Inhibition of wild-type and mutant Bcr-Abl by pyrido-pyrimidine-type small molecule kinase inhibitors.

Abstract:
Imatinib mesylate (STI571, Glivec), a 2-phenylaminopyrimidine small-molecule ATP competitor-type kinase inhibitor, proved to be active in Philadelphia-positive leukemias. Resistance toward imatinib develops frequently in advanced-stage Philadelphia-positive leukemia, and is even observed in chronic-phase chronic myelogenous leukemia. Point mutations within the BCR-ABL kinase domain emerged as a major mechanism of resistance toward imatinib. Mutations occur at positions that determine specific contacts of imatinib to the ATP-binding site. We aimed to examine whether pyrido-pyrimidine-type kinase inhibitors were capable of inhibiting both wild-type and mutant forms of BCR-ABL. We screened 13 different pyrido-pyrimidine with cells expressing wild-type and mutant BCR-ABL. All of the substances specifically suppressed the Bcr-Abl dependent phenotype and inhibited Bcr-Abl kinase activity with higher potency than imatinib. Two of the most active compounds were PD166326 and SKI DV-M016. Interestingly, these compounds suppressed the activation loop mutant Bcr-Abl H396P as effectively as wild-type Bcr-Abl. In addition, nucleotide-binding loop mutations (Y253H, E255K, and E255V) were selectively and potently inhibited. In contrast, T315I, a mutant located at a position that makes a direct contact with imatinib, was not
affected. This observation is consistent with the hypothesis that unlike imatinib, pyrido-pyrimidine inhibitors bind Bcr-Abl regardless of the conformation of the activation loop. We conclude that pyrido-pyrimidine-type kinase inhibitors are active against different frequently observed kinase domain mutations of BCR-ABL that cause resistance toward imatinib. Resistance as a consequence of selection of mutant BCR-ABL by imatinib may be overcome using second-generation kinase inhibitors because of their higher potency and their ability to bind Bcr-Abl irrespective of the conformation of the activation loop.