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NEW CYTOTOXIC CYCLOARTANE TRITERPENE FROM *Guarea macrophylla* ssp. Tuberculata (MELIACEAE)

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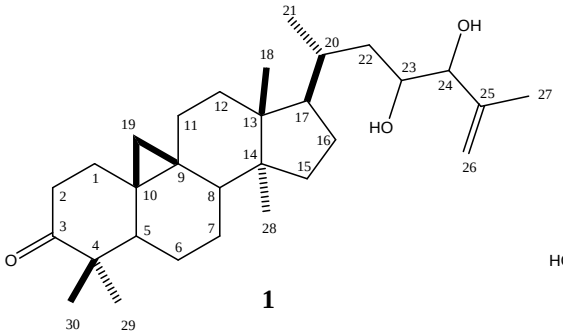
The Meliaceae family comprises approximately 50 genera and 1400 species. In Brazil, there are about six genera and 150 species, including *Guarea macrophylla* [1]. This plant produces several metabolites, including cycloartane triterpenoids [2]. As part of an extensive study aiming the discovery of cytotoxic derivatives in plant species from Brazilian Atlantic Forest, the crude EtOH extract from leaves of *G. macrophylla* displayed cytotoxic potential against B16F10Nex2 cell lines (murine melanoma). This crude extract was partitioned into the hexane, CH_2Cl_2 and EtOAc. After evaluation of cytotoxic potential, the hexane phase showed activity and was subjected to a bioactivity guided fractionation over SiO_2, Sephadex LH-20 and Florisil® to afford two active compounds (**1** and **2**). Compound **1** was obtained as an amorphous solid, displaying the protonated ion peak at *m/z* 457.3185 in the HRESIMS spectrum, indicative of molecular formula $C_{30}H_{48}O_3$. ^{1}H NMR spectrum exhibited two coupled doublets at δ 0.58 (1H, *J* = 4.6 Hz) and δ 0.80 (1H, *J* = 4.6 Hz), characteristic of cyclopropane hydrogens (H-19) of cycloartane derivatives [2]. ^{13}C NMR and DEPT 135^o spectra indicated the presence of signals related to thirty carbon atoms, including peaks attributed to C-19 at δ 29.7 (CH_2) and to carbonyl group at δ 216.6 (C-3). These spectra also revealed the presence of two peaks assigned to sp^2 carbon at δ 112.5 (CH_2) and δ 145.1 (C), attributed to C-26 and C-25, respectively, as well as two signals at δ 70.9 (CH) and δ 77.5 (CH), corresponding to carbinolic carbons. HMBC spectrum showed cross peaks between the signals at δ 77.5 (C-24)/δ 5.06 (H-26) and δ 1.77 (H-27), δ 70.9 (C-23)/δ 3.90 (H-24) and δ 1.68 (H-20), δ 145.1 (C-25)/δ 3.90 (H-24) as well as δ 112.9 (C-26)/δ 1.77 (H-27), positioning the hydroxyl groups at C-23 and C-24. Therefore, the structure of new compound **1** was elucidated as 23,24-dihydroxycycloart-25-en-3-one. Compound **2** was identified as cycloart-23*E*-en-3β,25-diol, previously described to *G. macrophylla* [2], based in the analysis of NMR spectra and comparison to data reported in the literature. Cytotoxic activity of compounds **1** and **2** were evaluated *in vitro* against a panel of tumor cell lines - B16F10-Nex2 (murine melanoma), A2058 (human melanoma), MCF7 (human adenocarcinoma), HL-60 (human leukemia), HeLa (human cervical carcinoma), and T75 (non-tumorigenic fibroblast). Comparatively to the positive control cisplatin, compound **1** displayed strong activity against B16F10Nex2 and MCF7 with IC_{50} = 9.8 ± 1.7 and 22.0 ± 1.8 µg/mL, respectively, while compound **2** showed high potential against HL-60 (IC_{50} = 8.0 ± 0.2 µg/mL). On the other hand, both compounds **1** and **2** showed moderate potential to the other tested cell lines (IC_{50} ranging from 19.4 ± 1.8 to 27.8 ± 0.1 µg/mL). Therefore, considering the cytotoxic activity displayed by compounds **1** and **2** isolated from leaves of *G. macrophylla*, these compounds could be used as scaffold to discovery of prototypes to be used as antineoplasic agents.



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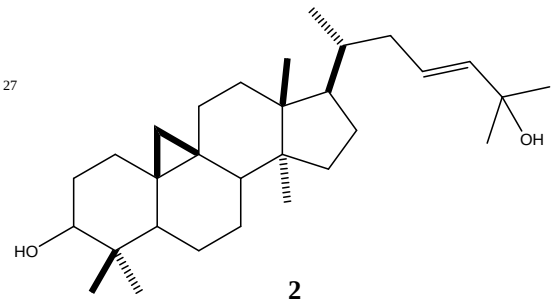

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