

Horisfieldones A and B, Two Aromatic Ring-contracted Dimeric Diarylpropanes with Human DOPA Decarboxylase Inhibitory Activity from *Horsfieldia kingii*

Rui Zhan,^{†,‡} You-Tian Hu,^{‡,§} Li-Dong Shao,^{§,‡} Xu-Jie Qin,[¶] Fang Kuang,[†] Shou-Zhen Du,[†] Fang Wu,^{*,‡} Ye-Gao, Chen^{*,†}

[†] School of Chemistry and Chemical Engineering, Yunnan Normal University, Kunming 650500, China

[‡] Key Laboratory of Systems Biomedicine (Ministry of Education), Shanghai Center for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai 200240, China

[§] Department of Traditional Chinese Medicine, Yunnan University of Chinese Medicine, Kunming 650500, China

[¶] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China

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Detailed experimental procedures

General Experimental Procedures. Optical rotations were measured using a Jasco P-1020 polarimeter equipped with a 1 dm pathlength cell. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer equipped with a DAD and a 1 cm pathlength cell. Samples in methanol solution were scanned from 190–400 nm in 1 nm steps. All ^1H , ^{13}C , and 2D NMR (HSQC, ^1H – ^1H COSY, HMBC, ROESY) spectra were collected with a Bruker AV III-800 spectrometer at 800 MHz for ^1H and 200 MHz for ^{13}C nuclei. Mass spectra were obtained on an Anilent 6540 Q-ToF instrument (ESI and HRESI mode). HRMS data were recorded via positive ion electrospray or electron impact mass spectrometry using a time of flight analyzer. Experimental ECD spectra were measured on a Chirascan instrument. Semi-preparative HPLC was performed on an Agilent 1260 HPLC with a Zorbax XDB- C_{18} (9.4 mm \times 25 cm) column. Chiral semi-preparative HPLC was performed on an Agilent 1260 HPLC with the Ultimate Cellu-DR (10 mm \times 25 cm) column. Column chromatography (CC) was performed using silica gel (200–300 mesh, Qingdao Marine Chemical Co. Ltd., Qingdao, People's Republic of China), MCI gel (75–150 μm ; Mitsubishi Chemical Corporation, Japan), and Sephadex LH-20 (Amersham Biosciences AB, Uppsala, Sweden).

Plant Material. The twigs and leaves of *Horsfieldia kingii* was collected from Xishuangbanna, Yunnan Province, People's Republic of China, and was identified by Mr. Shishun Zhou, Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences. A voucher specimen of this collection (No.140418) has been deposited at Herbarium of Yunnan Normal University, Kunming, China.

Extraction and Isolation. The twigs and leaves of *Horsfieldia kingii* (10 kg) were extracted with 70% aqueous acetone (20 L) four times (two days each time) at room temperature and filtered. The filtrate was evaporated in vacuo. Then the concentrate without acetone (6 L) was partitioned between EtOAc and H_2O . The EtOAc-soluble portion (376 g) was subjected to silica gel CC (2000 g, 100–200 mesh). Five fractions were produced from the silica gel column, eluting with CHCl_3 – Me_2CO (1:0–0:1 gradient system), and were each decolorized on MCI gel, eluted with 90% MeOH – H_2O , to yield fractions A–F.

Fraction B (28 g), a brown gum, was subjected to CC on Sephadex LH-20 and eluted with CHCl_3 -MeOH (3:2), to provide four fractions, B1-B4. B2 (320 mg) was purification by repeated semi-preparative HPLC was performed on an Agilent 1260 HPLC with a Zorbax XDB- C_{18} (9.4 mm \times 25 cm) column (MeOH- H_2O 48:52, v/v, 3 mL/min; Acetonitrile- H_2O 35:65 v/v, 3 mL/min) to afford horisfieldones A (3.7 mg) and B (3.3 mg). Horisfieldones A and B was then chiral separated on Agilent 1260 HPLC with Ultimate Cellu-DR (10 mm \times 25 cm) column (MeOH- H_2O 95:5, v/v, 3 mL/min) respectively to provide (+)-horisfieldone A (1.3 mg), (-)-horisfieldone A (1.1 mg), (+)-horisfieldone B (1.2 mg), and (-)-horisfieldone B (1.0 mg).

Horisfieldone A (1): brown oil; UV (MeOH) λ_{max} (log ϵ) 204 (4.05), 226 (3.60), 288 (3.30) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; negative-ion HRESIMS m/z 571.1971 $[\text{M-H}]^-$ (calcd for $\text{C}_{33}\text{H}_{32}\text{O}_9$, 571.1974).

(+)-horisfieldone A: $[\alpha]_{\text{D}}^{19.2} +138.6$ (c 0.06, MeOH); CD (MeOH), λ_{max} ($\Delta \epsilon$) 330 (1.61).

(-)-horisfieldone A: $[\alpha]_{\text{D}}^{18.9} -87.3$ (c 0.12, MeOH); CD (MeOH), λ_{max} ($\Delta \epsilon$) 333 (-1.67).

Horisfieldone B (2): brown oil; UV (MeOH) λ_{max} (log ϵ) 204 (3.78), 226 (3.33), 292 (3.05) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; negative-ion HRESIMS m/z 601.2071 $[\text{M-H}]^-$ (calcd for $\text{C}_{34}\text{H}_{34}\text{O}_{10}$, 601.2079).

(+)-horisfieldone B: $[\alpha]_{\text{D}}^{19.0} +86.4$ (c 0.17, MeOH); CD (MeOH), λ_{max} ($\Delta \epsilon$) 335 (1.55).

(-)-horisfieldone B: $[\alpha]_{\text{D}}^{18.8} -124.0$ (c 0.12, MeOH); CD (MeOH), λ_{max} ($\Delta \epsilon$) 334 (-1.68).

ECD Calculations of 1

ECD Calculations were performed by a Gaussian 09 software. More specifically, the 3D structures were first established randomly or according to the ROESY spectra, which were then subjected to conformational analysis using CONFLEX software with MMFF94S force fields to afford six reliable conformations with relative energy of less than 1.00 kcal/mol. The selected conformers were further optimized by using the Density Functional Theory (DFT) at the B3LYP/6-31+G(d) level in gas phase. The optimized geometries were subsequently checked by frequency calculation and resulted in no imaginary frequencies. The optimized conformations were subjected to ECD calculations using Time Dependent DFT (TDDFT) at the B3LYP/6-311++G(2d, p) level in CH_3OH . The calculated ECD curves were generated by SpecDis version 1.63 software. (Reference: Frisch, M.J.; Trucks, G. W.; Schlegel, H. B.; et al. *Gaussian 09*, Revision E. 01. Gaussian, Inc: Wallingford, CT, 2013. Bruhn, T.; Schaumlöffel, A., Hemberger, Y., Bringmann, G. *Chirality* **2013**, 25, 243–249.)

Molecular Modeling

The ligand and receptor were prepared using DiscoveryStudio 4.0 software. Autodock Tools v1.56¹ was used to perform grid and docking. Docking parameters were set as the default values AutoGrid v4.01 and AutoDock v4.01. The Grid box contained the whole active cavity of human DDC (PDB: 3rbf) was chosen.² Docking conformations were classified into different clusters by binding energy, and the cluster with the lowest binding energy was selected. In the selected cluster, conformations with the lowest binding energy and RMSD (<2.0 Å) were finally chosen to analyze the receptor-ligand interaction.

The activity assay of human cystathionine γ -lyase (hCSE).

The inhibition of compounds on the activity of hCSE was determined using our previously reported method that is based on a 192-tandem-well plate.³ Briefly, 25 μ L 50 mM HEPES buffer containing 500 nM purified recombinant GST-tagged hCSE protein and 100 μ M PLP (final concentrations; pH 7.4) was first incubated with 1 μ L DMSO or compounds in the reaction well at a concentration of 100 μ M for 45 min. Then, 50 μ L detection buffer (300 μ M DTNB in 262 mM Tris-HCl and 13 mM EDTA, pH 8.9) was added into the interlinked detection well. Finally, 25 μ L 50 mM HEPES buffer containing 5 mM L-Cys (final concentrations) was added in the reaction well and the plate was immediately and tightly sealed with UltraClear film (Platemax PCR-TS from Axygen, Union City, CA). The assay plate was then incubated for additional 60 min at 37 °C before the absorbance was measured at 413 nm with a microplate reader (Cytation5 from BioTek, Winooski, VT).

The activity assay of human DOPA decarboxylase (hDDC).

The DDC assay was performed under standard assay conditions as previously described.^{2b} Briefly, 1 μ L DMSO or compounds at a concentration of 100 μ M were mixed with 24.5 μ L of the enzyme mix [50 mM Tris-HCl, 50 mM NaCl, 0.015% (w/v) bovine serum albumin, 5 mM MgCl₂, 2 mM β -mercaptoethanol, 760 μ M NADH, 330 nM PEPC, 100 μ M PLP and 284 nM 6 \times His-tagged hDDC, pH 8.05; final concentrations]. Then, the reaction was started by adding 24.5 μ L substrate mix [50 mM Tris-HCl containing 50 mM NaCl, 0.015% (w/v) bovine serum albumin, 5 mM MgCl₂, 2 mM β -mercaptoethanol, 10 mM phosphoenolpyruvic acid, 0.49 U malate dehydrogenase and 1.5 mM 3,4-dihydroxy-L-phenylalanine, pH 8.05; final concentration]. The plates were then tightly sealed with UltraClear film and incubated for 30 min at 37 °C before the absorbance of 340 nm was measured in a microplate reader. The remaining activity of compound was expressed as percentage of control (DMSO) with the following equation: Remaining activity (%) = $\{[(OD_{0 \text{ min}} - OD_{30 \text{ min}}) \text{ of compound}] - [(OD_{0 \text{ min}} - OD_{30 \text{ min}}) \text{ of blank}]\} / \{[(OD_{0 \text{ min}} - OD_{30 \text{ min}}) \text{ of DMSO}] - [(OD_{0 \text{ min}} - OD_{30 \text{ min}}) \text{ of blank}]\} \times 100$.

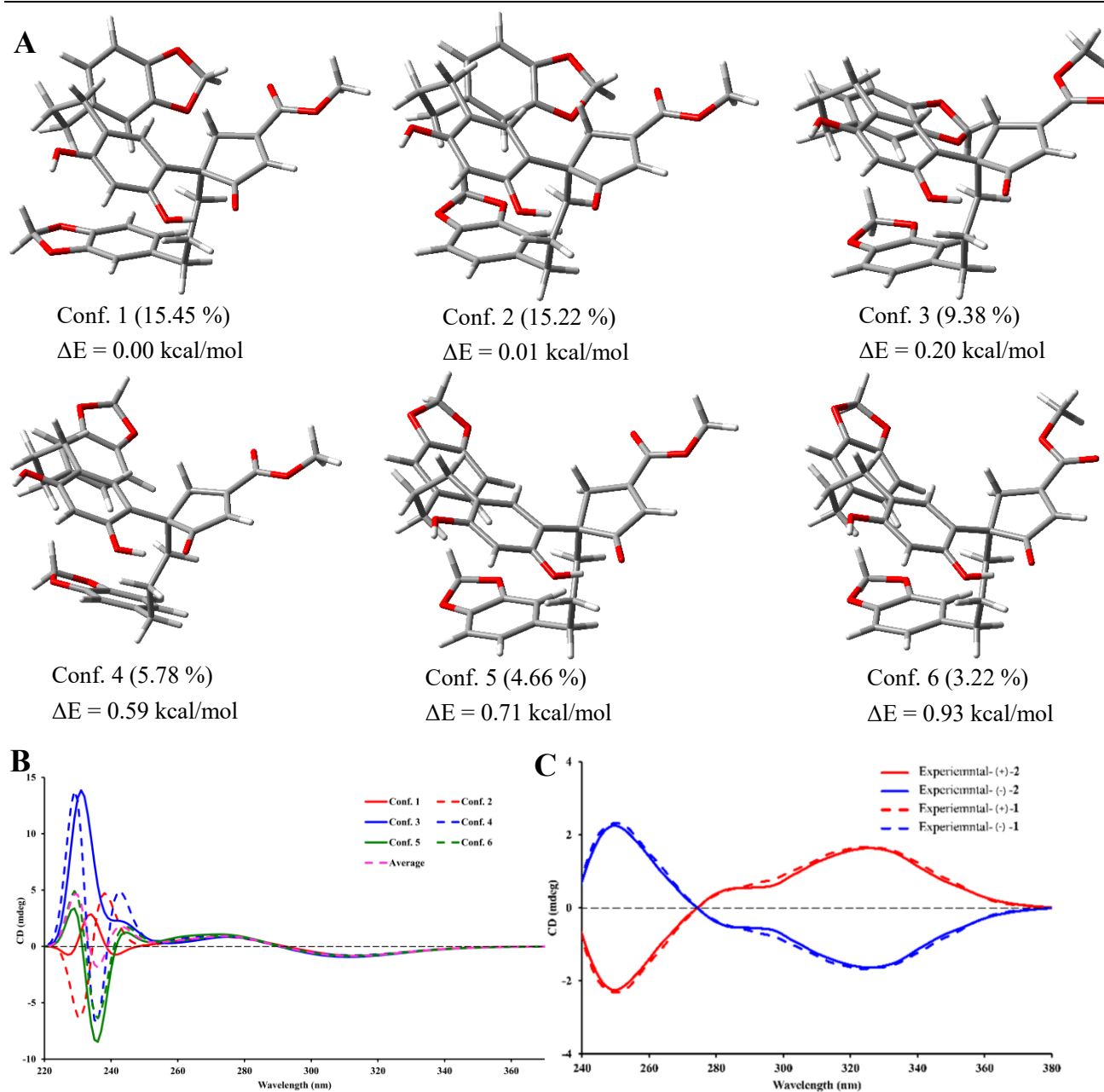


Figure S1. Computational data of **1**. (A) Six receivable conformers with lower relative energy of **1**. (B) Calculated ECD spectra for the low energy structures. (C) Experimental CD spectra of compounds **1** and **2**.

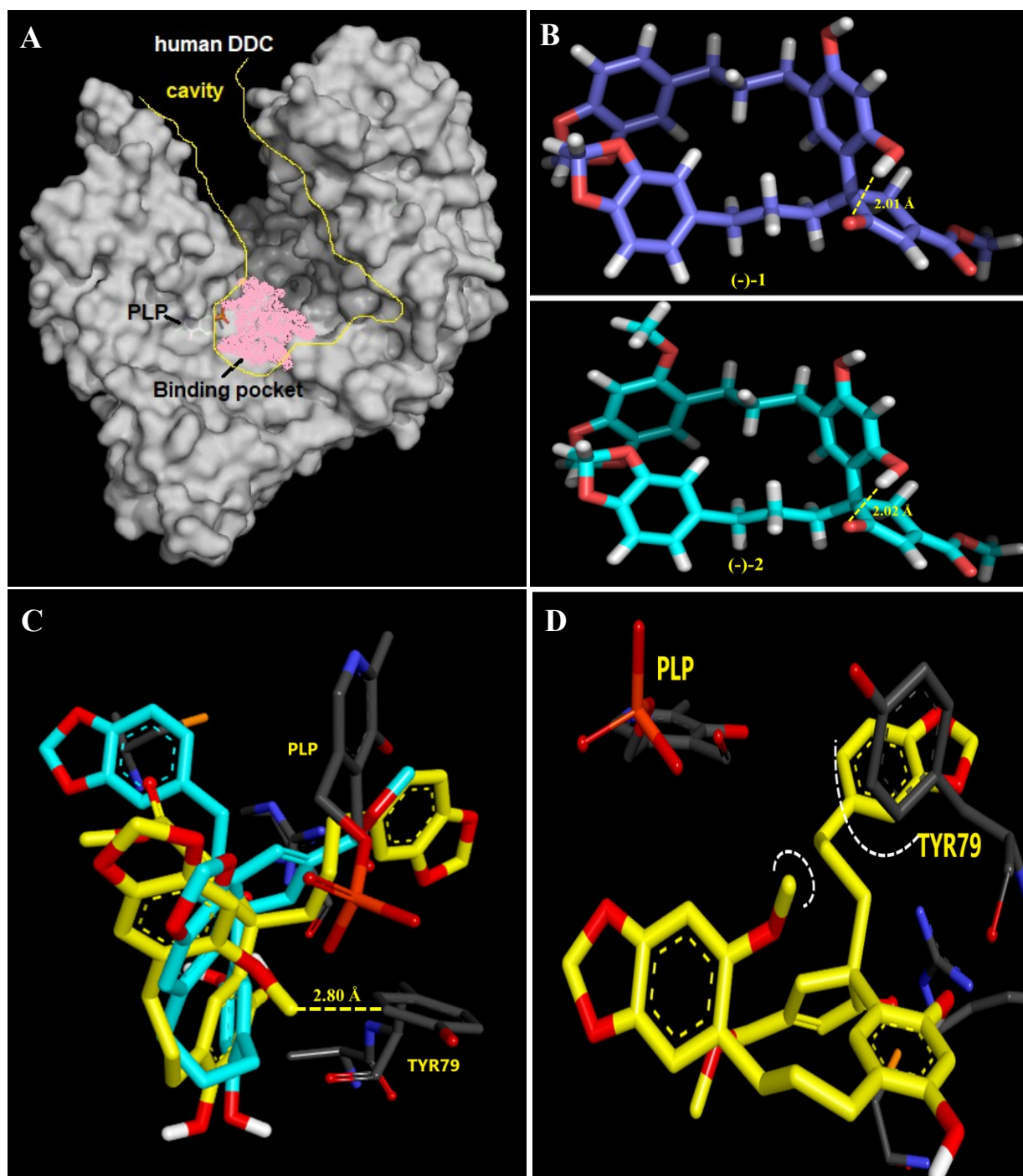


Figure S2. Molecular docking analysis of compounds (-)-1, (+)-1, (-)-2, and (+)-2 into human DOPA decarboxylase (hDDC) (pdb: 3rbf). (A) The active cavity of hDDC and the calculated binding pocket (shown in pink color, an approximate area overlapped the L-DOPA binding region [ref. 2a]) of compounds (-)-1, (+)-1, (-)-2, and (+)-2. The receptor was showed as solid surface in white with 20% transparency. PLP was shown as sticks. Ligands were shown as spheres. (B) Minimized configurations of (-)-1 and (-)-2, yellow-dotted lines represented intramolecular hydrogen bonds with length of 2.01 Å and 2.02 Å, respectively. (C) Superposition of (+)-1 and (+)-2 docking into the hDDC. Ligands were shown as sticks. Namely, (+)-1 was shown in cyan color, and (+)-2 was shown in yellow color. The key residues were shown as sticks (C, pale; O, red; N, blue; P, orange). (D) Zoomed docking pose of (+)-2. The white-dotted arcs represented the steric bump between the C6a''-OMe of (+)-2 with the aromatic ring of residue TYR79.

Supporting Information

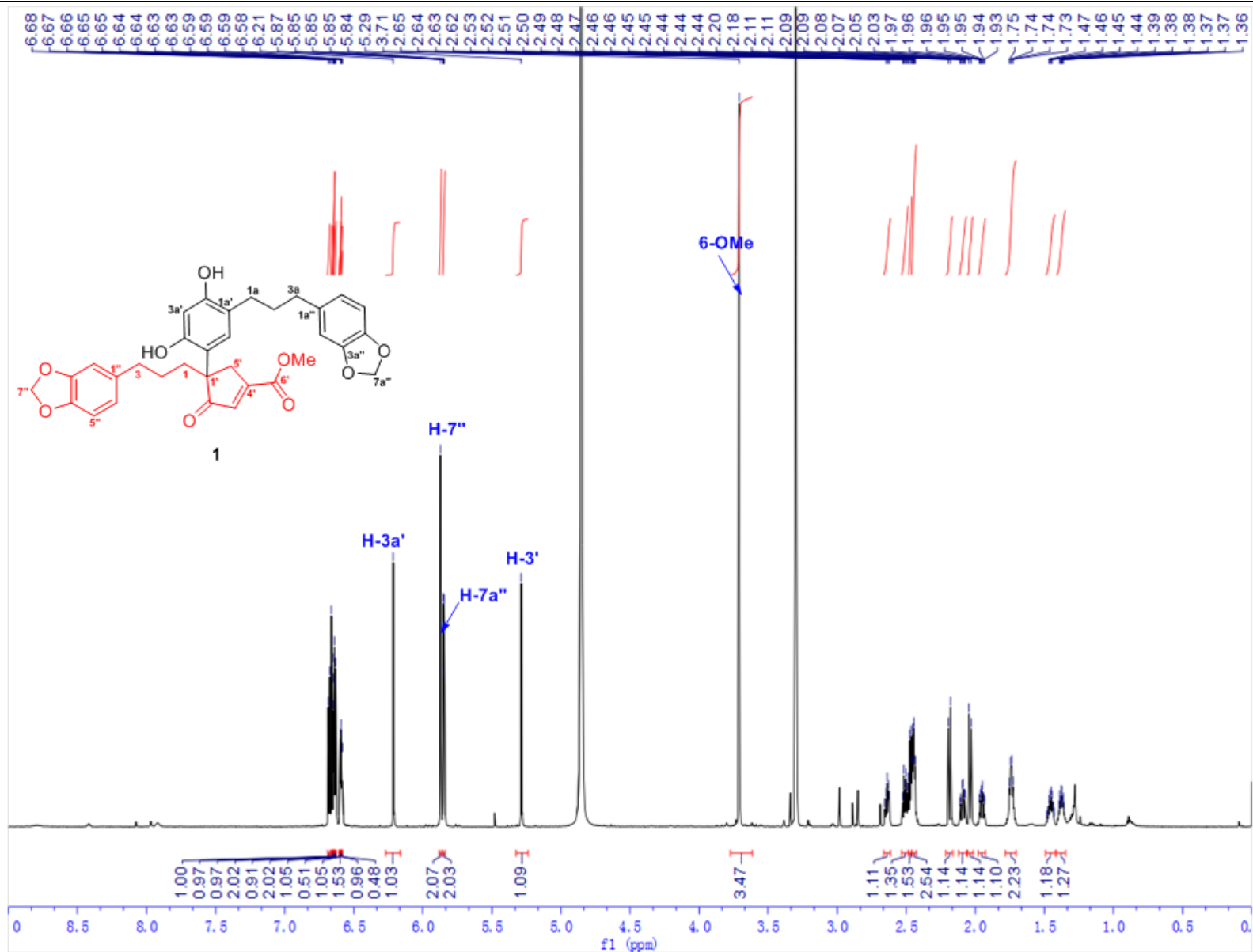


Figure S3. ¹H NMR spectrum (0-9 ppm) of compound **1**

Supporting Information

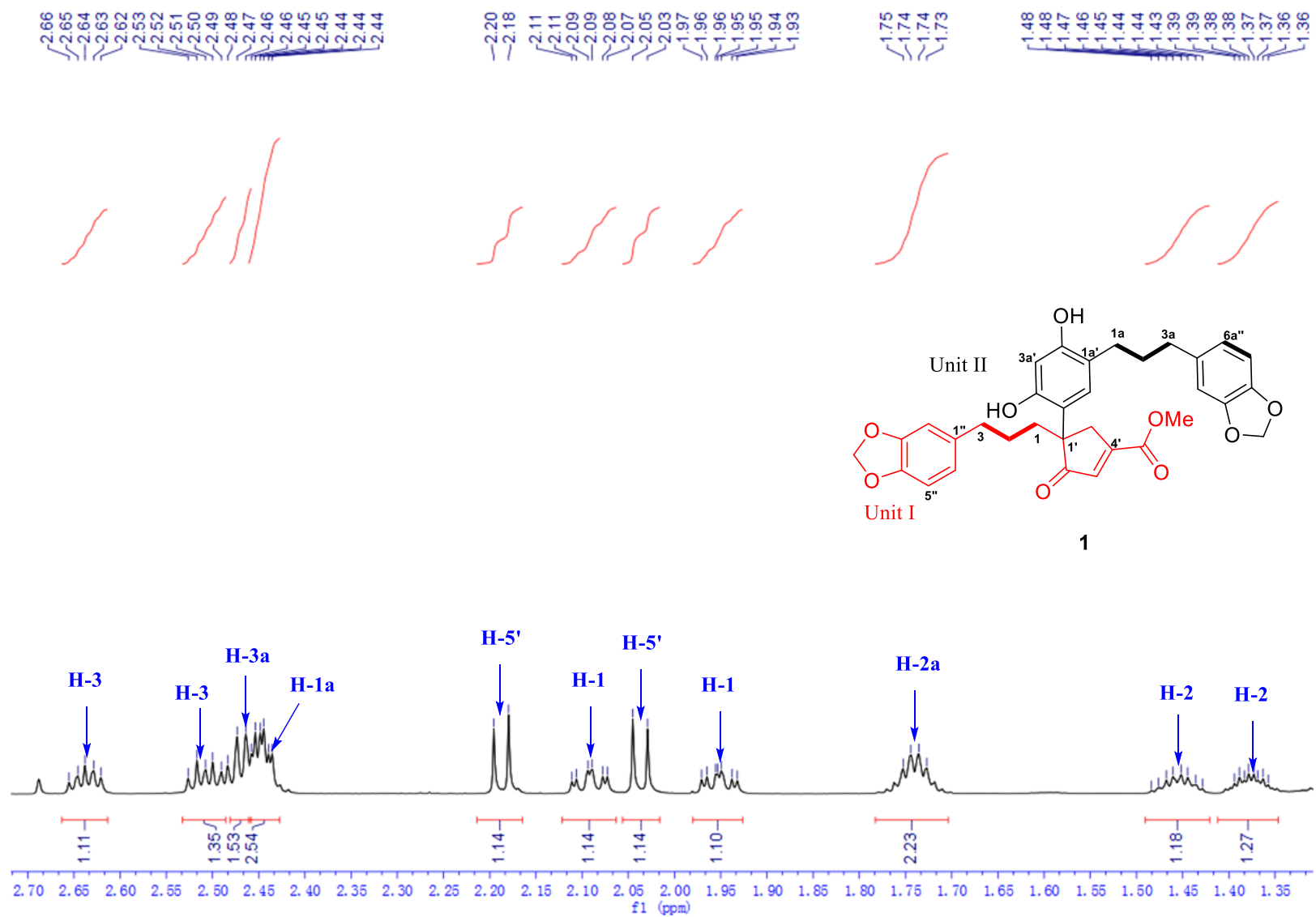


Figure S4. ^1H NMR spectrum (1.35-2.70 ppm) of compound **1**

Supporting Information

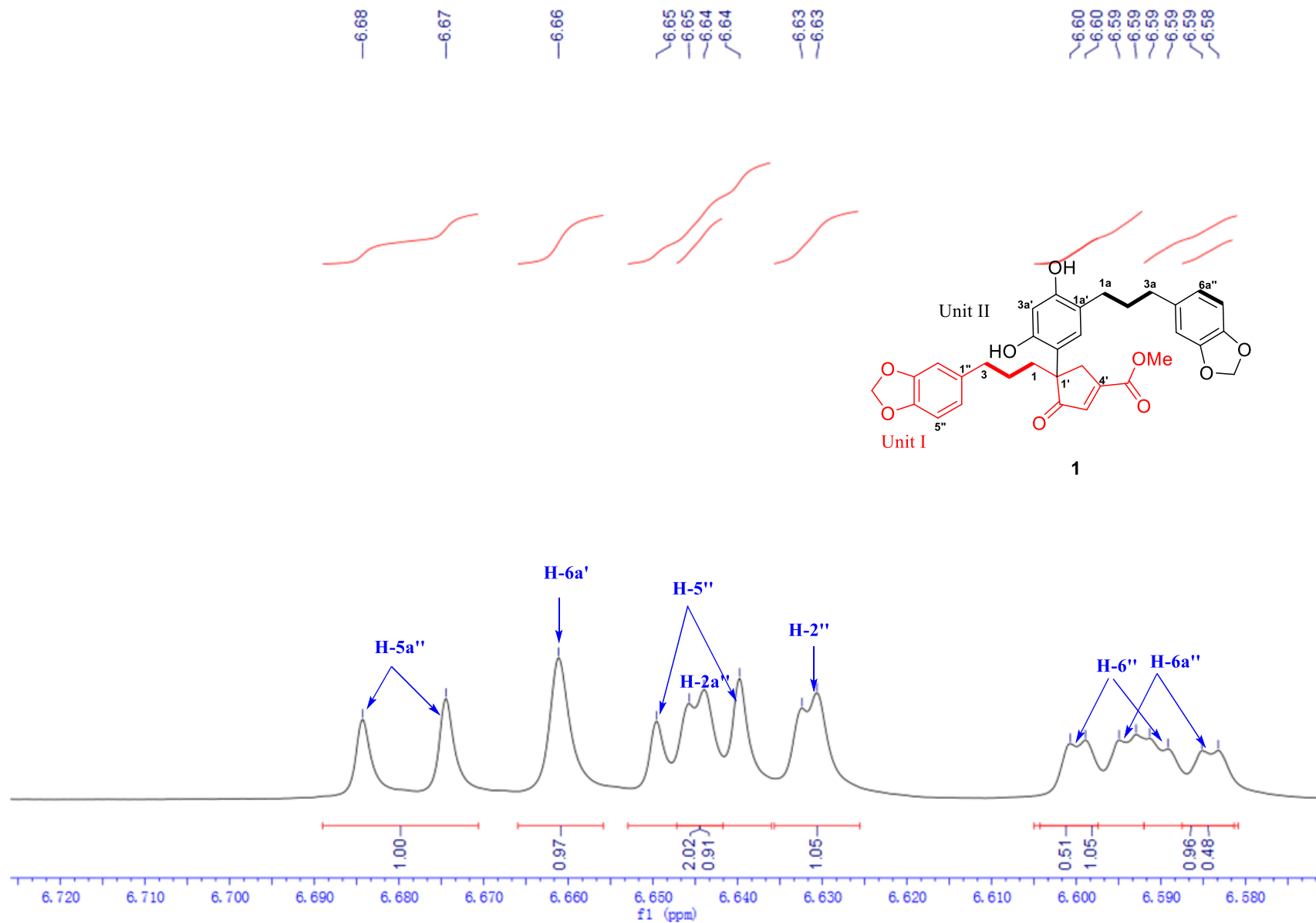


Figure S5. ^1H NMR spectrum (6.58-6.72 ppm) of compound **1**

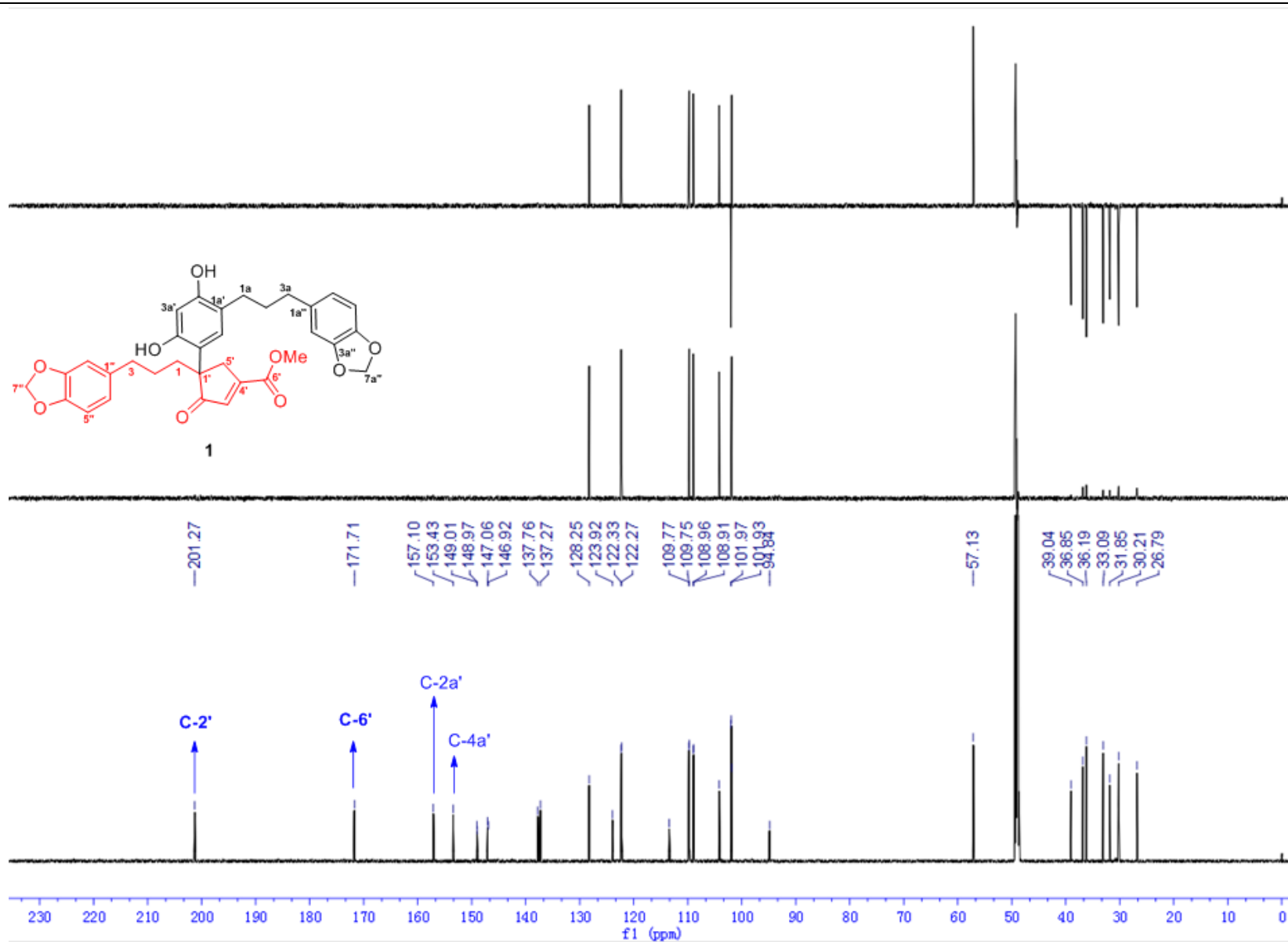


Figure S6. ^{13}C NMR spectra (0-230 ppm) of compound 1

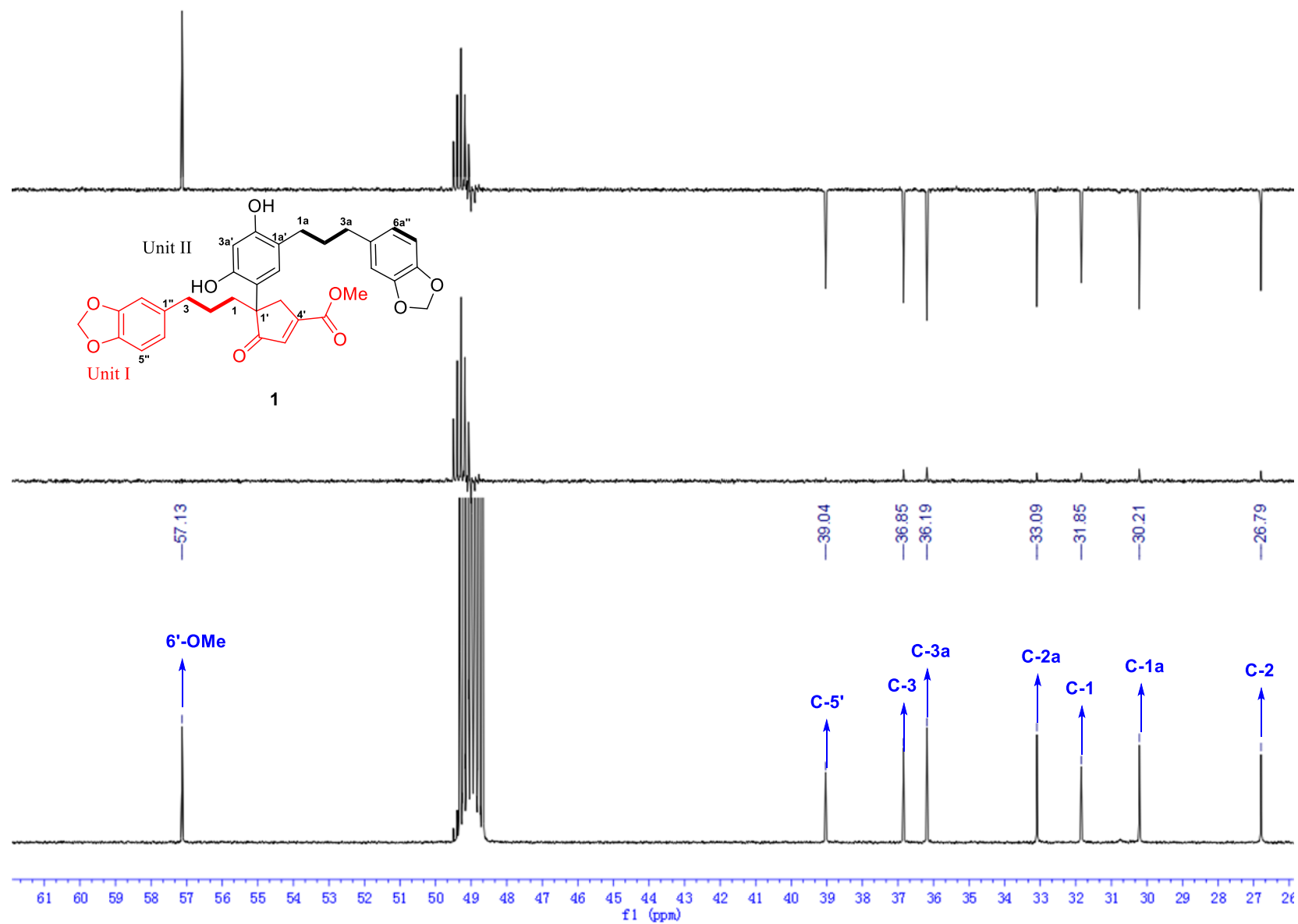


Figure S7. ^{13}C NMR spectra (20–61 ppm) of compound **1**

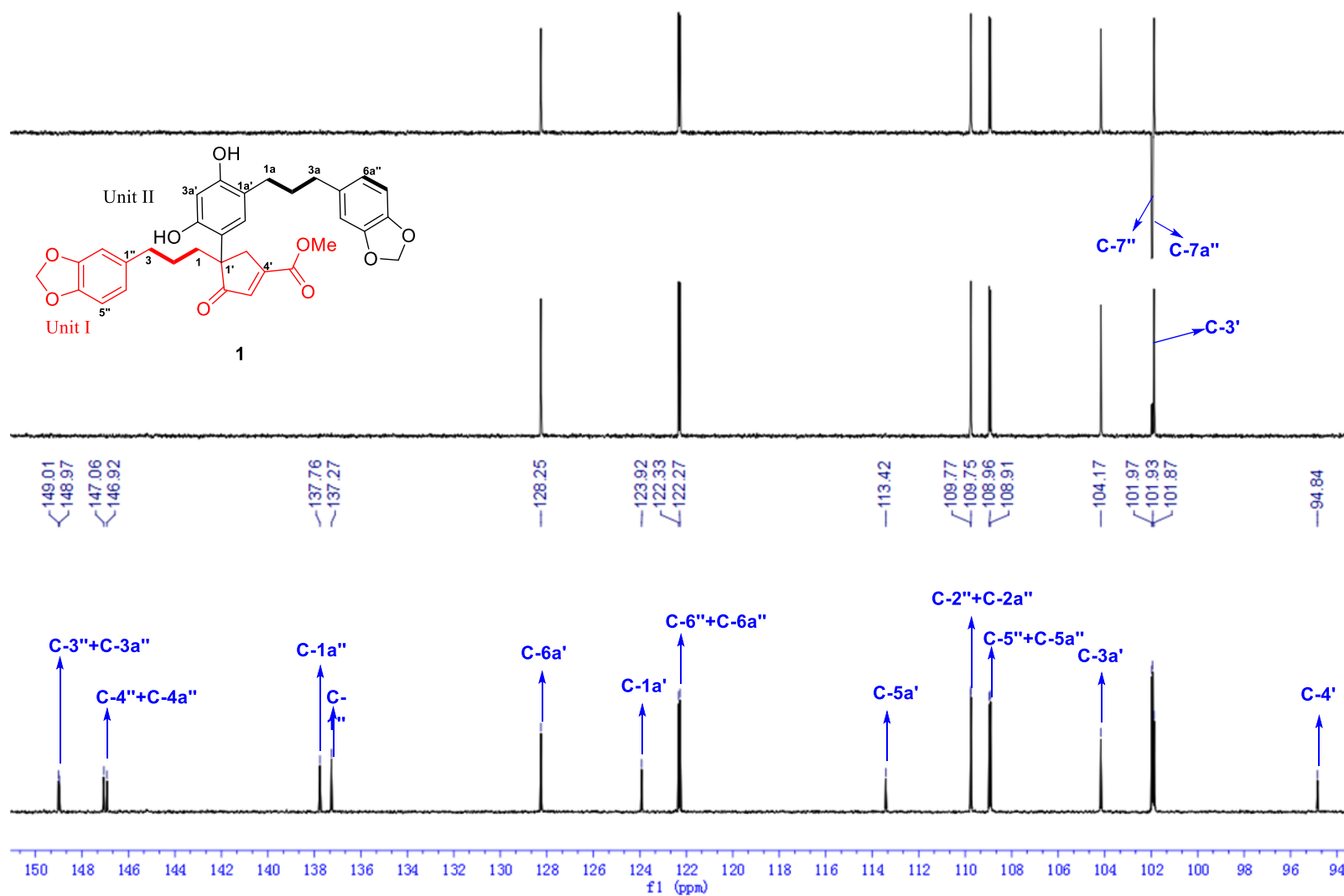


Figure S8. ^{13}C NMR spectra (94-170 ppm) of compound 1

Supporting Information

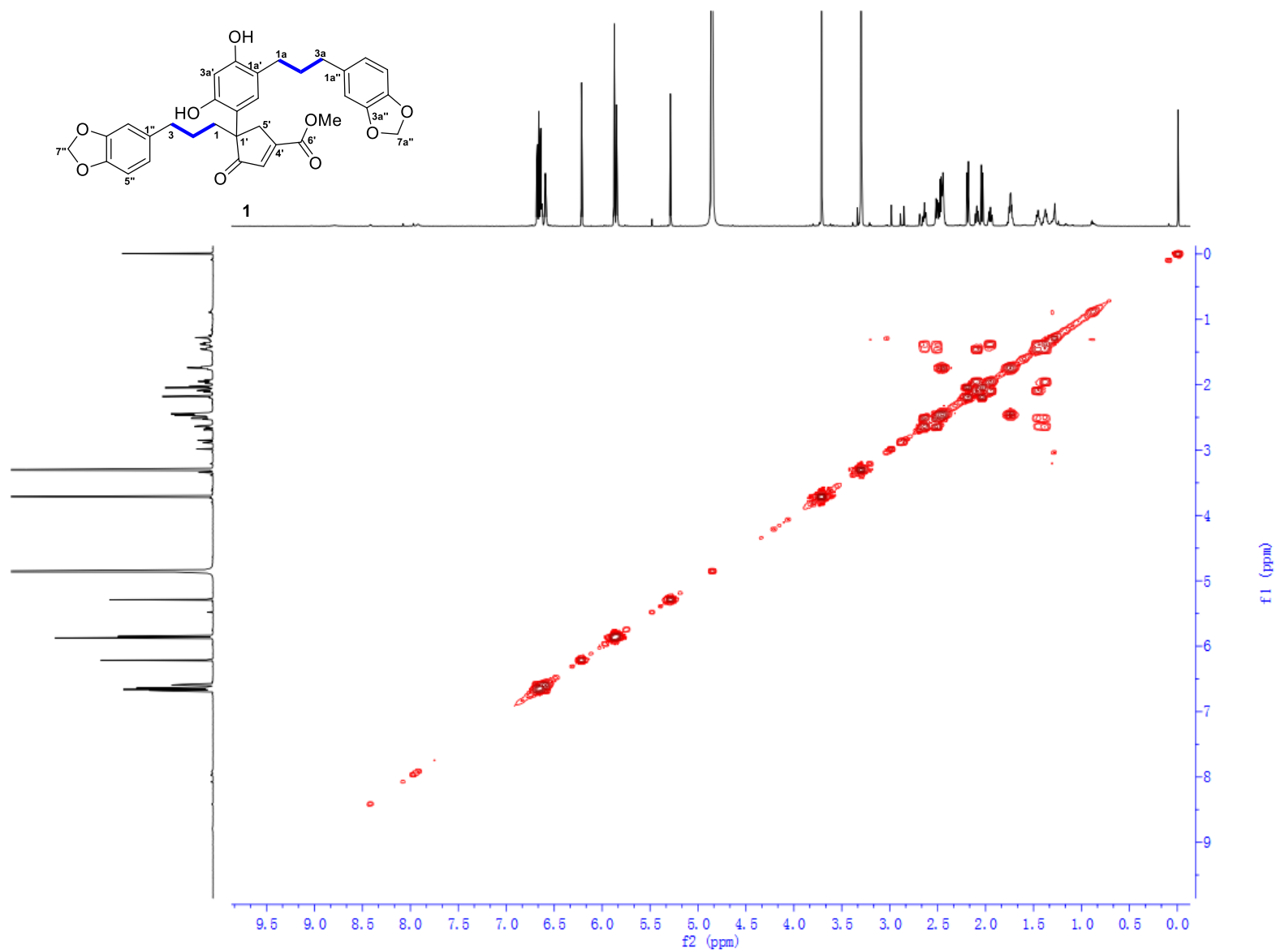
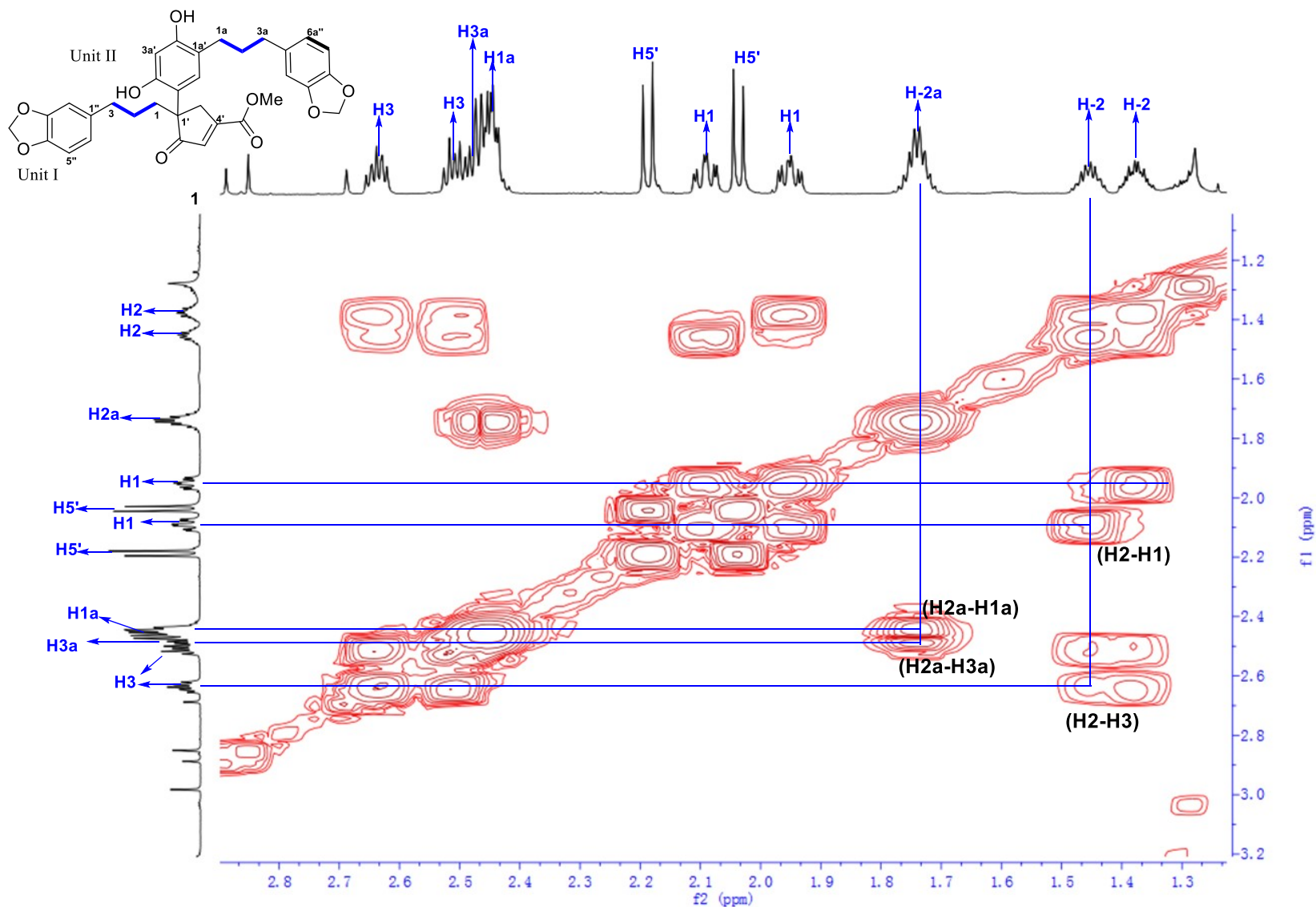


Figure S9. ^1H - ^1H COSY spectrum of compound **1**
S13



Supporting Information

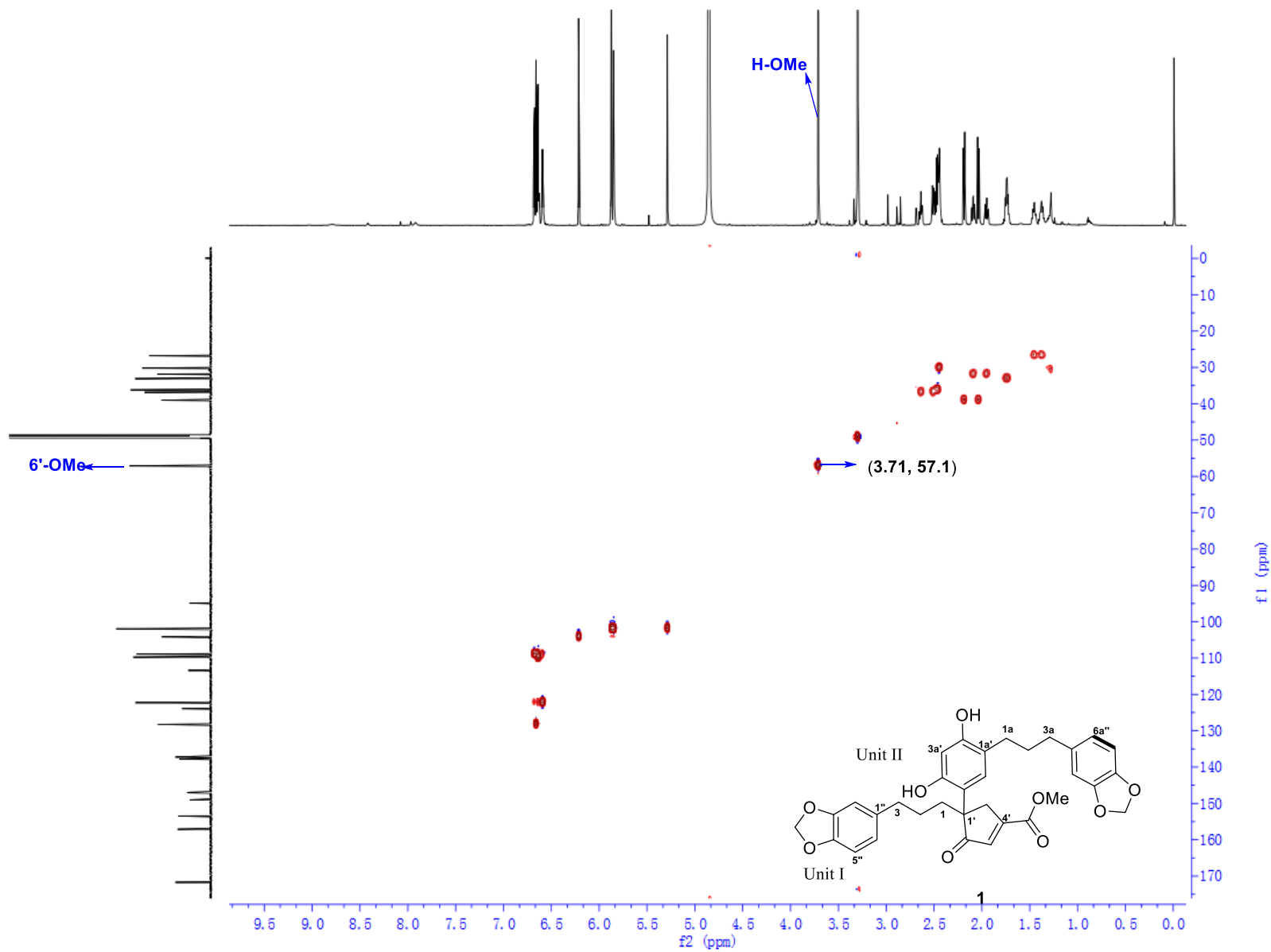


Figure S11. HSQC spectrum of compound **1**
S15

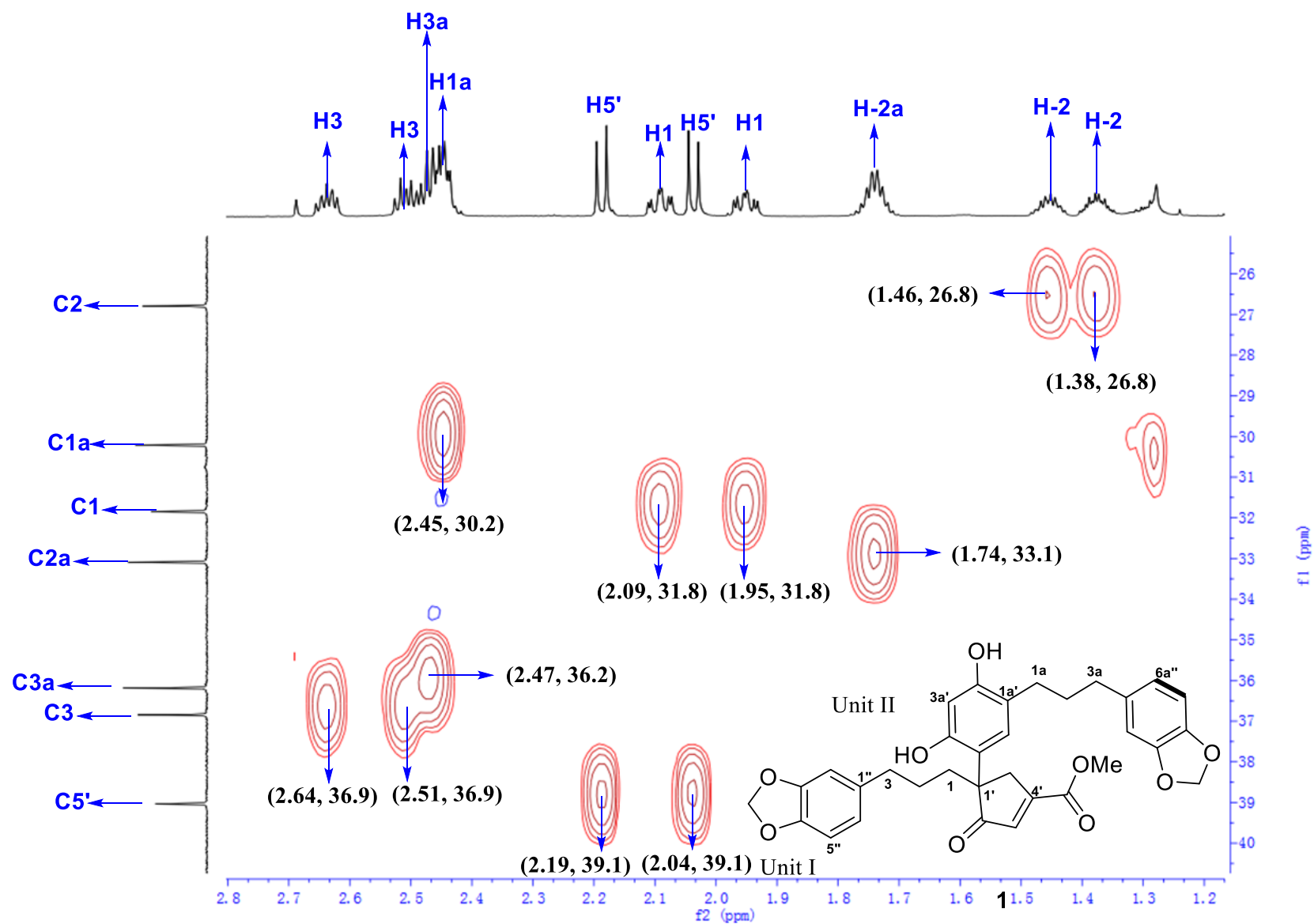


Figure S12. HSQC spectrum (δ_{H} 1.2–2.8 ppm and δ_{C} 26–40 ppm) of compound **1**

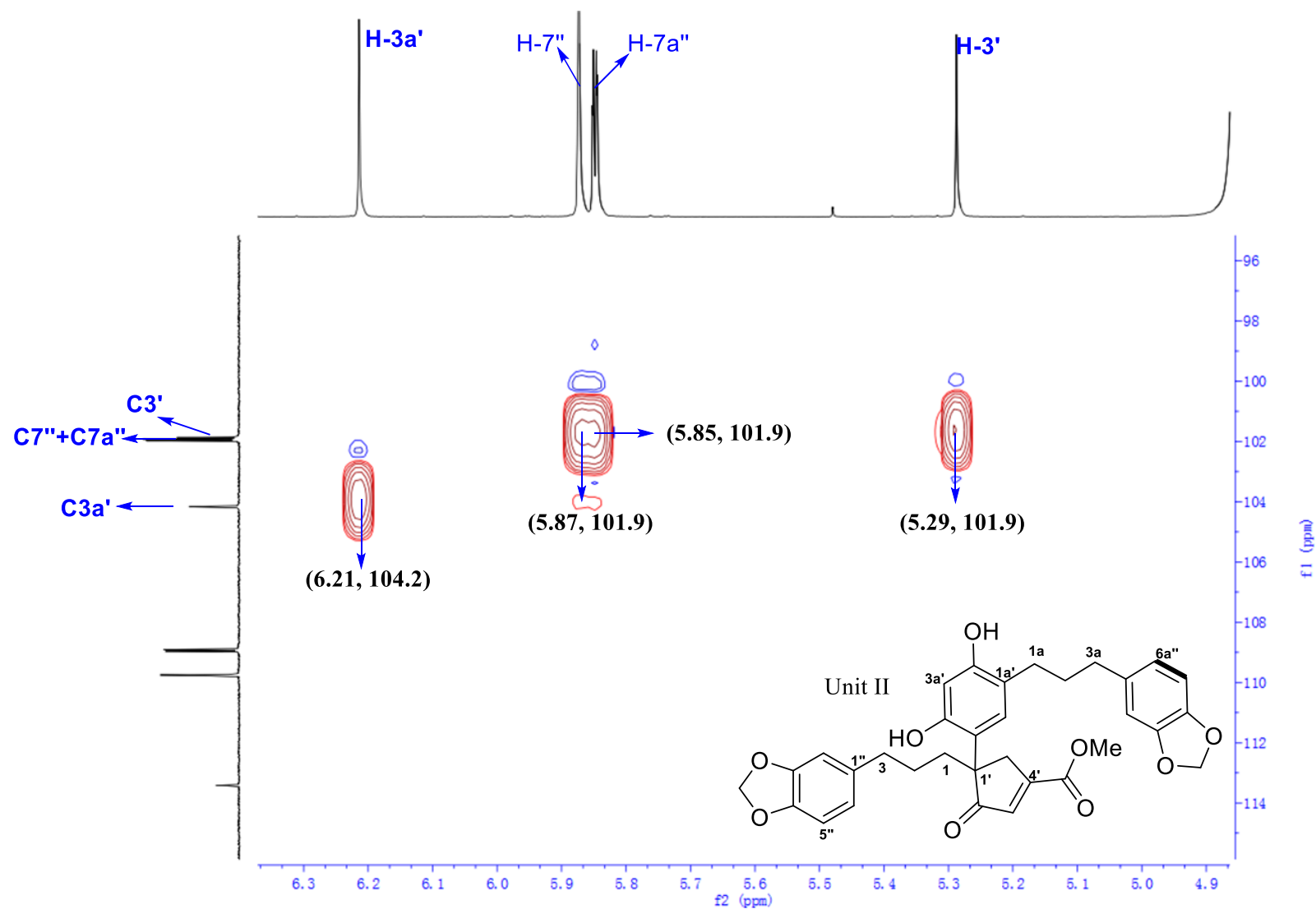
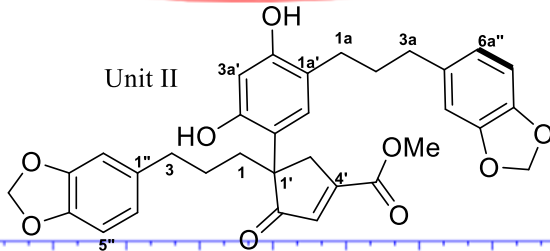


Figure S13. HSQC spectrum (δ_{H} 4.9–6.5 ppm and δ_{C} 96–114 ppm) of compound 1



S18

Supporting Information

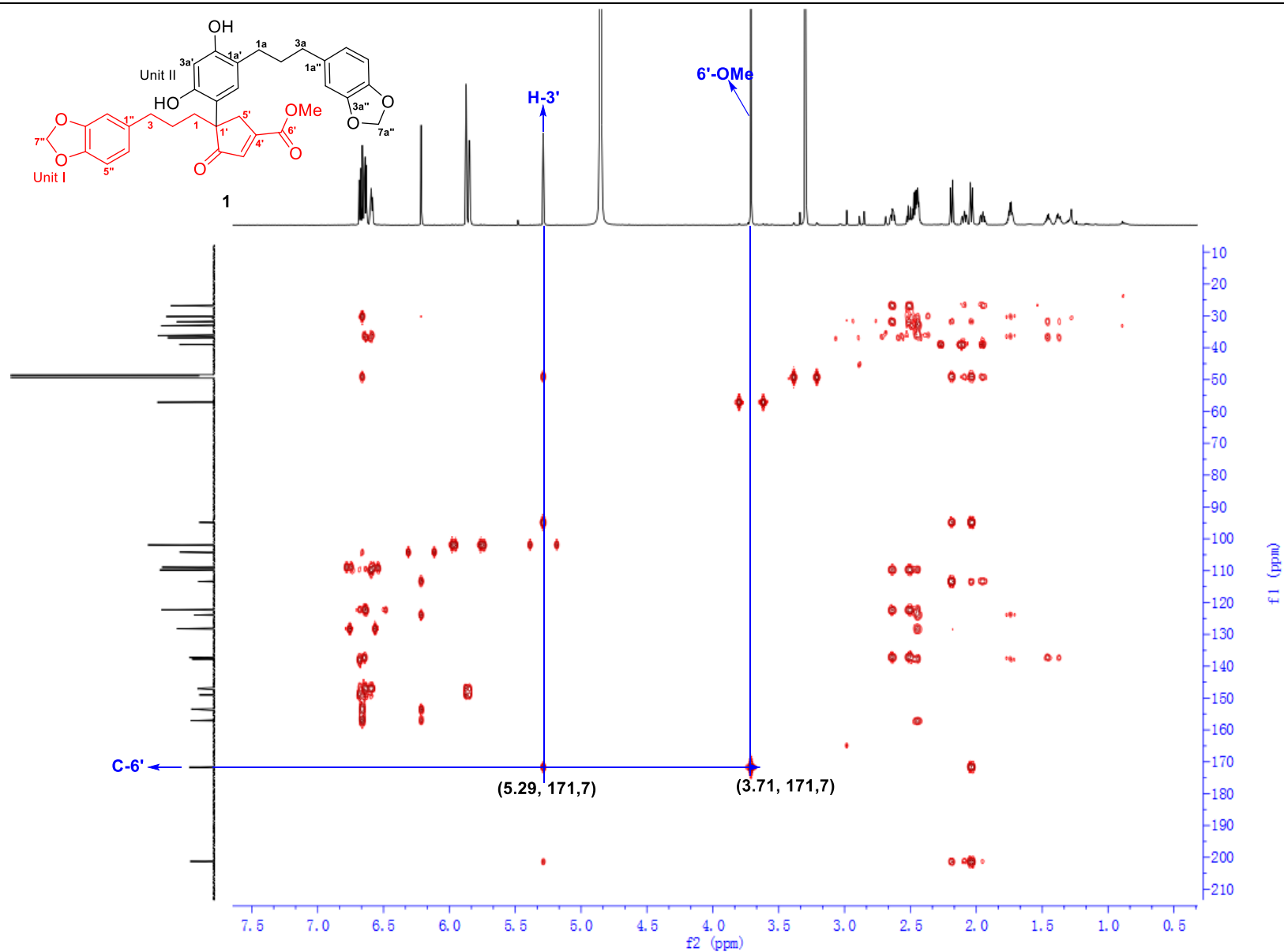


Figure S15. HMBC spectrum of compound **1**
S19

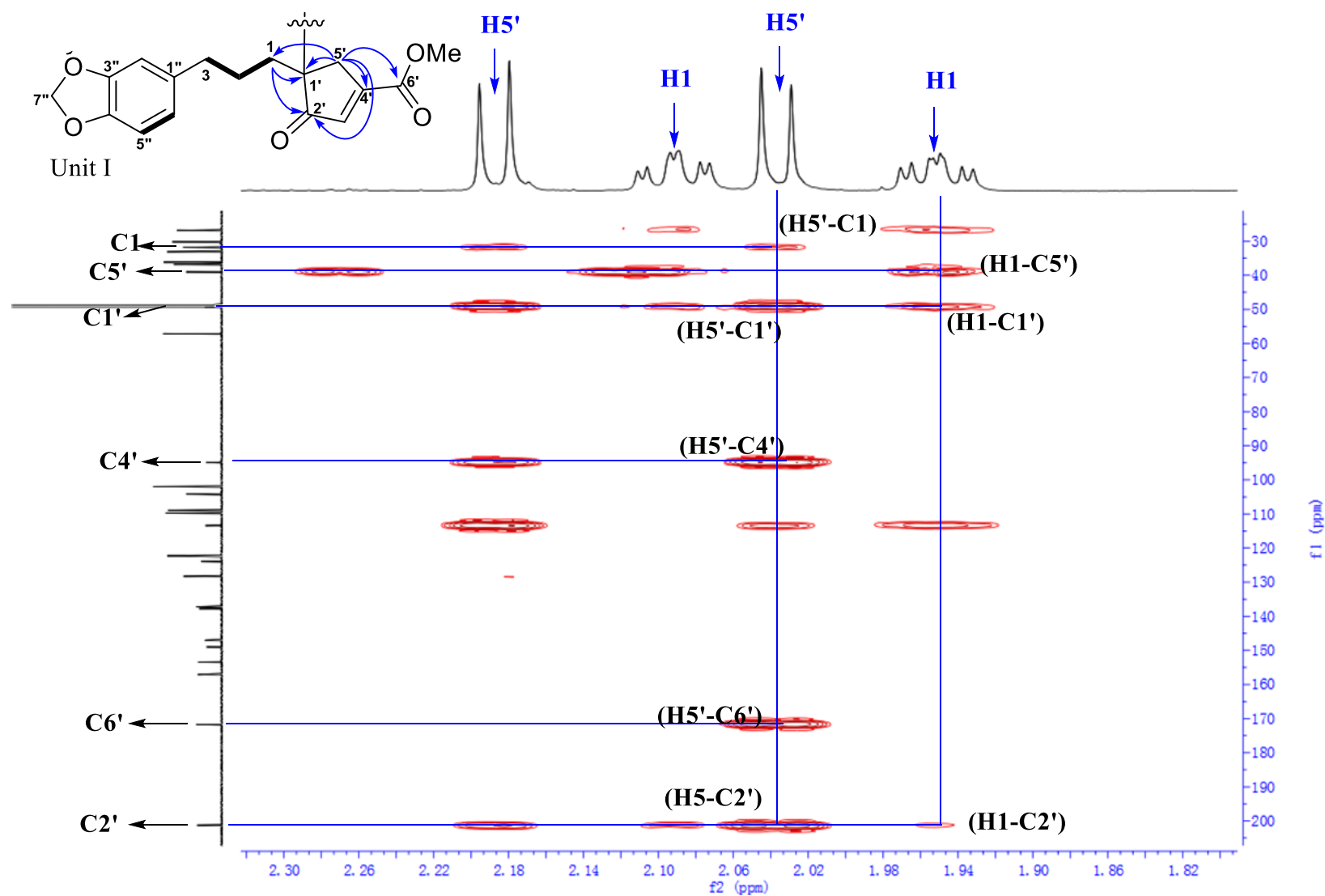


Figure S16. Key HMBC spectrum (δ_{H} 1.82–2.30 ppm and δ_{C} 30–200 ppm) of unit I in compound **1**

Supporting Information

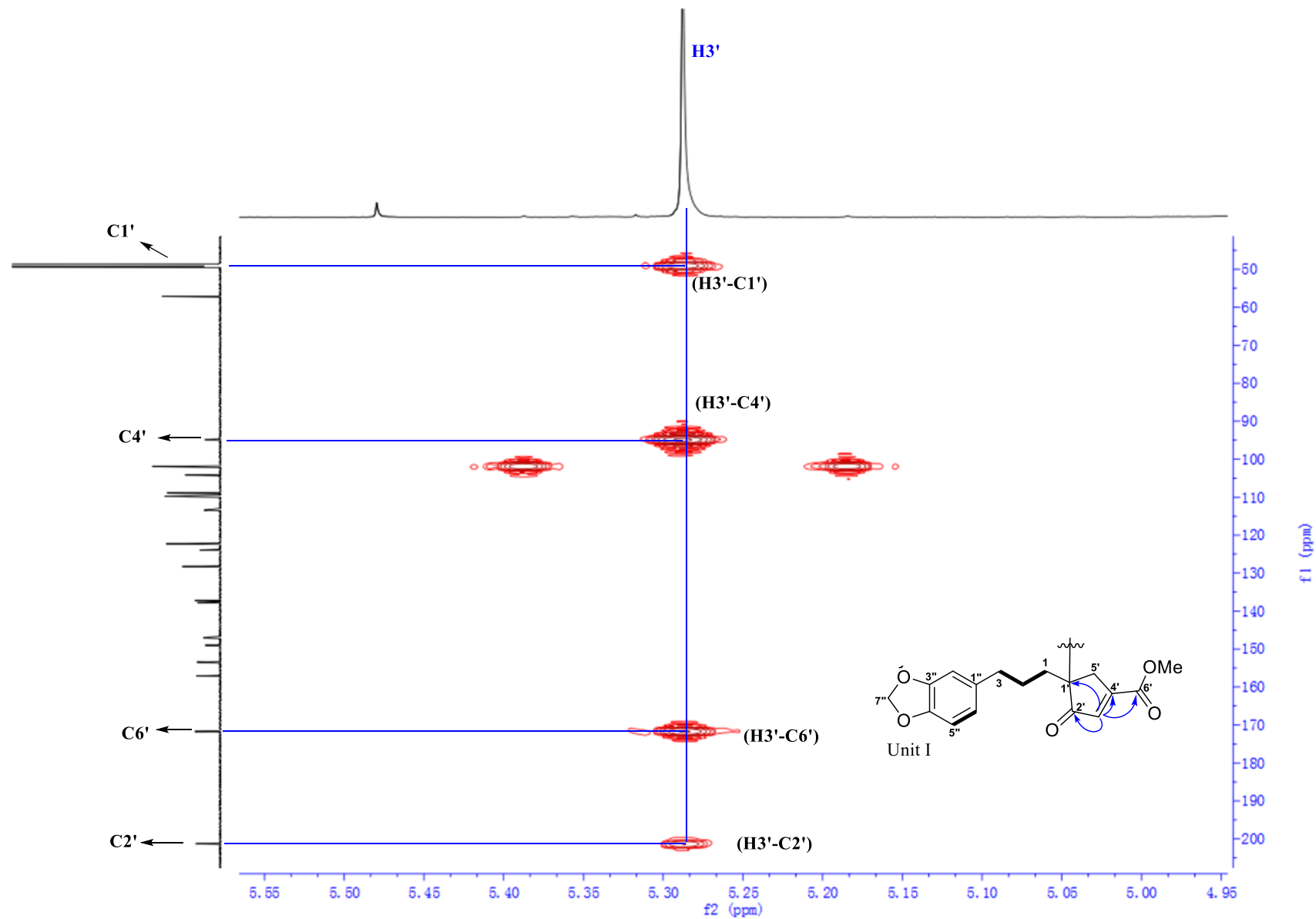


Figure S17. Key HMBC spectrum (δ_H 4.9–5.9 ppm and δ_C 40–200 ppm) of unit I in compound **1**

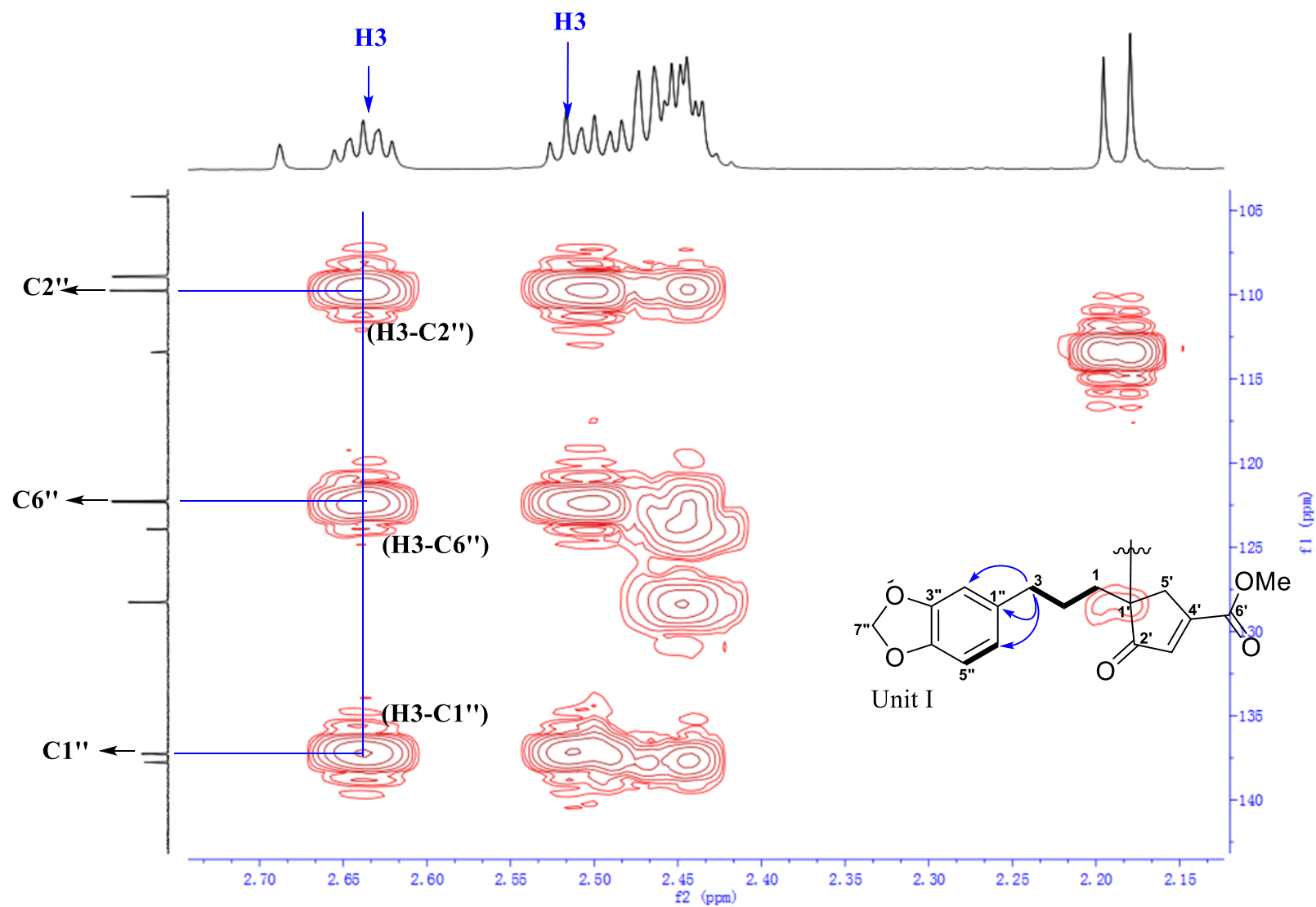


Figure S18. Key HMBC spectrum (δ_H 2.15–2.70 ppm and δ_C 105–140 ppm) of unit I in compound **1**

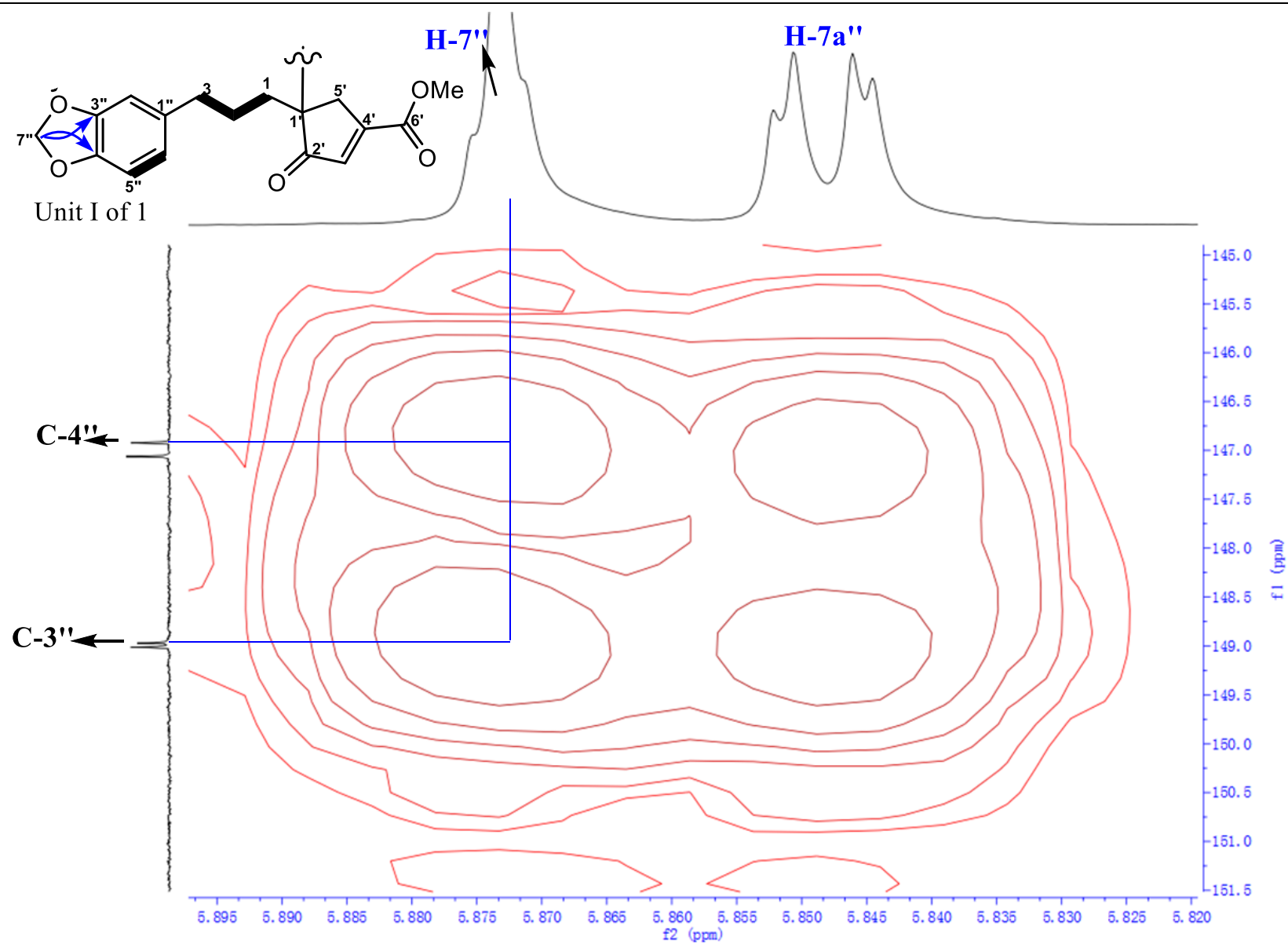


Figure S19. Key HMBC spectrum (δ_{H} 5.82–5.90 ppm and δ_{C} 145–151.5 ppm) of unit I in compound **1**

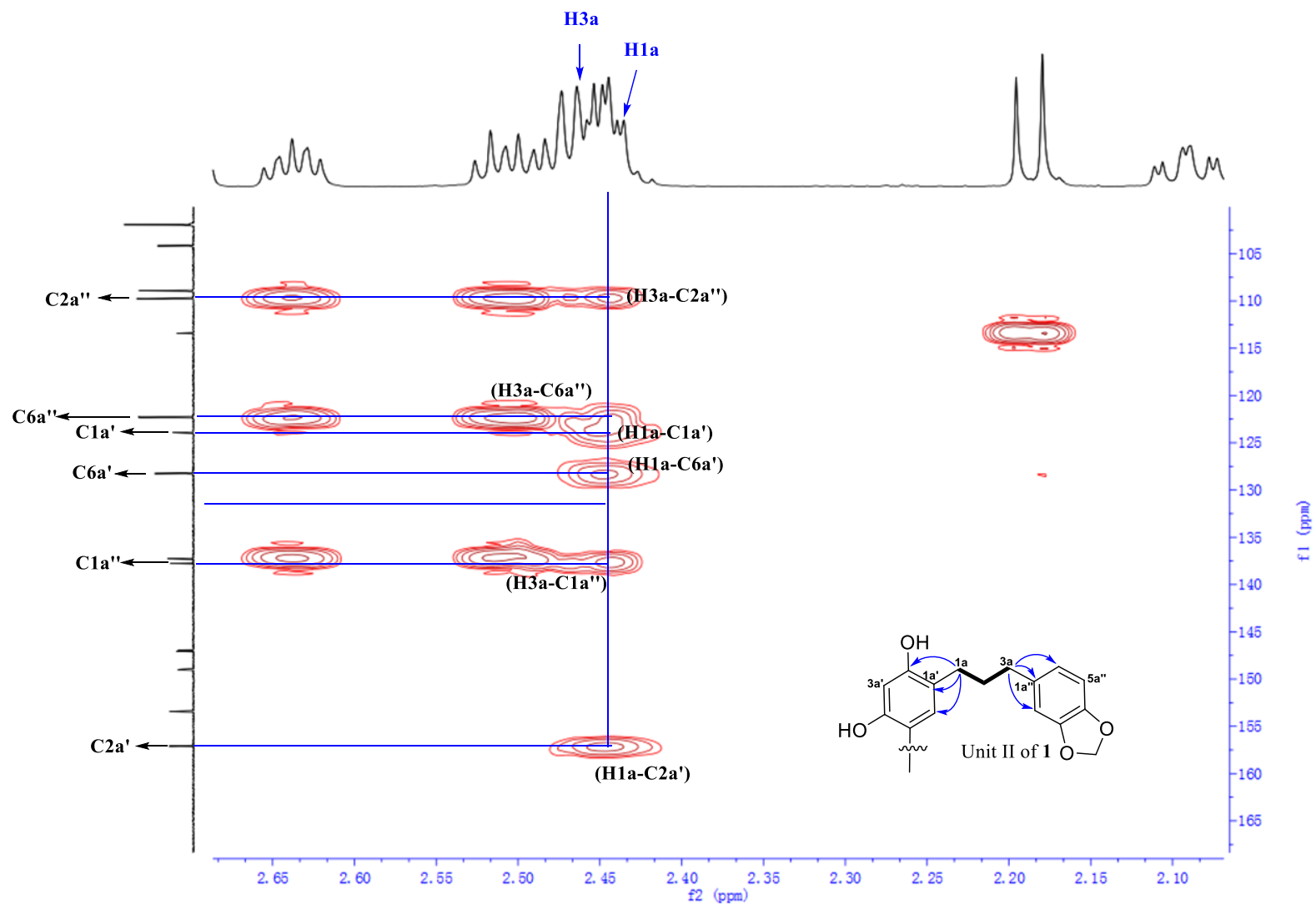


Figure S20. Key HMBC spectrum (δ_H 2.10–2.65 ppm and δ_C 145–165 ppm) of unit II in compound **1**

Supporting Information

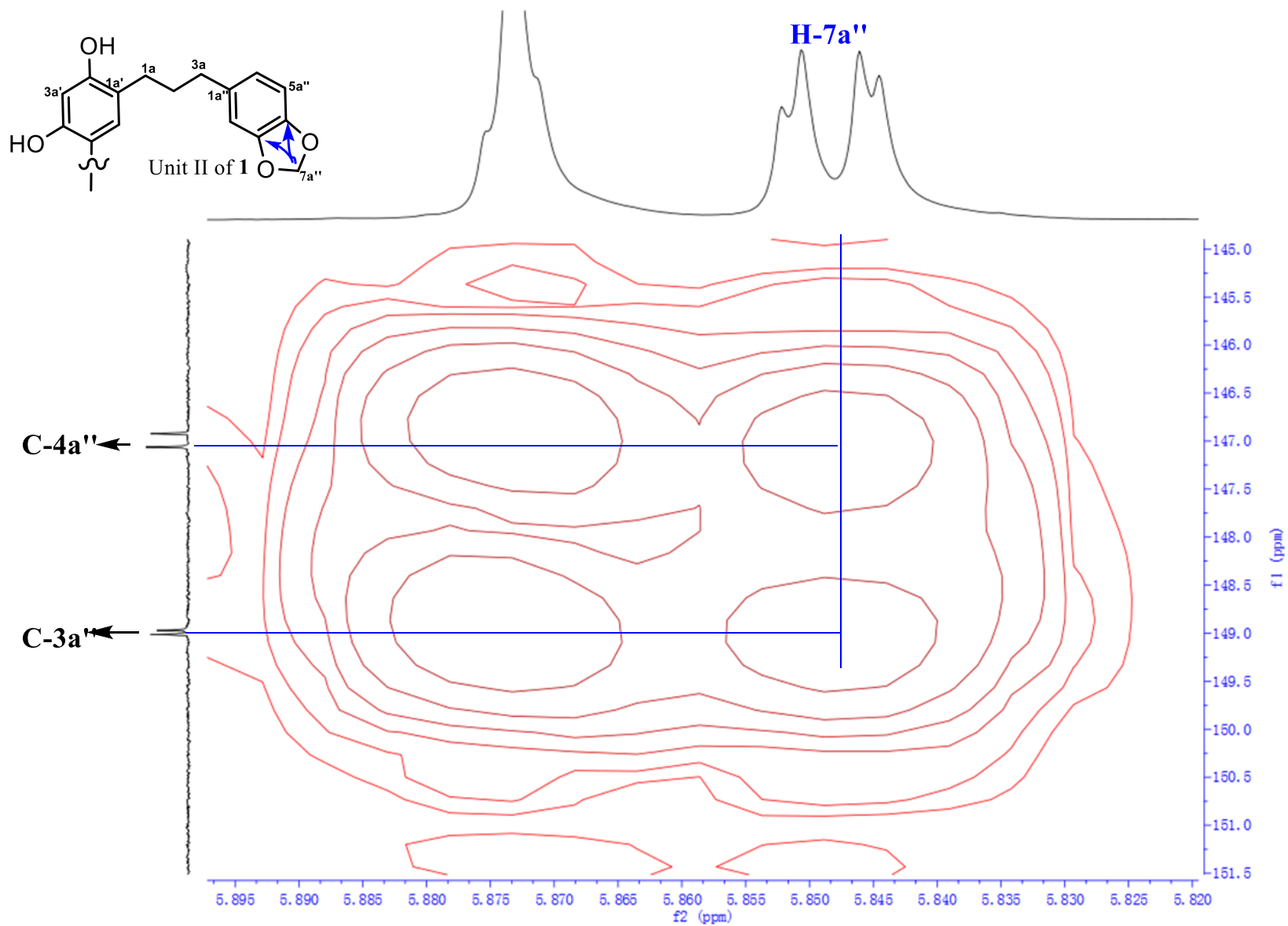


Figure S21. Key HMBC spectrum (δ_{H} 5.82–5.895 ppm and δ_{C} 145–150 ppm) of unit II in compound **1**

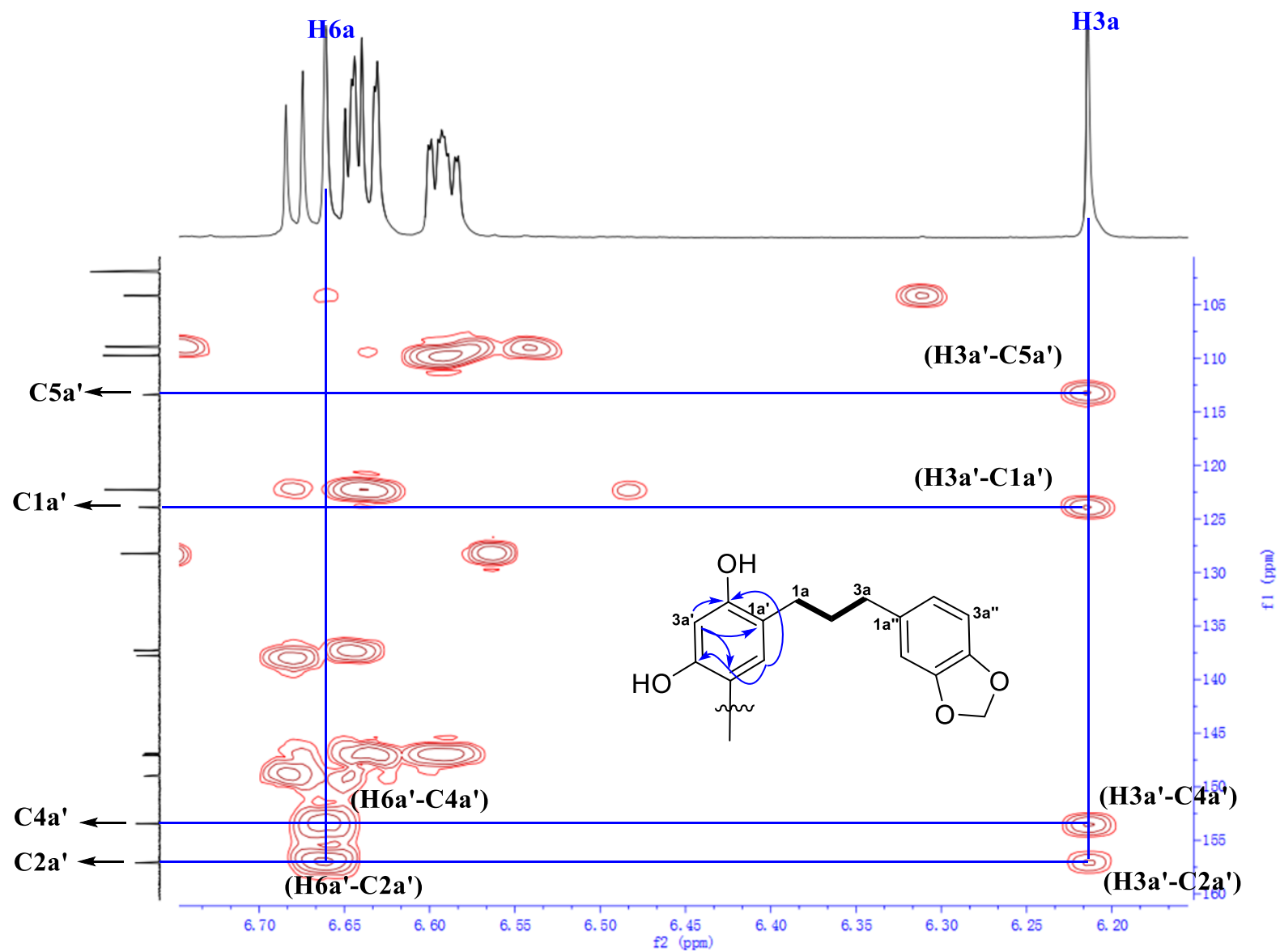


Figure S22. Key HMBC spectrum (δ_H 6.20–6.70ppm and δ_C 105–160 ppm) of unit II in compound 1

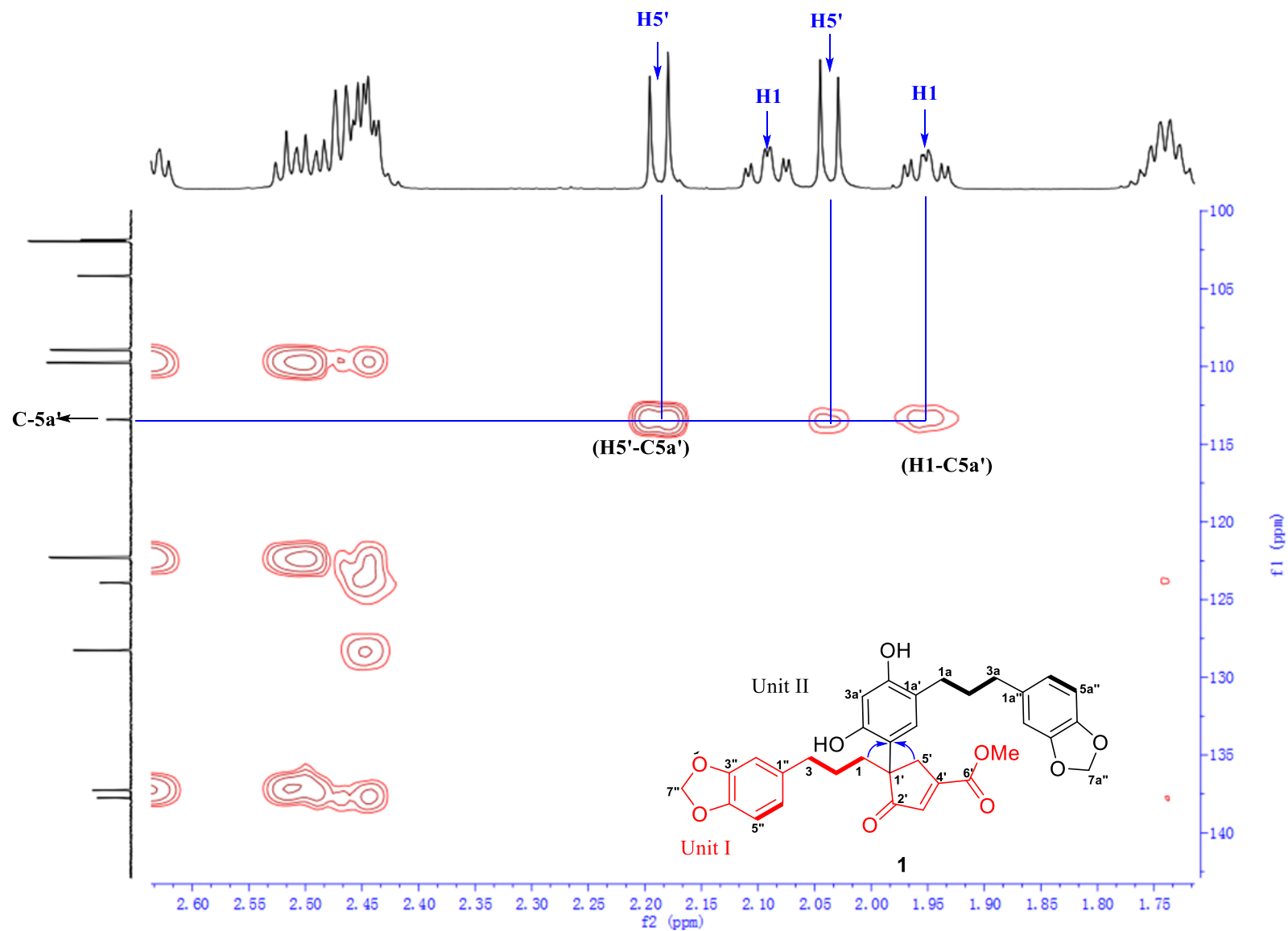


Figure S23. Key HMBC spectrum (δ_H 1.75–2.00 ppm and δ_C 100–140 ppm) of compound **1**

Supporting Information

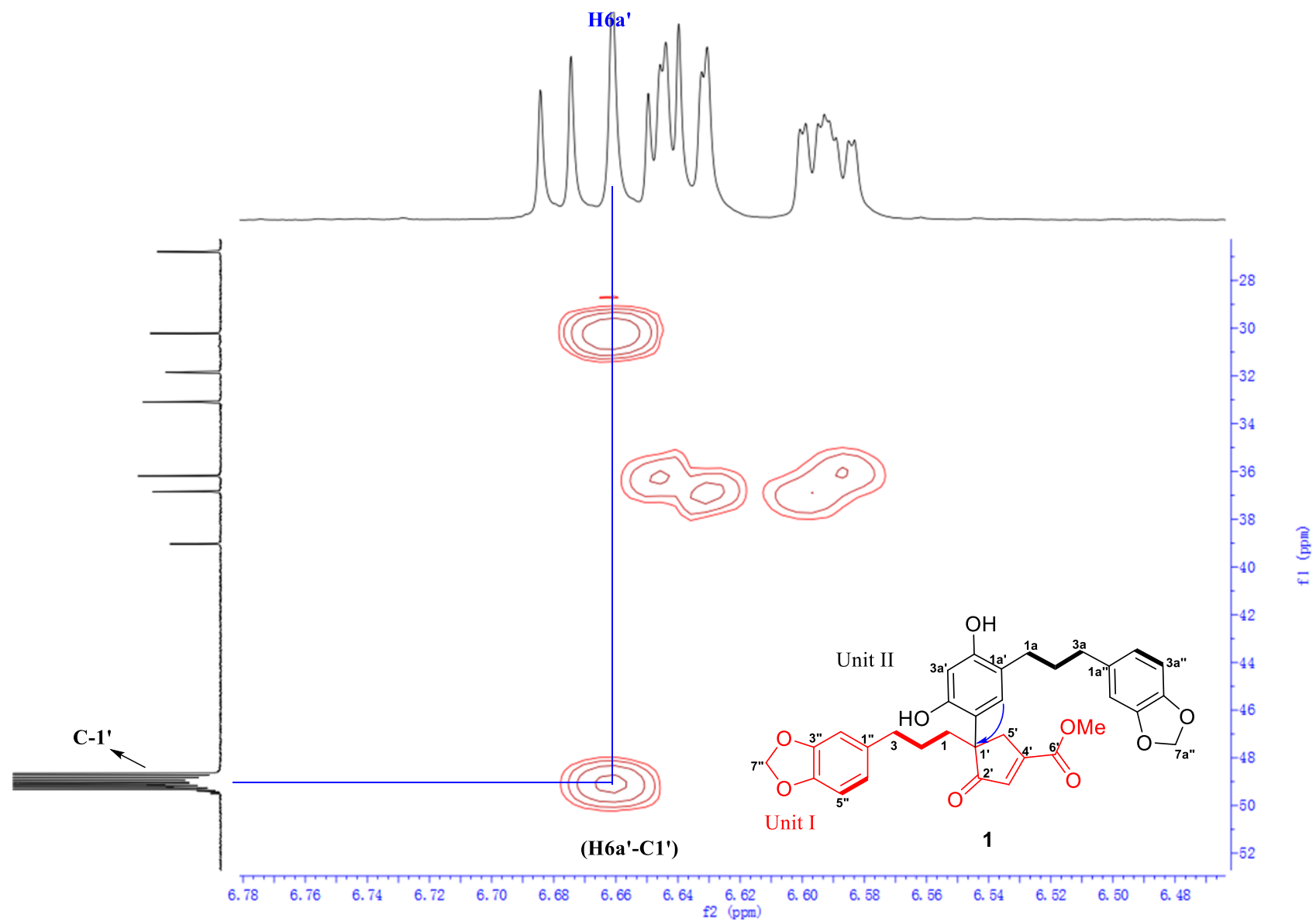
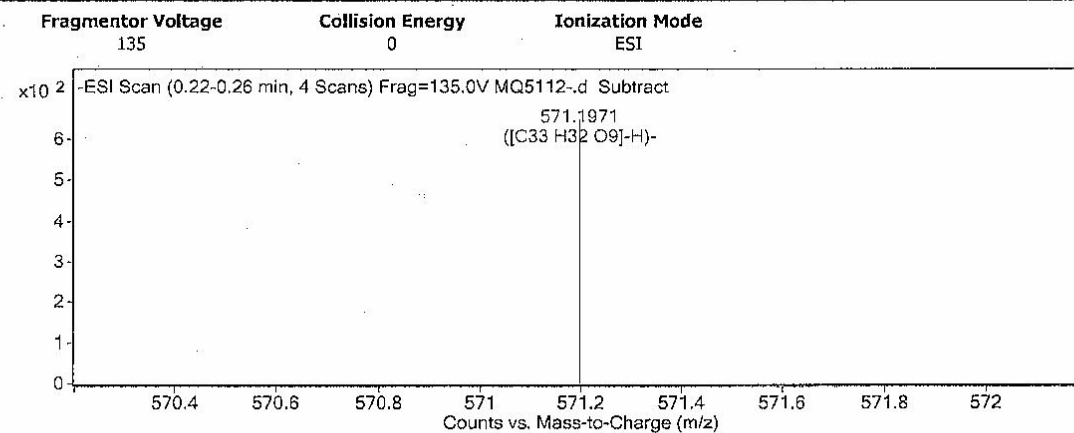


Figure S24. Key HMBC spectrum (δ_H 1.75–2.00 ppm and δ_C 100–140 ppm) of compound **1**
S28

Supporting Information

User Spectra



Peak List

m/z	z	Abund
112.9852		4620.68
133.014		4810.29
205.1598	1	4252.88
238.0332	1	5657.29
255.2329	1	9252.09
341.109	1	11531.95
377.0855	1	4949.85
404.1046	1	6599.28

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30

Formula Calculator Results

Formula	CalculatedMass	CalculatedMz	Mz	Diff. (mDa)	Diff. (ppm)	DBE
C33 H32 O9	572.2046	571.1974	571.1971	-0.1	-0.1	18.0000

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Figure S25. HR-ESIMS spectrum of compound **1**

Supporting Information

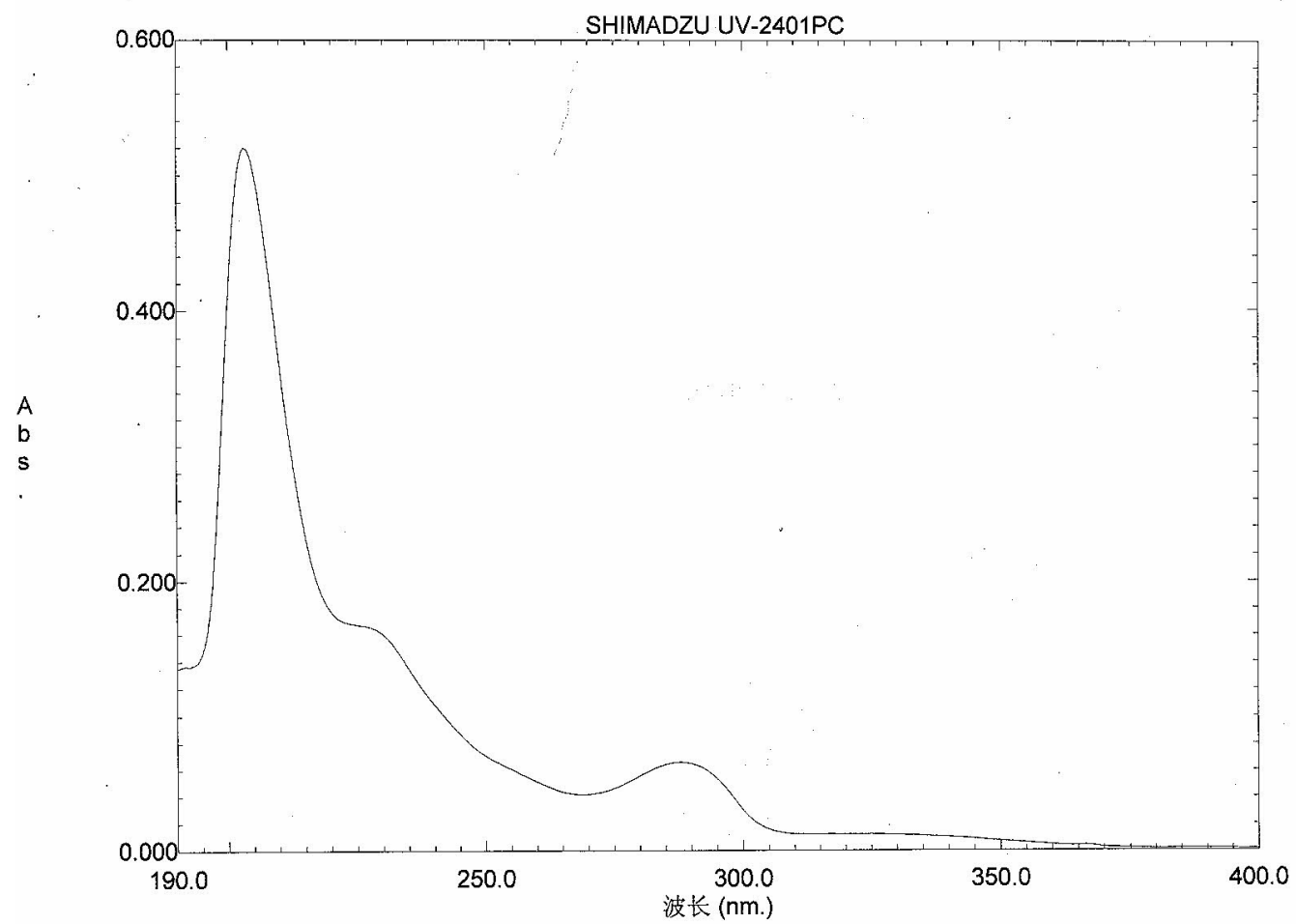


Figure S26. UV spectrum of compound **1**

Supporting Information

Optical rotation measurement

Model : P-1020 (A060460638)

No.	Sample	Mode	Data	Monitor Blank	Temp. Cell Temp Point	Date Comment Sample Name	Light Filter Operator	Cycle Time Integ Time
No.1	83 (1/3)	Sp.Rot	134.6670	0.0404 0.0000	19.2 50.00	Thu Jan 18 16:19:57 2018 0.00060g/mL MeOH 5112-1	Na 589nm	2 sec 2 sec
No.2	83 (2/3)	Sp.Rot	136.3330	0.0409 0.0000	19.1 50.00	Thu Jan 18 16:20:03 2018 0.00060g/mL MeOH 5112-1	Na 589nm	2 sec 2 sec
No.3	83 (3/3)	Sp.Rot	143.6670	0.0431 0.0000	19.1 50.00	Thu Jan 18 16:20:08 2018 0.00060g/mL MeOH 5112-1	Na 589nm	2 sec 2 sec
No.4	84 (1/3)	Sp.Rot	147.6670	0.0443 0.0000	19.1 50.00	Thu Jan 18 16:20:24 2018 0.00060g/mL MeOH 5112-1	Na 589nm	2 sec 2 sec
No.5	84 (2/3)	Sp.Rot	129.6670	0.0389 0.0000	19.0 50.00	Thu Jan 18 16:20:30 2018 0.00060g/mL MeOH 5112-1	Na 589nm	2 sec 2 sec
No.6	84 (3/3)	Sp.Rot	139.3330	0.0418 0.0000	19.0 50.00	Thu Jan 18 16:20:35 2018 0.00060g/mL MeOH 5112-1	Na 589nm	2 sec 2 sec

+138.5556°

Figure S27. ORD spectrum of compound (+)-1

Supporting Information

Optical rotation measurement

Model : P-1020 (A060460638)

No.	Sample	Mode	Data	Monitor Blank	Temp. Cell Temp Point	Date Comment Sample Name	Light Filter Operator	Cycle Time Integ Time
No.1	82 (1/3)	Sp.Rot	-87.5000	-0.0525 0.0000	18.9 50.00 Cell	Thu Jan 18 16:12:33 2018 0.00120g/mL MeOH 5112-2	Na 589nm	2 sec 2 sec
No.2	82 (2/3)	Sp.Rot	-85.6670	-0.0514 0.0000	18.9 50.00 Cell	Thu Jan 18 16:12:39 2018 0.00120g/mL MeOH 5112-2	Na 589nm	2 sec 2 sec
No.3	82 (3/3)	Sp.Rot	-88.8330	-0.0533 0.0000	19.0 50.00 Cell	Thu Jan 18 16:12:44 2018 0.00120g/mL MeOH 5112-2	Na 589nm	2 sec 2 sec

-87.5000°

Figure S28. ORD spectrum of compound (-)-1

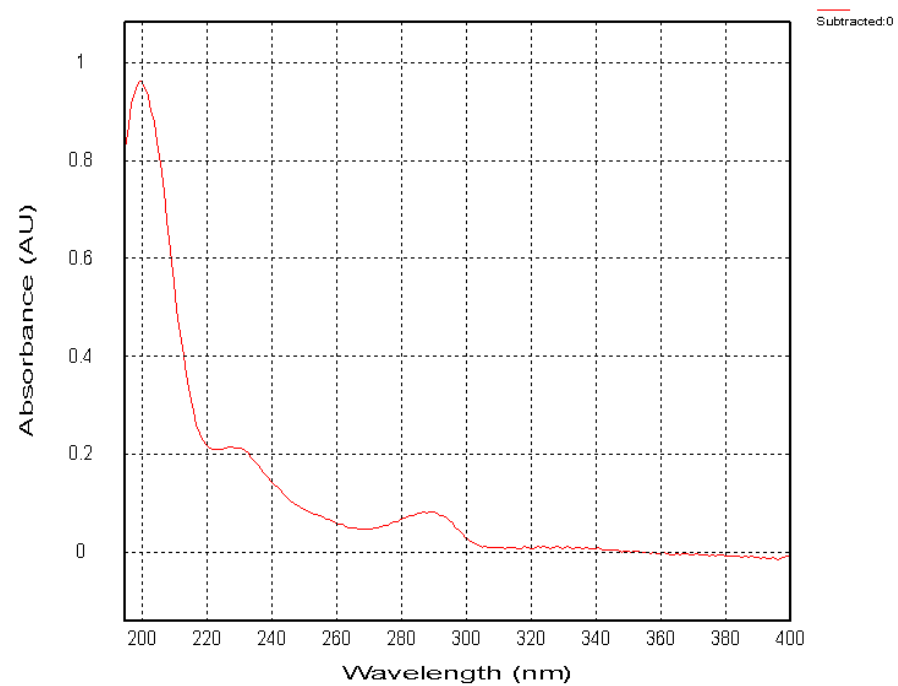
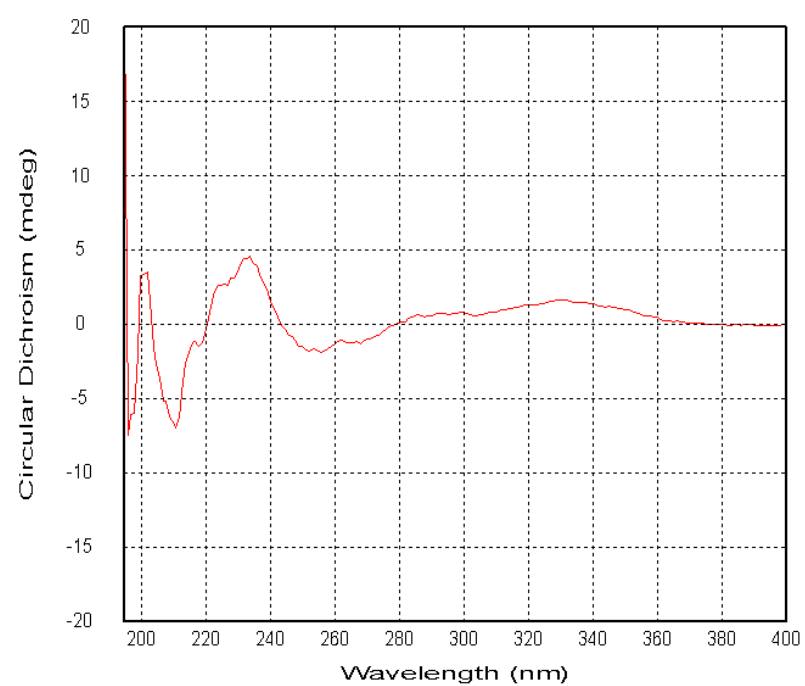


Figure S29. CD spectrum of compound (+)-1

Supporting Information

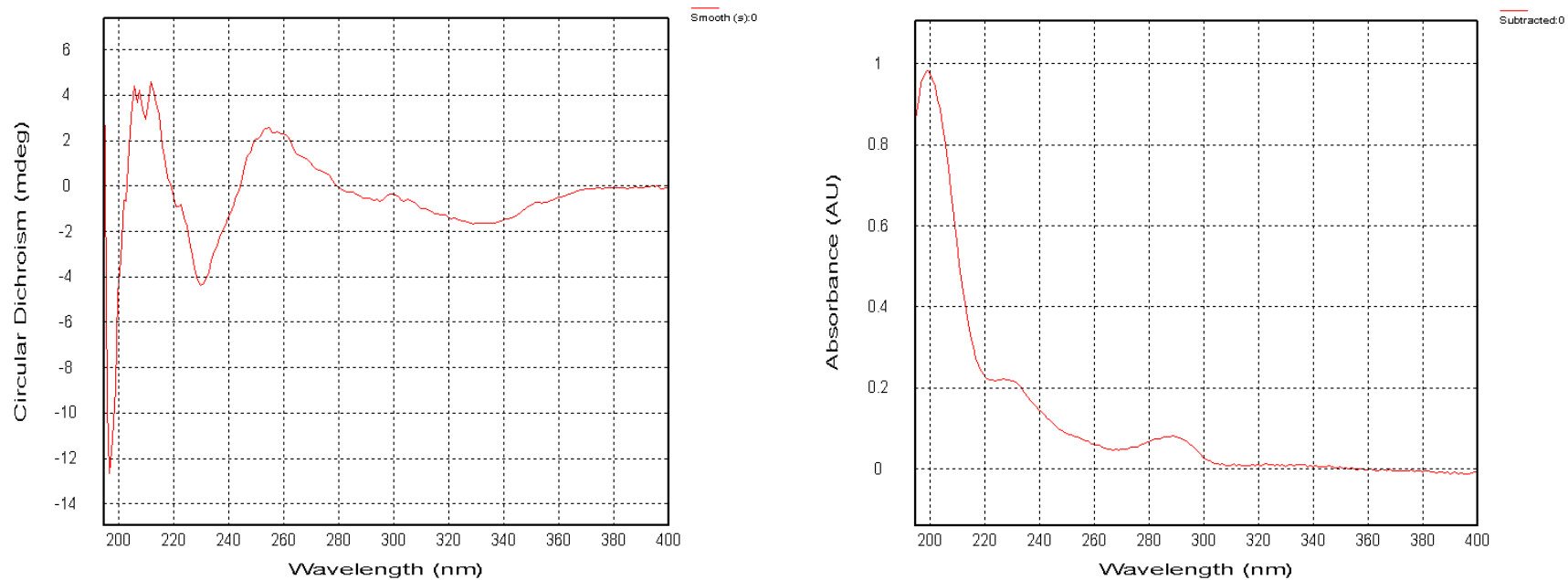


Figure S30. CD spectrum of compound (-)-1

Supporting Information

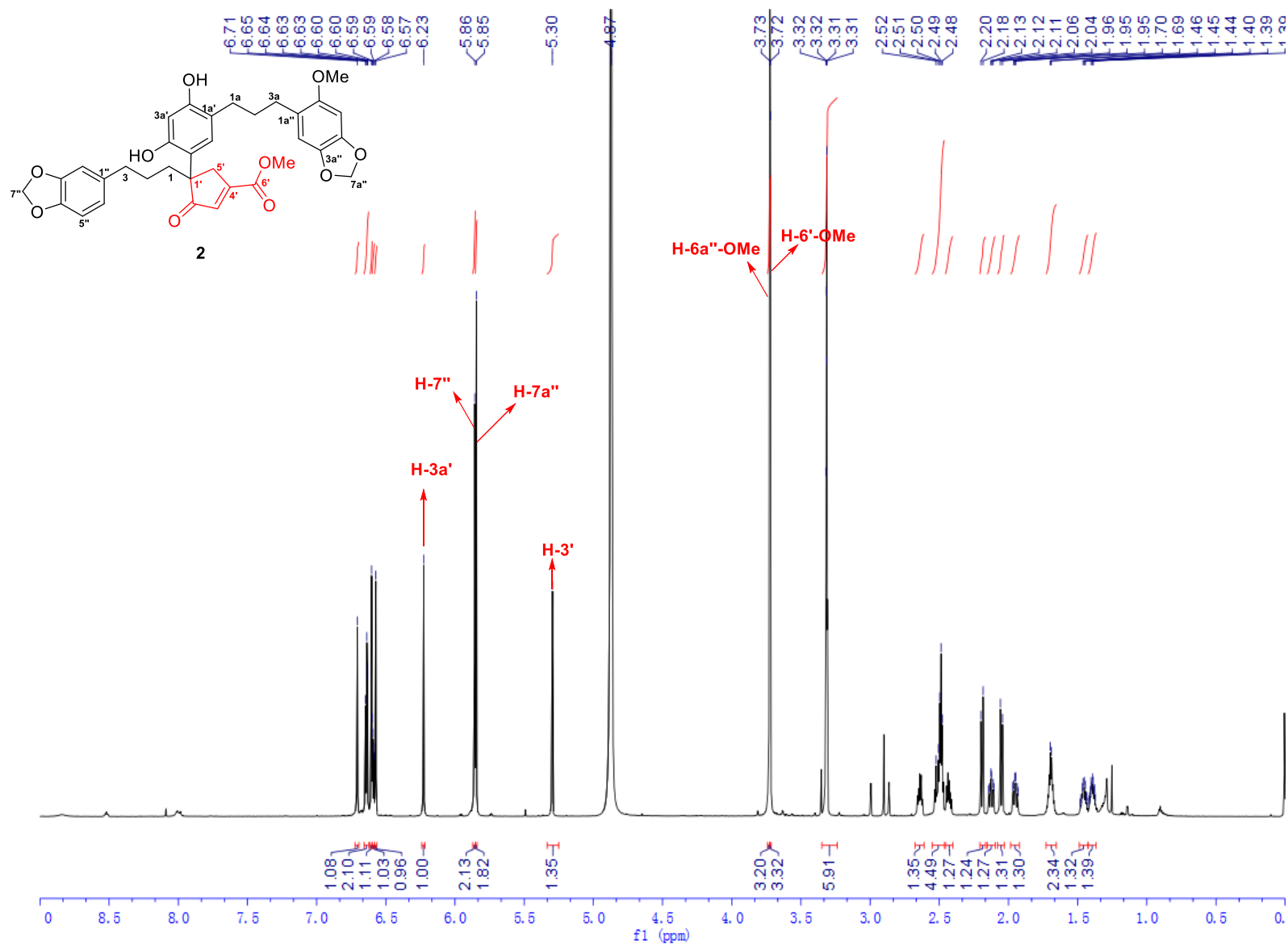


Figure S31. ¹H NMR spectrum (0-9 ppm) of compound **2**
S35

Supporting Information

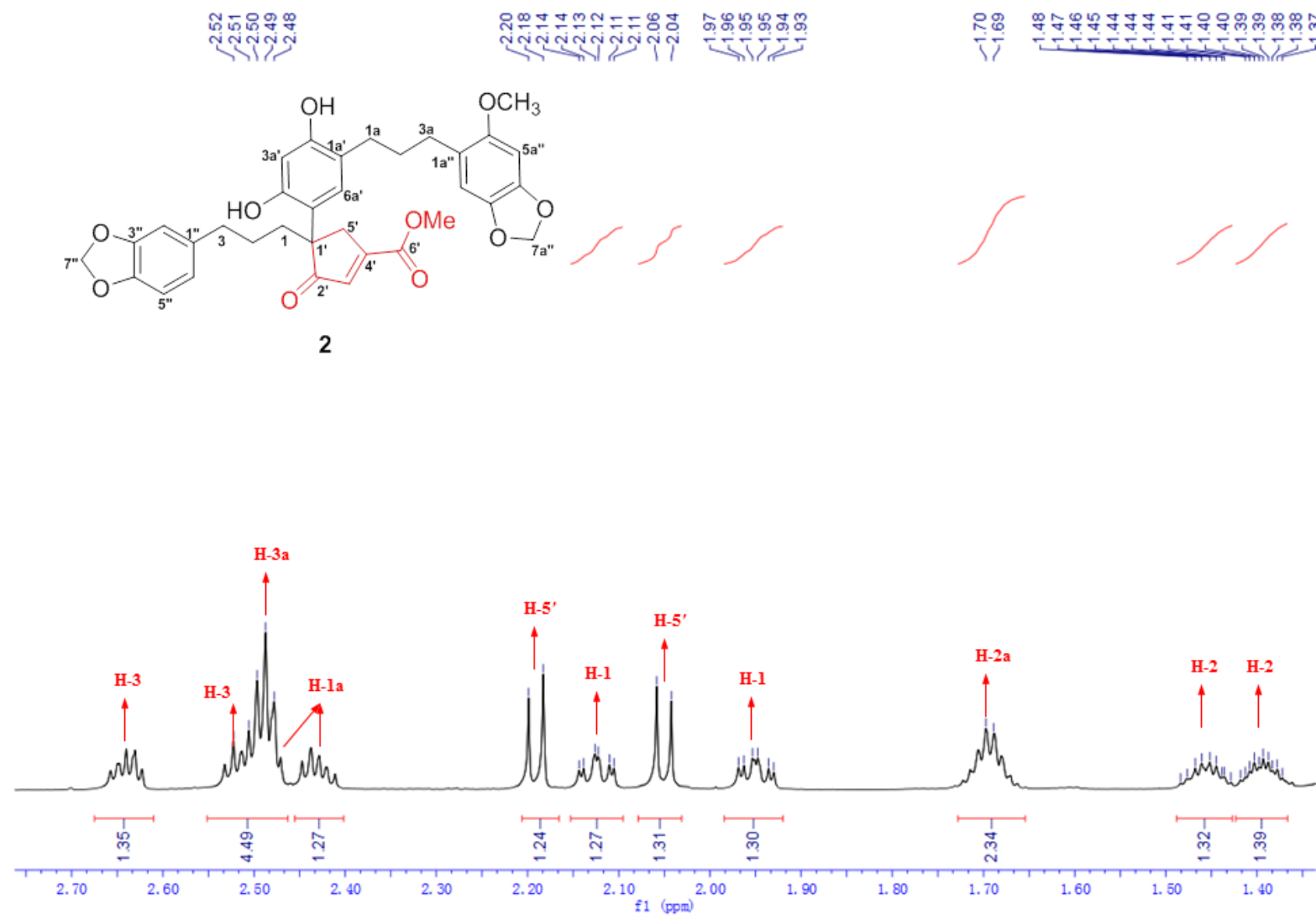


Figure S32. ^1H NMR spectrum (1.40-2.70 ppm) of compound 2

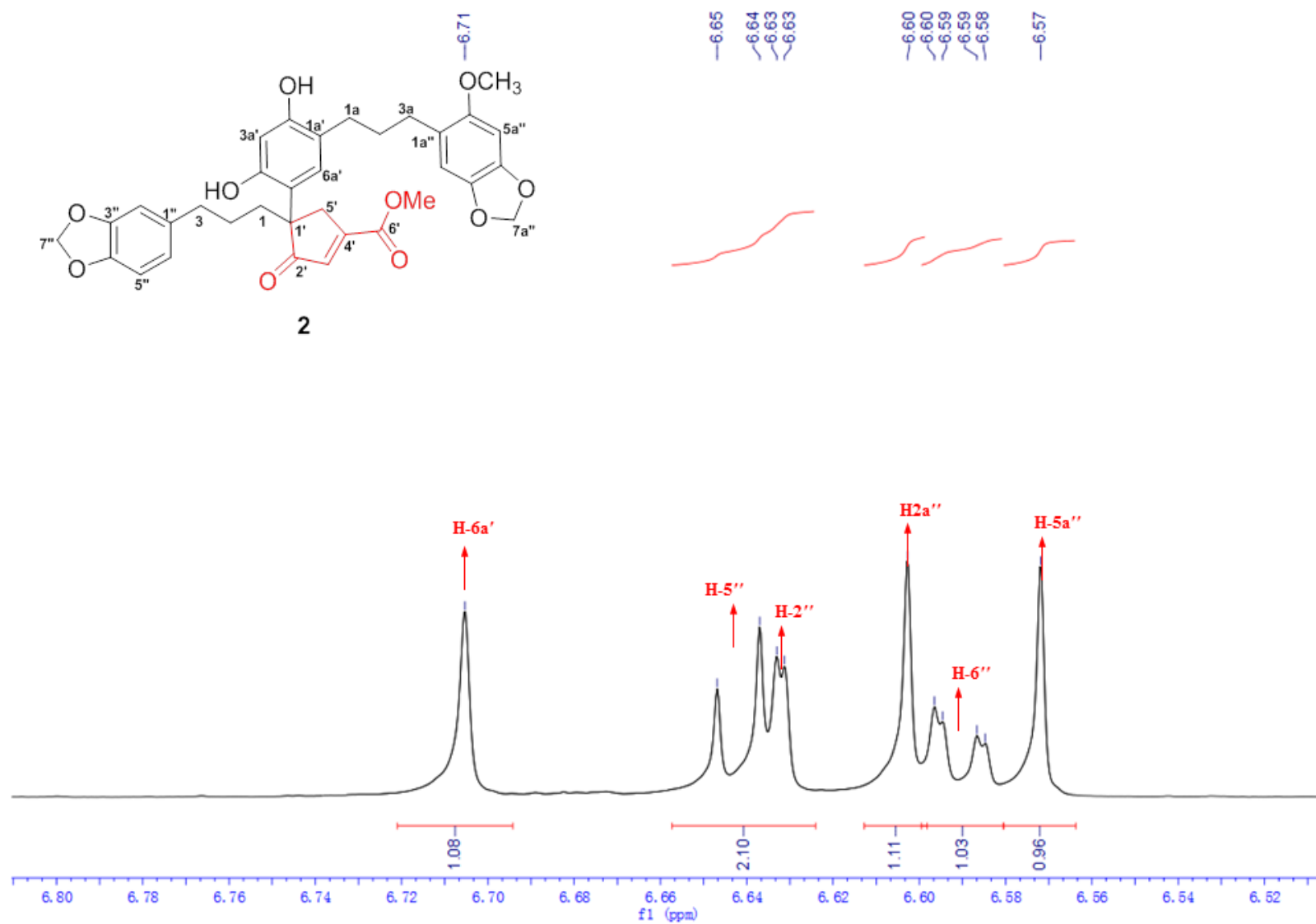


Figure S33. ^1H NMR spectrum (6.52–6.80 ppm) of compound **2**
S37

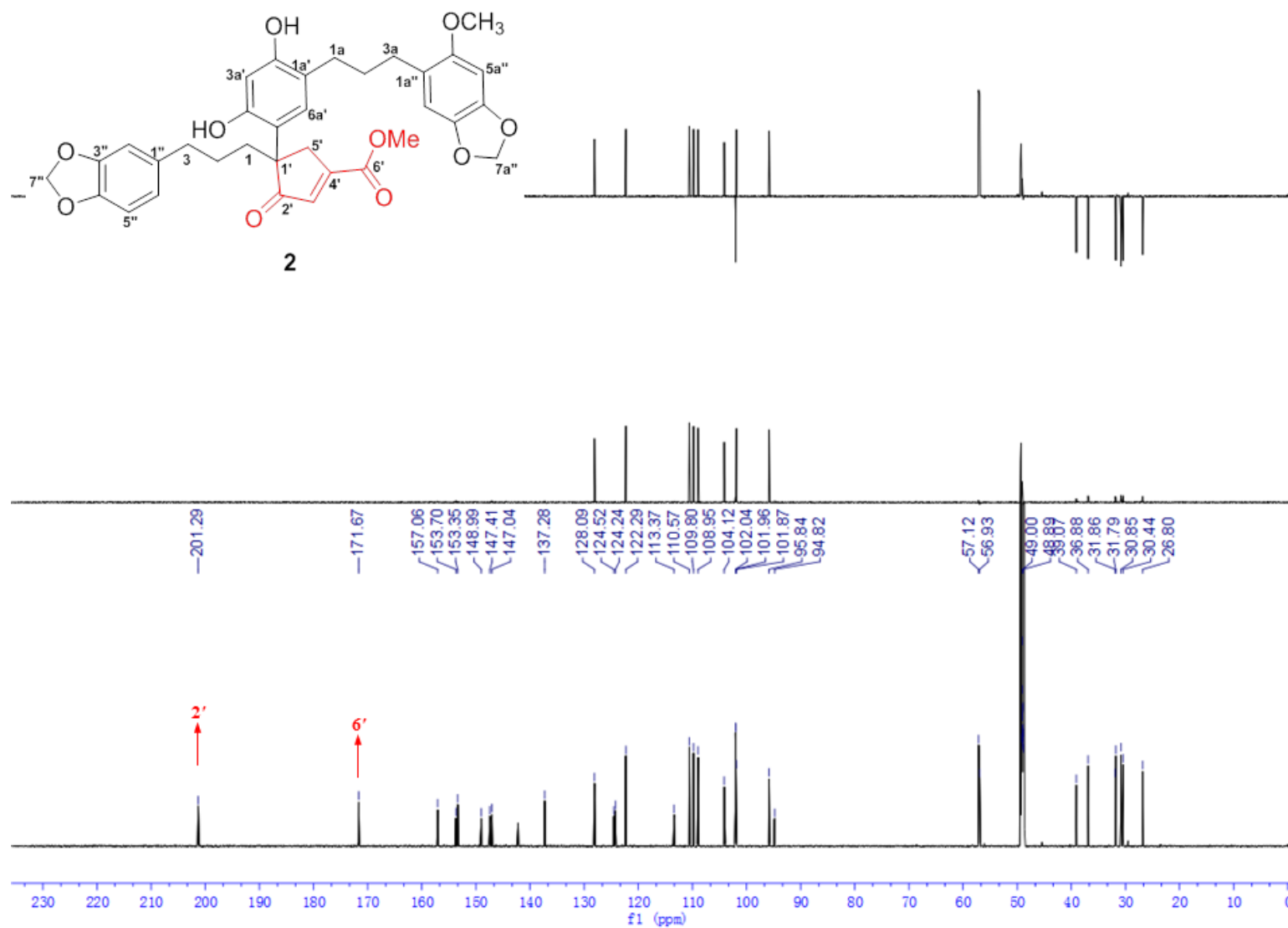


Figure S34. ^{13}C NMR spectra (0-230 ppm) of compound 2

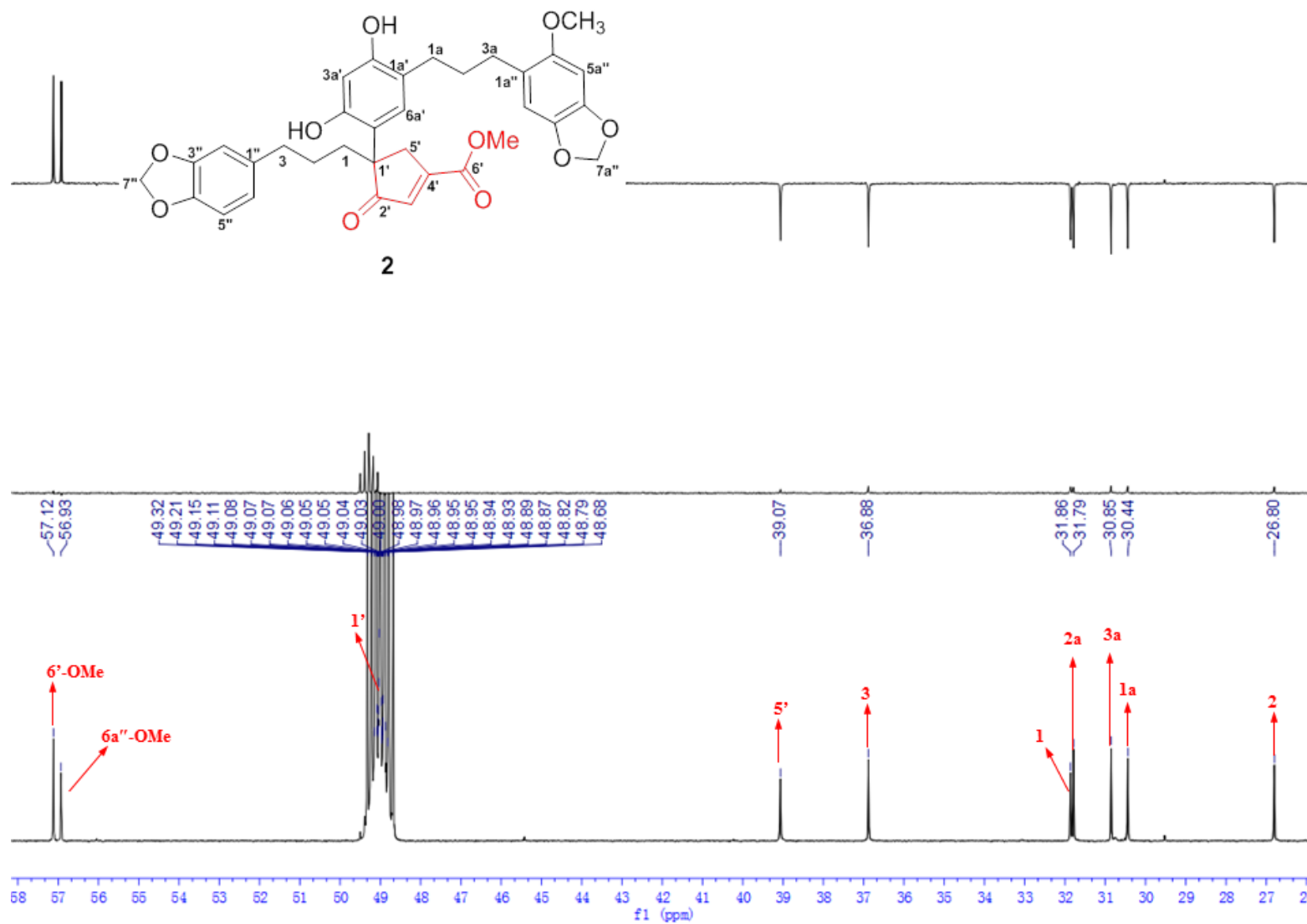


Figure S35. ^{13}C NMR spectra (26-58 ppm) of compound 2
S39

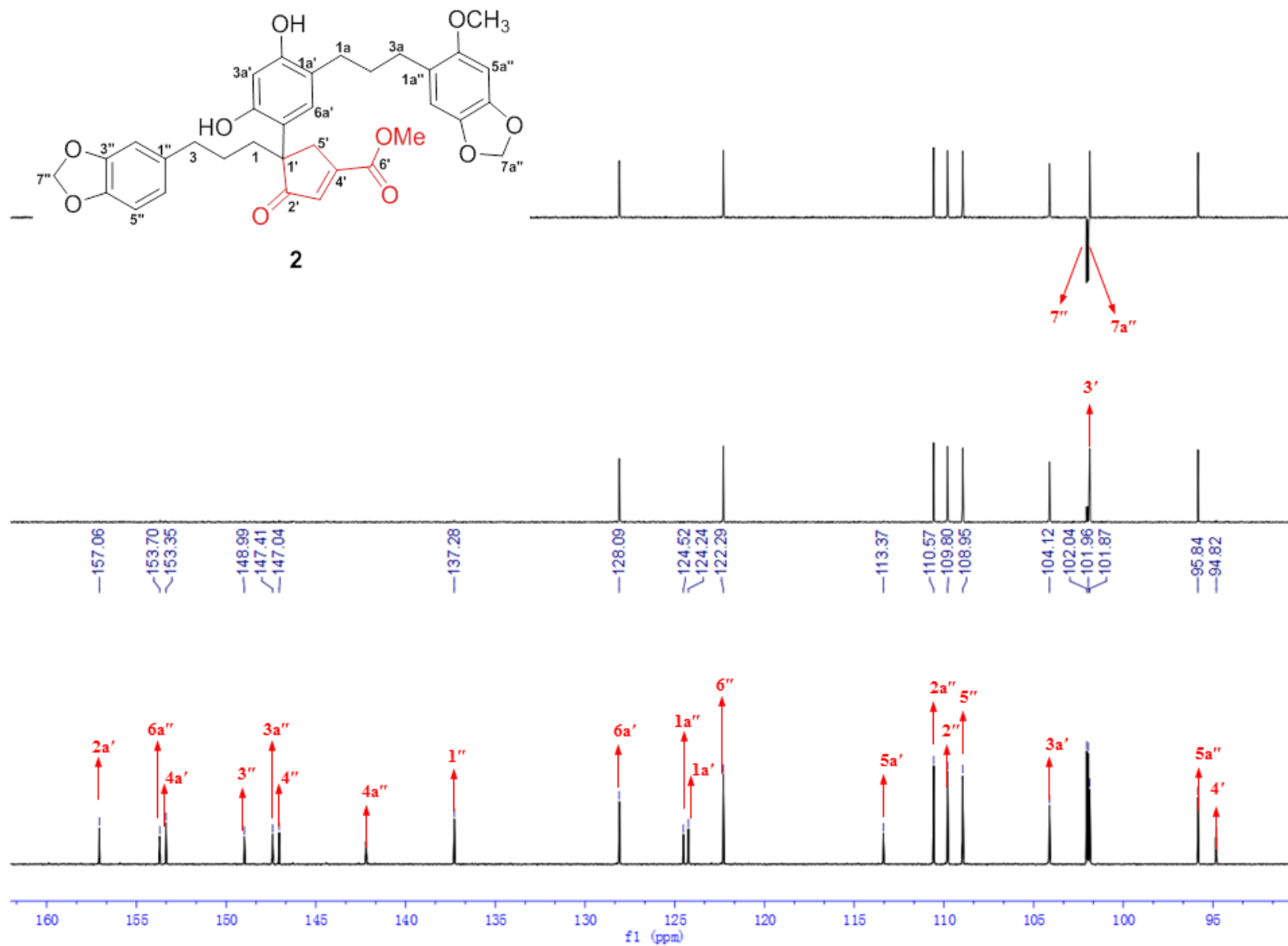


Figure S36. ^{13}C NMR spectra (93-160 ppm) of compound **2**

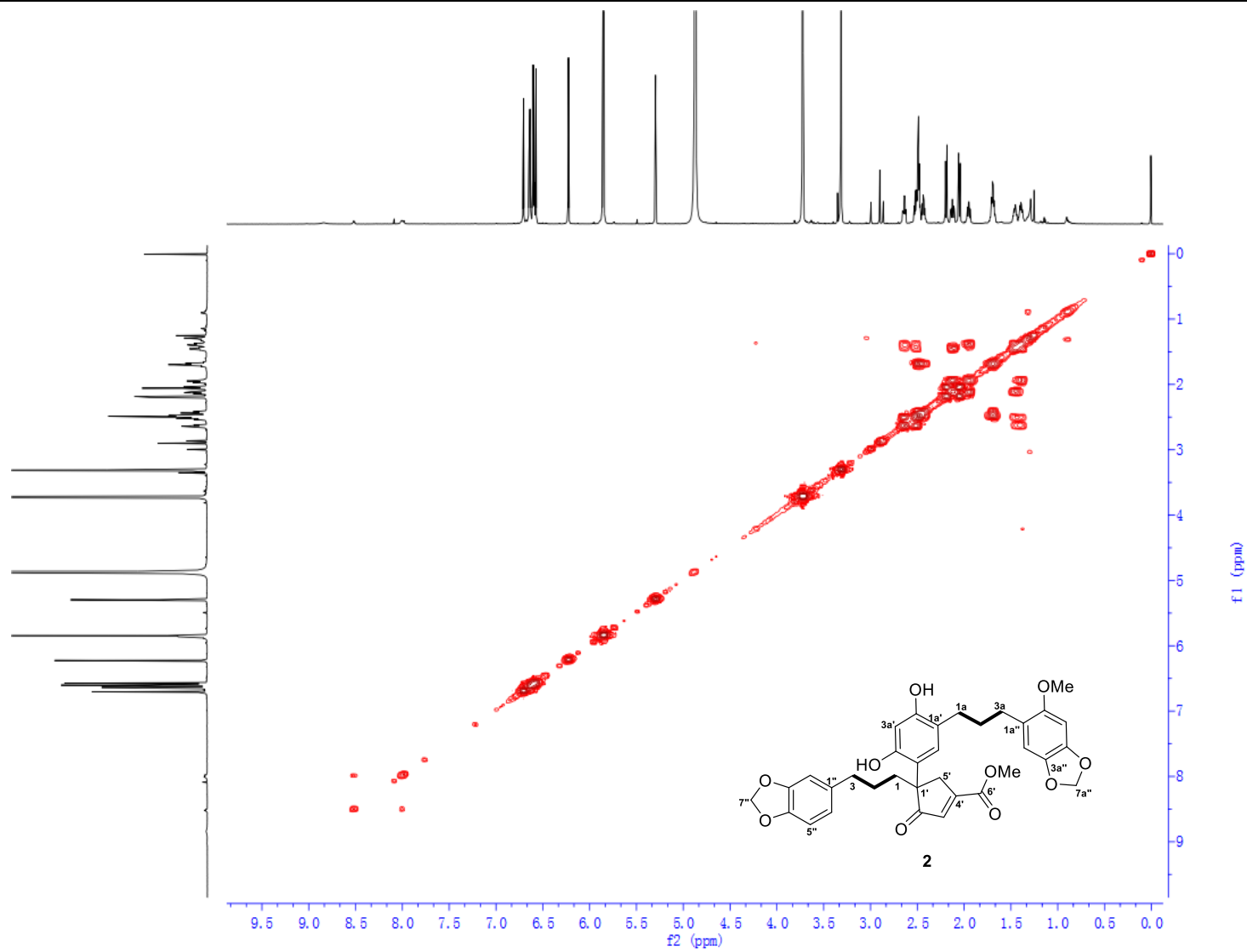


Figure S37. ^1H - ^1H COSY spectrum of compound **2**

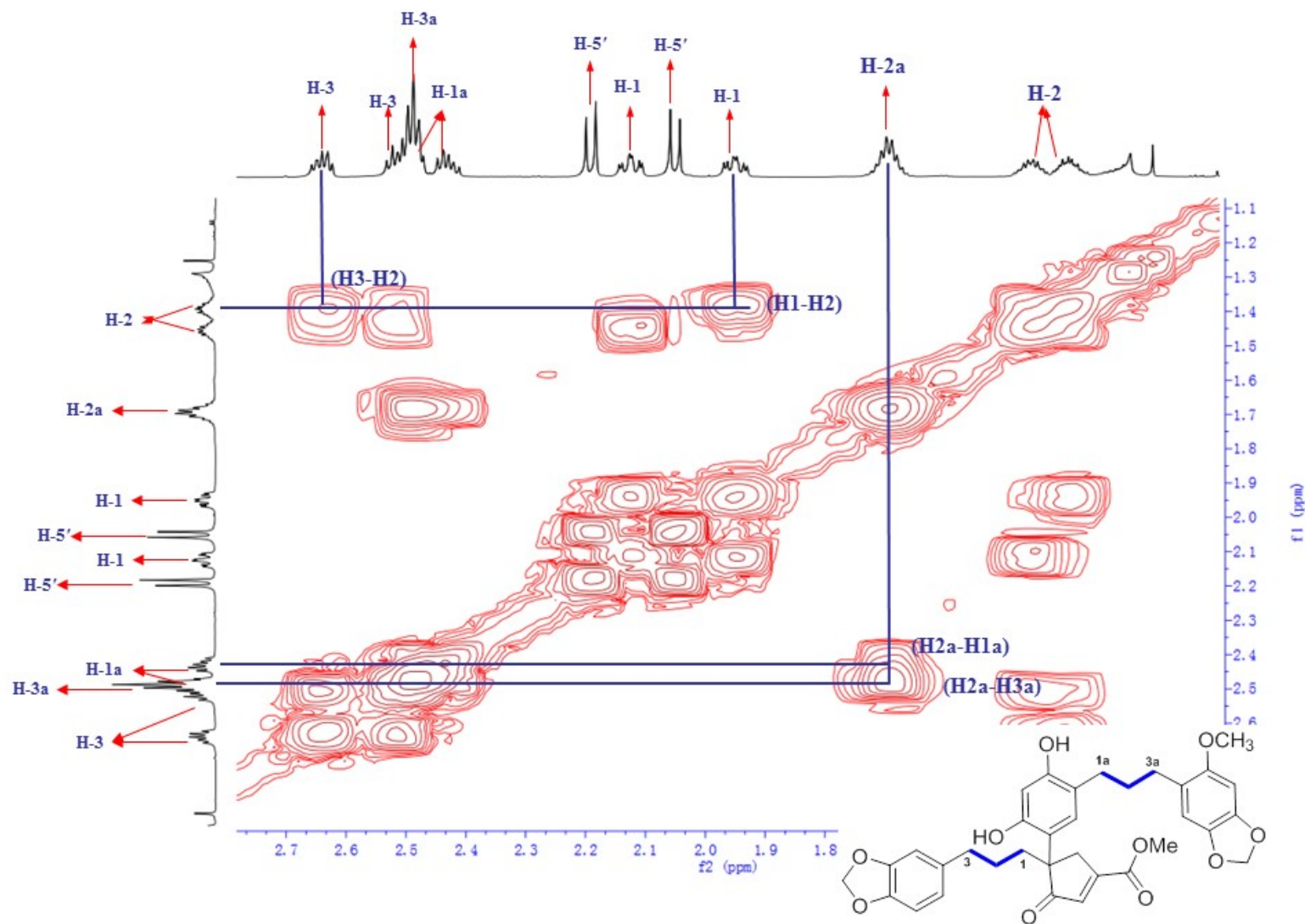


Figure S38. Key ^1H - ^1H COSY spectrum of compound **2**
S42

Supporting Information

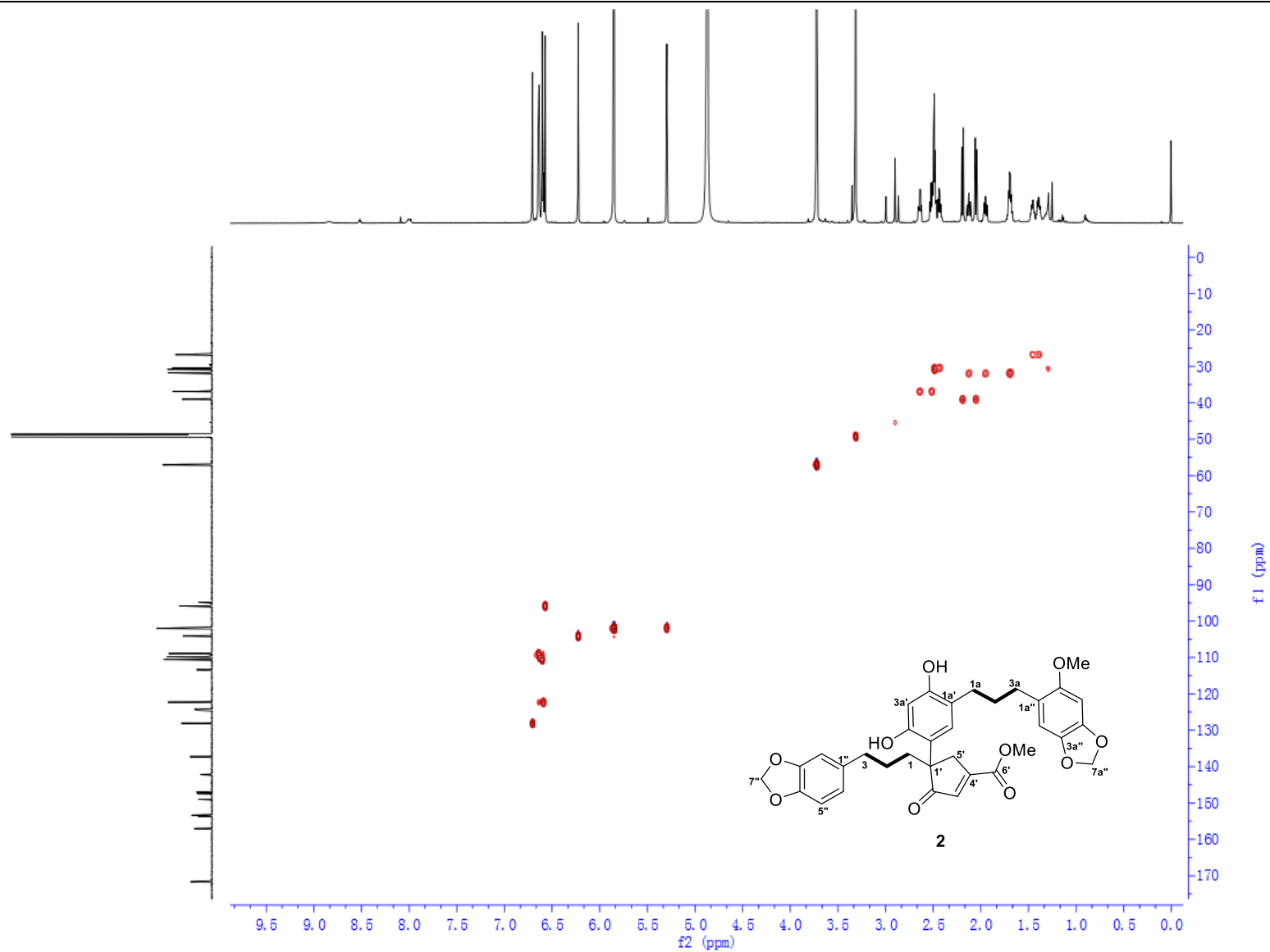


Figure S39. HSQC spectrum of compound 2

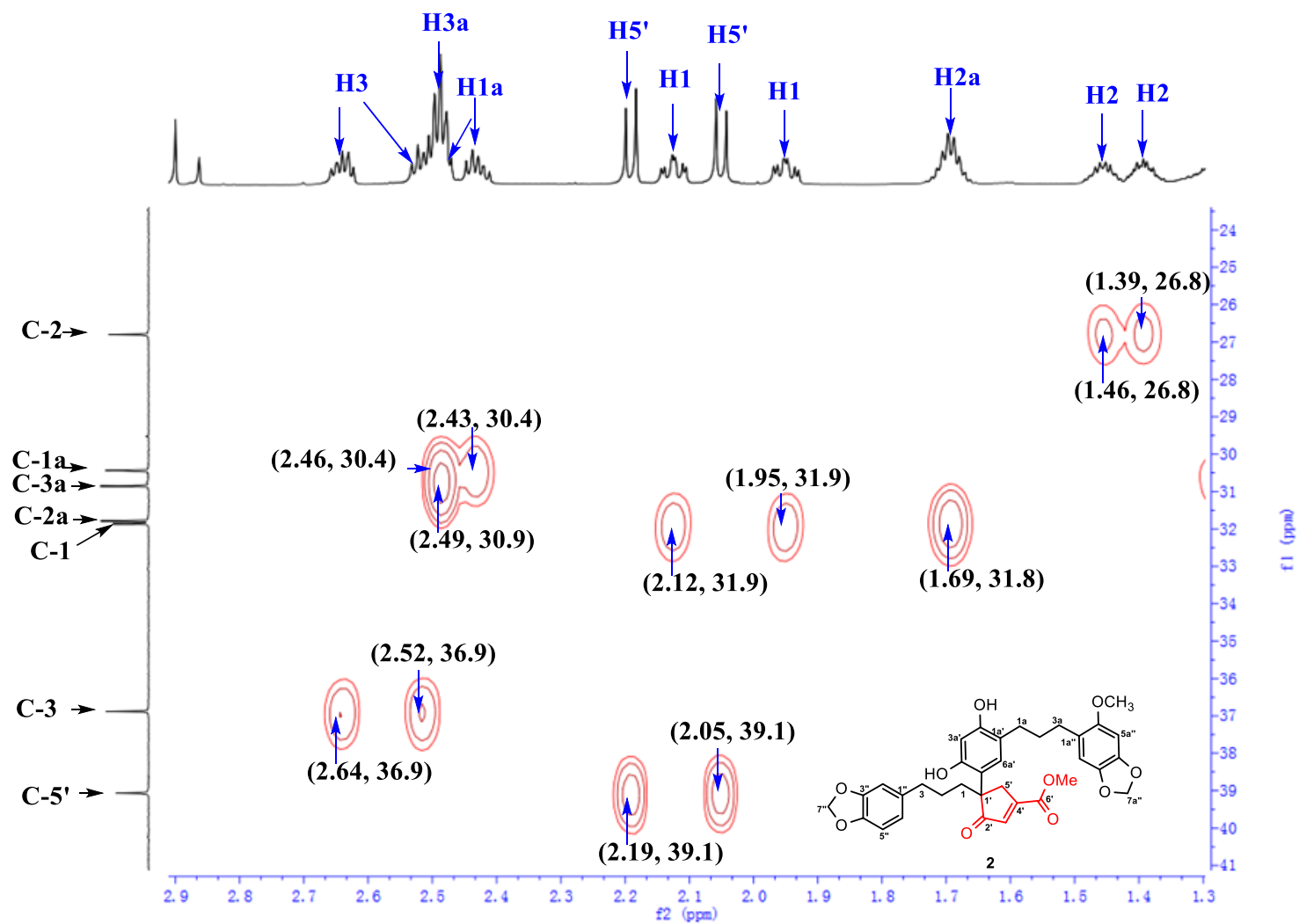


Figure S40. HSQC spectrum (δ_{H} 1.3-2.9 and δ_{C} 24-41) of compound **2**

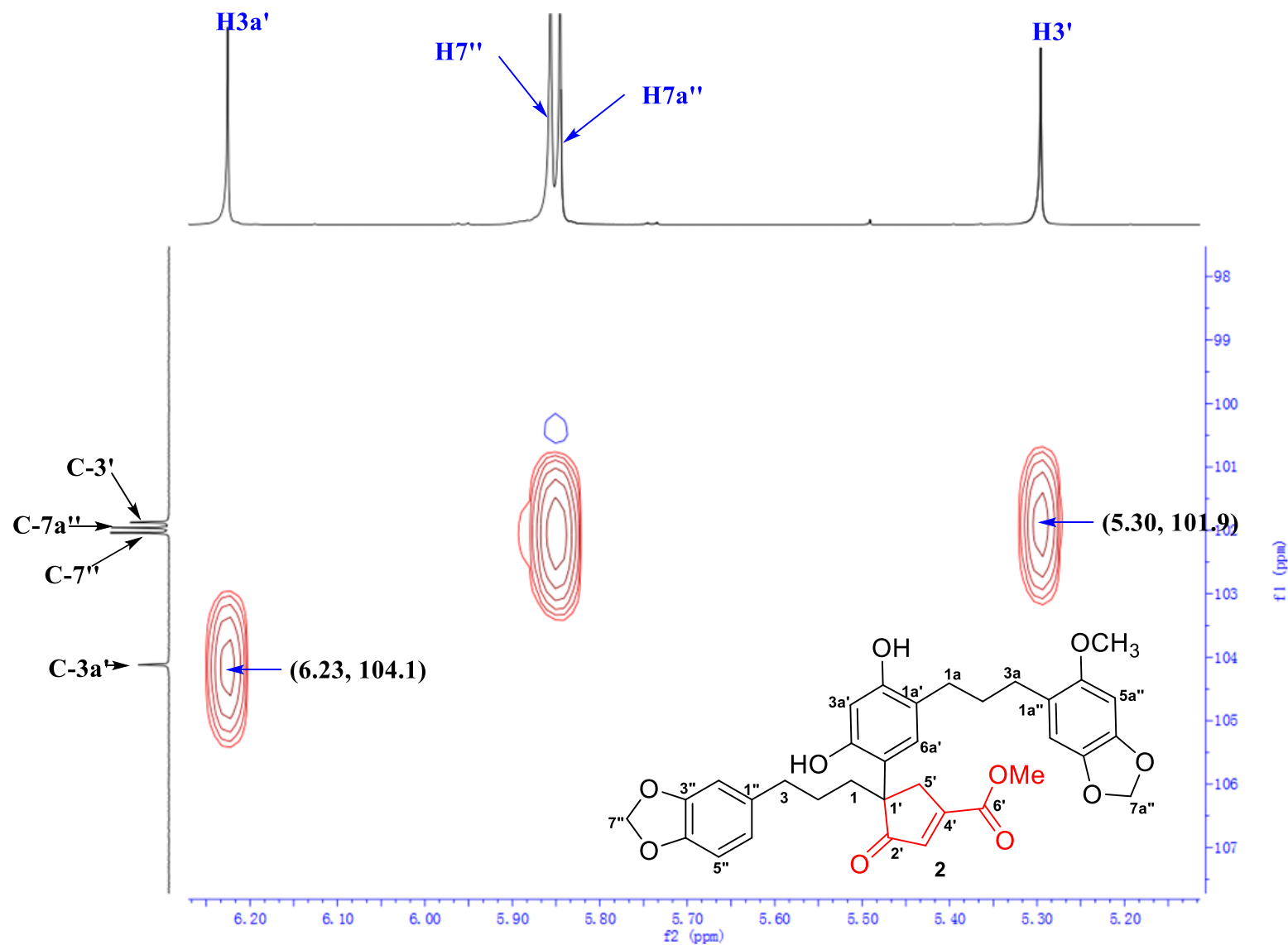


Figure S41. HSQC spectrum (δ_{H} 5.2-6.2 and δ_{C} 98-107) of compound 2

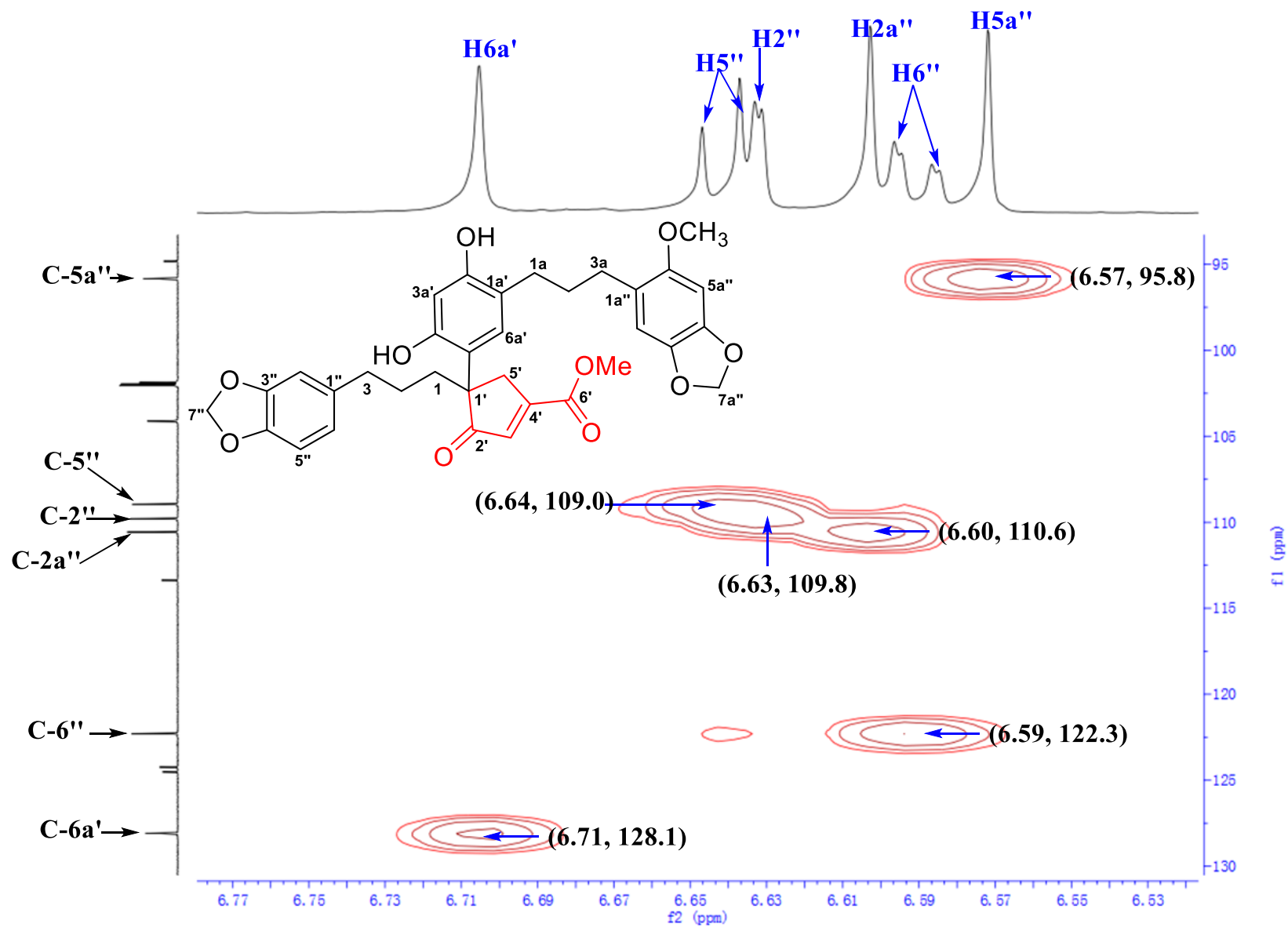


Figure S42. HSQC spectrum (δ_{H} 6.53-6.77 and δ_{C} 95-130) of compound 2

Supporting Information

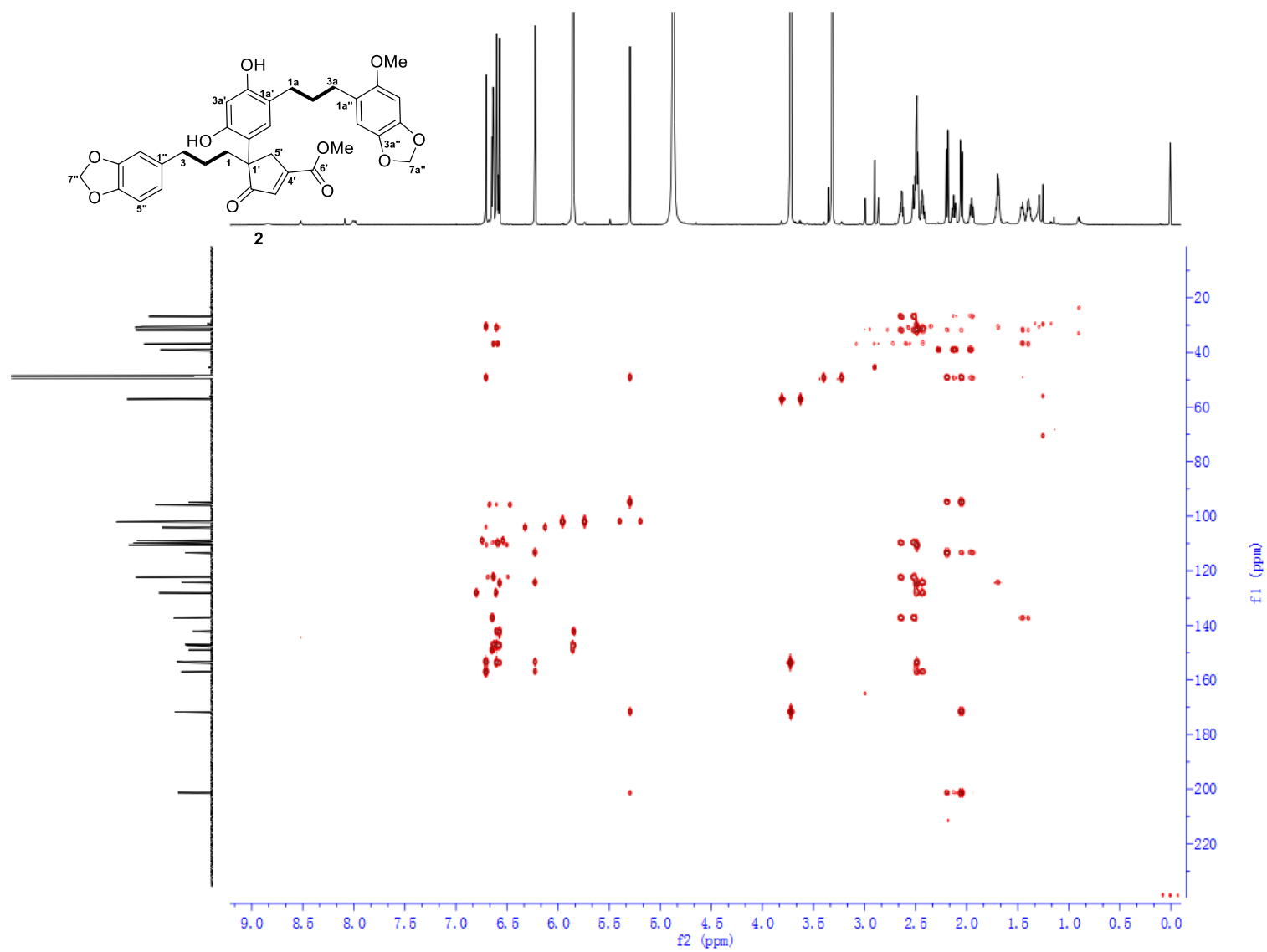


Figure S43. HMBC spectrum of compound **2**

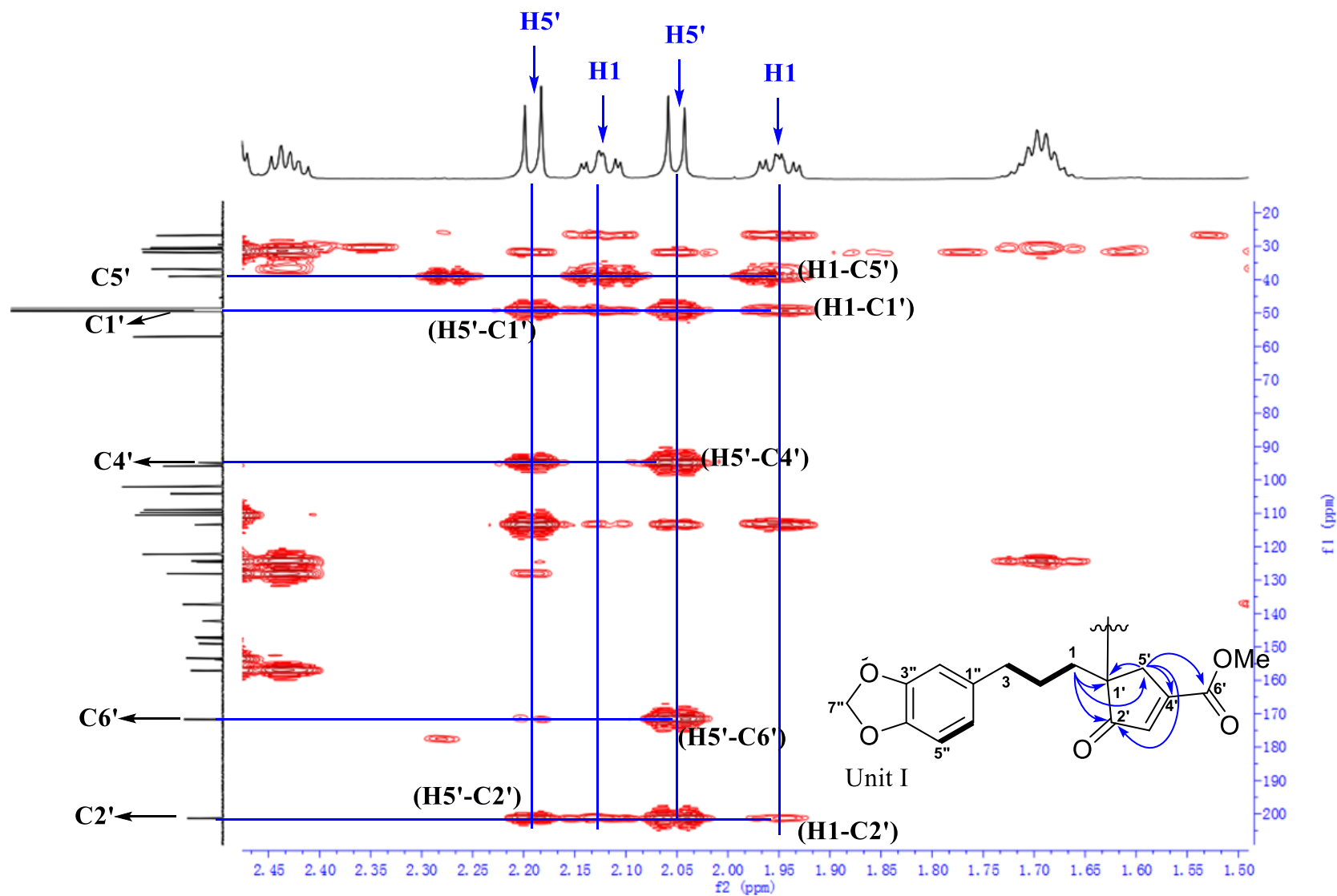


Figure S44. Key HMBC spectrum (δ_H 1.50-2.45 and δ_C 20-200) of unit I in compound 2

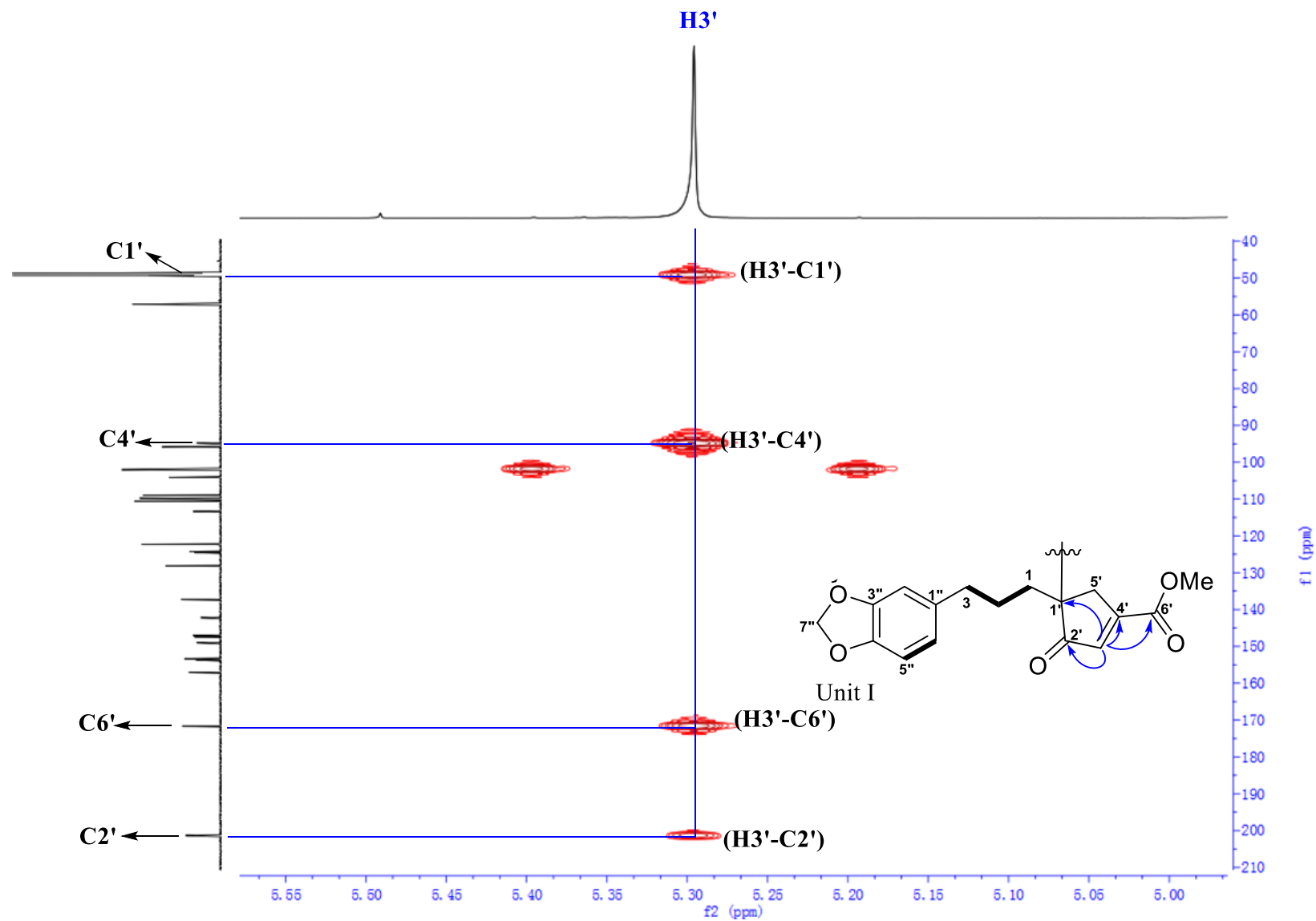


Figure S45. Key HMBC spectrum (δ_H 5.00-5.55 and δ_C 40-210) of unit I in compound **2**

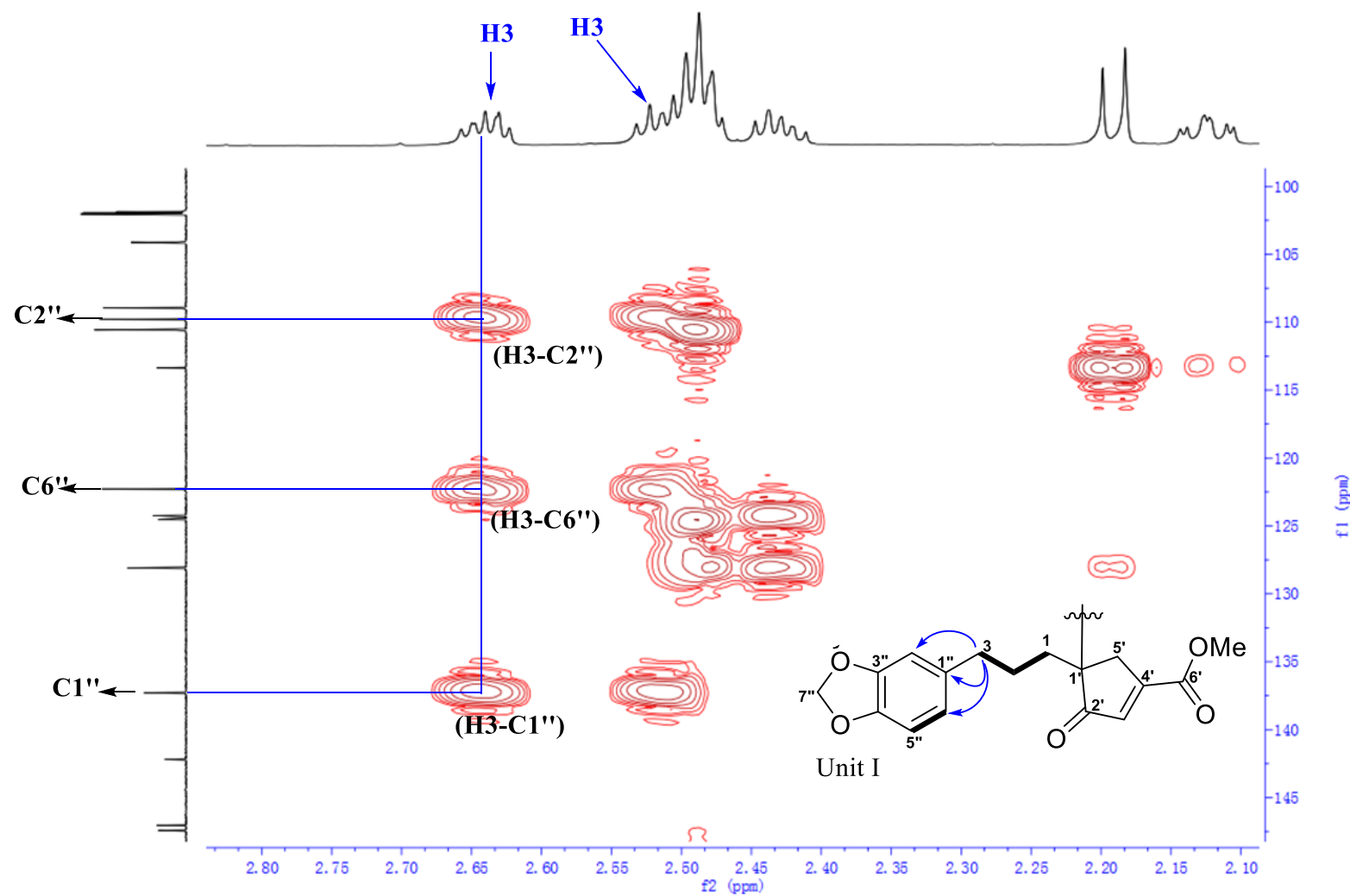


Figure S46. Key HMBC spectrum (δ_H 2.10-2.80 and δ_C 100-145) of unit I in compound **2**

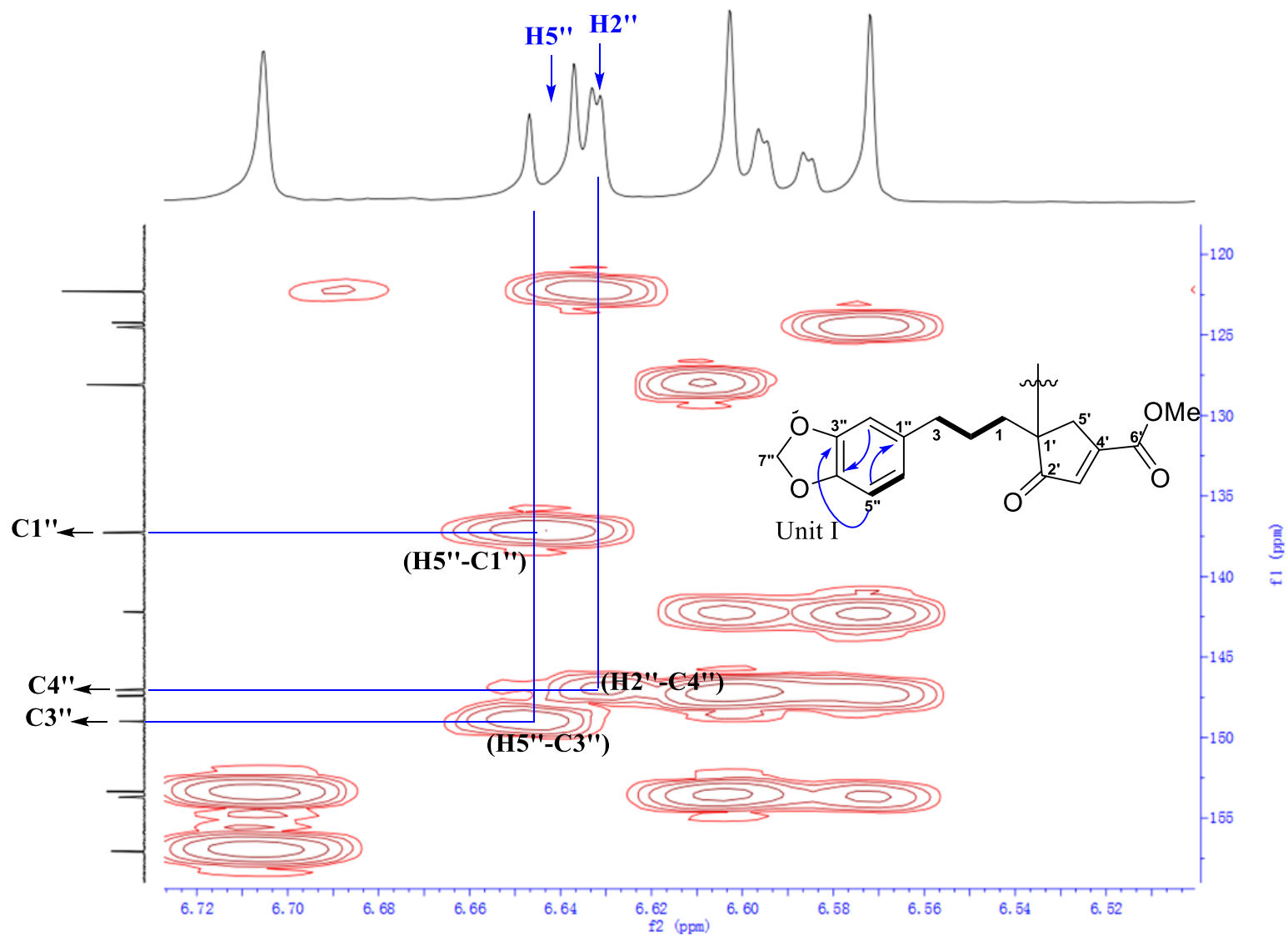


Figure S47. Key HMBC spectrum (δ_H 6.52-6.72 and δ_C 120-160) of unit I in compound 2

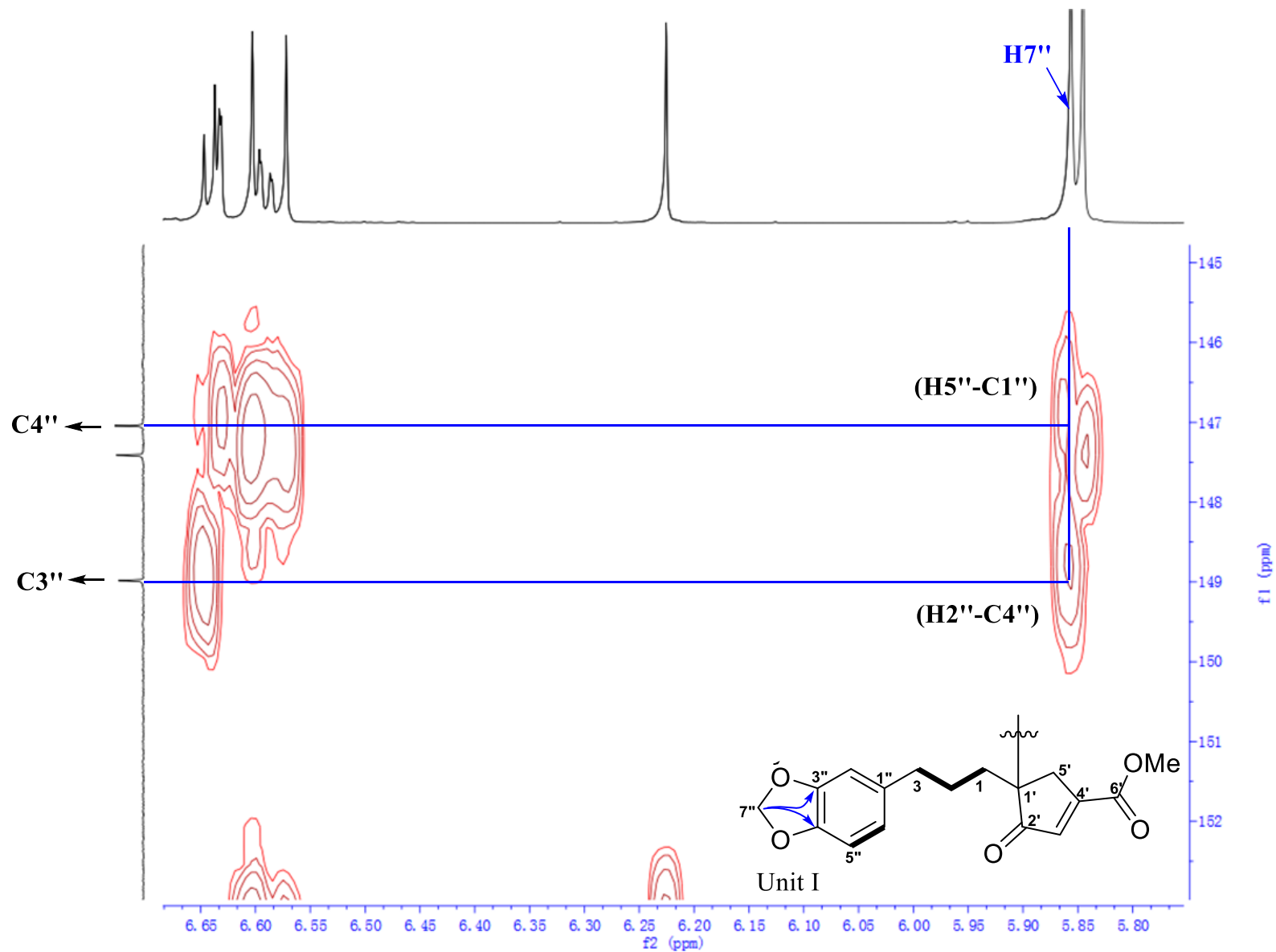


Figure S48. Key HMBC spectrum (δ_H 5.80-6.65 and δ_C 145-152) of unit I in compound 2
S52

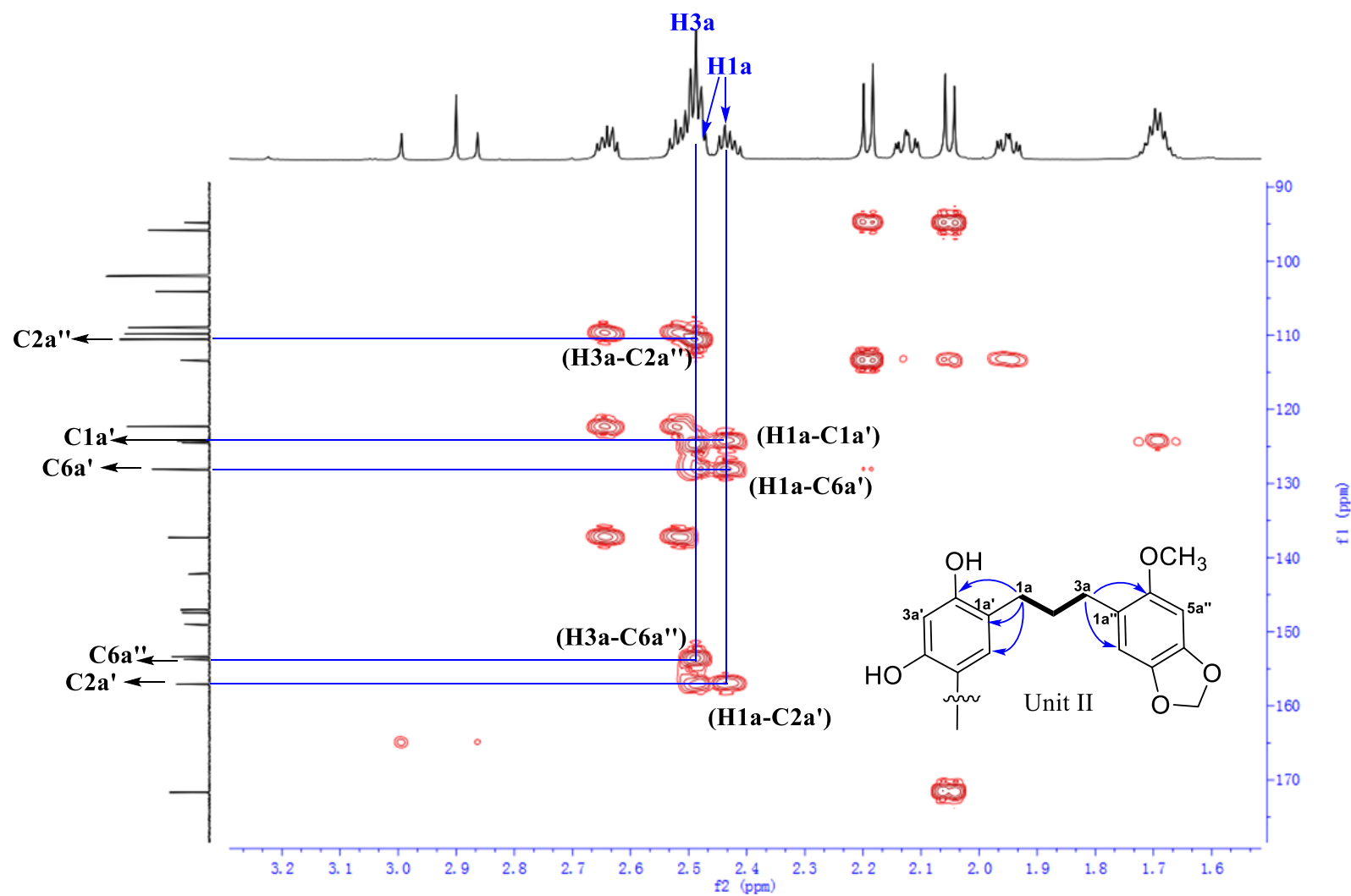


Figure S49. Key HMBC spectrum (δ_{H} 1.60-3.20 and δ_{C} 90-170) of unit II in compound 2

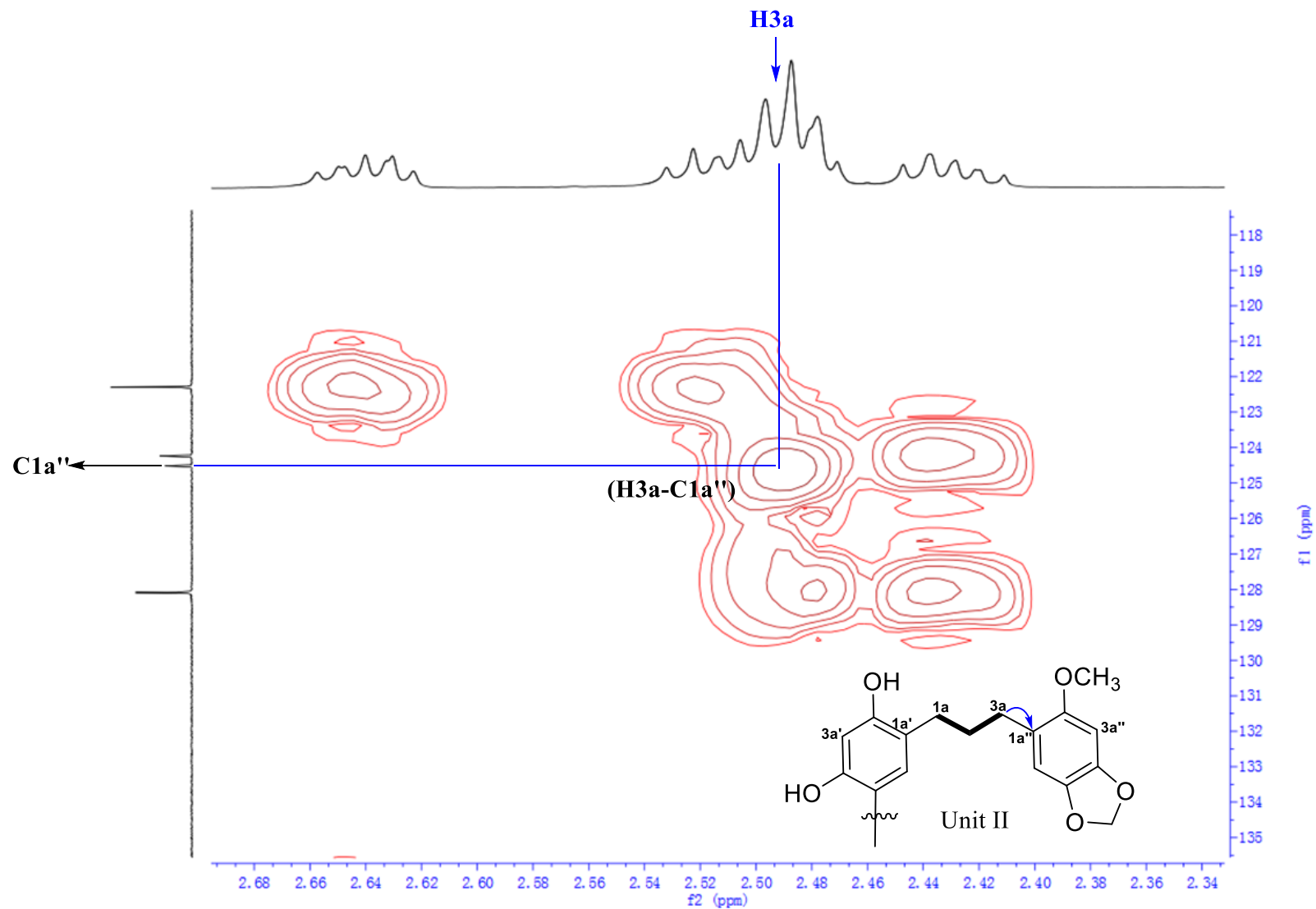


Figure S50. Key HMBC spectrum (δ_{H} 2.34-2.68 and δ_{C} 118-135) of unit II in compound 2

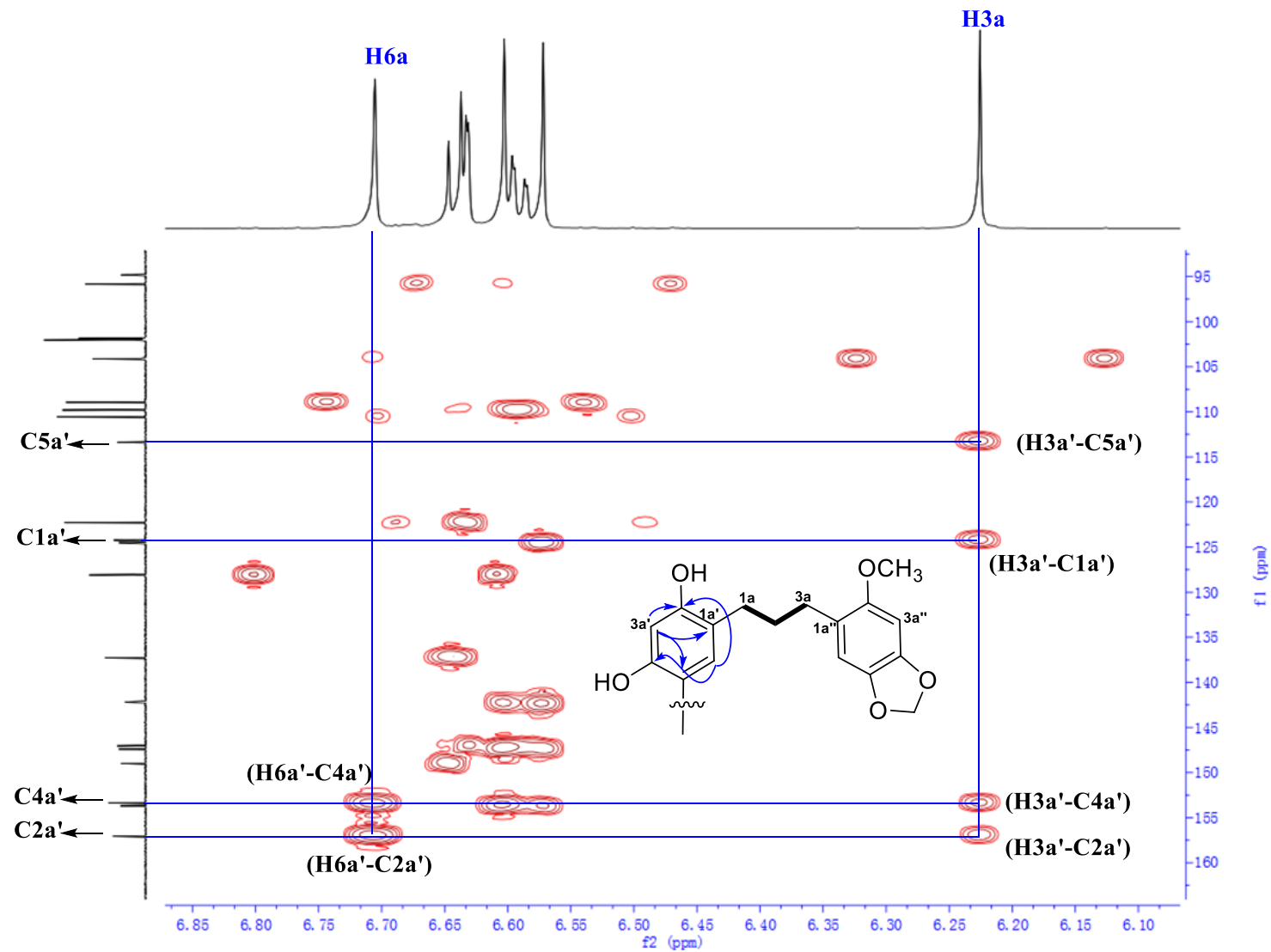


Figure S51. Key HMBC spectrum (δ_H 6.10-6.85 and δ_C 95-160) of unit II in compound 2

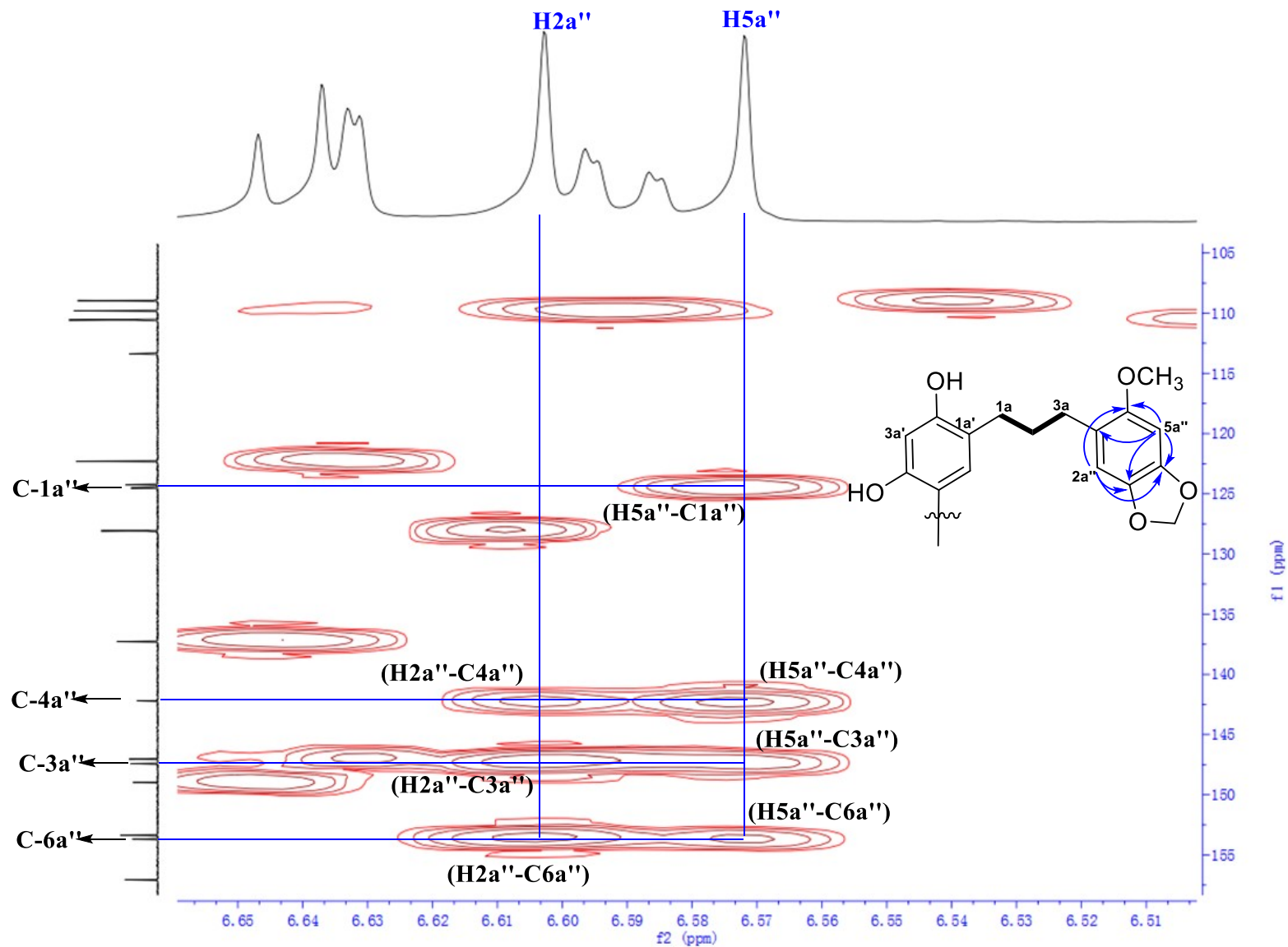


Figure S52. Key HMBC spectrum (δ_H 6.51-6.65 and δ_C 105-155) of unit II in compound 2

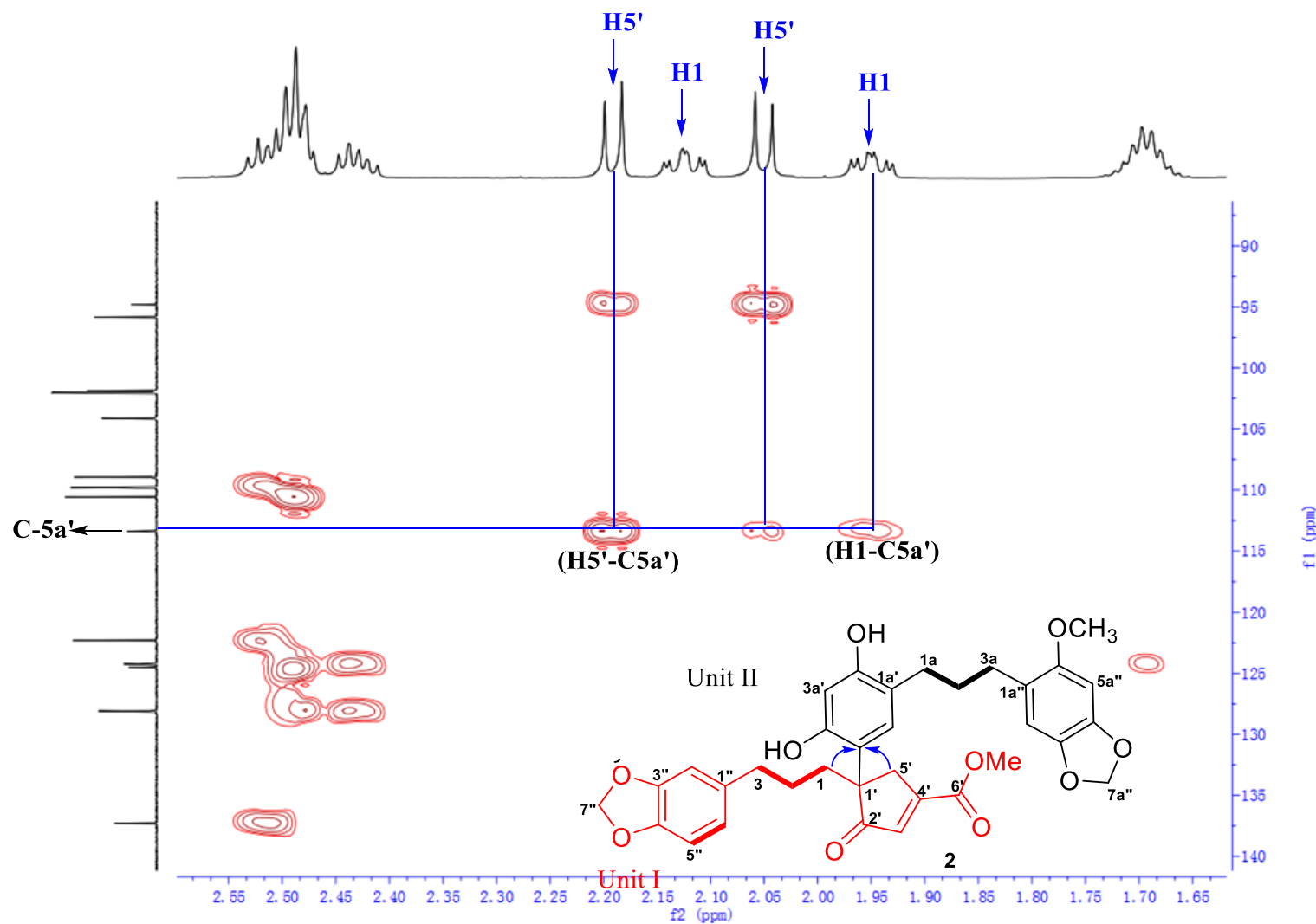


Figure S53. Key HMBC spectrum (δ_H 1.65-2.55 and δ_C 90-140) of compound 2

Supporting Information

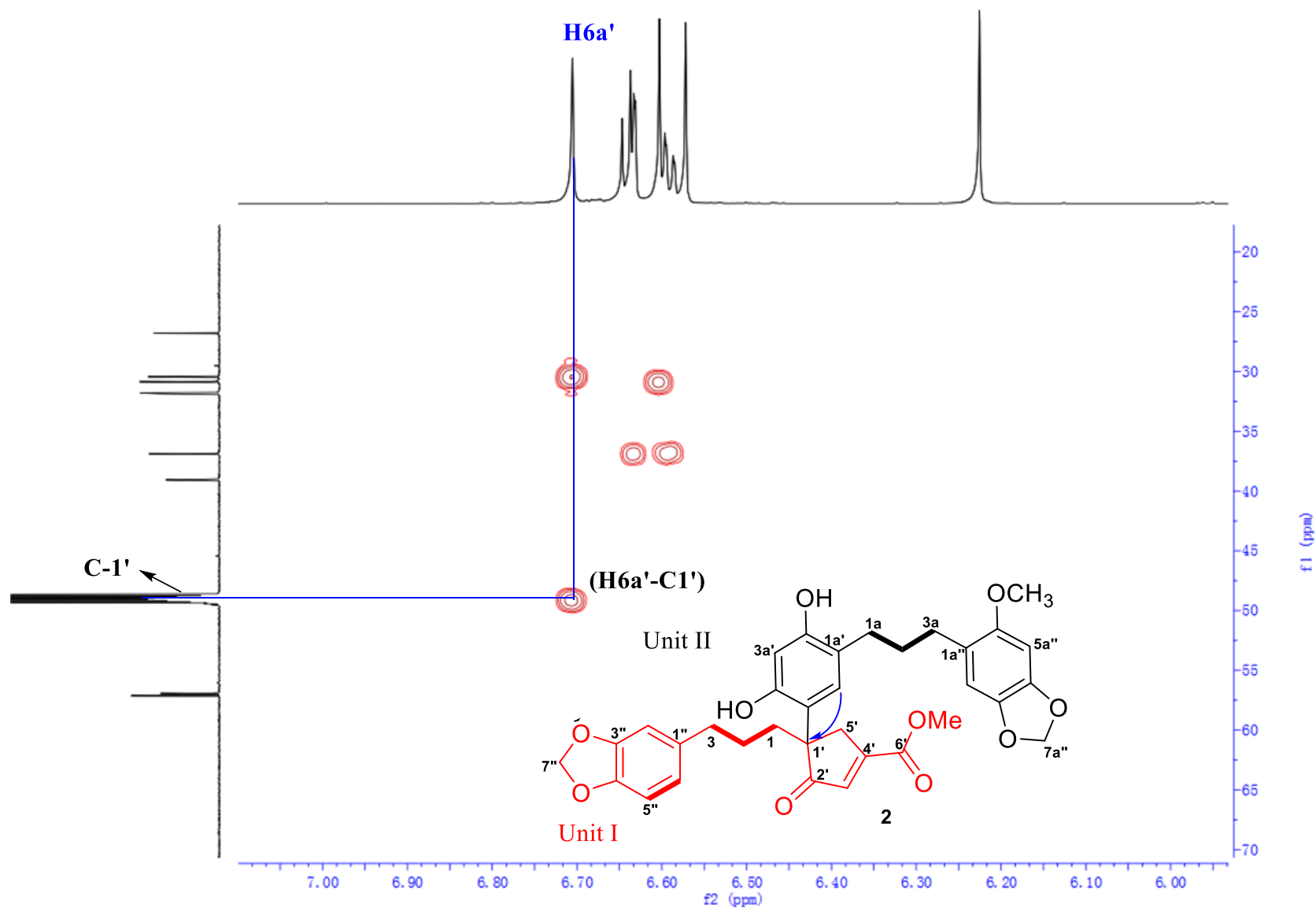


Figure S54. Key HMBC spectrum (δ_H 6.00-7.00 and δ_C 20-70) of compound **2**
S58

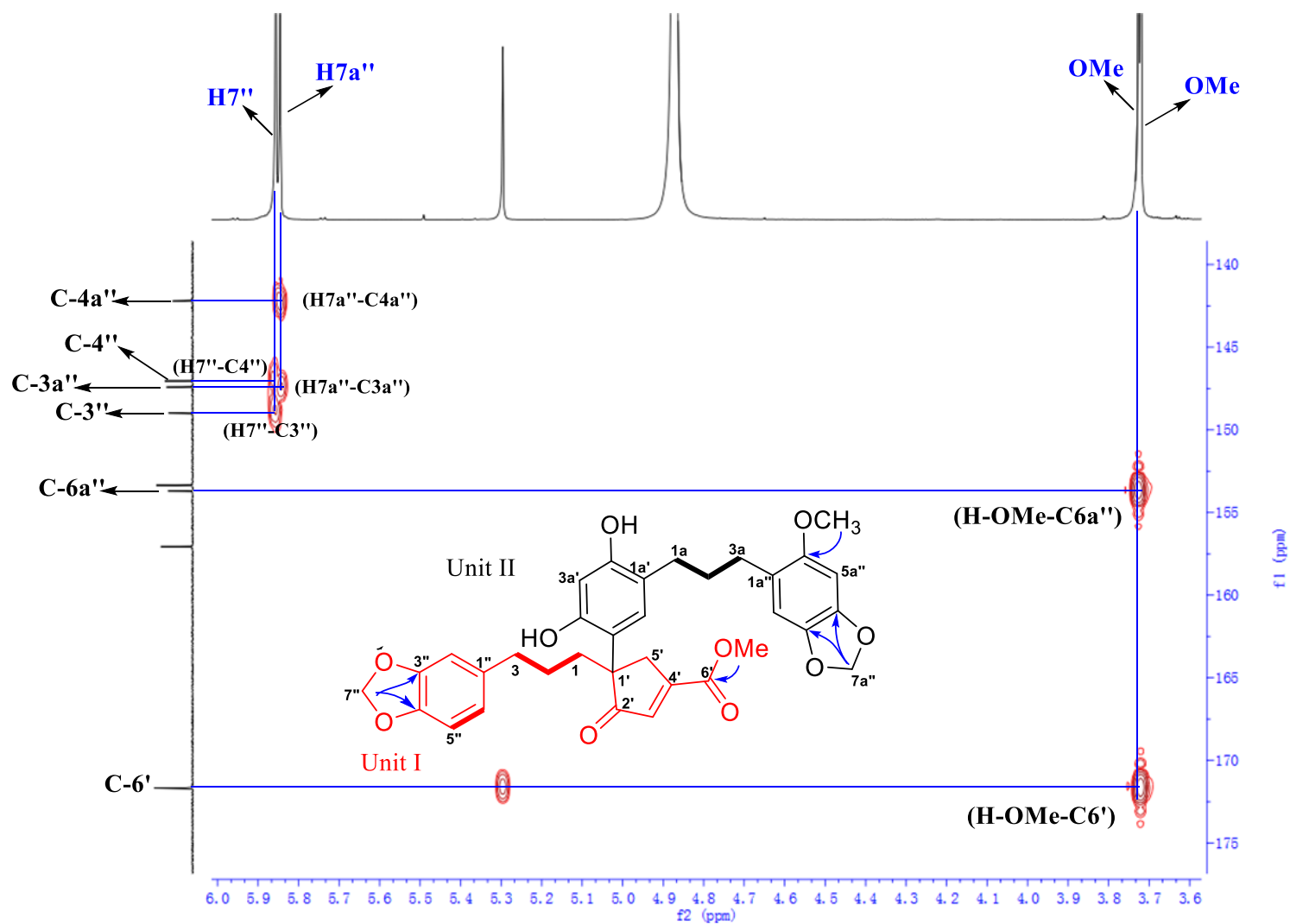
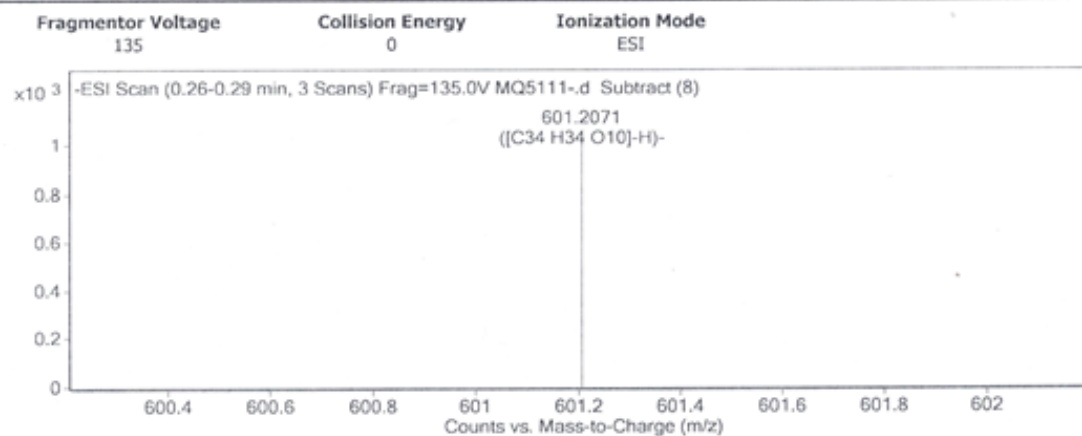


Figure S55. Key HMBC spectrum (δ_H 3.60-6.00 and δ_C 140-175) of compound 2

Supporting Information

User Spectra



Peak List

m/z	z	Abund
184.9874	1	2830.51
205.1596	1	6582.36
250.1446	1	3091.27
255.2322	1	7408.83
279.1231	1	3459.85
413.1957	1	3521.71
449.1734	1	7411.48
499.1709	1	2672.65

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30

Formula Calculator Results

Formula	CalculatedMass	CalculatedMz	Mz	Diff. (mDa)	Diff. (ppm)	DBE
C ₃₄ H ₃₄ O ₁₀	602.2152	601.2079	601.2071	0.2	0.3	18.0000

--- End Of Report ---

Figure S56. HRESI of compound **2**

S60

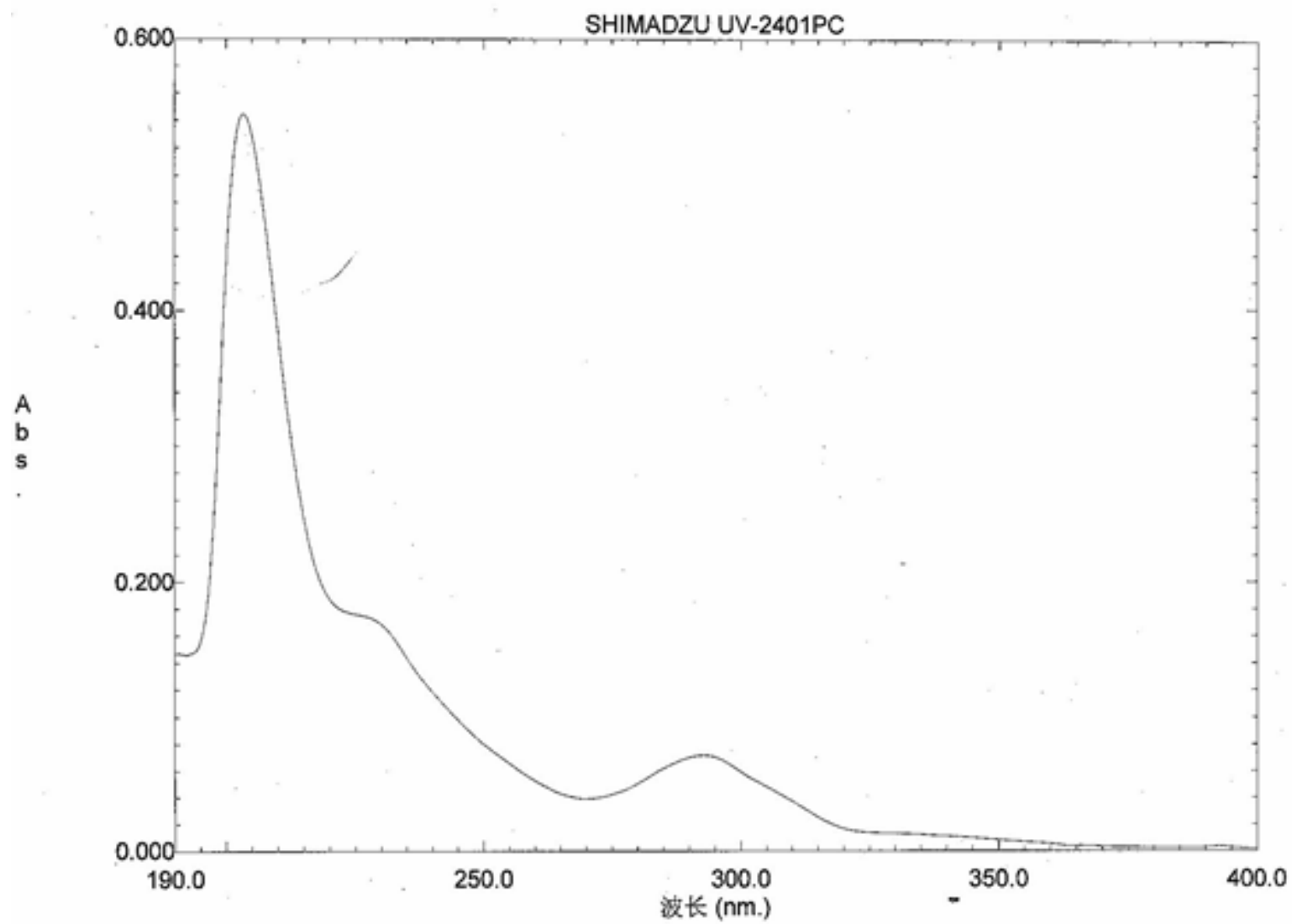


Figure S57. UV spectrum of compound 2

Supporting Information

Optical rotation measurement

Model : P-1020 (A060460638)

No.	Sample	Mode	Data	Monitor Blank	Temp. Cell Temp Point	Date Comment Sample Name	Light Filter Operator	Cycle Time Integ Time
No.1	79 (1/3)	Sp.Rot	87.0590	0.0740 0.0000	19.0 50.00 Cell	Thu Jan 18 15:48:47 2018 0.00170g/mL MeOH 5111-1	Na 589nm	2 sec 2 sec
No.2	79 (2/3)	Sp.Rot	84.8240	0.0721 0.0000	19.0 50.00 Cell	Thu Jan 18 15:48:53 2018 0.00170g/mL MeOH 5111-1	Na 589nm	2 sec 2 sec
No.3	79 (3/3)	Sp.Rot	87.4120	0.0743 0.0000	19.0 50.00 Cell	Thu Jan 18 15:48:58 2018 0.00170g/mL MeOH 5111-1	Na 589nm	2 sec 2 sec

+ 86.4314°

Figure S58. ORD of compound (+)-2

Supporting Information

Optical rotation measurement

Model : P-1020 (A060460638)

No.	Sample	Mode	Data	Monitor Blank	Temp. Cell Temp Point	Date Comment Sample Name	Light Filter Operator	Cycle Time Integ Time
No.1	81 (1/3)	Sp.Rot	-121.8330	-0.0731 0.0000	18.8 50.00 Cell	Thu Jan 18 16:07:21 2018 0.00120g/mL MeOH 5111-2	Na 589nm	2 sec 2 sec
No.2	81 (2/3)	Sp.Rot	-125.1670	-0.0751 0.0000	18.8 50.00 Cell	Thu Jan 18 16:07:26 2018 0.00120g/mL MeOH 5111-2	Na 589nm	2 sec 2 sec
No.3	81 (3/3)	Sp.Rot	-125.0000	-0.0750 0.0000	18.8 50.00 Cell	Thu Jan 18 16:07:31 2018 0.00120g/mL MeOH 5111-2	Na 589nm	2 sec 2 sec

-124.0000°

Figure S59. ORD of compound (-)-2

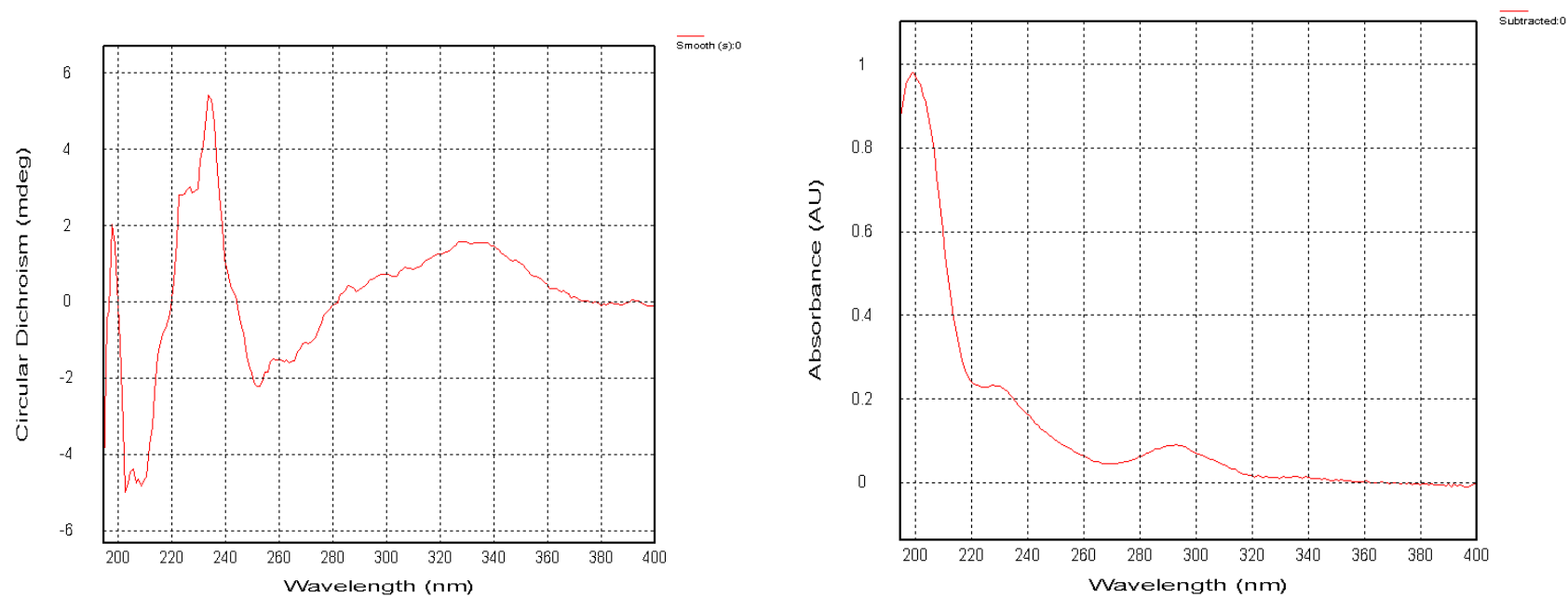
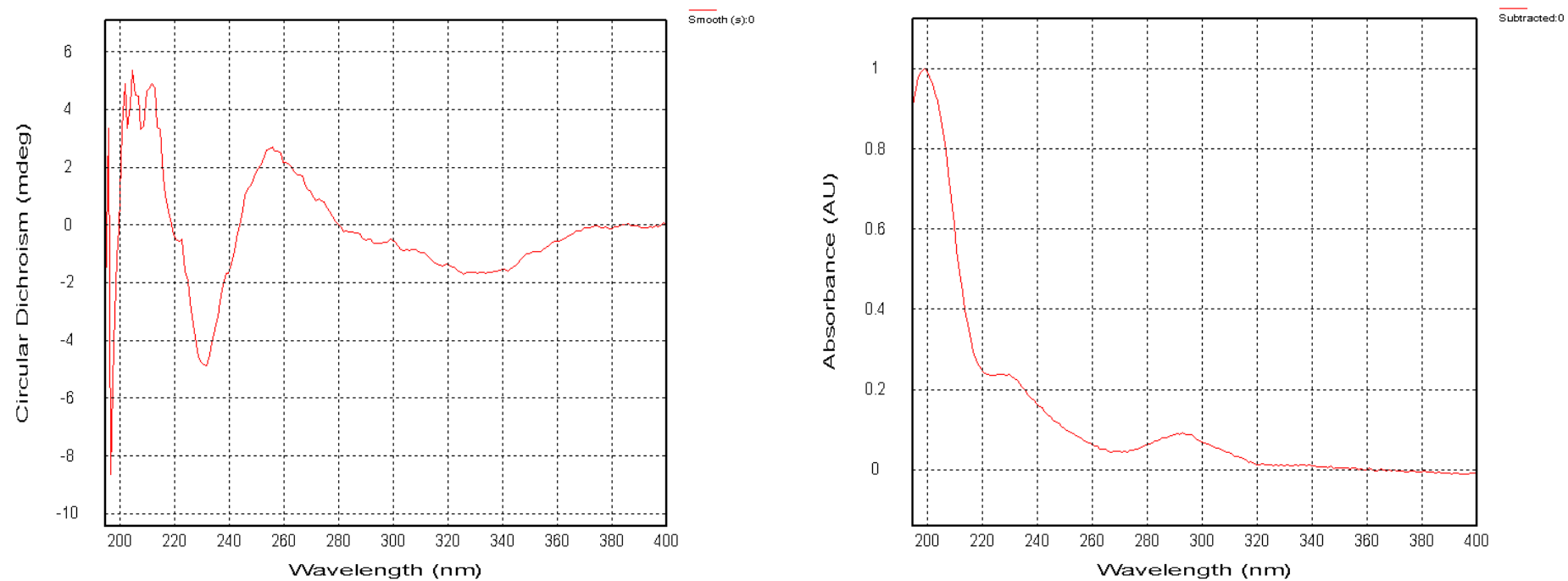


Figure S60. CD spectrum of compound (+)-2

Supporting Information



Reference

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3. Zhou, Y.; Yu, J.; Lei, X.; Wu, J.; Niu, Q.; Zhang, Y.; Liu, H.; Christen, P.; Gehring, H.; Wu, F., High-throughput tandem-microwell assay identifies inhibitors of the hydrogen sulfide signaling pathway. *Chemical Communications* **2013**, *49* (100), 11782-11784.