Structure-activity relationships of diverse Annonaceous acetogenins against multidrug resistant human mammary adenocarcinoma (MCF-7/Adr) cells.


Abstract

Fourteen structurally diverse Annonaceous acetogenins, representing the three main classes of bis-adjacent, bis-nonadjacent, and single-THF ring(s), were tested for their ability to inhibit the growth of adriamycin resistant human mammary adenocarcinoma (MCF-7/Adr) cells. This cell line is resistant to treatment with adriamycin, vincristine, and vinblastine and is, thus, multidrug resistant (MDR). Among a series of bis-adjacent THF ring acetogenins, those with the stereochemistry of threo-trans-threo-trans-erythro (from C-15 to C-24) were the most potent with as much as 250 times the potency of adriamycin. A spacing of 13 carbons between the flanking hydroxyl of the THF ring system and the gamma-unsaturated lactone seems to be optimum with a spacing of 11 and 9 carbons being significantly less active. Several single-THF ring compounds were also quite potent with gigantetrocin A (11) being the most potent compound tested. The acetogenins may, thus, have chemotherapeutic potential, especially with regard to MDR tumors.

PMID:9207950

The Annonaceous acetogenin bullatacin is cytotoxic against multidrug-resistant human mammary adenocarcinoma cells.


Abstract

Cytotoxic effects of the Annonaceous acetogenin, bullatacin, were studied in multidrug-resistant (MDR) human mammary adenocarcinoma (MCF-7/Adr) cells vs. the parental non-resistant wild type (MCF-7/wt) cells. Bullatacin was effectively cytotoxic to the MCF-7/Adr cells while it was more cytostatic to the MCF-7/wt cells. ATP depletion is the mode of action of the Annonaceous acetogenins, and these agents offer a special advantage in the chemotherapeutic treatment of MDR tumors that have ATP-dependent mechanisms.
Tumor cell growth inhibition by several Annonaceous acetogenins in an in vitro disk diffusion assay.


Source

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907-1333, USA.

Abstract

The cell inhibition activities of several Annonaceous acetogenins, covering the three major structural classes of bis-adjacent, bis-non-adjacent, and single tetrahydrofuran (THF) ring compounds and their respective ketolactone rearrangement products, were tested in in vitro disk diffusion assay against three murine (P388, PO3, and M17/Adr) and two human (H8 and H125) cancerous cell lines as well as a non-cancerous immortalized rat GI epithelial cell line (I18). The results demonstrate a dose-dependent inhibition of cancerous cell growth, while non-cancerous cell growth is not inhibited by the same dosages. All of the acetogenins, irrespective of their various structural types, inhibit the growth of adriamycin resistant tumor cells and non-resistant tumor cells at the same levels of potency. These results show that the Annonaceous acetogenins are an extremely potent class of compounds, and their inhibition of cell growth can be selective for cancerous cells and also effective for drug resistant cancer cells, while exhibiting only minimal toxicity to 'normal' non-cancerous cells.