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5-Methyl-4-thiazolidinones: Synthesis and evaluation as antitubercular agents

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ABSTRACT: This paper reports the synthesis, characterization and evaluation of some 5-methyl-4-thiazolidinone derivatives for their i*n vitro* antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv strain by microplate alamar blue assay. Also the crystal structures of the compounds (**2a** and **2c**) were determined by the single-crystal X-ray diffraction study. Among the target compounds, 2-(4-ethoxyphenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (**2g**) was promising with a minimum inhibitory concentration of 12.5 µg/mL against *M. tuberculosis*. Based on the preliminary results, **2g** was considered as a lead compound for further optimization of antimycobacterial activity.

KEYWORDS: Antimycobacterial; tuberculosis; 4-thiazolidinone; single-crystal X-ray diffraction.

1. INTRODUCTION

Tuberculosis (TB), an infectious disease caused by mycobacteria species such as *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium bovis*, is one of the most important causes of death worldwide, and it continues to infect millions of people every year. WHO estimates that TB caused 1.6 million deaths among HIV-negative and -positive people in 2017 [1]. There is a great need to identify and develop new drugs due to the emergence and spread of multidrug-resistant (MDR) and commonly drug-resistant (XDR) strains of *M. tuberculosis*, which are resistant to first and second-line drugs [1].

1,3-thiazolidin-4-one (or 4-thiazolidinone) ring belongs to the groups of nitrogen- and sulphur-containing five-membered heterocyclic compounds with important biological activities such as anticonvulsant, antibacterial, antihyperglycemic, anticancer, antihistaminic, antifungal, antiviral, anti-HIV, antioxidant, anti-inflammatory, carbonic anhydrase inhibitory etc. [2-6]. Moreover, many researchers demonstrated that 4-thiazolidinones (Figure 1) have significant antitubercular activity [7-14].

In the light of this consideration, we designed and synthesized some new 2-(4-substitutedphenyl)-5-methyl-3-(phenylamino)-thiazolidin-4-ones, investigated their antimycobacterial activities.

2. RESULTS AND DISCUSSION

2.1. Chemistry

The title compounds **2a-k** were synthesized via the pathway shown in Figure 2 [15]. The starting compounds, hydrazones (**1a-k**), were gained by the reaction of phenylhydrazine with appropriate benzaldehydes. The cyclization of these hydrazones with thiolactic acid afforded 4-thiazolidinone derivatives (**2a-k**). The structures and purity of the synthesized compounds were deduced using spectroscopic techniques (IR, ^{1}H-NMR, ^{13}C-NMR, mass) as well as single-crystal X-ray crystallographic studies and elemental analysis.

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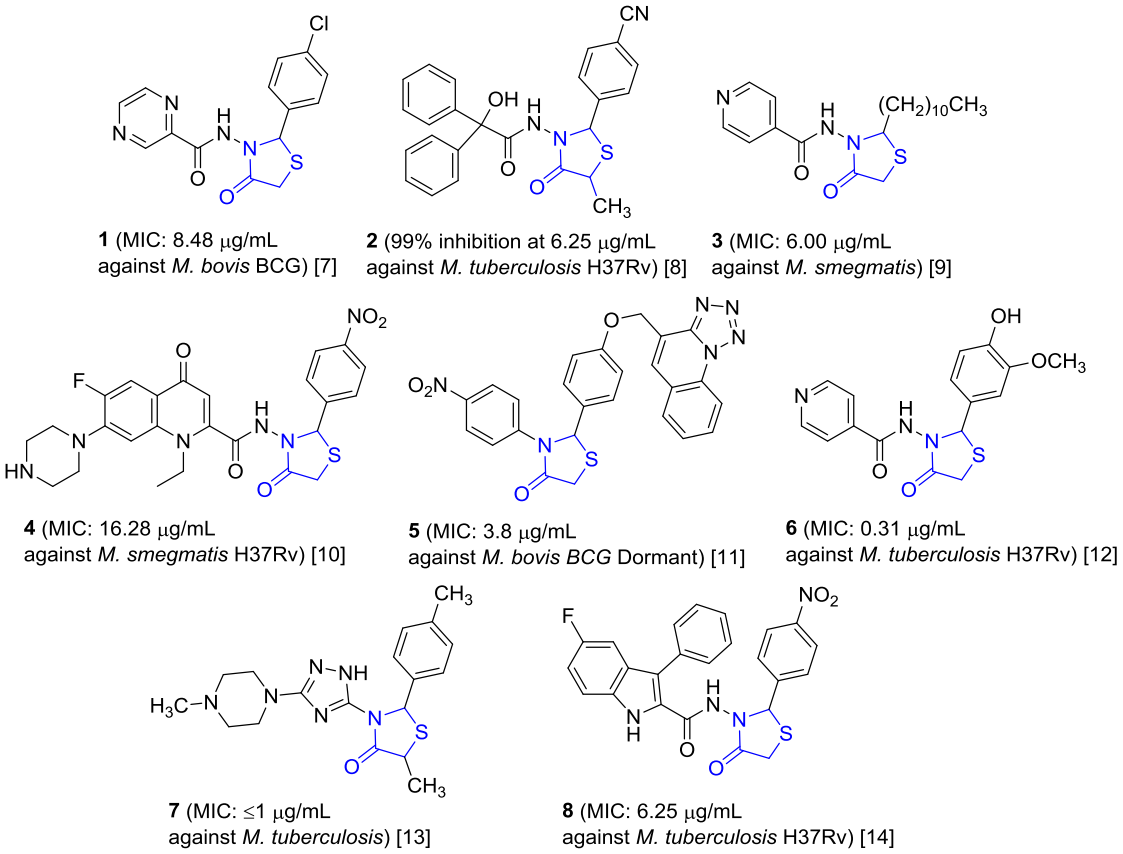


Figure 1. Chemical structures of 4-thiazolidinone derivatives possessing antimycobacterial activity.

The IR spectra of **2a-k** exhibited absorption bands at 3309-3244 cm^{-1} and 1691-1631 cm^{-1} regions attributed to N-H and C=O, respectively. In the ^{1}H-NMR spectra of **2a-k**, 4-thiazolidinone H_2 protons were observed at about 6.02-5.69 ppm as two singlets or a singlet and a doublet (J = 1.2-1.6 Hz) and 4-thiazolidinone H_5 protons resonated at about 4.30-4.06 ppm as two quartets or quartet of doublets and quartet with coupling constants in the range of 6.8-7.2 and 1.2-1.6 Hz. For the compounds, two doublets observed at about 1.54-1.48 ppm corresponding to the C_5 methyl protons (J = 6.8-7.0 Hz). In the ^{13}C-NMR spectra of **2a**, 4-thiazolidinone C_2, C_4 and C_5 carbons resonated at 60.29-59.79, 171.73-171.54 and 38.19-37.10 ppm regions as two peaks due to C_2 and C_5 chiral centres. $[M+Na]^+$ and $[M+H]^+$ molecular ion peaks observed in the ESI-MS confirmed the molecular weights of the target compounds. The results of the elemental analyses (C, H, N, S) were within ± 0.4% of the calculated amounts.

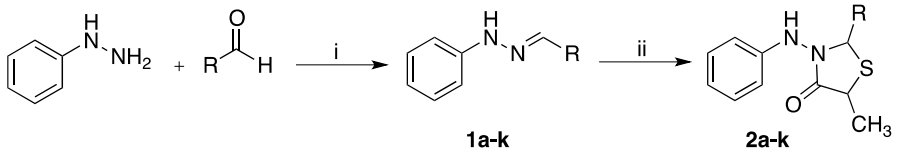


Figure 2. Synthesis of the compounds. Reagents and conditions: (i) CH_3COOH_{cat}, MeOH, rt, 6 h; (ii) thiolactic acid, 70 °C, 3 d.

Since 4-thiazolidinone ring contains C_2 and C_5 chiral centres, theoretically four different stereoisomers are expected to form. Indeed, **2a-k** were obtained as mixtures of two diastereomers, which were differentiated by ^{1}H- and ^{13}C-NMR spectra. The ratios of the diastereomers were determined by integration values of 4-thiazolidinone H_2 proton signals. Also, the crystal structure of **2a** and **2c** was determined by single-crystal X-ray diffraction studies. **2a** crystallizes in triclinic system with centrosymmetric space group $P\bar{1}$. The crystal structure of **2a** contains two crystallographic independent molecules. However, **2c** crystallizes in orthorhombic system with space group $Pca2_1$. The crystal structure of both racemic

compounds contains both 2*S*, 5*R* and 2*R*, 5*S* diastereomers generating through centre of symmetry (**2a**) or glides (**2c**) (Figure 3, See supplementary materials Figures S1 and S2).

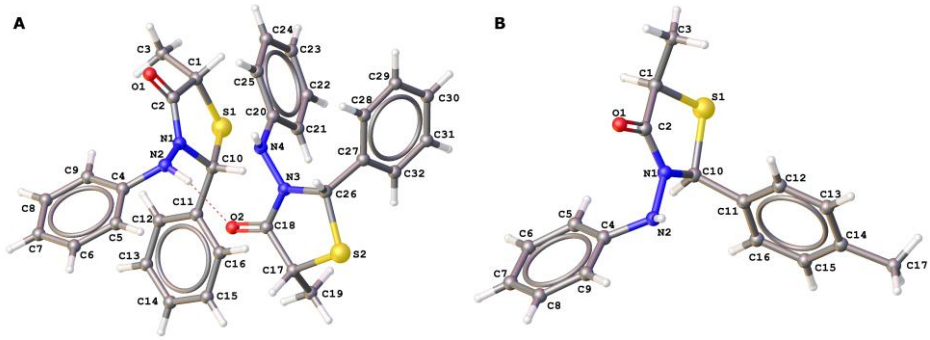
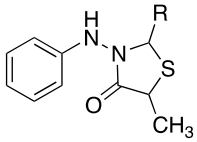


Figure 3. Molecular structure of **2a (A)** and **2c (B)** (atom colours of ball-and-stick view: carbon (grey), hydrogen (white), nitrogen (blue), oxygen (red)).

2.1. Antimycobacterial activity

The title compounds (**2a-k**) were evaluated for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv strain by microplate alamar blue assay (MABA). Results are presented in Table 1 as minimal inhibition concentration (MIC in µg/mL). According to the results, the best antimycobacterial activity was obtained for **2g** (MIC = 12.5 µg/mL) with C_2H_5 substitution on the phenyl ring in the series, which was promising compared to first-line Anti-TB drugs, isoniazid (MIC = 0.05 µg/mL), rifampicin (MIC = 0.1 µg/mL) and ethambutol (MIC = 1.56 µg/mL). On the other hand, introduction of methyl substituent to the phenyl ring deteriorated antimycobacterial activity (**2c** MIC > 25 µg/mL). Furthermore, derivatives with CF_3 (**2d**), OC_2H_5 (**2f**) or Cl (**2j**) substitution showed moderate antimycobacterial activity with a MIC of 25 µg/mL. In the case of thienyl (**2i**) and pyridyl (**2k**) instead of pheyl ring (**2a**) on the thiazolidinone core, the antimycobacterial activity did not increase (MICs > 25 µg/mL for all compounds).

Table 1. Antimycobacterial activities of the target compounds against *M. tuberculosis* H37Rv.



Compounds	R	MIC (µg/mL)
2a	C_6H_5	>25
2b	4-$OCH_3C_6H_4$	>25
2c	4-$CH_3C_6H_4$	>25
2d	4-$CF_3C_6H_4$	>25
2e	4-FC_6H_4	>25
2f	4-$OC_2H_5C_6H_4$	25
2g	**4-$C_2H_5C_6H_4$**	**12.5**
2h	4-$N(CH_3)_2C_6H_4$	>25
2i	2-Thienyl	>25
2j	4-ClC_6H_4	25
2k	3-Pyridyl	>25
Isoniazid		0.05
Rifampicin		0.1
Ethambutol		1.56

3. CONCLUSION

In summary, a series of novel 5-methyl-4-thiazolidinone derivatives were designed, synthesized and tested for their antimycobacterial effects. The X ray crystallography studies revealed that **2a** and **2c** were mixtures of diastereomers (2*S*, 5*R* and 2*R*, 5*S*). This was evident in ^{1}H-NMR spectra, by which diastereomeric ratio of each compound was determined. Antimycobacterial activities of some derivatives

were noteworthy. Among them, 2-(4-ethoxyphenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (**2g**) was promising with a MIC of 12.5 µg/mL against *M. tuberculosis*. Based on the preliminary results, **2g** was considered as a lead antimycobacterial compound for further optimization.

4. MATERIALS AND METHODS

4.1. Chemistry

Melting points were determined with a Thomas-Hoover capillary melting point apparatus (Thomas Scientific, Philadelphia, PA, USA) and were not corrected. Attenuated total reflection (ATR) Fourier transform IR (FTIR) spectra were obtained using a MIRacle ATR accessory (Pike Technologies, Fitchburg, WI, USA) in conjunction with a Spectrum BX FTIR spectrometer (Perkin Elmer, USA) and were reported in cm^{-1}. ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Varian Mercury 400 FT NMR spectrophotometer using tetramethylsilane as internal reference (chemical shifts represented in δ ppm). ESI-MS spectra were measured on a micromass ZQ-4000 single-quadruple mass spectrometer. Elemental analyses (C, H, and N) were performed on Leco CHNS 932 analyzer (Leco, St. Joseph, MI, USA). Data collection and cell refinement of compound **2a** and **2c** were performed on a Stoe Stadivari diffractometer with microfocused X-ray source Xenocs Genix3D Cu HF. The crystal was kept at 100 K during data collection. Using Olex2 [16], the structure was solved with the ShelXT [17] structure solution program using Intrinsic Phasing and refined with the ShelXL [18] refinement package using Least Squares minimisation.

4.1.1. General procedure for preparation of hydrazone derivatives (1a-k)

Equimolar amounts of phenylhydrazine and an appropriate benzaldehyde were refluxed in methanol in the presence of acetic acid as a catalytic reagent for 6 h. The solid precipitate was filtered and washed with cold methanol. The product was used for the next step without further purification.

4.1.2. General procedure for the preparation of 5-methyl-4-thiazolidinone derivatives (2a–k)

A mixture of hydrazones **1a-k** (2 mmol) and excess of thiolactic acid (1.5 mL) was heated at 70 °C until the reaction was completed. Ethyl acetate (30 mL) was added, the organic layer was washed with saturated $NaHCO_3$ (3x25 mL), water (1x25 mL), dried with Na_2SO_4 and concentrated to give an oily residue. The oily residue was purified by silica-gel column chromatography using hexane-ethyl acetate as eluent.

5-Methyl-2-phenyl-3-(phenylamino)thiazolidin-4-one (2a)

Yield 60.7%, mp. 132-4 °C, diastereomeric mixture (%) 64:36. IR; ν 3258 (N-H), 3057, 2985, 1678 (C=O), 1603, 1495, 1451, 1392, 750, 690 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.24 and 8.16 (1H, 2s, -NH-), 7.41-7.31 (5H, m, Ar-$H_{2''\text{-}6''}$), 7.18-7.11 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.77-6.71 (1H, m, Ar-$H_{4'}$), 6.65-6.62 (2H, m, Ar-$H_{2'}$, -$H_{6'}$), 5.89 and 5.83 (1H, s and d, thiazolidinone H_2, *J* = 1.2 Hz), 4.21 and 4.12 (1H, qd and q, thiazolidinone H_5, *J* = 6.8, *J* = 1.2, *J* = 7.0 Hz), 1.53 and 1.50 (3H, 2d, -CH_3, *J* = 7.2, *J* = 6.8 Hz) ppm. ^{13}C-NMR (DMSO-d_6); δ 171.73 and 171.54 (CO), 146.42, 146.29, 140.27, 139.33, 128.88, 128.77, 128.54, 128.49, 128.29, 127.44, 126.82, 119.16, 119.07, 112.06, 111.89, 60.29 and 59.79 (thiazolidinone C_2), 38.19 and 37.10 (thiazolidinone C_5), 20.11 and 18.99 (CH_3) ppm. ESI-MS (m/z); 309.29 $[M+Na+2]^+$, 308.30 $[M+Na+1]^+$, 307.30 ($[M+Na]^+$, 100%), 285.40 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85; S, 11.27. Found: C, 67.48; H, 5.57; N, 9.90; S, 11.16.

2-(4-Methoxyphenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (2b)

Yield 50.3%, mp. 76-8 °C, diastereomeric mixture (%) 60:40. IR; ν 3277 (N-H), 2930, 2836, 1690 (C=O), 1602, 1510, 1495, 1442, 1391, 1243, 750, 692 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.13 and 8.05 (1H, 2s, -NH-), 7.31 (2H, d, Ar-$H_{2''}$, -$H_{6''}$, *J* = 8.4 Hz), 7.16-7.09 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.91 (2H, d, Ar-$H_{3''}$, -$H_{5''}$, *J* = 8.8 Hz), 6.75-6.69 (1H, m, Ar-$H_{4'}$), 6.62-6.59 (2H, m, Ar-$H_{2'}$, -$H_{6'}$), 5.82 and 5.77 (1H, s and d, thiazolidinone H_2, *J* = 1.2 Hz), 4.18 and 4.08 (1H, qd and q, thiazolidinone H_5, *J* = 7.2, *J* = 1.6, *J* = 7.2 Hz), 3.74 (3H, d, -OCH_3; *J* = 1.6 Hz), 1.52 and 1.49 (3H, 2d, -CH_3, *J* = 6.8, *J* = 7.2 Hz) ppm. ESI-MS (m/z); 339.28 $[M+Na+2]^+$, 338.29 $[M+Na+1]^+$, 337.28 ($[M+Na]^+$, 100%), 215.37 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 65.37; H, 6.04; N, 9.03; S, 10.20.

5-Methyl-3-(phenylamino)-2-(p-tolyl)thiazolidin-4-one (2c)

Yield 52.5%; mp. 108-10 °C, diastereomeric mixture (%) 98:2. IR; ν 3258 (N-H), 3027, 2929, 1685 (C=O), 1597, 1496, 1444, 1392, 752, 694 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.09 (1H, s, -NH-), 7.27 (2H, d, Ar-$H_{2''}$, -$H_{4''}$, *J* = 7.6 Hz), 7.17 (2H, d, Ar-$H_{3''}$, -$H_{5''}$, *J* = 8.0 Hz), 7.11 (2H, t, Ar-$H_{3'}$, -$H_{5'}$, *J* = 7.2 Hz), 6.71 (1H, t, Ar-$H_{4'}$, *J* = 7.2 Hz),

6.61 (2H, dd, Ar-$H_{2'}$, -$H_{6'}$, *J* = 8.4, *J* = 0.8 Hz), 5.83 (1H, s, thiazolidinone H_2), 4.09 (1H, q, thiazolidinone H_5, *J* = 7.2 Hz), 2.49 (3H, m, -CH_3), 1.51 (3H, d, -CH_3, *J* = 7.2 Hz) ppm. ESI-MS (m/z); 323.32 $[M+Na+2]^+$, 322.32 $[M+Na+1]^+$, 321.32 ($[M+Na]^+$, 100%), 299.36 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39; S, 11.74. Found: C, 68.19; H, 6.22; N, 9.40; S, 10.57.

5-Methyl-3-(phenylamino)-2-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (2d)

Yield 78.1%; mp. 112-4 °C, diastereomeric mixture (%) 52:48. IR; ν 3296, 3249 (N-H), 2979, 1690 (C=O), 1602, 1496, 1447, 1374, 1320, 1155, 1113, 1065, 753, 694 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.30 and 8.24 (1H, 2s, -NH-), 7.74 (2H, dd, Ar-$H_{3''}$, -$H_{5''}$, *J* = 8.4, *J* = 2.8 Hz), 7.61 (2H, d, Ar-$H_{2''}$, -$H_{6''}$, *J* = 8.0 Hz), 7.18-7.11 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.74 (1H, q, Ar-$H_{4'}$, *J* = 7.1 Hz), 6.62 (2H, d, Ar-$H_{2'}$, -$H_{6'}$, *J* = 8.4), 6.02 and 5.96 (1H, 2s, thiazolidinone H_2), 4.22 and 4.14 (1H, 2q, thiazolidinone H_5, *J* = 7.2, *J* = 7.2 Hz), 1.52 and 1.48 (3H, 2d, -CH_3, *J* = 7.2, *J* = 7.2 Hz) ppm. ESI-MS (m/z); 377.24 $[M+Na+2]^+$, 376.25 $[M+Na+1]^+$, 375.25 ($[M+Na]^+$, 100%), 353.29 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{15}N_2OSF_3$: C, 57.95; H, 4.29; N, 7.95; S, 9.10. Found: C, 58.01; H, 4.32; N, 8.05; S, 9.12.

2-(4-Fluorophenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (2e)

Yield 70.2%; mp. 130-2 °C, diastereomeric mixture (%) 76:24. IR; ν 3255 (N-H), 3047, 2924, 1679 (C=O), 1602, 1505, 1495, 1451, 1390, 1220, 1156, 749, 691 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.22 and 8.14 (1H, 2s, -NH-), 7.47-7.44 (2H, m, Ar-$H_{2''}$, -$H_{6''}$), 7.22-7.11 (4H, m, Ar-$H_{3''}$, -$H_{5''}$, -$H_{3'}$, -$H_{5'}$), 6.74 (1H, m, Ar-$H_{4'}$), 6.61 (2H, d, Ar-$H_{2'}$, -$H_{6'}$, *J* = 8.4 Hz), 5.91 and 5.86 (1H, 2s, thiazolidinone H_2), 4.22 and 4.12 (1H, 2q, thiazolidinone H_5, *J* = 6.8, *J* = 7.2 Hz), 1.53 and 1.50 (3H, 2d, -CH_3, *J* = 6.8, *J* = 7.2 Hz) ppm. ESI-MS (m/z); 327.26 $[M+Na+2]^+$, 326.26 $[M+Na+1]^+$, 325.26 ($[M+Na]^+$, 100%). Anal. Calcd. for $C_{16}H_{15}N_2OSF$: C, 63.56; H, 5.00; N, 9.26; S, 10.60. Found: C, 63.39; H, 5.07; N, 9.28; S, 10.48.

2-(4-Ethoxyphenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (2f)

Yield 53.1%; mp. 87-9 °C, diastereomeric mixture (%) 56:44. IR; ν 3298, 3261 (N-H), 2983, 2933, 2887, 1688 (C=O), 1603, 1511, 1497, 1440, 1393, 1338, 1243, 1171, 1113, 1044, 752, 693 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.14 and 8.05 (1H, 2s, -NH-), 7.30 (2H, d, Ar-$H_{2''}$, -$H_{6''}$, *J* = 8.8 Hz), 7.17-7.09 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.89 (2H, d, Ar-$H_{3''}$, -$H_{5''}$, *J* = 8.8 Hz), 6.72 (1H, q, Ar-$H_{4'}$, *J* = 7.6 Hz), 6.62-6.59 (2H, m, Ar-$H_{2'}$, -$H_{6'}$), 5.81 and 5.77 (1H, 2s, thiazolidinone H_2), 4.18 and 4.09 (1H, qd and q, thiazolidinone H_5, *J* = 7.0, *J* = 1.2, *J* = 6.8 Hz), 4.01 (2H, qd, -O$C\underline{H}_2CH_3$, *J* = 6.8, *J* = 2.4 Hz), 1.52 and 1.49 (3H, 2d, -CH_3, *J* = 7.2, *J* = 7.2 Hz), 1.31 (3H, td, -$OCH_2C\underline{H}_3$, *J* = 6.8, *J* = 1.2 Hz) ppm. ESI-MS (m/z); 353.37 $[M+Na+2]^+$, 352.37 $[M+Na+1]^+$, 351.37 ($[M+Na]^+$, 100%), 329.40 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.69; H, 5.98; N, 8.57; S, 9.71.

2-(4-Ethylphenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (2g)

Yield 71.5%; mp. 97-9 °C, diastereomeric mixture (%) 60:40. IR; ν 3294 (N-H), 3018, 2963, 1691 (C=O), 1602, 1497, 1440, 1391, 1339, 1178, 753, 694 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.19 and 8.11 (1H, 2s, -NH-), 7.29 (2H, d, Ar-$H_{2''}$, -$H_{6''}$, *J* = 7.6 Hz), 7.19 (2H, d, Ar-$H_{3'}$, -$H_{5'}$, *J* = 8.0 Hz), 7.17-7.10 (2H, m, Ar-$H_{3''}$, -$H_{5''}$), 6.72 (1H, q, Ar-$H_{4'}$, *J* = 8.0 Hz), 6.60-6.63 (2H, m, Ar-$H_{2'}$, -$H_{6'}$), 5.84 and 5.79 (1H, 2s, thiazolidinone H_2), 4.17 and 4.09 (1H, 2q, thiazolidinone H_5, *J* = 6.8, *J* = 6.8 Hz), 2.59 (2H, q, -$C\underline{H}_2CH_3$, *J* = 7.6 Hz), 1.51 and 1.48 (3H, 2d, -CH_3, *J* = 7.2, *J* = 7.2 Hz), 1.16 (3H, t, -$CH_2C\underline{H}_3$, *J* = 7.6 Hz) ppm. ESI-MS (m/z); 337.30 $[M+Na+2]^+$, 336.30 $[M+Na+1]^+$, 335.30 ($[M+Na]^+$, 100%), 313.34 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{20}N_2OS$: C, 69.20; H, 6.45; N, 8.97; S, 10.26. Found: C, 68.90; H, 6.59; N, 8.99; S, 10.11.

2-(4-(Dimethylamino)phenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (2h)

Yield 54.8%; mp. 129-31 °C, diastereomeric mixture (%) 80:20. IR; ν 3309 (N-H), 3026, 2889, 2807, 1677 (C=O), 1604, 1521, 1496, 1444, 1398, 1344, 1184, 1063, 736, 686 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.05 and 7.97 (1H, 2s, -NH-), 7.18 (2H, d, Ar-$H_{2''}$, -$H_{6''}$, *J* = 8.8 Hz), 7.16-7.08 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.74-6.70 (1H, m, Ar-$H_{4'}$), 6.67 (2H, d, Ar-$H_{3''}$, -$H_{5''}$, *J* = 9.2 Hz), 6.62-6.58 (2H, m, Ar-$H_{2'}$, -$H_{6'}$), 5.74 and 5.69 (1H, s and d, thiazolidinone H_2, *J* = 1.6 Hz), 4.15 and 4.06 (1H, qd and q, thiazolidinone H_5, *J* = 6.8, *J* = 1.6, *J* = 7.2 Hz), 2.88 (6H, s, -$N(CH_3)_2$, *J* = 7.6 Hz), 1.51 and 1.49 (3H, 2d, -CH_3, *J* = 7.2, *J* = 7.2 Hz) ppm. ESI-MS (m/z); 352.25 $[M+Na+2]^+$, 351.25

$[M+Na+1]^+$, 350.25 ($[M+Na]^+$, 100%), 328.29 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{21}N_3OS$: C, 66.02; H, 6.46; N, 12.83; S, 9.79. Found: C, 65.55; H, 6.12; N, 12.72; S, 9.73.

5-Methyl-3-(phenylamino)-2-(thiophen-2-yl)thiazolidin-4-one (2i)

Yield 56.7%; mp. 104-6 °C, diastereomeric mixture (%) 96:4. IR; ν 3244 (N-H), 3041, 2928, 1680 (C=O), 1600, 1531, 1494, 1450, 1392, 1367, 1035, 754, 703, 698 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.12 (1H, s, -NH-), 7.57 (1H, dd, thienyl H_5, J = 4.8, J = 0.8 Hz), 7.15 (1H, dd, thienyl H_3, J = 3.6, J = 1.2 Hz), 7.10 (2H, t, Ar-$H_{3'}$, -$H_{5'}$, J = 7.6 Hz), 6.93 (1H, dd, thienyl H_4, J = 3.6, J = 5.0 Hz), 6.70 (1H, t, Ar-$H_{4''}$, J = 7.6 Hz), 6.59 (2H, d, Ar-$H_{2'}$, -$H_{6'}$, J = 7.6 Hz), 6.12 (1H, s, thiazolidinone H_2), 4.08 (1H, q, thiazolidinone H_5, J = 7.2 Hz), 1.54 and 1.48 (3H, 2d, -CH_3, J = 6.8, J = 7.2 Hz) ppm. ESI-MS (m/z); 315.25 $[M+Na+2]^+$, 315.25 $[M+Na+1]^+$, 313.25 ($[M+Na]^+$, 100%), 291.40 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}N_2OS_2$: C, 57.90; H, 4.86; N, 9.65; S, 22.08. Found: C, 57.92; H, 5.10; N, 9.75; S, 22.00.

2-(4-Chlorophenyl)-5-methyl-3-(phenylamino)thiazolidin-4-one (2j)

Yield 55.4%; mp. 127-9 °C (126-8 °C) [19], diastereomeric mixture (%) 73:27. IR; ν 3257 (N-H), 3034, 2985, 2933, 1687 (C=O), 1602, 1491, 1445, 1391, 1255, 1087, 807, 758, 694 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.23 and 8.15 (1H, 2s, -NH-), 7.44-7.39 (4H,m, Ar-$H_{2''}$, -$H_{3''}$, -$H_{5''}$, -$H_{6''}$), 7.17-7.10 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.73 (1H, m, Ar-$H_{4'}$), 6.60 (2H, d, Ar-$H_{2'}$, -$H_{6'}$, J = 7.2 Hz), 5.90 and 5.85 (1H, s and d, thiazolidinone H_2, J = 1.6 Hz), 4.20 and 4.11 (1H, 2q, thiazolidinone H_5, J = 7.2, J = 6.8 Hz), 1.51 and 1.48 (3H, 2d, -CH_3, J = 7.2, J = 7.2 Hz) ppm. ESI-MS (m/z); 344.27 $[M+Na+2]^+$, 343.27 $[M+Na+1]^+$, 341.27 ($[M+Na]^+$, 100%), 319.32 $[M+H]^+$.

5-Methyl-3-(phenylamino)-2-(pyridin-3-yl)thiazolidin-4-one (2k)

Yield 52.6%; mp. 130-2 °C, diastereomeric mixture (%) 56:44. IR; ν 3277 (N-H), 3171, 3113, 2955, 1691 (C=O), 1602, 1494, 1437, 1377, 1261, 1029, 805, 751, 708, 690 cm^{-1}. ^{1}H-NMR (DMSO-d_6); δ 8.58-8.60 (1H, m, pyridyl H_2), 8.53 (1H, dd, pyridyl H_6, J = 4.6, J = 1.6 Hz), 8.31 and 8.24 (1H, 2s, -NH-), 7.85 (1H, td, pyridyl H_4, J = 6.0, J = 1.6 Hz), 7.44-7.40 (1H, m, pyridyl H_5), 7.19-7.12 (2H, m, Ar-$H_{3'}$, -$H_{5'}$), 6.75 (1H, q, Ar-$H_{4'}$, J = 7.6), 6.62 (2H, d, Ar-$H_{2'}$, -$H_{6'}$, J = 8.0 Hz), 5.98 and 5.92 (1H, s and d, thiazolidinone H_2, J = 1.2 Hz), 4.30 and 4.16 (1H, qd and q, thiazolidinone H_5, J = 6.8, J = 1.2, J = 6.8 Hz), 1.54 and 1.51 (3H, 2d, -CH_3, J = 7.2, J = 7.2 Hz) ppm. ESI-MS (m/z); 310.24 $[M+Na+2]^+$, 309.24 $[M+Na+1]^+$, 308.24 ($[M+Na]^+$, 100%), 286.28 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{15}N_3OS$: C, 63.14; H, 5.30; N, 14.72; S, 11.23. Found: C, 62.73; H, 5.57; N, 14.40; S, 10.85.

4.1.2. Single crystal X-ray diffraction

The crystal data, data collection and refinement parameters are given in the Supplementary material (Tables S1–S3). The crystal packing of **2a** and **2c** are drawn in Figure S1 and S2, respectively. The crystal structures have been deposited in Cambridge Crystallographic Data Centre with CCDC nos. 1956431 and 1956432.

4.2. Antimycobacterial activity

The inoculum was prepared from fresh Löwnstein-Jensen (LJ) medium re-suspended in 7H9-S medium (7H9 broth, 0.1% casitone, 0.5% glycerol, supplemented oleic acid, albumin, dextrose, and catalase [OADC]), adjusted to a OD_{590} 1.0, and diluted 1:20; 100 µl was used as inoculum. Each drug stock solution was thawed and diluted in 7H9-S at four-fold the final highest concentration tested. Serial two-fold dilutions of each drug were prepared directly in a sterile 96-well microtiter plate using 100 µl 7H9-S. A growth control containing no antibiotic and a sterile control was also prepared on each plate. Sterile water was added to all perimetre wells to avoid evaporation during the incubation. The plate was covered, sealed in plastic bags and incubated at 37 °C in normal atmosphere. After 7 days of incubation, 30 µl of alamar blue solution was added to each well, and the plate was re-incubated overnight. A change in colour from blue (oxidised state) to pink (reduced) indicated bacteria growth, and the MIC was defined as the lowest concentration of drug that prevented this change in colour [20]. MICs of the compounds were reported in Table 1.

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Appendix A. Supplementary Material

Supplementary Material related to this article can be accessed at https://doi.org/10.35333/jrp.2020.110.

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