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QSAR Classification and Molecular Docking for Identifying BCL-2 Inhibitor Candidates

Nur Laily Harfita*[1], Harizahayu Harizahayu[2]

[1]Nutrition Study Program, Faculty of Health, Universitas Deztron Indonesia, Medan

[2]Informatics Management Study Program, Politeknik Negeri Medan

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*Corresponding Author:
Nur Laily Harfita
Email: nurlailyharfita@udi.ac.id

ABSTRACT

B-cell lymphoma 2 (BCL-2) is an anti-apoptotic protein implicated in the progression and chemoresistance of multiple cancers. This study integrates QSAR-based machine learning (ML) classification and molecular docking to identify potential BCL-2 inhibitors. The Gradient Boosting classifier trained on PubChem fingerprints (881 bits) achieved the best predictive performance (accuracy: 83.52%, ROC-AUC: 0.8829). External virtual screening further identified high-probability active compounds, including Beclomethasone Dipropionate (0.9880) and Ulipristal Acetate (0.9866), highlighting their potential for drug repurposing. Docking analysis showed that Ulipristal Acetate exhibited the strongest binding affinity (–8.187 kcal/mol), forming a hydrogen bond with GLY A:145 and engaging key residues within the BH3-binding pocket of BCL-2. These findings demonstrate the effectiveness of QSAR-ML–assisted virtual screening in prioritizing repurposable candidates for BCL-2 inhibition.

Keywords: BCL-2 Inhibitor, Machine Learning, Virtual Screening, Molecular Docking

INTRODUCTION

According to the World Health Organization (WHO), cancer is the second leading cause of death globally, accounting for an estimated 10 million deaths in 2020 (World Health Organization, 2021). A defining hallmark of cancer cells is their ability to evade apoptosis, a form of programmed cell death crucial for normal cellular homeostasis. The dysregulation of this process allows malignant cells to proliferate uncontrollably, and among the pivotal regulators of apoptosis is the B-cell lymphoma 2 (BCL-2) protein family.

Anti-apoptotic BCL-2 proteins, when overexpressed, block apoptosis by inhibiting mitochondrial outer membrane permeabilization (MOMP) and cytochrome c release (Sulkshane & Teni, 2022). This imbalance shifts the apoptotic threshold, promoting tumor cell survival. The frequent overexpression of BCL-2, particularly in hematological malignancies, confirms its oncogenic role and establishes it as a prime therapeutic target (Xu et al., 2021; Moustapha et al., 2024; Alam et al., 2021; D'Aguanno & Del Bufalo, 2020; Zhou et al., 2023). This makes understanding BCL-2's regulatory functions and the development of targeted therapies essential for improving cancer treatment outcomes.

In recent years, computational drug discovery approaches have become increasingly important for identifying novel therapeutic compounds (Lin et al., 2020). Virtual screening involves the use of computational methods to identify potentially bioactive compounds from large databases of small molecules. This approach is gaining widespread use in drug discovery as *in silico* techniques continue to evolve, improve in accuracy, and become more accessible to researchers (Gimeno et al., 2019).

Molecular docking is a widely used structure-based approach for virtual screening, enabling the identification of bioactive compounds from large molecular databases. However, as virtual libraries continue to grow in scale—now reaching tens of millions or even billions of compounds—conventional docking tools often struggle to keep up with the computational demands of such extensive screenings (Yu et al., 2022).

Machine learning (ML) methods have emerged as a significant advancement not only complementing molecular docking but also functioning as an efficient pre-screening filter capable of rapidly narrowing down large chemical libraries prior to computationally intensive docking simulations. These algorithms utilize quantitative

structure-activity relationship (QSAR) models, which correlate molecular descriptors or fingerprints derived from databases like PubChem with biological activity, such as IC_{50} values (Ashraf et al., 2023; T. Yu et al., 2023). ML has become an essential tool in the realm of drug discovery (Niazi & Mariam, 2023). This enables two key predictive functions: (i) classification, which estimates the probability that a compound will exhibit inhibitory activity against a target protein, and (ii) regression, which directly predicts continuous bioactivity metrics such as IC_{50} values. Through these dual predictive capabilities, ML accelerates the identification of promising candidates and reduces experimental and computational costs, thereby streamlining the overall drug discovery workflow.

Molecular docking is subsequently used to predict the binding affinity and interaction profiles of the top-ranked compounds with the BCL-2 protein. Prior studies have shown that natural compounds such as quercetin, pinostrobin, and 8-chrysoeriol exhibit promising binding affinities to BCL-2 or its homologs, supporting their potential as anticancer agents (Afriza et al., 2025; Gunasekaran & Dhakshinamurthy, 2024; Xu et al., 2019). By combining ML-based virtual screening with structure-based docking simulations, this integrative approach aims to enhance the efficiency and accuracy of early drug discovery efforts targeting BCL-2, ultimately contributing to the development of more effective cancer therapeutics.

This study integrates machine learning-based classification with molecular docking to virtually screen natural compounds as potential BCL-2 inhibitors. Its novelty lies in employing ML as an efficient pre-screening filter before docking, improving both the accuracy and computational efficiency of identifying promising BCL-2 inhibitor candidates. By utilizing curated bioactivity data and screening structurally diverse molecules from natural product databases, this project seeks to identify promising small molecules for further investigation. The synergy between predictive modeling and molecular docking is expected to provide a rational and efficient framework for early-stage drug discovery targeting apoptosis-related pathways in cancer.

RESEARCH METHODS

Materials

Bioactivity data for BCL-2 inhibitors were obtained from the ChEMBL database. Molecular fingerprints (PubChem, 881 bits) were calculated using PaDEL-Descriptor. Machine learning models (Logistic Regression, Random Forest, and Gradient Boosting) were built with scikit-learn in Python. External compounds were sourced from the COCONUT database. Protein structure (PDB ID: 6O0K), which contains BCL-2 co-crystallized with its native ligand venetoclax, was prepared using AutoDockTools, and docking simulations were performed with AutoDock Vina. Ligand and interaction visualization used PyMOL and Discovery Studio Visualizer.

Instrumentation

All computational work was performed on a laptop equipped with an AMD Ryzen 5 5600H processor (3.30 GHz), 8 GB RAM, integrated AMD Radeon graphics, and running Windows 11 Home (64-bit, version 23H2).

Data Collection and Preparation

Bioactivity data for the BCL-2 protein target were retrieved from the ChEMBL database using the chembl_webresource_client Python library. The target was identified by searching the keyword "Bcl-2" and selecting the appropriate ChEMBL target ID: CHEMBL4860. Activity data were filtered to include only records with IC_{50} values.

Entries lacking IC_{50} values or canonical SMILES were removed to ensure data quality. The resulting dataset contained unique compounds suitable for further predictive modelling (Bento et al., 2020). Molecular fingerprints were generated using PaDEL-Descriptor via the padelpy Python package (https://github.com/dataprofessor/padel), resulting in 881-bit PubChem fingerprints (Carracedo-Reboredo et al., 2021). These descriptors quantitatively represent structural features of each compound and were used as input features for the machine learning models, enabling effective classification based on molecular structure.

Model Evaluation

Three classification models—Logistic Regression (LR), Random Forest (RF), and Gradient Boosting (GB)—were implemented to classify compounds as active or inactive inhibitors of BCL-2. Model development and evaluation were carried out using the scikit-learn library in Python. To evaluate performance and reduce the risk of overfitting, the dataset was randomly divided into training and testing sets in an 80:20 ratio, ensuring a balanced distribution of Active and Inactive compounds.

Each model was further validated using five-fold cross-validation to ensure robustness and generalizability of the results. A range of performance metrics—accuracy, precision, recall, F1-score, and ROC-AUC—were calculated to capture different aspects of model effectiveness, from overall correctness to sensitivity and balance between false

positives and negatives. ROC curves were also generated and compared across models to provide a visual assessment of each classifier's ability to distinguish between active and inactive compounds (Lee et al., 2021).

Virtual Screening of Small Molecules

A total of 1000 natural compounds from the COCONUT database were processed using RDKit to standardize structures and generate descriptors. Compounds were filtered based on drug-likeness criteria, including molecular weight (250–600 Da) and QED ≥ 0.5, to retain molecules with a reasonable likelihood of oral bioavailability and favorable pharmacokinetic properties (Ritmaleni et al., 2025). Fifteen top candidates were selected for further machine learning evaluation against BCL-2. SMILES structures were saved in CSV format for integration into downstream analysis (Lo et al., 2018).

Molecular Docking

The 3D structure of BCL-2 (PDB ID: 6O0K) was retrieved from the Protein Data Bank and prepared using PyMOL by removing water molecules and co-crystallized ligands. The protein was converted to .pdbqt format using AutoDockTools with the addition of polar hydrogens and Gasteiger charges. Redocking of the native ligand venetoclax using AutoDock Vina yielded a binding affinity of -12 kcal/mol (original -14 kcal/mol) and an RMSD of 1.06 Å, confirming the accuracy of the docking protocol (RMSD ≤ 2.0 Å).

Test compounds selected from ML predictions were converted from .sdf to .pdb using Open Babel, then to .pdbqt using prepare_ligand4.py. Docking was performed with AutoDock Vina, using a grid box centered on the native ligand, which occupies the BH3-binding groove, a hydrophobic cleft of BCL-2. The best binding pose was selected based on the lowest binding affinity (kcal/mol), and ligand–protein interactions were analyzed using Discovery Studio.

RESULTS AND DISCUSSION

Data Collection and Preparation

The data for this study were obtained from the ChEMBL database, focusing on the BCL-2 target protein (CHEMBL4860). Bioactivity data were filtered based on the IC_{50} parameter, representing the inhibitory potency of compounds. From a total of 1,104 retrieved entries, data cleaning was performed by removing entries lacking *standard_value* (IC_{50}) and *canonical SMILES*, resulting in 1,055 valid entries. To obtain a set of unique compounds, duplicate entries representing the same molecule, identified by identical canonical SMILES, were consolidated.

In cases of multiple IC_{50} measurements for the same compound, one representative value was retained (e.g., the most reliable or average value). After this curation, 877 unique compounds were obtained. This process generated numerical representations of each compound in the form of vectors containing 881 binary features, each indicating the presence or absence of specific chemical substructures. The resulting descriptors were subsequently used as input features for machine learning models aimed at identifying potential BCL-2 inhibitors.

Machine Learning Modeling

Three classification models—Logistic Regression (LR), Random Forest Classifier (RFC), and Gradient Boosting Classifier (GBC)—were evaluated to classify BCL-2 inhibitor compounds as active or inactive. Model development was carried out using the *scikit-learn* library in Python, with a random 80:20 split for training and testing sets to ensure balanced class distribution, followed by five-fold cross-validation to enhance model generalizability.

Table 1. Performance of Machine Learning Models for BCL-2 Activity Prediction

No.	Model	Data Accuracy		Accuracy (%)	Precision	Recall	F1 Score	ROC-AUC
		Training (%)	Testing (%)					
1	Logistic Regression	94.86	81.25	81.25	0.8047	0.8125	0.8083	0.8815
2	Gradient Boosting	95.44	83.52	83.52	0.8329	0.8352	0.8340	0.8829
3	Random Forest	98.43	82.95	82.95	0.8302	0.8295	0.8292	0.8968

Based on the results presented in Table 1, the Gradient Boosting Classifier demonstrated the most balanced and optimal performance, achieving an accuracy of 83.52%, an F1-score of 0.8340, and a ROC-AUC of 0.8829. Metrics such as F1-score and ROC-AUC are emphasized over accuracy alone because they account for class imbalance and provide a more comprehensive assessment of the model's ability to correctly classify both active and inactive compounds, whereas accuracy can be misleading when classes are unevenly represented (Gürcan & Soylu, 2024). Its iterative boosting mechanism allows the model to effectively learn from errors and handle complex, non-linear patterns within molecular fingerprints, making it well-suited for virtual screening tasks (Nicholson et al., 2022).

The Random Forest Classifier achieved the highest ROC-AUC (0.8968), indicating excellent discriminative power. However, the notable gap between training accuracy (98.43%) and test accuracy (82.95%) suggests the presence of overfitting, where the model performs very well on known data but less effectively on unseen compounds (Al-Mamun et al., 2025). This highlights the need for careful tuning of hyperparameters when applying ensemble-based models.

Logistic Regression, though simpler and more interpretable, yielded solid performance with 81.25% accuracy and a ROC-AUC of 0.8815. Its strength lies in transparency and reproducibility, which supports decision-making in early drug discovery. As noted by Masseran (2024), Logistic Regression offers interpretable results and remains advantageous over more complex models such as neural networks or support vector machines, especially in scenarios where ease of understanding and application is essential.

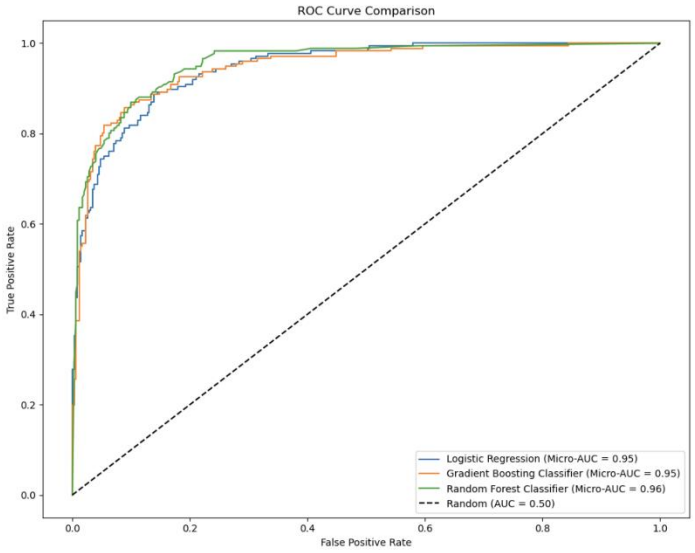

Figure 1. ROC Curve Comparison of ML Models for BCL-2 Prediction

The ROC curves of the three models (Figure 1) provide a visual comparison of their discriminative abilities. All curves are relatively close to the top-left corner, indicating good sensitivity and specificity across the models. Both GBC and RFC demonstrated slightly superior performance; however, GBC exhibited a smaller and more controlled discrepancy between training and testing accuracies, reflecting better stability and generalizability to unseen compounds. This makes GBC a more reliable choice for virtual screening of potential BCL-2 inhibitors.

Gradient Boosting proved to be the most robust and consistent model for this classification task, combining predictive strength with controlled risk of overfitting. Random Forest offered strong performance but requires additional attention to avoid overfitting, while Logistic Regression remains a reliable and interpretable baseline, providing a reference for the minimum performance achievable by a linear model.

Virtual Screening of Small Molecules

From a virtual screening of 1000 compounds from the COCONUT database, 15 top candidates were selected based on drug-likeness (MW 250–600 Da, QED ≥ 0.5, LogP −1–5, H-bond donors ≤5, acceptors ≤10) and Tanimoto similarity (≤0.7) to a reference ligand. A combined score (0.7×QED + 0.3×Tanimoto) was used to rank compounds for further machine learning evaluation as potential BCL-2 inhibitors. Several steroid-based compounds—such as Beclomethasone Dipropionate, Ulipristal Acetate, and Clogestone Acetate—showed strong predictive scores (>0.98) (Table 2), suggesting structural alignment with known BCL-2 inhibitors.

The high performance of the GBC using PubChem fingerprints (881 bits) likely reflects its ability to capture key structural features of the steroid core, enabling recognition of motifs relevant to BCL-2 binding. Other compounds like Methylprednisolone Aceponate and Meproscillarin also exhibited high activity potential, demonstrating the model's ability to recognize relevant molecular features (Patel et al., 2020).

In contrast, compounds such as Tazobactam Sodium and Nalfurafine were predicted inactive (probability < 0.5), reflecting the model's capacity to distinguish active from inactive structures. Their low scores are likely driven by insufficient hydrophobicity and poor structural complementarity to the BH3-binding pocket. The chemical diversity

among the top hits—spanning corticosteroids and hormonal analogues—illustrates the model's robustness in identifying structurally varied candidates. These results offer a prioritized set of compounds for docking studies to further assess their potential as BCL-2 inhibitors.

Table 2. ML-Based Activity Prediction of External Compounds for BCL-2 Target

No.	Name	Prediction	Probability
1	Naxaprostene	Active	0.9257
2	Hydrocortisone Butyrate	Active	0.8513
3	Methylprednisolone Aceponate	Active	0.9862
4	Dimethylaminoethyl Reserpilinate	Active	0.9517
5	Tazobactam Sodium	Inactive	0.0308
6	Ulipristal Acetate	Active	0.9866
7	Oxprenoate	Active	0.8345
8	Nalfurafine	Inactive	0.3691
9	Epicriptine	Active	0.5022
10	Ecalcidene	Active	0.8990
11	Formebolone	Active	0.8191
12	Clogestone Acetate	Active	0.9873
13	Diacetylnalorphine	Active	0.8315
14	Hydrocortisone Aceponate	Active	0.8513
15	Beclomethasone Dipropionate	Active	0.9880

Molecular Docking

Although the machine learning (ML) model used in this study predicts the potential bioactivity of compounds in terms of IC_{50} values, it does not directly account for the binding affinity typically assessed through molecular docking. However, combining both approaches offers complementary perspectives in early-stage drug discovery. While IC_{50}-based ML predictions reflect the likelihood of a compound exhibiting inhibitory activity, molecular docking evaluates the strength and nature of interactions between a ligand and its target binding site. The convergence of both metrics can be interpreted as mutual support for a compound's potential efficacy.

Table 3. Binding Affinity and Interactions of Selected Ligands with BCL-2

No.	Compound	Affinity (kcal/mol)	Hydrogen Bonds	Non-Hydrogen Interactions
1	Beclomethasone Dipropionate	-7.898	GLY A:145	-
2	Clogestone Acetate	-7.732	ARG A:146, ASP A:111	MET A:115
3	Ulipristal Acetate	-8.187	GLY A:145	ALA A: 149, PHE A:104, ARG A:146, TYR A:108

As shown in the Table 3 and Figure 2, Ulipristal Acetate shows the strongest binding affinity (–8.187 kcal/mol) among the three compounds, forming hydrogen bonds with GLY145 and hydrophobic interactions with ALA149, PHE104, ARG146 and TYR108. This supports its high predicted activity (0.987) from the ML model. Ulipristal Acetate (UA) exhibits significant antiproliferative effects, demonstrated by its ability to inhibit endometrial proliferation and reduce Ki-67 expression (Duran et al., 2022). Structurally, UA is a synthetic steroidal Selective Progesterone Receptor Modulator (SPRM) (Szydłowska et al., 2021), and its rigid structure is not a rationally designed BH3 mimetic. BH3 mimetics, such as Venetoclax (ABT-199), are small-molecule antagonists specifically engineered to structurally mimic the BH3 domain and directly bind the anti-apoptotic BCL-2 groove (Saraswathy et al., 2023).

Therefore, UA does not sterically mimic the key residues of the BH3 domain. However, these antiproliferative properties suggest potential anti-cancer activity involving the intrinsic apoptotic pathway, where the ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2/Bcl-xL is a critical regulator (Yan et al., 2022). Importantly, our current study predicts its

inhibitory activity against BCL-2. This functional effect may occur through downstream signaling events initiated by PR modulation or via PR-independent mechanisms (Hwang et al., 2023).

This PR-independent action, potentially involving the inhibition of the STAT3/CCL2 pathway (Hwang etal., 2023), suggests the possibility of non-canonical interactions where UA's steroidal scaffold engages the BCL-2 protein, leading to functional inhibition of the anti-apoptotic machinery.

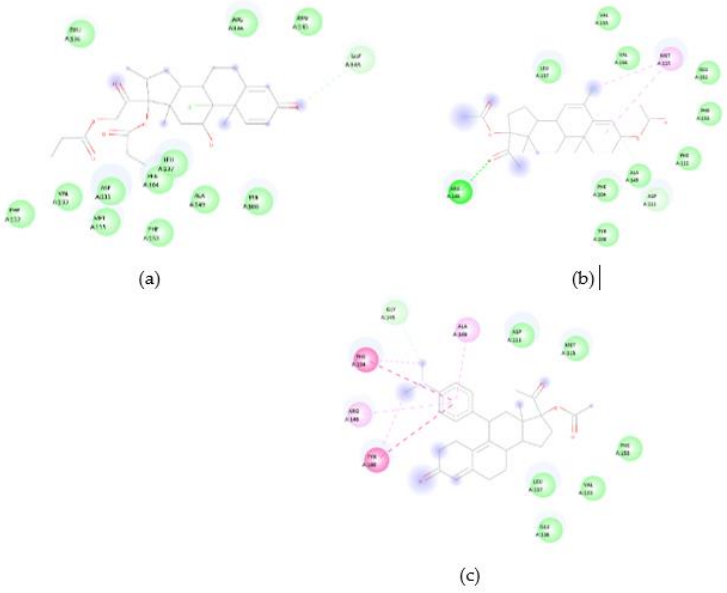

Figure 2. (a) Beclomethasone Dipropionate, (b) Clogestone Acetate, and (c) Ulipristal Acetate

Clogestone Acetate shows a comparable docking score (–7.732 kcal/mol), forming hydrogen bonds with ARG146 and ASP111 and engaging in nonpolar contacts around the active site. Its consistent ML-predicted activity supports its candidacy as a potential BCL-2 inhibitor. In contrast, Beclomethasone Dipropionate, with a docking affinity of –7.898 kcal/mol, forms a single hydrogen bond with GLY145. This observation aligns with previous reports showing that hydrophobic protein pockets—including the BH3-binding groove of BCL-2 and other steroid–protein complexes—are predominantly stabilized by van der Waals and hydrophobic packing interactions rather than hydrogen bonding (Hooks et al., 2024).

Similar findings across kinase and apoptosis-related targets demonstrate that strong binding energies can arise from extensive nonpolar complementarity within hydrophobic cavities (Saeed et al., 2025; Al-Ghamdi et al., 2025). Therefore, the high affinity of Beclomethasone Dipropionate, despite minimal hydrogen bonding, likely reflects the dominant contribution of steric fit and hydrophobic contacts within the BCL-2 pocket. Although the number of interactions is limited, its stable docking profile and established glucocorticoid activity may contribute to biological effects relevant to apoptosis. Glucocorticoids like Beclomethasone are widely used for their anti-inflammatory properties and have been shown to modulate gene expression in cancer-related pathways, including RANKL signaling (Lovšin & Marc, 2021; Manca et al., 2021). Elevated BCL-2 is known to confer resistance to glucocorticoid-induced apoptosis, demonstrating a functional intersection between GR signaling and BCL-2–mediated survival (Bortner et al., 2022).

This mechanistic overlap suggests that glucocorticoid-responsive steroids such as Beclomethasone can effectively engage the BCL-2 regulatory axis. Moreover, its rigid steroid backbone and hydrophobic surface complement the predominantly non-polar BCL-2 binding pocket, providing structural features consistent with a plausible BCL-2 inhibitor.

While ML and docking provide different insights—bioactivity probability versus binding energy—their integration offers a broader validation framework. This synergistic approach enhances confidence in compound prioritization and is increasingly recognized as an efficient strategy for accelerating the identification of promising drug candidates in silico.

CONCLUSION

This study demonstrated that the integration of machine learning and molecular docking is an

effective strategy for virtual screening of BCL-2 inhibitors. The Gradient Boosting model showed strong predictive performance and successfully prioritized compounds with potential activity. Ulipristal Acetate emerged as a promising candidate, showing both high ML-predicted probability and strong binding affinity. Its steroidal scaffold exhibits complementary docking into the BH3 groove, suggesting potential functional inhibition via non-canonical binding or downstream effects.

This supports its repurposing potential for cancer therapy. These results support the use of computational approaches to streamline early drug discovery targeting anti-apoptotic proteins like BCL-2 and highlight the critical need for subsequent experimental validation, including direct biochemical binding assays and cellular apoptosis studies, to precisely delineate the mechanism of BCL-2 inhibition.

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