

Structure-Based Drug Design of Bcl-XL Selective Inhibitors

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Dysfunction of apoptosis (programmed cell death) is a hallmark of cancer. The Bcl-2 family of proteins regulate this apoptotic pathway through binding interactions between its pro-apoptotic and anti-apoptotic family members thus making them key targets for cancer research. Bcl-XL, an anti-apoptotic member of the Bcl-2 family, is overexpressed in multiple solid tumors and in hematological malignancies, enabling tumor survival. Targeting protein-protein interactions like this is a challenging endeavor often resulting in beyond rule of 5 compounds. This presentation will cover the structure-based drug design and development of Bcl-XL selective inhibitors from fragment hits through lead optimization to a first in class orally active inhibitor.