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In silico screening of FDA-approved drugs for antiviral activity against the influenza virus: a novel approach to the repurposing of existing medications

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ABSTRACT

This study investigated the efficacy of FDA-recognized compounds in preventing influenza virus infections, using *in silico* analysis. By focusing on the structural characteristics of neuraminidase (a key target in antiviral therapy), the study identified 12 critical regions amenable to drug interaction. Among the evaluated compounds, lysine emerged as the most promising candidate, exhibiting an XP GScore of -9.912 and relatively high binding affinity. Molecular docking simulations revealed that lysine engages essential amino acid residues within the neuraminidase active site through hydrogen bonding and salt-bridge formation, thereby supporting its potential to inhibit viral replication. Other compounds, including iohexol and capastat, also demonstrated notably high binding constants. These findings underscore the feasibility of drug repurposing, particularly involving known dietary supplements such as lysine, as a strategic response to emerging antiviral resistance, severe influenza cases, and seasonal outbreaks. The results provide a preliminary experimental framework to guide future studies and support the clinical deployment of these agents against influenza and related infections.

1. Introduction

Influenza viruses are a major cause of respiratory illness, affecting an estimated 1 billion individuals annually worldwide. According to the

PHARMAKEFTIKI, 37, 2S, 2025 | 259-263

World Health Organization (WHO), influenza-related respiratory infections result in approximately 3–5 million cases of severe illness and 290,000 to 650,000 deaths each year[1]. The disease burden is especially pronounced among vulnerable populations – namely young children and the elderly – where complications often lead to significant morbidity and mortality. The rapid transmission of the virus in densely populated environments underscores the urgent need for effective antiviral therapies[2].

Current therapeutic options primarily consist of neuraminidase and M2 protein inhibitors, which have demonstrated efficacy, but are increasingly compromised by the emergence of drug-resistant viral strains[3]. In recent years, *in silico* approaches have gained recognition as powerful tools in drug discovery and repurposing. These computational strategies enable researchers to simulate molecular interactions and assess the antiviral potential of FDA-approved compounds against influenza viruses. Crucially, by leveraging existing safety and pharmacokinetic profiles, such methods can accelerate the identification of viable treatment candidates[4].

Among these candidates is lysine, an essential amino acid with known antiviral activity. Preliminary studies suggest that lysine may disrupt viral replication by interfering with the functional role of arginine in viral propagation[5]. This study aimed at evaluating the antiviral properties of FDA-approved drugs through *in silico* screening, with particular emphasis on lysine's potential as a repurposed therapeutic agent against influenza virus infection.

2. Methodology

2.1. Ligand preparation

A total of 1,379 FDA-approved drugs were included in the analysis. Three-dimensional (3D) molecular structures were retrieved from the ZINC15 database (https://zinc20.docking.org/substances/subsets/fda/). Ligand preparation was executed using the GLIDE suite within the Schrödinger software (Maestro v. 12.8.117). Partial atomic charges were assigned using the Optimized Potentials for Liquid Simulation 4 (OPLS4) force field. For each compound, the default number of low-energy conformers was generated at pH 7.0, while compounds containing more than 1,000 atoms were excluded in order to ensure computational tractability.

2.2. Protein preparation

The neuraminidase protein structure (PDB ID: 3CL0) was obtained from the Protein Data Bank. Structural refinement was performed using the Protein Preparation Wizard in GLIDE, which involved bond correction, addition of hydrogen atoms, and energy minimization under standard conditions (pH 7.0), utilizing the OPLS4 force field with a root-mean-square deviation (RMSD) cutoff of 0.30 Å.

2.3. Docking protocol

Molecular docking simulations were carried out with GLIDE in order to evaluate the binding interactions between the ligands and neuraminidase protein. The active site was defined based on previously characterized residues essential for ligand binding: Arg118, Arg152, Arg156, Arg224, Arg292, Asp151, Glu425, Glu276, Glu277, Arg371, Glu119, and Glu22. The docking protocol aimed at predicting the binding compatibility of each ligand with these target residues.

2.4. Binding affinity prediction

Binding affinity was quantified using the XP GScore metric provided by GLIDE. This score integrates various molecular interaction parameters (including hydrogen bonding, electrostatic forces, and steric fit) in order to estimate ligand-protein binding strength. Lower GScores correspond to stronger predicted affinities.

2.5. Analysis of docking results

Docking outcomes were assessed in order to identify lead compounds demonstrating high-affinity

PHARMAKEFTIKI, 37, 2S, 2025 | 259-263

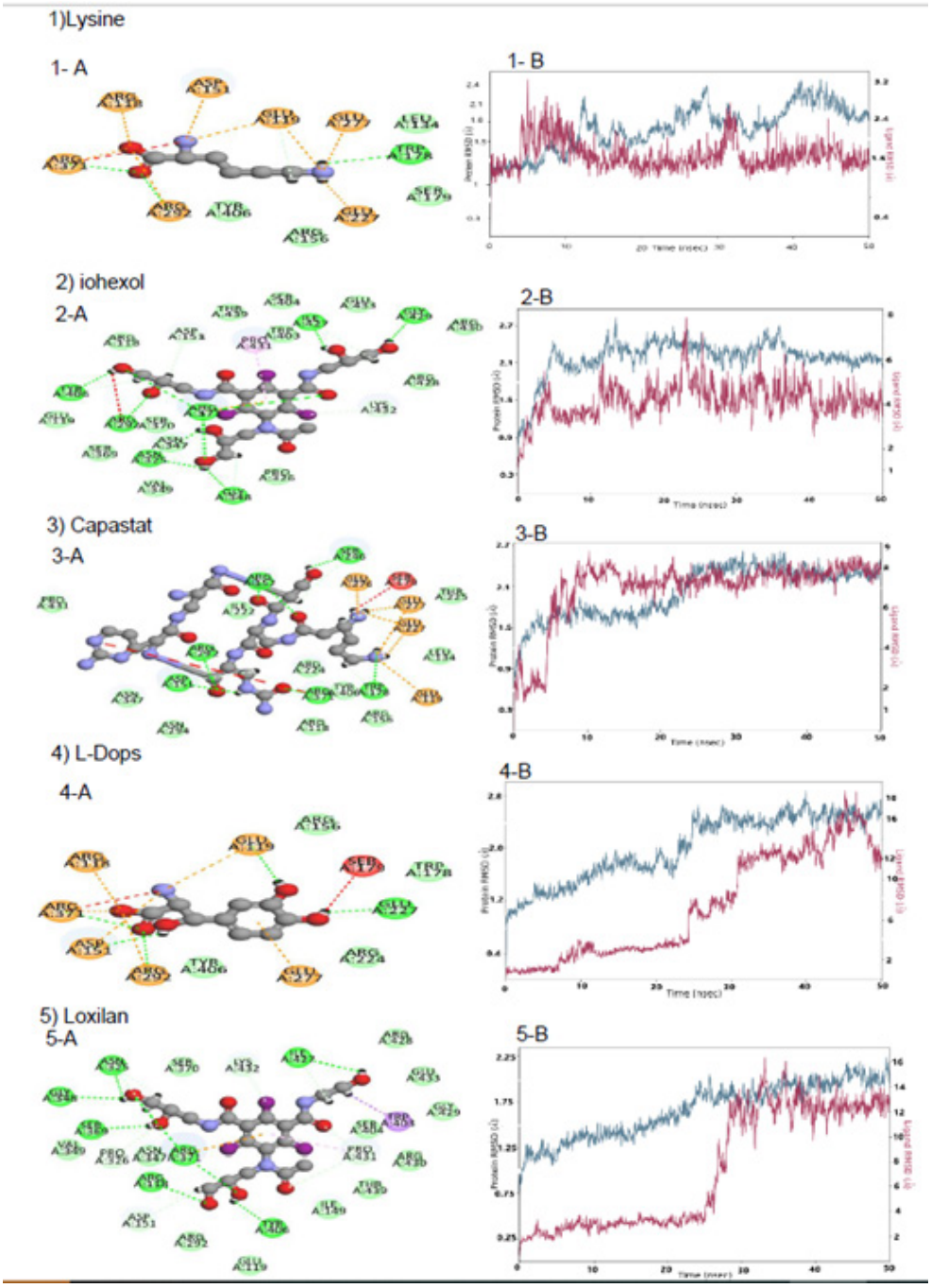

Figure 1. *Molecular docking and binding affinity analysis of five selected compounds: lysine (1), iohexol (2), capastat (3), L-DOPS (4), and loxilan (5). The left panels (A) present 2D diagrams of ligand–protein interactions, highlighting key hydrogen bonds and salt bridges. The right panels (B) displays root-mean-square deviation (RMSD) trajectories from molecular dynamics simulations, reflecting the structural stability of each ligand–protein complex over time.*

PHARMAKEFTIKI, 37, 2S, 2025 | 259-263

interactions with neuraminidase. Ligand-protein interactions were visualized by using Discovery Studio V20.1 (BIOVIA, Dassault Systèmes), focusing on conventional hydrogen bonds, salt bridges, and unfavourable contacts for each complex.

3. Results and Discussion

The *in silico* screening of FDA-approved compounds for anti-influenza activity has identified several promising candidates, most notably lysine[5]. Docking simulations have revealed robust binding affinities between these compounds and neuraminidase, specifically for those targeting its catalytic site[3].

Lysine has ranked highest among candidates, with an XP GScore of -9.912, thereby signifying strong predicted affinity for neuraminidase (PDB ID: 3CL0). It has formed conventional hydrogen bonds with Trp178, Arg292, and Arg371, as well as salt bridges with Glu227 and Arg118 (Figure 1.1)[6]. Additional attractive interactions with Glu119 and Asp151 have further reinforced lysine's therapeutic potential. Lysine's historical role as a dietary supplement in managing the herpes simplex virus (HSV) suggests a mechanistic crossover relevant to influenza[7]. By antagonizing the arginine-dependent replication pathways, lysine may disrupt the influenza viral life cycle; a strategy compounded by its established safety profile and clinical accessibility.

Beyond lysine, several other drugs have demonstrated strong binding affinities: (i) iohexol has exhibited an XP GScore of -10.908 and extensive hydrogen-bonding interactions with Gly429 and Arg371 (10 conventional hydrogen bonds; Figure 1.2)[8], (ii) capastat has yielded an XP GScore of -10.271, forming hydrogen bonds and salt bridges with Ser246 and Arg152, thereby potentially interfering with neuraminidase enzymatic activity and reducing viral release (Figure 1.3)[9], and (iii) L-DOPS and loxilan have scored -10.326 and -10.345, respectively, by engaging key residues including Arg292 and Arg371 *via* both hydrogen bonds and salt bridges (Figures 1.4–1.5)[10]. These compounds appear to exert antiviral effects by mimicking the binding of sialic acid to neuraminidase, thereby blocking its enzymatic function. Given neuraminidase's role in facilitating the release of progeny virions from infected cells, its inhibition presents a compelling strategy to curtail viral dissemination[9].

Collectively, these findings support the clinical repurposing of FDA-approved agents to combat influenza. The use of pharmacologically characterized compounds expedites therapeutic deployment, especially in the face of seasonal outbreaks and evolving viral strains[2]. Coupled with computational screening, this approach offers a scalable and responsive framework for antiviral drug development[4]. Targeting vulnerable populations remains an urgent priority, and this study contributes a rationale for broadening the therapeutic arsenal against influenza. Further experimental validation (including the undertaking of *in vitro* and *in vivo* assays) is essential in order to substantiate these predictions. Moreover, investigating combination therapies may reveal synergistic effects capable of enhancing antiviral efficacy.

4. Conclusion

The herein undertaken *in silico* docking analysis of FDA-approved compounds identified lysine and several other agents as promising inhibitors of influenza neuraminidase. These findings support the strategic repurposing of well-characterized drugs in order to mitigate influenza viral replication and transmission.

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Conflicts of interest

None exist.

PHARMAKEFTIKI, 37, 2S, 2025 | 259-263

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