Review Article

Research Progress in HIV and Mycobacterium tuberculosis Inhibitors Containing Sulfonamide Moiety

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Numerous studies have reported significant results regarding the efficacy of sulfonamides against Mycobacterium tuberculosis and various HIV strains. This scientific paper provides an overview of the progress made over a decade of sulfonamides against HIV-1 and mycobacteria and its development against extremely drug-resistant (XDR) and multidrug-resistant strains. The reviewed study offers novel insights into the structural design and structure-activity relationship (SAR) of sulfonamides that are effective and less toxic in combating HIV, Mycobacterium tuberculosis, and multidrug resistance.

1. Introduction

Sulfonamides, the earliest chemically synthesized antibacterial compounds dating back to the 1930s, have gained significant prominence worldwide, with over 5000 commonly utilized derivatives [1]. These antibiotics work similarly to para-aminobenzoic acid (PABA) by targeting the enzyme 6-hydroxymethyl-7,8-dihydropteroate synthase (DHPS), which is a critical component of the folate synthesis pathway [2, 3]. Sulphanilamide, the first sulfonamide antibiotic, was initially synthesized in 1906 and later employed in the late 1930s as an antimicrobial agent [4]. For many years, sulfonamide has been utilized in a broad range of biological activities, including anti-HIV, antifungal, anticancer, antibacterial, antitumor, antituberculosis, anti-inflammatory, insecticidal, antidiabetes, and antihepatitis applications [5–13]. These significant functions are attributed to biologically active molecules and their association with five or six heterocyclic-membered rings linked to the sulfonyl group [14]. Allergic responses, such as respiratory and digestive tract diseases, are frequently linked to the use of sulfonamide drugs and are primarily attributable to the substitution at the N4 arylamine group position. Examples of such drugs include sulfadiazine, sulfamethoxazole, and sulfasalazine. Sulfonamide drugs can be classified into two distinct groups based on their allergy-inducing effects: firstly, the antibacterial sulfonamides that contain an aromatic amine, and secondly, the nonantibacterial sulfonamides that do not contain an aromatic amine [15].

The incidence of mycobacterial infections has been increasing globally, with a concomitant rise in multidrug-resistant Mycobacterium tuberculosis strains. In HIV-infected individuals, the risk of developing tuberculosis is 26–36 times higher compared to noninfected individuals, with approximately 10,715 cases per 100,000 people [16, 17]. Tuberculosis, caused by Mycobacterium tuberculosis, is a major cause of mortality globally and can remain latent in a small percentage of the human population [18–20]. Tuberculosis (TB) has had a significant impact on both the socioeconomic status and health of societies. Its lethal character is exacerbated by the emergence of extremely drug-resistant (XDR) and multidrug-resistant (MDR) strains [21]. With the increasing number of MDR-TB and XDR-TB cases, treating tuberculosis has become a major challenge for clinicians. Although second-line and third-line agents being used are expensive and toxic [7, 22]. Unfortunately, the emergence of MDR and XDR-MTB strains cannot be effectively treated using currently available anti-TB drugs [23].
According to a report by the United Nations, drug-resistant infections may cause the annual mortality of up to 10 million people by 2050. The reactivation of latent bacteria, which is commonly observed in individuals with comorbidities such as diabetes, HIV, chronic renal insufficiency, and cancer, poses a significant threat [24].

Acquired immunodeficiency syndrome (AIDS), recognized as a fatal and life-threatening ailment, is caused by the human immunodeficiency virus (HIV) [25, 26]. According to the 2021 reports from the Joint United Nations Programme on HIV and AIDS (UNAIDS), out of the 37.7 million individuals living with HIV, there were 0.37 million recorded deaths, underscoring the ongoing threat posed by the HIV/AIDS epidemic [27]. The progress in HIV treatment and prevention continues unabated, persisting since the first reported cases of HIV emerged four decades ago [28]. Globally, the outreach of antiretroviral therapy has extended to 25.4 million individuals [29].

The approval of idoxuridine in 1963 marked a turning point in the development of antiviral drugs, ushering in a new era of treatment for millions of people worldwide. However, highly active antiretroviral therapy (HAART) still has some drawbacks, such as painful toxicities, difcult dosing regimens, poor adherence rates, and drug-drug interactions [30–32]. Despite being introduced as a health target in the United Nations Millennium Development Goals in 2000, the AIDS epidemic remains a pressing global issue [33]. However, the FDA has approved several drugs and synthetic nucleoside analogues that have demonstrated effectiveness against HIV infection. The current HIV treatment regimen consists of highly active antiretroviral therapy (HAART), which includes drugs from several classes, including nonnucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, postattachment inhibitors, fusion inhibitors, and CCR5 antagonists.

The distinctive attributes demonstrated by sulfonamides, including their crystalline nature, exceptional biological profile, and hydrolytic stability, have signifcantly heightened their appeal among synthetic chemists. Furthermore, a noteworthy number of FDA-approved therapeutic drugs are found to incorporate sulfonamide moieties [34]. The blending of sulfonamide with other drug compounds has led to the emergence of innovative formulations characterized by enhanced efacy and diminished toxicity [35]. This review aims to both furnish and inspire researchers with novel insights into the structural design and advancements associated with newly developed sulfonamide compounds, which exhibit exceptional inhibitory potential against mycobacteria and HIV. Over the course of this review, we delve into the extensive journey spanning decades, encompassing the synthesis and assessment of potential sulfonamides for combating tuberculosis and HIV. Moreover, a comprehensive summary is presented encompassing the synthesis, mechanism of action, in vivo/in vitro pharmacological activities, and the structure-activity relationship (SAR) of these novel sulfonamide compounds.

1.1. Sulfonamide Derivatives as Antimycobacterial Agents. Mycobacterium tuberculosis (MTB), first identifed in 1882 by the renowned German bacteriologist Robert Koch, remains a signifcant global health concern. Tuberculosis is one of the deadliest infectious diseases worldwide, with a higher mortality rate than many other diseases. In line with the World Health Organization’s (WHO) 2020 World Tuberculosis Report, it is estimated that around 10 million individuals contracted tuberculosis in 2019. Among these cases, approximately 3.3% of newly diagnosed tuberculosis cases and 17.7% of patients with a history of treatment experienced multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis (MDR/RR-TB) [36, 37].

The primary challenge facing the scientifc community in TB treatment is the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Out of hundreds of molecules reported annually, only a few anti-TB agents have successfully reached clinical development. Recently, the US Food and Drug Administration (FDA) approved the novel drugs (Figure 1) Bedaquiline 1 and Pretomanid 3, while Delamanid 2 was approved by the European Medicines Agency (EMA) for the treatment of MDR-TB and XDR-TB [38–40].

The antimycobacterial activity of the heterocyclic benzenesulfonamides moiety (Figure 2) was investigated, and the results showed that compound 4 and compound 5 exhibited signifcant inhibitory values of 78.34 and 79.84, respectively, against mycobacteria because of the two moieties –COOEt and –NH(O)(O)NSO2Cl [41].

Three novel azo dyes (Figure 3) based on sulfamethoxazole were synthesized, and the in vitro antimicrobial activity was evaluated against various microbial strains. All three compounds exhibited promising antitubercular activity, with compound 7 showing the highest inhibitory effect against Mycobacterium tuberculosis, with an IC50 of 6.25 μg/mL. The compounds were synthesized by reacting sulfamethoxazole diazonium salt with 1-ethyl-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (7), and 6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (8) [42]. Similarly, Manjunatha et al. investigated the antimycobacterial activity of sulfonamide-incorporated azo dyes. The results indicated that compound 11, which contains sulfamethazine and a pyran moiety, displayed potent activity with a Minimum Inhibitory Concentration (MIC) value of 3.85 μM. On the other hand, the novel azo dyes derivatives 9 and 10, which contain sulfapyridine and isoaxazolone, and compound 12 exhibited moderate inhibition with MIC values of 27.7 μM, 14.84 μM, and 32.38 μM, respectively. Overall, while sulfonamide-incorporated azo dyes derivatives 9, 10, and 12 demonstrated only moderate antimycobacterial efacy, compound 11 showed excellent efacy [43].

Metal-based compounds have been demonstrated to enhance bioavailability, chemical diversity, and specifcity, as well as air stability and water solubility when used in conjunction with peptides in metal complexes. Auronofin or ganite, a transition metal compound approved by the FDA for other diseases, has displayed some level of activity against...
MTB. Nonetheless, the utilization of metal-drug complexes for the treatment of MTB infections is yet to receive FDA endorsement [44]. Sulfamethoxazole complexed with metals (Au, Cd, Cu, Ni, and Hg) were assessed, and the findings revealed both bacterial and biofilm elimination, accompanied by minimal to negligible toxicity [45]. In addition, the Co (II)-sulfamethoxazole complexes reported by Mondelli et al. exhibit limited activity and reduced cytotoxicity towards \( M. \text{tuberculosis} \), potentially attributed to their diminished lipophilicity. This phenomenon presents a challenge as it impedes the compounds’ penetration of the lipid-rich hydrophobic cell wall characteristic of mycobacteria [46].

Novel \( M. \text{tuberculosis} \) human carbonic anhydrase inhibitors were derived from the alkylation of sulphanilamide with ethyl bromoacetate, and they showed promising inhibition against \( M. \text{tuberculosis} \), with inhibition constants (Kls) ranging from 127 nM to 2.12 \( \mu \text{M} \). Also, the presence of methoxy and halogen substituents led to a significant loss of inhibitory effects of the 4-((2-((3-(4-Chlorophenyl)-5-(pyridin-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl) amino) benzenesulphonamide [47]. Singh et al. reported the antibacterial activity of aminopyrimidine-sulphonamide (APYS1) against \( M. \text{tuberculosis} \). Figure 4 depicts the aminopyrimidine-sulphonamides (13–15) which exhibit low cytotoxicity and good potency against replicating \( M. \text{tuberculosis} \) (H37Rv). Among them, compound 13 showed the highest potency with a minimal bactericidal concentration (MBC99) of 0.6 mM, which is comparable to its minimal inhibitory concentration (MIC) of 0.3–0.6 mM. In addition, APYS1 showed activity against \( M. \text{smegmatis} \) in the presence of an efflux inhibitor [48].

A series of substituted sulfamides (16) was evaluated for their antimycobacterial activity against \( M. \text{smegmatis} \), as shown in Figure 5. Sulfamides with halogenated phenyl ring substitutions exhibited low antmycobacterial activity with MICs of 250 mg/mL, while those with azide substitution showed up to a 4-fold loss in activity (MIC >1000 mg/mL). In contrast, unsubstituted sulfamides did not inhibit \( M. \text{smegmatis} \) growth, even at a concentration of 1000 mg/mL, likely due to the hydrophilic nature of the sulfamide moiety [49]. Among the sulfonamides tested, indisulam 17, 3-bromosulfanilamide 18, acetazolamide 19 (ATZ), and dorzolamide 20 (DZA) efficiently inhibited \( \beta \)-CAs activity.
Figure 3: Novel Azo dyes.

Figure 4: Structures of the aminopyrimidine-sulfonamides as antitubercular agents.
(K1 values of 97–186 nM) and represent the first study to reveal MTB β-C1 (beta-carbonic anhydrase 1) as a potential antiTB drug target [50].

Brown et al. synthesized novel benzoxa-[2,1,3]-diazoles and screened them against MTB and other selected bacterial strains. The substituted benzoxa-[2,1,3]-diazoles containing sulphonamido amino acid moiety showed low specificity for mycolata bacteria [51]. Also, a series of novel N-trifluoromethylthio sulfonimidamide derivatives (Figure 6) (21) were tested against Mycobacterium tuberculosis (MTB). Two of the compounds exhibited high antimycobacterial activity, with MIC values ranging from 4–8 μg/mL, which compares favorably to ethambutol, the first-line drug approved by the World Health Organization. However, N-trifluoromethylthio sulfonimidamide derivatives 22 and 23 were found to be cytotoxic to HepG2 cells ([23, IC_{50} = 65 μg/mL]; [22, IC_{50} = 15 μg/mL]) likely due to the presence of the trifluoromethylthio moiety [52].

In this study, twenty-one novel fluoroquinolone derivatives substituted with alkyl, acyl, or sulfonyl moieties were synthesized and evaluated for their antituberculous and antibacterial activity. The derivatives were synthesized by modifying the secondary amine moiety of moxifloxacin. In vitro antimycobacterial activity of the compounds was evaluated against Mycobacterium tuberculosis H37Rv using the microplate alamar blue assay. The results showed that all compounds had minimal inhibitory concentration (MIC) values ranging from 0.39–25.00 μg/mL. The introduction of sulfonyl or acyl moieties to moxifloxacin decreased the antimycobacterial activity compared to alkyl substitutions. Interestingly, the sulfonyl group did not enhance the antituberculosis activity when introduced to the nitrogen of the secondary amine, while acyl substitution led to moderate activity [53]. The synthesis and in vitro evaluation of sixteen α-sulfonamidophosphonate moieties (Figure 7) were carried out using the Kabachnik-Fields reaction, a multiple component reaction (MCR). The compounds were screened for their antituberculosis activity against Mycobacterium tuberculosis H37Rv, and their minimum inhibitory concentration (MIC) values (μg/mL) were compared with those of standard drugs such as ciprofloxacin (Cfx), isoniazid (INH), ethambutol (E), pyrazinamide (Z), and rifampicin (R). Out of the sixteen compounds tested, five exhibited anti-TB activity with MIC values of 1.56 μg/mL, while one showed an MIC value of 3.125 μg/mL compared to the standard drug pyrazinamide (MIC of 6.25 μg/mL). Furthermore, these compounds demonstrated nontoxicity. Due to the decreasing polarity of γ-(N-hydroxyamino) phosphonates,
their ability to penetrate the lipophilic cell wall of MTB is limited, which results in their low anti-TB potency. The most potent compound among them exhibits an MTB MIC value of only 9.4 µg/mL [54].

Bhat et al. aimed to identify a potent anti-TB agent and designed 4-thiazolidinone derivatives (25; Figure 8) through a cyclo-condensation reaction involving aryl aldehyde, 4-amino-N-(5-methylisoxazol-3-yl) benzenesulfonamide, and mercapto acetic acid. Five compounds out of all screened showed good antimycobacterial activity against M. tuberculosis H37Ra strains (MTB) and M. Bovis (BCG) with IC₉₀ values ranging from 0.058–0.22 µg/mL for M. Bovis and 0.43–5.31 µg/mL for MTB strains. Furthermore, the researchers screened the cytotoxicity of the most active compounds in A549, HCT 116, and MCF-7 cell lines and found that they exhibited lower cytotoxicity, indicating high pharmacodynamic properties [55].

Investigation into the effect of linkers connecting pyrazine to benzene on antimicrobial activity was carried out. A series of N-(pyrazin-2-yl) benzenesulfonamides were screened for their anti-TB activity against M. tuberculosis H37Rv and were synthesized using different sulfonic chlorides and aminopyrazine or 6-chloroaminopyrazine in acetone. Among the series of compounds tested, 4-amino-N-(pyrazin-2-yl) benzenesulfonamide and 4-amino-N-(6-chloropyrazin-2-yl) benzenesulfonamide showed promising results with MIC values of 6.25 µg/mL, 25 µM and MIC = 6.25 µg/mL, 22 µM, respectively [56]. In another study, a series of purine-linked piperazine derivatives (26, 27; Figure 9) were evaluated as antimycobacterial agents. The purine-linked piperazine derivatives with sulfonamide groups showed excellent MIC values and good antimycobacterial activity. Interestingly, the presence of electron-negative substituents on the phenyl rings increased the antituberculosis activity, possibly due to the increased polarity [57].

Furthermore, due to the activity of 4-(3-heptylureido)-N-(5-methylisoxazol-3-yl) benzenesulfonamide against Nontuberculosis mycobacteria, fifteen sulfamethoxazole-based n-alkyl ureas were synthesized and tested against M. tuberculosis. The results indicate that the presence of a long alkyl substituent leads to an increase in MIC values. Nonetheless, all of the synthesized compounds exhibit good antimycobacterial properties when compared to sulfamethoxazole, with a minimum inhibitory concentration (MIC) value of 2 µM [58]. Malasala et al. investigated the inhibitory activity of thienopyrimidine derivatives containing a sulfonamide substituent (28, 29, Figure 10) against M. tuberculosis (ATCC 27294). The results indicated that these derivatives possess potent antimycobacterial activity, with MIC values ranging from 16–32 µg/mL, high selectivity index (SI = >12.5), and negligible toxicity to Vero cells (CC₅₀ = 50 µg/mL) [59].

A series of 6-(4-substituted piperazin-1-yl) phenanthridine derivatives 35, 36 starting from 9-fluorenone 30 (Scheme 1) was synthesized and screened against the M. TB H37Rv strain in the MTT assay. However, the compounds gave a good antitubercular activity with MIC value ranging between 1.56 and ≥50 mg/mL [60].

The investigation of sulfonyl-piperazino benzothiaziones (sPBTZ) 37 (Figure 11) derivatives provided insights into their structure-activity relationship. The presence of a sulfonyl group (i) enhances the solubility of the compounds and reduces their hydrophobicity, which could have an impact on their bioavailability. (ii) The activity of the compounds is positively influenced by small (methyl or ethyl) substituents, while long/hydrophobic substituents have a negative impact on activity. (iii) The presence of sulfone between cyclohexyl and piperazine reduces the activity by 30-fold. Moreover, compounds with alkyl substituents showed better antitubercular activity than those with aryl substituents [61].

In silico studies were conducted on 102 sulfonamides targeting the DHFR and DHPS proteins of MTB. The ADMET properties revealed that 4-amino-N-(9H-carbazol-2-yl) benzenesulfonamide and 4-amino-N-(6-hydroxypridin-2-yl) benzenesulfonamide have low toxicity and the potentially active, which encourages the synthesis and screening of substituted sulfonamides as a promising drug candidate in the future [62]. Celecoxib-derived compounds were synthesized and evaluated against mycobacteria. The aminosulfonamide series of Celecoxib-derived compounds were found to be highly potent against M. TB. Celecoxib-derived compounds 38 (Figure 12) exhibited greater potency in inhibiting M. TB growth, but with higher toxicity to human macrophages (26% cell death) compared to
compound 39, which had less toxicity (4% cell death) and less potency against M. TB growth in human macrophages. The amide side chain showed a significant decrease in the antimycobacterial activities [63].

The synthesis and screening of derivatives of 1,2,4-triazolethiols against M. tuberculosis revealed an inductive effect of 1,2,4-triazolethiol when attached to the para position of the phenyl ring. The results also indicate that these...
derivatives possess inhibitory potency, with MIC values of 2.45 ± 0.2 µg/mL [64]. The screening of benzenesulfonamide derivatives against Mycobacterium tuberculosis receptors yielded good activity at low micromolar concentrations. Although lipophilicity influences antimycobacterial activity, it does not necessarily correlate with MIC values. Furthermore, the presence of certain substituent groups (e.g., nitro groups and halo 3,5-disubstitution) negatively affects the inhibition of mycobacteria. Cytotoxicity was found to increase with an increase in atomic mass, with lower cytotoxicity observed for compounds containing hydrogen or nonbulky electron-donating groups (e.g. H, CH₃, OH, and CH₂O). Compound 41 was found to be toxic to mammalian cells (IC₅₀ = 16.0 µM) due to the replacement of the 5-nitrofuran-2-yl group with a salicyl ring [65, 66]. Variya et al. synthesized ten sulfonamide compounds from various sulfa drugs (sulfamethoxazole, sulfapyridine, sulfathiazole, and sulfamethazine) and 5-bromo-1H-pyrazolo [3,4-b] pyridine using chloroacetyl chloride. The screening results against Mycobacterium tuberculosis H37RV revealed excellent inhibitory activity for only three compounds 40 (Figure 13) [67].

In addition, benzofuran-based sulfamide derivatives 42 (Figure 13) were synthesized from various 7-methoxy analogues and ethyl benzofuran-2-carboxylate. They exhibited moderate in vitro activity (MIC values of 64 µg/mL) against M. tuberculosis, similar to the standards levofloxacin, streptomycin, ethambutol, rifampicin, amikacin, and isoniazid. Docking studies revealed that the target enzymes and the sulfamides formed a stable adduct with docking scores of −4.135 and −4.004 kcal/mol, respectively [68]. The structure-activity relationship of 1-(5-isquinolinesulfonyl) pipera- zine derivatives was determined from its antitubercular activity. Previous studies have demonstrated that cyclohexyl (4-(isoquinolin-5-ylsulfonyl) piperaizin-1-yl) methanone inhibits inosine-5′-monophosphate dehydrogenase (IMPDH) and showed activity against M. tuberculosis. The results reveal that piperazone, cyclohexyl, isoquinoline, and urea nitrogen are important substituents for enhancing the antitubercular activity of these derivatives [69].

Faiion et al. investigated the antitubercular activity of anthranilic acid derivatives. The study revealed that replacing the amide function with a sulfonamide function (43) resulted in a compound as potent as the reference compound (5-bromo-2-[(3,4-dichlorobenzoyl) amino] benzoic Acid). In contrast, methylation of the amide function led to a decrease in potency of more than five times. However, the replacement of the amide function by bioisosteres such as acylsulfonamides (44, 45; Figure 14) was well tolerated and produced compounds with IC₅₀ values ranging between 24 and 35 µM [70].

1.2. Sulfonamide Derivatives as Anti-HIV-1 Agents. HIV/AIDS continues to be a worldwide health crisis, posing a significant threat to millions of individuals across the globe. As of 2021, an estimated 38.4 million people were living with HIV/AIDS. Tragically, HIV-related complications resulted in the loss of over 650,000 lives in that same...
The advent of highly active antiretroviral therapy (HAART) has greatly improved the management of HIV infection, effectively transforming it into a manageable chronic condition in many cases. Nevertheless, the persistent need for new antiretroviral drugs remains, highlighting the ongoing demand for innovative solutions in HIV/AIDS treatment [71].

Sulfonamides constitute a group of chemical compounds characterized by the presence of the \(-\text{SO}_2\text{N}\) moiety within their structural framework [72]. The introduction of the sulfonamide group into biologically relevant molecules creates a novel effect; this makes sulfonamides a promising class of compounds, exhibiting a wide range of diverse biological activities, notably including their potential as anti-HIV agents [73–75]. By forming complexes with transition metals, sulfa drugs have witnessed an expansion in their potential applications [72]. In this way, the pharmacological properties of sulfa compounds are enhanced through their coordination with metal ions [76, 77]. Notably, metal complexes exhibit a range of distinct biological activities, spanning metals such as iron, manganese, copper, zinc, nickel, chromium, cobalt, and palladium [78]. Hassan et al. explores the bioactive site of bidentate sulfonamide metal complexes 46 (VO\(^{2+}\), Ni\(^{2+}\), Cu\(^{2+}\), Co\(^{2+}\), and Zn\(^{2+}\)) (Figure 15) as anti-HIV agents. The ligand was synthesized by combining 1-(2-hydroxyphenyl) ethan-1-one with 4-amino benzene-1-sulfonamide and subsequently complexed with the aforementioned metals. Zinc and cobalt complexes showed superior bioactivity compared to the other sulfonamide metal complexes. Interestingly, the ligands were observed to donate electrons to the coordinated metal ions through the imine nitrogen and deprotonate the phenolic group. Also, the maximum and minimum activity of ligand against protease was 87% and 56%, respectively. The molecular electrostatic potential showed that the sulfur and nitrogen atoms exert a strong negative effect on the ligand. In addition, all atoms with metal ions are active in binding to the receptors [79].

The incorporation of sulfonamide substitution within the dihydropyron template has resulted in a series of highly potent HIV protease inhibitors (Figure 16), as described in this research study. The structure-activity relationship study provided more insight into the binding interactions that are responsible for their potent enzymatic binding while crystallographic studies further validated important binding interactions. These research culminated in the development of Tipranavir (PNU-103017; 47), which demonstrates remarkable potency against HIV protease with an inhibition constant (Ki) value of 8 pM and an IC\(_{90}\) value of 100 nM in antiviral cell culture. Currently, clinical trials of this compound, known as PNU-140690 are underway for the treatment of HIV infection. Also, cycloalkane and sulfonamide modifications further enhance the enzymatic and antiviral activity of these inhibitors, as exemplified by dihydropyron inhibitors 48, which exhibits a Ki value of less than 1 nM and an antiviral IC\(_{50}\) of 1-2 \(\mu\)M [80]. GRL-09510, a protease inhibitor, has demonstrated efficacy against multidrug-resistant HIV-2ROD and HIV-1 variants. In 2013, a series of protease inhibitors, including GRL-0519,
were synthesized from sulphonamide isosteres and tris-tetrahydrofuranurethane (tris-THF). Clinical trials of these inhibitors on patients who were not responding to antiviral therapy showed high potency against multiprotease inhibitor-resistant HIV-1 variants [81, 82]. A novel HIV-1 protease inhibitor with a sulphonamide group was recently reported to exhibit increased antiviral activity and enzyme binding affinity compared to MK-8718, a novel aspartate-binding bicyclic piperazine sulphonamide core [83].

The synthesis of a novel protease inhibitor (GRL-0739, 49) from a sulphonamide isostere and cyclohexyl-bis-tetrahydrofuranurethane [THF] resulted in an effective inhibitor against multidrug-resistant HIV-1 and HIV-2ROD variants, as well as blocking the replication and infectivity of HIV-1NL4-3 [84]. A nonpeptidic HIV-1 protease inhibitor (GRL-10413) was also synthesized by Amano et al. which combined P2′ methoxybenzene moieties and P2 bis-THF with a modified P1 moiety containing chlorine and O-methoxy groups, responsible for the strong binding of the protease inhibitor to HIV-1 protease. Crystal structure analysis of HIV-1 protease complexed with GRL-10413 revealed that the modified P1 of GRL-10413 (50) forms a strong van der Waals force with amino acids in the active site of the protease and a more hydrophobic surface area, while the chlorine substituent interacts with the protease in two different configurations. Moreover, GRL-10413 (50)
blocked the replication and infectivity of HIV-1 \textsubscript{NL4-3} variants, thereby maintaining its antiviral activity against multidrug-resistant clinical HIV-1 variants \cite{85}.

Ghost et al. synthesized a series of macrocyclic HIV-1 protease inhibitors, revealing that cyclic inhibitors are generally more potent than acyclic inhibitors, and unsaturated derivatives have higher potency than their saturated counterparts \cite{86}. A novel isoindolinedione derivative, bearing sulphonamide, imine, thioamide, and amide linkages, was synthesized, characterized, and evaluated against the HIV-1 strain IIIB in MT-4 cells. In vitro studies showed that this compound inhibited HIV-1 replication at nanomolar concentrations (3-4 nM), with selectivity indices ranging from 33.75 to 73.33. Also, structure-activity relationship (SAR) studies revealed that the compounds with sulphonamide linkages were more potent as HIV-RT inhibitors, likely due to the NH group bonding with the carbonyl of Lys101, while the S=O bonds interact with Lys103 and Pro236. Moreover, compounds with benzene rings bearing substituents that can form hydrogen bonds showed better activity \cite{87}.

A chiral analogue (3,4-thiadiazole-based tri-sulfonamides and bis-sulfonamides \cite{54, 55}; Scheme 2) based on 1,3,4-thiadiazole tri-sulfonamide and bis-sulfonamides was synthesized from chiral amino acids (51) and evaluated against HIV-1 and HIV-2 in MT-4 cells assay. The results obtained showed that the compounds with a branched-chain aliphatic group with a methoxy substituent attached to the arylsulphonamide moiety exhibit significant anti-HIV-1 activity. However, at micromolar concentrations, the compounds exhibit cytotoxicity against MT-4 cells, which is further enhanced when the 1,3,4-thiadiazole ring bears three arylsulfonamido groups. Although one of the compounds effectively inhibits HIV-1 with a selectivity index of 6.6 and IC\textsubscript{50} of 9.5 \mu M \cite{88}.

A set of new glycoprotein 120 inhibitors were synthesized as potential anti-HIV agents using an environmentally friendly and convenient approach. Remarkably, all the compounds depicted in Figure 17 demonstrated inhibitory activity against HIV-1 glycoprotein 120 at nanomolar concentrations, which outperformed the standard BMS 806 likely due to the favorable interaction and binding with glycoprotein 120. Furthermore, these compounds exhibited 10-fold higher activity than BMS 806 (indole-based inhibitor) \cite{89}. In a pursuit to design a novel anti-HIV agent, Dang et al. synthesize an aloperine derivative through the structural modification of the aloperine structure. This derivative showed a remarkable 15-fold increase in anti-HIV-1 activity, effectively preventing viral fusion with the cell membrane, and binding strongly to the HIV-1 glycoprotein 120 protein \cite{90}.

To explore diverse interactions with the nonnucleoside reverse transcriptase binding pocket of HIV-1, Kang et al. designed and synthesized various thiophenepyrimidine derivatives and evaluated their activity against mutant HIV-1 strains. The results demonstrated high affinity and excellent potency against wild-type (WT) HIV-1, with N-(4-(N-(4-(4-cyano-2,6-dimethylphenoxo) thieno [3,2-d] pyrimidin-2-yl) amino) cyclohexyl) sulfamoyl) phenyl acetamide (IC\textsubscript{50} = 1.041 \mu M) and 4-cyano-N-(4-((4-(4-cyano-2,6-dimethylphenoxo) thieno [3,2-d] pyrimidin-2-yl) amino) cyclohexyl) benzensulfonamide (IC\textsubscript{50} = 1.138 \mu M) \cite{91}. In addition, molecular docking studies of 5-hydroxy-N-(4-methyl-2-oxo-1,2-dihydroquinolin-8-yl) thiophene-2-sulfonamide (nonnucleoside reverse transcriptase inhibitor) showed good anti-HIV activity against both HIV-1 and HIV-2, with selectivity indices of 2.65 and 2.32, respectively. Notably, molecular dynamics (MD) simulations indicated that this compound exhibited strong inhibitory activity through its binding energy in the active site and hydrogen-bonding interactions \cite{27}.

In this study, a new class of compounds was synthesized, namely, 3-(1,3,4-thiadiazol-2-yl) thiazolidin-4-one derivatives, and evaluated their potential to inhibit the polymerase activity of HIV-1 reverse transcriptase and replication of HIV-1 in MT-4 cell cultures. These derivatives were prepared using a synthetic route that involved the reaction of 1,3-thiazolidin-4-one with 1,3,4-thiadiazol-2-yl|sulfonyl]-N-arlyacetamide. Regrettably, the results obtained from the biological testing showed that all the derivatives exhibited low anti-HIV activity in MT-4 cell culture. Nevertheless, the findings suggest that the presence of arylacetamide moiety had a positive impact on the RT enzymatic inhibition \cite{92}. Che et al. synthesized a set of fifteen N-arylsulfonyl-3-formyldiones (Figure 18) through a two-step reaction and evaluated their potential as anti-HIV agents in vitro. In the first step, 3-formyldiones were synthesized using the Vilsmeier–Haack reaction, which were then reacted with arylsulfonyl chlorides to yield N-arylsulfonyl-3-formyldione derivatives. Among the tested compounds, one exhibited good antiviral activity and low cytotoxicity (CC\textsubscript{50} = 410.41 \mu M), and featured a nitro group substituent (meta position) on the arylsulfonyl moiety and a methyl group substituent (C-6 position) on the indolyl ring. Moreover, compounds with electron-withdrawing substituents displayed better antiviral activity than those with electron-donating substituents. Notably, N-nitrophenylsulfonyl-6-methyl-3-formyldione (61) and N-nitrophenylsulfonyl-3-formyldione (60) exhibited anti-HIV-1 activity with TI and EC\textsubscript{50} values of 81.69, 31.89, and 5.02, 9.57 \mu M, respectively. The study also suggests that compounds containing the formyl group (3-position) in N-arylsulfonyldiones were more potent compared to those with the 1,3-thiazolidin-4-ones group (62, 63). Therefore, deliberate chemical modifications are necessary to develop more potent inhibitors \cite{93}.

Recently, Gao et al. discovered sulfonamides-substituted indolylarylsulfones (64; Figure 19) as potent HIV-1 inhibitors that reduce the high level of cytotoxicity (CC\textsubscript{50} = 216.51 \mu M/L) and improve the safety profiles of Indolylarylsulfones (IASS). To further improve efficacy, forty-eight (48) Indolylarylsulfone derivatives were synthesized from sulfonamide groups linked by alkyl diamine. These derivatives were found to be more potent than etravirine and nevirapine, exhibiting significant inhibitory activity values (wild-type HIV-1: EC\textsubscript{50}(WT) = 0.007 \mu M/L, SI = 30930) and cytotoxicity (CC\textsubscript{50} = 216.51 \mu M/L) \cite{94}. In another study, new chiral indolylarylsulfones (Figure 19; 65)
were synthesized and evaluated as nonnucleoside reverse transcriptase inhibitors. They exhibited reduced neurotoxic effects and an improved resistance profile. In addition, alanine substitutes on the chiral indolylarylsulfones showed more potent inhibition as nonnucleoside reverse transcriptase inhibitors [95]. Similarly, novel indolylarylsulfones (66) bearing ethylene sulfonamide or acrylamide reactive groups were synthesized and evaluated against mutant HIV-1 IIIB and WT (wild-type) strains to inactivate Cys181-containing HIV-1 RT. The large size of the nonnucleoside reverse transcriptase inhibitors binding pocket facilitated an excellent fit in the mutant enzyme. Some indolylarylsulfone derivatives showed significant activity, but low selectivity index due to their cytotoxicity [96]. Zhao et al. synthesized a series of novel IASs (Figure 19; 67–71) as potential anti-HIV-1 agents. The compounds with a 5-chloro substituent at the indole ring and methyl groups on the 3-phenylsulfonyl moiety demonstrated activity against both mutant and wild-type HIV-1 strains. The IASs exhibited excellent potency against wild-type and mutant HIV-1 strains, with EC₅₀ values ranging from 0.0043 mM to 4.42 mM [97].

The tricyclic P2 ligand was synthesized via enzymatic desymmetrization of meso-1,2-(dihydroxymethyl)cyclohex-4-ene (72; Figure 20), in order to establish the van der Waals

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**Figure 17: HIV-1 glycoprotein inhibitors.**
and hydrogen bonding interactions at the protease active site (specifically the S2-subsite). However, the X-ray structure showed that the inhibitors maintain all hydrogen bonds with HIV-1 protease, and form a tetracoordinated water-mediated hydrogen bond interaction between one carbonyl oxygen and sulfonamide oxygen with amide nitrogen of Ile 50’ and Ile 50 similar to the darunavir-protease complex. HIV-1 protease inhibitors with sulfonamide moiety as P2’ ligands and tricyclic furanofuran derivatives as P2 ligands have been shown to be potent enzyme inhibitors and have excellent antiviral activity against multidrug-resistant (MDR) HIV-1 variants. In addition, one of the inhibitors with aminobenzothiazole as a P2’ ligand and difluorophenylmethyl as a P1 ligand (73), showed better inhibitory activity and antiviral activity compared to darunavir 72 [98]. In the synthesis of an HIV-1 protease inhibitor, Ghosh et al. sought to enhance the interaction between the ligand and backbone in the protease active site with various substituents and ring sizes investigated (74). From the structure-activity studies, tetrahydropyran oxygen is a critical component for the potency of inhibitors. The fused 6–5–5 ring system (P2 ligand), aminobenzothiazole (P2’ ligand), and difluorophenylmethyl (P1 ligand) all contributed to the outstanding enzyme inhibitory potency and antiviral activity of the compounds against MDR HIV-1 variants. The successful synthesis of the P2 ligand (74) was achieved using the key step of the Pauson–Khand cyclization reaction [99].

The introduction of sulfamide-substituted piperazine/piperidines and methylsulfonyl to diarylpyrimidine derivatives (DAPYs) (Figure 21; 75) was aimed at addressing the poor water solubility and resistance against E138K variant exhibited by the DAPYs. The anti-HIV activity of the compound was found to be 2 times more potent against E138K mutant HIV-1 and wild-type (EC50(E138K) = 0.0075 μM, EC50(WT) = 0.0035 μM) than etravirine, with low cytotoxicity (CC50 ≥ 173 μM). No acute toxicity was observed even with a high dosage of 2000 mg·kg⁻¹. Moreover, the compound showed improved water solubility and did not inhibit cytochrome P450 enzymes. In addition to this, another piperidine-substituted thiophene [2,3-d] pyrimidine derivative (76) was synthesized and tested against HIV-1 strain in MT-4 cells. The compound demonstrated excellent anti-HIV activity compared to etravirine (ETR), along with improved solubility, no phenotypic cross-resistance, and lower cardiotoxicity risk [100].

A novel class of HIV-1 protease inhibitors was synthesized, which incorporated the aryl thiazole derivatives of dasatinib and the pyridyl-pyrimidine nilotinib subunit as P2 ligands. Among these compounds, N-((2S,3R)-3-hydroxy-4-
((N-isobutyl-4-methoxyphenyl) sulfonamido) 1-phenylbutan-2-yl)-4-methyl-3-((4-(pyridin-3-yl) pyrimidin-2-yl) amino) benzamide (77), featuring a 4-methoxysulfonamide as the P2′ ligand, exhibited the highest potency, with antiviral activity of 154 nM and an enzyme inhibitory Ki of 28 pM. N-((2S,3R)-4-((4-amino-N-isobutylphenyl) sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)-4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl) amino) benzamide (78), with a 4-aminosulfonamide as the P2′ ligand, displayed potent antiviral activity (IC50 value of 66 nM). Interestingly, the incorporation of a lipophilic 1,3-difuorophenyl P1 ligand did not improve the antiviral activity. Although inhibitors 77 and 78 at the P2′ ligand differ in the presence of OMe instead of NH₂, the conformational differences in the P2-P3 rings, which remain unknown, may influence the binding potency. To gain further insight into the ligand-binding site interactions of HIV-1 inhibitor (78), an X-ray structural study was conducted, revealing intriguing molecular details [101]. In contrast, the antiviral activity of the darunavir derivative derived from the acetamide P2′ ligand (79) was reduced by 10-fold compared to darunavir. However, the selected protease inhibitors were specifically designed to establish enhanced hydrogen bonding interactions in the S2′ subsite. This was achieved by incorporating substituted acetamide derivatives as the P2′ ligand [102].

In the series of DAPY-type nonnucleoside reverse transcriptase inhibitors designed to enhance backbone-binding interactions, derivative 80 displayed hydrogen bonding interactions between its sulfonyl group and mutant strains L234 and F227 HIV-1 virus. In addition, the cyano group in the compound formed hydrophobic contacts with the side-chain atoms of V106 and F227. This compound has a lower likelihood of causing drug-drug interactions, improved water solubility, and further optimization for enhanced oral bioavailability. The potency order of the terminal substituents on piperazinyl (R2) was observed as follows: methyl sulfonyl ≥ ethyl sulfonyl ≥ cyclopropane sulfonyl ≥ 2-propane sulfonyl ≥ N,N-dimethyl sulfonyl ≥ acryloyl [103]. Significantly, the investigation of the structure-activity relationship (SAR) of arylsulfonamides and aliphatic sulfonamides by Wang et al. revealed a compelling finding: an increase in steric bulk corresponded to a decrease in potency. This observation sheds light on the impact of steric factors on the activity of these compounds [71]. A variety of structurally diverse DPAPYs (delavirdine and piperdin-4-ylaminopyrimidine) were...
synthesized using a molecular hybridization approach. Their effectiveness against the wild-type HIV-1 strain (IIIB) was evaluated, revealing a range of moderate to excellent inhibitory effects with EC₅₀ values spanning from 8.6 nM to 5.7 μM. Among the synthesized derivatives of DPAPYs, N-(2-(4-((4-(2,4,6-trimethylphenoxy) pyrimidin-2-yl) amino) piperidine-1-carbonyl)-1Hindol-5-yl) methanesulfonamide exhibited the highest potency against WT HIV-1 (EC₅₀ = 8.6 nM, SI = 2151). Notably, the presence of a methanesulfonamide group at position 5 on the indole moiety formed a hydrogen bond with Pro236. In addition, the carbonyl group of Lys101 and the hydrogen from the NH linker formed a crucial hydrogen bond. These interactions were favorable for enhancing the binding affinity of N-(2-(4-((4-(2,4,6-trimethylphenoxy) pyrimidin-2-yl) amino) piperidine-1-carbonyl)-1Hindol-5-yl) methanesulfonamide to the nonnucleoside binding pocket (NNIBP), resulting in improved anti-HIV-1 activity [104].

The importance of the sulfonamide linker and the impact of different substituents on the antiviral activity of oxazole-benzenesulfonamides against HIV-1 were highlighted by screening a series of oxazole-benzenesulfonamides for their ability to inhibit HIV-1 and reduce viral replication. The results demonstrate that the inhibition of HIV-1 by these compounds is complex and that the sulfonamide linker is crucial for their activity. Also, Figure 22 shows the structures of the oxazole-benzenesulfonamide derivatives with different substituents on the same substructure. Notably, while asymmetrical tertiary sulfonamides have been reported to be highly active, compound 85 was found to be inactive. In addition, the presence of a secondary sulfonamide with a hydrogen bond donor (NH group) appears to be responsible for the antiviral potency and lower binding affinity of compound 84 in HEK293T cells compared to compound 83. However, in HeLa cells, compound 84 is more potent than compound 83 [105].
A series of arylsulfonamide compounds were designed based on Lipinski’s rule of five, with hydrogen-bond acceptor and donor sites, and evaluated in vitro against HIV-1 using TZM-bl cells. Molecular docking studies showed lower EC\textsubscript{50} values and more stable complexes with the amino acid nonnucleoside inhibitor binding pocket (NNIBP) and the HIV-1 reverse transcriptase. One of the molecules, 4-(4-chloro-benzenesulfonylamino)-N (1H-indazole-5-yl) benzamide, demonstrated significant inhibition of HIV-1 with an EC\textsubscript{50} value in the range of 4.89 × 10\textsuperscript{-5} μM, but its selectivity index (SI) was 2.45, much lower than that of etravirine and nevirapine. Moreover, the molecules showed lower inhibition against HIV-1 under in vitro conditions, while the in silico results were promising due to high binding affinity, high ΔG values, and high reverse transcriptase-ligand stabilization energy [106]. A series of N-phenylbenzenesulfonamide (PBSA) derivatives based on delavirdine were evaluated for their anti-HIV activity against HIV-1 reverse transcriptase. Structure-activity relationship studies revealed that most of the compounds bearing substituents (H, Me, NO\textsubscript{2}, Cl, and MeO) at C-4 exhibited anti-HIV activity with high cytopathogenicity values in the range of 1.607–3.667 mmol/L and >123.11 mmol/L, respectively. Removal of the methyl group at C-2 resulted in improved inhibition, while the removal of the chlorine atom on the B-ring led to weak anti-HIV activity. The compounds were found to be potent against wild-type HIV-1 [107].

Yang et al. study suggests that the potency and selectivity of the compounds are dependent on the size and position of the substituents on the phenyl rings. The study also found that an increase in binding affinity is due to the strong electrophilic induction effect and larger size of the substituent (N(CH\textsubscript{3})\textsubscript{2} > OCH\textsubscript{3} > CH\textsubscript{3}) on the phenyl ring. Potency was also observed to increase with the presence of a large electron-withdrawing substituent (NO\textsubscript{2} > Br > Cl > F) at the ortho position, while the presence of this substituent at the meta-position decreased bioactivity. However, the presence of a bulky tri-substituted group had a negative impact on activity.
Based on structure-activity relationships of potent HIV-1 protease inhibitors designed and screened, those with 4-trifluoromethyl, 4-methoxyl, and 4-amino substituents exhibit more potent enzyme inhibition. The presence of oxygen in the methoxyl group facilitates the formation of a hydrogen bond with the carboxylate of Asp30' side-chain and the backbone NH, thereby improving the antiviral potency. A total of twenty-four compounds were synthesized, and all exhibited exceptional activity with maximal inhibitory concentration (IC$_{50}$) values below 20 nM. In particular, the compounds with 4-methoxyphenylsulfonamide (P2'-ligand) and (R)-piperidine-3-carboxamide (P2-ligand) gave the highest MIC value (IC$_{50}$ = 3.61 nM) and effectively inhibited wild-type HIV-1 [109].

The structure-activity relationship study of the benzene sulfonamide quinoline scaffold as anti-HIV-1 and anti-Rev revealed that (i) quinoline substructures play a crucial role in anti-HIV-1 and anti-Rev activities, (ii) 2,4-difluoro substitution has an electron-withdrawing property and showed potent anti-HIV-1 replication, and (iii) sulfonamides with methyl or ethyl substituents on their nitrogen atom exhibit anti-HIV-1 infectivity and anti-Rev activity [110]. Singh et al. developed quinoline-based scaffolds with amide and sulfonamide linkages, which exhibit anti-HIV activity. The observed anti-HIV activity could be attributed to the presence of the sulfonamide linkage, the para-methyl group on the benzene ring, or the presence of a thiophene ring [27]. Finally, Monforte et al. synthesized a series of sulfone derivatives that exhibit potent activity as HIV-1 nonnucleoside reverse transcriptase inhibitors. Among these derivatives, the most promising results were observed for the para-substituted derivative of sulfanyl-N-phenylacetamide, which demonstrated enzymatic inhibition at nanomolar concentrations and displayed a highly intriguing selectivity index (SI) [111].

2. Conclusion

Infectious diseases are a leading cause of death worldwide, with HIV and tuberculosis posing significant threats to public health. Therefore, research efforts continue to focus on preventing and treating these diseases. The aim of this review is to examine the biological activities of sulfonamide compounds as an anti-HIV and antimycobacterial agents, as well as its structure-activity relationship. Numerous sulfonamide compounds have been synthesized and assessed by researchers for their potential as anti-HIV and antimycobacterial agents. The reviewed study reveals that sulfonamide compounds exhibit excellent antimycobacterial and anti-HIV activity with low cytotoxicity, good MIC values, enhanced solubility, and high resistance profile against multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. However, both biological and in silico investigations have highlighted the critical significance of incorporating sulfonamide groups into these compounds. Moreover, the potency of sulfonamide compounds seems to be influenced by the size and position of substituents, as well as their electron-withdrawing or electron-donating substituents. Furthermore, the presence of different substituents, including alkyl groups, methoxy groups, halogens, and others, can lead to either a decrease or an enhancement in the potency of the HIV-1 and M. tuberculosis inhibitors.
Conflicts of Interest

The author declares that there are no conflicts of interest.

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