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Abstract

We report on a general structure- and NMR-based approach to derive druglike small molecule inhibitors of protein–protein interactions in a rapid and efficient manner. We demonstrate the utility of the approach by deriving novel and effective SMAC mimetics targeting the antiapoptotic protein X-linked inhibitor of apoptosis protein (XIAP). The XIAP baculovirus IAP repeat 3 (Bir3) domain binds directly to the N-terminal of caspase-9, thus inhibiting programmed cell death. It has been shown that in the cell this interaction can be displaced by the protein second mitochondrial activator of caspases (SMAC) and that its N-terminal tetrapeptide region (NH2-AVPI, Ala-Val-Pro-Ile) is responsible for this activity. However, because of their limited cell permeability, synthetic SMAC peptides are inefficient when tested in cultured cells, limiting their use as potential chemical tools or drug candidates against cancer cells. Hence, as an application, we report on the derivation of novel, selective, druglike, cell permeable SMAC mimics with cellular activity.