Supporting Information for

Annotinolides A–C, Three Lycopodane-derived 8,5-Lactones with Polycyclic Skeletons from *Lycopodium annotinum*

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Experimental Section

1. General Experimental Procedures

Optical rotations were measured with a Rudolph Autopol IV-T polarimeter. UV and IR spectra were recorded on a Hitachi U-2900E double-beam spectrophotometer and a Thermo Scientific Nicolet IS-5 FTIR spectrometer, respectively. NMR spectra were obtained on a Bruker Avance III 400, a Bruker Avance DRX-500, and/or a Bruker Avance 600 MHz spectrometer. Chemical shifts are expressed in δ (ppm), and referenced to the residual solvent signals. ESIMS were measured on an Agilent 1100 Series mass spectrometer, and HRESIMS were recorded on AB Sciex TripleTOF 5600 mass spectrometer. Semi-preparative HPLC was performed on a Waters e2695 system coupled to a 2998 Photodiode Array Detector (PAD) and a Sunfire or a Cosmosil ODS semi-prep (5 μm, 250 mm $\times$ 10 mm) column, using MeOH-H_2O or MeCN-H_2O as the mobile phase, at a flow rate of 3 mL/min. Column chromatography (CC) was performed using silica gel (100-200 or 200-300 mesh, Kang-Bi-Nuo Silysia Chemical Ltd., Yantai, China) and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden). Silica gel-precoated plates (GF254, 0.25 mm, Kang-Bi-Nuo Silysia Chemical Ltd., Yantai, China) were used for TLC detection. Spots were visualized using UV light (254 and/or 365 nm) and by spraying with Dragendorff reagent.

2. Plant Material

The whole plants of *Lycopodium annotinum* were collected in September 2013 from Taibai Mountains, Shaanxi Province of China. The plant was identified by Prof. Jian-Jun Liu (Northwest A&F University, PR China). A voucher specimen (No. 20130916) was deposited at the Herbarium of the Department of Natural Products Chemistry, School of Pharmacy at Fudan University.

3. Extraction and Isolation

The air-dried and powdered whole plant of *L. annotinum* (10 kg) was pulverized and extracted with 90% MeOH at room temperature for five times (5 $\times$ 30 L). After evaporation in vacuum, the crude extracts (1.1 kg, semi-dry) were partitioned between EtOAc and 3% tartaric acid. The water-soluble portion, adjusted to pH 9.0 with $NH_3 \cdot H_2O$, was extracted with $CHCl_3$. The concentrated $CHCl_3$-soluble portion (30 g) was chromatographed over silica gel, eluted with a gradient of CH_2Cl_2/MeOH (1:0–0:1, v/v) to afford seven fractions (Fr. 1–Fr. 7). Fr. 3 (2.0 g) was subjected to gel permeation chromatography (GPC) on Sephadex LH-20 (CH_2Cl_2-MeOH 2:1, v/v) and was

further fractionated by semi-preparative HPLC to afford three sub-fractions (Frs. 3.1–3.3). Fraction 3.1 (120 mg) was purified by semi-preparative HPLC [MeOH-H_2O (containing 0.05% diethylamine, v/v) 50:50, v/v] to yield compounds **2** (1.5 mg, 0.000015%, t_R = 25.9 min) and **5** (29.6 mg, 0.0003%, t_R = 15.4 min). Compound **4** (52.0 mg, 0.00052%,) was obtained from fraction 3.2 by using semi-preparative HPLC [t_R = 18.1 min, MeOH-H_2O (containing 0.05% diethylamine, v/v) 50:50, v/v]. Fraction 4 (5.1 g) was fractionated by CC over silica gel using CH_2Cl_2-MeOH (40:1 to 0:1, v/v) and five fractions (Frs. 4.1–4.5) were collected. Fraction 4.4 (400 mg) was then subjected to semi-preparative HPLC [MeCN-H_2O (containing 0.05% diethylamine, v/v) 35:65, v/v] to obtain three sub-fractions (Frs. 4.4A–4.4C). Frs. 4.4A (170 mg) was separated by semi-preparative HPLC [MeOH-H_2O (containing 0.05% diethylamine, v/v) 35:65, v/v] to afford compound **3** (1.6 mg, 0.000016%, t_R = 10.2 min). Fraction 4.4C was subjected to semi-preparative HPLC [MeCN-H_2O (containing 0.05% diethylamine, v/v) 22:78, v/v] to give compound **1** (0.8 mg, 0.000008%, t_R = 24.9 min). Fraction 5 (5.1 g) was fractionated by CC over silica gel using CH_2Cl_2-MeOH (40:1 to 0:1, v/v) and five fractions (Frs. 5.1–5.5) were collected. Fraction 5.4 was subjected to semi-preparative HPLC [MeCN-H_2O (containing 0.05% diethylamine, v/v) 35:65, v/v] to obtain three sub-fractions (Frs. 5.4A–5.4C). Fraction 5.4A was separated by semi-preparative HPLC [MeOH-H_2O (containing 0.05% diethylamine, v/v) 35:65, v/v] to afford **7** (3.3 mg, 0.000033%, t_R = 12.4 min). Fraction 5.4B was subjected to further semi-preparative HPLC purification using an isocratic elution of 20% (v/v) MeCN-H_2O (containing 0.05% diethylamine, v/v) to give **6** (26.0 mg, 0.00026%, t_R = 21.9 min).

4. Compound Characterization

Annotinolide A (1): colorless crystals from MeOH; $[\alpha]_D^{25}$ +12 (*c* 0.02, MeOH); IR (film) ν_{max}: 2935, 1723, 1649, 1566, 1457, 1397, 1167, 1108, 1045 and 1005 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; (+) ESIMS *m/z* 260 $[M+H]^+$; (+) HRESIMS *m/z* 260.1647 $[M+H]^+$ (calcd for $C_{16}H_{22}NO_2$, 260.1645, Δ = 0.6 ppm).

Annotinolide B (2): colorless crystals from MeOH; $[\alpha]_D^{25}$ –33 (*c* 0.1, MeOH); IR (film) ν_{max}: 2935, 1715, 1641, 1437, 1374, 1307, 1212, 1100, 1015, 983, 768 and 726 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; (+) ESIMS *m/z* 260 $[M+H]^+$, 541 $[2M+Na]^+$; (+) HRESIMS *m/z* 260.1646 $[M+H]^+$ (calcd for $C_{16}H_{22}NO_2$, 260.1645, Δ = 0.5 ppm).

Annotinolide C (3): colorless crystals from $CHCl_3$/MeOH (5:1); $[\alpha]_D^{25}$ –50 (*c* 0.09, MeOH); ^1H and ^{13}C NMR data, see Table 1; (+) ESIMS *m/z* 290 $[M+H]^+$; (+) HRESIMS *m/z* 290.1394 $[M+H]^+$ (calcd for $C_{16}H_{20}NO_4$, 290.1387, Δ = 2.6 ppm).

Acetylacrifoline (4): colorless gum; $[\alpha]_D^{25}$ –133 (*c* 0.1, MeOH); ^1H and ^{13}C NMR data (Table S2) were identical with those reported in ref 1; (+) ESIMS *m/z* 304 $[M+H]^+$.

Lannotinidine G (5): colorless crystals from MeOH; $[\alpha]_D^{25}$ –64 (*c* 0.1, MeOH) [lit.[2] $[\alpha]_D^{18}$ –2 (*c* 1.0, MeOH)]; (+) ESIMS *m/z* 260 $[M+H]^+$; (+) HRESIMS *m/z* 260.1655 $[M+H]^+$ (calcd for $C_{16}H_{22}NO_2$, 260.1645, Δ = 3.7 ppm). The ^1H and ^{13}C NMR data (measured in CD_3OD+TFA) of lannotinidine G (**5**) were identical with those reported by Kobayashi et al.[2] However, according to an X-ray diffraction analysis (see Table S5 and Figure S35), the Me-16 group should be revised to be at β-orientation (Figure S35). Interestingly, the NMR data of **5** measured in neat CD_3OD (without TFA) have considerable differences with those measured also in CD_3OD but with slight TFA (Table S1). This phenomenon may be caused by the protonation of the alkaloid in the presence of TFA.[3] It is worth to note that TFA is often used as a buffer in the mobile phase during the isolation of alkaloids, and salts will be obtained. In this case, the NMR data acquired would be different from those of the free base. Therefore, this difference should be taken into consideration if the structural elucidation of alkaloids is carried out just by comparing the NMR data with those of the related structure reported in literature.

Annotinolide D (6): colorless crystals from $CHCl_3$/MeOH (5:1); $[\alpha]_D^{25}$ +38 (*c* 0.1, MeOH); IR (film) ν_{max}: 3214, 2933, 1743, 1452, 1389, 1302, 1285, 1124, 1072, and 1015 cm^{-1}; ^1H and ^{13}C NMR data, see Table S2; (+) ESIMS *m/z* 276 $[M+H]^+$, 573 $[2M+Na]^+$; (+) HRESIMS *m/z* 276.1600 $[M+H]^+$ (calcd for $C_{16}H_{22}NO_3$, 276.1594, Δ = 2.2 ppm).

Annotinolide E (7): colorless crystals from MeOH; $[\alpha]_D^{25}$ +77 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 209 (3.92), 259 (3.40) nm; IR (film) ν_{max}: 3371, 2935, 2860, 1733, 1654, 1600, 1432, 1382, 1127, 1075, 1055, 1018, and 985 cm^{-1}; ^1H and ^{13}C NMR data, see Table S2; (+) ESIMS *m/z* 290 $[M+H]^+$, 579 $[2M+H]^+$, 601 $[2M+Na]^+$; (+) HRESIMS *m/z* 290.1395 $[M+H]^+$ (calcd for $C_{16}H_{20}NO_4$, 290.1387, Δ = 2.9 ppm).

5. X-ray Crystallographic Analyses

Colorless crystals of **1**, **2** and **5** were all obtained by recrystallization from MeOH, and **3** was

from $CHCl_3$/MeOH (5:1, v/v). The crystals data were collected on a Bruker Apex Duo diffractometer using graphite-monochromated Cu Kα radiation. The structures of **1**–**3** were solved by direct methods using SHELXS-97. Refinements were performed with SHELXL-2013 using full-matrix least-squares calculations on F^2, with anisotropic displacement parameters for all the non-hydrogen atoms. The hydrogen atom positions were geometrically idealized and allowed to ride on their parent atoms. The Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (deposition no. CCDC 1487076–1487078 for **1**–**3**, and 1487574 for **5**, resp.), which can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif.

6. Bioactivity Assays

6.1. Thioflavin T (ThT) Fluorescence Assay

The aggregation state of Aβ peptide was measured by thioflavin T (ThT) (Sigma-Aldrich, St. Louis, MO, USA) fluorometric assay according to published papers with some modifications.[4] A$\beta_{1\text{-}42}$ (50 μM) was incubated at 37 ℃ in the presence or absence of compounds for 24 h. A$\beta_{1\text{-}42}$ samples (34 μL) were mixed with 166 μL ThT solutions (15 μM in 0.2 M Glycine–NaOH buffer, pH 8.5). After 5 min' shaking, the fluorescence value is measured at 425/490 nm (excitation/emission) by a fluorescence spectrophotometer (Molecular Devices, CA, USA).

6.2. Anti-AChE Assay

Anti-AChE activity was measured by the Ellman's spectrophotometric method as described in our previous work.[5] Acetylthiochol ineiodide 2 mM was used as substrate for assay of AChE activity. The mixture, including substrates, 1 mL Na_3PO_4 buffer (0.1 mM), and 0.1 mL enzyme, was incubated in a total volume of 4 mL at 37 ℃ for 8 min. The reaction was terminated by adding 1 mL 3% sodium dodecyl sulfonate (SDS), and 1 mL 0.2% 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) was then added to produce the yellow anion of 5-thio-2-nitrobenzoic acid. The rate of color production was measured spectrophotometrically at 440 nm. Enzyme activity is expressed as a percentage of the activity observed in the absence of inhibitor. The IC_{50} was defined as the concentration of inhibitor necessary to yield 50% inhibition of enzyme activity. All the samples were tested in duplicate.

6.3 Neuroprotective Activity Assay

SH-SY5Y cell survival was evaluated according to the reported papers.[5,6] Cells were high passages from the ATCC (American Type Culture Collection) maintained at 37 ℃ in a humidified atmosphere containing 5% CO_2. Cells were seeded into 96-well plates at a density of 2×10^5 cells/mL in MEM/F12 medium supplemented with 10% (v/v) fetal bovine serum. Experiments were carried out 24 h after cells were seeded. Test compounds and positive control (epigallocatechin-3-gallate, EGCG) were made to 10^{-2} M stock solutions with DMSO and then diluted to corresponding concentrations with cell culture medium. Cells were incubated with test compounds (1 or 10 μM) or EGCG (10 μM, Sigma, purity >98%) for 2 h prior to treatment with 100 μM H_2O_2 or 10 μM Aβ_{25-35} for another 24 h without changing the culture medium. Then 10 μL of MTT (5 mg/mL) was added to each well and incubated at 37 ℃ for 3 h. The cells were finally lysed with 100 μL of DMSO, and the amount of MTT formazan was measured at 490 nm using a microplate reader.

7. Plausible Biosynthesis of Lycopodane-type Alkaloids from L-Lysine [7]

Briefly, L-Lysine could form cadaverine through decarboxylation. Cadaverine could be then transformed via 5-aminopentanal to afford Δ^1-piperideine, which could further be coupled to acetonedicarboxylic acid (or its bisCoA ester) to yield piperidyl acetoacetate (4PAA) (or piperidyl acetoacetyl-CoA, 4PAACoA). 4PAA/4PAACoA could be decarboxylated to form pelletierine. Accompanied by requisite decarboxylation, pelletierine and 4PAA/4PAACoA could then be coupled to form phlegmarine, which is then transformed to lycodane-type alkaloids through inter-molecular cyclization. Finally, lycopodane-type alkaloids (e.g., acrifoline) are formed from the cleavage of the C-1/*N* bond in ring A of lycodane-type alkaloids followed by a new C/*N* bond formation.

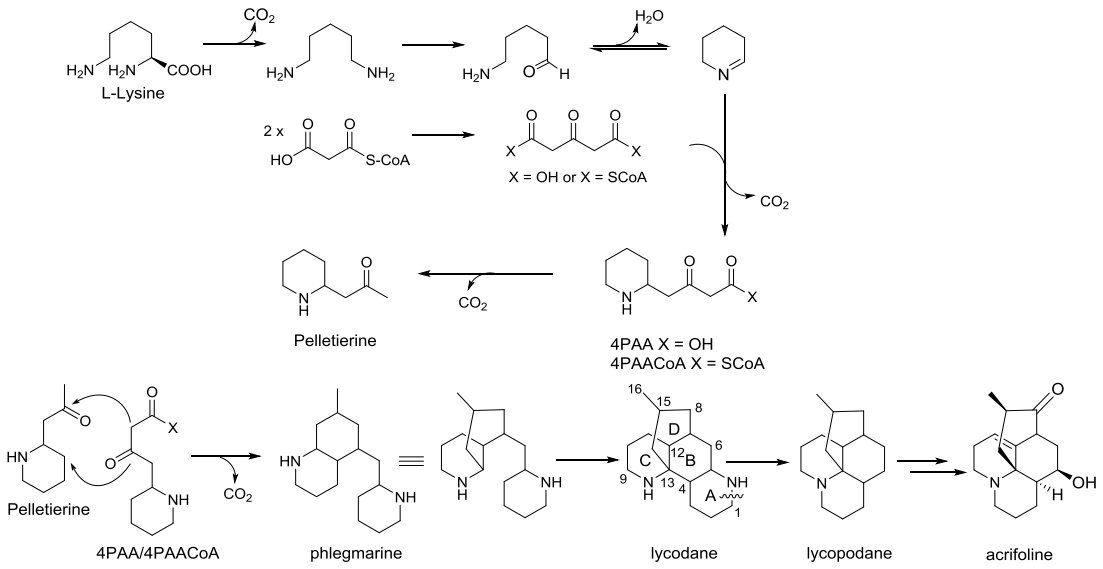

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Table S1. ^{1}H and ^{13}C NMR Data (δ in ppm, J in Hz) for Lannotinidine G (5)

no.	**5** [a, b]		**5** [c]		**5** [d]		Lannotinidine G [d] (ref. 2 in SI)	
	δ_H (J in Hz) [e]	δ_C [f]	δ_H (J in Hz) [e]	δ_C [g]	δ_H (J in Hz) [h]	δ_C [g]	δ_H (J in Hz)	δ_C
1a	2.67, ddd, overlapped	48.1	2.78, ddd (12.3, 12.3, 3.7)	49.4	3.45, ddd (13.1, 13.1, 3.8)	49.4	3.43, dt (17.0, 13.2, 3.8)	49.6
1b	2.67, ddd, overlapped		2.67, br d (12.3)		3.36, ddd (13.1, 4.8, 1.8)		3.43, dt (17.0, 13.2, 3.8)	
2a	1.78, m	25.4	1.81, m	26.0	2.08, m	24.0	2.08, m	24.1
2b	1.78, m		1.76, m		1.95, m		1.94, m	
3a	1.66, m	22.9	1.65, m	23.8	1.83, m	21.8	1.83, dd (8.2, 3.3)	21.8
3b	1.60, m		1.59, m		1.81, m		-	
4	1.97, dddd (12.2, 4.3, 3.6, 1.1)	44.4	2.01, br ddd, (12.4, 4.3, 3.8)	45.1	2.31, dddd (12.0, 4.3, 3.3, 1.6)	43.7	2.30, m	43.8
5	4.60, br dd (9.3, 4.3)	75.6	4.65, br dd (9.0, 4.3)	77.2	4.75, br dd (9.0, 4.3)	75.2	4.75, dd (8.9, 4.3)	75.2
6a	2.91, ddd (21.7, 9.3, 3.6)	32.3	2.97, ddd (21.9, 9.0, 3.7)	33.0	3.08, ddd (22.6, 9.0, 3.8)	32.6	3.07, m	32.7
6b	2.47, br dd (21.7, 3.6)		2.52, br dd (21.9, 3.7)		2.68, ddd, overlapped		2.67, m	
7	5.59, dd (3.6, 3.6)	122.1	5.70, dd (3.7, 3.7)	124.4	6.10, dd (3.8, 3.8)	131.0	6.10, t (3.7)	130.9
8		176.9		179.3		177.1		177.2
9a	3.21, dd (18.5, 4.3)	49.4	3.23, ddd (19.6, 3.6)	50.2	3.90, br d (18.8)	49.8	3.87, m	49.8
9b	3.14, dd (18.5, 3.0)		3.17, dd (19.6, 3.2)		3.81 dd (18.8, 4.8)		3.80, d (4.6)	
10	5.75, ddd (9.9, 4.3, 3.0)	124.9	5.77 ddd (10.0, 3.6, 3.2)	125.2	5.78, br dd (10.4, 4.8)	119.7	5.79, m	119.9
11	6.09, br d (9.9)	125.5	6.16, br d (10.0)	126.8	6.40, br d (10.4)	127.1	6.40, d (10.2)	127.1
12		137.4		138.2		132.9		133.1
13		55.2		57.1		62.7		62.0
14a	2.02, dd (13.3, 13.3)	24.7	2.10, dd (12.9, 12.9)	26.2	2.45, dd (13.3, 13.3)	28.3	2.44, t (13.1)	28.3
14b	1.41, ddd (13.3, 2.4, 1.1)		1.48, br dd (12.9, 2.2)		1.76, ddd (13.3, 2.0, 1.6)		1.76, dd (13.8, 2.1)	
15	2.53, m	33.6	2.61, m	34.7	2.67, m	34.1	2.67, m	34.2
16	1.15, d (6.5)	18.7	1.11, d (6.7)	18.9	1.20, d (6.6)	18.8	1.20, d (6.6)	18.8

[a] Assignments were made by a combination of 1D and 2D NMR experiment; [b] free base in $CDCl_3$; [c] free base in CD_3OD; [d] TFA salt in CD_3OD [e] recorded at 400 MHz; [f] recorded at 100 MHz; [g] recorded at 150 MHz; [h] recorded at 600 MHz

Table S2. ^{1}H and ^{13}C NMR Data (δ in ppm, J in Hz) for Compounds 4, 6, and 7.

no.	**4** [a] (ref. 1 in SI)		**6** [a, b]		**7** [a, b]	
	δ_H (J in Hz) [c]	δ_C [d]	δ_H (J in Hz) [c]	δ_C [d]	δ_H (J in Hz) [e]	δ_C [f]
1a	2.76, br dd (11.8, 11.8)	48.7	2.71, br d (11.3)	51.4	4.28, br d (13.4)	39.9
1b	2.58, m		2.24, ddd (11.3, 11.3, 3.3)		2.67, ddd (13.4, 13.4, 3.6)	
2a	1.77, m	24.5	1.72, overlapped	25.1	1.93, m	23.9
2b	1.60, m		1.69, overlapped		1.55, m	
3a	1.68, overlapped	23.3	1.68, overlapped	23.6	1.80, overlapped	22.7
3b	1.45, m		1.68, overlapped		1.76, dddd (13.4, 13.4, 13.4, 3.6)	
4	1.91, br d (12.5)	46.8	2.29, br d (13.6)	39.7	2.55, br d (13.4)	38.9
5	4.91, br dd (3.3, 2.3)	72.4	4.36, dddd (5.1, 3.1, 2.8, 1.6)	79.1	4.47, dddd (5.1, 3.1, 2.8, 1.3)	78.0
6a	2.38, ddd (14.4, 2.8, 2.5)	36.1	2.67, ddd (13.9, 3.1, 1.6)	29.9	2.76, ddd (14.2, 3.1, 1.3)	30.3
6b	1.85, ddd (14.4, 5.1, 3.4)		1.72, overlapped		1.79, overlapped	
7	2.91, dd (5.1, 2.8)	50.6	1.92, ddd (5.0, 1.6, 1.6)	46.2	2.18, ddd (4.9, 1.3, 1.3)	48.6
8		216.4		178.2		176.9
9a	2.67, m	45.3	3.34, ddd (18.7, 3.7, 1.2)	49.9		163.2
9b	2.67, m		2.86, ddd (18.7. 2.0, 2.0)			
10a	2.34, m	26.0	5.79, ddd (9.8, 3.7, 2.0)	127.5	6.03, d (9.7)	126.4
10b	2.03, overlapped					
11	5.56, dd (5.0, 2.6)	119.0	5.83, ddd (9.8, 2.0, 1.2)	130.6	6.66, d (9.7)	142.7
12		138.7		72.7		72.7
13		57.4		65.8		66.1
14a	2.03, overlapped	30.3	2.04, d (13.3)	31.4	2.50, d (13.8)	41.5
14b	1.68, overlapped		1.65, dd (13.3, 1.9)		1.65, dd (13.8, 1.8)	
15	2.51, m	43.4		42.6		42.8
16	1.11, d (6.5)	14.3	1.25, s	24.3	1.25, s	22.6
OAc	1.95, s	21.2				
		170.0				

[a] free base in $CDCl_3$; [b]Assignments were made by a combination of 1D and 2D NMR experiment; [c] recorded at 400 MHz; [d] recorded at 100 MHz;

[e] recorded at 600 MHz; [f] recorded at 150 MHz

Table S3. X-ray Crystallographic Data for 1

Identification code	cu_dm16310_0m	
Empirical formula	C16 H21 N O2	
Formula weight	259.34	
Temperature	296 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.59030(10) Å	α= 90 °.
	b = 9.11950(10) Å	β= 90 °.
	c = 17.5588(2) Å	γ = 90 °.
Volume	1375.54(3) $Å^3$	
Z	4	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.649 mm^{-1}	
F(000)	560	
Crystal size	0.12 x 0.08 x 0.05 mm^3	
Theta range for data collection	5.037 to 69.419 °.	
Index ranges	-10<=h<=10, -11<=k<=11, -21<=l<=21	
Reflections collected	11093	
Independent reflections	2539 [R(int) = 0.0343]	
Completeness to theta = 67.679 °	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7532 and 0.5254	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2539 / 0 / 173	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1399	
R indices (all data)	R1 = 0.0518, wR2 = 0.1489	
Absolute structure parameter	0.01(11)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.164 and -0.253 e.$Å^{-3}$	

Table S4. X-ray Crystallographic Data for 2

Identification code	cu_dm16230_0m	
Empirical formula	C16 H21 N O2	
Formula weight	259.34	
Temperature	130 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.73130(10) Å	α= 90 °.
	b = 10.04310(10) Å	β= 90 °.
	c = 14.6801(2) Å	γ = 90 °.
Volume	1287.29(3) $Å^3$	
Z	4	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	0.694 mm^{-1}	
F(000)	560	
Crystal size	0.15 x 0.10 x 0.08 mm^3	
Theta range for data collection	5.336 to 69.663 °.	
Index ranges	-10<=h<=10, -11<=k<=10, -17<=l<=17	
Reflections collected	10166	
Independent reflections	2379 [R(int) = 0.0269]	
Completeness to theta = 67.679 °	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7532 and 0.6039	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2379 / 0 / 173	
Goodness-of-fit on F^2	1.102	
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0879	
R indices (all data)	R1 = 0.0351, wR2 = 0.0885	
Absolute structure parameter	0.04(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.168 and -0.264 e.$Å^{-3}$	

Table S5. X-ray Crystallographic Data for 3

Identification code	cu_dm16105_0m	
Empirical formula	C16 H19 N O4	
Formula weight	289.32	
Temperature	296 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.8847(4) Å	α= 90 °.
	b = 12.7310(6) Å	β= 90 °.
	c = 13.5189(7) Å	γ = 90 °.
Volume	1357.03(12) $Å^3$	
Z	4	
Density (calculated)	1.416 Mg/m^3	
Absorption coefficient	0.837 mm^{-1}	
F(000)	616	
Crystal size	0.2 x 0.15 x 0.1 mm^3	
Theta range for data collection	4.771 to 69.137 °.	
Index ranges	-9<=h<=9, -15<=k<=15, -16<=l<=15	
Reflections collected	9131	
Independent reflections	2440 [R(int) = 0.0378]	
Completeness to theta = 67.679 °	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7532 and 0.5647	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2440 / 0 / 195	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0875	
R indices (all data)	R1 = 0.0340, wR2 = 0.0885	
Absolute structure parameter	0.05(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.144 and -0.197 $e.Å^{-3}$	

Table S6. X-ray Crystallographic Data for Lannotinidine G (5)

Identification code	cu_dm16092_0m	
Empirical formula	C16 H21 N O2	
Formula weight	259.34	
Temperature	296 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.7114(2) Å	α= 90 °.
	b = 9.1691(2) Å	β= 90 °.
	c = 16.9047(5) Å	γ = 90 °.
Volume	1350.27(6) $Å^3$	
Z	4	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	0.662 mm^{-1}	
F(000)	560	
Crystal size	0.3 x 0.22 x 0.2 mm^3	
Theta range for data collection	5.233 to 69.665 °.	
Index ranges	-10<=h<=10, -10<=k<=10, -20<=l<=19	
Reflections collected	10106	
Independent reflections	2483 [R(int) = 0.0330]	
Completeness to theta = 67.679 °	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7532 and 0.5922	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2483 / 0 / 174	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0920	
R indices (all data)	R1 = 0.0349, wR2 = 0.0925	
Absolute structure parameter	0.06(8)	
Extinction coefficient	0.0185(15)	
Largest diff. peak and hole	0.169 and -0.160 e.$Å^{-3}$	

Figure S1. ^{1}H NMR (400 MHz) spectrum of 1 in $CDCl_3$

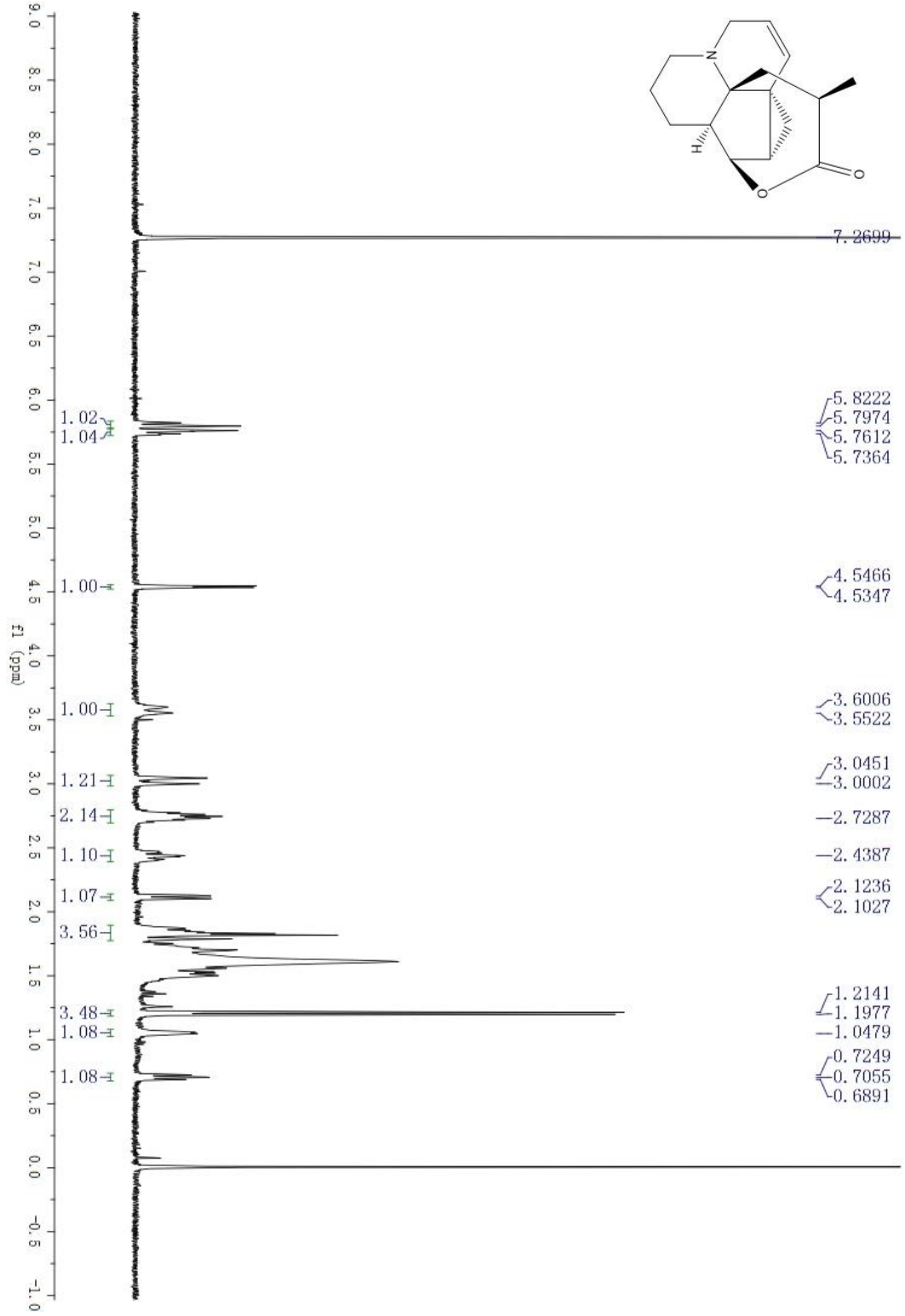


Figure S2. ^{13}C NMR (100 MHz) spectrum of 1 in $CDCl_3$

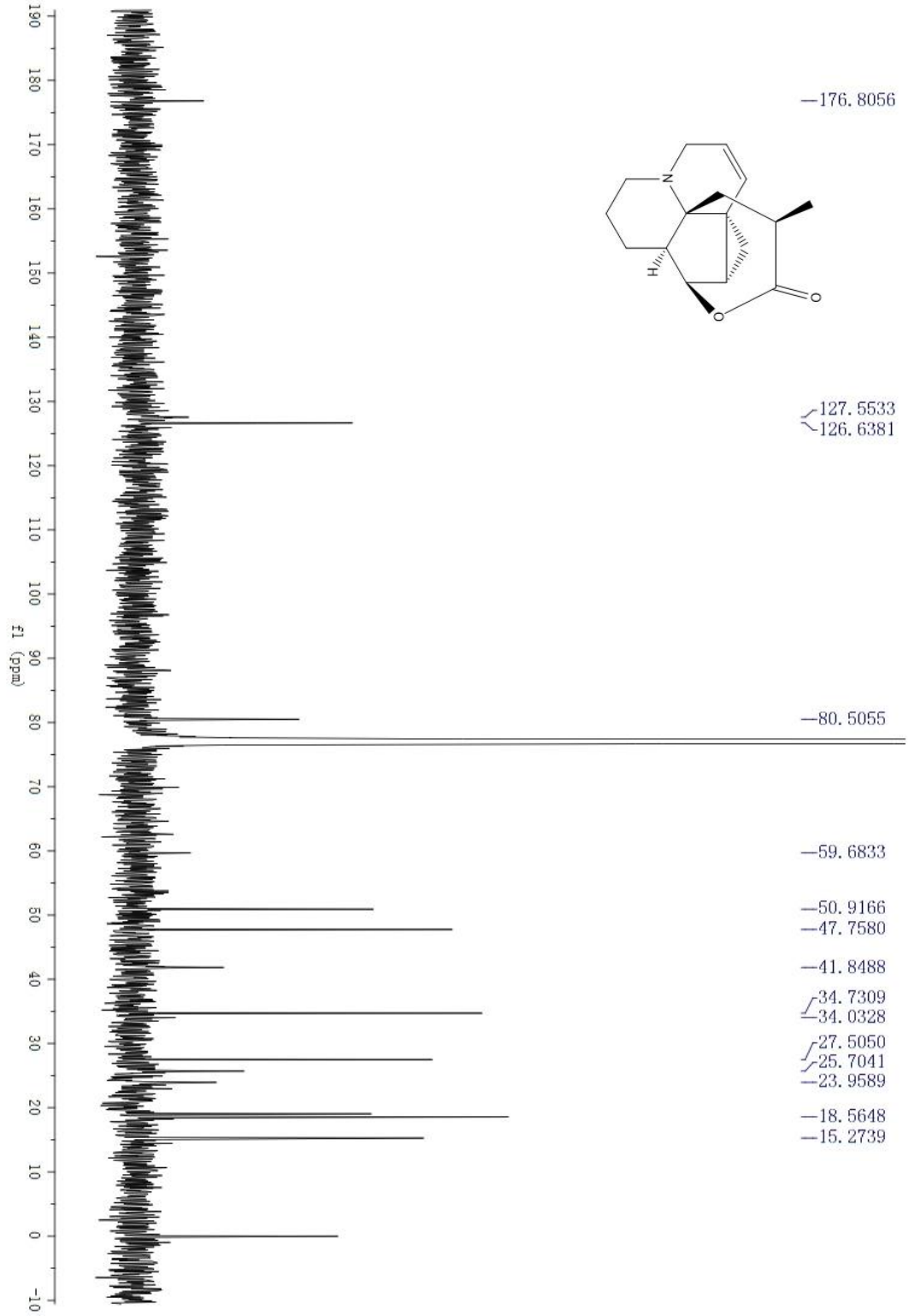


Figure S3. HSQC (600 MHz) spectrum of 1 in $CDCl_3$

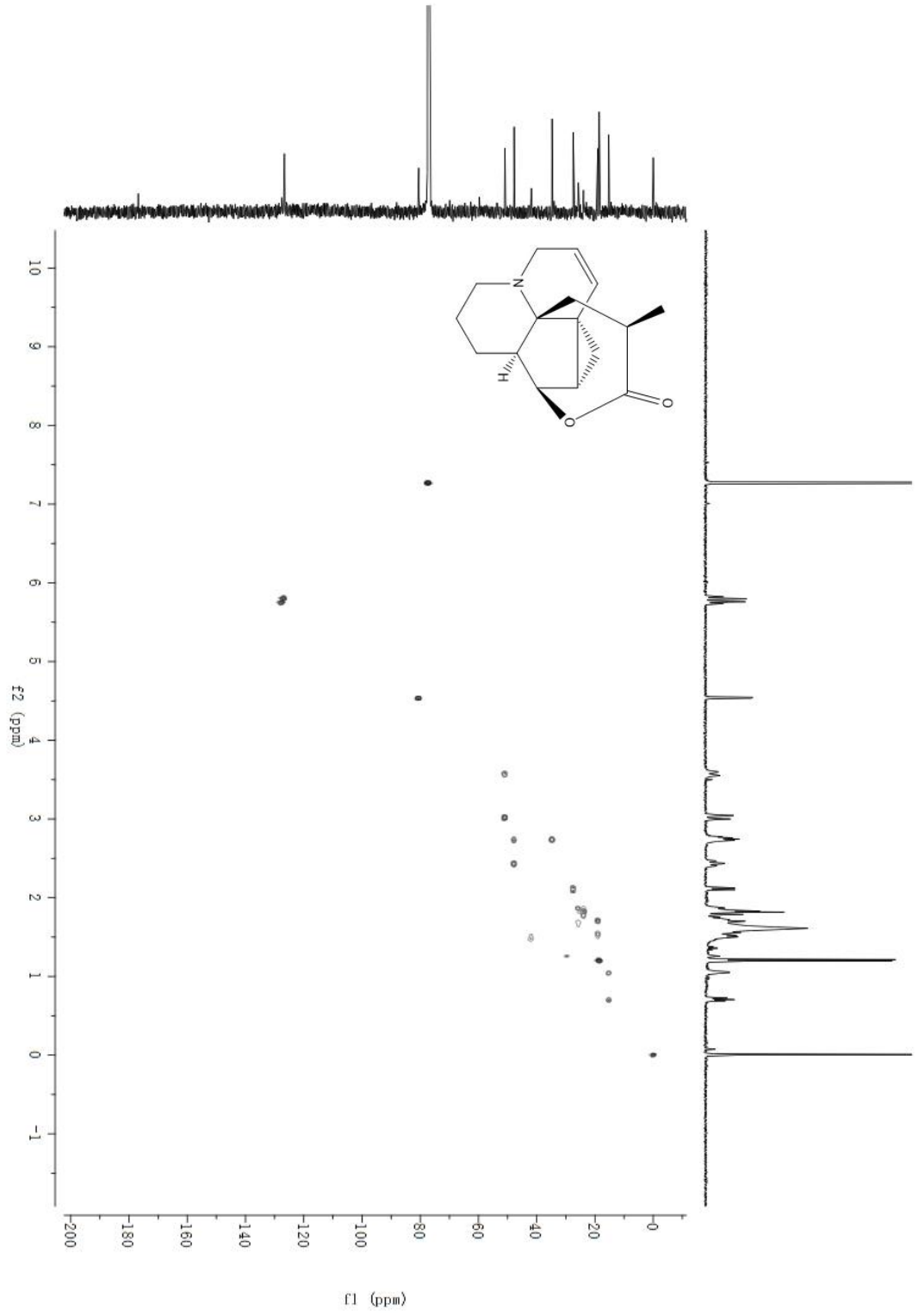


Figure S4. ^{1}H-^{1}H COSY (600 MHz) spectrum of 1 in $CDCl_3$

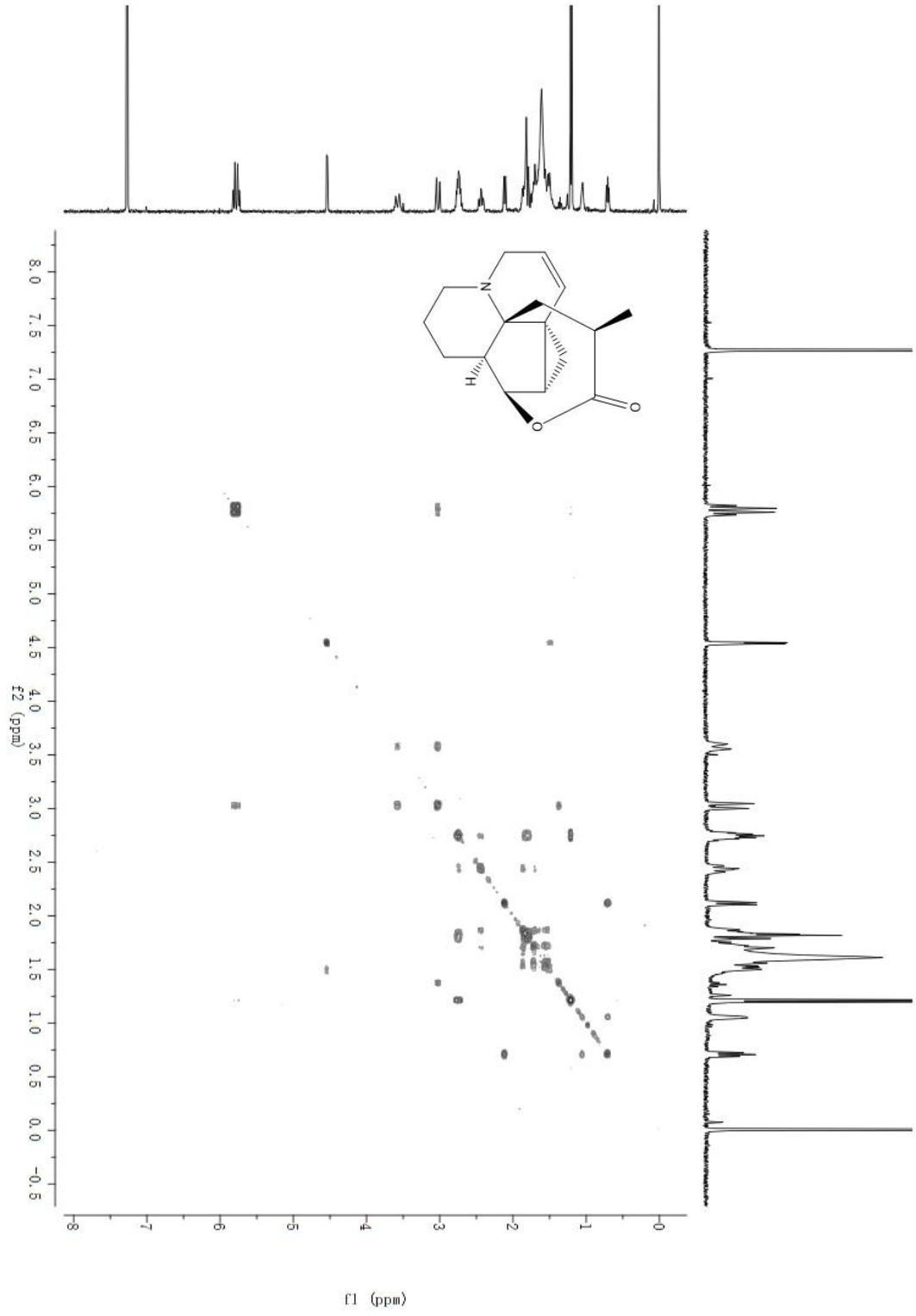


Figure S5. HMBC (600 MHz) spectrum of 1 in $CDCl_3$

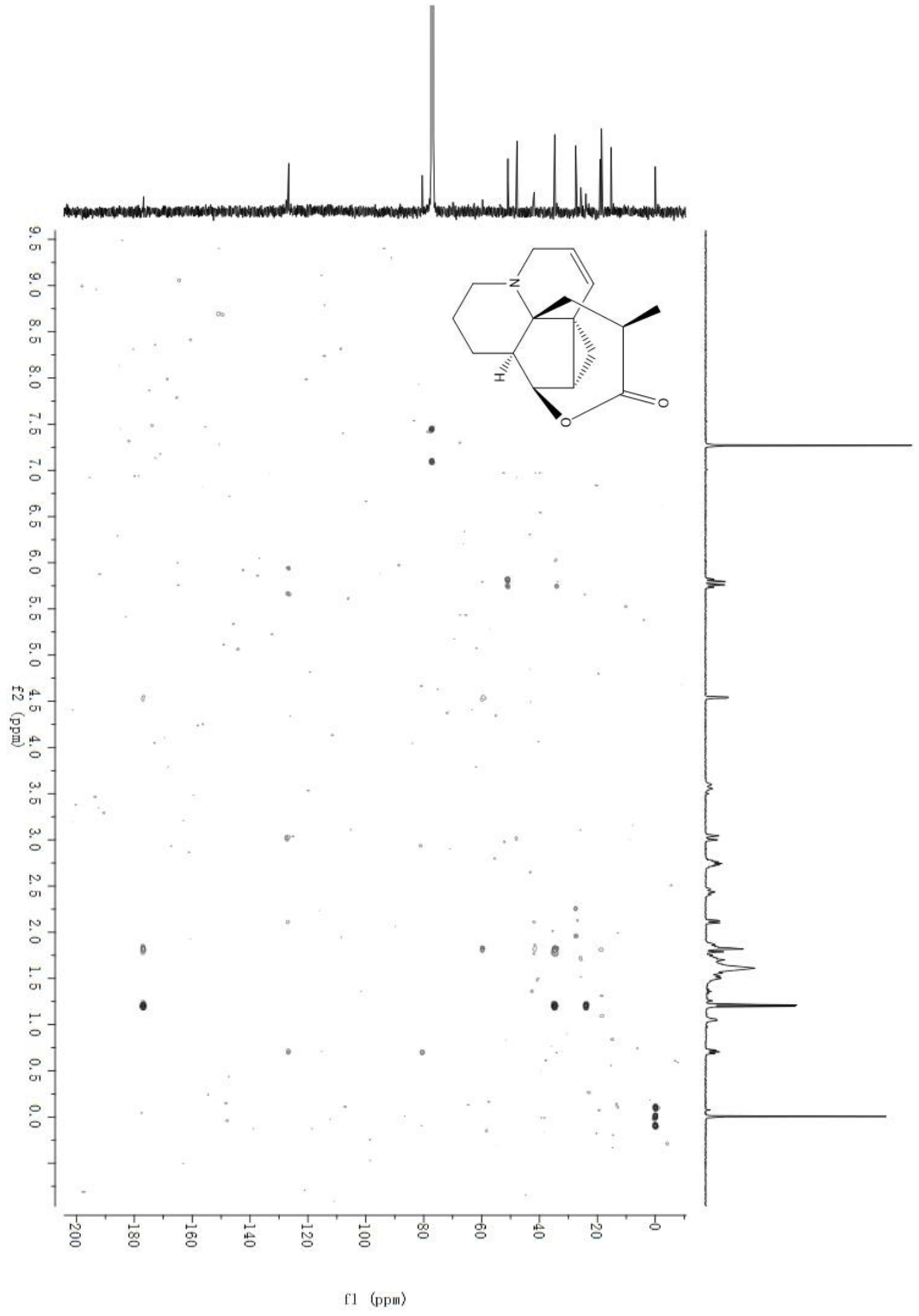


Figure S6. HMBC (500 MHz) spectrum of 1 in $CDCl_3$

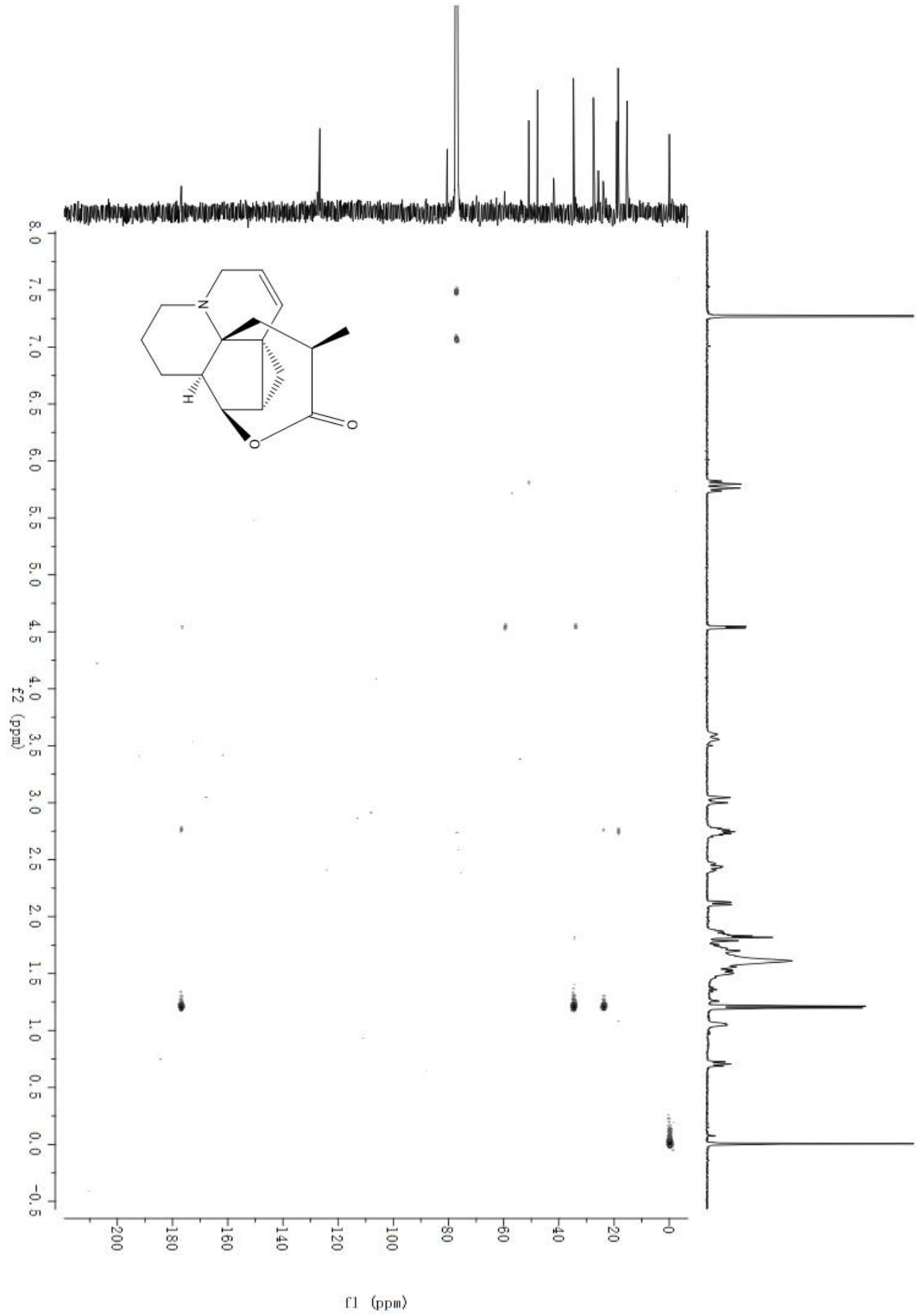


Figure S7. NOESY (600 MHz) spectrum of 1 in $CDCl_3$

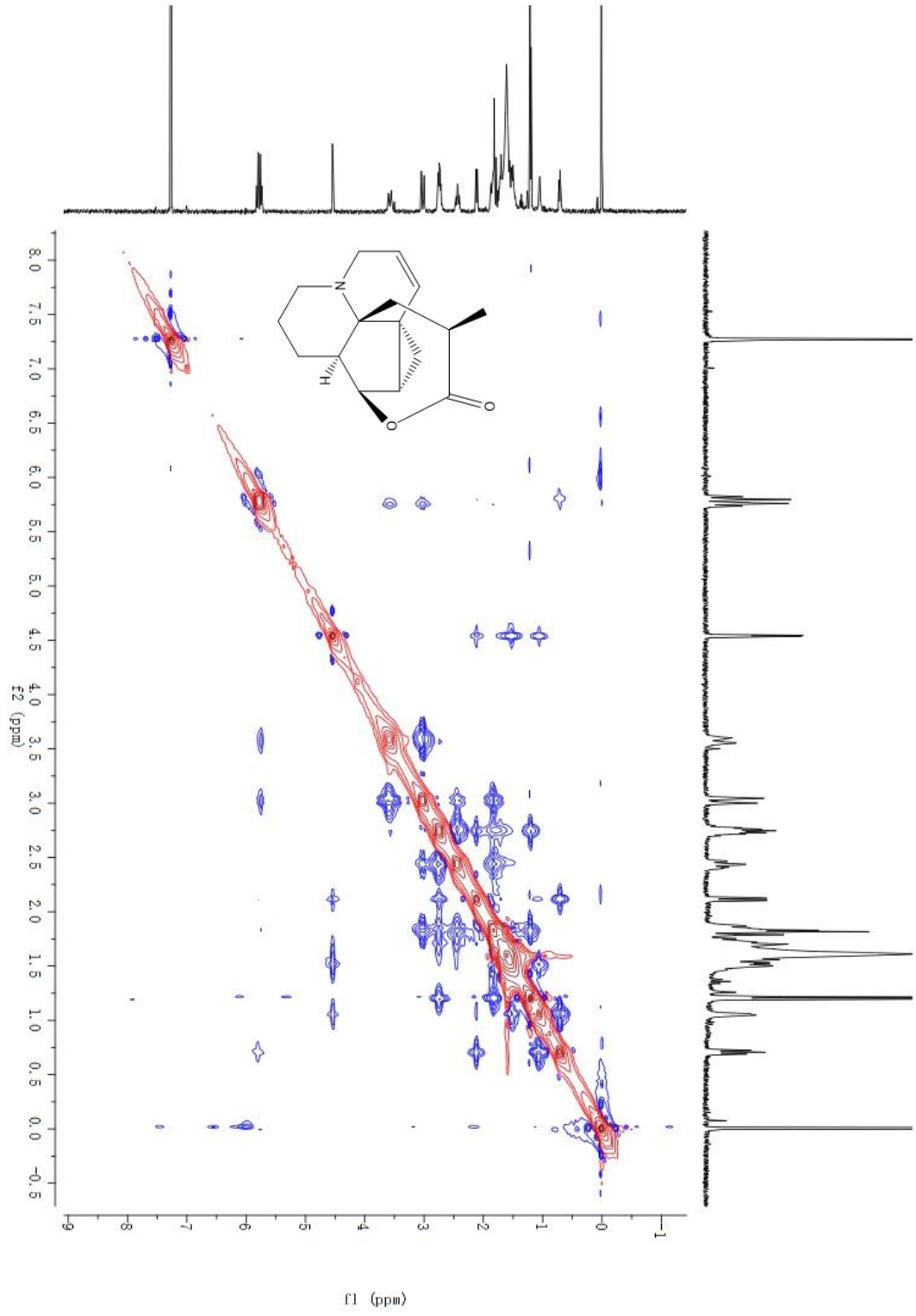


Figure S8. HRESIMS data of 1

Figure S9. ^{1}H NMR (400 MHz) spectrum of 2 in $CDCl_3$

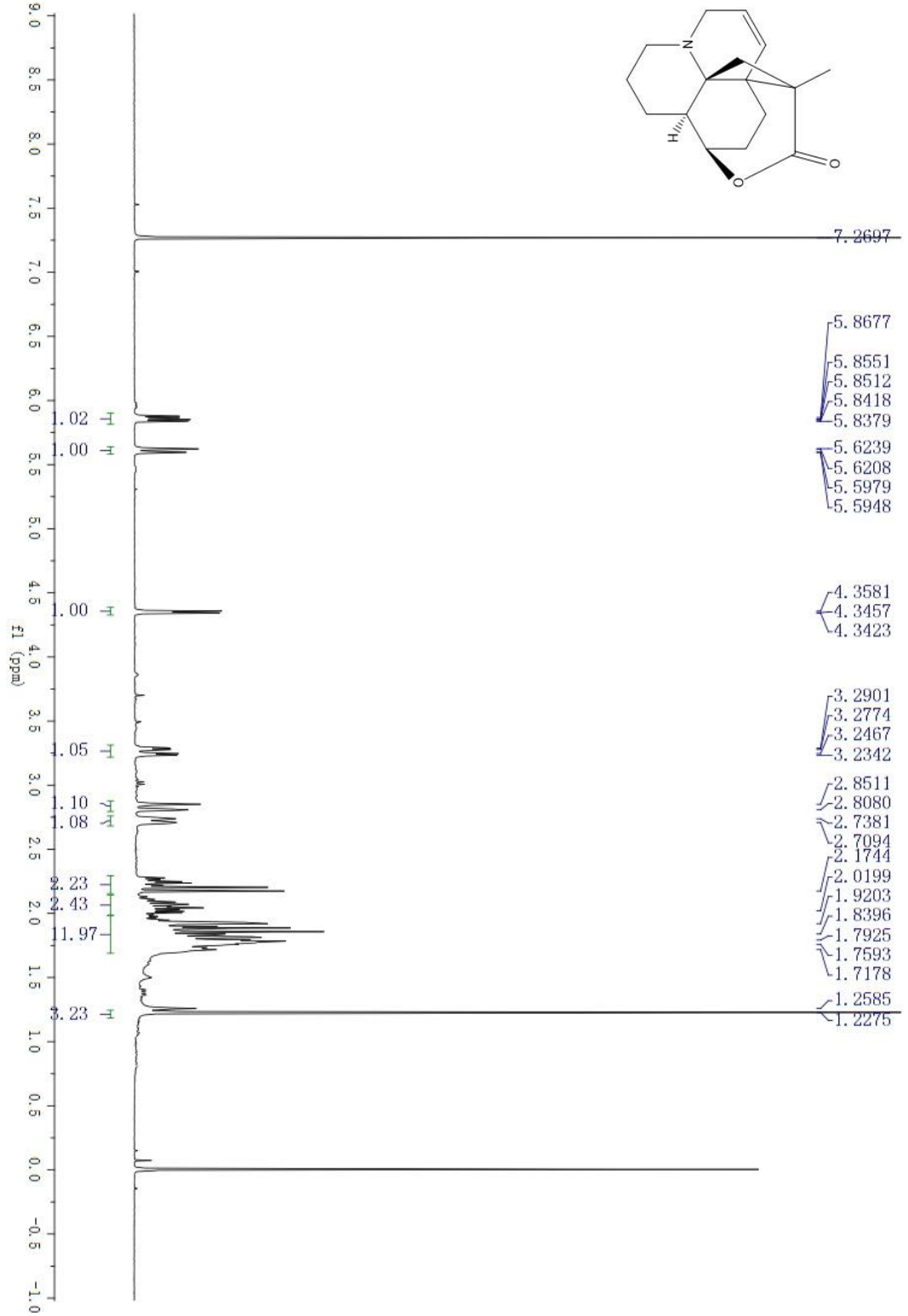


Figure S10. ^{13}C NMR (100 MHz) spectrum of 2 in $CDCl_3$

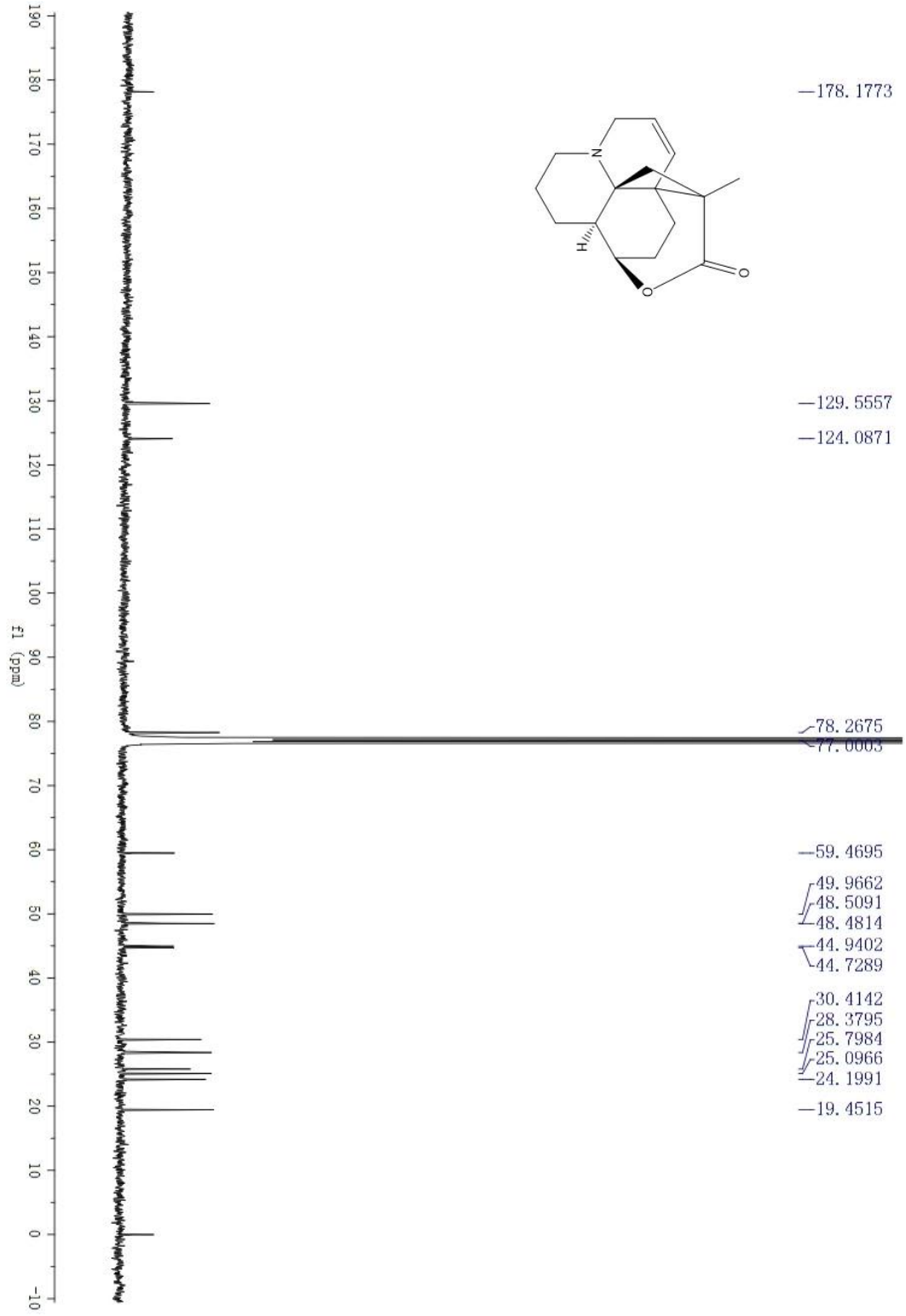


Figure S11. DEPT 135 (400 MHz) spectrum of 2 in $CDCl_3$

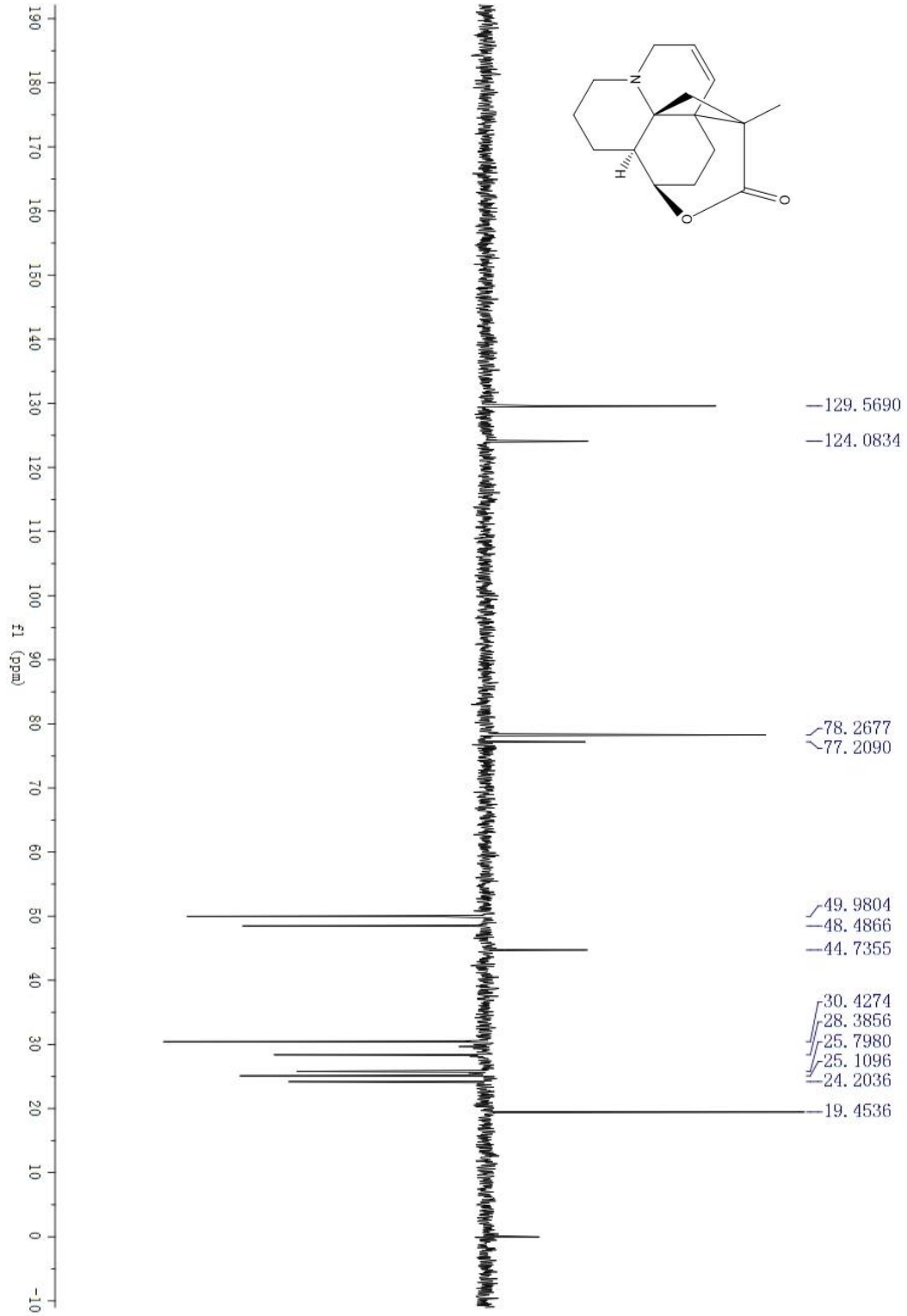


Figure S12. HSQC (400 MHz) spectrum of 2 in $CDCl_3$

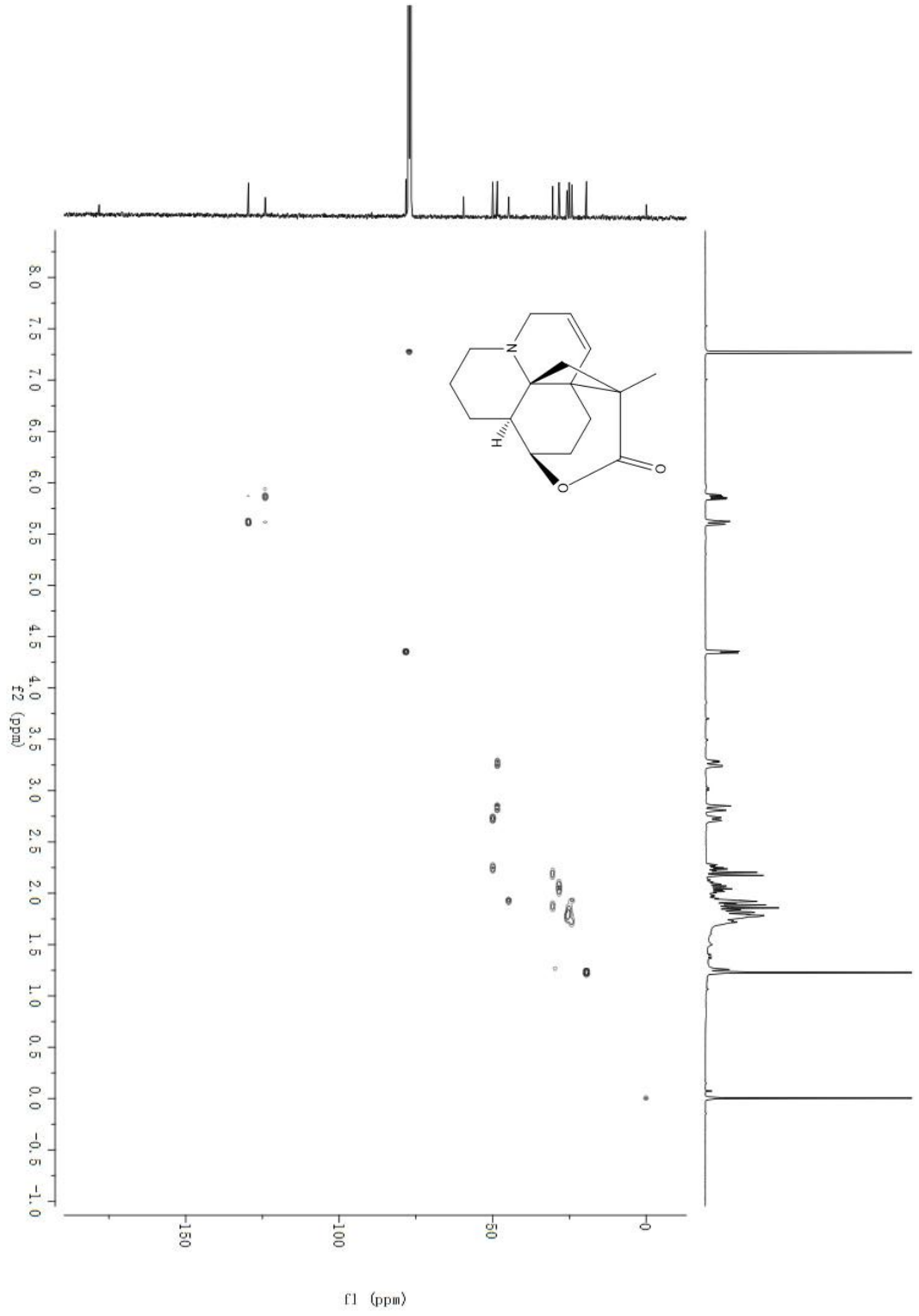


Figure S13. ^{1}H-^{1}H COSY (400 MHz) spectrum of 2 in $CDCl_3$

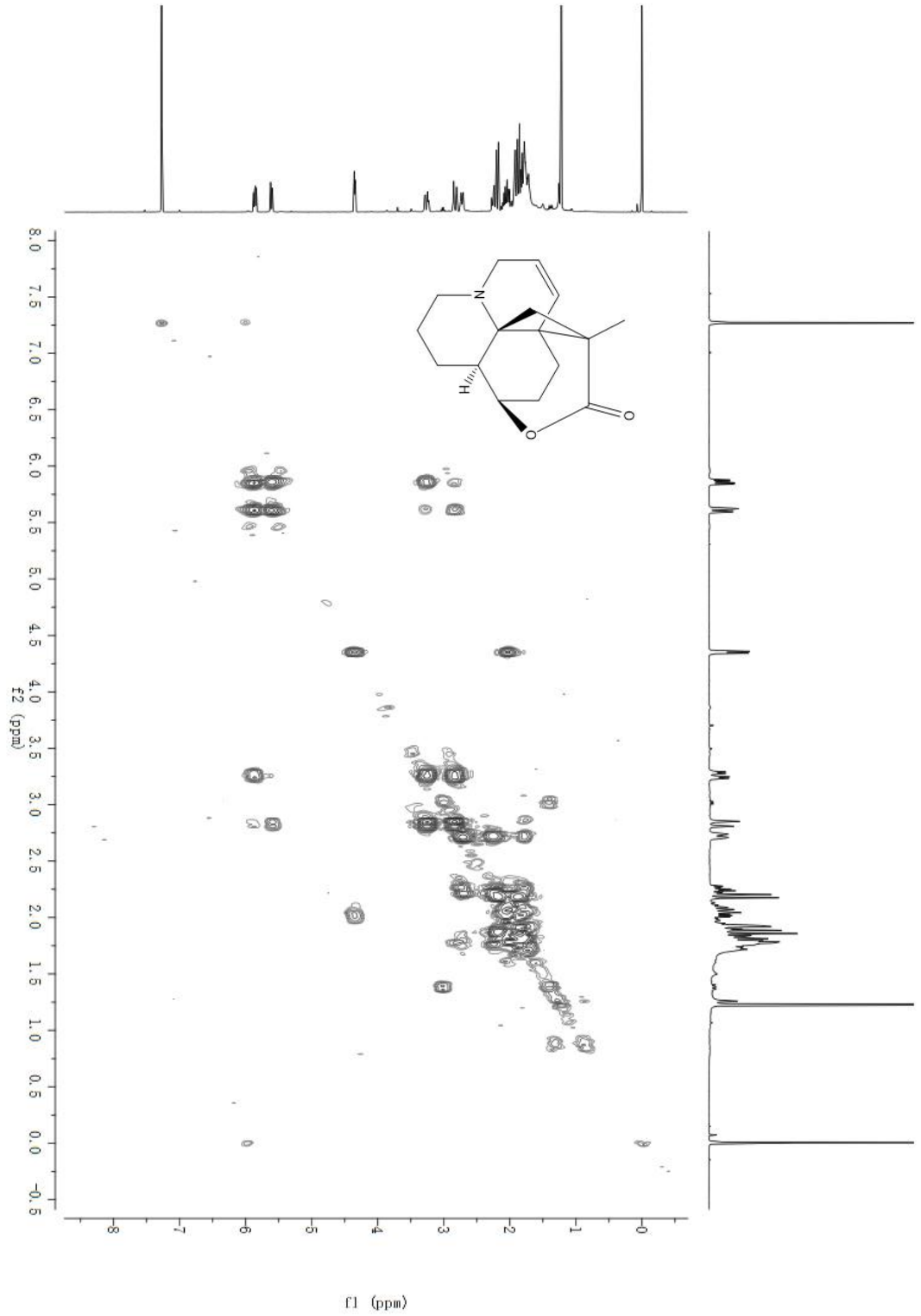


Figure S14. HMBC (400 MHz) spectrum of 2 in $CDCl_3$

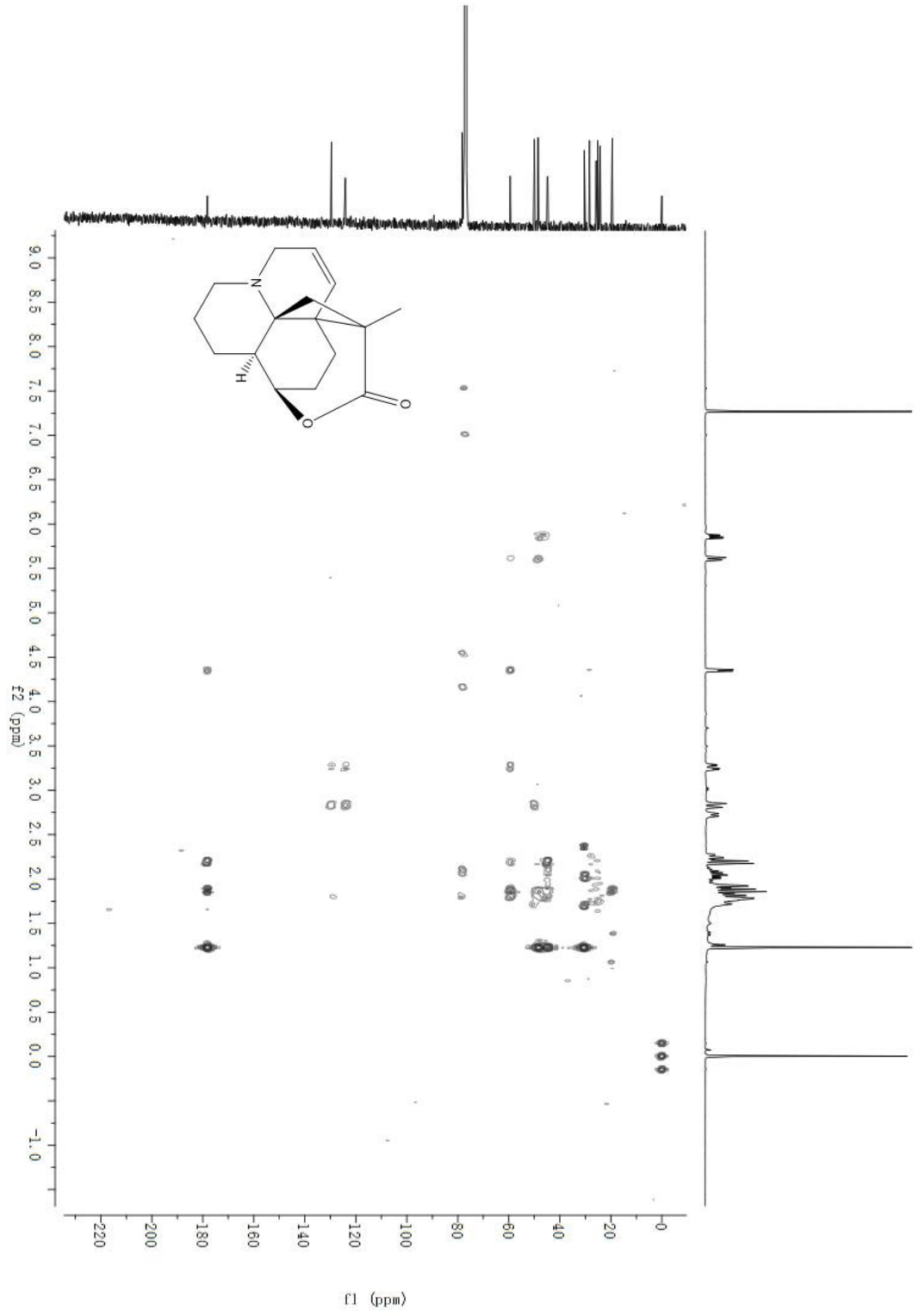


Figure S15. NOESY (400 MHz) spectrum of 2 in $CDCl_3$

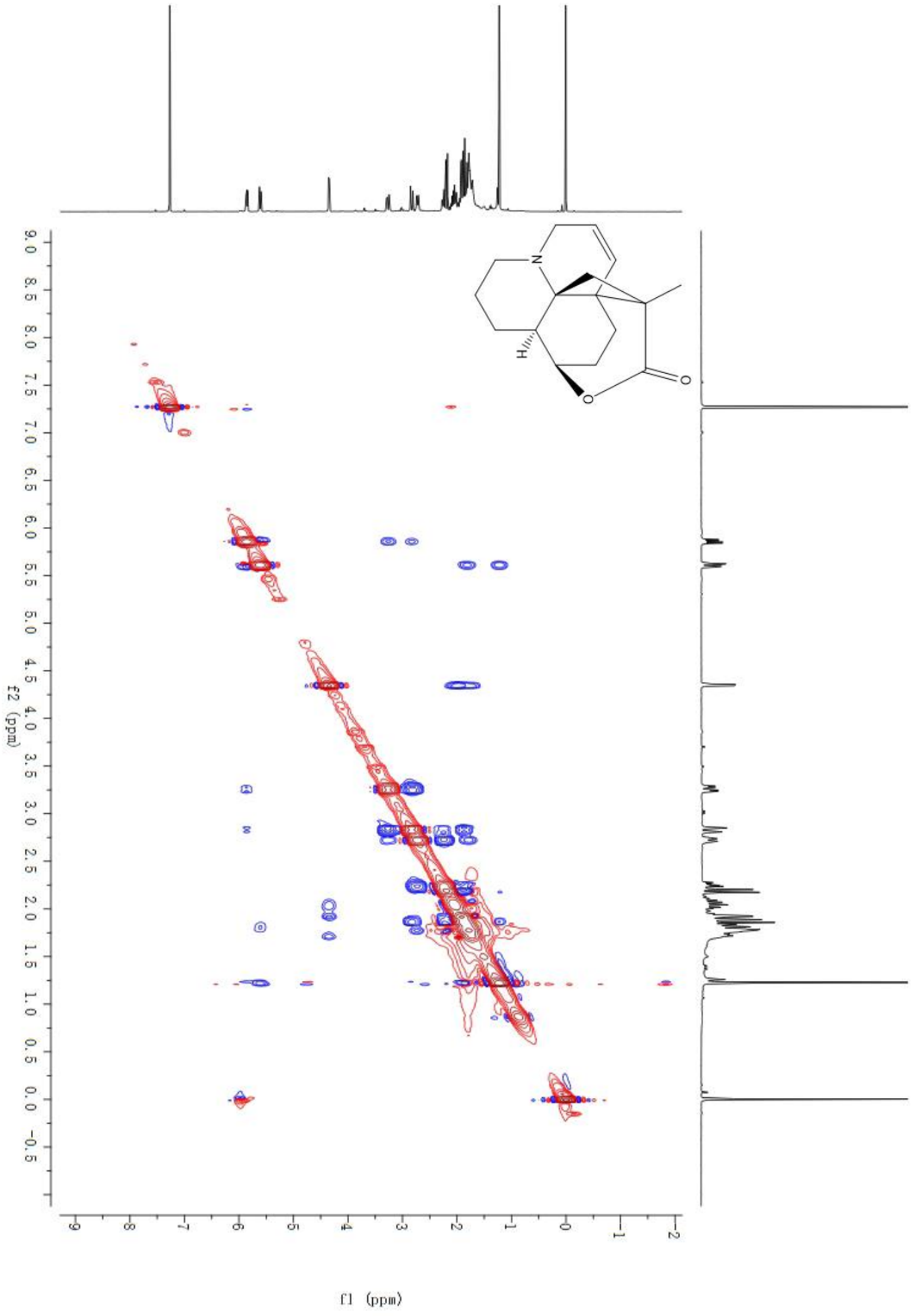


Figure S16. HRESIMS data of 2

	Compound Name (Library Hit)	Score	Formula	Intensity	Threshold	Expected m/z	Found at m/z	Error (ppm)	Expected RT (min)	Found RT (min)	RT Delta (min)	Isotope Diff (%)	Library Score(%)
✓ ● ✓ ● ●	(DS7) 259.157229128	97%	C16H21NO2	2580680	1000	260.1645	260.1646	0.5	0.00	0.39	0.39	0.1%	N/A

Figure S17. ^{1}H NMR (400 MHz) spectrum of 3 in $CDCl_3$

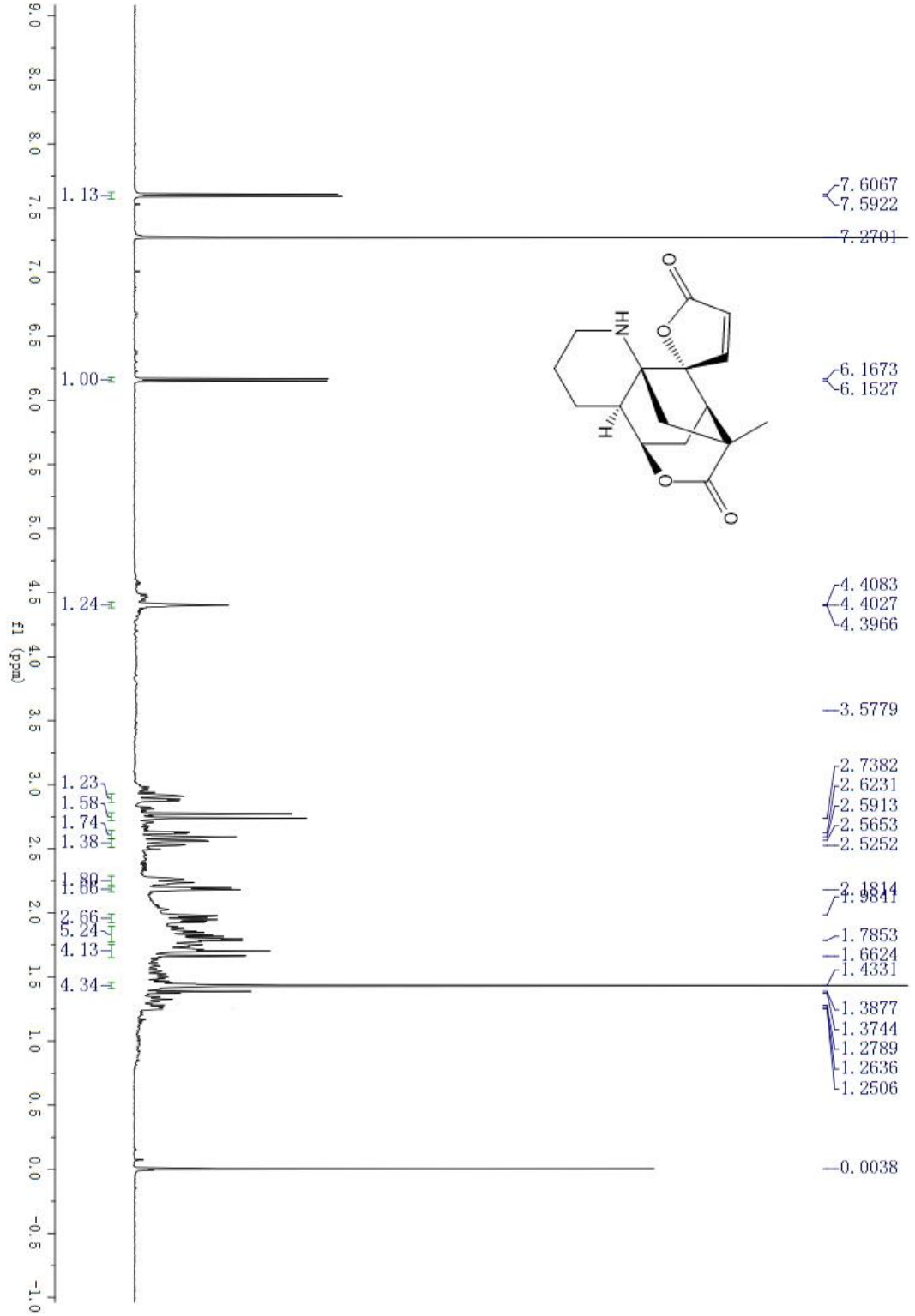


Figure S18. ^{13}C NMR (100 MHz) spectrum of 3 in $CDCl_3$

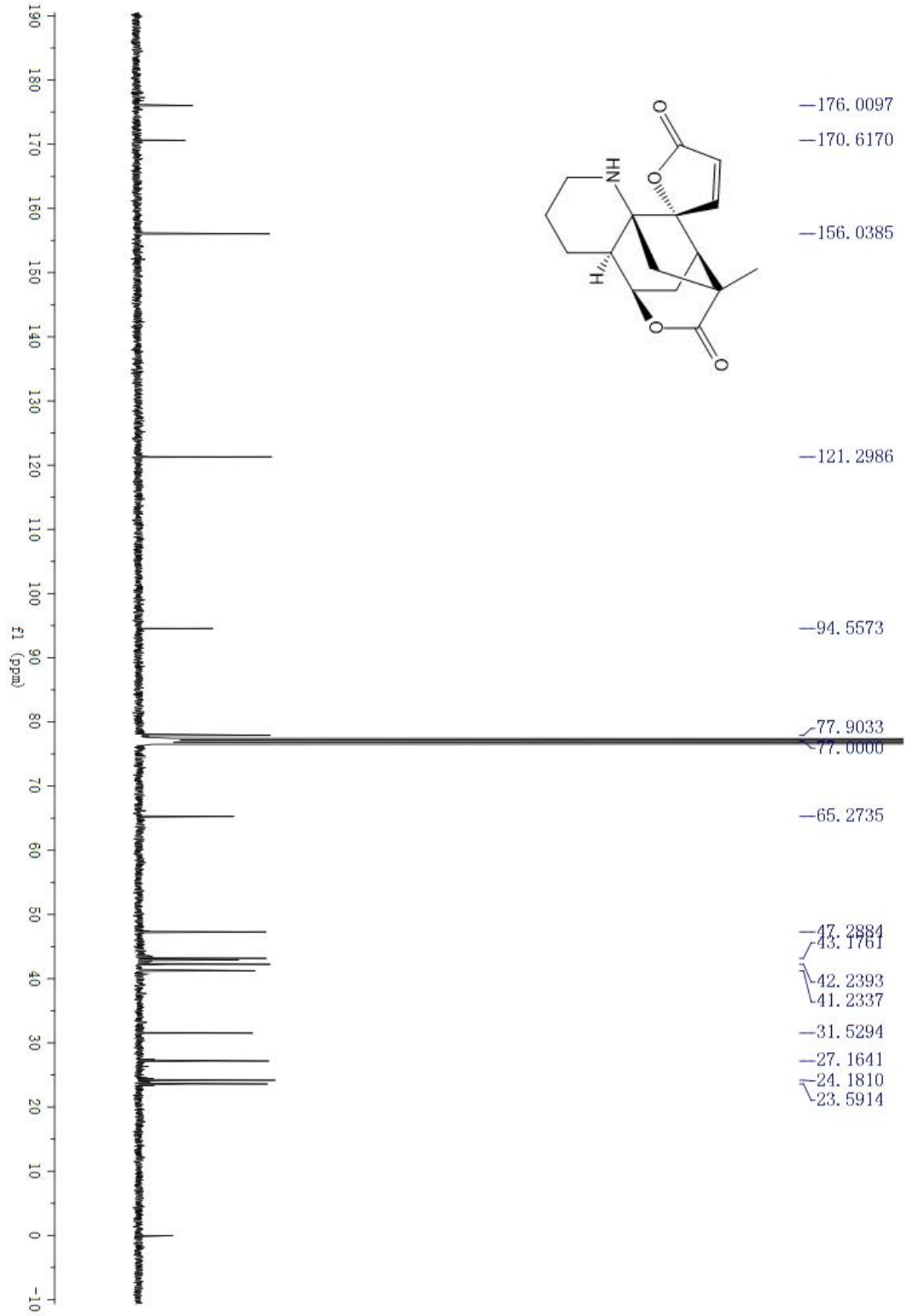


Figure S19. HSQC (400 MHz) spectrum of 3 in $CDCl_3$

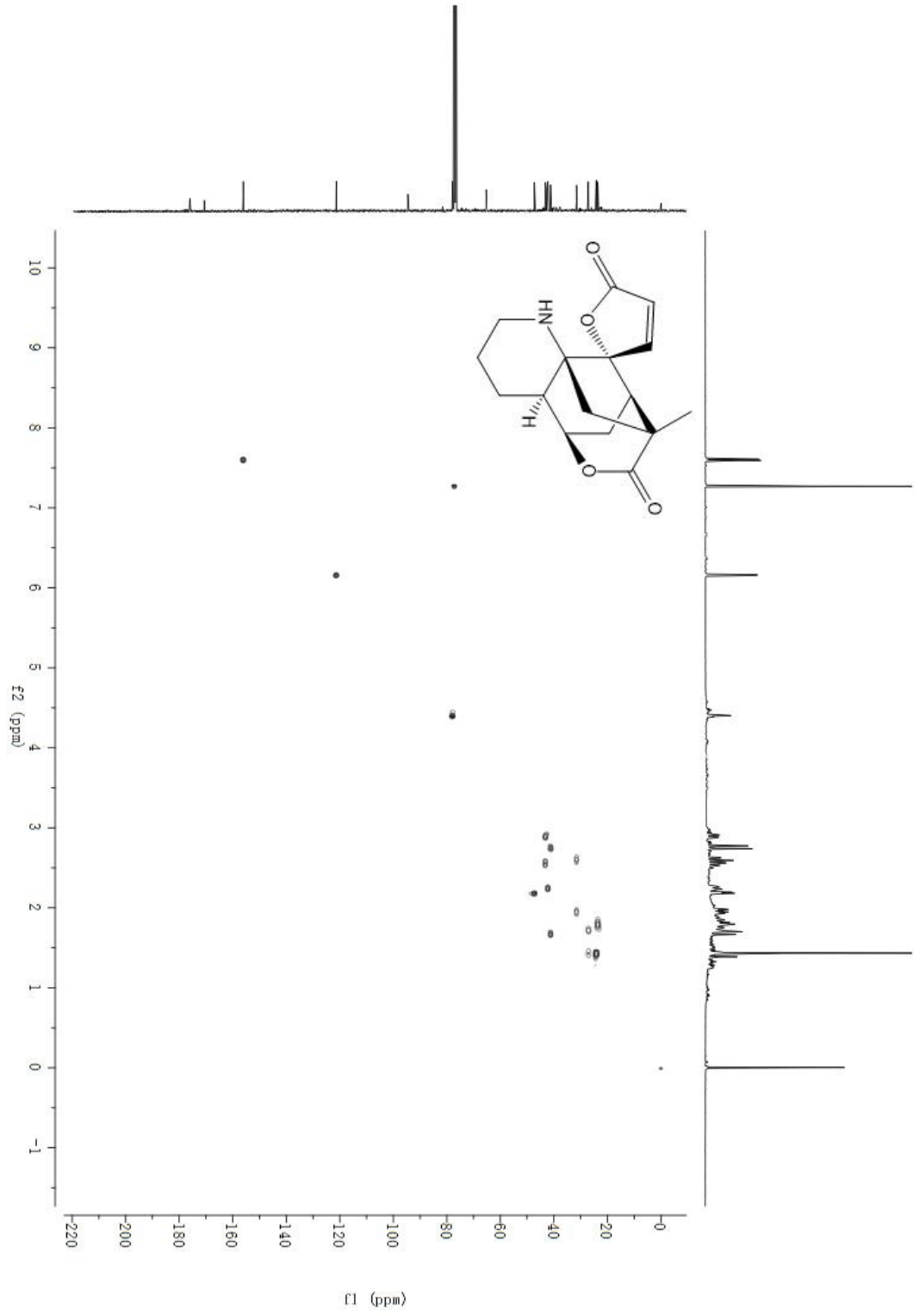


Figure S20. ^{1}H-^{1}H COSY (400 MHz) spectrum of 3 in $CDCl_3$

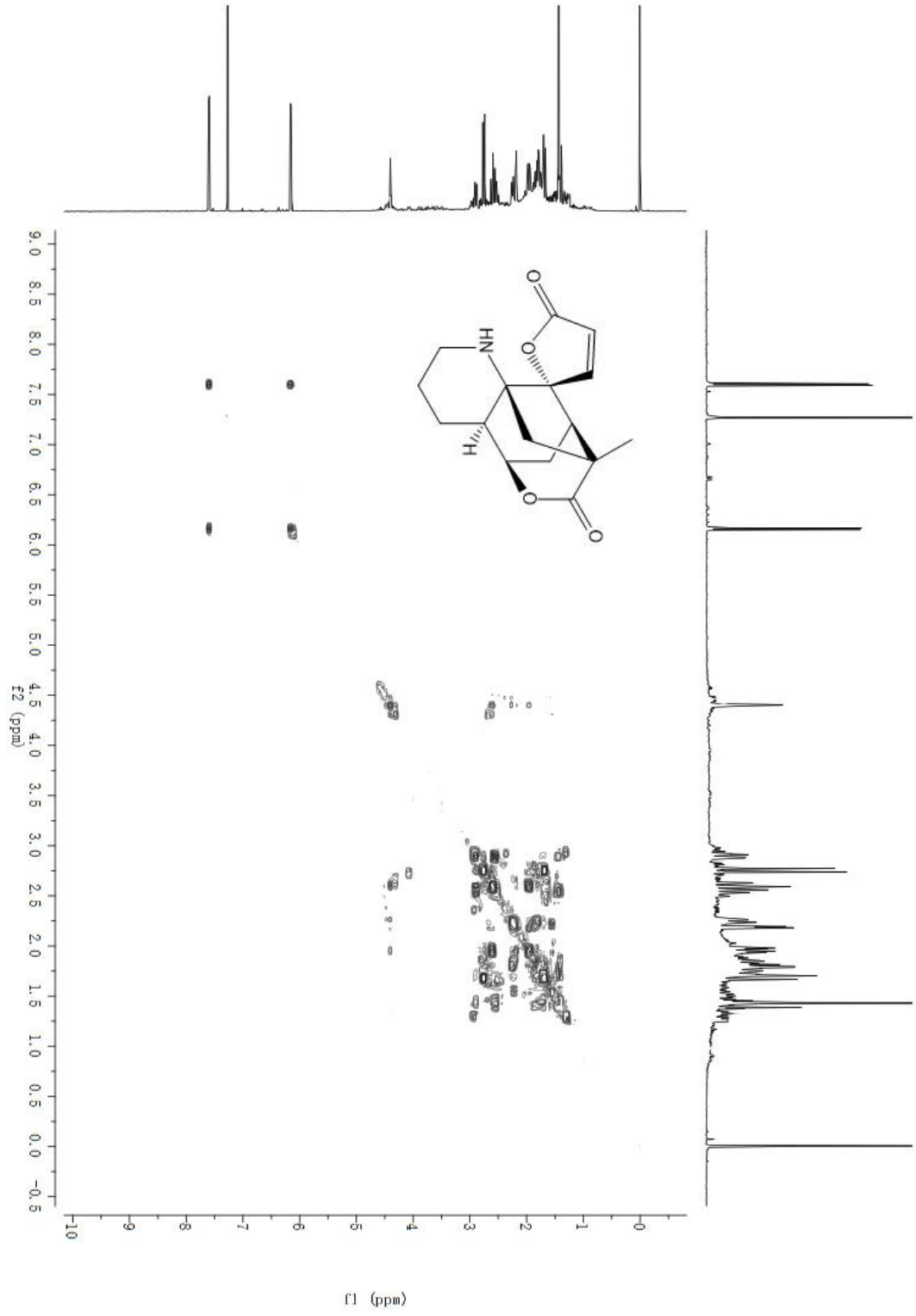


Figure S21. HMBC (400 MHz) spectrum of 3 in $CDCl_3$

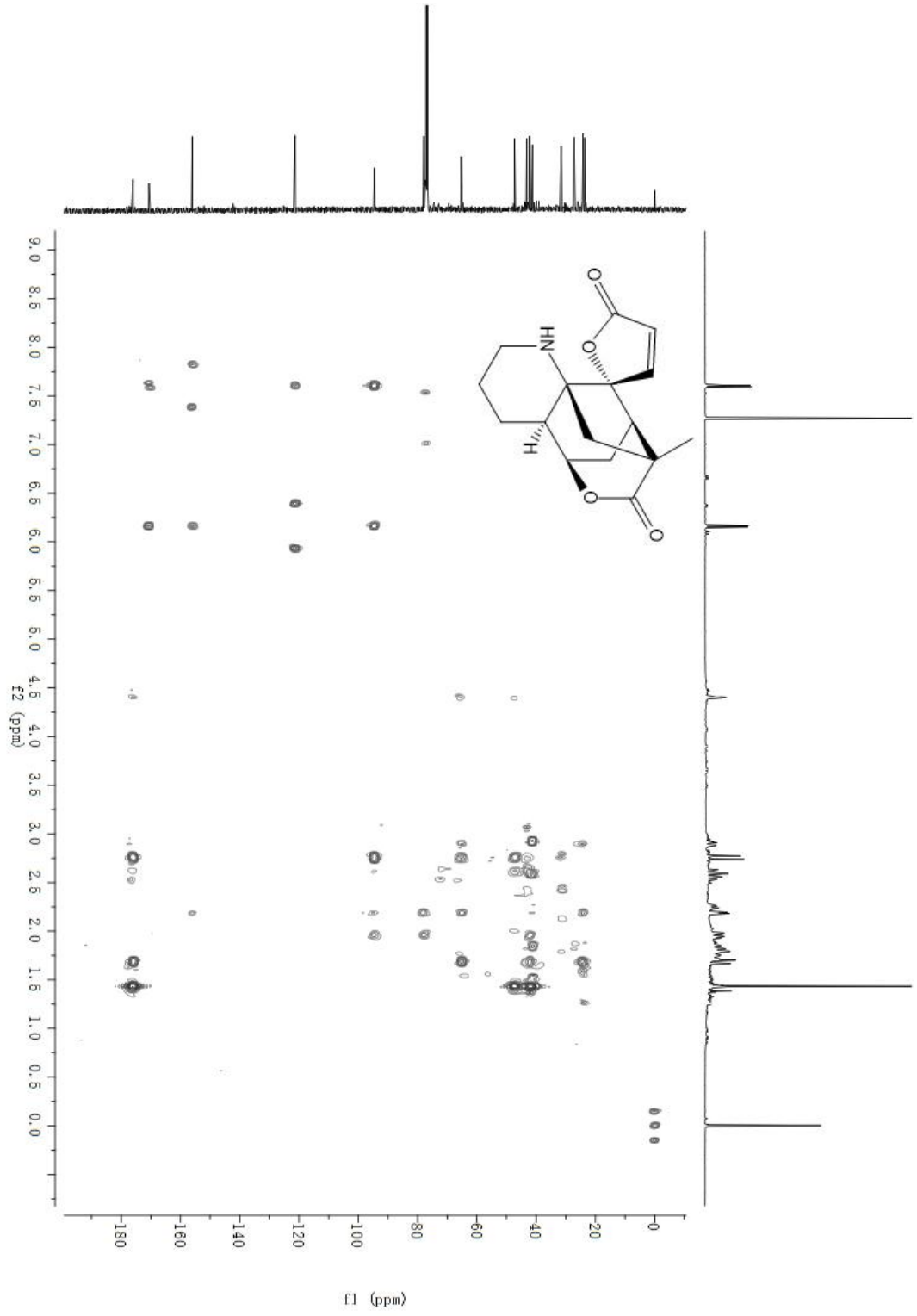


Figure S22. ROESY (600 MHz) spectrum of 3 in $CDCl_3$

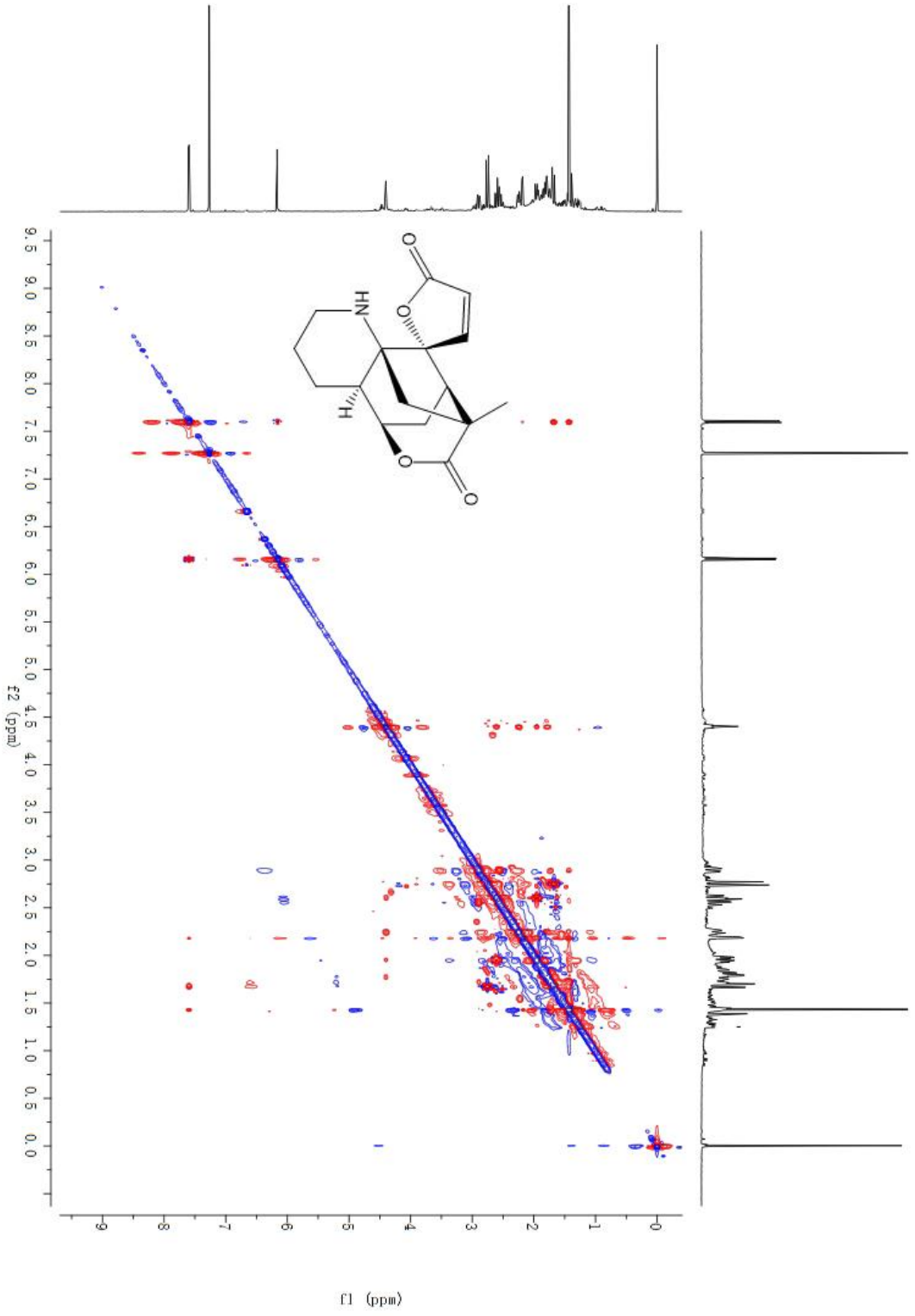
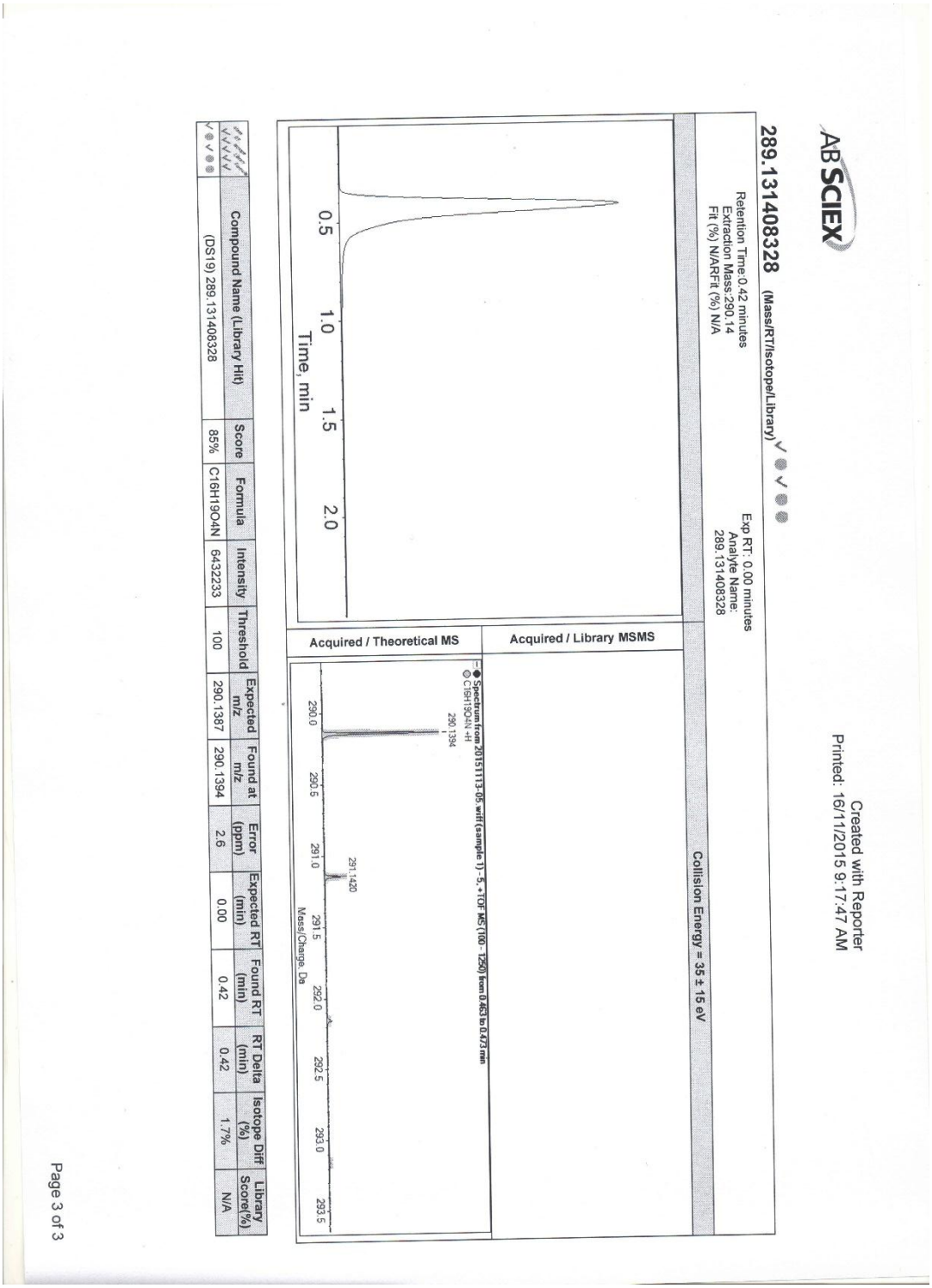


Figure S23. HRESIMS data of 3



	Compound Name (Library Hit)	Score	Formula	Intensity	Threshold	Expected m/z	Found at m/z	Error (ppm)	Expected RT (min)	Found RT (min)	RT Delta (min)	Isotope Diff (%)	Library Score(%)
✓ ● ✓ ● ●	(DS19) 289.131408328	85%	C16H19O4N	6432233	100	290.1387	290.1394	2.6	0.00	0.42	0.42	1.7%	N/A

Figure S24. ^{1}H NMR (400 MHz) spectrum of 4 in $CDCl_3$

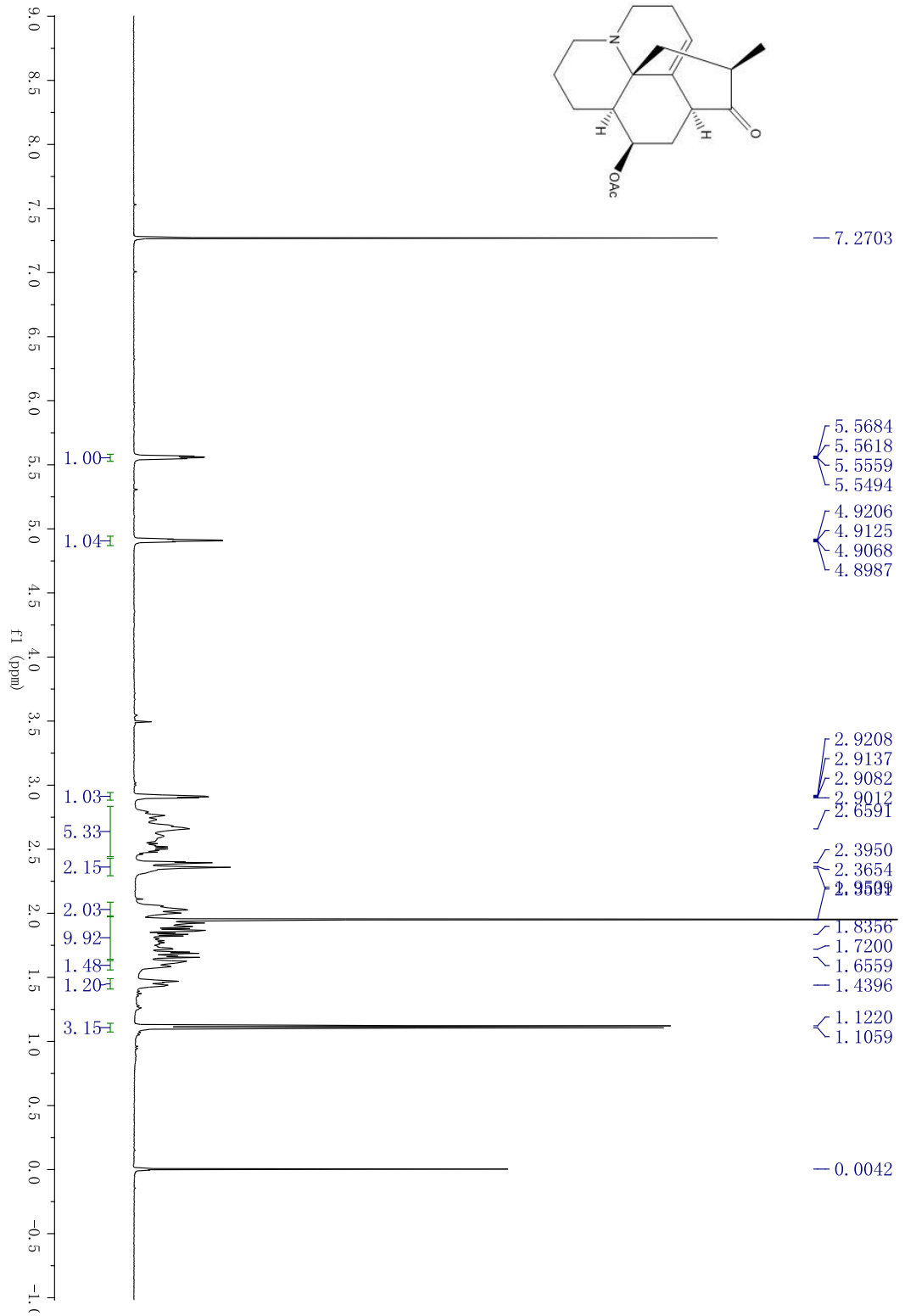


Figure S25. ^{13}C NMR (100 MHz) spectrum of 4 in $CDCl_3$

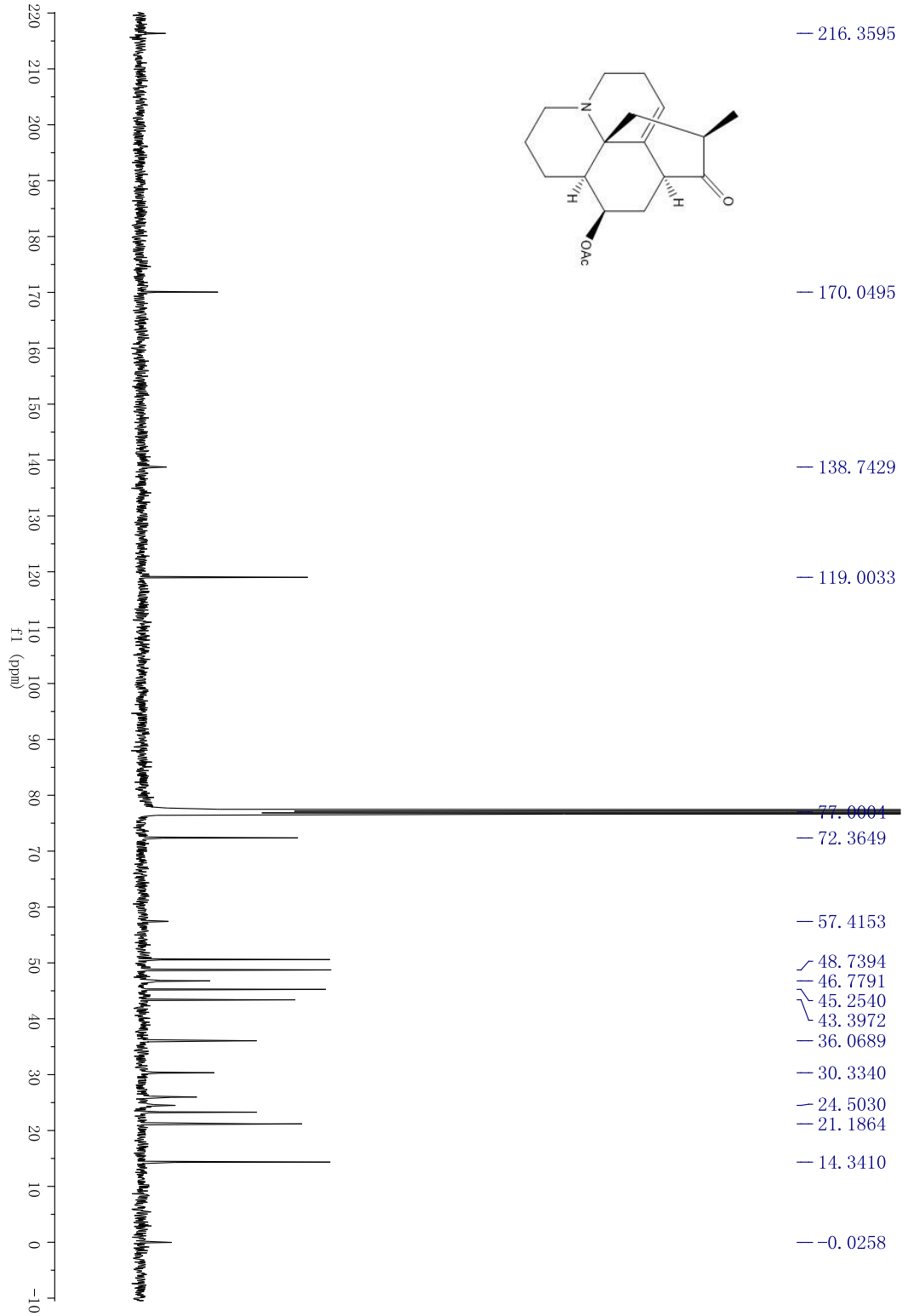


Figure S26. ESIMS data of 4

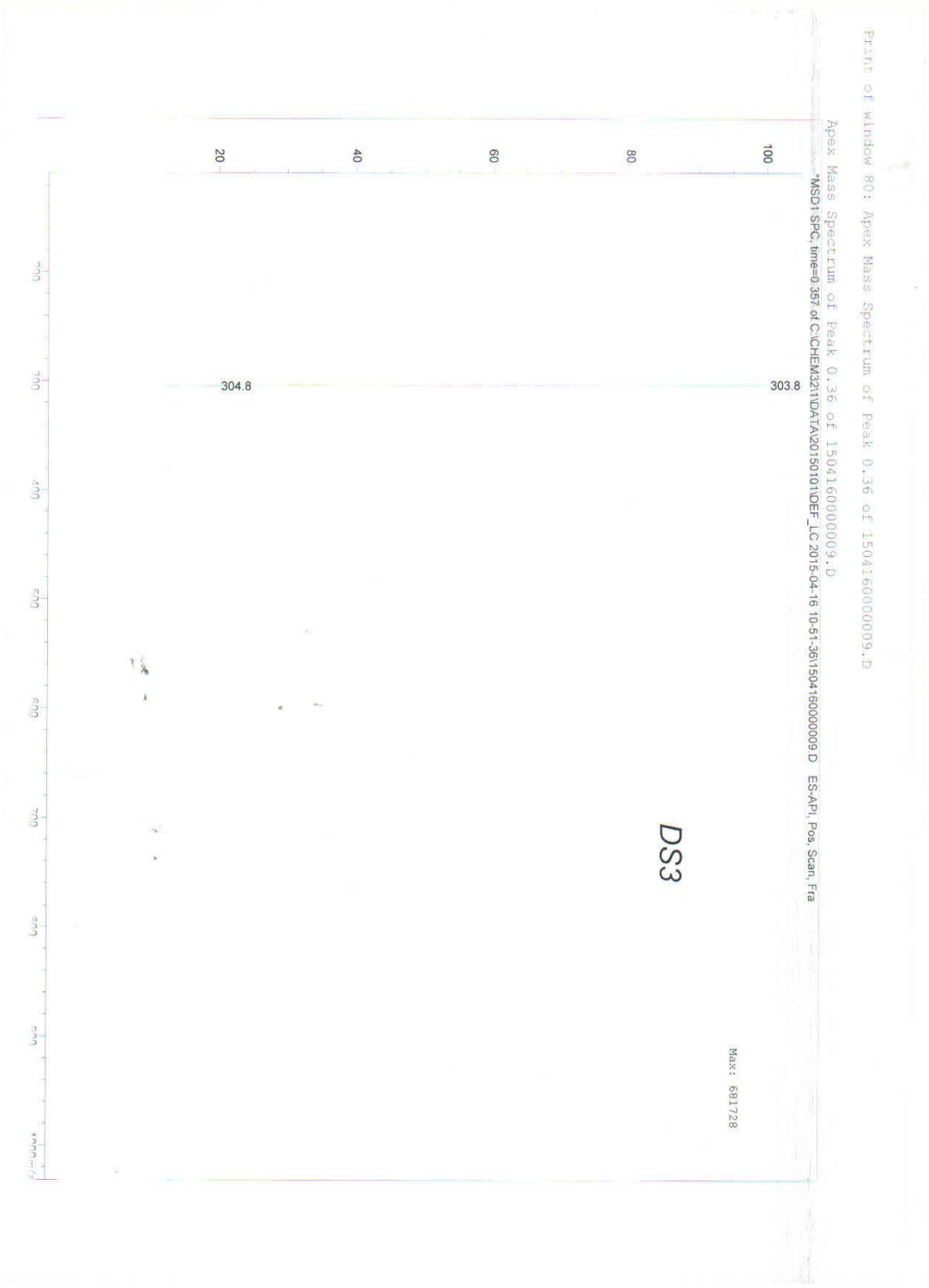


Figure S27. ^{1}H NMR (400 MHz) spectrum of 5 in $CDCl_3$

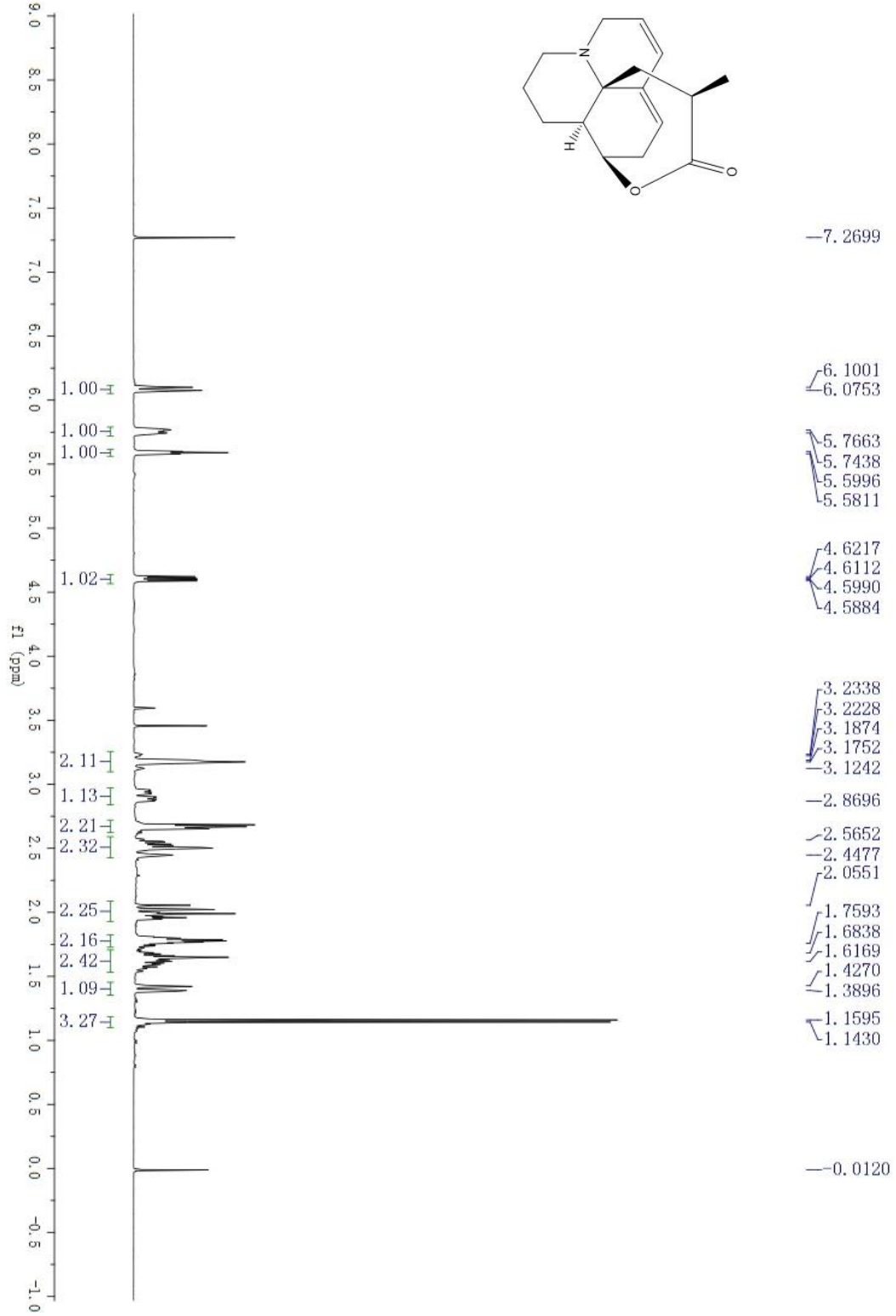


Figure S28. ^{13}C NMR (100 MHz) spectrum of 5 in $CDCl_3$

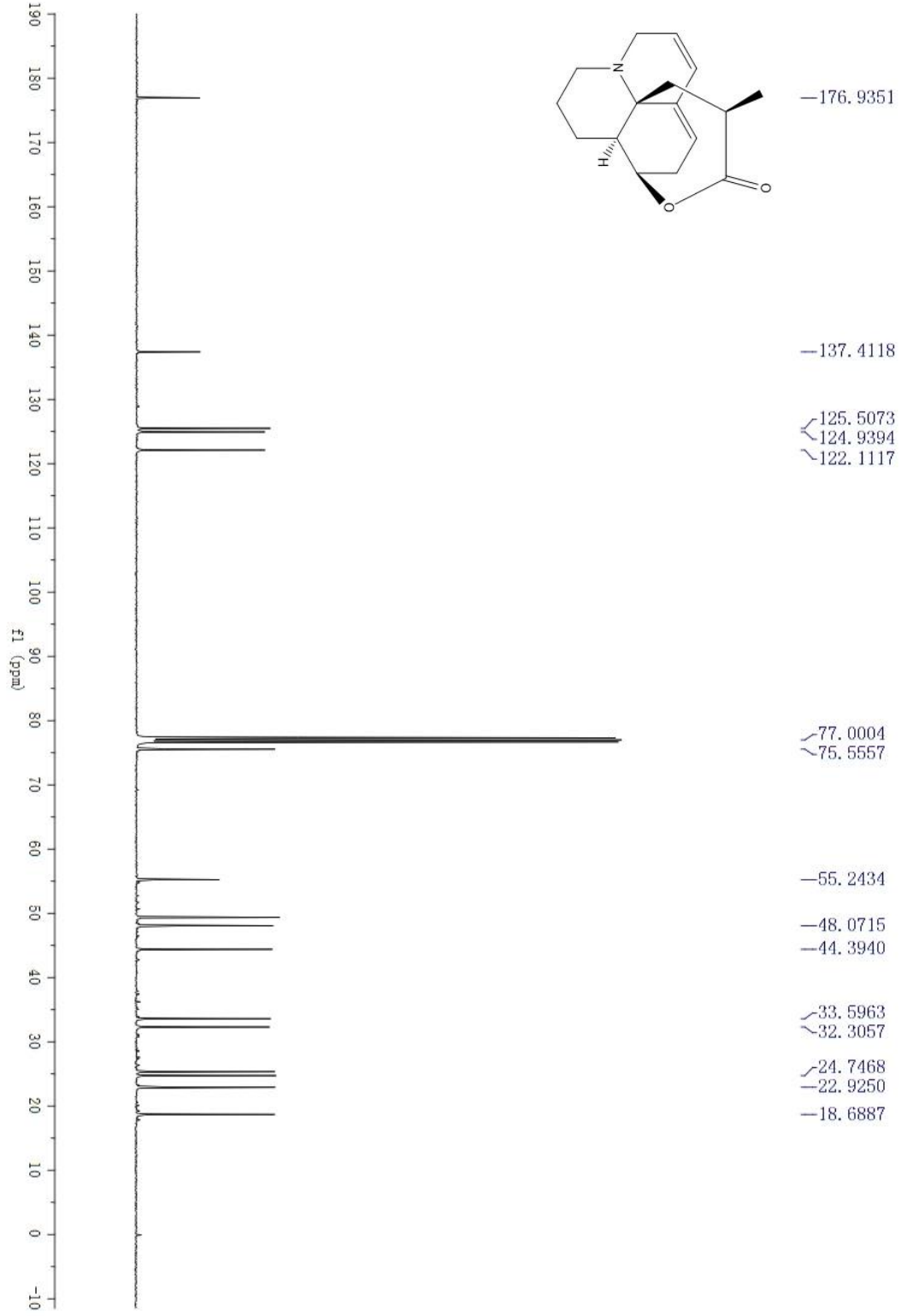


Figure S29. HSQC (400 MHz) spectrum of 5 in $CDCl_3$

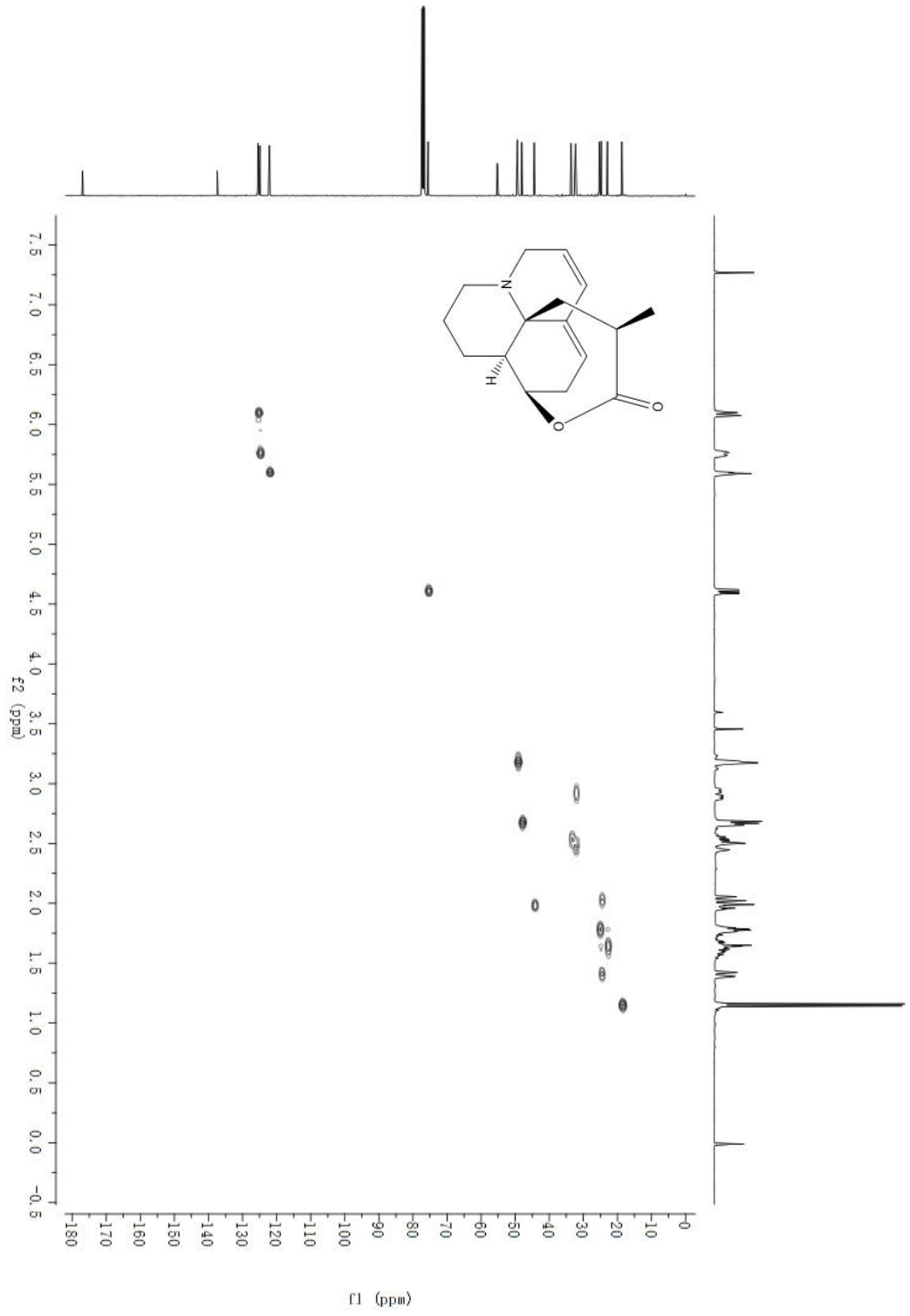


Figure S30. ^{1}H-^{1}H COSY (400 MHz) spectrum of 5 in $CDCl_3$

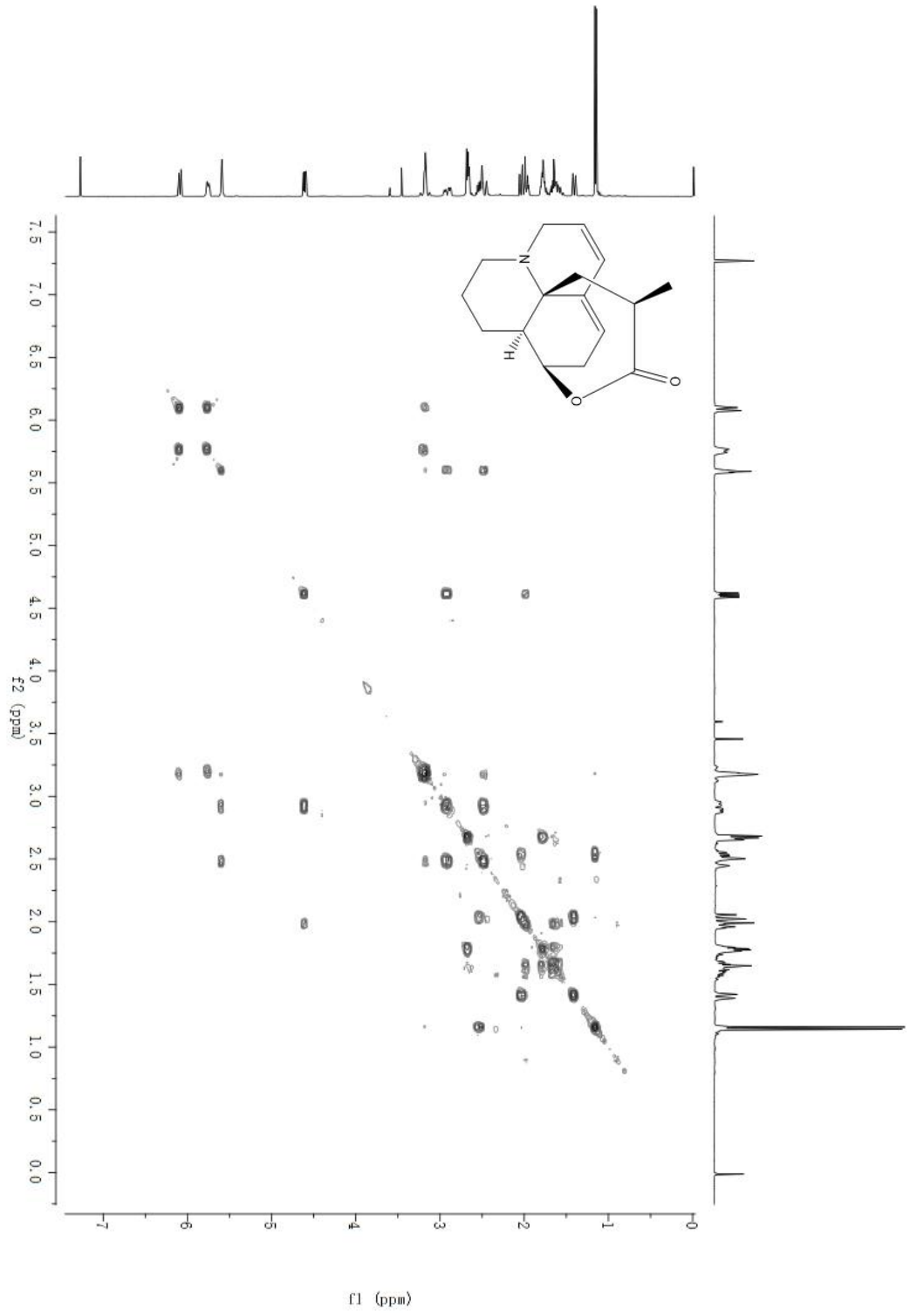


Figure S31. HMBC (400 MHz) spectrum of 5 in $CDCl_3$

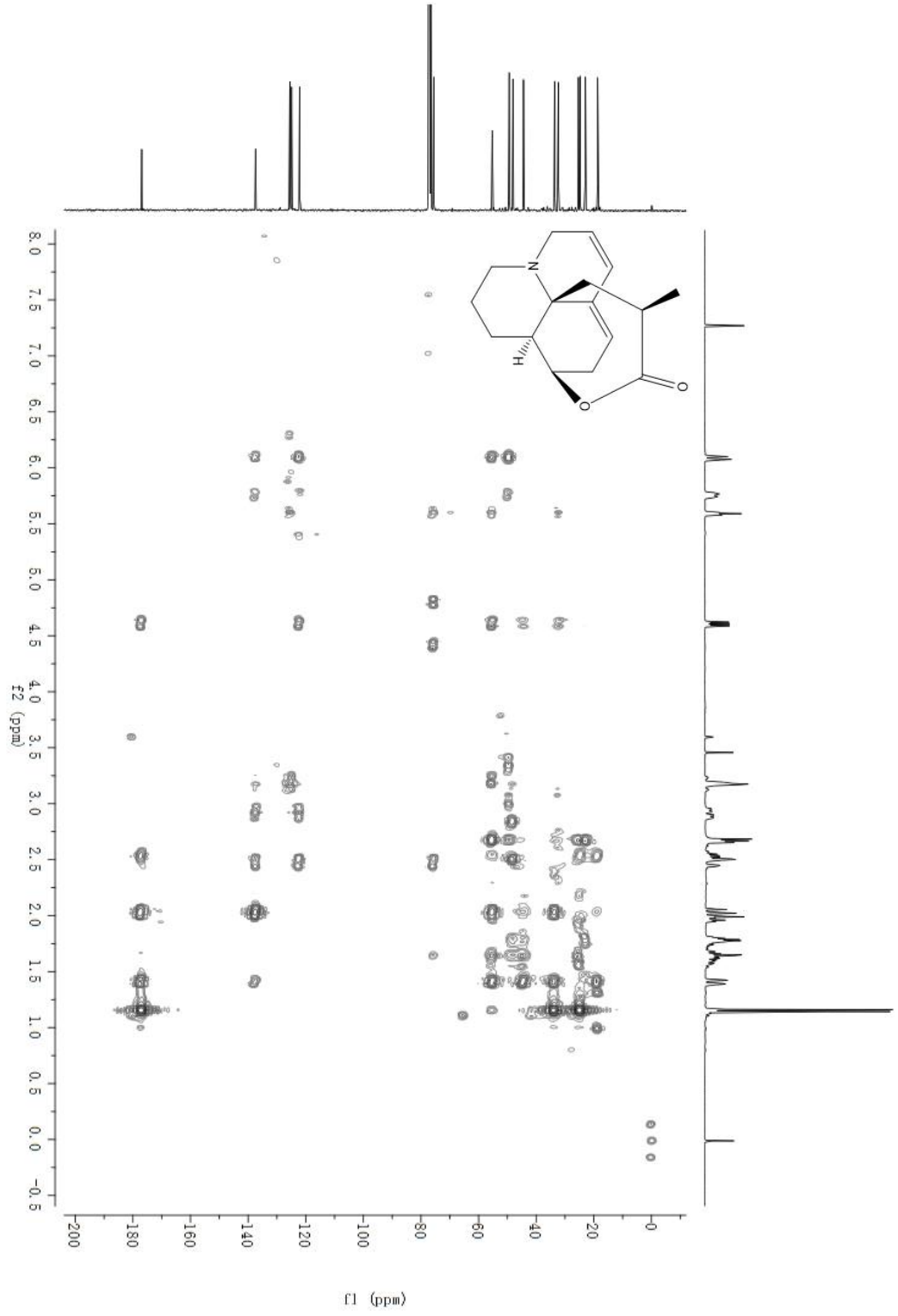


Figure S32. NOESY (400 MHz) spectrum of 5 in $CDCl_3$

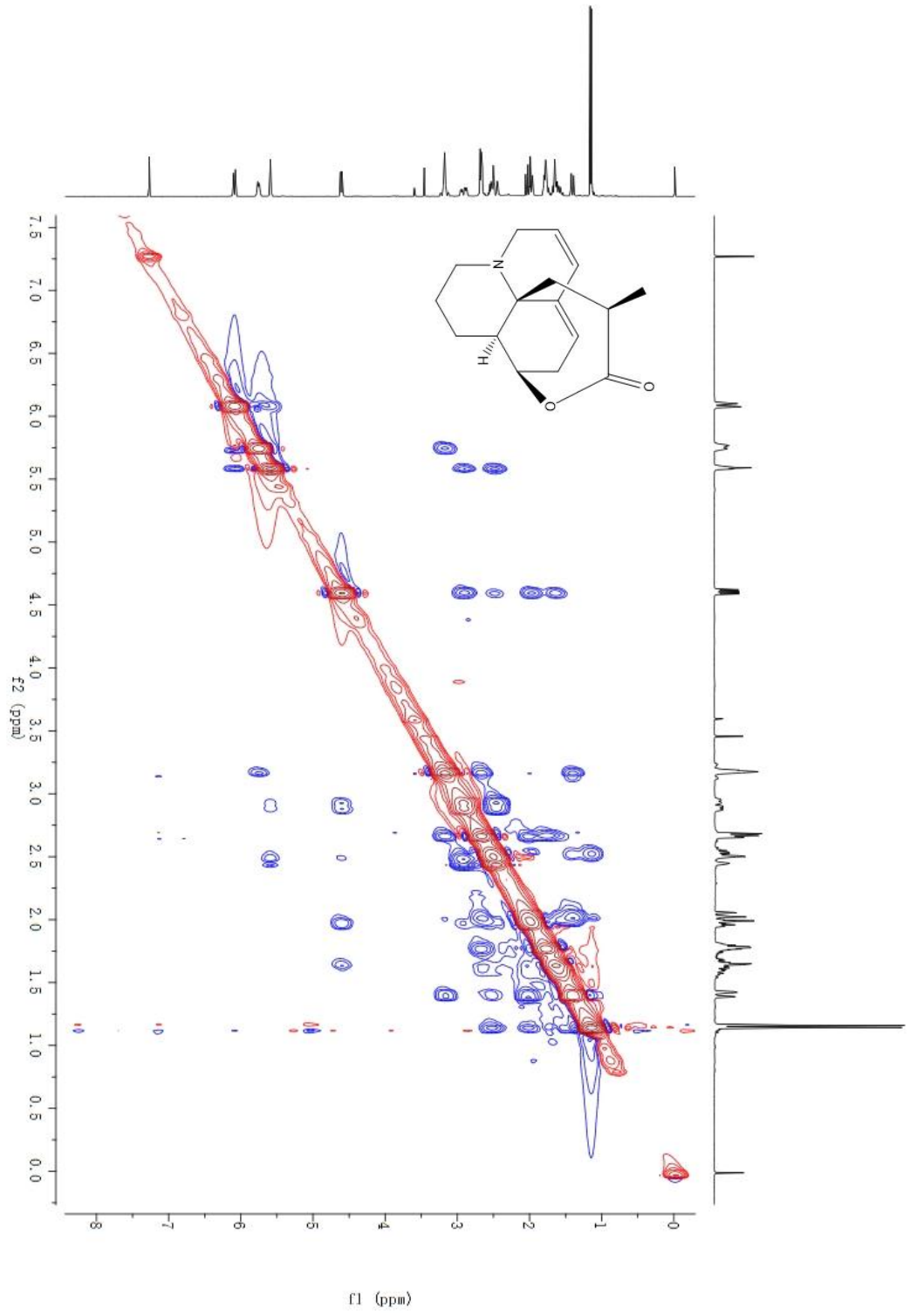


Figure S33. ^{1}H NMR (400 MHz) spectrum of 5 in CD_3OD

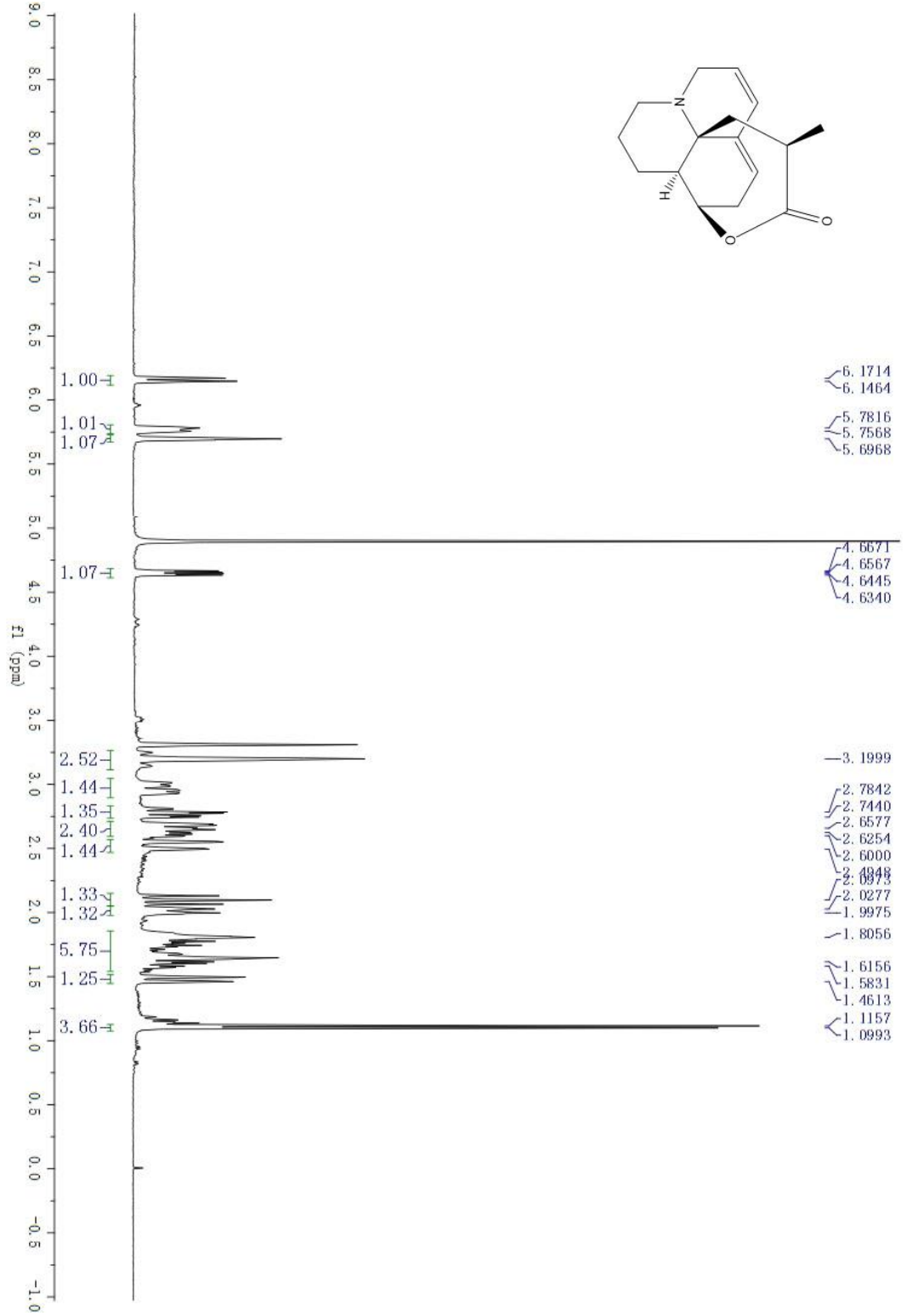


Figure S34. ^{13}C NMR (150 MHz) spectrum of 5 in CD_3OD

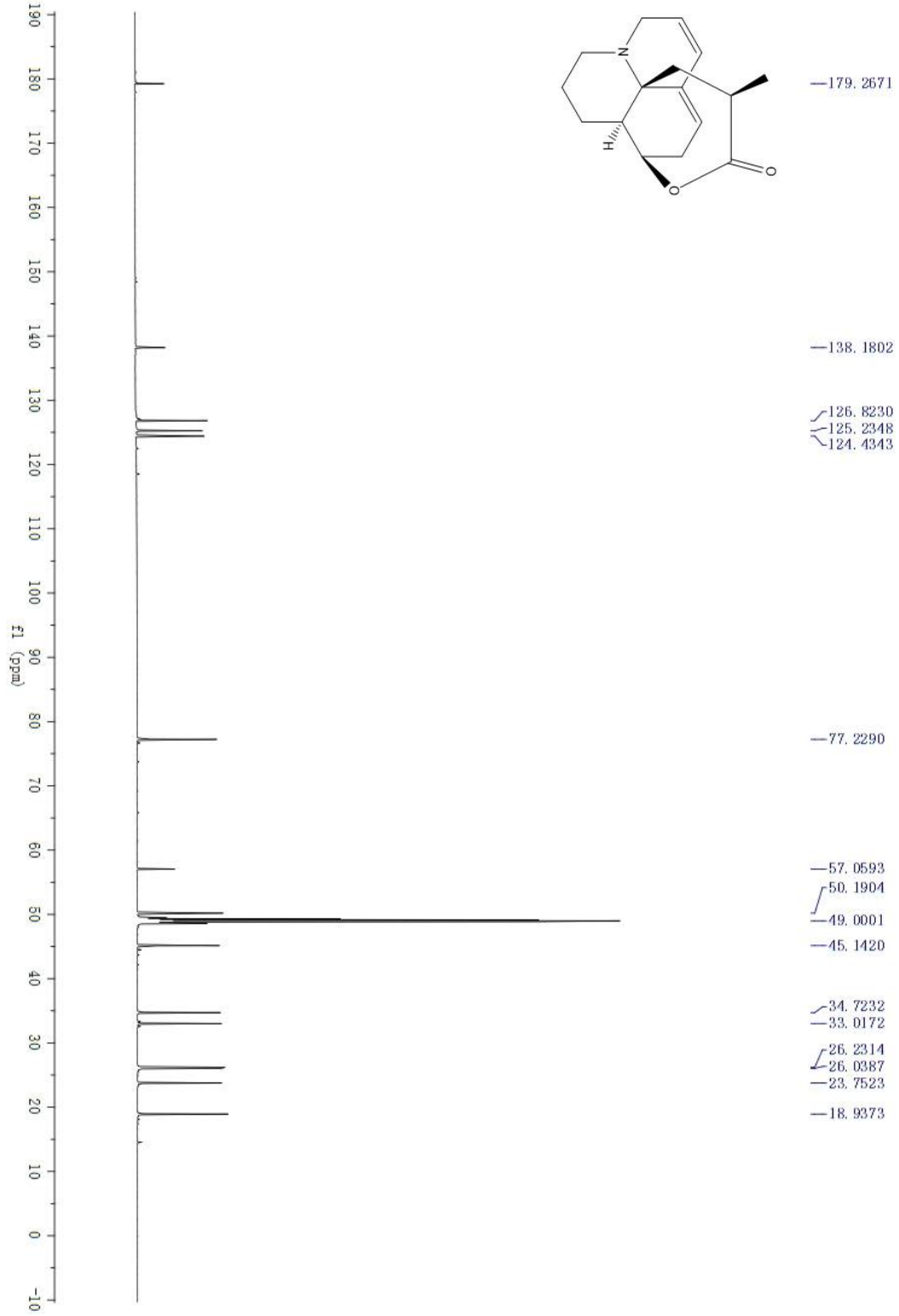


Figure S35. ^{1}H NMR (600 MHz) spectrum of 5 in CD_3OD+TFA

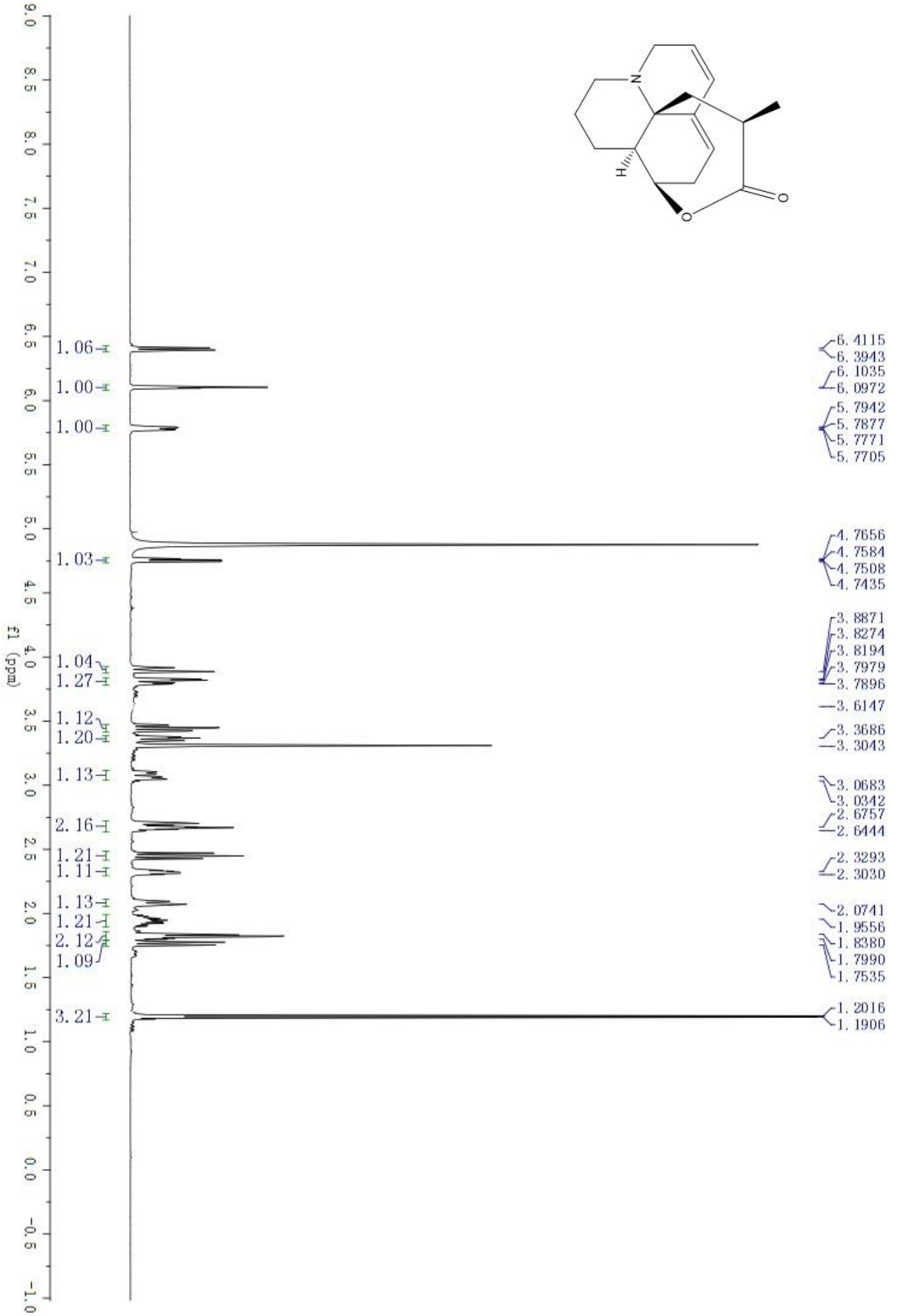


Figure S36. ^{1}H NMR (150 MHz) spectrum of 5 in CD_3OD+TFA

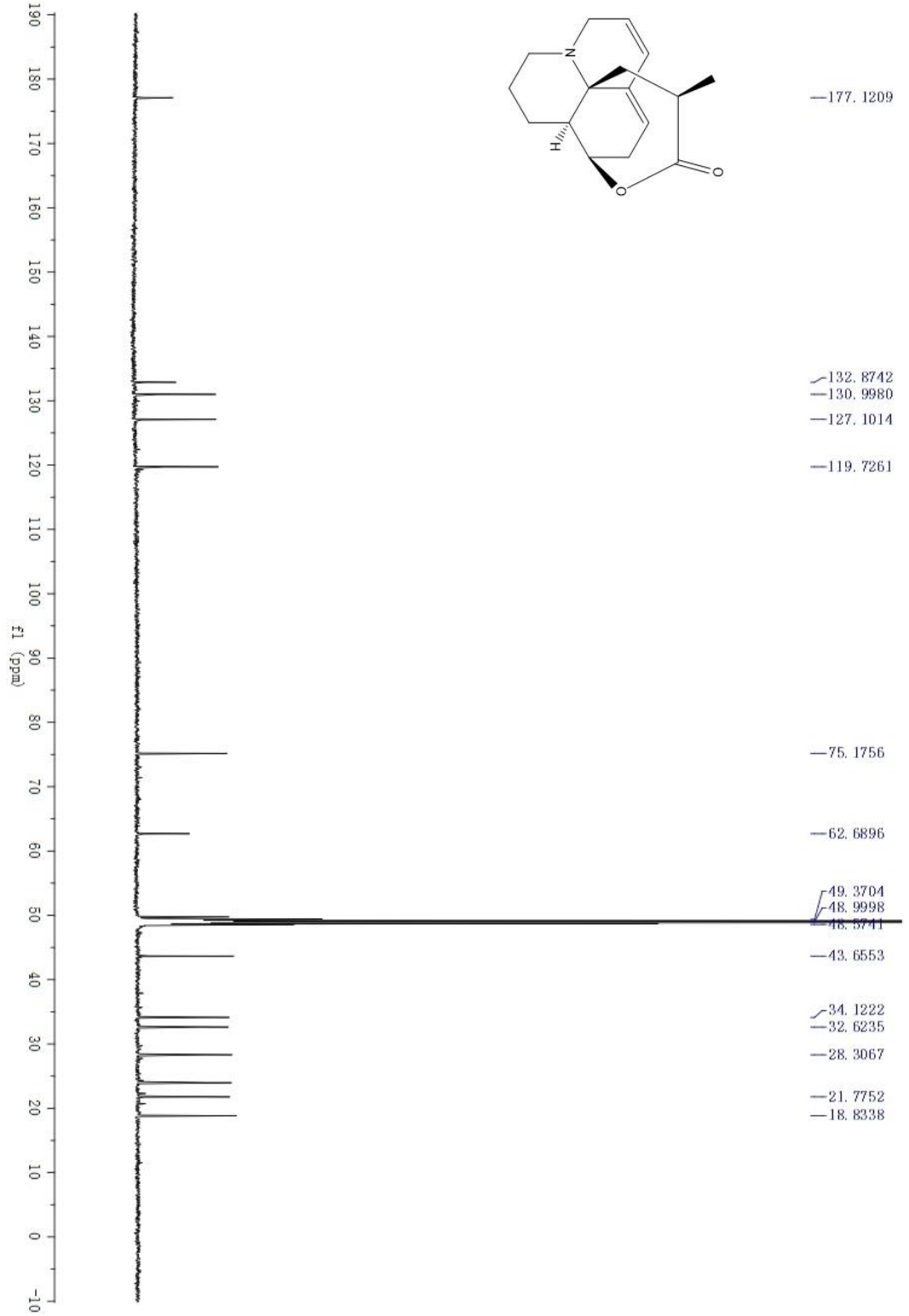


Figure S37. HRESIMS data of 5

Compound Name (Library Hit)	Score	Formula	Intensity	Threshold	Expected m/z	Found at m/z	Error (ppm)	Expected RT (min)	Found RT (min)	RT Delta (min)	Isotope Diff (%)	Library Score(%)
(DS5) 259.157229128	81%	C16H21NO2	6025471	1000	260.1645	260.1655	3.7	0.00	0.39	0.39	0.3%	N/A

Figure S38. ORTEP drawing of 5

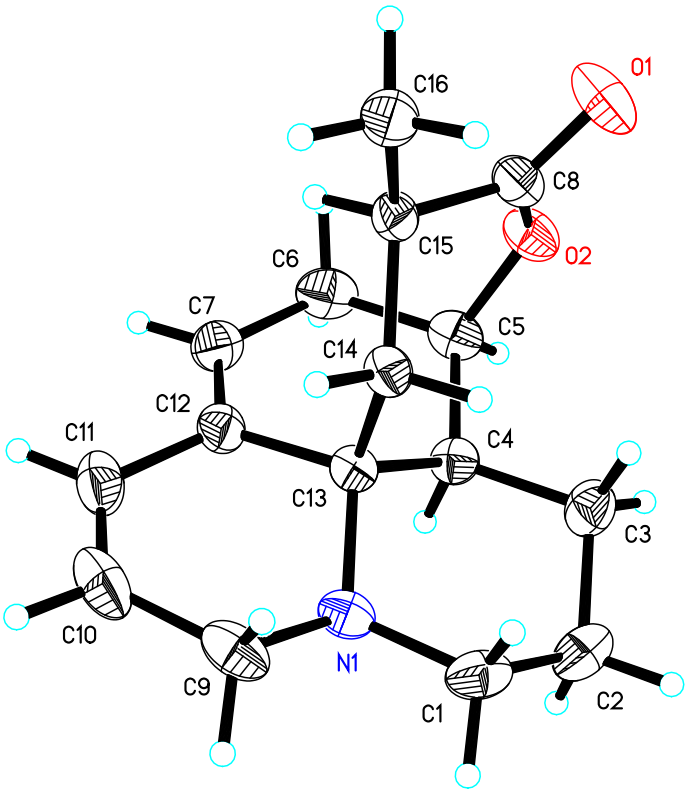


Figure S39. ^{1}H NMR (400 MHz) spectrum of 6 in $CDCl_3$

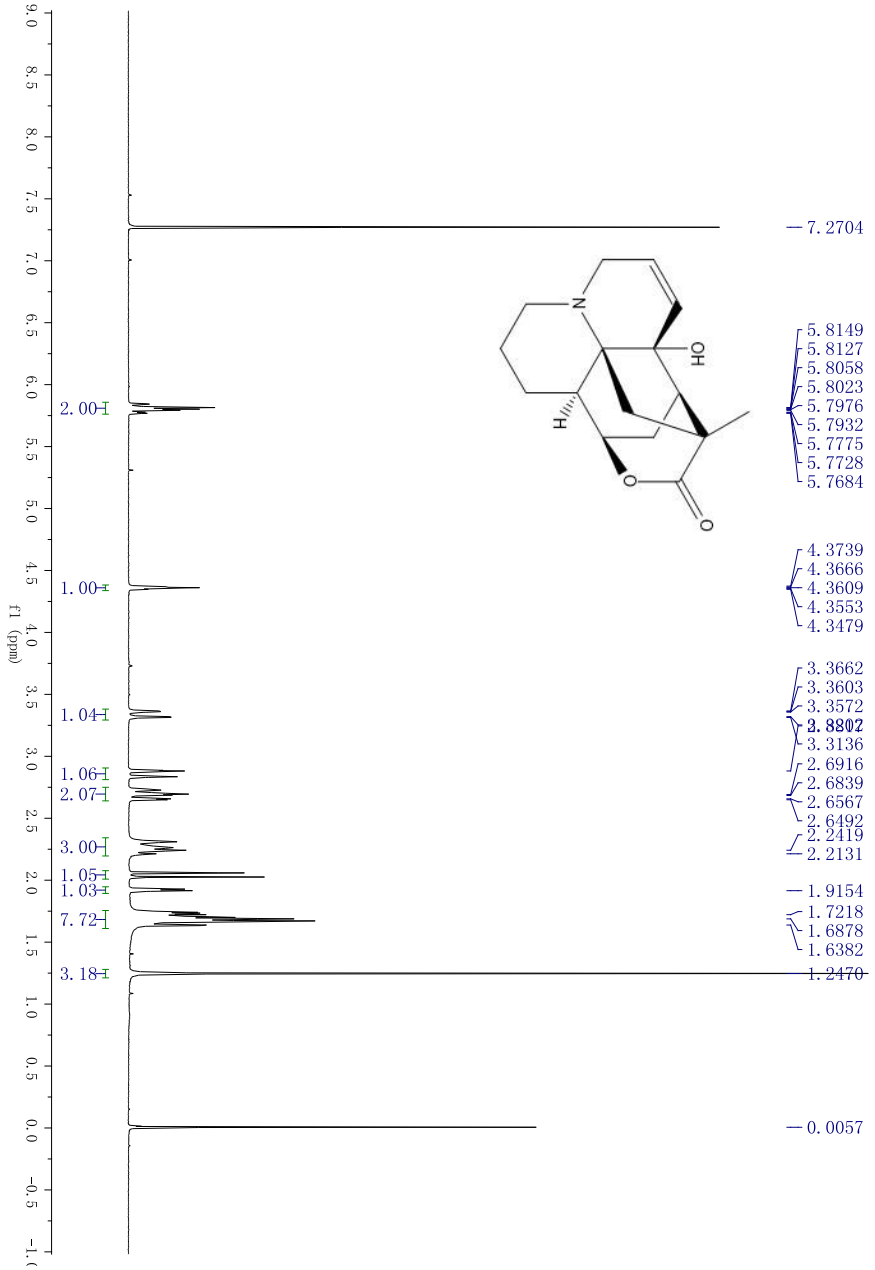


Figure S40. ^{13}C NMR (100 MHz) spectrum of 6 in $CDCl_3$

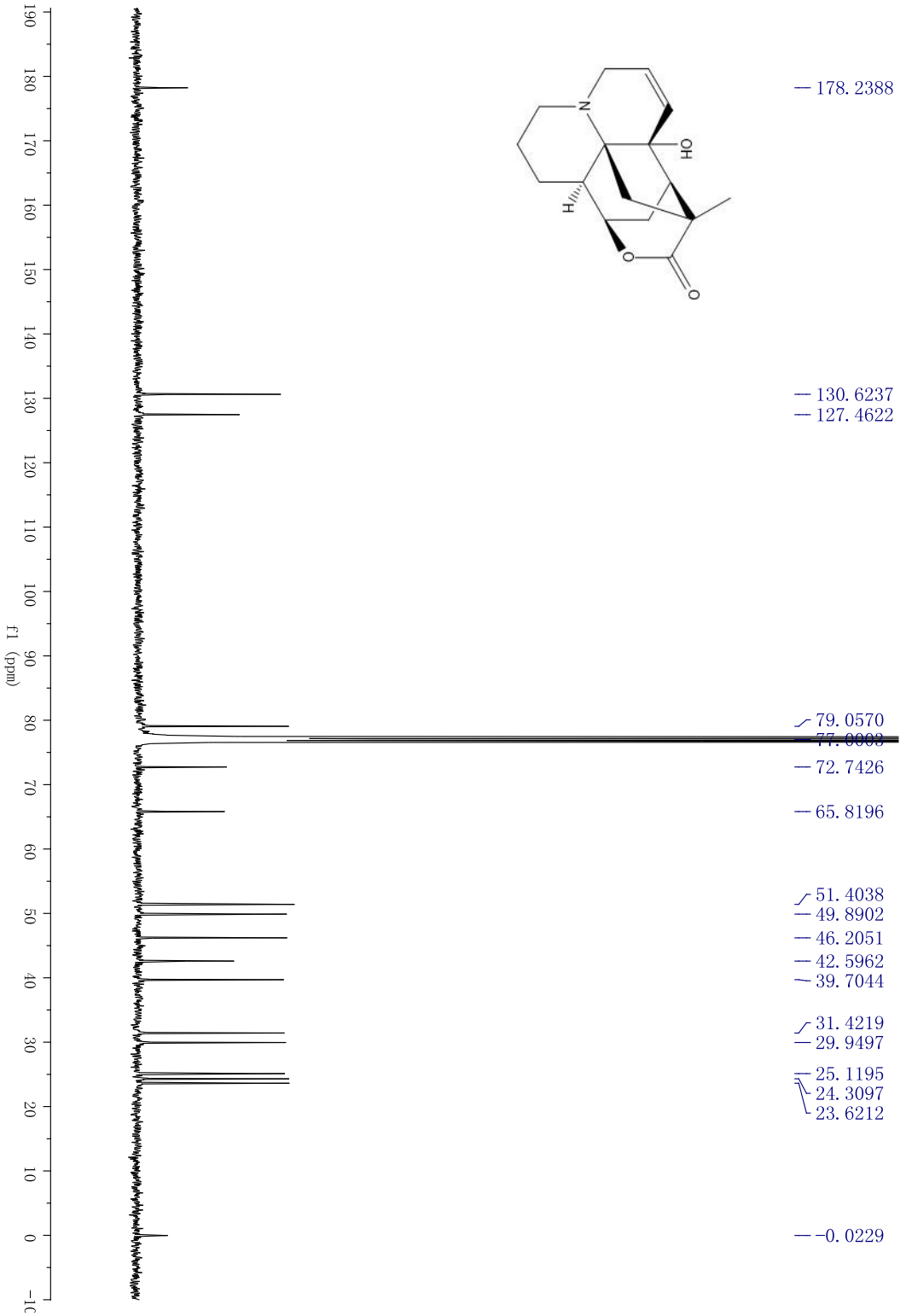
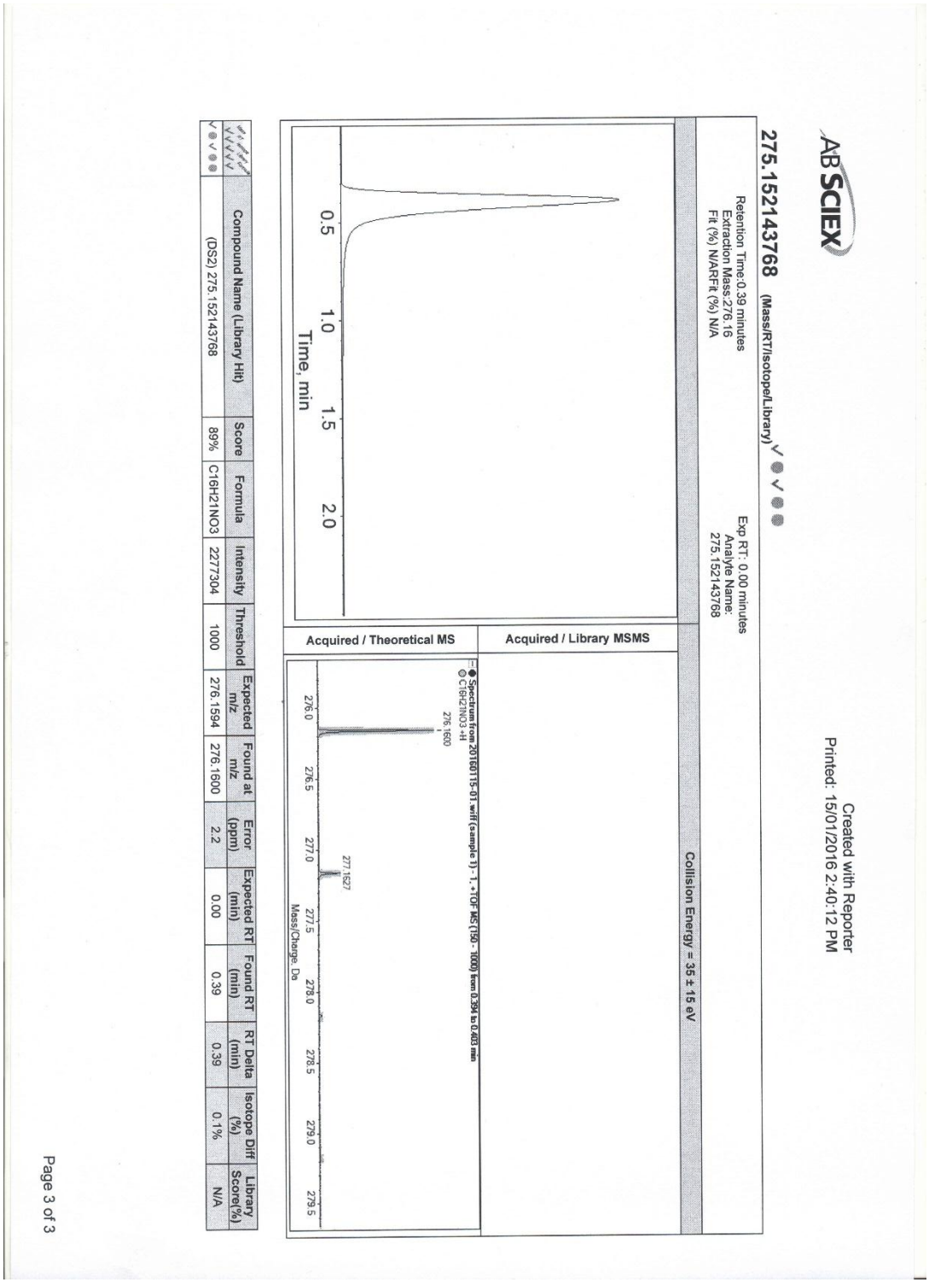


Figure S41. HRESIMS data of 6



Compound Name (Library Hit)	Score	Formula	Intensity	Threshold	Expected m/z	Found at m/z	Error (ppm)	Expected RT (min)	Found RT (min)	RT Delta (min)	Isotope Diff (%)	Library Score(%)
(DS2) 275.152143768	89%	C16H21NO3	2277304	1000	276.1594	276.1600	2.2	0.00	0.39	0.39	0.1%	N/A

Figure S42. ^{1}H NMR (600 MHz) spectrum of 7 in $CDCl_3$

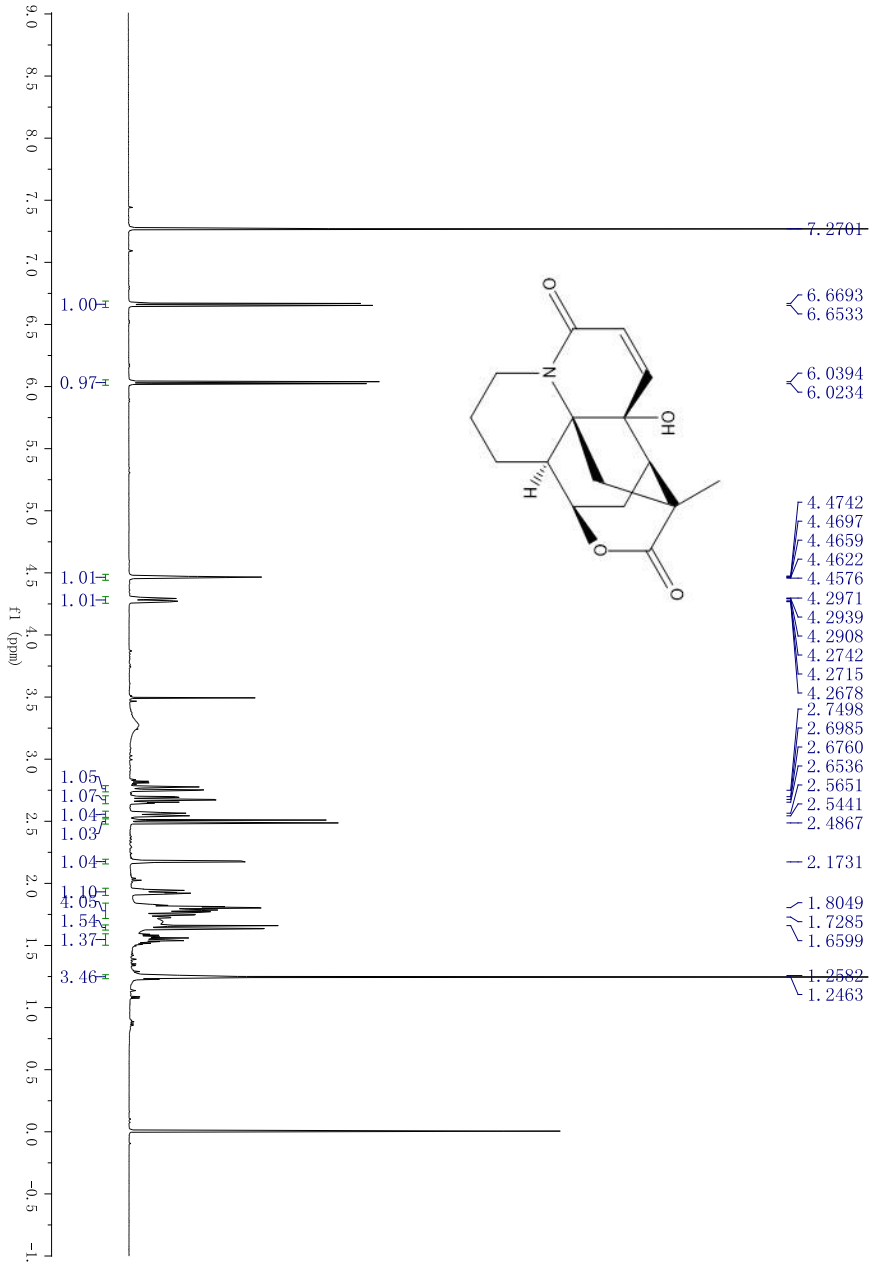


Figure S43. ^{13}C NMR (150 MHz) spectrum of 7 in $CDCl_3$

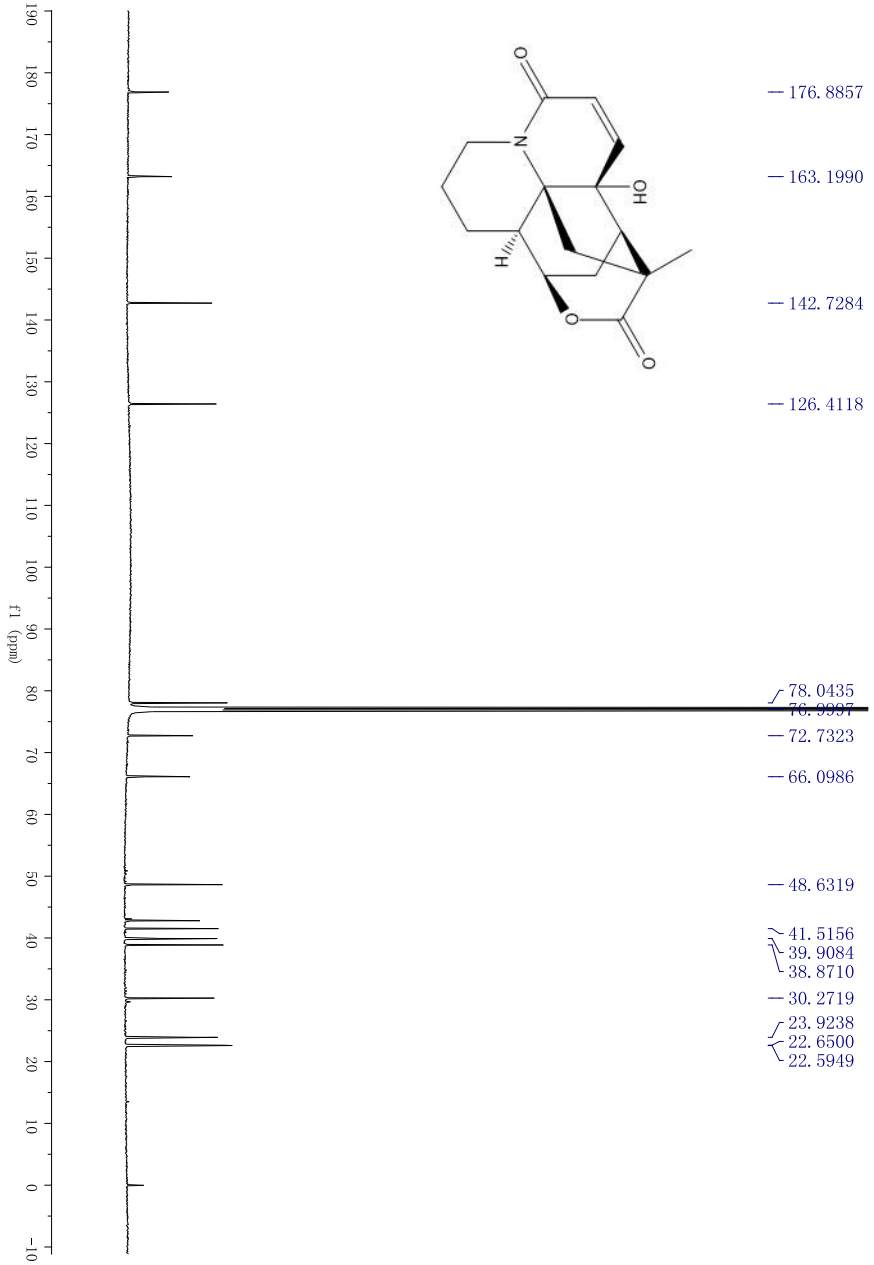
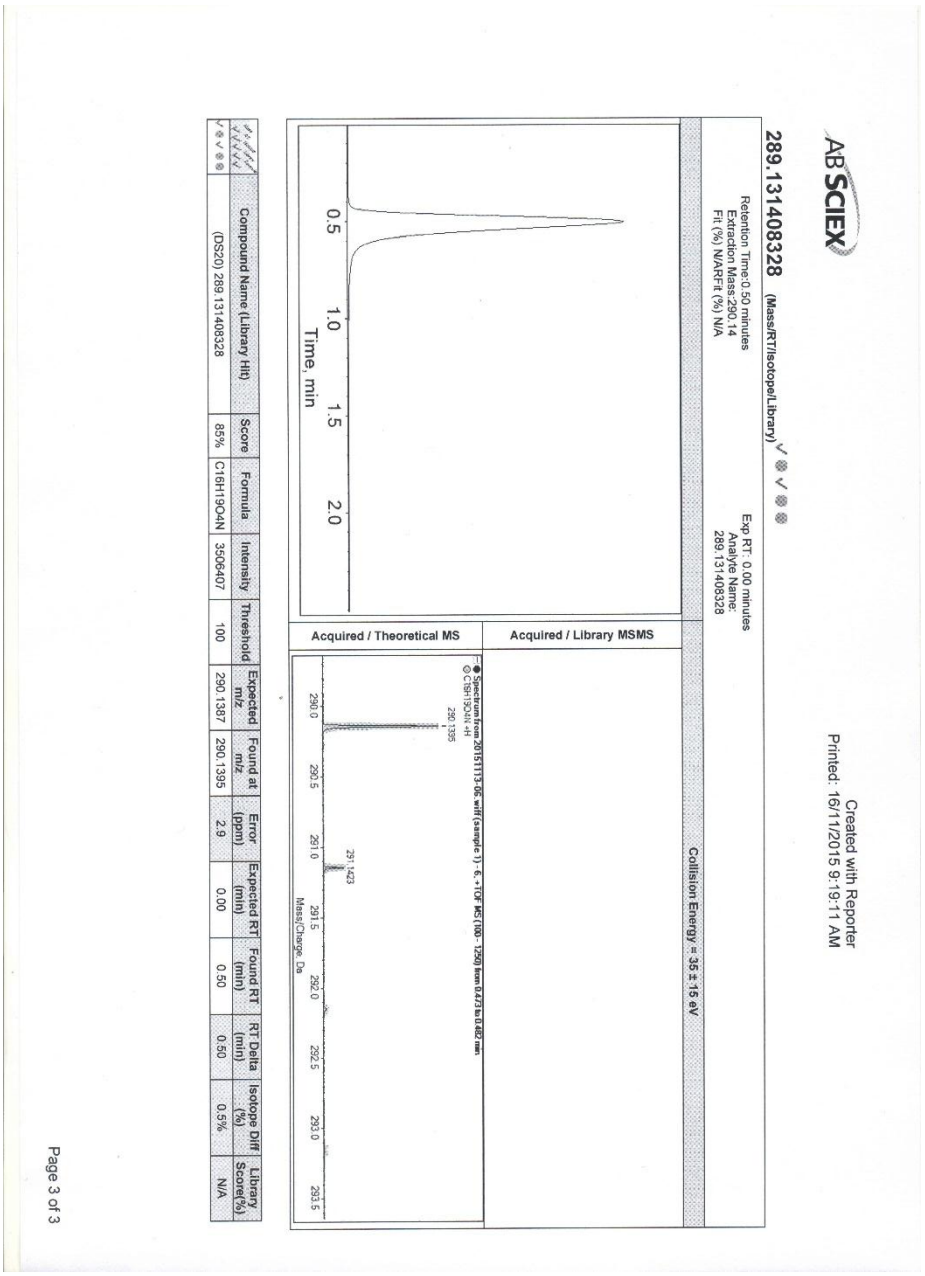


Figure S44. HRESIMS data of 7



	Compound Name (Library Hit)	Score	Formula	Intensity	Threshold	Expected m/z	Found at m/z	Error (ppm)	Expected RT (min)	Found RT (min)	RT Delta (min)	Isotope Diff (%)	Library Score(%)
✓ ⊗ ✓ ⊗ ⊗	(DS20) 289.13408328	85%	C16H19O4N	3506407	100	290.1387	290.1395	2.9	0.00	0.50	0.50	0.5%	N/A