Nototronesides A-C, Three Triterpene Saponins with a 6/6/9 Fused Tricyclic Tetranordammarane Carbon Skeleton from the Leaves of *Panax notoginseng*

Xin-Yi Liu, Chuang-Jun Li*, Fang-You Chen, Jie Ma, Shuo Wang, Yu-He Yuan, Li Li, and Dong-Ming Zhang*

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, People's Republic of China.

*Corresponding author. *E-mail*：lichuangjun@imm.ac.cn； zhangdm@imm.ac.cn; Fax/Tel: +86-01063165227

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1. NMR assignment of nototronesides B and C (2 and 3)

Table S1. ^{1}H (600 MHz) and ^{13}C NMR (150MHz) data of compounds **2** and **3** in C_5D_5N

	2		**3**	
no.	δc	δ_H (*J* in Hz)	δc	δ_H (*J* in Hz)
1	40.2	1.95, m; 1.42, m	40.2	1.95, m; 1.43, m
2	26.6	2.33, m; 1.93, m	26.6	2.31, m; 1.92, m
3	88.7	3.53, dd, 4.2, 11.4	88.6	3.52, dd, 4.2, 11.4
4	39.9		39.9	
5	55.8	1.05, d, 12.0	55.8	1.06, d, 12.0
6	18.3	1.51, m; 1.36, m	18.2	1.57, m; 1.40, m
7	36.0	1.92, m; 1.13, m	36.0	1.94, m; 1.16, m
8	44.3		44.4	
9	47.8	1.68, m	47.9	1.69, m
10	38.9		38.9	
11	36.8	1.87, m; 1.62, m	36.7	1.87, m; 1.62, m
12	81.1	4.61, m	81.3	4.63, m
13	219.6		219.7	
14	154.4		154.4	
15	31.0	2.34, 2H, m	31.0	2.34, 2H, m
16	28.7	2.66, m; 2.35, m	28.7	2.61, m; 2.34, m
17	62.4	3.41, d, 9.0	63.3	3.41, d, 9.0
18	15.5	0.86, s	15.5	0.85, s
19	20.8	0.91, s	20.8	0.91, s
20	82.5		82.6	
21	17.9	1.51, s	18.0	1.50, s
22	30.9	2.03, q, 7.2;	30.9	2.04, q, 7.2;
		1.71, q, 7.2		1.71, q, 7.2
23	7.7	1.18, t, 7.2	7.8	1.18, t, 7.2
24	16.9	1.16, s	16.9	1.16, s
25	27.9	1.40, s	28.0	1.42, s
26	113.7	5.17, s; 4.98, s	113.7	5.17, s; 4.97, s
Glu1-1′ (C-3)	105.1	5.04, d, 7.8	104.8	5.04, d, 7.8
2′	83.4	4.30, m	83.0	4.18, m
3′	78.4	4.35, m	77.8	4.17, m
4′	71.6	4.41, m	71.8	4.25, m
5′	78.1	3.97, m	77.95	3.90, m
6′	62.6	4.52, brd, 12.0;	62.8	4.52, brd, 11.4;
		4.32, dd, 12.0, 3.6		4.32, dd, 11.4, 3.6
Glu2-1″	106.1	5.43, d, 7.8	103.2	5.57, d, 7.8
2″	77.2	4.18, m	84.4	4.26, m
3″	78.0	4.28, m	78.3	4.00, m
4″	71.6	4.18, m	71.2	4.12, m

5″	78.5	4.19, m	77.9	4.32 ,m
6″	62.6	4.51, brd, 10.8;	62.9	4.51, brd, 11.4;
		4.38, dd, 10.8, 3.6		4.41, brd, 11.4
Xyl-1‴			106.4	5.45, d, 7.2
2‴			76.0	4.13, m
3‴			78.5	4.21, m
4‴			70.8	4.17, m
5‴			67.5	4.32, brd, 10.8;
				3.73, t, 10.8
Glu-1⁗ (C-20)	98.9	5.03, d, 7.2	98.9	4.98, d, 7.8
2⁗	75.2	3.87, m	75.1	3.89, m
3⁗	78.3	4.36, m	78.7	4.39, m
4⁗	70.7	4.38, m	71.0	4.38, m
5⁗	76.6	4.02, m	76.5	4.04, m
6⁗	69.7	4.88, brd, 10.8;	69.7	4.87, brd, 11.4;
		4.45, dd, 10.8, 3.6		4.43, brd, 11.4
Xyl (Arab)-1⁗′	105.9	4.88, d, 7.8	105.5	4.85, d, 6.6
2⁗′	74.9	3.97, m	73.3	4.42, m
3⁗′	78.3	4.10, m	74.3	4.17, m
4⁗′	71.2	4.15, m	69.2	4.32, m
5⁗′	67.1	4.30, m;	66.6	4.25, brd, 13.2
		3.60, t, 10.2		3.71, d, 13.2

2. NMR assignment of Nototrone A (1a)

Table S2. ^{1}H (600 MHz) and ^{13}C NMR (150MHz) data of compound **1a** in C_5D_5N

no.	δc	δ_H (J in Hz)
1	39.8	1.94, m; 1.30, m
2	27.7	1.89, m; 1.84, m
3	77.8	3.39, m
4	39.5	
5	55.7	0.90, brd, 9.6
6	18.5	1.56, brd, 12.6;
		1.45, td, 12.6, 3.6
7	36.3	1.71,dt, 13.2, 3.6;
		1.18, td, 13.2, 3.6
8	44.4	
9	47.8	1.67, m
10	39.2	
11	36.6	1.91, m; 1.63, m
12	81.2	4.69, d, 10.2

13	219.8	
14	154.3	
15	31.8	2.34, brd, 14.4;
		2.16, dd, 14.4, 13.2
16	29.3	2.48, m; 2.43, m
17	65.0	3.18, d, 10.2
18	15.5	0.89, s
19	20.8	0.95, s
20	75.0	
21	21.6	1.43, s
22	33.5	1.98, dq,7.2; 1.64, m
23	8.0	1.08, t, 7.2
24	16.4	1.04, s
25	28.5	1.26, s
26	114.0	5.24, s; 5.02, s

3. Key HMBC correlations of compounds 1a, 2 and 3

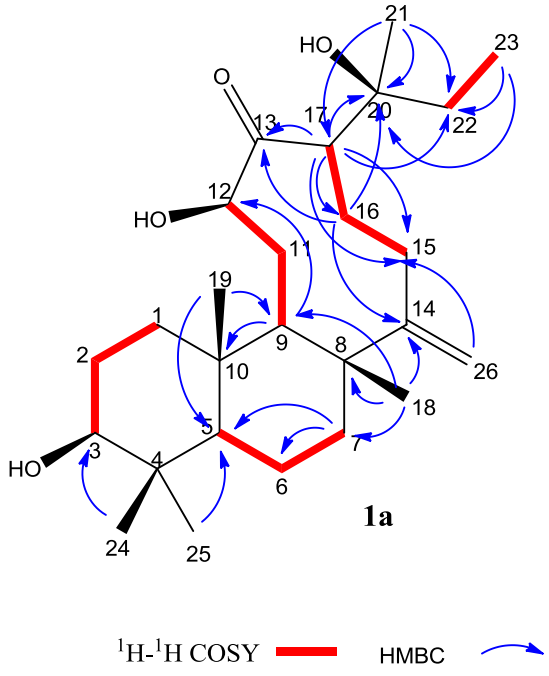


Figure S1. Key ^{1}H-^{1}HCOSY and HMBC correlations of compound **1a**

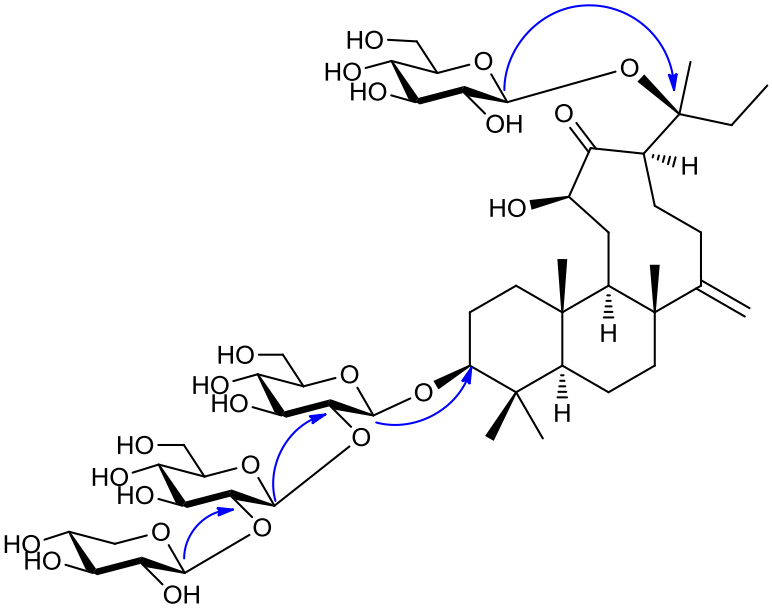
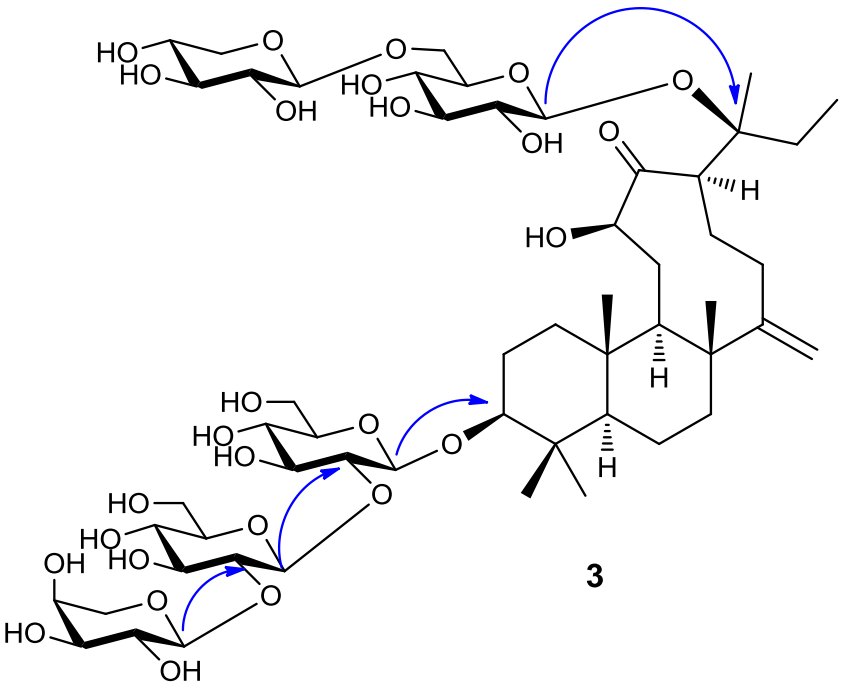


Figure S2. Key HMBC correlations of compound **2**



3

Figure S3. Key HMBC correlations of compound **3**

4. General experimental procedures

Optical rotations were measured on a JASCO P2000 automatic digital polarimeter. UV spectrum was recorded on a JASCO V-650 spectrophotometer. IR spectrum was recorded on a Nicolet 5700 spectrometer using an FT-IR microscope transmission method. NMR spectra were acquired with Bruker AVIIIHD 600 and VNS-600spectrometers in Pyridine-d_5 and D_2O. HR-ESI-MS spectra were collected on an Agilent 1100 series LC/MSD ion trap mass spectrometer. GC was conducted on Agilent 7890A gas chromatograph. MPLC system was composed of two C-605 pumps (Büchi), a C-635 UV detector (Büchi), a C-660 fraction collector (Büchi), and an ODS column (60 × 600 mm, 50 μm, 400 g; YMC). Semi-preparative HPLC was conducted using a Shimadzu LC-6AD instrument with an SPD-20A UV detector and an YMC-Pack ODS-A column (250×10 mm, 5 μm). Preparative HPLC was also performed on a Shimadzu LC-6AD instrument with a YMC-Pack ODS-A column (250 × 20 mm, 5 μm). Column chromatography (CC) was performed with HPD macroporous resin, silica gel (100-200 mesh, Qingdao shenghai Chemical Inc., Qingdao, People's Republic of China). TLC was carried out on glass precoated silica gel GF254 plates. Spots were visualized under UV light or by spraying with 10% sulfuric acid in EtOH followed by heating. Preparative HPLC was carried out (YMC Co., Kyoto, Japan) (250 × 20 mm) with CH_3CN/H_2O 22:78 (system I), 20:80 (system II), 51:49 (system III) as mobile phase.

5. Plant material

The leaves of *P. notoginseng* were collected in Wenshan, Yunnan, China in May 2015. A voucher specimen (ID-S-2767) was identified by Professor Lin Ma from the Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College and deposited at the Herbarium of Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College.

6. Extraction and isolation

Dried leaves of *P. notoginseng* (25 kg) were extracted with ethanol (2 h × 2) and water (2 h × 2) successively. The water extract (SSQY) was applied to a macroporous

resin column (1000 mm×200 mm) and eluted with water, 25% ethanol, 50% ethanol and 95% ethanol in sequence to yield 3 parts, SSQY-A (298.5 g), SSQY-B (365.4 g), and SSQY-C (93.4 g). The SSQY-B was further eluted with EtOAc, acetone, acetone/ethanol (1:1), 70% ethanol, 50% ethanol in order through a diatomite column to afford SSQY-BP1~5. SSQY-BP3 (146.682 g), the acetone/ethanol (1:1) part, was fractionated by a silica gel column using isocratic elution of $CHCl_3/CH_3OH/H_2O$ (6:4:0.5, 28L) to 28 parts. According to a TLC analysis, we mixed the 23rd part with 24th part as mixture A (8.460 g) and the 25th part to 27th part as mixture B (6.205 g). Mixture A was subjected to the RP-18 column chromatography (60 mm×600 mm) with gradient system ($MeOH/H_2O$, 40:60-75:25, 60 ml/min, 49 L) to yield 91 fractions, Fr. A1-A91. Fr. A33 was performed on HPLC by system II to get compound **1** (12 mg). Fr. A36 was performed on HPLC system I to obtain **2** (5 mg). Fr. A32 was performed on HPLC system II to give **3** (4 mg).

7. Enzyme hydrolysis of 1

Compound **1** (8.0 mg) was dissolved in water (5 ml) with snailase (12 mg, Beijing Biodee Biotechnology Co., ltd.) and stirred for 72 h at 37 ℃. The reactant was extracted by EtOAc (3 ml × 3) when it performed a relatively high ratio of aglycone (t_R = 22 min) on HPLC analysis. The EtOAc extract was purified on prepare HPLC (detected at 210 nm, CH_3CN/H_2O 51:49, 3 mL/min) to give **1a**.

8. Acid hydrolysis and determination of absolute configurations of monosaccharides

Compounds **1-3** (3.0 mg) were dissolved in 2.5 M HCl-H_2O (5 ml) and stirred for 10 h at 95 ℃ individually, then extracted by EtOAc (3 ml × 3). The aqueous layers were concentrated and dried totally to give residues A-C, respectively. L-cysteine methyl ester hydrochloride (double weight of the residues, J&K Scientific Ltd.) was added to the A-C residues and then anhydrous pyridine to dissolve the mixture. The mixture was stirred at 60 ℃ for 2 h and then concentrated. N-trimethylsilylimidazole (about 1.5 ml, J&K Scientific Ltd.) was added to the dried reaction products afterwards

and stirred at 60 ℃ for 2 h. Then the reaction mixture was put into ice water (5 ml) and extracted with n-hexane (5 ml × 3). The n-hexane layers were analyzed by GC under the following conditions: capillary column, HP-5 (60 m × 0.32 mm); H_2 flame ionization detector; detector temperature, 280 ℃; injection temperature, 200 ℃, and injection volume, 4 μL; initial temperature, 200 ℃, and raised to 280 ℃ at 10 ℃/min, final temperature maintained for 35 min; carrier gas, N_2 (1 mL/min); and split ratio, 1/50. The authentic samples, D-glucose (5 mg), L-glucose (5 mg), D-xylose (5 mg), L-xylose (5 mg), D-arabinose (5 mg) and L-arabinose (5 mg) were treated with the same method. Identification of the sugar moiety was carried out by comparison of its retention time (t_R): D-glucose 29.6 min, L-glucose 30.4 min, D-xylose 21.0 min, L-xylose 21.7 min, D-arabinose 21.8 min, L-arabinose 21.0 min. D-glucose and D-xylose were detected from the derivatives of A and B. D-glucose, L-arabinose and D-xylose were detected from the derivatives of C.

9. Physico-chemical constant of compounds 1~3 and 1a

Nototroneside A (**1**): Amorphous white powder; $[\alpha]_D^{20}$ -10.8 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 202.2 (3.1) nm; IR (microscope) ν_{max}: 3383, 2933, 1708, 1387, 1076 cm^{-1}; ^1H and ^{13}C NMR data see Table 1; HRESIMS *m/z* 1193.5578 $[M + Na]^+$ (calcd for $C_{54}H_{90}O_{27}Na$, 1193.5562).

Nototroneside B (**2**): Amorphous white powder; $[\alpha]_D^{20}$ -7.5 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 202.2 (3.25) nm; IR (microscope) ν_{max}: 3379, 2926, 1707, 1387, 1078 cm^{-1}; ^1H and ^{13}C NMR data see Table S1; HRESIMS *m/z* 1061.5136 $[M + Na]^+$ (calcd for $C_{49}H_{82}O_{23}Na$, 1061.5139).

Nototroneside C (**3**): Amorphous white powder; $[\alpha]_D^{20}$ -12.6 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 202.2 (3.53) nm; IR (microscope) ν_{max}: 3386, 2933, 1706, 1387, 1080 cm^{-1}; ^1H and ^{13}C NMR data see Table S1; HRESIMS *m/z* 1193.5525 $[M + Na]^+$ (calcd for $C_{54}H_{90}O_{27}Na$, 1193.5562).

Nototrone A (**1a**): colorless crystal (in MeOH: H_2O); ^1H and ^{13}C NMR data see Table S2; HRESIMS *m/z* 443.3146 $[M + Na]^+$ (calcd for $C_{26}H_{44}O_4Na$, 443.3132). ECD

(MeOH) λ_{max} ($\Delta\varepsilon$) 299 nm (-3.43), 218 nm (-5.88); IR (microscope) ν_{max}: 3413, 2927, 1707, 1381, 1041 cm^{-1}.

10. ECD computation of nototrone A (1a).

The conformers were further optimized at the B3LYP/6-31g (d,p) level in methanol. The energies, oscillator strengths, and rotational strengths of the first 100 electronic excitations were calculated using the TDDFT methodology at the B3LYP/6-31g (d,p) level. ECD spectra of the conformers were simulated using a Gaussian function with a half-bandwidth of 0.40 eV. The corresponding experimental ECD spectra of the **1a** were depicted by inverting that of calculated ECD spectra of **1aa** and **1ab**, respectively. All quantum computations were performed using Gaussian 09 program package, on an IBM cluster machine located at the High Performance Computing Center of Peking Union Medical College.

11. X-ray Crystallographic Analysis of nototrone A (1a) (See Table S3)

Single crystals of **1a** ($C_{26}H_{44}O_4$) were recrystallized from MeOH-H_2O (v/v, 9:1) mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal structure determination of crystal data $C_{26}H_{44}O_4$, M =420.61, orthorhombic, a =10.61438(13) Å, b =17.8619(2) Å, c =25.1750(3) Å, U = 4773.00(10) $Å^3$, T = 105.1, space group $P2_12_12_1$ (no. 19), Z = 8, μ (Cu Kα) = 0.600, 17819 reflections measured, 9029 unique (R_{int} = 0.0275) which were used in all calculations. The final wR (F_2) was 0.1004 (all data). Crystallographic data (excluding structure factor tables) for 1 have been deposited at the Cambridge Crystallographic Data Center as supplementary publication (CCDC 1847574). Copies of the data can be obtained free of charge by application to CCDC, 12, Union Road, Cambridge CB21EZ, UK [Fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

Table S3: Crystal data and structure refinement for exp_5187

Identification code	exp_5187
Empirical formula	$C_{26}H_{44}O_4$
Formula weight	420.61
Temperature / K	105.1

Crystal system	orthorhombic
Space group	$P2_12_12_1$
a / Å, b / Å, c / Å	10.61438(13), 17.8619(2), 25.1750(3)
α/°, β/°, γ/°	90, 90, 90
Volume / $Å^3$	4773.00(10)
Z	8
ρ_{calc} / mg mm^{-3}	1.171
μ / mm^{-1}	0.600
F(000)	1856
Crystal size / mm^3	0.250 ×0.250 ×0.240
2Θ range for data collection	6.068 to 142.344 °
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 21$, $-30 \le l \le 29$
Reflections collected	17819
Independent reflections	9029[R(int) = 0.0275 (inf-0.9Å)]
Data/restraints/parameters	9029/0/559
Goodness-of-fit on F^2	1.028
Final R indexes [I>2σ (I) i.e. F_o>4σ (F_o)]	R_1 = 0.0388, wR_2 = 0.0979
Final R indexes [all data]	R_1 = 0.0414, wR_2 = 0.1004
Largest diff. peak/hole / e $Å^{-3}$	0.240/-0.208
Flack Parameters	0.01(8)
Completeness	0.999

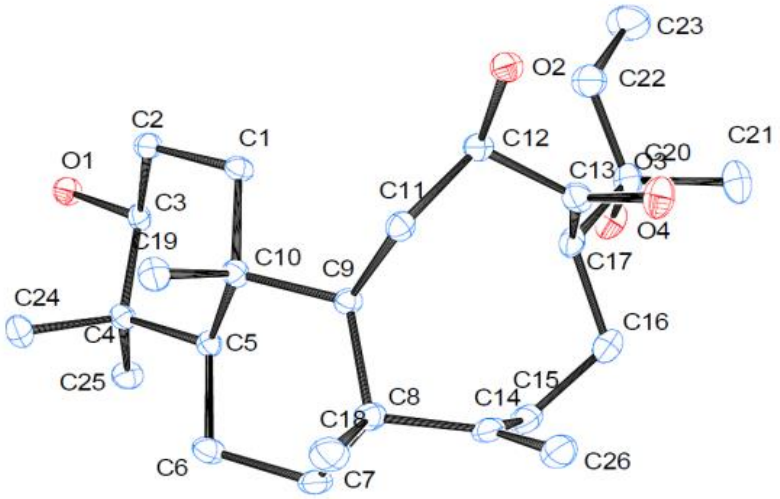


Figure S4. X-ray crystal structure of **1a**.

12. Neuroprotection Bioassays of compounds **1-3**

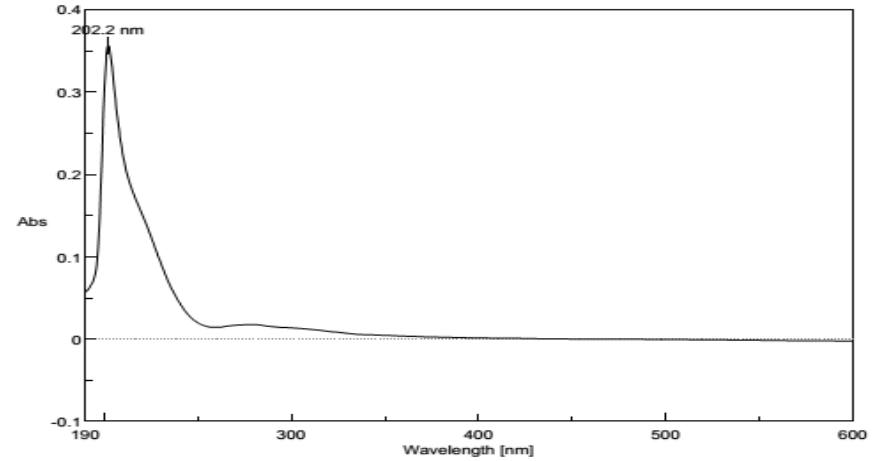
Pheochromocytoma (PC12) cells were incubated in DMEM supplied with 5% fetal bovine serum and 5% equine serum as basic medium. PC12 cells in logarithmic phase were cultured at a density of 5000 cells per well in a 96-well microtiter plate. After 24h incubation, the medium of model group was changed to DMEM without serum. Test compounds dissolved in dimethyl sulfoxide (DMSO) were added to each well for >1000 fold dilution in the model medium at the same time. Each sample was tested in triplicate. After the incubation at 37 ℃ in 5% CO_2 for 24 h, 10 μL of MTT (5 mg/ml) was added to each well and incubated for another 4 h, then liquid in the wells was removed. DMSO (100 μl) was added to each well. The absorbance was recorded on a microplate reader (Bio-Rad model 550) at a wavelength of 570 nm. Analysis of variance (ANOVA) followed by Newman-Keuls post hoc test were performed to assess the differences between the relevant control and each experimental group. P-values of < 0.05, < 0.01 and < 0.001 were regarded as statistically significant. Data were expressed as mean ± SEM as indicated.

Table S4. Neuroprotective activity of compounds **1-3** on PC12 cell model induced by serum deprivation (10.0 μM, 1.0 μM, and 0.1μM).

group	Cell viability (100%)
Control	100
Free-serum	61.58
NGF	101.6 ***
1 (10 μM)	53.33
1 (1.0 μM)	75.76
1 (0.10 μM)	71.66
2 (10 μM)	74.2
2 (1.0 μM)	79.33*
2 (0.10 μM)	69.9
3 (10 μM)	52.28
3 (1.0 μM)	72.41
3 (0.10 μM)	68.07

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

12. HRESI-MS, UV, IR, NMR spectra of nototronesides A-C (1-3)



[Comment]
Sample Name DBT
Comment 0.02
User
Division UV
Company 324
[Measurement Information]
Instrument Name V-650
Model Name V-650
Serial No. A034461150

Accessory PSC-718
Accessory S/N A001761114
Position 2
Cell Length 10 mm
Temperature 20.00 C
Control Sonsor Holder
Monitor Sensor Holder
Start Mode Start immediately

Photometric Mode Abs
Measurement range 600 - 190 nm
Data pitch 0.2 nm
Band width(UV/Vis) 2.0 nm
Response Medium
Scanning speed 200 nm/min
Source Change 340 nm
Light Source D2/WI
Filter Exchange Step
Correction Baseline

[Data Information]
Creation Date 2017-3-22 11:08

Data array type Linear data array
Horizontal Wavelength [nm]
Vertical Abs
Start 600 nm
End 190 nm
Data pitch 0.2 nm
Data points 2051

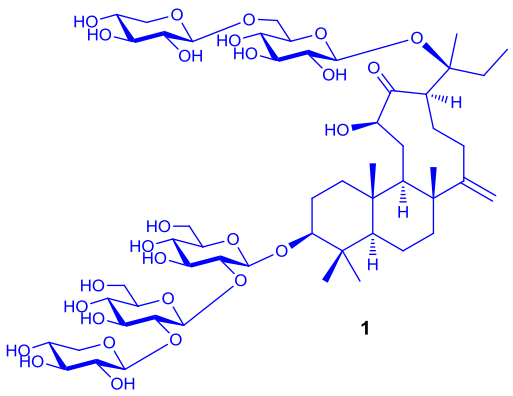


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Figure S5. The UV spectrum of nototroneside A (**1**) in CH_3OH

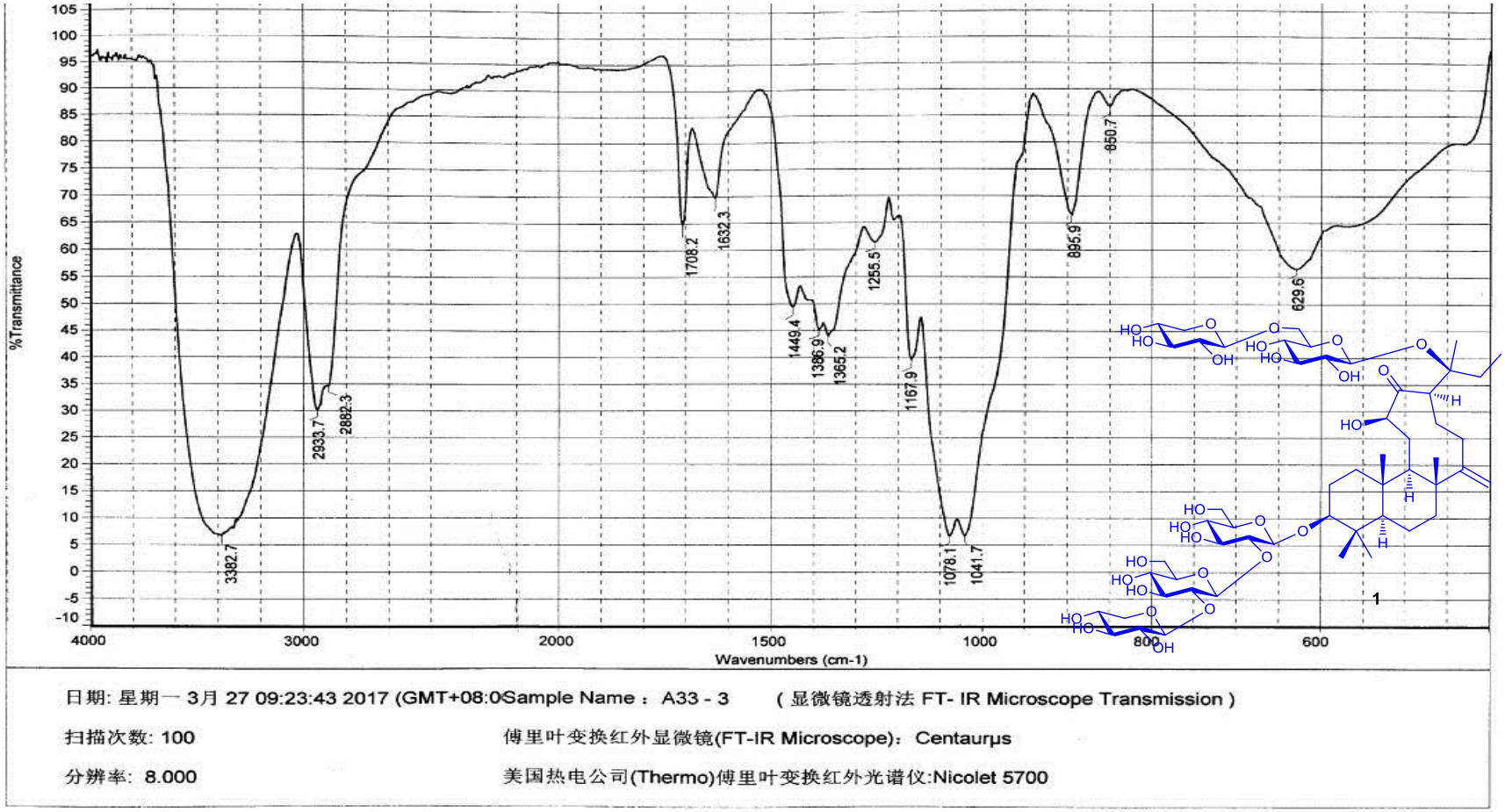

Figure S6. The IR spectrum of nototroneside A (**1**)

Qualitative Analysis Report

Data Filename	2016042901.d	**Sample Name**	S5QY-BP3-A33-3
Sample Type	Sample	**Position**	P1-C2
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	[redacted]
DA Method	TEST LCMS.m	**Comment**	

User Chromatograms

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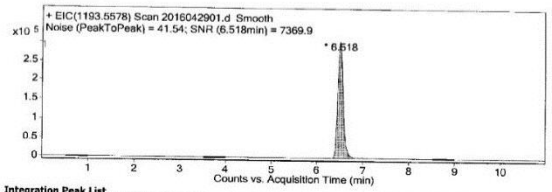

Integration Peak List

Peak	Start	RT	End	Height	Area	Area %	Signal To Noise
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User Spectra

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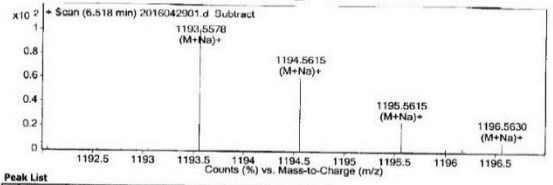

Peak List

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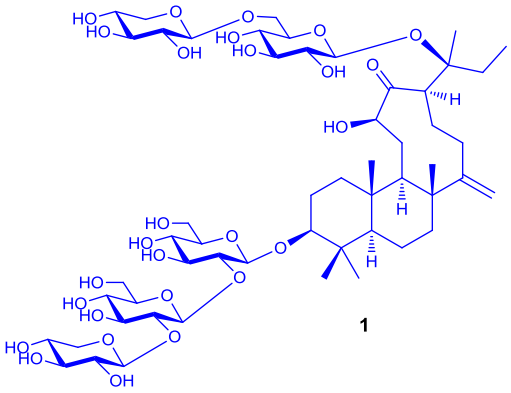
331.2629		33757		
367.2993		58594		
385.3102	1	119172		
403.3202		49667		
605.264	2	64984		
605.7694	2	45002		
1193.5578	1	388030	C54 H90 Na O27	(M+Na)+
1194.5615	1	235555	C54 H90 Na O27	(M+Na)+
1195.5615	1	91971	C54 H90 Na O27	(M+Na)+

Formula Calculator Element Limits

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



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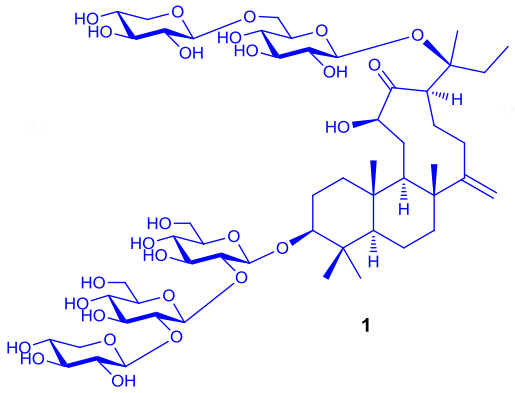
MS Formula Results: + Scan (5.518 min) Sub (2016042901.d)

m/z	Ion	Formula	Abundance
1193.5578	(M+Na)+	C54 H90 Na O27	388028.7

Best	Formula (M)	Ion Formula	Score	Cross Sco	Mass	Calc Mass	Calc m/z	Diff (ppm)	Abs Diff (ppm)	Mass Match	Abund Match	Spacing Match	DBE
✔	C54 H90 O27	C54 H90 Na O27	99.93		1170.5686	1170.5869	1193.5562	-1.42	1.42	99.93	99.92	99.94	10
	C51 H94 O27 S	C51 H94 Na O27 S	99.6		1170.5686	1170.5703	1193.5595	1.44	1.44	99.93	98.72	99.99	5
	C60 H86 N2 O21	C60 H86 N2 Na O21	99.52		1170.5685	1170.5723	1193.5615	3.15	3.15	99.64	98.96	99.93	19
	C49 H90 N2 O29	C49 H90 N2 Na O29	99.43		1170.5685	1170.5629	1193.5521	-4.87	4.87	99.15	99.47	99.95	6
	C58 H90 O22 S	C58 H90 Na O22 S	99.36		1170.5683	1170.5644	1193.5537	-3.58	3.58	99.54	98.54	99.99	14
	C46 H94 N2 O29 S	C46 H94 N2 Na O29 S	99.29		1170.5687	1170.5663	1193.5556	-2.02	2.02	99.85	97.75	99.99	1
	C55 H94 O22 S2	C55 H94 Na O22 S2	98.74		1170.5687	1170.5678	1193.557	-0.72	0.72	99.98	95.62	100	9
	C50 H94 N2 O24 S2	C50 H94 N2 Na O24 S2	98.45		1170.5687	1170.5638	1193.553	-4.17	4.17	99.37	95.61	99.99	5
	C48 H98 O27 S2	C48 H98 Na O27 S2	98.13		1170.5687	1170.5737	1193.5629	4.29	4.29	99.34	94.78	99.99	0
	C52 H98 O22 S3	C52 H98 Na O22 S3	97.25		1170.5687	1170.5712	1193.5604	2.14	2.14	99.83	90.67	99.98	4
	C47 H98 N2 O24 S3	C47 H98 N2 Na O24 S3	97.12		1170.5687	1170.5672	1193.5564	-1.31	1.31	99.94	90.07	99.96	0
	C59 H94 O17 S3	C59 H94 Na O17 S3	97.12		1170.5687	1170.5653	1193.5545	-2.87	2.87	99.7	90.44	99.99	13



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page 1

Figure S7. The HR-ESI-MS spectrum of nototroneside A (**1**)

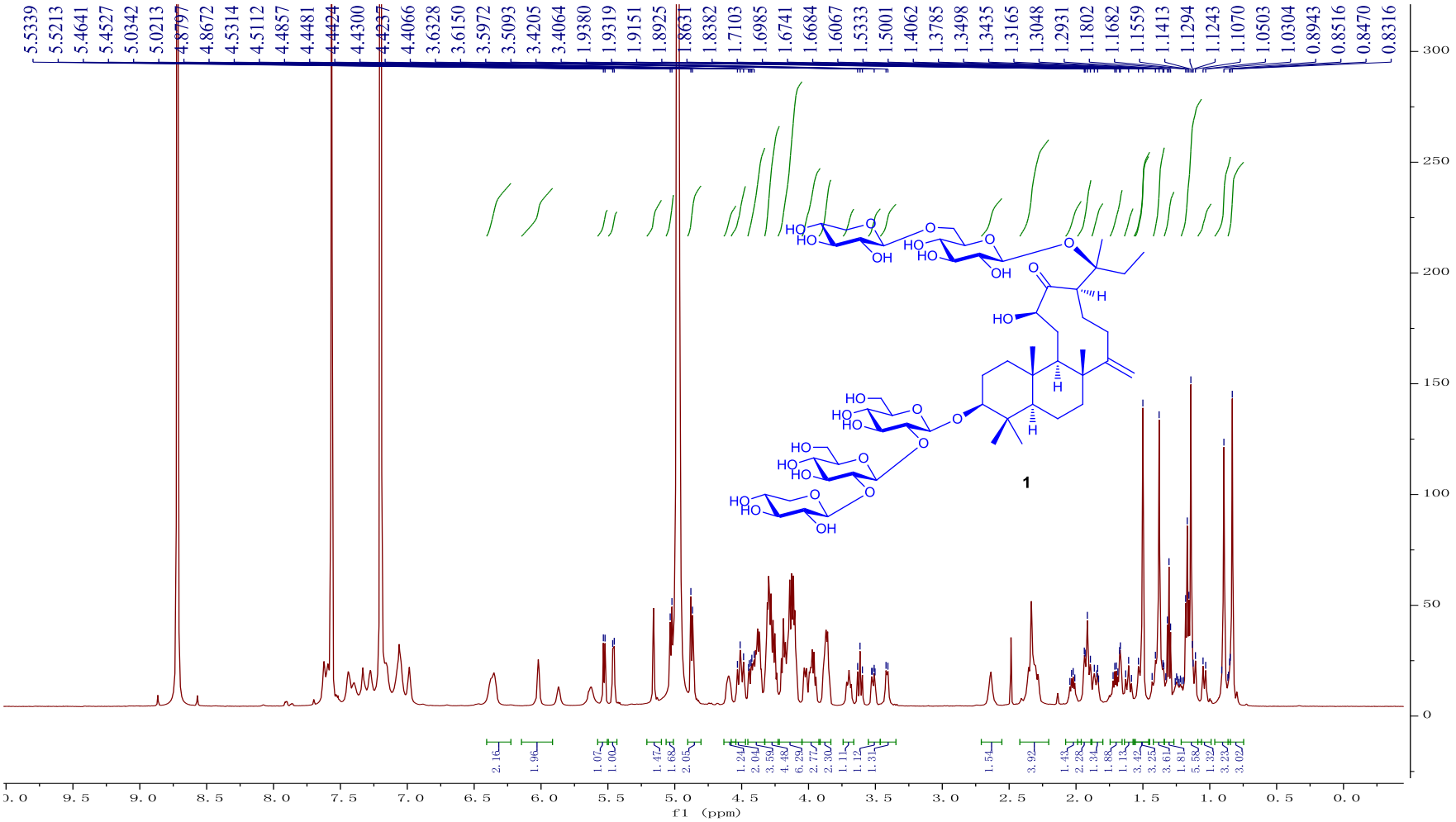


Figure S8. The ^{1}H NMR spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

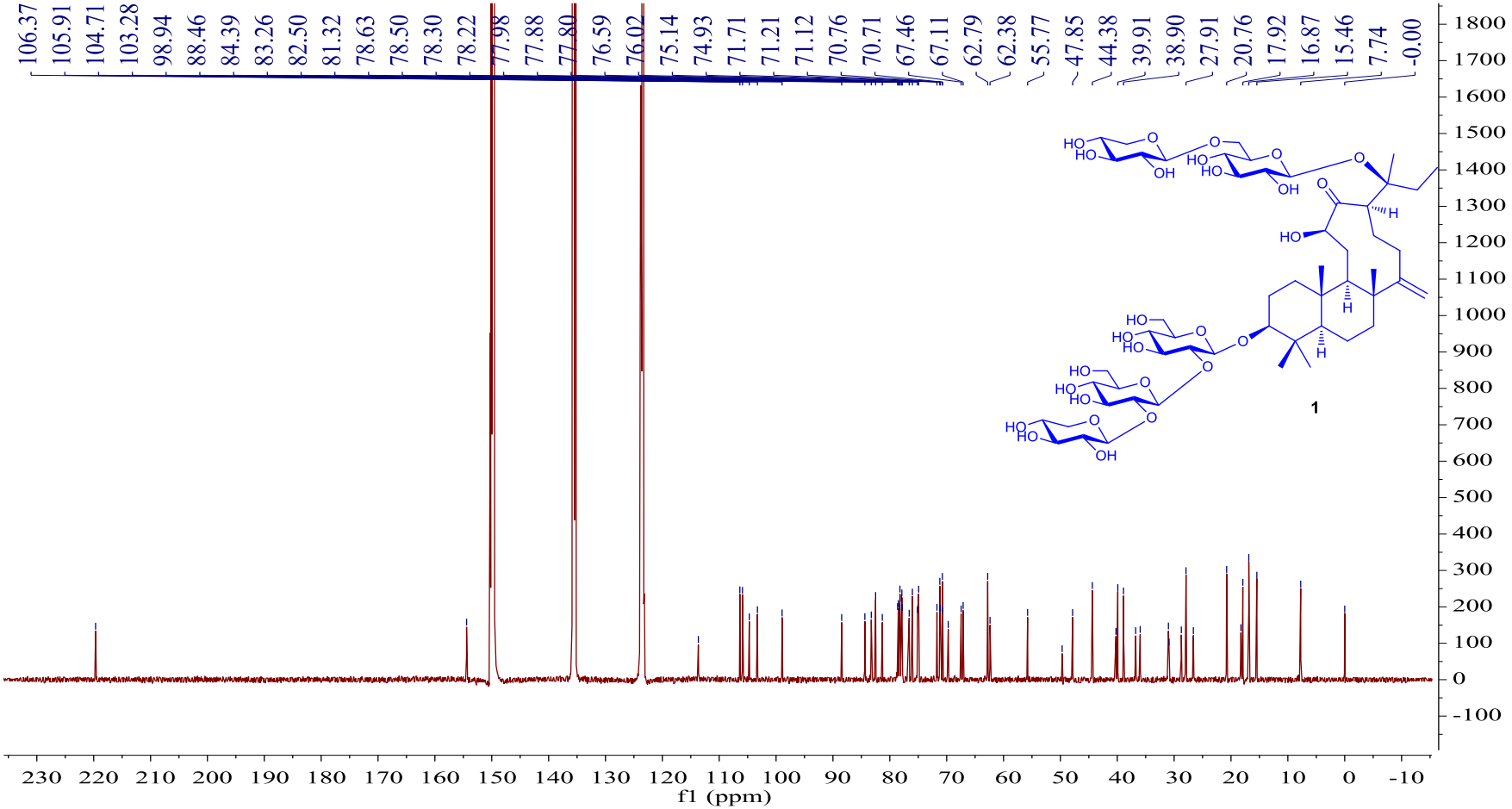


Figure S9. The ^{13}C NMR spectrum of nototroneside A (**1**) in C_5D_5N (150 MHz)

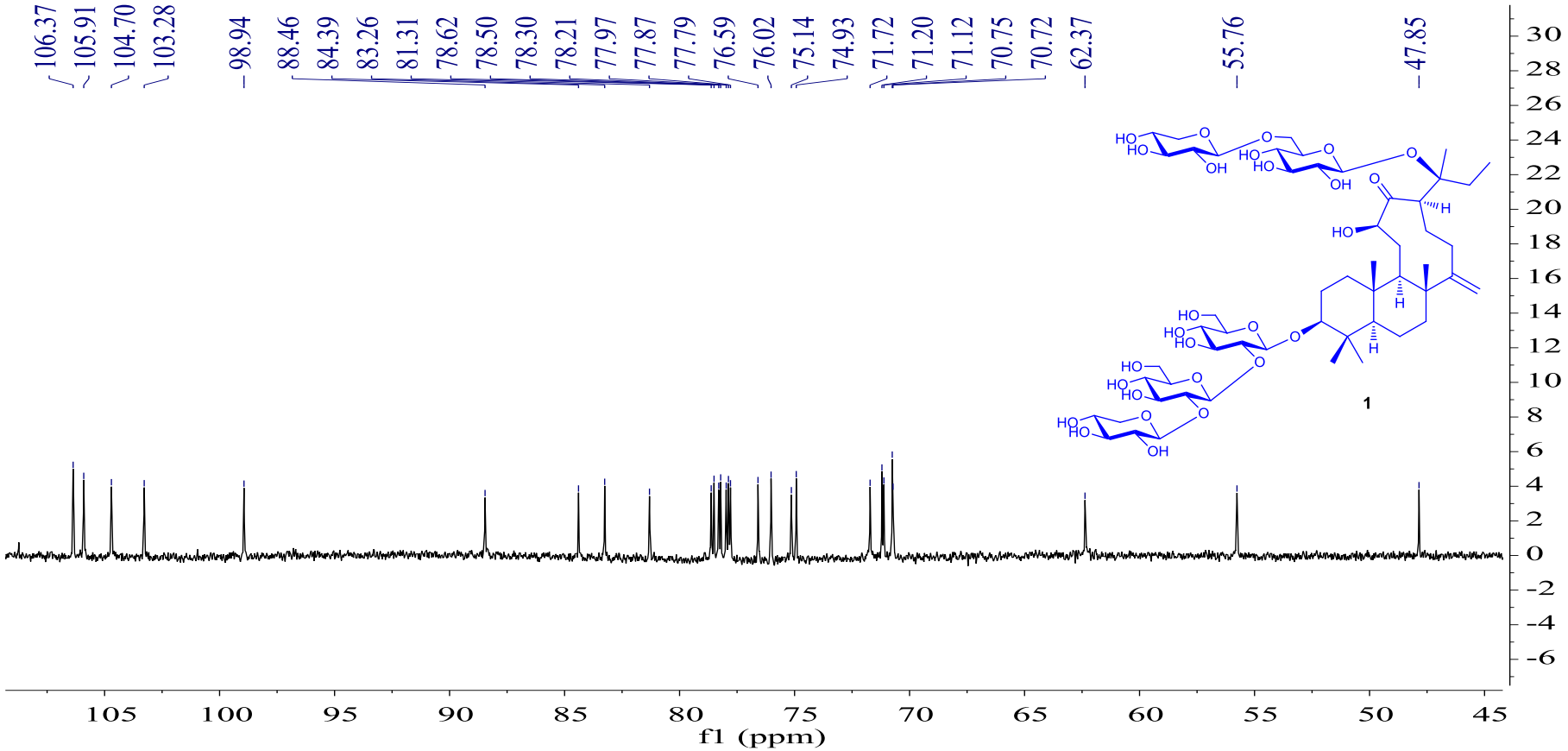


Figure S10. The ^{13}C NMR spectrum of nototroneside A (**1**) in C_5D_5N (150 MHz)

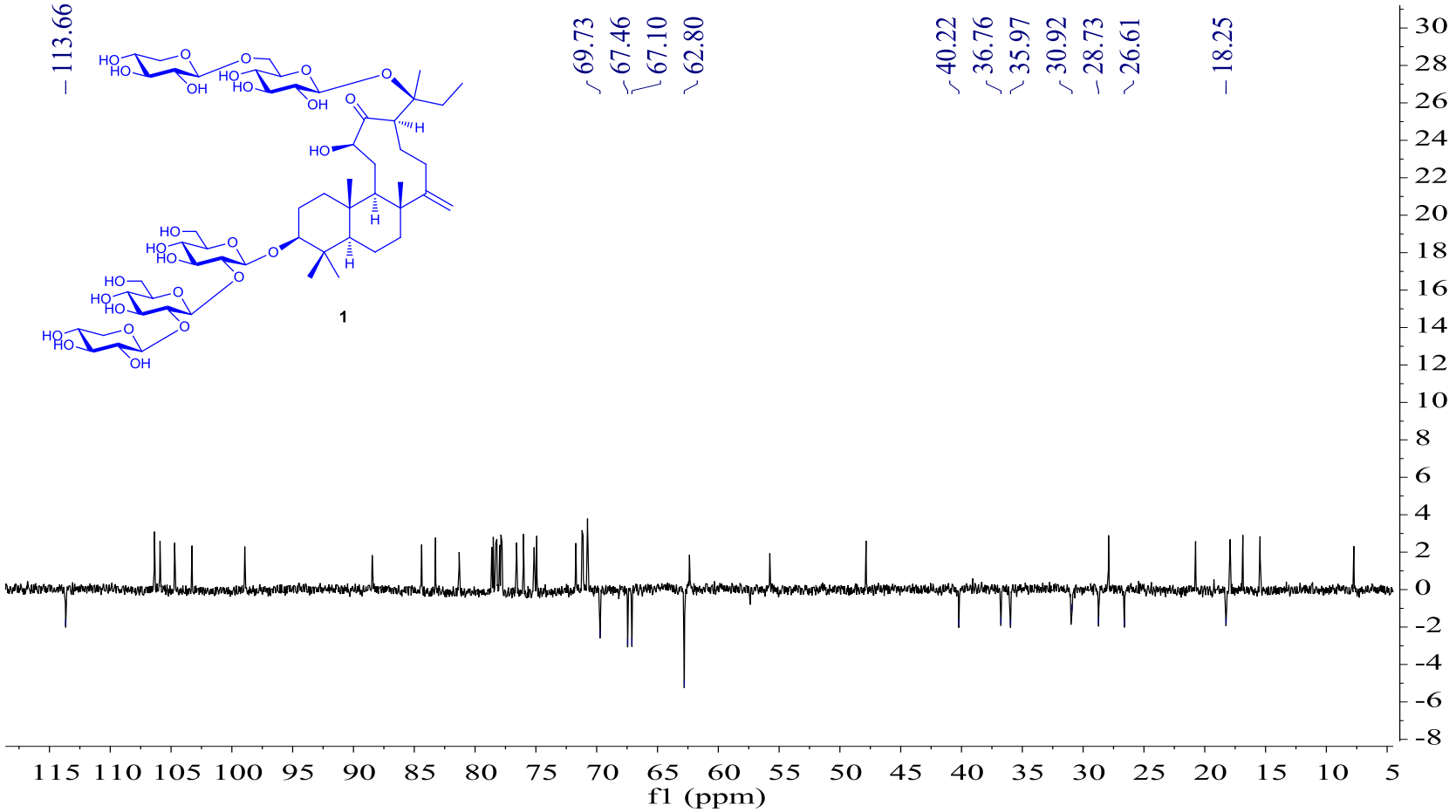


Figure S11. The DEPT135 spectrum of nototroneside A (**1**) in C_5D_5N (150 MHz)

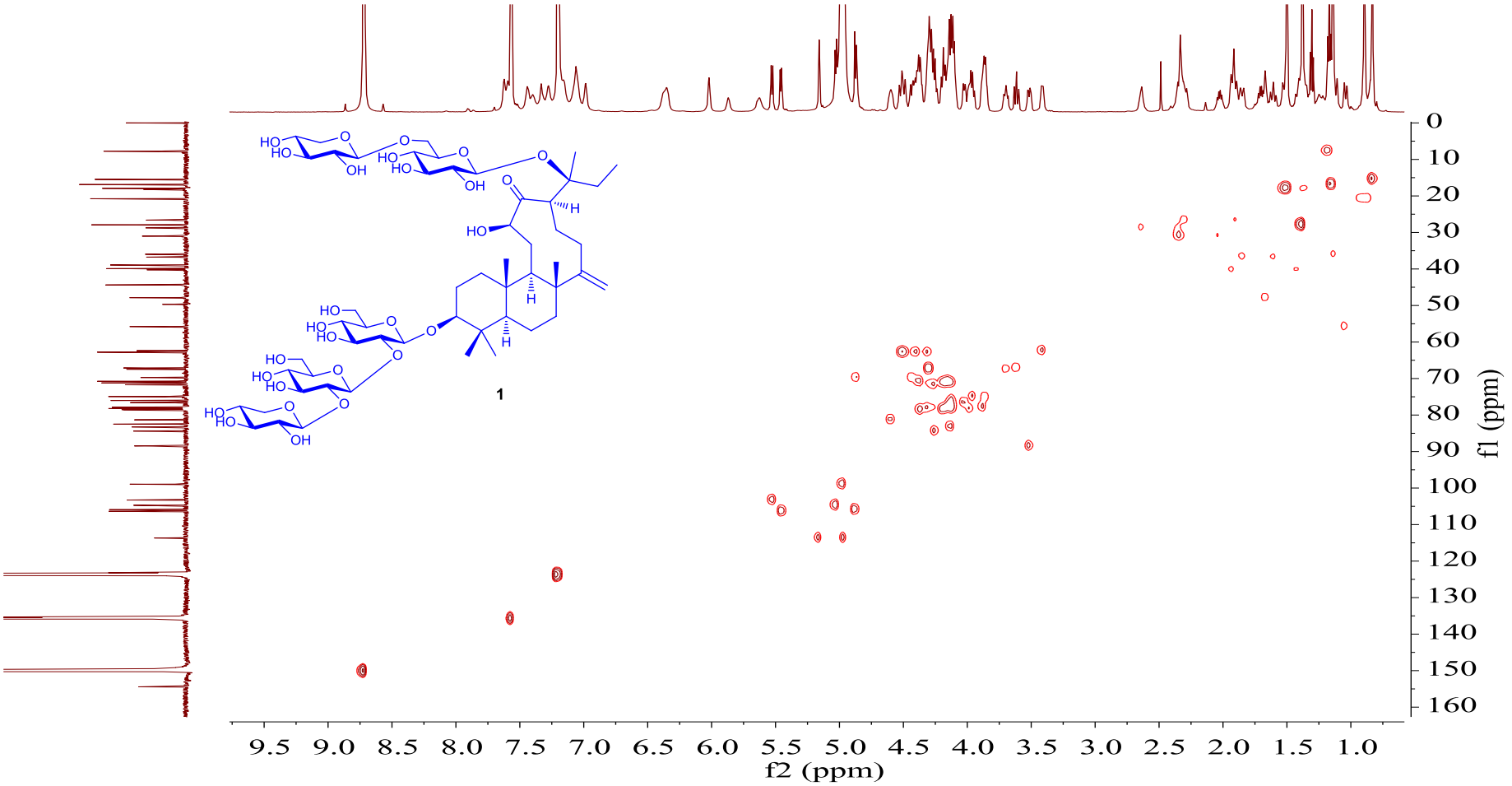


Figure S12. The HSQC spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

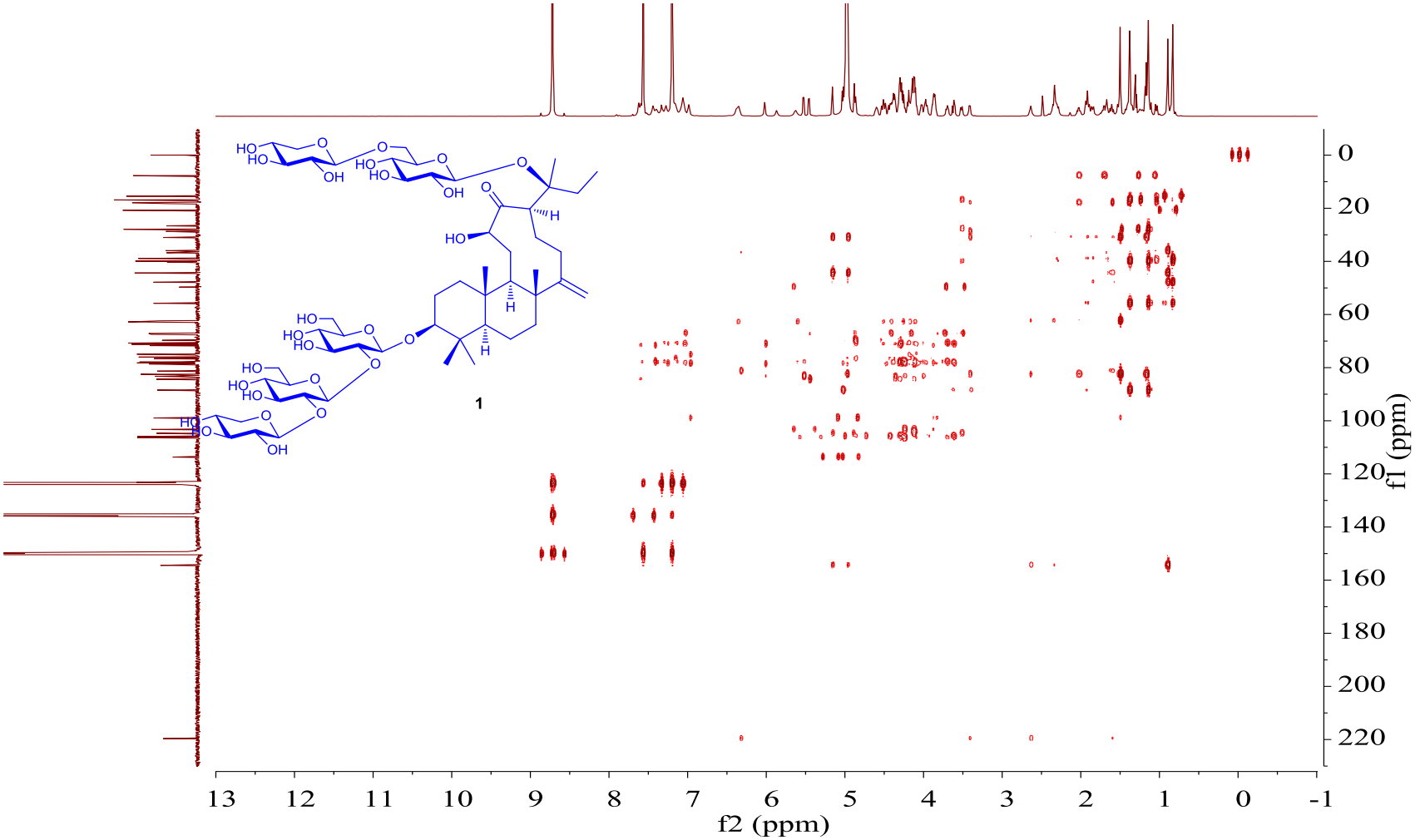


Figure S13. The HMBC spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

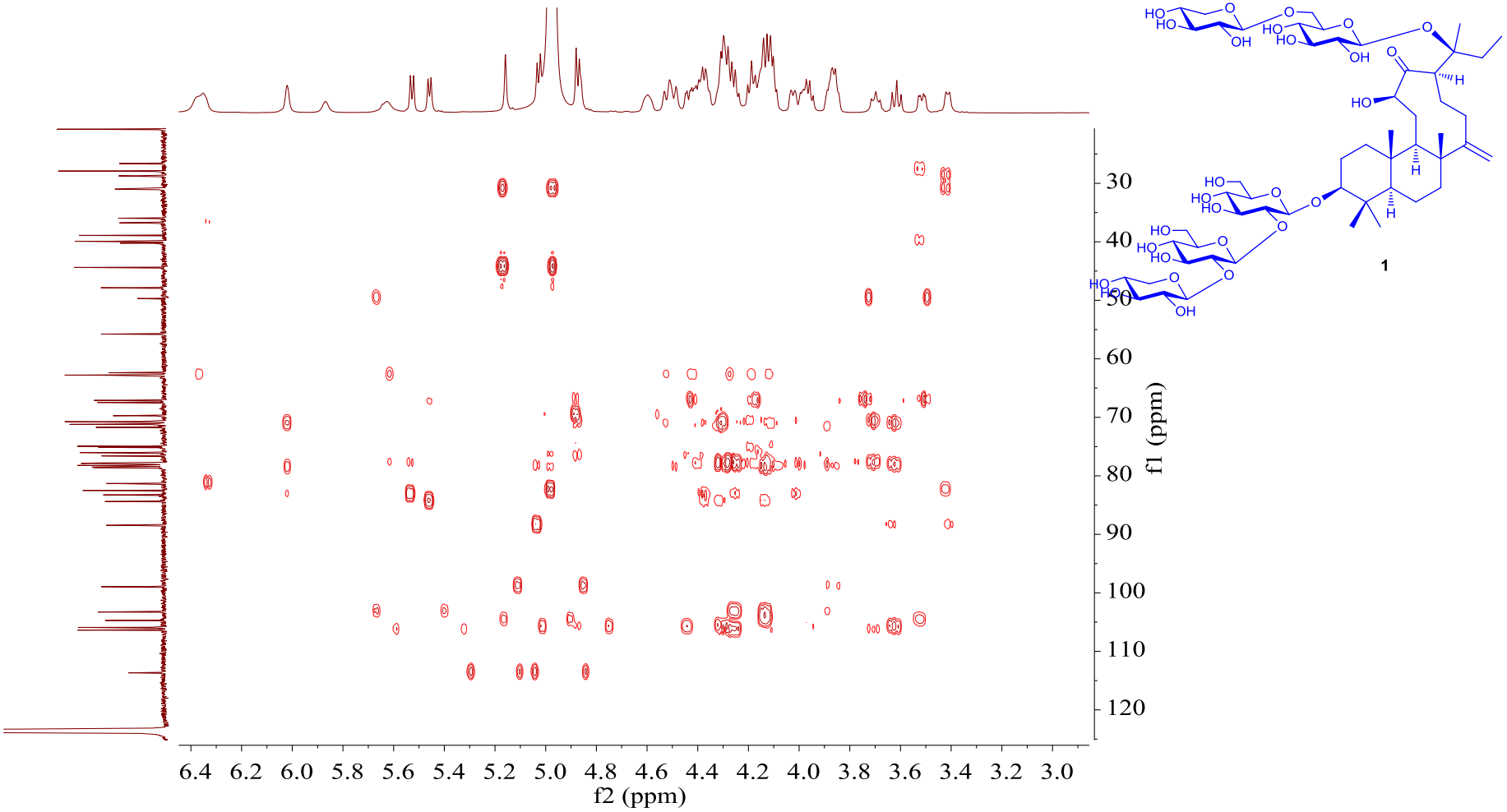


Figure S14. The HMBC spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

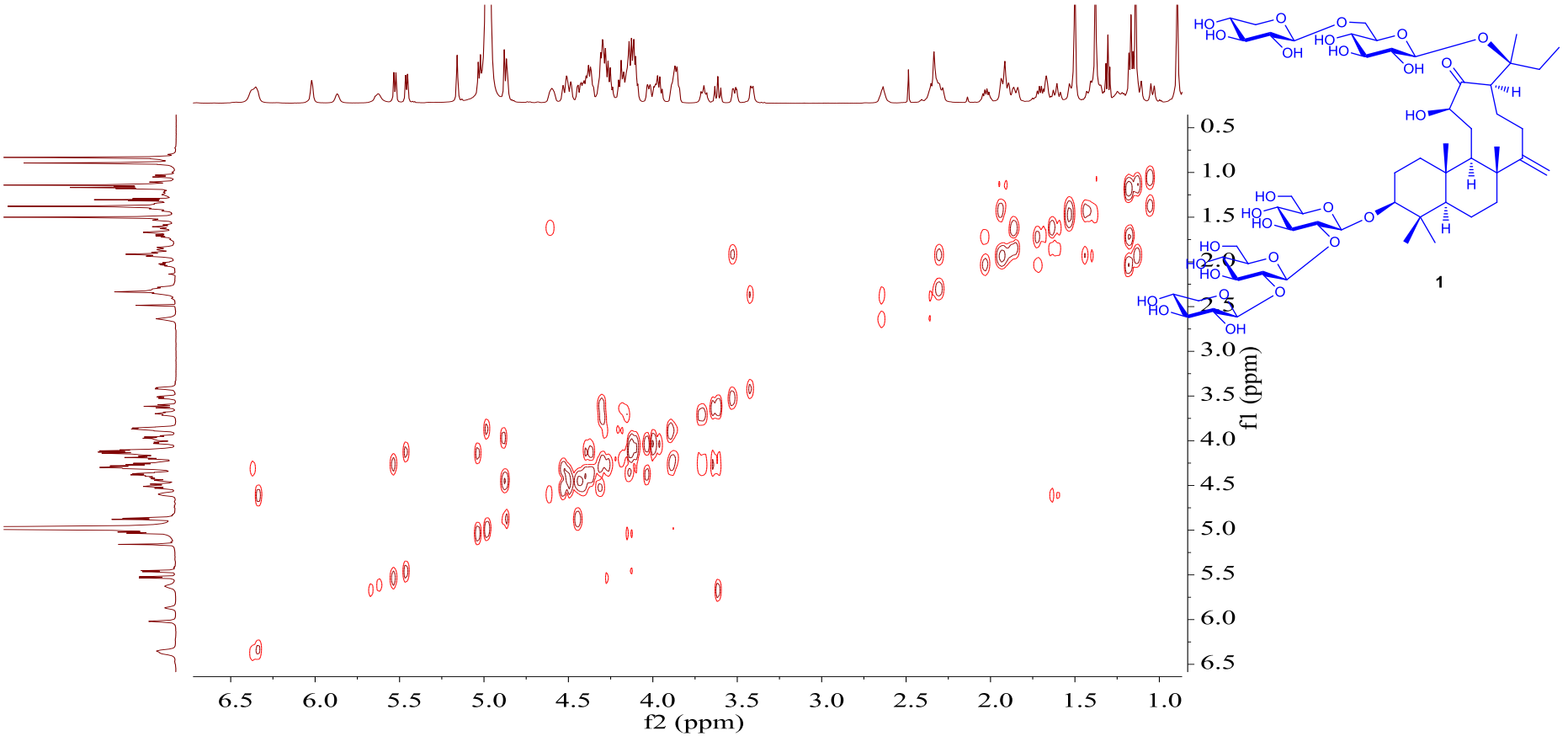


Figure S15. The ^{1}H-^{1}H COSY spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

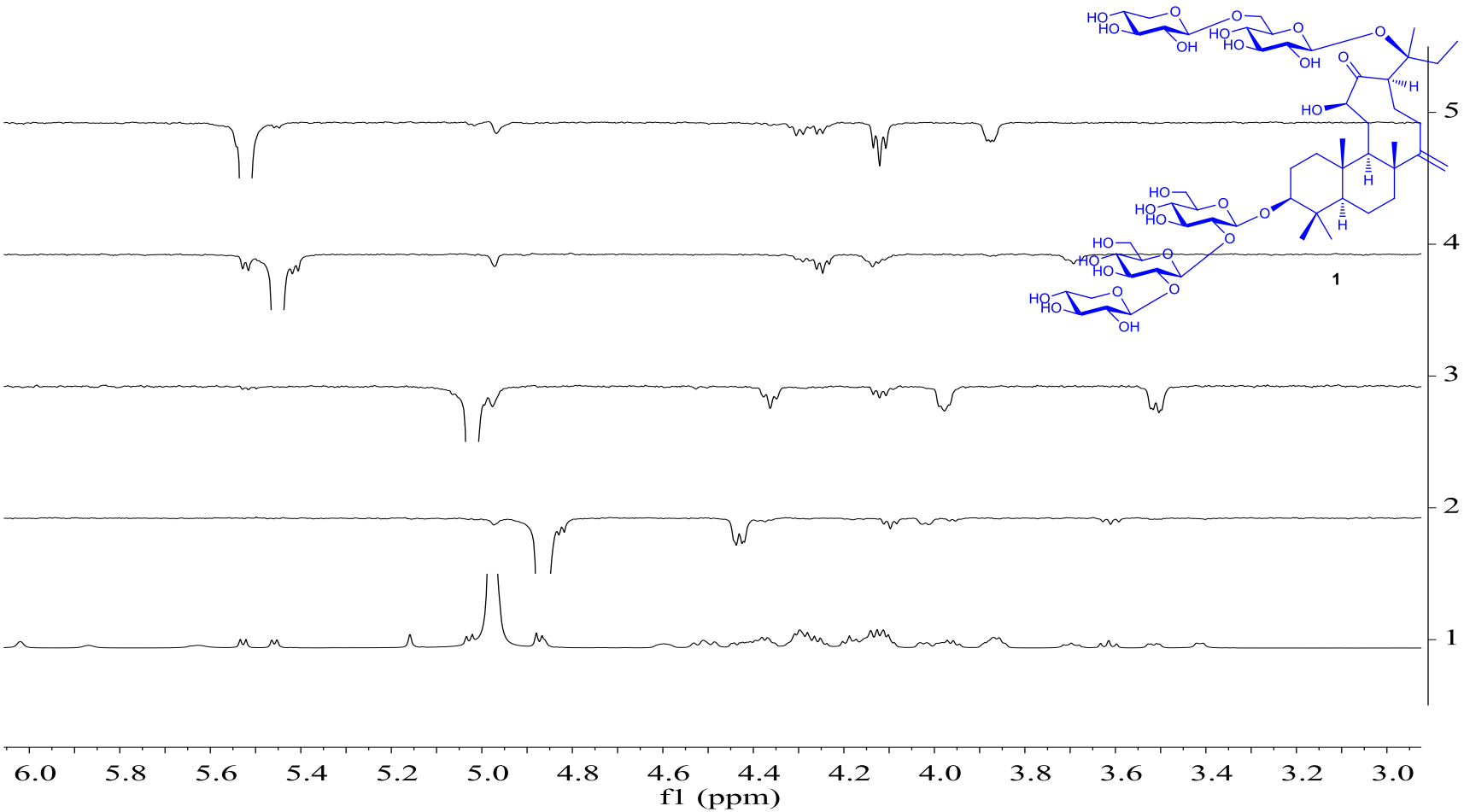


Figure S16. The NOE spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

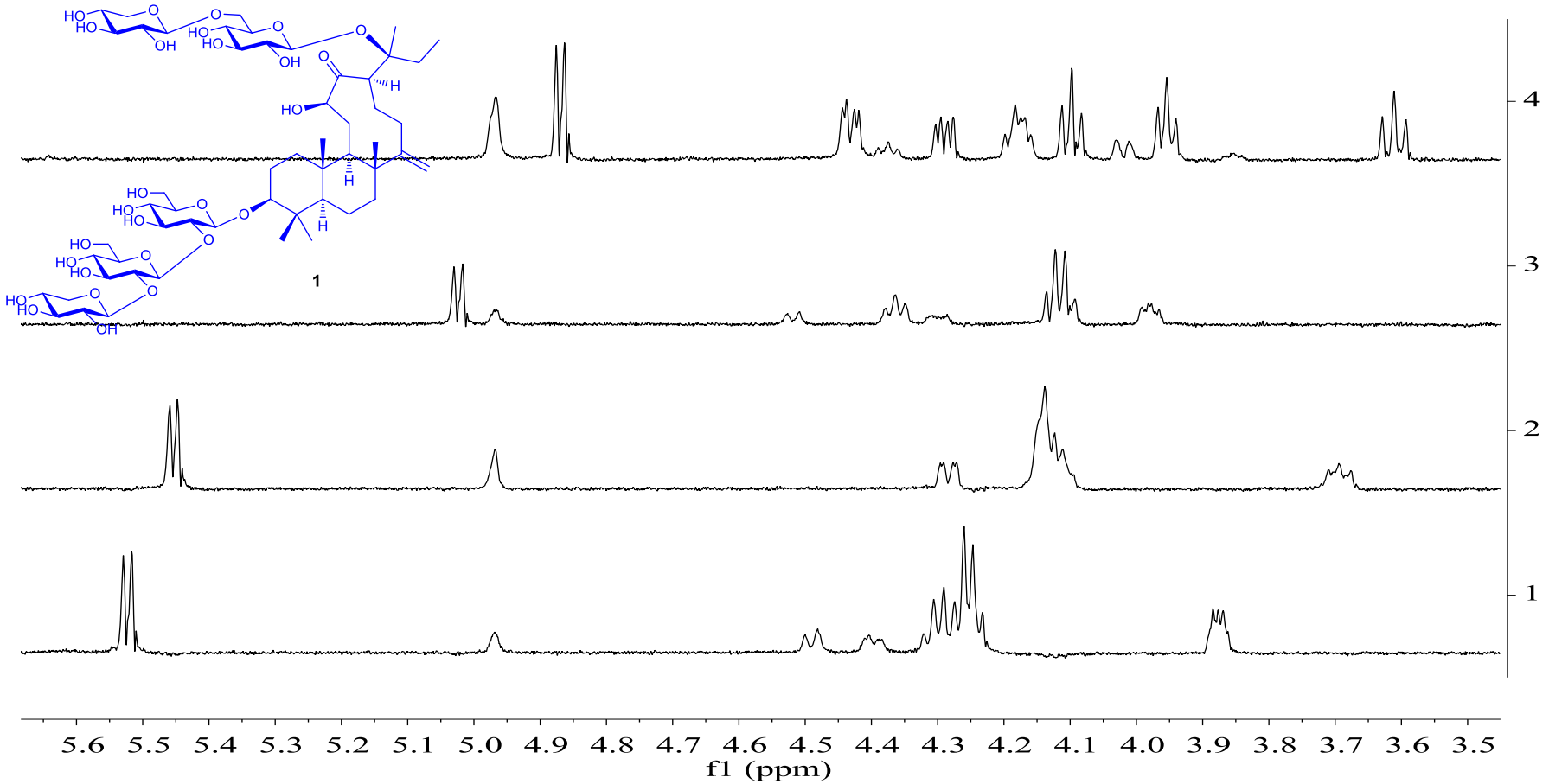


Figure S17. The 1D-TOCSY spectrum of nototroneside A (**1**) in C_5D_5N (600 MHz)

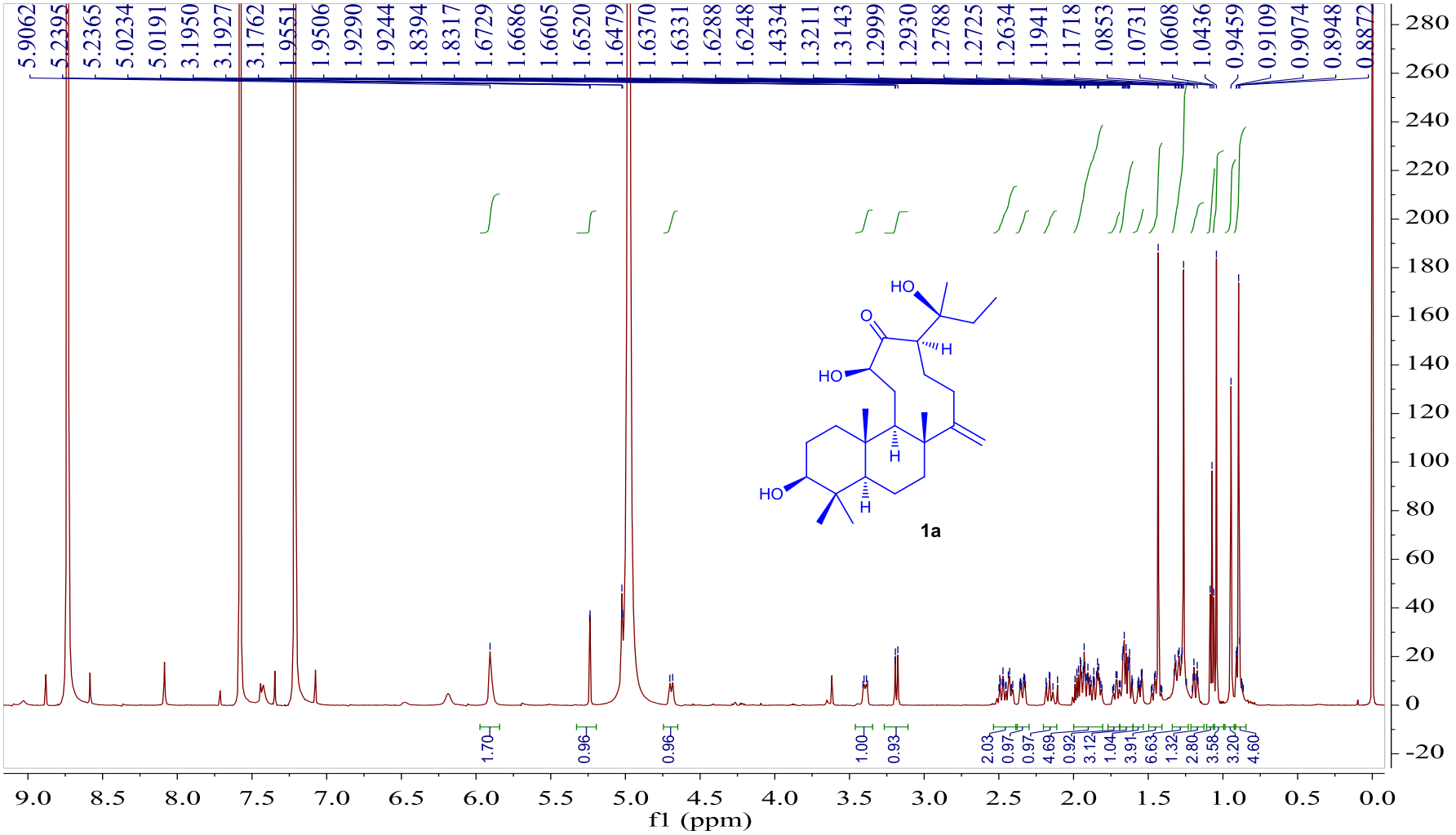


Figure S18. The ^{1}H NMR spectrum of nototrone A (**1a**) in C_5D_5N (600 MHz)

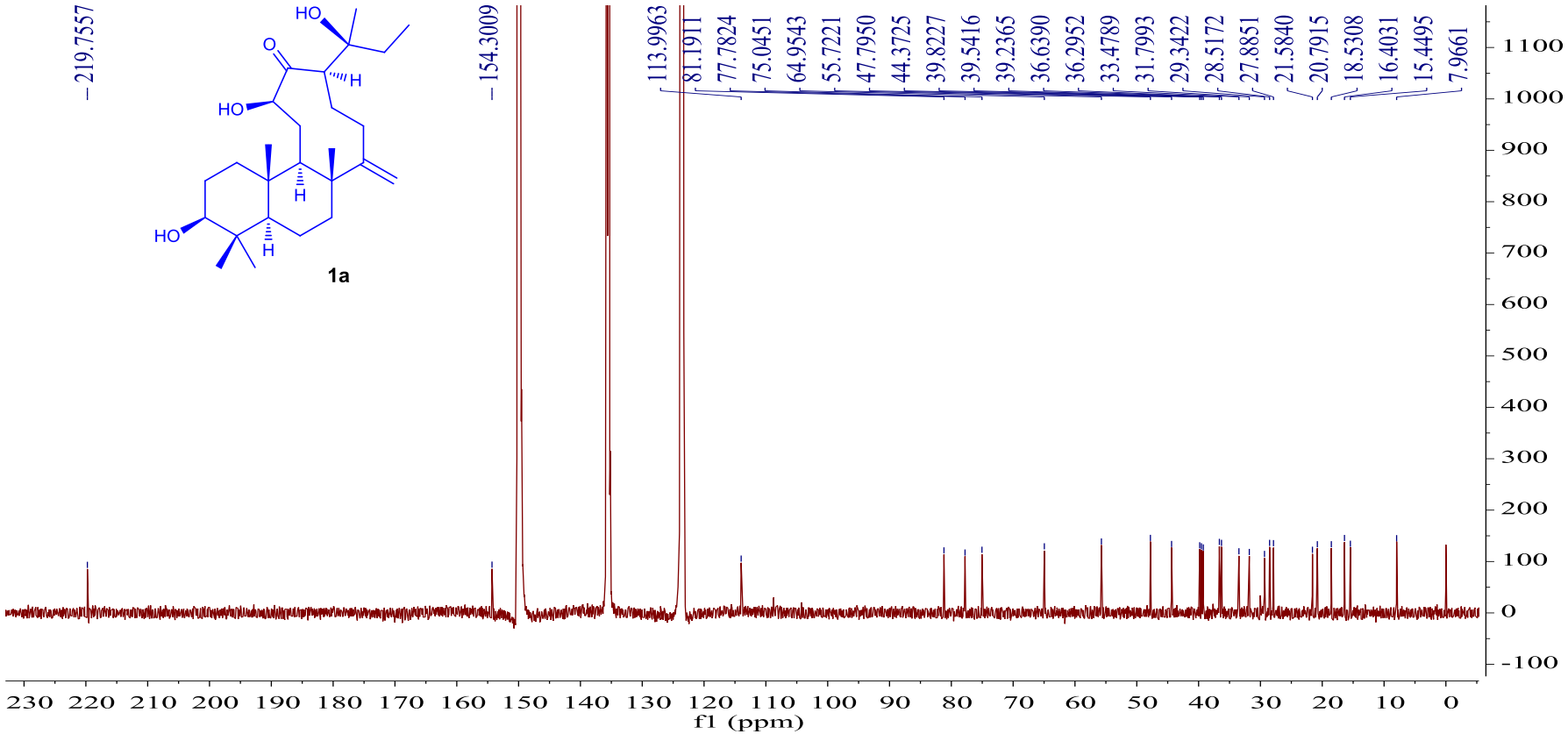


Figure S19. The ^{13}C NMR spectrum of nototrone A (**1a**) in C_5D_5N (150 MHz)

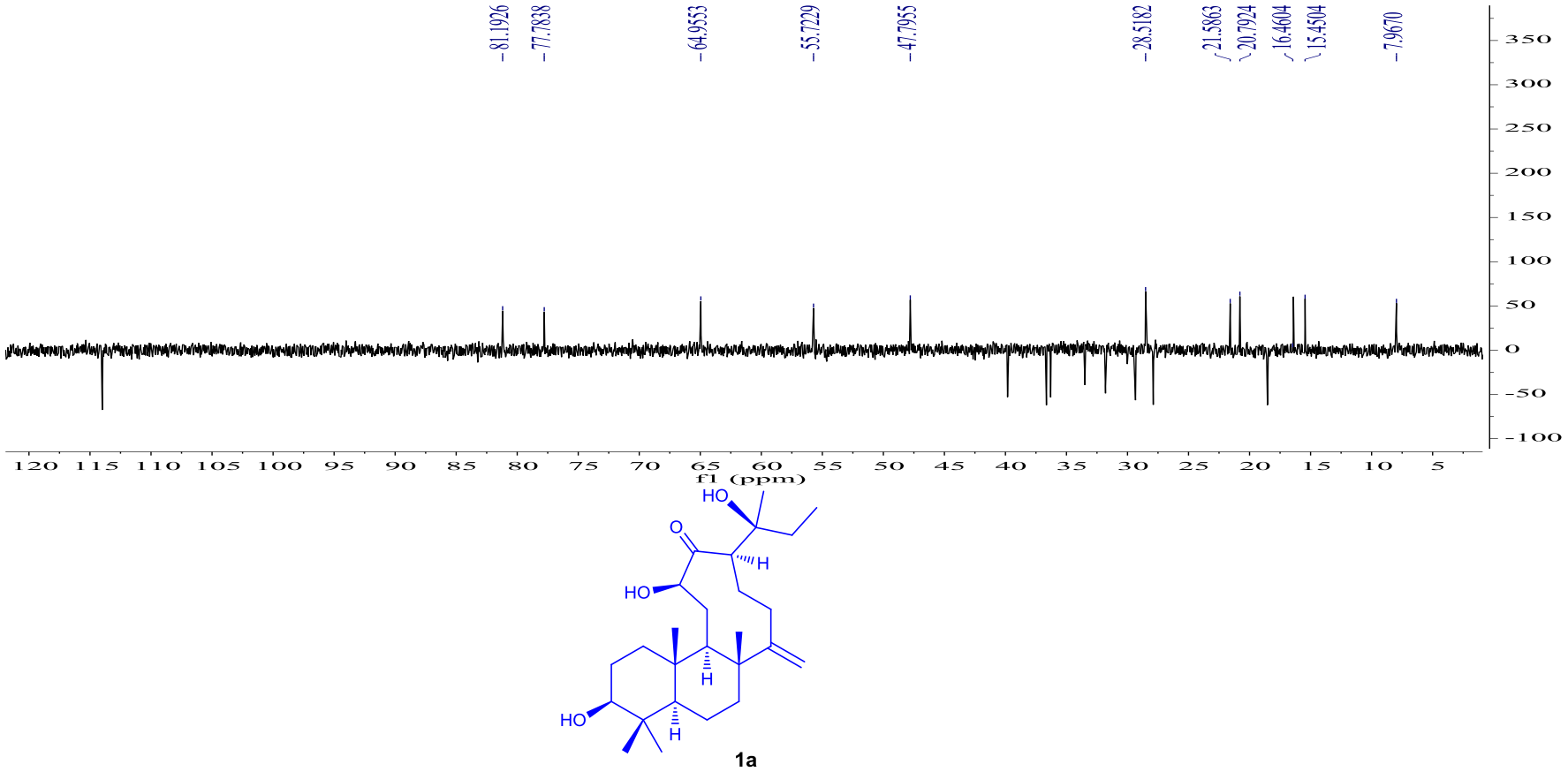


Figure S20. The DEPT spectrum of nototrone A (**1a**) in C_5D_5N (150 MHz)

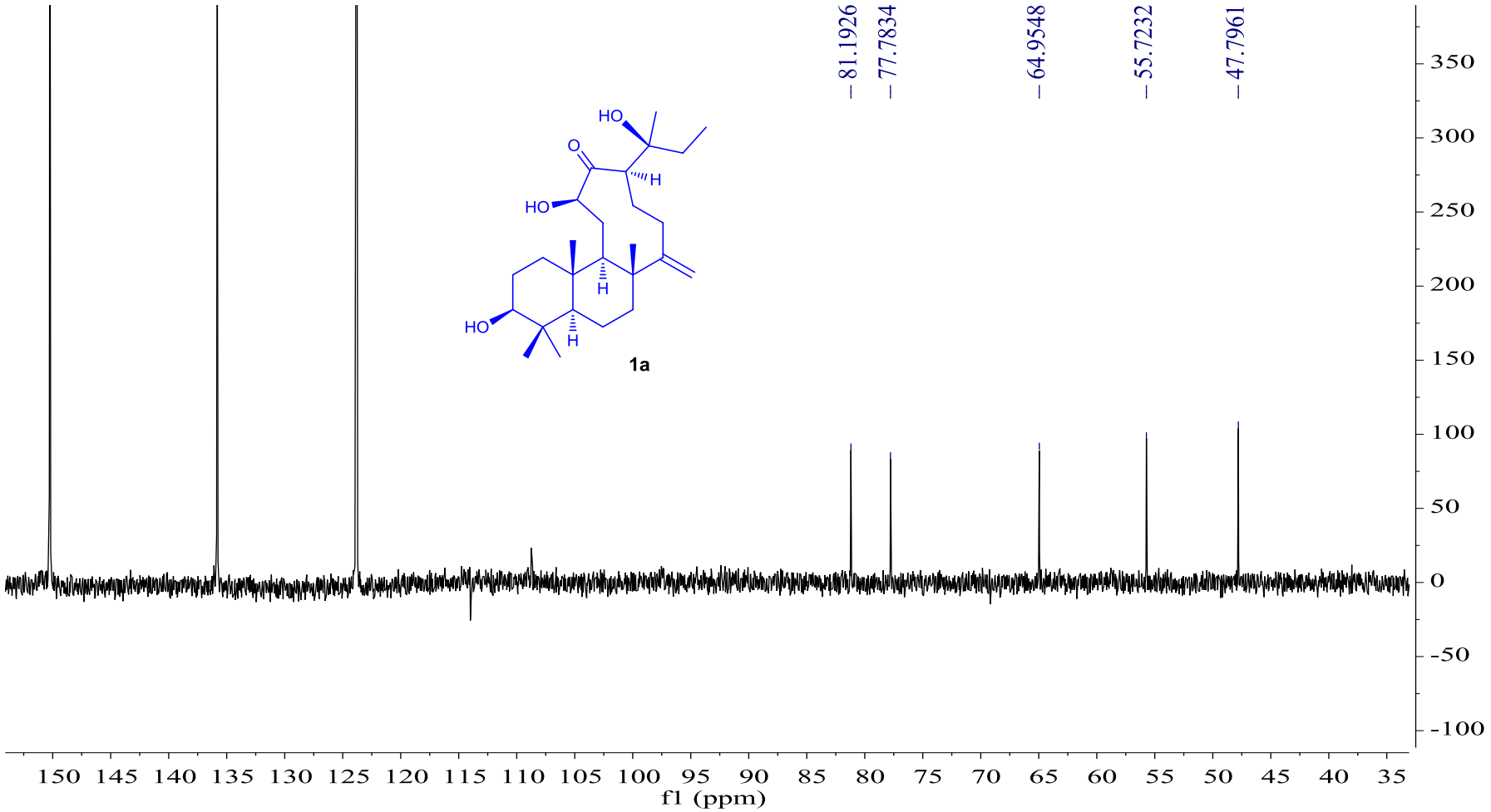


Figure S21. The DEPT90 spectrum of nototrone A (**1a**) in C_5D_5N (150 MHz)

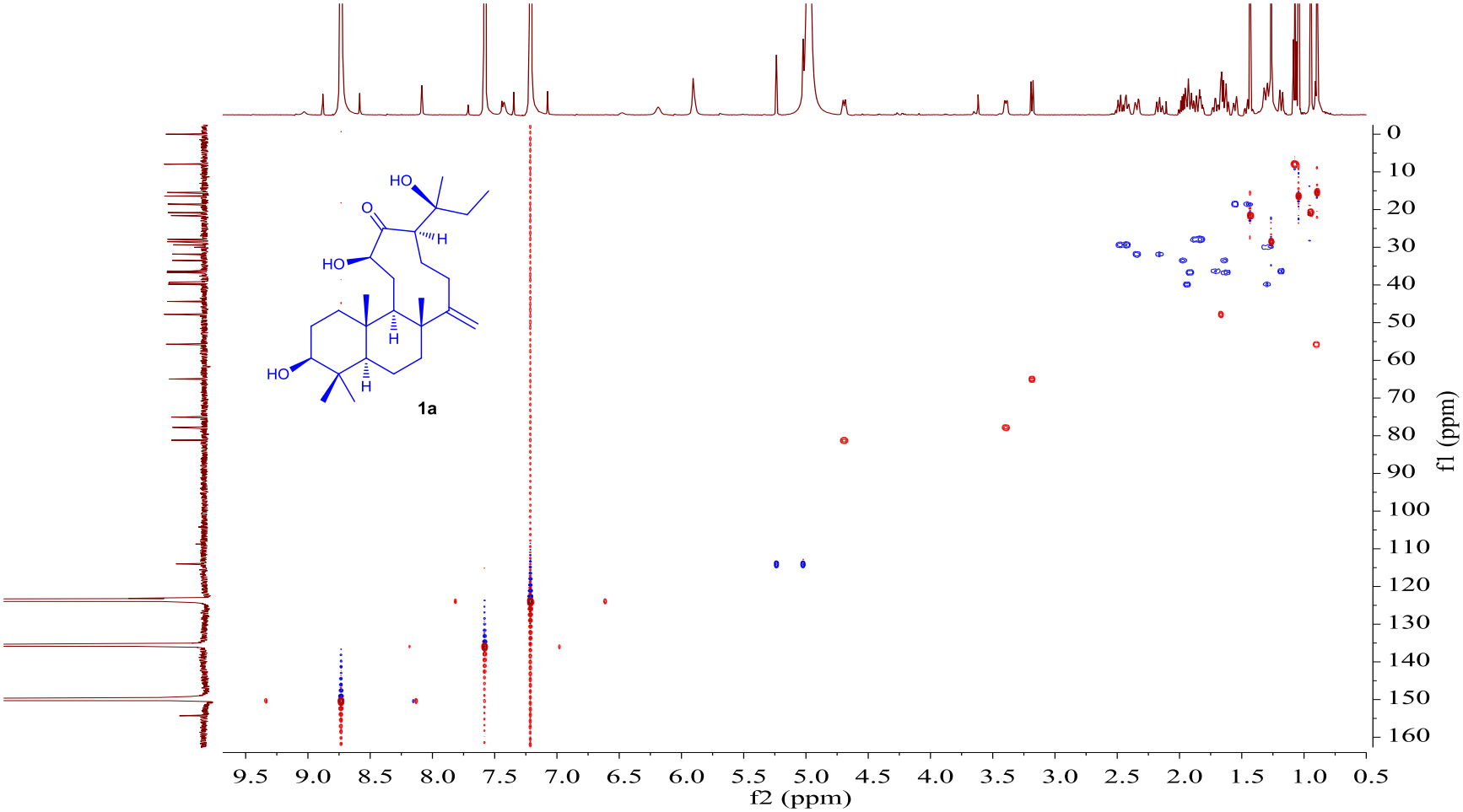


Figure S22. The HSQC spectrum of nototrone A (**1a**) in C_5D_5N (600 MHz)

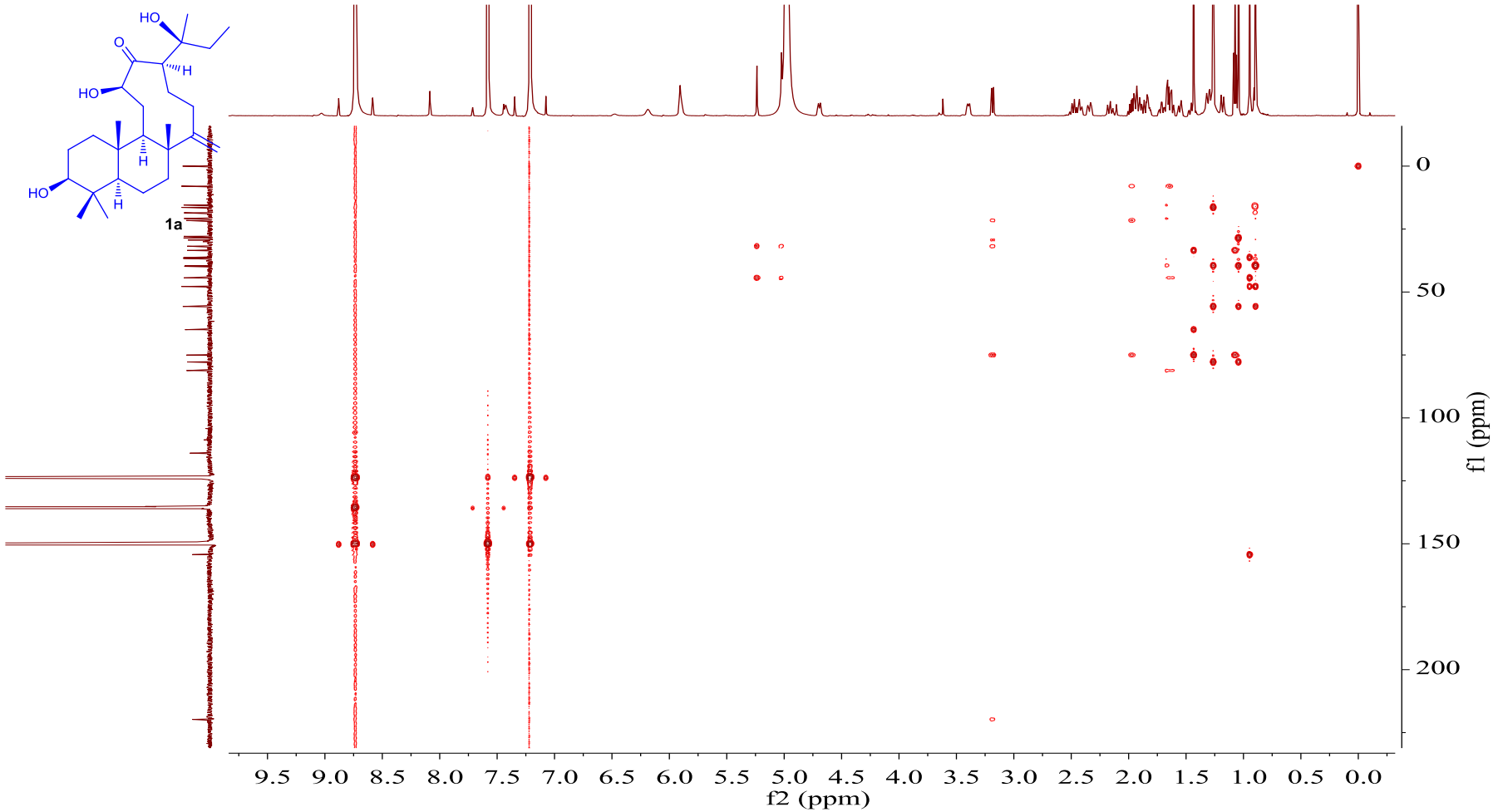


Figure S23. The HMBC spectrum of nototrone A (**1a**) in C_5D_5N (600 MHz)

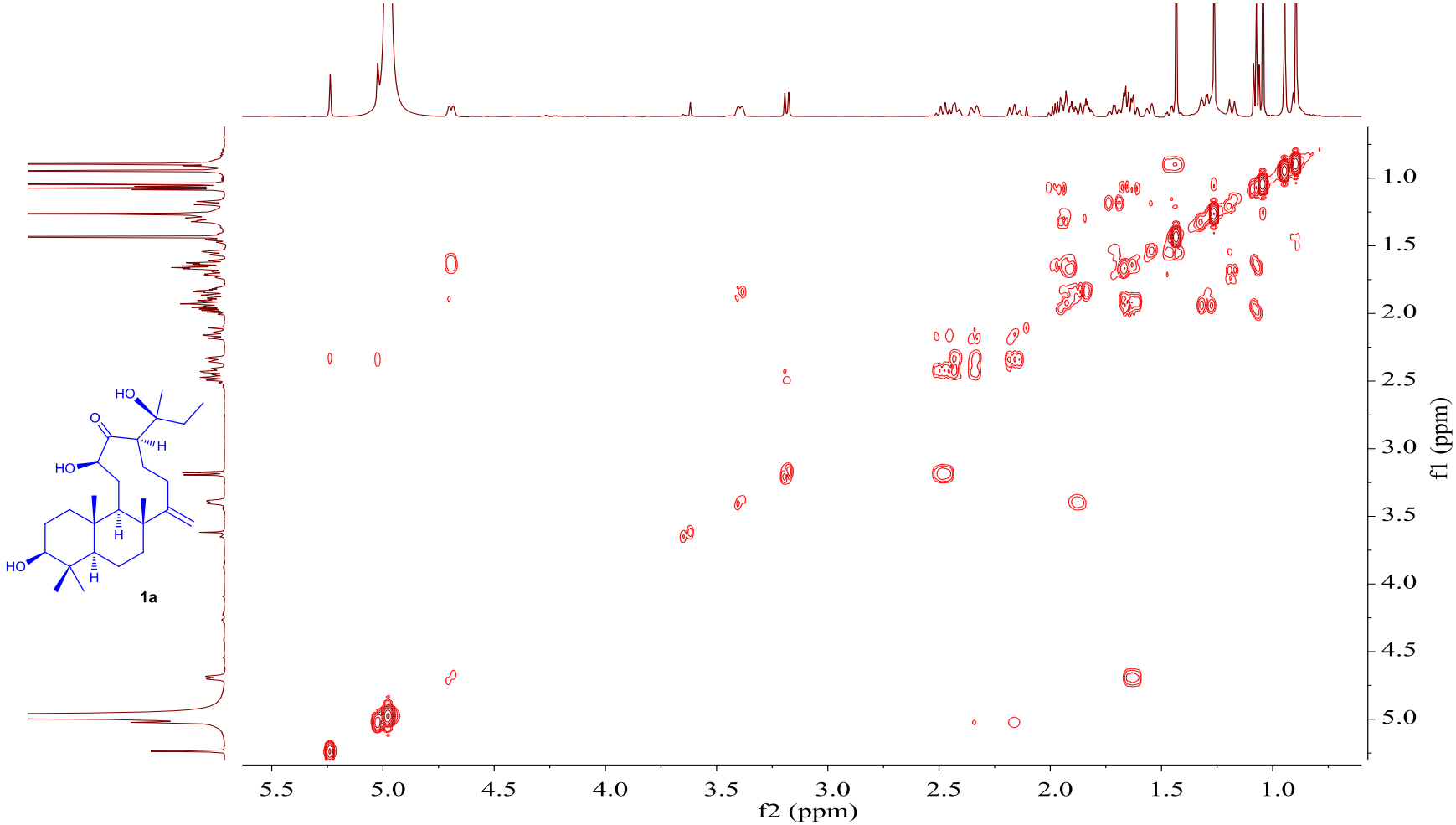


Figure S24. The ^{1}H-^{1}H COSY spectrum of nototrone A (**1a**) in C_5D_5N (600 MHz)

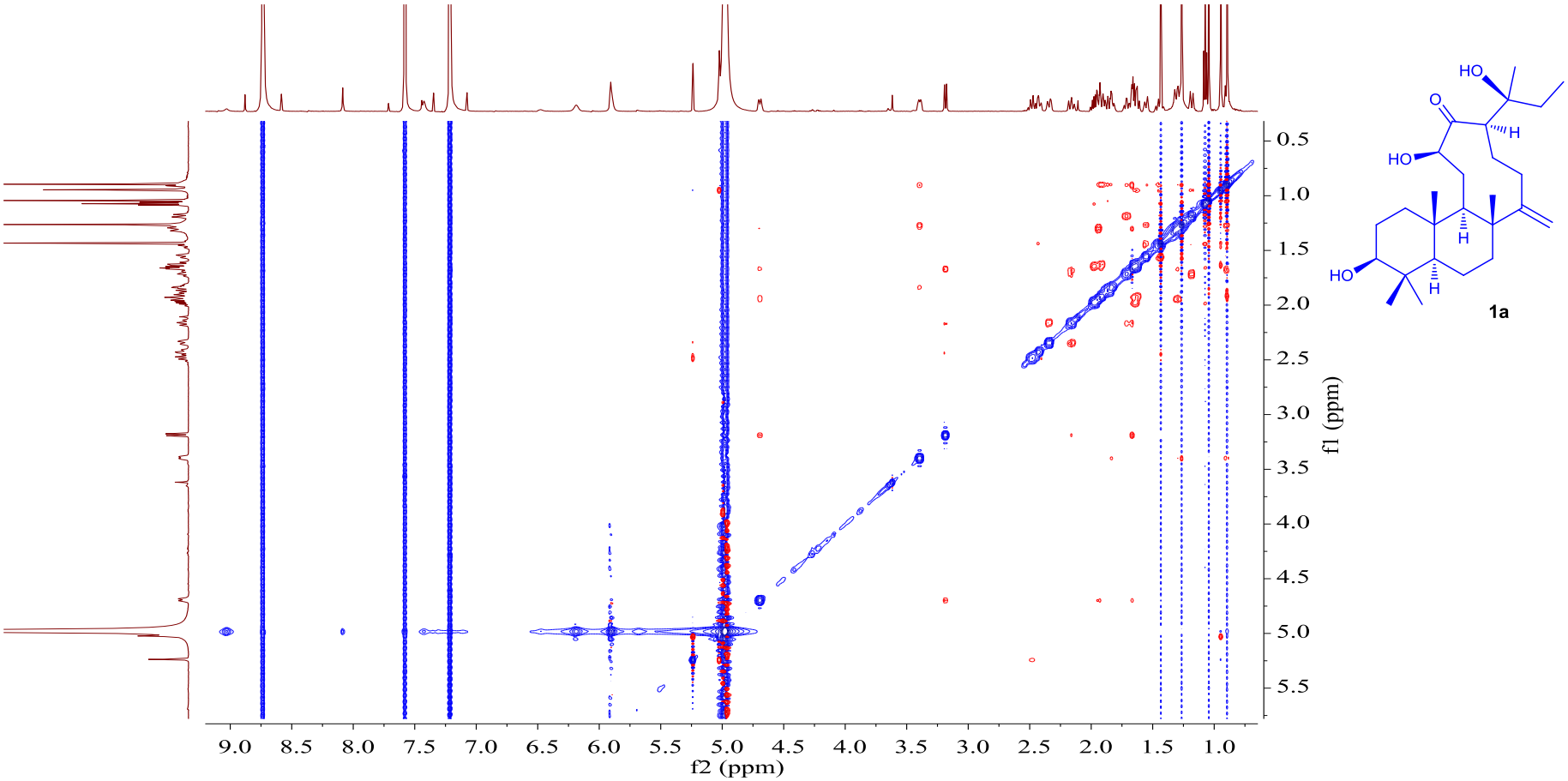


Figure S25. The NOESY spectrum of nototrone A (**1a**) in C_5D_5N (600 MHz)

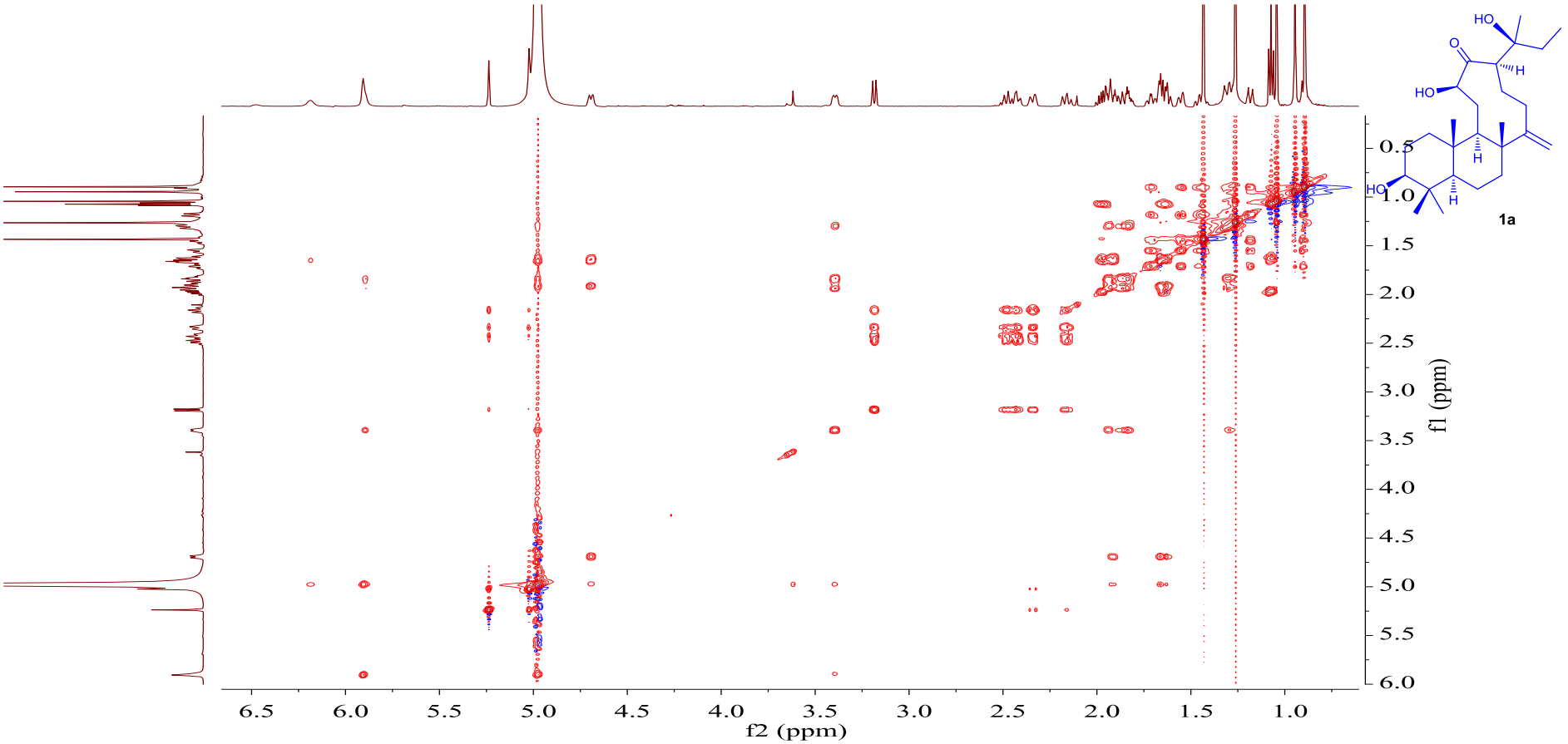


Figure S26. The TOCSY spectrum of nototrone A (1a) in C_5D_5N (600 MHz)

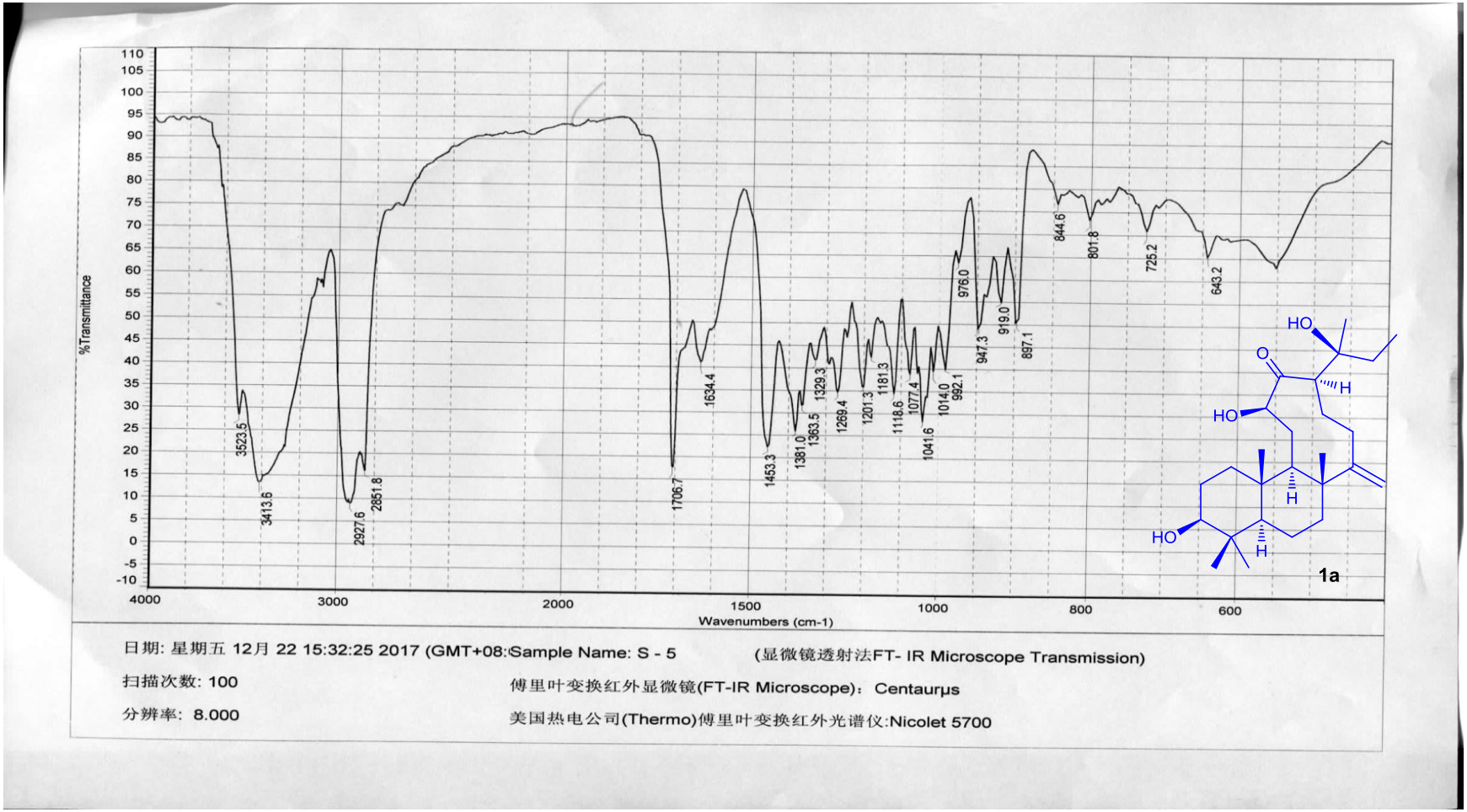


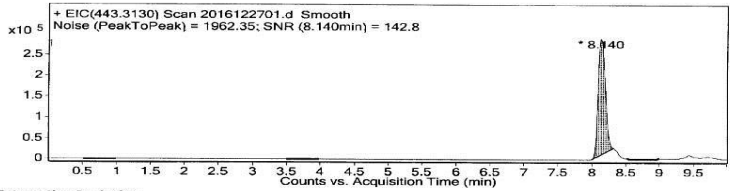
Figure S27. The IR spectrum of nototrone A (**1a**)

Qualitative Analysis Report

Data Filename	2016122701.d	**Sample Name**	S-5
Sample Type	Sample	**Position**	P1-C5
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	[redacted]
DA Method	TEST LCMS.m	**Comment**	

User Chromatograms

Fragmentor Voltage 150 **Collision Energy** 0 **Ionization Mode** ESI

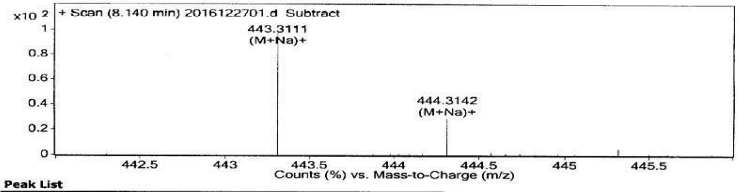


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %	Signal To Noise
1	7.995	8.14	8.317	280312	2024637	100	142.8

User Spectra

Fragmentor Voltage 150 **Collision Energy** 0 **Ionization Mode** Esi



Peak List

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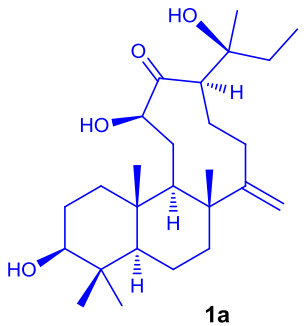
301.1399	1	163416		
302.3033	1	104328		
367.2974	1	82051		
385.3081	1	262403		
386.3114	1	73362		
403.318	1	109919		
443.3111	1	417268	C26 H44 Na O4	(M+Na)+
444.3142	1	119184	C26 H44 Na O4	(M+Na)+
505.28	1	90457		

Formula Calculator Element Limits

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



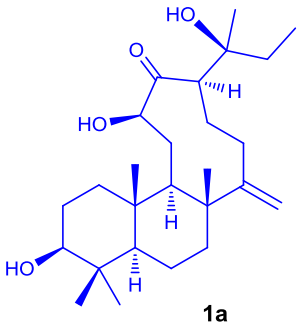
1a

MS Formula Results: + Scan (8.140 min) Sub (2016122701.d)

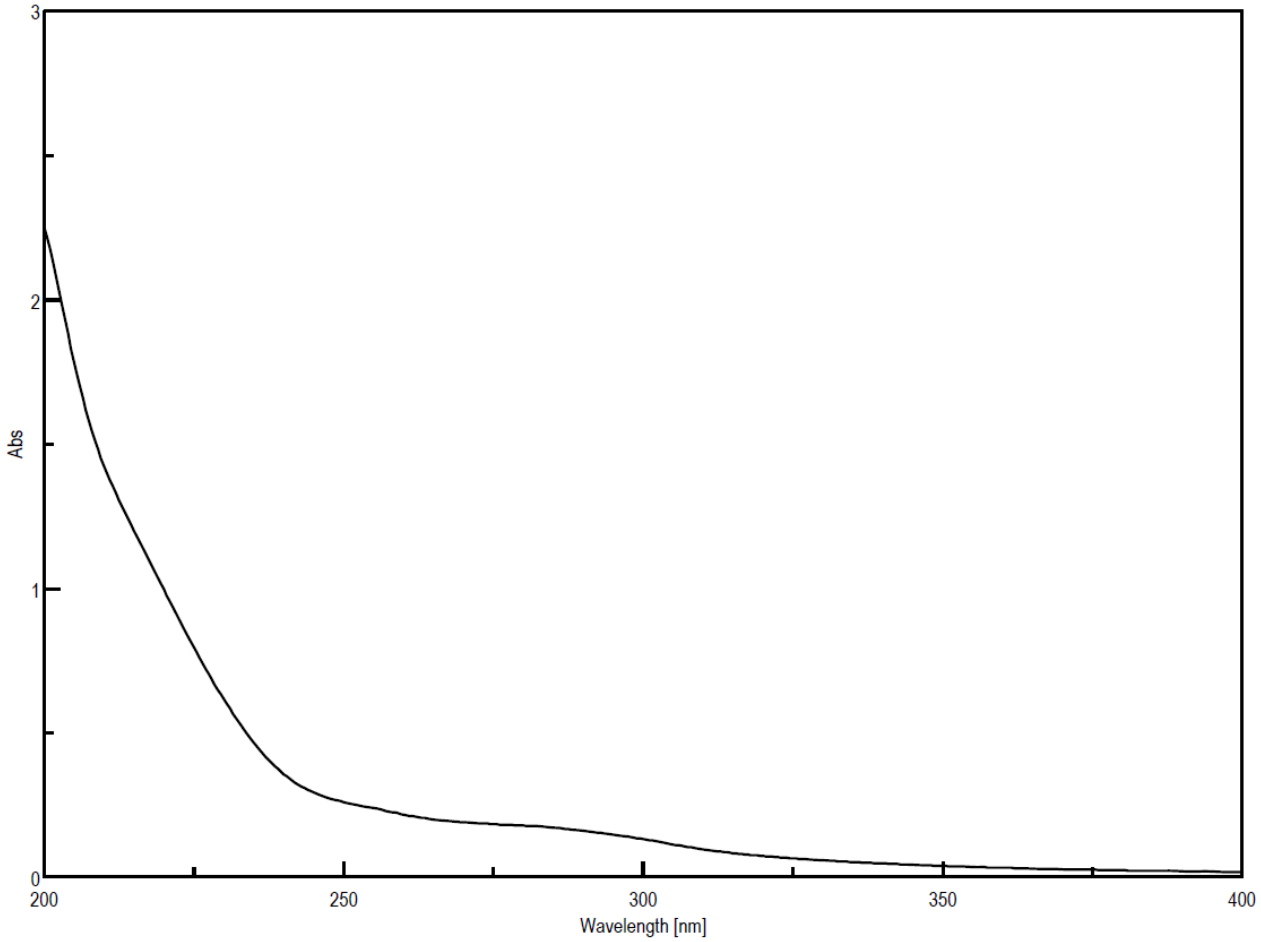
m/z	Ion	Formula	Abundance
443.3111	(M+Na)+	C26 H44 Na O4	417268.3

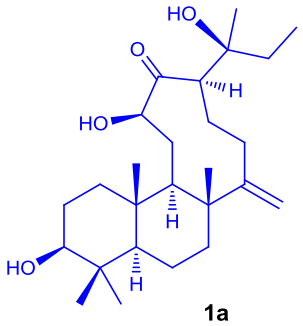
Best	Formula (M)	Ion Formula	Score	Cross Sco	Mass	Calc Mass	Calc m/z	Diff (ppm)	Abs Diff (ppm)	Mass Match	Abund Match	Spacing Match	DBE
☑	C26 H44 O4	C26 H44 Na O4	99.55		420.3219	420.324	443.3132	4.91	4.91	99.27	99.99	99.98	5
☐	C21 H44 N2 O6	C21 H44 N2 Na O6	99.22		420.3219	420.3199	443.3092	-4.67	4.67	99.34	98.37	100	1
☐	C22 H48 N2 O S2	C22 H48 N2 Na O S2	97.3		420.3219	420.3208	443.31	-2.62	2.62	99.79	91.5	99.26	0

Figure S28. The HR-ESI-MS spectrum of nototrone A (**1a**)



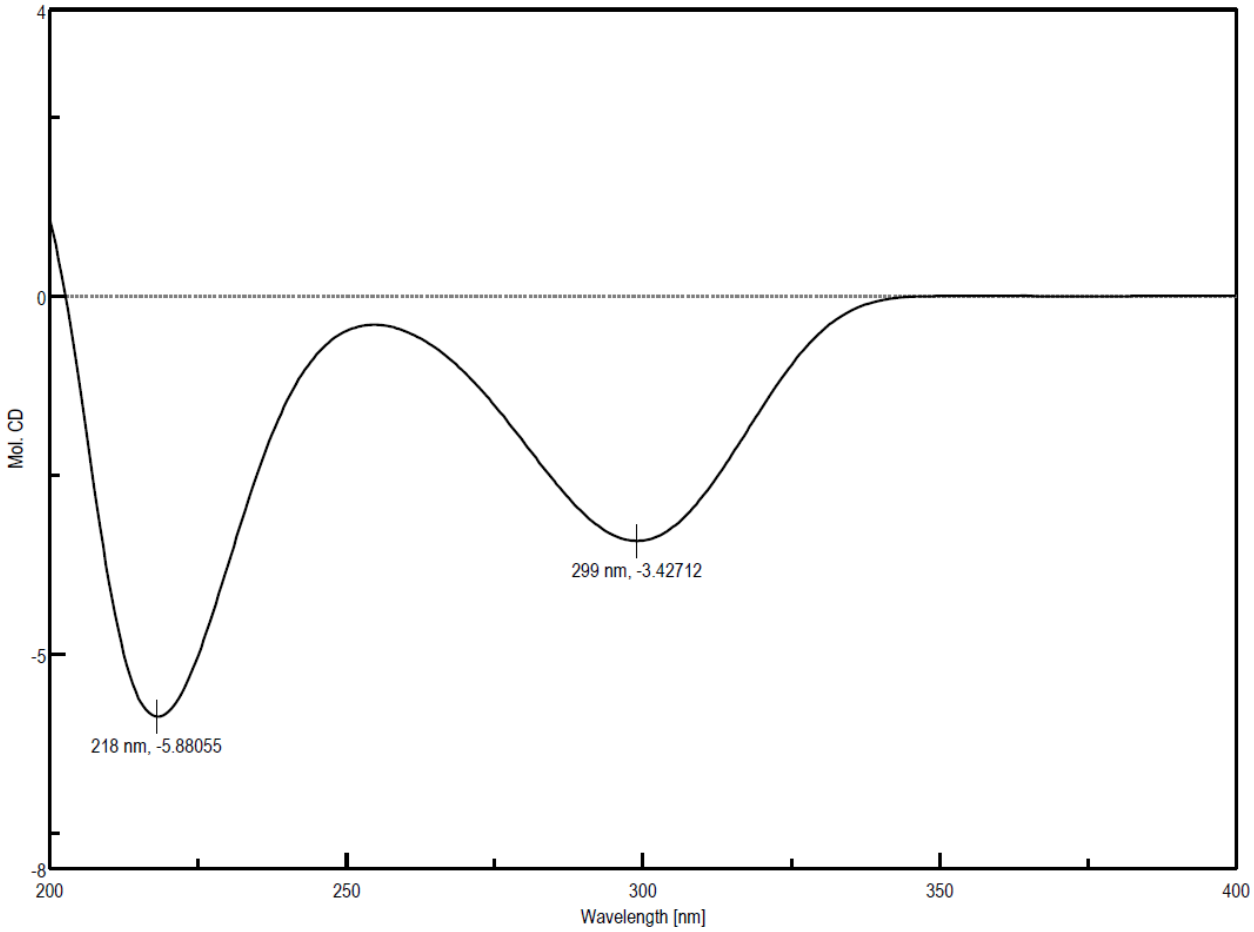
1a

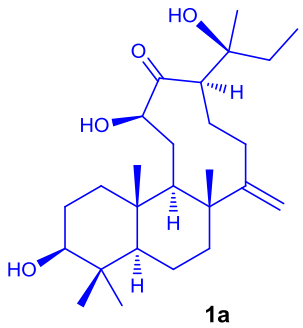




1a

Figure S29. The UV spectrum of nototrone A (**1a**)





1a

Figure S30. The CD spectrum of nototrone A (**1a**)

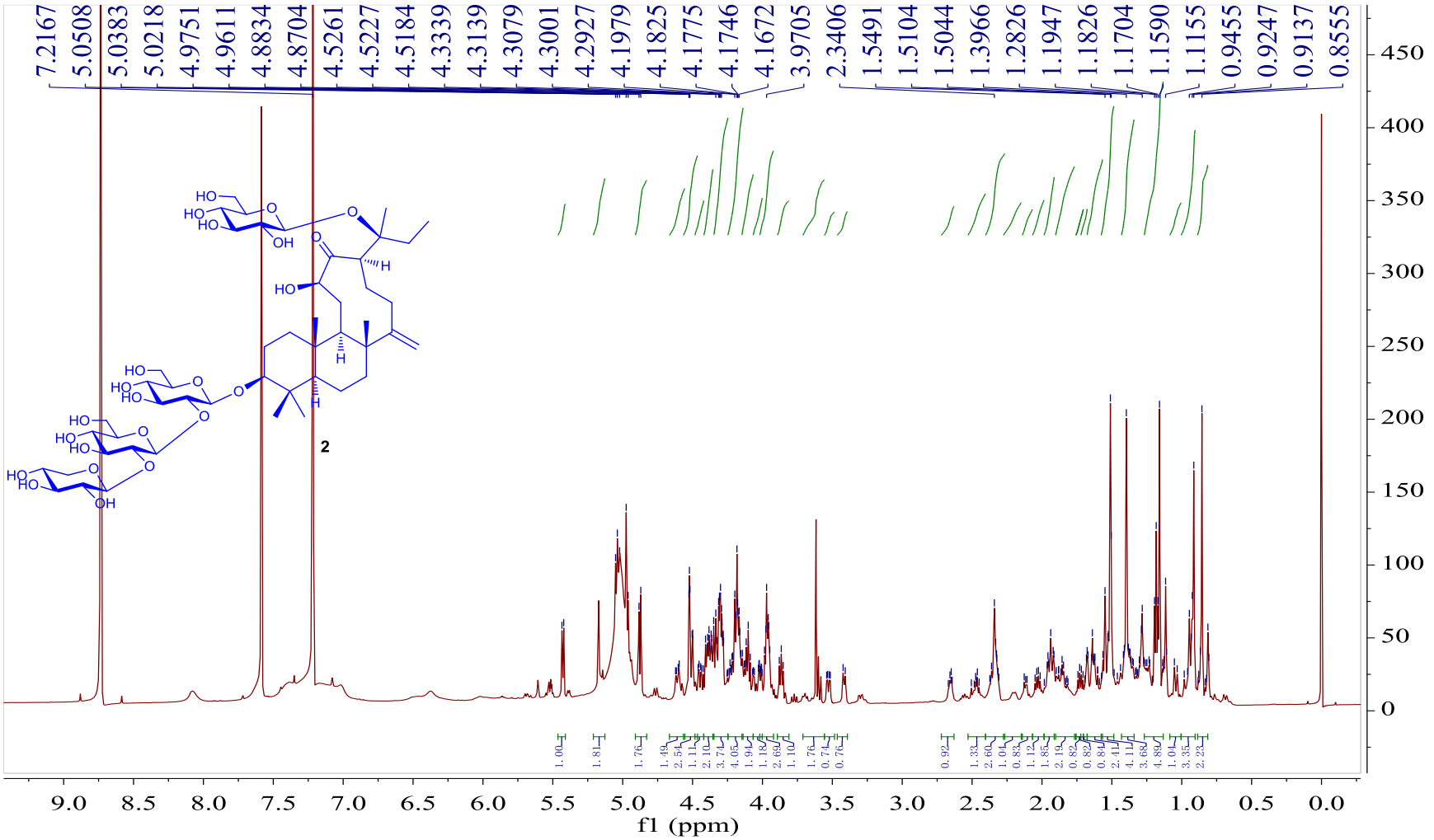


Figure S31. The ^{1}H NMR spectrum of nototroneside B (**2**) in C_5D_5N (600 MHz)

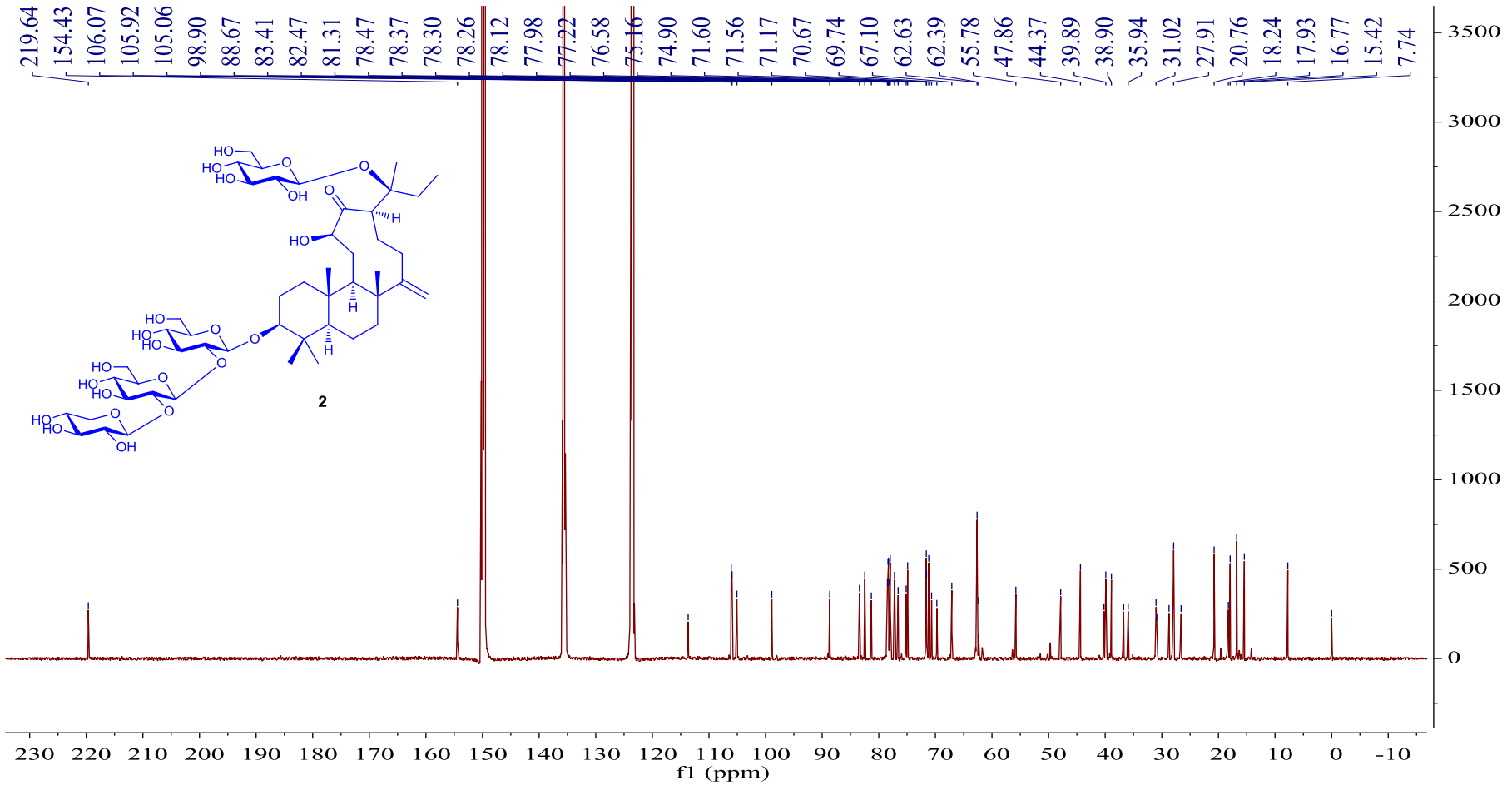


Figure S32. The ^{13}C NMR spectrum of nototroneside B (**2**) in C_5D_5N (150 MHz)

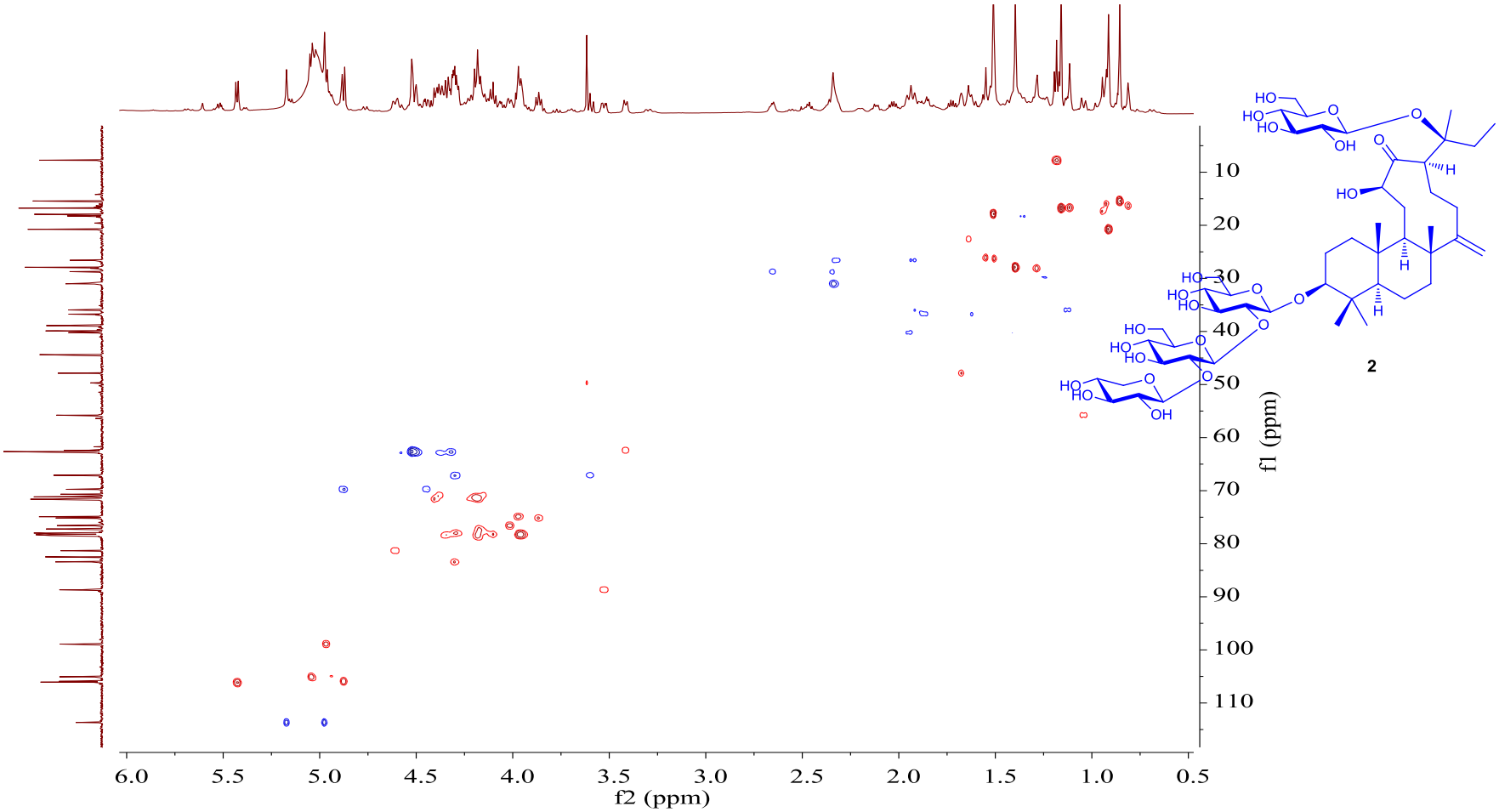


Figure S 33. The HSQC spectrum of nototroneside B (**2**) in C_5D_5N (600 MHz)

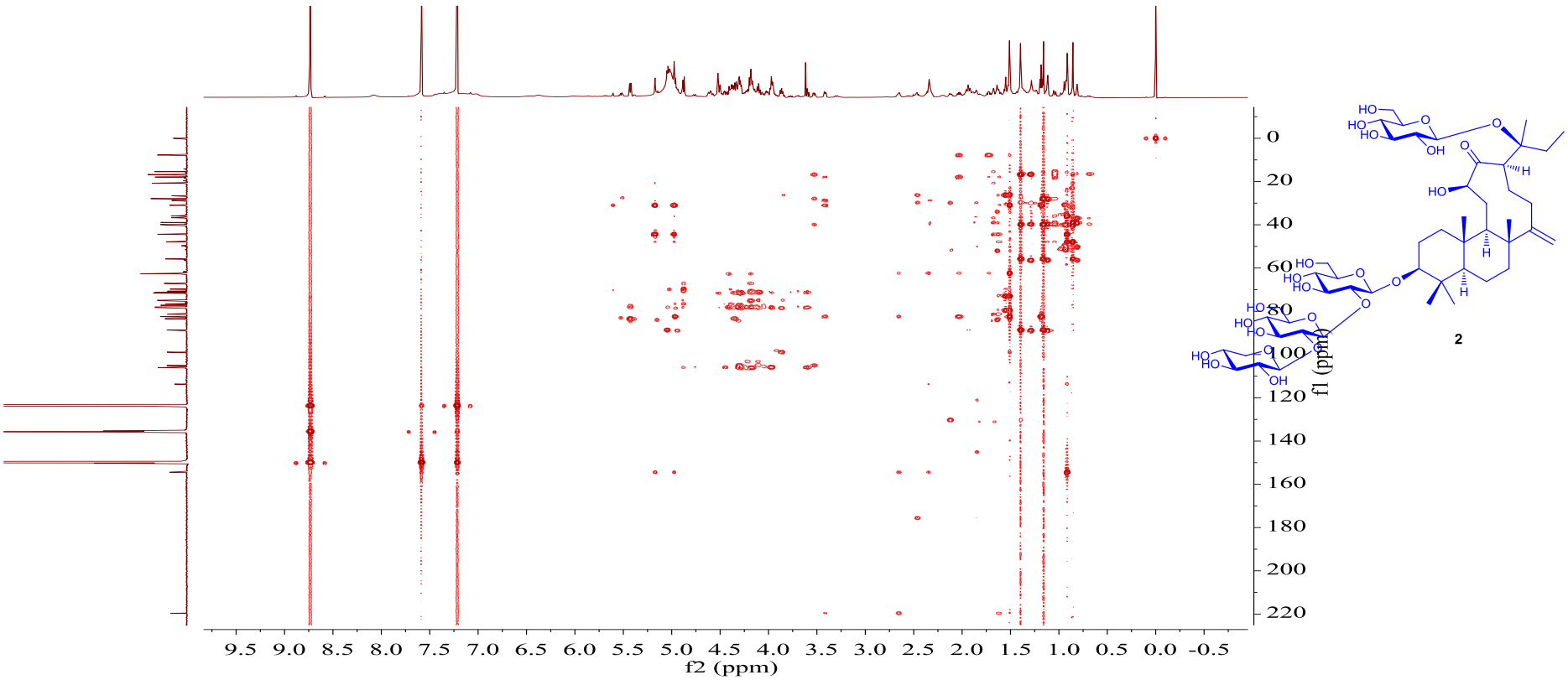


Figure S34. The HMBC spectrum of nototroneside B (**2**) in C_5D_5N (600 MHz)

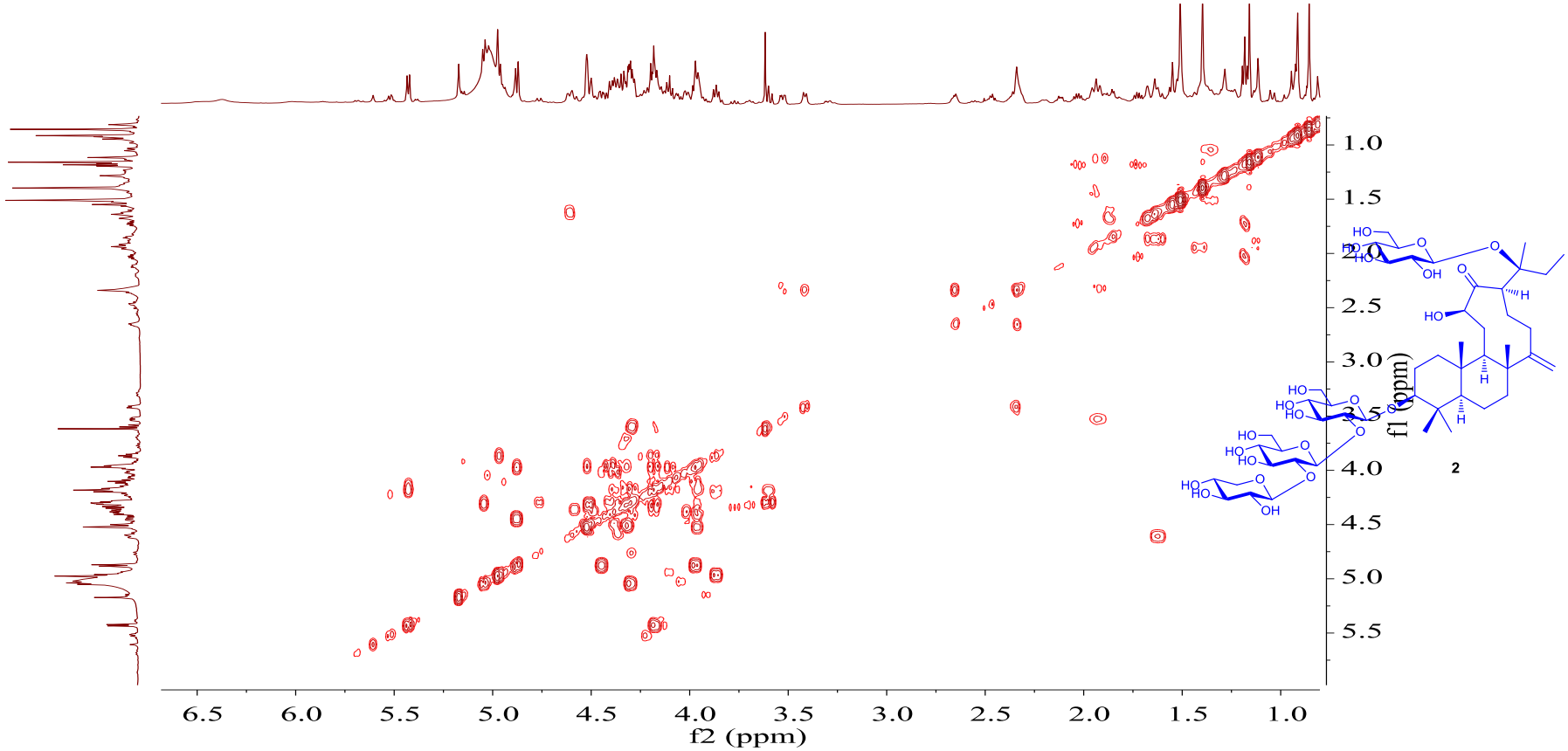


Figure S35. The ^{1}H-^{1}H COSY spectrum of nototroneside B (**2**) in C_5D_5N (600 MHz)

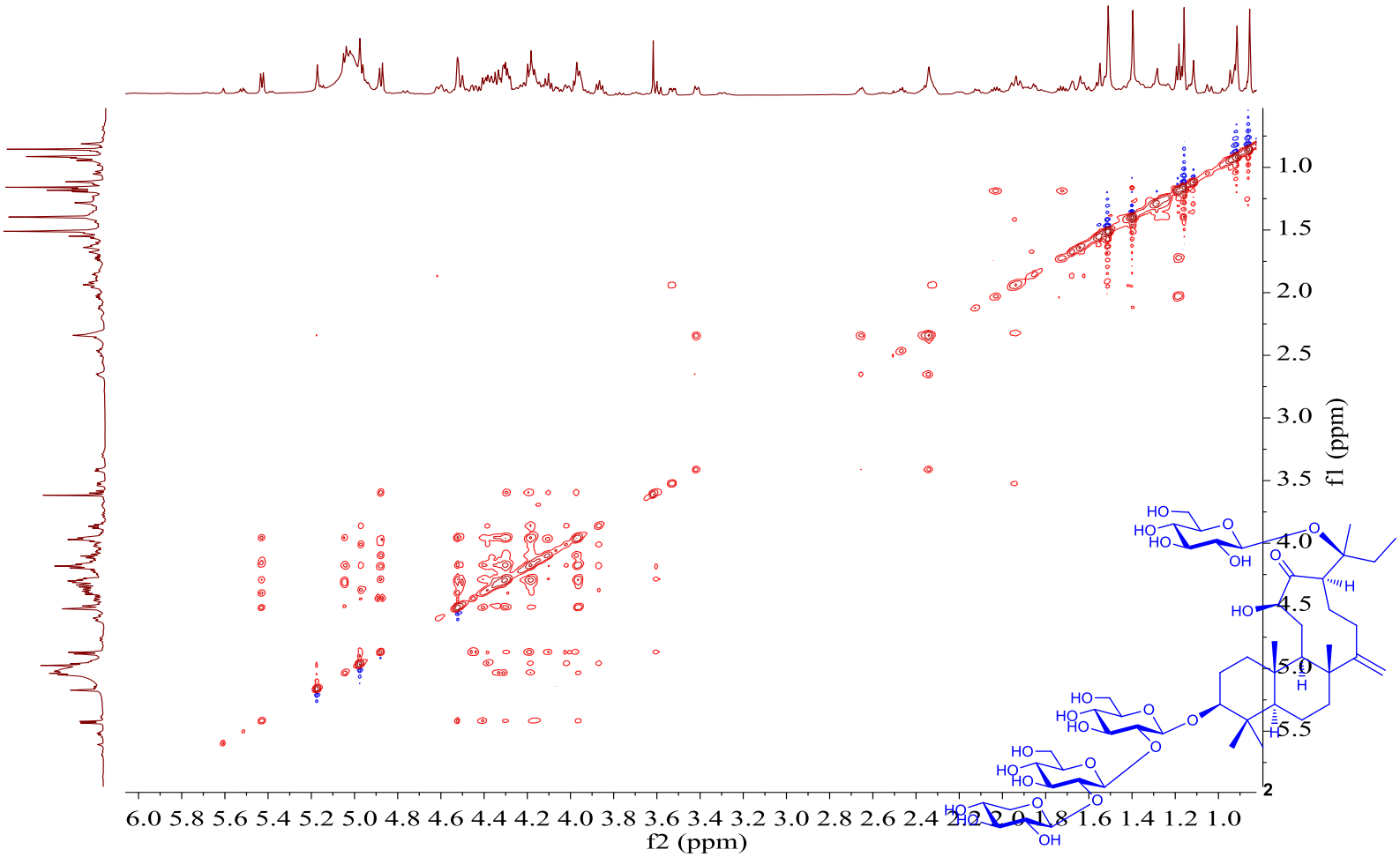
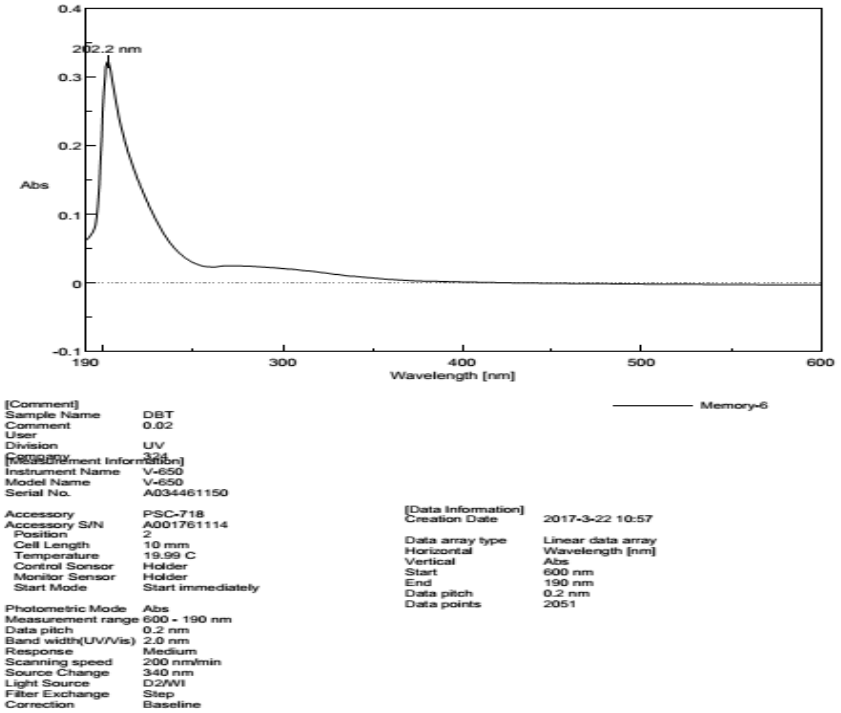


Figure S36. The TOCSY spectrum of nototroneside B (**2**) in C_5D_5N (600 MHz)



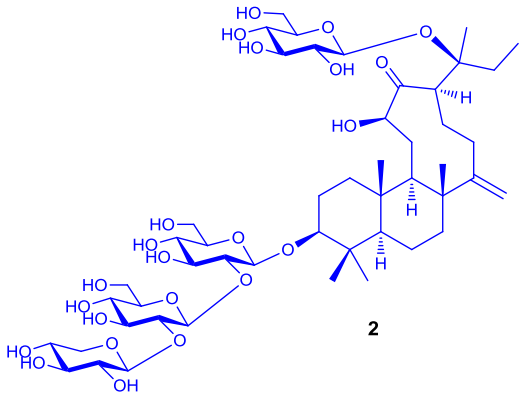


Figure S37. The UV spectrum of nototroneside B (**2**) in CH_3OH

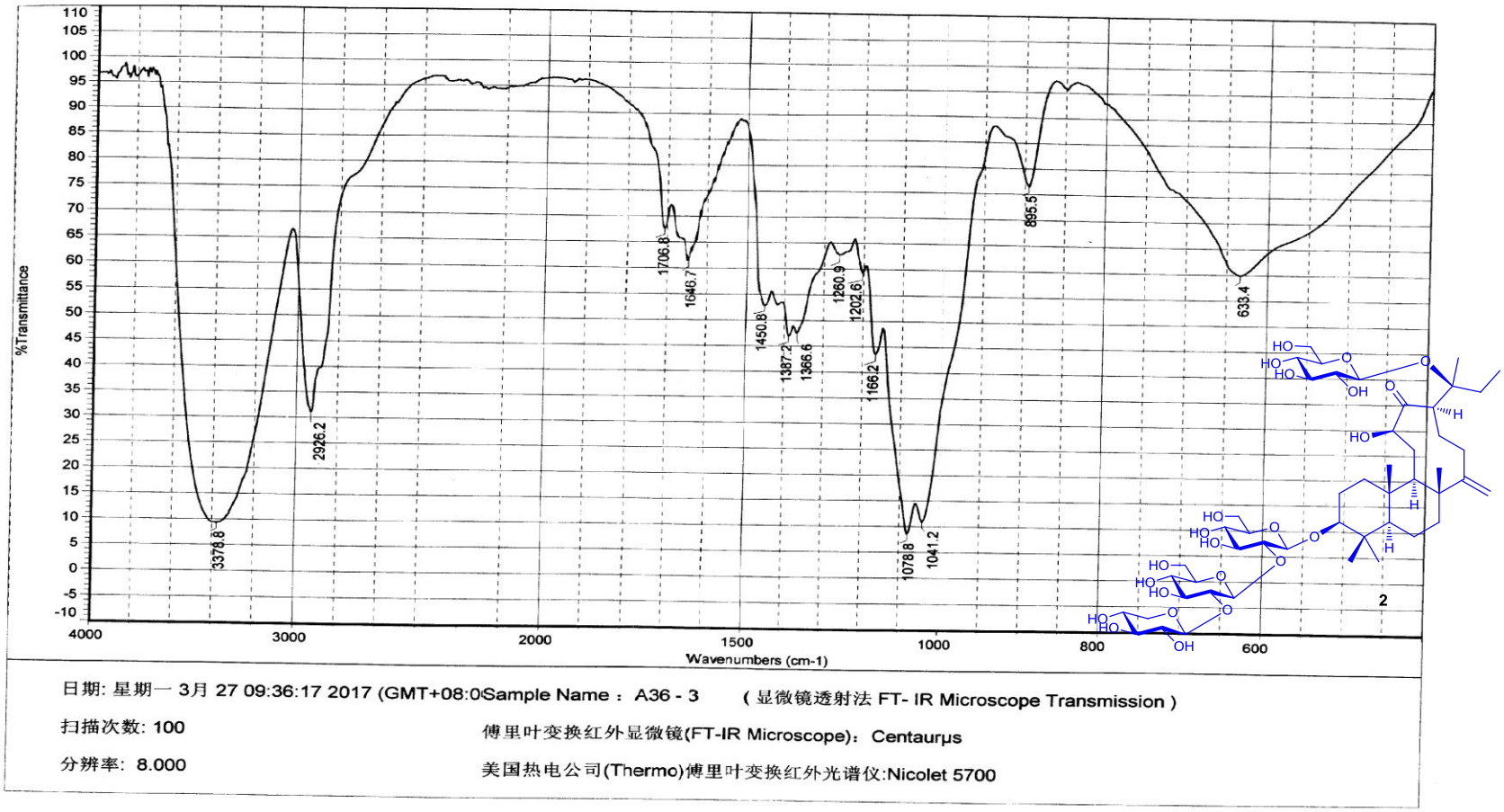


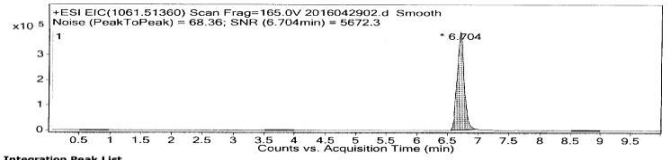
Figure S38. The IR spectrum of nototroneside B (**2**)

Qualitative Analysis Report

Data Filename	2016042902.d	**Sample Name**	SSQY-BP3-A36-3
Sample Type	Sample	**Position**	P1-C3
Instrument Name	Instrument 1	**User Name**	
Acq Method		**Acquired Time**	4/28/2016 7:22:13 PM
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

User Chromatograms

Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** ESI

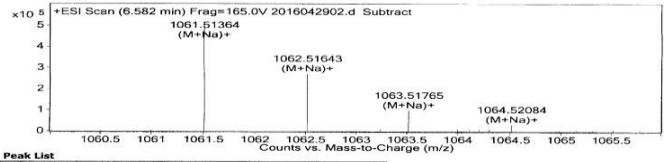


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %	Signal To Noise
1	6.543	6.704	6.978	387748	3111184	100	5672.3

User Spectra

Fragmentor Voltage 165 **Collision Energy** 0 **Ionization Mode** Esi



Peak List

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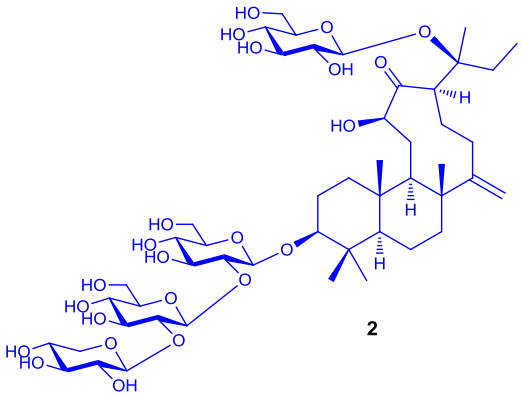
367.29971		54642		
385.30997	1	110706		
403.31957		42273		
539.24301	2	55983		
539.7481	2	34797		
1061.51364	1	498654	C49 H82 Na O23	(M+Na)+
1062.51643	1	270272	C49 H82 Na O23	(M+Na)+
1063.51765	1	96312	C49 H82 Na O23	(M+Na)+
1064.52084	1	29975	C49 H82 Na O23	(M+Na)+

--- End Of Report ---



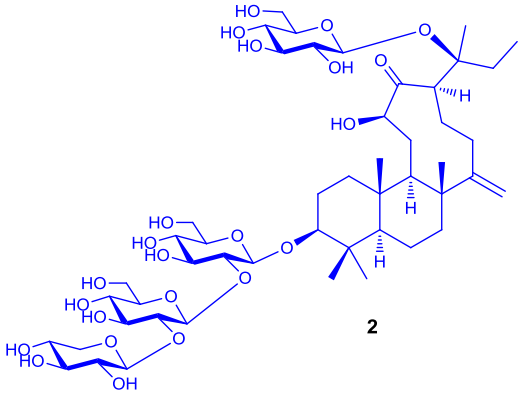
2

MS Formula Results: + Scan (6.582 min) Sub (2016042902.d)

m/z	Ion	Formula	Abundance
1061.51364	(M+Na)+	C49 H82 Na O23	498654

Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C49 H82 O23	C49 H82 Na O23	1061.51391	99.95		1038.52431	1038.52469	0.36	0.36	99.88	99.93	100	1061.51364	9
☐	C44 H82 N2 O25	C44 H82 N2 Na O25	1061.50989	99.64		1038.52433	1038.52067	-3.53	3.53	99.54	99.95	99.56	1061.51364	5
☐	C53 H82 O18 S	C53 H82 Na O18 S	1061.51141	99.42		1038.52433	1038.52219	-2.07	2.07	98.25	99.99	99.85	1061.51364	13
☐	C46 H86 O23 S	C46 H86 Na O23 S	1061.51728	99.41		1038.52434	1038.52806	3.59	3.59	98.72	99.99	99.54	1061.51364	4
☐	C41 H86 N2 O25 S	C41 H86 N2 Na O25 S	1061.51326	99.32		1038.52435	1038.52404	-0.3	0.3	97.64	99.99	100	1061.51364	0
☐	C48 H82 N2 O20 S	C48 H82 N2 Na O20 S	1061.50738	99.11		1038.52435	1038.51816	-5.95	5.95	98.98	99.99	98.75	1061.51364	9
☐	C56 H78 O18	C56 H78 Na O18	1061.50804	99.01		1038.52432	1038.51882	-5.3	5.3	98.26	99.92	99.01	1061.51364	18
☐	C55 H78 N2 O17	C55 H78 N2 Na O17	1061.51927	99		1038.52433	1038.53005	5.51	5.51	98.35	99.93	98.93	1061.51364	18
☐	C59 H78 N2 O12 S	C59 H78 N2 Na O12 S	1061.51677	98.67		1038.52434	1038.52755	3.08	3.08	95.92	99.99	99.66	1061.51364	22
☐	C50 H86 O18 S2	C50 H86 Na O18 S2	1061.51478	98.64		1038.52435	1038.52556	1.16	1.16	95.35	99.08	99.05	1061.51364	8
☐	C62 H74 N2 O12	C62 H74 N2 Na O12	1061.5134	98.56		1038.52433	1038.52418	-0.14	0.14	95.01	99.92	100	1061.51364	27
☐	C45 H86 N2 O20 S2	C45 H86 N2 Na O20 S2	1061.51076	98.55		1038.52437	1038.52153	-2.73	2.73	95.39	99.97	99.74	1061.51364	4
☐	C57 H82 O13 S2	C57 H82 Na O13 S2	1061.50891	97.89		1038.52435	1038.51988	-4.49	4.49	93.81	99.99	99.29	1061.51364	17
☐	C66 H74 N2 O7 S	C66 H74 N2 Na O7 S	1061.51089	97.61		1038.52434	1038.52167	-2.57	2.57	92.03	99.98	99.77	1061.51364	31
☐	C67 H74 O10	C67 H74 Na O10	1061.51742	97.57		1038.52432	1038.5282	3.74	3.74	92.41	99.91	99.5	1061.51364	31
☐	C63 H78 N2 O7 S2	C63 H78 N2 Na O7 S2	1061.51427	97.44		1038.52436	1038.52504	0.66	0.66	91.07	99.99	99.98	1061.51364	26
☐	C54 H86 O13 S3	C54 H86 Na O13 S3	1061.51228	97.05		1038.52436	1038.52306	-1.26	1.26	89.81	99.96	99.94	1061.51364	12
☐	C49 H86 N2 O15 S3	C49 H86 N2 Na O15 S3	1061.50825	96.85		1038.52438	1038.51903	-5.15	5.15	90.6	99.94	99.06	1061.51364	8
☐	C71 H74 O5 S	C71 H74 Na O5 S	1061.51492	96.85		1038.52433	1038.5257	1.31	1.31	89.11	99.97	99.94	1061.51364	35
☐	C47 H90 O18 S3	C47 H90 Na O18 S3	1061.51815	96.84		1038.52437	1038.52893	4.39	4.39	90.14	99.93	99.32	1061.51364	3
☐	C69 H70 N2 O7	C69 H70 N2 Na O7	1061.50752	96.73		1038.52433	1038.5183	-5.8	5.8	90.62	99.92	98.81	1061.51364	36
☐	C74 H70 O5	C74 H70 Na O5	1061.51155	96.38		1038.52432	1038.52233	-1.92	1.92	87.64	99.9	99.87	1061.51364	40
☐	C68 H78 O5 S2	C68 H78 Na O5 S2	1061.51829	96.34		1038.52434	1038.52907	4.55	4.55	88.41	99.99	99.27	1061.51364	30
☐	C60 H82 N2 O7 S3	C60 H82 N2 Na O7 S3	1061.51764	96.33		1038.52437	1038.52842	3.9	3.9	88.09	99.97	99.46	1061.51364	21
☐	C70 H74 N2 O2 S2	C70 H74 N2 Na O2 S2	1061.50839	95.85		1038.52435	1038.51917	-4.99	4.99	86.96	99.99	99.12	1061.51364	35
☐	C67 H78 N2 O2 S3	C67 H78 N2 Na O2 S3	1061.51176	95.58		1038.52436	1038.52254	-1.75	1.75	84.73	99.98	99.89	1061.51364	30
☐	C75 H74 S2	C75 H74 Na S2	1061.51241	95.39		1038.52434	1038.52319	-1.11	1.11	83.95	99.99	99.96	1061.51364	39
☐	C78 H70 S	C78 H70 Na S	1061.50904	95.17		1038.52433	1038.51982	-4.34	4.34	84.23	99.97	99.33	1061.51364	44
☐	C72 H78 S3	C72 H78 Na S3	1061.51579	94.78		1038.52435	1038.52856	2.13	2.13	82	99.99	99.84	1061.51364	34

Figure S39. The HR-ESI-MS spectrum of nototroneside B (**2**)



2

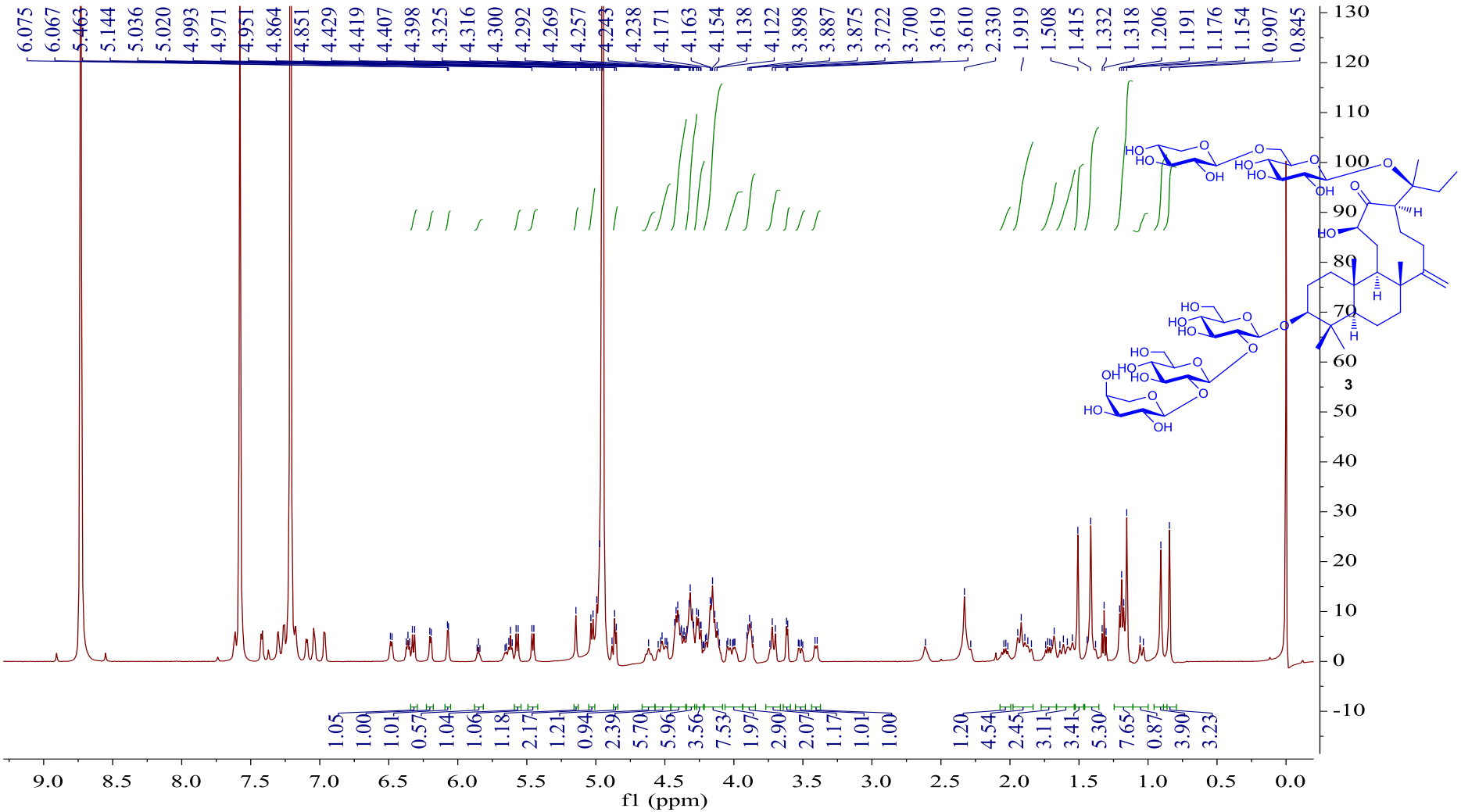


Figure S40. The ^{1}H NMR spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

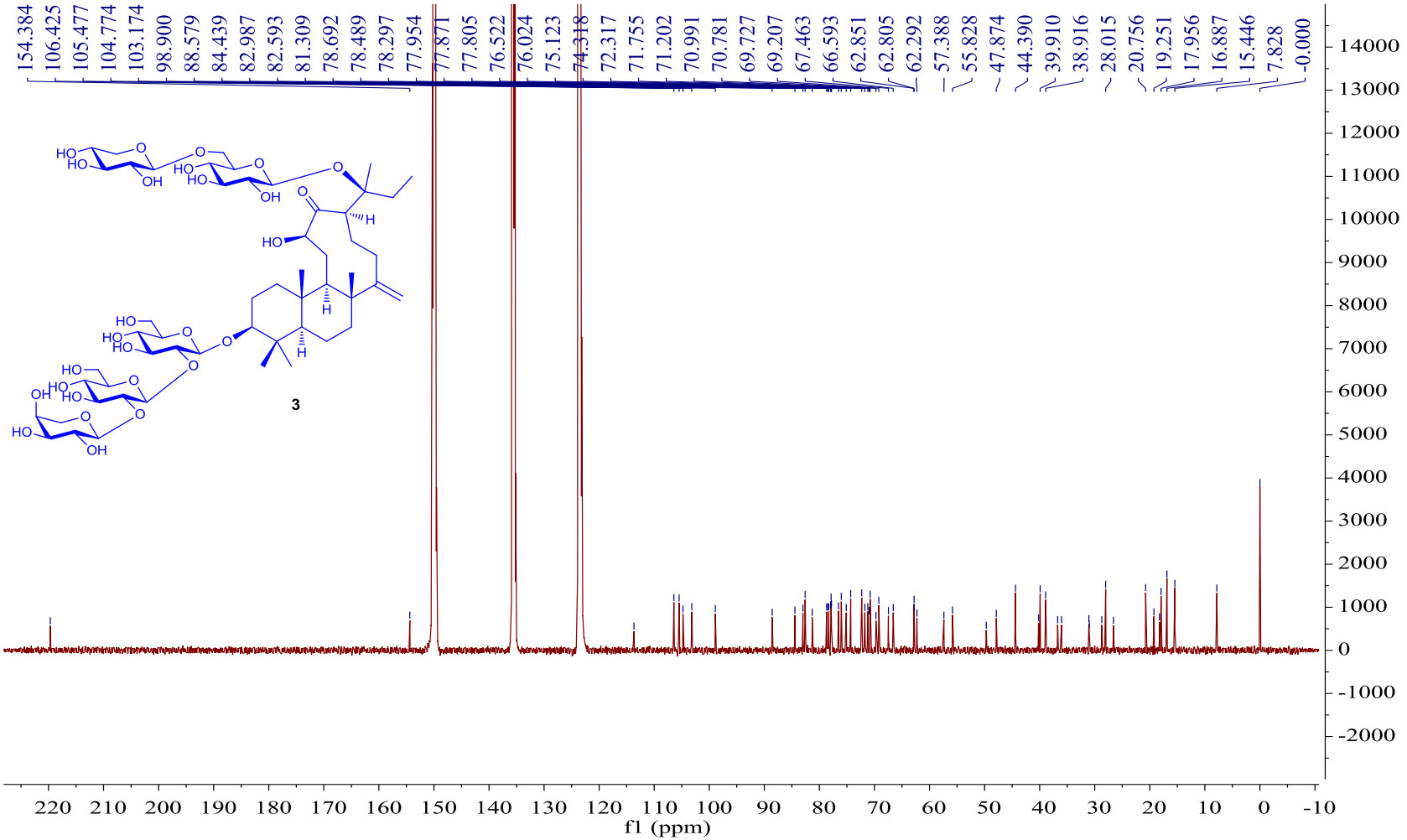


Figure S41. The ^{13}C NMR spectrum of nototroneside C (**3**) in C_5D_5N (150 MHz)

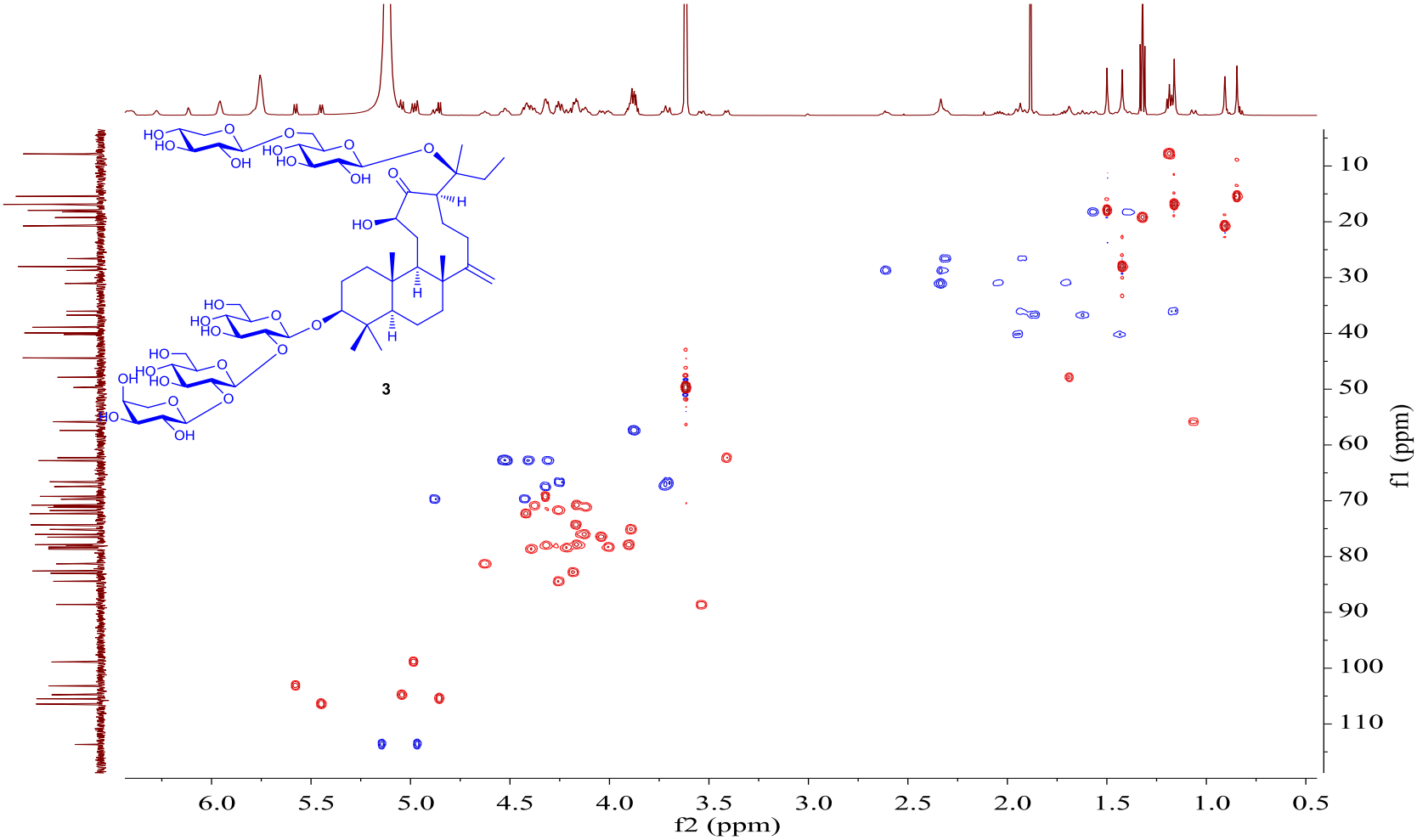


Figure S42. The HSQC spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

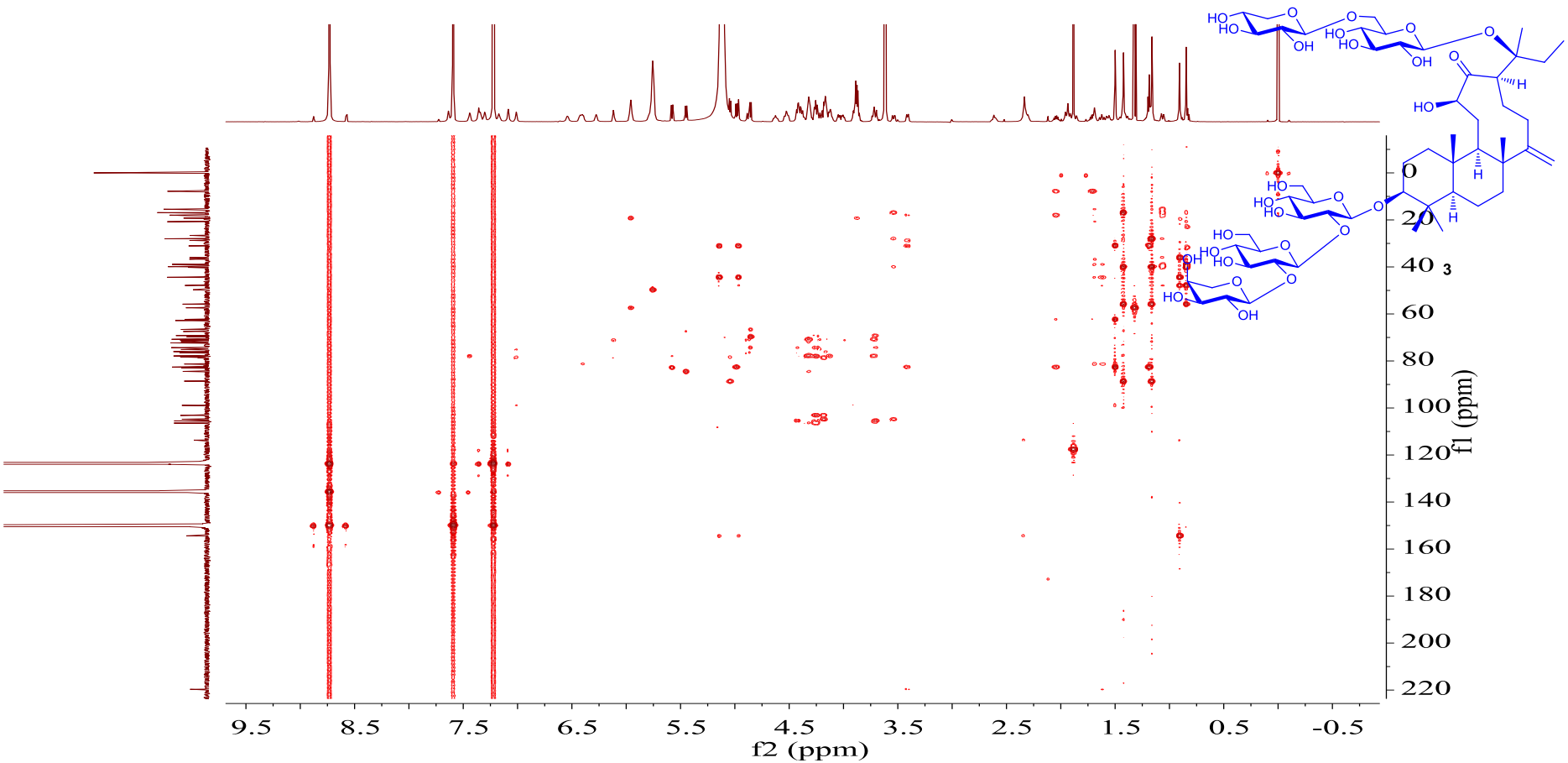


Figure S43. The HMBC spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

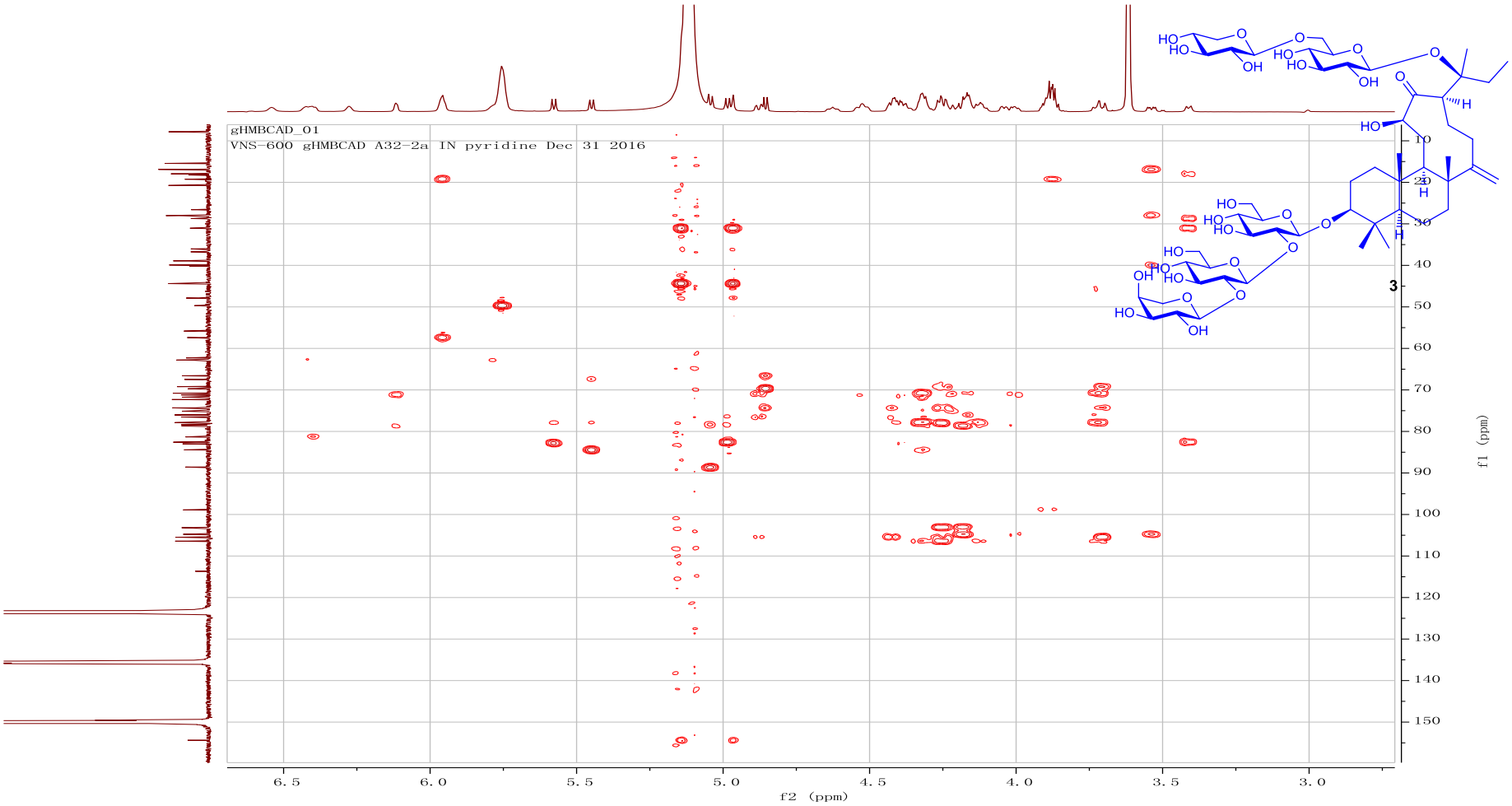


Figure S44. The HMBC spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

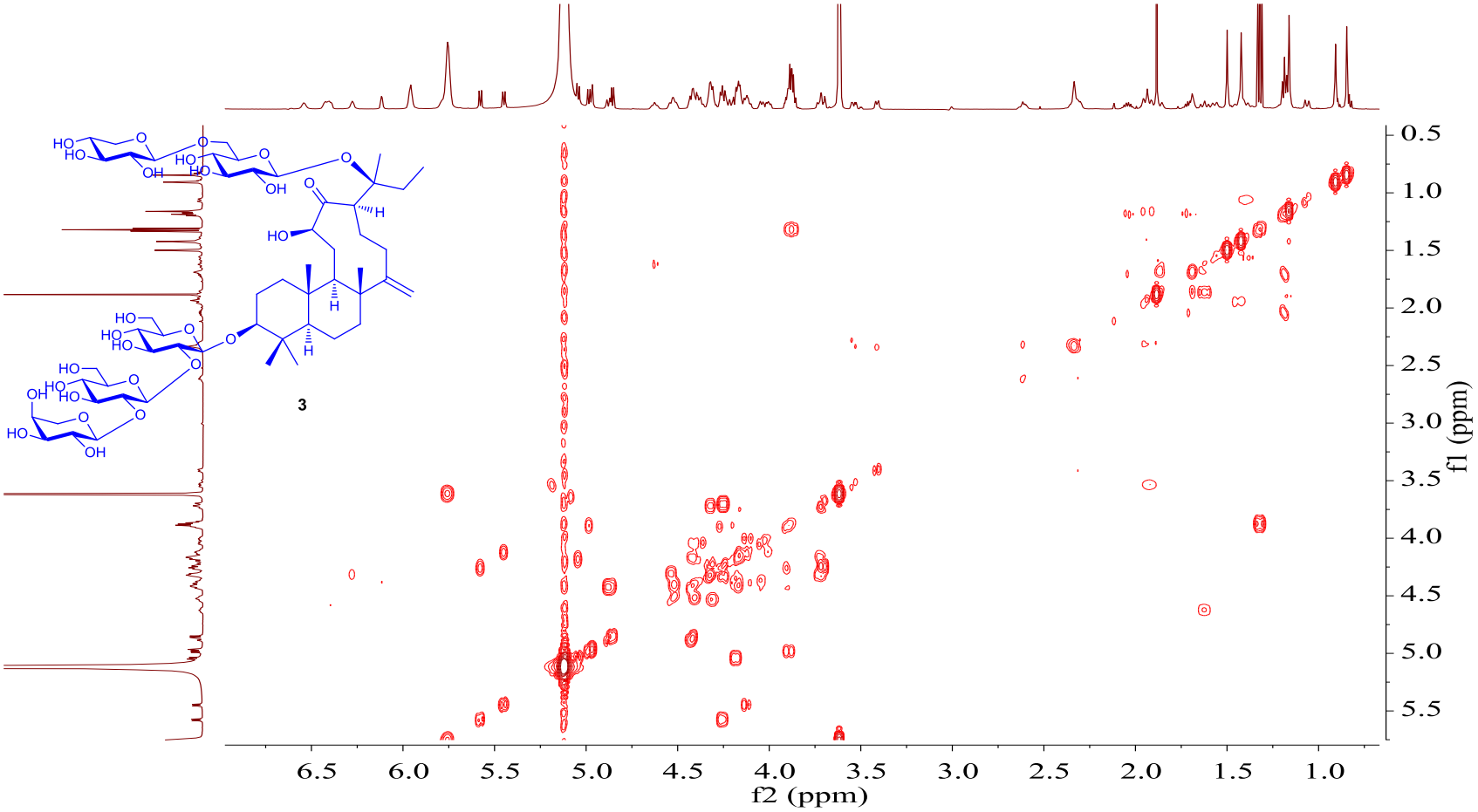


Figure S45. The ^{1}H-^{1}H COSY spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

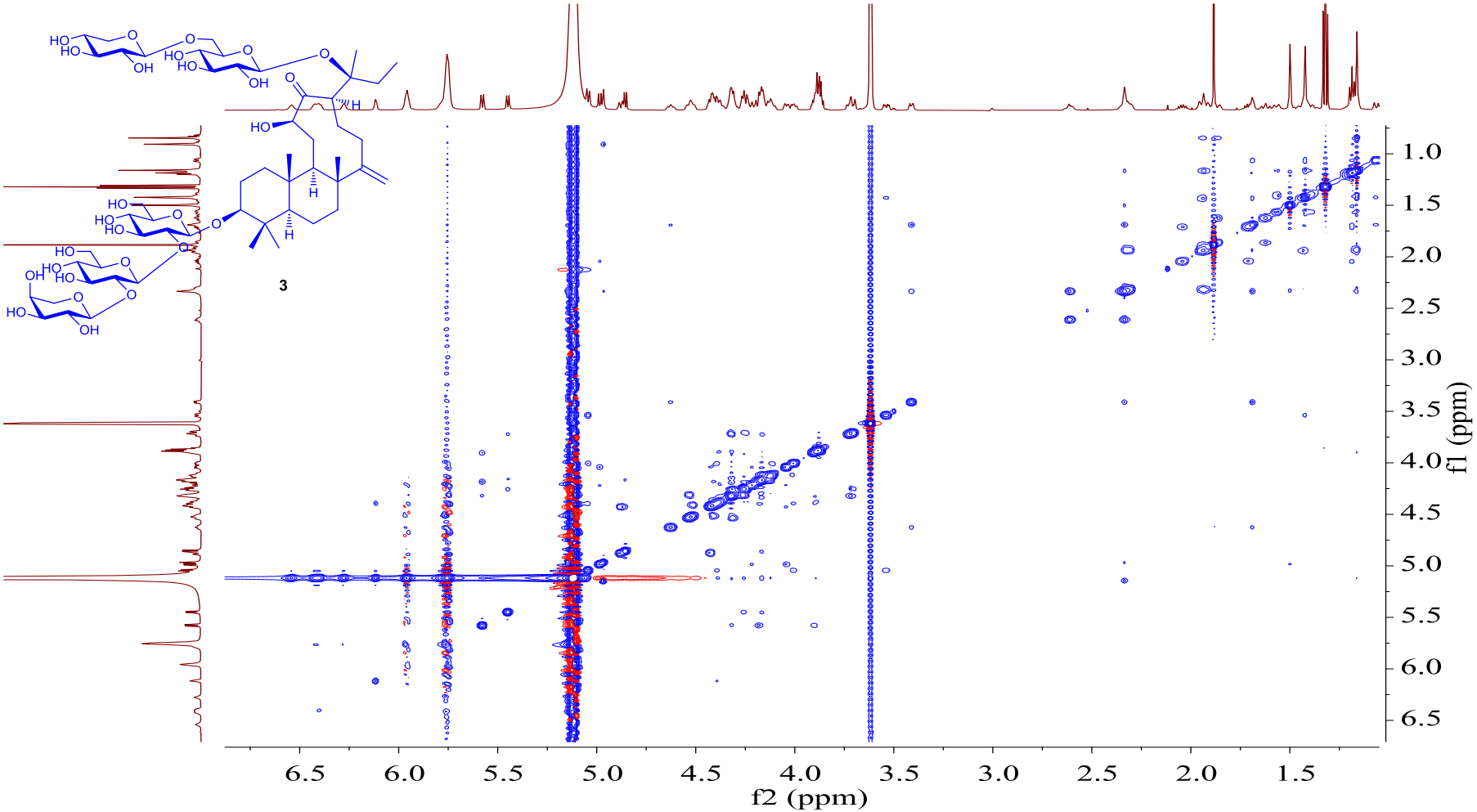


Figure S46. The NOESY spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

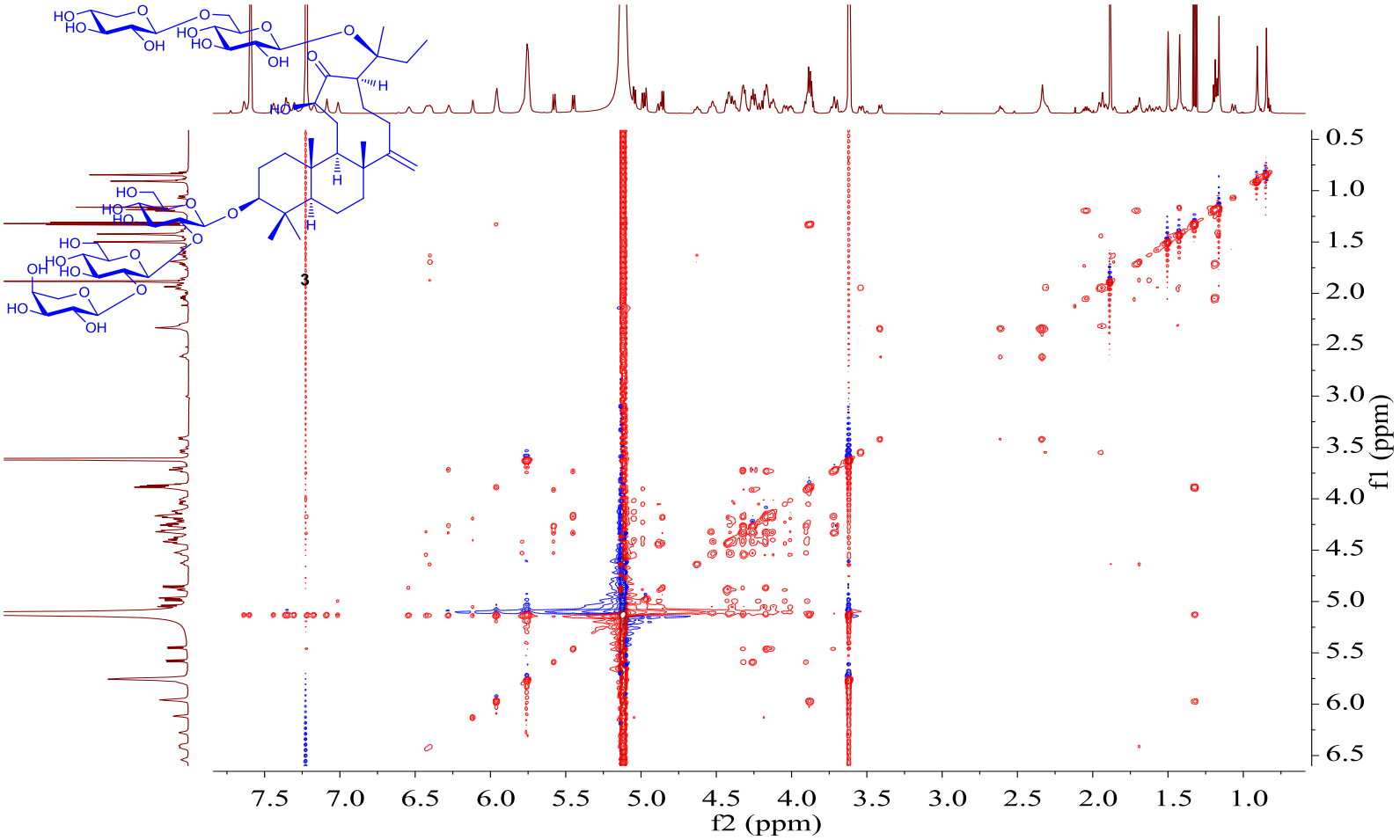


Figure S47. The TOCSY spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)

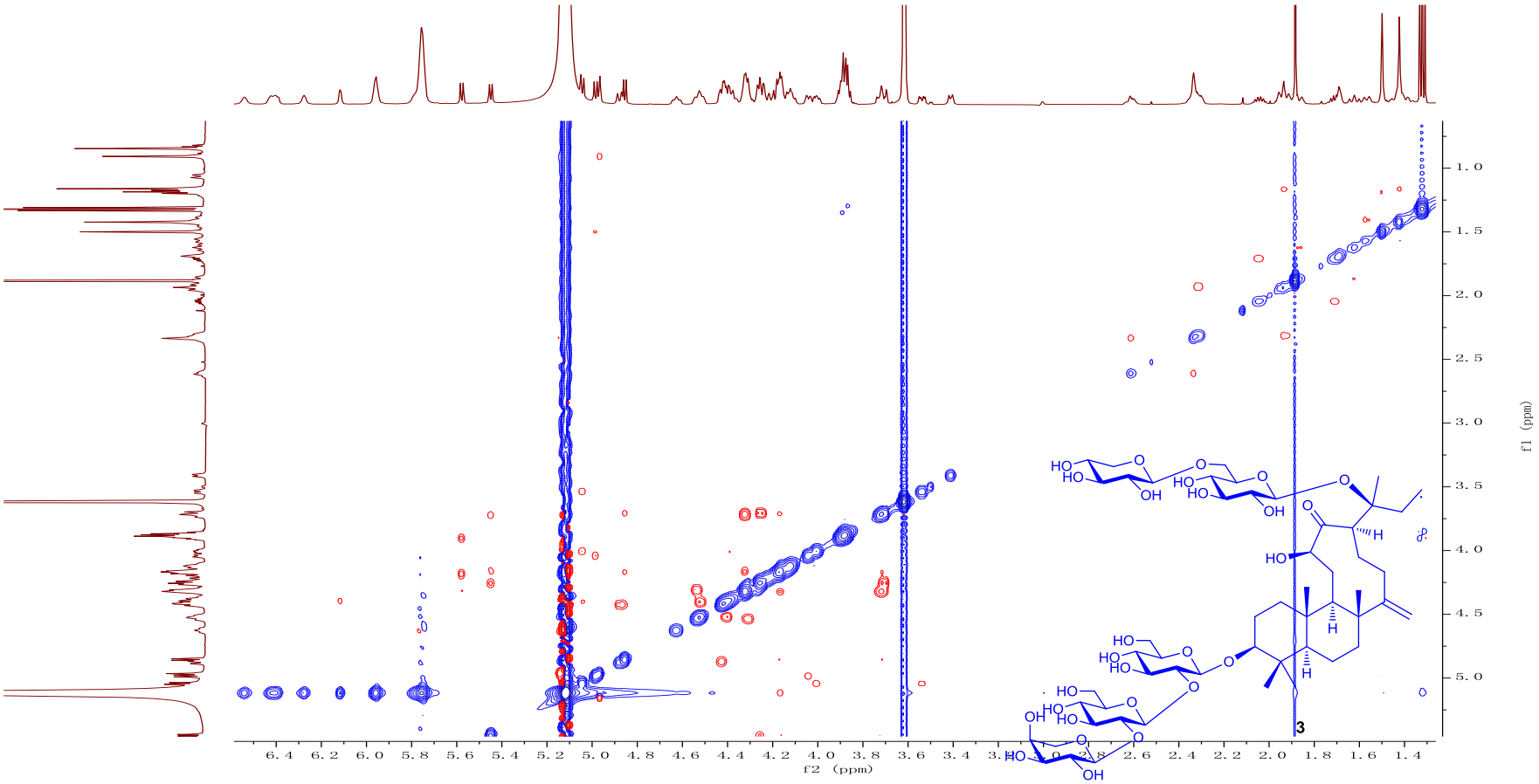
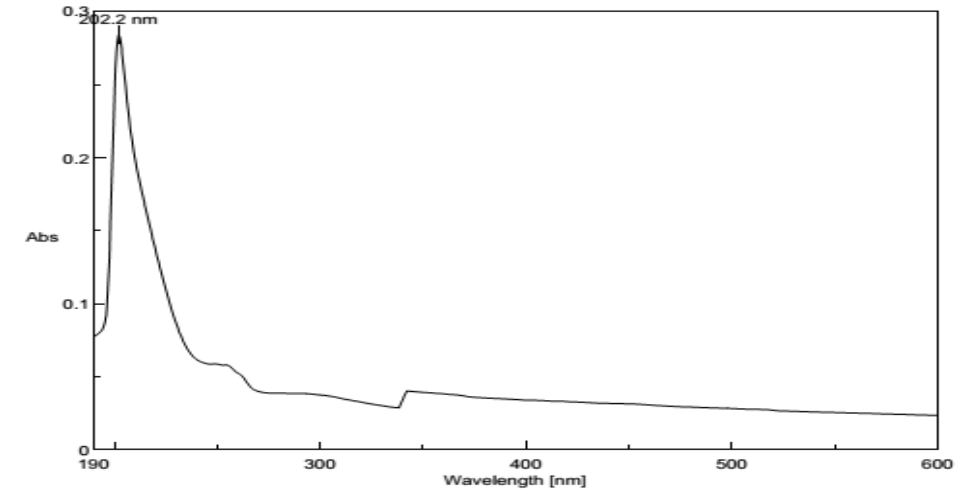


Figure S48. The ROESY spectrum of nototroneside C (**3**) in C_5D_5N (600 MHz)



[Comment]
Sample Name DBT
Comment 0.02
User
Division UV
Company 346

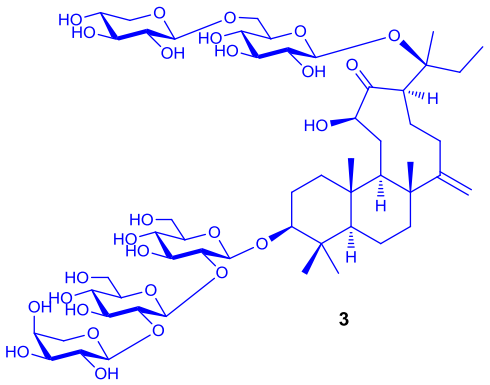
[Measurement Information]
Instrument Name V-650
Model Name V-650
Serial No. A034461150

Accessory PSC-718
Accessory S/N A001761114
Position 2
Cell Length 10 mm
Temperature 20.00 C
Control Sonsor Holder
Monitor Sensor Holder
Start Mode Start immediately

Photometric Mode Abs
Measurement range 600 - 190 nm
Data pitch 0.2 nm
Band width(UV/Vis) 2.0 nm
Response Medium
Scanning speed 200 nm/min
Source Change 340 nm
Light Source D2/WI
Filter Exchange Step
Correction Baseline

[Data Information]
Creation Date 2017-3-22 10:32

Data array type Linear data array
Horizontal Wavelength [nm]
Vertical Abs
Start 600 nm
End 190 nm
Data pitch 0.2 nm
Data points 2051



3

Figure S49. The UV spectrum of nototroneside C (**3**)

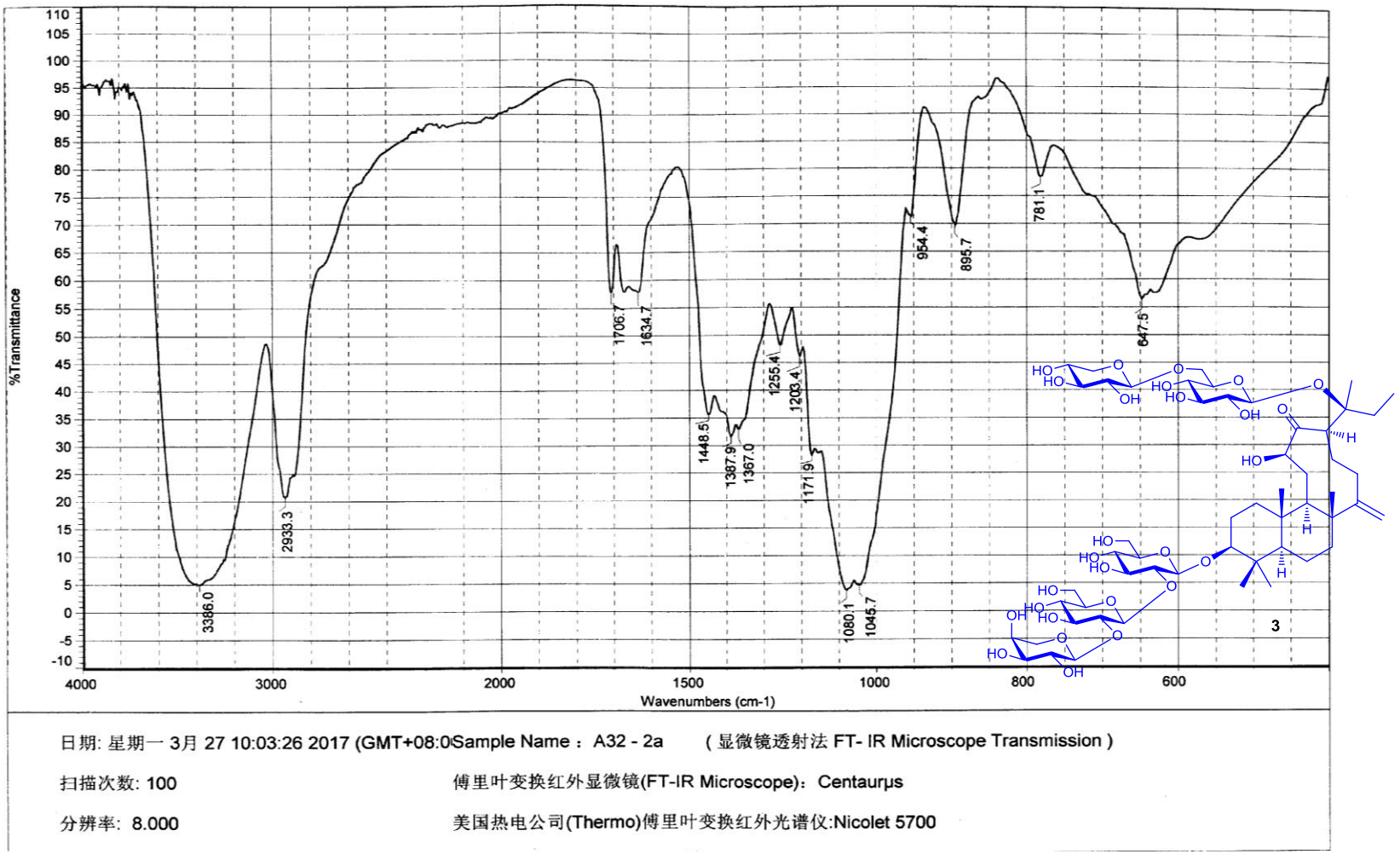


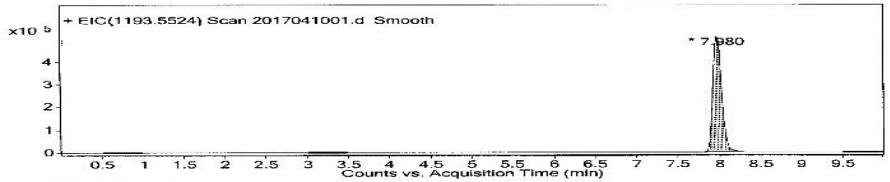
Figure S50. The IR spectrum of nototroneside C (**3**)

Qualitative Analysis Report

Data Filename	2017041001.d	**Sample Name**	A32-2a
Sample Type	Sample	**Position**	P1-C4
Instrument Name	Instrument 1	**User Name**	
Acq Method		**IRM Calibration Status**	Some Ions Missed
DA Method	TEST LCMS.m	**Comment**	

User Chromatograms

Fragmentor Voltage 150 **Collision Energy** 0 **Ionization Mode** ESI

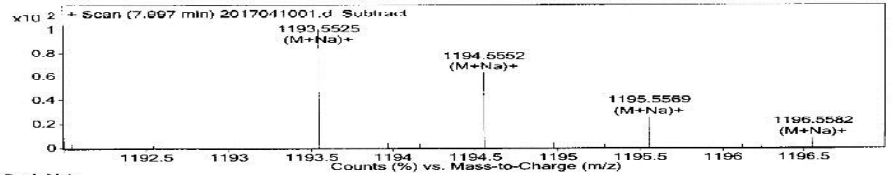


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %	Signal To Noise
1	7.803	7.98	8.222	512797	3681120	100	Infinity

User Spectra

Fragmentor Voltage 150 **Collision Energy** 0 **Ionization Mode** ESI

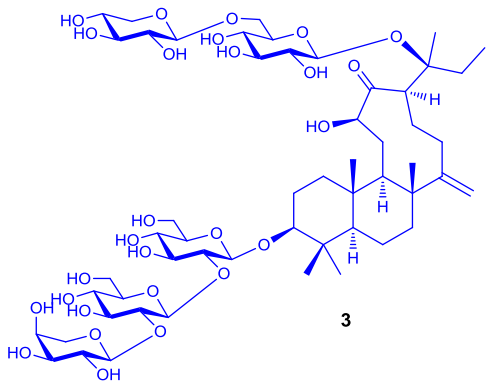


Peak List

m/z	z	Abund	Formula	Ion
265.188		74215		
605.2612	2	306113		
605.7644	2	182269		
606.2646	2	77690		
608.2689		73059		
1191.0419	2	88254		
1193.5525	1	964953	C54 H90 Na O27	(M+Na)+
1194.5552	1	607570	C54 H90 Na O27	(M+Na)+
1195.5569	1	240410	C54 H90 Na O27	(M+Na)+
1196.5582	1	72707	C54 H90 Na O27	(M+Na)+

Formula Calculator Element Limits

Element	Min	Max
C	3	80
H	0	150
O	0	50



3

MS Formula Results: + Scan (7.997 min) Sub (2017041001.d)

m/z	Ion	Formula	Abundance
1193.5525	(M+Na)+	C54 H90 Na O27	964952.6

Best	Formula (M)	Ion Formula	Score	Cross Sco	Mass	Calc Mass	Calc m/z	Diff (ppm)	Abs Diff (ppm)	Mass Match	Abund Match	Spacing Match	DBE
✓	C54 H90 O27	C54 H90 Na O27	99.76		1170.5631	1170.5669	1193.5562	3.26	3.26	99.62	99.85	99.96	10
	C61 H86 O22	C61 H86 Na O22	99.8		1170.5631	1170.5611	1193.5503	-1.76	1.76	99.89	99.52	99.95	19
	C62 H82 N4 O18	C62 H82 N4 Na O18	99.69		1170.5632	1170.5624	1193.5516	-0.64	0.64	99.99	98.99	99.96	24
	C49 H90 N2 O29	C49 H90 N2 Na O29	99.68		1170.5631	1170.5629	1193.5521	-0.19	0.19	100	98.92	99.97	6
	C55 H86 N4 O23	C55 H86 N4 Na O23	99.64		1170.5632	1170.5683	1193.5575	4.38	4.38	99.31	99.91	99.96	15
	C58 H90 O22 S	C58 H90 Na O22 S	99.64		1170.5632	1170.5644	1193.5537	1.1	1.1	99.96	98.81	99.99	14
	C53 H90 N2 O24 S	C53 H90 N2 Na O24 S	99.59		1170.5632	1170.5604	1193.5496	-2.35	2.35	99.8	98.9	99.99	10
	C59 H86 N4 O18 S	C59 H86 N4 Na O18 S	99.57		1170.5632	1170.5658	1193.555	2.22	2.22	99.82	98.79	99.99	19
	C56 H86 N2 O24	C56 H86 N2 Na O24	99.51		1170.5631	1170.5571	1193.5463	-5.21	5.21	99.03	99.94	99.96	15
	C67 H82 N2 O16	C67 H82 N2 Na O16	99.19		1170.5631	1170.5664	1193.5557	2.81	2.81	99.72	97.69	99.95	28
	C65 H86 O17 S	C65 H86 Na O17 S	99		1170.5632	1170.5586	1193.5478	-3.92	3.92	99.45	97.44	99.99	23
	C46 H94 N2 O29 S	C46 H94 N2 Na O29 S	99		1170.5632	1170.5663	1193.5555	2.66	2.66	99.75	96.91	99.99	1
	C66 H82 N4 O13 S	C66 H82 N4 Na O13 S	98.99		1170.5632	1170.5589	1193.5491	-2.8	2.8	99.72	96.93	99.99	28
	C44 H90 N4 O31	C44 H90 N4 Na O31	98.88		1170.5632	1170.5589	1193.5481	-3.64	3.64	99.52	96.91	99.97	2
	C48 H90 N4 O26 S	C48 H90 N4 Na O26 S	98.88		1170.5632	1170.5564	1193.5456	-5.81	5.81	98.79	98.1	99.99	6
	C64 H86 N2 O16 S	C64 H86 N2 Na O16 S	98.78		1170.5632	1170.5698	1193.559	5.67	5.67	98.85	97.67	99.99	23
	C50 H94 N2 O24 S2	C50 H94 N2 Na O24 S2	98.61		1170.5632	1170.5638	1193.553	0.5	0.5	99.99	95.19	99.98	5
	C71 H82 N2 O11 S	C71 H82 N2 Na O11 S	98.58		1170.5632	1170.5639	1193.5532	0.65	0.65	99.98	95.08	99.99	32
	C62 H90 O17 S2	C62 H90 Na O17 S2	98.54		1170.5632	1170.5619	1193.5512	-1.06	1.06	99.96	94.96	99.99	18
	C63 H86 N4 O13 S2	C63 H86 N4 Na O13 S2	98.53		1170.5632	1170.5633	1193.5525	0.06	0.06	100	94.88	99.99	23
	C69 H78 N4 O13	C69 H78 N4 Na O13	98.49		1170.5632	1170.5565	1193.5458	-5.65	5.65	98.86	96.66	99.95	33
	C55 H94 O22 S2	C55 H94 Na O22 S2	98.46		1170.5632	1170.5678	1193.557	3.96	3.96	99.44	95.57	99.98	9
	C57 H90 N2 O19 S2	C57 H90 N2 Na O19 S2	98.44		1170.5632	1170.5579	1193.5471	-4.51	4.51	99.27	95.78	99.99	14
	C56 H90 N4 O18 S2	C56 H90 N4 Na O18 S2	98.43		1170.5632	1170.5692	1193.5584	5.07	5.07	99.08	96.05	99.98	14
	C74 H78 N2 O11	C74 H78 N2 Na O11	98.4		1170.5631	1170.5606	1193.5498	-2.2	2.2	99.83	94.74	99.95	37
	C45 H94 N4 O26 S2	C45 H94 N4 Na O26 S2	98.08		1170.5632	1170.5598	1193.549	-2.96	2.96	99.69	93.84	99.97	1
	C68 H86 N2 O11 S2	C68 H86 N2 Na O11 S2	97.86		1170.5632	1170.5673	1193.5565	3.51	3.51	99.56	93.25	99.99	27
	C79 H78 O9	C79 H78 Na O9	97.83		1170.5631	1170.5646	1193.5538	1.24	1.24	99.94	92.55	99.94	41
	C76 H82 O9 S	C76 H82 Na O9 S	97.68		1170.5632	1170.568	1193.5572	4.1	4.1	99.4	92.89	99.98	36
	C70 H82 N4 O8 S2	C70 H82 N4 Na O8 S2	97.41		1170.5632	1170.5574	1193.5466	-4.95	4.95	99.12	92.41	99.99	32
	C80 H74 N4 O5	C80 H74 N4 Na O5	97.4		1170.5632	1170.5659	1193.5551	2.37	2.37	99.8	91.28	99.95	46
	C54 H94 N2 O19 S3	C54 H94 N2 Na O19 S3	97.36		1170.5632	1170.5613	1193.5505	-1.65	1.65	99.9	90.96	99.96	9
	C78 H78 N2 O6 S	C78 H78 N2 Na O6 S	97.28		1170.5632	1170.5581	1193.5473	-4.36	4.36	99.32	91.64	99.98	41
	C60 H90 N4 O13 S3	C60 H90 N4 Na O13 S3	97.25		1170.5632	1170.5667	1193.5559	2.92	2.92	99.89	90.92	99.97	18
	C59 H94 O17 S3	C59 H94 Na O17 S3	97.25		1170.5632	1170.5653	1193.5545	1.8	1.8	99.88	90.59	99.97	13
	C77 H78 N4 O5 S	C77 H78 N4 Na O5 S	97.23		1170.5632	1170.5693	1193.5585	5.23	5.23	99.02	91.93	99.98	41

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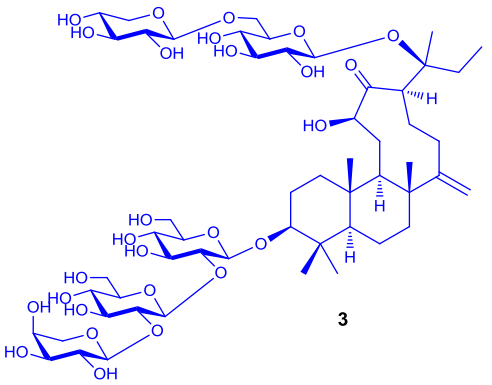
Figure S51. The HR-ESI-MS spectrum of nototroneside C (**3**)



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