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DESIGN AND IN-SILICO EVALUATION OF NOVEL MOLECULAR HYBRIDS AS POTENTIAL ANTIMICROBIAL AGENTS FOR OVERCOMING ANTIMICROBIAL RESISTANCE

[1]Ashwini Khodatkar, [2]Arpita Landge, [3]Bharti Jaisawal, [4]Shejal Jagtap
[1]Assistant Professor, [2]B.Pharm, [3]B.Pharm, [4]B.Pharm
[1]Agnihotri Institute of Pharmacy, Wardha
[1]Agnihotri Group of Institution, Wardha, India

1. Abstract

The major challenge associated with the treatment of infectious diseases in today's world is the problem of Antimicrobial Resistance (AMR). AMR occurs through mechanisms such as drug deactivation, change in target, reduced drug concentration inside the cell, change in permeability, biofilm formation and other mechanisms. Thus, approaches that allow developing structurally and mechanistically different compounds are required to discover new antibacterial agents. The medicinal chemistry approach "molecular hybridization" allows the combination of two pharmacologically important structural units into one chemical compound. This project proposes the rational design of molecular hybrids containing complementary antibacterial pharmacophoric features and their preliminary evaluation using computer-aided drug-design methods. A workflow involving literature review, target selection, ligand design, molecular docking, physicochemical and ADME prediction, toxicity alerts and structure–activity relationship analysis will be used. The best computational candidates can subsequently be synthesized and tested by appropriate microbiological and cytotoxicity assays. The work is intended to generate testable hypotheses rather than claim clinical efficacy or confirmed reversal of antimicrobial resistance.

2. Keywords

Computer-Aided Drug Design, Pharmacophore, SAR, ADME, Drug Discovery, Antibiotic Resistance, Molecular Hybridization, Antimicrobials, Medicinal Chemistry, Molecular Docking, and Resistant Microbes.

3. Introduction

Antibacterial medicines are essential for treating infections caused by pathogenic bacteria. However, microorganisms can adapt under selective pressure, and resistance can emerge or spread through genetic and biochemical mechanisms. The result may be treatment failure, longer illness, increased healthcare burden and limited therapeutic options [1-5]. New antibiotics remain necessary, but simply modifying an existing scaffold may not always provide sufficient differentiation. Medicinal chemistry therefore increasingly explores approaches that combine multiple structural features or biological mechanisms. Molecular hybridization is one such approach. Instead of developing two separate molecules, a chemist can join selected pharmacophores into a single hybrid scaffold. Depending on the design, the hybrid may show improved target recognition, altered physicochemical properties, or activity against more than one relevant pathway. The approach is particularly interesting for AMR research because resistant bacteria can possess several simultaneous defense mechanisms.

4. Background of Antimicrobial Resistance

Resistance can be developed naturally by a species or through mutation and transfer of genes horizontally. Antibiotic exposure can select organisms carrying advantageous resistance traits. Clinically important resistant bacteria include MRSA, resistant Enterobacter ales, Pseudomonas aeruginosa and Acinetobacter baumannii [1,5]. Resistance is not a single phenomenon; it is a collection of mechanisms that reduce the effective exposure of a bacterium to an antimicrobial agent [6,7].

5. Major Mechanisms of Bacterial Resistance

- Enzymatic inactivation: bacterial enzymes can chemically modify or destroy an antimicrobial molecule.
- Target modification: mutations or acquired genes can change the drug-binding site and reduce affinity.
- Reduced permeability: changes in bacterial membranes or porins can limit entry of drugs.
- Active efflux: transport proteins can pump antibacterial compounds out of the cell.
- Metabolic bypass: bacteria may use alternative biochemical pathways when one pathway is blocked.
- Biofilm-associated tolerance: cells in biofilms can become much less susceptible to antimicrobial treatment.
- Horizontal gene transfer: resistance determinants can spread between bacteria through mobile genetic elements [6].

6. Why New Molecular Designs Are Needed

A new antibacterial candidate should ideally combine sufficient target engagement with acceptable physicochemical, pharmacokinetic and safety properties. Molecular hybridization can provide a systematic way to explore new chemical space. However, combining two pharmacophores can also increase molecular size, lipophilicity or polarity, so optimization is essential.
The project therefore evaluates not only docking but also drug-likeness and ADME-related properties.

7. Molecular Hybridization: Concept

Molecular hybridization is the logical fusion of two or more biologically
pertinent molecular pieces in a single chemical framework [8-10]. The pieces could
be linked either directly or via a linker. The fragments may be connected directly or through a linker. The design can be based on pharmacophore fusion, linking or merging strategies. In a fusion approach, common structural features are integrated into a compact scaffold. In a linking approach, two recognizable pharmacophores remain connected by a spacer.

8. Proposed Design Logic

Validated antibacterial motif A → linker selection → antibacterial motif B → virtual library → docking → ADME/drug-likeness → SAR ranking → candidate selection → synthesis and biological validation.

9. Selection of Pharmacophores

- Choose motifs supported by published antibacterial evidence.
- Prefer pharmacophores associated with different or complementary biological mechanisms.
- Consider known structure–activity relationships before introducing substitutions.
- Evaluate whether the combined molecule can remain chemically and pharmacologically feasible.
- Check exact structures and close analogues in literature and patent databases before using the word "novel" [18].

10. Linker Design

The linker is not merely a connector. Its length, flexibility, polarity and geometry can influence whether both pharmacophoric regions reach their intended binding environments. Short linkers may create steric constraints, while overly long or flexible linkers may increase conformational entropy and molecular size [9,10]. A small set of systematically varied linkers is therefore preferable to an uncontrolled number of structures.

11. Proposed Conceptual Hybrid Series

Series Design Principle Purpose

H1 Pharmacophore A–short linker–B Explore compact dual-feature molecules

H2 A–polar linker–B Explore hydrogen-bonding and polarity effects

H3 A–flexible linker–B Explore conformational adaptability

H4 A/B substituent variants Generate preliminary SAR

H5 Optimized lead-like hybrids Balance binding and drug-like properties

Important: These are design categories, not experimentally validated compounds.

12. Aim

To design and computationally evaluate novel molecular hybrids as potential antibacterial candidates relevant to antimicrobial resistance.

13. Specific Objectives

- Review current antibacterial drug-discovery strategies and AMR mechanisms.
- Identify suitable bacterial proteins and ligands for structure-based design.
- Select two complementary antibacterial pharmacophoric motifs.
- Design a focused virtual library of hybrid molecules.
- Optimize structures for basic physicochemical and drug-like characteristics [14-16].
- Perform molecular docking using validated protocols [13].
- Analyze ligand–protein interactions and rank candidates.
- Predict ADME-related properties and identify structural liabilities.
- Establish preliminary SAR relationships.
- Recommend selected candidates for future chemical synthesis and biological testing.

Which structures should be prioritized for future synthesis and microbiological evaluation?

14. Suggested Bacterial Targets

Depending on the selected chemical series, the study may focus on validated targets involved in DNA replication, folate metabolism, cell-wall biosynthesis, protein synthesis or other essential bacterial processes. The final paper should identify the exact protein structures, database/PDB identifiers, resolution, bound ligands where applicable and the reason each target was selected [13].

15. Suggested Resistant Pathogens

- Staphylococcus aureus and MRSA
- Escherichia coli and resistant Enterobacter ales
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Acinetobacter baumannii [1,5]

16. Evaluation Parameters

Parameter What to record Interpretation Docking Score for each pose Used for comparative ranking only Binding interactions H-bonds, hydrophobic contacts, ionic interactions Helps explain predicted recognition Molecular weight Calculated value Very high values may reduce drug-like behavior Lipophilicity Predicted logP/logD Influences permeability and solubility TPSA Calculated polar surface area Useful for comparing polarity/permeability HBD/HBA Hydrogen-bond donors/acceptors
Describes hydrogen-bonding capacity Rotatable bonds Count Provides a simple flexibility measure ADME predictions

Absorption, metabolism, etc. Early prioritization Toxicity alerts Predicted alerts Identifies candidates needing caution Parameter What to record Interpretation SAR Substituent vs predicted effect Guides next-round design

17. Comparative Analysis

Include at least one suitable reference ligand or known antibacterial drug in the computational workflow [13]. Compare predicted interactions rather than simply selecting the compound with the lowest docking score. A good candidate should ideally show a plausible binding mode together with acceptable physicochemical and ADME predictions.

18. Expected Results

- A focused library of proposed molecular hybrids.
- Identification of compounds with favorable predicted target interactions.
- Preliminary relationships between linker/substituent changes and docking behavior.
- A ranked list of candidates for future synthesis.
- Early identification of physicochemical or toxicity-related liabilities.
- A computational framework that can support subsequent experimental studies.

19. Proposed Experimental Validation After In-Silico Screening

The computational phase should be followed by laboratory validation if facilities and approvals are available. The experimental stage should be performed under institutional biosafety and laboratory procedures. Candidate compounds can first undergo chemical identity/purity confirmation and then appropriate antimicrobial susceptibility testing against selected bacterial strains. MIC and related assays should be performed using recognized standardized procedures [1,4]. Cytotoxicity and selectivity should be investigated before drawing conclusions about therapeutic potential.

20. Possible Experimental Evaluation

- Chemical characterization and purity assessment
- Detection of Antibiotic Sensitivity
- Minimum Inhibitory Concentration (MIC)
- Where appropriate, Minimum Bactericidal Concentration (MBCTime-kill analysis for selected candidates
- Biofilm-related assays when scientifically justified
- Cytotoxicity/selectivity assessment
- Mechanistic studies to test the predicted target/pathway

21. Statistical Analysis

For experimental assays, perform adequate biological replicates and report mean ± appropriate variability measures. Select statistical tests based on experimental design and distribution. Computational rankings should be reported separately from experimental measurements.

22. Advantages of the Proposed Approach

- Reduces the number of compounds that need to be synthesized initially.
- Allows rapid comparison of multiple structural ideas.
- Supports rational SAR development.
- Can combine binding analysis with early ADME filtering.
- Provides hypotheses that can be experimentally tested.
- Creates a reproducible framework suitable for a B. Pharm research project.

23. Limitations

- Docking scores do not equal antimicrobial potency [13].
- Protein flexibility and solvent effects may be incompletely represented.
- Predicted ADME and toxicity values may differ from experimental results [14-16].
- Combining pharmacophores can increase molecular size and reduce permeability.
- Resistance reversal cannot be claimed without microbiological and mechanistic evidence.
- Novelty cannot be established without a current literature and patent search.

24. Conclusion

Molecular hybridization provides a rational medicinal-chemistry strategy for exploring new antibacterial chemical space [8-10] in the context of antimicrobial resistance. The proposed project combines pharmacophore selection, focused molecular design, docking, ADME/drug-likeness prediction and SAR analysis to prioritize candidates for future laboratory testing. The computational results should be treated as hypotheses. Confirmation of antibacterial activity, mechanism, selectivity and the ability to address resistance requires experimental validation.

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