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STRUCTURE-ACTIVITY RELATIONSHIP STUDIES IN PHARMACEUTICAL CHEMISTRY: ADVANCING DRUG DESIGN AND DEVELOPMENT

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ABSTRACT

Structure-activity relationship (SAR) studies play a central role in pharmaceutical chemistry by establishing the connection between molecular structure and biological activity, thereby guiding rational drug design and development. This review aims to provide a comprehensive synthesis of recent advancements in SAR and their contribution to modern drug discovery, with emphasis on structural determinants, computational modelling, artificial intelligence integration, applications, challenges, and emerging trends. A comprehensive literature review approach was employed, involving the systematic identification, screening, and thematic classification of relevant peer-reviewed studies from major scientific databases. The findings reveal that SAR remains a fundamental framework in drug discovery, significantly enhanced by computational techniques such as QSAR modelling, molecular docking, and molecular dynamics simulations, which improve predictive accuracy and reduce experimental effort. Additionally, artificial intelligence and machine learning have transformed SAR into a data-driven discipline capable of analysing complex datasets and generating novel drug candidates. Despite these advancements, challenges, including biological complexity, data limitations, and translational gaps, continue to hinder drug development success. Overall, the integration of classical SAR principles with modern computational and AI-driven approaches is reshaping pharmaceutical research and holds significant potential for accelerating the discovery of safer, more effective, and personalised therapeutic agents.

KEYWORDS: Structure-activity relationship, drug design, QSAR modelling, artificial intelligence, pharmaceutical chemistry

1. INTRODUCTION

Pharmaceutical chemistry is a key part of drug discovery and development by providing the chemical science in the design, synthesis and optimisation of drugs. It integrates organic chemistry, biochemistry and pharmacology in the conversion of biological active molecules to therapeutic drugs. The improvements in synthetic protocols and chemical technologies helped to make the discovery of new drugs faster and expand the chemical space to be examined to make drugs more effective (Danraka & Abdulmujeeb, 2023). Specifically, medicinal chemistry has implemented new functional groups and scaffolds, increasing the molecular space to drug discovery and development, enabling the creation of new molecules with more favorable pharmacological effects and reduced toxicity (Mäder & Kattner, 2020). The innovations highlight the role of pharmaceutical chemistry in dealing with global health issues and enhancing patient outcomes. A subfield of pharmaceutical chemistry of special interest is the structure-activity relationship (SAR) analysis, which studies the effects of changes in the structure of a molecule on pharmacological activity. SAR provides a systematic way of investigating drug-target interactions, and it is possible to explain the essential structural components that play a role in binding, selectivity and activity. SAR is able to refine lead compounds by systematically changing their chemical structure to enhance their effectiveness. To illustrate, research of heterocyclic molecules such as thiazoles revealed how the structure may be altered to change anticancer effects, and the importance of SAR in drug design (Ayati et al., 2019). SAR is a fundamental method that relates molecular structure with the role and plays a significant role in designing effective drugs. SAR has developed to be more quantitative than qualitative. During its initial years, SAR studies were heavily reliant on empirical findings. However, with the introduction of quantitative structure-activity relationship (QSAR) modelling mathematical and statistical methods were introduced to project biological responses based on molecular features. This has enhanced speed and accuracy of drug discovery by conducting virtual screening and modelling of

databases of large compounds (Brogi et al., 2020). Increased computational resources and algorithms also made it possible to integrate molecular docking, molecular dynamics and other in silico methods, making it possible to predict the binding of the ligand to the target receptor on an atomic scale (Buskes & Blanco, 2020). Such transition of conventional SAR to QSAR is a significant milestone in the field of medicinal chemistry. The recent progress in the field of artificial intelligence (AI) and machine learning resulted in the data-driven and predictive SAR approach. AI models are able to process complex and multidimensional data, patterns, as well as predict biological activity with a high accuracy. These technologies have accelerated the process of drug discovery by reducing time and costs in screening and optimisation of leads during experiments (Chan et al., 2019). Furthermore, based on their generative AI models are enabling the development of new molecular scaffold structures with desirable drug-like properties, which is a paradigm shift of drug discovery to analysis (Gangwal et al., 2024). The fact that deep learning and other methods of computation are being used is also enhancing the ability to model more effectively complex structure-activity relationships and create new-generation drugs (Gupta et al., 2021). But the process of drug discovery remains complicated and failure rates are very high, safety concerns and increased selectivity are needed. Many drug candidates do not succeed in clinical trials because of toxicity and pharmacokinetics issues, and lack of effectiveness. There are also structural factors, including stereochemistry and molecular flexibility, which are difficult to predict drug properties, which can be seen in drug candidates with atropisomerism and other complex structural elements (Glunz, 2018). These complexities suggest that there is a need to have more comprehensive and integrated modalities, which entail a combination of chemical, biological and computational skills in enhancing drug development success. In this regard, this review aims at bringing together the advances in SAR research in the field of pharmaceutical chemistry. Through the prism of the historical evolution of the traditional SAR to AI-based methods, this work will strive to present the key progress, applications and limitations in the field of SAR-driven drug discovery. Additionally, the review also brings out the importance of multidisciplinary approaches in enhancing prediction, optimisation and circumventing the shortfall of the traditional SAR methods. This research aims at improving understanding of the contribution of SAR in the future of drug design and development.

2. METHODOLOGY

In this research, a comprehensive review design is used to generalise the current academic evidence on the structure - activity relationship (SAR) research in pharmaceutical chemistry and its contribution to drug design and development. The peer-reviewed journals, academic books, and other relevant scientific databases were searched in Google Scholar, Science Direct, and DOAJ to identify relevant literature. The search was limited to peer-reviewed articles, review articles, and methodology papers on SAR, QSAR modelling, computational drug design, and the use of artificial intelligence in pharmaceutical research, but not non-scholarly materials and studies that are not directly related to SAR-based drug discovery. A systematic keyword search was utilised based on a combination of terms like structure activity relationship, SAR, QSAR, drug design, molecular docking, artificial intelligence drug discovery and medicinal chemistry. There was a preliminary screening of retrieved records by titles and abstracts, and full-text screening to check the relevance and quality of the retrieved records. A subset of selected studies was then divided and classified into thematic areas including structural determinants of biological activity, computational methods of data modelling, AI integration, drug discovery applications, challenges and future trends. Synthesis involved comparative and integration of results in these themes in a systematic way to uncover consistent patterns, methodological progress and research gaps. Figure 1 illustrates the overall review process which involves literature identification, literature screening, thematic classification and synthesis.

Figure 1. Overview of the Comprehensive Review Process

3. RESULTS

The comprehensive literature review of the literature on structure-activity relationship (SAR) in pharmaceutical chemistry has identified the key thematic areas that influence the present-day drug design, including structural determinants of biological activity, computational modelling tools, artificial intelligence integration, practical applications to drug discovery, challenges, and technological trends. The general findings indicate that there is the shift of the traditional empirical SAR methodology towards more sophisticated computational and data-driven models that are more efficient, predictive and innovative in drug development.

3.1 Structural Determinants Influencing Biological Activity

The functional groups, steric configuration, electronic properties and lipophilicity are structural features that are central in defining drug-target interaction and pharmacological reactions. These parameters affect the binding affinity, molecular stability, receptor selectivity and pharmacokinetic behaviour. Pharmacophore modelling goes on to combine these structural features to determine critical features needed to be active biologically and direct rational drug design. The most important structural determinants and their impact on drug activity are summarised in Table 1.

Table 1. Key Structural Features Influencing Biological Activity in SAR Studies

Structural Feature	Description	Effect on Drug Activity	Supporting References
Functional Groups	Specific chemical moieties in molecules	Influence binding affinity and receptor interaction	Ayati et al. (2019); Vaishnav et al. (2025)
Lipophilicity	Lipid solubility of compounds (logP)	Affects permeability and bioavailability	Tandon et al. (2019); Zhang & Tang (2018)
Steric Effects	Spatial arrangement of atoms	Determines receptor fit and selectivity	Glunz (2018); Itoh & Inoue (2019)
Electronic Effects	Electron distribution in molecules	Modulates reactivity and interaction strength	Hemmerich & Ecker (2020); Prieto-Martínez et al. (2019)
Pharmacophore Features	Essential structural elements for activity	Guides rational drug design	Prieto-Martínez et al. (2019); Itoh & Inoue (2019)

3.2 Advances in QSAR and Computational Modelling

Computational methods have also greatly boosted the analysis of SAR by allowing the ability to model the predictive behaviour of the biological activity and drug-target interaction. QSAR, molecular docking, molecular dynamics, and virtual screening are some of the techniques that can give appropriate information about molecular behaviour, binding affinity, and stability. Also, in silico toxicology may aid in the early safety assessment, enhancing the efficiency and cost-effectiveness of drug discovery. Table 2 provides a list of the major computational methods with their applications in SAR.

Table 2. Computational Techniques in SAR and Drug Design

Method	Description	Application in SAR	Impact	Supporting References
QSAR Modeling	Mathematical modelling of structure–activity relationships	Predicts biological activity	Reduces experimental cost	Rudrapal & Chetia (2020); Staszak et al. (2022)
Molecular Docking	Simulation of ligand–receptor binding	Identifies binding affinity	Enhances specificity	Naqvi et al. (2018); Brogi et al. (2020)
Molecular Dynamics	Time-dependent simulation of molecular systems	Evaluates the stability of complexes	Improves accuracy	Naqvi et al. (2018)
Virtual Screening	Computational screening of compounds	Identifies potential leads	Accelerates discovery	Poroikov (2020); Rudrapal & Chetia (2020)
In Silico Toxicology	Computational toxicity prediction	Assesses safety early	Reduces failure rates	Hemmerich & Ecker (2020)

3.3 Integration of Artificial Intelligence in SAR

Artificial intelligence is now an innovative aspect of contemporary SAR studies, as it allows for analysing large and intricate data with higher predictive quality. The patterns and nonlinear relationships between chemical structure and biological activity are identified using machine learning and deep learning models, whereas generative AI allows for the creation of new drug candidates. Also, big data analytics facilitates the combination of different datasets, enhancing the decision-making process and speeding up drug discovery. Table 3 provides a summary of the key AI methods and their use in SAR.

Table 3. Artificial Intelligence Applications in SAR-Based Drug Discovery

AI Technique	Description	Application in SAR	Outcome	Supporting References
Machine Learning	Data-driven predictive algorithms	Identifies SAR patterns	Improved accuracy	Gupta et al. (2021); Panteleev et al. (2018)
Deep Learning	Neural networks for complex modeling	Captures nonlinear SAR relationships	Enhanced modeling capability	Nag et al. (2022); Jiménez-Luna et al. (2021)
Generative AI	AI-based molecule design	Creates novel drug candidates	Accelerates innovation	Gangwal et al. (2024); Han et al. (2023)

Big Data Analytics	Integration of large datasets	Supports multidimensional SAR	Faster decision-making	Zhu (2020); Sarkar et al. (2023)
AI Platforms	Automated drug discovery systems	End-to-end drug design	Reduces time and cost	Chan et al. (2019); Schneider (2018)

3.4 SAR Applications in Drug Discovery

SAR is important in various drug discovery processes such as identification of leads, optimisation of leads and development of therapeutics. It allows the systematic structural changes to optimise potency, selectivity, and pharmacokinetic properties. The methods of SAR are also extensively used in drug development against certain diseases, such as anticancer and antiviral therapy, in the process of developing peptide drugs or drug repurposing strategies. Table 4 lists the key areas of application and their effects.

Table 4. Applications of SAR in Drug Development

Application Area	Description	Role of SAR	Impact	Supporting References
Lead Identification	Discovery of bioactive compounds	Identifies potential candidates	Accelerates early discovery	Sinha & Vohora (2018); Poroikov (2020)
Lead Optimization	Structural refinement of compounds	Improves potency and selectivity	Produces effective drugs	Kumar et al. (2020); Koley et al. (2024)
Target-Specific Design	Designing drugs for specific targets	Enhances binding specificity	Reduces side effects	La Monica et al. (2022); Meier-Menches et al. (2018)
Drug Repurposing	New uses for existing drugs	Utilizes SAR insights	Cost-effective	Zhang & Tang (2018)
Peptide Drug Development	Development of peptide therapeutics	Improves stability and activity	Expands applications	Muttenthaler et al. (2021)

3.5 Challenges and Limitations in SAR Studies

With all these progresses, SAR research has several constraints associated with biological complexity, quality of the data and predictive power. Complex biological pathways and multi-target interactions make modelling difficult, and scarce or biased data sets decrease reliability. The fact that drug failures during clinical trials are high further underscores the discrepancy between computer forecasts and reality. Also, other problems like overfitting of models and non-generalizability limits increased the applicability. Table 5 summarises the key challenges and their effects.

Table 5. Challenges in SAR-Based Drug Development

Challenge	Description	Impact	Supporting References
Data Quality	Limited or biased datasets	Reduces model reliability	Hemmerich & Ecker (2020); Staszak et al. (2022)
Biological Complexity	Multi-target interactions	Prediction difficulty	Sun et al. (2022)
Drug Failure	High clinical attrition rates	Increased cost and time	Sun et al. (2022); Sinha & Vohora (2018)
Model Limitations	Overfitting and poor generalisation	Reduced applicability	Staszak et al. (2022)
Translational Gap	Differences between prediction and clinical outcomes	Limits the success rate	Poroikov (2020); Zhang & Tang (2018)

3.6 Emerging Trends and Patterns in SAR-Based Drug Design

Recent advances show a shift to integrative and technology-based SAR methods that incorporate artificial intelligence, computational modelling, and state-of-the-art chemical methods. These trends comprise predictive modelling that is driven by AI, the creation of novel compounds with the help of generative design, the combination of multi-omics data, high-throughput screening, and enhanced safety prediction using in silico techniques. Collectively, these advances are transforming SAR into an interdisciplinary paradigm capable of enhancing innovation and accelerating drug discovery. Table 6 presents the key trends occurring and their implications.

Table 6. Emerging Trends in SAR-Based Drug Design

Emerging Trend	Description	Impact	Supporting References
AI-Driven Modelling	Machine learning-based predictions	Improves accuracy	Gupta et al. (2021); Jiménez-Luna et al. (2021)
Generative AI	AI-based molecule creation	Enables novel drug discovery	Gangwal et al. (2024); Han et al. (2023)
Multi-Omics Integration	Integration of biological datasets	Enhances target understanding	Zhu (2020)
High-Throughput Screening	Automated compound testing	Accelerates SAR studies	Buskes & Blanco (2020)

Late-Stage Functionalization	Advanced-stage molecular modification	Improves optimization	Moir et al. (2019)
In Silico ADMET	Computational safety prediction	Reduces drug failure	Hemmerich & Ecker (2020)

4. DISCUSSION

This review shows that the structure-activity relationship (SAR) studies played a critical and dynamic role in the evolution of pharmaceutical chemistry and modern drug design. The results have shown that the SAR remains a core structure to describe the relationship between molecular structure and biological activity, as well as is being modified to accommodate the use of computational and artificial intelligence-based techniques. The integration of structural knowledge and predictive modelling has made the discovery of drugs much more efficient and has permitted the development of therapeutic agents to be more focused and rational. The thematic analysis suggests that structural determinants like functional groups, steric configuration and electronic properties are still used to optimise drugs, whereas computational and AI-based methods are used to increase predictive accuracy and reduce the experimental load.

Compared to the previous studies, the present results can be linked to the earlier research that highlighted the role of SAR and QSAR in drug discovery. As an example, previous studies have defined QSAR as an important instrument to forecast biological activity and to optimise lead compounds, which contributes to less time and cost in drug development (Tandon et al., 2019). Likewise, recent reports reiterate the usefulness of SAR as a fundamental concept in medicinal chemistry, especially in dictating structural changes to enhance efficacy and selectivity (Vaishnav et al., 2025). The increasing presence of artificial intelligence revealed in this review is also aligned with the previous studies that showed that AI-based methods are more effective in drug discovery because they can be used to identify patterns, make predictions, and design molecules (Sellwood et al., 2018). Moreover, the use of case-based studies in the development of antiviral drugs demonstrates how SAR has long been used to optimise therapeutic agents, including non-nucleoside reverse transcriptase inhibitors, by systematic structural optimisation (Zhuang et al., 2020). Moreover, the significance of pharmacokinetics and drug metabolism recognised in the current review is justified by previous studies that highlight the use of metabolic profiling as an indicator to enhance the safety and efficacy of drugs (Zhang and Tang, 2018). These comparisons show that the basic principles of SAR have not changed, but the use of SAR has increased tremendously with the development of technology.

These findings have significant implications for the research and industry. SAR can be used in conjunction with computational tools and artificial intelligence to revolutionise drug discovery into a more efficient and cost-effective process. These strategies can improve the rate of failures and shorten the time to develop new therapeutics by allowing the anticipation of biological activity and toxicity in a timely manner. Also, the integration of multi-disciplinary approaches, such as chemistry, biology, and data science, facilitates the creation of personalised medicine since they enable more specific targeting of the disease pathways. The application of AI-based SAR methods in the industrial sector can improve productivity, efficiency of resource utilization and improved decision-making in pharmaceutical research and development.

Nevertheless, despite such enhancements, there are a number of drawbacks that are to be observed. The quality of the data and its availability is very essential to the accuracy of SAR and computational models and biased or incomplete data can lead to unreliable predictions. In addition, biological systems e.g. multi-target interactions and cellular environments are complex and thus they are challenging to model with precision. Translational gap between prediction of in silico and clinical outcome is an issue that is taken seriously since many promising compounds are unable to pass the test later in the development process. In addition, AI can be effectively used in drug design, yet has a number of challenges, including interpretability, data integration, and model validation that need to be considered to provide reliable use.

Future studies can be explicit in resolving these drawbacks by creating more feasible and perceptible models, better quality of data with standard datasets, and by experimental validation in conjunction with computational forecasts. It is anticipated that more recent technologies, including multi-omics analysis, high-throughput screening, and more sophisticated simulation methodologies will be incorporated in the prediction of SAR studies in the future. In addition, the interdisciplinary collaboration should be given more attention in bridging the gap between the computational predictions and clinical applications. The future of the field is evolving and as SAR is implemented with the newest technologies, it will be needed to determine the future of drug discoveries, as it will be able to make them safer, efficient and more personalised treatment interventions.

5. CONCLUSION

The review underlines the paramount importance of the structure-activity relationship (SAR) studies in pharmaceutical chemistry, and in the contemporary drug design. The results have revealed that SAR is one of the most significant methods to examine the complex mechanism of interaction between the molecular structure and the biological activity which facilitates the rational design and optimisation of therapeutic agents. Combination of old principles of SAR and the computational methods of QSAR modelling, molecular docking and molecular dynamics has also played a major role in efficiency and accuracy of drug discovery mechanisms. In addition, artificial intelligence and machine learning have turned SAR into a field with data and predictions, which allows finding promising candidates drugs in a short period of time and avoiding the use of time-consuming experiments. However, despite these advances, such issues as biological complexity, data limitations and high failure rates in clinical trials remain, implying that more robust and integrative approaches are needed. Modelling using AI, integration of multi-omics and high-throughput screening are some of the new directions that have the potential to be used in overcoming these limitations and enhancing the outcomes of drug discovery. The future of the SAR lies, as a rule, in the fact that it will be able to reinvent itself basing on interdisciplinary

cooperation, which will involve chemistry, biology and computational science in order to offer safer, more effective, and customized therapeutic options.

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