JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp

Article

Pauciflorins A−E, Unexpected Chromone−Monoterpene-Derived Meroterpenoids from *Centrapalus pauciflorus*

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Cite This: *J. Nat. Prod.* 2023, 86, 891−896

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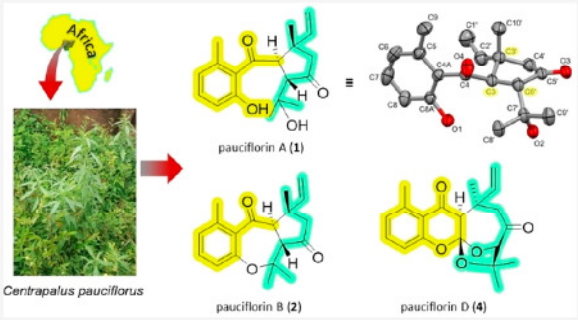
ABSTRACT: Five unusual meroterpenoids based on new carbon skeletons, pauciflorins A−E (**1**−**5**), were isolated by multistep chromatographic separations of a methanol extract of the aerial parts of *Centrapalus pauciflorus*. Compounds **1**−**3** are derived by the connection of a 2-nor-chromone and a monoterpene unit, whereas **4** and **5** are dihydrochromone−monoterpene adducts with a rarely occurring orthoester functionality. The structures were solved using 1D and 2D NMR, HRESIMS, and single-crystal X-ray diffraction. Pauciflorins A−E were evaluated for antiproliferative activity against human gynecological cancer cell lines, but were inactive (IC_{50} < 10 μM) in each case.



Meroterpenoids are natural products derived from hybrid terpenoid and polyketide or non-polyketide biosynthesis. These compounds consist of a ring system involving a mono-, sesqui-, or diterpenoid moiety and a phloroglucinol, syncarpic acid, phthalide, benzofuran, phenylfuran, chromane/chromone, coumarin, quinone, flavone, or alkaloid component.[1] Exceptionally diverse and complex structures are derived from connections of the structural fragments of different biosynthetic origins. Monoterpenoid-coupled chromones are rare compounds in plants that usually occur together with structurally related monoterpenoid coumarins in the genera of the family Asteraceae.[2−4] Species of the Nassauvieae, Mutisieae, and Vernonieae tribes from the Asteraceae family were found to synthesize monoterpenoid-type meroterpenes. *Nassauvia aculeata*,[5] *Triptilion benauentei*, and *T. spinosum*[6] from Nassauvieae, *Gerbera piloselloides*,[2] *G. delavayi*,[3] and *Mutisia friesiana*[7] from Mutisieae, and *Bothriocline ripensis*[8] from the Vernonieae tribe were reported to accumulate both coumarin- and chromone-based meroterpenoids, while only coumarin-monoterpene-derived meroterpenoids were isolated previously from *Gutenbergia*,[8] *Ethulia*,[9] and *Vernonia*[10] species of the Vernonieae tribe. Chromone-based meroterpenoids exhibit cytotoxic, antiproliferative, and anti-inflammatory activities.[2]

Centrapalus pauciflorus (Willd.) H.Rob. (Asteraceae family, Vernonieae tribe) was investigated as part of an ongoing effort to discover new bioactive metabolites from African plant species. This species is native to tropical African regions and is found predominantly in the Western and Eastern countries of the continent.[11] *C. pauciflorus* has been used in traditional medicine to treat chest and stomach pain.[12] In a preliminary experiment, fractions obtained from the chloroform-soluble extract of *C. pauciflorus* were assayed against the human breast (MCF-7 and MDA-MB-231), cervical (HeLa), and ovarian (A2780) cancer cell lines for antiproliferative activity. As presented in Figure S1 in the Supporting Information, fraction 3 eluted with 60% MeOH from the polyamide column exhibited the most potent activity; so therefore this fraction was selected for isolation of the chemical constituents. The present paper reports the isolation and structural determination of five chromone−monoterpene-type meroterpenoids (**1**−**5**) (Figure 1) from the leaves of *C. pauciflorus*.

RESULTS AND DISCUSSION

Pauciflorin A (**1**) was isolated as a colorless oily material with an optical rotation of $[\alpha]_D$ −157.8 (*c* 0.1, $CHCl_3$). The molecular formula of **1** was determined as $C_{19}H_{24}O_4$, based on the positive-ion HRESIMS peak at *m*/*z* 339.1567 $[M + Na]^+$ (calcd for $C_{19}H_{24}O_4Na^+$ 339.1567). The ^1H and ^{13}C NMR JMOD spectra revealed characteristic resonances of four methyl, two methylene, six methine, and seven quaternary carbon-containing groups (Tables 1 and 2). The aromatic ^1H NMR resonances at δ_H 6.71 d (8.0 Hz), 7.20 t (8.0 Hz), and 6.78 d (8.0 Hz) indicated a 1,2,3-trisubstituted aromatic ring,

Received: December 14, 2022
Published: March 18, 2023