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Comparative Efficacy and Selectivity of Pharmacological Inhibitors of DYRK and CLK Protein Kinases

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Abstract

Dual-specificity, tyrosine phosphorylation-regulated kinases (DYRKs) and cdc2-like kinases (CLKs) play a large variety of cellular functions and are involved in several diseases (cognitive disorders, diabetes, cancers, etc.). There is, thus, growing interest in pharmacological inhibitors as chemical probes and potential drug candidates. This study presents an unbiased evaluation of the kinase inhibitory activity of a library of 56 reported DYRK/CLK inhibitors on the basis of comparative, side-by-side, catalytic activity assays on a panel of 12 recombinant human kinases, enzyme kinetics (residence time and K_d), in-cell inhibition of Thr-212-Tau phosphorylation, and cytotoxicity. The 26 most active inhibitors were modeled in the crystal structure of DYRK1A. The results show a rather large diversity of potencies and selectivities among the reported inhibitors and emphasize the difficulties to avoid "off-targets" in this area of the kinome. The use of a panel of DYRKs/CLKs inhibitors is suggested to analyze the functions of these kinases in cellular processes.

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