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Research Article

Synthesis and Antitubercular Activity of Some Novel Thiazolidinone Derivatives

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Abstract

***Purpose**: To synthesize and characterize novel thiazolidinone derivatives and screen them for antitubercular activity.*
***Methods:** A series of twelve novel thiazolidinones **4a-l** have been synthesized by cyclocondensation of various Schiff bases of amino thiadiazole with thioglycollic acid. Various Schiff bases **3a-l** were synthesized by condensation of 2-amino-5-aryl-5H-thiazolo[4,3-b]-l,3,4-thiadiazole with various aryl aldehydes. The synthesized compounds were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry. Docking studies were carried out for the synthesized compounds which were also evaluated for in vitro anti-tubercular activity at a concentration of 0.1 – 100.0 µg/mL by Microplate Blue Alamar Assay method. Pyrazinamide and streptomycin were used as standard antitubercular agents.*
***Results:** The synthesized compounds showed good docking score, compared to standard drugs. Two of the compounds (labelled **4f** and **4i**) showed higher antitubercular activity than the standards (pyrazinamide and streptomycin) while compounds four others compounds (labeled **4b, 4c, 4e, 4h, 4k** and **4l**) showed comparable activity to pyrazinamide but greater activity than streptomycin.*
***Conclusion:** We report the successful synthesis of novel thiazolidinones, as well as their spectral characterization, docking properties and in vitro antitubercular activities which, for some, are superior to currently used anti-tubercular agents.*

***Keywords:** Thiadiazole, Schiff base, Thiazolidinone, Anti-tubercular activity, Docking*

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INTRODUCTION

Despite the ready availability of effective treatments, tuberculosis remains a major public health threat worldwide. The emergence of drug-resistant strains of *Mycobacterium tuberculosis*, particularly multiple drug resistant strains [1-4], has complicated treatment protocols and raises the concern that tuberculosis may once again become an incurable disease. For this reason, it is critical to discover new drugs acting with a mechanism different from those presently in use.

Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties. Among this type of molecules, 1,3,4-thiadiazoles and 4-thiazolidinones were shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, tuberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti-inflammatory and analgesic properties [5-12].

In order to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of heterocycles by incorporating thiadiazole and thiazolidinone moieties in a single molecular framework. The present work deals with the synthesis of these compounds as well as their anti-tubercular screening.

EXPERIMENTAL

Materials

Analytical grade solvents and commercially available reagents were used without further purification. All chemicals were obtained from Spectrochem Ltd (Mumbai, India). Column chromatography was carried out over silica gel (60 - 120 mesh), purchased from Sisco Research Laboratories Pvt Ltd. Mumbai, India. Melting point was determined in a programmable melting point apparatus (Servewell Instruments Pvt Ltd). Fourier transform infrared spectroscopy (FTIR) in KBr disk were recorded from 4000 to 400 cm^{-1} on a Shimadzu FT-IR spectrometer (model no. 00518). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on AMX 400-MHz and 500-MHz Bruker spectrometer in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS while the coupling constants are given in Hz. Mass spectra were recorded using Agilent 1100 MSD spectrometer in electrospray mode.

Synthesis

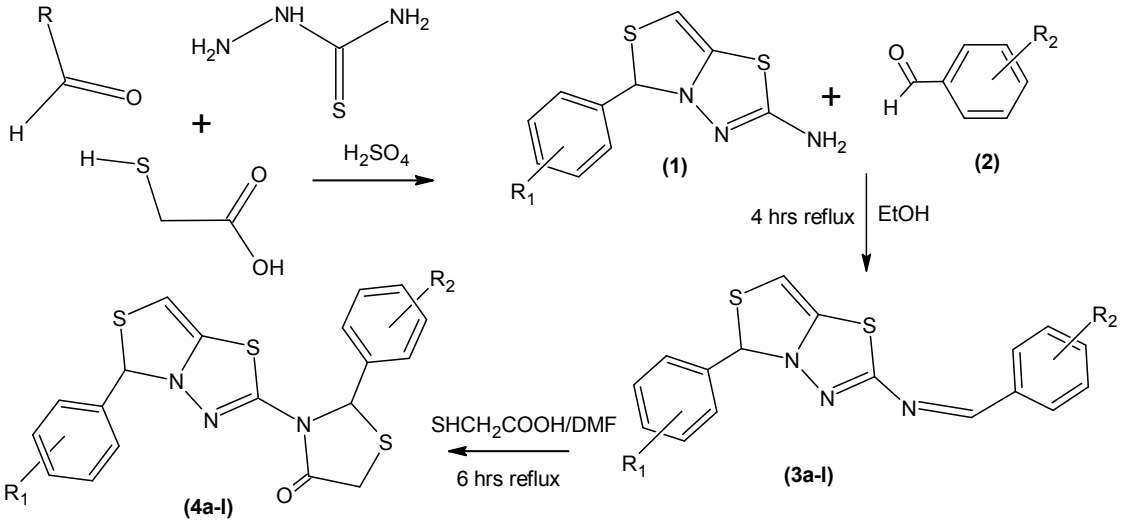
All the compounds were synthesized according to the scheme shown in Figure 1. The purity of the compounds was determined on TLC plates using silica gel G as a stationary phase and iodine vapor as visualizing agent.

Preparation of 2-amino-5-aryl-5H-thiazolo[4,3-b]-l,3,4-thiadiazole (1)

2-amino-5-aryl-5H-thiazolo[4,3-b]-l,3,4-thiadiazoles were prepared according to the procedure reported in the literature [13]. An aromatic aldehyde (0.02M) and thioglycolic acid (0.02M) were mixed, and after 10-15 min. Thiosemicarbazide (0.022M) was added; then 10 mL of concentrated H_2SO_4 was added in portions upon cooling. The mixture was homogenized and left for 18 - 24 h at -20 °C. The reaction mass was treated with 30 - 50 g ice, the precipitated solid decanted, water added, and the resulting suspension neutralized with 40 % NaOH solution. The synthesized compound was recrystallized from aqueous dioxane solution.

General procedure for the synthesis of compounds 3a-3l

To a stirred solution of compound 1(0.01M) in ethanol (50 ml) containing sulphuric acid (2 ml) was added appropriate aromatic aldehyde (0.01M) and the mixture refluxed for



R_1= -H, R_2= -H, (4a)
R_1= -H, R_2= 2-Cl, (4b)
R_1= -H, R_2= 4-Cl, (4c)
R_1= 4-CH_3, R_2= H, (4d)
R_1= 4-CH_3, R_2= 2-CH_3, (4e)
R_1= 4-CH_3, R_2= 4-CH_3, (4f)
R_1= 4-OH, R_2= -H, (4g)
R_1= 4-OH, R_2= 2-OH, (4h)
R_1= 4-OH, R_2= 4-OH, (4i)
R_1= 4-$N(CH_3)_2$, R_2= H, (4j)
R_1= 4-$N(CH_3)_2$, R_2= 2-OCH_3, (4k)
R_1= 4-$N(CH_3)_2$, R_2= 4-OCH_3, (4l)

R_1= -H, R_2= -H, (3a)
R_1= -H, R_2= 2-Cl, (3b)
R_1= -H, R_2= 4-Cl, (3c)
R_1= 4-CH_3, R_2= H, (3d)
R_1= 4-CH_3, R_2= 2-CH_3, (3e)
R_1= 4-CH_3, R_2= 4-CH_3, (3f)
R_1= 4-OH, R_2= -H, (3g)
R_1= 4-OH, R_2= 2-OH, (3h)
R_1= 4-OH, R_2= 4-OH, (3i)
R_1= 4-$N(CH_3)_2$, R_2= H, (3j)
R_1= 4-$N(CH_3)_2$, R_2= 2-OCH_3, (3k)
R_1= 4-$N(CH_3)_2$, R_2= 4-OCH_3, (3l)

Fig 1: Synthesis of novel thiazolidinone derivatives 4a-4l

4 - 6 h on a water bath. The separated solid was filtered and recrystallized from ethanol to give compounds **3a-3l**.

General procedure for the synthesis of compounds 3a-3l

To a stirred solution of compound 1(0.01M) in ethanol (50 ml) containing sulphuric acid (2 ml) was added appropriate aromatic aldehyde (0.01M) and the mixture refluxed for 4 - 6 h on a water bath. The separated solid was filtered and recrystallized from ethanol to give compounds **3a-3l**.

General procedure for the synthesis of compounds 4a-4l

To a stirred solution of the particular 5-phenyl-N-[(substituted) phenylmethylene][1,3] thiazolo[4,3-b][1,3,4]thiadiazol-2-amine (Schiff base **3a-l**, 0.01M) and thioglycollic acid (0.01M) in DMF (30 ml). The reaction mixture refluxed for 6 h and the solid obtained after removal of the solvent was crystallized from benzene to give compounds 4a-4l.

Evaluation of anti-tubercular activity

The antimycobacterial activity of the synthesized compounds **3a-l** and **4a-l** were

assessed against M. tuberculosis $H_{37}Rv$ (ATCC 2729411) using the Microplate Alamar Blue Assay (MABA) [14,15]. This methodology is non-toxic, uses thermally stable reagent, and shows good correlation with proportional and BACTEC radiometric methods [16], The activity was expressed as minimum inhibitory concentration (MIC) in µg/mL. The drug concentration tested were in the range 0.1 – 100.0 µg/mL. A blue color in the well was interpreted as absence of bacterial growth, and pink color was scored as growth. MIC (minimal inhibition concentration) was defined as the lowest drug concentration, which prevented a color change from blue to pink. Streptomycin and pyrazinamide were used as reference standards.

Data analysis

Docking was carried out for the synthesized compounds **3a-l,** and **4a-l** using Hex 5.1 software Scotland, UK. Molecular docking involves the following steps using Hex 5.1 software:

1. Identify a target protein 2YES from the protein data bank.
2. Download PDB FILE (text) and save in Example Folder of Hex 5.1.
3. Draw all the ligands using ChemSketch software.
4. Generate 3-D view (SDF format) and convert it into MOL file.
5. Convert into PDB format by using Swiss PDB viewer and save it.
6. Open Hex 5.1 software, select appropriate protein and ligand and perform docking.

RESULTS

The physicochemical parameters of the synthesized compounds, including melting point, are shown in Table 1 while docking score and anti-tubercular results are listed in Tables 2 and 3, respectively. In Schiff base series compounds **3f**, **3h** and **3i** showed good antitubercular activity compared to standard streptomycin. In Thiazolidinone series compounds 4f and 4i showed good antitubercular activity compared to both standards pyrazinamide and streptomycin and compounds **4b**, **4c**, **4e**, **4h**, **4k**, **4l** showed similar activity compared to standard pyrazinamide but showed better than standard streptomycin. The detail spectral data of the compounds are as follows.

5-phenyl-N-[(1E)-phenylmethylene][1,3] thiazolo[4,3-b][1,3,4]thiadiazol-2-amine (3a): FTIR (KBr) cm^{-1}: 3115 (Ar C-H), 2960 (C-H), 2880 (C-H thiazole), 1590 (-N=CH), 702 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.14 (s, 1H, CH), 8.14 (s, 1H, -N=CH), 7.98 (s, 1H, CH), 7.30-7.68 (m, 10H, Ar-H); MS spectrum, m/z: 324[M+1] $^+$; Anal. Calcd for $C_{17}H_{13}N_3S_2$: C (63.13), H (4.05), N (12.99). Found: C (63.11), H (4.01) and N (12.95).

N-[(1E)-(2-chlorophenyl)methylene]-5-phenyl[1,3]thiazolo[4,3-b][1,3,4]thiadiazol-2-amine (3b): FTIR (KBr) cm^{-1}: 3110 (Ar C-H), 2890 (C-H), 2810 (C-H thiazole), 1598 (-N=CH), 682 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.05 (s, 1H, CH); 8.04 (s, 1H, -N=CH); 7.86 (s, 1H, CH); 7.40-7.75 (m, 9H, Ar-H); MS spectrum, m/z: 359[M+1] $^+$.

N-[(1E)-(4-chlorophenyl)methylene]-5-phenyl[1,3]thiazolo[4,3-b][1,3,4]thiadiazol-2-amine (3c): FTIR (KBr) cm^{-1}: 3095 (Ar C-H); 2930 (C-H); 2820 (C-H thiazole), 1582 (-N=CH), 710 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.10 (s, 1H, CH), 8.20 (s, 1H, N=CH), 7.90 (s, 1H, CH), 7.15-7.72 (m, 9H, Ar-H); MS spectrum, m/z: 358[M+1] $^+$.

5-(4-methylphenyl)-N-[(1E)-phenylmethylene][1,3]thiazolo[4,3-b][1,3,4]thiadiazol-2-amine (3d): FTIR (KBr) cm^{-1}: 3157 (Ar C-H), 2929 (C-H), 2850 (C-H thiazole), 1598 (-N=CH), 705 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.30 (s, 1H, CH), 8.37 (s, 1H, N=CH), 7.72 (s, 1H, CH), 6.86-7.52 (m, 9H, Ar-H), 1.45 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-

Table 1: Physical data of synthesized compounds **3a-3l** and **4a-4l.**

Compd	R_1	R_2	Yield (%)	M.P. (^oC)	Mol. formula
3a	-H	-H	62	140	$C_{17}H_{13}N_3S_2$
3b	-H	2-Cl	58	144	$C_{17}H_{12}ClN_3S_2$
3c	-H	4-Cl	63	109	$C_{17}H_{12}ClN_3S_2$
3d	4-CH_3	-H	71	114	$C_{18}H_{15}N_3S_2$
3e	4-CH_3	2-CH_3	78	132	$C_{19}H_{17}N_3S_2$
3f	4-CH_3	4-CH_3	76	156	$C_{19}H_{17}N_3S_2$
3g	4-OH	-H	72	179	$C_{17}H_{13}N_3OS_2$
3h	4-OH	2-OH	75	186	$C_{17}H_{13}N_3O_2S_2$
3i	4-OH	4-OH	78	154	$C_{17}H_{13}N_3O_2S_2$
3j	4-$N(CH_3)_2$	-H	76	156	$C_{19}H_{18}N_4S_2$
3k	4-$N(CH_3)_2$	2-OCH_3	72	179	$C_{20}H_{20}N_4OS_2$
3l	4-$N(CH_3)_2$	4-OCH_3	66	141	$C_{20}H_{20}N_4OS_2$
4a	-H	-H	67	158	$C_{19}H_{15}N_3OS_3$
4b	-H	2-Cl	61	163	$C_{19}H_{14}ClN_3OS_3$
4c	-H	4-Cl	65	129	$C_{19}H_{14}ClN_3OS_3$
4d	4-CH_3	-H	71	136	$C_{20}H_{17}N_3OS_3$
4e	4-CH_3	2-CH_3	73	146	$C_{21}H_{19}N_3OS_3$
4f	4-CH_3	4-CH_3	74	156	$C_{21}H_{19}N_3OS_3$
4g	4-OH	-H	71	167	$C_{19}H_{15}N_3O_2S_3$
4h	4-OH	2-OH	73	123	$C_{19}H_{15}N_3O_3S_3$
4i	4-OH	4-OH	75	167	$C_{19}H_{15}N_3O_3S_3$
4j	4-$N(CH_3)_2$	-H	70	189	$C_{21}H_{20}N_4OS_3$
4k	4-$N(CH_3)_2$	2-OCH_3	71	134	$C_{22}H_{22}N_4O_2S_3$
4l	4-$N(CH_3)_2$	4-OCH_3	67	156	$C_{22}H_{22}N_4O_2S_3$

Table 2: Antitubercular activity and docking score of compounds **3a-3l**

Compound	R_1	R_2	MIC (µg/mL)	PDB code	E score (kJ/ mol)
3a	-H	-H	12.5	2YES	-139.92
3b	-H	2-Cl	6.25	2YES	-144.60
3c	-H	4-Cl	6.25	2YES	-144.60
3d	4-CH_3	-H	12.5	2YES	-143.75
3e	4-CH_3	2-CH_3	6.25	2YES	-145.74
3f	4-CH_3	4-CH_3	3.125	2YES	-145.74
3g	4-OH	-H	12.5	2YES	-138.60
3h	4-OH	2-OH	3.125	2YES	-144.07
3i	4-OH	4-OH	3.125	2YES	-144.07
3j	4-$N(CH_3)_2$	-H	6.25	2YES	-145.62
3k	4-$N(CH_3)_2$	2-OCH_3	6.25	2YES	-147.61
3l	4-$N(CH_3)_2$	4-OCH_3	6.25	2YES	-147.61
Streptomycin	-	-	6.25	2YES	-125.43
Pyrazinamide	-	-	3.12	2YES	-123.07

Table 3: Antitubercular activity and docking score of compounds **4a-4l**

Compound	R_1	R_2	MIC (µg/mL)	PDB code	E score (kJ/ mol)
4a	-H	-H	6.25	2YES	-147.51
4b	-H	2-Cl	3.12	2YES	-147.31
4c	-H	4-Cl	3.12	2YES	-147.31
4d	4-CH_3	-H	6.25	2YES	-147.53
4e	4-CH_3	2-CH_3	3.12	2YES	-146.04
4f	4-CH_3	4-CH_3	1.6	2YES	-146.04
4g	4-OH	-H	6.25	2YES	-146.99
4h	4-OH	2-OH	3.12	2YES	-147.00
4i	4-OH	4-OH	1.6	2YES	-147.00
4j	4-$N(CH_3)_2$	-H	6.25	2YES	-146.01
4k	4-$N(CH_3)_2$	2-OCH_3	3.12	2YES	-146.62
4l	4-$N(CH_3)_2$	4-OCH_3	3.12	2YES	-146.62
Streptomycin	-	-	6.25	2YES	-125.43
Pyrazinamide	-	-	3.12	2YES	-123.07

d_6): δ 32.65, 43.74, 130.60, 134.86, 140.93, 144.85, 150.86, 153.55, 160.17, 160.68, 163.23, 164.40;MS spectrum, m/z: 338 $[M+1]^+$; Anal. Calcd for $C_{18}H_{15}N_3S_2$: C (64.06), H (4.48), N (12.45). Found: C (64.01), H (4.44) and N (12.39).

5-(4-methylphenyl)-N-[(1E)-(2-methylphenyl)methylene][1,3]thiazolo[4,3-b][1,3,4] thiadiazol-2-amine (3e): FTIR (KBr) cm^{-1}: 3108 (Ar C-H), 2950(C-H), 2870 (C-H thiazole), 1585 (-N=CH), 712 (C-S-C); ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.16 (s, 1H, CH), 8.39 (s, 1H, N=CH), 7.86 (s, 1H, CH), 7.25-7.63 (m, 8H, Ar-H), 2.45 (s, 6H, CH_3); MS spectrum, m/z: 353 $[M+1]^+$.

5-(4-methylphenyl)-N-[(1E)-(4-methylphenyl)methylene][1,3]thiazolo[4,3-b][1,3,4] thiadiazol-2-amine (3f): FTIR (KBr) cm^{-1}: 3005 (Ar C-H), 2890 (C-H), 2750 (C-H thiazole), 1583 (-N=CH), 712 (C-S-C); ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.14 (s, 1H, CH), 8.36 (s, 1H, N=CH), 7.81 (s, 1H, CH), 7.22-7.68 (m, 8H, Ar-H), 2.35 (s, 6H, CH_3); MS spectrum, m/z: 352 $[M+1]^+$.

4-(2-{[(1E)-phenylmethylene]amino}[1,3] thiazolo[4,3-b][1,3,4]thiadiazol-5-yl)phenol (3g): FTIR (KBr) cm^{-1}: 3545 (O-H), 3005 (ArC-H), 2955 (C-H), 2875 (C-H thiazole), 1515 (-N=CH), 695 (C-S-C); ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH), 7.83 (s, 1H, CH), 8.19 (s, 1H, N=CH), 7.18-7.34 (m, 9H, Ar-H), 5.28 (s, 1H, OH); MS spectrum, m/z: 341 $[M+1]^+$.

2-[(E)-{[5-(4-hydroxyphenyl)[1,3]thiazolo [4,3-b][1,3,4]thiadiazol-2-yl]imino}methyl] phenol (3h): FTIR (KBr) cm^{-1}: 3515 (O-H), 3005 (Ar C-H), 2965 (C-H), 2885 (C-H thiazole), 1550 (-N=CH), 702 (C-S-C); ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.82 (s, 1H, CH), 7.95 (s, 1H, CH), 8.22 (s, 1H, N=CH), 7.05-7.45 (m, 8H, Ar-H), 5.20 (s, 2H, OH); MS spectrum, m/z: 356 $[M+1]^+$.

4-(2-{[(1E)-(4-hydroxyphenyl)methylene] amino}[1,3]thiazolo[4,3-b][1,3,4]thiadiazol-5-yl)phenol (3i): FTIR (KBr) cm^{-1}: 3530 (O-H), 3005 (ArC-H), 2955 (C-H), 2875 (C-H thiazole), 1535 (-N=CH), 780 (C-S-C); ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.85 (s, 1H, CH), 7.98 (s, 1H, CH), 8.30 (s, 1H, N=CH), 7.10-7.38 (m, 8H, Ar-H),

5.18 (s, 2H, OH); MS spectrum, m/z: 357 $[M+1]^+$.

5-[4-(dimethylamino)phenyl]-N-[(1E)-phenylmethylene][1,3]thiazolo[4,3-b][1,3,4]thiadiazol-2-amine (3j): FTIR (KBr) cm^{-1}: 3111 (Ar C-H), 2962 (C-H), 2875 (C-H thiazole), 1583 (-N=CH), 714 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.86 (s, 1H, CH), 9.39 (s, 1H, N=CH), 6.34 (s, 1H, CH), 7.17-7.72 (m, 9H, Ar-H), 1.42-1.47(s, 6H, CH_3); MS spectrum, m/z: 368 $[M+1]^+$.

5-[4-(dimethylamino)phenyl]-N-[(1E)-(2-methoxyphenyl)methylene][1,3]thiazolo [4,3-b] [1,3,4]thiadiazol -2-amine (3k): FTIR (KBr) cm^{-1}: 3120 (Ar C-H), 2965 (C-H), 2892 (C-H thiazole), 1585 (-N=CH), 718 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.92 (s, 1H, CH), 9.28 (s, 1H, N=CH), 6.37 (s, 1H, CH), 7.80-7.95 (m, 8H, Ar-H), 3.15 (s, 3H, $-OCH_3$), 1.42-1.47(s, 6H, CH_3); MS spectrum, m/z: 398 $[M+1]^+$.

5-[4-(dimethylamino)phenyl]-N-[(1E)-(4-methoxyphenyl)methylene][1,3]thiazolo [4,3-b][1,3,4] thiadiazol-2-amine (3l): FTIR (KBr) cm^{-1}: 3122 (Ar C-H), 2972 (C-H), 2892 (C-H thiazole), 1594 (-N=CH), 722 (C-S-C); ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.80 (s, 1H, CH), 9.30 (s, 1H, N=CH), 6.43 (s, 1H, CH), 7.75-7.98 (m, 8H, Ar-H), 3.52 (s, 3H, $-OCH_3$), 1.52-1.58(s, 6H, CH_3); MS spectrum, m/z: 397 $[M+1]^+$.

2-phenyl-3-(5-phenyl[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl)-1,3-thiazolidin-4-one(4a): FTIR (KBr) cm^{-1}: 3121 (Ar C-H); 2972 (C-H); 2877 (C-H thiazole); 1692 (-C=O), 705 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.21 (s, 1H, CH); 7.82 (s, 1H, CH); 7.28-7.58 (m, 10H, Ar-H); 4.11 (s, 1H, -N-CH), 4.08 (s, 2H, SCH_2); MS spectrum, *m/z*: 399$[M+1]^+$; Anal. Calcd. for $C_{19}H_{15}N_3OS_3$: C (57.40), H (3.80), N (10.57). Found: C (57.35), H (3.74) and N (10.49).

2-(2-chlorophenyl)-3-(5-phenyl[1,3] thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl)-1,3-thiazolidin-4-one (4b): FTIR (KBr) cm^{-1}: 3112 (Ar C-H); 2950 (C-H); 2870 (C-H thiazole); 1685 (-C=O), 703 (C-S-C), 761 (-C-Cl). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.11 (s, 1H, CH); 7.92 (s, 1H, CH); 7.35-7.75 (m, 9H, Ar-H) 4.12 (s, 1H, -N-CH), 4.17 (s, 2H, SCH_2); MS spectrum, *m/z*: 432$[M+1]^+$.

2-(4-chlorophenyl)-3-(5-phenyl[1,3] thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl)-1,3-thiazolidin-4-one (4c): FTIR (KBr) cm^{-1}: 3115 (Ar C-H); 2972 (C-H); 2869 (C-H thiazole); 1674 (-C=O), 710 (C-S-C), 755 (-C-Cl). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.09 (s, 1H, CH); 7.76 (s, 1H, CH); 7.30-7.70 (m, 9H, Ar-H); 4.10 (s, 1H, -N-CH), 4.18 (s, 2H, SCH_2); MS spectrum, *m/z*: 433$[M+1]^+$.

3-[5-(4-methylphenyl)[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl]-2-phenyl-1,3-thiazolidin-4-one (4d): FTIR (KBr) cm^{-1}: 3153 (Ar C-H); 2928 (C-H); 2358 (C-H thiazole); 1693 (-C=O), 723 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.05 (s, 1H, CH); 7.87 (s, 1H, CH); 7.21-7.24 (m, 9H, Ar-H); 2.84 (s, 3H, CH_3); 4.44 (s, 1H, -N-CH), 4.72 (s, 2H, SCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.02, 28.27, 28.32, 32.87, 37.26, 128.93, 130.60, 132.44, 137.26, 140.97, 144.65, 153.55, 160.17, 160.68, 163.33, 164.43, 177.97; MS spectrum, MS spectrum, *m/z*: 412 $[M+1]^+$; Anal. Calcd. for $C_{20}H_{17}N_3OS_3$: C (58.37), H (4.16), N (10.21). Found: C (58.31), H (4.14) and N (10.14).

2-(2-methylphenyl)-3-[5-(4-methylphenyl)[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one (4e): FTIR (KBr) cm^{-1}: 3110 (Ar C-H); 2960 (C-H); 2880 (C-H thiazole); 1685 (-C=O), 669 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.16 (s, 1H, CH); 7.86 (s, 1H, CH); 7.32-7.63 (m, 8H, Ar-H); 2.74 (s, 6H, CH_3); 4.06 (s, 1H, -N-CH),

4.19 (s, 2H, SCH_2); MS spectrum, MS spectrum, *m/z*: 426 $[M+1]^+$.

2-(4-methylphenyl)-3-[5-(4-methylphenyl)[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one (4f): FTIR (KBr) cm^{-1}: 3153 (Ar C-H); 2980 (C-H); 2895 (C-H thiazole); 1748 (-C=O), 713 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.15 (s, 1H, CH); 7.81 (s, 1H, CH); 7.32-7.48 (m, 8H, Ar-H); 2.24 (s, 6H, CH_3); 4.12 (s, 1H, -N-CH), 4.30 (s, 2H, SCH_2); MS spectrum, MS spectrum, *m/z*: 427 $[M+1]^+$.

3-[5-(4-hydroxyphenyl)[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl]-2-phenyl-1,3-thiazolidin-4-one (4g): FTIR (KBr) cm^{-1}: 3545 (O-H); 3005 (Ar C-H); 2955 (C-H); 2875 (C-H thiazole); 1738 (-C=O), 675 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.83 (s, 1H, CH); 7.18-7.34 (m, 9H, Ar-H); ; 5.28 (s, 1H, OH); 4.15 (s, 1H, -N-CH), 4.19 (s, 2H, SCH_2); MS spectrum, *m/z*: 415 $[M+1]^+$.

2-(2-hydroxyphenyl)-3-[5-(4-hydroxyphenyl)[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one (4h): FTIR (KBr) cm^{-1}: 3515 (O-H); 3005 (Ar C-H); 2955 (C-H); 2875 (C-H thiazole); 1750 (-C=O), 705 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.83 (s, 1H, CH); 7.28-7.44 (m, 8H, Ar-H); 5.20 (s, 2H, OH); 4.10 (s, 1H, -N-CH), 4.17 (s, 2H, SCH_2); MS spectrum, *m/z*: 430 $[M+1]^+$.

2-(4-hydroxyphenyl)-3-[5-(4-hydroxyphenyl)[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one (4i): FTIR (KBr) cm^{-1}: 3530 (O-H); 3005 (Ar C-H); 2955 (C-H); 2875 (C-H thiazole); 1738 (-C=O), 715 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.83 (s, 1H, CH); 7.32-7.54 (m, 8H, Ar-H); 5.28 (s, 2H, OH); 4.11 (s, 1H, -N-CH), 4.23 (s, 2H, SCH_2); MS spectrum, *m/z*: 431 $[M+1]^+$.

3-{5-[4-(dimethylamino)phenyl][1,3] thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl}-2-phenyl-1,3-thiazolidin-4-one (4j): FTIR (KBr) cm^{-1}: 3105 (Ar C-H); 2945 (C-H); 2785 (C-H thiazole); 1695 (-C=O), 703 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.84 (s, 1H, CH); 6.36 (s, 1H, CH); 7.39-7.72 (m, 9H, Ar-H); 1.42-1.47(s, 6H, CH_3); 4.18 (s, 1H, -N-CH), 4.25 (s, 2H, SCH_2); MS spectrum, *m/z*: 442 $[M+1]^+$.

2-(2-methoxyphenyl)-3-{5-[4-(dimethylamino)phenyl][1,3]thiazolo[4,3-*b*][1,3,4] thiadiazol-2-yl}-1,3-thiazolidin-4-one(4k): FTIR (KBr) cm^{-1}: 3095 (Ar C-H); 2895 (C-H); 2760 (C-H thiazole); 1675 (-C=O), 675 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.77 (s, 1H, CH); 6.45 (s, 1H, CH); 7.80-7.95 (m, 8H, Ar-H); 3.15 (s, 3H, $-OCH_3$); 1.42-1.47(s, 6H, CH_3); 4.13 (s, 1H, -N-CH), 4.21 (s, 2H, SCH_2); MS spectrum, *m/z*: 472 $[M+1]^+$.

2-(4-methoxyphenyl)-3-{5-[4-(dimethylamino)phenyl][1,3]thiazolo[4,3-*b*][1,3,4] thiadiazol-2-yl}-1,3-thiazolidin-4-one (4l): FTIR (KBr) cm^{-1}: 3105 (Ar C-H); 2925 (C-H); 2880 (C-H thiazole); 1666 (-C=O), 708 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.67 (s, 1H, CH); 6.49 (s, 1H, CH); 7.66-7.89 (m, 8H, Ar-H); 3.55 (s, 3H, $-OCH_3$); .1.40-1.49(s, 6H, CH_3); 4.05 (s, 1H, -N-CH), 4.19 (s, 2H, SCH_2); MS spectrum, *m/z*: 473 $[M+1]^+$.

Docking

The synthesized compounds showed good docking score compared to the standard drugs, streptomycin and pyrazinamide. Tabulation of ligands docking score for **3a-l** and **4a-l** are shown in Tables 2 and 3, respectively.

Anti-tubercular activity

The synthesized compounds showed higher *in vitro* activity than the standard drugs, streptomycin and pyrazinamide. In the Schiff base series **3a-l,** compounds **3f, 3h** and **3i**

showed good antitubercular activity compared to streptomycin. In the Thiazolidinone series **4a-l,** compounds **4f** and **4i** showed higher antitubercular activity than both pyrazinamide and streptomycin; compounds **4b, 4c, 4e, 4h, 4k, 4l** showed similar activity to pyrazinamide but they all exhibited greater activity than streptomycin.

DISCUSSION

FTIR, ^{1}H-NMR, ^{13}C-NMR and mass spectra are in agreement with the proposed structures. All synthesized compounds showed good docking score compared to the standard drugs while the thiazolidinone series showed better docking scores than the Schiff base series. This suggests that cyclisation increases the docking scores. A closer look at the anti-tubercular results reveals that in Schiff base series (**3a-l)**, increasing the substitution on nitrogen gave better activity (**4a-l**), perhaps due to increase in hydrophobicity resulting in better penetration of the Mtb cell wall. The structure - activity relationship of the compounds show that the presence of pharmacophoric moieties such as 1,3,4-thiadiazole nucleus (thiazolidinone moiety), increases antitubercular activity. A substituent, such as 4-methyl, 4-hydroxy group, attached to the phenyl ring and increases the substitution on nitrogen (NH_2 group) with thiazolidinone moiety to give higher activity, perhaps due to increase in hydrophobicity resulting in better penetration into the Mtb cell wall..

CONCLUSION

The overall outcome of these results reveals that thiazolidinone ring is a satisfactory backbone for antitubercular activity. These preliminary buy encouraging anti-tubercular results could offer an excellent framework in the field that may lead to the discovery of potent antitubercular agents.

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