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# Synthesis of new 2-(thiazol-4-yl)thiazolidin-4-one derivatives as potential anti-mycobacterial agents

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ABSTRACT

To search for potent antimycobacterial lead compounds, a new series of 3-substituted phenyl-2-(2-(substituted phenyl)thiazol-4-yl) thiazolidin-4-one (**5a-t**) derivatives have been synthesized by the condensation of 2-substituted phenyl thiazole-4-carbaldehyde with aromatic amine followed by cyclocondensation with thioglycolic acid. The structure of the newly synthesized 2-(thiazol-4-yl)thiazolidin-4-one derivatives were characterized by the spectroscopic analysis. The synthesized compounds were screened for antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra (MTB) (ATCC 25177) and *Mycobacterium bovis* BCG (BCG, ATCC 35743). Most of the 2-(thiazol-4-yl)thiazolidin-4-one derivatives showed good to excellent antimycobacterial activity against both the *Mtb* strains. Nine derivatives **5c**, **5g**, **5j**, **5m**, **5n**, **5o**, **5p**, **5s,** and **5t** showed excellent activity against *M. bovis* BCG with MIC 4.43 to 24.04 μM were further evaluated for the cytotoxicity activity against HeLa A549, and HCT-116 cell lines and showed no significant cytotoxic activity at the maximum concentration evaluated. The potential antimycobacterial activities enforced that the thiazolyl-thiazolidin-4-one derivatives could lead to compounds that could treat tuberculosis.

## 1. Introduction

Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis* (MTB) is one of the deadliest infectious diseases having high mortality [1]. The treatment of *M. tuberculosis* infections has become one of the leading challenges worldwide and, an urgent need for effective new antibiotics is warranted [2,3].

Thiazole and thiazolidinone derivatives are proved as versatile and promising tools to combat antibiotic resistance [4]. Thiazole is an important nucleus of several bioactive natural products [5,6], it has been reported for wide range antimycobacterial activity [7-11]. Thiazolidinone pharmacophore is the core of many drugs such as, antihypertensive drug etozolines, anticonvulsant drug ralitoline, thiazolidomycin which is active against *streptomyces* species, and pioglitazone as a hypoglycemic agent. The thiazolidinone containing antibiotic actithiazic acid exhibits a specific *in vitro* activity against *Mycobacterium tuberculosis* [12]. The synthetic thiazolidinone derivative is an important scaffold in medicinal chemistry that possessed a broad spectrum of biological activities such as antitubercular [13], antiviral [14], antimicrobial [15,16], anti-inflammatory [17], antileukemic [18], antihyperglycemic [19], anticancer [20], anticonvulsant [21], and antioxidant [22] activities.

Thiazole and thiazolidinone containing scaffolds have been reported as potential antimycobacterial agents with various mechanism of actions [23] such as targeting PrrB–PrrA [24], mycobacterial Enoyl-acyl carrier protein reductase [25], Mtb-ATP Synthase [26], O-acetylserine sulfhydrylase (CysK1) [27], uridine 5′-diphosphate (UDP) galactopyranose mutase (UGM) inhibitors [28], β-ketoacyl synthase enzyme mtFabH [29], (MTB) DNA gyrase [30]. The biological importance of thiazole and thiazolidinone has made them prominent scaffolds for the discovery of new lead candidates.

Thiazole clubbed with other azoles such as thiazole (A) [31,32], oxazole (B) [33], 1,2,3-triazole (C) [34], pyrazole, (D) [35], thiadiazole (E) [25] and oxadiazole (F) [36] have received attention due to their potential antimycobacterial activity (Fig. 1). Thiazole tethered thiazolidinone was reported for antitubercular [37,38], antimicrobial [15,39],

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anticonvulsant [40], and anti-inflammatory [41] activities. In view of these findings, in this present work, we have reported the synthesis of clubbed thiazolyl-thiazolidin-4-one derivatives as potential anti-mycobacterial agents.

## 2. Results and discussion

### 2.1. Chemistry

The synthetic approaches for the preparation of target 3-aryl-2-(2-aryl-thiazol-4-yl) thiazolidin-4-one derivatives **5a-t** were illustrated in Scheme 1. Ethyl 2-aryl thiazole-4-carboxylate **1a-e** on reduction with $LiAlH_4$ in dry diethyl ether gave corresponding alcohol **2a-e**. Alcohol **2a-e** on selective oxidation using 2-iodoxybenzoic acid (IBX) in DMSO gave 2-aryl thiazole-4-carbaldehyde **3a-e.** Aldehyde **3a-e** on condensation reaction with substituted aromatic amines **4a-f** in toluene followed by cyclocondensation reaction with thioglycolic acid furnished 3-aryl-2-(2-aryl-thiazol-4-yl) thiazolidin-4-one derivatives **5a-t**. The synthetic methodology of the reaction was conducted in achiral environment and the products formed as a racemic mixture.

The structure of the title compounds **5a-t** was confirmed by the spectroscopic analysis. As a representative analysis of 3-(4-fluorophenyl)-2-(2-phenylthiazol-4-yl)thiazolidin-4-one (**5d**), the $^1$H NMR spectrum showed a doublet at $\delta$ 3.77 ($^2J$ = 15.5 Hz, geminal coupling) and doublet of doublet at $\delta$ 4.22 ($^2J$ = 15.5 Hz, geminal coupling and $^4J$ 1.2 Hz, long range coupling) of thiazolidinone methylene protons, the methine proton appeared as a doublet at $\delta$ 6.02 ($^4J$ 1.2 Hz, long range coupling)). The ortho and meta protons of 4-fluoro phenyl ring couples with fluorine at $\delta$ 6.99 and 7.19, respectively. A C-5 thiazole proton resonates as a singlet at $\delta$ 7.01. The five protons of the phenyl ring attached to the thiazole ring appeared as multiplates at $\delta$ 7.98–7.88 and 7.50–7.39. The $^{13}$C NMR spectrum of compound **5d** revealed two signals in the aliphatic region at $\delta$ 33.12 and 61.80 are assigned for thiazolidinone methylene and methine carbons, respectively. The C-2, C-4, and C-5 thiazole carbons have appeared at $\delta$ 169.83, 155.81, and 115.56 respectively. The carbons of 4-fluorophenyl ring coupled with fluorine showed four doublets at $\delta$ 162.64, 160.18 ($^1J_{C\text{-}F}$ = 246 Hz), 133.63, 133.60 ($^4J_{C\text{-}F}$ = 3 Hz), 127.99, 127.91 ($^3J_{C\text{-}F}$ = 8 Hz) and 116.37, 116.15 ($^2J_{C\text{-}F}$ = 22 Hz). A carbonyl carbon of thiazolidinone ring appeared at $\delta$ 171.63 and the carbons of phenyl ring attached to C-2 thiazole resonate at $\delta$ 133.03, 130.62, 129.04, and 126.61. The structure of compound **5d** was further confirmed by molecular ion peak at *m/z* 357.0535 $(M + H)^+$. The structure of all the derivatives was established accordingly.

### 2.2. Antimycobacterial activity

The preliminary screening of newly synthesized compounds found to possess a certain inhibitory activity against avirulent strain of *M. tuberculosis* $H_{37}$Ra (ATCC 25177) and *M. bovis* BCG (ATCC 35743) at 30, 10 and 3 μg/mL concentrations using the XRMA and NR assays, respectively [42-44]. The compounds which inhibited the growth of both *Mycobacterium* strains at 30 μg/mL were further screened for dose-dependent activity using concentrations range from 30 to 0.23 μg/mL. The results of $IC_{50}$ and $MIC_{90}$ of compounds **5a-t** are summarized in Table 1.

The results of antimycobacterial activity suggested that most of the 2-(thiazol-4-yl)thiazolidin-4-one derivatives displayed significant activity against *M. tuberculosis* H37Ra and *M. bovis*. Furthermore, the substituents like Cl, F, $CH_3$, Br, and $CF_3$ on phenyl ring influence the activity.

The Structure-Activity Relationship (SAR) study revealed that, amongst the unsubstituted phenyl ring at 2-position of thiazole and the substituted phenyl ring at 3-position of thiazolidinone in compounds 2-(2-phenylthiazol-4-yl)-3-(substituted phenyl)thiazolidin-4-one (**5a-f**), compounds **5a** ($R^1$ = H) and **5e** ($R^1$ = 4-$CH_3$) showed similar antimicrobial profiles towards *M. tuberculosis* H37Ra with the $MIC_{90}$ 84.17 and 82.75 μM, respectively. Against the *M. bovis*, the compound **5c** ($R^1$ = 3-Cl,4-F) exhibited excellent activity with $MIC_{90}$ 24.15 μM and compounds **5d** ($R^1$ = 4-F) showed reduced inhibition as compared to **5c** with $MIC_{90}$ 83.20 μM. Compound **5f** ($R^1$ = 4-$CF_3$) showed similar activity against both *Mycobacterium* strains with $MIC_{90}$ values 73.05 and 69.68 μM, respectively. The phenyl ring at 2-position of thiazole was substituted by

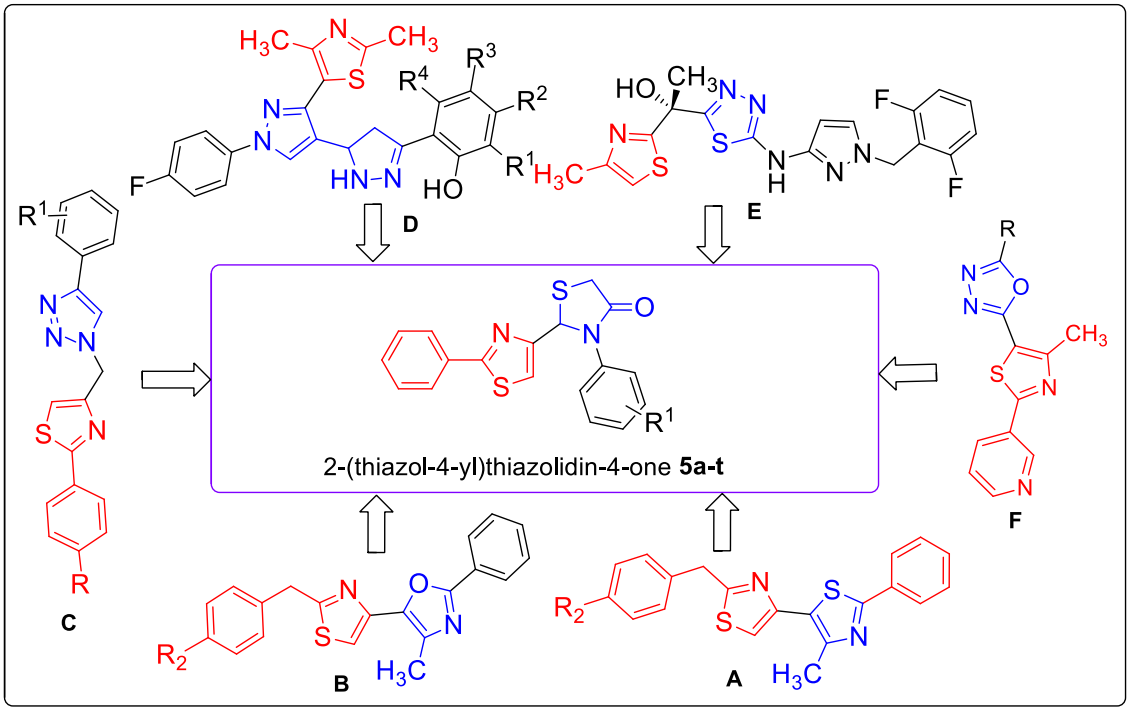
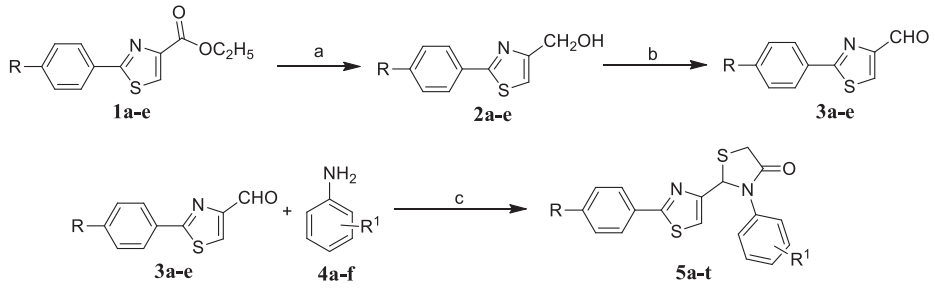



**Fig. 1.** Thiazole clubbed with thiazole (A), oxazole (B), triazole (C), pyrazole (D-F) and synthesized 2-(thiazol-4-yl)thiazolidin-4-one derivatives (**5a-t**) have shown antimycobacterial activity.




Reagents and conditions: a) $LiAlH_4$, $Et_2O$, 0 °C - rt, 3h, 88-95%; b) 2-iodoxybenzoic acid (IBX) DMSO, 0 °C - rt, 0.5h, 85-90%; c) i. AcOH, tolune, reflux, ii. $HSCH_2COOH$, Toluene, reflux, 60-72%

| Comp | R | $R^1$ | Comp | R | $R^1$ | Comp | R | $R^1$ | Comp | R | $R^1$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | H | H | **5f** | H | 4-$CF_3$ | **5k** | 4-F | 4-F | **5p** | 4-$CH_3$ | 4-$CH_3$ |
| **5b** | H | 4-Cl | **5g** | 4-Cl | 4-F | **5l** | 4-F | 4-$CH_3$ | **5q** | 4-$CH_3$ | 4-$CF_3$ |
| **5c** | H | 3-Cl,4-F | **5h** | 4-Cl | 4-$CH_3$ | **5m** | 4-$CH_3$ | H | **5r** | 4-Br | H |
| **5d** | H | 4-F | **5i** | 4-Cl | 4-$CF_3$ | **5n** | 4-$CH_3$ | 4-Cl | **5s** | 4-Br | 3-Cl,4-F |
| **5e** | H | 4-$CH_3$ | **5j** | 4-F | 4-Cl | **5o** | 4-$CH_3$ | 4-F | **5t** | 4-Br | 4-$CF_3$ |

**Scheme 1.** Synthetic route of compounds **5a-t.**

4-chlorophenyl in compounds 2-(2-(4-chlorophenyl)thiazol-4-yl)-3-(substituted phenyl)thiazolidin-4-one (**5 g-i**), compound **5 g** ($R^1$ = 4-F) showed moderate activity against *M. tuberculosis* H37Ra with $MIC_{90}$ 70.49 μM and excellent activity against *M. bovis* with $MIC_{90}$ 12.25 μM. Compound **5 h** ($R^1$ = 4-$CH_3$) showed moderate activity against *M. tuberculosis* H37Ra with $MIC_{90}$ 73.70 μM, whereas compound **5i** ($R^1$ = 4-$CF_3$) showed good activity against both the strains of *Mycobacterium*. The phenyl group at 2-position of thiazole was substituted by 4-fluorophenyl in compounds 2-(2-(4-fluorophenyl)thiazol-4-yl)-3-(substituted phenyl)thiazolidin-4-one (**5j-l**), compound **5j** presented excellent activity against *M. bovis* with $MIC_{90}$ 5.44 μM, compounds **5 k** ($R^1$ = 4-F) and **5 l** ($R^1$ = 4-$CH_3$) showed moderate activity against both *Mycobacterium* strains ($MIC_{90}$ values between 67.17 and 80.73 μM). The phenyl group at 2-position of thiazole was substituted by *p*-tolyl in compounds 2-(2-(*p*-tolyl)thiazol-4-yl)-3-(substituted phenyl) thiazolidin-4-one (**5 m-q**). Compound **5 m** ($R^1$ = H) was more effective against *M. tuberculosis* H37Ra with $MIC_{90}$ 63.49 μM compared to the compounds **5n** ($R_1$ = 4-Cl), **5o** ($R^1$ = 4-F), **5p** ($R^1$ = 4-$CH_3$) and **5q** ($R^1$ = 4-$CF_3$). Against *M. bovis* strain compounds **5 m** ($R^1$ = H), **5n** ($R^1$ = 4-Cl), **5o** ($R^1$ = 4-F) and **5p** ($R^1$ = 4-$CH_3$) showed excellent inhibitory activity with $MIC_{90}$ values 4.43 to 24.04 μM. It must be noted that 3-(4-fluorophenyl)-2-(2-(p-tolyl)thiazol-4-yl)thiazolidin-4-one, **5o** presented only two-fold less of activity against the *M. bovis*, with respect to the standard drug Rifampicin. The phenyl group at 2-position of thiazole was substituted by 4-bromophenyl in compounds 2-(2-(4-bromophenyl) thiazol-4-yl)-3-(substituted phenyl)thiazolidin-4-one **5r-t**, compounds **5r** ($R^1$ = H) and **5 t** ($R^1$ = 4-$CF_3$) showed good activity against the *M. tuberculosis* H37Ra strain. The compounds **5 s** ($R^1$ = 3-Cl,4-F) and **5 t** ($R^1$ = 4-$CF_3$) displayed encouraging inhibitory activity against *M. bovis* with $MIC_{90}$ 29.61 and 5.10 μM, respectively.

From the SAR analysis, it was noted that, the unsubstituted phenyl ring at the C-2 position of thiazole and 3-chloro-4-fluoro phenyl ring at 3-position of thiazolidinone, as well as 4-chlorophenyl at the C-2 position of thiazole and 4-fluorophenyl at 3-position of thiazolidinone and vice-versa presented excellent activity against *M. bovis*. Similarly, the *p*-tolyl substituent at the C-2 position of thiazole and H/4-Cl/4-F/4-$CH_3$ substituted phenyl at 3-position of thiazolidinone, as well as 4-Bromo phenyl at the C-2 position of thiazole and 3-Cl,4-F or 4-$CF_3$ substituted phenyl ring at 3-position of thiazolidinone came out as most potent against *M. Bovis* with $MIC_{90}$ 4.43–29.61 μM.

### 2.3. Cytotoxicity and selectivity index

In order to check the cytotoxicity profiles, only the most active 2-(thiazol-4-yl)thiazolidin-4-one derivatives were screened against tumorigenic eukaryotic cell lines such as HeLa, A549 and HCT 116 at a concentration range 25–250 μg/mL (Table 2) [45,46].

The calculated $GI_{50}$ and $GI_{90}$ values of the compounds are shown in Table 2. The $GI_{90}$ is the concentration required to reduce the eukaryotic cells viability by 90%. The $GI_{90}$ = >100 μg/mL states that the compounds are potent and specific inhibitors against MTB. All the active compounds are displayed a non-toxic effect in the cytotoxicity assay when, HeLa A549, and HCT 116 cells were exposed to the test compounds indicating no differences among the three cell lines concerning their sensitivity to the compounds. The observations are consistent with findings in this study where the compounds tested a lack of cytotoxicity.

To assess the antimycobacterial specificity of these compounds, the Selectivity Index (SI) was calculated as $GI_{50}/MIC_{90}$ [47]. In the current report the Selectivity Index of the selected entities towards human cell lines against MTB and BCG has been described in Table 3. We did not observe the cytotoxicity ($GI_{50}$) up to a concentration of > 80 μg/mL, which gives 2-(thiazol-4-yl)thiazolidin-4-one derivatives SI of 3–156. The SI for strains of Dormant BCG was significantly higher than the dormant MTB. The relatively high Selectivity Index indicates that these active compounds may be useful in managing MTB infections in animals as well as in human beings.

## 3. Conclusions

In summary, we have synthesized 3-substituted phenyl-2-(2-(substituted phenyl)thiazol-4-yl) thiazolidin-4-one, **5a-t** derivatives and evaluated for antimycobacterial activity. Most of the thiazolyl thiazolidin-4-one derivatives presented good to excellent activity against *M. tuberculosis* H37Ra and *M. bovis* BCG strains. All active derivatives were further screened for cytotoxicity against three cancer cell lines and showed no significant cell toxicity at the maximum concentration evaluated. Four derivatives 3-(4-chlorophenyl)-2-(2-(4-fluorophenyl)thiazol-4-yl)thiazolidin-4-one (**5j**), 3-phenyl-2-(2-*p*-tolylthiazol-4-yl)thiazolidin-4-one (**5 m**), 3-(4-fluorophenyl)-2-(2-*p*-tolylthiazol-4-yl)thiazolidin-4-one (**5o**) and 2-(2-(4-bromophenyl)thiazol-4-yl)-3-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (**5 t**) presented the most inhibitory activity against the *M. bovis* BCG with $MIC_{90}$ values less than 9 μM. Thus, these results warrant the need for a synthesis of similar

**Table 1**
Antimycobacterial activity in $MIC_{90}$ and $IC_{50}$ in μM (μg/mL) of compounds **5a-t**.

| Compound | R | $R_1$ | *M. tuberculosis* H37Ra | | *M. bovis* BCG | |
|---|---|---|---|---|---|---|
| | | | $MIC_{90}$ | $IC_{50}$ | $MIC_{90}$ | $IC_{50}$ |
| **5a** | H | H | 84.17 (28.45) | 39.23 (13.26) | >100 (>30) | **18.96** (18.96) |
| **5b** | H | 4-Cl | >100 (>30) | **21.93** (8.16) | >100 (>30) | 52.66 (52.66) |
| **5c** | H | 3-Cl,4-F | >100 (>30) | 76.61 (29.88) | **24.15** (9.42) | **7.97** (3.11) |
| **5d** | H | 4-F | >100 (>30) | **20.41** (7.33) | 83.20 (29.62) | **19.43** (6.92) |
| **5e** | H | 4-$CH_3$ | 82.75 (29.13) | **14.26** (5.02) | >100 (>30) | **12.67** (4.46) |
| **5f** | H | 4-$CF_3$ | 73.05 (29.66) | **17.36** (7.05) | 69.38 (28.17) | **23.60** (9.58) |
| **5g** | 4- Cl | 4-F | 70.49 (27.49) | **23.38** (9.12) | **12.25** (4.78) | **0.77** (0.3) |
| **5h** | 4- Cl | 4-$CH_3$ | 73.70 (28.52) | **9.84** (3.81) | >100 (>30) | >100 (>30) |
| **5i** | 4- Cl | 4-$CF_3$ | 61.25 (25.18) | **6.96** (2.86) | 70.63 (29.30) | **19.78** (8.13) |
| **5j** | 4-F | 4-Cl | >100 (>30) | **19.07** (7.44) | **5.44** (2.12) | **0.56** (0.22) |
| **5k** | 4-F | 4-F | 67.17 (25.19) | **19.47** (7.3) | 73.23 (27.46) | 35.52 (13.32) |
| **5l** | 4-F | 4-$CH_3$ | 80.73 (29.87) | 46.89 (17.35) | 78.03 (28.87) | 50.14 (18.55) |
| **5m** | 4-$CH_3$ | H | 63.49 (22.35) | **4.63** (1.63) | **8.27** (2.91) | **0.57** (0.2) |
| **5*n*** | 4-$CH_3$ | 4-Cl | >100 (>30) | 52.46 (20.25) | **18.23** (7.04) | **2.28** (0.88) |
| **5o** | 4-$CH_3$ | 4-F | >100 (>30) | **17.21** (6.37) | **4.43** (1.64) | **0.24** (0.09) |
| **5p** | 4-$CH_3$ | 4-$CH_3$ | >100 (>30) | **22.62** (8.25) | **24.04** (8.89) | **8.06** (2.95) |
| **5q** | 4-$CH_3$ | 4-$CF_3$ | >100 (>30) | >100 (>30) | >100 (>30) | **10.69** (4.49) |
| **5r** | 4-Br | H | 62.40 (25.96) | **6.63** (2.76) | >100 (>30) | >100 (>30) |
| **5 s** | 4- Br | 3-Cl,4-F | >100 (>30) | >100 (>30) | **29.61** (13.86) | **5.08** (2.38) |
| **5 t** | 4- Br | 4-$CF_3$ | 61.50 (29.73) | **7.89** (3.82) | **5.10** (2.47) | **0.76** (0.37) |
| **Rifampicin** | | | 0.91 (0.75) | 0.021 (0.014) | 1.01 (0.83) | 0.04 (0.029) |

$MIC_{90}$: minimum inhibitory concentration, $IC_{50}$: 50% inhibitory concentration

**Table 2**
*In vitro* cytotoxicity of selected 2-(thiazol-4-yl)thiazolidin-4-one derivatives.

| Comp. | HeLa (Cervix) | | A549 (Lung) | | HCT 116 (Colorectal) | |
|---|---|---|---|---|---|---|
| | $GI_{50}$ μM | $GI_{90}$ μM | $GI_{50}$ μM | $GI_{90}$ μM | $GI_{50}$ μM | $GI_{90}$ μM |
| **5c** | 387.5 | >655 | 236.9 | >655 | 315.8 | >655 |
| **5g** | 305.2 | 444.7 | 309.5 | 603.6 | 311.6 | 630 |
| **5j** | >655 | >655 | >655 | >655 | >655 | >655 |
| **5m** | 295.4 | 517 | 413.9 | 629 | 504.9 | 704.8 |
| **5n** | >662 | >662 | >662 | >662 | >662 | >662 |
| **5o** | >692 | >692 | >692 | >692 | >692 | >692 |
| **5p** | 234.9 | 434.7 | 373.7 | 540.3 | 239.3 | 441.3 |
| **5s** | 201.9 | >545 | 310.1 | >545 | 184.8 | 315.9 |
| **5t** | >528 | >528 | >528 | >528 | >528 | >528 |
| **Rifampicin** | >121.5 | >121.5 | >121.5 | >121.5 | >121.5 | >121.5 |
| Paclitaxel | 0.0065 | 0.097 | 0.0048 | 0.091 | 0.164 | 6.90 |

($GI_{50}$ : 50% growth inhibition; The highest concentration used is 256 μg/mL for 72 h incubation)

libraries with other substituents to ascertain the trend described in this work.

## 4. Materials and methods

### 4.1. General

The chemicals and solvents used were laboratory grade and were purified as per literature methods. All the reactions have been monitored by the Thin Layer Chromatography (TLC). TLC was performed on the Merck 60F-254 silica gel plates. Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and were uncorrected. The Infrared spectra were recorded on the Shimadzu FTIR (KBr) − 408 in KBr. $^1$H (300 MHz) NMR and $^{13}$C (75 MHz) NMR spectra were recorded on the Varian mercury XL-300 and Bruker at either 400 or 500 MHz ($^1$HNMR) and 100 or 125 MHz ($^{13}$C NMR), spectrometer instruments. The HRMS spectra were recorded on the Bruker Compass Data Analysis 4.2. The column chromatography was performed on Silica Gel for column chromatography (100-200mesh) which was supplied by the Thermo Fisher Scientific India Pvt. Ltd.

### 4.2. Chemistry

#### 4.2.1. General procedure for the synthesis of 2-(2-phenylthiazol-4-yl) methanol (2a)

To a cold solution of lithium aluminum hydride (20 mmol) in diethyl ether (20 mL) 2-phenylthiazole-4-carboxylate, **1a** (10 mmol) in diethyl ether (20 mL) was added dropwise over a period of 30 min and the reaction mixture was further stirred for 1 h at 0 °C. After the completion of the reaction (TLC), the reaction mixture was quenched by a saturated solution of sodium sulphate. The reaction mixture was filtered and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic layer was washed with water, brine, and dried over sodium sulphate. 2-(2-phenylthiazol-4-yl) methanol was obtained by removing the solvent by distillation.

#### 4.2.2. General procedure for the synthesis of 2-phenylthiazole-4-carbaldehyde (3a)

To a solution of 2 (2-phenylthiazol-4-yl) methanol, **2a** (14 mmol) in DMSO (30 mL), IBX (18 mmol) was added, and the reaction mixture was stirred at 20 °C. The progress of the reaction was monitored on the TLC. After the completion of the reaction, the mixture was filtered. Water (90 mL) was added in the filtrate and the filtrate was extracted with diethyl ether (3 × 30 mL). The organic layer was washed with water, brine and dried over sodium sulphate. The product was obtained by distillation of the solvent.

#### 4.2.3. General procedure for the synthesis of 3-phenyl-2-(2-phenylthiazol-4-yl)thiazolidin-4-one (5a)

To a solution of 2-phenylthiazole-4-carbaldehyde **3a** (0.378 g; 2 mmol) in dry toluene (10 mL), aniline **4a** (0.20 g, 2.2 mmol) and glacial acetic acid (0.1 mL) was added. The reaction mixture was refluxed for 3 h with azeotropic separation of water. After the completion of the reaction as monitored on the TLC, thioglycolic acid (0.23 g, 2.5 mmol) was added and the reaction mixture was further refluxed for 3 h (TLC). The solvent was removed under reduced pressure and the residue was treated with a saturated solution of $NaHCO_3$. The product was extracted with ethyl acetate, washed with water, brine, and dried over sodium sulphate. The solvent was removed under reduced pressure. Purification of the crude product by column chromatography using ethyl acetate: hexane (2:8) afforded 3-phenyl-2-(2-phenylthiazol-4-yl)thiazolidin-4-one (**5a**), 0.44 g (65%). The compounds **5b-t** was synthesized similarly.

*4.2.3.1. 3-Phenyl-2-(2-phenylthiazol-4-yl)thiazolidin-4-one (5a).* Yield: 65 %; mp 120–122 °C. IR (KBr): 1356, 1512, 1601, 1684 $cm^{-1}$; $^1$H NMR

**Table 3**
Selectivity index values (SI) of selected 2-(thiazol-4-yl)thiazolidin-4-one derivatives.

| Comp. | SI on HeLa | | SI on A549 | | SI on HCT 116 | |
|---|---|---|---|---|---|---|
| | Against H37Ra | Against BCG | Against H37Ra | Against BCG | Against H37Ra | Against BCG |
| **5c** | 5 | 16 | 3 | 10 | 4 | 13 |
| **5g** | 4 | 25 | 4 | 25 | 4 | 25 |
| **5j** | >9 | >121 | >9 | >121 | >9 | >121 |
| **5m** | 5 | 36 | 7 | 50 | 8 | 61 |
| **5n** | >9 | >36 | >9 | >36 | >9 | >36 |
| **5o** | >9 | >156 | >9 | >156 | >9 | >156 |
| **5p** | 3 | 10 | 5 | 15 | 3 | 10 |
| **5s** | 3 | 7 | 5 | 11 | 3 | 6 |
| **5t** | >9 | >104 | >9 | >104 | >9 | >104 |
| **Rifampicin** | >133 | >120 | >133 | >120 | >133 | >120 |

(The SI values > 10: The antimycobacterial activity of an agent is considered to be specific [47]. Bacterial pathogens: Dormant *M. tuberculosis* H37Ra and *M. bovis* (BCG).

(400 MHz, $CDCl_3$) $\delta$ 7.97 – 7.86 (m, 2H, Ar-H), 7.47 – 7.40 (m, 3H, Ar-H), 7.34 – 7.17 (m, 5H, Ar-H), 7.00 (s, 1H, Thiazole-H), 6.11 (d, $J = 1.1$ Hz, 1H, Thiazolidinone C-2H), 4.22 (dd, $J = 15.4$, 1.2 Hz, 1H, Thiazolidinone C-5H), 3.77 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 169.7 (C, Thiazole C-2), 156.1 (C, Thiazole C-4), 137.8, 133.1, 130.5, 129.3, 129.0, 127.3, 126.6, 125.6, 115.2 (CH, Thiazole C-5), 61.8 (CH, Thiazolidinone C-2), 33.3 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{15}N_2OS_2$, 339.0626, Found: 339.0627 $(M + H)^+$.

*4.2.3.2. 3-(4-Chlorophenyl)-2-(2-phenylthiazol-4-yl)thiazolidin-4-one* ***(5b)***. Yield: 62%; mp 125–126 °C. IR (KBr): 1356, 1512, 1604, 1680 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 – 7.86 (m, 2H, Ar-H), 7.47 – 7.39 (m, 3H, Ar-H), 7.27 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.20 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.01 (s, 1H, Thiazole-H), 6.07 (d, $J = 0.8$ Hz, 1H, Thiazolidinone C-2H), 4.20 (dd, $J = 15.5$, 1.0 Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 169.9 (C, Thiazole C-2), 155.8 (C, Thiazole C-4), 136.3, 133.0, 132.9, 130.6, 129.4, 129.1, 126.9, 126.6, 115.4 (CH, Thiazole C-5), 61.5 (CH, Thiazolidinone C-2), 33.2 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{14}ClN_2OS_2$, 373.0236, Found: 373.0240 $(M + H)^+$, 375.0206 $(M + H + 2)^+$.

*4.2.3.3. 3-(3-Chloro-4-fluorophenyl)-2-(2-phenylthiazol-4-yl)thiazolidin-4-one* ***(5c)***. Yield: 70 %; mp 166–168 °C. IR (KBr): 1356, 1512, 1604, 1680 $cm^{-1}$; $^1$H NMR (400 MHz, CDCl3) $\delta$ 7.92 (dd, $J = 6.6$, 3.0 Hz, 2H, Ar-H), 7.49 – 7.42 (m, 3H, Ar-H), 7.39 (dd, $J = 6.5$, 2.4 Hz, 1H, Ar-H), 7.14 – 7.02 (m, 3H, Ar-H, Thiazole-H), 6.03 (d, $J = 1.0$ Hz, 1H, Thiazolidinone C-2H), 4.21 (dd, $J = 15.6$, 1.1 Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J = 15.6$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6 (C═O, Thiazolidinone C-4), 170.0 (C, Thiazole C-2), 158.1, 155.6, 155.5 (C, Thiazole C-4), 134.2, 134.2, 132.9, 130.7, 129.1, 128.26, 126.6, 125.8, 125.7, 121.7, 121.5, 117.1, 116.9, 115.7 (CH, Thiazole C-5), 61.5 (CH, Thiazolidinone C-2), 33.0 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{13}ClFN_2OS_2$, 391.0142, Found: 391.0156 $(M + H)^+$, 393.0131 $(M + H + 2)^+$.

*4.2.3.4. 3-(4-Fluorophenyl)-2-(2-phenylthiazol-4-yl)thiazolidin-4-one* ***(5d)***. Yield: 68 %; mp 133–135 °C. IR (KBr): 1356, 1512, 1604, 1682 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 – 7.88 (m, 2H, Ar-H), 7.50 – 7.39 (m, 3H, Ar-H), 7.19 (dd, $J = 9.0$, 4.8 Hz, 2H, Ar-H), 7.05 – 6.93 (m, 3H, Ar-H, Thiazole-H), 6.02 (d, $J = 1.2$ Hz, 1H, Thiazolidinone C-2H), 4.22 (dd, $J = 15.5$, 1.2 Hz, 1H, Thiazolidinone C-5H), 3.77 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6 (C═O, Thiazolidinone C-4), 169.8 (C, Thiazole C-2), 162.6, 160.2, 155.8 (C, Thiazole C-4), 133.6, 133.6, 133.0, 130.6, 129.0, 128.0, 127.9, 126.6, 116.4, 116.2, 115.6 (CH, Thiazole C-5), 61.8 (CH, Thiazolidinone C-2), 33.1 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{14}FN_2OS_2$, 357.0532, Found: 357.0535 $(M + H)^+$.

*4.2.3.5. 2-(2-Phenylthiazol-4-yl)-3-(4-methyl phenyl)thiazolidin-4-one* ***(5e)***. Yield: 72 %; mp 112–114 °C. IR (KBr): 1356, 1512, 1604, 1682 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 – 7.78 (m, 2H, Ar-H), 7.42 – 7.29 (m, 3H, Ar-H), 7.03 (s, 4H, Ar-H), 6.91 (s, 1H, Thiazole-H), 5.98 (d, $J = 1.0$ Hz, 1H, Thiazolidinone C-2H), 4.13 (dd, $J = 15.4$, 1.2 Hz, 1H, Thiazolidinone C-5H), 3.68 (d, $J = 15.4$ Hz, 1H, Thiazolidinone C-5H), 2.19 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 169.6 (C, Thiazole C-2), 156.2 (C, Thiazole C-4), 137.4, 135.1, 133.2, 130.5, 130.0, 129.0, 126.6, 125.7, 115.3 (CH, Thiazole C-5), 61.8 (CH, Thiazolidinone C-2), 33.2 ($CH_2$, Thiazolidinone C-5), 21.1 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{17}N_2OS_2$, 353.0782, Found: 353.0788 (M + H) + .

*4.2.3.6. 3-(4-(Trifluoromethyl)phenyl)-2-(2-phenylthiazol-4-yl)thiazolidin-4-one* ***(5f)***. Yield: 68 %; mp 130–132 °C. IR (KBr): 1356, 1512, 1604, 1680 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (dd, $J = 6.7$, 3.0 Hz, 2H, Ar-H), 7.58 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.50 – 7.39 (m, 5H, Ar-H), 7.04 (s, 1H, Thiazole-H), 6.18 (d, $J = 0.8$ Hz, 1H, Thiazolidinone C-2H), 4.21 (dd, $J = 15.6$, 1.1 Hz, 1H, Thiazolidinone C-5H), 3.78 (d, $J = 15.6$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 170.1 (C, Thiazole C-2), 155.6 (C, Thiazole C-4), 141.0, 132.9, 130.7, 129.2, 129.1, 128.9, 128.5, 128.2, 126.6, 126.4, 126.4, 126.33, 126.3, 125.1, 124.8, 122.4, 115.2 (CH, Thiazole C-5), 61.3 (CH, Thiazolidinone C-2), 33.2 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{14}F_3N_2OS_2$, 407.0500, Found: 407.0513 $(M + H)^+$.

*4.2.3.7. 2-(2-(4-Chlorophenyl)thiazol-4-yl)-3-(4-fluorophenyl)thiazolidin-4-one* ***(5 g)***. Yield: 64 %; mp 114–116 °C. IR (KBr): 1356, 1512, 1604, 1681 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.41 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.23 – 7.15 (m, 2H, Ar-H), 7.04 (s, 1H, Thiazole-H), 7.00 (t, $J = 8.6$ Hz, 2H, Ar-H), 6.03 (s, 1H, , Thiazolidinone C-2H), 4.20 (d, $J = 14.9$ Hz, 1H, Thiazolidinone C-5H), 3.78 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6 (C═O, Thiazolidinone C-4), 168.5 (C, Thiazole C-2), 162.6, 160.2, 156.0 (C, Thiazole C-4), 136.6, 133.6, 133.5, 131.5, 129.3, 127.9, 127.8, 116.4, 116.2, 115.8 (CH, Thiazole C-5), 61.7 (CH, Thiazolidinone C-2), 33.09 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{13}ClFN_2OS_2$, 391.0142, Found: 391.0139 $(M + H)^+$, 393.0110 $(M + H + 2)^+$.

*4.2.3.8. 2-(2-(4-Chlorophenyl)thiazol-4-yl)-3-p-tolylthiazolidin-4-one* ***(5 h)***. Yield:70%; mp 117–119 °C. IR (KBr): 1356, 1512, 1604, 1682 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.40 (d, $J = 8.7$ Hz, 2H, Ar-H), 7.11 (s, 4H, Ar-H), 7.01 (s, 1H, Thiazole-H), 6.07 (d, $J = 1.3$ Hz, 1H, , Thiazolidinone C-2H), 4.19 (dd, $J = 15.4$, 1.3 Hz, 1H,

Thiazolidinone C-5H), 3.76 (d, $J = 15.4$ Hz, 1H, Thiazolidinone C-5H), 2.28 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6 (C═O, Thiazolidinone C-4), 169.0 (C, Thiazole C-2), 155.5 (C, Thiazole C-4), 136.5, 134.22, 133.5, 131.42, 129.8, 129.3, 128.5, 125.6, 115.8 (CH, Thiazole C-5), 61.5 (CH, Thiazolidinone C-2), 33.1 ($CH_2$, Thiazolidinone C-5), 21.4 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{16}ClN_2OS_2$, 387.0393, Found: 387.0396 (M + H)+, 389.0369 (M + H + 2) + .

*4.2.3.9. 2-(2-(4-Chlorophenyl)thiazol-4-yl)-3-(4-(trifluoromethyl)phenyl) thiazolidin-4-one (**5i**).* Yield: 72 %; mp 104–105 °C. IR (KBr): 1356, 1512, 1604, 1681 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.58 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.46 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.41 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.07 (s, 1H, Thiazole-H), 6.19 (d, $J = 0.7$ Hz, 1H, Thiazolidinone C-2H), 4.19 (dd, $J = 15.7$, 1.0 Hz, 1H, Thiazolidinone C-5H), 3.79 (d, $J = 15.7$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4 (C═O, Thiazolidinone C-4), 168.8 (C, Thiazole C-2), 155.4 (C, Thiazole C-4), 139.6, 134.21, 132.0, 129.7, 128.9, 127.9, 126.5, 125.8, 117.6, 115.8 (CH, Thiazole C-5), 61.4 (CH, Thiazolidinone C-2), 33.0 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{13}ClF_3N_2OS_2$, 441.0110, Found: 441.0114 (M + H)+, 443.0085 (M + H + 2) + .

*4.2.3.10. 3-(4-Chlorophenyl)-2-(2-(4-fluorophenyl)thiazol-4-yl)thiazolidin-4-one (**5j**).* Yield: 70 %; mp 109–110 °C. IR (KBr): 1356, 1512, 1604, 1682 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.90 (dd, $J = 8.9$, 5.2 Hz, 2H, Ar-H), 7.28 (d, $J = 8.9$ Hz, 2H, Ar-H), 7.20 (d, $J = 8.9$ Hz, 2H, Ar-H), 7.13 (t, $J = 8.6$ Hz, 2H, Ar-H), 7.01 (s, 1H, Thiazole-H), 6.07 (d, $J = 1.0$ Hz, 1H, Thiazolidinone C-2H), 4.19 (dd, $J = 15.5$, 1.1 Hz, 1H, Thiazolidinone C-5H), 3.77 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4 (C═O, Thiazolidinone C-4), 168.7 (C, Thiazole C-2), 165.4, 162.9, 155.8 (C, Thiazole C-4), 136.8, 132.41, 129.4, 129.3, 128.6, 128.6, 127.0, 120.9, 116.3, 116.1, 115.4 (CH, Thiazole C-5), 61.4 (CH, Thiazolidinone C-2), 33.2 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{13}ClFN_2OS_2$, 391.0142, Found: 391.0139 (M + H)+, 393.0110 (M + H + 2) + .

*4.2.3.11. 3-(4-Fluorophenyl)-2-(2-(4-fluorophenyl)thiazol-4-yl)thiazolidin-4-one (**5 k**).* Yield: 60 %; mp 105–107 °C. IR (KBr): 1356, 1512, 1604, 1680 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88–7.92 (m, 2H, Ar-H), 6.92–7.12 (m, 7H, Ar-H, Thiazole-H), 6.07 (d, $J = 1.0$ Hz, 1H, Thiazolidinone C-2H), 4.20 (dd, $J = 15.5$ and 1.0 Hz, 1H, Thiazolidinone C-5H), 3.78 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 169.1 (C, Thiazole C-2), 161.4, 159.8, 155.5 (C, Thiazole C-4), 136.5, 129.3, 128.8, 125.9, 116.4, 116.2, 115.8 (CH, Thiazole C-5), 61.5 (CH, Thiazolidinone C-2), 33.3 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{13}F_2N_2OS_2$, 375.0437, Found: 375.0440 (M + H) + .

*4.2.3.12. 2-(2-(4-Fluorophenyl)thiazol-4-yl)-3-p-tolylthiazolidin-4-one (**5 l**).* Yield: 72 %; mp 139–141 °C. IR (KBr): 1356, 1512, 1604, 1681 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (dd, $J = 8.7$, 5.3 Hz, 2H, Ar-H), 7.18 – 7.06 (m, 6H, Ar-H), 6.99 (s, 1H, Thiazole-H), 6.06 (s, 1H, Thiazolidinone C-2H), 4.19 (d, $J = 15.4$ Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J = 15.4$ Hz, 1H, Thiazolidinone C-5H), 2.28 (s, 3H, Ar-$CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 168.4 (C, Thiazole C-2), 165.4, 162.9, 156.2 (C, Thiazole C-4), 137.4, 135.0, 130.0, 129.5, 129.5, 128.6, 128.6, 125.7, 116.2, 116.0, 115.3 (CH, Thiazole C-5), 61.8 (CH, Thiazolidinone C-2), 33.2 ($CH_2$, Thiazolidinone C-5), 21.1 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{16}FN_2OS_2$, 371.0688, Found: 371.0690 (M + H) + .

*4.2.3.13. 3-Phenyl-2-(2-p-tolylthiazol-4-yl)thiazolidin-4-one (**5 m**).* Yield: 68 %; mp: 118–120 °C. IR (KBr): 1356, 1512, 1604, 1684 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.33–7.27 (m, 7H, Ar-H), 6.97 (s, 1H, Thiazole-H), 6.10 (s, 1H, Thiazolidinone C-2H), 4.22 (dd, $J = 15.4$, 0.6 Hz, 1H, Thiazolidinone C-5H), 3.77 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H), 2.40 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4 (C═O, Thiazolidinone C-4), 169.7 (C, Thiazole C-2), 155.8 (C, Thiazole C-4), 140.7, 137.7, 130.4, 129.5, 129.2, 127.2, 126.5, 125.5, 114.7 (CH, Thiazole C-5), 61.7 (CH, Thiazolidinone C-2), 33.2 ($CH_2$, Thiazolidinone C-5), 21.4 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{17}N_2OS_2$, 353.0782, Found: 353.0788 (M + H) + .

*4.2.3.14. 3-(4-Chlorophenyl)-2-(2-p-tolylthiazol-4-yl)thiazolidin-4-one (**5n**).* Yield: 70 %; mp 100–102 °C. IR (KBr): 1356, 1512, 1604, 1684 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.27 (d, $J = 8.9$ Hz, 2H, Ar-H), 7.24 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.20 (d, $J = 8.9$ Hz, 2H, Ar-H), 6.97 (s, 1H, Thiazole-H), 6.05 (d, $J = 1.0$ Hz, 1H, Thiazolidinone C-2H), 4.20 (dd, $J = 15.5$, 1.2 Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H), 2.40 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4 (C═O, Thiazolidinone C-4), 170.0 (C, Thiazole C-2), 155.5 (C, Thiazole C-4), 140.1, 136.3, 132.8, 130.4, 129.6, 129.4, 126.8, 126.5, 114.9 (CH, Thiazole C-5), 61.5 (CH, Thiazolidinone C-2), 33.1 ($CH_2$, Thiazolidinone C-5), 21.4 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{16}ClN_2OS_2$, 387.0393, Found: 387.0388 $(M + H)^+$, 389.0366 $(M + H + 2)^+$.

*4.2.3.15. 3-(4-Fluorophenyl)-2-(2-p-tolylthiazol-4-yl)thiazolidin-4-one (**5o**).* Yield: 64 %; mp 128–129 °C. IR (KBr): 1356, 1512, 1604, 1682 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.24 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.19 (dd, $J = 9.0$, 4.9 Hz, 2H, Ar-H), 7.01 – 6.97 (m, 2H, Ar-H), 6.96 (s, 1H, Thiazole-H), 6.00 (d, $J = 1.1$ Hz, 1H, Thiazolidinone C-2H), 4.22 (dd, $J = 15.5$, 1.2 Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J = 15.5$ Hz, 1H, Thiazolidinone C-5H), 2.39 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6 (C═O, Thiazolidinone C-4), 169.9 (C, Thiazole C-2), 162.3, 160.3, 155.5 (C, Thiazole C-4), 140.9, 133.6, 130.4, 129.6, 127.9, 127.8, 126.5, 116.3, 116.1, 115.0 (CH, Thiazole C-5), 61.8 (CH, Thiazolidinone C-2), 33.0 ($CH_2$, Thiazolidinone C-5), 21.4 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{16}FN_2OS_2$, 371.0688, Found: 371.0688 (M + H) + .

*4.2.3.16. 3-p-Tolyl-2-(2-p-tolylthiazol-4-yl)thiazolidin-4-one (**5p**).* Yield: 66 %; mp 141–143 °C. IR (KBr): 1356, 1512, 1604, 1682 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.23 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.11 (s, 4H, Ar-H), 6.95 (s, 1H, Thiazole-H), 6.04 (d, $J = 1.3$ Hz, Thiazolidinone C-2H), 4.21 (dd, $J = 15.4$, 1.3 Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J = 15.4$ Hz, 1H, Thiazolidinone C-5H), 2.39 (s, 3H, Ar-$CH_3$), 2.28 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4 (C═O, Thiazolidinone C-4), 169.7 (C, Thiazole C-2), 156.0 (C, Thiazole C-4), 140.8, 137.3, 135.1, 130.5, 129.8, 129.6, 126.5, 125.6, 114.7 (CH, Thiazole C-5), 61.8 (CH, Thiazolidinone C-2), 33.1 ($CH_2$, Thiazolidinone C-5), 21.4 ($CH_3$, Ar-$CH_3$), 21.0 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{20}H_{19}N_2OS_2$, 367.0939, Found: 367.0941 (M + H) + .

*4.2.3.17. 3-(4-(Trifluoromethyl)phenyl)-2-(2-p-tolylthiazol-4-yl)thiazolidin-4-one (**5q**).* Yield: 60 %; mp 120–122 °C. IR (KBr): 1356, 1512, 1604, 1680 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.55 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.08–7.20 (m, 4H, Ar-H), 7.01 (s, 1H, Thiazole-H), 6.10 (d, $J = 1.0$ Hz, 1H, Thiazolidinone C-2H), 4.20 (dd, $J = 15.5$ and 1.0 Hz, 1H, Thiazolidinone C-5H), 3.77 (d, $J = 15.7$ Hz, 1H, Thiazolidinone C-5H), 2.44 (s, 3H, Ar-$CH_3$); $^{13}$C NMR (100 MHz $CDCl_3$) $\delta$ 171.6 (C═O, Thiazolidinone C-4), 169.7 (C, Thiazole C-2), 155.2 (C, Thiazole C-4), 137.8, 134.20, 132.5, 131.1, 129.8, 128.0, 127.1, 125.8, 124.8, 115.9 (CH, Thiazole C-5), 61.4 (CH, Thiazolidinone C-2), 33.0 ($CH_2$, Thiazolidinone C-5), 21.3 ($CH_3$, Ar-$CH_3$); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{20}H_{16}F_3N_2OS_2$, 421.0656, Found: 421.0660 (M + H) + .

*4.2.3.18. 2-(2-(4-Bromophenyl)thiazol-4-yl)-3-phenylthiazolidin-4-one (**5r**).* Yield: 72%; mp 125–127 °C. IR (KBr): 1356, 1512, 1604, 1682 $cm^{-1}$; $^1H$ NMR: (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 8.0 Hz, 2H, Ar-H) 7.10–7.30 (m, 7H, Ar-H), 6.96 (s, 1H, Thiazole-H), 6.05 (d, $J$ = 1.0 Hz, 1H, Thiazolidinone C-2H), 4.21 (dd, $J$ = 16.0 and 1.0 Hz, 1H, Thiazolidinone C-5H), 3.77 (d, $J$ = 16.0 Hz, 1H, Thiazolidinone C-5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.4 (C═O, Thiazolidinone C-4), 169.2 (C, Thiazole C-2), 155.7 (C, Thiazole C-4), 138.1, 133.4, 129.6, 129.1, 128.7, 127.0, 125.8, 125.2, 114.8 (CH, Thiazole C-5), 61.6 (CH, Thiazolidinone C-2), 33.4 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{14}BrN_2OS_2$, 416.9731, Found: 416.9735 (M + H)+, 418.9714 (M + H + 2)+.

*4.2.3.19. 2-(2-(4-Bromophenyl)thiazol-4-yl)-3-(3-chloro-4-fluorophenyl) thiazolidin-4-one (**5 s**).* Yield: 66 %; mp 138–140 °C; IR (KBr): 1356, 1512, 1604, 1680 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.38–7.42 (m, 1H, Ar-H), 7.34 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.06–7.10 (m, 2H, Ar-H), 7.03 (s, 1H, Thiazole-H), 6.06 (d, $J$ = 1.0 Hz, 1H, Thiazolidinone C-2H), 4.20 (dd, $J$ = 15.4 and 1.0 Hz, 1H, Thiazolidinone C-5H), 3.76 (d, $J$ = 15.4 Hz, 1H, Thiazolidinone C-5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 169.8 (C, Thiazole C-2), 158.5, 156.0, 155.2 (C, Thiazole C-4), 134.5, 134.5, 132.2, 130.1, 130.0, 129.7, 126.8, 125.6, 125.5, 123.5, 121.7, 121.5, 117.0, 116.8, 115.4 (CH, Thiazole C-5), 61.5 (CH, Thiazolidinone C-2), 33.4 ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{18}H_{12}BrClFN_2OS_2$, 468.9247, Found: 468.9252 (M + H)+, 470.9230 (M + H + 2)+, 472.9206 (M + H + 4)$^+$.

*4.2.3.20. 2-(2-(4-Bromophenyl)thiazol-4-yl)-3-(4-(trifluoromethyl) phenyl)thiazolidin-4-one (**5 t**).* Yield: 67 %; mp 110–112 °C. IR (KBr): 1356, 1512, 1604, 1682 $cm^{-1}$; $^1H$ NMR (400 MHz $CDCl_3$) $\delta$ 7.91 (dd, $J$ = 6.7, 3.0 Hz, 1H, Ar-H), 7.77 (d, $J$ = 8.6 Hz, 1H, Ar-H), 7.61 – 7.55 (m, 3H, Ar-H), 7.48 – 7.43 (m, 3H, Ar-H), 7.06 (d, $J$ = 8.4 Hz, 1H, Thiazole-H), 6.19 (s, 1H, Thiazolidinone C-2H), 4.20 (ddd, $J$ = 15.7, 9.7, 1.0 Hz, 1H, Thiazolidinone C-5H), 3.78 (dd, $J$ = 15.7, 0.9 Hz, 1H, Thiazolidinone C-5H). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, Thiazolidinone C-4), 168.8 (C, Thiazole C-2), 155.9 (C, Thiazole C-4), 140.9, 132.2, 130.7, 129.2, 129.1, 128.9, 128.5, 128.2, 128.0, 126.4, 126.4, 126.3, 126.3, 125.0, 124.7, 115.5 (CH, Thiazole C-5), 61.2 (CH, Thiazolidinone C-2), 33.2, ($CH_2$, Thiazolidinone C-5); HRMS (*m/z*): calculated for $(M + H)^+$, $C_{19}H_{13}BrF_3N_2OS_2$, 484.9605, Found: 484.9608 (M + H)+, 486.9586 (M + H + 2) + .

### 4.3. Biological evaluation

#### 4.3.1. Antitubercular assay

*4.3.1.1. Primary screening.* An activity against dormant stage MTB was determined through the XTT reduction menadione assay (XRMA), reading absorbance at 470 nm as per the protocol described by Singh *et al.* [42-44] A compound solution (2.5 μL) was added in a total volume of 250 μL of M. pheli medium consisting of the MTB; sealed with plate sealers and allowed to incubate for 12 days at 37 °C. The XRMA was then carried out to estimate viable cells present in different wells of the assay plate. To all wells, 200 μM XTT was added and incubated at 37 °C for 20 min. It was followed by the addition of 60 μM of menadione and incubated at 37 °C for another 40 min. The optical density was measured using a microplate reader (Spectra Max Plus 384 plate reader, Molecular Devices Inc.) at 470 nm filter against a blank prepared from a well free of cells. Absorbance obtained from the cells treated with 1% DMSO alone was considered as 100% cell growth. The nitrate reductase (NR) assay was performed to estimate the inhibition of the *M. bovis* BCG by the compounds. In the NR assay, 80 μL of culture from an incubated 96 well plate was taken into another 96 well plate, then 80 μL of 1% sulfanilic acid in 20% of conc. HCl was added, incubated for 10 min at room temperature and then 80 μL of 0.1 % N-(1-naphthyl)ethylenediamine dihydrochloride solution in distilled water was added. Finally, absorbance for the NR assay was measured at 540 nm.

The % inhibition in the presence of test material is calculated by using the following formula,

% inhibition = (Average of Control-Average of Compound) / (Average of Control-Average of Blank) X 100)

Where, Control is culture medium with cells and DMSO and blank is culture medium without cells. For all samples, each compound concentration was tested in triplicates in a single experiment and the quantitative value was expressed as the mean ± standard deviation (S. D.).

#### 4.3.2. Cytotoxicity assay

The cytotoxicity of selected 3-aryl-2-(2-arylthiazol-4-yl)thiazolidin-4-one (**5a-t**) derivatives was assessed using three different cell lines HeLa, A549, and HCT 116 under replicating conditions. The cells were incubated with compounds for 72 hrs at 37 °C (the final DMSO concentration of 1%), 5% $CO_2$ in 95% air humidified environment. MTT assay was used to assess cell viability [45,46]. Each concentration was tested in duplicates in a single experiment. $GI_{50}/GI_{90}$ values were calculated using Origin Pro Software. $GI_{50}$ is the concentration required to reduce cell viability after 2 days by 50%. Controls were 1% DMSO only (growth control) and paclitaxel (positive control).

#### 4.3.3. Selectivity Index

The Selectivity Index (SI) was calculated by dividing the 50% growth inhibition concentration ($GI_{50}$) for cell lines (HeLa, A549, and HCT 116) by the MIC for *in vitro* activity against dormant MTB and BCG [47].

## 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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2021.105192.

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