Monco: A Novel Deep Learning Pipeline to Predict Drug Candidates for the Inhibition of EZH2 Cofactors in Pediatric Neuroblastoma

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Pediatric Neuroblastoma (NB) is one of the most common cancers among infants, with 90% of its cases occurring in children under the age of five and only 50% of youth with high-risk NB surviving after five years. Currently, there are no clinically approved drugs successful in treating high-risk NB due to cancerous side effects and undruggable MYC transcription factors. However, recent CRISPR-Cas9 loss-of-function screens have revealed the enhancer of zeste homolog 2 (EZH2) as a strong therapeutic target for NB due to its proclivity for immune evasion. Drug discovery is a time-consuming and costly process, with the typical timeframe ranging from 10-20 years and developmental costs ranging from 500 million to 2.6 billion dollars. Hence, computer-aided drug design (CADD) has become widely adopted; however, existing CADD remains largely incomprehensive due to its inability to account for dynamic protein structure, sufficient chemical descriptors for drug-like compounds, and efficient early screening of compounds. The purpose of this study was to develop a novel, robust, and production-ready in silico deep learning pipeline for de novo drug design using an ensemble of machine learning techniques. The pipeline consists of three main functions: (1) identification of relevant cofactors through a graph neural network and Kruskal's algorithm, (2) development and optimization of drug-like compounds through deep learning (i.e., variational autoencoders) after cryptic pocket discovery, and (3) validation of compounds through molecular simulations and Tanimoto's similarity. To this end, this work serves as an efficient screening and discovery process for oncological therapeutics as a whole.

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