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Triazole Derivatives as Potential MCR-1 Inhibitors: A Promising Approach to Overcome Colistin Resistance

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Abstract

BACKGROUND/AIMS: Colistin, a last-resort antibiotic, is crucial in treating multidrug-resistant Gram-negative infections. However, the rise of colistin resistance, particularly due to plasmid-mediated *MCR-1* genes, poses a significant challenge. This study explored the possibility of using triazole derivatives as potential MCR-1 inhibitors. The study aimed to explore various triazole derivatives as bioisosteric replacements for these heterocycles, given their similar electronic properties and interactions with biological targets to design new molecules with improved efficacy and pharmacokinetic profiles.

MATERIALS AND METHODS: Triazole derivatives were created by applying modifications to their R1 groups on the triazole ring. After modifications, their efficacy was evaluated through molecular docking and molecular dynamics simulations using AutoDock4 and GROMACS software.

RESULTS: The results demonstrated that triazole derivatives with the N-phenylsulfonamide modification exerted superior activity and pharmacokinetic profile over other derivatives formed. Notably, this compound interacted strongly with MCR-1 residues in the catalytic domain, making it a promising candidate to combat colistin resistance.

CONCLUSION: This study highlights that triazole derivatives might be promising candidates for MCR-1 inhibition to combat colistin-resistant infections.

Keywords: MCR-1, colistin-resistance, multidrug-resistant Gram-negative infections, triazoles, computer-aided drug design

INTRODUCTION

Polymyxins, such as colistin, are effective against Gram-negative bacteria like *Acinetobacter* spp., *Pseudomonas aeruginosa*, and *Klebsiella* spp.[1-3] Colistin targets bacterial membranes by interacting with lipid A in lipopolysaccharides, disrupting membrane integrity and causing cell death.[4] Resistance to polymyxins has evolved through chromosomal mutations and plasmid-mediated mechanisms, particularly via the *MCR-1* gene.[5] This gene, discovered in 2015, encodes a phosphoethanolamine (pEtN) transferase (MCR-1) that modifies lipid A, reducing the binding and antimicrobial efficacy of colistin.[6] The *MCR-1* gene, which encodes pEtN transferase, modifies lipid A by adding pEtN, thereby reducing the negative charge on the membrane and enhancing lipid packing.[7] This alteration decreases the binding and penetration of polymyxins, leading to increased resistance by reinforcing the membrane and reducing antimicrobial peptide efficacy.[7] The dissemination of plasmid-borne MCR-1 confers colistin resistance, with mobile *MCR-1* gene cassettes facilitating genetic transfer across various hosts, including animals, food products, and humans.[8] Recent studies have identified inhibitors featuring pyrazolone, imidazole, and oxazole structures

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as agents targeting *MCR* genes (MCR-1 to MCR-10).[9-11] These inhibitors aimed to restore the effectiveness of colistin against resistant bacterial strains by inhibiting the enzymatic activity of MCR proteins. Beyond pyrazolone and other derivatives, various other bioisosteric heterocyclic compounds, including triazoles, could explored as promising candidates for the development of MCR inhibitors. The ultimate goal of this approach is to address the growing challenge of colistin resistance and to enhance treatment options for multidrug-resistant Gram-negative infections.

MATERIALS AND METHODS

Preparation of Data Set and Molecular Docking

This study does not involve the use of human or animal samples; therefore, ethical approval is not applicable. In this study, seven triazole derivatives (Ligand 1-7), each varying by the R groups attached to the N-4 position of the triazole ring, were chosen from the ZINC and ChemDiv ligand libraries. The main differences between triazole-containing ligands are illustrated in Figure 1. Ligand preparation was performed using LigandScout 4.0, followed by molecular optimization with the Avogadro tool (https://avogadro.cc/). AutoDock4 was utilized to conduct molecular docking studies to determine the binding affinities of the triazole derivatives to the MCR-1 catalytic domain (PDB ID: 5LRM).[12] The docking results were assessed by analyzing binding energies and protein-ligand interactions.

Statistical Analysis

GROMACS software was used to assess the statistical analysis of the complex stability, and Molecular Mechanics/Poisson-Boltzmann Surface Area (MM/PBSA) calculations were performed with g_mmpbsa to estimate binding free energies with mean standard deviations.[13] The stability of the most effective ligand was confirmed further by the root mean square (RMSD) plot.

Pharmacokinetic Predictions

Pharmacokinetic properties absorption, distribution, metabolism, excretion, toxicity of the triazole derivatives were assessed using ProTox II and SwissADME, analyzing key factors like LogP, gastrointestinal (GI) absorption, plasma protein binding, and enzyme inhibition potential to evaluate their pharmacokinetic profile and drug interaction risks.[14]

RESULTS

The *in silico* analysis of the seven triazole derivatives demonstrated varying levels of interaction with MCR-1, with Ligand 6 emerging as the most promising candidate. The MM/PBSA binding energy of Ligand 6 was calculated to be -29.72±1.82 kJ/mol, representing the strongest binding affinity among the compounds. Its docking score of -12.4 kcal/mol further confirmed this high affinity, indicating robust interactions with the MCR-1 protein. This was likely due to the presence of a 4-sulfonamide moiety in Ligand 6, which facilitated stronger interactions with critical amino acid residues in the protein's active site (Figure 2). Specifically, aspartate and arginine amino acids were key residues involved in stabilizing the ligand-protein complex. The RMSD values for both the MCR-1 and Ligand 6 indicated a stable interaction throughout the molecular dynamics simulation (Figure 3). Similarly, Ligand 5 exhibited favorable results, with a binding energy of -26.33±1.63 kJ/mol and a docking score of -11.7 kcal/mol, making it the second most effective compound in the series. While slightly less potent than Ligand 6, Ligand 5 still showed a strong potential for MCR-1 inhibition due to its high binding energy and favorable interactions with the protein. However, other ligands such as Ligand 1 and Ligand 3 showed weaker binding energies and docking scores. For instance, Ligand 1 presented a binding energy of -16.23±1.32 kJ/mol and a docking score of -7.3 kcal/mol, while Ligand 3 had the weakest values among the derivatives, with a binding energy of -14.84±1.72 kJ/mol, and a docking score of -6.7 kcal/mol. Moreover, pharmacokinetic predictions revealed optimal properties for all ligands, with Ligand 6

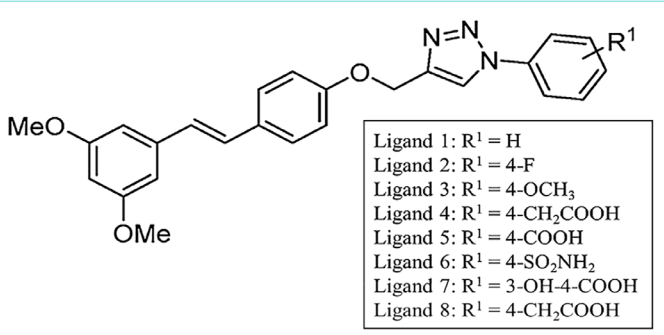

Figure 1. General structure of triazole derivatives with different R1 groups on triazole ring.

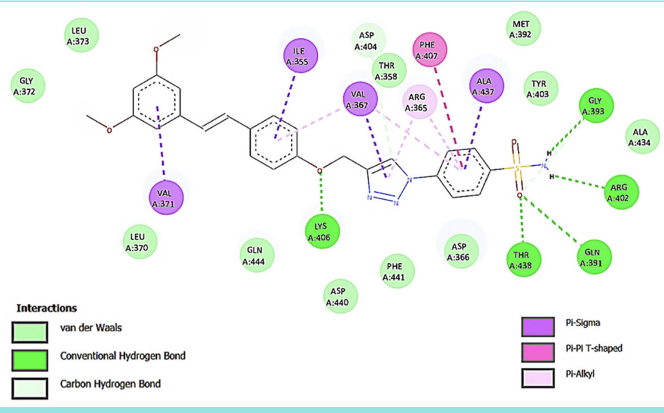

Figure 2. 2D interaction map of Ligand 6 within the MCR-1 active site, highlighting various interactions contributing to its binding affinity.

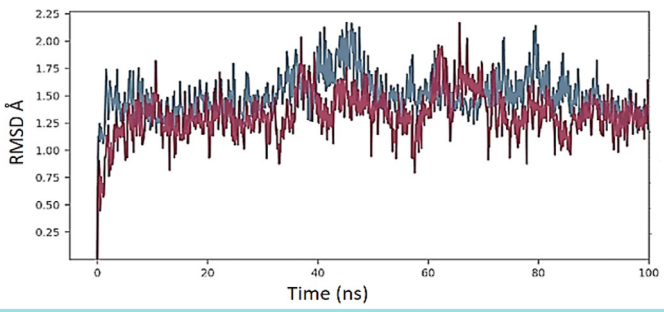

Figure 3. RMSD graph of Ligand 6 and MCR-1 in a 100 ns simulation period. The blue color indicates the RMSD of MCR-1, while the red color indicates the RMSD of Ligand-6.

RMSD: Root mean square deviation.

emerging as the most promising. It exhibited a favorable LogP value of 0.472, which supports good membrane permeability and absorption, as confirmed by a GI absorption score of 0.511. Ligand 6 also had 73% plasma protein binding, ensuring sufficient free drug in circulation, and showed no inhibition of major CYP450 enzymes, indicating low drug-drug interaction potential. In addition, the half-life of Ligand 6 was predicted as 5.242 hours, making it suitable for regular dosing intervals.

DISCUSSION

Resistance to colistin, especially driven by the *MCR-1* gene, poses a major global health concern, as it compromises the effectiveness of one of the last-resort antibiotics used to treat multidrug-resistant Gram-negative bacterial infections.[15] In the current study, several triazole derivatives were evaluated as potential inhibitors of MCR-1. Ligand 6 showed the most promising results, with strong binding energy and favorable docking scores. The presence of a 4-sulfonamide group facilitated significant interactions in the MCR-1 binding pocket. As mentioned earlier, these interactions are crucial for the inhibition of MCR-1 activity, indicating the potential of Ligand 6 for restoring the efficacy of colistin. The strong binding interactions at aspartate and arginine residues suggested that Ligand 6 could inhibit the activity of MCR-1, potentially restoring the efficacy of colistin against resistant bacterial strains. The results from the present study aligned with earlier research on MCR-1 inhibitors. For instance, Hanpaibool et al.[16] investigated pyrazolone-based compounds as potential MCR-1 inhibitors. The study reported that some of these compounds enhanced colistin efficacy by lowering the minimal inhibitory concentration of colistin in *MCR-1*-expressing *E. coli* strains. Compared to research by Hanpaibool et al.[16], reporting the most effective compound (Py4i) exhibiting a binding free energy of -6.64 kcal/mol, the current study on the triazole derivative Ligand 6 demonstrated a significantly stronger binding affinity with a docking score of -12.4 kcal/mol, suggesting that triazoles may provide a more effective approach for overcoming colistin resistance.

In the present study, MM/PBSA calculations were used to estimate the binding free energies, providing a detailed insight into the strength of the ligand-protein interactions, similar to previous reports.[13] The superior inhibitory effects of Ligands 5 and 6 might be due to the nature of their functional groups and interactions with the MCR-1 catalytic domain. The carboxyl group (COOH) of Ligand 5 at the 4-position is negatively charged and highly polar. This might be attributed to its enhanced binding affinity and inhibitory potency. Likewise, the sulfonamide group (SO_2NH_2) of Ligand 6 exhibited strong polarity and electrostatic interaction potential, forming extensive hydrogen and ionic bonds with the active site. The large size of the sulfonamide group further increased surface interactions, leading to stronger binding affinity and inhibitory efficacy. On the other hand, Ligand 3, which contains a methoxy group (OCH_3), demonstrated weaker interactions with the MCR-1 catalytic site. The methoxy group is electron-donating and lacks significant polarity, reducing its ability to engage in strong electrostatic interactions. As a result, the binding energy and docking scores for Ligand 3 were less favorable. Ligand 2, which contains a fluorine atom (F) at the 4-position, exhibited slightly stronger binding than Ligand 3 due to the electron-withdrawing nature of fluorine. However, its small size might limit the extent of its interactions with the binding pocket, resulting in weaker inhibition compared to Ligands 5 and 6. In addition, Ligand 6 exhibited a highly favorable pharmacokinetic profile, particularly with its optimal LogP and GI absorption values, indicating desirable membrane permeability and potential for effective oral bioavailability. Furthermore, its lack of CYP450 enzyme inhibition suggests a low risk of drug-drug interactions, making it a promising candidate for further development.

Study Limitations

The key limitation of this study is its reliance on *in silico* methods, meaning that the results need to be validated through experimental *in vitro* and *in vivo* studies.

CONCLUSION

This study highlighted the potential of triazole derivatives, particularly Ligand 6, as promising MCR-1 inhibitors to combat colistin resistance. Despite the limitations of this *in silico* study, the results provided a solid foundation for further *in vitro* and *in vivo* studies, with the long-term goal of developing alternative strategies to combat antibiotic resistance in critical bacterial infections.

MAIN POINTS

- All triazole derivatives exhibited optimal pharmacokinetic properties.
- A triazole derivative with a 4-sulfonamide group demonstrated the highest binding affinity.
- Strong interactions with MCR-1 residues, particularly aspartate and arginine, confirmed the inhibitory potential of all triazole derivatives.

ETHICS

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Concept: E.E., C.S.Ö., C.B., Design: E.E., C.S.Ö., C.B., Data Collection and/or Processing: E.E., Analysis and/or Interpretation: E.E., C.S.Ö., C.B., Literature Search: C.B., Writing: E.E., C.S.Ö., C.B.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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