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Towards rational design of fluorine substitution in small molecule inhibitors targeting protein-protein interactions

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Fluorine has become increasingly common in medicinal chemistry and is present in ~20% of known dugs. Fluorine is the most electronegative element and is frequently used to substitute hydrogen in organic molecules. In medicinal chemistry, fluorine substitutions are being used to enhance the activity, metabolic stability and physicochemical properties of active molecules. Despite highly desired properties, rational design of fluorine substitutions to improve binding affinity of small molecule inhibitors is challenging. Since the fluorine chemistry might be complex, reliable prediction of the effect of fluorine substitution would significantly improve rational drug discovery.

The goal of our project is to develop novel drugs for acute leukemia by targeting protein-protein interaction between menin and MLL fusion proteins. Employing high-throughput screening we have identified potent small molecule inhibitors with thienopyrimidine scaffold which bind to menin and inhibit the menin interaction with MLL. Extensive medicinal chemistry optimization of these compounds showed that substitutions of two distinct sites with fluorines led to significant enhancement in the binding affinity to menin. To explain the effect of fluorine addition we synthesized number of analogs by systematic fluorine scanning and we determined high resolution crystal structures for these compounds bound to menin. Employing quantum mechanical calculations we were able to accurately reproduce binding energies for fluorine substituted compounds. Altogether, our studies pave the way towards rational prediction of the effect for fluorine substitution onto the activity of small molecule ligands.

Biography

Tomasz Cierpicki is an Assistant Professor in the Department of Pathology at the University of Michigan. His scientific interest is in structure-function studies of cancer-related proteins and development of small molecule inhibitors of protein-protein interactions relevant to cancer. He is co-author of over 40 scientific publications and determined structures of nearly 30 proteins and protein complexes using NMR and X-ray crystallography. He is also an inventor on several patent applications.

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