

[P21] Exploring Selectivity of Multi-kinase Inhibitors across the Human Kinome

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Inhibitors of human kinome are among the most intensely investigated compounds in medicinal chemistry and drug development [1-3]. Most of the currently available kinase inhibitors are type I inhibitors, which target the largely conserved adenosine triphosphate (ATP) cofactor binding site [4]. Hence type I inhibitors are often expected to be promiscuous and lack selectivity [5,6]. In this work, we present a large-scale analysis of selectivity trends among known promiscuous (multi-kinase) inhibitors, which are expected to be least selective. More than 10,000 inhibitors targeting 141 human kinases were analyzed. Kinase pairs sharing inhibitors were systematically generated and selectivity profiles were determined. Compound-based selectivity profiles of kinase pairs revealed many inhibitors that were highly selective for individual kinases over others. Inhibitor sets associated with pairs frequently contained compounds with varying selectivity, ranging from nonselective to highly selective inhibitors. Moreover, inhibitor selectivity was not determined by specific gatekeeper residues and did not correlate with phylogenetic distance between kinases. Taken together, these findings indicate that multi-kinase inhibitors are often more selective than one might assume [7]. Selectivity of type I inhibitors is thought to primarily arise from subtle differences between ATP binding pockets and/or dynamical features of binding sites that are difficult to deduce from X-ray structures. To support further exploration of kinase inhibitor selectivity, our data set consisting of kinase pairs and associated inhibitors has been made freely available as an open access deposition [8].

Bibliography:

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