Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.


**Supporting Information**

# Novel Anthraquinone Derivatives as Inhibitors of Protein Tyrosine Phosphatases and Indoleamine 2,3-Dioxygenase 1 from the Deep-sea Derived Fungus *Alternaria tenuissima* DFFSCS013

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**EXPERIMENTAL SECTION**

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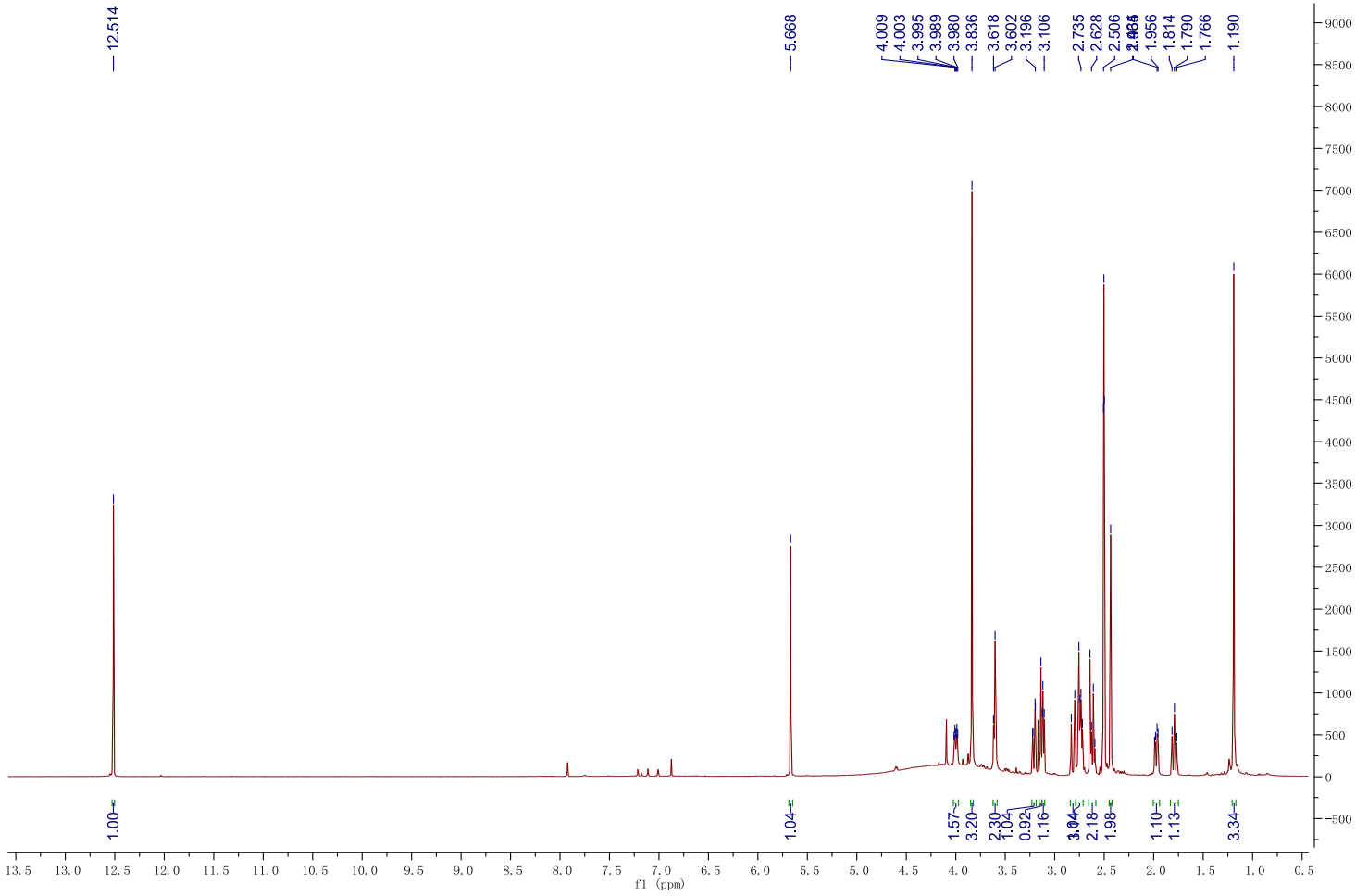
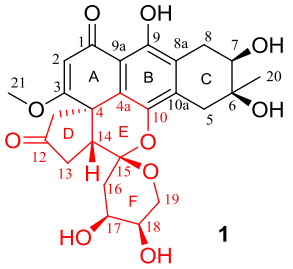
**Phosphatase Enzyme Inhibition Assays**. Recombinant human phosphatase PTP1B, PTP1B, SHP1, SHP2, MEG2 and TCPTP were expressed in *Escherichia coli* and purified. The enzyme inhibition assays were measured using *p*-nitrophenyl phosphate (pNPP) as a substrate in a 96-well plate with a final volume of 100 $\mu$L. Human recombinant PTP1B, SHP1, SHP2, MEG2 or TCPTP (0.05 $\mu$g) in 50 $\mu$L reaction buffer (pH 6.5) containing 50 mM HEPES, 100 mM NaCl, 1 mM EDTA, and 1 mM dithiothreitol (DTT) and test compounds were added to each well of a 96-well plate. $Na_3VO_4$ was used as the positive control and DMSO as the negative control to evaluate the high-throughput screening (HTS) system. After preincubation for 15 min at room temperature, 50 μL of reaction buffer containing 50 mM pNPP was added and incubated at 37 ℃ for 60 min. The phosphatase activity was determined by measuring the absorbance at 405 nm for the amount of produced *p*-nitrophenol. $IC_{50}$ values were determined by analyzing the data using Gen5 software (Synergy2 Multi-Mode Microplate Reader, BioTek Instruments, Inc.). Each compound was assayed in triplicate.

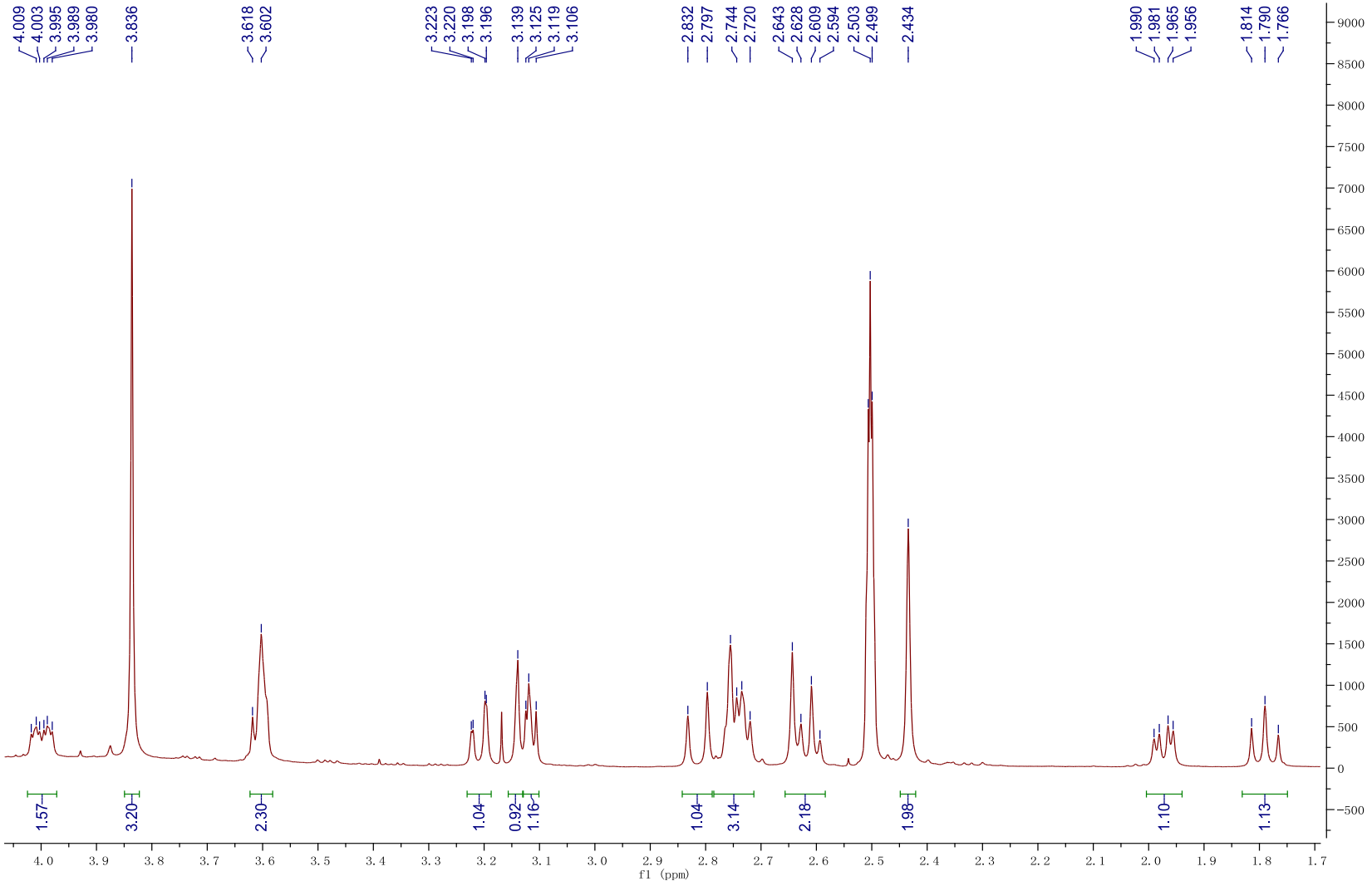
**IDO Enzyme Inhibition Assays**. Recombinant human IDO was expressed in *E. coli* and purified. Briefly, the reaction mixture (200 $\mu$L) contained potassium phosphate buffer (50 mM, pH 6.5), ascorbic acid (10 mM), methylene blue (5 $\mu$M), purified recombinant IDO1 (43 $\mu$M), L-Trp (100 $\mu$M), and DMSO (10 $\mu$L). The inhibitors were serially diluted 3-fold from 50 to 0.02 mM in pure DMSO. The reaction was conducted at 37 $^{o}$C for 6 min and stopped by addition of 30% (w/v) trichloroacetic acid (40 $\mu$L). To convert N-formylkynurenine to kynurenine, the tubes were incubated at 37 ℃ for 30 min, followed by centrifugation at 20,000 g for 20 min. Finally, 150 $\mu$L of supernatant is added to 150 $\mu$L of *p*–dimethylaminobenzaldehyde (pDMAB) (2%, v/v) in acetic acid to generate a Schiff base with kynurenine that was detected at a wavelength of 480 nm. We used NLG919 as the positive control and DMSO as the negative control to evaluate the high-throughput screening (HTS) system. $IC_{50}$ values were determined by analyzing the data using Gen5 software (Synergy2 Multi-Mode Microplate Reader, BioTek Instruments, Inc.). Each compound was assayed in triplicate.

**Calcium imaging assay.** The calcium imaging assay was performed by an automated, cell-based fluorescence-imaging system (Arrayscan) by a previously reported method with slight modification. The human embryonic kidney 293 (HEK293) cells were seeded in medium containing 10% FBS and incubated at 37 $^{o}$C with 5% $CO_2$ to a suitable quantity, and then cells were plated in poly-D-lysine-coated 96-well plates at a density of approximately 20000 cells/well for 24 h. Later, the cells were stained with 5 μM Fluo-4 AM for 60 min and subsequently washed three times with HBSS buffer. And then the cells were treated with up-to 10 μM of the tested samples in a 96-well plate containing 50 μl HBSS/well. For the bioactive compound **1**, its bioactivity was further tested at concentrations of 10, 5, 2.5, 1.25, and 0.625 μM, respectively. The purities of the tested compounds were >95%. The experiment was repeated three times. The false positive activity caused by the color of the tested samples was excluded. Calcium images of cells in HBSS buffer were acquired and analyzed using an Array Scan VTI HCS Reader (Cellomics, Thermo Scientific, Pittsburgh, PA, USA).

**Figure S1. $^{1}$H NMR spectrum of compound 1**

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3.106
2.832
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2.503
2.499
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f1 (ppm)

**Figure S2. $^{13}$C NMR spectrum of compound 1**

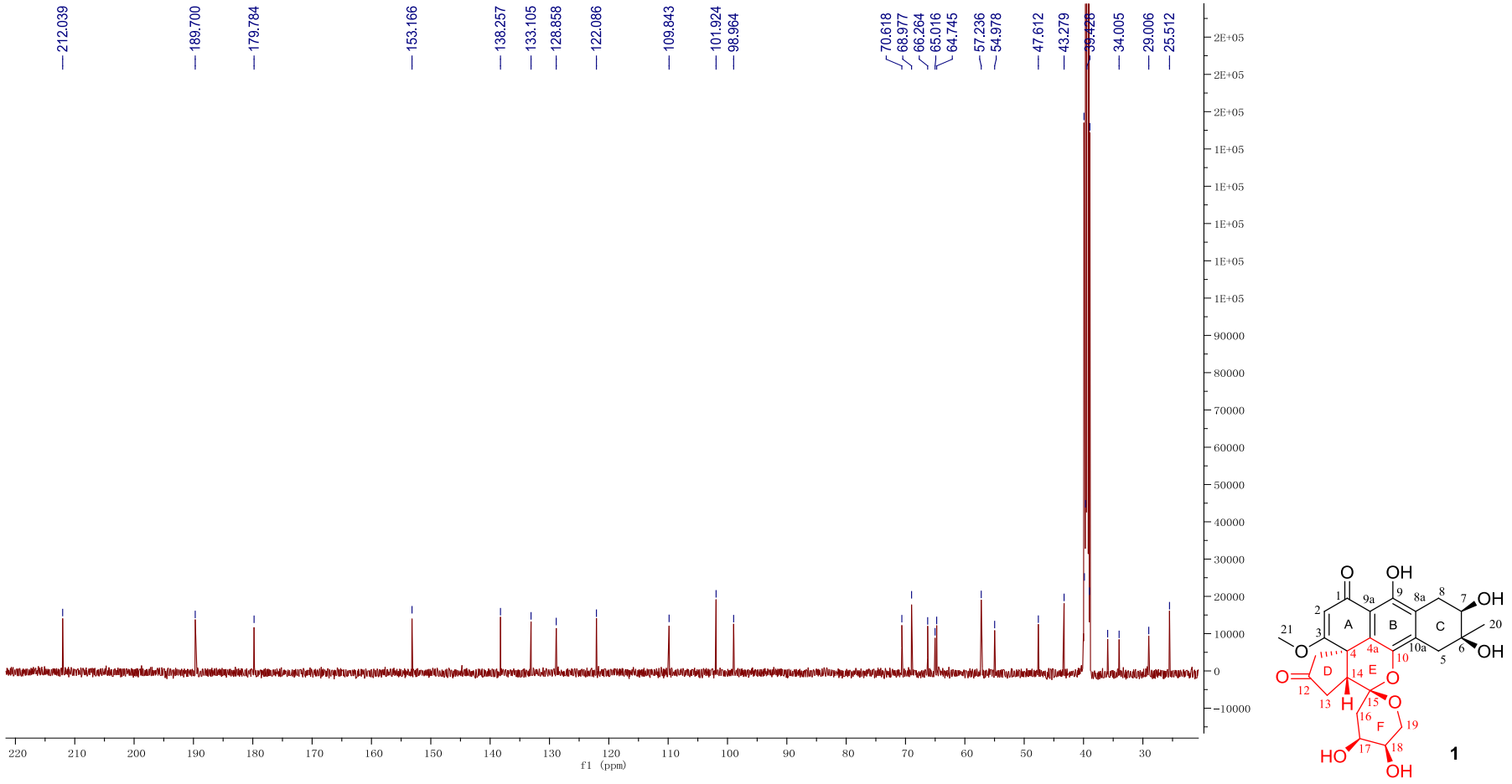


**Figure S3. DEPT NMR spectrum of compound 1**

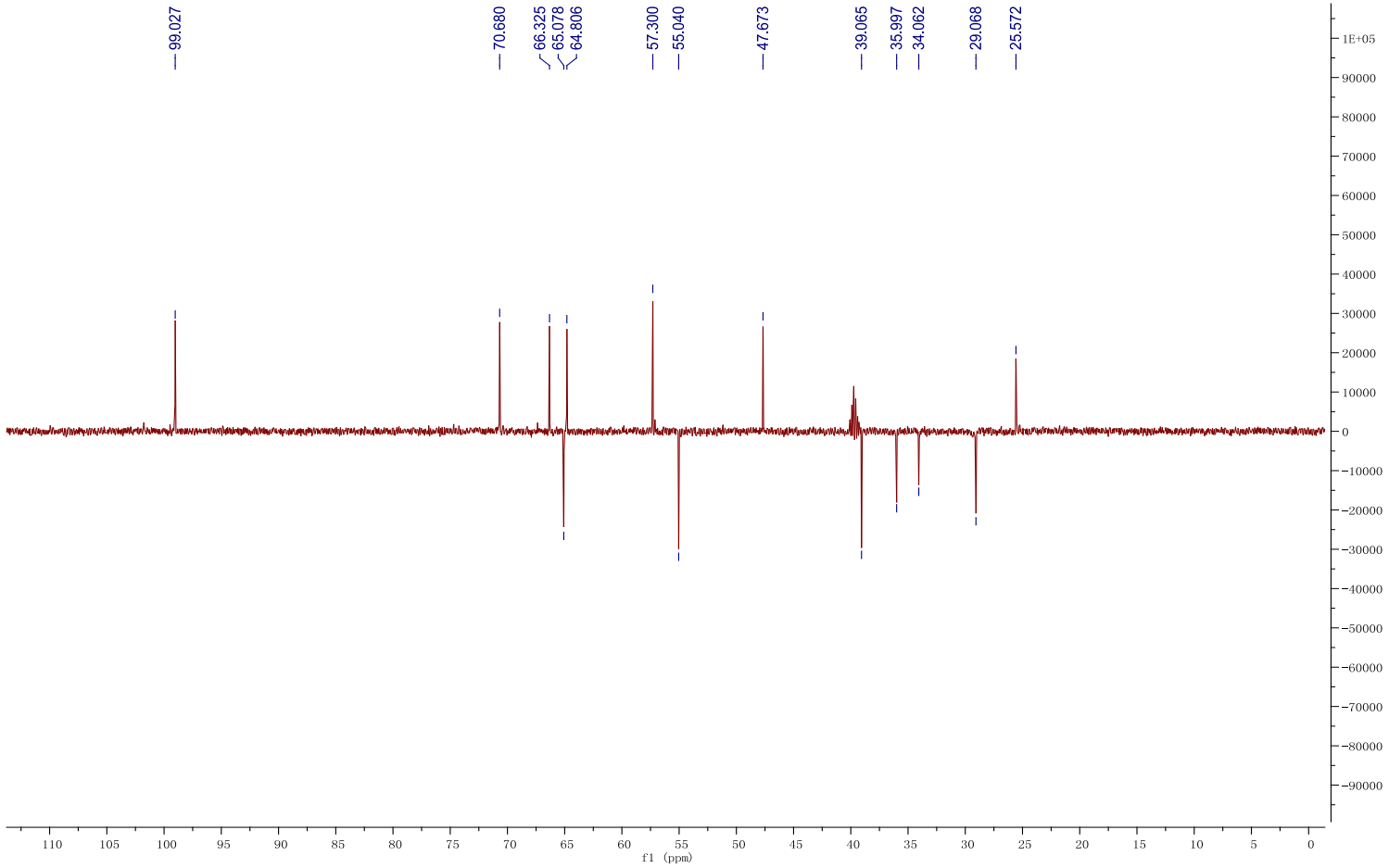
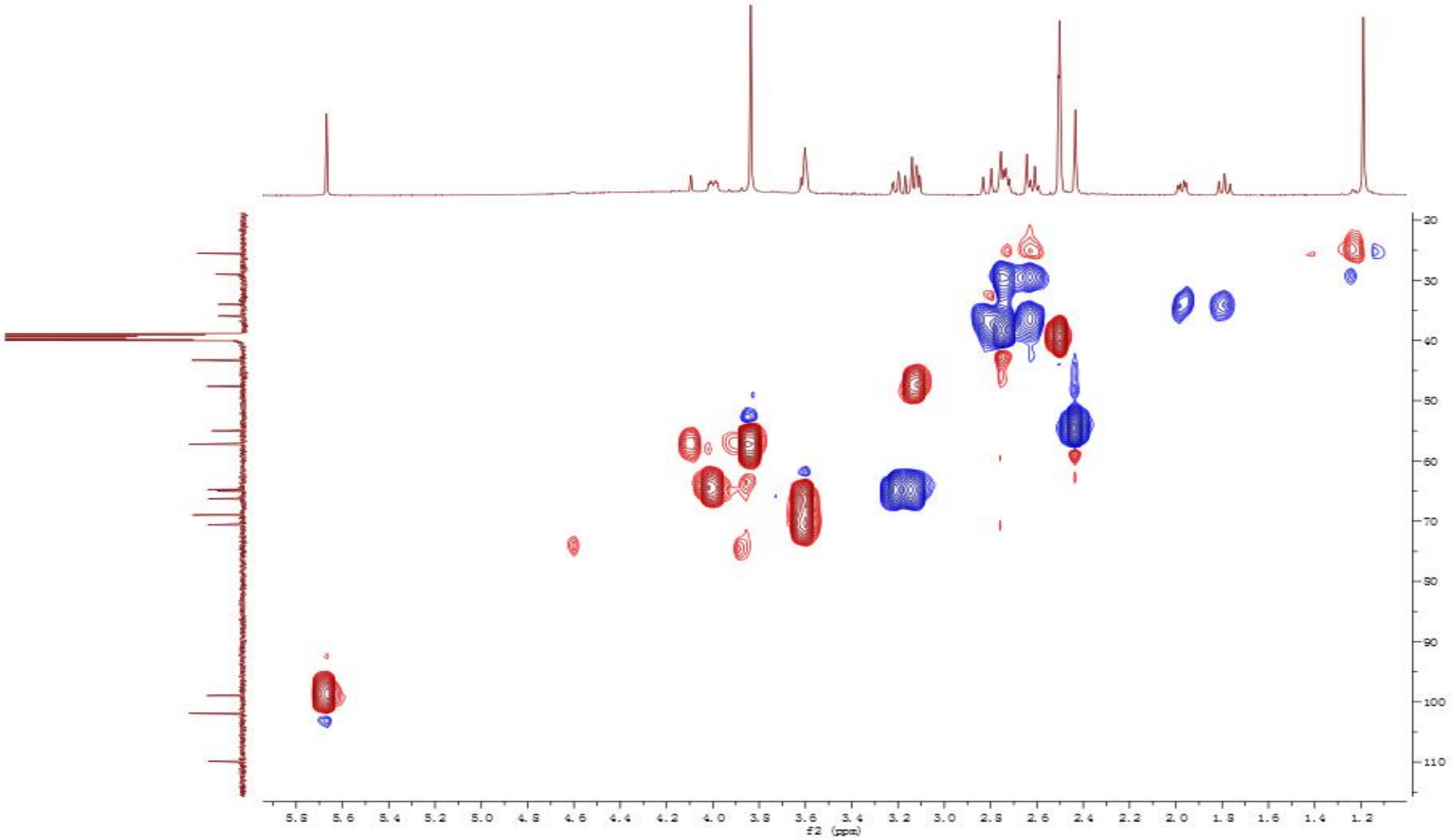


**Figure S4. HSQC spectrum of compound 1**



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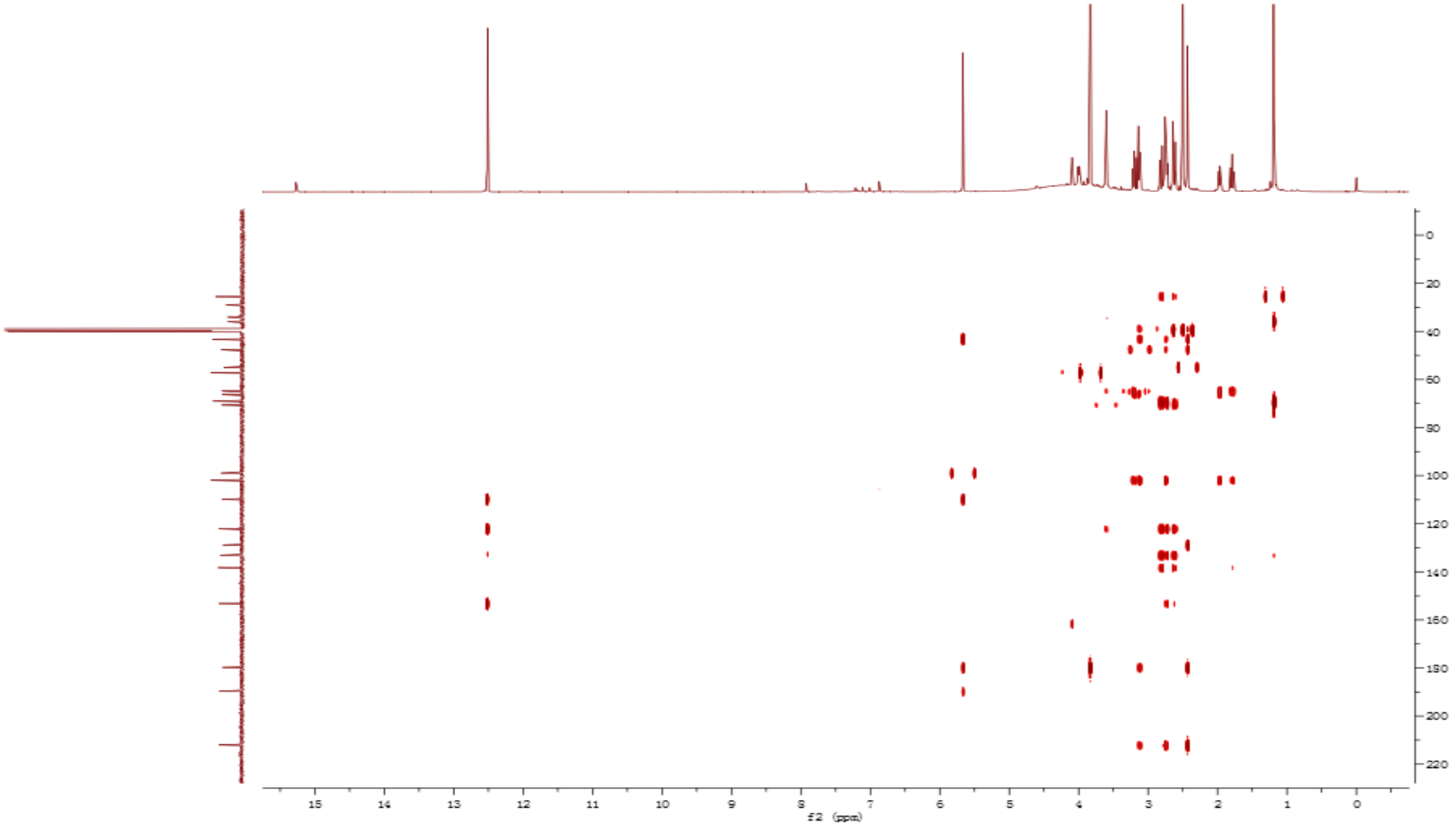

**Figure S6. $^{1}H$-$^{1}H$ COSY spectrum of compound 1**

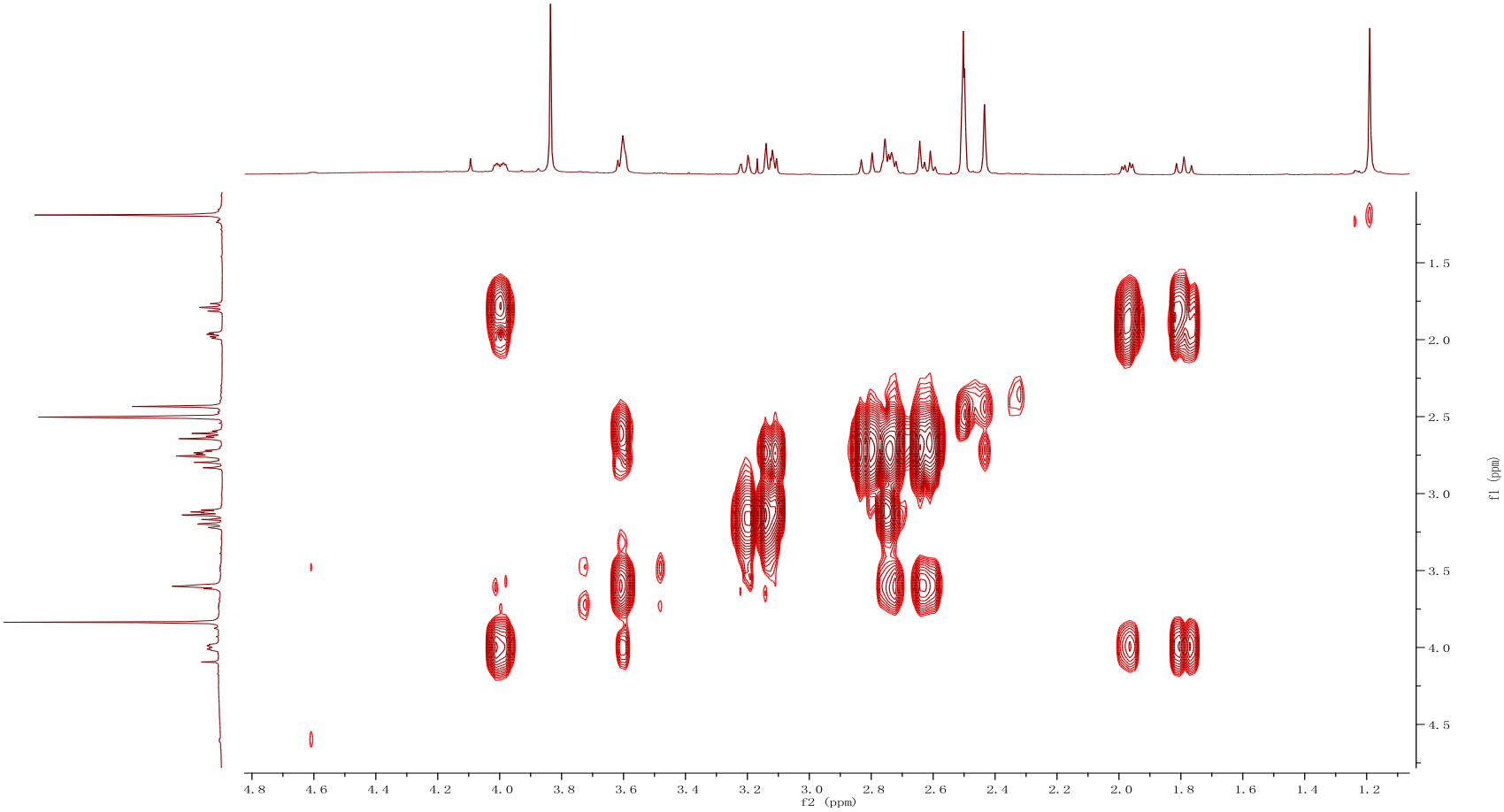

**Figure S7. NOESY spectrum of compound 1**

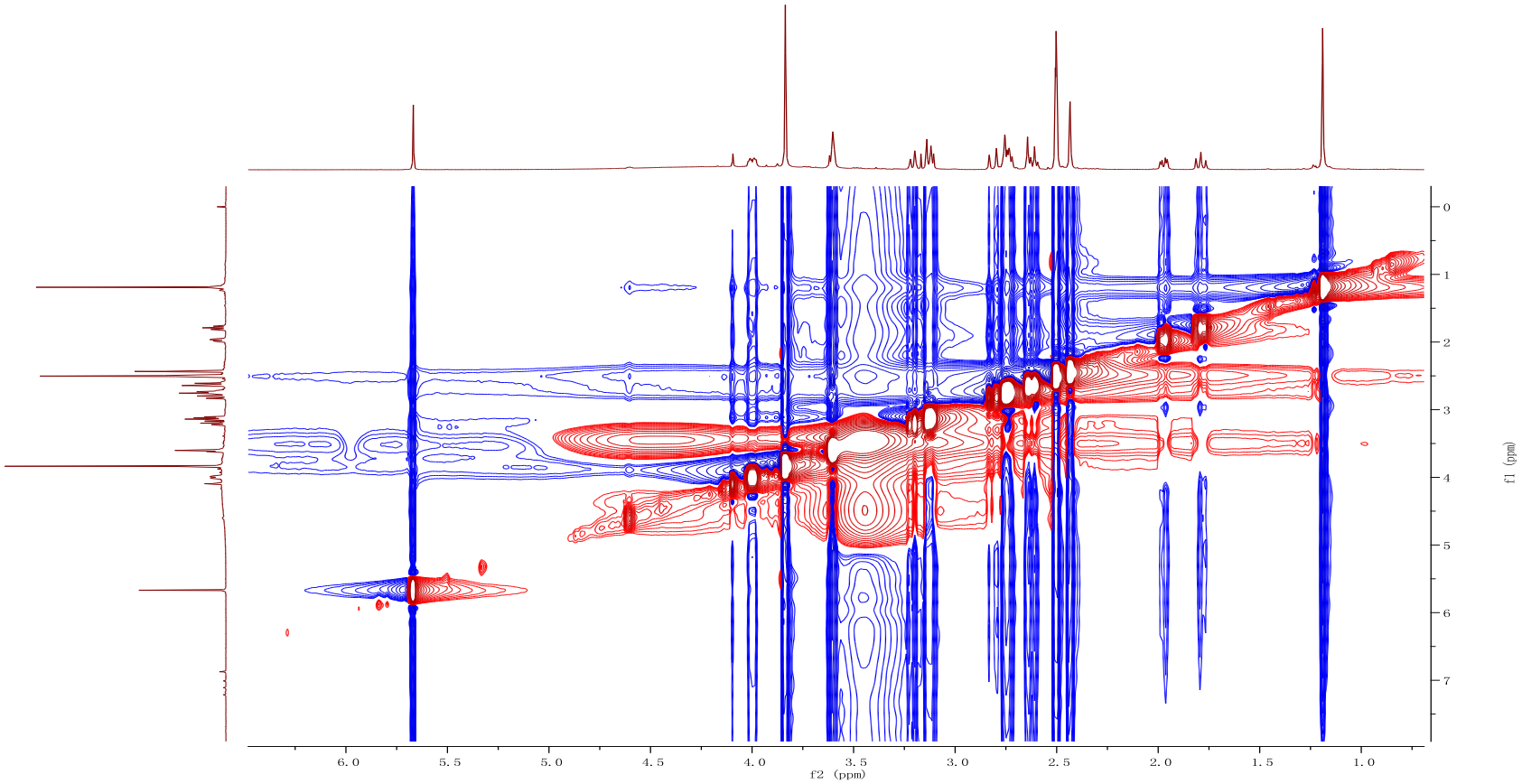

**Figure S8. HRESIMS spectrum of compound 1**

## Mass Spectrum SmartFormula Report

**Analysis Info**

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| Sample Name | pandongyan_PDY-DP-25_pos | Instrument | maXis 255552.00029 |
| Comment | | | |

**Acquisition Parameter**

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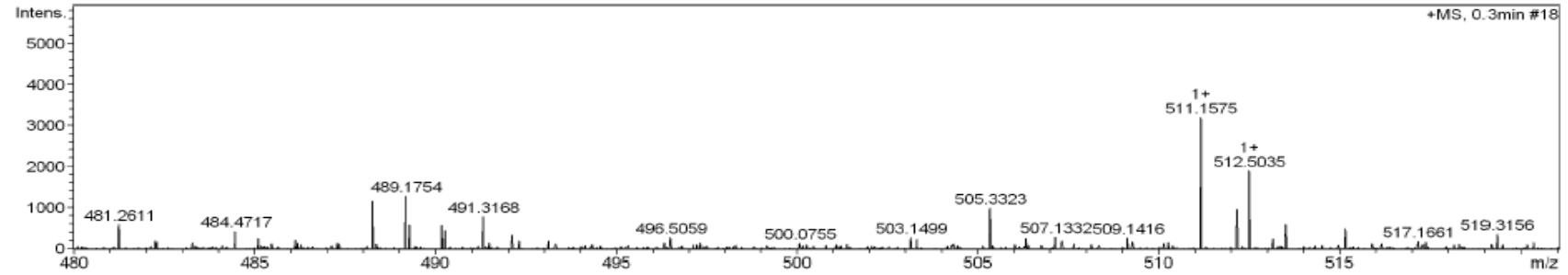
| Scan End | 1500 m/z | Set Charging Voltage | 0 V | Set Divert Valve | Waste |
| | | Set Corona | 0 nA | Set APCI Heater | 0 °C |

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| 511.157498 | 1 | C25H28NaO10 | 100.00 | 511.157468 | -0.1 | -0.0 | 17.5 | 11.5 | even | ok |
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**Figure S9. IR spectrum of compound 1**

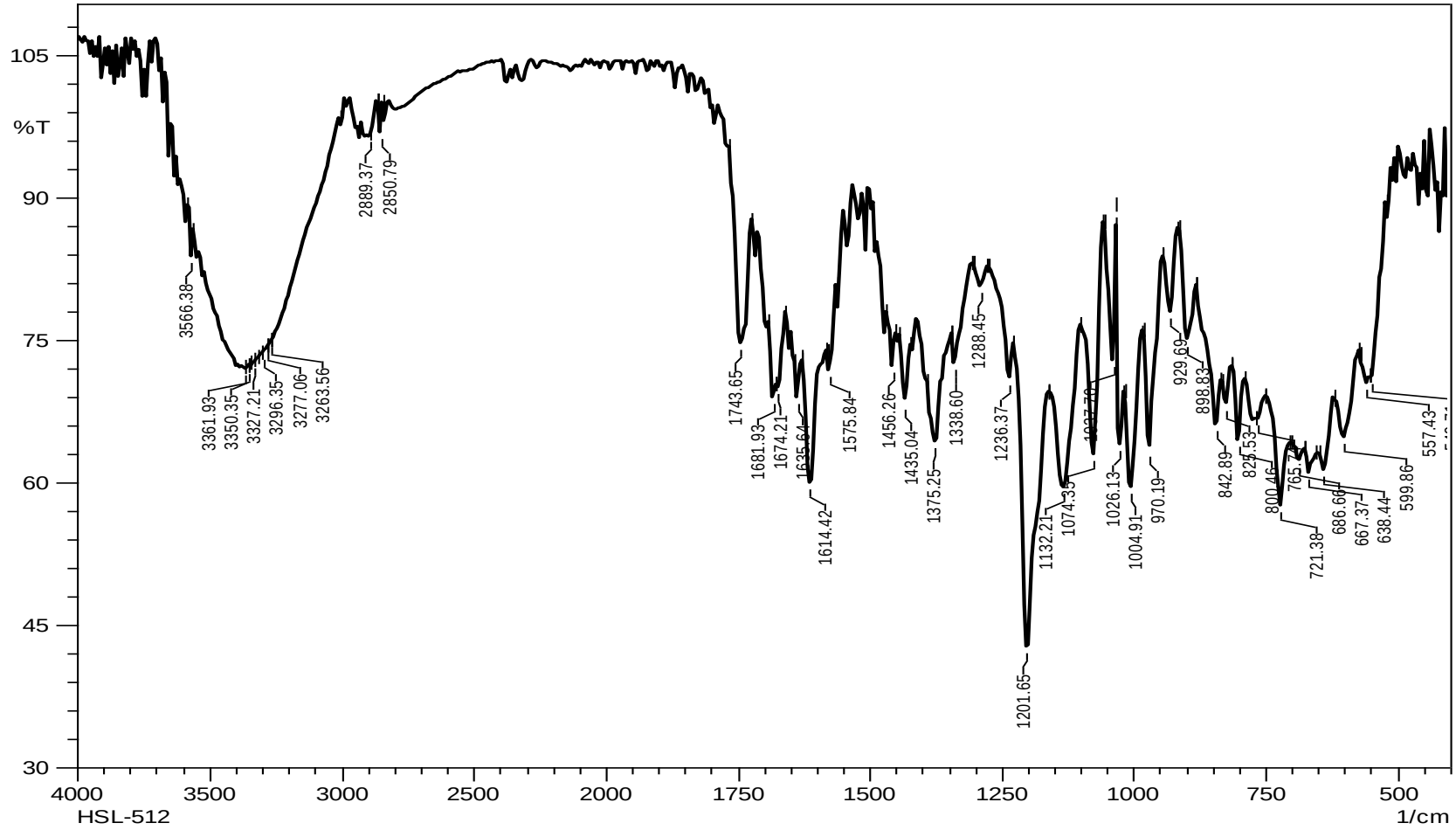

**Figure S10. UV spectrum of compound 1**

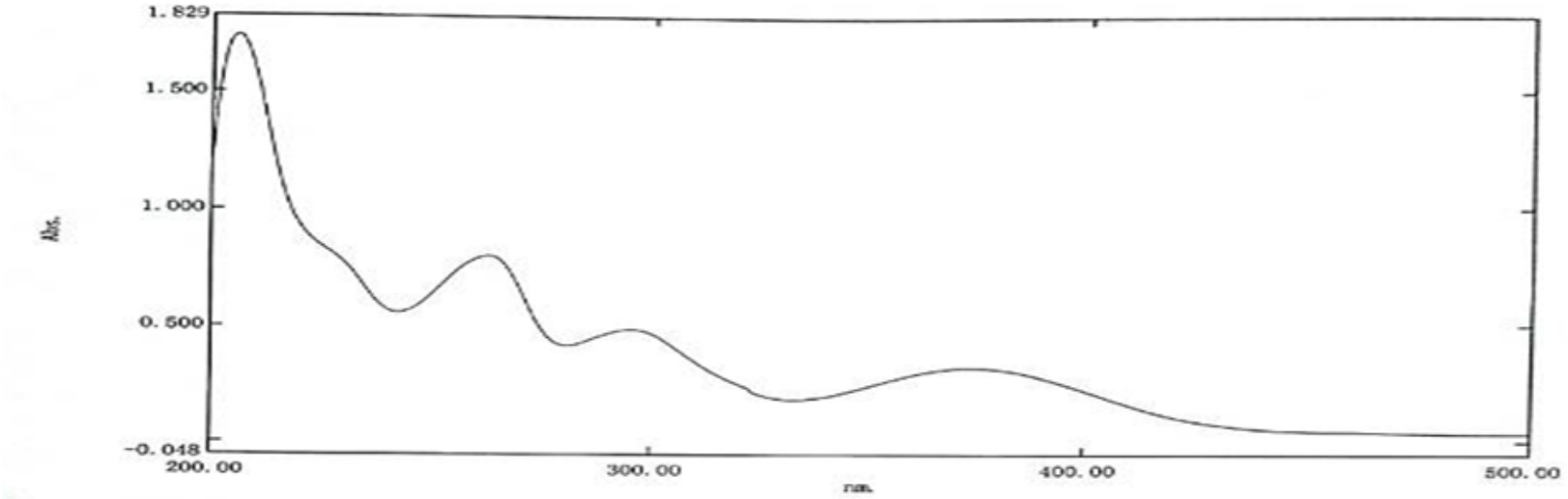

**Figure S11**. Crystal data and structure refinement for compound **1**

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                alpha=90        beta=100.124(4)     gamma=90
Temperature:    100 K

                Calculated                Reported
Volume          2069.83(12)               2069.83(12)
Space group     I 2                       I 1 2 1
Hall group      I 2y                      I 2y
Moiety formula  C25 H28 O10               C25 H28 O10
Sum formula     C25 H28 O10               C25 H28 O10
Mr              488.47                    488.47
Dx,g cm-3       1.567                     1.568
Z               4                         4
Mu (mm-1)       1.025                     1.025
F000            1032.0                    1032.0
F000'           1035.67
h,k,lmax        14,8,33                   14,8,32
Nref            4189[ 2285]               4013
Tmin,Tmax       0.929,0.980               0.911,1.000
Tmin'           0.857

Correction method= # Reported T Limits: Tmin=0.911 Tmax=1.000
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Data completeness= 1.76/0.96      Theta(max)= 73.867

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S = 1.095                 Npar= 326
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| 2 | \w | -58.00 | -31.00 | 0.50 | 2.80 | -- | 0.00 | -19.00 | 30.00 | 54 |
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| 5 | \w | -30.00 | 31.00 | 0.50 | 2.80 | -- | 0.00 | -82.00 | 30.00 | 122 |
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| 7 | \w | 6.00 | 31.00 | 0.50 | 25.36 | -- | 94.60 | -82.00 | -30.00 | 50 |
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| 9 | \w | 6.00 | 115.00 | 0.50 | 25.36 | -- | 94.60 | -61.00 | 90.00 | 218 |

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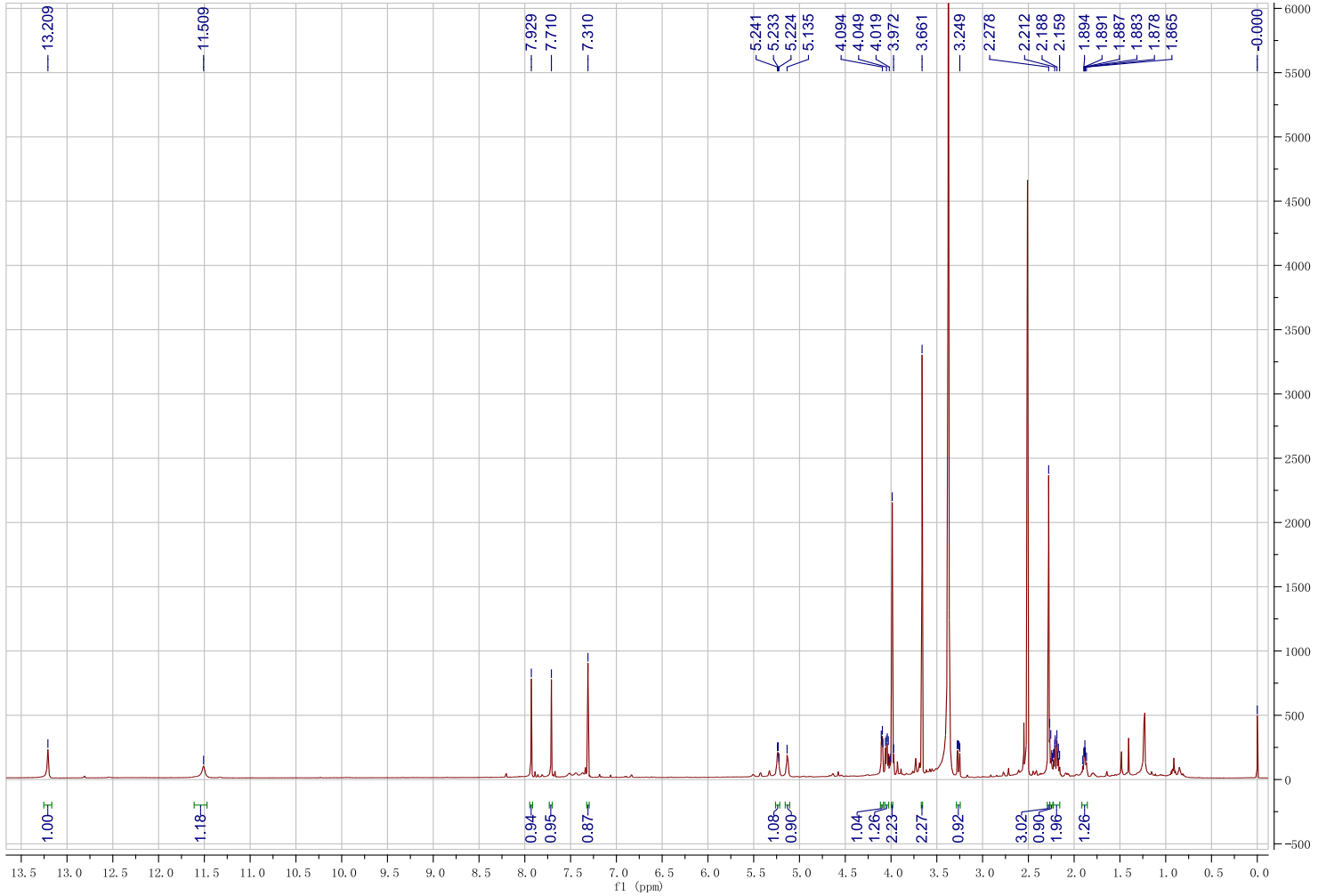
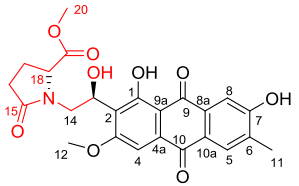
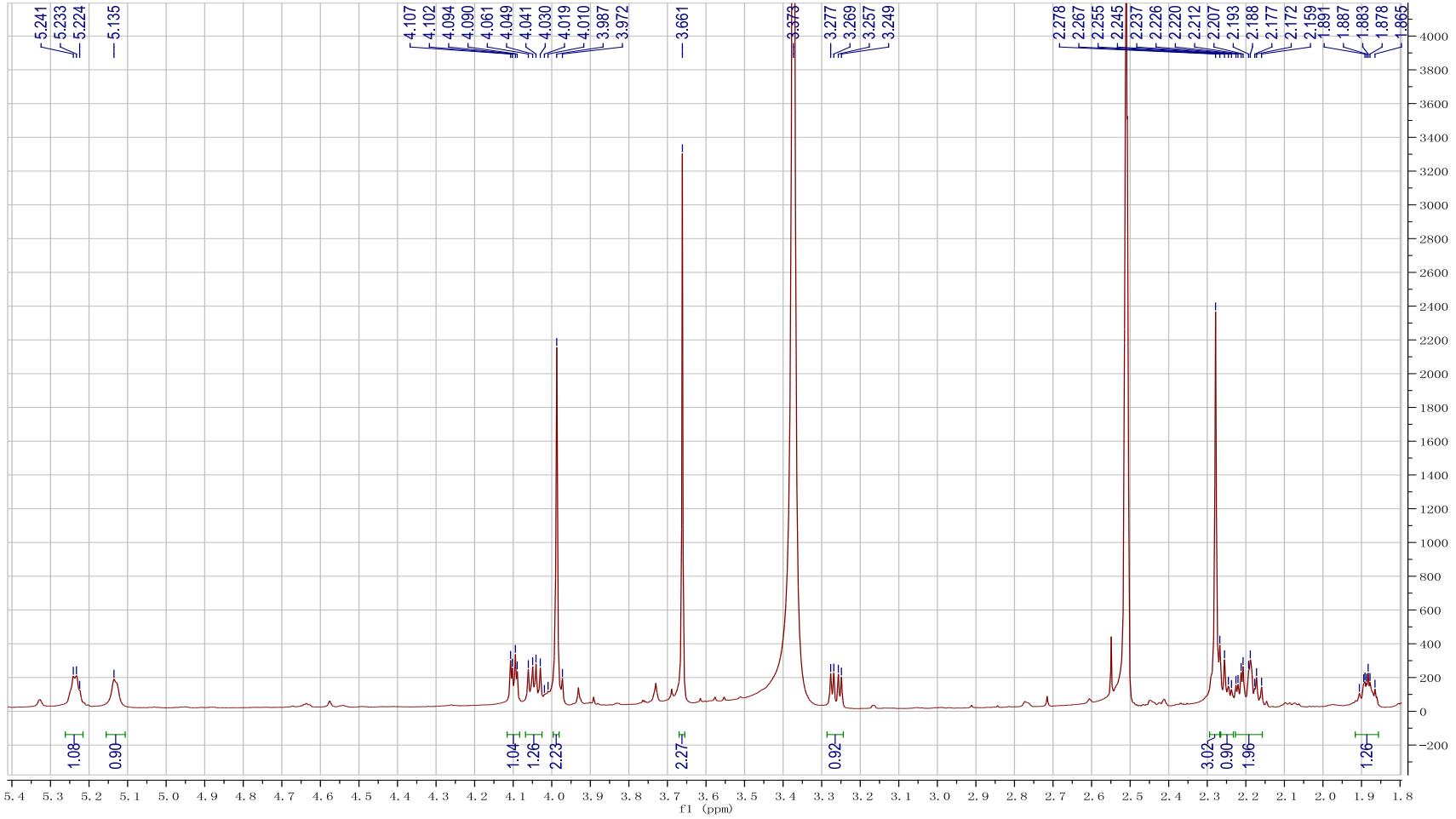
**Figure S12**. $^{1}$H NMR spectrum of compound **2**




**2**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2.207
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1.865
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0.90
1.04
1.26
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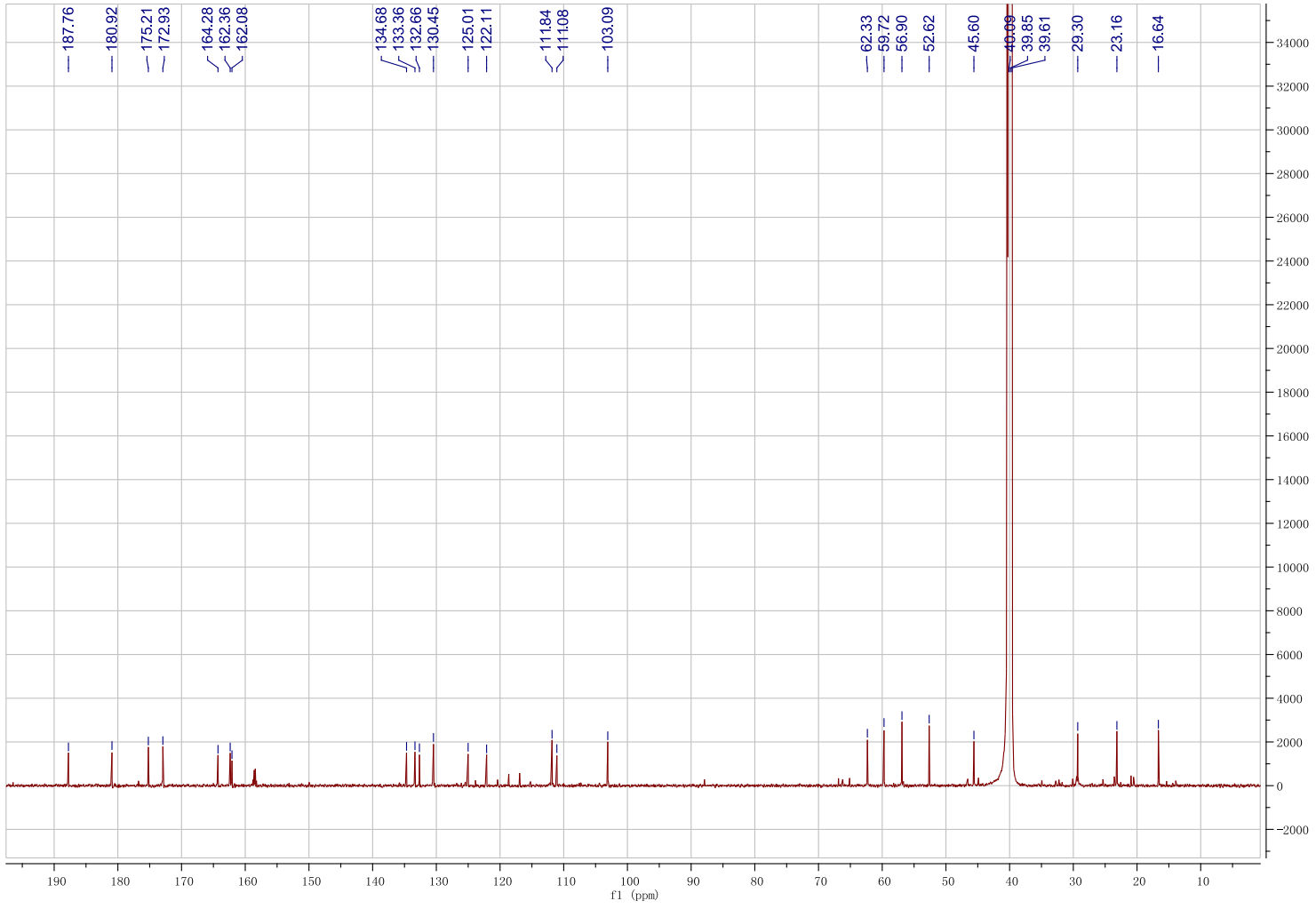
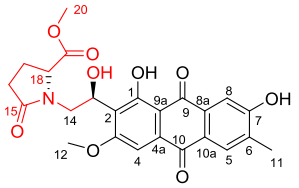
f1 (ppm)

**Figure S13. $^{13}$C NMR spectrum of compound 2**




**2**

**Figure S14.** DEPT NMR spectrum of compound **2**

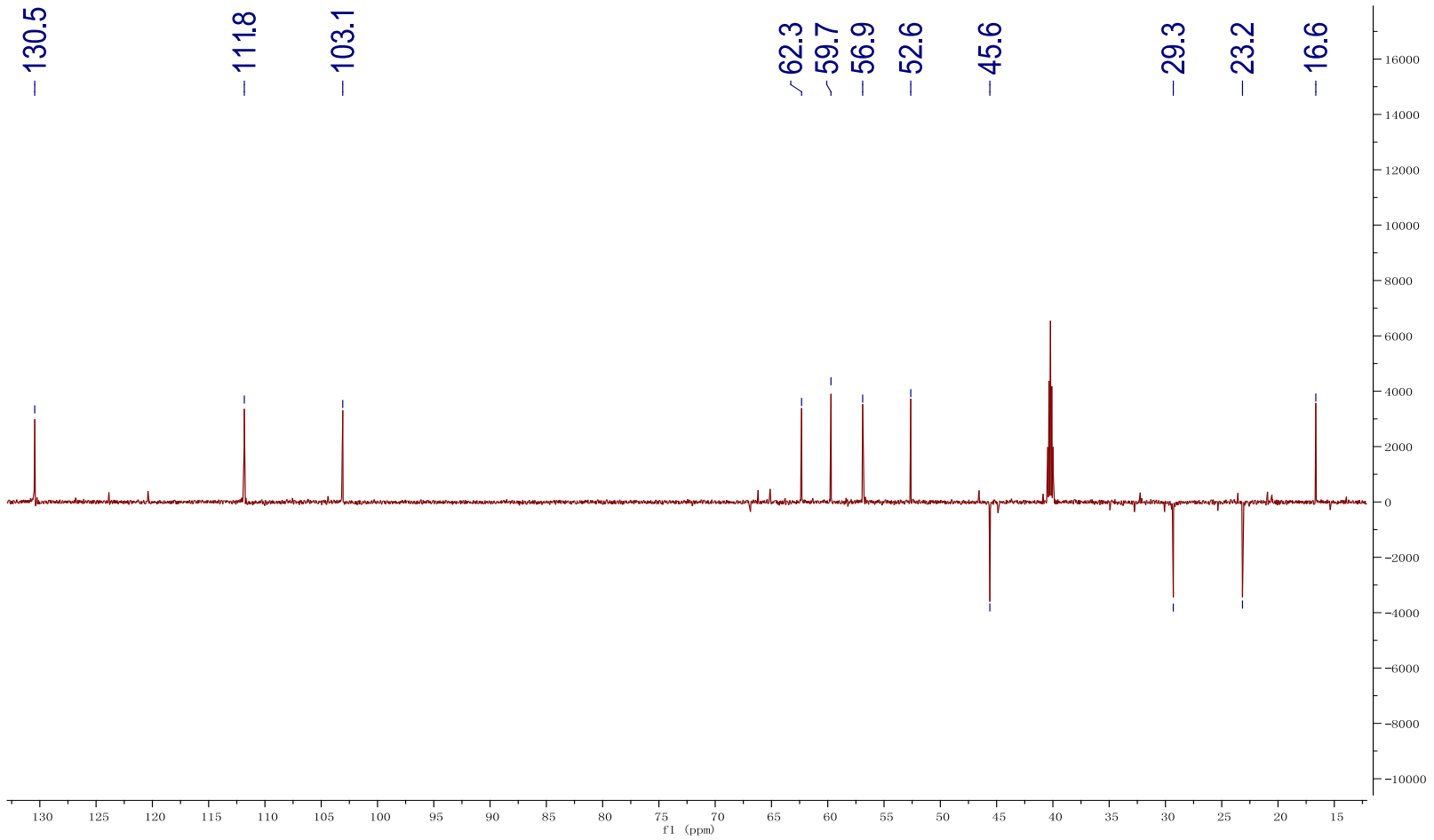


**Figure S15. HSQC spectrum of compound 2**

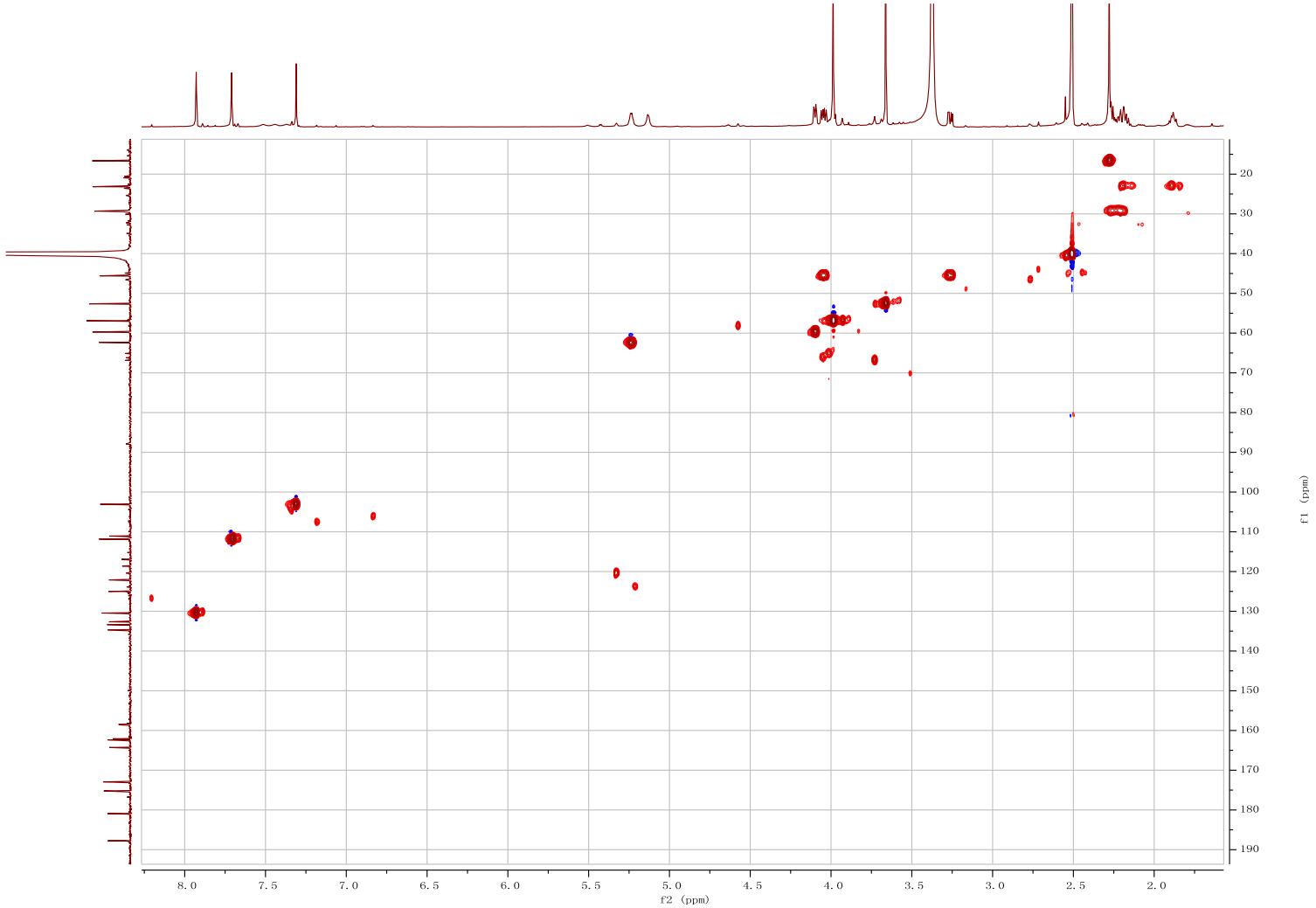
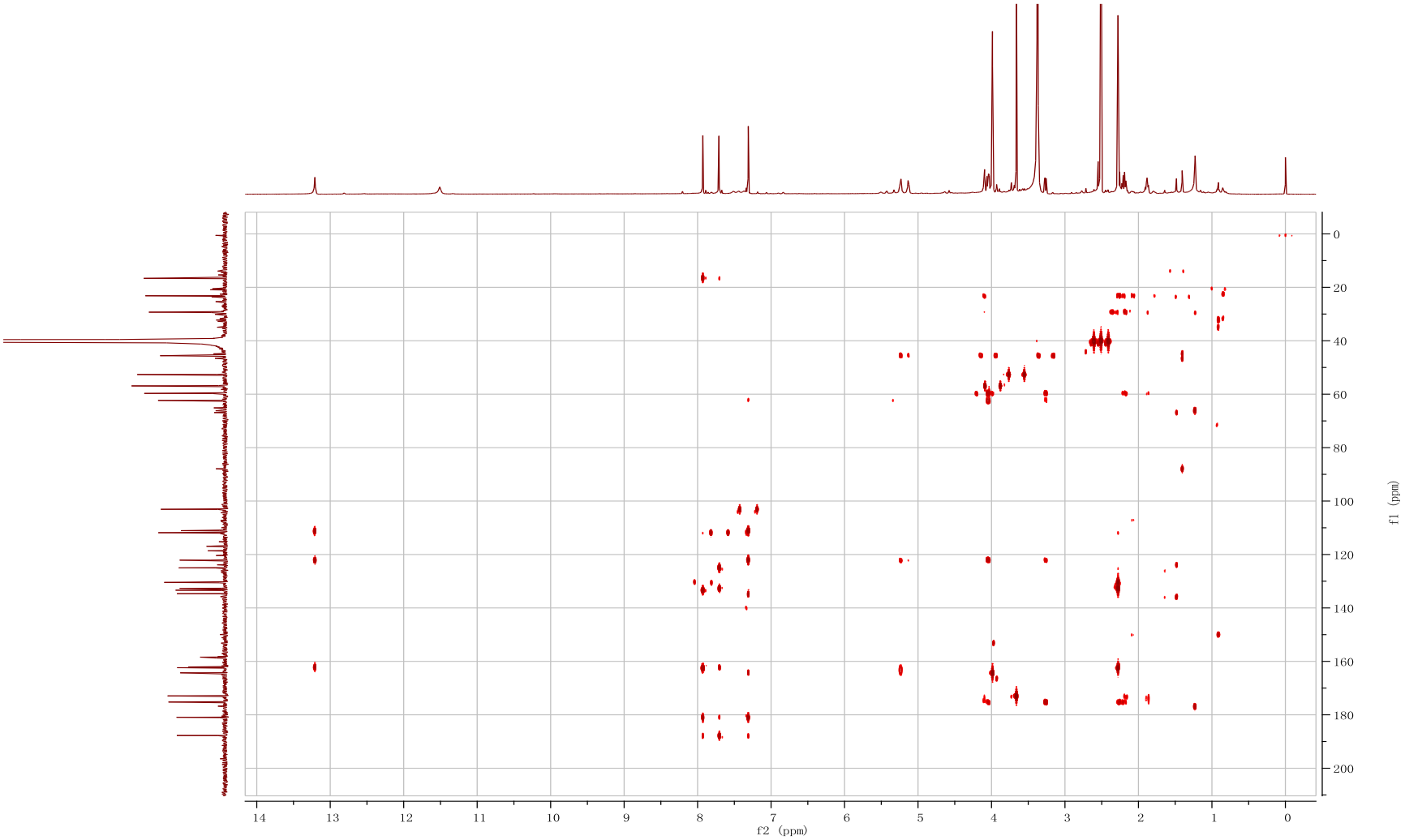


**Figure S16. HMBC spectrum of compound 2**



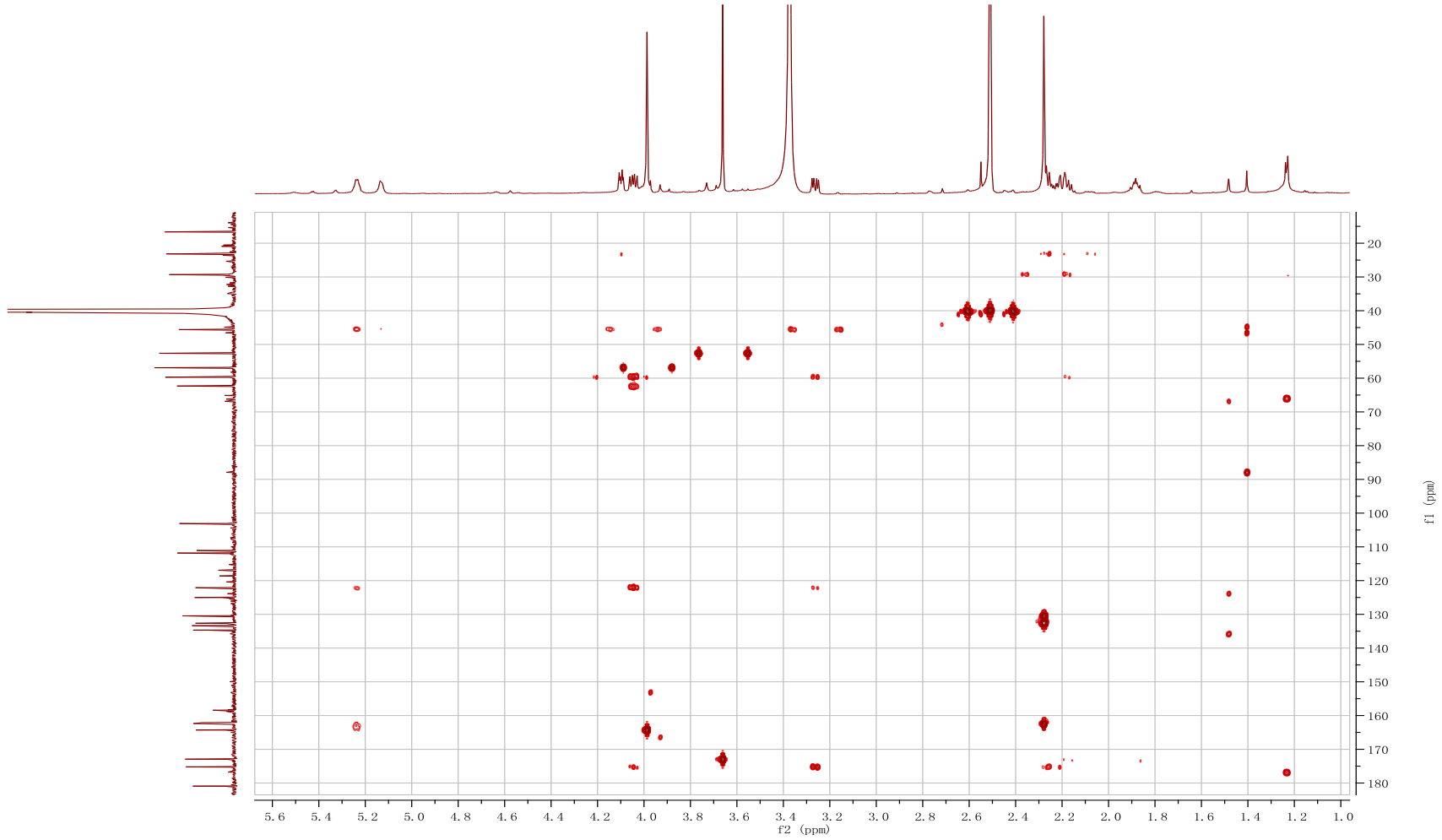
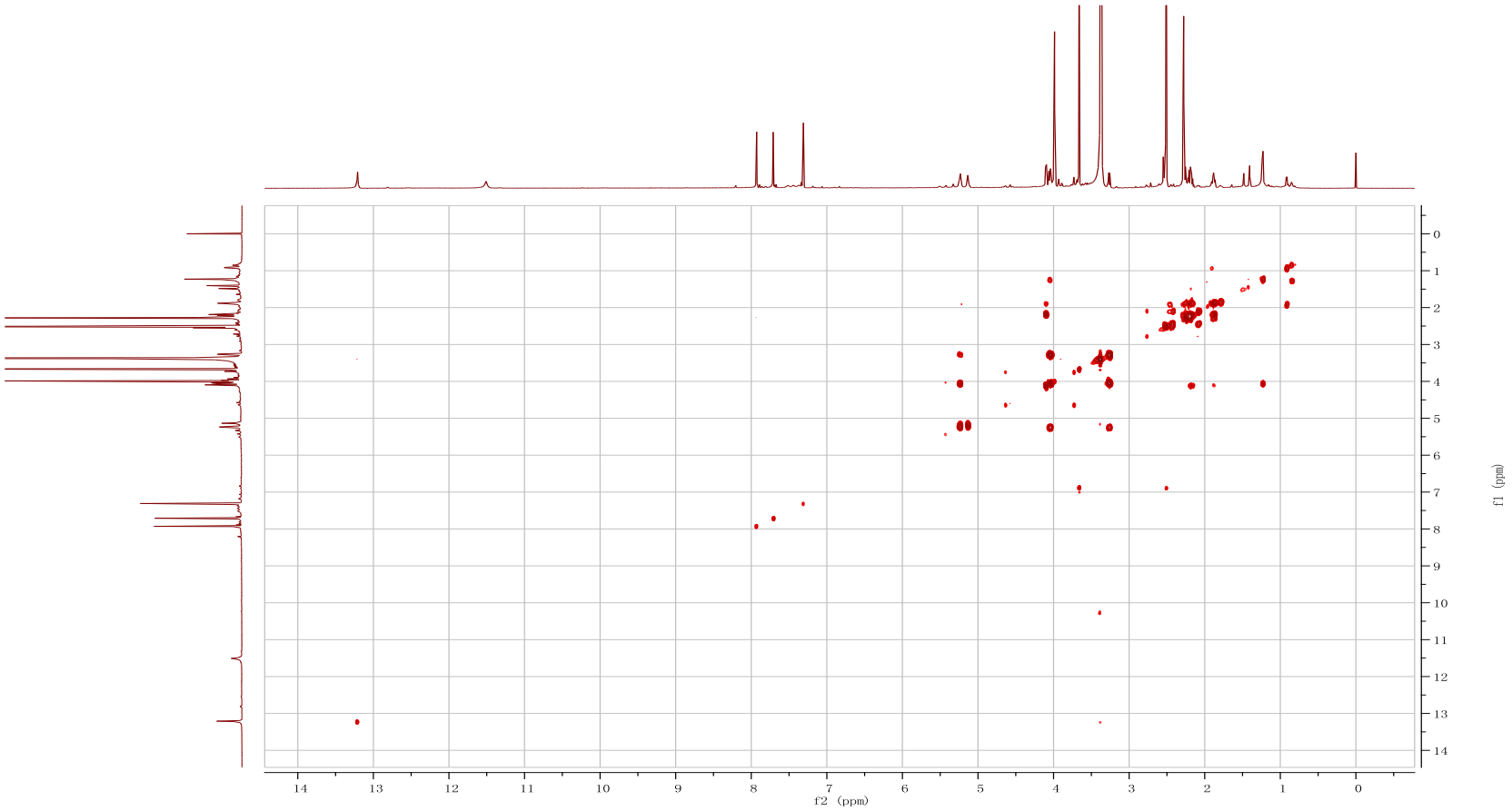

5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f2 (ppm)
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)

**Figure S17. $^{1}H$-$^{1}H$ COSY spectrum of compound 2**



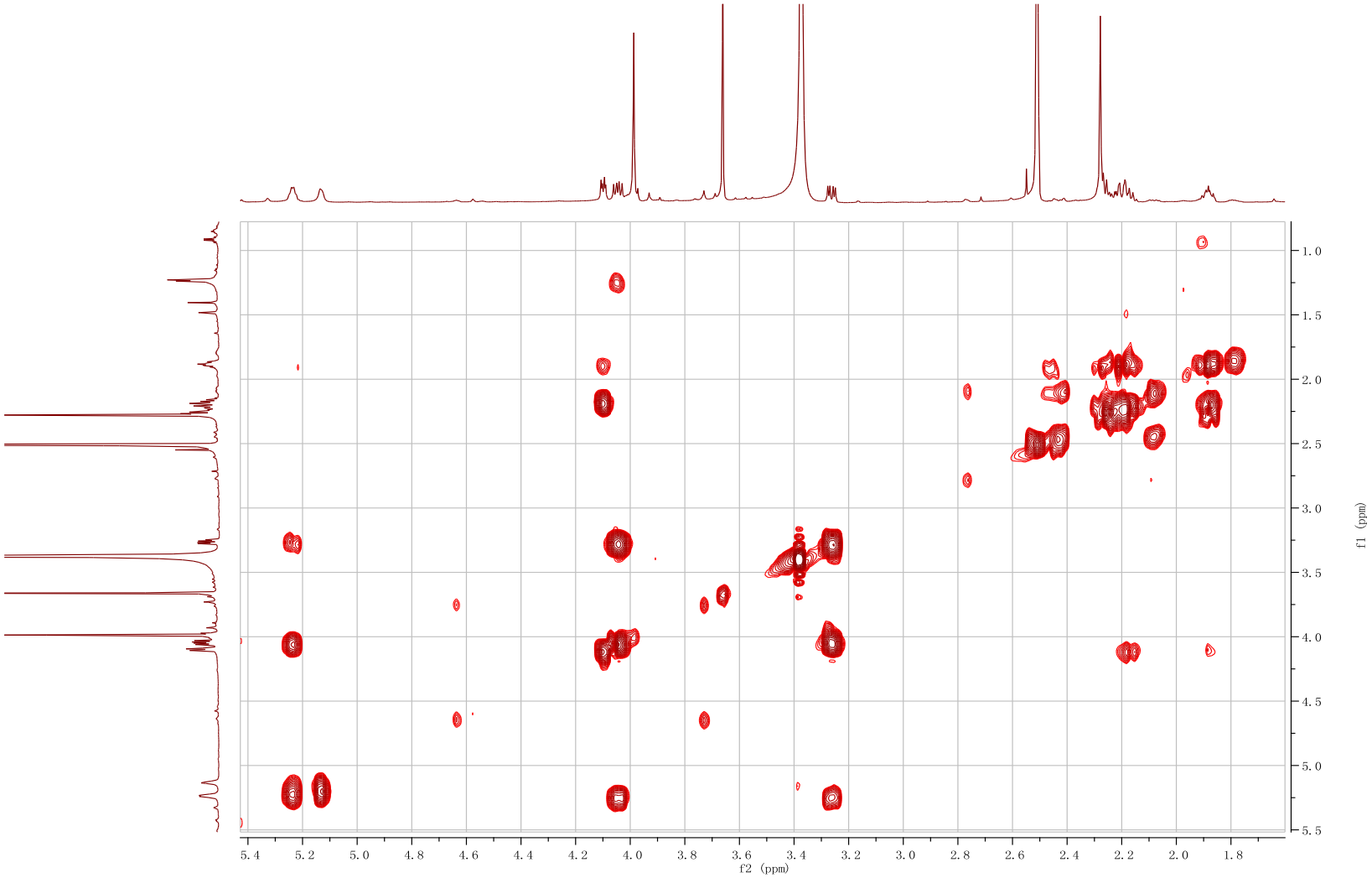

5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)

**Figure S18. NOESY spectrum of compound 2**

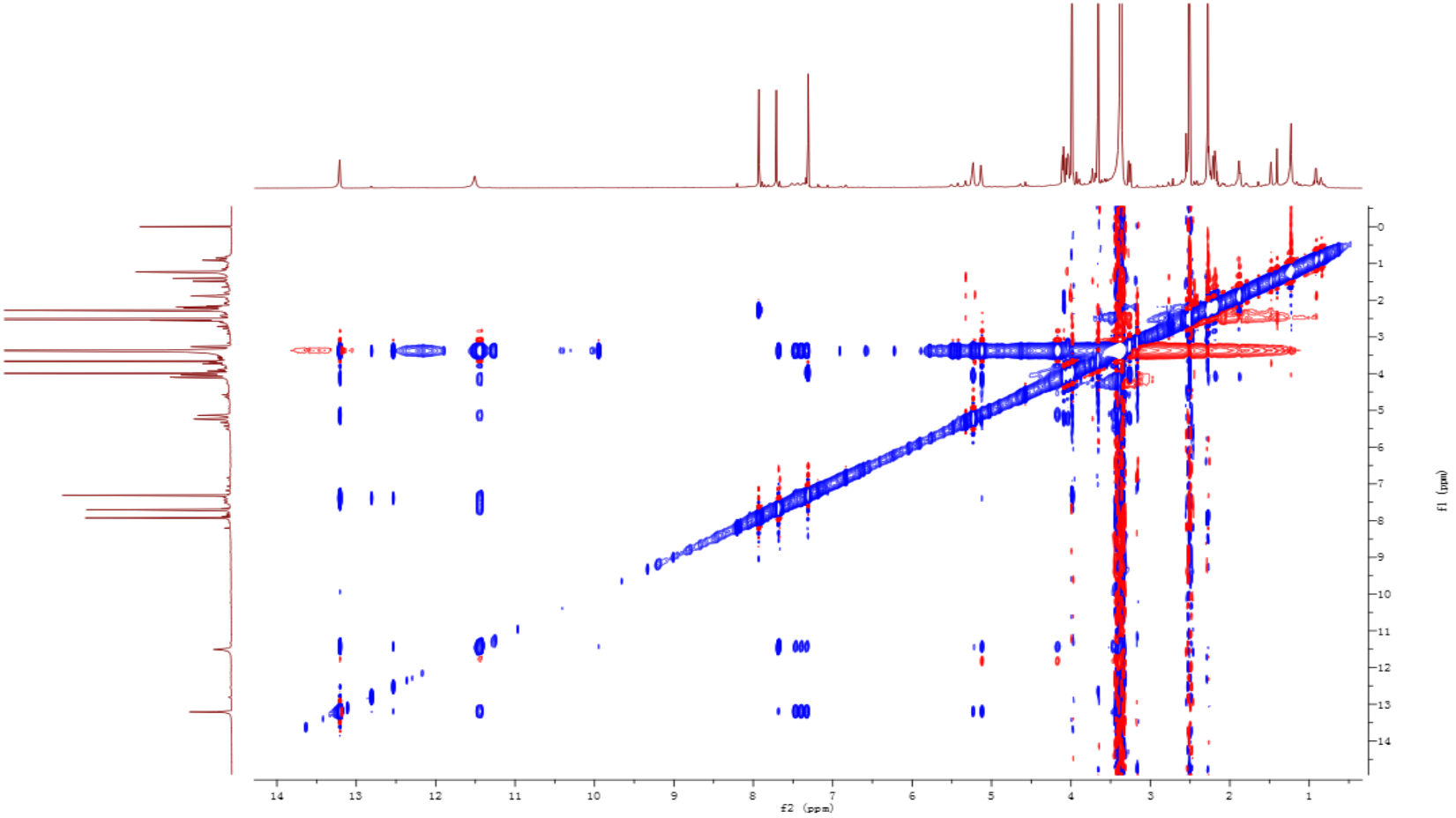
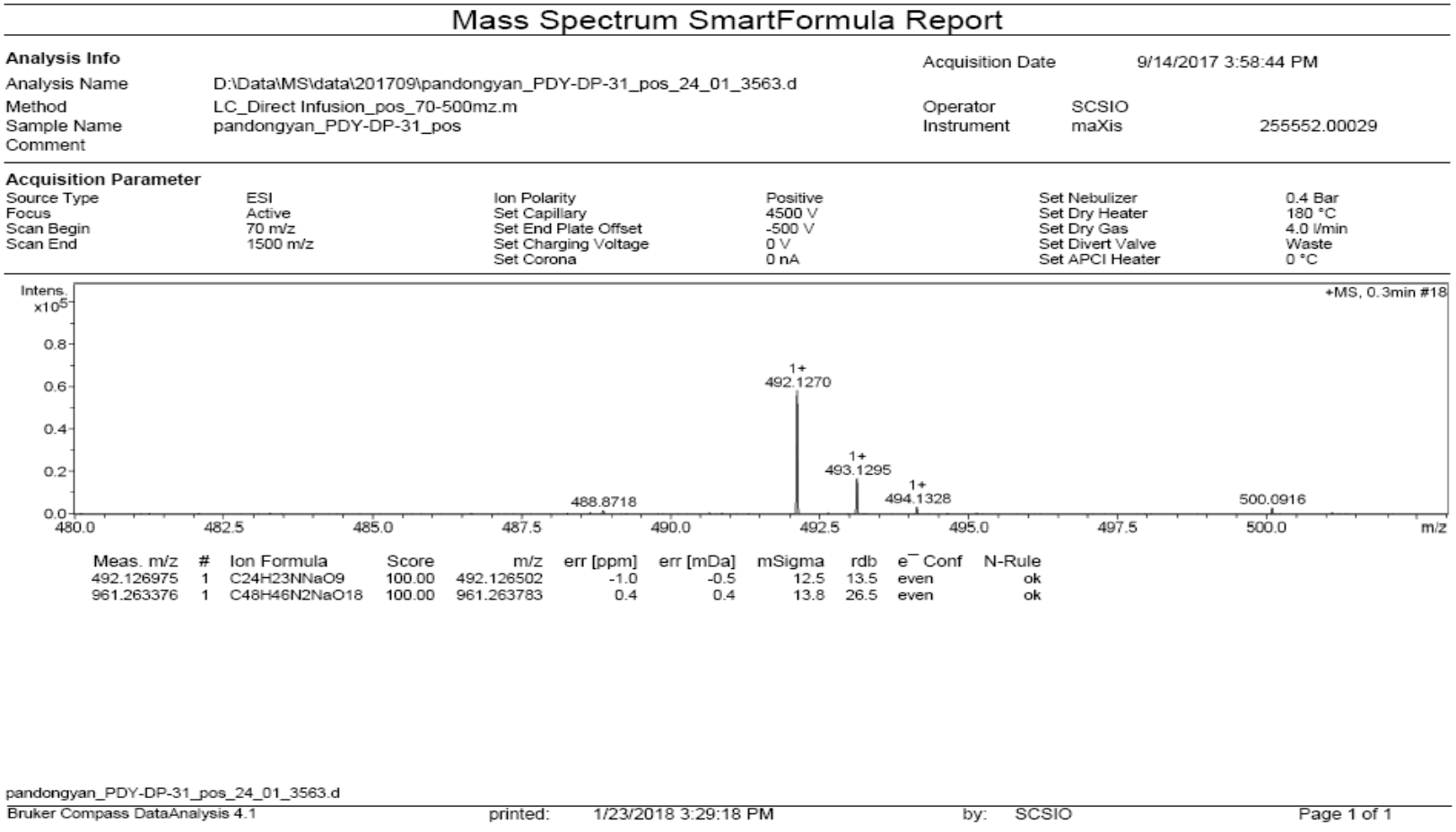


**Figure S19.** HRESIMS spectrum of compound **2**



Mass Spectrum SmartFormula Report

**Analysis Info**

| | | | |
|---|---|---|---|
| Analysis Name | D:\Data\MS\data\201709\pandongyan_PDY-DP-31_pos_24_01_3563.d | Acquisition Date | 9/14/2017 3:58:44 PM |
| Method | LC_Direct Infusion_pos_70-500mz.m | Operator | SCSIO |
| Sample Name | pandongyan_PDY-DP-31_pos | Instrument | maXis 255552.00029 |
| Comment | | | |

**Acquisition Parameter**

| | | | | | |
|---|---|---|---|---|---|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Active | Set Capillary | 4500 V | Set Dry Heater | 180 °C |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 4.0 l/min |
| Scan End | 1500 m/z | Set Charging Voltage | 0 V | Set Divert Valve | Waste |
| | | Set Corona | 0 nA | Set APCI Heater | 0 °C |



| Meas. m/z | # | Ion Formula | Score | m/z | err [ppm] | err [mDa] | mSigma | rdb | e¯ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 492.126975 | 1 | C24H23NNaO9 | 100.00 | 492.126502 | -1.0 | -0.5 | 12.5 | 13.5 | even | ok |
| 961.263376 | 1 | C48H46N2NaO18 | 100.00 | 961.263783 | 0.4 | 0.4 | 13.8 | 26.5 | even | ok |

**Figure S20.** IR spectrum of compound **2**

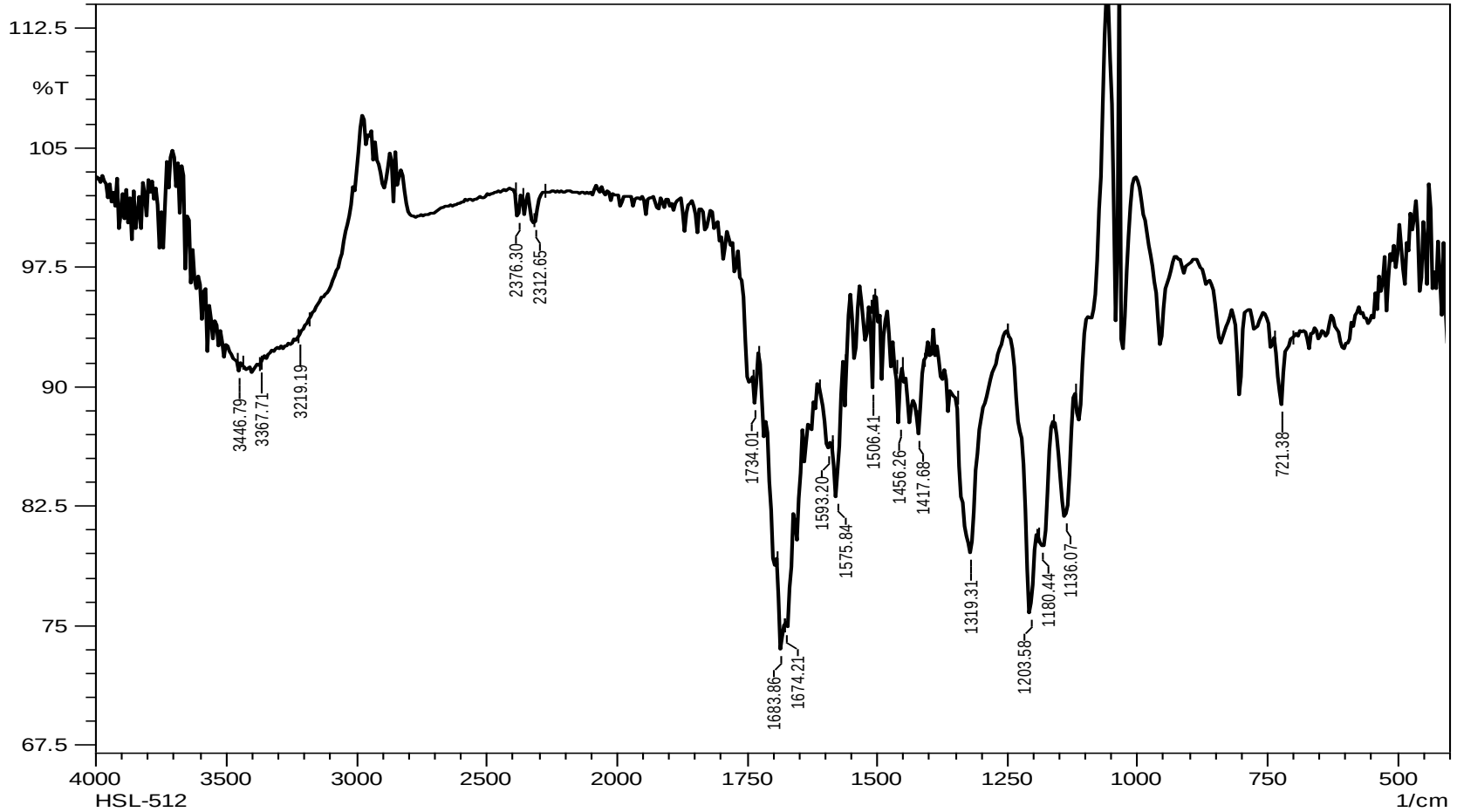
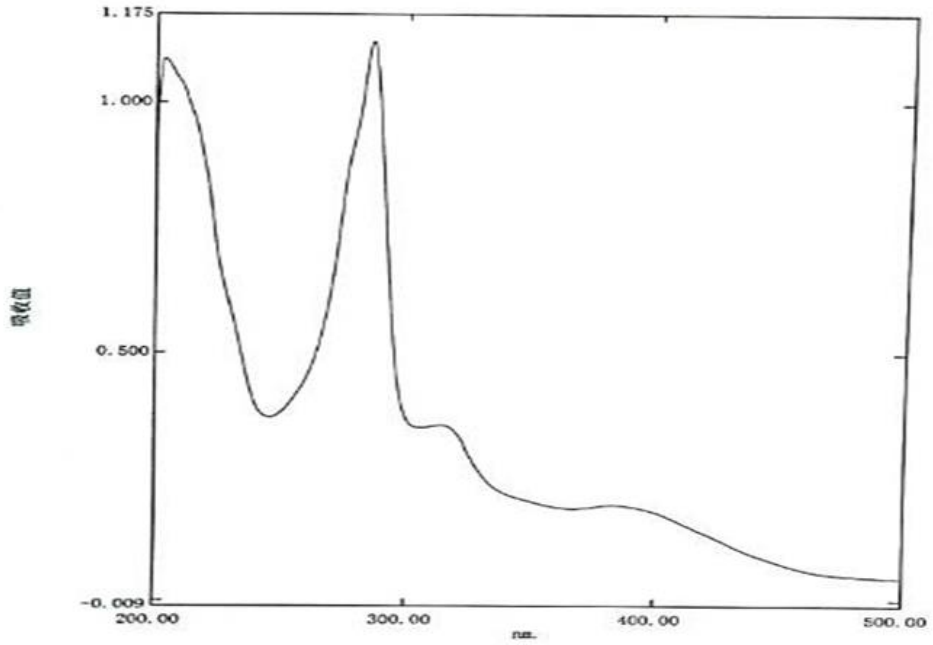
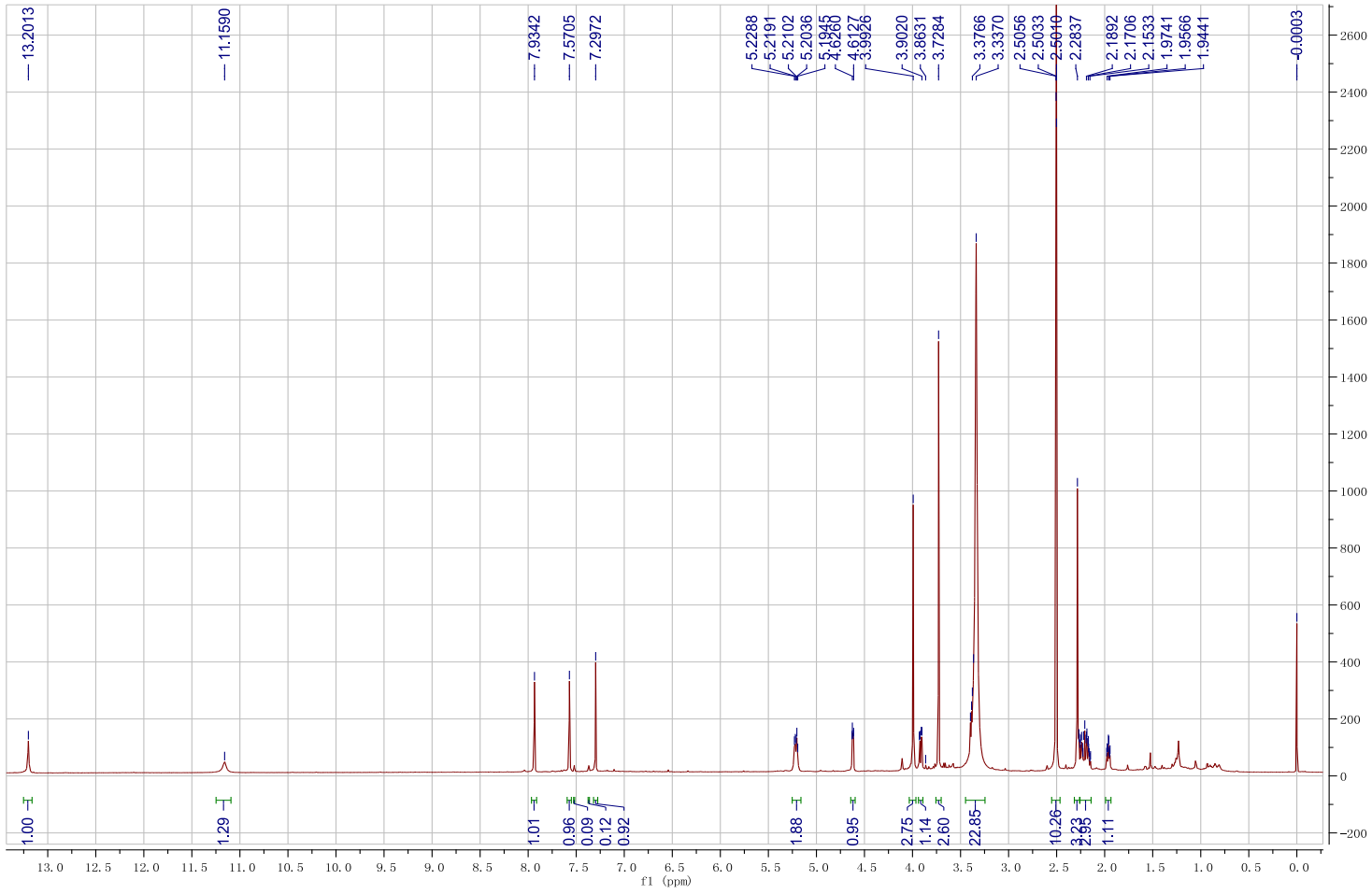


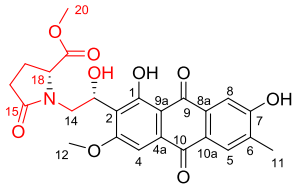
**Figure S21.** UV spectrum of compound **2**




| No. | P/V | 波长(nm) | 吸收值 | 描述 |
|---|---|---|---|---|
| 1 | ⓟ | 383.60 | 0.195 | |
| 2 | ⓟ | 312.80 | 0.357 | |
| 3 | ⓟ | 285.60 | 1.121 | |
| 4 | ⓟ | 203.00 | 1.085 | |

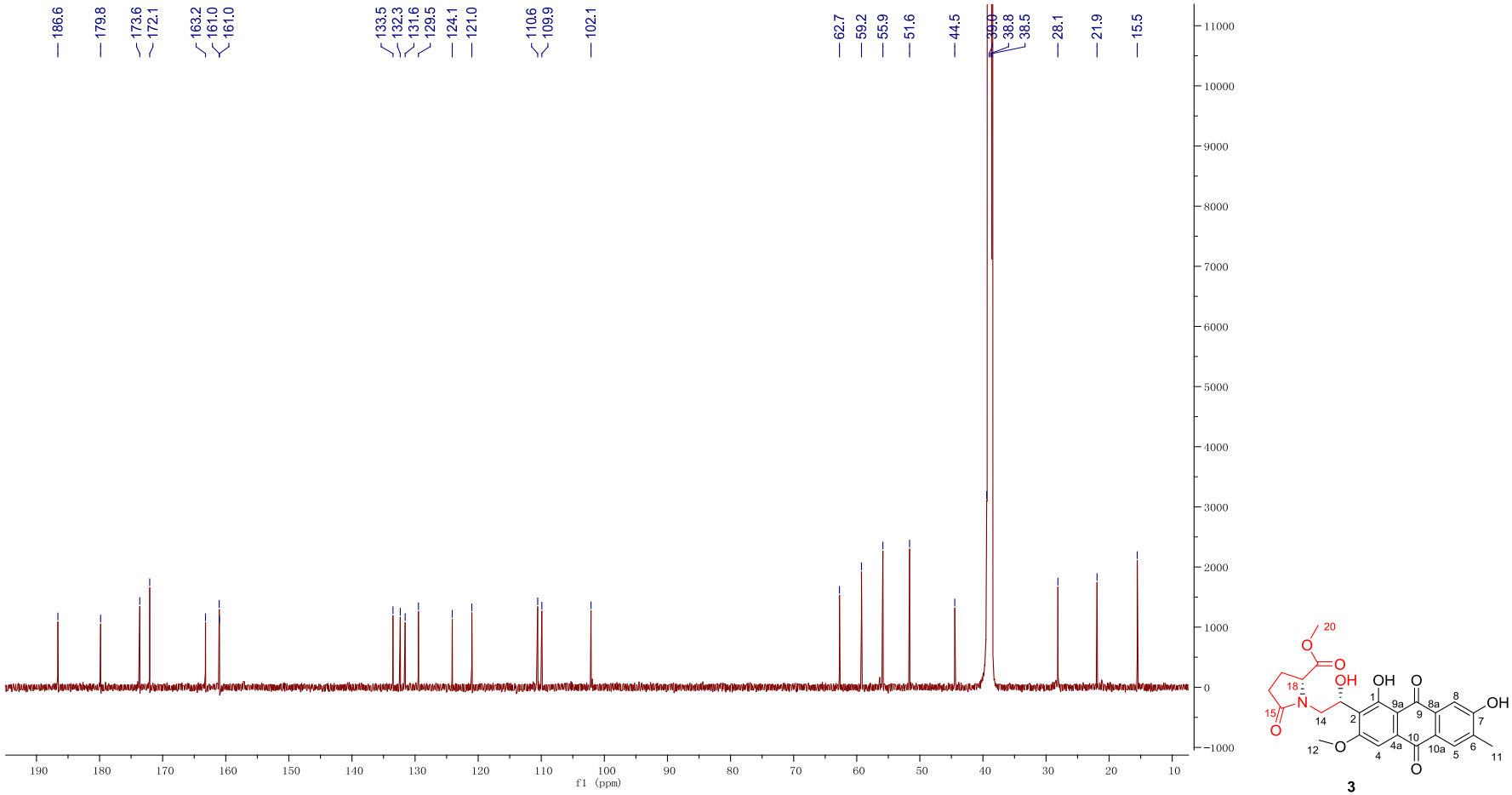
**Figure S22. $^{1}$H NMR spectrum of compound 3**




3

**Figure S23. $^{13}C$ and DEPT NMR spectrum of compound 3**




3

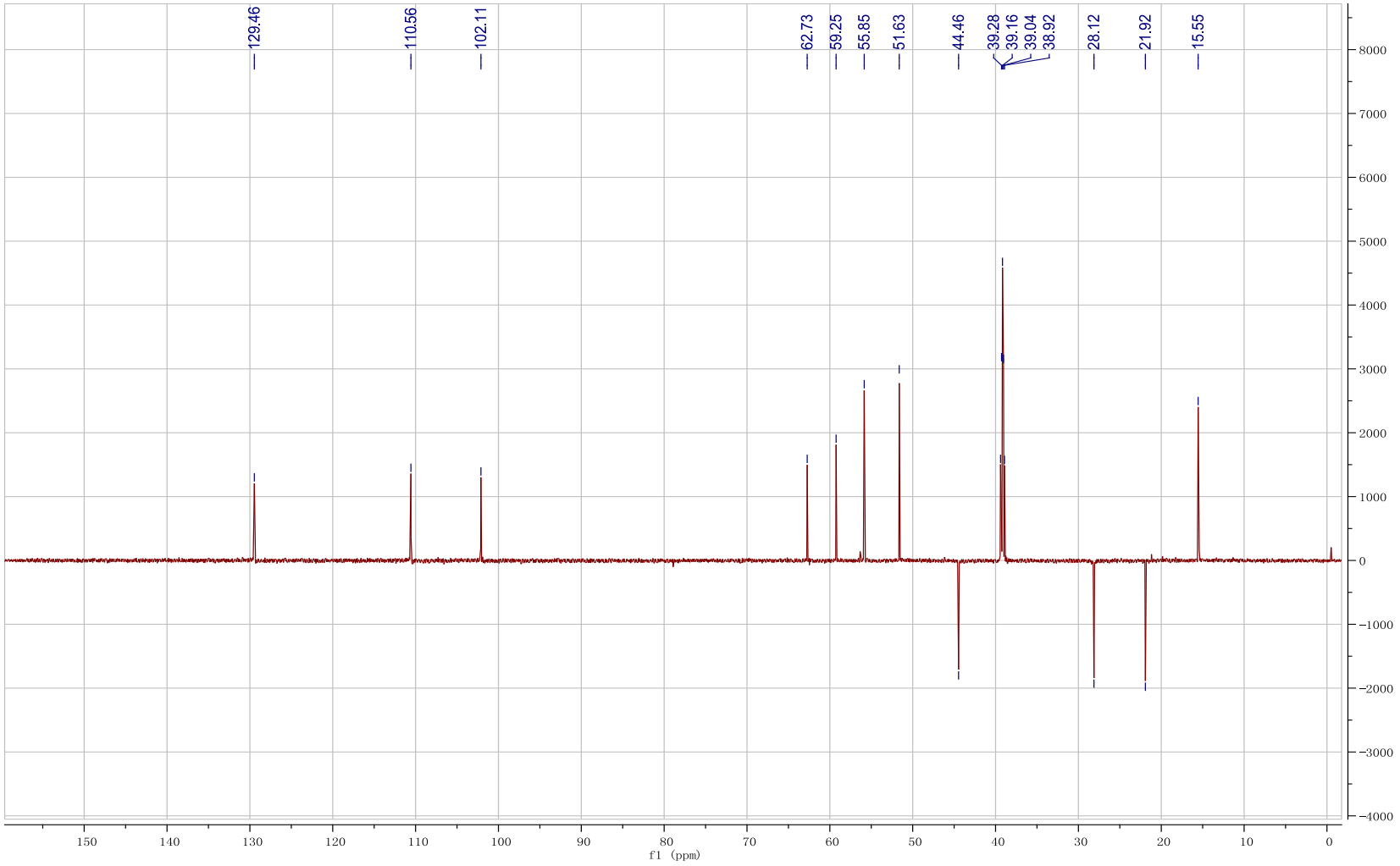
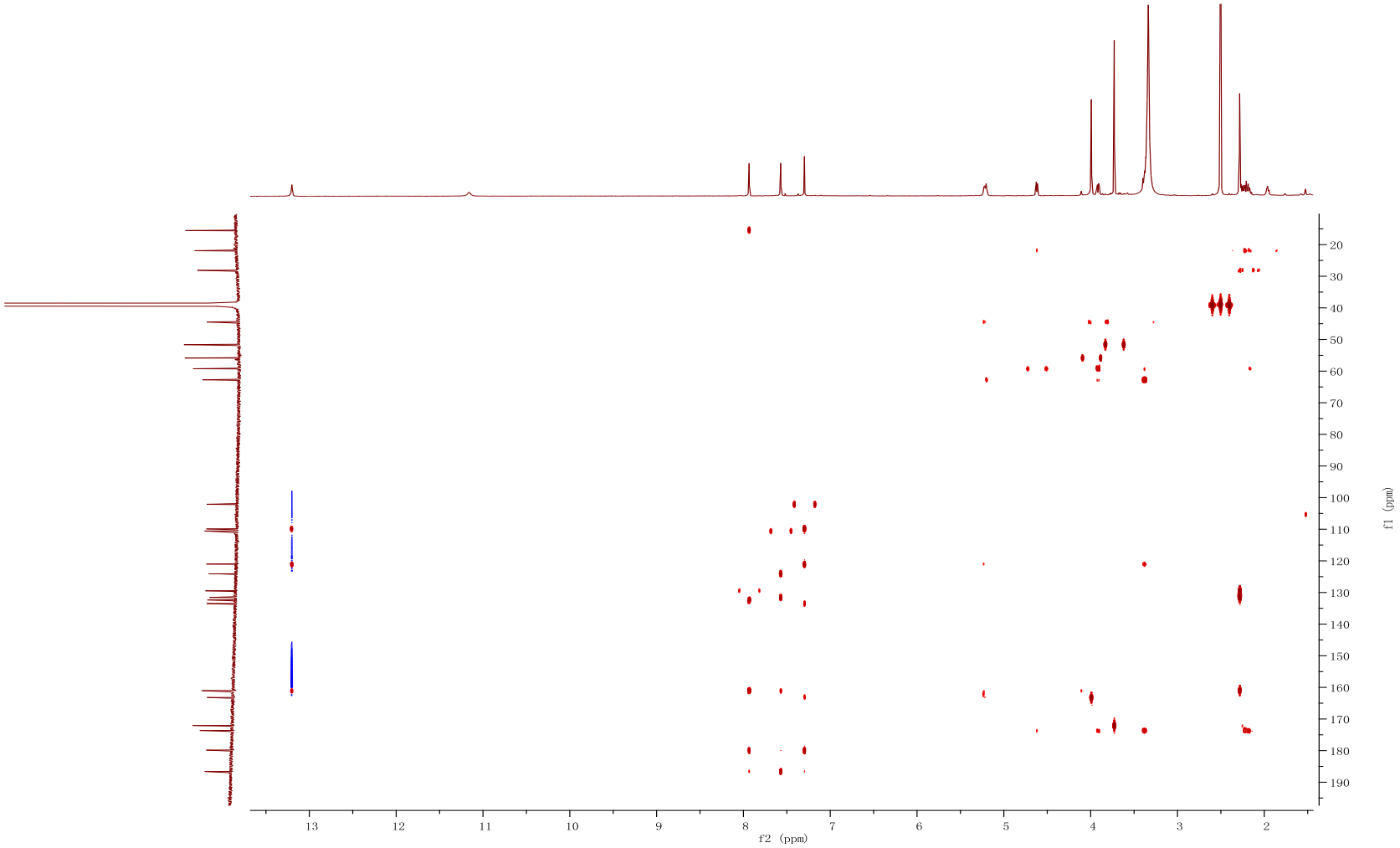

129.46
110.56
102.11
62.73
59.25
55.85
51.63
44.46
39.28
39.16
39.04
38.92
28.12
21.92
15.55
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
−3000
−4000
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

**Figure S24**. HMBC spectrum of compound **3**



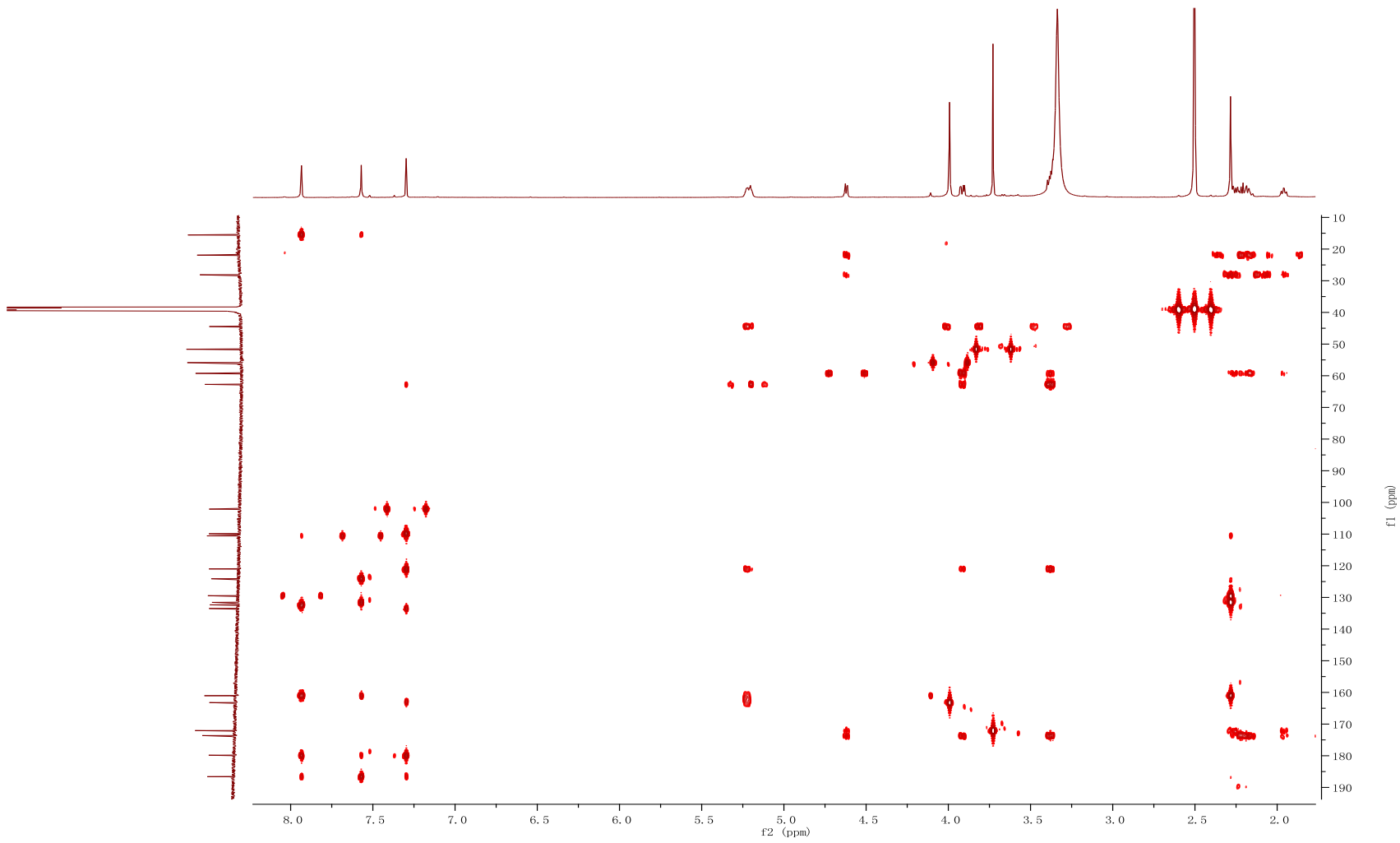

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

**Figure S25. $^{1}H$-$^{1}H$ COSY spectrum of compound 3**

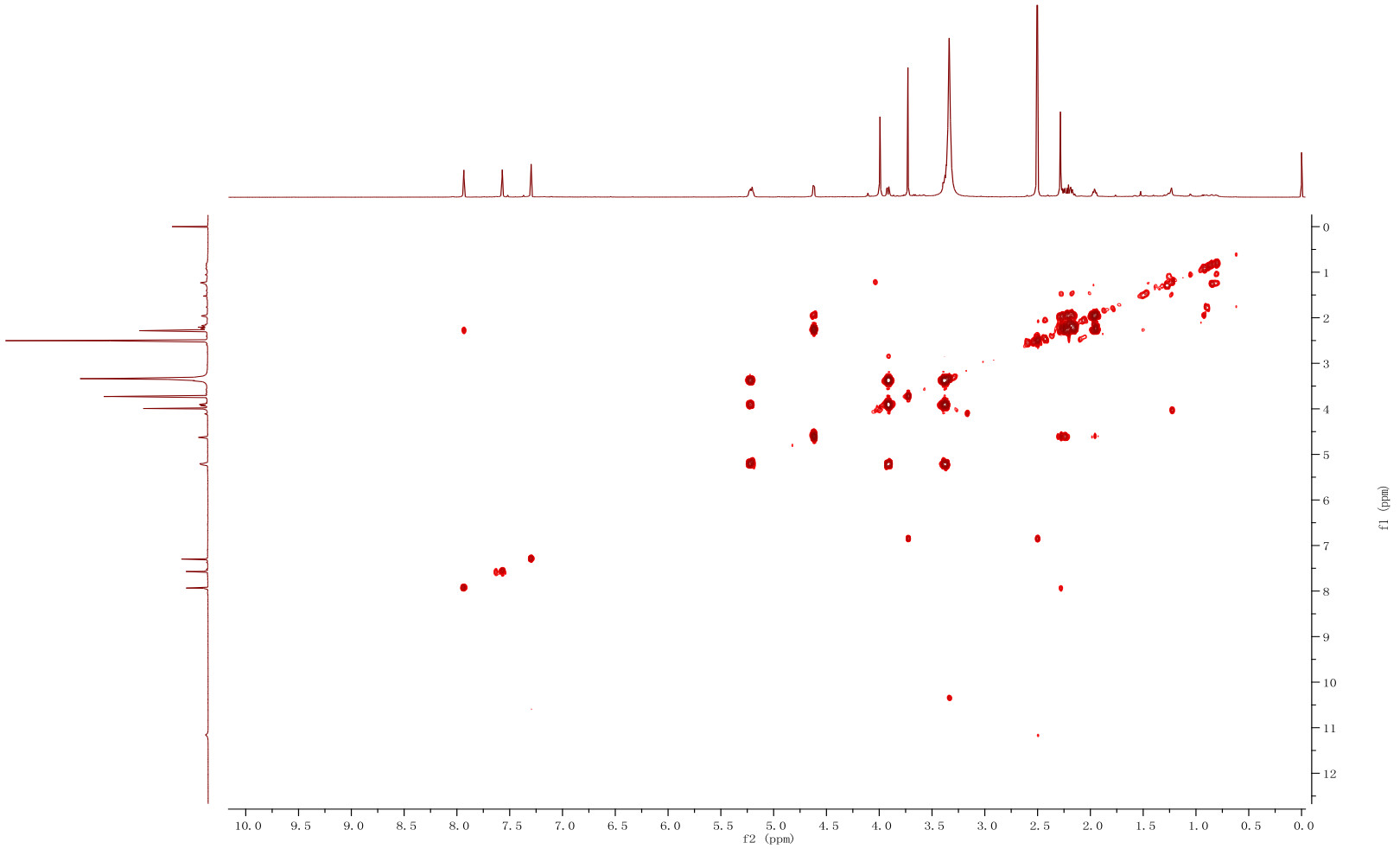


**Figure S26. NOESY spectrum of compound 3**

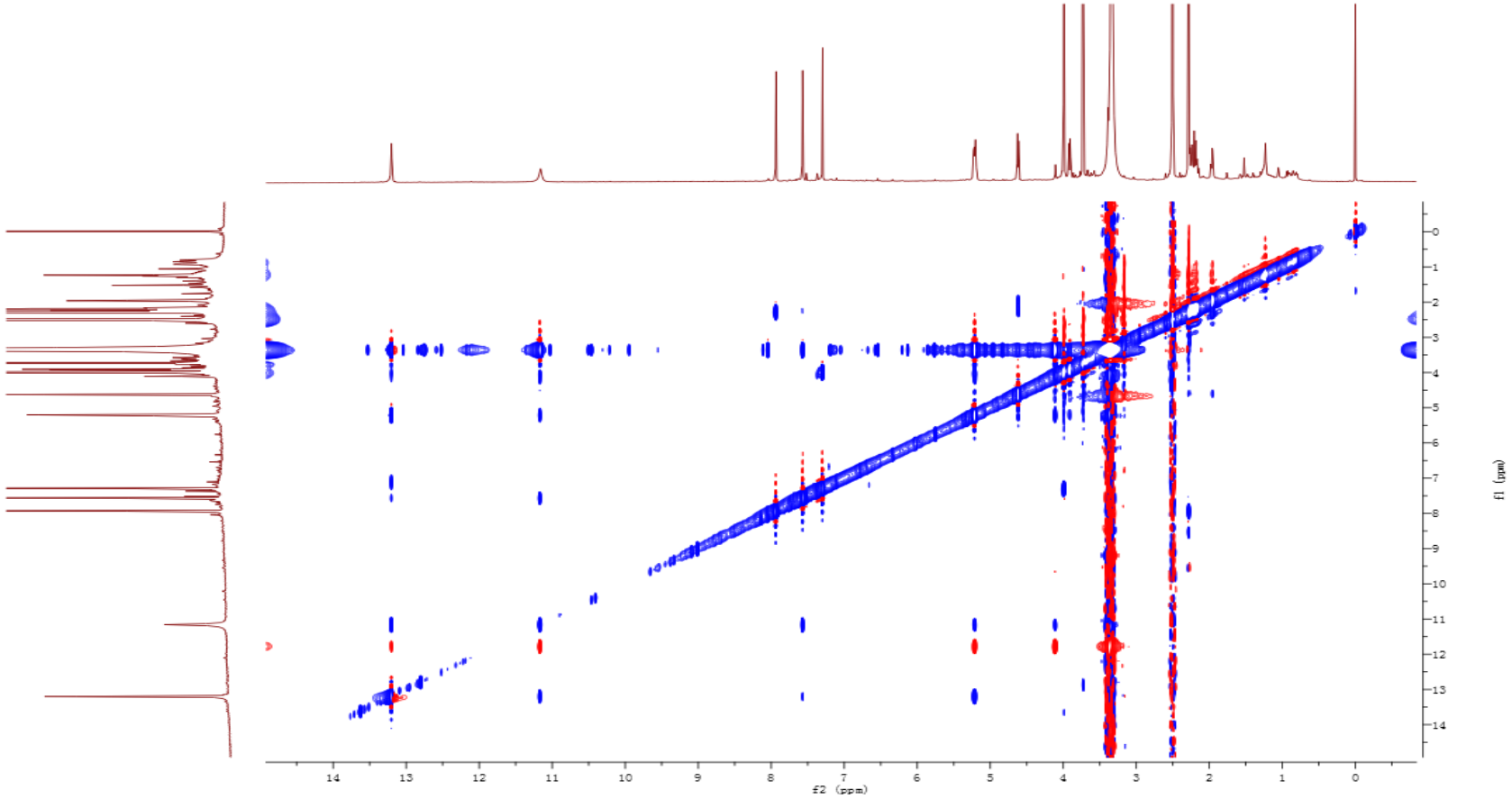


**Figure S27. HRESIMS spectrum of compound 3**

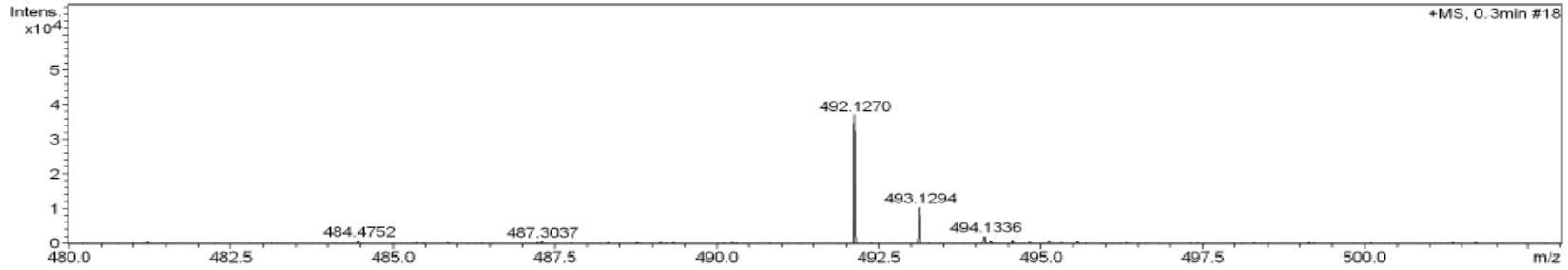
## Mass Spectrum SmartFormula Report

**Analysis Info**

| | | | |
|---|---|---|---|
| Analysis Name | D:\Data\MS\data\201801\pandongyan_PDY-DP-33-1_pos_43_01_4190.d | Acquisition Date | 1/23/2018 2:48:39 PM |
| Method | LC_Direct Infusion_pos_70-500mz.m | Operator | SCSIO |
| Sample Name | pandongyan_PDY-DP-33-1_pos | Instrument | maXis 255552.00029 |
| Comment | | | |

**Acquisition Parameter**

| | | | | | |
|---|---|---|---|---|---|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 0.4 Bar |
| Focus | Active | Set Capillary | 4500 V | Set Dry Heater | 180 °C |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 4.0 l/min |
| Scan End | 1500 m/z | Set Charging Voltage | 0 V | Set Divert Valve | Waste |
| | | Set Corona | 0 nA | Set APCI Heater | 0 °C |




| Meas. m/z | # | Ion Formula | Score | m/z | err [ppm] | err [mDa] | mSigma | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 492.1270 | 1 | C24H23NNaO9 | 100.00 | 492.1265 | -1.1 | -0.5 | 13.8 | 13.5 | even | ok |
| 961.2650 | 1 | C48H46N2NaO18 | 100.00 | 961.2638 | -1.3 | -1.3 | 69.6 | 26.5 | even | ok |

**Figure S28. IR spectrum of compound 3**

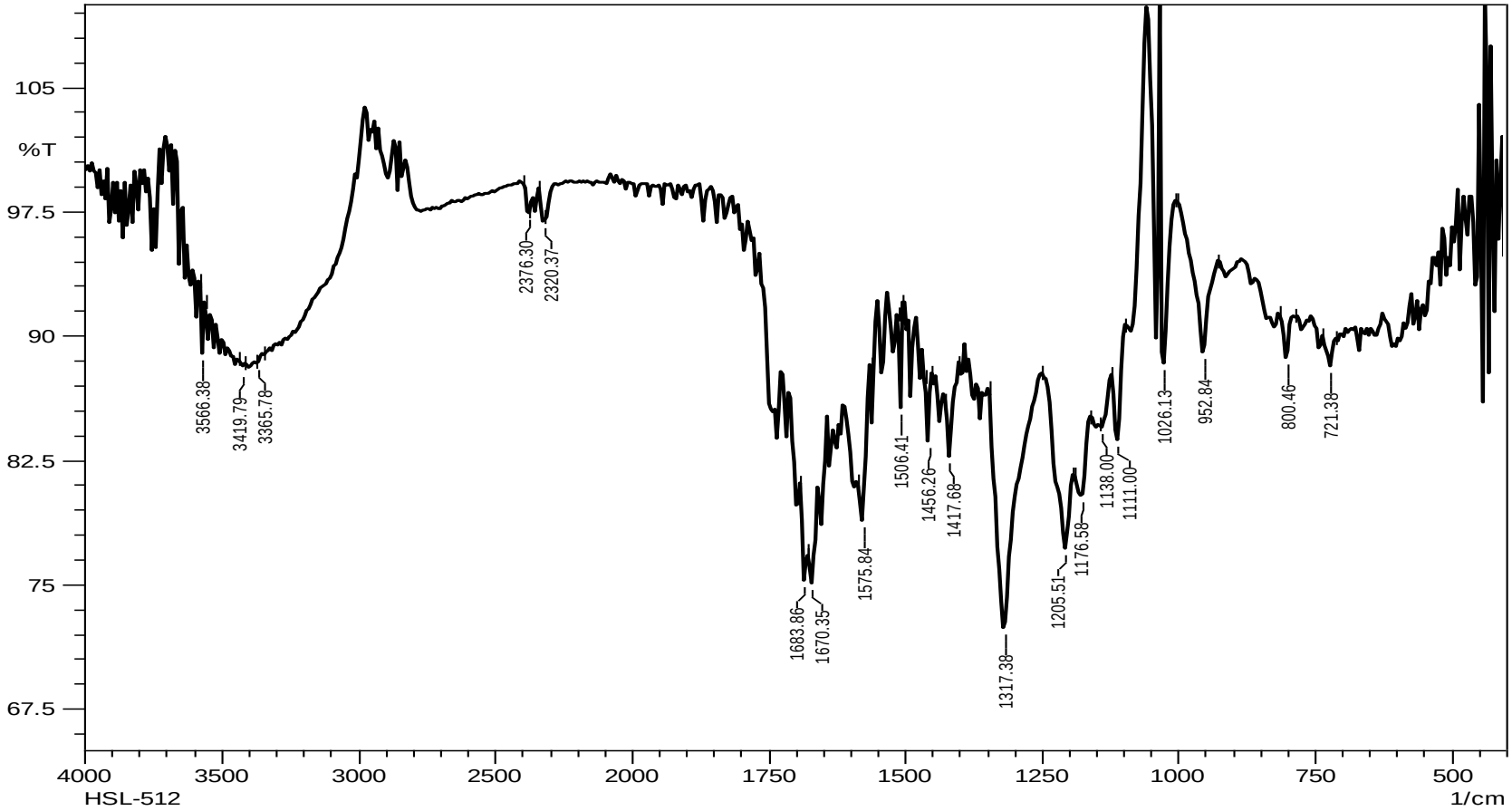
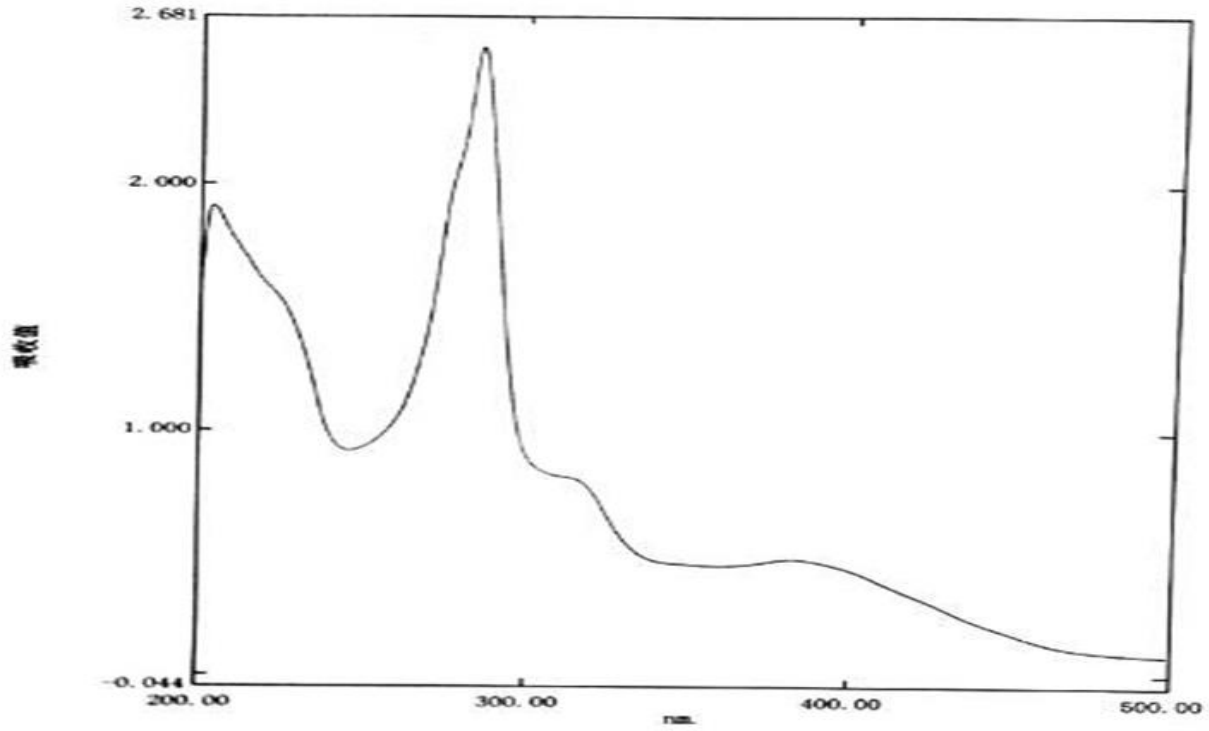


**Figure S29.** UV spectrum of compound **3**




| No. | P/V | 波长(nm) | 吸收值 | 描述 |
|---|---|---|---|---|
| 1 | | 382. 40 | 0. 479 | |
| 2 | | 285. 80 | 2. 557 | |
| 3 | | 203. 40 | 1. 909 | |

**Figure S30.** Stimulation of calcium signaling in HEK293 cells by compound **1**

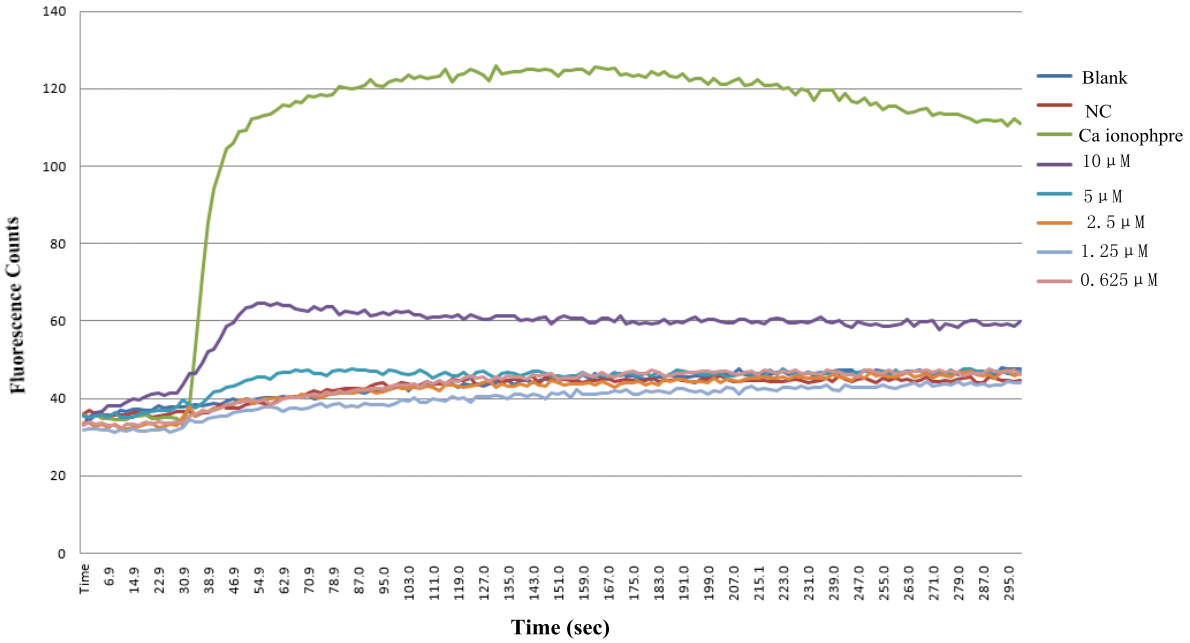
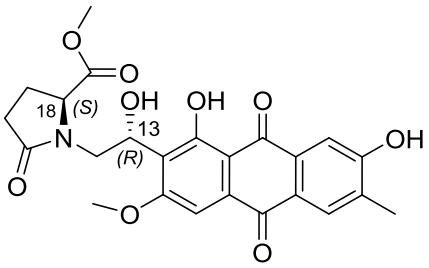
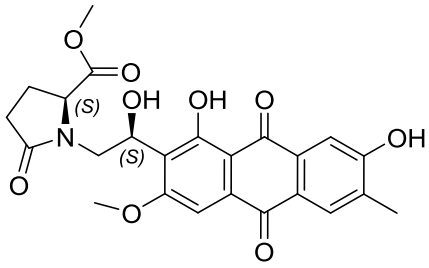


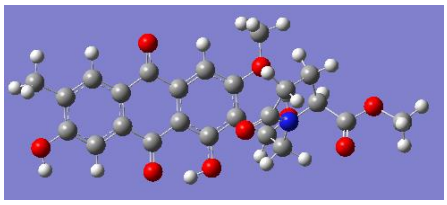
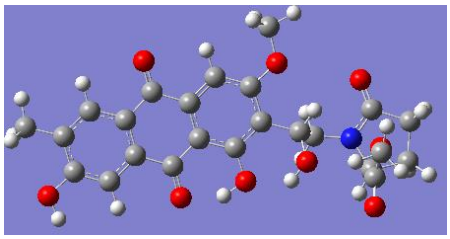
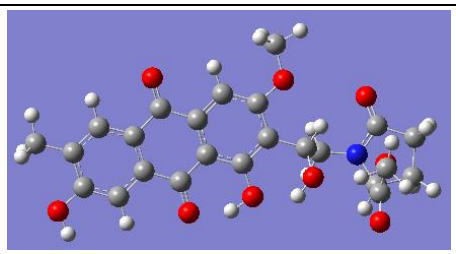
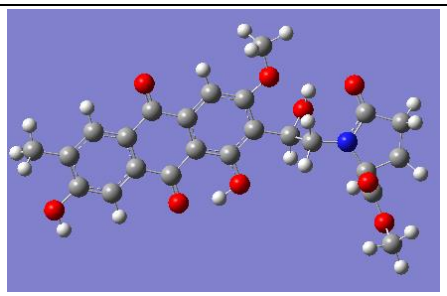
**Table S1.** Stable conformers of compounds **2** and **3** used for ECD calculation

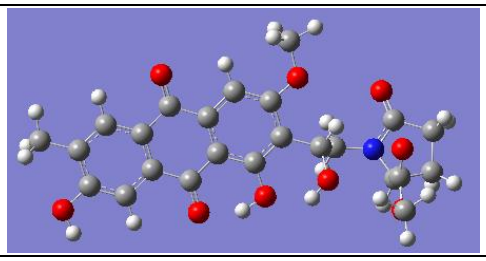
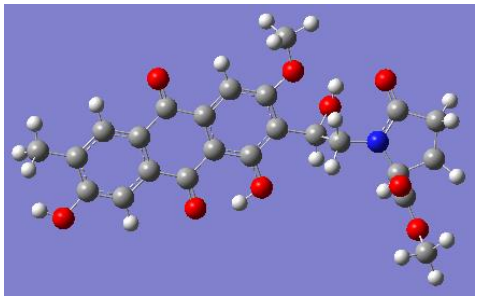
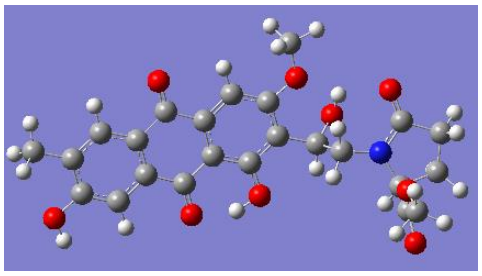
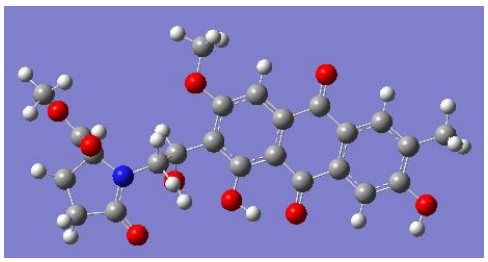
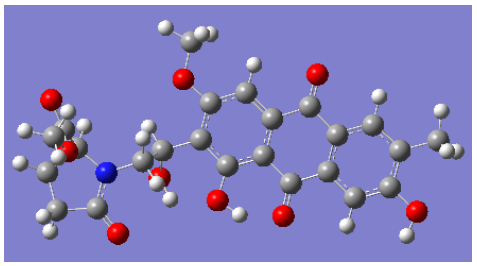
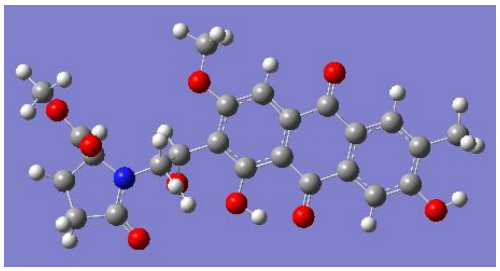


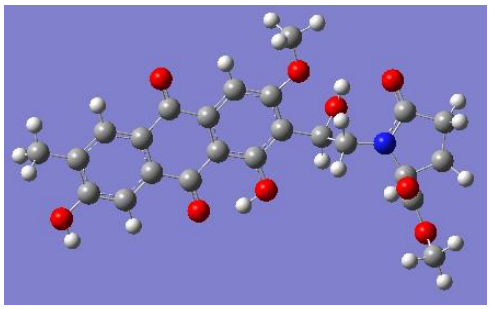
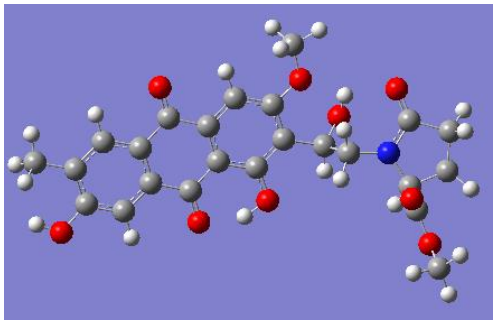
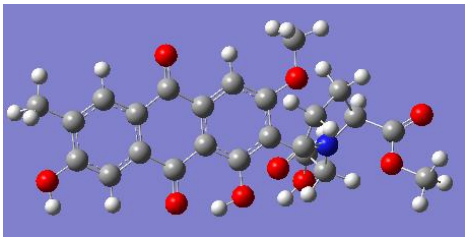
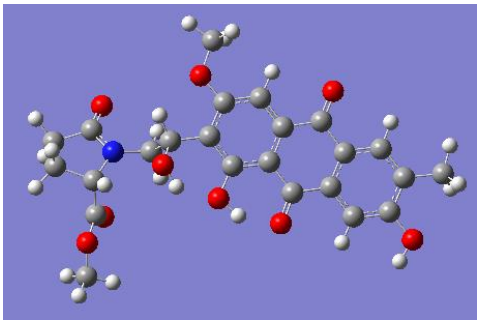
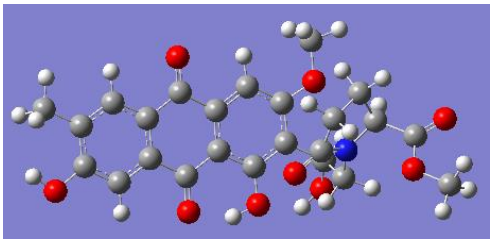

13*R*,18*S*- **2**




13*S*,18*S*-**3**

| **Conformer** | **Conformation** | **Energy（Kcal/mol）** | **Percent (%)** |
|---|---|---|---|
| (13*R*,18*S*)-**2**-1 |  | -1041599.686146 | 6.20 |
| (13*R*,18*S*)-**2**-2 |  | -1041599.444617 | 4.12 |
| (13*R*,18*S*)-**2**-3 |  | -1041599.444554 | 4.12 |
| (13*R*,18*S*)-**2**-4 |  | -1041600.177862 | 14.22 |

| | | | |
|---|---|---|---|
| (13*R*,18*S*)-**2**-5 |  | -1041599.151884 | 2.51 |
| (13*R*,18*S*)-**2**-6 |  | -1041599.535230 | 4.80 |
| (13*R*,18*S*)-**2**-7 |  | -1041599.621387 | 5.56 |
| (13*R*,18*S*)-**2**-8 |  | -1041600.425101 | 21.60 |
| (13*R*,18*S*)-**2**-9 |  | -1041600.002034 | 10.57 |
| (13*R*,18*S*)-**2**-10 |  | -1041599.777009 | 7.23 |

| | | | |
|---|---|---|---|
| (13*R*,18*S*)-**2**-11 |  | -1041600.178552 | 14.24 |
| (13*R*,18*S*)-**2**-12 |  | -1041599.535355 | 4.80 |
| **Conformer** | **Conformation** | **Energy（Kcal/mol）** | **Percent (%)** |
| (13*S*,18*S*)-**3**-1 |  | -1041600.026507 | 44.67 |
| (13*S*,18*S*)-**3**-2 |  | -1041598.761071 | 5.27 |
| (13*S*,18*S*)-**3**-3 |  | -1041599.355448 | 14.38 |

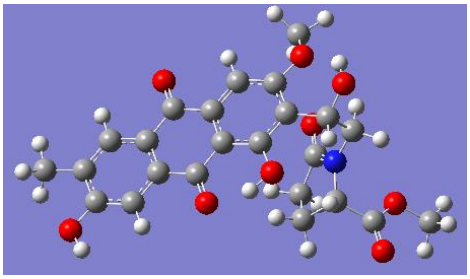
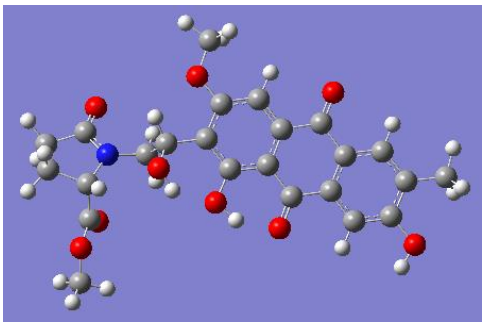
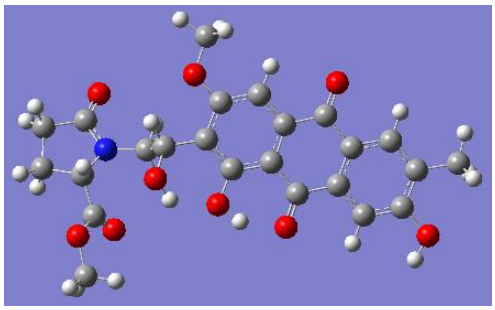
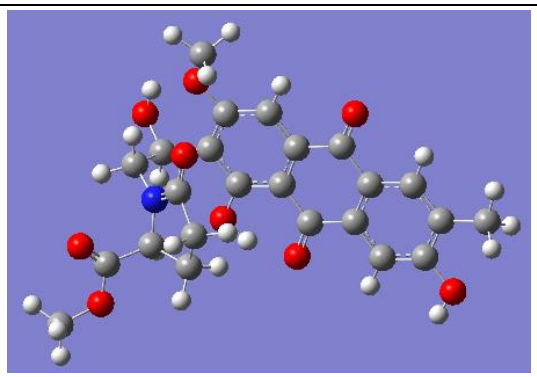
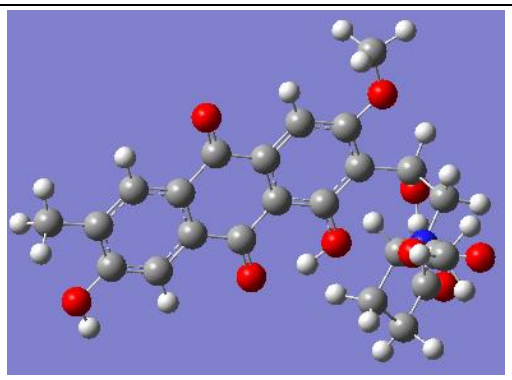
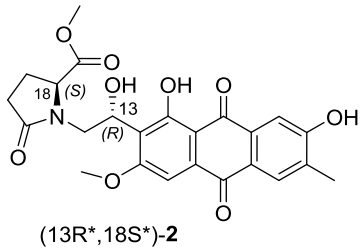
| | | | |
|---|---|---|---|
| (13*S*,18*S*)-**3**-4 |  | -1041598.363795 | 2.69 |
| (13*S*,18*S*)-**3**-5 |  | -1041598.761699 | 5.27 |
| (13*S*,18*S*)-**3**-6 |  | -1041598.583737 | 3.91 |
| (13*S*,18*S*)-**3**-7 |  | -1041598.952211 | 7.28 |
| (13*S*,18*S*)-**3**-8 |  | -1041599.403578 | 15.60 |

**Table S2.** Stable conformers of (13*R**,18*S**)-**2** and their calculated $^{13}$C NMR data used for the $^{13}$C NMR calculation of (13*R**,18*S**)-**2**

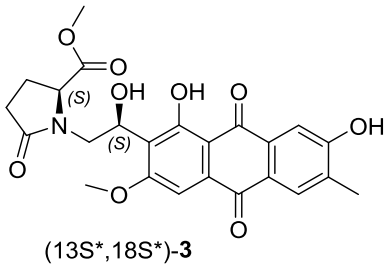


(13R*,18S*)-**2**

| conformer | E(au) | ϕE(au) | kcal/mol | ΔG(kcal/mol) | Pi | bolzt |
|---|---|---|---|---|---|---|
| q4_9 | -1660.2789392 | -1660.278939 | -1041840.640970 | -0.790913 | 3.802980 | 0.227284 |
| q4_12 | -1660.2785333 | -1660.278533 | -1041840.386264 | -0.536207 | 2.473435 | 0.147824 |
| q4_13 | -1660.2785332 | -1660.278533 | -1041840.386201 | -0.536144 | 2.473173 | 0.147809 |
| q4_18 | -1660.2776838 | -1660.277684 | -1041839.853195 | -0.003138 | 1.005313 | 0.060082 |
| q4_21 | -1660.2788318 | -1660.278832 | -1041840.573576 | -0.723518 | 3.393838 | 0.202832 |
| q4_22 | -1660.2765457 | -1660.276546 | -1041839.139026 | 0.711031 | 0.300932 | 0.017985 |
| q4_25 | -1660.2766060 | -1660.276606 | -1041839.176865 | 0.673192 | 0.320791 | 0.019172 |
| q4_28 | -1660.2776788 | -1660.277679 | -1041839.850057 | 0.000000 | 1.000000 | 0.059765 |
| q4_30 | -1660.2766956 | -1660.276696 | -1041839.233090 | 0.616967 | 0.352747 | 0.021082 |
| q4_37 | -1660.2765510 | -1660.276551 | -1041839.142352 | 0.707705 | 0.302627 | 0.018086 |
| q4_40 | -1660.2776839 | -1660.277684 | -1041839.853257 | -0.003200 | 1.005420 | 0.060089 |
| q4_47 | -1660.2765459 | -1660.276546 | -1041839.139152 | 0.710905 | 0.300996 | 0.017989 |
| | | | | | 16.732251 | |

| conformer | q4_9 | q4_12 | q4_13 | q4_18 | q4_21 | q4_22 | q4_25 | q4_28 | q4_30 | q4_37 | q4_40 | q4_47 | bolzt |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | δC | δC | δC | δC | δC | δC | δC | δC | δC | δC | δC | δC | |
| 1 | 168.4 | 169.25 | 169.25 | 167.58 | 169.3 | 167.65 | 167.56 | 169.97 | 169.91 | 170.03 | 167.58 | 167.65 | 168.85 |
| 2 | 127.64 | 126.63 | 126.63 | 128.53 | 126.66 | 128.59 | 128.45 | 127.7 | 127.46 | 127.73 | 128.53 | 128.58 | 127.30 |
| 3 | 171.26 | 168.59 | 168.59 | 171.57 | 168.59 | 171.54 | 171.53 | 168.73 | 168.74 | 168.7 | 171.57 | 171.54 | 169.73 |
| 4 | 107.59 | 107.57 | 107.57 | 107.55 | 107.6 | 107.48 | 107.5 | 107.3 | 107.27 | 107.23 | 107.55 | 107.48 | 107.54 |
| 4a | 138.3 | 138.84 | 138.84 | 138.88 | 138.83 | 138.89 | 138.93 | 138.75 | 138.8 | 138.77 | 138.88 | 138.89 | 138.72 |
| 5 | 137.11 | 137.22 | 137.22 | 137.05 | 137.2 | 137.32 | 137.06 | 137.15 | 137.16 | 137.43 | 137.05 | 137.32 | 137.17 |
| 6 | 139.36 | 139.57 | 139.57 | 139.17 | 139.56 | 135.35 | 139.19 | 139.37 | 139.41 | 135.59 | 139.17 | 135.35 | 139.23 |
| 7 | 167.33 | 167.32 | 167.32 | 167.26 | 167.31 | 167.72 | 167.28 | 167.32 | 167.32 | 167.76 | 167.26 | 167.72 | 167.33 |
| 8 | 115.94 | 115.91 | 115.91 | 115.85 | 115.92 | 117.53 | 115.86 | 115.86 | 115.87 | 117.59 | 115.85 | 117.53 | 116.00 |
| 8a | 138.55 | 138.35 | 138.35 | 138.58 | 138.36 | 139.28 | 138.56 | 138.49 | 138.47 | 139.2 | 138.58 | 139.28 | 138.49 |
| 9 | 192.86 | 193.19 | 193.19 | 192.7 | 193.25 | 192.79 | 192.68 | 192.97 | 193.02 | 193.07 | 192.7 | 192.79 | 193.03 |
| 9a | 114.14 | 114.01 | 114.01 | 113.76 | 114.02 | 113.92 | 113.79 | 114.16 | 114.17 | 114.31 | 113.76 | 113.92 | 114.02 |
| 10 | 186.53 | 186.51 | 186.51 | 186.67 | 186.5 | 186.57 | 186.66 | 186.62 | 186.61 | 186.53 | 186.67 | 186.57 | 186.55 |
| 10a | 130.25 | 130.2 | 130.2 | 130.23 | 130.27 | 129.89 | 130.21 | 130.23 | 130.24 | 129.88 | 130.23 | 129.89 | 130.21 |
| 11 | 20.08 | 20.11 | 20.11 | 20.05 | 20.12 | 17.12 | 20.05 | 20.09 | 20.09 | 17.12 | 20.05 | 17.12 | 19.93 |
| 12 | 57.56 | 57.74 | 57.74 | 56.99 | 57.76 | 56.98 | 56.99 | 57.63 | 57.68 | 57.61 | 56.99 | 56.98 | 57.56 |
| 13 | 76.62 | 72.83 | 72.83 | 68.95 | 72.29 | 68.95 | 69.05 | 68.83 | 68.7 | 68.77 | 68.95 | 68.95 | 72.50 |
| 14 | 50.29 | 50.47 | 50.47 | 47.37 | 49.46 | 47.36 | 47.55 | 47.2 | 47.35 | 47.18 | 47.37 | 47.36 | 49.36 |
| 15 | 180.16 | 181.14 | 181.14 | 184.49 | 180.73 | 184.44 | 184.63 | 182.06 | 182.02 | 181.96 | 184.48 | 184.44 | 181.51 |
| 16 | 32.33 | 33.6 | 33.6 | 33.17 | 33.05 | 33.18 | 33.4 | 33.19 | 33.39 | 33.2 | 33.17 | 33.18 | 33.09 |
| 17 | 28.76 | 29.53 | 29.53 | 29.32 | 29.72 | 29.31 | 30.09 | 28.91 | 28.87 | 28.89 | 29.32 | 29.31 | 29.31 |
| 18 | 65.12 | 67.76 | 67.76 | 63.13 | 65.34 | 63.1 | 64.53 | 61.59 | 63.24 | 61.52 | 63.13 | 63.1 | 65.31 |
| 19 | 183.29 | 181.84 | 181.84 | 182.98 | 184.03 | 182.98 | 182.79 | 182.97 | 182.91 | 182.97 | 182.98 | 182.98 | 182.92 |
| 20 | 55.27 | 54.57 | 54.57 | 55.34 | 54.72 | 55.34 | 55.4 | 55.23 | 55.28 | 55.22 | 55.34 | 55.34 | 54.96 |

**Table S3.** Stable conformers of (13*S**,18*S**)-**3** and their calculated $^{13}$C NMR data used for the $^{13}$C NMR calculation of (13*S**,18*S**)-**3**

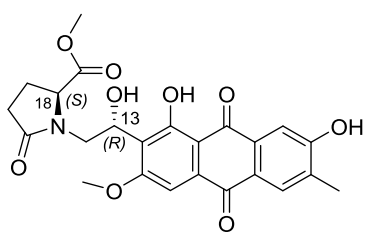


(13S*,18S*)-**3**

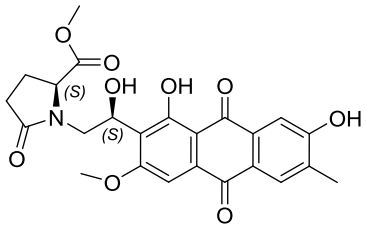
| A | B | C | D | E | F |
|---|---|---|---|---|---|
| Conformer | E(au) | kcal/mol | ΔG(kcal/mol) | Pi | bolzt |
| q3_4 | -1660.2793176 | -1041840.878420 | 0.000000 | 1.000000 | 0.324209 |
| q3_5 | -1660.2760190 | -1041838.808517 | 2.069903 | 0.030322 | 0.009831 |
| q3_10 | -1660.2779329 | -1041840.009507 | 0.868912 | 0.230497 | 0.074729 |
| q3_14 | -1660.2781742 | -1041840.160925 | 0.717494 | 0.297665 | 0.096506 |
| q3_17 | -1660.2778349 | -1041839.948011 | 0.930408 | 0.207758 | 0.067357 |
| q3_20 | -1660.2760190 | -1041838.808517 | 2.069903 | 0.030322 | 0.009831 |
| q3_23 | -1660.2767474 | -1041839.265595 | 1.612825 | 0.065617 | 0.021274 |
| q3_24 | -1660.2768145 | -1041839.307701 | 1.570719 | 0.070453 | 0.022841 |
| q3_28 | -1660.2765164 | -1041839.120640 | 1.757779 | 0.051368 | 0.016654 |
| q3_33 | -1660.2788216 | -1041840.567175 | 0.311245 | 0.591162 | 0.191660 |
| q3_49 | -1660.2786809 | -1041840.478884 | 0.399535 | 0.509268 | 0.165109 |
| | | | | 3.084430 | |

| A | B | C | D | E | F | G | H | I | J | K | L |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Conformer | q3_4 | q3_10 | q3_14 | q3_17 | q3_20 | q3_23 | q3_24 | q3_28 | q3_33 | q3_49 | bolzt |
| no. | δC | δC | δC | δC | δC | δC | δC | δC | δC | δC | |
| 1 | 170.66 | 167.03 | 170.72 | 168.28 | 169.35 | 168.37 | 167.1 | 169.22 | 168.32 | 170.71 | 167.95 |
| 2 | 127.68 | 130.45 | 127.76 | 129.09 | 126.49 | 129.19 | 130.53 | 126.5 | 129.21 | 129.41 | 127.38 |
| 3 | 169.64 | 172.19 | 169.62 | 174.59 | 168.57 | 174.6 | 172.17 | 168.47 | 174.69 | 168.83 | 169.46 |
| 4 | 106.98 | 107.83 | 106.92 | 110.42 | 107.63 | 110.39 | 107.77 | 107.58 | 110.52 | 107.47 | 107.08 |
| 4a | 138.58 | 138.29 | 138.59 | 138.7 | 138.85 | 138.72 | 138.31 | 138.8 | 138.63 | 138.83 | 137.26 |
| 5 | 137.16 | 137.01 | 137.44 | 137.13 | 137.19 | 137.4 | 137.27 | 137.2 | 137.13 | 137.05 | 135.81 |
| 6 | 139.38 | 139.1 | 135.59 | 139.49 | 139.57 | 135.63 | 135.34 | 139.58 | 139.5 | 139.32 | 137.48 |
| 7 | 167.3 | 167.23 | 167.76 | 167.23 | 167.3 | 167.7 | 167.67 | 167.3 | 167.24 | 167.31 | 165.70 |
| 8 | 115.86 | 115.83 | 117.58 | 115.89 | 115.92 | 117.65 | 117.51 | 115.94 | 115.91 | 115.92 | 114.98 |
| 8a | 138.46 | 138.62 | 139.15 | 138.43 | 138.34 | 139.13 | 139.32 | 138.45 | 138.4 | 138.67 | 137.23 |
| 9 | 193.11 | 192.7 | 193.21 | 193.63 | 193.26 | 193.73 | 192.8 | 193.19 | 193.65 | 193.75 | 191.44 |
| 9a | 114.07 | 113.82 | 114.22 | 113.46 | 114.04 | 113.61 | 113.98 | 114.04 | 113.4 | 114.7 | 112.87 |
| 10 | 186.66 | 186.67 | 186.56 | 186.5 | 186.5 | 186.4 | 186.58 | 186.52 | 186.5 | 186.58 | 184.75 |
| 10a | 130.26 | 130.31 | 129.92 | 130.39 | 130.24 | 130.03 | 129.97 | 130.27 | 130.38 | 130.23 | 128.97 |
| 11 | 20.1 | 20.05 | 17.14 | 20.11 | 20.11 | 17.17 | 17.12 | 20.07 | 20.11 | 20.09 | 19.48 |
| 12 | 57.64 | 57.33 | 57.62 | 59.59 | 57.8 | 59.59 | 57.32 | 57.75 | 59.66 | 57.61 | 57.60 |
| 13 | 69.23 | 72.37 | 69.23 | 69.1 | 75.47 | 69.13 | 72.35 | 74.12 | 69.1 | 75.38 | 69.98 |
| 14 | 47.68 | 53.83 | 47.72 | 47.75 | 47.37 | 47.77 | 53.85 | 46.26 | 47.53 | 52.54 | 48.57 |
| 15 | 180.14 | 182.21 | 180.11 | 180.65 | 180.44 | 180.67 | 182.22 | 179.08 | 180.47 | 187.4 | 179.86 |
| 16 | 32.62 | 34.66 | 32.63 | 32.71 | 32.8 | 32.72 | 34.68 | 34.63 | 32.5 | 33.28 | 32.63 |
| 17 | 29.28 | 28.5 | 29.26 | 29.69 | 28.25 | 29.62 | 28.52 | 29.26 | 28.76 | 29.81 | 28.93 |
| 18 | 64.24 | 68.55 | 64.24 | 64.51 | 64.17 | 64.56 | 68.58 | 64.19 | 63.2 | 65.57 | 64.07 |
| 19 | 182.95 | 185.95 | 182.97 | 182.92 | 183.55 | 182.9 | 185.96 | 183.56 | 182.9 | 182.43 | 181.36 |
| 20 | 55.3 | 55.25 | 55.3 | 55.33 | 55.17 | 55.32 | 55.25 | 54.88 | 55.21 | 55.14 | 54.70 |

**Table S4**. DP4$^{+}$ analysis result table for compound **2** (experimental for **2**, isomer 1 for (13S*,18S*)-**3**, isomer 2 for (13R*,18S*)-**2**)



(13R*,18S*)-**2** isomer 2



(13S*,18S*)-**3** isomer 1

| Functional | Solvent? | Basis Set | Type of Data |
|---|---|---|---|
| mPW1PW91 | PCM | 6-311G(d,p) | Unscaled Shifts |

| | | DP4+ | 0.00% | 100.00% | – | – | – |
|---|---|---|---|---|---|---|---|
| Nuclei | sp2? | xperimenta | Isomer 1 | Isomer 2 | Isomer 3 | Isomer 4 | Isomer 5 |
| C | x | 162.4 | 168.0 | 168.8 | | | |
| C | x | 122.1 | 127.4 | 127.3 | | | |
| C | x | 164.3 | 169.5 | 169.7 | | | |
| C | x | 103.1 | 17.1 | 107.5 | | | |
| C | x | 134.7 | 137.3 | 138.7 | | | |
| C | x | 130.5 | 135.8 | 137.2 | | | |
| C | x | 132.7 | 137.5 | 139.2 | | | |
| C | x | 162.1 | 165.7 | 167.3 | | | |
| C | x | 111.8 | 115.0 | 116.0 | | | |
| C | x | 125 | 137.2 | 138.5 | | | |
| C | x | 187.8 | 191.4 | 193.0 | | | |
| C | x | 111.1 | 112.87 | 114.02 | | | |
| C | x | 180.9 | 184.75 | 186.55 | | | |
| C | x | 133.4 | 128.97 | 130.21 | | | |
| C | | 16.6 | 19.48 | 19.93 | | | |
| C | | 56.9 | 57.60 | 57.56 | | | |
| C | | 62.3 | 69.98 | 72.50 | | | |
| C | | 45.6 | 48.57 | 49.36 | | | |
| C | x | 175.2 | 179.86 | 181.50 | | | |
| C | | 29.3 | 32.63 | 33.09 | | | |
| C | | 23.2 | 28.93 | 29.31 | | | |
| C | | 59.7 | 64.07 | 65.31 | | | |
| C | x | 172.9 | 181.36 | 182.92 | | | |
| C | | 52.6 | 54.70 | 54.96 | | | |

| Functional | Solvent? | Basis Set | Type of Data |
|---|---|---|---|
| mPW1PW91 | PCM | 6-311G(d,p) | Unscaled Shifts |

| | Isomer 1 | Isomer 2 | Isomer 3 | Isomer 4 | Isomer 5 | Isomer 6 |
|---|---|---|---|---|---|---|
| sDP4+ (H data) | – | – | – | – | – | – |
| sDP4+ (C data) | 0.00% | 100.00% | – | – | – | – |
| sDP4+ (all data) | 0.00% | 100.00% | – | – | – | – |
| uDP4+ (H data) | – | – | – | – | – | – |
| uDP4+ (C data) | 0.00% | 100.00% | – | – | – | – |
| uDP4+ (all data) | 0.00% | 100.00% | – | – | – | – |
| DP4+ (H data) | – | – | – | – | – | – |
| DP4+ (C data) | 0.00% | 100.00% | – | – | – | – |
| DP4+ (all data) | 0.00% | 100.00% | – | – | – | – |

**Table S5**. DP4$^{+}$ analysis result table for compound **3** (experimental for **3**, isomer 1 for (13S*,18S*)-**3**, isomer 2 for (13R*,18S*)-**2**)

| Functional | Solvent? | Basis Set | Type of Data |
|---|---|---|---|
| mPW1PW91 | PCM | 6-311G(d,p) | Unscaled Shifts |

| | | DP4+ | 87.50% | 12.50% | – | – | – |
|---|---|---|---|---|---|---|---|
| Nuclei | sp2? | xperimenta | Isomer 1 | Isomer 2 | Isomer 3 | Isomer 4 | Isomer 5 |
| C | x | 161 | 168.0 | 168.8 | | | |
| C | x | 121 | 127.4 | 127.3 | | | |
| C | x | 163.2 | 169.5 | 169.7 | | | |
| C | x | 102.1 | 107.1 | 107.5 | | | |
| C | x | 133.5 | 137.3 | 138.7 | | | |
| C | x | 129.5 | 135.8 | 137.2 | | | |
| C | x | 131.6 | 137.5 | 139.2 | | | |
| C | x | 161 | 165.7 | 167.3 | | | |
| C | x | 110.6 | 115.0 | 116.0 | | | |
| C | x | 124.1 | 137.2 | 138.5 | | | |
| C | x | 186.6 | 191.4 | 193.0 | | | |
| C | x | 109.9 | 112.87 | 114.02 | | | |
| C | x | 179.8 | 184.75 | 186.55 | | | |
| C | x | 132.3 | 128.97 | 130.21 | | | |
| C | | 15.5 | 19.48 | 19.93 | | | |
| C | | 55.9 | 57.60 | 57.56 | | | |
| C | | 62.7 | 69.98 | 72.50 | | | |
| C | | 44.5 | 48.57 | 49.36 | | | |
| C | x | 173.6 | 179.86 | 181.50 | | | |
| C | | 28.1 | 32.63 | 33.09 | | | |
| C | | 21.9 | 28.93 | 29.31 | | | |
| C | | 59.2 | 64.07 | 65.31 | | | |
| C | x | 172.1 | 181.36 | 182.92 | | | |
| C | | 51.6 | 54.70 | 55.22 | | | |

| Functional | Solvent? | Basis Set | Type of Data |
|---|---|---|---|
| mPW1PW91 | PCM | 6-311G(d,p) | Unscaled Shifts |

| | Isomer 1 | Isomer 2 | Isomer 3 | Isomer 4 | Isomer 5 | Isomer 6 |
|---|---|---|---|---|---|---|
| sDP4+ (H data) | – | – | – | – | – | – |
| sDP4+ (C data) | 83.25% | 16.75% | – | – | – | – |
| sDP4+ (all data) | 83.25% | 16.75% | – | – | – | – |
| uDP4+ (H data) | – | – | – | – | – | – |
| uDP4+ (C data) | 58.47% | 41.53% | – | – | – | – |
| uDP4+ (all data) | 58.47% | 41.53% | – | – | – | – |
| DP4+ (H data) | – | – | – | – | – | – |
| DP4+ (C data) | 87.50% | 12.50% | – | – | – | – |
| DP4+ (all data) | 87.50% | 12.50% | – | – | – | – |