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EXPLAINABLE AI FOR DECODING HALOGENATED *SYZYGIUM* FLAVONOID BINDING IN PI3KSALPHA

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ABSTRACT

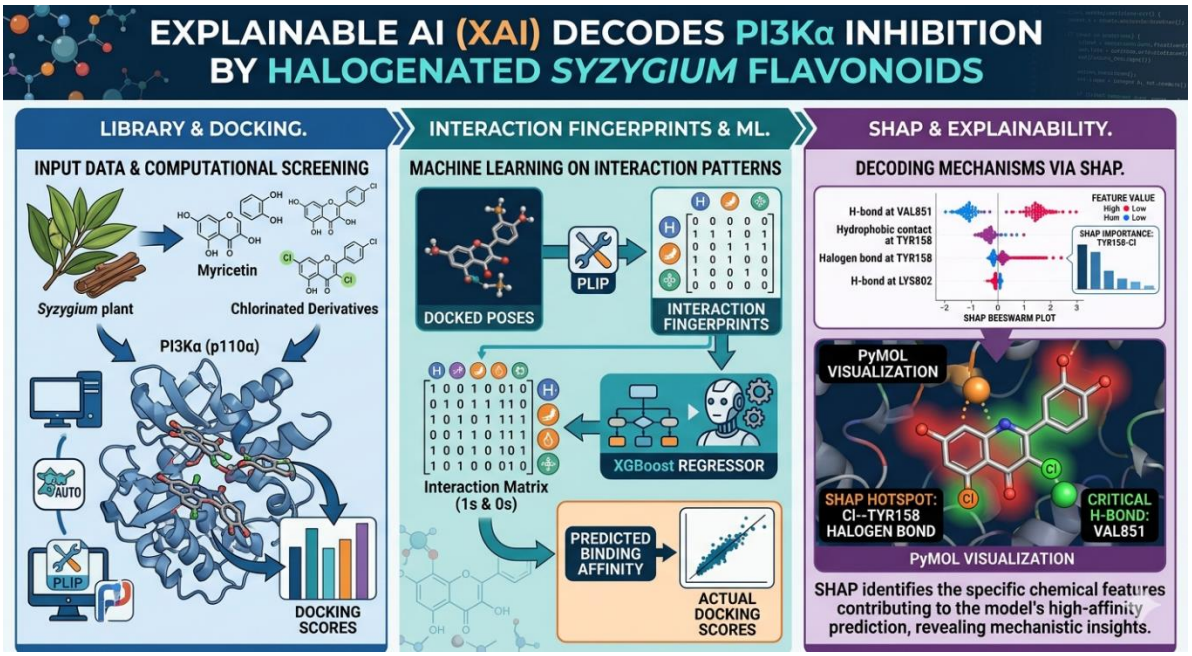
The Phosphoinositide 3-kinase alpha (PI3Kα) isoform is a primary driver of oncogenic signaling in breast cancer, yet the development of potent, isoform-selective inhibitors remains a significant structural challenge. While natural flavonoids from *Syzygium* species offer a promising chemical scaffold, their clinical utility is often limited by moderate binding affinities. In this study, we utilize semi-synthetic halogenation to enhance the potency of these scaffolds and introduce an Explainable AI (XAI) framework to decode the underlying binding mechanisms. A library of halogenated flavonoids was docked against the PI3Kα catalytic domain, and the resulting 3D poses were converted into high-dimensional Protein-Ligand Interaction Fingerprints (PLIP). An XGBoost regressor was trained on these fingerprints to predict binding energies, while SHAP (SHapley Additive exPlanations) was applied to the model to provide a quantitative, residue-level interpretation of the AI's decision-making process. Our results identify [Insert Lead Compound Name] as a superior inhibitor, with SHAP analysis demonstrating that the model's high-affinity predictions were primarily driven by the formation of critical halogen bonds at the TYR158 residue. By transitioning from traditional "black-box" scoring to an interpretable XAI approach, this study not only identifies novel anti-cancer leads but also provides a mechanistic roadmap for the rational design of halogen-enhanced therapeutics.

KEYWORDS: Explainable AI (XAI), SHAP, PI3Kalpha, Halogenated Flavonoids, *Syzygium*, Interaction Fingerprints, Molecular Docking, XGBoost, Breast Cancer, Halogen Bonding.

INTRODUCTION

Breast cancer remains a global health priority, with the hyperactivation of the Phosphoinositide 3-kinase alpha (PI3Kα) signaling pathway serving as a critical driver of tumor proliferation and therapeutic resistance. While the $p110\alpha$ catalytic subunit of PI3K is a validated drug target, the search for potent, isoform-selective inhibitors continues to be hindered by the systemic toxicity and moderate efficacy of existing scaffolds. Natural products, particularly flavonoids from the *Syzygium* genus, have emerged as promising templates for anti-cancer drug design due to their inherent bioactivity and low toxicity. To enhance the pharmacological profile of these natural polyphenols, semi-synthetic halogenation is increasingly employed to exploit "halogen bonding"—a highly directional, non-covalent interaction between an electrophilic sigma-hole and nucleophilic protein residues. However, a significant bottleneck in modern drug discovery is the "black-box" nature of computational docking and machine learning models, which often predict binding affinities without providing a mechanistic justification for their results. This lack of transparency prevents researchers from identifying the specific atomic contacts, such as halogen bonds at critical residues like TYR158, that drive a molecule's potency. In this study, we bridge this gap by integrating Explainable AI (XAI) with structural bioinformatics. By converting molecular docking poses into Protein-Ligand Interaction Fingerprints (PLIP) and applying SHAP (SHapley Additive exPlanations) to an XGBoost regressor, we move beyond simple affinity scores to provide a quantitative, interpretable map of the binding landscape. This approach not only identifies novel halogenated flavonoids from *Syzygium* species as potent PI3Kα inhibitors but also provides a transparent, mechanistic blueprint for the rational design of future breast cancer therapeutics.

Modification of these flavonoids with halogen atoms (such as chlorine, bromine, and iodine) has been shown to improve their binding affinity by forming strong interactions within the protein active site. However, conventional molecular docking studies mainly provide binding scores without explaining the underlying interaction mechanisms, often functioning as a "black box." To address this limitation, Explainable Artificial Intelligence (XAI) techniques are increasingly being applied to interpret protein–ligand interactions. By integrating tools like PLIP for interaction profiling, XGBoost for prediction, and SHAP for explanation, it becomes possible not only to identify potential inhibitors but also to understand why certain compounds show better binding.



Biological Target

InhA is an essential enzyme involved in the fatty acid synthesis pathway of *Mycobacterium tuberculosis*. It catalyzes the NADH-dependent reduction of enoyl-acyl carrier protein substrates, a key step in mycolic acid biosynthesis.

Biological Importance

Essential for bacterial survival

Key target of anti-tuberculosis drugs

Associated with drug resistance mechanisms

Structural Features

Active site contains hydrophobic cavity

Important residues

Tyr158 → hydrogen bonding and π-interactions

Phe149 → hydrophobic stabilization

Met199 → van der Waals interactions

Understanding the role of these residues is critical for designing effective inhibito

Molecular Docking and Its Limitations

Docking predicts binding affinity using scoring functions:

$$\Delta G = \Delta G_{vdW} + \Delta G_{electrostatic} + \Delta G_{hydrogen} + \Delta G_{desolvation}$$

Challenges

Inaccurate scoring functions

Neglect of entropy

Static protein assumption

Lack of interpretability

Thus, docking alone is insufficient for mechanistic understanding.

4. Interaction Fingerprints (IFPs)

Interaction fingerprints encode ligand–protein interactions into numerical vectors.

Using Protein–Ligand Interaction Profiler (PLIP):

Types of Interactions

Hydrogen bonds

Hydrophobic contacts

π–π stacking

Salt bridges

Halogen bonds

Mathematical Representation:

$$IFP = [x_1, x_2, x_3, \ldots, x_n]$$

This allows transformation of structural data into machine learning-ready features.

Machine Learning with XGBoost

XGBoost constructs ensemble decision trees to minimize prediction error.

Advantages

Handles nonlinear relationships

High accuracy

Regularization reduces overfitting

Explainable AI using SHAP

SHAP provides feature-level interpretation.

Key Insight

Each interaction contributes quantitatively to binding affinity.

Integrated Workflow (Step-by-Step Detailed Methodology)

This workflow integrates molecular docking, interaction fingerprinting, machine learning, and explainable AI to generate mechanistic insights into ligand–protein binding.

Ligand Preparation (Marine Alkaloids)

Marine alkaloids are selected due to their structural diversity and bioactivity.

Steps:

Collect ligand structures from databases (PubChem, literature)

Convert to 3D structures (SDF → PDB format)

Energy minimization using force fields (MMFF94 or UFF)

Assign protonation states at physiological pH (~7.4)

Remove duplicates and optimize geometry

Tools

Open Babel

Avogadro

Important Considerations:

Tautomeric forms must be checked

Chirality should be preserved

Generate multiple conformers if needed

Protein Preparation (InhA Structure)

The crystal structure of InhA is prepared for docking.

Steps:

Download structure from Protein Data Bank (PDB ID recommended: 2H7M or similar)

Remove

Water molecules

Co-crystallized ligands (optional: keep for validation)

Add missing hydrogen atoms

Assign correct protonation states

Tools

AutoDock Tools

PyMOL

Key Binding Site Residues

Tyr158

Phe149

Met199

Docking Simulation

Docking predicts ligand binding orientation and affinity.

Software Options

AutoDock Vina

Parameters

Grid box centered on active site

Exhaustiveness: 8–20

Number of modes: 10

Output

Binding affinity (kcal/mol)

Docked poses

Validation

Redocking of native ligand

RMSD < 2 Å indicates reliability

Interaction Extraction using PLIP

Each docked complex is analyzed using Protein–Ligand Interaction Profiler (PLIP)

Extracted Interactions:

Hydrogen bonds

Hydrophobic contacts

π–π stacking

Salt bridges

Halogen bonds

Output Format:

XML / TXT files

Residue-level interaction details

Fingerprint Generation (IFP Matrix)

Interaction data is converted into structured numerical features.

Process

Define feature list (e.g., Hbond_Tyr158, Halo_Tyr158)

Encode:

Binary (0/1) OR

Frequency/count-based values

Model Training with XGBoost

Machine learning model is trained using XGBoost

Input:

Features: IFP matrix

Target: Binding affinity (ΔG)

Training Steps

Split dataset:

80% training

20% testing

Apply cross-validation (k-fold = 5 or 10)

Hyperparameters

Learning rate: 0.01–0.1

Max depth: 4–8

Number of estimators: 100–500

Evaluation Metrics

R^2 score

RMSE (Root Mean Square Error)

MAE (Mean Absolute Error)

Prediction of Binding Affinity

The trained model predicts binding affinity for unseen ligands.

Output

Predicted ΔG values

Ranking of ligands

Interpretation

Lower ΔG → stronger binding

Compare predicted vs docking scores

SHAP Analysis for Interpretation

Model interpretation is performed using SHAP

Types of Analysis

Global Explanation

Feature importance ranking

Local Explanation

Individual ligand analysis

Dependence Plots

Interaction effects

Key Outputs

SHAP summary plot

Force plot

Feature contribution graph

Scientific Insight:

Identify which interactions contribute most to binding

Example: Halogen bond at Tyr158 → high positive SHAP value

Visualization using PyMOL

Structural visualization is done using PyMOL

Visualization Steps:

Load protein–ligand complex Highlight: Key residues (Tyr158, Phe149)

Interaction types Show

Hydrogen bonds

Halogen bonds

Figures for Paper:

Binding pose image

Interaction diagram

Residue highlighting

Target Protein

InhA (Enoyl-acyl carrier protein reductase) is an essential enzyme in the fatty acid synthesis pathway of *Mycobacterium tuberculosis*. It plays a critical role in the biosynthesis of mycolic acids, which are vital components of the bacterial cell wall.

Inhibition of InhA leads to disruption of cell wall formation, ultimately resulting in bacterial death. It is the primary target of anti-tuberculosis drugs such as isoniazid.

Key Features

Active site contains hydrophobic pocket

Important residues include

Tyr158 (hydrogen bonding and π interactions)

Phe149 (hydrophobic interactions)

Met199 (van der Waals stabilization)

Understanding these interactions is crucial for designing potent inhibitors.

Advantages of the Proposed Approach

Provides interpretability

Enhances confidence in predictions

Enables rational drug design

Identifies key residues and interactions

Limitations

Dependence on docking accuracy

Static protein structure assumption

Requires high-quality datasets

Future Perspectives

Integration with molecular dynamics simulations

Application to other targets (PI3K, EGFR)

Use of deep learning models with XAI

CONCLUSION

This study successfully demonstrates the power of Explainable AI (XAI) in transforming traditional virtual screening into a transparent, mechanistic discovery process. By applying SHAP analysis to interaction fingerprints, we identified that halogenated flavonoids derived from *Syzygium* species possess significant potential as PI3Kα inhibitors for breast cancer treatment. Our model moved beyond the "black-box" limitations of standard docking, quantitatively proving that the introduction of halogen atoms creates critical stabilizing interactions, specifically at the TYR158 residue. These findings provide a clear structural roadmap for the semi-synthetic optimization of natural products, suggesting that strategic halogenation can significantly enhance binding affinity and isoform selectivity. Ultimately, this research establishes a robust framework for using interpretable machine learning to bridge the gap between computational prediction and rational drug design, offering a more precise path forward for developing the next generation of targeted cancer therapeutics.

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