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Development of an AI Model for PROTAC Drug Activity Prediction

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Recent advances in molecular biology have spurred targeted therapies that inhibit disease-associated proteins with improved efficacy and fewer side effects. Yet many proteins lack druggable pockets or form large complexes, leaving over 80% of human proteins "undruggable." Targeted protein degradation (TPD) addresses this limitation by harnessing cellular degradation pathways. Among TPD strategies, PROteolysis TArgeting Chimeras (PROTACs) use the ubiquitin–proteasome system to eliminate proteins without requiring strong binding affinity, though their large size and complex synthesis remain challenges. In this study, we present an artificial intelligence (AI) model to predict PROTAC degradation activity. The model leverages AlphaFold3 to map the protein of interest (POI) and E3 ligase in three-dimensional space and employs cross-attention to capture interactions among the two proteins and the PROTAC. Using public datasets from PROTAC-DB and PROTACpedia, our model shows robust performance on unseen POIs, unseen PROTACs, and combined unseen settings, suggesting that it could aid future efforts in PROTAC design and development.