Designing and Synthesizing a Warhead-Fragment Inhibitory Ligand for Ivyp1 through Fragment-Based Drug Discovery

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Title

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Abstract

Fragment-based drug discovery (FBDD) is a powerful tool for developing anticancer and antimicrobial agents. Within this, magnetic resonance spectroscopy (NMR) provides a comprehensive qualitative and quantitative approach to screening and validating weak and robust binders with targeted proteins, making NMR among the most attractive strategies in FBDD. Inhibitor of vertebrate lysozyme (Ivyp1) of *P. aeruginosa* serves as an excellent target because of its active cellular location and implications in clinical prognosis for cystic fibrosis and immunocompromised patients. This study uses current NMR and biophysical techniques to develop a covalent, fragment-linked warhead inhibitor for Ivyp1 through synthetic methods, warhead linking, and fragment growth. The protein of interest was expressed using commonly recognized biochemical and chromatographic techniques, with supplemental procedures for isotopic labeling as required in multinuclear NMR experiments. This work has chemically elaborated a prior fragment hit with yield and purity suitable for subsequent studies. Coupling this product with promising warheads is ongoing and preliminary results of this process will be presented. Subsequent efforts aim to study the structure-activity relationships between the warhead-fragment ligand and Ivyp1, compared to standalone compounds, by employing NMR, X-ray crystallography, and other biophysical techniques to gain the necessary information for favorable warhead-fragment growth.

Keywords: heteronuclear-single quantum coherence spectroscopy, inhibitor of vertebrate lysozyme, fragment growing, C-type lysozyme, X-ray crystallography, nuclear magnetic resonance spectroscopy, cystic fibrosis, fragment screening, differential scanning fluorometry, covalent warhead