Structure-based design, synthesis, and evaluation of the biological activity of novel phosphoroorganic small molecule IAP antagonists.

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Streszczenie

One of the strategies employed by novel anticancer therapies is to put the process of apoptosis back on track by blocking the interaction between inhibitor of apoptosis proteins (IAPs) and caspases. The activity of caspases is modulated by the caspases themselves in a caspase/procaspase proteolytic cascade and by their interaction with IAPs. Caspases can be released from the inhibitory influence of IAPs by proapoptotic proteins such as secondary mitochondrial activator of caspases (Smac) that share an IAP binding motif (IBM). The main purpose of the present study was the design and synthesis of phosphorus-based peptidyl antagonists of IAPs that mimic the endogenous Smac protein, which blocks the interaction between IAPs and caspases. Based on the structure of the IAP antagonist and recently reported thiadiazole derivatives, we designed and evaluated the biochemical properties of a series of phosphonic peptides bearing the N-Me-Ala-Val/Chg-Pro-OH motif (Chg: cyclohexylglycine). The ability of the obtained compounds to interact with the binding groove of the X-linked inhibitor of apoptosis protein baculovirus inhibitor of apoptosis protein repeat (XIAP BIR3) domain was examined by a fluorescence polarization assay, while their potential to induce autoubiquitination followed by proteasomal degradation of cellular IAP1 was examined using the MDA-MB-231 breast cancer cell line. The highest potency against BIR3 was observed among peptides containing C-terminal phosphonic phenylalanine analogs, which displayed nanomolar K_i values. Their antiproliferative potential as well as their proapoptotic action, manifested by an increase in caspase-3 activity, was examined using various cell lines.

Słowa kluczowe

IAP antagonist, smac mimetic, apoptosis, phosphoroorganic