

Design of new non-peptide foldamers of SMAC.

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The X-linked Inhibitor of Apoptosis Protein (XIAP) binds to and inhibits caspases 3, 7 and 9, which are some of the enzymes responsible for cell death; and therefore stopping apoptosis. XIAP is naturally regulated (inhibited) by the mitochondrial protein SMAC/DIABLO. However, XIAP is overexpressed in tumorous cells (particularly in ovarian cancer) making them resist to cell death. This is why XIAP makes a suitable drug target.

The aim of the project is design of new non-peptide inhibitors of XIAP in order to promote apoptotic cell death in ovarian tumours. This could be done by “mimicking” the AVPI tetra-peptide of SMAC (β strand) that is used by the latter to bind to the BIR3 domain of XIAP.

First, a pharmacophore model was built based on two ligands of XIAP-BIR3 found in the literature. Then a series of compounds were designed. The binding of these compounds to the active site was studied by docking. Molecular dynamics simulations were then performed to assess the stability of the ligands in the active site. The best compounds were synthesized and tested *in vitro* by Fluorescence Polarisation Assay (FPA). The most promising candidates were selected in order to carry out new pharmacomodulations (Figure 1).

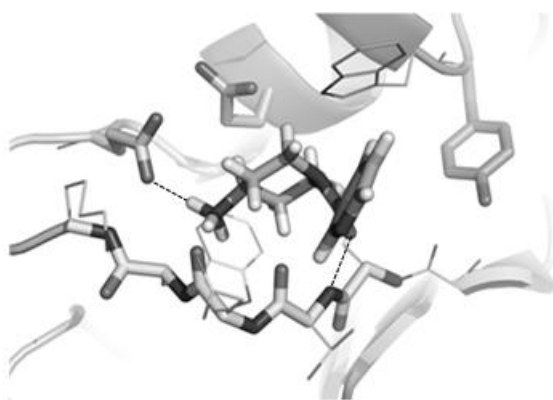


Figure 1. Docking of mr34659 compound in the XIAP bir3 binding site.