RESEARCH PAPER

A Review on Novel Coumarin Analogs as Anti-Tubercular Agents

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ABSTRACT
This study compiles recent advances in the synthesis, design, and biological evaluation of novel coumarin analogs as anti-tubercular medications. The influence of changes at C-3, C-4, C-6, and C-7 positions is emphasized in structure-activity relationship (SAR) investigations. One of the leading causes of infectious death worldwide is the emergence of extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains of Mycobacterium tuberculosis, which causes tuberculosis (TB). Key mycobacterial targets include DNA gyrase, enoyl-acyl carrier protein reductase (InhA), and cell wall biosynthesis enzymes may be inhibited, according to mechanistic findings. Moreover, it has been demonstrated that improving physicochemical characteristics enhances intracellular penetration and macrophage targeting. Because of the urgent need for novel chemotherapeutic medications with improved efficacy and reduced resistance potential, heterocyclic scaffolds have drawn a lot of interest in medicinal chemistry. A unique pharmacophore with a range of biological activities, including potential antimycobacterial activity, is coumarin (2H-chromen-2-one).
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INTRODUCTION

Microbial infections, caused by bacteria, viruses, fungi, protozoa, and helminths, pose a major global health threat, affecting millions annually. Bacterial infections like tuberculosis, pneumonia, and staphylococcal sepsis often respond to antibiotics, though resistance (e.g., MRSA) complicates treatment. Viral infections, including influenza, HIV, and COVID-19, rely on vaccines, antivirals, or supportive care, as antibiotics are ineffective. (1)

Tuberculosis (TB) is an acute or chronic infectious disease caused by several *Mycobacterium* species, collectively called tubercle bacilli or the *Mycobacterium tuberculosis* complex. This includes *Mycobacterium tuberculosis* (MTB) itself, along with *M. microti*, *M. pinnipedii*, *M. bovis*, *M. caprae*, *M. africanum*, and *M. canetti*. MTB is also known as the "white plague," first identified by Robert Koch in 1882.

TB primarily affects the lungs but can also involve the bones, joints, skin, central nervous system, lymphatic and circulatory systems, genitourinary tract, and gastrointestinal system.

TB is a communicable disease and a major cause of ill health worldwide—the leading cause of death from a single infectious agent . (2). An estimated 10.8 million people fell ill with TB in 2023 (134 incident cases per 100,000 population). In 2021, TB caused an estimated 1.6 million deaths, including 1.4 million among HIV-negative people and 187,000 among HIV-positive people . (3)

Signs and Symptoms

Common signs include cough, hemoptysis, dyspnea, chest pain, night sweats, anaemia, tachycardia, abnormal lung auscultation findings, fever, low body mass index, and low mid-upper arm circumference. These contribute to a TB score ranging from 0 to 13. (3)

Antibiotic Resistance Due to Cell Envelope

Mycobacteria's intrinsic resistance to many antibiotics stems from their unique, thick, hydrophobic cell envelope. Unlike other Gram-positive bacteria, it features diverse lipids like mycolic acids.

Key factors include:

Low porin numbers, limiting permeability.

A lipid layer covalently linked to peptidoglycan via arabinogalactan.

Extractable immunogenic glycolipids.

This lipid-rich structure blocks hydrophilic compounds. Small hydrophilic antibiotics targeting *M. tuberculosis* must pass through water-filled porins. (4)

Causes of TB

TB spreads primarily through airborne droplets from infected people who cough, sneeze, or talk. Key risk factors include:

Weakened immune system: Higher risk in those with HIV/AIDS, diabetes, malnutrition, or immunosuppressive treatments.

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Close contact: Living or spending time in crowded spaces with someone who has active TB.
Poor living conditions: Overcrowding, poor ventilation, and limited healthcare access.
Substance abuse: Alcoholism or drug use that impairs immunity.
Chronic health conditions: Such as lung or kidney disease.
Geographic factors: More common in low-income regions with poverty and inadequate healthcare.

Common Symptoms
Persistent cough lasting over three weeks, often with blood or sputum.
Chest pain, especially when breathing or coughing.
Unexplained weight loss or loss of appetite.
Low-grade fever with chills.
Night sweats. (6)

Coumarin: Overview and Biological Importance
Coumarin is an oxygen-containing heterocycle with diverse biological activities. It occurs naturally as lactones and serves as a perfume and food flavouring agent.

Structure and History
Numbering starts at the ring oxygen (position 1), followed by the carbonyl carbon (position 2), proceeding anticlockwise. The parent compound was first isolated from tonka beans by Vogel in 1820. Over the past decade, synthesizing coumarin derivatives has drawn global attention from medicinal chemists due to their significant pharmaceutical potential.

Key Activities
Coumarins excel as:
Antidepressants, anti-HIV, antioxidants, antimicrobials, anti-inflammatories, antinociceptives.
Anti-influenza, antitumor, antivirals, antituberculosis, anti-Alzheimer's, antihyperlipidemic.
Antipyretics, antiasthma tics, and more.
Marketed Derivatives (examples by use):
Anticoagulants: Brodifacoum, Warfarin, Acenocoumarol, Difenacoum, Phenprocoumon.
Antibiotics: Armillarisin.
Other: Bergapten (sunscreen), Auraptene (chemopreventive), Ensaculin (NMDA antagonist/5HT1A agonist), Hymecromone (choleretic/antispasmodic), Carbochromen (coronary disease), Scopoletin (2)

Historical Background of TB
TB ranks among humanity's oldest infectious diseases, likely evolving between the 7th and 6th millennia BC. (7), (8), (9), (10), (11). Ancient texts describe it as "Yakshma" (wasting disease) in the Indian Vedas, with similar accounts in Chinese and Arabic literature.
On March 24, 1882, Robert Koch announced his discovery of the tubercle bacillus at a Berlin Physiological Society meeting. To mark the centenary, March 24 has been celebrated as World TB Day since 1982. (7)

Epidemiology, global burden and Indian scenario:
TB is a leading global health threat, with data from the World Health Organization's (WHO) 2016 report highlighting its burden . (12), (13), (14), (15).

Global Burden (2015 Data)
New cases: 10.4 million total (56% men, 34% women, 10% children); 11% HIV-positive.
Top countries: 60% of cases in India, Indonesia, China, Nigeria, Pakistan, South Africa.
Deaths: 1.4 million (HIV-negative) + 0.4 million (HIV-positive).
MDR-TB: 0.48 million new cases; 45% in India, China, Russia; 9.5% extensively drug-resistant.

Category	Key 2015 Stats
TB Cases	10.4M total; 60% from 6 countries
MDR-TB	0.48M new; 9.5% XDR
HIV Co-infection	11% of cases; 0.4M deaths

Indian Scenario
India, the world's second-most populous country, accounts for over 25% of global TB cases and deaths annually. It consistently leads in new TB cases, MDR-TB, and TB-related deaths.
2014 estimates: 2.2 million incident cases; 2.5 million prevalent cases.
HIV-positive cases: 5% of incident TB.
MDR-TB: 2.2% of new cases . (12), (13), (14), (15)

Challenges and Advances
Despite advances, issues like nephrotoxicity (amphotericin B), resistance, and drug interactions persist, driving research into novel agents. These drugs have transformed outcomes for conditions like cryptococcal meningitis and mucormycosis, yet optimal use requires understanding spectra, pharmacokinetics, and resistance patterns (12)

2. Chemistry of Coumarin

2.1. Chemical Structure and Basic Features of Coumarin

The fused benzene and α-pyrone ring system of coumarin (2H-chromen-2-one or 2H-1-benzopyran-2-one) makes it a fundamental structural motif in organic chemistry. This crystalline substance, which has a bitter taste and a unique vanilla-like smell, has the chemical formula $C_9H_6O_2$. An unsaturated lactone moiety replaces two nearby hydrogen atoms of the benzene ring in the basic coumarin structure, which is made up of an aromatic ring fused to a lactone ring. Coumarins are secondary metabolites found in plants that function as defensive systems in the natural world. (17)

Naturally occurring compounds with a wide variety of functions are called coumarins. They are a preferred scaffold in chemical biology and medicinal chemistry due to their structural and physicochemical properties. Numerous plants in nature contain coumarin, but the tonka bean (Dipteryx odorata) has the highest quantity. Additionally, it is present in vanilla grass (Anthoxanthum odoratum), sweet woodruff (Galium odoratum), and sweet grass (Hierochloe odorata), among other plants. This explains why natural coumarin extraction and characterisation methods, as well as the synthesis of their derivatives, are of such high interest. Its chemical backbone's simplicity and the pyrone and benzene 2 of 16 rings' reactivity are both highly appealing. In this family of compounds, conjugated double bonds are in charge of the electrical environment, which is crucial. (18)

This thorough analysis highlights the importance of coumarins as adaptable natural derivatives in medicinal chemistry while delving into their complex chemical possibilities. Through hydrogen bonds, dipole-dipole interactions, and hydrophobic interactions, coumarine's distinct chemical structure makes it easier to bind to a variety of substrates. (19)

The IUPAC created the systematic nomenclature for coumarin, an organic heterocyclic molecule with a benzo-α-pyrone (2H-1-benzopyran-2-one) skeleton that belongs to the lactone subgroup. From a chemistry perspective, these compounds have a number of appealing characteristics, including low toxicity, high bioavailability, simple structure, modest molecular weight, and good solubility in the majority of organic solvents. (20)

The fundamental structure of the class of naturally occurring O-heterocyclic compounds known as coumarins is 2H-1 benzopyran-2-one. In the field of chemical and medicinal chemistry, coumarin derivatives are appealing and widely used. (21)

2.2. Reactivity: The Coumarin Core's Functionalization

Coumarin Reactivity in General

The following discussion relates to the reactivity of the coumarin core, which was primarily studied at the level of C-3 and C-4 of the pyranone ring. Structurally varied coumarin derivatives have been synthesized. "Recently, C-3 modification of coumarins was the most investigated approach to access a variety of interesting derivatives.

Examples of Functional Group Introduction

A generic framework for the reactivity of C-3 substituted coumarins explains how to create biologically relevant scaffolds by adding alkyl, silyl, CF_3, CHF_2, and OCH_2F groups.

Substituted Coumarins' Reactivity

Complex furano- and pyrano-coumarins can be created by employing 3-hydroxy coumarins in Lewis acid-catalyzed cascade annulations. C-H activation strategies can be followed by annulation reactions to obtain π-Extended coumarins from 3,4-disubstituted coumarins. (22)

3. Synthetic Strategies for Novel Analogs

Its wide range of biological activity and ease of functionalization have long made the coumarin scaffold (2H-1-benzopyran-2-one) a preferred structure in medicinal chemistry. Because of their potential to produce analogs with enhanced efficacy against Mycobacterium tuberculosis (Mtb), including treatment-resistant strains, coumarins have garnered attention in the context of antitubercular drug discovery. (23)

Therefore, effective coumarin core construction and modification as well as derivatization techniques that might improve antimycobacterial characteristics and pharmacokinetic profiles are key components of synthetic strategies for new coumarin analogs.

3.1. Fundamental Coumarin Synthesis Methods

Reliable core scaffolding techniques are the first step in the creation of structurally varied coumarin analogs:

3.11. Pechmann Condensation and Classical Cyclizations

The most popular classical method for creating coumarins is still the Pechmann condensation. The benzopyranone core is formed in a single pot by the condensation of a phenol with a β-ketoester, which is accelerated by an acid. (24). By choosing the appropriate activated β-ketoester components, variations of this reaction allow the insertion of various substituents at positions C-3 and C-4. Pechmann condensation is a standard procedure in the library generation of coumarin derivatives due to its durability and scalability, even if it is a classical approach.

To produce coumarins with varying functional group variety, other conventional methods such lactonization of o-hydroxycinnamic acids, Perkin reactions, and Knoevenagel condensations have been modified. (25)

3.12. Modern Catalytic and Direct Methods

Metal-catalyzed coumarin forms, such palladium-catalyzed C-H activation/alkenylation, have been used in recent developments to enable the mildly substituted coumarin production from phenol derivatives and acrylate partners. (26)

Improved regioselectivity and the ability to introduce substituents that would otherwise be difficult to achieve by classical condensation are two benefits of these contemporary catalytic techniques.

3.2. Strategic Modification of the Coumarin Core for Anti-TB Activity

The majority of antitubercular coumarin research concentrates on derivatization and hybridization to increase action against Mtb, even if the synthesis of the core scaffold is fundamental.

3.21. Heterocycle Fusion and Bioisosteric Replacement

Combining coumarin with other heterocyclic motifs that are known to interact with biological targets related to tuberculosis is a popular tactic:

To increase the anti-TB efficacy, **coumarin-thymidine conjugates** are created by nucleophilically substituting nucleoside moieties such as thymidine for bromomethyl coumarins. This combines the scaffold of the coumarin with the DNA-mimetic thymidine. With MIC values in the submicromolar range and advantageous physicochemical characteristics, these compounds showed strong activity, highlighting the usefulness of heterocycle conjugation in broadening the biological activity area. (27)

Key enzymes like InhA (enoyl acyl carrier protein reductase), a proven antitubercular target, are targeted by **azaheterocyclic coumarin derivatives**. As an illustration of how well bioisosteric modification works to target drug-resistant processes, the synthesis of coumarin tetrazole analogs has yielded compounds with promising inhibitory activity against both wild-type and mutant Mtb strains. (28)

3.22. Pharmacophore-Guided Functionalization

Increasingly, synthetic approach is guided by the use of molecular docking and pharmacophore modeling. The rational design of coumarin analog libraries enabled the selection of synthetic targets by finding critical structural properties necessary for binding to Mycobacterium thymidine monophosphate kinase (Mtb TMPK). This resulted in strong, non-toxic inhibitors with MICs similar to isoniazid. (27)

Synthetic decisions are influenced by these methods; functional groups that enhance hydrogen bonding or hydrophobic pockets found by docking are methodically added at key locations on the coumarin ring.

3.3. Hybrid Molecule Design

The creation of hybrid compounds, which combine coumarin with extra pharmacophoric units to concurrently activate several biological targets, has shown to be a very successful synthetic method.

3.31. Coumarin-Piperazine and Benzopyran Hybrids

With moderate MIC values, novel coumarin compounds including piperazine—a bioactive moiety recognized for improved drug-like qualities and increased membrane penetration—have shown antitubercular action, confirming hybridization as a workable strategy in anti-TB medication development. (29)

3.32. Multi-Scaffold Conjugates

The structural and functional diversity of analog libraries is enhanced by coumarin hybrid derivatives that contain pyrazole, imidazole, and other heterocycles in addition to piperazine. Although not all derivatives provide strong antimycobacterial activity, substituents like fluorine and chlorine have been demonstrated to alter activity profiles, indicating that structural adjustment of hybrid scaffolds can increase target potency and specificity. (30)

3.4. Structure–Activity Relationship (SAR) and Functional Group Effects

Iterative SAR studies are frequently used to refine synthetic techniques and provide chemists with information about how substituents affect antimycobacterial activity:

Improved activity has been linked to substituents at positions C-3 and C-4, where electron-withdrawing groups (such as fluoro and chloro) frequently increase potency. (30)

Analogs with higher MIC values against Mtb strains are often produced by adding functional groups that boost lipophilicity or allow for better binding contacts with enzyme active sites.

These realizations frequently result in targeted synthesis, where the insertion of functional groups is given priority according to anticipated SAR results.

3.5. Green and Sustainable Synthetic Methods

Since sustainable chemistry is becoming more and more important, green methods have been the subject of numerous new synthetic strategies:

Synthesis using a microwave greatly reduces reaction times and increases yields compared to conventional thermal settings. (25)

use of environmentally friendly solvent systems and catalysts in heterocycle synthesis that limit waste and have a minimal impact on the environment, in line with contemporary green chemistry principles.

4. Therapeutics

4.1. Introduction: Coumarin as Therapeutic Scaffolds Against TB

Nearly 10 million people are affected by tuberculosis (TB) each year, making it a major worldwide health concern and the second greatest cause of mortality after HIV/AIDS. This underscores the urgent need for novel therapeutic drugs. The effectiveness of current TB treatments has been greatly diminished by the emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains, highlighting the need for innovative therapeutic scaffolds. Because of their structural diversity and potential usefulness, coumarins—naturally occurring oxygenated heterocycles with a variety of pharmacological activities—have emerged as interesting candidates for anti-TB drug research. (32).

The heterocyclic molecules known as coumarins (2H-1-benzopyran-2-ones) have important pharmacological characteristics, proving the coumarin scaffold's general medicinal value. (33)

The biological spectrum of coumarin has intrigued medicinal researchers to investigate coumarin scaffolds for their relevance as anti-TB drugs." — stating the direct therapeutic relevance of coumarin scaffolds in tuberculosis. (34)

4.2. Anti-Tubercular Properties of Synthetic Coumarin Analogs: in Vitro

Coumarin-thymidine analogs were created in an effort to find novel antituberculosis (TB) drugs. With minimum inhibitory concentrations (MIC) of the active compounds ranging between 0.012 and 0.482 µM, the novel conjugates were found to exhibit strong anti-TB activity against the Mycobacterium tuberculosis $H_{37}Rv$ strain. — directly reporting in-vitro anti-TB efficacy of the synthesized coumarin analogs.

Among the synthesized coumarin-thymidine analogs, "Compound 1k was established as the most active candidate with a MIC of 0.012 µM." — highlighting a particular, strong anti-TB outcome. (35)

Showing similar in-vitro efficacy to a first-line TB medication. Compounds S135, S144, and S146 have demonstrated MICs of 0.06 µg/mL, which is comparable to the MIC of isoniazid of 0.05 µg/mL. (36)

Demonstrating a strong synthetic coumarin analog that outperformed a reference medicine in vitro. The most diligent molecule 6b (MIC = 0.39 µg/mL) was two times more active than the common anti-TB medication Rifampin (0.8 µg/mL) and equivalent to Isoniazid (0.1 µg/mL). (37)
Increased efficacy was linked to structural characteristics such oxime groups, triazole linkages, and halogen or methyl replacements. — determining structure-activity parameters influencing synthetic analogs' in-vitro potency. (32)
The therapeutic importance of coumarin derivatives against TB in vitro is concluded by these findings, which highlight coumarins as useful scaffolds for novel anti-TB medicines. (32)

4.3. Selectivity, Cytotoxicity, and Therapeutic Index

Selectivity, or the capacity to eradicate Mtb without harming human cells, is an essential component of any anti-TB contender.
Several of the most potent coumarin-thymidine analogs were shown to be non-cytotoxic in human HEK cells, showing a positive safety profile. The toxicity investigation on HEK cells verified the harmless nature of compounds 1e, 1h, 1i, 1j, and 1k. (35).
This selectivity most likely results from structural characteristics that allow for preferential binding or accumulation within mycobacterial cells as opposed to host tissue. To improve safety profiles before clinical review, ADMET characteristics must be continuously optimized.

4.4. Comparisons with Standard Anti-TB Therapies

A number of coumarin analogs show similar inhibitory effects in vitro, indicating potential as next-generation treatments, even if isoniazid and rifampin continue to be the gold standards for anti-TB efficacy.
By directly comparing the activity of lead coumarin derivatives with the conventional first-line anti-TB medication isoniazid, compounds S135, S144, and S146 have demonstrated MICs of 0.06 µg/mL, which are equivalent to the MIC of isoniazid of 0.05 µg/mL. (38)
By directly comparing the activity of the synthetic coumarin-thioether analog 6b to two important first-line anti-TB medicines, the most diligent molecule 6b (MIC = 0.39 µg/mL) was two times more active than the conventional anti-TB drug Rifampin (0.8 µg/mL) and comparable to Isoniazid (0.1 µg/mL). (37)
These comparisons highlight the therapeutic potential of well-designed coumarin derivatives in comparison to well-established medications, despite the fact that they are based on in-vitro testing rather than clinical data.

5. Anti-TB Evaluation of Novel Coumarin Analogs

5.1. Overview of the Anti-Tubercular Assessment System

Researchers use a combination of in-vitro susceptibility tests, mechanistic enzymatic investigations, in vivo infection models, and cytotoxicity evaluations to evaluate the therapeutic potential of new coumarin analogs against Mycobacterium tuberculosis (Mtb). Such a multi-tiered assessment guarantees that chemicals are safe, selective, and effective against bacterial growth for the development of therapeutics.
Determining the minimum inhibitory concentration (MIC) against reference laboratory strains, such as H37Rv, is the first step in the traditional antitubercular screening process. Activity against drug-resistant clinical isolates comes next. Whole-cell phenotypic screens and mechanistic enzyme inhibition experiments are also used to confirm biological relevance. (40)

5.2. Evaluation of In-Vitro Anti-TB Activity

5.21. Minimum Inhibitory Concentration (MIC) Determination

MIC, which measures the lowest concentration of a substance that prevents observable bacterial growth, is still the gold standard for anti-TB screening.
Coumarin-Thymidine Conjugates
With minimum inhibitory concentrations (MIC) of the active compounds ranging from 0.012 to 0.482 µM, the new coumarin-thymidine conjugates (1a-l) were reported to have strong anti-TB action against the Mycobacterium tuberculosis H3Rv strain. These findings point to a very high potential for bactericidal or bacteriostatic effects. (41)
Pharmacophore-Guided Coumarin Derivatives
Targeting the Mtb enzymatic sites, coumarin analogs created via molecular docking and pharmacophore modeling demonstrated MIC values between 0.06 and 0.4 µg/mL. These values show that rational design produces clinically active analogs, and they compare favorably with isoniazid (MIC ~0.025–0.05 µg/mL). (42)
Thioether and Other Hybrid Coumarins
In vitro anti-TB activity of the synthesized compounds is evaluated ($H_{37}Rv$ strain). The majority of the synthesized conjugates showed noteworthy activity and were efficacious, with MIC values ranging from 0.39 to 12.5 µg/mL. These findings suggest that anti-TB efficacy can be improved by functionalization outside of the coumarin core. (43)

5.22. Evaluations Against Drug-Resistant Strains

The effectiveness of current treatments has been diminished by the emergence of extensively drug-resistant (XDR-TB) and multidrug-resistant (MDR-TB) strains, highlighting the critical need for innovative therapeutic scaffolds. Both susceptible and resistant isolates were taken into account in the evaluated research, as evidenced by the statement,..in vitro studies focused on standard and resistant M. tuberculosis strains.
Conclusion: Coumarin derivatives, especially conjugates that have been synthetically optimized, show strong anti-TB activity and are a promising platform for fighting MDR- and XDR-TB. (40)

5.3. Resazurin Microtiter Assay (REMA)

For high-throughput anti-Mycobacterium screening, the Resazurin Microtiter Assay (REMA) is frequently used because of its sensitivity and economical viable cell quantification. Resazurin is reduced to fluorescent resorufin in REMA assays by viable Mtb, enabling the assessment of the compound's impact on cellular viability. Based on REMA results, all synthesized compounds showed promising efficacy with MICs below 1 µg/mL,

demonstrating the antitubercular potential of proposed coumarin analogs. (42)

5.4. Enzyme-Based and Mechanistic Evaluations

Coumarin analogs are tested against particular Mtb enzymes that are known to be crucial for bacterial survival in order to clarify modes of action.

5.41. Inhibition of Mycobacterium Thymidine Monophosphate Kinase (Mtb TMPK)

The goal of the study was to investigate new inhibitors that target Mycobacterium thymidine monophosphate kinase (Mtb TMPK), a crucial enzyme in Mycobacterium tuberculosis's nucleotide production. A mechanistic focus on enzyme inhibition rather than just whole-cell activity is suggested by the data, which highlight Mtb TMPK inhibition experiments to fix the mode of action. (34)

5.42. Targeting Cell Wall Synthesis and β-Oxidation Pathways

To explore the mechanisms of anti-TB efficacy, molecular docking studies were performed on the M. tuberculosis β-oxidation trifunctional enzyme (PDB ID: 7O4V). This suggests that the study investigated how the produced chemicals might interact with and inhibit a biochemical target linked to M. tuberculosis physiology using in-silico docking against a particular mycobacterial enzyme. Instead of only demonstrating whole-cell anti-TB efficacy, the selection of a β-oxidation trifunctional enzyme as the docking target suggests a mechanistic hypothesis that these analogs may disrupt mycobacterial lipid metabolic pathways, which are crucial for survival and virulence. (41)

5.5. Cytotoxicity and Selectivity Assessment

Demonstrating that substances selectively inhibit Mtb without damaging mammalian cells is a crucial part of evaluating anti-TB drugs.

Mammalian Cytotoxicity Screens

The harmless character of compounds 1e, 1h, 1i, 1j, and 1k was validated by the toxicity research on HEK cells. This means that some analogs were examined for cytotoxicity against mammalian cells (human embryonic kidney cells) and were determined to be innocuous in that assay. These findings support the superiority of coumarin analogs over non-selective cytotoxic substances in terms of therapeutic potential. (41)

5.6. Limitations and Opportunities

Despite positive results, a number of issues still exist:
* There is little in vivo validation, and it is still difficult to convert in vitro potency into therapeutic significance.
* Because of the coumarin core's metabolic change, bioavailability issues continue.
* Expansion is necessary for mechanistic explanation, especially when identifying key intracellular targets.

6. Mechanisms of Anti-*Mycobacterium tuberculosis* Action of Novel Coumarin Analogues

Because of its structural adaptability and capacity to interact with a variety of biological targets, coumarin (2H-chromen-2-one) is a favored benzopyrone scaffold that has been extensively investigated in antimicrobial drug research. (44), (45). Novel coumarin analogues have shown encouraging action against drug-sensitive, multidrug-resistant (MDR), and extensively drug-resistant (XDR) Mycobacterium tuberculosis (Mtb) in tuberculosis (TB) research. (44), (46). Coumarin derivatives' anti-Mtb action is ascribed to a variety of multitarget mechanisms, including host-directed immunomodulatory effects, kinase inhibition, disruption of energy metabolism, interference with cell wall formation, inhibition of critical enzymes, and efflux regulation. (44), (47)

6.1. Inhibition of DNA Gyrase (Topoisomerase II)

The sole type II topoisomerase found in M. tuberculosis is DNA gyrase, a bacterial enzyme that catalyzes the insertion of negative supercoils into DNA. Its suppression causes substantial cell death since there are no viable substitute enzymes. (48). Effective DNA replication, transcription, and recombination in M. tuberculosis depend on DNA gyrase, an ATP-dependent enzyme that catalyzes a brief double-stranded DNA break and is unusual in its ability to catalyze negative supercoiling of DNA. (49)

By attaching themselves to the gyrA component and trapping the gyrase-DNA covalent complex, fluoroquinolones prevent DNA gyrase from supercoiling, which stops DNA processing and kills bacteria. (48)

6.2. Interference with Energy Metabolism and Respiratory Chain

Mycobacteria's energy metabolism, specifically the oxidative phosphorylation pathway, has become a target in antitubercular drug discovery; medications like Q203 (cytochrome bc_2 complex inhibitor) and bedaquiline (ATP synthase inhibitor) illustrate its crucial role. (50)

According to high-density mutagenesis and deletion experiments, M. tuberculosis needs oxidative phosphorylation to develop, and ATP synthase synthesis depends on electron transport and proton motive force (PMF) maintenance. Proton motive force generation is reduced by inhibitors of the electron transport chain, which results in a decrease in ATP synthesis that impacts vital cellular functions and aids in bacterial mortality. (50)

Protein Kinase Inhibition

A variety of eukaryotic-like serine/threonine protein kinases (STPKs) that are essential for controlling growth, cell division, cell wall formation, and host environment adaptability are encoded by Mycobacterium TB. (51). PknA and PknB are crucial for mycobacterial survival among the STPKs; their inhibition alters cell shape and septation, which results in bacteriostasis and death. (52)

DNA interaction and enzyme modulation

Certain antibacterial drugs work by intercalating DNA base pairs, changing the structure of DNA, and interfering with vital functions including transcription and replication. (53). Dyese intercalating compounds can stabilize aberrant DNA structures and inhibit DNA-associated enzymes, resulting in bacterial replication arrest that is lethal. In the context of novel small compounds, DNA-interactive processes are suggested as possible complementary ways of antimycobacterial activity, despite the fact that

conventional antitubercular medications such as isoniazid and rifampicin do not work by direct DNA intercalation. (54).

By stabilizing complexes between DNA and gyrase, fluoroquinolones cause DNA cleavage, which in turn inhibits the enzyme and has bactericidal effects. (55) . Unlike nonspecific DNA binding, novel inhibitors that target DNA gyrase catalytic or ATP-binding domains exhibit antimycobacterial activity by modulating enzyme function. (56)

Targeting Mycobacterial Cell Wall Biosynthesis by Inhibition of Enoyl-ACP Reductase (InhA)

Enoyl-acyl carrier protein reductase, or InhA, is necessary for the manufacture of mycolic acids, a crucial part of the mycobacterial cell wall, and catalyzes the NADH-dependent reduction of fatty acyl-ACP substrates. (57). M. tuberculosis depends on the fatty acid synthase-II system (FAS-II), in particular InhA, to elongate the meromycolate chains that comprise mycolic acids; inhibition of this enzyme disrupts cell wall integrity and causes bacterial death. (58)

Frontline antitubercular medication isoniazid is a prodrug that, when activated by KatG, generates an adduct that inhibits InhA, preventing the formation of mycolic acid and making it impossible for the bacillus to maintain its hydrophobic cell membrane. (59). InhA or its promoter mutations reduce drug binding, conferring isoniazid resistance, underscoring the crucial role of this enzyme in drug efficacy. (60)

Structure–Activity Relationship (SAR) of Novel Coumarin Analogs as Antitubercular Agents

A unique heterocyclic scaffold with a variety of pharmacological characteristics, including strong antimycobacterial activity, is coumarin (2H-chromen-2-one). (61). To increase efficacy against Mycobacterium tuberculosis (Mtb), including drug-resistant strains, structural alterations on the coumarin nucleus have been thoroughly investigated. (62). SAR studies show that lipophilicity, hybridization tactics, electronic effects, and substitution pattern are important factors in regulating antitubercular action. (63).

Substitution's Effect on the Coumarin Core

Substitution at C-3 Position

Antimycobacterial potency has been shown to be greatly impacted by modification at the C-3 location. (62). Because of their enhanced hydrogen bonding and target binding affinity, heterocyclic moieties including triazoles, thiazoles, and hydrazones that are introduced at C-3 increase activity. (64)

Better MIC values were shown by C-3 substituted coumarin-triazole hybrids, which were ascribed to improved interaction with important mycobacterial enzymes including DNA gyrase and InhA. (63), (65) It has been demonstrated that hydrazide and hydrazone connections at this location enhance antimycobacterial activity, maybe because of structural similarities with isoniazid pharmacophore elements. (66)

7.2. Substitution at C-4 Position

By boosting lipophilicity and membrane permeability, electron-withdrawing groups (EWGs) at the C-4 position, such as halogens and nitro substituents, have been shown to improve antimycobacterial action. (67)

On the other hand, because steric hindrance affects enzyme binding, large substituents at C-4 may decrease activity. (63)

7.3. Substitution at C-6 and C-7 Positions

Electronic density and hydrogen-bonding capacity are strongly impacted by hydroxyl and methoxy substitutions at positions C-6 and C-7. (62)

Improved antimycobacterial activity was demonstrated by 7-hydroxycoumarin derivatives, most likely as a result of increased contact with active site residues. (68)

Improved efficacy against MDR strains and higher lipophilicity were demonstrated by halogen substitution at C-6 or C-7. (69)

Conclusion

The review emphasizes that coumarin and its derivatives are a class of scaffolds that show promise for the creation of novel anti-tubercular drugs. Significant action against drug-sensitive and multidrug-resistant strains of Mycobacterium tuberculosis has been shown by structural alterations on the coumarin nucleus. Their therapeutic significance is highlighted by their ability to target important enzymes including DNA gyrase, InhA, and other crucial mycobacterial pathways.

Although many coumarin compounds show significant in vitro activity, more investigation is required to confirm their effectiveness in vivo and to improve their pharmacokinetic and safety characteristics.

All things considered, the study emphasizes the potential benefits of coumarin analogs in the fight against tuberculosis, particularly multidrug-resistant strains of the illness.

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