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ANTIMITOTIC PLAKORTIDES ISOLATED FROM THE MARINE SPONGE Plakortis angulospiculatus

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As part of a bioprospecting study to identify novel marine anticancer compounds from the northeast coast of Brazil, we investigated the chemistry and cytotoxicity of an extract derived from the sponge*Plakortis angulospiculatus*. This sponge is widely known as a source of cyclic endoperoxides with various pharmacological activities, such as antiparasitic, antimicrobial and anticancer [1]. Specimens of *P. angulospiculatus* were obtained during an expedition to Flecheiras Beach, Ceará, Brazil, in 2014 and extracted with ethanol. The obtained extract was then fractionated using a combination of hydrophobic polystyrene resins and silica gel chromatography, and cytotoxicity of collected samples was evaluated using the MTT assay [2]. The isolated compounds were characterized using a combination of optical rotation, HR-ESI-MS and 1D/2D NMR spectroscopy and tested against colon (HCT-116) and breast cancer cell lines (MCF-7), and a non-tumor human cell line (MRC-5). Flow cytometry, optic and confocal microscopy were used to evaluate the mechanisms underlying cytotoxic action. A new endoperoxide, 8-methylplakortide M, along with a known related natural product plakortide P, were isolated from the ethanolic extract, and IC_{50} values for cancer cell lines ranged from 3.2 to 20 uM, after 24 hours of incubation. Using flow cytometry, plakortide P was shown to decrease cell density and induce loss of membrane integrity in cultures in lower concentrations, when compared to 8-methylplakortide M. Both compounds induced a G_2/M arrest and an accumulation of mitotic figures, indicating an antimitotic response. Confocal analysis of α,β and γ-tubulin demonstrated that microtubules were not altered after treatment, therein suggesting that the mitotic response appears to be independent of microtubule polymerization. In this study, we report the identification of a new plakortide with cytotoxic activity and identified an antimitotic effect, mainly that of plakortide P, but the mechanisms related to the cytotoxicity of this compound still requires further investigation.

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