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Chinese Journal of Natural Medicines 2019, **17**(12): 0918–0923
Chinese Journal of Natural Medicines

Four new corynanthe-type alkaloids from the roots of *Alstonia scholaris*

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Available online 20 Dec., 2019

[ABSTRACT] Four new corynanthe-type alkaloids, meloslines C–F (**1**–**4**), together with four known ones (**5**–**8**) were isolated from the roots of *Alstonia scholaris*. Their structures including absolute configurations were elucidated by extensive spectroscopic analysis and electronic circular dichroism (ECD) calculation. Compounds **1** and **2** exhibited potent vasorelaxant activity on endothelium-intact renal arteries precontracted with KCl.

[KEY WORDS] *Alstonia scholaris*; Apocynaceae; Corynanthe-type alkaloids; Vasorelaxant activity

[CLC Number] R284 **[Document code]** A **[Article ID]** 2095-6975(2019)12-0918-06

Introduction

The genus *Alstonia* (Apocynaceae) contains about 50 species all over the world, and 6 of them are distributed in southern China. *Alstonia scholaris* is one of the representative plants, which commonly known as devil's tree has been used for the treatment of many human ailments such as headache, asthma bronchitis and pneumonia in Southeast Asia [1-3]. A large number of pharmacological investigations pointed out that *A. scholaris* exhibits a remarkably broad range of bioactivities such as anti-microbial, anti-inflammatory, and anticancer [4-8]. Many documents have proved that monoterpenoid indole alkaloids (MIAs) are the main bioactive ingredient of plants from Apocynaceae family [9]. It is well known that MIAs have played a significant role in the discovery and research of new drugs due to their structural diversity and wide range of bioactivities. Being interested in structurally novel and pharmacologically efficacious MIAs [10-15], we had isolated two novel alkaloids from the leaves and twigs of *A. scholaris* [5]. In our following research, four new corynanthe-type alkaloids, meloslines C–F (**1**–**4**), together with four known ones deacetyldeformopicraline (**5**) [16], antirhine N_4-oxide (**6**) [17], sitsirikin (**7**) [18], isositsirikine (**8**) [19] have been isolated from the root of the same plant. In this paper, we reported the isolation and structure elucidation, and vasorelaxant activities of **1**–**8**.

[Received on] 09-Oct.-2019
[Research funding] This work was supported by the National Key R&D Program of China (No. 2017YFC1703802), the National Natural Science Foundation of China (Nos. U1801287, 81630095, and 81803398), the Science and Technology Planning Project of Guangdong Province (No. 2018B020207008), the High-performance Super Computing Platform of Jinan University.
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These authors have no conflict of interest to declare.
Dedicated to Professor SUN Han-Dong on the Occasion of His 80th Birthday

Results and Discussion

Melosline C (**1**) was obtained as yellow amorphous powder, possessed a molecular formula $C_{20}H_{22}N_2O_4$, as deduced from its HRESI-MS data (*m/z* 355.1658 $[M + H]^+$, Calcd. for $C_{20}H_{23}N_2O_4$: 355.1652), corresponding to 11 degrees of unsaturation. The UV spectrum of **1** showed the characteristic absorptions maxima at 287 and 206 nm. The IR spectrum revealed the existence of amino (3413 cm^{-1}), hydroxyl (3304 cm^{-1}), and carbonyl (1734 cm^{-1}) groups, as well as aromatic ring (1483 cm^{-1}). The ^1H and ^{13}C NMR spectra of **1** revealed the presence of a substituted indole ring [δ_H 7.03 (1H, d, J = 7.8 Hz, H-9), 6.70 (1H, t, J = 7.8 Hz, H-10), 7.05

(1H, t, J = 7.8 Hz, H-11), and 6.78 (1H, d, J = 7.8 Hz, H-12); δ_C 109.6 (C-2), 54.2 (C-7), 135.8 (C-8), 125.6 (C-9), 120.8 (C-10), 129.0 (C-11), 111.4 (C-12), and 149.5 (C-13)]. Besides the signals of indole ring, compound **1** exhibited the signals of one methyl, one methoxyl, three methylenes, four methines, and three quaternary carbons. The above NMR data of **1** was highly similar to that of deacetyldeformopicraline (**5**), except a sp^3 methine signal (δ_C 53.0) assigned as C-3 in **5** was replaced by one quaternary carbon (δ_C 86.9) in **1**, which was supported by the HMBC correlations between H-5/H-15/H-21 and C-3 (Fig. 2). The NOESY correlations between H-15 and H-14α, and between H-14α and H-21α indicated that these protons had the same orientation. Similarly, H-5, H-14β, H-16 and H-21β were assigned as β-orientation based on their NOE correlations between H-5 and H-21β, and between H-16 and H-14β.

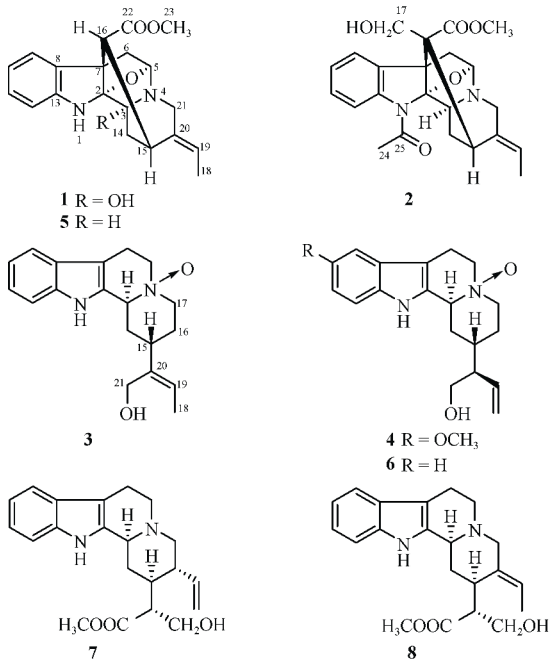

Fig. 1 Structures of compounds 1–8

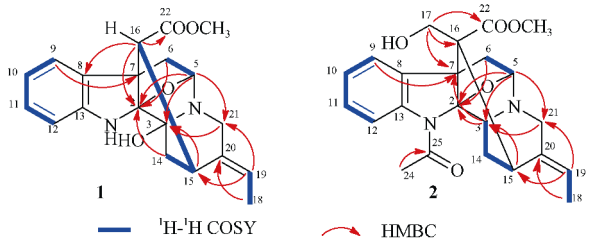

Fig. 2 ^{1}H–^{1}H COSY and key HMBC correlations of 1 and 2

It is well known that when the internuclear distance was more than 3 Å, the nuclear Overhauser effect (NOE) correlations could not be observed even for the two spin systems bearing consistent orientation. To confirm the orientation of 3-OH, the computer-generated 3D drawing and molecular structure model methods were conducted. First, 3-OH was randomly assigned to be β-direction, and the distances of H-21β with H-5/H-6β were 3.24 and 3.87 Å, respectively. However, the obvious NOE correlations between H-5/H-6β and H-21β, were 2.73 and 2.67 Å. Thus, the 3-OH must be α-oriented. Furthermore, the calculated ECD curve of (2*R*, 3*R*, 5*S*, 7*R*, 15*R*, 16*R*)-**1** revealed a good agreement with the measured one. Thus, the absolute structure of **1** was determined as 2*R*, 3*R*, 5*S*, 7*R*, 15*R*, 16*R* (Fig. 3).

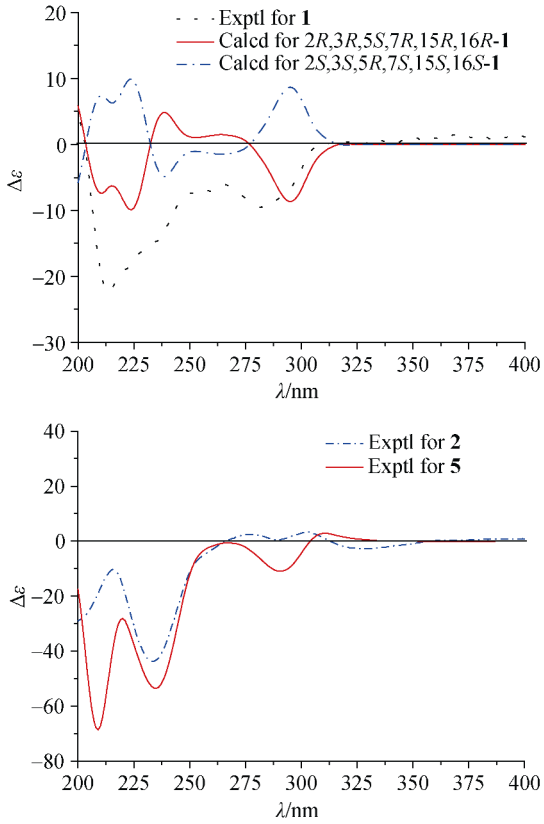

Fig. 3 Experimental ECD spectra of 1, 2 and 5, and calculated ECD spectra of 1

Melosline D (**2**) was obtained as yellow powder. The molecular formula was assigned as $C_{23}H_{26}N_2O_5$ by the quasi-molecular ion at m/z 411.1917 $[M + H]^+$ in its HRESI-MS (Calcd. for $C_{23}H_{27}N_2O_5$: 411.1914). The UV spectrum showed absorption maxima at 288 and 207 nm, while the IR spectrum suggested the presence of hydroxyl (3429 cm^{-1}), carbonyl (1740 and 1729 cm^{-1}) groups, as well as an aromatic ring (1463 cm^{-1}). Preliminary analysis of ^{1}H and ^{13}C NMR data (Table 1) suggest that **2** was closely matched those of deacetyldeformopicraline (**5**), except for the absence of one methine, and the presence of one quaternary carbon, one hydroxymethyl, and one acetyl group, which were assigned to C-16 (δ_C 57.4), C-17 (δ_C 68.2), C-24 (δ_C 20.2), and C-25 (δ_C 171.7). The above data were supported by the HMBC correlations between H_2-17 (δ_H 4.52, 3.89) and C-7 (δ_C 53.9)/C-16/C-22 (δ_C 173.6), and between H_3-24 (δ_H 1.54) and C-25 (Fig. 2). Furthermore,

Table 1 ^{1}H and ^{13}C NMR data of compounds 1–4 (CD_3OD, δ in ppm, *J* in Hz)

Position		**1**[a]		**2**[b]		**3**[b]		**4**[c]	
		δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		-	109.6	-	108.8	-	130.7	-	131.4
3		-	86.9	3.54 d (3.5)	52.7	4.70 s	71.8	4.61 s	71.7
5		4.82 d (2.4)	87.0	4.73 d (2.4)	88.0	3.78 m	69.4	3.72 m	69.2
6	*α* *β*	2.06 dd (13.6, 2.4) 3.22 d (13.6)	40.3	2.37 dd (13.6, 2.4) 3.28 m	45.1	3.20 m 3.13 d (2.5)	20.7	3.06 m	20.6
7		-	54.2	-	53.9	-	106.8	-	106.3
8		-	135.8	-	135.0	-	127.7	-	128.0
9		7.03 d (7.8)	125.6	7.37 d (7.6)	128.4	7.49 d (7.9)	119.1	6.93 d (2.4)	101.0
10		6.70 t (7.8)	120.8	6.79 t (7.6)	121.3	7.08 t (7.3)	120.7	-	155.6
11		7.05 t (7.8)	129.0	7.05 t (7.6)	128.9	7.16 t (7.3)	123.3	6.78 dd (8.0, 2.4)	113.3
12		6.78 d (7.8)	111.4	6.74 d (7.6)	111.9	7.37 d (8.1)	112.5	7.24 d (8.0)	113.2
13		-	149.5	-	150.6	-	139.0	-	133.9
14	*α* *β*	2.17 dd (14.1, 3.6) 1.92 dd (14.1, 3.6)	30.0	2.04 m	22.6	3.00 m 2.22 d (14.2)	28.3	2.58 m 2.25 d (13.6)	28.6
15		3.40 br s	34.9	3.41 s	36.5	2.54 m	31.2	1.54 m	30.7
16	a b	2.36 d (3.6)	53.3	-	57.4	2.59 m 1.45 d (12.8)	25.4	2.07 m 1.54 m	23.6
17	a b	-	-	4.57 d (11.2) 3.89 d (11.2)	68.2	3.69 t (12.2) 3.11 m	59.4	3.57 m 3.05 m	59.2
18		1.49 d (6.8)	13.7	1.64 d (6.8)	13.6	1.58 d (6.9)	13.0	5.15 m	118.4
19		5.46 q (6.8)	121.3	5.48 q (6.8)	122.5	5.62 q (6.9)	124.0	5.69 m	138.3
20		-	136.4	-	137.8	-	141.9	2.17 m	52.3
21	*α* *β*	3.80 m 3.30 m	48.0	3.77 m 3.25 m	46.9	4.12 s	64.8	3.59 m	63.9
22		-	173.8	-	173.6	-	-	-	-
23		3.65 s	52.0	3.54 s	52.0		-	-	-
24		-	-	1.54 s	20.2	-	-	-	-
25		-	-	-	171.7	-	-	-	-
OCH_3		-	-	-	-	-	-	3.80 s	56.2

[a] Recorded at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR; [b] Recorded at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR; [c] Recorded at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR

according to the molecular formula and IR information allowed the attachment of N-1 to C-25. Finally, the ECD spectrum of **2** exhibited Cotton effects similar to those of **5**, which allowed the absolute configuration of **2** was 2*R*, 3*S*, 5*S*, 7*S*, 15*S*, 16*R* (Fig. 3).

Melosline E (**3**) was obtained as light yellow amorphous powder, possessed a molecular formula of $C_{19}H_{24}N_2O_2$ as deduced its HRESI-MS data (*m/z* 313.1913 $[M + H]^+$, Calcd. for $C_{19}H_{25}N_2O_2$: 313.1911), indicating 9 degrees of unsaturation. The UV spectrum of **3** showed absorption maxima at 273 and 216 nm. The IR spectrum suggested the characteristic absorptions due to amino (3406 cm^{-1}), hydroxyl (3260 cm^{-1}), and an aromatic ring (1456 cm^{-1}). The NMR spectra of **3** (Table 1) were very similar to that those of antirhine N_4-oxide (**6**), except for the terminal double bond coverts to a non-terminal double bond, which was supported by the HMBC correlation between H-18 (δ_H 1.58) and C-20 (δ_C 141.9), and ^{1}H–^{1}H COSY correlation between H-18 and H-19 (Fig. 4). The NOE correlations between H-14*α*/H-16*α* and H-21, and between H-3 and H-16*α* indicated that these protons H-3, H-14*α*, H-16*α* and H-21 had the same orientation. Similarly, H-15, H-16*β*, and H-17*β* were *β*-orientation based on their NOE correlations. Furthermore, the NOE correlation between H-19 and H-21 led to the configuration of the double bond C-19–C-20 was *E*-type. Finally, the ECD spectrum of **3** showed positive Cotton effect at 268 (Δ*ε* +56.9) nm, and negative Cotton effect at 215 (Δ*ε* −42.2) nm, which were in good agreement with the calculated ECD spectra for the (3*S*, 15*S*)-**3** diastereoisomer (Fig. 5). Thus, the absolute configuration of **3** was determined as 3*S*, 15*S*.

Melosline F (**4**) was isolated as yellow powder. The molecular formula $C_{20}H_{26}N_2O_3$ was established from its HRESI-MS data (*m/z* 343.2012 $[M + H]^+$, Calcd. for $C_{20}H_{27}N_2O_3$: 343.2016), 30 mass units higher than that of antirhine N_4-oxide (**6**).

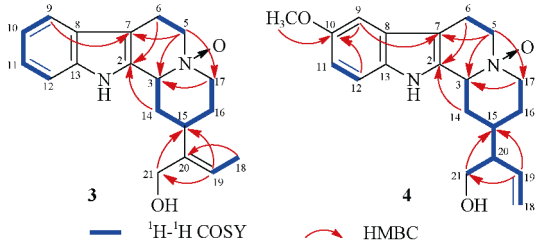

Fig. 4 ^{1}H–^{1}H COSY and key HMBC correlations of 3 and 4

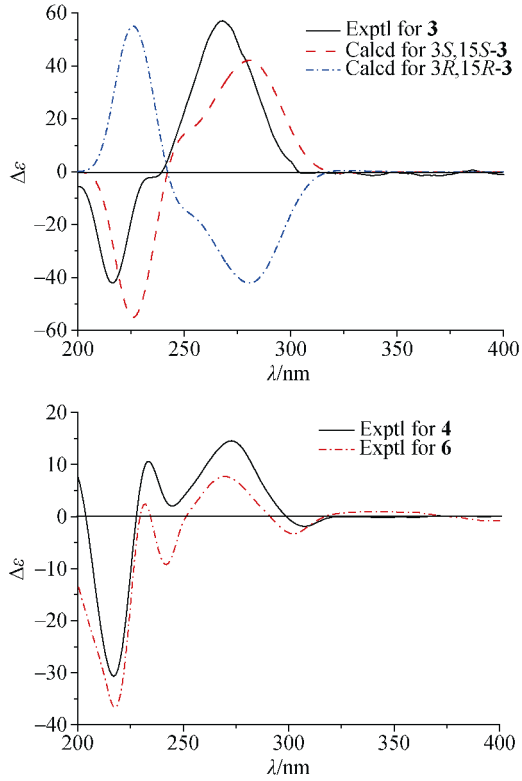

Fig. 5 Experimental ECD spectra of 3, 4 and 6, and calculated ECD spectra of 3

Compound **4** was readily identified as 10-methoxyl antirhine N_4-oxide from its 1D (Table 1) and 2D NMR data, which was confirmed by its chemical shift [δ_C 155.6 (C-10)] and the HMBC correlations between methoxyl (δ_H 3.80) and C-10, and between H-9 (δ_H 6.93)/H-12 (δ_H 7.24) and C-10 (Fig. 4). Additionally, the ECD spectrum of **4** showed the same Cotton effects as **6**, confirmed the absolute configuration of **4** to be 3*S*, 15*S*, 20*R* (Fig. 5).

All compounds were evaluated for their vasorelaxant activity on endothelium-intact renal arteries precontracted with KCl. Compound **1** and **2** exhibited potent vasorelaxant activity on renal arteries with EC_{50} value of 38.62 and 41.43 μmol·L^{-1}, respectively.

Experimental

General procedures

Optical rotations were measured using CH_3OH solutions on a JASCO P-1020 digital polarimeter (Jasco, Tokyo, Japan) at room temperature. IR spectra were obtained by a JASCO FT/IR-480 Plus infrared spectrometer (Jasco, Tokyo, Japan) using KBr pellets. UV spectra were recorded using CH_3OH solutions on a JASCO V-550 UV/Vis spectrometer (Jasco, Tokyo, Japan). HRESI-MS were carried out on an Agilent 6210 ESI-TOF mass spectrometer (Agilent Technologies, CA, USA). NMR spectra were executed on Bruker AV-400/500/600 spectrometers (Bruker, Fä llanden, Switzerland). Column chromatography (CC) was performed on silica gel (80−100 mesh and 200−300 mesh, Qingdao Marine Chemical Plant, Qingdao, China), Sephadex LH20 (Pharmacia Biotech AB, Uppsala, Sweden), and ODS (Merck, Darmstadt, Germany). Preparative HPLC (pHPLC) was finished on an Agilent 1260 system (equipped with a G1310B Iso pump and G1365D MWD VL detector) with a Waters Xbridge™ C_{18} OBD reversed-phase column (19 mm × 250 mm, 5 μm, USA). All solvents used in chromatography column and HPLC were of analytical grade (Tianjin Damao Chemical Plant, Tianjin, China) and chromatographic grade (Oceanpak, Sweden), respectively.

Plant material

The roots of *Alstonia scholaris* (L.) R. Br. were collected in Kunming, Yunnan Province, China, in March of 2017, and identified by Professor ZHOU Guang-Xiong (College of Pharmacy, Jinan University). A voucher specimen (No. CP2017031501) was deposited in the herbarium of the College of Pharmacy, Jinan University, Guangzhou, China.

Extraction and isolation

The air-dried and powdered roots of *A. scholaris* (19.8 kg) were percolated at room temperature with 95% EtOH (24 h × 7 d). The filtrate was evaporated under reduced pressure to give a residue (498.7 g), which was then suspended in water and added with 10% hydrochloric acid to adjust the pH to 2−3. After partitioned with $CHCl_3$, the acidic aqueous phase was alkalified with 10% ammonia to pH 9−10, and extracted with $CHCl_3$ to obtain a total alkaloid extract (48.6 g), then subjected to a silica gel column eluted with gradient mixtures of $CHCl_3$/CH_3OH (100 : 0 to 0 : 100, *V/V*). Twelve fractions (Fr. A−L) were collected and examined by TLC and HPLC analyses. Fr. A (6.1 g) was chromatographed on a ODS column (CH_3OH/H_2O, 10 : 90 to 100 : 0, *V/V*) to give twelve subfractions (Fr. A1−A12). Fr. A2 (473.5 mg) was purified by a Sephadex LH20 column ($CHCl_3$/CH_3OH, 1 : 1, *V/V*) and preparative HPLC [CH_3CN/(H_2O + 0.1‰ Et_2NH), 23 : 77] to afford **7** (5.9 mg, t_R 35.1 min) and **8** (6.3 mg, t_R 73.8 min). Fr. C (6.3 g) was chromatographed on a ODS column (CH_3OH/H_2O, 10 : 90 to 100 : 0, *V/V*) to give eleven subfractions (Fr. C1−C11). Fr. C3 (360.7 mg) was purified by a Sephadex LH20 column ($CHCl_3$/CH_3OH, 1 : 1, *V/V*) and preparative HPLC [CH_3CN/(H_2O + 0.1‰ Et_2NH), 25 : 75] to afford **3** (11.7 mg, t_R 64.3 min), **4** (5.1 mg, t_R 23.2 min), **6** (8.9 mg, t_R 41.5 min). Fr. C7 (109.8 mg) was purified by a Sephadex LH20 column ($CHCl_3$/CH_3OH, 1 : 1, *V/V*) and preparative HPLC [CH_3CN/(H_2O + 0.1‰ Et_2NH), 30 : 70] to afford **1** (7.4 mg, t_R 88.6 min). Fr. F (6.4 g) was chromatographed on ODS column (CH_3OH/H_2O, 10 : 90 to 100 : 0, *V/V*) to give twenty

two subfractions (Fr. F1−F22). Fr. F6 (134.3 mg) was purified by a Sephadex LH20 column ($CHCl_3$/CH_3OH, 1 : 1, *V/V*) and reversed phase preparative HPLC [CH_3CN/(H_2O + 0.1‰ Et_2NH), 30 : 70] to afford **2** (5.8 mg, t_R 35.7 min) and **5** (13.6 mg, t_R 22.1 min).

Identification of compounds

Melosline C (**1**). Yellow powder; [*α*]25 D−86.3 (*c* 0.67, MeOH); UV *λ*MeOH max (log *ε*): 206 (3.44), 287 (2.70) nm; IR (KBr): 3413, 3304, 3057, 2948, 2919, 1734, 1611, 1483, 1463, 1095, 747 cm^{-1}; CD (MeOH, Δ*ε*) *λ* max: 284 (−9.6), 235 (−14.8), 212 (−22.3) nm; ^1H and ^{13}C NMR data, see Table 1; HRESI- MS: *m/z* $[M + H]^+$, Calcd. for $C_{20}H_{23}N_2O_4$ 355.1652, found: 355.1658.

Melosline D (**2**). Yellow powder; [*α*]25 D−55.9 (*c* 0.56, MeOH); UV *λ*MeOH max (log *ε*): 207 (3.55), 288 (2.84) nm; IR (KBr): 3429, 2945, 1740, 1729, 1608, 1463, 1383, 1105, 753 cm^{-1}; CD (MeOH, Δ*ε*) *λ* max: 234 (−43.1), 202 (−27.4) nm; ^1H and ^{13}C NMR data, see Table 1; HRESI-MS: *m/z* $[M + H]^+$, Calcd. for $C_{23}H_{27}N_2O_5$ 411.1914, found: 411.1917.

Melosline E (**3**). Yellow powder; [*α*]25 D+76.0 (*c* 0.73, MeOH); UV *λ*MeOH max (log *ε*): 216 (3.36), 273 (2.76) nm; IR (KBr): 3406, 3260, 2952, 2870, 1632, 1456, 1385, 1115, 743 cm^{-1}; CD (MeOH, Δ*ε*) *λ* max: 268 (+56.9), 215 (−42.2) nm; ^1H and ^{13}C NMR data, see Table 1; HRESI-MS: *m/z* $[M + H]^+$, Calcd. for $C_{19}H_{25}N_2O_2$ 313.1911, found: 313.1913.

Melosline F (**4**). Yellow powder; [*α*]25 D+49.0 (*c* 1.01, MeOH); UV *λ*MeOH max (log *ε*): 211 (3.34), 275 (2.83) nm; IR (KBr): 3211, 3065, 2959, 2928, 1625, 1592, 1456, 1290, 802 cm^{-1}; CD (MeOH, Δ*ε*) *λ* max: 273 (+14.4), 233 (+10.7), 217 (−30.6) nm; ^1H and ^{13}C NMR data, see Table 1; HRESI-MS: *m/z* $[M + H]^+$, Calcd. for $C_{20}H_{27}N_2O_3$ 343.2016, found: 343.2012.

*ECD calculations of **1** and **3***

Conformational searches were performed in the Sybyl 8.1 software (Tripos Inc., USA) by using the MMFF94S molecular force field, which afforded 18 and 10 conformers for **1** and **3**, respectively, with an energy cutoff of 10 kcal·mol^{-1}. The ECD calculation for the optimized conformers was carried out by means of time-dependent DFT (TDDFT) methods at the B3LYP/6-31 + G(d) level in gas phase by using Gaussian 09 software (Gaussian Inc., Wallingford, USA). The overall ECD curves of **1** and **3** were weighted by Boltzmann distribution of each conformer (with a half-bandwidth of 0.3 eV). The calculated ECD spectra of **1** and **3** were subsequently compared with the experimental ones. The ECD curves were produced by SpecDis 1.6 software (University of Wuerzburg, Germany).

Vasorelaxant assay

The vasorelaxant activity of the isolates against KCl-induced contractions of rat renal artery rings was measured as described previously [20]. Renal arteries was removed rapidly out from SD rats, immediately placed into 4 ºC oxygenated K-H solution, cleaned of its surrounding fat and connective tissues, and then cut into about 2 mm in length. Each segment was mounted in a Multi Myograph System (Danish Myo Technology A/S, Denmark), and bathed in K-H solution [composition (in mmol·L^{-1}): NaCl, 120; KCl, 4.6; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 25; glucose, 10; $CaCl_2$, 2.5], bubbled with 95% O_2−5% CO_2 and maintained at 37 ºC. The isometric tension of renal artery rings was collected by four-channels psychological force transducers. All the rings were set to an optimal tension of 2 g and stabilized in normal K-H solution for 90 min. The rings were then contracted by 0.5 μmol·L^{-1} phenylephrine and challenged with 3 μmol·L^{-1} acetylcholine to confirm the integrity of the endothelium. Endothelium-intact rings contraction was evoked by a depolarizing KCl (60 m mol·L^{-1}) solution. The EC_{50} values of the test compounds and the positive control (phentolamine mesylate) were calculated from cumulative concentration-tension curves by linear regression.

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Cite this article as: ZHANG Jian, LI Hua, LI Yong, LI Zi-Wei, SANG Chen-Chen, GAO Mei-Hua, ZHANG Dong-Mei, ZHANG Xiao-Qi, YE Wen-Cai. Four new corynanthe-type alkaloids from the roots of *Alstonia scholaris* [J]. *Chin J Nat Med*, 2019, **17**(12): 918-923.

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