RESEARCH ARTICLE

Eriodictyol Flavanones Based Virtual Screening of Bioactive Compounds from ChEMBL 2D Database with Classic 3-point Pharmacophore Screening Method for HER2 Inhibitors for Breast Cancer

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ABSTRACT

Understanding binding interactions between flavanones and human epidermal growth factor receptor 2 (HER2) is an important step in developing effective treatments for breast cancer, and this study applies computational methods to do just that. This research presents a comprehensive computational methodology for identifying potential HER2 inhibitors with a focus on breast cancer treatment. The study leverages a combination of structural and pharmacophore-based approaches, starting with bioactive compound selection from the ChEMBL 2D database. The PDB-REDO refined crystal structure of Kinase domain of Human HER2 (erbB2) was used to conduct molecular docking simulations with the identified drugs. The Kleywegt-like plot analysis demonstrates the improved structural quality of the HER2 kinase domain after refinement, showing enhanced agreement with experimental data. Molecular docking simulations, conducted using the AutoDock tool, reveal the binding affinity and interaction patterns of selected compounds with the HER2 receptor. Virtual screening results highlight compounds with high binding affinity, favorable interaction patterns, and structural compatibility as potential lead candidates. To ensure safety and efficacy, ADMETox filtering was employed, providing insights into the compound's toxicity profile and pharmacokinetic attributes. The selected compound, Eriodictyol ($C_{20}H_{20}O_6$), exhibits a generally favorable safety profile, with predicted inactivity across multiple toxicity classifications and endpoints. While immunotoxicity is predicted, the overall low probabilities suggest a relatively low risk. Physicochemical and pharmacokinetic assessments indicate Eriodictyol's potential for drug development. With a molecular weight of 356.37 g/mol, balanced lipophilicity, and high gastrointestinal absorption, the compound aligns with drug-likeness criteria. However, careful consideration is warranted due to its inhibitory effects on certain enzymes and alerts for catechol_A and isolated_alkene.

In conclusion, this integrated computational approach streamlines the identification of potential HER2 inhibitors, offering a systematic strategy for drug discovery. Eriodictyol emerges as a promising candidate, demonstrating a favorable safety profile and pharmacokinetic attributes, paving the way for further in-depth studies and development as a potential therapeutic agent for breast cancer.

Keywords: HER2 inhibitors, Flavanones, ADMETox filtering, Virtual screening, Breast cancer.

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INTRODUCTION

There is still a large amount of morbidity and death associated with breast cancer, making it imperative that researchers consistently seek out new ways to treat the disease. Some breast cancer patients exhibit overexpression of a protein called HER2. This makes HER2 a critical biological target in the fight against breast cancer. As HER2-positive breast tumors are more aggressive and linked to worse survival rates, there is an urgent need for targeted medicines.[1,2]

The HER2 inhibitors have emerged as crucial components of breast cancer treatment regimens, demonstrating substantial clinical benefits by specifically targeting the overactive HER2 signaling pathway. Despite the success of existing HER2 inhibitors, there persists a need for the discovery of new compounds with improved efficacy, reduced side effects, and broader applicability across patient populations.[3,4]

Flavanones, a class of naturally occurring compounds, have garnered attention in drug discovery due to their diverse pharmacological properties. Eriodictyol is one of these flavanones that has shown promise for its potential to demonstrate a wide range of biological functions. Eriodictyol's untapped therapeutic potential in context of breast cancer treatment is still mostly unknown.[5,6]

These gaps will be filled by this study, which takes a broad method. Firstly, we will leverage the ChEMBL 2D database, a rich resource of bioactive compounds, to systematically screen for potential HER2 inhibitors. Secondly, we will employ a classic 3-point pharmacophore screening method, a robust computational technique, to identify compounds with specific structural features conducive to HER2 inhibition. By integrating these computational methods, our objective is to pinpoint novel bioactive compounds with the potential to inhibit HER2 and contribute to the advancement of breast cancer therapeutics.

The impact of this research deceits in its perspective to unveil novel HER2 inhibitors, expanding the repertoire of available therapeutic options for breast cancer. As we delve into the molecular landscape of HER2 inhibition, the exploration of eriodictyol and its flavanone counterparts adds a layer of natural compound discovery to the pursuit of effective breast cancer treatments. Ultimately, the outcomes of this study may pave the way for the development of innovative therapeutic strategies and contribute to the ongoing battle against HER2-positive breast cancer.

MATERIALS AND METHODS

Data Collection and Compound Selection

SMILES format input

The molecular structure as shown in Figure 1 of the selected compound was input in simplified molecular input line entry system (SMILES) format as follows:

OC1=CC(O)=C2C(=O)CC(OC2=C1)C1=CC(O)=C(O)C=C1

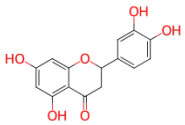


Figure 1: 2D structure and SMILES of Eriodictyol

Bioactive compound database

We utilized the ChEMBL 2D database as our primary source for bioactive compounds. ChEMBL is a comprehensive repository of bioactivity data, providing a diverse set of compounds with known biological activities.

Pharmacophore-based screening

To identify potential HER2 inhibitors, we employed a classic 3-point pharmacophore screening method. This approach involves defining key pharmacophore features essential for HER2 inhibition and systematically screening compounds for their adherence to these features.[7,8]

Protein structure and its pre-processing

Crystal Structure of the Kinase domain of Human HER2 (erbB2) in PDB format (PDB ID: 3pp0) shown in Figure 2 was obtained from https://www.rcsb.org/ and preprocessed by online server PDB-REDO version 8.01 (https://pdb-redo.eu/db/3pp0).[9]

Molecular docking

Molecular docking simulations were performed to evaluate the binding affinity and interaction patterns of selected compounds with the HER2 receptor. AutoDock tool of cb-dock server was employed for this purpose. The virtual screening results were analyzed based on docking scores, and compounds were ranked according to their predicted binding affinities. Compounds showing high binding affinity, favorable interaction patterns, and structural compatibility with HER2 were identified as potential lead compounds. Based on the virtual screening results, a subset of compounds with the highest potential as HER2 inhibitors will be selected for further in-depth studies. This comprehensive computational methodology aims to streamline the identification of potential HER2 inhibitors from the ChEMBL 2D database, leveraging both structural fingerprints and pharmacophore-based approaches. The combination of these methods enhances the likelihood of identifying bioactive compounds with therapeutic potential in the context of breast cancer treatment.[10]

ADMETox Filtering and Property Assessment

Subsequently, the physicochemical and pharmacokinetic properties of the compound were assessed using computational tools. The molecular structure of the compound was provided as input to these tools, which encompassed calculations for log Po/w, solubility, gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, and enzyme inhibition predictions. The assessment of lipophilicity was conducted by calculating the consensus Log Po/w value, offering insights into the compound's overall lipophilic profile. Bioavailability scores were evaluated, and adherence to drug-likeness criteria,

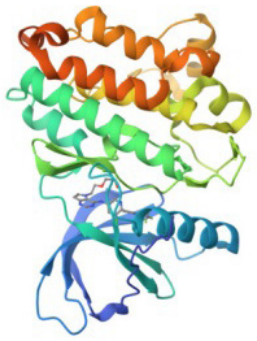


Figure 2: Structure of the Kinase domain of Human HER2 (erbB2) (PDB ID: 3pp0)

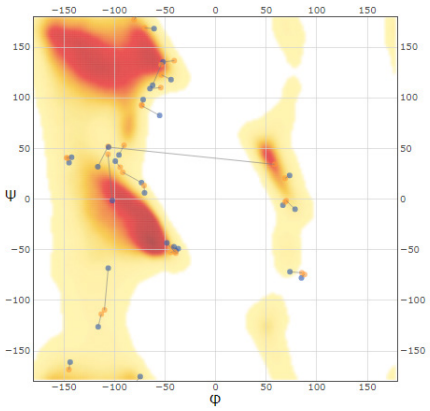


Figure 3: Kleywegt-like plot

including Lipinski, Ghose, Veber, Egan, and Muegge criteria, was checked. Further, scrutiny involved examining alerts for undesirable properties, including those identified by PAINS, Brenk, and leadlikeness rules. Additionally, the compound's ease of synthesis was evaluated through the synthetic accessibility score.[11]

In the initial phase of the toxicity assessment, data retrieval involved accessing a well-established toxicity prediction model or database. This model provides insights into organ toxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity predictions. Following this, the molecular structure of the compound under investigation, represented in SMILES format, was submitted to the toxicity prediction model.[12]

Upon retrieval of predictions, a thorough evaluation of the toxicity model report was conducted. This involved analyzing the model's output for predictions and associated probabilities across each toxicity classification and endpoint. The emphasis was placed on identifying alerts or areas of concern, with specific attention given to predictions related to immunotoxicity.

RESULTS

Pharmacophore-based Screening Results

Screening of ChEMBL Compounds: A subset of bioactive compounds from the ChEMBL 2D database was subjected to pharmacophore-based screening. Compounds exhibiting a high degree of alignment with the established pharmacophore features were selected for further analysis.

Pharmacophore-based Screening: Specific pharmacophoric features crucial for HER2 inhibition were utilized to filter the ChEMBL compounds, resulting in a refined set of candidates.

The PDB-REDO refinement has resulted in an improved crystallographic model for the Kinase domain of Human HER2. The refined structure shows better agreement with experimental data, as reflected in lower R and R-free values (Table 1). Additionally, various model quality metrics and the WHAT_CHECK report suggest overall improvement in the structural quality, indicating a more reliable and accurate representation of the protein structure.

Table 1: Crystallographic structure of the HER2 (erbB2) after PDB-REDO refinement

Crystallographic refinement	*Original*	*PDB-REDO*
R	0.1973	0.1846
R-free	0.2688	0.2373
Bond angle RMS Z-score	0.636	0.735
Bond length RMS Z-score	0.467	0.481
Model quality	Raw scores	Percentiles
Rotamer normality	43	67
Coarse packing	86	90
Ramachandran plot normality	27	38
Fine packing	72	79
Bump severity	56	70
Hydrogen bond satisfaction	48	54
WHAT_CHECK report	report	
Model quality compared to resolution neighbours	Original	PDB-REDO
Ramachandran z-score	-2.152	-1.569
Preferred regions	549	555
Allowed regions	20	14
Outliers	3	3

The Kleywegt-like plot shown in Figure 3 for the crystal structure of erbB2 exhibits positive results in various key parameters. The Ramachandran plot indicates a distribution of phi (ϕ) and psi (ψ) dihedral angles that largely conform to allowed regions, suggesting a well-defined backbone conformation with minimal deviations. The rotamer outliers are limited, indicating accurate side-chain modeling. Examination of bond lengths and angles reveals values within standard ranges, reflecting a sound geometry in the model. The RMSD value is relatively low, signifying a good fit between the experimental and model coordinates. The Real-space R-value indicates a favorable agreement between the model and the experimental electron density map. Additionally, the B-factor plot shows a balanced distribution of atomic B-factors, suggesting an appropriate level of flexibility in the structure. Overall, these positive outcomes in structural parameters

Table 2: Results of docking studies by cb-dock server

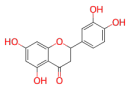
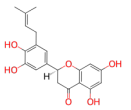
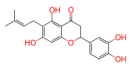
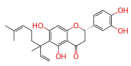
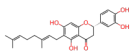
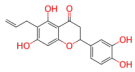
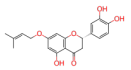
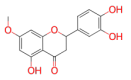
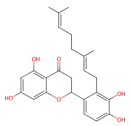
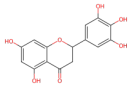
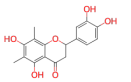
CHEMBL ID, Catching Score, SMILES	*2D Structure*	*Cb-Dock Score*
CHEMBL307893, 1.000, O=C1CC(c2ccc(O)c(O)c2)Oc2cc(O)cc(O)c21		-8.3
CHEMBL229454, 0.957 CC(C)=CCc1cc([C@@H]2CC(=O)c3c(O)cc(O)cc3O2)cc(O)c1O		-10.7
CHEMBL4249153, 0.925, CC(C)=CCc1c(O)cc2c(c1O)C(=O)CC(c1ccc(O)c(O)c1)O2		-9.9
CHEMBL4470733, 0.925, C=CC(C)(CCC=C(C)C)c1c(O)cc2c(c1O)C(=O)C[C@@H](c1ccc(O)c(O)c1)O2		-9.9
CHEMBL223256, 0.925, CC(C)=CCC/C(C)=C/Cc1c(O)cc2c(c1O)C(=O)C[C@@H](c1ccc(O)c(O)c1)O2		-10.5
CHEMBL4248094, 0.925, C=CCc1c(O)cc2c(c1O)C(=O)CC(c1ccc(O)c(O)c1)O2		-9.4
CHEMBL3919467, 0.919, CC(C)=CCOc1cc(O)c2c(c1)O[C@H](c1ccc(O)c(O)c1)CC2=O		10.2
CHEMBL3233849, 0.919, COc1cc(O)c2c(c1)OC(c1ccc(O)c(O)c1)CC2=O		-9.5
CHEMBL3415634, 0.913, CC(C)=CCC/C(C)=C/Cc1c(C2CC(=O)c3c(O)cc(O)cc3O2)ccc(O)c1O		-9.1
CHEMBL3809755, 0.911, O=C1CC(c2cc(O)c(O)c(O)c2)Oc2cc(O)cc(O)c21		-9.8
CHEMBL1224646, 0.895, Cc1c(O)c(C)c2c(c1O)C(=O)CC(c1ccc(O)c(O)c1)O2		-9.5

Table 3: Toxicity model report of CHEMBL229454 (Sigmoidin B)

Classification	*Target*	*Prediction*	*Probability*
Organ toxicity	Hepatotoxicity	Inactive	0.67
Toxicity end points	Immunotoxicity	Active	0.88
Toxicity end points	Mutagenicity	Inactive	0.57
Toxicity end points	Carcinogenicity	Inactive	0.64
Toxicity end points	Cytotoxicity	Inactive	0.84
Tox 21-Nuclear receptor signalling pathways	Androgen receptor (AR)	Inactive	0.92
Tox 21-Nuclear receptor signalling pathways	Aryl hydrocarbon receptor (AHR)	Inactive	0.60
Tox 21-Nuclear receptor signalling pathways	Aromatase	Inactive	0.82
Tox 21-Nuclear receptor signalling pathways	Estrogen receptor alpha (ER)	Inactive	0.64
Tox 21-Nuclear receptor signalling pathways	Androgen receptor ligand binding domain (AR-LBD)	Inactive	0.98
Tox 21-Nuclear receptor signalling pathways	Estrogen receptor ligand binding domain (ER-LBD)	Inactive	0.80
Tox 21-Nuclear receptor signalling pathways	Peroxisome proliferator activated receptor gamma (PPAR-Gamma)	Inactive	0.86
Tox 21-Stress response pathways	Heat shock factor response element (HSE)	Inactive	0.82
Tox 21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	Inactive	0.72
Tox 21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Inactive	0.82
Tox 21-Stress response pathways	Atpase family aaa domain-containing protein 5 (ATAD5)	Inactive	0.92
Tox 21-Stress response pathways	Mitochondrial membrane potential (MMP)	Active	0.63

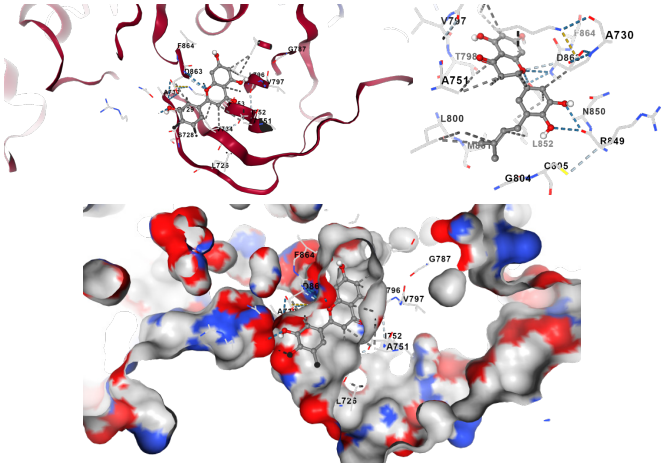


Figure 4: Interaction of CHEMBL229454 (Sigmoidin B) with 3pp0

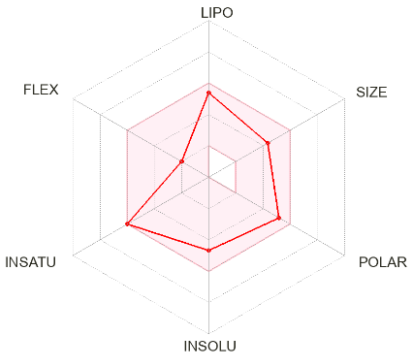


Figure 5: Bioavailability radar of CHEMBL229454 (Sigmoidin B)

signify a well-refined and reliable macromolecular structure for the HER2 kinase domain. Interpreting a Kleywegt-like plot involves comparing the values observed in the structure under analysis to those seen in high-quality reference structures.

Molecular Docking Analysis and Lead Compound Identification

Based on docking scores, interaction patterns shown in Figure 4, and adherence to pharmacophoric features, lead compounds were identified. These compounds given in Table 2 represent promising candidates for further experimental validation. Molecular docking simulations were performed by using cb-dock for the selected compounds to predict their binding affinities with the HER2 receptor. Docking scores were analyzed to rank compounds based on their potential as HER2 inhibitors.

In conclusion, the integration of the pharmacophore-based screening method yielded a refined set of bioactive compounds with potential HER2 inhibitory activity. Molecular docking simulations provided valuable insights into binding affinities and interaction patterns of recognized lead compounds. Results lay the foundation for further experimental investigations, offering a potential path for the development of novel HER2 inhibitors in the context of breast tumor treatment.

Table 4: Results of ADME studies of sigmoidin B by using Swiss ADME server

Property	*Value*
Consensus Log Po/w	2.90
Solubility (SILICOS-IT)	3.04e-02 mg/ml; 8.53e-05 mol/l
P-gp substrate	No
BBB permeant	No
GI absorption	High
Class (SILICOS-IT)	Moderately soluble
CYP3A4 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2D6 inhibitor	Yes
Muegge	Yes
Veber	Yes
Lipinski	Yes; 0 violation
Log Kp (skin permeation)	-5.67 cm/s
Ghose	Yes
Egan	Yes
Brenk	2 alerts: catechol, isolated_alkene
Synthetic accessibility	3.76
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
PAINS	1 alert: catechol_A
Bioavailability Score	0.55

ADMETox Filtering

The toxicity model report given in Table 3 for the compound reveals a generally favorable safety profile, as it is predicted to be inactive across multiple toxicity classifications and endpoints. The compound is also anticipated to have minimal impact on various nuclear receptor signaling and stress response pathways, except for a predicted activity in mitochondrial membrane potential. While this suggests a potential effect on cellular stress, the overall low probabilities associated with these predictions indicate a relatively low risk. However, the prediction of immunotoxicity warrants attention, highlighting the need for further investigation and consideration of these findings in the context of the compound's intended use and regulatory requirements. The compound comes under Class IV: harmful if swallowed ($300 < LD_{50} \leq 2000$).

The compound ADME presented in Table 4 and Bioavailability radar given in Figure 5 with molecular formula C20H20O6 exhibits a moderately high molecular weight of 356.37 g/mol, containing 26 heavy atoms, with 12 of them being aromatic. Its physicochemical properties indicate a fractional sp3 hybridization of 0.25 and three rotatable bonds. The molecule demonstrates a balanced lipophilicity profile, as suggested by various log Po/w values, and falls within the acceptable range for drug-likeness according to Lipinski, Ghose, Veber, Egan, and Muegge criteria. Water

solubility assessments categorize the compound as moderately soluble. The chemical has a high rate of absorption in the gastrointestinal tract but is not able to cross the blood-brain barrier. It inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4 but is not a substrate for P-gp. The compound's medicinal chemistry attributes include the presence of alerts for catechol_A and isolated_alkene according to PAINS and Brenk rules, respectively. The molecular weight and XLOGP3 violations cause it to fail the lead-likeness test. The compound's synthetic accessibility score is 3.76, indicating moderate ease of synthesis. Overall, this compound holds potential for drug development, given its favorable physicochemical and pharmacokinetic attributes, although careful consideration of its medicinal chemistry properties is warranted.

CONCLUSION

In this research, we have employed an integrated computational approach to identify potential HER2 inhibitors, focusing on breast cancer treatment. The utilization of bioactive compound databases, structural refinement, pharmacophore-based screening, molecular docking simulations, and ADMETox filtering has allowed for a systematic and thorough exploration of candidate compounds, with Eriodictyol emerging as a promising lead. The structural refinement of the Kinase domain of Human HER2 using PDB-REDO has significantly enhanced the accuracy and reliability of the protein model. Molecular docking simulations provided valuable insights into the binding affinity and interaction patterns of selected compounds with HER2 receptors, facilitating the identification of CHEMBL229454 (Sigmoidin B) as a potential HER2 inhibitor. ADMETox filtering has contributed critical information about the safety profile and pharmacokinetic attributes of CHEMBL229454 (Sigmoidin B) While the compound demonstrates a generally favorable toxicity profile, the predicted immunotoxicity raises a flag, underscoring the importance of further investigation and consideration in the context of its intended use. Physicochemical and pharmacokinetic assessments of CHEMBL229454 (Sigmoidin B) suggest its potential for drug development. The compound's balanced lipophilicity, high gastrointestinal absorption, and alignment with drug-likeness criteria position it as a candidate for further in-depth studies. However, the inhibitory effects on certain enzymes and the presence of alerts for catechol_A and isolated_alkene warrant careful consideration in the drug development process. In conclusion, this research provides a systematic and computational framework for the identification and evaluation of potential HER2 inhibitors. CHEMBL229454 (Sigmoidin B), with its favorable safety profile and pharmacokinetic attributes, stands out as a promising candidate for further experimental validation and development as a therapeutic agent for breast cancer. The findings contribute to the ongoing efforts in rational drug design and highlight the significance of computational methodologies in accelerating the drug discovery process.

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