Uncommon Bis-Amide Matrine-type Alkaloids From *Sophora alopecuroides* With Anti-inflammatory Effects

Ding Luo1, Zhenchao Tu1, Wenjing Yin2, Chunlin Fan1, Nenghua Chen1, Zhongnan Wu1, Weilong Ding2, Yaolan Li1*, Guocai Wang1* and Yubo Zhang1,3*

1Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, Institute of Traditional Chinese Medicine & Natural Products, College of Pharmacy, Jinan University, Guangzhou, China, 2Department of Neurosurgery, The First Affiliated Hospital of Jinan University, Guangzhou, China, 3Guangdong Clinical Translational Center for Targeted Drug, Department of Pharmacology, School of Medicine, Jinan University, Guangzhou, China

Four new alkaloids (1–4) belonging to rare examples of bis-amide matrine-type were isolated from the seeds of *Sophora alopecuroides*. Their structures including absolute configuration were determined by extensive spectroscopic analysis, electronic circular dichroism (ECD) interpretation, and X-ray diffraction crystallography. Chemically, bis-amide matrine-type alkaloids can provide new molecular template for structural modification. Compounds 3–4 displayed obvious anti-inflammatory effects based on the inhibition of two key pro-inflammatory cytokines [tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)] in a dose-dependent manner, with IC50 values from 35.6 to 45.8 μM.

Keywords: matrine-type alkaloids, water-soluble alkaloids, *Sophora alopecuroides*, structure modification, structure elucidation

INTRODUCTION

*Sophora alopecuroides* L. which belongs to the family of Leguminosae, is a salt-tolerant perennial herb plant and distributed in arid desert grassland of northwest China (Wang et al., 2012; Deng et al., 2019). The seeds of *S. alopecuroides* (Chinese name: Ku-Dou-Zi) has been regarded as a well-known traditional Chinese medicine for the treatment of fever, rheumatism, bacterial infection and inflammatory diseases (Huang et al., 2016). Previous phytochemical investigations on *S. alopecuroides* revealed alkaloids as one of principal active chemical constituents. Among them, matrine-type alkaloids exhibit diverse bioactivities such as antiviral (Zou et al., 2020), anti-insect (Huang et al., 2017), anti-tumor (Li et al., 2020), and promising anti-inflammatory activities (Huang et al., 2016; Li et al., 2020).

Chemically, matrine-type alkaloids are considered as ideal lead compounds for further structure modifications because of special chemical structure, widespread biological activities, high safety threshold, as well as available commercial sources. In order to improve the activities and amplify their applicants, many matrine-type derivatives have been synthesized and reported in the recent years (Huang et al., 2017; Cai et al., 2018; Cheng et al., 2018; Lv et al., 2018; Cheng et al., 2020; Xu et al., 2020). Interestingly, we have noticed that almost all structural modifications were concentrated in the variations of D ring, such as introducing substituents to C-13 and C-14 sites, opening D ring, fusing D ring and further molecular simplification. However, the amide bond located at D ring is a
critical part that can responsible for many biological activities according to the molecular docking analysis (Peng et al., 2020). It is necessary to search more matrine-type template for the development of structural modification strategy.

As a part of continuous systematic search for structurally unique and biologically meaningful natural products from the *Sophora* species (Fan et al., 2019; Luo et al., 2021; Zhang et al., 2018a; Zhang et al., 2018b; Zhang et al., 2016; Zhang et al., 2017), four new matrine-type alkaloids (1–4) were obtained and identified (Figure 1). It is worth mentioning that compounds 1–4 are uncommon examples of bis-amine matrine with the second amide group at C-2 or C-10. To date, hundreds of matrine-type alkaloids have been reported but only few cases such as 2-oxymatrine, 10-oxy-5,6-dehydromatrine, and 10-oxysoforidine that possessed the bis-amide bond at C-2 or C-10 (Zhang et al., 2016; Zhang et al., 2018a). Additionally, all isolates were evaluated their anti-inflammatory activities in vitro based on production of two key pro-inflammatory cytokines (TNF-α and IL-6) in lipopolysaccharides (LPS)-stimulated RAW264.7 cells. Herein, the isolation, structure elucidation, and anti-inflammatory activices of those isolates are discussed.

**MATERIALS AND METHODS**

**General Experimental Procedures**

The UV spectra, optical rotations, and IR spectra were determined on a JASCO V-550 UV/VIS spectrophotometer in MeOH solutions, an Autopol JASCO FT-IR-480 plus FT-IR spectrometer with KBr disks and peaks reported in cm⁻¹ (JASCO corporation, Tokyo, Japan), respectively. ECD spectrum were carried out on a JASCO J-810 spectrometer. NMR experiments including 1D and 2D spectra were run on a Bruker Avance 600 NMR (600 MHz for 1H/150 MHz for 13C) spectrometer using standard Bruker pulse sequences (Bruker-Biospin, United States). HRESIMS data were measured from an electrospray ionization mass spectrometer using standard Bruker pulse sequences (Bruker-Biospin, United States). After removal of the nonalkaloid components with CHCl₃, the remaining acidic solvent was subsequently adjusted to pH 9–10 basified with saturated NH₄OH solution in water and partitioned with CHCl₃ five times to yield total alkaloids (0.8 kg, extraction coefficient: 2.67%). The CHCl₃ layer alkaloid was fractionated via D–101 macroporous resin CC eluting with EtOH–H₂O (from 10:90 to 95:5, v/v) to yield five major fractions (Fr.1–5), based on the ratio of ethanol and water. Fr. 1 was dissolved in deionized water, and extracted twice with ethyl acetate (EtOAc) to remove the fatsoluble part. Subsequently, Fr. 1A (50.1 g) was subjected to Al₂O₃-based chromatography column (200–300 mesh) eluted with CH₂Cl₂ containing increasing amount of MeOH (100:0 to 100:100, v/v) added 1% Et₂NH to produce seven portions (Fr.1Aa–Fr.1Ag), based on Al₂O₃-based TLC analysis. Fr.1Af (18.0 g) was separated on a RP-MCI column chromatography with a gradient of CH₃OH/H₂O/Et₂NH (95:0.01 to 60:40:0.01) to generate five fractions (Fr.1Af.1–5). Fr.1Af.1 was applied to a Sephadex LH–20 column (CH₃OH/H₂O, 2:1, v/v) to obtain three subfractions (Fr.1Af.1.1–Fr.1Af.1.3). Fr.1Af.1.2 was purified by ODS CC (CH₃OH/H₂O, 5:95→40:60, v/v) and further separated by preparative HPLC with CH₃CN/H₂O/Et₂NH (15:85:0.01, v/v/v) to give compounds 1 (19.4 mg, tᵣ = 21.4 min), 2 (11.1 mg, tᵣ = 23.8 min), 3 (23.2 mg, tᵣ = 17.8 min), 4 (24.9 mg, tᵣ = 16.9 min).

(+-)-10-Oxy-9β-hydroxymatrine (1): colorless crystals in MeOH; mp 147–148°C [α]D = +840 (c 0.01, CH₃OH); UV (CH₃OH) λmax (log e) 205 (3.52) nm; IR (KBr) νmax 3,252, 2,927, 2,867, 1,627, 1,597, 1,408, 1,058 cm⁻¹; 1H and 13C NMR data, see Table 1; HRESIMS m/z 279.17698 [M + H]+ (calcld for C₁₅H₂₃N₂O₃, 279.1703).

(+-)-10-Oxy-9α-hydroxysoforidine (2): pale yellow oil in MeOH [α]D = −29.2 (c 0.01, CH₃OH); UV (CH₃OH) λmax (log e) 206 (3.33) nm; ECD (CH₃OH) λmax (Δε) 228 (+1.9) nm; IR (KBr) νmax 3,412, 3,256, 2,932, 2,867, 1,625, 1,603, 1,409, and 1,186 cm⁻¹; 1H and 13C NMR data, see Table 1; HRESIMS m/z 279.1702 [M + H]+ (calcld for C₁₅H₂₃N₂O₂, 279.1703).

(+-)-2-Oxy-5,6-hydroxy-6,7-dehydromatrine (3): colorless block crystals in MeOH; mp 135–136°C [α]D = −8.9 (c 0.01, CH₃OH); UV (CH₃OH) λmax (log e) 201 (4.08), 242 (3.11) nm; IR (KBr)
**TABLE 1** $^1$H (600 MHz) and $^{13}$C NMR (150 MHz) data of compounds one to four in CDCl$_3$ (δ in ppm, J in Hz).

| No | 1 | 2 | 3 | 4 |
|----|---|---|---|---|
|    | δC | δH | δC | δH | δC | δH | δC | δH |
| 2  | 42.3 | a 4.55 dd (11.6, 2.5); b 2.73 | 44.1 | a 4.69 dd (13.2, 4.4); b 2.59 dd (13.2, 2.9) | 167.8 | a 2.92 m; b 2.54 | 39.5 | a 3.76; b 3.76 |
| 3  | 19.7 | a 1.66; b 1.66 | 25.0 | a 1.79; b 1.53 | 27.8 | a 1.96 m; b 1.76 | 20.4 | a 1.93; b 1.62 |
| 4  | 26.5 | a 1.78; b 1.67 | 29.8 | a 1.94; b 1.29 | 29.7 | a 1.96 m; b 1.76 | 32.0 | a 1.88; b 1.84 |
| 5  | 34.4 | 1.94 | 35.8 | 1.83 | 65.1 | 68.1 |
| 6  | 57.0 | 3.54 days (3.4) | 59.6 | 3.27 dd (11.0, 9.0) | 133.2 | 134.9 |
| 7  | 40.7 | 1.83 | 36.1 | 2.34 | 113.7 | 117.2 |
| 8  | 29.3 | a 2.18; b 1.95 | 28.4 | a 2.13; b 1.87 | 24.1 | a 2.20 m; b 1.87 dd (17.0, 4.8) | 21.3 | a 2.39; b 2.09 |
| 9  | 66.8 | 4.18 days (5.9) | 64.3 | 4.01 dd (10.4, 4.2) | 21.3 | a 2.00; b 1.63 | 32.4 | a 2.55; b 2.48 |
| 10 | 172.8 | 170.5 | 53.3 | 3.67 m | 58.6 | 3.92 dd (11.3, 3.8) | 56.8 | 4.12 (11.3, 4.1) |
| 11 | 54.0 | 3.77 m | 53.3 | 3.67 m | 58.3 | 3.23 days (13.5); b 1.49 m | 26.8 | a 2.22; b 1.35 |
| 12 | 27.4 | 2.41 m; 1.45 | 27.7 | 2.21; 1.43 | 20.0 | a 1.97; b 1.75 m | 19.4 | a 1.88; b 1.73 |
| 13 | 19.0 | a 1.81; b 1.66 | 19.1 | a 1.93; b 1.67 | 32.2 | a 2.55 m; b 2.43 | 31.2 | a 2.38; b 2.32 |
| 14 | 32.9 | a 2.44; b 2.26 | 32.3 | a 2.46 m; b 2.34 | 32.2 | a 2.55 m; b 2.43 | 31.2 | a 2.38; b 2.32 |
| 15 | 168.7 | a 4.46 dd (15.2, 4.1); β 2.71 t (13.2) | 170.2 | a 3.66 m; β 3.14 t (13.2) | 170.7 | a 4.81 days (13.2); β 2.67 t (13.2) | 170.0 | a 4.63 days (13.2); β 2.90 days (13.2) |

*Overlapped signals were reported without designating multiplicity.

γ$_{\text{max}}$ 3,408, 2,925, 2,765, 1,626, 1,459, and 1,098 cm$^{-1}$; $^1$H and $^{13}$C NMR data, see Table 1; HRESIMS m/z 277.1541 [M + H]$^+$ (calcd for C$_{15}$H$_{21}$N$_2$O$_3$, 277.1547).

(--)-10-Oxy-5-hydroxy-6,7-dehydromatrine (4): pale yellow oil in MeOH [$\alpha$]$_D$ 12.2 (c 0.01, CH$_2$OH); UV (CH$_2$OH) λ$_{\text{max}}$ (log ε) 206 (3.25) nm; ECD (CH$_2$OH) λ$_{\text{max}}$ (Δε) 209 (--1.9), 228 (+2.5), 257 (--4.8) nm; IR (KBr) γ$_{\text{max}}$ 3,408, 2,933, 2,803, 1,623, 1,411, 1,393 cm$^{-1}$; $^1$H and $^{13}$C NMR data, see Table 1; HRESIMS m/z 277.1546 [M + H]$^+$ (calcd for C$_{15}$H$_{21}$N$_2$O$_3$, 277.1547).

**Single X-Ray Diffraction Data Analysis**

The single-crystal X-ray diffraction data of one and three were acquired on an Agilent diffractometer with Cu Kα radiation. The structures were solved by the SHELX structure solution program and refined with full-matrix least-squares minimization on $F^2$ using SHELXL via OLEX2 software package. Crystallographic data for one and three have been deposited in the Cambridge Crystallographic Data Centre (free of charge at https://www.ccdc.cam.ac.uk/) under deposition numbers CCDC are 2055031 and 2095514, respectively.

Crystal Data for (--)10-oxy-9β-hydroxymatrine (1): C$_{15}$H$_{22}$N$_2$O$_4$ (M = 296.36 g/mol): orthorhombic, space group P2$_1$2$_1$2$_1$ (no. 19), a = 8.4437 (2) Å, b = 10.5310 (3) Å, c = 33.5834 (7) Å, V = 2,986.26 (13) Å$^3$, Z = 8, T = 149.99 (10) K, μ(Cu Kα) = 0.784 mm$^{-1}$, Dcalc = 1.318 g/cm$^3$, 13,927 reflections measured (5,262$^\circ$ ≤ 2θ ≤ 147.692$^\circ$), 5,895 unique (R$_{\text{int}}$ = 0.0312, R$_{\text{sigma}}$ = 0.0387) which were used in all calculations. The final R$_1$ was 0.0285 (I > 2σ(I)) and wR$_2$ was 0.0714 (all data). Flack parameter --0.01 (6). Hooft parameter: --0.05 (5). CCDC number is 2095514.

**Electronic Circular Dichroism Calculations**

Conformational analysis was initially performed using sysy Y-2.1.1. program. Conformers occurring within a 10 kcal/mol energy window from the global minimum were chosen for geometry optimization and energy calculation using DFT with the B3LYP functional and the 6–311+G (d,p) basis set with the Gaussian09 program. Calculated results were completed using TD-DFT with the CPCM model in MeOH based on the optimized geometries. Finally, the Boltzmann-averaged ECD spectra of the two compounds were obtained and visualized with SpecDis 1.61 and drawn using the Origin Pro nine program. The half bandwidth (σ) and UV correction values applied in SpecDis for the final calculated ECD spectra are 0.30 eV and –5 nm, 0.30 eV and –6 nm for compounds 2 and 4, respectively, which are within the reasonable range. Their optimized conformation geometries, thermodynamic parameters, and populations of all conformations (2 and 4) are provided in supporting information.

**In vitro Cytotoxicity Assay**

The cytotoxicity of those isolated alkaloids on RAW 264.7 cells were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide (MTT) assay. Various concentrations of test alkaloids were used to treat the cells by the methods that published previously (He et al., 2019; Zhang et al., 2021).

**In vitro Anti-inflammatory Assay**

The anti-inflammatory activities of 1–4 on LPS-stimulated TNF-α and IL-6 expression in RAW 264.7 cells were assessed using enzyme-linked immunosorbent assay (ELISA) as published...
previously (He et al., 2019). Dexamethasone and the medium without LPS were selected as the positive or negative control group.

RESULTS AND DISCUSSION

Compound 1 was isolated as colorless block crystals from CH₃OH, mp 147–148°C [α]D\text{25} +84.0 (c 0.01, CH₃OH). The molecular formula was deduced to be C\textsubscript{15}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3} on the basis of the HRESIMS protonated molecular ion peak [M + H]\textsuperscript{+} at m/z 278.1630, suggesting six indices of hydrogen deficiency. The UV spectrum showed maximum absorption at 206 nm was typical for non-conjugated amide of matrine-type backbone. The IR spectrum displayed a hydroxy group (3,202 cm\textsuperscript{-1}) and two lactam functionalities (1,627 and 1,597 cm\textsuperscript{-1}). The 1H NMR spectrum (Table 1) exhibited signals for \[δ\textsubscript{H} 4.70 \text{ dd (} J = 13.2, 4.6 \text{ Hz), 2.69 m}], ascribed to two sets diagnostic methylene protons adjacent to N-atom of amide bond. The \textsuperscript{13}C NMR spectrum (Table 1) revealed 15 carbon resonances categorized by DEPT experiments as two carbonyls (δ\textsubscript{C} 172.4 and 170.3), five methines (δ\textsubscript{C} 74.5, 54.6, 54.3, 42.0, and 31.5), and eight methylenes (δ\textsubscript{C} 46.7, 32.4, 32.1, 28.4, 27.9, 25.3, 20.0, 18.9). The above spectroscopic data as well as biogenetic considerations indicated that compound 1 was a derivative of matrine (Zhang et al., 2018b).

The planar structure and relative configuration of one was ascertained by comprehensive analysis of 2D NMR experiment (including \textsuperscript{1}H–\textsuperscript{1}H COSY, HSQC, HMBC, and NOESY spectra). The characteristic HMBC correlations from H\textsubscript{2}-17 to C-4/C-5/C-6/C-11/C-17, from H-6 to C-2/C-5/C-7/C-10/C-11, from H-2 to C-6/C-7/C-9/C-10/C-11, and from H-9 to C-7/C-8/C-10, together with \textsuperscript{1}H–\textsuperscript{1}H COSY correlations of H-6/H-7/H-8/H-9 in B ring (Figure 2), implied one more amide bond occurring at C-10 and a hydroxy group locating on C-9 of matrine-based skeleton. Furthermore, the coupling constant between H-9 and H\textsubscript{2}-8 (\textsuperscript{3}J = 5.6 Hz) suggested H-9 occupied the equatorial position (α) in six-member ring, supported by the absence of H-9/H-11 cross-peak signal in the NOESY spectrum. Finally, the absolute configuration of (5S,6S,7,9,11R)-1 was unequivocally established by a single crystal X-ray diffraction (Figure 3) using Cu Kα radiation [Flack parameter: 0.09 (13)]. Thus, the structure of one was deduced as shown in Figure 1, and named as (+)-10-oxy-9β-hydroxymatrine.

Compound 2 [α]D\text{25} −29.2 (c 0.01, CH₃OH), possessed a molecular formula of C\textsubscript{15}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3} (calcd for C\textsubscript{15}H\textsubscript{23}N\textsubscript{2}O\textsubscript{3}, 279.1703) via the HRESIMS ion peak at m/z 279.1704 [M + H]\textsuperscript{+} and \textsuperscript{13}C NMR data. Its spectroscopic values showed that two is structurally similar to sophoridine (Zhang et al., 2018a), while
the obviously differences were that an additional amide carbon \((\delta C 170.5)\) and a more \(O\)-bearing methine \((\delta C 64.3, \delta H 4.01 \text{ dd (} J = 10.4, 4.2 \text{ Hz)}\) are observed. The key HMBC cross-peaks of H-2 to C-6/C-7/C-9/C-10/C-11 and H-6 to C-2/C-4/C-8/C-10, together with sequential COSY correlations of H-6/H-7/H-2-8/H-9 in B ring (Figure 2) lead to the full structural assignment of 2, as shown in Figure 1. The configuration of OH-9 was deduced as equatorial orientation \((\alpha)\), which was determined by the large coupling constant of H-8/\(H-9\) \((J_{H-9/11} = 10.4 \text{ Hz})\) and NOE cross-peaks (Figure 4) of H-9 \((\delta H 4.01)/H-8a (\delta H 2.13)/H-11 (\delta H 3.67)\). Consequently, the absolute structure of two was corroborated by comparing the experiment and calculated CD curve (Figure 5). Compound 2 was thereby deduced and named as \((-)\)-10-oxo-9\(\alpha\)-hydroxysophridine.

Compound 3, colorless block crystals, showed an \([M + H]^+\) ion peak at \(m/z 277.1541\) (calcld for C\(_{15}\)H\(_{21}\)N\(_2\)O\(_3\), 401.1571) in the HRESIMS spectrum, consistent with the molecular formula of C\(_{15}\)H\(_{20}\)N\(_2\)O\(_3\). The \(^1\text{H}\) and \(^13\text{C}\) NMR data of 3 (Table 1) were similar to those of 5-hydroxy-6,7-dehydro-matrine (Zhang et al., 2018b). The most notable difference was that the methylene at C-10 was replaced by another lactam group \((\delta C 172.8)\), which was verified by the key \(^1\text{H}\)-\(^1\text{H}\) COSY correlation of H-2/H-3, and HMBC cross-peaks from H\(_2\)-3 to C-2/C-4, from H\(_2\)-10 to C-2/C-6/C-8, and from H\(_2\)-17 to C-4/C-5/C-6/C-11 (Figure 2). Moreover, the planar structure and absolute configuration of three were determined by X-ray crystallography (Figure 3) with an excellent Flack parameter \([-0.01 (6)]\). Hence, the complete structure of three was established and named as \((-)\)-2-oxo-5-hydroxy-6,7-dehydrmatrine.

Compound 4 \([\alpha]_{25}^D -12.2 \ (c 0.01, \text{CH}_3\text{OH})\), was obtained simultaneously with three in the same preparation liquid phase condition. Comprehensive analysis of its spectroscopic data indicated that four possessed the same molecular formula and almost identical 1D NMR resonances (Table 1) as that of 3, except for the second amide group exchanged from A ring to B ring. In the 2D NMR spectra of 4, the \(^1\text{H}\)-\(^1\text{H}\) COSY correlations of H\(_2\)-2/H\(_2\)-3/H\(_2\)-4 and H\(_2\)-8/H\(_2\)-9, as well as HMBCs from H\(_2\)-2 to C-10, and from H\(_2\)-8 to C-6/C-7/C-9 suggested the second amide group is located on B ring (Figure 2). Additionally, good consistency between the experimental CD curve and calculated ECD curve (Figure 5) allowed the assignment of \((5R,11R)\) absolute configuration. Thus, compound 4 was elucidated and named as \((-)\)-10-oxo-5-hydroxy-6,7-dehydrmatrine.

At present, the structural modifications of matrine-type alkaloids have mainly focused on the variations of D ring due to the amide group at C-15 is an active reaction site. (Cai et al., 2018; Cai et al., 2020). Compounds 1–4 possessing rare bis-amide matrine-type motif could provide new molecular template and ideas for synthetic chemists. For example, new derivatives could be designed by the introduction of a protecting group on the D ring and subsequent structural modification via the second amide bond at C-2 or C-10 position on the A or B ring. So that the key part of D ring responsible for biological activity can be retained, and some unexpected good results may emerge.

IL-6 and TNF-\(\alpha\) are essential mediators in inflammation processes. Owing to the extracts of S. alopecuroides possessing remarkable clinical effects on various kinds of inflammation, all...
isolated alkaloids (1–4) were evaluated for their LPS-stimulated TNF-α and IL-6 production in RAW 264.7 cells using ELISA. Firstly, a MTT cytotoxicity assay was used to examine the cell viability of murine RAW 264.7 cells. The results displayed that all alkaloids at the concentration ranges from 3.125 to 50 μM were nontoxic on RAW 264.7 cells after 24 h treatment. Therefore, the tested alkaloids were applied to those concentration range to perform the next experiment. The production of IL-6 and TNF-α in the culture medium of the LPS-treated group both increased significantly (p < 0.001) in comparison with the control group after 24 h. However, co-incubation with compounds 3–4 suppressed the secretion of IL-6 and TNF-α in a dose-dependent manner, suggesting that compounds 3–4 are inhibitor of the initial phase of the inflammatory cascade initiated by LPS stimulation. As shown in Table 2, compounds 3–4 can inhibit the expression of those pro-inflammatory mediator secretions (TNF-α and IL-6) with IC₅₀ values from 35.6 to 45.8 μM, while compounds 1–2 were inactive. In light of the structures and the anti-inflammatory activity, the existence of unsaturated double bond of Δ⁶(7) may favor this inhibitory effect.

**CONCLUSIONS**

The systematic investigation of the seeds of *Sophora alopecuroides* led to the isolation of four uncommon bis-amide matrine-type alkaloids. Their special chemical structure can provide a new perspective for developing novel modification strategies based on A or B ring. The biological assay revealed two new compounds displayed obvious anti-inflammatory activity. This study not only enriched the structural diversity of matrine-type alkaloids, but also provided an attractive molecular candidate for pharmaceutical chemists.

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**DATA AVAILABILITY STATEMENT**

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

**AUTHOR CONTRIBUTIONS**

DL performed the extract, isolation, and structural elucidation of all chemical structures, and wrote the preliminary manuscript. ZT and WY contributed to the pharmacological assay. CF, NC, and ZW assisted in acquiring the experimental data. YZ, GW, and YL supervised and guided all experiments, rewrote and reviewed the manuscript. All authors have read and approved the published version of manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article including original UV, CD, IR, HRESIMS, 1D/2D NMR spectra can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2021.740421/full#supplementary-material

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