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Original article

Hyperisampsins N and O, two new benzoylated phloroglucinol derivatives from *Hypericum sampsonii*

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ABSTRACT

Twenty-one benzoylated phloroglucinol derivatives bearing homoadamantyl frameworks were isolated from the aerial parts of *Hypericum sampsonii*, including two new ones named hyperisampsins N and O (**1** and **2**). The structures of **1** and **2** were elucidated by extensive NMR and mass spectrometric analyses. Their absolute configurations were further determined by using TDDFT ECD calculations. Compounds **2**, **7**, and **8** were evaluated for their cytotoxic activities against five human cancer cell lines, of which, **2** and **8** exhibited significant cytotoxic activities toward HL-60 cell and moderate activities against others cell lines.

1. Introduction

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a class of structurally intriguing and biologically active secondary metabolites from the family Guttiferae [1]. Homoadamantyl-PPAPs are subclass of PPAPs containing a homoadamantane core structure. Recently, many PPAPs with diverse structures were isolated and identified by natural product chemists around the world [2–5]. Most of those PPAPs are bicyclo[3.3.1]-type, however, homoadamantyl-PPAPs are rarely reported [6].

In our continuing efforts on bioactive PPAPs from the medicinal plants *Hypericum sampsonii*, scores of numerous novel PPAPs were previously identified [7–9], such as hyperisampsins A–D. Further chemical investigation on *H. sampsonii* has led to the isolation of two new PPAPs with a homoadamantyl framework, hyperisampsins N and O (**1** and **2**), along with 19 known analogs (**3**–**21**) (Fig. 1). The structures of these known compounds were determined by comparison of their NMR data with those reported in the literature, and identified as plukenetione C (**3**) [10], otogirinin B (**4**) [11], peroxysampsones A (**5**) [10] and B (**6**) [10], hypersampsonones G (**7**) [12] and F (**8**) [12], hypersampsone P (**9**) [13], attenuatumione D (**10**) [14], hypercohone A (**11**) [15], sampsoniones C (**12**) [16], F (**13**) [16], G (**14**) [16], and H (**15**) [16], plukenetione B (**16**) [17], hypersampsone I (**17**) [18], 7β-*H*-1-benzoyl-5α-hydroxy-6,6,13,13-tetramethyl-11-(3-methyl-2-butenyl)tetracyclo [7.3.1.1.$0^{3,11}0^{3,7}$] tetradecane-2,12,14-trione (then named as sampsonione R, **18**) [19,20], sampsoniones A (**19**) [21] and B (**20**) [21], and otogirinin C (**21**) [11]. Herein, we report the isolation, structural elucidation, and absolute configuration determination of these new PPAPs. In addition, cytotoxic activities of compounds **2**, **7**, and **8** against five human cancer cell lines were evaluated, and compounds **2** and **8** showed moderate cytotoxic activities.

2. Results and discussion

The molecular formula of hyperisampsin N (**1**) was established as $C_{38}H_{50}O_7$ by HR-ESIMS at *m/z* 641.3373 $[M+Na]^+$. The ^1H NMR spectrum of **1** (Table 1) showed five protons for a phenyl group [δ_H 7.13 (br d, 2H, *J* = 8.1 Hz; 7.28 (br t, 2H, *J* = 8.1 Hz); 7.42 (br t, 1H, *J* = 7.4 Hz)], two olefinic protons [δ_H 5.28 (t, 1H, *J* = 7.4 Hz) and 5.06 (t, 1H, *J* = 6.3 Hz)], an oxygenated methine [δ_H 4.89 (dd, 1H, *J* = 11.0,

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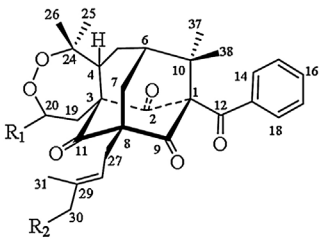
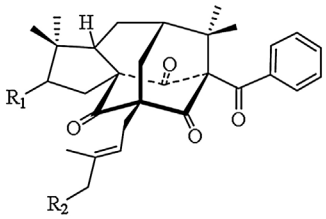
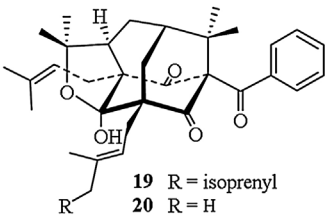


H-4	R_1	R_2
1 β	α-CMe_2OH	isoprenyl
2 α	β-CMe_2OOH	isoprenyl
3 α	β-CMe_2OH	H
4 α	β-CMe_2OH	isoprenyl
5 α	β-CMe_2OOH	H
6 β	α-CMe_2OH	H

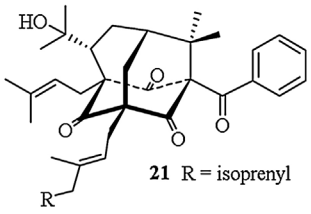


H-7	R_1	R_2
7 α	β-CMe_2OH	isoprenyl
8 α	α-CMe_2OOH	isoprenyl
9 β	H	H
10 β	α-CMe_2OH	isoprenyl
11 β	α-CMe_2OH	H
12 α	α-CMe_2OH	isoprenyl



19 R = isoprenyl
20 R = H

H-7	R_1	R_2
13 β	β-CMe_2OH	isoprenyl
14 β	β-CMe_2OH	H
15 β	H	isoprenyl
16 α	α-CMe_2OH	H
17 α	H	isoprenyl
18 β	α-OH	H



21 R = isoprenyl

Fig. 1. Structures of **1**–**21**.

Table 1
NMR data for compounds **1** and **2**.[a]

No.	Hyperisampsin N (**1**)		Hyperisampsin O (**2**)	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1		82.0		81.9
2		203.8		208.2
3		66.6		66.5
4	2.56 m	41.2	2.79 dd (10.9, 8.0)	42.6
5a	2.06 m	28.9	2.42 ddd (16.3, 11.4, 5.0)	31.4
5b	1.89 m		1.52 m	
6	2.06 m	43.0	2.10 dd (8.9, 4.9)	44.4
7a	2.60 m	36.2	2.59 dd (14.2, 6.3)	41.2
7b	2.06 m		1.88 d (14.2)	
8		69.0		68.5
9		204.5		204.3
10		48.6		50.2
11		207.7		205.1
12		193.2		192.1
13		135.6		134.8
14	7.13 br d (8.1)	128.6	7.16 br d (8.3)	128.8
15	7.28 br t (8.1)	128.3	7.29 br t (7.8)	128.0
16	7.42 br t (7.4)	132.6	7.40 br t (7.4)	132.4
17	7.28 br t (8.1)	128.3	7.29 br t (7.8)	128.0
18	7.13 br d (8.1)	128.6	7.16 br d (8.3)	128.8
19a	3.10 dd (14.7, 11.0)	31.3	3.53 dd (15.0, 11.7)	30.9
19b	1.66 dd (14.7, 4.2)		1.56 dd (15.0, 2.8)	
20	4.89 dd (11.0, 3.9)	88.5	4.93 dd (11.7, 2.8)	85.6
21		73.7		84.2
22	1.27 s	27.2	1.20 s	21.4
23	1.15 s	25.6	1.16 s	20.5
24		88.6		88.5
25	1.19 s	19.5	1.30 s	28.1
26	1.32 s	29.6	1.08 s	17.8
27	2.63 m	29.1	2.62 d (7.0)	29.6
28	5.28 t (7.4)	118.9	5.14 t (7.1)	118.7
29		139.5		139.0
30	2.06 m	40.2	2.00 m	40.0
31	1.67 s	16.5	1.68 s	16.5
32	2.06 m	26.8	2.02 m	26.7
33	5.06 t (6.3)	124.3	5.05 t (6.8)	124.1
34		131.7		131.5
35	1.66 s	25.9	1.65 s	25.7
36	1.59 s	17.9	1.57 s	17.7
37	1.36 s	22.6	1.35 s	22.6
38	1.44 s	25.1	1.49 s	24.9

[a] 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, in $CDCl_3$.

3.9 Hz)], and nine methyl singlets (δ_H 1.67, 1.66, 1.59, 1.44, 1.36, 1.32, 1.27, 1.19, and 1.15). The ^{13}C NMR (Table 1) and DEPT spectra of **1** displayed 38 carbon signals including four carbonyls (δ_C 207.7, 204.5, 203.8, and 193.2), ten olefinic carbons (δ_C 139.5, 135.6, 132.6, 131.7, 128.6, 128.6, 128.3, 128.3, 124.3, and 118.9), and three quaternary carbons and a methine located at the range of 70.0–90.0 ppm. These data showed high degrees of similarity to those of otogirinin B (**4**) [21], which suggested that **1** is also a PPAP with an 1,2-dioxepane functionality.

The planar structure of **1** was determined by extensive analyses of its HMBC and ^{1}H–^{1}H COSY spectra (Fig. 2). ^{1}H–^{1}H COSY correlations of H-4/H-5/H-6/H-7 and HMBC correlations from Me-37 and Me-38 to C-1, C-6, and C-10, from H-7 to C-8, C-9, and C-11, and from H-4 to C-2, C-3, and C-11 established the homoadamantyl framework of **1**. In addition, HMBC interactions from Me-25 and Me-26 to C-4 and C-24 (δ_C 88.6), from Me-22 and Me-23 to C-20 (88.5) and C-21, and from H-19 to C-3 and C-11 together with ^{1}H–^{1}H COSY cross peak between H-19/H-20 indicated the presence of 1,2-dioxepane ring system fused to the homoadamantyl core. Finally, the geranyl group was located at C-8 by HMBC correlations from H-27 to C-8, C-9, and C-11, and the remained benzoyl was located at C-1 in the same manner as those of **4** as considering the chemical shift of C-1 (δ_C 82.0). Consequently, compound **1** shared the same planar structure with **4**.

The relative configuration of **1** was determined by conducting NOESY experiment (Fig. 3). NOESY correlations from H-4 to H-20 and H-7b were observed (H-7b is overlapped with H-30 and H-32, but it is impossible to observe any NOESY correlation between H-4 and H-30 or H-32 for their large distances in molecular modeling), suggesting β-orientations both for H-4 and for H-20. The elucidated structure of **1** including relative configuration were identical to that of **6** [10], excepting the side chain at C-8, and a detailed comparison of their ^{13}C NMR further supported the elucidated structure and relative configuration of **1**.

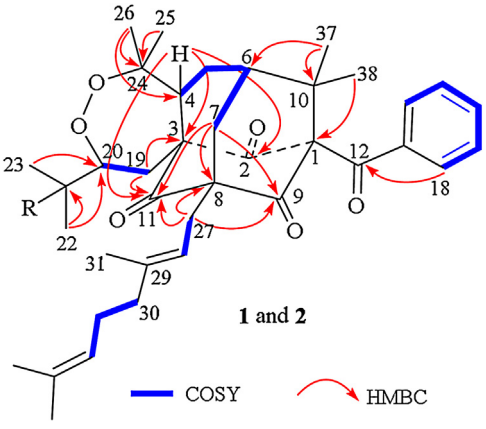


Fig. 2. Key ^{1}H–^{1}H COSY and HMBC correlations of **1** and **2**.

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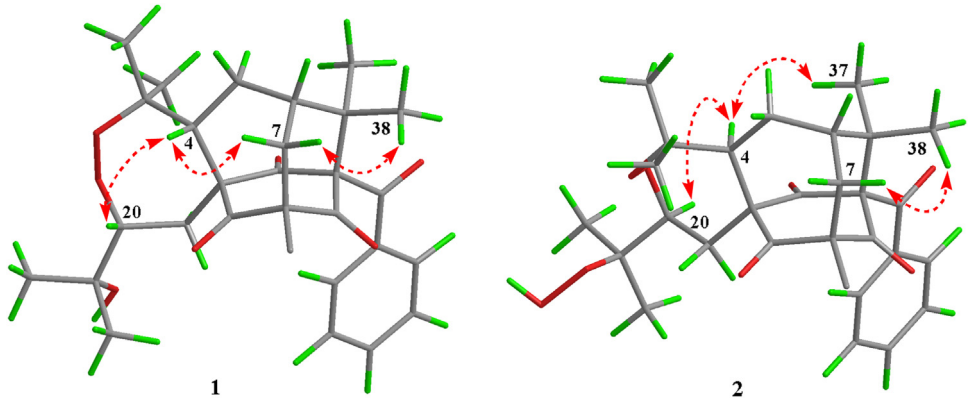

Fig. 3. Key NOESY correlations of **1** and **2**.

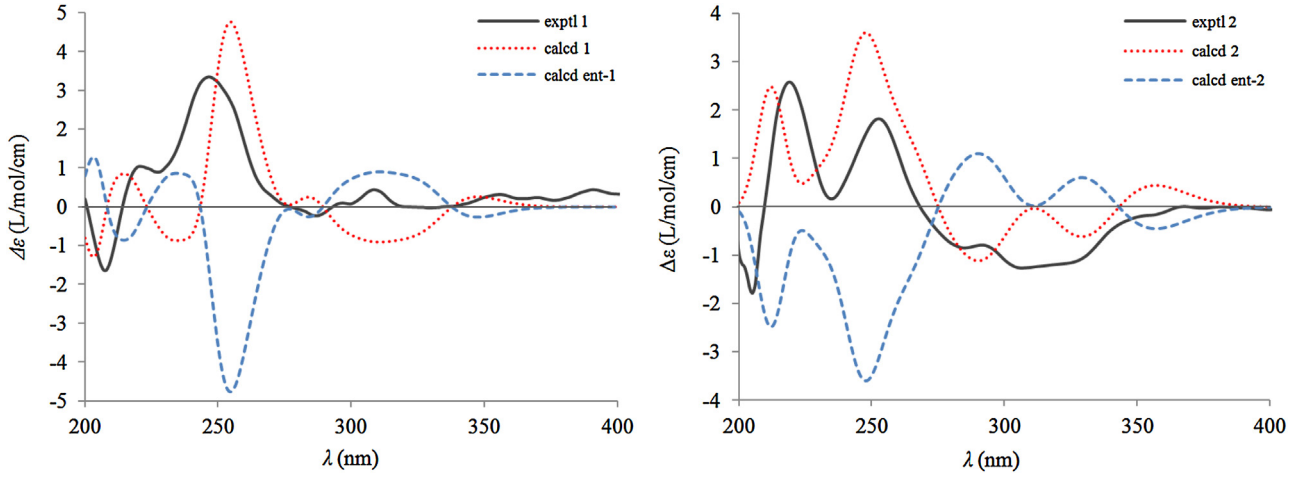

Fig. 4. Calculated and experimental ECD spectra of **1** and **2**.

Hyperisampsin Q (**2**) showed an $[M+Na]^+$ ion at *m*/*z* 657.3383 ($C_{38}H_{50}O_8Na$), which was 16 mass units more as compared with **1** and **4**. Detailed comparison of the NMR data of **2** with those of **4** revealed that **2** possesses a hydroperoxyl group at C-21 (δ_C 84.2), as evidenced by the deshielded chemical shift of C-21. In the NOESY spectrum of **2**, cross-peaks for Me-38/H-7a, Me-37/H-4, and H-4/H-20 implied that both H-4 and H-20 were α-oriented, which were identical with **4**. Further comparison of ^{13}C NMR of **2** and **5** [10] supported the elucidated structure and relative configuration of **2**.

To determine the absolute configurations of compounds **1** and **2**, ECD calculations were performed for both of them. The absolute configurations of **1** and **2** were thus determined as 1*R*,3*R*,4*R*,6*S*,8*S*,20*R* and 1*R*,3*R*,4*S*,6*S*,8*S*,20*S* by comparison of their experimental ECD spectra with the calculated ECD curves (Fig. 4).

Compounds **2**, **7**, and **8** were tested for their cytotoxic activities against five human tumor cell lines, including a myeloid leukemia line (HL-60 cells), a hepatocellular carcinoma line (SMMC-7721), a lung carcinoma line (A-549), a breast cancer line (MCF-7), and a colon cancer line (SW480). *Cis*-platin (DDP) was used as positive control for antitumor activity (Table 2). Among them, compounds **2** and **8** showed moderate cytotoxic activities, with IC_{50} values over a range of 3.83–25.92 μmol/L. Compound **7** was inactive against all the tested cell lines at concentrations as high as 40 μmol/L.

Table 2
Cytotoxic activities of **2**,**7**, and **8** (IC_{50} in μmol/L).

No.	HL-60	SMMC-7721	A-549	MCF-7	SW480	BEAS-2B
2	3.83	11.64	10.22	15.03	19.63	15.08
7	>40	>40	>40	>40	>40	–
8	4.22	13.70	9.41	16.16	25.92	14.42
DDP[a]	1.17	6.43	9.24	15.86	13.42	11.11

"–" not tested.
[a] DDP (*cis*-platin) was used as a positive control.

3. Conclusion

In conclusion, twenty one benzoylated PPAPs with homoadamantyl framework were isolated from *H. sampsonii*, including two new ones. As far as we know, there are only eight examples of PPAPs with a 1,2-dioxepane moiety that fused to the homoadamantyl core structure, and compound **2** represents the fourth example of this compound class possessing two peroxide moieties. Moreover, compounds **2** and **8** exhibit significant cytotoxic activities toward HL-60 cell and moderate activities against others cell lines, which may depend on the hydroperoxyl group as compound **7** showed no cytotoxic activity at concentrations as high as 40 μmol/L.

4. Experimental

4.1. General

Optical rotations were determined with a Perkin-Elmer 341 polarimeter. UV, ECD, and IR spectra were measured using a

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Varian Cary 50, a JASCO-810 spectrometer, and a Bruker Vertex 70, respectively. NMR spectra were recorded on a Bruker AM-400 spectrometer, and the ^{1}H and ^{13}C NMR chemical shifts were referenced to the solvent or solvent impurity peak for $CDCl_3$ (δ_H 7.26 and δ_C 77.0). High-resolution electrospray ionization mass spectra (HRESIMS) were obtained in the positive ion mode with a Thermo Fisher LC-LTQ-Orbitrap XL spectrometer. Semi-preparative HPLC was performed on an Ultimate 3000 pump, an Ultimate 3000 autosampler injector, and an Ultimate 3000 diode array detector (DAD) controlled by Chromeleon software (version 6.80) using a reverse-phase C_{18} column (5 μm, 10 × 250 mm, Welch Ultimate XB-C_{18}). Column chromatography was performed using silica gel (100–200 and 200–300 mesh; Qingdao Marine Chemical Inc., China), ODS (50 μm, Merck, Germany), Sephadex LH-20 (Merck, Germany), and MCI gel (75–150 μm, Merck, Germany). Thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} (Yantai Chemical Industry Research Institute) and RP-C_{18} F_{254} plates (Merck, Germany).

4.2. Plant material

The aerial parts of *H. sampsonii* were collected from the Da-bie Mountain areas of Hubei Province, China, in October 2011, and were identified by associate professor Jianping Wang. A voucher specimen (ID 20111008) has been deposited with the Herbarium of Materia Medica, Faculty of Pharmacy, Tongji Medical College of Huazhong University of Science and Technology, China.

4.3. Extraction and isolation

The air-dried aerial parts of *H. sampsonii* (50 kg) were extracted with 95% EtOH, and the extract was partitioned successively with petroleum ether and $CHCl_3$ against water. The petroleum ether soluble extract (800 g) was separated by chromatography on a silica gel column (5 kg, 20 × 120 cm; petroleum ether to acetone, 100:0 → 0:100) to furnish eight fractions (Fr. 1–Fr. 8). Fr. 3 was further purified by column chromatography (silica gel CC, 1 kg, 10 × 100 cm), eluting with a gradient of petroleum ether in isopropyl alcohol to yield three subfractions (Fr. 3.1–Fr. 3.3). Fr. 3.1 was separated over silica gel (petroleum ether to acetone, 100:1 → 5:1) to obtain ten further fractions (Fr. 3.1.1–Fr. 3.1.10). Fr.3.1.2 was purified over Sephadex LH-20 (MeOH) followed by ODS (MeOH·H_2O, 80%) and finally by semi-preparative HPLC (MeCN-H_2O, 82%) to yield **3** (10 mg). Fr.3.1.4 was also purified over Sephadex LH-20 (MeOH) followed by ODS (MeOH-H_2O, 80%) and finally by semi-preparative TLC (petroleum ether–acetone, 8:1) to obtain **19** (16 mg) and **20** (34 mg). Fr. 3.2 was separated over silica gel (petroleum ether to acetone, 20:1 → 5:1) to obtain six parts (Fr. 3.2.1–Fr. 3.2.6). These parts were subjected to Sephadex LH-20 (MeOH) and ODS (MeOH-H_2O) and were then purified by semi-preparative HPLC. Compounds **9** (2 mg) and **15** (7 mg) were obtained from Fr. 3.2.1, while **13** (8 mg) was obtained from Fr. 3.2.2, **12** (6 mg), **14** (8 mg), and **18** (5 mg) were purified from Fr. 3.2.3, and **4** (38 mg), and **5** (8 mg) were isolated from Fr. 3.2.3. Fr. 4 was applied to ODS (MeOH to H_2O, 50% → 100%) and then to Sephadex LH-20 (MeOH) and repeated silica gel CC to obtain two mixtures (I and II). Mixture I was purified by semi-preparative HPLC (silica gel, hexane–isopropanol, 97:3) to obtain **7** (4 mg) and **1** (2 mg), and mixture II was purified by semi-preparative HPLC (MeCN-H_2O, 50%) to obtain **11** (8 mg), **16** (6 mg), and **6** (25 mg). Fr. 6 was applied to ODS (MeOH to H_2O, 50% → 100%) to obtain six subfractions (Fr. 6.1–Fr. 6.6). Fr. 6.3 was separated with Sephadex LH-20 (MeOH) and ODS (MeOH to H_2O, 60% → 100%) to obtain three mixtures (III–V). Mixture III was purified by semi-preparative HPLC (CH_3CN-H_2O, 88%) to obtain **10** (9 mg), while mixture IV was purified by semi-preparative HPLC (CH_3OH-H_2O, 92%) to yield **21** (5 mg).

The $CHCl_3$ soluble extract (approximately 1 kg) was also separated by chromatography on silica gel (6 kg, 20 × 120 cm; petroleum ether to acetone, 100:0 → 0:100) to furnish six parts (A–F). Fraction B was subjected to silica gel CC and was eluted with petroleum ether to acetone (50:1 → 1:1) to obtain seven subfractions (B.1–B.7). Subfraction B.2 was further subjected to Sephadex LH-20 (MeOH) and then MPLC (ODS, MeOH to H_2O, from 40% to 100%) to obtain six additional subfractions (B.2.1–B.2.6). B.2.1 was further purified by Sephadex LH-20 (MeOH), silica gel CC, and finally by semi-preparative HPLC (CH_3OH-H_2O, 85%) to obtain **8** (30 mg). Similarly, **2** (12 mg) was obtained from B.2.4 (CH_3CN-H_2O, 90%) and **17** (17 mg) was obtained from B.2.6 (CH_3OH-H_2O, 92%).

4.3.1. Hyperisampsin N (*1*)

Colorless oil, $[\alpha]_D^{20}$ −31 (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} (log ε) = 204 (4.34) and 245 (3.88) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 208 (−1.6), 247 (+3.4) nm; IR ν_{max} = 3414, 1736, and 1701 cm^{-1}; for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data see Table 1; HR-ESIMS $[M+Na]^+$ *m/z* 641.3373 (calcd. for $C_{38}H_{50}O_7Na$, 641.3454).

4.3.2. Hyperisampsin O (*2*)

Colorless oil, $[\alpha]_D^{20}$ +12 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε) = 205 (4.06) and 245 (3.64) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 220 (+2.5), 254 (+1.8), 315 (−1.2) nm; IR ν_{max} = 3419, 1734, and 1700 cm^{-1}; for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data see Table 1; HR-ESIMS $[M+Na]^+$ *m/z* 657.3383 (calcd. for $C_{38}H_{50}O_8Na$, 657.3403).

4.4. Computational details

The theoretical calculations of compounds **1** and **2** were performed using Gaussian 09. Conformational analysis was initially performed using Maestro in Schrödinger 2010 conformational searching together with the OPLS_2005 molecular mechanics methods. The optimized conformation geometries and thermodynamic parameters of all conformations were provided. The OPLS_2005 conformers were optimized at the B3LYP/6-31G(d, p) level. The theoretical calculation of ECD was performed using time-dependent density functional theory (TDDFT) at the B3LYP/6-31G(d,p) level in methanol with a PCM model. The calculated ECD curve was generated using SpecDis 1.51. R_{vel} was used in this work.

4.5. Cytotoxic assay

The cytotoxic activities were measured with MTs method as described in our previously literature [7]. Five human cancer cell lines including HL-60, SMMC-7721, A-549, MCF-7, and SW-480, together with a noncancerous cell line (Beas-2B human bronchial epithelial) were tested in the cytotoxic activity assay.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data includes HRESIMS, IR, UV, CD, 1D and 2D NMR spectra, and details for ECD calculations and can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.11.014.

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