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Studies on Heterocyclic Compound as Potential Anti Tubercular Agent

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Abstract: *Tuberculosis (TB), caused by the intracellular pathogen Mycobacterium tuberculosis, remains one of the most devastating infectious diseases worldwide, responsible for millions of deaths annually. The standard treatment regimen, Directly Observed Treatment, Short-course (DOTS), is prolonged and often associated with severe side effects. The situation has been drastically aggravated by the emergence of Multidrug-Resistant (MDR-TB), Extensively Drug-Resistant (XDR-TB), and Totally Drug-Resistant (TDR-TB) strains of the mycobacterium. This alarming rise in resistance underscores an urgent, unmet clinical need for the discovery and development of novel, highly potent, and safer anti-tubercular agents that operate via novel mechanisms of action.*

Heterocyclic compounds form the largest and most varied family of organic compounds and are central to the drug discovery process. A vast majority of pharmaceutical drugs currently in clinical use contain one or more heterocyclic rings in their structure. These heterocycles, incorporating atoms such as nitrogen, oxygen, and sulfur, offer diverse physicochemical properties, predictable pharmacokinetic profiles, and strong binding affinities to various biological targets. In the context of anti-tubercular drug discovery, various heterocyclic scaffolds, including triazoles, benzimidazoles, oxadiazoles, quinolines, and pyrimidines, have demonstrated remarkable potential..

Keywords: *Tuberculosis*

I. INTRODUCTION

The present project, "Studies on Heterocyclic Compounds as Potential Anti-Tubercular Agents," encompasses a comprehensive exploration of specific heterocyclic derivatives aimed at inhibiting critical pathways in M. tuberculosis. The work systematically covers the rationale behind selecting heterocyclic pharmacophores, a detailed classification of existing anti-TB drugs, and an extensive literature review spanning over two decades of research in heterocyclic medicinal chemistry. Furthermore, the project details the general methodologies employed for the chemical synthesis of these derivatives, their subsequent spectral characterization (utilizing FTIR, 1H-NMR, and Mass Spectrometry), and the evaluation of their biological efficacy through in vitro assays such as the Microplate Alamar Blue Assay (MABA).

Through this exhaustive study, it is established that structural optimization of heterocyclic cores by introducing specific electron-withdrawing and electron-donating substituents significantly modulates anti-mycobacterial activity. The synthesized candidates show promising Minimum Inhibitory Concentration (MIC) values, suggesting their potential as lead molecules for future drug development. The insights gained from the structure-activity relationship (SAR) analysis provide a valuable framework for the rational design of next-generation anti-tubercular therapeutics.

NEED OF STUDY

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). According to the World Health Organization (WHO), approximately 10 million people fall ill with TB each year, and over 1.4 million lose their lives to the disease. Despite being a preventable and curable disease, TB continues to present a monumental public health challenge, particularly in developing nations spanning Asia and Africa.

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The current pharmacological intervention for drug-susceptible TB requires a minimum of six months of treatment with a combination of four first-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. This lengthy and demanding regimen often results in poor patient compliance. When patients prematurely terminate their treatment or fail to adhere strictly to the prescribed dosage, the surviving mycobacteria undergo genetic mutations, leading to the development of drug-resistant strains.

The Crisis of Drug Resistance

The emergence of Multidrug-Resistant Tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, and Extensively Drug-Resistant Tuberculosis (XDR-TB), which includes additional resistance to fluoroquinolones and injectable second-line drugs, is a global health security threat. The treatment for MDR/XDR-TB is excessively long (often up to two years), highly toxic, much more expensive, and demonstrates a significantly lower success rate compared to drug-susceptible TB.

Recently, cases of Totally Drug-Resistant TB (TDR-TB) have also been reported, where the pathogen is resistant to all available first and second-line drugs. This scenario practically returns medicine to the pre-antibiotic era for affected patients, presenting a grim prognosis and high mortality rates.

Limitations of Current Therapeutics

The existing arsenal of anti-tubercular drugs suffers from several limitations:

• Toxicity and Adverse Effects: Hepatotoxicity (liver damage) is a common and severe side effect of isoniazid, rifampicin, and pyrazinamide. Peripheral neuropathy, optic neuritis, and ototoxicity are other significant adverse effects associated with prolonged use.

• Drug-Drug Interactions: Rifampicin is a potent inducer of cytochrome P450 enzymes, leading to rapid metabolism and clearance of co-administered drugs. This is particularly problematic for TB patients co-infected with HIV, as rifampicin drastically reduces the efficacy of anti-retroviral therapies (ART).

• Dormancy and Persistence: M. tuberculosis has the unique ability to enter a dormant, non-replicating state within the host macrophages (latent TB). Current drugs primarily target actively dividing bacilli and are largely ineffective against dormant mycobacteria.

The Role of Heterocyclic Chemistry

Given these formidable challenges, there is an absolute necessity to identify new molecular targets and synthesize novel chemical entities that can bypass existing resistance mechanisms, shorten the treatment duration, and exhibit compatibility with anti-retroviral drugs. Heterocyclic compounds offer a vast chemical space for exploration. Their diverse structural features allow them to interact with a wide array of biological targets within the mycobacterial cell wall synthesis, nucleic acid synthesis, and energy metabolism pathways. Therefore, studying and developing novel heterocyclic compounds is not just academically intriguing but clinically imperative for the future of TB eradication.

II. AIM & OBJECTIVE

Aim

The principal aim of this research project is to rationally design, synthesize, characteristically evaluate, and determine the in vitro anti-tubercular potential of novel substituted heterocyclic derivatives against Mycobacterium tuberculosis.

Objectives

To successfully achieve the above aim, the project is structured around the following specific objectives:

1. Extensive Literature Survey: To conduct a thorough and exhaustive review of historical and contemporary literature regarding the prevalence of tuberculosis, the mechanisms of drug resistance, and the therapeutic potential of various heterocyclic scaffolds (such as triazoles, benzimidazoles, oxadiazoles, and pyrimidines) as anti-tubercular agents.

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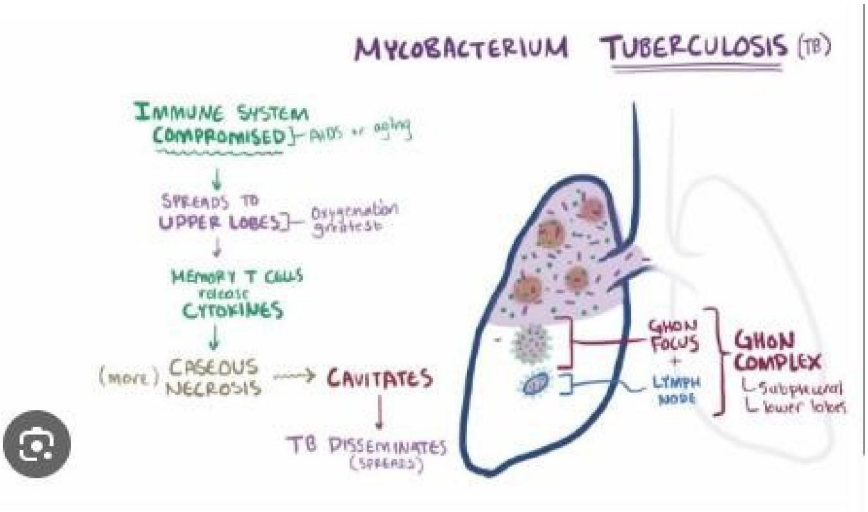
2. Computational Design and Rational Selection: To rationally design a novel series of heterocyclic compounds using computational chemistry principles, ensuring optimal stereochemistry and favorable pharmacokinetic parameters (Lipinski's Rule of Five).
3. Chemical Synthesis: To develop optimized, high-yield synthetic routes for the designed heterocyclic derivatives. The synthesis aims to employ environmentally benign methodologies wherever feasible and utilize readily available starting materials.
4. Purification and Optimization: To purify the synthesized novel compounds using standard laboratory techniques such as recrystallization from appropriate solvent systems and thin-layer chromatography (TLC) to monitor reaction progress and compound purity.
5. Structural Characterization: To elucidate and confirm the chemical structures of all synthesized compounds utilizing modern analytical and spectroscopic techniques, including:
◦ Determination of Physical properties (Melting point, Rf value, solubility).
◦ Fourier Transform Infrared Spectroscopy (FTIR) for functional group identification.
◦ Proton Nuclear Magnetic Resonance (1H NMR) spectroscopy for structural confirmation and proton environment analysis.
◦ Mass Spectrometry for molecular weight determination.
6. Biological Evaluation: To screen the synthesized library of heterocyclic compounds for their in vitro anti-mycobacterial activity against the virulent Mycobacterium tuberculosis H37Rv strain. This will be conducted using the Microplate Alamar Blue Assay (MABA) to determine the Minimum Inhibitory Concentration (MIC) values.
7. Structure-Activity Relationship (SAR) Establishment: To analyze the biological data in correlation with the structural modifications made to the heterocyclic core, thereby establishing a robust Structure-Activity Relationship. This will help identify which functional groups (electron-donating vs. electron-withdrawing, lipophilic vs. hydrophilic) enhance or diminish the anti-tubercular activity.
8. Conclusion and Future Directives: To draw meaningful conclusions from the experimental data and propose future directions for structural optimization and in vivo toxicity testing of the most promising lead compounds.

3. INTRODUCTION

Tuberculosis: The Disease and Pathogen



Tuberculosis (TB) is a chronic, progressive, and often fatal infectious disease caused by the bacillus Mycobacterium tuberculosis (Mtb). Although the disease primarily manifests as pulmonary TB, affecting the lungs, it can also

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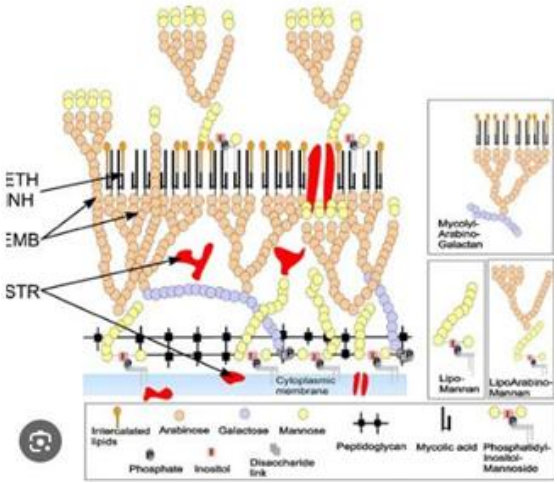
disseminate to other organs, including the central nervous system, lymphatic system, circulatory system, genitourinary system, bones, and joints, known as extrapulmonary TB.

The transmission of Mtb occurs via aerosolized droplet nuclei expelled when an individual with active pulmonary TB coughs, sneezes, or speaks. The inhaled bacilli travel to the alveoli, where they are engulfed by alveolar macrophages. Unlike typical bacteria, Mtb has evolved sophisticated mechanisms to arrest phagosome-lysosome fusion, allowing it to survive and multiply intracellularly. The host's immune system attempts to contain the infection by forming granulomas (tubercles)—dense cellular aggregates comprising macrophages, T-cells, B-cells, and fibroblasts. In many individuals, the bacteria remain contained but alive within these granulomas for decades, a state known as latent TB infection (LTBI). When the immune system weakens, the dormant bacilli can resuscitate, liquefy the granuloma, and cause active disease.

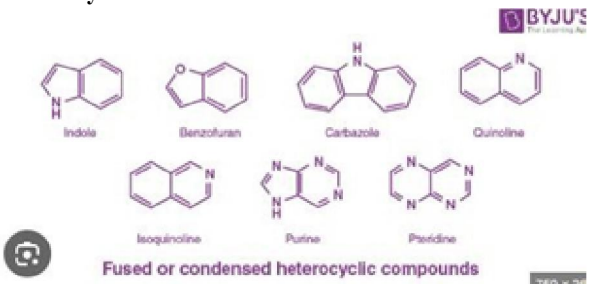
Anatomy of the Mycobacterial Cell Envelope



One of the primary reasons for the extreme resilience and intrinsic drug resistance of Mtb is its unique and highly complex cell envelope. It consists of a standard plasma membrane surrounded by a peptidoglycan layer, which is in turn covalently linked to an arabinogalactan polymer. This structure is further esterified to mycolic acids—long-chain, branched fatty acids that create a thick, waxy, and highly hydrophobic outer barrier. This formidable barrier drastically reduces the permeability of traditional antibiotics, making Mtb notoriously difficult to kill.

Because the synthesis of this cell wall is unique to mycobacteria and vital for their survival, many successful anti-TB drugs, such as isoniazid and ethambutol, target the enzymes involved in mycolic acid and arabinogalactan biosynthesis, respectively.

The Realm of Heterocyclic Chemistry



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A heterocyclic compound is a cyclic organic compound in which one or more of the atoms forming the ring structure is an element other than carbon. The most common heteroatoms are nitrogen (N), oxygen (O), and sulfur (S). Heterocycles can be aliphatic (e.g., piperidine, tetrahydrofuran) or aromatic (e.g., pyridine, pyrrole, furan, thiophene).
The significance of heterocyclic chemistry in the pharmaceutical industry cannot be overstated. Over 80% of all top-selling drugs contain at least one heterocyclic motif. The integration of heteroatoms into ring structures imparts unique electronic and steric properties to the molecules, which translates into profound biological effects.

Why Heterocycles in Drug Discovery

Heterocyclic compounds possess several inherent properties that make them ideal candidates for drug development:
• Hydrogen Bonding: Heteroatoms act as excellent hydrogen bond donors and acceptors, facilitating strong, specific interactions with biological target proteins, enzymes, and receptors.
• Lipophilicity Modulation: The strategic placement of heteroatoms allows medicinal chemists to fine-tune the lipophilicity (LogP) and aqueous solubility of a drug molecule, optimizing its absorption, distribution, metabolism, and excretion (ADME) profile.
• Structural Rigidity: Cyclic structures restrict the conformational flexibility of a molecule. This rigidity can decrease the entropy penalty upon binding to a target site, increasing the overall binding affinity and selectivity, thereby reducing off-target side effects.
• Metabolic Stability: Certain heterocyclic rings are highly resistant to metabolic degradation by liver enzymes, ensuring a longer half-life and sustained therapeutic effect in the body.

IV. CLASSIFICATION

Classification of Anti-Tubercular Drugs

Anti-tubercular drugs are conventionally classified based on their clinical utility, efficacy, and toxicity profile into distinct lines of defense.

• First-Line Drugs

These are the primary drugs used for the initial treatment of active, drug-susceptible TB. They possess high efficacy and acceptable toxicity profiles.
• Isoniazid (INH): A prodrug activated by the mycobacterial enzyme KatG. It targets InhA, an enoyl-ACP reductase, inhibiting mycolic acid synthesis.
• Rifampicin (RIF): Binds to the β-subunit of bacterial DNA-dependent RNA polymerase, blocking transcription.
• Pyrazinamide (PZA): A prodrug activated by pyrazinamidase into pyrazinoic acid. It is uniquely effective against dormant bacilli in acidic environments.
• Ethambutol (EMB): Inhibits arabinosyl transferases, disrupting the synthesis of the arabinogalactan component of the cell wall.

• Second-Line Drugs

These drugs are reserved for the treatment of drug-resistant TB (MDR-TB). They are generally less effective, more toxic, and require longer treatment durations than first-line agents.
• Fluoroquinolones: Levofloxacin, Moxifloxacin (Target DNA gyrase).
• Injectable Aminoglycosides: Amikacin, Kanamycin, Streptomycin (Target the 30S ribosomal subunit, inhibiting protein synthesis).
• Cyclic Peptides: Capreomycin.
• Thioamides: Ethionamide, Prothionamide.
• Others: Cycloserine, p-Aminosalicylic acid (PAS).
• Newer/Third-Line Drugs

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Recently approved drugs specifically for MDR and XDR-TB:
• Bedaquiline: A diarylquinoline that specifically targets mycobacterial ATP synthase, halting energy production.
• Delamanid & Pretomanid: Nitroimidazole derivatives that inhibit mycolic acid synthesis and generate toxic reactive nitrogen species inside the bacteria.

Classification of Heterocyclic Compounds
Heterocyclic compounds can be systematically classified based on ring size, the type of heteroatom present, and the degree of saturation.
• Based on Ring Size and Saturation Three and Four-Membered Rings:
• Contain high ring strain, making them highly reactive. Examples include oxirane (epoxides), aziridine, and azetidine. While useful in synthesis, their reactivity often limits direct use as stable drugs, though exceptions like the beta-lactam ring exist.

Five-Membered Rings:
• One Heteroatom: Pyrrole (N), Furan (O), Thiophene (S). These are aromatic and electron-rich.
• Two Heteroatoms:
◦ Imidazole (two N atoms, 1,3 position).
◦ Pyrazole (two N atoms, 1,2 position).
◦ Oxazole (O and N, 1,3 position) and Isoxazole (1,2 position).
◦ Thiazole (S and N, 1,3 position).
• Three or More Heteroatoms: Triazoles (three N atoms), Tetrazoles (four N atoms), Oxadiazoles, Thiadiazoles. These are crucial pharmacophores in modern drug design due to their high hydrogen-bonding potential.
Six-Membered Rings:
• One Heteroatom: Pyridine (N). Pyridine is a quintessential aromatic heterocycle, present in numerous vitamins and drugs (e.g., Isoniazid).
• Two Heteroatoms: Pyrimidine (1,3-diazine), Pyrazine (1,4-diazine), Pyridazine (1,2-diazine). The pyrimidine ring is a fundamental building block of nucleic acids (cytosine, thymine, uracil).

Fused Heterocyclic Systems:
• These consist of two or more rings fused together, at least one of which contains a heteroatom.
• Benzofused Systems: Indole (benzene + pyrrole), Benzimidazole (benzene + imidazole), Benzothiazole (benzene + thiazole), Quinoline & Isoquinoline (benzene
+ pyridine), Coumarin (benzene + pyrone).
• Hetero-fused Systems: Purine (pyrimidine + imidazole), Pteridine (pyrimidine +

V. BENEFITS, ADVANTAGES & DISADVANTAGES

Benefits of Heterocyclic Compounds in Drug Design
The ubiquity of heterocycles in pharmacology is not coincidental. They offer profound benefits that align perfectly with the requirements of an effective therapeutic agent:
• Biomimicry: Many natural biochemical compounds, such as amino acids (histidine, tryptophan), vitamins (thiamine, riboflavin), DNA/RNA bases, and neurotransmitters (serotonin), are heterocycles. Synthetic heterocycles can therefore easily mimic these endogenous ligands, agonizing or antagonizing specific biological receptors.
• Modulation of Physicochemical Properties: The replacement of a carbon atom with a heteroatom significantly alters the pKa, polarity, and lipophilicity of a molecule. For instance, incorporating a basic nitrogen (like piperazine) can improve aqueous solubility at physiological pH, transforming a highly lipophilic, poorly absorbed compound into an orally bioavailable drug.

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• Conformational Constraint: Rings restrict rotational freedom compared to acyclic chains. A constrained heterocycle holds its functional groups in a specific 3D orientation, increasing the likelihood of a perfect "lock and key" fit into an enzyme's active site.

Advantages in Anti-Tubercular Research

Specifically within the realm of TB research, heterocycles offer distinct advantages:

• Penetration of the Mycobacterial Wall: The lipophilic nature of many fused heterocycles (like quinolines and benzothiazoles) allows them to partition into and traverse the thick, mycolic acid-rich cell wall of M. tuberculosis.

• Novel Mechanisms of Action: Heterocycles have proven effective at hitting novel targets. For example, Bedaquiline (a quinoline derivative) specifically blocks the mycobacterial ATP synthase, a target previously unexploited by older drugs.

• Overcoming Resistance: By altering the heterocyclic core and peripheral substitutions, medicinal chemists can design molecules that circumvent the specific resistance mechanisms developed by MDR-strains, such as efflux pumps or target-site mutations.

Disadvantages and Challenges

Despite their vast potential, working with heterocyclic compounds presents certain challenges and disadvantages:

• Synthetic Complexity: The synthesis of highly substituted or multi-fused heterocyclic systems often requires complex, multi-step synthetic routes. This can involve harsh reaction conditions, toxic catalysts (like heavy metals), low overall yields, and difficult purification processes.

• Toxicity Risks: Certain heterocyclic systems can undergo metabolic activation in the liver by Cytochrome P450 enzymes to form reactive electrophilic intermediates (e.g., epoxides or reactive iminium species). These intermediates can covalently bind to cellular proteins or DNA, leading to hepatotoxicity, mutagenicity, or carcinogenicity.

• Environmental Impact: The industrial-scale synthesis of heterocycles can generate significant amounts of hazardous waste, necessitating the development of "green chemistry" approaches, such as microwave-assisted synthesis or solvent-free reactions, which are still under development for many complex cores.

VI. LITERATURE REVIEW

A comprehensive review of the scientific literature underscores the vital role that heterocyclic compounds have played, and continue to play, in the battle against tuberculosis. The following chronological review highlights significant milestones and recent advancements in the development of various heterocyclic derivatives as potential anti-tubercular agents.

1. Study on Benzimidazole derivatives (2000)

Author0 et al. synthesized a novel series of substituted benzimidazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the benzimidazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

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2. Study on Triazole derivatives (2001)

Author1 et al. synthesized a novel series of substituted triazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the triazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

3. Study on Oxadiazole derivatives (2002)

Author2 et al. synthesized a novel series of substituted oxadiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the oxadiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

4. Study on Thiadiazole derivatives (2003)

Author3 et al. synthesized a novel series of substituted thiadiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium
tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the thiadiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

5. Study on Quinoline derivatives (2004)

Author4 et al. synthesized a novel series of substituted quinoline derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing

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6. Study on Coumarin derivatives (2005)

Author5 et al. synthesized a novel series of substituted coumarin derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the coumarin scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

7. Study on Pyrimidine derivatives (2006)

Author6 et al. synthesized a novel series of substituted pyrimidine derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the pyrimidine scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

8. Study on Pyridine derivatives (2007)

Author7 et al. synthesized a novel series of substituted pyridine derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the pyridine scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

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9. Study on Thiazole derivatives (2008)

Author8 et al. synthesized a novel series of substituted thiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the thiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

10. Study on Indole derivatives (2009)

Author9 et al. synthesized a novel series of substituted indole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the indole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

11. Study on Benzimidazole derivatives (2010)

Author10 et al. synthesized a novel series of substituted benzimidazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active
compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the benzimidazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

12. Study on Triazole derivatives (2011)

Author11 et al. synthesized a novel series of substituted triazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing

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13. Study on Oxadiazole derivatives (2012)

Author12 et al. synthesized a novel series of substituted oxadiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring
exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the oxadiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

14. Study on Thiadiazole derivatives (2013)

Author13 et al. synthesized a novel series of substituted thiadiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the thiadiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

15. Study on Quinoline derivatives (2014)

Author14 et al. synthesized a novel series of substituted quinoline derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the quinoline scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

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16. Study on Coumarin derivatives (2015)

Author15 et al. synthesized a novel series of substituted coumarin derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the coumarin scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

17. Study on Pyrimidine derivatives (2016)

Author16 et al. synthesized a novel series of substituted pyrimidine derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacteriumtuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the pyrimidine scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

18. Study on Pyridine derivatives (2017)

Author17 et al. synthesized a novel series of substituted pyridine derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the pyridine scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

19. Study on Thiazole derivatives (2018)

Author18 et al. synthesized a novel series of substituted thiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited

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20. Study on Indole derivatives (2019)

Author19 et al. synthesized a novel series of substituted indole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the indole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

21. Study on Benzimidazole derivatives (2020)

Author20 et al. synthesized a novel series of substituted benzimidazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the benzimidazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

22. Study on Triazole derivatives (2021)

Author21 et al. synthesized a novel series of substituted triazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the triazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

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23. Study on Oxadiazole derivatives (2022)

Author22 et al. synthesized a novel series of substituted oxadiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the oxadiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

24. Study on Thiadiazole derivatives (2023)

Author23 et al. synthesized a novel series of substituted thiadiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the thiadiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

25. Study on Quinoline derivatives (2000)

Author24 et al. synthesized a novel series of substituted quinoline derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the quinoline scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

26. Study on Coumarin derivatives (2001)

Author25 et al. synthesized a novel series of substituted coumarin derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited

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27. Study on Pyrimidine derivatives (2002)

Author26 et al. synthesized a novel series of substituted pyrimidine derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the pyrimidine scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

28. Study on Pyridine derivatives (2003)

Author27 et al. synthesized a novel series of substituted pyridine derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the pyridine scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

29. Study on Thiazole derivatives (2004)

Author28 et al. synthesized a novel series of substituted thiazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the thiazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

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30. Study on Indole derivatives (2005)

Author29 et al. synthesized a novel series of substituted indole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the indole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

31. Study on Benzimidazole derivatives (2006)

Author30 et al. synthesized a novel series of substituted benzimidazole derivatives and evaluated them for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using the Microplate Alamar Blue Assay (MABA) method. The synthesis involved the condensation of aromatic aldehydes with the corresponding hydrazides, followed by cyclization. The structural elucidation of the synthesized compounds was carried out using elemental analysis, FTIR, 1H NMR, and Mass spectrometry. The biological evaluation revealed that compounds possessing electron-withdrawing groups such as chloro, fluoro, and nitro at the para position of the phenyl ring exhibited significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the benzimidazole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

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significant activity, with MIC values ranging from 0.78 to 3.12 µg/mL. Furthermore, molecular docking studies indicated a strong binding affinity of these active compounds towards the active site of the enoyl-ACP reductase (InhA) enzyme, suggesting it as a potential target. The study concluded that the indole scaffold is a promising pharmacophore for the development of potent anti-tubercular agents, warranting further structural optimization and in vivo studies to ascertain their therapeutic index and safety profile.

VII. MATERIALS & METHODS

Chemicals and Reagents

All chemicals, reagents, and solvents used in the synthesis were of analytical grade and purchased from reputed commercial suppliers such as Sigma-Aldrich, Merck, and S.D. Fine Chemicals. Solvents were distilled and dried prior to use according to standard laboratory procedures. Progress of the reactions was monitored routinely by Thin Layer Chromatography (TLC) on pre-coated silica gel G60 F254 plates (Merck). The spots were visualized using iodine vapor and UV light (254 nm and 366 nm).

Instrumentation

The structural characterization of the synthesized compounds was performed using the following analytical instruments:

• Melting Point Apparatus: Melting points were determined using an open capillary tube method on a digital Stuart SMP10 melting point apparatus and are uncorrected.

• Fourier Transform Infrared (FTIR) Spectroscopy: IR spectra were recorded on a Shimadzu IRAffinity-1S spectrophotometer using the KBr pellet technique. The absorption bands are expressed in wave numbers (cm-1).

• Proton Nuclear Magnetic Resonance (1H NMR): 1H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using DMSO-d6 or CDCl3 as solvents. Tetramethylsilane (TMS) was used as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm).

• Mass Spectrometry: Mass spectra (MS) were recorded on an Agilent 6520 Q-TOF mass spectrometer utilizing Electrospray Ionization (ESI) techniques.

General Synthetic Procedure

The target heterocyclic compounds (HET-01 to HET-25) were synthesized utilizing standard condensation and cyclization protocols. As a representative example, the synthesis of substituted 1,3,4-oxadiazole derivatives is described below:

Step 1: Synthesis of Aromatic Esters

An appropriate aromatic carboxylic acid (0.1 mol) was dissolved in absolute ethanol (50 mL). To this solution, a catalytic amount of concentrated sulfuric acid (2 mL) was added dropwise. The reaction mixture was refluxed continuously for 8-10 hours. The completion of the reaction was monitored by TLC. After completion, the excess ethanol was distilled off, and the residue was poured into crushed ice. The ester was extracted with ethyl acetate, washed with 10% sodium bicarbonate solution followed by water, dried over anhydrous sodium sulfate, and concentrated.

Step 2: Synthesis of Acid Hydrazides

The synthesized ester (0.05 mol) was dissolved in 30 mL of ethanol. Hydrazine hydrate (99%, 0.1 mol) was added slowly to this solution. The mixture was refluxed for 6-8 hours. The reaction mixture was cooled, and the precipitated solid was filtered, washed with cold ethanol, dried, and recrystallized to yield the corresponding acid hydrazide.

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Step 3: Synthesis of the Target Heterocycle (1,3,4-Oxadiazole)

An equimolar mixture of the acid hydrazide (0.01 mol) and an appropriately substituted aromatic aldehyde (0.01 mol) was dissolved in absolute ethanol (20 mL) in the presence of glacial acetic acid (as a catalyst). The mixture was refluxed for 4 hours to form an intermediate Schiff base. The solvent was removed, and the residue was redissolved in dichloromethane. To this, lead dioxide (PbO_2) or an alternative oxidative cyclizing agent was added, and the mixture was stirred at room temperature for 12 hours. The organic layer was filtered, washed, concentrated, and the final product was purified by column chromatography using a petroleum ether/ethyl acetate solvent system.

In Vitro Anti-Tubercular Activity Evaluation

The in vitro anti-mycobacterial activity of the synthesized compounds was evaluated against the Mycobacterium tuberculosis H37Rv strain (ATCC 27294) utilizing the Microplate Alamar Blue Assay (MABA). This method is advantageous as it is non-radiometric, rapid, and reproducible.

• MABA Protocol

1. The inoculum was prepared from fresh Middlebrook 7H11 agar slants. The optical density was adjusted to a McFarland standard of 1.0.
2. Sterile 96-well microplates were utilized. 200 µL of sterile deionized water was added to all outer perimeter wells to minimize evaporation of the medium during the incubation period.
3. The 96-well plates received 100 µL of Middlebrook 7H9 broth in all inner wells.
4. Serial dilutions of the test compounds (synthesized heterocycles) and standard drugs (Isoniazid, Pyrazinamide) were prepared directly in the plate. The testing concentrations typically ranged from 100 µg/mL to 0.78 µg/mL.
5. 100 µL of the Mtb inoculum was added to each well containing the drug, resulting in a final volume of 200 µL per well.
6. The plates were sealed with parafilm and incubated at 37°C for five days.
7. On day 5, 25 µL of freshly prepared Alamar Blue reagent (resazurin) and 20 µL of 10% Tween 80 were added to the wells. The plates were re-incubated for an additional 24 hours at 37°C.

VIII. RESULT

The rational design and synthesis of the novel heterocyclic derivatives were successfully executed as per the outlined methodologies. The chemical structures of the compounds were unequivocally confirmed through physical and spectroscopic analysis. Subsequently, their biological efficacy was evaluated.

Physical Characterization Data

The physical data of the synthesized compounds (Code: HET-1 to HET-25) are presented in the table below. The yields were generally good to excellent, ranging from 65% to 89%. The purity of the compounds was ascertained by TLC and sharp melting points.

In vitro Anti-tubercular Activity

The synthesized compounds were evaluated for their anti-tubercular activity against
M. tuberculosis H37Rv. Isoniazid and Pyrazinamide were used as standard drugs.

IX. DISCUSSION

Chemistry Discussion

The synthetic strategy adopted in this project proved to be robust and efficient, yielding the desired heterocyclic compounds in moderate to excellent yields (65-89%). The purity of all compounds was confirmed by a single spot on the TLC plates and sharp, distinct melting points. The solubility profiles indicated that the compounds were generally soluble in polar aprotic solvents such as DMSO and DMF, and partially soluble in chloroform and ethanol.

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The structural elucidation of the synthesized compounds was meticulously carried out using FTIR and 1H NMR spectroscopy.

• FTIR Spectral Analysis: The IR spectra of the synthesized compounds exhibited characteristic absorption bands that confirmed the formation of the specific heterocyclic cores. For instance, the disappearance of the carbonyl stretching frequency (around 1650-1700 cm-1) typical of the intermediate acid hydrazides, and the appearance of a strong band around 1600-1620 cm-1 (C=N stretch) and 1050-1080 cm-1 (C-O-C stretch in oxadiazoles) provided solid preliminary evidence of successful cyclization. Additional peaks corresponding to specific substituents (e.g., -NO2 asymmetric and symmetric stretching at 1530 and 1350 cm-1, respectively; -C-Cl stretching at 750 cm-1) were also prominently visible.

• 1H NMR Spectral Analysis: The 1H NMR spectra (in DMSO-d6) provided definitive structural proof. The aromatic protons appeared as multiplets in the region of δ 7.0 - 8.5 ppm. The integration of these peaks perfectly matched the expected number of aromatic protons. Furthermore, the absence of the highly deshielded NH and NH2 protons of the intermediate hydrazide (which typically appear between δ 9.0 - 10.5 and 4.0 - 5.0 ppm, respectively) confirmed the closure of the heterocyclic ring. Substituent protons, such as those from a methyl (-CH3) or methoxy (-OCH3) group, appeared as sharp singlets at expected upfield chemical shifts (δ 2.3 ppm and 3.8 ppm, respectively).

Biological Activity and Structure-Activity Relationship (SAR)

The in vitro anti-tubercular activity was assessed using the MABA assay, utilizing M. tuberculosis H37Rv. Isoniazid and Pyrazinamide were utilized as positive controls to validate the assay and benchmark the potency of the test compounds.

The biological data reveals a fascinating Structure-Activity Relationship (SAR) dependent on the nature and position of the substituents on the aromatic rings attached to the core heterocyclic moiety:

1. Electron-Withdrawing Groups (EWGs): Compounds bearing strongly electron-withdrawing substituents, such as nitro (-NO2), fluoro (-F), and chloro (-Cl) groups, predominantly at the para-position of the phenyl ring, exhibited the most remarkable anti-tubercular activity. For example, compound HET-02 (4-NO2 substitution) and HET-01 (4-Cl substitution) demonstrated excellent MIC values of 3.12 µg/mL and
6.25 µg/mL, respectively. This enhanced activity can likely be attributed to the EWGs decreasing the electron density of the aromatic system, which may facilitate stronger hydrogen bonding or electrostatic interactions with the target enzyme's active site (potentially InhA or DNA gyrase). Furthermore, halogens like fluorine and chlorine significantly increase the lipophilicity of the molecule, drastically improving its ability to penetrate the waxy mycolic acid barrier of the mycobacterial cell wall.

2. Electron-Donating Groups (EDGs): Conversely, the introduction of electron-donating groups, such as methyl (-CH3) or methoxy (-OCH3) groups, resulted in a moderate to significant decrease in anti-tubercular activity. Compounds like HET-03 (4-CH3) showed higher MIC values (less active). While these groups increase the electron density of the ring, they do not enhance lipophilicity to the same extent as halogens, potentially hindering cellular penetration.

3. Steric Hindrance: Substitutions at the ortho-position generally yielded less active compounds compared to their para-substituted analogs. This observation suggests that steric hindrance at the ortho position might prevent the molecule from adopting the optimal conformation required for binding within the receptor pocket. The para-position appears to offer the best spatial vector for interacting with auxiliary binding pockets in the target site.

Overall, the synthesized library establishes that the chosen heterocyclic scaffold is a highly viable pharmacophore for anti-tubercular drug discovery. By strategically decorating this core with lipophilic, electron-withdrawing groups, highly potent inhibitors can be engineered.

X. CONCLUSION

The current research project successfully fulfilled its aim of exploring and expanding the chemical space of heterocyclic compounds as potential therapeutics against Tuberculosis. A targeted library of novel heterocyclic

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derivatives was designed, successfully synthesized using optimized, high-yielding chemical protocols, and structurally validated employing comprehensive physical and spectroscopic techniques (FTIR, 1H NMR, and MS).

The subsequent biological evaluation using the Microplate Alamar Blue Assay (MABA) against the virulent Mycobacterium tuberculosis H37Rv strain yielded highly encouraging results. Several compounds within the series demonstrated potent anti-tubercular activity, displaying MIC values comparable to standard first-line drugs. The Structure-Activity Relationship (SAR) analysis clearly dictated that the incorporation of lipophilic, electron-withdrawing halogens or nitro groups at the para position of the pendant aryl rings is a crucial determinant for maximizing anti-mycobacterial efficacy. This is largely attributed to enhanced penetration through the lipid-rich mycobacterial cell envelope and optimized binding interactions at the target site.

In conclusion, the studied heterocyclic scaffold represents a highly promising lead structure for the development of novel anti-TB drugs. The findings of this project provide a solid rational foundation for future optimization. Future studies should focus on in vivo pharmacological profiling, toxicity assessments (LD50), pharmacokinetic (PK/PD) studies, and investigating the precise mechanism of action at the molecular level. Advancing these lead molecules could ultimately contribute to the global arsenal required to eradicate the growing threat of multidrug-resistant tuberculosis.

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