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Research Article

SYNTHESIS, CHARACTERISATION AND ANTI-TUBERCULAR ACTIVITY OF SOME NEW 3,5-DISUBSTITUTED-2,4-THIAZOLIDINEDIONES

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ABSTRACT

As per world health organization by 2020, the number of tuberculosis infected patients will be 25% of the world population. Now, it is challenging and essential target for medicinal chemists in drug search for tuberculosis. Hence the present work includes synthesis of a series of 3,5-disubstituted thiazolidine-2,4-dione derivatives by condensation of thiazolidine-2,4-dione with aromatic aldehydes at 5th position-Knoevenagel reaction followed by condensation of these 5-substituted thiazolidine-2,4-diones by using various aromatic and alkali halides at 3rd position yielding to 3,5-disubstituted thiazolidine-2,4-diones. The synthesized 3,5-disubstituted thiazolidine-2,4-dione compounds were characterized by IR, ^{1}H NMR, Mass spectroscopy and CHNO Elemental analysis. The synthesized compounds were predicted for biological activities by using Prediction of Activity Spectra for Substances computerized program-(*Insilico* method) based on those results the compounds were screened against *Mycobacterium tuberculosis H37RV* strain in the Middlebrook 7H9 broth by microplate alamar blue assay using Streptomycin and Pyrazinamide as standard drugs. The results revealed that among those synthesized new 3,5-disubstituted thiazolidinediones 3a, 3b, 3e and 3h were showed good antitubercular activity.

Keywords: Thiazolidine-2,4-dione, knoevenagel reaction, *Mycobacterium tuberculosis,* antitubercular activity.

INTRODUCTION

Currently, the treatment for tuberculosis diseases still remains an important and challenging problem because of emerging resistance to current regimen and also appearance of drug-resistant strains in tuberculosis like *mycobacterium tuberculosis H37RV* strain. Now, it is challenging and essential target for medicinal chemists in drug search for treatment of tuberculosis. From the literature survey reveals that 1,3-thiazolidine-2,4-dione class of chemical products were associated with interesting biological and pharmacological activities [1,2] such as antidiabetic activity[3-5], aldose reductase inhibitory activity[6,7], antimicrobial activity[8,9], anti-inflammatory activity[10], oncostatic[11], anti-cancer activity[12,13] and tuberculostatic[14]. The present work designed and developed to synthesize some new compounds with significant medicinal value. Here we reported the synthesis and characterization of various 3,5-disubstituted thiazolidine-2,4-diones. These compounds screened for their antitubercular activity against *mycobacterium tuberculosis* $H_{37}RV$.

MATERIALS AND METHODS

Melting points of the synthesized compounds were determined in an open capillary tube using digital melting point apparatus and are uncorrected. The purity of the compounds were established by thin layer chromatography by using pre-coated silica gel strips, chloroform and acetone (1:2) as solvent system and iodine vapors as visualizing agent. Infrared spectra (υ cm^{-1}) were recorded on a SHIMADZU FT-IR 4000 using KBr disks. CHNO elemental analysis carried by Perkin Elmer Series II 2400 CHNS/O Elemental analyzer. Mass spectra were obtained on JEOL GC mate II GC- Mass spectrometer at 70ev using direct insertion probe method. NMR spectra were taken on BRUKER AV400-400MHz High Resolution Multinuclear FT – NMR spectrometer by using TMS as internal standard and the solvent used was DMSO.

EXPERIMENTAL WORK

To synthesize a series of 3,5-disubstituted thiazolidine-2,4-diones, first start with the preparation of thiazolidine-2,4-dione (1) by treating chloro acetic acid with thiourea by using HCl. The synthesized thiazolidine-2,4-dione reacted with aromatic aldehydes at 5th position (Knoevenagel reaction) gives 5- substituted thiazolidine-2,4-diones (2a-c). Finally these 5-substituted thiazolidine-2,4-diones condensed by using various aromatic and alkali halides yielding to 3,5-disubstituted thiazolidine-2,4-diones (3a-i). Completion of the reactions was determined by thin layer chromatography chloroform and acetone as solvent system and iodine vapors as visualizing agent.

General procedure for the synthesis of 2,4-Thiazolidinedione (1):

Dissolve chloroacetic acid (56.5g, 0.6mol) in 30mL of water and thiourea (45.6g, 0.6mol) in 30mL of water then these solutions were mixed and the mixture was stirred for 15 min to obtain a white precipitate, accompanied by considerable cooling. Then add 30mL of conc. HCl from a dropping funnel slowly to the content of flask. After which the reaction mixture was refluxed for 10hrs. On cooling, the contents of the flask solidified into a cluster of white needles and product was filtered and washed with water to remove traces of hydrochloric acid and dried, purified by recrystallization with ethyl alcohol.

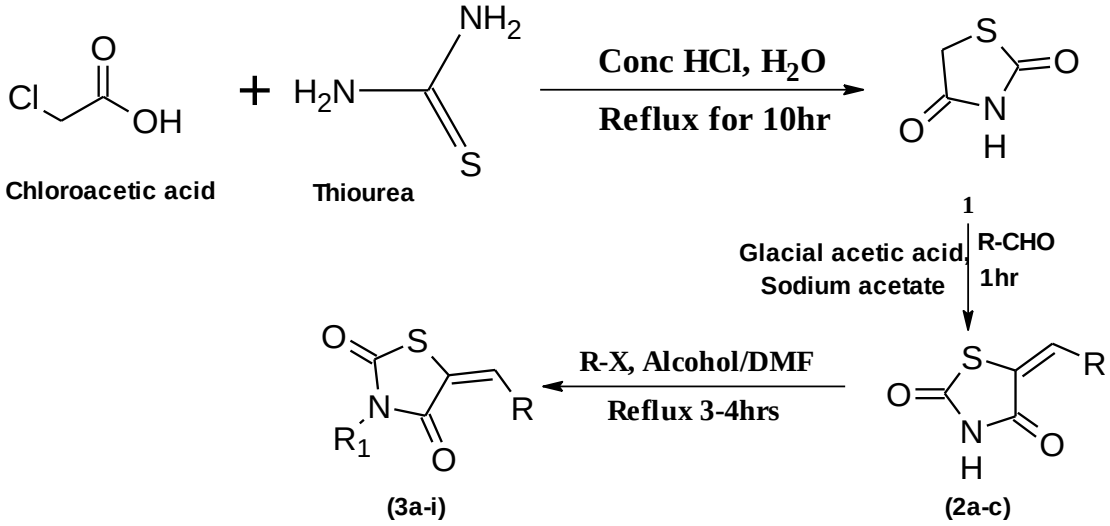
General procedure for the synthesis of 5-substituted-1,3-thiazolidine-2,4-dione (2a-c):

A mixture of 2,4-thiazolidinedione **1** (11.7g, 0.1mol), aldehyde (0.1mol), glacial acetic acid (50mL) and fused sodium acetate (1.8g) was refluxed for 1 hr with occasional shaking. Cool, then the reaction mixture was poured in water (500mL), the product obtained was filtered, washed with water, alcohol and ether and was recrystallized with glacial acetic acid. [15]

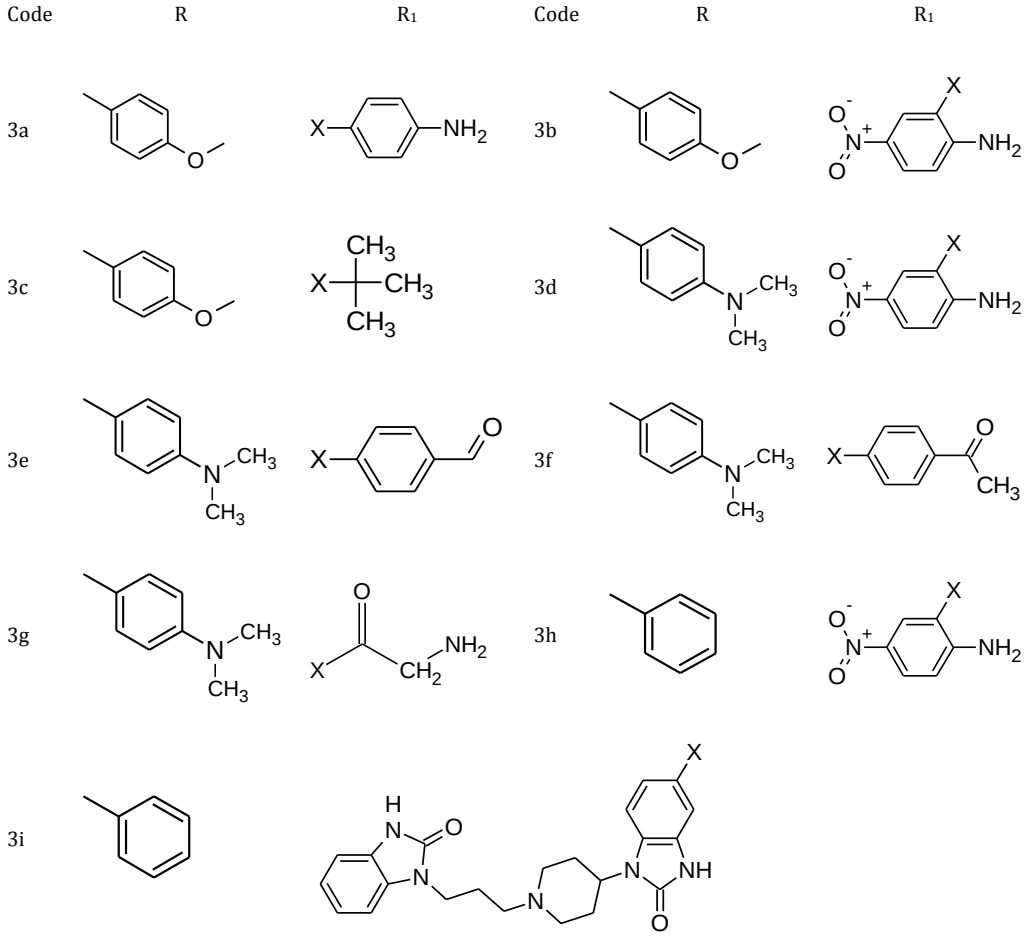
1,3-thiazolidinedione-2,4-dione 1:

Compound (**1**) analyzed for $C_3H_3O_2NS$, Yield was 93% & m.p. 123-125^{0}C. IR (υ cm^{-1}) spectrum showed characteristic bands 619.23 (C-S), 1265.46 (C-N), 1749.65 (C=O), 3356.55 (N-H), 1776.66 (CO-NH-CO).

General scheme of the work:



Various coupling components (R and R_1) in 3a-i:



Where X = Cl (3b, 3c, 3d, 3e, 3g, 3h, 3i); X = Br (3a, 3f).

5-(4-methoxybenzylidene)-1, 3-thiazolidine-2,4-dione (2a):

Compound (**2a)** analyzed for $C_3H_3O_2NS$, Yield-82% & m.p. 254-258^{0}C. IR (υ cm^{-1}) spectrum showed characteristic bands 628.87 (C-S), 1331.04 (C-N), 1751.58 (C=O), 3335.33 (N-H), 1670.56 (C=C),

1873.11 (C-H aromatic out of plane summation bands), 1251.95 (C-O), 2972.67 (C-H str), 2833.78 (C-H of OCH_3), 1466.08 (C-H def).

5-[4-(dimethyl amino)benzylidene]-1,3-thiazolidine-2,4-dione (2b):

Compound (2b**)** analyzed for $C_3H_3O_2NS$, Yield-82% & m.p 254-258^{0}C. IR (υ cm^{-1}) spectrum showed characteristic bands 626.94 (C-S), 1269.32, 1334.90 (C-N), 1724.57 (C=O), 3317.97 (N-H), 1658.98 (C=C), 1875.04 (C-H aromatic out of plane summation bands), 2968.81 (C-H str), 1433.28 (C-H def).

5-benzylidene-1,3-thiazolidine-2,4-dione (2c):

Compound (**2c)** analyzed for $C_3H_3O_2NS$, Yield-82% & m.p 254-258^{0}C. IR (υ cm^{-1}) spectrum showed characteristic bands 634.66 (C-S), 1290.53, 1334.90 (C-N), 1738.07 (C=O), 3319.90 (N-H), 1672.49 (C=C), 1846.10, 1934.84 (C-H aromatic out of plane summation bands), 3032.47 (C-H).

General procedure for the synthesis of 3,5-disubstituted-1,3-thiazolidine-2,4-dione (3a-i):

A mixture of 5-substituted-1,3-thiazolidine-2,4-dione (2.35g, 0.01mol), aromatic/alkyl halide (0.01mol) and ethanol (20mL) was refluxed for 3-4hrs at 30-40°C. Then the reaction mixture was cooled, poured in crushed ice, the solid separated was filtered, recrystallized with ethanol.[16]

3-(4-aminophenyl)-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione (3a):

Yield-78%, m.p. 275-280^{0}C; IR (υ cm-1) spectrum showed characteristic bands at 628.87 (C-S), 1307.54 (C-N), 1277.03 (aryl-O), 1458.36 (C-H def), 1734.22 (C=O), 1670.56 (C=C), 1844.17, 1902.04 (C-H aromatic out of plane summation bands), 2970.74 (C-H str), 2812.56 (C-H of OCH3); ^{1}H NMR (400MHz, DMSO) δ 3.8 (3H, s, OCH_3), δ 7.0-7.6 (8H, m, aromatic protons), δ 3.295 (2H, s, NH_2), δ 7.537 (1H, s, CH); Mass m/z 326.44; Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58; O, 14.71. Found: C, 62.58; H, 4.31; N, 8.54; O, 14.76.

3-(2-amino-5-nitrophenyl)-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione (3b):

Yield-92%, m.p. 282-286^{0}C; IR (υ cm-1) spectrum showed characteristic bands 628.87 (C-S), 1317.54 (C-N), 1278.96 (aryl-O), 1458.36 (C-H def), 1732.29 (C=O), 1670.56 (C=C), 1844.17, 1929.05 (C-H aromatic out of plane summation bands), 2970.74 (C-H str), 2808.70 (C-H of OCH_3), 1508.52 (C-NO_2); ^{1}H NMR (400MHz, DMSO) δ 3.81 (3H, s, OCH_3), δ 7.0-7.6 (7H, m, aromatic protons), δ 3.301 (2H, s, NH_2), δ 7.74 (1H, s, CH); Mass m/z 371.07; Anal. Calcd for $C_{17}H_{13}N_3O_5S$: C, 54.98; H, 3.53; N, 11.31; O, 21.54. Found: C, 54.96; H, 3.54; N, 11.29; O, 21.58.

3-tert-butyl-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione (3c):

Yield-64%, m.p. 225-230^{0}C; IR (υ cm-1) spectrum showed characteristic bands 628.87 (C-S), 1317.54 (C-N), 1394.70 (C-H def), 1732.29 (C=O), 1672.49 (C=C), 1838.39, 1965.70 (C-H aromatic out of plane summation bands), 2872.36 (C-H str), 2814.48 (C-H of OCH_3); Mass m/z 291.18; Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; O, 16.47. Found: C, 61.78; H, 5.85; N, 4.83; O, 16.44.

3-(2-amino-5-nitrophenyl)-5-[4-(dimethylamino)benzylidene]-1,3-thiazolidine-2,4-dione (3d):

Yield-88%, m.p. 305-310^{0}C; IR (υ cm-1) spectrum showed characteristic bands 640.44 (C-S), 1379.27, 1261.60 (C-N 3^0, 1^0), 1441.00 (C-H def), 1724.57 (C=O), 1626.19 (C=C), 1878.90, 1925.19 (C-H aromatic out of plane summation bands), 2959.16 (C-H str), 3497.37 (N-H), 1554.81 (C-NO_2); Mass m/z 384.10; Anal. Calcd for $C_{18}H_{10}N_4O_4S$: C, 56.24; H, 4.20; N, 14.57; O, 16.68. Found: C, 56.26; H, 4.21; N, 14.55; O, 16.68.

4-{5-[4-(dimethyl amino) benzylidene]-2,4-dioxo-1,3-thiazolidin-3-yl}benzaldehyde (3e):

Yield-74%, m.p. 268-274^{0}C; IR (υ cm-1) spectrum showed characteristic bands 626.94 (C-S), 1334.90 (C-N), 1433.28 (C-H def), 924.02 (C-H def of CHO), 1726.50 (C=O), 1658.98 (C=C), 1795.95, 1822.95 (C-H aromatic out of plane summation bands), 2972.67 (C-H str), 1689.85 (aryl-C=O); ^{1}H NMR (400MHz, DMSO) δ 3.003 (6H, s, CH_3) δ 6.7-7.7 (8H, m, aromatic protons) δ 9.659 (1H, s, CHO) δ 7.918 (1H, s, CH); Mass m/z 352.28; Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95; O, 13.62 . Found: C, 64.79; H, 4.61; N, 7.92; O, 13.60.

3-(4-acetylphenyl)-5-[4-(dimethyl amino) benzylidene]-1,3-thiazolidine-2,4-dione (3f):

Yield-77%, m.p. 272-276^{0}C; IR (υ cm-1) spectrum showed characteristic bands 644.30 (C-S), 1371.55 (C-N of 3^0), 1456.43 (C-H def of CH_3), 1740.00, 1726.50 (C=O), 1658.98 (C=C), 1865.39 (C-H aromatic out of plane summation bands), 2951.45 (C-H), 2907.08 (C-H of CH_3-CO); ^{1}H NMR (400MHz, DMSO) δ 2.979 (6H, s, CH_3) δ 6.8-7.7 (8H, m, aromatic protons) δ 2.494 (3H, s, CO-CH_3) δ 7.466 (1H, s, CH); Mass m/z 366.36; Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.55; H, 4.95; N, 7.64; O, 13.10. Found: C, 65.58; H, 4.93; N, 7.68; O, 13.08.

3-(amino acetyl)-5-[4-(dimethyl amino) benzylidene]-1,3-thiazolidine-2,4-dione (3g):

Yield-69%, m.p. 235-240^{0}C; IR (υ cm-1) spectrum showed characteristic bands 632.73 (C-S), 1336.83, 1313.68 (C-N str of 3^0, 1^0), 1458.36 (C-H def of CH_3), 1471.87 (C-H def of CH_2), 1724.57 (C=O), 1660.91 (C=C), 1844.17 (C-H aromatic out of plane summation bands), 2941.80 (C-H), 3385.48 (N-H); Mass m/z 305.02; Anal. Calcd for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; O, 15.72. Found: C, 55.12; H, 4.98; N, 13.74; O, 15.76.

3-(2-amino-5-nitrophenyl)-5-benzylidene-1,3-thiazolidine-2,4-dione (3h):

Yield-84%, m.p. 290-295^{0}C; IR (υ cm-1) spectrum showed characteristic bands 634.66 (C-S), 1317.54 (C-N), 1749.65 (C=O), 1672.49 (C=C), 1844.17, 1896.26 (C-H aromatic out of plane summation bands), 2895.50 (C-H), 3487.72 (N-H), 1491.16 (C-NO_2); ^{1}H NMR (400MHz, DMSO) δ 6.7-8.25 (8H, m, aromatic protons) δ 4.757 (2H, s, NH_2) δ 7.859 (1H, s, CH); Mass m/z 341.71; Anal. Calcd for $C_{16}H_{11}N_3O_4S$: C, 56.30; H, 3.25; N, 12.31; O, 18.75. Found: C, 56.32; H, 3.22; N, 12.29; O, 18.78.

5-benzylidene-3-(2-oxo-1-(1-(3-(2-oxo-2,3-dihydrobenzo[d]imidazol-1-yl)propyl)piperidin -4-yl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)thiazolidine-2,4-dione (3i):

Yield-54%, m.p. 335-340^{0}C; IR (υ cm-1) spectrum showed characteristic bands 632.73 (C-S), 1336.83 (C-N), 1458.36 (C-H def), 1740.00 (C=O), 1672.49 (C=C), 1871.18, 1925.19 (C-H aromatic out of plane summation bands), 2916.72 (C-H str), 3325.68 (N-H); Mass m/z 594.13; Anal. Calcd for $C_{32}H_{30}N_6O_4S$: C, 64.63; H, 5.08; N, 14.13; O, 10.76. Found: C, 64.67; H, 5.06; N, 14.12; O, 10.78.

Prediction of biological activity:

Prediction of Activity Spectra for Substances (PASS) is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. It operates with many thousands of substances from the training set, and provides more objective estimation. PASS compares the structure of a new compound with structures of well known biologically active substance and therefore it is possible to estimate if a new compound may have a particular effect. So, all the title compounds SMILES notations were entered in PASS software, among those possible biological activities the compounds showed more probability to be active for anti-inflammatory, anti-tuberculosic and antidiabetic [17]. Data presented in table 1.

Table 1: Predicted biological activities by PASS

Code	Antidiabetic		anti-inflammatory		anti-tuberculosic	
	Pa	Pi	Pa	Pi	Pa	Pi
3a	0.594	0.006	0.683	0.014	0.473	0.015
3b	0.507	0.015	0.522	0.046	0.442	0.021
3c	0.724	0.004	0.529	0.044	0.405	0.031
3d	0.476	0.019	0.683	0.014	0.473	0.015

3e	0.567	0.008	0.577	0.030	0.432	0.023
3f	0.580	0.007	0.721	0.010	0.308	0.066
3g	0.688	0.005	0.364	0.145	0.334	0.053
3h	0.535	0.011	0.519	0.047	0.440	0.021
3i	0.497	0.016	0.413	0.106	---	---

Pa = probability "to be active"; Pi = probability "to be inactive"

Antitubercular activity

The anti mycobacterial activity of synthesized compounds were assessed against *M. tuberculosis H37Rv* using Microplate Alamar Blue Assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric methods. 200µL of sterile de-ionized water was added to all outer perimeter wells of sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100µL of the Middle brook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. At the end of 5th day, 25µL of freshly prepared 1:1 mixture of Alamar blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no mycobacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink. [17]. Results were shown in table 2.

RESULTS AND DISCUSSION

In the present work, all the title compounds 3,5-disubstituted thiazolidine-2,4-diones (3a-i) were synthesized in mild conditions and yields were satisfactory. The reaction led to the expected products; however they were purified by recrystallization from suitable solvents. The synthesized compounds were characterized by IR, ^{1}H NMR, Mass and elemental analysis. Then antitubercular activity of the synthesized compounds was screened against *Mycobacterium tuberculosis H37RV* strain.

Table 2: Anti-tubercular activity of synthesized compounds (3a-i)

Compound code	MIC µg/mL
3a	12.5
3b	12.5
3c	25
3d	50
3e	12.5
3f	25
3g	25
3h	12.5
3i	50
Pyrazinamide	3.125
Streptomycin	6.25

From the results of the anti-tubercular activity revealed that the synthesized 3,5-disubstituted thiazolidine-2,4-diones exhibited activity at concentrations ranging from 12.5 to 100µg/mL. It is clear from the results that the substitution at 3rd position i.e., at N atom in thiazolidinedione by arylation may exhibit marked activity and having electron releasing groups like dimethyl amino and methoxy groups at para position of benzylidene at 5th position of the thiazolidinediones may also enhance the activity. In particular, compounds **3a, 3b, 3e** and **3h** having substituted phenyl rings with amino, aldehyde and nitro groups showed more activity (12.5µg/mL). Rest of the compounds exhibited moderate to mild activity. Our findings may have an impact on further investigations in this field in search of potent antitubercular agents.

CONCLUSION

In the present study, some new 3,5-disubstituted thiazolidinedione derivatives were synthesized, characterized by IR, ^{1}H NMR, Mass spectroscopy and CHNO Elemental analysis. All the synthesized compounds show characteristic absorption peaks in IR and NMR spectra.

The synthesized compounds were evaluated for anti-tubercular activity by Microplate alamar blue assay (MABA). The results revealed that the synthesized new 3,5-disubstituted thiazolidinediones showed good anti-tubercular activity having electron releasing groups like dimethyl amino and methoxy groups at para position of phenyl rings at 5th position exhibited relatively marked activity and also N-arylation shows better activity. The study revealed the necessity of synthesizing many more compounds having other electron releasing substituents. Such compounds may emerge as much more potent anti-tubercular agents.

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