

**INSIGHTS INTO SELECTIVITY OF STI571 (Gleevec™)
FROM X-RAY CRYSTALLOGRAPHY**

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STI571 (Gleevec™, Imatinib mesylate) is a potent inhibitor of the Abelson tyrosine kinase (ABL), which has been approved by Food and Drug Administration for treatment of Chronic Myelogenous Leukemia (CML). The clinical success of this small molecule kinase inhibitor has created a new paradigm for cancer therapeutics [1]. One of the most striking properties of STI571 is its high selectivity towards molecular targets. STI571 potently inhibits ABL, PDGFR and c-Kit tyrosine kinases ($IC_{50} < 0.3 \mu M$), while being essentially non-active towards other known protein kinases. The molecular origin of this selectivity is poorly understood at the moment.

We present two crystal structures of STI571 bound to the focal adhesion kinase (FAK), that provide insights into Gleevec's selectivity towards its molecular targets. FAK is a non-receptor tyrosine kinase [2,3], which is only weakly inhibited by STI571 ($IC_{50} > 10 \mu M$). In the crystal structure, Gleevec binds FAK in the conserved nucleotide binding site, but assumes a different conformation from what was observed in the crystal structure of STI571-abl complex [4,5]. In this non-selective binding mode, the majority of the contacts between the inhibitor and the protein occur in the hinge region, reminiscent of other less-selective kinase inhibitors. Comparison of the non-selective conformation of Gleevec with a second structure of STI571 bound to a FAK mutant, which has an increased affinity for the inhibitor, illuminates the structural features of the kinase active site that confer STI571 selectivity.

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