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Hypoestenonols A and B, new fusicoccane diterpenes from *Hypoestes forskalei*

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ABSTRACT

Two new fusicoccane diterpenes hypoestenonols A (**1**) and B (**2**), along with two known compounds verticillarone (**3**) and hypoestenone (**4**) were isolated from the *n*-hexane fraction of the methanolic extract of the aerial parts of *Hypoestes forskalei* (Acanthaceae) growing in Saudi Arabia. The structures were established by UV, IR, HRESIMS, 1D (^{1}H and ^{13}C NMR) and 2D (^{1}H–^{1}H COSY, HSQC, HMBC, and NOESY) NMR experiments, in addition to comparison with literature data. The total MeOH extract and isolated compounds were tested for their antiprotozoal and cytotoxic activities. The MeOH extract showed moderate activity against *Plasmodium falciparum*, *Leishmania infantum*, *Trypanosoma cruzi*, and *Trypanosoma brucei* with IC_{50} values of 8.8, 8.1, 9.1 and 8.1 μg/mL without cytotoxicity (IC_{50} >64 μg/mL on MRC_5 cells). A very weak *in vitro* antiplasmodial effect was observed for hypoestenonol A (1) (IC_{50} 18.9 μM), verticillarone (3) (IC_{50} 25.1 μM), and hypoestenone (4) (IC_{50} 16.7 μM).

1. Introduction

The family Acanthaceae includes about 346 genera and around 4300 species distributed in the Mediterranean, Australia, Central America, Brazil, Africa and Indo-Malaysia (El-Shanawany et al., 2012). Several species are medicinally useful and others are economically important as ornamentals since they have large flowers with colorful petals, which are considered as a source of natural dyes (El-Shanawany et al., 2012; Chopra, 1973). Species of the genus *Hypoestes* are used for chest and heart diseases, gonorrhea, cancer, liver protection and as antipyretic and antiphlogistic (Shen et al., 2004; Al-Rehaily et al., 2002; Muhammad et al., 1997). Various biological properties have been attributed, including antiplasmodial, antifungal, antileishmanial, antitrypanosomal and cytotoxic properties (Mothana et al., 2012; Almehdar et al., 2012; Ojo-Amaize et al., 2007; Shen et al., 2004; Rasoamiaranjanahary et al., 2003; Pettit et al., 1984). *Hypoestes forskalei* Vahl. Roem. & Schult. (Acantheceae) is a perennial bushy and leafy herb which is widely distributed throughout the southern region of Saudi Arabia (Muhammad et al., 1997). It is used as piscicidal for fishing by fish farmers in Cross River State of Nigeria (Ubaha et al., 2012). Previous phytochemical studies of *H. forskalei* identified fusicoccane tricyclic diterpenes (Muhammad et al., 1998, 1997). As part of an ongoing search for novel bioactive compounds, further investigation of the aerial parts of *H. forskalei* identified two new fusicoccane diterpenes hypoestenonols A (**1**) and B (**2**), along with two known compounds verticillarone (**3**) and hypoestenone (**4**) (Fig. 1). The antiprotozoal activity against *Plasmodium falciparum*, *Leishmania infantum*, *Trypanosoma cruzi*, and *Trypanosoma brucei* and cytotoxicity on MRC_5 cells of the total MeOH extract and the isolated compounds were evaluated.

2. Results and discussion

Compound **1** was obtained as colorless needles. It showed a pseudo-molecular ion peak at *m*/*z* 361.2312 $[M+H]^+$ in HRESIMS

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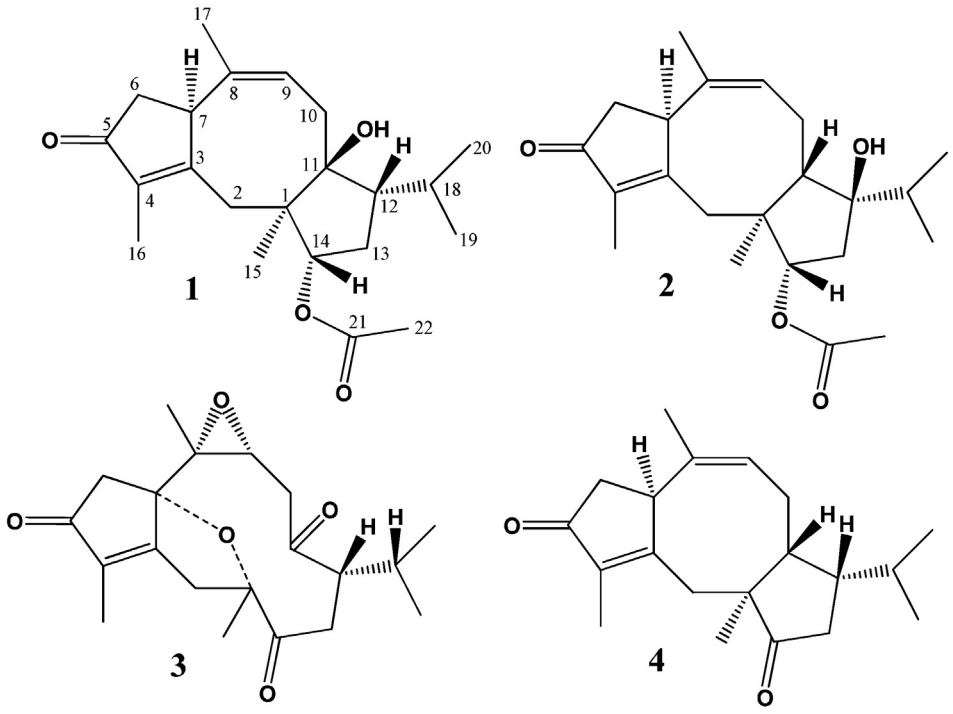

Fig. 1. Structures of the isolated compounds **1**–**4**.

compatible with the molecular formula $C_{22}H_{32}O_4$, requiring seven degrees of unsaturation. The IR spectrum showed characteristic absorption bands at 3435 (hydroxyl group), 1725 (ester group), and 1710 (α,β-unsaturated ketone) cm^{-1}. Its fusicoccane carbon skeleton was suggested on the basis of its ^1H and ^{13}C NMR spectral data (Muhammad et al., 1998, 1997; Adesomojou and Okogun, 1984; Adesomojou et al., 1983) (Table 1). The ^{13}C NMR and HMQC revealed the presence of 22 carbon resonances including six methyls, four methylenes, five methines, and seven quaternary carbons, two of them for ketonic (209.5, C-5) and ester (171.1, C-21) carbonyl groups. The ^1H NMR spectrum (Table 1) showed an olefinic proton signal at δ_H 5.70 (t, J = 7.6 Hz, H-9) which showed a cross peak with the carbon resonated at δ_C 129.0 in HMQC, indicating the presence of tri-substituted double bond. The olefinic double bond was positioned at C_8–C_9 based on the HMBC correlations of H-9 to C-7, C-10, C-11, and C-17 and H-7 and

Table 1
NMR spectral data of compounds **1** and **2** (600 and 150 MHz).

No.	**1**[a]				**2**[b]			
	δ_H [mult., J (Hz)]	δ_C (mult.)	^1H–^1H COSY	HMBC	δ_H [mult., J (Hz)]	δ_C (mult.)	^1H–^1H COSY	HMBC
1	–	47.0 C	–	–	–	47.9 C	–	–
2	2.58 d (14.5) 1.81 d (14.5)	37.6 CH_2	–	3, 7, 11	2.61 m	38.1 CH_2	–	3, 4, 11
3	–	173.5 C	–	–	–	175.5 C	–	–
4	–	138.1 C	–	–	–	139.4 C	–	–
5	–	209.5 C	–	–	–	211.8 C	–	–
6	2.48 brd (13.5) 2.03 brd (13.5)	37.1 CH_2	7	3, 5, 8	2.71 brd (13.8) 2.47 brd (13.8)	33.7 CH_2	7	3, 4, 7, 8
7	3.92 brs	42.7 CH	6	1, 3, 8, 9	3.98 brs	43.7 CH	–	3, 6, 9
8	–	134.7 C	–	–	–	138.4 C	–	–
9	5.70 t (7.6)	129.0 CH	10	3, 7, 10, 11, 17	5.64 t (7.8)	125.4 CH	10	7, 11, 17
10	2.52 dd (14.5, 7.6) 2.46 dd (14.5, 7.6)	22.1 CH_2	9	8, 9, 11	3.01 ddd (13.8, 8.5, 7.8) 2.01 ddd (13.8, 11.5, 7.8)	24.8 CH_2	9, 11	1, 8, 9, 12
11	–	82.0 C	–	–	1.61 dd (11.5, 8.5)	44.9 CH	10	2, 12, 18
12	1.99 m	35.2 CH	13, 18	9, 10, 11, 14	–	76.2 C	–	–
13	2.85 m 2.05 m	39.0 CH_2	14	1, 11, 14	2.37 dd (14.5, 9.8) 1.65 m	28.6 CH_2	14	1, 2, 11, 12, 18
14	5.00 dd (10.5, 5.5)	78.6 CH	13	12, 13, 15, 21	4.63 t (9.8)	78.3 CH	13	12, 15, 21
15	0.90 s	15.5 CH_3	–	2, 11, 13, 14	1.02 s	14.9 CH_3	–	2, 11, 13, 14
16	1.69 s	8.7 CH_3	–	3, 4, 5	1.70 s	8.6 CH_3	–	3, 4, 5
17	1.51 s	18.6 CH_3	–	7, 8, 9	1.61 s	18.8 CH_3	–	7, 8, 9
18	1.26 m	29.7 CH	12, 19, 20	11, 13, 19, 20	1.79	29.8 CH	19, 20	12, 13, 19, 20
19	0.98 d (6.8)	19.9 CH_3	18	12, 18, 20	1.02 d (6.6)	18.7 CH_3	18	12, 18, 20
20	1.07 d (6.8)	18.1 CH_3	18	12, 19	1.11 d (6.6)	18.9 CH_3	18	12, 18, 19
21	–	171.1 C	–	–	–	172.6 C	–	–
22	2.11 s	21.1 CH_3	–	21	2.09 s	20.9 CH_3	–	21

[a] NMR spectra were measured in $CDCl_3$.
[b] NMR spectra were measured in CD_3OD.