Annals of
Biotechnology and Biomedical Science

Research Article

Molecular Docking Studies of Compounds Containing Acyl Groups are Conducted to Investigate Antiviral Activity within the Framework of Drug Repurposing

Thomas Kurian*

Government Medical College, India.

Submission: June 15, 2025; Published: June 24, 2025

***Corresponding author:** Thomas Kurian, Associate Professor at the College of Pharmacy, Government Medical College, Alappuzha, Kerala, India.

ABSTRACT

Ten chemical compounds, including existing drugs with acyl groups, were tested in silico using PyRX docking and MZ DOCK. The ligands were docked onto the receptor associated with the retroviral disease; HIV-1 protease mutant bound to Indinavir. Indinavir served as the standard drug for method validation. The promising candidates selected for further studies included 4-[(1-benzyl-4-chloro-2,5-dioxopyrrol-3-yl)amino]-N-(5-chloro-2-methoxyphenyl)benzamide (-8.6 PyRX, -9.7 MZ dock), melatonina (-7.9 PyRX, -7.9 MZ dock), 1-[(E)-[5-(4-nitrophenyl)furan-2-ylmethylidene amino imidazolidine-2,4-dione] (-9.0 PyRX, -8.3 MZ dock), 5-[(2-chlorophenyl)methylidene]-3-phenylimidazolidine-2,4-dione (-7.6 PyRX, -7.8 MZ dock), and simvastatin (-9.1 PyRX, -8.9 MZ dock), based on a comparison to Indinavir (-10.5 PyRX, -10.9 MZ dock). The Swiss-ADME parameters were deemed satisfactory, and the Lipinski rule was followed. Acyl compounds have been widely used in drug development for viral diseases. Further pharmacological, structure-activity relationship (SAR), and synthetic studies are essential to clarify their therapeutic potential and confirm their effectiveness in combating retroviral diseases, thereby advancing the search for life-saving treatments in medicinal chemistry.

KEYWORDS

Antiviral, PyRX, Acyl, MZ Dock, Validation

Citation: Thomas Kurian (2025) Molecular Docking Studies of Compounds Containing Acyl Groups are Conducted to Investigate Antiviral Activity within the Framework of Drug Repurposing. Ann Biotech & Biomed Sci 1(1): 1-7.

INTRODUCTION

The urgent need to find new and efficient treatment agents stems from the serious health problems that retroviral illnesses, especially those brought on by HIV-1 protease [1] mutations, continue to pose. Compounds with acyl groups have attracted much interest in medicinal chemistry's continuous search for life-saving therapies due to their potential to create drugs that combat viral infections. By using in-silico docking techniques, specifically PyRX and MZ DOCK, to assess the binding affinities of ten chemical compounds, including currently available medications, against the HIV-1 protease mutant linked to Indinavir, this study sought to uncover promising therapeutic candidates [2,3]. The preferred orientation of the ligand when bound to the receptor (HIV-1 protease mutant) was computationally predicted using MZ DOCK, another molecular docking program, and PyRX, a virtual screening tool. This procedure aids in determining the degree of the ligand-receptor non-covalent interaction, which is frequently represented as binding affinity scores and is a critical determinant of a compound's possible therapeutic effectiveness [4].

MATERIALS AND METHODS

A computer with an i7 processor installed, BIOVIA Discovery Studio (DS) Visualizer, PyRX 0. 8 free versions, and MZ dock software are among the applications used. Additionally, the study used web resources such as Swiss ADME, Protein Data Bank (RCSB PDB), and the NCBI PubChem database [5].

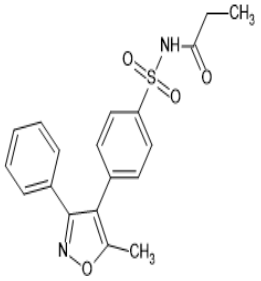
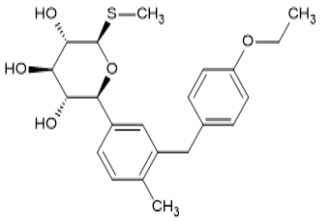
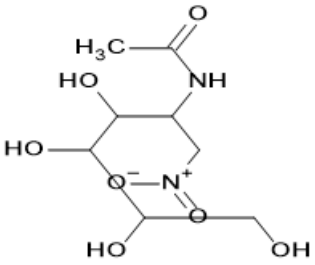
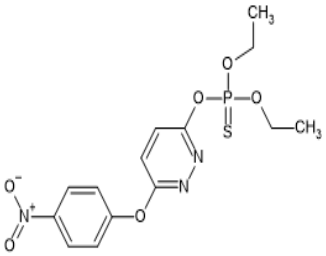
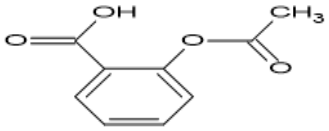
MZ-DOCK

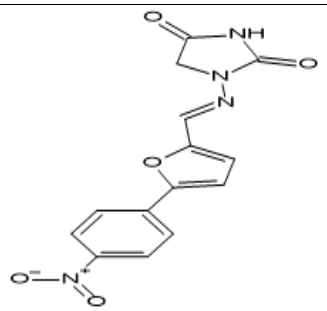
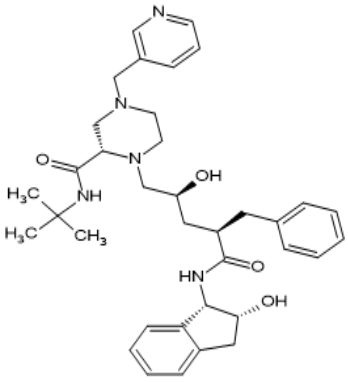
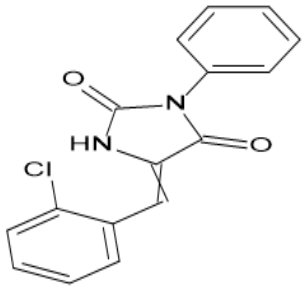
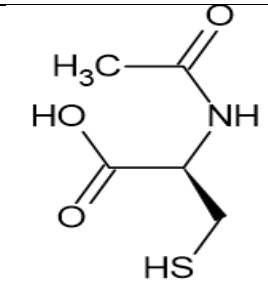
This new GUI-based pipeline for the Windows operating system aims to simplify molecular docking and enhance its repeatability, particularly for beginners. Alongside batch scripts and Python, MZ DOCK offers several valuable features, including co-crystallized ligand-based binding site configuration, enantiomer generation from SMILES input, energy minimization using various force fields (MMFF94, MMFF94s, UFF, GAFF, Ghemical), retention of selectable ions and cofactors, support for multiple input file formats (SMILES, PDB, SDF, Mol2, Mol), sidechain flexibility of selectable binding site residues, and generation of reports and images for interactive visualization [6].

PyRX

PyRX 0.8 (https://pyrx.sourceforge.io/; https://sourceforge.net/projects/pyrx/) is an easy-to-use and multi-OS-compatible version. For seamless DBVS, this tool combines several open-source applications, including AutoDock Vina, AutoDock, and Open Babel. To identify potential compounds for analysis in a lab [7]

RESULTS

Ligands (8-15) Name And (Pub Chem.Id)	Chemical Structure Chem Sketch	Binding Energy Pyrx (Ad Vina)	Binding Energy Mz Dock (Ad Vinardo)	RMSD/Ub
4-[(1-benzyl-4-chloro-2,5-dioxopyrrol-3-yl) amino]-*N*-(5-chloro-2-methoxyphenyl) benzamide (1194964)		-8.6	-9.7	0
(2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-6-methylsulfanyloxane-3,4,5-triol (24831714) SOTAGLIFLOZIN		-7.9	7.9	0
N-(3,4,5,6-tetrahydroxy-1-nitrohexan-2-yl) acetamide (536755)		-5.3	-5.5	0
(198311) diethoxy-[6-(4-nitro phenoxy)pyridazin-3-yl]oxy-sulfanylidene-lambda5-phosphane		-5.2	-6.6	0
2- acetyloxy benzoic acid (2244)		-5.8	-7.8	0

1-[(E)-[5-(4-nitrophenyl)furan-2-yl]methylideneamino]imidazolidine-2,4-dione (6914273) Dantrolene		-9	-8.3	0
(2S)-1-[(2S,4R)-4-benzyl-2-hydroxy-5-[[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl] amino]-5-oxopentyl]-N-tert-butyl-4-(pyridin-3- ylmethyl) piperazine-2-carboxamide (5362440) INDINAVIR		-10.5	-10.9	0
5-[(2-chlorophenyl) methylidene]-3-phenylimidazolidine-2,4-dione (53441)		-7.6	-7.8	0
(2R)-2-acetamido-3-sulfanylpropanoic acid (12035)		-4.4	-4.2	0

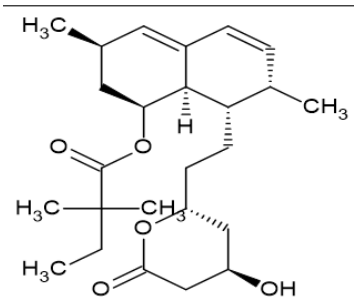
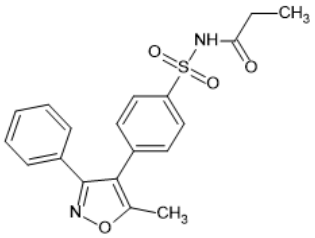
[(1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] 2,2-dimethylbutanoate (54454) SIMVASTATIN		-9.1	-8.9	0
N-[4-(5-methyl-3-phenyl-1,2-oxazole-4-yl)phenyl] sulfonylpropanamide (119828) PARECOXIB		-8.5	-9	0

Table 1: Results of Molecular Docking of Selected Drugs and Chemicals for Antiviral Activity Using Pyrx and Mz Dock Software Against Receptor (Pdbid 2b7z).

Compound	LOG P o/w Lipophilicity	LOG S w/o Hydrophilicity	Absorption	BBB Penetration	LIPINSKI Violations
Dantrolene	1.34	-2.95	high	no	0
Indinavir	4.05	-4.86	high	no	1
Parecoxib	2.28	-4.28	high	no	0
Simvastatin	3.74	-4.92	high	no	0
5-[(2-chlorophenyl) methylidene]-3-phenylimidazolidine-2,4-dione	2.66	-4.16	high	no	0
4-[(1-benzyl-4-chloro-2,5-dioxopyrrol-3-yl) amino]-N-(5-chloro-2-methoxyphenyl) benzamide	3.52	-5.93	high	no	0

Table 2: ADME Parameters of Selected Ligands Based on Binding Energies (Swiss ADME).

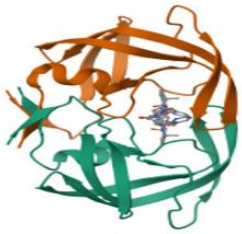


Figure 1: Structure of HIV-1 protease mutant bound to Indinavir

DISCUSSION

Utilizing PyRX docking and MZ DOCK, ten exceptional chemical compounds, including existing medications with acyl ligands, were analyzed in silico. Indinavir, the standard utilized to validate the methodology, serves as evidence of the potential of these compounds. Among the promising candidates selected for further investigation are 4-[(1-benzyl-4-chloro-2,5-dioxopyrrol-3-yl) amino]-N-(5-chloro-2-methoxyphenyl) benzamide (-8.6 PyRX) and (-9.7 MZ dock), Melatonin (-7.9 PyRX and MZ dock), 1-[(E)-[5-(4-nitrophenyl) furan-2-yl] methylidene amino] imidazolidine-2,4-dione (-9.0 PyRX) and (-8.3 MZ dock), 5-[(2-chlorophenyl)methylidene]-3-phenylimidazolidine-2,4-dione (-7.6 PyRX) and (-7.8 MZ dock), and Simvastatin (-9.1 PyRX) and (-8.9 MZ dock), each illustrating promise when compared to Indinavir (-10.5 PyRX) and (-10.9 MZ dock) (Table 1). The Swiss-ADME parameters yielded encouraging outcomes, conforming to Lipinski's rule (Table 2). Acyl compounds have become crucial in the pursuit of innovative drug development against viral diseases. The path forward necessitates further pharmacological studies, structure-activity relationship (SAR) analysis, and synthesis, with investigations aimed at elucidating their therapeutic potential and confirming their efficacy in combating retroviral diseases, thereby advancing the development of life-saving treatments in medicinal chemistry.

CONCLUSION

Several potential chemical compounds, including currently available medications with acyl groups, were effectively identified by this in-silico study. These compounds showed substantial binding affinities to the HIV-1 protease mutant target. Using the docking techniques of PyRX and MZ DOCK, substances like 4-[(1-benzyl-4-chloro-2,5-dioxopyrrol-3-yl) amino] Melatonin, 1-[(E)-[5-(4-nitrophenyl) furan-2-yl] methylidene amino, and N-(5-chloro-2-methoxyphenyl) benzamide imidazolidine-2,4-dione, 5-[methylidene (2-chlorophenyl)] Simvastatin and -3-phenylimidazolidine-2,4-dione were found to be noteworthy possibilities, with binding energies that were on par with, and in some cases even closer to, those of the approved standard medication Indinavir. These chosen compounds' drug-likeness and possible bioavailability are highlighted by their good Swiss-ADME characteristics and compliance with Lipinski's Rule. Considering the well-established function of acyl molecules in creating antiviral drugs, our results offer an essential computational basis. Additional pharmacological, structure-activity

relationship (SAR), and synthetic research are vital to determine their therapeutic utility and prove their effectiveness in treating retroviral illnesses. This methodology furthers medicinal chemistry's crucial hunt for novel, life-saving therapies.

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