Explainable AI-Driven Enhancement of in silico Drug Screening for Chronic Toxoplasma gondii Infection

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Toxoplasma gondii infects up to one-third of the global human population. In its dormant state, this parasite can persist in its host for life. No treatments exist for this chronic stage of infection. In immunocompromised individuals, parasite reactivation can cause severe neurological effects. Computational drug screening approaches specifically targeting chronic toxoplasmosis remain underexplored. This project aimed to identify key molecular features and substructures that influence T. gondii drug-target interactions, allowing for the identification of biologically relevant drug candidates. Two classical machine learning models and a graph neural network were trained to predict compound binding affinity with the protein T. gondii Cathepsin L. Explainable artificial intelligence (XAI) tools were used to identify key features and substructures influencing the models' predictions, helping guide the refinement of molecular representations for a second-stage compound screening model. Top-ranked compounds were further assessed through molecular docking and pharmacokinetic predictions. Ten molecular substructures with significant influence on the model's binding affinity predictions were identified. These insights allowed for the prioritization of compounds with a higher likelihood of strong binding. After incorporating the XAI insights, the model achieved a testing R^2 value of 0.71 and training R^2 value of 0.95, indicating strong predictive performance. The final framework filtered over 86,000 compounds within 5 hours, prioritizing candidates with favorable binding and pharmacokinetic properties. This project shows that integrating XAI into drug screening improves model interpretability, helping inform model refinement and enabling more reliable drug candidate prediction.

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