Asperterpenes A and B, Two Unprecedented Meroterpenoids with BACE1 Inhibitory Activities from *Aspergillus terreus*

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CONTENTS

Table S1. NMR data of compounds **1**–**3** (in $CDCl_3$, 400 MHz for ^1H and 100 MHz for ^{13}C)

no.	**1**			**2**			**3**		
	δ_H (*J* in Hz)	δ_C	DEPT	δ_H (*J* in Hz)	δ_C	DEPT	δ_H (*J* in Hz)	δ_C	DEPT
1a	1.98 m	30.6	CH_2	1.97 m	31.9	CH_2	2.14 m	40.3	CH_2
1b	1.35 m			1.48 m			1.55 m		
2a	2.64 ddd (15.8, 12.0, 6.1)	33.0		2.20 m	30.1		2.78 m	33.4	
2b	2.26 ddd (15.8, 9.8, 2.6)		CH_2			CH_2	2.24 m		CH_2
3		218.8	C		174.6	C		213.6	C
4		47.0	C		75.0	C		46.8	C
5	2.36 dd (13.2, 2.3)	44.0	CH	1.44 m	47.0	CH	2.67 s	64.1	CH
6a	1.54 m	18.8	CH_2	1.73 m	21.4	CH_2		209.1	CH_2
6b	1.34 m								
7a	1.98 m	32.2		1.90 m	31.7		4.07 d (13.2)	52.1	CH_2
7b	1.37 m		CH_2	1.24 m		CH_2	2.79 d (13.2)		
8		46.3	C		46.3	C		44.5	C
9	1.30 m	49.4	CH	2.18 m	48.7	CH	1.85 dd (13.7, 3.7)	50.7	CH
10		36.6	C		41.4	C		42.3	C
11a	2.18 t (13.7)	39.8	CH_2	2.24 m	36.9		2.50 dd (16.1, 3.5)	28.2	
11b	1.82 dd (13.7, 2.8)			1.88 m		CH_2	2.71 m		CH_2
12		49.5	C		49.3	C		142.5	C
13		163.9	C		162.2	C		57.8	C
14		131.3	C		131.9	C		72.6	C
15		198.2	C		197.4	C		210.1	C
16		67.4	C		68.7	C		74.7	C
17		210.2	C		210.7	C		210.2	C
18	1.05 s	29.3	CH_3	1.35 s	32.0	CH_3	1.15 s	24.0	CH_3
19	0.99 s	19.2	CH_3	1.35 s	35.0	CH_3	1.52 s	21.8	CH_3
20	1.34 s	25.2	CH_3	1.28 s	20.0	CH_3	1.41 s	19.8	CH_3
21	0.74 s	22.4	CH_3	1.14 s	24.7	CH_3	1.22 s	16.2	CH_3
22	1.28 s	18.6	CH_3	1.29 s	20.9	CH_3	5.12 s; 4.95 s	117.2	CH_2
23	2.02 s	17.7	CH_3	2.02 s	17.6	CH_3	1.56 s	23.2	CH_3
24	1.18 s	14.2	CH_3	1.17 s	12.6	CH_3	1.43 s	25.3	CH_3
25		166.8	C		166.9	C		168.0	C
26	3.82 s	52.5	OCH_3	3.82 s	52.4	OCH_3	3.69 s	52.9	OCH_3
27				3.66 s	51.7	OCH_3			

Table S2. Predicted binding free energies of compounds and target (MF docking scores) [a]

PDB-ID	Protein name	Compounds	
		1	2
4Y6K	PSH	-140.2	-176.5
4QO6	GlpG	-77.0	-73.8
4J36	KMO	-110.4	-51.4
2MXU	Amyloid Fibril	-138.5	-109.2
1GS9	APOE4	-57.9	-68.5
4NF5	NMDA receptor	-81.9	-85.1
4EY6	Acetylcholinesterase	-100.3	-75.2
4XXS	BACE1	-193.9	-178.8

[a] Docking score/interaction potential of compounds with targets (kcal/mol).

Table S3. Inhibitory activities of compounds **1**–**3**

Compound	Inhibitory activities against BACE1
	IC_{50} (nM)
1	78.8
2	59.1
3	n.i.[a]
LY2811376	260.2

[a] n.i. is no inhibition detected in the experiments (IC_{50} □ 40 μM).

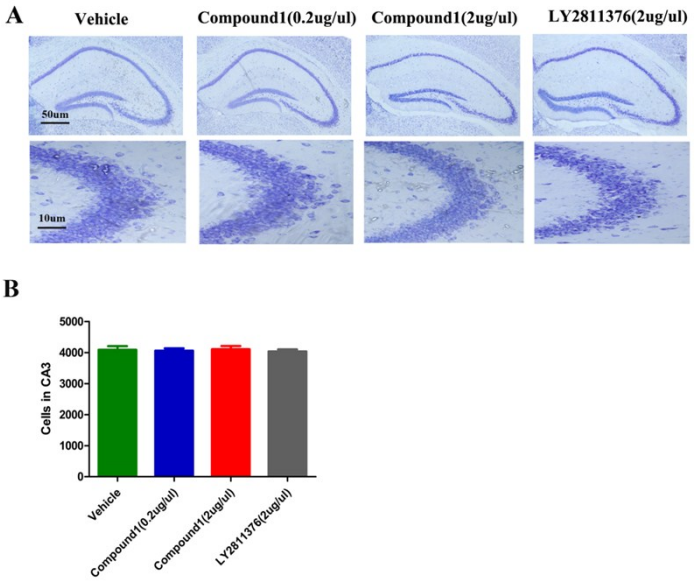


Figure S1. Nissl staining of the cells numbers in hippocampus from compound **1** (2 μg/μL×5μL，0.2 μg/μL×5μL), LY2811376 (2 μg/μL×5μL) and vehicle groups. A) Nissl staining (upper row, cells in hippocampus; lower row, cells in CA3. B) the quantification of cells in CA 3. The data were expressed as mean ± SD, (n= 3).

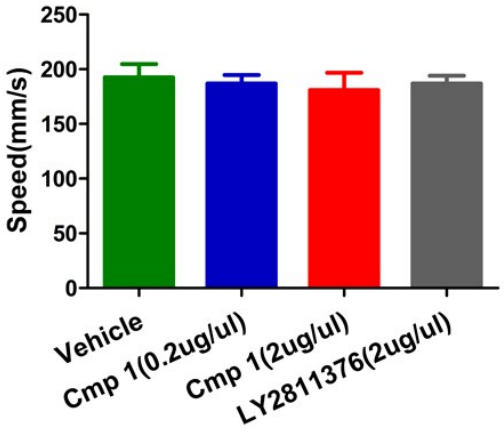


Figure S2. The effects of 1 on learning and memory in 3xTg mice. Compound **1** (2 μg/μL×5μL, 0.2 μg/μL ×5μL), LY2811376 (2 μg/μL×5μL) or vehicle was infused into the cerebroventricles of 3xTg mice 48 hours before starting the task. The speed to find the hidden platform was recorded daily. Data are presented as means ± sd (n = 7).

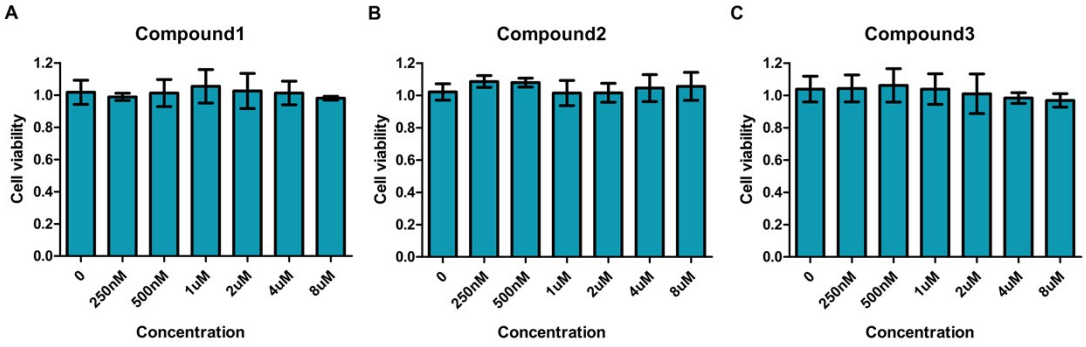


Figure S3. Cell viability was assessed through MTT assay. HEK293 cells were treated with 0, 0.25, 0.5, 1, 2, 4 and 8 μM. Data represent mean±SD. Student t-Test compared to cell treated with vehicle alone.

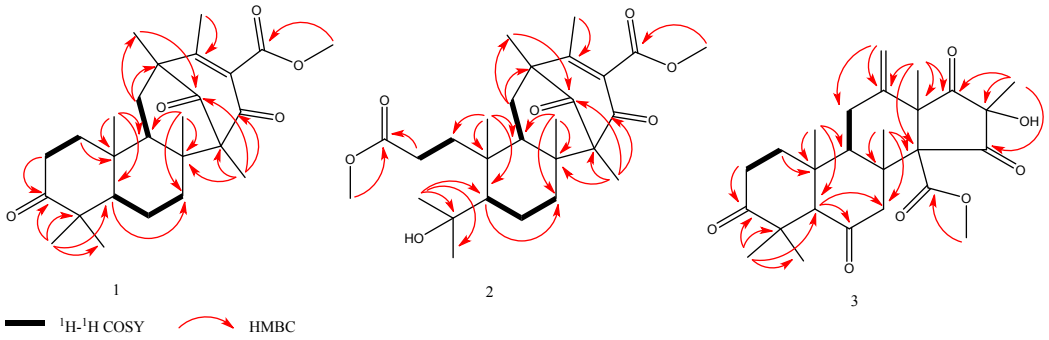
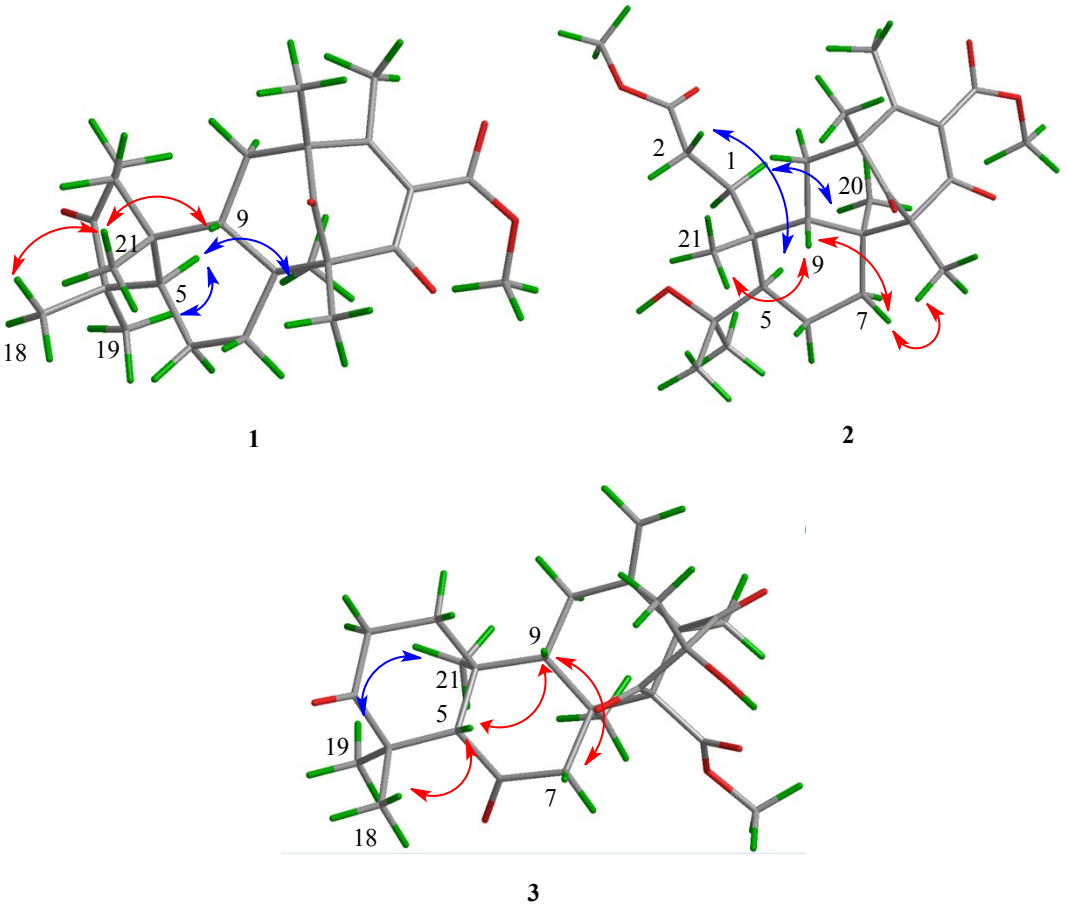


Figure S4. Key HMBC correlations of **1-3**.



1 **2** **3**

Figure S5. Key NOESY correlations of **1**-**3**.

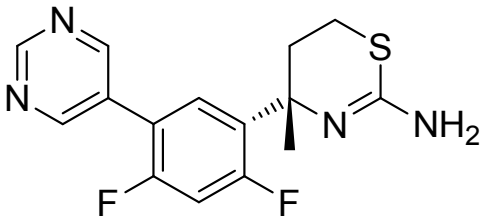
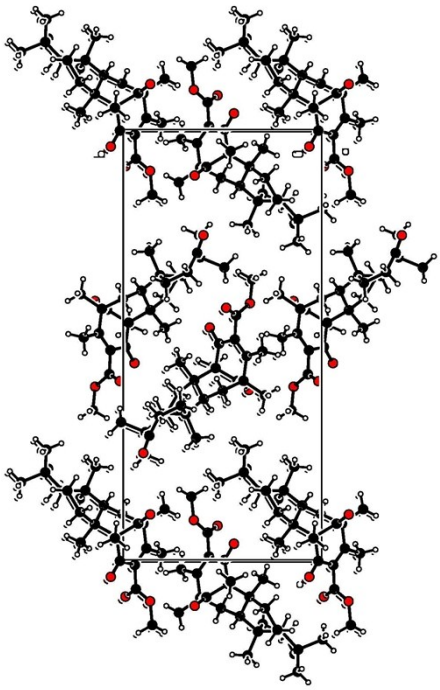


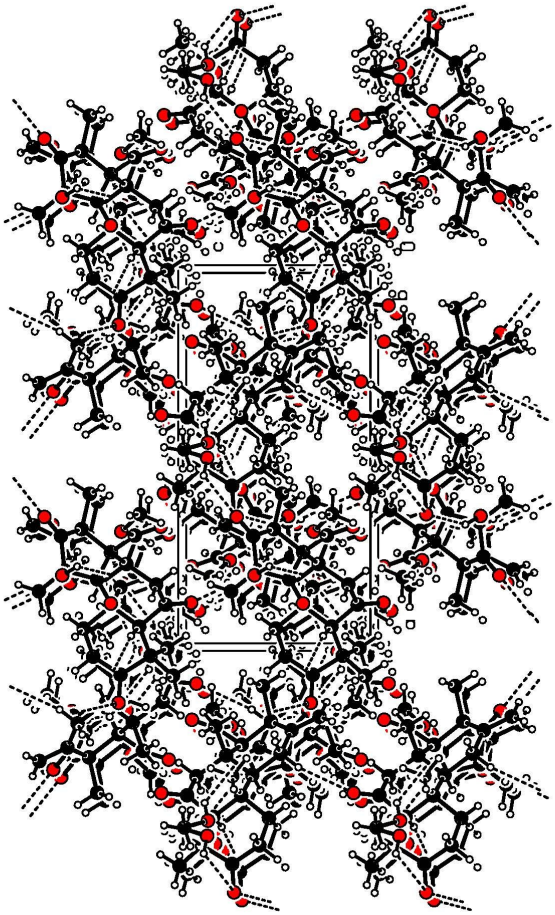
Figure S6. The structure of LY2811376.

Crystal data for compound 1: $C_{26}H_{36}O_5$, M = 428.55, orthorhombic, a = 7.9305(2) Å, b = 11.6311(3) Å, c = 25.2575(5) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 2329.76(10) Å^3, T = 296(2) K, space group $P212121$, Z = 4, μ(CuKα) = 0.666 mm^{-1}, 9987 reflections measured, 3701 independent reflections (R_{int} = 0.0304). The final R_1 values were 0.0354 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1015 ($I > 2\sigma(I)$). The final R_1 values were 0.0358 (all data). The final $wR(F^2)$ values were 0.1021 (all data). The goodness of fit on F^2 was 1.080. Flack parameter = 0.0(2). The Hooft parameter is -0.02(7) for 1531 Bijvoet pairs. (CCDC 1416500)



View of the hydrogen-bonded motif of **1** (hydrogen-bonds are shown as dashed lines)

Crystal data for compound 3: $C_{26}H_{36}O_7$, M = 474.55, orthorhombic, a =15.9092(4) Å, b = 18.9397(5) Å, c = 8.0829(2) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 2435.50(11) Å^3, T = 298(2) K, space group $P2(1)2(1)2$, Z = 4, μ(CuKα) = 0.770 mm^{-1}, 13869 reflections measured, 3931 independent reflections ([R(int) = 0.0479]). The final R_1 values were 0.0407 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1136 ($I > 2\sigma(I)$). The final R_1 values were 0.0411 (all data). The final $wR(F^2)$ values were 0.1140 (all data). The goodness of fit on F^2 was 1.046. Flack parameter = 0.14(18). The Hooft parameter is 0.0119(8) for 1939 Bijvoet pairs. （CCDC 1416501）



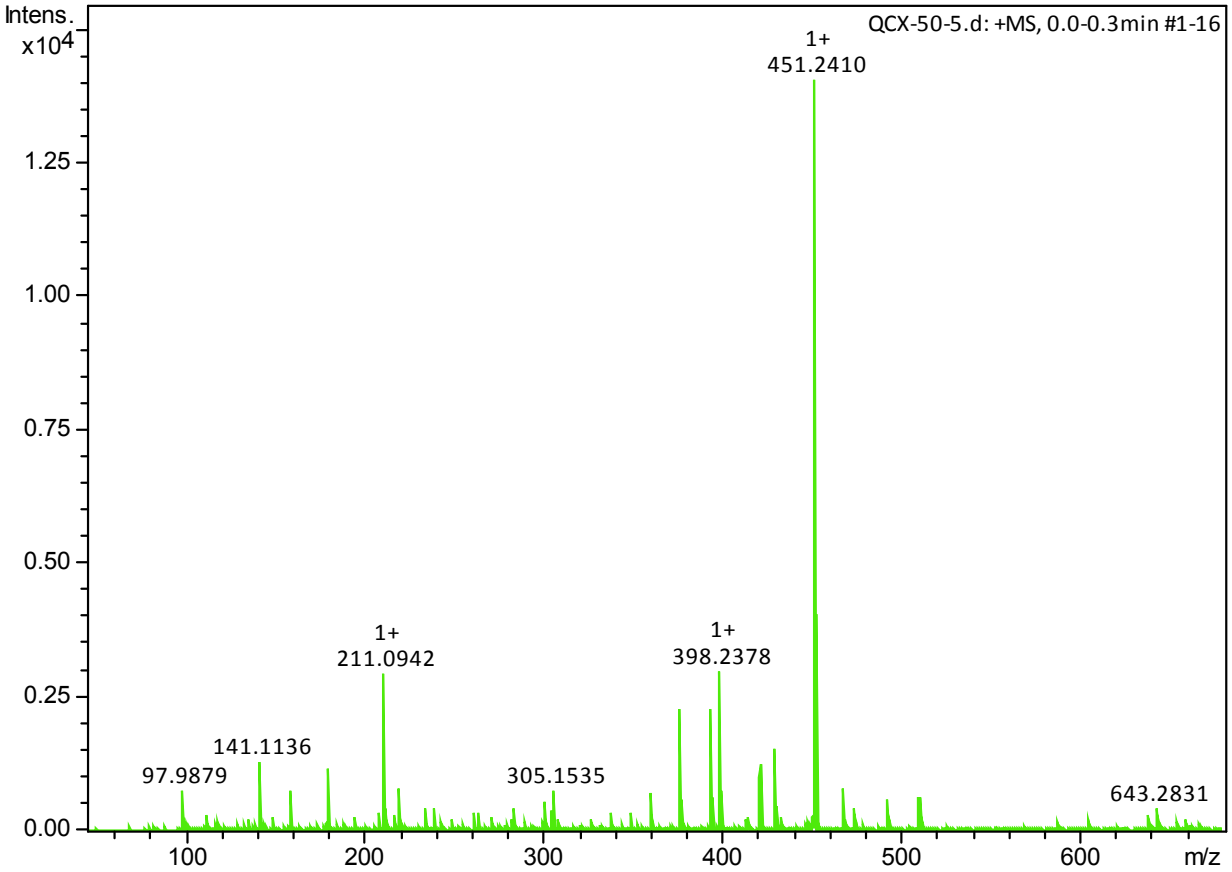
View of the hydrogen-bonded motif of **3** (hydrogen-bonds are shown as dashed lines)

Compound 1: Colorless crystals, $[\alpha]$ +47.7 (c = 0.9, MeOH); UV (MeOH) λ_{max} (log ε) = 249 (3.99) and 202 (3.74) nm; for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data see Tables S1; HRESIMS $[M + Na]^+$ *m/z* 451.2410 (calcd for $C_{26}H_{36}O_5Na$, 451.2460).

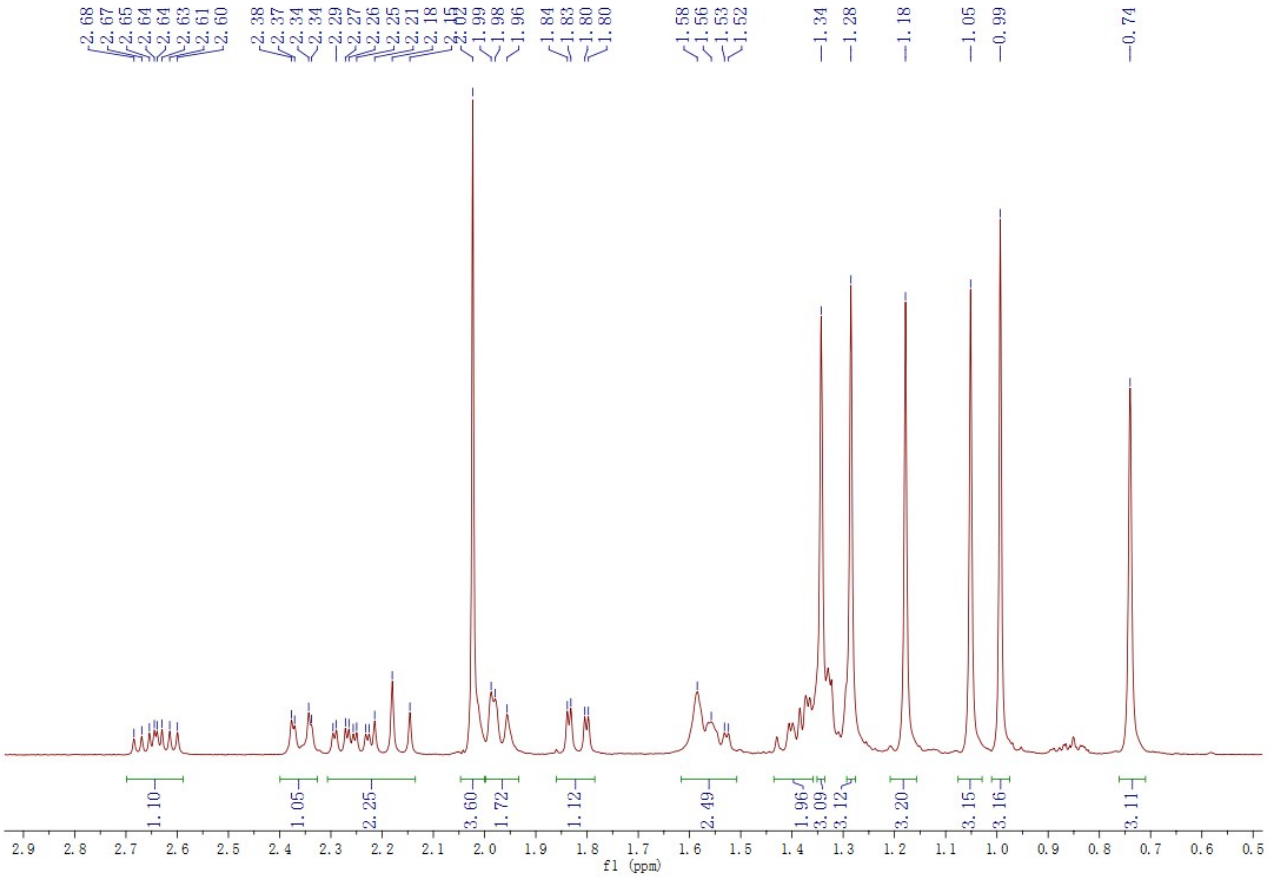
Compound 2: Optically active white gum, $[\alpha]$ +44.2 (c = 1.5, MeOH); UV (MeOH) λ_{max} (log ε) = 253 (3.12) and 209 (3.31) nm; for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data see Tables S1; HRESIMS $[M + Na]^+$ *m/z* 499.2637 (calcd for $C_{26}H_{36}O_5Na$, 499.2672).

Compound 3: Colorless crystals, $[\alpha]$ -84.5 (c = 2, MeOH); UV (MeOH) λ_{max} (log ε) = 231 (3.28) and 202 (3.81) nm; for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data see Tables S1; HRESIMS $[M + Na]^+$ *m/z* 481.2199 (calcd for $C_{26}H_{34}O_7Na$, 881.2202).

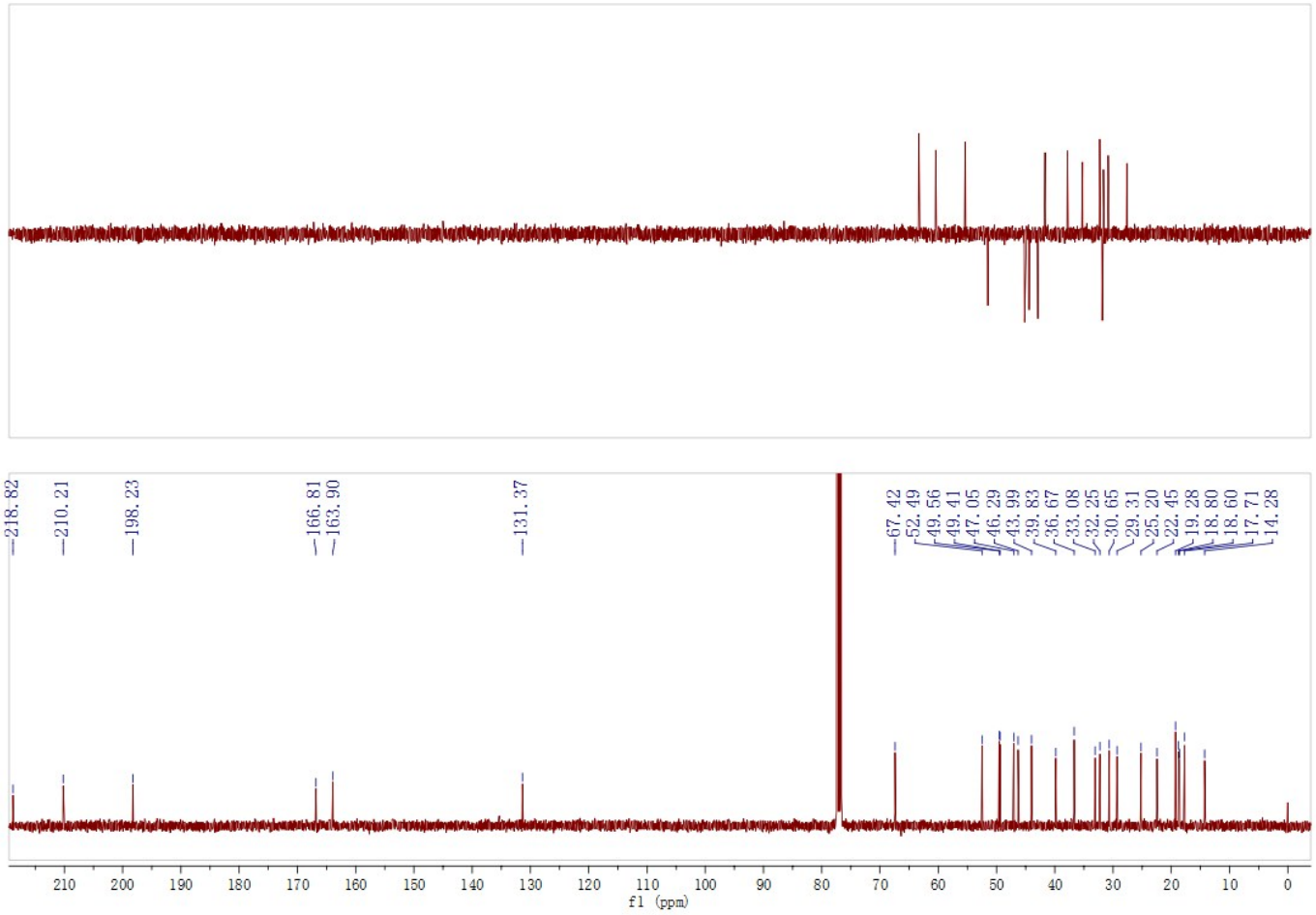
HRESIMS of compound **1**



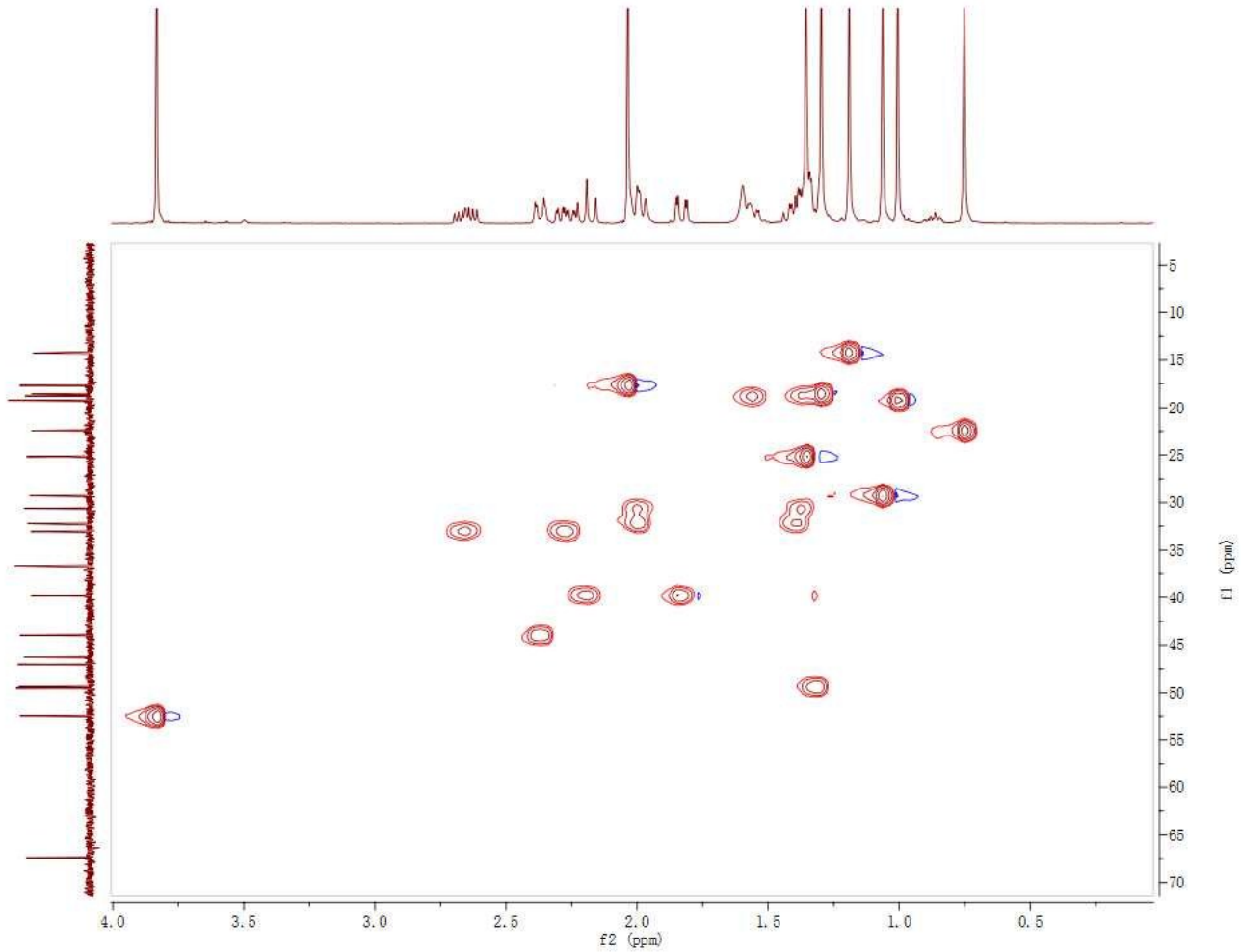
^{1}H NMR of compound **1** (in $CHCl_3$)



^{13}C NMR of compound **1** (in $CHCl_3$)



HSQC of compound **1** (in $CHCl_3$)



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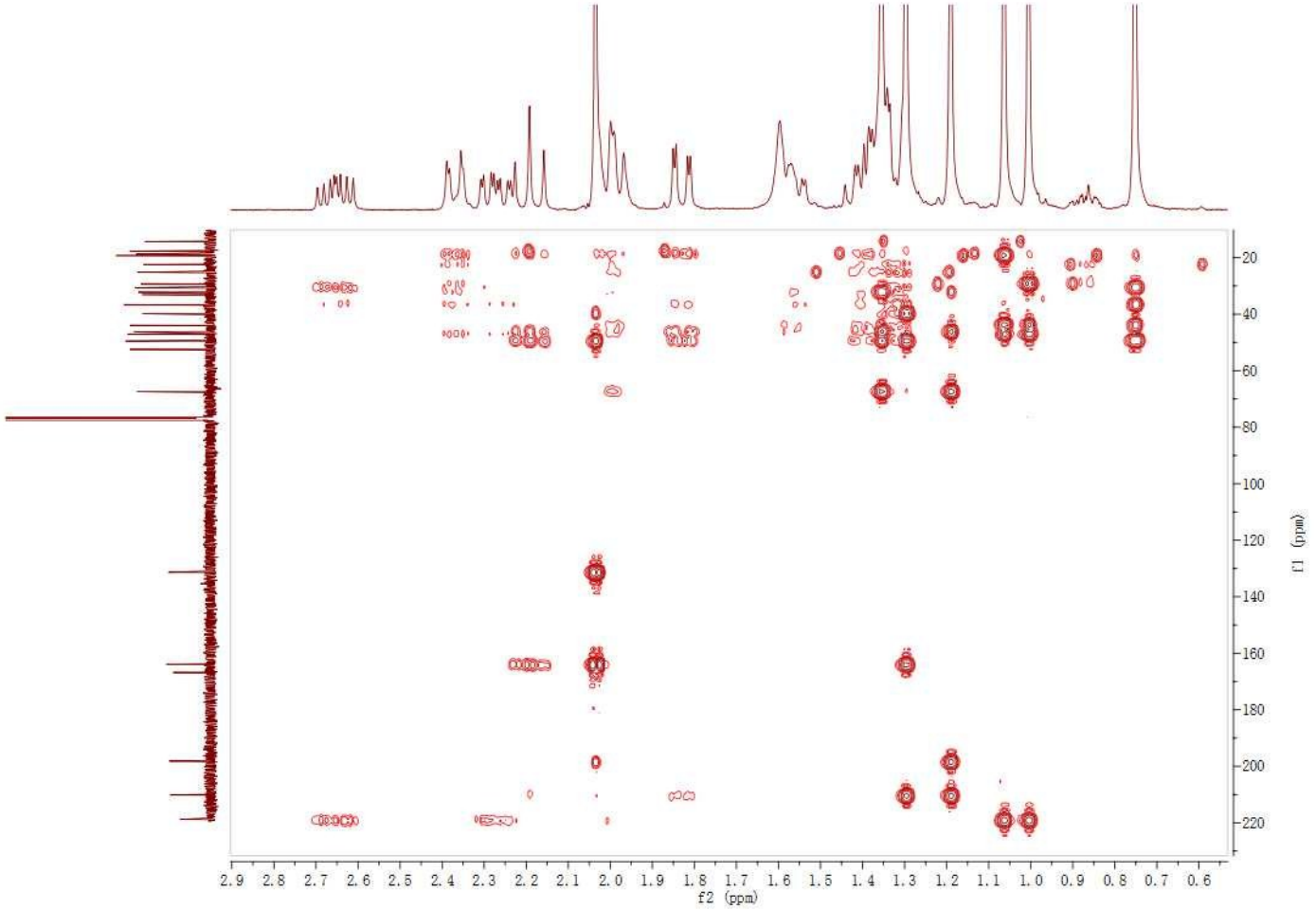
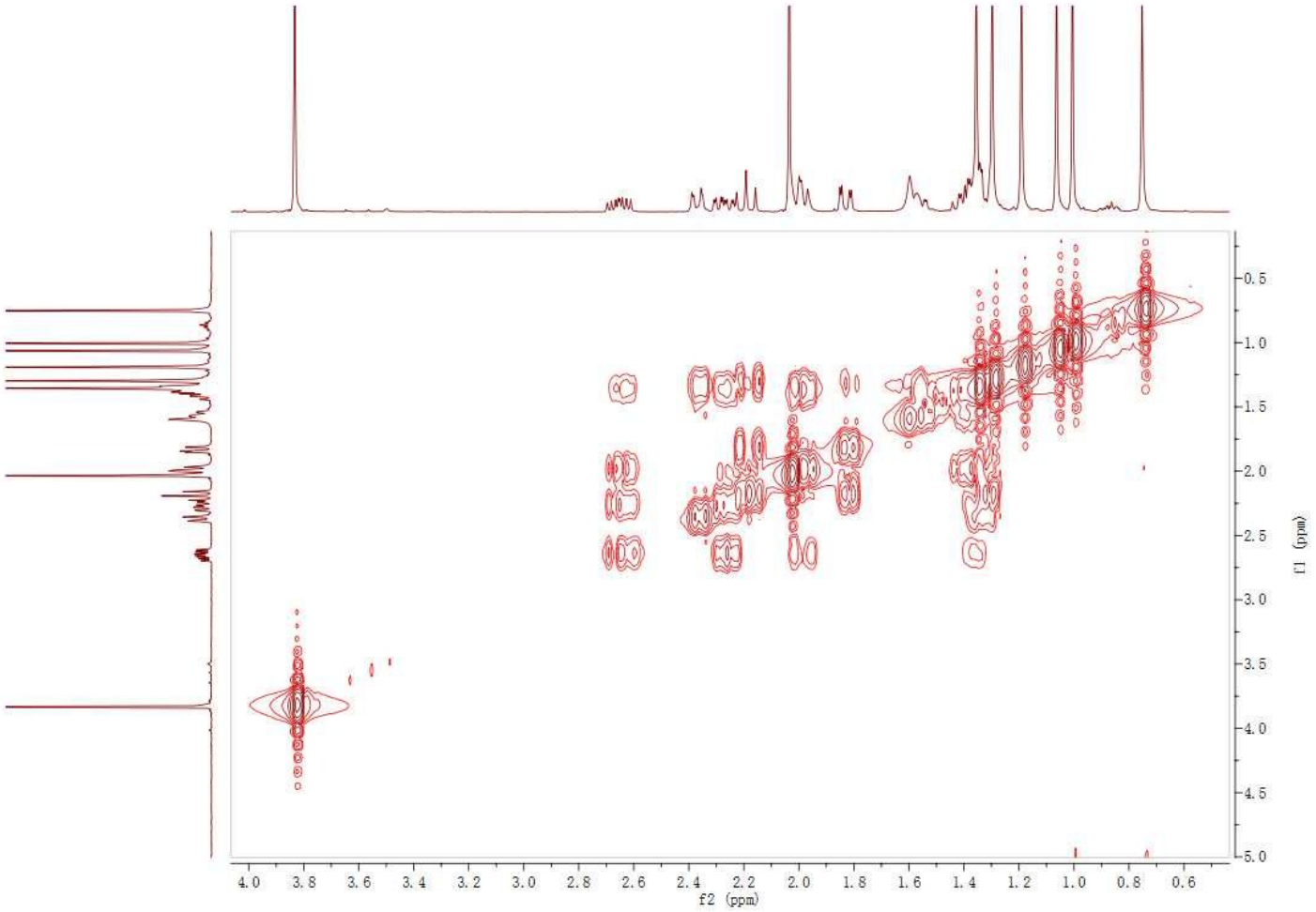
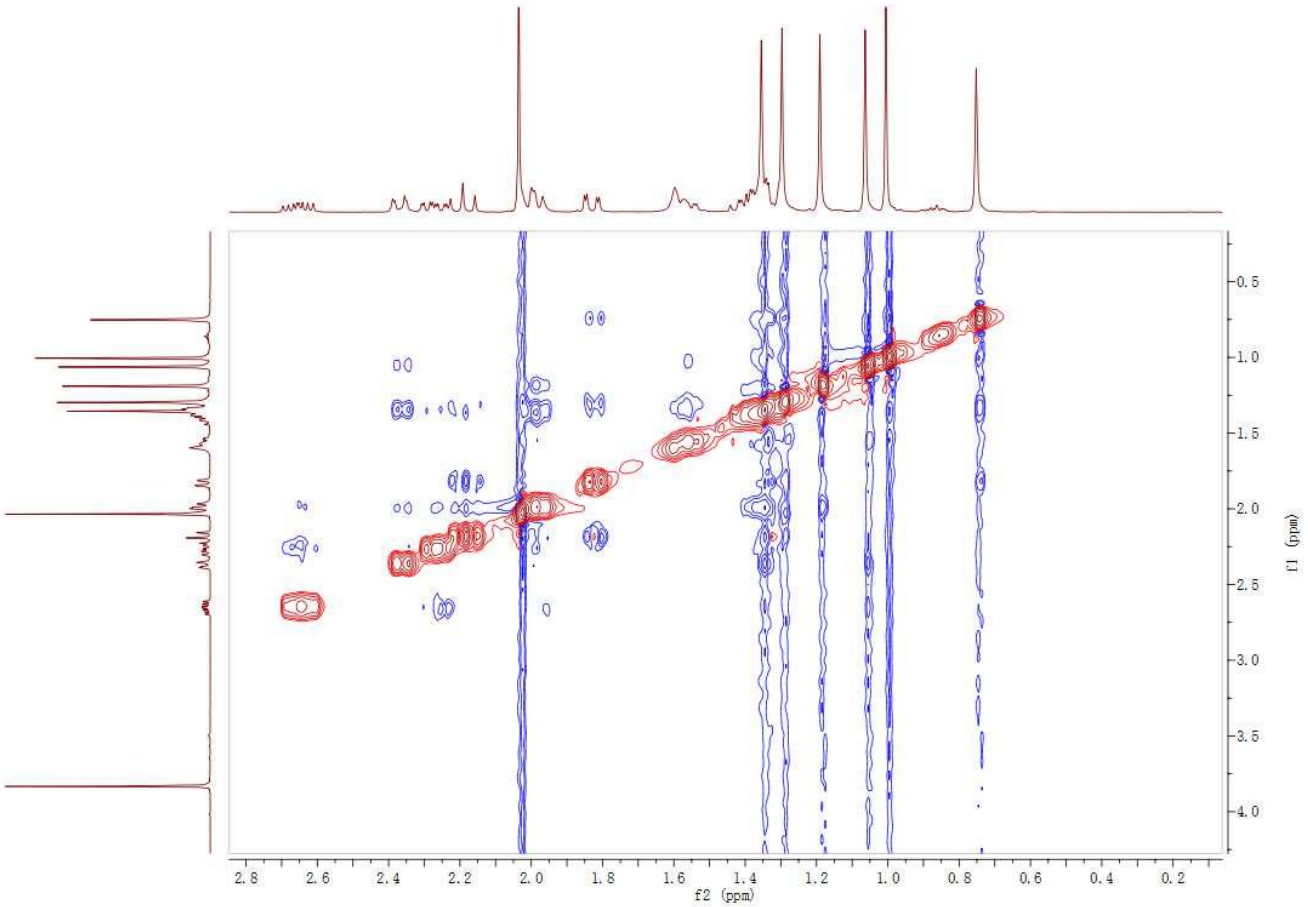


^{1}H–^{1}H COSY of compound **1** (in $CHCl_3$)



NOESY of compound **1** (in $CHCl_3$)



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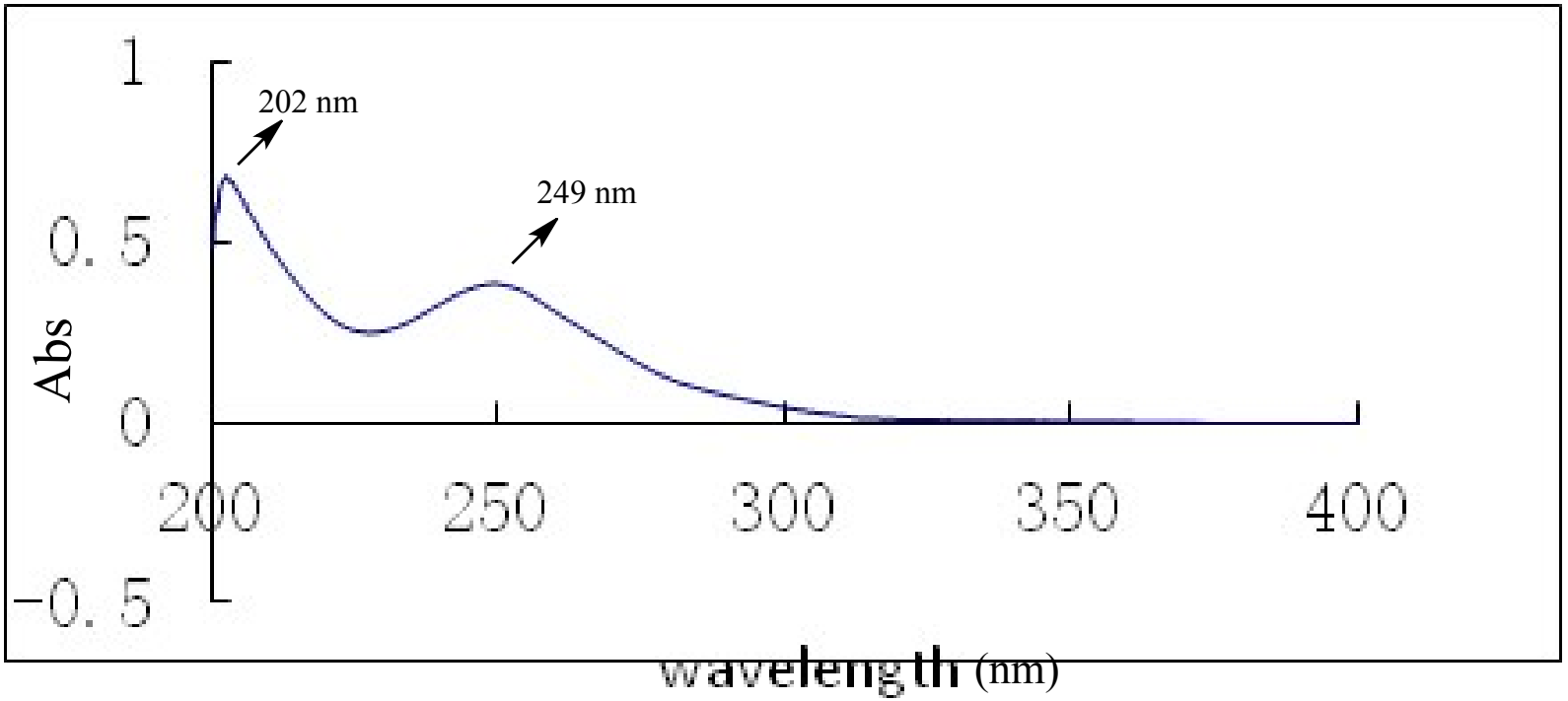

IR of compound **1**

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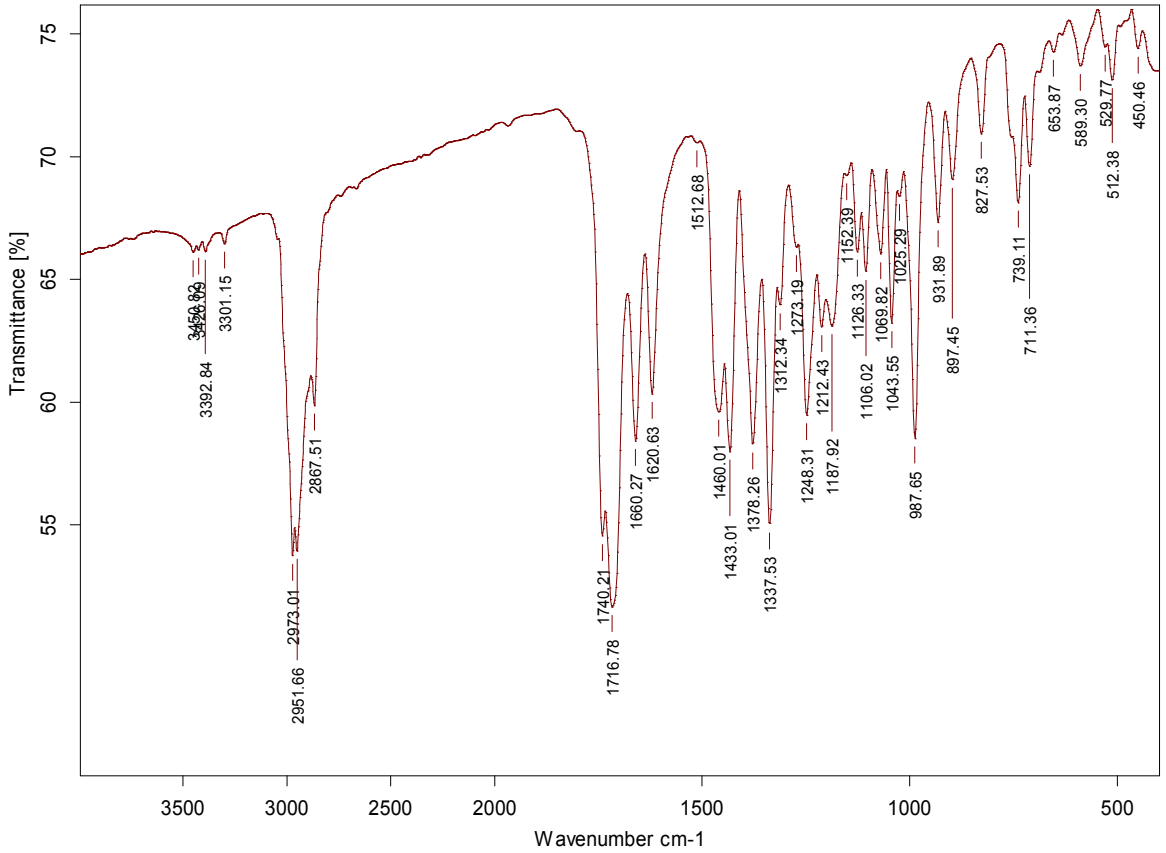

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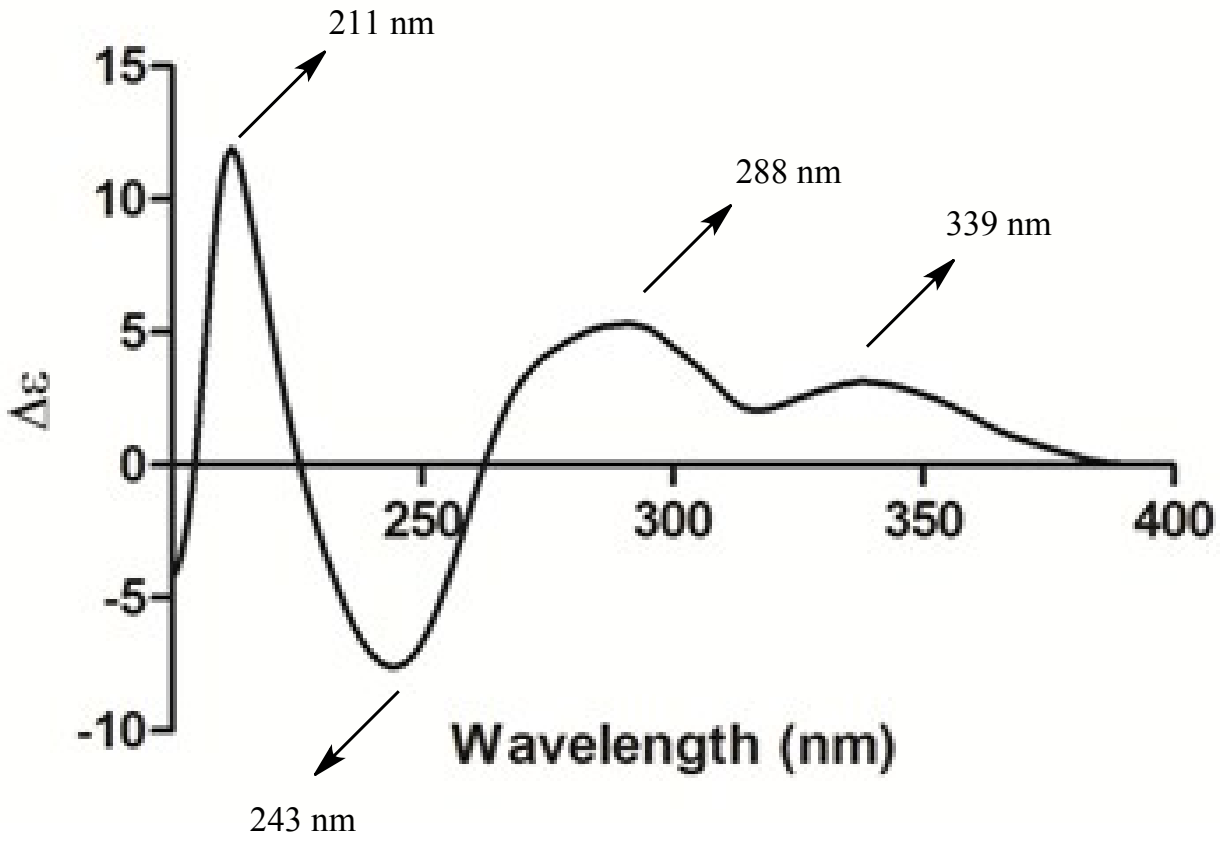

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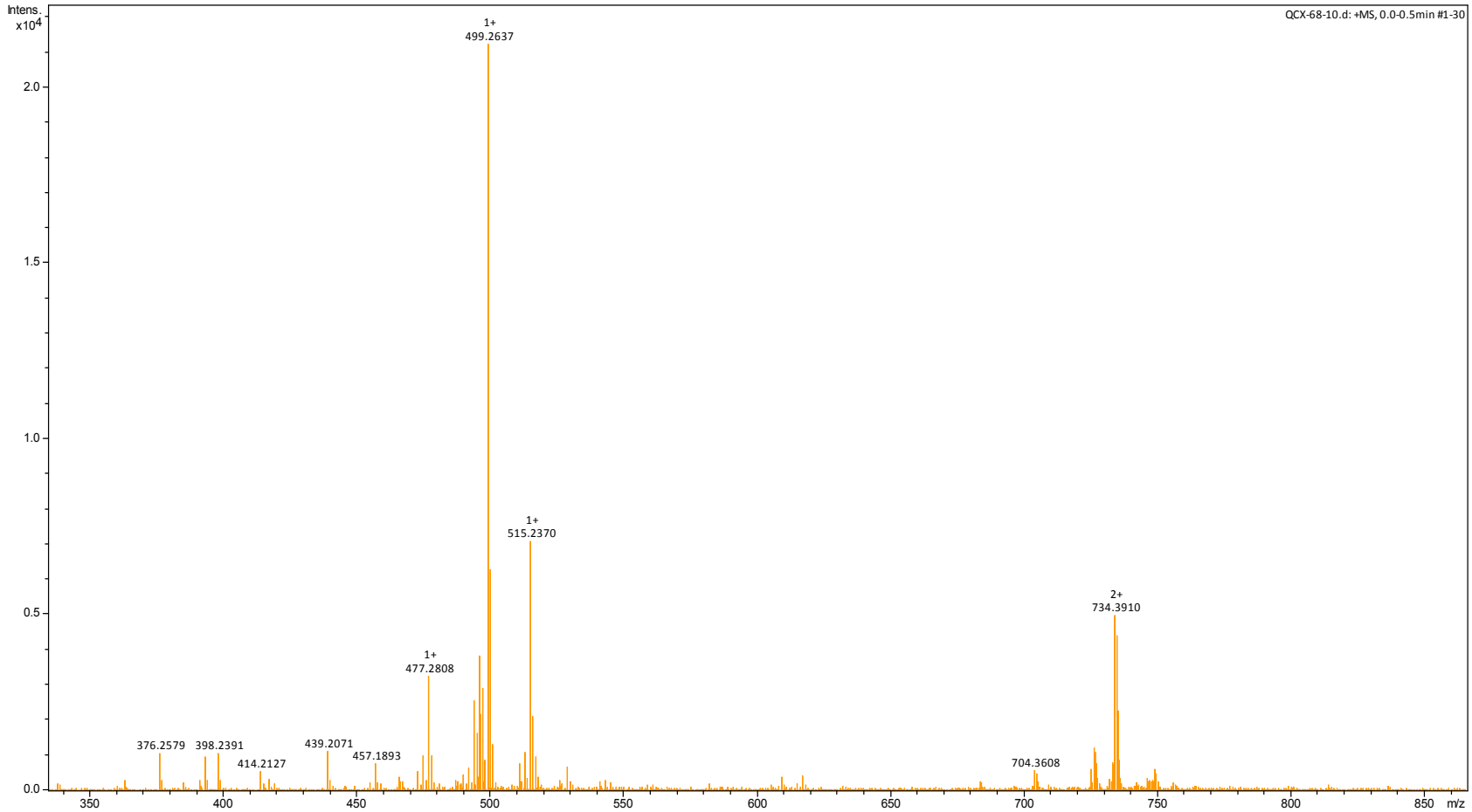
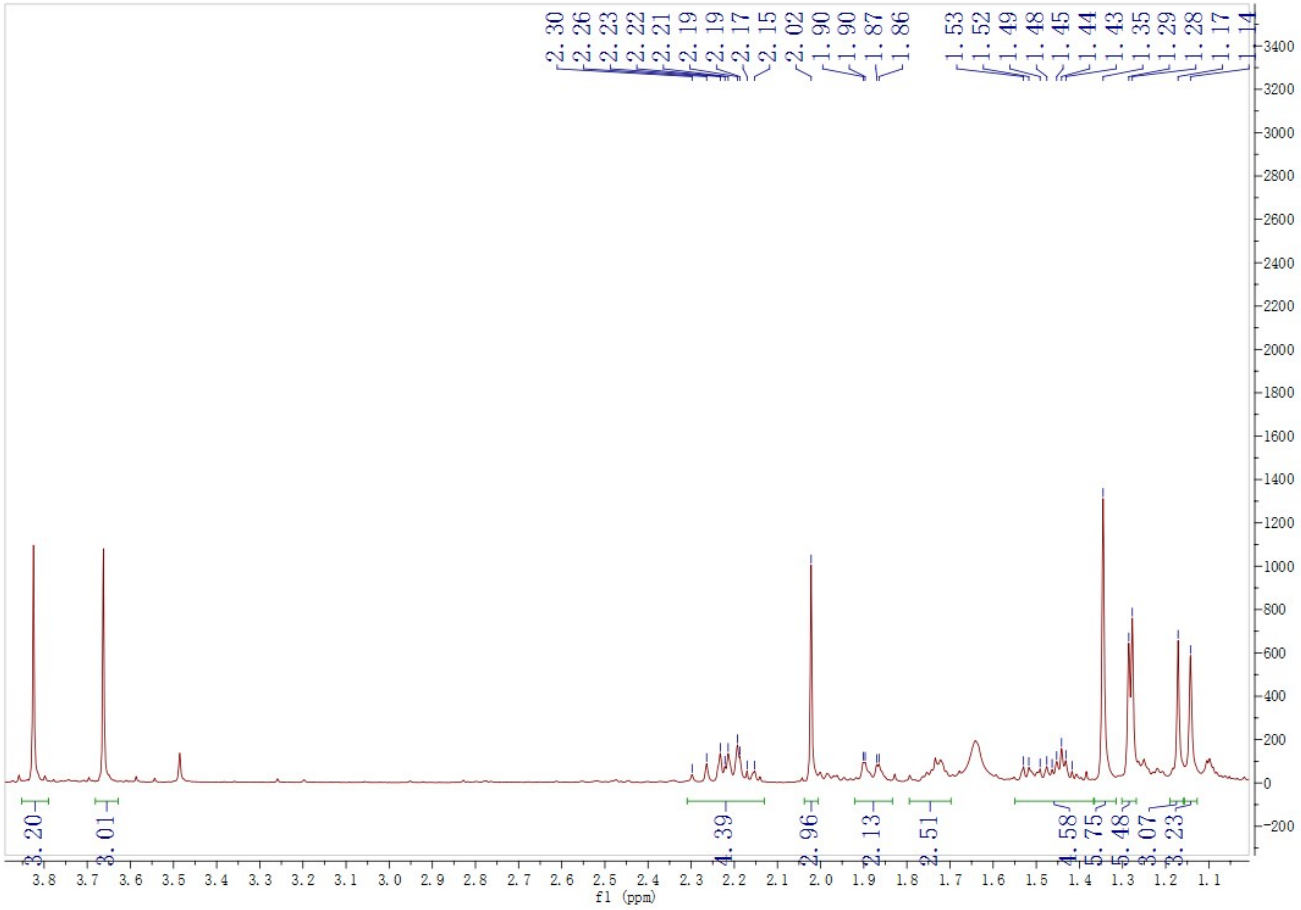


^{1}H NMR of compound **2** (in $CHCl_3$)



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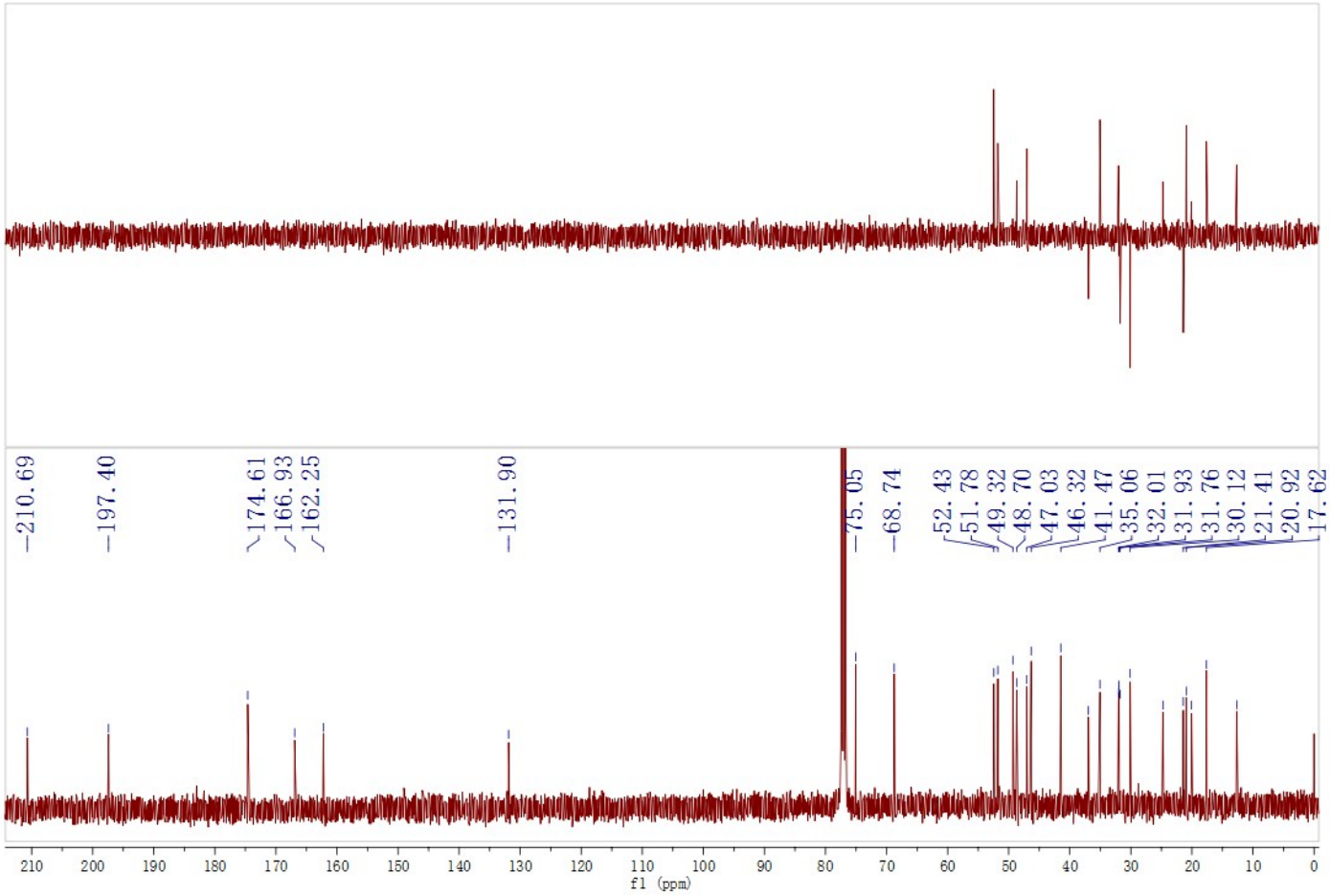

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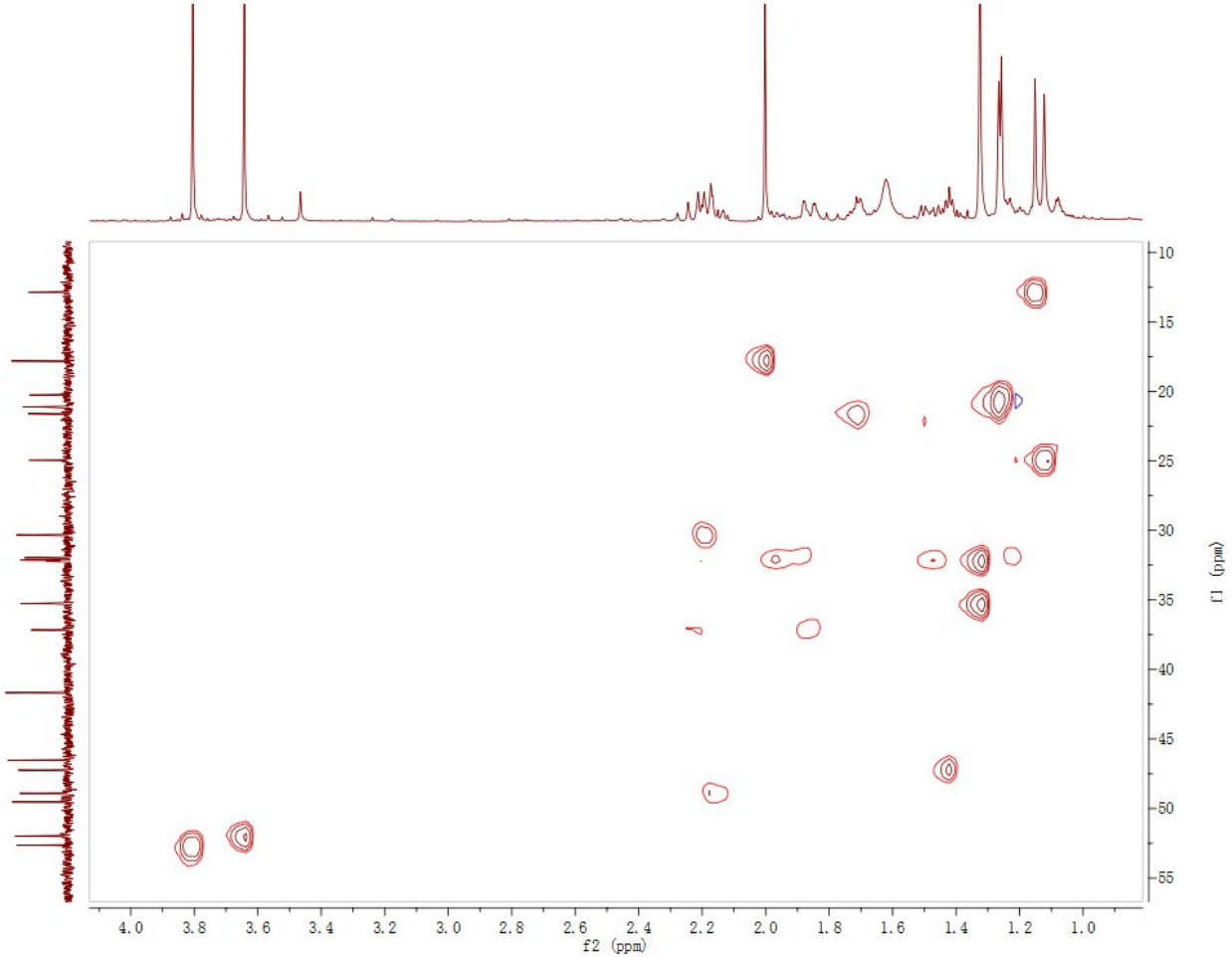
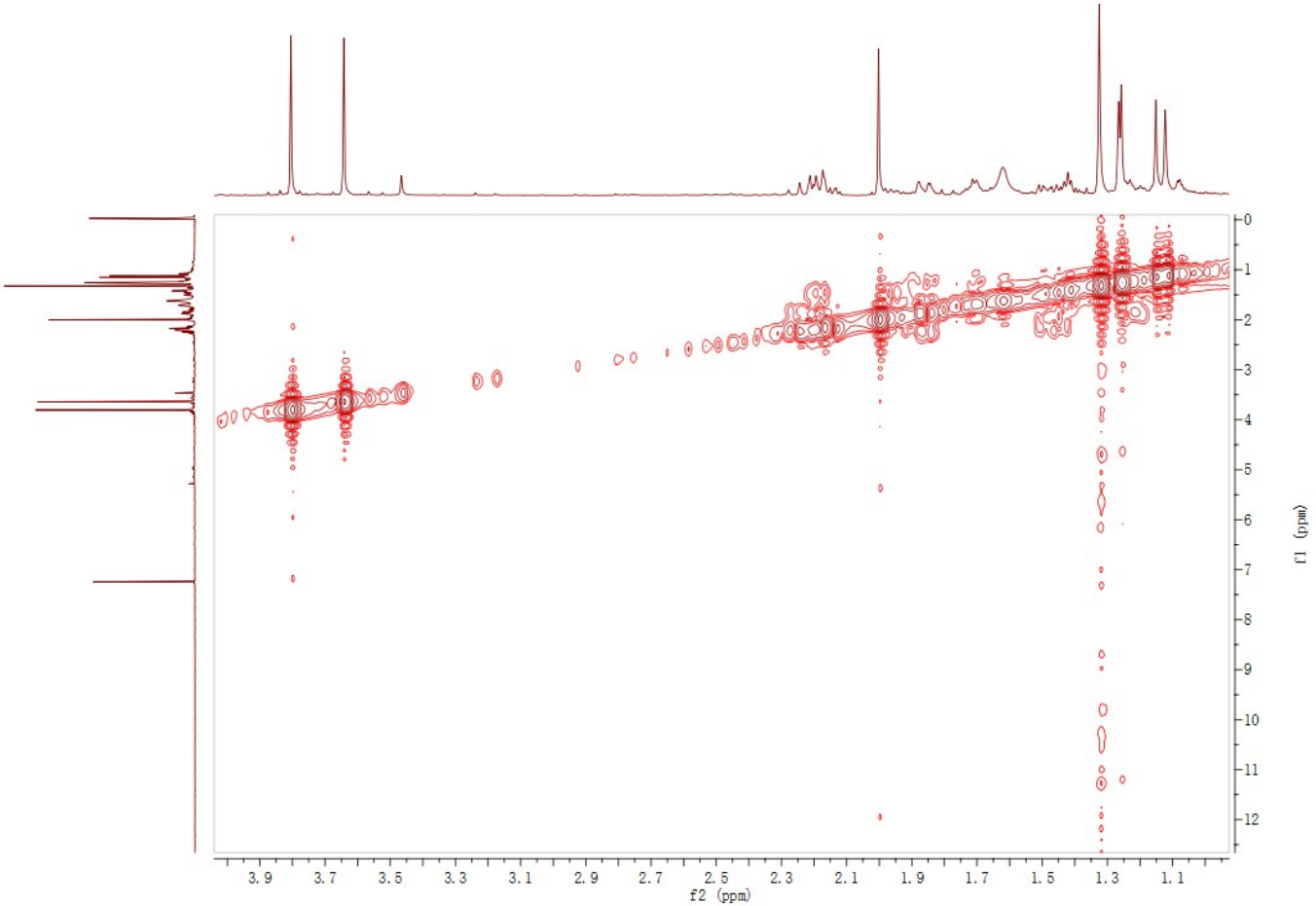


^{1}H–^{1}H COSY of compound **2** (in $CHCl_3$)



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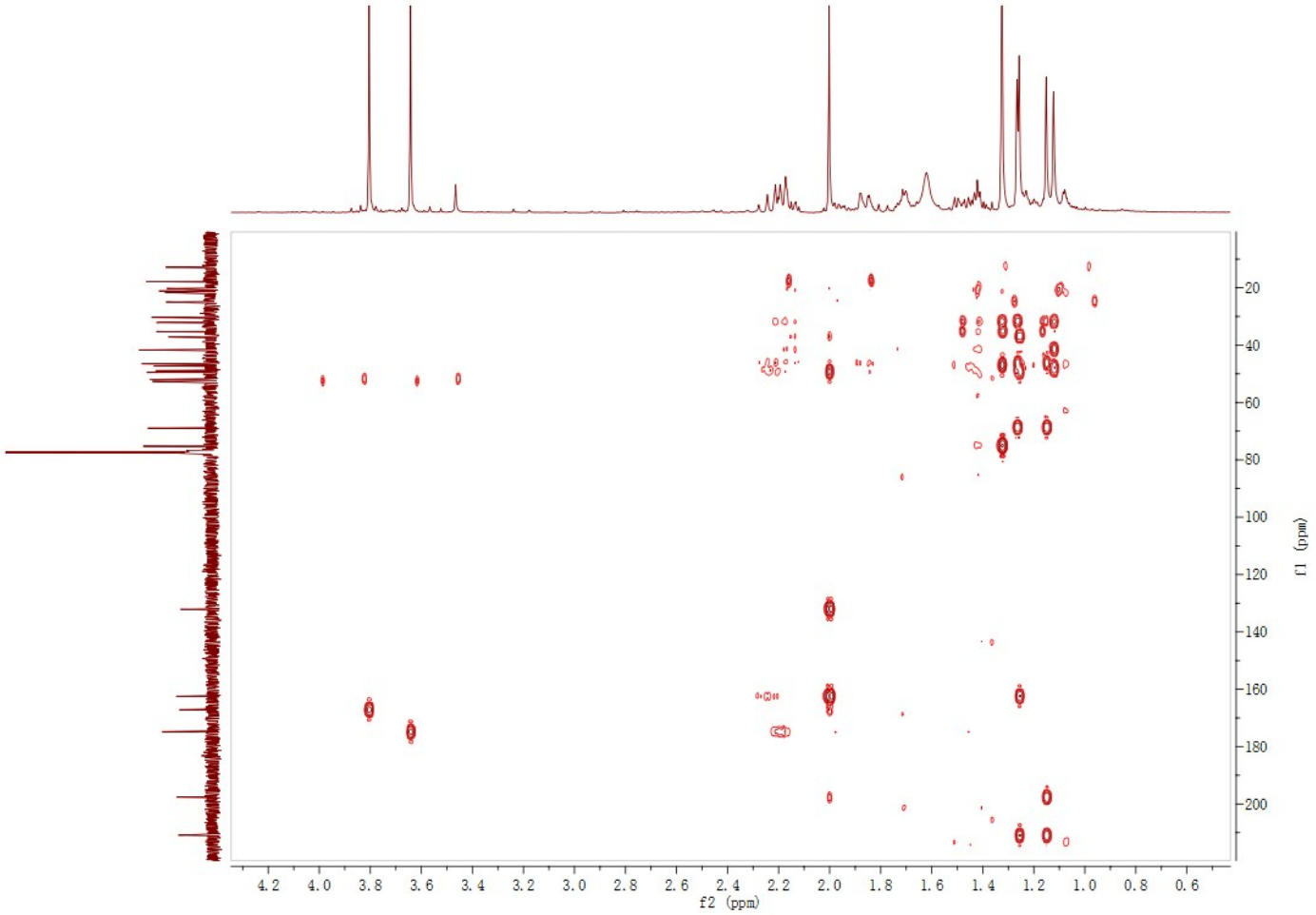

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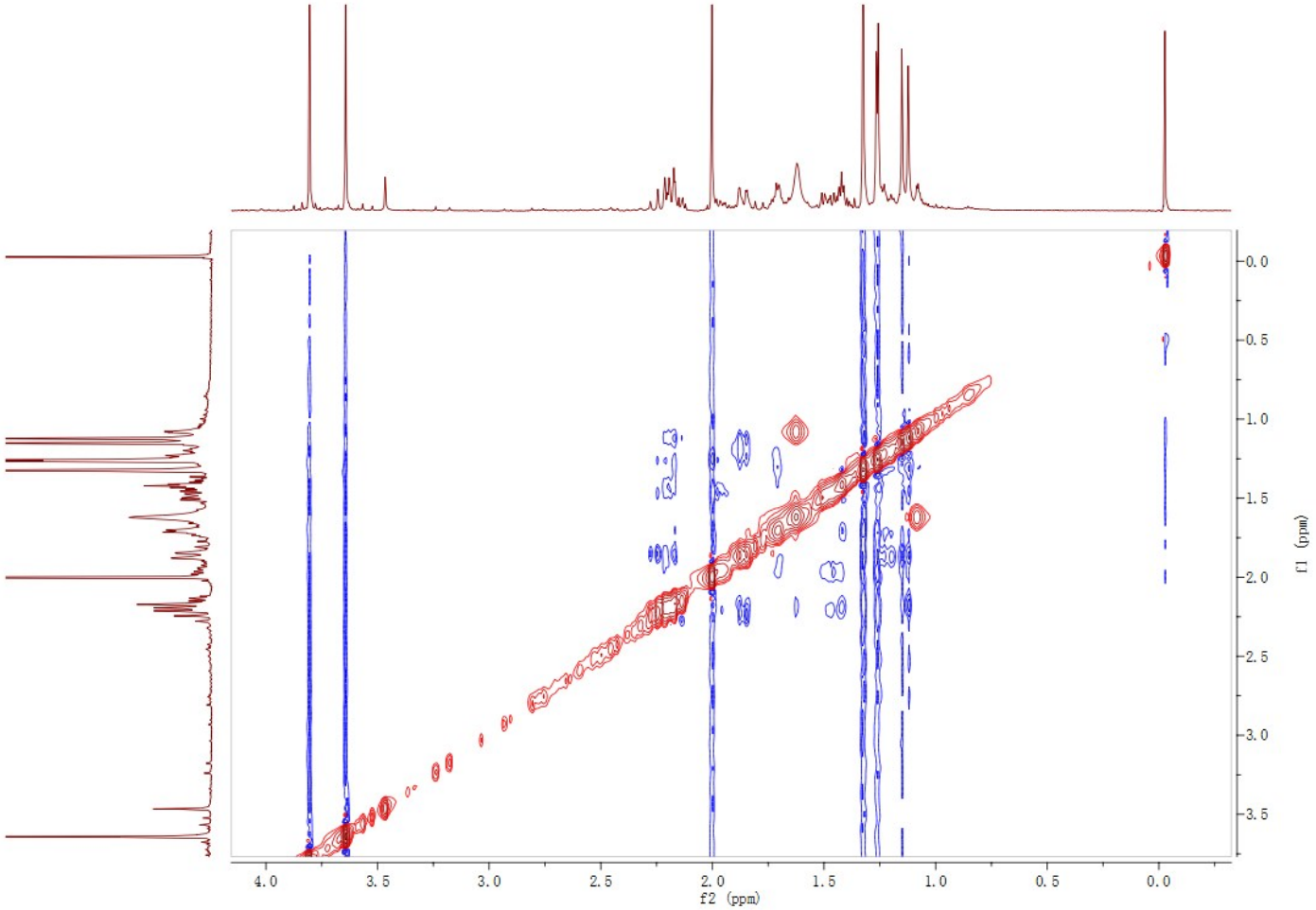

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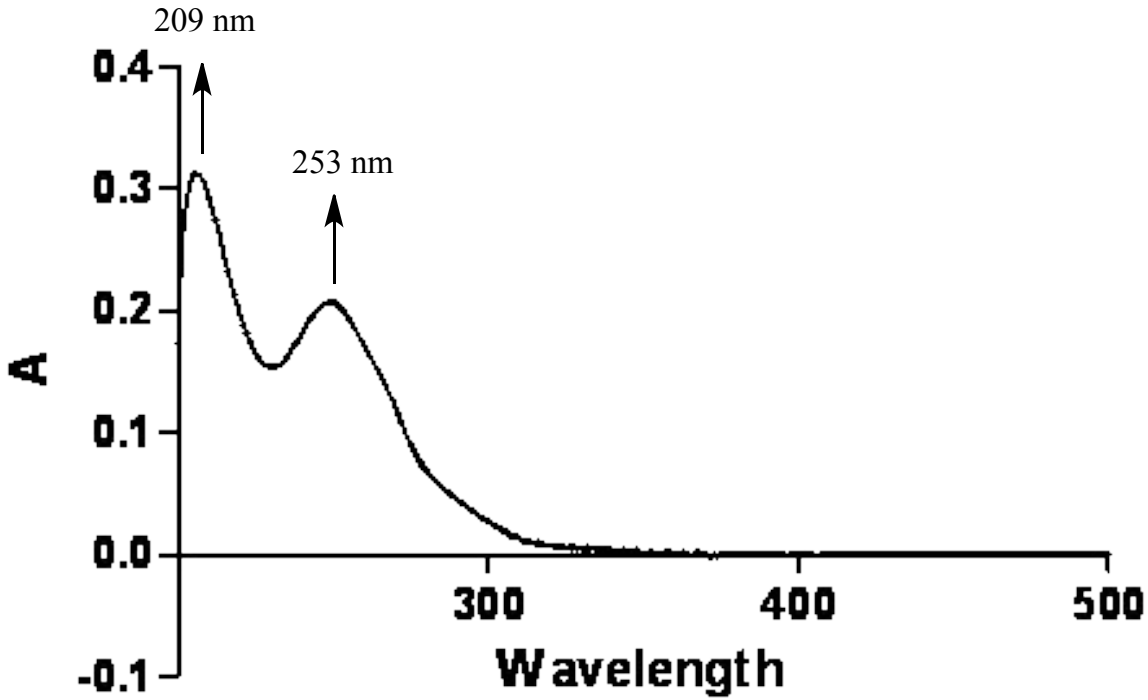

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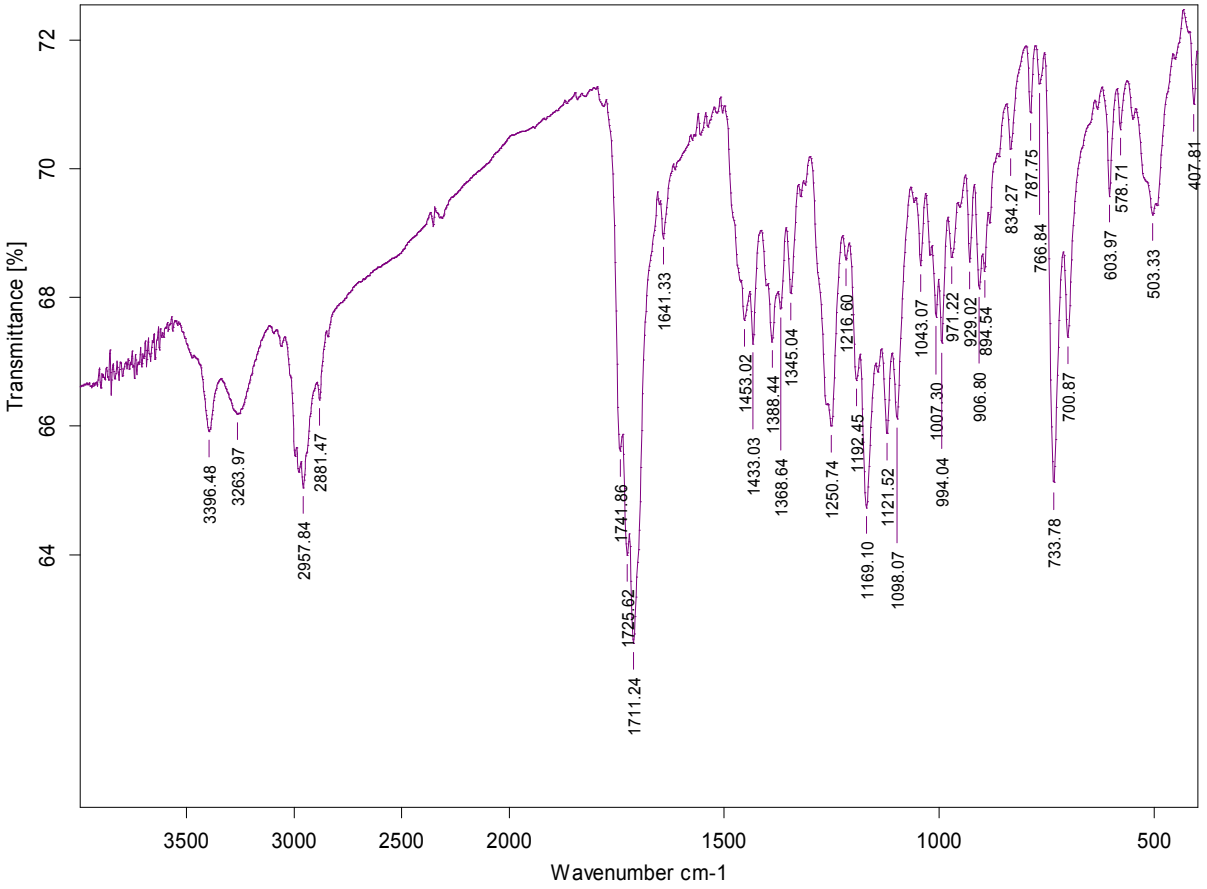

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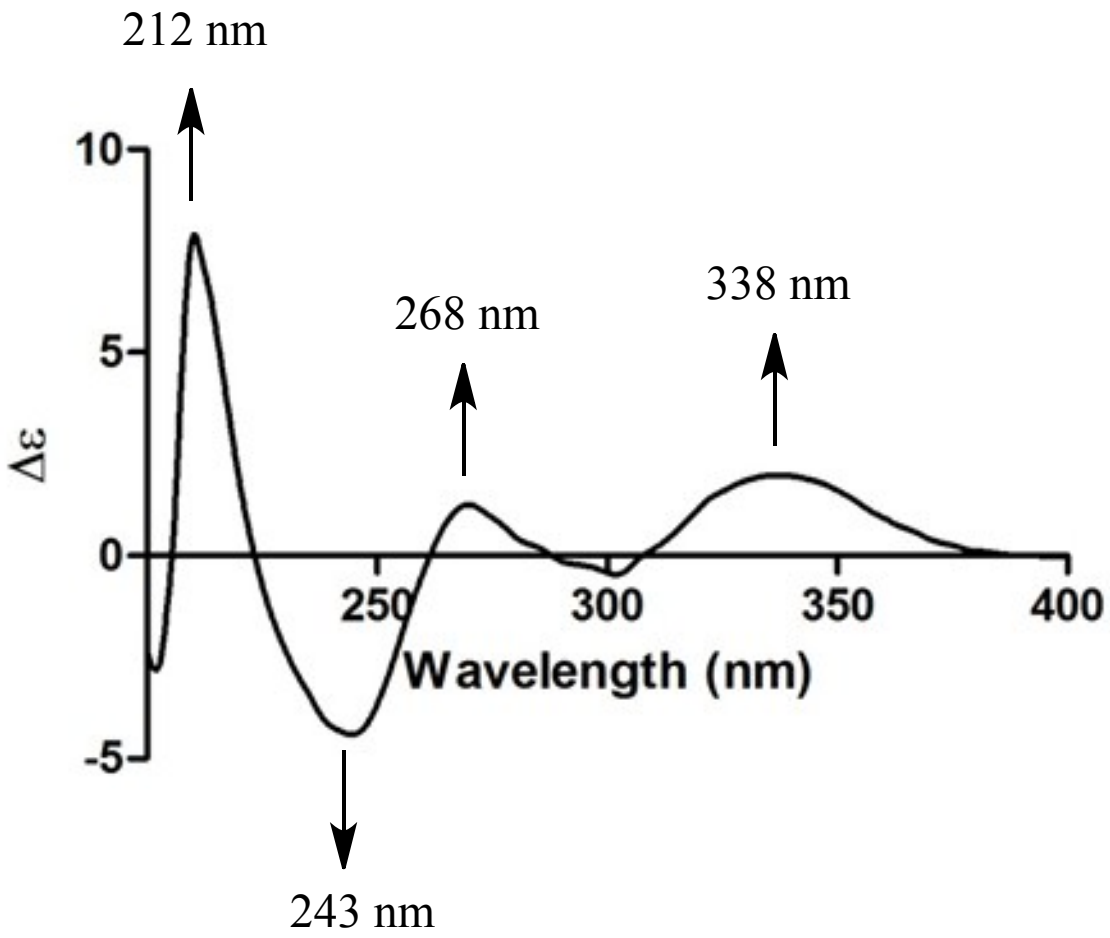
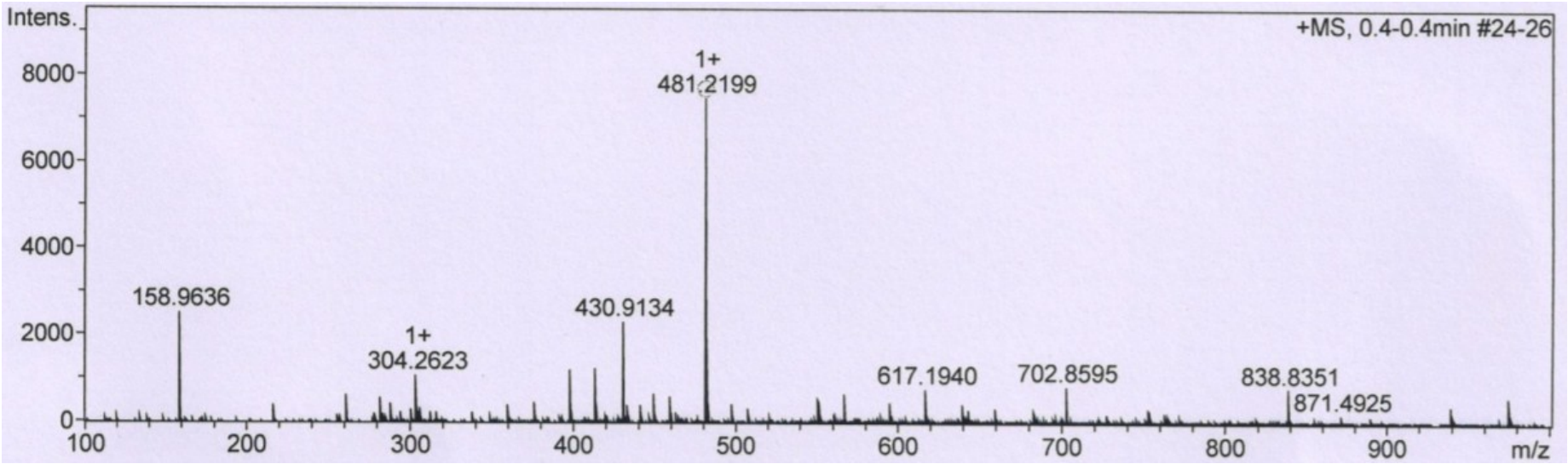


HRESIMS of compound **3**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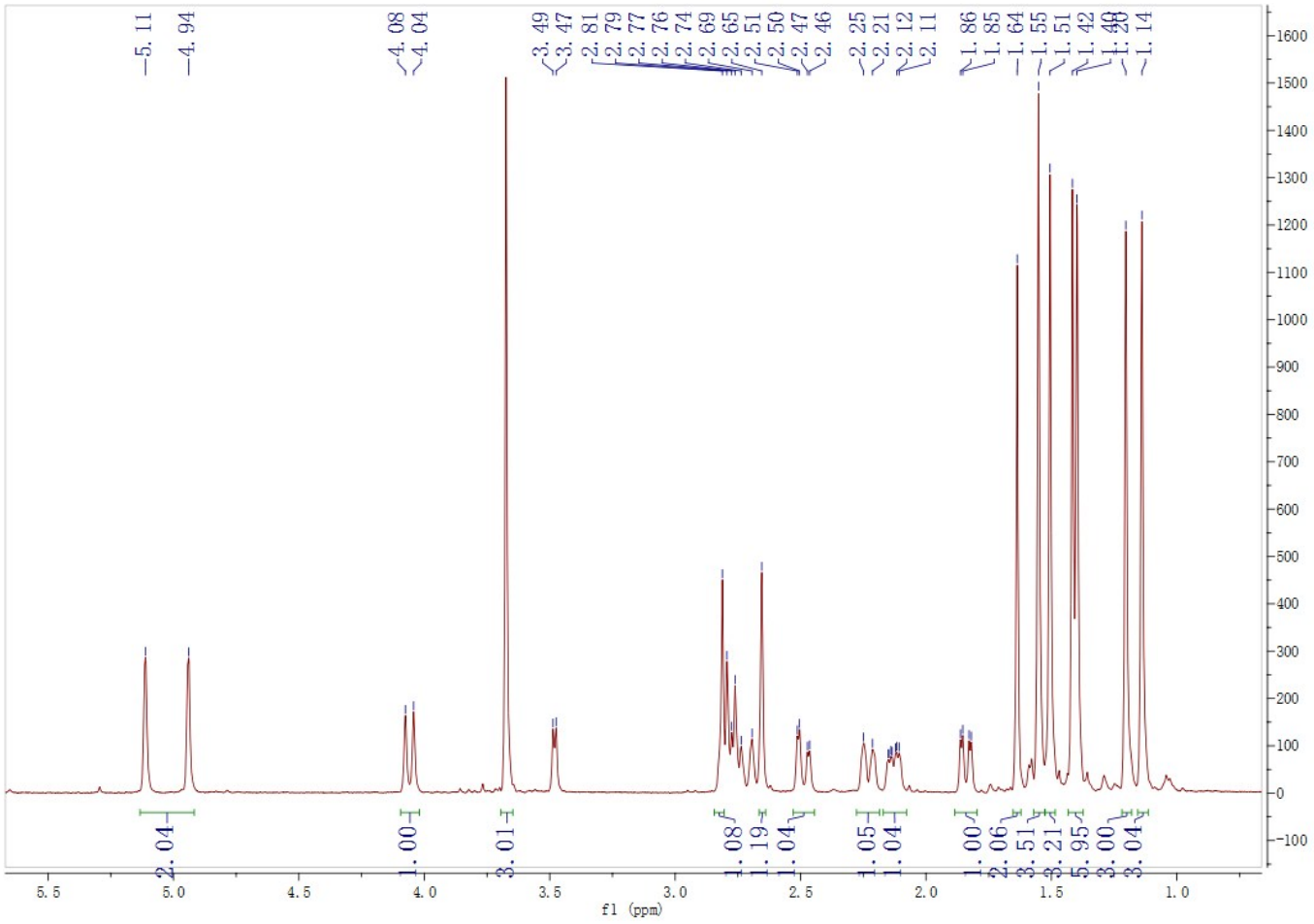
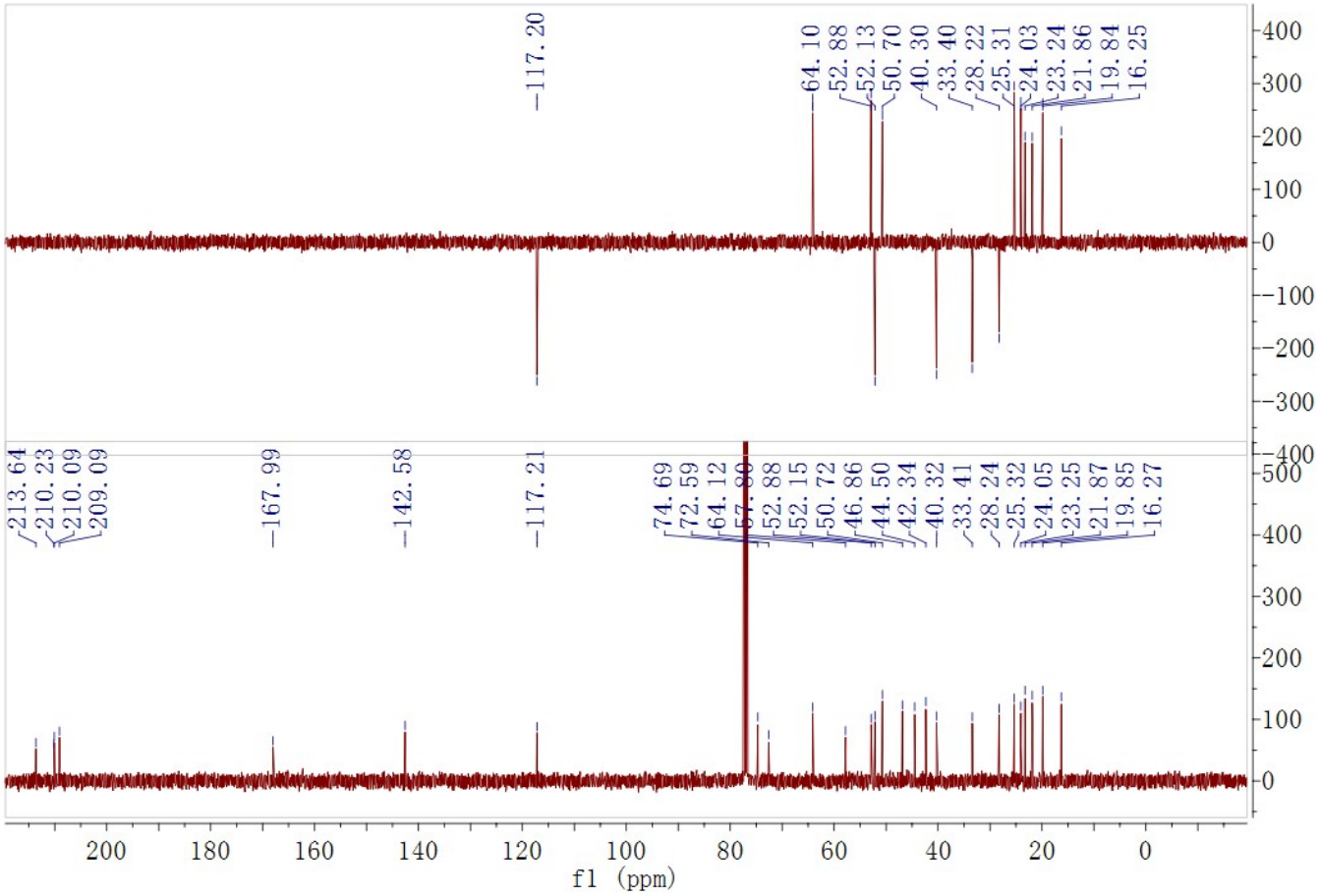
m/z

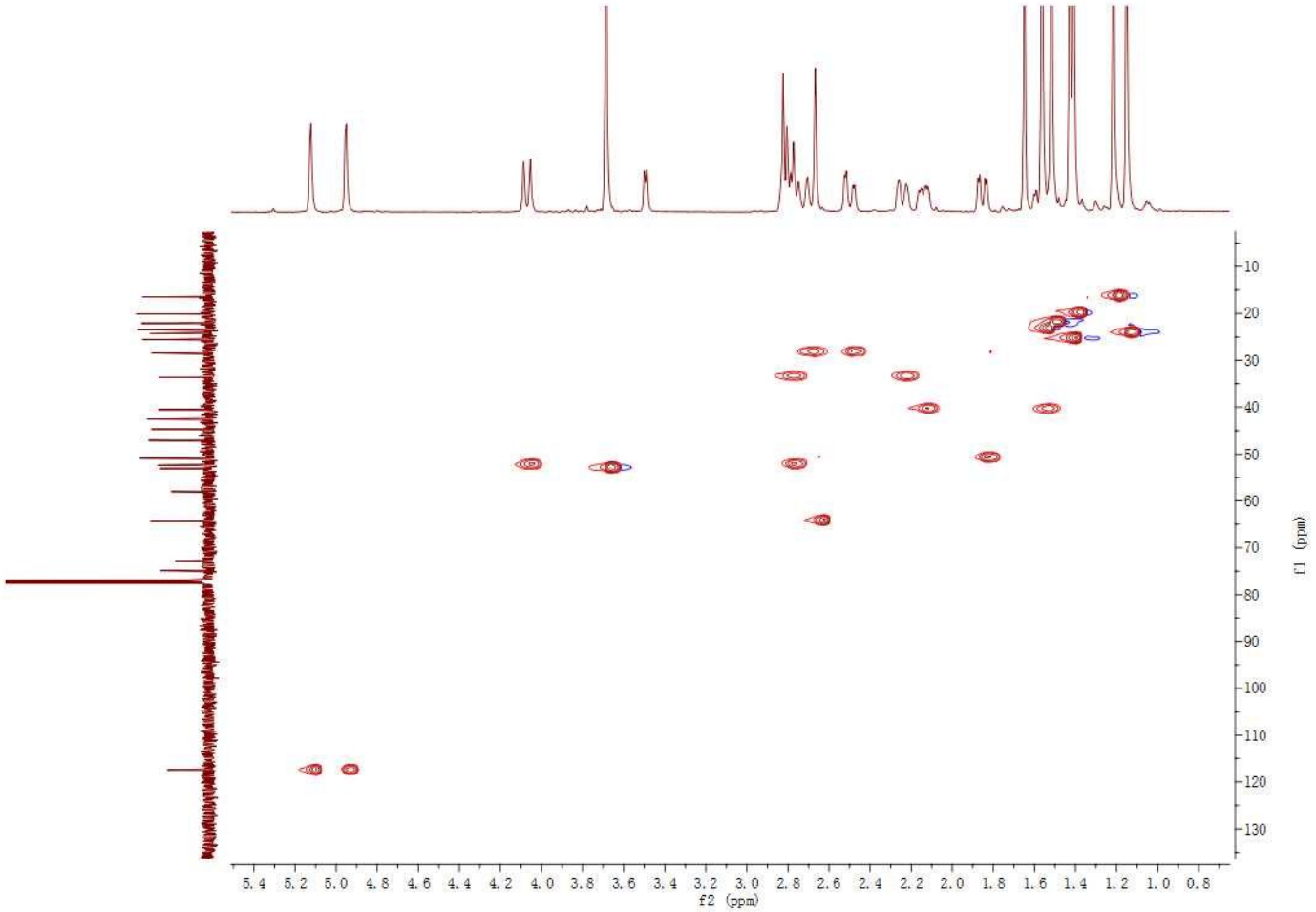
^{1}H NMR of compound **3** (in $CHCl_3$)



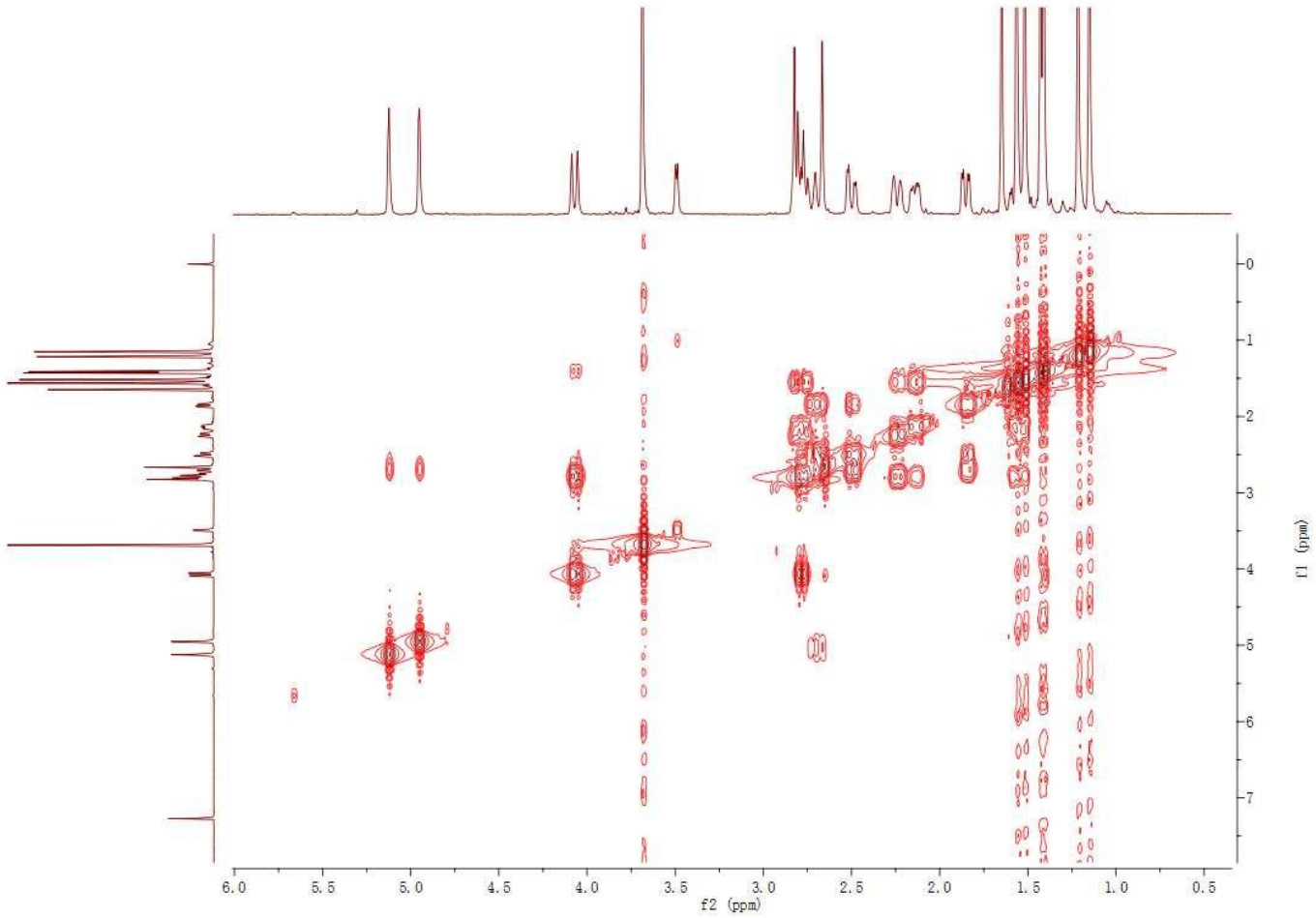
^{13}C NMR of compound **3** (in $CHCl_3$)



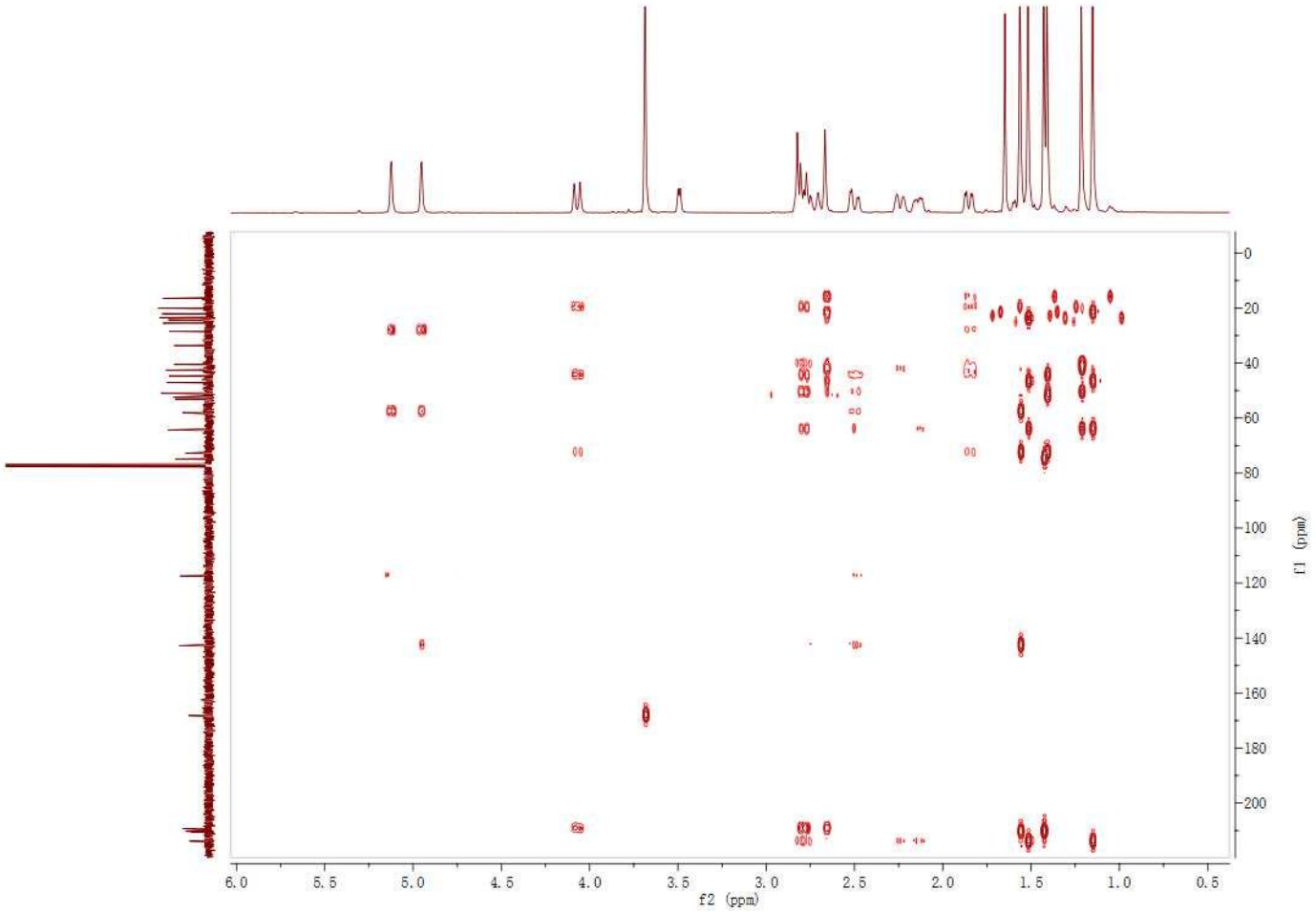
HSQC of compound **3** (in $CHCl_3$)



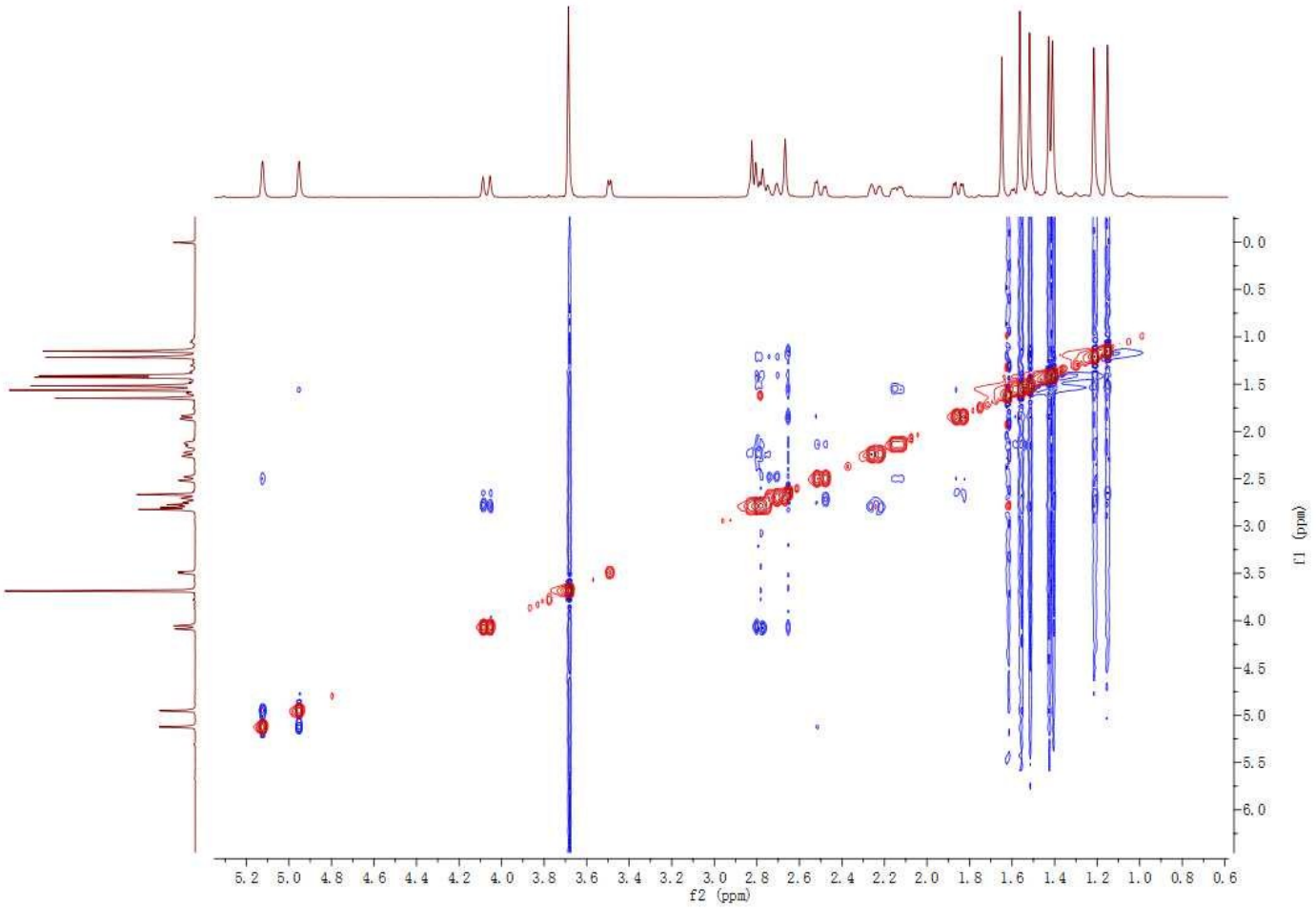
^{1}H–^{1}H COSY of compound **3** (in $CHCl_3$)



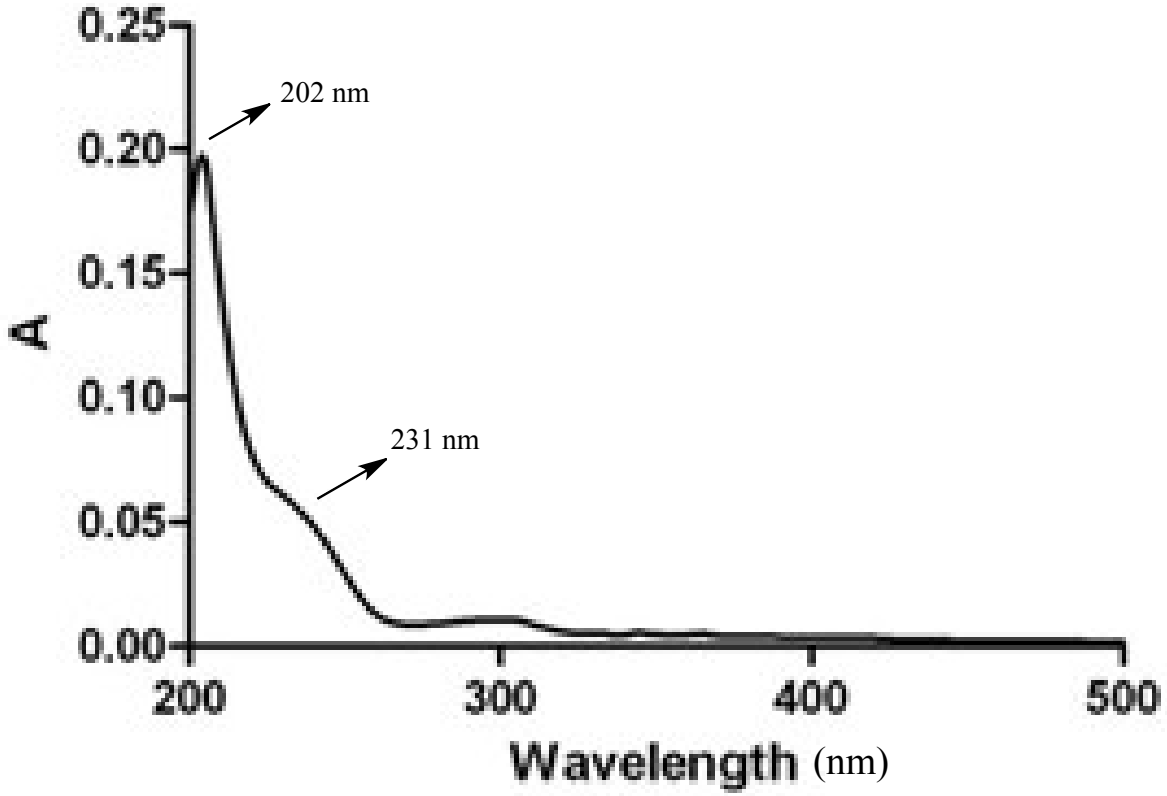
HMBC of compound **3** (in $CHCl_3$)



NOESY of compound **3** (in $CHCl_3$)

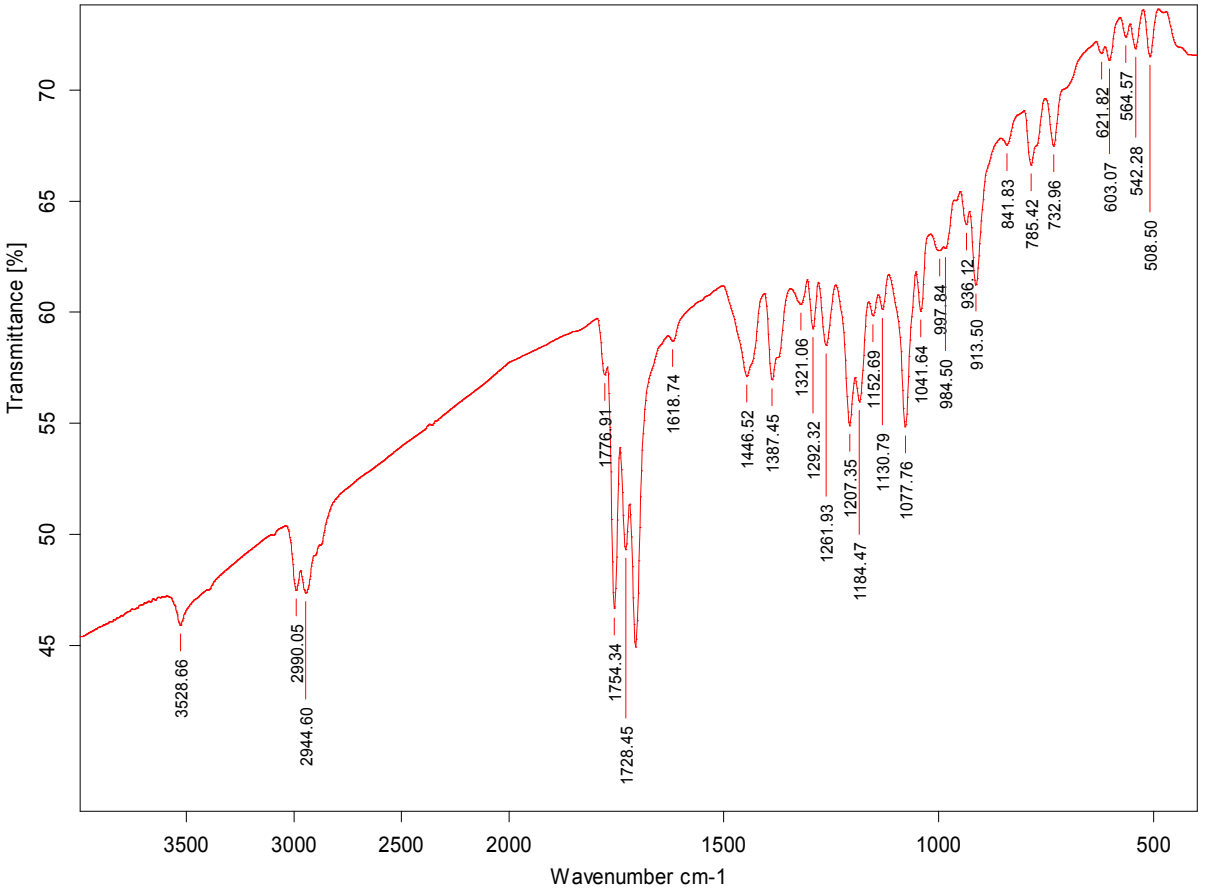


UV of compound **3**

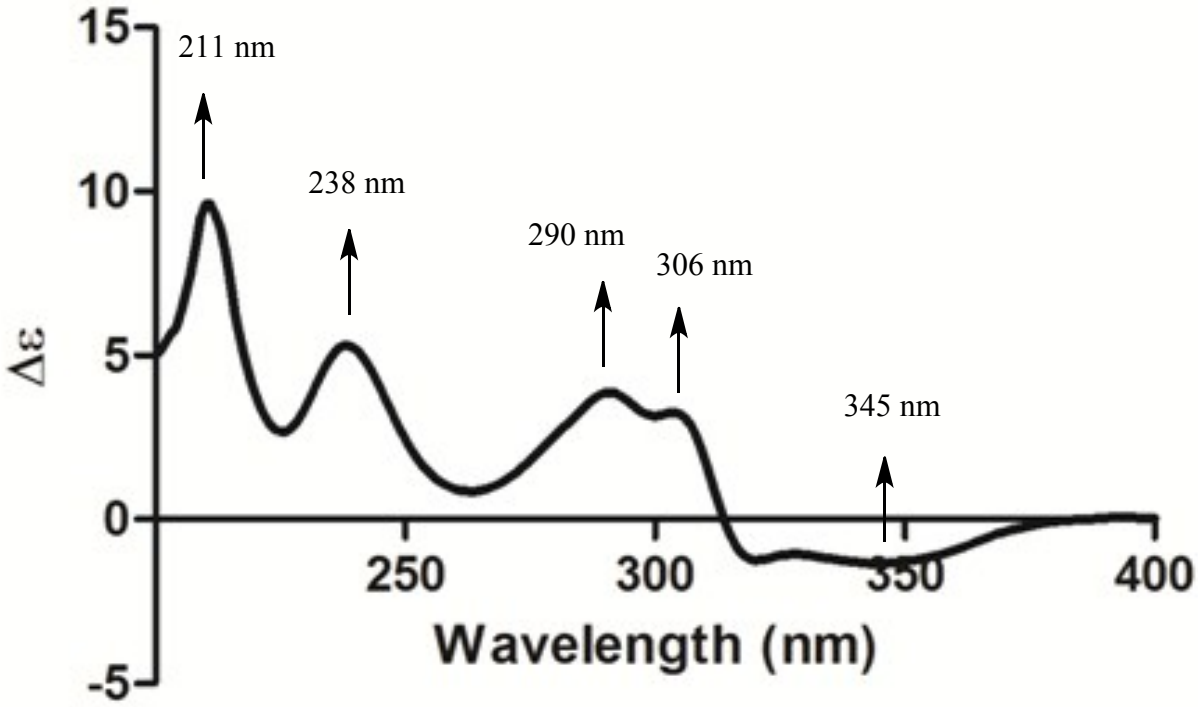


IR of compound **3** (KBrfilm)

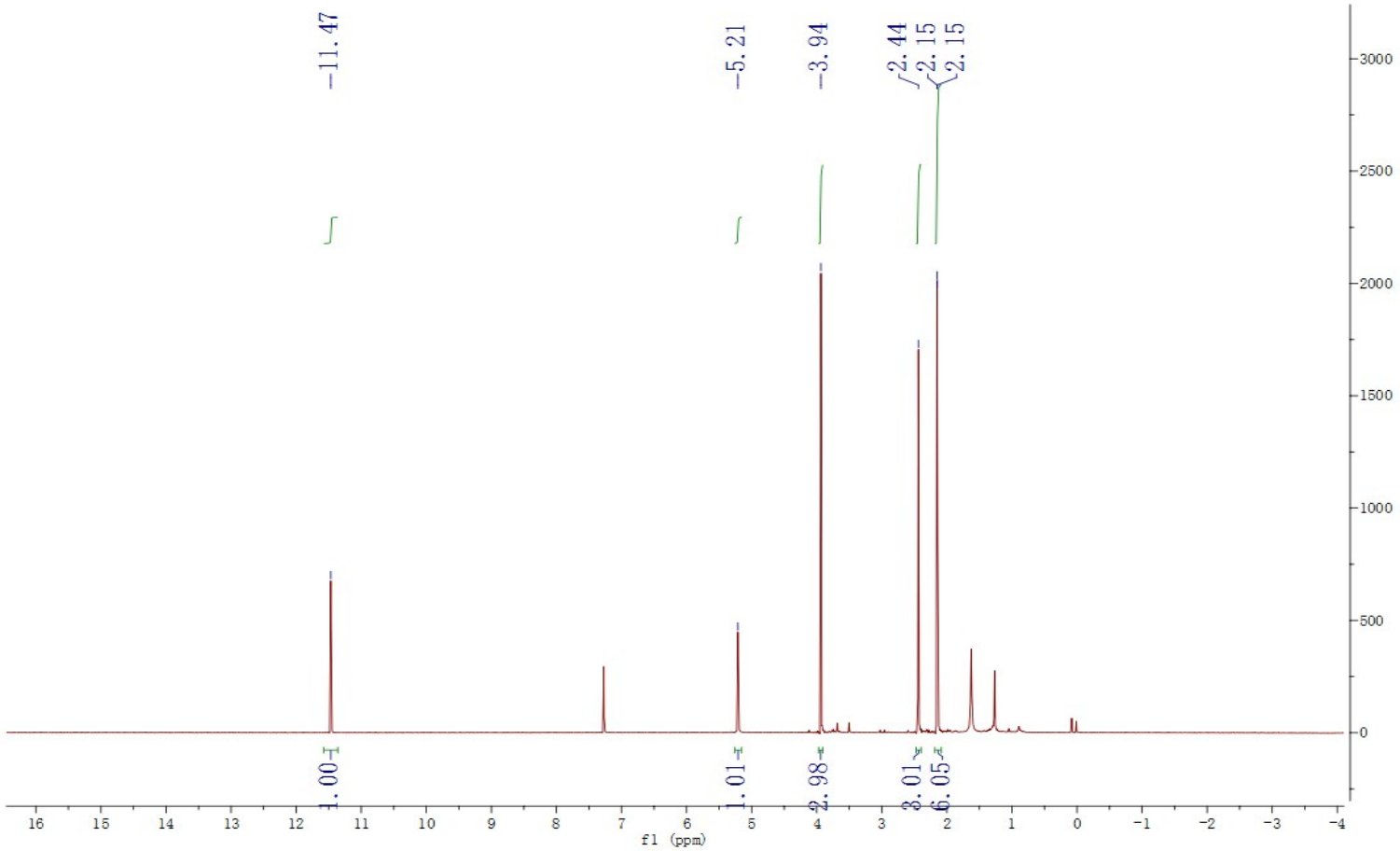
E:\□ □ □ □ □ □ \□ □ □ \20141229\001.0



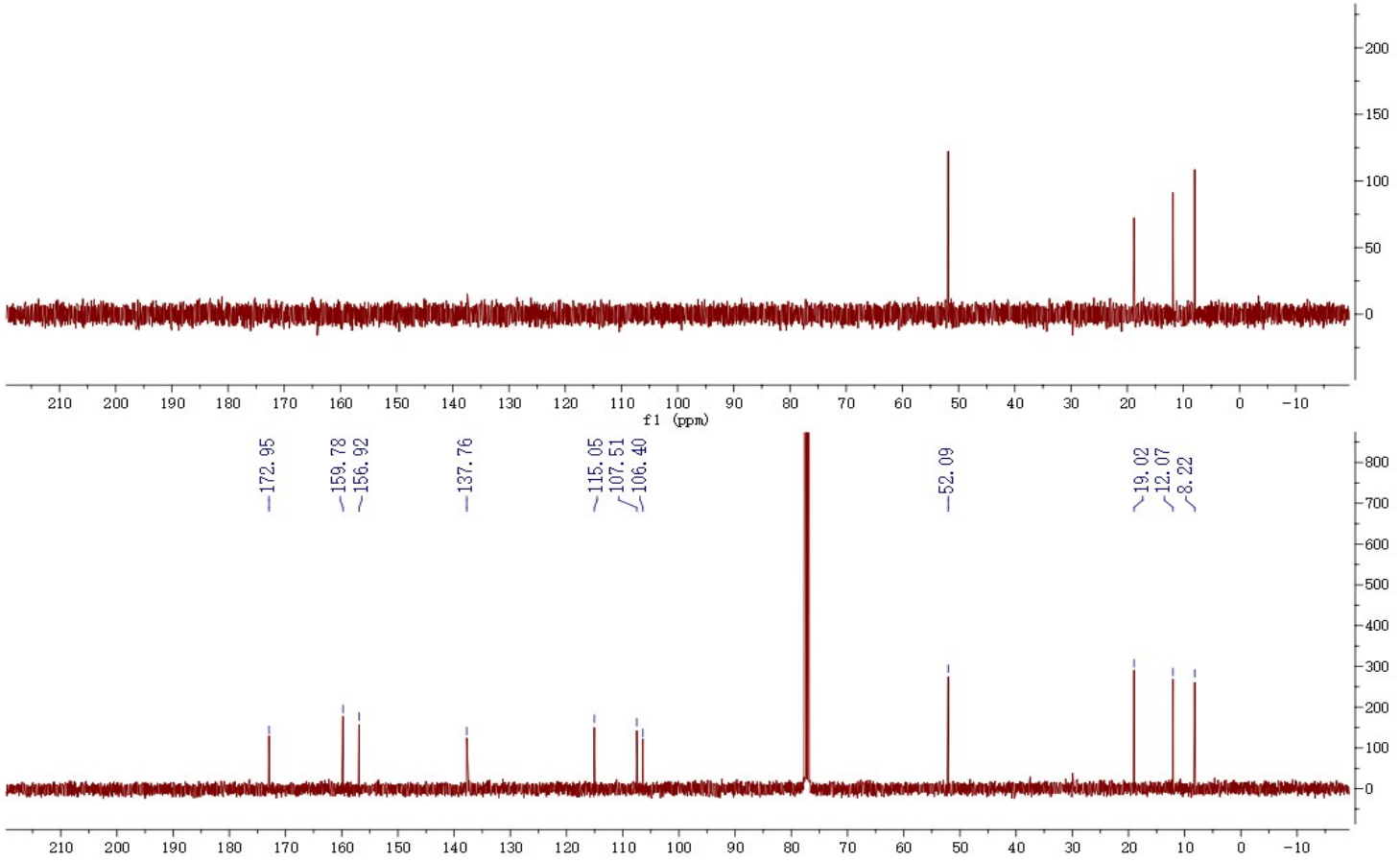
CD of compound **3**



^{1}H NMR of compound **4** (in $CHCl_3$)



^{13}C NMR of compound **4** (in $CHCl_3$)


f1 (ppm)
172.95
159.78
156.92
137.76
115.05
107.51
106.40
52.09
19.02
12.07
8.22