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Sesquiterpenoids from the aerial parts of *Conyza japonica* and their inhibitory activity against nitric oxide production

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ABSTRACT

Four new sesquiterpenoids, conyterpenols A − D (**1**–**4**), along with nineteen known analogues (**5**–**23**) were isolated from the aerial parts of *Conyza japonica*. The structures of **1**–**4** were determined through spectroscopic analysis, while their absolute configurations were determined by comparison of calculated and experimental electronic circular dichroism (ECD) spectra. Conyterpenol D (**4**) was a new type of sesquiterpenoid with a seven-membered lactone ring. Compounds **1**–**23** were evaluated for their inhibitory activity against LPS-induced nitric oxide production in RAW264.7 macrophages and cytotoxicity against human hepatoma cell line (HepG2) and human breast adenocarcinoma cell line (MCF-7). Compounds **3**, **4**, and **12** displayed moderate inhibition against NO production with IC_{50} values in the range of 26.4–33.6 μM. And all compounds showed no obvious cytotoxicity against these two cancer cell lines at 100 μM.

1. Introduction

Conyza japonica (Thunb.) Less., a species of family Compositae, is an annual or biennial herb widely distributed in the southern regions of China. The plant *C. japonica* has a long history of medicinal use for treating various diseases such as pneumonia, pleurisy, laryngitis and keratitis in children [1]. Previous phytochemical researches on *C. japonica* showed there are a variety of constituents such as strictic acids, flavonoids and their glycosides [2,3], phenylpropanoid glycosides [4], triterpenoid saponins [5], diterpenoids and their glycosides [6]. The research on the constituents of *C. japonica* has attracted our attention because its secondary metabolites mainly contain terpenoids, which show a variety of biological activities, including anti-inflammatory, antitumor, antioxidant and against acute gastric ulcer [7–10].

Our phytochemical research was carried out on the 95% EtOH extract of the aerial parts of *C. japonica*, which resulted in the isolation of four new sesquiterpenoids (**1**–**4**) along with nineteen known analogues. The isolated compounds were screened for their inhibitory e□ects against LPS-induced nitric oxide (NO) production in RAW264.7 macrophages and their cytotoxicity against HepG2 and MCF-7 cancer cell lines. Herein, we report the isolation, structural elucidation, and biological evaluation of these sesquiterpenoids.

2. Experimental

2.1. General experiments

Optical rotations were measured on a Perkin-Elmer 341 polarimeter (PerkinElmer, Inc. Shelton, USA). UV spectra were recorded on a Shimadzu UV-2450 spectrophotometer. CD spectraC6Z = 9v*II)ki–Waofi)–ecsellEé

Collection. HepG2 and MCF-7 cell lines were purchased from China Center for Type Culture Collection in Wuhan.

2.2. Plant material

The aerial parts of *C. japonica* were collected in Quanzhou, Fujian Province, People's Republic of China in May 2018, and identified by Dr. Gui-Hua Tang from the School of Pharmaceutical Sciences, Sun Yat-sen University. A voucher specimen (No. 2018051101) was deposited at the School of Pharmaceutical Sciences, Sun Yat-sen University.

2.3. Extraction and isolation

The air-dried and powdered aerial parts of *C. japonica* (20.0 kg) were extracted with 95% EtOH (40 l × 3) at room temperature to obtain a crude extract (971 g), which was suspended in 10 l water and then extracted continuously with petroleum ether (10 l × 3) and ethyl acetate (10 l × 3) to afford the petroleum ether extract (324.9 g) and EtOAc extract (85.2 g). The petroleum ether extract was subjected to column chromatography over silica gel with petroleum ether – EtOAc mixture (gradient from 1:0 to 0:1, *v*/v) and $CHCl_3$ – MeOH (gradient from 1:0 to 0:1, *v*/v) to give twelve fractions (Fr.1 – Fr.12). Fr.3 was separated using silica gel column eluting with petroleum ether – EtOAc and further purified by using Sephadex LH-20 column (CH_2Cl_2 – MeOH, 1:1, v/v) to afford **22** (13.0 mg). Fr.4 was separated using silica gel column eluting with petroleum ether – EtOAc further purified by using semi-preparative HPLC (MeOH/H_2O, 80% → 100%, 3.0 ml/min) to afford **17** (20.8 mg, t_R = 18.5 min). Fr.5 was separated using silica gel column eluting with petroleum ether – EtOAc and further purified by using semi-preparative HPLC (82% MeOH in H_2O, 3.0 ml/min) to yield **12** (9.4 mg, t_R = 26.0 min). Fr.6 was separated by MCI gel column (MeOH/H_2O, 50% → 100%, *v*/v) followed by silica gel column (petroleum ether – CH_2Cl_2, 2:1, *v*/v) and Sephadex LH-20 column (MeOH) to yield **16** (9.3 mg). Fr.7 was separated by MCI gel column (MeOH/H_2O, 50% → 100%, *v*

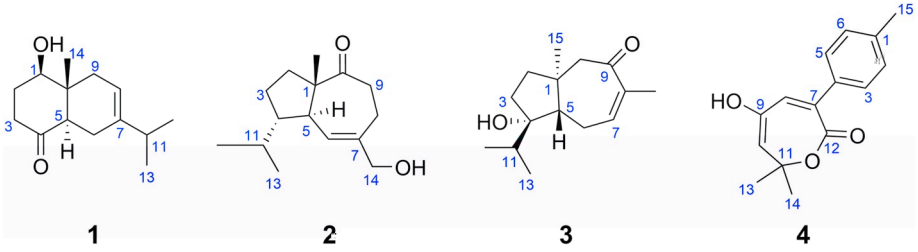

Fig. 1. Structures of compounds **1–4**.

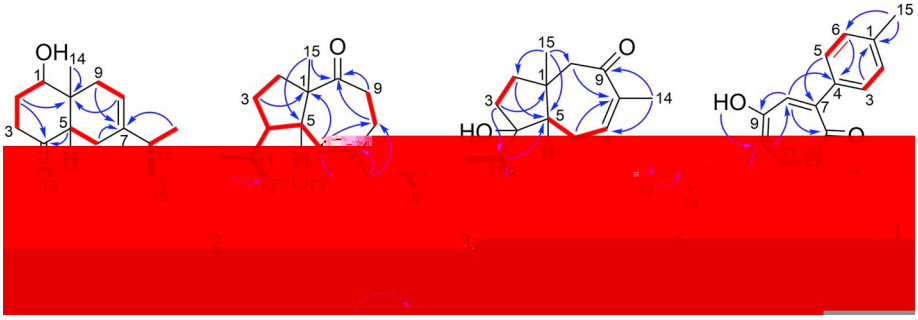

Fig. 2. The key $^{1}H-^{1}H$ COSY and HMBC correlations of compounds **1–4**.

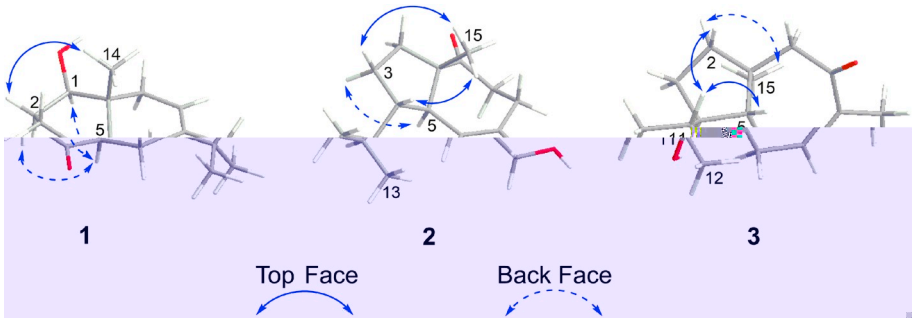

Fig. 3. The key NOESY correlations of compounds **1–3**.

Conyterpenol B (***2***): Colorless oil; $[\alpha]_D^{20}$ −43.1 (*c* 0.26, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.65) nm, 193(2.79) nm; IR (KBr) ν_{max} 3400, 2954, 2931, 2872, 1687, 1610, 1499, 1453, 1373, 1261, 1054, 702 cm^{-1}; NMR ($CDCl_3$) data, see Tables 1 and 2; HRESIMS *m/z* 259.1679 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.1669).

Conyterpenol C (***3***): Colorless oil; $[\alpha]_D^{20}$ −27.3 (*c* 0.30, MeOH); UV (MeOH) λ_{max} (log ε) 240 (3.58) nm, 201(3.32) nm, 197(3.19) nm; IR (KBr) ν_{max} 3483, 2957, 2928, 1645, 1455, 1385, 1283, 1040, 816 cm^{-1}; NMR ($CDCl_3$) data, see Tables 1 and 2; HRESIMS *m/z* 259.1668 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.1669).

Conyterpenol D (***4***): Light yellow oil; UV (MeOH) λ_{max} (log ε) 202 (3.95) nm, 317 (3.93) nm, 231 (3.61) nm; IR (KBr) ν_{max} 3428, 2925, 2855, 1762, 1664, 1611, 1521, 1458, 1369, 1096, 961, 824 cm^{-1}; NMR ($CDCl_3$ and DMSO-d_6) data see Tables 1 and 2; HRESIMS *m/z* 267.0999 $[M + Na]^+$ (calcd for $C_{15}H_{16}O_3Na$, 267.0992).

2.5. Anti-inflammatory assay

Compounds **1–23** were tested for their anti-inflammatory activity in vitro by measuring the LPS-induced NO production in RAW 264.7 mouse macrophages [11]. Cell viability was determined by MTT method at 60 μM, an initial concentration. Cells were treated with compounds in different concentrations with or without LPS (1 μg/ml) for 24 h in 96-well culture plates. The supernatant was collected and then mixed with an equal volume of Griess reagent I and Griess reagent II, the absorbance of the samples was read at 540 nm with a microplate reader. Quercetin was used as a positive control and DMSO was set as blank control in experiments. Experiments were operated in triplicate. The results were described as mean ± SD of three independent experiments.

2.6. MTT assay

Cytotoxic activity of the compounds against HepG2 and MCF-7 cell lines was analyzed by MTT assay as previously reported [12,13]. Briefly, the cancer cells were treated with the compounds at concentrations ranging from 10^{-8} to 10^{-4} M, after incubation for 72 h at 37 °C, the MTT solution (20 μl, 2.5 mg/ml) in PBS was fed to each well of the culture plate. After 4 h incubation, the formazan crystal formed in the well was dissolved with 100 ml DMSO for optical density reading at 570 nm. Camptothecin was used as a positive control and DMSO was set as blank control in experiments, and the experiments were conducted for three independent replicates.

3. Results and discussion

The petroleum ether extract from the aerial parts of *C. japonica* was fractionated by silica gel CC and further purified by various columns to obtain twenty-three sesquiterpenoids, including four new sesquiterpenoids, conyterpenols A − D (**1–4**) (Fig. 1) and nineteen known sesquiterpenoids (**5–23**) (Fig. S1), which were identified as 1β,11-dihydroxy-5-eudesmene (**5**) [14], 1β,6α-dihydroxy-4(15)-eudesmane (**6**) [15], 6β,14-epoxyeudesm-4(15)-en-1β-ol (**7**) [16], 3-epichenopotriol (**8**) [17], 7-epi-

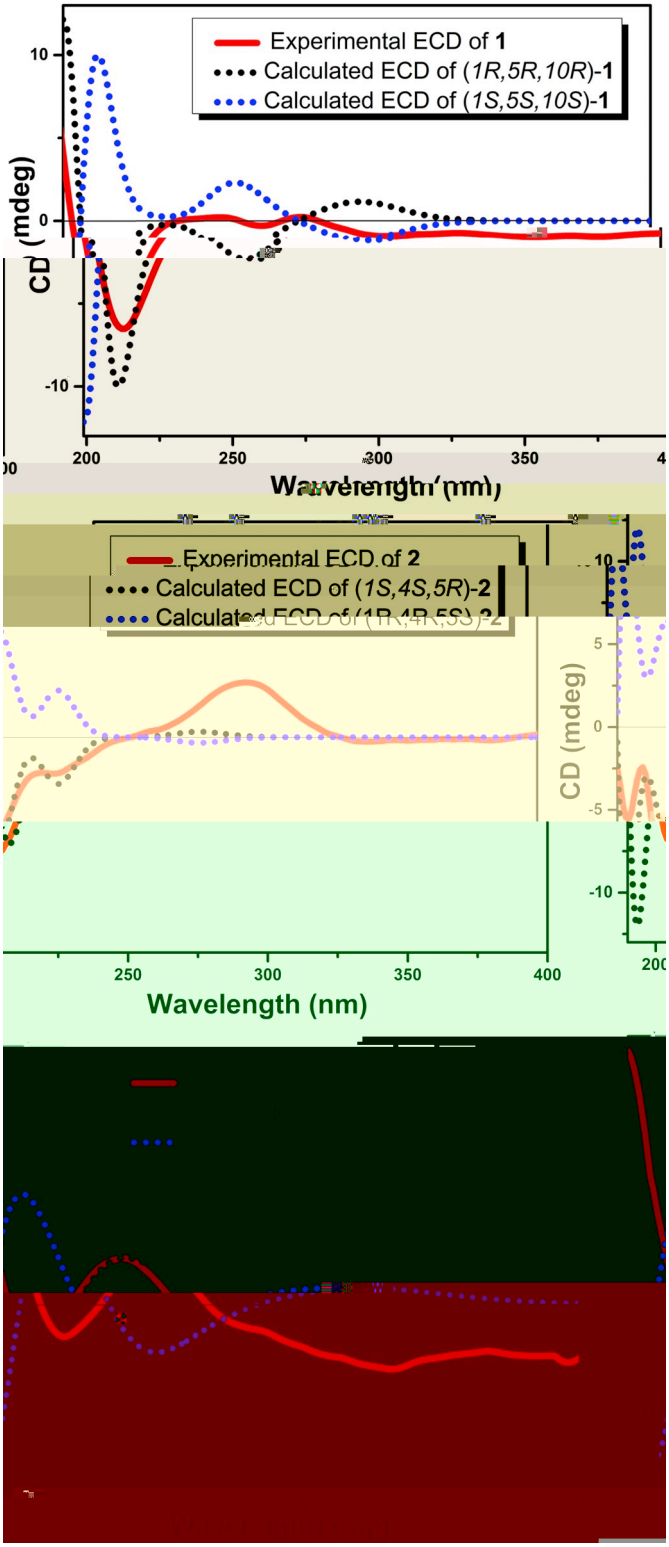

Fig. 4. Experimental and calculated ECD spectra for **1**–**3** in MeOH.

eudesm-4(15)-ene-1α,6α-diol (**9**) [18], 4(15)-eudesmene-1β,5α-diol (**10**) [19], oplodiol (**11**) [20], schisansphenins A (**12**) [21], 10β,15-hydroxy-α-cadinol (**13**) [22], artabotrol (**14**) [23], (+)-aphanamol I (**15**) [24], macrocarp-11(15)-en-8-ol (**16**) [25], spathulenol (**17**) [26], 4α,7α-aromodendranediol (**18**) [27], oplopanone (**19**) [20], (7R*)-opposit-4(15)-ene-1β,7-diol (**20**) [16], dehydrovomifoliol (**21**) [28], inflatenone (**22**) [29], pubescone (**23**) [30], respectively, by comparing the detailed NMR spectroscopic data with those reported in the literature.

Compound **1** was obtained as colorless oil. Its HRESIMS gave an ion peak at *m/z* 245.1524 $[M + Na]^+$, suggesting a molecular formula of $C_{14}H_{22}O_2$ (calcd for $C_{14}H_{22}O_2Na$, 245.1512) with four degrees of unsaturation. The IR spectrum showed absorption of hydroxy group (3422 cm^{-1}) and carbonyl group (1705 cm^{-1}). The ^1H, ^{13}C NMR (Tables 1 and 2) and HSQC spectra showed one carbonyl carbon at δ_C 212.3 (C-4), one double bond [δ_H 5.35 (1H, s, H-8), δ_C 115.6 (C-8), 140.8 (C-7)], one oxymethine group [δ_H 3.84 (1H, d, J = 11.7 Hz, H-1), δ_C 76.3 (C-1)], three methyl groups [δ_H 1.02 (3H, m, H-12), δ_H 1.02 (3H, m, H-13), δ_H 0.69 (3H, s, H-14), δ_C 20.6 (C-12), δ_C 20.1 (C-13), δ_C 10.4 (C-14)]. The carbonyl group, and one double bond unit accounted for two degrees of unsaturation. The remaining two degrees of unsaturation were due to a bicyclic carbon skeleton. The $^1H-^1H$ COSY correlations between H-1/H-2/H-3, H-5/H-6, H-8/H-9, H-11/H-12, H-11/H-13 as drawn in red bold bonds (Fig. 2) built up four spin-spin coupling systems, which could be linked together via three quaternary carbons (C-4, C-7, and C-10) by the HMBC correlations from H-2 and H-5 to C-4 (δ_C 212.3), H-6, H-9, and H-13 to C-7 (δ_C 140.8), H-2, H-8, and H-14 to C-10 (δ_C 40.7). Following the establishment of the planar structure, the relative configuration of compound **1** was then assigned by analysis of NOESY spectrum (Fig. 3). The NOESY correlations between H-1/H-5, H-5/H-2a (δ_H 2.04), and H-14/H-2b (δ_H 1.85) indicated that Me-14 and H-2b were on the same side of the ring, while H-4, H-5, and H-2a on the opposite side. In order to establish the absolute configuration of compound **1**, the ECD spectrum of **1** was calculated by time-dependent density functional theory (TDDFT) means at the B3LYP/6–311 + G(d) level in MeOH [31]. The results exhibited that the experimental CD curve matched well with the calculated ECD of (*1R,5R,10R*)-isomer (Fig. 4). Therefore**,** the compound **1** could be identified as (*1R,5R,10R*)-1-hydroxy-7-isopropyl-10-methyl-1,2,5,6,9,10-hexahydronaphthalen-4(2H)-one and the trivial name conyterpenol A was given for compound **1**.

Compound **2** was obtained as colorless oil. Its HRESIMS spectrum gave an ion peak at *m/z* 259.1679 $[M + Na]^+$ suggesting a molecular formula of $C_{15}H_{24}O_2$ (calcd for $C_{15}H_{24}O_2Na$, 259.1669) with four degrees of unsaturation. The IR spectrum revealed the presence of hydroxyl group (3400 cm^{-1}) and carbonyl group (1687 cm^{-1}). The ^1H, ^{13}C NMR (Tables 1 and 2) and HSQC spectra of **2** showed one carbonyl carbon at δ_C 215.1 (C-10), one double bond [δ_H 5.70 (1H, s, H-6), δ_C 129.3 (C-6) and 140.6 (C-7)], one hydroxymethyl group [δ_H 4.13 (2H, s, H-14), δ_C 67.6 (C-14)], three methyl groups [δ_H 0.89 (3H, d, J = 6.7 Hz, H-12), δ_H 0.82 (3H, d, J = 6.7 Hz, H-13), δ_H 1.02 (3H, s, H-15), δ_C 21.8 (C-12), δ_C 18.3 (C-13), δ_C 19.4 (C-15)]. The NMR data suggested that compound **2** was an isodaucane-type sesquiterpenoid. The COSY spectrum showed correlations between H-2/H-3/H-4, H-4/H-11/ H-13, H-12/H-11/H-13, H-5/H-6, H-8/H-9 as drawn in red bold bonds (Fig. 2). The HMBC spectrum showed correlations from H-3 and H-6 to C-1 (δ_C 59.8), H-6 and H-14 to C-8 (δ_C 26.1), H-6 to C-14 (δ_C 67.6), H-14 to C-7 (δ_C 140.6), H-8, H-9, and H-15 to C-10 (δ_C 215.1). The NMR spectra indicated that compounds **2** and **15** shared the same planar structure with slight di□erence in the ^{13}C NMR spectrum caused by variation in configuration. The relative configuration of compound **2** was determined by NOESY spectra (Fig. 3). The NOESY correlations between H-15/H-3b (δ_H 1.77), H-15/H-4, and H-5/H-3a (δ_H 1.44) indicated that Me-15, H-3b, and H-4 were on the same side of the ring, while H-5 and H-3a on the opposite side. The absolute configuration of **2** was identified as (*1S,4S,5R*)-isomer by comparison of the calculated and experimental ECD spectra (Fig. 4). Thus, the compound **2** could be defined as (*1S,4S,5R*)-1-methyl-4-isopropyl-7-hydroxymethyl-1,2,3,5,8,9-hexahydroazulen-10(1H)-one (Fig. 1), and conyterpenol B as trivial name.

Compound **3** was obtained as colorless oil. Its HRESIMS spectrum gave an ion peak at *m/z* 259.1668 $[M + Na]^+$ suggesting a molecular formula of $C_{15}H_{24}O_2$ (calcd for $C_{15}H_{24}O_2Na$, 259.1669) with four degrees of unsaturation. The two distinct absorption bands at 3483 and 1645 cm^{-1} in the IR spectrum demonstrated the existence of hydroxyl and α, β-unsaturated carbonyl groups. The ^1H, ^{13}C NMR (Tables 1 and 2) and HSQC spectra of **3** showed one carbonyl carbon δ_C 203.0 (C-9), one double bond [δ_H 6.38 (1H, d, J = 7.0 Hz, H-7), δ_C 137.4 (C-7), and 139.1

(C-8)], one oxygenated quaternary carbon δ_C 85.7 (C-4), four methyl groups [δ_H 0.92 (3H, d, J = 6.7 Hz, H-12), δ_H 0.96 (3H, d, J = 6.7 Hz, H-13), δ_H 1.86 (3H, s, H-14), δ_H 1.09 (3H, s, H-15), δ_C 17.4 (C-12), δ_C 18.2 (C-13), δ_C 22.2 (C-14), δ_C 20.1 (C-15)]. The NMR data suggested that compound **3** was a daucane-type sesquiterpenoid and closely comparable to the known compound Trichocarotin A [32]. The di□erence between the two compounds is that compound **3** bears a methylene group instead of the oxymethine group in Trichocarotin A. The COSY correlations between H-3/H-2 as drawn in red bold bonds (Fig. 2) and the HMBC correlations from H-3 to C-1 (δ_C 40.9), H-3 to C-11 (δ_C 36.9) also confirmed this variety. Thus, the planar structure of **3** was elucidated as shown in Fig. 1. The relative configuration of compound **3** was determined by NOESY spectra (Fig. 3). The NOESY correlations between H-5/H-11, H-11/H-2b (δ_H 1.32), and, H-15/H-2a (δ_H 1.66) indicated that Me-15 and H-2a were on the same side of the ring, while the isopropyl, H-5 and H-2b on the opposite side. By comparison of the experimental and calculated ECD spectra (Fig. 4), compound **3** could be identified as (*1S,4S,5S*)-1,8-dimethyl-4-isopropyl-4-hydroxy-1,2,3,5,6,10-hexahy-droazulen-9(1H)-one (Fig. 1), and conyterpenol C as trival name.

Compound **4** was obtained as light-yellow oil. The HRESIMS spectrum

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Appendix A. Supplementary data

Experimental details including IR, CD, HRESIMS, and NMR (^{1}H NMR, ^{13}C NMR, DEPT135, ^{1}H−^{1}H COSY, HSQC, and HMBC) spectra of compounds **1**–**4**, and NOESY spectra of compounds **1**–**3**. Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2020.104473.

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