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Supporting Information

Asperspiropene A, a Novel Fungal Metabolite as an Inhibitor of Cancer Associated Mutant Isocitrate Dehydrogenase 1

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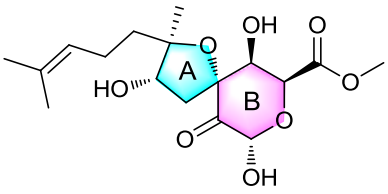

1 (Asperspiropene A)

Table S1. NMR Spectroscopic Data for compound **1**[a]

NO.	δ_H (J in Hz)	δ_C	DEPT
2		85.2	C
3	3.95 dd (13.8, 7.4)	74.4	CH
4a	2.16 dd (13.0, 7.1)	34.7	CH_2
4b	2.36 dd (13.0, 8.5)		
5		82.7	C
6		195.7	C
7	5.24 s	99.2	CH
9	4.51 s	66.6	CH
10	3.70 s	75.0	CH
11	1.39 m	40.1	CH_2
12	1.93 m	22.2	CH_2
13	5.07 t (7.11)	124.7	CH
14		130.7	C
15	1.62 s	25.6	CH_3
16	1.55 s	17.6	CH_3
17	0.91 s	20.3	CH_3
18		175.0	C
19	3.69 s	56.1	CH_3

[a] Recorded in DMSO-d_6 at 400 MHz for ^{1}H, 100 MHz for ^{13}C.

Detailed structure elucidation of 2D NMR data of compound 1

The planar structure of **1** was elucidated on the basis of 2D NMR spectra including ^{1}H-^{1}H COSY and HMBC correlations (Fig. 3. in the main article). Two spin systems, H-3/H_2-4 and H_2-11/H_2-12/H-13 were revealed by the ^{1}H-^{1}H COSY spectrum of **1**, as well as HMBC correlations of H_2-12/C-14 and H_3-15/C-13, C-14, and C-16 indicated the direct linkages of C-3–C-4 and C-11–C-16 (C-15), respectively. In addition, the HMBC interactions from H_3-17 to C-2, C-3, and C-11 and from H_2-4 to C-5 indicated the linkages of C-2/C-11 and C-4/C-5, as well as the location of the methyl group at C-17. An ether bond between C-2 and C-5 was proposed to form the tetrahydrofuran ring A, which is supported by the relative downfield chemical shifts of C-2 (δ_C 85.2) and C-5 (δ_C 82.7). The highly functionalized pyran ring B formed from an ether linkage between C-7 and C-9 and the presence of a methyl ester substitution at the C-9 position was similar to the hexanose

sugar unit of trichothosporon A, which was isolated from the fungus *Trichothecium* sp, except that the epoxy group at C-10 (δ_C 56.1) was replaced by a hydroxy group at C-10 (δ_C 75.0) in **1**, as further verified by the ^{1}H-^{1}H COSY correlation of OH-10 (δ_H 5.35, br s)/H-10. Considering the molecular formula and degrees of unsaturation of **1**, the HMBC correlations of H_2-4 with C-5, C-6, and C-10, and of H-7 with C-5 revealed that parts A and B joined at C-5, generating the 1,8-dioxaspiro[4.5]decane core. Thus, the planar structure of **1** was determined.

The relative configuration of **1** was deduced on the basis of a NOESY experiment (Fig. 3. in the main article) with a molecular modeling. The NOESY interactions of H-11, H-3, and H-4b indicate that they are co-facial and randomly assigned to be β-oriented, and consequently, Me-17 should adopt an α-orientation. Moreover, the key NOESY correlation of H-4b/H-10 suggests that the carbon-carbon bond of C-5–C-10 is in the axial position with a β-orientation, while H-10 was α-oriented. In the chairlike ring B of **1**, H-9 (ax bond) and H-10 (eq bond) showed no recognizable coupling constant (≈0 Hz) with each other, indicating that H-9 was also α-oriented. If H-7 and H-9 were in the axial positions, signals corresponding to H-7/H-9 should exist, which conflicted with the absence of NOESY correlation, suggesting that H-7 should be β-oriented. Thus, the relative configuration of **1** was determined.

Table S2. Antiproliferative activity of compounds **1**–**4** in a panel of human cancer cell lines and WI-38 fibroblast nomal cells.

Comp.	Antiproliferative activity (IC_{50}, μM)									
	A-549		SMMC-7721		MCF-7		SW480		WI-38 fibroblast	
	Average	SD	Average	SD	Average	SD	Average	SD	Average	SD
1	26.54	0.76	20.15	0.77	23.32	0.98	20.47	3.12	80.27	3.65
2	7.37	0.40	13.32	0.26	2.25	2.03	12.68	1.39	28.95	0.70
3	9.07	2.31	19.45	1.33	4.66	0.27	7.74	1.28	20.00	1.12
4	20.66	1.42	38.45	1.61	27.12	4.58	24.54	0.64	32.41	1.45
Paclitaxel[a]	<0.008		<0.008		<0.008		<0.008		<0.008	

[a] Paclitaxel were used as positive control.

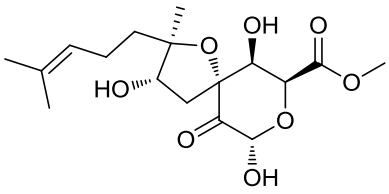

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Table S3. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized **1**(2*R*,3*S*,5*S*,*7S*,9*S*,10*R*) at LC-wPBE/6-311++G**// B3LYP/6-311++G** level in the MeOH.

Conformations	E+ZPE	G	Ratio
1a (BAL016	-1264.795169	-1264.853011	7.96%
1b BAL032	-1264.795090	-1264.852916	7.11%
1c BAL034	-1264.795612	-1264.853482	11.14%
1d BAL046	-1264.795931	-1264.853265	5.67%
1e BAL064	-1264.795020	-1264.852336	1.55%
1f OME048	-1264.796474	-1264.855075	31.01%
1g BAL081	-1264.793066	-1264.851739	9.58%
1h OME012	-1264.796197	-1264.854308	12.37%
1i OME021	-1264.794817	-1264.853207	8.28%
1j OME032	-1264.794168	-1264.852096	2.63%
1k OME039	-1264.794169	-1264.852038	2.70%

E+ZPE, G: total energy (E) in the DMSO at LC-wPBE/6-311++G**//B3LYP/6-311++G** level with IEFPCM solvent continuum model, zero point energy (ZPE) and Gibbs free energy (G) in the MeOH at B3LYP/6-311++G** level with IEFPCM solvent continuum model. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

Table S4. Optimized coordinate of **1**(2*R*,3*S*,5*S*,7*S*,9*S*,10*R)* at B3LYP/6-311++G**level in the MeOH.

1a				**1b**			
C	-1.86846	-1.965235	0.034457	C	1.807879	-1.964953	0.305026
C	4.544449	0.916458	-0.592208	C	-4.478687	1.058671	-0.858982
C	5.508315	1.5387	0.105831	C	-5.386185	1.55245	-0.001082
C	-3.467903	2.007868	0.2369	C	3.500267	1.94931	-0.138717
C	-0.166377	-1.309204	-1.796185	C	-0.210791	-1.065413	1.644234
C	-2.749318	-1.486265	1.199904	C	2.914963	-1.653143	-0.715285
C	-2.585525	0.783403	0.468919	C	2.656416	0.696856	-0.364053
C	1.084472	-1.975531	-1.195446	C	-1.337072	-1.80627	0.902315
C	-1.806933	0.418155	-0.806148	C	1.631912	0.514096	0.768001
C	-0.97875	-0.868227	-0.580189	C	0.837398	-0.797277	0.56496
C	1.313436	-1.18962	0.134562	C	-1.282149	-1.204559	-0.536632
C	6.196837	2.761594	-0.455236	C	-6.065959	2.874017	-0.276027
C	6.004743	1.115678	1.467546	C	-5.824841	0.883505	1.279411
C	1.73551	-2.068409	1.306411	C	-1.516519	-2.226825	-1.642557
C	-3.388442	4.325216	-0.219667	C	3.381957	4.307729	-0.053199
C	3.744529	-0.302232	-0.2098	C	-3.694856	-0.22499	-0.765132

C	2.242206	0.024808	-0.068034	C	-2.176913	0.044413	-0.67186
O	-1.825737	-3.141579	-0.283206	O	1.676331	-3.082792	0.773435
O	-4.677927	2.004349	0.206627	O	4.678069	1.960231	0.140009
O	-3.446714	-0.302556	0.811422	O	3.545668	-0.420266	-0.36769
O	-0.013141	-0.616272	0.47034	O	0.108194	-0.709051	-0.684902
O	-1.980232	-1.330734	2.358794	O	2.398235	-1.672344	-2.015644
O	0.938969	-3.378395	-1.033484	O	-1.195134	-3.218052	0.954726
O	-2.700221	0.242814	-1.896921	O	2.284715	0.502844	2.029799
O	-2.695211	3.087486	0.053895	O	2.731212	3.037803	-0.279604
H	4.28148	1.336759	-1.565241	H	-4.25477	1.654166	-1.746623
H	0.107576	-0.427343	-2.382984	H	-0.568534	-0.111347	2.042422
H	-0.711675	-1.990869	-2.451568	H	0.175764	-1.652359	2.479448
H	-3.529493	-2.220591	1.403792	H	3.704025	-2.403281	-0.650272
H	-1.889386	1.007529	1.284286	H	2.140641	0.794636	-1.325409
H	1.950082	-1.844857	-1.850202	H	-2.310431	-1.592053	1.351336
H	-1.12335	1.228266	-1.072856	H	0.927609	1.349914	0.774503
H	7.279397	2.596348	-0.54978	H	-5.880566	3.589846	0.537177
H	5.806881	3.034662	-1.440971	H	-5.721576	3.32478	-1.21228
H	6.073883	3.625453	0.213103	H	-7.156632	2.751721	-0.336309
H	5.883774	1.93349	2.19135	H	-6.906396	0.689706	1.262804
H	5.491275	0.237451	1.865646	H	-5.318228	-0.064814	1.473207
H	7.079911	0.891175	1.433727	H	-5.643695	1.543529	2.139022
H	1.86575	-1.459022	2.207332	H	-1.454039	-1.744392	-2.624049
H	2.680995	-2.574034	1.091256	H	-2.504834	-2.6846	-1.544775
H	0.986182	-2.838209	1.504584	H	-0.774963	-3.027181	-1.592424
H	-4.032784	4.589583	0.621577	H	3.768485	4.356591	0.967123
H	-3.988456	4.228818	-1.127079	H	2.609844	5.059897	-0.208037
H	-2.606377	5.071159	-0.353197	H	4.200011	4.443416	-0.763857
H	3.87684	-1.069278	-0.987525	H	-4.023778	-0.827189	0.088179
H	4.11562	-0.741433	0.720217	H	-3.894495	-0.826464	-1.662532
H	1.907283	0.57887	-0.955208	H	-1.984547	0.711332	0.178199
H	2.101496	0.697752	0.78618	H	-1.850557	0.58585	-1.568518
H	-1.097449	-0.999425	2.096329	H	1.486913	-1.316895	-1.986833
H	0.005184	-3.557912	-0.812018	H	-0.240596	-3.423084	0.957609
H	-3.489663	-0.218185	-1.560179	H	3.116112	0.005595	1.927328
1c				**1d**			
C	-2.095895	-1.79198	0.20707	C	-2.665475	-0.728464	0.032507
C	3.753686	1.226489	-0.16277	C	3.927216	-1.163689	0.407429
C	5.045756	1.444271	0.131821	C	4.551186	-0.008895	0.122726
C	-2.709659	2.450676	0.202282	C	-0.89119	3.178634	0.124779
C	-0.503602	-1.681031	-1.823632	C	-1.023731	-1.555425	-1.781863
C	-2.712759	-1.044359	1.399942	C	-2.934354	0.279194	1.162669
C	-2.113387	1.068958	0.459657	C	-1.178756	1.703097	0.386565

C	0.633126	-2.56873	-1.286232	C	-0.568709	-2.87673	-1.137268
C	-1.579454	0.449985	-0.843283	C	-0.915366	0.857652	-0.870906
C	-1.049724	-0.979145	-0.580337	C	-1.261453	-0.622842	-0.593221
C	1.191766	-1.744927	-0.081883	C	0.20826	-2.402905	0.13092
C	5.842057	2.485232	-0.621075	C	6.001052	-0.001587	-0.304411
C	5.826411	0.716909	1.200051	C	3.918317	1.360481	0.194265
C	1.605156	-2.605063	1.106186	C	0.037821	-3.32357	1.332886
C	-2.146436	4.654247	-0.437124	C	0.85855	4.700155	-0.336052
C	2.797124	0.242055	0.458652	C	2.500197	-1.376647	0.841181
C	2.316684	-0.806373	-0.565405	C	1.688132	-2.143874	-0.222633
O	-2.361367	-2.961306	-0.012318	O	-3.475717	-1.593954	-0.24991
O	-3.885727	2.729704	0.26623	O	-1.72252	4.055753	0.058559
O	-3.159196	0.241934	0.970205	O	-2.559321	1.588851	0.73402
O	0.056365	-0.901812	0.355201	O	-0.410677	-1.105418	0.478147
O	-1.808776	-0.997379	2.466953	O	-2.294731	-0.130455	2.338095
O	0.197213	-3.878581	-0.956655	O	-1.652039	-3.75487	-0.871164
O	-2.598533	0.422151	-1.832784	O	-1.677749	1.347179	-1.964909
O	-1.731189	3.306312	-0.124106	O	0.428138	3.353061	-0.03967
H	3.318702	1.824919	-0.966494	H	4.508409	-2.082767	0.305719
H	-0.118425	-0.931759	-2.521148	H	-0.23889	-1.139015	-2.419504
H	-1.259894	-2.26769	-2.348388	H	-1.914866	-1.693484	-2.39699
H	-3.613517	-1.558776	1.736913	H	-4.005139	0.342039	1.360144
H	-1.30098	1.171277	1.187051	H	-0.53697	1.366021	1.207262
H	1.423158	-2.698692	-2.031308	H	0.11006	-3.429768	-1.792999
H	-0.760972	1.057149	-1.238609	H	0.138314	0.921427	-1.155011
H	6.712665	2.03389	-1.117693	H	6.612614	0.599157	0.383657
H	5.238977	2.98944	-1.382933	H	6.422534	-1.011318	-0.340696
H	6.238995	3.249785	0.061719	H	6.118112	0.453512	-1.298063
H	6.213929	1.425184	1.945619	H	4.005474	1.872875	-0.773953
H	5.240906	-0.038851	1.72864	H	2.860908	1.342196	0.468247
H	6.703569	0.219136	0.763762	H	4.444845	1.991699	0.923888
H	2.467663	-3.225029	0.840329	H	0.510899	-2.895537	2.221383
H	0.791059	-3.269182	1.403464	H	0.502065	-4.294463	1.130651
H	1.881074	-1.980208	1.960452	H	-1.020453	-3.490944	1.542736
H	-2.831861	4.649998	-1.287385	H	0.393667	5.0497	-1.260352
H	-1.2305	5.188925	-0.684188	H	1.939955	4.639796	-0.448136
H	-2.635451	5.107498	0.427874	H	0.593119	5.368752	0.485691
H	3.249835	-0.257599	1.319905	H	2.499505	-1.949068	1.779209
H	1.918078	0.783199	0.834937	H	2.000595	-0.427983	1.054691
H	3.166423	-1.429856	-0.871854	H	2.159496	-3.11664	-0.415946
H	1.975734	-0.285934	-1.470323	H	1.739669	-1.585376	-1.166091
H	-0.90577	-0.912987	2.099354	H	-1.448576	-0.556805	2.093679
H	-0.72581	-3.818336	-0.644267	H	-2.437991	-3.211342	-0.671862

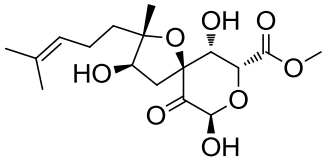
H	-3.433009	0.183031	-1.390779	H	-2.550608	1.608639	-1.620138
1e				**1f**			
C	-1.908126	-1.862627	0.035631	C	-1.89737	-1.890774	0.273313
C	4.111536	0.837947	0.401838	C	3.745052	1.48797	-0.330608
C	4.129039	2.143448	0.086682	C	4.999482	1.849434	-0.015294
C	-2.023994	2.448125	0.103796	C	-2.885276	2.210918	-0.24168
C	-0.062759	-1.849647	-1.772101	C	-0.238413	-1.912275	-1.706663
C	-2.620029	-1.083665	1.154929	C	-2.571584	-1.068096	1.384065
C	-1.705623	0.982609	0.375555	C	-2.124081	0.953444	0.181847
C	0.954856	-2.80167	-1.11864	C	0.937	-2.640045	-1.032476
C	-1.08282	0.346531	-0.877758	C	-1.521921	0.213437	-1.026892
C	-0.709115	-1.124581	-0.590434	C	-0.875565	-1.107207	-0.57337
C	1.417268	-2.012027	0.145776	C	1.397159	-1.630558	0.067551
C	5.41622	2.81826	-0.328661	C	5.755042	2.83991	-0.871099
C	2.928684	3.059646	0.109379	C	5.774769	1.340911	1.176406
C	1.699173	-2.898697	1.352334	C	1.82746	-2.299777	1.367586
C	-3.676843	4.092806	-0.216428	C	-3.642266	4.337176	0.450179
C	2.940796	-0.006877	0.832608	C	2.833329	0.524379	0.384059
C	2.601593	-1.089519	-0.212736	C	2.471115	-0.682702	-0.504472
O	-2.220685	-3.009007	-0.235203	O	-2.092006	-3.089922	0.172919
O	-1.136662	3.258066	-0.081194	O	-3.423699	2.349599	-1.329332
O	-2.885637	0.251154	0.716911	O	-3.097955	0.140884	0.849958
O	0.260934	-1.157023	0.488173	O	0.192761	-0.822179	0.361405
O	-1.872954	-1.146294	2.336475	O	-1.671273	-0.869268	2.43973
O	0.405464	-4.081993	-0.846311	O	0.577472	-3.924091	-0.544471
O	-1.985274	0.423512	-1.972136	O	-2.51121	-0.159347	-1.968387
O	-3.328029	2.717969	0.065619	O	-2.902575	3.122391	0.724182
H	5.056905	0.295323	0.332939	H	3.309272	1.93299	-1.228013
H	0.437661	-1.121513	-2.416766	H	0.117627	-1.225623	-2.48021
H	-0.78641	-2.393281	-2.382486	H	-0.93328	-2.612377	-2.173678
H	-3.601682	-1.518351	1.347021	H	-3.436168	-1.607514	1.7733
H	-0.985511	0.966883	1.200005	H	-1.326878	1.246007	0.873861
H	1.815162	-2.977664	-1.770885	H	1.758492	-2.808617	-1.734799
H	-0.179066	0.891414	-1.162927	H	-0.741514	0.848901	-1.473857
H	5.662498	3.649097	0.347687	H	6.051634	3.722054	-0.28611
H	6.261106	2.122121	-0.333559	H	6.685308	2.399488	-1.256931
H	5.326912	3.255079	-1.333339	H	5.160677	3.182155	-1.724432
H	2.789117	3.530624	-0.873519	H	6.712343	0.868804	0.851573
H	1.994744	2.558085	0.373079	H	6.061317	2.172804	1.834915
H	3.083229	3.881003	0.823272	H	5.223657	0.613273	1.776495
H	1.911934	-2.293811	2.238505	H	2.036883	-1.552815	2.138803
H	2.567612	-3.535666	1.154738	H	2.73602	-2.888885	1.204933
H	0.845293	-3.545765	1.563036	H	1.048919	-2.973513	1.731459

H	-3.260014	4.751526	0.548218	H	-3.549451	4.938445	1.352796
H	-4.765185	4.122547	-0.199068	H	-4.688307	4.099717	0.247232
H	-3.29761	4.382544	-1.198664	H	-3.205588	4.853694	-0.406776
H	3.188709	-0.490761	1.787775	H	3.281943	0.178675	1.31984
H	2.052095	0.603461	1.013735	H	1.902761	1.042204	0.65426
H	3.47977	-1.726339	-0.383289	H	3.374203	-1.275283	-0.699056
H	2.392768	-0.592692	-1.168873	H	2.128411	-0.313231	-1.480191
H	-0.923717	-1.145843	2.099427	H	-0.780392	-0.735909	2.056133
H	-0.543168	-3.966554	-0.64737	H	-0.362567	-3.893871	-0.28288
H	-2.879543	0.24709	-1.627981	H	-3.04104	0.647017	-2.131414
1g				**1h**			
C	-1.886924	-2.020869	0.563857	C	1.847187	-1.907053	-0.107249
C	4.483944	1.200268	-0.388252	C	-4.212516	0.889009	-0.343122
C	5.583172	1.458512	0.338677	C	-4.285267	2.189882	-0.017482
C	-3.543426	1.892779	0.160911	C	2.500762	2.277233	0.266243
C	-0.505995	-1.812752	-1.613163	C	0.013897	-1.948941	1.713094
C	-2.495156	-1.275663	1.765892	C	2.563147	-1.093098	-1.198092
C	-2.580934	0.755837	0.494203	C	1.869952	0.947955	-0.153815
C	0.94868	-1.307025	-1.634926	C	-1.03031	-2.806265	0.978473
C	-2.060199	0.083626	-0.789569	C	1.203461	0.227588	1.031923
C	-1.128248	-1.100491	-0.414627	C	0.699403	-1.159678	0.598096
C	1.268365	-1.016419	-0.148211	C	-1.449503	-1.902525	-0.226706
C	6.259794	2.807719	0.259101	C	-5.590211	2.79756	0.443197
C	6.252011	0.482268	1.276371	C	-3.131883	3.162676	-0.072216
C	1.684635	-2.268858	0.626191	C	-1.675404	-2.678074	-1.519491
C	-3.653637	4.033715	-0.833906	C	3.308987	4.357413	-0.502745
C	3.669818	-0.066214	-0.449713	C	-3.017892	0.101637	-0.815708
C	2.230659	0.16206	0.060883	C	-2.656048	-1.028059	0.170176
O	-2.010146	-3.220073	0.423163	O	2.114646	-3.081798	0.078617
O	-4.735683	1.888638	0.370568	O	2.824502	2.550906	1.411596
O	-3.306708	-0.206202	1.260147	O	2.953852	0.175474	-0.686415
O	-0.024193	-0.543889	0.3578	O	-0.293472	-1.002871	-0.443583
O	-1.515594	-0.856594	2.667811	O	1.753566	-1.011808	-2.339264
O	1.87427	-2.24315	-2.166781	O	-0.533481	-4.08571	0.61555
O	-3.146637	-0.360375	-1.588417	O	2.116873	-0.017584	2.085528
O	-2.867567	2.894967	-0.419432	O	2.666628	3.087853	-0.772859
H	4.105087	2.005387	-1.021755	H	-5.12864	0.301063	-0.252927
H	-1.049215	-1.596532	-2.536043	H	-0.470386	-1.249373	2.400284
H	-0.515851	-2.89523	-1.458068	H	0.708071	-2.56141	2.291065
H	-3.192883	-1.927866	2.292658	H	3.494938	-1.586366	-1.478204
H	-1.743609	1.166453	1.067917	H	1.124888	1.150983	-0.931691
H	1.006428	-0.360998	-2.190956	H	-1.905029	-2.995066	1.607359
H	-1.492319	0.801456	-1.387304	H	0.338703	0.822827	1.363702

H	6.295481	3.290123	1.246097	H	-5.490207	3.233245	1.447374
H	7.30287	2.707784	-0.073071	H	-5.899552	3.618411	-0.219303
H	5.745913	3.483393	-0.432171	H	-6.398655	2.0599	0.470819
H	7.284797	0.284632	0.956785	H	-3.355567	3.989333	-0.760976
H	6.318691	0.905908	2.287979	H	-2.966966	3.619678	0.913359
H	5.734274	-0.476996	1.348378	H	-2.192549	2.705701	-0.391958
H	2.632417	-2.662588	0.251217	H	-1.855847	-1.995927	-2.355288
H	0.935435	-3.061373	0.537288	H	-2.546115	-3.334202	-1.418273
H	1.803089	-2.023788	1.687111	H	-0.809717	-3.301053	-1.754112
H	-4.40338	3.727905	-1.566896	H	3.367354	4.859569	-1.466767
H	-2.943302	4.72928	-1.278425	H	4.305979	4.191266	-0.090208
H	-4.146104	4.48593	0.029645	H	2.70813	4.937055	0.200769
H	3.624587	-0.418071	-1.489244	H	-3.252378	-0.336736	-1.79604
H	4.143075	-0.868736	0.123682	H	-2.144195	0.742674	-0.961276
H	1.798796	1.036175	-0.443326	H	-3.520154	-1.693979	0.29644
H	2.260835	0.400356	1.131744	H	-2.463204	-0.582759	1.154852
H	-0.720867	-0.607238	2.152144	H	0.824172	-0.923094	-2.044198
H	1.73787	-2.27843	-3.12692	H	0.42205	-3.997045	0.43592
H	-3.82341	-0.724484	-0.989651	H	2.533404	0.846048	2.278477
1i				**1j**			
C	-1.874043	-1.893559	0.21428	C	1.807879	-1.964953	0.305026
C	3.723886	1.534834	-0.198283	C	-4.478687	1.058671	-0.858982
C	4.991281	1.876989	0.084776	C	-5.386185	1.55245	-0.001082
C	-2.624988	2.344198	0.085675	C	3.500267	1.94931	-0.138717
C	-0.254208	-1.738783	-1.792067	C	-0.210791	-1.065413	1.644234
C	-2.554354	-1.155154	1.377944	C	2.914963	-1.653143	-0.715285
C	-2.04856	0.968209	0.403128	C	2.656416	0.696856	-0.364053
C	0.931494	-2.535337	-1.219857	C	-1.337072	-1.80627	0.902315
C	-1.459449	0.350702	-0.87653	C	1.631912	0.514096	0.768001
C	-0.858789	-1.041003	-0.572938	C	0.837398	-0.797277	0.56496
C	1.423932	-1.640098	-0.038448	C	-1.282149	-1.204559	-0.536632
C	5.68636	2.970182	-0.69383	C	-6.065959	2.874017	-0.276027
C	5.839217	1.248426	1.164429	C	-5.824841	0.883505	1.279411
C	1.910701	-2.430758	1.169854	C	-1.516519	-2.226825	-1.642557
C	-4.549446	3.676812	-0.158055	C	3.381957	4.307729	-0.053199
C	2.862557	0.482571	0.450405	C	-3.694856	-0.22499	-0.765132
C	2.465485	-0.622736	-0.549152	C	-2.176913	0.044413	-0.67186
O	-2.067861	-3.080712	0.017767	O	1.676331	-3.082792	0.773435
O	-1.904848	3.269449	-0.232726	O	4.678069	1.960231	0.140009
O	-3.061286	0.09636	0.910046	O	3.545668	-0.420266	-0.36769
O	0.221826	-0.886811	0.382484	O	0.108194	-0.709051	-0.684902
O	-1.675136	-1.034971	2.459464	O	2.398235	-1.672344	-2.015644
O	0.573695	-3.858171	-0.84964	O	-1.195134	-3.218052	0.954726

O	-2.459983	0.247064	-1.879957	O	2.284715	0.502844	2.029799
O	-3.954445	2.399072	0.164246	O	2.731212	3.037803	-0.279604
H	3.232969	2.073377	-1.012043	H	-4.25477	1.654166	-1.746623
H	0.087271	-0.986245	-2.508598	H	-0.568534	-0.111347	2.042422
H	-0.96582	-2.38826	-2.30526	H	0.175764	-1.652359	2.479448
H	-3.432995	-1.70965	1.709785	H	3.704025	-2.403281	-0.650272
H	-1.257728	1.120123	1.14524	H	2.140641	0.794636	-1.325409
H	1.735183	-2.638948	-1.954393	H	-2.310431	-1.592053	1.351336
H	-0.670113	0.996453	-1.270397	H	0.927609	1.349914	0.774503
H	6.01311	3.782234	-0.028949	H	-5.880566	3.589846	0.537177
H	6.593464	2.589846	-1.184527	H	-5.721576	3.32478	-1.21228
H	5.037867	3.400834	-1.46354	H	-7.156632	2.751721	-0.336309
H	6.761021	0.8317	0.735388	H	-6.906396	0.689706	1.262804
H	6.155233	2.004483	1.896715	H	-5.318228	-0.064814	1.473207
H	5.331306	0.448079	1.707642	H	-5.643695	1.543529	2.139022
H	2.119895	-1.762958	2.010523	H	-1.454039	-1.744392	-2.624049
H	2.831642	-2.968686	0.921523	H	-2.504834	-2.6846	-1.544775
H	1.162987	-3.163924	1.478692	H	-0.774963	-3.027181	-1.592424
H	-5.621861	3.534014	-0.034371	H	3.768485	4.356591	0.967123
H	-4.312314	3.952807	-1.187727	H	2.609844	5.059897	-0.208037
H	-4.181181	4.446408	0.523464	H	4.200011	4.443416	-0.763857
H	3.364434	0.040589	1.316079	H	-4.023778	-0.827189	0.088179
H	1.943107	0.952425	0.826027	H	-3.894495	-0.826464	-1.662532
H	3.362042	-1.180401	-0.848873	H	-1.984547	0.711332	0.178199
H	2.077624	-0.151226	-1.462007	H	-1.850557	0.58585	-1.568518
H	-0.769567	-0.919971	2.106853	H	1.486913	-1.316895	-1.986833
H	-0.356314	-3.846504	-0.553009	H	-0.240596	-3.423084	0.957609
H	-3.283408	-0.039813	-1.445706	H	3.116112	0.005595	1.927328
1k							
C	-1.751096	-1.931321	0.043314	O	-4.606203	1.903792	0.172671
C	4.617843	1.043988	-0.603248	H	4.338038	1.454112	-1.575943
C	5.579457	1.685295	0.080449	H	0.23171	-0.417648	-2.382585
C	-3.28669	2.090999	0.176869	H	-0.567786	-1.991971	-2.424606
C	-0.035393	-1.290519	-1.779517	H	-3.427525	-2.179242	1.395811
C	-2.649127	-1.443079	1.19193	H	-1.794709	1.042988	1.253588
C	-2.486192	0.818355	0.434609	H	2.087363	-1.804505	-1.808529
C	1.218655	-1.930399	-1.156942	H	-1.022621	1.253937	-1.103912
C	-1.697856	0.439173	-0.829896	H	6.113913	3.781108	0.169196
C	-0.862149	-0.836541	-0.577635	H	7.326655	2.766042	-0.601005
C	1.429397	-1.115386	0.157501	H	5.837772	3.176272	-1.478287
C	6.242785	2.915223	-0.495378	H	7.175408	1.06773	1.393443
C	6.097782	1.278073	1.438834	H	5.974546	2.099028	2.158673
C	1.867893	-1.962249	1.346629	H	5.601229	0.395656	1.848999

C	-5.405355	3.079496	-0.091965	H	1.985706	-1.3329	2.235441
C	3.842063	-0.18538	-0.205677	H	2.823322	-2.45315	1.141386
C	2.333731	0.113845	-0.066501	H	1.133841	-2.742583	1.559441
O	-1.695532	-3.111652	-0.25681	H	-6.439064	2.7396	-0.051226
O	-2.730754	3.152358	-0.024723	H	-5.168754	3.480415	-1.079827
O	-3.349388	-0.267294	0.78006	H	-5.218828	3.840761	0.668381
O	0.090267	-0.564925	0.480385	H	3.988758	-0.95887	-0.974435
O	-1.895004	-1.267353	2.357492	H	4.222501	-0.606276	0.729017
O	1.085742	-3.331149	-0.96626	H	1.986833	0.646795	-0.961794
O	-2.584074	0.238373	-1.922089	H	2.180587	0.797327	0.777118



ent-**1**

Table S5. Important thermodynamic parameters (a.u.) and Boltzmann distributions of the optimized *ent*-**1** (2*S*,3*R*,5*R*,7*R*,9*R*,10*S*) at B3LYP/6-311++G**level in the MeOH.

Conformations	E+ZPE	G	Ratio
***ent*-1 a** (BAL000)	-1264.795089	-1264.852916	6.92%
***ent*-1 b** BAL017	-1264.795931	-1264.853266	5.51%
***ent*-1 c** BAL027	-1264.794078	-1264.851821	8.07%
***ent*-1 d** BAL054	-1264.794170	-1264.852044	2.64%
***ent*-1 e** OME032	-1264.793097	-1264.851992	10.27%
***ent*-1 f** BAL067	-1264.795828	-1264.854552	18.74%
***ent*-1 g** BAL074	-1264.793064	-1264.851726	9.19%
***ent*-1 h** OME001	-1264.793577	-1264.852116	8.57%
***ent*-1 i** BAL095	-1264.793557	-1264.851615	4.95%
***ent*-1 j** OME031	-1264.796311	-1264.855021	25.13%

E+ZPE, G: total energy (E) in the DMSO at LC-wPBE/6-311++G**//B3LYP/6-311++G** level with IEFPCM solvent continuum model, zero point energy (ZPE) and Gibbs free energy (G) in the MeOH at B3LYP/6-311++G** level with IEFPCM solvent continuum model. %: Boltzmann distributions, using the relative Gibbs free energies as weighting factors

Table S6. Optimized coordinate of *ent*-**1**(2*S*,3*R*,5*R*,7*R*,9*R*,10*S*) at B3LYP/6-311++G** level in the MeOH.

***ent*-1 a**				***ent*-1 b**			
C	-1.807892	-1.964944	0.305142	C	2.665486	-0.728421	0.03249
C	4.478516	1.058616	-0.859122	C	-3.927191	-1.163738	0.407456
C	5.385801	1.55253	-0.001072	C	-4.551164	-0.008954	0.122719
C	-3.500036	1.949443	-0.138793	C	0.891131	3.178644	0.124785
C	0.210898	-1.065482	1.644217	C	1.023739	-1.555413	-1.78186
C	-2.915107	-1.653087	-0.715011	C	2.934357	0.27924	1.162652

C	-2.656313	0.696885	-0.364012	C	1.178729	1.703112	0.386564
C	1.337126	-1.806381	0.902244	C	0.568744	-2.876726	-1.137262
C	-1.631723	0.514127	0.767965	C	0.915339	0.857661	-0.870903
C	-0.837342	-0.797325	0.564979	C	1.261457	-0.622825	-0.593223
C	1.282115	-1.204739	-0.5367	C	-0.208223	-2.402911	0.130931
C	6.065565	2.874102	-0.275991	C	-6.001033	-0.001661	-0.30441
C	5.82427	0.883688	1.279537	C	-3.918296	1.360425	0.19421
C	1.516623	-2.22703	-1.64258	C	-0.037769	-3.323577	1.332894
C	-3.381411	4.307852	-0.053274	C	-0.858643	4.700132	-0.336024
C	3.694726	-0.225061	-0.765265	C	-2.500168	-1.37668	0.841202
C	2.176765	0.044293	-0.671989	C	-1.688099	-2.143896	-0.222616
O	-1.676322	-3.082834	0.773455	O	3.475744	-1.593893	-0.249939
O	-4.677874	1.960549	0.139741	O	1.722442	4.055781	0.058567
O	-3.545678	-0.420151	-0.367475	O	2.559299	1.58889	0.734005
O	-0.108259	-0.709357	-0.684961	O	0.410703	-1.10542	0.478157
O	-2.398562	-1.672395	-2.01547	O	2.294747	-0.130416	2.338083
O	1.195176	-3.218171	0.95472	O	1.652089	-3.754847	-0.87116
O	-2.284406	0.503054	2.029826	O	1.677701	1.347202	-1.964916
O	-2.73079	3.037838	-0.279525	O	-0.428201	3.353044	-0.039655
H	4.254762	1.654005	-1.746875	H	-4.508383	-2.082819	0.305779
H	-0.175662	-1.652484	2.479395	H	1.91487	-1.693456	-2.396996
H	0.568649	-0.111449	2.042468	H	0.238886	-1.139017	-2.419496
H	-3.704205	-2.403176	-0.649831	H	4.005143	0.342102	1.360117
H	-2.140601	0.794526	-1.325423	H	0.536959	1.366024	1.20727
H	2.310534	-1.592163	1.351169	H	-0.11002	-3.429775	-1.792989
H	-0.927345	1.349889	0.774319	H	-0.138345	0.921419	-1.154996
H	7.156276	2.751908	-0.335757	H	-6.118102	0.453429	-1.298064
H	5.721549	3.324631	-1.212492	H	-6.422505	-1.011397	-0.340686
H	5.87973	3.590079	0.536982	H	-6.612597	0.599081	0.383658
H	5.643697	1.544067	2.138992	H	-4.444846	1.991679	0.923785
H	5.317104	-0.064261	1.473701	H	-2.860896	1.342153	0.468227
H	6.905704	0.689206	1.262789	H	-4.00542	1.872771	-0.774036
H	2.504936	-2.68478	-1.544652	H	-0.502013	-4.294471	1.130664
H	1.454229	-1.744644	-2.6241	H	-0.51084	-2.895545	2.221396
H	0.775079	-3.027405	-1.592505	H	1.020507	-3.490947	1.542734
H	-3.767889	4.356904	0.96706	H	-1.940047	4.639752	-0.448102
H	-4.199482	4.443518	-0.763915	H	-0.393772	5.049694	-1.260324
H	-2.609224	5.059916	-0.208248	H	-0.593221	5.368728	0.485722
H	3.894343	-0.826524	-1.662676	H	-2.000576	-0.428011	1.054712
H	4.023677	-0.827268	0.088032	H	-2.499465	-1.949103	1.779229
H	1.850377	0.585644	-1.568686	H	-1.739647	-1.585398	-1.166074
H	1.984358	0.711242	0.178042	H	-2.159453	-3.116667	-0.415928
H	-1.487148	-1.317193	-1.986779	H	1.448607	-0.556799	2.093671

H	0.240632	-3.423212	0.957371	H	2.438036	-3.211305	-0.671875
H	-3.115838	0.005837	1.927491	H	2.550563	1.608666	-1.620156
***ent*-1 c**				***ent*-1 d**			
C	1.857665	-1.955135	0.011377	C	1.750751	-1.931181	0.043206
C	-4.559963	0.94485	-0.580016	C	-4.618213	1.043606	-0.603062
C	-5.523879	1.555758	0.127877	C	-5.5799	1.68509	0.080358
C	3.529949	1.959611	0.275112	C	3.287325	2.090702	0.177198
C	0.156205	-1.25857	-1.804269	C	0.035283	-1.289776	-1.779656
C	2.710977	-1.513571	1.211167	C	2.648921	-1.443248	1.191853
C	2.606586	0.761809	0.496247	C	2.486502	0.818241	0.434835
C	-1.094986	-1.937573	-1.218906	C	-1.218801	-1.929733	-1.157203
C	1.816116	0.430148	-0.778112	C	1.698082	0.4394	-0.829719
C	0.967645	-0.844871	-0.576483	C	0.862106	-0.836181	-0.577705
C	-1.328687	-1.170072	0.121236	C	-1.429385	-1.115084	0.157553
C	-6.209184	2.790211	-0.411483	C	-6.243425	2.914665	-0.495994
C	-6.023082	1.108547	1.480799	C	-6.098118	1.278391	1.438928
C	-1.751044	-2.067373	1.278924	C	-1.867601	-1.962351	1.346506
C	3.534371	4.255923	-0.283139	C	5.406253	3.078396	-0.092487
C	-3.761164	-0.280983	-0.218143	C	-3.842214	-0.185422	-0.204924
C	-2.259782	0.04493	-0.065639	C	-2.333907	0.114068	-0.065974
O	1.828232	-3.11916	-0.350814	O	1.694892	-3.111526	-0.256884
O	4.735029	1.948921	0.378919	O	2.731732	3.152369	-0.023666
O	3.426512	-0.331563	0.892254	O	3.349456	-0.267634	0.780209
O	-0.005031	-0.597743	0.466646	O	-0.090299	-0.564485	0.480343
O	1.901854	-1.397163	2.352841	O	1.894837	-1.267418	2.35751
O	-0.944682	-3.341476	-1.077171	O	-1.086092	-3.330542	-0.967042
O	2.769746	0.211036	-1.810967	O	2.5842	0.238674	-1.922009
O	2.796799	3.038804	-0.039891	O	4.606778	1.902956	0.17214
H	-4.294807	1.382678	-1.544708	H	-4.33851	1.453293	-1.575977
H	0.698942	-1.927495	-2.475224	H	0.567607	-1.991145	-2.424904
H	-0.12763	-0.364069	-2.368727	H	-0.231744	-0.416735	-2.382502
H	3.474166	-2.265224	1.417347	H	3.427074	-2.17971	1.39561
H	1.897633	1.02661	1.290969	H	1.795066	1.04294	1.253834
H	-1.958348	-1.799295	-1.874978	H	-2.087554	-1.803473	-1.808661
H	1.144499	1.266029	-1.006724	H	1.022982	1.254339	-1.103561
H	-5.81724	3.080799	-1.391405	H	-6.114331	3.780943	0.168025
H	-7.291956	2.629116	-0.51056	H	-5.838733	3.175124	-1.479191
H	-6.085351	3.641259	0.27295	H	-7.327327	2.765414	-0.601167
H	-7.098424	0.885848	1.441027	H	-7.175652	1.067552	1.393576
H	-5.511142	0.222655	1.863531	H	-5.601202	0.396415	1.849609
H	-5.902519	1.912868	2.21962	H	-5.975305	2.099799	2.158324
H	-2.693576	-2.574015	1.053388	H	-2.823149	-2.453054	1.141354
H	-1.88706	-1.471363	2.187889	H	-1.985074	-1.333295	2.235571

H	-0.998618	-2.836275	1.46878	H	-1.133587	-2.742858	1.558843
H	2.782962	5.006945	-0.522963	H	6.439857	2.738116	-0.052229
H	4.223277	4.12001	-1.11975	H	5.220314	3.839564	0.668104
H	4.093495	4.543203	0.6101	H	5.169456	3.479669	-1.080165
H	-4.134889	-0.737576	0.70239	H	-4.222498	-0.60588	0.730044
H	-3.890829	-1.033203	-1.010648	H	-3.988862	-0.95937	-0.973236
H	-2.123095	0.704065	0.799913	H	-2.180731	0.797382	0.777778
H	-1.922292	0.614429	-0.942055	H	-1.987247	0.647304	-0.961196
H	1.039797	-1.025726	2.075534	H	1.009115	-0.938923	2.101634
H	-0.009441	-3.522548	-0.862698	H	-0.151743	-3.515738	-0.752922
H	2.318328	0.285197	-2.666838	H	3.365799	-0.234321	-1.583675
***ent*-1 e**				***ent*-1 f**			
C	1.945586	-1.819885	0.795383	C	1.754785	-1.959723	0.108796
C	-4.065712	0.958879	-0.453743	C	-4.62178	0.995091	-0.637332
C	-4.398774	2.141713	0.088048	C	-5.532324	1.746776	0.002347
C	2.594561	2.129989	-0.576713	C	3.483789	1.910998	-0.21945
C	0.482421	-2.490626	-1.232245	C	-0.032643	-1.494639	-1.697332
C	2.347296	-0.697	1.76901	C	2.665217	-1.37723	1.202974
C	1.894261	0.926298	0.056622	C	2.528114	0.787853	0.18767
C	-1.053518	-2.381334	-1.22688	C	-1.262051	-2.053729	-0.962036
C	1.527151	-0.141573	-0.991761	C	1.693928	0.282743	-1.003203
C	0.933502	-1.378742	-0.283281	C	0.843122	-0.92723	-0.58043
C	-1.378681	-1.838089	0.183311	C	-1.421619	-1.092748	0.257457
C	-5.831585	2.622442	0.068404	C	-6.207861	2.901767	-0.700504
C	-3.432207	3.095147	0.748655	C	-5.9771	1.542637	1.430609
C	-1.393421	-2.947831	1.241332	C	-1.819542	-1.796352	1.549734
C	3.185162	4.395998	-0.274789	C	4.806715	3.699447	0.570857
C	-2.709187	0.306564	-0.52946	C	-3.841787	-0.184767	-0.116501
C	-2.675046	-1.015	0.263961	C	-2.326955	0.111092	-0.072069
O	2.387447	-2.945018	0.901249	O	1.701028	-3.161331	-0.090442
O	3.176216	2.100193	-1.650239	O	3.868401	2.10308	-1.362525
O	2.83013	0.416704	1.015229	O	3.373098	-0.248654	0.704471
O	-0.254858	-0.938237	0.437163	O	-0.068915	-0.522237	0.467783
O	1.298878	-0.372719	2.636097	O	1.910805	-1.102923	2.35221
O	-1.734623	-3.608317	-1.438399	O	-1.11968	-3.423951	-0.615385
O	2.664471	-0.602105	-1.697837	O	2.508362	-0.181558	-2.064128
O	2.505407	3.207421	0.195962	O	3.854822	2.638769	0.82799
H	-4.871543	0.368322	-0.895321	H	-4.391102	1.261951	-1.670903
H	0.787521	-3.466166	-0.844374	H	0.471151	-2.262992	-2.286407
H	0.916278	-2.367981	-2.226708	H	-0.317576	-0.684417	-2.37508
H	3.199544	-1.017152	2.370144	H	3.435631	-2.101981	1.469611
H	0.986844	1.280741	0.558162	H	1.862506	1.167414	0.971418
H	-1.369834	-1.645181	-1.976084	H	-2.155285	-2.00011	-1.590328

H	0.76446	0.275672	-1.66754	H	1.015444	1.088278	-1.323696
H	-6.204428	2.793577	1.088167	H	-6.020588	3.848291	-0.174023
H	-5.918595	3.583944	-0.457131	H	-5.861946	3.011934	-1.733239
H	-6.497854	1.905298	-0.421763	H	-7.29885	2.769226	-0.717912
H	-3.431816	4.064968	0.231718	H	-5.466686	0.717417	1.932381
H	-3.73933	3.298615	1.783868	H	-5.804617	2.45366	2.020159
H	-2.404243	2.726229	0.770212	H	-7.057655	1.347581	1.474793
H	-1.460409	-2.500974	2.238708	H	-2.785012	-2.297649	1.437107
H	-0.491598	-3.565799	1.200776	H	-1.899431	-1.070988	2.366786
H	-2.256933	-3.602184	1.094831	H	-1.081645	-2.555102	1.819683
H	3.015259	5.146892	0.494854	H	4.990669	4.160035	1.539852
H	2.760793	4.715965	-1.228519	H	4.380409	4.422323	-0.127441
H	4.251769	4.194823	-0.392185	H	5.7275	3.283024	0.157779
H	-2.476711	0.10878	-1.58578	H	-4.189132	-0.480381	0.877354
H	-1.922349	0.968318	-0.159023	H	-4.023801	-1.046485	-0.775948
H	-3.484822	-1.674004	-0.076648	H	-2.135561	0.885556	0.680151
H	-2.882028	-0.793567	1.31849	H	-2.012349	0.532815	-1.035921
H	0.463086	-0.435594	2.128783	H	1.038622	-0.762174	2.066192
H	-1.654605	-3.830296	-2.379348	H	-0.173737	-3.592518	-0.442043
H	3.10615	0.201669	-2.037211	H	3.137622	0.543818	-2.249631
***ent*-1 g**				***ent*-1 h**			
C	1.887079	-2.021012	0.563639	C	2.162745	-1.726612	0.203816
C	-4.483621	1.200771	-0.387494	C	-3.780895	1.102577	-0.131432
C	-5.583447	1.458321	0.338755	C	-5.074691	1.289702	0.176621
C	3.543415	1.892812	0.161088	C	2.522743	2.566527	0.144958
C	0.505957	-1.812603	-1.613245	C	0.538246	-1.714437	-1.79905
C	2.495478	-1.275953	1.765675	C	3.035341	-0.921663	1.188925
C	2.581031	0.755735	0.494248	C	2.113023	1.118296	0.388629
C	-0.948657	-1.306683	-1.634874	C	-0.577754	-2.62248	-1.250301
C	2.060122	0.083753	-0.789574	C	1.490241	0.487338	-0.865475
C	1.128353	-1.100515	-0.41469	C	1.059506	-0.966704	-0.56591
C	-1.268274	-1.016302	-0.148095	C	-1.138945	-1.799631	-0.047282
C	-6.260037	2.807594	0.259904	C	-5.908265	2.29948	-0.578506
C	-6.253027	0.481192	1.274998	C	-5.822079	0.554819	1.263456
C	-1.684706	-2.268816	0.626098	C	-1.52379	-2.659691	1.152082
C	3.653414	4.033691	-0.833879	C	1.65623	4.715326	-0.320712
C	-3.669532	-0.065692	-0.449589	C	-2.790634	0.150805	0.487931
C	-2.230418	0.162256	0.061229	C	-2.296397	-0.897609	-0.529214
O	2.010209	-3.220216	0.422811	O	2.328749	-2.93163	0.117337
O	4.735598	1.889013	0.371154	O	3.660147	2.980594	0.117762
O	3.306959	-0.206499	1.259839	O	3.302184	0.38372	0.698489
O	0.024351	-0.544026	0.357986	O	-0.028961	-0.931578	0.374668
O	1.516092	-0.856989	2.667833	O	2.36223	-0.919583	2.41614

O	-1.87443	-2.242535	-2.166849	O	-0.11736	-3.923355	-0.920816
O	3.146482	-0.359854	-1.588735	O	2.414718	0.538109	-1.943581
O	2.867495	2.894824	-0.419511	O	1.427291	3.315499	-0.048049
H	-4.104214	2.006506	-1.019894	H	-3.372412	1.70249	-0.947982
H	0.515678	-2.895089	-1.458225	H	1.309043	-2.290336	-2.314858
H	1.04915	-1.59635	-2.536136	H	0.13437	-0.988165	-2.510367
H	3.193288	-1.928206	2.292272	H	4.01603	-1.402906	1.253337
H	1.743837	1.16618	1.068288	H	1.404424	1.079764	1.222274
H	-1.006276	-0.360527	-2.19072	H	-1.367888	-2.771515	-1.991825
H	1.49206	0.80161	-1.387094	H	0.603109	1.046939	-1.172097
H	-6.297474	3.288608	1.247505	H	-6.77259	1.818922	-1.058517
H	-5.745052	3.484262	-0.429566	H	-6.317267	3.061772	0.099777
H	-7.302532	2.707995	-0.074204	H	-5.328779	2.810278	-1.354255
H	-5.735144	-0.477999	1.346808	H	-6.217954	1.261257	2.006434
H	-6.320874	0.904067	2.286853	H	-6.691751	0.029487	0.844781
H	-7.28545	0.283567	0.954228	H	-5.209582	-0.179143	1.792077
H	-0.935585	-3.061392	0.537121	H	-1.797846	-2.031934	2.004699
H	-2.6325	-2.662418	0.251009	H	-0.692493	-3.303426	1.446584
H	-1.803213	-2.023883	1.687039	H	-2.377808	-3.29871	0.903644
H	2.943248	4.728474	-1.279894	H	0.666484	5.14993	-0.45301
H	4.404335	3.727761	-1.565607	H	2.252217	4.830878	-1.228603
H	4.144443	4.486931	0.029964	H	2.172718	5.183443	0.520146
H	-4.142842	-0.868511	0.123338	H	-1.919878	0.71762	0.844899
H	-3.624207	-0.417012	-1.489308	H	-3.217966	-0.349521	1.361804
H	-2.260687	0.400265	1.132156	H	-1.978777	-0.37854	-1.443799
H	-1.798358	1.03644	-0.442693	H	-3.134195	-1.545124	-0.818977
H	0.721207	-0.607687	2.152364	H	2.98815	-0.6203	3.098158
H	-1.736494	-2.279372	-3.126717	H	0.77562	-3.824673	-0.535063
H	3.822834	-0.725278	-0.990284	H	3.295288	0.341032	-1.576056
***ent*-1 i**				***ent*-1 j**			
C	-1.679462	-1.89912	0.330398	C	1.95379	-1.821491	0.131041
C	4.593777	1.158726	-0.878708	C	-4.236245	0.679919	0.295139
C	5.495251	1.685743	-0.034392	C	-4.369554	1.982647	-0.002626
C	-3.392932	1.989167	-0.195006	C	2.397167	2.38893	-0.241844
C	0.321112	-0.938828	1.655126	C	0.147708	-1.956179	-1.712787
C	-2.760202	-1.644053	-0.733231	C	2.615936	-0.970778	1.228416
C	-2.578448	0.714239	-0.40146	C	1.830221	1.031168	0.175288
C	1.459345	-1.68755	0.939648	C	-0.864064	-2.860497	-0.98933
C	-1.5595	0.572485	0.737664	C	1.230409	0.272791	-1.023897
C	-0.72398	-0.713611	0.561615	C	0.779855	-1.132987	-0.590655
C	1.410042	-1.115718	-0.51206	C	-1.341865	-1.974899	0.207547
C	6.164101	3.004566	-0.346752	C	-5.693724	2.531724	-0.481995
C	5.936679	1.058795	1.266195	C	-3.271371	3.013297	0.104337

C	1.655294	-2.161101	-1.59405	C	-1.545546	-2.758466	1.49932
C	-5.51503	2.968524	0.062236	C	2.784274	4.617887	0.43305
C	3.819853	-0.12789	-0.748386	C	-3.014813	-0.055803	0.782187
C	2.299987	0.133855	-0.669444	C	-2.583386	-1.158978	-0.205091
O	-1.547531	-2.99494	0.848514	O	2.278486	-2.983312	-0.044588
O	-2.85194	3.074549	-0.109622	O	2.935283	2.598261	-1.318459
O	-3.432815	-0.423375	-0.467351	O	2.946126	0.318132	0.724375
O	0.019723	-0.628129	-0.677872	O	-0.233376	-1.020033	0.436258
O	-2.188744	-1.708813	-2.014167	O	1.789838	-0.935099	2.360424
O	1.325833	-3.098103	1.022073	O	-0.309926	-4.113129	-0.615653
O	-2.302645	0.491457	1.948938	O	2.185166	0.057227	-2.04667
O	-4.707751	1.785394	-0.129285	O	2.245001	3.302137	0.710188
H	4.366299	1.725591	-1.784003	H	-5.118223	0.047898	0.169215
H	-0.06038	-1.507258	2.5057	H	0.877892	-2.53607	-2.27991
H	0.67568	0.029826	2.02257	H	-0.360131	-1.281334	-2.407906
H	-3.528773	-2.415567	-0.670297	H	3.568721	-1.415419	1.518939
H	-2.033495	0.844569	-1.345415	H	1.06127	1.192803	0.937826
H	2.427231	-1.455916	1.391793	H	-1.719842	-3.094105	-1.629172
H	-0.890973	1.440875	0.720921	H	0.350229	0.826047	-1.387061
H	5.97145	3.74196	0.445229	H	-6.060334	3.321152	0.189358
H	7.255872	2.889969	-0.402155	H	-5.594112	2.993235	-1.474613
H	5.817525	3.42564	-1.295981	H	-6.461524	1.753782	-0.543391
H	5.745584	1.74134	2.105847	H	-3.108613	3.50444	-0.865039
H	5.439387	0.111101	1.48535	H	-3.554997	3.808225	0.80816
H	7.020257	0.876174	1.258496	H	-2.316523	2.598369	0.435299
H	2.641838	-2.61799	-1.476271	H	-1.763792	-2.084214	2.332419
H	1.603919	-1.698948	-2.58588	H	-0.655193	-3.342064	1.742795
H	0.911775	-2.959183	-1.535743	H	-2.385195	-3.45284	1.390928
H	-5.364119	3.667323	-0.763382	H	2.562647	5.210227	1.318959
H	-5.25493	3.453651	1.005565	H	2.29918	5.041077	-0.448649
H	-6.544571	2.614094	0.083128	H	3.861586	4.552466	0.268949
H	4.027651	-0.75487	-1.626312	H	-2.174279	0.623328	0.948997
H	4.149767	-0.701398	0.124208	H	-3.246226	-0.513108	1.754569
H	1.97565	0.652951	-1.579945	H	-2.395985	-0.698188	-1.183673
H	2.098438	0.818991	0.163832	H	-3.411773	-1.865373	-0.349654
H	-1.298269	-1.305231	-1.968916	H	0.860698	-0.890295	2.05473
H	0.372651	-3.309799	1.029426	H	0.637209	-3.976592	-0.421557
H	-1.713832	0.718426	2.686051	H	2.641775	0.913367	-2.176127

Table S7. Deviations between the calculated and experimental ^{13}C NMR chemical shifts of **1** at B3LYP/6-311++G(d,p) level in DMSO

No.	Experimental	Calculated	Calibration	Δδ
2	85.2	86.5	84.7374	-1.7516
3	74.4	76.0	73.9482	-2.0588
4	34.7	37.6	34.2879	-3.3059
5	82.7	82.9	82.2399	-0.6827
6	195.7	197.9	195.1269	-2.7861
7	99.2	97.1	98.7234	1.6204
9	66.6	66.7	66.156	-0.4989
10	75.0	76.9	74.5476	-2.3491
11	40.1	41.4	39.6825	-1.7054
12	22.2	22.5	21.8004	-0.6989
13	124.7	121.5	124.1979	2.6819
14	130.7	132.8	130.1919	-2.6541
15	25.6	25.3	25.197	-0.1506
16	17.6	18.8	17.205	-1.5597
17	20.3	19.2	19.9023	0.6705
18	175.0	175.0	174.4476	-0.5414
19	56.1	55.4	55.6665	0.2284

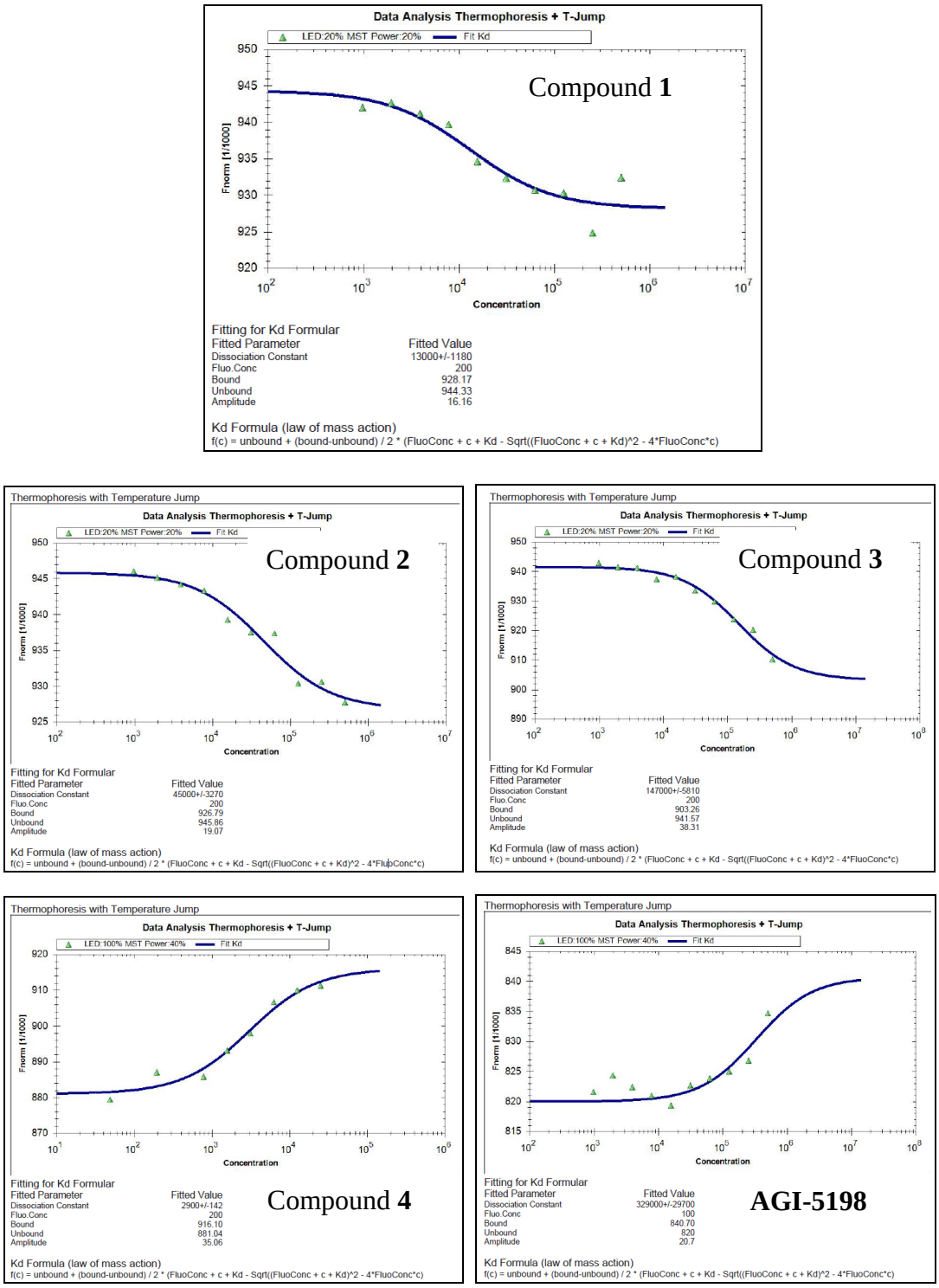


Figure S1. Measurement of affinity between compounds **1–4** and AGI-5198 with $IDH1^{R132H}$ by MST in standard treated capillaries, the resulting binding curves of the tested compounds were shown. From the resulting binding curve, K_d of 13.0 ± 1.18 μM for **1**, 45.0 ± 3.27 μM for **2**, 147.0 ± 5.81 μM for **3**, 329.0 ± 2.97 μM for **4**, and 2.90 ± 0.14 μM for AGI-5198 (as a reference), were calculated

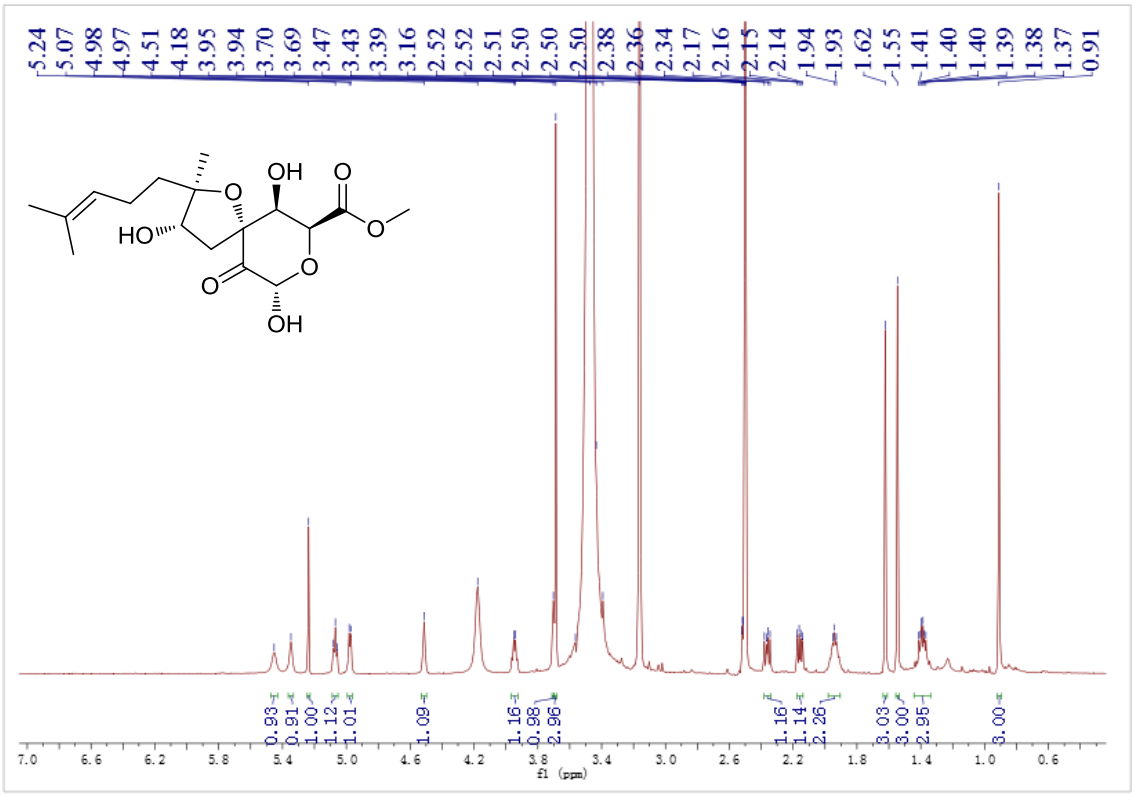


Figure S2. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **1**

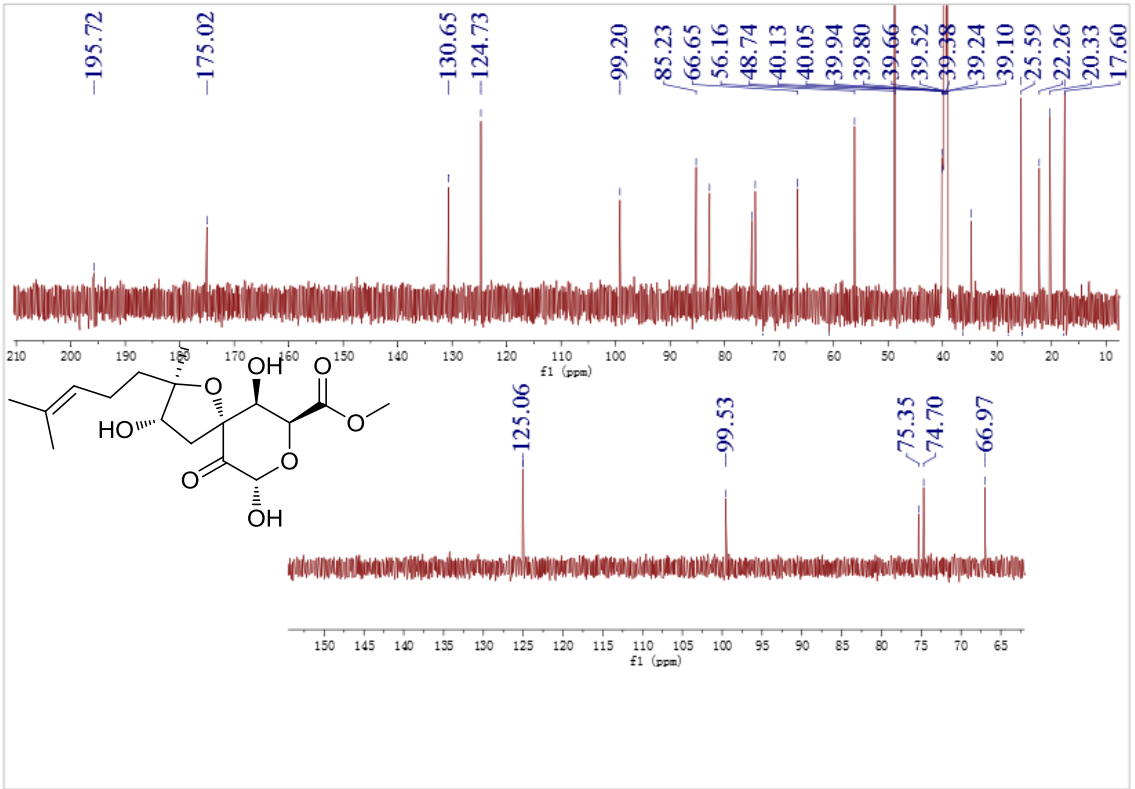


Figure S3. ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **1**

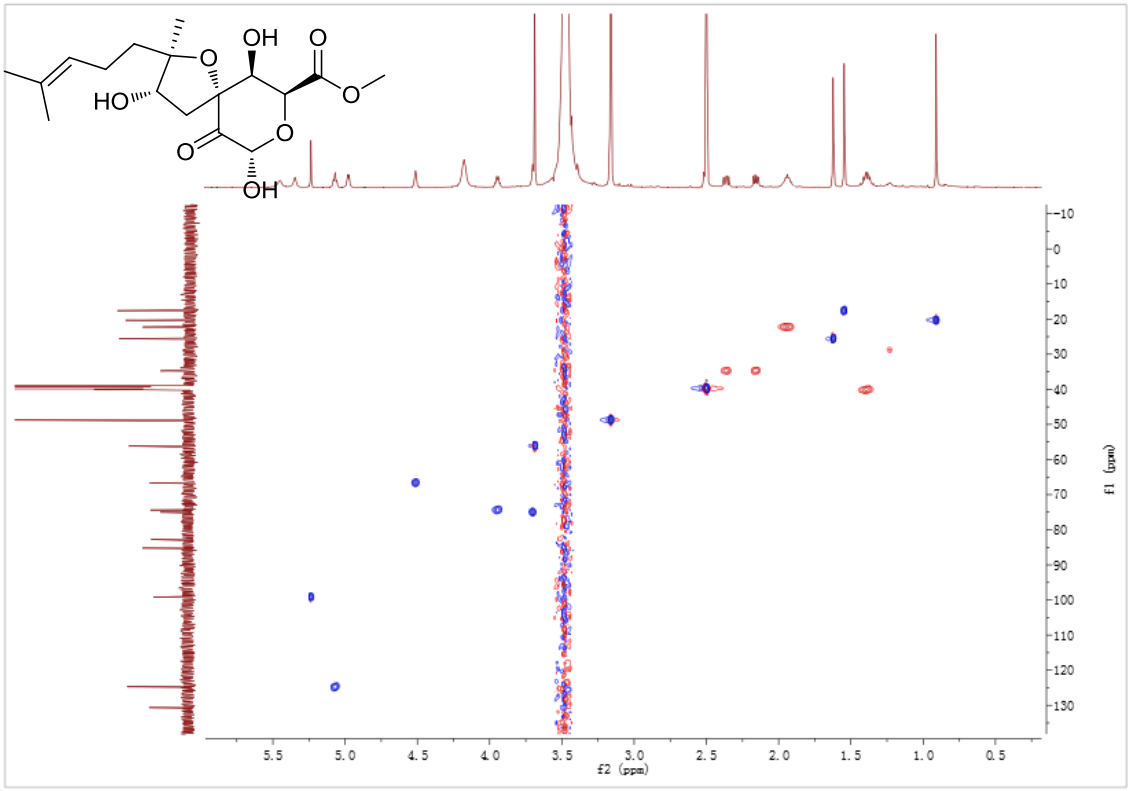


Figure S4. HMQC spectrum of compound **1** (in DMSO-d_6)

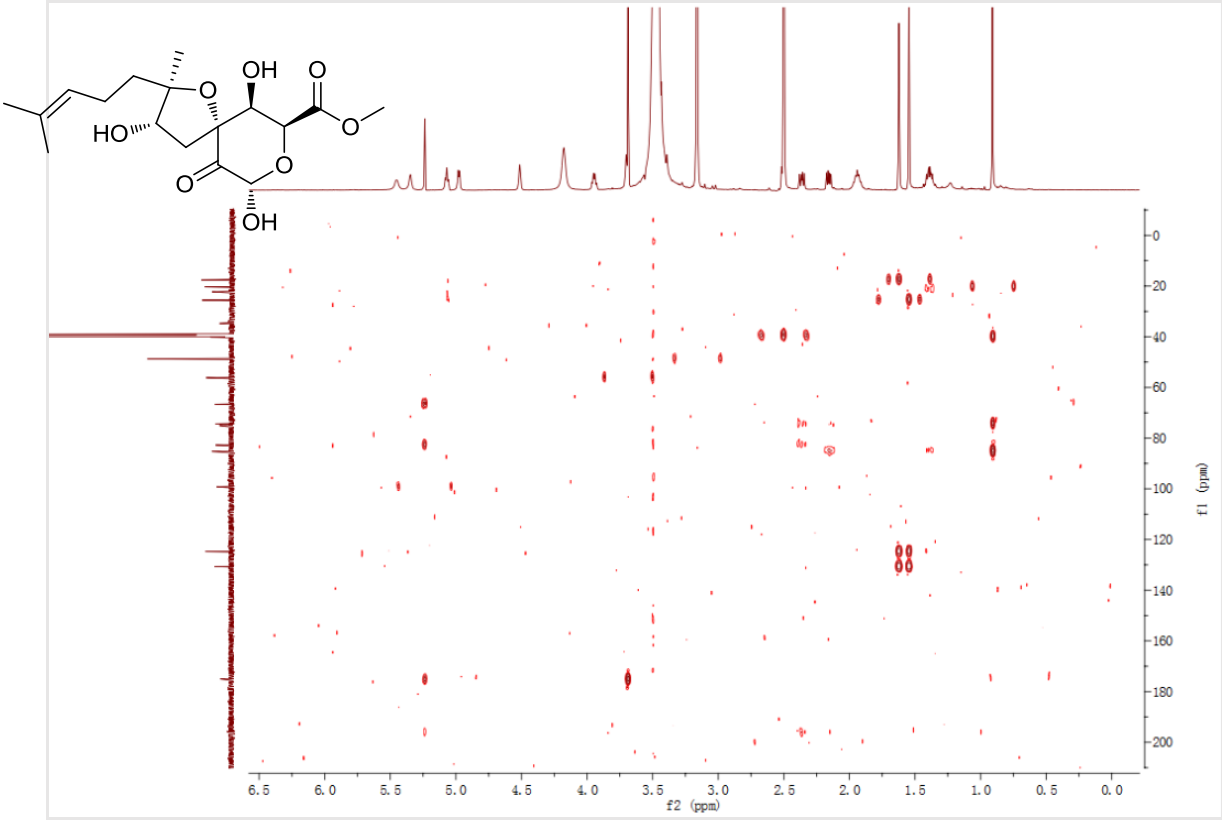


Figure S5. HMBC spectrum of compound **1** (in DMSO-d_6)

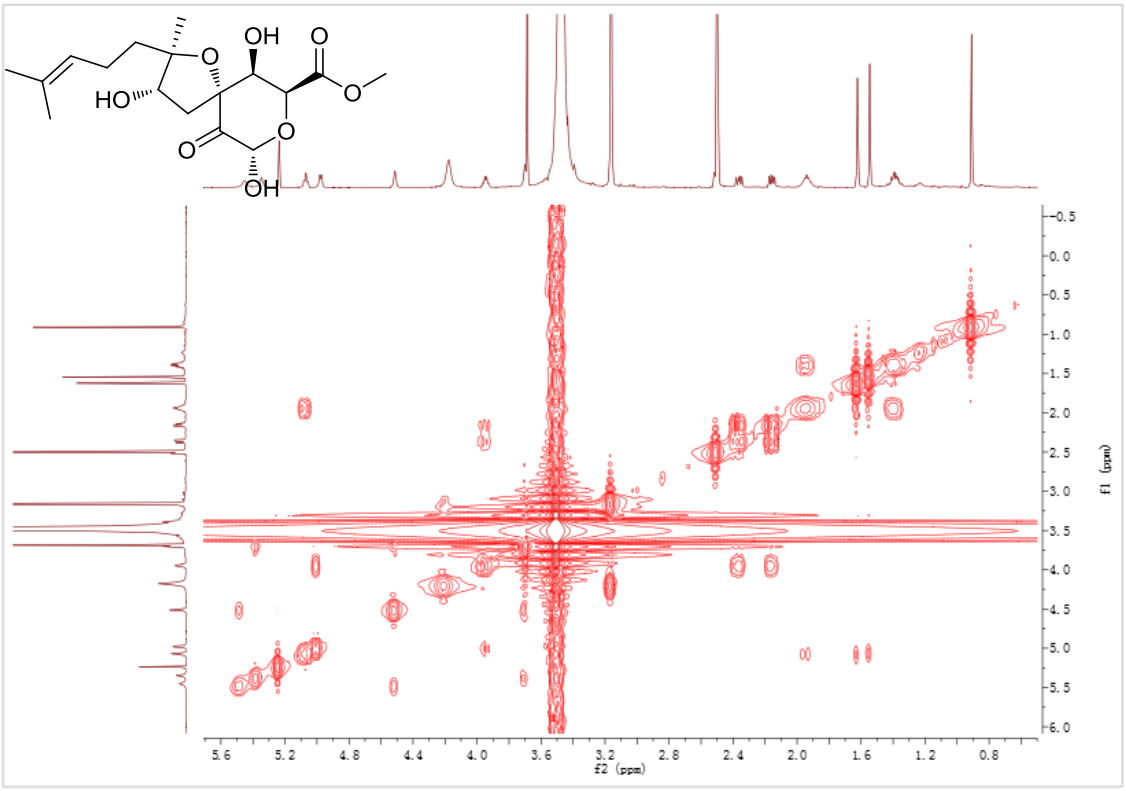


Figure S6. ^{1}H-^{1}H COSY spectrum of compound **1** (in DMSO-d_6)

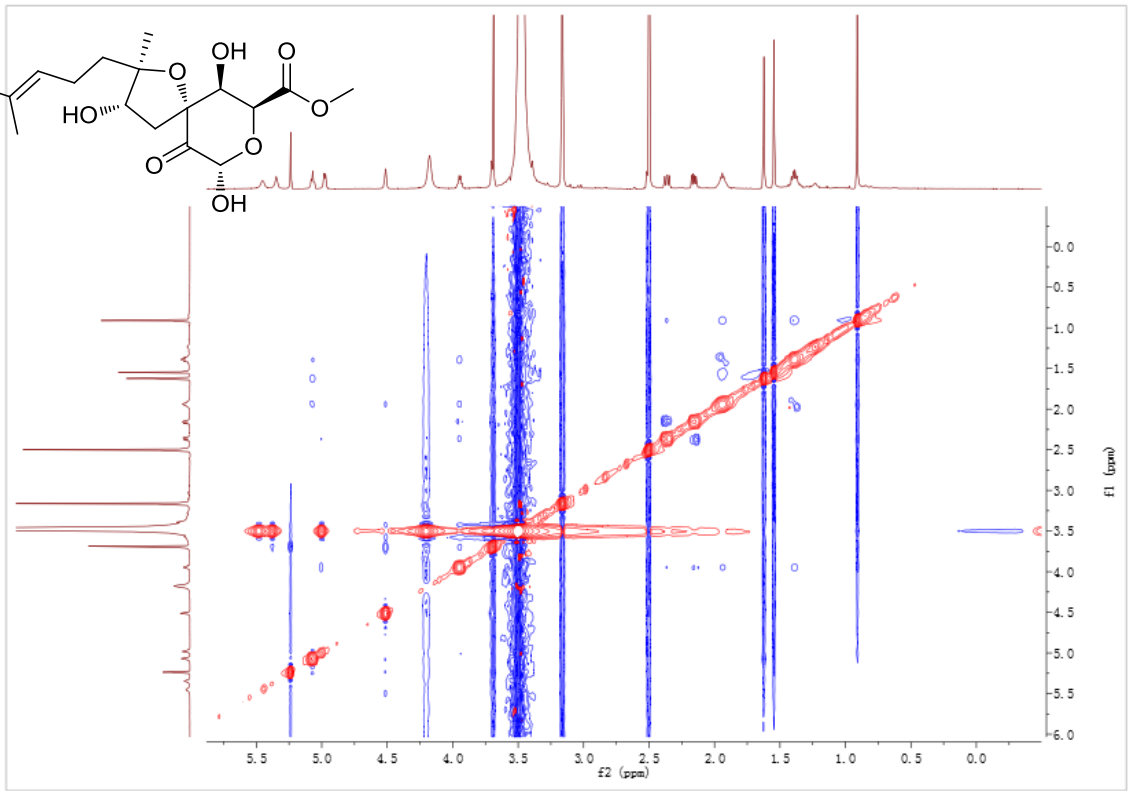


Figure S7. NOESY spectrum of compound **1**(in DMSO-d_6)

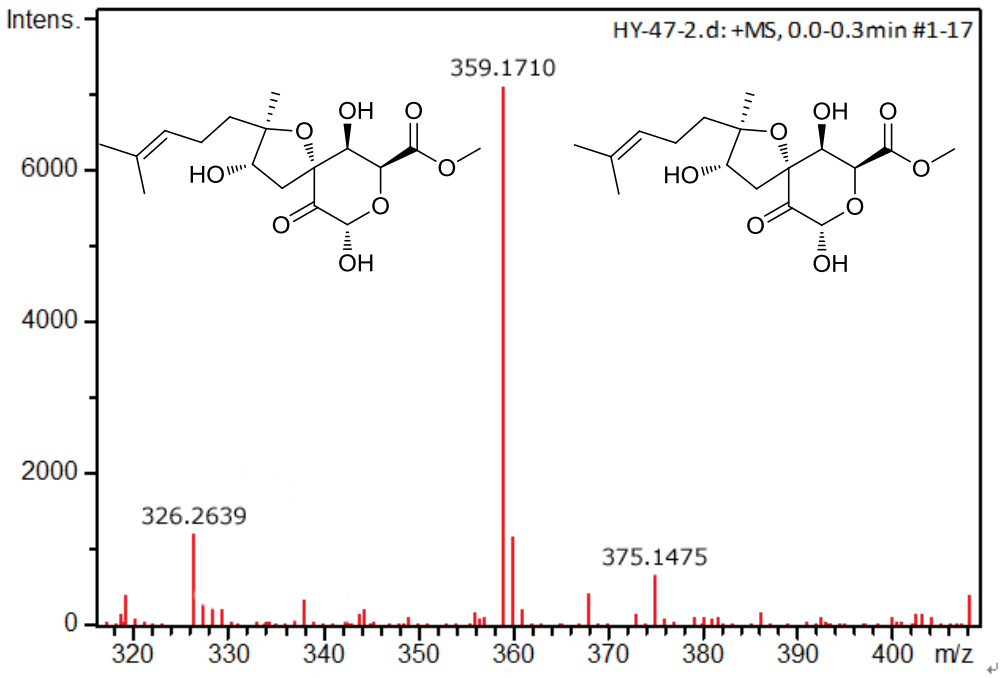


Figure S8. HRESIMS spectrum of compound **1**

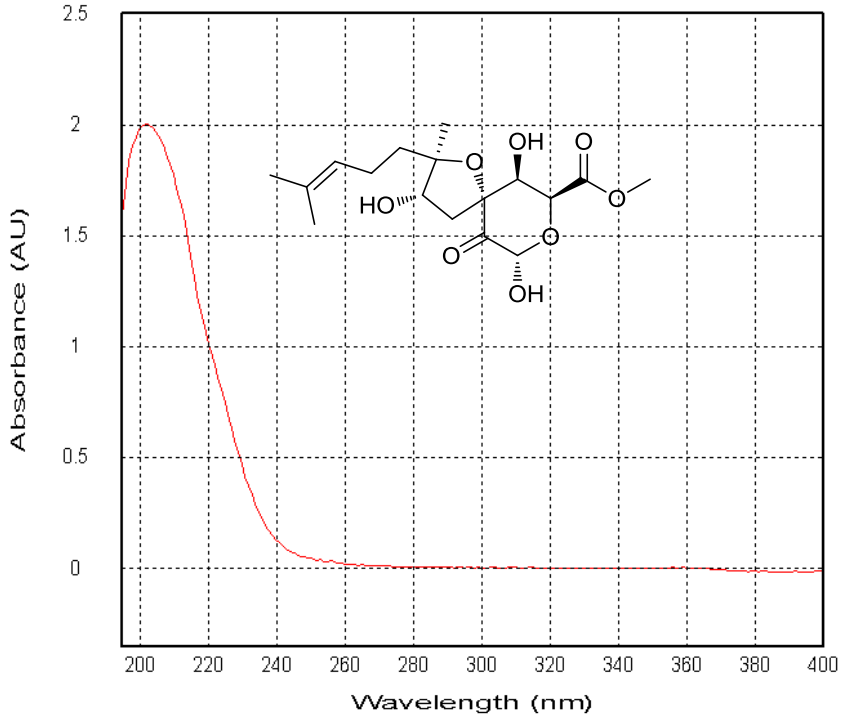


Figure S9. UV spectrum of compound **1**

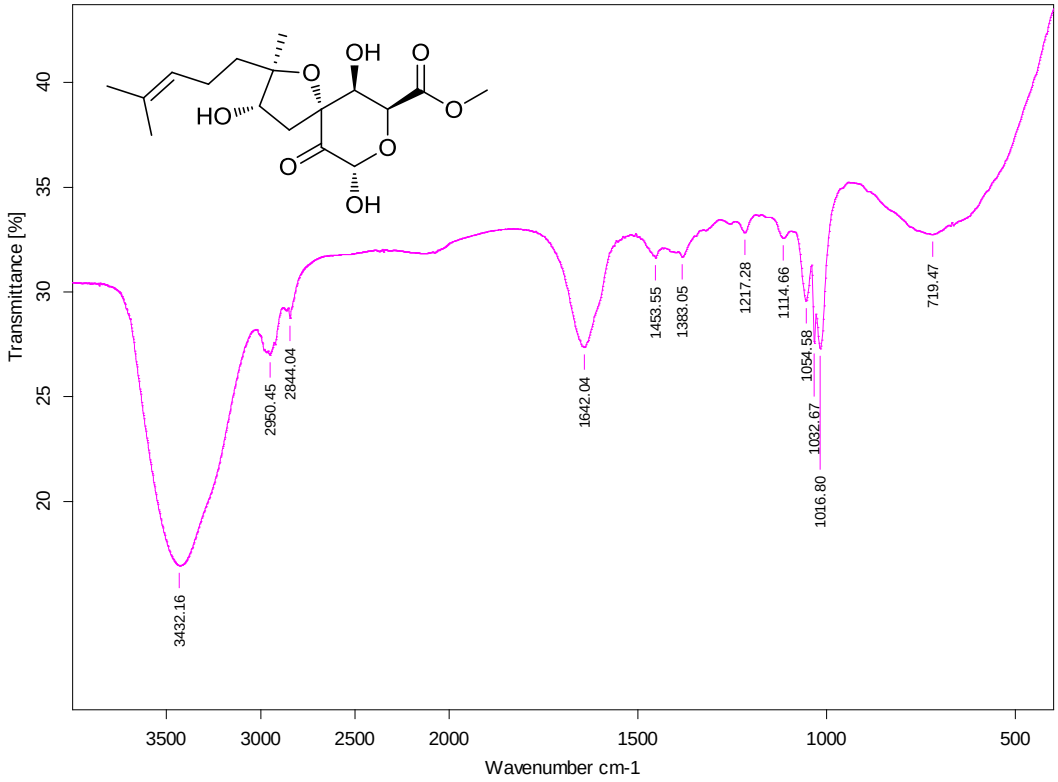


Figure S10. IR spectrum of compound **1**

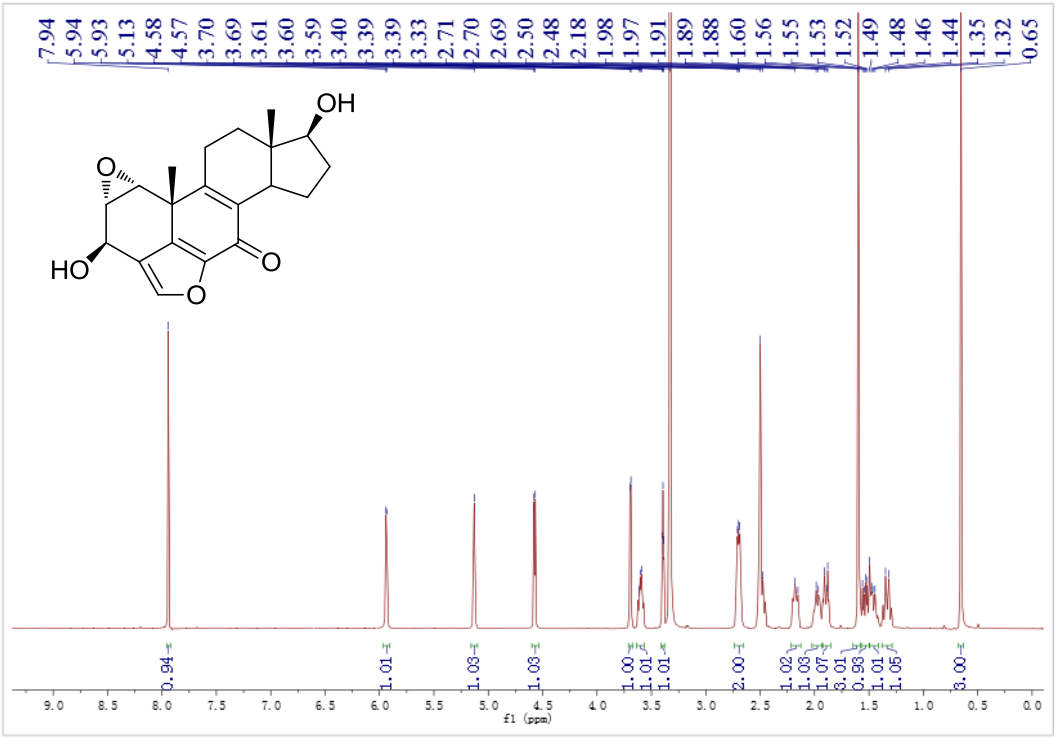


Figure S11. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **2**

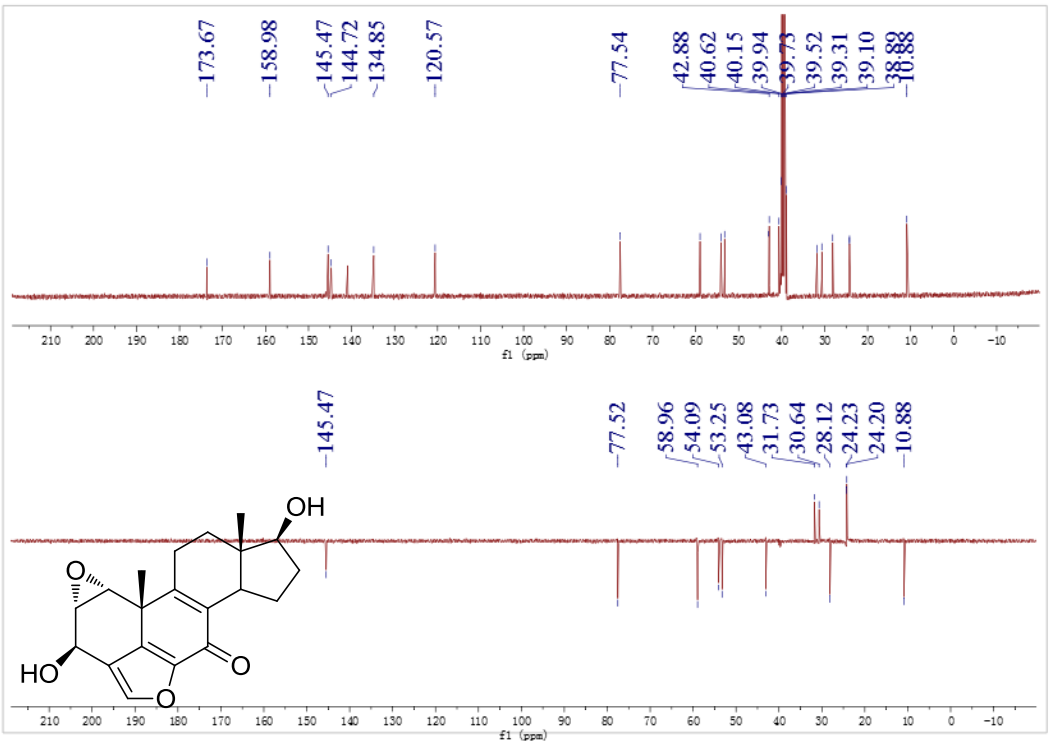


Figure S12. ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **2**

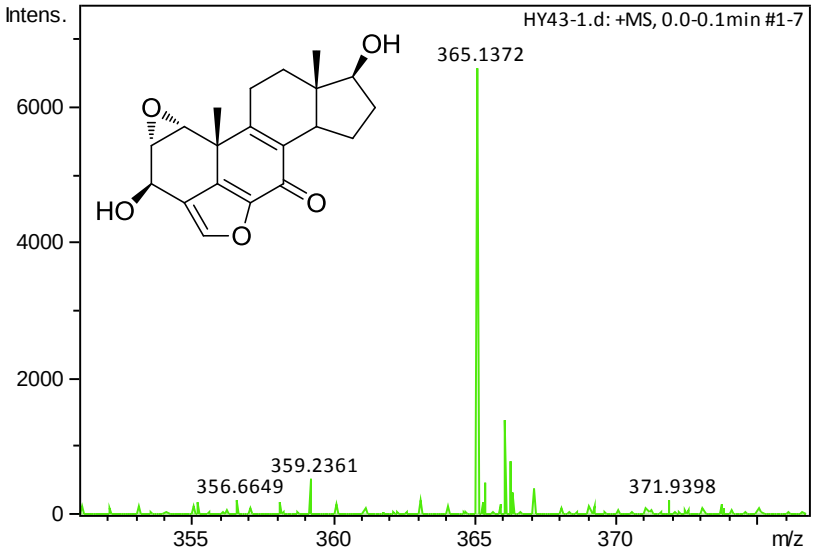


Figure S13. HRESIMS spectrum of compound **2**

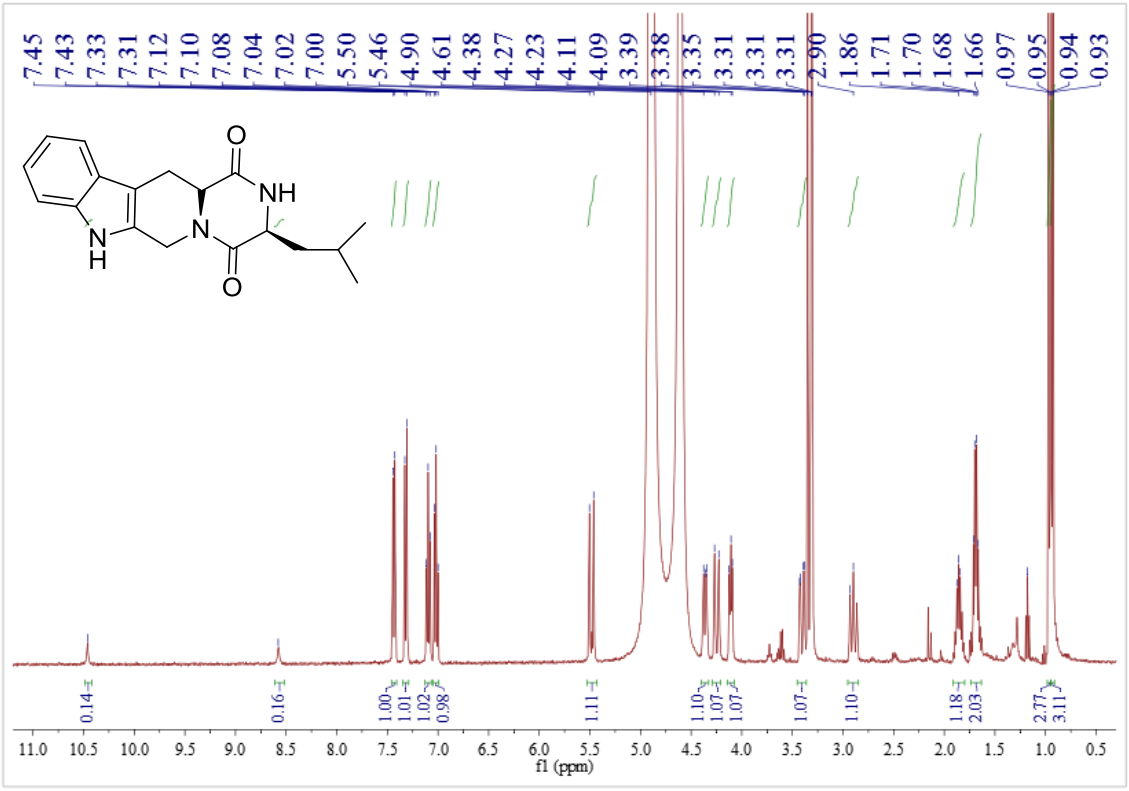


Figure S14. ^{1}H NMR spectrum (CD_3OD, 400 MHz) of compound **3**

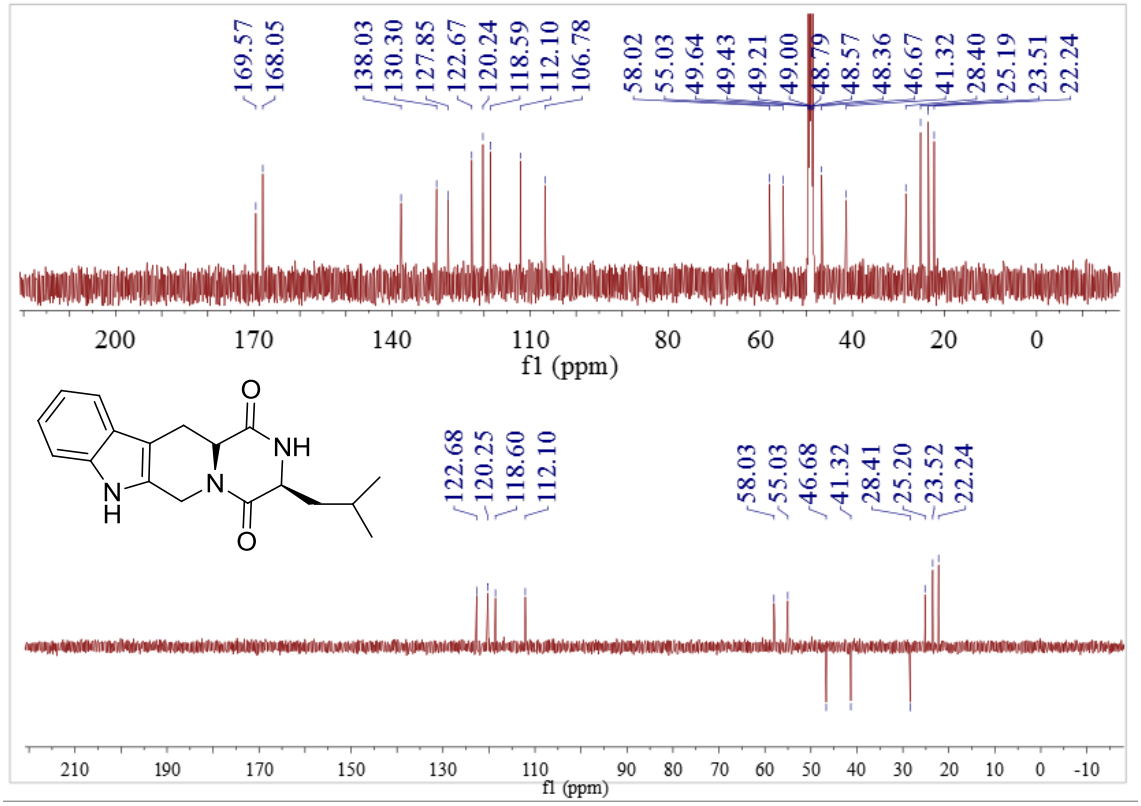


Figure S15. ^{13}C NMR spectrum (CD_3OD, 100 MHz) of compound **3**

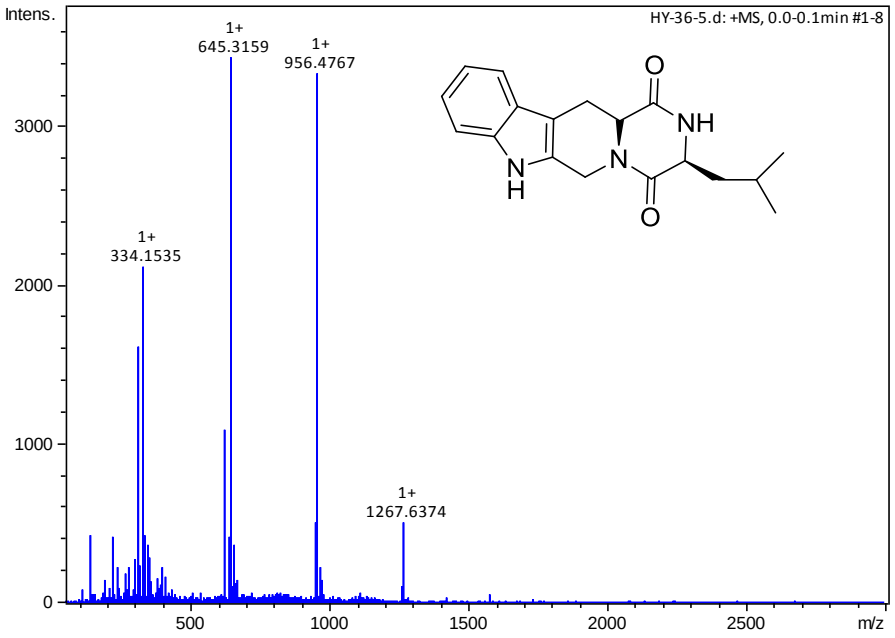


Figure S16. HRESIMS spectrum of compound **3**

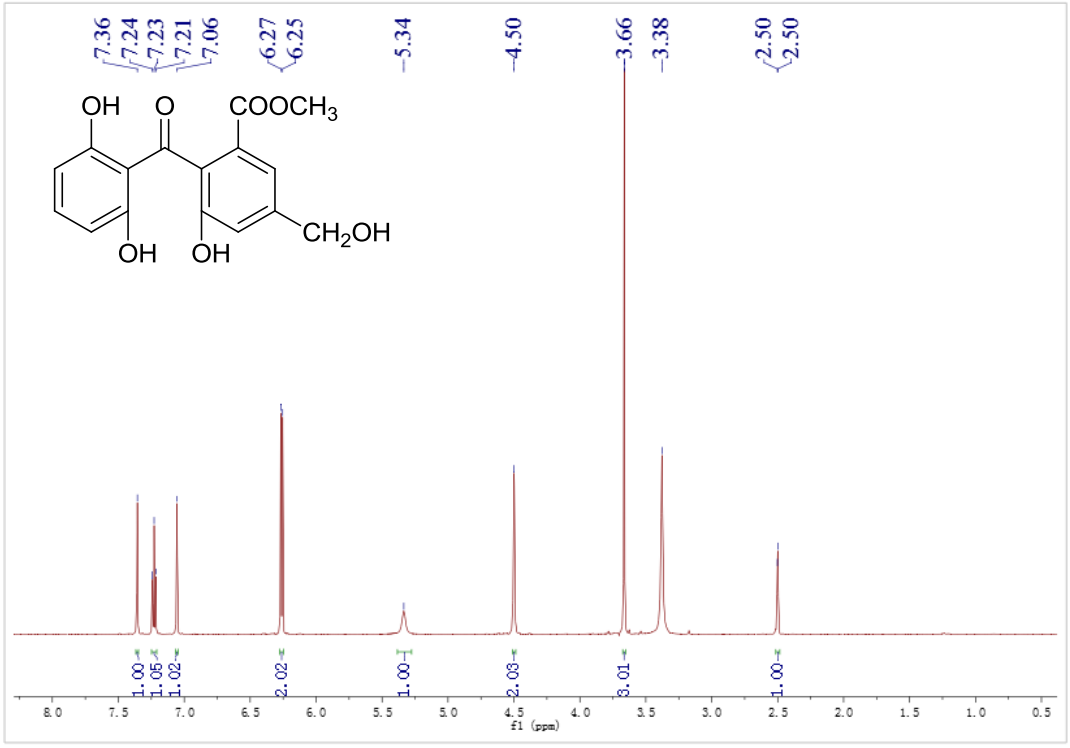


Figure S17. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) of compound **4**

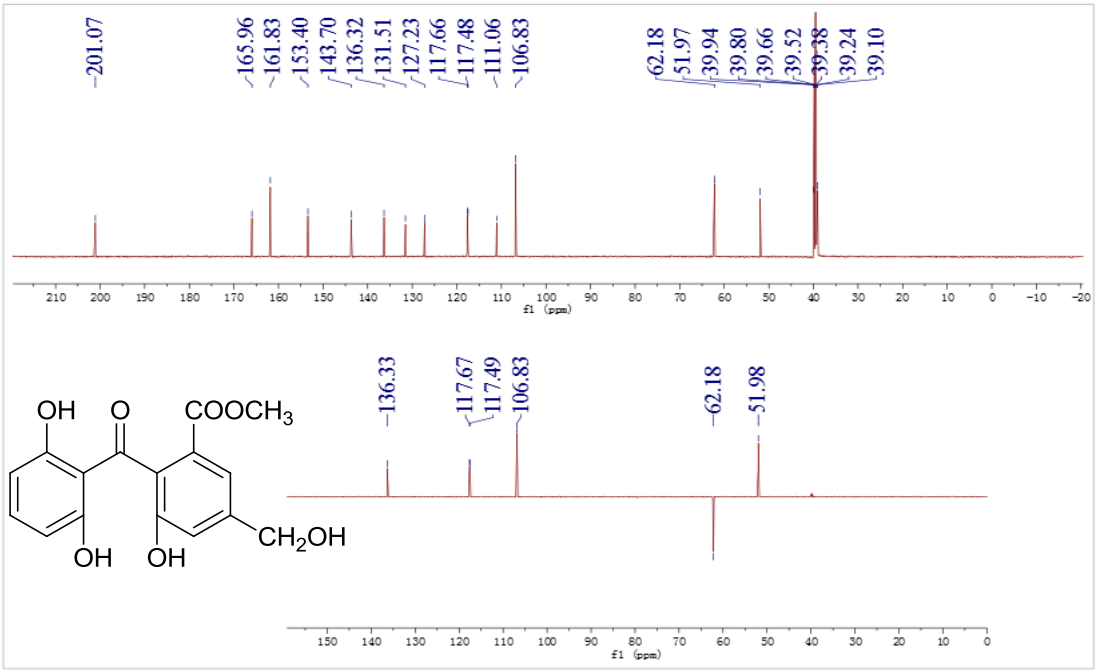


Figure S18. ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) of compound **4**

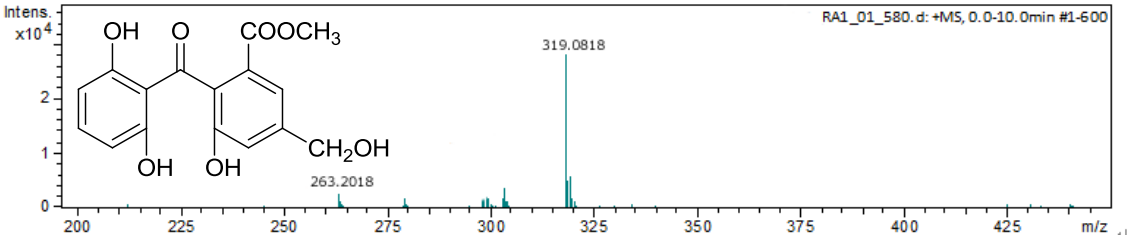


Figure S19. HRESIMS spectrum of compound **4**