Structure–antitumor activity relationship of hybrid acetogenins focusing on connecting groups between heterocycles and the linker moiety

Abstract

We studied hybrid molecules of annonaceous acetogenins and mitochondrial complex I-inhibiting insecticides to develop a novel anticancer agent. A structure–antitumor activity relationship study focusing on the connecting groups between the heterocycles and the linker moiety bearing the tetrahydrofuran moiety was conducted. Eleven hybrid acetogenins with 1-methylpyrazole instead of γ-lactone were synthesized and their growth inhibitory activities against 39 human cancer cell lines were evaluated. The nitrogen atom at the 2'-position of the linker moiety was essential for inhibiting cancer growth. The 1-methylpyrazole-5-sulfonamide analog showed potent growth inhibition of NCI-H23, a human lung cancer cell line, in a xenograft mouse assay without critical toxicity. Hence, the results of this study may pave the way for the development of novel anticancer agents, with both selective and broad anticancer activities.