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Design and Synthesis of Novel Antimicrobial and Antitubercular 4-thiazolidinones

Nirali S. Mewada
Department of Chemistry, Government Science College, Gandhinagar, Gujarat, India

ABSTRACT

A series of new 4-thiazolidinone derivatives was designed, synthesized and screened for their antimicrobial activity and antitubercular activity. The structures of the compounds were elucidated with the aid of IR, 1H NMR, mass spectroscopy, and elemental analysis. The antimicrobial activity of the compounds was tested against four bacterial strains (Staphylococcus aureus MTCC 443 and Staphylococcus pyogenus MTCC 443, Escherichia coli MTCC 442 and Pseudomonas aeruginosa MTCC 443) and three fungal strains (Candida albicans MTCC 227, Aspergillus niger MTCC 282, Aspergillus clavatus MTCC 1323). The title compounds were also investigated for their antitubercular activity against M. tuberculosis H37Rv (MTCC 200) strain using L. J. agar dilution method.

Keywords : 4-Thiazolidinones, Antimicrobial Activity, Antitubercular Activity

I. INTRODUCTION

A widespread medical problem of advanced occurrence of opportunistic microbial infections originated by multidrug-resistant microorganisms. Stringent morbidity and transience in injured and resistance compromised patients is most commonly caused by such infections [1]. Such infections most frequently influence resistance compromised individuals, patients with malignancies, and transplant recipients. Moreover, with a signal of around two million deaths each year, TB remains a severe epidemiological crisis, set up chiefly in the pulmonary system, and is caused by some mycobacteria of the Mycobacterium tuberculosis complex, chiefly Mycobacterium tuberculosis [2]. According to the World Health Organization, in 2010, there were 8.8 million happening cases of TB, 1.1 million deaths from TB among HIV-negative people, and further 0.35 million deaths from HIV-associated TB [3]. These particulars additionally highlight the imperative inevitability to find novel effectual and secure compounds to sustain and get better the running, avoidance of opportunistic microbial and tubercular infections in a new period of severe infectious disease control, removal, and abolition.

4-thiazolidinone derivatives are implicated in a variety of biological applications, such as antimicrobial [4], anticancer [5], Antimalarial [6], and antiviral [7], fungicidal [8], antitubercular [9] agents. Several workers functionalized 4-thiazolidinone derivatives with respective aldehydes and evaluated their biological profile. Based on these facts and in continuation of our research on the synthesis of new bioactive scaffolds [10], we have synthesized novel 4-thiazolidinones as the bioactive heterocyclic ring with the expectation of enhanced biological activity of the molecule.

II. METHODS AND MATERIALS

All reagents were of analytical grade and used directly. All the melting points were determined in

open glass capillary and are uncorrected. Progress of reaction was monitored by thin layer chromatography (TLC) using silica gel-G coated aluminium plates (0.5 mm thickness, Merck) and spots were visualized under UV radiation. The synthesized compounds were purified by recrystallization and/or column chromatography. The IR spectra were recorded on BRUKER TENSOR Series using KBr pellets. ^{1}H NMR spectra were recorded on 300 MHz BRUKER ULTRASHIELD using DMSO-d_6 as a solvent and TMS as an internal reference and chemical shift values were expressed in δ ppm.

Preparation of 2-chloro-4-(4-cyano-phenylamino)-5-nitro-benzoic acid (3)

A mixture of compound **2** (10 g, 0.0423 mol) and 4-amino-benzonitrile (5.6 g, 0.0423 mol) in DMF (20 ml) in the presence of K_2CO_3 (5.8 g, 0.0423 mol) was stirred at room temperature for 1 h. The temperature was gradually raised to 80-90°C and refluxed for 2-3 h. The progress of reaction was monitored by TLC using hexane: acetone (8:2) as eluent. After the completion of reaction, the reaction mixture was dumped in to water. The solid product obtained was filtered, dried and crystallized from acetone to get the title compound. M.P: 85-90 °C

3.3 Preparation of 4-(4-cyano-phenylamino)-2-(4-*N*-methyl-piperazin-1-yl)-5-nitro- benzoic acid (4)

To a stirred solution of compound **3** (10 g, 0.0299 mol) in DMF (20 ml), 1-methyl-piperazine (5.5 ml, 0.0599 mol) in DMF (10 ml), CS_2CO_3 (2.0 g) was added and refluxed for 6-8 h at 80 °C. The pH was adjusted to neutral by the dropwise addition of CS_2CO_3 solution. The progress of reaction was monitored by TLC using toluene: ethyl acetate (6:4) as eluent. After the completion of reaction it was dumped to crushed ice. The solid product obtained was filtered, dried and crystallized from ethyl acetate to get the title compound. M.P: 70-75 °C.

3.4. Preparation of 5-amino-4-(4-cyano-phenylamino)-2-(-4-N-methyl-piperazin-1-yl)-benzoic acid (5)

Compound **4** (8.0 g, 0.0209 mol) was suspended in water (10 ml) containing acetic acid (2.6 ml, 0.0418 mol) at 70 °C and Iron dust (2.3 g, 0.0418 mol) in ethanol (4.7 ml, 0.0836 mol) was added portion wise. The progress of reaction was monitored by TLC using toluene: methanol (6:4) as eluent. After the completion of reaction, the refluxed content was poured into crushed ice. The solid product obtained was filtered and dried. The crude product was purified by crystallization from ethanol to get the title compound. M.P: 110 -112 °C.

3.5. Preparation of 5-(benzylidene-amino)-4-(4-cyano-phenylamino)-2-(4-*N*-methyl-piperazin-1-yl)-benzoic acid (6a-6j)

To a well-stirred solution of Compound **5** (10.0 g, 0.0284 mol) in ethanol (20 ml), Substituted benzaldehyde (6.2 ml, 0.0568 mol) and acetic acid (1.0 ml) was added. The reaction mixture was refluxed for 4 h at 70-80 °C. The progress of reaction was monitored by TLC using toluene:acetone (8:2) as eluent. After the completion of reaction, the refluxed content was dumped in to water. The pH was adjusted to neutral. The crude product was purified by crystallization from ethanol to get the title compound. M.P: 180-200 °C.

3.6. Preparation of 4-(4-cyano-phenylamino)-2-(4-methyl-piperazin-1-yl)-5-(4-oxo-2-substituted phenyl-thiazolidin-3-yl)-benzoic acid (7a-7j)

A mixture of Compounds **(6a-6j)** (10 g, 0.0227 mol), thioglycolic acid (5.4 ml, 0.0454 mol) in DMF (20 ml) and anhydrous zinc chloride (6.0 g, 0.0454 mol) was refluxed for 6-8 h. The progress of reaction was monitored by TLC using hexane: ethyl acetate (8:2) as eluent. After the completion of reaction it was poured in to crushed ice. The product obtained was washed with $NaHCO_3$ to remove unreacted acid, filtered,

dried and recrystallized from ethanol to get the title compounds.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(4-oxo-2-phenylthiazolidin-3-yl)benzoic acid (7a)

^{1}H NMR: 2.85 (s, 3H), 2.93 (t, 4H), 3.04 (t, 4H), 4.02 (s, 2H), 4.51 (s, 1H), 5.49 (s, 1H), 6.89-7.66 (m, 11H), 9.46 (s, 1H). **IR (KBr cm^{-1}):** 3420 (-OH), 3256 (-NH), 3067 (-CH), 2961-2856 (-CH), 1712, 1675 (-2CO), 1615 (-C-N), 725 (-C-S). **MS (m/z):** 514.02 (M^+). **Anal. Calcd. For** $C_{28}H_{27}N_5O_3S$: C, 65.41; H, 5.25; N, 13.62, **Found:** C, 65.36; H, 5.22; N, 13.59, **m.p.** 162 ˚C, **Yield:** 70 %.

5-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (7b)

^{1}H NMR: 2.82 (s, 3H), 2.94 (t, 4H), 3.06 (t, 4H), 3.99 (s, 2H), 4.55 (s, 1H), 5.42 (s, 1H), 6.81-7.64 (m, 10H), 9.40 (s, 1H). **IR (KBr cm^{-1}):** 3424 (-OH), 3252 (-NH), 3069 (-CH), 2969-2859 (-CH), 1710, 1675 (-2CO), 1611 (-C-N), 823 (C-Cl), 724 (-C-S). **MS (m/z):** 548.92 (M^+). **Anal. Calcd. For** $C_{28}H_{26}ClN_5O_3S$: C, 61.40; H, 4.75; N, 12.79, **Found:** C, 61.44; H, 4.72; N, 12.76, **m.p.** 155 ˚C, **Yield:** 65 %.

5-(2-(3-chlorophenyl)-4-oxothiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (7c)

^{1}H NMR: 2.80 (s, 3H), 2.93 (t, 4H), 3.05 (t, 4H), 4.10 (s, 2H), 4.57 (s, 1H), 5.44 (s, 1H), 6.85-7.65 (m, 10H), 9.41 (s, 1H). **IR (KBr cm^{-1}):** 3429 (-OH), 3250 (-NH), 3065 (-CH), 2963-2855 (-CH), 1717, 1671 (-2CO), 1613 (-C-N), 821 (C-Cl), 728 (-C-S). **MS (m/z):** 549.12 (M^+). **Anal. Calcd. For** $C_{28}H_{26}ClN_5O_3S$: C, 61.40; H, 4.71; N, 12.79, **Found:** C, 61.42; H, 4.69; N, 12.81, **m.p.** 151 ˚C, **Yield:** 56 %.

5-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)benzoic acid (7d)

^{1}H NMR: 2.80 (s, 3H), 2.91 (t, 4H), 3.11 (t, 4H), 4.08 (s, 2H), 4.53 (s, 1H), 5.47 (s, 1H), 6.80-7.62 (m, 11H), 9.43 (s, 1H). **IR (KBr cm^{-1}):** 3424 (-OH), 3258 (-NH), 3061 (-CH), 2971-2853 (-CH), 1718, 1670 (-2CO), 1622 (-C-N), 825 (C-Cl), 720 (-C-S). **MS (m/z):** 549.10 (M^+). **Anal. Calcd. For** $C_{28}H_{26}ClN_5O_3S$: C, 61.40; H, 4.75; N, 12.79, **Found:** C, 61.38; H, 4.71; N, 12.82, **m.p.** 144 ˚C, **Yield:** 62 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(4-oxo-2-o-tolylthiazolidin-3-yl)benzoic acid (7e)

^{1}H NMR: 2.32 (s, 3H), 2.89 (s, 3H), 2.98 (t, 4H), 3.08 (t, 4H), 4.07 (s, 2H), 4.55 (s, 1H), 5.49 (s, 1H), 6.75-7.72 (m, 10H), 9.53 (s, 1H). **IR (KBr cm^{-1}):** 3432 (-OH), 3257 (-NH), 3069 (-CH), 2966-2858 (-CH), 1710, 1675 (-2CO), 1611 (-C-N), 720 (-C-S). **MS (m/z):** 528.76 (M^+). **Anal. Calcd. For** $C_{29}H_{29}N_5O_3S$: C, 65.95; H, 5.49; N, 13.26, **Found:** C, 65.90; H, 5.45; N, 13.24, **m.p.** 147 ˚C, **Yield:** 70 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(4-oxo-2-m-tolylthiazolidin-3-yl)benzoic acid (7f)

^{1}H NMR: 2.29 (s, 3H), 2.82 (s, 3H), 2.96 (t, 4H), 3.05 (t, 4H), 4.11 (s, 2H), 4.50 (s, 1H), 5.41 (s, 1H), 6.71-7.80 (m, 10H), 9.51 (s, 1H). **IR (KBr cm^{-1}):** 3443 (-OH), 3253 (-NH), 3064 (-CH), 2963-2858 (-CH), 1706, 1673 (-2CO), 1613 (-C-N), 721 (-C-S). **MS (m/z):** 528.40 (M^+). **Anal. Calcd. For** $C_{29}H_{29}N_5O_3S$: C, 65.95; H, 5.49; N, 13.26, **Found:** C, 65.92; H, 5.52; N, 13.23, **m.p.** 159 ˚C, **Yield:** 64 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(4-oxo-2-p-tolylthiazolidin-3-yl)benzoic acid (7g)

^{1}H NMR: 2.34 (s, 3H), 2.81 (s, 3H), 2.98 (t, 4H), 3.09 (t, 4H), 4.09 (s, 2H), 4.51 (s, 1H), 5.47 (s, 1H), 6.69-7.78 (m, 10H), 9.51 (s, 1H). **IR (KBr cm^{-1}):** 3433 (-OH), 3252 (-NH), 3068 (-CH), 2967-2853 (-CH), 1701, 1676 (-2CO), 1613 (-C-N), 720 (-C-S). **MS (m/z):** 528.56 (M^+). **Anal. Calcd. For** $C_{29}H_{29}N_5O_3S$: C, 65.95; H, 5.49; N, 13.26, **Found:** C, 65.91; H, 5.50; N, 13.22, **m.p.** 146 ˚C, **Yield:** 54 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)benzoic acid (7h)

^{1}H NMR: 2.85 (s, 3H), 2.93 (t, 4H), 3.04 (t, 4H), 4.02 (s, 2H), 4.51 (s, 1H), 5.49 (s, 1H), 6.89-7.66 (m, 11H), 9.46 (s, 1H). **IR (KBr cm^{-1}):** 3420 (-OH), 3256 (-NH), 3067 (-CH), 2961-2856 (-CH), 1712, 1675 (-2CO), 1615 (-C-N), 1553, 1372 (N-O), 725 (-C-S). **MS (m/z):** 559.85 (M^+). **Anal. Calcd. For** $C_{28}H_{26}N_6O_5S$: C, 60.14; H, 4.65; N, 15.03, **Found:** C, 60.10; H, 4.61; N, 15.01, **m.p.** 141 ˚C, **Yield:** 69 %.

4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)benzoic acid (7i)

^{1}H NMR: 2.81 (s, 3H), 2.91 (t, 4H), 3.05 (t, 4H), 4.06 (s, 2H), 4.58 (s, 1H), 5.42 (s, 1H), 6.81-7.60 (m, 11H), 9.42 (s, 1H). **IR (KBr cm^{-1}):** 3424 (-OH), 3258 (-NH), 3065 (-CH), 2970-2858 (-CH), 1715, 1670 (-2CO), 1610 (-C-N), 1551, 1371 (N-O), 723 (-C-S). **MS (m/z):** 559.93 (M^+). **Anal. Calcd. For** $C_{28}H_{26}N_6O_5S$: C, 60.14; H, 4.65; N, 15.04, **Found:** C, 60.17; H, 4.62; N, 15.06, **m.p.** 149 ˚C, **Yield:** 63 %.

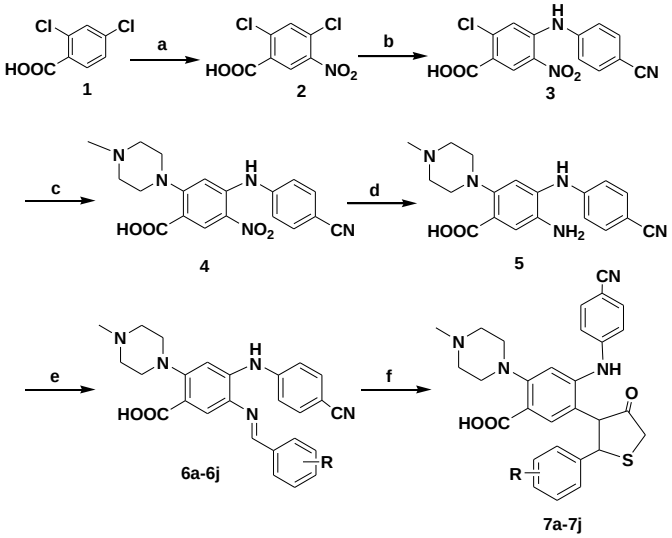
4-(4-cyanophenylamino)-2-(4-methylpiperazin-1-yl)-5-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)benzoic acid (7j)

^{1}H NMR: 2.83 (s, 3H), 2.93 (t, 4H), 3.06 (t, 4H), 4.09 (s, 2H), 4.58 (s, 1H), 5.40 (s, 1H), 6.82-7.64 (m, 11H), 9.43 (s, 1H). **IR (KBr cm^{-1}):** 3423 (-OH), 3254 (-NH), 3063 (-CH), 2972-2855 (-CH), 1717, 1674 (-2CO), 1613 (-C-N), 1552, 1375 (N-O), 721 (-C-S). **MS (m/z):** 559.74 (M^+). **Anal. Calcd. For** $C_{28}H_{26}N_6O_5S$: C, 60.14; H, 4.65; N, 15.04, **Found:** C, 60.11; H, 4.63; N, 15.05, **m.p.** 143 ˚C, **Yield:** 58 %.

III. RESULTS AND DISCUSSION

Chemistry

The synthesis of compounds **7a-7j** is outlined in the **Scheme 1**. 2, 4-dichloro-5-nitro-benzoic acid **(2)** was prepared by nitration of 2, 4-dichloro benzoic acid **(1)** with concentrated HNO_3 and H_2SO_4. Refluxed **(2)** with 4-amino-benzonitrile in DMF using K_2CO_3 affords 2-chloro-4-(4-cyano-phenylamino)-5-nitro-benzoic acid **(3)**. Treatment of compound **(3)** with 1-methyl-piperazine in DMF yielded the 4-(4-cyano-phenylamino)-2-(4-N-methyl-piperazin-1-yl)-5-nitro- benzoic acid **(4)**. Reaction of compound **(4)** with Fe in acetic acid in ethanol yieled 5-amino-4-(4-cyano-phenylamino)-2-(-4-N-methyl-piperazin-1-yl)-benzoic acid **(5)**. Compound **(5)** reacted with various substituted benzaldehydes in presence of acetic acid to form 5-(benzylidene-amino)-4-(4-cyano-phenylamino)-2-(4-N-methyl-piperazin-1-yl)-benzoic acid **(6a-6j)**. Cyclisation of compounds **(6a-6j)** with thioglycolic acid in DMF yielded 4-(4-cyano-phenylamino)-2-(4-methyl-piperazin-1-yl)-5-(4-oxo-2-substituted phenyl-thiazolidin-3-yl)-benzoic acid **(7a-7j)**.



Scheme 1. Synthesis of the title compounds. (a) HNO_3/H_2SO_4, 0-5 ℃ (b) 4-Aminobenzonitrile, K_2CO_3, DMF, 100 ℃ (c) 1-Methyl Piperazine, CS_2CO_3, 100 ℃ (d) Fe/CH_3COOH, Ethanol, 80 ℃ (e) Substituted aryl benzaldehydes, Ethanol, 70 ℃ (f) Thioglycolic acid, Anhydrous $ZnCl_2$, DMF

Biological Evaluation

Antibacterial Activity

The minimum inhibitory concentration (MIC) of the synthesized compound were tested against two representative Gram-positive (*Staphylococcus aureus* MTCC 443 and *Staphylococcus pyogenus* MTCC 443)

and two Gram-negative (*Escherichia coli* MTCC 442 and *Pseudomonas aeruginosa* MTCC 443) and assayed *in vitro* using broth micro dilution method by standards gradual dilution starting from (250, 200, 125, 100, 50, 25, 12.5, 6.25, 3.125) µg/mL.

Ciprofloxacin and Chloramphenicol were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The *in vitro* results of the antibacterial activity of the newly synthesize compounds are presented in **Table 1**.

The antibacterial potency of the synthesized compounds was compared with broad spectrum antibiotics, Ciprofloxacin & Chloroamphenicol. From the table, it is observed that some of the compounds displayed moderate to good antibacterial activity in the range of 62.5-125 µg/ml.

Table 1. Antibacterial activity of title compounds.

Compd.	ANTIBACTERIAL ACTIVITY TABLE				
	MINIMUM INHIBITORY CONCENTRATION				
	-R	*E.c* µg/ml	*P.a* µg/ml	*S.a*µg/ml	*S.p* µg/ml
7a	-H	250	250	100	125
7b	2-Cl	250	200	125	100
7c	3-Cl	200	125	100	250
7d	4-Cl	125	100	250	250
7e	2-CH_3	100	200	200	200
7f	3-CH_3	200	250	125	200
7g	4-CH_3	100	250	200	125
7h	2-NO_2	250	62.5	250	62.5
7i	3-NO_2	500	500	200	200
7j	4-NO_2	100	500	250	125
Ciprofloxacin		25	25	50	50
Chloramphenicol		50	50	50	50

Antifungal Activity

The minimum inhibitory concentration (MIC) of the synthesized compound was tested against fungi (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323) and assayed *in vitro* using broth micro dilution method standards with gradual dilution starting from (250, 200, 125,100, 50, 25, 12.5, 6.25, 3.125) µg/mL. Nystatin and Griseofulvin were used as reference antibacterial agents. Solution of the test compounds and reference drugs were dissolved in DMSO. The *in vitro* results of the antifungal activity of the newly synthesized compounds are presented in **Table 2**.

The antifungal activity results shows that halogen and methyl substituted analogs 7b and 7f appeared with high efficacy against *C.albicans* and *A.clavatus* at 100 µg/ml MIC level.

Table 2. Antifungal activity of title compounds

Compd.	ANTIFUNGAL ACTIVITY TABLE			
	MINIMUM INHIBITORY CONCENTRATION			
	-R	*C.a.* µg/ml	*A.n.* µg/ml	*A.c.* µg/ml
7a	-H	500	>1000	1000
7b	2-Cl	100	1000	100
7c	3-Cl	1000	200	500
7d	4-Cl	250	500	500
7e	2-CH_3	500	1000	1000
7f	3-CH_3	100	500	250
7g	4-CH_3	250	1000	>1000
7h	2-NO_2	500	500	>1000
7i	3-NO_2	250	500	>1000
7j	4-NO_2	200	250	250
Nystatin		100	100	100
Griseofulvin		500	100	100

Antitubercular Activity

Antitubercular screening of compounds 7a-7j was performed against *M. tuberculosis* H37Rv by using

Lowenstein–Jensen medium (conventional method). A primary screen was conducted at primary dilution 6.25 lg/ml against M.tuberculosis H37Rv, where 6.25 lg/ml of each test compound were added to liquid Lowenstein–Jensen Medium and then media were sterilized by inspissations method. A culture of M. tuberculosis H37Rv growing on Lowenstein–Jensen Medium was harvested in 0.85 % saline in bijou bottles. DMSO was used as vehicle to get desired concentration. These tubes were then incubated at 37 °C for 24 h followed by streaking of M.tuberculosis H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37 °C. The drugs found active in primary screening were similarly diluted to obtain 200, 100, 50, 25, 12.5, 6.25, and 3.50 lg/ml concentrations. The antitubercular activity data were compared with the standard drug Isoniazid. The *in vitro* results of the antituberculosis activity of the newly synthesized 20 compounds are presented in **Table 3**. The result shows that compounds 7d containing chloro at fourth position of phenyl ring exhibited excellent antituberculosis activity.

Table 3 Antitubercular activity of the synthesized compounds

Compd. No.	MINIMUM INHIBITORY CONCENTRATION	
	-R	*M.tuberculosis* H37Rv MTCC 200 µg/ml
7a	-H	250
7b	2-Cl	500
7c	3-Cl	200
7d	4-Cl	62.5
7e	2-CH_3	250
7f	3-CH_3	500
7g	4-CH_3	500
7h	2-NO_2	100
7i	3-NO_2	250
7j	4-NO_2	250
Isoniazid		0.2

IV. CONCLUSION

A new series of 4-thiazolidinones was designed, synthesized and screened for antimicrobial and antitubercular activity. The compounds showed good to moderate antimicrobial and antitubercular activity. It can be concluded that these compounds represent new structural scaffolds which can be further optimized for future development of more potent and selective antimicrobial & antitubercular agents.

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