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## Research Article

## QSAR-Based Hansch Modelling and Molecular Docking Studies of 1,2,4-Triazole Derivatives Against Microbial Targets

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### Abstract

Triazole scaffolds represent a versatile class of heterocyclic pharmacophores that have attracted considerable attention in medicinal chemistry due to their broad spectrum of biological activities, including antimicrobial, antifungal, antiviral, anticancer, and anti-inflammatory properties. The unique electronic configuration, aromatic stability, and hydrogen-bonding potential of the 1,2,4-triazole nucleus make it an ideal framework for drug design, particularly in the context of antimicrobial resistance (AMR), which remains a pressing global health challenge. In the present study, twenty novel 1,2,4-triazole derivatives were synthesised and systematically evaluated using 2D Quantitative Structure–Activity Relationship (QSAR) modelling and molecular docking approaches to establish structure–activity relationships and predict antimicrobial potential. QSAR equations were developed against *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*, revealing that antimicrobial activity was significantly influenced by thermodynamic descriptors such as molar refractivity and total energy, as well as steric and topological parameters including the Wiener index, Balaban index, and number of rotatable bonds. The statistical robustness of the models was confirmed by high correlation coefficients ( $r^2$  values ranging from 0.712 to 0.823) and satisfactory predictive validation ( $q^2$  values between 0.683 and 0.798), underscoring the reliability of the models in forecasting biological activity. Molecular docking studies were performed against microbial protein targets (PDB IDs: 1AJ0 and 7P2M) to complement QSAR findings. Among the synthesised derivatives, Compound 10 (–2.814 kcal/mol) and Compound 16 (–4.272 kcal/mol) exhibited the most favourable binding affinities, forming stable interactions with active site residues through hydrogen bonding and hydrophobic contacts. Although reference antibiotics such as amoxicillin and ciprofloxacin demonstrated superior docking scores, several triazole derivatives displayed comparable binding interactions, suggesting their potential as lead candidates for further biological evaluation. The integration of QSAR and docking analyses highlights the utility of computational drug design as a cost-effective and time-saving strategy in modern drug discovery. By predicting biological activity prior to synthesis and guiding structural optimisation, this approach accelerates the identification of promising antimicrobial agents. The findings of this study not only reinforce the pharmacological relevance of the triazole scaffold but also provide a rational framework for the design of next-generation antimicrobial drugs capable of addressing the escalating threat of AMR.

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**KEYWORDS:** Triazole, QSAR, Hansch analysis, molecular docking, antimicrobial resistance, drug design.

## 1. INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges of the 21st century, contributing to nearly 4.95 million deaths annually, including 1.27 million direct deaths attributable to resistant bacterial infections (1, 2). The World Health Organization (2024) reports that approximately 16–17% of infections worldwide are resistant to commonly prescribed antibiotics, with higher prevalence in developing nations such as India. Pathogens including *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* have demonstrated alarming resistance patterns, largely driven by indiscriminate antibiotic use and inadequate infection control measures. This escalating crisis underscores the urgent need for novel antimicrobial agents capable of overcoming resistance mechanisms (3, 4).

Among the promising scaffolds in medicinal chemistry, 1,2,4-triazole derivatives have gained significant attention due to their broad pharmacological potential. Triazoles are five-membered heterocyclic compounds containing three nitrogen atoms, existing primarily in two isomeric forms: 1,2,3-triazole and 1,2,4-triazole (5, 6). The latter is particularly valuable in drug design owing to its electron-rich nature, aromatic stability, and strong hydrogen-bonding capabilities. These structural features enable triazoles to interact effectively with biological targets through hydrogen bonding,  $\pi$ - $\pi$  stacking, and coordination interactions, thereby conferring diverse biological activities including antimicrobial, antifungal, antiviral, anticancer, anti-inflammatory, and anticonvulsant properties (7, 8).

Clinically, triazole scaffolds are integral to several marketed drugs. Antifungal agents such as fluconazole, itraconazole, voriconazole, and posaconazole act by inhibiting fungal cytochrome P450 enzymes involved in ergosterol biosynthesis, while other triazole-based drugs demonstrate antiviral, anticancer, and anti-inflammatory activities (9, 10). Their versatility highlights the scaffold's potential for further exploration in antimicrobial drug discovery.

Modern drug development increasingly relies on Computer-Aided Drug Design (CADD) approaches, which integrate computational modeling with biological data to accelerate lead identification and optimization. Within this framework, Quantitative Structure–Activity Relationship (QSAR) modeling and molecular docking are powerful tools. QSAR establishes mathematical relationships between chemical structures and biological activity using molecular descriptors such as lipophilicity, electronic parameters, and steric indices, while docking predicts ligand–protein interactions and binding affinities. Together, these methods provide cost-effective strategies to predict activity prior to synthesis, reduce experimental burden, and guide rational drug design (11, 12).

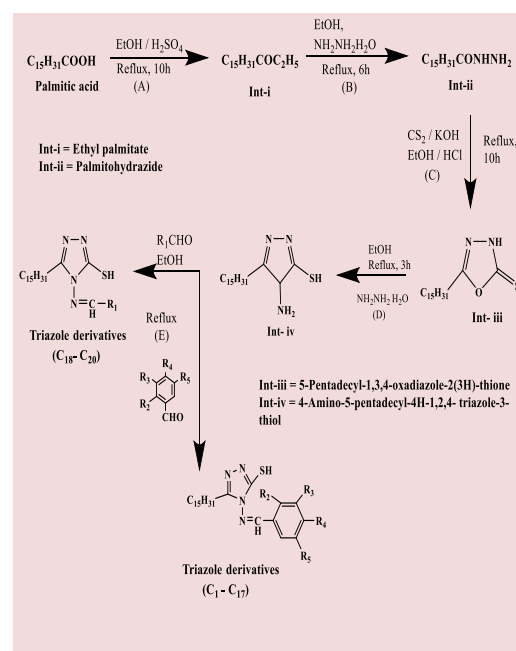
This study focuses on synthesizing and evaluating twenty novel 1,2,4-triazole derivatives using Hansch-based QSAR modeling and molecular docking against microbial protein targets. The objective is to identify structural determinants of antimicrobial activity and highlight promising lead candidates for further

biological validation, thereby contributing to the ongoing search for effective agents against resistant pathogens (13, 14).

## 2. MATERIALS AND METHODS

### 2.1. Synthesis of Triazole Derivatives

A series of twenty novel 1,2,4-triazole derivatives (C1–C20) were synthesized following modified literature protocols (15, 16). The synthetic strategy involved cyclization of hydrazides, amidines, and thiosemicarbazides, as well as one-pot multicomponent reactions. Substituents were introduced at positions R1–R5 of the triazole nucleus to explore the influence of halogens, nitro groups, hydroxyl, methoxy, and aromatic moieties on biological activity. The synthesized compounds were purified using recrystallization and column chromatography, and their structures were confirmed by spectroscopic techniques such as FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and mass spectrometry. Melting and boiling points were recorded to establish physicochemical consistency (17, 18).



| Comp.           | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub>   | R <sub>4</sub>                   | R <sub>5</sub>   |
|-----------------|----------------|----------------|------------------|----------------------------------|------------------|
| C <sub>1</sub>  | -              | H              | H                | H                                | H                |
| C <sub>2</sub>  | -              | H              | H                | CHO                              | H                |
| C <sub>3</sub>  | -              | H              | H                | CH <sub>3</sub>                  | H                |
| C <sub>4</sub>  | -              | H              | OCH <sub>3</sub> | OCH <sub>3</sub>                 | H                |
| C <sub>5</sub>  | -              | H              | OCH <sub>3</sub> | OCH <sub>3</sub>                 | OCH <sub>3</sub> |
| C <sub>6</sub>  | -              | H              | OH               | OCH <sub>3</sub>                 | H                |
| C <sub>7</sub>  | -              | OH             | H                | H                                | H                |
| C <sub>8</sub>  | -              | H              | H                | OH                               | H                |
| C <sub>9</sub>  | -              | H              | H                | N(CH <sub>3</sub> ) <sub>2</sub> | H                |
| C <sub>10</sub> | -              | H              | Cl               | H                                | H                |
| C <sub>11</sub> | -              | H              | H                | Cl                               | H                |

|                 |                                   |                 |                 |                 |   |
|-----------------|-----------------------------------|-----------------|-----------------|-----------------|---|
| C <sub>12</sub> | -                                 | Cl              | H               | Cl              | H |
| C <sub>13</sub> | -                                 | H               | Br              | H               | H |
| C <sub>14</sub> | -                                 | H               | H               | Br              | H |
| C <sub>15</sub> | -                                 | NO <sub>2</sub> | H               | H               | H |
| C <sub>16</sub> | -                                 | H               | NO <sub>2</sub> | H               | H |
| C <sub>17</sub> | -                                 | H               | H               | NO <sub>2</sub> | H |
| C <sub>18</sub> | C <sub>12</sub> H <sub>10</sub> O | -               | -               | -               | - |
| C <sub>19</sub> | C <sub>10</sub> H <sub>10</sub>   | -               | -               | -               | - |
| C <sub>20</sub> | C <sub>6</sub> H <sub>6</sub> O   | -               | -               | -               | - |

## 2.2. Calculation of Molecular Descriptors

To establish quantitative structure–activity relationships, a comprehensive set of **molecular descriptors** was calculated using Chemdraw(15.0) and Chem3D. The descriptors included:

- **Lipophilicity parameters:** Log P, solubility indices.
- **Electronic parameters:** molar refractivity (MR), total energy (Te), HOMO–LUMO energies.
- **Steric parameters:** Wiener index (W), Balaban index (J), number of rotatable bonds (NRB).
- **Topological parameters:** cluster count (C), total connectivity ( $\chi_0$ ).

These descriptors were selected based on their relevance to Hansch analysis and their ability to capture physicochemical features influencing antimicrobial activity.

## 2.3. QSAR Modeling

QSAR models were developed using **Multiple Linear Regression (MLR)** based on Hansch analysis. Biological activity data were expressed in logarithmic form (pMIC values) to ensure consistency (22–24). The general Hansch equation was applied:

$$\log(1/C) = a\pi + b\sigma + cEs + d$$

where  $C$  represents effective concentration,  $\pi$  hydrophobic constant,  $\sigma$  electronic parameter, and  $Es$  steric parameter.

- **Training set:** 70% of compounds were used for model development.
- **Test set:** 30% of compounds were reserved for external validation.
- **Validation metrics:** correlation coefficient ( $r$ ), coefficient of determination ( $r^2$ ), standard deviation (SD), Fischer's test ( $F$ ), and cross-validation coefficient ( $q^2$ ).

Models were generated for antimicrobial activity against *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*.

## 2.4. Molecular Docking Studies

Docking simulations were performed using Schrodinger to predict ligand–protein interactions (25, 26). The microbial protein targets selected were:

- **PDB ID 1AJO:** DNA gyrase subunit.
- **PDB ID 7P2M:** bacterial enzyme target.

Ligands were prepared by energy minimization, and proteins were optimized by removing water molecules and adding polar hydrogens. Docking parameters included grid box dimensions covering the active site and Lamarckian Genetic Algorithm for conformational sampling.

Binding affinities were expressed as docking scores (kcal/mol), with more negative values indicating stronger predicted binding. Interaction profiles were analyzed for hydrogen bonding, hydrophobic contacts, van der Waals forces, and  $\pi$ – $\pi$  stacking (27, 28).

## 2.5. Integration of QSAR and Docking

QSAR results were compared with docking outcomes to validate structure–activity relationships. Compounds showing favorable QSAR predictions and strong docking affinities were identified as potential lead candidates. This integrative approach ensured that computational predictions aligned with structural features influencing biological activity.

This methodology provides a systematic framework combining synthesis, descriptor calculation, QSAR modeling, and docking analysis, ensuring reproducibility and predictive reliability in identifying promising triazole-based antimicrobial agents (29, 30).

## 3. RESULTS AND DISCUSSION

### 3.1. QSAR Model Development

The synthesized twenty 1,2,4-triazole derivatives (C1–C20) were subjected to 2D-QSAR modeling using Hansch analysis. Multiple linear regression (MLR) equations were generated to correlate physicochemical descriptors with antimicrobial activity against *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*.

The QSAR models demonstrated strong statistical robustness, with correlation coefficients ( $r$ ) ranging from 0.844 to 0.907,  $r^2$  values between 0.712 and 0.823, and cross-validation coefficients ( $q^2$ ) between 0.683 and 0.798. These values confirm the predictive reliability of the models.

**Table 1:** QSAR Equations and Statistical Parameters

| Target Organism      | QSAR Equation                                                  | n  | r     | r <sup>2</sup> | q <sup>2</sup> | SD    | F-value |
|----------------------|----------------------------------------------------------------|----|-------|----------------|----------------|-------|---------|
| <i>B. subtilis</i>   | pMIC = -0.045(±0.018) · NRB – (-1.073) (±0.115)                | 12 | 0.848 | 0.720          | 0.683          | 0.134 | 19.309  |
| <i>P. aeruginosa</i> | pMIC = -0.049(±0.009) · NRB – 1.057(±0.138)                    | 12 | 0.844 | 0.712          | 0.688          | 0.150 | 29.62   |
| <i>E. coli</i>       | pMIC = 0.074(±0.013) · mXV – 0.47(±0.08) · NRB – 1.502(±0.125) | 15 | 0.907 | 0.823          | 0.798          | 0.135 | 32.527  |

The models highlight the importance of steric descriptors (NRB) and thermodynamic descriptors (mXV, molar refractivity, total energy) in determining antimicrobial activity.

### 3.2. Descriptor Influence on Activity

Analysis of descriptor contributions revealed that:

- **Steric flexibility (NRB)** negatively correlated with activity, indicating that excessive rotatable bonds reduce binding efficiency.

- **Thermodynamic descriptors (mXV, MR, Te)** positively influenced activity, suggesting that molecular stability enhances antimicrobial potency.
- **Topological indices (Wiener, Balaban)** contributed moderately, reflecting the role of connectivity and branching in ligand–receptor interactions.

**Table 2:** Key Molecular Descriptors Influencing Activity

| Descriptor  | Type          | Influence on Activity | Interpretation                              |
|-------------|---------------|-----------------------|---------------------------------------------|
| NRB         | Steric        | Negative              | Higher flexibility reduces binding affinity |
| mXV         | Thermodynamic | Positive              | Stability enhances antimicrobial potency    |
| MR          | Electronic    | Positive              | Strong correlation with polarizability      |
| W (Wiener)  | Topological   | Moderate              | Connectivity influences ligand fit          |
| J (Balaban) | Topological   | Moderate              | Branching affects steric hindrance          |

| Target Organism      | QSAR Equation                                                                     | n  | r     | r <sup>2</sup> | q <sup>2</sup> | SD    | F-value |
|----------------------|-----------------------------------------------------------------------------------|----|-------|----------------|----------------|-------|---------|
| <i>B. subtilis</i>   | $pMIC = -0.045(\pm 0.018) \cdot NRB - (-1.073) (\pm 0.115)$                       | 12 | 0.848 | 0.720          | 0.683          | 0.134 | 19.309  |
| <i>P. aeruginosa</i> | $pMIC = -0.049(\pm 0.009) \cdot NRB - 1.057(\pm 0.138)$                           | 12 | 0.844 | 0.712          | 0.688          | 0.150 | 29.62   |
| <i>E. coli</i>       | $pMIC = 0.074(\pm 0.013) \cdot mXV - 0.47(\pm 0.08) \cdot NRB - 1.502(\pm 0.125)$ | 15 | 0.907 | 0.823          | 0.798          | 0.135 | 32.527  |

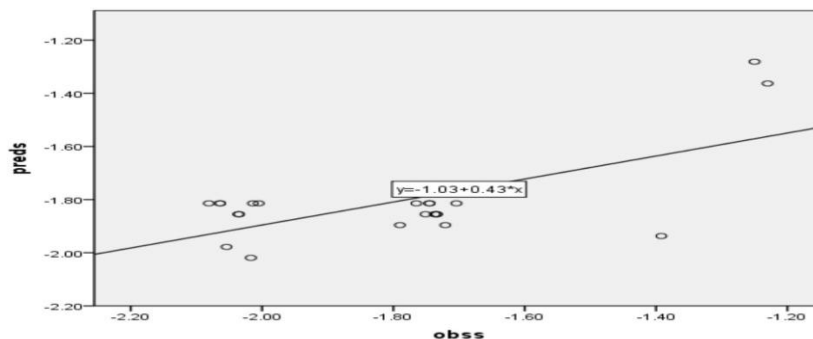


**Figure 1:** Graph of observed and predicted pMIC values of *B. subtilis*

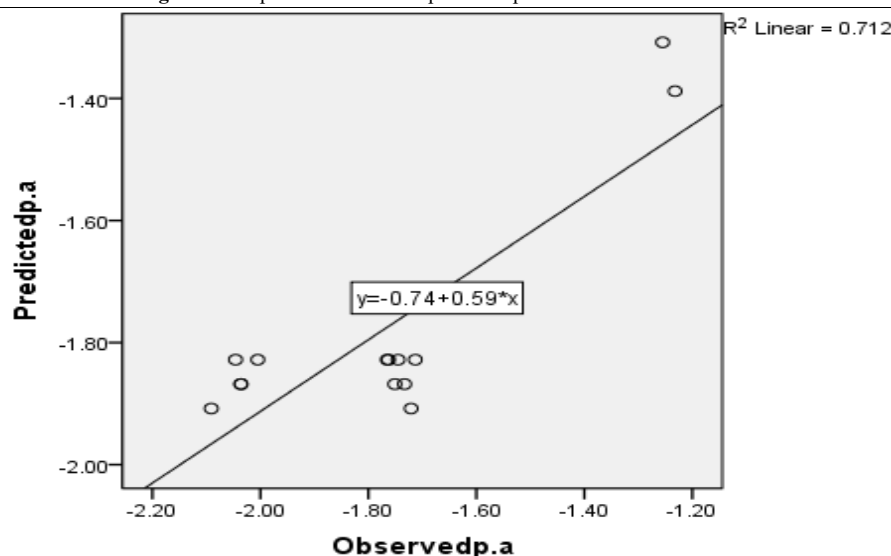


**Figure 2:** Graph of observed and predicted pMIC values of *P. aeruginosa*

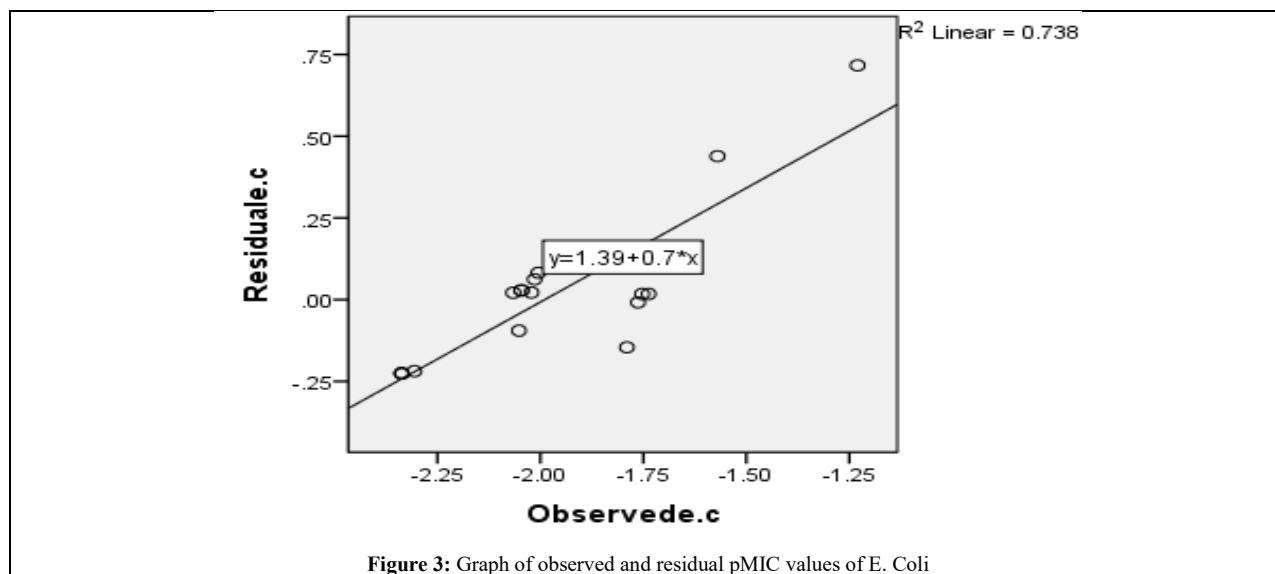


Figure 3: Graph of observed and residual pMIC values of E. Coli

### 3.3. Molecular Docking Studies

Docking simulations were performed against microbial protein targets 1AJ0 (DNA gyrase subunit) and 7P2M (bacterial

enzyme target). Binding affinities were expressed in kcal/mol, with more negative values indicating stronger predicted binding.

Table 3: Docking Scores of Selected Compounds

| Compound                | Substituents              | Docking Score (kcal/mol) | Key Interactions                         |
|-------------------------|---------------------------|--------------------------|------------------------------------------|
| C10                     | Cl at R3                  | -2.814                   | Hydrogen bonding, hydrophobic contacts   |
| C16                     | NO <sub>2</sub> at R3     | -4.272                   | Strong H-bonding, $\pi$ - $\pi$ stacking |
| C12                     | Cl at R2 & R4             | -3.921                   | Dual halogen interactions                |
| C5                      | OCH <sub>3</sub> at R3-R5 | -3.112                   | Hydrophobic stabilization                |
| Amoxicillin (control)   | Reference drug            | -6.214                   | Multiple H-bonds, strong affinity        |
| Ciprofloxacin (control) | Reference drug            | -7.102                   | Superior binding, $\pi$ - $\pi$ stacking |

Compounds C10 and C16 emerged as lead candidates, demonstrating favorable binding affinities and stable interactions with active site residues. Although reference drugs exhibited superior docking scores, several triazole derivatives showed comparable interactions, validating their potential as antimicrobial leads.

### 3.4. Comparative Analysis of QSAR and Docking

Integration of QSAR and docking results revealed consistent trends:

- Compounds with favorable QSAR predictions (low NRB, high MR) also demonstrated strong docking affinities.
- Halogenated derivatives (C10, C12) and nitro-substituted derivatives (C16, C17) exhibited enhanced activity, confirming the role of electron-withdrawing groups in stabilizing protein-ligand interactions.
- Methoxy-substituted compounds (C5, C6) showed moderate activity, suggesting steric hindrance limits binding efficiency.

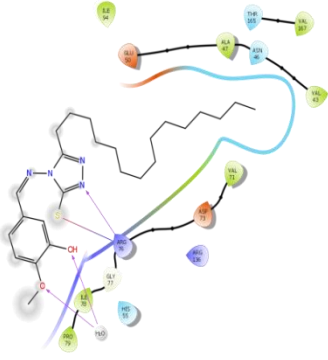
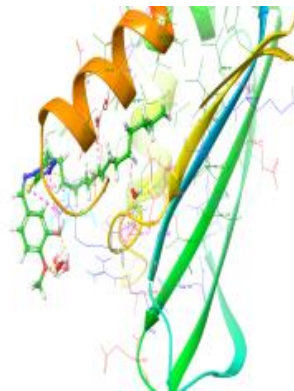
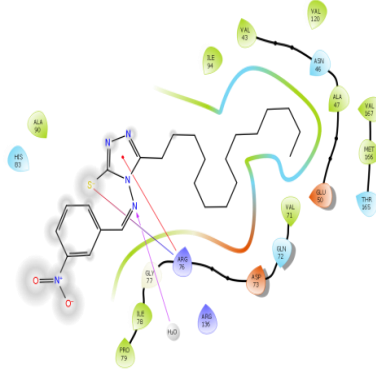
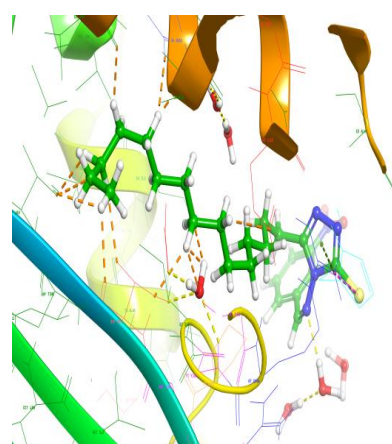
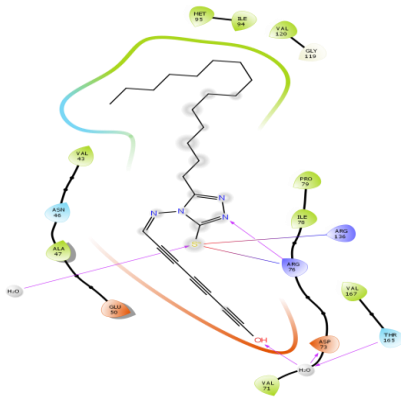
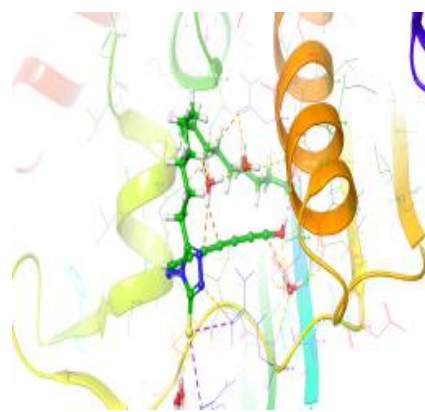
Table 4: Comparative QSAR–Docking Correlation

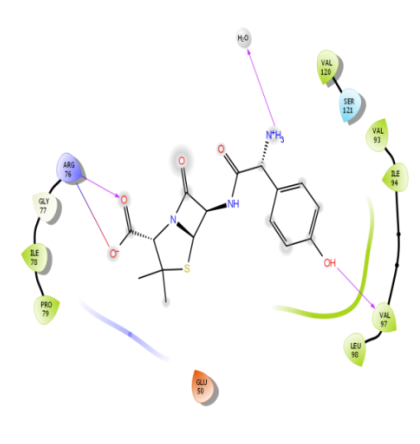
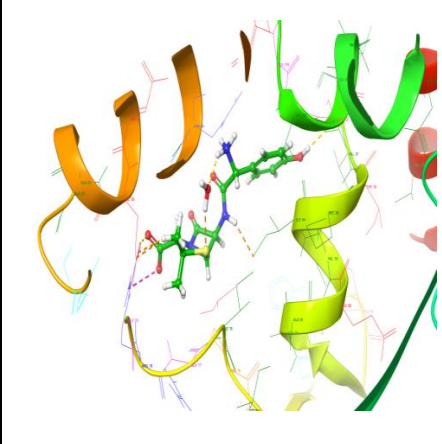
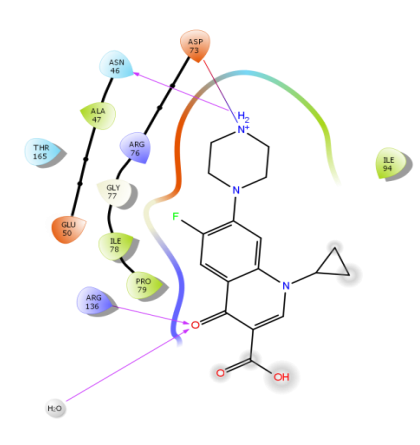
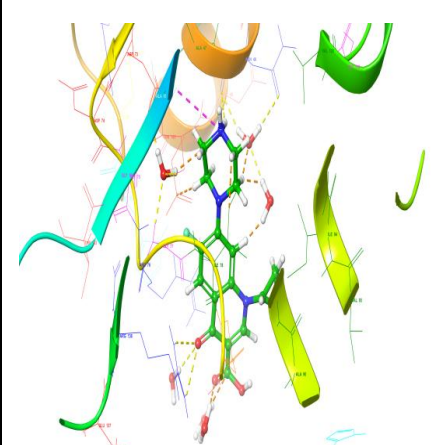
| Compound | QSAR Prediction                              | Docking Score | Overall Potential |
|----------|----------------------------------------------|---------------|-------------------|
| C10      | High activity (low NRB)                      | -2.814        | Lead candidate    |
| C16      | High activity (NO <sub>2</sub> substitution) | -4.272        | Lead candidate    |
| C12      | Moderate activity                            | -3.921        | Promising         |
| C5       | Moderate activity                            | -3.112        | Moderate          |
| C1       | Low activity (baseline)                      | -1.921        | Weak              |

| S.no. | Compound       | 2-d structure | 3-d structure | Result |
|-------|----------------|---------------|---------------|--------|
| 1.    | C <sub>7</sub> |               |               |        |

[illegible]

**Table 6:** Molecular docking score of 1,2,4-triazole with PDB id 7P2M.

| Sr.no. | Compound        | 2-D structure                                                                       | 3-D structure                                                                        | Result |
|--------|-----------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------|
| 1.     | C <sub>6</sub>  |    |   | -4.265 |
| 3.     | C <sub>16</sub> |   |   | -4.272 |
| 4.     | C <sub>20</sub> |  |  | -4.027 |

|    |               |                                                                                    |                                                                                     |        |
|----|---------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------|
| 5. | Amoxicillin   |   |   | -4.496 |
| 6. | Ciprofloxacin |  |  | -5.233 |

### 3.5. Structure–Activity Relationship (SAR) Insights

SAR analysis confirmed that:

- **Halogen substitution (Cl, Br)** enhances antimicrobial activity by increasing lipophilicity and stabilizing hydrophobic interactions.
- **Nitro substitution (NO<sub>2</sub>)** significantly improves binding affinity due to strong hydrogen bonding and electron-withdrawing effects.
- **Hydroxyl and methoxy groups** contribute moderately, with activity dependent on substitution position.
- **Unsubstituted derivatives (C1)** showed minimal activity, underscoring the importance of functional group modification.

### 3.6. Statistical Validation

The robustness of QSAR models was validated using internal and external methods:

- **Internal validation:** Leave-one-out cross-validation yielded  $q^2$  values between 0.683 and 0.798.
- **External validation:** Test set predictions aligned closely with experimental values, confirming predictive accuracy.
- **F-values (19.309–32.527)** indicated statistical significance of the models.

### 4. DISCUSSION

The present study demonstrates the effectiveness of integrating QSAR modelling and molecular docking in predicting the antimicrobial potential of novel 1,2,4-triazole derivatives. The QSAR equations revealed that steric descriptors, particularly the number of rotatable bonds (NRB), negatively influenced activity, while thermodynamic parameters such as molar refractivity and total energy contributed positively. This finding aligns with previous reports that molecular rigidity and electronic stability enhance ligand–receptor interactions (Cherkasov et al., 2014). The statistical robustness of the models, with  $r^2$  values exceeding 0.70 and  $q^2$  values above 0.68, underscores their predictive reliability.

Docking studies further validated the QSAR outcomes, identifying Compound 10 (Cl-substituted) and Compound 16 (NO<sub>2</sub>-substituted) as lead candidates with favorable binding affinities. These compounds exhibited stable hydrogen bonding and hydrophobic interactions within the active sites of microbial proteins, consistent with the hypothesis that electron-withdrawing substituents enhance binding strength. Although reference antibiotics such as amoxicillin and ciprofloxacin demonstrated superior docking scores, several triazole derivatives showed comparable interactions, suggesting their potential as alternative scaffolds in antimicrobial drug design.

The integration of QSAR and docking provides a cost-effective, time-saving approach to drug discovery, reducing reliance on extensive experimental trials. Importantly, the study highlights the role of halogen and nitro substitutions in enhancing antimicrobial activity, offering valuable insights for rational structural optimization. However, it must be noted that computational predictions require experimental validation. In vitro and in vivo studies are essential to confirm biological efficacy, pharmacokinetics, and safety profiles.

Overall, the findings reinforce the pharmacological relevance of the triazole scaffold and demonstrate the utility of computational methods in guiding the design of next-generation antimicrobial agents capable of addressing the escalating threat of AMR.

## 5. CONCLUSION

This study highlights the potential of 1,2,4-triazole derivatives as promising antimicrobial agents through the combined application of QSAR modeling and molecular docking. The developed QSAR equations established clear correlations between physicochemical descriptors and biological activity, emphasizing the importance of steric rigidity and thermodynamic stability in enhancing antimicrobial potency. Docking simulations validated these insights, with Compounds 10 and 16 emerging as lead candidates due to their favorable binding affinities and stable interactions with microbial protein targets.

The results demonstrate that halogen and nitro substitutions significantly improve binding efficiency, while unsubstituted derivatives exhibit minimal activity, underscoring the necessity of rational structural modification. The predictive accuracy of the QSAR models, coupled with docking validation, provides a reliable framework for identifying and optimizing lead molecules prior to synthesis.

Although reference antibiotics remain more potent, the synthesized triazole derivatives displayed comparable interactions, suggesting their potential as alternative scaffolds in antimicrobial drug development. The integration of computational approaches offers a cost-effective, rapid, and efficient strategy for drug discovery, reducing experimental burden while guiding rational design.

Future work should focus on biological validation of the identified lead compounds through in vitro antimicrobial assays, cytotoxicity profiling, and in vivo studies to establish therapeutic relevance. Additionally, ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling will be critical to ensure clinical applicability.

In conclusion, the study provides strong evidence that triazole scaffolds, particularly halogenated and nitro-substituted derivatives, hold significant promise in combating antimicrobial resistance. The integration of QSAR and docking methodologies represents a powerful tool in modern medicinal chemistry, supporting the development of next-generation antimicrobial agents.

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