CL02 Targetting Protein-Kinase—The Selectivity Problem

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The protein kinase family offers a challenge but also a huge opportunity for drug discovery. About 22% of the "druggable" human genome codes target protein kinases (1). There are, however, only few drugs (worldwide 8 registered drugs, e.g. Gleevec®, Iressa®) on the market that address protein kinase targets. Kinases regulate many different cell proliferation, differentiation, and signaling processes. Devastating diseases such as cancer, autoimmune diseases, inflammation, psoriasis, allergic reactions, neurological disorders and hormone-related diseases 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, have revealed that there are regions within or close to the binding cleft that ATP does not fully occupy. These regions, unoccupied by ATP, show structural diversity between members of the kinase family. These are mainly the hydrophobic region I (HR I or selectivity pocket) and a solvent exposed hydrophobic surface (HR II). Many drugs or candidates follow this strategy. 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)(2). 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, we tried to minimize the structures by using only templates with interactions to the hinge region and the hydrophobic regions ("linear binders")(3). No spacers or central aryl pattern should be used. A third structural requirement was reducing conformational flexibility of the inhibitors. A rigid structure should allow only less induced fit to other than the target (off-target) kinases. Starting from initial benzophenone leads(4,5), we developed dibenzosuberones (X,Y: C,O,S)(6) and optimized them down to single digit nanomolar IC50s against p38 and excellent selectivity profiles against other protein kinases(7). The computer-based design approach was finally confirmed by x-ray crystallographic studies and protein-NMR experiments in solution.

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