RESEARCH ARTICLE

Repurposing Existing FDA-Approved Medications by Virtual Screening for Combatting *Pseudomonas aeruginosa* Infections

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ABSTRACT

Pseudomonas aeruginosa, a notorious pathogen, poses significant challenges due to its resistance to multiple antibiotics. This study aims to identify potential FDA-approved drugs that could be repurposed to combat *P. aeruginosa* infections through virtual screening. The target protein, DNA gyrase B 24kDa ATPase subdomain (PDB ID: 7PTF), was refined using PDB-REDO, improving geometric parameters despite a slight increase in R and R-free values. The virtual screening revealed several promising candidates with high binding affinities, including acetyldigitoxin (-9.9), digoxin (-9.5), digitoxin (-9.4), posaconazole (-9.3), venetoclax (-8.8), and itraconazole (-8.7). These top hits, primarily comprising cardiac glycosides and antifungal agents, exhibited large molecular weights, numerous hydrogen bond donors and acceptors, and significant molecular flexibility. The findings suggest potential repurposing opportunities for these drugs in treating *P. aeruginosa* infections, warranting further *in-vitro* and *in-vivo* investigations to validate their antimicrobial efficacy.

Keywords: *Pseudomonas aeruginosa*, FDA-approved drugs, Virtual screening, DNA gyrase, PDB-REDO, Drug repurposing, Antimicrobial resistance, Cardiac glycosides, Antifungal agents, Molecular docking.

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INTRODUCTION

Pseudomonas aeruginosa, an opportunistic pathogen, poses significant clinical challenges, particularly in immunocompromised patients and those with chronic lung diseases like cystic fibrosis.[1] Despite advancements in antibiotic development, the emergence of multidrug-resistant strains of *P. aeruginosa* necessitates the continuous search for novel therapeutic strategies[2]. Drug repurposing, which involves finding new uses for existing FDA-approved drugs, offers a promising and efficient approach to identifying effective treatments against this pathogen.[3]

Traditional drug discovery is often time-consuming and costly, with high rates of failure during clinical trials.[4] In contrast, drug repurposing leverages existing data on drug safety, pharmacokinetics, and pharmacodynamics, potentially expediting the drug development process and reducing costs.[5] This approach has the potential to rapidly expand the arsenal of treatments available for infectious diseases, including those caused by *P. aeruginosa*.[6]

DNA gyrase is a well-known target for antibacterial agents due to its crucial role in bacterial DNA replication.[7] Inhibiting Gyr can effectively disrupt bacterial growth and replication, making it an attractive target for therapeutic intervention.[8] Given its importance, this study focuses on Gyr as the primary target for virtual screening of FDA-approved drugs.

Recent advancements in computational modeling and virtual screening techniques have significantly enhanced the drug discovery process.[9] Virtual screening allows for the rapid evaluation of large compound libraries to identify potential lead compounds with favorable binding characteristics.[10] By

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utilizing these methodologies, researchers can expedite the identification of candidate drugs for further experimental validation.

This study aims to harness the power of drug repurposing and virtual screening to identify FDA-approved drugs with potential activity against *P. aeruginosa*. Through the use of the DrugRep virtual screening server and AutoDockVina, we conducted virtual screening against the Gyr protein. The structural fidelity of the Gyr complex was validated through PDB-REDO refinement, enhancing the reliability of the predicted binding interactions. The findings of this study have the potential to uncover novel therapeutic options for treating *P. aeruginosa* infections, offering hope for improved patient outcomes and addressing the unmet medical needs in infectious disease therapy.

MATERIAL AND METHODS

Data Collection

FDA-approved drugs and P. aeruginosa-related targets

- *FDA-approved drugs*

A comprehensive list of FDA-approved drugs was curated from DrugBank, including their molecular structures and pharmacological profiles.[11]

- *P. aeruginosa-related targets*

The DNA gyrase (Gyr), a key protein implicated in bacterial DNA replication, was selected as the target for virtual screening.[12]

Virtual Screening Using DrugRep Virtual Screening Server

Target protein preparation

- *Selection of targets*

The DNA gyrase (Gyr) relevant to *P. aeruginosa* was selected from the Protein Data Bank (PDB) (PDBID: 4PRV).

- *Protein structure preparation*

The structure of the target protein was prepared using the PDB-REDO online tool.[13]

Binding pocket detection with curpocket

- *CurPocket algorithm*

The CurPocket algorithm was employed to identify potential binding pockets on the surface of the target proteins. This curvature-based cavity detection approach analyzes the geometric properties of the protein surface to locate regions likely to accommodate small molecule ligands.[14]

- *Selection of binding pockets*

Identified binding pockets were reviewed interactively, and one was selected for further docking studies.

Ligand preparation

- *Molecular structures*

The molecular structures of FDA-approved drugs were obtained in SDF format.

- *Optimization*

These structures were optimized by adding hydrogen atoms, calculating Gasteiger charges, and converting them to PDBQT format suitable for docking.

Docking simulation using autodockvina

- *Docking setup*

The selected binding pocket from the CurPocket analysis was used as the docking site.

- *Auto Dock Vina*

The prepared ligands were docked into the selected binding pocket using Auto Dock Vina, known for its accuracy and speed in predicting ligand-receptor interactions.

- *Scoring and ranking*

AutoDockVina calculated binding affinities for each ligand-protein interaction, and the ligands were ranked based on these scores.

Analysis of results

- *Top-ranking compounds*

The top-ranking compounds, based on their binding affinity scores, were identified and analyzed for their potential as therapeutics against *P. aeruginosa*.

3D conformation visualization

The interactive 3D conformations of the docked complexes were reviewed to ensure proper binding modes and interactions with the target proteins.

The combination of CurPocket for binding pocket detection and AutoDockVina for docking simulation provided a robust platform for virtual screening. This approach efficiently identified FDA-approved drugs with high binding affinities to *P. aeruginosa*-related targets, highlighting their potential for repurposing as therapeutics. The workflow used for this is represented in Figure 1.[15]

RESULTS AND DISCUSSION

Protein Structure Preparation

The structure of the target protein was prepared using the PDB-REDO online tool. The PDB-REDO re-refinement of the *P. aeruginosa* DNA gyrase B 24kDa ATPase subdomain complexed with novobiocin (PDB entry 7PTF) yielded mixed results. While the crystallographic refinement metrics showed a slight increase in R and R-free values from 0.1484 to 0.1497 and from 0.1766 to 0.1781, respectively, indicating a minor decrease in model fit, the geometric parameters improved significantly, with the bond length RMS Z-score reduced from 1.188 to 0.884 and the bond angle RMS Z-score from 0.882 to 0.838. Model quality metrics such as the Ramachandran

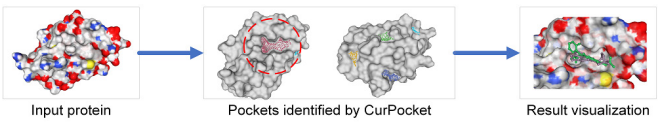

Figure 1: Workflow for DrugRep

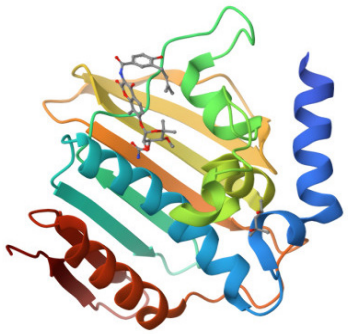

Figure 2: *P. aeruginosa* DNA gyrase B 24kDa ATPase subdomain complexed with novobiocin (PDB ID:7PTF)

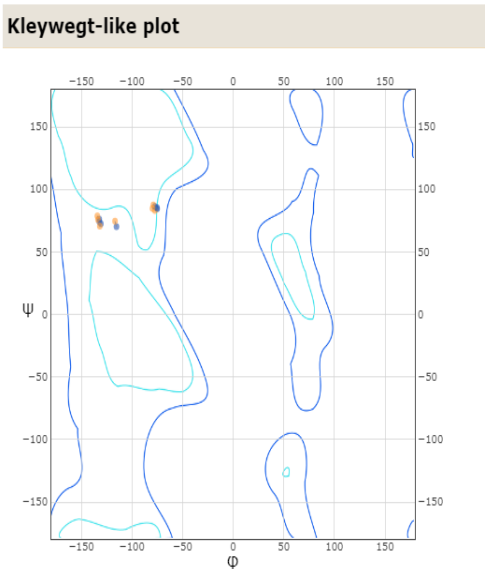

Figure 3: The Kleywegt-like plot

plot normality and rotamer normality remained unchanged, but there were slight improvements in fine packing and bump severity, suggesting enhanced local structural accuracy. Despite these improvements, some metrics like hydrogen bond satisfaction, slightly decreased, indicating potential areas of structural stress. Overall, the PDB-REDO re-refinement process achieved a more geometrically accurate model, though with a slight trade-off in overall fit to the experimental data, underscoring the complexity of balancing crystallographic and geometric refinement in structural biology. Figure 2 provides the illustration of *P. aeruginosa* DNA gyrase B 24kDa ATPase subdomain complexed with novobiocin.[16,17]

The Kleywegt-like plot shown in Figure 3 provides insights into the conformational space occupied by the protein residues of *P. aeruginosa* DNA gyrase B 24kDa ATPase subdomain complexed with novobiocin, based on their phi (ϕ) and psi (ψ) dihedral angles. The plot features axes labeled "ψ" (psi) and "φ" (phi), which represent these dihedral angles, with contour lines enclosing regions where certain angle values are met. These regions vary in size and shape, indicating different levels of density or stability. A well-refined protein structure will have most of its data points within favored regions, suggesting stability and accurate refinement. Conversely, if many points fall outside these regions, it might indicate potential issues with the structure's accuracy. Specific points marked in brown could denote residues that warrant further investigation. In this case, the majority of points falling within favored regions would suggest a well-refined and stable structure, while outliers might point to areas needing refinement. This plot, while useful, should be considered alongside other validation tools for a comprehensive analysis of protein quality.[18,19]

Results of Virtual Screening

The virtual screening identified several FDA-approved drugs with high binding affinities to *P. aeruginosa*-related targets.[20] The top hits included:

The virtual screening results provided in Table 1 reveal several FDA-approved drugs with high binding affinities to *P. aeruginosa*-related targets. The top hits structure given in Figure 4 include acetyldigitoxin, digoxin, digitoxin, posaconazole, venetoclax, and itraconazole, with binding scores ranging from -9.9 to -8.7. These scores indicate strong binding affinities, with acetyldigitoxin showing the highest affinity.[21,22]

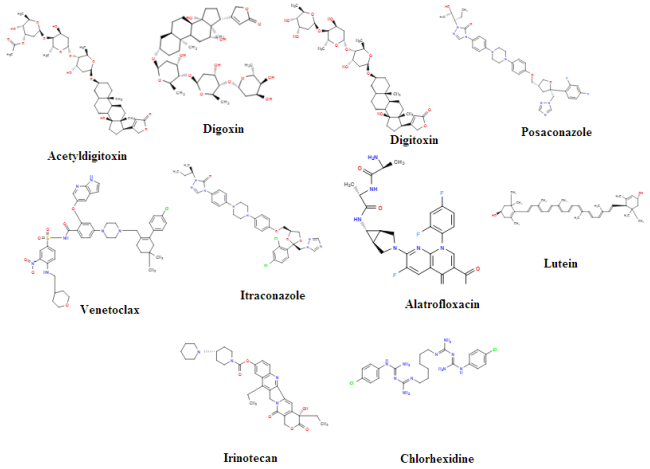

Figure 4: Chemical structures of selected top drugs

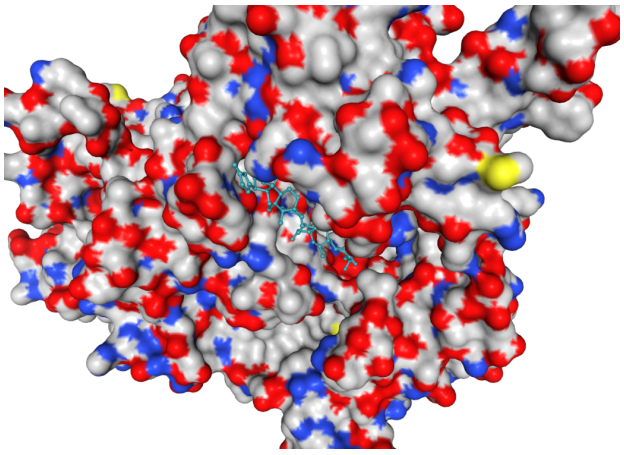

Figure 5: Interaction of acetyldigitoxin with gyrase

Table 1: Results of virtual screening by DrugRep server

Name	*Score*	*MW*	*HBD*	*HBA*	*RB*	*LogP*
Acetyldigitoxin	-9.9	806.9757	4	6	13	3.3
Digoxin	-9.5	780.9385	6	7	13	1.6
Digitoxin	-9.4	764.9391	5	6	12	2.8
Posaconazole	-9.3	700.7774	1	5	13	6.1
Venetoclax	-8.8	868.45	2	6	13	8.1
Itraconazole	-8.7	705.633	0	4	11	7.2
Alatrofloxacin	-8.6	558.518	4	6	10	0.9
Lutein	-8.3	568.886	2	2	12	11.0
Irinotecan	-8.1	586.678	1	5	7	4.6
Chlorhexidine	-8.1	505.447	6	0	13	2.7
Beta carotene	-8.0	536.888	0	0	10	13.6
Zeaxanthin	-7.9	568.886	2	2	12	10.9
Glimepiride	-7.9	490.62	3	5	11	3.8
Indocyanine green acid form	-7.8	753.99	2	6	16	8.5
Delamanid	-7.8	534.492	0	3	7	5.6
Avapritinib	-7.7	498.57	1	5	5	1.8
Ponatinib	-7.6	532.5595	1	3	6	4.1
Sonidegib	-7.5	485.507	1	2	6	5.8
Dasatinib	-7.3	488.006	3	5	9	3.5
Avatrombopag	-7.2	649.65	2	5	9	3.9
Cinacalcet	-7.2	357.412	1	0	6	6.1
Demecarium	-7.2	556.7797	0	2	19	6.5
Nintedanib	-7.1	539.6248	2	3	9	3.3
Dabigatranetexilate	-7.1	627.7332	2	5	19	5.6
Aripiprazolelauroxil	-7.0	660.72	0	2	20	9.9
Isocarboxazid	-7.0	231.2505	2	2	5	1.6
Arbutamine	-7.0	317.3795	5	4	12	2.2
Fulvestrant	-6.9	606.78	2	3	14	9.1
Pentamidine	-6.9	340.4195	2	0	10	2.5
Calcium glubionate anhydrous	-6.9	592.513	13	15	30	-7.7
Paliperidone	-6.9	426.4839	1	4	5	3.3
Regorafenib	-6.8	482.815	3	3	8	4.1
Tegaserod	-6.8	301.394	2	0	9	2.9
Lycopene	-6.8	536.888	0	0	16	15.5
Brexpiprazole	-6.7	433.57	0	1	7	6.2
Panobinostat	-6.7	349.434	3	2	9	2.9
Siponimod	-6.7	516.605	1	2	10	4.7
Salmeterol	-6.6	415.5656	4	3	19	3.9
Tedizolid phosphate	-6.6	450.323	2	8	8	0.3
Vilanterol	-6.6	486.43	4	3	19	3.8
Hexobendine	-6.6	592.686	0	2	21	3.9
Copanlisib	-6.5	480.529	2	3	9	-0.2
Folic acid	-6.5	441.3975	5	9	12	0.4
Glycerol phenylbutyrate	-6.5	530.6512	0	3	20	6.7
Pretomanid	-6.4	359.2574	0	3	4	2.7
Mirabegron	-6.4	396.506	4	3	11	2.0
Montelukast	-6.4	586.183	2	4	14	7.7

Doxazosin	-6.3	451.4751	1	3	5	2.3
Vorinostat	-6.3	264.3202	3	3	11	1.5
Naloxegol	-6.3	651.794	2	2	26	0.9
Safinamide	-6.3	302.349	2	1	7	2.2
Deferoxamine	-6.2	560.684	6	8	31	-2.1
Selpercatinib	-6.2	525.613	1	5	9	2.5
Aripiprazole	-6.2	448.385	1	1	7	4.6
Cefoperazone	-6.2	645.67	4	11	14	0.0
Nebivolol	-6.1	405.435	3	2	8	3.0
Estradiol dienanthate	-6.1	496.732	0	2	14	9.4
Mebeverine	-6.1	429.557	0	1	14	5.2
Thonzonium	-6.0	511.818	0	2	22	9.9
Dequalinium	-5.9	456.6654	2	0	11	7.3
Cisapride	-5.9	465.945	2	1	10	3.4
Octinoxate	-5.9	290.3972	0	1	10	5.3
Florbetapir (18F)	-5.9	359.432	1	1	12	3.4
Levomefolic acid	-5.8	459.4558	6	7	12	1.2
Benorilate	-5.8	313.309	1	3	7	2.2
Cabozantinib	-5.7	501.514	2	3	10	5.3
Dopexamine	-5.6	356.5017	4	2	15	4.0
Lapyrium	-5.6	363.521	1	2	17	5.4
Pantethine	-5.6	554.721	8	8	27	-2.1
Ibutilide	-5.5	384.576	2	3	15	4.0
Iophendylate	-5.5	416.3368	0	1	12	6.9
Chloramphenicol palmitate	-5.5	561.54	2	5	23	8.8
Pramocaine	-5.4	293.407	0	0	9	3.1
Ritodrine	-5.4	287.3535	4	3	9	2.3
Docosanol	-5.3	326.6	1	1	21	10.5
Fingolimod	-5.3	307.4708	3	2	14	4.1
Pegvaliase	-5.3	318.414	3	3	17	-2.2
Moclobemide	-5.2	268.739	1	1	5	1.4
Nonoxynol-9	-5.2	616.8235	1	1	36	4.6
Orlistat	-5.1	495.7348	1	3	24	9.9
Pitolisant	-5.1	295.85	0	0	8	4.2
Lorpiprazole	-5.1	405.469	0	2	4	3.3
Stearic acid	-5.0	284.4772	1	2	17	8.2
Dolasetron	-5.0	324.38	0	2	3	2.7
Oxolamine	-5.0	245.326	0	2	6	2.8
Tromantadine	-5.0	280.412	1	1	7	2.1
Benzododecinium	-5.0	304.541	0	0	13	7.3
Cetylpyridinium	-4.9	304.541	0	0	15	8.6
Vorapaxar	-4.8	492.5817	1	3	7	5.2
Succinylcholine	-4.8	290.399	0	2	11	-0.0
Linoleic acid	-4.7	280.4455	1	2	15	6.5
Cinoxate	-4.6	250.294	0	1	8	2.3
Miltefosine	-4.6	407.576	1	2	21	6.7
Decamethonium	-4.6	258.4863	0	0	11	3.9
Bufexamac	-3.8	223.272	2	2	8	1.8
Cobicistat	-3.6	776.03	3	5	24	5.7

Glutathione	-3.5	307.323	5	6	14	-4.5
Pimozide	-3.1	461.5462	0	1	7	6.9
Conivaptan	-1.8	498.5744	1	3	6	5.6
Zafirlukast	-1.4	575.675	2	4	11	5.5

Acetyldigitoxin (-9.9), whose interaction with protein is shown in Figure 5, digoxin (-9.5), and digitoxin (-9.4) exhibit the highest binding affinities. These compounds are structurally related cardiac glycosides, suggesting a potential class effect in binding to the target. Posaconazole (-9.3), an antifungal agent, also shows strong binding, indicating potential repurposing opportunities beyond its traditional use. Venetoclax (-8.8) and itraconazole (-8.7), which are used in oncology and antifungal treatments, respectively, highlight the diverse therapeutic classes that may interact with the target.[23]

The drugs with high binding affinities tend to have large molecular weights (e.g., Venetoclax at 868 and acetyldigitoxin at 806), suggesting that larger molecules may have more complex interactions with the target. Most of the top compounds have a moderate to high number of hydrogen bond donors (HBD) and acceptors (HBA), facilitating strong interactions with the target protein. For instance, digoxin has 6 HBDs and 7 HBAs. High-affinity compounds tend to have many rotatable bonds (RB) and a high number of atoms (NOA), indicating that flexibility and size are important for binding. Venetoclax, with 13 RBs and 14 NOAs, exemplifies this trend.[24,25]

Lipophilicity, indicated by LogP, varies among the top compounds. Venetoclax (LogP 8.1) and Itraconazole (LogP 7.2) are highly lipophilic, while others like digoxin (LogP 1.6) are less so. This suggests that both hydrophilic and lipophilic interactions are important for binding. The data indicates that structurally diverse drugs, including cardiac glycosides, antifungals, and oncology agents, have high binding affinities to *P. aeruginosa*-related targets.[26,27]

The high-affinity binding of these FDA-approved drugs suggests potential repurposing opportunities for treating *P. aeruginosa* infections. Particularly, the cardiac glycosides (Acetyldigitoxin, Digoxin, and Digitoxin) could be further explored for antimicrobial properties, given their strong binding scores. The structural features contributing to high binding affinities include large molecular size, numerous hydrogen bond donors and acceptors, and flexibility. These findings warrant further *in-vitro* and *in-vivo* investigations to validate the antimicrobial efficacy of these compounds and to explore their potential use in treating infections caused by *P. aeruginosa*.[28,29]

CONCLUSION

This study investigates the potential of repurposing FDA-approved drugs to combat *P. aeruginosa* infections through virtual screening. The target protein, DNA gyrase B 24kDa ATPase subdomain (PDB ID: 7PTF), underwent structure preparation and refinement using the PDB-REDO tool. Despite a slight increase in R and R-free values (from 0.1484–0.1497 and from 0.1766–0.1781, respectively), indicating a minor decrease in model fit, there were significant improvements in geometric parameters, such as a reduction in the bond length RMS Z-score from 1.188 to 0.884 and the bond angle RMS Z-score from 0.882 to 0.838.

The virtual screening identified several FDA-approved drugs with high binding affinities to *P. aeruginosa*-related targets. The top hits included acetyldigitoxin with a score of -9.9, digoxin at -9.5, and digitoxin at -9.4, all of which are cardiac glycosides. Posaconazole, an antifungal agent, also showed a strong binding score of -9.3, while Venetoclax and Itraconazole, used in oncology and antifungal treatments, respectively, had scores of -8.8 and -8.7.

The top compounds generally exhibited large molecular weights, such as venetoclax at 868 and acetyldigitoxin at 806, and had numerous hydrogen bond donors and acceptors, exemplified by digoxin with 6 HBDs and 7 HBAs. These high-affinity compounds also featured many rotatable bonds and a high number of atoms, indicating the importance of molecular flexibility and size in binding. For instance, venetoclax had 13 rotatable bonds and 14 atoms.

Lipophilicity varied among the top candidates, with venetoclax having a high LogP of 8.1 and digoxin a lower LogP of 1.6, suggesting the significance of both hydrophilic and lipophilic interactions in effective binding.

These findings highlight the potential for repurposing structurally diverse FDA-approved drugs, including cardiac glycosides, antifungals, and oncology agents, to treat *P. aeruginosa* infections. Particularly, the strong binding affinities of acetyldigitoxin, digoxin, and digitoxin suggest their potential antimicrobial properties. The study underscores the need for further *in-vitro* and *in-vivo* investigations to validate the antimicrobial efficacy of these compounds, potentially accelerating the development of new therapeutic strategies against *P. aeruginosa* by leveraging existing pharmacological knowledge.

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