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## SYNTHESIS, ANTITUBERCULAR EVALUATION AND DOCKING STUDIES OF NOVEL BENZIMIDAZOLE ANALOGUES

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**ABSTRACT:** A series of (Z)-3-((1H-benzo[d]imidazol-2-yl)methyl)-substituted thiazolidine-2,4-dione (9a-n) have been synthesized and evaluated for their mycobacterium inhibitory activity against *Mycobacterium tuberculosis* H37Rv strain. The structures of the newly synthesized compounds were characterized by FTIR and NMR spectral analysis. Most of the synthesized compounds showed moderate to good anti-tubercular activity. Among these compounds 9a, 9d, 9f and 9g have displayed good anti-tubercular activity (MIC 6.25 µg/ml). Further, the molecular docking studies were carried out in order to rationalize the biological activity.

**INTRODUCTION:** Tuberculosis is a chronic necrotizing bacterial infection caused by ubiquitous organism *Mycobacterium tuberculosis* (Mtb) and other species; *M. caprae*, *M. microti*, *M. pinipedii*, *M. bovis*, *M. africanum*<sup>1</sup>. Its primary site of infection is the lungs (pulmonary TB) followed by propagation *via* the circulatory and lymphatic system to secondary sites including the bones, joints, liver and spleen (extra pulmonary TB)<sup>2</sup>. Due to tremendous increase in the mortality and morbidity tuberculosis has been identified by WHO as one of the three priority disease for drug research and development<sup>3</sup>. According to WHO in 2014, 9.6 million people were infected with TB and 1.5 million died from this disease. An estimated 1 million children were infected & 140,000 children died of TB<sup>4</sup>.

Every year there are around 2-2.5 million cases of TB in India, which thus brings us into the category of the most TB vulnerable nation in the world<sup>5</sup>. The current treatment for tuberculosis include isoniazid, pyrazinamide, ethambutol and streptomycin (first line drugs) PAS, ethionamide, cycloserine, amikacin, kanamycin (second line drugs)<sup>6</sup>.

To combat the global dominance of tuberculosis WHO has launched an empiric treatment programme, termed DOTS (Directly Observed Therapy Short-course) which includes a dosage regimen of isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA) for initial 2 months followed by intermittent therapy of INH and RIF for subsequent 4-7 months<sup>7</sup>. Poor patient compliance due to prolonged therapies moreover the synergy of this disease with HIV infection has resulted in the emergence of multi-drug resistance tuberculosis (MDR-TB) and extreme-drug resistance tuberculosis (XDR-TB). It was also reported that about 3.6% of the new patients and 20% of the previously treated ones had MDR-TB<sup>8,9</sup>.

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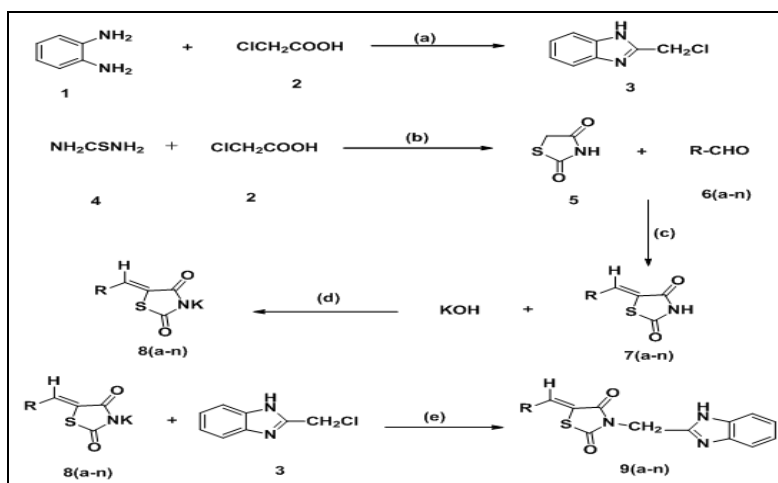
In MDR-TB, Mtb strains are resistant to INH and RIF whereas in XDR-TB, the strains are resistant to fluoroquinolones and 2<sup>nd</sup> line injectable drugs. This scenario is even more serious with a deadlier designation of totally-drug resistant tuberculosis (TDR-TB) wherein the Mtb strains are resistant to all the 1<sup>st</sup> and 2<sup>nd</sup> line drugs<sup>7</sup>. In 2006, WHO had developed a global plan named 'The stop TB strategy' which demanded to reduce the global burden of TB till 2015. It reinforced the development of new and effective tools to prevent the vulnerable populations from TB and aims to eliminate TB as a public health problem till 2050<sup>10</sup>.

Various nitrogen containing heterocyclic compounds have been studied extensively for the development of pharmaceutically important agents. They have played a major role in drug discovery due to their diverse pharmacological actions. Most of the administered anti-TB drugs contain nitrogen in their heterocyclic moiety, thus potential anti-TB drugs are searched in this group<sup>2</sup>. Benzimidazole is a well-known pharmacophore which has played a crucial role in the theoretical development of heterocyclic chemistry and organic synthesis. It possess multifarious bioactivities as antimicrobial<sup>11</sup>, antitubercular<sup>12</sup>, anticancer<sup>13</sup>, proton pump

inhibitors<sup>14</sup>, antiviral<sup>15</sup>, antioxidant<sup>16</sup>, anti-parasitic<sup>17</sup>, anthelmintics<sup>18</sup>, anti-HIV<sup>19</sup>, anti-convulsant<sup>20</sup>, anti-inflammatory<sup>21</sup>, antihypertensive<sup>22</sup>. It is also an important constituent of Vitamin-B<sub>12</sub><sup>23</sup>. It also represents biosterism with indole and purine nuclei that are present in many fundamental cellular components and bioactive compounds.

Its derivatives could compete with purines, resulting in distinct inhibition of the synthesis of nucleic acids and proteins<sup>24</sup>. The effectiveness of benzimidazole nucleus is attributed to both its inhibitory activity and favourable selectivity ratio<sup>25</sup>. According to the literature survey, benzimidazole derivatives are reported as potent anti-TB agents, due to their polar and ionisable properties they have been used to optimize the lipophilicity and bioavailability parameters<sup>26</sup>. Hence we have synthesized a series of 2-substituted benzimidazole derivatives and evaluated for their anti-tubercular activity.

**MATERIALS AND METHODS:** The target, (Z)-3-((1H-benzo[d]imidazol-2-yl)methyl) - substituted thiazolidine-2,4-dione derivatives (9a-n) were synthesized according to the synthetic route as presented in **Scheme 1**.



SCHEME 1

Code	a	b	C	d	e	f	g
R	C <sub>6</sub> H <sub>5</sub>	4-(Cl)C <sub>6</sub> H <sub>4</sub>	4-(Br)C <sub>6</sub> H <sub>4</sub>	4-(F)C <sub>6</sub> H <sub>4</sub>	4-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	4-(OH)C <sub>6</sub> H <sub>4</sub>	4-(CH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>
Code	h	I	j	k	l	m	n
R	4-(OCH <sub>3</sub> ) C <sub>6</sub> H <sub>4</sub>	3,4-(OCH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	2-Cl C <sub>6</sub> H <sub>4</sub>	N-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		

2-(chloromethyl)-1H-benzo[d]imidazole (3) was synthesized by reaction between ortho-phenylenediamine (1) and chloroacetic acid (2) in presence

of 4N hydrochloric acid under reflux condition (18 h). The key intermediate thiazolidine-2,4-dione (5) was prepared by cyclo-addition between thiourea

(4) and chloroacetic acid (2) in presence of concentrated hydrochloric acid. The obtained thiazolidine-2,4-dione was subjected to Knoevenagel's condensation with appropriate aromatic or heteroaromatic aldehydes in the presence of catalytic amount of piperidine acetate to offer 5-substituted thiazolidine-2,4-dione derivatives (7a-n). The obtained derivatives of 5-substituted thiazolidine-2,4-dione were further converted into their corresponding potassium salts in the presence of ethanol under reflux condition. The target compounds (Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-substituted thiazolidine-2,4-dione derivatives (9a-n) were prepared by the reaction between potassium salts of substituted thiazolidine-2,4-dione (8a-n) and 2-(chloromethyl)-1H-benzo [d]imidazole (3) in acetonitrile, under reflux condition.

**General Procedure for the Synthesis of Substituted Thiazolidine-2,4-dione (7a-7n):** A mixture of thiazolidine-2,4-dione (5) (0.0188 moles, 2.16g), various substituted aromatic or heterocyclic aldehydes (6a-6n) (0.0188 moles) and catalytic amount of piperidine acetate (1ml) was refluxed for 8h in toluene (60 ml), using Dean-Stark apparatus. After complete removal of water, the reaction mixture was cooled, filtered and washed with cold toluene to yield the corresponding compounds (7a-7n).

**General Procedure for the Synthesis of Potassium Salts of Substituted Thiazolidine-2,4-dione (8a-8n):** Substituted thiazolidine-2,4-dione (7a-7n) (0.0085 moles, 2gms) and potassium hydroxide (0.009 moles, 0.5gms) was refluxed in ethanol (80ml) for 5hrs. The reaction mixture was cooled and filtered to obtain various potassium salts of substituted thiazolidine-2,4-dione (8a-8n).

**General Procedure for the Synthesis of (Z)-3-((1H-benzo[d]imidazol-2-yl)methyl)-substituted thiazolidine-2,4-dione (9a-9n):** A mixture of 2-(chloromethyl)-1H-benzo[d]imidazole (3) (0.0061 moles, 1.02g) and potassium salts of substituted thiazolidine-2,4-dione (8a-8n) (0.0041 moles, 1g) was refluxed in acetonitrile for 72 h. The reaction was monitored by TLC. The solvent was evaporated and the residue obtained was washed with water, dried and then washed with diethyl ether to yield the corresponding derivatives (9a-9n).

**RESULTS AND DISCUSSION:** The synthesized compounds were characterized by FTIR and NMR spectroscopy. The formation of 2-(chloromethyl)-1H-benzo[d]imidazole (3) was confirmed by the presence of N-H band around  $3155\text{ cm}^{-1}$  in the IR spectrum and a singlet signal of methylene at  $\delta$  4.91 ppm in  $^1\text{H-NMR}$  spectrum.

The IR spectrum of thiazolidine-2,4-diones (5) displayed a characteristic N-H stretching band at around  $3460\text{ cm}^{-1}$  and C=O peak around  $1730\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum of thiazolidine-2,4-diones revealed a characteristic methylene and amine peak at  $\delta$  4.14 and 12 ppm respectively.

The IR spectra of 5-substituted thiazolidine-2,4-dione (7a-n) clearly showed sharp band for C=O stretching at around  $1680\text{ cm}^{-1}$  and a N-H peak at around  $3300\text{ cm}^{-1}$ . The disappearance of methylene proton and appearance of benzylidene proton at around  $\delta$  7.8 ppm in  $^1\text{H-NMR}$  spectra of the compound supported the formation of 5-substituted thiazolidine-2,4-dione derivatives (7a-n).

The target compounds (Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-substituted thiazolidine-2,4-dione derivatives (9a-n) were confirmed by IR, NMR, mass spectral studies. The IR spectrum of 2-substituted benzimidazole derivatives (9a-n) displayed sharp C=O stretching band at around  $1720\text{ cm}^{-1}$  and the N-H singlet signal for thiazolidine-2,4-diones proton in  $^1\text{H-NMR}$  spectrum was absent. A new signal for methylene proton was observed at around  $\delta$  4.8 ppm in the  $^1\text{H-NMR}$  spectrum, thus substantiating the formation of 2-substituted benzimidazole derivatives (9a-n). The molecular weight of the synthesized compounds was confirmed by mass spectroscopy. All the chemicals and solvents were purchased from spectrochem, sd-fine chemicals, rankem, Hi Media and used without further purification. Melting points were determined by open capillary tube method and are reported as uncorrected values.  $^1\text{H NMR}$  spectra were recorded on AMX-400, Bruker-400 liquid-state NMR spectrometer using tetramethylsilane (TMS) as the internal standard.

A solution of thiourea (4) (0.197 moles, 15gms) in water (30 ml) and chloroacetic acid (2) (0.197 moles, 18.52 gms) in water (30 ml) was stirred for

1 h and white precipitate was obtained. Conc hydrochloric acid (33 ml) was added dropwise, while maintaining in cold condition. The reaction mixture was refluxed for 15 h. It was further cooled, filtered and washed with cold water to yield white crystals (5). Yield 46%, Mp: 122-124 °C. FTIR (KBr)  $\text{cm}^{-1}$ : 3469 (N-H), 2872(C-H), 1739(C=O)  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12(s, 1H, N-H), 4.14 (s, 2H, -CH $_2$ -).

**Charaterization:** (Z)-5-benzylidenethiazolidine-2, 4-dione (7a). Creamish coloured product; yield: 85.4%; MP 242 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3145(N-H), 3039 (Ar-H), 2787 (C-H), 1735(C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.6 (s, 1H, NH), 7.8 (s, 1H, -CH=), 7.45-7.60 (m, 5H, Ar-H).

(Z)-5-(4-chlorobenzylidene)thiazolidine-2, 4-dione (7b). White coloured product; yield: 80%; MP: 230 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3149(N-H), 3053 (Ar-H), 2765 (C-H), 1718 (C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.25 (s, 1H, NH), 8.01 (s, 1H, -CH=), 7.72-7.77 (m, 2H, Ar-H), 7.25-7.30 (m, 2H, Ar-H).

(Z)-5-(4-bromobenzylidene) thiazolidine-2, 4-dione (7c). White coloured product; yield: 75%; MP: 225°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3149 (N-H), 3053 (Ar-H), 2765 (C-H), 1747(C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.75 (s, 1H, NH), 8.29 (s, 1H, -CH=), 7.94 (d, 2H, Ar-H), 7.85 (d, 2H, Ar-H).

(Z)-5-(4-fluorobenzylidene) thiazolidine-2, 4-dione (7d). Yellow coloured product; yield: 82%; MP: 215 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3153 (N-H), 3049 (Ar-H), 2771 (C-H), 1751 (C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 13.85 (s, 1H, NH), 7.70 (s, 1H, -CH=), 7.60 (m, 2H, Ar-H), 7.34 (m, 2H, Ar-H).

(Z)-5-(4-nitrobenzylidene) thiazolidine-2, 4-dione (7e). Creamish flakes; yield: 82.5%; MP: 272 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3201 (N-H), 3120 (Ar-H), 2852 (C-H), 1751 (C=O), 1533 (-NO $_2$ ).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.59 (s, 1H, NH), 7.9 (s, 1H, -CH=), 7.75 (d, 2H, Ar-H), 7.5 (d, 2H, Ar-H).

(Z)-5-(4-hydroxybenzylidene) thiazolidine-2, 4-dione (7). Light yellow product; yield: 75.6%; MP: 298°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3427 (OH), 3132 (N-H), 3007 (Ar-H), 2796 (C-H), 1762. (C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 11.5 (b, s, 1H, NH),

10.02 (s, 1H, OH), 7.8 (s, 1H, -CH=), 7.5 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H).

(Z)-5-(4-methylbenzylidene)thiazolidine-2, 4-dione (7g). Off white coloured granules; yield: 82%; MP: 230 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3169 (N-H), 3053 (Ar-H), 2771 (C-H), 1735 (C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.53 (s, 1H, NH), 7.73 (s, 1H, CH), 7.45 (d, 2H, Ar-H), 7.33 (d, 2H, Ar-H), 2.2(s, 3H, Ar-CH $_3$ ).

(E)-5-(4-methoxybenzylidene) thiazolidine-2, 4-dione (7h). White coloured product; yield: 86.5%; MP: 210 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3226 (N-H), 3095 (Ar-H), 2856 (C-H), 1753 (C=O), 1253(-OCH $_3$ ).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.45 (s, 1H, NH), 7.69 (s, 1H, -CH=), 7.50 (d, 2H, Ar-H), 7.05 (d, 2H, Ar-H), 3.78 (s, 3H, OCH $_3$ ).

(Z)-5-(3,4-dimethoxybenzylidene)thiazolidine-2, 4-dione (7i). Yellow flakes; yield: 79 %; MP: 210 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3115 (N-H), 3022 (Ar-H), 2850 (C-H), 1735 (C=O), 1199 (OCH $_3$ );  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.13 (s, 1H, NH), 8.62 (d, 2H, Ar-H), 7.82 (s, 1H, -CH=), 7.52 (s, 1H, Ar-H), 3.72 (s, 6H, OCH $_3$ ).

(Z)-5-(3,4,5-trimethoxybenzylidene)thiazolidine- 2, 4-dione (7j). Light whitish yellow flakes; yield: 81%; MP: 174 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3209 (N-H), 3064 (Ar-H), 2837 (C-H), 1750 (C=O), 1249 (-OCH $_3$ ).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.56 (s, 1H, NH), 7.9 (s, 1H, -CH=), 6.89 (s, 2H, Ar-H), 3.82 (s, 6H, OCH $_3$ ), 3.71(s, 3H, Ar-OCH $_3$ ).

(Z)-5-(2-chlorobenzylidene) thiazolidine-2, 4-dione (7k). White shiny product; yield: 74.5%; MP: 160°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3057 (N-H), 3012(Ar-H), 2848(C-H), 1701(C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 11.59 (s, 1H, NH), 7.72 (s, 1H, -CH=), 7.26 (m, 4H, Ar-H).

(Z) - 5 - (4-(dimethylamino) benzylidene) thiazolidine-2, 4-dione (7l). Orange product; yield: 76.5%; MP: 300°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3127 (N-H), 3008 (Ar-H), 2827 (C-H), 1735 (C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.13 (s, 1H, NH), 7.8 (s, 1H, -CH=), 7.91 (m, 4H, Ar-H), 3.01 (s, 6H, CH $_3$ ).

(Z)-5-(furan-3-ylmethylene) thiazolidine-2, 4-dione (7m). Beige coloured product; yield: 86.5%; MP:



230°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3165 (N-H), 3034 (Ar-H), 2806 (C-H), 1776 (C=O), 1612 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.49 (s, 1H, NH), 8.01 (d, 1H, furan), 7.56 (s, 1H, -CH=), 7.1 (d, 1H, furan), 6.5 (m, 1H, furan).

(Z)-5-(thiophen-3-ylmethylene) thiazolidine - 2, 4-dione (7n). Light yellow coloured product; yield: 78%; MP: 242°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3361 (N-H), 3091 (Ar-H), 2806 (C-H), 1766 (C=O).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.52 (s, 1H, NH), 8.02 (s, 1H, -CH=), 7.97 (d, 1H, thiophene), 7.67 (d, 1H, thiophene), 7.26 (m, 1H, Ar).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl) - 5-benzylidenethiazolidine-2,4-dione (9a). Greenish yellow powder; yield: 82% MP: 210 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3053 (N-H), 2912 (C-H), 1685 (C=O), 1608 (C=C), 1558 (C=N).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.50 (s, 1H, NH), 7.99 (s, 1H, CH=), 7.36-7.56 (m, 9H, Ar-H), 5.07 (s, 2H,  $\text{CH}_2$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl) - 5 - (4-chlorobenzylidene) thiazolidine - 2, 4-dione (9b). Beige colour powder; yield: 89.5%; MP: 160 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3055 (N-H), 2824 (C-H) 1724 (C=O), 1680 (C=N), 1608 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.52 (s, 1H, NH), 7.97 (s, 1H, CH=), 7.40-7.54 (m, 8H, Ar-H), 5.17 (s, 2H,  $\text{CH}_2$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-5-(4-bromobenzylidene) thiazolidine-2, 4-dione (9c). Brown flakes; yield: 89%; MP: 210 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3155 (N-H), 2848 (C-H), 1751 (C=O), 1610 (C=N), 1581 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.56 (s, 1H, NH), 7.96 (s, 1H, CH=), 7.12-7.38 (m, 8H, Ar-H), 5.11 (s, 2H,  $\text{CH}_2$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-5-(4-fluorobenzylidene) thiazolidine-2, 4-dione (9d). Light orange coloured product; yield: 86.5%; MP: 160 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3294 (N-H), 2922 (C-H), 1753 (C=O), 1697 (C=N), 1585 (C=C).

$^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.56 (s, 1H, NH), 7.97 (s, 1H, CH=), 7.02-7.26 (m, 8H, Ar-H), 5.08 (s, 2H,  $\text{CH}_2$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-5-(4-nitrobenzylidene) thiazolidine - 2, 4 - dione (9e). Brown coloured product; yield 86%; MP: 180°C;

FTIR (KBr)  $\text{cm}^{-1}$ : 3277 (N-H), 2848 (C-H), 1693 (C=N), 1517 (NO<sub>2</sub>).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.52 (s, 1H, NH), 7.89 (s, 1H, CH=), 7.33-7.60 (m, 8H, Ar-H), 5.13 (s, 2H,  $\text{CH}_2$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-5-(4-hydroxybenzylidene) thiazolidine-2, 4-dione (9f). Light yellow coloured product; yield 89.5%; MP: 220 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3051 (N-H), 2802 (C-H), 1728 (C=O), 1685 (C=N), 1577 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.43 (s, 1H, NH), 10.29 (s, 1H, OH), 7.98 (s, 1H, CH=), 7.25-7.61 (m, 8H, Ar-H), 4.94 (s, 2H,  $\text{CH}_2$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-5-(4-methylbenzylidene) thiazolidine-2, 4-dione (9g). Buff colour coloured product; yield: 81.4%; MP: 172 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3053(N-H), 2850 (C-H), 1737 (C=O), 1667 (C=N), 1595 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.56 (s, 1H, NH), 7.91 (s, 1H, CH=), 7.10-7.25 (m, 8H, Ar-H), 5.17 (s, 2H,  $\text{CH}_2$ ), 2.34 (s, 3H,  $\text{CH}_3$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-5-(4-methoxybenzylidene) thiazolidine-2, 4-dione (9h). Greenish yellow coloured product; yield: 84%; MP: 198 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3057 (N-H), 2853 (C-H), 1697 (C=O), 1618 (C=N), 1558 (C=C), 1028 ( $\text{OCH}_3$ ).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.54 (s, 1H, NH), 7.96 (s, 1H, CH=), 7.22-7.59 (m, 8H, Ar-H), 5.08 (s, 2H,  $\text{CH}_2$ ), 3.58 (s, 3H,  $\text{OCH}_3$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl)methyl)-5-(3,4-dimethoxybenzylidene)thiazolidine-2, 4-dione (9i). Greenish yellow coloured product; yield: 86%; MP: 192°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3055 (N-H), 2853 (C-H), 1701 (C=O), 1593 (C=N), 1514 (C=C), 1145 (- $\text{OCH}_3$ ).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.56 (s, 1H, NH), 7.98 (s, 1H, CH=), 7.26-7.51 (m, 7H, Ar-H), 5.13 (s, 2H,  $\text{CH}_2$ ), 3.54 (s, 6H,  $\text{OCH}_3$ ).

(Z)-3-((1H-benzo[d]imidazol-2-yl)methyl)-5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione (9j). Greenish yellow coloured product; yield 92.3%; MP: 162°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3298 (N-H), 2837 (C-H), 1753 (C=O), 1685 (C=N), 1577 (C=C), 1136 ( $\text{OCH}_3$ ).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $\text{d}_6$ ): 12.52 (s, 1H, NH), 7.94 (s, 1H, CH=), 7.14-7.56 (m, 6H, Ar-H), 5.10 (s, 2H,  $\text{CH}_2$ ), 3.83 (s, 6H,  $\text{OCH}_3$ ), 3.74 (s, 3H,  $\text{OCH}_3$ ).

(Z)-3-((1H-benzo[d] imidazol-2-yl) methyl)-5-(2-chlorobenzylidene) thiazolidine-2, 4-dione (9k). Beige coloured product; yield 81.8%; MP: 140 °C; FTIR (KBr)  $\text{cm}^{-1}$ : 3292 (N-H), 2873 (C-H), 1743 (C=O), 1689 (C=N), 1604 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.52 (s, 1H, NH), 7.96 (s, 1H, CH=), 7.46-7.68 (m, 8H, Ar-H), 5.17 (s, 2H,  $\text{CH}_2$ ).



(Z)-3-((1H-benzo[d] imidazol-2-yl) methyl)-5-(4-dimethylamino)benzylidene) thiazolidine-2,4-dione (9l). Orange coloured product; yield %; MP: 242°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3095 (N-H), 2864 (C-H), 1724 (C=O), 1683 (C=N), 1577 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.58 (s, 1H, NH), 7.98 (s, 1H, CH=), 7.21-7.55 (m, 8H, Ar-H), 5.08 (s, 2H,  $\text{CH}_2$ ), 3.60 (s, 6H,  $\text{CH}_3$ ).

(Z)-3-((1H-benzo[d] imidazol-2-yl) methyl)-5-(furan-3-ylmethylene) thiazolidine-2, 4-dione (9m). Brown coloured product; yield 71.7%; MP: 92°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3034 (N-H), 2835 (C-H), 1735 (C=O), 1685 (C=O), 1616 (C=N), 1544(C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.54 (s, 1H, NH), 8.01 (d, 1H, furan), 7.88 (s, 1H, CH=), 7.35-7.71 (m, 4H, Ar-H), 7.75-7.84 (m, 2H, furan), 4.86 (s, 2H,  $-\text{CH}_2$ ).

(Z)-3-((1H-benzo[d] imidazol-2-yl) methyl)-5-(thiophen-3-ylmethylene) thiazolidine-2, 4-dione (9n). Brown coloured product; yield 85.2%; MP: 208°C; FTIR (KBr)  $\text{cm}^{-1}$ : 3057 (N-H), 2827 (C-H), 1735 (C=O), 1683 (C=N), 1600 (C=C).  $^1\text{H-NMR}$  (400 MHz,  $\delta$ , ppm, DMSO- $d_6$ ): 12.54 (s, 1H, NH), 7.79-7.88 (m, 2H, thiophene), 7.92 (s, 1H, CH=), 7.33-7.58 (m, 4H, Ar-H), 7.61 (d, 1H, thiophene), 4.99 (s, 2H,  $-\text{CH}_2$ ).

**Anti-Tubercular Activity:** *In-vitro* antitubercular activity of compounds (9a-n) was assessed against *Mycobacterium tuberculosis* H37Rv strain **Table 1**. The results obtained indicated revealed that, 4 out of 14 compounds 9a, 9f, 9g and 9d exhibited good Mtb inhibitory activity with MIC of 6.25  $\mu\text{g/ml}$ . These compounds were considered as most potent analogs against mycobacterium and were found to indicate similar anti tuberculosis potency as that of standard drug streptomycin. Compound 9b, 9c, 9e, 9h, 9k, 9m and 9n showed moderate activity with MIC of 12.5  $\mu\text{g/ml}$ , whereas compound 9i, 9j and 9l showed least anti-mycobacterial activity when compared to standard drugs like pyrazinamide and streptomycin.

**TABLE 1: ANTI-TUBERCULAR ACTIVITY OF THE SYNTHESIZED COMPOUNDS**

S. no	Compound	R	M.P	Yield (%)	MIC( $\mu\text{g/ml}$ )	Drug likeness score
1	9a	$\text{C}_6\text{H}_5$	210	82	6.25	-0.45
2	9b	4-(Cl) $\text{C}_6\text{H}_4$	160	89	12.5	0.09
3	9c	4-(Br) $\text{C}_6\text{H}_4$	210	85	12.5	-0.22
4	9d	4-(F) $\text{C}_6\text{H}_4$	160	86.5	6.25	-0.00
5	9e	4-( $\text{NO}_2$ ) $\text{C}_6\text{H}_4$	180	86	12.5	-0.75
6	9f	4-(OH) $\text{C}_6\text{H}_4$	220	88	6.25	-0.27
7	9g	4-( $\text{CH}_3$ ) $\text{C}_6\text{H}_4$	172	81.4	6.25	-0.32
8	9h	4-( $\text{OCH}_3$ ) $\text{C}_6\text{H}_4$	198	84	12.5	-0.23
9	9i	3,4-( $\text{OCH}_3$ ) $_2\text{C}_6\text{H}_3$	192	86	25	-0.10
10	9j	3,4,5-( $\text{OCH}_3$ ) $_3\text{C}_6\text{H}_2$	162	92.3	25	-0.09
11	9k	2-Cl $\text{C}_6\text{H}_4$	140	81.8	12.5	-0.51
12	9l	N-( $\text{CH}_3$ ) $_2\text{C}_6\text{H}_4$	242	79	25	-0.39
13	9m		92	71.7	12.5	-0.70
14	9n		208	85.2	12.5	-0.66
15	Pyrazinamide	-			3.125	
16	Streptomycin	-			6.25	



**Molecular Docking:** Molecular docking studies of the compounds showing potent activity were carried out in order to predict the hypothetical binding mode of these compounds to filamenting temperature sensitive mutant Z (FtsZ) protein

(1RLU.pdb). Molecular docking study was performed by using Auto Dock tools 1.5.6 (ADT 4.2). The 3D structures of compounds were prepared in pdb form by using Marvin Chem axon. The 3D structure of filamenting temperature-sensitive

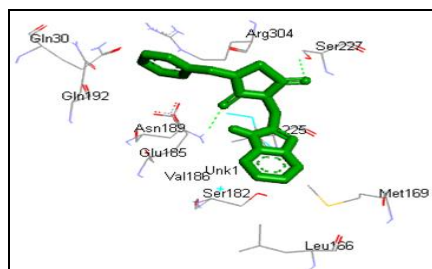
mutant Z (FtsZ), was downloaded from Protein Data Bank under the accession code 1RLU.pdb<sup>5</sup>. Heteroatoms and water molecules were removed then hydrogen atoms were added to protein for correct calculation of partial atomic charges. The grid box was set at 60, 60 and 60 Å (x, y and z). The Lamarckian Genetic Algorithm (LGA) was applied to search conformers that possessed lowest binding energy. Results of molecular docking analysis were obtained as estimated free energy of binding in kcal/mol. The drug-likeness studies of the synthesized compounds were analyzed for

Lipinski rule of 5 to determine if the given compound has the potency to be orally active. The orally active compound should not violate more than one of the following criteria: (a) molecular weight (MW)  $\leq$  500 Da, (b)  $\log P \leq 5$ , (c) number of hydrogen bond acceptors (HBA)  $\leq 10$ , (d) number of hydrogen bond donors (HBD)  $\leq 5$ . The predicted Lipinski parameters for all the compounds (9a-n) satisfied the criteria's of Lipinski's rule, with molecular weight ranging from 328.44-425.47, HBA from 4-8, HBD from 1-3 and  $\log P$  values from 2-3.55 **Table 2**.

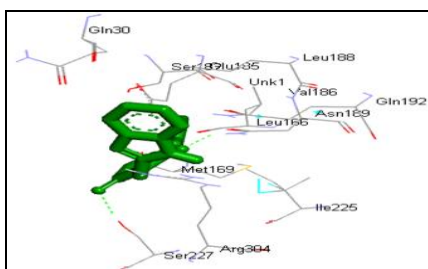
**TABLE 2: MOLECULAR PARAMETERS OF (Z)-3-((1H-BENZO[D]IMIDAZOL-2-YL)METHYL)-SUBSTITUTED THIAZOLIDINE-2,4-DIONE (9a-n)**

Compound	TPSA <sup>a</sup>	n-roth <sup>b</sup>	nON <sup>c</sup>	nOHNH <sup>d</sup>	miLogP <sup>e</sup>	MW	R
Rule of 5	-	-	$\leq 10$	$\leq 5$	$\leq 5$	$\leq 500$	
9a	67.76	3	5	1	2.74	335.76	C <sub>6</sub> H <sub>5</sub>
9b	67.76	3	5	1	3.42	369.83	4-(Cl)C <sub>6</sub> H <sub>4</sub>
9c	67.76	3	5	1	3.55	414.28	4-(Br)C <sub>6</sub> H <sub>4</sub>
9d	67.76	3	5	1	2.91	353.38	4-(F)C <sub>6</sub> H <sub>4</sub>
9e	113.58	4	8	1	2.70	380.38	4-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>
9f	87.99	3	6	2	2.26	351.39	4-(OH)C <sub>6</sub> H <sub>4</sub>
9g	67.76	3	5	1	3.19	349.42	4-(CH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>
9h	76.99	4	6	1	2.80	365.41	4-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>
9i	86.23	5	7	1	2.39	395.44	3,4-(OCH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>
9j	95.46	6	8	1	2.37	425.47	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>
9k	67.76	3	5	1	3.37	369.83	2-Cl
9l	71.00	4	6	1	2.84	378.44	N-(CH <sub>3</sub> ) <sub>2</sub>
9m	80.90	3	6	1	2.00	325.35	
9n	67.76	3	5	1	2.64	341.42	
INH <sup>g</sup>	68.013	1	4	3	-0.969	137	-

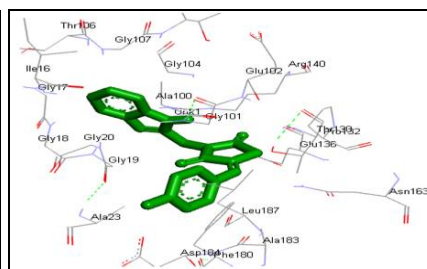
<sup>a</sup>TPSA, topological polar surface area, <sup>b</sup>n-roth, number of rotatable bonds, <sup>c</sup>nON, number of hydrogen bond acceptors, <sup>d</sup>nOHNH, number of hydrogen bond donors, <sup>e</sup>miLogP, logarithm of compound partition coefficient, <sup>f</sup>MW, molecular weight, <sup>g</sup>INH: Isoniazid, <sup>h</sup>PZA: Pyrazinamide



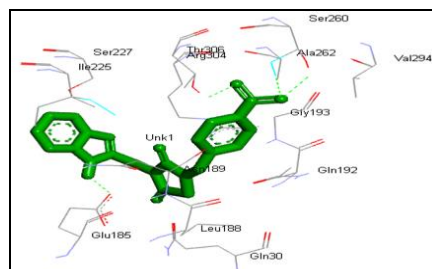
**FIG. 1: ORIENTATION OF 9a IN THE FtsZ ACTIVE POCKET**



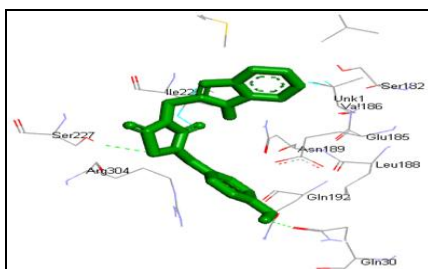
**FIG. 2: ORIENTATION OF 9c IN THE FtsZ ACTIVE POCKET**



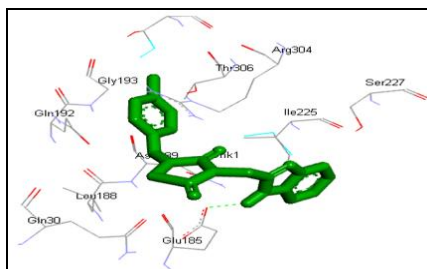
**FIG. 3: ORIENTATION OF 9d IN THE FtsZ ACTIVE POCKET**



**FIG. 4: ORIENTATION OF 9e IN THE FtsZ ACTIVE POCKET**



**FIG. 5: ORIENTATION OF 9f IN THE FtsZ ACTIVE POCKET**



**FIG. 6: ORIENTATION OF 9g IN THE FtsZ ACTIVE POCKET**

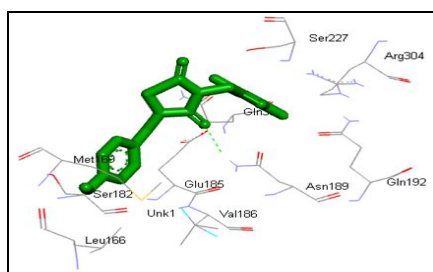


FIG. 7: ORIENTATION OF 9h IN THE FtsZ ACTIVE POCKET

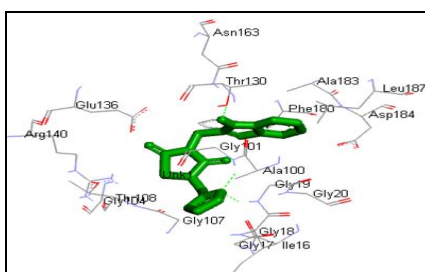


FIG. 8: ORIENTATION OF 9m IN THE FtsZ ACTIVE POCKET

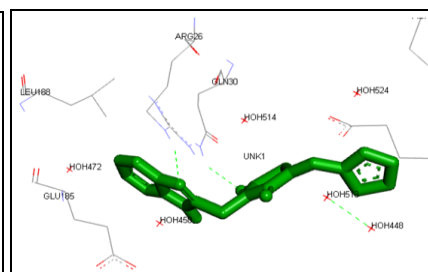


FIG. 9: ORIENTATION OF 9n IN THE FtsZ ACTIVE POCKET

The docking studies revealed that the compounds 9a and 9f were bonded to FtsZ *via* two hydrogen bonds. One of the oxygen atoms of thiazolidine-2,4-dione of compound 9a was bonded to amino hydrogen of the SER-227 residue (O---H:SER 227) and the other oxygen atom of thiazolidine-2,4-dione of compound 9a was bonded to hydrogen of ASN 189 residue (O---H:ASN 189). The hydrogen atom of hydroxyl group of compound 9f was bonded to oxygen atom of GLN 30 residue (H---O:GLN 30) and the sulphur atom of thiazolidine-2,4-dione of compound 9f was bonded to hydrogen atom of SER 227 residue (S---H:SER 227).

Compounds 9d and 9g were bonded *via* one hydrogen bond. The amino hydrogen of the benzimidazole ring of compound 9d was bonded to oxygen atom of GLY 101 residue (NH---O:GLY 101) and the amino hydrogen of compound 9g was bonded to oxygen atom of GLU 185 residue (NH---O:GLU 185). It was observed that the compound 9d exhibited binding energy of -5.81kcal/mol. Thus the molecular docking studies revealed that these compounds have better binding interactions with filamenting temperature sensitive mutant Z (FtsZ) protein.

**CONCLUSION:** A series of (Z)-3-((1H-benzo[d]imidazol-2-yl) methyl)-substituted thiazolidine-2,4-dione derivatives (9a-n) have been synthesized. The structural elucidation of synthesized compounds was carried out by FTIR, NMR and Mass spectroscopy. The target compounds were evaluated for their inhibitory activity against *Mycobacterium tuberculosis* H37Rv strain by Microplate Almar Blue Assay (MABA) method. Among all the tested derivatives, compound 9a, 9d, 9f and 9g exhibited good anti-tubercular activity (MIC-6.25µg/ml). Further, the molecular docking study revealed that these compounds have better binding interactions with FtsZ protein.

Thus the results obtained in this study suggest that 2-substituted benzimidazole derivatives can be further developed as promising anti-tubercular agents.

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**CONFLICT OF INTEREST:** The authors declare that they have no conflict of interest.

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