Supporting Information

Swieteliacates S-U, phragmalin limonoids from the leaves of *Swietenia macrophylla*

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[1] The authors contributed equally to this work.

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1. Supplementary Figures

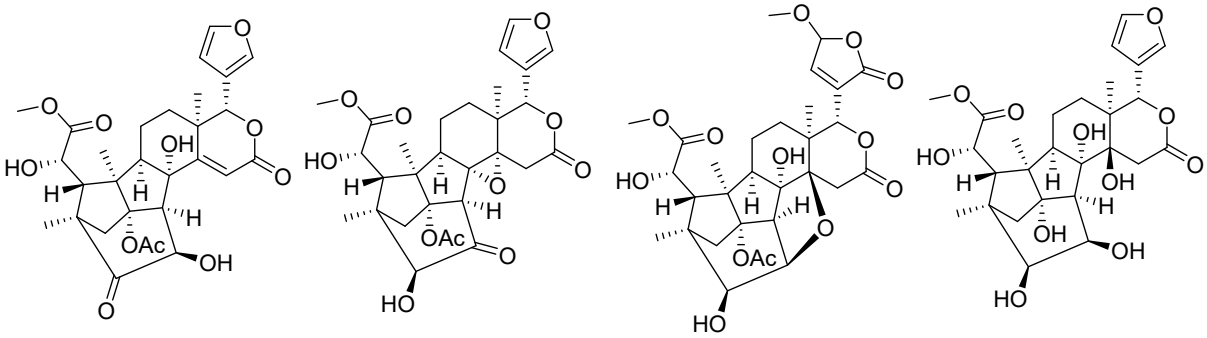


Figure S1.1. Structures of compounds (**4**-**7**) isolated from *S. macrophylla*.

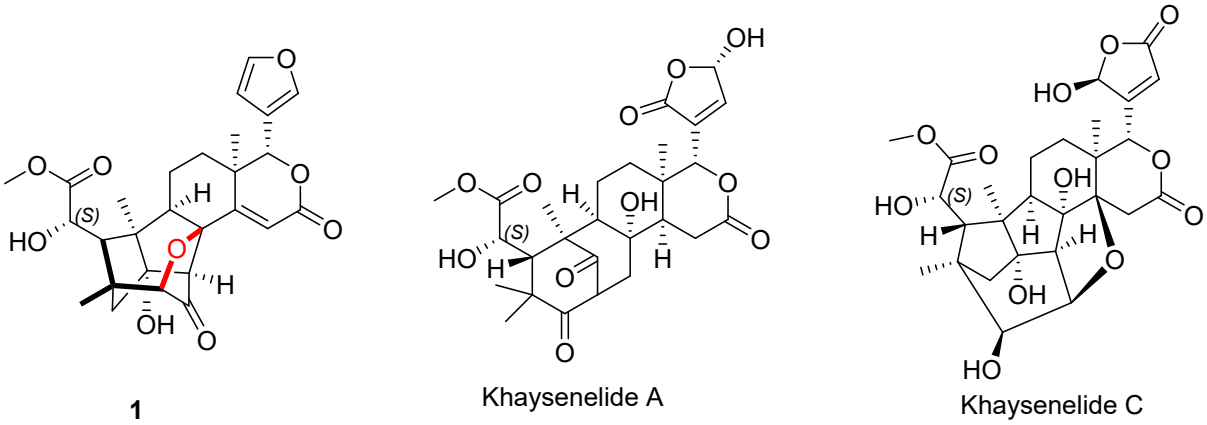


Figure S1.2. Structures of **1** and swieteliacate M[1] isolated from *S. macrophylla*, khaysenelides A and C isolated from *Khaya senegalensis*[2], hainanxylogranins B and F isolated from *Xylocarpus granatum*[3].

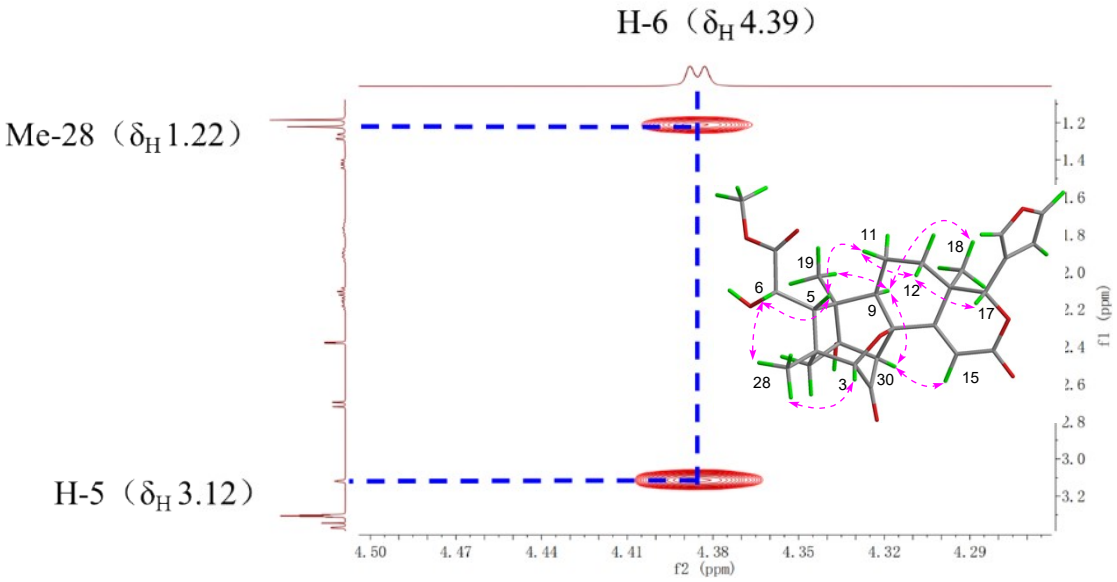


Figure S1.3 Key ROESY correlations of compound **1**

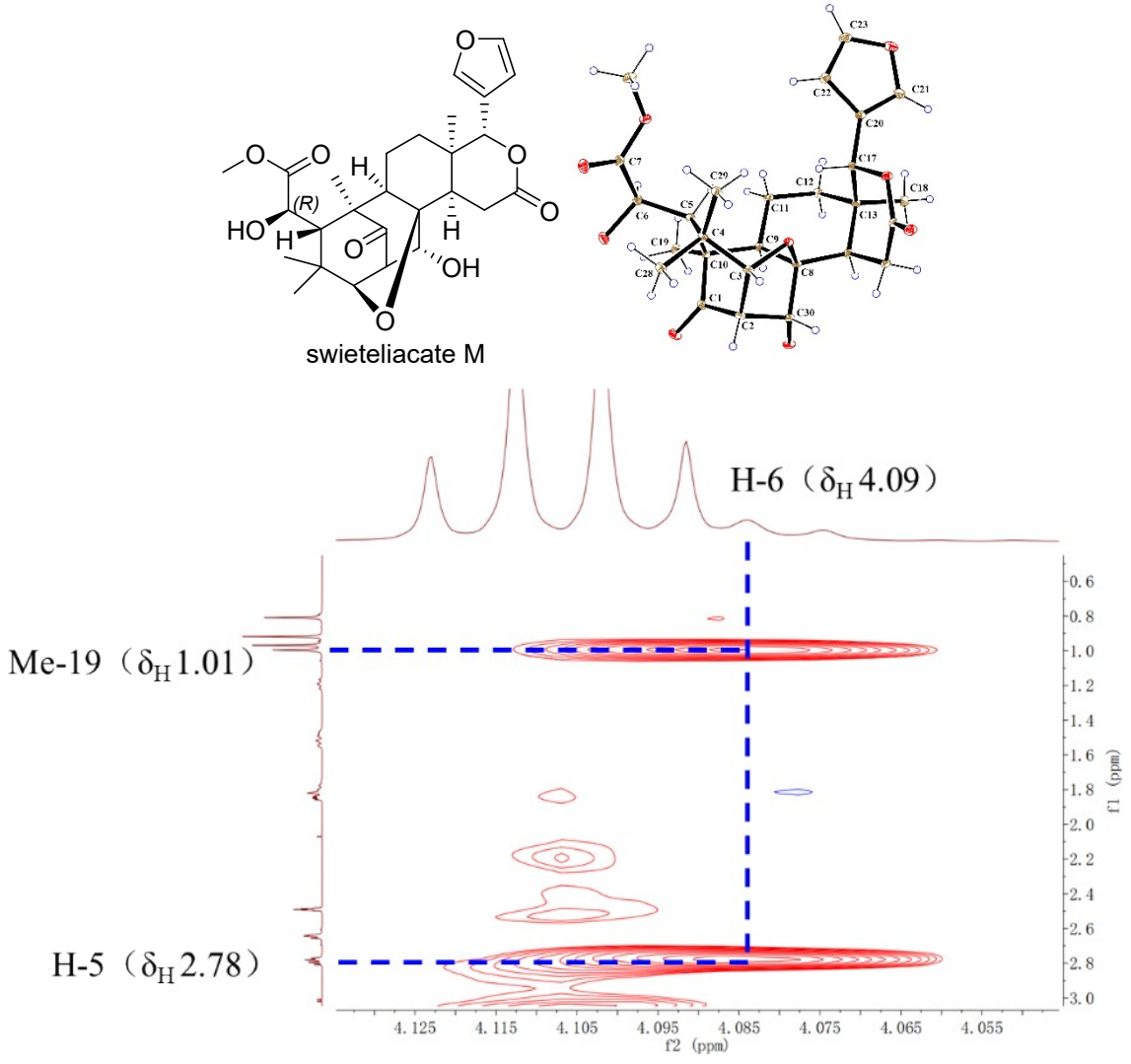


Figure S1.4 X-ray structure and key ROESY correlations of swieteliacate M

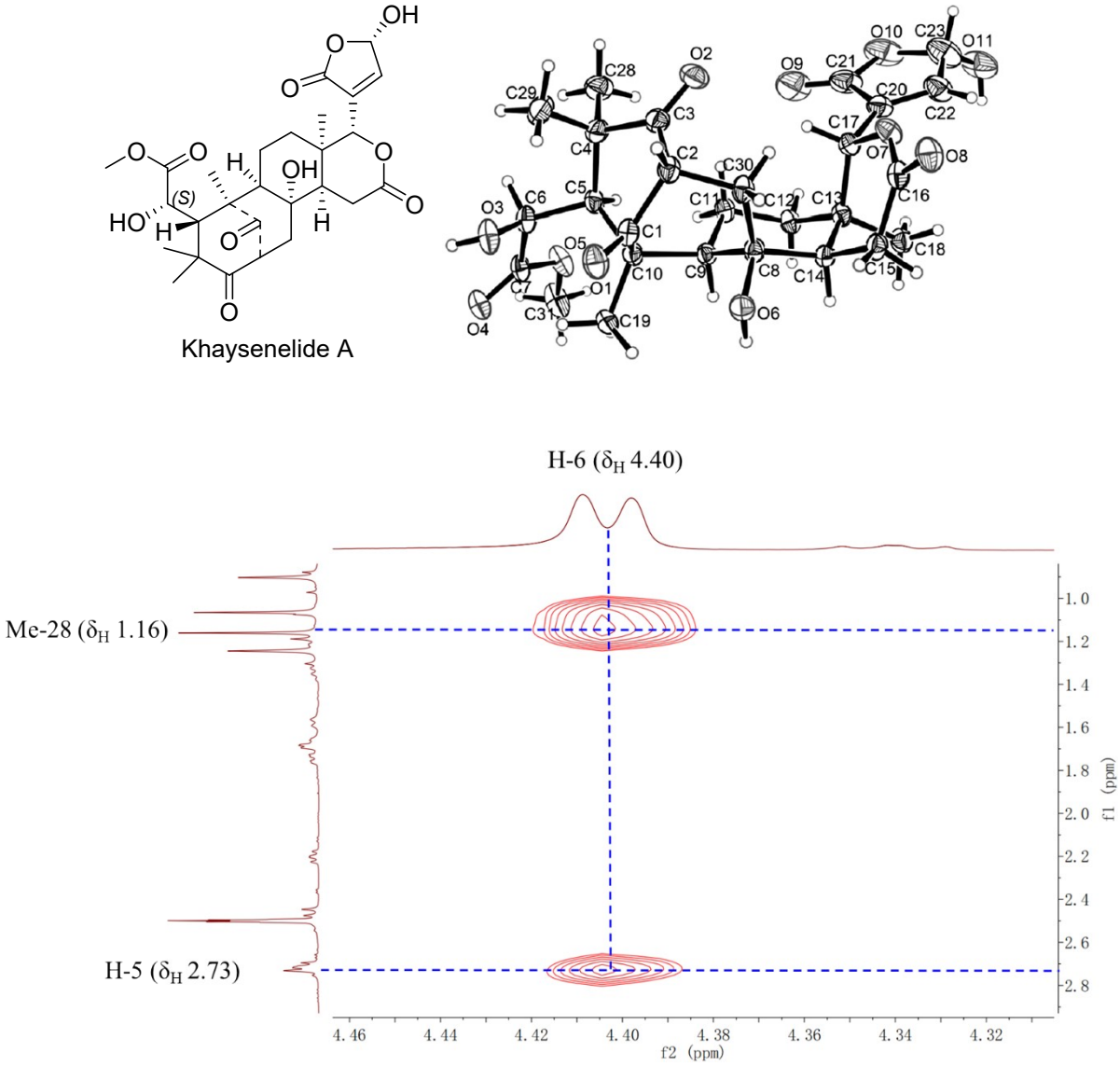
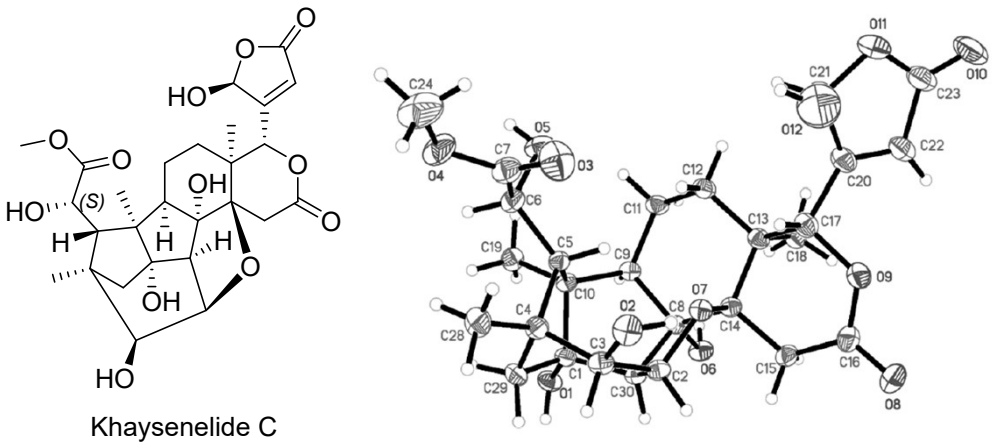


Figure S1.5 X-ray structure and key ROESY correlations of khaysenelide A



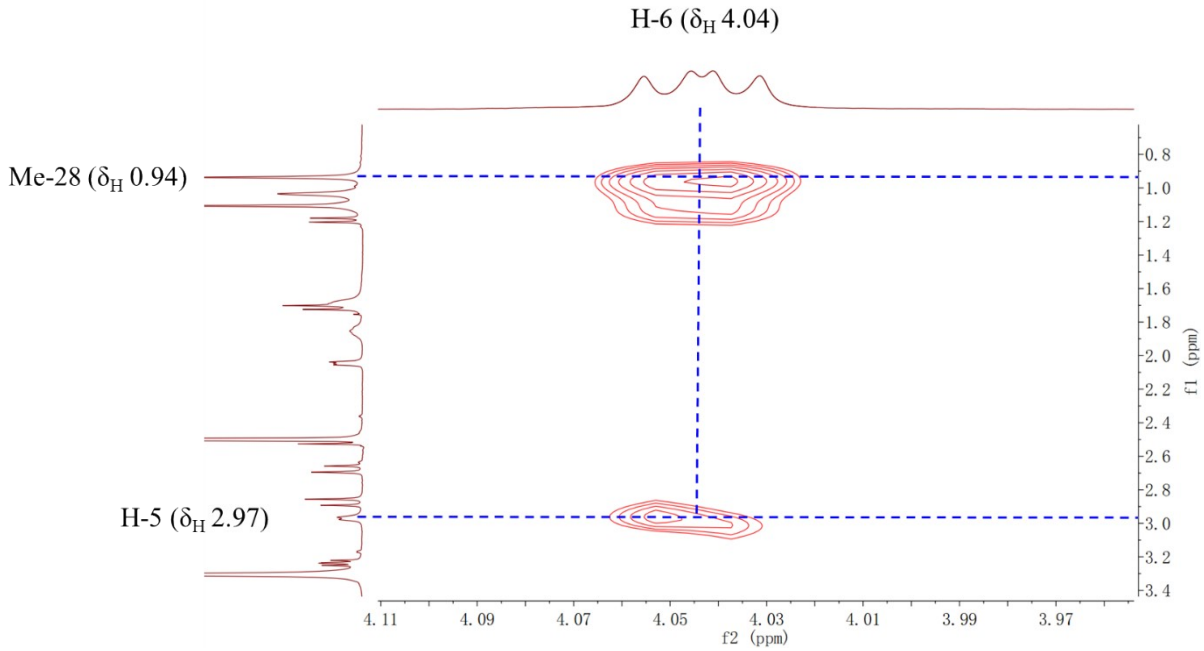


Figure S1.6 X-ray structure and key ROESY correlations of khaysenelide C

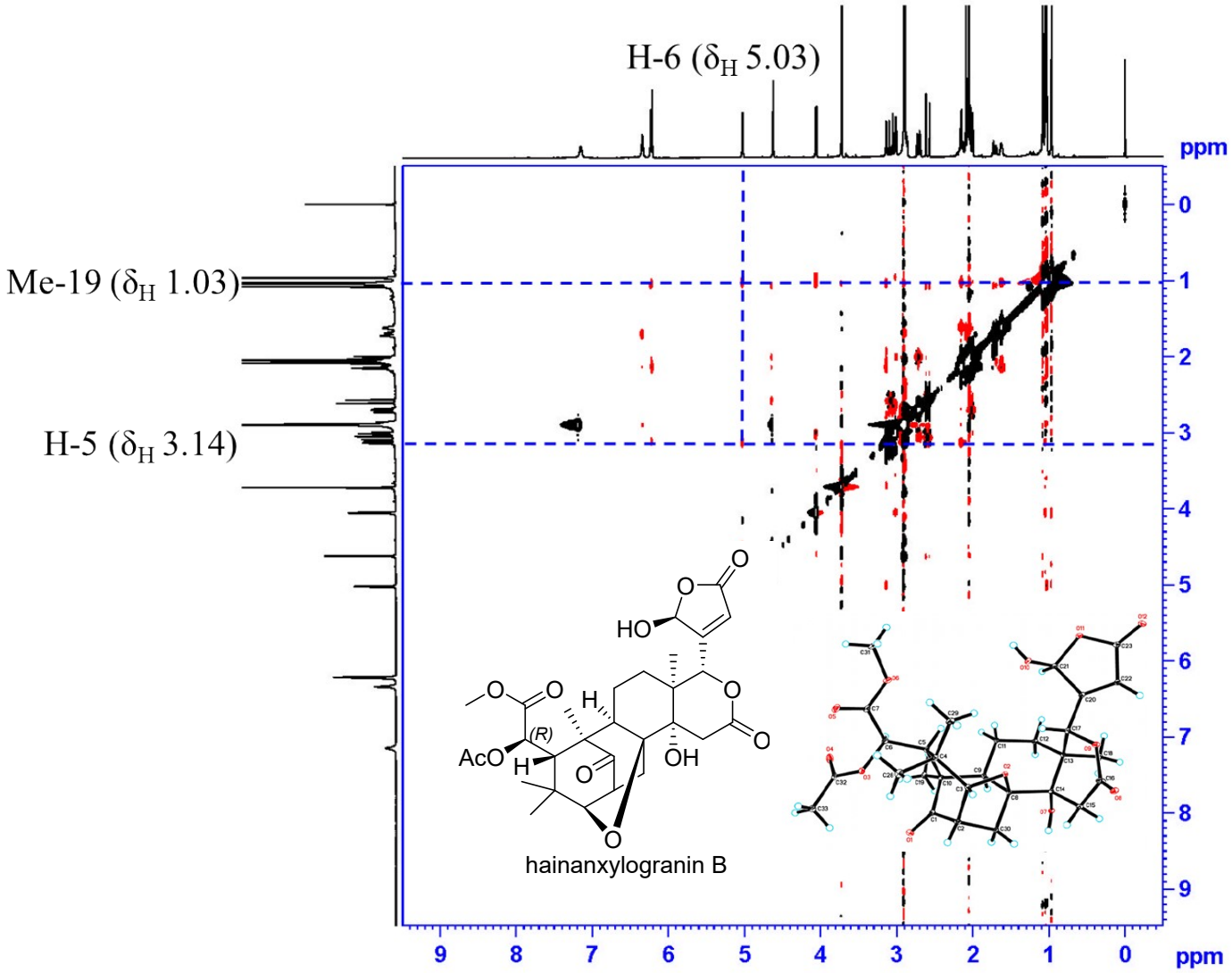


Figure S1.7 X-ray structure and key ROESY correlations of hainanxylogranin B

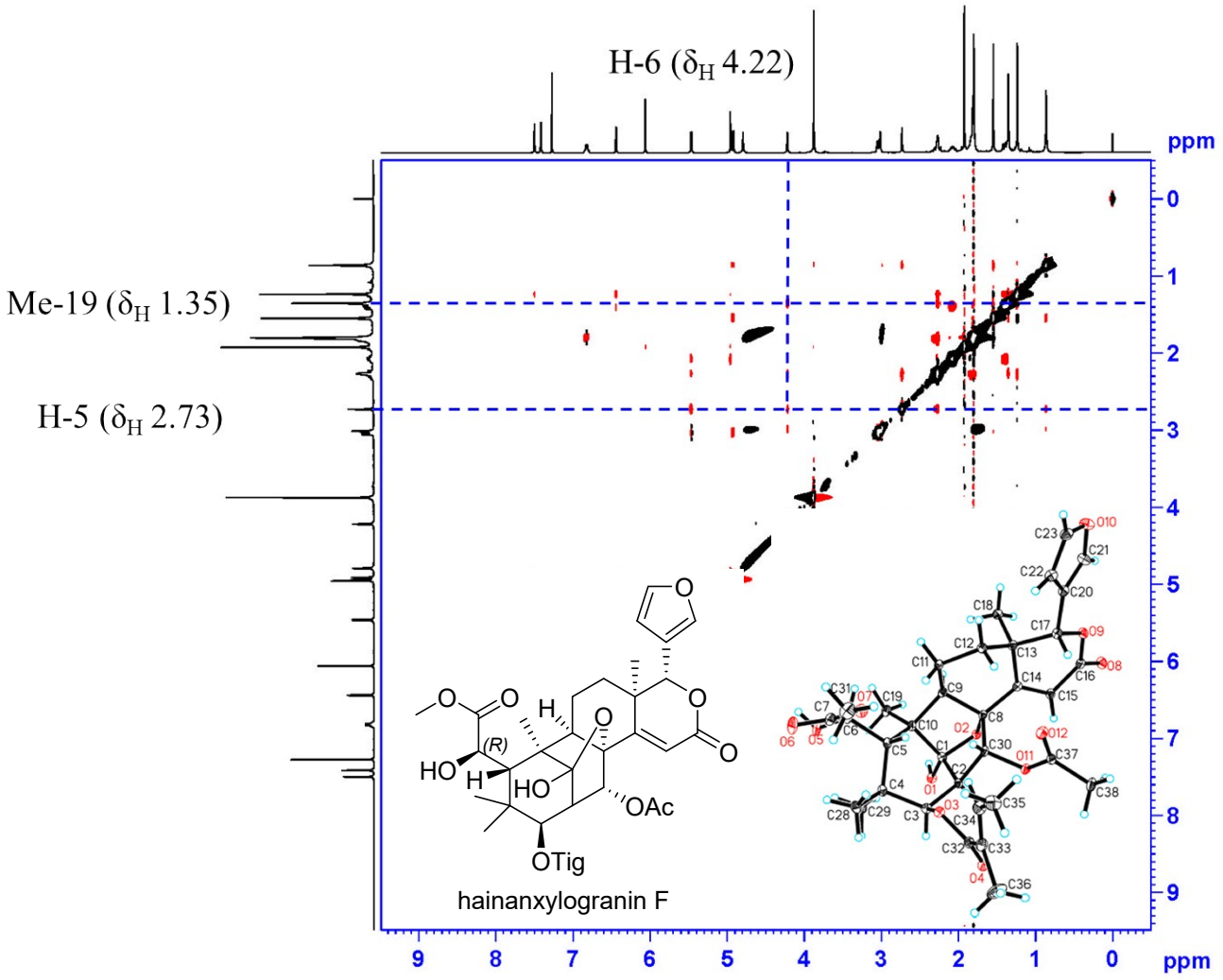


Figure S1.8 X-ray structure and key ROESY correlations of hainanxylogranin F

References

[1] G.-K. Wang, Y.-P. Sun, W.-F. Jin, Y. Yu, J.-Y. Zhu and J.-S. Liu, *Bioorg. Chem.* 2022, **123**, 105780

[2] Y. Li, Q. P Lu, J. Luo, J. S. Wang, X. B. Wang, M. D. Zhu and L. Y. Kong, *Chem. Pharm. Bull.* 2015, **63**, 305–310.

[3] J. C. Zhang, Q. Liao, L. Shen and J. Wu, *Bioorg. Chem*. 2020, **100**, 103903.

2. Biological assays

2.1 Cell culture

Hep G2 cells were resuscitated, passaged and stabilized to a density of 80 % for subsequent experiments.

Male C57/BL6J mice aged 7-8 weeks were selected. Following weighing, intraperitoneal injection of Amobarbital sodium was administered for anesthesia. The abdominal cavity was opened to expose the liver, and the inferior vena cava was incised. Sequential perfusion of the liver was achieved through the portal vein using heparin sodium solution, Krebs-Ringer buffer containing EGTA, and Krebs-Ringer buffer containing $CaCl_2$ and collagenase I. The liver was collected, filtered through a 70 μm cell strainer, and centrifuged at 4 ℃ and 50 $\times g$. The liver pellet was resuspended in pre-cooled RPMI 1640 medium, centrifuged, and the supernatant was discarded and repeated twice. The suspended cells were then seeded into a well plate at an appropriate density using 1640 culture medium containing 10% FBS, obtaining mouse primary hepatocytes (MPH). The protocols and materials for animal experiments adhered to the 'Animal Research: Reporting In Vivo Experiments' (ARRIVE) 2.0 guidelines and received approval from the Institutional Animal Care and Use Committee of Hubei University (Protocol No: 20220048).

2.2 Hepatocyte glucose production (HGP) assay

MPH were seeded in a 6-well plate, and upon stabilization of cellular status, the medium was immediately replaced with sugar-free culture medium. The final concentrations of substrates for hepatic gluconeogenesis, such as sodium pyruvate and sodium lactate, were set at 2 mM and 20 mM, respectively. Cells were co-incubated with 30 μM FSK and 1 μM Dex to induce gluconeogenesis. After a 12 h co-incubation with limonoids (40 μM), glucose content in the supernatant culture medium was measured, and protein quantification was performed. Metformin (2 mM) served as a positive control.[1]

2.3 Cellular TG analysis

HepG2 cells were inoculated in 6-well plates, and treated with FFAs and limonoids (40 μM) for 24 h. Intracellular TG levels were measured using a TG assay kit according to the manufacturer's recommendation. The protein concentration in each well was measured by a BCA protein assay kit to standardize the data.[2]

References

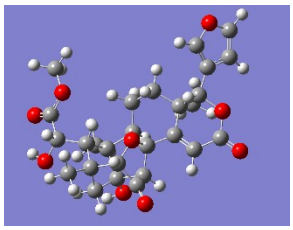
[1] L. Logie, Z. Lee, J. W. Allwood, G. McDougall, C. Beall, G. Rena, *Diabetes, Obes. Metab.* 2018, 20, 2748−2758.

[2] X. Y. Liu, M. Hu, C. Ye, L. H. Liao, C. Ding, L. J. Sun, J. C. Liang, Y. Chen, *Chem-Biol. Interact.* 2022, 368, 110250.

3. ECD Computational details of compounds

The initial conformational analysis of the compounds **1-3** were executed by employing Monte Carlo searching algorithm via the MMFF94 molecular mechanics force field,[1] with the aid of the SPARTAN'16 program package, leading to afford a panel of relatively favored conformations in an energy range of 3 kcal/mol above the global minimum. The force field minimum energy conformers thus obtained were subsequently optimized by applying the density functional theory (DFT) with the B3LYP/6-31G(d) level in vacuum, implemented in the Gaussian 09 software package.[2] Harmonic vibrational frequencies were also performed to confirm no imaginary frequencies of the finally optimized conformers. These predominant conformers were subjected to theoretical calculation of ECD by utilizing Time-dependent density functional theory (TDDFT) calculations at the B3LYP/6-311g (2d, p) level in MeOH using the Polarizable Continuum Model (PCM) solvent model. The energies, oscillator strengths, and rotational strengths of each conformers were carried out with Gaussian 09 software package. The oretical calculations of ECD spectra for each conformer were then approximated by the Gaussian distribution. The final ECD spectrum of the individual conformers was summed up on the basis of Boltzmann-weighed population contribution by the SpecDisv1.64.[3]

Table S3.1. Energy analyses of conformers (1*S*,3*R*,4*R*,5*R*,6*S*,8*R*,9*R*,10*S*,13*R*,17*R*,30*S*)-**1**a-f

NO.	3D comformers	Free energy		
		E (Hartree)	ΔE (Kcal/mol)	Boltzmann distribution
1a		-1722.131521	0.0000	34.48%

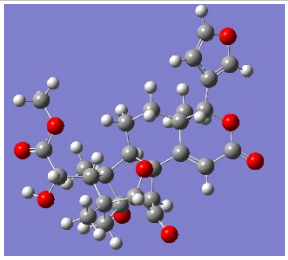
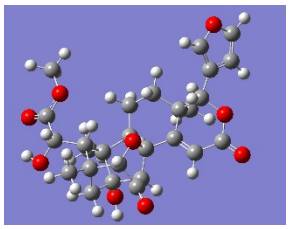
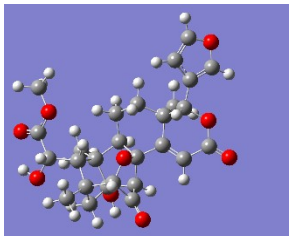
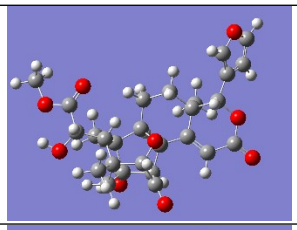
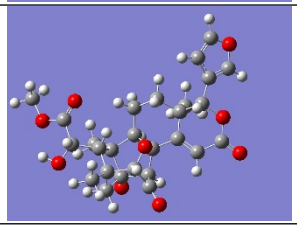
1b		-1722.130999	0.3275	19.83%
1c		-1722.130904	0.3869	17.94%
1d		-1722.130386	0.7118	10.36%
1e		-1722.130344	0.7383	9.91%
1f		-1722.130081	0.9037	7.49%

Table S3.2. Energy analyses of conformers (1*S*,3*R*,4*R*,5*R*,6*S*,8*S*,9*R*,10*S*,13*R*,17*R*,30*S*)-**2**a-c

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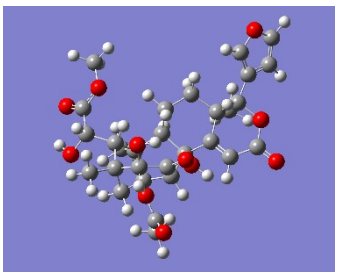
2a		-1951.002984	0.0000	34.40%

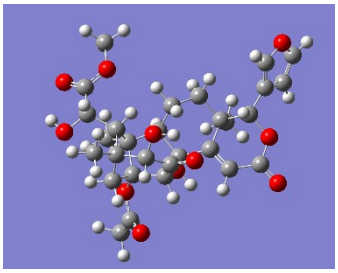
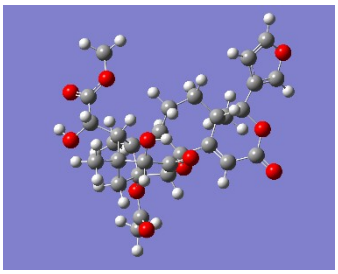
2b		-1951.002984	0.0000	34.40%
2c		-1951.002874	0.0690	30.62%

Table S3.3. Energy analyses of conformers (1*S*,3*R*,4*R*,5*R*,8*S*,9*R*,10*S*,13*R*,17*R*,30*S*)-**3**a-f

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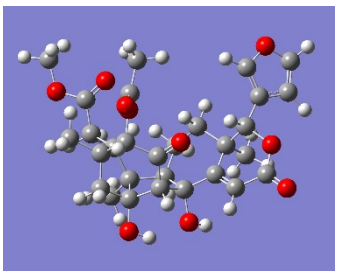
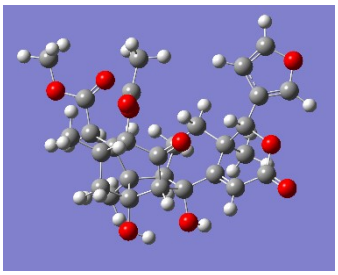
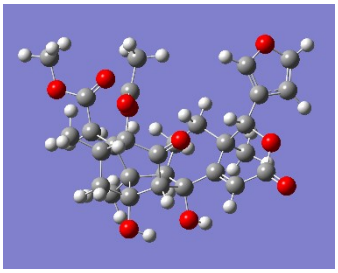
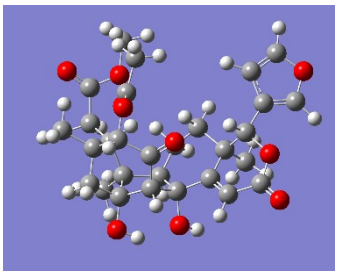
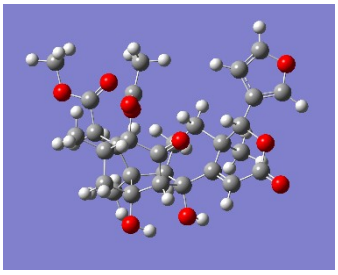
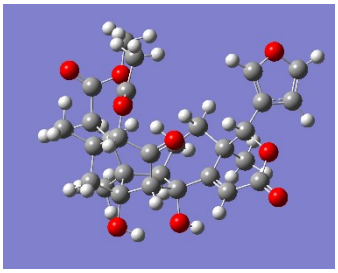
3a		-1875.851332	0.0000	42.89%
3b		-1875.850901	0.2706	27.16%

3c		-1875.849992	0.8410	10.36%
3d		-1875.849922	0.8846	9.63%
3e		-1875.849483	1.1599	6.05%
3f		-1875.849071	1.4189	3.91%

References

[1] Halgren TA. *J Comput Chem*, 1999, **20**, 730-748.

[2] Frisch MJ, Trucks GW, Schlegel H B, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian H P, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery Jr JA, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC,

Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ, Gaussian 09, Rev. C 01; Gaussian, Inc., Wallingford CT, 2009.

[3] Bruhn T, Schaumloffel A, Hemberger Y, Bringmann G. *Chirality*, 2013, **25**, 243-24.

4. Original spectra of compound

NMR, MS, ORD, UV and CD spectra of compound 1

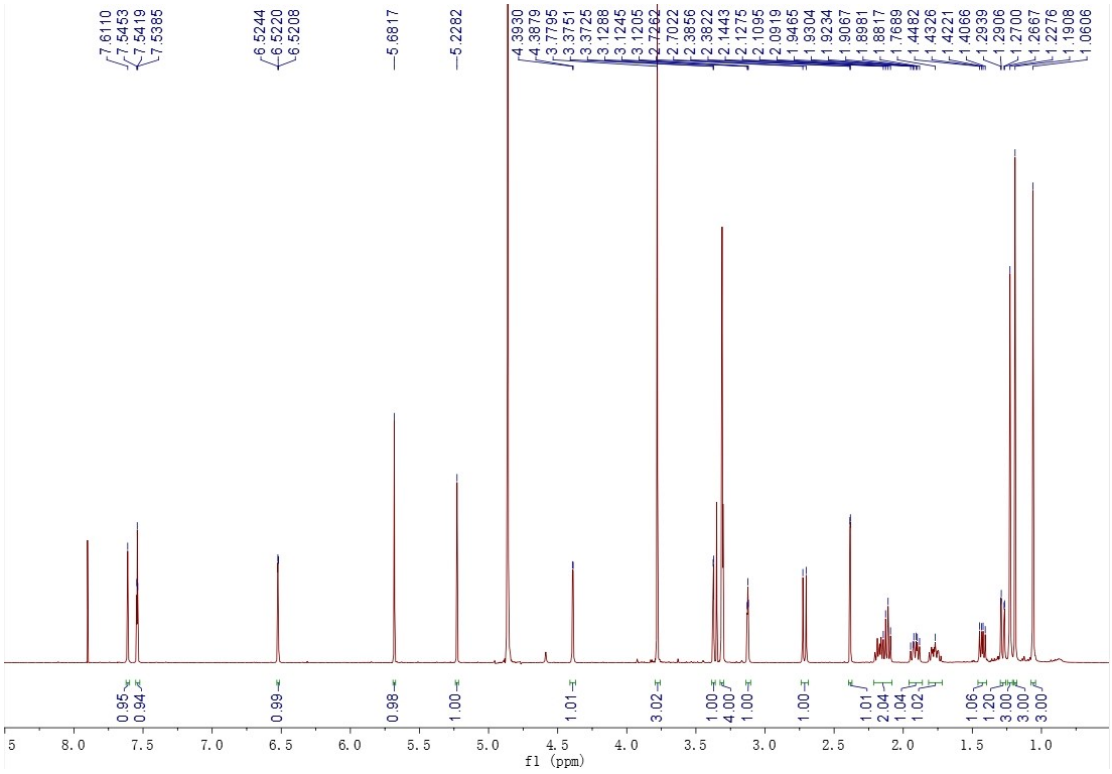


Figure 4.1.1. ^{1}H NMR spectrum of compound **1** in CD_3OD

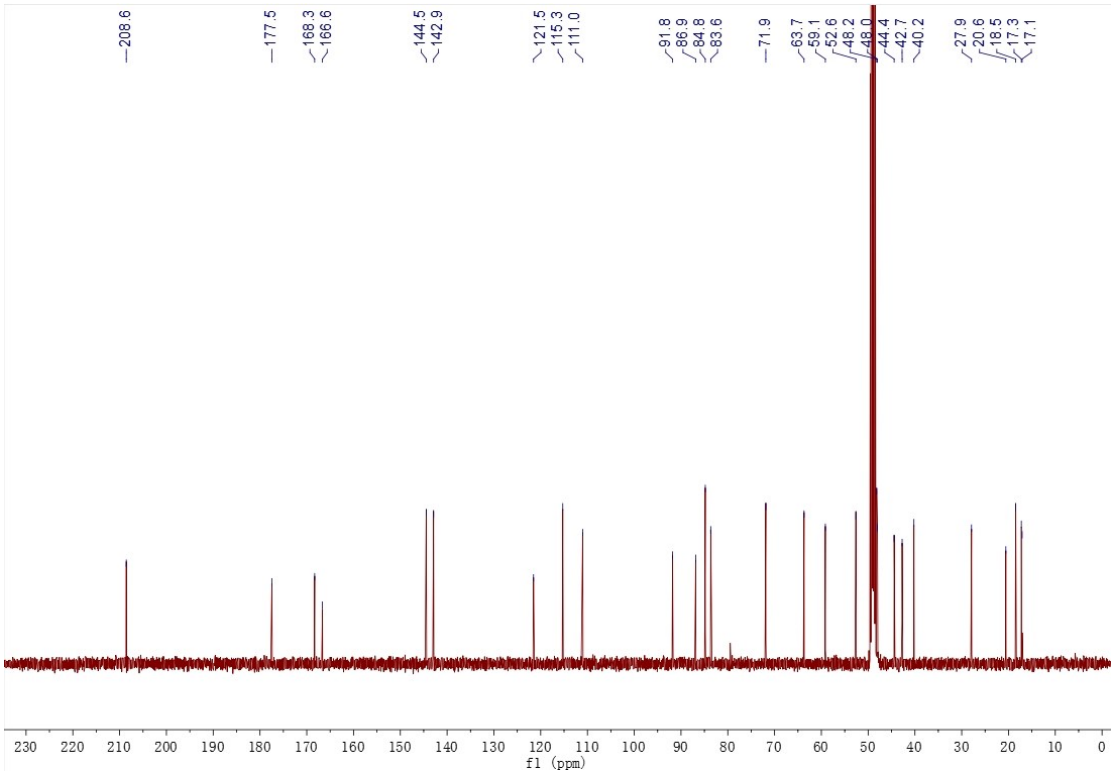


Figure 4.1.2. ^{13}C NMR spectrum of compound **1** in CD_3OD

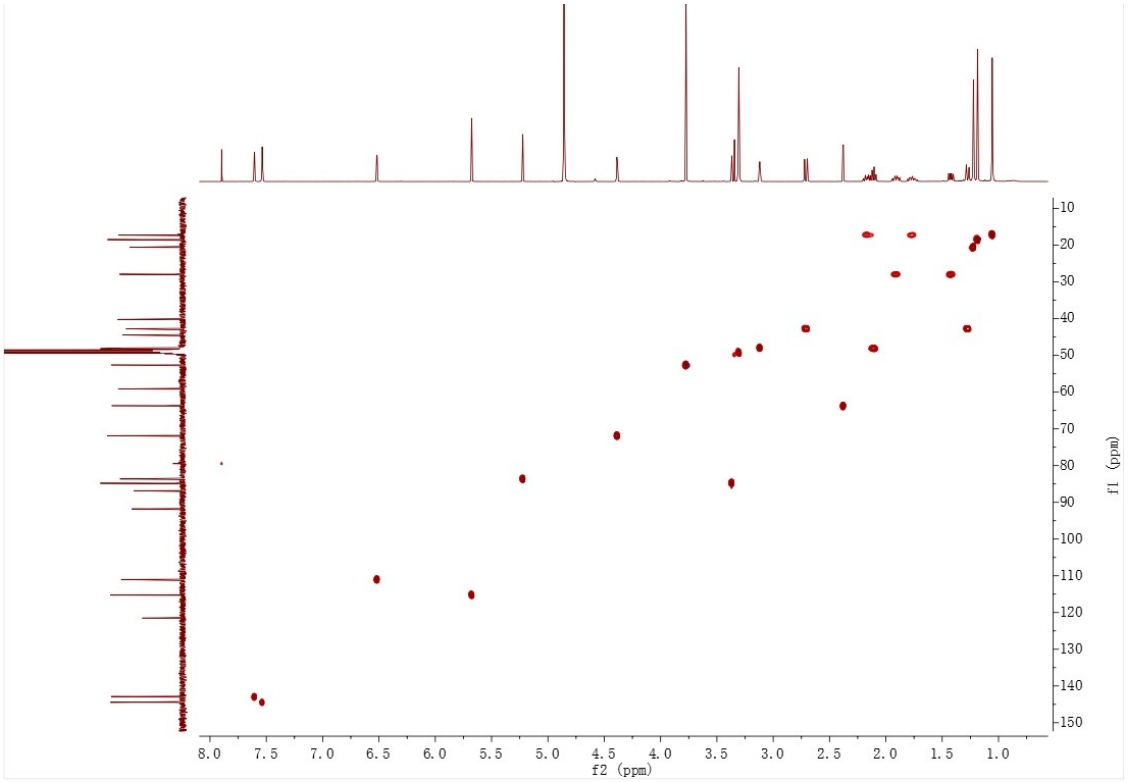


Figure 4.1.3. HSQC spectrum of compound **1** in CD_3OD

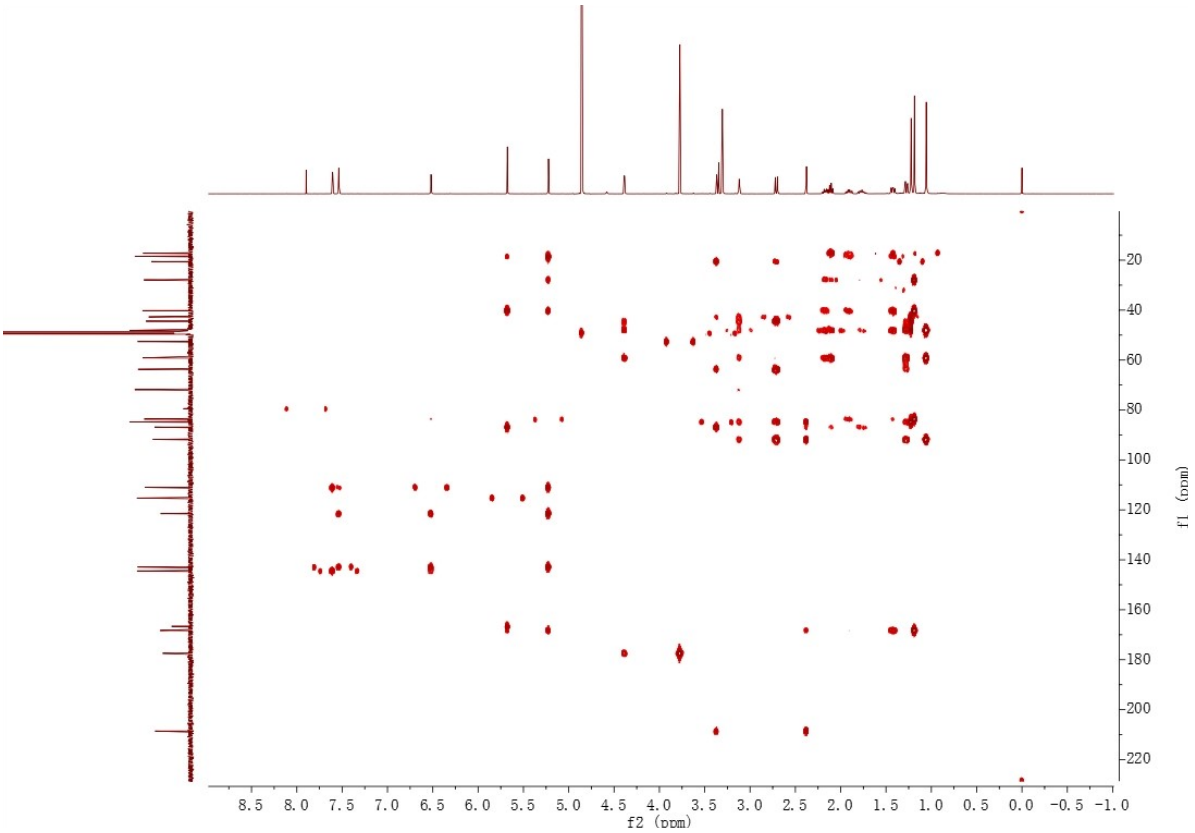


Figure 4.1.4. HMBC spectrum of compound **1** in CD_3OD

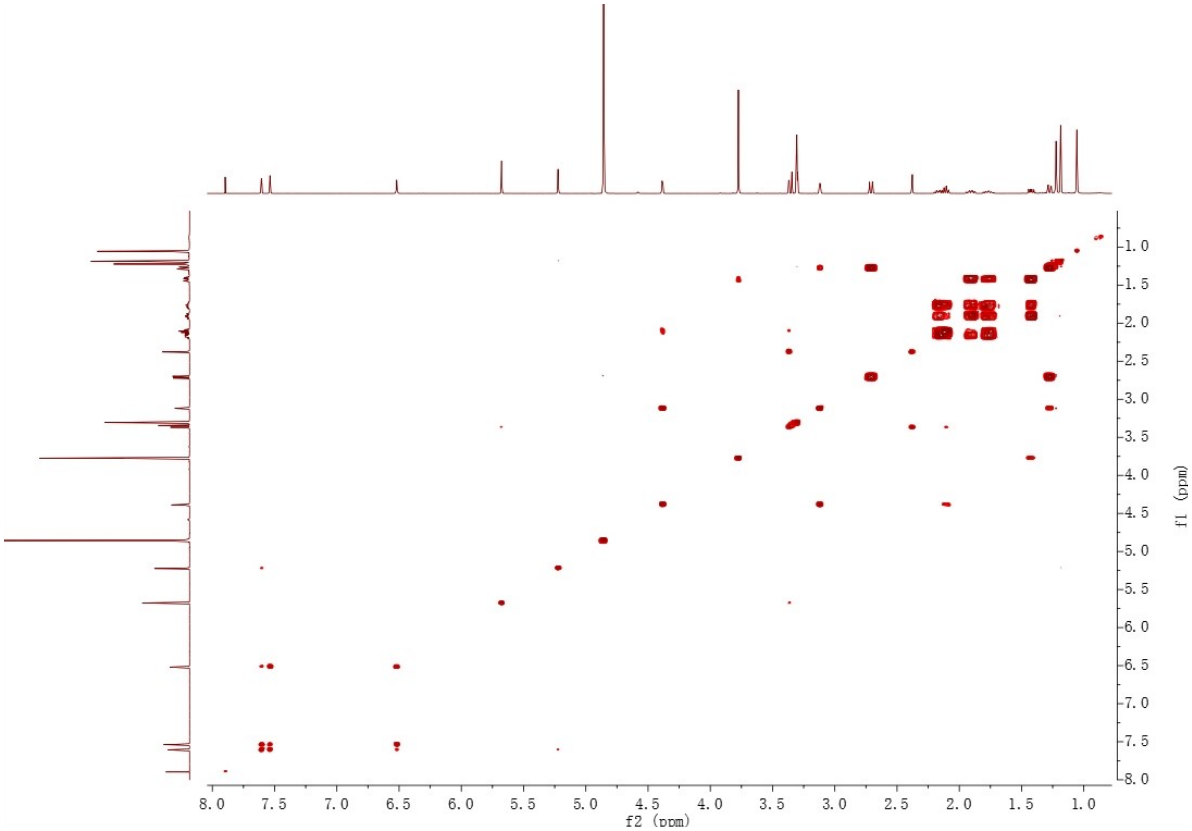


Figure 4.1.5. ^{1}H-^{1}H COSY spectrum of compound **1** in CD_3OD

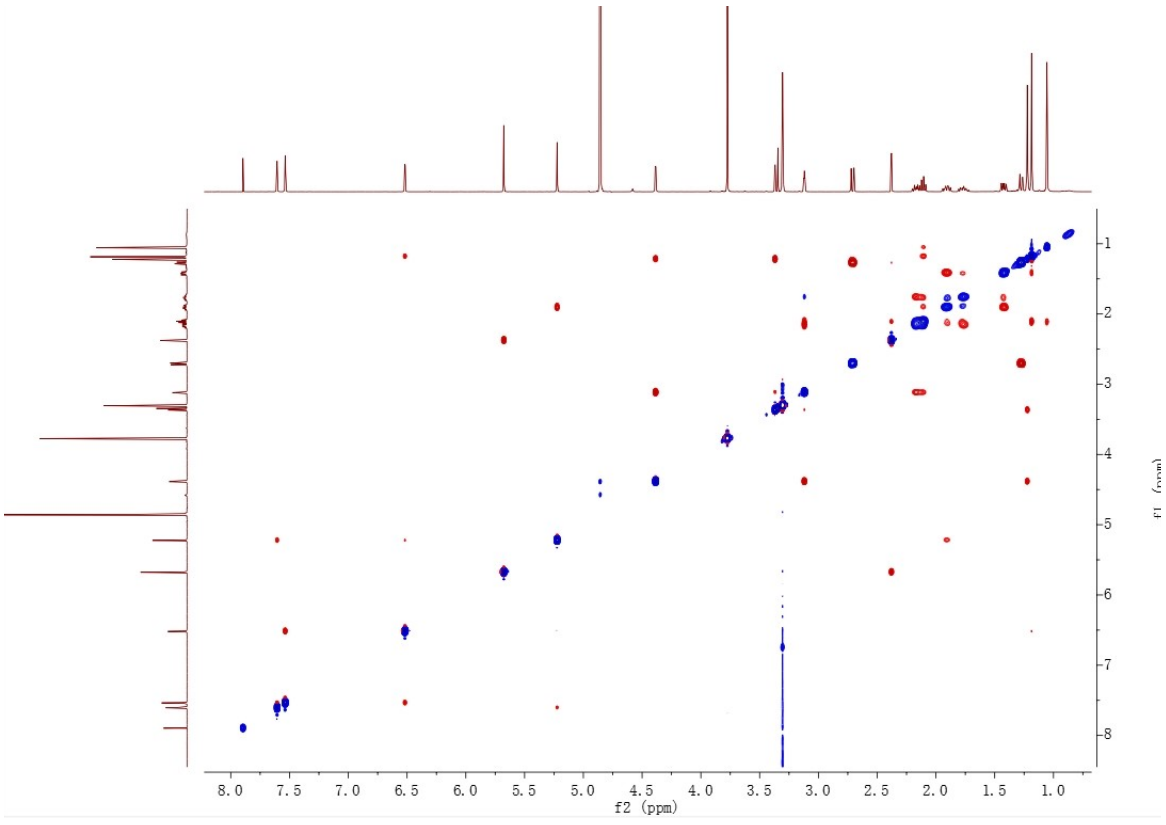


Figure 4.1.6. ROESY spectrum of compound **1** in CD_3OD

Formula Predictor Report - wjy-67.lcd

Page 1 of 1

Data File: E:\DATA\2021\0118\wjy-67.lcd

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2H	1	0	0	Na	1	0	0	Cl	1	0	0	Pd	2	0	0	
C	4	5	50	Mg	2	0	0	Co	2	0	0	Ag	1	0	0	
N	3	0	10	Si	4	0	0	Cu	2	0	0	I	3	0	0	
O	2	0	30	P	3	0	0	Se	2	0	0					

Error Margin (ppm): 5
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

DBE Range: -2.0 - 100.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: OR

Electron Ions: both
Use MSn Info: yes
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Max Results: 20

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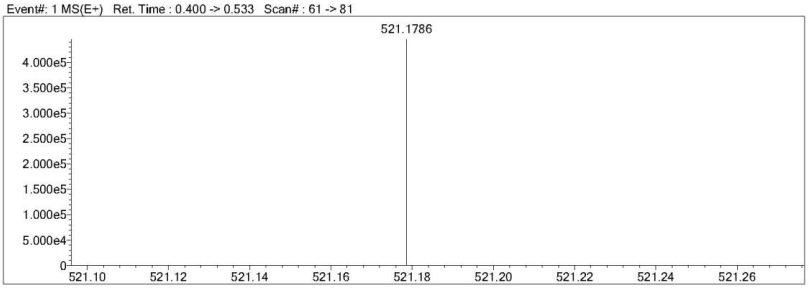
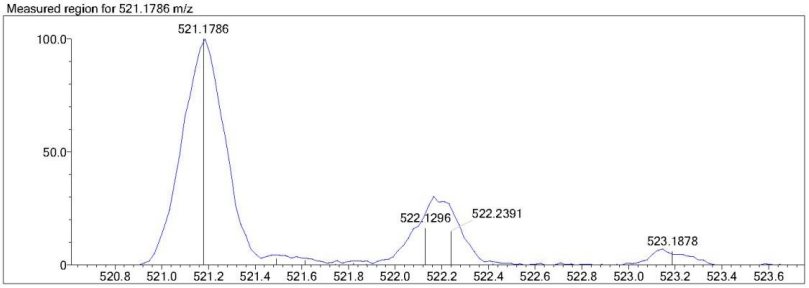
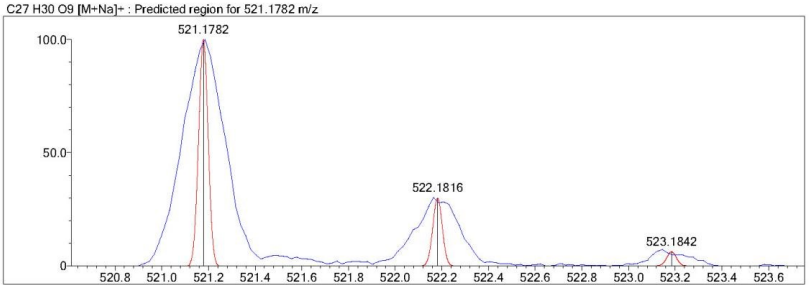


Measured region for 521.1786 m/z



C27 H30 O9 [M+Na]+ : Predicted region for 521.1782 m/z



Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	DBE
C27 H30 O9	[M+Na]+	521.1786	521.1782	0.4	0.77	13.0

Figure 4.1.7. HRESIMS spectrum of compound **1**

Rudolph Research Analytical

This sample was measured on an Autopol VI, Serial #91058
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Measurement Date : Wednesday, 07-SEP-2022

Set Temperature : OFF

Time Delay : Disabled

Delay between Measurement : Disabled

n	Average	Std.Dev.	% RSD	Maximum	Minimum
5	-115.20	1.30	-1.12	-113.00	-116.00

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG.nm	Lg.mm	Conc.g/100ml	Temp.
1	WJY67	05:38:50 PM	-113.00	SR	-0.113	589	100.00	0.100	24.2
2	WJY67	05:38:57 PM	-115.00	SR	-0.115	589	100.00	0.100	24.2
3	WJY67	05:39:03 PM	-116.00	SR	-0.116	589	100.00	0.100	24.1
4	WJY67	05:39:09 PM	-116.00	SR	-0.116	589	100.00	0.100	24.1
5	WJY67	05:39:18 PM	-116.00	SR	-0.116	589	100.00	0.100	24.1

Figure 4.1.8. Optical Rotation of compound **1**

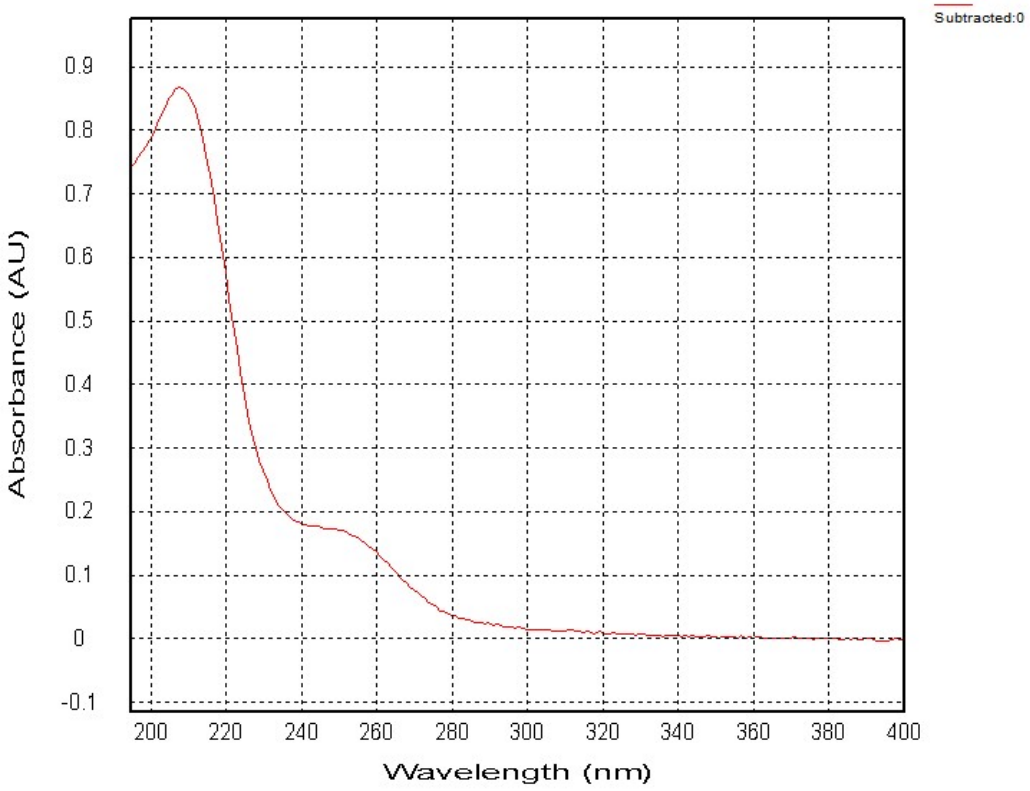


Figure S4.1.9. UV (MeOH) spectrum of **1**

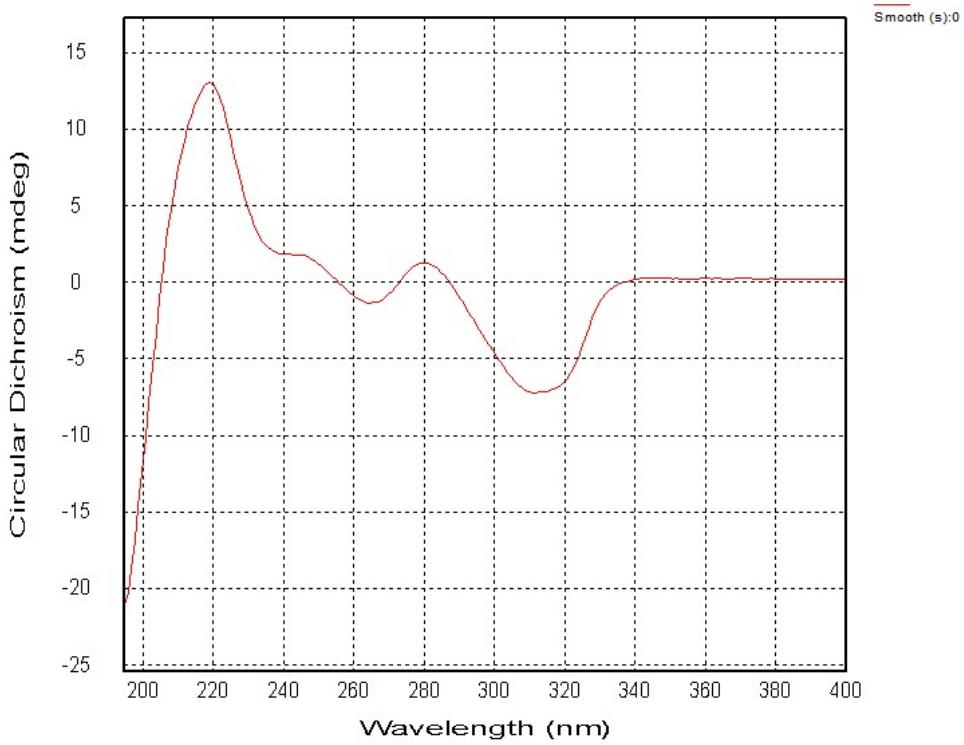


Figure S4.1.10. CD (MeOH) spectrum of **1**

NMR, MS, ORD, UV and CD spectra of compound 2

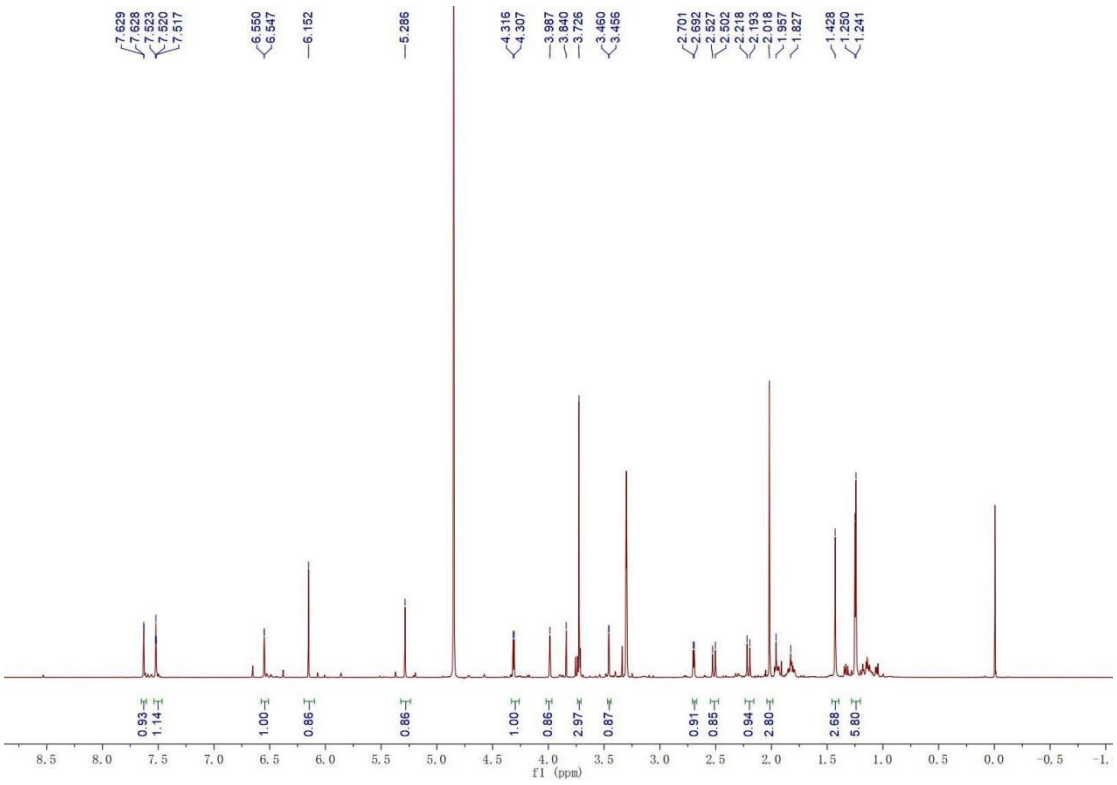


Figure 4.2.1. ^{1}H NMR spectrum of compound **2**

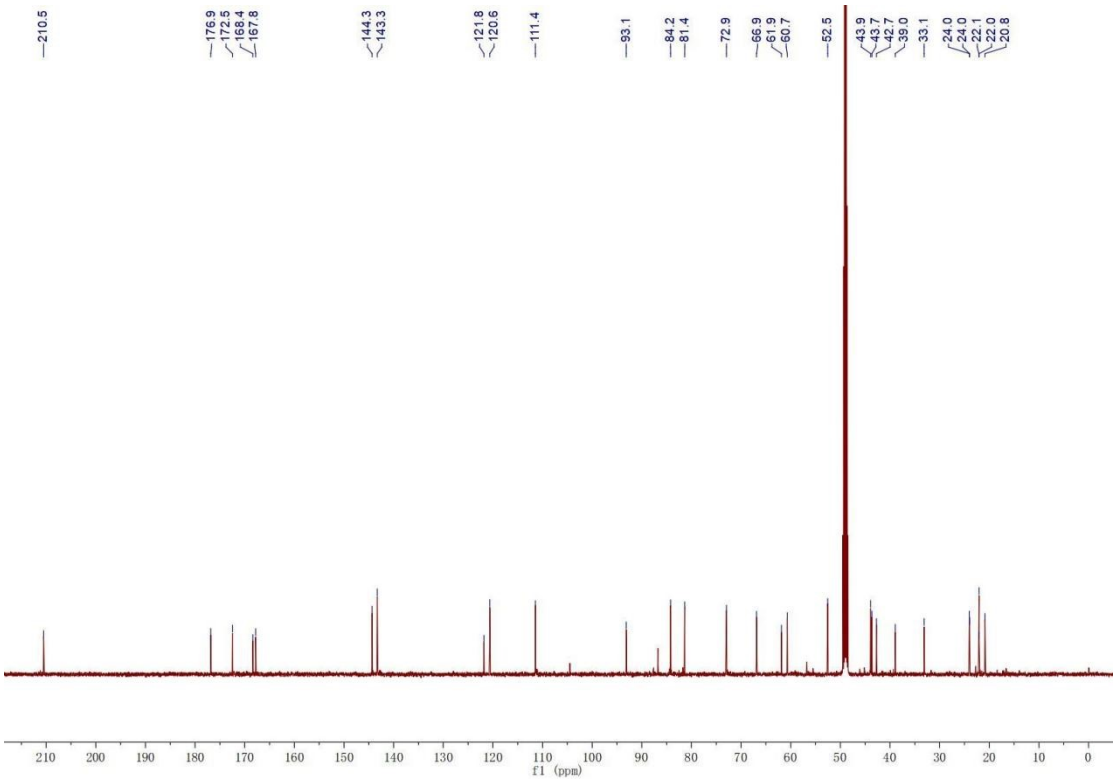


Figure 4.2.2. ^{13}C NMR spectrum of compound **2**

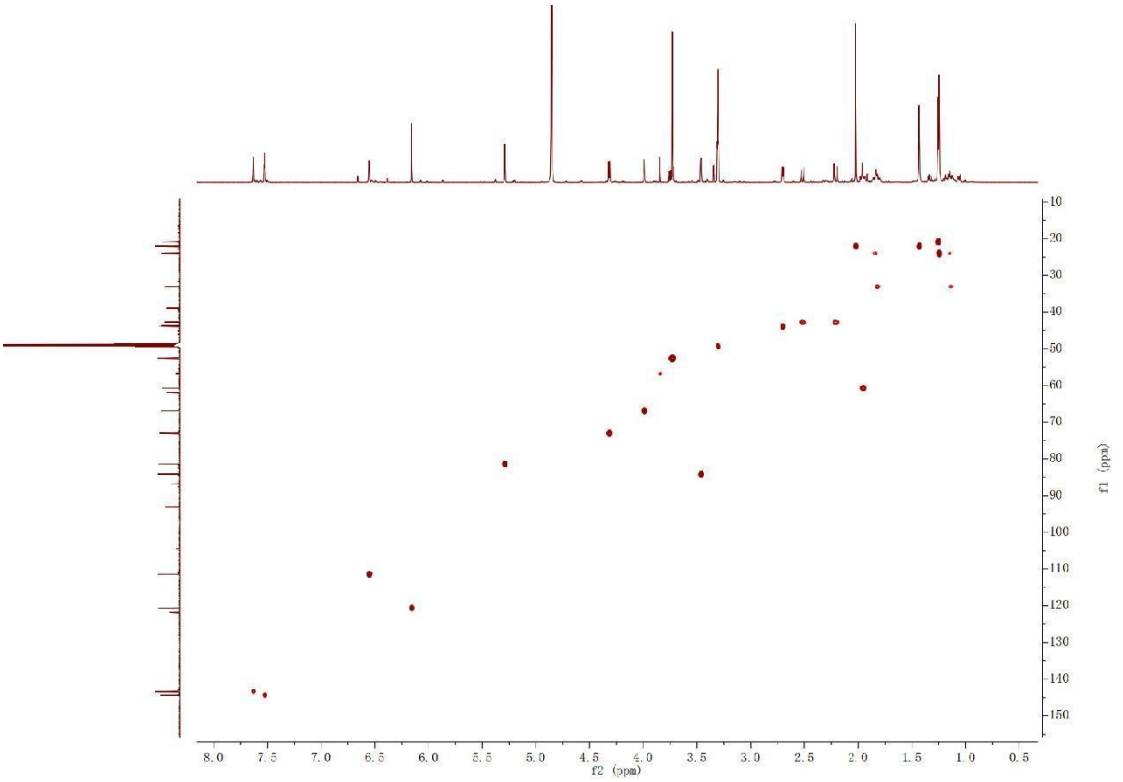


Figure 4.2.3. HSQC spectrum of compound **2**

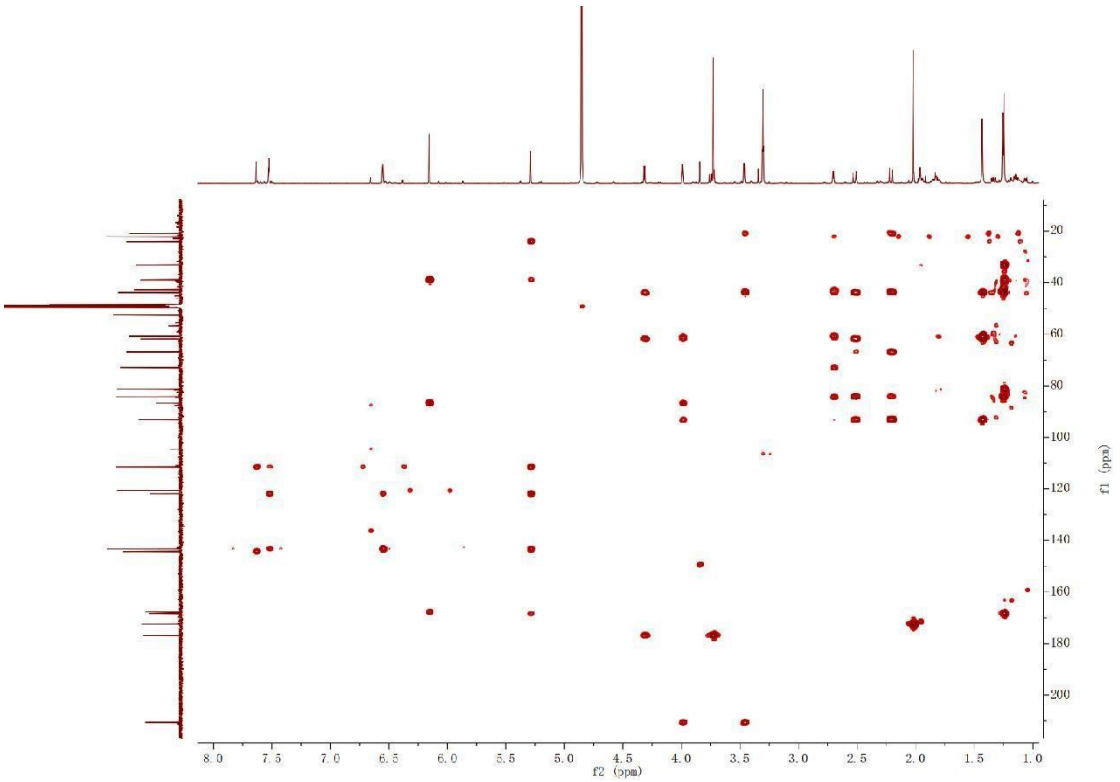


Figure 4.2.4. HMBC spectrum of compound **2**

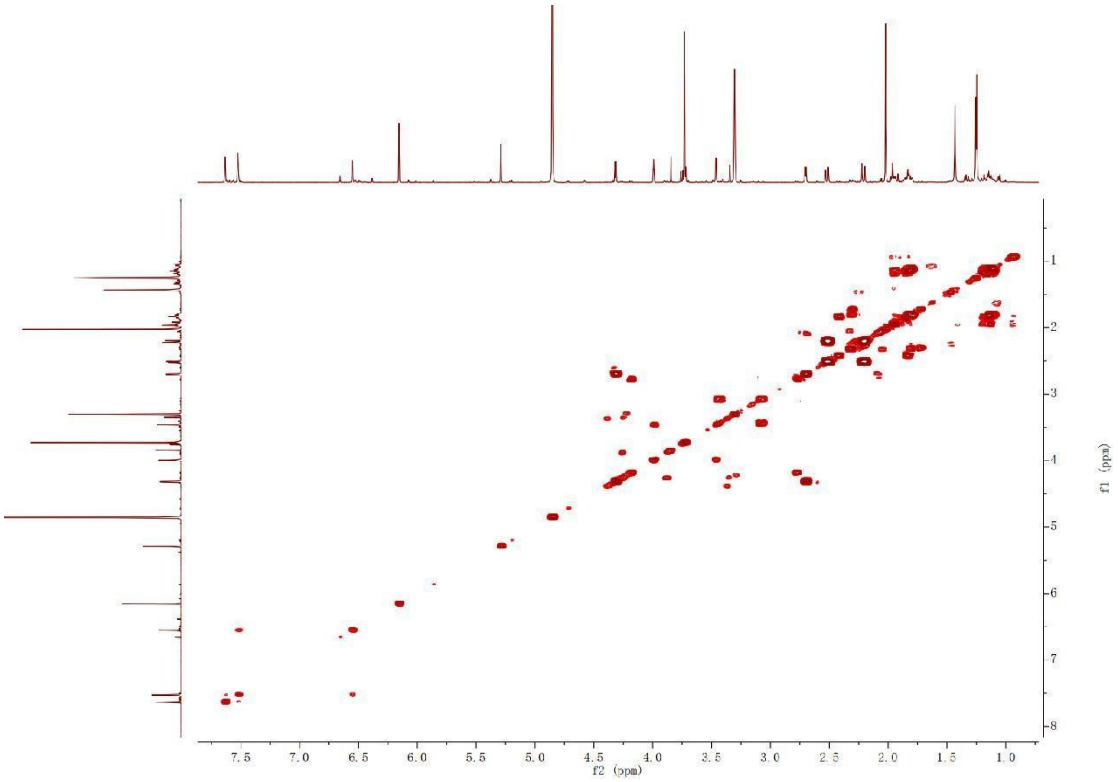


Figure 4.2.5. ^{1}H-^{1}H COSY spectrum of compound **2**

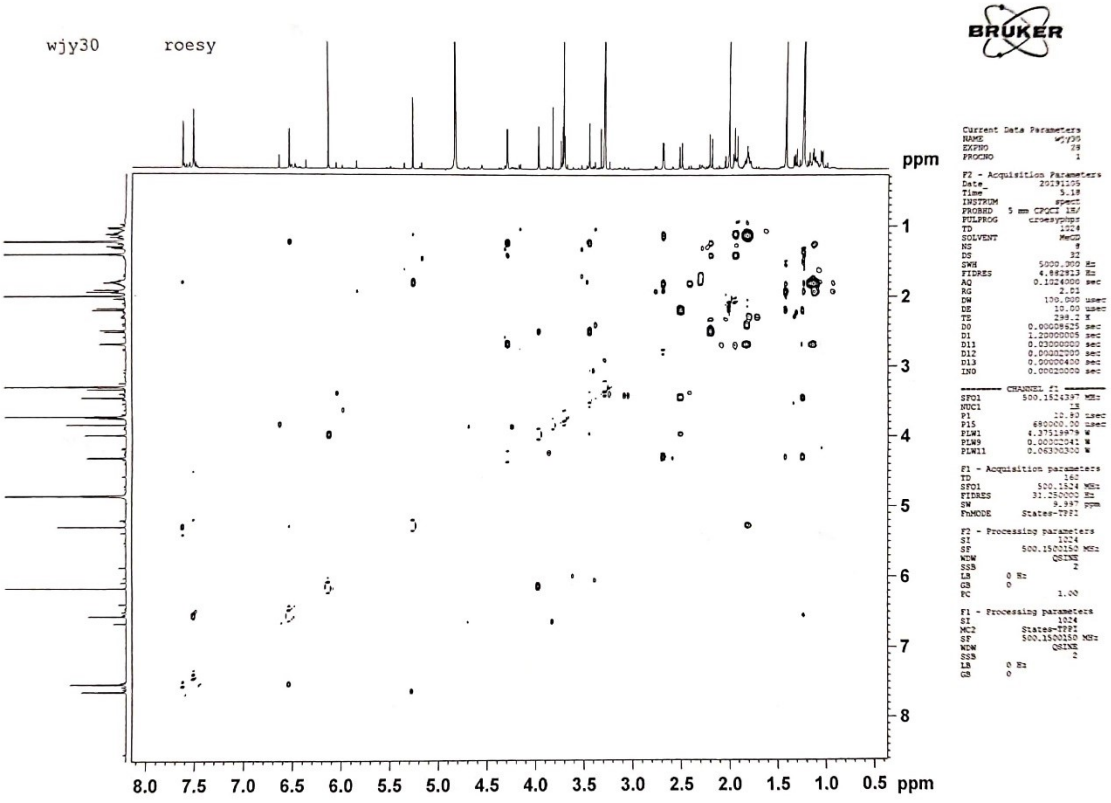


Figure 4.2.6. ROESY spectrum of compound **2**

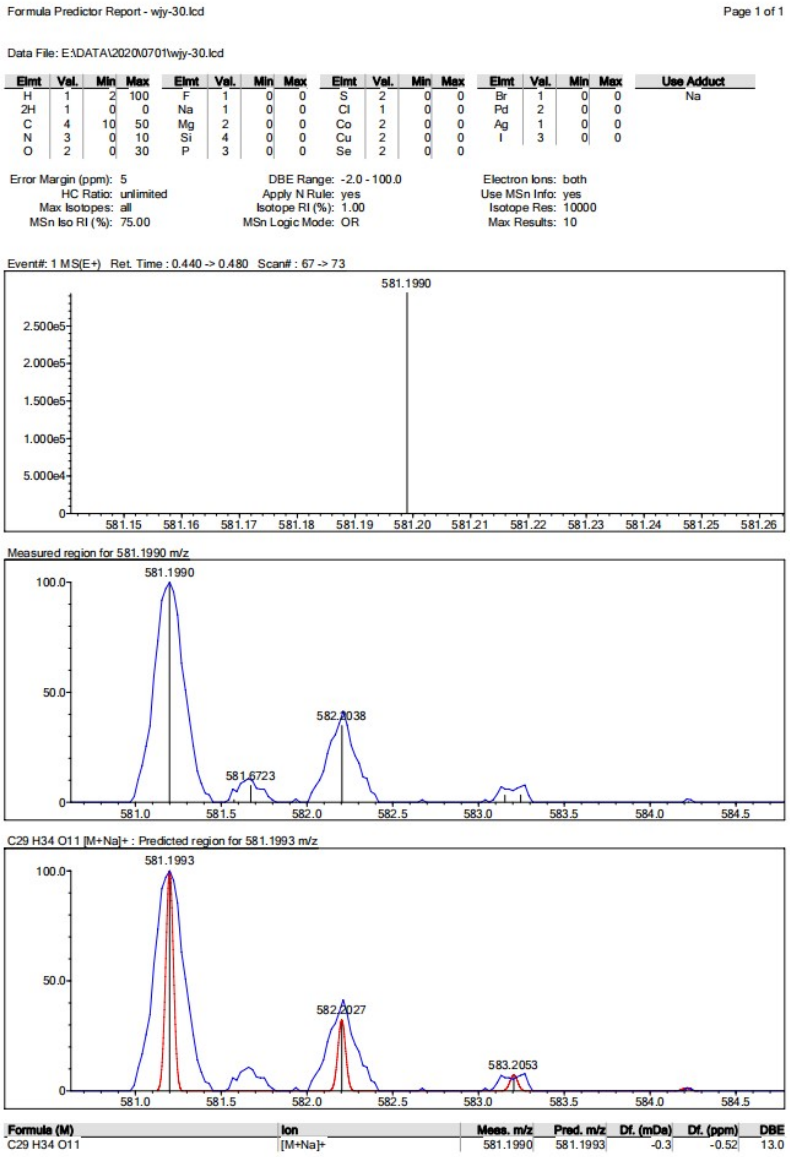


Figure 4.2.7. HRESIMS spectrum of compound **2**

Rudolph Research Analytical

This sample was measured on an Autopol VI, Serial #91058
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Measurement Date : Tuesday, 16-AUG-2022

Set Temperature : 25.0

Time Delay : Disabled

Delay between Measurement : Disabled

n	Average	Std.Dev.	% RSD	Maximum	Minimum
5	131.82	1.11	0.84	133.64	130.91

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG.nm	Lg.mm	Conc.g/100ml	Temp.
1	WJY30	07:00:23 PM	133.64	SR	0.147	589	100.00	0.110	25.0
2	WJY30	07:00:29 PM	131.82	SR	0.145	589	100.00	0.110	25.0
3	WJY30	07:00:35 PM	131.82	SR	0.145	589	100.00	0.110	25.0
4	WJY30	07:00:42 PM	130.91	SR	0.144	589	100.00	0.110	25.0
5	WJY30	07:00:48 PM	130.91	SR	0.144	589	100.00	0.110	25.0

Figure 4.2.8. Optical Rotation of compound **2**

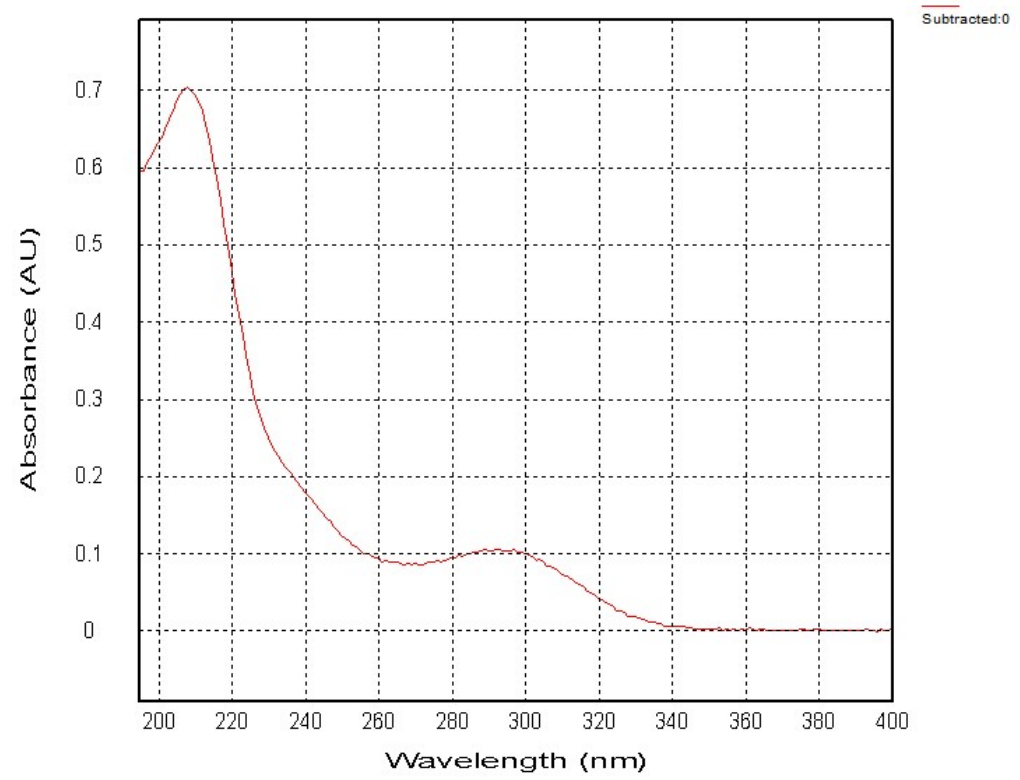


Figure S4.2.9. UV (MeOH) spectrum of **1**

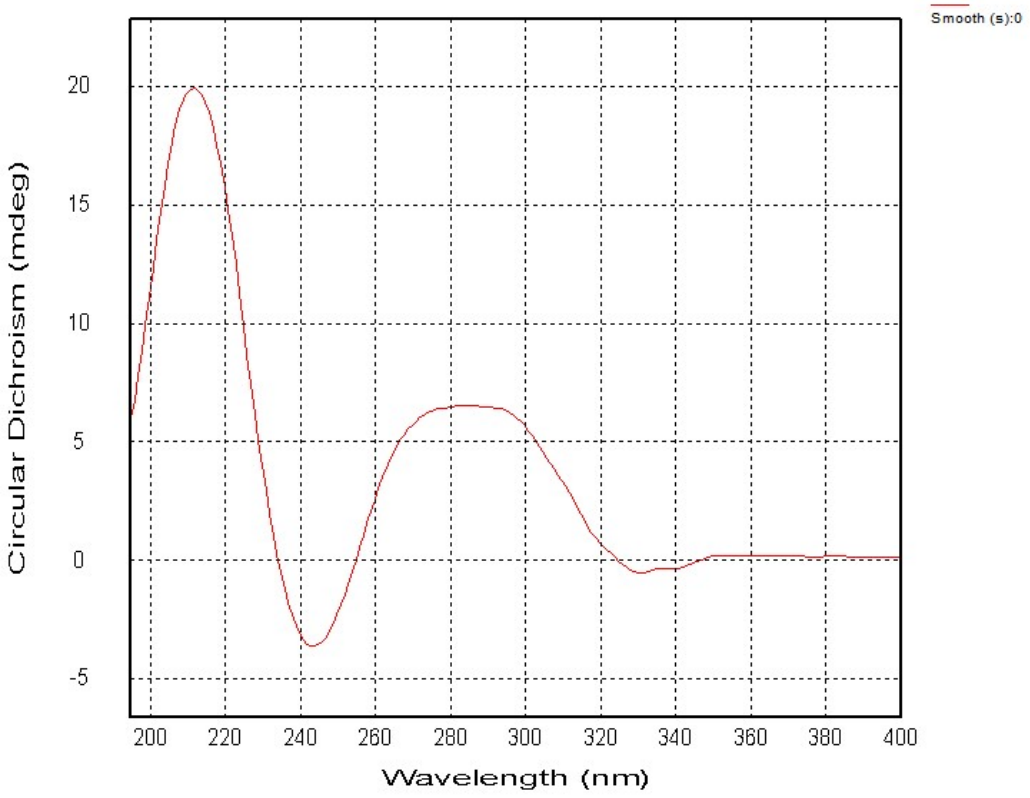


Figure S4.2.10. CD (MeOH) spectrum of **1**

NMR, MS, ORD, UV and CD spectra of compound 3

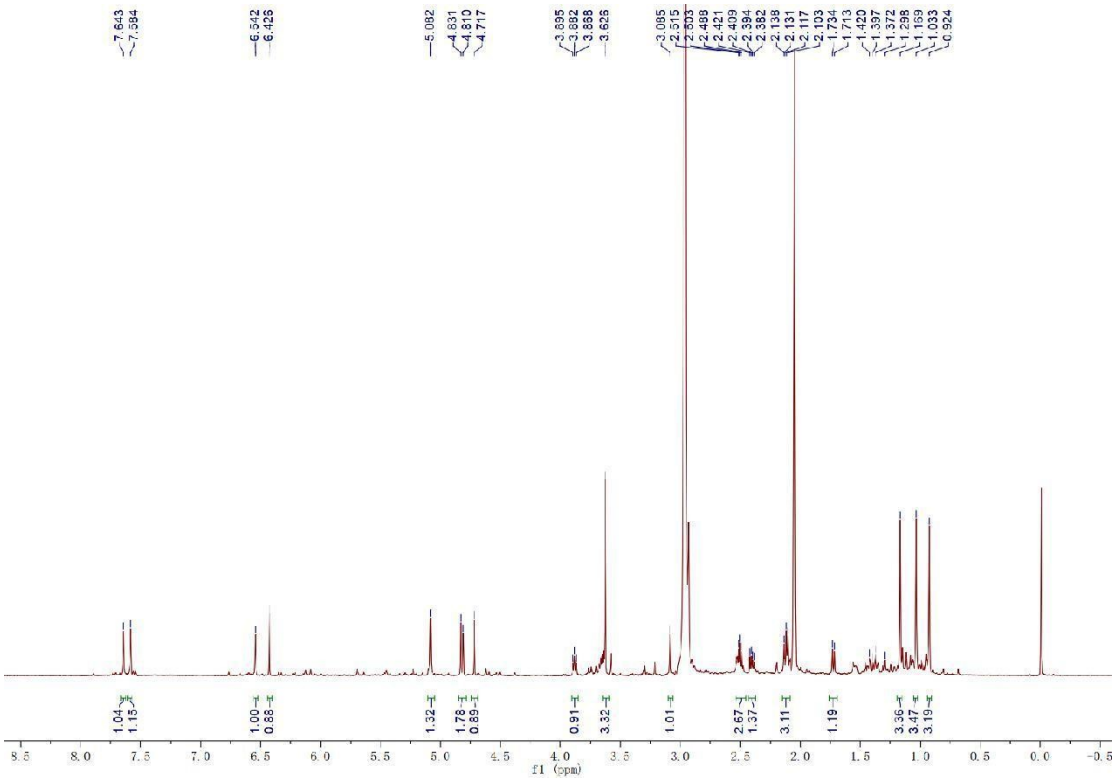


Figure 4.3.1. ^{1}H NMR spectrum of compound **3** in CD_3COCD_3

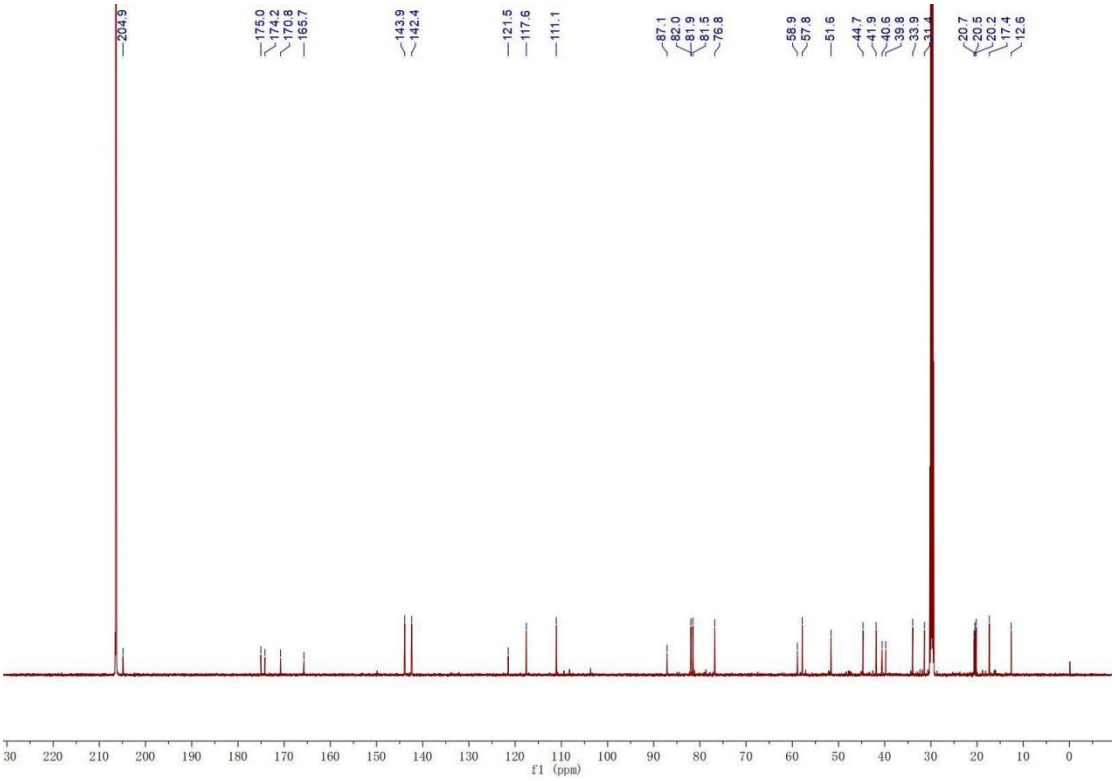


Figure 4.3.2. ^{13}C NMR spectrum of compound **3** in CD_3COCD_3

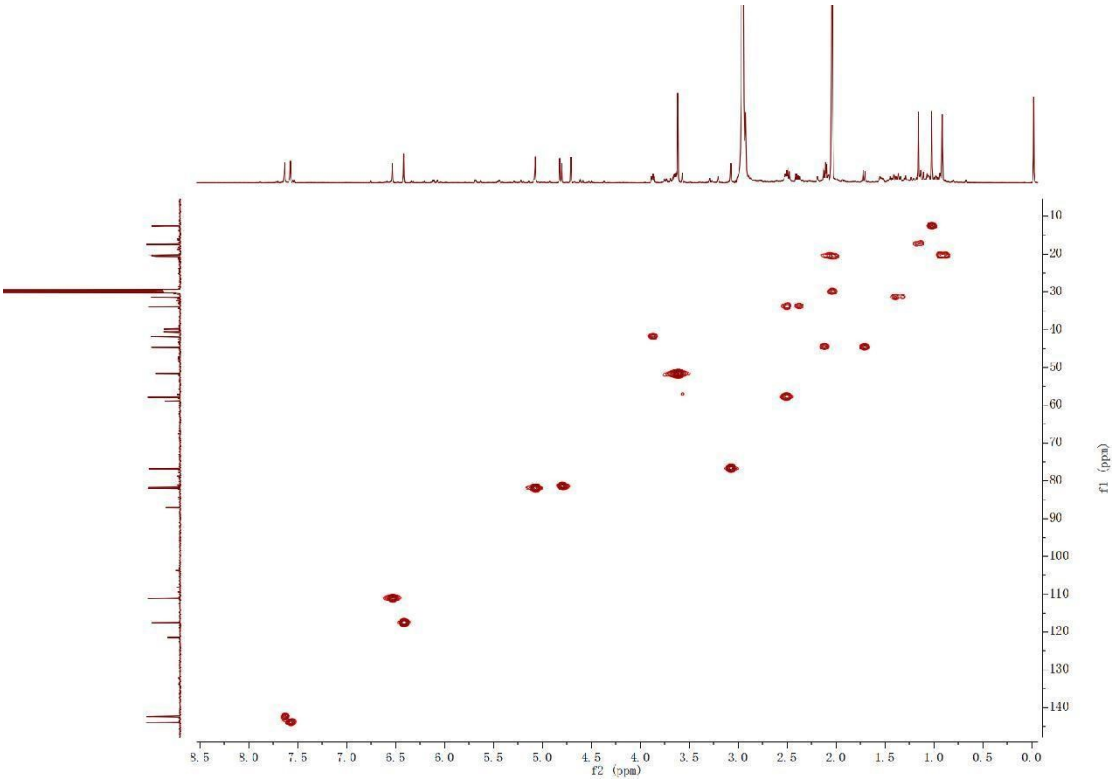


Figure 4.3.3. HSQC spectrum of compound **3** in CD_3COCD_3

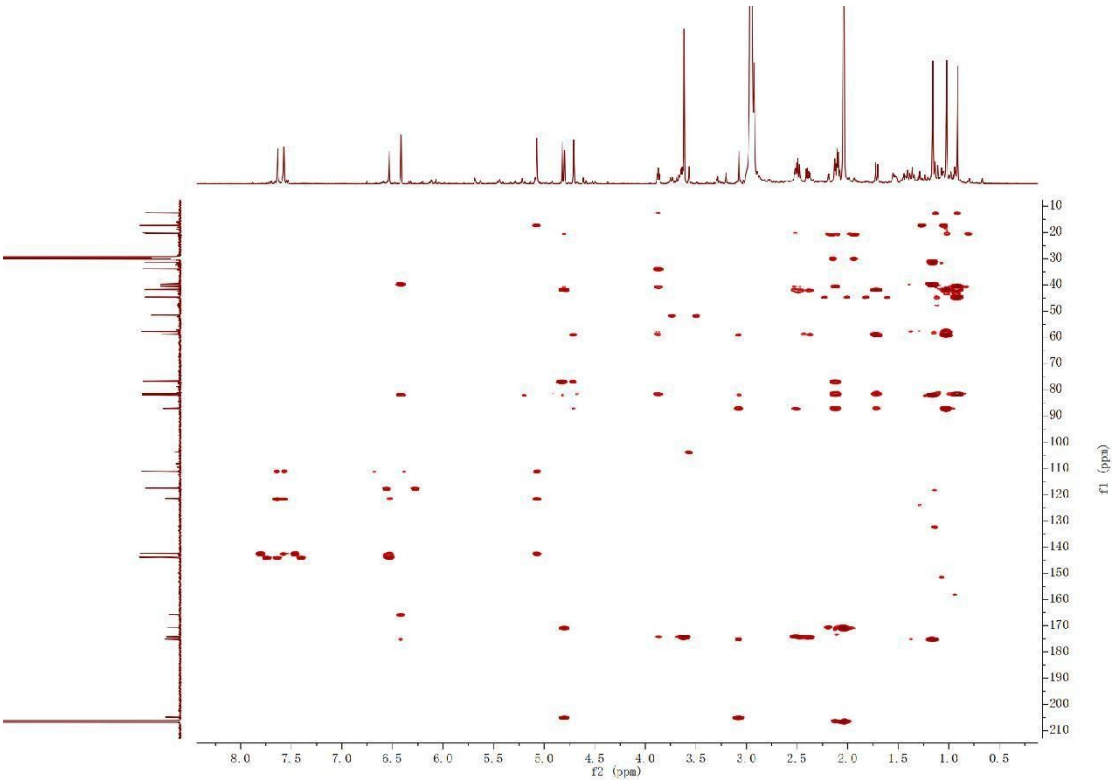


Figure 4.3.4. HMBC spectrum of compound **3** in CD_3COCD_3

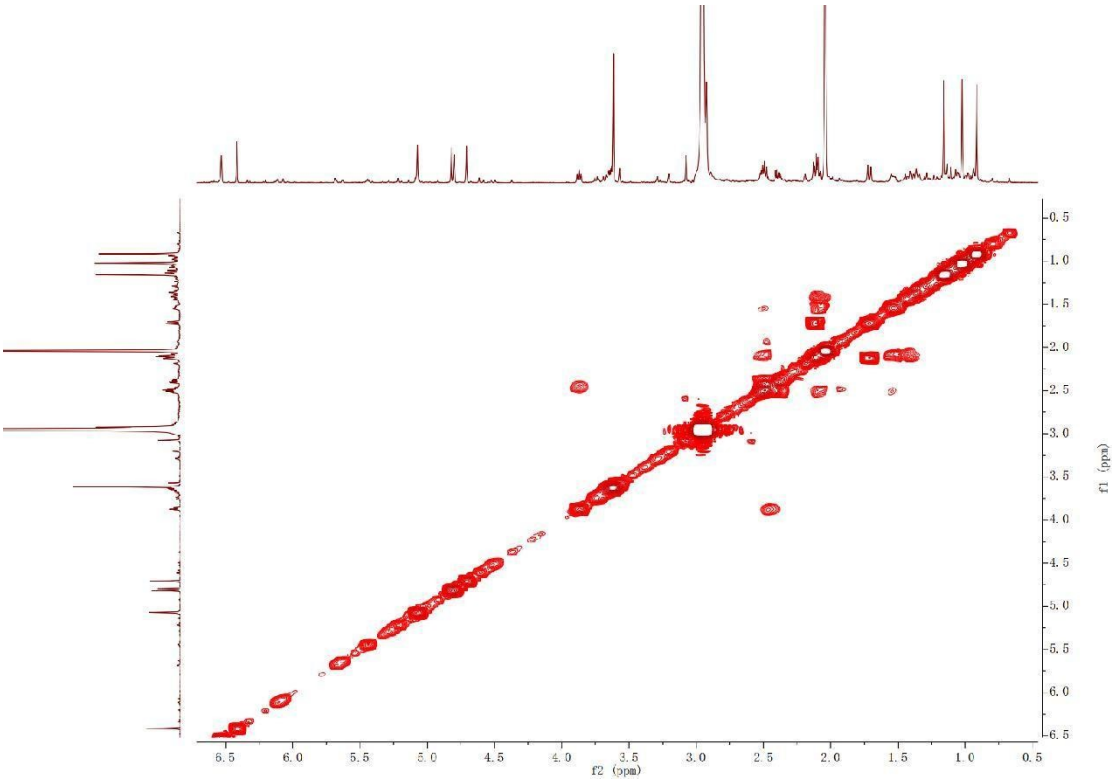


Figure 4.3.5. ^{1}H-^{1}H COSY spectrum of compound **3** in CD_3COCD_3

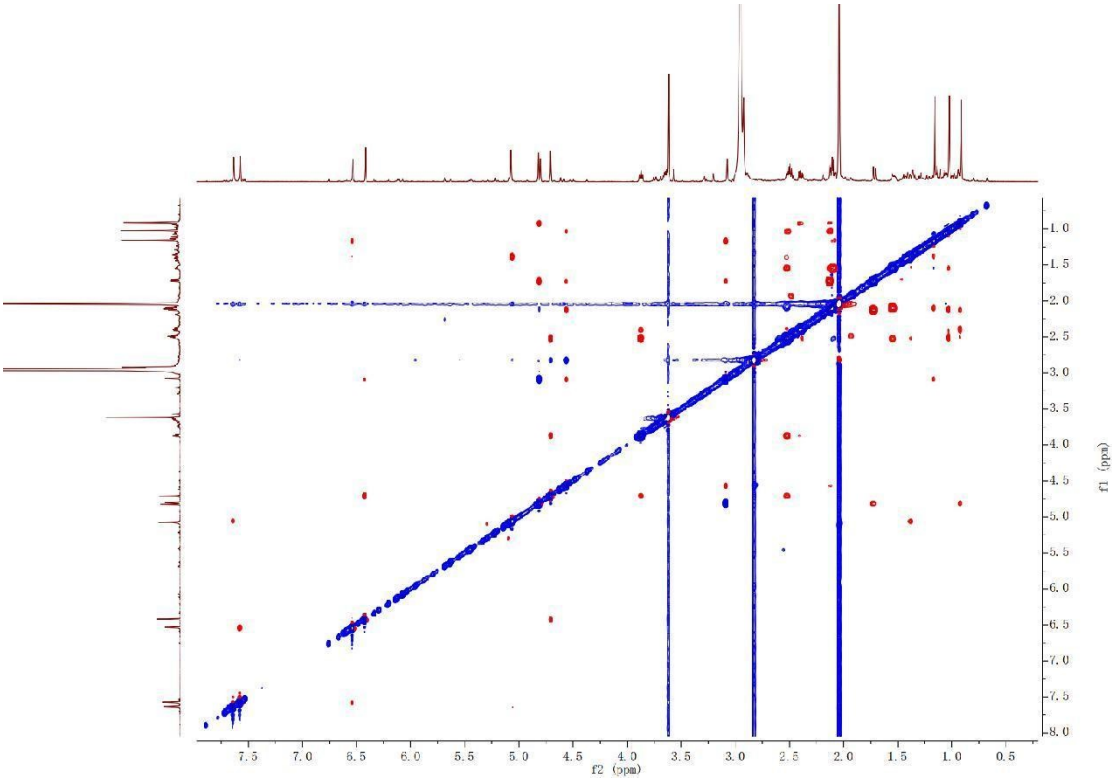


Figure 4.3.6. ROESY spectrum of compound **3** in CD_3COCD_3

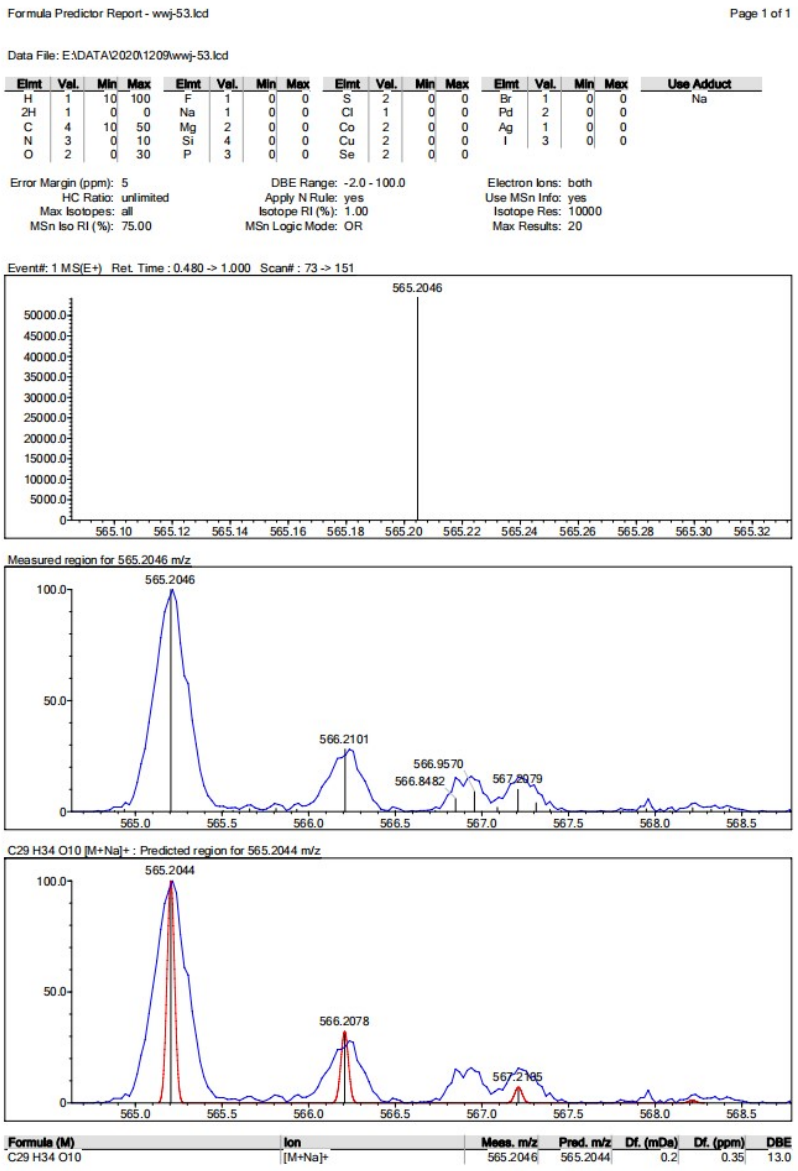


Figure 4.3.7. HRESIMS spectrum of compound **3**

Rudolph Research Analytical

This sample was measured on an Autopol VI, Serial #91058
Manufactured by Rudolph Research Analytical, Hackettstown, NJ, USA.

Measurement Date : Wednesday, 07-SEP-2022

Set Temperature : OFF

Time Delay : Disabled

Delay between Measurement : Disabled

n	Average	Std.Dev.	% RSD	Maximum	Minimum
5	89.80	1.10	1.22	91.00	89.00

S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG.nm	Lg.mm	Conc.g/100ml	Temp.
1	WJY53	05:34:45 PM	91.00	SR	0.091	589	100.00	0.100	24.2
2	WJY53	05:34:52 PM	91.00	SR	0.091	589	100.00	0.100	24.2
3	WJY53	05:35:03 PM	89.00	SR	0.089	589	100.00	0.100	24.2
4	WJY53	05:35:09 PM	89.00	SR	0.089	589	100.00	0.100	24.2
5	WJY53	05:35:16 PM	89.00	SR	0.089	589	100.00	0.100	24.1

Figure 4.3.8. Optical Rotation of compound **3**

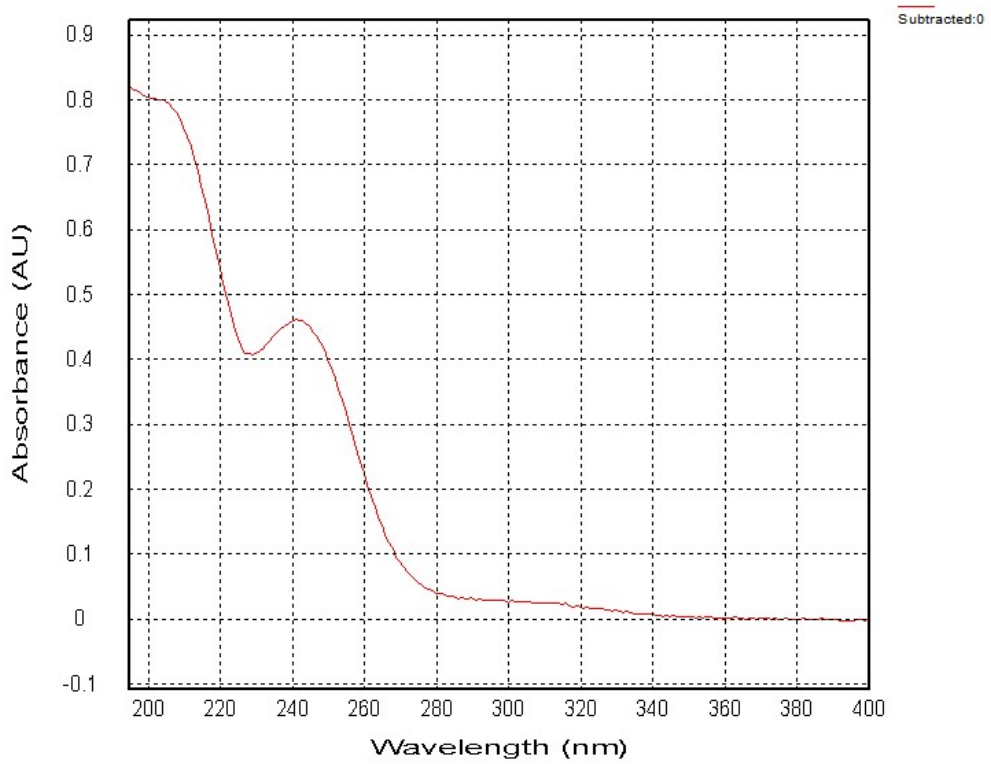


Figure S4.3.9 UV (MeOH) spectrum of **3**

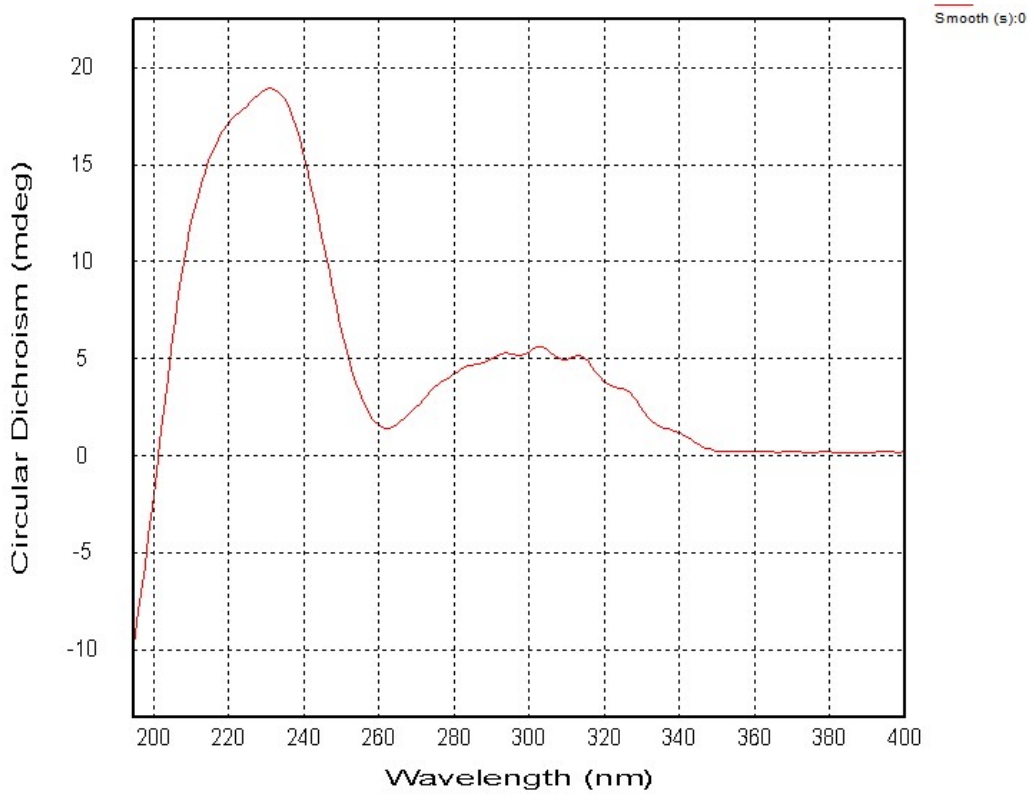


Figure S4.3.10 CD (MeOH) spectrum of **3**