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New angucycline antibiotic produced by *Streptomyces* sp.1B1, a commensal microbe of *Maytenus hookeri* Loes.

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Abstract: A compound from the fermentation extracts of the commensal microbe(*Streptomyces* sp.1B1) of *Maytenus hookeri* was elucidated as a new angucycline antibiotic on the basis of 1D-NMR, 2D-NMR and HREIMS techniques.

Key words: medicinal chemistry; structure identification; NMR; HREIMS; *Streptomyces* sp. 1B1; *Maytenus hookeri*; angucycline antibiotic

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The strain 1B1, isolated from the fresh stem barks of *Maytenus hookeri*, was identified as *Streptomyces* sp. on the genus level. Investigation on the secondary metabolites of this strain led to the isolation of a new angucycline antibiotic, compound **1**, from the crude extracts of the solid state fermentation by column chromatography and was identified based on its NMR and HREIMS.

Compound **1**, $[\alpha]_D^{20}$ - 51.5(c 3.4, MeOH), was determined to have the molecular formula $C_{19}H_{18}O_7$ based on the HREIMS peak at *m/z* 358.1056(calcd: 358.1053), and showed the presence of the carbonyl group(1678 cm^{-1}) and aromatic residue(1638 cm^{-1}) in the IR spectrum. Inspection of the NMR data(^1H, ^{13}C, DEPT, HMQC and HMBC)(Table 1) revealed **1** as an angucycline antibiotic[1]. The ^1H-NMR spectra of **1** indicated a tertiary alkyl methyl singlet at δ 1.78(s), and the ^{13}C-NMR and DEPT spectra showed nineteen carbon signals of one methyl, three methylene, four methine, and eleven quaternary carbon atoms. The ^1H- and ^{13}C-NMR resonances of **1** were assigned by HMQC and HMBC experiments. The protons of the two methylenes at δ_C 30.2(δ_H 2.08/2.21) and 33.8(δ_H 2.60/2.81) that were assigned to H-9 and H-10, respectively, on the basis of HMBC experiment and exhibited correlation peaks in the ^1H-^1H COSY spectrum, revealing that they were on vicinal carbons and establishing a tetrahydro-*p*-benzoquinone moiety(fragment **1a**, C-8-11, C-7a and C-11a). The HMBC correlations of the *cis*-double bond(C-5/C-6) protons with corresponding carbons can establish a nine-carbon residue composed of C-4-7, C-4a, C-6a, C-12, C-12a and C-12b(fragment **1b**). The AB system at δ_H 2.26(d, J = 16.8 Hz) and 2.43(d, J = 16.8 Hz) attributed to another methylene(C-4, δ_C 43.3) showed ^1H-^{13}C long-range correlations with the carbons at δ 23.2(C-13), 76.4(C-12b), 76.8(C-4a), 123.6(C-2) and 156.8(C-3), adding three more carbons(C-2, C-3 and C-13) to the above nine-carbon residue.

Additionally, the hydroxyl proton at δ 6.11

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(HO-12b) showed HMBC correlations with carbons at δ 76.4(C-12b), 122.5(C-12a) and 198.9(C-1). Therefore, the fragment **1c** was identified. The extraordinary downfield shift of C-3 contributed to the conjugation between the C-1 carbonyl and the C-2/C-3 double bond, further supporting the assignment of δ 156.8. The HMBC correlations of the hydroxyl protons at δ 9.19(HO-7) and 12.62 (HO-12) with the carbons allowed the linkage of the tetrahydrobenzoquinone moiety with the eastern residue(fragment **1c**) via carbon-carbon bonds, revealing the plane structure of **1**.

Table 1 The NMR data on compound 1①

No.	^{13}C	^{1}H②	HMBC
1	198.9	/	/
2	123.6	6.00(s)	C-4, C-12b, C-13
3	156.8	/	/
4	43.3	2.26(d, 16.8), 2.43(d, 16.8)	C-2, C-3, C-4a, c-12b, C-13
4a	76.8	/	/
5	139.8	6.11(d, 10.0)	C-4, C-4a, C-6, C-12b
6	120.5	6.81(d, 10.0)	C-4, C-4a, C-6a, C-7, C-12, C-12a
6a	130.6	/	/
7	143.1	/	/
7a	131.3	/	/
8	63.1	5.13(br s)	C-7, C-7a, C-10, C-11a
9	30.2	2.08(m), 2.21(m)	C-7a, C-8, C-10, C-11
10	33.8	2.60(m), 2.81(m)	C-8, C-9, C-11, C-11a
11	204.8	/	/
11a	114.4	/	/
12	152.2	/	/
12a	122.5	/	/
12b	76.4	/	/
13	23.2	1.78(s, 3H)	C-2, C-3, C-4
OH-4a	/	5.24(br s)	C-4, C-4a, C-12b
OH-7	/	9.19(br s)	C-6a, C-7, C-7a
OH-12	/	12.62(br s)	C-11a, C-12, C-12a
OH-12b	/	6.11(br s)	C-1, C-12a, C-12b

①^{1}H-NMR, ^{13}C-NMR and HMBC spectra were measured at 400 MHz, 100 MHz and 500 MHz, and recorded in DMSO-d_6 at room temperature, respectively.

②Coupling constants are presented in Hertz. Unless otherwise indicated, all the proton signals integrate to 1H.

The chemical shift of the hydroxyl proton at C-12 is similar to that at the C-5 of flavonoids, and that at the C-7 of **1** is similar to that at the C-3 of flavonols endowed by the intermolecular hydrogen bonds (Fig. 1), illustrating difference between the chemical shifts of the two carbonyls (C-1 and C-11). The proton signals for C-4a and C-12b hydroxyl groups were observed due to the formation of intermolecular hydrogen bonds as well (Fig. 1), therefore, the *cis*-orientation of OH-4a and OH-12b was determined. However, the absolute configuration of **1** has not been resolved yet.

Angucycline antibiotics are a group of bioactive natural products having evident structure diversities[2]. Their structures varied in the substitutions of rings-A, -B and -C. However, among those reported angucyclines, ring-D had the least change. Compound **1** was the first one with the ring-D in a reduced-form.

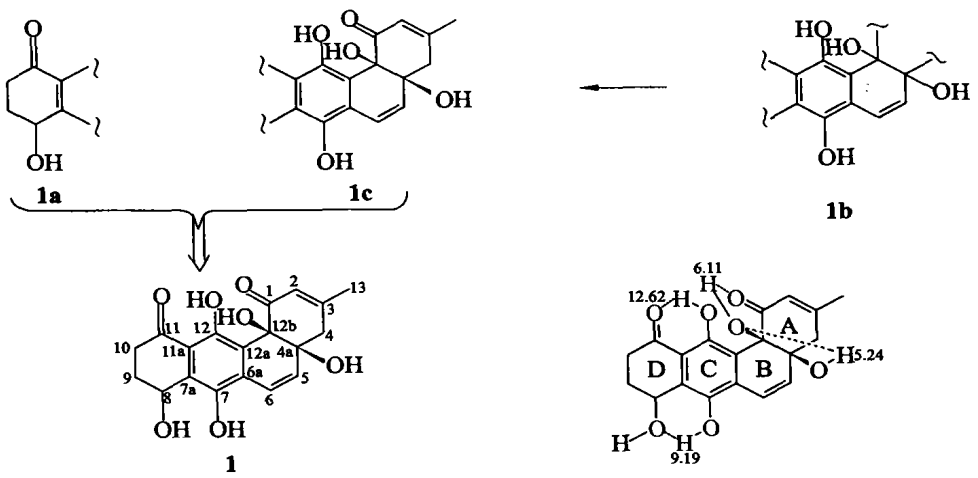

Fig.1 The structure of compound 1 and the putative intermolecular hydrogen bond(H—H)

Antimicrobial activities of **1** against some pathogens, including bacteria and fungi were analyzed by the conventional paper-disk assay method[3] at the concentration of 10 mg/mL. Compound **1** showed growth inhibitory activity against *Staphylococcus aureus*, *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* with the minimal inhibitory amount 100 μg/disc, 50 μg/disc and 100 g/disc, respectively. No inhibitory activity was observed against *Penicillium avellanceum* UC-4376.

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云南美登木共生放线菌菌株 1B1 产生的一个新的 angucycline 抗生素

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摘 要：从云南美登木共生放线菌菌株 1B1 的发酵提取物中分离得到了一个新的 angucycline 抗生素，并通过其谱学特征鉴定了化合物 **1** 的化学结构。

关键词：药物化学；结构鉴定；核磁共振波谱；高分辨质谱；放线菌菌株 1B1；云南美登木；angucycline 抗生素