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Anti-inflammatory and antiproliferative prenylated carbazole alkaloids from *Clausena vestita*

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ABSTRACT

Twelve prenylated carbazole alkaloids, containing a novel prenylated carbazole alkaloid, named as clausevestine (**1**), and 11 known prenylated carbazole alkaloids (**2–12**), were isolated and identified from the stems and leaves of *Clausena vestita,* which is a Chinese endemic plant. The chemical structure of **1** was established by means of comprehensive spectroscopic data analyses and the known compounds were determined *via* comparing their NMR and MS data as well as optical rotation values with those reported in literature. Especially, clausevestine (**1**) is an unusual prenylated carbazole alkaloid possessing an unprecedented carbon skeleton holding 20 carbon atoms. The anti-inflammatory effects and antiproliferative activities of those isolated prenylated carbazole alkaloids were tested. Prenylated carbazole alkaloids **1–12** displayed remarkable inhibitory effects on NO (nitric oxide) production with IC_{50} values equivalent to that of the positive control (hydrocortisone). Meanwhile, prenylated carbazole alkaloids **1–12** exhibited remarkable antiproliferative activities against diverse human cancer cell lines *in vitro* holding the IC_{50} values ranging from 0.32 ± 0.04 to 18.76 ± 0.18 μM. These findings indicate that these prenylated carbazole alkaloids possessing remarkable anti-inflammatory effects and antiproliferative activities could be meaningful to the discovery of new anti-inflammatory and anti-tumor candidate drugs.

1. Introduction

Cancers are a common and frequently-occurring disease characterized by high incidence and poor prognosis, which is currently the second killer of serious threats to human life and health, only after cardiovascular disease. According to the report published by the World Health Organization, up to 2030, the number of new cases of global cancers will reach 18 million, and the number of death cases from cancers will exceed 12 million. By then, the incidence and mortality of cancers will exceed cardiovascular disease, and cancers will become the No. 1 killer of human life and health. At present, it is generally believed that lots of cancers are caused by inflammation, chronic irritation and infection [1–4]. A large number of studies have confirmed that inflammation is closely related to cancer, moreover inflammation and its carcinogenesis have been extensively studied at the molecular level. These studies have revealed possible mechanisms of action and potential new targets for the treatment and chemoprevention of many different types of cancers [5–7]. Lots of clinical practices have shown that anti-inflammatory treatment is effective for early tumor progression and malignant transformation. Therefore, searching and discovering compounds with remarkable anti-inflammatory effects and anti-tumor activities from natural products is of great significance for the research and development of new anti-tumor drugs.

The genus *Clausena* belonging to the Rutaceae family contains approximately 30 species, found in Asia, Africa and Oceania. Among them, 10 species and 2 variety are distributed throughout southern China, with the largest variety in Yunnan, Guangxi and Guangdong Province [8]. Up to now, a series of structurally interesting compounds such as alkaloids, limonoids, diterpenes, coumarins and glycosides have been isolated and identified from the genus *Clausena*, which displayed extensive biological activity such as anti-tumor, anti-inflammatory, neuroprotective, anti-fungal, anti-obesity, anti-microbial, hepatoprotective, hypoglycemic as well as nematicidal activities [9–21]. *Clausena vestita* is a Chinese endemic plant, only growing in Yunnan Province. So far, there is only a initial investigation on the chemical constituents and biological activities of *C. vestita* [22,23]. Our preliminary findings

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indicated that the ethanol extract of the stems and leaves of *C. vestita* collected from Yunnan Province of China displayed remarkable inhibitory effect on NO production possessed the IC_{50} value of 6.18 ± 0.21 μg/mL as well as antiproliferative activities with the IC_{50} values ranging from 3.63 ± 0.12 to 22.97 ± 0.22 in vitro. In continuation of our ongoing research into natural products of structural diversity and biological diversity from tropical medicinal plants [24–29], a systematic phytochemical study on the stems and leaves of *C. vestita* was therefore implemented and had resulted in the isolation of 12 prenylated carbazole alkaloids, containing a novel prenylated carbazole alkaloid, clausevestine (**1**), along with 11 known prenylated carbazole alkaloids (**2**–**12**). The chemical structure of **1** was established on by means of comprehensive spectroscopic data analyses and the known compounds were determined *via* comparing their NMR and MS data with those reported in literature. Especially, clausevestine (**1**) is an unusual prenylated carbazole alkaloid possessing an unprecedented carbon skeleton holding 20 carbon atoms. Furthermore, the anti-inflammatory effects and antiproliferative activities of those isolated prenylated carbazole alkaloids were tested. As a result, prenylated carbazole alkaloids **1**–**12** displayed remarkable inhibitory effects on NO production with IC_{50} values equivalent to that of the positive control (hydrocortisone). Meanwhile, prenylated carbazole alkaloids **1**–**12** exhibited remarkable antiproliferative activities against diverse human cancer cell lines *in vitro* holding IC_{50} values ranging from 0.32 ± 0.04 to 18.76 ± 0.18 μM. In this paper, we reports on the isolation and structure characterization of the novel prenylated carbazole alkaloid, clausevestine (**1**), together with the anti-inflammatory effects and antiproliferative activities of these isolated prenylated carbazole alkaloids.

2. Experimental

2.1. General experiment procedure

Optical rotations were measured with a JASCO P-1020 digital polarimeter. UV spectra were recorded on a Beckman DU 640 spectrophotometer. IR spectra were recorded on a Nicolet Nexus 470 spectrophotometer in KBr discs. NMR spectra were recorded on Bruker 400 MHz spectrometers using TMS as an internal standard, with chemical shifts recorded as δ values. HR-ESI-MS spectra were measured on a Micromass Q-TOF Ultima Global GAA076 LC mass spectrometer. Semi-preparative HPLC was performed on an Agilent 1260 LC series with a DAD detector using an Agilent Eclipse XDB-C_{18} column (250 × 9.4 mm, 5 μm). Silica gel (300–400 mesh, Qingdao Marine Chemical Inc., China), Lichroprep RP-18 gel (40–63 μm, Merck, Darmstadt, Germany) and Sephadex LH-20 gel (40–70 μm, Amersham Biosciences, Sweden) were used for column chromatography.

2.2. Plant material

The stems and leaves of *C. vestita* were collected from Lijiang City, Yunnan Province, China, in April 2016, and authenticated by one of the authors, Professor Yan-Hui Fu, Hainan Normal University. A voucher specimen (No. CLVE20160408) has been deposited at the Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education, Hainan Normal University.

2.3. Extraction and isolation

The air-dried stems and leaves of *C. vestita* (28.8 Kg) were powdered and extracted by solvent cold soak extraction for five times (each for 7 days) with 90% ethanol (50.0 L) at room temperature. The ethanol extraction solution were evaporated under reduced pressure to give a crude extract (2506.8 g), which were suspended in water (15.0 L) and then partitioned with petroleum ether for six times (each for 15.0 L) and ethyl acetatefor six times (each for 15.0 L) successively to yield the petroleum ether extract (971.2 g) and the ethyl acetate extract (536.6 g). The ethyl acetate extract (535.0 g) was subjected to silica gel column chromatography, eluted with $CHCl_3$/acetone (100:0 to 50:50, *v/v*) to afford 12 fractions (Fr. 1 − Fr. 12). Fr. 3 (36.2 g) was further subjected to a RP-18 gel medium-pressure column chromatography (CH_3OH/H_2O, 40:60 to 100:0, *v/v*) to give 10 fractions (Fr. 3A–Fr. 3 J). Compounds **1** (6.8 mg), **5** (10.7 mg), **6** (67.2 mg), **9** (41.3 mg) and **11** (9.3 mg) were obtained from Fr. 3B (1.7 g) *via* being purified using Sephadex LH-20 gel column chromatography and prepared by semi-preparative HPLC. Fr. 3C (1.5 g) was purified *via* Sephadex LH-20 gel column chromatography and prepared using semi-preparative HPLC to afford **2** (7.2 mg), **7** (6.6 mg) and **12** (108.9 mg). Compounds **3** (8.6 mg), **4** (27.9 mg), **8** (63.1 mg) and **10** (78.3 mg) were gotten from Fr. 3B (1.7 g) *via* being purified by Sephadex LH-20 gel column chromatography and prepared using semi-preparative HPLC.

2.4. Clausevestine (1)

White amorphous powder; mp 218.6–219.8 °C; $[\alpha]_D^{25}$ +26.8 (c 0.12, MeOH); IR (KBr) ν_{max} 3482, 2972, 2848, 1769, 1758, 1619, 1506, 1468, 1382, 1239, 1167, 1067 and 798 cm^{-1}; UV (MeOH) λ_{max} (log ε) 233 (4.72), 288 (4.19), 302 (3.99) and 342 (3.58) nm; ^1H and ^{13}C NMR data (see Table 1); ESI-MS *m/z* 424 $[M+Na]^+$; HR-ESI-MS *m/z* 424.1372 $[M+Na]^+$ (calcd for $C_{21}H_{23}NNaO_7$, 424.1367).

2.5. Anti-inflammatory activity bioassays

The anti-inflammatory effects of all isolated prenylated carbazole alkaloids (**1**–**12**) were tested *via* examining the inhibitory effect on NO (nitric oxide) production induced by lipopolysaccharide in mouse macrophage RAW 264.7 cells in vitro, with hydrocortisone as the positive control, according to the protocol described previously [29].

2.6. Antiproliferative activity bioassays

The antiproliferative activities of all isolated prenylated carbazole alkaloids (**1**–**12**) were tested against five human tumor cell lines, namely HL-60, SMMC-7721, A-549, MCF-7 and SW480 using the MTT method, with cisplatin as the positive control, according to the protocol described previously [26].

Table 1
^1H and ^{13}C NMR data of clausevestine (**1**) in DMSO-d_6.

Position	δ_H[a]	δ_C[b]
1		149.6 s
2	6.51 (1H, s)	131.6 d
3		123.9 s
4		147.3 s
5	7.83 (1H, d, *J* = 8.6 Hz)	119.6 d
6	7.10 (1H, d, *J* = 8.6 Hz)	110.8 d
7		155.7 s
8		114.0 s
4a		115.8 s
5a		118.6 s
8a		139.7 s
9a		136.2 s
1′*α*	3.14 (1H, d, *J* = 13.2 Hz)	27.1 t
1′*β*	2.81 (1H, dd, *J* = 13.2, 10.4 Hz)	
2′	3.36 (1H, d, *J* = 10.4 Hz)	78.1 d
3′		72.1 s
4′	1.17 (3H, s)	26.2 q
5′	1.16 (3H, s)	25.2 q
3-CH_3	2.03 (3H, s)	15.5 q
1-COOH		183.1 s
4-COOH		179.9 s
7-OCH_3	3.83 (3H, s)	56.6 q

[a] Measured at 400 MHz.
[b] Measured at 100 MHz.

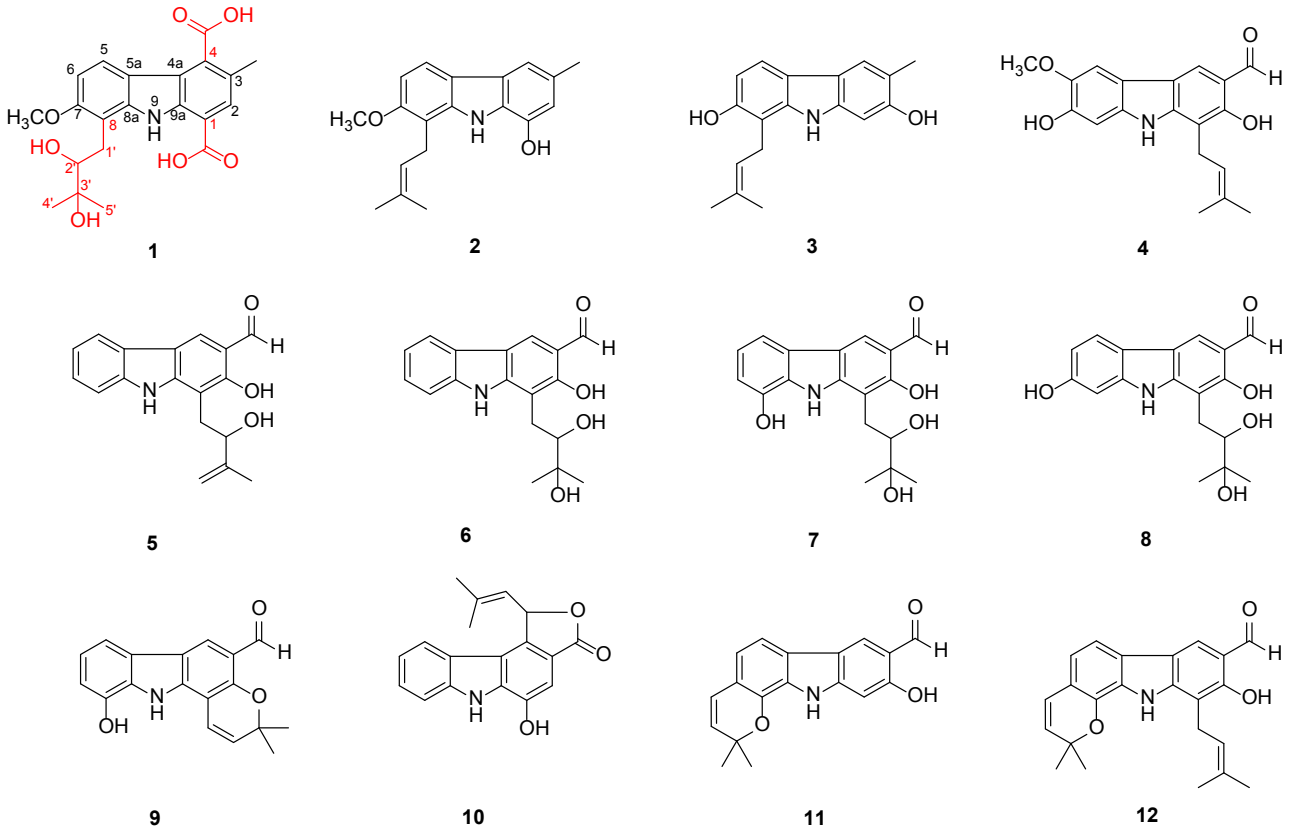

Fig. 1. Chemical structures of compounds **1–12** isolated from the stems and leaves of *C. vestita*.

3. Results and discussion

Clausevestine (**1**) was isolated as a white amorphous powder holding a specific rotation of $[\alpha]_D^{25}$ +26.8 (c 0.12, CH_3OH). The molecular formula of **1** was established as $C_{21}H_{23}NO_7$ based on its HR-ESI-MS (*m/z* 424.1372 $[M+Na]^+$, calcd 424.1367), with 11 degrees of unsaturation. The IR spectrum of **1** implied the presence of hydroxyl group (3482 cm^{-1}), carboxyl group (1769 and 1753 cm^{-1}) as well as double bond groups (1619, 1506 and 1468 cm^{-1}). The UV absorption bands in the UV spectrum of **1** at 233, 288, 302 and 342 nm were the characteristic absorption bands of carbazole alkaloid [16,17,27]. The ^{13}C NMR data combined with DEPT data suggested the presence of 21 carbon signals, which were classified into 14 sp^2 carbon atoms, four methyls, one sp^3 methylene, one sp^3 methine together with one sp^3 quaternary carbon. Moreover, the 14 sp^2 carbon atoms along with 11 degrees of unsaturation were assigned to one carbazole ring group together with two carboxyl groups. All the above data suggested that the chemical structure of **1** was similar to that of murrayafoline B (**2**) [30]. Further comparisons of ^1H NMR, ^{13}C NMR as well as DEPT data of **1** with those of murrayafoline B (**2**) suggested that there were three major differences between their structures. First of all, the hydroxyl group located at C-1 in murrayafoline B (**2**) was replaced by a carboxyl group in **1**, which was supported by the presence of the carboxyl carbon resonating at δ_C 183.1, the HMBC correlations of H-2 to C-1 (δ_C 149.6), C-3 (δ_C 123.9), C-4 (δ_C 147.3), C-9a (δ_C 136.2), the carboxyl carbon resonating at δ_C 183.1 and the methyl carbon resonating at δ_C 15.5. Secondly, the hydrogen atom located at C-4 in murrayafoline B (**2**) was substituted by one carboxyl group in **1**, which was supported by the HMBC correlations of the methyl hydrogens resonating at δ_H 2.03 (3H, s) to C-2 (δ_C 131.6), C-3, C-4 and the carboxyl carbon resonating at δ_C 179.9. Finally, the 3-methylbut-2-ene group located at C-8 in murrayafoline B (**2**) was replaced by a 3-methylbutane-2,3-diol group in **1**, supported by the HMBC correlations of H-1′*α*, H-1′*β*, H_3-4′ and H_3-5′ to C-2′ (δ_C 78.1) and C-3′ (δ_C 72.1), H-1′*α* and H-1′*β* to C-7 (δ_C 155.7), C-8 (δ_C 114.0) and C-8a (δ_C 139.7), H-2′ to C-8, as well as the ROESY correlation of the methoxy hydrogens resonating at δ_H 3.83 (3H, s) with H-1′*α* and H-1′*β*. The planar structure of **1** was further established by the HSQC, HMBC, ^1H-^1H COSY and ROESY spectra as shown in Fig. 2. Unfortunately, the absolute configuration of C-2′ cannot be assigned by the available data. Accordingly, the chemical structure of **1** was elucidated as depicted in Fig. 1.

With the exception of the novel prenylated carbazole alkaloid, clausevestine (**1**), 11 known prenylated carbazole alkaloids were isolated and identified as murrayafoline B (**2**) [30], euchrestine A (**3**) [31], claulansine H (**4**) [32], clausine S (**5**) [33], harmandianamine C (**6**) [34], clauszoline D (**7**) [35], clausine U (**8**) [33], clauszoline G (**9**) [36], harmandianamine A (**10**) [34], clauszoline B (**11**) [35] and clauszoline A (**12**) [35], by comparing their experimental and reported spectral data.

All isolated prenylated carbazole alkaloids were tested their anti-inflammatory effects by means of examining the inhibitory effects on NO production. As a consequence, prenylated carbazole alkaloids **1–12** manifested remarkable inhibitory effects holding the IC_{50} values in range of 0.63 ± 0.06 to 8.75 ± 0.14 μM, which was equivalent to that of hydrocortisone (as shown in Table 2). No cytotoxicity was detected in the macrophage RAW 264.7 cells treated by those tested prenylated carbazole alkaloids (cell viability > 90%). Further investigations on the structure-activity relationships and the mechanisms of action for these isolated prenylated carbazole alkaloids with significant anti-inflammatory activities are needed.

In additon, the antiproliferative activities of all isolated prenylated carbazole alkaloids were evaluated for against five human cancer cell lines, HL-60, SMMC-7721, A-549, MCF-7 and SW480 by means of the MTT method. Cisplatin was used as a positive control in this assay. It is worth mentioning that all isolated prenylated carbazole alkaloids (**1–12**) exhibited remarkable inhibitory activities against a variety of

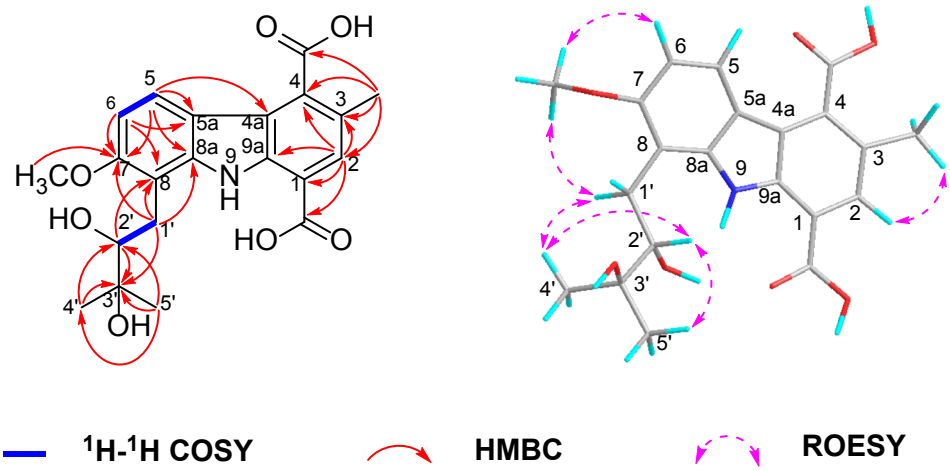

Fig. 2. Selected 2D NMR correlations for clausevestine (**1**).

Table 2
Anti-inflammatory activities of compounds **1–12**.

Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]
1	0.63 ± 0.06	**7**	8.34 ± 0.16
2	2.03 ± 0.09	**8**	3.27 ± 0.09
3	1.29 ± 0.07	**9**	8.75 ± 0.14
4	6.23 ± 0.13	**10**	1.09 ± 0.07
5	5.27 ± 0.15	**11**	4.21 ± 0.11
6	0.98 ± 0.05	**12**	3.02 ± 0.06
Hydrocortisone[b]	3.89 ± 0.13		

[a] IC_{50} value was defined as 50% inhibitory concentration on NO production induced by lipopolysaccharide in mouse macrophage RAW 264.7 cells *in vitro* and expressed as the mean ± SD of triplicate determinations.
[b] Positive control.

human cancer cell lines with the IC_{50} values in the range of 0.32 ± 0.04 to 18.76 ± 0.18 μM (as shown in Table 3), equivalent to cisplatin, even more significant antiproliferative effects than cisplatin in most human cancer cell lines. Detailed antiproliferative activity data analyses and preliminary structure-activity relationship studies suggest that each isolated compound possesses remarkable antiproliferative activities and exhibits its own unique selective effects against each human cancer cell lines. Therefore, further investigations on their inhibitory effects against more human cancer cell lines and their mechanisms of action for their antiproliferative activities are necessary and extremely valuable.

4. Conclusions

In our current study, the phytochemical investigation on the stems and leaves of *C. vestita* was performed and had resulted in the isolation and identification of 12 prenylated carbazole alkaloids including a novel prenylated carbazole alkaloid, clausevestine (**1**), along with 11 known prenylated carbazole alkaloids (**2–12**). Especially, clausevestine (**1**) is an unusual prenylated carbazole alkaloid with an unprecedented carbon skeleton holding 20 carbon atoms. Moreover, the anti-inflammatory effects and antiproliferative activities of all isolated prenylated carbazole alkaloids were also tested, and confirmed to be very powerful. These findings indicate that these prenylated carbazole alkaloids possessing remarkable anti-inflammatory effects and antiproliferative activities could be meaningful to the discovery of new anti-inflammatory and anti-tumor candidate drugs.

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Table 3
Antiproliferative activities of compounds **1–12**[a] (IC_{50}[b], μM).

Compound	HL-60	SMMC-7721	A-549	MCF-7	SW480
1	0.89 ± 0.06	2.17 ± 0.09	0.32 ± 0.04	1.68 ± 0.09	3.86 ± 0.12
2	1.56 ± 0.10	2.98 ± 0.16	3.95 ± 0.13	0.72 ± 0.05	3.29 ± 0.15
3	2.91 ± 0.09	1.45 ± 0.07	0.89 ± 0.06	5.38 ± 0.11	6.46 ± 0.18
4	2.46 ± 0.08	1.89 ± 0.10	8.64 ± 0.15	4.86 ± 0.13	1.57 ± 0.08
5	1.63 ± 0.07	7.43 ± 0.17	2.15 ± 0.09	5.28 ± 0.11	1.36 ± 0.07
6	4.75 ± 0.14	2.67 ± 0.09	1.73 ± 0.12	6.42 ± 0.16	12.75 ± 0.21
7	1.68 ± 0.06	3.86 ± 0.07	2.27 ± 0.11	0.98 ± 0.06	7.39 ± 0.12
8	2.48 ± 0.13	8.37 ± 0.15	9.35 ± 0.16	18.76 ± 0.18	1.57 ± 0.10
9	1.62 ± 0.08	7.53 ± 0.13	12.67 ± 0.14	15.39 ± 0.12	4.76 ± 0.08
10	2.86 ± 0.07	5.39 ± 0.11	1.64 ± 0.09	6.35 ± 0.09	1.68 ± 0.07
11	3.28 ± 0.11	9.42 ± 0.15	1.38 ± 0.06	13.76 ± 0.11	15.37 ± 0.12
12	1.36 ± 0.06	4.28 ± 0.12	14.59 ± 0.16	6.42 ± 0.12	2.03 ± 0.11
Cisplatin[c]	1.45 ± 0.08	10.96 ± 0.12	16.03 ± 0.13	19.89 ± 0.16	25.16 ± 0.15

[a] All results are expressed as mean + SD; n = 3 for all groups.
[b] IC_{50}: 50% inhibitory concentration.
[c] Positive control.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103107.

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