Supporting information

A Novel Withanolide with An Unprecedented Carbon Skeleton from *Physalis angulata*

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Content

Experimental details

General Experimental Procedures.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. UV spectra were measured with a Shimadzu UV 2201 spectrophotometer. ECD spectra were measured with a Bio-Logic Science MOS-450 spectrometer. IR spectra were recorded on a Bruker IFS 55 spectrometer. Bruker ARX-400 and AV-600 spectrometers were used to record NMR spectra. Chemical shift values are expressed in δ (ppm) using the peak signals of the solvent MeOH-d_4 (δ_H 3.31 and δ_C 49.2) or DMSO-d_6 (δ_H 2.50 and δ_C 39.5) as references, and coupling constants (J in Hz) are given in parentheses. HRESIMS data were acquired on an Agilent 6210 TOF mass spectrometer. Silica gel GF_{254} prepared for TLC was purchased from Qingdao Marine Chemical Factory (Qingdao, China). Silica gel (200−300 mesh, Qingdao Marine Chemical Factory, Qingdao, China) and octadecyl silica gel (Merck Chemical Company Ltd, German) were used for column chromatography (CC). RP-HPLC separations were conducted using an LC-6AD liquid chromatograph and a SPD-20A UV detector (Shimadzu, Kyoto, Japan) with a RP-C_{18} column (250 × 20 mm, 120 Å, 5 μm, YMC Co. Ltd). Spots were detected on TLC plates under UV light or by heating after spraying with anisaldehyde-H_2SO_4 reagent.

Plant Material.

The stems and leaves of *P. angulata* were collected from Nanning, Guangxi Province, China, in July 2013, and identified by Pharmacist Jia-Fu Wei, Guangxi Institute for Food and Drug Control. A voucher specimen (PA-20130826) has been deposited in the herbarium of the Department of Natural Products Chemistry, Shenyang Pharmaceutical University.

Extraction and Isolation.

The dried stems and leaves of *P. angulata* (9.5 kg) were extracted with 75% EtOH

(110 L × 2 h × 2). The resulting extracts (1.3 kg) were concentrated *in vacuo*, suspended in H_2O (5 L), and partitioned with petroleum ether (5 L × 3), EtOAc (5 L × 3), and *n*-BuOH (5 L × 3), successively. The EtOAc extracts (116 g) were subjected to silica gel CC (10 × 80 cm) eluted with CH_2Cl_2−MeOH (100:1, 80:1, 60:1, 40:1, 20:1, 10:1, 8:1, 5:1, 3:1, 1:1, and 0:1, v/v) to obtain six fractions (E1−E6). Fraction E3 (35 g) was subjected to silica gel CC (6 × 80 cm), using petroleum ether−acetone (10:1 to 0:1) as a solvent, to produce seven subfractions (E31−E37). Subfraction E33 (4 g) was separated by ODS CC (3 × 50 cm) eluted with MeOH−H_2O (1:9 to 1:0) to afford three subfractions (E331−E333). Subfraction E331 (2 g) was chromatographed over silica gel CC (2 × 50 cm) eluted with a gradient of increasing acetone in petroleum ether (1:10 to 1:0) to afford four subfractions (E3311−E3314). Separation of subfraction E3314 (1.1 g) by silica gel CC (2 × 50 cm) eluted with $CHCl_3$−MeOH (80:1 to 1:1), preparative TLC (CH_2Cl_2−acetone, 4:1), and preparative HPLC (40% MeOH−H_2O, 6 mL/min) yielded compound 1 (3.5 mg, t_R = 28 min).

Aromaphysalin A (1): amorphous powder; $[\alpha]$ −68.0 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 222 (3.7), 284 (3.2) nm; ECD (*c* 0.5, MeOH) nm ($\Delta\varepsilon$) 210 (−2.8), 227 (+1.1), 240 (−1.2), 288 (−0.7); IR (KBr) ν_{max} 3423, 2922, 2852, 1782, 1765, 1728, 1633, 1459, 1384, 1262, 1162, 1113, 1064, 804, 616 cm^{-1}; ^1H (400 MHz, MeOH-d_4) and ^{13}C NMR (100 MHz, MeOH-d_4) data, see Table 1; HRESIMS *m/z* 549.1744 $[M + Na]^+$ (calcd for $C_{28}H_{30}O_{10}Na$, 549.1737).

^{13}C NMR, ^1H-^1H spin-spin coupling constants, and ECD calculations.

All calculations were performed using Gaussian 09, Revision A.02. Geometries of **1a-1d** were optimized at the B3LYP/6-31G(d) level of DFT theory. Chemical shifts were computed using GIAO at mPW1PW91/6-311+G(d,p) level of theory. ^1H-^1H spin-spin coupling constants were computed with the relativistic force field method, based on parametric scaling of DFT-computed Fermi contacts.[1-3] ECD spectrum is calculated at the B3LYP/6-311+G(d,p) TDDFT level of theory.[4]

NO Production Bioassay.

Compound 1 was assayed for the inhibition of NO production according to the Griess method.[5-7] 1×10^6 Cells/well of RAW 264.7 cells were added into the 96-well plates, and incubated at 37 °C for 24 h by the stimulation of LPS (1 μg/mL) with or without test compounds. After the addition of Griess reagent [0.1% *N*-(1-naphthyl)-ethylenediamine (50 μL); 1% sulfanilamide in 5% H_3PO_4 (50 μL)], absorbance (540 nm) was recorded by using a microplate reader. The standard curve was used to calculate the NO concentrations and inhibitory rates.

References

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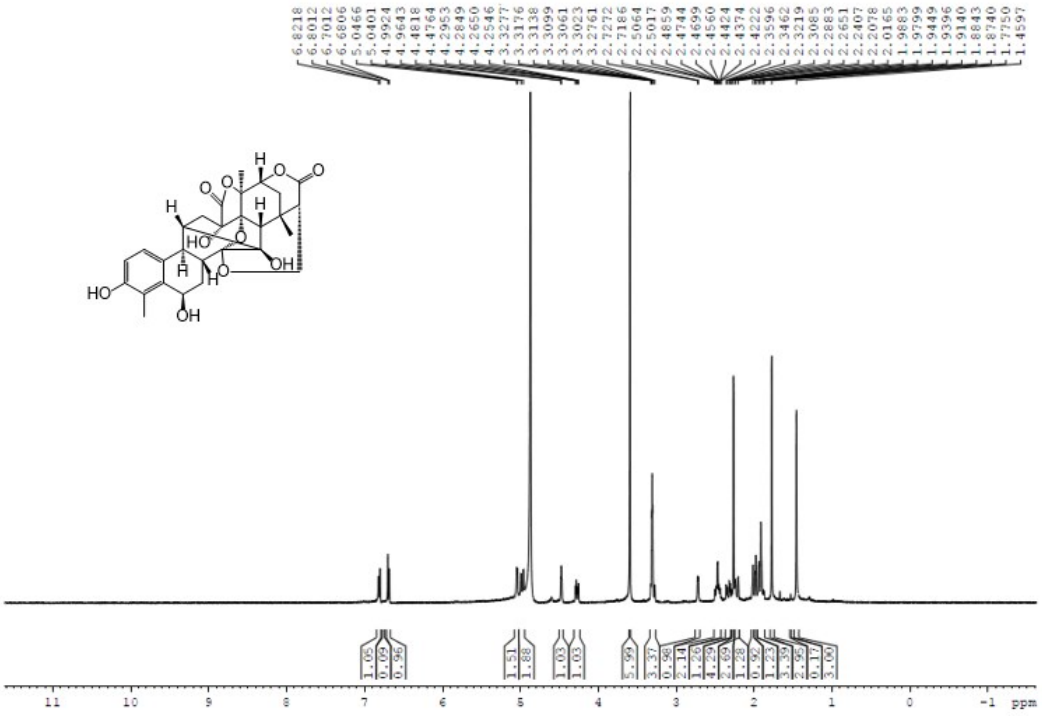


Figure S1. ^{1}H NMR spectrum of 1 (400 MHz, MeOH-d_4)

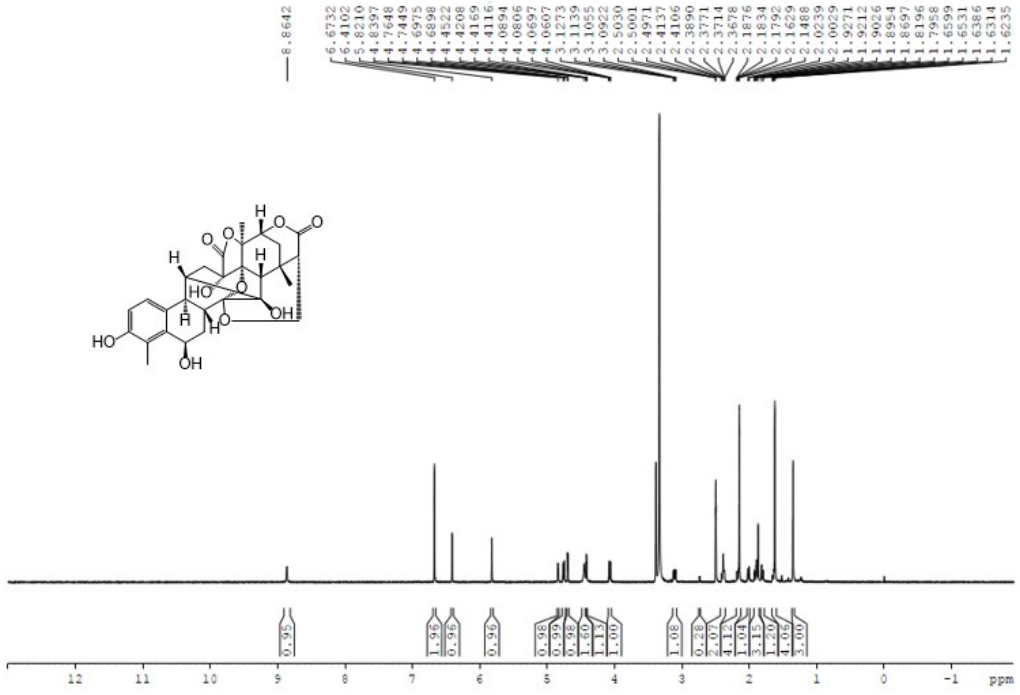


Figure S2. ^{1}H NMR spectrum of 1 (600 MHz, DMSO-d_6)

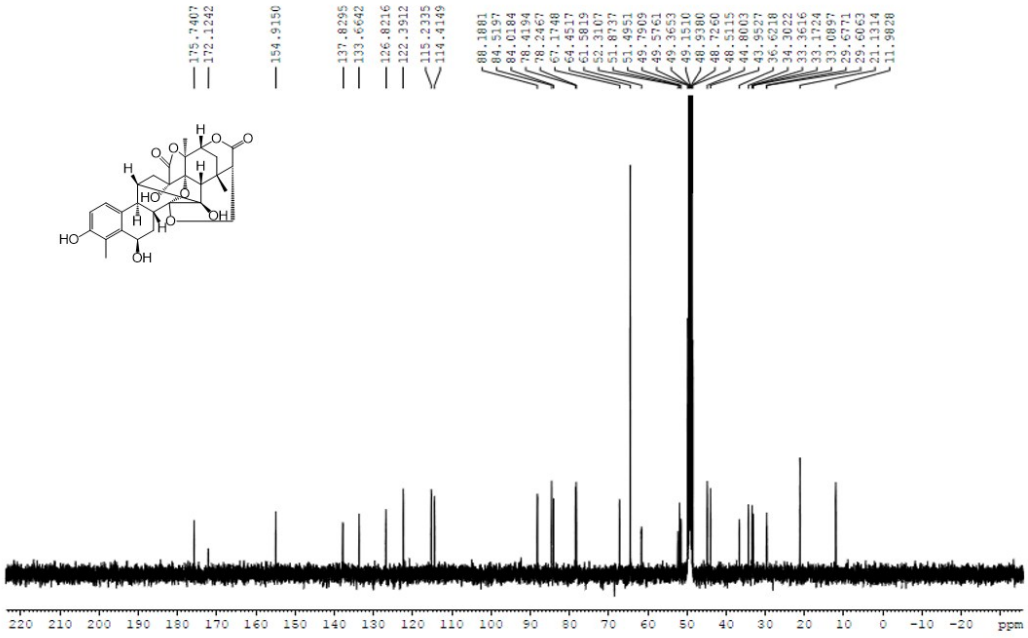


Figure S3. ^{13}C NMR spectrum of 1 (100 MHz, MeOH-d_4)

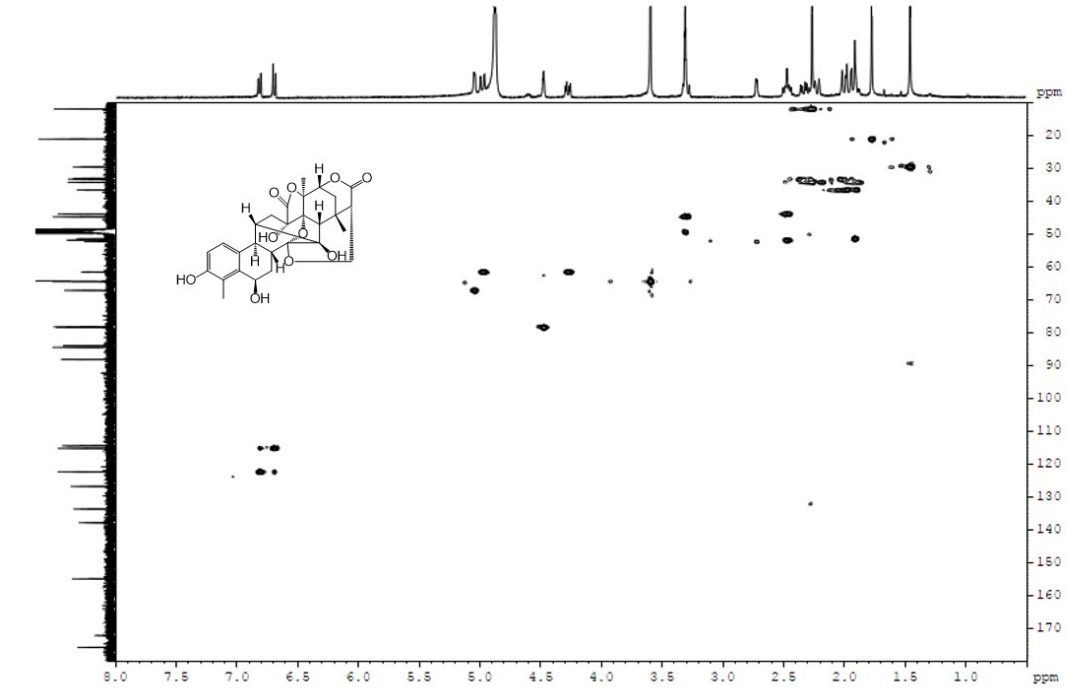


Figure S4. HSQC spectrum of 1(400 MHz, MeOH-d_4)

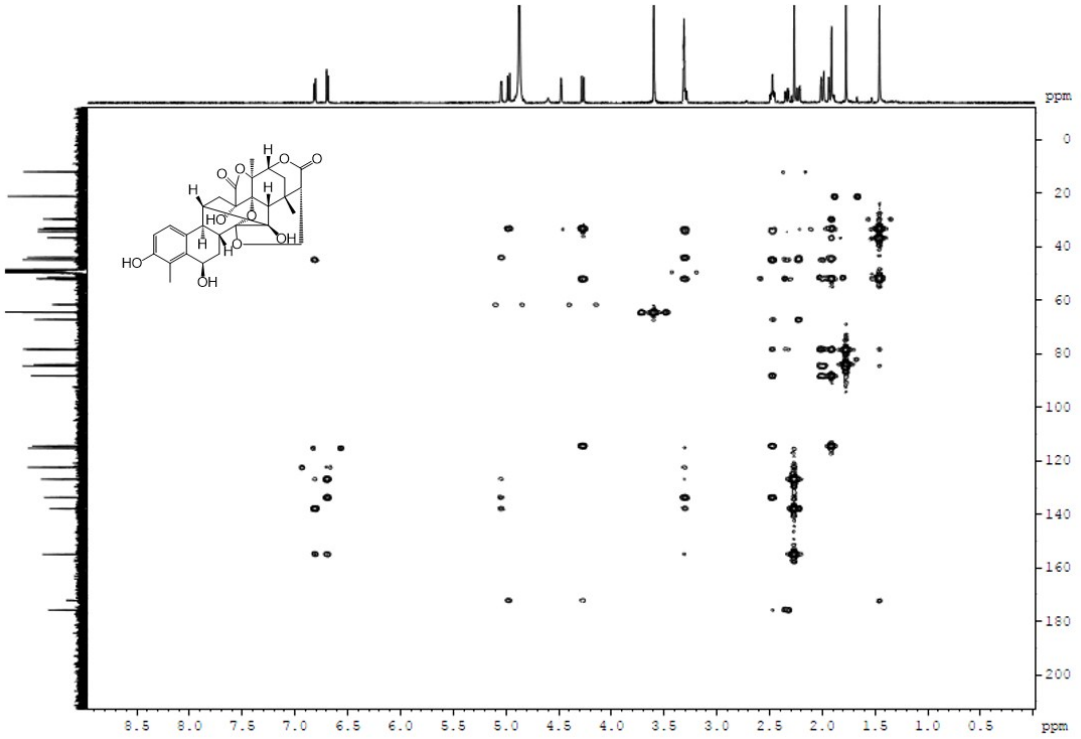


Figure S5. HMBC spectrum of 1 (400 MHz, MeOH-d_4)

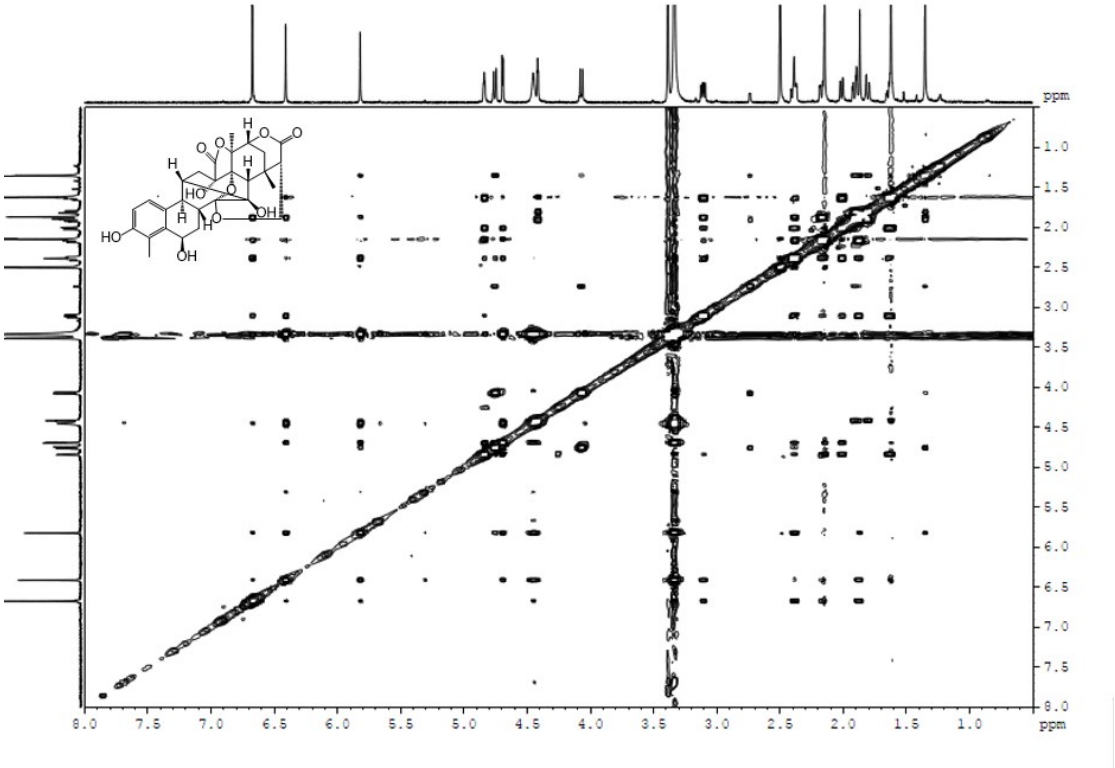


Figure S6. NOESY spectrum of 1 (400 MHz, DMSO-d_6)

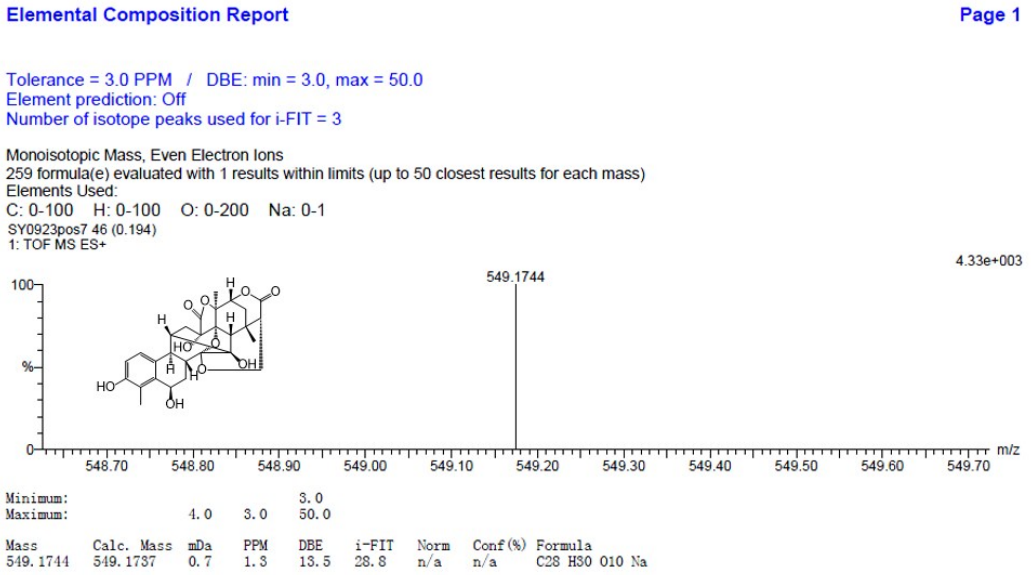
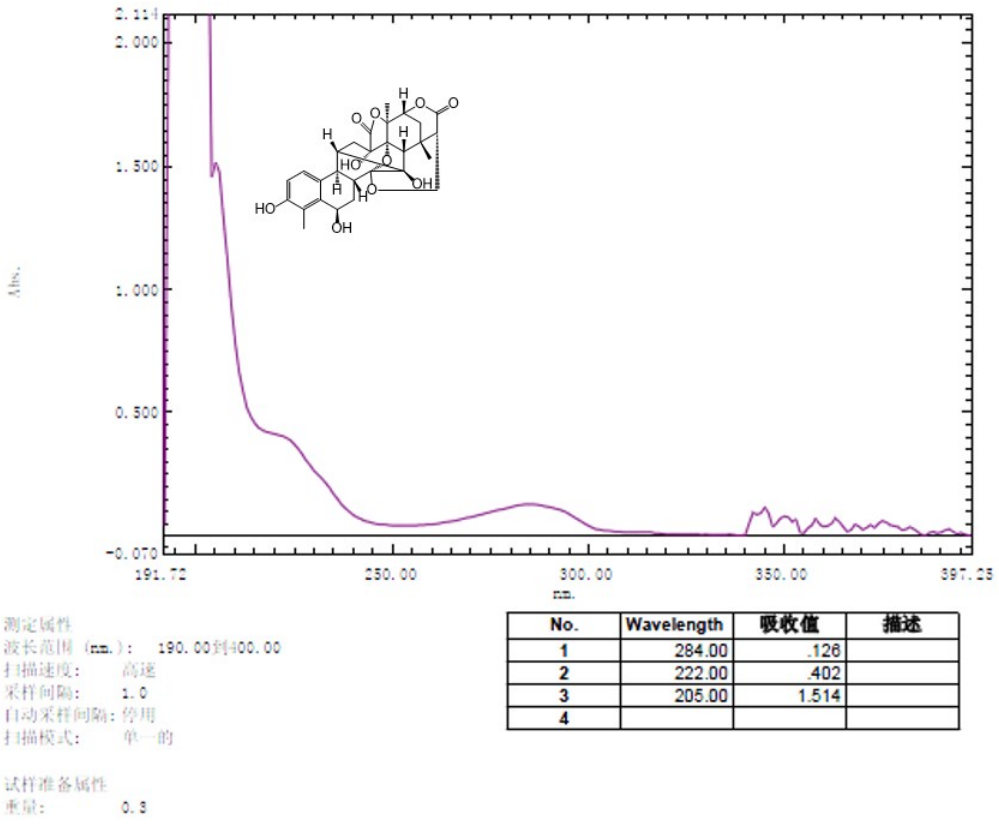


Figure S7. HRESIMS spectrum of 1



No.	Wavelength	吸收值	描述
1	284.00	.126	
2	222.00	.402	
3	205.00	1.514	
4			

Figure S8. UV spectrum of 1

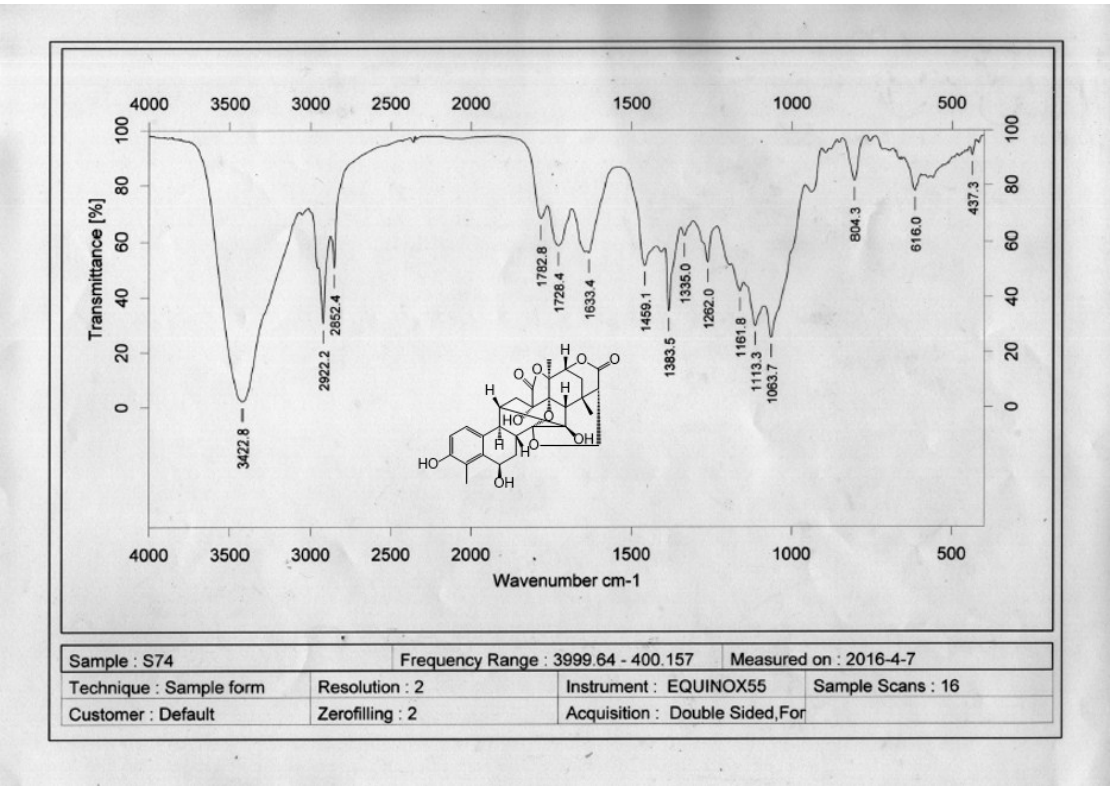


Figure S9. IR spectrum of 1

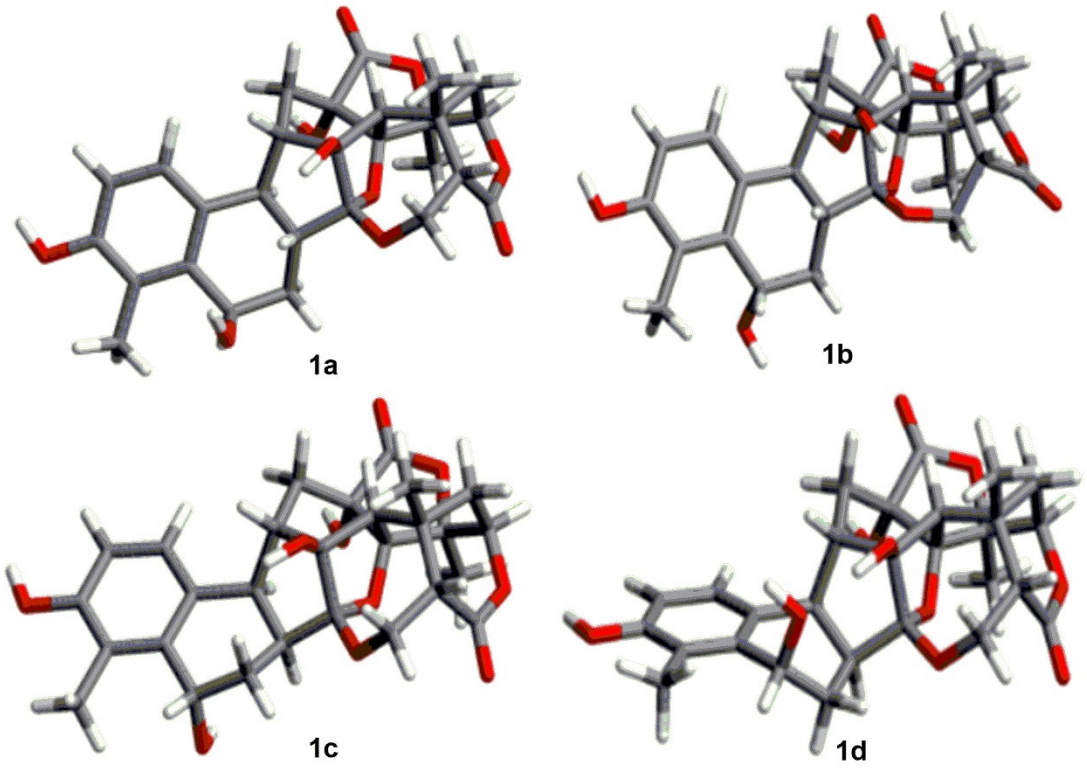


Figure S10. Optimized geometries of conformers of 1a-1d at the B3LYP/6-31G(d) level

Table S1. Optimized Structures of 1a-1d at B3LYP/6-31G(d) Level

1a				**1b**			
C	-5.0421	1.6703	1.065	C	-5.1608	1.4548	1.3084
C	-5.8714	0.8111	0.344	C	-5.9744	0.519	0.6723
C	-5.3378	-0.256	-0.4016	C	-5.4256	-0.494	-0.1366
C	-3.9367	-0.4277	-0.4287	C	-4.0272	-0.5271	-0.3178
C	-3.0893	0.4584	0.2833	C	-3.1969	0.4098	0.344
C	-3.662	1.4944	1.0247	C	-3.7799	1.3905	1.1467
C	-3.3699	-1.6367	-1.1856	C	-3.4458	-1.6318	-1.2083
C	-1.8391	-1.6354	-1.3799	C	-1.9015	-1.6683	-1.3266
C	-1.1938	-1.1383	-0.0982	C	-1.2796	-1.1337	-0.0503
C	-1.5889	0.3165	0.132	C	-1.701	0.3293	0.1286
C	0.317	-1.1292	0.1069	C	0.2252	-1.0668	0.1461
C	0.9127	2.1018	-0.3219	C	0.8691	2.0542	-0.4747
C	-0.0428	2.2279	0.8805	C	-0.1112	2.2749	0.6966
C	-0.6255	0.8467	1.2399	C	-0.7126	0.9369	1.1821
C	0.5176	-0.2471	1.3778	C	0.3985	-0.1562	1.3779
C	1.9185	0.3472	1.1466	C	1.8199	0.3982	1.1472
C	1.6953	0.7551	-0.3344	C	1.6595	0.7216	-0.3552
H	-1.3196	0.843	-0.7909	H	-1.4803	0.8233	-0.8251
O	0.2267	2.2612	-1.5679	O	0.2128	2.0793	-1.7468
O	0.9948	-0.3475	-0.9139	O	0.9144	-0.3896	-0.896
O	0.4183	-0.9481	2.6036	O	0.1625	-0.8581	2.5765
O	0.7773	-2.4357	0.1206	O	0.7648	-2.3579	0.4033
O	-7.2345	0.9677	0.3344	O	-7.3403	0.5444	0.8127
C	-6.285	-1.158	-1.1634	C	-6.3678	-1.4953	-0.7663
O	-3.7588	-2.8569	-0.5175	O	-4.0348	-1.4921	-2.5073
H	-1.1257	0.9053	2.2133	H	-1.1977	1.0773	2.1521
C	3.1759	-0.5393	1.395	C	3.0751	-0.4581	1.4879
C	4.3713	0.249	0.8243	C	4.2593	0.4128	1.0125
C	4.2439	0.372	-0.6833	C	4.2831	0.4415	-0.505
C	2.9724	1.1159	-1.1428	C	2.9799	1.0081	-1.1363
O	4.284	-0.9201	-1.3178	O	4.6142	-0.8733	-1.0018
C	3.1859	-1.9329	0.6915	C	3.2454	-1.8779	0.7972
C	3.6595	-1.9956	-0.7704	C	4.3886	-1.9629	-0.2147
O	3.5953	-3.0137	-1.4142	O	4.9779	-2.9914	-0.4437
C	1.9401	-2.8127	0.8625	C	2.0986	-2.5655	-0.0308
C	3.3936	-0.7225	2.9116	C	3.1919	-0.635	3.0162
H	5.0999	0.9069	-1.1043	H	5.0907	1.079	-0.8753
C	2.0687	3.1123	-0.323	C	2.0065	3.076	-0.5626
O	3.2025	2.5165	-0.77	O	3.1498	2.4563	-0.9505
C	2.8047	1.0291	-2.6595	C	2.9004	0.7124	-2.631
O	2.0105	4.2799	-0.0272	O	1.9332	4.2661	-0.3856
H	2.0641	1.2325	1.7735	H	1.9536	1.3196	1.7224
H	-5.4742	2.4818	1.6486	H	-5.6048	2.2273	1.9344
H	-3.0278	2.1812	1.5786	H	-3.1556	2.12	1.655

H	-3.8425	-1.6986	-2.172	H	-3.7687	-2.5911	-0.7682
H	-1.5571	-0.9785	-2.2124	H	-1.6059	-1.0352	-2.171
H	-1.5326	-2.6546	-1.6321	H	-1.5752	-2.6933	-1.5454
H	-1.5819	-1.7609	0.7267	H	-1.6477	-1.7152	0.8071
H	0.481	2.6661	1.7361	H	0.4024	2.7889	1.516
H	-0.844	2.9309	0.6252	H	-0.9061	2.9543	0.3683
H	-0.1066	3.1751	-1.5904	H	-0.1441	2.977	-1.8619
H	-0.4499	-1.3828	2.6302	H	0.4062	-1.7852	2.3906
H	-7.4651	1.7221	0.8982	H	-7.575	1.2674	1.4146
H	-6.4087	-0.8122	-2.1992	H	-7.2911	-1.5657	-0.1874
H	-5.9173	-2.1851	-1.1893	H	-6.6279	-1.2033	-1.7893
H	-7.2764	-1.1489	-0.7051	H	-5.9192	-2.4911	-0.8281
H	-3.8729	-2.6525	0.4229	H	-3.7703	-2.2679	-3.0277
H	5.312	-0.263	1.063	H	5.2125	0.0062	1.374
H	4.4268	1.2492	1.2692	H	4.1762	1.4313	1.406
H	3.9772	-2.4993	1.2087	H	3.5117	-2.5792	1.592
H	1.6911	-2.881	1.9245	H	2.2609	-3.6427	0.0336
H	2.1791	-3.8069	0.4839	H	2.1735	-2.2786	-1.0814
H	4.3507	-1.2256	3.0969	H	4.1567	-1.0905	3.269
H	2.595	-1.301	3.3771	H	2.3942	-1.2584	3.4227
H	3.431	0.2525	3.4125	H	3.1377	0.3354	3.5236
H	2.599	0.0009	-2.9597	H	2.8054	-0.3611	-2.804
H	3.7301	1.3579	-3.144	H	3.8152	1.0624	-3.1199
H	1.9797	1.662	-2.9865	H	2.0377	1.2167	-3.0685
1c				**1d**			
C	-4.9941	1.9829	0.5409	C	-5.109	2.0063	-0.3051
C	-5.8792	0.9179	0.3516	C	-5.8879	0.8672	-0.0962
C	-5.4062	-0.3445	-0.0358	C	-5.2992	-0.4101	-0.042
C	-4.0151	-0.5236	-0.1991	C	-3.9044	-0.5062	-0.2136
C	-3.112	0.545	-0.023	C	-3.105	0.6382	-0.4062
C	-3.6322	1.7944	0.3444	C	-3.7309	1.8864	-0.4613
C	-3.4981	-1.8956	-0.602	C	-3.2175	-1.8555	-0.1939
C	-2.0434	-2.1066	-0.1811	C	-2.0664	-1.9475	-1.1965
C	-1.1409	-0.9905	-0.7154	C	-1.0944	-0.7416	-1.2558
C	-1.6106	0.4159	-0.2686	C	-1.5998	0.538	-0.5366
C	0.3024	-1.0789	-0.2033	C	0.2913	-0.9741	-0.6233
C	1.0444	2.1362	-0.2894	C	1.0005	2.1778	0.1038
C	-0.047	2.1978	0.792	C	-0.1895	1.9941	1.0623
C	-0.7118	0.8172	0.9685	C	-0.838	0.6137	0.8488
C	0.3648	-0.3184	1.1542	C	0.229	-0.5505	0.8723
C	1.8041	0.239	1.153	C	1.6541	-0.0093	1.1198
C	1.7919	0.7722	-0.3033	C	1.7593	0.8454	-0.1672
H	-1.3548	1.1092	-1.0744	H	-1.265	1.3926	-1.1264
O	0.5117	2.3973	-1.5922	O	0.591	2.757	-1.142
O	1.1437	-0.2481	-1.0549	O	1.1887	0.0327	-1.1873
O	0.1087	-1.1026	2.3057	O	-0.1171	-1.5688	1.7749

O	0.7266	-2.3963	-0.2455	O	0.7415	-2.2449	-0.9373
O	-7.2306	1.0666	0.5325	O	-7.2491	0.9423	0.0535
C	-6.3896	-1.4696	-0.2709	C	-6.1901	-1.6157	0.1781
O	-3.6778	-2.1413	-2.007	O	-2.7026	-2.1553	1.1353
H	-1.3162	0.8419	1.8815	H	-1.5323	0.4226	1.6717
C	2.9936	-0.7114	1.4844	C	2.8224	-1.0195	1.3277
C	4.2746	0.0741	1.1397	C	4.1218	-0.1923	1.2788
C	4.3503	0.3225	-0.3553	C	4.3172	0.3927	-0.1074
C	3.1714	1.1493	-0.9092	C	3.1813	1.3397	-0.5487
O	4.4329	-0.916	-1.0865	O	4.4675	-0.6453	-1.0954
C	3.0524	-2.0427	0.6731	C	2.9641	-2.1349	0.2449
C	3.7096	-2.0062	-0.7167	C	3.7343	-1.7888	-1.0403
O	3.6989	-2.9651	-1.4483	O	3.7997	-2.558	-1.9677
C	1.7658	-2.8784	0.6106	C	1.6965	-2.9219	-0.1145
C	3.0123	-1.0234	2.9958	C	2.7124	-1.6644	2.7255
H	5.2702	0.8531	-0.6168	H	5.2518	0.9581	-0.165
C	2.2112	3.1105	-0.0732	C	2.136	3.0558	0.648
O	3.3834	2.5085	-0.3972	O	3.3368	2.538	0.2853
C	3.1994	1.1889	-2.437	C	3.3391	1.7367	-2.0161
O	2.1375	4.2599	0.2846	O	2.0232	4.0866	1.2646
H	1.89	1.062	1.8691	H	1.6644	0.6249	2.0118
H	-5.3748	2.961	0.8312	H	-5.5832	2.9852	-0.3555
H	-2.9662	2.6429	0.4738	H	-3.1356	2.7785	-0.6399
H	-4.1043	-2.6678	-0.1185	H	-3.933	-2.646	-0.4423
H	-1.6962	-3.076	-0.5461	H	-2.5354	-2.0588	-2.1807
H	-2.0178	-2.1535	0.918	H	-1.5107	-2.8723	-1.0176
H	-1.124	-1.0648	-1.808	H	-0.9167	-0.5159	-2.3107
H	0.3788	2.5404	1.7406	H	0.14	2.108	2.1003
H	-0.7856	2.9546	0.5081	H	-0.9204	2.7934	0.892
H	0.238	3.3311	-1.599	H	0.3203	3.6706	-0.9448
H	-0.8198	-1.3825	2.2837	H	-1.0376	-1.8516	1.572
H	-7.4148	1.9904	0.7624	H	-7.5175	1.8731	0.0106
H	-7.3949	-1.0738	-0.4271	H	-7.1269	-1.3155	0.6515
H	-6.1044	-2.0594	-1.146	H	-6.4503	-2.1047	-0.7702
H	-6.4399	-2.1495	0.591	H	-5.7175	-2.371	0.8138
H	-3.4728	-1.3193	-2.4792	H	-3.3318	-1.8059	1.7863
H	5.1614	-0.4905	1.454	H	4.9837	-0.8256	1.5245
H	4.2977	1.0328	1.6704	H	4.096	0.6173	2.0171
H	3.751	-2.6828	1.2359	H	3.6207	-2.8907	0.7056
H	1.3735	-3.0157	1.621	H	1.2114	-3.2674	0.8004
H	2.0198	-3.85	0.1861	H	1.9945	-3.7798	-0.7181
H	3.926	-1.5726	3.2548	H	3.5949	-2.2851	2.9252
H	2.148	-1.6093	3.3097	H	1.8151	-2.2748	2.8277
H	3.0104	-0.0933	3.5769	H	2.6738	-0.8878	3.4992
H	2.9979	0.1982	-2.8461	H	3.183	0.8706	-2.6604
H	4.1905	1.5125	-2.7722	H	4.3515	2.1203	-2.1811

H	2.4458	1.8817	-2.8116	H	2.6119	2.5046	-2.2797

Table S2. Experimental and Calculated ^{13}C NMR Data for 1a and 1b (δ_C in ppm).

No.	**1a**[a]			**1b**[b]		
	δexp.	δcalcd.	$\Delta\delta$	δexp.	δcalcd.	$\Delta\delta$
1	154.9	153.79	1.11	154.9	153.67	1.23
2	115.2	111.87	3.33	115.2	111.1	4.10
3	122.4	120.11	2.29	122.4	119.28	3.12
4	133.7	133.19	0.51	133.7	133.51	0.19
5	137.8	140.55	-2.75	137.8	138.08	-0.28
6	67.2	66.32	0.88	67.2	69.67	-2.47
7	34.3	32.01	2.29	34.3	33.44	0.86
8	44.0	44.07	-0.07	44	44.77	-0.77
9	44.8	43.61	1.19	44.8	45.82	-1.02
10	126.8	128.96	-2.16	126.8	129.04	-2.24
11	51.9	52.07	-0.17	51.9	46.12	5.78
12	33.4	33.78	-0.38	33.4	33.52	-0.12
13	78.2	77.51	0.69	78.2	78.18	0.02
14	114.4	111.5	2.90	114.4	110.65	3.75
15	88.2	89.05	-0.85	88.2	85.97	2.23
16	51.5	51.42	0.08	51.5	53.36	-1.86
17	84.5	83.76	0.74	84.5	87.9	-3.40
18	175.7	173.98	1.72	175.7	173.05	2.65
19	12.0	9.39	2.61	12	12.55	-0.55
20	84.0	84.38	-0.38	84	85.37	-1.37
21	21.1	18.83	2.27	21.1	17.84	3.26
22	78.4	74.37	4.03	78.4	76.49	1.91
23	36.6	35.55	1.05	36.6	39.77	-3.17
24	33.2	34.28	-1.08	33.2	35.34	-2.14
25	52.3	52.59	-0.29	52.3	52.73	-0.43
26	172.1	166.4	5.70	172.1	169.28	2.82
27	61.6	59.4	2.20	61.6	61.5	0.10
28	29.7	27.77	1.93	29.7	30.25	-0.55

[a]RMSD = 2.09; [b]RMSD = 2.36.

Table S3. Experimental and Calculated ^{13}C NMR Data for 1c and 1d (δ_C in ppm).

No.	**1c**[a]			**1d**[b]		
	δexp.	δcalcd.	$\Delta\delta$	δexp.	δcalcd.	$\Delta\delta$
1	154.9	153.62	1.28	154.9	153.7	1.20
2	115.2	113.38	1.82	115.2	112.89	2.31
3	122.4	124.18	-1.78	122.4	126.97	-4.57
4	133.7	131.76	1.94	133.7	136.35	-2.65
5	137.8	138.73	-0.93	137.8	137.59	0.21
6	67.2	63.95	3.25	67.2	67.41	-0.21
7	34.3	32.01	2.29	34.3	27.61	6.69
8	44.0	40.46	3.54	44.0	43.13	0.87
9	44.8	40.16	4.64	44.8	43.77	1.03
10	126.8	126.64	0.16	126.8	123.73	3.07
11	51.9	59.23	-7.33	51.9	60.14	-8.24
12	33.4	35.09	-1.69	33.4	32.98	0.42
13	78.2	76.96	1.24	78.2	77.85	0.35
14	114.4	114.04	0.36	114.4	115.27	-0.87
15	88.2	89.17	-0.97	88.2	87.76	0.44
16	51.5	52.09	-0.59	51.5	52.33	-0.83
17	84.5	82.39	2.11	84.5	82.37	2.13
18	175.7	174.27	1.43	175.7	174.56	1.14
19	12.0	9.02	2.98	12.0	9.38	2.62
20	84.0	84.23	-0.23	84.0	84.27	-0.27
21	21.1	19.46	1.64	21.1	19.36	1.74
22	78.4	75.42	2.98	78.4	74.64	3.76
23	36.6	35.40	1.2	36.6	35.42	1.18
24	33.2	32.84	0.36	33.2	34.24	-1.04
25	52.3	52.51	-0.21	52.3	51.83	0.47
26	172.1	166.69	5.41	172.1	167.27	4.83
27	61.6	59.87	1.73	61.6	60.33	1.27
28	29.7	28.08	1.62	29.7	27.71	1.99

[a]RMSD = 2.57; [b]RMSD = 2.82.

Table S4. The Inhibitory Effect of 1 on NO Production Induced by LPS in Macrophages

compound	IC_{50} ± SD (μM)
1	51.64 ± 3.52
hydrocortisone[a]	58.79 ± 3.32

[a]Positive control