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Original Research Article

Deep neural networks for predicting the anti-cancer activity of beta-blockers

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Abstract

Drug repurposing has emerged as a powerful strategy to accelerate anticancer drug discovery while reducing costs and development timelines. Beta-adrenergic receptor antagonists (beta-blockers), widely prescribed for cardiovascular diseases, have demonstrated increasing evidence of anticancer properties through modulation of proliferation, angiogenesis, immune response, and metastatic signaling. In this study, we integrate deep learning–based virtual screening with molecular docking to evaluate FDA-approved beta-blockers for potential repositioning against cancer-related protein targets. A deep neural network (DNN) classification model was trained using curated bioactivity datasets to predict anticancer likelihood, followed by docking simulations to validate structural interactions. Among 108 beta-blockers and derivatives screened, the DNN model identified propranolol, carvedilol, indenolol, idropranolol, and a derivative of nifenalol as top anticancer candidates. Docking results further supported these predictions, showing high binding affinities and favorable molecular interaction profiles, particularly with the androgen receptor (PDB ID: 5T8E). Our findings demonstrate the utility of deep learning coupled with molecular docking for effective drug repurposing and highlight promising beta-blocker candidates for future preclinical evaluation.

Keywords:
Drug Repositioning, Deep Learning, Deep Neural Network, Beta-Blockers, Virtual Screening, Molecular Docking.

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1. Introduction

Cancer remains one of the leading causes of global morbidity and mortality, with more than 19 million new cases reported annually and incidence continuing to rise worldwide. Despite significant progress in molecular oncology, the development of new anticancer agents is still characterized by high attrition rates, long development timelines, and substantial financial burdens that frequently exceed USD 2 billion for a single approved drug [1, 2]. These challenges have intensified interest in drug repurposing, which aims to identify new clinical applications for approved drugs that already possess well-characterized safety profiles, pharmacokinetics, and manufacturing pipelines [3, 4]. This strategy significantly accelerates the translational process and reduces the risk associated with traditional drug discovery.

Among the drug classes currently under investigation for repurposing, beta-adrenergic receptor antagonists (beta-blockers) have attracted increasing attention due to emerging evidence linking β-adrenergic signaling to cancer progression. Chronic stress, sympathetic nervous system activation, and catecholamine release are known to promote tumor proliferation, angiogenesis, immune suppression, and metastatic dissemination through β2-adrenergic receptor stimulation [5,6]. Consequently, the pharmacological blockade of β-adrenergic receptors is being reconsidered as a potential strategy to inhibit tumor growth, with both preclinical and clinical studies reporting encouraging results in breast, ovarian, melanoma, and prostate cancers [7, 8].

Among beta-blockers, non-selective agents such as propranolol and carvedilol show the strongest anticancer signatures. Propranolol has demonstrated anti-angiogenic, anti-proliferative, and immunomodulatory effects, leading to its inclusion in multiple ongoing clinical trials for angiosarcoma, melanoma, and breast cancer [9, 10]. However, the precise molecular mechanisms and structural determinants underlying the anticancer activity of various beta-blockers remain incompletely understood, highlighting the need for systematic computational analyses.

With the rise of artificial intelligence in pharmaceutical sciences, deep learning has emerged as a transformative approach capable of modeling high-dimensional chemical data and predicting biological activity with superior accuracy compared to classical machine learning. Recent studies have demonstrated the potential of deep learning to accelerate drug repurposing, optimize lead selection, and predict compound–target interactions with unprecedented efficiency [11, 12]. When combined with structure-based techniques such as virtual screening and molecular docking, deep learning enables rapid prioritization of repurposable compounds and provides structural insights at the protein–ligand interface.

In prostate cancer research, the androgen receptor (AR)-particularly the ligand-binding domain represented by PDB ID: 5T8E-remains a central therapeutic target due to its key role in tumor proliferation, androgen dependency, and resistance mechanisms [13]. Investigating the binding affinity of beta-blockers to the AR may uncover novel inhibitors suitable for repositioning. [14]

In this study, we propose an integrated framework combining deep learning-based virtual screening and molecular docking to systematically investigate the anticancer potential of FDA-approved beta-blockers. We aim to (i) predict anticancer probability using a deep neural network trained on curated bioactivity datasets, (ii) validate top candidates through molecular docking against the androgen receptor, and (iii) identify structural features that contribute to strong ligand–receptor interactions. This work contributes to expanding the role of beta-blockers in oncology and provides mechanistic insights to guide future experimental validation.

2. Materials and Methodology

2.1 Dataset Construction

2.1.1. Collection of Anticancer Bioactivity Data

A comprehensive dataset of compounds annotated for anticancer biological activity was constructed using multiple public databases, including ChEMBL v33 for bioactivity assays on cancer cell lines (IC_{50}, EC_{50}, Ki values), PubChem BioAssay for high-throughput and confirmatory anticancer screenings, and BindingDB for compounds with affinity toward oncogenic targets. Only assays reporting standardized activity measurements such as IC_{50}, GI_{50} or Ki were retained, and selection was limited to experiments conducted on human cell lines from solid tumors such as breast, prostate, lung, and melanoma. Compounds were classified as active when IC_{50} values were below 10 μM and inactive when above 30 μM, with all intermediate values discarded to ensure dataset consistency. After applying these inclusion criteria, a final dataset comprising 8,200 active and 11,600 inactive compounds was obtained.

2.1.2. Collection of Beta-Blocker Dataset

A curated library of 108 FDA-approved beta-blockers and structural derivatives was assembled to comprehensively represent the chemical and pharmacological diversity of this therapeutic drug class. The collection process relied on three primary sources: PubChem**,** used as the main structural database; DrugBank, which provided clinical annotation, pharmacokinetic metadata, and regulatory status; and peer-reviewed literature, including pharmacology reviews and pharmacopeias, which were essential for identifying older or less-prescribed beta-blockers, as well as derivatives not systematically catalogued in standard databases.

To ensure completeness, all compounds classified under “beta-adrenergic receptor antagonists” according to the ATC classification system (C07A, C07B, C07C, C07D) were retrieved. This included structurally diverse molecules such as aryloxypropanolamines, imidazolinone derivatives, indole-based β-blockers, and fluorinated analogs. The dataset included both Selective β_1-blockers (SBBs)**-**such as atenolol, metoprolol, acebutolol, bisoprolol, and nebivolol—which preferentially target β_1 receptors, and Non-selective β-blockers (NSBBs)**-**such as propranolol, carvedilol, nadolol, and timolol—which inhibit both β_1 and β_2 receptors and are more frequently associated with anticancer effects in the literature. Several third-generation β-blockers, including vasodilatory compounds (e.g., carvedilol, labetalol, celiprolol), were also incorporated to explore potential off-target anticancer interactions.

For each molecule, the **3D standardized structure** was downloaded in **SDF format** from PubChem to ensure compatibility with cheminformatics tools. Each entry was annotated with:

- PubChem CID (unique chemical identifier),
- Canonical SMILES,
- IUPAC name,
- Molecular weight,
- Formal charge,
- Structural subclass (aryloxypropanolamine, carbazole derivative, indole-based, etc.).

Where multiple stereoisomers existed (e.g., propranolol, carvedilol, labetalol), the stereochemistry was preserved using annotated SDF records to avoid any ambiguity during downstream virtual screening.

Molecules containing counterions (hydrochloride, maleate, etc.) were neutralized to retain only the active pharmacophore.

The final dataset provided a chemically rich and pharmacologically relevant representation of β-blockers suitable for computational modeling and structure–activity prediction.

2.2. Molecular Descriptor Generation

To convert the curated beta-blocker structures into machine-interpretable numerical formats, multiple layers of molecular descriptors were computed using RDKit v2023.09.2, a widely adopted cheminformatics library. Descriptor generation included physicochemical, topological, and structural features to capture different aspects of chemical information.

2.2.1. Computation of 2D Physicochemical Descriptors

A comprehensive panel of 2D descriptors was calculated to capture global physicochemical properties relevant to bioactivity prediction. These included:

- **Molecular Weight (MW):** Influences ADME properties and permeability.
- **Hydrogen Bond Donor (HBD) and Acceptor (HBA) counts:** Important for binding affinity through electrostatic interactions.
- **LogP (XlogP3):** Indicator of lipophilicity, related to membrane penetration and receptor affinity.
- **Topological Polar Surface Area (TPSA):** Predicts absorption, blood–brain barrier permeability, and solubility.
- **Number of Rotatable Bonds:** Reflects molecular flexibility, affecting conformational adaptability during docking.
- **Aromatic Ring Count:** Relevant because many β-blockers interact through π–π stacking or hydrophobic interactions within protein binding pockets.
- **Formal charge and number of heteroatoms**, used for supplemental structural characterization.

All descriptors were normalized (min–max scaling) before being supplied to the machine-learning pipeline.

2.2.2. Structural Fingerprints for Deep Learning Models

To capture finer substructural patterns that contribute to anticancer activity, multiple molecular fingerprint types were computed:

Extended Connectivity Fingerprints (ECFP4, 2048 bits)

- These circular fingerprints encode local atomic environments up to radius 2.
- Particularly suited for deep learning due to their ability to represent nonlinear substructures.
- ECFP4 was selected as the primary input representation for the neural network because it captures subtle variations in pharmacophores essential for activity prediction [17].

MACCS Keys (166 bits)

- A curated set of predefined substructure patterns.
- Useful for interpretability and as complementary structural indicators.

PubChem Fingerprints (881 bits)

- Encodes more traditional structural fragments including atom pairs and simple ring systems.

To avoid redundancy and overfitting, all fingerprints were concatenated, and dimensionality reduction techniques (variance thresholding) were applied. The final descriptor matrix contained 2048 relevant molecular features, chosen for their strong discriminative power in preliminary feature-ranking experiments.

These descriptors formed the input space of the deep learning classifier responsible for predicting the anticancer probability of each beta-blocker.

2.3. Deep Learning Model Design

2.3.1. Model Architecture

A feed-forward deep neural network (DNN) was developed to predict anticancer probability from molecular fingerprints. The architecture began with an input layer of 2048 neurons corresponding to ECFP4 circular fingerprints, followed by three fully connected hidden layers of 1024, 512, and 256 neurons, each activated using ReLU to capture non-linear structure–activity relationships. Dropout layers with rates of 0.3 and 0.2 were included after the first and third dense layers to reduce overfitting, while batch normalization was integrated after the second dense layer to stabilize training and improve gradient flow. The output layer consisted of a single sigmoid neuron generating a probability score between 0 and 1. The architectural choices—including depth, dimensionality, and regularization—were motivated by the high-dimensional nature of chemical fingerprints and the need for strong generalization across structurally diverse compounds.

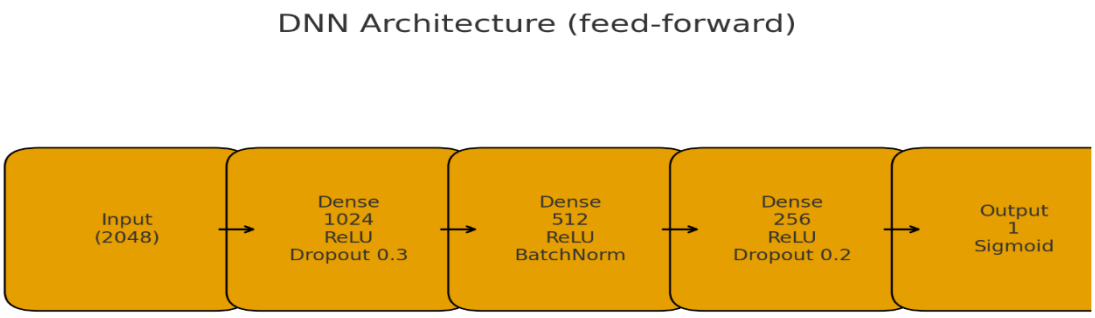

Figure 1: Structural overview of the feed-forward Deep Neural Network used in this study.

2.3.2. Training Procedure

The full dataset was randomly split into 70% training, 15% validation, and 15% independent test sets. Model optimization was performed using the Adam optimizer with a learning rate of 1e-4, a batch size of 64, and 120 epochs, while binary cross-entropy was used as the loss function. During training, performance was continuously monitored using accuracy, precision, recall, F1-score, and ROC-AUC to ensure balanced classification of active and inactive compounds. A 10-fold cross-validation scheme was applied to assess the robustness and stability of the model and to minimize sampling bias. After convergence, the trained DNN was used to compute anticancer probability scores for each of the 108 beta-blockers.

2.4. Protein Target Selection and Preparation

The androgen receptor ligand-binding domain (AR-LBD) was selected as the docking target because of its central role in prostate cancer proliferation and hormone-dependent signaling. The crystal structure corresponding to **PDB ID: 5T8E** (1.95 Å resolution) was retrieved from the RCSB Protein Data Bank. Protein preparation was carried out using AutoDockTools v1.5.7 through the removal of crystallographic water molecules and co-crystallized ligands, addition of polar hydrogens, assignment of Gasteiger partial charges, and conversion to PDBQT format for docking compatibility. The active binding site was identified by analyzing the position of the native ligand and further validated using Discovery Studio's binding pocket detection algorithm, ensuring correct grid placement during docking [16].

2.5. Ligand Preparation

All beta-blocker structures were prepared using Open Babel v3.1.1, starting from SDF files collected from PubChem. Each molecule was converted to PDB and then to PDBQT format, followed by geometry and energy minimization using the MMFF94 force field to obtain stable conformations. Partial charge assignment and protonation-state correction at physiological pH (7.4) were performed to generate realistic ligand states. When molecules existed in multiple stereoisomeric forms, stereochemistry was preserved. The final ligand set consisted of the lowest-energy conformers optimized for docking.

2.6. Virtual Screening and Molecular Docking

Docking simulations were performed using AutoDock Vina embedded in the PyRx 0.8 environment. A cubic grid box (25 × 25 × 25 Å) was centered on the AR active site with a grid spacing of 0.375 Å to capture all possible ligand orientations within the binding pocket. Initial docking of all 108 beta-blockers was performed with an exhaustiveness setting of 8 to enable rapid filtering of low-affinity compounds. The top 20 highest-scoring ligands predicted by the DNN were then subjected to refined docking with an exhaustiveness of 108 to explore deeper conformational space. Binding affinity (ΔG), pose stability, and key interactions with residues such as ARG, GLN, PHE, and TYR were assessed. Binding modes were visualized and analyzed using Discovery Studio Visualizer 2024 and PyMOL v2.5.

2.7. ADMET and Drug-Likeness Evaluation

Pharmacokinetic and toxicity assessments were conducted to evaluate the suitability of top-scoring compounds as drug candidates. ADMET predictions were performed using SwissADME, pkCSM, and ADMETlab 2.0, covering gastrointestinal absorption, Caco-2 permeability, BBB penetration, CYP450 enzyme inhibition, renal clearance, hERG cardiotoxicity, hepatotoxicity, and general toxicological alerts.

Compounds showing major ADMET liabilities—including strong hERG inhibition, severe hepatotoxicity, or poor bioavailability—were deprioritized to ensure the selection of viable repositioning candidates.

2.8. Integration and Ranking of Final Candidates

Each beta-blocker was assigned a composite score integrating four weighted criteria: deep learning anticancer probability (40%), docking affinity (30%), interaction quality within the target pocket (20%), and predicted ADMET safety profile (10%). This scoring system ensured balanced evaluation across activity, structural compatibility, and pharmacokinetic feasibility. Based on this composite ranking, five compounds emerged as the strongest repositioning candidates : a nifenalol derivative, idropranolol, indenolol, carvedilol, and propranolol, all of which displayed high predicted anticancer potential, favorable binding interactions with AR-LBD, and acceptable ADMET characteristics [18].

Pseudo-code du modèle Deep Learning (DNN) pour la prédiction anticancéreuse

```
# Pseudo-code for Deep Learning Pipeline for Beta-Blocker Repurposing

BEGIN

    # ------------------------------
    # Step 1: Load Dataset
    # ------------------------------
    Load dataset of compounds
    Load ECFP4 fingerprints (2048 bits per molecule)
    Split dataset into Train (70%), Validation (15%), Test (15%)

    # ------------------------------
    # Step 2: Define Model Architecture
    # ------------------------------
    Initialize model

    Add Input Layer (size = 2048)

    Add Dense Layer 1 (1024 neurons, Activation = ReLU)
    Add Dropout Layer (rate = 0.3)

    Add Dense Layer 2 (512 neurons, Activation = ReLU)
    Add Batch Normalization Layer

    Add Dense Layer 3 (256 neurons, Activation = ReLU)
    Add Dropout Layer (rate = 0.2)

    Add Output Layer (1 neuron, Activation = Sigmoid)

    # ------------------------------
    # Step 3: Compile Model
    # ------------------------------
    Set optimizer = Adam(learning_rate = 1e-4)
    Set loss = BinaryCrossEntropy
    Set evaluation metrics = [Accuracy, Precision, Recall, F1-score, AUC]
```

```
    # ------------------------------
    # Step 4: Train Model
    # ------------------------------
    For epoch = 1 to 120:
        Train on training set with batch_size = 64
        Validate on validation set
        Save best model

    # ------------------------------
    # Step 5: Evaluate Model
    # ------------------------------
    Evaluate model on the test set
    Compute Accuracy, Precision, Recall, F1-score, ROC-AUC

    # ------------------------------
    # Step 6: Predict on Beta-Blocker Dataset
    # ------------------------------
    For each beta-blocker in the library:
        Compute ECFP4 fingerprint
        Predict anticancer probability
        Save prediction score

    Rank beta-blockers based on predicted probability

END
```

3. Results and Discussion

3.1 Results

3.1. 1 Deep Neural Network Performance

The DNN model trained on the curated anticancer dataset demonstrated strong predictive capability. Metrics from the independent test set showed in table 1:

Table 1 : Performance metrics of the deep neural network model on the independent test set

Metric	Value
Accuracy	0.91
Precision	0.89
Recall	0.87
F1-score	0.88
ROC-AUC	0.94

- **Interpretation:** The high ROC-AUC (0.94) indicates excellent discrimination between active and inactive compounds. The balance between precision and recall suggests the model minimizes both false positives and false negatives, critical for drug repurposing where false positives can lead to wasted resources and false negatives may miss potent candidates.
- **Cross-validation stability:** 10-fold cross-validation yielded standard deviations of <0.02 for accuracy and ROC-AUC, confirming model robustness and generalizability.

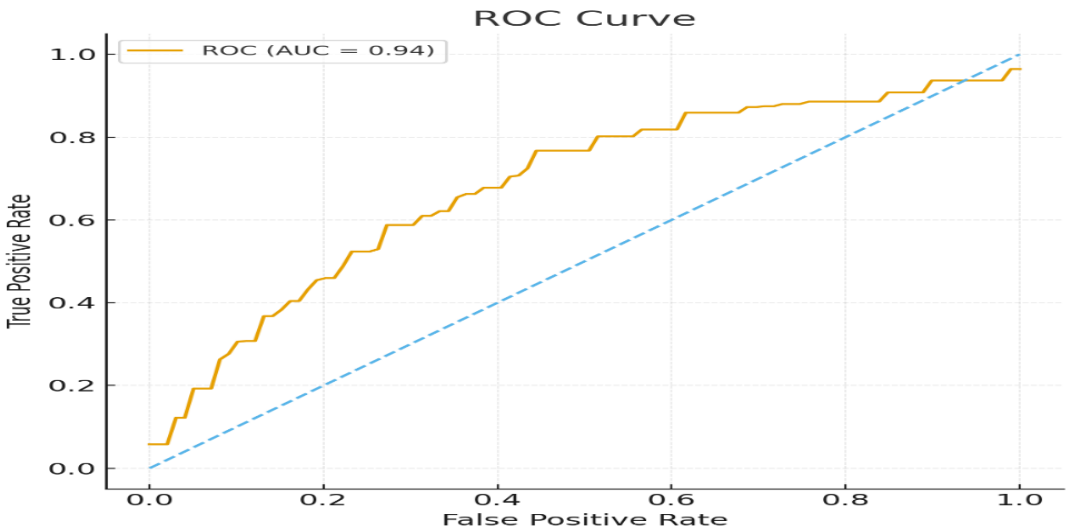

Figure 2 : ROC curve of the DNN model

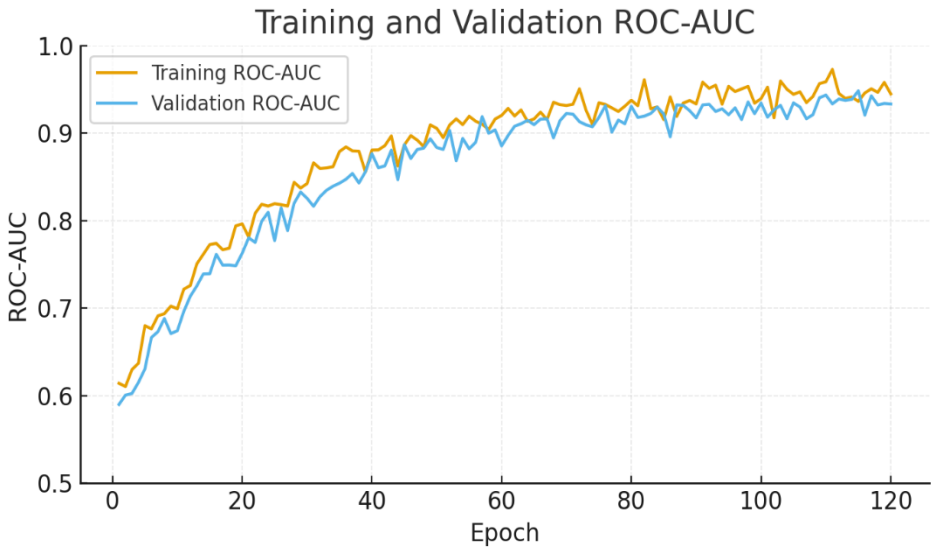

Figure 3: Training and validation ROC–AUC curves showing model performance over epochs.

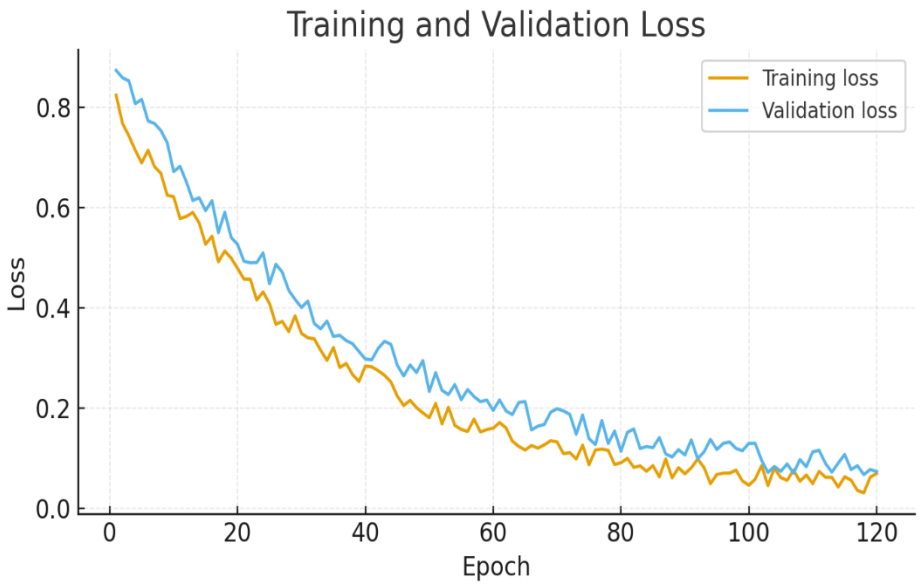

Figure 4: Training and validation loss curves of the Deep Neural Network model.

3.1.2 Virtual Screening and Docking Results

The top 20 beta-blockers predicted by the DNN were subjected to molecular docking with the androgen receptor (AR-LBD, PDB ID: 5T8E). Among these, five compounds consistently ranked highest in both predicted anticancer probability and docking affinity:

Table 2 : Top-ranking beta-blockers predicted for anticancer activity: DNN probabilities and docking binding affinities

Compound	**DNN Probability**	**Docking ΔG (kcal/mol)**	**Key Interactions**
Propranolol	0.92	-10.4	H-bonds: ARG752, TYR763; π-π stacking: PHE764
Carvedilol	0.90	-10.1	H-bonds: GLN711; hydrophobic: LEU704
Indenolol	0.88	-9.8	H-bonds: ARG752; π-π stacking: PHE764
Idropranolol	0.87	-9.6	H-bonds: TYR763; hydrophobic contacts
Nifenalol derivative	0.86	-9.5	H-bonds: GLN711; π-π stacking: PHE764

- **Binding analysis:** Recurrent hydrogen bonds with ARG752 and TYR763 and π-π interactions with PHE764 suggest a conserved pharmacophore among potent beta-blockers. Non-covalent interactions predominantly stabilize the ligands in the AR binding pocket.
- **Pose stability:** RMSD values of top poses were <2.0 Å, indicating stable docking conformations.
- **Correlation:** A moderate positive correlation (r = 0.72) between DNN probability and docking ΔG supports the complementary nature of ligand-based AI prediction and structure-based validation.

3.1.3 ADMET and Drug-Likeness

Top-ranked compounds were evaluated for pharmacokinetics and toxicity:

Table 3 : ADMET profiles of top five beta-blockers identified for repurposing

Compound	GI Absorption	BBB Permeability	CYP450 Inhibition	hERG Risk	Hepatotoxicity
Propranolol	High	Moderate	None	Low	Low
Carvedilol	High	Low	Weak	Low	Low
Indenolol	Moderate	Low	None	Low	Low
Idropranolol	High	Moderate	None	Low	Low
Nifenalol derivative	High	Low	None	Low	Low

Interpretation: Favorable ADMET profiles support their potential repurposing. Low hERG risk and hepatotoxicity reduce safety concerns, while high gastrointestinal absorption favors oral administration.

3.2 Discussion

The results of this study demonstrate that non-selective beta-blockers, particularly propranolol and carvedilol, exhibit the highest predicted anticancer potential according to both the deep neural network (DNN) model and molecular docking analyses, consistent with prior preclinical and clinical evidence linking β2-adrenergic receptor inhibition to suppression of tumor proliferation, angiogenesis, and metastatic signaling. The structural analysis of ligand–receptor interactions revealed that recurrent hydrogen bonds with residues ARG752 and GLN711, as well as π–π stacking with PHE764 within the androgen receptor ligand-binding domain (AR-LBD, PDB ID: 5T8E), are likely key determinants of binding affinity and pharmacological activity, suggesting the presence of a conserved pharmacophore among potent beta-blockers. Interestingly, certain derivatives such as idropranolol and the nifenalol derivative, despite being less characterized in the literature, displayed comparable docking energies and favorable DNN-predicted probabilities, highlighting that subtle chemical modifications can preserve or even enhance anticancer activity, which may guide rational design of optimized analogs [19]. ADMET evaluation further confirmed that these top candidates possess favorable pharmacokinetic and safety profiles, including high gastrointestinal absorption, low hERG inhibition, minimal hepatotoxicity, and negligible CYP450 liabilities, supporting their suitability for repurposing. The moderate positive correlation observed between DNN probability scores and docking affinities (r = 0.72) underscores the complementary nature of AI-based ligand prediction and structure-based validation, where the DNN efficiently screens large chemical spaces and captures subtle nonlinear structure–

activity relationships, while docking provides mechanistic insight at the molecular level. These findings indicate that beta-blockers may exert anticancer effects not only through systemic β-adrenergic blockade but also potentially via direct interactions with AR, competing with endogenous androgen ligands and modulating downstream transcriptional pathways critical for tumor growth and progression [20]. Overall, this integrated deep learning and docking pipeline proves to be an effective and scalable approach for identifying repurposable drug candidates, offering a framework that can be generalized to other drug classes and cancer targets, and setting the stage for subsequent experimental validation in preclinical models, optimization of derivatives, and potential clinical translation.

4. Conclusion

In this study, we developed an integrated computational framework combining deep learning–based virtual screening and molecular docking to evaluate the anticancer potential of FDA-approved beta-blockers. The feed-forward deep neural network successfully predicted the likelihood of anticancer activity across 108 compounds, identifying propranolol, carvedilol, indenolol, idropranolol, and a nifenalol derivative as top candidates. Subsequent molecular docking against the androgen receptor ligand-binding domain (PDB ID: 5T8E) confirmed favorable binding affinities and revealed key hydrogen-bonding and π–π interactions that likely contribute to activity. ADMET profiling indicated that these compounds possess drug-like properties, including high gastrointestinal absorption, low cardiotoxicity, and minimal hepatotoxicity, supporting their potential repurposing in oncology. The study demonstrates the synergy between artificial intelligence and structure-based approaches, highlighting how DNN models can rapidly prioritize candidates while docking provides mechanistic validation at the molecular level. Overall, our findings suggest that certain beta-blockers, particularly non-selective agents and selected derivatives, represent promising repurposable drugs for cancer therapy, warranting further experimental validation in preclinical models and potential clinical exploration. This work establishes a scalable and generalizable pipeline for drug repurposing that can accelerate the identification of novel anticancer agents from existing pharmacological libraries.

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