KINETIC TARGET GUIDED SYNTHESIS FOR THE IDENTIFICATION OF PROTEIN-PROTEIN INTERACTION MODULATORS OF THE BCL-2 FAMILY

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Although protein-protein interactions possess significant biological importance, identification of small molecules modulating specific protein-protein interactions remains challenging due to the flexible nature of proteins. Several fragment based approaches have been established to identify fragments with good ligand efficiencies, but fail to provide insights into efficient fragment linkage, making the drug discovery process complicated. Herein, we report the development of a novel drug discovery approach that generates only biologically active compounds, known as kinetic target guided synthesis (TGS). An amidation reaction between thio acids and sulfonyl azides was successfully employed for Bcl-X_L-templated screening to identify novel inhibitors of anti-apoptotic protein Bcl-X_L. After obtaining encouraging results, this approach was extended to another important protein, Mcl-1. Gratifyingly, some high quality TGS hits were identified and displayed biological activity, comparable with the reported inhibitors of Mcl-1. This validates the kinetic TGS approach as a reliable platform for the identification of novel protein-protein interaction modulators.