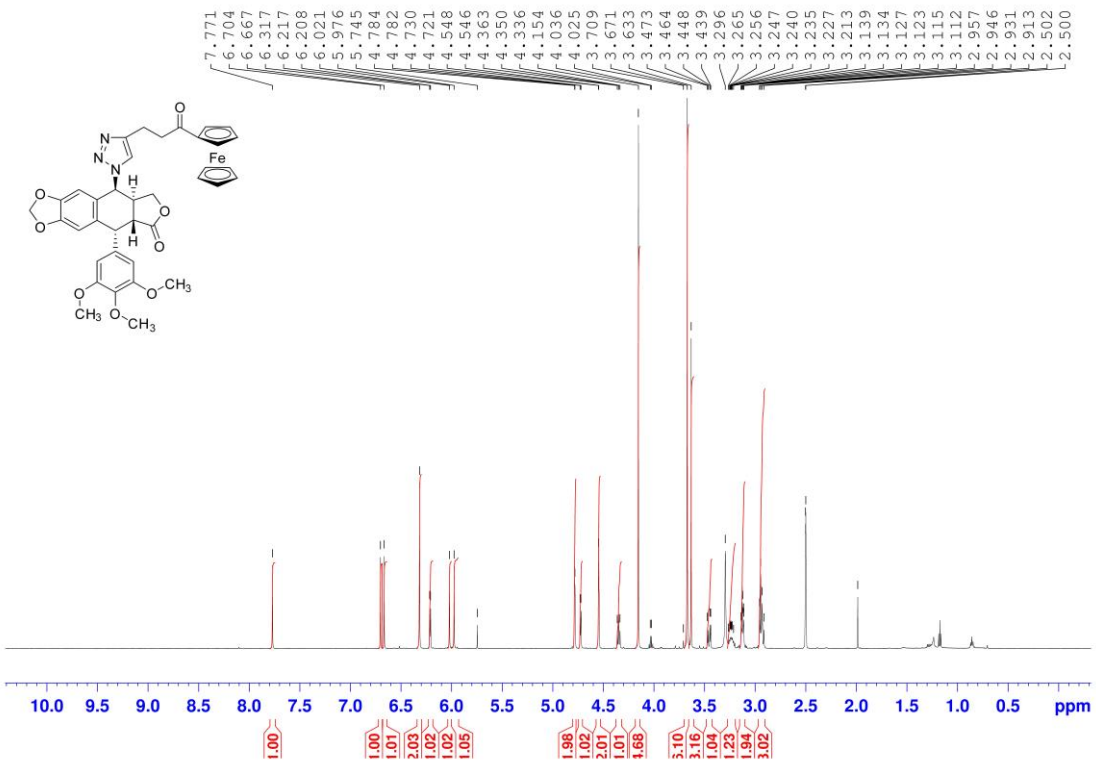
^{1}H-^{13}C HSQC spectra of **34**



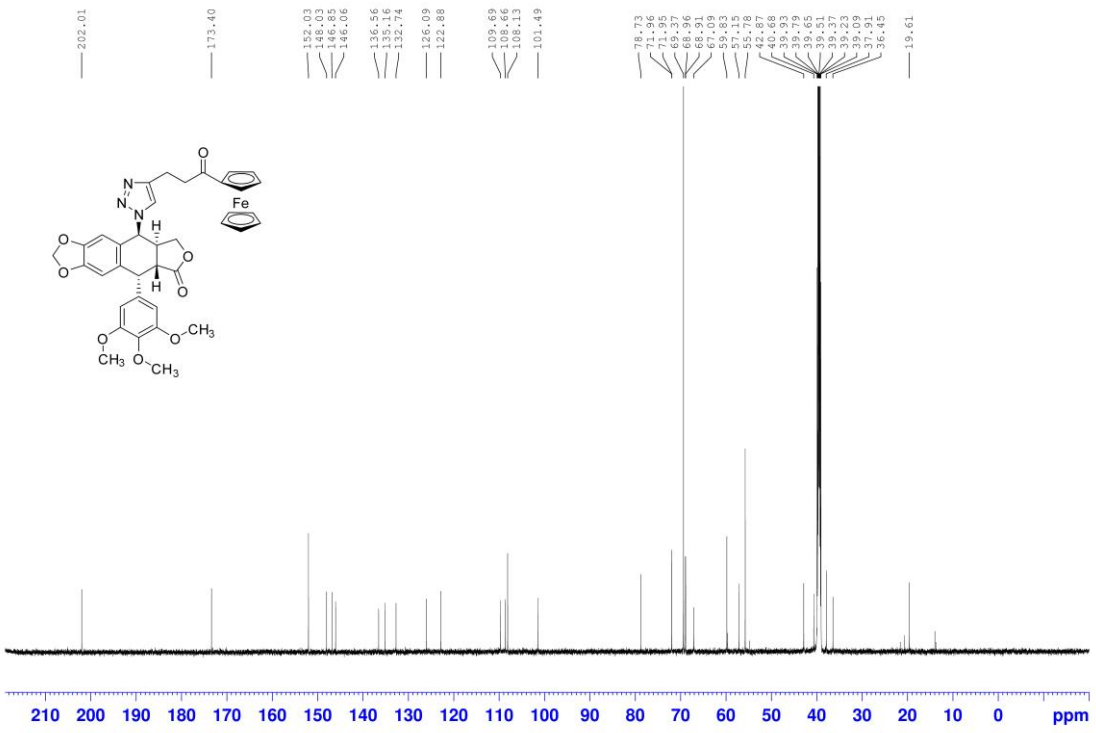
^{1}H-^{13}C HMBC spectra of **34**



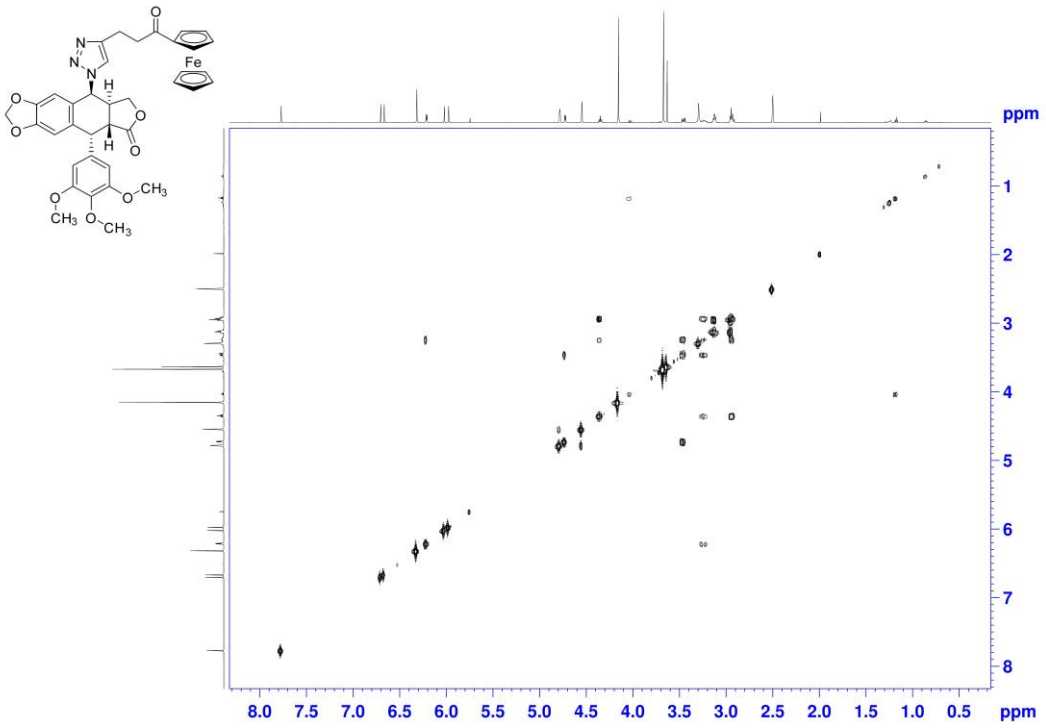
^{1}H NMR spectra of **35**



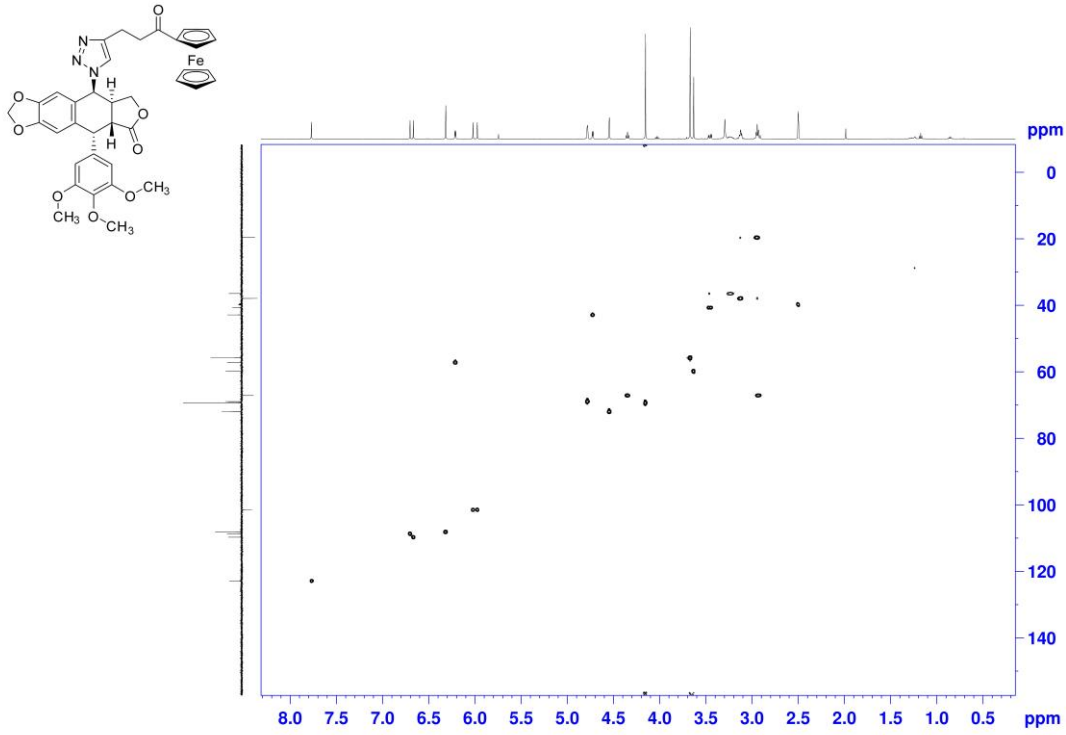
^{13}C{^{1}H} NMR spectra of **35**



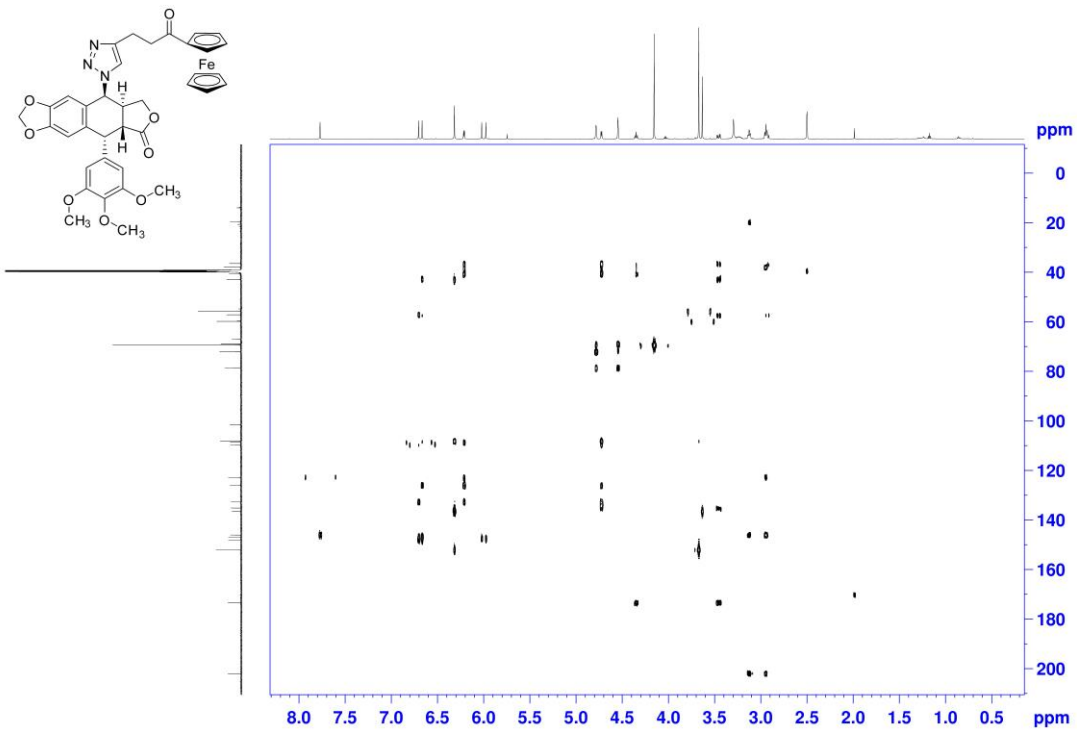
^{1}H-^{1}H COSY spectra of **35**



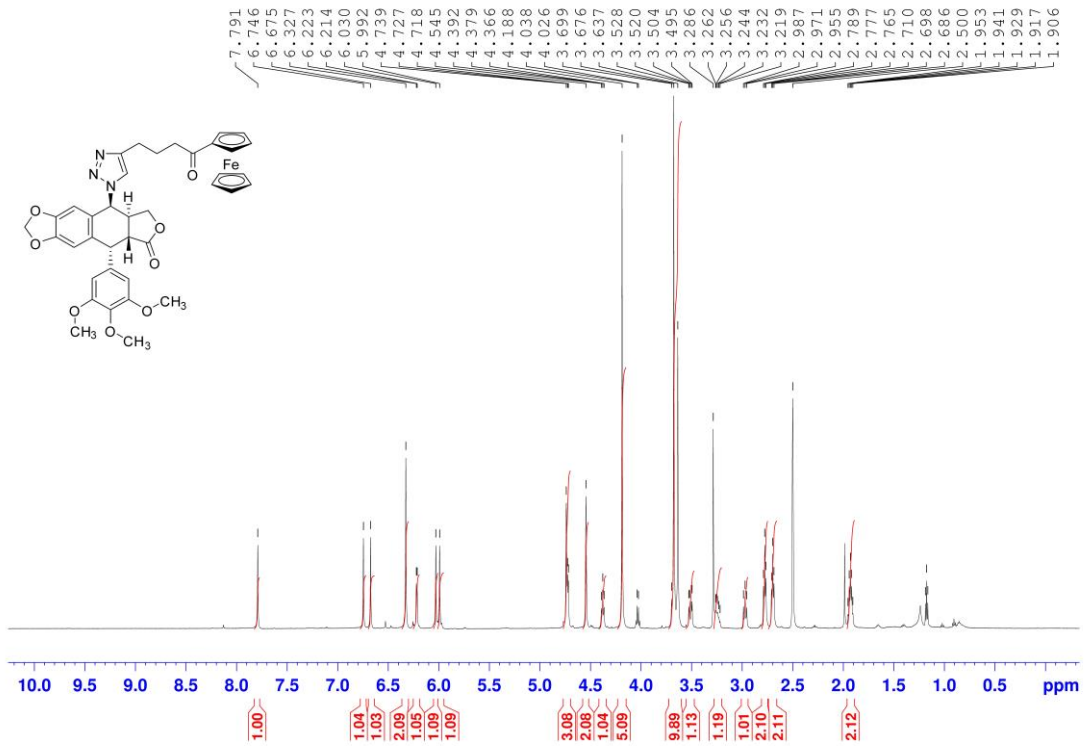
^{1}H-^{13}C HSQC spectra of **35**



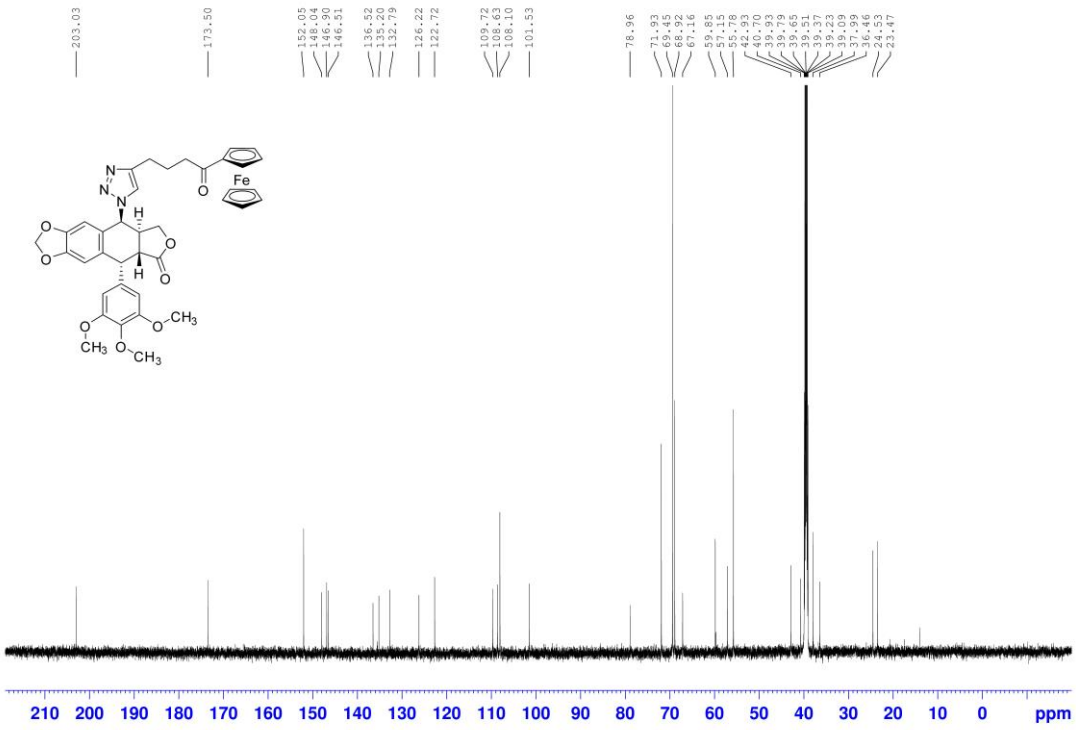
^{1}H-^{13}C HMBC spectra of **35**



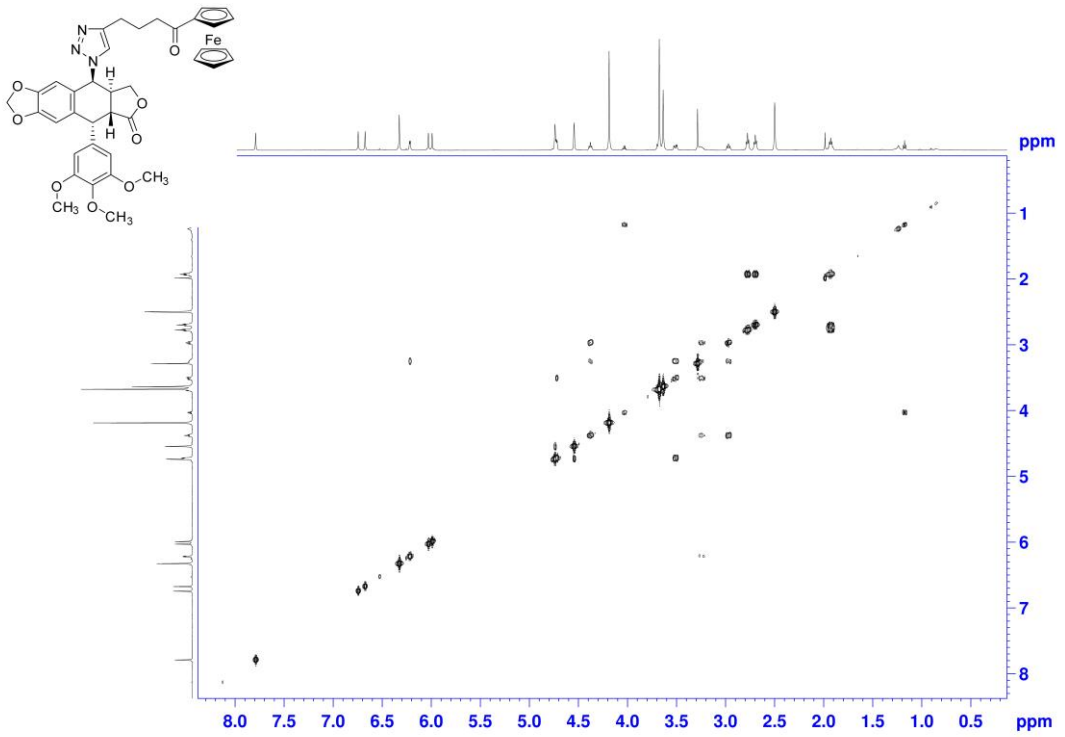
^{1}H NMR spectra of **36**



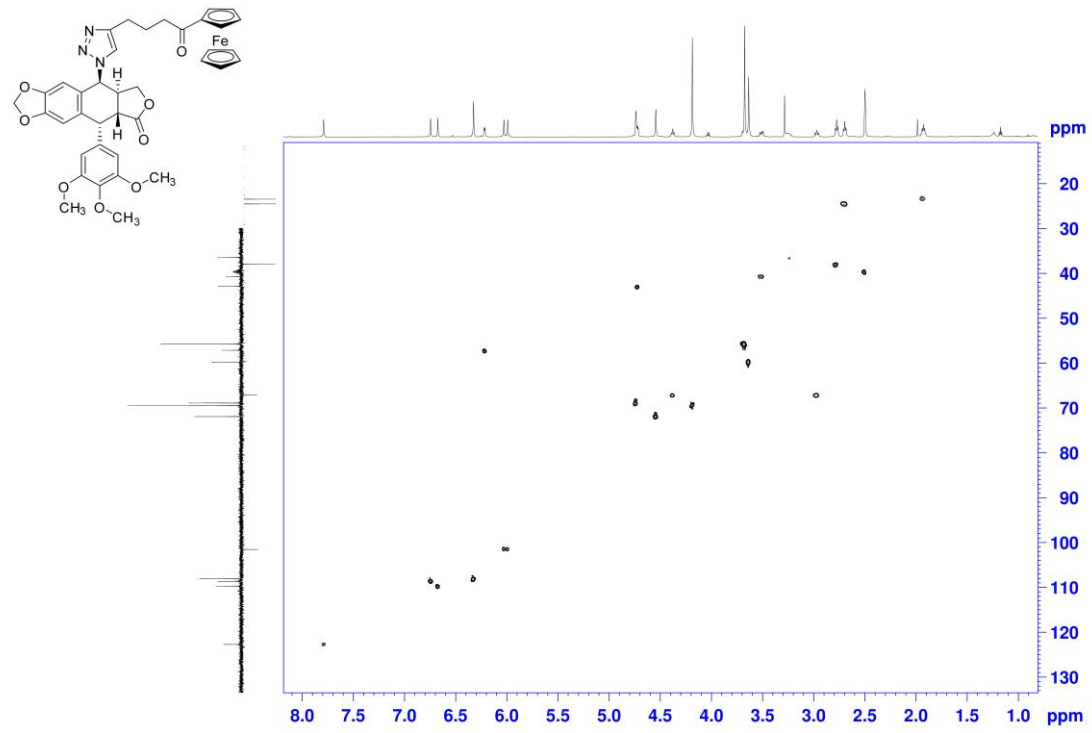
$^{13}C\{^{1}H\}$ NMR spectra of **36**



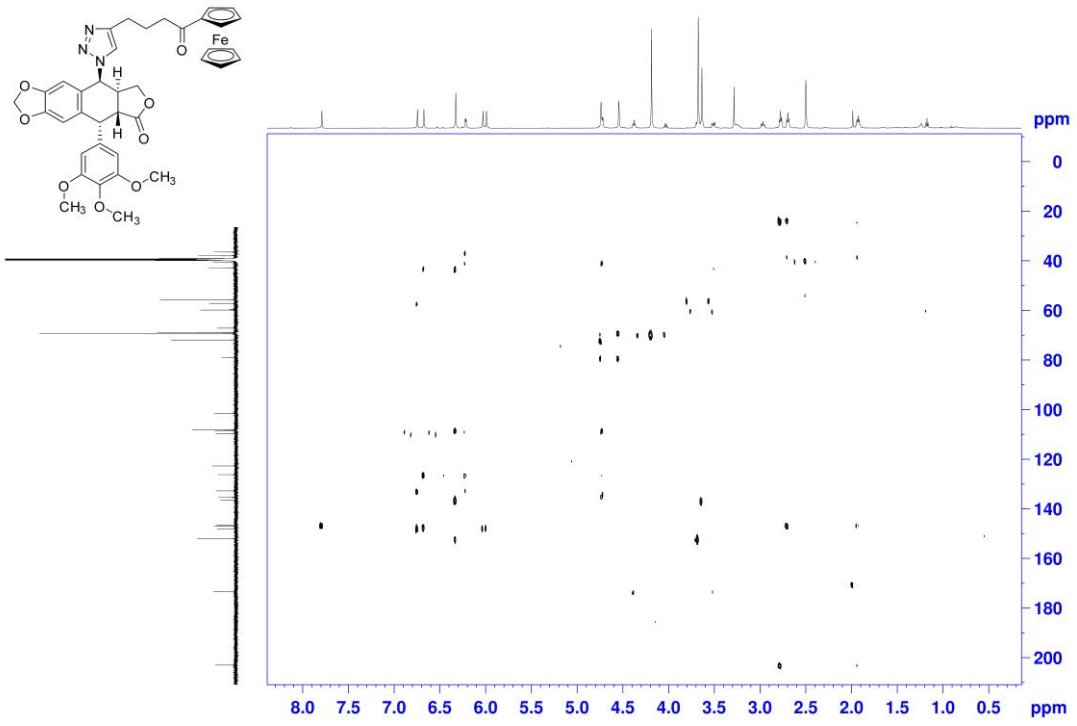
^{1}H-^{1}H COSY spectra of **36**



^{1}H-^{13}C HSQC spectra of **36**



^{1}H-^{13}C HMBC spectra of **36**



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