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CANCERAG: STRUCTURE-AWARE MACHINE LEARNING PIPELINE FOR IDENTIFYING BIASED AGONISTS FOR G-PROTEIN COUPLED RECEPTORS

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Background: biased agonism in GPCRs enables selective G protein versus β-arrestin pathway activation, offering therapeutic advantages. GPER modulates oncogenic MAPK and PI3K/Akt signaling in cancer[1]. However, predicting signaling bias remains challenging.
Methods: we developed a structure-aware machine learning pipeline integrating chemical and receptor features to predict GPCR bias. Biased agonists from BiasDB[2] across 61 GPCRs were supplemented with unbiased ligands from ChEMBL and BindingDB. After Lipinski filtering and PAINS removal, RDKit extracted 200+ molecular descriptors including TPSA, logP, and ECFP4. Automated docking with GPCRdb[3] structures and AlphaFold2 models generated interaction metrics. K-Means, DBSCAN, Random Forest, and Gradient Boosting with SMOTE balancing and Boruta feature selection were implemented. SHAP[4] analysis quantified feature contributions.
Results: anticipated >80% cross-validation accuracy with balanced performance. SHAP[4] reveals scaffold and interaction motifs associated with pathway selectivity. Validation on GPER ligands demonstrates predictive capability. The pipeline accepts receptor-ligand pairs and outputs predicted bias with feature attribution, enabling batch screening.
Conclusion: this structure-aware approach integrates ligand chemistry, receptor structure, and explainable AI[4] to advance GPCR bias prediction, accelerating rational drug discovery.