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Hybrid Isoquinolines from *Thalictrum foetidum*: A New Type of Aporphine Inhibiting Staphylococcus aureus by combined mechanisms

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Author Contributions

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Supporting Information

Contents of Supporting Information

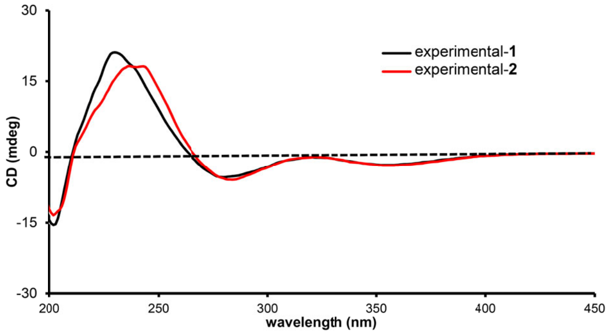

Figure S1. Experimental CD spectra of **1** and **2**

Table S1. The computed ^{13}C NMR spectral data for 1.

No.	1	*δ* exptl	Methanol			
			δ calcd (6a*S*)	Δ*δ*	*δ* calcd (6a*R*)	Δ*δ*
1	**2**	145.2	144.8	-0.4	145.7	0.5
2	**1**	150.2	149.3	-0.9	150.6	0.4
3	**11b**	121.8	123.1	1.3	124.4	2.6
4	**11c**	131.8	133.8	2.0	135.0	3.2
5	**3a**	123.4	125.4	2.0	126.7	3.3
6	**3**	151.0	149.0	-2.0	150.0	-1.0
7	**6a**	62.6	60.5	-2.1	62.2	-0.4
8	**5**	52.9	47.2	-5.7	49.0	-3.9
9	**4**	23.7	19.8	-3.9	21.6	-2.1
10	**11a**	135.4	136.9	1.5	137.2	1.8
11	**7a**	128.0	128.2	0.2	129.4	1.4
12	**7**	33.5	37.2	3.7	39.0	5.5
13	**11**	111.0	109.1	-1.9	110.0	-1.0
14	**10**	155.4	152.9	-2.5	153.0	-2.4
15	**9**	126.1	125.0	-1.1	125.6	-0.5
16	**8**	128.0	129.1	1.1	129.2	1.2
17	**N-CH3**	44.0	42.2	-1.8	44.0	0
18	**9a**	200.5	197.0	-3.5	198.2	-2.3
19	**1'**	115.8	118.8	3.0	115.8	0
20	**2'**	157.5	150.0	-7.5	158.8	1.3
21	**3'**	136.3	132.4	-3.9	134.3	-2.0
22	**4'**	158.6	154.4	-4.2	157.4	-1.2
23	**5'**	102.7	100.5	-2.2	101.5	-1.2
24	**6'**	130.5	126.1	-4.4	130.0	-0.5
25	**1-OCH$_3$**	60.9	58.8	-2.1	60.5	-0.4
26	**2-OCH$_3$**	61.0	60.0	-1.0	61.7	0.7
27	**3-OCH$_3$**	60.4	58.2	-2.2	59.9	-0.5
28	**10-OCH$_3$**	55.9	53.9	-2.0	55.3	-0.6
29	**3′-OCH$_3$**	60.7	57.9	-2.8	58.9	-1.8
30	**4′-OCH$_3$**	115.8	118.8	3.0	55.9	-0.2

1. Experimenmtal section

1.1. General Experimental Procedures

An Agilent 1290 UPLC/6540 Q-TOF spectrometer were used to measure ESIMS and HREIMS spectra, respectively. UV spectra were detected on a Shimadzu UV-2401 PC spectrophotometer. IR spectra were scanning with a Bruker Tensor-27 infrared spectrometer and a KBr disk. Optical rotations were determined on a JASCO P-1020 digital polarimeter. CD spectra were detected on an Applied Photophysics Circular dichromatograph. 1D and 2D NMR spectra were recorded on a Bruker AVANCE 600 spectrometers with TMS as internal standard. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Marine Chemical CO., Ltd., Qingdao, China), Sephedex LH-20 (20–150μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden) and Rp-C18 (40–63 μm, Fuji). Thin layer chromatography (TLC) was performed on silica gel plates (GF254, Qingdao Marine Chemical CO., Ltd., Qingdao, China) and RP-18 F254 (Merck). Fractions were monitored by TLC and spots were visualized by spraying with Dragendorff's reagent. Methanol, hydrochloric, ethyl acetate, chloroform ammonia solution and acetone were purchased from Tianjin Chemical Reagents Co. (Tianjin, China).Main Text Paragraph. Scanning Electron Microscope was used to evaluated the membrane morphology (Hitachi S-3000N). Laser Scanning Confocal Microscopy was used to evaluated the intracellular nucleic acid content (Japan, FV1000).

1.2. Plant material

The roots of *Thalictrum foetidum* were harvested at Yunnan in March 2017. Botanical identification was done at the Kunming Medical University by Mr. Jun Zhang and where a voucher specimen was kept under the reference number (No. 20170301).

1.3 Extraction and Isolation

Air-dried and powdered roots (7.2 kg) of *Thalictrum foetidum* were collected from Yunnan and extracted with methanol (2 h × 3) under reflux conditions. The solvent was evaporated *in vacuo* to give a residue, which was dissolved in 0.5% hydrochloric acid and then adjusted to a pH of 2. The solution was filtered and adjusted to a pH of 10 with 10% ammonia, and the basified solution was then partitioned with EtOAc to afford the alkaloidal extract (90.0 g). The extract was chromatographed on a silica gel column (chloroform-methyl, 100:0 to 0:100 v/v) to afford fractions I- IX. Fraction IV (2.2 g) was subjected to a preparative reversed-phase Rp-C18 column with a gradient elution of 0-100% (v/v) methanol-water to yield subfractions IV-1 to IV-6. Subfraction IV-4 (1.3 g) was further separated on sephedex-LH20, silica gel column (petroleum ether-ethyl acetate, 2:1 to 1:1 v/v) and purified by semi-preparative HPLC (Acetonitrile-H_2O, 80:20, V/V) to yield compound **1** (18.0 mg) and compound **2** (24.0 mg). Fraction I (180.0 mg) was subjected to a silica gel column (Petroleum ether-acetone, 6:1 to 2:1 v/v) to afford fractions I-1 to I-5. Subfraction I-4 (140.0 mg) was further separated on sephedex-LH20 and purified by semi-preparative HPLC (Acetonitrile-H_2O, 90:10, V/V) to yield compound **3** (1.0 mg) and compound **4** (1.5 mg).

1.4 Compounds

Thalfoetine A (**1**): Light yellow amorphous powder; HRESIMS at m/z 536.2279 $[M + H]^+$ (calcd 536.2279, $C_{30}H_{33}NO_8$); $[\alpha]_D^{25}$ = -36.4 (c 0.45, CH_3OH); UV (MeOH) λ_{max} (log ε): 219 (4.67), 289 (4.35) and 330 (4.18); IR (KBr) ν_{max}: 3447, 2928,1627, 1502, 1461,1452, 1285, 1101, 791 and 774 cm^{-1}; ^1H and ^{13}C NMR data see Table S1.

Thalfoetine B (**2**): Yellow amorphous powder; HRESIMS at m/z 536.2279 $[M + H]^+$ (calcd 536.2279, $C_{30}H_{33}NO_8$); $[\alpha]_D^{25}$ = -12.2 (c 0.58, CH_3OH); UV (MeOH) λ_{max} (log ε): 216 (4.25), 284 (3.92) and 352 (3.73); IR (KBr) ν_{max}: 3447, 1630, 1465, 1396, 1343, 1102, 804 and 470 cm^{-1}; ^1H and ^{13}C NMR data see Table S1.

Thalfoetine C (**3**): Yellow amorphous powder; HRESIMS at m/z 556.1941 $[M + Na]^+$ (calcd 556.1942, $C_{30}H_{31}NO_8$); UV (MeOH) λ_{max} (log ε): 209 (3.92), 238 (3.77), 266 (3.66), 316 (3.56) and 416 (2.92); IR (KBr) ν_{max}: 3441, 2922, 1632, 1464, 1386, 1053 and 584 cm^{-1}; ^1H and ^{13}C NMR data see Table S1.

Thalfoetine D (**4**): Yellow amorphous powder; HRESIMS at m/z 556.1941 $[M + Na]^+$ (calcd 556.1942, $C_{30}H_{31}NO_8$); UV (MeOH) λ_{max} (log ε): 205 (4.21), 248 (4.25), 287 (4.10) and 339 (3.92); IR (KBr) ν_{max}: 3441, 2922, 1630, 1463, 1385, 1062 and 583 cm^{-1}; ^1H and ^{13}C NMR data see Table S1.

1.5. Quantum Chemical ECD and NMR Calculations

The theoretical calculation of compound **1** was performed using Gaussian 09[1] and figured using Gauss View 5.0[2]. Conformation search using molecular mechanics calculations was performed in Discovery Studio 3.5 Client with MMFF force field with 20 kcal mol^{-1} upper energy limit.[3]

The optimized conformation geometries and thermodynamic parameters of all selected conformations were provided. The predominant conformers were optimized at B3LYP/6-31G (d, p) level. The theoretical calculation of ECD was performed using time dependent Density Functional Theory (TDDFT) at B3LYP/6-31G (2d, p) level in MeOH with PCM model[4]. The ECD spectrum of compound **1** was obtained by weighing the Boltzmann distribution rate of each geometric conformation[5]. The ECD spectra were simulated by overlapping Gaussian functions for each transition.

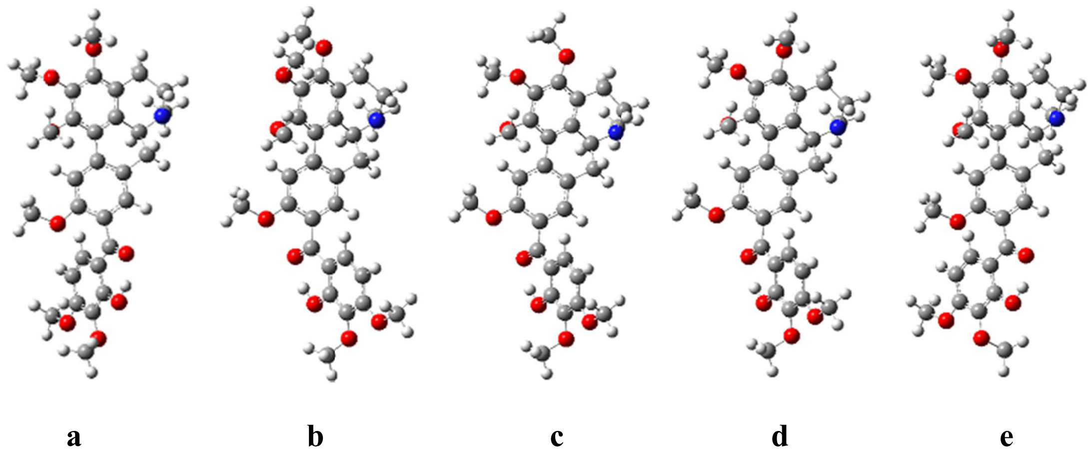

Figure 1.5.1 Optimized geometries of predominant conformers for compound 1 at the B3LYP/6-31G(d,p) level in the gas phase.

Table 1.5-1 Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized compound **1** (6a*R*) at B3LYP/6-31G(d,p) level in the gas phase

Conformations	E+ZPE	G	%
1 (6a*R*)-a	-1818.988793	-1819.060341	27.5
1 (6a*R*)-b	-1818.984712	-1819.056840	0.7
1 (6a*R*)-c	-1818.985929	-1819.059370	9.9
1 (6a*R*)-d	-1818.987841	-1819.059937	18
1 (6a*R*)-e	-1818.988817	-1819.060782	43.9

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy in the gas phase at B3LYP/6-31G(d,p) level., %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors.

Table 1.5-2. Optimized Z-matrixes of compound **1** in the gas phase (Å) at B3LYP/6-31G(d,p) level

1 (6aR)-a				**1 (6aR)-b**			
C	4.76336	-1.46827	0.143037	C	-4.80935	-1.1867	0.584094
C	3.375623	-1.41803	-0.06709	C	-3.44043	-1.35014	0.303718
C	2.680928	-0.19282	-0.03933	C	-2.65492	-0.26578	-0.1376
C	3.434264	0.984646	0.21408	C	-3.27992	1.001394	-0.27061
C	4.824056	0.947375	0.373075	C	-4.6411	1.171966	0.003196
C	5.488402	-0.29075	0.346153	C	-5.40689	0.065574	0.398656
C	2.669568	2.307205	0.271814	C	-2.41564	2.173964	-0.73219
N	3.486287	3.526498	0.362748	N	-3.03011	3.509266	-0.6418
C	4.836104	3.368501	-0.17293	C	-4.17013	3.585792	0.268084
C	5.610239	2.23123	0.505162	C	-5.25644	2.550925	-0.05364
C	1.223441	-0.0614	-0.31186	C	-1.19788	-0.37281	-0.42589
C	0.74317	1.176782	-0.79663	C	-0.40656	0.789461	-0.29978
C	1.691456	2.346069	-0.91407	C	-1.07329	2.106473	0.01557
C	0.309367	-1.11323	-0.12062	C	-0.58446	-1.57195	-0.83269
C	-1.04588	-0.95805	-0.4193	C	0.786812	-1.63297	-1.08777
C	-1.52719	0.271209	-0.91157	C	1.586892	-0.48211	-0.9305
C	-0.60802	1.30598	-1.10763	C	0.965469	0.706146	-0.53716
C	3.459866	4.149869	1.681598	C	-3.28558	4.121142	-1.94076
H	2.047317	2.271963	1.177442	H	-2.18425	1.994409	-1.7923
C	-2.94942	0.514542	-1.32671	C	3.04009	-0.49156	-1.3069
C	-4.06886	0.329446	-0.40358	C	4.059484	-0.07724	-0.33859
O	-3.13605	0.945873	-2.4836	O	3.351182	-0.82709	-2.46524
C	-5.40042	0.515977	-0.88509	C	5.415643	0.040027	-0.77272
C	-6.49532	0.338349	-0.02208	C	6.413998	0.444771	0.129258
C	-6.27428	0.010702	1.326102	C	6.078877	0.711571	1.467912
C	-4.96065	-0.12824	1.819237	C	4.745677	0.585685	1.907237
C	-3.88917	0.024929	0.958258	C	3.765863	0.194243	1.011517
O	-5.65486	0.858671	-2.15512	O	5.781593	-0.22643	-2.03313
O	2.720115	-2.61845	-0.25794	O	-2.90173	-2.61238	0.434577
C	2.89101	-3.18973	-1.5626	C	-2.54671	-2.9875	1.765362
O	5.415302	-2.68455	0.108151	O	-5.52973	-2.29015	0.979478
C	5.364272	-3.40178	1.347793	C	-6.16549	-2.20257	2.26177
O	6.842103	-0.31376	0.581514	O	-6.75432	0.240916	0.647676
C	7.665564	-0.80287	-0.48529	C	-7.61438	-0.33818	-0.34266
O	-1.96336	-1.9629	-0.29119	O	1.434392	-2.77209	-1.45869

C	-1.53022	-3.22658	0.187249	C	0.670442	-3.94671	-1.6828
O	-7.77735	0.5611	-0.45234	O	7.705455	0.634229	-0.28742
C	-8.30105	-0.42673	-1.34383	C	8.440387	-0.56449	-0.55079
O	-7.39123	-0.14064	2.080441	O	7.112677	1.077678	2.265291
C	-7.24238	-0.43323	3.462276	C	6.844072	1.385672	3.625874
H	4.763797	3.163356	-1.24864	H	-3.81597	3.422701	1.294096
H	5.364219	4.321775	-0.06448	H	-4.5727	4.603275	0.227432
H	6.601348	2.106185	0.058819	H	-6.08841	2.613354	0.653628
H	5.787794	2.474222	1.561535	H	-5.68121	2.754363	-1.04642
H	2.257694	2.312203	-1.85618	H	-1.25602	2.221852	1.094019
H	1.143304	3.292167	-0.90203	H	-0.44266	2.944585	-0.29452
H	0.677992	-2.05704	0.247853	H	-1.19528	-2.45391	-0.94281
H	-0.97589	2.247908	-1.50383	H	1.569622	1.604916	-0.44748
H	2.424649	4.365164	1.964105	H	-2.35903	4.148261	-2.52252
H	3.994772	5.104355	1.639332	H	-3.61226	5.155949	-1.79464
H	3.909114	3.54694	2.491718	H	-4.04956	3.608828	-2.55433
H	-4.78422	-0.35853	2.862064	H	4.484279	0.779156	2.939533
H	-2.88193	-0.08188	1.342581	H	2.745072	0.083375	1.358032
H	-4.76093	0.989474	-2.57847	H	4.9501	-0.53503	-2.49202
H	2.331864	-4.12779	-1.56138	H	-2.10103	-3.98218	1.69722
H	2.483819	-2.52606	-2.33405	H	-1.81444	-2.29127	2.19206
H	3.946743	-3.39351	-1.76254	H	-3.42698	-3.03573	2.414561
H	5.83764	-2.82507	2.150645	H	-5.42764	-2.01421	3.051848
H	4.329481	-3.63595	1.618493	H	-6.92197	-1.41466	2.285472
H	5.919582	-4.32876	1.190275	H	-6.63169	-3.17516	2.430959
H	8.696165	-0.70321	-0.13881	H	-8.63619	-0.11127	-0.03199
H	7.44745	-1.84951	-0.70932	H	-7.42742	0.105251	-1.32804
H	7.529745	-0.19728	-1.39015	H	-7.47675	-1.42258	-0.40068
H	-2.41898	-3.85886	0.20184	H	1.384371	-4.70974	-1.99555
H	-0.77737	-3.67325	-0.47392	H	0.159252	-4.28024	-0.77071
H	-1.11744	-3.15829	1.201622	H	-0.07363	-3.79988	-2.4751
H	-9.32408	-0.11879	-1.56974	H	9.442696	-0.24687	-0.84544
H	-7.72123	-0.47387	-2.27056	H	8.510377	-1.18809	0.349513
H	-8.3198	-1.41557	-0.86797	H	7.985346	-1.13823	-1.36375
H	-8.25512	-0.50097	3.861532	H	7.804145	1.665279	4.06132
H	-6.72643	-1.38823	3.622039	H	6.146204	2.226566	3.71966
H	-6.69955	0.361793	3.987909	H	6.440837	0.520025	4.165875
1 (6aR)-c				**1 (6aR)-d**			
C	-4.83173	-1.02417	0.70186	C	4.8108	1.091933	0.654235
C	-3.46825	-1.22761	0.40912	C	3.452492	1.292305	0.357675
C	-2.66121	-0.20546	-0.11598	C	2.664609	0.253442	-0.17456
C	-3.26749	1.064714	-0.3112	C	3.293746	-1.00006	-0.39906
C	-4.5934	1.304127	0.046445	C	4.630584	-1.22348	-0.05216

C	-5.39612	0.247918	0.532012	C	5.394315	-0.1646	0.468445
C	-2.39862	2.166278	-0.91682	C	2.439087	-2.11292	-1.00511
N	-2.99475	3.50826	-0.96696	N	3.058573	-3.44452	-1.07107
C	-4.0155	3.723493	0.055545	C	4.108595	-3.65057	-0.07672
C	-5.16017	2.705524	-0.01817	C	5.228314	-2.60641	-0.17399
C	-1.21025	-0.35761	-0.40602	C	1.209358	0.381886	-0.46041
C	-0.39989	0.799556	-0.39234	C	0.420894	-0.79	-0.44721
C	-1.03924	2.154409	-0.19872	C	1.088538	-2.13309	-0.27005
C	-0.61268	-1.59936	-0.69286	C	0.58849	1.614023	-0.73773
C	0.757542	-1.70614	-0.93632	C	-0.78549	1.696469	-0.97036
C	1.575348	-0.55787	-0.89063	C	-1.58163	0.533888	-0.92149
C	0.970578	0.67207	-0.61832	C	-0.95386	-0.68643	-0.66004
C	-3.42686	3.904781	-2.30307	C	3.457069	-3.83654	-2.41898
H	-2.19442	1.868589	-1.95504	H	2.216982	-1.8121	-2.03876
C	3.029779	-0.62542	-1.25426	C	-3.04169	0.579023	-1.26904
C	4.049066	-0.12557	-0.32643	C	-4.04326	0.089556	-0.31775
O	3.344018	-1.08338	-2.36919	O	-3.37309	1.011022	-2.38904
C	5.408008	-0.06364	-0.76315	C	-5.40885	0.014816	-0.73102
C	6.406234	0.420942	0.098724	C	-6.39103	-0.45671	0.156071
C	6.068027	0.822474	1.40255	C	-6.0295	-0.83372	1.461094
C	4.732122	0.751191	1.845804	C	-4.68633	-0.75193	1.880148
C	3.752452	0.281164	0.988469	C	-3.72273	-0.29413	0.998479
O	5.776263	-0.45743	-1.98922	O	-5.79821	0.384632	-1.95803
O	-2.95349	-2.48549	0.669533	O	2.936791	2.556254	0.567606
C	-2.63785	-2.71094	2.050467	C	2.681744	2.875153	1.941969
O	-5.56701	-2.04963	1.265916	O	5.55919	2.131082	1.169694
C	-5.84634	-3.15858	0.401455	C	6.042564	3.04341	0.175221
O	-6.67231	0.605963	0.856719	O	6.726248	-0.38296	0.72611
C	-7.74026	-0.33814	0.898579	C	7.147189	-0.22678	2.087339
O	1.38868	-2.88668	-1.18958	O	-1.44054	2.865531	-1.21587
C	0.609711	-4.06783	-1.28763	C	-0.68362	4.060733	-1.32035
O	7.700764	0.55977	-0.32834	O	-7.69213	-0.60659	-0.24616
C	8.427512	-0.66338	-0.4763	C	-8.42457	0.611814	-0.40561
O	7.101656	1.258291	2.164402	O	-7.04877	-1.25783	2.248237
C	6.829691	1.706232	3.48483	C	-6.75392	-1.67742	3.573147
H	-3.53924	3.654917	1.04188	H	3.657835	-3.60219	0.922887
H	-4.39534	4.745934	-0.04437	H	4.505755	-4.66391	-0.19886
H	-5.86234	2.855409	0.807142	H	5.977345	-2.75591	0.609515
H	-5.74385	2.851334	-0.93743	H	5.766425	-2.71808	-1.125
H	-1.18749	2.381935	0.867226	H	1.255323	-2.36472	0.792295
H	-0.40531	2.944607	-0.61092	H	0.465218	-2.93304	-0.67951
H	-1.23493	-2.47978	-0.71432	H	1.19517	2.505077	-0.76214
H	1.588096	1.56621	-0.61414	H	-1.55577	-1.59121	-0.65388

H	-2.57894	3.852214	-2.99308	H	2.58944	-3.79313	-3.08463
H	-3.76672	4.945362	-2.27689	H	3.808477	-4.87344	-2.40302
H	-4.24296	3.293634	-2.72917	H	4.254017	-3.21659	-2.86789
H	4.468067	1.047515	2.852742	H	-4.40445	-1.03085	2.887189
H	2.729412	0.213075	1.339197	H	-2.69383	-0.21798	1.330072
H	4.944096	-0.80617	-2.41737	H	-4.97462	0.726833	-2.4069
H	-2.25948	-3.73325	2.116572	H	2.296915	3.897081	1.952779
H	-1.86272	-2.01461	2.390217	H	1.928273	2.200156	2.364569
H	-3.53042	-2.60834	2.675001	H	3.601817	2.824289	2.53115
H	-6.45242	-2.84307	-0.45747	H	6.68968	2.52796	-0.54364
H	-4.92401	-3.62454	0.0469	H	5.209861	3.521466	-0.35062
H	-6.4156	-3.87326	0.999654	H	6.621962	3.800372	0.707936
H	-8.65065	0.263515	0.947835	H	8.211602	-0.4696	2.101871
H	-7.76773	-0.94964	-0.01056	H	6.993895	0.79664	2.436722
H	-7.67681	-0.9904	1.770861	H	6.610398	-0.92386	2.743253
H	1.313735	-4.86989	-1.51333	H	-1.40387	4.850125	-1.53924
H	0.092091	-4.29384	-0.34649	H	-0.1618	4.295365	-0.38371
H	-0.13064	-3.99893	-2.09419	H	0.050496	4.005084	-2.1335
H	9.433686	-0.38129	-0.79316	H	-9.43522	0.321179	-0.69961
H	8.488487	-1.20218	0.47783	H	-8.47068	1.169046	0.538707
H	7.972156	-1.30616	-1.23564	H	-7.98391	1.240632	-1.18502
H	7.7903	2.020531	3.894699	H	-7.70687	-1.98507	4.005285
H	6.139167	2.558306	3.488133	H	-6.06137	-2.5278	3.582977
H	6.415943	0.904132	4.10856	H	-6.332	-0.86137	4.172794
1 (6aR)-e							
C	4.800464	-1.40753	0.108692				
C	3.41264	-1.3846	-0.10509				
C	2.687214	-0.1788	-0.03778				
C	3.409774	1.007592	0.259797				
C	4.799587	0.999223	0.423361				
C	5.494865	-0.22014	0.356231				
C	2.612238	2.308297	0.359422				
N	3.398685	3.543725	0.494036				
C	4.753341	3.436105	-0.04169				
C	5.553383	2.296759	0.601556				
C	1.228211	-0.07462	-0.31387				
C	0.718815	1.16736	-0.75767				
C	1.637308	2.363951	-0.8283				
C	0.340646	-1.1557	-0.16668				
C	-1.01615	-1.02572	-0.47047				
C	-1.52646	0.207758	-0.92213				
C	-0.63326	1.272427	-1.07374				
C	3.353511	4.122095	1.832729				

H	1.988556	2.227266	1.261132				
C	-2.9509	0.426703	-1.34288				
C	-4.07449	0.166432	-0.44264				
O	-3.1389	0.902844	-2.48167				
C	-5.40588	0.311237	-0.93845				
C	-6.50351	0.059041	-0.0982				
C	-6.28836	-0.29529	1.243773				
C	-4.97688	-0.41722	1.746742				
C	-3.90129	-0.18898	0.907591				
O	-5.65875	0.685956	-2.19958				
O	2.789264	-2.59401	-0.34154				
C	2.972029	-3.10762	-1.66838				
O	5.482829	-2.60495	0.032367				
C	5.450016	-3.3654	1.246554				
O	6.848104	-0.21761	0.595842				
C	7.686306	-0.64529	-0.48586				
O	-1.90665	-2.05834	-0.38689				
C	-1.44214	-3.33056	0.036859				
O	-7.78479	0.112205	-0.58297				
C	-8.29942	1.430776	-0.7856				
O	-7.40955	-0.49057	1.98204				
C	-7.26766	-0.87126	3.343127				
H	4.688738	3.264272	-1.12371				
H	5.25762	4.39802	0.099215				
H	6.548673	2.211135	0.155184				
H	5.721674	2.508753	1.666061				
H	2.207629	2.378798	-1.76847				
H	1.064921	3.294696	-0.78487				
H	0.731081	-2.10223	0.17084				
H	-1.02284	2.217875	-1.43971				
H	2.312731	4.305409	2.117549				
H	3.867801	5.088775	1.824478				
H	3.812631	3.502416	2.62444				
H	-4.80501	-0.67803	2.783137				
H	-2.89571	-0.27494	1.301436				
H	-4.76687	0.873202	-2.60408				
H	2.438159	-4.05959	-1.7043				
H	2.545403	-2.42432	-2.41167				
H	4.03241	-3.27484	-1.87777				
H	5.907895	-2.8043	2.069195				
H	4.421522	-3.63553	1.50766				
H	6.029301	-4.27169	1.05806				
H	8.713114	-0.53881	-0.13026				

H	7.490974	-1.68609	-0.75374				
H	7.541856	-0.0059	-1.36581				
H	-2.3138	-3.98595	0.016658				
H	-0.67401	-3.7262	-0.639				
H	-1.0369	-3.29746	1.056025				
H	-9.3189	1.305668	-1.15647				
H	-8.32581	1.992132	0.157056				
H	-7.70769	1.978378	-1.52579				
H	-8.28243	-0.98441	3.726623				
H	-6.73537	-1.82506	3.442555				
H	-6.7443	-0.10395	3.9271				

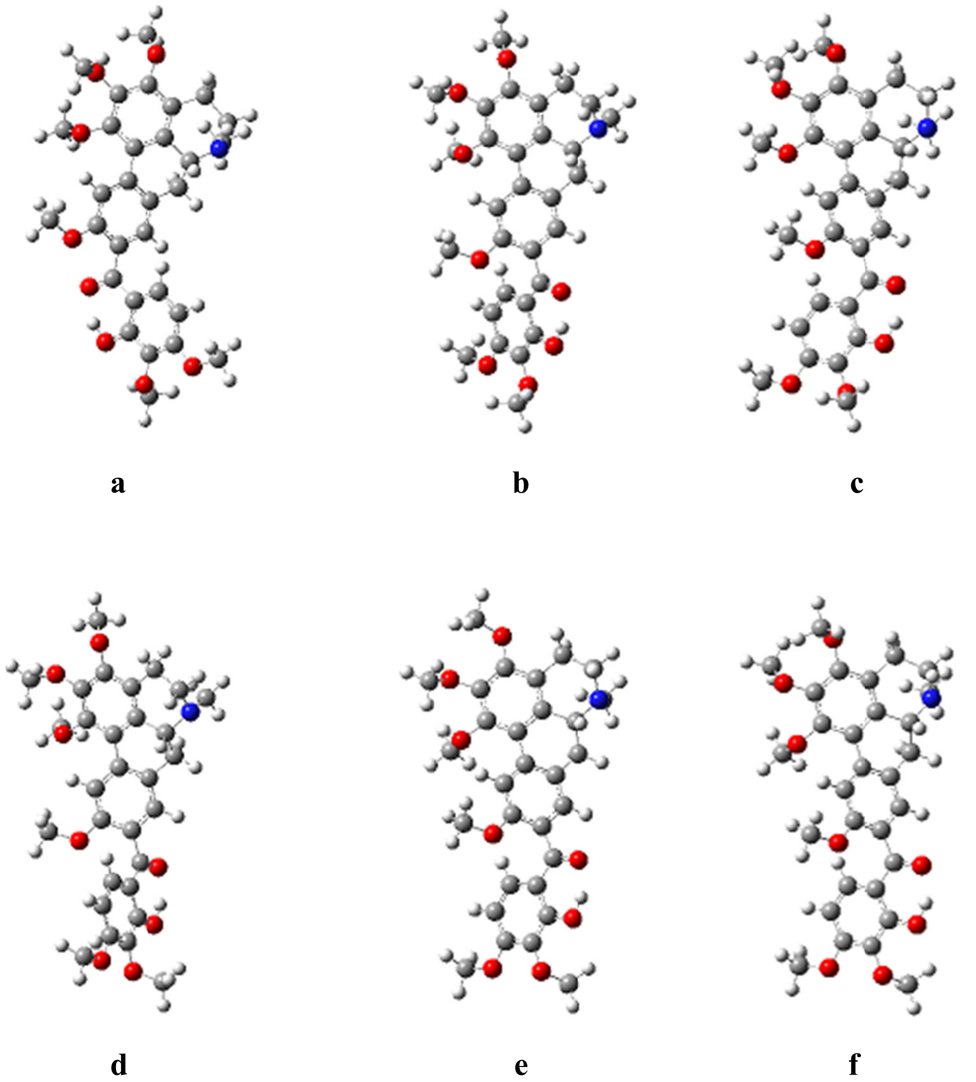

Figure 1.5.2 Optimized geometries of predominant conformers for compound 1 at the B3LYP/6-31G(d,p) level in the gas phase.

Table 1.5.3. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized compound **1**(6a*S*) at B3LYP/6-31G(d,p) level in the gas phase

Conformations	E+ZPE	G	%
1 (6aS)-a	-1818.988535	-1819.060090	14.4
1 (6aS)-b	-1818.989647	-1819.061279	55.6
1 (6aS)-c	-1818.984148	-1819.054905	0.1
1 (6aS)-d	-1818.989450	-1819.060610	26.1
1 (6aS)-e	-1818.987746	-1819.058215	1.7
1 (6aS)-f	-1818.986764	-1819.058403	2.1

E+ZPE, G: total energy with zero point energy (ZPE) and Gibbs free energy in the gas phase at B3LYP/6-31G(d,p) level., %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

Table S1.5.4. Optimized Z-matrixes of compound **1** (6a*S*) in the gas phase (Å) at B3LYP/6-31G(d,p) level

1 (6a*S*)-a				**1 (6a*S*)-b**			
C	5.010531	-0.83645	-0.26315	C	-4.55216	1.671889	-0.05759
C	3.665586	-1.19875	-0.09124	C	-3.16971	1.439554	-0.11486
C	2.659493	-0.21881	0.023443	C	-2.65559	0.127318	-0.13472
C	3.059432	1.143174	0.003701	C	-3.58102	-0.94625	-0.05322
C	4.394693	1.512745	-0.20026	C	-4.9636	-0.72224	-0.02735
C	5.372262	0.512284	-0.32566	C	-5.44448	0.59678	-0.02285
C	1.988112	2.226466	0.18245	C	-3.04145	-2.38256	-0.03276
N	2.516841	3.558132	0.506742	N	-4.01439	-3.39273	0.401891
C	3.588434	3.891751	-0.43295	C	-5.26492	-3.20717	-0.33566
C	4.808561	2.967326	-0.30785	C	-5.95353	-1.87059	-0.02392
C	1.210332	-0.53524	0.143528	C	-1.207	-0.18777	-0.25964
C	0.356082	0.433776	0.709368	C	-0.75104	-1.44903	0.181009
C	0.940002	1.739494	1.186002	C	-1.73888	-2.42348	0.770253
C	0.65049	-1.73583	-0.33224	C	-0.285	0.691673	-0.85552
C	-0.71541	-1.99542	-0.21017	C	1.066163	0.357791	-0.96649
C	-1.56707	-1.04044	0.383059	C	1.534859	-0.87657	-0.47305
C	-1.00776	0.163989	0.816808	C	0.597899	-1.7684	0.057853
C	2.913632	3.765209	1.898476	C	-4.22669	-3.49738	1.844128
H	1.470942	2.337762	-0.78477	H	-2.78013	-2.64607	-1.07068
C	-3.01564	-1.34642	0.630404	C	2.954637	-1.34889	-0.58806
C	-4.06234	-0.47121	0.096316	C	4.073565	-0.57618	-0.04761

O	-3.29862	-2.34153	1.324273	O	3.141052	-2.46877	-1.10833
C	-5.42164	-0.72138	0.459232	C	5.404406	-1.05401	-0.24764
C	-6.44648	0.108514	-0.02555	C	6.499112	-0.32952	0.254833
C	-6.13328	1.1714	-0.8908	C	6.27778	0.848993	0.986791
C	-4.79978	1.398804	-1.28634	C	4.964288	1.300026	1.230051
C	-3.79347	0.586841	-0.79316	C	3.893611	0.594576	0.711694
O	-5.76418	-1.73654	1.262959	O	5.658999	-2.18988	-0.91106
O	3.370418	-2.54795	-0.07882	O	-2.34288	2.543355	-0.19395
C	3.647869	-3.20162	1.166508	C	-2.14854	3.228965	1.04926
O	5.979621	-1.81424	-0.35043	O	-5.02921	2.965966	-0.01895
C	6.115082	-2.38226	-1.65944	C	-5.17034	3.568716	-1.31168
O	6.66979	0.889392	-0.58113	O	-6.80362	0.805389	-0.05961
C	7.626888	0.5846	0.440602	C	-7.37569	1.412807	1.104984
O	-1.3133	-3.12688	-0.67607	O	1.989514	1.159003	-1.57681
C	-0.50597	-4.12545	-1.27901	C	1.561054	2.388841	-2.14118
O	-7.76057	-0.1455	0.266462	O	7.779975	-0.79674	0.116668
C	-8.15139	0.12637	1.615161	C	8.315932	-0.72741	-1.20735
O	-7.18743	1.918811	-1.30053	O	7.393948	1.479377	1.430324
C	-6.95041	2.987911	-2.20571	C	7.243168	2.654938	2.212888
H	3.883355	4.936145	-0.28086	H	-5.93701	-4.04383	-0.11433
H	3.173533	3.820212	-1.44648	H	-5.02838	-3.25967	-1.40598
H	5.47757	3.095416	-1.1653	H	-6.75052	-1.66981	-0.74747
H	5.406	3.246349	0.570456	H	-6.45326	-1.9233	0.952657
H	1.407977	1.597354	2.169636	H	-1.94078	-2.15573	1.816446
H	0.158783	2.497295	1.302689	H	-1.33245	-3.43956	0.76523
H	1.2994	-2.46307	-0.79371	H	-0.64071	1.635498	-1.23649
H	-1.6576	0.90914	1.267725	H	0.948913	-2.74357	0.382066
H	2.039947	3.725283	2.553623	H	-3.31884	-3.8535	2.337131
H	3.339314	4.769719	1.987784	H	-5.00619	-4.24483	2.022895
H	3.658591	3.047982	2.28429	H	-4.5366	-2.56206	2.342228
H	-4.55601	2.201807	-1.96996	H	4.787742	2.194645	1.813246
H	-2.77077	0.760496	-1.10643	H	2.886776	0.944848	0.903647
H	3.038024	-2.77724	1.972529	H	-1.66996	2.572223	1.78545
H	3.382813	-4.25175	1.027859	H	-1.4887	4.072386	0.834865
H	4.709549	-3.12217	1.418655	H	-3.09968	3.599552	1.44244
H	6.392631	-1.61349	-2.38957	H	-5.87758	3.003252	-1.92877
H	6.913695	-3.1239	-1.59157	H	-5.55991	4.574601	-1.14162
H	5.18575	-2.8716	-1.96828	H	-4.20154	3.632059	-1.81813
H	8.579359	0.989007	0.092195	H	-8.4497	1.472901	0.91788
H	7.355302	1.068644	1.387197	H	-7.1997	0.794935	1.99458
H	7.714434	-0.49397	0.592846	H	-6.97109	2.414914	1.268513
H	-1.18634	-4.93419	-1.54866	H	2.454644	2.846295	-2.56787
H	-0.0076	-3.7539	-2.18339	H	0.819002	2.233101	-2.93387

H	0.252653	-4.50649	-0.58418	H	1.137125	3.059363	-1.38308
H	-9.21913	-0.09529	1.670989	H	9.338813	-1.10367	-1.13973
H	-7.60924	-0.50848	2.322344	H	7.743239	-1.34954	-1.90166
H	-7.98968	1.182563	1.865688	H	8.336802	0.308537	-1.56922
H	-7.92638	3.435492	-2.39719	H	8.255092	2.977724	2.460835
H	-6.28388	3.744892	-1.77415	H	6.736276	3.452157	1.654933
H	-6.52545	2.629894	-3.15128	H	6.690466	2.456074	3.139156
H	-4.9123	-2.21963	1.459164	H	4.765198	-2.57508	-1.13045
1 (6a*S*)-c				**1 (6a*S*)-d**			
C	-4.54484	1.652131	0.08137	C	4.742734	1.421261	0.056659
C	-3.15426	1.445115	-0.00061	C	3.391278	1.344251	-0.313
C	-2.6322	0.131216	-0.091	C	2.662079	0.14888	-0.15117
C	-3.53892	-0.95819	-0.06285	C	3.353802	-0.98142	0.359236
C	-4.9241	-0.75568	-0.02276	C	4.692782	-0.90222	0.762821
C	-5.41131	0.552206	0.076585	C	5.387464	0.30714	0.600835
C	-2.98529	-2.38841	-0.1131	C	2.595864	-2.30858	0.497358
N	-3.94806	-3.43011	0.267176	N	3.456754	-3.484	0.679176
C	-5.2005	-3.22133	-0.45956	C	4.424285	-3.21201	1.742436
C	-5.90352	-1.91211	-0.07349	C	5.406351	-2.08551	1.387398
C	-1.1779	-0.16683	-0.23414	C	1.211251	0.01696	-0.45637
C	-0.71219	-1.44436	0.147487	C	0.689641	-1.27166	-0.70198
C	-1.68914	-2.45146	0.695798	C	1.619846	-2.45774	-0.67169
C	-0.2563	0.734268	-0.79833	C	0.330575	1.113784	-0.46476
C	1.093971	0.4086	-0.93246	C	-1.03255	0.94546	-0.71707
C	1.568434	-0.84449	-0.49758	C	-1.55686	-0.34059	-0.95464
C	0.63585	-1.75796	0.00004	C	-0.66901	-1.42005	-0.96612
C	-4.15888	-3.61366	1.701708	C	4.088742	-4.00626	-0.53114
H	-2.71519	-2.59839	-1.16098	H	1.984639	-2.24164	1.412314
C	2.989581	-1.30431	-0.63973	C	-2.9952	-0.61392	-1.28712
C	4.103295	-0.55974	-0.05152	C	-4.08169	-0.22537	-0.38784
O	3.181679	-2.38993	-1.22616	O	-3.22629	-1.24868	-2.33705
C	5.436886	-1.01833	-0.27565	C	-5.43174	-0.44729	-0.79661
C	6.526181	-0.32074	0.273954	C	-6.49444	-0.0819	0.047049
C	6.296704	0.810782	1.074491	C	-6.22427	0.469612	1.310451
C	4.980372	1.241205	1.338636	C	-4.89345	0.673368	1.728961
C	3.914745	0.563185	0.77501	C	-3.85324	0.32767	0.885552
O	5.698801	-2.11062	-1.00639	O	-5.73452	-1.00312	-1.9776
O	-2.26536	2.481594	0.104584	O	2.802421	2.49563	-0.79859
C	-2.48787	3.704906	-0.59752	C	3.116197	2.790167	-2.16624
O	-5.03275	2.932022	0.255274	O	5.438987	2.597065	-0.13327
C	-5.86366	3.431561	-0.80295	C	5.276038	3.543967	0.930243
O	-6.77706	0.747364	0.156048	O	6.683505	0.38968	1.053915
C	-7.2486	1.104013	1.462419	C	7.687582	0.582642	0.050089

O	2.015666	1.236739	-1.51122	O	-1.9193	1.982803	-0.77705
C	1.593904	2.500838	-1.99493	C	-1.443	3.30307	-0.56641
O	7.809737	-0.77325	0.111699	O	-7.79579	-0.21376	-0.36309
C	8.350176	-0.61423	-1.20254	C	-8.29626	-1.55337	-0.36892
O	7.408456	1.417822	1.55985	O	-7.31362	0.76581	2.06247
C	7.249241	2.541245	2.414059	C	-7.11586	1.341412	3.34582
H	-5.86237	-4.07686	-0.28409	H	4.96892	-4.13422	1.974093
H	-4.96435	-3.21234	-1.53131	H	3.858714	-2.939	2.642472
H	-6.70707	-1.68235	-0.78138	H	5.952737	-1.75577	2.277273
H	-6.39695	-2.02575	0.900974	H	6.174077	-2.45876	0.696353
H	-1.89907	-2.22753	1.750559	H	2.178436	-2.51289	-1.61595
H	-1.2712	-3.4619	0.651069	H	1.058387	-3.3914	-0.56894
H	-0.60617	1.695131	-1.13536	H	0.729022	2.099145	-0.28351
H	0.988117	-2.74616	0.280546	H	-1.06734	-2.40819	-1.17705
H	-3.24744	-3.98629	2.175333	H	3.333907	-4.4094	-1.21058
H	-4.93083	-4.37742	1.839933	H	4.743165	-4.83588	-0.24545
H	-4.47778	-2.7094	2.248876	H	4.69597	-3.277	-1.09502
H	4.797328	2.098251	1.973956	H	-4.67915	1.086172	2.706322
H	2.905408	0.896386	0.984319	H	-2.83252	0.474201	1.217475
H	-3.13926	4.377467	-0.03754	H	2.756269	1.99409	-2.82843
H	-1.50172	4.163089	-0.71616	H	2.598359	3.721164	-2.40614
H	-2.91645	3.524397	-1.59035	H	4.193688	2.92679	-2.29692
H	-6.74264	2.800009	-0.94906	H	5.637516	3.12966	1.878198
H	-6.17104	4.433829	-0.49761	H	5.877208	4.415095	0.661582
H	-5.30186	3.496789	-1.74311	H	4.226419	3.839752	1.02915
H	-8.33345	1.197304	1.381729	H	8.643846	0.591468	0.576963
H	-7.00554	0.322292	2.192156	H	7.682053	-0.24383	-0.67164
H	-6.8179	2.054465	1.792364	H	7.544836	1.529949	-0.47586
H	2.487295	2.976297	-2.40216	H	-2.31356	3.952029	-0.66968
H	0.843567	2.401281	-2.78949	H	-1.01553	3.426381	0.43661
H	1.184819	3.127904	-1.19222	H	-0.68902	3.584299	-1.31182
H	9.372627	-0.9951	-1.15766	H	-9.33816	-1.48687	-0.6891
H	7.77935	-1.18714	-1.93953	H	-7.73899	-2.18225	-1.07008
H	8.372857	0.443989	-1.49289	H	-8.25594	-1.99284	0.635893
H	8.258684	2.85186	2.686501	H	-8.11382	1.501575	3.755771
H	6.741298	3.369971	1.905116	H	-6.55599	0.671032	4.009727
H	6.693296	2.282223	3.323369	H	-6.59336	2.303619	3.281098
H	4.807364	-2.48611	-1.25073	H	-4.85898	-1.24237	-2.39024
1 (6a*S*)-e				**1 (6a*S*)-f**			
C	-4.59805	1.604673	0.12635	C	-4.55947	1.659738	-0.0335
C	-3.21181	1.385324	0.032823	C	-3.17444	1.438749	-0.11551
C	-2.66916	0.091251	-0.05523	C	-2.64824	0.130419	-0.11431
C	-3.56971	-1.00203	0.02885	C	-3.55111	-0.9524	0.029946

C	-4.95025	-0.80347	0.101155	C	-4.93651	-0.74623	0.042094
C	-5.47186	0.506757	0.150312	C	-5.4333	0.564128	-0.01166
C	-3.00175	-2.42714	-0.00976	C	-2.99031	-2.3779	0.108226
N	-3.93463	-3.46689	0.441462	N	-3.94298	-3.37438	0.61364
C	-5.21643	-3.29002	-0.24208	C	-5.20136	-3.25172	-0.12386
C	-5.91571	-1.97142	0.118235	C	-5.90879	-1.90762	0.107254
C	-1.2203	-0.18448	-0.23859	C	-1.19957	-0.1711	-0.26802
C	-0.72125	-1.44961	0.139297	C	-0.71189	-1.40275	0.219611
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C	1.011635	0.436897	-1.01137	C	1.038221	0.367487	-1.08196
C	1.524399	-0.80481	-0.58344	C	1.541126	-0.83373	-0.5419
C	0.62769	-1.73535	-0.04946	C	0.636998	-1.70994	0.066423
C	-4.0885	-3.60198	1.888971	C	-4.14224	-3.38859	2.061685
H	-2.78055	-2.66052	-1.06408	H	-2.74711	-2.69227	-0.91974
C	2.947542	-1.23979	-0.77419	C	2.963758	-1.28977	-0.6854
C	4.070927	-0.46325	-0.24742	C	4.086359	-0.47655	-0.21638
O	3.137795	-2.33342	-1.3461	O	3.152263	-2.42774	-1.1633
C	5.402668	-0.89113	-0.53442	C	5.418366	-0.93285	-0.45433
C	6.500051	-0.16319	-0.04382	C	6.515194	-0.17138	-0.01598
C	6.283814	0.966289	0.762501	C	6.297399	1.023624	0.689358
C	4.971914	1.381992	1.068583	C	4.984966	1.46987	0.946289
C	3.896902	0.671529	0.56567	C	3.910842	0.724049	0.495712
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O	-5.0853	2.885742	0.295723	O	-5.01591	2.957734	-0.04306
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C	-7.57356	1.689807	-0.21183	C	-7.34843	1.306097	-1.19683
O	1.894788	1.279234	-1.62524	O	1.928363	1.146756	-1.76377
C	1.419878	2.515137	-2.13599	C	1.461363	2.334793	-2.38584
O	7.782422	-0.51479	-0.37726	O	7.798954	-0.55404	-0.30642
C	8.286981	-1.67092	0.296398	C	8.289495	-1.6598	0.456404
O	7.404228	1.587165	1.209614	O	7.416738	1.675363	1.092617
C	7.260223	2.747302	2.016128	C	7.271992	2.902196	1.793469
H	-5.86544	-4.14149	-0.00839	H	-5.86054	-4.08132	0.155377
H	-5.0218	-3.32194	-1.32177	H	-4.97117	-3.36996	-1.19037
H	-6.74121	-1.77447	-0.57445	H	-6.70876	-1.76661	-0.62776
H	-6.38455	-2.04472	1.108419	H	-6.41157	-1.90558	1.083158
H	-1.82795	-2.23275	1.797517	H	-1.85258	-2.0426	1.918628
H	-1.23924	-3.46965	0.681752	H	-1.24825	-3.3696	0.919813
H	-0.73045	1.685423	-1.16908	H	-0.69777	1.607165	-1.35615

H	1.011037	-2.71397	0.224042	H	1.01356	-2.6629	0.426266
H	-3.15615	-3.95178	2.338958	H	-3.22541	-3.70144	2.567412
H	-4.84791	-4.36601	2.083192	H	-4.91062	-4.13221	2.295775
H	-4.39431	-2.68159	2.41577	H	-4.45912	-2.42653	2.50048
H	4.799554	2.243682	1.700661	H	4.811462	2.38324	1.500555
H	2.891167	0.988382	0.81368	H	2.904654	1.065612	0.70633
H	-1.56288	2.240408	1.946921	H	-1.37051	2.399541	1.611284
H	-1.4829	3.87695	1.237386	H	-1.31948	3.973986	0.770017
H	-3.03111	3.266992	1.887546	H	-2.81105	3.46071	1.597138
H	-5.46899	3.388669	-1.70028	H	-5.15403	3.25818	2.023156
H	-5.37178	4.721493	-0.51793	H	-6.00098	4.41575	0.962137
H	-3.87797	3.91083	-1.07262	H	-6.67814	2.780667	1.228139
H	-7.47416	2.566169	0.43038	H	-8.42622	1.374494	-1.03721
H	-7.26945	1.94984	-1.2325	H	-6.9377	2.299566	-1.39882
H	-8.61321	1.354993	-0.22727	H	-7.14939	0.650331	-2.05292
H	2.286848	3.004129	-2.58207	H	2.332462	2.776778	-2.87102
H	0.651472	2.365939	-2.90452	H	0.694346	2.120526	-3.13988
H	1.011237	3.154134	-1.34292	H	1.05407	3.044219	-1.65459
H	9.311969	-1.80463	-0.05576	H	9.319618	-1.81967	0.131203
H	8.296785	-1.51994	1.38339	H	8.282409	-1.43129	1.529797
H	7.698712	-2.56082	0.05201	H	7.702908	-2.56401	0.267014
H	8.274386	3.078134	2.243481	H	8.285963	3.247544	1.998992
H	6.730426	3.546602	1.483655	H	6.749979	3.65389	1.18892
H	6.733352	2.527831	2.95309	H	6.737246	2.767668	2.741967
H	4.764282	-2.38583	-1.46035	H	4.780628	-2.49663	-1.2594

For the calculations of ^{13}C NMR chemical shifts, B3LYP/6-31G (d, p) method was used to optimize the selected conformations. For all optimized structures, vibrational spectra were calculated to ensure that no imaginary frequencies for energy minimum were obtained. NMR calculations were performed at the levels of mPW1PW91/6-31G (d, p) with the gauge-independent atomic orbital (GIAO) method.[2] The solvent effect was considered by using chloroform in the calculations to resemble the experimental condition. The polarized continuum model (PCM) of Tomasietal was used.[3] These calculated ^{13}C NMR chemical shifts were analyzed by subtracting the isotopic shifts for TMS calculated with the same methods.[4] Different conformers for structure **1** were considered. The ^{13}C NMR chemical shifts in each compound were considered as the average values of the same atoms in the different conformers. The average values were obtained by the Boltzmann distributions, using the relative Gibbs free energies as weighting factors.[5] These differences $\Delta\delta$ were determined by subtracting the experimental chemical shifts δexptl from the calculated chemical shifts δcalcd (see Table S1).

2. Antibacterial assays

2.1 Micoorganism strains and growth conditions:

The microorganisms used in antibacterial assays were obtained from the American Type Culture Collection (ATCC) (*Staphyloccus aureus* ATCC 25922, *Escherichia coli* ATCC 8739, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC2002 and *Trichophyton rubrum* ATCC 28188. The culture media: Lysogeny Broth (LB, Conda) was used for culturing bacteria and Salouraud liquid medium broth for fungus, while Mueller Hinton Broth (MHB, Conda) was used for the determination of minimum inhibitory.

2.2 Determination of minimum inhibitory concentration (MIC):

The inocula of bacteria were prepared from 24 h old agar cultures, were incubated to logarithmic phase. Berberine have long been used clinically for infection diseases, was used as positive reference substances. Finally, to measure the MIC value of compounds by the broth microdilution method in 96-well micro-titre plates as described in the literature.[6] The MIC was defined as the lowest concentration without any colony growth after and incubating fungus at 28°C for 16 h, respectively. All tests were performed in thrice, the values as shown in Table 2.

3. Cytotoxic assays

3.1 Cell lines and cultures

Human normal cell lines 293T and GES cells were established from Kunming Institute of Zoology, and were cultured in DMEM complete medium.

3.2 Cell viability assay by MTS method

The human normal cell 293T and GES were seeded on laminin pre-coated 96-well-plate with 20,000 cells / well. Compounds **1**, **3** and the positive group were added with a serial dilution (60, 30, 15, 7.5, 3.75, 1.875, 0.937, 0.468 μg/ml) and cultured in cell incubator for 72 h. MTS reagent was diluted 1:5 with fresh medium and subsequently the fresh medium was added with 100 μL/well. The cells were incubated for 1.5 h. Absorbance was measured by Hybrid Reader (BioTek Synergy H1) at 490 nm. The half-maximal inhibitory concentration (IC_{50}) was measured and calculated by Graph Pad Prism 5 software.

4. Antibacterial Kinetics Experiment

The bacteria solution of *Staphyloccus aureus* was prepared from 24 h old agar cultures, was incubated to logarithmic phase. 0.9% sodium chloride solution as negative control. Then three different concentrations of compound **1** (1× MIC, 5× MIC and 10× MIC) were added into tubes containing bacterial inoculumc roughly 1× 10^5 CFU/Ml. All samples were incubated at 37℃ and 180 rpm for 0 min, 1 min, 10 min, 30 min, 1 h and 3 h, followed 10 *μ*L samples were collected from each tube for colony counting were diluted 500 times, after 50 *μ*L diluted bacterial juice samples were collected from different time points, coated on LB plates, at 37℃ incubated for 24 h, count the colonies.[7] At least, two replications were performed for each sample.

5. Scanning Electron Microscopy (SEM)

According to the previous method, *S. aureus* was grown to the exponential-phase in lysogeny broth medium and then centrifuged at 1000 rpm for 5 min. The pellet was then washed with PBS twice and resuspended in LB medium. Compound **1** (10 × MIC) was incubated with *S. aureus* at 37 °C for 1h and then centrifuged at 1000 rpm for 10 min. Negative control group received the same volume of vehicle. The pellet was then washed with PBS twice and resuspended in 2.5% glutaraldehyde solution at 4 °C for 2 h. Then the *S. aureus* were centrifuged (2000 rpm for 0 min) and washed with PBS. The pellet was then fixed in 1% osmium tetroxide in PBS for 1 h. Cells were rinsed with same buffer, dehydrated in a grade series of ethanol, frozen in liquid nitrogen-cooled tert-butyl alcohol, and then vacuum-dried overnight. The samples were mounted onto aluminum stubs. After sputtercoating with gold, they were analyzed by Hitachi S-3000N Scanning Electron Microscope.

6. SYTOX Green Assay

The method[8-9] was used to determine the membrane integrity of *S. aureus* after treatmented by compound **1**. Briefly, collected the exponential-phase *S. aureus* was grown in lysogeny broth medium and then centrifuged at 1000rpm for 10 min. The bacterium pellet was then washed twice, resuspended in PBS (10 mM, pH 7.4) give a cell density of 10^5 CFU/mL, and incubated with SYTOX Green nucleic acid stain at a final concentration of 0.1 μM at 37 °C for 15 min on a shaking table. SYTOX Green-treated *S. aureus* were loaded into a FlexStation microplate reader (Molecular Devices, Sunnyvale, CA), and test samples were added robotically. One hour in the dark, then monitoring was initiated, and the fluorescence of each well was recorded every 2 min using an excitation of 488 nm and emission of 530 nm. Results were determined as relative fluorescence units (RFU).

7. DAPI Staining Assay

The compound **1** was diluted into the concentration of 5× MIC with lysogeny broth medium and added into the bacteria suspension at final concentration of 10^5 CFU/mL. Physiological saline group was used as control. The cultures were incubated at 37 °C and 180 rpm with shaking table for 24 h. Then 1.0 mL suspension was mixed with 1 μg/mL 2-(4-amidinophenyl)-1H-indole-6-carboxami-dine (DAPI), after incubated at room temperature under the dark for 10 min. A small drop of the mixture was dispered on the glass slide to observe DNA fluorescence intensity by Olympus. Japan FV1000.

Reference

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Figure S2. HREIMS spectrum of thalfoetine A (1)

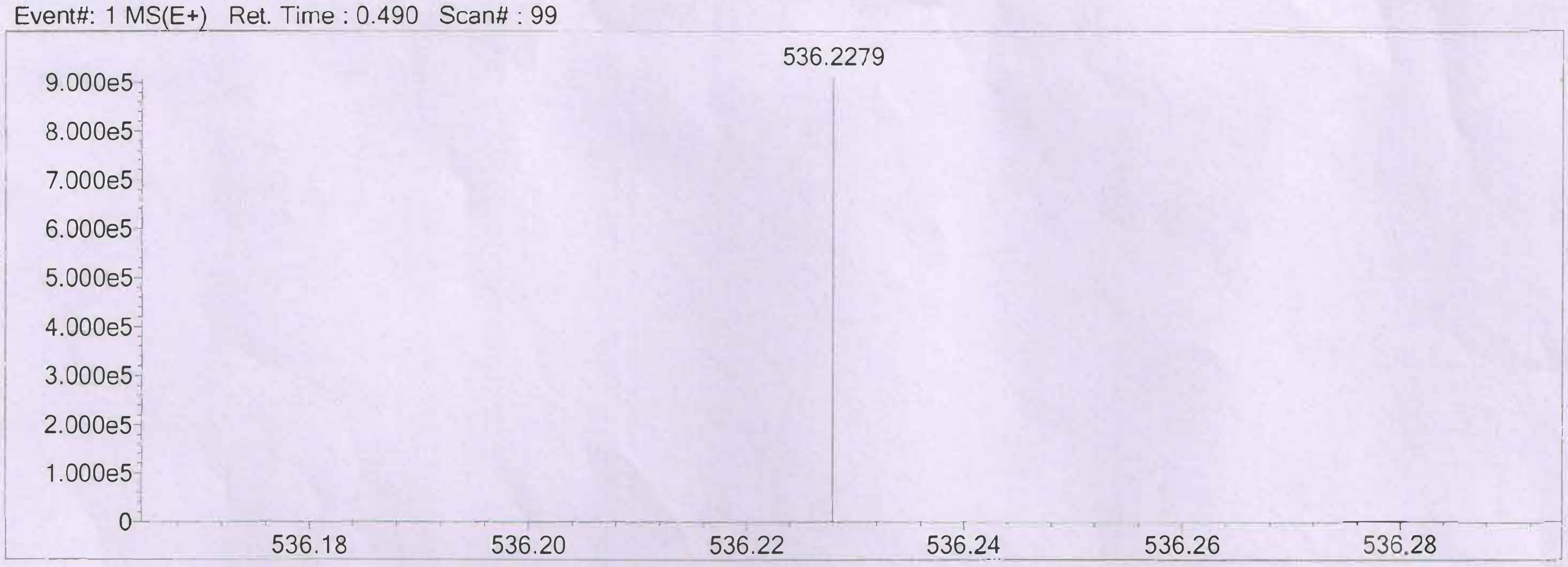
Formula Predictor Report - wtflr-29a.lcd

Data File: E:\DATA\2017\1218\wtflr-29a.lcd

Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	100	O	2	0	50	Cl	1	0	0	H
C	4	0	50	F	1	0	0	Br	1	0	0	
N	3	0	10	S	2	0	0	I	3	0	0	

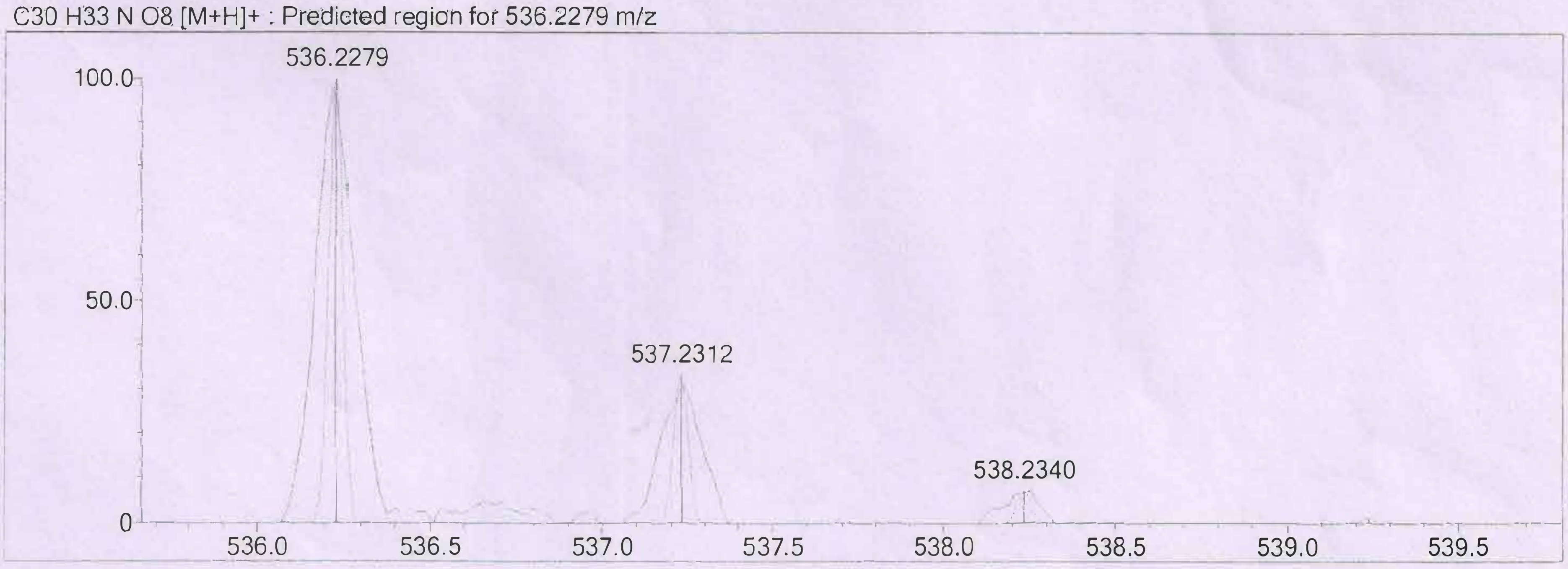
Error Margin (ppm):	5	DBE Range:	-2.0 - 100.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	yes	Use MSn Info:	yes
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	10

Event#: 1 MS(E+) Ret. Time : 0.490 Scan# : 99



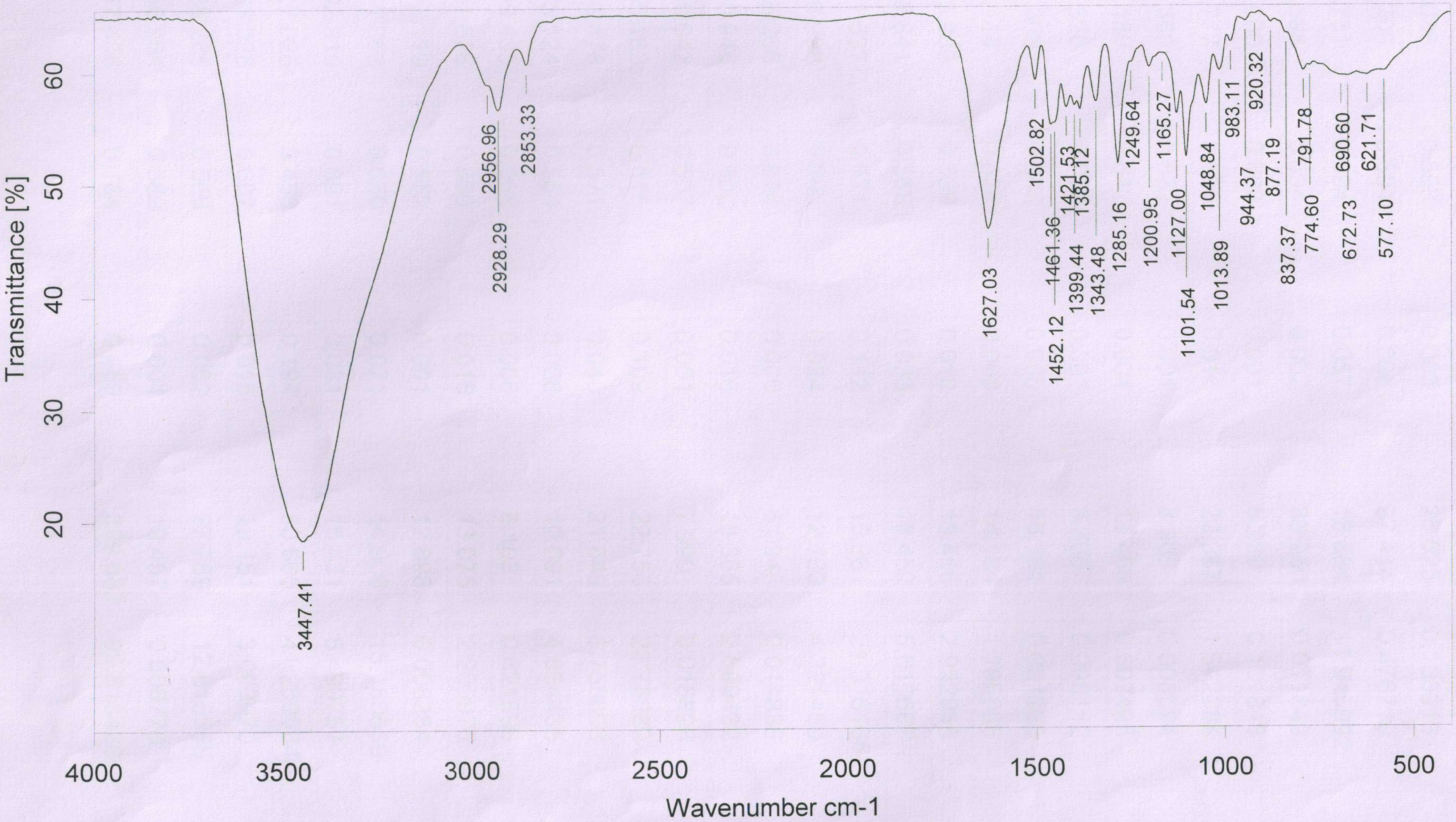
Measured region for 536.2279 m/z

C30 H33 N O8 [M+H]+ : Predicted region for 536.2279 m/z



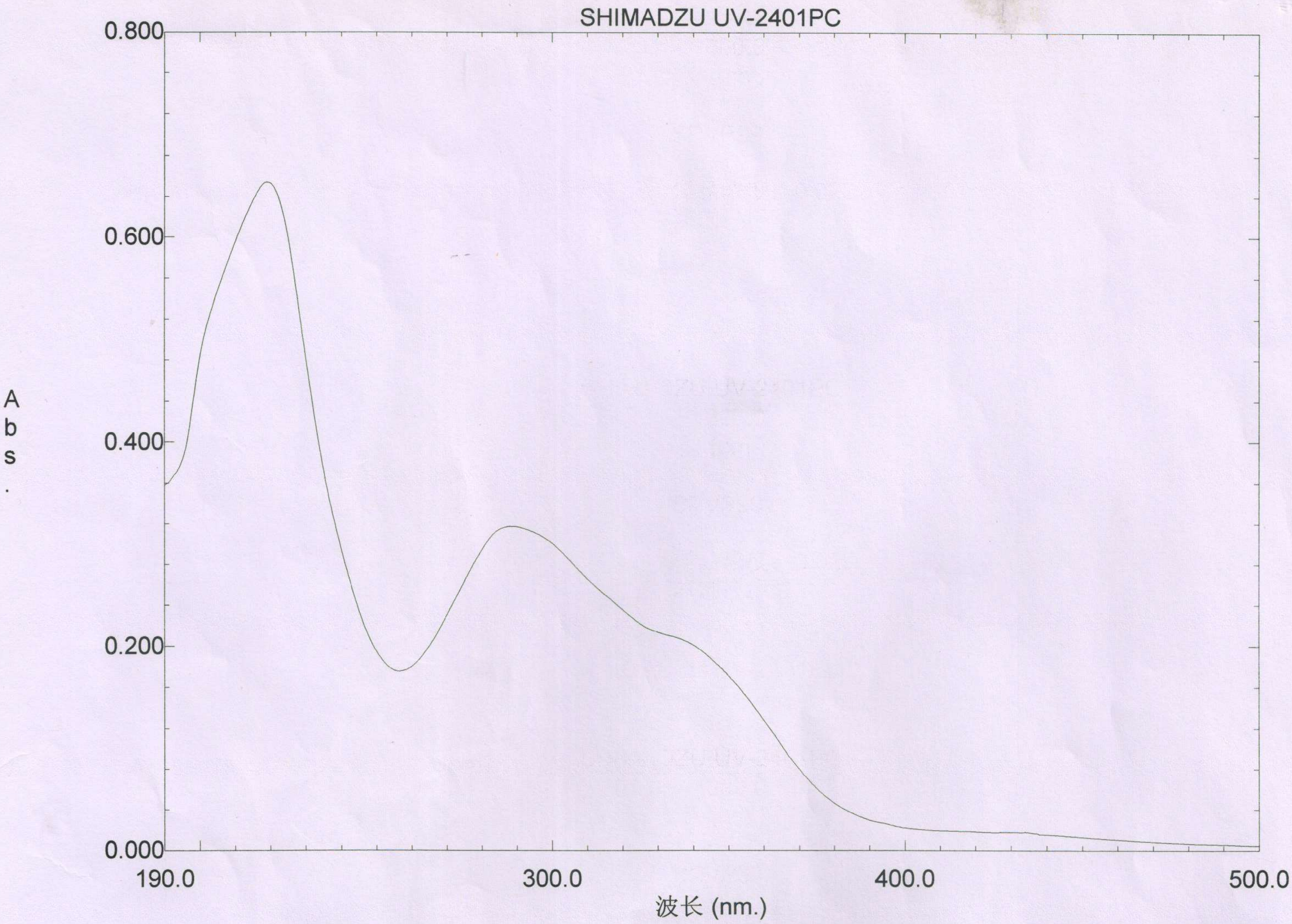
Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	DBE
C30 H33 N O8	[M+H]+	536.2279	536.2279	0.0	0.00	15.0

Figure S3. IR spectrum of thalfoetine A (1)



Sample : wtflr-29a	Frequency Range : 399.246 - 3996.32	Measured on : 28/03/2018	
Technique : KBr	Resolution : 4	Instrument : Tensor27	Sample Scans : 16
Filename : 180328IR.3	Zerofilling : 2	Acquisition : Double Sided,For	

Figure S4. UV spectrum of thalfoetine A (1)



文件名: 18012901
样品名称：WTFLR-29A

创建于: 11:20 18-01-29
数据: 原始

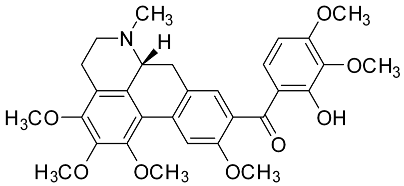
18012901

样品浓度：0.0075毫克/毫升
溶剂：甲醇

测量模式: Abs.
扫描速度: 中速
狭缝: 5.0
采样间隔: 0.5

否.	波长 (nm.)	Abs.
1	219.00	0.6538
2	289.00	0.3174
3	329.50	0.2140

Figure S5. ^{1}H NMR spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



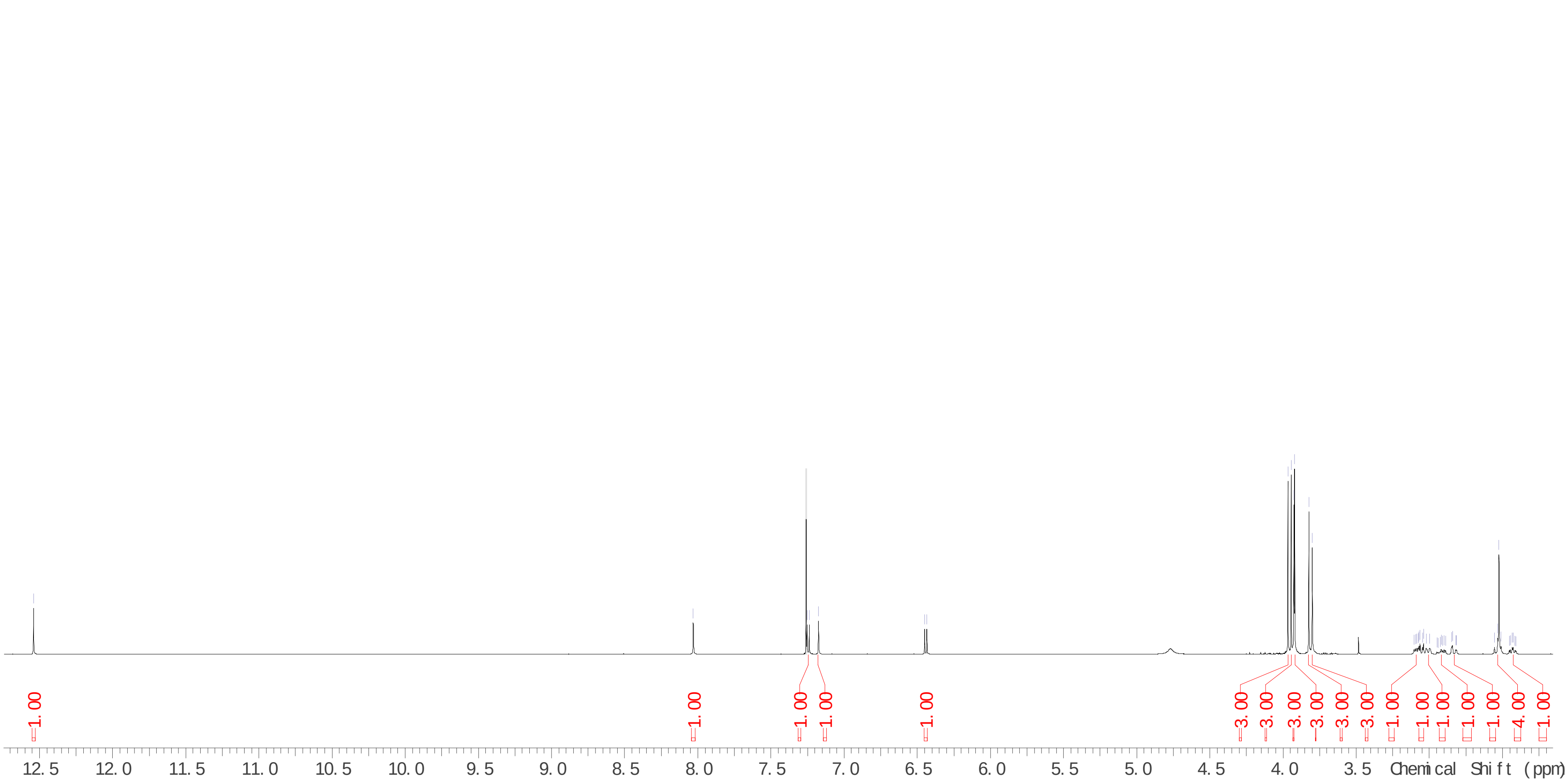


Figure S6. ^{13}C NMR spectrum of thalfoetine A (1) in $CDCl_3$ (150 MHz)

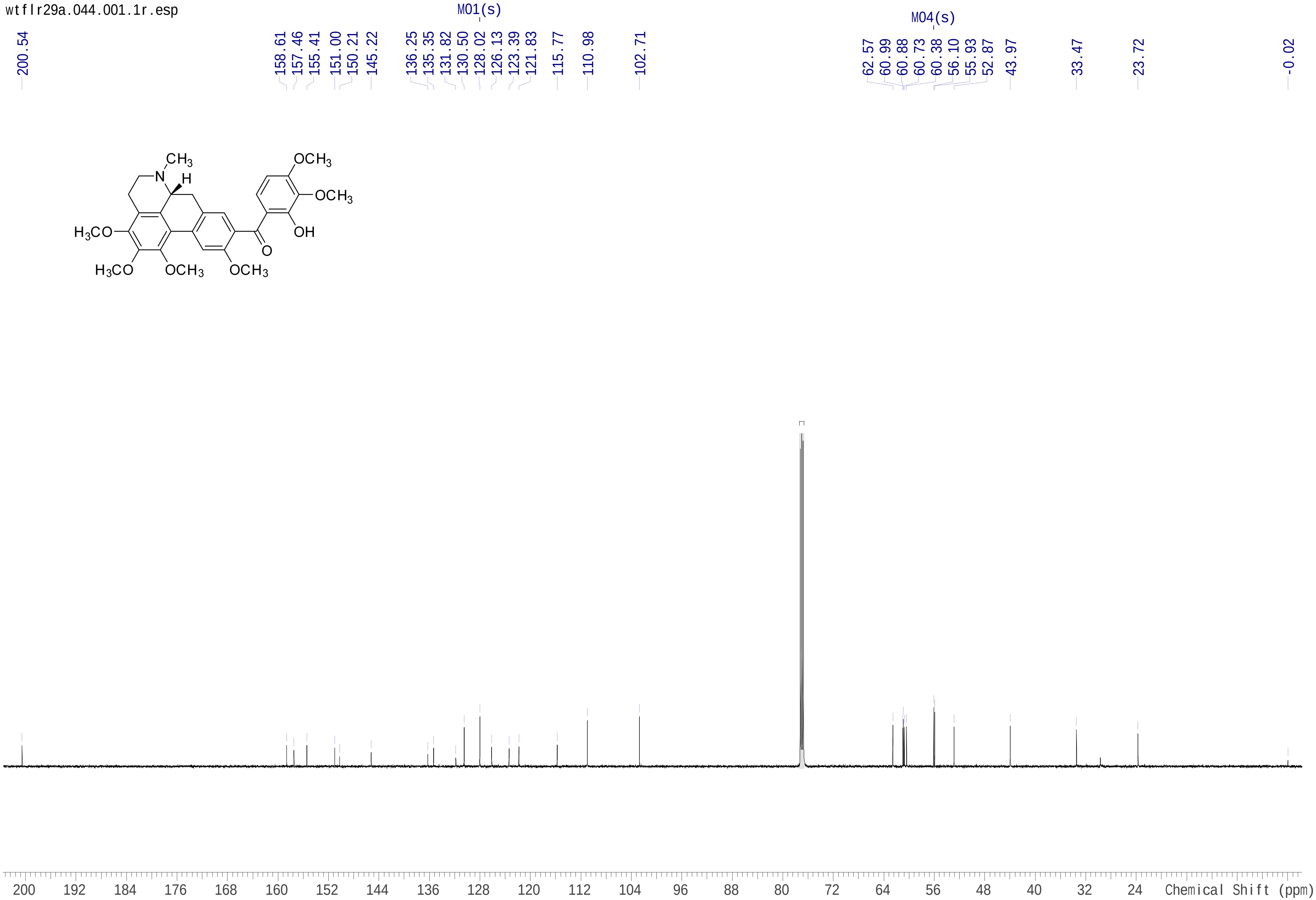


Figure S6-1. DEPT 90 spectrum of thalfoetine A (1) in $CDCl_3$ (150 MHz)

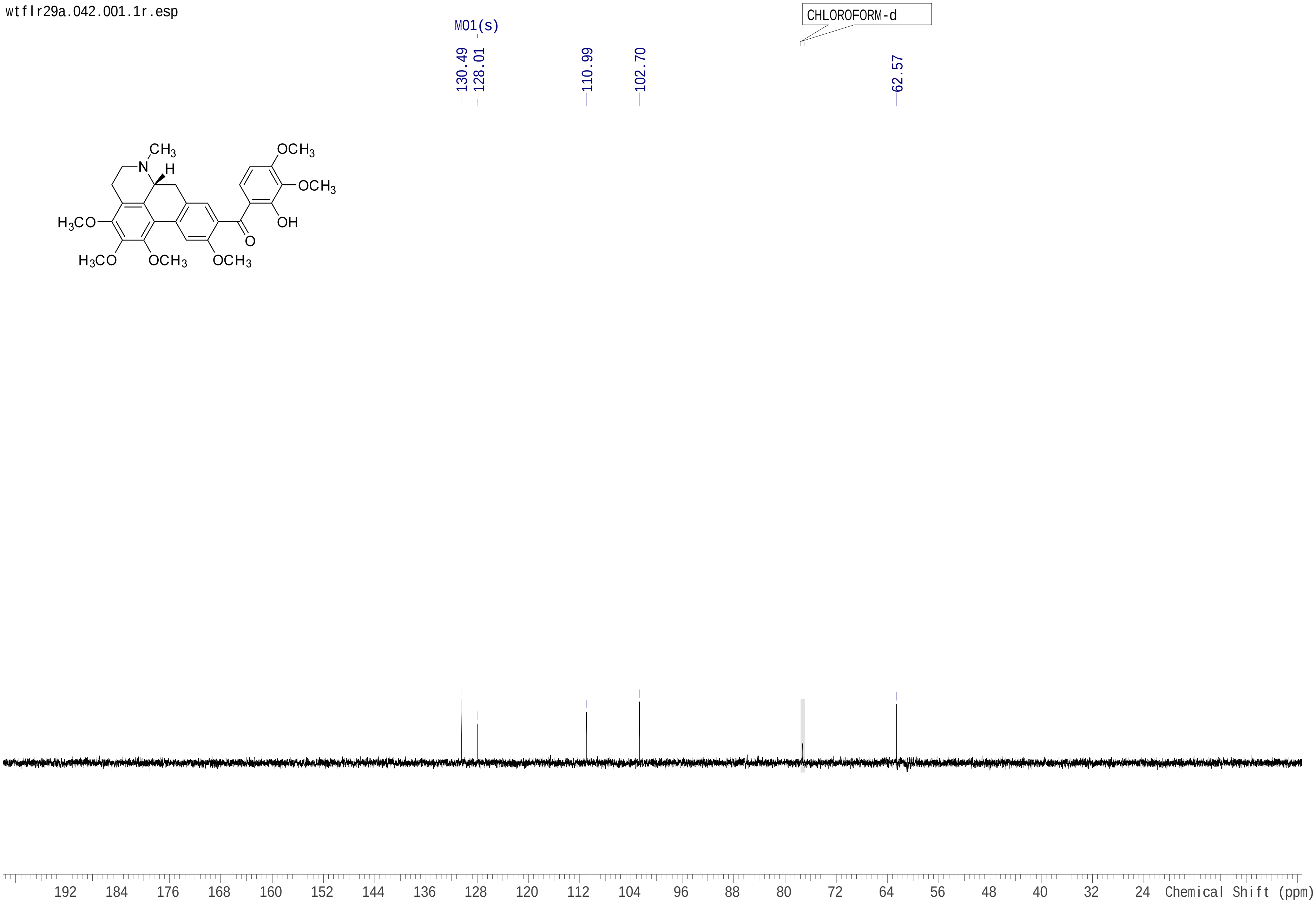


Figure S6-2. DEPT 135 spectrum of thalfoetine A (1) in $CDCl_3$ (150 MHz)

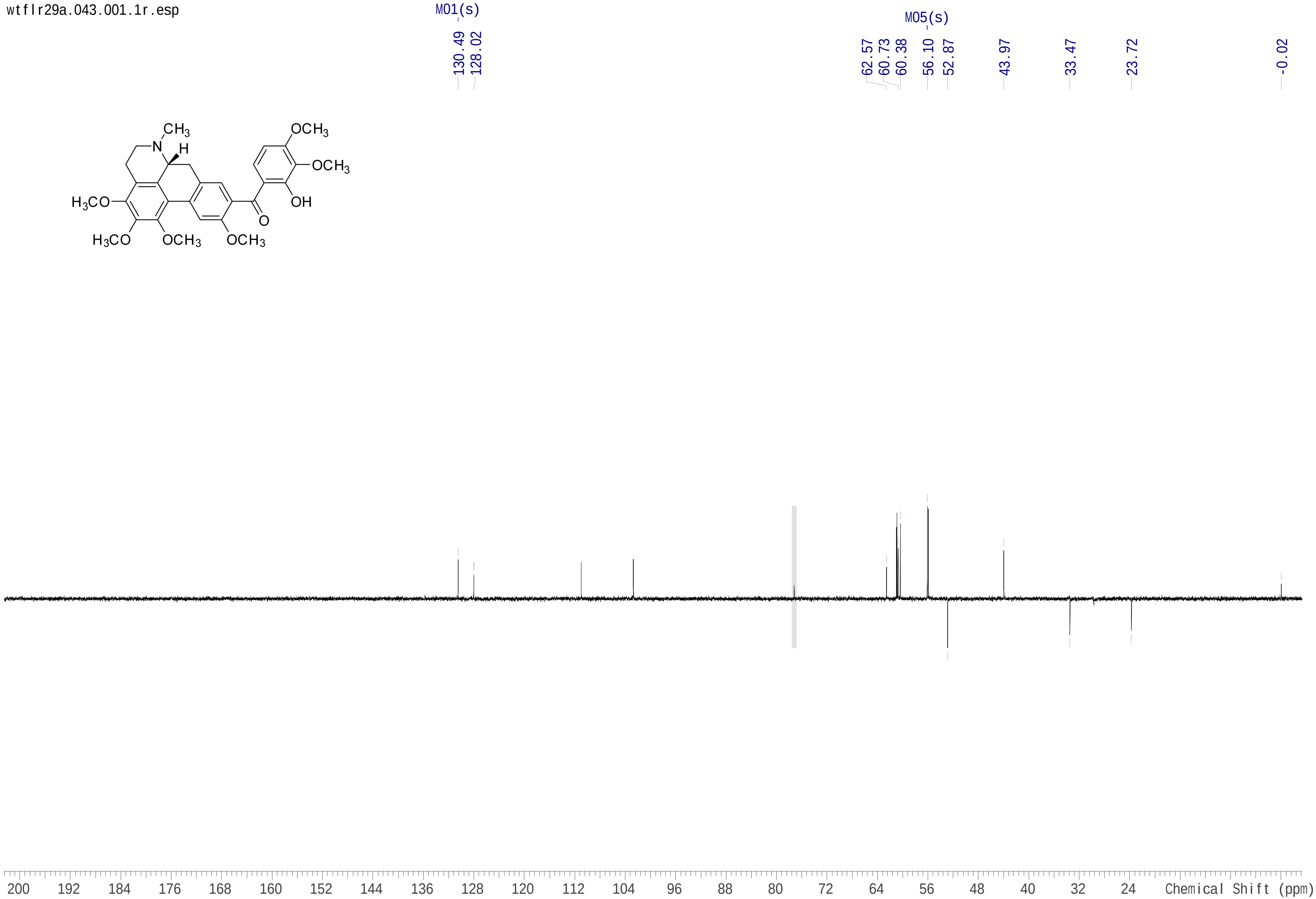
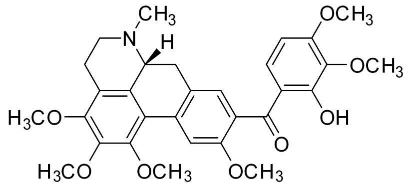


Figure S7. HSQC spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



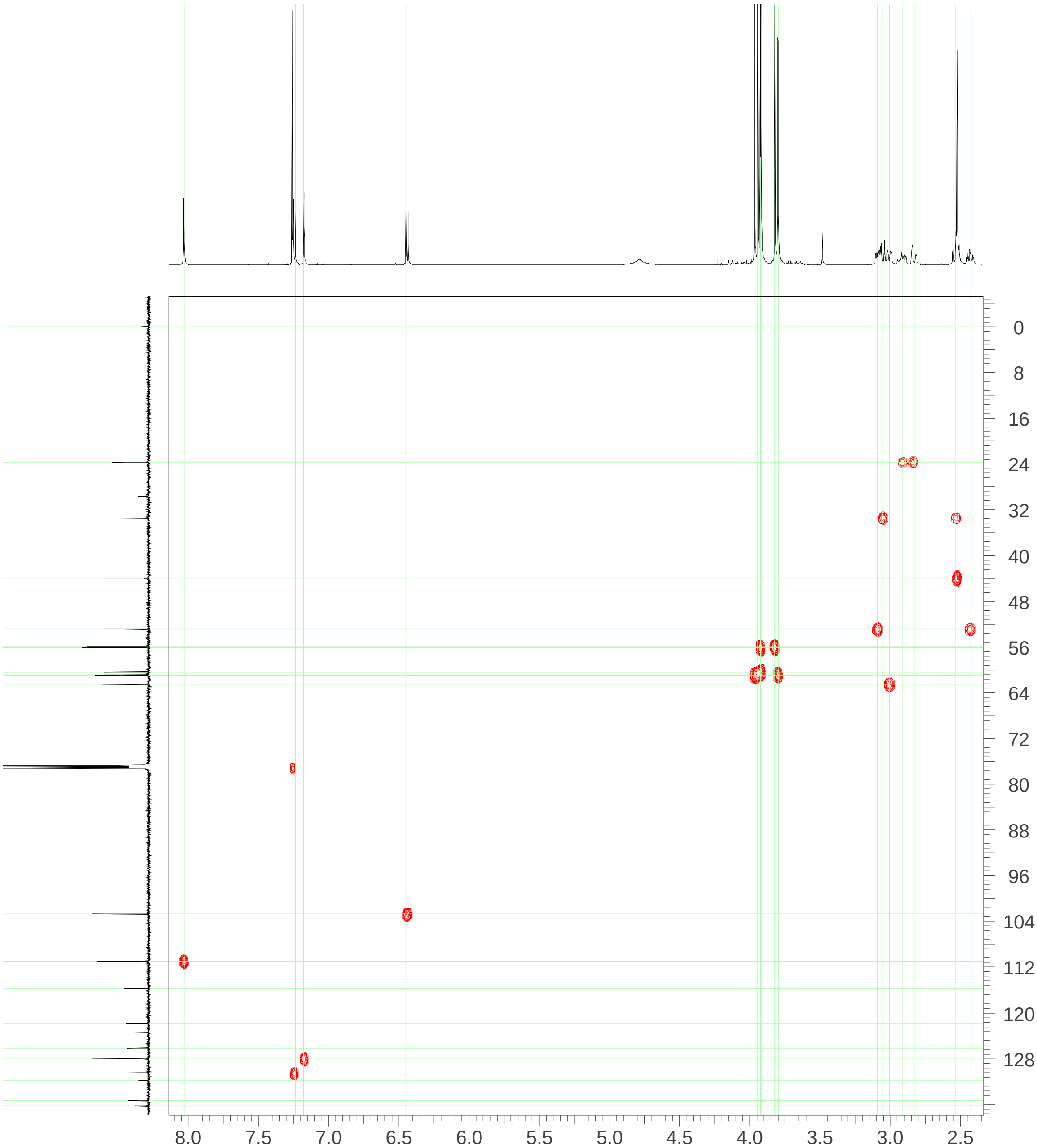
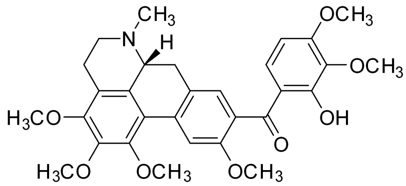


Figure S8. HMBC spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



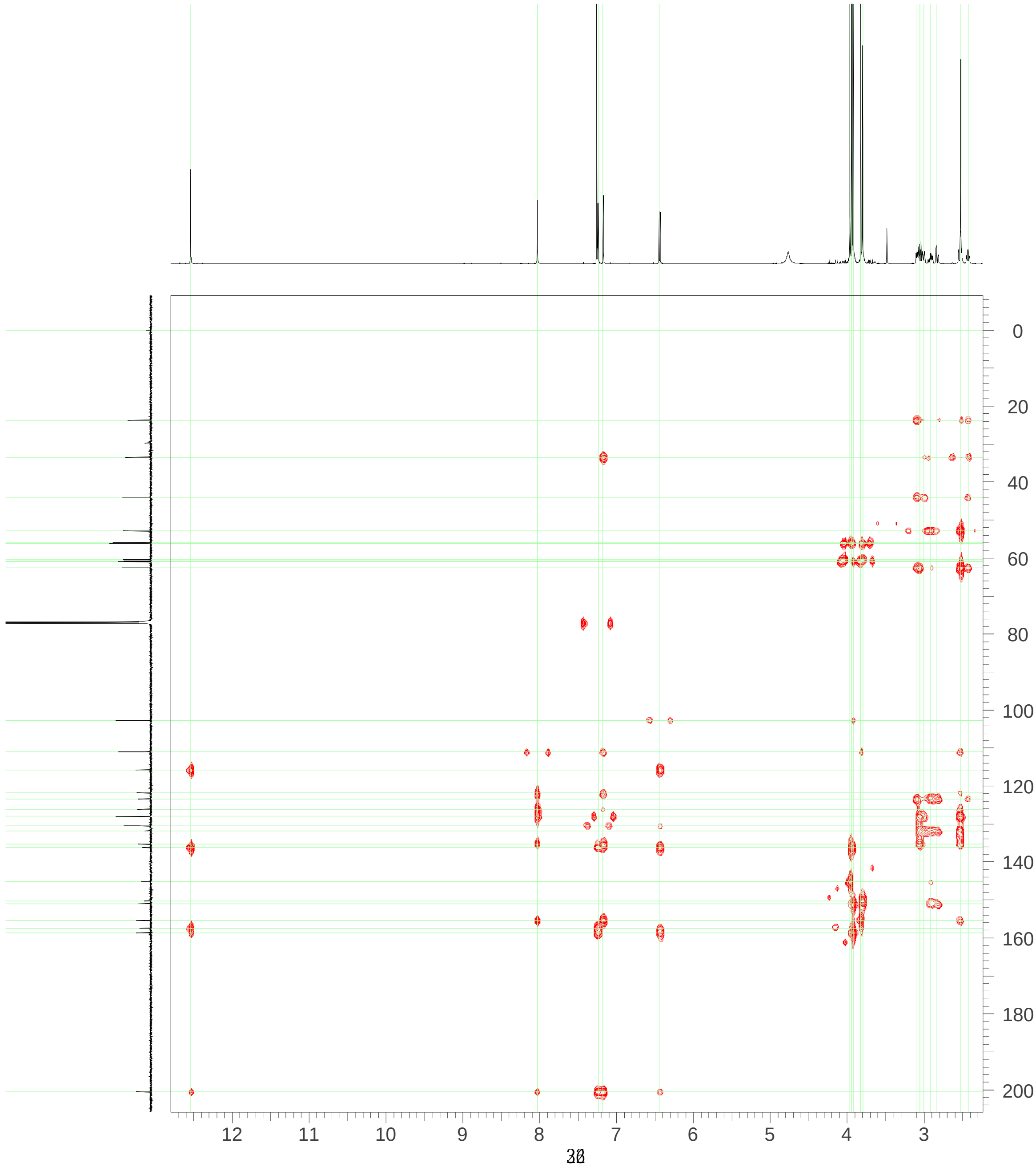
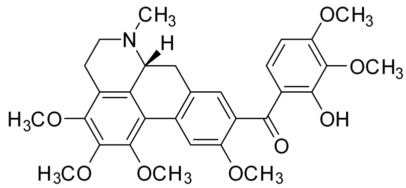


Figure S8-1. The partially enlarged HMBC spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



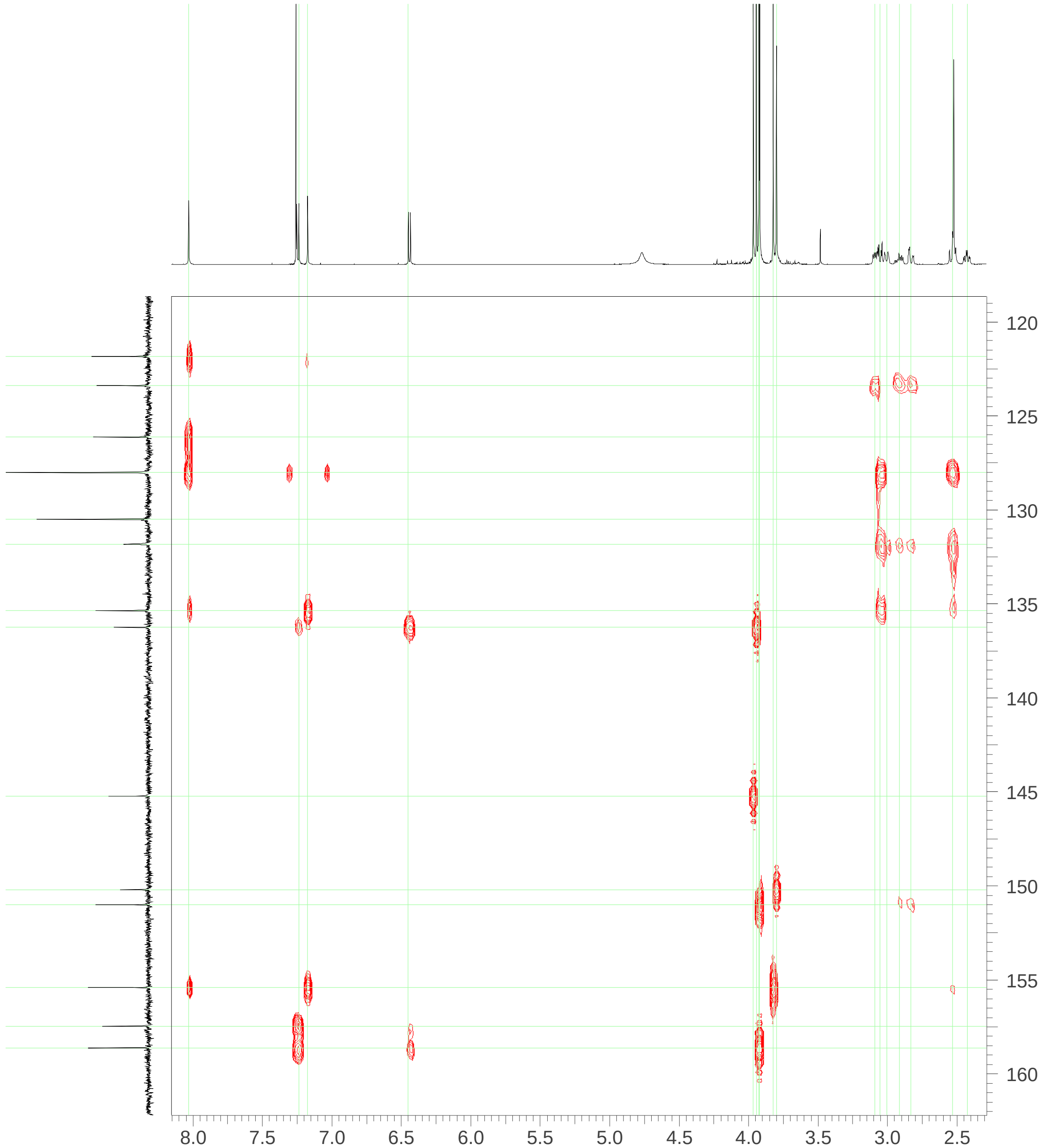
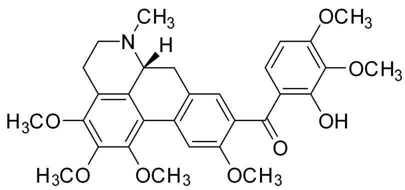


Figure S8-2. The partially enlarged HMBC spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



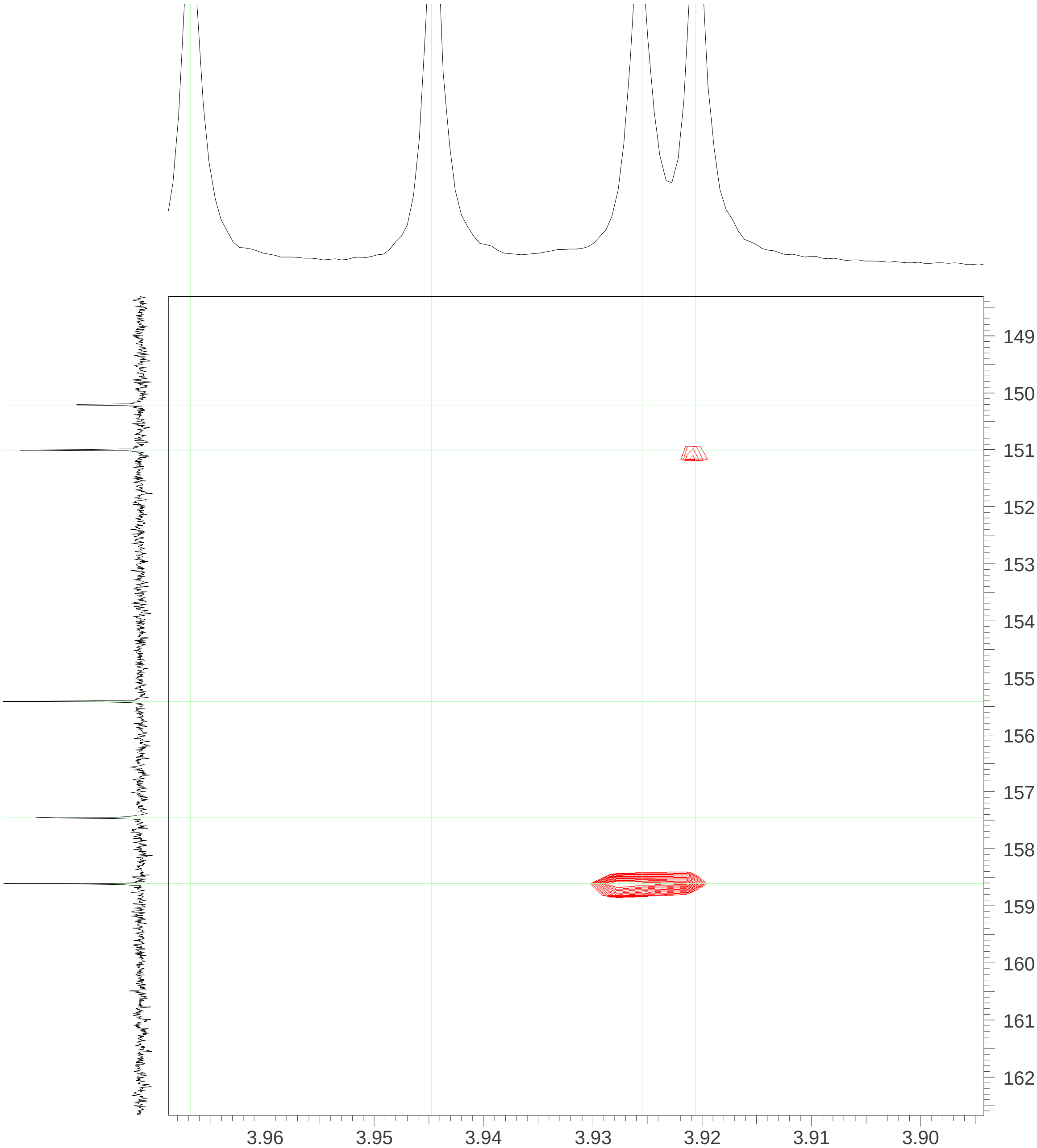
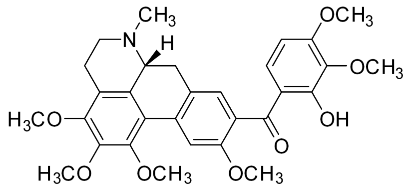


Figure S8-3. The partially enlarged HMBC spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



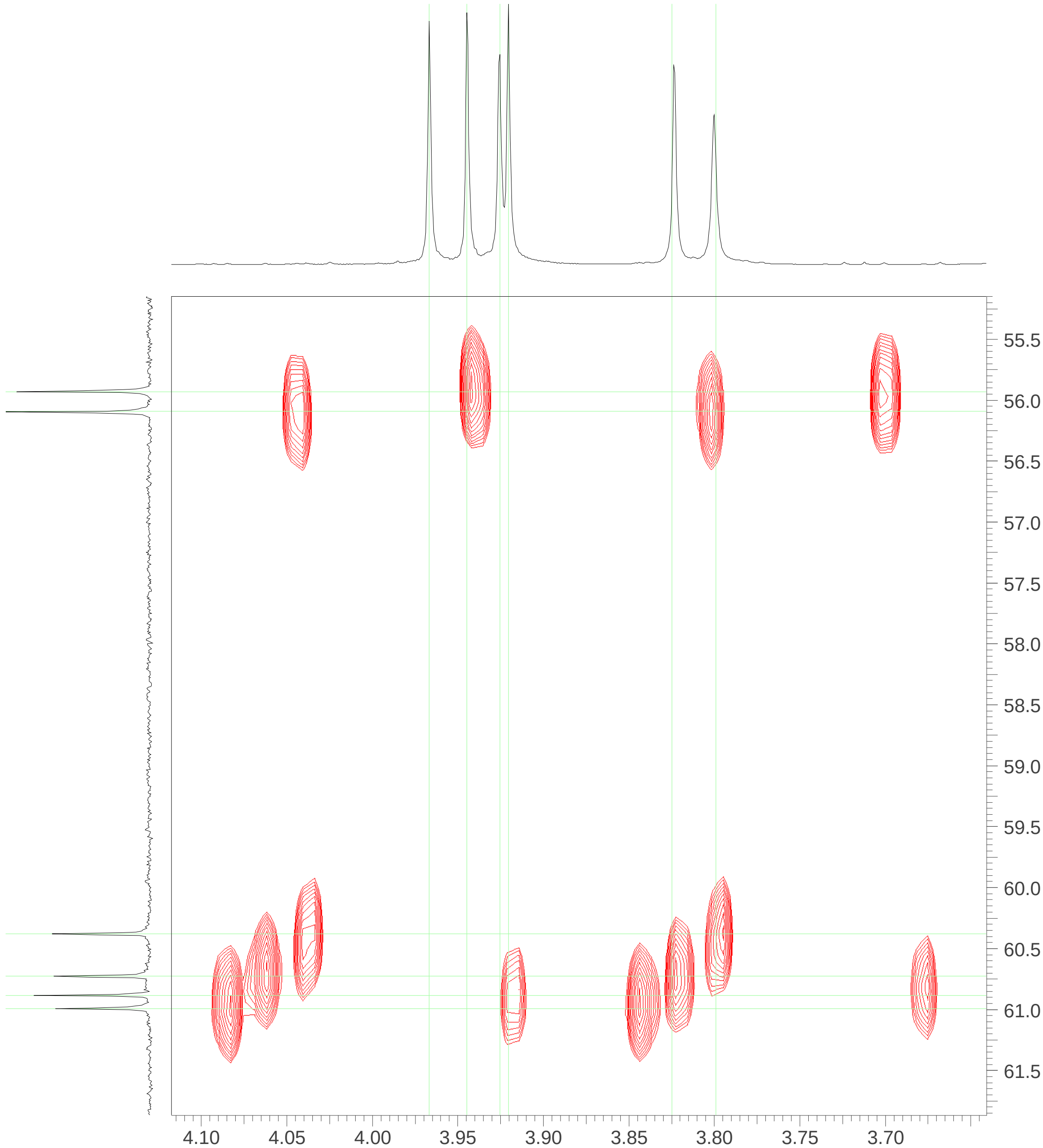
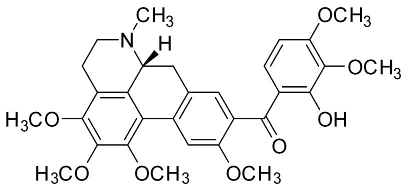


Figure S9. ^{1}H-^{1}H COSY spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



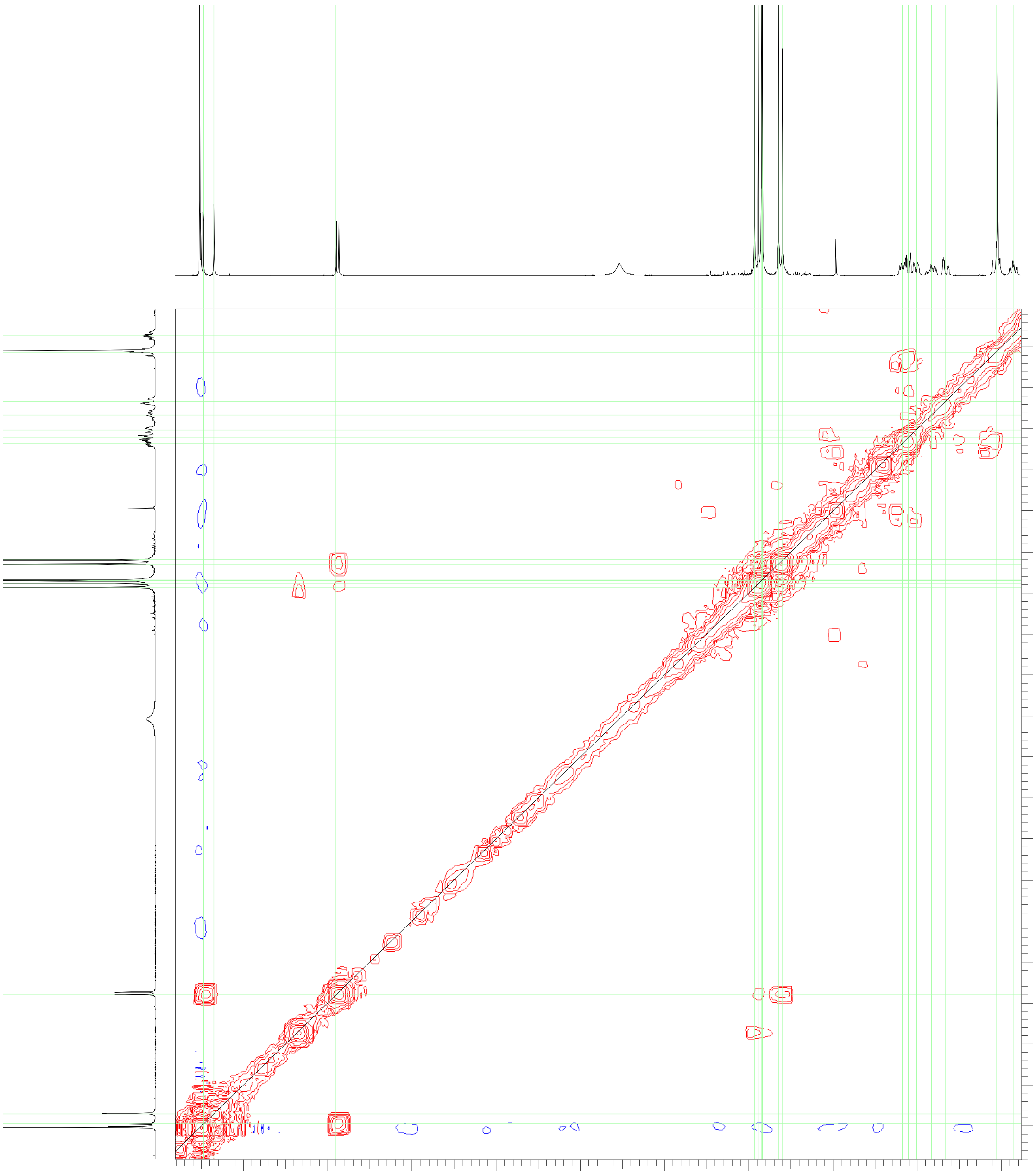
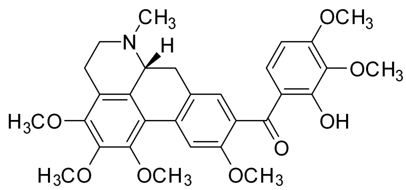


Figure S10. ROESY spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



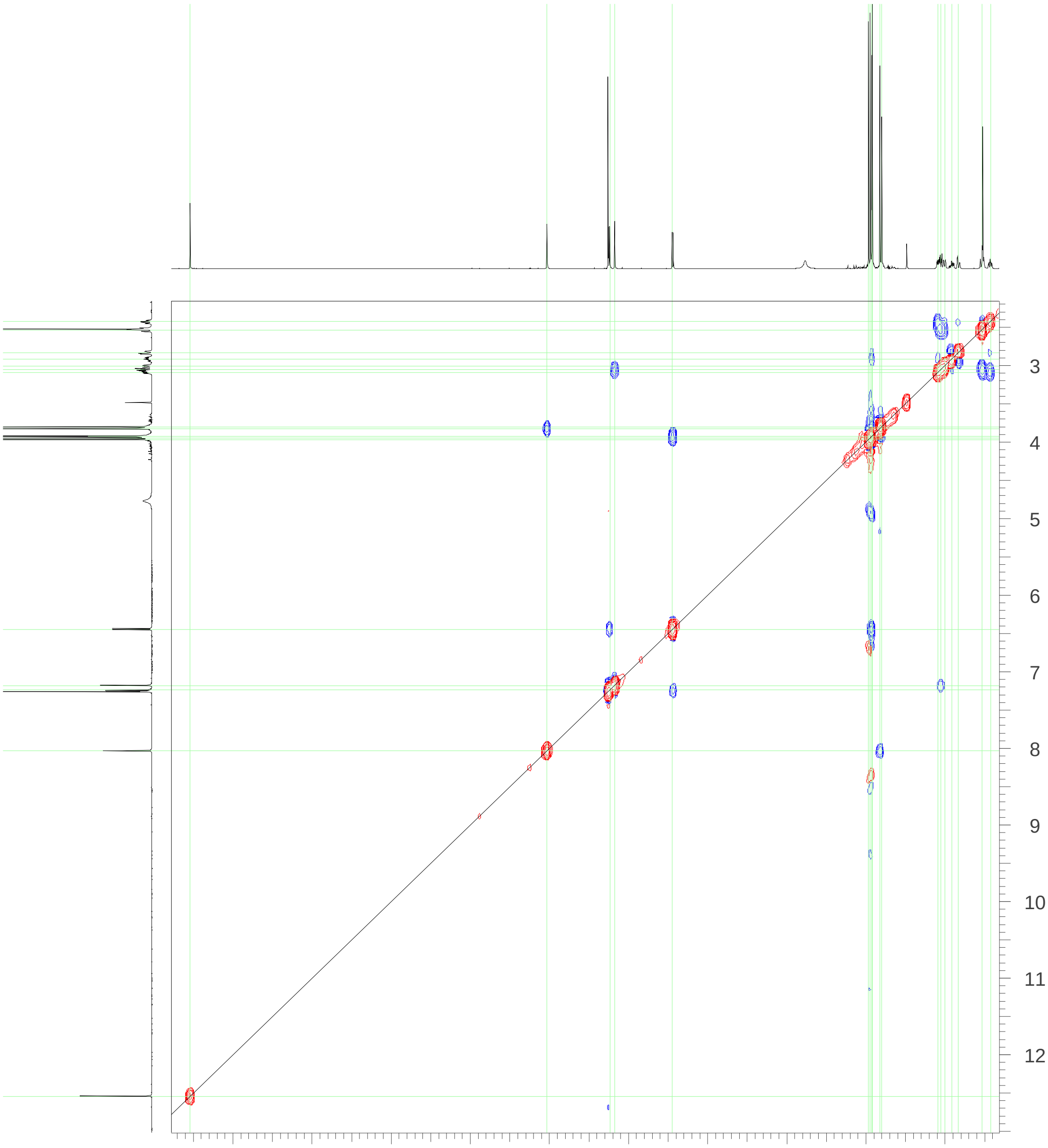
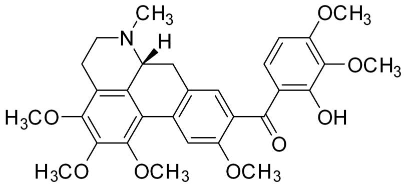


Figure S10-1. The partially enlarged ROESY spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



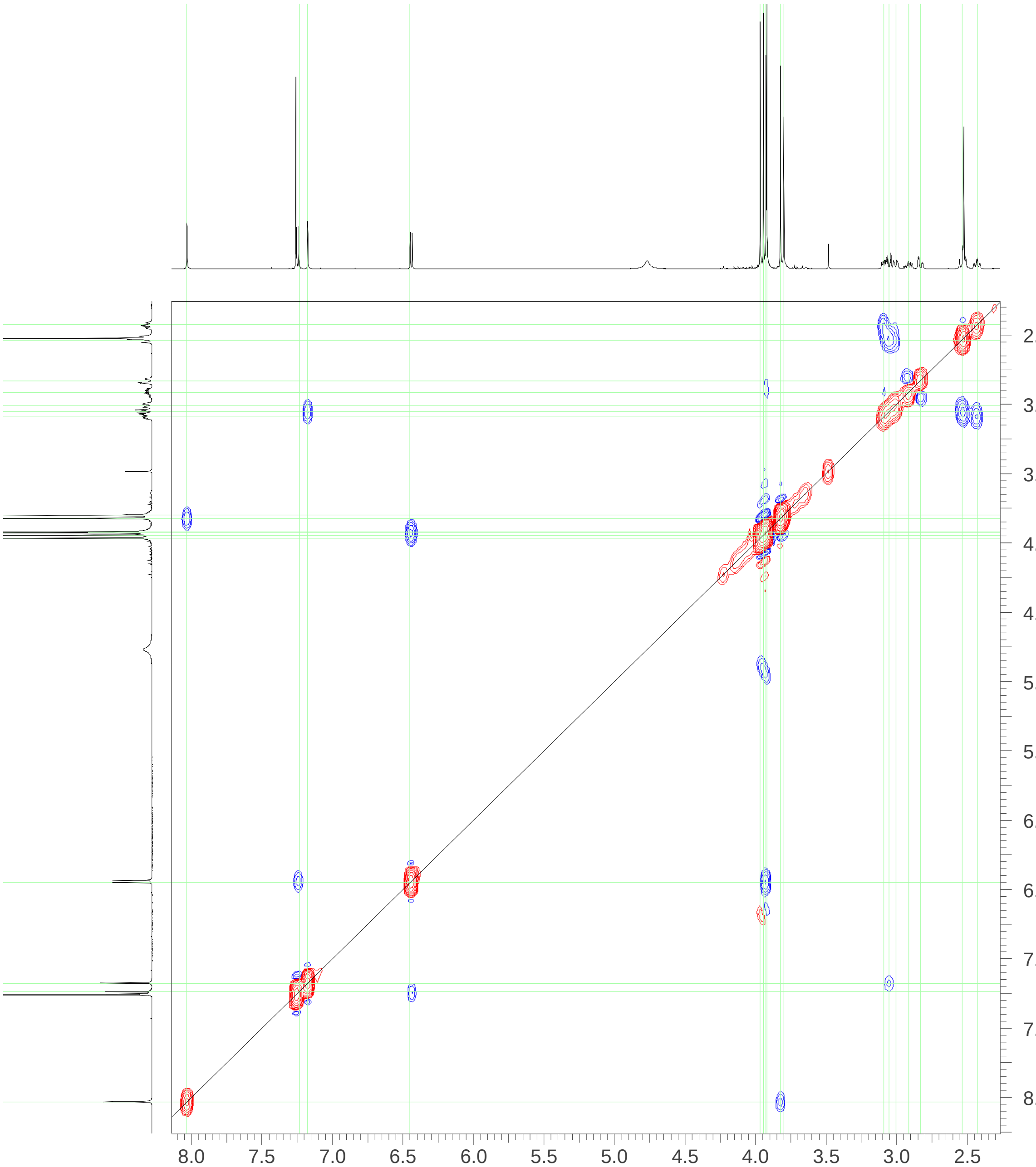
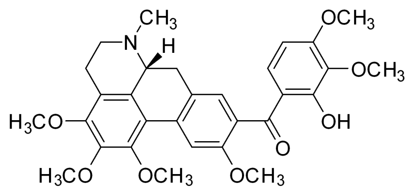


Figure S10-2. The partially enlarged ROESY spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)



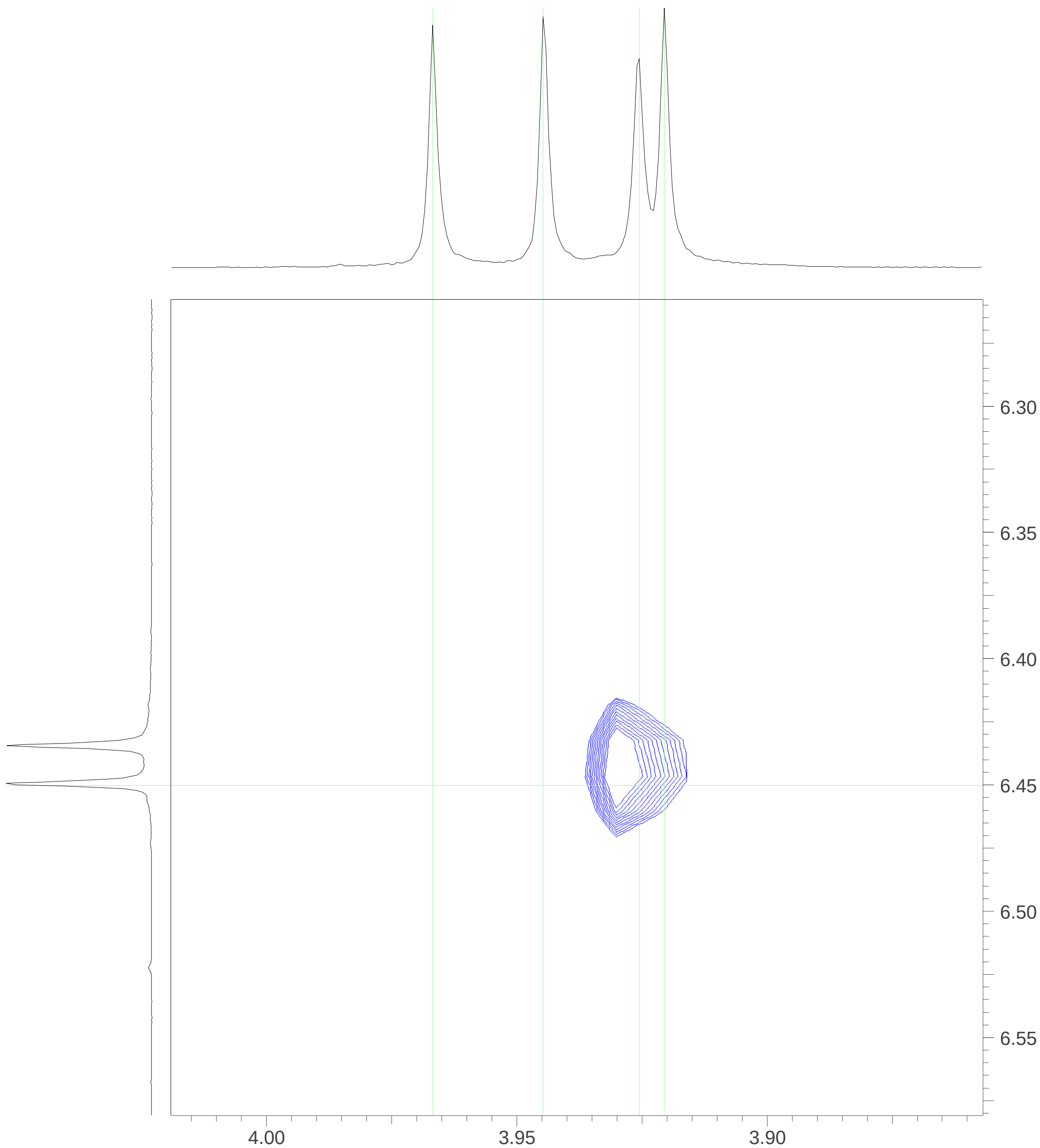


Figure S10-3. The partially enlarged ROESY spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)

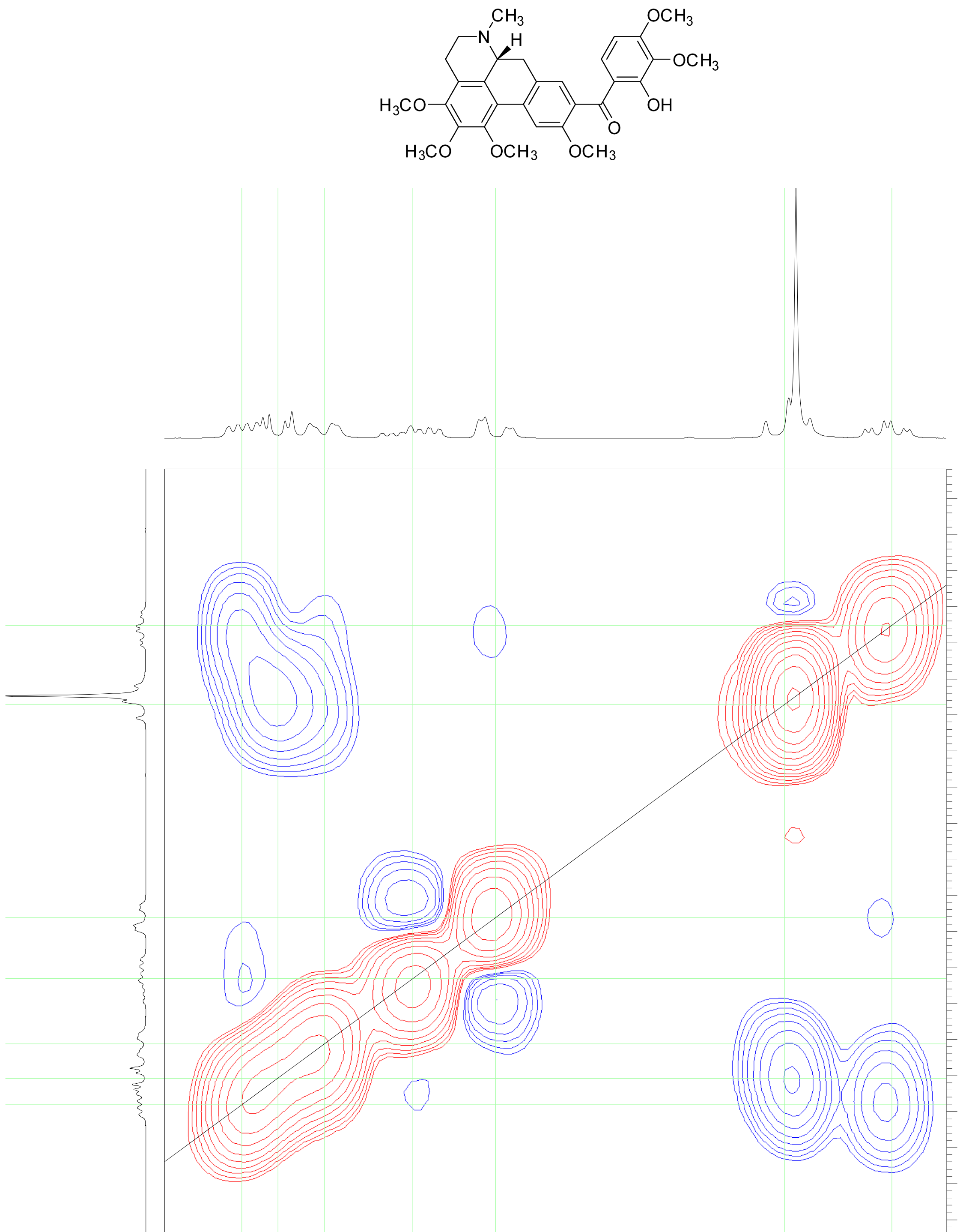


Figure S10-4. The partially enlarged ROESY spectrum of thalfoetine A (1) in $CDCl_3$ (600 MHz)

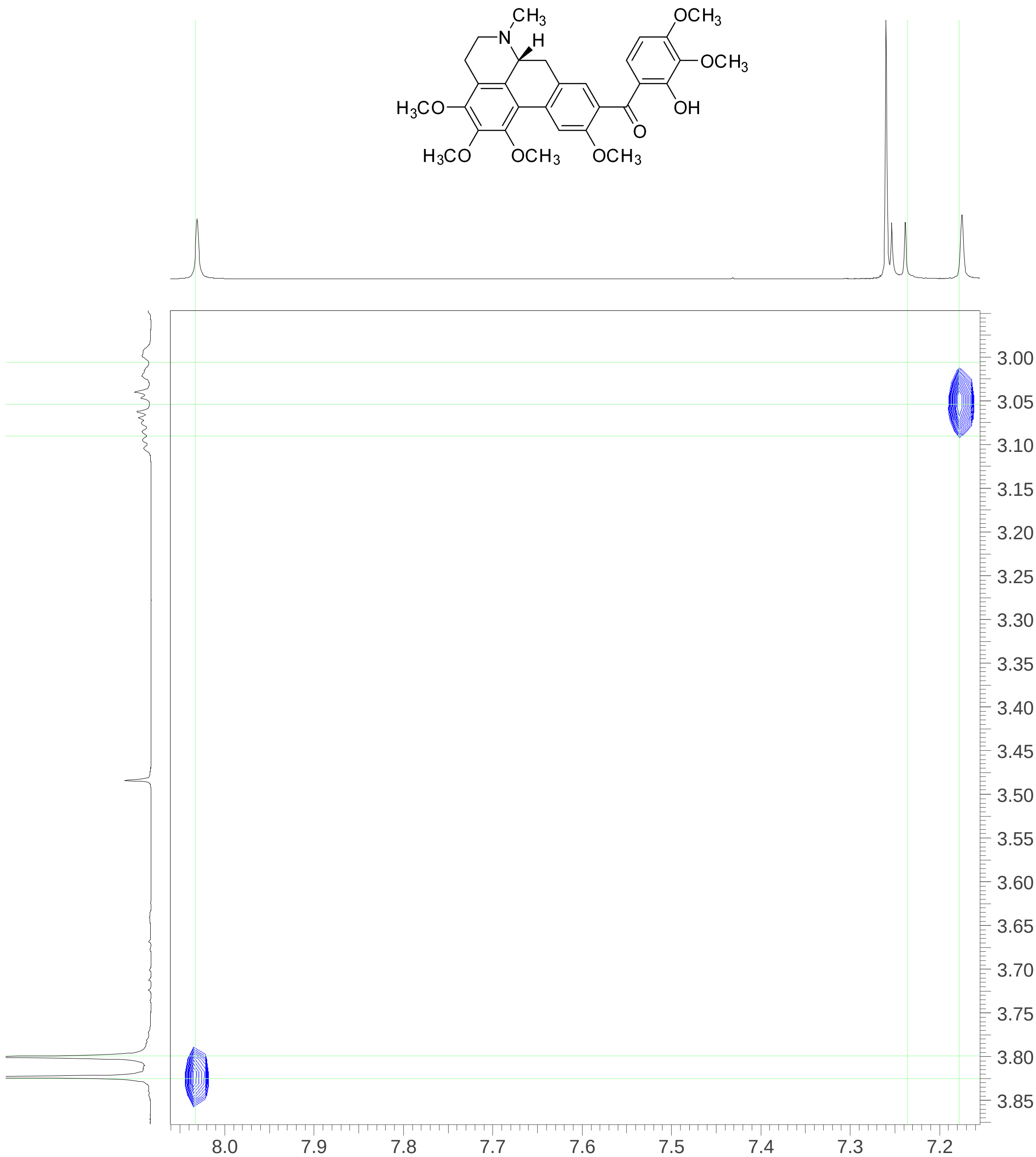


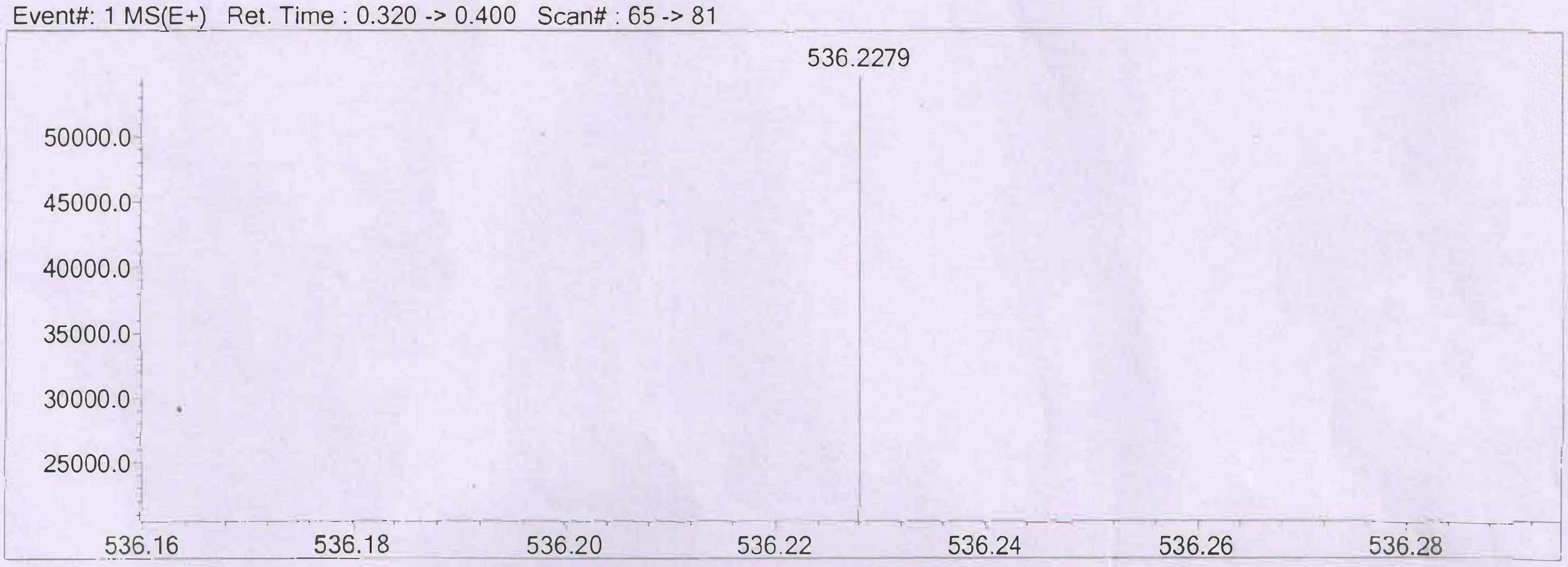
Figure S11. HREIMS spectrum of thalfoetine B (**2**)

Data File: E:\DATA\2017\1218\wtflr-80a.lcd

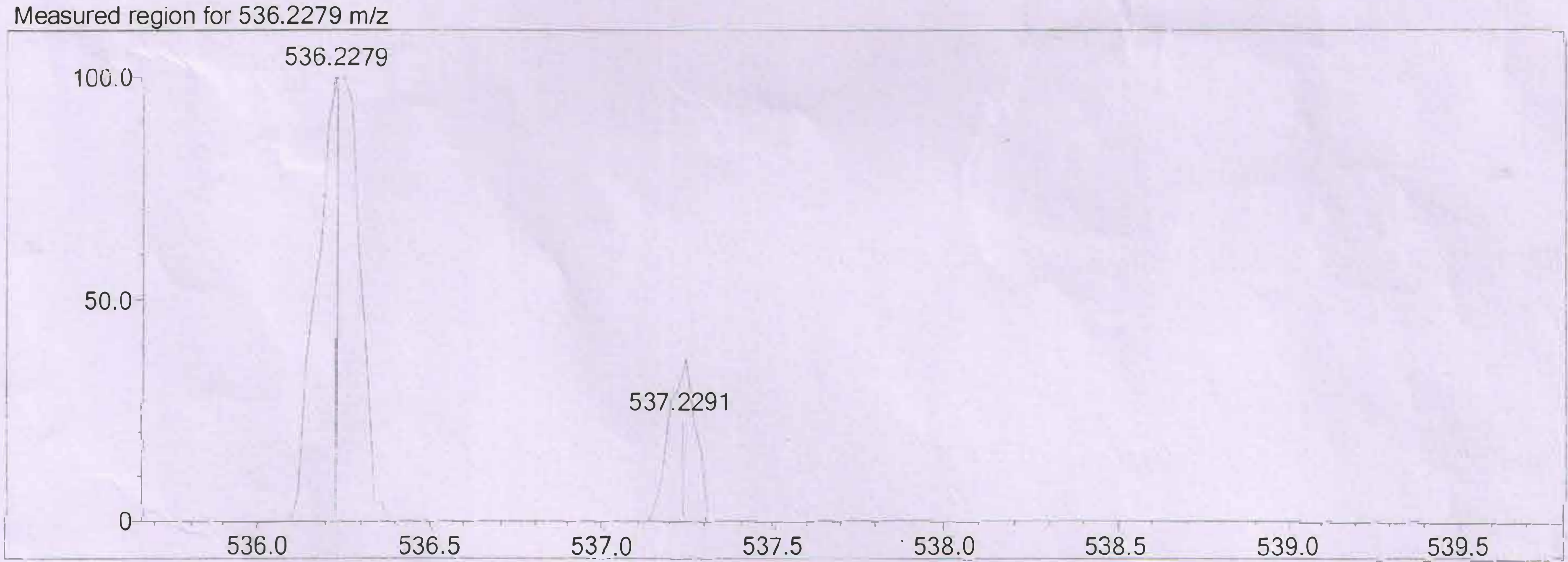
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	100	O	2	0	50	Cl	1	0	0	H
C	4	0	50	F	1	0	0	Br	1	0	0	
N	3	0	10	S	2	0	0	I	3	0	0	

Error Margin (ppm):	5	DBE Range:	-2.0 - 100.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	yes	Use MSn Info:	yes
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	10

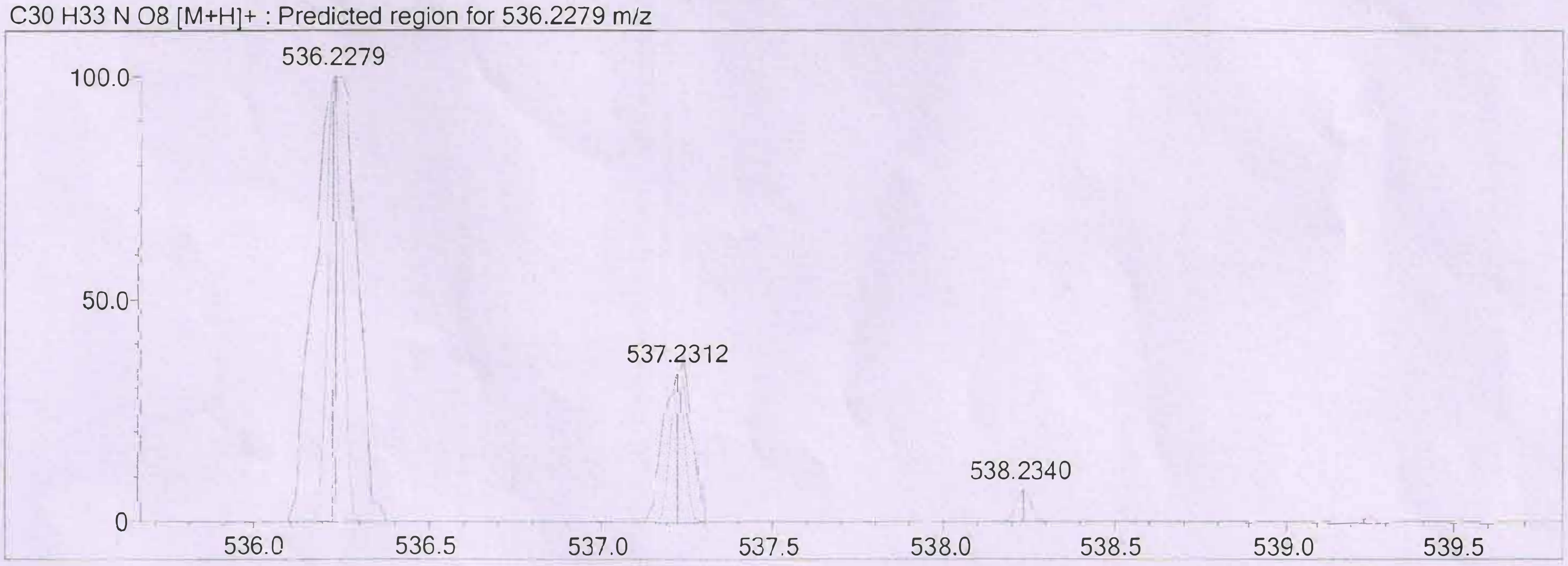
Event#: 1 MS(E+) Ret. Time : 0.320 -> 0.400 Scan# : 65 -> 81



Measured region for 536.2279 m/z

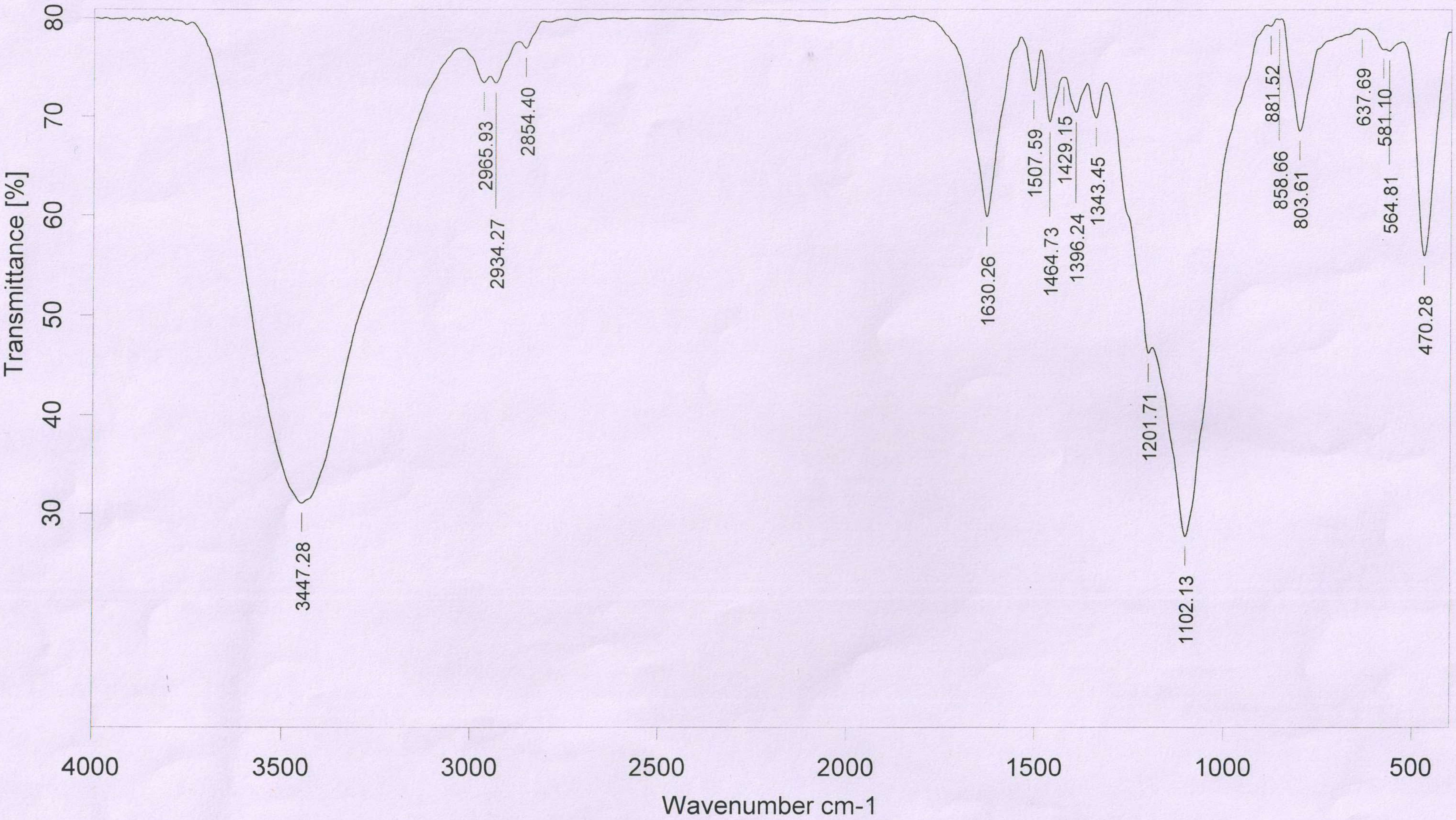


C30 H33 N O8 [M+H]+ : Predicted region for 536.2279 m/z



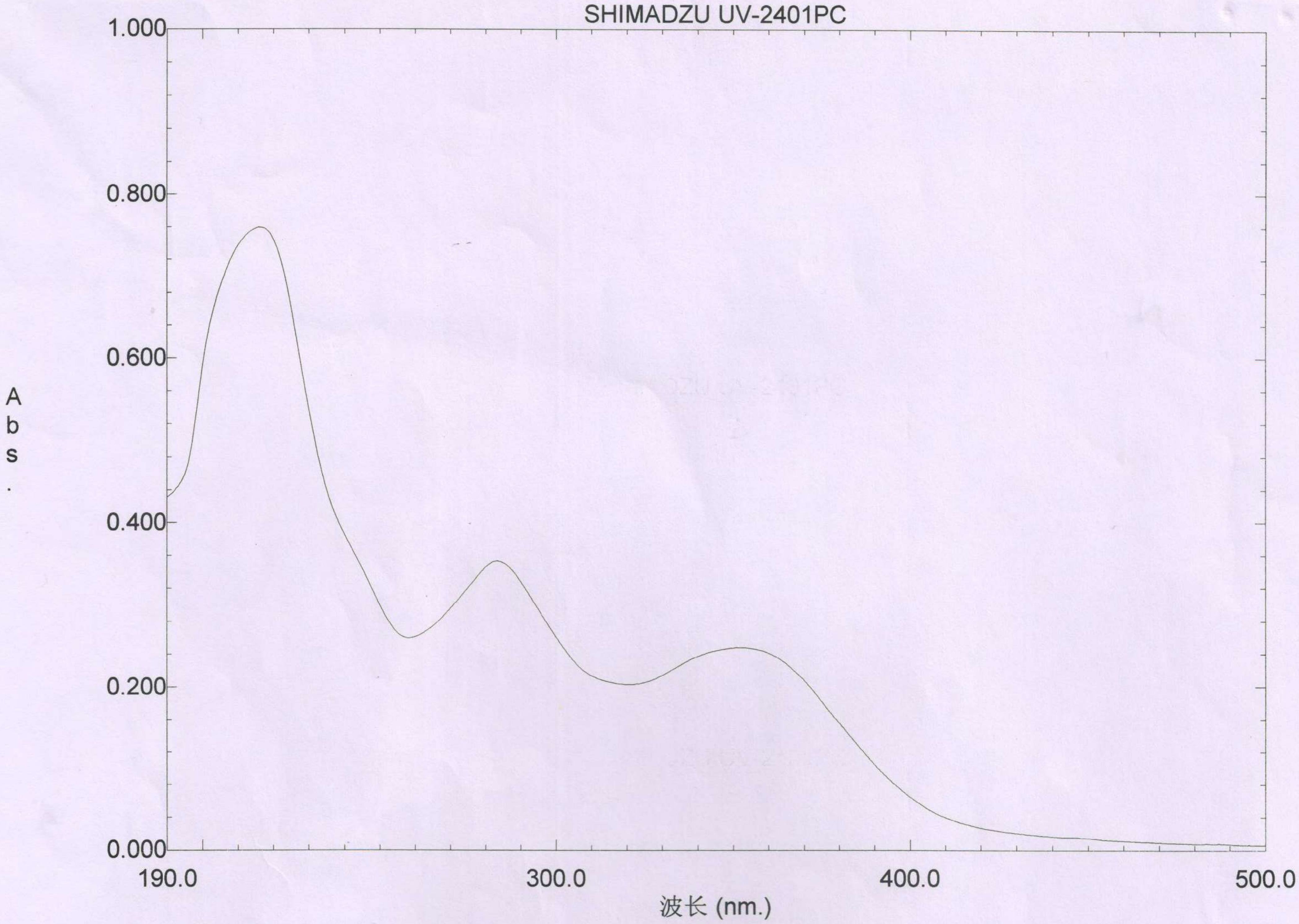
Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	DBE
C30 H33 N O8	[M+H]+	536.2279	536.2279	0.0	0.00	15.0

Figure S12. IR spectrum of thalfoetine B (**2**)



Sample : wtflr-80a	Frequency Range : 399.246 - 3996.32	Measured on : 28/03/2018	
Technique : KBr	Resolution : 4	Instrument : Tensor27	Sample Scans : 16
Filename : 180328IR.4	Zerofilling : 2	Acquisition : Double Sided,For	

Figure S13. UV spectrum of thalfoetine B (**2**)



文件名: 18012902
样品名称：WTFLR-80A

创建于: 11:30 18-01-29
数据: 原始

测量模式: Abs.
扫描速度: 中速
狭缝: 5.0
采样间隔: 0.5

否.	波长 (nm.)	Abs.
1	352.00	0.2476
2	283.50	0.3526
3	216.00	0.7592

18012902

样品浓度：0.0227毫克/毫升
溶剂：甲醇

Figure S14. ^{1}H NMR spectrum of thalfoetine B (**2**) in DMSO-d_6 (600 MHz)

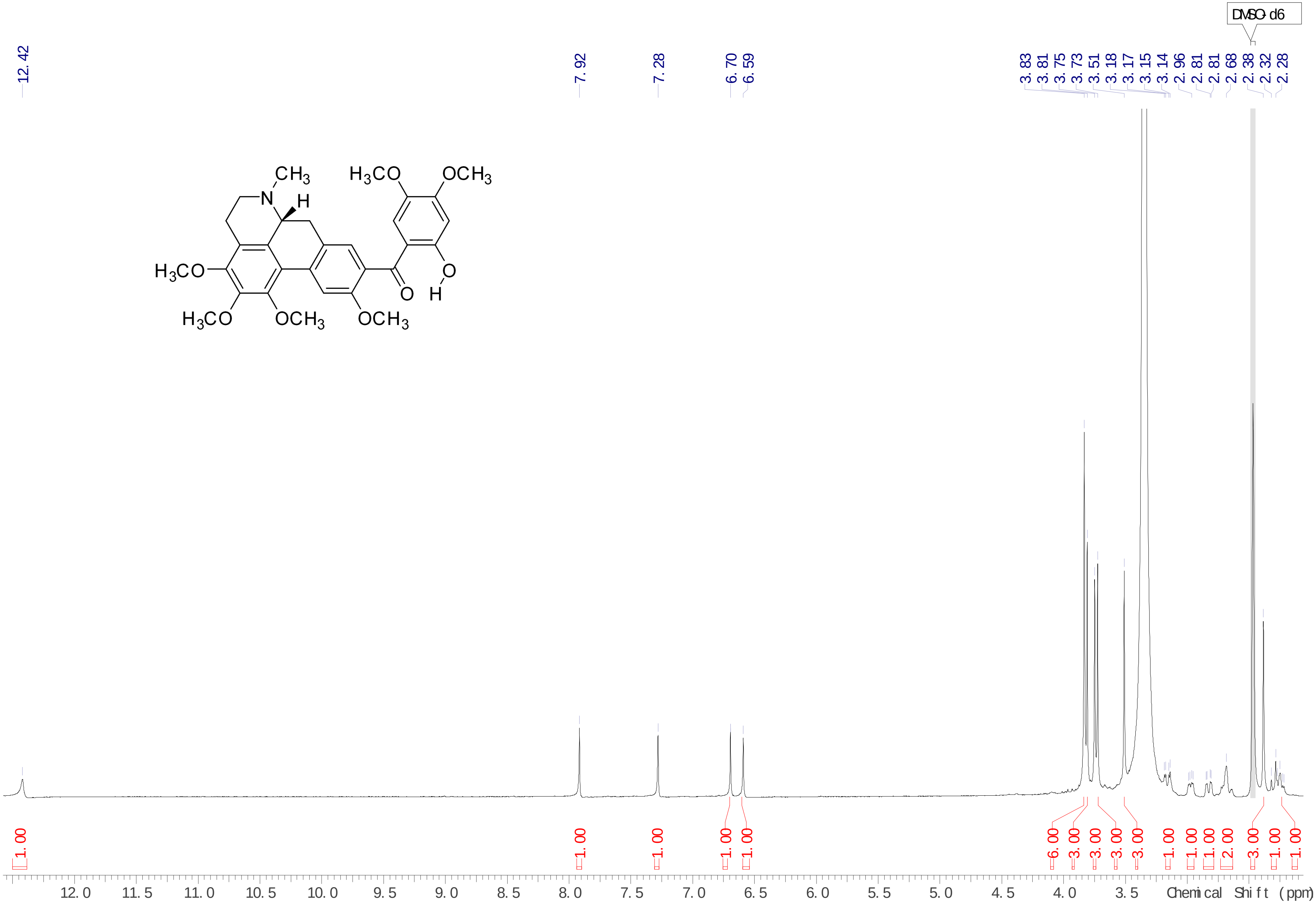


Figure S15. ^{13}C NMR spectrum of thalfoetine B (**2**) in DMSO-d_6 (150 MHz)

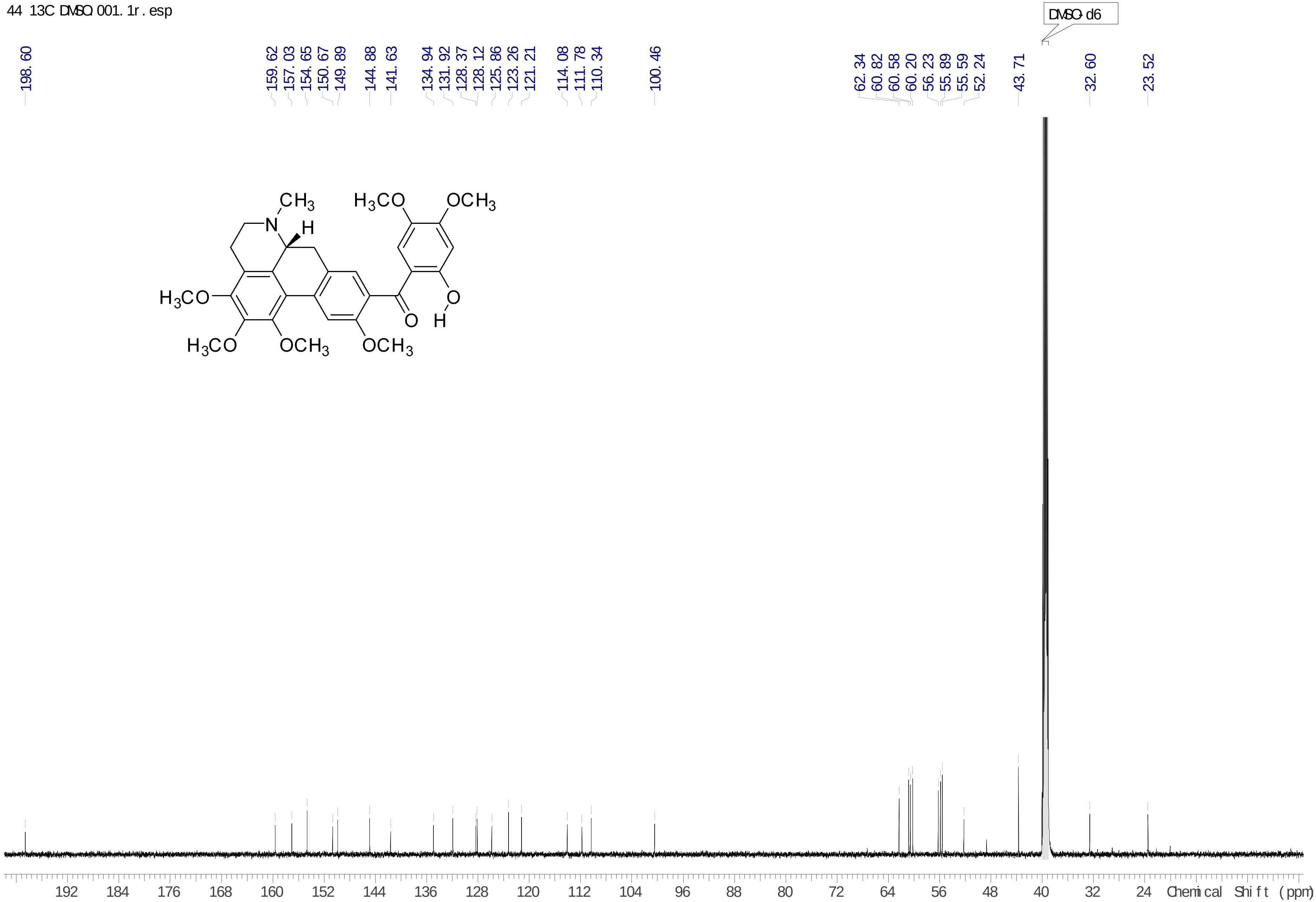


Figure S15-1. DEPT 90 spectrum of thalfoetine B (**2**) in DMSO-d_6 (150 MHz)

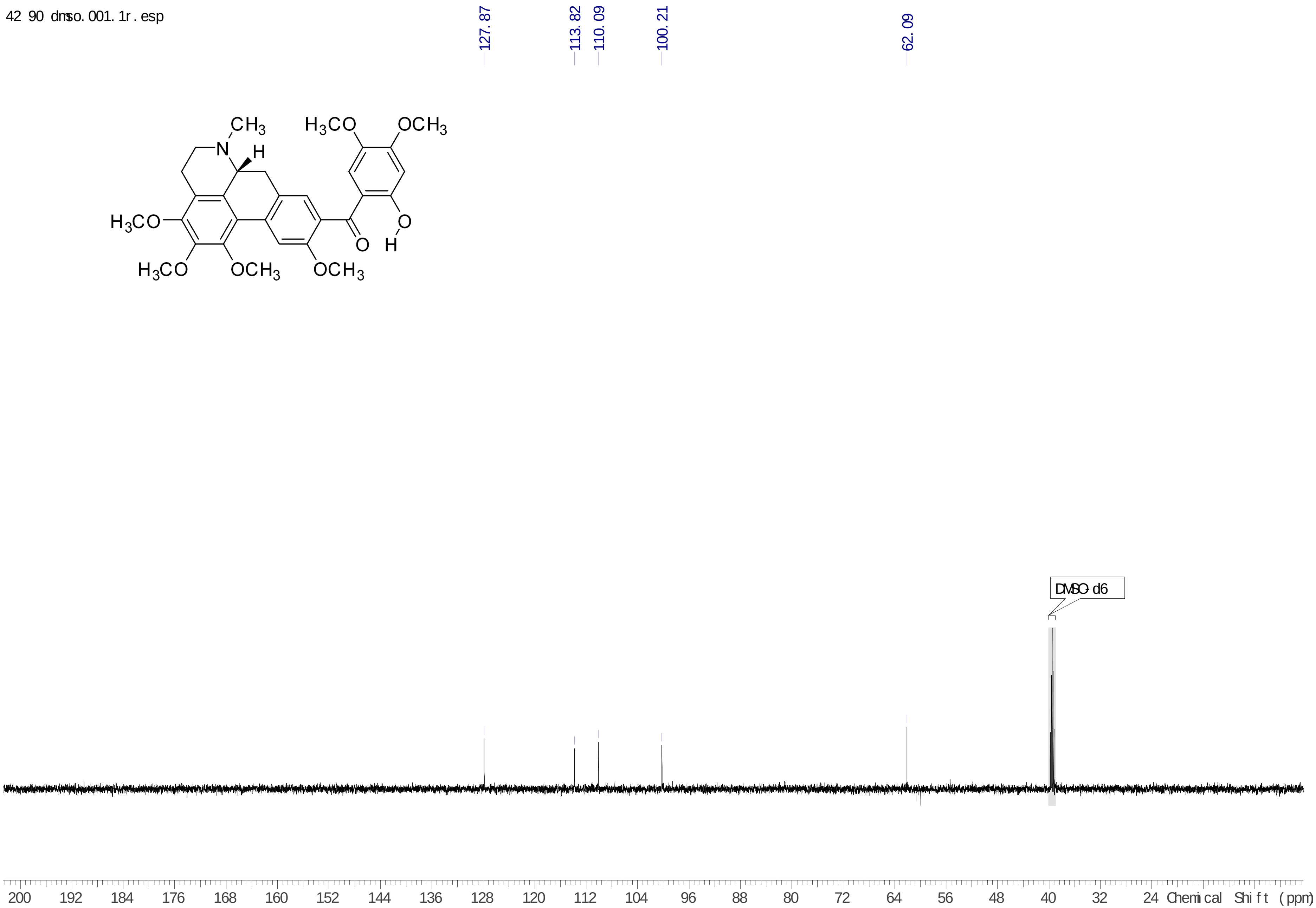


Figure S15-2. DEPT 135 spectrum of thalfoetine B (**2**) in DMSO-d_6 (150 MHz)

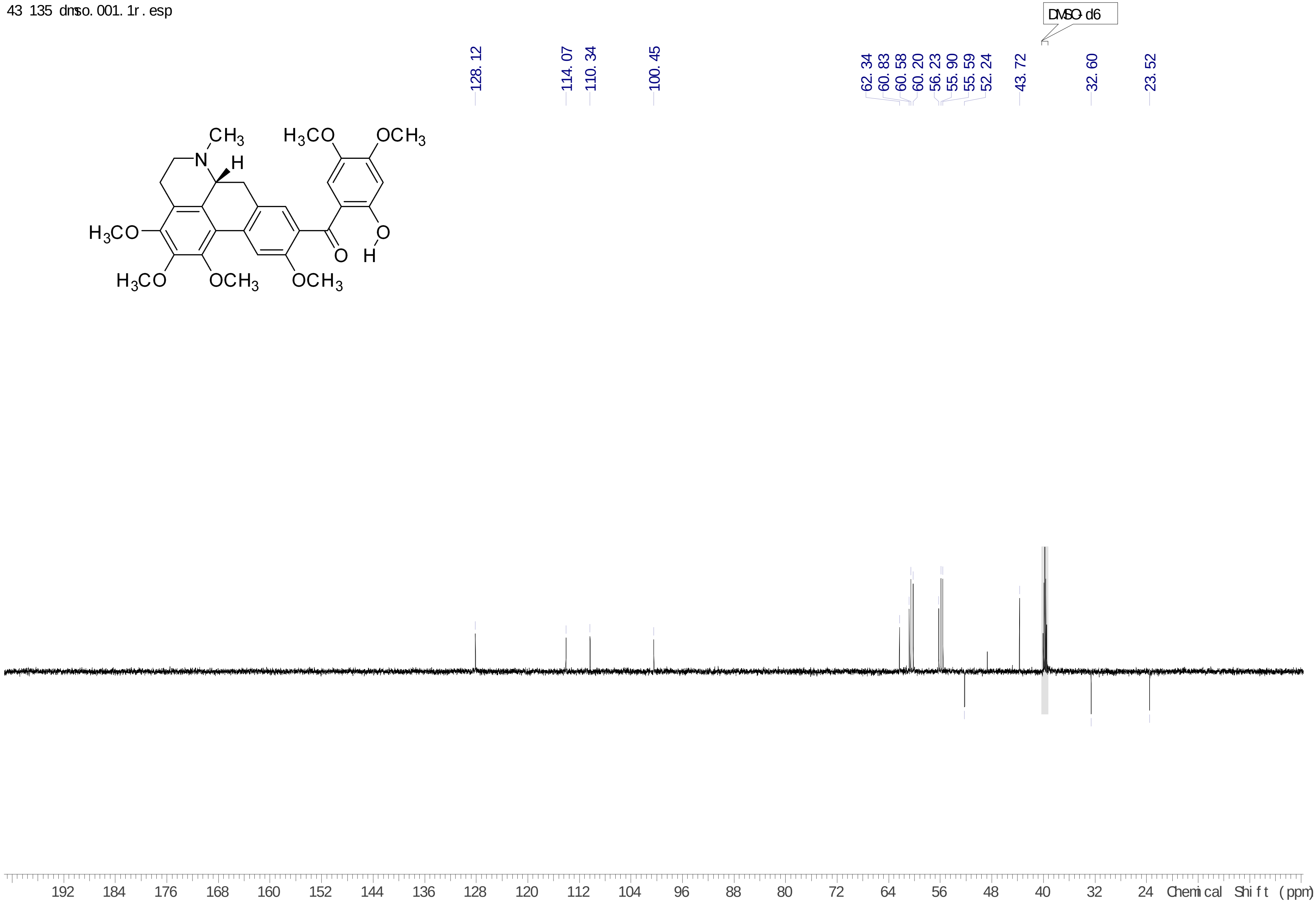
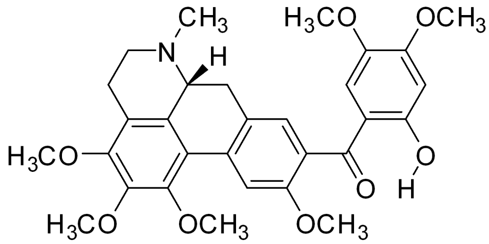


Figure S16. HSQC spectrum of thalfoetine B (**2**) in DMSO-d_6 (600 MHz)



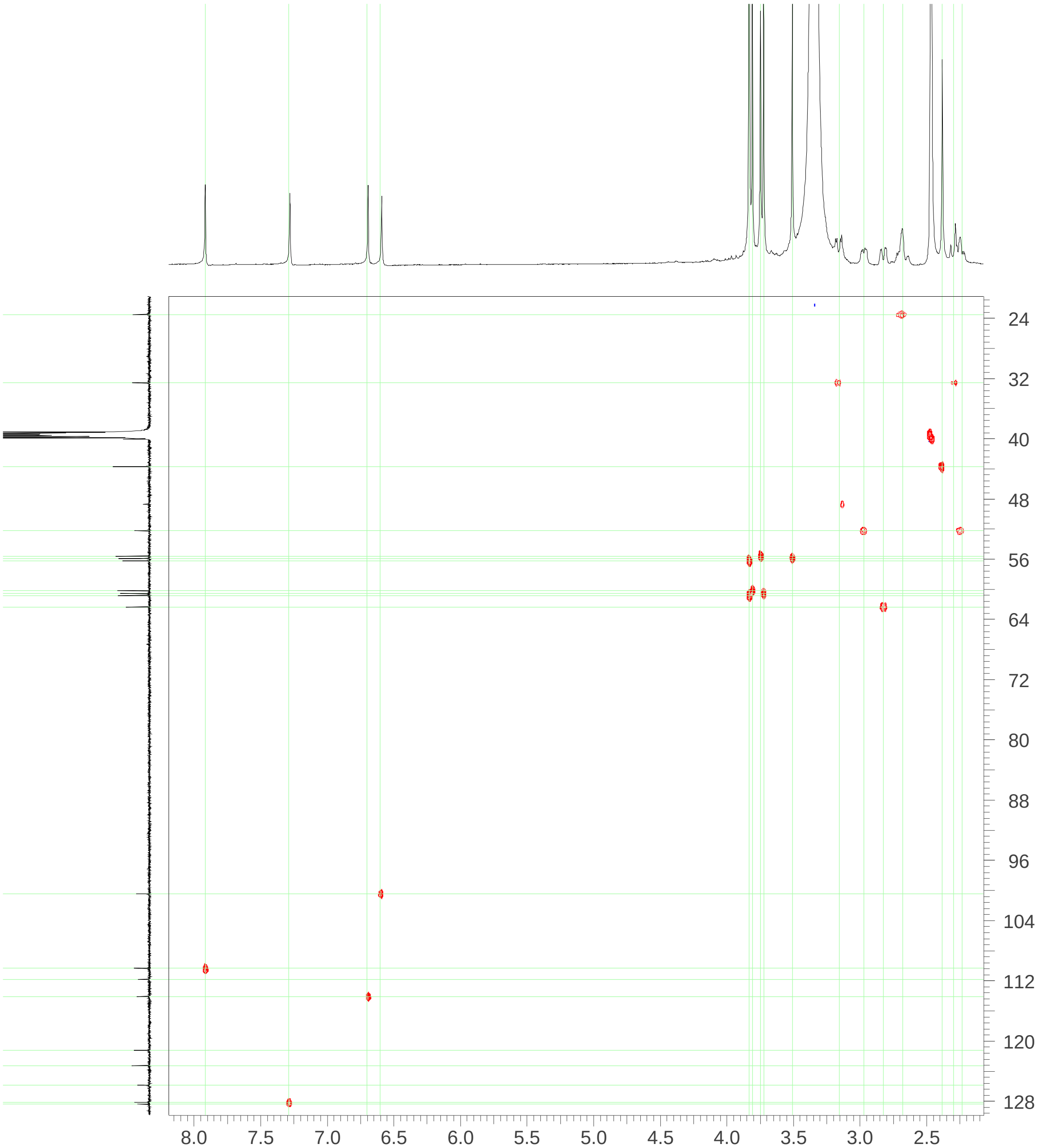
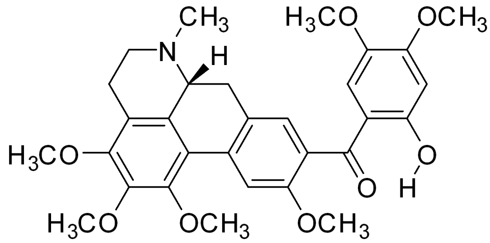


Figure S16-1. The partially enlarged HSQC spectrum of thalfoetine B (**2**)



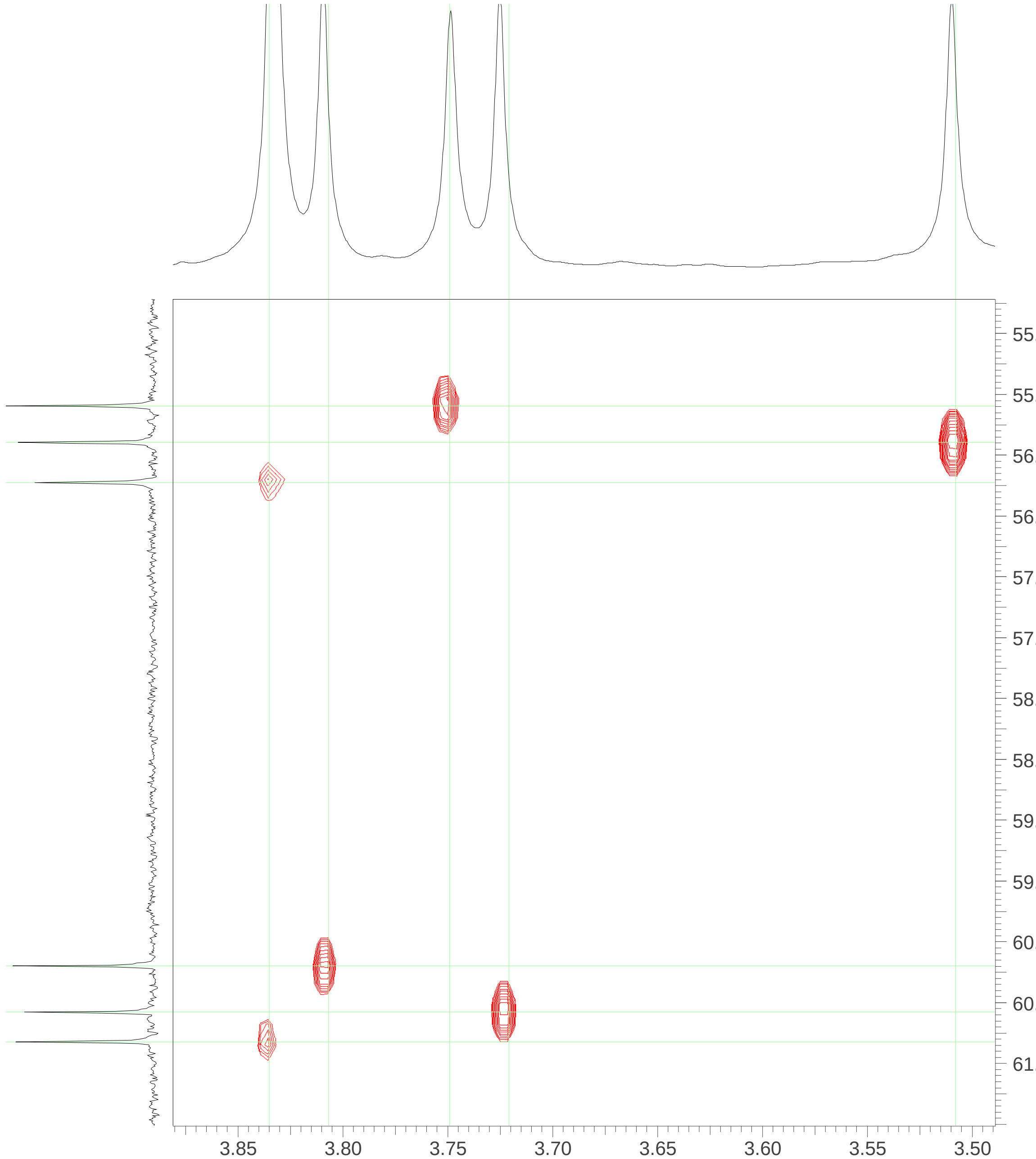
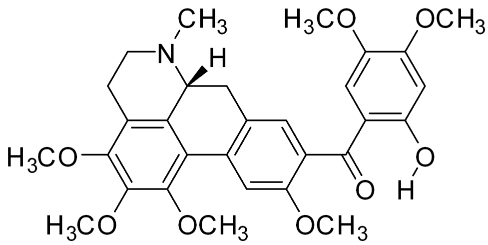


Figure S16-2. The partially enlarged HSQC spectrum of thalfoetine B (**2**)



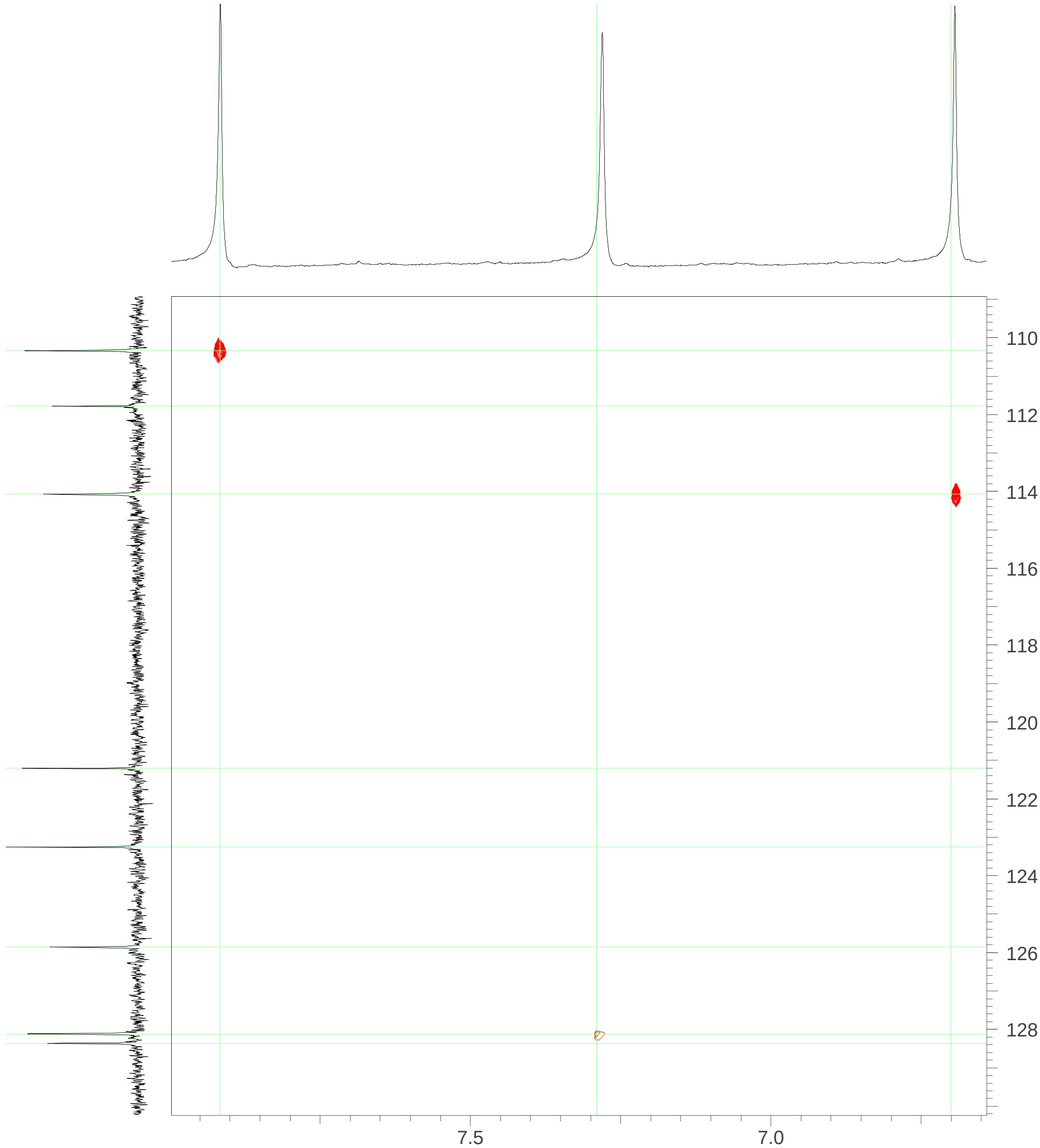
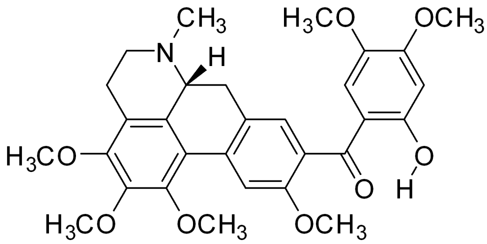


Figure S17. HMBC spectrum of thalfoetine B (**2**) in DMSO-d_6 (600 MHz)



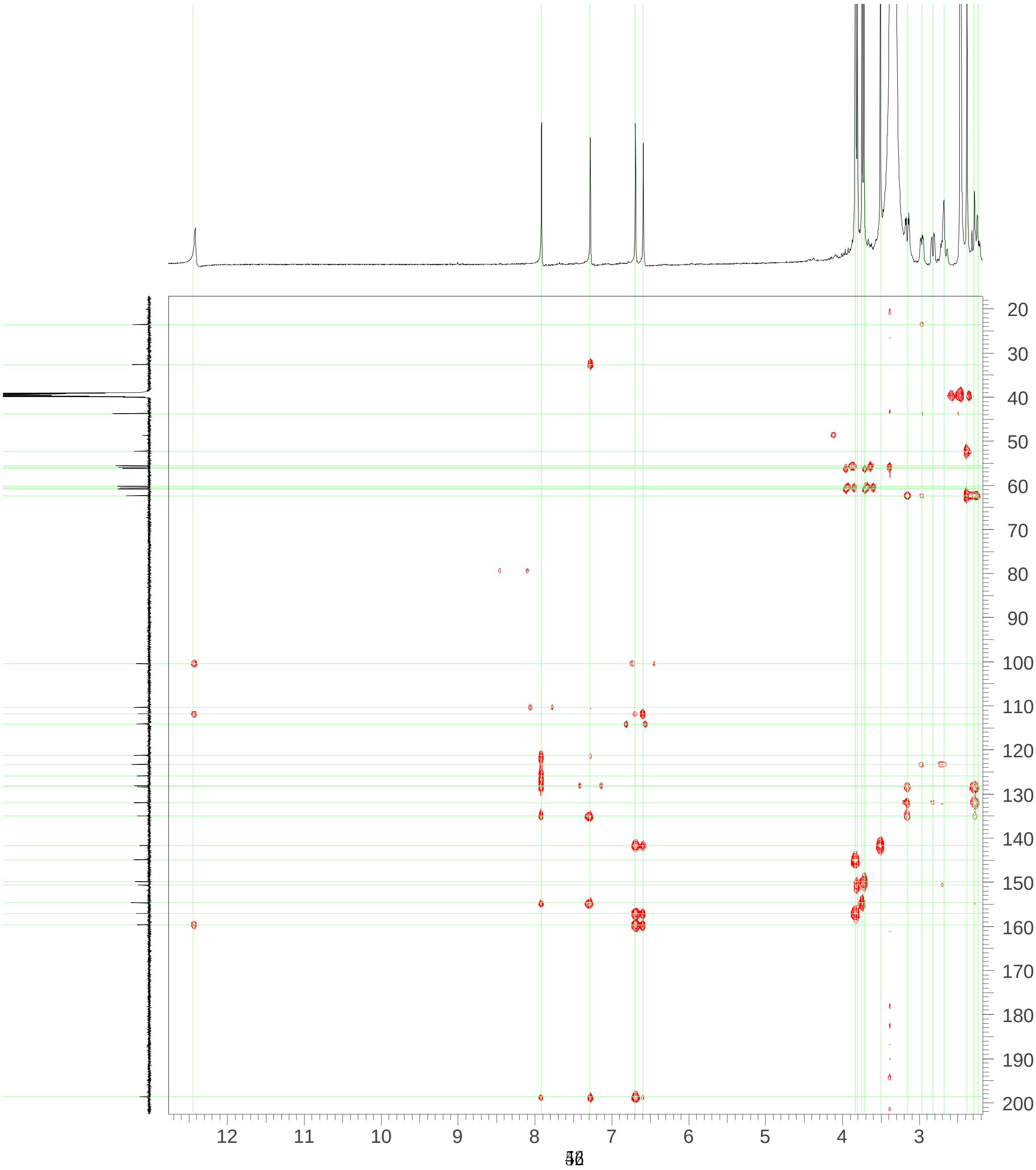
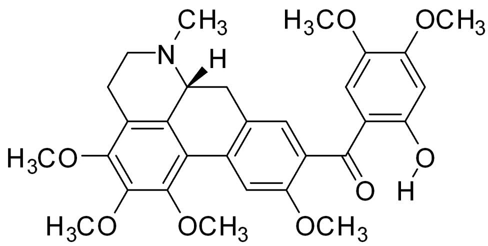


Figure S17-1. The partially enlarged HMBC spectrum of thalfoetine B (**2**)



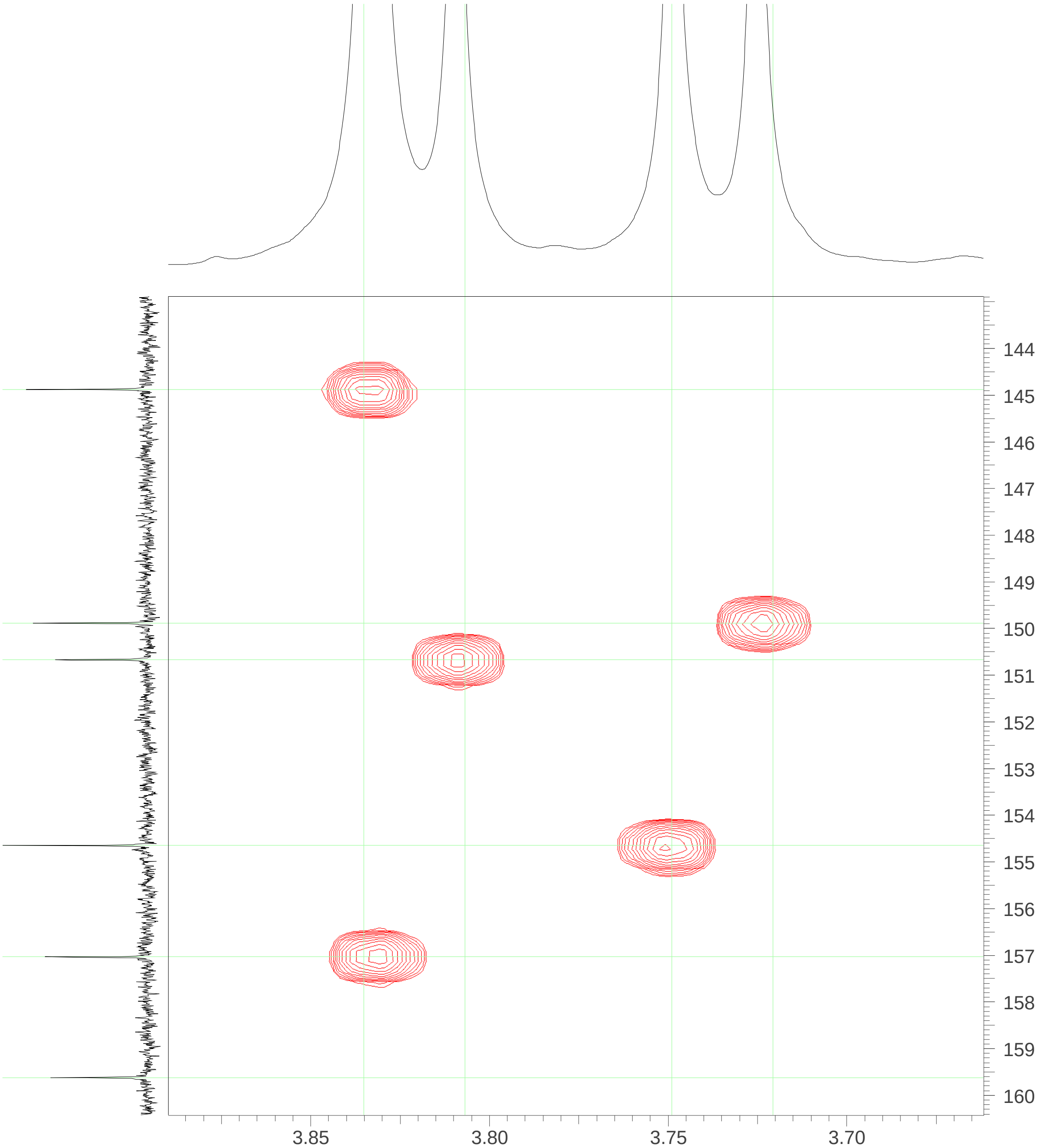


Figure S17-2. The partially enlarged HMBC spectrum of thalfoetine B (**2**)

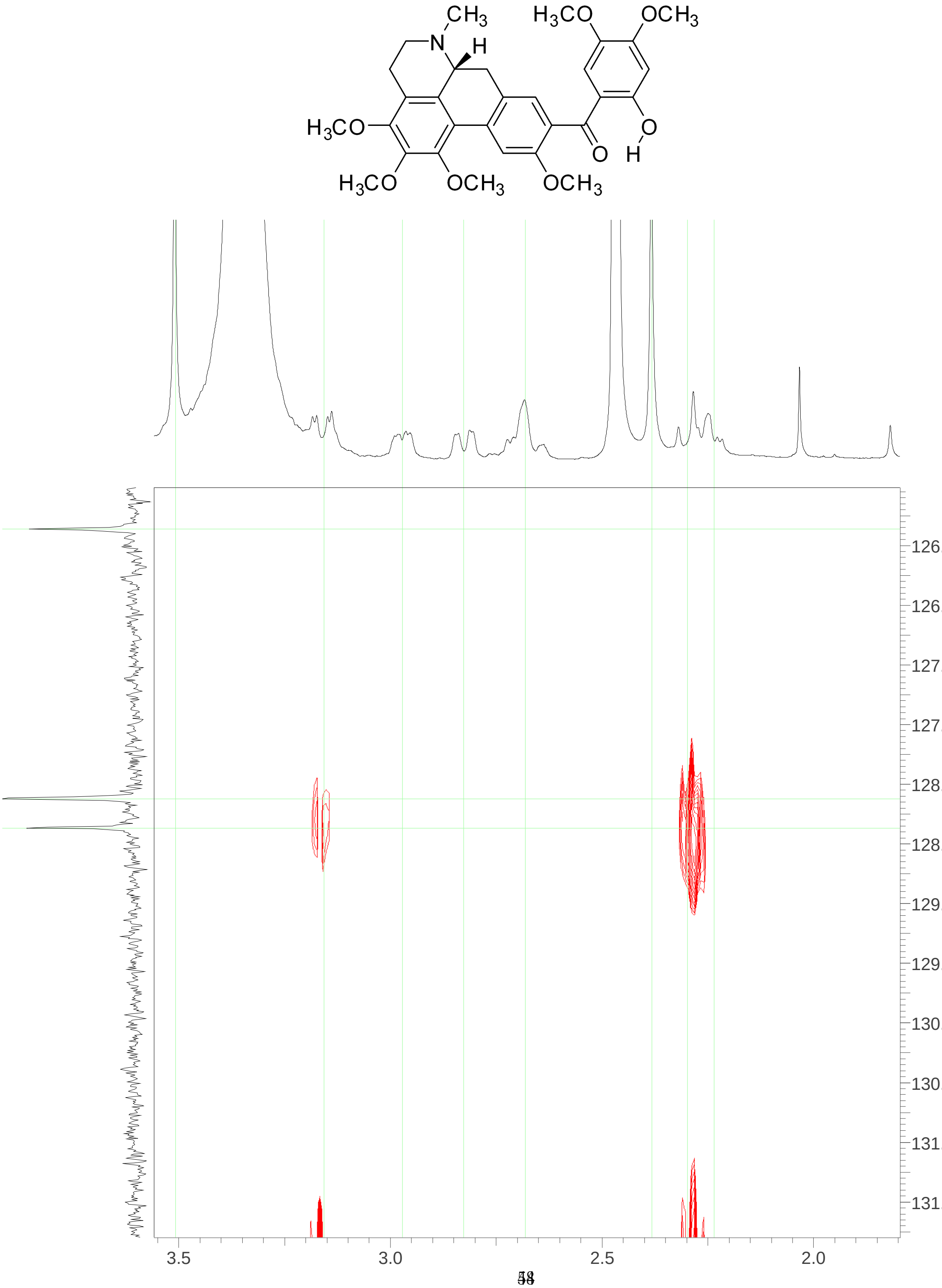


Figure S17-3. The partially enlarged HMBC spectrum of thalfoetine B (**2**)

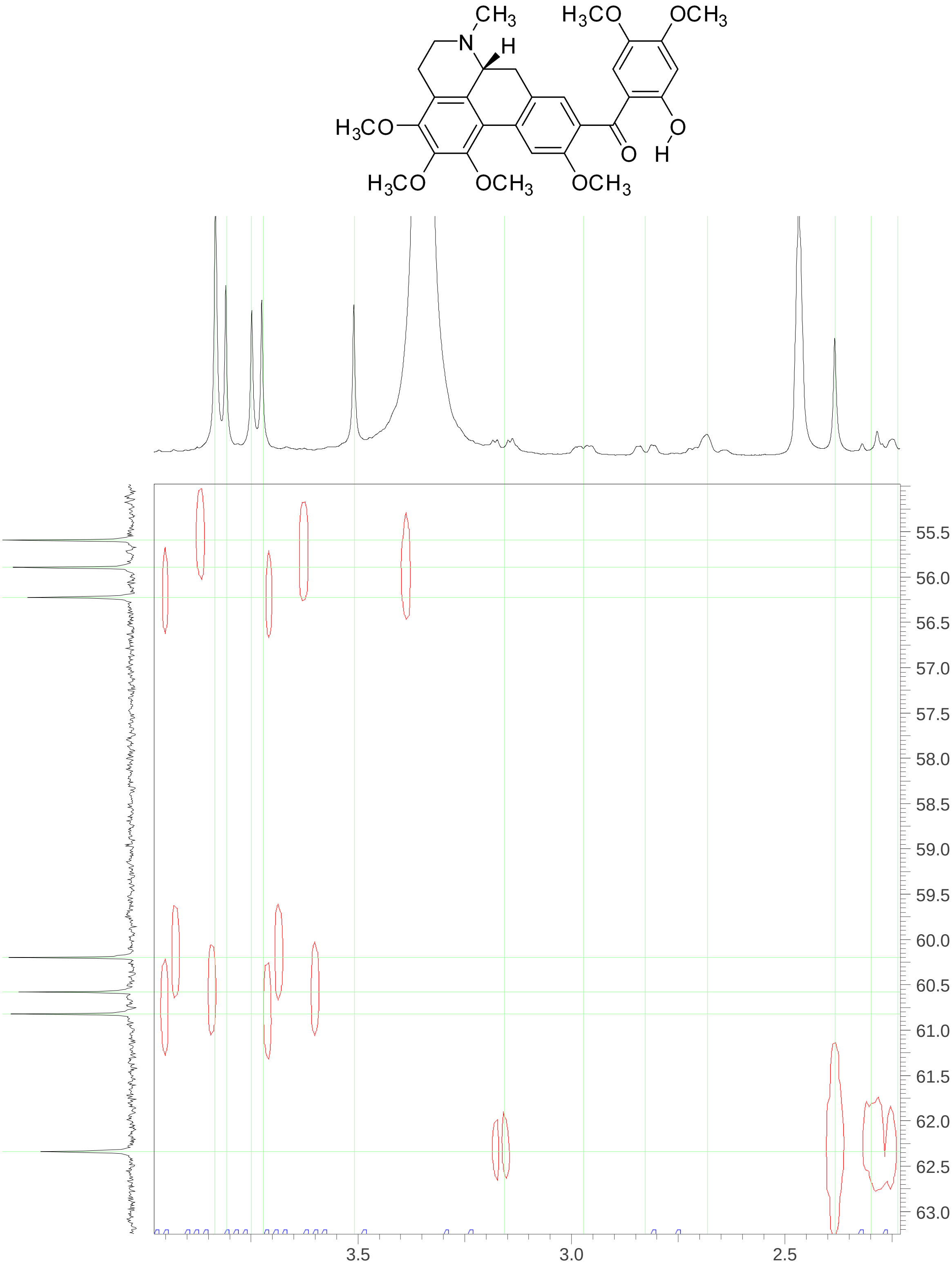
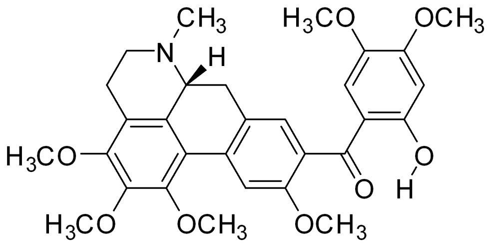


Figure S18. ^{1}H-^{1}H COSY spectrum of thalfoetine B (**2**) in DMSO-d_6 (600 MHz)



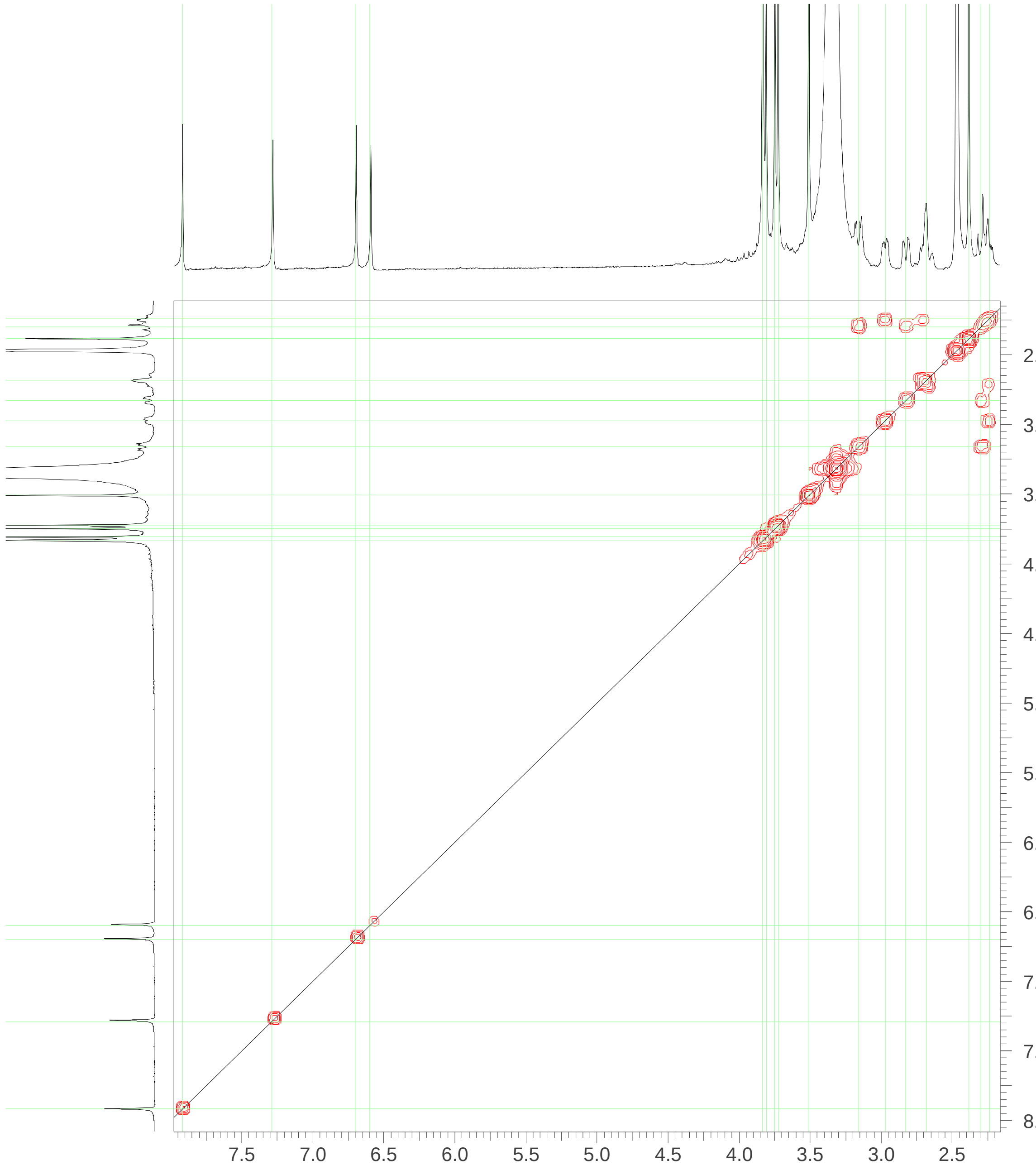
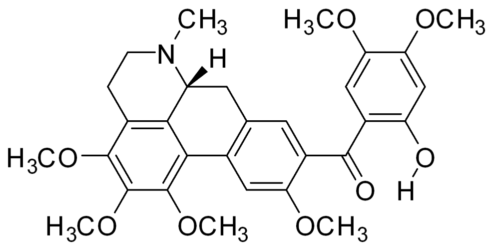


Figure S18-1. The partially enlarged ^{1}H-^{1}H COSY spectrum of thalfoetine B (**2**)



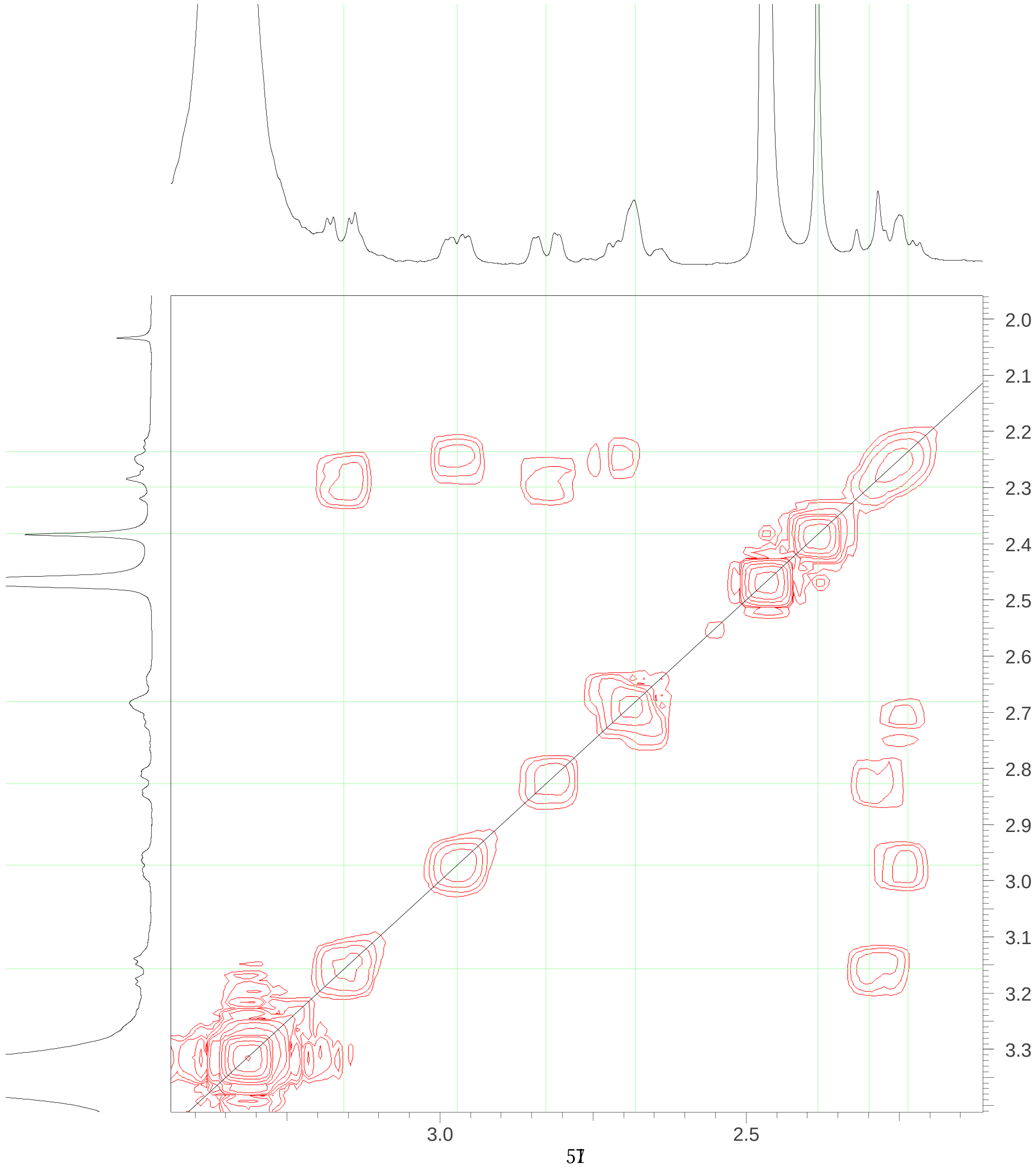
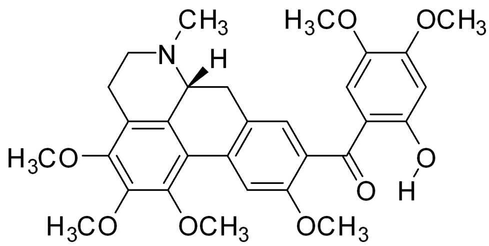


Figure S19. ROESY spectrum of voacafricine B (**2**) in DMSO-d_6 (600 MHz)



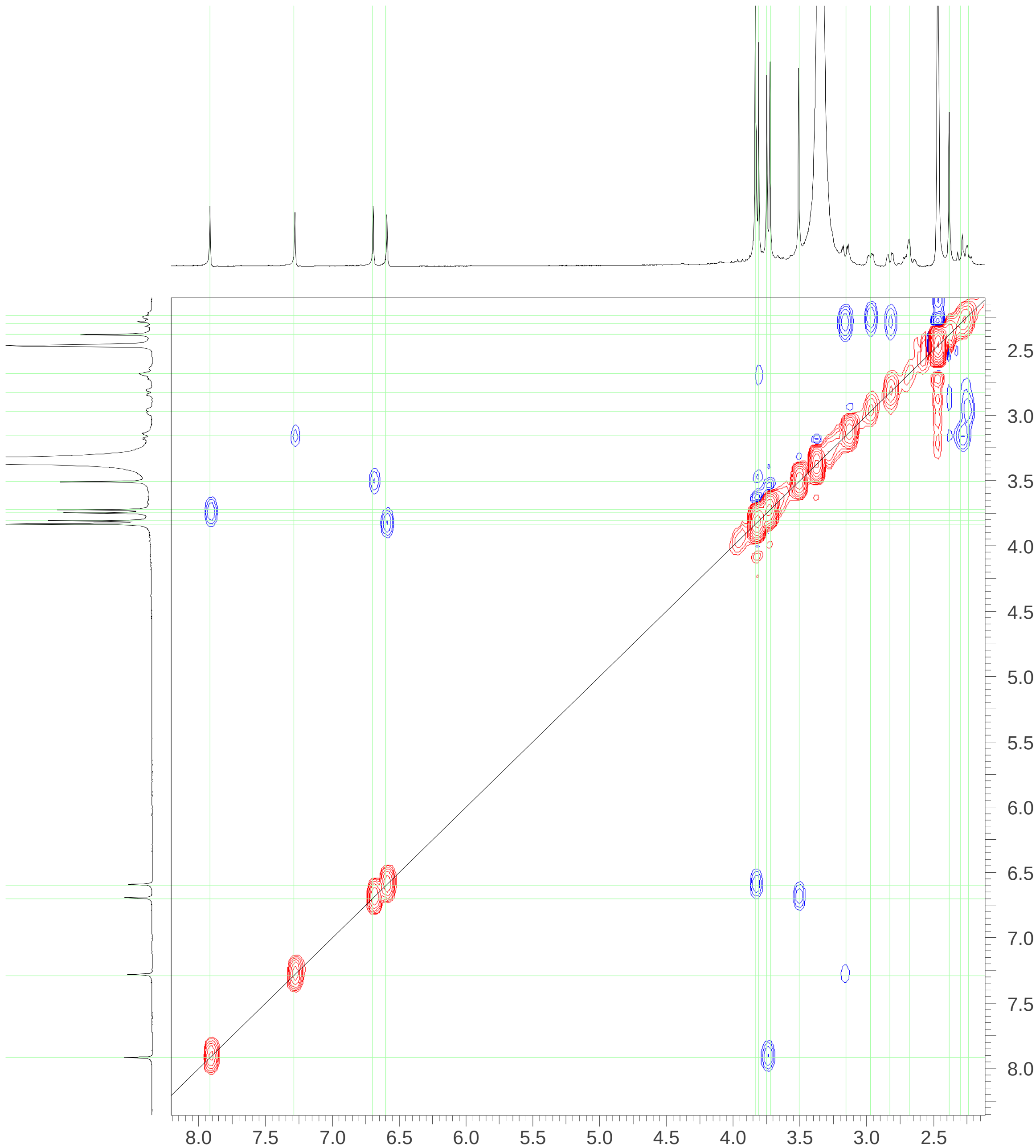


Figure S19-1. The partially enlarged ROESY spectrum of voacafricine B (**2**)

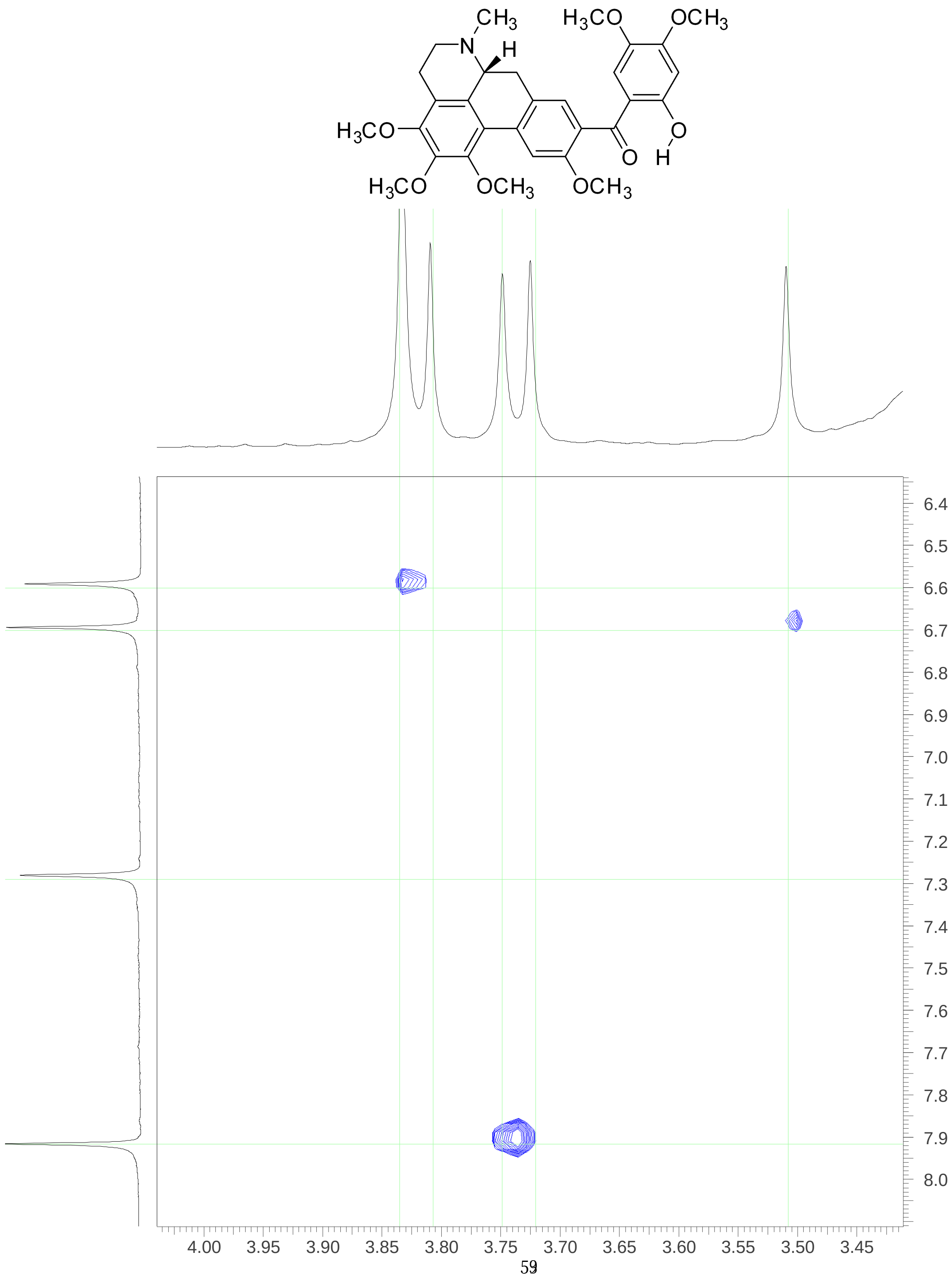


Figure S19-2. The partially enlarged ROESY spectrum of voacafricine B (**2**)

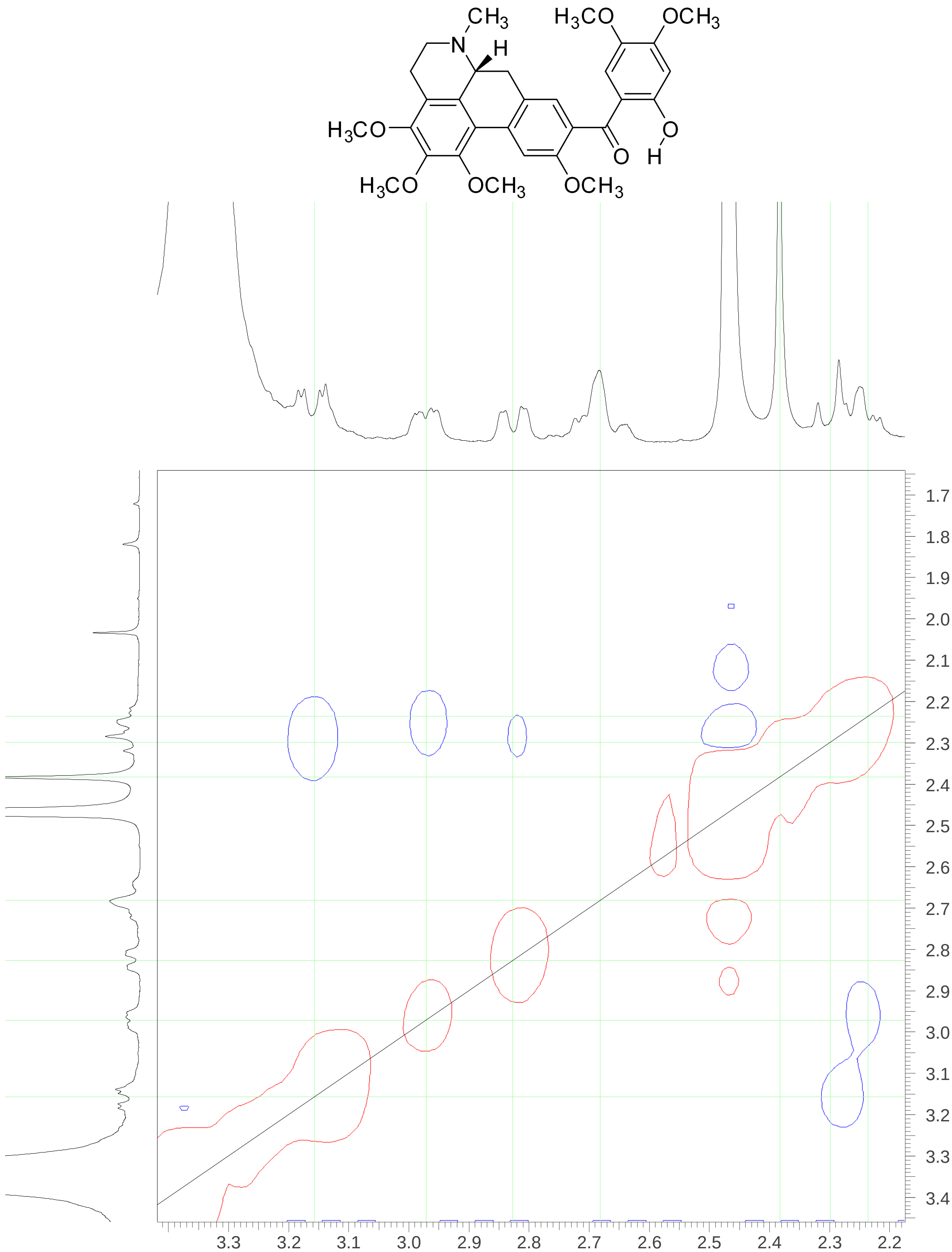


Figure S20. HREIMS spectrum of thalfoetine C (**3**)

Formula Predictor Report - wtflr-9.lcd

Data File: E:\DATA\2017\0531\wtflr-9.lcd

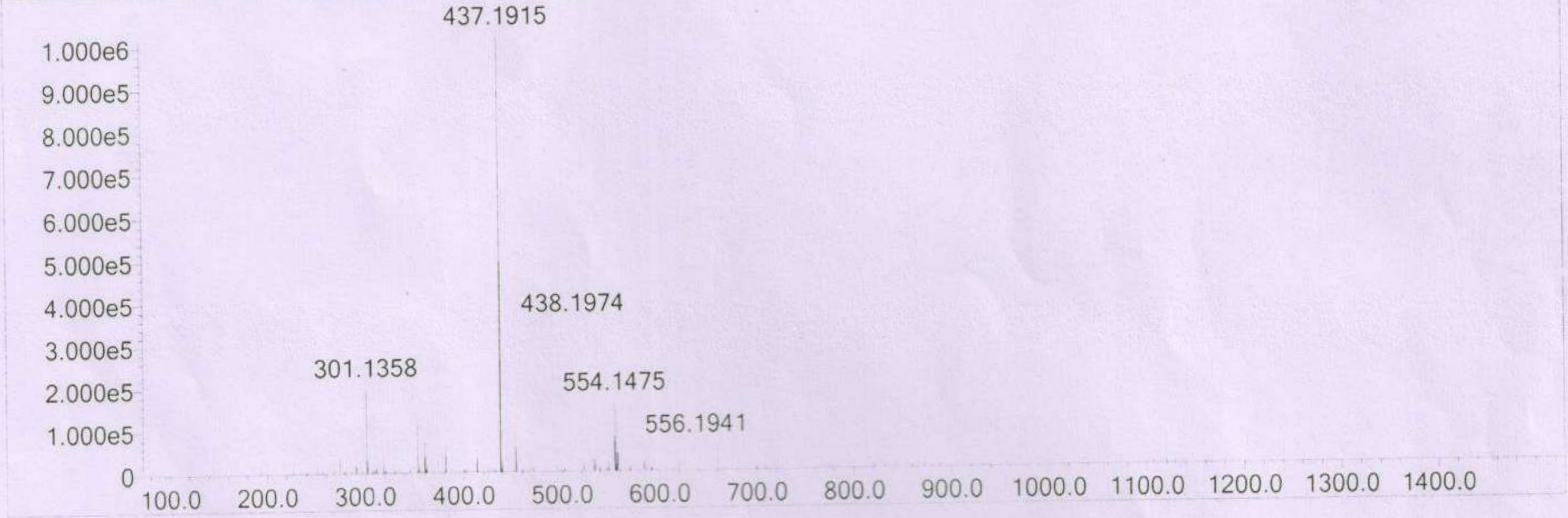
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	150	O	2	0	50	S	2	0	0	Pt	2	0	0	Na
B	3	0	0	F	1	0	0	Cl	1	0	0					
C	4	0	100	Na	1	0	0	Br	1	0	0					
N	3	0	15	Si	4	0	0	I	3	0	0					

Error Margin (ppm): 10
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

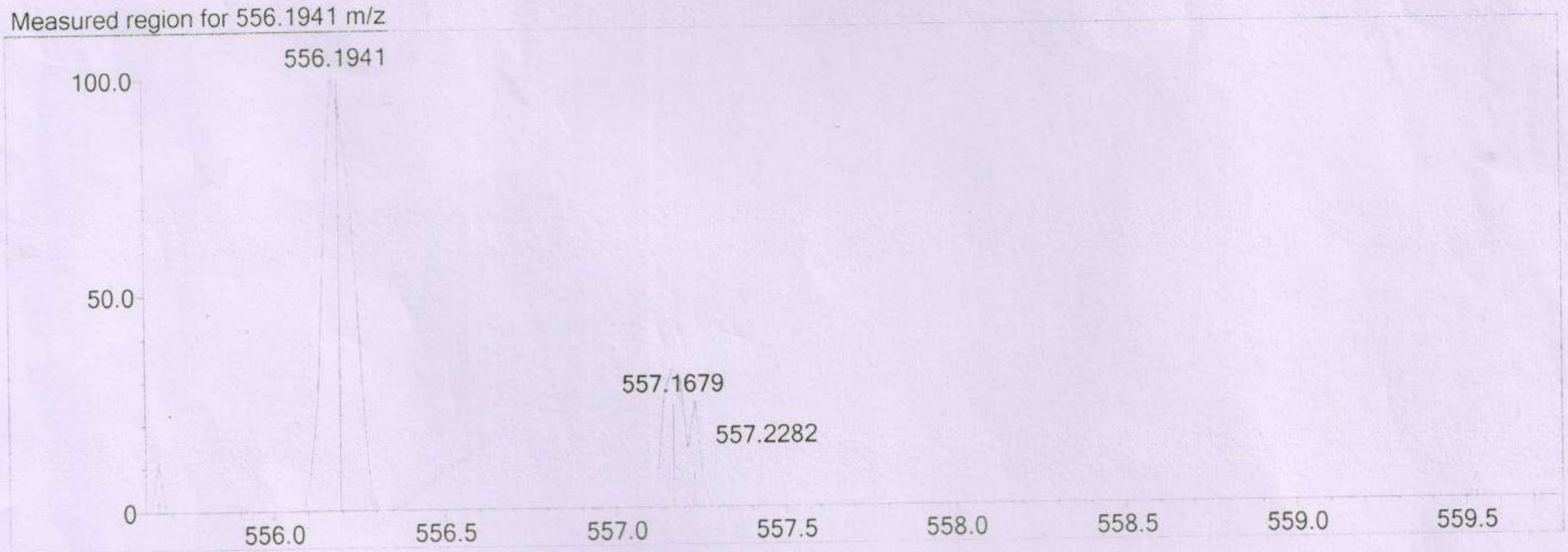
DBE Range: -2.0 - 100.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: yes
Isotope Res: 10000
Max Results: 100

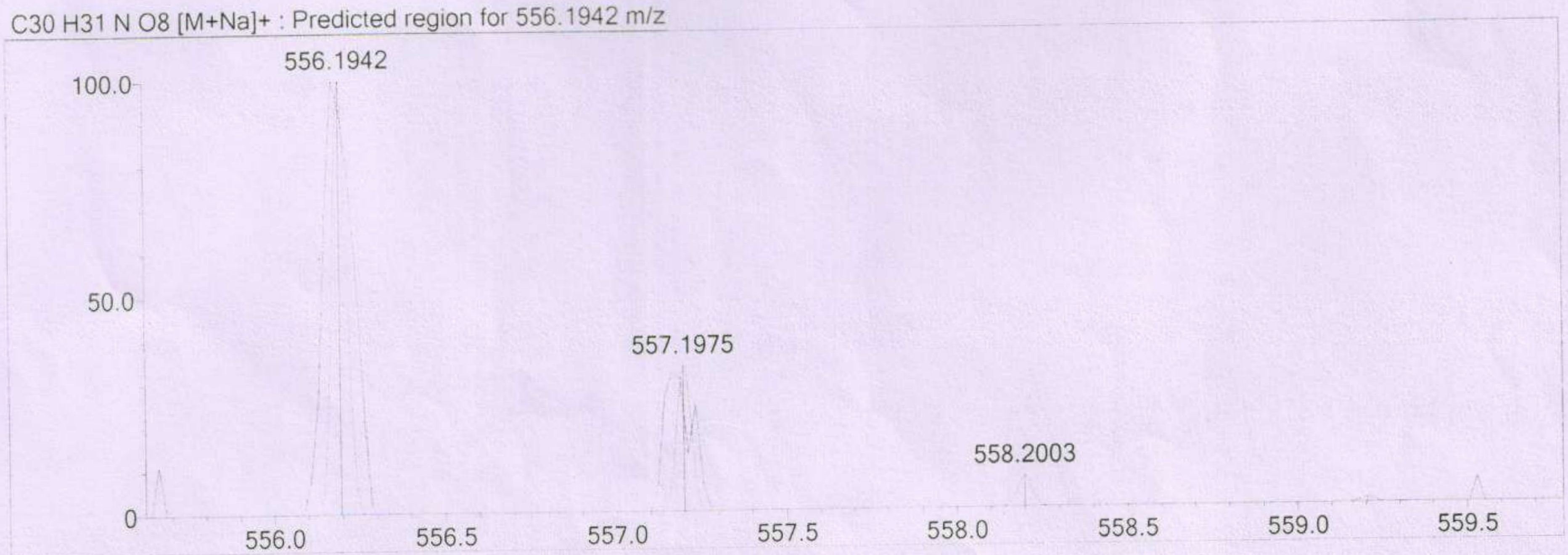
Event#: 1 MS(E+) Ret. Time : 0.420 -> 0.460 Scan# : 85 -> 93



Measured region for 556.1941 m/z

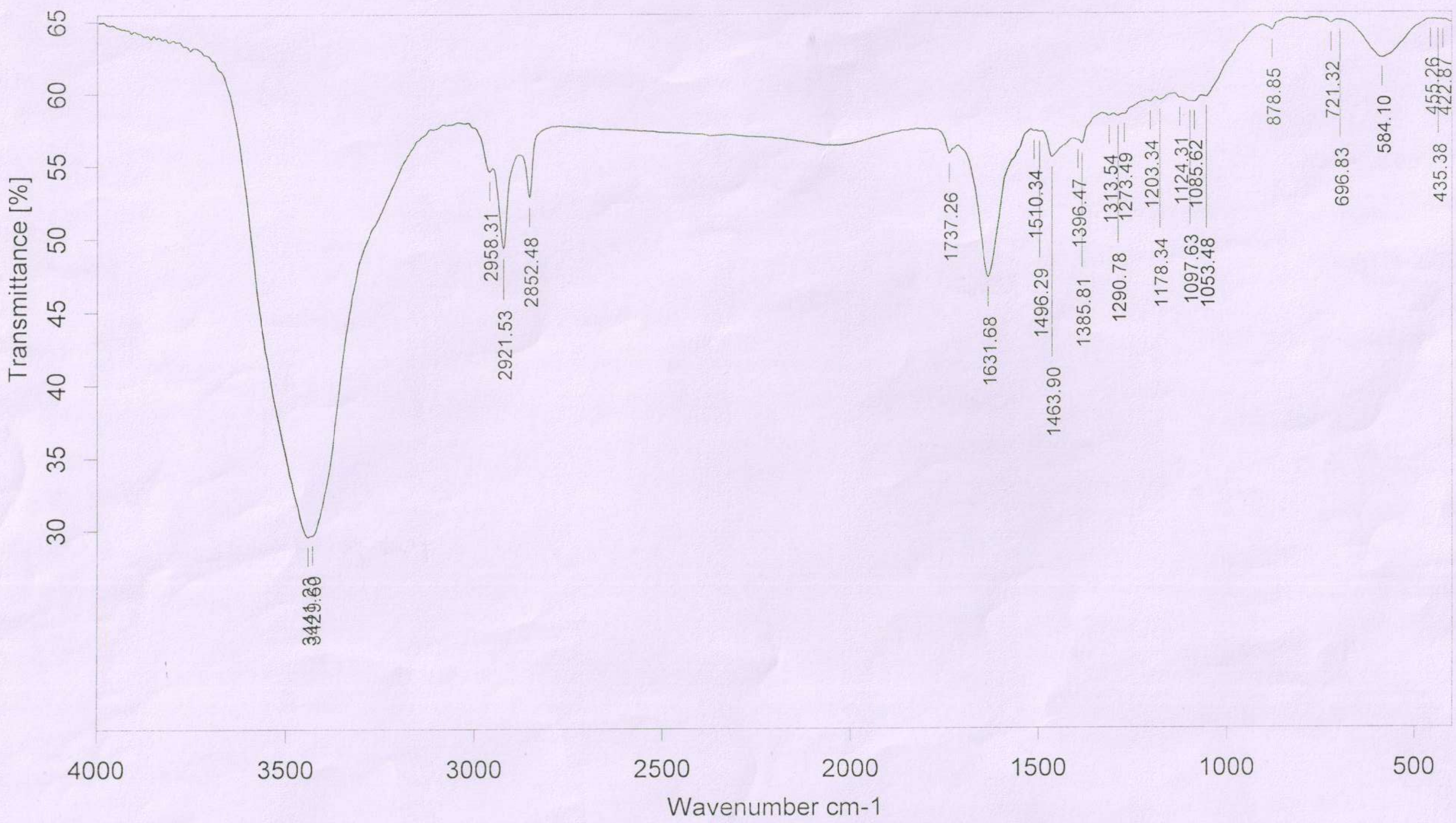


C30 H31 N O8 [M+Na]+ : Predicted region for 556.1942 m/z



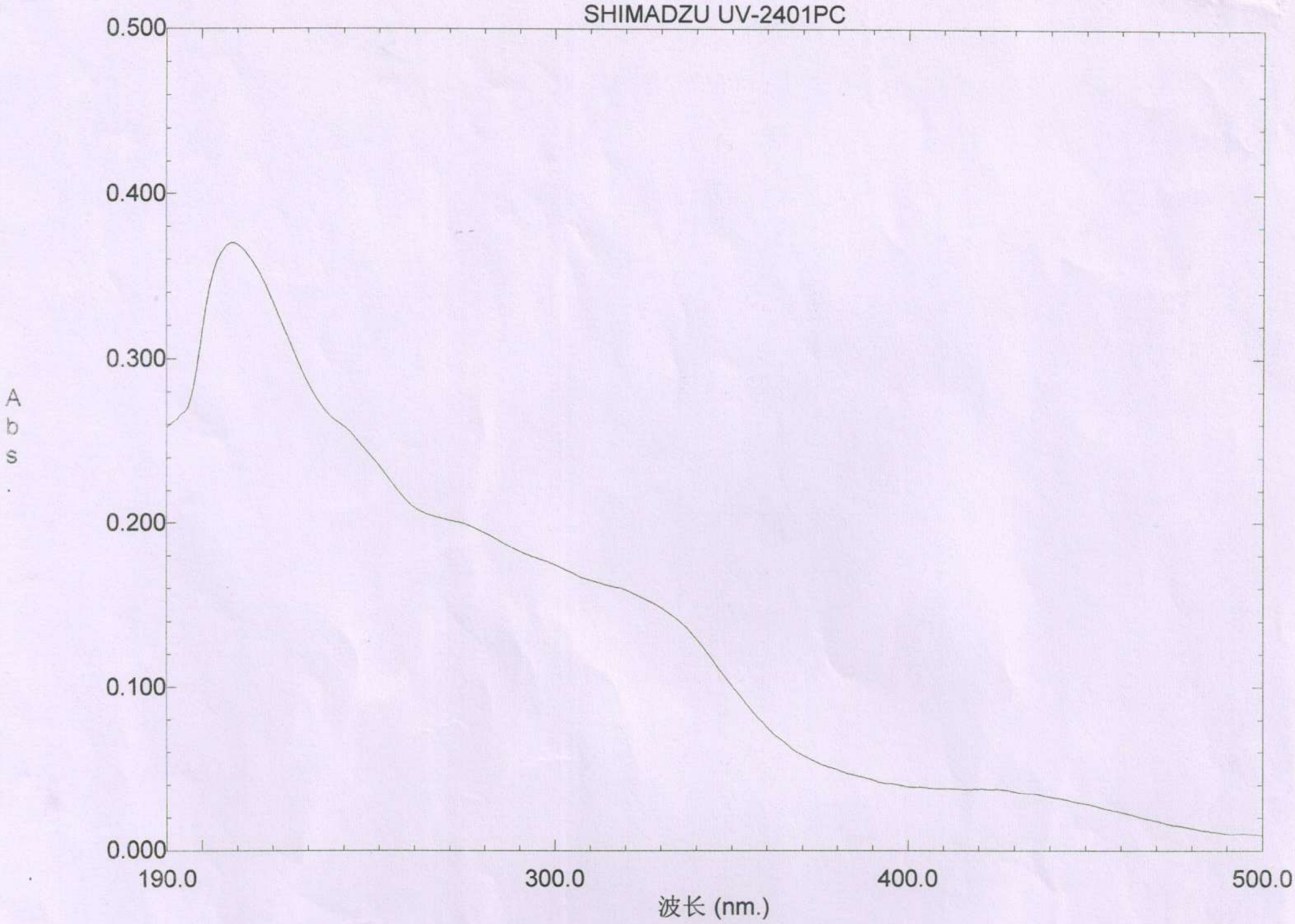
Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	DBE
C30 H31 N O8	[M+Na]+	556.1941	556.1942	-0.1	-0.18	16.0

Figure S21. IR spectrum of thalfoetine C (**3**)



Sample : wtflr-9	Frequency Range : 399.246 - 3996.32		Measured on : 04/09/2017
Technique : KBr压片	Resolution : 4	Instrument : Tensor27	Sample Scans : 16
Customer : 170904IR2	Zerofilling : 2	Acquisition : Double Sided,For	

Figure S22. UV spectrum of thalfoetine C (**3**)



文件名: WTFLR-9

WTFLR-9———

样品浓度：0.0239毫克/毫升
溶剂：甲醇

创建于: 18:09 17-09-05
数据: 原始

测量模式: Abs.
扫描速度: 中速
狭缝: 5.0
采样间隔: 0.5

否.	波长 (nm.)	Abs.
1	208.50	0.3698
2	238.00	0.2618
3	265.50	0.2039
4	315.50	0.1615
5	416.00	0.0369

Figure S23. ^{1}H NMR spectrum of thalfoetine C (**3**) in $CDCl_3$ (600 MHz)

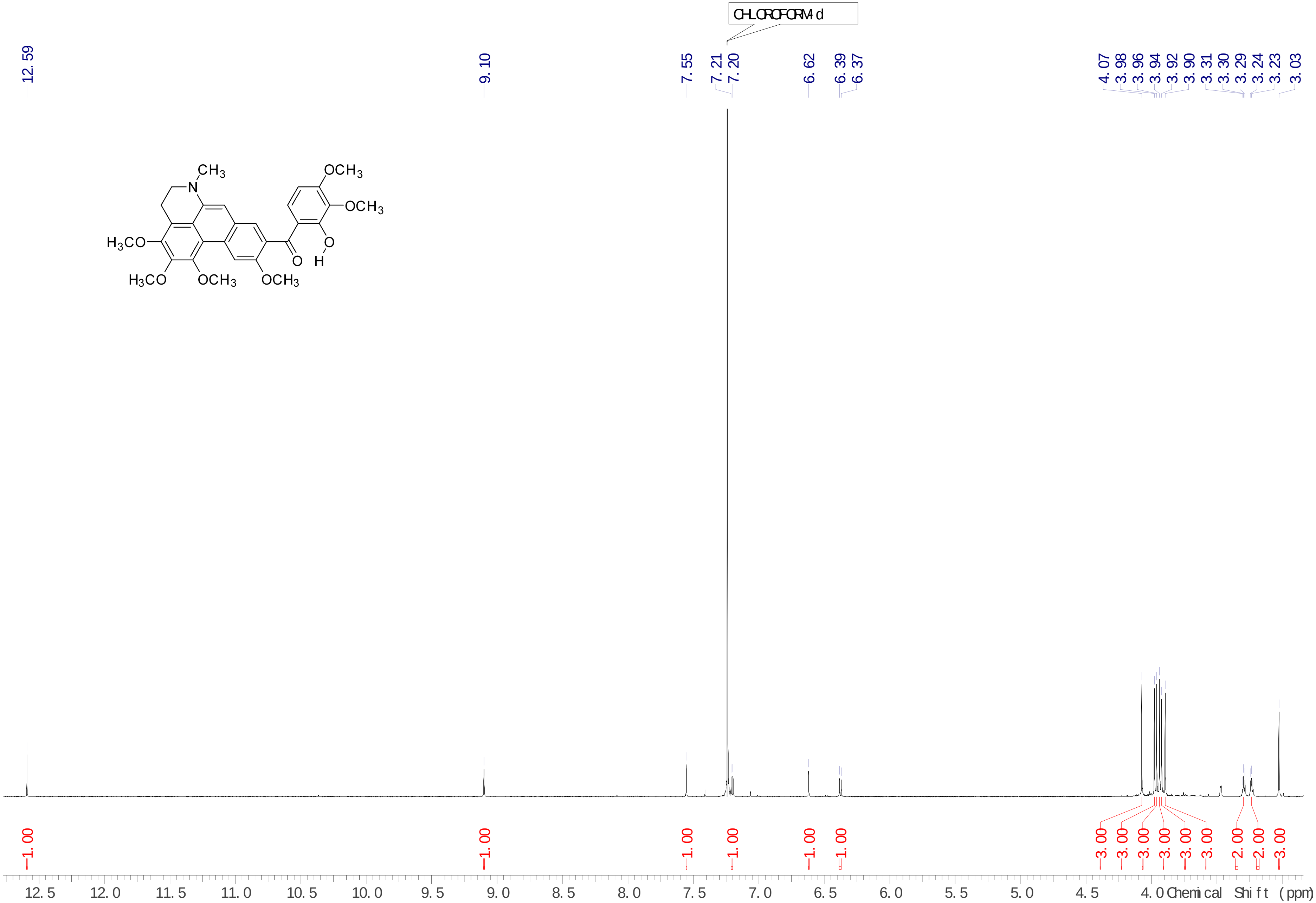


Figure S24. ^{13}C NMR spectrum of thalfoetine C (**3**) in $CDCl_3$ (150 MHz)

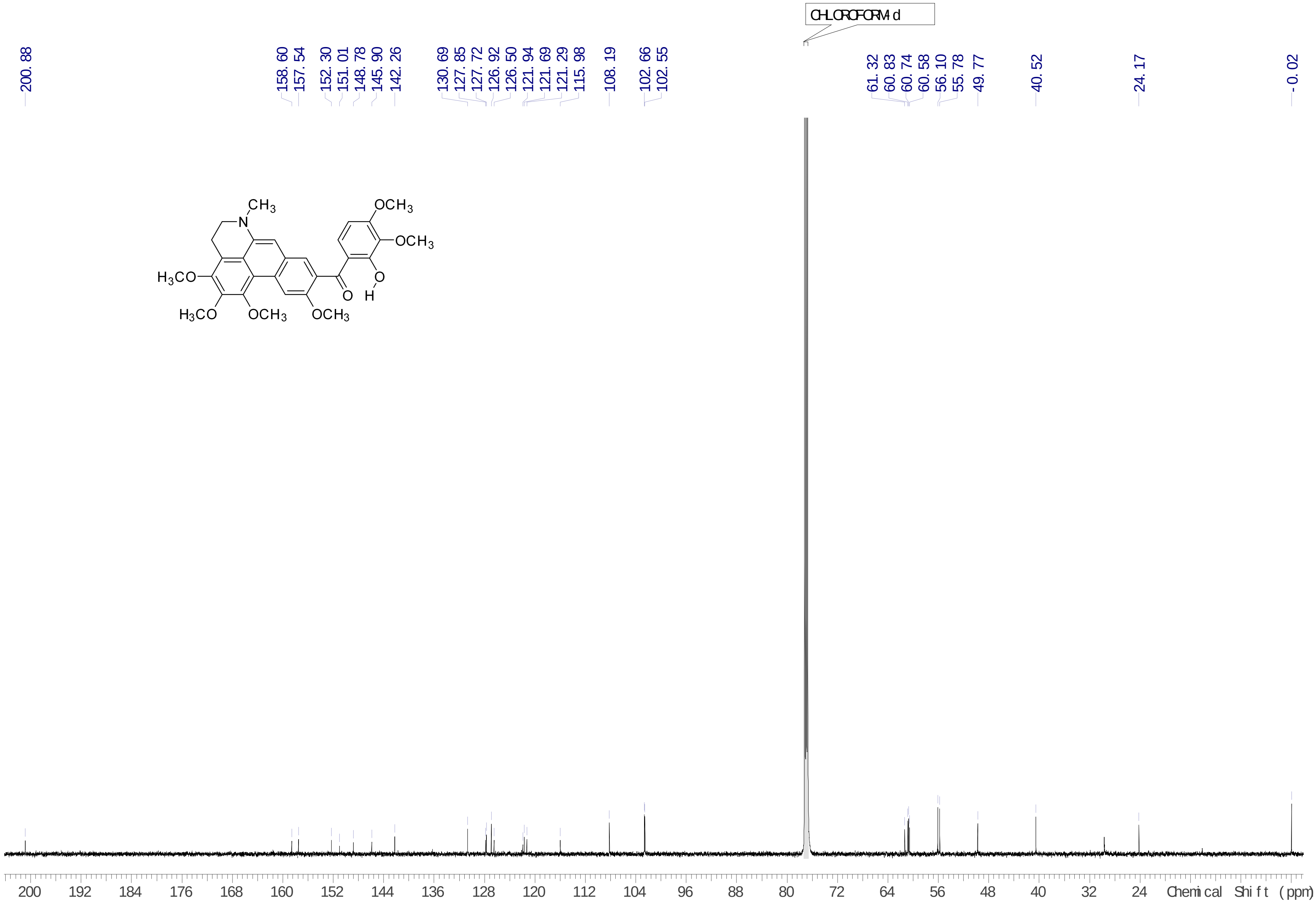
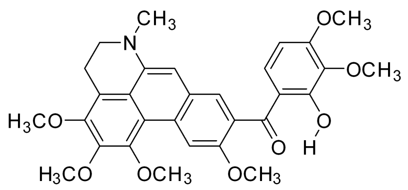


Figure S24-1. DEPT 90 spectrum of thalfoetine C (**3**) in $CDCl_3$ (150 MHz)



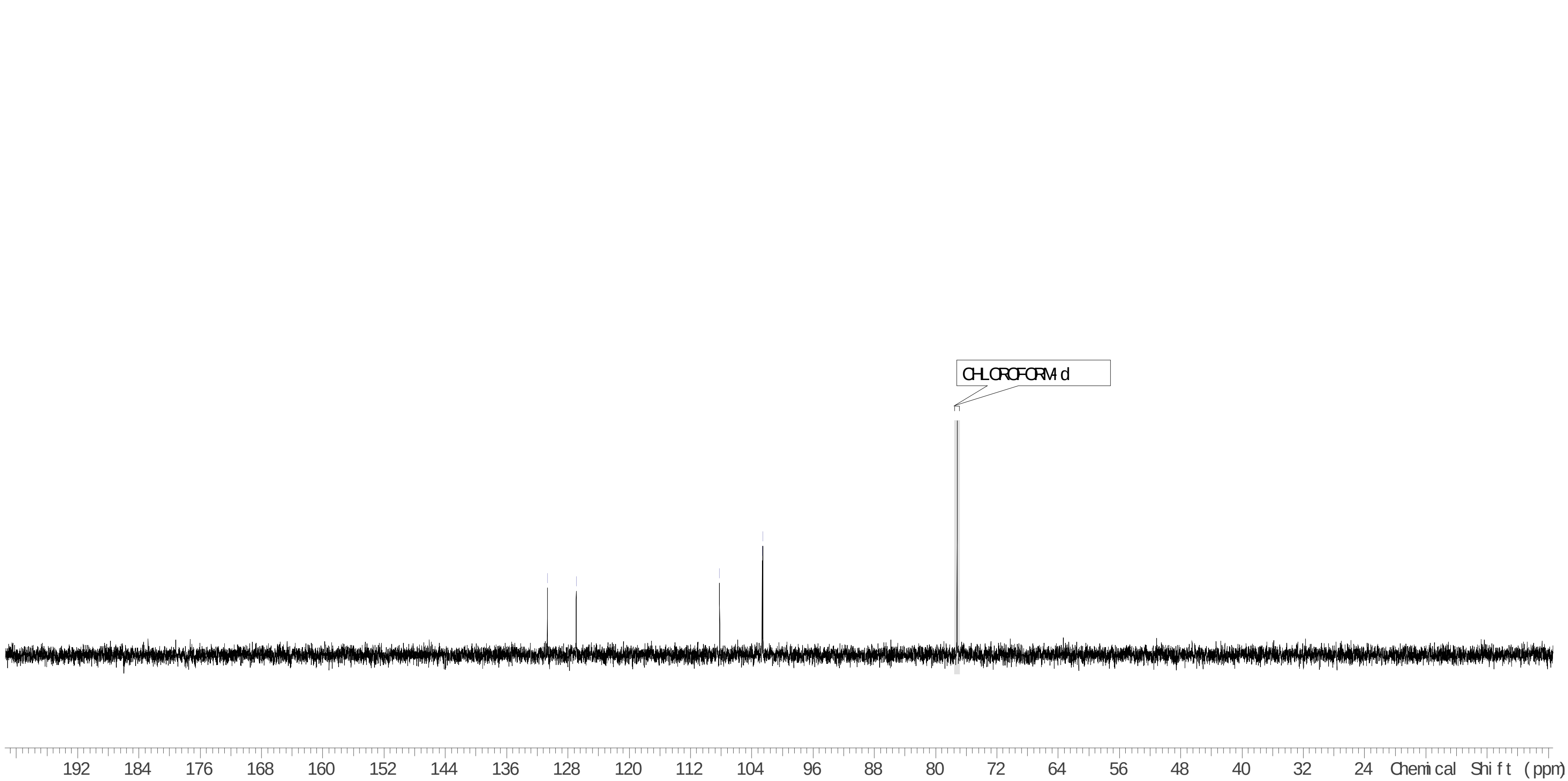


Figure S24-2. DEPT 135 spectrum of thalfoetine C (**3**) in $CDCl_3$ (150 MHz)

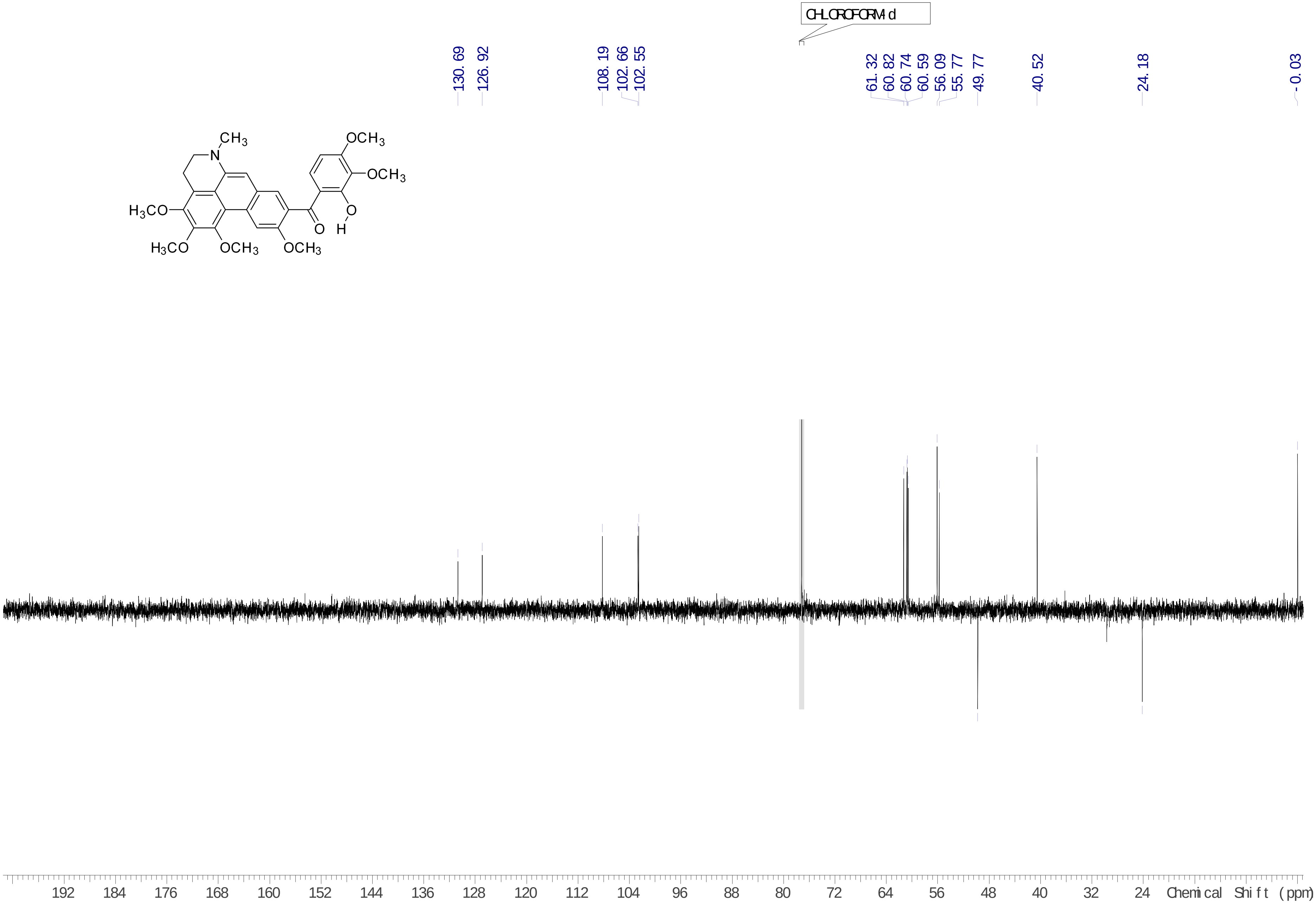
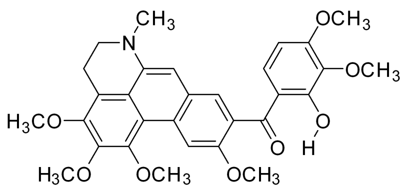


Figure S25. HSQC spectrum of thalfoetine C (**3**) in $CDCl_3$ (600 MHz)



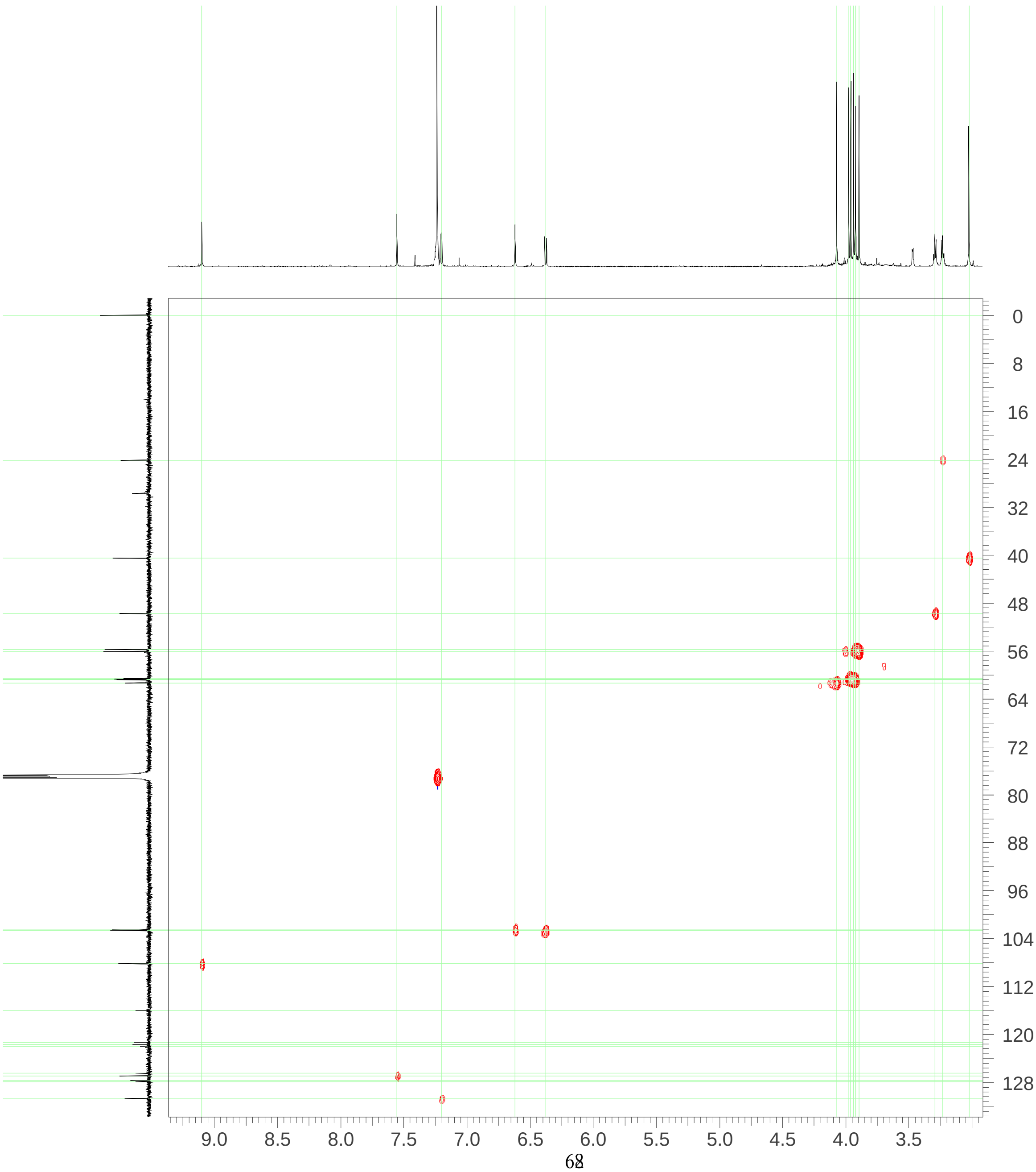


Figure S25-1. The partially enlarged HSQC spectrum of thalfoetine C (**3**)

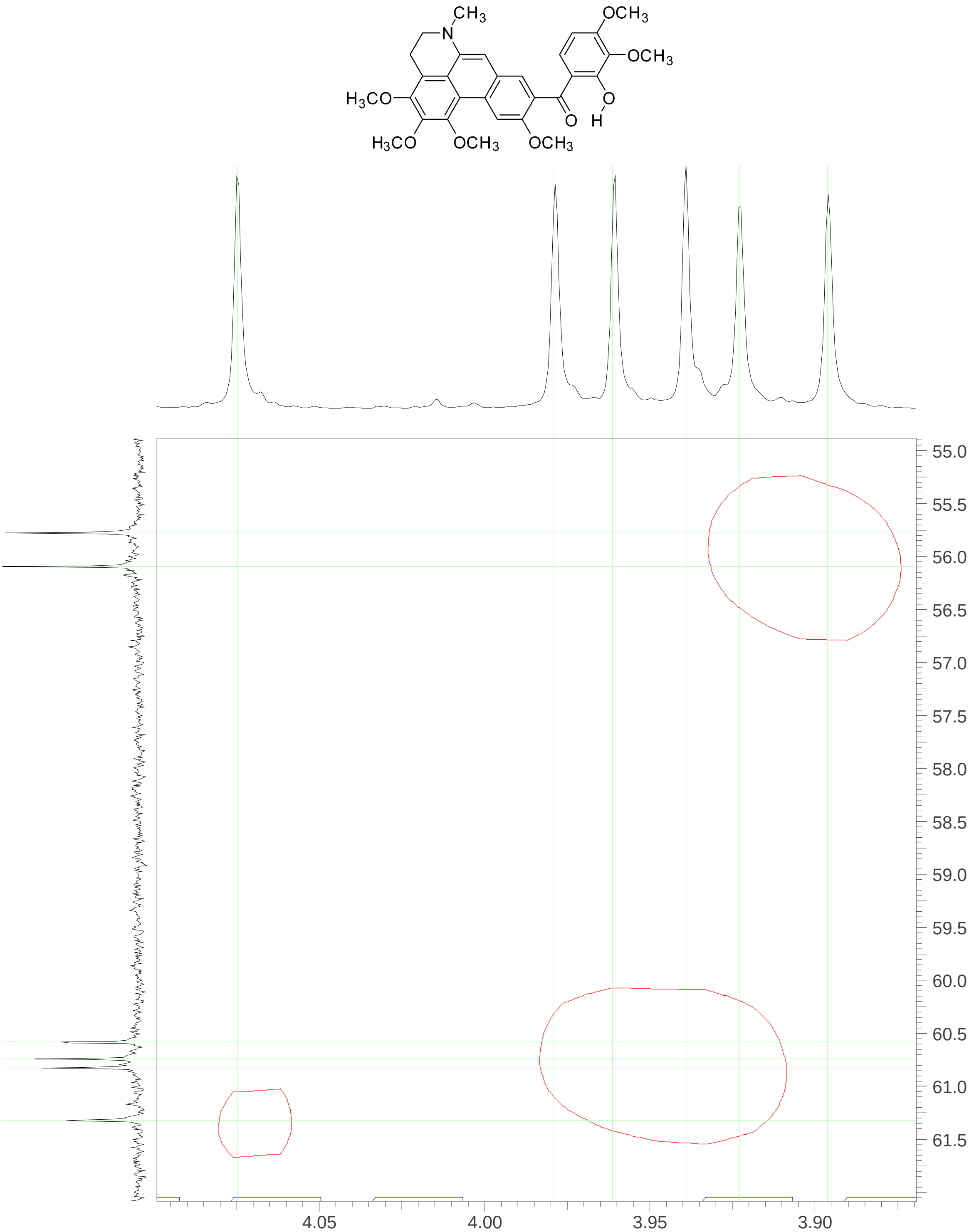


Figure S25-2. The partially enlarged HSQC spectrum of thalfoetine C (**3**)

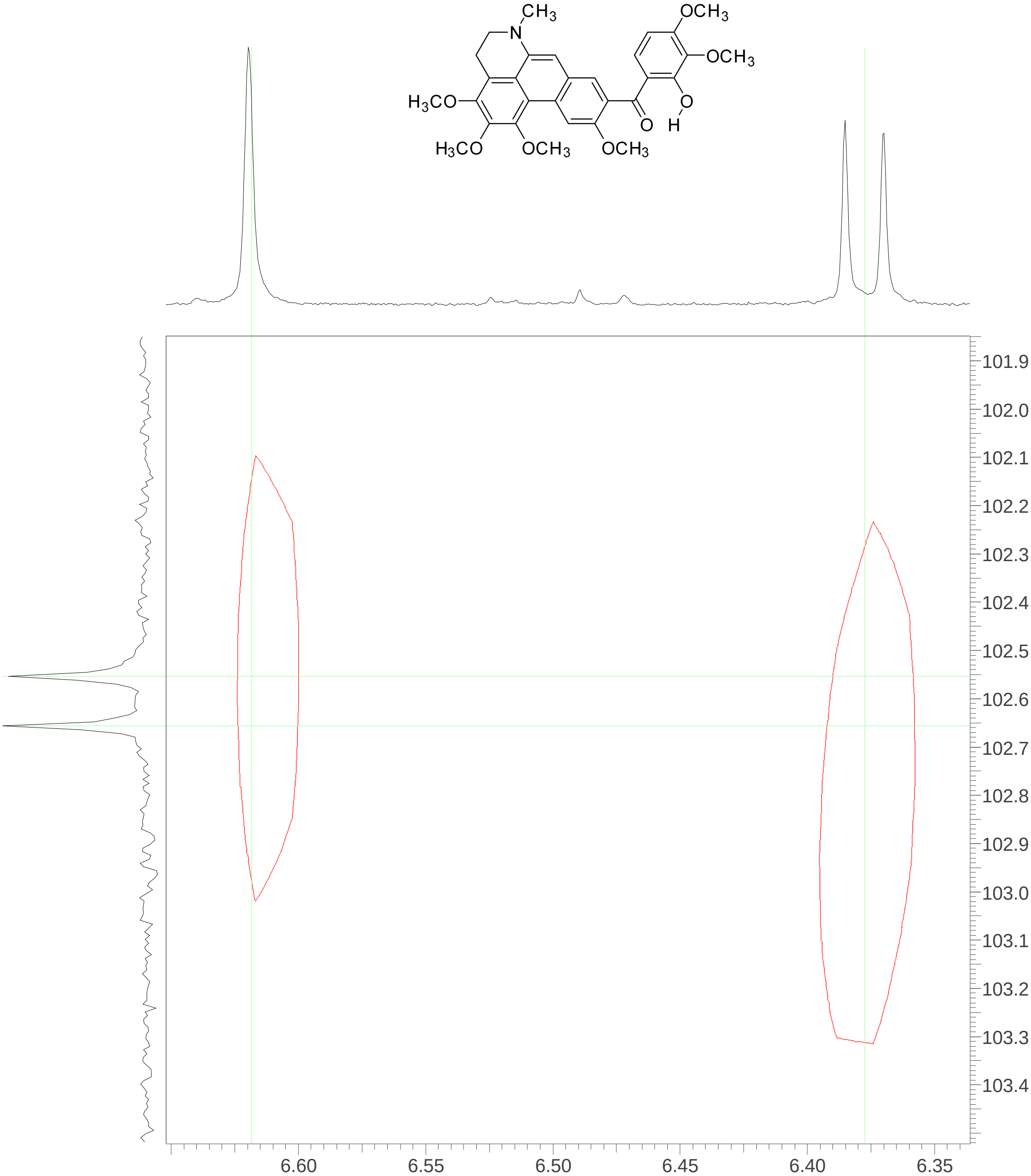
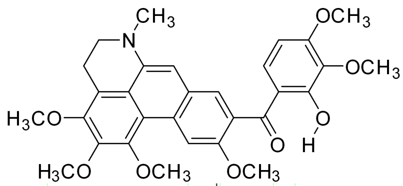


Figure S26. HMBC spectrum of thalfoetine C (**3**) in $CDCl_3$ (600 MHz)



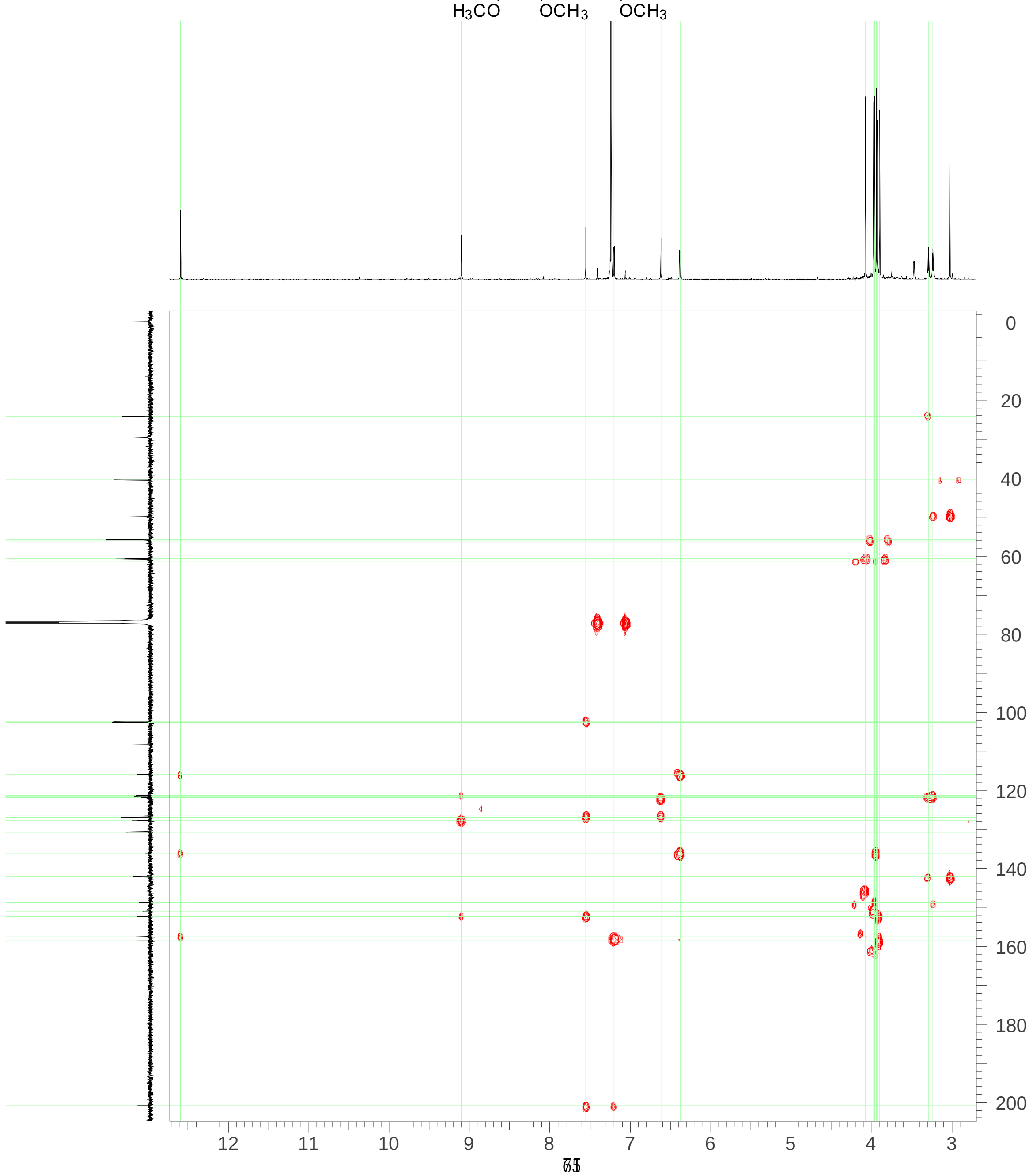
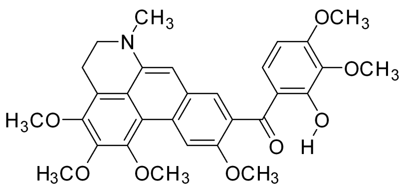


Figure S26-1. The partially enlarged HMBC spectrum of thalfoetine C (**3**)



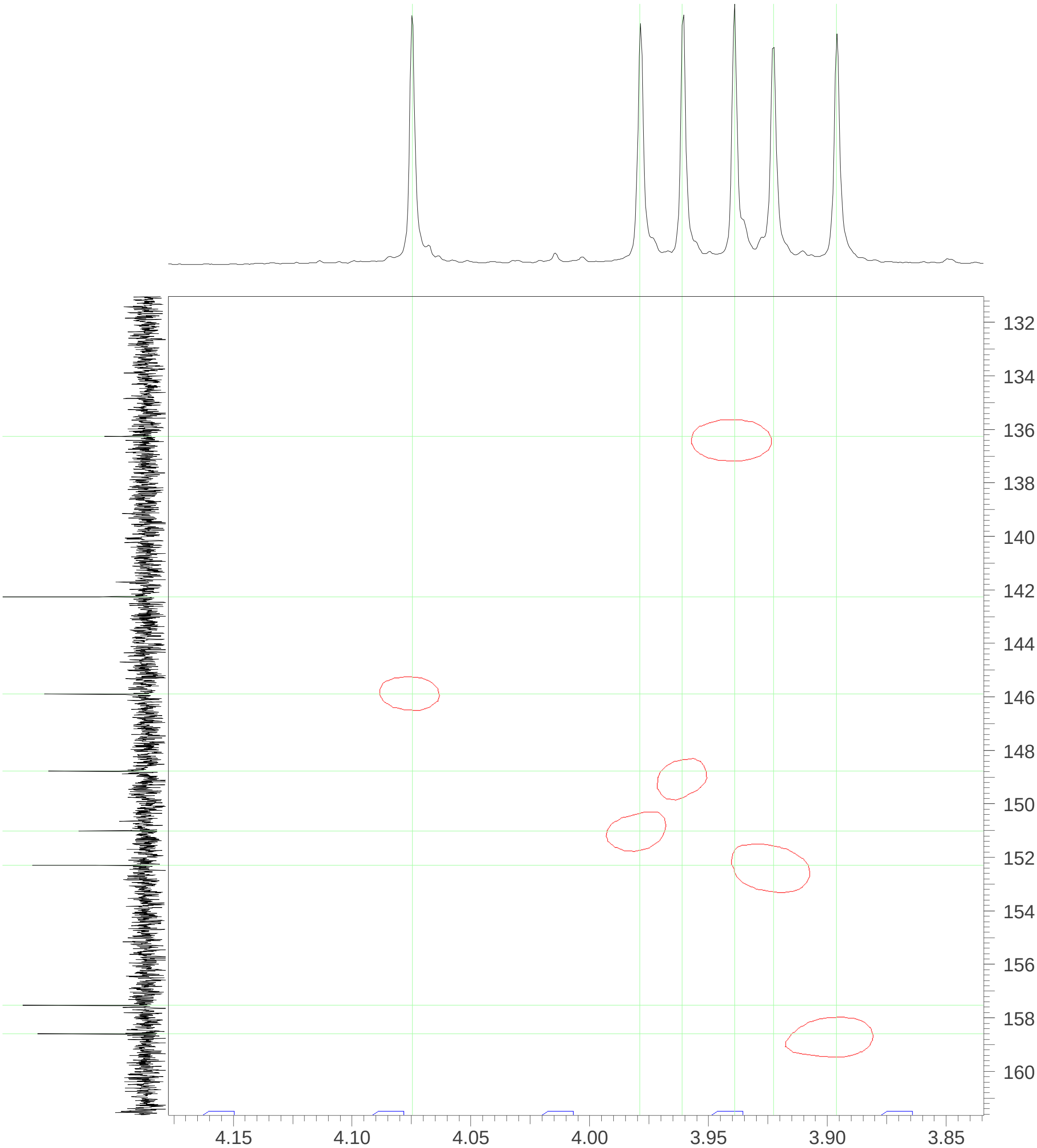
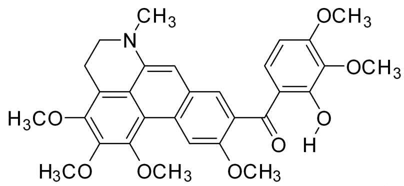


Figure S26-2. The partially enlarged HMBC spectrum of thalfoetine C (**3**)



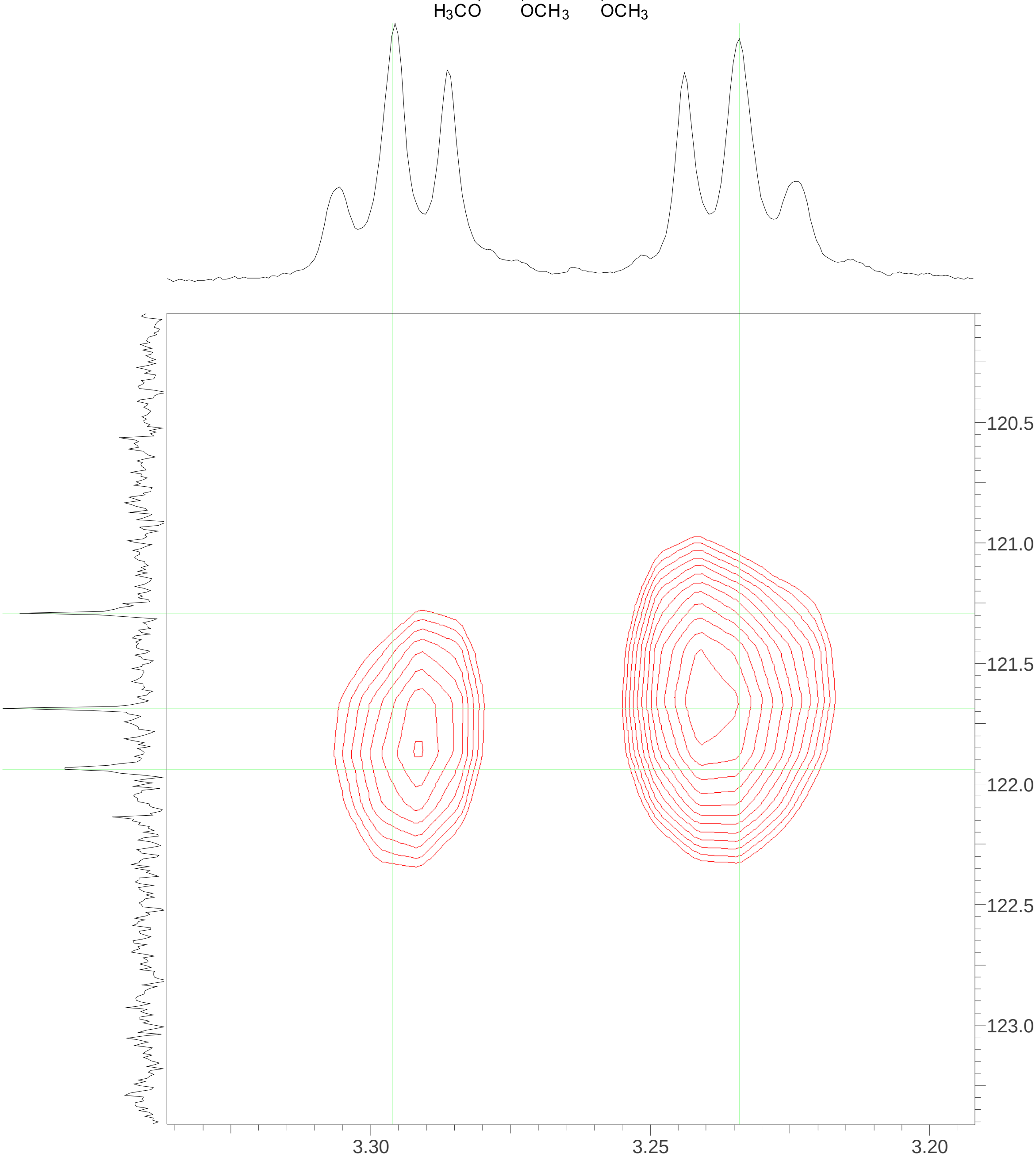
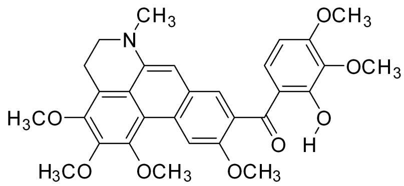


Figure S26-3. The partially enlarged HMBC spectrum of thalfoetine C (**3**)



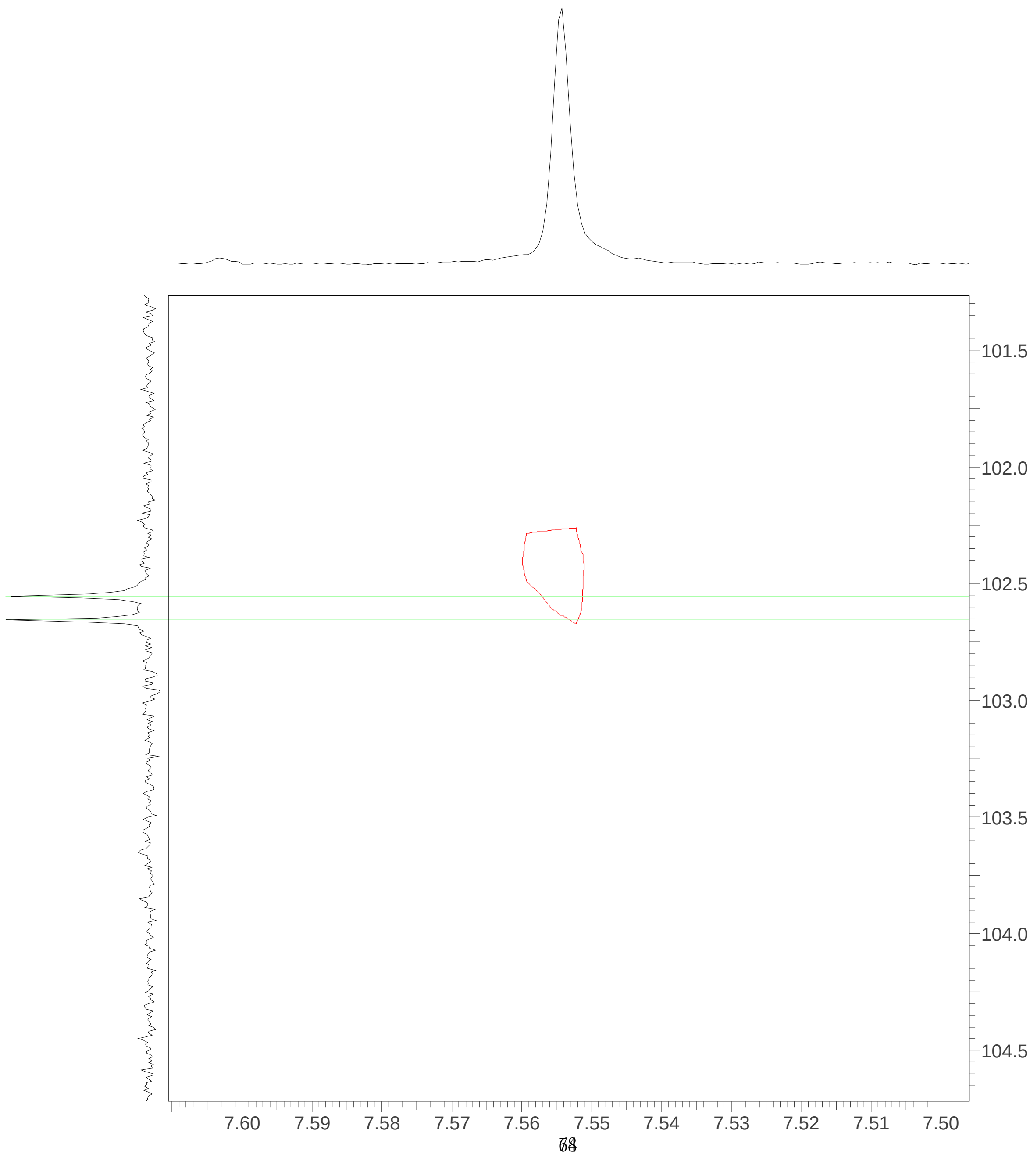
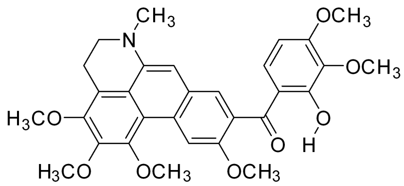


Figure S26-4. The partially enlarged HMBC spectrum of thalfoetine C (**3**)



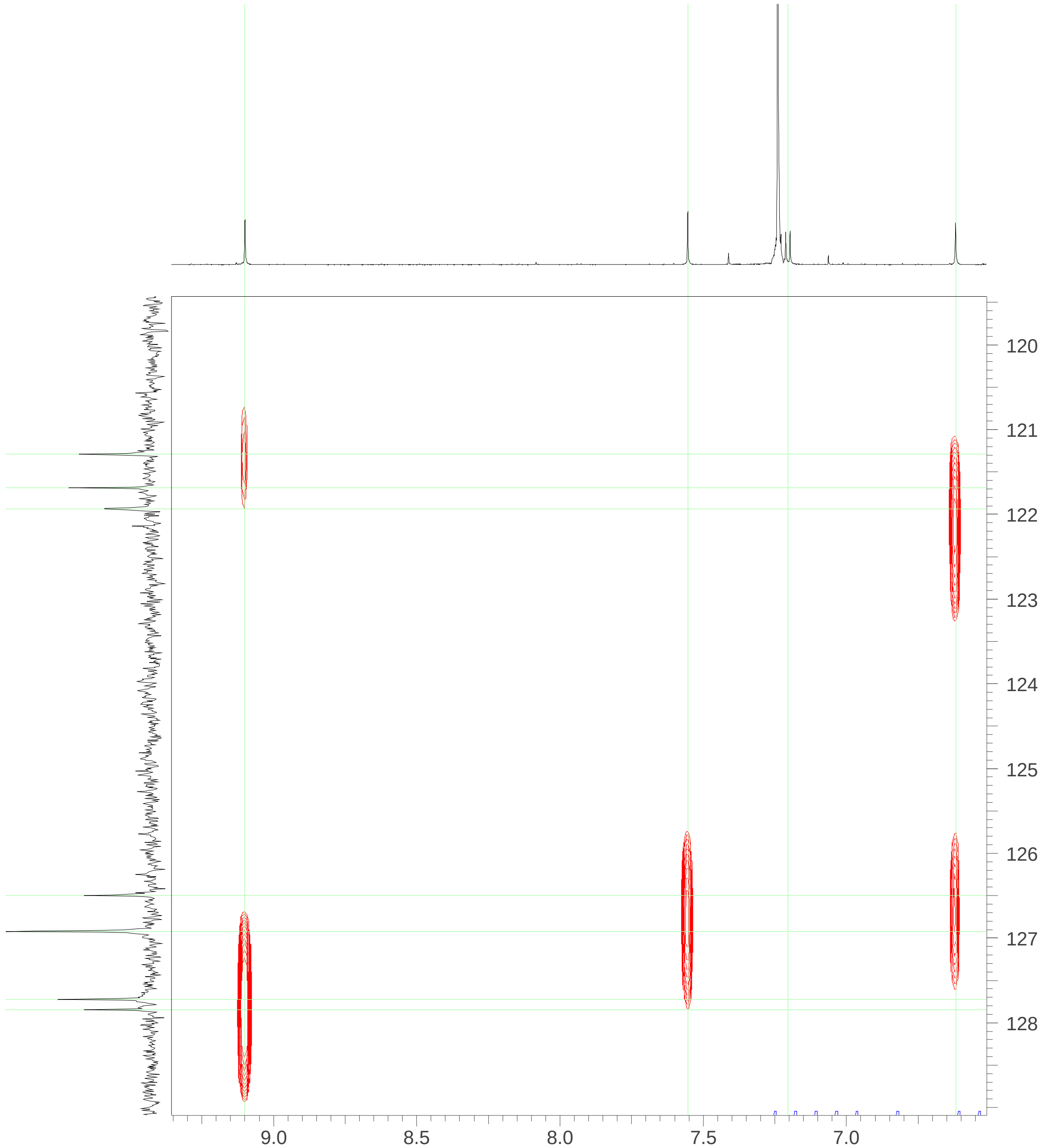


Figure S26-5. The partially enlarged HMBC spectrum of thalfoetine C (**3**)

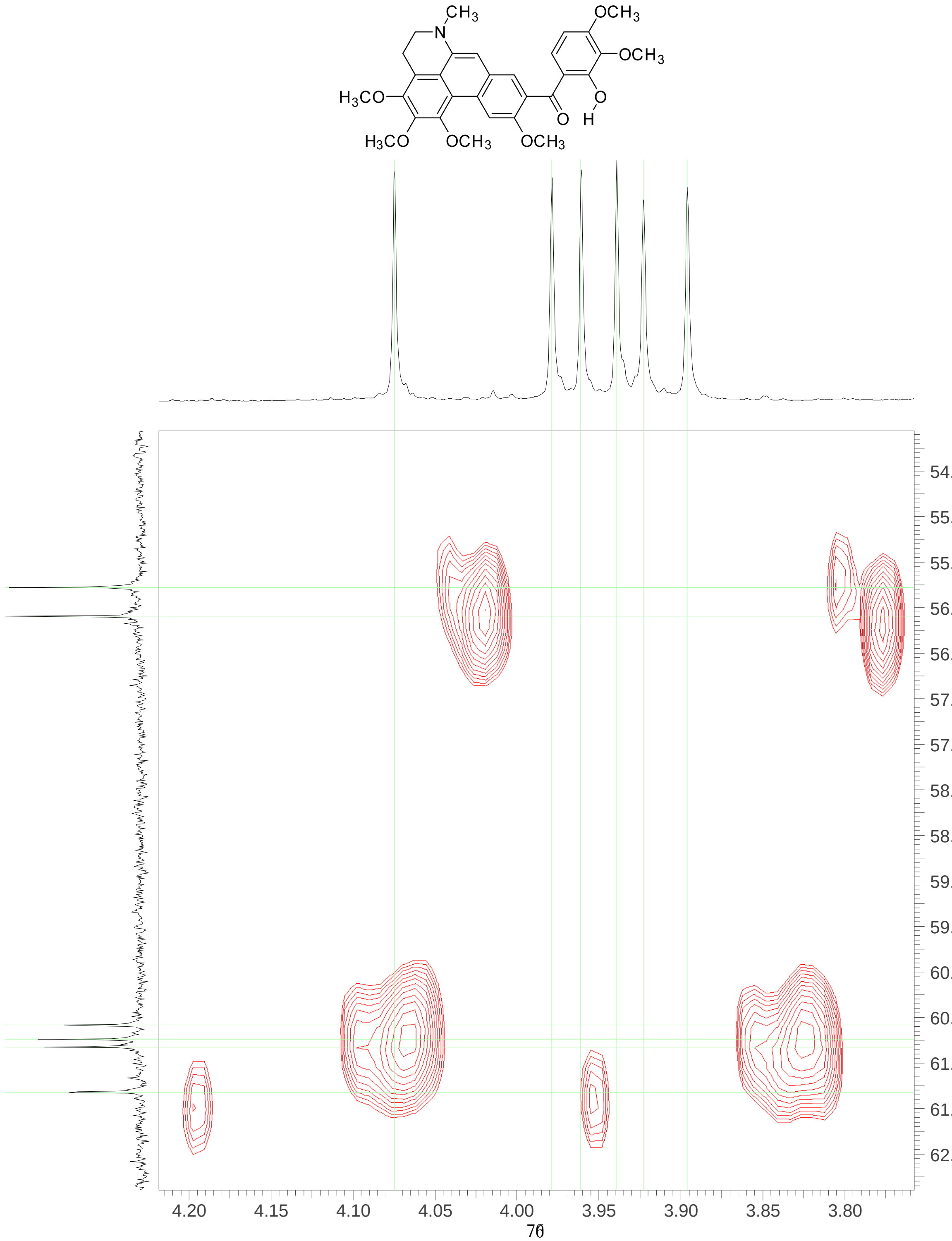


Figure S27. ROESY spectrum of thalfoetine C (**3**) in $CDCl_3$ (600 MHz)

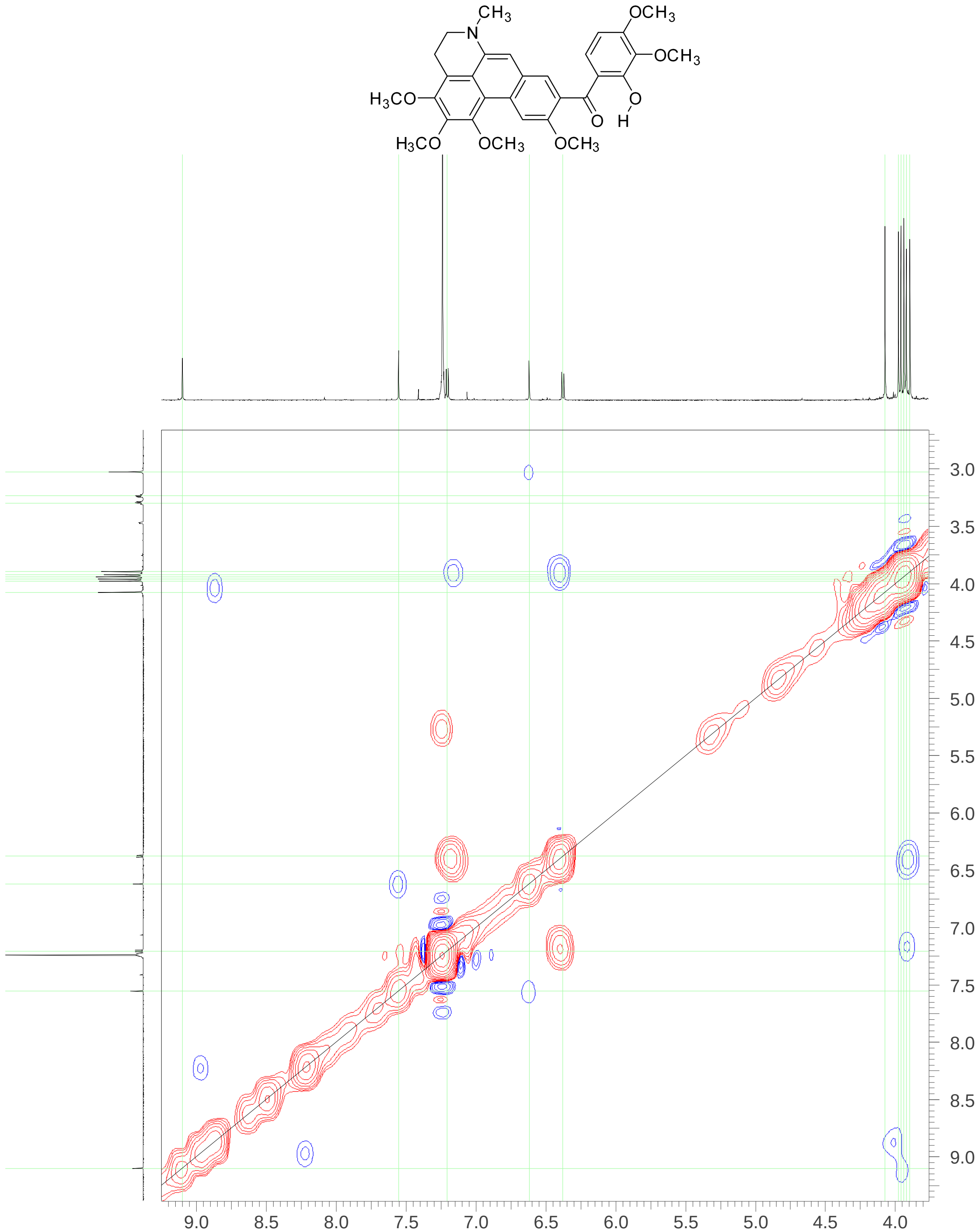


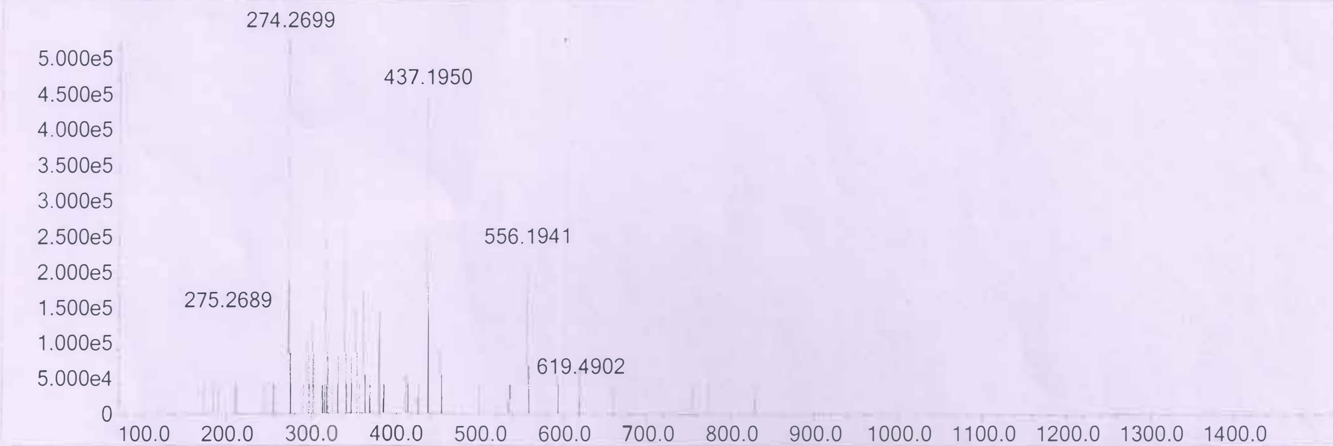
Figure S28. HREIMS spectrum of thalfoetine D (**4**)

Data File: E:\DATA\2017\0531\wtflr-8.lcd

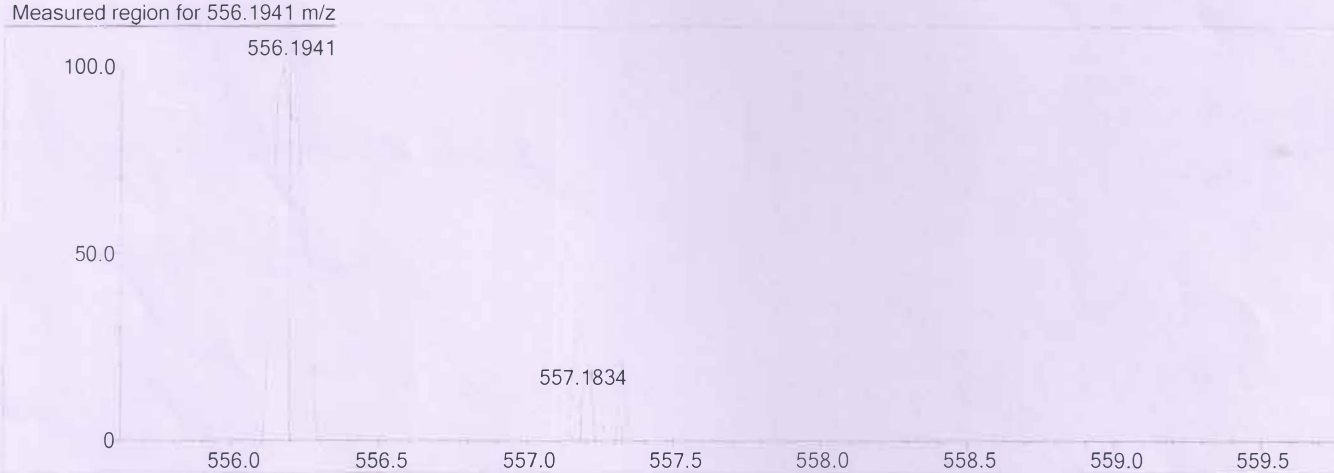
Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Elmt	Val.	Min	Max	Use Adduct
H	1	0	150	O	2	0	50	S	2	0	0	Pt	2	0	0	Na
B	3	0	0	F	1	0	0	Cl	1	0	0					
C	4	0	100	Na	1	0	0	Br	1	0	0					
N	3	0	15	Si	4	0	0	I	3	0	0					

Error Margin (ppm):	10	DBE Range:	-2.0 - 100.0	Electron Ions:	both
HC Ratio:	unlimited	Apply N Rule:	yes	Use MSn Info:	yes
Max Isotopes:	all	Isotope RI (%):	1.00	Isotope Res:	10000
MSn Iso RI (%):	75.00	MSn Logic Mode:	AND	Max Results:	100

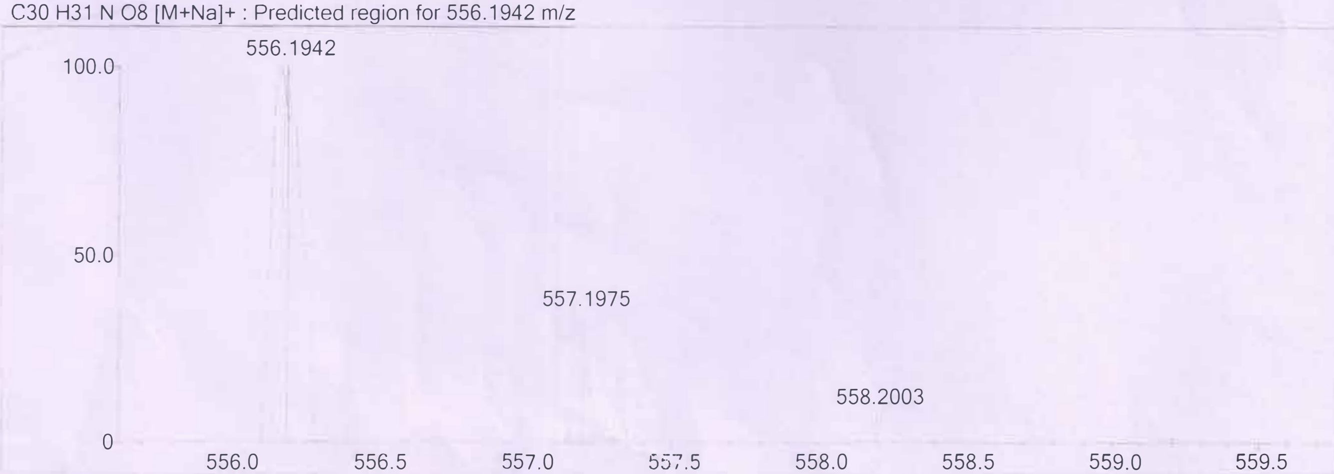
Event#: 1 MS(E+) Ret. Time : 0.420 Scan# : 85



Measured region for 556.1941 m/z

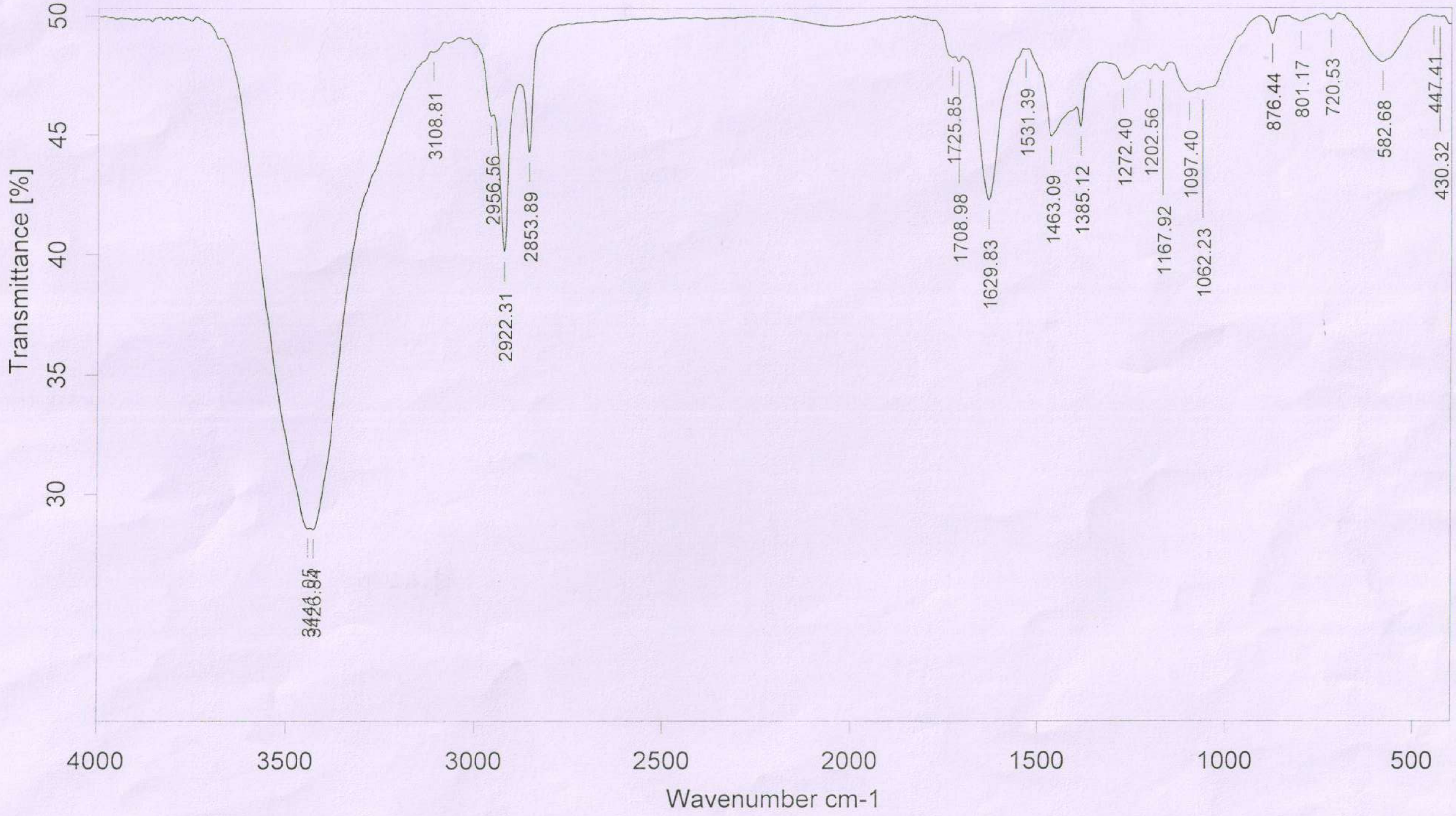


C30 H31 N O8 [M+Na]+ : Predicted region for 556.1942 m/z



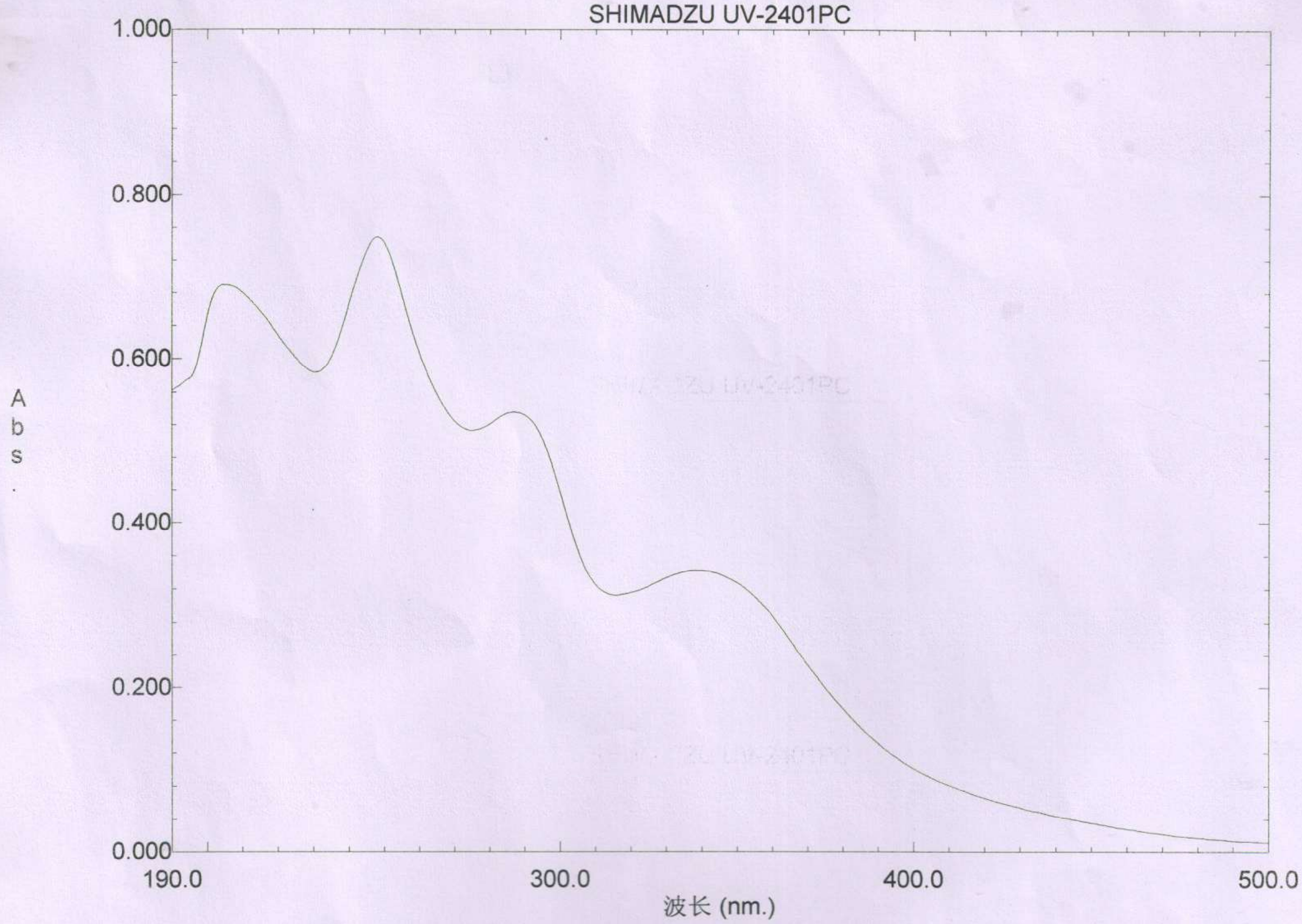
Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	DBE
C30 H31 N O8	[M+Na]+	556.1941	556.1942	-0.1	-0.18	16.0

Figure S29. IR spectrum of thalfoetine D (**4**)



Sample : wtflr-8	Frequency Range : 399.246 - 3996.32	Measured on : 04/09/2017	
Technique : KBr压片	Resolution : 4	Instrument : Tensor27	Sample Scans : 16
Customer : 170904IR0	Zerofilling : 2	Acquisition : Double Sided,For	

Figure S30. UV spectrum of thalfoetine D (**4**)



文件名: WTFLR-8

WTFLR-8

样品浓度：0.0224毫克/毫升
溶剂：甲醇

创建于: 18:02 17-09-05
数据: 原始

测量模式: Abs.
扫描速度: 中速
狭缝: 5.0
采样间隔: 0.5

否.	波长 (nm.)	Abs.
1	339.00	0.3424
2	287.00	0.5352
3	248.00	0.7476
4	205.00	0.6892

Figure S31. ^{1}H NMR spectrum of thalfoetine D (**4**) in $CDCl_3$ (600 MHz)

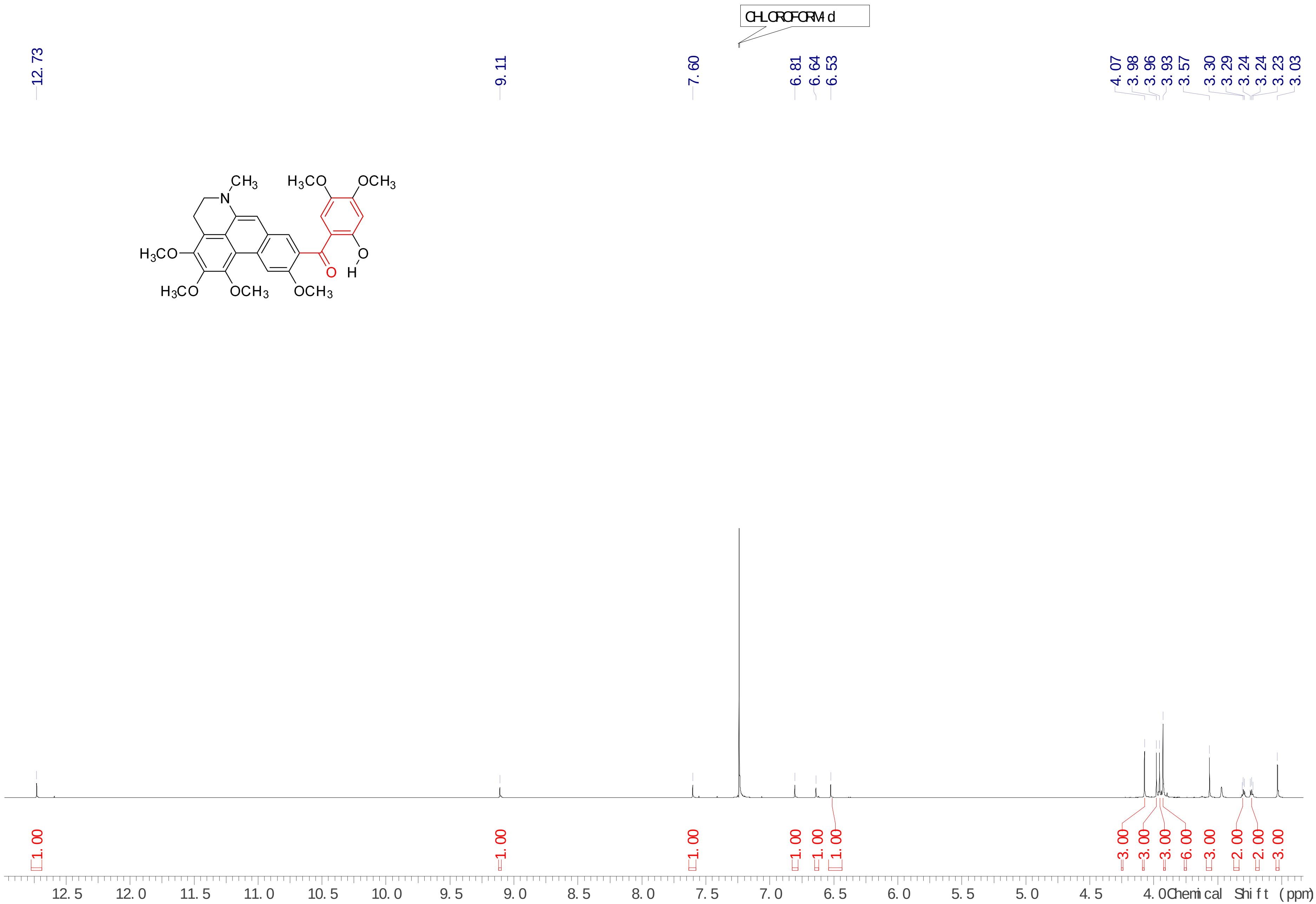


Figure S32. ^{13}C NMR spectrum of thalfoetine D (**4**) in $CDCl_3$ (150 MHz)

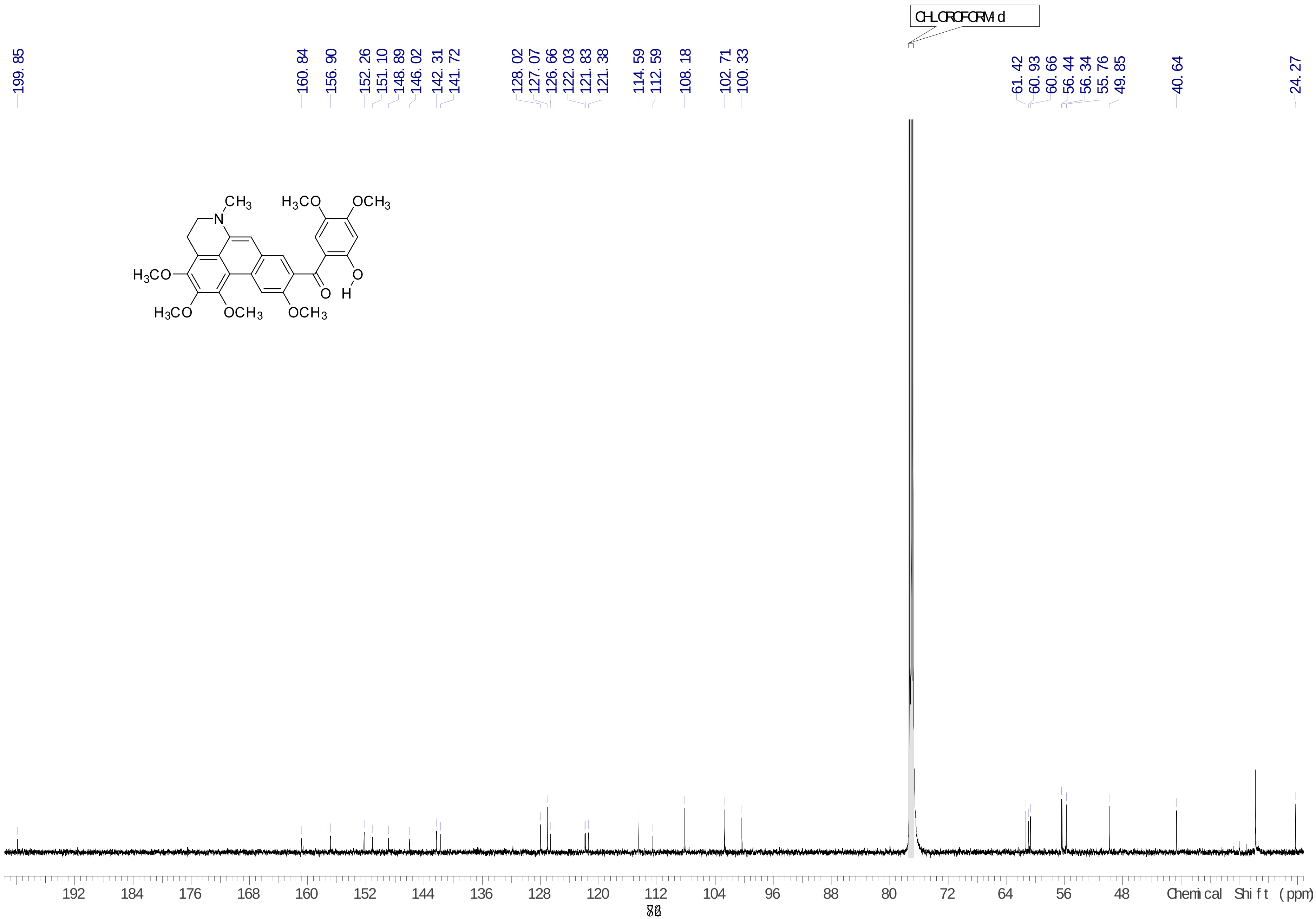
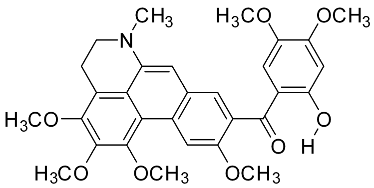


Figure S32-1. DEPT 90 spectrum of thalfoetine D (**4**) in $CDCl_3$ (150 MHz)



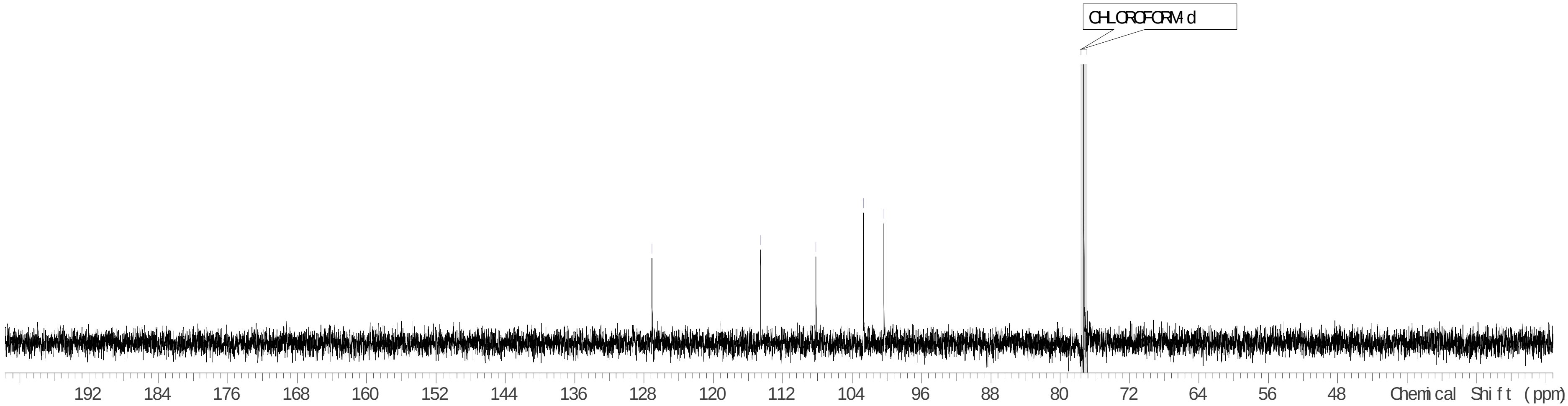


Figure S32-2. DEPT 135 spectrum of thalfoetine D (**4**) in $CDCl_3$ (150 MHz)

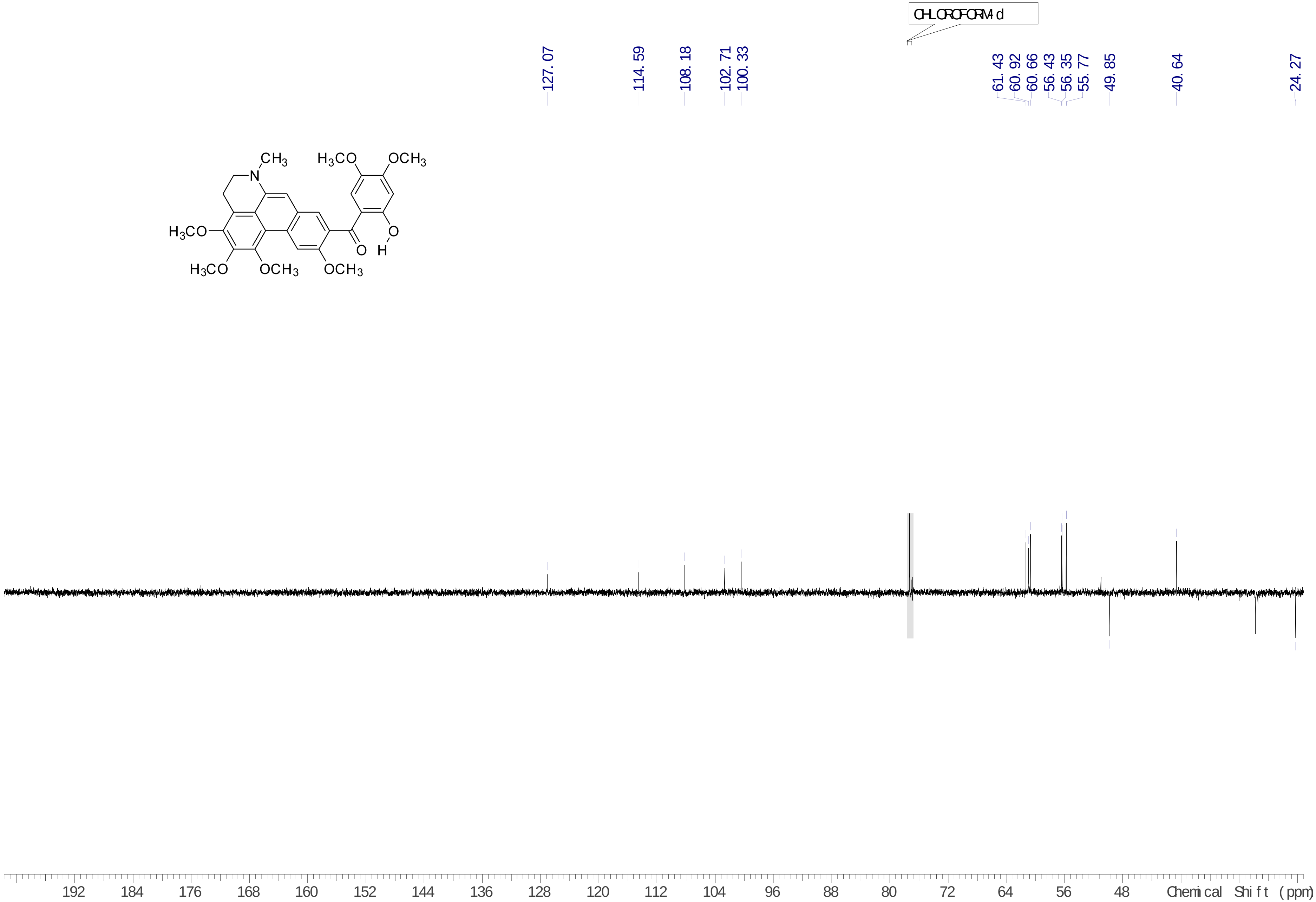
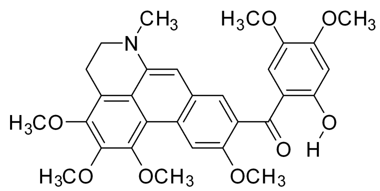


Figure S33. HSQC spectrum of thalfoetine D (**4**) in $CDCl_3$ (600 MHz)



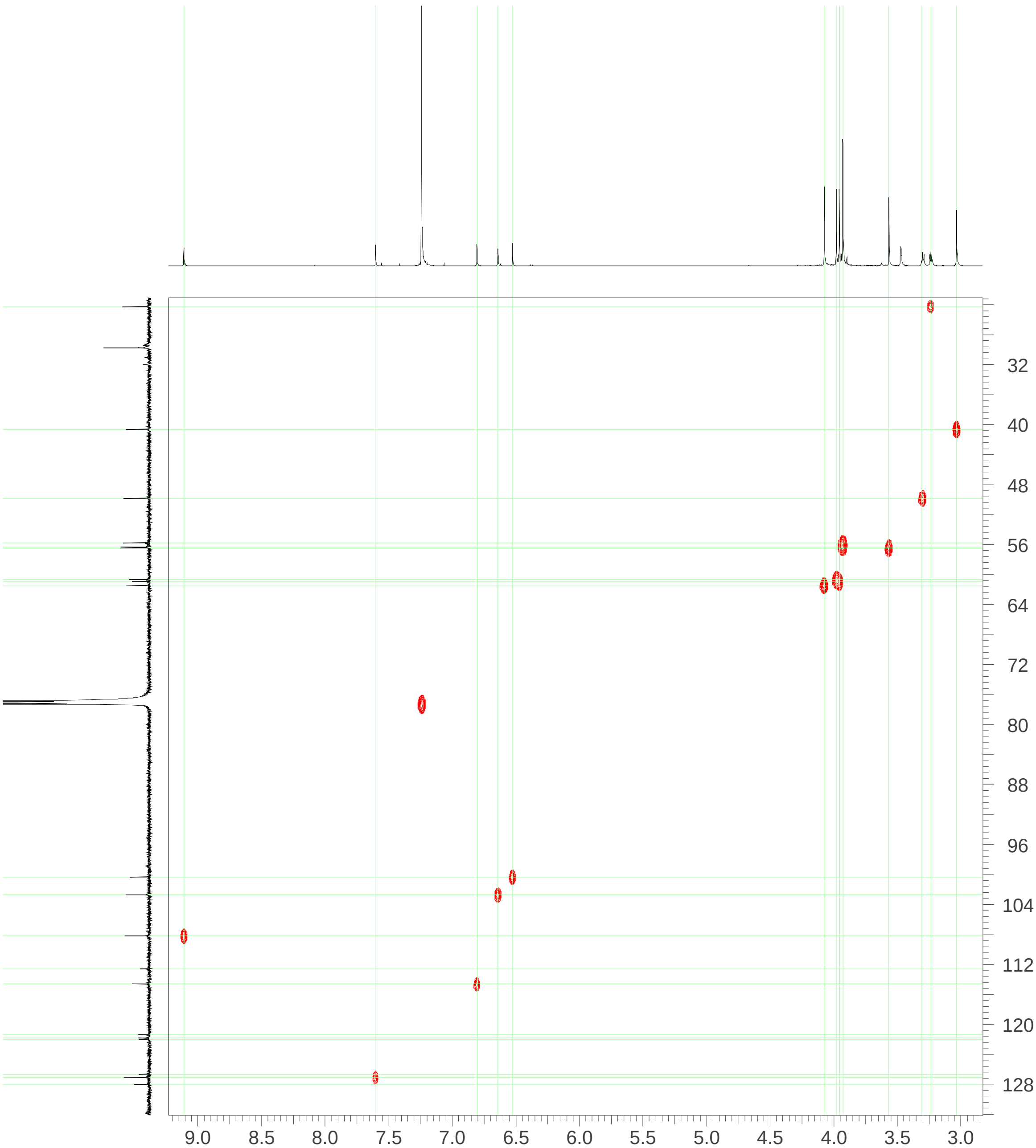
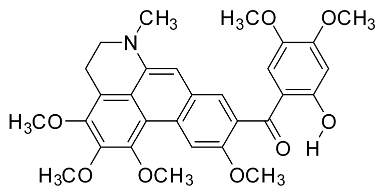


Figure S33-1. The partially enlarged HSQC spectrum of thalfoetine D (**4**)



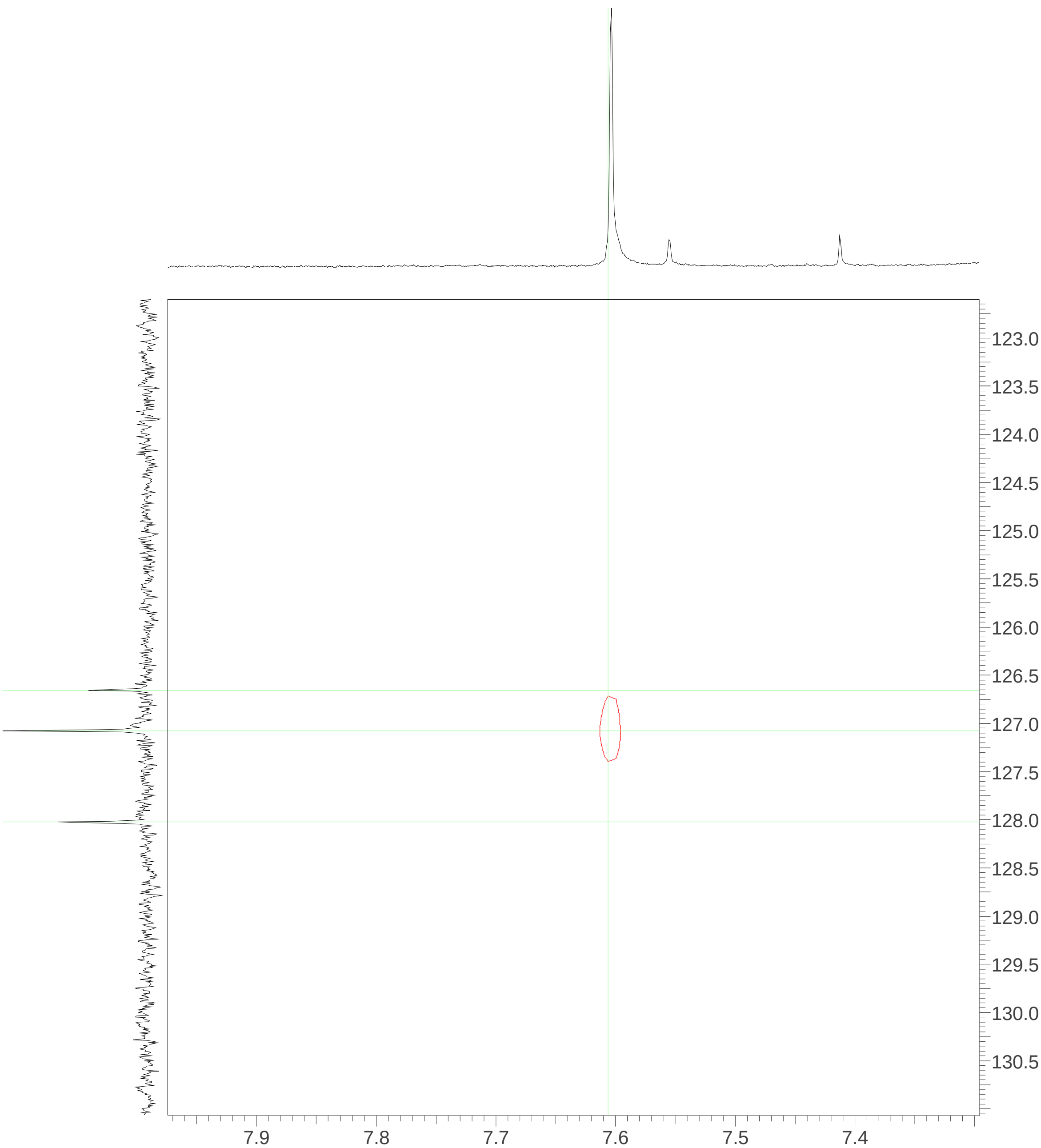
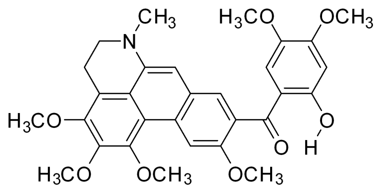


Figure S34. HMBC spectrum of thalfoetine C (**4**) in $CDCl_3$ (600 MHz)



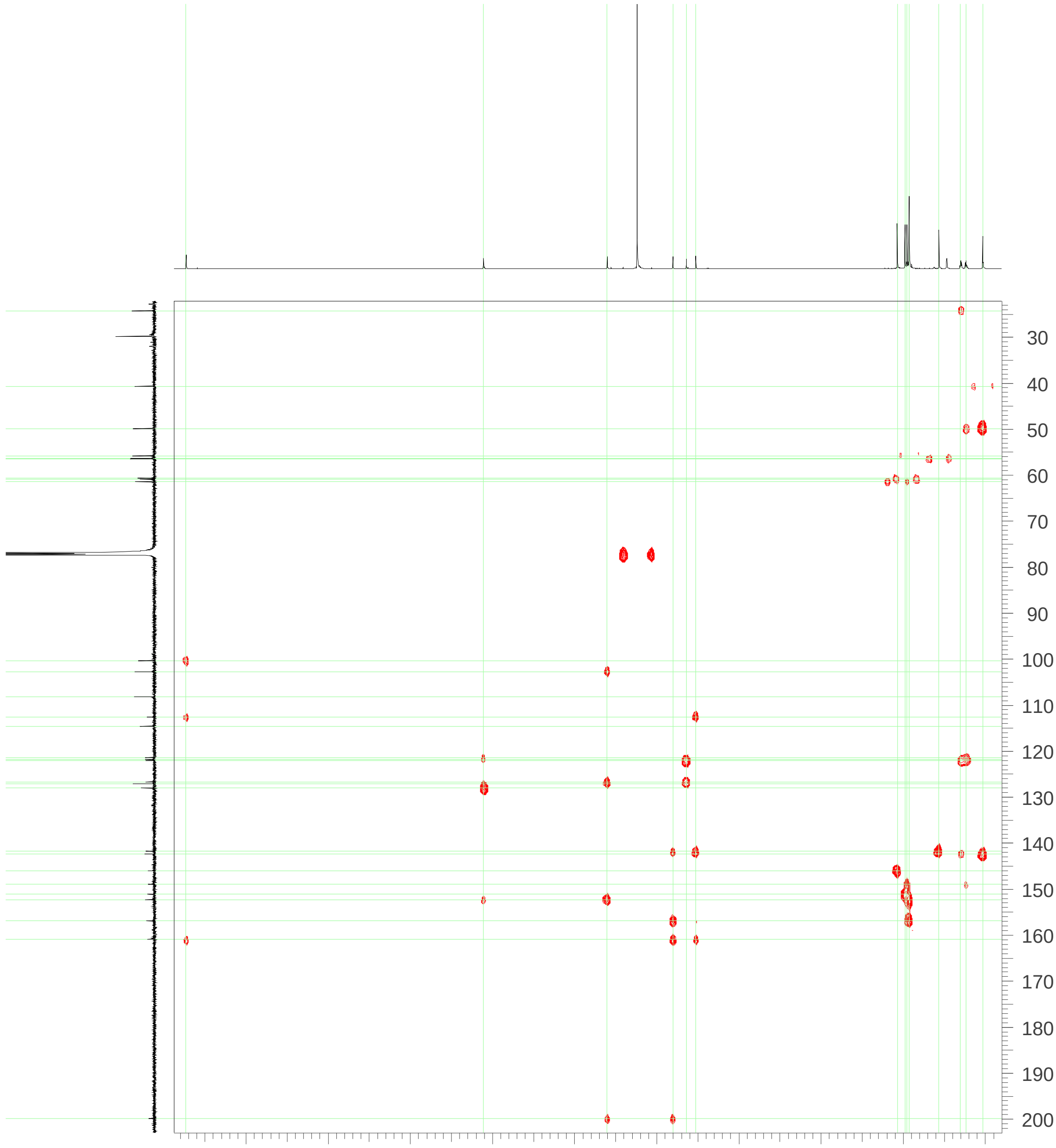
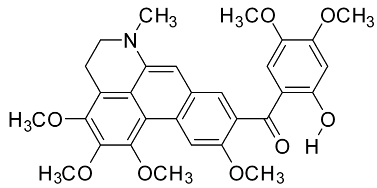


Figure S34-1. The partially enlarged HMBC spectrum of thalfoetine C (**4**)



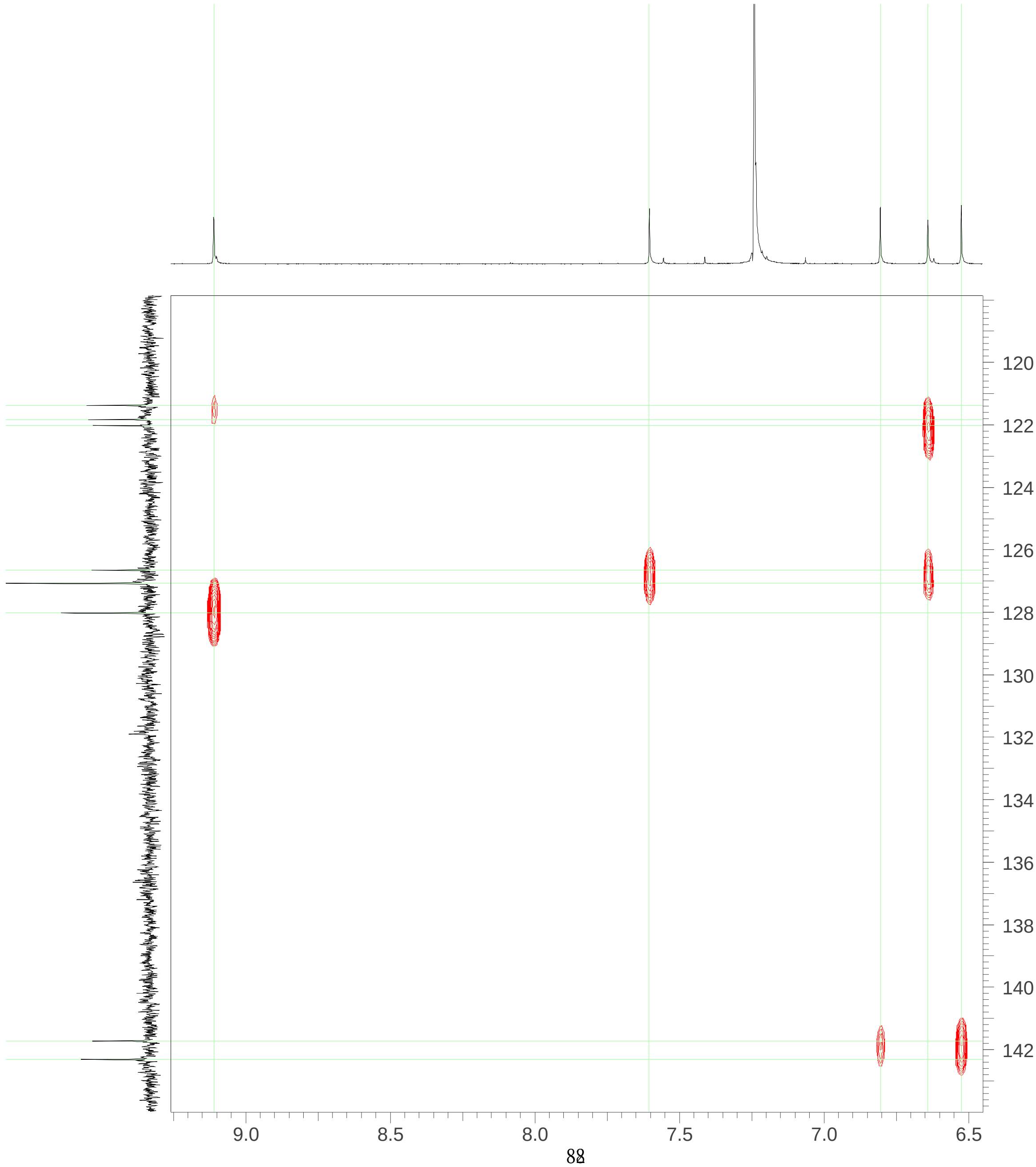
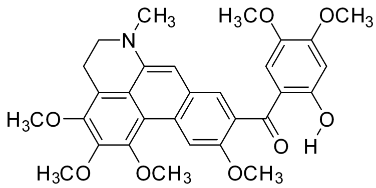


Figure S34-2. The partially enlarged HMBC spectrum of thalfoetine C (**4**)



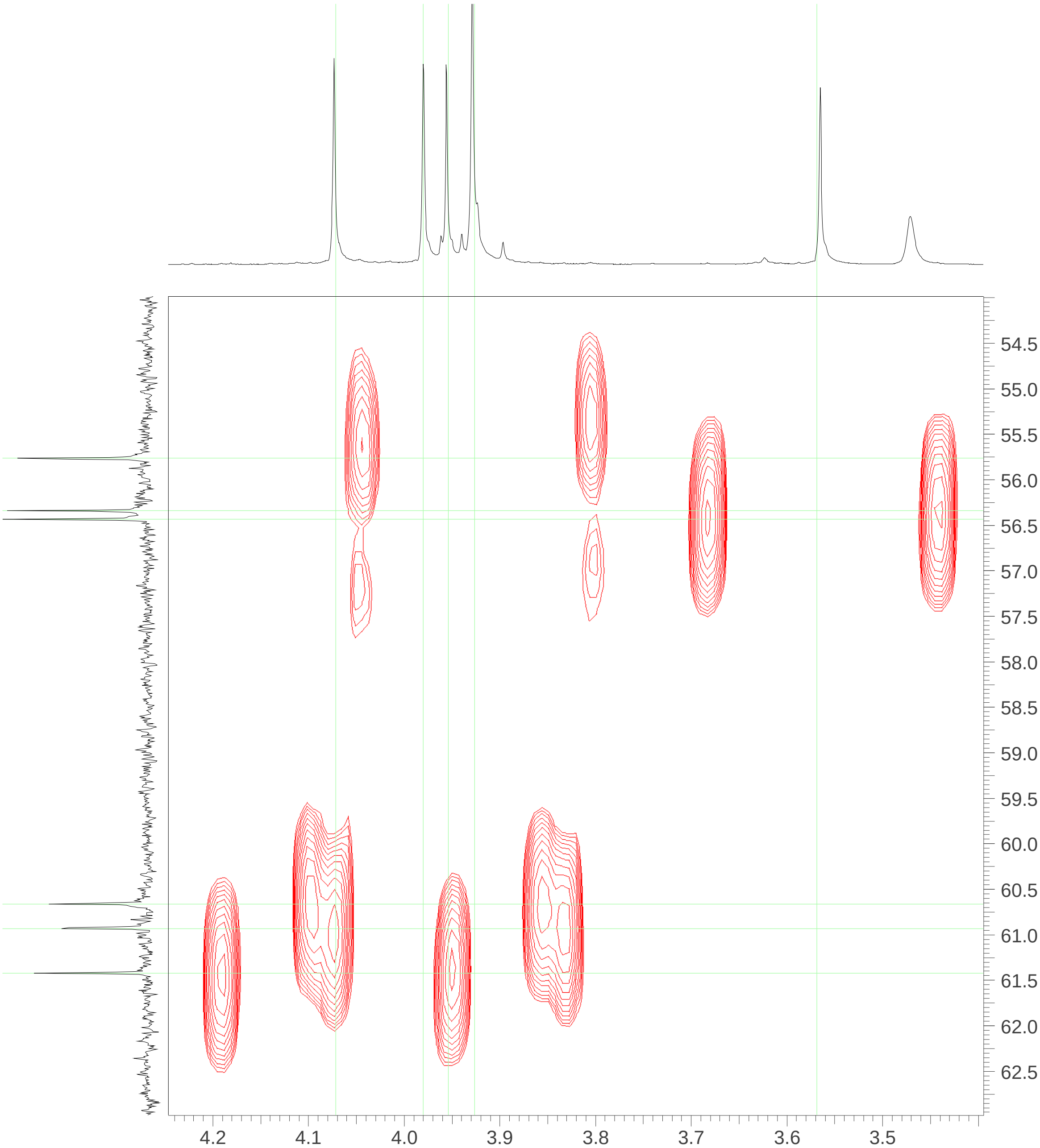


Figure S34-3. The partially enlarged HMBC spectrum of thalfoetine C (**4**)

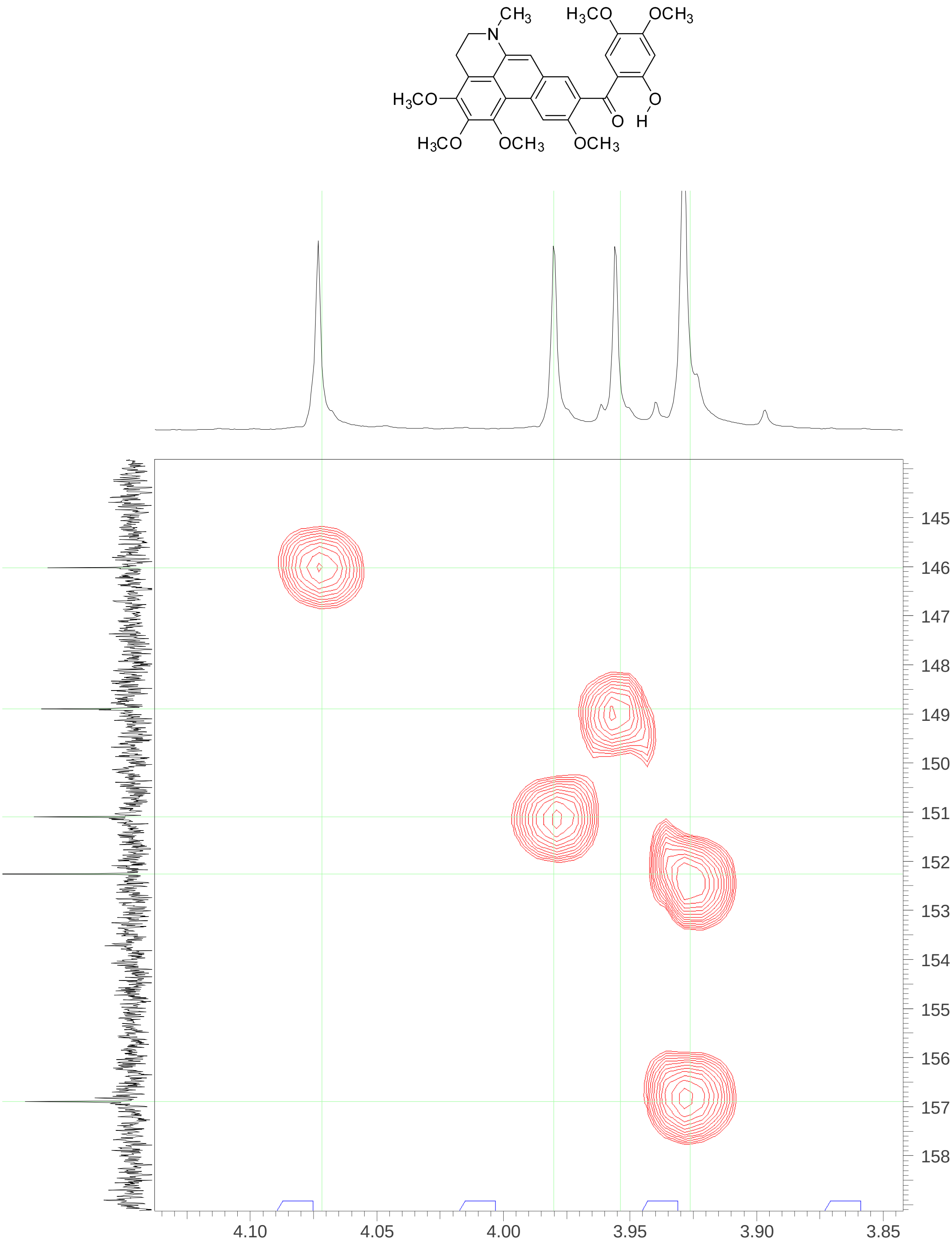
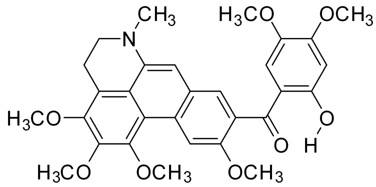


Figure S34-4. The partially enlarged HMBC spectrum of thalfoetine C (**4**)



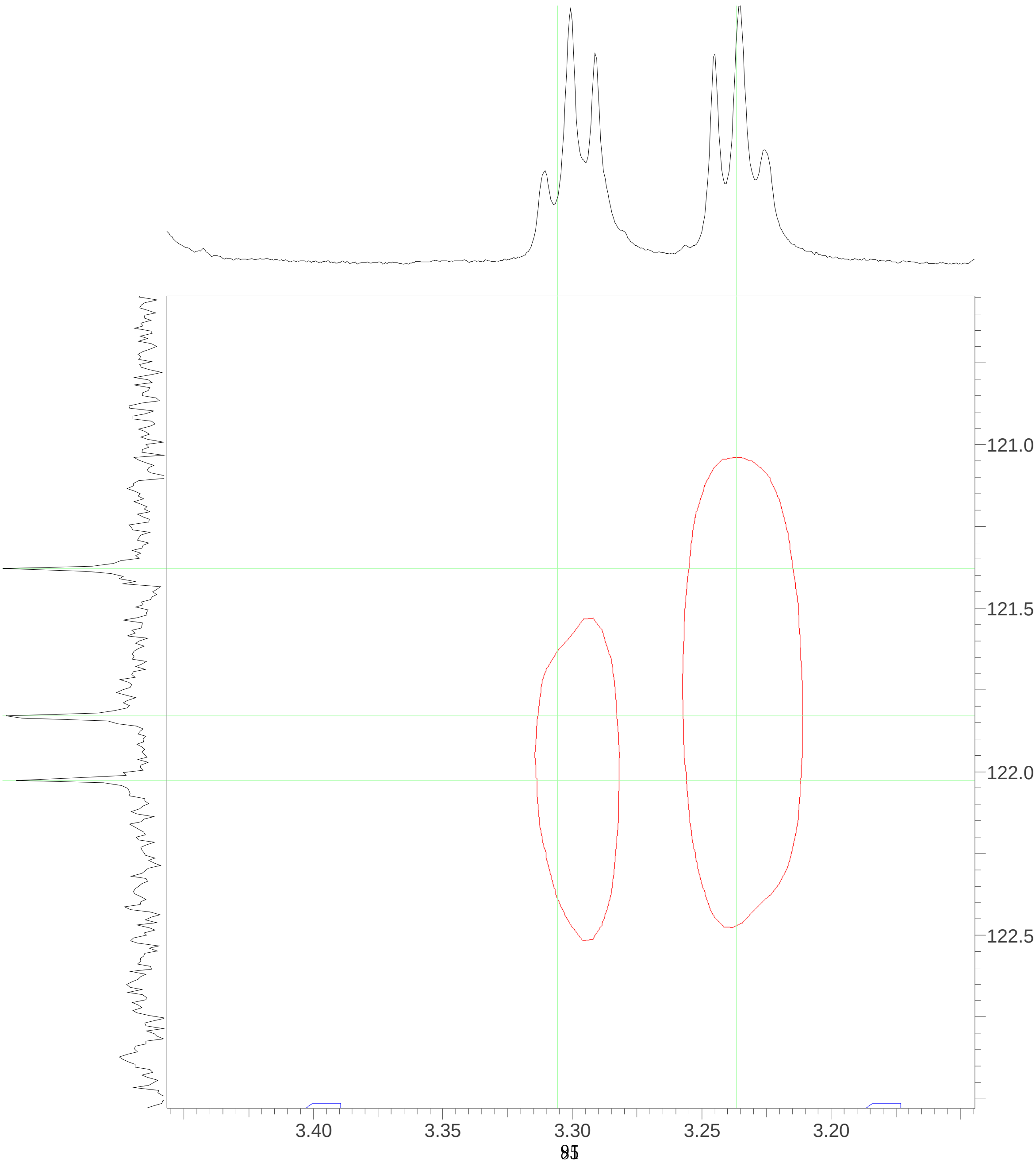


Figure S35. ROESY spectrum of thalfoetine C (**4**) in $CDCl_3$ (600 MHz)