Synthesis of newer 5-benzylidene-2, 4-thiazolidinediones as potential antimicrobials

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ABSTRACT

A series of 2-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidine}-2,4-dioxo-thiazolidin-3-yl)-*N*-heterocycle-acetamide were synthesized and evaluated for antimycobacterial and antimicrobial activity. All the synthesized compounds have been established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. *In vitro* antimycobacterial activity was carried out against *(M. tuberculosis) $H_{37}Rv$* strain using Lowenstein-Jensen medium and antimicrobial activity against two gram positive bacteria (*S. aureus, S. pyogenes*), two gram negative bacteria (*E. coli*, *P. aeruginosa*) and three fungal species (*C. albicans*, *A. niger*, *A. clavatus*) using the broth microdilution method. Compounds 6a, 6b, 6d, 6e, 6g, and 6i exhibited promising antimicrobial activity whereas compounds 6g showed very good antimycobacterial activity.

Keywords: Thiazolidionedione; antimicrobial activity

1. INTRODUCTION

Tuberculosis (TB) is becoming a global health threat due to the emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* (MTB) and the deadly synergy of TB with HIV (Bloom BR, 1992). The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on tuberculosis control programs contribute to the disease's resurgence in industrialized countries (Barnes PF, 1991).

Resistance of Mycobacterium tuberculosis strains to antimycobacterial agents is an increasing problem worldwide (Janin YL, 2007; Telzak EE, 1995; Bastian I, 1999). In spite of severe toxicity on repeated dosing of isoniazid (INH), it is still considered to be a first line drug for the chemotherapy of tuberculosis. The azole antitubercular may be regarded as a new class providing truly effective drugs, which is reported to inhibit the bacteria by blocking the biosynthesis of certain bacterial lipids and/or by additional mechanism (Joshi SD, 2008; Zampieri D; 2009, Ulusoy N, 2001). Thiazolidinedione derivatives are active against mycobacteria (Babaoglu K, 2003) and also possess wide variety of biological activity (Sohda T, 1983; Chandrappa S, 2008; Pattan SR, 2009; Oya B, 2007; Tunçbilek M, 2003; Tuncbilek M, 2006, Madhavan GR, 2006; Maccari R, 2007; Katritzky AR, 2009). Benzothiazole moiety has already been reported for its mycobacterial activity(Katritzky AR, 2009; Vicini P, 2003) and also possesses a wide range of biological activities (Gasparová R, 1997; Lin KS, 2009; Serdons K, 2009; Turan-Zitouni G, 2003; Huang ST, 2006, Lion CJ, 2005; Siddiqui N, 2007).

In an ongoing effort to develop scaffolds against tuberculosis, we reported a series of azole with good antitubercular activities(Patel NB, 2010; Patel NB,2011). Herein, we report the synthesis of 2-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidine}-2,4-dioxo-thiazolidin-3-yl)-*N*-heterocycle-acetamide compounds, their evaluation as inhibitors of *M.tb* strain $H_{37}Rv$ and antimicrobial activity.

2. MATERIAL AND METHODS

All chemical were of analytical grade and us e directly. Melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of compound was confirmed by TLC using Merck silica gel 60 F254. IR spectra were recorded on Perkin-Elmer RX 1 FTIR spectrophotometer in KBr (γ_{max} in cm^{-1}). ^{1}H-NMR spectra were recorded in DMSO on a Bruker Avance II 400 NMR spectrometer (400 MHz) using TMS as internal standard (δ in ppm). ^{13}C-NMR spectra were recorded in DMSO on a Bruker Avance II 400 NMR spectrometer operating at 100 MHz (δ in ppm). The microanalyses were performed on a Heraeus Carlo Erba 1180 CHN analyzer. The mass spectra were recorded on micromass Q-T of micro (TOF MS ES+).

2.1. Synthesis of 5-benzylidene-2, 4-thiazolidinediones:

2.1.1. 4 - (2 - (5-ethylpyridin-2-l) ethoxy) benzaldehyde 3 was prepared by the literature procedure (Gaonkar SL, 2006; Momose Y, 1991, Rattan A, 2000).

2.1.2. (E)-5-(4-(2-(5-ethylpyridin-2-yl) ethoxy) benzylidene) thiazolidine-2, 4-dione 4: A mixture of 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde 3 (0.01 mol), thiazolidine-2,4-dione (0.012 mol) and pyrrolidine (0.01 mol) was stirred in round bottom flask and heated to about 65° C. for about 14 hours. After completion of the reaction the reaction mass is

cooled to about 25° C. and methanol is charged and it is stirred for about 15 minutes. The pH is adjusted to about 6 to about 6.5 by using acetic acid followed by addition of methanol and stirred for about 15 minutes. The obtained reaction solution is heated to about 65° C. and stirred for about 60 to 90 minutes and then cooled to 25° C. The separated solid is filtered and washed with methanol and dried.

Yeild:76%; m.p. 156-160°C; IR (KBr, γ_{max}, cm^{-1}): 3580 (NH), 3051 (-C=CH),1742 (C=O), 1228, 1028 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 12.29 (b, 1H, NH), 8.32 (s, 1H, CH), 7.76 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.21 Hz, CH), 7.43 (dd, 1H, CH), , 7.21 (d, 1H, *J* = 7.88 Hz, CH), 7.00 (d, 2H, *J* = 8.84 Hz, CH), 4.38 (t, 2H, -CH_2), 3.32 (t, 2H, -CH_2), 2.59 (q, 2H, -CH_2), 1.18 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 167.67 (C_2, C=O, thiazolidinedione), 167.21 (C_5, C=O, thiazolidinedione), 160.09, 154.87, 148.38, 143.30 (=CH-), 136.58, 135.50, 131.79, 125.41, 122.91, 120.91, 115.05, 66.98, 36.59, 25.06, 15.19; (m/z): 457 (M^+); Anal. Calc. for $C_{22}H_{22}N_2O_5S$: C, 64.31; H, 5.12; N, 7.90. Found: C, 64.34; H, 5.09; N, 7.87.

2.1.3. (E)-ethyl 2-(5-(4-(2-(5-ethylpyridin-2-yl) ethoxy) benzylidene) - 2, 4-dioxothiazolidin-3-yl)acetate 5: A mixture of (*E*)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione 4 (0.01 mol), bromoethyl acetate (0.01 mol) and K_2CO_3 (0.012 mol) was stirred and refluxed in 1,4-dioxane for 10 h. The reaction was monitored by TLC on silica gel using ethyl acetate: toluene (2.5:7.5). Cool the reaction mass to room temperature; then it was poured into crushed ice. The solid separated was filtered, washed with excess of water and recrystallized from ethanol providing pure compound.

Yeild:68%; m.p. 168-170°C; IR (KBr, γ_{max}, cm^{-1}): 3049 (-C=CH), 1748 (C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 8.32 (s, 1H, CH), 7.78 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.41 Hz, CH), 7.43 (dd, 1H, CH), 7.21 (d, 1H, *J* = 7.84 Hz, CH), 7.01 (d, 2H, *J* = 8.84 Hz, CH), 4.72 (s, 2H, -CH_2), 4.38 (t, 2H, -CH_2), 4.32 (t, 2H, -CH_2), 3.32 (t, 2H, -CH_2), 2.59 (q, 2H, -CH_2), 1.18 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 168.66 (C_2, C=O, thiazolidinedione), 167.19 (C_5, C=O, thiazolidinedione), 166.92 (C=O), 160.11, 154.91, 148.39, 143.33 (=CH-), 136.60, 135.51, 131.80, 125.43, 122.93, 120.92, 115.07, 66.99, 49.19, 45.76, 36.61, 25.08, 15.21; (m/z): 440 (M^+); Anal. Calc. for $C_{23}H_{24}N_2O_5S$: C, 62.61; H, 5.49; N, 6.36. Found: C, 62.58; H, 5.53; N, 6.40.

2.1.4. General procedure for the synthesis of 2-(5-{4-[2-(5-Ethyl-pyridin-2-yl)-ethoxy]-benzylidine}-2,4-dioxo-thiazolidin-3-yl)-N-heterocycle-acetamide.6a-n: A mixture of *(E)-ethyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)-2,4-dioxothiazolidine-3-carboxylate 5* (0.01 mol) and 2-amino-5-methyl thiazole (0.01 mol) in 1,4-dioxane was heated under reflux on a sand-bath for 8-10 h. The reaction was monitored by TLC on silica gel using ethyl acetate: toluene (2.5:7.5). Cool the reaction mass to room temperature; then it was poured into crushed ice. The solid separated was filtered, washed with excess of water and recrystallized from chloroform providing pure compound. The other compounds of the series were prepared by similar procedure.

2.1.5. (E)-2-(5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)-2,4-dioxothiazolidin-3-yl)-N-(5-methylthiazol-2-yl)acetamide 6a: Yeild 76%; m.p. 180-182°C; IR (KBr, γ_{max}, cm^{-1}): 3434 (NH), 3049 (-C=CH), 1748 (C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 10.02 (s, 1H, NH), 8.32 (s, 1H, CH), 7.78 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.44 Hz, CH), 7.43 (dd, 1H, CH), 7.21 (d, 1H, *J* = 7.88 Hz, CH), 7.01 (d, 2H, *J* = 8.84 Hz, CH), 6.74 (s, 1H, CH), 4.72 (s, 2H, -CH_2), 4.38 (t, 2H, -CH_2), 4.32 (t, 2H, -CH_2), 3.32 (t, 2H, -CH_2), 2.59 (q, 2H, -CH_2), 2.30 (s, 3H, -CH_3), 1.18 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 168.12 (C_2, C=O, thiazolidinedione), 167.05 (C_5, C=O, thiazolidinedione), 165.53 (C=O), 161.81, 160.11, 154.91, 148.39, 143.33 (=CH-), 136.60, 135.51, 135.41, 131.80, 125.43, 122.93, 120.92, 120.05, 115.07, 66.99, 49.98, 45.76, 36.61, 25.08, 15.21, 11.81; (m/z): 508 (M^+); Anal. Calc. for $C_{25}H_{24}N_4O_4S_2$: C, 59.04; H, 4.76; N, 11.02. Found: C, 59.07; H, 4.79; N, 11.04.

2.1.6. (E) – 2 - (5 - (4 - (2 - (5 – ethylpyridin – 2 - yl) ethoxy) benzylidene) - 2, 4-dioxothiazolidin-3-yl)-N-(6-fluorobenzo[d]thiazol-2-yl)acetamide 6b: Yeild 60%; m.p. 167-169°C; IR (KBr, γ_{max}, cm^{-1}): 3436 (NH), 3051 (-C=CH), 1750 (C=O), 1228, 1028 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.89 (s, 1H, NH), 8.31 (s, 1H, CH), 8.03 (s, 1H, CH), 7.77 (s, 1H, -C=CH), 7.73 (d, 1H, CH), 7.49 (d, 2H, *J* = 7.56 Hz, CH), 7.43 (dd, 1H, CH), 7.26 (d, 1H, CH), 7.22 (d, 1H, *J* = 8.02 Hz, CH), 7.00 (d, 2H, *J* = 8.84 Hz, CH), 4.73 (s, 2H, -CH_2), 4.39 (t, 2H, -CH_2), 4.34 (t, 2H, -CH_2), 3.33 (t, 2H, -CH_2), 2.60 (q, 2H, -CH_2), 1.19 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.51, 168.67 (C_2, C=O, thiazolidinedione), 167.21 (C_5, C=O, thiazolidinedione), 165.53 (C=O), 160.13, 154.92, 158.50, 148.81, 148.40, 143.34 (=CH-),

136.61, 135.49, 131.83, 131.63, 125.47, 122.95, 120.95, 117.81, 115.10, 113.96, 108.85, 66.99, 49.98, 45.78, 36.63, 25.11, 15.23; (m/z): 562 (M^+); Anal. Calc. for $C_{28}H_{23}N_4O_4S_2$: C, 59.77; H, 4.12; N, 9.96. Found: C, 60.01; H, 4.09; N, 9.98.

2.1.7. (E) – 2 - (5 - (4 - (2 - (5 – ethylpyridin – 2 - yl) ethoxy) benzylidene) - 2,4 – dioxothiazolidin – 3 - yl) - N-(6-nitrobenzo[d]thiazol-2-yl) acetamide 6c: Yeild 69%; m.p. 175-177°C; IR (KBr, γ_{max}, cm^{-1}): 3441 (NH), 3053 (-C=CH), 1760 (C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.15 (s, 1H, NH), 8.62 (s, 1H, CH), 8.32 (s, 2H, CH), 8.01 (d, 1H, CH), 7.79 (s, 1H, -C=CH), 7.50 (d, 2H, *J* = 7.88 Hz, CH), 7.43 (dd, 1H, CH), 7.22 (d, 1H, *J* = 7.84 Hz, CH), 7.04 (d, 2H, *J* = 8.88 Hz, CH), 4.75 (s, 2H, -CH_2), 4.39 (t, 2H, -CH_2), 4.34 (t, 2H, -CH_2), 3.36 (t, 2H, -CH_2), 2.60 (q, 2H, -CH_2), 1.19 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.21, 168.89 (C_2, C=O, thiazolidinedione), 167.20 (C_5, C=O, thiazolidinedione), 165.53 (C=O),160.09, 154.93,158.30, 148.41, 144.31, 143.38 (=CH-), 136.64, 135.55, 131.86, 131.33, 125.46, 122.94, 121.33, 120.97,119.12, 117.31, 115.08, 66.95, 49.23, 45.75, 36.68, 25.04, 15.25; (m/z): 589 (M^+); Anal. Calc. for $C_{28}H_{23}N_5O_6S_2$: C, 57.03; H, 3.93; N, 11.88. Found: C, 57.07; H, 3.97; N, 11.91.

2.1.8. (E)-2-(5-(4-(2-(5-ethylpyridin-2-yl) ethoxy) benzylidene) - 2, 4 - dioxothiazolidin - 3 - yl) - N - (4 - nitrobenzo [d] thiazol-2-yl) acetamide 6d: Yeild 57%; m.p. 146-148°C; IR (KBr, γ_{max}, cm^{-1}): 3439 (NH), 3056 (-C=CH), 1762 (C=O), 1229, 1028 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.38 (s, 1H, NH), 8.42 (d, 1H, CH), 8.31 (d, 2H, CH), 7.83 (t, 1H, CH), 7.76 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.08 Hz, CH), 7.43 (dd, 1H, CH), 7.22 (d, 1H, *J* = 7.84 Hz, CH), 7.01 (d, 2H, *J* = 8.02 Hz, CH), 4.71 (s, 2H, -CH_2), 4.39 (t, 2H, -CH_2), 4.35 (t, 2H, -CH_2), 3.35 (t, 2H, -CH_2), 2.54 (q, 2H, -CH_2), 1.19 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.61, 168.66 (C_2, C=O, thiazolidinedione), 167.14 (C_5, C=O, thiazolidinedione), 165.77 (C=O),160.14, 154.98, 148.75 144.93, 143.37 (=CH-), 142.87, 136.66, 135.57, 131.86, 127.93, 125.61. 125.43, 125.47, 122.99, 122.41, 120.92, 115.05, 66.97, 49.85, 45.72, 36.85, 25.78, 15.27; (m/z): 589 (M^+); Anal. Calc. for $C_{28}H_{23}N_5O_6S_2$: C, 57.03; H, 3.93; N, 11.88. Found: C, 56.99; H, 3.90; N, 11.85.

2.1.9. (E)- 2 - (5 - (4 - (2 - (5-ethylpyridin-2-yl) ethoxy)benzylidene) – 2 , 4 – dioxothiazolidin – 3 – yl) – N - (5-nitrobenzo[d]thiazol-2-yl)acetamide 6e: Yeild 66%; m.p. 165-167°C; IR (KBr, γ_{max}, cm^{-1}): 3435 (NH), 3043 (-C=CH), 1750 (C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 10.02 (s, 1H, NH), 9.16 (s, 1H, CH), 8.32 (d, 2H, CH), 8.27 (d, 1H, CH), 7.76 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.82 Hz, CH), 7.43 (dd, 1H, CH), 7.23 (d, 1H, *J* = 7.94 Hz, CH), 7.01 (d, 2H, *J* = 8.80 Hz, CH), 4.74 (s, 2H, -CH_2), 4.39 (t, 2H, -CH_2), 4.32 (t, 2H, -CH_2), 3.30 (t, 2H, -CH_2), 2.58 (q, 2H, -CH_2), 1.17 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.55, 168.68 (C_2, C=O, thiazolidinedione), 167.18 (C_5, C=O, thiazolidinedione), 152.52 (C=O), 160.14, 154.91, 149.52, 148.34, 146.23, 143.34 (=CH-), 136.91, 136.66, 135.51, 131.89, 125.48, 122.99, 122.71, 120.98, 119.23, 117.34, 115.08, 66.99, 49.68, 45.74, 36.64, 25.04, 15.28; (m/z): 589 (M^+); Anal. Calc. for $C_{28}H_{23}N_5O_6S_2$: C, 57.03; H, 3.93; N, 11.88. Found: C, 57.00; H, 3.91; N, 11.90.

2.1.10. (E) – N - (6-chlorobenzo[d]thiazol-2-yl) - 2 - (5 - (4 - (2 - (5-ethylpyridin-2-yl) ethoxy) benzylidene) - 2, 4-dioxothiazolidin-3-yl)acetamide 6f: Yeild 61%; m.p. 159-161°C; IR (KBr, γ_{max}, cm^{-1}): 3441 (NH), 3089 (-C=CH), 1762 (C=O), 1232, 1030 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.16 (s, 1H, NH), 8.31 (s, 1H, CH), 8.13 (s, 1H, CH), 7.76 (s, 1H, -C=CH), 7.69 (d, 1H, CH), 7.56 (d, 1H, CH), 7.49 (d, 2H, *J* = 8.08 Hz, CH), 7.42 (dd, 1H, CH), 7.20 (d, 1H, *J* = 7.88 Hz, CH), 7.00 (d, 2H, *J* = 8.88 Hz, CH), 4.69 (s, 2H, -CH_2), 4.38 (t, 2H, -CH_2), 4.31 (t, 2H, -CH_2), 3.35 (t, 2H, -CH_2), 2.54 (q, 2H, -CH_2), 1.19 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.35, 168.58 (C_2, C=O, thiazolidinedione), 167.21 (C_5, C=O, thiazolidinedione), 165.81 (C=O), 160.24, 154.89, 151.32, 148.36, 143.36 (=CH-), 132.31, 136.59, 135.50, 131.74, 129.83, 125.86, 125.38, 122.86, 121.21, 120.84, 118.33, 115.09, 67.02, 49.68, 45.81, 36.31, 25.10, 15.23; (m/z): 578 (M^+), 580 (M^++2); Anal. Calc. for $C_{28}H_{17}ClN_4O_4S_2$: C, 58.07; H, 4.00; N, 9.67. Found: C, 58.03; H, 3.98; N, 9.71.

2.1.11. (E) – 2 - (5 - (4 - (2 - (5 – ethylpyridin – 2 - yl) ethoxy) benzylidene) – 2 ,4 – dioxothiazolidin – 3 - yl) – N -(6-methylbenzo[d]thiazol-2-yl)acetamide 6g: Yeild 72%; m.p. 148-150°C; IR (KBr, γ_{max}, cm^{-1}): 3433(NH), 3059 (-C=CH), 1759 (C=O), 1228, 1028 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.39 (s, 1H, NH), 8.32 (s, 1H, CH), 7.89 (d, 1H, CH), 7.81 (d, 1H, CH),7.75 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.24 Hz, CH), 7.43 (dd, 1H, CH), 7.33 (s, 1H, CH), 7.21 (d, 1H, *J* = 7.88 Hz, CH), 7.00 (d, 2H, *J* = 8.22 Hz, CH), 4.72 (s, 2H, -CH_2), 4.31 (t, 2H, -CH_2), 4.36 (t, 2H, -CH_2), 3.32 (t, 2H, -CH_2), 2.34 (s, 3H, -CH_3), 2.59 (q, 2H, -CH_2), 1.18 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.21, 168.58(C_2, C=O, thiazolidinedione), 167.18 (C_5, C=O, thiazolidinedione), 165.68 (C=O),160.18, 154.89,

150.22, 148.41, 143.38 (=CH-), 136.62, 135.49, 134.18, 131.78, 130.71, 126.66, 125.39, 122.89, 121.31, 120.92, 117.18, 115.09, 66.92, 49.92, 45.76, 36.59, 25.11, 20.38, 15.31; (m/z): 558 (M^+); Anal. Calc. for $C_{29}H_{26}N_4O_4S_2$: C, 62.35; H, 4.69; N, 10.03. Found: C, 62.38; H, 4.72; N, 10.05.

2.1.12. (E) – 2 - (5- (4- (2- (5-ethylpyridin-2-yl) ethoxy) benzylidene) -2, 4 – dioxothiazolidin – 3 - yl) – N - (6-methoxybenzo [d] thiazol – 2 - yl) acetamide 6h: Yeild 70%; m.p. 161-163°C; IR (KBr, γ_{max}, cm^{-1}): 3433 (NH), 3059 (-C=CH), 176 (C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.41 (s, 1H, NH), 8.32 (s, 1H, CH), 7.77 (s, 1H, -C=CH), 7.53 (d, 1H, CH), 7.52 (s, 1H, CH), 7.50 (d, 2H, *J* = 7.41 Hz, CH), 7.43 (dd, 1H, CH), 7.21 (d, 1H, *J* = 7.84 Hz, CH), 7.01 (d, 4H, *J* = 8.84 Hz, CH), 4.63 (s, 2H, -CH_2), 4.39 (t, 2H, -CH_2), 4.33 (t, 2H, -CH_2), 3.38 (s, 3H, -OCH_3), 3.33 (t, 2H, -CH_2), 2.60 (q, 2H, -CH_2), 1.21 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 171.23, 168.76 (C_2, C=O, thiazolidinedione), 167.29 (C_5, C=O, thiazolidinedione), 165.72 (C=O), 160.23, 156.78, 154.93, 148.36, 145.52, 143.35 (=CH-), 136.64, 135.55, 131.92, 131.85, 125.44, 122.96, 120.63, 118.25, 114.63, 115.09, 104.96, 66.96, 55.80, 49.96, 45.81, 36.64, 25.11, 15.21; (m/z): 574 (M^+); Anal. Calc. for $C_{29}H_{26}N_4O_5S_2$: C, 60.61; H, 4.56; N, 9.75. Found: C, 60.58; H, 4.53; N, 9.78.

2.1.13. (E) – N - (4, 6-dimethoxypyrimidin-2-yl) – 2 - (5 - (4 - (2 - (5-ethylpyridin-2-yl)ethoxy)benzylidene) - 2, 4-dioxothiazolidin-3-yl)acetamide 6i: Yeild 65%; m.p. 151-153°C; IR (KBr, γ_{max}, cm^{-1}): 3434 (NH), 3049 (-C=CH), 1756 (C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.26 (s, 1H, NH), 8.32 (s, 1H, CH), 7.78 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.48 Hz, CH), 7.43 (dd, 1H, CH), 7.21 (d, 1H, *J* = 7.88 Hz, CH), 7.01 (d, 2H, *J* = 8.92 Hz, CH), 5.71 (s, 1H, CH), 4.73 (s, 2H, -CH_2), 4.38 (t, 2H, -CH_2), 4.32 (t, 2H, -CH_2), 3.80 (s, 6H, -OCH_3), 3.32 (t, 2H, -CH_2), 2.59 (q, 2H, -CH_2), 1.18 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 170.21, 168.66 (C_2, C=O, thiazolidinedione), 167.19 (C_5, C=O, thiazolidinedione), 165.72 (C=O), 160.13, 154.91, 153.56, 148.39, 143.34 (=CH-), 136.60, 135.55, 131.80, 125.44, 122.94, 120.95, 115.08, 71.54, 66.99, 54.18, 49.92, 45.77, 36.64, 25.09, 15.26; (m/z): 549 (M^+); Anal. Calc. for $C_{27}H_{27}N_5O_6S$: C, 59.00; H, 4.95; N, 12.74. Found: C, 59.03; H, 4.98; N, 12.79.

2.1.14. (E) – N - (4, 6-dichloropyrimidin-2-yl) – 2 - (5 - (4 - (2 - (5 – ethylpyridin – 2 - yl) ethoxy) benzylidene) - 2, 4-dioxothiazolidin-3-yl) acetamide 6j: Yeild 66%; m.p. 159-161°C; IR (KBr, γ_{max}, cm^{-1}): 3442 (NH), 3048(-C=CH), 1760 (C=O), 1228, 1028 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 9.14 (s, 1H, NH), 8.31 (s, 1H, CH), 7.76 (s, 1H, -C=CH), 7.50 (d, 2H, *J* = 7.44 Hz, CH), 7.44 (dd, 1H, CH), 7.28 (s, 1H, CH), 7.22 (d, 1H, *J* = 7.88 Hz, CH), 7.03 (d, 2H, *J* = 8.84 Hz, CH), 4.70 (s, 2H, -CH_2), 4.36 (t, 2H, -CH_2), 4.33 (t, 2H, -CH_2), 3.37 (t, 2H, -CH_2), 2.58 (q, 2H, -CH_2), 1.21 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 170.21, 168.59 (C_2, C=O, thiazolidinedione), 167.14 (C_5, C=O, thiazolidinedione), 165.62 (C=O), 160.10, 165.02, 159.15, 154.86, 148.34, 143.29 (=CH-), 136.58, 135.47, 131.78, 125.39, 122.91, 120.90, 115.05, 112.22, 66.97, 49.91, 45.74, 36.59, 25.06, 15.19; (m/z): 557 (M^+), 545 (M^++2); Anal. Calc. for $C_{25}H_{21}Cl_2N_5O_4S$: C, 53.77; H, 3.79; N, 12.70. Found: C, 53.79; H, 3.82; N, 12.67.

2.1.15. (E) – 5 - (4 - (2 - (5 – ethylpyridin - 2-yl) ethoxy) benzylidene) - 3 - (2 - oxo - 2 - (piperazin-1-yl)ethyl)thiazolidine-2,4-dione 6k: Yeild 60%; m.p. 165-170°C; IR (KBr, γ_{max}, cm^{-1}): 3324 (NH), 3042 (-C=CH), 1765(C=O), 1230, 1029 (C-O-C); ^{1}H NMR (DMSO, δ, ppm): 8.32 (s, 1H, CH), 7.78 (s, 1H, -C=CH), 7.49 (d, 2H, *J* = 7.41 Hz, CH), 7.43 (dd, 1H, CH), 7.21 (d, 1H, *J* = 7.84 Hz, CH), 7.01 (d, 2H, *J* = 8.84 Hz, CH), 4.69 (s, 2H, -CH_2), 4.38 (t, 2H, -CH_2), 4.32 (t, 2H, -CH_2), 3.32 (t, 2H, -CH_2), 3.42 (t, 4H, -CH_2), 2.81 (t, 4H, -CH_2), 2.59 (q, 2H, -CH_2), 1.91 (s, 1H, NH),1.18 (t, 3H, -CH_3); ^{13}C NMR (DMSO, δ, ppm): 168.65 (C_2, C=O, thiazolidinedione), 167.15 (C_5, C=O, thiazolidinedione), 164.25 (C=O), 160.11, 154.94, 152.72, 148.39, 143.32 (=CH-), 136.65, 135.52, 131.83, 125.45, 122.96, 120.93, 115.06, 66.99, 53.93, 49.91, 46.72, 45.75, 36.64, 25.07, 15.24; (m/z): 480 (M^+); Anal. Calc. for $C_{25}H_{28}N_4O_4S$: C, 62.48; H, 5.87; N, 11.66. Found: C, 62.51; H, 5.89; N, 11.69.

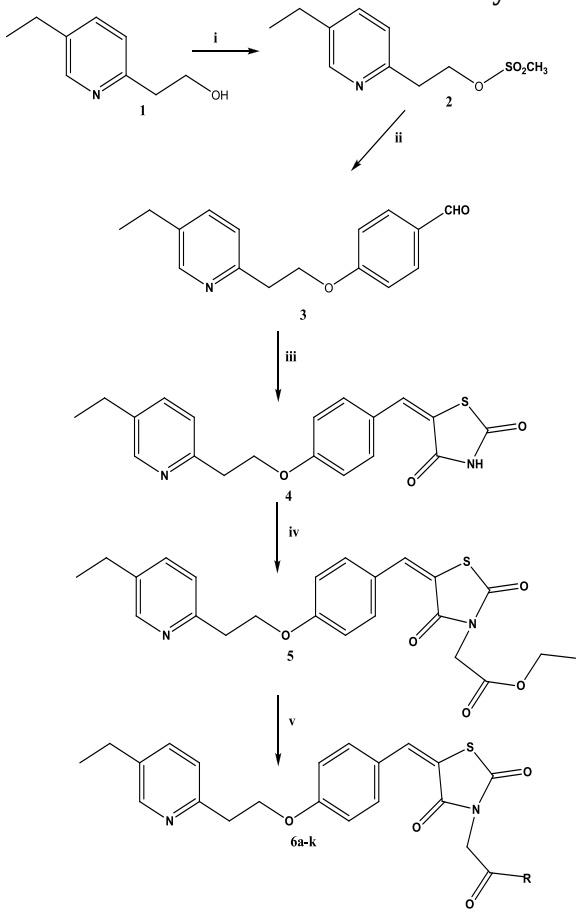
2.2. Biological assay

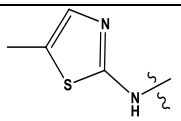
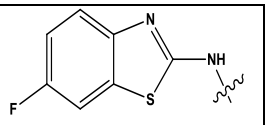
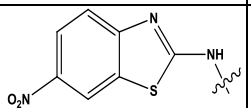
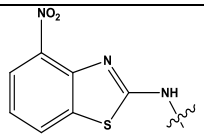
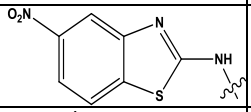
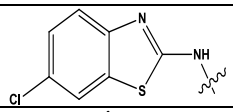
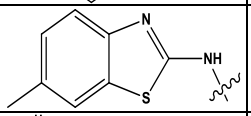
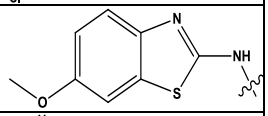
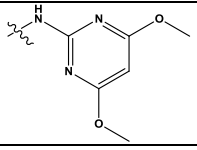
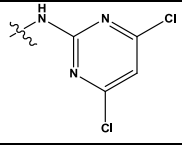
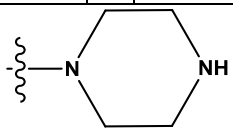
2.2.1. In *vitro* evaluation of antimicrobial activity: The MICs of synthesized compounds were carried out by broth microdilution method. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a

reduced number of colonies indicating a partial or slow Inhibition activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 µg/mL concentration, as a stock solution. In primary screening 500, 250 and 125 µg/mL concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 µg/mL concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC.

2.2.2. In *vitro* evaluation of antimycobacterial activity: Drug susceptibility and determination of MIC of the test compounds against *M. tuberculosis* $H_{37}Rv$ were performed by L. J. agar (MIC) method [27, 30] where primary 1000, 500, 250 and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25, 3.25 µg/mL dilutions of each test compound were added liquid L. J. medium and then media were sterilized by inspissation method. A culture of *M. tuberculosis* $H_{37}Rv$ growing on L. J. medium was harvested in 0.85% saline in bijou bottles. All test compound make first stock solution of 2000 µg/mL concentration of compounds was prepared in DMSO. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* $H_{37}Rv$ (5 × 104 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 12, 22 and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* $H_{37}Rv$. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. The standard strain M.tuberculosis $H_{37}Rv$ was tested with known drug Clotrimazole, Econazole and Rifampicin.

Scheme 1: Synthetic protocol for compounds 6a-k



6 a		**6 b**	
6 c		**6 d**	
6 e		**6f**	
6 g		**6 h**	
6i		**6j**	
6 k			

R=

Reagents and conditions: (i) methane sulphonyl chloride, toluene, triethylamine; (ii) 4-hydroxy benzaldehyde, ethanol, NaOH; (iii) substituted acetophenone, methanol, 2% NaOH; (iv) urea, sodium ethoxide, methanol; (v) thiourea, sodium ethoxide, methanol.

3. RESULTS AND DISCUSSION

3.1. Chemistry: Reaction of of 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde 3, thiazolidine-2,4-dione

and pyrrolidine yields (*E*)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione 4. IR spectra of 4 showed stretching band around 3580, 3051, 1742 and 1228 cm^{-1} for (NH), (-C=CH), (C=O) and (-C-O-C-). Broad ^1H NMR resonances observed for NH at δ 12.29.(*E*)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione 4 on reaction with bromoethyl acetate and K_2CO_3 yields (E) - ethyl 2- (5- (4 - (2- (5- ethylpyridin – 2 -yl) ethoxy) benzylidene) - 2, 4 – dioxothiazolidin – 3 - yl)acetate 5. IR spectra of 5 showed disappearance of stretching band at 3584 cm^{-1} for NH and lack ^1H NMR resonances at δ 12.29 for NH proves formation of compound 5. Condensation of 5 with various substituted heterocycles results in 2- (5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidine}-2, 4 - dioxo-thiazolidin-3-yl) – *N* - heterocycle-acetamide.6a-n. ^1H NMR resonances observed with NH function at 10.02 of 6a proved the condensation of 5 and 2-amino-5-methylthoazole.. This was substantiated by ^{13}C NMR data of 6a which showed a peak at δ168.12, δ167.05 and δ 165.53 due to C_2 and C_5 of thiazolidinedione and (C=O). Mass spectrum of 6a displayed a molecular ion at *m/z* 508 which confirmed its molecular weight.

3.2. Pharmacology: Antimycobacterial activity of all the synthesized compounds were accessed by L. J. method and antimicrobial activity were assessed by broth microdilution method. The minimal Inhibition Concentrations (MICs) of synthesized compounds are shown in Table 1. All the compounds were tested for their *in vitro* antibacterial activity against two gram positive bacteria (*S. aureus* MTCC 96, *S. pyogenes* MTCC 442) and two gram negative bacteria (*E. coli* MTCC 443, *P. aeruginosa* MTCC 2488). Ampicillin was used as a standard drug. The results revealed that compound 4 and 5 showed good activity against *S. aureus* and *S. pyogenes* as compared with ampicillin. Compounds 6a-k showed good activity (100-250 μg/mL)against *S. aureus* and *S. pyogenes* as compared with ampicillin except 6a and 6g (50 μg/mL) showed better activity against *S. aureus* whereas 6g (50 μg/mL) showed better activity against *S. pyogenes*. Compounds 6d, 6e, 6g, 6i (50 μg/mL) and 6b (50 μg/mL) possessed very good activity as compared with ampicillin, while other compound showed moderate activity against *E. coli*. Compound 6d and 6j possessed good activity (50-62.5 μg/mL), whereas other compound showed moderate activity as compared with ampicillin against *P. aeruginosa*.

The Minimal Inhibition Concentrations (MICs) of compounds are shown in Table 2. All the compounds were sceened for antifungal actvity against three fungal species *C. albicans*, *A. niger* and *A. clavatus*. The results showed that imidazolones 6a-k possessed good activity (100-500 μg/mL) as comapared with greseofulvin against *C. albicans* while 6c (50 μg/mL) possessed very good activity. Compounds 6a-k displayed weak activity (250-500 μg/mL) against *A. niger* and *A. clavatus* as compared with greseofluvin.

From first preliminary examination of the antimycobacterial activity results (Table 3), compound 6g containing methyl group at para position on aromatic ring of benzothiazole, showed better activity (25 μg/mL) against *M. tuberculosis* and compound 6a and 6e showef good activity (50-62.5 μg/mL). Due to the better activity against tested microorganisms and mycobacteria, compound 6g has been selected for further development and studies to acquire more information about structure activity relationships are in progress in our laboratories.

Table 1. Antibacterial activtiy of compounds 4, 5 and 6a-k.

Compound	Minimal Inhibition Concentration (MIC) (μg/mL)			
	Gram positive bacteria		Gram negative bacteria	
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*
	MTCC-96	MTCC-442	MTCC-443	MTCC-2488
4	100	100	250	125
5	125	125	100	125
6a	50	100	125	125
6b	250	100	62.5	100
6c	100	100	100	100
6d	250	100	50	50
6e	250	100	50	100
6f	125	100	100	125
6g	50	50	50	125
6h	250	125	250	250
6i	125	100	50	125
6j	100	100	125	32.5
6k	100	100	125	125
Ampicillin	250	100	100	100

Table 2. Antifungal activtiy of compounds 4, 5 and 6a-k

Compound	Minimal Inhibition Concentration (MIC) (μg/mL)		
	Fungal species		
	C. albicans	*A. niger*	*A. clavatus*
	MTCC-227	MTCC-282	MTCC-323
4	500	125	1000
5	250	250	250
6a	125	250	500
6b	250	250	500
6c	50	250	500
6d	125	250	250
6e	125	500	500
6f	125	500	1000
6g	500	1000	1000
6h	250	1000	1000
6i	100	250	500
6j	1000	250	250
6k	250	250	250
Greseofulvin	500	100	100

Table 3. Antitubercular activtiy of compounds 4, 5 and 6a-k.

Compound	MIC values (μg/mL) of *M .tuberculosis* $H_{37}Rv$	% Inhibition
4	250	96%
5	250	97%
6a	50	96%
6b	250	98%
6c	500	97%
6d	125	98%
6e	50	99%
6f	250	96%
6g	25	98%
6h	250	98%
6i	500	99%
6j	1000	98%
6k	500	99%
Clotrimazole	20.4	96%
Econazole	12.5	99%
Rifampicin	40	98%

CONCLUSION

A series of 2-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidine}-2,4-dioxo-thiazolidin-3-yl)-*N*-heterocycle-acetamide were synthesized and evaluated for antimycobacterial and antimicrobial activity. All the synthesized compounds have been established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. Compounds 6a, 6b, 6d, 6e, 6g, and 6i exhibited promising antimicrobial activity whereas compounds 6g showed very good antimycobacterial activity.

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