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 μM), 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.