Structure-guided design of Mcl-1 inhibitors

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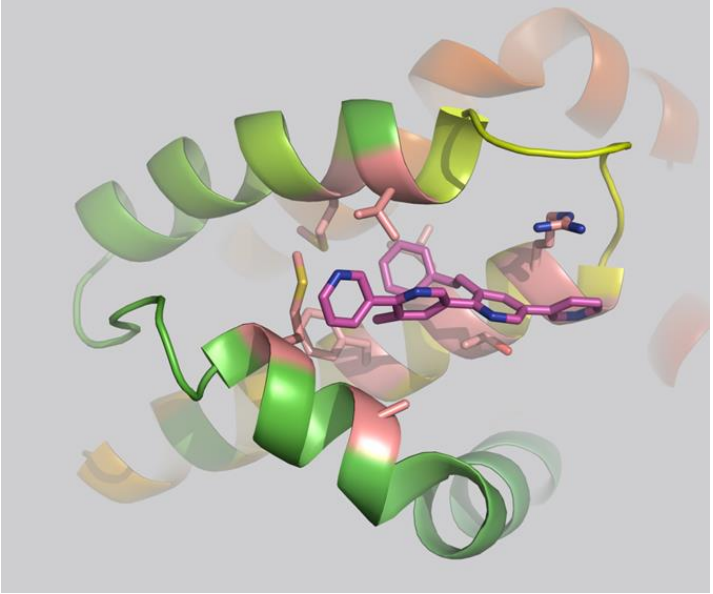
Protein-protein interactions are attractive targets because they control numerous cellular processes. In oncology, apoptosis regulating Bcl-2 family proteins are of particular interest. Bcl-2 proteins are crucial regulators of the intrinsic mitochondrial pathway of apoptosis and comprise both pro-apoptotic and anti-apoptotic proteins.[1] Apoptotic cell death is controlled *via* PPIs between the anti-apoptotic proteins hydrophobic groove and the pro-apoptotic proteins BH3 domain. Mcl-1 (an anti-apoptotic Bcl-2 member) is a key regulator of cancer cell survival and a known resistance factor to Bcl-2/Bcl-x_L pharmacological inhibitors making it an attractive therapeutic target. As interaction among Bcl-2 family proteins occurs through α-helices, our laboratory has developed a new family of compounds able to mimic α-helix side chain distribution (abiotic foldamers) using as structural chemical units pyridine and/or phenyl.[2] The designed and synthesized oligopyridines were evaluated by their capacity to inhibit Mcl-1 in live cells and to sensitize ovarian carcinoma cells to Bcl-x_L-targeting strategies and Pyridoclax was emerged a lead.[3,4] Then, a combined experimental and theoretical approach was applied to investigate the binding mode of Pyridoclax to Mcl-1 and to guide the future pharmacomodulations.[5]



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