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New flavans and stilbenes from *Cyperus conglomeratus*

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ABSTRACT

The chromatographic investigation of Cyperus conglomeratus Rottb. aerial parts resulted in the isolation of three new flavan derivatives, 7,3′-dihydroxy-8,4′-dimethoxyflavan (**1**), 7,4′-dihydroxy-5,3′-dimethoxy-8-methylflavan (**2**) and 7,4′-dihydroxy-5,3′-dimethoxy-8-prenylflavan (**3**), and two new stilbene derivatives, 4-hydroxy-5′-methoxy-6″,6″-dimethylpyran[2″,3″: 3′, 2′]stilbene (**4**) and 4′-hydroxy-3,5-dimethoxy-2-prenylstilbene (**5**), along with four known compounds, 5,4′-dihydroxy-7,3′-dimethoxyflavan (**6**), 3′,4′-dimethoxyluteolin (**7**), 3′,4-dihydroxy-5′-methoxy-2′-prenylstilbene (**8**), and 4,4′-dihydroxy-3,3′-dimethoxy-2′-prenylstilbene (**9**). The structures were established by their 1D, 2D NMR and MS spectral data. The new compounds **1**-**5** were tested for cannabinoid and opioid receptor binding. Compounds **1**, **3**, **4**, and **5** exhibited moderate activity (> 50% displacement) towards μ-opioid receptor.

1. Introduction

The genus Cyperus belongs to sedge family (Cyperaceae) consists of about 600 species distributed worldwide. Cyperus is chemically characterized by the presence of flavonoids, stilbenes, coumarins, sesquiterpenes, triterpenes, sterols, and quinines. Cyperus rotundus has been reported in Indian, Chinese and Japanese traditional medicine for treatment of spasms, stomach and bowel disorders. Cyperus conglomeratus Rottb. is distributed through coastal sand dunes of Egypt and the southern coast of Iran. It has been used in traditional medicine as pectoral, anthelmintic, antidiarrheal, emollient, stimulant, aromatic stomachic in nervous gastraglia, carminative, tonic, diuretic, and analgesic (Abdel-Mogib et al., 2000; Feizbakhsh and Naeemy, 2011; Nassar et al., 1998). Previous phytochemical studies on C. conglomeratus reported that the plant contains flavans, terpenoids, sterols and aromatic shikimates (Abdel-Mogib et al., 2000). The opioid and cannabinoid g-protein coupled receptors; are mainly located in the central nervous system (CNS) (Gao et al., 2011) and extensively involved in drug therapy. Various subtypes of these receptors have been recognized; the opioid receptor system includes μ (mu), κ (kappa), and δ (delta) receptors, while the CB1 and CB2 receptors are the main subtypes of cannabinoid receptor system. A powerful analgesia for the treatment of various neuropathic pains is produced by agonists of the opioid and cannabinoid receptors (Gao et al., 2011). Based on traditional uses and literature survey, the current information about the chemistry of C. conglomeratus is limited. Herein, we report the chromatographic investigation of the chloroform extract of C. conglomeratus aerial parts. Five new compounds (**1**-**5**), along with previously known compounds (**6**-**9**) were isolated and identified. The new compounds were tested for their binding affinity on cannabinoid and opioid receptor.

2. Results and discussions

The chromatographic investigation of chloroform fraction resulted in isolation of five new compounds (**1**-**5**) together with four known compounds **6**-**9** (Fig. 1). The structure of **6**-**9** were established by comparing their observed data with those published in literature, and identified as 5,4‘-dihydroxy-7,3‘-dimethoxyflavan (**6**) (Li et al., 2011), 3‘,4‘-dimethoxyluteolin (**7**) (Maskey et al., 2003), 3‘,4-dihydroxy-5‘-methoxy-2‘-prenylstilbene (**8**) (Dawidar et al., 1994), and 4,4‘-dihydroxy-3,3‘-dimethoxy-2‘-prenylstilbene (**9**) (Abu-Mellal et al., 2012).

Compound **1** was obtained as brownish-yellow powder. It has a molecular formula $C_{17}H_{18}O_5$ deduced from HRESIMS. Seventeen carbon signals were observed in ^{13}C NMR spectrum, discriminated by DEPT experiment into two methyl, two methylene, six methine, and seven quaternary carbon signals. Analysis of ^{1}H NMR spectrum in CD_3OD immediately revealed the presence of flavan framework bearing a prenyl moiety. Carbon signals at δ_C 79.1 (δ_H4.94), 31.4 (δ_H 1.95, 2.13) and 25.7 (δ_H2.67 and 2.87) were assigned and characteristic for

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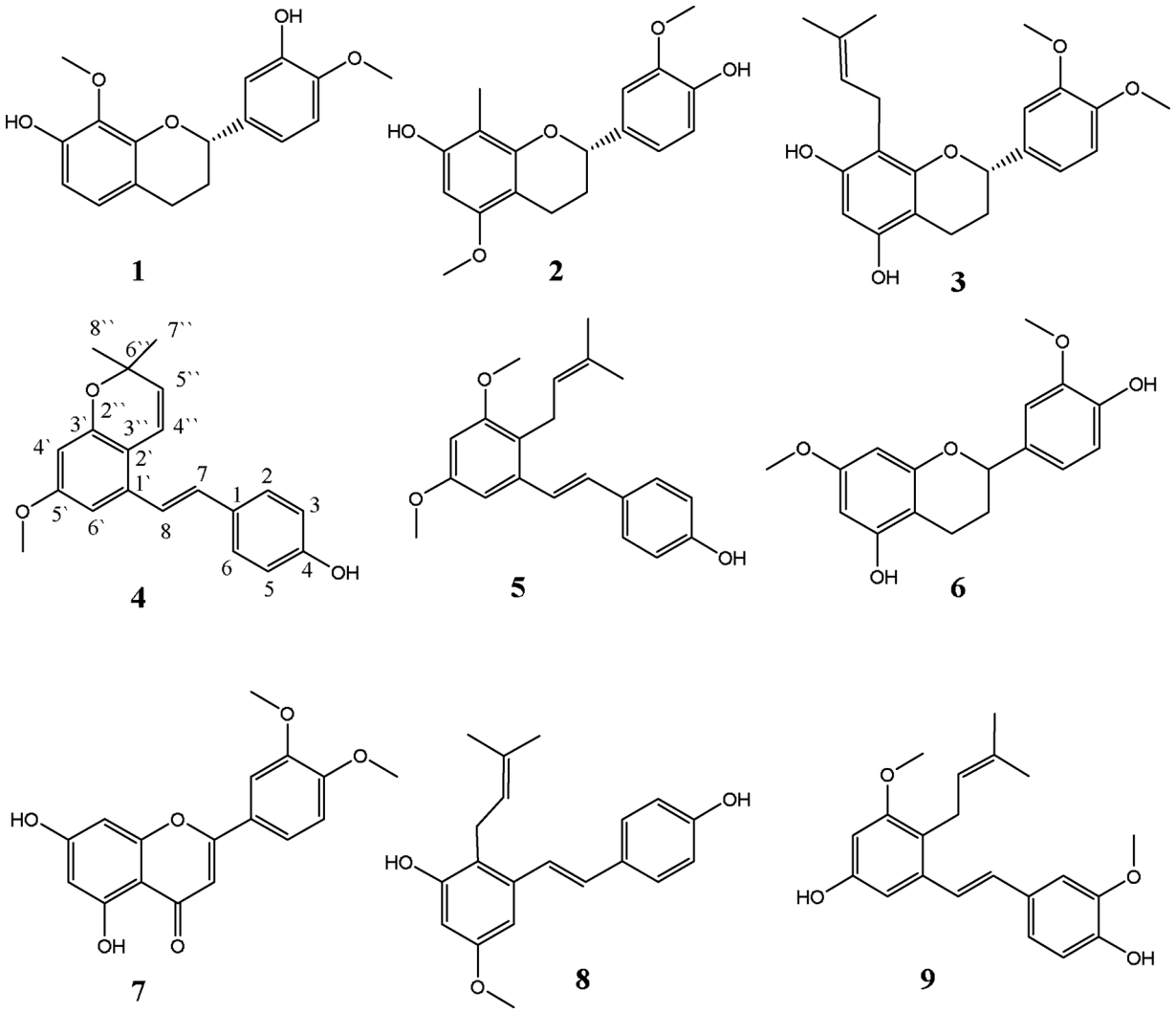

Fig. 1. Structures of compounds **1–9.**

C-2, C-3 and C-4, respectively, of the flavan skeleton. Two aromatic protons at δ_H 6.91 (1H, d, J = 2.0 Hz) and 6.37 (1H, dd, J = 8.3, 2.0 Hz) showed correlation with C-2 in HMBC spectrum (Fig. 2) and were assigned for C-2‘ and C-6‘, respectively. The H-2‘ showed correlation with proton signal at 6.89 (1H, d, J = 8.3 Hz) which was assigned for H-5‘. The splitting of H-2‘, 5‘ and 6‘ indicated the tri-substituted benzene ring B. The downfield resonances at δ_C 147.8 and 148.8 were assigned to the C-3‘ and C-4‘, respectively, based on the HMBC correlations of H-2‘, H-5‘ and H-6‘. The ring A showed two o-coupled aromatic protons at δ_H 6.62 (1H, d, J = 8.4 Hz) and 6.37 (1H, d, J = 8.3 Hz) in ^{1}H NMR spectrum, were assigned for carbon signals at δ_C125.1 and 109.2, respectively in the HMQC spectrum. Carbon signal at δ_C125.1 was assigned to C-5 confirmed by the observed correlation between 2H-4 protons and C-5 in HMBC spectrum. The proton signal at δ_H 6.37 was assigned for H-6, confirmed by ^{1}H–^{1}H correlation in COSY spectrum. The C-7 (δ_C 149.8) and C-8 (δ_C 137.3) were substituted which confirmed by H-5 and 6 correlations in HMBC spectrum. Furthermore, the ^{1}H NMR spectrum showed two signals at δ_H3.84 (3H, s)) and 3.80 (3H, s) were ascribed for two methoxy carbons at δ_C56.7 and 61.3, respectively. The location of the methoxy groups confirmed through the HMBC correlations of protons at δ_H3.84 with C-4‘ (δ_C148.8), and protons at δ_H 3.80 with C-8 (δ_C 137.3). Significant NOESY correlations were observed between 4‘-OMe and H-5‘, and between 8-OMe and H-2, confirmed the proposed assignment. Thus, the structure of **1** was established as 7,3‘-dihydroxy-8,4‘-dimethoxyflavan.

Compound **2** had the molecular formula of $C_{18}H_{20}O_5$, as deduced from HRESIMS. The ^{1}H and ^{13}C NMR spectra of compound **2** were close to those of flavan **1**, except for different substitution signals of the aromatic rings A and B. The ^{1}H NMR spectrum showed aromatic protons at δ_H7.0 (1H, d, J = 2.0 Hz), 6.79 (1H, d, J = 8.0 Hz), and 6.86 (1H, dd, J = 8.0, 2.0 Hz) attributed to tetra-substituted benzene ring and were assigned for C-2‘, C-5‘, and C-6‘, respectively, confirmed by the HMBC correlations between H-2‘, H-6‘ and C-2 (δ_C 78.3) and ^{1}H–^{1}H COSY correlations between H-6‘, H-2‘, and H-5‘. The ^{13}C NMR spectrum showed upfield carbon signal at δ_C 7.7 correlated with proton signal δ_H 1.98 (s, 3H) in HMQC spectrum and attributable to aromatic methyl group located at C-8. The downfield shift of C-8 and HMBC correlations (Fig. 2) between 8-Me protons and carbon signals at δ_C 154.6 (C-7), 104.5 (C-8), and 155.1 (C-9) confirmed the assignment. A singlet aromatic proton appeared in ^{1}H spectrum at δ_H 6.03, assigned to an isolated proton on an aromatic penta-substituted ring and attributed to C-6, confirmed by HMBC correlations between H-6 and C-8 (δ_C 104.5) and C-10 (δ_C102.8). The ^{1}H and ^{13}C NMR spectra together with DEPT experiment revealed the presence of a methoxy group at δ_H 3.83 (δ_C56.0) located at C-3‘ confirmed by observed NOESY correlation between 3‘-OMe and H-2‘ (δ_H7.0). Additional methoxy group at δ_H 3.72 (δ_C 55.2) was located at C-5, confirmed by NOESY cross peak between the 5-OMe protons and H-2 and H-6. Thus, **2** was identified as 7,4‘-dihydroxy-5,3‘-dimethoxy-8-methylflavan.

Compound **3** was isolated as brownish-red amorphous solid with