Computational Modeling of Triazole Derivatives: QSAR, Docking, and AI Perspective

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Abstract

Computational modeling has gained remarkable prominence in medicinal chemistry, offering a powerful framework for accelerating the discovery and optimization of triazole-based therapeutics. These derivatives, widely recognized for their antifungal, anticancer, and antiviral activities, have been extensively studied through the combined application of Quantitative Structure Activity Relationship (QSAR) modeling and molecular docking. While QSAR analysis quantitatively links molecular descriptors to biological activity, docking simulations reveal binding orientations, interaction profiles, and affinity patterns. Recent advances incorporating machine learning and artificial intelligence have markedly improved predictive performance, enabling more rational lead selection. Nonetheless, current limitations such as incomplete or low-quality datasets, reduced interpretability, and biological oversimplifications pose significant challenges. To address these, hybrid approaches that integrate physics-based modeling with data-driven algorithms, together with innovations such as ensemble docking, explainable AI, and quantum mechanics-based simulations, are emerging as promising solutions. By leveraging these developments, computational strategies can more effectively bridge the translational gap between in silico predictions and experimental validation, ultimately reducing attrition rates and expediting the drug development pipeline.

Keywords: Drug discovery; Triazole derivatives; QSAR modeling;AI-enhanced modeling; Molecular docking.

Introduction

Computational modeling has become an indispensable tool in modern medicinal chemistry, fundamentally transforming the drug discovery process. Medicinal chemistry, at its core, involves the identification, synthesis, and development of bioactive compounds capable of modulating biological targets to treat diseases effectively [1]. Traditionally, the discovery and optimization of these compounds depended heavily on labor-intensive and costly experimental approaches, which often faced challenges such as low hit rates, extensive resource consumption, and prolonged timelines for achieving successful drug candidates. However, recent advancements in computational methodologies have provided promising

solutions to these limitations, significantly enhancing the efficiency, speed, and cost-effectiveness of drug discovery pipelines [2]

Computational modeling, particularly QSAR analysis and molecular docking, has transformed medicinal chemistry. QSAR modeling predicts compound optimization by correlating chemical compound structural properties with biological activities using statistical and machine learning methods. However, computer techniques model small-molecule-biological target interactions to predict binding affinity and effectiveness in molecular docking. These methods have sped the identification and refining of new therapeutic medicines by virtual screening enormous chemical libraries, eliminating empirical trials, and precisely predicting pharmacokinetic and pharmacodynamic characteristics [3].

This review paper examines current computational modeling work using triazole derivatives, focusing on QSAR and molecular docking research. It analyzes existing approaches' strengths and drawbacks, recent computational algorithm advances, and successful case studies where computational modeling has greatly improved triazole medicinal chemistry. It also discusses key methodological issues, offers practical answers, and indicates future directions for computational techniques. This review will promote computational methods in medicinal chemistry, improving triazole derivative drug discovery accuracy, efficiency, and success [4].

Understanding Triazole Derivatives: Structure and Function

Triazole derivatives, a prominent class of nitrogen-containing heterocycles, exhibit diverse pharmacological activities. These five-membered aromatic rings, in either 1,2,3- or 1,2,4-configurations, possess distinct electronic distributions and substitution patterns that influence biological activity[5]. Their high dipole moments and multiple nitrogen atoms enable hydrogen bonding, electrostatic interactions, and metal coordination with biological targets. Synthetic accessibility and structural versatility allow extensive SAR exploration, where electron-donating or withdrawing substituents can enhance binding affinity and selectivity. Notably, 1,2,4-triazoles inhibit fungal cytochrome P450 enzymes in ergosterol biosynthesis, while 1,2,3-triazoles synthesized via click chemistry show anticancer, antiviral, and antibacterial potential [6]. They also target kinases, GPCRs, and epigenetic regulators. Advances in computational modeling, including QSAR, molecular docking, and molecular dynamics, have clarified the structural determinants of bioactivity, enabling the rational design of triazole-based therapeutics with improved drug-likeness, bioavailability, and safety [7].

The structural and functional characteristics of triazole derivatives make them drug design candidates. If computational and experimental validation improves triazole-based drugs, they may become more effective and selective. Medical chemistry research requires examining their chemistry and biology [8].

This comprehensive review examines the computer modeling of triazole-based medical drug discovery and development. It uses QSAR analysis and molecular docking to predict biological activities, explain binding, and change structures. By critically assessing recent methodological breakthroughs and computational tool synergy, the research consolidates current trends and future opportunities. The objective is to rationally generate more potent and selective triazole molecules and boost computational drug discovery, as shown in Figure 1 [9].
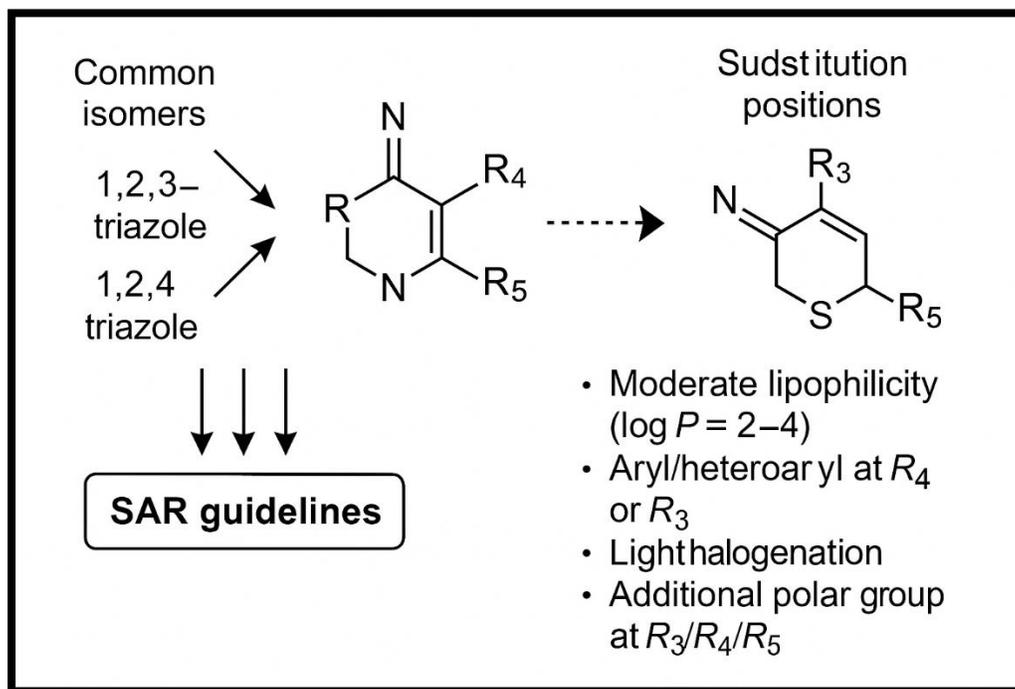
Figure 1. Triazole Derivatives SAR Diagram.

QSAR Analysis: Techniques and Applications in Triazole Research

Computer modeling has transformed drug development in medicinal chemistry. Medicinal chemistry relies on bioactive compounds that alter biological targets to treat diseases. Traditional experimental approaches for identifying and improving these compounds were arduous, costly, and resource-intensive, with low hit rates and long drug candidate development timeframes. Recently developed computer technologies have removed these limits, enhancing drug discovery pipeline speed, efficiency, and cost [10].

Medical chemistry has been altered by computational modeling, especially QSAR analysis and molecular docking. QSAR modeling predicts compound optimization by linking chemical compound structural features with biological activities, utilizing statistical and machine learning methodologies. Computer models of small-molecule-biological target interactions predict molecular docking efficacy and binding affinity. By virtual screening vast compound libraries, reducing empirical experimentation, and accurately predicting pharmacokinetic and pharmacodynamic behaviors, these tools have greatly accelerated the discovery and refinement of novel therapeutic agents. Despite these advances, computational modeling faces several hurdles. Variables, including experimental data quality, biological system complexity, and computer algorithm restrictions, limit predictive model accuracy. Oversimplification of biological surroundings and poor modeling of dynamic molecular activities sometimes cause inconsistencies between computer predictions and experimental results. Researchers regularly integrate new information, refine modeling algorithms, and use hybrid ways to increase computational methods' prediction power and dependability [11].

Due to its antibacterial, anticancer, antifungal, antiviral, and anti-inflammatory properties, computational modeling of triazole compounds has garnered interest. Triazoles are important heterocyclic molecules with nitrogen-rich ring structures that bind to biological targets. Recent investigations have shown triazole compounds' remarkable medicinal potential. However, traditional experimental approaches are inadequate to explore their chemical space fully. QSAR studies have been used to predict biological activities using molecular descriptors, enabling rational design and structural optimization of triazole derivatives. Chemistry may examine structural variations without extensive synthesis and testing using QSAR models to understand how small molecule structure changes affect biological function [12].

Due to the quick growth and rising complexity of computational modeling approaches, triazole derivative-related developments, methodological innovations, and applications must be reviewed frequently. A thorough review paper in this field is important since it consolidates research results, identifies crucial gaps, and suggests future paths. This synthesis improves our knowledge and spreads best practices and methodological modifications, facilitating the development and optimization of new triazole-based therapies [13].

Triazole derivatives have a five-membered heterocyclic ring with three nitrogen and two carbon atoms in a 1,2,3- or 1,2,4-triazole configuration. This core scaffold is chemically flexible and aromatically stable, making structural change easy. Triazole rings are favored in drug design due to their electron-rich nature and ability to participate in hydrogen bonding, π-π stacking, and metal coordination. Medicinal chemists have used triazole frameworks to produce several therapeutic medicines for various diseases. Triazole derivatives' specific enzyme and receptor interactions provide them with biological activity. Fluconazole and itraconazole, for example, block fungal cytochrome P450 enzymes involved in ergosterol production. Strategic alterations on the ring or neighboring functional groups may affect the antibacterial, anticancer, anti-inflammatory, and anticonvulsant properties of several triazole-based drugs. Triazoles may target kinases, proteases, and epigenetic regulators, according to the current study [14].

Triazole derivatives are used in high-throughput screening chemical libraries due to their structural flexibility. Researchers have synthesized enormous collections of triazole-containing compounds using click chemistry and microwave-assisted synthesis. Physicochemical characteristics, pharmacokinetic profiles, and toxicity are important for therapeutic candidates. Hence, these substances have been studied. Several computational investigations of triazole structure-activity correlations (SAR) have shown that functional groups at certain places on the ring strongly affect binding affinity and bioactivity [15]. These findings have guided rational design, particularly early lead optimization. If chosen properly based on computational modeling and experimental validation, these alterations may greatly increase potency, selectivity, and drug-likeness.

Due to theoretical and experimental findings, the triazole derivative structure and function have been better understood. As medicinal chemistry incorporates these techniques, triazole derivatives will remain crucial to next-generation medicines. Thus, studying their structural and functional features is vital for medicinal chemistry and drug development. Quantitative Structure-Activity Relationship (QSAR) analysis is a fundamental tool in computational drug design for determining how molecular characteristics affect biological activity. In essence, QSAR develops mathematical correlations between chemical compound structure descriptors and experimental bioactivities. QSAR, which uses statistical modeling, cheminformatics, and machine learning, is used as a prediction tool when experimental resources are few or quick screening is needed [16].

In triazole research, QSAR is quite useful. Triazoles are useful for QSAR modeling because of their structural variety and complex biological characteristics. Traditional linear approaches like MLR and PLS have been used to study triazole scaffolds and their therapeutic benefits. Recent research has also used non-linear methods, including ANN, SVM, and RF algorithms. These models improve forecast accuracy, particularly with big datasets and structurally heterogeneous analogues [17].

QSAR models use molecular weight, hydrogen bond acceptors and donors, topological indices, log P, polar surface area, and electronic parameters. If chosen and evaluated, these characteristics may detect lead chemicals well. In various investigations, electron-withdrawing or electron-donating groups on the triazole ring considerably influence action against carbonic anhydrase, acetylcholinesterase, and fungal enzymes. Thus, QSAR models with these qualities provide more accurate predictions. The combination of 3D-QSAR technologies like Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) has allowed spatial imaging of molecular interactions. These approaches let researchers assess steric and electrostatic fields that affect target binding, especially for flexible triazole-containing ligands. Some investigations have used CoMFA and CoMSIA to create potent and selective triazole compounds [18].

However, model validation is essential to QSAR development. Without cross-validation, Y-randomization, or test sets, a model's predictive power is uncertain. OECD standards emphasize statistical robustness, mechanistic transparency, and application domain. Therefore, the model must follow them to be credible. QSAR has helped identify and optimize physiologically active triazole compounds by offering mechanistic insights. QSAR integrates with molecular docking, ADMET prediction, and pharmacophore modeling to provide a multi-layered computational approach. Therefore, triazole-based medication development becomes more focused, cost-effective, and scientifically logical. If these integrative methodologies are improved, QSAR models may play a larger role in early triazole drug development [19]. Random Forest (RF) models are valued for their robustness to noisy data and ability to handle high-dimensional descriptor sets. Artificial Neural Networks (ANN) excel in modeling complex, non-linear relationships between molecular features and biological activity. Graph Neural Networks (GNN) are particularly suited for capturing topological and structural information directly from molecular graphs, enhancing property prediction without extensive feature engineering [20].

Computational Approaches for Triazole Design

The integration of molecular docking and Quantitative Structure–Activity Relationship (QSAR) analysis has emerged as a cornerstone in the rational design and optimization of triazole derivatives. These computational tools enable the prediction of biological activity, elucidation of structure–activity relationships (SAR), and improvement of pharmacokinetic and pharmacodynamic profiles prior to experimental validation. Molecular docking provides a structural basis for drug design by predicting the most favorable orientation and binding affinity of triazole ligands within biological targets, taking into account key interactions such as hydrogen bonding, π–π stacking, hydrophobic contacts, and metal coordination. This capacity to visualize and quantify molecular interactions accelerates the identification of high-potential candidates, as demonstrated by clinically relevant antifungal agents such as fluconazole and itraconazole, which inhibit fungal lanosterol 14α-demethylase and disrupt ergosterol biosynthesis.

QSAR modeling complements docking by establishing mathematical correlations between molecular descriptors—such as hydrophobicity (logP), polar surface area, hydrogen bond donor/acceptor count, and electronic parameters—and experimentally determined bioactivities. This quantitative approach facilitates the rational modification of molecular scaffolds, allowing chemists to predict the impact of structural changes on potency, selectivity, and safety. The adoption of advanced machine learning algorithms, including Random Forest (RF), Support Vector Machines (SVM), and Artificial Neural Networks (ANN), has significantly enhanced QSAR predictive accuracy, particularly when dealing with structurally diverse triazole analogues. Furthermore, three-dimensional QSAR techniques like Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) allow for the spatial mapping of steric and electrostatic fields that govern target binding, thereby guiding precise substituent modifications.

When integrated, docking and QSAR offer a multi-layered computational strategy. Docking simulations identify favorable binding conformations and interactions, while QSAR models quantify and predict their impact on bioactivity. Coupled with ADMET prediction, pharmacophore modeling, and molecular dynamics simulations, this synergy enhances the reliability of computational forecasts and reduces the translational gap between in silico and in vitro results. As triazole derivatives exhibit diverse biological properties—antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory these approaches are invaluable for prioritizing compounds with optimal drug-likeness, metabolic stability, and reduced toxicity. In the context of medicinal chemistry, the continued evolution of integrated computational workflows, supported by explainable artificial intelligence and hybrid modeling techniques, is expected to further accelerate the discovery of next-generation triazole-based therapeutics while minimizing experimental costs and development timelines.

Table1. Summary table of the main QSAR studies on triazole derivatives (descriptors, R² value, biological targets.

Key Findings	R² / Statistical Metrics	Activity / Indication	Biological Target	Reference
14 descriptors; electron-withdrawing/donating groups affect activity; validated by docking	R^2 (MLR) = 0.724, R^2 (MNLR) = 0.68	Antifungal	*Trichophyton rubrum*	[21]
DFT-based QSAR identified electronic descriptors influencing antibacterial potency	Not reported	Antibacterial	Quinolone–triazole derivatives	[22]
kNN-MFA 3D-QSAR identified steric/electrostatic fields improving cytotoxic activity	Not reported	Anticancer	Substituted 1,2,4-triazoles	[12]
Random Forest QSAR captured nonlinear structure–activity relationships	External validation >85%	Anticancer	Various cancer targets	[23]
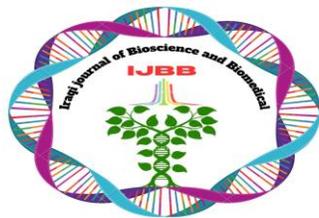
QSAR + docking + MD predicted higher efficacy and lower toxicity analogues	Not reported	Antifungal	Fluconazole analogues	24

Molecular Docking Studies: Methodologies and Significance

Molecular docking has also benefited from faster processing and better algorithms. High-throughput virtual screening lets researchers test millions of compounds against one target in silico. This technique, combining AI and ML, may improve forecast speed and accuracy. Various studies have found promising COVID-19, cancer, and Alzheimer's inhibitors using docking-guided drug development. Molecular docking is a powerful drug discovery method; however, receptor architecture and ligand libraries are needed for accuracy. Forecasts may be inaccurate if these inputs are poorly specified. Therefore, docking studies and experimental validation are usually required. In conclusion, molecular docking is essential to drug development and will become more important in biomedical research as technologies improve [25].

Scientific Essay: Successful QSAR Models for Triazole Derivatives

Pharmaceutical chemistry still predicts the biological activity of chemical compounds using quantitative Structure-Activity Relationship (QSAR) modeling. Recently, triazole compounds have gained popularity for their antifungal, antibacterial, anticancer, and anti-inflammatory activities. Use of QSAR models on triazole compounds has received scientific interest. Chemical stability and bioavailability characterize 1,2,4- and 1,2,3-triazole derivatives. The triazole frameworks are important for model development since QSAR reveals that chemical structure impacts biological function. Topological indices, electrical properties, and hydrophobicity parameters help researchers create reliable QSAR models. If relevant and accurate, QSAR models may reduce in vitro testing and speed drug development. The clear relationship between triazole ring substituent alterations and biological activity makes triazole derivative QSAR models effective. Patel et al. (2021) observed that 1,2,4-triazole derivatives containing electron-withdrawing groups are more antifungal. Electronic characteristics may be measured using Hammett sigma constants or HOMO-LUMO energy gaps to create models with great predictive ability [26].

Recently, QSAR modeling has included machine learning approaches like SVM, RF, and ANN to linear regression. These sophisticated methods excel at managing nonlinear structure-activity interactions. In 2022, Zhang and coworkers used a random forest system to predict triazole derivative anticancer efficacy with over 85% external validation. This strong performance shows how machine learning-based QSAR models may catch complicated chemical patterns that simpler models miss. Additionally, curated chemical databases and open-source cheminformatics tools like PaDEL-Descriptor and RDKit have accelerated the construction of high-quality QSAR models. Trustworthy and chemically varied input data guarantee model generalizability. Small or chemically biased datasets may limit model prediction ability [27].

The 1,2,4-triazole antifungal fluconazole is a notable example. Retroactive QSAR simulations of fluconazole analogues revealed novel compounds with higher efficacy and reduced toxicity. These models' precise biological activity predictions have enabled the development of new medications with improved preclinical pharmacological characteristics. QSAR has identified promising lead compounds and driven triazole derivative structural optimization. When a QSAR model discovers critical molecular features,

scientists may modify the chemical composition to improve efficacy or reduce side effects. QSAR promotes rational drug design and prediction, as shown in Figure 2 [28].

Docking Studies in Drug Design: Insights from Triazole Compounds

Docking studies are essential for drug design because they anticipate small-molecule-biological target interactions. Researchers can assess ligand binding affinity and orientation in protein active sites using this computational technique. Molecular docking is used early in drug discovery because of its cost-effectiveness and efficiency. A drug with good docking findings is more likely to be tested in vitro and in vivo. Docking studies help identify the most promising candidates for development. In pharmaceutical chemistry, triazole molecules, especially those with 1,2,3- or 1,2,4-rings, are popular. Chemical stability and antibacterial, antiviral, anticancer, and antifungal effects characterize these heterocyclic structures. Thus, they are often found in pharmacologically active agent architectures. Triazoles have high binding affinity for biological targets due to their ability to establish numerous hydrogen bonds and π-π interactions. Docking studies favor them because of this characteristic [29].

Recent docking studies using triazole-based compounds have shown promise. Researchers employed AutoDock, Glide, and MOE to explore triazole derivative binding to cytochrome P450, kinases, and proteases. Research indicates that triazole-based antifungals like fluconazole and itraconazole efficiently inhibit the fungal lanosterol 14α-demethylase enzyme. Ergosterol production, necessary for fungal cell membrane integrity, is inhibited. A new triazole derivative with excellent enzyme docking scores may be antifungal. Target protein shape, scoring functions, and ligand and receptor flexibility affect docking simulations. Optimizing these variables may match experimental docking findings. However, limits persist. Docking techniques may model receptors rigidly, which may not reflect protein-ligand interactions. Molecular dynamics simulations enhance docking studies and provide a more detailed binding image [30].

SBDD has been used to create numerous triazole-based molecules recently. Researchers synthesized and docked new triazole derivatives to find molecules with improved selectivity and potency. In vitro experiments validate docking predictions. AI and machine learning have improved docking tools' prediction power by improving scoring systems and virtual screening. Drugs having triazole moieties have better pharmacokinetic characteristics. The metabolic stability and resistance to enzymatic degradation of triazole-containing medicines provide them with longer half-lives and higher oral bioavailability. Docking studies may identify such molecules early and optimize them for medicinal use. Medicinal chemists may change drug scaffolds without affecting biological activity by using triazoles as bioisosteres of amides and esters [31].

For instance, docking simulations of a 1,2,4-triazole derivative with the COX-2 enzyme yielded a binding affinity of -9.2 kcal/mol, with key hydrogen bonds formed between the triazole nitrogen and the Tyr385 residue, illustrating the compound's strong potential for enzyme inhibition [32].

## Future Perspectives: Innovations in Computational Modeling for Medicinal Chemistry

Computational modeling has long served as a cornerstone in medicinal chemistry, providing valuable insights into the structure, dynamics, and function of biological molecules. It enables the prediction

of molecular behavior, drug-receptor interactions, and physicochemical properties with remarkable precision. As drug discovery becomes increasingly data-driven, computational tools have continued to evolve in both accuracy and application. Indeed, computational modeling has not only accelerated the drug development process but has also reduced the costs and time associated with experimental screening. If these modeling tools continue to advance at their current pace, they are likely to become indispensable across all stages of drug discovery [33]. Traditionally, computational methods such as molecular docking, quantitative structure-activity relationship (QSAR) models, and molecular dynamics (MD) simulations have been used to predict how molecules interact with biological targets. These tools have significantly improved the efficiency of lead identification and optimization. However, they often rely on static or semi-flexible representations of proteins and ligands, which may not fully capture the dynamic complexity of biological systems. As a result, there has been a growing need for more robust and adaptable modeling approaches [34].

In recent years, the integration of artificial intelligence (AI) and machine learning (ML) into computational chemistry has revolutionized the field. These technologies have allowed for the rapid analysis of vast chemical datasets, leading to the identification of novel drug candidates that might otherwise be overlooked. Researchers have developed ML algorithms capable of predicting bioactivity, toxicity, and pharmacokinetic properties with increasing accuracy. Because these models learn from existing data, they become more precise as they are exposed to new and diverse chemical information. Moreover, deep learning architectures such as convolutional neural networks and graph neural networks have shown exceptional promise in predicting molecular properties directly from raw data without the need for handcrafted features [35].

Another recent development lies in the application of quantum mechanics (QM)-based methods for drug design. Although QM calculations have traditionally been computationally intensive, recent improvements in computational power and algorithm efficiency have made them more accessible. If these trends continue, quantum-based simulations will likely play a more prominent role in accurately modeling electronic interactions within drug molecules. This is particularly useful when predicting the behavior of compounds that include transition metals or exhibit significant electronic delocalization [36]. Additionally, the emergence of hybrid modeling techniques that combine physics-based and data-driven approaches has led to a new era of predictive modeling. For example, researchers have successfully employed physics-informed neural networks to bridge the gap between classical molecular simulations and AI models. This hybrid approach offers the benefits of both physical interpretability and computational efficiency. Consequently, it may become a key strategy in addressing the limitations of purely empirical models [37].

It is also worth noting that computational modeling has increasingly been used in the design of personalized medicine. By integrating patient-specific genetic and proteomic data, models can now predict individual responses to therapeutic agents. This approach has already shown promise in oncology and rare diseases, where traditional one-size-fits-all therapies often fall short. If such personalized modeling becomes more widespread, it could revolutionize treatment protocols and significantly improve patient outcomes. Looking ahead, one of the primary goals in computational medicinal chemistry is to create models that are not only accurate but also explainable. While AI models are powerful, they often operate as "black boxes," providing predictions without a clear rationale. To address this issue, researchers are now
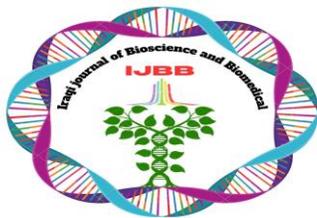
focusing on developing interpretable models that offer mechanistic insights into drug action. This is essential for gaining the trust of regulatory bodies and for facilitating rational drug design [38].

Challenges and Limitations in QSAR and Docking Approaches

Modern drug development uses molecular docking and QSAR models. Both techniques predict the biological activity of chemical compounds, enabling researchers to choose molecules for tests. QSAR employs statistical correlations between molecular profiles and biological activity, whereas docking simulates the physical interaction between ligand and target protein. These technologies dramatically reduce drug candidate identification cost and time. QSAR and docking have various disadvantages that may diminish their accuracy and predictive power, despite their widespread usage[39].

High-quality, diverse, and well-annotated datasets limit QSAR models. If training data is skewed or chemically limited, the model may not generalize to novel substances. Thus, this model may provide inaccurate predictions. QSAR models also assume that comparable structures have similar biological effects, which is not always accurate. Because of activity cliffs, even minor structural changes might affect activity. Due to this issue, trustworthy QSAR models need data curation and validation. QSAR model interpretability relies on the modeling technique. Support vector machines and neural networks are "black boxes," making predictions difficult to read, whereas multiple linear regression is visible. If researchers don't understand model results, rational drug design is challenging. Recent projects use explainable AI (XAI) to simplify complex models. Model performance and interpretability remain tough to balance. Molecular docking is limited by scoring function accuracy. These functions measure ligand-receptor binding affinity but typically oversimplified complicated chemical interactions. Thus, anticipated binding postures may not match experimental data. Many docking techniques ignore protein dynamics and consider the receptor as a solid structure[40]. This rigid-body approximation may cause erroneous docking positions, particularly when induced fit or allosteric effects affect ligand binding. Docking simulations frequently misrepresent water molecules and the solvent environment, exacerbating matters. Ligand binding affinity and orientation may be mispredicted if solvent effects are ignored. MD simulations and ensemble docking, which account for receptor flexibility and solvent effects, are being used to address the issue. These strategies are computationally costly and time-consuming, yet enhance forecast accuracy [41].

QSAR and docking struggle with new chemotypes and underrepresented target classes. If a drug interacts with a poorly known target or is beyond a model's sphere of application, predictions may be inaccurate. Drug development for neglected illnesses, where data and structural details are few, has highlighted this challenge. Therefore, developing chemical and biological information is essential for model robustness. Despite these restrictions, QSAR and docking have advanced. Researchers created hybrid models that blend the qualities of each strategy to enhance prediction. Docking findings may be utilized as QSAR model descriptions, providing synergy. In addition, AI and machine learning have improved scoring algorithms and descriptor creation. These advances have mitigated the traditional shortcomings of these techniques [42].

Integrating Machine Learning with Computational Modeling in Drug Discovery

Machine learning (ML) and computer modeling have revolutionized drug development by predicting molecular attributes, optimizing drug candidates, and discovering new therapeutic targets. ML

algorithms can find complicated, non-linear correlations in huge datasets, unlike physics-based or rule-based computational modeling. This complimentary link greatly improves the drug design tool prediction. Integrating ML enables quick processing of large volumes of chemical and biological data. ML may find patterns without rules if molecular interaction assumptions constrain traditional computational models. This allows researchers to create more precise activity, toxicity, and pharmacokinetic models. Convolutional neural networks can predict protein-ligand binding affinities from molecular structures. Graph neural networks, which consider molecules as graphs, are good at property prediction [43].

Moreover, ML has recently been used to improve scoring functions in molecular docking. Traditional scoring functions often oversimplify binding interactions, leading to false positives or negatives. By training ML models on experimental binding data, scientists have developed scoring functions that better correlate with real-world outcomes. Therefore, ML-enhanced docking methods have demonstrated improved reliability in virtual screening campaigns.

Furthermore, ML supports the design of de novo drug candidates. Generative models, such as variational autoencoders and generative adversarial networks, have enabled the creation of novel chemical structures with desired properties. If these structures pass initial computational filters, they can be synthesized and tested experimentally, accelerating the pipeline from concept to candidate. Despite these benefits, challenges remain. ML models require large, diverse, and high-quality datasets. If data is biased or sparse, predictions may be unreliable. Additionally, model interpretability is still an issue, particularly with deep learning methods. Nevertheless, integrating ML into computational modeling has already reshaped modern drug discovery [44]. As algorithms become more transparent and datasets more comprehensive, this synergy will likely play a central role in developing safer and more effective therapeutics [45].

The Role of Computational Techniques in Advancing Medicinal Chemistry

Computational techniques have become integral to modern medicinal chemistry, significantly transforming the way researchers identify, design, and optimize drug candidates. These methods, which include molecular docking, QSAR modeling, molecular dynamics simulations, and, more recently, machine learning algorithms, provide powerful tools for understanding complex biological interactions and predicting molecular behavior. They save time and money by rapidly screening enormous chemical libraries and predicting drug-target interactions at the atomic level. Computational methods let chemists make reasonable drug design choices based on structural and physicochemical data. Synthesis and biological assessment are more probable for compounds with good docking or QSAR predictions. Thus, computational techniques improve early-stage drug development efficiency and prevent subsequent failure [46].

Many recent breakthroughs in machine learning and artificial intelligence have improved computational models. Researchers have created predictive algorithms to scan vast datasets and find hidden patterns, resulting in innovative drug candidates and improved ADMET (absorption, distribution, metabolism, excretion, and toxicity) predictions. Hybrid models that combine physics-based simulations with data-driven insights provide more accurate and comprehensive molecular interaction representations. However, computational methods have limits. They may oversimplify biological systems depending on

input data quality. The area has made great strides in resolving these difficulties via better algorithms, datasets, and multidisciplinary cooperation [47].

Reflection on the Practical and Clinical Translation of Computational Models

Although computational approaches such as QSAR and molecular docking have demonstrated considerable potential in accelerating the identification of bioactive compounds, their translation from in silico predictions to practical and clinical applications remains limited. Certain models, particularly those enhanced by artificial intelligence, have successfully identified triazole derivatives with high biological activity in in vitro assays, including potent antifungal and anticancer agents, with several candidates progressing to preclinical evaluation. Nevertheless, challenges related to ADMET properties, development costs, and clinical validation continue to hinder the advancement of these leads into approved therapeutics. These observations underscore the role of computational models as complementary tools rather than replacements for laboratory and clinical investigations, and they highlight the need for more advanced algorithms capable of capturing the complex biological context within which drug–target interactions occur [48,49].

Literature Review

Rajitha Balavanthapu et al (2025), Molecular docking studies in the research utilized X-ray crystal structures of EGFR and CDK-4, employing the Schrödinger suite for ligand preparation and Glide's extra-precision docking modes, revealing diverse binding affinities of 5-oxo-1,2,4-triazole-3-carboxamide derivatives. Successful synthesis of 5-oxo-1,2,4-triazole-3-carboxamide derivatives and Diverse binding affinities observed in molecular docking studies [50].

Hawraa Abdul Kadhim Mazyed et al (2024) conducted molecular docking simulations for the triazole derivatives A and B against hepatitis C virus targets 6UE3 and 8DK6, revealing good binding energies of -7.16 and -7.03 kcal/mol, indicating their potential as anti-HCV agents. DFT methods predicted spectroscopic properties that matched experimental results, and Triazole derivatives showed good binding energy against HCV targets [51].

Afaq Abdullayeva (2024) performed molecular docking of 4-azido-2-(4-substituted-phenyl)-5-(2-nitrophenyl)-2H-1,2,3-triazoles using SwissADME software. The analysis analyzed interactions with P-glycoprotein and Cytochrome P450 isoenzymes. The BOILED-Egg method also assessed pharmacokinetic properties and brain or intestine permeability. Positive results for brain or intestine permeability and Compounds meet medicinal substance synthesis requirements [52].

Tatiane Paulino da Cruz et al. (2024), Molecular docking studies in the research elucidated the mechanism of action of glycerol-derived triazole derivatives, suggesting their potential as antifungal agents by interacting with the HvCYP51 enzyme, which is crucial for ergosterol biosynthesis in Hemileia vastatrix. Triazole derivatives effectively suppressed H. vastatrix germination, and Triazole 4f showed the highest preventive and curative efficacy [53].

D.I. Guryev, K.M. Verbilo, et al. (2024). Antiproliferative activity of triazole derivatives was investigated. A Molecular docking prediction algorithm was developed for diverse applications[54].

Yevhen Karpun et al. (2023), 23 compounds based on binding energy for ADME analysis. Six molecules showed high binding affinity to NO-synthase [55].

Ruchika Sharma et al. (2023). The molecular docking analysis of the triazole derivative (4FAMTT) indicates a high binding affinity for the COX-2 protein (PDB ID: 5KIR), demonstrating its ability to bind effectively to the active site with relatively strong interactions. Crystal structure stabilized by N2-H2•••S1 interaction and High binding affinity for COX-2 protein [56].
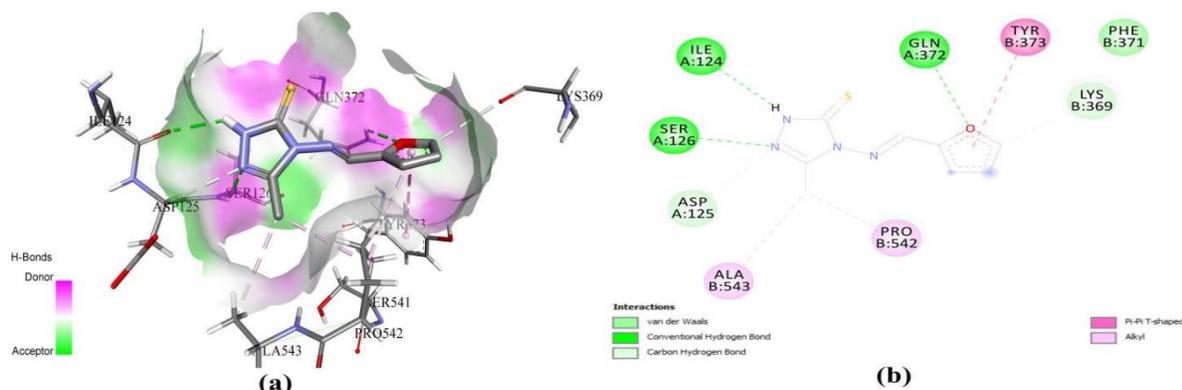
Figure 2 : (a) Molecular Binding Interaction of 4FAMTT to 5KIR Binding Site and (b) The 2D Binding Interaction of 4FAMTT to 5KIR Binding Site.

Meng-Yu Xia et al. (2023) synthesized fifteen 1,2,4-triazole derivatives with varying MIC values, and Compound 4 showed the strongest activity, an MIC of 2 μg/mL [57].
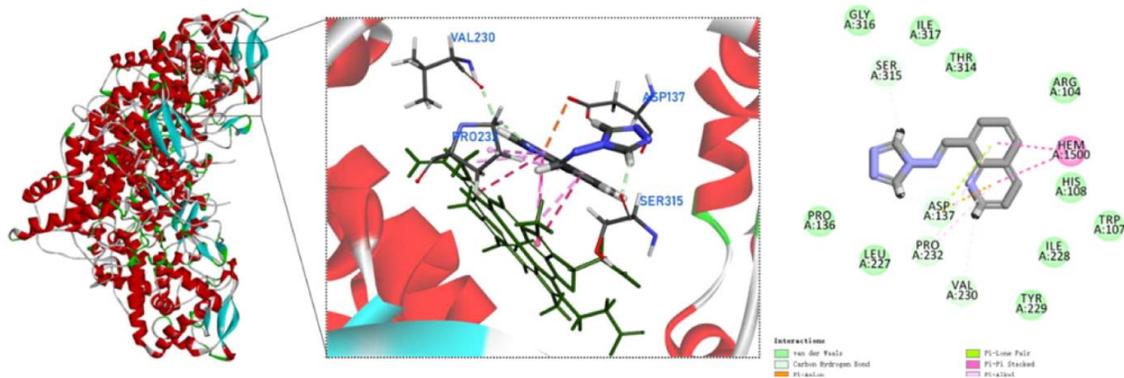

Figure 3. Molecular docking analysis for the compound

Nataliya Korol, et al (2023). Six bis-1,2,4-triazole compounds were synthesized and characterized. Compounds 2 and 6 showed strong thymidine phosphorylase inhibition [58].

Soukaina Bouamrane (2021), Fourteen descriptors determined for twenty-four triazole compounds, and Correlation coefficients R^2 of MLR and MNLR are 0.724 and 0.68 [59].
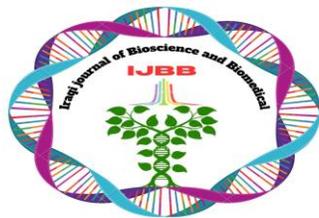
Conclusion

Computational modeling is pivotal in medicinal chemistry, especially for discovering and optimizing triazole derivatives with diverse pharmacological activities. The integration of QSAR modeling and molecular docking enables accurate prediction of biological activity, exploration of structure–activity relationships, and identification of lead compounds with enhanced binding and pharmacokinetic profiles, while reducing experimental time and cost. Remaining challenges—such as model interpretability, data quality, and limited representation of biological dynamics—can be mitigated through hybrid modeling, explainable AI, and quantum-based simulations. The incorporation of machine learning into QSAR and docking offers opportunities to refine scoring functions and expand applicability. Given their versatile structures and bioactive potential, triazole derivatives remain highly valuable in drug discovery, and advances in computational methodologies will further drive next-generation drug development.

Acknowledgment

Authors' Declaration

- We hereby confirm that all the Figures in the manuscript are original and have been created by us.
- We have obtained ethical clearance for our study from the local ethical committee at [Al-Nahrain University]. This approval underscores our commitment to ethical research practices and the well-being of our participants.

Authors' Contribution Statement

Baneen S. Rasool[1]: Collect and write a review.

Nasreen R. Jber[2]: Design and supervisor of a review.

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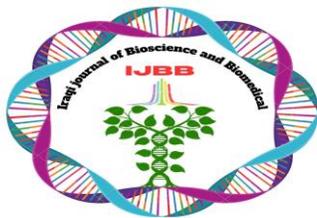
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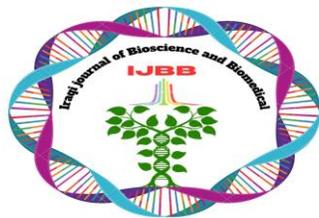
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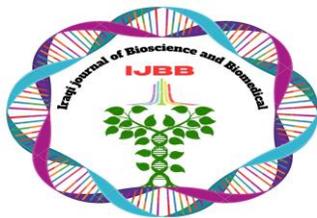
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