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Nafithromycin (Miqnaf®) as next-generation antibiotic combating drug-resistant community-acquired bacterial pneumonia (CABP): molecular docking insights

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Author contributions

Ansari Vikhar Danish Ahmad contributed to conceptualization, software, writing-original draft preparation, and writing-review and editing. Mohd Sayeed Shaikh was involved in writing-review and editing, and data compilation. Qazi Yasar performed the molecular docking studies. Mohd Mukhtar Khan conducted the formal analysis. All authors carefully reviewed and approved the final version of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

AMR, antimicrobial resistance; CABP, community-acquired bacterial pneumonia; rRNA, ribosomal ribonucleic acid; MD, molecular docking; SDF File, structured data file; UFF, universal force field.

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Abstract

Background: Community-acquired bacterial pneumonia (CABP) poses a serious public health threat, particularly with the emergence of drug-resistant bacterial strains. This study aims to investigate the molecular interactions of Nafithromycin (Miqnaf®), India's first indigenous next-generation macrolide antibiotic, and evaluate its potential against *Streptococcus pneumoniae*, a key pathogen responsible for CABP. Targeting 23S rRNA is critical for overcoming antibiotic resistance since it is involved in bacterial protein production. Many antibiotics, including macrolides target this rRNA. Mutations in 23S rRNA frequently result in resistance; therefore, designing medicines that bind new or conserved areas of 23S rRNA can circumvent current resistance mechanisms and restore antibiotic potency. Nafithromycin has excellent therapeutic potential, with a short three-day regimen and much higher efficacy than conventional macrolides. Its high lung tissue penetration and robust effectiveness against drug-resistant respiratory bacteria make it a promising next-generation antibiotic. **Methods:** To elucidate the interaction of Nafithromycin with bacterial ribosomal RNA, molecular docking studies were performed using AutoDock Vina. The three-dimensional structure of *Streptococcus pneumoniae* 23S rRNA was retrieved from the Protein Data Bank (PDB). The ligand structure of Nafithromycin was obtained from the PubChem database and prepared using Open Babel. Docking simulations targeted key functional regions-Domains II and V of 23S rRNA-known to be critical for bacterial protein synthesis. Binding affinities were calculated, and molecular interactions such as hydrogen bonds, hydrophobic contacts, and conformational stabilities were analyzed using Discovery Studio and PyMOL. **Results:** Nafithromycin exhibited a high binding affinity of −10.3 kcal/mol toward *S. pneumoniae* 23S rRNA. The compound formed stable interactions with both Domain II and Domain V, crucial regions involved in the inhibition of bacterial protein synthesis. Hydrogen bonding and hydrophobic interactions further stabilized the ligand-receptor complex. Compared to azithromycin, Nafithromycin demonstrated superior binding efficacy and a greater potential to inhibit resistant bacterial strains, indicating its structural advantages and enhanced ribosomal targeting. **Conclusion:** Nafithromycin demonstrates significant potential as a potent therapeutic agent against drug-resistant CABP. Its strong binding affinity, stable interactions with bacterial rRNA, favorable pharmacokinetic profile, and reduced resistance risk support its clinical utility and suggest its advantage over traditional macrolide antibiotics such as azithromycin.

Keywords: Nafithromycin; miqnaf®; antimicrobial resistance; community-acquired bacterial pneumonia; 23S rRNA

Background

Antimicrobial resistance (AMR) has emerged as a critical global health threat, responsible for significant morbidity and mortality worldwide. According to the GRAM (Global Research on Antimicrobial Resistance) project, AMR was linked to approximately 569,000 deaths across 35 countries in the Americas alone, and it is projected to cause over 39 million deaths globally by 2050 [1–3]. Antibiotic consumption continues to rise, increasing by 16.3% between 2016 and 2023, from 29.5 to 34.3 billion defined daily doses [4]. Among the many diseases exacerbated by AMR, community-acquired bacterial pneumonia (CABP) stands out due to its global prevalence and high mortality, accounting for around 4 million deaths annually-approximately 7% of all deaths worldwide, 41,108 deaths in the United States in 2022 (12.3 per 100,000), and is commonly caused by *S. pneumoniae*, the primary pathogen in severe cases of all ages and comorbidities [5–7]. Alarmingly, resistance to critical antibiotics such as imipenem has increased significantly, with susceptibility in *Escherichia coli* decreasing from 81.4% in 2017 to 62.7% in 2023, and in *K. pneumoniae* from 58.5% to 35.6% [8]. In India, CABP is particularly severe, representing 23% of the global pneumonia burden, with case fatality rates ranging from 14–30%, and up to 47% in severe cases [9]. Intensive care unit admission rates for CABP range from 8 to 73%, and 30-day mortality among older adults is 15%, indicating its serious impact [10, 11].

CABP, often caused by *Streptococcus pneumoniae*, is increasingly becoming resistant to conventional antibiotic therapies. Macrolides have long been a cornerstone in the treatment of respiratory infections due to their ability to inhibit bacterial protein synthesis by binding to the 23S rRNA within the 50S ribosomal subunit, specifically targeting domains that block peptide translocation [1]. However, the widespread emergence of resistance mechanisms-particularly *erm*-mediated target site methylation and *mef*-mediated efflux-has significantly reduced the clinical utility of traditional macrolides such as azithromycin and clarithromycin [12–15].

To address these limitations, Nafithromycin, a novel next-generation lactone ketolide antibiotic, has been developed. Recently launched in India as “Miqnaf®” by Wockhardt in collaboration with the Biotechnology Industry Research Assistance Council, Nafithromycin is the country’s first indigenously developed antibiotic targeting AMR with a specific focus on CABP. Distinguished by its potent activity against macrolide-resistant *S. pneumoniae*, Nafithromycin binds with high affinity to both domains II and V of the 23S rRNA, thereby overcoming *erm*-mediated resistance. Additionally, it avoids *mef*-mediated efflux, ensuring effective intracellular concentrations necessary for bacterial eradication [9]. This dual-binding mechanism also inhibits RlmAII, a 23S rRNA methyltransferase essential for resistance development, ultimately restoring antibiotic susceptibility and enhancing treatment outcomes. With a short three-day regimen and efficacy reportedly ten times higher than azithromycin, Nafithromycin offers a promising therapeutic option in the global fight against drug-resistant CABP [16]. This study aims to elucidate the molecular interactions and binding mechanism of Nafithromycin with the 23S rRNA target in *Streptococcus pneumoniae* using *in-silico* molecular docking approaches. Specifically, the focus is on the proposed target, methyltransferase RlmAII in 23S rRNA (*S. pneumoniae*, PDB ID: 5ZQ0), to provide deeper insights into the drug’s potential to combat community-acquired bacterial pneumonia.

Materials and methods

Molecular docking

Molecular docking (MD) experiments were carried out to investigate the interactions between Nafithromycin and *Streptococcus pneumoniae*’s methyltransferase RlmAII 23S rRNA (PDB ID: 5ZQ0). The study used Autodock Vina (v1.1.2) in PyRx-Virtual Screening Tool 0.8, Chimera version 1.10.2, and BIOVIA Discovery Studio Visualizer (version 19.1.0.18287). The Discovery Studio software was used to analyze docking poses and ligand-protein interactions, allowing for the identification of interaction types.

Ligand preparation

In this study, Nafithromycin and native ligands (SDF file) were obtained from the US National Library of Medicine PubChem website (https://pubchem.ncbi.nlm.nih.gov/compound/Nafithromycin, accessed on 23 December 2024). The structures were then imported into PyRx-Virtual Screening Tool 0.8 software via the open babel tool, and Energy minimization of the ligands, including Nafithromycin and co-crystallized ligands, was conducted using Universal Force Field (UFF) parameters within the PyRx software suite. The structural optimization ensured the ligands attained a stable and low-energy conformation before docking, which is critical for generating accurate binding predictions [17]. Discovery Studio software was used to predict the active sites of the chosen 5ZQ0: Crystal structure of spRlmCD with U747loop RNA (Target protein).

Target preparation

In The MD Study, a 3D grid box was generated to define the binding site within the 5ZQ0 receptor. The active amino acid residues were identified by locating the binding pocket surrounding the native or co-crystallized ligand present in the protein structure. The protein-ligand complex was first visualized using discovery studio to observe the ligand’s position within the active site. The active site residues were identified based on the coordinates of the ligand, with amino acid residues located within a 5 Å radius of the ligand considered as part of the active site. These co-ordinates were then used in PyRx, where the “Toggle Selection Spheres” option was employed to define the docking grid box dimensions were set to (size_x = −0.1129 Å; size_y = 12.1280 Å; size_z = 33.1448 Å), with an exhaustiveness value of 8. Docking of the drug and receptors was then used to determine their potential affinities/interactions. The molecular docking procedure followed the methodology outlined by Ahmad et al. and Shaikh et al., The full crystal structure of *streptococcus pneumoniae* (PDB ID: 5ZQ0) was used for the MD study [17, 18].

Results

The current study uses a computational approach to investigate the potential therapeutic role of Nafithromycin (MIQNAF®) in CABP. The study is focused on evaluating Nafithromycin efficiency in targeting key proteins linked to CABP, such as 23S rRNA of *Streptococcus pneumonia*. Targets was selected due to its crucial role proteins synthesis, making it essential for bacterial survival. Inhibiting this enzyme disrupts peptidoglycan formation, presenting a viable antibacterial target. CABP is a significant public health challenge, marked by high recurrence rates and escalating resistance to conventional antimicrobial therapies. These issues underscore the pressing necessity for innovative therapeutic approaches. Nafithromycin, a next-generation macrolide, has emerged as a promising candidate due to its unique mechanism of action. It selectively inhibits the 23S rRNA within domain V of the 50S ribosomal subunit, resulting in exceptional potency against Gram-positive bacterial pathogens. Preclinical and clinical studies indicate Nafithromycin’s potential to address unmet therapeutic needs in CABP management while mitigating the resistance associated with traditional macrolides. The computational modeling approach speeds up the evaluation of molecular interactions, saving time and resources in preclinical drug development.

Molecular docking

Molecular docking was performed to evaluate the binding affinities and interaction profiles of Nafithromycin with their respective target 23S rRNA. The molecular docking simulations were carried out using AutoDock Vina, and the binding modes were analyzed based on binding affinity (kcal/mol), interacting residues, bond lengths, bond

types, and bond categories as shown in Table 1 and represented in Figure 1. The redocking of Nafithromycin into the original active site cavity demonstrated an RMSD value (0.9054) indicative of excellent conformational alignment with the native ligand, thereby validating the docking protocol and supporting the reliability of the binding interactions predicted as represented in Figure 2. The molecular docking analysis of Nafithromycin targeting 23S rRNA (PDB ID: 5ZQ0) revealed a docking score of −10.3 kcal/mol, which is significantly higher than the native ligand's score of −8.0 kcal/mol, indicating that Nafithromycin has a higher binding affinity to the target protein. This increased affinity is due to its various interactions with key active site residues. Nafithromycin forms conventional hydrogen bonds with ILE251 (2.31 Å) and ASN196 (2.54 Å), as well as carbon-hydrogen bonds with GLU333 (3.67 Å and 3.43 Å). Additionally, it forms hydrophobic bonds with ILE251 (3.71 Å), PHE145 (5.09 Å), HIS151 (5.07 Å), and PHE281 (4.93 Å) residues. The native ligand interacts with the protein through electrostatic interactions with ASP310 and ASP381, conventional hydrogen bonds with TYR293 (2.87 Å), ILE315 (2.20 Å), THR317 (2.45 Å, 2.30 Å), SER313 (2.91 Å), and GLU333 (2.17 Å, 3.26 Å), and hydrophobic interactions with PHE281 (3.69 Å) via Pi-Sulfur bonding. When compared to the native ligand, Nafithromycin has a higher binding affinity and a diverse interactions, utilizing both hydrophobic and hydrogen bonds. Its bond lengths are optimal for stable interactions, resulting in improved binding stability. Nafithromycin has a high potential as an effective inhibitor of the 23S rRNA, as evidenced by its superior docking score. Its increased binding affinity and specificity are due to hydrogen bonding with key residues and additional hydrophobic interactions, particularly with PHE145, HIS151, and PHE281, which stabilize the ligand-receptor complex.

Nafithromycin, with a molecular weight of 859.0 g/mol, demonstrates significantly higher binding affinity (−10.3 kcal/mol) to the protein target (PDB ID: 5ZQ0) compared to the native ligand, S-Adenosyl-L-homocysteine (SAH), which has a molecular weight of 384.41 g/mol and a binding affinity of −8.0 kcal/mol. This increased affinity can be attributed to the distinct and more extensive binding interactions that Nafithromycin establishes within the binding pocket. Nafithromycin forms four hydrogen bonds with residues ILE251, ASN196, and GLU333 (twice), along with four hydrophobic interactions involving ILE251, PHE145, HIS151, and PHE281. These hydrophobic contacts, particularly the π-alkyl and π-sigma interactions, contribute significantly to the ligand's stabilization within the binding site. In contrast, the native ligand relies heavily on conventional hydrogen bonds (seven in total) with residues such as TYR293, ILE315, THR317 (twice), SER313, and GLU333 (twice), as well as electrostatic interactions with ASP310 and ASP381 and a single π-sulfur interaction with PHE281.

While both ligands interact with GLU333 and PHE281, Nafithromycin uniquely exploits key hydrophobic residues like PHE145 and HIS151 that the native ligand does not engage. Furthermore, Nafithromycin's larger macrolide ring and flexible structure enable it to occupy a broader surface area within the binding site, allowing for more extensive van der Waals contacts and enhanced structural complementarity. Unlike the native ligand, which is more compact and dependent on polar and charged interactions, Nafithromycin's broader interaction spectrum-including robust hydrophobic anchoring-makes its binding more stable and energetically favorable. Overall, the superior binding affinity of Nafithromycin arises from its ability to engage in multiple types of interactions-hydrogen bonding, hydrophobic, and π-stacking-while leveraging a greater number of key amino acid residues within the binding pocket, resulting in a stronger and more versatile binding mode compared to the native ligand. These characteristics point to Nafithromycin as a promising candidate for future development, particularly in overcoming resistance to traditional therapies. Experimental studies are required to validate these computational predictions and assess their therapeutic potential.

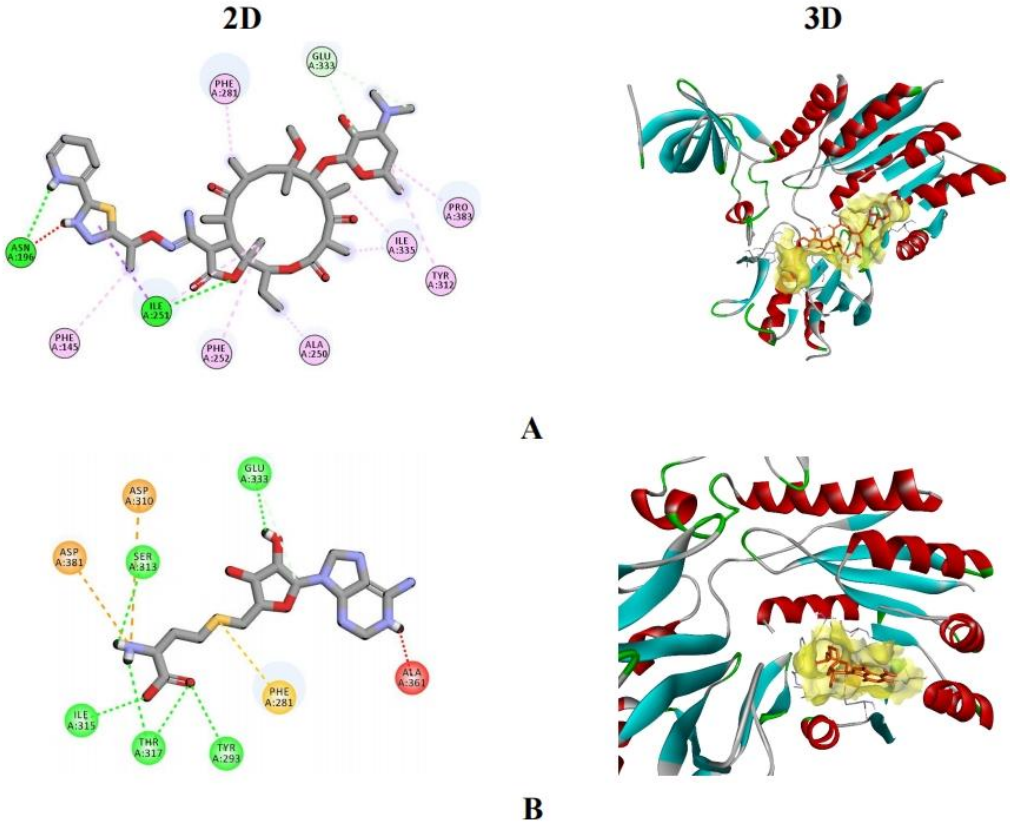

Figure 1 Illustrates (A) 2D and 3D docking poses of Nafithromycin (Miqnaf®) with proteins 23S rRNA (PDB ID: 5ZQ0).The Key interacting residues are ASN196, PHE145, HIS151, ILE251, PHE281 and GLU333. (B) 2D and 3D docking poses of native ligand with proteins 23S rRNA (PDB ID: 5ZQ0). The Key interacting residues are PHE281, TYR293, ASP310, SER313, ILE315, THR317, GLU333, and ASP381.

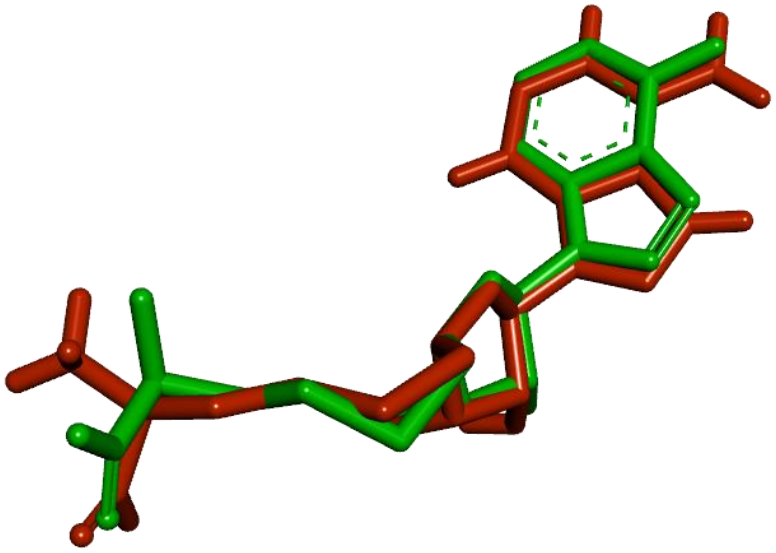

Figure 2 Illustrates the super imposable conformer pose of Nafithromycine for redocking validation by replacing the native ligand the active cavity of the methyltransferase RlmAIIin 23S rRNA in *Streptococcus pneumoniae* (PDB ID: 5ZQ0).

Table 1 Molecular docking study of Nafithromycin

Sr. No	Compound name	Molecular formula/molecular weight (gm/mol)	Target (PDB ID)	Docking score/binding affinity (kcal/mol)	Active amino acid residue	Bond length (Å)	Bond xategory	Bond types
1	Nafithromycin	$C_{42}H_{62}N_6O_{11}S$/ 859.0 g/mol	5ZQ0	−10.3			Hydrogen bond	Conventional Hydrogen bond
					ILE251	2.31	Hydrogen bond	Conventional Hydrogen bond
					ASN196	2.54	Hydrogen bond	Carbon hydrogen bond
					GLU333	3.67	Hydrogen bond	Carbon hydrogen bond
					GLU333	3.43	Hydrophobic	Pi-Sigma
					ILE251	3.71	Hydrophobic	Pi-Alkyl
					PHE145	5.09	Hydrophobic	Pi-Alkyl
					HIS151	5.07	Electrostatic	Attractive charge
					PHE281	4.93	Electrostatic	Attractive charge
	Native ligand (S-Adenosyl-L-homocysteine)	$C_{14}H_{20}N_6O_5S$/384.41 g/mol		−8			Hydrogen bond	Conventional hydrogen bond
					ASP310	5.09	Hydrogen bond	Conventional hydrogen bond
					ASP381	4.15	Hydrogen bond	Conventional hydrogen bond
					TYR293	2.87	Hydrogen bond	Conventional hydrogen bond
					ILE315	2.20	Hydrogen bond	Conventional hydrogen bond
					THR317	2.45	Hydrogen bond	Conventional hydrogen bond
					THR317	2.30	Hydrogen bond	Conventional hydrogen bond
					SER313	2.91	Hydrogen bond	Conventional hydrogen bond
					GLU333	2.17	Hydrogen bond	Conventional hydrogen bond
					GLU333	3.26	Hydrogen bond	Carbon hydrogen bond
					PHE281	3.69	Other	Pi-Sulfur

It represents the binding affinities (kcal/mol), hydrogen bonds, and active amino acid residues with their bond length (Å). gm/mol: Gram per mole; PDB ID: Protein Data Bank Identifier; kcal/mol: Kilocalories per mole (binding affinity); Å: Ångstrom.

Discussion

Computational studies have become critical tools in the early stages of drug discovery and development, particularly for understanding the molecular interactions that underpin therapeutic efficacy. These *in-silico* methods, such as molecular docking, provide extensive insights into ligand-receptor binding mechanisms and aid in the prioritization of lead candidates by assessing their binding affinity and stability with the target biomolecule. In the case of community-acquired bacterial pneumonia, where drug resistance has significantly hampered the efficacy of traditional antibiotics, such

investigations are critical in developing and testing new treatments capable of overcoming resistance barriers. In this study, molecular docking simulations were performed to assess the interaction of Nafithromycin with the 23S rRNA of *Streptococcus pneumoniae* (PDB ID: 5ZQ0), focusing on its potential to inhibit the RlmAII methyltransferase-an enzyme associated with macrolide resistance. The docking score of Nafithromycin (−10.3 kcal/mol) was significantly more favorable compared to the native ligand (−8.0 kcal/mol), indicating stronger binding affinity. This enhanced binding was attributed to a combination of conventional hydrogen bonding (e.g., ILE251, ASN196), carbon-hydrogen bonding (GLU333), and critical hydrophobic interactions with residues such as PHE145, HIS151, and PHE281. The optimal bond lengths and the diversity of interactions suggest a stable and specific ligand-receptor complex, highlighting Nafithromycin's potential as an effective 23S rRNA inhibitor.

The increased binding affinity and diversified interaction profile of Nafithromycin, particularly its strong hydrogen bonding and extensive hydrophobic interactions with critical residues, indicate a more sustained and robust engagement with its bacterial target than the native ligand. These features are crucial in combating resistance processes, which frequently jeopardize the efficacy of current antibiotics. Nafithromycin's capacity to generate strong contacts even in mutant or changed binding sites demonstrates its potential as a therapeutic agent against drug-resistant bacteria. This is especially important in the treatment of community-acquired bacterial pneumonia, since resistance to macrolides and other frontline antibiotics is increasing. The structural insights revealed here support Nafithromycin's potential as a next-generation antibiotic capable of meeting critical clinical needs in the fight against resistant respiratory infections.

The challenge of combating drug-resistant CABP underscores the urgent need for novel antimicrobial agents. CABP remains a leading cause of mortality globally, especially in countries like India, where it accounts for nearly a quarter of the global pneumonia burden. Resistance to macrolides and beta-lactams, particularly in *S. pneumoniae*, has become a critical public health concern. Nafithromycin addresses this need by exhibiting high *in-vitro* activity against macrolide-resistant strains of *S. pneumoniae*, *S. pyogenes*, and other *streptococci*. It acts on both domains II and V of the 23S rRNA, allowing it to overcome traditional resistance mechanisms mediated by ermB, mef, and mutations in ribosomal proteins such as L4 and L22.

Agar dilution MIC testing further confirmed Nafithromycin's superior potency, with MICs ranging from 0.03–0.5 µg/mL against various resistant *S. pneumoniae* strains and MSSA. Compared to telithromycin, azithromycin, and penicillin G, Nafithromycin consistently demonstrated lower MIC values, suggesting stronger antimicrobial efficacy. *In vivo* murine models of peritonitis and systemic pneumococcal infection reinforced these findings, showing that Nafithromycin cleared resistant strains from the lungs more effectively than existing macrolides. Its activity against *H. influenzae* in neutropenic mice and its consistent performance in the face of multiple resistance mechanisms further support its utility in complex clinical scenarios. Additionally, Nafithromycin exhibits a low tendency to induce resistance, an essential trait for sustaining long-term therapeutic efficacy. Clinical studies further support its development: Phase I trials confirmed its safety and tolerability, with linear pharmacokinetics and excellent lung accumulation. Phase II and III data, including studies specific to the Indian population, demonstrated clinical efficacy with minimal adverse events, establishing non-inferiority to oral moxifloxacin [9, 19, 20]. Together, these findings validate Nafithromycin as a strong candidate for treating drug-resistant CABP. Its robust *in-vitro* activity, favorable pharmacokinetics, low resistance potential, and superior molecular interactions with the bacterial ribosome underscore its promise as a next-generation macrolide. Continued clinical evaluation and post-market surveillance will be crucial to fully realize its therapeutic potential and integrate it into global antimicrobial stewardship strategies. The molecular docking studies demonstrated that Nafithromycin has a strong binding affinity to key bacterial target, which supports its antibacterial action. Stable interactions show that critical bacterial functions can be effectively inhibited. These findings correlate with Nafithromycin's known clinical efficacy. The findings emphasize its potential in combating bacterial resistance.

Conclusion

Nafithromycin (Miqnaf®) holds great promise as a next-generation macrolide for treating drug-resistant CABP. Molecular docking analyses demonstrated that Nafithromycin has a higher binding affinity and stability against *Streptococcus pneumoniae*'s 23S rRNA. It works extremely well against resistance mechanisms because it targets Domains II and V and interacts effectively with key residues. Its superior potency over traditional macrolides such as azithromycin, combined with favorable pharmacokinetics and low resistance induction, highlight its potential as a useful treatment option.

Limitations and future prospects

The Limitation of this study is its dependence on *in silico* techniques without biological validation. While computational predictions provide useful information, experimental confirmation via *in vitro* assays with relevant cell models is required. In addition, *in vivo* studies are required to determine the efficacy, safety, and pharmacokinetics of the proposed candidates. Future research should incorporate molecular, cellular, and animal studies to increase the translational relevance. Clinical validation would help to establish the findings' therapeutic potential.

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