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# Click chemistry in tuberculosis research: From drug design to therapeutic delivery - A systematic review

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REVIEW ARTICLE

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ABSTRACT

The molecular hybridization of 1,2,3-triazoles with various bioactive scaffolds has become a promising approach to the development of new antitubercular drugs, offering a versatile platform for improving drug efficacy and specificity. This review covers key advancements over the past decade in creating triazole-based hybrids that integrate azoles, coumarin/chromene, isoniazid, quinoline/dihydroquinoline, quinolone, ferrocene, isatin, furan, and other structures. These hybrid molecules generally show improved potency against both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* strains while maintaining favorable toxicity profiles, making them particularly valuable in the current landscape of rising drug resistance. Structure-activity relationship (SAR) studies highlight that strategic substituent positioning and optimal linker selection are critical in enhancing antimycobacterial efficacy. Furthermore, modifications to the electronic and steric properties of the hybrids have been shown to influence their ability to bypass common resistance mechanisms, underscoring the potential of these compounds to overcome treatment barriers. In particular, several of these hybrids demonstrate promising activity against MDR-TB and XDR-TB strains, suggesting potential applications for immunocompromised patients, such as those with HIV co-infection. Collectively, these findings offer valuable insights for the rational design of next-generation antituberculosis agents that could transform tuberculosis (TB) treatment paradigms in both resistant and sensitive cases of TB.

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## 1. Introduction

Tuberculosis, a bacterial infection caused by *Mycobacterium tuberculosis*, is one of the oldest known diseases, with a global mortality rate higher than that of AIDS and a high prevalence among socioeconomically disadvantaged and marginalized groups [1,2]. Despite decades of research and intervention programs, tuberculosis remains the leading cause of death from a single infectious agent. The disease mainly affects the lungs (pulmonary tuberculosis) but can also affect other organs (extrapulmonary tuberculosis) [3].

The emergence of drug-resistant strains, particularly Multiple Drug-Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB), has complicated treatment protocols and reduced success rates. In 2024, approximately 484,000 cases of MDR-TB were reported worldwide, highlighting the urgent need for innovative therapeutic approaches [4]. The WHO-recommended TB treatment regimens face significant challenges [5]. Drug-sensitive tuberculosis requires 6-8 months of first-line therapy, leading to poor patient compliance and potential development of MDR tuberculosis. Treatment of MDR-TB and XDR-TB requires more expensive, more toxic and less effective second- and third-line drugs with extended treatment durations. Additional complications arise from drug interactions between TB medications and antiretroviral therapy in HIV/AIDS patients, and the difficulty in identifying and treating latent TB before an active disease develops [6].

The interplay between TB and HIV greatly intensifies the public health challenge, with HIV-positive individuals facing an 18-fold higher risk of developing active TB. Furthermore, the COVID-19 pandemic has severely impacted TB services globally, undoing years of progress in TB control. The World Health Organization estimates that disruptions due to the pandemic have resulted in a 20% increase in tuberculosis deaths from 2020 to 2024 [7,8].

Click chemistry represents a groundbreaking paradigm in chemical synthesis, comprising a suite of highly efficient, selective, and modular reactions that proceed rapidly under mild conditions to form covalent bonds between molecular building blocks [9-11]. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, the quintessential example of click chemistry, has revolutionized diverse fields, including drug discovery [12-16], materials science [17], and bioconjugation [18-20]. This methodology, first conceptualized by Sharpless and colleagues, is characterized by stringent criteria: stereospecificity, high yields, simple reaction conditions, readily available starting materials, and environmentally benign solvents. In the context of tuberculosis research, click chemistry has emerged as an invaluable tool for developing novel antimycobacterial agents, particularly in the modification


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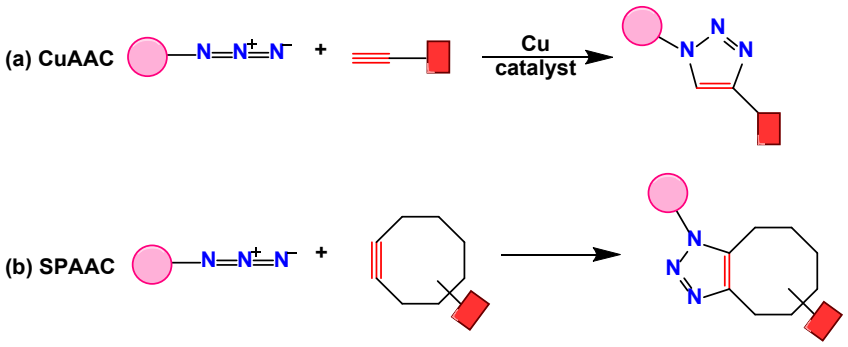


**Figure 1.** (a) Cu-catalyzed azide-alkyne cycloaddition (CuAAC) and (b) strain-promoted azide-alkyne cycloaddition (SPAAC) reactions as powerful tools for bioorthogonal labeling and efficient molecular assembly.

of existing drug scaffolds and the synthesis of targeted drug delivery systems against *Mycobacterium tuberculosis*. The bioorthogonal nature of the reaction, coupled with its compatibility with physiological conditions, has facilitated the development of fluorescent probes to study the components of the mycobacterial cell wall and enabled the strategic modification of lead anti-TB compounds, including the functionalization of the isoniazid and rifampicin derivatives. The versatility of click chemistry is further exemplified by its expanding repertoire, which now includes strain-promoted azide-alkyne cycloaddition (SPAAC), thiol-ene reactions, and inverse electron-demand Diels-Alder reactions, collectively providing a robust toolkit for the rational design of novel anti-TB therapeutics and diagnostic tools, particularly significant in addressing the challenges posed by drug-resistant TB strains [21-24].

This review examines the transformative role of click chemistry in tuberculosis research, focusing on its use in drug discovery over the past decade. We critically analyze how click chemistry methodologies have advanced our understanding of TB pathogenesis and contributed to the development of novel therapeutic strategies against drug-resistant *Mycobacterium tuberculosis* strains. Special emphasis is placed on copper(I)-catalyzed azide-alkyne cycloaddition reactions in anti-TB drug development, biomarker detection, and the modification of existing drug scaffolds. Furthermore, this review evaluates emerging click chemistry approaches that show promise in addressing current challenges in TB treatment and diagnosis, providing insight into future directions for combating this persistent global health threat.

## 2. Fundamentals of click chemistry in TB research

### *2.1. Conventional TB drug modification approaches face critical limitations*

Isoniazid, the most widely prescribed antituberculosis agent [23,25], requires KatG-encoded catalase-peroxidase activation to form the inhibitory INH-NAD adduct, where specific molecular geometry and hydrogen bonding networks are [16] synthetic methodologies struggling to maintain critical hydrogen bonding networks while introducing novel functional groups, given the spatial constraints inherent in the mechanism of action of the drug and the target interaction [26].

Rifampicin exhibits significant pH-dependent stability characteristics, demonstrating complex degradation kinetics across physiologically relevant pH ranges. Studies utilizing HPLC-MS/MS analysis reveal that rifampicin undergoes rapid degradation under strongly acidic conditions (pH = 1.2), primarily through hydrolytic cleavage that leads to the formation of 3-formyl rifamycin SV as the predominant degradation product. The stability profile shows marked improvement at pH = 4.5, with optimal stability observed at pH = 6.8, while slightly alkaline conditions (pH = 7.4) initiate a secondary degradation pathway. This pH-dependent degradation pattern significantly influences both pharmaceutical formulation strategies and drug bioavailability profile, necessitating careful consideration in drug delivery system design and stability optimization protocols [27].

The pronounced thermal sensitivity of rifampicin presents significant constraints for chemical modification strategies. The drug exhibits critical instability at temperatures above 40 °C, undergoing oxidative degradation that predominantly produces rifampicin quinone, following the first-order degradation kinetics [28]. This thermal liability poses substantial challenges for conventional synthetic methodologies, which often require elevated temperatures for efficient reactivity [28].

### *2.2. Click chemistry's unique synthetic advantages in TB drug development*

#### *2.2.1. Mechanistic insights into click chemistry*

Click chemistry in the development of TB drugs uses primarily two fundamental cycloaddition approaches (Figure 1). Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and strain-promoted azide-alkyne cycloaddition (SPAAC).

The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, representing the cornerstone of click chemistry applications in TB research, demonstrates remarkable efficacy under physiological conditions, enabling precise molecular modifications of antitubercular compounds. This reaction proceeds through a stepwise mechanism involving the formation of copper(I) acetylide, followed by azide coordination and metallocycle formation, which ultimately produces 1,2,3-triazole and 1,2,4-triazole products with exceptional regioselectivity [29] (Figure 2). The catalytic system, typically employing $CuSO_4$/sodium ascorbate or Cu(I) salts with specialized ligands such as TBTA, ensures rapid reaction kinetics while maintaining biocompatibility [30].

#### *2.2.2. Click chemistry from structural modification to biological applications*

Structural modification of existing TB drugs, particularly isoniazid and ethambutol, where CuAAC enables the precise integration of triazole linkers. These modifications serve two purposes: enhancing lipophilicity to improve mycobacterial cell wall penetration and to provide new pharmacophoric elements that often strengthen binding to target enzymes [31]. The hydrogen bond capabilities of the triazole ring and rigid geometry have been proven to be particularly valuable in optimizing drug-target interactions.

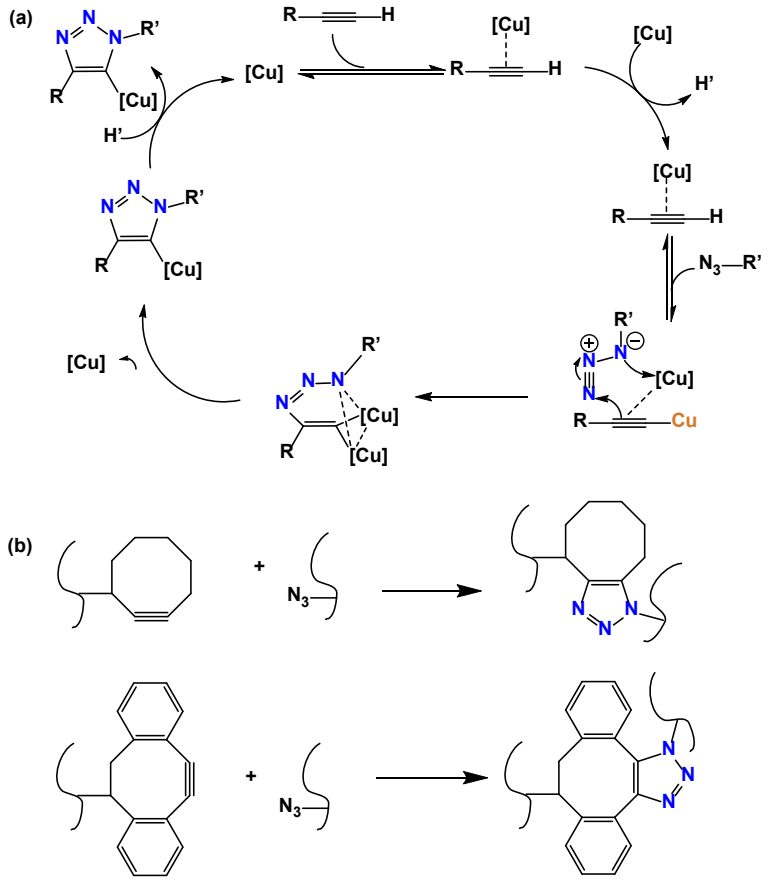


**Figure 2.** (a) Mechanism of the copper-catalyzed azide-alkyne aycloaddition (CuAAC). The diagram illustrates the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) process, showing the formation of 1,2,3-triazoles from azide and alkyne reactants. (b) Mechanism of the strain-promoted azide-alkyne cycloaddition. The figure illustrates the use of the cyclooctyne ring tension to promote 1,3-dipole cycloaddition with azide groups.

CuAAC also facilitates the creation of hybrid molecules, combining TB drugs with other bioactive compounds [32]. This approach has yielded dual-action compounds, where the triazole linker not only connects the pharmacophores but also contributes to the overall biological activity. The synthetic flexibility of CuAAC allows systematic exploration of linker length and positioning, which are critical to optimizing the efficacy of hybrid molecules. The reaction enables the development of conjugated delivery systems, particularly in the creation of targeted nanocarriers [33]. Here, the efficiency of CuAAC in aqueous conditions proves crucial for the surface modification of delivery vehicles, allowing the attachment of targeting ligands and drug molecules while maintaining their biological activity.

The Mubarak H. Shaikh research group employed CuAAC methodology to design and synthesize novel isoniazid-coumarin hybrid molecules. The synthesized compounds demonstrated minimum inhibitory concentrations (MIC) as low as 0.12 μg/mL against M. tuberculosis H37Rv strain. Structure-activity relationship analysis revealed that electron-withdrawing substituents on the coumarin ring enhanced antimycobacterial activity, while electron-donating substituents diminished potency. This investigation exemplifies the successful application of click chemistry in the development of potential antituberculosis agents through the strategic integration of pharmacophoric features of isoniazid and coumarin scaffolds [34].

In mycobacterial systems, the application of click chemistry necessitates careful consideration of reaction parameters, including catalyst selection, pH optimization, and solvent compatibility. The emergence of copper-free alternatives, particularly strain-promoted azide-alkyne cycloaddition (SPAAC) (Figure 1), has addressed concerns about copper toxicity in biological systems, facilitating live-cell applications and intracellular targeting of mycobacterial components. These methodologies have proven instrumental in developing fluorescent probes to study the assembly and metabolic processes of mycobacterial cell walls [35].

Anna Krajczyk's team engineered a series of 5'-O-[*N*-(salicylidene) aminosulfonyl]-2-aryl-8-azido-3-deazaadenosines catalytically catalyzed by copper-free palladium to block the biosynthesis of mycobacteriocin in *Mycobacterium tuberculosis* (Mtb) by inhibiting the essential adenylate lyase MbtA. These modified nucleosides were shown to inhibit MbtA with apparent Ki values ranging from 6.1 to 25 nM and inhibit Mtb growth under iron-deficient conditions with minimum inhibitory concentrations ranging from 12.5 to > 50 μM [36].

The mechanistic versatility of click reactions extends to thiol-ene [37] and [38] chemistries, which have particular relevance in targeting mycothiol-dependent processes in *M. tuberculosis*. These reactions provide complementary approaches for drug modification and conjugation, expanding the synthetic toolkit available for anti-TB drug development. The optimization of these reactions for mycobacterial applications has required a systematic evaluation of reaction kinetics, stability profiles, and biological compatibility, particularly regarding cell wall penetration and intracellular accessibility.

The analytical validation of click chemistry applications in TB research employs sophisticated instrumentation, including [39], advanced NMR techniques [40], ultrasonic irradiation-assisted method [41], and specialized chromatographic methods [42]. These analytical approaches ensure precise

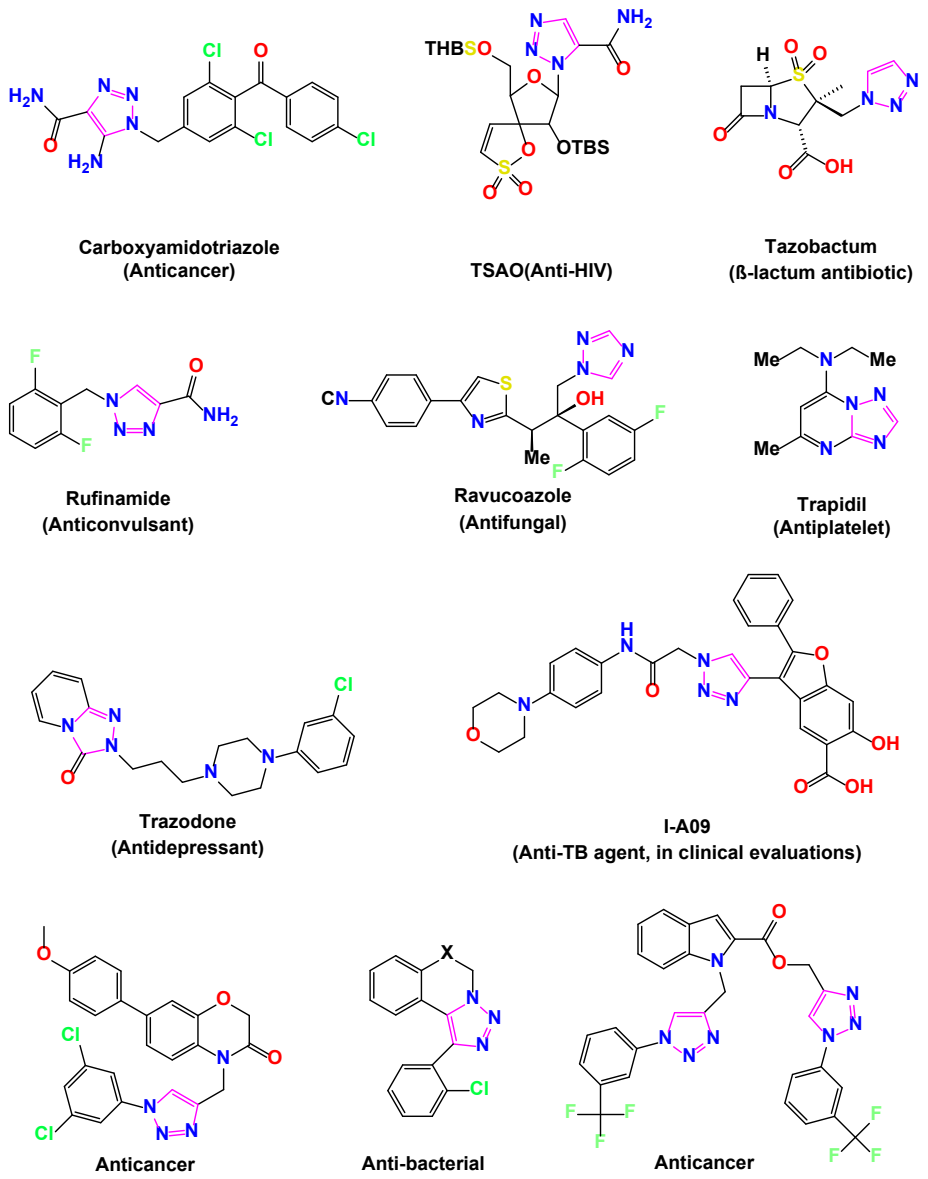


**Figure 3.** Structure of various triazole-appended potent drug candidates against various diseases.

characterization of click-chemistry products and their biological effects on mycobacterial systems, supporting both drug development and mechanistic studies in TB research.

## 3. Triazole heterocycle as a valuable scaffold in drug discovery

Triazole, a fundamental building block, is a five-member heterocyclic compound with three nitrogen atoms and exists in isomeric forms known as 1,2,3-triazole and 1,2,4-triazole. Natural and synthetic molecules that have a triazole framework attract medicinal chemists due to their enormous therapeutic potential (Figure 3) such as antifungal [43], antivirus [10,23], anticancer [44-46], antitubercular [47], antibacterial [48,49], anticonvulsant [50] and anti-inflammatory [51].

## 4. 1,2,3-Triazole hybrids as potent anti-TB agents

It is well known that 1,2,3-triazoles and their derivatives possess a wide range of pharmacological activities, including antituberculosis activity. Molecular hybridization of 1,2,3-triazoles with various pharmacophores may provide novel, effective, and safe drug candidates to combat tuberculosis. This section will introduce various emerging 1,2,3-triazole compounds.

### *4.1. Azole-1,2,3-triazole hybrids*

A promising strategy involves the combination of nitroimidazoles with 1,2,3-triazoles, given that nitroimidazoles and related compounds show broad antimicrobial activity against mycobacteria, parasites, and both Gram-positive and Gram-negative anaerobic bacteria [52] (Figure 4). Following this approach, a structural modification of the delamanid was performed where rings D and E were substituted with a 1,2,3-triazole and aryl system. The resulting 1,2,3-triazole-imidazo-oxazole hybrid compound showed significant antitubercular activity against MTB H37Rv with MIC values ranging from 0.23 to 8.58 μM [53].

Similarly, the 1, 2, 3-triazole-imidazo[2, 1-b][1, 3, 4]thia-diazole hybrids demonstrated notable antitubercular activity against MTB-H37Rv (ATCC27294), with MIC values ranging from 3.12 to 50.0 μg/mL.

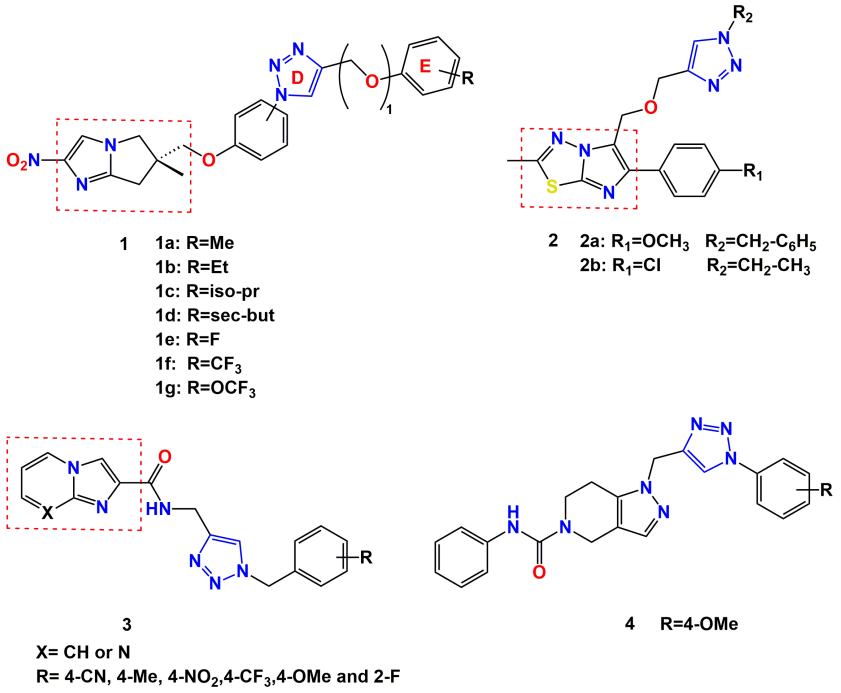


**Figure 4.** Structure of some 1,2,3-triazole-azole hybrids (1a-g), 2a and 2b, 3 and 4 with antitubercular activity.

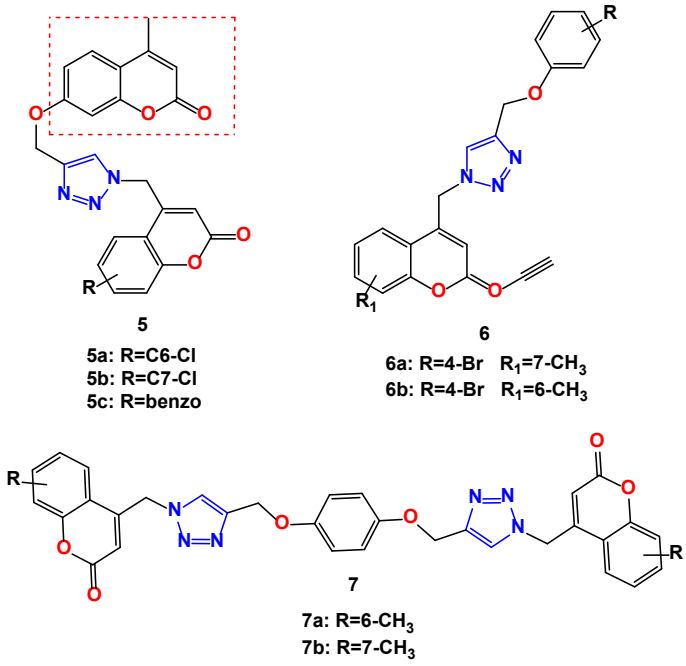


**Figure 5**. Structures of some 1,2,3-triazole-coumarin hybrids (5a-c, 6a-b and 7a-b) as potent antitubercular agents.

Structural modification of the delamanid, replacing rings D and E with 1,2,3-triazole and aryl systems, yielded active hybrid 1. The triazole group showed optimal activity at C-ring positions 3 or 4, with -F or -OCF3 substituents enhancing potency. The lead compound 1a demonstrated strong *in vivo* efficacy and synergy with first-line TB drugs [53]. Two compounds in particular, hybrids 2a and 2b, showed potency equivalent to the first-line drug ethambutol, all with MIC values of 3.12 μg/mL. Structure-activity relationship (SAR) studies revealed that biological activity could be optimized through appropriate modification of substituents R1 and R2 on the hybrid scaffold. Importantly, cytotoxicity studies of hybrids 2a and 2b using NIH 3T3 mouse embryonic fibroblasts demonstrated their safety profile, showing no toxicity to normal cells [54]. The modification of Zolpidem yielded hybrid compounds 3, incorporating 1,2,3-triazole and imidazo[1,2-a] pyridine scaffolds. Compounds 3 showed improved anti-TB activity (MIC 1.56 μg/mL) versus Zolpidem and Pyrazinamide (both MIC 3.12 μg/mL), with molecular docking confirming InhA binding through Tyr158 [55]. Pyrazolo[4,3-c]pyridine-5(4H)-carboxamide hybrids 4 showed activity against MTB strains (MIC 24.72-200 μM), including drug resistant Spec. 210 and sensitive Spec. 192. The lead compound 4 demonstrated

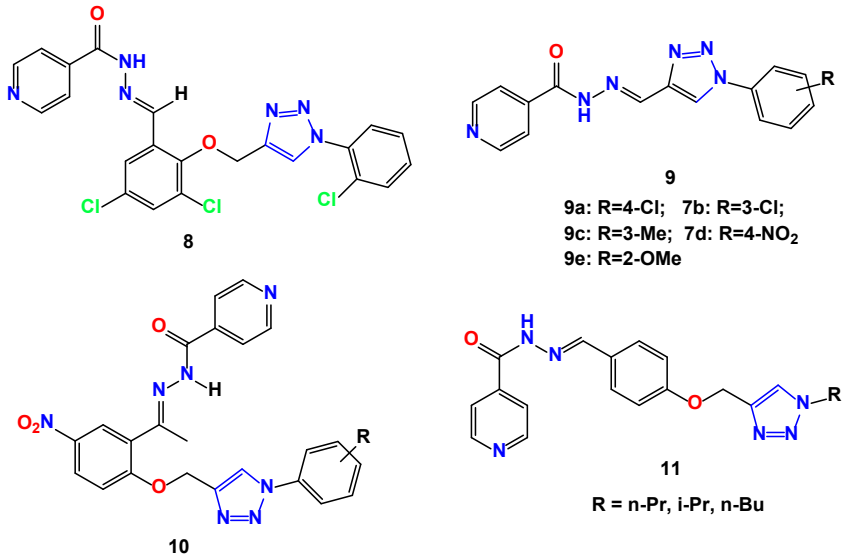


**Figure 6.** Structures of INH-1,2,3-triazole hybrids 8, 9, 10 and 11 as potential antitubercular agents.

potent MTB-PS inhibition ($IC_{50}$ 1.01 μM), good anti-TB activity (MIC 24.72 μM), and low toxicity to RAW 264.7 cells [56].

### *4.2. Coumarin/chromene-1,2,3-triazole hybrids*

Coumarin, structurally known as 2*H*-1-benzopyran-2-one, represents a key scaffold found in numerous complex natural products that exhibit various biological activities [57]. The strategy of combining the coumarin framework with 1,2,3-triazole heterocycles through molecular hybridization offers the potential to develop new anti-TB agents with enhanced efficacy and safety profiles (Figure 5). For example, 1,4-disubstituted bis-chromene-1,2,3-triazole hybrids 5a, 5b, and 5c (Figure 4) showed promising *in vitro* potency against the *Mycobacterium tuberculosis* H37Rv strain with MIC values of 6.25 μg/mL, comparable to the reference drug streptomycin (MIC: 6.25 μg/mL) [58]. The introduction of benzo and chloro substituents demonstrated enhanced antimycobacterial activity. Comparative analysis revealed that these hybrids showed superior activity compared to 2*H*-chromen-2-one compounds containing hydrazone units (MIC: 50-100 μg/mL) and benzyl triazoles (MIC: 16 μg/mL), validating the effectiveness of this molecular hybridization strategy for developing potent anti-TB agents. In particular, bis-chromenyl triazole hybrids exhibited significantly higher potency (MIC: 0.2-12.5 μg/mL) against MTB H37Rv compared to their monochromenyl triazole counterparts (MIC: 50-100 μg/mL), highlighting the beneficial effect of incorporating two triazole units along with the coumarin core for improved antimycobacterial activity (6a, 6b, 7a, 7b) [59].

### *4.3. Isoniazid-1,2,3-triazole hybrids*

Isoniazid (INH) and 1,2,3-triazole compounds share a similar mechanism of action through inhibition of the bacterial cell wall. Therefore, the combination of these pharmacophores into hybrid molecules presents an opportunity to develop novel antitubercular agents with enhanced activity [60]. The isoniazid-1,2,3-triazole hybrid 6 (Figure 6) exhibited anti-tubercular activity against the MTB-H37RV strain with an MIC value of 1.56, while showing minimal toxicity towards RAW 264.7 macrophages. Two key enzymes involved in myco-bacterial cell wall synthesis and bacterial growth are enoyl-ACP reductase (InhA) and DNA gyrase. Molecular docking studies revealed that compound 8 demonstrates a strong binding affinity for DNA gyrase and InhA, suggesting its potential as a promising lead compound for the development of mechanism-based antituberculosis agents [61]. Hybrids 9a-e demonstrated favorable safety profiles with low cytotoxicity ($MDL_{50}$ > 1000 μg/mL) when tested against both hepatoma HepG2 liver cells and BGM kidney cells. Their high selectivity index suggests that these compounds could be promising candidates for the development of safe and effective antitubercular agents [62]. Similarly, INH-incorporated triazole compounds 8 showed notable antitubercular activity against *M. tuberculosis* H37RV strain (MIC: 0.78-3.125 μg/mL) while demonstrating no toxicity to RAW 264.7 macrophages at concentrations up to 25 μg/mL. Molecular modeling analysis revealed that these hybrids 10 interact with InhA's active sites through a complex network of bonded and non-bonded interactions. Further optimization of these compounds could provide a foundation for the development of InhA-specific antitubercular agents [63]. Hybrid 11 showed potent anti-TB activity (MIC99 0.39-0.78 μM) against the H37Rv strain with no toxicity to THP-1 cells at 50 μM [64].

### *4.4. 1,2,3-Triazole-Quinoline/dihydroquinoline hybrids*

Quinoline serves as a core scaffold in medicinal chemistry [65]. A significant breakthrough occurred in 2013 when bedaquiline, the first drug based on diarylquinoline, received FDA approval to treat pulmonary MDR-TB. Bedaquiline works by inhibiting mycobacterial ATP synthase, preventing M. tuberculosis growth [66]. However, it has several limitations, including side effects (nausea, chest pain, joint pain, headache) and stereochemical constraints, since only the 1R,2S isomer shows activity. To address these limitations, the molecular hybridization strategy combining quinoline with 1,2,3-triazole scaffolds was used to develop more potent and selective analogues (Figure 7).

Quinoline-4-yl-1,2,3-triazole derivatives containing amide 12, sulfonamide 13, and amidopiperazine 14 moieties demonst-rated significant antimycobacterial activity *in vitro*. These compounds were effective against multiple mycobacterial strains, including *M. tuberculosis* H37Rv, *M. smegmatis*, and *M. fortuitum*, with MIC values in the range of 0.625 to 10 μg/mL [67]. SAR analysis of 1,2,3-triazole-dihydroquinoline hybrids 12 (MIC: 1.56-25 μg/mL) confirmed the importance of substituents attached to the 1,2,3-triazole ring.

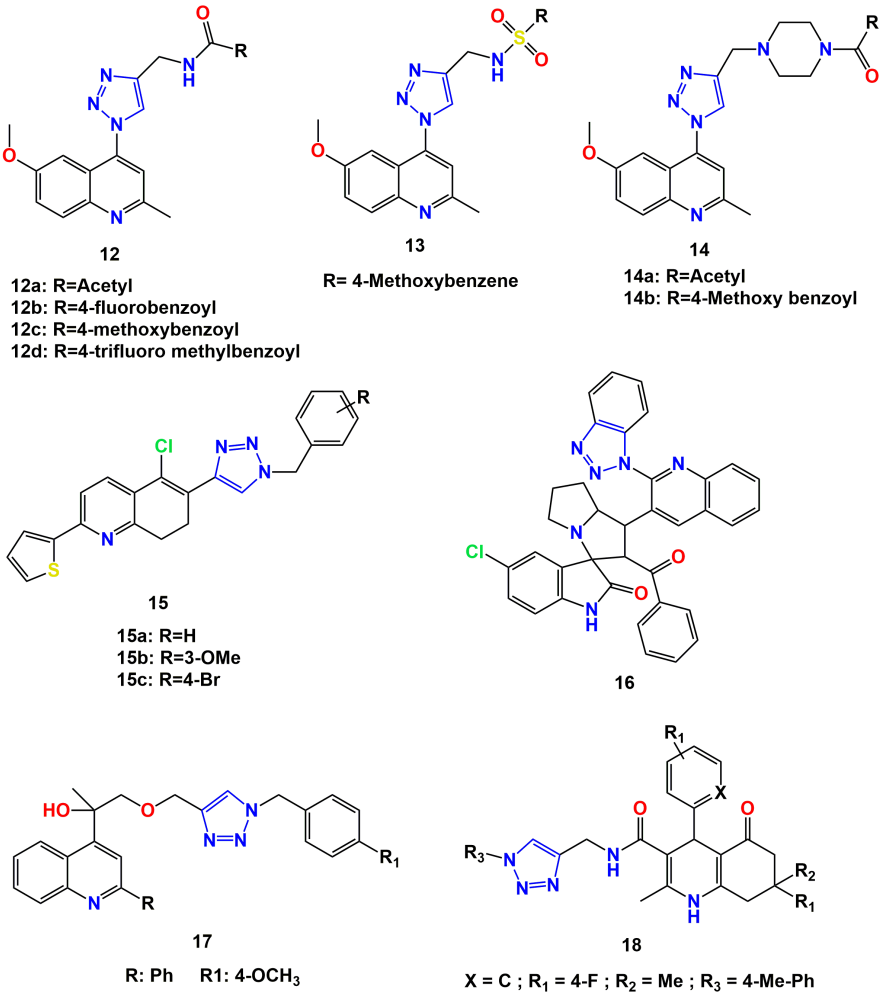


**Figure 7.** 1,2,3-Triazole-quinoline/dihydroquinoline hybrids 12-18 as potent antitubercular agents.

Hybrid 15a (MIC: 1.56 μg/mL) emerged as a significant compound in this series with low cytotoxicity against HEK-293T cell lines [68]. Related spiro-hybrid systems 16 (MIC: 1.13-25.0 μM) showed promising antitubercular activity against *M. tuberculosis* H37Rv (ATCC27294) compared to the standard drug ethambutol (MIC: 7.64 μM), while maintaining low toxicity against RAW-264.7 cell lines. The presence of electron-withdrawing groups (-F, -Cl, -Br) at the 4th position of the benzoyl system in hybrid 16 proved crucial for activity. Additionally, substitution at the fifth position of the isatin moiety in 16 also influences its biological activity [69].

The derivative 17 has been tested for *in vitro* antibacterial activity against *Mycobacterium tuberculosis* H37Rv, Escherichia coli, Proteus mirabilis, Bacillus subtilis and Corynebacterium diphtheriae, showing good antibacterial activity and excellent to good antituberculosis activity, with MIC values of 62.5 and 3.33 μM, respectively. The compound also achieved high docking scores in two targets, 8.291 and 8.885 Kcal/mol. Molecular dynamics studies investigated the structural and dynamic transitions of Staphylococcus aureus DNA gyrase (PDB code 2XCT) and *Mycobacterium tuberculosis* DNA gyrase (PDB code 5BS8) at the atomic level. The results indicated that throughout the MD simulation, the residues in the active binding pockets of the Staphylococcus aureus and *Mycobacterium tuberculosis* DNA gyrase proteins that interacted with compound 17 remained relatively consistent, reflecting the conformational stability of the respective complexes [70].

Compound 18 has been tested for *in vitro* antibacterial activity against *Mycobacterium tuberculosis* H37Rv, which shows excellent antituberculosis activity with an MIC value of 6.24 μg/mL. This compound also showed promising antibacterial activity against *Escherichia coli* and other Gram-positive bacteria, with MIC values in the low micromolar range. **18** achieved high docking scores on two targets, 8.291 and 8.885 Kcal/mol, indicating a strong affinity for the active sites of the enzymes. Molecular dynamics studies revealed that throughout the MD simulation, the residues in the active binding pockets of Staphylococcus aureus DNA gyrase (PDB code 2XCT) and *Mycobacterium tuberculosis* DNA gyrase (PDB code 5BS8) that interacted with compound 18 remained relatively consistent, reflecting the conformational stability of the respective complexes, which underscores/highlighting ? its potential as a leading candidate for further development in tuberculosis therapeutics [71].

### *4.5. 1,2,3-Triazole-quinolone hybrids*

Quinolones represent a significant and widely studied class of traditional antibiotics known for their broad-spectrum antibacterial activity. These compounds are particularly effective against a variety of bacterial infections due to their mechanism of action, which involves inhibiting bacterial DNA gyrase and topoisomerase IV enzymes essential for DNA replication and repair. Over the years, quinolones have been extensively developed and optimized, resulting in various

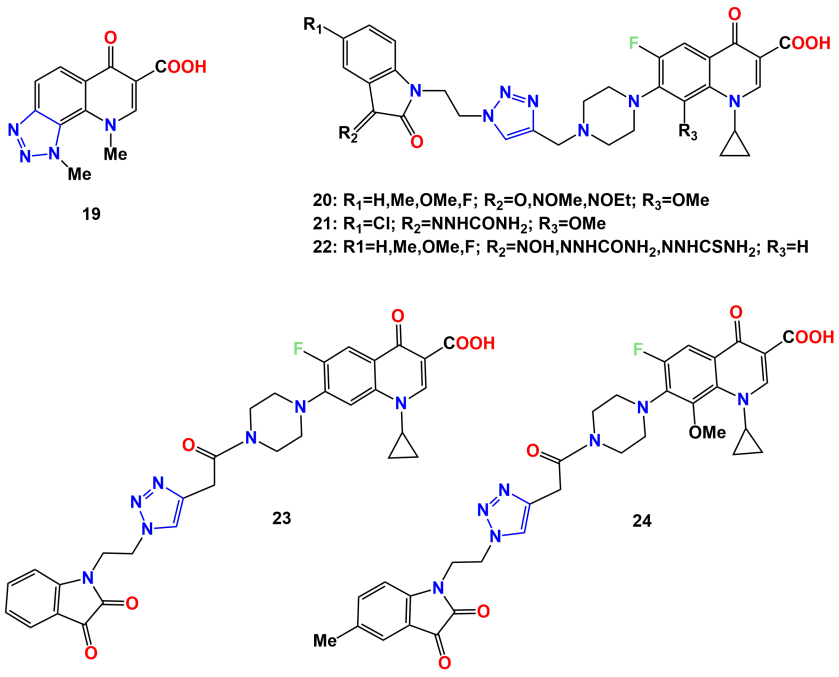


**Figure 8.** Structure of some 1,2,3-triazole-quinolone hybrids 17-22 as potential anti-TB activity.

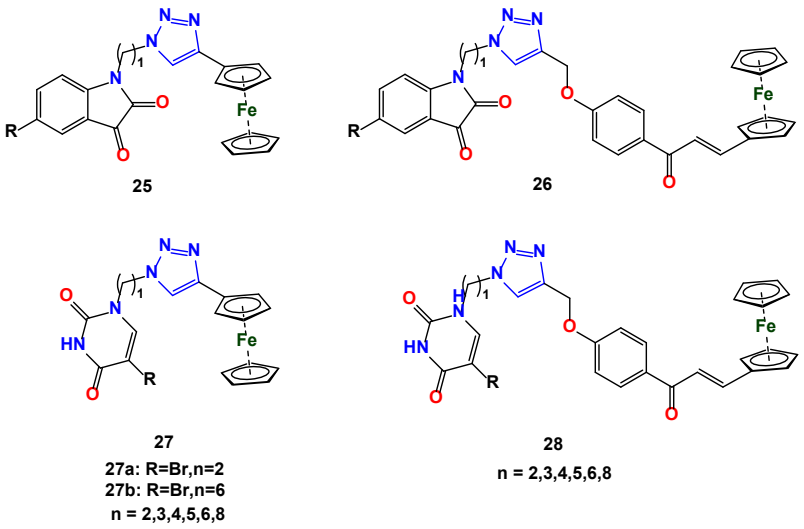


**Figure 9.** Structure of some antitubercular active 1,2,3-triazole-ferrocene hybrids 25-28.

generations that address Gram-positive and Gram-negative bacteria [72]. Their versatility and effectiveness have established quinolones as valuable agents in the treatment of respiratory, urinary tract, gastrointestinal, and skin infections, making them indispensable in modern antibiotic therapy. Several fluoroquinolones, including ciprofloxacin (CPFX), ofloxacin, gatifloxacin (GTFX), moxifloxacin (MXFX), and levofloxacin, have demonstrated exceptional activity profiles. Some of these compounds have been designated by the WHO as second-line treatments for tuberculosis [73]. Fluoroquinolones function by inhibiting type II topoisomerases (specifically topoisomerase IV and DNA gyrase) in bacteria, making them attractive candidates for antitubercular drug development [74]. Since the penetration of fluoroquinolones in the bacterial cell wall depends on lipophilicity, enhancing the lipophilic character in position C-7 can lead to improved antitubercular activity [75].

Given the notable characteristics of 1,2,3-triazole rings under physiological conditions, combining this framework with quinolones offers potential for the development of anti-tubercular drug candidates with improved therapeutic efficacy (Figure 8). For example, compound 19, which features a methyl group at the N-9 position, demonstrated significant in vitro antituberculosis activity (MIC: 0.5 μg/mL) against both M. tuberculosis H37Rv and H37Ra strains, while showing a favorable cytotoxicity profile against MT4 cells ($CC_{50}$ > 100 μg/mL).

1*H*-1,2,3-triazole-linked 8-OMe-CPFX-isatin hybrids 20 showed enhanced activity against both MTB-H37Rv and MDR-TB compared to ciprofloxacin (CPFX), 8-OMe-CPFX and rifampicin (RIF). SAR studies revealed that the C-5 substituents on isatin followed the potency order -F > -H > -Me > -OMe, while for the imine/carbonyl position, methyloxime ≥ ethyloxime > carbonyl group. Hybrid 21 demonstrated significantly higher activity than CPFX and 8-OMe-CPFX, matching RIF's potency.

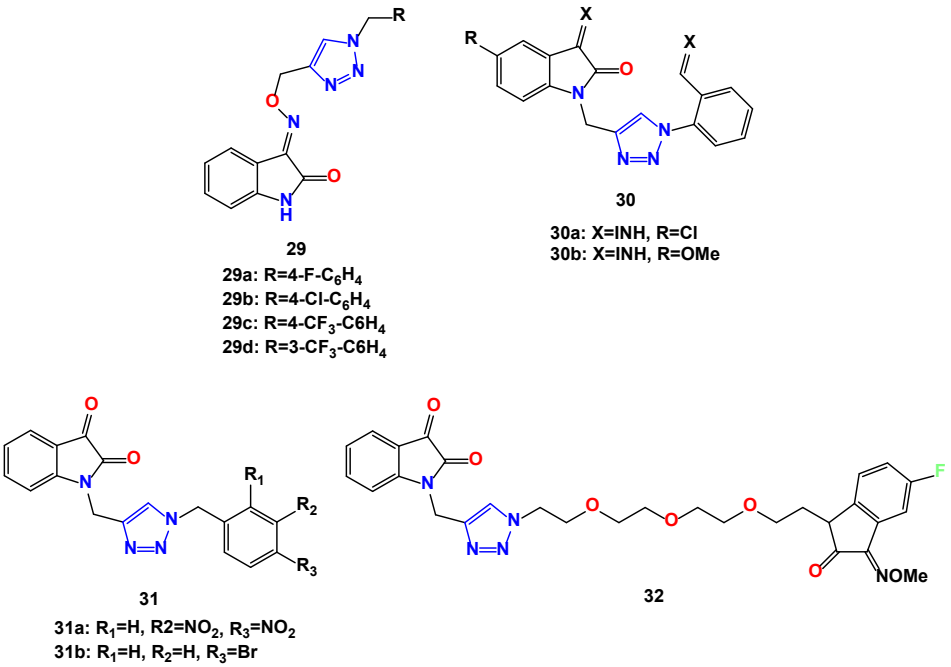


**Figure 10.** 1,2,3-Triazole-Isatin hybrids as a potent antitubercular agent 29-32.

The derivative 22 showed that replacing 8-OMe with H on the CPFX moiety maintained similar activity levels [76-78]. Compound 23 showed comparable potency to first-line anti-TB drugs against MTB-H37Rv and demonstrated significantly higher activity against MDR-TB, suggesting a novel mechanism for treating drug-resistant TB. While these hybrids maintained acceptable cytotoxicity profiles, their toxicity was somewhat higher than that of ciprofloxacin [79]. Acetyl-linked gatifloxacin-1,2,3-triazole-isatin hybrids 24 demonstrated strong activity against H37Rv and two MDR-MTB strains: MDR-MTB1 and MDR-MTB2, showing favorable activity profiles compared to the reference compounds gatifloxacin (GTFX), rifampicin (RIF), and isoniazid (INH) [80].

### *4.6. 1,2,3-Triazole-ferrocene hybrids*

Ferrocene-1,2,3-triazole hybrids offer a highly promising approach to the development of new antitubercular drug candidates. These hybrid compounds leverage the unique redox properties of ferrocene alongside the bioactivity of the 1,2,3-triazole ring, creating a potent framework to target *Mycobacterium tuberculosis*. By combining these distinct molecular characteristics, ferrocene-1,2,3-triazole hybrids have shown significant potential to enhance antimycobacterial activity, making them a valuable focus in the search for effective treatments against tuberculosis, including drug resistant strains (Figure 9). Compounds 25 and 26 (MIC: 107-463 μM) showed moderate to significant antitubercular activity against *M. tuberculosis* mc2 7000, compared to the standards ampicillin, ethambutol, isoniazid, and rifampicin (MIC: 72-144, 90.36, 2.92, and 0.12 μM, respectively). The studies confirmed that isatin moieties contributed more positively to activity than β-lactam groups [81]. The 1,2,3-triazole-linked uracil-ferrocene hybrids 27 and 28 were generally inactive at 50 μg/mL, although ferrocene improved activity compared to N-alkylazido-uracils, while ferrocenyl-chalcone decreased it. The SAR showed that activity depends on C-5 substituents and spacer length. Compounds 25a, b, with C-5 bromine and spacer lengths n = 2 or 6, were most active (MIC 27 μg/mL) and showed no toxicity to HeLa cells at 100 μg/mL [82].

### *4.7. 1,2,3-Triazole-Isatin hybrids*

1*H*-indole-2,3-dione (Isatin) represents a privileged scaffold, and its hybrids with 1,2,3-triazoles have shown promise as new antitubercular agents (Figure 10). Isatin-oxime ether-triazole hybrids that met drug-likeness criteria demonstrated significant activity against *M. tuberculosis* H37Rv strain, with compounds 29a-d showing promising MIC values and good selectivity indices [83].

Hybrids containing an isoniazid core showed superior activity against *M. tuberculosis* mc2 6230 compared to those with semicarbazide or pyrazine-2-carbohydrazide units, while maintaining low cytotoxicity. Notably, hybrids 30a-b, featuring isoniazid units and electron-donating groups at isatin's C-5 position, emerged as the most potent compounds, although further optimization is needed for INH-resistant strains [84]. Isatin-1,2,3-triazole hybrids 31 showed activity against MTB H37Rv, with activity influenced by phenyl ring substitution patterns. Compounds 31a and 31b ($IC_{90}$: 7.56 and 8.09 μg/mL) were most active, although less potent than rifampicin ($IC_{90}$: 0.043 μg/mL) and isoniazid ($IC_{90}$: 0.075 μg/mL) [85]. 1,2,3-triazole-isatin **32**, connected to isatin through tetraethylene glycol, showed activity against H37Rv and MDR-TB (MIC: 64-512 μg/mL). N-1 aryl substitution-controlled lipophilicity, while C-5 fluorination enhanced activity. The activity of the C-3 substituent was classified as: -NOMe > -NOEt > -$NNHCONH_2$ > –O > –NOH. Hybrid 30 (MIC: 128 μg/mL H37Rv, 64 μg/mL MDR-TB) was 8 times more potent than isoniazid against MDR-TB [86].

### *4.8. 1,2,3-Triazole-furan hybrids*

Furans, particularly nitrofurans, represent significant antimicrobial pharmacophores due to their activation by nitroreductase enzymes in microorganisms. Therefore, the combination of nitrofuran scaffolds with 1,2,3-triazoles could yield promising new antitubercular candidates [87] (Figure 11).

The furan/nitrofuran-1,2,3-triazole hybrids 33 showed effective activity against *M. tuberculosis* H37Rv, comparable to ethambutol.

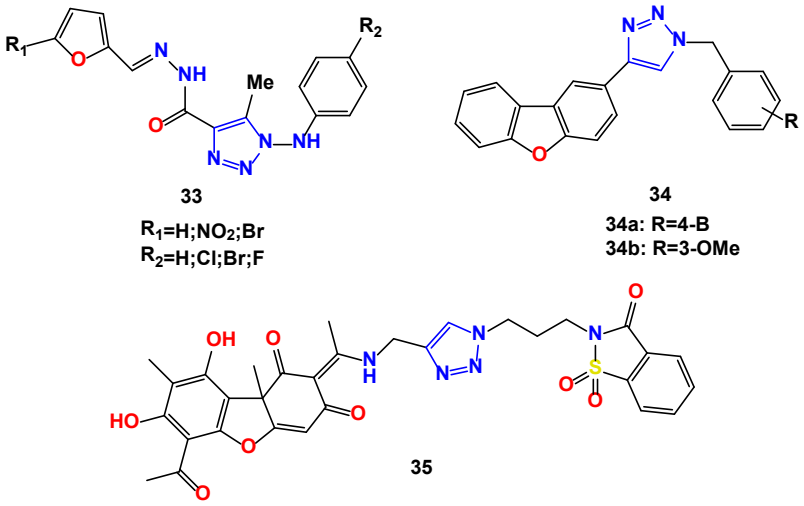


**Figure 11**. Chemical structures of 1,2,3-triazole-furan hybrids 33-35.

SAR studies demonstrated that nitrofuran variants were more potent than furan hybrids, with increased activity observed in compounds with lower lipophilicity and smaller R1 substituents [88]. Hybrids 34a, b emerged as the most effective compounds in the series, demonstrating high potency and low cytotoxicity [89]. The SAR analysis of hybrid 32 showed that the electron-donating groups (like -OMe) provided better activity compared to the electron-withdrawing groups (such as -$NO_2$, -COOMe). (+) Ustic acid, a lichen metabolite, shows anti-TB activity. Ustic acid 35 (MIC: 2.5 μM) demonstrated enhanced potency through the substitution of fluorine and the incorporation of cyclic sulfonamide in the usnic acid scaffold, suggesting potential as a lead compound [82].

### *4.9. Miscellaneous 1,2,3-triazoles*

Triclosan functions as an antibacterial and antifungal agent commonly found in various consumer and medical products. As an antitubercular compound, it directly inhibits the InhA enzyme without requiring KatG activation, distinguishing it from some other TB drugs [90]. Poor bioavailability limits the use of triclosan as an antitubercular agent. Molecular hybridization with pharmacophores such as 1,2,3-triazoles can enhance its biological activity. Researchers have explored various modifications of these hybrids to study how substituent properties, phenyl groups, alkyl chain length, and triazole link positions affect their efficacy [91] (Figure 12).

The SAR analysis revealed that the methylenic links between the triazole and aromatic frameworks reduced the activity. On the contrary, increasing the length of the alkyl chain increased the potency, with optimal activity observed in compounds containing a 12-carbon chain (36, MIC: 0.25 μg/mL) [92]. 1,2,3-Triazoles combined with tricyclic frameworks showed promising anti-TB activity, with potency following the order: dibenzo[b,d]thiophene > dibenzo[b,d] furan > 9-methyl-9*H*-carbazole. Hybrids 37a-b demonstrated high potency with minimal cytotoxicity against multiple cell lines, showing superior activity compared to pyrazinamide and ethambutol [93,94]. Phenanthridine-triazole hybrids 38 showed notable activity against M. tuberculosis H37Rv. SAR studies revealed that para-OMe substituents enhanced activity 15 times compared to meta-substitution. The introduction of a sulfonyl group between triazole and phenyl rings significantly improved activity, likely because of hydrogen bond acceptability. Compound 38a demonstrated superior potency compared to hybrids 38b,c [95].

Linezolid, an oxazolidinone-class antibiotic with a MIC of 1.0 μg/mL, is recognized for its role in inhibiting protein synthesis and has been endorsed by the WHO for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis [96]. However, the prolonged use of oxazolidinones is associated with adverse effects, underscoring the urgent need to develop novel compounds within this class that exhibit improved efficacy. In this context, a 1,2,3-triazole oxazolidinone hybrid, designated as compound 39, has been synthesized by modifying the morpholine ring of linezolid and replacing the amide group with its bioisosteric 1,2,3-triazole. This modification resulted in a compound exhibiting potent activity against the M. tuberculosis H37Rv strain, with a reduced MIC of 0.5 μg/mL [97]. Furthermore, a diarylpyrrole-oxazolidinone-1,2,3-triazole hybrid, known as compound 40, has demonstrated significant antibacterial activity against M. tuberculosis H37Rv, M. tuberculosis RifR, and M. tuberculosis XDR, with MIC values of 2.0, 4.0, and 8.0 μg/mL, respectively [98]. These hybrid compounds have also shown nontoxicity against mouse macrophage cells (J-774A), with a selectivity index (SI) greater than 10, suggesting their potential as leads for the optimization of new antitubercular drugs. Additionally, a simple 1,2,3-triazole derivative, compound 41, has shown notable activity against the M. tuberculosis H37Rv strain, with a MIC of 3.75 μg/mL, which is comparable to the activity of the standard anti-TB drug, isoniazid [99]. This finding underscores the potential of these chemical modifications to improve the efficacy of antitubercular agents and warrants further exploration for the development of more effective tuberculosis therapies.

The 1,4-disubstituted-1,2,3-triazolyl fatty esters, specifically compounds 42a and 42b, with MIC values of 1.9 and 1.7 μM respectively, have demonstrated significant anti-tuberculosis activity against the M. tuberculosis H37Rv strain, as reported in reference [100]. Structure-activity relationship (SAR) analysis has indicated that the length of the alkyl chain attached at the fourth position of the triazole ring plays a key role in determining the activity of the compounds. Additionally, ester derivatives have been observed to exhibit higher potency compared to those of their corresponding acid or alcohol forms. Furthermore, the study has shown that 1,4-substituted triazoles possess a superior antituberculosis potency over their 1,5-substituted counterparts. These findings underscore the importance of structural modifications in enhancing the efficacy of antituberculosis agents.

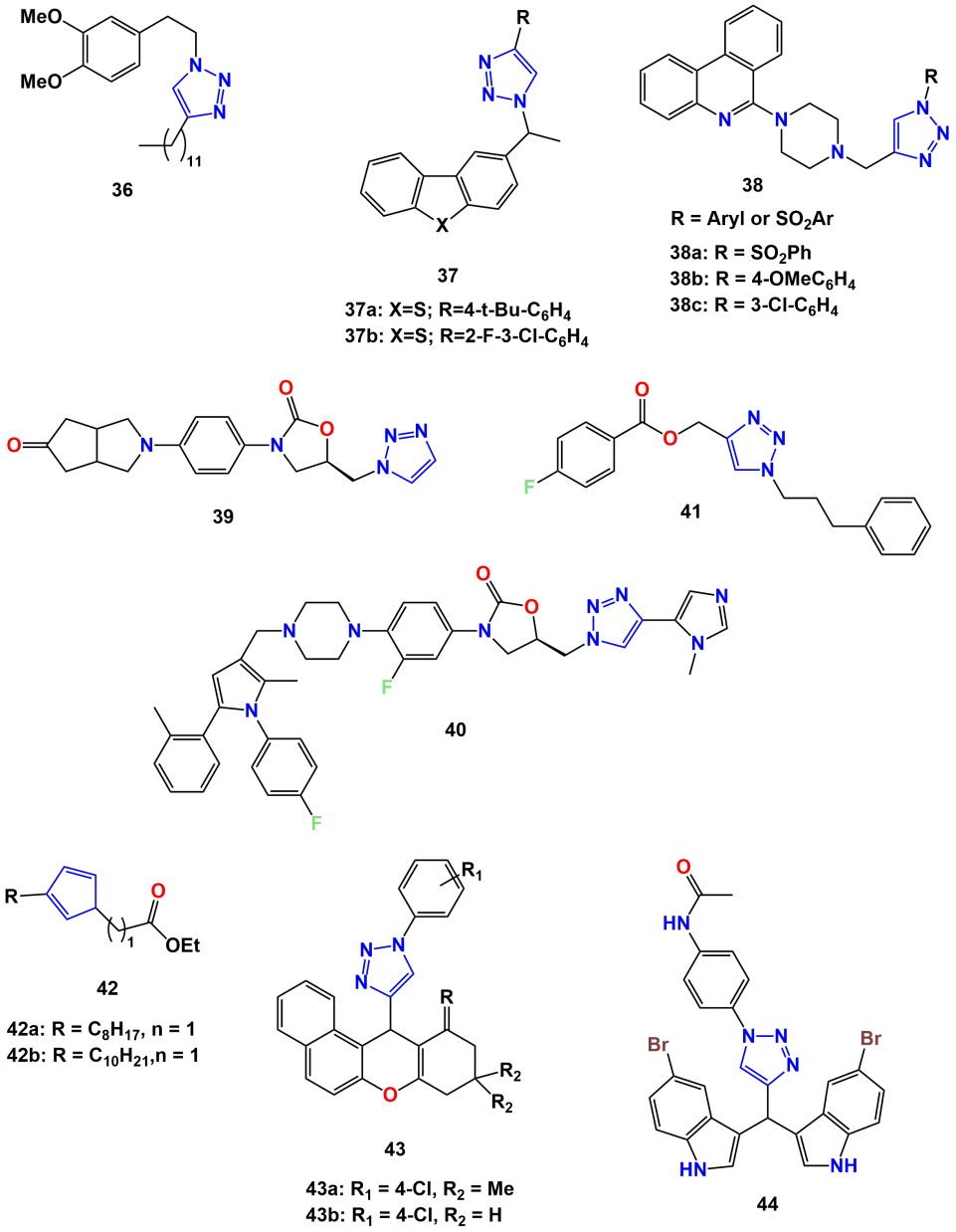


**Figure 12.** Structure of some miscellaneous 1,2,3-triazole hybrids 36-44 as potential antitubercular activity.

Compounds 43a and 43b, which are 1,2,3-triazolyl xanthenones, have shown a range of modest to significant antituberculosis activity against the M. tuberculosis H37Rv strain, with minimum inhibitory concentrations (MICs) ranging from 3.125 μg/mL to ≥25 μg/mL, and have been found to be cytotoxic against HEK cell lines, as documented in reference [101]. Structure-activity relationship (SAR) studies have highlighted that substitution at the 4-position (specifically 4-Cl and 4-OMe) on the triazole ring (designated as the R1 position) significantly influences the potency of the compounds. The MIC values of the hybrid compounds 43a and 43b, both at 3.125 μg/mL, have confirmed that an R1 substitution of 4-Cl is optimal for activity. Furthermore, it has been observed that the presence of methyl groups on the 1,3-cyclodione moiety does not affect the potency of these compounds. These insights into the structure-activity relationship are crucial for the design of more effective antituberculosis agents.

The 1,2,3-triazole-linked diindolylmethane derivative, compound 44, has exhibited moderate to significant activity against *Mycobacterium tuberculosis* H37Rv, affecting both the dormant and active stages of the bacteria with an $IC_{50}$ of up to 1.0 μg/mL, as reported in the reference [102]. This hybrid compound was particularly potent, with $IC_{50}$ values of 1.0 μg/mL against the active state and 3.0 μg/mL against the dormant state of tuberculosis.

Structure-activity relationship (SAR) analysis of these hybrid compounds has indicated that electron-withdrawing groups (EWGs), such as -$NO_2$ or halogen atoms (-X), generally enhance activity, while electron-donating groups (EDGs), such as -Me or -OMe, tend to reduce the bioactivity. Furthermore, the position of the substituents on the triazole ring significantly influences the potency, with the order of activity being 2-$NO_2$ > 3-$NO_2$ > 4-$NO_2$ versus both the active and dormant forms of M. tuberculosis H37Rv. These findings provide valuable insights for the optimization of antituberculosis agents.

## 5. Conclusions

Molecular hybridization of 1,2,3-triazoles with bioactive scaffolds represents a crucial strategy for developing novel antitubercular agents. The incorporation of triazoles with pharmaceutically active frameworks such as azoles, coumarin/chromene, isoniazid, quinoline/dihydroquinoline, Quinolone, ferrocene, isatin, furan, and others has yielded compounds with enhanced efficacy and improved safety profiles compared to those of parent molecules.

This review covers the innovations of the last decade in triazole-based antitubercular drug development, highlighting significant advances in both *in vitro* and *in vivo* studies. The hybridization approach has successfully opened new avenues for the development of potent antitubercular agents, providing medicinal chemists with valuable insights for rational drug design.

Comprehensive SAR studies have illuminated the optimal structural features, guiding the selection of substituents and scaffolds to maximize therapeutic potential. These insights facilitate the development of compounds targeting both drug-sensitive and resistant tuberculosis strains (MDR and XDR-TB), including cases complicated by immunosuppressive conditions.

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## Abbreviations

SAR: Structure-activity relationship; MDR-TB: Multiple-drug-resistant tuberculosis; XDR-TB: stands for Extensively Drug-Resistant Tuberculosis; CuAAC: Copper(I)-catalyzed azide-alkyne cycloaddition; SPAAC: Strain-promoted azide-alkyne cycloaddition; INH: Isonicotinic acid hydrazide; NAD: Nicotinamide Adenine Dinucleotide; MIC: Minimum inhibitory concentrations; Mtb: *Mycobacterium tuberculosis*; MbtA: Mycobactin biosynthesis protein A; MTB-PS: *Mycobacterium tuberculosis* Pantothenate Synthetase; InhA: Enoyl-ACP Reductase; $IC_{50}$: Half maximal Inhibitory Concentration; $MDL_{50}$: Median Lethal Dose; CPFX: ciprofloxacin; GTFX: gatifloxacin; MXFX: moxifloxacin; RIF: rifampicin; $IC_{90}$: 90% Inhibitory Concentration; KatG: Catalase-peroxidase.

## CRediT authorship contribution statement

Conceptualization: Paolo Coghi; Methodology: Ren Zimo; Software: Ren Zimo; Validation: Ren Zimo; Formal Analysis: Ren Zimo; Resources: Ren Zimo; Data Curation: Ren Zimo; Writing - Original Draft: Ren Zimo; Writing - Review and Editing: Ren Zimo and Paolo Coghi; Visualization: Paolo Coghi; Funding acquisition: Paolo Coghi; Supervision: Paolo Coghi; Project Administration: Paolo Coghi.

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## References

[1]. Tripathi, R. P.; Tewari, N.; Dwivedi, N.; Tiwari, V. K. Fighting tuberculosis: An old disease with new challenges. *Med. Res. Rev.* **2005**, *25* (1), 93–131.
[2]. Bagcchi, S. WHO's Global Tuberculosis Report 2022. *Lancet Microbe.* **2023**, *4* (1), e20.
[3]. Furin, J.; Cox, H.; Pai, M. Tuberculosis. *Lancet* **2019**, *393* (10181), 1642–1656.
[4]. Dheda, K.; Gumbo, T.; Maartens, G.; Dooley, K. E.; McNerney, R.; Murray, M.; Furin, J.; Nardell, E. A.; London, L.; Lessem, E.; Theron, G.; van Helden, P.; Niemann, S.; Merker, M.; Dowdy, D.; Van Rie, A.; Siu, G. K.; Pasipanodya, J. G.; Rodrigues, C.; Clark, T. G.; Sirgel, F. A.; Esmail, A.; Lin, H.; Atre, S. R.; Schaaf, H. S.; Chang, K. C.; Lange, C.; Nahid, P.; Udwadia, Z. F.; Horsburgh, C. R.; Churchyard, G. J.; Menzies, D.; Hesseling, A. C.; Nuermberger, E.; McIlleron, H.; Fennelly, K. P.; Goemaere, E.; Jaramillo, E.; Low, M.; Jara, C. M.; Padayatchi, N.; Warren, R. M. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir. Med.* **2017**, *5* (4), 291–360.
[5]. Falzon, D.; Jaramillo, E.; Schünemann, H.; Arentz, M.; Bauer, M.; Bayona, J.; Blanc, L.; Caminero, J.; Daley, C.; Duncombe, C.; Fitzpatrick, C.; Gebhard, A.; Getahun, H.; Henkens, M.; Holtz, T.; Keravec, J.; Keshavjee, S.; Khan, A.; Kulier, R.; Leimane, V.; Lienhardt, C.; Lu, C.; Mariandyshev, A.; Migliori, G.; Mirzayev, F.; Mitnick, C.; Nunn, P.; Nwagboniwe, G.; Oxlade, O.; Palmero, D.; Pavlinac, P.; Quelapio, M.; Raviglione, M.; Rich, M.; Royce, S.; Rüsch-Gerdes, S.; Salakaia, A.; Sarin, R.; Sculier, D.; Varaine, F.; Vitoria, M.; Walson, J.; Wares, F.; Weyer, K.; White, R.; Zignol, M. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur. Respir. J.* **2011**, *38* (3), 516–528.
[6]. Zumla, A. I.; Gillespie, S. H.; Hoelscher, M.; Philips, P. P.; Cole, S. T.; Abubakar, I.; McHugh, T. D.; Schito, M.; Maeurer, M.; Nunn, A. J. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect. Dis.* **2014**, *14* (4), 327–340.
[7]. Getahun, H.; Matteelli, A.; Chaisson, R. E.; Raviglione, M. Latent*Mycobacterium tuberculosis*Infection. *N. Engl. J. Med.* **2015**, *372* (22), 2127–2135.
[8]. Nathavitharana, R. R.; Friedland, J. S. A tale of two global emergencies: tuberculosis control efforts can learn from the Ebola outbreak. *Eur. Respir. J.* **2015**, *46* (2), 293–296.
[9]. Zhao, G.; Li, Z.; Zhang, R.; Zhou, L.; Zhao, H.; Jiang, H. Tetrazine bioorthogonal chemistry derived in vivo imaging. *Front. Mol. Biosci.* **2022**, *9*, 1055823 https://doi.org/10.3389/fmolb.2022.1055823.
[10]. Kuan, H.; Xie, Y.; Guo, Y.; Gianoncelli, A.; Ribaudo, G.; Coghi, P. (2R, 4S, 5S) 1-(4-(4-(((7-Chloroquinolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione. *Molbank* **2023**, *2023* (3), M1681.
[11]. Fai, L. K.; Anyanwu, M.; Ai, J.; Xie, Y.; Gianoncelli, A.; Ribaudo, G.; Coghi, P. 4-(4-(((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-7-chloroquinoline. *Molbank* **2022**, *2022* (3), M1404.
[12]. Jiang, X.; Hao, X.; Jing, L.; Wu, G.; Kang, D.; Liu, X.; Zhan, P. Recent applications of click chemistry in drug discovery. *Expert Opin. Drug Discov.* **2019**, *14* (8), 779–789.
[13]. Yun, X.; Xie, Y.; Ng, J. P.; Law, B. Y.; Wong, V. K.; Coghi, P. 2-Bromo-3-((1-(7-chloroquinolin-4-yl)-1H-1,2,3-triazol-4-yl)-methoxy)-benz aldehyde. *Molbank* **2022**, *2022* (1), M1351.
[14]. Ng, J. P.; Xiao Yun, Y.; Adnan Nasim, A.; Gianoncelli, A.; Yuan Kwan Law, B.; Ribaudo, G.; Kam Wai Wong, V.; Coghi, P. Synthesis, docking studies and biological evaluation of 1H-1,2,3-triazole-7-chloroquinoline derivatives against SARS-CoV-2. *Bioorg. Chem.* **2023**, *141*, 106882.
[15]. Ren, Z.; Coghi, P. Exploring medicinal potential and drug delivery solutions of Celastrol from the Chinese "Thunder of God Vine". *Eur. J. Chem.* **2024**, *15* (2), 194–204.
[16]. Bandi, S. R.; Kavitha, N.; Nukala, S. K.; Thirukovela, N. S.; Manchal, R.; Palabindela, R.; Narsimha, S. Synthesis and biological evaluation of novel [1,2,3]triazolo-pyrrolo[1,2-a]pyrido[4,3-d]pyrimidines as EGFR targeting anticancer agents. *J. Mol. Struct.* **2023**, *1274*, 134378.
[17]. Jamagne, R.; Power, M. J.; Zhang, Z.; Zango, G.; Gibber, B.; Leigh, D. A. Active template synthesis. *Chem. Soc. Rev.* **2024**, *53* (20), 10216–10252.
[18]. Saraiva, N. M.; Alves, A.; Costa, P. C.; Correia-da-Silva, M. Click Chemistry in Polymersome Technology. *Pharmaceuticals* **2024**, *17* (6), 747.
[19]. Agrahari, A. K.; Bose, P.; Jaiswal, M. K.; Rajkhowa, S.; Singh, A. S.; Hotha, S.; Mishra, N.; Tiwari, V. K. Cu(I)-Catalyzed Click Chemistry in Glycoscience and Their Diverse Applications. *Chem. Rev.* **2021**, *121* (13), 7638–7956.
[20]. Mamidyala, S. K.; Finn, M. G. In situ click chemistry: probing the binding landscapes of biological molecules. *Chem. Soc. Rev.* **2010**, *39* (4), 1252.

[21]. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* **2001**, *40* (11), 2004–2021.

[22]. Agalave, S. G.; Maujan, S. R.; Pore, V. S. Click Chemistry: 1,2,3-Triazoles as Pharmacophores. *Chemistry An Asian Journal* **2011**, *6* (10), 2696–2718.

[23]. Teneva, Y.; Simeonova, R.; Valcheva, V.; Angelova, V. T. Recent Advances in Anti-Tuberculosis Drug Discovery Based on Hydrazide–Hydrazone and Thiadiazole Derivatives Targeting InhA. *Pharmaceuticals* **2023**, *16* (4), 484.

[24]. Palomino, J. C. Current Developments and Future Perspectives For Tb Diagnostics. *Future Microbiol.* **2011**, *7* (1), 59–71.

[25]. Peloquin, C. A.; Davies, G. R. The Treatment of Tuberculosis. *Clin. Pharma Therapeutics* **2021**, *110* (6), 1455–1466.

[26]. Inturi, B.; Pujar, G. V.; Purohit, M. N. Recent Advances and Structural Features of Enoyl-ACP Reductase Inhibitors of *Mycobacterium tuberculosis*. *Arch. Pharm.* **2016**, *349* (11), 817–826.

[27]. Karaźniewicz-Łada, M.; Kosicka-Noworzyń, K.; Rao, P.; Modi, N.; Xie, Y. L.; Heysell, S. K.; Kagan, L. New approach to rifampicin stability and first-line anti-tubercular drug pharmacokinetics by UPLC-MS/MS. *J. Pharm. Biomed. Anal.* **2023**, *235*, 115650.

[28]. Sutradhar, I.; Zaman, M. H. Evaluation of the effect of temperature on the stability and antimicrobial activity of rifampicin quinone. *J. Pharm. Biomed. Anal.* **2021**, *197*, 113941.

[29]. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical–Biology Applications. *Chem. Rev.* **2013**, *113* (7), 4905–4979.

[30]. Li, L.; Zhang, Z. Development and Applications of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) as a Bioorthogonal Reaction. *Molecules* **2016**, *21* (10), 1393.

[31]. Sharma, A.; Agrahari, A. K.; Rajkhowa, S.; Tiwari, V. K. Emerging impact of triazoles as anti-tubercular agent. *Eur. J. Med. Chem.* **2022**, *238*, 114454.

[32]. Bonandi, E.; Christodoulou, M. S.; Fumagalli, G.; Perdicchia, D.; Rastelli, G.; Passarella, D. The 1,2,3-triazole ring as a bioisostere in medicinal chemistry. *Drug Discov. Today* **2017**, *22* (10), 1572–1581.

[33]. Voigt, M.; Fritz, T.; Worm, M.; Frey, H.; Helm, M. Surface Modification of Nanoparticles and Nanovesicles via Click-Chemistry. *Methods Mol. Biol.* **2019**, 235–245.

[34]. Shaikh, M. H.; Subhedar, D. D.; Arkile, M.; Khedkar, V. M.; Jadhav, N.; Sarkar, D.; Shingate, B. B. Synthesis and bioactivity of novel triazole incorporated benzothiazinone derivatives as antitubercular and antioxidant agent. *Bioorg. Med. Chem. Lett.* **2016**, *26* (2), 561–569.

[35]. Jewett, J. C.; Bertozzi, C. R. Cu-free click cycloaddition reactions in chemical biology. *Chem. Soc. Rev.* **2010**, *39* (4), 1272.

[36]. Krajczyk, A.; Zeidler, J.; Januszczyk, P.; Dawadi, S.; Boshoff, H. I.; Barry, C. E.; Ostrowski, T.; Aldrich, C. C. 2-Aryl-8-aza-3-deazaadenosine analogues of 5′-O-[N-(salicyl)sulfamoyl]adenosine: Nucleoside antibiotics that block siderophore biosynthesis in Mycobacterium tuberculosis. *Bioorg. Amp; Med. Chem.* **2016**, *24* (14), 3133–3143.

[37]. Hoyle, C.; Bowman, C. Thiol–Ene Click Chemistry. *Angew. Chem. Int. Ed.* **2010**, *49* (9), 1540–1573.

[38]. Lü, S.; Wang, Z.; Zhu, S. Thiol-Yne click chemistry of acetylene-enabled macrocyclization. *Nat. Commun.* **2022**, *13* (1), https://doi.org/10.1038/s41467-022-32723-0.

[39]. Bajaj, A. O.; Saraswat, S.; Knuuttila, J. E.; Freeke, J.; Stielow, J. B.; Barker, A. P. Accurate Identification of Closely Related Mycobacterium tuberculosis Complex Species by High Resolution Tandem Mass Spectrometry. *Front. Cell. Infect. Microbiol.* **2021**, *11*, https://doi.org/10.3389/fcimb.2021.656880.

[40]. Romanov, R. S.; Mariasina, S. S.; Efimov, S. V.; Klochkov, V. V.; Rodina, E. V.; Polshakov, V. I. Backbone resonance assignment and dynamics of 110 kDa hexameric inorganic pyrophosphatase from Mycobacterium tuberculosis. *Biomol NMR. Assign* **2020**, *14* (2), 281–287.

[41]. Johnpasha, S.; Palabindela, R.; Azam, M.; Kapavarapu, R.; Nasipireddy, V.; Al-Resayes, S. I.; Narsimha, S. Synthesis and anti-breast cancer evaluation of fused imidazole-imidazo[1,2-c][1,2,3]triazoles: PEG-400 mediated one-pot reaction under ultrasonic irradiation. *J. Mol. Struct.* **2024**, *1312*, 138440.

[42]. Brozyna-Heredia, I. Y.; Ganoza-Yupanqui, M. L.; Moreno-Exebio, L.; Dos Santos, J. L. Chromatographic Methods for the Determination of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, and Main Metabolites in Biological Samples: A Review. *Crit. Rev. Anal. Chem.* **2022**, *54* (7), 1971–1986.

[43]. Peyton, L.; Gallagher, S.; Hashemzadeh, M. Triazole antifungals: A review. *Drugs Today* **2015**, *51* (12), 705.

[44]. Kaur, R.; Ranjan Dwivedi, A.; Kumar, B.; Kumar, V. Recent Developments on 1,2,4-Triazole Nucleus in Anticancer Compounds: A Review. *ACAMC.* **2016**, *16* (4), 465–489.

[45]. Nagavelli, V. R.; Nukala, S. K.; Narsimha, S.; Battula, K. S.; Tangeda, S. J.; Reddy, Y. N. Synthesis, characterization and biological evaluation of 7-substituted- 4-((1-aryl-1H-1,2,3-triazol-4-yl) methyl)-2H-benzo[b] [1,4]oxazin- 3(4H)-ones as anticancer agents. *Med. Chem. Res.* **2016**, *25* (9), 1781–1793.

[46]. Narsimha, S.; Satheesh Kumar, N.; Kumara Swamy, B.; Vasudeva Reddy, N.; Althaf Hussain, S.; Srinivasa Rao, M. Indole-2-carboxylic acid derived mono and bis 1,4-disubstituted 1,2,3-triazoles: Synthesis, characterization and evaluation of anticancer, antibacterial, and DNA-cleavage activities. *Bioorg. amp; Med. Chem. Lett.* **2016**, *26* (6), 1639–1644.

[47]. Zhang, S.; Xu, Z.; Gao, C.; Ren, Q.; Chang, L.; Lv, Z.; Feng, L. Triazole derivatives and their anti-tubercular activity. *Eur. J. Med. Chem.* **2017**, *138*, 501–513.

[48]. Zhang, B. Comprehensive review on the anti-bacterial activity of 1,2,3-triazole hybrids. *Eur. J. Med. Chem.* **2019**, *168*, 357–372.

[49]. Ramya Sucharitha, E.; Krishna, T. M.; Manchal, R.; Ramesh, G.; Narsimha, S. Fused benzo[1,3]thiazine-1,2,3-triazole hybrids: Microwave-assisted one-pot synthesis, in vitro antibacterial, antibiofilm, and in silico ADME studies. *Bioorg. Med. Chem. Lett.* **2021**, *47*, 128201.

[50]. Song, M.; Deng, X. Recent developments on triazole nucleus in anticonvulsant compounds: a review. *J. Enzyme Inhib. Med. Chem.* **2018**, *33* (1), 453–478.

[51]. Sambasiva Rao, P.; Kurumurthy, C.; Veeraswamy, B.; Santhosh Kumar, G.; Poornachandra, Y.; Ganesh Kumar, C.; Vasamsetti, S. B.; Kotamraju, S.; Narsaiah, B. Synthesis of novel 1,2,3-triazole substituted-N-alkyl/aryl nitrone derivatives, their anti-inflammatory and anticancer activity. *Eur. J. Med. Chem.* **2014**, *80*, 184–191.

[52]. Ang, C. W.; Jarrad, A. M.; Cooper, M. A.; Blaskovich, M. A. Nitroimidazoles: Molecular Fireworks That Combat a Broad Spectrum of Infectious Diseases. *J. Med. Chem.* **2017**, *60* (18), 7636–7657.

[53]. Munagala, G.; Yempalla, K. R.; Singh, S.; Sharma, S.; Kalia, N. P.; Rajput, V. S.; Kumar, S.; Sawant, S. D.; Khan, I. A.; Vishwakarma, R. A.; Singh, P. P. Synthesis of new generation triazolyl- and isoxazolyl-containing 6-nitro-2,3-dihydroimidazooxazoles as anti-TB agents: in vitro, structure–activity relationship, pharmacokinetics and in vivo evaluation. *Org. Biomol. Chem.* **2015**, *13* (12), 3610–3624.

[54]. Ramprasad, J.; Nayak, N.; Dalimba, U.; Yogeeswari, P.; Sriram, D. One-pot synthesis of new triazole—Imidazo[2,1-b][1,3,4]thiadiazole hybrids via click chemistry and evaluation of their antitubercular activity. *Bioorg. amp; Med. Chem. Lett.* **2015**, *25* (19), 4169–4173.

[55]. Reddyrajula, R.; Dalimba, U. K. Structural modification of zolpidem led to potent antimicrobial activity in imidazo[1,2-*a*]pyridine/pyrimidine-1,2,3-triazoles. *New J. Chem.* **2019**, *43* (41), 16281–16299.

[56]. Amaroju, S.; Kalaga, M. N.; Srinivasarao, S.; Napiórkowska, A.; Augustynowicz-Kopeć, E.; Murugesan, S.; Chander, S.; Krishnan, R.; Chandra Sekhar, K. V. Identification and development of pyrazolo[4,3-c]pyridine carboxamides as Mycobacterium tuberculosis pantothenate synthetase inhibitors. *New J. Chem.* **2017**, *41* (1), 347–357.

[57]. Bouhaoui, A.; Eddahmi, M.; Dib, M.; Khouili, M.; Aires, A.; Catto, M.; Bouissane, L. Synthesis and Biological Properties of Coumarin Derivatives. A Review. *Chemistry Select* **2021**, *6* (24), 5848–5870.

[58]. Naik, R. J.; Kulkarni, M. V.; Sreedhara Ranganath Pai, K.; Nayak, P. G. Click Chemistry Approach for Bis-Chromenyl Triazole Hybrids and Their Antitubercular Activity. *Chem. Biol. Drug. Des.* **2012**, *80* (4), 516–523.

[59]. Anand, A.; Naik, R. J.; Revankar, H. M.; Kulkarni, M. V.; Dixit, S. R.; Joshi, S. D. A click chemistry approach for the synthesis of mono and bis aryloxy linked coumarinyl triazoles as anti-tubercular agents. *Eur. J. Med. Chem.* **2015**, *105*, 194–207.

[60]. Hu, Y.; Zhang, S.; Zhao, F.; Gao, C.; Feng, L.; Lv, Z.; Xu, Z.; Wu, X. Isoniazid derivatives and their anti-tubercular activity. *Eur. J. Med. Chem.* **2017**, *133*, 255–267.

[61]. Badar, A. D.; Sulakhe, S. M.; Muluk, M. B.; Rehman, N. N.; Dixit, P. P.; Choudhari, P. B.; Rekha, E. M.; Sriram, D.; Haval, K. P. Synthesis of isoniazid-1,2,3-triazole conjugates: Antitubercular, antimicrobial evaluation and molecular docking study. *J. Heterocyclic Chem.* **2020**, *57* (10), 3544–3557.

[62]. Boechat, N.; Ferreira, V. F.; Ferreira, S. B.; Ferreira, M. d.; da Silva, F. d.; Bastos, M. M.; Costa, M. d.; Lourenço, M. C.; Pinto, A. C.; Krettli, A. U.; Aguiar, A. C.; Teixeira, B. M.; da Silva, N. V.; Martins, P. R.; Bezerra, F. A.; Camilo, A. L.; da Silva, G. P.; Costa, C. C. Novel 1,2,3-Triazole Derivatives for Use against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) Strain. *J. Med. Chem.* **2011**, *54* (17), 5988–5999.

[63]. Patil, P. S.; Kasare, S. L.; Haval, N. B.; Khedkar, V. M.; Dixit, P. P.; Rekha, E. M.; Sriram, D.; Haval, K. P. Novel isoniazid embedded triazole derivatives: Synthesis, antitubercular and antimicrobial activity evaluation. *Bioorg. amp; Med. Chem. Lett.* **2020**, *30* (19), 127434.

[64]. Kumar, D.; Beena; Khare, G.; Kidwai, S.; Tyagi, A. K.; Singh, R.; Rawat, D. S. Synthesis of novel 1,2,3-triazole derivatives of isoniazid and their in vitro and in vivo antimycobacterial activity evaluation. *Eur. J. Med. Chem.* **2014**, *81*, 301–313.

[65]. Ajani, O. O.; Iyaye, K. T.; Ademosun, O. T. Recent advances in chemistry and therapeutic potential of functionalized quinoline motifs – a review. *RSC Adv.* **2022**, *12*, 18594–18614.

[66]. Worley, M. V.; Estrada, S. J. Bedaquiline: A Novel Antitubercular Agent for the Treatment of Multidrug-Resistant Tuberculosis. *Pharmacotherapy* **2014**, *34* (11), 1187–1197.

[67]. Thomas, K.; Adhikari, A. V.; Chowdhury, I. H.; Sumesh, E.; Pal, N. K. New quinolin-4-yl-1,2,3-triazoles carrying amides, sulphonamides and amidopiperazines as potential antitubercular agents. *Eur. J. Med. Chem.* **2011**, *46* (6), 2503–2512.
[68]. Marvadi, S. K.; Krishna, V. S.; Sriram, D.; Kantevari, S. Synthesis and evaluation of novel substituted 1,2,3-triazolyldihydroquinolines as promising antitubercular agents. *Bioorg. amp; Med. Chem. Lett.* **2019**, *29* (4), 529–533.
[69]. Pogaku, V.; Krishna, V. S.; Balachandran, C.; Rangan, K.; Sriram, D.; Aoki, S.; Basavoju, S. The design and green synthesis of novel benzotriazoloquinolinyl spirooxindolopyrrolizidines: antimyco bacterial and antiproliferative studies. *New J. Chem.* **2019**, *43* (44), 17511–17520.
[70]. Shinde, A. D.; Nandurkar, Y. M.; Bhalekar, S.; Walunj, Y. S.; Ugale, S.; Ahmad, I.; Patel, H.; Chavan, A. P.; Mhaske, P. C. Investigation of new 1,2,3-triazolyl-quinolinyl-propan-2-ol derivatives as potential antimicrobial agents:*in vitro* and *in silico* approach. *J. Biomol. Struct. Dyn.* **2023**, *42* (3), 1191–1207.
[71]. Kushawaha, A. K.; Jaiswal, A. K.; Gupta, J.; Katiyar, S.; Ansari, A.; Bhatt, H.; Sharma, S. K.; Choudhury, A. D.; Bhatta, R. S.; Singh, B. N.; Sashidhara, K. V. Antitubercular evaluation of dihydropyridine–triazole conjugates: design, synthesis, *in vitro* screening, SAR and *in silico* ADME predictions. *RSC. Med. Chem.* **2024**, *15* (8), 2867–2881.
[72]. Lungu, I.; Moldovan, O.; Biriș, V.; Rusu, A. Fluoroquinolones Hybrid Molecules as Promising Antibacterial Agents in the Fight against Antibacterial Resistance. *Pharmaceutics* **2022**, *14* (8), 1749.
[73]. Ramachandran, G.; Swaminathan, S. Safety and Tolerability Profile of Second-Line Anti-Tuberculosis Medications. *Drug Saf.* **2015**, *38* (3), 253–269.
[74]. De Souza, M.; Vasconcelos, T.; Almeida, M.; Cardoso, S. Fluoroquinolones: An Important Class of Antibiotics Against Tuberculosis. *CMC.* **2006**, *13* (4), 455–463.
[75]. Sriram, D.; Aubry, A.; Yogeeswari, P.; Fisher, L. Gatifloxacin derivatives: Synthesis, antimycobacterial activities, and inhibition of Mycobacterium tuberculosis DNA gyrase. *Bioorg. Med. Chem. Lett.* **2006**, *16* (11), 2982–2985.
[76]. Xu, Z.; Song, X.; Qiang, M.; Lv, Z. 1*H*-1,2,3-triazole-tethered 8-OMe Ciprofloxacin and Isatin Hybrids: Design, Synthesis and *in vitro* Anti-mycobacterial Activities. *J. Heterocyclic Chem.* **2017**, *54* (6), 3735–3741.
[77]. Xu, Z.; Song, X.; Hu, Y.; Qiang, M.; Lv, Z. Design, Synthesis and *In Vitro* Anti-mycobacterial Activities of 8-OMe Ciprofloxacin-1*H*-1,2,3-triazole-isatin-(thio) Semicarbazide/Oxime Hybrids. *J. Heterocyclic Chem.* **2017**, *55* (1), 192–198.
[78]. Xu, Z.; Lv, Z.; Song, X.; Qiang, M. Ciprofloxacin-isatin-1*H*-1,2,3-triazole Hybrids: Design, Synthesis, and *in vitro* Anti-tubercular Activity against *M. tuberculosis*. *J. Heterocyclic Chem.* **2017**, *55* (1), 97–102.
[79]. Chen, R.; Zhang, H.; Ma, T.; Xue, H.; Miao, Z.; Chen, L.; Shi, X. Ciprofloxacin-1,2,3-triazole-isatin hybrids tethered via amide: Design, synthesis, and in vitro anti-mycobacterial activity evaluation. *Bioorg. Med. Chem. Lett.* **2019**, *29* (18), 2635–2637.
[80]. Ding, Z.; Hou, P.; Liu, B. Gatifloxacin-1,2,3-triazole-isatin hybrids and their antimycobacterial activities. *Arch. Pharm.* **2019**, *352* (10), https://doi.org/10.1002/ardp.201900135.
[81]. Kumar, K.; Carrère-Kremer, S.; Kremer, L.; Guérardel, Y.; Biot, C.; Kumar, V. 1*H*-1,2,3-Triazole-Tethered Isatin–Ferrocene and Isatin–Ferrocenylchalcone Conjugates: Synthesis and in Vitro Antitubercular Evaluation. *Organometallics* **2013**, *32* (20), 5713–5719.
[82]. Singh, A.; Biot, C.; Viljoen, A.; Dupont, C.; Kremer, L.; Kumar, K.; Kumar, V. 1*H*-1,2,3-triazole-tethered uracil-ferrocene and uracil-ferrocenylchalcone conjugates: Synthesis and antitubercular evaluation. *Chem. Biol. Drug. Des.* **2016**, *89* (6), 856–861.
[83]. Kancharla, S. K.; Birudaraju, S.; Pal, A.; Krishnakanth Reddy, L.; Reddy, E. R.; Vagolu, S. K.; Sriram, D.; Bonige, K. B.; Korupolu, R. B. Synthesis and biological evaluation of isatin oxime ether-tethered aryl 1*H*-1,2,3-triazoles as inhibitors of *Mycobacterium tuberculosis*. *New J. Chem.* **2022**, *46* (6), 2863–2874.
[84]. Sharma, B.; Kumar, S.; Preeti; Johansen, M. D.; Kremer, L.; Kumar, V. 1*H*-1,2,3-triazole embedded Isatin-Benzaldehyde-bis(heteronuclear hydrazones): design, synthesis, antimycobacterial, and cytotoxic evaluation. *Chem. Biol. Drug. Des.* **2021**, *99* (2), 301–307.
[85]. Shaikh, M. H.; Subhedar, D. D.; Khan, F. A.; Sangshetti, J. N.; Nawale, L.; Arkile, M.; Sarkar, D.; Shingate, B. B. Synthesis of Novel Triazole-incorporated Isatin Derivatives as Antifungal, Antitubercular, and Antioxidant Agents and Molecular Docking Study. *J. Heterocyclic Chem.* **2016**, *54* (1), 413–421.
[86]. Zhao, S.; Lv, Z.; Deng, J.; Gao, F.; Zhang, G.; Xu, Z. Design, Synthesis, and *In Vitro* Anti-mycobacterial Activities of 1,2,3-Triazole-tetraethylene Glycol Tethered Isatin Dimers. *J. Heterocyclic Chem.* **2018**, *55* (12), 3006–3010.
[87]. Kedderis, G. L.; Miwa, G. T. The metabolic activation of nitroheterocyclic therapeutic agents. *Drug Metab. Rev.* **1988**, *19* (1), 33–62.
[88]. Jordão, A. K.; Sathler, P. C.; Ferreira, V. F.; Campos, V. R.; de Souza, M. C.; Castro, H. C.; Lannes, A.; Lourenco, A.; Rodrigues, C. R.; Bello, M. L.; Lourenco, M. C.; Carvalho, G. S.; Almeida, M. C.; Cunha, A. C. Synthesis, antitubercular activity, and SAR study of N-substituted-phenylamino-5-methyl-1H-1,2,3-triazole-4-carbohydrazides. *Bioorg. Med. Chem.* **2011**, *19* (18), 5605–5611.
[89]. Yempala, T.; Sridevi, J. P.; Yogeeswari, P.; Sriram, D.; Kantevari, S. Rational design and synthesis of novel dibenzo[b,d]furan-1,2,3-triazole conjugates as potent inhibitors of Mycobacterium tuberculosis. *Eur. J. Med. Chem.* **2014**, *71*, 160–167.
[90]. McMurry, L. M.; McDermott, P. F.; Levy, S. B. Genetic Evidence that InhA of *Mycobacterium smegmatis* Is a Target for Triclosan. *Antimicrob. Agents Chemother.* **1999**, *43* (3), 711–713.
[91]. Menendez, C.; Chollet, A.; Rodriguez, F.; Inard, C.; Pasca, M. R.; Lherbet, C.; Baltas, M. Chemical synthesis and biological evaluation of triazole derivatives as inhibitors of InhA and antituberculosis agents. *Eur. J. Med. Chem.* **2012**, *52*, 275–283.
[92]. Shanmugavelan, P.; Nagarajan, S.; Sathishkumar, M.; Ponnuswamy, A.; Yogeeswari, P.; Sriram, D. Efficient synthesis and in vitro antitubercular activity of 1,2,3-triazoles as inhibitors of Mycobacterium tuberculosis. *Bioorg. amp; Med. Chem. Lett.* **2011**, *21* (24), 7273–7276.
[93]. Patpi, S. R.; Pulipati, L.; Yogeeswari, P.; Sriram, D.; Jain, N.; Sridhar, B.; Murthy, R.; T, A. D.; Kalivendi, S. V.; Kantevari, S. Design, Synthesis, and Structure–Activity Correlations of Novel Dibenzo[*b,d*]furan, Dibenzo[*b,d*]thiophene, and *N*-Methylcarbazole Clubbed 1,2,3-Triazoles as Potent Inhibitors of *Mycobacterium tuberculosis*. *J. Med. Chem.* **2012**, *55* (8), 3911–3922.
[94]. Pulipati, L.; Yogeeswari, P.; Sriram, D.; Kantevari, S. Click-based synthesis and antitubercular evaluation of novel dibenzo[ b , d ]thiophene-1,2,3-triazoles with piperidine, piperazine, morpholine and thiomorpholine appendages. *Bioorg. Med. Chem. Lett.* **2016**, *26* (11), 2649–2654.
[95]. Shaikh, M. H.; Subhedar, D. D.; Nawale, L.; Sarkar, D.; Kalam Khan, F. A.; Sangshetti, J. N.; Shingate, B. B. 1,2,3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study. *Med. Chem. Commun.* **2015**, *6* (6), 1104–1116.
[96]. Alghamdi, W. A.; Al-Shaer, M. H.; An, G.; Alsultan, A.; Kipiani, M.; Barbakadze, K.; Mikiashvili, L.; Ashkin, D.; Griffith, D. E.; Cegielski, J. P.; Kempker, R. R.; Peloquin, C. A. Population Pharmacokinetics of Linezolid in Tuberculosis Patients: Dosing Regimen Simulation and Target Attainment Analysis. *Antimicrob. Agents Chemother.* **2020**, *64* (10), https://doi.org/10.1128/AAC.01174–20.
[97]. Bhattarai, D.; Lee, S. H.; Seo, S. H.; Nam, G.; Kang, S. B.; Pae, A. N.; Kim, E. E.; Oh, T.; Cho, S.; Keum, G. Synthesis and *In Vitro* Antibacterial Activity of Novel 3-Azabicyclo[3.3.0]octanyl Oxazolidinones. *Chem. Biol. Drug. Des.* **2012**, *80* (3), 388–397.
[98]. Kamal, A.; Swapna, P.; Shetti, R. V.; Shaik, A. B.; Narasimha Rao, M.; Sultana, F.; Khan, I. A.; Sharma, S.; Kalia, N. P.; Kumar, S.; Chandrakant, B. Anti-tubercular agents. Part 7: A new class of diarylpyrrole–oxazolidinone conjugates as antimycobacterial agents. *Eur. J. Med. Chem.* **2013**, *64*, 239–251.
[99]. Kaushik, C.; Kumar, K.; Singh, S.; Singh, D.; Saini, S. Synthesis and antimicrobial evaluation of 1,4-disubstituted 1,2,3-triazoles with aromatic ester functionality. *Arab. J. Chem.* **2016**, *9* (6), 865–871.
[100]. Ghiano, D. G.; de la Iglesia, A.; Liu, N.; Tonge, P. J.; Morbidoni, H. R.; Labadie, G. R. Antitubercular activity of 1,2,3-triazolyl fatty acid derivatives. *Eur. J. Med. Chem.* **2017**, *125*, 842–852.
[101]. Goud, G. L.; Ramesh, S.; Ashok, D.; Reddy, V. P.; Yogeeswari, P.; Sriram, D.; Saikrishna, B.; Manga, V. Design, synthesis, molecular-docking and antimycobacterial evaluation of some novel 1,2,3-triazolyl xanthenones. *Med. Chem. Commun.* **2017**, *8* (3), 559–570.
[102]. Danne, A. B.; Choudhari, A. S.; Chakraborty, S.; Sarkar, D.; Khedkar, V. M.; Shingate, B. B. Triazole–diindolylmethane conjugates as new antitubercular agents: synthesis, bioevaluation, and molecular docking. *Med. Chem. Commun.* **2018**, *9* (7), 1114–1130.