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THREE NEW QUINOLINE ALKALOIDS FROM THE WHOLE PLANT OF *THALICTRUM ATRIPLEX* AND THEIR BIOACTIVITIES

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Abstract – Three new quinoline alkaloids, thalicalkaloids A-C (**1**-**3**) together with three known alkaloids were isolated from the whole plant of *Thalictrum atriplex*. Their structures were elucidated by spectroscopic methods, including extensive ^{1}H, ^{13}C, and 2D-NMR techniques. Compounds **1**-**6** were tested for their antibacterial and anti-rotavirus activities. The results revealed that compound **3** exhibited high anti-rotavirus activity with therapeutic index (TI) valves of 24.0, and this valve is close to the positive control. Compounds **1**, **2**, **4**-**6** also showed potent anti-rotavirus activities with therapeutic index (TI) valves in the range of 11.0~15.8, respectively. In addition, compounds **1**-**6** showed good anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) activities with IZD of 12.2±1.5, 15.8±1.4, 14.5±1.2, 12.6±1.2, 13.4±1.4, and 14.0±1.5 mm, respectively.

The genus *Thalictrum* comprises about 200 species,[1,2] and around 67 species had been recorded in the flora of China,[2] of which about 43 species have been used as traditional folk medicines.[3,4] The previous studies on the chemical constituents have indicated that the plants of this genus are a rich resource of alkaloids, and most of which possess many kinds of biological activities.[4-12] *Thalictrum atriplex* commonly called 'Ma Wei Lian' or 'Shui Huang Lian', is a traditional herbal medicine, and mainly distributes in Tibet, Sichuan and Yunnan provinces, and this plant had been used for the treatment of infectious hepatitis, carbuncles, dysenteric diarrhea and certain gastroenteric disorders in China.[13] Modern medicinal chemistry investigations also revealed that alkaloids, triterpenoids, flavonoids and the like, are the main constituents of the plant.[14-17]

Quinoline alkaloids are important classes of *N*-based heterocyclic compounds, and they had attracted tremendous attention from researchers worldwide since the 19th century.[18,19] No quinoline alkaloids from *T. atriplex*, or their biological activity had been reported in the literature. In order to discover more bioactive components from Thalictrum species, we now investigated the chemical constituents of the whole plant of *T. atriplex* collected in Yulong County, Lijiang Prefecture, Yunnan Province. As a result, three new quinoline alkaloids, thalicalkaloids A-C (**1**-**3**), together with three known alkaloids (**4**-**6**) were isolated. This paper describes the elucidation of the structures of these compounds, and a preliminary evaluation of their antibacterial and anti-rotavirus activity.

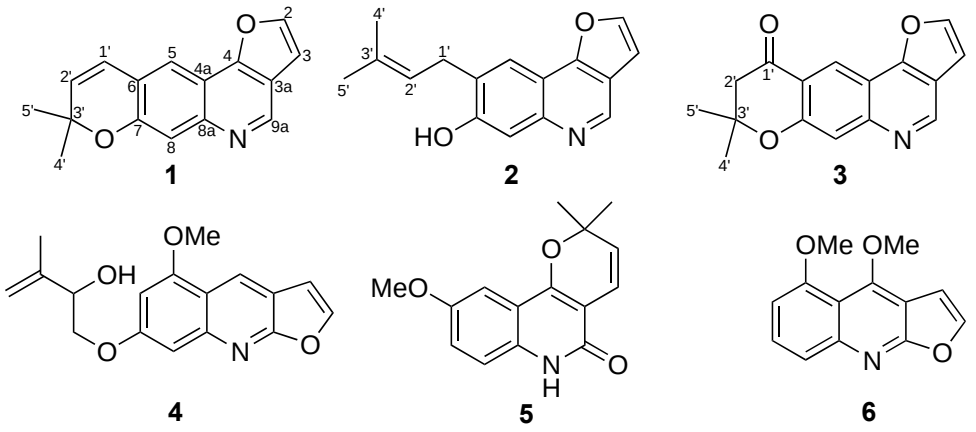

Figure 1. The quinoline alkaloids from *T. atriplex*

A 95% aq. ethanol extract prepared from whole plant of *T. atriplex* was partitioned between EtOAc and 3% tartaric acid. The aqueous layer was adjusted to pH 9.0 with saturated Na_2CO_3 aq. and extracted with EtOAc again. The EtOAc-soluble alkaloidal materials were subjected repeatedly to column chromatography on silica gel and preparative HPLC to afford three new quinoline alkaloids, thalicalkaloid A (**1**), thalicalkaloid B (**2**), and thalicalkaloid C (**3**), together with three known alkaloids (**4**-**6**). The structures of compounds **1**-**6** were shown in Figure 1, and the ^1H and ^{13}C NMR data of **1**-**3** were listed in Table 1. The known compounds, by compared with the published literature, were identified as cyclomegistine (**4**),[20] haplamine (**5**),[21] and 5-methoxydictamnine (**6**).[22]

Compound **1** was obtained as a pale-yellow gum. Its molecular formula $C_{16}H_{13}NO_2$ was deduced from its (+)-HRESIMS which showed the pseudo-molecular ion $[M+Na]^+$ at *m/z* 274.0848 (calc. 274.0844 for $C_{16}H_{13}NNaO_2$), with 11 degree of unsaturations. Its infrared spectrum exhibited bands due to aromatic protons (=C-H at 3086 cm^{-1}), imines (-C=N- at 1812 cm^{-1}), and aromatic carbons (-C=C- at 1614, 1457, and 1372 cm^{-1}). Its ^1H, ^{13}C, and DEPT NMR data displayed resonances for 16 carbons and 13 hydrogen atoms, which were ascribed to a 1,2,4,5-tetrasubstituted benzene ring (C-5~C-8, C-4a and C-8a, H-5 and H-8), a furan moiety (C-2 and C-3, H-2 and H-3),[23] a 2,2-dimethyl-2*H*-pyran moiety

(-CH=CH-C(CH_3)$_2$-O-, C-1′~C-5′; H-1′, H-2′, and H_6-4′, 5′),[24] and a –C=C-CH=N- moiety (C-4, C-3a, C-9a, and H-9a).[23] The existence of furan moiety was supported by the HMBC correlations (Figure 2) from H-2 to C-4, C-3a, From H-3 to C-4, C-3a, C-9a, from H-9a to C-3, the existence of 2,2-dimethyl-2*H*-pyran moiety was supported by the HMBC correlations from H-1′ to C-6, C-2′, C-3′, from H-2′ to C-6, C-1′, C-4′,5′, from H_6-4′,5′ to C-2′, C-3′, the existence of a –C=C-CH=N- moiety was also supported by the HMBC correlations from H-9a to C-4, C-3a. In addition, benzene ring, furan ring and 2,2-dimethyl-2*H*-pyran moiety in compound **1** were accounted for 10 of the 11 degrees of unsaturation, the still one ring was needed to meet 11 degrees of unsaturations, and the HMBC correlations from H-5 to C-4, C-4a, C-8a, from H-8 to C-4a, C-8a, from H-9a to C-3, C-4, C-3a, C-8a, from H-2 to C-4, C-3a, and from H-3 to C-4, C-3a, C-9a, also led to us to conclude that the benzene and –C=C-CH=N- moiety should be fused to a quinoline to form a furo[3,2-*c*]quinoline skeleton.[23]

Table 1. ^{1}H and ^{13}C NMR Data of compounds **1-3** ($CDCl_3$, δ in ppm, *J* in Hz)

NO.	Compound **1**		Compound **2**		Compound **3**	
	δ_C	δ_H (m, *J* in Hz)	δ_C	δ_H (m, *J* in Hz)	δ_C	δ_H (m, *J* in Hz)
2	144.1 d	7.94 d (2.8)	143.9 d	7.93 d (2.8)	145.7 d	7.93 d (2.8)
3	105.7 d	7.58 d (2.8)	105.4 d	7.53 d (2.8)	105.6 d	7.60 d (2.8)
4	156.0 s		156.4 s		158.5 s	
5	127.2 d	7.80 s	128.1 d	7.70 s	130.6 d	8.27 s
6	131.7 s		130.5 s		131.2 s	
7	155.8 s		158.3 s		160.4 s	
8	107.2 d	7.45 s	108.4 d	7.42 s	106.7 d	7.51 s
3a	115.8 s		115.5 s		116.9 s	
4a	113.4 s		113.1 s		115.5 s	
8a	140.2 s		138.2 s		140.6 s	
9a	142.7 d	8.73 s	142.5 d	8.73 s	142.5 d	8.74 s
1'	118.3 d	6.81 d (9.8)	28.4 t	3.37 d (6.8)	190.9 s	
2'	128.4 d	5.64 d (9.8)	123.4 t	5.34 t (6.8)	48.2 t	2.81 s
3'	78.0 s		133.6 s		78.6 s	
4'	26.9 q	1.59 s	25.3 q	1.58 s	25.9 q	1.55 s
5'	26.9 q	1.59 s	18.3 q	1.87 s	25.9 q	1.55 s
Ar-OH				10.84 s		

Since the furo[3,2-*c*]quinoline skeleton was determined, the positions of substituents (2,2-dimethyl-2*H*-pyran moiety) can also be determined by further analysis of its HMBC data. Long-range correlations from H-1' to C-5, C-6, C-7, from H-2' to C-6, and from H-5 to C-1' were observed. This led us to conclude that the 2,2-dimethyl-2*H*-pyran moiety was fused at C-6 and C-7, and C-1' linked to C-6. Accordingly, the structure of **1** was established, and gave the trivial name of thalicalkaloid A.

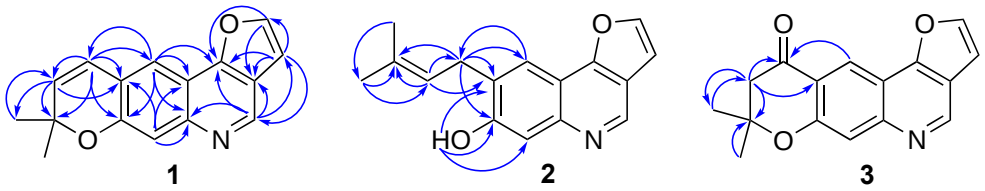

Figure 2. Key HMBC (⌒) correlations of compounds **1-3**

Thalicalkaloid B (**2**) was also obtained as pale-yellow gum with a molecular formula as $C_{16}H_{15}NO_2$, according to the ion peak of *m/z* 276.0996 ($[M+Na]^+$) in the HRESIMS. Its NMR spectra were similar to those of **1**. The chemical shift differences resulted from the disappearance of a 2,2-dimethyl-2*H*-pyran moiety, and appearance of a prenyl group ($-CH_2CH=C(CH_3)_2$, C-1′~C-5′, H_2 -1′, H-2′, H_3-4′, and H_3-6′)[25] and a phenolic hydroxyl group (δ_H 10.84 s) in **2**. These changes indicated that the 2,2-dimethyl-2*H*-pyran moiety in **1** was converted into a prenyl group and phenolic hydroxyl group in **2**. The existence of the prenyl group was also supported by the HMBC correlations (Figure 2) from H_2-1′ to C-2′, C-3′, from H-2′ to C-1′, C-3′, C-4′, C-5′, and from H-4′ and H-5′ to C-2′, C-3′. In addition, the HMBC correlation from to H_2-1′ to C-5, C-6, C-7, from H-5 to C-1′ supported the prenyl group located at C-6. The positions of the phenolic hydroxyl group located at C-7 can also be determined by the HMBC correlation from phenolic hydroxyl proton (δ_H 10.84) to C-6, C-7, C-8. The structure of **2** was therefore defined.

Thalicalkaloid C (**3**) was obtained as a yellow gum and showed a quasi-molecular ion at *m/z* 290.0784 $[M+Na]^+$ in the HRESIMS (calcd *m/z* 290.0793), corresponding to the molecular formula $C_{16}H_{13}NO_3$. The ^1H and ^{13}C NMR spectra of **3** were also similar to those of **1**. The marked differences between them were due to the disappearance of 2,2-dimethyl-2*H*-pyran moiety signals, and appearance of a 3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-pyrano moiety signal ($-CO-CH_2-C(CH_3)_2-O-$, C-1′~C-5′, H_2 -2′, H-2′, H_6-4′,5′).[25] This indicated that the 2,2-dimethyl-2*H*-pyran moiety in **1** was substituted by a 2,2-dimethyl-4-oxo-2*H*-pyrano moiety in **3**. The existence of 2,2-dimethyl-4-oxo-2*H*-pyrano moiety was also supported by the HMBC correlations (Figure 2) from H_2-2′ to C-6, C-1′, C-3′, C-4′,5′, from H-5 to C-1′, and from H6-4′,5′ to C-2′, C-3′. In addition, the 2D HMBC data of two or three-bond correlations from H_2-2′ to C-6, and from H-5 to C-1′ also revealed that the 2,2-dimethyl-4-oxo-2*H*-pyrano moiety located at C-6 and C-7, and C-1′ linked to C-6. Therefore, the structure of **3** was established as shown.

Since certain of the alkaloids from *Thalictrum* genus exhibit potential anti-viral activities,[23,26,27] compounds **1**-**3** were tested for their anti-rotavirus activities. Their ability to prevent the cytopathic effects of rotavirus in MA104 cells was tested according to our previous literatures,[28,29] and their effects were measured in parallel with the determination of antiviral activity using ribavirin as positive control. The results (Table 2) revealed that compound **3** exhibited high anti-rotavirus activity with therapeutic index (TI) valves of 24.0, and this valve is close to this postive control. Compounds **1**, **2**, **4**-**6** also showed anti-rotavirus activities with therapeutic index (TI) valves in the range of 11.0~15.8, respectively.

Table 2. Anti-rotavirus activity of compounds **1**-**6**

No.	CC_{50} (μg/mL)	EC_{50} (μg/mL)	TI (CC_{50}/EC_{50})	No.	CC_{50} (μg/mL)	EC_{50} (μg/mL)	TI (CC_{50}/EC_{50})
1	215.2	13.6	15.8	**5**	197.8	14.5	13.6
2	208.7	14.2	14.7	**6**	181.4	15.2	11.9
3	276.4	11.5	24.0	Ribavirin	279.2	11.4	24.5
4	231.5	18.4	12.6				

CC_{50}: mean (50%) value of cytotoxic concentration; EC_{50}: mean (50%) value of effective concentration; TI: therapeutic index, CC_{50}/EC_{50}.

Since certain of the alkaloids from *Thalictrum* genus exhibit potential antibacterial activities.[11,30] Compounds **1**-**6** were also tested for their antibacterial. The anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) activities were screened according to arbitrary criterion[31] with diameter of inhibition zone (IZD) as follow: very weak inhibition (with IZD of 6-8 mm), weak inhibition (with IZD of 8-12 mm), good inhibition (with IZD of 12-16 mm), and strong inhibition (with IZD of >16 mm) activities, respectively. The IZD of the positive control (vancomycin) was 31.4 ± 2.2 mm and the negative control to zero. The results revealed that compound **1**-**6** showed good inhibitions with IZD of 12.2 ± 1.5, 15.8 ± 1.4, 14.5 ± 1.2, 12.6 ± 1.2, 13.4 ± 1.4, and 14.0 ± 1.5 mm, respectively. The IZD of all compounds are lower than that of positive control (vancomycin).

EXPERIMENTAL

General Experimental Procedures. UV spectra were obtained using a Shimadzu UV-1900 spectrophotometer. A Bio-Rad FTS185 spectrophotometer was used for scanning IR spectra. ^{1}H, ^{13}C, and 2D-NMR spectroscopic data were recorded on a DRX-500 NMR spectrometer with TMS as internal standard. ESIMS and HRESIMS analyses were measured on Agilent 1290 UPLC/6540 Q-TOF mass spectrometer. Chemical shifts (δ) are expressed in ppm with reference to the TMS signal. Semi-preparative HPLC was performed on an Agilent 1260 preparative liquid chromatograph with Zorbax PrepHT GF C_{18} (2.12 mm × 25 cm) or Venusil MP C_{18} (2.0 mm × 25 cm) columns. Column

chromatography was performed using silica gel (200-300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China), Sephadex LH-20 (Sigma-Aldrich, Inc, USA), or MCI gel (75-150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan). Column fractions were monitored by TLC visualized by spraying with 5% H_2SO_4 in EtOH and heating.

Plant Material. The whole plant of *Thalictrum atriplex* Finet & Gagnep. were collected in Yulong in County, Lijiang Prefecture, Yunnan Province, People's Republic of China, in September 2019. The identification of plant material was verified by Prof. Ning Yuan. A voucher specimen (Ynni-19-09-157) has been deposited in Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, P. R. China.

Extraction and Isolation. The air-dried and powdered whole plant of *T. atriplex* (3.6 kg) were extracted with 95% aq. EtOH, and the extract was partitioned between EtOAc and 3% tartaric acid. The aqueous layer was adjusted to pH 9 with saturated Na_2CO_3 aq., extracted with EtOAc, and removed the pigments with MCI gel. The purified EtOAc-soluble alkaloidal materials (62.5 g) were applied to silica gel column chromatography (150 - 200 mesh, 8×50 cm), eluting with $CHCl_3$/MeOH gradient system (10:0, 9:1, 8:2, 7:3, 6:4, 5:5) to give six fractions A-F. Further separation of fraction B (9:1, 8.53 g) by silica gel column chromatography (200-300 mesh, 5×50 cm), eluted with $CHCl_3$/Me_2CO (9:1-2:1), yielded the mixtures of B1–B7. Sub-fraction B1 (9:1, 2.25 g) was subjected to silica gel column chromatography (200 - 300 mesh, 2×50 cm) using petroleum ether/acetone, and then semi-preparative HPLC (65% MeOH/H_2O, flow rate 20 mL/min) to give the crude compounds **1** and **3**. Sub-fraction B2 (8:2, 3.16 g) was subjected to silica gel column chromatography (200-300 mesh, 2×50 cm) using petroleum ether/acetone, and then semi-preparative HPLC (56% MeOH/H_2O, flow rate 20 mL/min) to give the crude compounds **2**, **4**, **5** and **6**. The crude compounds was applied to Sephadex LH-20 column (1.5 × 120 cm) eluting with MeOH to give pure compounds, **1** (15.6 mg), **2** (16.2 mg), **3** (14.6 mg), **4** (15.8 mg), **5** (18.0 mg) and **6** (16.5 mg).

Anti-rotavirus assay. The human rotavirus Wa group was used to infect the cell culture MA104 *in vitro*, the 50% cytotoxicity concentration (CC_{50}) and half maximal effective concentration (EC_{50}) were evaluated, and the ribavirin was used as positive control.[28,29] MA-104 cells (1×10^5 cells *per* well) were grown in 96-well plates for 48 h. The media were removed and replaced by new media containing serial dilutions of compounds under test. After incubation for 72 h, the media were discarded, and 5 μL of MTT solution was added to each well. Plates were then incubated at 37 ℃ for 4 h. The solution was removed, and 100 μL of 0.04 mol/L HCl-isopropanol were added to each well to dissolve formazan crystals. Using a microplate reader, the absorbance of each well was measured at 540 nm. After subtracting the background absorbance at 655 nm, the 50% CC_{50} of each compound was estimated by regression analysis.

In the mixed treatment assay, each compound was mixed with a 0.01 multiplicity of infection (MOI) of the rotaviruses at various concentrations (1-160 μg/mL) and incubated at 4 ℃ for 1 h. The mixtures were inoculated in triplicates onto near confluent MA-104 cell monolayers (1×10^5 cells per well) for 1 h with occasional rocking. The solution was removed and the cells replaced with eagles minimum essential medium (EMEM) containing 1.0 μg/mL trypsin. The cells were incubated for 72 h at 37 ℃ under 5% CO_2 atmosphere until the cells in the control showed complete viral cytopathic effect (CPE) by light microscopy. EC_{50} was estimated by regression analysis.

Anti-MRSA assay. The MRSA strain ZR11 was clinical isolated from infectious samples of critically ill patients in the Clinical Laboratory of the First People's Hospital of Yunnan Province, and confirmed by standard cefoxitin disk diffusion test following CLSI standard procedures.[31] The anti-MRSA activity of the compounds was evaluated via the disc diffusion method. The ZR11 strain was inoculated in Müeller Hinton Broth and were incubated at 37 ℃ for 24 h. The turbidity of bacterial suspension was adjusted to 0.5 McFarland standard which equals to 1.5×10^8 colny-forming units (CFU)/mL. Sterile filter paper discs (6 mm) were impregnated with 20 μL (50 μg) of each compound and placed on inoculated Müeller Hinton agar containing bacterial suspension which adjusted to 0.5 McFarland standard. The commercial available discs containing 30 μg Vancomycin were used as positive control whereas discs without samples (5% DMSO) acted as negative control . The inhibition zones including the diameter of the disc (mm) were measured and compared after incubation at 37 ℃ for 24 h. The tests were carried out in triplicate for each sample.

Thalicalkaloid A (**1**), $C_{16}H_{13}NO_2$, obtained as pale-brown gum; UV (MeOH), λ_{max} (log ε) 220 (4.38), 252 (4.34), 355 (3.93) nm; IR (KBr) ν_{max} 3086, 2308, 1812, 1614, 1457, 1372, 1155, 1068, 946 cm^{-1}; ^1H and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz), Table 1; ESI-MS (positive ion mode) *m/z* 274 $[M+Na]^+$; HR-ESI-MS (positive ion mode) *m/z* 274.0848 $[M+Na]^+$ (calcd 274.0844 for $C_{16}H_{13}NNaO_2$).

Thalicalkaloid B (**2**), $C_{16}H_{15}NO_2$, obtained as pale-yellow gum; UV (MeOH), λ_{max} (log ε) 220 (4.26), 243 (4.28), 342 (3.86) nm; IR (KBr) ν_{max} 3412, 3094, 2310, 1815, 1612, 1469, 1358, 1162, 1070, 925 cm^{-1}; ^1H and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz), Table 1; ESI-MS (positive ion mode) *m/z* 276 $[M+Na]^+$; HR-ESI-MS (positive ion mode) *m/z* 276.0996 $[M+Na]^+$ (calcd 276.1001 for $C_{16}H_{15}NNaO_2$).

Thalicalkaloid C (**3**), $C_{16}H_{13}NO_3$, obtained as pale-yellow gum; UV (MeOH), λ_{max} (log ε) 220 (4.34), 250 (4.28), 348 (3.86) nm; IR (KBr) ν_{max} 3102, 2314, 1809, 1684, 1615, 1453, 1362, 1154, 1062, 892 cm^{-1}; ^1H and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz), Table 1; ESI-MS (positive ion mode) *m/z* 290 $[M+Na]^+$; HR-ESI-MS (positive ion mode) *m/z* 290.0784 $[M+Na]^+$ (calcd 290.0793 for $C_{16}H_{13}NNaO_3$).

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REFERENCES AND NOTES

1. E. A. Khamidullina, A. S. Gromova, V. I. Lutsky, and N. L. Owen, *Nat. Prod. Rep*., 2006, **23**, 117.
2. D. Z. Fu and G. H. Zhu, *Flora China*, 2001, **6**, 282.
3. S. B. Chen, S. L. Chen, and P. G. Xiao, *J. Asian Nat. Prod. Res*., 2003, **5**, 263.
4. D. C. Hao, *Chapter-7, Biodiversity, Chemodiversity, and Pharmacotherapy of Thalictrum Medicinal Plants, Ranunculales Medicinal Plants*., Academic Press, 2019, p 261.
5. B. Wang, Y. J. Zhao, Y. L. Zhao, Y. P. Liu, X. N. Li, H. B. Zhang, and X. D. Luo, *Org. Lett*., 2020, **22**, 257.
6. D. Luo, N. Lv, L. J. Zhu, L. M. Liao, Y. Xu, J. Wang, W. S. Kong, H. T. Huang, M. Zhou, G. Y. Yang, Q. F. Hu, and X. X. Si, *Chem. Nat. Compd*., 2020, **56**, 504.
7. Q. F. Hu, L. M. Liao, H. T. Huang, Y. Xu, J. Wang, W. S. Kong, Q. L. Mi, M. Zhou, G. Y. Yang, and C. M. Song, *Chem. Nat. Compd*., 2020, **56**, 500.
8. N. Sharma, V. Kumar, M. P. Chopra, A. Sourirajan, K. Dev, and M. El-Shazly, *J. Ethnopharmacol*., 2020, **255**, 112736.
9. G. H. Kong, Y. P. Wu, E. Yin, B. Liu, Z. Y. Xia, H. T. Huang, G. Y. Yang, Q. F. Hu, and C. M. Song, *Heterocycles*, 2019, **98**, 1437.
10. J. J. Xue, C. Y. Jiang, D. L. Zou, B. J. Li, J. C. Lu, D. H. Li, B. Lin, Z. L. Li, and H. M. Hua, *Org. Lett*., 2020, **22**, 7439.
11. C. F. Ding, X. J. Qin, H. F. Yu, Y. P. Liu, X. H. Wang, and X. D. Luo, *Tetrahedron Lett*., 2019, **60**, 151135.
12. C. F. Ding, Z. Dai, H. F. Yu, X. D. Zhao, and X. D. Luo, *Chin. J. Nat. Med*., 2019, **17**, 698.
13. *New compendium of Chinese materia medica*, ed. by Z. Y. Wu, T. Y. Zhou, and P. G. Xiao, vol. 1, Shanghai Scientific and Technical Publishers, 1988, p 84.
14. F. C. Meng, X. D. Wei, Y. Sun, Q. H. Zeng, G. W. Wang, X. Z. Lan, Z. H. Liao, and M. Chen, *Nat. Prod. Res.*, 2021, **35**, 5757.
15. G. Y. Gao, S. B. Chen, S. L. Chen, L. W. Wang, and P. G. Xiao, *J. Asian Nat. Prod. Res*., 2005, **7**, 805.
16. X. D. Su, T. Bo, R. K. Li, K. A. Li, and H. W. Liu, *Chromatographia*, 2002, **55**, 63.

17. G. Y. Gao, S. B. Chen, J. S. Yang, and P. G. Xiao, *Fitoterapia*, 2020, **71**, 627.
18. X. F. Shang, S. L. Morris-Natschke, Y. Q. Liu1, X. Guo, X. S. Xu, M. Goto, J. C. Li, G. Z. Yang, and K. H. Lee, *Med. Res. Rev*., 2018, **38**, 775.
19. X. F. Shang, S. L. Morris-Natschke, Y. Q. Liu1, X. Guo, X. S. Xu, M. Goto, J. C. Li, G. Z. Yang, and K. H. Lee, *Med. Res. Rev*., 2018, **38**, 1614.
20. I. S. Chen, S. J. Wu, I. L. Tsai, T. S. Wu, and C. M. Teng, *J. Nat. Prod*., 1994, **57**, 1206.
21. O. Jansen, V. Akhmedjanova, L. Angenot, Angenot, G. Balansard, A. Chariot, E. Ollivier, M. Tits, and M. Frédérich, *J. Ethnopharmacol*., 2006, **105**, 241.
22. J. Liu, X. Y. Wei, E. L. Kim, X. P. Lin, X. W. Yang, X. F. Zhou, B. Yang, J. H. Jung, and Y. H. Liu, *Tetrahedron*, 2015, **71**, 271.
23. G. H. Kong, G. H. Zhang, Z. L. Lin, G. K. Zhao, Y. K. Li, H. Yao, G. Y. Yang, Q. F. Hu, and Y. P. Wu, *Heterocycles*, 2021, **102**, 2190.
24. Y. Xu, Q. L. Mi, Y. K. Li, W. L. Zeng, Q. Gao, C. M. Song, H. T. Huang, H. Y. Xiang, X. M. Li, G. Y. Yang, Q. F. Hu, and J. Wang, *Heterocycles*, 2019, **98**, 875.
25. Q. L. Mi, W. S. Kong, Y. K. Li, X. Liu, W. L. Zeng, H. Y. Xiang, D. Miao, G. Y. Yang, Q. F. Hu, W. G. Wang, Q. Gao, and M. Zhou, *Chem. Nat. Compd.*, 2021, **57**, 432.
26. Q. F. Hu, F. Wu, Y. N. Zhu, L. Liu, M. X. Liu, B. B. Cai, M. F. Li, D. Miao, M. Zhou, and G. Y. Yang, *Heterocycles*, 2021, **102**, 1588.
27. Q. F. Hu, F. Wu, T. Zhou, M. Zhou, Y. N. Zhu, B. B. Cai, M. X. Liu, M. F. Li, G. Y. Yang, and Y. K. Li, *Heterocycles*, 2021, **102**, 1810.
28. B. K. Ji, X. M. Gao, D. Cui, S. S. Wang, W. Z. Huang, Y. K. Li, S. X. Mei, Z. Yang, G. P. Li, M. Y. Jiang, Y. H. He, Z. Y. Jiang, G. Du, X. X. Pan, W. X. Liu, and Q. F. Hu, *Nat. Prod. Res*., 2017, **31**, 1544.
29. X. M. Gao, B. K. Ji, Y. K. Li, Y. Q. Ye, Z. Y. Jiang, H. Y. Yang, G. Du, M. Zhou, X. X. Pan, W. X. Liu, and Q. F . Hu, *J. Braz. Chem. Soc*., 2016, **27**, 10.
30. J. Jiang, H. R. Ma, S. Hu, L. Cheng, F. Q. Wang, and G. Zhang, *Nat. Prod. Res*., 2019, **33**, 2964.
31. Clinical and Laboratory Standards Institute, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Approved Standard, vol. 32, Clinical and Laboratory Standards Institute, Wayne, Pa, USA, 2012, 9th edition.