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Repurposing beta blockers drugs as anti-cancer agents: virtual screening, molecular docking simulations

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Abstract

The repurposing of existing drugs represents a strategic approach to accelerate the discovery of novel anticancer agents while reducing the time, cost, and risk associated with traditional drug development pipelines [1,2]. Beta-adrenergic receptor antagonists (beta-blockers), primarily indicated for cardiovascular conditions, have shown emerging potential as modulators of tumor progression via β-adrenergic signaling pathways [3,4]. This study employed *in silico* methodology combining virtual screening and molecular docking to evaluate a library of FDA-approved beta-blockers and its derivates for anticancer potential. Protein targets associated with hormonal receptor (androgen receptor) were selected to assess the antiproliferation properties of : selective beta blockers (SBBs) and non-selective beta blockers (NSBBs) against prostate cancer [5]. Docking simulations were conducted using PyRx 0.8 virtual Screening tool (https://pyrx.sourceforge.io › downloads) [6] via AutodockVina v1.1.2 [7], molecular interactions, were visualized using BIOAVIA Discovery Studio Visualizer v25.14.0 (https://discover.3ds.com/discovery-studio-visualizer-download) [8]. Several beta-blockers, notably propranolol and carvedilol, exhibited high binding affinities and favorable interaction profiles with multiple oncogenic targets, suggesting their potential utility in anticancer therapy. These findings provide computational evidence supporting the repurposing of beta-blockers in oncology and highlight the value of virtual screening in drug discovery.

This work aims to explore the distinctions between the major types of BBs: NSBBs and SBBs, and their contributions to combinatory cancer treatment via virtual screening technique.

Within the last decade, researchers have studied the potential use of BBs as a therapeutic option for cancer treatment, but could beta-blockers respond optimally to repositioning, as an anticancer treatment, against prostate cancer?

Keywords:
Repurposing, Beta blockers, virtual screening, molecular Docking, anticancer agents

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, despite the continuous development of novel therapeutic agents [10]. Conventional drug discovery is a time-consuming and costly process, often taking over a decade and billions of dollars to bring a single compound to market [11]. As a result, drug repurposing—the strategy of identifying new therapeutic uses for existing drugs—has emerged as an efficient alternative to traditional de novo drug development [1,12]. Repurposed drugs benefit from already-established pharmacokinetics, safety profiles, and manufacturing processes, thereby significantly reducing the risk of failure during clinical development [2].

Among the many candidates for repurposing, beta-adrenergic receptor antagonists, commonly referred to as beta-blockers, have gained attention due to their pleiotropic effects beyond cardiovascular modulation. Originally developed for the treatment of hypertension, arrhythmias, and ischemic heart disease [13], beta-blockers have been increasingly investigated for their role in modulating cancer progression via adrenergic signaling pathways [14]. Preclinical and epidemiological studies have suggested that beta-blockers may inhibit tumor growth, angiogenesis, and metastasis, particularly in breast, prostate, and ovarian cancers [15-16].

The potential anticancer activity of beta-blockers is thought to be mediated through the blockade of β-adrenergic receptors, which are known to influence cellular proliferation, apoptosis, angiogenesis, and immune responses in various tumor microenvironments [17]. However, the mechanistic understanding of beta-blocker interactions with specific oncogenic targets remains limited.

With the increasing availability of structural data and computational tools, *in silico* approaches such as virtual screening and molecular docking have become indispensable in the early stages of drug discovery and repurposing [09]. These techniques allow rapid evaluation of drug-target interactions and prediction of binding affinities, thereby guiding the identification of promising drug candidates for experimental validation.

In this study, we investigate the anticancer potential of FDA-approved beta-blockers through *in silico* methods. Using molecular docking and virtual screening against key cancer-associated proteins, we aim to identify beta-blockers with high binding affinities and favorable interaction profiles. This work contributes to the growing body of evidence supporting beta-blocker repurposing and underscores the power of computational approaches in uncovering new therapeutic roles for established drugs.

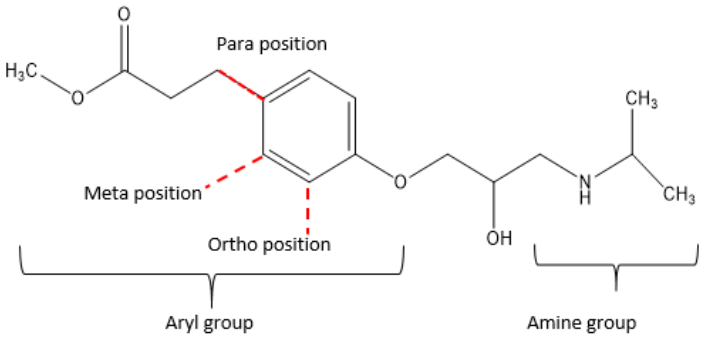


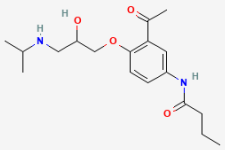
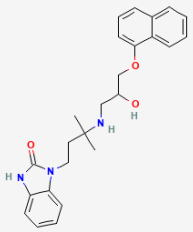
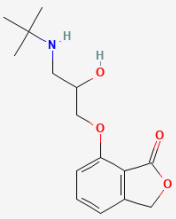
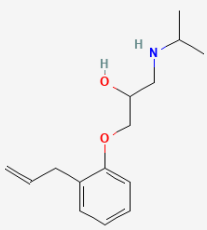
Figure.01. General 2D structure of beta blockers.

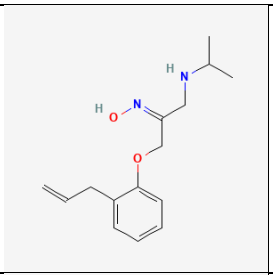
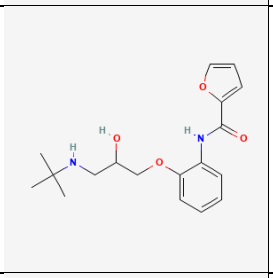
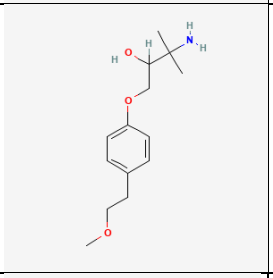
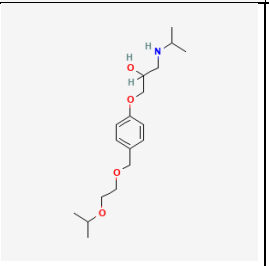
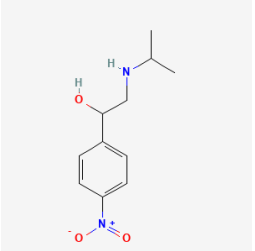
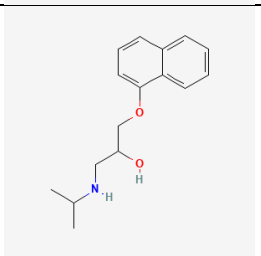
2 Materials and Methodology

2.1. Ligand Preparation

A curated list of beta blockers FDA-approved were collected from the literature and are summarized in **Table 1** along with their structure, smiles and Molecular weight [18]. BBs structures were from the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/), including commonly prescribed compound such as propranolol, atenolol, metoprolol, bisoprolol, carvedilol, and labetalol. The 3D structures of these ligands were retrieved in SDF format and converted into PDBQT format using **Open Babel** (version 3.1.1) [19]. Ligands were energy-minimized using the MMFF94 force field to ensure optimized geometry for docking via PyRx 0.8 Virtual Screening Software.

Table 1: List of some selective and non-selective beta blockers.

Molecule	Compound CID	Molecular weight (g/mol)	Structures	3D Similarity
Acebutalol	1978	336.43		83
Adimolol	10049692	456		02
Afurolol	176877	279.33		278
Alprenolol	2119	249.35		96

Alprenoxime	6537084	262.35		03
Ancarolol	170339	332.4		19
Arnolol	65653	253.34		07
Bisoprolol	2405	325.4		38
Nifenalol	6317	224.26		441
Propranolol	4946	259.339		287

2.2. Target Protein Selection and Preparation

Protein targets implicated in cancer proliferation, angiogenesis, and metastasis were selected based on literature review. 3D Crystal structures of the androgenic receptor (PDB ID: 5T8E) were obtained from the Protein Data Bank (RCSB PDB) [3]. Protein preparation involved removal of water molecules and heteroatoms, addition of polar hydrogens, and assignment of Gasteiger charges using **AutoDock Tools (ADT) v1.5.7** [4].

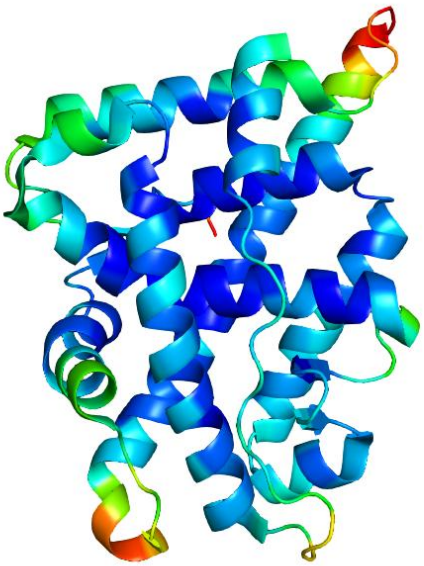


Figure.02. 3D Crystal structure of androgen receptor (PDB ID : 5T8E) from RCSB database.

2.3. Virtual Screening and Molecular Docking

Docking simulations were conducted Docking simulations were conducted using PyRx 0.8 virtual Screening tool (https://pyrx.sourceforge.io › downloads). Grid boxes were defined to encompass the entire protein target with protein target. Exhaustiveness was set to 8 for initial screening and increased to 108 for selected ligands and them derivates.

2.4. Docking Evaluation

Binding affinities (ΔG, kcal/mol) were used to rank ligand-protein interactions of top two from the most stable complexes (ligand-protein). The top-scoring ligands for androgen receptor (PDB ID : 5T8E), were subjected to detailed interaction analysis using **Discovery Studio Visualizer (v21.1.0)** and **PyMOL (v2.5)** for visualization of hydrogen bonds, π-π stacking, hydrophobic contacts, and other molecular interactions.

3. Results and discussion

Table 02. Minimiszation energy and binding affinity of 108 ligands of beta blockers and its derivates.

Molecule	PubChem CID	Binding affinity (Kcal/mol)	Minimization energy (MMFF)
Acetubol	13550350	-7.5	62.07
Adaprolol	60732	-6.5	99.60
Adimolol	71227	-5.7	72.68
Alfuralol	191018	-8.0	301.11
Alprenolol	191018	-8.0	75.85
Alprenoxime	9578167	-6.6	105.77
Amosulalol	2169	-6.6	45.36
Ancralol	148060	-8.3	100.41
Arnolol	12774250	-6.6	54.79
Arotinolol	2239	-7.1	17.33
Atenolol	40603932	-7.7	86.63
Befunolol	4713263	-8.1	267.86
Betaxolol	37060	-7.1	210.14
Bevantolol	68563	-7.8	255.59
Bisoprolol	209609	-7.4	256.23
Bopindolol	3268431	-7.6	947.47
Bornaprolol	29982023	-7.9	212.55
Brefonalol	65880	-8.4	306.26
Bucindolol	613663	-8.4	506.31
Bucumolol	128612	-8.4	214.51
Bufetolol	101643516	-8.0	223.21
Bufuralol	12367263	-7.7	363.79
Bunitrolol	192210	-8.0	213.36
Bupicomide	207592	-7.1	104.12
Bupranolol	91536	-8.1	203.15
Butaxamine	60903667	-7.7	133.14
Butofilolol	6447157	-7.7	515.56
Butidrine	15177	-8.6	73.56
Capsinolol	9887704	-6.8	235.54
Carteolol	101152869	-8.3	205.69
Carvedilol	18709543	-8.5	535.23
Celiprolol	9077583	-8.0	310.86
Cetamolol	15916952	-7.4	544.39
Cicloprolol	85921692	-7.9	302.73
Cinamolol	76958407	-7.5	429.56
Cloranolol	191018	-8.0	301.11
Cyanopindolol	101152869	-8.4	205.69
Dalbraminol	4443823	-7.6	274.61
Desacytlmetipranolol	91565	-7.4	227.29
Dichloroisoprenaline	5806	-6.9	55.86
Dihydroalprenolol	154144038	-7.1	162.55
Diprafenone	1352793	-8.2	290.73
Draquionolol	92977265	-7.2	495.04
Ecastolol	208905	-6.7	585.44

Epanolol	12841707	-6.4	332.23
ecricolol	102329231	-7.1	339.85
Ersentilide	14739907	-7.1	495.03
Esmolol	14853072	-8.0	281.92
Eugnodilol	9930145	-6.0	291.55
Nifenalol 4,4,4-trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol	**6317 294101**	**-9.1**	**177.58**
Idropranolol	**163314**	**-8.9**	**85.89**
Indenolol	**71955**	**-8.9**	**85.89**
Indopanolol	101641924	-8.6	111.98
Pronethalol	62787456	-8.6	1431.84
Metipranolol	4713263	-8.4	267.86
Ronactolol	6445659	-8.4	297.02
Hydroxycarteolol	101152869	-8.3	131.68
exaprolol	101667940	-8.3	85.78
Penbutolol	44389661	-8.3	249.49
Hydroxytertatolol	128614	-8.2	76.44
Afurolol	5311179	-8.2	68.22
Iprocrolol	76971122	-8.2	93.33
ICI-118,551	3682	-8.1	70.78
Labetalol	3869	-8.1	68.35
LEVOBUNOLOL	12672905	-8.1	89.91
Mepindolol	101489628	-8.1	241.59
Metoprolol	44276727	-8.1	322.20
Nadolol	12882845	-8.1	313.81
Practolol	44276727	-8.1	322.20
Propranolol	3682	-8.1	351.37
Soquinolol	104824	-8.1	334.19
Talinolol	217353	-8.1	304.10
Moprolol	191018	-8.0	301.11
Oxprenolol	12478009	-8.0	224.73
Pamatolol	85921692	-8.0	302.73
Pindolol	101152868	-8.0	203.03
Iodocyanopindolol	4713263	-7.9	29.15
Tazolol	13147204	-7.9	172.73
Pargolol	22797798	-7.8	29.09
Spirendolol	21138	-7.8	205.87
Tertatolol	21279654	-7.8	211.39
Isoxaprolol	13015339	-7.7	87.15
Nebivolol	71301	-7.7	320.31
Pindobind	25266786	-7.6	496.43
Primidolol	200616	-7.6	346.69
Procinolol	16877002	-7.6	533.63
Ridazolol	13387156	-7.5	271.47
Sotalol	12367263	-7.5	363.79
Flestolol	13603834	-7.4	10.71
Iodopindolol	52918356	-7.4	72.25
Pafenolol	12376511	-7.3	229.40
Falintolol	12380554	-7.2	92.13
Flusoxolol	71765	-7.1	108.31
Landiolol	114905	-6.9	68.45
Medroxalol	41835	-6.9	559.13

Nipradilol	14839765	-6.9	303.03
Isamoltane	127404	-6.1	89.45
Pacrinolol	6436098	-6	495.97

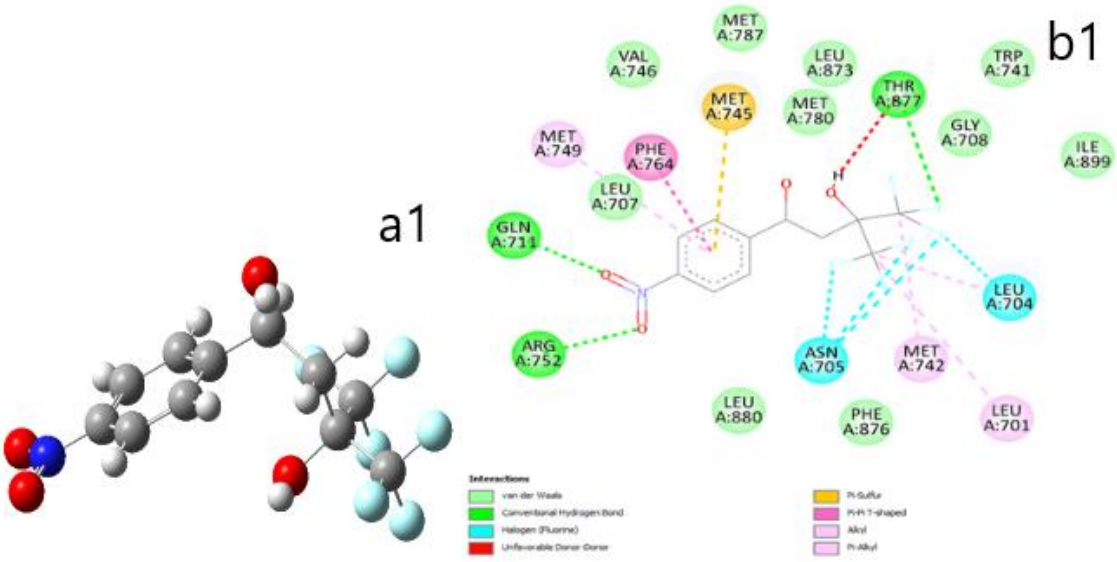


Figure.3. 3D Structure of 4,4,4-Trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol (a1) and predicted 2D interaction map of 4,4,4-trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol-5t8e (b1)

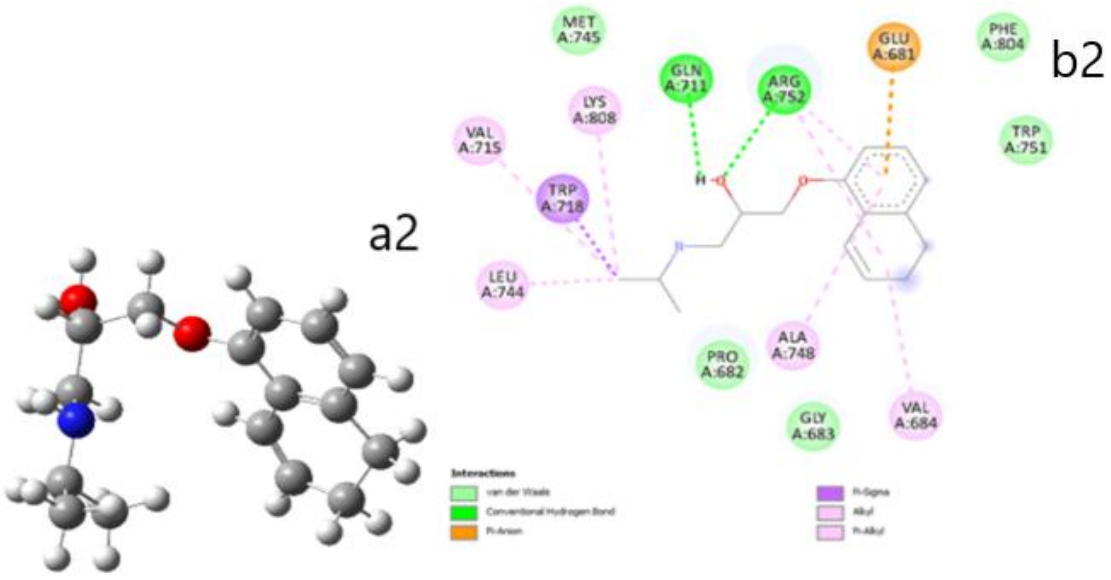


Figure.04. 3D structure of Idropranolol (a2) and predicted 2D interaction map of idropranolol-5t8e (b2)

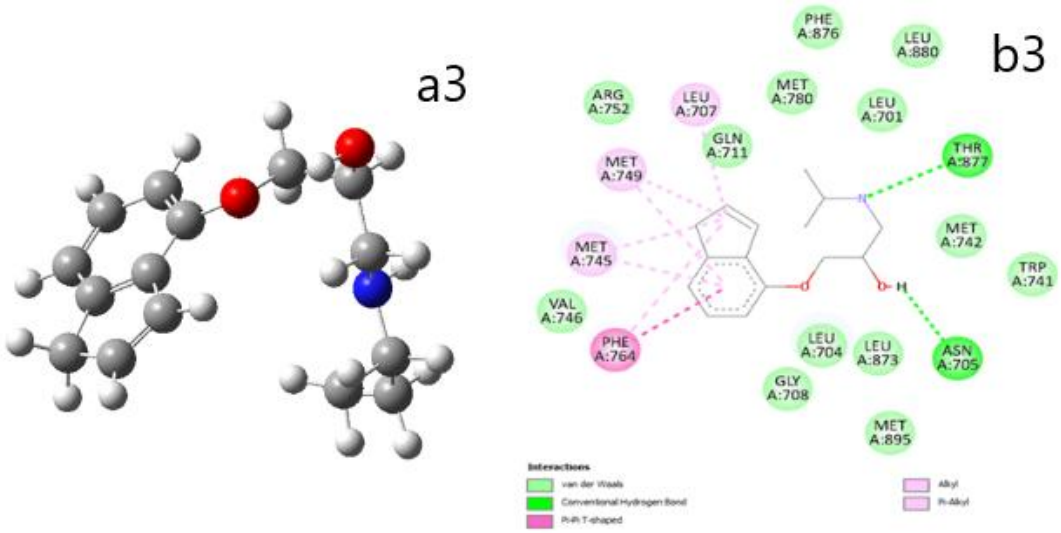


Figure .05. 3D structure if indenolol and predicted 2D interaction map of indenolol-5t8e (b3)

Following the virtual screening phase, three top-ranking ligands ; 4,4,4-trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol, Idropranolol and Indenolol with -9.1 kcal/mol, -8.9 kcal/mol and -8.9 kcal/mol respectively, were selected based on their binding affinities and pharmacophoric features. These ligands were subsequently subjected to molecular docking studies to investigate their binding modes and interaction profiles within the active site of the target receptor. The docking results revealed that the stability and specificity of ligand–receptor complexes are primarily governed by a network of hydrogen bonds, van der Waals forces, and π–π stacking interactions. In particular, hydrogen bonding was observed as a key stabilizing interaction, frequently involving polar residues within the binding pocket. Additional contributions from hydrophobic contacts and electrostatic interactions were also noted, suggesting a multifaceted binding mechanism.

Figures 3, 4, and 5 illustrate the molecular docking poses of the three ligands, highlighting critical amino acid residues involved in ligand recognition. These visualizations further support the role of non-covalent interactions in modulating binding affinity and orientation within the receptor cavity. Overall, the docking data corroborate the predicted ligand efficiency and provide valuable insights for subsequent in vitro validation or lead optimization.

Conclusion

This study demonstrates the potential of repurposing beta blockers as anticancer agents through an integrated virtual screening and molecular docking simulation approach. By systematically evaluating a library of beta blockers against the cancer-related protein target with PDB ID: 5T8E, three molecules-Nifenalol's derivate (4,4,4-trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol), Idropranolol and Indenolol were identified as top candidates, exhibiting higher binding affinity and forming stable complexes with the target protein.

The use of computational methods such as virtual screening and molecular docking has proven to be a powerful and efficient strategy for drug repurposing, allowing rapid identification of promising candidates with favorable interaction profiles and stability, as supported by recent literature in the field. The identification of Nifenalol's derivate 4,4,4-Trifluoro-1-(4-nitrophenyl)-3-(trifluoromethyl)butane-1,3-diol, Idropranolol and Indenolol as strong binders to 5T8E suggests their potential utility as lead compounds for further preclinical and clinical evaluation in cancer therapy.

Overall, this work highlights the value of *in silico* drug repurposing for accelerating the discovery of novel anticancer agents, while also underscoring the need for subsequent experimental validation to confirm the therapeutic efficacy and safety of these candidates. The findings provide a solid foundation for future studies aimed at harnessing the anticancer potential of beta blockers and advancing them toward clinical application.

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