Supplementary Materials: Chemical and Biological Study of Novel Aplysiatoxin Derivatives from the Marine Cyanobacterium *Lyngbya* sp.

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1. Experimental Details

1.1. Morphological and Molecular Identification of Cyanobacterium

The cyanobacterium strain used in this study were collected from Harbor of Hainan Sanya, China, Named as cyanobacterium HN. Colonies of cyanobacterium HN appeared as dark red, brown, or black tufts ranging from 15 to 25 cm in length and grew attached to sea rock and surface of the sea.

Filament width, cell width, and cell length of cyanobacterium HN were measured on the compound light microscope (Zeiss, Germany) with a 20× objective and 10× ocular lens with a calibrated optical micrometer. Filaments were long, of indeterminate length, 55–65 μm wide, formed by a uniseriate row of discoid cells encased in a firm, colorless, hyaline sheath which, when old, became yellowed and distinctly lamellated. Cells were discoid, 6–8 μm long, 30–40 μm broad, with rounded end cells without calyptra. Cell contents were finely granular without prominent granular inclusions (Figure S1.1A).

16S rDNA was used to characterize the identity of cyanobacterium samples. Total cyanobacterium genomic DNA from lyophilized samples was extracted by using TianGen Plant Genomic DNA Kit (TIANGEN Biotech Co., Ltd., Beijing, China) according to the manufacturer's instructions. Three PCR primer sets, CYA106F (5′-TACGGCTACCTTGTTAACGCGTGA-3′)/781R (5′-GACTACTGGGGTATC-TAATCCCATT-3′), 27F (5′-AGAGTTTGATCCTGGCTCAG-3′)/809R (5′-GC-TTCGGCACGGCTCGGGTCGATA-3′) and MSR2F (5′-CGGTAATACGGGG-GAGGCAA-3′)/2R (5′-CCAACATCTCACGACACGAG-3′), were used for amplifying 16S rDNA. PCR reactions were performed in a BIO-RAD Cycler C1000, according to the following profile: 5 min at 95 °C and 35 cycles of 30 s at 95°C, 1 min at 58 °C for CYA106F/781R, 30 s at 50 °C for 27F/809R or MSR2F/2R, and 1 min at 72 °C, followed by 10 min at 72 °C. The products were analyzed by electrophoresis in 0.7% (*w*/*v*) agarose gels electrophoresis. 16S rDNA sequences of other cyanobacterial taxa were acquired from NCBI GenBank and EzBioCloud databases and aligned by using MUSCLE implemented in MEGA7.0, and the phylogenetic tree was reconstructed by MrBayes.

Cyanobacterium HN held the highest 16S rRNA gene similarity with *Lyngbya* sp. CENA128^T with the value of 99%, revealing that cyanobacterium HN might belong to *Lyngbya* sp. The phylogenetic trees based on the 16S rRNA gene sequences, reconstructed with the Bayesian MCMC methods, showed that cyanobacterium HN fell into the clade comprising *Lyngbya* species and formed a stable clade with *Lyngbya* sp. CENA128^T (Figure S1.1B). According to these results, cyanobacterium HN belonged to *Lyngbya* sp.

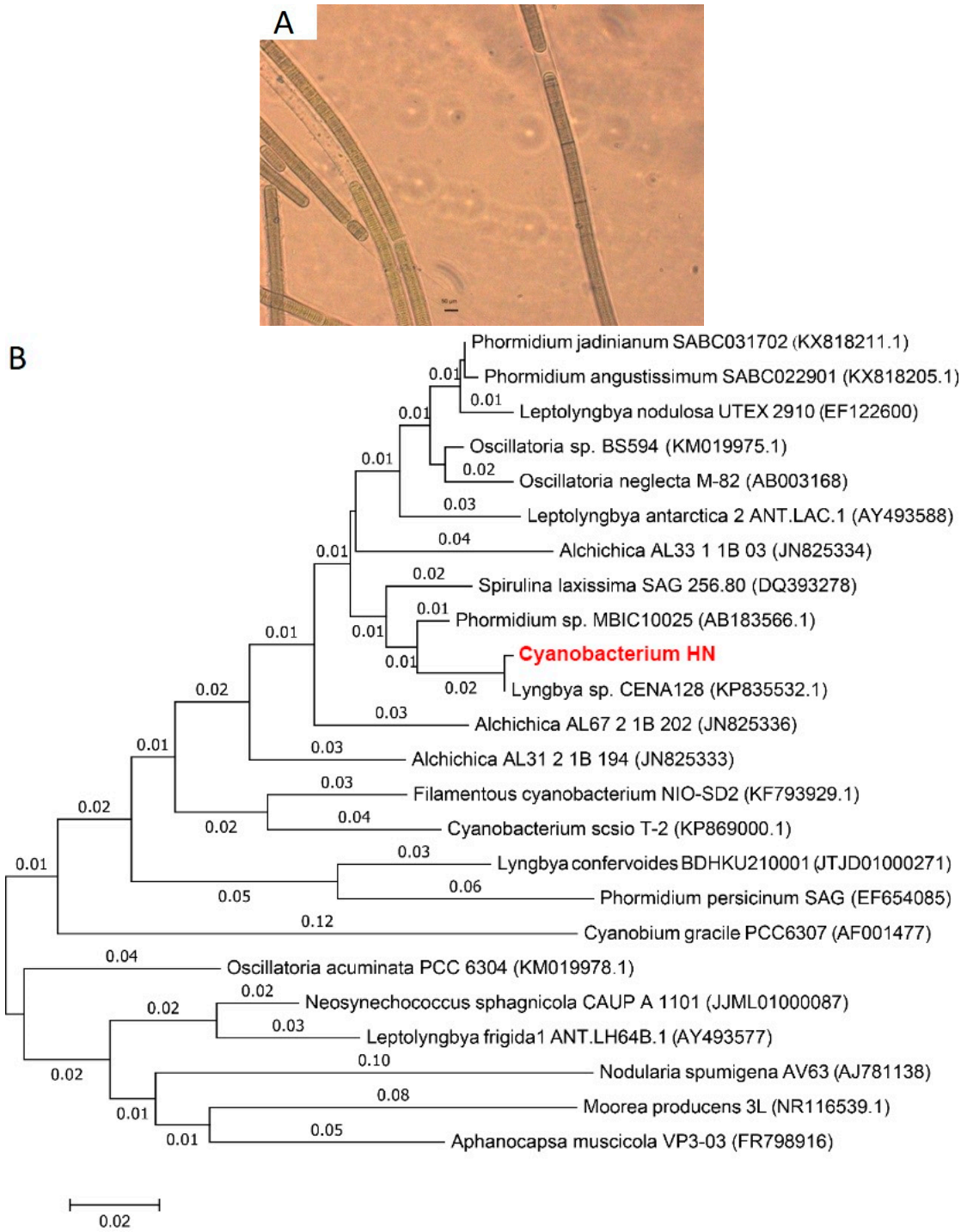

Figure S1.1. (**A**) *Lyngbya* sp. collected in Harbor of Hainan. The specie, as identified based on morphological features, is shown in light micrographs. (**B**) Bayesian phylogenetic tree of *Lyngbya* sp. HN and its close relatives. Bootstrap was set as 20,000 replicates. Bar, 0.02 substitutions per nucleotide position.

1.2. Extraction and Isolation

The freeze-dried powder of the Cyanobacterium (150 g) was extracted with CH_2Cl_2 /MeOH (1:1, *v*/*v*). The resultant extract was suspended in 1 L of MeOH/H_2O (9:1, *v*/*v*) and partitioned with CH_2Cl_2 (3 × 1 L) to yield the CH_2Cl_2 extract (20 g), which was subjected to VLC over silica gel using gradients of PE/EtOAc (5:1, 2:1, 1:1, 1:2, 1:5, 0:1, *v*/*v*) to obtain seven subfractions (F.A-G). F.D (800 mg) was further separated by reversed-phase ODS (10–100% MeCN/H_2O, 180 min, flow rate 20 mL/min, UV

detection at 190 nm) to afford twenty-one subfractions (F.D.1-21). Subsequently, the subfraction F.D.11 (55.4 mg) was purified by preparative HPLC (Waters SunFire Prep C18, 42% MeCN/H_2O, 8.0 mL/min, UV detection at 190 nm) to yield neo-debromoaplysiatoxin G (**1**) (3.6 mg), subfraction F.D.17 (93.2 mg) was further separated by semi-preparative HPLC (YMC-Pack Pro C18, 85% MeOH/H_2O, 3.0 mL/min, UV detection at 190 nm) to obtain neo-debromoaplysiatoxin H (**2**) (4.3 mg). Neo-debromoaplysiatoxin A, neo-debromoaplysiatoxin B, neo-debromoaplysiatoxin C, neo-debromoaplysiatoxin D, neo-debromoaplysiatoxin E, neo-debromoaplysiatoxin F, debromoaplysiatoxin, 3-methoxydebromoaplysiatoxin, anhydrodebromoaplysiatoxin, 4-hydroperoxyoscillatoxin B, oscillatoxin E and oscillatoxin F also were obtained from the same collection.

1.3. Bioassays

1.3.1. Ion Channel Experiment

Cell preparation. One day before the experiment, the density of 60–80% CHO cells (Sigma Chemical Co., St. Louis, MO, USA) was digested with trypsin and placed in DMEM medium without P/S, added After 10% FBS, it was cultured overnight in an incubator.

Electrophysiology. The cells were transferred to a perfusion tank and perfused with extracellular fluid. The intracellular fluid (mM) was: K Aspartate, 130; $MgCl_2$, 5; EGTA 5; HEPES, 10; Tris-ATP 4; pH 7.2 (KOH titration). The intracellular fluid was stored in small portions in a refrigerator at −80 °C and thawed on the day of the experiment. The electrodes were filled with intracellular fluid and drawn with PC-10 (Narishige, Japan). Whole-cell patch-clamp recording, noise is filtered using one-fifth of the sampling frequency. The cells were clamped at –80 mV and then depolarized to 20 mV with a square wave lasting 2 s to obtain Kv1.5 current. This procedure is repeated every 20 s. After it was stabilized, compound **1**, compound **2,** and acacetin were perfused, and when the reaction was stabilized, the strength of the blocking was calculated.

Data analysis and statistics. Data acquisition and analysis were carried out using pCLAMP 10 (Molecular Devices, Union City, CA). Data fitting and statistical analyses were performed using ORIGIN 8.0 (GraphPad Software Inc., San Diego, CA). The IC_{50} value was determined by fitting the data points to the equation. Where IC_{50} is the concentration at which half-maximal currents were inhibited, all the data were presented as mean ± SEM.

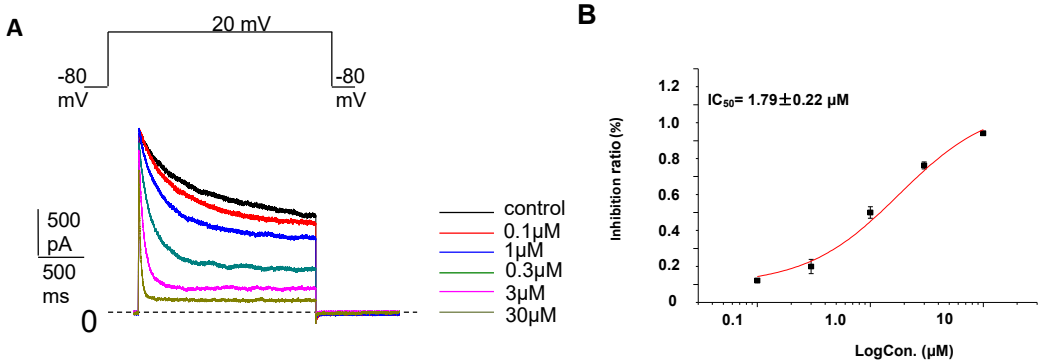

Figure S1.3.1.1. (**A**) Kv1.5 traces elicited by 5 s pulses from −80 to + 20 mV and tail currents recorded at −80 mV in the absence and presence of 0.1 μM, 0.3 μM, 1 μM, 3 μM, 10 μM, and 30 μM neo-debromoaplysiatoxin G (**1**). (**B**) Percent blocked-Concentration curves. The abscissa represents the concentration, and the ordinate represents the percentage of Kv1.5 current that is blocked at different concentrations of neo-debromoaplysiatoxin G (**1**). Data points represent mean ± SEM of 3 to 5 measurements, and the inhibitory effect showed an IC_{50} value of 1.79 ± 0.22 μM.

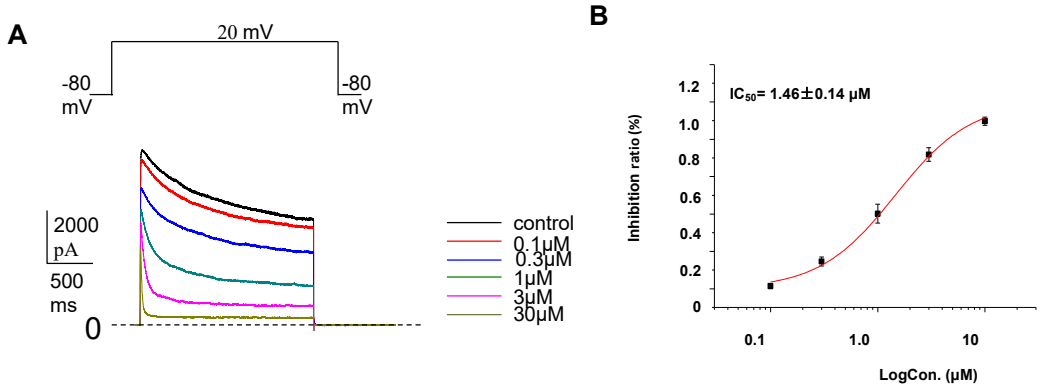

Figure S1.3.1.2. (**A**) Kv1.5 traces elicited by 5 s pulses from −80 to + 20 mV and tail currents recorded at −80 mV in the absence and presence of 0.1 μM, 0.3 μM, 1 μM, 3 μM, 10 μM and 30 μM neo-debromoaplysiatoxin H (**2**). (**B**) Percent blocked-concentration curves. The abscissa represents the concentration, and the ordinate represents the percentage of Kv1.5 current that is blocked at different concentrations of neo-debromoaplysiatoxin H (**2**). Data points represent the mean ± SEM of 3 to 5 measurements, and the inhibitory effect showed an IC_{50} value of 1.46 ± 0.14 μM.

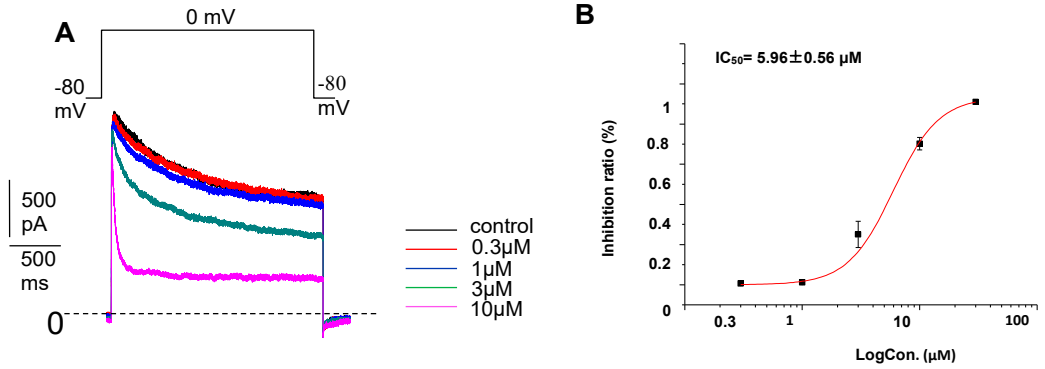

Figure S1.3.1.3. (**A**) Kv1.5 traces elicited by 5 s pulses from −80 to + 20 mV and tail currents recorded at −80 mV in the absence and presence of 0.3 μM, 1 μM, 3 μM, 10 μM, and 30 μM acacetin. (**B**) Percent blocked-concentration curves. The abscissa represents the concentration, and the ordinate represents the percentage of Kv1.5 current that is blocked at different concentrations of acacetin. Data points represent mean ± SEM of 3 to 5 measurements, and the inhibitory effect showed an IC_{50} value of 5.96 ± 0.56 μM.

1.3.2. Brine Shrimp Cytotoxicity Assay

Commercially available *Artemia salina* (*A. salina)* or brine shrimp cysts were purchased and cultivated in 3.2% of saline water. Before cultivation, the saline was aerated, and then cysts were kept at room temperature for 24 h. For toxicity screening, hatched larvae were collected and introduced in saline water. Add saline water and equivalent larvae in per well of 96 wells to make test culture plate. Aplysiatoxins with 0.1 μM, 1 μM, 10 μM, 30 μM was added to test culture plate, while DMSO and dichloromethane were added as blank control test and positive control separately. After 24 h in 25 °C, the percent of survival of *A. salina* was calculated.

Table S1.3.2.1. Effect of compound **1** and **2** to *Artemia salina (A. salina)*. *A. salina* were treated with indicated concentration (0.1 μM, 1 μM, 10 μM, 30 μM) of dichloromethane (DCM), debromoaplysiatoxin (DAT), anhydrodebromoaplysiatoxin (Anhydro DAT), 3-methoxydebromoaplysaitoxin (3-OCH_3 DAT), 4-hydroperoxyosciliatoxin B (4-OOH OAT), osciliatoxin F (OAT F), neo-debromoaplysiatoxin A (NEO-A), neo-debromoaplysiatoxin B (NEO-B), neo-debromoaplysiatoxin C (NEO-C), compound **1** and **2** for 24 h. The percentage of *A. salina* with all different kinds of aplysiatoxins (ATXs).

Compounds	Percentage of Survival of *Artemia salina* after 24 h（μM）			
	0.1	1	10	30
Debromoaplysiatoxin	70.88 ± 6.30	0	0	0
Anhydrodebromoaplysiatoxin	93.98 ± 3.46	91.34 ± 6.94	0	0
3-methoxydebromoaplysiatoxin	94.46 ± 1.87	85.82 ± 6.30	0	0
4-hydroperoxyoscillatoxin B2	96.77 ± 3.23	88.92 ± 4.38	0	0
Oscillatoxin F	97.50 ± 2.20	98.85 ± 1.99	95.32 ± 1.92	85.54 ± 2.91
Neo-debromoaplysiatoxin A	96.50 ± 0.59	98.89 ± 1.92	95.25 ± 4.21	89.97 ± 4.74
Neo-debromoaplysiatoxin C	98.67 ± 2.31	99.05 ± 1.65	98.89 ± 1.92	94.90 ± 5.27
Neo-debromoaplysiatoxin G	98.04 ± 3.40	92.57 ± 1.54	92.39 ± 4.71	91.84 ± 7.73
Neo-debromoaplysiatoxin H	97.27 ± 2.38	98.88 ± 1.93	97.33 ± 4.62	95.53 ± 1.93
Methylenechloride		0	0	0
Control	97.78 ± 1.93	98.77 ± 2.13	97.74 ± 1.96	98.77 ± 2.14

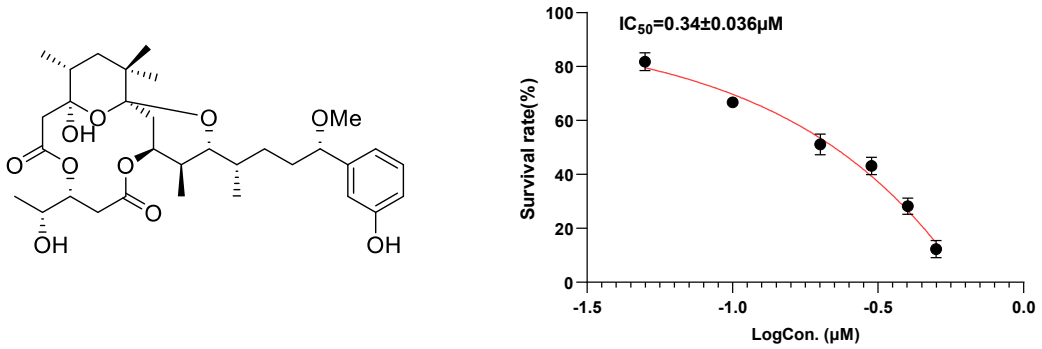

Figure S1.3.2.1. Effect of debromoaplysiatoxin to *Artemia salina (A. salina)*. *A. salina* were treated with debromoaplysiatoxin with indicated concentration 0.05 μM, 0.1 μM, 0.2 μM, 0.3 μM, 0.4 μM, 0.5 μM and inhibitory effect showed IC_{50} value of 0.034 ± 0.036 μM.

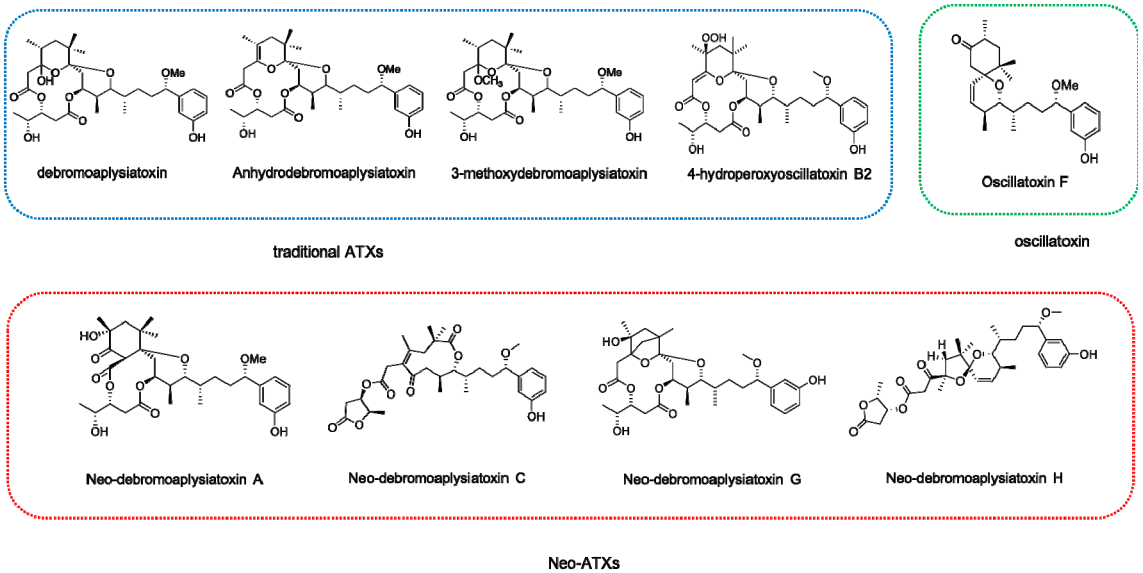

Figure S1.3.2.2. Structures of different types of aplysiatoxins to brine shrimp toxicity assay.

1.4. Methods for NMR Calculation of Neo-Debromoaplysiatoxin G (1)

Monte Carlo conformational searches were carried out by means of the Spartan's 10 software (Spartan Software, San Francisco, CA, USA) using Merck Molecular Force Field (MMFF). The conformers with Boltzmann-population of over 1% were chosen for NMR calculations, and then the conformers were initially optimized at B3LYP/6–31g (d, p) level in gas. Meanwhile, gauge-independent atomic orbital (GIAO) calculations of ^{1}H and ^{13}C NMR chemical shifts were accomplished by density functional theory (DFT) at the mPWLPW91-SCRF (methanol)/6−311+g (d, p) level with the PCM solvent continuum model in Gaussian 09 software (Gaussian, Wallingford, CT, USA). The calculated NMR data of the lowest energy conformers for isomer 1, isomer 2 were averaged according to the Boltzmann distribution theory and their relative Gibbs free energy. The ^{1}H and ^{13}C NMR chemical shifts for TMS were calculated by the same protocol and used as reference. The experimental and calculated data were analyzed by the improved probability DP4+ method for isomeric compounds. A significant higher DP4+ probability score suggested the correctness of its configuration.

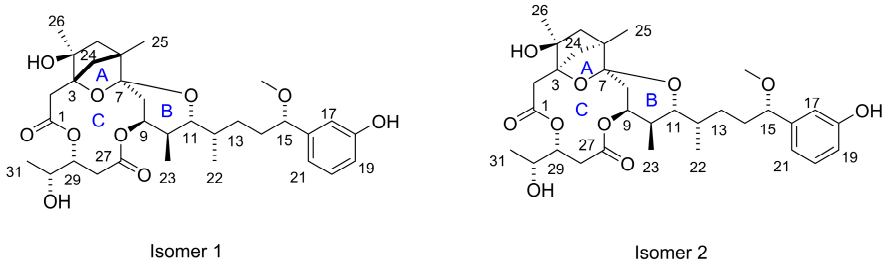

Figure S1.4.1. isomer 1 (3R, 6S) and isomer 2 (3S, 6R) of neo-debromoaplysiatoxin G (**1**).

Table S1.4.1.a. Gibbs free energies[a] and equilibrium populations[b] of low-energy conformers of isomer 1.

Conformers	In MeOH	
	Δ*G*	*P* (%)
isomer 1-1	0	62.82
isomer 1-2	1.77	5.23
isomer 1-3	0.38	23.18
isomer 1-4	1.65	8.78

[a]B3LYP/6−31+G(d, p), in kcal/mol. [b]From Δ*G* values at 298.15 K.

Table S1.4.1.b. Cartesian coordinates for the low-energy reoptimized MMFF conformers of isomer 1 at B3LYP/6−31G (d, p) level of theory in CH_3OH.

Isomer 1-1			Standard Orientation (Ångstroms)		
Center Number	Atomic Number	Atomic Type	X	Y	Z
1.	6.	0.	4.047422	1.995133	0.487903
2.	6.	0.	4.880462	1.592217	1.542568
3.	6.	0.	5.389948	0.297816	1.559078
4.	6.	0.	5.082094	−0.611455	0.542304
5.	6.	0.	4.255568	−0.214943	−0.513626
6.	6.	0.	3.746161	1.088362	−0.537320
7.	6.	0.	3.859563	−1.182160	−1.626720
8.	8.	0.	3.574934	3.267349	0.501653
9.	6.	0.	2.455209	−1.778798	−1.423483
10.	8.	0.	4.766216	−2.271954	−1.761597

11.	6.	0.	5.983568	−1.928749	−2.398860
12.	6.	0.	2.317400	−2.687523	−0.194300
13.	6.	0.	0.869960	−3.172364	0.045533
14.	6.	0.	0.819608	−4.480665	0.849031
15.	6.	0.	−0.067015	−2.074693	0.607739
16.	6.	0.	−0.129531	−1.906447	2.145356
17.	6.	0.	−1.248178	−0.913240	2.498987
18.	6.	0.	1.197813	−1.502528	2.802171
19.	6.	0.	−2.436714	−1.526214	0.357586
20.	8.	0.	−0.782001	0.394873	2.034075
21.	6.	0.	−2.268825	0.944694	−2.330839
22.	6.	0.	−2.969979	−0.069024	−1.406223
23.	6.	0.	−4.414123	0.301919	−0.941510
24.	6.	0.	−4.837818	−1.033089	−0.242182
25.	6.	0.	−3.652828	−2.009961	−0.488070
26.	6.	0.	−1.061199	1.594448	−1.685532
27.	8.	0.	0.074590	1.486587	−2.125076
28.	8.	0.	−1.378936	−2.429075	0.104219
29.	6.	0.	−3.999726	−3.484173	−0.341877
30.	8.	0.	−5.142026	0.506070	−2.163854
31.	6.	0.	−2.583358	−1.331110	1.865857
32.	8.	0.	−1.364604	2.323319	−0.597638
33.	6.	0.	−1.518989	1.482029	2.303171
34.	8.	0.	−2.525283	1.481544	2.983333
35.	6.	0.	−0.917909	2.756437	1.719958
36.	6.	0.	−0.282719	2.651812	0.333029
37.	6.	0.	0.456812	3.939775	−0.082115
38.	6.	0.	−0.465907	5.086112	−0.492071
39.	8.	0.	1.414986	3.677537	−1.116658
40.	6.	0.	−3.163702	−1.517072	−1.877373
41.	8.	0.	−2.167387	−0.233851	−0.215883
42.	6.	0.	−4.541502	1.538327	−0.058696
43.	1.	0.	5.114838	2.306528	2.325076
44.	1.	0.	6.037278	−0.009134	2.376360
45.	1.	0.	5.478596	−1.620542	0.557563
46.	1.	0.	3.109731	1.405050	−1.359814
47.	1.	0.	3.838506	−0.615822	−2.573465
48.	1.	0.	2.942086	3.401970	−0.239026
49.	1.	0.	1.746981	−0.943333	−1.377478
50.	1.	0.	2.205582	−2.352843	−2.324773
51.	1.	0.	6.549173	−1.175457	−1.834481
52.	1.	0.	6.578097	−2.843277	−2.465929
53.	1.	0.	5.808918	−1.543540	−3.415404
54.	1.	0.	2.706210	−2.174309	0.689678
55.	1.	0.	2.960353	−3.561747	−0.342914
56.	1.	0.	0.441760	−3.393002	−0.941368
57.	1.	0.	1.308966	−4.389397	1.825067
58.	1.	0.	−0.213729	−4.801552	1.014125
59.	1.	0.	1.333935	−5.278095	0.303396
60.	1.	0.	0.210291	−1.109231	0.168993
61.	1.	0.	−0.450859	−2.866472	2.569423
62.	1.	0.	−1.370416	−0.840782	3.584853
63.	1.	0.	1.935437	−2.305686	2.748495
64.	1.	0.	1.629949	−0.614212	2.334335
65.	1.	0.	1.038200	−1.275181	3.862274
66.	1.	0.	−1.909481	0.459456	−3.239406
67.	1.	0.	−2.983439	1.718474	−2.628345
68.	1.	0.	−5.733838	−1.422637	−0.735266

69.	1.	0.	−5.074460	−0.904545	0.817618
70.	1.	0.	−3.126100	−4.111394	−0.530548
71.	1.	0.	−4.788634	−3.762512	−1.048367
72.	1.	0.	−4.367504	−3.708104	0.666267
73.	1.	0.	−6.024954	0.822614	−1.930928
74.	1.	0.	−2.866852	−2.287338	2.320248
75.	1.	0.	−3.351952	−0.600376	2.109885
76.	1.	0.	−1.707527	3.510351	1.738932
77.	1.	0.	−0.138887	3.083392	2.420145
78.	1.	0.	0.430802	1.824923	0.316069
79.	1.	0.	1.051430	4.246458	0.786833
80.	1.	0.	−1.134309	5.376311	0.325238
81.	1.	0.	−1.078821	4.806128	−1.352981
82.	1.	0.	0.138838	5.953528	−0.766271
83.	1.	0.	1.078215	2.933627	−1.657028
84.	1.	0.	−2.230783	−1.986863	−2.192554
85.	1.	0.	−3.924654	−1.606578	−2.654885
86.	1.	0.	−4.199026	2.433211	−0.585628
87.	1.	0.	−3.975750	1.446475	0.868363
88.	1.	0.	−5.595524	1.687028	0.210204

Isomer 1-2			**Standard Orientation (Ångstroms)**		
Center Number	**Atomic Number**	**Atomic Type**	**X**	Y	Z
1.	6.	0.	4.071921	2.107031	0.410127
2.	6.	0.	5.027380	1.824747	1.397574
3.	6.	0.	5.641827	0.577137	1.419460
4.	6.	0.	5.322735	−0.404160	0.475651
5.	6.	0.	4.366380	−0.130512	−0.505728
6.	6.	0.	3.744550	1.124287	−0.532882
7.	6.	0.	3.964917	−1.163405	−1.548593
8.	8.	0.	3.507406	3.342214	0.406398
9.	6.	0.	2.541702	−1.719428	−1.310355
10.	8.	0.	4.941953	−2.203038	−1.557415
11.	6.	0.	4.972350	−2.967957	−2.743440
12.	6.	0.	2.413844	−2.556383	−0.030680
13.	6.	0.	0.982529	−3.074547	0.231710
14.	6.	0.	0.974218	−4.338962	1.104497
15.	6.	0.	0.005925	−1.981520	0.731915
16.	6.	0.	−0.072384	−1.740070	2.258845
17.	6.	0.	−1.229219	−0.773775	2.559899
18.	6.	0.	1.236164	−1.253518	2.897862
19.	6.	0.	−2.380616	−1.530572	0.444432
20.	8.	0.	−0.807444	0.526124	2.035550
21.	6.	0.	−2.284679	0.811633	−2.359815
22.	6.	0.	−2.955710	−0.181599	−1.391095
23.	6.	0.	−4.414715	0.159375	−0.951022
24.	6.	0.	−4.793935	−1.153663	−0.187951
25.	6.	0.	−3.573773	−2.098715	−0.381450
26.	6.	0.	−1.094346	1.516571	−1.740460
27.	8.	0.	0.048150	1.402313	−2.160478
28.	8.	0.	−1.289317	−2.405607	0.239257
29.	6.	0.	−3.868449	−3.575301	−0.163152
30.	8.	0.	−5.142808	0.277581	−2.184314
31.	6.	0.	−2.543897	−1.269218	1.941029
32.	8.	0.	−1.423350	2.299339	−0.698486
33.	6.	0.	−1.584367	1.598706	2.244536

34.	8.	0.	−2.595434	1.597414	2.917359
35.	6.	0.	−1.021167	2.859787	1.598239
36.	6.	0.	−0.360905	2.693817	0.229291
37.	6.	0.	0.369303	3.966808	−0.243072
38.	6.	0.	−0.559834	5.077889	−0.728231
39.	8.	0.	1.347238	3.660442	−1.245961
40.	6.	0.	−3.094593	−1.656907	−1.791285
41.	8.	0.	−2.155423	−0.258961	−0.190074
42.	6.	0.	−4.590101	1.432803	−0.131058
43.	1.	0.	5.275866	2.595393	2.119977
44.	1.	0.	6.387578	0.364742	2.181024
45.	1.	0.	5.816828	−1.367647	0.484858
46.	1.	0.	3.008225	1.349247	−1.300146
47.	1.	0.	3.967852	−0.667303	−2.534190
48.	1.	0.	2.862864	3.420980	−0.331489
49.	1.	0.	1.848279	−0.870446	−1.303852
50.	1.	0.	2.250026	−2.333314	−2.173098
51.	1.	0.	5.121999	−2.333778	−3.631094
52.	1.	0.	5.817289	−3.655719	−2.657013
53.	1.	0.	4.057327	−3.559247	−2.894093
54.	1.	0.	2.784949	−1.979926	0.821683
55.	1.	0.	3.085982	−3.417362	−0.118988
56.	1.	0.	0.565451	−3.362370	−0.742666
57.	1.	0.	1.458748	−4.178175	2.073778
58.	1.	0.	−0.047878	−4.685525	1.286525
59.	1.	0.	1.516219	−5.147061	0.602990
60.	1.	0.	0.255258	−1.031079	0.245907
61.	1.	0.	−0.359197	−2.689422	2.728924
62.	1.	0.	−1.360399	−0.654909	3.640671
63.	1.	0.	2.003949	−2.029761	2.887944
64.	1.	0.	1.635959	−0.375022	2.385091
65.	1.	0.	1.063345	−0.977351	3.944125
66.	1.	0.	−1.914099	0.298836	−3.248458
67.	1.	0.	−3.019497	1.554028	−2.686056
68.	1.	0.	−5.673580	−1.598927	−0.663062
69.	1.	0.	−5.039570	−0.980844	0.863356
70.	1.	0.	−2.972626	−4.179558	−0.319987
71.	1.	0.	−4.645547	−3.916213	−0.855195
72.	1.	0.	−4.229995	−3.762024	0.854780
73.	1.	0.	−6.036937	0.575380	−1.970206
74.	1.	0.	−2.796032	−2.212425	2.438970
75.	1.	0.	−3.340364	−0.556371	2.145916
76.	1.	0.	−1.836960	3.584609	1.560893
77.	1.	0.	−0.265855	3.254485	2.289367
78.	1.	0.	0.364151	1.878030	0.268265
79.	1.	0.	0.946327	4.327212	0.617132
80.	1.	0.	−1.245043	5.402190	0.061878
81.	1.	0.	−1.155017	4.744849	−1.582727
82.	1.	0.	0.038962	5.937173	−1.038657
83.	1.	0.	1.023758	2.891007	−1.757405
84.	1.	0.	−2.143609	−2.107605	−2.079289
85.	1.	0.	−3.847345	−1.811445	−2.566625
86.	1.	0.	−4.270554	2.311216	−0.698584
87.	1.	0.	−4.032058	1.405775	0.804932
88.	1.	0.	−5.651157	1.560812	0.120397

isomer 1-3	**Standard Orientation**

			(Ångstroms)		
Center Number	**Atomic Number**	**Atomic Type**	**X**	Y	Z
1.	6.	0.	4.059949	2.000111	0.474233
2.	6.	0.	4.887574	1.601696	1.534668
3.	6.	0.	5.393400	0.305988	1.561084
4.	6.	0.	5.086959	−0.608738	0.548796
5.	6.	0.	4.265960	−0.216527	−0.513016
6.	6.	0.	3.760579	1.088105	−0.546678
7.	6.	0.	3.871650	−1.189120	−1.622012
8.	8.	0.	3.590465	3.273938	0.477803
9.	6.	0.	2.464963	−1.781054	−1.420902
10.	8.	0.	4.776119	−2.281727	−1.747436
11.	6.	0.	5.996808	−1.945097	−2.381931
12.	6.	0.	2.320771	−2.685085	−0.189059
13.	6.	0.	0.871361	−3.166354	0.046415
14.	6.	0.	0.815458	−4.475100	0.848791
15.	6.	0.	−0.064956	−2.066890	0.606683
16.	6.	0.	−0.130759	−1.900909	2.144462
17.	6.	0.	−1.250398	−0.908868	2.497478
18.	6.	0.	1.195256	−1.497923	2.804526
19.	6.	0.	−2.436948	−1.520746	0.354612
20.	8.	0.	−0.783989	0.399859	2.032629
21.	6.	0.	−2.285392	0.953422	−2.326930
22.	6.	0.	−2.986964	−0.063284	−1.404284
23.	6.	0.	−4.438877	0.293734	−0.931870
24.	6.	0.	−4.844751	−1.044356	−0.243591
25.	6.	0.	−3.651991	−2.009678	−0.489346
26.	6.	0.	−1.066518	1.585055	−1.681832
27.	8.	0.	0.068313	1.449453	−2.114232
28.	8.	0.	−1.375435	−2.418301	0.098239
29.	6.	0.	−3.989732	−3.486316	−0.346192
30.	8.	0.	−5.275573	0.442721	−2.092352
31.	6.	0.	−2.584212	−1.327991	1.863072
32.	8.	0.	−1.364359	2.331066	−0.605004
33.	6.	0.	−1.521326	1.486978	2.299086
34.	8.	0.	−2.529031	1.488660	2.976899
35.	6.	0.	−0.918312	2.760304	1.714601
36.	6.	0.	−0.281105	2.650142	0.329407
37.	6.	0.	0.469419	3.929952	−0.088092
38.	6.	0.	−0.442219	5.088100	−0.489273
39.	8.	0.	1.416086	3.659094	−1.131592
40.	6.	0.	−3.171123	−1.509801	−1.879081
41.	8.	0.	−2.174535	−0.225772	−0.217185
42.	6.	0.	−4.568880	1.525269	−0.043379
43.	1.	0.	5.120765	2.320065	2.313793
44.	1.	0.	6.036548	0.002274	2.382841
45.	1.	0.	5.480631	−1.618764	0.571954
46.	1.	0.	3.129154	1.401653	−1.374252
47.	1.	0.	3.855603	−0.627939	−2.571963
48.	1.	0.	2.956090	3.401968	−0.262242
49.	1.	0.	1.758593	−0.943667	−1.379985
50.	1.	0.	2.216642	−2.357793	−2.320814
51.	1.	0.	6.561613	−1.189287	−1.820117
52.	1.	0.	6.589727	−2.861226	−2.440557
53.	1.	0.	5.827092	−1.566239	−3.401683
54.	1.	0.	2.707064	−2.169440	0.694591
55.	1.	0.	2.962733	−3.560935	−0.332152
56.	1.	0.	0.445394	−3.385303	−0.941781

57.	1.	0.	1.302683	−4.385983	1.826093
58.	1.	0.	−0.219138	−4.793315	1.010996
59.	1.	0.	1.328980	−5.273462	0.303763
60.	1.	0.	0.216233	−1.101476	0.169977
61.	1.	0.	−0.452742	−2.861555	2.566531
62.	1.	0.	−1.373254	−0.835927	3.583206
63.	1.	0.	1.932614	−2.301437	2.752281
64.	1.	0.	1.629064	−0.609652	2.338077
65.	1.	0.	1.033257	−1.270987	3.864352
66.	1.	0.	−1.939857	0.476924	−3.245405
67.	1.	0.	−2.980473	1.750697	−2.611690
68.	1.	0.	−5.737921	−1.429384	−0.742736
69.	1.	0.	−5.087605	−0.917437	0.814520
70.	1.	0.	−3.113226	−4.108388	−0.538337
71.	1.	0.	−4.779101	−3.766615	−1.051223
72.	1.	0.	−4.354242	−3.714630	0.662144
73.	1.	0.	−5.295861	1.379487	−2.328032
74.	1.	0.	−2.866050	−2.285292	2.316207
75.	1.	0.	−3.355067	−0.599611	2.107021
76.	1.	0.	−1.707063	3.515132	1.730305
77.	1.	0.	−0.139915	3.088183	2.415025
78.	1.	0.	0.424229	1.816413	0.313900
79.	1.	0.	1.073710	4.227565	0.777372
80.	1.	0.	−1.099094	5.386931	0.334200
81.	1.	0.	−1.066003	4.815984	−1.344905
82.	1.	0.	0.171141	5.947670	−0.768971
83.	1.	0.	1.080155	2.905165	−1.657495
84.	1.	0.	−2.237489	−1.972992	−2.202184
85.	1.	0.	−3.936826	−1.601002	−2.652108
86.	1.	0.	−4.240170	2.430917	−0.568469
87.	1.	0.	−3.977383	1.444213	0.868119
88.	1.	0.	−5.619587	1.656457	0.235001

Isomer 1-4			**Standard Orientation (Ångstroms)**		
Center Number	**Atomic Number**	**Atomic Type**	**X**	Y	Z
1.	6.	0.	4.045504	1.994768	0.481904
2.	6.	0.	4.878316	1.593618	1.537465
3.	6.	0.	5.387807	0.299300	1.556404
4.	6.	0.	5.080148	−0.611805	0.541180
5.	6.	0.	4.253847	−0.217117	−0.515602
6.	6.	0.	3.744381	1.086147	−0.541759
7.	6.	0.	3.858085	−1.186388	−1.626973
8.	8.	0.	3.573293	3.266914	0.493373
9.	6.	0.	2.453976	−1.783217	−1.422328
10.	8.	0.	4.764693	−2.276295	−1.760372
11.	6.	0.	5.982584	−1.933735	−2.397205
12.	6.	0.	2.317275	−2.690675	−0.192050
13.	6.	0.	0.870079	−3.175367	0.049621
14.	6.	0.	0.820326	−4.481624	0.856474
15.	6.	0.	−0.065791	−2.075828	0.609597
16.	6.	0.	−0.129758	−1.904513	2.146401
17.	6.	0.	−1.246028	−0.907308	2.496227
18.	6.	0.	1.197789	−1.501603	2.803478
19.	6.	0.	−2.434590	−1.523191	0.356851
20.	8.	0.	−0.778201	0.397195	2.025538
21.	6.	0.	−2.284527	0.958516	−2.328848

22.	6.	0.	−2.974532	−0.064257	−1.406716
23.	6.	0.	−4.424476	0.302426	−0.935330
24.	6.	0.	−4.841520	−1.040908	−0.250090
25.	6.	0.	−3.650204	−2.011207	−0.488581
26.	6.	0.	−1.071602	1.603581	−1.687039
27.	8.	0.	0.061042	1.493307	−2.134147
28.	8.	0.	−1.378880	−2.429375	0.106137
29.	6.	0.	−3.990095	−3.487275	−0.342875
30.	8.	0.	−5.237540	0.612921	−2.075223
31.	6.	0.	−2.582920	−1.322884	1.864054
32.	8.	0.	−1.368428	2.327272	−0.595677
33.	6.	0.	−1.506419	1.487432	2.310417
34.	8.	0.	−2.499794	1.487049	3.008470
35.	6.	0.	−0.912217	2.761474	1.719554
36.	6.	0.	−0.282081	2.655440	0.330448
37.	6.	0.	0.456339	3.942826	−0.088716
38.	6.	0.	−0.467225	5.088050	−0.499559
39.	8.	0.	1.413723	3.678248	−1.123678
40.	6.	0.	−3.151202	−1.517712	−1.874709
41.	8.	0.	−2.161881	−0.235135	−0.222758
42.	6.	0.	−4.538789	1.526040	−0.037018
43.	1.	0.	5.112621	2.309352	2.318677
44.	1.	0.	6.035026	−0.006151	2.374318
45.	1.	0.	5.476845	−1.620783	0.558312
46.	1.	0.	3.108205	1.401600	−1.364970
47.	1.	0.	3.836492	−0.621645	−2.574666
48.	1.	0.	2.940265	3.400648	−0.247366
49.	1.	0.	1.745640	−0.947763	−1.376673
50.	1.	0.	2.204054	−2.358446	−2.322836
51.	1.	0.	6.547557	−1.179664	−1.833314
52.	1.	0.	6.577228	−2.848289	−2.462580
53.	1.	0.	5.808577	−1.549913	−3.414363
54.	1.	0.	2.706576	−2.176423	0.691086
55.	1.	0.	2.960195	−3.564977	−0.340155
56.	1.	0.	0.441726	−3.398585	−0.936718
57.	1.	0.	1.309957	−4.387594	1.832040
58.	1.	0.	−0.212767	−4.802634	1.023047
59.	1.	0.	1.334775	−5.280259	0.312744
60.	1.	0.	0.212122	−1.111537	0.168964
61.	1.	0.	−0.453483	−2.862951	2.572237
62.	1.	0.	−1.369223	−0.831098	3.581579
63.	1.	0.	1.934352	−2.305862	2.751678
64.	1.	0.	1.631387	−0.614551	2.334633
65.	1.	0.	1.037520	−1.272470	3.863043
66.	1.	0.	−1.929648	0.485860	−3.246243
67.	1.	0.	−3.006625	1.732732	−2.608140
68.	1.	0.	−5.741071	−1.434854	−0.736434
69.	1.	0.	−5.087826	−0.916308	0.807476
70.	1.	0.	−3.113503	−4.110686	−0.529567
71.	1.	0.	−4.778024	−3.771168	−1.048657
72.	1.	0.	−4.358105	−3.710878	0.664958
73.	1.	0.	−5.337936	−0.182759	−2.613399
74.	1.	0.	−2.870648	−2.276295	2.321664
75.	1.	0.	−3.349140	−0.588148	2.104362
76.	1.	0.	−1.704558	3.512510	1.739271
77.	1.	0.	−0.132010	3.093801	2.415899
78.	1.	0.	0.430712	1.827985	0.310572
79.	1.	0.	1.052376	4.251369	0.778509

80.	1.	0.	−1.135561	5.378499	0.317627
81.	1.	0.	−1.080658	4.807216	−1.359802
82.	1.	0.	0.136919	5.955557	−0.774814
83.	1.	0.	1.073449	2.937671	−1.666058
84.	1.	0.	−2.212502	−1.980180	−2.182646
85.	1.	0.	−3.893045	−1.648375	−2.669848
86.	1.	0.	−4.203951	2.425124	−0.561285
87.	1.	0.	−3.953543	1.419101	0.874992
88.	1.	0.	−5.589840	1.667391	0.231460

Table S1.4.2.a. Gibbs free energies[a] and equilibrium populations[b] of low−energy conformers of isomer 2.

Conformers	In MeOH	
	Δ*G*	*P* (%)
isomer 2-1	0	71.59
isomer 2-2	1.32	14.48
isomer 2-3	1.96	6.82
isomer 2-4	1.91	7.11

[a]B3LYP/6−31+G(d, p), in kcal/mol. [b]From Δ*G* values at 298.15 K.

Table S1.4.2.b. Cartesian coordinates for the low-energy reoptimized MMFF conformers of isomer 2 at B3LYP/6−31G (d, p) level of theory in CH_3OH.

Isomer 2-1			Standard Orientation (Ångstroms)		
Center Number	Atomic Number	Atomic Type	X	Y	Z
1.	6.	0.	2.129215	3.024983	−0.851007
2.	6.	0.	2.831412	3.787841	0.092536
3.	6.	0.	4.006555	3.284867	0.640400
4.	6.	0.	4.494588	2.029562	0.264858
5.	6.	0.	3.806649	1.272412	−0.687681
6.	6.	0.	2.624440	1.777722	−1.246564
7.	6.	0.	4.294552	−0.115220	−1.102880
8.	8.	0.	0.976852	3.555640	−1.349550
9.	6.	0.	3.423699	−1.239974	−0.518422
10.	8.	0.	5.639817	−0.368545	−0.714916
11.	6.	0.	6.604615	0.222535	−1.567906
12.	6.	0.	3.442103	−1.368197	1.014004
13.	6.	0.	2.267975	−2.229085	1.539495
14.	6.	0.	2.557119	−2.882266	2.898328
15.	6.	0.	0.925060	−1.462965	1.476230
16.	6.	0.	0.474113	−0.665439	2.718529
17.	6.	0.	−0.940868	−0.100679	2.501468
18.	6.	0.	1.437569	0.450596	3.148583
19.	6.	0.	−1.318465	−1.916654	0.747948
20.	8.	0.	−0.859851	1.033491	1.580588
21.	6.	0.	−1.832740	−0.482648	−2.591226
22.	6.	0.	−1.812511	−1.582636	−1.528444
23.	6.	0.	−1.077854	−2.897000	−1.989651
24.	6.	0.	−1.456988	−3.866641	−0.822160
25.	6.	0.	−2.282587	−2.997645	0.159005
26.	6.	0.	−1.761466	0.932771	−2.051208
27.	8.	0.	−0.907168	1.733192	−2.393662
28.	8.	0.	−0.082189	−2.470051	1.153091
29.	6.	0.	−3.090019	−3.799263	1.172190
30.	8.	0.	0.317982	−2.670264	−2.104388

31.	6.	0.	−1.906888	−1.133210	1.927267
32.	8.	0.	−2.765290	1.216635	−1.212361
33.	6.	0.	−1.909706	1.862687	1.571154
34.	8.	0.	−2.813114	1.818782	2.394480
35.	6.	0.	−1.857281	2.843329	0.420410
36.	6.	0.	−2.888141	2.571037	−0.696758
37.	6.	0.	−4.386735	2.726148	−0.350255
38.	6.	0.	−4.723602	4.131375	0.157987
39.	8.	0.	−4.867973	1.719519	0.519736
40.	6.	0.	−3.075492	−2.107526	−0.841792
41.	8.	0.	−1.068541	−1.065387	−0.395138
42.	6.	0.	−1.525531	−3.418359	−3.353227
43.	1.	0.	2.438946	4.758270	0.378101
44.	1.	0.	4.548090	3.875044	1.374735
45.	1.	0.	5.401931	1.631406	0.704581
46.	1.	0.	2.076569	1.203040	−1.990651
47.	1.	0.	4.218787	−0.185680	−2.201355
48.	1.	0.	0.484988	2.896970	−1.872936
49.	1.	0.	2.403480	−1.058264	−0.876007
50.	1.	0.	3.745937	−2.187386	−0.966713
51.	1.	0.	6.525883	1.317761	−1.588008
52.	1.	0.	7.587392	−0.055668	−1.179507
53.	1.	0.	6.510780	−0.152607	−2.598469
54.	1.	0.	3.420288	−0.374576	1.471725
55.	1.	0.	4.391630	−1.821328	1.317790
56.	1.	0.	2.134677	−3.051105	0.823285
57.	1.	0.	1.703164	−3.477297	3.237814
58.	1.	0.	3.417816	−3.553717	2.816852
59.	1.	0.	2.792123	−2.148757	3.676435
60.	1.	0.	0.966009	−0.761655	0.636271
61.	1.	0.	0.368190	−1.378865	3.546807
62.	1.	0.	−1.333492	0.284112	3.446473
63.	1.	0.	1.637417	1.146408	2.329723
64.	1.	0.	0.999832	1.024443	3.972959
65.	1.	0.	2.391857	0.052008	3.498067
66.	1.	0.	−0.956599	−0.595300	−3.232809
67.	1.	0.	−2.732007	−0.574592	−3.209947
68.	1.	0.	−0.564456	−4.293724	−0.363445
69.	1.	0.	−2.080281	−4.691620	−1.184098
70.	1.	0.	−2.431236	−4.326492	1.870663
71.	1.	0.	−3.769745	−3.168589	1.752328
72.	1.	0.	−3.697118	−4.550997	0.657590
73.	1.	0.	0.600214	−2.321732	−1.245939
74.	1.	0.	−2.851709	−0.654873	1.663045
75.	1.	0.	−2.116666	−1.856752	2.721518
76.	1.	0.	−0.858096	2.860010	−0.012329
77.	1.	0.	−2.061971	3.839479	0.824608
78.	1.	0.	−2.648479	3.261188	−1.512708
79.	1.	0.	−4.916851	2.560050	−1.296339
80.	1.	0.	−4.366795	4.911380	−0.523940
81.	1.	0.	−4.285625	4.309521	1.145641
82.	1.	0.	−5.807869	4.227061	0.253722
83.	1.	0.	−4.420337	1.834645	1.376162
84.	1.	0.	−3.664464	−1.309449	−0.383027
85.	1.	0.	−3.723318	−2.699289	−1.495744
86.	1.	0.	−1.229754	−2.733762	−4.152796
87.	1.	0.	−2.608252	−3.566730	−3.395902
88.	1.	0.	−1.041818	−4.380842	−3.544522

Isomer 2-2			Standard Orientation (Ångstroms)		
Center Number	**Atomic Number**	**Atomic Type**	**X**	Y	Z
1.	6.	0.	1.964059	3.186829	−0.912486
2.	6.	0.	2.687095	4.089483	−0.120965
3.	6.	0.	3.946823	3.730279	0.345284
4.	6.	0.	4.501226	2.483541	0.040441
5.	6.	0.	3.782805	1.579789	−0.746576
6.	6.	0.	2.512592	1.938064	−1.222966
7.	6.	0.	4.349594	0.210587	−1.103316
8.	8.	0.	0.736452	3.586026	−1.351926
9.	6.	0.	3.500713	−0.944902	−0.529780
10.	8.	0.	5.698871	0.144236	−0.650381
11.	6.	0.	6.487418	−0.831090	−1.299754
12.	6.	0.	3.522115	−1.050859	1.003936
13.	6.	0.	2.416682	−1.985521	1.549788
14.	6.	0.	2.759239	−2.590324	2.918888
15.	6.	0.	1.019722	−1.324246	1.481942
16.	6.	0.	0.519526	−0.540253	2.714503
17.	6.	0.	−0.939064	−0.095163	2.506131
18.	6.	0.	1.397122	0.657987	3.105953
19.	6.	0.	−1.187688	−1.961722	0.784649
20.	8.	0.	−0.955279	1.027379	1.569356
21.	6.	0.	−1.852859	−0.615470	−2.566286
22.	6.	0.	−1.728096	−1.697528	−1.491386
23.	6.	0.	−0.893492	−2.952973	−1.944561
24.	6.	0.	−1.179844	−3.934728	−0.761153
25.	6.	0.	−2.065559	−3.124476	0.218113
26.	6.	0.	−1.861734	0.806484	−2.038586
27.	8.	0.	−1.044188	1.646396	−2.374956
28.	8.	0.	0.091434	−2.410583	1.185034
29.	6.	0.	−2.793227	−3.979303	1.247906
30.	8.	0.	0.477994	−2.613909	−2.078775
31.	6.	0.	−1.825456	−1.211126	1.958418
32.	8.	0.	−2.890652	1.045279	−1.215863
33.	6.	0.	−2.068864	1.768629	1.550651
34.	8.	0.	−2.970114	1.654518	2.369423
35.	6.	0.	−2.084783	2.746521	0.397100
36.	6.	0.	−3.092610	2.398207	−0.719782
37.	6.	0.	−4.598978	2.471831	−0.379311
38.	6.	0.	−5.016976	3.861922	0.111067
39.	8.	0.	−5.025021	1.450736	0.501932
40.	6.	0.	−2.937681	−2.314150	−0.785150
41.	8.	0.	−1.016677	−1.107995	−0.371835
42.	6.	0.	−1.310511	−3.527559	−3.296492
43.	1.	0.	2.248239	5.055323	0.106872
44.	1.	0.	4.508897	4.431846	0.955799
45.	1.	0.	5.486115	2.210163	0.396710
46.	1.	0.	1.942182	1.255148	−1.848803
47.	1.	0.	4.339806	0.117321	−2.203128
48.	1.	0.	0.285760	2.872756	−1.839204
49.	1.	0.	2.477837	−0.800683	−0.895857
50.	1.	0.	3.836872	−1.894579	−0.964976
51.	1.	0.	6.153022	−1.857524	−1.090322
52.	1.	0.	6.493160	−0.686672	−2.391160
53.	1.	0.	7.507204	−0.716505	−0.924291
54.	1.	0.	3.432290	−0.052308	1.442343
55.	1.	0.	4.501650	−1.427441	1.318099

56.	1.	0.	2.341245	−2.828650	0.849696
57.	1.	0.	3.667757	−3.196700	2.845759
58.	1.	0.	2.940706	−1.827164	3.682657
59.	1.	0.	1.953630	−3.241632	3.272847
60.	1.	0.	1.003006	−0.638046	0.628844
61.	1.	0.	0.482450	−1.242281	3.558013
62.	1.	0.	−1.351449	0.271314	3.450134
63.	1.	0.	1.530109	1.346632	2.267726
64.	1.	0.	0.926257	1.215880	3.922934
65.	1.	0.	2.384446	0.344297	3.450533
66.	1.	0.	−0.989140	−0.675078	−3.231292
67.	1.	0.	−2.761387	−0.776657	−3.156144
68.	1.	0.	−0.250542	−4.278772	−0.305955
69.	1.	0.	−1.735507	−4.813599	−1.105823
70.	1.	0.	−2.084209	−4.450235	1.937468
71.	1.	0.	−3.510933	−3.401379	1.837480
72.	1.	0.	−3.348266	−4.778764	0.746578
73.	1.	0.	0.735333	−2.214851	−1.234636
74.	1.	0.	−2.807999	−0.813360	1.698677
75.	1.	0.	−1.969023	−1.937150	2.765079
76.	1.	0.	−1.087392	2.832705	−0.031770
77.	1.	0.	−2.360270	3.726660	0.798152
78.	1.	0.	−2.889769	3.088913	−1.545205
79.	1.	0.	−5.115873	2.264545	−1.324592
80.	1.	0.	−4.704034	4.653332	−0.579241
81.	1.	0.	−4.592524	4.076307	1.097367
82.	1.	0.	−6.105157	3.895871	0.203927
83.	1.	0.	−4.577293	1.592978	1.354340
84.	1.	0.	−3.584678	−1.560246	−0.329936
85.	1.	0.	−3.541801	−2.964795	−1.424822
86.	1.	0.	−1.080179	−2.831696	−4.107787
87.	1.	0.	−2.377697	−3.764846	−3.325390
88.	1.	0.	−0.751253	−4.449604	−3.481085

Isomer 2-3			**Standard Orientation (Ångstroms)**		
Center Number	**Atomic Number**	**Atomic Type**	**X**	Y	Z
1.	6.	0.	3.717850	−2.449443	−1.533096
2.	6.	0.	4.258587	−3.488371	−0.765518
3.	6.	0.	5.103276	−3.181570	0.300257
4.	6.	0.	5.403402	−1.853728	0.609969
5.	6.	0.	4.856542	−0.813811	−0.151670
6.	6.	0.	4.026152	−1.121118	−1.233958
7.	6.	0.	5.109362	0.649150	0.197840
8.	8.	0.	2.868893	−2.672117	−2.584170
9.	6.	0.	3.845657	1.342038	0.732363
10.	8.	0.	5.509359	1.406855	−0.942127
11.	6.	0.	6.794882	1.076381	−1.434636
12.	6.	0.	3.356772	0.781618	2.078160
13.	6.	0.	1.920622	1.171365	2.502888
14.	6.	0.	1.727934	2.692599	2.599196
15.	6.	0.	0.781520	0.512071	1.692010
16.	6.	0.	0.867586	−1.023483	1.568200
17.	6.	0.	−0.231651	−1.560740	0.643495
18.	6.	0.	0.859871	−1.742012	2.923825
19.	6.	0.	−0.362952	0.759871	−0.421997
20.	8.	0.	−1.516450	−1.498594	1.335548

21.	6.	0.	−3.745475	2.182535	−0.125561
22.	6.	0.	−2.300224	2.091472	−0.615352
23.	6.	0.	−1.514943	3.451837	−0.534554
24.	6.	0.	−0.223951	3.087546	−1.341716
25.	6.	0.	−0.408095	1.599598	−1.738433
26.	6.	0.	−4.318312	0.944218	0.540637
27.	8.	0.	−4.843577	0.956206	1.632424
28.	8.	0.	0.743001	1.126984	0.377712
29.	6.	0.	0.508705	1.139725	−2.864505
30.	8.	0.	−1.266087	3.789729	0.819688
31.	6.	0.	−0.327035	−0.758209	−0.651431
32.	8.	0.	−4.226446	−0.165940	−0.230442
33.	6.	0.	−2.477957	−2.313899	0.882162
34.	8.	0.	−2.279017	−3.218380	0.081871
35.	6.	0.	−3.843710	−1.963618	1.422100
36.	6.	0.	−4.768735	−1.395296	0.325706
37.	6.	0.	−4.985155	−2.327941	−0.892201
38.	6.	0.	−6.276770	−1.989089	−1.625402
39.	8.	0.	−5.047359	−3.687076	−0.490552
40.	6.	0.	−1.937817	1.562330	−2.003505
41.	8.	0.	−1.580946	1.167074	0.251819
42.	6.	0.	−2.253841	4.648076	−1.131488
43.	1.	0.	4.022064	−4.523571	−1.002107
44.	1.	0.	5.529231	−3.986783	0.891784
45.	1.	0.	6.060772	−1.624447	1.443993
46.	1.	0.	3.617686	−0.330932	−1.854700
47.	1.	0.	5.905205	0.692111	0.962174
48.	1.	0.	2.737333	−3.623574	−2.690364
49.	1.	0.	4.074309	2.409429	0.820843
50.	1.	0.	3.060598	1.249650	−0.021501
51.	1.	0.	6.996615	1.749350	−2.271359
52.	1.	0.	7.571072	1.222125	−0.667180
53.	1.	0.	6.850567	0.038653	−1.790974
54.	1.	0.	4.038650	1.117370	2.871477
55.	1.	0.	3.439268	−0.310902	2.067905
56.	1.	0.	1.792241	0.774976	3.519285
57.	1.	0.	0.747786	2.940489	3.021486
58.	1.	0.	2.487923	3.133254	3.253115
59.	1.	0.	1.797470	3.177296	1.623379
60.	1.	0.	−0.162675	0.756880	2.198771
61.	1.	0.	1.802683	−1.262893	1.046100
62.	1.	0.	−0.040740	−2.611638	0.412439
63.	1.	0.	−0.017078	−1.461836	3.514752
64.	1.	0.	0.829728	−2.827270	2.779706
65.	1.	0.	1.754883	−1.514098	3.508060
66.	1.	0.	−3.814477	2.968581	0.629247
67.	1.	0.	−4.396453	2.457792	−0.963363
68.	1.	0.	0.670986	3.259338	−0.743890
69.	1.	0.	−0.146006	3.693675	−2.250868
70.	1.	0.	1.557113	1.154749	−2.548788
71.	1.	0.	0.272929	0.129584	−3.211228
72.	1.	0.	0.413677	1.813356	−3.722374
73.	1.	0.	−0.962150	2.971412	1.241912
74.	1.	0.	−1.189394	−1.092396	−1.231181
75.	1.	0.	0.568527	−0.985986	−1.238312
76.	1.	0.	−3.767561	−1.243731	2.236020
77.	1.	0.	−4.314959	−2.879567	1.788163
78.	1.	0.	−5.722962	−1.160082	0.806384

79.	1.	0.	−4.133755	−2.169265	−1.569235
80.	1.	0.	−6.294384	−0.933610	−1.912397
81.	1.	0.	−7.139146	−2.193049	−0.982231
82.	1.	0.	−6.370726	−2.601326	−2.525771
83.	1.	0.	−4.124166	−3.952646	−0.336084
84.	1.	0.	−2.346179	0.567488	−2.194970
85.	1.	0.	−2.234029	2.230748	−2.817606
86.	1.	0.	−3.148894	4.887744	−0.551430
87.	1.	0.	−2.540833	4.472785	−2.172343
88.	1.	0.	−1.596301	5.522235	−1.103640

isomer 2-4			**Standard Orientation (Ångstroms)**		
Center Number	**Atomic Number**	**Atomic Type**	**X**	Y	Z
1.	6.	0.	5.069767	−2.394771	−1.517908
2.	6.	0.	5.649149	−3.242518	−0.565537
3.	6.	0.	6.055463	−2.714337	0.655522
4.	6.	0.	5.890723	−1.354847	0.938016
5.	6.	0.	5.299737	−0.509730	−0.005595
6.	6.	0.	4.893003	−1.038368	−1.237336
7.	6.	0.	5.062149	0.966320	0.290840
8.	8.	0.	4.696440	−2.953157	−2.709203
9.	6.	0.	3.603870	1.274849	0.667495
10.	8.	0.	5.349697	1.787712	−0.840165
11.	6.	0.	6.729219	1.881967	−1.147302
12.	6.	0.	3.161838	0.631371	1.988896
13.	6.	0.	1.718324	0.928630	2.459822
14.	6.	0.	1.465750	2.427376	2.690949
15.	6.	0.	0.591313	0.301448	1.613569
16.	6.	0.	0.688373	−1.222644	1.399831
17.	6.	0.	−0.434775	−1.704061	0.471477
18.	6.	0.	0.714258	−2.022685	2.708886
19.	6.	0.	−0.571415	0.674422	−0.467458
20.	8.	0.	−1.701446	−1.665403	1.195682
21.	6.	0.	−3.926335	2.126829	−0.041774
22.	6.	0.	−2.491102	2.040814	−0.561945
23.	6.	0.	−1.682049	3.383050	−0.425451
24.	6.	0.	−0.411198	3.041782	−1.273845
25.	6.	0.	−0.625432	1.578904	−1.740286
26.	6.	0.	−4.497959	0.865619	0.582105
27.	8.	0.	−4.993216	0.832513	1.687229
28.	8.	0.	0.549591	0.987340	0.333988
29.	6.	0.	0.266176	1.161119	−2.902563
30.	8.	0.	−1.403023	3.647146	0.938958
31.	6.	0.	−0.553396	−0.830921	−0.775186
32.	8.	0.	−4.440777	−0.207438	−0.242581
33.	6.	0.	−2.690607	−2.428105	0.707525
34.	8.	0.	−2.526921	−3.275283	−0.159703
35.	6.	0.	−4.035977	−2.092327	1.304477
36.	6.	0.	−4.985067	−1.455796	0.267912
37.	6.	0.	−5.254214	−2.321310	−0.988516
38.	6.	0.	−6.565585	−1.930004	−1.658096
39.	8.	0.	−5.320632	−3.698819	−0.656546
40.	6.	0.	−2.159824	1.576992	−1.981135
41.	8.	0.	−1.773638	1.060090	0.243223
42.	6.	0.	−2.411665	4.619991	−0.945784
43.	1.	0.	5.778283	−4.292754	−0.804214

44.	1.	0.	6.514774	−3.367097	1.392350
45.	1.	0.	6.224196	−0.951819	1.890205
46.	1.	0.	4.460025	−0.372635	−1.980999
47.	1.	0.	5.717830	1.260141	1.129112
48.	1.	0.	4.341961	−2.260966	−3.282728
49.	1.	0.	3.516152	2.364848	0.725610
50.	1.	0.	2.953839	0.952045	−0.149880
51.	1.	0.	6.819844	2.562730	−1.997172
52.	1.	0.	7.302523	2.292442	−0.301878
53.	1.	0.	7.162095	0.910024	−1.420368
54.	1.	0.	3.835551	0.973552	2.787390
55.	1.	0.	3.308127	−0.453359	1.930618
56.	1.	0.	1.623436	0.444988	3.441379
57.	1.	0.	0.504074	2.587887	3.191292
58.	1.	0.	2.243322	2.853261	3.333744
59.	1.	0.	1.448207	2.993535	1.757833
60.	1.	0.	−0.356368	0.505717	2.130867
61.	1.	0.	1.614750	−1.422970	0.845336
62.	1.	0.	−0.259355	−2.742573	0.179262
63.	1.	0.	−0.149148	−1.782445	3.336109
64.	1.	0.	0.683451	−3.097064	2.499141
65.	1.	0.	1.622602	−1.826993	3.284019
66.	1.	0.	−3.972397	2.880107	0.747373
67.	1.	0.	−4.590331	2.443920	−0.854092
68.	1.	0.	0.497709	3.169993	−0.686221
69.	1.	0.	−0.340171	3.690859	−2.153492
70.	1.	0.	1.317554	1.124920	−2.597379
71.	1.	0.	−0.008694	0.182440	−3.307240
72.	1.	0.	0.184036	1.888024	−3.717055
73.	1.	0.	−1.104989	2.804447	1.314438
74.	1.	0.	−1.427207	−1.130056	−1.356853
75.	1.	0.	0.330621	−1.027166	−1.390129
76.	1.	0.	−3.927688	−1.419201	2.154005
77.	1.	0.	−4.508409	−3.021574	1.633913
78.	1.	0.	−5.919943	−1.231404	0.789847
79.	1.	0.	−4.424237	−2.136794	−1.685122
80.	1.	0.	−6.579859	−0.860623	−1.888420
81.	1.	0.	−7.408188	−2.158458	−0.997214
82.	1.	0.	−6.697832	−2.492375	−2.585775
83.	1.	0.	−4.396528	−3.985030	−0.554597
84.	1.	0.	−2.586427	0.598527	−2.213145
85.	1.	0.	−2.459566	2.288636	−2.756301
86.	1.	0.	−3.293587	4.841267	−0.339050
87.	1.	0.	−2.717467	4.505541	−1.989631
88.	1.	0.	−1.740241	5.481554	−0.881579

Table S1.4.3. DP4+ evaluation of theoretical and experimental data for isomer 1 and isomer 2.

Funtional	**Solvent**	**Bassis Set**	**Type of Data**	
mPW1PW91	**PCM**	**6–311+G(d, p)**	**Unscaled Shifts**	
		DP4+	**0.00%**	**100.00%**
Nuclei	**Sp2**	**Experimental**	**Isomer 1**	**Isomer 2**
C	x[1]	172.1	177.2	176.7
C		34.8	35.2	36.8
C		85	86.0	87.6
C		79.2	79.8	79.5
C		47.1	46.8	42.0
C		48.7	51.7	50.6

C		105.5	103.7	105.8
C		105.5	28.1	33.5
C		105.5	78.2	75.5
C		105.5	36.3	36.2
C		105.5	69.8	72.4
C		105.5	36.79	36.03
C		105.5	28.46	28.99
C		105.5	36.81	32.75
C		105.5	81.37	81.76
C	x	105.5	144.66	144.98
C	x	105.5	112.55	111.75
C	x	105.5	159.05	158.46
C	x	105.5	115.38	114.87
C	x	105.5	129.65	129.53
C	x	105.5	115.07	117.43
C		105.5	13.81	13.52
C		105.5	13.81	12.06
C		105.5	45.30	44.55
C		105.5	13.57	15.38
C		105.5	21.18	22.55
C	x	105.5	170.25	174.64
C		105.5	39.66	34.64
C		105.5	81.56	76.67
C		105.5	70.73	69.22
C		105.5	14.75	18.39
C		105.5	54.25	54.43
H		105.5	2.79	2.834
H		105.5	2.499	2.343
H		105.5	1.827	2.07
H		105.5	1.567	1.523
H		105.5	2.353	1.792
H		105.5	1.343	1.336
H		105.5	4.17	4.449
H		105.5	1.334	1.338
H		105.5	3.542	3.609
H		105.5	1.334	1.244
H		105.5	1.334	1.244
H		105.5	1.362	1.307
H		105.5	1.815	2.07
H		105.5	1.815	1.599
H		105.5	4.17	4.016
H	x	105.5	6.345	6.272
H	x	105.5	6.467	6.286
H	x	105.5	6.868	6.831
H	x	105.5	6.541	6.601
H		105.5	0.777	0.785
H		105.5	0.631	0.499
H		105.5	2.026	2.245
H		105.5	2.026	1.244
H		105.5	0.929	0.828
H		105.5	1.087	1.244
H		105.5	2.253	3.34
H		105.5	2.026	2.244
H		105.5	5.081	4.51
H		105.5	3.642	3.729
H		105.5	0.986	1.134
H		105.5	2.911	3.034

[1] x: The atoms are Sp2 hybrid.

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

	Isomer 1	Isomer 2	Isomer 3	Isomer 4	Isomer 5	Isomer 6
sDP4+ (H data)	0.00%	100.00%	–	–	–	–
sDP4+ (C data)	0.00%	100.00%	–	–	–	–
sDP4+ (all data)	0.00%	100.00%	–	–	–	–
uDP4+ (H data)	0.62%	99.38%	–	–	–	–
uDP4+ (C data)	19.31%	80.69%	–	–	–	–
uDP4+ (all data)	0.15%	99.85%	–	–	–	–
DP4+ (H data)	0.00%	100.00%	–	–	–	–
DP4+ (C data)	0.00%	100.00%	–	–	–	–
DP4+ (all data)	0.00%	100.00%	–	–	–	–

2.

Spectra Data of 1 and 2

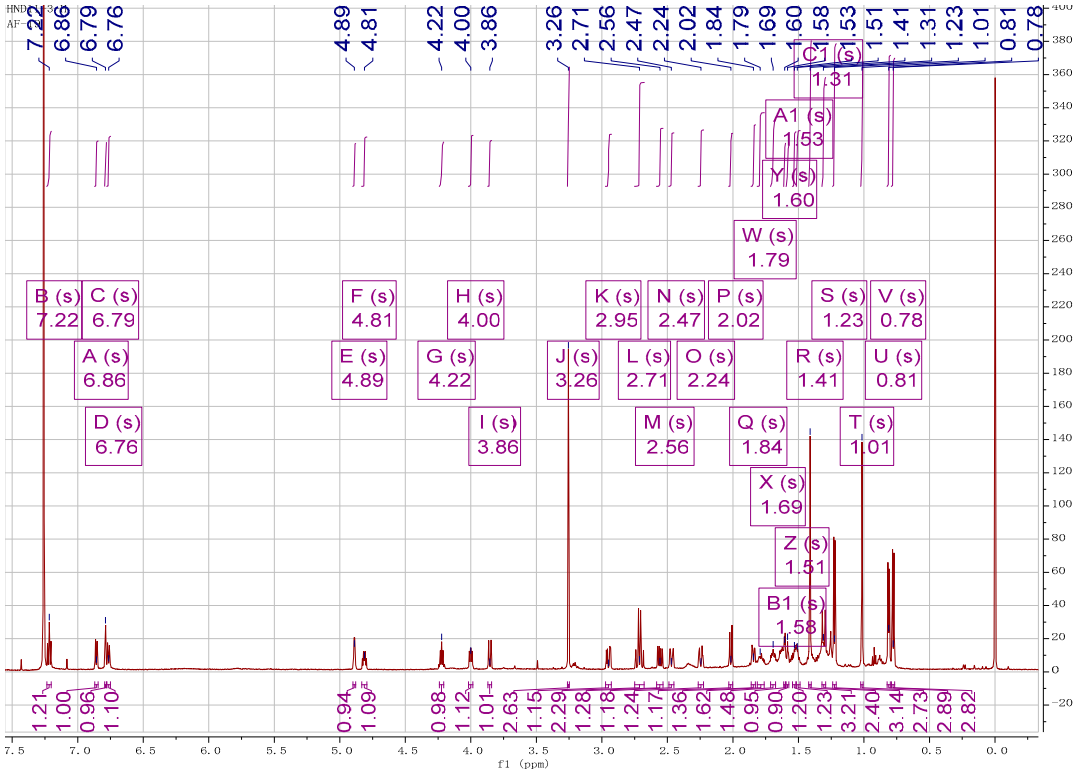

Figure S2.1. ^{1}H NMR spectrum of compound **1** in $CDCl_3$.

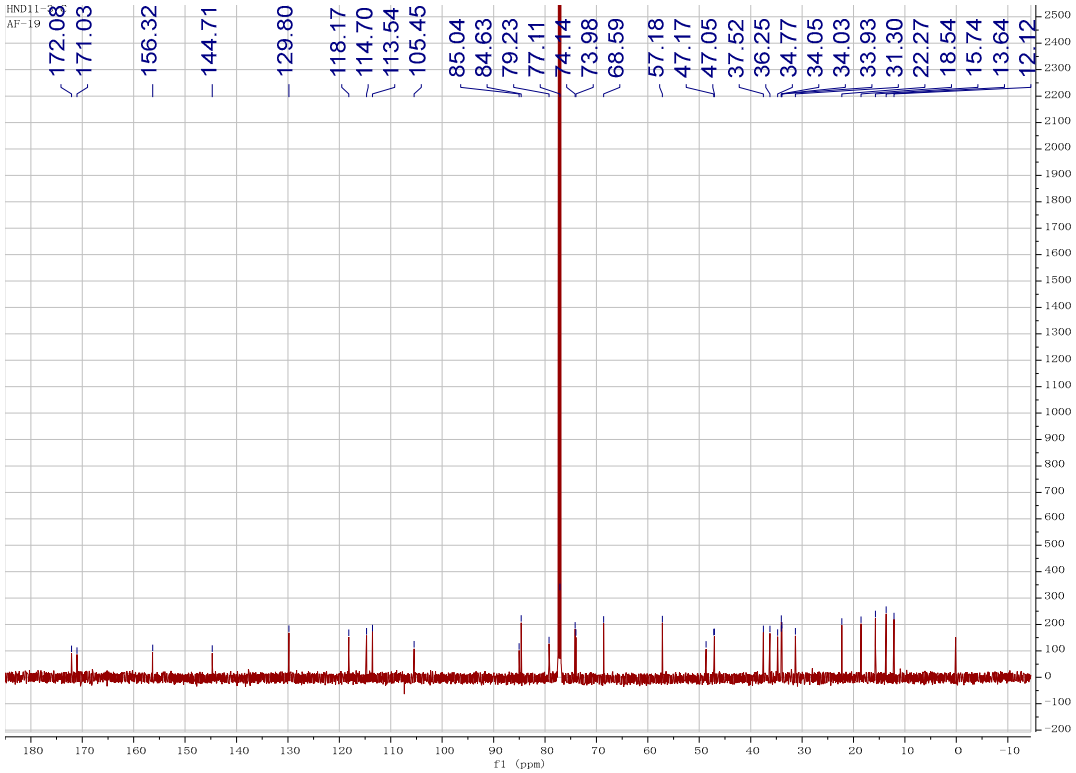

Figure S2.2. ^{13}C NMR spectrum of compound **1** in $CDCl_3$.

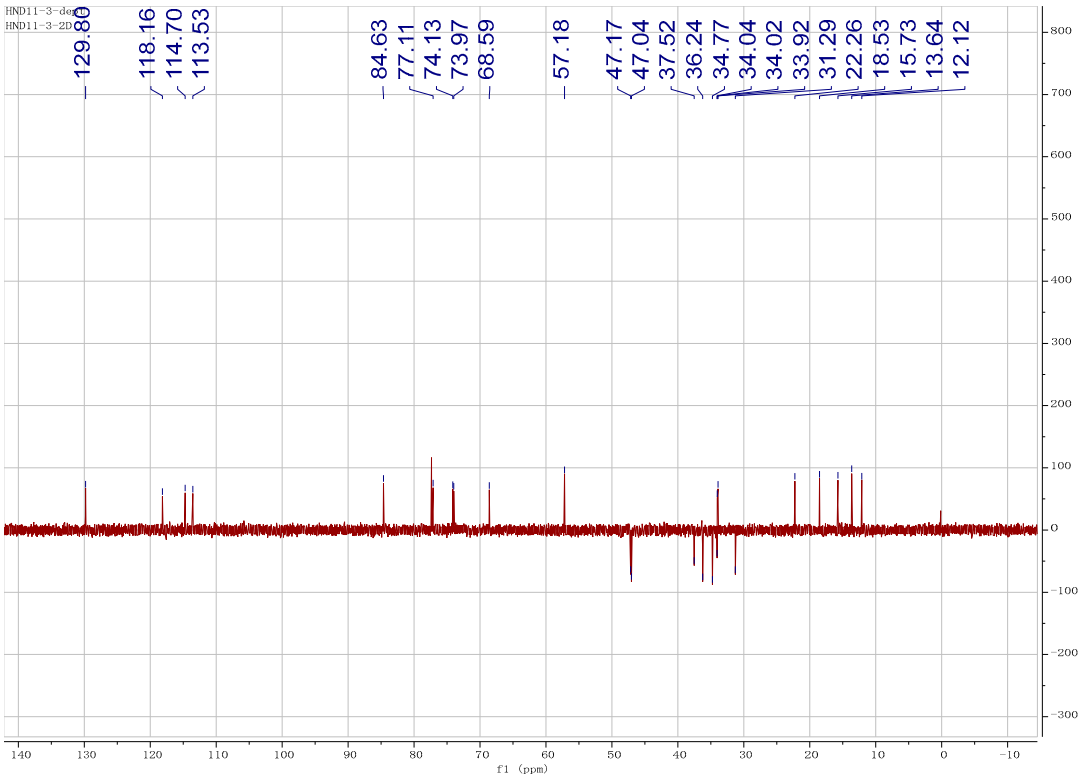

Figure S2.3. DEPT spectrum of compound **1** in $CDCl_3$.

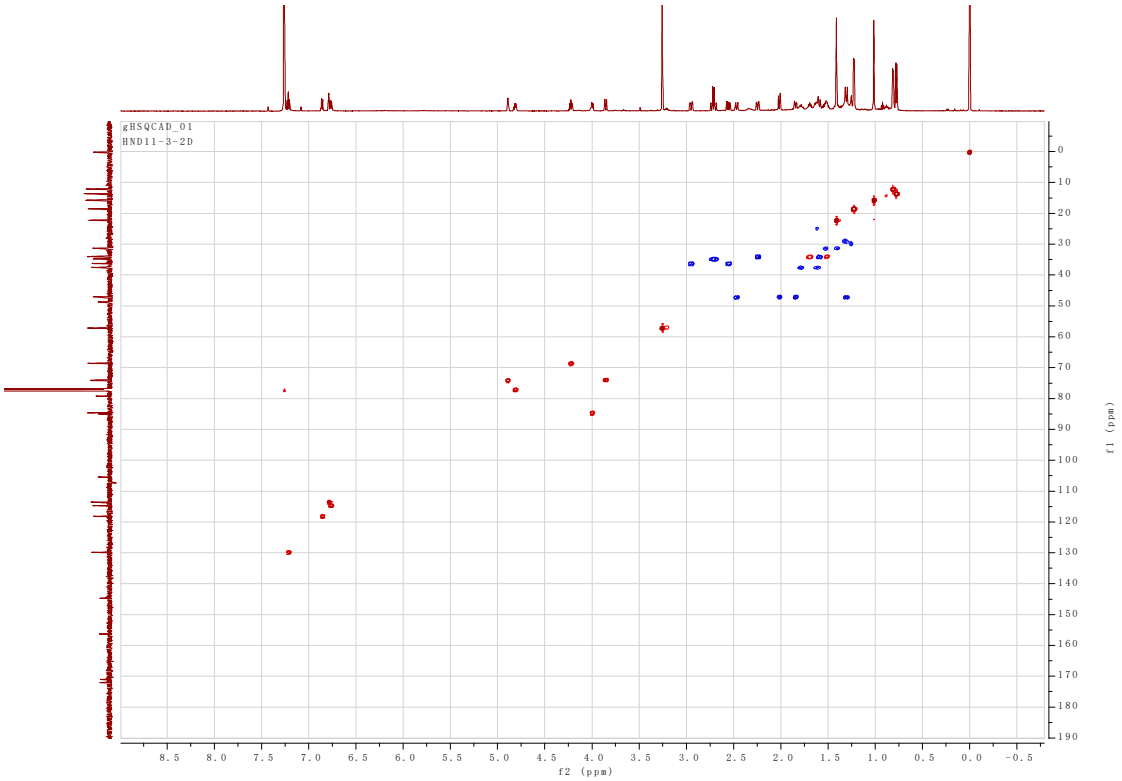

Figure S2.4. HSQC spectrum of compound **1** in CDCl3.

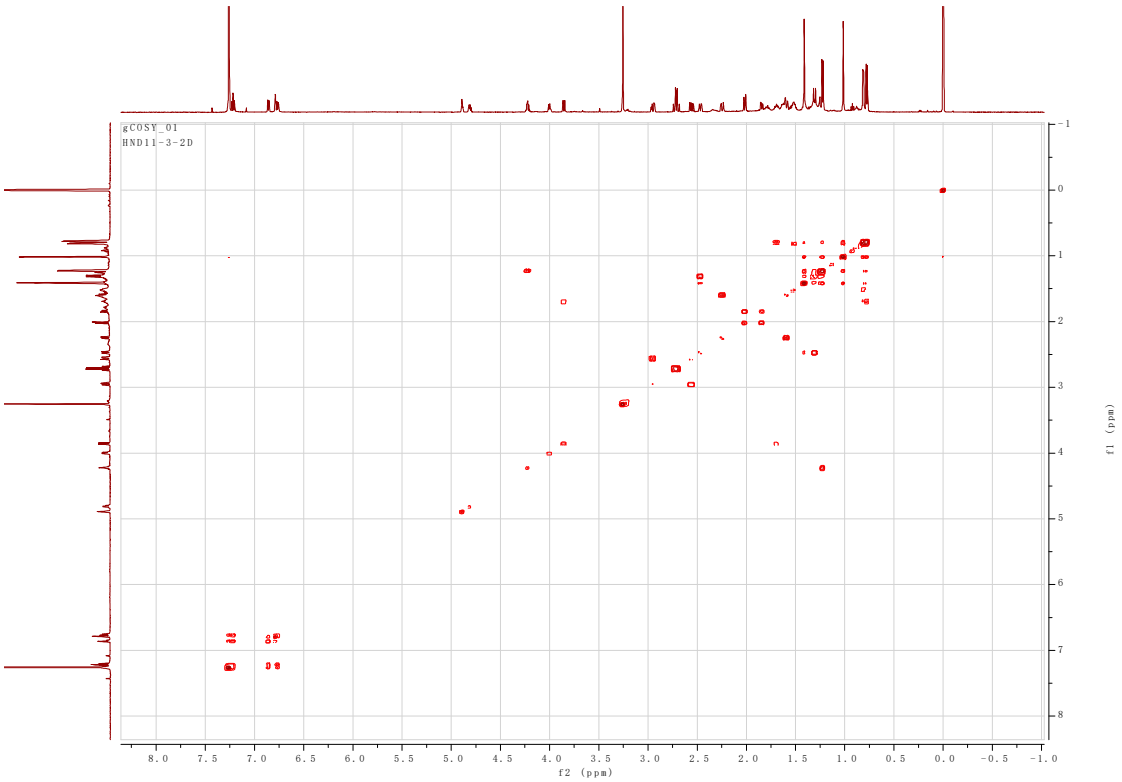

Figure S2.5. 1H-1H COSY spectrum of compound **1** in CDCl3.

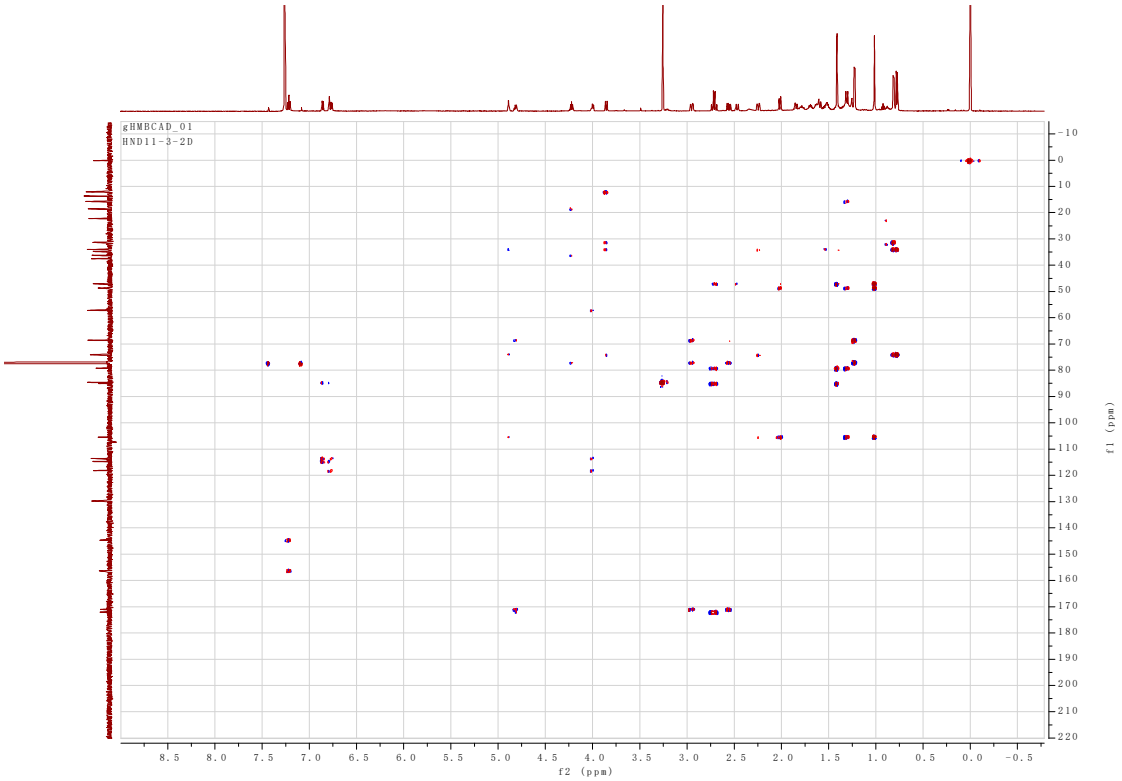

Figure S2.6. HMBC spectrum of compound **1** in CDCl3.

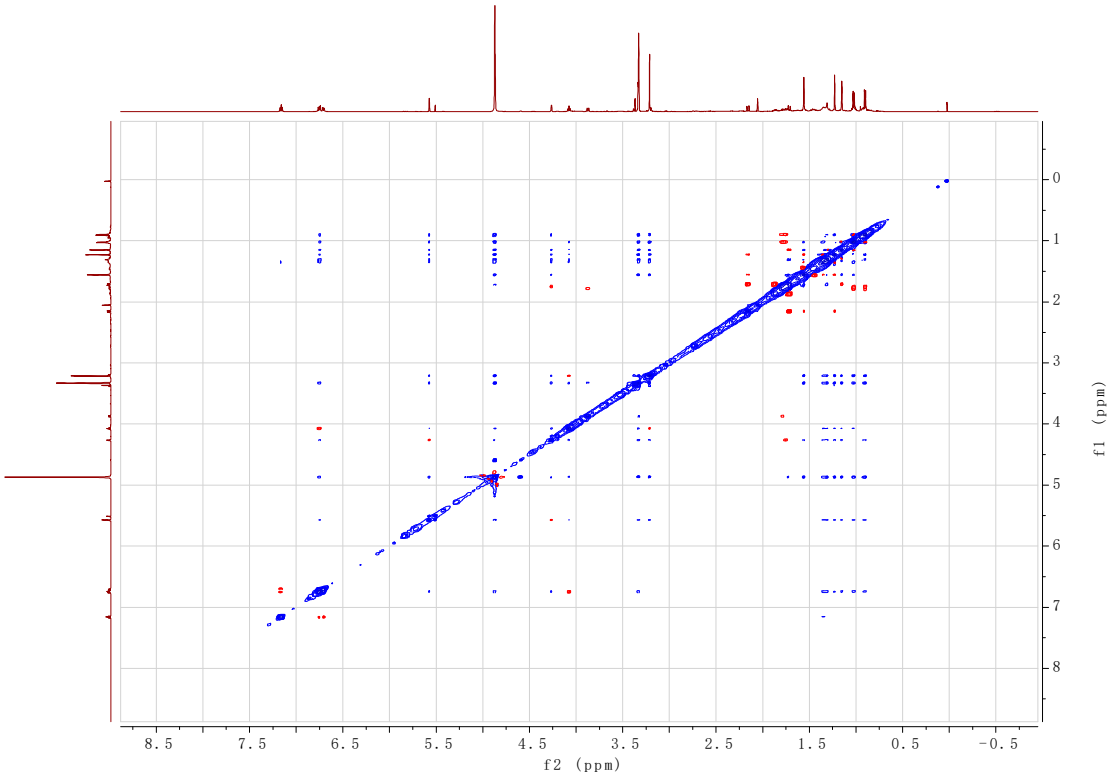

Figure S2.7. NOESY spectrum of compound **1** in $CDCl_3$.

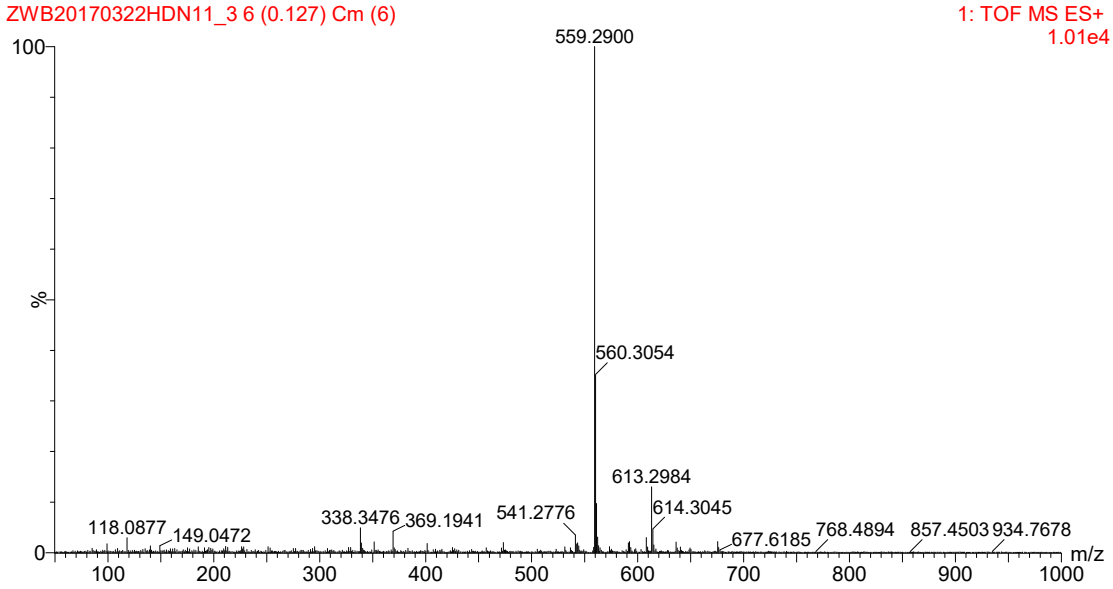

Figure S2.8. HRESIMS spectrum of compound **1** in MeOH.

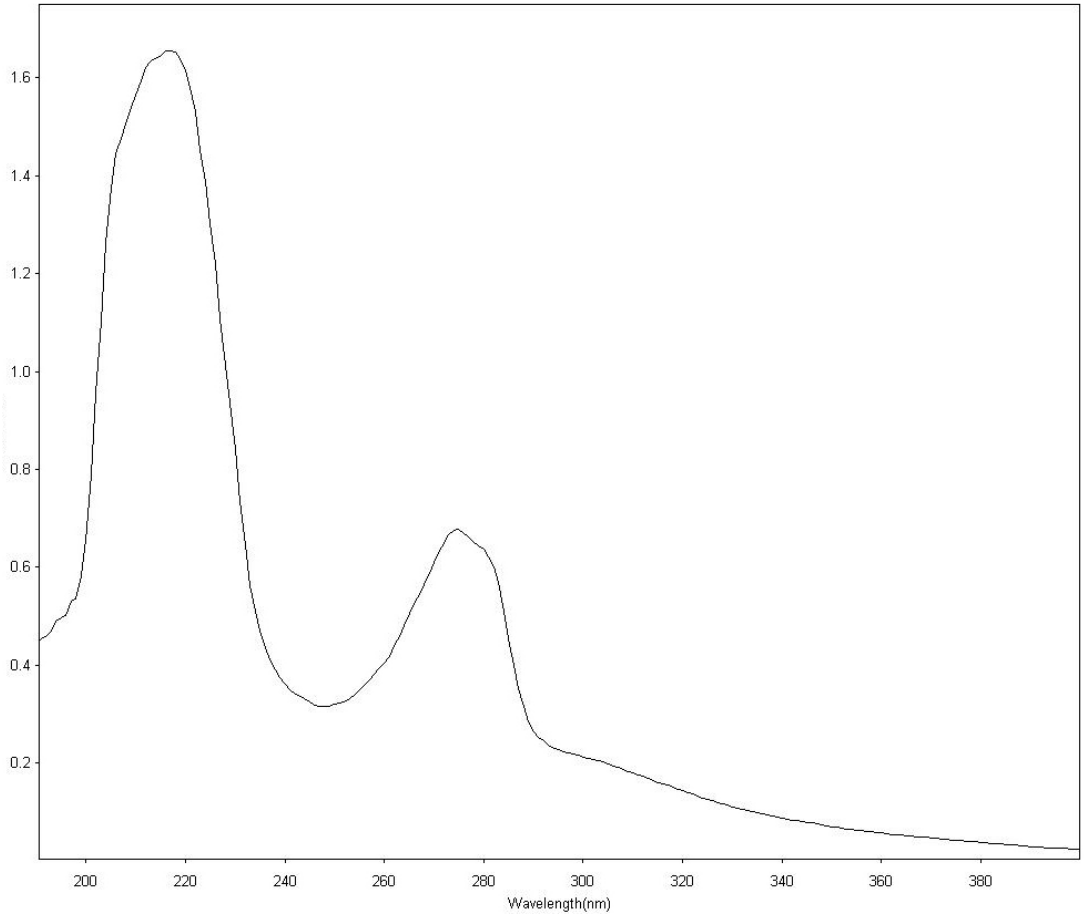

Figure S2.9. UV spectrum of Neo-debromoaplysiatoxin G (**1**) in MeOH.

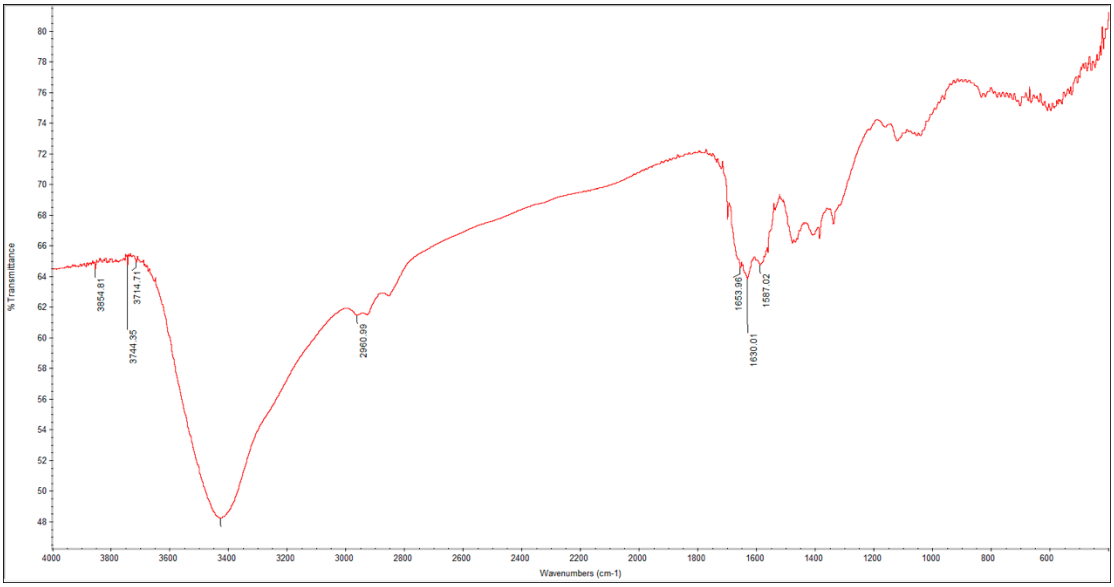

Figure S2.10. IR spectrum of Neo-debromoaplysiatoxin G (**1**).

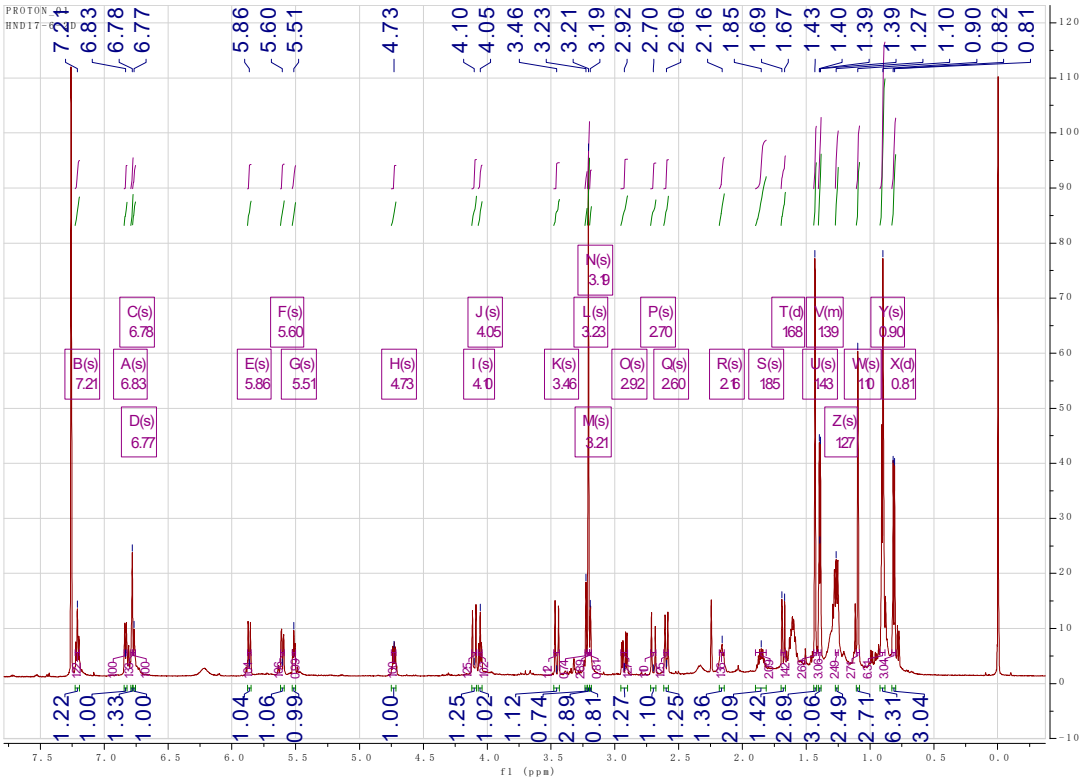

Figure S2.11. ^{1}H NMR spectrum of compound **2** in CDCl3.

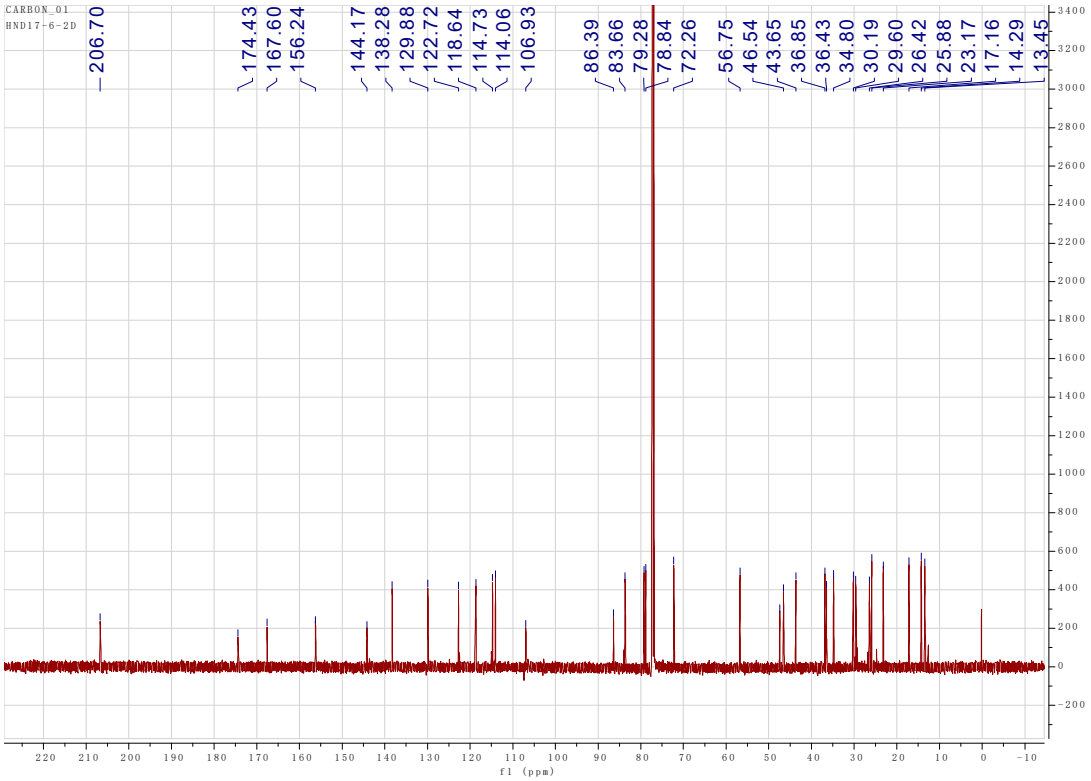

Figure S2.12. ^{13}C NMR spectrum of compound **2** in $CDCl_3$.

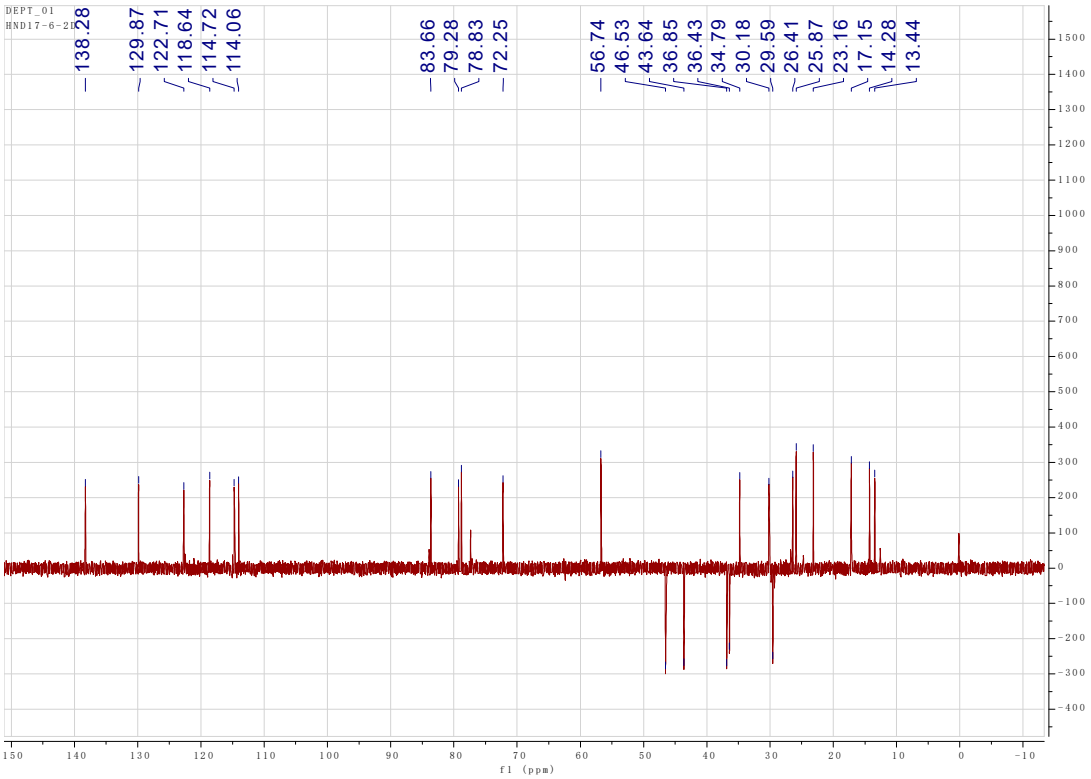

Figure S2.13. DEPT spectrum of compound **2** in $CDCl_3$.

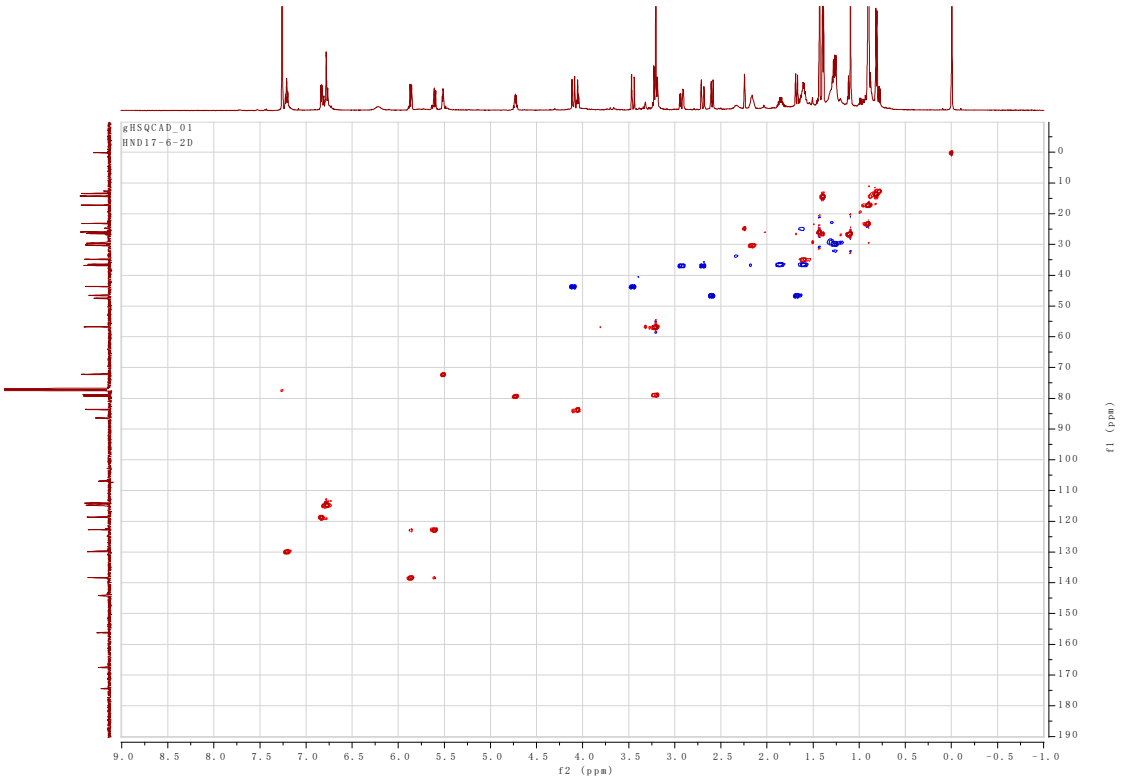

Figure S2.14. HSQC spectrum of compound **2** in $CDCl_3$.

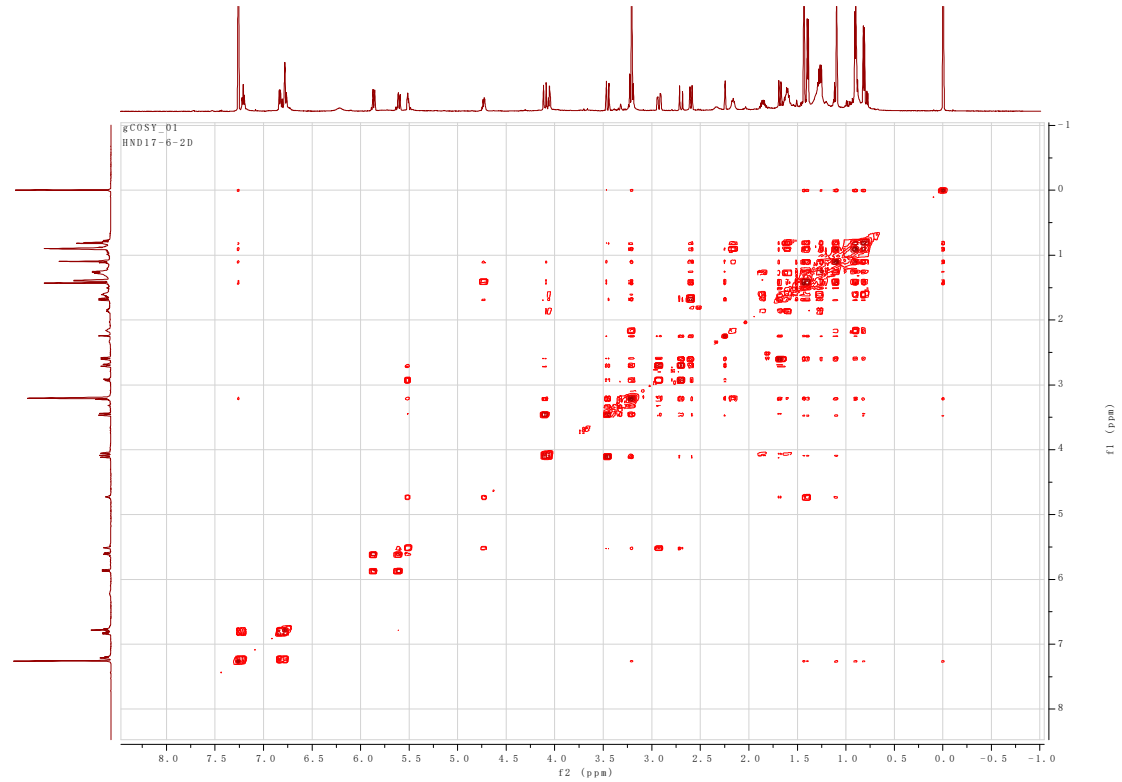

Figure S2.15. ^{1}H-^{1}H COSY spectrum of compound **2** in $CDCl_3$.

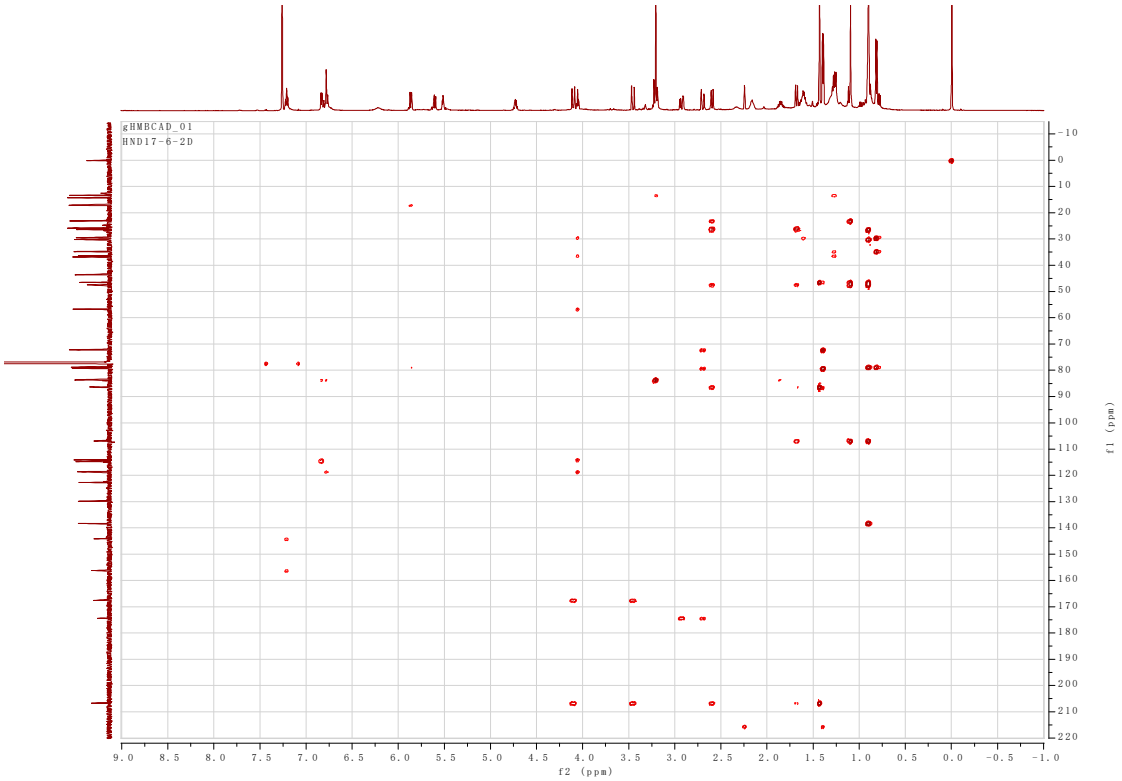

Figure S2.16. HMBC spectrum of compound **2** in $CDCl_3$.

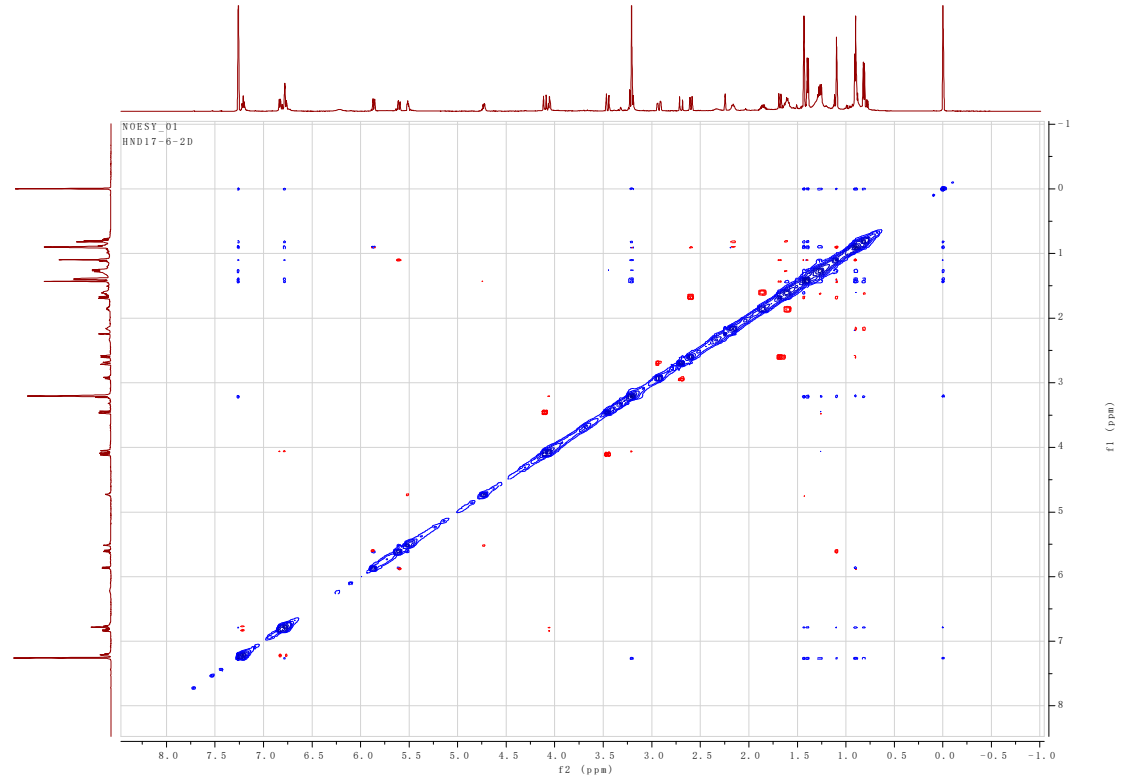

Figure S2.17. NOESY spectrum of compound **2** in $CDCl_3$.

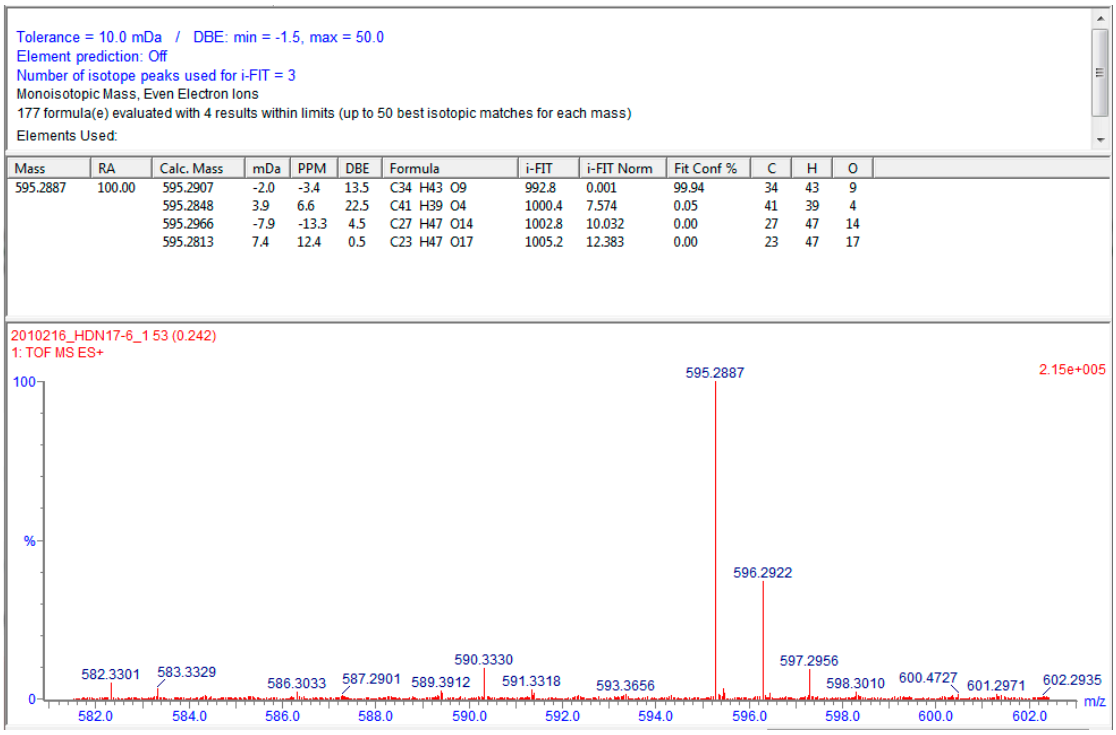

Figure S2.18. HRESIMS spectrum of compound **2** in MeOH.

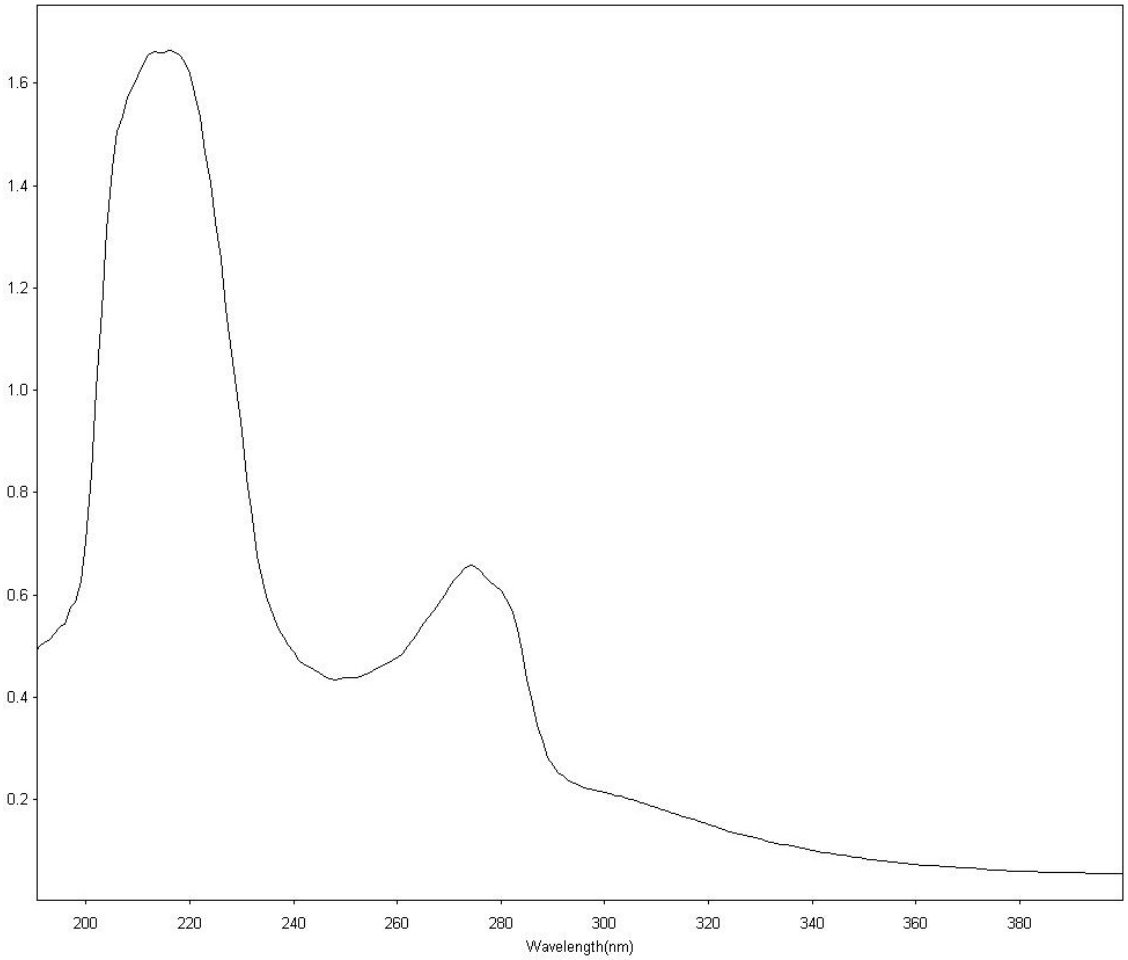

Figure S2.19. UV spectrum of Neo-ebromoaplysiatoxin H (**2**) in MeOH.

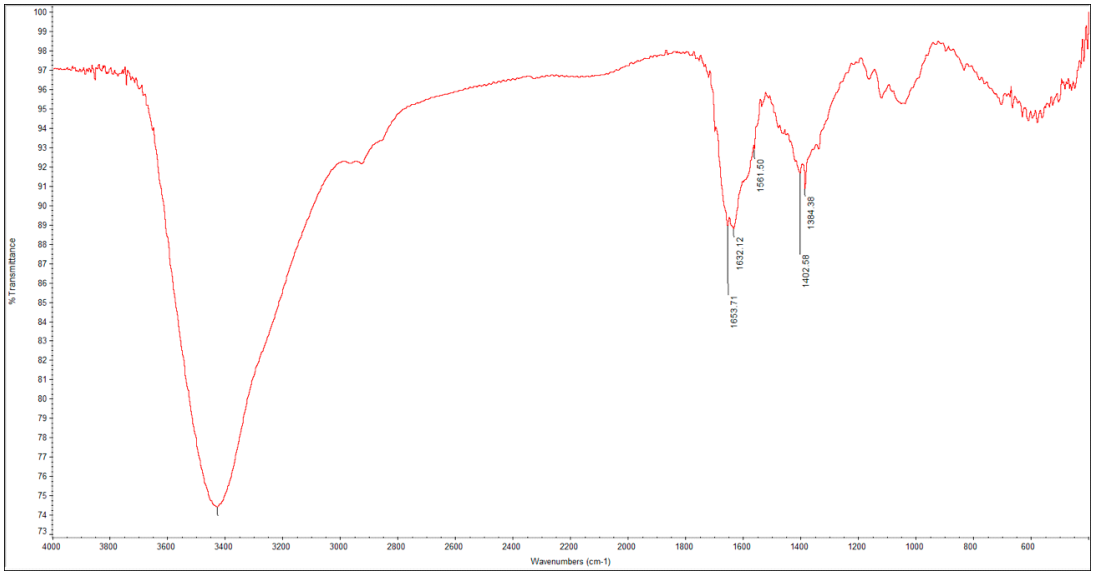

Figure S2.20. IR spectrum of Neo-debromoaplysiatoxin H (**2**).

3. The Distribution of All ATXs Produced in Different Sea Areas

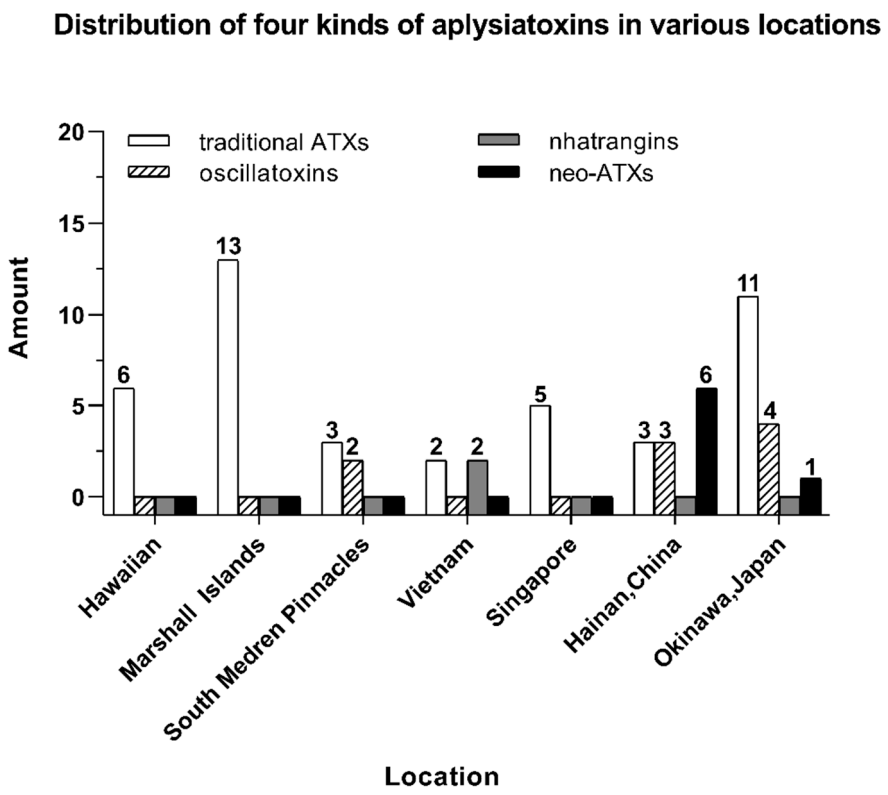

Figure S3.1. The distribution of four types of ATXs in various locations (traditional ATXs; oscillatoxins; nhatrangins; intriguing neo-ATXs). The values on the bar represent the number of ATXs of the corresponding type for different sea areas (Table S3.1).

Table S3.1. The distribution of all ATXs produced in different sea areas.

Name	Time	Location	Source	References
Aplysiatoxin (1) Debromoaplysiatoxin (2)	1969	Hawaiian	*Aplysia pulmonica* *Dolabella auricularia* *Dolabrfera dolabrfera* *Stylocheilus longicauda*	1
	1974	Hawaiian	*Stylocheilus longicauda*	2
	1980	Hawaiian windward Oahu	*Lyngbya majuscula*	3
Debromoaplysiatoxin (2)	1977	Enewetak Atoll, Marshall Islands	*Oscillatoria* sp.	4
Oscillatoxin A (3) 17-bromooscillatoxin A(4) 17,19-dibromooscillatoxin A (5) 19-bromoaplysiatoxin(6) 19-bromodebromoaplysiatoxin(7) 21-bromooscillatoxin (8) 19,21-dibromoaplysiatoxin(9) Anhydroaplysiatoxins(10)(11)(12)(13) Anhydrooscillatoxin A(14)	1978	Enewetak Atoll, Marshall Islands	*Oscillatoria nigroviridis* *Schizothrix calcicola*	5
Debromoaplysiatoxin(2) OscillatoxinA(3)	1984	Enewetak Atoll, Marshall Islands	*Lyngbya majuscula*	6
Oscillatoxin B1 (15) Oscillatoxin B2 (16) 31-noroscillatoxin B(17) Oscillatoxin D (18) 30-methyloscillatoxin D(19)	1985	South Medren Pinnacles	*Lyngbya majuscula* *Oscillatoria nigroviridis* *Schizothrix calcicola*	7
Aplysiatoxin (1) Debromoaplysiatoxin (2)	1996	Waiehu, Maui, Hawaiian	*Gracilaria coronopifolia*	8
Aplysiatoxin(1) Debromoaplysiatoxin(2) ManauealideA-C(20)(21)(22) Anhydebromoaplysiatoxins(23)	1998	Hawaiian	*Gracilaria coronopifolia*	9
Anhydroaplysiatoxin(10) Anhydebromoaplysiatoxins(23) NhatranginA(24) NhatranginB(25)	2010	Vietnam	*Lyngbya Majuscula*	10
Aplysiatoxin(1) Debromoaplysiatoxin(2) Ahydebromoaplysiatoxins(23) 3-methoxyaplysiatoxin(26) 3-methoxydebromoaplysiatoxin(27)	2014	Pulau Seringat Kias, Singapore	*Trichodesmium erythraeum*	11
Neo-debromoaplysiatoxinA(28) Neo-debromoaplysiatoxinB(29)	2018	Sanya, Hainan, China	*Lyngbya* sp.	12
Neo-debromoaplysiatoxinC(30) Neo-debromoaplysiatoxinD(31) OscillatoxinE(32) OscillatoxinF(33) Debromoaplysiatoxin(2) 30-methyloscillatoxinD(19) Anhydebromoaplysiatoxins(23) 3-methoxydebromoaplysiatoxin(27)	2019	Sanya, Hainan, China	*Lyngbya* sp.	13/14
Aplysiatoxin(1) Debromoaplysiatoxin(2) Anhydroaplysiatoxins(10) OscillatoxinB1(15) OscillatoxinB2(16) Anhydebromoaplysiatoxins(23) 2-hydroxyanhydroaplysiatoxin(34) 17-BromooscillatoxinB2(35) 17-Bromo-4-hydroperoxyoscillatoxinB2(36) 4-hydroperoxyoscillatoxinB2(37) 17-Bromo-4,26-epoxyoscillatoxinB2(38)	2019	Okinawa, Japan	*Moorea producens*	15
OscillatoxinI(39) OscillatoxinG(40) OscillatoxinH(41) 17-Bromo-30-methyloscillatoxinD(42)	2019	Okinawa, Japan	*Moorea producens*	16
Neo-debromoaplysiatoxinE(43) Neo-debromoaplysiatoxinF(44)	2019	Sanya, Hainan, China	*Lyngbya* sp.	17
Neo-aplysiatoxinA(45)	2020	Okinawa, Japan	*Moorea producens*	18

Table S3.2. NMR Data for debromoaplysiatoxin in $CDCL_3$ (δ in ppm, *J* in *Hz*).

Pos.	Debromoaplysiatoxin	
	δ_H (*J* in Hz)	δ_C
1		169.2
2	a 2.76, d (12.7) b 2.52, d (12.7)	46.9
3		98.8
4	1.84, m	35.7
5	a 1.62, t (13.1) b 1.05, dd (13.1, 3.6)	41.1
6		39.0
7		100.08
8	a 2.68, dd (14.7, 3.0) b 1.71, dd (14.8, 3.6)	33.6
9	5.23, m	73.2
10	1.71, m	35.4
11	3.93, dd (10.9, 2.1)	69.8
12	1.52, m	34.2
13	a 1.31, m b 1.39, m	31.2
14	a 1.97, m b 1.63, m	36.1
15	4.0, dd (8.5, 6.5)	85.8
16		145.9
17	6.92, t (1.1)	114.6
18		158.3
19	6.71, dt (7.9, 1,1)	115.0
20	7.13, t (7.8, 7.8)	129.8
21	6.84, dt (7.9, 1,1)	119.3
22	0.79, d (6.8)	13.6
23	0.71, d (6.9)	13.0
24	0.83, s	26.8
25	0.80, s	16.5
26	0.86, d (6.8)	23.6
27		170.4
28	a 2.92, dd (18.2, 11.1) b 2.87, dd (18.1, 2.8)	34.6
29	5.23, m	74.3
30	4.03, m	67.0
31	1.12, d (6.4)	17.7
15−OCH_3	3.17, s	56.6

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1. Watson M. Aspects of the pharmacology, chemistry, and biology of the midgut gland toxins of some Hawaiian sea hares, especially Dolabella auricularia and Aplysia pulmonica [D]. 1969.
2. Kato Y, Scheuer P J. ChemInform Abstract:Aplysiatoxin and debromoaplysiatoxin, constituents of the marine mollusk stylocheilus longicauda (quoy and gaimard, 1824) [J]. Chemischer Informationsdienst, 1974, 5(24): 2245−2246.
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