

Discovering Small-Molecule Inhibitors of the c-MET/HGFR Tyrosine Kinase via Machine Learning

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Hepatocyte growth factor receptor (HGFR or c-MET) is a receptor tyrosine kinase that has been found to be linked to cancer, with malignant mutations causing tumor growth, angiogenesis, and metastasis. While previous research has explored the potential of inhibiting c-MET to prevent various oncogenic pathways, there exists no comprehensive inhibitor treatment against c-MET. This research presents a novel two-model machine learning pipeline for predicting new small-molecule inhibitors of the c-MET tyrosine kinase, discovering potential drug candidates more quickly and effectively than traditional in-vitro methods. The first model used in this pipeline is an ensemble of five K-Nearest Neighbors (KNN) Classifiers, which were trained to identify molecules as potential inhibitors or non-inhibitors of c-MET based on patterns in molecular structure. The potential inhibitors identified by the KNN Classifiers were then fed into the second model of the pipeline, a regression Neural Network trained to predict a molecule's potency in inhibiting c-MET. Potency was measured with half-maximal inhibitory concentration (IC₅₀), which indicates the molar concentration required to inhibit c-MET function by 50%. Out of the over 1.9 million molecules screened by the pipeline, 4456 molecules were selected as potential inhibitors (IC₅₀ less than 10 μ M), and 12 of them were predicted to be especially potent inhibitors, with IC₅₀ values less than 10 nM. Overall, the designed computational pipeline can potentially serve as a powerful drug discovery tool, able to screen molecules in seconds, and was able to identify several molecules that represent highly promising drug candidates against c-MET.