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Development of Bir1-targeting Compounds for Cancer Treatment: Study of Iaps Modulation in Nf- κb Pathway

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Inhibitor of Apoptosis Proteins (IAPs) are key negative regulators of apoptosis, frequently overexpressed in cancer. Their functions are mediated by Baculovirus IAP Repeat (BIR) domains, classified as type I (BIR1) and type II (BIR2 and BIR3). While type II BIRs inhibit caspases to prevent apoptosis, BIR1 domains regulate NF-κB signalling by assembling macromolecular complexes. XIAP-BIR1 interacts with TAB1 to promote pro-survival signaling, while cIAP1/2-BIR1 recruit TRAFs to TNF-α receptor complexes, acting as E3 ubiquitin ligases in apoptosis regulation. Traditional IAPs inhibition strategies focus on Smac-mimetic (SM) compounds targeting type II BIRs mimicking the endogenous IAPs antagonist SmacDIABLO, but resistance linked to cIAP1/2 E3 ligase activity limits their effectiveness. The BIR1 domain has emerged as an alternative therapeutic target. A virtual screening of compound libraries led to the discovery of FC2, which modulates NF-κB signaling in MDA-MB-231 cells and enhances cytotoxicity when combined with SMs and TNF-α. A new FC2-based compound library was designed, with selected compounds showing strong BIR1 binding (fluorescence-based assays) and improved cytotoxicity in cancer cells. Ongoing research evaluates compounds effects on isolated proteins (BIRs and full length) and structurally characterizes IAPs-ligand complexes to guide drugs design optimization.