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Bioactive aporphine alkaloids from the stems of *Dasymaschalon rostratum*

Zhangxin Yu[a,b], Changri Han[a,c], Xiaoping Song[a,c,*], Guangying Chen[a,*], Jinxiong Chen[a]

[a] *Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, College of Chemistry and Chemical Engineering, Hainan Normal University, Haikou 571158, China*

[b] *Hainan Provincial Key Laboratory of Resources Conservation and Development of Southern Medicine, Hainan Branch of the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Haikou 570311, China*

[c] *Key Laboratory of Medicinal and Edible Plant Resources of Hainan Province, School of Chemical and Material Engineering, Hainan Institute of Science and Technology, Haikou 571126, China*

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ABSTRACT

Three undescribed aporphine alkaloids dasymaroine A (**1**), 3-methoxyoxoputerine *N*-oxide (**2**), and dasymaroine B (**3**), along with nine known analogues (**4–12**) were isolated from the stems of *Dasymaschalon rostratum* Merr. The structures were elucidated using spectroscopic methods and by comparison with published NMR spectroscopic data. Compound **1** is a rarely reported nitro aporphine alkaloid and its absolute configuration was defined based on negative specific rotation and single-crystal X-ray diffraction. Compound **2** represents the first example of oxoaporphine alkaloid *N*-oxide. All compounds were evaluated for their activities of six pathogenic bacteria, **1** exhibited significant inhibition against *Escherichia coli* and *Saphylococcus aureus* with MIC values of 1.2 and 2.5 μM, respectively. As well as compounds **1–5**, **7**, **10**, **12** were evaluated for their anti-HIV activities with EC_{50} ranged from 1.93 to 9.70 μM.

1. Introduction

Dasymaschalon (Annonaceae) is a member of a genus comprising about 16 species, which are widely distributed in temperate and subtropical regions. *Dasymaschalon rostratum* is a deciduous arbor plant comprising three species growing in Hainan Island, China [1]. Previous phytochemical investigations on plants of this genus resulted in the isolation of a number of alkaloids, flavonoids, and triterpenoids [2–4]. Our previous studies focussing on the ethyl acetate extract of this plant, led to the isolation of phenylpropanoid and 6H-dibenzo[*b*,*d*]pyran-6-one derivatives, and some of them showed anti-HIV activities [5]. In a continuing work, three undescribed aporphine alkaloids dasymaroine A (**1**), 3-methoxyoxoputerine *N*-oxide (**2**), and dasymaroine B (**3**), along with nine known analogues (**4–12**) were isolated from a petroleum ether extract of the stems of *D. rostratum.* All compounds were evaluated for their activities of six pathogenic bacteria. Compounds **1–5**, **7**, **10**, and **12** showed anti-HIV activities with EC_{50} values ranging from 1.93 to 9.70 μM. Herein, the isolation, structural elucidation and the biological activities of these compounds are reported.

2. Experimental

2.1. General experimental procedures

NMR spectra were recorded on a Bruker AV 400 NMR spectrometer by using $CDCl_3$ or methanol-d_4 as a solvent. Preparative HPLC was performed on an Agilent 1260 LC series equipped with a quaternary pump VL, a DAD detector, and a Waters XBridge C_{18} (250 × 10 mm, 5 μm) semi-preparative column. The other experimental procedures, in this study, were performed as previously described [5,6].

2.2. Plant material

The plants of *D. rostratum* were collected from Bawangling Nature Reserve, Hainan Island, China. A voucher specimen (No. HAN20140725) was deposited at the Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, Hainan Normal University [5].

2.3. Extraction and isolation

Dried stems of *D. rostratum* (22.5 kg) were extracted with 75% EtOH (3 × 20 L, each for 5 days) to yield a semisolid residue (920 g) that

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* Corresponding authors at: Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, Hainan Normal University, Haikou 571158, PR China.

E-mail addresses: sxp628@126.com (X. Song), chgying123@163.com (G. Chen).

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constituted the crude extract. After being suspended in water (3.0 L), the solution was successively extracted with petroleum ether (PE) and EtOAc (EA), respectively. The petroleum ether extract (260 g) was subjected to silica gel column chromatograph, eluted with $CHCl_3$/MeOH (100:1 to 1:100, *v/v*) yielding six fractions (Fr. 1–Fr. 6). Fr. 3 (41.5 g) was subjected to CC on silica gel using PE/EA (100:1 to 1:100, *v/v*) to afford six subfractions 3A–3F. Fr. 3B (5.3 g) was further subjected to CC on silica gel using petroleum ether/EtOAc (3:1, *v/v*) and followed by ODS with eluting with MeOH/H_2O (40:60, *v/v*) to give **8** (12.1 mg) and **9** (8.9 mg), respectively. Fr. 3C (2.8 g) was subjected to CC on silica gel using $CHCl_3/CH_3OH$ (10:1, *v/v*), then purified by semi-preparative HPLC using Waters XBridge C_{18} (250 × 10 mm, 5 μm, 55% CH_3CN/H_2O) to afford **2** (2.1 mg). Fr. 3D (6.7 g) was subjected to CC on silica gel using $CHCl_3$/MeOH (8:1, *v/v*) and chromatographed over Sephadex LH-20 gel column eluted with $CHCl_3/CH_3OH$ (1:3, *v/v*), then further purified by semi-preparative HPLC using Waters XBridge C_{18} (250 × 10 mm, 5 μm, 45% CH_3CN/H_2O) to yield **6** (2.7 mg), **10** (7.1 mg) and **11** (6.2 mg), respectively. Fr. 4 (38.2 g) was subjected to CC on silica gel using $CHCl_3/CH_3COCH_3$ (100:1 to 1:100, v/v) to afford six subfractions 4A–4F. Fr. 4B (5.8 g) was subjected to CC on silica gel using PE/EA (3:1, v/v) to give **4** (8.7 mg) and **5** (9.2 mg). Subfraction 4C (5.2 g) was subjected to CC on silica gel using PE/EA (2:1, v/v) and chromatographed over Sephadex LH-20 gel column eluted with MeOH to afford **7** (15.6 mg). Fr. 4D (3.4 g) was subjected to CC on silica gel using petroleum $CHCl_3$/MeOH (6:1, v/v), and followed by semi-preparative HPLC using Waters XBridge C_{18} (250 × 10 mm, 5 μm, 60% CH_3CN/H_2O) to give **1** (9.6 mg), **3** (6.1 mg) and **12** (7.8 mg).

2.4. Dasymaroine A (1)

Light yellow crystals; $[\alpha]_D^{25}$ −158.2 (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ε) 282 (4.5), 310 (3.6) nm; IR (KBr) ν_{max} 2934, 1611, 1521, 1437, 1395, 1337, 1213, 1085, 753, 669 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS with *m/z* 401.1344 $[M+H]^+$ (calcd for $C_{20}H_{21}N_2O_7$, 401.1344).

X-ray crystallographic analysis of dasymaroine A (**1**): Crystal data were collected on a Bruker APEX DUO diffractometer with Mo Kα radiation (λ = 0.71073 Å) at 293(2) K: $C_{20}H_{20}N_2O_7{\cdot}H_2O$, *MW* = 418.39, orthorhombic, *C*2221, *a* = 8.1386(9) Å, *b* = 26.612(3) Å, *c* = 18.9563(16) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 4105.7(7) $Å^3$, *Z* = 8, D_c = 1.354 g/cm^3, 8945 reflections measured, 2032 independent reflections (R_{int} = 0.0587), R_1 = 0.2067 [$I > 2\sigma(I)$]. wR_2 (F^2) = 0.2046 [$I > 2\sigma(I)$]. The structure was solved by direct methods (SHELXS-97) and refined using full-matrix least squares difference Fourier techniques. Carbon, oxygen and nitrogen atoms were refined anisotropically. Crystal **1** was obtained by slow evaporation of a solution in MeOH. Crystallographic data (excluding structure factor) for **1** has been deposited with the Cambridge Crystallographic Data Centre: CCDC reference number 1523391. The data can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures-beta/.

Table 1
^1H NMR spectroscopic data for **1–3** (400 MHz, δ in ppm, *J* in Hz, $CDCl_3$).

NO.	1	2	3
3			6.56 s
4	2.83 m	8.02 d (7.2)	2.62 m
			2.95 m
5	3.35 m	8.25 d (7.2)	2.97 m
	2.87 m		3.32 m
6a	3.71 dt (14.8, 2.0)		3.71 dd (14.4, 4.0)
7	2.78 dd (14.8, 4.0)		3.30 dd (13.6, 4.0)
	2.44 t (14.8)		2.25 t (14.0)
8		8.06 br d (8.0)	
9		7.51 t (8.0)	
10	6.51 s	7.24 br d (8.0)	6.52 s
OCH_2O	5.84 s	6.23 s	5.84 s
	6.00 s		6.00 s
OMe-3	4.02 s	4.27 s	
OMe-8			3.74 s
OMe-9	3.93 s		3.90 s
OMe-11	3.94 s	4.00 s	3.87 s

Table 2
^{13}C NMR spectroscopic data for **1–3** (100 MHz, δ in ppm, $CDCl_3$).

NO.	1	2	3
1	144.4	151.2	142.5
1a	106.7	110.7	113.9
1b	129.7	124.9	129.1
2	135.4	136.6	146.8
3	140.8	136.5	107.1
3a	119.2	119.3	126.1
4	24.1	120.6	29.2
5	42.9	138.1	43.2
6a	53.2	136.1	53.7
7	33.4	176.9	30.9
7a	131.9	135.0	131.6
8	134.9	120.7	139.9
9	151.7	129.0	153.0
10	95.2	115.9	96.5
11	158.1	156.4	153.5
11a	113.6	120.7	112.9
OCH_2O	100.5	102.0	100.2
OMe-3	59.6	60.4	
OMe-8			61.1
OMe-9	56.2		56.0
OMe-11	56.6	56.2	56.5

2.5. 3-Methoxyoxoputerine N-oxide (2)

Light yellow oil; UV (MeOH) λ_{max} (log ε) 273 (4.2), 338 (3.8) nm; IR (KBr) $\nu_{max}{}^{-1}$ 3412, 2931, 1643, 1522, 1440, 1392, 1215, 1091, 776 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m/z* 352.0815 $[M+H]^+$ ($C_{19}H_{14}NO_6$; calcd for 351.0816).

2.6. Dasymaroine B (3)

Light yellow oil; $[\alpha]_D^{25}$ −132.7 (*c* 0.32, MeOH); UV (MeOH) λ_{max} (log ε) 276 (4.2), 308 (3.8) nm; IR (KBr) ν_{max} 2936, 1614, 1525, 1441, 1392, 1335, 1225, 1092, 760, 678 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS with *m/z* 356.1489 $[M+H]^+$ (calcd for $C_{20}H_{22}NO_5$, 356.1492).

2.7. Antibacterial assays

Antibacterial activity was determined by the conventional broth dilution assay [7]. Six terrestrial pathogenic bacteria: *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Micrococcus tetragenus*, *Saphylococcus aureus* and *Staphylococcus albus* were used, and ciprofloxacin was used as a positive control.

2.8. Anti-HIV assays

Anti-HIV activity of compounds was evaluated by the cytopathic effects of HIV-1(EC_{50}) and the cytotoxicity assay against the C8166 cell line (CC_{50}) with MTT methods as described in the literature and earlier researches [8]. The concentration of the antiviral sample reducing HIV-1 replication by 50% (EC_{50}) was calculated and determined with the dose-response standard curve. AZT (3ʹ-azido-3ʹ-deoxythymidine) was used as a positive control. The therapeutic index (TI) was calculated with the ratio of CC_{50}/EC_{50}.

3. Results and discussion

3.1. Structure elucidation

Compound **1** was obtained as light yellow crystals with a specific rotation of −158.2 (*c* 0.25, MeOH). Its molecular formula was determined as $C_{20}H_{20}N_2O_7$ by HRESIMS with *m/z* 401.1344 $[M+H]^+$ (calcd for $C_{20}H_{20}N_2O_7$, 401.1344), indicating twelve indices of hydrogen deficiency. The existence of an even number of nitrogen atoms could be confirmed from the *m/z* by the nitrogen rule. The ^1H NMR spectrum (Table 1) displayed signals attributable to a single aromatic proton at δ_H 6.51 (1H, s, H-10), a methylenedioxy at δ_H 5.84 (1H, s, H-OCH_2O) and 6.00 (1H, s, H-OCH_2O), a methine at δ_H 3.71 (1H, dt, J = 14.8, 2.0 Hz, H-6a) and three methoxyls δ_H 4.02 (3H, s, OMe-3), 3.93 (3H, s, OMe-9), 3.94 (3H, s, OMe-11). ^{13}C NMR and DEPT data (Table 2) revealed the presence of 20 carbon atoms, including eleven sp^2 quaternary carbons, one sp^2 and one sp^3 CH, four sp^3 CH_2 and three methoxyls which are characteristic signals of the aporphine alkaloid [9]. The ^1H and ^{13}C NMR spectroscopic data indicated that **1** closely resembled those of *O*-methoxyduguevanine **4** [10], except for the absence of an aromatic proton signal at C-8 and the molecular weight of **1** is larger than that of **4** by 45 units. These data indicated that the aromatic proton on C-8 in **4** δ_H 6.44 (d, J = 2.0 Hz) was replaced by a nitro group in **1**, which was corroborated by the HRESIMS and HMBC (Fig. 2). By slow crystallization from MeOH, single crystals of **1** suitable for X-ray (Fig. 3) diffraction analysis using Mo Kα radiation were obtained, allowing the structure of **1** (CCDC No. 1523391) to be fully established. The absolute configuration of **1** was defined to be 6a*R* by negative specific rotation ($[\alpha]_D^{25}$ −158.2) and X-ray diffraction analysis [11]. Thus, the structure of dasymaroine A (**1**) was established as shown in Fig. 1.

Compound **2** was obtained as a light-yellow oil. Its molecular formula was determined as $C_{19}H_{13}NO_6$ by HRESIMS (*m/z* 352.0815 $[M+H]^+$; calc'd 352.0816) data, indicating fourteen indices of hydrogen deficiency. In the ^1H NMR spectrum of **2**, thirteen protons were classified as being from a pair of *ortho*-coupling of hydrogen signals in down-field region at δ_H 8.25 (1H, d, J = 7.2 Hz, H-5) and 8.02 (1H, d, J = 7.2 Hz, H-4), a *vic*-trisubstituted benzene unit at δ_H 8.06 (1H, br d, J = 8.0 Hz, H-8), 7.51 (1H, t, J = 8.0 Hz, H-9), 7.24 (1H, br d, J = 8.0 Hz, H-10), a methylenedioxy signal at δ_H 6.23 (2H, s, H-OCH_2O), and two methoxyl signals at δ_H 4.27 (3H, s, OMe-3), 4.00 (3H, s, OMe-11). The ^{13}C NMR and DEPT (Table 2) spectra displayed 19 resonances, including a carbonyl carbon at δ_C 176.9 (C-7), five aromatic methine carbons, nine aromatic quaternary carbons, a nitrogenated aromatic quaternary carbon at δ_C 136.1 (C-6a), a methylenedioxy carbon at δ_C 102.0 (C-OCH_2O), and two methoxyl carbons at δ_C 60.4 (OMe-3), 56.2 (OMe-11), which was characteristic for a aporphine skeleton [9]. The 1D NMR spectroscopic data indicated that **2** was similar to those of 3-methoxyoxoputerine **8** [11], except for the deshielded C-1b ($\Delta\delta_C$ +1.7) and C-4 ($\Delta\delta_C$ +1.9), and the strongly shielded C-5 ($\Delta\delta_C$ −6.6) and C-6a ($\Delta\delta_C$ −8.2) in **2**. Besides, a significant γ-effect on C-3a (δ_C 119.3) and C-7 (δ_C 176.9) resonance was also observed in **2** [12], as compared with the chemical shift of C-3a (δ_C 130.9) and C-7 (δ_C 182.8) in **8**. Furthermore, comparison of the HRESIMS data of **2** to those of **8** suggested that the molecular weight of **2** is larger than that of **8** by 16 units. These data indicated the presence of an *N*-oxide function in **2**, as expected in aporphine alkaloids bearing quaternization of the ring nitrogen [13]. The complete assignment for **2** was confirmed by the ^1H,^1H-COSY, HSQC, and HMBC spectra (Fig. 2) Accordingly, compound **2** was unambiguously identified as a new oxoaporphine alkaloid *N*-oxide, named 3-methoxyoxoputerine *N*-oxide.

Compound **3** was obtained as light yellow oil, possessed a molecular formula of $C_{20}H_{21}NO_5$ as established by HRESIMS *m/z* 356.1489 $[M+H]^+$ (calcd for $C_{20}H_{22}NO_5$, 356.1492), which indicated eleven indices of hydrogen deficiency. Comparison of the ^1H NMR and ^{13}C NMR (Table 2) spectroscopic data of **3** with those of *O*-methylcalycinine [10] suggested that **3** was also an aporphine alkaloid. The obvious differences were the absence of an aromatic proton signal at C-8 and the presence of a methoxyl (δ_H 3.74 and δ_C 61.1) in **3**. These data indicated that the aromatic proton was replaced by a methoxyl. The above elucidation was supported by the HMBC correlations of OMe-8 (δ_H 3.74), H-7 (δ_H 2.25) and H-10 (δ_H 6.52) to C-8 (δ_C 139.9) (Fig. 2). The ^1H,^1H-COSY, HSQC and HMBC spectra allowed the complete assignment for **3**. The absolute configuration of **3** was the same with **1**, as demonstrated

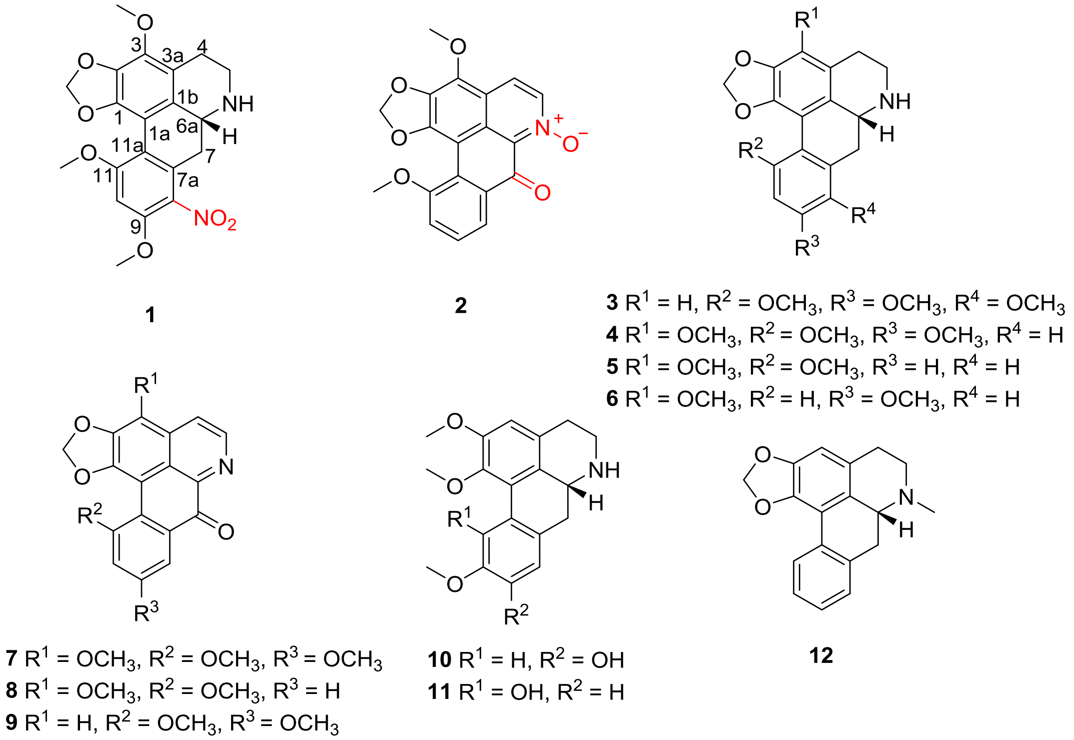

Fig. 1. Structures of compounds **1–12**.

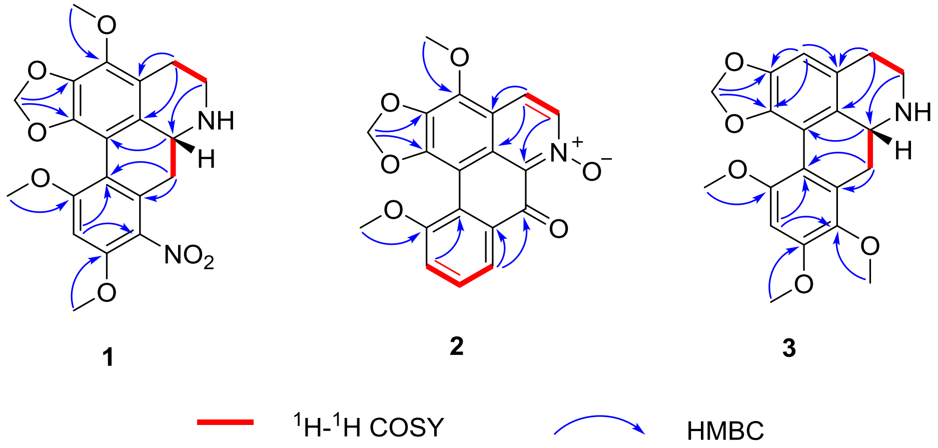

Fig. 2. ^{1}H,^{1}H-COSY and key HMBC correlations of compounds **1–3**.

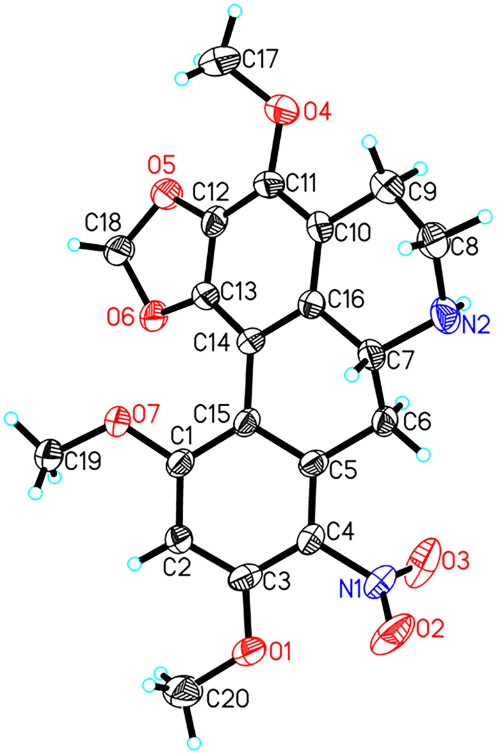

Fig. 3. ORTEP drawing of compound **1**.

by comparison of its specific rotation ($[\alpha]_D^{25}$ −132.7) with that of **1**. Therefore, the structure of **3** was established as dasymaroine B.

Nine known compounds were isolated and identified as *O*-methoxyduguevanine (**4**) [10], (−)-3-methoxyputerine (**5**) [11], buxifoline (**6**) [14], duguevalline (**7**) [15], 3-methoxyoxoputerine (**8**) [11], oxodiscoguattine (**9**) [16], laurotetanine (**10**) [17], norisocorydine (**11**) [18], and roemerine (**12**) [19] by comparing the experimental and reported spectral data.

3.2. Antibacterial activity

The antibacterial activities of all compounds were determined against six terrestrial pathogenic bacteria. Compound **1** exhibited significant inhibition against *E. coli* and *S. aureus* with MIC values of 1.2 and 2.5 μM, respectively (positive control, ciprofloxacin, MIC 0.3 μM and 0.7 μM, respectively). Compound **2** showed moderate inhibitory effects on *E. coli* with MIC value of 5.0 μM. The MIC values of other compounds were higher than 10 μM in the assay.

Table 3
Anti-HIV of compounds **1–5**, **7**, **10**, and **12**.

No.	CC_{50} (μM)[a]	EC_{50} (μM)[b]	TI[c]
1	28.7	1.93	14.9
2	56.6	2.18	25.9
3	43.6	5.80	7.5
4	64.7	2.48	26.2
5	81.5	9.70	8.4
7	36.8	4.50	8.2
10	78.2	6.30	12.4
12	> 200	8.10	> 24.7
AZT[d]	5231.60	0.0152	337605.26

[a] CC_{50}: 50% cytotoxic concentration.
[b] EC_{50}: 50% effective concentration.
[c] TI(therapeutic index) = CC_{50}/EC_{50}.
[d] AZT(3′-azido-3′-deoxythymidine) was used as a positive control.

3.3. Anti-HIV activity

Compounds **1–5**, **7**, **10**, **12** were tested for anti-HIV bioactivity (Table 3). They were evaluated by the inhibition assay for the cytopathic effects of HIV-1(EC_{50}) and cytotoxicity assay against C8166 cell line (CC_{50}) by MTT methods. All the compounds showed moderate activities with EC_{50} ranged from 1.93 to 9.70 μM.

4. Conclusions

Twelve aporphine alkaloids (**1–12**), including three undescribed natural products (**1–3**), were isolated and identified from the stems of *D. rostratum.* All isolated alkaloids were evaluated for their activities of six pathogenic bacteria, compound **1** exhibited significant inhibition against *E. coli* and *S. aureus* with MIC values of 1.2 and 2.5 μM, respectively. Compounds **1–5**, **7**, **10**, **12** were evaluated for their anti-HIV activities with EC_{50} ranged from 1.93 to 9.70 μM. This work demonstrated that aporphine alkaloids are typical bioactive compounds of the genus *Dasymaschalon*, that these could be helpful for explaining the use of *D. rostratum* in folk medicine. In conclusion, our findings might be useful as characteristic markers in chemotaxonomic research.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103069.

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