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Review Article

1, 4 - Naphthoquinone: Drug Design, Sar And Molecular Docking Studies For Anti-Tubercular Activity

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ABSTRACT

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis bacteria. TB majorly affects the organ i.e. Lungs as well as organs other than lungs such as abdomen, genitourinary tract, joints and bones. It is a most prevalent disease after AIDS and as per WHO news update 2022, about 10.6 million people were diagnosed with TB including 5.8 million men, 3.5 million women and 1.3 million children. The most defined cause of deaths in TB is due to drug resistance in patients which are already on antitubercular drug therapy. The pathogens have developed resistance to drugs phenotypically as well as genetically hence it would be a major challenge to design drug candidates with potential effects. Many aromatic and heterocyclic analogues were evaluated for their efficacy against bacteria, among them 1,4-naphthoquinone moiety has diverse structural features and properties. The significant peculiarity of 1,4-naphthoquinone is generation of ROS in destruction of genetic material of MTB which makes them different from other analogues. Cardioprotective, hepatoprotective and neuroprotective properties have been found, among them antimicrobial and antitumor activity has been studied in depth. Many derivatives of 1,4-naphthoquinone have been developed with potential activities. In this review we summarized potential derivatives of 1,4-naphthoquinone and its structure-function relationship along with challenges associated with it also the newly found derivatives based on SAR are assessed for their binding affinity.

INTRODUCTION

Tuberculosis:-

The infectious disease tuberculosis is triggered by the germ Mycobacterium tuberculosis (MTB). Concerning taxonomic information, Mycobacterium has existed on our planet for approximately 150 years (Order: Actinomycetales,

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Class: Actinomycetes, Family: Mycobacteriacae, Genus: Mycobacterium). Trailing HIV or AIDS, it is a grave deadly sickness.

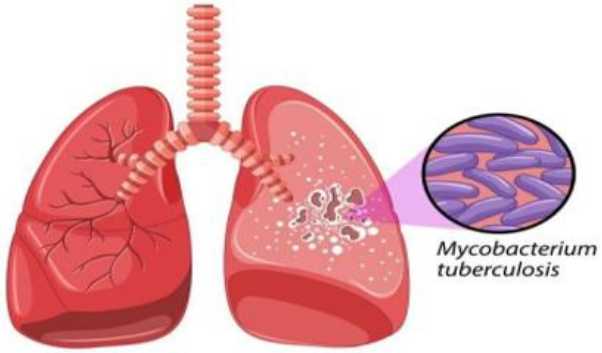
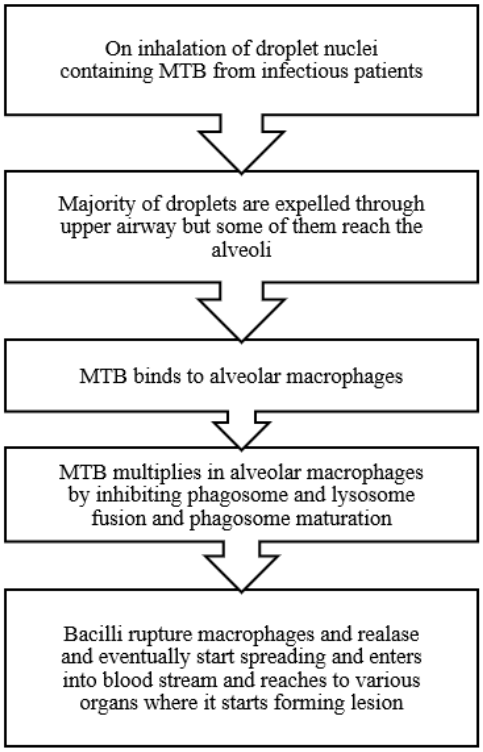


Fig.1: Tuberculosis

As indicated by the WHO update in 2022, about 10.6 million individuals- including 5.8 million males, 3.5 million females, and 1.3 million children- acquired a tuberculosis diagnosis. The goal of the national strategic plan (spanning 2017 to 2025) is to eliminate tuberculosis before 2025. The main reason for TB deaths is drug resistance in TB patients getting treatment. NQs have been shown to provide effective therapies for drug-resistant tuberculosis. [1]

TB is a bacterial infection that primarily affects the lungs but can affect other parts of the body. It can spread through the air when an infected person coughs or sneez-es.

2. Pathogenesis: -



Types of TB:-

A. **Tuberculosis outside the Lungs (EPTB):** The pleura was the most frequently impacted area in Korea, with lymph nodes, digestive system organs, bones and joints, the brain and spinal cord (CNS), and urinary and reproductive organs following behind. The documented proportion of EPTB in all TB cases was roughly 14% between 2005 and 2007; however, it climbed to nearly 20% between 2010 and 2013. The reason for the increase is still a mystery. Because of underreporting, the difficulty of detecting EPTB, and undetected instances, the real percentage of EPTB was most likely considerably higher than reported. Several variables linked to EPTB have been identified in the research. Being infected with the human immunodeficiency virus (HIV), having Asian or African roots, being young, and being female are all independent risk factors for EPTB.[2]

Diagnosis:-

1. Mycobacterial dye and growth Only by growing Mycobacterium tuberculosis germs from a patient's sample can a conclusive diagnosis of tuberculosis be established. Diagnosing EPTB is difficult, though, because clinical specimens from relatively inaccessible locations may have few bacteria, which reduces the diagnostic tests' effectiveness. Because typical smear microscopy has a poor sensitivity, ranging from 0% to 40%, negative results cannot completely rule out the chance of TB being present.
2. **Biopsy:-** Standard AFB smears possess limited sensitivity, and the cultivation process delays the observable presence of M. tuberculosis. Consequently, histological findings play a vital role in EPTB diagnosis. To determine a positive result in histological diagnosis, AFB presence, granulomas, and caseation are frequently employed as indicators. However, a less robust immune reaction from the host may be indicated by histopathological results displaying granulomas that are not fully developed and a more pronounced suppurative response.
3. **Body fluid examination:-** Analyzing Bodily Fluids Although tissue biopsy offers the most precise method for EPTB diagnosis, it remains an intrusive procedure and isn't always accessible. As a result, easily obtainable bodily fluids like pleural, peritoneal, and pericardial fluids can often provide significant diagnostic insights in individuals with EPTB. EPTB cannot be excluded based on the absence of typical signs since body fluid analysis may uncover unusual traits. In roughly 90% of cases, tuberculous pleural fluid, invariably an exudate, exhibits a prevalence of lymphocytes.
4. **Nucleic acid amplification test:-** The primary advantage of nucleic acid amplification tests (NAAT), such as PCR, lies in their ability to provide a quick diagnosis. The most promising application is the prompt identification of potentially deadly diseases, such as TB meningitis. Given that EPTB is characterized by a low number of bacteria, PCR's capacity to detect even a small quantity of mycobacteria may enhance its sensitivity30. A systematic review indicates that NAAT generally exhibits elevated specificity in EPTB, but its sensitivity tends to be lower and exhibits substantial variability depending on the testing methods and the types of samples analyzed.
5. **Immunological tests:-** These tests contribute to the detection of EPTB, even though their effectiveness in diagnosis is somewhat limited. The interpretation of TST results can be challenging due to potential cross-reactivity with prior exposure to bacilli. In regions with

a high prevalence of TB, the IFN-γ releasing assay (IGRA) and tuberculin skin test (TST) may serve as beneficial tools for identifying latent TB infection or previous exposure to the Calmette-Guerin vaccine. Factors such as HIV infection, poor nutrition, recent infections (bacterial or viral), or immunization with live viruses can diminish the response to the TST.

Treatment:-

Anti-TB medication forms the fundamental approach to managing EPTB. However, the specific treatment plan represents one of the debated elements in the management of EPTB. Current prevailing guidelines suggest utilizing the same treatment plan for both EPTB and PTB, despite the evidence supporting the recommended treatment for the majority of other EPTB types not being as thoroughly researched as the evidence for PTB. Furthermore, the ability of the blood-brain barrier to regulate the concentration of anti-TB drugs within the brain plays a crucial role in the treatment of TB meningitis. While ethambutol and p-aminosalicylic acid demonstrate minimal to no penetration into the cerebrospinal fluid (CSF), isoniazid, pyrazinamide, protionamide, and cycloserine do .[3]

B. Pulmonary TB (PTB):-

The lungs are primarily affected by pulmonary TB, which is a form of tuberculosis infection. Signs and symptoms of pulmonary TB include cough, sputum production, coughing up blood, difficulty breathing, weight reduction, loss of appetite, fever, general feeling of discomfort, weakening, and severe wasting.

Diagnosis:-

Though culture is preferred if feasible, the majority of TB programs rely on direct sputum smear examination. Reliable susceptibility testing, while especially beneficial for re-treatment, is an advantage that few underdeveloped countries can manage. Rapid susceptibility testing and culture procedures are frequently available in wealthier countries. Though culture is recommended when resources are available, most TB programs employ direct smear examination of sputum. Molecular techniques have enabled the development of rapid, sensitive, and specific tests for Mycobacterium tuberculosis, including polymerase chain reaction, DNA and RNA probes, and interferons. Even though it is especially needed for re-treatment, dependable susceptibility testing is a luxury that only a small number of impoverished countries can afford. The affluent countries frequently have access to quick susceptibility testing and culture methods. Although costly and technologically challenging, molecular methods such as polymerase chain reaction, DNA and RNA probes, and interferon assays have led to the creation of quick, sensitive, and specific tests for Mycobacterium tuberculosis.

Treatment:-

The British Thoracic Society, the World Health Organization, the International Union Against Tuberculosis and Lung Disease, and the National Institute for Health and Clinical Excellence (NICE) all advise using standard chemotherapy. It involves two months of ethambutol and pyrazinamide, followed by six months of rifampicin and isoniazid (typically administered as combination tablets). A combination tablet including pyrazinamide, isoniazid, and rifampicin is also available, along with a tablet that contains all four of these first-line medications. Fixed-dose medication combinations in a single tablet offer a number of benefits, one of which is a lower chance of developing drug resistance. [4]

Newer Drugs for TB Treatment:-

In 2015, the WHO added bedaquiline (Bdq), a diarylquinoline class medication that inhibits ATP synthase and inhibits MTB from obtaining energy, to the MDR TB regimen. Delamanid (Dlm) is a nitroimidazole class medicine that prevents the production of mycolic acid and produces nitric oxide, which is toxic to MTB. Linezolid usage, according to safety studies on bedaquiline and delamanid, has been associated with QT prolongation, peripheral neuropathy, and myelosuppression, all of which can be lessened by optimizing dosage. [5]

Basic structure of 1,4-Naphthoquinone : -

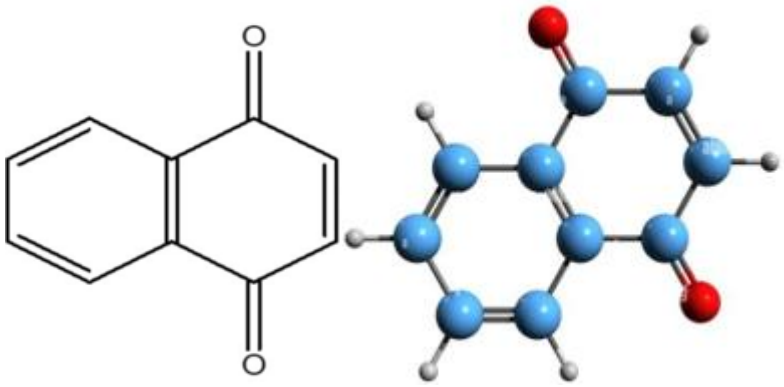


Fig. 2 : 1,4-Naphthoqinone

Derivatives of 1,4 – Naphthoquinone:-

The structural design of 1,4-NQs, which participate in oxidation-reduction reactions, bears resemblance to the arrangement of naphthalene. Investigations have focused on the properties of 1,4-NQ derivatives, including their ability to combat bacteria, fungi, viruses, cancer cells, and parasites. The following sections will explore 1,4-NQs, compounds found both naturally and produced synthetically, which possess considerable potential to fight various bacterial infections. Naphthoquinones, molecules abundant in phenol groups, are present in significant quantities in numerous plants, animals, and fungi. The minimum inhibitory concentration (MIC) serves as a distinct measure of an antimicrobial agent's practical effectiveness. The lowest concentration that prevents visible bacterial growth is the minimum inhibitory concentration (MIC). The minimum bactericidal concentration (MBC) refers to the lowest concentration of a substance needed to eradicate an organism, thereby halting its growth. Consequently, MIC and MBC values are crucial for assessing the suitability of any antimicrobial drug for potential medicinal use.[6]

Structure Activity Relationship:-

1. Attaching substituents like hydrogen, hydroxyl, methyl, nitrogen, sulfur, or halide groups can change the architecture of NQs.
2. The positioning of hydroxyl groups also plays a role in influencing the effectiveness of NQs.
3. Locations C-2, C-5, and C-8 represent viable sites for hydroxyl groups to attach, resulting in a molecule that demonstrates effectiveness.
4. Juglone features a hydroxyl group at C-5, Laws One at C-2, while Shikon contains two hydroxyl groups positioned at C-5 and C-8.[6]
5. Since elements belonging to groups 14 to 17 are non-metallic and exhibit strong oxidizing capabilities, they are employed. Thiophenol, amide groups, and acid chlorides are examples of groups that demonstrate potent antibacterial effects.

6. The typical sites for the addition or removal of groups are the C-2 and C-3 positions.
7. The antifungal and antibacterial effects of the compound are amplified when chlorine is introduced at the C-2 and C-3 positions.
8. The connection of fluoro groups to the -meta position enhances antibacterial activity, while their attachment to both -meta and -para positions diminishes it.
9. NQs containing more than ten carbon atoms exhibit reduced activity. The antibacterial and anticancer characteristics of 1,4-naphthoquinone are amplified by powerful electron-withdrawing groups. [7]
10. NQs are chemically altered using heterocyclic rings like furan, pyran, pyrazole, triazole, and indole to synthesize dual hybrids of heterocyclic fragments, showing enhanced efficacy against a variety of bacterial strains.
11. The indole ring stands out as the favoured option when considering structural modifications because of its capacity to interact with a variety of receptors. NQs featuring triazole cores are likewise highly efficient against a wide array of microorganisms because each fundamental moiety independently inhibits bacterial growth. [8]

DNA gyrase activity of NQs:-

DNA gyrase, a type of DNA topoisomerase, has been a popular target for medications that fight infections because it is present in bacteria and plants but not in animals. All cells require DNA topoisomerases, which are enzymes that cause changes in the structure of DNA. Depending on whether their processes involve brief breaks in a single strand (type I) or both strands (type II) of DNA, they are divided into two groups. While all topoisomerases have the ability to unwind supercoiled DNA, gyrase, a type II enzyme, is also able to generate negative supercoils in a process that is connected to ATP hydrolysis. The subunits GyrA and GyrB make up gyrase, and when the enzyme is active, they combine to form an A2B2 complex with a section of DNA that encircles the protein. The GyrA subunit, which interacts with DNA, contains the active-site tyrosine that causes DNA to break and creates a covalent protein-DNA connection during the reaction cycle. DNA is also bound by GyrB, which houses the ATPase active site. Due to its unique features, gyrase has been a successful target for antibacterial medications. Gyrase is the target of fluoroquinolones, including moxifloxacin and ciprofloxacin, which are highly successful clinical treatments for TB. Fluoroquinolone-resistant tuberculosis, however, is still a major concern despite their efficacy.[7]

Molecular Docking:

Molecular docking is a crucial computational technique used in drug discovery and design to forecast the best orientation of small molecules when they are linked to target proteins. This technique helps to understand the interactions between chemicals and proteins, which encourages the creation of innovative medicinal therapies.

The docking procedure entails the following steps:

Step 1 - Protein and Ligand Preparation: Download the protein's 3D structure from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (PDB). The downloaded structure needs to be pre-processed after that. This includes getting rid of water molecules, stabilizing charges, filling in any gaps, and adding hydrogen atom side chains.

Step 2 - Ligand Preparation: Ligand molecules can be downloaded using databases like ZINC and Pub Chem. It can be drawn as a mol file using the

Chem sketch tool. Then, use LIPINSKY'S RULE OF 5 on these ligand molecules. It is used to identify molecules that are similar to or unlike drugs. It raises the likelihood of success and lowers the possibility of failure due to the molecules' drug-like characteristics.

Step 3 - Grid Generation: In this location, rotatable groups, excluded volumes, and constraints are held constant. The primary factor in deciding the number of operations carried out (crossover, migration, mutation). Binding cavity prediction must be completed.

Step 4 - The active site of protein molecule should be predicted. After that Preparation of protein, the water molecules and hetero atoms if present they are removed from cavity

Types of molecular Docking :

Sr. No.	Types of Molecular Docking	Method	Application	Limitation
1.	Rigid Docking	a. Preparation	a. Post-processing and Analysis	a. Neglect of Flexibility
		b. Search Algorithm	b. Protein-interactions	b. Scoring Function Accuracy
		c. Scoring Function	c. Enzyme Mechanisms	c. Computationan Cost
		d. Post - Processing and Analysis	d. Virtual Screening	d. Treatment of solvent effect
2.	Flexible Docking	a. Docking Algorithm	a. Computational Cost	a. Computational Cost
		b. Scoring Function	b. Scoring Function Accuracy	b. Scoring Function Accuracy
		c. Induced-Fit Modelling	c. Conformational Sampling	c. Conformational Sampling
		d. Post - Processing and Analysis	d. Modelling Receptor	d. Modelling Receptor Flexibility

			Flexibility	
3.	Induced Fit Docking	a. Conformational Sampling	a. Lead Optimization	a. Computational Cost
		b. Docking Algorithm	b. Fragment-Based Drug Design	b. Scoring Function Accuracy
		c. Scoring Function	c. Virtual Screening	c. Conformational
		d. Post - Marketing and Analysis	d. Understanding Binding Mechanism	d. Sampling
4.	Ligand Based Docking	a. Ligand Selection and Dataset Preparation	a. Lead Identification	a. Dependency on Reference Ligands
		b. Pharmacophore Generation	b. Virtual Screening	b. Limited Structural Information
		c. Similarity Search and Virtual Screening	c. Lead Optimization	c. Scoring Function Performance
		d. Scoring and Validation	d. Bio isosteric Replacement	d. Target Flexibility
5.	Protein-Protein Docking	a. Preparation of Protein Structure	a. Structural Elucidation	a. Conformational Sampling
		b. Search Algorithm	b. Drug Discovery	b. Scoring Function Accuracy
		c. Scoring Function	c. Functional Annotation	c. Treatment of Protein Flexibility

		d. Post - Processing and Analysis	d. Virtual Screening	d. Experimental Validation

A) Rigid Docking: Docking that involves rigid bodies produces many docked shapes that fit well together, and after that, these are rearranged based on an estimation of their free energy.

Methods of rigid docking:

a) Preparation: To prepare the ligand and receptor structures, water molecules are first taken out, hydrogen atoms are added, partial charges are assigned, and the geometry is optimized if needed.

b) Search algorithm: To find the best binding pose and investigate the ligand's conformational space, docking algorithms use a variety of search techniques. Among the popular search algorithms are systematic grid-based search, genetic algorithms, Monte Carlo methods, and geometric hashin

c) Scoring function: A scoring function is used to assess and rank the candidate ligand poses that have been created, based on their anticipated binding affinity. Typically, scoring functions take into account things like van der Waals forces, electrostatic interactions, geometric complementarity, and desolation energy.

d) Post-processing and analysis: In the end, post-processing methods are used to improve the predicted binding poses and examine the intermolecular interactions. Researchers can use visualization tools to study the docked complexes and pinpoint crucial binding residues and interactions.[9]

Limitations of rigid docking

Even though rigid docking stands as a beneficial instrument within molecular modeling, its utility encounters various constraints:

a) Ignoring flexibility: Rigid docking works on the premise that both the ligand and the receptor keep their structures unchangeable, thereby disregarding structural adaptations that might transpire when binding occurs. This restraint could result in errors while determining binding strengths and configurations, most notably concerning adaptable ligands or receptors.

b) Scoring function precision: The correctness of rigid docking projections greatly hinges on the scoring method applied to assess binding placements. Nevertheless, current scoring methods may fail to precisely encapsulate all pertinent molecular connections, thus producing incorrect positives or incorrect negatives within the estimations.

c) Computational expense: Docking simulations can demand substantial computing capability, particularly when probing broad configurational ranges or undertaking extensive virtual assessments. This puts a limit to the scale of the systems that are amenable to investigation and necessitates streamlined procedures coupled with corresponding computing capabilities.

d) Handling solvent influences: Rigid docking generally posits an absence of solvent at the binding location, thus disregarding the impact

of solvent particles on ligand-receptor interplays. Nevertheless, solvent phenomena possess the capacity to considerably sway binding propensities coupled with selectivity, thereby mandating more refined modeling tactics.[10]

B) Flexible Docking: These modifications enable the receptor to shift its binding site based on the ligand's position. The ligand's position is determined within a dimensional space that takes into account translational, rotational, and conformational elements within the receptor's complex environment.

Methods of Flexible Docking:

a) Docking algorithm: In flexible docking, docking algorithms often use a combination of conformational sampling and standard docking methods to determine the best way the ligand binds within the receptor's flexible binding area. To assess how well each ligand shape fits with the receptor, these algorithms might use scoring functions that steer the search toward the most favorable binding positions.

b) Scoring function: In flexible docking, scoring functions are essential for determining the energy levels of ligand-receptor interactions and arranging the expected binding positions by their likelihood. These scoring functions usually take into account aspects like how well the shapes match, electrostatic forces, van der Waals forces, how solvation affects things, and conformational strain

c) Induced-Fit modeling: Certain flexible docking strategies employ induced-fit modeling techniques to simulate how the receptor's shape changes when a ligand binds to it. To accurately capture these induced-fit effects, this could entail flexible modeling of side-chains, refining loops, or even allowing the entire protein backbone to be flexible.

d) Post-processing and analysis: After producing potential ligand positions, post-processing techniques are utilized to enhance the predictions and assess the interactions between molecules. Researchers can utilize visualization tools to analyze the docked complexes and pinpoint crucial binding residues and shape changes.

Limitations of Flexible Docking:

a) Computational cost: Flexible docking simulations can be computationally expensive, especially when modeling large biomolecular systems or performing extensive conformational sampling. High computational costs limit the scalability of flexible docking approaches and require efficient algorithms and parallel computing resources.

b) Scoring function accuracy: The accuracy of flexible docking predictions relies heavily on the scoring functions used to evaluate ligand-receptor interactions and rank binding poses. Current scoring functions may not accurately capture all relevant molecular interactions, leading to inaccuracies in the predicted binding affinity and pose.

c) Conformational sampling: Conformational sampling is a critical aspect of flexible docking, as it determines the diversity of ligand and receptor conformations explored during the docking process. However, exhaustive conformational sampling can be challenging, particularly for large biomolecular systems with complex energy landscapes.

d) Modeling receptor flexibility: Modeling receptor flexibility accurately remains a

significant challenge in flexible docking. While some methods allow for explicit modeling of receptor flexibility, such as induced-fit docking, others rely on simplified representations of receptor flexibility or predefined conformational ensembles.[11]

Following this, the most favorable binding configuration is identified

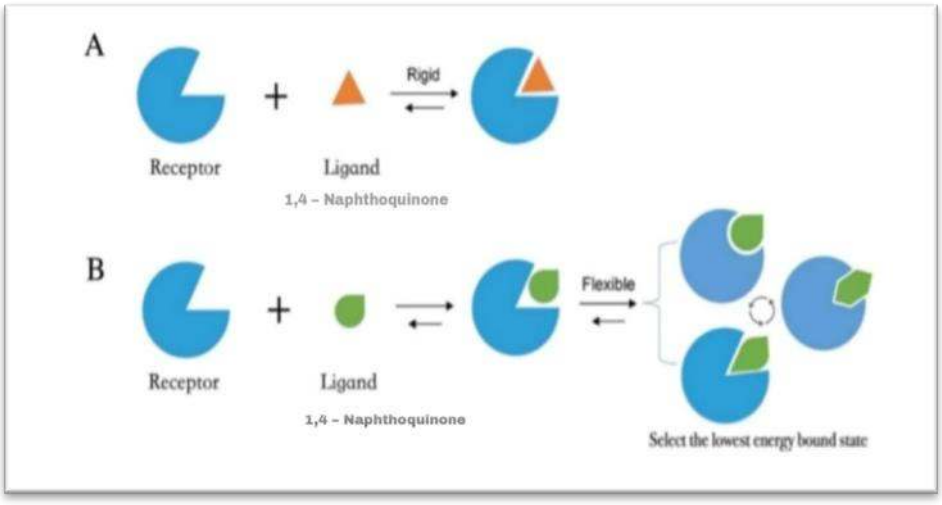


Fig no. 3: Rigid and Flexible Docking

PyRx Software:

To conduct the molecular docking analyses, the PyRx virtual screening program, along with its Graphical User Interface (GUI), was used to create a grid, produce a dockscore, and analyze various conformers. As a computational drug discovery tool, PyRx facilitates the comparison of compound collections against specific therapeutic targets through virtual screening. This software effectively shortens the time and lowers the costs associated with assessing an entire database trial by pinpointing the most suitable candidates. The docking-based virtual screening (DBVS) strategy is beneficial in identifying the best molecular interaction for experimentation and understanding how small compounds attach to their targets.[12]

Objectives

1. To investigate existing scholarly work and structural repositories for the purpose of identifying appropriate targets for combating tuberculosis.
2. To discover compounds effective against tuberculosis from both natural and artificially created sources and establish connections between them using current databases and published research.
3. To develop shared ligands that target DNA gyrase, with the aim of stopping the replication of Mycobacterium tuberculosis.
4. To generate and validate the designed ligands for their intended target action.
5. Improving compounds, detailing their properties, and assessing their effectiveness against tuberculosis by examining how well they prevent the action of anti-TB drugs that focus on DNA gyrase.[13]

Need of study

The urgent need for innovative medications to treat tuberculosis arises from several significant challenges present in contemporary TB care. The main factors contributing to this demand include:

1. Drug Resistance: The increasing occurrence of TB strains resistant to drugs, notably extensively drug-resistant TB (XDR-TB) and multidrug-resistant TB (MDR-TB), has reduced the effectiveness of established treatment methods. New treatment approaches are vital for fighting these resistant bacteria.
2. Extended Treatment Time: Current treatments for TB commonly require 18 to 24 months, especially for drug-resistant types. This lengthy duration can lead to treatment not working as expected and patients not sticking to the treatment plan. Shorter, more effective treatments are needed to improve patient results and adherence.
3. Adverse Reactions: Several existing TB drugs can cause significant side effects, including damage to the kidneys, liver, and nerves, especially in second-line treatments for drug-resistant TB.
4. Advantages of NQs Compared to Limitations: New medications with fewer negative effects are essential to enhance the quality of life for patients.

Given that several NQs and their related compounds have shown promise in tackling these challenges, research indicates a greater opportunity to produce a variety of NQ derivatives to improve their performance and minimize the possibility of drug resistance.[14]

Materials and Method

Programs:

Table No. 1 – Software Utilized for Docking Simulation and the Companies Behind Them

Softwares	Company Names
ChemDraw	Cheminformatics
ChemSketch	ACD/Labs
BIOVIA Discovery Studio	Dassault Systemes
PyRx 0.8 program	SourceForge

Method:-

Ligand preparation:

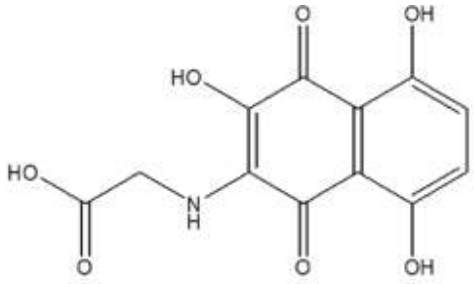
The chemical structures of the intended compounds were sketched out, and their SMILES notations were created using ACD/ChemDraw software. The structures were then protonated with BIOVIA Discovery Studio to fix any tautomeric or ionization problems. The Avogadro software was used to reduce the energy levels of the chemical structures produced. Energy minimization of the synthesized compounds was performed using chem 3D ultra. The structure of the ligands that were just created was then displayed.

Preparing Proteins:

The "extremely open" clamp structure of DNA gyrase, previously published as a crystal form structure (PDB ID: 6GAV) with a resolution of 2.6 Å, can be accessed from the RCSB Protein Data Bank. All heteroatoms and water molecules were then taken out. To protonate the amino acid residues, polar hydrogen atoms were introduced to a purified protein crystal structure. BIOVIA

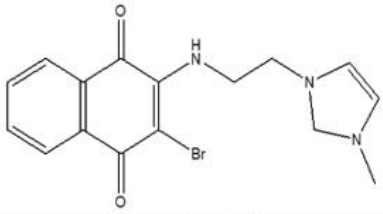
Discovery Studio was used to carry out the protein structure refinement process.[12,15]

The newly designed 1,4-Naphthoquinone Derivatives as follow:

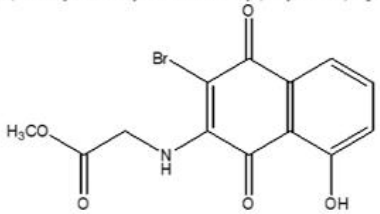


2-(3,5,8-trihydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)acetic acid

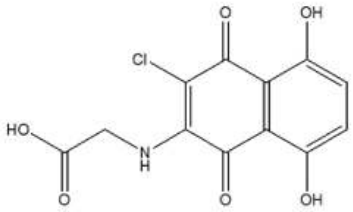
O



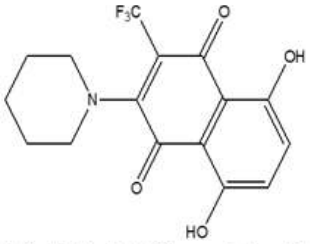
2-bromo-3-(2-(3-methyl-2,3-dihydroimidazol-1-yl)ethylamino)naphthalene-1,4-dione



methyl 2-(3-bromo-8-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)acetate



2-(3-chloro-5,8-dihydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)acetic acid



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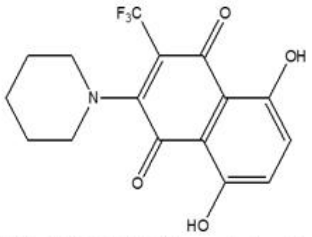
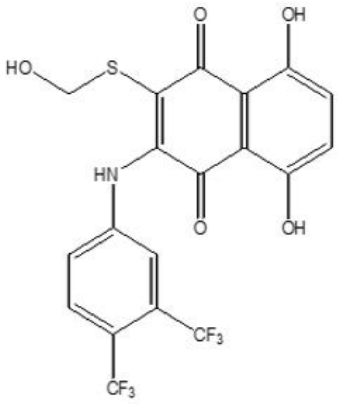
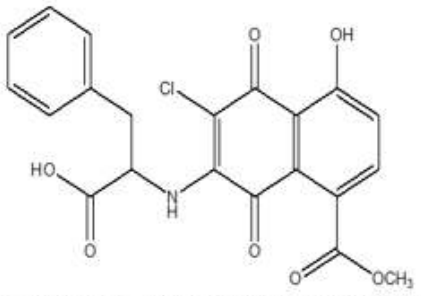


5,8-dihydroxy-2-(piperidin-1-yl)-3-(trifluoromethyl)naphthalene-1,4-dione



2-(3,4-bis(trifluoromethyl)phenylamino)-5,8-dihydroxy-3-(hydroxymethylthio)naphthalene-1,4-dione



2-(3-chloro-5-hydroxy-8-(methoxycarbonyl)-1,4-dioxo-1,4-dihydronaphthalen-2-ylamino)-3-phenylpropanoic acid

Future Perspective

1. Advanced Optimization of Structure-Activity Relationships (SAR)

a. Future SAR studies should prioritize precisely adjusting electron-donating and electron-withdrawing substituents in order to boost selective toxicity against MTB and modify the redox potential.

b. Substituting quinone moieties with heterocyclic analogues, for example, could be beneficial in decreasing cytotoxicity without affecting activity.

c. The integration of machine learning-assisted QSAR models may speed up the prediction of potent analogues before to synthesis.

2. Drug Design with a Specific Target:

1,4-naphthoquinones have strong interactions with MTB proteins, including:

1. DprE1, also known as decaprenylphosphoryl - β- D-ribose epimerase

2. InhA, also known as enoyl-ACP reductase

3. ATP synthase

Enzymes are part of the pathway that produces menaquinones.

To avoid toxicity to the host, future design strategies should focus on selective, target-guided inhibitors that use structure-based pharmacophore models.

3. Translational Research from In Vitro to In Vivo:

Even if many compounds show in-vitro effectiveness, further research must include:

1. TB models using mice and zebrafish

2. Assessment of pharmacokinetics.

3. Evaluation of long-term toxicity.

This will decide whether it's possible to develop the lead compounds for preclinical use.

4. Combining AI-Powered Drug Discovery:

AI-guided de novo design can be used to produce novel naphthoquinone analogues with:

1. Enhanced binding prediction

2. Reduced toxicity

3. Improved physiochemical characteristics

The discovery of innovative anti-TB leads can be greatly expedited by combining generative models with docking/MDS.[16]

CONCLUSION

The highlighted paper emphasizes how crucial it is to have innovative medication development tactics to combat chronic illnesses, like tuberculosis (TB), which remains a major health concern worldwide. In conclusion, this study provides valuable information on the efficacy of naphthoquinone derivatives in addition to emphasizing the ongoing need for research and development of new antimicrobial agents in order to accomplish global health objectives like the WHO's End TB Strategy and to address the rising threat of drug-resistant infections. Insights from this paper will be helpful for future research aimed at enhancing our understanding and treatment of infectious diseases. The docking study of 1,4-naphthoquinone revealed that a large number of these substances had high binding affinities. It was discovered that Compound 7 had the strongest binding affinity of all the compounds tested. As a result, based on the data presented above, it was concluded that 1,4-naphthoquinone derivatives may be helpful in the treatment of tuberculosis.

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