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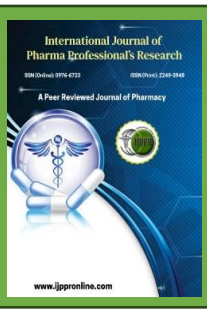

A Review on Structure-Activity Relationship Studies of New Anti-microbial Compounds

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ABSTRACT

The increasing prevalence of antimicrobial resistance (AMR) has prompted urgent efforts to discover and develop new antimicrobial compounds. Structure-Activity Relationship (SAR) studies are crucial in the design of these compounds, helping to elucidate the link between molecular structure and biological activity. This review provides an in-depth analysis of SAR studies in the context of antibiotics, antifungals, antivirals, and antiparasitics. It highlights the role of SAR in optimizing the potency, selectivity, and pharmacokinetic properties of antimicrobial agents. Key molecular features influencing activity, including functional groups, lipophilicity, hydrogen bonding, and steric factors, are examined for their impact on antimicrobial efficacy. The review also explores various SAR methodologies, including experimental approaches such as chemical modifications and analog synthesis, alongside computational techniques like Quantitative SAR (QSAR) modeling and molecular docking. Furthermore, case studies on β-lactam antibiotics, azole antifungals, and natural product derivatives demonstrate the practical applications of SAR in identifying promising antimicrobial candidates. Advances in SAR, particularly through the use of AI, machine learning, and high-throughput screening, are also discussed. Despite significant progress, challenges remain, such as the complexity of biological systems, multi-target interactions, and the predictive accuracy of computational tools. The review concludes by emphasizing the need for multidisciplinary approaches to overcome these challenges and accelerate the development of new, more effective antimicrobial therapies.

Keywords: *Structure-Activity Relationship, antimicrobial resistance, antibiotics, antifungals, antivirals and antiparasitic*

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1. Introduction

Structure-Activity Relationship (SAR) refers to the relationship between the chemical structure of a molecule and its biological activity. This concept is crucial in the fields of medicinal chemistry and drug development, as it helps researchers understand how modifications to a molecular structure can influence its efficacy and safety. The concept of SAR was first introduced by Alexander Crum Brown and Thomas Richard Fraser in 1868. Since then, it has evolved into a systematic approach used in drug discovery to identify which chemical groups are responsible for a specific biological effect, allowing for the optimization of drug candidates through structural modifications.[1-3]

1.2 Importance of SAR in drug design

Structure-Activity Relationship (SAR) is crucial in drug design as it establishes a direct link between the chemical structure of a compound and its biological activity. By analyzing how specific structural features influence efficacy and safety, SAR enables researchers to predict the biological activity of new compounds, significantly streamlining the drug discovery process. It guides molecular modifications, allowing medicinal chemists to enhance desirable properties such as potency, selectivity, and metabolic stability while minimizing side effects. Moreover, SAR helps elucidate the mechanisms of action of drugs, facilitating the design of targeted therapies that interact specifically with biological targets. The integration of Quantitative Structure-Activity Relationship (QSAR) models further enhances predictive capabilities, allowing for the optimization of lead compounds based on existing data. Historical examples, such as the development of selective serotonin reuptake inhibitors (SSRIs), demonstrate how SAR analyses can lead to significant improvements in drug efficacy. Overall, SAR is indispensable in developing effective and safe pharmaceuticals, contributing to better therapeutic outcomes and advancing modern pharmacology.[4-6]

1.3 Rising antimicrobial resistance

Rising antimicrobial resistance (AMR) is becoming a critical global health threat, with projections indicating that it could lead to more than 39 million deaths over the next 25 years. A recent study published in The Lancet highlights that over 1 million people died annually from AMR-related infections between 1990 and 2021, with this number expected to rise significantly. By 2050, it is estimated that AMR could directly cause approximately 1.91 million deaths per year and contribute to around 8 million deaths annually, either as a direct cause or a contributing factor.[7]

The increase in AMR is attributed primarily to the misuse and overuse of antibiotics in healthcare, agriculture, and animal husbandry. This has led to rising resistance rates among key pathogens, particularly Gram-negative bacteria, which are notoriously difficult to treat. For instance,

resistance to carbapenems—a class of last-resort antibiotics—has surged, complicating treatment options for common infections46. The World Health Organization has reported alarming resistance rates, with significant implications for public health across all regions and income levels, particularly affecting low- and middle-income countries.[8]

The COVID-19 pandemic has exacerbated the situation by increasing antibiotic use and hindering infection control efforts, resulting in a resurgence of resistant infections3. Without urgent action, including improved healthcare access, better infection prevention strategies, and the development of new antibiotics, AMR could undermine decades of medical advances and lead to catastrophic health outcomes globally56. Therefore, addressing AMR is not only a matter of public health but also essential for economic stability and development worldwide.[9]

1.4 Role of SAR in developing new compounds

The role of Structure-Activity Relationship (SAR) in developing new compounds is pivotal in the field of medicinal chemistry and drug design. SAR provides a systematic approach to understanding how the chemical structure of a molecule correlates with its biological activity, enabling researchers to make informed modifications to enhance drug efficacy and safety. By analyzing the structural characteristics associated with desired biological effects—such as enzyme inhibition or antimicrobial activity—scientists can identify which specific modifications improve or diminish a compound's effectiveness.[10]

During the early stages of drug development, particularly in hit-to-lead and lead optimization phases, SAR analyses guide medicinal chemists in making multiple chemical modifications to a lead compound. This iterative process allows for the exploration of various structural changes, helping to pinpoint key pharmacophores essential for activity and optimize interactions with biological targets. For instance, slight alterations in functional groups or core structures can lead to significant differences in a drug's potency or selectivity.[11]

Moreover, SAR facilitates the development of Quantitative Structure-Activity Relationship (QSAR) models, which employ mathematical relationships to predict the biological activity of new compounds based on their structural attributes. This predictive capability not only accelerates the discovery process but also enhances the efficiency of designing compounds with improved therapeutic profiles.[12]

Overall, SAR serves as a foundational tool in drug discovery, allowing for the rational exploration of chemical space and guiding the synthesis of novel compounds that meet specific therapeutic needs while minimizing undesirable side effects. By leveraging existing knowledge from SAR studies, researchers can effectively design and optimize new therapeutic agents tailored for specific diseases.[13]

1.5 Classes of Antimicrobial Compounds

Antimicrobial compounds are categorized based on their target organisms and mechanisms of action. The major classes include antibiotics, antifungals, antivirals, and antiparasitics. Each class has distinct subcategories that target specific pathogens (Figure 1).[14,15]

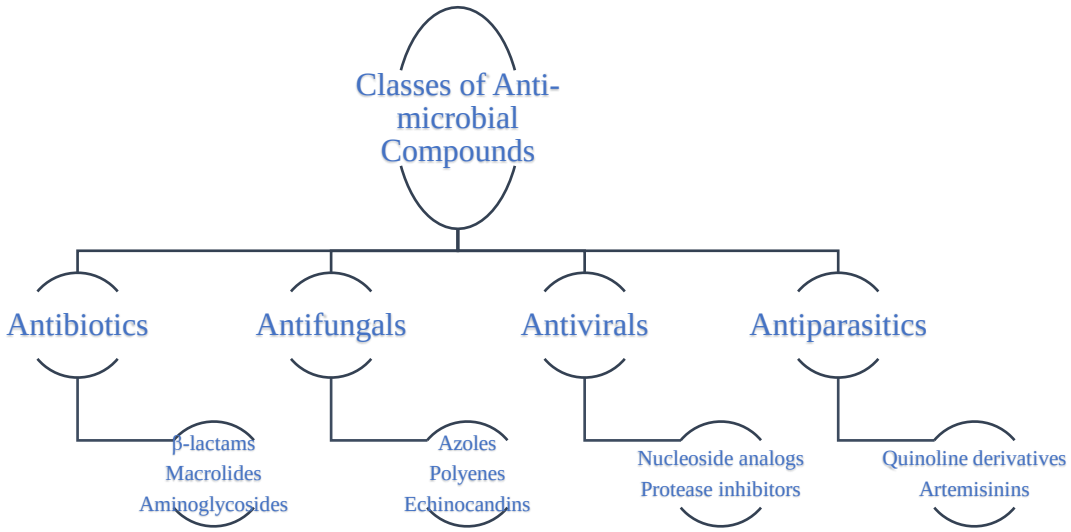

Figure 1: Classes of Anti-microbial Compounds

1.5.1 Antibiotics

1.5.1.1 β-lactams

β-lactams are a broad class of antibiotics characterized by their β-lactam ring structure. They include penicillins, cephalosporins, carbapenems, and monobactams. These antibiotics work by inhibiting bacterial cell wall synthesis, which is crucial for bacterial growth and survival. Common examples include penicillin and amoxicillin, which are effective against a variety of Gram-positive bacteria. However, the emergence of β-lactamase enzymes in bacteria has led to resistance against many β-lactam antibiotics, necessitating the development of newer agents or combinations to overcome this challenge.[16,17]

1.5.1.2 Macrolides

Macrolides are another class of antibiotics that inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome. They are particularly effective against Gram-positive bacteria and some atypical pathogens such as Mycoplasma and Chlamydia. Common macrolides include erythromycin, azithromycin, and clarithromycin. They are often used to treat respiratory tract infections and skin infections. While generally well-tolerated, resistance can develop through methylation of the ribosomal RNA or efflux mechanisms.[18,19]

1.5.1.3 Aminoglycosides

Aminoglycosides are a class of antibiotics that also inhibit protein synthesis but do so by binding to the 30S ribosomal subunit. They are primarily effective against aerobic Gram-negative bacteria and are often used in serious infections due to their potent bactericidal activity. Examples include gentamicin and amikacin. However, aminoglycosides can be nephrotoxic and ototoxic, limiting their use in certain populations.[20,21]

1.5.2 Antifungals

1.5.2.1 Azoles

Azoles are a major class of antifungal agents that inhibit the synthesis of ergosterol, a critical component of fungal cell membranes. This class includes both imidazoles (e.g., ketoconazole) and triazoles (e.g., fluconazole, itraconazole). Azoles are widely used to treat various fungal infections, including candidiasis and aspergillosis. While they are generally safe, resistance can develop through mutations in the target enzyme or increased drug efflux.[22,23]

1.5.2.2 Polyenes

Polyenes, such as amphotericin B and nystatin, bind to ergosterol in fungal cell membranes, creating pores that lead to cell death. Amphotericin B is particularly effective against a broad range of fungi but is associated with significant toxicity, including nephrotoxicity. Lipid formulations have been developed to reduce toxicity while maintaining efficacy.[24,25]

1.5.2.3 Echinocandins

Echinocandins (e.g., caspofungin, micafungin) inhibit the synthesis of glucan in the fungal cell wall, leading to cell lysis. They are particularly effective against Candida and Aspergillus species and have minimal toxicity compared to polyenes. Echinocandins are often used as first-line therapy for invasive candidiasis due to their safety profile.[26,27]

1.5.3 Antivirals

1.5.3.1 Nucleoside Analogs

Nucleoside analogs mimic the building blocks of viral nucleic acids and interfere with viral replication. Examples include acyclovir for herpes simplex virus and zidovudine for HIV. These agents can be highly effective but may lead to resistance through mutations in viral polymerases.[28,29]

1.5.3.2 Protease Inhibitors

Protease inhibitors block the activity of viral proteases necessary for processing viral proteins during replication. Drugs like ritonavir and lopinavir are used in HIV treatment regimens. While effective at controlling viral loads, resistance can arise from mutations in the viral protease gene.[30]

1.5.4 Antiparasitics

1.5.4.1 Quinoline Derivatives

Quinoline derivatives, such as chloroquine and mefloquine, are primarily used to treat malaria by interfering with the parasite's ability to digest hemoglobin within red blood cells. Resistance has emerged due to mutations in the parasite's transport proteins.[31]

1.5.4.2 Artemisinins

Artemisinins (e.g., artemether) are derived from the sweet wormwood plant and are highly effective against malaria due to their rapid action against Plasmodium parasites. They work by generating reactive oxygen species that damage parasite proteins. Resistance has been reported in some regions, emphasizing the need for combination therapies to enhance efficacy.[32]

1.6 SAR Methodologies

Structure-activity relationship (SAR) methodologies are essential in the field of drug discovery and development. They help establish the relationship between the chemical structure of compounds and their biological activities. SAR methodologies can be broadly categorized into experimental approaches and computational approaches. Each category encompasses various techniques that facilitate the identification, optimization, and development of new bioactive compounds.[33,34]

1.6.1 Experimental Approaches

1.6.1.1 Chemical Modifications

Chemical modifications involve systematically altering the structure of a compound to assess how these changes affect its biological activity. This process is fundamental in SAR studies as it allows researchers to identify specific functional groups or structural features that contribute to a compound's efficacy. By introducing different substituents or altering existing ones, medicinal chemists can explore a wide array of derivatives, enabling them to pinpoint optimal structures for desired biological effects. For example, modifying the side chains of a lead compound can enhance its potency or selectivity against a target enzyme or receptor.[35,36]

1.6.1.2 Analogue Synthesis

Analogue synthesis is a technique where new compounds (analogs) are synthesized based on the structure of known bioactive molecules. This approach often involves creating a series of related compounds that differ by specific structural elements, allowing researchers to evaluate how these variations influence biological activity. By comparing the activities of these analogs, scientists can derive insights into which structural modifications lead to improved efficacy or reduced toxicity. This method is particularly useful in refining drug candidates during the lead optimization phase, where small changes can have significant impacts on therapeutic outcomes.[37-38]

1.6.2 Computational Approaches

1.6.2.1 QSAR Modeling

Quantitative Structure-Activity Relationship (QSAR) modeling is a computational method that quantifies the relationship between chemical structure and biological activity using statistical techniques. QSAR models utilize molecular descriptors—quantitative representations of molecular properties—to predict the activity of new compounds based on existing data. These models can help identify promising drug candidates by allowing researchers to screen large virtual libraries of compounds efficiently. The predictive power of QSAR models can significantly accelerate the drug discovery process by guiding experimental efforts toward the most promising candidates.[39,40]

1.6.2.2 Molecular Docking

Molecular docking is a computational technique used to predict how a small molecule (ligand) interacts with a target protein (receptor). By simulating the binding process, researchers can assess the affinity and orientation of ligands within the active site of proteins. This approach helps in understanding the molecular basis of drug action and aids in optimizing lead compounds for better binding characteristics. Molecular docking also allows for virtual screening of large compound libraries, identifying potential drug candidates that may exhibit strong interactions with specific biological targets.[41]

1.6.2.3 Machine Learning in SAR

Machine learning (ML) has emerged as a powerful tool in SAR studies, enhancing traditional approaches by enabling more sophisticated analysis of complex datasets. ML algorithms can identify patterns and relationships within large sets of chemical and biological data that may not be apparent through conventional methods. Techniques such as neural networks and support vector machines are increasingly used to develop predictive models that accurately correlate molecular structures with their biological activities. By leveraging machine learning, researchers can improve the accuracy and efficiency of SAR analyses, facilitating the identification of novel compounds with desirable properties.[42]

1.7 Molecular Features Affecting Activity

The activity of pharmaceutical compounds is influenced by various molecular features that determine how effectively a drug interacts with its biological target. Understanding these features is crucial for optimizing drug design and enhancing therapeutic efficacy. Key molecular features that affect activity include functional groups, lipophilicity (Log P), hydrogen bonding capacity, electronic properties, and steric factors.[43]

1.7.1 Functional Groups

Functional groups are specific groups of atoms within molecules that are responsible for the characteristic chemical reactions of those molecules. They play a critical role in determining the biological activity of drugs by influencing their interactions with biological targets such as enzymes and receptors. For example:

1.7.1.1 Hydroxyl Groups (-OH): Often enhance solubility in water and can participate in hydrogen bonding, which may improve binding affinity to target proteins.
1.7.1.2 Amino Groups (-NH2): Can increase basicity and solubility, facilitating interactions with acidic sites on receptors or enzymes.
1.7.1.3 Carboxyl Groups (-COOH): Contribute to the acidity of a compound and can form ionic bonds with positively charged sites on biological targets.

The presence, position, and nature of functional groups can significantly impact a drug's pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (the effects of the drug on the body).[44-46]

1.7.2 Lipophilicity (Log P)

Lipophilicity refers to the affinity of a compound for lipid (fat) environments compared to aqueous (water) environments. It is quantitatively expressed as the logarithm of the partition coefficient (Log P), which measures how well a compound partition between an organic solvent (usually octanol) and water.

1.7.2.1 High Lipophilicity: Compounds with high Log P values tend to be more soluble in lipids, facilitating cell membrane penetration and absorption. However, excessive lipophilicity can lead to poor solubility in aqueous environments, potentially hindering bioavailability.

1.7.2.2 Low Lipophilicity: Compounds with low Log P values are more hydrophilic, which can enhance solubility but may limit their ability to cross lipid membranes.

Balancing lipophilicity is crucial in drug design; optimal Log P values typically fall within a range that maximizes absorption while minimizing toxicity.[47,48]

1.7.3 Hydrogen Bonding Capacity

Hydrogen bonding capacity refers to the ability of a molecule to form hydrogen bonds with other molecules. This property is essential for determining the interaction strength between drugs and their targets.

1.7.3.1 Hydrogen Bond Donors: Molecules that can donate hydrogen bonds (e.g., -OH or -NH groups) may enhance binding affinity to receptors or enzymes by stabilizing interactions through hydrogen bonding.

1.7.3.2 Hydrogen Bond Acceptors: Molecules that can accept hydrogen bonds (e.g., carbonyl groups) also contribute to binding interactions.

The overall hydrogen bonding capacity affects not only the binding affinity but also the solubility and stability of the drug in biological systems. A well-balanced hydrogen bonding profile can improve oral bioavailability by enhancing solubility while ensuring effective target engagement.[49,50]

1.7.4 Electronic Properties

The electronic properties of a molecule, including its charge distribution and electronegativity, significantly influence its reactivity and interaction with biological targets. These properties include:

1.7.4.1 Dipole Moment: A measure of the separation of positive and negative charges in a molecule; higher dipole moments often correlate with stronger interactions with polar biological targets.

1.7.4.2 Electronegativity: The tendency of an atom to attract electrons; variations in electronegativity among atoms within a molecule can affect reactivity and binding affinity.

Understanding these electronic characteristics helps researchers predict how changes in molecular structure will impact a compound's activity and selectivity toward specific biological targets.[51,52]

1.7.5 Steric Factors

Steric factors refer to the spatial arrangement of atoms within a molecule and how this affects its ability to interact with biological targets. Key aspects include:

1.7.5.1 Molecular Size: Larger molecules may have difficulty fitting into active sites of enzymes or receptors, potentially reducing their efficacy.

1.7.5.2 Conformation: The three-dimensional shape of a molecule can influence its ability to bind effectively to its target. Conformational flexibility may enhance or hinder binding depending on how well the drug fits into the target site.

Steric hindrance caused by bulky groups can prevent effective interaction with targets, while optimal spatial arrangements can facilitate strong binding interactions. Understanding steric factors is essential for designing compounds that maximize efficacy while minimizing side effects.[53,54]

2. Case Studies

2.1 Example 1: SAR Studies on Novel β-Lactam Antibiotics

β-lactam antibiotics, including penicillins and cephalosporins, have been extensively studied for their ability to inhibit bacterial cell wall synthesis. Recent SAR studies have focused on developing novel β-lactam derivatives that can overcome resistance mechanisms, particularly those associated with β-lactamase production. For instance, researchers have synthesized a series of novel cephalosporin conjugates designed to deliver thiol-based inhibitors of metallo-β-lactamases (MBLs) in a controlled manner. These studies revealed that while the β-lactam ring was hydrolyzed, the release of the inhibitor was not observed, indicating a need for further optimization of the prodrug design. Nonetheless, certain compounds demonstrated potent inhibition against IMP-type MBLs, showcasing the potential for developing effective treatments against carbapenem-resistant bacteria. Additionally, structural relationship mapping of β-lactams has helped categorize various compounds based on their efficacy and resistance profiles, guiding future drug development efforts to create broad-spectrum treatments.[55,56]

2.2 Example 2: SAR of Azole Antifungals

Azole antifungals are a prominent class of medications used to treat fungal infections by inhibiting the synthesis of ergosterol, a vital component of fungal cell membranes. SAR studies in this class have focused on modifying the azole core structure to enhance antifungal activity and reduce toxicity. For example, modifications in the side chains of triazole derivatives have led to improved potency against resistant strains of fungi, such as Candida auris. Researchers have identified key functional groups that contribute to increased binding affinity to fungal cytochrome P450 enzymes involved in ergosterol biosynthesis. These modifications not only enhance antifungal efficacy but also improve pharmacokinetic properties such as solubility and bioavailability. Furthermore,

understanding the electronic and steric properties of azole compounds has facilitated the design of new agents that can circumvent common resistance mechanisms observed in clinical isolates.[57,58]

2.3 Example 3: Natural Product Derivatives in SAR Studies

Natural products have historically served as a rich source of bioactive compounds, and their derivatives continue to be an important area of SAR research. For instance, derivatives of natural products like curcumin and resveratrol have been synthesized to enhance their biological activities against various diseases, including cancer and infections. SAR studies on these derivatives often involve systematic modifications to functional groups and structural frameworks to assess their effects on activity and selectivity. In one case, researchers explored modifications that increased the lipophilicity and hydrogen bonding capacity of curcumin derivatives, resulting in compounds with improved anticancer properties. Additionally, natural product scaffolds are often used as templates for creating libraries of analogs that can be screened for activity against specific targets. This approach not only aids in discovering new therapeutic agents but also provides insights into the mechanisms by which these compounds exert their effects.[59]

3. Advances in SAR Studies

Recent advancements in Structure-Activity Relationship (SAR) studies have significantly enhanced the efficiency and effectiveness of drug discovery processes. These advancements leverage cutting-edge technologies and methodologies, including artificial intelligence (AI) and machine learning, high-throughput screening (HTS), integration with omics data, and the application of CRISPR technology for target identification.[60]

3.1 Use of AI and Machine Learning

The incorporation of AI and machine learning into SAR studies has revolutionized the way researchers analyze large datasets generated during drug discovery. Machine learning algorithms can identify complex patterns and relationships between molecular structures and their biological activities that may not be apparent through traditional analysis methods. For instance, these algorithms can predict the activity of novel compounds based on existing SAR data, allowing for more informed decision-making in compound selection and optimization. AI-driven models can also facilitate virtual screening of compound libraries, significantly reducing the time and resources required to identify promising drug candidates. By training models on historical data, researchers can prioritize compounds with the highest likelihood of success, thus streamlining the lead optimization process. Furthermore, machine learning can assist in predicting pharmacokinetic properties and potential toxicity, enhancing the overall safety profile of new drug candidates.[61]

3.2 High-Throughput Screening (HTS)

High-throughput screening is a powerful technique that allows researchers to rapidly evaluate thousands to millions of compounds for biological activity. HTS employs automated systems to conduct assays in microtiter plates, enabling the simultaneous testing of large compound libraries. This approach is particularly beneficial in SAR studies as it generates vast amounts of biological data that can be analyzed to extract preliminary SAR information. Recent advancements in HTS have included quantitative high-throughput screening (qHTS), which tests compounds at multiple concentrations to generate concentration-response curves. This method provides more detailed insights into the activity profiles of compounds, helping researchers to better understand dose-response relationships and optimize lead candidates based on their efficacy. Moreover, HTS can be integrated with functional genomics approaches, allowing for the identification of targets and pathways involved in drug action. By combining HTS with genetic screens, researchers can gain a deeper understanding of how specific compounds interact with biological systems, further informing SAR analyses.[62,63]

3.3 Integration with Omics Data (Genomics, Proteomics)

The integration of omics data—such as genomics, proteomics, and metabolomics—into SAR studies represents a significant advancement in understanding drug action mechanisms. By analyzing large datasets from these fields, researchers can identify biomarkers associated with drug response and resistance. For example, genomic data can reveal mutations in target proteins that affect drug binding or efficacy, while proteomic analyses can provide insights into the expression levels of target proteins under different conditions. This comprehensive approach enables a more holistic understanding of how molecular features influence activity and helps guide modifications to enhance therapeutic outcomes. Additionally, integrating omics data with SAR studies allows for the identification of off-target effects and potential toxicities associated with new compounds. By correlating molecular features with omics profiles, researchers can design safer and more effective drugs tailored to specific patient populations or disease states.[64,65]

3.4 Role of CRISPR in Target Identification

CRISPR technology has emerged as a powerful tool for target identification in drug discovery. By enabling precise editing of genes within cellular models, CRISPR allows researchers to investigate the roles of specific genes in disease processes and drug responses. This capability is particularly valuable in SAR studies as it facilitates the identification of novel targets that may be modulated by new compounds. Using CRISPR-based screens, researchers can systematically knock out or modify genes to observe changes in cellular responses to drug treatments. This approach helps elucidate mechanisms of action for existing drugs while also identifying new targets for therapeutic intervention. The ability to rapidly assess gene function in a high-throughput manner accelerates the discovery process and enhances the precision of SAR analyses.[66,67]

4. Challenges and Limitations in SAR Studies

Structure-activity relationship (SAR) studies are integral to drug discovery, providing insights into how molecular structures correlate with biological activity. However, several challenges and limitations can hinder the effectiveness of SAR methodologies. Key challenges include the complexity of biological systems, predictive accuracy of computational tools, and multi-target effects.[68]

4.1 Complexity of Biological Systems

Biological systems are inherently complex, involving intricate networks of interactions among various biomolecules, including proteins, nucleic acids, and lipids. This complexity poses significant challenges for SAR studies:

4.1.1 Non-linear Relationships: Many biological processes do not follow simple linear relationships between structure and activity. For instance, the interaction of a drug with its target may be influenced by multiple factors, such as the presence of other biomolecules or environmental conditions. This non-linearity can complicate the development of predictive models that accurately reflect real-world biological interactions.[69]

4.1.2 Variability in Biological Responses: The biological activity of a compound can vary significantly based on factors such as cell type, genetic background, and environmental conditions. This variability makes it difficult to establish reliable SAR models that can predict activity across different biological contexts.

4.1.3 Multi-layered Interactions: Drugs often interact with multiple targets within a biological system, leading to off-target effects that can complicate the interpretation of SAR data. Understanding these multi-target interactions requires comprehensive modeling approaches that account for the complexity of biological networks.[70]

4.2 Predictive Accuracy of Computational Tools

While computational tools have advanced significantly in recent years, their predictive accuracy remains a concern:

4.2.1 Quality of Data: The effectiveness of machine learning and other computational methods heavily relies on the quality and diversity of the data used to train models. Inadequate datasets can lead to unreliable predictions when applied to new compounds that differ significantly from those in the training set.

4.2.2 Domain of Applicability: Many predictive models have a limited domain of applicability; they are only reliable for compounds that share structural features with those included in the training dataset. If a new molecule falls outside this domain, predictions may be inaccurate or misleading.

4.2.3 Interpretability Issues: Some advanced machine learning models function as "black boxes," making it challenging to interpret how specific structural features influence predicted activity. This lack of transparency can hinder the understanding necessary for optimizing compounds based on SAR findings.[71]

4.3 Multi-Target Effects

The phenomenon of multi-target effects complicates SAR studies by introducing additional layers of complexity:

4.3.1 Polypharmacology: Many drugs exhibit activity against multiple targets, which can lead to synergistic or antagonistic effects that are difficult to predict using traditional SAR approaches. Understanding how modifications to a compound's structure affect its interactions with various targets is crucial for optimizing therapeutic efficacy while minimizing side effects.

4.3.2 Activity Cliffs: In SAR landscapes, "activity cliffs" refer to regions were small structural changes lead to significant differences in biological activity. These cliffs can pose challenges in predicting how modifications will impact overall drug efficacy and safety. Identifying and navigating these cliffs requires sophisticated modeling techniques that can accurately capture the nuances of structure-activity relationships.[72]

5. Future directions

Future directions in Structure-Activity Relationship (SAR) studies are poised to reshape the landscape of drug discovery, particularly in the development of personalized antimicrobials, synergistic drug combinations, and bioinformatics-driven approaches. The rise of personalized medicine emphasizes tailoring antimicrobial therapies to individual patient profiles, including genetic makeup and microbiome composition. SAR studies can facilitate the identification of specific compounds that target pathogens prevalent in a patient’s unique microbiome, thereby enhancing treatment efficacy while minimizing adverse effects. By integrating patient-specific data with SAR analyses, researchers can develop targeted therapies that address the complexities of individual infections. Combining multiple drugs to achieve synergistic effects is a promising strategy to combat antimicrobial resistance. SAR studies can identify combinations of compounds that work together more effectively than when administered separately. By analyzing the interactions between different drugs at a molecular level, researchers can optimize dosages and enhance therapeutic outcomes. This approach not only improves efficacy but also reduces the likelihood of resistance development by employing multiple mechanisms of action against pathogens. The integration of bioinformatics into SAR studies represents a significant advancement in understanding structure-activity relationships. By leveraging large datasets from omics technologies and computational tools, researchers can uncover complex patterns linking molecular structures with biological activity. This data-driven approach enables the rapid

identification of promising drug candidates and facilitates the exploration of vast chemical spaces, ultimately accelerating the drug discovery process.[73,74]

6. Conclusion

Structure-activity relationship (SAR) studies have made significant contributions to the development of antimicrobial agents, providing essential insights into how molecular modifications influence biological activity. By systematically analyzing the relationship between chemical structure and antimicrobial efficacy, researchers have been able to identify key functional groups and optimize lead compounds for enhanced potency against a variety of pathogens. The integration of multidisciplinary approaches, including synthetic chemistry, computational modeling, and high-throughput screening, has further accelerated the discovery of novel antimicrobials. For instance, advances in machine learning and bioinformatics allow for the rapid analysis of large datasets, facilitating the identification of promising drug candidates and their mechanisms of action. Moreover, combining SAR with omics technologies enables a deeper understanding of drug-target interactions and resistance mechanisms, paving the way for personalized antimicrobial therapies tailored to individual patient profiles. The exploration of synergistic drug combinations through SAR studies has also proven effective in overcoming resistance, as these combinations can enhance therapeutic outcomes while minimizing adverse effects. As the challenge of antimicrobial resistance continues to grow, the emphasis on collaborative efforts across disciplines—ranging from molecular biology to pharmacology—will be crucial in developing innovative solutions. Ultimately, the future of antimicrobial development lies in harnessing the power of SAR studies alongside cutting-edge technologies and interdisciplinary collaboration to create effective treatments that can adapt to the evolving landscape of infectious diseases.

7. Conflict of interest

The authors have no conflict of interest.

8. Acknowledgement

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