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Targeting Proteinkinases: The Selectivity Problem

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About 22% of the "druggable" human genome codes target protein kinases. However, only 8 registered drugs worldwide address protein kinase targets (e. g. Gleevec®, Iressa®). Kinases regulate many different signaling processes. Devastating diseases such as cancer, autoimmune diseases and neurological disorders can result from abnormal signal transduction. At present 518 kinases are identified, in which all of them bind the cofactor ATP in a very similar way. The conservation of structural features within the ATP binding cleft initially indicated that specificity for ATP-site directed inhibitors would be difficult to achieve. Structure elucidation of ATP complexes bound to protein kinases, revealed regions within or close to the binding cleft that ATP does not fully occupy. Another way to induce selectivity makes use of a peptide flip at the hinge region, induced by a carbonyl-interaction of the inhibitor with two backbone NH-groups (in case of p38 MAPK, Met109, Gly 110) [1]. We tried to combine both approaches by using carbonyl-groups for targeting the hinge region and aryl-residues to interact with the HR I and/or II. In addition, minimization of the structures was attempted by using only templates with interactions to both the hinge and the hydrophobic regions ("linear binders") [2]. A third structural requirement was reducing conformational flexibility. A rigid structure should allow only less induced fit to other than the target (off-target) kinases. Starting from initial benzophenone leads [3, 4], we developed dibenzo-suberones [5] and optimized them down to single digit nanomolar IC_{50}s against p38 and excellent selectivity profiles against other protein kinases.

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