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In-Silico Evaluation of Nonsteroidal Anti-inflammatory Drugs as Antimicrobial Agents Against MDR Urinary Tract Infections

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ABSTRACT

The growing antibiotic resistance in urinary tract infection (UTI) pathogens underscores the need for alternative treatment strategies. This study employed Density Functional Theory (DFT) and molecular docking to investigate the repurposing potential of five nonsteroidal anti-inflammatory drugs (NSAIDs) celecoxib, indomethacin, ketoprofen, piroxicam, and salsalate against the fimbrial adhesin protein of *Proteus mirabilis* (PDB ID: 6H2L). DFT calculations at the B3LYP/6-311G(d,p) level revealed distinct electronic properties: ketoprofen exhibited the largest HOMO–LUMO band gap (4.575 eV), indicating high chemical stability, while piroxicam displayed the smallest band gap (2.719 eV), suggesting enhanced reactivity. Electrophilicity indices ranged from 14.822 eV (celecoxib) to 19.031 eV (piroxicam), reflecting differential binding propensities. Docking studies showed that ketoprofen achieved the strongest binding affinity (−7.8 kcal/mol), forming three stable hydrogen bonds with residues THR80, LYS78, and HIS186. Indomethacin exhibited a binding affinity of −7.2 kcal/mol and the highest number of hydrogen bonds (four), while piroxicam displayed strong binding (−7.4 kcal/mol) with the shortest hydrogen bond distance (1.96 Å), highlighting its potential for stable protein interactions. Celecoxib and salsalate showed moderate binding affinities (−7.0 kcal/mol). Collectively, ketoprofen and piroxicam emerged as the most promising candidates for further evaluation. This study demonstrates the potential of NSAIDs as antibacterial agents and underscores the value of computational approaches in guiding drug repurposing efforts against multidrug-resistant uropathogens However, experimental validation through microbiological assays is required before clinical translation

Keywords: drug repositioning, anti-inflammatory, urinary tract infections, molecular docking, antibiotic resistance**.**

1.0 INTRODUCTION

Urinary tract infection (UTIs) is the most commonly encountered infectious disease worldwide, estimated to impact over 150 million individuals each year (Paul, 2024). Current research indicates that out of 100 individuals, 50% of women tends to suffer this infection, while fewer men and children are affected by it **(**Kalhori, *et al.,* 2024**),** another report reveals this infection has resulted to not less than 8 million visits to health facilities in the United States annually **(**Amiri *et al***.,** 2025).Gram-positive and Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas*, *Klebsiella*, *Staphylococcus*, and *Enterococcus*,and *Proteus mirabilis* which are collectively called Entorobacterales, are the primary contributors to this infection (Timm *et al***.,**2024; Al Lawati e*t al*.,2024) most especially *Escherichia coli* which has continued to remain the most frequently isolated pathogen, thereby accounting for about 80% community acquired UTIs and roughly 65% of hospital-acquired UTIs (Kazmi *et al.,* 2024**).** The urinary system which includes the bladder, urethra and kidneys is structured to eliminate these microbes, but various factors can alter these defences leading to infection (Mancuso *et al*.,2023). Factors such as, certain contraceptive methods to prevent pregnancy, sexual activity, hormonal changes like menopause-related changes, urinary tract abnormalities, kidney stones, weak body defences, catheter use, and recent urinary procedures (Ross *et al*., 2024). When this infection impacts the lower urinary tract, it manifests itself as cystitis (bladder infection), leading to frequent urination, lower abdominal pain, and a sensation of pressure or burning during urination; in some instances, it can affect the upper urinary tract (pyelonephritis), including the ureters and kidneys, potentially resulting in fever, vomiting, back pain, and hematuria. This particular aspect is less common but more severe compared to the lower urinary tract infection **(**Herrera-Espejo *et al*., 2024).

Recently, to treat urinary tract infections, antibiotics like trimethoprim-sulfamethoxazole, ciprofloxacin, nitrofurantoin, fosfomycin, and beta-lactam antibiotics (such as amoxicillin-clavulanate) are used **(**Maladkar *et al*., 2024; Nguyen, 2024; Moreno-Mellado *et al*.,2025;

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Takagi *et al*., 2025). These medications are usually effective in eliminating this infection when observed and administered at the early stage **(**Schmiemann *et al***.,** 2024). However, the inappropriate use of these antibiotics has led to an increase in bacteria that are resistant to multiple drugs, making treatment very difficult (Ferreira da Silva *et al*.,2025). Also, prolonged use of antibiotics can cause stomach upset, allergic reactions, and a higher chance of getting infections again (Babaei *et al*., 2024). Due to this current challenge, there is an urgent need for a new approach to mitigate UTIs.

Nonsteroidal anti-inflammatory drugs (NSAIDs), often taken for pain relief and reducing inflammation, have recently garnered attention for their ability to fight against UTIs causing bacteria (Wirth *et al*., 2024; Khatun *et al*.,2024). New computational based methods, like molecular docking and Density Functional Theory (DFT), have become handy tools to explore how these drugs interact with bacteria (Kumar *et al*., 2024; Rathod *et al*., 2024). Molecular docking is used to estimate how well drugs bind to bacterial proteins and understand their interaction (Sahin *et al*., 2024; Zheng *et al*.,2024), while DFT helps examine the electronic structure and binding properties at a deeper level (Chen *et al*., 2025). While NSAIDs such as ibuprofen and diclofenac have shown incidental antimicrobial effects (Babaei et al., 2024), there is limited systematic computational evaluation of their direct interaction with UTI-associated virulence proteins such as fimbrial adhesins. This study therefore addresses this gap.

Though computational studies have focused on conventional antibiotics, but research on NSAIDs as potential antibacterial agents remains limited. For instance, Selvakumaran *et al.* (**2**024) conducted a study using molecular docking and DFT analyses to investigate the anti-inflammatory and anti-diabetic activity of newly synthesized 4AP2BOB. Considering the findings of the study, it was established that NSAIDs offer a great deal as a potent therapeutic agent for managing inflammation and diabetes. Additionally, Mohammed *et al.* **(**2024), employed ADMET and molecular docking method to predict NSAIDs that exhibited selectivity for the cyclooxygenase-2 (COX-2) iso form which is located in the prostaglandins within the inflamed tissues. The docking results revealed that all drugs demonstrated a predictive ability for specific binding to COX-2 enzymes in comparison to the standard drug, with docking scores spanning from -10.07 to -10.66 kcal/mole. Building on these studies, this research aims to take a more comprehensive computational approach to evaluate the potentials for the repurposing of the selected NSAIDs (celecoxib, indomethacin, ketoprofen, piroxicam, and salsalate) against UTIs target proteins. Specifically, molecular docking will be used to predict how NSAIDs bind to UTIs target proteins and DFT calculations to analyze their electronic properties like HOMO-LUMO energies.

2.0 MATERIALS AND METHODS

2.1 Computational details

The NSAIDs structures (as shown in Figure 1) were optimized for calculations using the DFT method at the theory's B3LYP/6-311G (d,p) level as implemented in the Gaussian09 software. The B3LYP/6-311G (d,p) provides a balanced approach to computational chemistry, useful for the prediction of molecular structure. B3LYP, which is a hybrid of Hartree-Fock exchange and density functional theory (DFT) correlate on terms, offers better accuracy in characterizing electron correlation effects. The 6-311G(d,p) basis set, a split-valence triple-zeta set supplemented with polarization functions, improves the description of valence electron flexibility and more accurately considers molecular interactions (Krishnan *et al***.,**1980). This combination is widely accepted in quantum chemical calculations for organic systems because it is well known for its capacity to predict geometries, vibrational frequencies, and thermochemical properties with dependable precision while keeping computing costs low. Structural visualization and confirmation were done using the GaussView 6.0.16 software **(**Frisch, 2009). GaussView 6.0.16 software was also used for electronic properties calculation in computing quantum descriptors such HOMO and LUMO energies, band gap, chemical hardness, softness, electronegativity, chemical potential, electrophilicity index among others. Visualization of the HOMO-LUMO iso surface was done using the ChemCrafts software **(**Andrienko,2010)**.** Molecular docking was done using the Autodock vina 4.2 **(**Trott andOlson, 2010)**,** and the PrRx **(**Dallakyan and Olson, 2015). Visualization of 2D and 3D ligand-protein target interactions was done using BIOVIA discovery studio 2021 (BIOVIA,2021)**,** and PyMOL softwares (Schrödinger and DeLano,2020). respectively.

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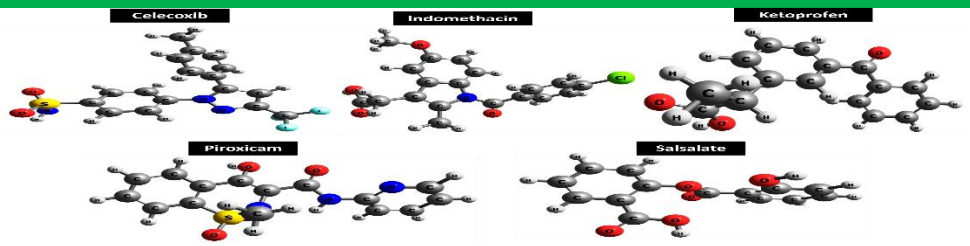

Figure 1: Optimized structure of the NSAIDS; Celecoxib, Indomethacin, Ketoprofen, Piroxicam and Salsalate optimized using the DFT method at the B3LYP/6-311G (d,p) level of the theory

2.2 Molecular Docking Protocol and Reasons for Choosing Target Receptor

Molecular docking is a computational approach that is used in drug design (Stanzione *et al*., 2021**).** This approach helps in understanding the strength of interaction that exist between the interacting species**,** it virtually predicts the binding affinity, bond distance, and the number of conventional hydrogen bond as well as the type of interaction that occur between the interacting species (Meli *et al*., 2022). The spatial parameters of protein 6H2L, as presented in Table 7, were characterized to ensure accurate docking simulations. The protein is centered at coordinates X: 48.36, Y: 32.19, Z: 36.73, with bounding dimensions of X: 52.13, Y: 61.13, Z: 105.05. These metrics were used to define the docking grid and optimize ligand placement.

For this study, the docking was done to identify the drug with the best performance based on the parameters mentioned earlier highlighting its potential as a drug candidate for further studies. The result of this interaction was evaluated and analysed using the result that was generated by pyrex software package (Shami *et al.*,2023). BIOVIA Discovery Studio and PyMOL provided the visualization of the pyrex result in 2D and 3D structures as presented in Figure 2 , showing the H-bond and bond distance as well as the amino acid residues. The selected proteins for this study were downloaded online from protein data bank (PDB) with the protein ID code 6h2l for *Proteus mitabilis*. 6h2l is an important protein of the uropathogen *Proteus mirabilis,* which encodes a record number of chaperone/usher-pathway adhesive fimbriae. Such fimbriae, which are used for adhesion to cell surfaces/tissues and for biofilm formation, are typically important virulence factors in bacterial pathogenesis (Jiang *et al*., 2018). Protein was prepared by removing water molecules and native ligand with the addition of polar hydrogen, for specificity enhancement (Zheng *et al*., 2022)**.** Moreover, the selected drugs are the approved drugs for UTIs treatment and were downloaded from drug data bank (DDB) in PDB (protein data bank) format. Root Mean Square Deviation (RMSD) values have been added in **Tables 1 and 2,** as well as spatial coordinates and bounding dimensions of Protein 6H2L. Furthermore, the proteins did not come with native ligands.

Table 1: Spatial Coordinates and Bounding Dimensions of Protein 6H2L

protein	center_x	center_y	center_z	size_x	size_y	size_z
6H2L	48.3550697056	32.1884045777	36.7258973289	52.1346111537	61.131829288	105.051780903

Table 2 : RMSD Bound Analysis of Ligand–6h2l Receptor Complexes

Ligands_receptor	rmsd upper bound	rmsd lower bound
Celecoxib-6h2l	37.155	34.4
Indomenthacin-6h2l	3.127	2.643
Ketoprofen-6h2l	7.206	2.167
Piroxicam_6h2l	2.18	2.004
Salsalate_6h2l	28.307	27.365

3.0 RESULTS AND DISCUSSION

3.1 HOMO- LUMO analysis

The HOMO-LUMO analysis is a basic method of chemistry used to determine the electronic structure of molecules (Jawal and Jasim, 2024). HOMO, which stands for the Highest Occupied Molecular Orbital, reflects the energy of the most active electrons in a molecule. On the other hand, LUMO, or the Lowest Unoccupied Molecular Orbital, indicates the lowest energy levels that can accept these electrons **(**Williamson *et al***.,** 2024**)**. This analysis is

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very important in designing new medicines. It helps to predict how a drug can connect to enzymes, receptors, or other biomolecules (Akbari *et al*., 2024**)**. **Table 3** provides the HOMO and LUMO energy for the five pharmaceutical compounds while **Figure 4** displays the HOMO-LUMO isosurface plots. Celcoxib, Indomethacin, Ketoprofen, Piroxicam and Salsalate. These energies are first shown in nuclear units (au) and then converted to Electron Volt (eV) with a standard conversion factor (1 au = 27.2114 eV). From these figures, we calculated the band gap, ionization capacity (IP), electron affinity (EA), chemical hardness (η), chemical capacity (μ), and electrophilicity index (Ω). Using the following equations (1) – (6).

$$Eg = E_{LUMO} - E_{HOMO} \quad (1)$$

$$\boldsymbol{\mu} = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2} \quad (2)$$

$$\eta = \frac{E_{HOMO} - E_{LUMO}}{2} \quad (3)$$

$$\sigma = \frac{1}{\eta} \quad (4)$$

$$\chi = -\mu = \frac{IP + EA}{2} \quad (5)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (6)$$

According to the result, Celecoxib had a band Gap of 3.501 eV, showcasing the chemical stability and reactivity which makes it stable enough to remain in the body **(**Pishnamazi *et al*., 2024). The ionization capacity (IP) of 8,949 indicates that it takes the right amount of energy to remove an electron (Aygun *et al*., 2025), Indomethacin has a small band of 2.836 eV, indicating higher reactivity compared to celecoxib. The IP shows a value of 8,402 eV while EA exhibited a value of 5.566 eV and a high electrophilicity index (Ω) at 17,212 eV, indicating strong electron observations of indomethacin thereby, suggesting its ability to bind with biological targets (Thiruchenthooran *et al*.,2024). Ketoprofen stands out with the largest band gap of 4.575 eV among the selected NSAID compounds, indicating more chemical stability and low reaction **(** Tavassoli *et al*., 2024). With IP of 10.873 eV and EA of 6.298 eV indicating moderate ability to accept electrons (Yang *et al*., 2024**)**, while its chemical stiffness (η) showed a value of 2.288 eV which indicates, less reactive nature **(**Vijayarangan *et al*., 2024). However, the electrophilicity index (Ω) had value of 16.103 eV.

Piroxicam, has a band gap of 2,719 eV (the smallest) of the group, suggesting high chemical reaction, which can translate into a rapid biological reaction **(**Xie *et al*., 2024). IP value of 8.553 eV supports the idea, indicating that piroxicam donates more easily and accepts electrons than the other compounds (Hu *et al*.,2024). Moreso, its electrophilicity index (Ω) exhibited a value of 19,031 eV. Finally, salsalate showed a band gap of 3.696 eV close to celecoxib, suggesting a steady balance between stability and reaction (Choudhary *et al*.,2019). The IP value of 9,426 eV and EA of value of 5.730 eV shows that it is a little more stable than piroxicam, but still reactive enough to engage effectively with a biological target (Jayaprakash *et al*.,2019).

Table 3: Electronic Structure and Reactivity Descriptors (HOMO, LUMO, IP, EA, η, μ, Ω) of Selected NSAIDs

Compound	LUMO (au)	HOMO (au)	LUMO (eV)	HOMO (eV)	Band Gap (eV)	IP (eV)	EA (eV)	η (eV)	μ (eV)	Ω (eV)
Celecoxib	-0.20029	-0.32889	-5.448	-8.949	3.501	8.949	5.448	1.750	-7.198	14.822
Indomethacin	-0.20455	-0.30873	-5.566	-8.402	2.836	8.402	5.566	1.418	-6.984	17.212
Ketoprofen	-0.23136	-0.3996	-6.298	-10.873	4.575	10.873	6.298	2.288	-8.586	16.103
Piroxicam	-0.21434	-0.31415	-5.834	-8.553	2.719	8.553	5.834	1.360	-7.194	19.031
Salsalate	-0.21068	-0.34638	-5.730	-9.426	3.696	9.426	5.730	1.848	-7.578	15.538

3.2 Molecular docking analysis

This study analyzed the binding of five drugs (Celecoxib, Indomethacin, Ketoprofen, Piroxicam, and Salsalate) with proteins 6H2L. As presented in **Table 2** below, binding affinity measures how strongly a drug binds to a protein. A lower value (more negative) means a stronger interaction. Among the drugs tested with protein 6H2L, Ketoprofen showed the best binding affinity (-7.8 kcal/mol). This suggests that Ketoprofen is the best candidate for 6H2L. Hydrogen bonds help in stabilizing

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the interaction between drugs and proteins. A higher number of hydrogen bonds usually means a stronger binding. For protein 6H2L, Indomethacin formed the most hydrogen bonds (4), followed by Ketoprofen and Salsalate with 3 bonds each. Bond distance measures the closeness between the interacting atoms. A shorter bond distance indicates a stronger interaction. The shortest bond distances were observed in Piroxicam-6H2L (1.96 Å) and Salsalate-6H2L (1.96 Å), suggesting strong bonding and stability. To complement these findings, Root Mean Square Deviation results was obtained to evaluate the conformational flexibility and stability of each ligand-receptor complex. As show in **Table 2** the RMSD values are presented as upper and lower bounds, which reflects the range of positional deviation during docking simulations. The lower RMSD bounds indicates the minimum deviation observed, representing the most stable pose while the upper RMSD bounds reflects the maximum deviation, capturing the extent of conformational flexibility or instability (Maruyama *et al.*, 2023).

Piroxicam_6h2l and Indometacin-6h2l showed the narrowest RMSD ranges (2.004 – 2.180 Å and 2.643 - 3.127Å, respectively). This suggests highly stable and consistent binding conformations; these narrow bounds imply that the ligands maintained their pose with minimal fluctuations, reinforcing their structural reliability. Celecoxib-6h2l and Salsalate_6h2l exhibited wide RMSD ranges (34.4 – 37.155 Å and 27.365 – 28.307 Å, respectively), which indicates a significant conformational variability and potential instability in binding. Such wide bounds may reflect a poor fit within the receptor pocket. Lastly, Ketoprofen-6h2l displayed a moderate RMSD value (2.167- 7.206 Å), suggesting a mix of stable and flexible poses.

Ketoprofen interacted best with protein 6H2L. These findings suggest that these two drugs should be further studied for their effectiveness in targeting these proteins.

Table 4: Protein–Ligand Interaction Profiles of NSAIDs Docked Against 6H2L

Protein-ligand interaction	Amino acid residue	Binding affinity (Kcal/mol	Bond distance (Å)	Type of interaction	Number of H-bond
Celecoxib-6h2l	A:THR80:HG1 - N:UNK0:F	-7.0	2.98577	Conventional H-bond	2
	A:THR80:HG1 - N:UNK0:F		2.6459	Conventional H-bond	
Indomenthacin-6h2l	B:LYS78:HZ1 - N:UNK0:O	-7.2	2.29752	Conventional H-bond	4
	B:THR80:HN - N:UNK0:O		3.02221	Conventional H-bond	
	B:THR80:HG1 - N:UNK0:O		2.54165	Conventional H-bond	
	N:UNK0:H - B:LYS78:O		2.15607	Conventional H-bond	
Ketoprofen-6h2l	A:THR80:HG1 - N:UNK0:O	-7.8	2.43937	Conventional H-bond	3

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	N:UNK0:H - A:LYS78:O		2.1271	Conventional H-bond	
	N:UNK0:H - A:HIS186:O		2.44079	Conventional H-bond	
Piroxicam_6h2l	B:THR99:HN1 - N:UNK0:O	-7.4	2.53098	Conventional Hydrogen bond	6
	B:SER102:HG - N:UNK0:O		1.95898	Conventional Hydrogen bond	
	B:LEU129:HN - N:UNK0:O		2.39655	Conventional Hydrogen bond	
	N:UNK0:H - B:LEU129:O		2.33278	Conventional Hydrogen bond	
	N:UNK0:HN - N:UNK0:O		2.41746	Conventional Hydrogen bond	
	N:UNK0:H - B:LEU129:O		2.31155	Conventional Hydrogen bond	
Salsalate_6h2l	B:PHE93:HN - N:UNK0:O	-7.0	2.20953	Conventional Hydrogen bond	3
	N:UNK0:H - B:TYR91:O		2.97954	Conventional Hydrogen bond	
	N:UNK0:H - B:GLN100:O		1.96384	Conventional Hydrogen bond	

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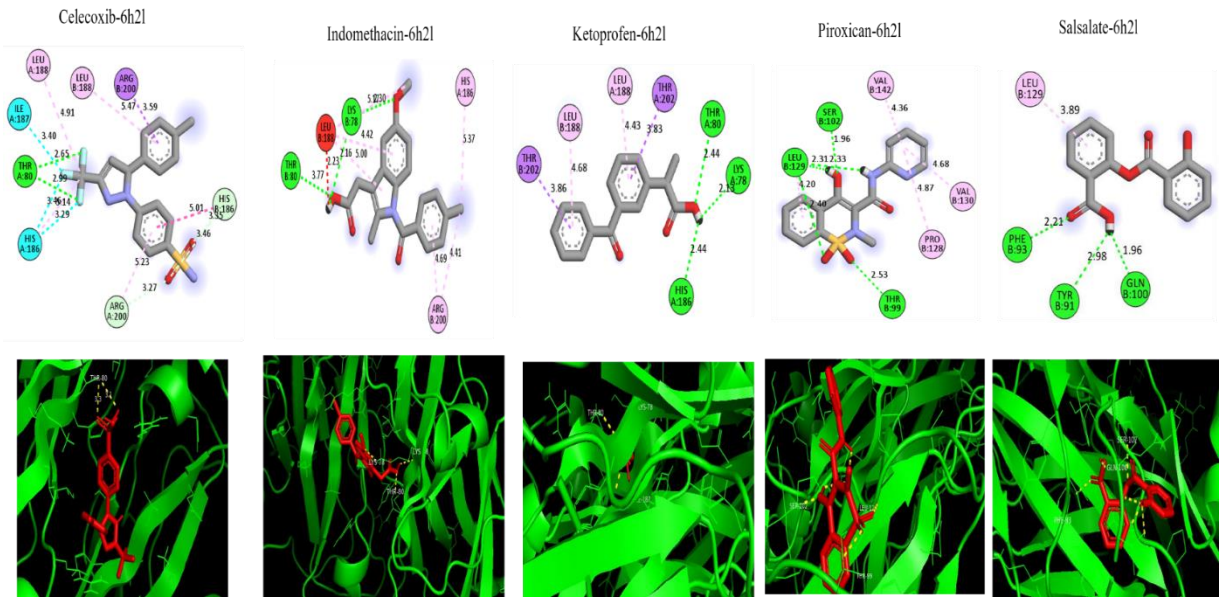

Figure 2: 2D and 3D Visualizations of Docking Interactions of NSAIDS with Protein 6H2L

4.0 CONCLUSION

This study demonstrates the potential of repurposing nonsteroidal anti-inflammatory drugs (NSAIDs) as therapeutic agents against urinary tract infections caused by *Proteus mirabilis*. Density Functional Theory (DFT) calculations revealed that ketoprofen exhibited the highest chemical stability (band gap 4.575 eV), while piroxicam displayed the greatest reactivity (band gap 2.719 eV) and highest electrophilicity index, suggesting strong biological interaction potential. Molecular docking further supported these findings, with ketoprofen achieving the strongest binding affinity (−7.8 kcal/mol) and indomethacin forming the highest number of hydrogen bonds, while piroxicam exhibited the shortest hydrogen bond distances. Thus, indicating potential antimicrobial activity. These findings highlight the translational relevance of computational modeling in identifying repurposing opportunities for existing NSAIDs. Further experimental validation is however required to confirm their efficacy and optimize these compounds for possible therapeutic application. Collectively, ketoprofen and piroxicam emerged as the most promising candidates for further investigation. These results underscore the utility of computational approaches in drug repurposing and provide a strong foundation for experimental validation of NSAIDs as adjunct or alternative therapies in managing multidrug-resistant urinary tract infections.

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