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A New Dopamine Derivative from *Cotidius chinensis*

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Abstract: A new dopamine derivative (**1**), along with three known analogues (**2**–**4**), was isolated from the medical insect *Cotidius chinensis*. Their chemical structures were identified by spectral data including HR-ESI-MS, 1D and 2D NMR.

Keywords: *Cotidius chinensis*; *Aspongopus chinensis*; dopamine derivative; medical insect; cotidione A.

1. Introduction

Cotidius chinensis synonym *Aspongopus chinensis* is one of medical insects in Pentatomidae family, which is mainly distributed among Guizhou, Sichuan, and Yunnan Provinces of China [1, 2]. The Compendium of Materia Medica recorded *C. chinensis* has the functions of regulating qi-flowing for relieving pain and reinforcing yang for warm the middle warmer. Previous chemical investigations on this insect showed that dopamine derivatives were the major secondary metabolites [3, 4]. Modern pharmacological studies revealed that *C. chinensis* has the activities of anti-bacterial, anti-inflammatory, and anti-cancer, particularly on gastric cancer [5-7]. In this paper, a new dopamine derivative (**1**), along with three known analogues (**2**–**4**) (Figure 1), was isolated from the medical insect *C. chinensis*.

2. Materials and Methods

2.1. Instruments and materials

Agilent DD2400-MR nuclear magnetic resonance instrument, TMS is internal standard (Agilent company, USA); LTQ Orbitrap XL mass spectrometer (Thermo Fisher, USA); J-1500 Circular Dichroism Chiroptical Spectrometer (JASCO company, Japan), LC3000 high performance liquid

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chromatograph (Chuang Xing Tong Heng Science And Technology Co., Ltd., Beijing, China); ODS column (Daisogel C_{18} 10 μm 30 mm×250 mm; YMC C_{18} 5 μm 10 mm×250 mm); GF_{254} and 300-400 mesh silica gel (Marine Chemical Industry Factory, Qingdao, China); Sephadex LH-20 gel (Merck company, Germany). The insects were bought from Bozhou in AnHui Province, China, in October 2017, and identified as *Cotidius chinensis* by Prof. Xiaohui Hou (Zunyi Medical University). A voucher specimen (No.20171010) was deposited at School of Basic Medical Sciences, Zunyi Medical University.

2.2. Isolation of Compounds

The air-dried insect of *C. chinensis* (10 kg) was crushed, and extracted twice with 50% methanol by ultrasound-assisted. The extract was concentrated under reduced pressure to obtain a crude extract. The crude extract was dispersed into water, and extracted successively with ethyl acetate and *n*-BuOH (3 times each), respectively. The extract was concentrated to obtain ethyl acetate extract (800 g) and *n*-BuOH extract (400 g). The ethyl acetate extract was subjected to silica gel column chromatography, eluted with a gradient of petroleum ether-ethyl acetate (*v*/*v* 100:0, 50:1, 30:1, 20:1, 10:1, 5:1, 3:1, 2:1, 1:1, 1:3, 0:100) to afford eight fractions, Fr.1-8, which were monitored by TLC. Fr.6 was further separated and purified by semi-preparative HPLC (10% MeOH in water to 90% MeOH in water, *v*/*v*, 6.0 ml/min) to obtain compound **1** (t_R=21 min) and compound **2** (t_R=26 min). Fr.7 was further separated and purified by semi-preparative HPLC (acetonitrile:water, 25:75, *v*/*v*, 6.0 ml/min) to get compound **3** (t_R=23.3 min) and compound **4** (t_R= 24.9 min).

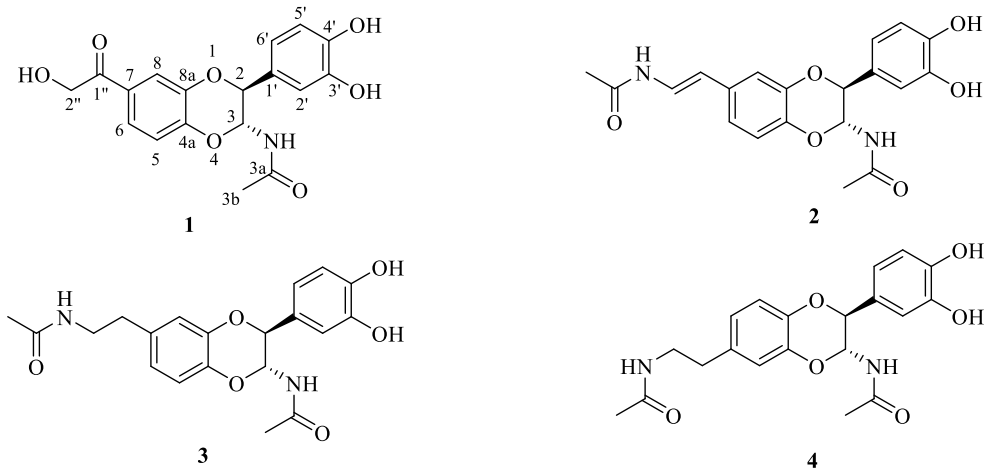

Figure 1. The structures of compounds **1-4**

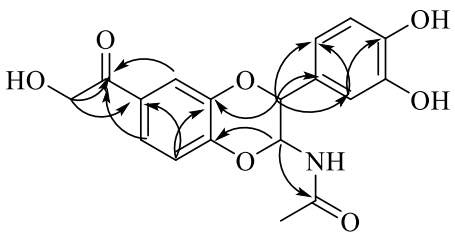

Figure 2. Key HMBC correlations of compound **1**

3. Results and Discussion

3.1. Structure Elucidation

Compound **1** was isolated as a yellow powder. Its molecular formula was determined as $C_{18}H_{17}NO_7$ based on the HR-ESI-MS (*m/z*: $[M+H]^+$ 360.1086 calculated for $C_{18}H_{18}NO_7$: 360.1083), with 11 degrees of unsaturation. The ^{1}H NMR (Table 1) and HSQC spectra of compound **1** showed two sets of ABX spin systems at δ_H 7.56 (1H, d, *J* = 1.6 Hz, H-8), 7.00 (1H, d, *J* = 8.0 Hz, H-5), 7.55 (1H, dd, *J* = 8.0, 1.6 Hz, H-6), and 6.85 (1H, d, *J* = 1.5 Hz, H-2'), 6.76 (1H, overlapped, H-5'), 6.76 (1H, overlapped, H-6'), suggested the presence of two 1,3,4-trisubstituted aromatic rings.

Table 1. NMR spectral data of compounds **1–4** (400/100 MHz, in CD_3OD**)**

No.		**1**	**2**	**3**	**4**
	δ_H (*J* in Hz)	δ_C	δ_C	δ_C	δ_C
2	4.76 (1H, d, 7.3)	78.3	76.8	76.8	76.7
3	5.81 (1H, d, 7.3)	78.9	76.9	76.9	76.8
3a		173.4	171.8	171.8	171.9
3b	1.89 (1H, s)	22.7	21.2	21.1	21.2
5	7.00 (1H, d, 8.0)	118.5	116.8	116.5	116.4
6	7.55 (1H, dd, 8.0, 1.6)	123.5	119.1	121.7	121.6
7		129.7	130.4	132.7	132.8
8	7.56 (1H, d, 1.6)	117.9	118.8	116.6	116.7
4a		144.7	141.1	140.7	141.5
8a		149.0	143.1	142.8	142.0
1'		128.2	127.2	127.3	127.4
2'	6.85 (1H, d, 1.5)	115.7	114.1	114.1	114.1
3'		146.7	145.0	145.0	145.0
4'		147.5	145.7	145.6	145.7
5'	6.76 (1H, overlapped)	116.3	114.7	114.6	114.7
6'	6.76 (1H, overlapped)	120.8	120.7	119.1	119.2
1"		198.7	113.2	34.3	34.3
2"	4.77 (2H, s)	66.3	123.0	40.7	40.7
2"a			169.2	171.7	171.8
2"b			21.2	21.1	21.1

The ^{1}H NMR and HSQC spectra also displayed the presence of two oxygenated methine signals at δ_H 4.76 (1H, d, *J* = 7.3 Hz, H-2), 5.81 (1H, d, *J* = 7.3 Hz, H-3), an oxygenated methylene at δ_H 4.77 (2H, s, H-2"), and a methyl at δ_H 1.89 (3H, s, H-3). The ^{13}C NMR and HSQC spectra of compound **1** showed 18 carbon signals, including two carbonyl signals at δ_C 198.7, 173.4, 12 aromatic carbon signals at δ_C 129.7, 117.9, 144.7, 149.0, 118.5, 123.5, 128.2, 115.7, 146.7, 147.5, 116.3, 120.8, two oxygenated

methylene carbon signals at δ_C 78.3, 78.9, an oxygenated methylene carbon signal at δ_C 66.3, and a methyl carbon signal at δ_C 22.7. These spectroscopic features suggested that compound **1** should be a dopamine derivative [8,9]. The HMBC correlations (Figure 2) of H-6/C-1", H-8/C-1" (δ_C 198.7), H-2"/C-1", and H-2"/C-7, confirmed a carbonyl located at C-1". The HMBC correlations of H-2/C-8a indicated one epoxy bridge at C-2 and C-8a, the HMBC correlations of H-3/C-4a deduced the other epoxy bridge at C-3 and C-4a. The HMBC correlations of H-3/C-3a (δ_C 173.4) showed the presence of an acetyl amino group at C-3. Compound **1** showed the same vicinal coupling constants of H-2/H-3 (J = 7.3 Hz) with those observed in known compounds **3** and **4** [10], suggesting a *trans*-H-2/H-3 relationship [11,12]. The absolute configuration of compound **1** was elucidated as 2*S*,3*R* on the basis of the positive Cotton effect at 286 nm in its circular dichroism (CD) spectrum [13], contrary to negative Cotton effect at 292 nm in aspongopusamide A [4]. Therefore, the structure of compound **1** was established and named as cotidione A.

Additionally, the known compounds were identified as *trans*-2-(3',4'-dihydroxyphenyl)-3-acetylamino-7-(*N*-acetyl-2"-aminoethylene)-1,4-benzodioxane [14], *trans*-2-(3',4'-dihydroxyphenyl)-3-acetylamino-7-(*N*-acetyl-2"-aminoethyl)-1,4-benzodioxane [10], and *trans*-2-(3',4'-dihydroxyphenyl)-3-acetylamino-6-(*N*-acetyl-2"-aminoethyl)-1,4-benzodioxane [10].

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Supporting Information

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