iJournals: International Journal of Software & Hardware Research in Engineering
ISSN:2347-4890, ijournals.in/ijshre
Volume 13 Issue 9, September 2025

Design and in Silico Evaluation of Pseudoephedrine Derivatives with Reduced Blood-Brain Barrier Permeability

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ABSTRACT

Pseudoephedrine is a widely used sympathomimetic agent for nasal decongestion. However, its central nervous system (CNS) side effects and potential misuse in the illicit synthesis of methamphetamine have raised concerns, prompting a search for peripheral-selective analog. This study aimed to design novel pseudoephedrine derivatives that exhibit reduced blood-brain barrier (BBB) permeability while retaining biological activity, using in silico methods. In this study. Two pseudoephedrine derivatives were constructed by introducing tert-butyl (tBu) only, and both tert-butyl and phosphate at the meta position of the aromatic ring. Their physicochemical properties, pharmacokinetic profiles, and BBB permeability were predicted using SwissADME. Molecular docking was performed using the β2-adrenergic receptor (PDB ID: 2RH1) as the target to evaluate binding affinity. The derivative with both tBu and phosphate groups showed the most favorable profile, with a significantly reduced BBB permeability (as indicated by high Topological Polar Surface Area (TPSA)) and maintained comparable docking affinity to the original pseudoephedrine. TPSA, and synthetic accessibility scores supported its drug-likeness. These results demonstrate that rational functionalization of pseudoephedrine can improve pharmacokinetic selectivity by limiting CNS exposure. Although experimental validation was restricted due to regulatory limitations, this in silico study provides a promising scaffold for the development of safer sympathomimetic agents.

Keywords: Computational Chemistry, Molecular Design, Pharmacokinetics, Molecular Docking

1. INTRODUCTION

Pseudoephedrine is a widely used sympathomimetic agent, commonly employed as a nasal decongestant due to its vasoconstrictive properties. Structurally, it is a chiral phenylethanolamine closely related to ephedrine and exerts pharmacological activity through α- and β- adrenergic receptors. While it demonstrates effective peripheral action, its ability to cross the blood-brain barrier (BBB) contributes to central nervous system (CNS) effects such as insomnia, agitation, or addiction-like behaviors in sensitive individuals. More critically, pseudoephedrine has been exploited as a precursor in the illicit synthesis of methamphetamine, leading to stringent regulatory controls in many countries [1].

These regulatory restrictions have significantly limited experimental research on pseudoephedrine and its analogs, especially in high school and undergraduate laboratory environments. As a result, there is a growing need for computational approaches that can predict the pharmacokinetic and pharmacodynamic profiles of novel pseudoephedrine derivatives without relying on restricted substances.

In this study, we aim to computationally design and evaluate pseudoephedrine derivatives with reduced BBB permeability while retaining or

improving their target receptor binding affinity. To achieve this, we introduce various substituents—such as tert-butyl and phosphate groups—at the meta-position of the phenyl ring. These functional groups are hypothesized to increase polarity and topological polar surface area (TPSA), thereby impeding passive diffusion across the BBB [2].

Given the limitations of experimental access to pseudoephedrine, we adopted an entirely silico methodology, incorporating ADME prediction via SwissADME[3] and molecular docking using SwissDock[4]. Through this workflow, we assess the drug-likeness, BBB permeability, and binding affinity to the β2-adrenergic receptor (2RH1) to evaluate the potential of each derivative as a safer alternative to the parent compound.

2. METHOD

2.1 Molecule design and geometric optimization

Pseudoephedrine structure modification was conducted using Avogadro (version 1.2.0), a molecular modeling software that enables structure editing, geometry optimization, and file format export. In this study, two derivative candidates were designed and constructed for comparative analysis with the original pseudoephedrine molecule.

The first derivative involved the introduction of a bulky tert-butyl group at the met a position of the aromatic ring, intended to increase steric hindrance and potentially affect blood-brain barrier (BBB) permeability. The second derivative was designed by introducing a phosphate group at the opposite meta position of the same aromatic ring. This polar, hydrophilic functional group was selected to investigate how increased polarity and hydrogen bonding potential could alter physicochemical properties such as solubility and permeability. Each of the three structures, the original pseudoephedrine and the two modified derivatives—underwent a valency check and 3D conformation adjustment to ensure proper chemical bonding and realistic molecular geometry.

2.2 Pharmacokinetics Analysis

SwissADME (www.swissadme.ch), web-based pharmacokinetics analysis platform was used to predict physicochemical and pharmacokinetic properties of the designed molecules. Each molecule, including the parent pseudoephedrine structure and its two modified analogs, was converted into SMILES format, which served as the input for SwissADME. SMILES representation allowed seamless integration into the platform and ensured standardized structural interpretation across all compounds. For assessing potential medicinal efficacy and biopharmaceutical behavior, several key physicochemical and pharmacokinetic parameters were selected and analyzed: Topological Polar Surface Area (TPSA), Biocompatibility-related parameters (GI absorption, BBB permeability, Cytochrome P450 (CYP) inhibition potential), drug-likeness filters (Lipinski's Rule, Veber's Rule), synthetic accessibility (SA) score.

2.3 Molecular Docking Analysis

The well-known pseudoephedrine target receptor, β2- adrenergic receptor (PDB ID: 2RH1) was selected as the molecular target for docking studies, representing the adrenergic receptor subtype related to pseudoephedrine's mechanism of action. Before the docking analysis, preprocessing of receptor molecules was performed by AutoDock Tools (ADT), such as irrelevant ligand removal, addition of Gasteiger charge, inclusion of polar molecule. After preprocessing of receptor molecule, molecular docking analysis was performed by SwissDock (www.swissdock.ch), a web- based interface for docking simulations. Results were summarized with binding affinity, intermolecular energy, and intramolecular energy.

3. RESULT

3.1 Phosphate attached pseudoephedrine derivative shows lower blood brain barrier (BBB) permeability

Structure modification of pseudoephedrine was performed by introducing tert-butyl, phosphate substituents to meta position of aromatic ring. Molecular structures of each molecule are shown in Figure 1. Main objective of this molecular design is lowering BBB permeability, so bulky substituents were introduced to aromatic ring. Tert-butyl group

is one of the well-known bulky substituents and phosphate is widely used substituents for prodrug strategy in medicinal chemistry [1].

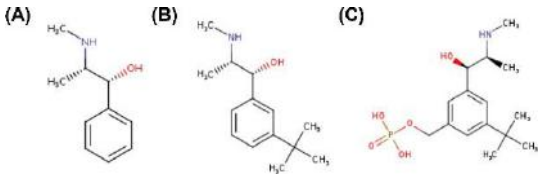

Figure 1. Designed Molecular Structure of pseudoephedrine derivatives (A) Pseudoephedrine, (B) 3-tert-butyl-pseudoephedrine, (C) 3-tert-butyl-5- phosphate-pseudoephedrine.

Following molecular design, ADME (Absorption, Distribution, Metabolism, and Excretion) property predictions were conducted using SwissADME, and the results are summarized in Table 1. Notably, the introduction of only the tert-butyl group did not significantly alter the Topological Polar Surface Area (TPSA), reflecting minimal changes in polarity.

However, in the compound where both tert-butyl and phosphate substituents were incorporated, a substantial increase in TPSA was observed. This dramatic shift indicates a pronounced change in polarity and molecular surface characteristics, which may contribute to reduced BBB permeability

Table 1. Pharmacokinetics result of various pseudoephedrine derivatives

	Pseudoephedrine	tBu-Pseudoephedrine	tBu-Phosphate-Pseudoephedrine
GI absorption	High	High	High
BBB permeant	Yes	Yes	No
TPSA	32.26	32.26	108.83
CYP2D6 inhibitor	No	Yes	No
Lipinski #violations	0	0	0
Veber #violations	0	0	0
Synthetic Accessibility	1.76	2.44	3.64

4. DISCUSSION

This study mainly aimed to modulate the central nervous system (CNS) permeability of pseudoephedrine through molecular design. First, tert-butyl group was introduced at the meta-position of the aromatic ring in order to increase steric hindrance and reduce BBB permeability however, there was not major difference in BBB permeability from original pseudoephedrine molecule. Thus, a phosphate group was incorporated as a polar substituent for enhancing hydrophilicity and preventing BBB penetration. Phosphate group is well- known hydrophilic substituent in prodrug strategy and have been widely utilized in prodrug approaches to alter pharmacokinetic properties, including CNS delivery restrictions. [5-8]

As a result of pharmacokinetics, phosphate group attached pseudoephedrine molecule dramatically increased TPSA and reduced BBB penetration ability. However, several values related to biocompatibility have not changed. This result indicates that introduction phosphate group successfully modulates physical property of pseudoephedrine without alteration of biocompatibility. Synthetic accessibility score has been increased but still in the acceptable range, indicating that this derivative is synthetically feasible from current synthetic method of medicinal chemistry. Molecular docking results with β2-adrenergic receptor shows that pseudoephedrine derivatives suggest no significant loss in binding affinity, and in fact, improved ΔG values.

3.2 Phosphate attached pseudoephedrine derivative shows higher binding affinity of 2RH1 receptor

Molecular docking simulations were carried out to investigate the binding interactions between the designed pseudoephedrine derivatives and the β_2-adrenergic receptor (PDB ID: 2RH1), which serves as a well-known target of pseudoephedrine's pharmacological activity. The docking was performed using SwissDock, a web-based platform employing the EADock DSS engine, which predicts possible binding modes and estimates binding energies based on a hybrid scoring function.

The docking results for all compounds are summarized in Table 2. Derivative which have two substituents (tert- butyl and phosphate) showed no significant difference from original pseudoephedrine molecule suggesting that there was no disadvantage of binding to receptor by introducing two substituents to aromatic ring.

Table 2. Molecular Docking Result of various pseudoephedrine derivatives

	Pseudoephedrine	tBu-Pseudoephedrine	tBu-Phosphate-Pseudoephedrine
Binding Affinity (kcal/mol)	-4.571	-4.955	-5.076
Intermolecular Energy	-5.506	-6.258	-7.598
Intramolecular Energy	-0.233	-0.523	-0.851

This study was designed to computationally evaluate pseudoephedrine derivatives for reduced BBB permeability and retain receptor binding affinity. However, there are several limitations of this experiment. First, due to the controlled nature of pseudoephedrine and its close association with the illegal synthesis of methamphetamine, direct use of this compound in laboratory synthesis and biological assays is highly restricted. Therefore, validation of this prediction results through real laboratory synthesis. Second, although molecular docking was conducted to assess binding affinity to the β2-adrenergic receptor, lack of molecular dynamics (MD) simulation result may reduce the prediction accuracy. Without MD simulations, factors such as receptor flexibility, solvation effects, and binding stability under physiological conditions remain unexamined, potentially reducing the predictive accuracy of docking results.

5. CONCLUSION

In this study, we designed and evaluated pseudoephedrine derivatives with the aim of reducing their blood-brain barrier (BBB) permeability while maintaining or improving their biological activity.
Given the regulatory restrictions associated with pseudoephedrine due to its potential use in the synthesis of methamphetamine, our investigation was conducted entirely through computational methods, including SwissADME-based pharmacokinetic profiling and molecular docking simulations against the β2-adrenergic receptor.

Among the designed analogs, the compound bearing both a tert-butyl (tBu) and phosphate substituent at the meta position of aromatic ring exhibited a significantly improved predicted BBB impermeability, while maintaining comparable docking affinity to the target receptor. This suggests the potential of such modifications in shifting the pharmacodynamic and pharmacokinetic profile of pseudoephedrine-like molecules toward peripheral selectivity, which may be beneficial in avoiding central nervous system (CNS)- related side effects.

Although our findings are promising, the lack of experimental synthesis and validation still remains as a major limitation. Additionally, the absence of molecular dynamics (MD) simulations leaves uncertainty regarding the binding stability of these molecules over time.

Nevertheless, this work demonstrates the feasibility of using in silico methods to rationally design and screen CNS-sparing analogs of existing drugs, laying the groundwork for future synthesis of structurally related, but legally accessible, lead compounds. Future studies may focus on expanding the chemical space around these derivatives, including experimental validation of structurally similar, non-regulated scaffolds that mimic the behavior of pseudoephedrine without its associated legal barriers.

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