Artificial *Erythrina* Alkaloids from Three *Erythrina* Plants, *E. variegata*, *E. crista-galli* and *E. arborescens*

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Abstract

Fourteen unprecedented artificial *Erythrina* alkaloids were isolated from the *Erythrina variegata*, *E. crista-galli* and *E. arborescens* (Fabaceae). The structures of these alkaloids were determined by spectroscopic analyses. Their possible formations were proposed. All isolated compounds showed no cytotoxicity and hypoglycemic activity at cell screening bioassay.

Keywords Fabaceae · *Erythrina variegata* · *E. crista-galli* · *E. arborescens* · Artificial products · *Erythrina* alkaloids

1 Introduction

The *Erythrina*-type alkaloids with 6/5/6/6 spirocycle systems and stable 5*S*-chiral center are derived from two tyrosine units via oxidative coupling and intramolecular rearrangement. Since the first phytochemical research on *Erythrina* alkaloid in 1930s [1], the total number now stands at well over 110 alkaloids reported from plants of *Erythrina* genus [2]. Bioassay screening of these alkaloids showed anxiolytic-like activity [3], induced sleep [4], anticonvulsant activity [5], neuronal nicotinic acetylcholine receptor antagonism [6], leishmanicidal [7], anticataract [7], and antifeedant activity [8]. Our previous research disclosed natural dimeric [9, 10] and trimeric [11] *Erythrina* alkaloids, alkaloidal glucosides [10], and complex monomers [12–14]. However, during the extraction and separation of *Erythrina* alkaloids, some artificial products would be

produced. Consideration of the NMR spectra characteristics and potential activities of *Erythrina* alkaloid, we here systematically summarized these artifacts from *E. arborescens*, *E. crista-galli* and *E. variegata* (Fig. 1). Their cytotoxicity against three cancer cells and hypoglycemic activity on 3T3-L1 myoblasts cell were screened. This paper will describe their isolation, structure determination and possible mechanism of formation.

2 Results and Discussion

Alkaloid **1** was obtained as white amorphous powder. Its IR absorption bands at 3441, 1640, 1503, 1480 cm⁻¹ indicated the presence of the hydroxyls and aromatic rings. Moreover, the UV absorptions at 204, 239 and 290 nm indicated a tetrahydroisoquinoline chromophore [15]. These spectra were consistent with the characteristics of an *Erythrina* alkaloid. Alkaloid **1** had a molecular formula C₃₉H₄₀N₂O₉ as established by the HRESIMS *m/z* at 681.2811 [M+H]⁺, together with the ¹H and ¹³C NMR spectroscopic data. In the ¹H NMR spectrum of **1** (Table 1), four aromatic singlet proton (δ_{H} 7.08, 7.01, 6.74 × 2), two pairs of olefin [δ_{H} 7.16 (*dd*, *J* = 10.2, 4.2 Hz), 5.92 (*d*, *J* = 10.2 Hz), and 6.56 (*dd*, *J* = 10.2, 2.4 Hz), 6.06 (*d*, *J* = 10.2 Hz)], two methylenedioxy group (δ_{H} 5.96, 5.94, 5.93 and 5.92), and two methoxyl group (δ_{H} 3.29 and 3.24) signals indicated that **1** might be an *Erythrina* alkaloid dimer. In comparison with the reported dimer, erythrivarine A [9], alkaloid **1** had three more signals at δ_{C} 208.1, 47.5 and 31.2 in the ¹³C NMR spectra and 56 mass units higher in molecular weight, which showed

Bing-Jie Zhang and Jing Wu have contributed equally to this work.

Dedicated to Professor Han-Dong Sun on the occasion of his 80th birthday.

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Fig. 1 Chemical structures of 14 artificial *Erythrina* alkaloids

an extra 2-oxopropyl group in **1**. In the HMBC spectrum, correlations of δ_{H} 4.20 (H-8) with δ_{C} 53.9 (C-10), δ_{C} 136.2 (C-7) and δ_{C} 208.1 (C=O) indicated the 2-oxopropyl group at C-8. Further analysis of the 2D NMR revealed that the other parts of compound **1** were consistent with those of erythravarine A.

Alkaloids **2** and **3** showed the same molecular formula C₄₀H₄₂N₂O₉ as established by HRESIMS (m/z 695.2968 [M+H]⁺ in **2**; m/z 695.2970 [M+H]⁺ in **3**). In the ¹H and ¹³C NMR spectra, the chemical shifts of **2** and **3** showed good agreement with those of **1**, except those signals around the C-11' position (C-10'/11'/12'). The C-11' carbon of **1** was resonated at δ 64.9, however, signals of the same carbon were observed at δ 74.7 and δ 74.5 in **2** and **3**, respectively. In addition, an extra methoxyl group (δ_{H} 3.54 in **2**, δ_{H} 3.36 in **3**) was observed, which indicated that both **2** and **3** had a methoxyl group at the C-11' position instead of a hydroxyl group in **1**. Chemical shifts of H-10', H-11' and H-17' protons (Table 1) of **2** and **3** implied the configuration of 11'-OCH₃ in **2** and **3** were different. In the ROESY spectrum, the NOE correlation of H-3'/ β /H-4' β and H-11'/H-4' α in **3** suggested its 11'-OCH₃ was in β -orientation. The NOE correlation of H-11'/H-4' β in **2** suggested its 11'-OCH₃ was in α -orientation.

The HRESIMS of **4** showed the pseudomolecular ion at m/z 370.1651 [M+H]⁺ (calc. for C₂₁H₂₃NO₅, 370.1652). The ¹³C NMR spectrum of **4** showed a methine at 64.7 ppm, which indicated the existence of hydroxy substituent. The

HMBC correlation between δ_{H} 7.05 (H-17) with δ_{C} 64.7 suggested the hydroxy at C-11. Through detailed comparison of the 1D and 2D NMR spectrum, **4** was basically the same as erythranine [16] except for the 2-oxopropyl substituent (δ_{C} 207.9, 47.8 and 30.8). The HMBC spectrum showed correlations from δ_{H} 3.98 (H-8) to δ_{C} 52.6 (C-10), δ_{C} 127.6 (C-7) and δ_{C} 207.9 (C=O) disclosed **4** to be 8-(2-oxopropyl)-erythranine.

Alkaloid **5** displayed a hydrogen adduct ion at m/z 354.1709 [M+H]⁺ (calc. for C₂₁H₂₃NO₄, 354.1707). The 1D NMR spectroscopic data of compound **5** were similar to those of **4** except for the following differentiations: in the ¹H NMR spectrum, the signal displayed at δ_{H} 4.72 in **4** which was assigned to the active hydrogen in the hydroxy was disappeared in compound **5**. Correspondingly, the methine signal at δ_{C} 64.7 (C-11) in compound **4** was replaced with a methylene (δ_{C} 26.0) in **5**. Thus, compound **5** was an analogue of **4** without the hydroxy moiety and determined to be 8-(2-oxopropyl)-erythraline.

The HRESIMS of **6** gave a hydrogen adduct ion at m/z 384.1806 [M+H]⁺, indicative of a molecular formula of C₂₂H₂₅NO₅. In comparing with those of **4**, the ¹H NMR spectrum of **6** gave signal of an additional methoxyl group (δ_{H} 3.55, s, 3H), and its ¹³C NMR spectrum showed an downfield chemical shift δ_{C} 74.8. These findings suggested the C-11 of **6** was substituted by a methoxy rather than a hydroxy. Thus, the structure of **6** was determined to be 8-(2-oxopropyl)-11-methoxy-erythraline.

Table 1 ^1H and ^{13}C NMR spectroscopic data for **1–3** in acetone- d_6 (δ in ppm and J in Hz)

Enrty	1		2		3	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1	7.16, dd (10.2, 4.2)	124.6 d	7.16, d (10.2)	124.8 d	7.06, overlap	124.7 d
2	5.92, d (10.2)	132.1 d	6.00, d (10.2)	132.2 d	6.00, d (10.2)	132.2 d
3	3.68, m	76.9 d	3.73, m	76.8 d	3.73, m	77.0 d
4	2.38, dd (11.4, 6.0)	43.6 t	2.44, dd (10.8, 6.0)	42.9 t	2.40, dd (10.8, 6.0)	43.0 t
	1.68, t (11.4)		1.69, t (10.8)		1.70, t (10.8)	
5		69.2 s		68.9 s		69.2 s
6		139.6 s		139.7 s		138.2 s
7		136.2 d		136.8 d		135.6 d
8	4.20, m	69.7 d	4.30, m	68.3 d	4.23, br s	69.2 d
10	3.48, dd (11.4, 5.4)	53.9 t	3.34, dd (11.4, 4.8)	50.7 t	3.47, dd (11.4, 4.8)	53.2 t
	2.51, overlap		2.77, br d (11.4)		2.61, overlap	
11	4.65, m	64.7 d	4.66, m	64.7 d	4.75, m	64.8 d
12		134.1 s		133.9 s		133.9 s
13		132.2 s		132.6 s		132.6 s
14	6.74, s	106.1 d	6.73, s	105.8 d	6.90, s	106.1 d
15		147.7 s		147.3 s		147.3 s
16		147.2 s		147.3 s		147.3 s
17	7.01, s	108.7 d	7.01, s	108.6 d	7.06, s	107.3 d
OCH ₂ O	5.96, s	101.8 t	5.96, s	101.8 t	5.96, s	102.0 t
	5.94, s		5.95, s		5.95, s	
3-OCH ₃	3.29, s	56.3 q	3.26, s	56.2 q	3.25, s	56.2 q
11-OH					4.63, d (5.4)	
CH ₂ COCH ₃	3.21, overlap	47.5 t	3.42, m	47.1 t	3.35, m	47.5 t
	2.71, m		2.71, m		2.64, m	
CH ₂ COCH ₃		208.1 s		207.8 s		208.2 s
CH ₂ COCH ₃	2.14, s	31.2 q	2.13, s	31.0 q	2.13, s	31.2 q
1'	6.56, dd (10.2, 2.4)	125.5 d	6.55, dd (10.2, 1.8)	125.5 d	6.54, dd (10.2, 1.8)	125.7 d
2'	6.06, d (10.2)	133.6 d	6.06, d (10.2)	133.6 d	6.09, d (10.2)	133.6 d
3'	3.32, m	76.8 d	3.93, m	76.8 d	4.06, m	76.6 d
4'	2.46, dd (11.4, 5.4)	41.6 t	2.44, dd (10.8, 6.0)	41.6 t	2.49, dd (10.8, 6.0)	40.9 t
	1.79, t (11.4)		1.79, t (10.8)		1.77, t (10.8)	
5'		68.2 s		68.4 s		68.3 s
6'		142.8 s		143.2 s		143.4 s
7'	5.58, s	127.3 d	5.57, s	127.4 d	5.58, s	127.4 d
8'	4.92, s	66.4 d	4.90, s	64.6 d	4.92, s	64.5 d
10'	3.36, dd (13.2, 4.8)	50.5 t	3.42, dd (13.2, 4.0)	47.0 t	3.21, m	43.2 t
	2.83, overlap		2.83, dd (13.2, 5.0)		3.15, m	
11'	4.78, m	64.9 d	4.24, s	74.7 d	4.00, s	74.5 d
12'		132.5 s		129.2 s		129.2 s
13'		133.4 s		132.6 s		132.6 s
14'	6.74, s	105.9 d	6.78, s	106.0 t	6.75, s	105.8 d
15'		147.3 s		147.3 s		148.4 s
16'		147.2 s		147.3 s		147.3 s
17'	7.08, s	106.8 d	6.92, s	108.1 d	7.37, s	110.3 d
OC'H ₂ O	5.93, s	101.7 t	5.95, s	101.8 t	5.95, s	101.8 t
	5.92, s		5.94, s		5.94, s	
3'-OCH ₃	3.24, s	56.2 q	3.29, s	56.2 q	3.35, s	56.3 q
11'-OCH ₃			3.54, s	58.1 q	3.36, s	58.0 q

 ^1H NMR recorded at 600 MHz, ^{13}C NMR recorded at 150 MHz

The molecular formula of **7** was determined to be $C_{21}H_{25}NO_5$ from the HRESIMS m/z at 394.1626 $[M+Na]^+$. Its 1H NMR spectrum showed two aromatic singlet protons (δ_H 6.84 and 6.76), three conjugate olefin signals (δ_H 6.60, 6.10 and 5.67), and four methoxy groups (δ_H 3.28, 3.70, 3.78 and 3.97). The ^{13}C NMR spectrum of **7** showed three methylenes (δ_C 24.6, 43.3, 44.4), two methines (δ_C 76.9 and 70.5) and a carbonyl (δ_C 172.1). These data suggested **7** might be a carbomethoxyl derivative of erysotrine [17]. The HMBC correlations from δ_H 3.78 (OCH_3) and δ_H 4.33 (H-8) to δ_C 172.1 (C=O) assigned the carbomethoxy at C-8. The molecular formula of **8** was determined to be $C_{20}H_{21}NO_6$ from the HRESIMS m/z at 372.1444 $[M+H]^+$. The 1H and ^{13}C NMR the structural pattern of **8** was identical to that of **5**, and the additional carbomethoxyl moiety was identical to that of **7**. Accordingly, the structures of **7** and **8** were determined to be 8-carbomethoxyerysotrine and 8-carbomethoxyerythranine, respectively.

Alkaloid **9** showed molecular ion peaks at m/z 370.1652 $[M+H]^+$, suggesting the molecular formulae $C_{21}H_{24}NO_5$. In comparing with compound **5**, the 1H and ^{13}C NMR signal of δ_H 2.13 (CH_3) and δ_C 207.7 (CH_2COCH_3) in **5** were changed to δ_H 3.61 (OCH_3) and δ_C 172.5 (CH_2COOCH_3) in **9**, respectively. The remaining NMR data were almost identical to those of **5**. Thus, the structure of **9** was determined to be 8-acetatemethoxyerythraline.

The molecular formulas of compounds **10** and **11** were deduced to be $C_{21}H_{23}NO_6$ and $C_{22}H_{25}NO_6$ from the HRESIMS at m/z 386.1599 $[M+H]^+$ and 400.1758 $[M+H]^+$, respectively. The 1H and ^{13}C NMR data of both **10** and **11** are very similar to those of **9** except that the methylene signal was replaced by an oxymethine signal at the C-11 position. Further, in the ^{13}C NMR, the signal for C-11 appeared at 64.8 and 74.7 ppm for compounds **10** and **11**, similar to that of **4** and **6**, respectively. Thus, **10** was identified as 8-acetatemethoxyerythranine. **11** had an extra methoxy and was identified as 8-acetatemethoxy-10 β -methoxyerythraline.

The molecular formula **12** was established as $C_{22}H_{27}NO_5$ based on the HRESIMS m/z = 386.1964 $[M+H]^+$. From the 1H and ^{13}C NMR data, the structure of **12** was very similar to **9** except for the replacement of methylenedioxy group by two methoxys at C-15 and C-16. This was confirmed from the HMBC and HSQC spectra. Alkaloid **12** was thus identified as 8-acetatemethoxyerysotrine.

The HRESIMS m/z at 394.1628 $[M+Na]^+$ of **13** assigned the molecular formula to be $C_{21}H_{25}NO_5$, 58 mass units higher than that of erysotrine. Its ^{13}C NMR spectrum gave an additional methylene (δ_C 34.9) and a carbonyl (δ_C 172.3) signals, indicating the existence of an acetyl group. The HMBC correlations from δ_H 2.51 (CH_2CO) and δ_H 4.14 (H-8) to δ_C 172.3 (C=O) suggested that the acetyl group was located at C-8. Accordingly, the structure of **13** was determined to be 8-acetylerysotrine. The molecular formula of

14 was determined to be $C_{20}H_{21}NO_5$ by the HRESIMS m/z at 378.1313 $[M+Na]^+$. The 1D NMR spectrum gave signals similar to that of erythraline expect for the replacement of a methylene by an acetyl group (δ_C 35.4 and δ_C 172.3). In the HMBC spectrum, the correlations from δ_H 4.07 (H-8) to δ_C 172.3 (COOH) and δ_H 2.74 (CH_2COOH) to δ_C 65.4 (C-8) and δ_C 172.3 (COOH) confirmed that **14** was an 8-acetyl derivative of erythraline.

The configurations of H-8 for compound **1–14** were determined to be β based on ROESY experiments with correlations of H-3 β /H-4 $_{eq}$, H-4 $_{eq}$ /H-10 $_{ax}$ and H-10 $_{eq}$ /H-8 (Fig. 2). Further, together with 5*S*-configuration in all *Erythrina* alkaloids [18], so absolute configuration of alkaloids **1–14** could be determined.

Since N-containing compounds were main candidates of anticancer and hypoglycemic drugs, so alkaloids **1–14** were evaluated for their cytotoxicity against human A-549 lung cancer, SGC-7901 gastric cancer, and HeLa cell lines using the MTT method. In addition, their hypoglycemic activity on 3T3-L1 myoblasts cell were screened. Unfortunately, none of them showed positive activity. Alkaloids **1–14** possessed acetyl, acetyl methyl, acetate, or methyl formate groups, which indicated they were artificial products. Without considering the artificial units, these alkaloids are known. During the extraction and isolation, methanol, acetone, petroleum ether, especial ethyl acetate, were used as solvents. Accordingly, acetone and residual of acetic acid, methyl acetate and methyl formate in above solvents would become reaction reagents. Alkaloids **1–6** and **9–14** were formed firstly through an iminium intermediate by oxidation, then by nucleophilic attack from carbanion of acetone, acetic acid, and methyl acetate in base condition. On the other hand, the iminium intermediate could be tautomerized to imine and

Fig. 2 Selected NOE interaction of alkaloid **9**

attacked to methyl formate, generating the carbomethoxy substituted products (7–8) (Fig. 3).

3 Experimental Section

3.1 General Experimental Procedures

Optical rotations were measured with a Jasco p-1020 digital polarimeter. UV spectra were recorded on a Shimadzu 2401PC spectrophotometer. IR spectra were obtained on a Bruker Tensor 27 infrared spectrophotometer with KBr pellets. ^1H , ^{13}C and 2D NMR spectra were obtained on Bruker AV-600, AVANCE III-500 and 400 MHz spectrometers with SiMe_4 as an internal standard. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. MS data were recorded on an UPLC-IT-TOF MS. Column chromatography (CC) was performed on either silica gel (200–300 mesh, Qingdao Marine Chemical Co., Ltd., Qingdao, China) or RP-18 silica gel (20–45 μm , Fuji Silysia Chemical Ltd., Japan). Fractions were monitored by TLC on silica gel plates (GF254, Qingdao Marine Chemical Co., Ltd., Qingdao, China), and spots were visualized with Dragendorff's reagent spray. MPLC was performed using a Buchi pump system coupled with RP-18 silica gel-packed glass columns (15 $\times$ 230 and 26 $\times$ 460 mm, respectively). HPLC was performed using Waters 1525 pumps coupled with analytical or preparative Sunfire C_{18} columns (4.6 $\times$ 150 and 19 $\times$ 250 mm, respectively). The HPLC

system employed a Waters 2998 photodiode array detector and a Waters fraction collector III.

3.2 Plant Material

Flowers of *E. variegata* Linn and *E. crista-galli* Linn were collected in February and April, respectively, 2014 in Simao of Yunnan Province, People's Republic of China. Leaves and flowers of *Erythrina arborescens* Roxb. Hort. Beng were collected in October 2014 in Jianshui of Yunnan Province. These plant samples were identified by Dr. Chun-Xia Zeng. The voucher specimens (Cai20140207, Cai20140407, Cai20141003 and Cai20141004) have been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, the Chinese Academy of Sciences.

3.3 Extraction and Isolation

The dried and powdered flowers of *E. variegata* (10.0 kg) were extracted with 90% MeOH (25 L) for three times. The extracts were concentrated under reduced pressure, and then dissolved in 2% acetic acid to adjust pH to 2–3 and then partitioned twice with EtOAc. The aqueous layers were basified with $\text{NH}_3 \cdot \text{H}_2\text{O}$ to adjust pH to 8–9 and then extracted with EtOAc to give a crude alkaloid fraction (110 g). The crude alkaloid was subjected to column chromatography (CC) over silica gel with gradient CHCl_3 -Acetone (1:0 to 1:1) to afford seven fractions (Fr. I–Fr. VII). Fr. I (6.1 g) was divided into 2 subfractions (Fr. I-1–Fr. I-2) by using RP-MPLC eluting

Fig. 3 Possible formation of two typically artificial *Erythrina* alkaloids

with MeOH–H₂O (50–100%). Fr. I-2 was isolated by preparative C₁₈ HPLC column with a gradient of MeOH–H₂O (60:40–70:30, v/v) to obtain **9** (35 mg) and **11** (41 mg). Fr. II (4.5 g) was separated using C₁₈ MPLC column with a gradient of MeOH–H₂O (40:60–90:40, v/v) to afford **10** (35 mg) and **8** (13 mg). Fr. IV (8.5 g) was fractionated by C₁₈ MPLC column with a gradient of MeOH–H₂O (10:90–90:10, v/v) to give six subfractions (Fr. IV-1–Fr. IV-6). Fr. IV-2 was subjected to a preparative C₁₈ HPLC column with a gradient of MeOH–H₂O (50:50–60:40, v/v) to afford **6** (20 mg) and **5** (32 mg). Fr. IV-4 was subjected to a preparative C₁₈ HPLC column with a gradient of MeOH–H₂O (70:30–80:20, v/v) to give **1** (5 mg). Fr. V (12 g) was chromatographed on a C₁₈ MPLC column eluted with a gradient of MeOH–H₂O (10:80–100:0, v/v) to give six subfractions (Fr. V-1–Fr. V-6). **2** (29 mg) and **3** (21 mg) was obtained from Fr. V-5 using a preparative C₁₈ HPLC column with a gradient of MeOH–H₂O (65:35–25:75, v/v).

Flowers of *E. crista-galli* (11 kg) were powdered and extracted with 90% MeOH (25 L) for three times. The extract was concentrated in vacuo to give a brown residue. The crude alkaloid (90 g) were obtained using the same acid–base treatment method described above, and then subjected to column chromatography (CC) over silica gel and eluted with gradient CHCl₃–Acetone (1:0 to 1:1) to afford four fractions (Fr. I–Fr. IV). Fr. I (12.1 g) was further chromatographed on a C₁₈ MPLC column eluted with a gradient of MeOH–H₂O (50:50–100:0, v/v) to give the two subfractions (Fr. I-1–Fr. I-2). Alkaloid **12** (51 mg) was obtained from Fr. I-1 using a column chromatography (CC) over silica gel and eluted with petroleum ether–acetone (4:1).

Crude alkaloid extract (85.2 g) and (62.5 g) were obtained from the leaves (15.8 kg) and flowers (6.5 kg) of *Erythrina arborescens*, respectively. The crude alkaloid of leaves was divided into nine fractions (Fr. I–Fr. IX). Fr. V (7.1 g) was fractionated by C₁₈ MPLC column with a gradient of MeOH–H₂O (20:80–80:20, v/v) to give three subfractions (Fr. V-1–Fr. V-3). Fr. V-3 was subjected to a preparative C₁₈ HPLC column with a gradient of MeOH–H₂O (60:40–70:30, v/v) to afford **4** (1 mg) and **14** (5 mg). The crude alkaloid of flowers was divided into seven fractions (Fr. I–Fr. VII). **7** was obtained from Fr. II by C₁₈ MPLC column with a gradient of MeOH–H₂O (40:60–100:0, v/v) and then purified by preparative C₁₈ HPLC column with a gradient MeOH–H₂O (50:50–60:40, v/v). Fr. IV (4.5 g) was chromatographed on a C₁₈ MPLC column eluted with a gradient of MeOH–H₂O (20:80–70:30, v/v) to give four subfractions (Fr. IV-1–Fr. IV-4). Fr. IV-3 was further purified by a preparative C₁₈ HPLC column with a gradient of MeCN–H₂O (25:75–35:65, v/v) to afford **13** (20 mg).

8 α -(2-oxopropyl)-erythrivarine A (1): white powder; $[\alpha]_D^{20}$ – 121.2 (*c* 0.2, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 204 (4.26), 239 (3.88) and 290 (3.46) nm; IR (KBr) $\nu_{\max}$

3441, 2924, 1640, 1503, 1480, 1226, 1100, 1041 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Table 1; positive HRESIMS *m/z* 681.2811 [M+H]⁺ (calcd. for C₃₉H₄₁N₂O₉, 681.2110).

8 α -(2-oxopropyl)-11'-O-methyl-erythrivarine A (2): white powder; $[\alpha]_D^{20}$ – 114.1 (*c* 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 203 (4.12), 238 (3.66) and 289 (3.43) nm; IR (KBr) $\nu_{\max}$ 3441, 1639, 1490, 1234, 1101, 1040 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Table 1; positive HRESIMS *m/z* 695.2968 [M+H]⁺ (calcd. for C₄₀H₄₃N₂O₉, 695.2969).

8 α -(2-oxopropyl)-11'-epi-O-methyl-erythrivarine A (3): white powder; $[\alpha]_D^{20}$ – 165.2 (*c* 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 204 (4.22), 238 (3.88) and 289 (3.46) nm; IR (KBr) $\nu_{\max}$ 3441, 2924, 1629, 1503, 1482, 1234, 1100, 1040 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Table 1; positive HRESIMS *m/z* 695.2970 [M+H]⁺ (calcd. for C₄₀H₄₃N₂O₉, 695.2969).

8 α -(2-oxopropyl)-erythrine (4): white powder; $[\alpha]_D^{20}$ + 133.0 (*c* 0.2, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 204 (4.71), 239 (3.63) and 289 (3.32) nm; IR (KBr) $\nu_{\max}$ 2930, 1630, 1503, 1489 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Tables 2 and 4; positive HRESIMS *m/z* 370.1651 [M+H]⁺ (calcd. for C₂₁H₂₄NO₅, 370.1652).

8 α -(2-oxopropyl)-erythraline (5): white powder; $[\alpha]_D^{23}$ + 80.5 (*c* 0.10, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 201 (4.11), 238 (2.37), 289 (1.29) nm; IR (KBr) $\nu_{\max}$ 1712, 1480, 1423 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Tables 2 and 4; positive HRESIMS *m/z* 354.1709 [M+H]⁺ (calcd. for C₂₁H₂₃NO₄, 354.1707).

8 α -(2-oxopropyl)-11-methoxy-erythraline (6): white powder; $[\alpha]_D^{20}$ + 95.3 (*c* 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 204 (4.76), 238 (3.74) and 288 (3.48) nm; IR (KBr) $\nu_{\max}$ 1631, 1504, 1483 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Tables 2 and 4; positive HRESIMS *m/z* 384.1806 [M+H]⁺ (calcd. for C₂₂H₂₆NO₅, 384.1805).

8 α -carbomethoxyerysotrine (7): white powder; $[\alpha]_D^{22}$ + 74.0 (*c* 0.21, CH₃OH); UV (CH₃OH) $\lambda_{\max}$ (log ϵ) 203 (3.79), 225 (3.45) and 277 (3.05) nm; ¹H (400 Hz) and ¹³C (125 Hz) NMR data (acetone-*d*₆), Tables 2 and 4; Positive ESIMS *m/z* 394 [M+Na]⁺, HRESIMS *m/z*. 394.1626 [M+Na]⁺; (calcd. for C₂₁H₂₅NO₅Na, 394.1625).

8 α -carbomethoxyerythrine (8): white powder; $[\alpha]_D^{20}$ + 118.3 (*c* 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 205 (4.69), 239 (3.79) and 289 (3.51) nm; IR (KBr) $\nu_{\max}$ 2923, 1630, 1503, 1488 cm^{–1}; ¹H (600 MHz) and ¹³C NMR (150 MHz) data (acetone-*d*₆), see Tables 2 and 4; positive HRESIMS *m/z* 372.1444 [M+H]⁺ (calcd. for C₂₀H₂₂NO₆, 372.1443).

8 α -acetatemethoxyerythraline (9): white powder; $[\alpha]_D^{20}$ + 171 (*c* 0.1, MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ) 204

Table 2 ^1H NMR spectroscopic data for **4–8** in acetone- d_6 (δ in ppm and J in Hz)

Entry	δ_{H} (4) ^a	δ_{H} (5) ^a	δ_{H} (6) ^a	δ_{H} (7) ^b	δ_{H} (8) ^a
1	6.55, dd (10.2, 2.4)	6.72, dd (10.2, 2.4)	6.55, dd (10.2, 1.8)	6.60 dd (10.2, 1.9)	6.59, dd (10.2, 2.4)
2	6.01, d (10.2)	6.68, d (10.2)	6.03, d (10.2)	6.10, d (10.2)	6.07, d (10.2)
3	3.79, m	3.85, m	3.92, m	3.97, m	3.85, m
4	2.38, dd (11.4, 5.4)	2.48, dd (11.4, 5.6)	2.46, dd (11.4, 5.4)	2.53, dd (11.2, 5.7)	2.45, dd (11.4, 5.4)
	1.65, t (11.4)	1.68, t (11.4)	1.66, t (11.4)	1.78, t (11.2)	1.73, t (11.4)
7	5.67, s	5.63, s	5.64, s	5.67, s	5.71, s
8	4.20, m	3.98, m	4.33, m	4.33, s	4.68, s
10	3.48, dd (13.8, 4.8)	3.38, m	3.39, dd (13.8, 4.2)	3.49, m	3.57, dd (13.2, 4.8)
	2.68, dd (13.8, 6.6)	2.77 (overlap)	3.09, dd (13.8, 4.2)	3.02 dd (12.9, 5.7)	2.92, dd (13.2, 4.8)
11	4.75, m	2.77 (overlap)	4.18, t (4.2)	2.93, m	4.77, m
		2.65, m		2.64, m	
14	6.70, s	6.72, s	6.74, s	6.84, s	6.73, s
17	7.05, s	6.68, s	6.89, s	6.76, s	7.04, s
3-OCH ₃	3.25, s	3.28, s	3.28, s	3.28, s	3.23, s
11-OCH ₃			3.55, s		
11-OH	4.72, d (4.8)				4.64, br s
15-OCH ₃				3.70, s	
16-OCH ₃				3.97, s	
OCH ₂ O	6.01, s	5.92, s	5.96, s		5.95, s
	5.99, s	5.90, s	5.94, s		5.94, s
CH ₂ COCH ₃	2.90, dd (15.6, 4.8)	2.85 (overlap)	2.94, overlap		
	2.55, dd (15.6, 4.8)	2.58, dd (16.8, 8.0)	2.55, dd (15.6, 9.0)		
CH ₂ COCH ₃	2.13, s	2.13, s	2.12, s		
COOCH ₃				3.78, s	3.72, s

^a ^1H NMR recorded in 600 MHz^b ^1H NMR recorded in 400 MHz

(4.78), 239 (3.88) and 290 (3.52) nm; IR (KBr) ν_{max} 1628, 1501, 1489 cm^{-1} ; ^1H (600 MHz) and ^{13}C NMR (150 MHz) data (acetone- d_6), see Tables 3 and 4; positive HRESIMS m/z 370.1652 $[\text{M}+\text{H}]^+$ (calcd. for $\text{C}_{21}\text{H}_{24}\text{NO}_5$, 370.1653).

8 α -acetatemethoxyerythrinine (10): white powder; $[\alpha]_{\text{D}}^{20} + 89.4$ (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.65), 238 (3.68) and 290 (3.33) nm; IR (KBr) ν_{max} 2924, 1628, 1488 cm^{-1} ; ^1H (600 MHz) and ^{13}C NMR (150 MHz) data (acetone- d_6), see Tables 3 and 4; positive HRESIMS m/z 386.1599 $[\text{M}+\text{H}]^+$ (calcd. for $\text{C}_{21}\text{H}_{24}\text{NO}_6$, 386.1598).

8 α -acetatemethoxy-11 β -methoxyerythraline (11): white powder; $[\alpha]_{\text{D}}^{20} + 154.2$ (c 0.2, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.62), 238 (3.74) and 289 (3.41) nm; IR (KBr) ν_{max} 1630, 1503, 1484 cm^{-1} ; ^1H (600 MHz) and ^{13}C NMR (150 MHz) data (acetone- d_6), see Tables 3 and 4; positive HRESIMS m/z 400.1758 $[\text{M}+\text{H}]^+$ (calcd. for $\text{C}_{22}\text{H}_{26}\text{NO}_6$, 400.1757).

8 α -acetatemethoxyerysotrine (12): white powder; $[\alpha]_{\text{D}}^{20} + 113.3$ (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.72), 239 (3.66) and 288 (3.51) nm; IR (KBr) ν_{max} 1628, 1503, 1488 cm^{-1} ; ^1H (600 MHz) and ^{13}C NMR (150 MHz)

data (acetone- d_6), see Tables 3 and 4; positive HRESIMS m/z 386.1964 $[\text{M}+\text{H}]^+$ (calcd. for $\text{C}_{22}\text{H}_{28}\text{NO}_5$, 386.1965).

8 α -acetylerythrosotrine (13): white powder; $\text{C}_{21}\text{H}_{25}\text{NO}_5$; $[\alpha]_{\text{D}}^{22} + 5.2$ (c 0.18, CH_3OH); UV (CH_3OH) λ_{max} (log ϵ) 203 (3.90), 229 (3.56) and 282 (2.93) nm; ^1H (400 Hz) and ^{13}C (125 Hz) NMR data (acetone- d_6), Tables 3 and 4; Positive ESIMS m/z 394 $[\text{M}+\text{Na}]^+$, HRESIMS m/z . 394.1628 $[\text{M}+\text{Na}]^+$; (calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{Na}$, 394.1625).

8 α -acetylerythraline (14): white powder; $[\alpha]_{\text{D}}^{20} + 105$ (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.71), 249 (3.72) and 289 (3.62) nm; IR (KBr) ν_{max} 3341, 1639, 1503, 1442 cm^{-1} ; ^1H (600 MHz) and ^{13}C NMR (150 MHz) data (acetone- d_6), see Tables 3 and 4; positive HRESIMS m/z 378.1313 $[\text{M}+\text{H}]^+$ (calcd. for $\text{C}_{20}\text{H}_{22}\text{NO}_5$, 378.1314).

3.4 Cytotoxicity

The human A-549 lung cancer, SGC-7901 gastric cancer, and HeLa cell lines were used in the cytotoxic assay. These cells were grown in DMEM media (HyClone, USA) supplemented with 10% fetal bovine serum (HyClone, USA) at 37 °C in 5% CO_2 . The cytotoxicity of all alkaloids were

Table 3 ^1H NMR spectroscopic data for **9–14** in acetone- d_6 (δ in ppm, J in Hz)

Entry	$\delta_{\text{H}}(\mathbf{9})^{\text{a}}$	$\delta_{\text{H}}(\mathbf{10})^{\text{a}}$	$\delta_{\text{H}}(\mathbf{11})^{\text{a}}$	$\delta_{\text{H}}(\mathbf{12})^{\text{a}}$	$\delta_{\text{H}}(\mathbf{13})^{\text{b}}$	$\delta_{\text{H}}(\mathbf{14})^{\text{a}}$
1	6.54, dd (10.2, 2.4)	6.55, dd (10.2, 2.4)	6.56, dd (10.2, 1.8)	6.57, dd (10.2, 2.4)	6.60, d (10.2)	6.58, dd (10.2, 2.2)
2	6.00, d (10.2)	5.99, d (10.2)	6.04, d (10.2)	6.05, d (10.2)	6.14, d (10.20)	6.11, d (10.2)
3	3.8, m	3.77, m	3.91, m	4.01, m	4.09, m	3.92, m
4	2.48, dd (11.4, 5.4)	2.38, overlap	2.46, dd (11.4, 5.4)	2.50, m	2.63, dd (10.9, 5.7)	2.66, dd (11.4, 5.5)
	1.69, t (11.4)	1.64, t (11.4)	1.66, t (11.4)	1.69, t (10.8)	1.78, t (10.9)	1.77, t (11.4)
7	5.66, s	5.70, s	5.69, s	5.64, s	5.68, s	5.72, s
8	3.94, m	4.16, m	4.31, m	4.05, m	4.14, m	4.07, m
10	3.40, m	3.50, dd (12.0, 5.4)	3.39, dd (13.8, 4.2)	3.37, m	3.49, m	3.53, m
	2.75, m	2.65, dd (12.0, 6.6)	3.06, dd (13.8, 4.2)	2.95, m	3.16, m	3.03, m
11	2.84, overlap	4.77, m	4.19, t (4.2)	2.96, m	3.03, m	2.98, m
	2.65, overlap			2.57, m	2.72, overlap	2.84, m
14	6.70, s	6.69, s	6.90, s	6.83, s	6.84, s	6.73, s
17	6.68, s	7.05, s	6.74, s	6.81, s	6.78, s	6.74, s
3-OCH ₃	3.25, s	3.23, s	3.29, s	3.28, s	3.31, s	3.30, s
11-OCH ₃			3.55, s			
11-OH		4.60, d (5.4)				
15-OCH ₃				3.78, s	3.68, s	
16-OCH ₃				3.67, s	3.79, s	
OCH ₂ O	5.91, s	5.95, s	5.96, s			5.96, s
	5.89, s	5.94, s	5.94, s			5.95, s
CH ₂ COO–	2.68, dd (15.0, 4.8)	2.73, dd (15.0, 4.8)	2.81, dd (15, 4.2)	2.72, dd (15.0, 4.8)	2.76, overlap	2.74, dd (16.8, 5.8)
	2.39, dd (15.0, 7.8)	2.36, overlap	2.36, dd (15, 6.0)	2.41, dd (15.0, 7.8)	2.51, dd (16.5, 2.8)	2.51, dd (16.8, 1.8)
CH ₂ COOCH ₃	3.61, s	3.60, s	3.62, s	3.63, s		

^a ^1H NMR recorded in 600 MHz^b ^1H NMR recorded in 400 MHz

determined based on the MTT method in 96-well microplates. In short, 100 μL adherent cells were seeded into each well and incubated for 12 h before the addition of the test alkaloids/drug. At the same time, the suspended cells were seeded at an initial density of 1×10^5 cells/mL just before the addition of the alkaloids/drug. Each tumor cell line was exposed to a test compound at concentration 20 μM in DMSO in triplicate for 48 h, with camptothecin as the positive control. After treatment, cell viability was assessed.

3.5 Hypoglycemic Activity

3T3-L1 myoblasts cells were purchased from American Type Culture Collection (Manassas, VA). Cells were maintained in DMEM supplemented with 10% FBS or CS (for 3T3-L1

cells), 100 units/ml penicillin and 100 mg/ml streptomycin in 10 cm diameter dishes in a humidified atmosphere of 95% air and 5% CO_2 at 37 °C. Cells were maintained in continuous passages by trypsinization of subconfluent cultures and fed fresh medium every 48 h. For differentiation, L6 myoblasts were transferred to DMEM with 2% FCS in tissue culture plates for 5–6 days, 3T3-L1 cells were exposed to 0.5 mM IBMX, 1 mM dexamethasone, 1 mM rosiglitazone and 1 mg/mL insulin for 3 days, and 1 mg/mL insulin for the other day. For glucose uptake assay, cells were serum starved for 4 h in 96-well plates, followed by incubated with insulin and alkaloids **1–14** for 24 h. Finally, the supernatants of cultured cells were collected and subjected to glucose assay using a commercially kit. The quantified values were normalized based on the results of the MTS assay.

Table 4 ^{13}C NMR spectroscopic data from **4** to **14** in acetone- d_6 (δ in ppm)

Entry	δ_{C} (4) ^a	δ_{C} (5) ^a	δ_{C} (6) ^a	δ_{C} (7) ^b	δ_{C} (8) ^a	δ_{C} (9) ^a	δ_{C} (10) ^a	δ_{C} (11) ^a	δ_{C} (12) ^a	δ_{C} (13) ^b	δ_{C} (14) ^a
1	125.4 d	125.6 d	125.7 d	125.3 d	125.2 d	125.4 d	125.3 d	125.5 d	125.6 d	125.1 d	125.0 d
2	133.1 d	133.1 d	133.1 d	134.0 d	134.2 d	133.1 d	133.2 d	133.1 d	133.2 d	134.1 d	134.1 d
3	76.9 d	77.0 d	76.8 d	76.9 d	76.8 d	76.8 d	76.9 d	76.7 d	77.0 d	76.6 d	76.5 d
4	43.3 t	43.8 t	42.7 t	43.3 t	43.1 t	43.8 t	43.6 t	42.7 t	43.4 t	42.3 t	42.7 t
5	69.3 s	69.3 s	68.6 s	69.4 s	69.7 s	69.6 s	69.7 s	68.9 s	68.9 s	69.1 s	69.7 s
6	142.3 s	142.6 s	142.4 s	144.4 s	144.2 s	142.7 s	142.4 s	142.4 s	142.9 s	143.1 s	143.0 s
7	127.6 d	127.6 d	127.9 d	121.7 d	122.4 d	126.9 d	127.1 d	127.3 d	126.7 d	125.2 d	125.6 d
8	67.7 d	65.1 d	65.8 d	70.5 d	73.2 d	66.1 d	68.5 d	66.4 d	64.4 d	63.9 d	65.4 d
10	52.6 t	43.9 t	45.2 t	44.4 t	53.1 t	44.2 t	53.0 t	45.4 t	42.6 t	40.8 t	42.3 t
11	64.7 d	26.0 t	74.8 d	24.6 t	65.1 d	26.0 t	64.8 t	74.7 d	24.6 t	24.1 t	25.5 t
12	132.2 s	129.4 s	130.1 s	128.0 s	133.3 s	129.4 s	133.5 s	130.0 s	127.7 s	126.8 s	128.7 s
13	133.4 s	134.0 s	133.0 s	132.2 s	131.9 s	133.9 s	132.2 s	132.9 s	132.7 s	130.9 s	132.2 s
14	105.9 d	106.5 d	105.9 d	110.6 d	105.8 d	106.4 d	105.8 d	105.7 d	110.6 d	110.4 d	106.4 d
15	147.3 s	146.7 s	148.0 s	148.2 s	147.6 s	146.6 s	147.3 s	147.8 s	148.9 s	148.5 s	147.0 s
16	147.2 s	147.0 s	147.2 s	149.1 s	147.5 s	146.9 s	147.3 s	147.1 s	148.1 s	149.4 s	147.5 s
17	107.4 d	109.4 d	109.0 d	113.1 d	108.1 d	109.3 d	107.2 d	108.8 d	113.0 d	113.1 d	109.5 d
3-OCH ₃	56.2 q	56.3 q	56.3 q	56.0 q	56.3 q	56.1 q	56.1 q	56.2 q	56.0 q	55.9 q	56.4 q
11-OCH ₃			57.9 q					57.7 q		56.0 q	
15-OCH ₃				56.1 q					56.1 q	56.3 q	
16-OCH ₃				56.1 q					55.9 q		
OCH ₂ O	101.7 t	101.7 t	101.9 t		101.9 t	101.5 t	101.7 t	101.7 t			101.9 t
CH ₂ COCH ₃	47.8 t	48.1 t	47.4 t							34.9 t	35.4 t
CH ₂ COCH ₃	207.9 s	207.7 s	207.7 s							172.3 s	172.3 s
CH ₃ COCH ₃	30.8 q	30.9 q	30.8 q								
(CH ₂)COOCH ₃						39.5 t	39.3 t	38.8 t	39.3 t		
(CH ₂)COOCH ₃				172.1 s	172.2 s	172.5 s	172.4 s	172.3 s	172.9 s		
(CH ₂)COOCH ₃				52.0 q	52.1 q	51.5 q	51.5 q	51.5 q	51.6 q		

^a ^{13}C NMR recorded in 150 MHz^b ^{13}C NMR recorded in 125 MHz

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Compliance with Ethical Standards

Conflicts of interest The authors declare no conflict of interest.

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