Title

Machine Learning Uncovers Potential Kinesin-5 Inhibitors

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Abstract

Chemotherapeutics targeting kinesin-5 remain an untapped treatment option for various forms of cancer. Kinesin-5, the molecular motor protein which establishes spindle bipolarity in dividing cells, is a promising target for small-molecule inhibitors. However, no kinesin-5 inhibitors have entered the market due to various factors. One suspected difficulty includes rescue mutations at the allosteric inhibitor binding pocket. In this work, we leverage crystallographic and assay data available for kinesin-5 allosteric inhibitors to develop machine learning (ML) models for kinesin-5 binding affinity prediction in the hopes of diversifying known kinesin-5 inhibitors. Specifically, four algorithms are trained and tested using ligand-based and structure-based features. Structure-based and ligand-based models are compared for their ability to reproduce binding affinity data and for their computational cost. The top-performing ligand-based model, a hierarchical clustering scheme, and the top-preforming structure-based model are then used to screen the Goldilocks subset of the ZINC20 dataset to ensure a diverse set of potential hit compounds is formed. Compounds predicted to have potent anti-kinesin-5 activity are shortlisted for further in vitro experimentation. Their binding modes and structural similarities are analyzed and compared to known kinesin-5 inhibitors.