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Design, synthesis and docking studies of new molecular hybrids bearing benzimidazole and thiazolidine-2,4-dione as potential antitubercular agents

M.S. Raghu [a], Amar Yasser Jassim [b], C.B. Pradeep Kumar [c], K. Yogesh Kumar [d], M.K. Prashanth [e,*], Fahd Alharethy [f], Byong-Hun Jeon [g,**]

[a] Department of Chemistry, New Horizon College of Engineering, Bengaluru, 560 103, India
[b] Department of Marine Vertebrate, Marine Science Center, University of Basrah, Basrah, Iraq
[c] Department of Chemistry, Malnad College of Engineering, Hassan, 573 202, India
[d] Department of Chemistry, Faculty of Engineering and Technology, Jain University, Ramanagara, 562 112, India
[e] Department of Chemistry, B N M Institute of Technology, Bengaluru, 560 070, India
[f] Department of Chemistry, College of Science, King Saud University, Riyadh, 11451, Saudi Arabia
[g] Department of Earth Resources and Environmental Engineering, Hanyang University, 222, Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea

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ABSTRACT

Finding novel therapeutic medications to combat tuberculosis (TB) is crucial, as evidenced by the disease's growth as a worldwide health concern in recent decades and the rise of drug-resistant forms of *Mycobacterium tuberculosis* (Mtb). In this article, we describe the synthesis and design of a novel class of thiazolidine-2,4-dione derivatives (5a-i) based on 1*H*-benzo [*d*]imidazoles as antitubercular drugs. Spectroscopic techniques and elemental analysis were used to characterize each of the newly synthesized molecules. The antitubercular activity of all the newly synthesized title compounds was assessed against drug-sensitive Mtb H37Rv, multidrug-resistant (MDR-TB), and extensively drug-resistant (XDR-TB) tuberculosis. Compounds 5e and 5 h had the most antitubercular activity among all the newly synthesized hybrids against drug-sensitive, MDR-TB, and XDR-TB strains, with MIC values ranging from 0.21 to 47.84 μM. When it comes to drug-sensitive, drug-resistant, and XDR Mtb strains, compound 5 h with a trifluoromethyl group is 1.71, 10.86, and 3.50 times more potent, whereas compound 5e with a nitro group is 1.12, 8.50, and 2.61 times more active. Remarkably, the compounds' *in vitro* cytotoxicity test demonstrated good selectivity indices, highlighting their safety on the normal lung fibroblast (WI-38) cell line experiment. To further understand the interactions between potent hybrids and the target enzyme, molecular docking investigations were conducted against the decaprenyl-phosphoryl-ribose 2′-epimerase (DprE1) enzyme. The target protein exhibited preferentially positive interactions with the potent compounds 5e, 5f, 5 h, and 5i. Relationships between structure-activity as well as drug-likeness were used to connect the freshly synthesized compounds' physical and biological properties. When considered collectively, these results suggest that compounds 5e and 5 h might be promising candidates for the development of drug-sensitive and drug-resistant TB therapies in the future.

1. Introduction

Mycobacterium tuberculosis (Mtb) is the primary cause of tuberculosis (TB), an infectious illness that affects humans. Since it has been around for millennia, tuberculosis has been a serious health risk to people. It is believed that the TB bacterium infects around 25 % of people worldwide [1]. In 2022, an estimated 7.5 million people worldwide acquired tuberculosis (TB), and 1.3 million fatalities related to the disease were reported [2]. Despite being a disease that dates back to many years, money and effort are constantly put towards making tuberculosis obsolete. The death rate from tuberculosis is too high, even with several attempts to improve diagnostic and treatment protocols [3]. The

* Corresponding author.
** Corresponding author.
E-mail addresses: prashanthmk87@gmail.com (M.K. Prashanth), bhjeon@hanyang.ac.kr (B.-H. Jeon).

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mainstay of TB treatment is first-line, highly effective medication. Due to the prolonged latent period and sluggish development rate of Mtb, TB infection treatment now involves lengthy treatment durations for an effective therapy. Although first- and second-line multicomponent TB therapies are currently in use, they are currently under grave danger [4]. The overuse and misuse of these antibiotics has led to the development of novel strains of tuberculosis, such as extensively drug-resistant tuberculosis (XDR-TB) and multidrug-resistant tuberculosis (MDR-TB), rendering front- and second-line *anti*-TB medications ineffective [5].

Both MDR- and XDR-TB strains are currently found around the world, and because there are few effective treatment options available, both strains are linked to a greater death rate [6–8]. The World Health Organisation predicts that the number of new cases of MDR and XDR TB will rise annually. However, MDR-TB and XDR-TB pose significant threats to the efficacy of existing treatment protocols. Additionally, due to high toxicity and susceptibility, the lengthy and multi-drug therapy regimen has a substantial disadvantage in patients with tuberculosis [9]. Thus, efforts to control tuberculosis are gravely jeopardised by these strains. In order to combat sensitive and resistant TB strains, concerted attempts are being made to develop an effective *anti*-TB medication. Given the gravity of the aforementioned risks, it is now discovered that finding the right *anti*-TB medications to treat effectively is receiving greater focus [10]. Chemists are therefore focusing more on creating novel chemical entities in the hopes of improving antitubercular efficacy while reducing toxicity and lengthening treatment times.

Among the practical fields of organic chemistry, a particular class of heterocycles containing nitrogen-sulphur heteroatoms is crucial, and the creation of new compounds is the focus of a great deal of study [11–14]. Among all the nitrogen-based heterocyclic compounds, benzimidazole and its derivatives are extremely important from a biological and industrial standpoint. Because of their structural similarities to some naturally occurring moieties, like purines, benzimidazoles are easier to attach to enzymes or receptors in living things [15]. An extensive review of FDA-approved medications revealed that 59 % of small-molecule therapeutics included a nitrogen heterocycle ring, with the benzimidazole moiety ranking fifteenth on the list of significant compounds having a fused ring system [16]. Because of this, they are the most important and favoured heterocyclic structures. However, it has been recognised that thiazolidine-2,4-dione is the essential framework for drug discovery and design [17]. This moiety is of interest to researchers since it regulates a number of physiological processes. The fifth position of the thiazolidine-2,4-dione ring is amenable to alteration, which facilitates the search for novel compounds with the necessary activity [18]. A review of the literature showed that different biological activities are produced when thiazolidine-2,4-dione is coupled with other heterocycles [19]. Derivatives of thiazolidine-2,4-dione have antimycobacterial activity in addition to other kinds of activity. Some of them are now undergoing preclinical TB drug development [20]. The literature studies on the *anti*-TB activity of several benzimidazole and thiazolidine-2,4-dione based compounds [21–28] led us to investigate these compounds as potential candidates for our novel *anti*-TB pharmacophore (Fig. 1).

In recent years, it has become apparent that the pharmacophore hybridization approach is being used to create new bioactive molecules with improved therapeutic characteristics. Better results are usually seen when two or more diverse bioactive units with different modes of action or consistent pharmacophoric activities hybridise [29]. In drug research and development, "smart drugs" are pharmaceuticals that have the ability to specifically target targets that are relevant to a certain condition. Proper linker chemistry is typically necessary for the creation of smart pharmaceuticals in order to maintain the potency of the active ingredient [30]. Over the past several years, there has been significant advancement in the invention of novel linker activation techniques [31]. Here, the methylene group connects two physiologically active pharmacophores, such as the thiazolidine-2,4-dione and 1*H*-benzo [*d*]imidazole motifs (Fig. 2). In light of the previously mentioned results and as part of a continuing study to create novel therapeutic agents [32–40], we designed and synthesized a number of novel thiazolidine-2,4-dione derivatives based on 1*H*-benzo [*d*]imidazole that have strong *in vitro* antitubercular activity against drug-sensitive MTB H37Rv, MDR-TB, and XDR-TB. To supplement the *in vitro* antitubercular activity results of the related compounds, we have additionally performed cytotoxic activity, molecular docking, and drug-likeness prediction.

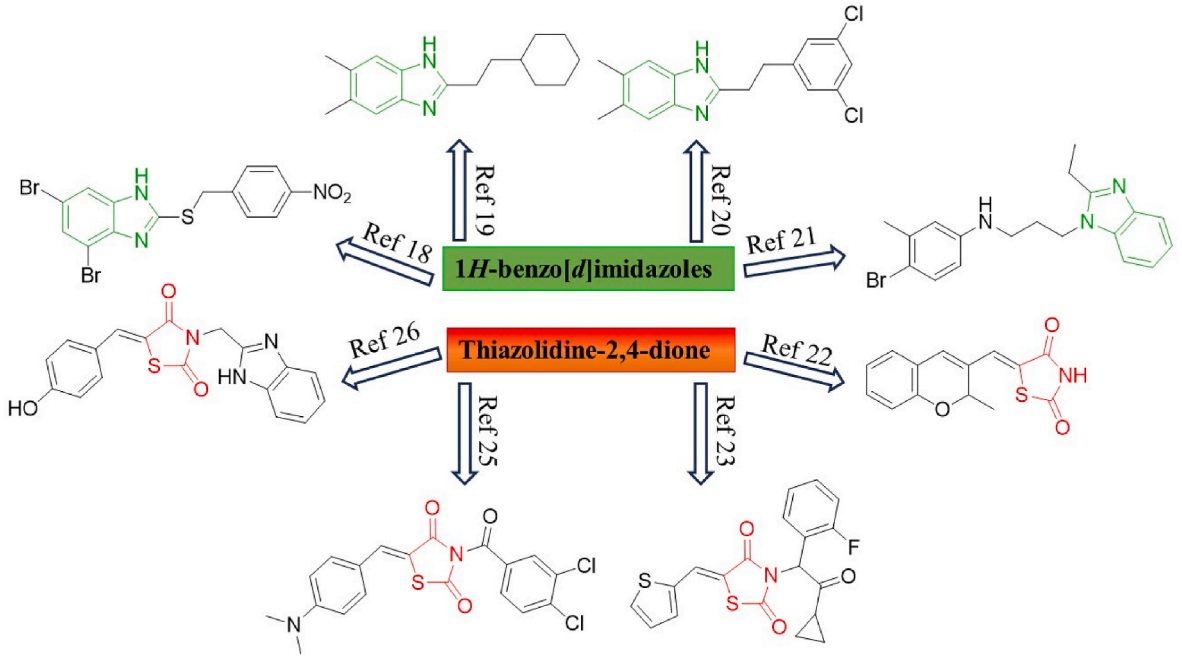


Fig. 1. Reported benzimidazole and thiazolidinedione derivatives as potent *anti*-TB lead molecules.

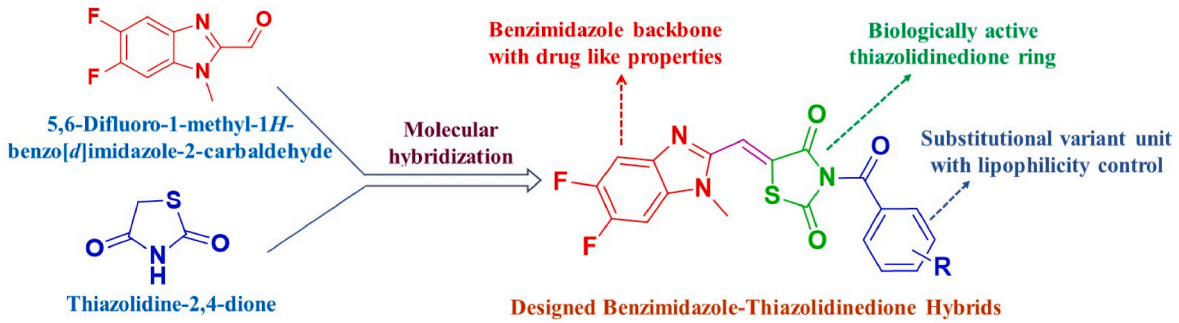


Fig. 2. Design strategy for the synthesis of benzimidazole-thiazolidinedione hybrids.

2. Experimental

2.1. Materials

Solvents and reagents have been obtained commercially and used without further purification. Melting points were determined in open capillaries with the Guna melting point equipment. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were acquired on a Bruker AM 400 spectrometer using DMSO-d_6 solvent and TMS as the internal reference standard, and the chemical shift values were represented in ppm. The mass spectra of the compounds were obtained using a PerkinElmer PE Sciex API/65 L C-MS instrument. The elements analysis was carried out using a PerkinElmer 2400 series II Elemental CHN analyzer.

2.2. Synthesis of 5-((5,6-difluoro-1-methyl-1H-benzo [d]imidazole-2-yl) methylene)thiazolidine −2,4-dione (3)

A mixture consisting of 5,6-difluoro-1-methyl-1*H*-benzo [*d*]imidazole-2-carbaldehyde (1) (5 mmol), thiazolidine-2,4-dione (2) (5 mmol), and piperidine (0.5 mmol) was refluxed in EtOH (25 mL) for 18 h. The reaction process was monitored by TLC, and the reaction mixture was cooled to room temperature overnight; the precipitate was filtered, washed with ice cold ethanol, and dried. Finally, the compound was recrystallized with EtOH to produce a white solid in 87 % yield. mp.: 183–185 °C. Anal. calc. for $C_{12}H_7F_2N_3O_2S$: C, 48.81; H, 2.39; N, 14.23. found: C, 48.78; H, 2.36; N, 14.27.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, *N*–CH_3), 7.38 (s, 2H, Ar–H), 7.57 (s, 1H, –CH), 10.03 (s, 1H, –NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.2, 104.1, 122.6, 131.4, 136.1, 141.5, 143.2, 143.8, 166.3, 167.1. MS, *m/z*: 296 (M+1).

2.3. General procedure for the synthesis of compounds 5a-i

Compound 3 (2 mmol) was dissolved in 10 mL of ethanol and combined with 2 mmol of the different substituted benzoyl chlorides (5a-i). Triethylamine (5.2 mmol) was added to the aforementioned reaction mixture, which was then refluxed for 5 h. When the reaction was completed, the mixture was cooled in water before being extracted with ethyl acetate. The isolated product was washed with 5 % $NaHCO_3$, dried over Na_2SO_4, concentrated in vacuo, and recrystallized in ethanol to provide the desired target compounds 5a-i with a yield of 85–93 %.

3-Benzoyl-5-((5,6-difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)thiazolidine-2,4-dione (5a): Yield: 91 %. mp.: 227–229 °C. Anal. calc. for $C_{19}H_{11}F_2N_3O_3S$: C, 57.14; H, 2.78; N, 10.52. found: C, 57.11; H, 2.75; N, 10.56.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.85 (s, 3H, *N*–CH_3), 7.36 (s, 2H, Ar–H), 7.50 (s, 1H, –CH), 7.68 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.76 (d, 2H, *J* = 7.2 Hz, Ar–H), 7.90 (t, 1H, *J* = 7.2 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.2, 104.2, 122.5, 127.5, 128.6, 131.2, 131.8, 132.6, 136.1, 141.5, 143.2, 143.8, 162.3, 165.4, 168.3. MS, *m/z*: 400 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(4-methylbenzoyl)thiazo lidine-2,4-dione (5b): Yield: 86 %. mp.: 234–236 °C. Anal. calc. for $C_{20}H_{13}F_2N_3O_3S$: C, 58.11; H, 3.17; N, 10.16. found: C, 58.08; H, 3.15; N, 10.19.^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.24 (s, 3H, –CH_3), 3.84 (s, 3H, *N*–CH_3), 7.35 (s, 2H, Ar–H), 7.56 (s, 1H, –CH), 7.68 (d, 2H, *J* = 6.4 Hz, Ar–H), 7.91 (d, 2H, *J* = 7.6 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.4, 34.2, 104.1, 122.6, 127.4, 128.3, 129.5, 131.4, 136.1, 141.5, 142.3, 143.2, 143.8, 162.2, 165.3, 168.5. MS, *m/z*: 414 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(4-methoxybenzoyl) thiazolidine-2,4-dione (5c): Yield: 88 %. mp.: 231–233 °C. Anal. calc. for $C_{20}H_{13}F_2N_3O_4S$: C, 55.94; H, 3.05; N, 9.79. found: C, 55.91; H, 3.02; N, 9.83.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.81 (s, 3H, –OCH_3), 3.89 (s, 3H, *N*–CH_3), 7.12 (d, 2H, *J* = 7.6 Hz, Ar–H), 7.36 (s, 2H, Ar–H), 7.55 (s, 1H, –CH), 7.94 (d, 2H, *J* = 7.2 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.1, 55.9, 104.2, 114.4, 122.5, 123.7, 128.5, 131.4, 136.5, 141.5, 143.4, 143.8, 162.3, 164.8, 165.1, 168.2. MS, *m/z*: 430 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(4-hydroxybenzoyl)thiazo lidine-2,4-dione (5d): Yield: 91 %. mp.: 221–223 °C. Anal. calc. for $C_{19}H_{11}F_2N_3O_4S$: C, 54.94; H, 2.67; N, 10.12. found: C, 54.91; H, 2.64; N, 10.16.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, *N*–CH_3), 5.81 (s, 1H, –OH), 6.88 (d, 2H, *J* = 7.6 Hz, Ar–H), 7.37 (s, 2H, Ar–H), 7.56 (s, 1H, –CH), 7.87 (d, 2H, *J* = 7.6 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.1, 104.2, 116.3, 122.7, 124.1, 128.9, 131.2, 136.1, 141.5, 143.2, 143.7, 161.5, 162.4, 165.2, 168.1. MS, *m/z*: 416 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(4-nitrobenzoyl)thiazol idine-2,4-dione (5e): Yield: 87 %. mp.: 242–244 °C. Anal. calc. for $C_{19}H_{10}F_2N_4O_5S$: C, 51.35; H, 2.27; N, 12.61. found: C, 51.33; H, 2.24; N, 12.67.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.88 (s, 3H, *N*–CH_3), 7.38 (s, 2H, Ar–H), 7.57 (s, 1H, –CH), 8.02 (d, 2H, *J* = 8.4 Hz, Ar–H), 8.45 (d, 2H, *J* = 7.6 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.1, 104.2, 122.6, 124.1, 129.6, 131.4, 136.1, 137.5, 141.5, 143.2, 143.8, 151.3, 162.6, 165.3, 168.2. MS, *m/z*: 445 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(4-fluorobenzoyl)thiazol idine-2,4-dione (5f): Yield: 85 %. mp.: 219–221 °C. Anal. calc. for $C_{19}H_{10}F_3N_3O_3S$: C, 54.68; H, 2.42; N, 10.07. found: C, 54.65; H, 2.40; N, 10.11.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.86 (s, 3H, *N*–CH_3), 7.38 (s, 2H, Ar–H), 7.57 (s, 1H, –CH), 7.86 (d, 2H, *J* = 7.6 Hz, Ar–H), 8.12 (d, 2H, *J* = 7.6 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.1, 104.5, 115.6, 122.6, 127.2, 129.2, 131.6, 136.1, 141.5, 143.2, 143.8, 162.4, 165.2, 166.3, 168.3. MS, *m/z*: 418 (M+1).

3-(4-Chlorobenzoyl)-5-((5,6-difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)thiazol idine-2,4-dione (5g): Yield: 91 %. mp.: 224–226 °C. Anal. calc. for $C_{19}H_{10}ClF_2N_3O_3S$: C, 52.60; H, 2.32; N, 9.69. found: C, 52.57; H, 2.30; N, 9.74.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.92 (s, 3H, *N*–CH_3), 7.36 (s, 2H, Ar–H), 7.57 (s, 1H, –CH), 7.68 (d, 2H, *J* = 7.6 Hz, Ar–H), 7.91 (d, 2H, *J* = 7.2 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.2, 104.3, 122.6, 128.4, 129.5, 130.4, 131.4, 136.1, 137.7, 141.5, 143.2, 143.8, 162.1, 165.1, 168.5. MS, *m/z*: 434 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(4-(trifluoromethyl) benzoyl)thiazolidine-2,4-dione (5h): Yield: 86 %. mp.:

212–214 °C. Anal. calc. for $C_{20}H_{10}F_5N_3O_3S$: C, 51.40; H, 2.16; N, 8.99. found: C, 51.36; H, 2.14; N, 9.04.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, *N*–CH_3), 7.37 (s, 2H, Ar–H), 7.56 (s, 1H, –CH), 7.76 (d, 2H, J = 7.6 Hz, Ar–H), 7.95 (d, 2H, J = 7.6 Hz, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.4, 104.2, 122.6, 124.3, 125.2, 127.8, 131.4, 134.1, 134.7, 136.1, 141.5, 143.2, 143.8, 162.2, 165.4, 168.4. MS, *m/z*: 468 (M+1).

5-((5,6-Difluoro-1-methyl-1H-benzo[d]imidazole-2-yl)methylene)-3-(3,4,5-trifluorobenzoyl) thiazolidine-2,4-dione (5i): Yield: 89 %. mp.: 204–206 °C. Anal. calc. for $C_{19}H_8F_5N_3O_3S$: C, 50.34; H, 1.78; N, 9.27. found: C, 50.31; H, 1.75; N, 9.35.^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, *N*–CH_3), 7.36 (s, 2H, Ar–H), 7.44 (s, 2H, Ar–H), 7.58 (s, 1H, –CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.1, 104.5, 109.5, 122.6, 131.4, 133.2, 136.1, 141.5, 143.2, 143.8, 144.6, 159.7, 162.1, 165.2, 168.3. MS, *m/z*: 454 (M+1).

2.4. Antitubercular assay

The target 1*H*-benzo [*d*]imidazole based thiazolidine-2,4-dione derivatives (5a-i) were evaluated for their minimum inhibitory concentrations (MICs) against drug-sensitive, MDR, and XDR strains of Mtb. With respect to the mycobacterial cultures, Mtb H37Rv (ATCC 27294), a drug-sensitive strain and MDR-TB (ATCC 35822) was procured from ATCC. Furthermore, the XDR-TB (RCMB 2674) strain was obtained from the culture collection unit of the Regional Centre for Mycology and Biotechnology (RCMB). As previously mentioned [41,42], a two-fold serial dilution from 125 to 0.1 μM was used for this study. The MIC, was the lowest dosage of the drug that prevented the development of bacteria. Each compound concentration was determined in triplicate in a single experiment, and the mean SD was computed.

2.5. Cytotoxicity assay

Using the MTT assay, the novel synthesized compounds were examined for their cytotoxic effects on the normal lung fibroblast (WI-38) cell line. The protocols that we previously published [43] were used to conduct the cytotoxic test.

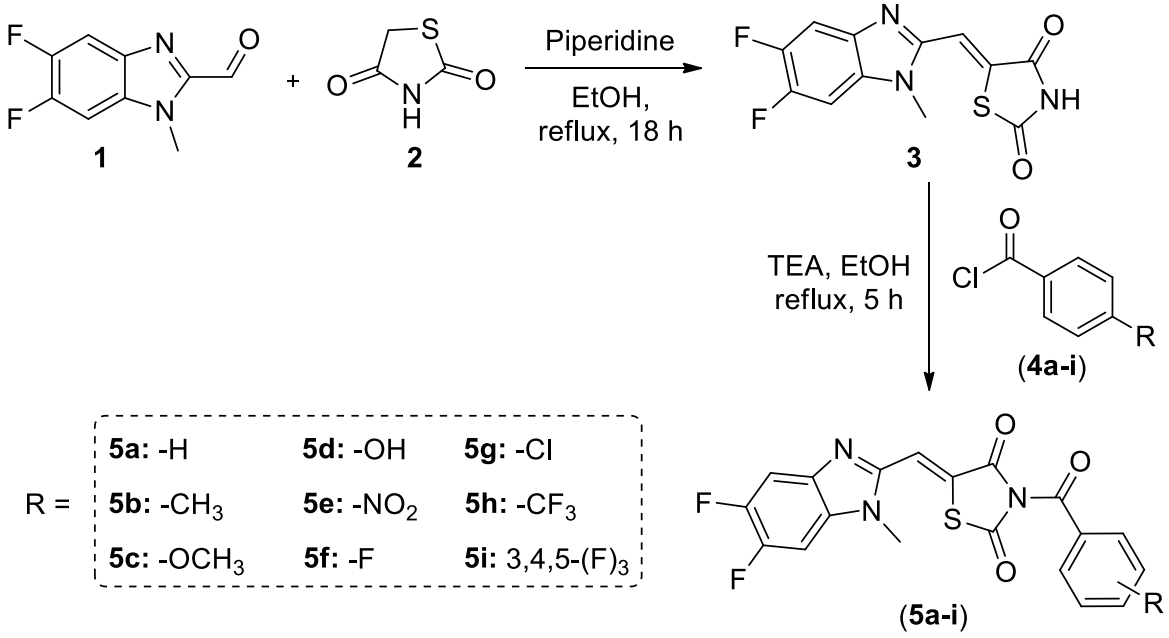
2.6. Molecular docking

The UCSF Chimaera tool was used to conduct docking studies of the potent compounds. The DprE1 protein's crystal structure (PDB ID: 4KW5) was obtained from the Protein Data Bank. Protein and ligand optimization has been completed. Protein structures were generated by rearranging charges, adding hydrogen, and removing ligands and water molecules using AutoDock Tools. The Lamarckian genetic algorithm calculation method takes default values for the remaining parameters and uses the ligand molecular coordinates from the original crystal structure as the centre of the box. The AutoDock Vina was used to compute and assess the docking between the ligand and target proteins. Only the ideal conformation was chosen so that the protein-ligand interaction could be investigated. The Discovery Studio Visualizer was used to analyse every ligand-protein interaction. Additionally, the free web server http://www.swissadme.ch and http://lmmd.ecust.edu.cn/admetsar2/was used to evaluate compounds for drug-likeness and ADMET properties, respectively.

3. Results and discussion

3.1. Synthesis

As a result of the presence of 1H-benzo [d] imidazole and thiazolidine-2,4-dione rings in a large number of compounds that exhibit biological and pharmacological activity, this skeleton becomes extremely significant. Scheme 1 shows the synthesis pathway used to synthesize the new series of 1*H*-benzo [*d*]imidazole based thiazolidine-2,4-dione derivatives (5a-i). The 5-((5,6-Difluoro-1-methyl-1*H*-benzo [*d*]imidazole-2-yl)methylene) thiazolidine-2,4-dione (3) was first produced in a good yield of 87 % by piperidine-promoting Knoevenagel condensation reaction between 5,6-difluoro-1-methyl-1*H*-benzo [*d*] imidazole-2-carbaldehyde (1) and thiazolidine-2,4-dione (2) in ethanol under reflux. The Knoevenagel condensation reaction is confirmed by two singlet peaks in the ^{1}H NMR spectra of compound 3, which are attributed to the vinylic proton and the –NH proton of the thiazolidine-2,4-dione ring, respectively, at 7.57 ppm and 10.03 ppm. Ultimately, in order to obtain our desired compounds 5a-i, compound 3 was acylated with various substituted aryl chlorides (4a-i). A yield ranges from 85 to



Scheme 1. Synthetic route for the preparation of target compounds 5a-i.

93 % was found for the target compounds 5a-i. The newly synthesized 1H-benzo [d] imidazole based thiazolidine-2,4-dione derivatives (5a-i) were characterized using mass spectroscopy, ^{1}H NMR, and ^{13}C NMR techniques in addition to elemental analysis. The –NH group singlet peak's disappearance at 10.03 ppm in the ^{1}H NMR spectra of compounds 5a-i confirm the acylation process between compound 3 and substituted acyl chlorides (4a-i). Compounds 5a-i ^{1}H NMR spectra revealed singlets at 3.84–3.92 ppm, which are indicative of protons in *N*-methyl groups. At 7.35–7.38 ppm, the two aromatic protons of these molecules in the 1*H*-benzo [*d*]imidazole ring show up as a singlet signal. The compounds 5a-i exhibits their vinylic proton around 7.55–7.58 ppm. Compounds 5a-i have aromatic protons in the predicted range for the phenyl ring. A singlet peak was seen in compounds 5 b, 5c, and 5 d at 2.24, 3.81, and 5.81 ppm, respectively, corresponding to the methyl, methoxy, and hydroxyl groups. Additionally, M+1 peaks were visible in the mass spectra of the compounds, supporting the suggested structure and agreeing with the molecular weight of the constituents. There was good agreement between the elemental analysis results and the values derived from theoretical calculations and experimental results.

3.2. Antitubercular activity

All of the newly synthesized compounds were tested for their *in vitro* antitubercular efficacy against drug-resistant MDR- and XDR-Mtb strains, as well as the drug-sensitive Mtb H37Rv strain. Isoniazid, the first-line medication, served as a point of comparison. Table 1 displayed the MIC values for test compounds 5a-i. The findings showed that, when tested against drug-sensitive Mtb strains and MDR-Mtb strains, respectively, all named compounds exhibited considerable inhibitory action in the range of 0.21–5.03 μM and 11.51–92.05 μM. Conversely, compounds 5 b, 5c, and 5 d show MIC values more than 125 μM against XDR-Mtb bacteria, whereas compounds 5 d-i shows MIC values between 35.68 and 117.68 μM. With MIC values of 0.32, 0.86, 0.21, and 0.44 μM, respectively, the synthesized compounds 5e, 5f, 5 h, and 5i shown potential antimycobacterial action against the drug-sensitive Mtb H37Rv strain. Additionally, these substances demonstrated a strong antimycobacterial effect against the MDR and XDR strains of Mtb. The MIC values of compounds 5e, 5f, 5 h, and 5i against the MDR-Mtb strain were 14.69, 37.91, 11.51, and 23.06 μM, while the MIC values against the XDR-Mtb strain were 47.84, 86.59, 35.68, and 59.18 μM. The newly synthesized compounds 5e and 5 h, had the strongest activity against the drug-sensitive Mtb strain, with an MIC value that was lower than that of the reference medication isoniazid (see Table 2).

A thorough structure-activity relationship (SAR) analysis was carried out to confirm the potential of 1*H*-benzo [*d*]imidazole based thiazolidine-2,4-dione derivatives (5a-i) and investigate the relevance of these compounds inhibitory action on Mtb strains. The antitubercular activities of the novel synthesized compounds and the various types of substituents attached to the phenyl ring of 1H-benzo [d] imidazole based thiazolidine-2,4-dione derivatives were shown to be related, according to the study's results on antitubercular activity. It is important to note that the examined compounds' structural diversity and substitution variations significantly influenced their biological activities. The findings, as presented in Table 1, unequivocally demonstrate that the compounds 5a-i antitubercular actions are significantly influenced by the substituents on the phenyl ring connected to the thiazolidine-2,4-dione molecule. The impact of electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) on the inhibitory activity of the phenyl ring associated with thiazolidine-2,4-dione moiety was examined. Compound 5 h, which possesses a trifluoromethyl group on its phenyl ring, demonstrated noteworthy inhibitory efficacy against drug-resistant and drug-sensitive MDR and XDR strains of MTB. The antitubercular actions are considerably reduced when the trifluoromethyl group on the phenyl ring is replaced with other groups, such as 4-methyl, 4-methoxy, 4-hydroxy, 4-nitro, 4-fluoro, 4-chloro, 3,4,5-trifluoro group, or unsubstituted phenyl ring. The structure activity correlations of potent compounds with drug-sensitive Mtb are shown in Fig. 3.

Potency of compounds was ranked as follows: CF_3>NO_2 > 3,4,5-$(F)_3$>F > Cl > H > CH_3> OCH_3>OH. Compounds (5e-i) with EWGs substitution showed more promising antimycobacterial action than compounds with unsubstituted rings (5a) and EDGs (5 b-d). Furthermore, compound 5 b-d's insertion of EDGs on the phenyl ring connected to the thiazolidine-2,4-dione moiety showed less antitubercular action than compound 5a, which had an unsubstituted phenyl ring. This suggests that antitubercular action is favoured more by aromatic substitution with an EWGs on the phenyl ring connected to the thiazolidine-2,4-dione molecule than by EDGs substitution. Furthermore, compared to drug-sensitive, MDR and XDR Mtb strains, compound 5 h, which has a trifluoromethyl group on the phenyl ring, is 1.71, 10.86, and 3.50 times more effective. Compared to the other EWGs, trifluoromethyl substituents have more lipophilicity, making them more beneficial. However, compound 5e showed an increase in activity against drug-sensitive, MDR, and XDR Mtb strains of around 1.12, 8.50, and 2.61-fold, respectively. Our research led us to the conclusion that activity optimization requires EWGs on the phenyl connected to thiazolidine-2,4-dione molecule. Because compound 5 h is more effective than compounds 5e (-NO_2), 5f (F), 5 g (Cl), and 5i (3,4,5-trifluoro), the trifluoromethyl group on the phenyl ring is significant. Moreover, these groups could have a greater positive impact on ligand binding, which would enhance activity.

Table 1
The *anti*-TB activity of the compounds 5a-i against drug sensitive, MDR, and XDR Mtb strains.

Compound	MIC (μM)		
	Mtb H37Rv	MDR Mtb	XDR Mtb
5a	2.06 ± 0.55	65.38 ± 0.97	117.68 ± 1.42
5 b	2.84 ± 0.91	71.26 ± 1.04	>125
5c	3.79 ± 0.83	83.64 ± 1.36	>125
5 d	5.03 ± 0.72	92.05 ± 0.67	>125
5e	0.32 ± 0.08	14.69 ± 0.81	47.84 ± 0.97
5f	0.86 ± 0.22	37.92 ± 0.55	86.59 ± 1.18
5 g	1.28 ± 0.63	51.03 ± 1.22	96.41 ± 1.55
5 h	0.21 ± 0.04	11.51 ± 0.37	35.68 ± 1.05
5i	0.44 ± 0.15	23.06 ± 1.18	59.18 ± 1.22
Isoniazid	0.36 ± 0.07	>125	>125

Table 2
Cytotoxic effect of compounds 5a-i towards normal WI-38 cell line and their selectivity indexes.

Compound	IC_{50} (μM)	Selectivity index (SI)		
	WI-38	Mtb H37Rv	MDR Mtb	XDR Mtb
5a	>50	24.27	0.76	0.43
5 b	>50	17.61	0.71	0.40
5c	>50	13.19	0.59	0.40
5 d	>50	9.94	0.54	0.40
5e	>50	156.25	3.40	1.05
5f	>50	58.14	1.39	0.58
5 g	>50	39.06	0.98	0.52
5 h	>50	238.09	4.34	1.40
5i	>50	113.64	2.17	0.84
Isoniazid	>50	138.89	0.40	0.40

3.3. Cytotoxic activity

It is critically important to find novel antimycobacterial agents that have less cytotoxicity. Therefore, the MTT assay was used to evaluate the cytotoxic effects of the newly synthesized compounds 5a-i against the non-tumorigenic WI-38 cell line. Table 3 presents the cytotoxicity information for the recently synthesized compounds. The findings demonstrated that the newly synthesized chemicals examined had an

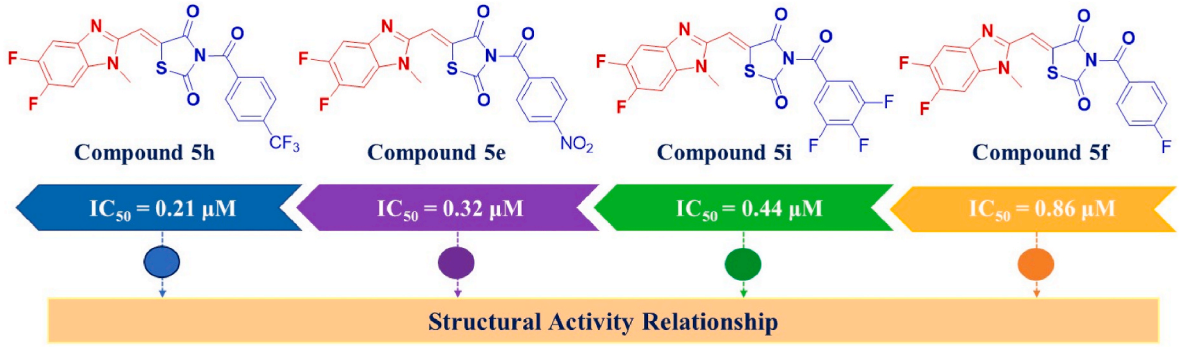


Fig. 3. Structure activity correlations of potent compounds with drug-sensitive Mtb.

Table 3
Docking scores and binding interactions of potent compounds with target protein.

Compound	Docking score (kcal/mol)	Interacting residues			
		H-bond	Bond length (Å)	Hydrophobic	π-alkyl
5e	−9.22	Thr-29 Arg-54	1.62 2.25	Leu-27, Asp-31, Met-34, Ile-35, Ile-52, Gly-55, Met-74, Pro-76, Gly-124, Leu-152, Ile-184	Arg-28, Ile-72, Ile-183
5f	−8.49	Arg-54	2.49	Leu-27, Thr-29, Pro-30, Asp-31, Met-34, Ile-35, Ala-38, Ile-52, Gly-55, Met-74, Gly-124, Ile-184	Arg-28, Ile-72, Ile-183
5 h	−9.61	Thr-29 Ile-35 Asp-73	1.64 2.17 2.26	Leu-27, Arg-28, Asp-31, Met-34, Ile-52, Ala-53, Arg-54, Gly-55, Met-74, Pro-76, Gly-124, Ile-184	Arg-28, Ile-72, Ile-183
5i	−8.74	Thr-29 Arg-54	1.67 2.29	Leu-27, Arg-28, Pro-30, Asp-31, Met-34, Ile-35, Ala-53, Gly-55, Asp-73, Met-74, Pro-76, Ile-184	Arg-28, Ile-72, Ile-183
TCA1	−8.53	Thr-29 Ile-35	1.71 2.36	Leu-27, Arg-28, Asp-31, Met-34, Val-36, Ala-38, Ala-53, Arg-54, Gly-55, Ile-72, Met-74, Ile-184,	Pro-30, Pro-76, Ile-183

IC_{50} value greater than 50 µM, suggesting that they are not harmful to normal WI-38 cell lines. Furthermore, the compounds' Selectivity Index (SI) was ascertained by dividing their MIC values by their IC_{50} values in relation to a normal cell line. According to the results, newly synthesized compounds demonstrated high selectivity index values against Mtb strains that were both drug-sensitive and drug-resistant. All of the recently synthesized compounds in this series, however, were seen to exhibit superior selectivity towards the drug-sensitive Mtb H37Rv strain as compared to the drug-resistant MDR and XDR strains of Mtb. With the exception of compound 5 d, all newly synthesized compound has a SI value more than 10 when tested against the drug-sensitive Mtb H37Rv strain. According to Quispe [44], Valdes-Garcia, and coworkers [45], a compound was deemed to belong to the selected compound category if its SI value was more than or equal to 10. In comparison to the drug-sensitive, MDR, and XDR Mtb strains, the most potent molecule, 5 h, had SI values of 238.09, 4.34, and 1.40, respectively. In comparison to the drug-sensitive, MDR, and XDR Mtb strains, compound 5e had SI values of 156.25, 3.40, and 1.05, respectively. When it came to drug-sensitive, MDR, and XDR Mtb strains, isoniazid's SI values were 113.64, 2.17, and 0.84, respectively. Additionally, compounds 5e and 5 h were found to exhibit greater SI values against the studied drug-resistant and drug-sensitive strains when compared to the reference medication isoniazid.

3.4. Molecular docking

In recent years, molecular docking has become a crucial component of *in-silico* drug development as a technique for optimising issue solutions. The molecular docking techniques have been effectively applied in pharmaceutical research to analyse the behaviour of molecules within a target protein's binding region and comprehend the underlying connections. Combining computational and experimental approaches has tremendously aided in the identification and development of novel, promising compounds. The 1*H*-benzo [*d*]imidazole based thiazolidine-2,4-dione derivatives 5e, 5f, 5 h, and 5i were selected for further in silico tests to explore their likely molecular target because of their exceptional *anti*-TB activity. In an effort to combat the worldwide risk of tuberculosis, new drugs have been developed during the last decade using a number of druggable targets. Some of these targets have significant biological functions, such as the enzymes DprE1, InhA, ATP synthase, and MmpL3. A preliminary docking study was carried out to evaluate the possible binding interactions and docking scores of the 1H-benzo [*d*] imidazole based thiazolidine-2,4-dione derivatives that were disclosed herewith with these four target proteins. The findings of our potent compounds' docking investigation with target proteins MmpL3, DprE1, ATP synthase and InhA showed that DprE1 was a potential target with a high docking score when compared to other targets. Therefore, in this study, DprE1 enzyme has been chosen as the valid target protein for docking investigation of the newly synthesized potent molecules. A flavoenzyme called DprE1 contributes to the formation of arabinogalactan, a vital component of the Mtb cell wall [46]. Inhibiting DprE1 hinders the production of arabinogalactan, which inhibits the creation of mycobacterial cell walls. Catalyzed by DprE1, decaprenyl-phospho-ribose is epimerized into decaprenyl-phospho-arabinose in two steps. Ortholog analysis has shown that DprE1 is necessary for mycobacteria to develop, and that epimerization occurs in the periplasmic area, which accounts for DprE1's susceptibility to attack [47]. Furthermore, the formation of a bonding interaction between the ligand and the enzyme results in the loss of catalytic function, which leads to the mycobacterium's death. This Perspective summarizes several DprE1 inhibitors as *anti*-TB drugs that have been described to date. Consequently, flavoenzyme DprE1 is thought to be a viable target for creating innovative treatment options to combat TB. The molecular docking analysis using Autodock Vina was carried out to anticipate the possible binding mode of potent compounds 5e, 5f, 5 h, and 5i with DprE1 receptor (PDB ID: 4KW5). Given the significance of docking validation, we redocked the co-crystallized ligand TCA1 in this

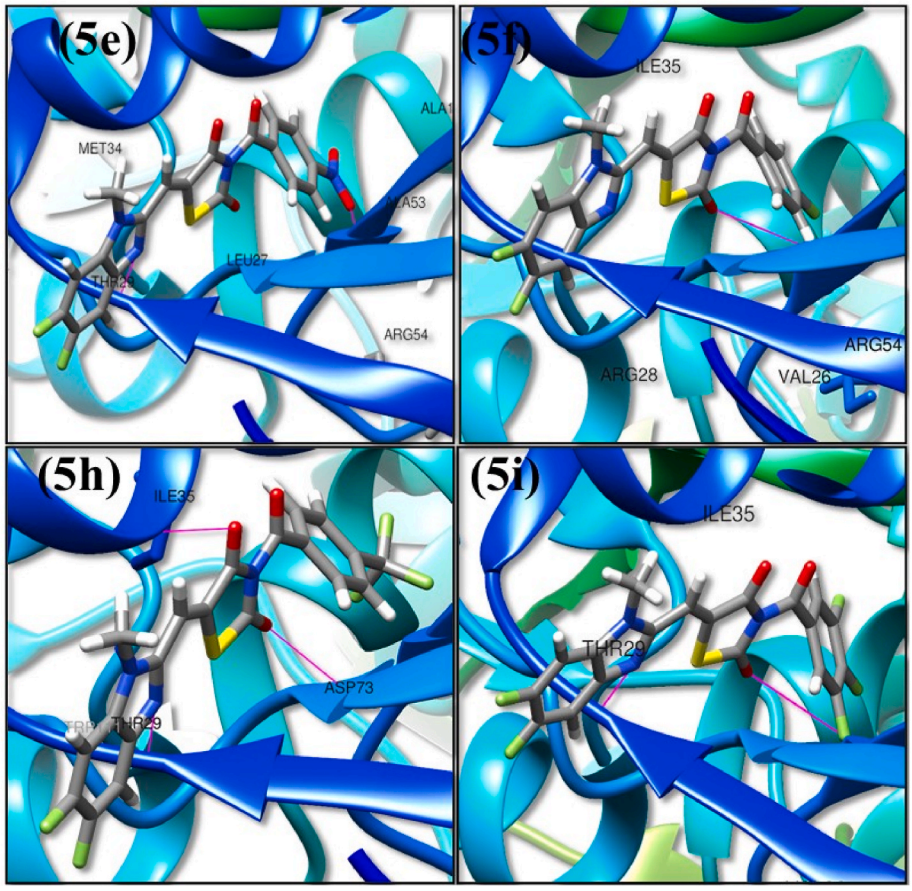


Fig. 4. Docking poses of potent compounds 5e, 5f, 5 h and 5i with target 4KW5 protein.

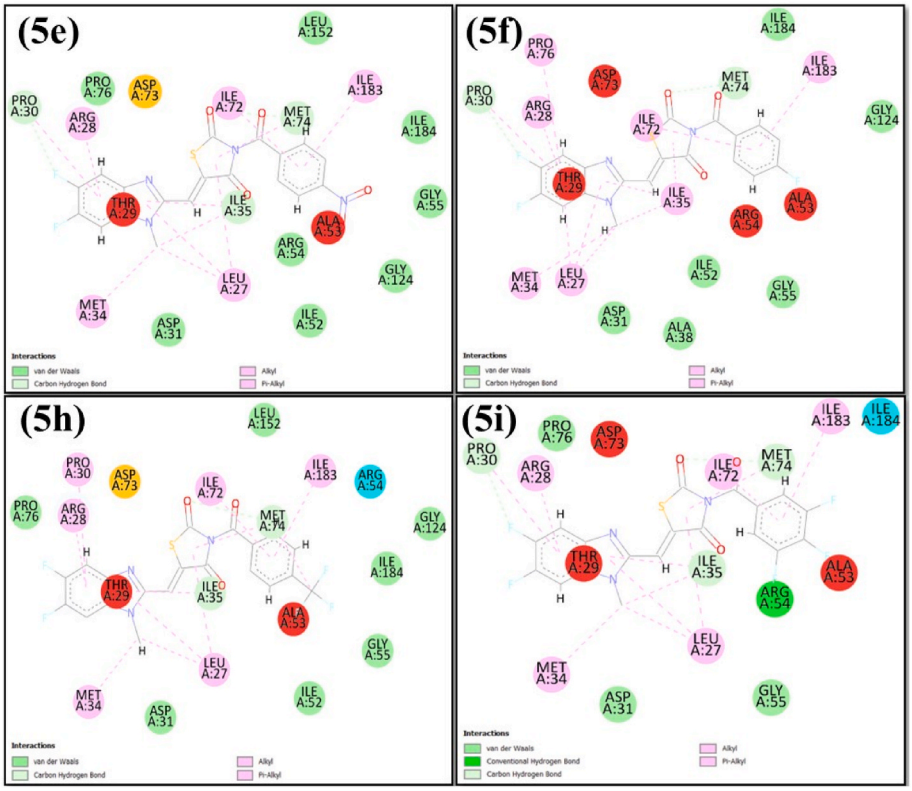


Fig. 5. 2D Molecular interaction of potent compounds with target 4KW5 protein.

Table 4
Predicted physicochemical parameters of the titled compounds.

Compound	Mol. Wt.	Rotatable bonds	HBA	HBD	LogP	Molar Refractivity	Log K_p (cm/s)	TPSA (Å^2)
5a	399.37	3	6	1	2.22	103.41	−6.20	97.57
5 b	413.40	3	6	1	2.56	108.37	−6.02	97.57
5c	429.40	4	7	1	2.74	109.90	−6.41	106.80
5 d	415.37	3	7	2	2.01	105.43	−6.55	117.80
5e	444.37	4	8	1	2.06	112.23	−6.60	133.29
5f	417.36	3	7	1	2.37	103.37	−6.24	97.57
5 g	433.82	3	6	1	2.66	108.42	−5.96	97.57
5 h	467.37	4	9	1	2.18	108.41	−5.98	97.57
5i	453.34	3	9	1	2.33	103.28	−6.32	97.57

instance to validate the docking processes. Figs. 4 and 5 show the 3D and 2D docking postures of the potent compounds 5e, 5f, 5 h, and 5i, respectively. Table 3 compiled docking scores and comprehensive interactions of strong chemicals with target protein amino acid residues.

The investigation's findings show that compounds 5e, 5f, 5 h, and 5i exhibit exceptional binding affinities with the target protein, as evidenced by their respective docking scores of −9.22, −8.49, −9.61, and −8.74 kcal/mol. The findings show that, out of all the compounds examined, compound 5 h has the highest binding affinity with the target protein. Upon examining compound 5 h′s binding within the DprE1 active site, it was discovered that the molecule in question had strong binding interactions with the target protein's essential amino acids. Compound 5 h, on the other hand, demonstrates three hydrogen bonding interactions with the residues Thr-29, Ile-35, and Asp-73, at bond distances of 1.64, 2.17, and 2.26 Å, respectively. Furthermore, when compared to the docking score attained by the co-crystallized ligand TCA1, the compounds 5e, 5 h, and 5i demonstrated outstanding binding scores with their probable target. Compound 5e exhibited two hydrogen bonding interactions, with bond distances of 1.62 and 2.25 Å, respectively, with Thr-29 and Arg-54. Additionally, two hydrogen bonding interactions between compound 5i and Thr-29 and Arg-54 were established, with bond distances of 1.67 and 2.29 Å, respectively. Furthermore, the compounds under investigation have the potential to form pi-alkyl interactions with the target protein's Arg-28,

Table 5
ADMET profile of the potent compounds.

Parameters		Compound			
		5e	5f	5 h	5i
Absorption/distribution	BBB	0.8344 (BBB+)	0.9543 (BBB+)	0.9419 (BBB+)	0.9543 (BBB+)
	HIA	0.9856 (HIA+)	0.9969 (HIA+)	0.9936 (HIA+)	0.9969 (HIA+)
	Caco-2 Permeability	0.5394 (Caco-2-)	0.5905 (Caco-2+)	0.5745 (Caco-2+)	0.5905 (Caco-2+)
	P-glycoprotein Substrate	0.5527	0.5586	0.5305	0.5586
		Non-substrate	Non-substrate	Non-substrate	Non-substrate
	P-glycoprotein Inhibitor	0.9400	0.9696	0.9621	0.9696
		Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
	LogS	−3.7917	−3.7554	−3.9483	−3.7554
	Subcellular localization	0.3766	0.4324	0.4558	0.4324
		Mitochondria	Mitochondria	Mitochondria	Mitochondria
Metabolism	CYP450 2C9 Inhibitor	0.7944	0.7685	0.7645	0.7685
		Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
	CYP450 2D6 Inhibitor	0.8455	0.8462	0.8518	0.8462
		Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
	CYP450 2C19 Inhibitor	0.6338	0.6519	0.6820	0.6519
		Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP450 3A4 Inhibitor	0.7564	0.7246	0.7171	0.7246
		Non-Inhibitor	Inhibitor	Inhibitor	Inhibitor
	CYP450 1A2 Inhibitor	0.6107	0.6113	0.5801	0.6113
		Non-Inhibitor	Inhibitor	Non-Inhibitor	Inhibitor
	CYP Inhibitory Promiscuity	0.6401	0.7133	0.7421	0.7133
		High	High	High	High
Excretion	Biodegradation	0.9847	0.9877	0.9942	0.9877
		Not biodegradable	Not biodegradable	Not biodegradable	Not biodegradable
Toxicity	AMES toxicity	0.5132	0.5523	0.5690	0.5523
		Non-AMES Toxic	Non-AMES Toxic	Non-AMES Toxic	Non-AMES Toxic
	Acute oral toxicity	0.5621	0.5845	0.5607	0.5845
		III	III	III	III
	Carcinogenicity	0.4701	0.4829	0.4916	0.4829
		Non Carcinogenic	Non Carcinogenic	Non Carcinogenic	Non Carcinogenic
	Fish Toxicity	0.9508	0.8916	0.8695	0.8916
		High FHMT	High FHMT	High FHMT	High FHMT
	Tetrahymena Pyriformis Toxicity (TPT)	0.9969	0.9928	0.9939	0.9928
		High TPT	High TPT	High TPT	High TPT
	Honey Bee Toxicity (HBT)	0.7246	0.7038	0.6948	0.7038
		Low HBT	Low HBT	Low HBT	Low HBT
	Carcinogens	0.7180	0.8972	0.8895	0.8972
		Non-carcinogens	Non-carcinogens	Non-carcinogens	Non-carcinogens

HIA: Human intestinal absorption BBB: Blood-brain barrier.

Ile-72, and Ile-183 residues. The compounds within the pocket may stabilize as a result of these interactions, producing *anti*-TB activity. As a result, the docking studies provided a structural basis for the development of future *anti*-TB drugs and were highly well-coordinated with the experimental results.

3.5. Drug-likeness prediction

Drug development optimization and pharmacokinetic research benefit from the application of drug-likeness ideas. Using the Lipinski Rules of Five, the SwissADME web server was used to analyse the drug-likeness features of newly synthesized molecules [48]. Pharmaceutical chemists frequently utilize Lipinski's rule of five to forecast the oral bioavailability of possible leads or therapeutic compounds during the drug design and development process. The molecular weight lower than 500 Da in order to comply with this requirement. As a result, the molecular mass of the molecules under investigation in the present study ranged from 399.37 to 467.37 Da. Furthermore, it is recommended that HBD and HBA not exceed 5 and 10, respectively. The number of HDB and HBA count for the investigated molecules was observed in the range of 1–2 and 6–9, respectively. While Table 4 shows that the LogP value is achieved between 2.01 and 2.74, LogP should have values below five. This indicates that the title compounds have the potential to be pharmaceutically beneficial. It is necessary to be less than ten rotatable bonds in order to determine the molecular flexibility. For the newly synthesized molecules, there are three to four rotatable bonds. Transdermal medication delivery takes skin permeability into account when assessing the effectiveness of products [49]; the compounds under study exhibit skin permeability within the range of −5.96 to 6.60 cm/s. All the compounds exhibit TPSA values less than 140. These parameters have been predicted and are summarized in Table 4. If one or more Lipinski criteria are violated, the target compounds' bioavailability issues as anticipated medications may be indicated. Findings indicated that all the newly synthesized molecules complied with Lipinski's criterion and would be suitable as oral active medications. The compounds molar refractivity value was obtained between 103.28 and 112.23, which serve as indicators of their superior intestine absorption and oral bioavailability.

3.6. ADMET properties

Pharmacology and toxicology are fields that require a deep understanding for successful therapeutic medication development. Throughout the whole drug discovery and development process, the characteristics of substances related to absorption, distribution, metabolism, excretion, and toxicity (ADMET) are crucial [50]. Thus, it is imperative to identify effective compounds with improved ADMET characteristics. The more potent 1H-benzo [*d*]imidazole based thiazolidine-2,4-dione derivatives 5e, 5f, 5 h, and 5i have their ADME characteristics predicted using the admetSAR 2.0 web server. Table 5 displayed the ADMET characteristics determined results. The absorption of all the potent compounds in the human intestine is very likely, as evidenced by their respective HIA + values of 0.9856, 0.9969, 0.9936, and 0.9969 for compounds 5e, 5f, 5 g, and 5 h. Compounds 5f and 5i are calculated to have the highest penetration across the blood-brain barrier; compound 5i exhibits similarity to these compounds and a somewhat greater penetration than compound 5e. The LogS values of these potent compounds fall within the range of the drug's projected water solubility, which is between −1 and −5 [51]. This suggests that the compounds have high potential for absorption and distribution. The cytochrome P450 enzyme family is responsible for drug metabolism. Regarding metabolism, all potent molecules investigated in this study was found to be non-inhibitor. The potent investigated compounds were determined to be neither carcinogenic nor biodegradable based on the results. Furthermore, these potent compounds with the acute oral toxicity and AMES toxicity showed no toxicity, making them to be excellent safety medications.

4. Conclusion

In conclusion, a novel series of thiazolidine-2,4-dione derivatives based on 1*H*-benzo [*d*]imidazole was created, synthesized, and assessed as possible antitubercular agents against drug-sensitive and drug-resistant Mtb strains. Strong antimycobacterial activity was demonstrated by the synthesized compounds against drug-sensitive strains of MDR-TB and XDR-TB, with MIC values ranging from 0.21 to 5.03 μM, 11.51–92.05 μM, and 35.68–125 μM, respectively. Furthermore, as compared to the reference medication isoniazid, compounds 5e and 5 h shown greater antitubercular action against the studied drug-sensitive and drug-resistant strains. The SAR indicates that the kind of substituent group on the phenyl ring has a significant impact on the antimycobacterial action. The addition of EWGs to the phenyl ring connected to the thiazolidine-2,4-dione moiety significantly increases the compounds' antimycobacterial activity (5e-i) as compared to compounds with EGDs substituents (5 b-d). The phenyl ring's nitro (5e) and trifluoromethyl (5 h) groups exhibit a noticeably different gradation of activity from the other substituents in this series. Compounds 5a-i exhibited antitubercular action together with comparatively low levels of cytotoxicity, indicating their therapeutic potential for advancement in the *anti*-TB drug area. Compound 5e displays 156.25, 3.40, and 1.05 SI values, whereas compound 5 h demonstrated 238.09, 4.34, and 1.40 SI values against drug-sensitive, MDR, and XDR Mtb strains, in that order. Our potent compounds are interacting with the 4KW5 protein in a rather good way, according to the docking studies. When potent compounds 5e, 5f, 5 h, and 5i were compared to the co-crystallized ligand TCA1, their binding mode and docking score revealed remarkable binding, which may be the underlying target for their great antitubercular potency. Based on these findings, we deduce that the pharmacological action has been amplified by combining two distinct heterocyclic systems, namely 1*H*-benzo [*d*]imidazole and thiazolidine-2,4-dione. As a consequence, these systems are well-suited for additional modifications to provide more potent antitubercular agents.

CRediT authorship contribution statement

M.S. Raghu: Writing – original draft, Methodology, Investigation. **Amar Yasser Jassim:** Software, Resources, Formal analysis, Data curation. **C.B. Pradeep Kumar:** Software, Formal analysis, Data curation. **K. Yogesh Kumar:** Resources, Formal analysis, Data curation. **M. K. Prashanth:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Fahd Alharethy:** Validation, Software, Resources, Formal analysis, Data curation. **Byong-Hun Jeon:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jics.2024.101346.

References

[1] V. Pflegr, L. Horvath, J. Stolarikova, A. Pal, J. Kordulakova, S. Bosze, J. Vinsova, M. Kratky, Design and synthesis of 2-(2-isonicotinoylhydrazineylidene) propanamides as InhA inhibitors with high antitubercular activity, Eur. J. Med. Chem. 223 (2021) 113668.

[2] TB Reports, 2023. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report.

[3] M.S. Raghu, C.B. Pradeep Kumar, K. Yogesh Kumar, M.K. Prashanth, M. Y. Alshahrani, I. Ahmad, R. Jain, Design, synthesis and molecular docking studies of imidazole and benzimidazole linked ethionamide derivatives as inhibitors of InhA and antituberculosis agents, Bioorg. Med. Chem. Lett. 60 (2022) 128604.

[4] D.S. Rawat, Antituberculosis drug research: a critical overview, Med. Res. Rev. 33 (2013) 693–764.

[5] M. Mallea, A. Acuna, A.H. Klahn, V. Artigas, F. Rogerio, F. Manaia, L. Lemus, D. H. Jara, P.M. Toro, Cyrhetrenyl and cymantrenyl N-acylhydrazone complexes based on isoniazid: synthesis, characterization. x-ray crystal structures and antitubercular activity evaluation, J. Organomet. Chem. 964 (2022) 122299.

[6] K.J. Seung, S. Keshavjee, M.L. Rich, Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, Cold Spring Harb. Perspect. Med. 5 (2015) a017863.

[7] B. Pobitra, P.K. Deb, K.N. Venugopala, A.A. Nizar, S. Vinayak, D. Satyendra, S. Amavya, T. Vinod, M.P. Raghu, Tuberculosis: an update on pathophysiology, molecular mechanisms of drug resistance, newer anti-TB drugs, treatment regimens and host- directed therapies, Curr. Top. Med. Chem. 21 (2021) 547–570.

[8] S.R. Tetali, E. Kunapaeddi, R.P. Mailavaram, V. Singh, P. Borah, P.K. Deb, K. N. Venugopala, W. Hourani, R.K. Tekade, Current advances in the clinical development of anti-tubercular agents, Tuberculosis 125 (2020) 101989.

[9] S. Ammaji, S. Masthanamma, R.R. Bhandare, S. Annadurai, A.B. Shaik, Antitubercular and antioxidant activities of hydroxy and chloro substituted chalcone analogues: synthesis, biological and computational studies, Arab. J. Chem. 15 (2022) 103581.

[10] S.S. R Alsayed, S. Lun, A. Payne, W.R. Bishai, H. Gunosewoyo, Facile synthesis and antimycobacterial activity of isoniazid, pyrazinamide and ciprofloxacin derivatives, Chem. Biol. Drug Des. 97 (2021) 1137–1150.

[11] P.K. Sharma, A. Amin, M. Kumar, A review: medicinally important nitrogen sulphur containing heterocycles, Open Med. Chem. J. 14 (2020) 49–64.

[12] T.A. Yousef, A.G. Alhamzani, M.M. Abou-Krisha, G. Kanthimathi, M.S. Raghu, K. Yogesh Kumar, M.K. Prashanth, B.H. Jeon, Synthesis, molecular docking study and anticancer activity of novel 1, 3, 4-oxadiazole derivatives as potential tubulin inhibitors, Heliyon 9 (2023) e13460.

[13] M.S. Raghu, K. Yogesh Kumar, K. Veena, C.B. Pradeep Kumar, A.S. Almalki, G. Mani, F.A. Alasmary, M.K. Prashanth, Synthesis, characterization, antimicrobial and interaction studies of pteridines with human serum albumin: a combined multi-spectroscopic and computational study, J. Mol. Struct. 1250 (2022) 131857.

[14] M.K. Prashanth, M. Madaiah, H.D. Revanasiddappa, K.N. Amruthesh, Synthesis, characterization, characterization, and BSA binding studies of some new benzamides related to Schiff base, ISRN Org. Chem. 2013 (2013) 1–12.

[15] C.E. Theodore, G. Sivaiah, S.B. Benaka Prasad, K.Y. Kumar, M.S. Raghu, F. Alharethy, M.K. Prashanth, B.H. Jeon, Design, synthesis, anticancer activity and molecular docking of novel 1H-benzo[d]imidazole derivatives as potential EGFR inhibitors, J. Mol. Struct. 1294 (2023) 136341.

[16] T.M. Dhameliya, K.I. Patel, R. Tiwari, S.K. Vagolu, D. Panda, D. Sriram, A. K. Chakraborti, Design, synthesis, and biological evaluation of benzo[d]imidazole-2-carboxamides as new anti-TB agents, Bioorg. Chem. 107 (2021) 104538.

[17] Q. Zhang, H. Zhou, S. Zhai, B. Yan, Natural product-inspired synthesis of thiazolidine and thiazolidinone compounds and their anticancer activities, Curr. Pharmaceut. Des. 16 (16) (2010) 1826–1842.

[18] D. Mech, A. Kurowska, N. Trotsko, The bioactivity of thiazolidin-4-ones: a short review of the most recent studies, Int. J. Mol. Sci. 22 (2021) 11533.

[19] K. Venu, B. Saritha, B.B.V. Sailaja, New molecular hybrids containing benzimidazole, thiazolidine-2,4-dione and 1,2,4-oxadiazole as EGFR directing cytotoxic agents, Tetrahedron 124 (2022) 132991.

[20] N. Trotsko, J. Golus, P. Kazimierczak, A. Paneth, A. Przekora, G. Ginalska, M. Wujec, Design, synthesis and antimycobacterial activity of thiazolidine-2,4-dione-based thiosemicarbazone derivatives, Bioorg. Chem. 97 (2020) 103676.

[21] Z. Kazimierczuk, M. Andrzejewska, J. Kaustova, V. Klimesova, Synthesis and antimycobacterial activity of 2-substituted halogenobenzimidazoles, Eur. J. Med. Chem. 40 (2005) 203–208.

[22] K. Gobis, H. Foks, M. Serocki, E. Augustynowicz-Kopev, A. Napiorkowska, Synthesis and evaluation of in vitro antimycobacterial activity of novel 1H-benzo [d]imidazole derivatives and analogues, Eur. J. Med. Chem. 89 (2014) 13–20.

[23] K. Gobis, H. Foks, K. Suchan, E. Augustynowicz-Kopec, A. Napiorkowska, K. Bojanowski, Novel 2-(2-phenalkyl)-1H-benzo[d]imidazoles as antitubercular agents. Synthesis, biological evaluation and structure-activity relationship, Biorg. Med. Chem. 23 (2015) 2112–2120.

[24] B. Park, D. Awasthi, S.R. Chowdhury, E.H. Melief, K. Kumar, S.E. Knudson, R. A. Slayden, I. Ojima, Design, synthesis and evaluation of novel 2,5,6-trisubstituted benzimidazoles targeting FtsZ as antitubercular agents, Bioorg. Med. Chem. 22 (2014) 2602–2612.

[25] V.T. Angelova, V. Valcheva, N. Vassilev, R. Buyukliev, R. Mihaylova, G. Momekov, Synthesis, in vitro antiproliferative and antimycobacterial activity of thiazolidine-2,4-dione and hydantoin derivatives, Bulg. Chem. Commun. 49 (2017) 643–651.

[26] S. Ponnuchamy, S. Kanchithalaivan, R.R. Kumar, M.A. Ali, T.S. Choon, Antimycobacterial evaluation of novel hybrids arylidene thiazolidine-2,4-diones, Bioorg. Med. Chem. Lett. 24 (2014) 1089–1093.

[27] F.M. Shaikh, N.B. Patel, D. Rajani, Synthesis of new thiazolidine-2,4-dione derivatives and their antimicrobial and antitubercular activity, Indian J. Res. Pharm. Biotechnol. 1 (2013) 496–503.

[28] D.M.L. Araujo, M.M. Maste, S. Alegaon, A. Saxena, Synthesis, antitubercular evaluation and docking studies of novel benzimidazole analogues, Int. J. Pharma Sci. Res. 9 (2018) 3696–3704.

[29] C.V. Junior, A. Danuello, V.D.S. Bolzani, E.J. Barreiro, C.A.M. Fraga, Molecular hybridization: a useful tool in the design of new drug prototypes, Curr. Med. Chem. 14 (2007) 1829–1852.

[30] X. Yang, Z. Pan, M.R. Choudhury, Z. Yuan, A. Anifowose, B. Yu, W. Wang, B. Wang, Making smart drugs smarter: the importance of linker chemistry in targeted drug delivery, Med. Res. Rev. 40 (2020) 2682–2713.

[31] R. Sheyi, B.G. de la Torre, F. Albericio, Linkers: an assurance for controlled delivery of antibody-drug conjugate, Pharmaceutics 14 (2022) 396.

[32] G. Sivaiah, R. Raveesha, S.B. Benaka Prasad, K. Yogesh Kumar, M.S. Raghu, F. A. Alharti, M.K. Prashanth, B.H. Jeon, Synthesis, biological evaluation and molecular docking studies of novel pyrrolo [2, 3-d] pyrimidin-2-amine derivatives as EGFR inhibitors, J. Mol. Struct. 1275 (2023) 134728.

[33] T.A. Yousef, A.G. Alhamzani, M.M. Abou-Krisha, G. Kanthimathi, M.S. Raghu, K. Yogesh Kumar, M.K. Prashanth, B.H. Jeon, Synthesis, molecular docking study and anticancer activity of novel 1, 3, 4-oxadiazole derivatives as potential tubulin inhibitors, Heliyon 9 (2023) e13460.

[34] M.K. Prashanth, M. Madaiah, H.D. Revanasiddappa, K.N. Amruthesh, Synthesis, characterization, and BSA binding studies of some new benzamides related to Schiff base, ISRN Org. Chem. 2013 (2013) 1–12.

[35] H.N. Deepakumari, B.K. Jayanna, M.K. Prashanth, H.D. Revanasiddappa, B. Veeresh, Synthesis and anticonvulsant activity of N-(Substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4H)-carboxamides, Arch. Pharm. 349 (2016) 566–571.

[36] M. Madaiah, M.K. Prashanth, H.D. Revanasiddappa, B. Veeresh, Synthesis and pharmacological evaluation of Novel 1′-[2-(Difluoromethoxy) benzyl]-2′H,5′H-spiro [8-azabicyclo[3.2.1]octane-3,4′-imidazolidine]-2′,5′-diones and their derivatives, Arch. Pharm. 347 (2014) 370–380.

[37] M.K. Prashanth, H.D. Revanasiddappa, Synthesis and antioxidant activity of novel quinazolinones functionalized with urea/thiourea/thiazole derivatives as 5-lipoxygenase inhibitors, Lett. Drug Des. Discov. 11 (2014) 712–720.

[38] M. Madaiah, M.K. Prashanth, H.D. Revanasiddappa, Novel synthesis of 4,4difluoropyrido[4,3- b]indoles via intramolecular Heck reaction, Tetrahedron Lett. 54 (2013) 1424–1427.

[39] M.K. Prashanth, M. Madaiah, H.D. Revanasiddappa, K.N. Amruthesh, Synthesis, characterization, and BSA binding studies of some new benzamides related to Schiff base, ISRN Org. Chem. 2013 (2013) 1–12.

[40] K. Veena, S. Chandrasekhar, M. Raghu, K.Y. Kumar, C.P. Kumar, A.M. Alswieleh, V. A. Devi, M. Prashanth, B.-H. Jeon, Facile green synthesis of samarium sesquioxide nanoparticle as a quencher for biologically active imidazole analogues: computational and experimental insights, J. Mol. Struct. 1264 (2022) 133235.

[41] C.B. Pradeep Kumar, M.S. Raghu, B.S. Prathibha, M.K. Prashanth, K. Yogesh Kumar, H.D. Revanasiddappa, B.K. Jayanna, F.A. Alharthi, Click synthesis of 1,2,3-triazole based imidazoles: antitubercular evaluation, molecular docking and HSA binding studies, Bioorg. Med. Chem. Lett. 36 (2021) 127810.

[42] M.S. Raghu, C.B. Pradeep Kumar, K.N.N. Prasad, S. Chandrasekhar, K. Yogesh Kumar, M.K. Prashanth, B. Veeresh, MoS 2-calix[4]arene catalyzed synthesis and molecular docking study of 2,4,5-trisubstituted imidazoles as potent inhibitors of Mycobacterium tuberculosis, ACS Comb. Sci. 22 (2020) 509–518.

[43] G. Sivaiah, R. Raveesha, S.B. Benaka Prasad, K.Y. Kumar, M.S. Raghu, F. Alharethy, M.K. Prashanth, B.H. Jeon, Synthesis, anticancer activity and molecular docking of new pyrazolo[1,5-a]pyrimidine derivatives as EGFR/HER2 dual kinase inhibitors, J. Mol. Struct. 1289 (2023) 135877.

[44] A. Quispe, C. Zavala, J. Rojas, M. Posso, A. Vaisberg, Efecto citotoxico selectivo in vitro de murcin H (acetogenina de Annona muricata) en cultivos celulares de cancer de pulmon, Rev. Peru. Med. Exp. Salud Pública 23 (2006) 265–269.

[45] S. Valdes-Garcia, G. Del barrio-Alonso, Y. Gutierrez-Gaiten, L. Morier-Díaz, Evaluacion preliminar de la actividad antiviral del extracto acuoso de Phyllathus orbicularis frente al virus VHS-1, Rev. Cuba, Med. Trop. 55 (2003) 169–173.

[46] S.T. Cole, G. Riccardi, New tuberculosis drugs on the horizon, Curr. Opin. Microbiol. 14 (2011) 570–576.

[47] M. Brecik, I. Centarova, R. Mukherjee, G.S. Kolly, S. Huszar, A. Bobovska, E. Kilacskova, V. Mokosova, Z. Svetlikova, S. Michal, J. Neres, J. Kordulakova, S. T. Cole, K. Mikusova, DprE1 is a vulnerable tuberculosis drug target due to its cell wall localization, ACS Chem. Biol. 10 (2015) 1631–1636.

[48] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv. Drug Deliv. Rev. 64 (2012) 4–17.

[49] D.F. Veber, S.R. Johnson, H.Y. Cheng, B.R. Smith, K.W. Ward, K.D. Kopple, Molecular properties that influence the oral bioavailability of drug candidates, J. Med. Chem. 45 (2002) 2615–2623.
[50] A.G. Alhamzani, T.A. Yousef, M.M. Abou-Krisha, M.S. Raghu, K.Y. Kumar, M. K. Prashanth, B.H. Jeon, Design, synthesis, molecular docking and pharmacological evaluation of novel triazine-based triazole derivatives as potential anticonvulsant agents, Biorg. Med. Chem. Lett 77 (2022) 129042.
[51] N. Bergenhem, Preclinical candidate nomination and development, in: K. Tsaioun, S.A. Kate (Eds.), Admet for Medicinal Chemists, John Wiley and Sons, Singapore, 2011, pp. 399–415.