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Design and Synthesis of Biologically Active Kinase Inhibitors through Rational Design

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Although the constitutively activated break-point cluster region-Abelson (BCR-ABL) tyrosine kinase was well known to be responsible for chronic myelogenous leukemia (CML), the existence of drug-resistant mutants of BCR-ABL has made it difficult to develop effective anti-CML drugs. We studied application of the structure-based virtual screening to identify two common inhibitors equipotent for the wild type and the most drug-resistant T315I mutant of BCR-ABL. Because both inhibitors were screened for having desirable physicochemical properties as a drug candidate and revealed micromolar inhibitory activities, they deserve consideration for further development by structure-activity relationship (SAR) studies to optimize the anti-CML activity. We address the structural features relevant to the stabilizations of the identified inhibitors in the ATP-binding sites. Chromenone derivatives such as flavones and neoflavones constitute a major class of naturally occurring compounds and privileged medicinal scaffolds that exhibit a broad range of biological and pharmaceutical properties. Driven by the need for a more efficient synthetic route to the kinase inhibitor scaffolds, we have been exploring efficient approaches to functionalized cyclic enolone and enaminone scaffolds directly from simple saturated ketones for the development of potent kinase inhibitors.