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Research Article

Computational Analysis of Phenylpropyl Amine Derivatives as Potential Calcium Channel Blockers Using an Ancestral Bacterial Channel as a Structural Proxy

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Objective: Phenyl propylamine derivatives were evaluated for calcium channel-blocking activity using molecular docking and molecular dynamics simulations against the amlodipine receptor complex. Materials and methods: Docking studies were performed with the Ginna program, and molecular dynamics simulations were conducted on the NeuroSnap platform. Results and discussion: Chlorpheniramine and 3-(4-bromophenyl)-N, N-dimethyl-3-pyridin-2-propanamine showed favorable binding affinities relative to the reference drug amlodipine. Redocking of amlodipine was performed to validate the docking protocol. Molecular dynamics analysis indicated stable ligand–receptor interactions, with acceptable structural confidence and root-mean-square deviation values. Pharmacokinetic and toxicity predictions were performed using web servers. Conclusion: The results suggest that selected phenyl propylamine derivatives may serve as promising lead molecules for further in vitro and in vivo evaluation as calcium channel blockers.

Keywords: Phenyl propylamine, Calcium channel, docking, dynamics, Amlodipine.

INTRODUCTION

Phenylpropylamines act as calcium channel blockers and are used to treat cardiovascular diseases. Verapamil is a typical example. They block calcium influx into cardiac smooth muscle cells, thereby reducing heart rate. They also have vasodilatory effects. Amlodipine is a calcium channel blocker that acts as a vasodilator by blocking calcium channels. It is a complex drug molecule containing a propoxy side chain. The propyl amino group contributes to a molecule's lipophilicity, thereby enhancing its penetration of the blood-brain barrier[1-3]. The amino (-NH2) group or the oxo group can act as a hydrogen-bond donor or acceptor in interactions with biological targets. The propyl amino group can fit into the hydrophobic pockets of several biological receptors, enhancing biological activity. Calcium channel blockers such as amlodipine and verapamil are frequently used to treat angina pectoris, hypertension, and certain cardiac arrhythmias.[4-5] Derivatives of phenyl propylamines are a significant family of bioactive substances with a wide range of pharmacological actions. Both aromatic and amino functional groups in the phenyl propylamine scaffold promote hydrophobic, hydrogen bonding, and electrostatic interactions with biological targets. These molecules can adopt favorable conformations within receptor binding pockets due to the flexibility of the propylamine chain, thereby improving ligand–receptor interactions. Because structural changes to the phenyl propylamine nucleus have been shown to affect pharmacokinetic and pharmacodynamic characteristics, this scaffold is a desirable option for the creation of new medicinal compounds. The crystal structure of the CavAb–Amlodipine complex (PDB ID: 5KMD) provides important insights into the molecular underpinnings of calcium channel blockade. A helpful structural model for understanding ligand interactions with calcium

channels is CavAb, a voltage-gated calcium channel from bacteria. The co-crystallized amlodipine molecule makes it easier to evaluate possible calcium channel blockers using computational methods by identifying significant binding sites within the channel pore. Identifying substances with favorable binding properties and potential antihypertensive efficacy can be facilitated by analyzing ligand interactions with the 5KMD receptor. In contemporary pharmaceutical research, computational drug discovery methods such as molecular docking and molecular dynamics simulations have become essential tools. Molecular docking helps identify prospective lead compounds by estimating binding affinity and predicting a ligand's preferred binding orientation inside a target receptor.[6-7] By assessing the stability and dynamic behavior of protein–ligand complexes under physiological settings, molecular dynamics simulations supplement docking investigations. When combined, these methods reduce the time and expense of experimental screening while providing useful information on molecular recognition, binding stability, and structure–activity relationships. These propylamine chemicals can be tested in silico for their β-adrenergic binding properties, BBB permeability, and hydrophilic interactions[8]. The 5-KMD receptor is a transporter protein (CavAb in Complex with Amlodipine). Phenylalkylamines and benzothiazepines are primarily used for the treatment of cardiac arrhythmias, as they physically block the pores of the calcium channel, which is inhibited by dihydropyridines and phenylalkylamines[9].

Molecular dynamics

The GROMACS molecular dynamics online web server enables researchers to run simulations. Molecular docking and dynamic simulations of different ligand-target interactions using GROMACS are widely used open-source Software in chemistry [10]. Several advanced techniques are available for regulating temperature/pressure stimulation, employing various geometric constraints and utilizing both explicit and implicit solvents.

Molecular docking

GNINA is an open-source molecular docking tool that integrates several convolutional neural networks to enhance the accuracy of protein-ligand binding predictions. The GNINA online web server can be accessed with a NeuroSnap account. It integrates Convolutional Neural Networks (CNNs) to improve performance. It supports flexible docking and assesses machine learning11. Calcium channel blockers are widely used to control blood pressure and manage angina symptoms. They are well-tolerated and safe medications12. Verapamil is an example of a phenylpropanolamine compound. These compounds are also used to treat coronary heart spasm.

MATERIALS AND METHODS

Docking was performed using GNINA. Molecular dynamics were performed using GROMACS. ADME was evaluated using Swiss ADME. The target receptor, RCSBPDB:5KMD, was downloaded from the RCSB Protein Data Bank (PDB) web server (Figure:1-2). The ligands were downloaded from the PubChem database in 3D SDF format. The laptop, equipped with an Intel i7 processor and Windows 11 OS, featured Iris Graphics. The molecular dynamics simulations were performed using GROMACS and the Neurosnap web server, which uses the GROMACS framework to simulate solvent-solute interactions13. The Neurosnap web server enables you to run GROMACS M.D. with an account registered with the software company. It simulates a broad range of molecular systems, providing RMSD, RMSF, and radius of gyration (Figure:3).

GNINA

It is an open-source molecular docking tool that integrates Convolutional Neural Networks (CNNs) to enhance the accuracy of protein-ligand binding predictions[14]. The Receptor PPDB form was uploaded and optimized. Ligands were uploaded over time, and docking was performed. The optimized results were obtained as a CSV file. The CNN Pose score, CNN affinity (kcal/mol), and intramolecular energy were provided at [15].

ADME Study

Swiss-ADME was used to obtain log P, BBB penetration, and synthetic accessibility. It is an online web server where ligand structures can be uploaded to obtain the results. The chemical structure was

uploaded as a SMILES string. The results were obtained after the run time. The The bioavailability radar and boiled-egg diagram summarized the results. The values obtained are shown in Table [16].

Protox for Toxicity Prediction

The Protox web server was utilized for toxicity prediction. The ligand of interest was tested by uploading its chemical structure; the output showed variation in toxicity parameters[17].

Dynamic Bind (Molecular dynamics (MD) simulations)

In contrast to conventional docking techniques that consider proteins as static and computationally costly molecular dynamics (MD) simulations, Dynamic-Bind offers a "dynamic docking" method for examining protein–ligand interactions. Its ability to study large-scale protein dynamics has important implications for drug discovery, particularly for compounds targeting cryptic pockets [18].

RESULTS

Table 1. Data from molecular docking of different phenylpropylamines

SI No.	Ligand PubChem ID and Chemical Name (https://pubchem.ncbi.nlm.nih.gov/docs/compounds)	*CNN Pose Score	**CNN Affinity (K Cal/mol)	*** Binding Affinity (K Cal/mol)	****Inter molecular energy
1	16783118 1-(4-Propoxy Phenyl) Propane–1Amine	0.8321	5.066	-6.45	-0.36
2	176088253-(2- Propoxy Phenyl) Propan – 1 – amine	0.8072	5.528	-5.9	-0.38
3	321155 N-(1-oxopropyl) alanine	0.7119	5.303	-5.59	-0.05
4	1001 2- phenyl ethylamine	0.7377	4.473	-5.62	-0.08
5	6834 3-(4-bromophenyl)–N, N–dimethyl l-3- pyridine –-2-propan – 1- amine	0.9062	6.132	-7.22	0.51
6	2725 – Chlorpheniramine	09526	6.479	-7.24	0.76
7	832424- Phenyl butylamine	0.8188	5.458	-5.75	-0.19
8	Amlodipine (Ca^{2+}channel blocker) (3–0-ethyl 5-0 – methyl 2- (2-aminooxyethyl)–4-(2-chlorophenyl) 6–methyl–1–4–dihydro pyridine. (complex molecule)	0.4535	5.547	-6.83	-0.48

* Convolutional Neural Network (CNN) that evaluates the quality of a given protein-ligand pose leverages the power of deep learning to evaluate protein-ligand poses more accurately

** CNN affinity score attempts to quantify the strength of the interaction, often as a binding energy (e.g., in kcal/mol)

*** The more negative the value, the more the biological activity

*** The less the intramolecular energy, the more stable the binding and the better the results

Table. 2. Results of the Molecular dynamics simulation study of the 5KMD receptor

Conformation Rank	Model ID	*Mean pLDDT	**Uniqueness	***RMSD Best
1	8	97.484	19.286	0
2	1	97.416	20.323	14.725
3	6	97.401	13.925	18.983
4	3	97.318	20.613	23.184

5	0	96.665	13.652	17.634
6	4	96.576	15.735	18.649
7	7	96.248	20.695	23.679
8	9	95.649	15.303	20.27
9	2	95.625	13.644	17.828
10	5	94.718	13.828	18.624

*Mean pLDDT (predicted Local Distance Difference Test), a higher score indicates greater confidence in the predicted local structure ** The "uniqueness" of each conformation sampled during the simulation contributes to a more comprehensive understanding of the entire binding

*** RMSD (Root Mean Square Deviation) is a critical metric used to quantify the average distance between the atoms. A lower RMSD value indicates a higher degree of similarity between the structures.

Table. 3 ADME Parameters of selected ligand

Ligand Name and I D	Log P (o/w)	Log's (Sol)	GI Observation	penetration BBB	Lipinski Violation
6834 Bromo Pheniramine	3.29	-4.13	High	Yes	0
2725 Chlorpheniramine	3.17	-3.8	High	Yes	0
167831181 3-(4-bromophenyl)–N, N–dimethyl-3- pyridin –-2-propan – 1- amine	2.77	-2.64	High	Yes	0
83242 4 – phenyl butyl amine	2.2	-2.42	High	Yes	0
2162 Amlodipine (Reference)	3.17	-3.76	High	No	0

DISCUSSION

Molecular Docking results interpretations

The molecular docking results for 8 Ligands with receptor PDB ID 5KMD revealed that they are all propyl phenylamine derivatives. The binding energy experiment has a negative value for compound (PubChem ID 6834), 3-(4-bromophenyl)-N, N-dimethyl-3-Pyridin-2-Propan-1-amine, and for compound (ID-2725), Chlorpheniramine (−7.24 kcal/mol).[19] The values are close to the reference, with a drug docked to target 5KMD: Amlodipine, an established Calcium channel blocker, at -6.83, and a CNN affinity of 5.547[20]. Amlodipine is a complex molecule compared to the ligands under test. The test results showed higher docking binding energy and greater stability than those of Amlodipine[21]. Amlodipine is a dihydropyridine derivative that binds more stably to the target (5KMD) than the phenylpropylamine derivatives under test (Table 1)[22]

Dynamic Study Analysis and Interpretation

5KMD is the crystal Structure of CavAb, which is a bacterial homotetrameric model voltage-gated Ca2+ channel in complex with amlodipine. [23]. The mean PLDDT is 97.484, representing the average Predicted Local Distance Difference Test. It runs from 0-100. It is the standard pre-residue confidence score used by AlphaFold-style predictions. Mean 97.484 is very high. The model coordinates are predicted with high confidence, and the local geometry is reliable. The backbone placement and most side chain orientations are high. It exhibits moderate uniqueness (19.3), which depends on how distinct this conformation is when compared to other models. RMSD: the root-mean-square deviation. The entry serves as the reference/Centroid for its cluster. Ten Sampled Confirmations were generated. The internal clustering geometry is cubic. The dynamic simulation study reveals that the selected model is reliable locally and accurately predicts residue positions [24]. (Table 2- 3)

CONCLUSION

The docking and dynamics simulation study of several ligands containing a propyl phenyl amino

group against the receptor target (PDB ID: 5KMD) indicates that the best predicted cardiac depressant/antihypertensive/calcium channel-blocking activity is observed for Chlorpheniramine and 3-(4-bromophenyl)–N, N–dimethyl–3–pyridin–2–propan–1–amine. Compared with Amlodipine, the reference compound, the seven selected ligands have simpler chemical structures, thereby enabling better binding characteristics. The selected ligands may block voltage-gated ion channels in myocardial cells and in the heart's blood vessels, thereby preventing calcium influx, which is necessary for excitation–contraction coupling and vascular smooth muscle contraction.[25] The ligands selected based on docking results are considered HITS and may block voltage-gated calcium channels via reported mechanisms, thereby acting as vasodilators and antihypertensive agents.[26] Further in vitro and in vivo toxicity testing, as well as preclinical and clinical trials, may be conducted to obtain approval for their use in humans. Any new or repurposed molecule established to treat a disease is a milestone in pharmacotherapeutics and the history of drug discovery

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Conflict of interest

The authors declare no conflict of interest.

Declaration of Generative AI

During the preparation of this work, the authors used AI-assisted tools for language refinement and structural modification. After using these tools, the authors reviewed and edited the content. and take full responsibility for the Content of the article.

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