Improving Kinase Inhibitors: Molecular editing of resorcylic acid lactones

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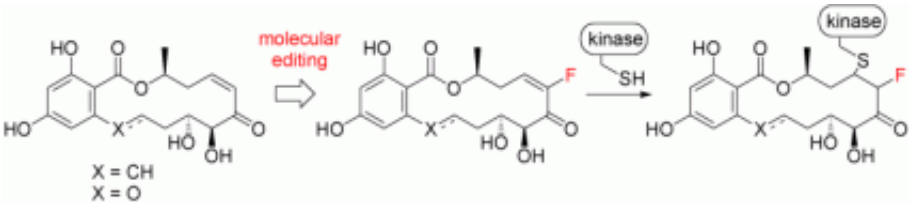

(PhysOrg.com) -- Given the great number and wide range of biological activities they regulate, kinases are among the most important enzyme targets for drug development efforts, particularly in the field of oncology. One of the main challenges faced by researchers in this area is inhibitor specificity; many compounds that effectively block the activity of a given target kinase also show significant inhibition of other kinases.

Nicolas Winssinger and colleagues, at the University of Strasbourg in France, have developed some promising kinase inhibitor lead compounds based on an entirely different molecular scaffold, the resorcylic acid lactones (RAL), and their results are published in *ChemMedChem*.

Kinases, by definition, phosphorylate their substrates, and so adenosine triphosphate (ATP) is a co-substrate common to all kinases. As many current kinase inhibitors are based on the adenosine scaffold, such

compounds can often present difficulty in engineering specificity. Winssinger and co-workers focused their attention on the unique RAL pharmacophore, as various RAL-based small molecules had been shown previously to irreversibly and selectively inhibit certain kinases.

Winssinger's research group subjected the fundamental RAL pharmacophore to 'molecular editing' in order to generate two fluoroenones with improved properties; these, along with other compounds resulting from diversification of the RAL scaffold, also shed light on modifications that affect other important aspects such as metabolic stability.

"The significance of this work does not lie solely in the chemistry and IC50 values, but also in the fact that there is a tremendous interest in irreversible kinase inhibitors that can be used to engineer kinase specificity and to profile kinase activity," says Winssinger. "The cis-enone resorcylic acid lactones represent an alternative scaffold to the heterocyclic ones, which have been previously exploited. From a therapeutic perspective, compounds derived from this pharmacophore are the first irreversible inhibitors of kinases involved in angiogenesis [vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs)]."

More information: Nicolas Winssinger, Molecular Editing of Kinase-Targeting Resorcylic Acid Lactones (RAL): Fluoroenone RAL, *ChemMedChem* 2010, 5, No. 8, 670-673, dx.doi.org/10.1002/cmdc.201000047

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