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RESEARCH ARTICLE

In-Silico Study of Diphenhydramine and Orphenadrine to H1 and NMDA Receptors

Andrea Dhieta Utama[1*], Azura Luna Widiyanto[1], Ervin[1], Lia Elvina[1], Rachel Josephine[1], Silvania Feliecia[1], Stevanie Putri[1]

[1]Department of Pharmacy, Institut Bio Scientia Internasional Indonesia, Jakarta, Indonesia
**Corresponding author: andrea.utama@i3l.ac.id*

A B S T R A C T

Diphenhydramine and orphenadrine are both oral antihistamines but with different functional groups, which modulate their interaction with H1 and NMDA receptors, resulting in different therapeutic uses. This study investigates the comparative binding affinities of both drugs to these receptors and compares their physicochemical properties to understand structural influences on receptor interaction and potential pharmacokinetic profiles. Physicochemical properties, including Log P, pKa, and Lipinski's Rule of Five compliance, were evaluated using Swiss-ADME, and the compounds' binding affinities were screened through molecular docking using PyRx and visualized with BIOVIA Drug Discovery Studio. Results show that even though both drugs exhibit comparable affinities to the H1 receptor, orphenadrine has a slightly stronger affinity to the NMDA receptor than diphenhydramine. This interaction may explain the reason for their different therapeutic effects. Additionally, factors like Log P, pKa values, Boiled Egg analysis, and Lipinski's Rule all point to both drugs having good absorption, distribution, and oral bioavailability. These findings provide information on some of the mechanisms and pharmacokinetic factors that may differentiate diphenhydramine from orphenadrine, providing insights that may guide further empirical studies on their pharmacological effects and safety profiles.

K E Y W O R D S

Diphenhydramine, Orphenadrine, molecular docking, binding affinity, in-silico study

H I G H L I G H T S

- Diphenhydramine and orphenadrine have a comparable binding affinity toward H1 (8X5X) receptor
- Orphenadrine has a slightly higher binding affinity than diphenhydramine in NMDA (5EWL) receptor
- Orphenadrine has a higher bioavailability and a lower distribution to the brain in comparison to diphenhydramine

INTRODUCTION

Diphenhydramine (generic) or 2-(diphenylmethoxy)-N,N-dimethylethanamine belongs to the group of drugs known as antihistamines. It is commonly found in a salt form, such as diphenhydramine hydrochloride (HCl), diphenhydramine citrate, diphenhydramine salicylate in medications (Wang et al., 2017). Several brand names of diphenhydramine are Acetadryl (Aidarex Pharmaceuticals LLC), Benadryl (Pfizer), Calagel (Tec Laboratories INC), and much more (National Library of Medicine, n.d.). Diphenhydramine functions by preventing the body's natural production of histamine, which is a substance that triggers allergic reactions (American Society of Health-System Pharmacists, 2022). Diphenhydramine is used to treat runny noses brought on by hay fever, allergies, or the common cold; it also relieves red, irritated, itchy, watery eyes and sneezing. Additionally, diphenhydramine is used to relieve coughs caused by mild irritation of the airways or throat. Diphenhydramine reverses the effects of histamine on capillaries by acting as an inverse agonist at the H1 receptor, which reduces the symptoms of allergic reactions (Sicari & Zabbo, 2023). Some of the known side effects include nausea, dizziness, vomiting, constipation, and increased chest congestion (American Society of Health-System Pharmacists, 2022).

Diphenhydramine can be administered in various forms, including topical application, intramuscular or intravenous injection, as well as in tablet, capsule, or solution form. Oral administration of diphenhydramine achieves up to 80% bioavailability, with no reported age-related differences in absorption (Gelotte et al., 2018). This drug is widely distributed throughout the body, including the CNS, with a volume of distribution range of 3.3 - 6.8 L/kg. Metabolism of this drug is done by the liver into N,N-demethyl diphenhydramine, N-didesmethyl diphenhydramine, and finally diphenyl methoxy acetic acid through demethylation and oxidative deamination reactions using CYP2D6 (Rodrigues et al., 2012). Its half-life is between 3.4 and 9.2 hours, and it is eliminated in the urine where 2% is unaltered (Sicari & Zabbo, 2020). The medication takes two hours to peak in serum (Sicari & Zabbo, 2023).

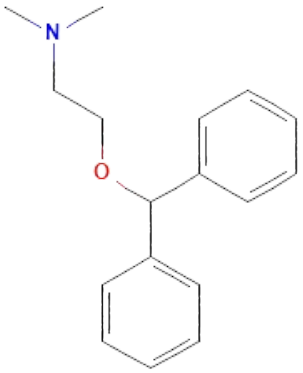


Figure 1. Chemical structure of diphenhydramine

Orphenadrine (generic) or *N*,*N*-dimethyl-2-[(2-methylphenyl)-phenylmethoxy]ethylamine is a centrally acting non-opiate analgesic and muscle relaxant. It may exhibit anticholinergic properties and modulate central pain perception. Orphenadrine is marketed under numerous brand names, including Norflex (Inova Pharmaceuticals), Banflex (Forest Pharmaceuticals), Flexoject (Merz), and many more (Cerner Multum, 2023). According to the DrugBank database, orphenadrine works by binding and inhibiting NMDA and histamine H1 receptors (Knox et al., 2024). By binding to the NMDA receptor, it alleviates the hyperkinesia and other motor abnormalities induced by neuroleptics. This effect is particularly relevant in the context of a striatal dopamine deficit, which intensifies the excitatory influence of the cholinergic system. Some side effects that could occur after administration are drowsiness, constipation, upset stomach, blurred vision, and difficulty urinating (American Society of Health-System Pharmacists, n.d.).

Orphenadrine is currently administered orally or parenterally to treat acute, painful musculoskeletal disorders ("Orphenadrine," 2012). Orphenadrine takes one hour to start working after oral administration. The onset of action occurs around five minutes after intramuscular injection and almost immediately when administered intravenously. The medication acts for four to six hours, with a plasma half-life of fourteen hours (Waldman, 2009). When administered orally, orphenadrine is rapidly absorbed in the gastrointestinal tract and exhibits high tissue retention, leading to a slow release into the bloodstream. Before it can exert its effect, orphenadrine needs to be biotransformed in the liver first into its active metabolites N-demethyl orphenadrine and N,N-didemethyl orphenadrine (Cheah et al., 2020).

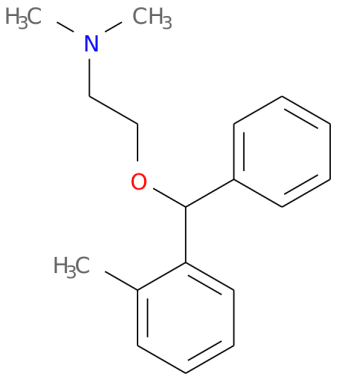


Figure 2. Chemical structure of orphenadrine

The arrangement of essential chemical functional groups within a drug's structure determines its overall configuration, enabling it to exert its intended pharmacological effects. While having different properties from diphenhydramine, orphenadrine shares a structural similarity with it (S.Al-Otaibi et al., 2022).

Molecular docking is a computational method that analyzes a molecule's orientation and conformation into the macromolecule's binding site such as RNA, DNA, enzymes, receptors, and other bigger macromolecules. Using a simulation of the small molecule's molecular interactions with the target biomolecule, the approach can reveal information about the binding location, affinity, and potential mode of action (Torres et al., 2019).

While both orphenadrine and diphenhydramine are recognized as Histamine 1 (H1) receptor antagonists, many studies on these drugs have not included a comparison of H1 receptor binding affinity between them at the molecular level. Additionally, both drugs also interact with the N-methyl-D-aspartic acid (NMDA) receptor, potentially contributing to their differing pharmacological effects and therapeutic applications. Therefore, this study aims to address the knowledge gap by examining the binding affinities of these drugs to both H1 and NMDA receptors. In addition to molecular docking, this research includes a comparison of the physicochemical properties of diphenhydramine and orphenadrine, providing insights that may guide further empirical studies on their pharmacological effects and safety profiles.

In this study, we analyze binding affinities using molecular docking methods. Structures for each compound and receptor were sourced from online databases. Each compound was docked against the H1 and NMDA receptor to compare binding affinities and determine whether binding occurs at an allosteric or orthosteric site. Furthermore, a web tool was used to calculate the physicochemical properties of each drug, providing additional insights into pharmacokinetic factors that could influence receptor binding and pharmacological effects. This comprehensive approach seeks to clarify how binding characteristics, and physicochemical properties affect the therapeutic roles and mechanisms of diphenhydramine and orphenadrine.

MATERIALS

Software

Initial analysis of the ligand was done using Swiss-ADME (http://www.swissadme.ch/index.php). PyMOL was used to remove water molecules from the protein. PyRx (Vina AutoDock) was used for the ligand-protein docking study, and BIOVIA Drug Discovery Studio version 2024 software was used to visualize and analyze the ligands and targets. The allosteric site was checked by using AllositePro (https://mdl.shsmu.edu.cn/AST/).

Preparation of Target Protein

The 3D structure of the histamine-1 (H1) receptor (8X5X) and N-methyl-D-aspartic acid (NMDA) (5EWL) receptor were retrieved from the Protein Data Bank (https://rcsb.org/). Removal of the water molecules for the NMDA receptor was done using PyMOL. Meanwhile, since the H1 protein is in apo-form, the water molecules removal was unnecessary. The protein quality was assessed by the "Structure assessment" tool by Swiss-Model (https://swissmodel.expasy.org/).

Ligand selection

The chemical structures of Diphenhydramine and Orphenadrine were downloaded in PDB format from PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/).

METHOD

Physicochemical properties

Both of the ligands were analyzed using Swiss-ADME to predict their physicochemical properties. Lipinski's Rule of Five was analyzed using this method.

Ligands Optimization

The ligands were optimized by minimizing the energy and having a stable conformation. BIOVIA Drug Discovery Studio was used to minimize and create a forcefield on the ligands. CHARMm and MMFF94 were used as forcefields. The optimized ligands were then saved as PDB.

Protein-Ligand Docking

The optimized ligands were docked by using PyRx "Vina AutoDock" feature, both protein and ligands were uploaded to the program and were analyzed using the Vina wizard. Blind docking was done as the grid box was set to "Maximize" to encase the whole protein. After obtaining the best docking conformations, mode 0 in the ligand panel was selected and saved as PDB. Data of the binding affinity in other modes was also saved as CSV data.

Protein-Ligand Visualization and Analysis

Using the BIOVIA Drug Discovery Studio, the protein/receptor file is opened, then followed by dragging and dropping the mode zero ligand to the same window. Both will be displayed in 3D. To obtain the interaction, the "Ligand Interactions" button was clicked and the interacting amino acids will appear. Once done, the 3D structure and 2D diagram were saved as PDB and PNG respectively.

Allosteric Site

The information regarding the protein allosteric site was found using AlloSitePro 2016 (https://mdl.shsmu.edu.cn/AST/). The PDB ID was inserted or a PDB file of the protein can be uploaded to the site. The ID or file was run and once finished the information was obtained and downloaded.

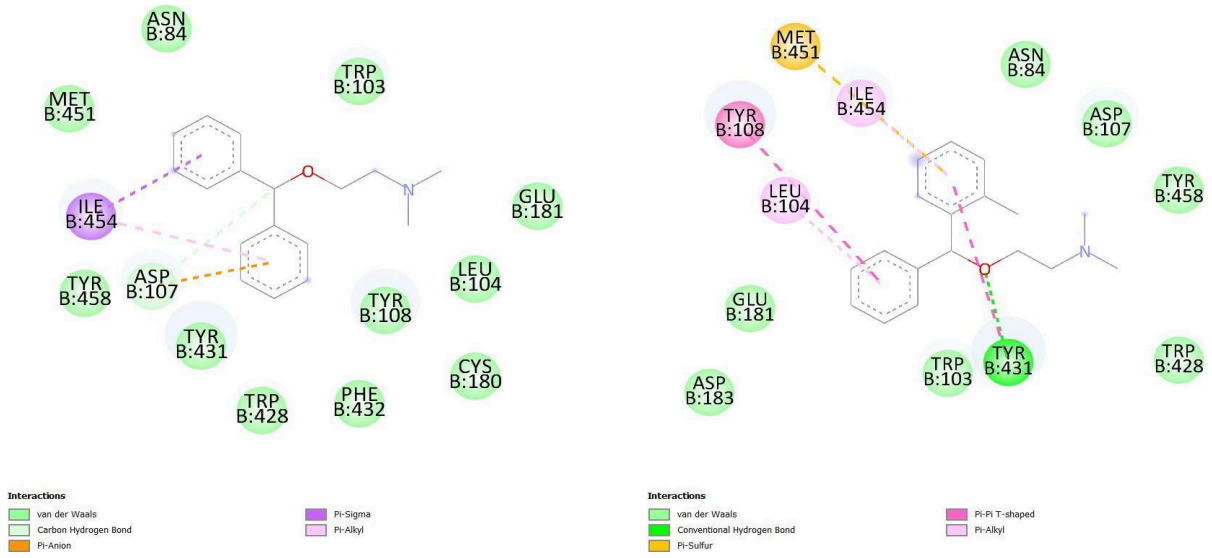
RESULT

Binding affinity

Binding affinity indicates the strength of the interaction between a ligand and its receptor. As shown in **Table 2**, the binding affinity from the best pose of diphenhydramine and orphenadrine in the H1 receptor has the same value (-6.6 kcal/mol). Whereas, in the NMDA receptor, orphenadrine has a higher binding affinity compared to diphenhydramine with the value of -6.6 kcal/mol and -6.4 kcal/mol respectively.

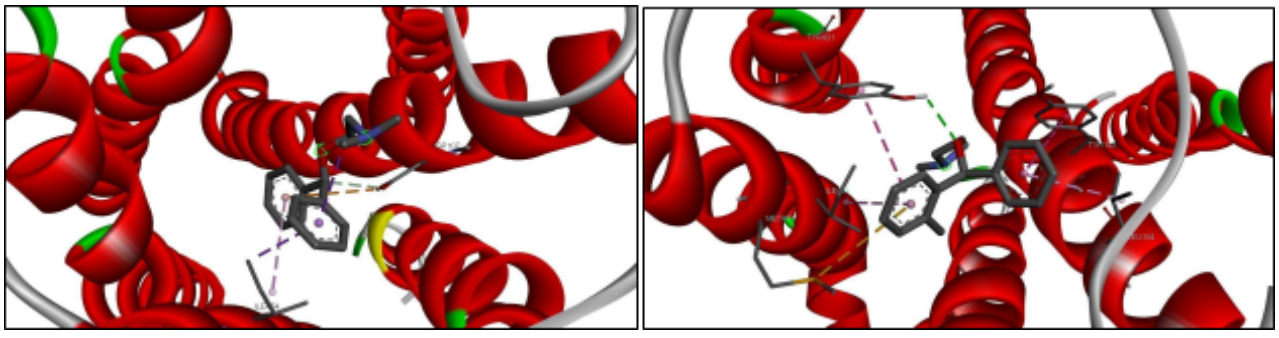
Table 1. Binding affinity of diphenhydramine and orphenadrine to 8X5X (H1) and 5EWL (NMDA) receptor.

Receptor	Binding Affinity Diphenhydramine (kcal/mol)	Binding Affinity Orphenadrine (kcal/mol)
8X5X (H1)	-6.6	-6.6
5EWL (NMDA)	-6.4	-6.6



(A) (B)

Figure 3. 2D model interaction between diphenhydramine **(A)** and orphenadrine **(B)** with histamine 1 receptor

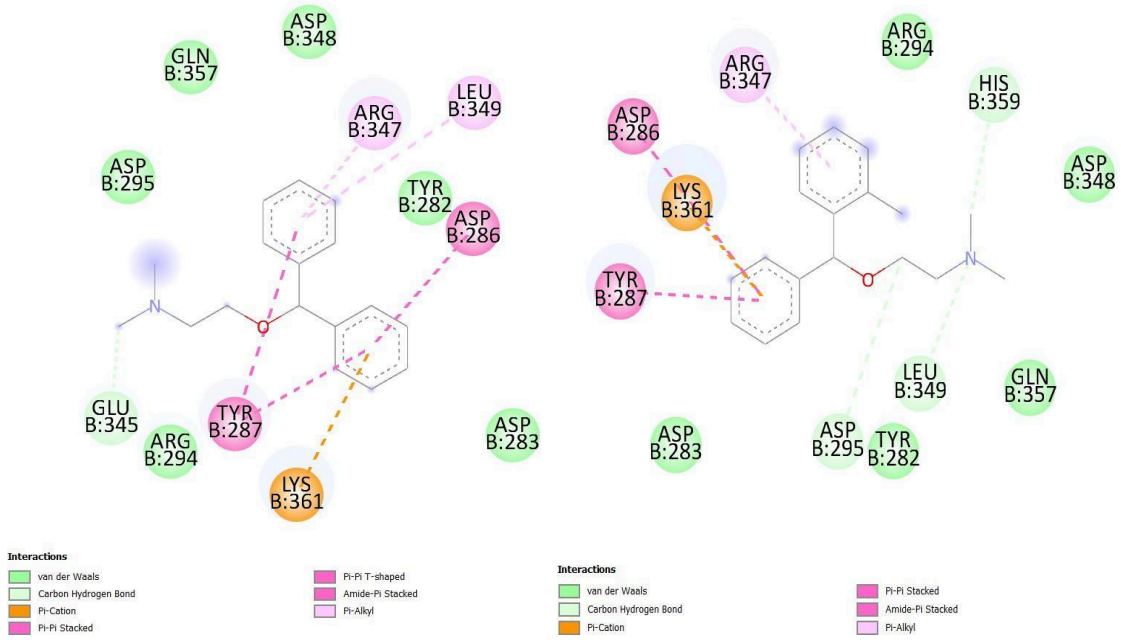


(A) (B)

Figure 4. 3D model interaction between diphenhydramine **(A)** and orphenadrine **(B)** with histamine 1 receptor

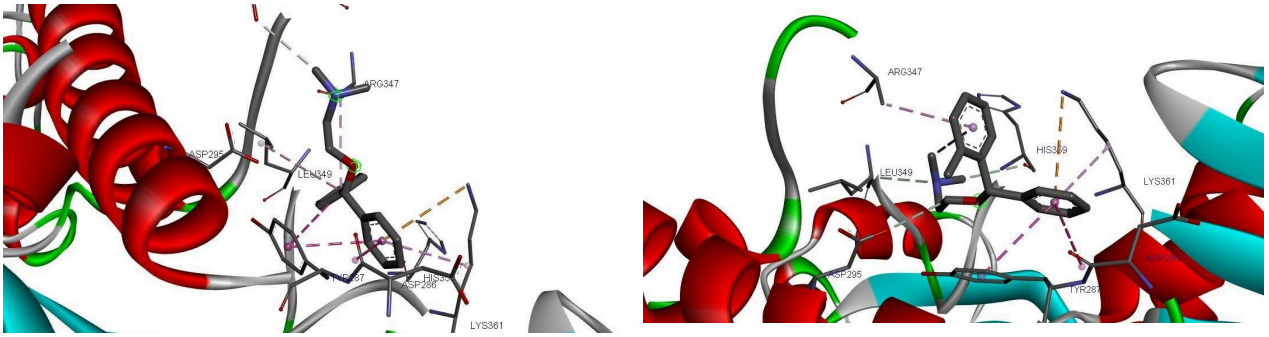
The ligand-protein interaction of diphenhydramine and orphenadrine with the H-1 receptor is presented in the 2D and 3D models (**Figures 2 and 3** respectively). The benzene rings of diphenhydramine

interacted with two amino acids, which are isoleucine (ILE, B:454) and aspartic acid (ASP, B:107). Meanwhile, the benzene rings of orphenadrine interacted with five amino acids which include tyrosine (TYR, B:108; B:431), leucine (LEU, B:104), isoleucine (ILE, B:454), and methionine (MET, B:415).



(A) (B)

Figure 5. 2D model interaction between diphenhydramine **(A)** and orphenadrine **(B)** with NMDA receptor



(A) (B)

Figure 6. 3D model interaction between diphenhydramine **(A)** and orphenadrine **(B)** with NMDA receptor

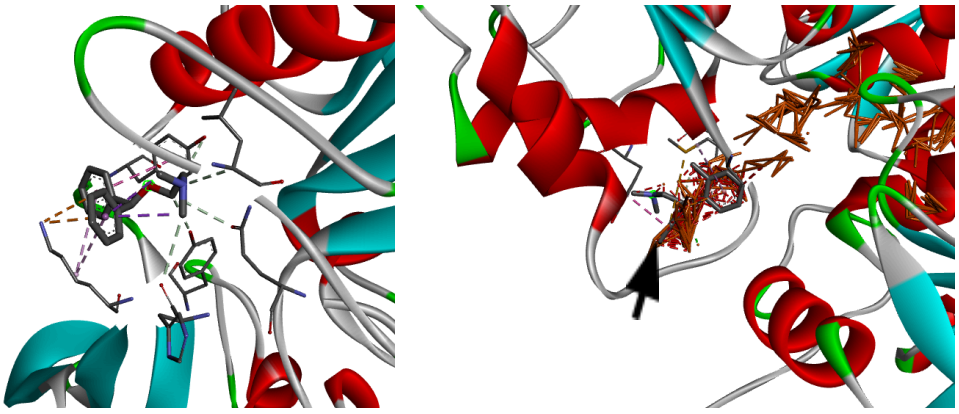
The ligand-protein interaction of diphenhydramine and orphenadrine with the NMDA receptor in the 2D and 3D models are presented in **Figures 4 and 5**. The benzene rings of diphenhydramine interacted with five amino acids, which are aspartic acid (ASP, B: 286), tyrosine (TYR, B:287), arginine (ARG, B:347), leucine (LEU, B:349), and lysine (LYS, B: 361). Meanwhile, the benzene rings of orphenadrine interacted with four amino acids which include arginine (ARG, B: 347), aspartic acid (ASP, B:286), and tyrosine (TYR, B:387). The carbon (alkyl group) interacts with aspartic acid (ASP, B: 295) while the carbon (N-methyl) interacts with histidine (HIS, B: 359). Lastly, the amine interacts with leucine (LEU, B:349).

Allosteric site

There are two categories of antagonists: competitive and non-competitive. While competitive antagonists compete with agonists for binding at the active site, Non-competitive antagonists bind to

allosteric regions (Salahudeen & Nishtala, 2017). Using an online tool for allosteric site prediction, we investigated the receptors' allosteric sites and visualized them with the best-posed ligand from our molecular docking to ascertain the binding locations of our ligands.

Our findings indicated that the H1 receptor's 8x5x allosteric site was absent. As a result, orphenadrine and diphenhydramine bonded to the active site of the H1 receptor. On the other hand, the NMDA receptor (5EWL) was shown to have three allosteric pockets. Orphenadrine bonded to the NMDA receptor at an allosteric location and diphenhydramine at the active site (**Figure 6**), according to the visualization.



(A) (B)

Figure 7. 3D model interaction of diphenhydramine with the active site of NMDA receptor **(A)**; and orphenadrine **(B)** with the allosteric site of NMDA receptor (arrow points to allosteric pocket (bronze area))

Physicochemical Properties

Log P is a crucial metric that establishes how well a medication will be made and dosed in addition to determining how well it will be absorbed, transported, and dispersed throughout the body (Morak-Młodawska et al., 2023). According to the data from **Table 1**, diphenhydramine and orphenadrine have log P values of 3.22 and 3.58, respectively, indicating moderate lipophilicity, which facilitates their permeability across lipid membranes in the body. Additionally, pKa values are used to predict a drug's ionization status; drugs with lower pKa values are more acidic. Diphenhydramine and orphenadrine have pKa values of 9.00 and 8.87, respectively, suggesting that both are largely unionized at physiological pH, which can enhance membrane permeation and bioavailability.

The Boiled Egg analysis further evaluates a drug's potential for brain and intestinal permeation by analyzing its lipophilicity and polarity. As shown in **Figure 1** and **Table 1**, both diphenhydramine and orphenadrine fall within the yellow region of the Boiled Egg model, which predicts good permeability through the blood-brain barrier (BBB) and likely distribution in the central nervous system. This property is significant given the therapeutic roles of both drugs, which may benefit from CNS penetration.

Lipinski's Rule of Five is a well-established framework for predicting a drug's ADME (absorption, distribution, metabolism, and excretion) properties, particularly for orally administered drugs (Karami et al., 2022). This rule suggests that compounds with Log P ≤ 5, molecular weight ≤ 500 Da, hydrogen bond acceptors (HBA) ≤ 10, and hydrogen bond donors (HBD) ≤ 5 are more likely to be orally bioavailable(Kralj et al., 2023). **Table 1** shows that diphenhydramine has a molecular weight of 255.35 g/mol, no hydrogen bond donors, fewer than 10 hydrogen bond acceptors, and a Log P below 5, all indicating good oral absorption potential. Similarly, orphenadrine meets all Lipinski's criteria, with a molecular weight of 269.38 g/mol, comparable hydrogen bond characteristics, and a slightly higher Log P of 3.58, supporting its suitability for oral administration as well.

In summary, the Log P, pKa values, Boiled Egg analysis, and Lipinski's Rule of Five collectively provide a comprehensive view of the pharmacokinetic properties of diphenhydramine and orphenadrine, highlighting their favorable profiles for absorption, distribution, and especially oral bioavailability.

Table 2. Physicochemical properties comparison of diphenhydramine and orphenadrine

Physicochemical Properties		Diphenhydramine	Orphenadrine
Log P		3.22	3.58
pKa		9.00	8.87
Boiled egg analysis		Yellow	Yellow
Lipinski's rule of 5	Molecular weight	255.35 g/mol	269.38 g/mol
	Hydrogen bond donor (HBD)	0	0
	Hydrogen bond acceptor	2	2
	Lipinski's rule of 5 (violations)	0	0

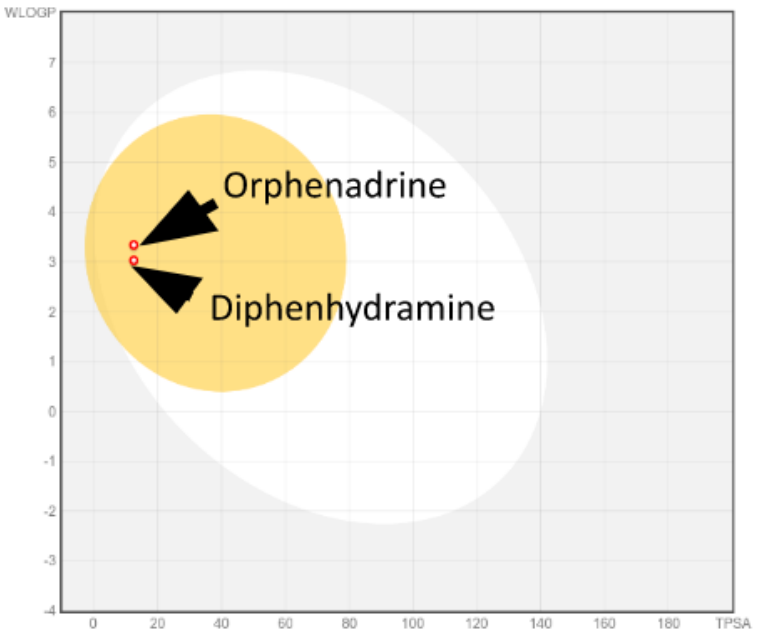


Figure 8. BOILED-Egg model of diphenhydramine and orphenadrine

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DISCUSSION

The H1 receptor belongs to the big superfamily of G protein-coupled receptors (GPCRs) and participates in physiological regulation of histamine and other neurotransmitters in the Central Nervous System (Obara et al., 2020). There are four main types of histamine receptors: H1, H2, H3, and H4. Each type has different mechanisms of action and functions. Stimulation of H1 receptor causes contraction of smooth muscle, increased vascular permeability, and stimulation of sensory nerve endings.

H1 antagonists, known as antihistamines, are commonly used in the relief of symptoms associated with allergies and allergic reactions (Obara et al., 2020). These agents act by binding to the orthosteric site of the H1 receptor, thus blocking histamine from binding and subsequently activating the receptor (Baroody & Naclerio, 2000). As shown in **Table 1**, Docking results for both diphenhydramine and orphenadrine on the H1 receptor (8X5X) yielded the same binding affinity of -6.6 kcal/mol at the orthosteric site as expected.

NMDA-type glutamate receptors are ligand-gated ion channels that represent a major class involved in excitatory neurotransmission in the central nervous system (Hansen et al., 2017). Dysregulation in NMDA receptor (NMDAR) function has been implicated in numerous neurological conditions, such as epilepsy, seizures, stroke, traumatic brain injury, Alzheimer's disease, Huntington's disease, and neuropathic pain, as well as in neuropsychiatric disorders (e.g., depression, schizophrenia, addiction, and anxiety) and neurodevelopmental disorders (e.g., autism) (Hansen et al., 2021; Paoletti et al., 2013; Salimando et al., 2020; Traynelis et al., 2010). From **Table 2**, orphenadrine has a slightly higher binding affinity, with a score of -6.6 kcal/mol compared to diphenhydramine's -6.4 kcal/mol. This suggests that orphenadrine may bind more favorably and stably to the receptor, potentially resulting in a stronger pharmacological effect (Hossen et al., 2024; Salahudeen & Nishtala, 2017).

Orphenadrine binding to the allosteric site is consistent with its known function as a non-competitive NMDA receptor inhibitor (Kornhuber et al., 1995). The binding to the NMDA receptors likely contributes to orphenadrine's muscle relaxation and pain relief by orphenadrine, since the activation of the receptors is associated with hyperalgesia (Liu et al., 2022). Binding to the allosteric site enables the antagonist to induce conformational changes in the receptor, which may inhibit its activity or affect agonist binding at the active site (Abdel-Magid, 2015). This type of binding often results in non-competitive inhibition, where the antagonist modulates receptor activity independently of the agonist concentration. Such a mechanism allows a more subtle approach to regulating receptor function and is potentially advantageous because it changes receptor behavior without directly competing with agonists at the active site (Nickols & Conn, 2014).

In contrast, diphenhydramine, despite being expected to bind at the allosteric site, did not show this result in the docking study. This could be explained by the limitations of docking using static models of receptors. These results suggest that receptor dynamics in a physiological environment may enable diphenhydramine to bind to other or transient binding sites that were not detected in our initial docking screen (Gioia et al., 2017). To address this, further investigation through dynamic simulation techniques, such as molecular dynamics, may provide deeper insight into how structural flexibility within the NMDA receptor may enable binding modes not apparent in static models (De Vivo et al., 2016). This approach could clarify the non-competitive binding behavior of diphenhydramine observed in experimental studies.

Although diphenhydramine and orphenadrine are structurally similar, they interact with receptors in distinct ways. Small modifications in functional groups, such as the addition of a methyl group, can

significantly impact drug-receptor interactions. In fact, adding a methyl group to diphenhydramine converts it to orphenadrine, altering how the molecule binds and orients itself on the receptor. As shown in **Figure 5**, diphenhydramine and orphenadrine engage different amino acids within the same receptor site, each taking on a unique binding position. These differences are thought to lead to variations in the effects each drug has on the receptor (Salahudeen & Nishtala, 2017).

One of the approaches used in drug design is changing the functional groups of a known drug in order to alter its properties (Price & Patel, 2023). Drug absorption, or bioavailability, is highly affected by properties such as polarity and pKa, so functional group modifications are an important tool in shifting absorption rates. For instance, the addition of methyl groups results in orphenadrine, a more non-polar and lipophilic compound. This change in polarity increases the absorption of orphenadrine, making its bioavailability roughly 90%, compared to 40-60% for diphenhydramine (Knox et al., 2024).

The addition of a functional group can also affect how a drug is distributed in the body. The boiled egg analysis shows lipophilicity-based prediction of blood-brain barrier permeability, placing both diphenhydramine and orphenadrine into the 'yellow area' that suggests a potential for passive diffusion (Zafar et al., 2020). However, the extra methyl group in orphenadrine increased the molecular size and changed its interaction with the transporters of the blood-brain barrier, which may have reduced its brain distribution compared to diphenhydramine (Pandit et al., 2020; Salahudeen & Nishtala, 2017). Another predictor, ADMESAR, shows that diphenhydramine is more likely to cross the BBB than orphenadrine, as it exhibits predicted ADMET feature scores of 0.9381 for diphenhydramine and 0.9134 for orphenadrine (Knox et al., 2024). This score suggests that orphenadrine has a weaker sedative effect compared to diphenhydramine (Meleger, 2006).

Pharmacodynamic and pharmacokinetic properties are strongly correlated with lipophilicity, a parameter often regarded as the key measure in estimating the potential biological activity of drug candidates. Lipophilicity is defined by the logarithmic n-octanol-water partition coefficient (log P) of a molecule. That parameter has been widely applied in research on the quantitative structure-biological activity relationship (Morak-Młodawska et al., 2023). Compounds with log P values exceeding 5 tend to accumulate in tissues, exhibit rapid metabolic turnover, bind strongly to plasma proteins, or demonstrate poor water solubility, as observed in the results of this study (Morak-Młodawska et al., 2023).

Another important physicochemical factor is the acid-base dissociation constant of a drug, pKa, which in many cases exerts marked effects on many biopharmaceutical properties. The pKa is simply the negative base-10 logarithm of the dissociation constant of an acid solution (Ka) (Manallack, 2007). It shows an indication that when the pH environment is equal to pKa, half of the drug is ionized and the other half is unionized. Every drug has a specific pKa that influences the rate of absorption and its renal excretion (Manjooran, 2020). This study highlights the unique pKa values for diphenhydramine (9.00) and orphenadrine (8.87). These findings align with previous studies confirming diphenhydramine's pKa (Albishri et al., 2022) and orphenadrine’s value of approximately 8.91 (Sangster, 1994).

Two primary factors influence the pKa distributions of drugs: the types and prevalence of functional groups commonly found in drugs and the specific biological targets these compounds are designed to interact with (Manallack, 2007). The relatively high values of pKa for both diphenhydramine and orphenadrine show that absorption will occur more in basic environments such as the intestine.

This study demonstrates the in silico investigation of molecular docking and pharmacokinetic parameter prediction for diphenhydramine and orphenadrine. The two compounds showed almost identical affinities for the H1 receptors, but orphenadrine showed a slightly higher affinity for the NMDA receptors, indicating a difference in pharmacological effects due to structural modifications. Structural modification has a striking impact on drug-receptor interactions and bioavailability, and the trend of findings was that diphenhydramine can easily cross the blood-brain barrier compared with orphenadrine. The present study has some limitations: the docking models are static and can not fully explain the dynamic interactions

between these drugs and their receptors. The Vina AutoDock method utilized in this study was only partially flexible, allowing flexibility solely for the ligand (Fadlan & Nusantoro, 2021). Biological systems are complex, and it is hard to accurately emulate this complexity using computational models (Puniya et al., 2024). Le et al. (2024) suggest that incorporating flexibility in both the protein and ligands during docking simulations can better represent the system's dynamic nature (T.T. Le et al., 2024). Adopting fully flexible docking methods could enhance predictive accuracy and pose estimation, achieving improvements of 80-95% (Lexa & Carlson, 2012). Additionally, future research should aim to validate these findings through in vitro and in vivo models to provide a more comprehensive understanding of the pharmacological properties and therapeutic potential of these compounds.

CONCLUSION

The pharmacological differences between orphenadrine and diphenhydramine as oral medications are elucidated through their binding affinities to the H1 receptor. The present study found a similar affinity for both compounds, corresponding to previously reported antihistaminic activities. Meanwhile, orphenadrine has a higher affinity for the NMDA receptor than diphenhydramine, suggesting that the different binding affinity of the NMDA receptor could be one reason for the different pharmacological actions. Knowledge of these affinities can help optimize therapeutic use, pointing out benefits, risks, and mechanisms of action for each drug. In addition, the structural differences between both drugs could also explain the difference in absorption, distribution, and pharmacological effects. However, the study is quite constrained by being based solely on an in silico docking calculation that cannot mimic the exact complexities of a real biological system. To overcome these limitations, future research should focus on experimental validation of in silico findings and expand into in vitro and in vivo investigations, including molecular dynamics, in order to fill the gaps identified by this investigation.

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