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Design of Dual-Target Wnt Pathway Inhibitors
Using Hybrid Machine Learning / Molecular Modeling Approaches

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The simultaneous inhibition of the PI3Kα (phosphoinositide-3-kinase α) and tankyrase enzymes involved in the Wnt pathway has synergistic effects making it a promising approach to the colorectal cancer therapy. The design of their dual-target inhibitors represents an interesting problem of rational polypharmacology. We have shown that the reliable prediction or ranking of activities towards multiple relevant targets can be achieved by using hybrid machine learning models (especially Deep Neural Networks) based on the molecular modeling data.

The molecular docking-based virtual screening workflow can be significantly enhanced by the machine learning approach to the development of target-specific scoring functions. Using the empirical potential values derived from the Smina scoring functions as descriptors, the Deep Neural Network classification models achieve high external test AUC ROC values. [1]

To predict binding affinities from the analysis of short molecular dynamics trajectories, they can be considered as multidimensional time series represented by 2D tensors containing the ligand-protein interaction descriptor values for each timestep. The convolutional neural network models trained on a relatively small dataset provide the best predictive power, outperforming the commonly employed molecular docking and MM-PBSA scores. Thanks to its relatively low computational complexity and the increasing GPU power, this approach can be used as an advanced virtual screening filter for compound prioritization. [2]

Using these methods, we have successfully performed virtual screening and design of potential dual-target PI3Kα and tankyrase inhibitors and identified a number of promising scaffolds.

References
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