Available online on 15.06.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

# Molecular Docking: An Important Computational Tool in Virtual Screening of Some Imidazole Phenanthroline Derivatives

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Article Info:

Article History:

Received 19 March 2025
Reviewed 28 April 2025
Accepted 26 May 2025
Published 15 June 2025

Cite this article as:

Salam S, Jat RK, Molecular Docking: An Important Computational Tool in Virtual Screening of Some Imidazole Phenanthroline Derivatives, Journal of Drug Delivery and Therapeutics. 2025; 15(6):111-115 *DOI: http://dx.doi.org/10.22270/jddt.v15i6.7231*

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Abstract

**Purpose:** To evaluate the antimicrobial potential of few newly synthesized imidazole phenanthroline derivatives using molecular docking simulation approach.

**Method:** The novel 1H-imidazo [4,5-f] [1,10] phenanthroline compounds developed from the commercially available 1,10-phenanthroline (starting compound) via a series of reactions, were subjected to the molecular docking studies. Using the software program Autodock Vina, all compounds were positioned in the active location of the target enzyme DNA gyrase (receptor) B subunit. The software generates different conformations and calculates a docking score.

**Results:** The binding interactions and properties of four synthetic compounds (4a–4d) with DNA gyrase were assessed. Compound 4d has the highest docking score of all (-5.286), indicating that it binds to the target DNA gyrase more efficiently than the others. With the most favourable free energy (-55.46), compound 4c appears to have a robust contact with the receptor. Compound 4b (-15.99) makes a significant positive contribution, indicating strong electrostatic interactions. The maximum positive value (6.15), displayed by compound 4a, suggests that whereas covalent contacts may have advantages, they also put more pressure on binding. Compound 4c appears to have strong hydrophobic interactions since it has the largest negative lipophilic contribution (-16.50). Strong van der Waals contributions are seen in compound 4c (-45.03). Compound 4c is structurally favourable for binding since it has the lowest strain energy (3.46).

**Conclusion:** The synthesized compounds were found to possess good antimicrobial action in the inhibition of enzyme DNA gyrase, which are essential for the survival of the microorganisms.

**Keywords:** 1,10-phenanthroline, 1H-imidazo [4,5-f] [1,10] phenanthroline, molecular docking, DNA gyrase.

## INTRODUCTION

The use of molecular docking research is necessary for the discovery and development of novel medications. It allows researchers to predict the orientation of a ligand or drug candidate when it binds to a protein target like an enzyme or receptor [1]. This provides information related to the strength and nature of binding interaction, thus helping in the design of synthesis of novel therapeutic compounds [2-5].

Auto Dock Vina, Schrodinger, Haddock, Rosetta etc. are some popular software tools and platforms used for research on molecular docking. Auto Dock Tools (ADT) serves as the graphical interface for configuring and executing the Auto Dock software. It is among the most accurate docking tools effective for protein docking of ligands. It is easily available software, accessible to the public at no cost with better efficiency and time-saving benefits [6,7].

The binding site's energy is calculated using the Auto Grid approach, followed by a comparison of the ligand's energetics with the values produced by the interaction terms derived from the affinity grid calculations. The Auto Dock applications include protein-protein docking, virtual screening (HTS), structure-based drug design, X-ray crystallography, combinatorial library construction and chemical mechanism studies. The knowledge about how a ligand can block the enzyme's active site assists in designing suitable enzyme inhibitors. Large chemical libraries may be quickly virtual screened to find hit compounds for biological testing. Details about a drug's mechanism of action may be found in its ligand binding modes. The COVID-19 drug discovery was a prime illustration of docking: Molecular docking was utilized in the urgent search for anti-SARS-CoV-2 medicines, to identify potential inhibitors of vital viral proteins, including spike protein and the major protease (Mpro). Researchers have targeted specific pathways in cancer biology using docking studies to identify small molecules, leading to the discovery of promising anti-cancer agents. Docking is also utilized in the medication design process to investigate how heterocyclic compounds interact with various proteins [8].

Numerous methods are being used to find novel medications by targeting drug targets such as enzymes or receptors [9]. One attractive target in E. coli is DNA gyrase, a type II topoisomerase, which participates in the replication and transcription of this bacterium [10, 11]. Two GyrA subunits and two GyrB subunits make up the heterotetramer. This enzyme is seen in micro-organisms as it is important for maintaining its cellular functions but is absent in humans. While the B subunit possesses the ATPase active site, the A subunit connects with DNA and has the tyrosine active site, which promotes DNA breaking. The gyrase enzyme works by inducing double-stranded breaks in the DNA, passing another segment of the DNA by way of the break, followed by closing the break again. This results in negative supercoils, which are essential for the DNA in the bacterial cell to function correctly. [12,13].

There could be different approaches to DNA gyrase in antimicrobial docking studies [14]. (i) Molecular Docking: It is a computer method that calculates how strongly ligands attach to receptor proteins. (ii) Docking Based on Ligands: It involves docking a library of compounds onto the receptor to identify potential binders. (iii) Structure-Based Docking: It uses a known protein structure (eg: DNA gyrase) to dock ligands and assess their binding affinity. Several factors such as structural features of imidazole phenanthroline compounds, AT-rich regions in DNA, and binding mechanism affect binding.

## METHOD

### Instrumentation

Auto Dock Tools (ADT) 1.5.6 is an analysis software program that works in collaboration with the Auto Dock suite (including Auto Dock Vina) for molecular docking studies.

### *Compounds*

*4a: 2-(4-chloro-2-methoxyphenyl)-1H-imidazo[4,5-f] [1,10] phenanthroline*

*4b: 4-chloro-2-(1H-imidazo[4,5-f] [1,10] phenanthroline-2-yl)-6-iodophenol*

*4c: 2-(3-iodo-4-methoxyphenyl)-1H-imidazo[4,5-f][1,10]phenanthroline*

*4d: 2-(2-bromo-4-chlorophenyl)-1H-imidazo[4,5-f] [1,10] phenanthroline*

### Docking procedure

The stepwise procedure for docking is as follows. (i) The receptor is loaded first into the program, usually in the PDB (Protein Data Bank) file format. This file contains all data related to its structure about the target macromolecule, including atomic coordinates and connectivity. (ii) The receptor is prepared for docking by the addition of hydrogen, setting charges etc. (iii) Next, the ligand or the desired compound (either in .pdb or mol2 format) is loaded with defined grid parameters. The grid creates the search space for docking since the binding point is located in the middle of the grid box. (iv). The docking program is run. (v) After the docking procedure is finished, the binding poses are visualized to examine the docking findings. The docking scores are generated that determines the attraction strength between a ligand and a receptor. The other key features relevant to binding such as hydrogen bonds, hydrophobic interactions etc. can be seen [15]. In general, the stronger the expected binding affinity, the lower (more negative) the binding energy score.

Imidazole phenanthroline chemicals' interaction to DNA's minor groove is a topic of significant interest. The minor groove in DNA is a typical location for small molecules or ligands to interact, and their binding can interfere with DNA replication and transcription processes [16-18]. It can also produce significant biological effects. Hydrogen bonds between the nucleobases in DNA constitute the double helix of DNA's backbone. The pair that cytosine (C) and guanine (G) create is different from that of adenine (A) and thymine (T). Adenine (A) is a purine which forms two hydrogen bonds with thymine (T) which is a pyrimidine. This binding is important for the stability of the DNA structure and ensures that genetic information is correctly replicated and transmitted [19].

The Adenosine-thymine (AT) - rich regions are parts of DNA that have a higher concentration of adenine and thymine bases. These regions possess unique structural properties and biological functions. Many genes have AT-rich promoter regions that promote the binding of transcription factors and RNA polymerase. AT-rich DNA regions (with two hydrogen bonds) have lower melting temperatures compared to GC-rich regions (with three hydrogen bonds). This can influence the flexibility and accessibility of these DNA regions. Proteins that recognize and bind to AT-rich regions regulate gene transcription and hence are essential for cell functions. Therefore, small molecules or drugs that bind specifically to AT-rich regions in the DNA minor groove can modulate the activity of target genes, with potential biological activities. The newly synthesized compounds were screened to study all possible ligand-protein interactions based on docking scores. These interactions are depicted pictorially [20].

## RESULTS

The software program generates images which helps us to better understand the binding interactions between the ligands and the receptor. Pictorial representations of ligand interactions with DNA gyrase were obtained from the software, which clearly gives information related to the binding poses, distances of key interactions and any conformational changes brought about by binding in the ligand or protein. The binding of compounds 4a with DNA is shown by Figure 1, 4b by Figure 2, 4c by Figure 3 and 4d by Figure 4 respectively.

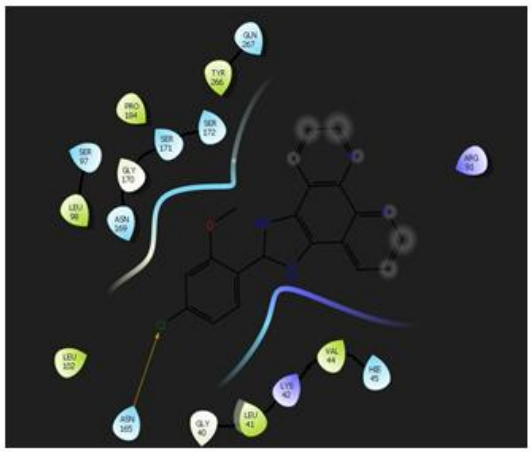

**Figure 1: Binding of 4a with DNA**

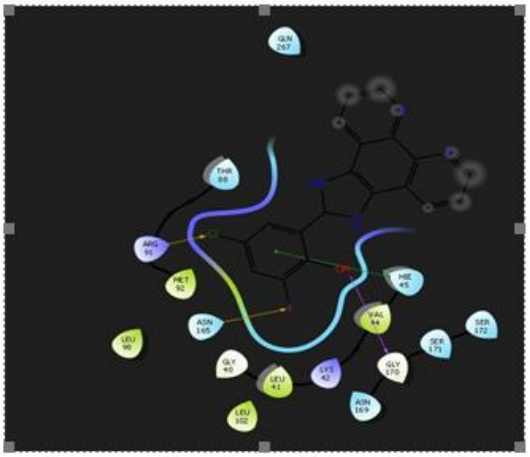

**Figure 2: Binding of 4b with DNA**

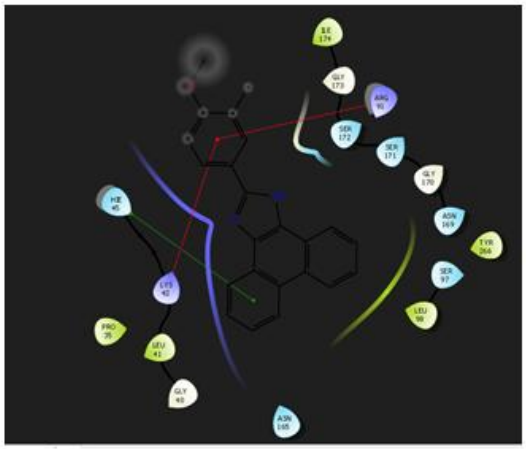

**Figure 3: Binding of 4c with DNA**

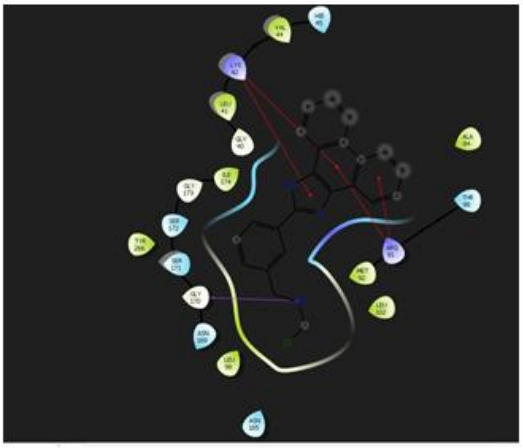

**Figure 4: Binding of 4d with DNA**

The binding free energy and interaction calculations between synthesized compounds and DNA gyrase are essential for understanding their potential as antimicrobial agents or drug candidates. The ligand-receptor complex's stability is determined by the binding free energy (ΔG bind). It describes the degree to which the synthetic compounds and DNA gyrase interact to create complexes. A lower binding free energy indicates stronger binding affinity, reflecting effective enzyme inhibition. Nonpolar interactions, hydrogen bonds, and Van der Waals forces are examples of interactions that have a big impact on the compound's binding affinity to DNA gyrase active site residues.

When it comes to drug design and molecular interactions, the calculation of binding affinity using binding free energy, which is expressed in kcal/mol, is a crucial element of pharmacological research. The interactions between the synthesized chemicals and their binding free energy with DNA-gyrase through hydrogen bonding is summarized in the table below:

**Table 1: Binding free energy and interactions among the synthesized compounds [4a-4d] with DNA-gyrase**

| Names | Docking Scores | MM-GBSA dG Bind | MM-GBSA dG Bind Coloumb | MM-GBSA dG Bind Covalent | MM-GBSA dG Bind Lipo | MM-GBSA dG Bind Solv GB | MM-GBSA dG Bind vdW | Ligand Strain Energy |
|---|---|---|---|---|---|---|---|---|
| **4a** | -4.123 | -41.49 | -10.58 | 6.15 | -11.29 | 24.04 | -42.5 | 6.50 |
| **4b** | -4.128 | -39.58 | -15.99 | 3.79 | -10.47 | 24.41 | -34.08 | 5.08 |
| **4c** | -3.766 | -55.46 | 8.21 | 4.61 | -16.50 | 0.75 | -45.03 | 3.46 |
| **4d** | -5.286 | -34.53 | 5.53 | 2.66 | -9.94 | 6.61 | -37.11 | 6.49 |

The docking scores generated determine the affinity of the ligand for the receptor. Docking scores are inversely proportional to their binding affinity. In other words, a lower docking score indicates a stronger binding affinity, while a higher score suggests weaker binding. Based on these scores, compounds with better affinities can be ranked and synthesized accordingly. Structural modifications in the resulting compounds can be made and their binding interactions can well be predicted.

## DISCUSSION

The binding interactions and characteristics of four synthesized compounds (4a to 4d) with the target enzyme, DNA gyrase was evaluated based on parameters such as binding free energy and docking scores using thorough computational investigations. The Molecular Mechanics Generalized Born Surface Area (MM-GBSA) approach is used in the study to compute a number of binding metrics. Amongst all, compound 4d has the best docking score (-5.286), which suggests that it binds more effectively to target DNA gyrase compared to the others. MMGBSA dG Bind (in kcal/mol) values closer to zero or more negative indicates better binding affinity. Here, compound 4c has the most favourable free energy (-55.46), suggesting it has a strong interaction with the protein. MMGBSA Bind Coulomb measures the binding energy contributions from electrostatic forces. It is the energy obtained via the Coulombic interactions between the protein and the ligand's charged groups. Lower values (more negative) indicate stronger favourable interactions. Compound 4b (-15.99) has notable favourable contributions in this regard, suggesting strong electrostatic interactions. Conversely, 4c has a positive value (8.21), indicating repulsion which may affect its overall binding affinity. MMGBSA dG Bind Covalent refers to the energy from covalent bonding. Compound 4a shows the highest positive value (6.15), which implies that while there may be benefits from covalent interactions, it also increases the strain on binding. As most of these compounds are not covalent bond inhibitors, positive values indicate a less favourable energetics. MMGBSA dG Bind Lipo refers to the lipophilic energy contribution to binding. For this, negative values indicate favourable hydrophobic interactions. Compound 4c has the most negative lipophilic contribution (-16.50), which suggests that it has strong hydrophobic interactions. MMGBSA dG Bind Solv GB is the solvation free energy. Lower (or less positive) values are favourable and indicates the energy cost of solvation. Van der Waals interactions that are non-polar between the protein and the ligand are known as MMGBSA dG Bind vdW. Negative values suggest stronger favourable van der Waals interactions. Compound 4c shows strong van der Waals contributions (-45.03). Ligand Strain Energy accounts for the internal strain the ligand experiences in achieving its bound conformation. Lower values indicate a more favourable or less hindered structure for the ligand. Compound 4c has the lowest strain energy (3.46), making it structurally favourable for binding.

In short, compound 4d is the strongest candidate in terms of docking score overall but has higher ligand strain energy compared to others. While 4c has a strong binding energy, but the positive Coulombic contribution may indicate it may not be the best binder among the candidates.

## CONCLUSION

Docking of molecules is an important asset in structure-oriented rational drug design. The mechanism of interaction between the produced compounds and the receptor or target is made clearer by the docking studies. Molecular docking studies using Auto Dock Tools (ADT) has become an important approach in computational biology and drug discovery. By preparing the receptor and ligand, running the docking program and analysing their outcomes, researchers can get valuable information regarding binding interactions that are required for understanding their mechanisms and development of newer therapies.

**Acknowledgments:** The authors thank Sophisticated Analytical Instrument Facility, IIT Madras, Chennai, Tamil Nadu for molecular docking studies.

**Sponsorship:** "This research received no specific grant from any funding agency."

**Conflict of interest statement:** There is no conflict of interest with this work.

**Authors' contributions:** The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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