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New bioactive dihydrofuranocoumarins from the roots of the Tunisian *Ferula lutea* (Poir.) Maire

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ABSTRACT

A phytochemical investigation of the roots of *Ferula lutea* (Poir.) Maire led to the isolation of new dihydrofuranocoumarins as two inseparable isomers, (−)-5-hydroxyprantschimgin **1** and (−)-5-hydroxydeltoin **2**, together with eight known compounds, (−)-prantschimgin **3**, (−)-deltoin **4**, psoralen **5**, xanthotoxin **6**, umbelliferone **7**, caffeic acid **8**, β-sitosterol **9** and stigmasterol **10**. Their structures were elucidated on the basis of extensive spectroscopic methods, including 1D and 2D NMR experiments and mass spectroscopy analysis, as well as by comparison with literature data. The anti-acetylcholinesterase and cytotoxic effects of the isolates and antioxidant activities of the mixture (**1**+**2**) were also evaluated in this work. Results showed that the mixture (**1**+**2**) has the most cytotoxic activity with IC_{50} values 0.29 ± 0.05 and 1.61 ± 0.57 μM against the cell lines HT-29 and HCT 116, respectively. The greatest acetylcholinesterase inhibitory activity (IC_{50} = 0.76 ± 0.03) was exhibited by the xanthotoxin **6**. In addition, the mixture (**1**+**2**) was investigated for its antioxidant activity and showed IC_{50} values 18.56, 13.06, 7.59, and 4.81 μM towards DPPH free radical scavenging, ABTS radical monocation, singlet oxygen and hydrogen peroxide, respectively.

The genus *Ferula*, belonging to the family Apiaceae, includes about 170 species, among which 133 species occurring from central Asia westward throughout the Mediterranean region to northern Africa and 30 species from Iran.[1–3] The Tunisian flora comprises four species: *Ferula communis*, *Ferula tingitana*, *Ferula tunetana* and *Ferula lutea*.[4] Its chemistry was largely investigated by many research groups.[5–9] Several species of this genus are used as spices and are well-known medicinal plants since ancient times.[10] The gum resins of the roots from several *Ferula* species are reported to be used for stomach disorders, rheumatism, headache, arthritis, and dizziness.[11,12] Some species are used in traditional foods as well as in folk medicine as treatment for skin infections[13] and diabetes, as well as to prevent convulsion and hysteria.[10] *Ferula* spp. are also known for their toxicity. A chemotype of *F. communis* containing a prenylated coumarin known as ferulenol and related analogues were responsible for ferulosis, a lethal haemorrhagic disease which affect domestic animals in Sardinia.[14] The *Ferula* genus is well documented as a good source of biologically active compounds such as sesquiterpene derivatives[15–19] daucanes, humulanes, himachalanes, germacranes, eudesmanes, and guainanes.[15,20–25] Sesquiterpene derivatives, especially sesquiterpene coumarins, were stored in the roots of the plants; therefore the roots are a better source for isolating sesquiterpene coumarins than the aerial parts.[9,26]

Daucane esters from *F. communis* and *Ferula arrigonii* showed antiproliferative activity on human colon cancer lines and calcium ionophoretic and apoptotic effects in the human jurkat T-cell line.[27,28] A recent study carried out on the roots of *F. tunetana* has led to the isolation of two new sesquiterpenes, tunetanin A and tunetacoumarin A, in addition to eight known compounds, 13-hydroxyfeselol, 3-angeloxycoladin coladin, coladonin, isosmarcandin, umbelliprenin, propiophenone, β-sitosterol and stigmasterol.[9] Currently, there is a considerable interest in the chemistry and pharmacology of *Ferula* species that have not been studied so far. The biological importance of some species of this genus prompted us to investigate the roots of the Tunisian *F. lutea* (Poir.) Maire previously not chemically studied. In this context, we report here the investigation of the roots of *F. lutea* which allowed the isolation and structure elucidation of two new furanocoumarins in mixture, **1** and **2**, together with eight known compounds, **3**–**10** (see Fig. 1). Furthermore, the cytotoxic, anti-acetylcholinesterase activities of the isolates and the antioxidant activity of the two new inseparable isomers **1** and **2** were evaluated.

The CH_2Cl_2-soluble portion obtained from the MeOH extract of the roots of *F. lutea* was further fractionated by successive column chromatography to afford two new dihydrofuranocoumarins **1** and **2** in mixture, together with eight known compounds, **3**–**10**.[29]

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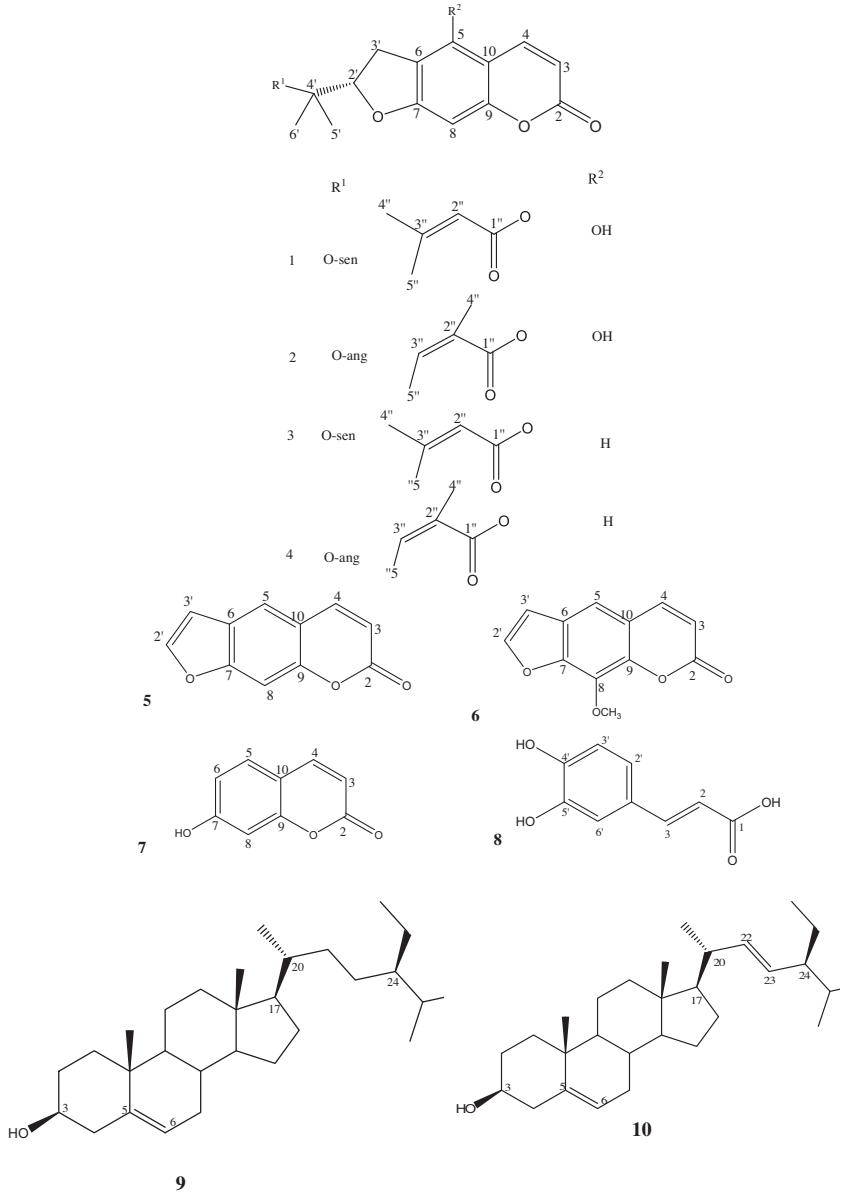

Figure 1. Structures of compounds **1**–**10**.

The mixture of compounds **1** and **2** was isolated as yellow oil and showed on TLC a spot featuring a characteristic blue fluorescence under UV light. The common molecular formula of **1** and **2** was found to be $C_{19}H_{20}O_6$, on the basis of the pseudomolecular ion peak at m/z 345 for the $[MH]^+$ in the ES-MS. The IR spectrum showed the presence of OH (3350 cm^{-1}) and COO (1730 and 1700 cm^{-1}) groups. The structure of **1** and **2** were elucidated on the basis of the ^1H and ^{13}C NMR spectral data (Table 1).

The ^1H NMR spectrum showed the presence of all proton signals of prantschimgin **3**[30] and deltoin, **4**,[31] except those of H-5 of the two structures. This spectrum showed two signals at δ 5.96 (1H, d, J = 9.6 Hz) and 7.96 (1H, d, J = 9.9 Hz) as AB-type signals, attributable to H-3 and H-4 of the two structures, respectively. The same ^1H NMR spectrum displayed an ABX system at δ 4.96 (1H, dd, J = 9.6, 7.8 Hz, H-2′), δ 3.07 (1H, dd, J = 15.9, 8.7 Hz, H-3′a) and δ 2.96 (1H, dd, J = 15.6, 7.8, H-3′b) relative to compound **3,** analogous of prantschimgin and the same system at δ 4.9 (1H, dd, J = 10.2, 8.1 Hz, H-2′) and δ 3.24 (2H, m, H-3′) corresponding to compound **4**, analogous of deltoin. These data suggested the presence of the dihydrofuranocoumarin skeleton in **1** and **2**. The presence of two singlets very close to δ_H 6.20 and 6.21, attributable in prantschimgin **3** and deltoin **4** to the aromatic proton H-8, respectively and the disappearance of that of H-5 at around δ_H (7.17, s) suggest the substation of C-5 in both **1** and **2**. The NMR spectroscopic data together with the molecular formula, suggested that the proton H-5 is substituted by a hydroxyl group in **1** and **2**.

The other signals on the same spectrum coincide with the spectral data of a senecioyl and angeloyl moieties in both **1** and **2**, respectively.

The ^{13}C NMR spectrum shows 24 signals including 11 attributed to the common dihydrofuranocoumarin system. The disappearance of the signal of C-5 at δ_C 123.2 ppm in prantschimgin **3** and at 127.3 ppm deltoin **4** and the appearance in of a signal at δ_C 168.1 ppm reinforces the presence of a hydroxyl group attached to C-5.

The ^{13}C NMR spectrum shows perfectly that this compound is a mixture of two isomeric forms, and that it is just out of the two substituents that are senecioyle and angeloyl. Moreover, the