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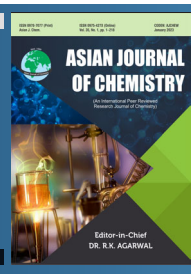

Design, Synthesis, Characterization of Novel Sulfathiazole Derivatives and their *in silico* and *in vitro* Analysis against Multidrug-Resistance Tuberculosis using Docking Studies

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In this study, seven novel sulfathiazole derivatives were synthesized from sulfathiazole using different substituted aldehydes and characterized by IR, NMR and LC-MS analysis. Using molecular docking and toxicity prediction, all the seven novel sulfathiazole derivatives (**Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43**) were virtually screened from generated 70 compounds and assessed their effectiveness against multidrug resistant *Mycobacterium tuberculosis* (MDR-TB). The Inha protein of TB were performed and all the compounds found to have good docking scores in the range of -7.2 to -9.1 Kcal/mol. Compound, 4-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-*N*-(1,3-thiazol-2-yl)benzene-1-sulfonamide (**Mol-27**) shown to inhibit the MDR-TB and wild-type TB strain with an MIC value of 1 µg/mL and 0.25, respectively. The standard sulfathiazole and isoniazid were compared to the minimal inhibitory concentration (MIC) of the synthesized **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** new sulfathiazole derivatives. Based on the results, these compounds shows promising activity against MDR-TB.

Keywords: *Mycobacterium tuberculosis*, Sulfathiazole, Docking studies, ADMET, Virtual screening.

INTRODUCTION

The two leading infectious disease killers in the world are tuberculosis (TB) and the emergence of multidrug-resistant TB (MDR-TB). This year, more than any other year in history, there are expected to be roughly 10.4 million new TB cases [1,2]. MDR-TB, which is resistant to at least rifampin (RIF) and isoniazid (INH), the two most significant first-line medications now used in clinics, is now expected to account for 5% of all TB cases [3,4]. In general, TB incidence in HIV-positive patients is 50 times higher than it is in HIV-negative people [5-7]. The protracted course of TB treatment, the development of drug resistance and co-infection with HIV/AIDS provide management challenges. According to the year 2019 WHO study, latent MDR-TB infections affect almost one-fourth of the world's population. In 2018, 10.9 million people were diagnosed with TB, a figure that has remained largely steady in recent years. In addition to the 0.25 million HIV-positive deaths in 2018, 1.2 million HIV-negative persons worldwide passed away from TB in 2018.

Tuberculosis (TB) is now the worst infectious illness in the world, killing more people than HIV/AIDS and ranking in the top ten leading causes of death globally [8]. For the difficult current treatment regimen, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) must be administered for a minimum of six months to cure drug-sensitive TB [9]. Due to poor patient compliance, this prolonged course of treatment and high pill dosage, along with its adverse effects, led to a partial eradication of TB and, ultimately, the formation of drug-resistant TB [10-12]. Prominently, the length of treatment for second-line anti-TB drugs used for multi- and extensively drug-resistant TB strains (MDR- and XDR-TB, respectively) may be extended by up to 2 years, even though they are less effective, more toxic and cost more than first-line anti-TB drugs [13]. Therefore, the need for anti-TB medications with an unique mode of action to combat existing drug resistance and shorter treatment durations is critical.

Chemists have been interested in a variety of heterocyclic compounds with nitrogen, sulphur and oxygen heteroatoms because of their biological characteristics over the years. Due to its wide range of biological effects, including antibacterial [14,15], antidiabetic [16], antibiofilm [17], anticancer [18], antifungal [19,20], anti-inflammatory [21], tyrosinase inhibitory

[22], cyclooxygenase-2 inhibitory [23] and anti-HIV [24] properties, this intriguing core has attracted significant attention. The biological activities of thiazolidinones revealed that the substitution at various locations would result in diversified activities [25].

Emerging resistance to the two most potent first-line medications necessitates the use of second-line treatment regimens that are more toxic, more expensive and less successful than those used for cases that are drug-susceptible, which results in worse clinical outcomes. To make matters worse, existing second-line regimens for treating MDR-TB infections result in clinically practically incurable results due to increased resistance to fluoroquinolones and second-line injectable medicines. Because of this, there is a pressing need for novel antibiotics with enhanced safety, tolerability and effectiveness. There is an urgent need to find new classes of molecules that do not share resistance with existing anti-mycobacterial medications because no novel chemical scaffold for the treatment of this disease has been introduced in the last 40 years [26,27]. In this study, the most promising and safe novel sulfathiazole derivatives against multidrug-resistant tuberculosis were virtually screened. Additionally, the virtually screened compounds were chosen for synthesis and their biological activity against MDR-TB was assessed.

EXPERIMENTAL

Drug design: An important area of study in the development and improvement of drugs is ligand-based drug design. As a result, employing a three-step synthetic possibility method, this technique was used to generate 70 new sulfathiazole derivatives from a sulphonamide molecule.

Molecular docking studies: An InhA protein from mycobacterium TB bound to NITD-916 has a crystal structure, which may be found in the RCSB protein data bank (http://www.pdb.org/pdb/home/home.do). AutoDock 4.2 was applied to investigate how the active substances interacted with the enzyme. All heteroatoms were eliminated from the proteins to render the complex receptor devoid of any ligand prior to docking. The enzyme's water molecule was removed and hydrogen atoms were added in the typical geometry before docking with AutoDock tools.

***in silico* Toxicity predictions:** Predictions of the intended drugs' absorption, distribution, metabolism, excretion and toxicity (ADMET) were made using the SwissADME and PreADMET online programmes (http://www.swissadme.ch/). The plasma protein binding (PPB), cytochrome CYP2D6 inhibition, blood-brain-barrier penetration (BBB), hepatotoxicity levels, aqueous solubility and human intestinal absorption (HIA) pharmacokinetic parameters were assessed in this investigation [28-30].

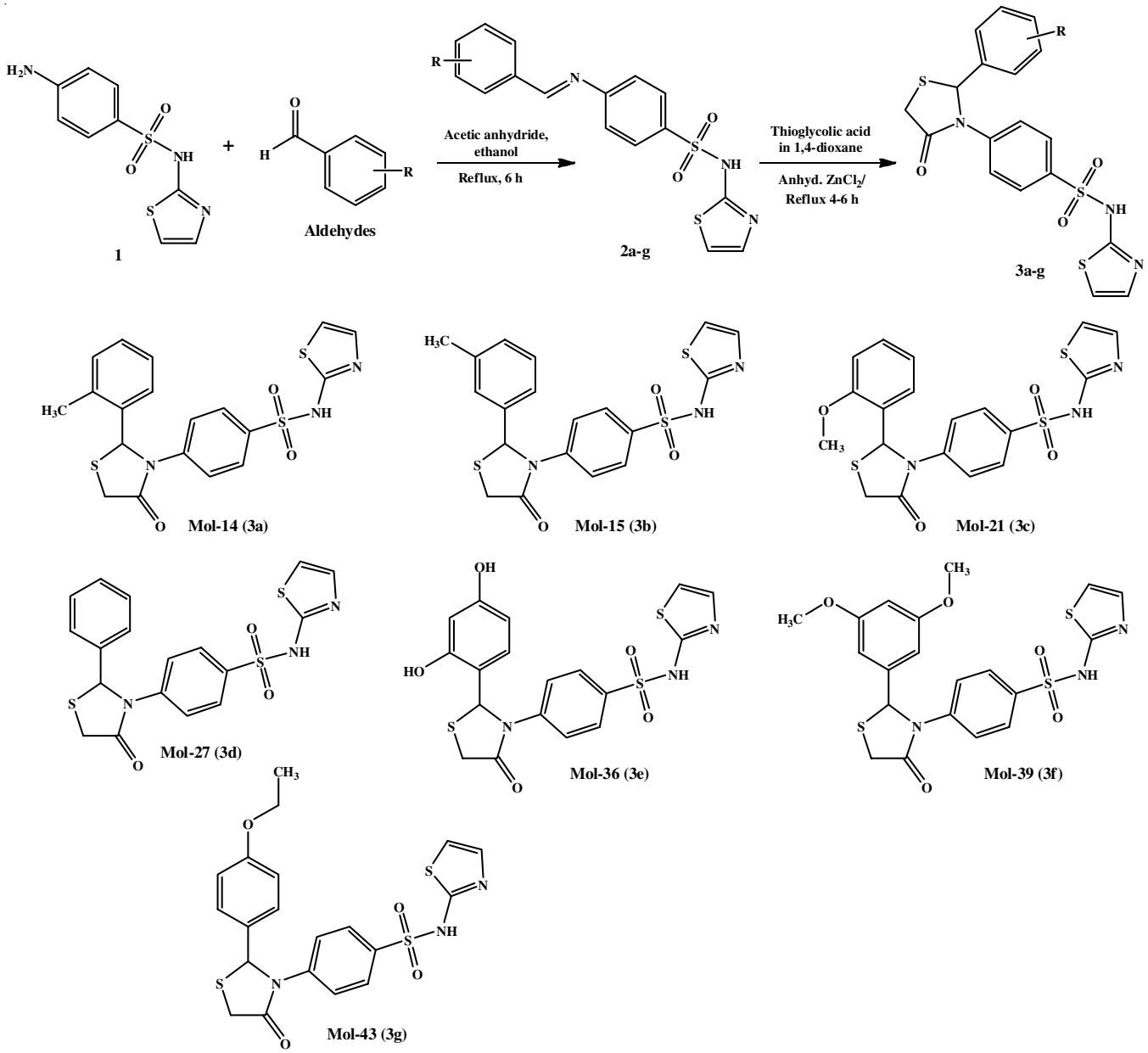
General procedure for the synthesis of sulfathiazole Schiff bases (2a-g): Absolute ethanol (20 mL), substituted aromatic aldehydes (0.001 mol), sulfathiazole (0.001 mol) and acetic anhydrides (1 mL) were mixed in a portionwise manner and then the stirred reaction mixture, which was refluxed for 12 h. TLC was used to track the reaction's development (eluent: 30% *n*-hexane/ethyl acetate). A precipitate formed after cooling, which was separation by filtering, washed with ice-cold ethanol and then re-crystallized from ethanol [12].

General procedure for the synthesis of sulfathiazole Schiff bases (3a-g): Thioglycolic acid was combined with a solution of Schiff base (0.001 mol) in 80 mL of toluene. The Dean stark trap was used to reflux the resultant solution. TLC was used to track the reaction's development (eluent: 50% *n*-hexane/ethyl acetate). Ethyl acetate and brine were used to wash the mixture. Over Na_2SO_4, the organic layer was dried before being concentrated in a vacuum. In ethanol, the products were recrystallized (**Scheme-I**). The final compound was purified by column chromatography (eluent: *n*-hexane/ethyl acetate 40%).

4-[2-(2-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-14): Yield: 72%, m.p.: 123-125 ºC, IR (KBr, ν_{max}, cm^{-1}): 1632 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 2.21 (3H, s, -CH_3) 3.40 (1H, d, *J* = 14.0 Hz, 1,3-thiazolidinone -CH_2), 3.80 (1H, d, *J* = 13.5 Hz, 1,3-thiazolidinone -CH_2), 6.28 (1H, s, 1,3-thiazolidinone -CH), 7.09-7.85 (6H, m, 1,3-thiazole and aromatic benzene), 8.52-8.90 (4H, ddd, *J* = 7.0 Hz, benzene), 11.40 (1H, s, -NH). ^{13}C NMR (400 MHz, DMSO): ^{13}C NMR: δ 21.41 (1C, s, -CH_3), 39.22 (1C, s, 1,3-thiazolidinone-S-CH_2), 65.34 (1C, s, 1,3-thiazolidinone- S-CH), 108.10 (1C, s, benzene), 114.38 (1C, s, 1,3-thiazole- S-CH), 121.05-141.64 (8C, s, benzene), 147.20 (1C, s, 1,3-thiazole -N-CH), 160.87 (1C, s 1,3-thiazole-N-C), 172.30 (1C, s, 1,3-thiazolidinone- C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{19}H_{17}N_3O_3S_3$ is 431.05 *m/z*. It was confirmed in LC-MS analysis: 432.20 [M+1] *m/z*.

4-[2-(3-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-15): Yield: 81%, m.p.: 128-130 ºC, IR (KBr, ν_{max}, cm^{-1}): 1737 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 2.80 (3H, s, -CH_3) 3.65 (1H, d, *J* = 14.8 Hz, 1,3-thiazolidinone -CH_2), 4.05 (1H, d, *J* = 14.2 Hz, 1,3-thiazolidinone -CH_2), 6.10 (1H, s, 1,3-thiazolidinone -CH), 7.23-8.10 (6H, m, 1,3-thiazole and aromatic benzene), 8.65-8.95 (4H, ddd, *J* = 7.8 Hz, benzene), 11.52 (1H, s, -NH). ^{13}C NMR (400 MHz, DMSO): ^{13}C NMR: δ 19.27 (1C, s, -CH_3), 40.38 (1C, s, 1,3-thiazolidinone- S-CH_2), 64.16 (1C, s, 1,3-thiazolidinone- S-CH), 105.45 (1C, s, benzene), 116.21 (1C, s, 1,3-thiazole- S-CH), 122.40-142.54 (8C, s, benzene), 148.20 (1C, s, 1,3-thiazole-N-CH), 161.85 (1C, s 1,3-thiazole-N-C), 174.36 (1C, s, 1,3-thiazolidinone- C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{19}H_{17}N_3O_3S_3$ is 431.05 *m/z*. It was confirmed in LC-MS analysis: 432.10 [M+1] *m/z*.

4-[2-(2-Methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-21): Yield: 80%, m.p.: 135-137 ºC, IR (KBr, ν_{max}, cm^{-1}): 1738 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 2.23 (3H, s, -O-CH_3) 3.78 (1H, d, *J* = 15.2 Hz, 1,3-thiazolidinone -CH_2), 4.30 (1H, d, *J* = 15.9 Hz, 1,3-thiazolidinone -CH_2), 5.68 (1H, s, 1,3-thiazolidinone -CH), 7.05-7.92 (6H, m, 1,3-thiazole and aromatic benzene), 8.50-8.90 (4H, ddd, *J* = 7.0 Hz, benzene), 11.78



Scheme-I: Synthesis of novel sulfathiazole derivatives (**3a-g**)

(1H, s, -NH). ^{13}C NMR (400 MHz, DMSO): ^{13}C NMR: δ 41.02 (1C, s, 1,3-thiazolidinone- S-CH_2), 55.35 (1C, s, O-CH_3), 64.68 (1C, s, 1,3-thiazolidinone- S-CH), 102.74 (1C, s, benzene), 112.40 (1C, s, 1,3-thiazole- S-CH), 122.12-146.80 (8C, s, benzene), 149.60 (1C, s, 1,3-thiazole -N-CH), 162.64 (1C, s 1,3-thiazole-N-C), 175.20 (1C, s, 1,3-thiazolidinone- C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{19}H_{17}N_3O_4S_3$ is 447.09 *m/z*. It was confirmed in LC-MS analysis: 448.20 [M+1] *m/z*.

4-(4-Oxo-2-phenyl-1,3-thiazolidin-3-yl)-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-27): Yield: 80%, m.p.: 115-117 ºC, IR (KBr, ν_{max}, cm^{-1}): 1639 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 3.63 (1H, d, *J* = 15.8 Hz, 1,3-thiazolidinone -CH_2), 4.84 (1H, d, *J* = 16.8 Hz, 1,3-thiazolidinone -CH_2), 6.56 (1H, s, 1,3-thiazolidinone -CH), 7.10-7.82 (6H, m, 1,3-thiazole and aromatic benzene), 8.63-9.01 (4H, ddd, *J* = 7.0 Hz, benzene), 11.80 (1H, s, -NH). ^{13}C NMR (400 MHz, DMSO): ^{13}C NMR: δ 44.12 (1C, s, 1,3-thiazolidinone-S-CH_2), 65.20 (1C, s, 1,3-thiazolidinone- S-CH), 100.78 (1C, s, benzene), 110.63 (1C, s, 1,3-thiazole- S-CH), 120.89-148.01 (8C, s, benzene), 150.40 (1C, s, 1,3-thiazole -N-CH), 165.50 (1C, s 1,3-thiazole-N-C), 175.28 (1C, s, 1,3-thiazolidinone-C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{18}H_{15}N_3O_3S_3$ is 417.03 *m/z*. It was confirmed in LC-MS analysis: 418.15 [M+1] *m/z*.

4-[2-(2,4-Dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-*N*-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-36): Yield: 75%, m.p.: 130-132 ºC, IR (KBr, ν_{max}, cm^{-1}): 1727 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 3.01 (1H, d, *J* = 15.6 Hz, 1,3-thiazolidinone -CH_2), 4.11 (1H, d, *J* = 16.2 Hz,

1,3-thiazolidinone -CH_2), 6.59 (1H, s, 1,3-thiazolidinone -CH), 7.23-8.04 (6H, m, 1,3-thiazole and aromatic benzene), 8.71-9.25 (4H, ddd, *J* = 7.3 Hz, benzene), 11.27 (1H, s, -NH), 13.41 (2H,s, 2-OH) ^{13}C NMR (400 MHz, DMSO): ^{13}C NMR: δ 44.98 (1C, s, 1,3-thiazolidinone- S-CH_2), 60.13 (1C, s, 1,3-thiazolidinone- S-CH), 106.29 (1C, s, benzene), 110.68 (1C, s, 1,3-thiazole-S-CH), 121.79-146.06 (8C, s, benzene), 155.38 (1C, s, 1,3-thiazole -N-CH), 165.33 (1C, s 1,3-thiazole-N-C), 170.49 (1C, s, 1,3-thiazolidinone- C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{18}H_{15}N_3O_5S_3$ is 449.01 *m/z*. It was confirmed in LC-MS analysis: 450.18 [M+1] *m/z*.

4-[2-(3,5-Dimethoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-*N*-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-39): Yield: 74%, m.p.: 142-144 ºC, IR (KBr, ν_{max}, cm^{-1}): 1726 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 2.29 (6H,s, -OCH_3), (3H, s, -O-CH_3) 3.47 (1H, d, *J* = 12.5 Hz, 1,3-thiazolidinone -CH_2), 4.29 (1H, d, *J* = 17.8 Hz, 1,3-thiazolidinone -CH_2), 6.07 (1H, s, 1,3-thiazolidinone -CH), 7.20-8.18 (5H, m, 1,3-thiazole and aromatic benzene), 8.53-9.20 (4H, ddd, *J* = 7.0 Hz, benzene), 11.03 (1H, s, -NH); ^{13}C NMR (400 MHz, DMSO): ^{13}C NMR: δ 42.38 (1C, s, 1,3-thiazolidinone- S-CH_2), 62.78 (1C, s, 1,3-thiazolidinone- S-CH), 102.31 (1C, s, benzene), 114.20 (1C, s, 1,3-thiazole- S-CH), 121.14-141.12 (8C, s, benzene), 150.16 (1C, s, 1,3-thiazole -N-CH), 162.64 (1C, s, 1,3-thiazole-N-C), 172.82 (1C, s, 1,3-thiazolidinone- C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{20}H_{19}N_3O_5S_3$ is 477.16 *m/z*. It was confirmed in LC-MS analysis: 478.27 [M+1] *m/z*.

4-[2-(4-Ethoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-*N*-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-43): Yield: 82%, m.p.: 120-122 ºC, IR (KBr, ν_{max}, cm^{-1}): 1613 (C=O, sharp peak). ^{1}H NMR (400 MHz, DMSO): δ 2.06 (3H, s, -CH_3), 2.89 (t, 2H, -CH_2), 3.84 (1H, d, *J* = 12.8 Hz, 1,3-thiazolidinone -CH_2), 4.61 (1H, d, *J* = 14.2 Hz, 1,3-thiazolidinone -CH_2), 6.37 (1H, s, 1,3-thiazolidinone -CH), 7.08-7.95 (5H, m, 1,3-thiazole and aromatic benzene), 8.41-9.16 (4H, ddd, *J* = 7.0 Hz, benzene), 11.64 (1H, s, -NH); ^{13}C NMR (400 MHz, DMSO): δ 14.56 (1C, s, CH_3) 40.62 (1C, s, 1,3-thiazolidinone- S-CH_2), 61.04 (1C, s, 1,3-thiazolidinone- S-CH), 64.32 (1C, s, -CH_2) 101.60 (1C, s, benzene), 107.85 (1C, s, 1,3-thiazole- S-CH), 125.61-145.15 (8C, s, benzene), 152.41 (1C, s, 1,3-thiazole -N-CH), 165.18 (1C, s 1,3-thiazole-N-C), 172.63 (1C, s, 1,3-thiazolidinone- C=O). The molecular weight and purity of the isolated compound was analyzed by LC-MS (ESI). The calculated molecular weight of $C_{20}H_{19}N_3O_4S_3$ is 461.23 *m/z*. It was confirmed in LC-MS analysis: 462.06 [M+1] *m/z*.

Biological activity: The multidrug-resistant tuberculosis (MDR-TB) was collected from K.A.P. Viswanatham Government Medical College, Tiruchirappalli, India and its resistance was confirmed using methicillin, ciprofloxacin, isoniazid strip (HiMedia-MD031 MET (B)) The MDR-TB strain was cultured in a Brain Heart Infusion (BHA) medium and stored in a glycerol stock (30%) at -20 ºC for future analysis. The synthesized compounds Mol-14, Mol-15, Mol-21, Mol-27, Mol-36, Mol-39 and Mol-43 were subjected to the biological activity on MDR-TB and wild-type TB using MIC method.

RESULTS AND DISCUSSION

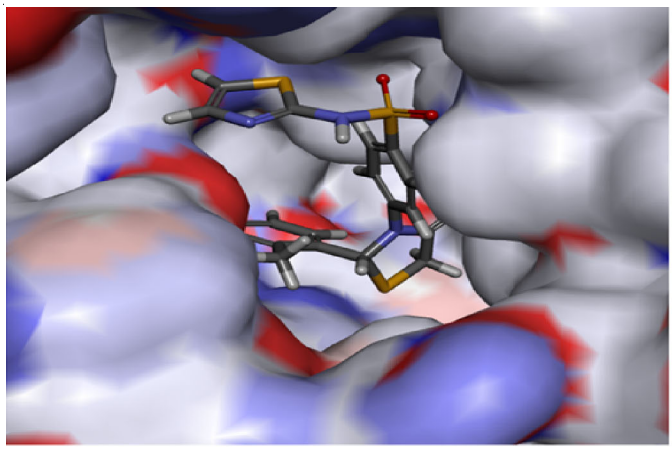
The FT-IR spectrum of the synthesized sulfathiazole derivatives (**Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43**) showed the characteristic IR band at 1738-1613 cm^{-1}**,** which indicated the presence of -C=O group in the substituted 4-thiazolidinone ring of sulfathiazole derivatives. The ^{1}H NMR of the synthesized compounds were recorded and the appearance of a singlet at δ 2.21, δ 2.80 and δ 2.23 ppm confirmed the presence of substituted new aromatic aldehydes (**Mol-14**, **Mol-15**, **Mol-21**) in Schiff base moiety in the synthesized sulfathiazoles. Further, the doublet signal at δ 3.65-4.80 ppm of all the ^{1}H NMR indicate the presence 1,3-thiazolidinone -CH_2 group of the derivatives. The 1,3-thiazolidinone -CH- group of the derivatives shown singlet at δ 5.68- 6.59 ppm. The multiplate signal at δ 7.05-8.90 ppm confirmed the presence of 1,3-thiazole and aromatic benzene groups. The presence of -NH group showed a sharp singlet peak at δ 11.80-11.80 ppm. The singlet peak at δ 13.41 ppm displayed the presence of *ortho* and *para* substituted on the aromatic group of **Mol-36**.

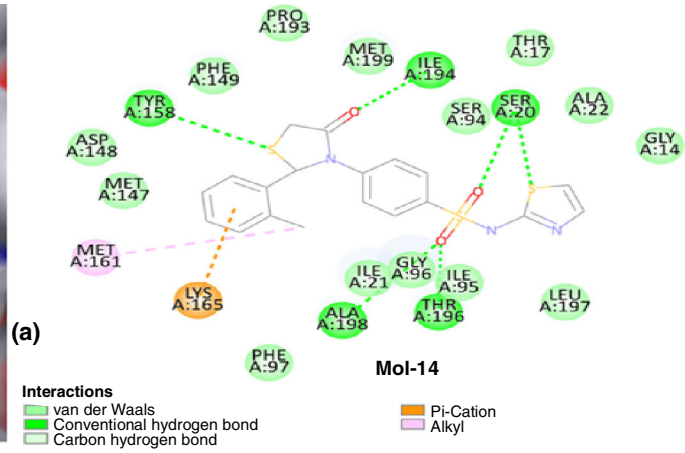
In the ^{13}C NMR spectrum, the signal of δ 21.41, δ 19.27 ppm indicate the presence of -CH_3 substituted on **Mol-14**, **Mol-15** and δ 55.35 signal conform the O-CH_3 group of **Mol-21**. The C atom of the 3-thiazolidinone- S-CH_2 and - S-CH- were confirmed by signal at δ 39.22 and 65.34 ppm in **Mol-14**. Moreover, the aromatic ring carbons of all the compounds appear signal at δ 100.78-145.15 ppm. The 3-thiazolidinone-C=O was confirmed by signal at from δ 170.49-175.28 ppm in all the ^{13}C NMR spectrum. The ESI mass spectra were recorded at 70 eV and maintained at 150 ºC. The molecular weight (*m/z*) of the all the synthesized compounds were confirmed by MS.

Docking studies: *in silico* study, 70 new sulfathiazole derivatives were docked using AutoDock 4.2 software to identify the potent molecules with good binding interactions compared to standard drugs for further synthesis and biological activity.

Molecular docking studies of MDR-TB: In MDR-TB molecular docking studies, *Mycobacterium tuberculosis* Inha protein was used as the target protein for sulfathiazoles. From molecular docking results and ADMET analysis with designed 70 new sulfathiazole derivatives, **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** showed more binding energy compared to standard isoniazid standard drug and these compounds were virtually screened for further biological activity. The binding energy of **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** was -9.1, -8.3, -9.0, -8.2, -7.5, -8.1, -8.5 $Kcal/mol^{-1}$ respectively. Furthermore, the binding energy of the isoniazid is -3.8 Kcal/mol. **Mol-14** forms six strong H-bonds with Tyr 158, Ile 194, Ser 20, Al 198 and Thr 196 amino acids. Further, Lys 165 shows pi-cation integration with the aromatic benzene of **Mol-14** (Fig. 1a).

Likewise, **Mol-15** interacted with the MDR-TB receptor using three strong H-bond with Lys 165 Tyr 158 and Met 98 amino acids. In this docking analysis, Ile 21, Gly 96, Ala 198, Ile 194 were interacted with MDR-TB receptor by alkyl and pi-alkyl interactions (Fig. 1b). Further, the sulphur and ketone group of **Mol-21** shows three strong H-bond with the Ile 21, Ile 194 and Ser 20 amino acids. The -OH group of **Mol-21**

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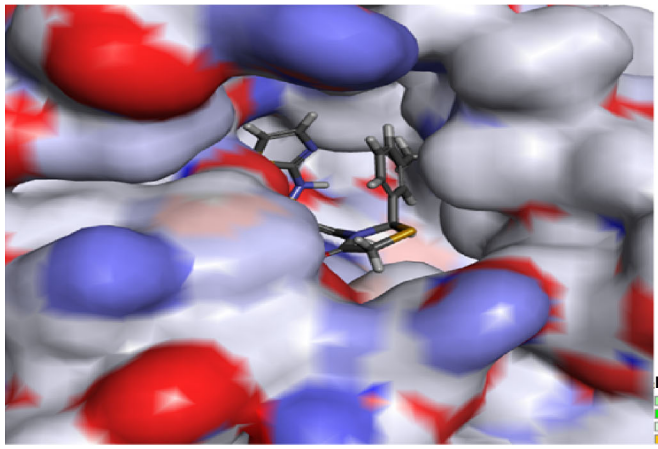
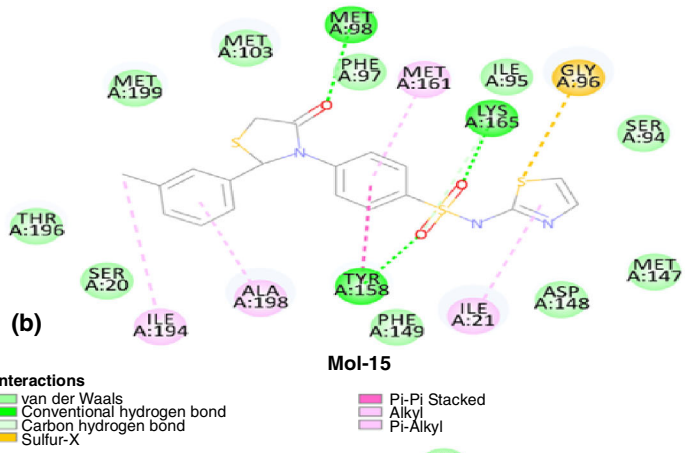
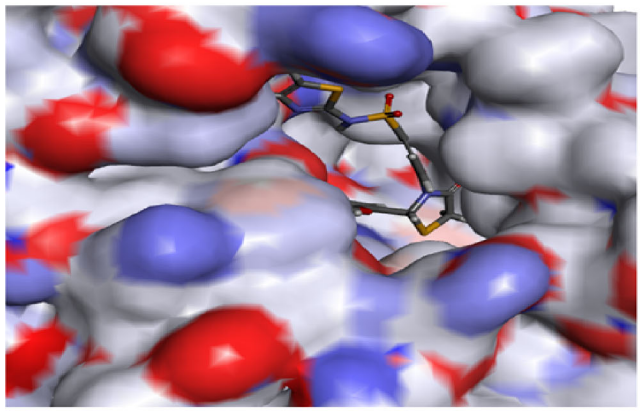
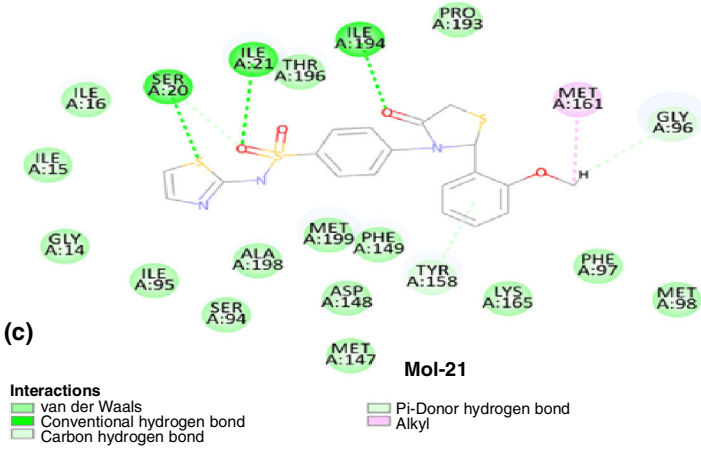
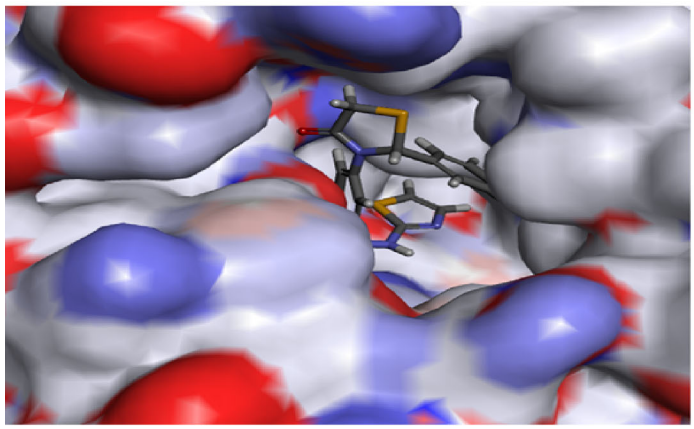
Mol-14
Interactions
van der Waals
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Cation
Alkyl

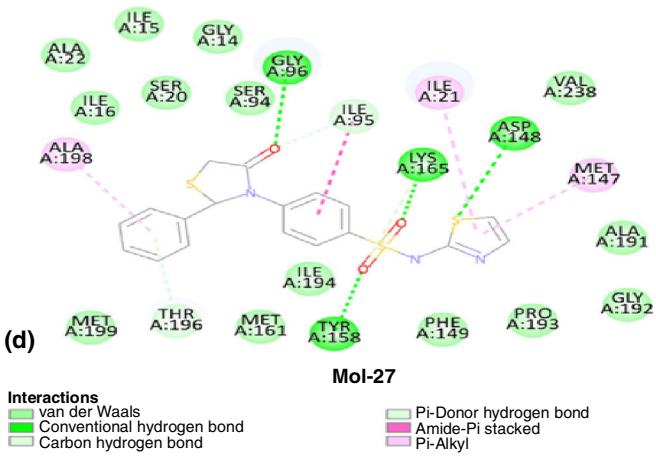



(b)
Mol-15
Interactions
van der Waals
Conventional hydrogen bond
Carbon hydrogen bond
Sulfur-X
Pi-Pi Stacked
Alkyl
Pi-Alkyl




(c)
Mol-21
Interactions
van der Waals
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Donor hydrogen bond
Alkyl




(d)
Mol-27
Interactions
van der Waals
Conventional hydrogen bond
Carbon hydrogen bond
Pi-Donor hydrogen bond
Amide-Pi stacked
Pi-Alkyl

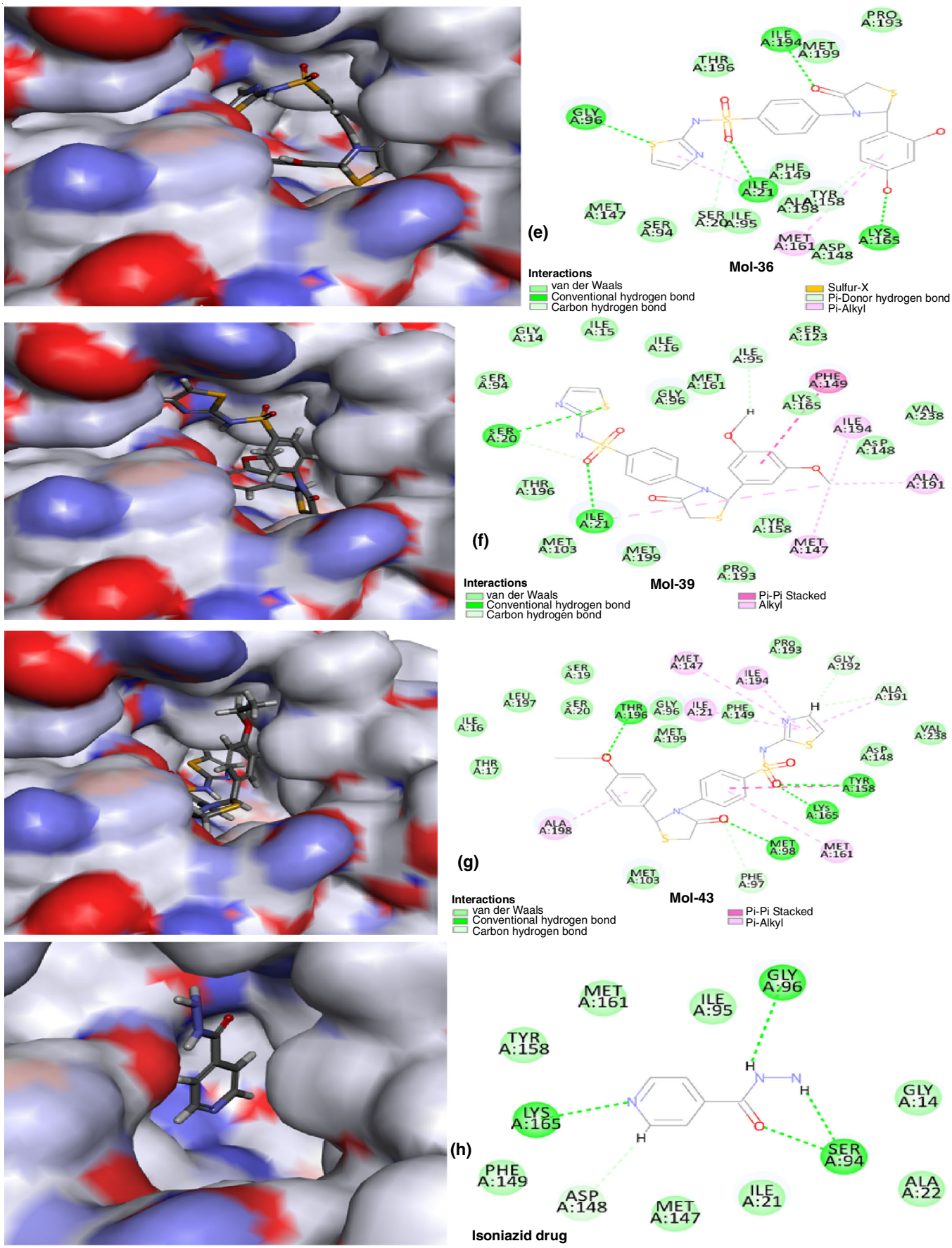


Fig. 1. Molecular binding interaction of the (a) **Mol-14**, (b) **Mol-15**, (c) **Mol-21**, (d) **Mol-27**, (e) **Mol-36**, (f) **Mol-39**, (g) **Mol-43** and (h) isoniazid drug with the MDR-TB protein

TABLE-1
ADMET PREDICTION OF SCREENED **Mol-14, Mol-15, Mol-21, Mol-27, Mol-36, Mol-39** AND **Mol-43** MOLECULES

Molecule name	Absorption level	Solubility level	BBB level	PPB level	Hepatotoxic level	CYP 2D6	PSA 2D	AlogP98
Mol-14	Extremely good	Extremely good	Low	< 90%	No	No	57.23	4.2
Mol-15	Extremely good	Extremely good	Low	< 90%	No	No	65.21	4.6
Mol-21	Extremely good	Extremely good	Low	< 90%	No	No	56.37	4.3
Mol-27	Extremely good	Extremely good	Low	< 90%	No	No	68.14	4.7
Mol-36	Extremely good	Extremely good	Low	< 90%	No	No	61.78	3.9
Mol-39	Extremely good	Extremely good	Low	< 90%	No	No	61.78	3.9
Mol-43	Extremely good	Extremely good	Low	< 90%	No	No	61.78	3.9

interacted with active site **Met 161** amino acids of MDR-TB by alkyl interactions (Fig. 1c). The 3D and 2D binding interactions of **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** with MDR-TB receptor are shown in Fig. 1a-g. The standard drug isoniazid forms three H-bond interactions with the Gly 96, Ser 94 and Lys 165 amino acids (Fig. 1h). The remaining amino acids of the MDR-TB show the van der Waals interactions with isoniazid.

ADMET analysis: Swiss ADMET was used to forecast the results of research on the absorption, distribution, metabolism, excretion and toxicity (ADMET) of isolated substances. Pharmacokinetic and toxicity problems account for the vast majority of early and late pipeline medication failures. If these issues could be resolved at an early stage, the drug discovery process would greatly benefit from them. The results of such analysis are shown in Table-1. Seven new sulfathiazole derivatives (**Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43**) were screened based on the good binding affinity and drug-like features of the 70 new sulfathiazole molecules after molecular docking and ADMET analysis.

The absorption and solubility level of **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** show extremely good and BBB level is low. Furthermore, the PPB level is less than < 90% and no induced hepatotoxicity has been predicted for any of the substances. Present research indicated that all derivatives have a significant first-pass effect and are safe for the liver. Sulfathiazole derivatives cannot be CYP2D6 inhibitors since all ligands are equally potent against CYP2D6 in the liver. Finally, the ADMET analysis shows good drug-like properties of the virtually screened **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** molecules.

Biological activity: The broth dilution method was used to test the virtually screened and synthesized **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** compounds for their antibacterial efficacy against MDR-TB and wild-type TB. The antibacterial activities of the synthesized sulfathiazole derivatives are shown in Table-2. The MIC range of the all the molecules from 1.0-2.25 µg/mL for MDR-TB and 0.25-1.75 µg/mL. When standard sulfathiazole and isoniazid were compared to the minimal inhibitory concentration (MIC) of **Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43** new sulfathiazole derivatives, it became clear that all the derivatives had excellent antibacterial activity against both MDR-TB and wild-type TB. The molecular mechanism behind MDR-in TB's *vitro* antibacterial activity is revealed by the molecular docking investigations of these compounds with MDR-TB receptors.

TABLE-2
ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS AGAINST MDR-TB AND WILD-TYPE TB BY BROTH DILUTION METHOD

Compd.	Molecules	R	Minimum inhibitory concentration (µg/mL)	
			MDR-TB	Wild-type TB
3a	**Mol-14**	2-CH_3	1.55	0.50
3b	**Mol-15**	3-CH_3	1.75	1.00
3c	**Mol-21**	2-OCH_3	1.25	0.75
3d	**Mol-27**	H	1.00	0.25
3e	**Mol-36**	2,4-OH	2.50	0.50
3f	**Mol-39**	3,5-OCH_3	2.50	0.25
3g	**Mol-43**	4-OC_2H_5	2.25	1.25
Sulfathiazole		–	15.00	1.75
Isoniazid		–	12.00	1.50

Conclusion

The newly synthesized and virtually screened sulfathiazole derivatives (**Mol-14**, **Mol-15**, **Mol-21**, **Mol-27**, **Mol-36**, **Mol-39** and **Mol-43**) represent a viable treatment option for MDR-TB. With the help of molecular docking and an examination of ADMET drug-like qualities, newly seven and highly potent sulfathiazole derivatives were synthesized from the developed 70 compounds for this investigation. When compared to the usual medication, the synthesized compounds exhibit drug-like features and strong binding contacts in the MDR-TB receptor's active region. Present findings further implied that these substances might represent a promising new class of anti-MDR tubercular medications. It is necessary to conduct additional, in-depth toxicity research, *in vivo* efficacy research and mechanism of action research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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