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RAPID COMMUNICATION

Derivatives of benzamide of the extracts from the bark of Maqian (*Zanthoxylum myriacanthum* var. *pubescens*)

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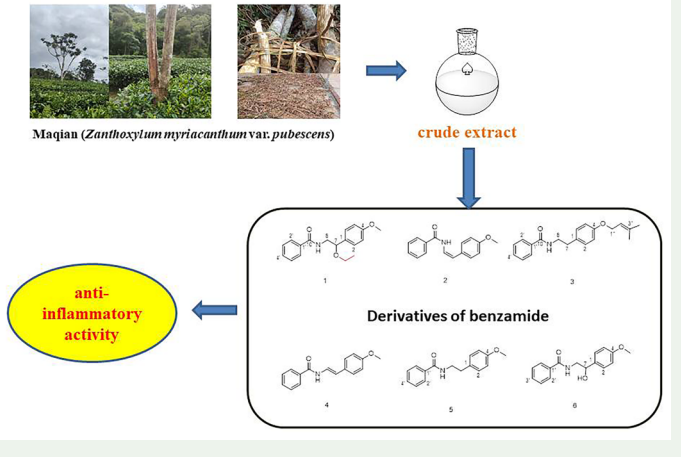
ABSTRACT

Two newly discovered natural derivatives of benzamide, *O*-Ethyltembamide (**1**) and N-[(Z)-2-(4-Methoxyphenyl)vinyl]benzamide(**2**), together with four known compounds, hortiamide (**3**), N-[(E)-2-(4-Methoxyphenyl)vinyl] benzamide (alatamide) (**4**), dihydroaltamide (**5**) and tembamid (**6**), were isolated from the barks of of *Zanthoxylum myriacanthum* var. *pubescens* (Huang) Huang. Their structures were determined on the basis of spectral data. The anti-inflammatory activity of the isolated compounds (**1**-**6**) were scanned against NO production in LPS-activated RAW 264.7 macrophages by MTS assay, however no significant activities were observed.



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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the gastrointestinal tract (Farrell et al. 2016, Voskens et al. 2023). It mainly affects young adults in developed countries like North America and Europe (Ng et al. 2017). It is characterised by recurrence and remission, resulting in poor quality of life and a significant medical, economic, and social burden (Bhala et al. 2023, Yarlas et al. 2018). UC has become more prevalent in Asia, particularly in China and India, due to industrialisation and changing lifestyles (Kaplan and Ng 2016). Interestingly, the prevalence rate among the Dai ethnic minority in Yunnan Province is lower than that of the Han Chinese, possibly due to their unique environment and use of Dai medicine (Niu et al. 2016, Tang et al. 2015).

Our team found that one Dai medicine 'Maqian' is commonly used to treat intestinal infections and stomach ulcers. Maqian, also known as *Zanthoxylum myriacanthum* var. *pubescens* (Huang) Huang, is a variety of *Zanthoxylum myriacanthum*. Previous research focused on the fruit's essential oil, showing anti-inflammatory effects and potential for colitis treatment (Ji et al. 2016, Li et al. 2014). However, research on the chemical composition of Maqian bark is limited (Zhang et al. 2017).

Two new derivatives of benzamide, *O*-Ethyltembamide (**1**) and N-[(*Z*)-2-(4-Methoxyphenyl)vinyl] benzamide (**2**), and four known compounds, hortiamide (**3**), N-[(E)-2-(4-Methoxyphenyl)vinyl] benzamide (alatamide) (**4**), dihydroaltamide (**5**) and tembamid (**6**) **(**Figure 1**)** were isolated and identified from the bark, providing a basis for its application in medicine.

2. Results and discussion

Compound **1** was isolated as a white amorphous powder. Its HREIMS showed a molecular ion peak at m/z 322.1416 [M + Na]+ (calcd 322.1414), the molecular formula was inferred to be $C_{18}H_{21}NO_3$. IR spectrum suggested the presence of amidogen groups (3332 cm^{-1}) and a conjugated ketone group (1636 cm^{-1}), which indicated the presence of amide group in the compound.

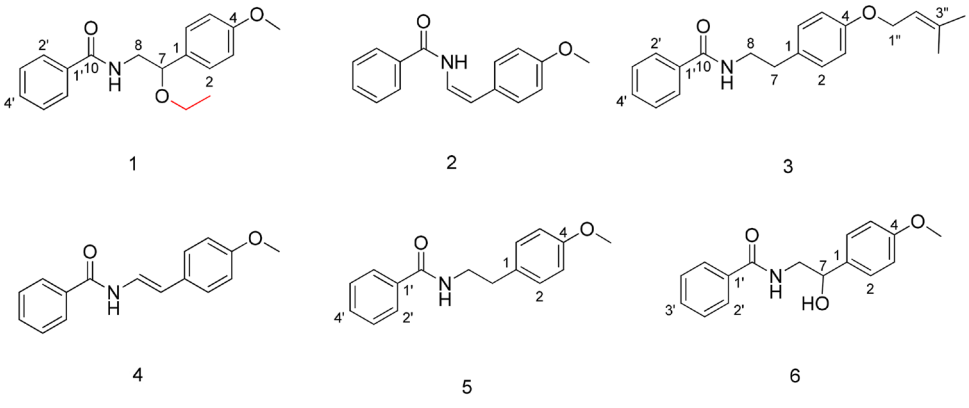

Figure 1. Isolated compounds of the barks of of *Zanthoxylum myriacanthum* var. *pubescens* (Huang) Huang.

Its ^{1}H and ^{13}C NMR spectra suggest it to be a derivative of benzamide (Table S1). The ^{1}H-NMR and ^{13}C-NMR spectra of **1** were similar to those of *O*-Methyltembamide (Faizi et al. 2009). A major difference was in the signals of 65.3 (7-O$\underline{C}H_2CH_3$), 15.7 (7-OCH$_2\underline{C}H_3$), which indicated that the methyl group (C-7) of *O*-Methyltembamide was replaced by the ethyl group. The ^{1}H NMR spectrum of the compound showed a triplet methyl signal (δ_H 1.14) and a singlet methyl signal (δ_H 3.75). The 1D NMR data indicated that the compound has a skeleton containing 18 carbons, which could be classified as two methyl groups, two methylenes, ten methines and four quaternary carbons based on the DEPT spectrum. The ^{13}C NMR spectrum showed a carboxyl carbon signal (δ 167.3) for the compound. In the HMBC spectrum, the correlation of H-7 (3.52, m) with δ_C 81.1 (C-7) was observed in the benzamide skeleton. In the ROESY spectrum (Figure S11), H-7 showed cross peaks with H-8, and hydrogen of oxymethyl had cross peaks with H-3 and H-5. From these results, the structure of **1** was established as *O*-Ethyltembamide. Compared with the data reported in the literature, compound **2** was determined to be N-[(Z)-2-(4-Methoxyphenyl)vinyl]benzamide, as the coupling constant of H-7 was less than **4** (Maxwell and Ramprasad 1989). The compound is also a newly discovered natural product.

Four known compounds isolated were identified as hortiamide (**3**) (Tinto et al. 1992), N-[(E)-2-(4-Methoxyphenyl)vinyl] benzamide (alatamide) (**4**) (Maxwell and Ramprasad 1989), dihydroaltamide (**5**) (Liao Liang et al) and tembamid (**6**) (Niu et al. 2001) by comparison with spectroscopic data in the literature.

The anti-inflammatory activity of the isolated compounds (**1**-**6**) were scanned against NO production in LPS-activated RAW 264.7 macrophages by MTS assay, however no significant activities were observed (Table S2).

3. Experimental

3.1. General experimental procedures

See Supplementary material for this information.

3.2. Plant material

See Supplementary material for this information.

3.3. Extraction and isolation

Maqian barks (33 kg) were extracted with 95% aqueous ethanol, and the extract was filtered and concentrated. The concentrated extract was then fractionated using petroleum ether and ethyl acetate. The ethyl acetate (900 g) was subjected to macroporous resin chromatography eluted with ethanol/water (30%, 50%, 80% and 95%) gradient. The above parts were treated by reversed-phase, semi-preparative and gel column chromatography. The ethyl acetate fraction (900 g) was further separated using chromatography techniques to obtain several sub-fractions. Subfractions were further purified, resulting in the isolation of compounds **1**-**6**.

***O*-Ethyltembamide** (**1**): White amorphous powder. $[\alpha]^{23.1}_{D}$ −14.93 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε): 196.00 (7.2908), 226.50 (7.4242); IR (neat) max: 3332, 1636 cm^{-1}; HR-ESI(+)-MS $[M+Na]^+$: 322.1416 *m/z* for $C_{18}H_{21}NNaO_3^+$ (calcd. 322.1414). ^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD) see Table S1.

3.4. Anti-inflammatory assay

See Supplementary material for this information.

4. Conclusions

It is an important edible spice and ethnic medicinal plant in the Xishuangbanna region, two new derivatives of benzamide, *O*-Ethyltembamide (**1**) and N-[(Z)-2-(4-Methoxyphenyl)vinyl]benzamide(**2**), together with four known compounds, hortiamide (**3**), N-[(E)-2-(4-Methoxyphenyl)vinyl] benzamide (alatamide) (**4**), dihydroaltamide (**5**) and tembamid (**6**) were isolated from *Z. myriacanthum* var. *pubescens* (Huang) Huang. The anti-inflammatory activities of compounds (**1**-**6**) were scanned against NO production in LPS-activated RAW 264.7 macrophages by MTS assay, however no significant activities were observed. Maybe, other activities would be tested according to the characteristics of these compounds.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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