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Synthesis Characterization and Antitubercular Evaluation of Thiazolo-Triazole Derivatives Using Microwave Irradiation

Mr. Mayur Gaikar*, Mr. Vikas Kunde, Dr. Kiran Dhamak, Dr. Vinayak Gaware

Assistant Professor, PRES's College of Pharmacy (For Women), Chincholi, Tal. Sinnar, Dist. Nashik.

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KEYWORDS

Thiazolo-triazole derivatives; Antitubercular activity; Microwave synthesis; IC_{50} estimation; H37Rv strain

ABSTRACT:

The present study focuses on the synthesis, characterization, and evaluation of novel thiazolo–triazole derivatives as potential antitubercular agents. A series of compounds (A1–A24) were synthesized using microwave-assisted techniques, offering advantages such as reduced reaction time, improved yields, and environmentally friendly conditions. The synthesized compounds were characterized by standard analytical methods including FT-IR, ^1H NMR, and mass spectrometry to confirm their chemical structures. The antitubercular activity of the synthesized derivatives was evaluated against *Mycobacterium tuberculosis* H37Rv strain using the Middle brook 7H9 agar method at different concentrations (25, 50, and 100 mcg/ml). The results demonstrated a concentration-dependent activity, with most compounds showing sensitivity at higher concentrations. Among the tested compounds, **A16** exhibited the most significant antitubercular activity, while compounds remaining compounds showed moderate activity. Statistical analysis indicated an approximate IC_{50} value around 85 mcg/ml, suggesting moderate potency of the synthesized derivatives. Overall, the study highlights the potential of thiazolo–triazole hybrids as promising scaffolds for the development of new antitubercular agents, warranting further optimization and pharmacological investigation.

INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis*, remains a major global health challenge, responsible for millions of infections and deaths annually. The disease primarily affects the lungs but can also spread to other organs, leading to severe complications. The rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has significantly reduced the effectiveness of conventional therapies, thereby necessitating the development of new antitubercular agents with novel mechanisms of action. Heterocyclic compounds have long been recognized as key structural motifs in medicinal chemistry due to their wide range of biological activities. Among them, thiazole derivatives are particularly important because of their diverse pharmacological properties, including antimicrobial, anticancer, anti-inflammatory, and antitubercular activities[1]. Similarly, triazole derivatives have gained prominence owing to their remarkable stability, hydrogen bonding capability, and ability to interact with biological targets, making them valuable scaffolds in drug design. The hybridization of thiazole and triazole moieties into a single molecular framework (thiazolo-triazole derivatives) has emerged as an effective strategy to enhance biological activity through synergistic effects and improved target binding. Recent studies have demonstrated that triazole-based hybrids exhibit significant biological potential, including antimicrobial and anticancer activities, highlighting their importance in modern drug discovery. Moreover, the incorporation of multiple pharmacophores into a single molecular entity has been shown to improve pharmacokinetic and pharmacodynamic properties, making such hybrid systems promising candidates for antitubercular drug development[2]. Traditional synthetic approaches for the preparation of heterocyclic compounds often involve prolonged reaction times, high energy consumption, and the use of hazardous solvents, which limit their applicability in sustainable chemistry. In contrast, microwave-assisted organic synthesis (MAOS) has emerged as a powerful and green alternative technique. Microwave irradiation enables rapid and uniform heating through dipolar polarization

and ionic conduction mechanisms, significantly accelerating chemical reactions and improving product yields. Recent advancements have highlighted the efficiency of microwave-assisted synthesis in constructing triazole and related heterocyclic systems. For instance, microwave-assisted methods have been reported to reduce reaction times from several hours to a few minutes while increasing yields up to 90–97%, demonstrating their superiority over conventional heating techniques. Additionally, microwave-assisted protocols enable solvent-free or minimal-solvent conditions, aligning with green chemistry principles and reducing environmental impact. Furthermore, microwave-assisted synthesis has been successfully applied in the preparation of various biologically active heterocyclic hybrids, including thiazole-based compounds, which exhibit good yields (68–85%) and enhanced biological activities. The ability of microwave irradiation to facilitate one-pot, multicomponent reactions further enhances its applicability in the rapid synthesis of complex molecular architectures such as thiazolo-triazole derivatives. In light of these considerations, the present study focuses on the design and microwave-assisted synthesis of novel thiazolo-triazole derivatives, followed by their characterization and evaluation for antitubercular activity. This approach aims to combine the pharmacological potential of thiazole and triazole scaffolds with the efficiency and sustainability of microwave-assisted synthesis, ultimately contributing to the development of new therapeutic agents against tuberculosis [3, 4].

MATERIALS

All reagents, solvents, and synthetic starting materials used in the study were of analytical grade and obtained from commercial sources without further purification. The synthesis and characterization of the target compounds were performed using the following standard analytical techniques:

- Determination of physical constants (melting point)
- Thin-layer chromatography (TLC)
- Elemental analysis
- Fourier-transform infrared (FT-IR) spectroscopy
- Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy
- Mass spectrometry (MS)

Microwave-assisted synthesis was carried out using a scientific microwave synthesizer (RAGA Model No. RG34L4R).

- **Melting Point Determination**

  Melting points of the synthesized compounds were determined using the open capillary tube method with a liquid paraffin bath. The values reported are uncorrected. A sharp and consistent melting point was indicative of the compound’s purity.

Thin-Layer Chromatography (TLC)

TLC was employed to monitor reaction progress and assess compound purity. The separation was based on differential adsorption on a stationary phase. R_f values were calculated to identify the formation of the target compounds and assess their purity.

Fourier-Transform Infrared (FT-IR) Spectroscopy

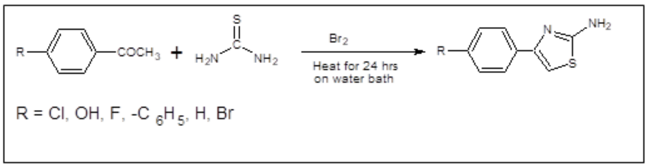
FT-IR spectra were recorded using an Agilent FT-IR spectrophotometer via the potassium bromide (KBr) disc method. The resulting data were analyzed to confirm the presence of functional groups through characteristic absorption bands.

Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy

^{1}H NMR spectra were recorded on a Bruker 500 MHz spectrometer using tetramethylsilane (TMS) as the internal standard. The spectra provided detailed information on proton environments, supporting structural elucidation of the synthesized molecules.

Mass Spectrometry (MS)

Mass spectra of the proto compounds were recorded to confirm molecular mass and assess the fragmentation pattern. The results further corroborated the molecular structure proposed for the synthesized compounds [5].



EXPERIMENTAL

Synthesis of Thiazolo-Triazole Derivatives

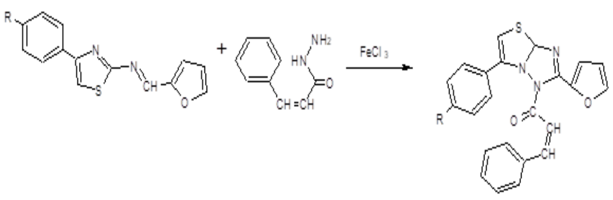
Part I

General Synthesis of 2-amino-4-aryl-thiazole

Procedure

A mixture of substituted acetophenone (0.1 mol) and thiourea (0.2 mol) was taken in a suitable microwave reaction vessel. To this, bromine (0.2 mol) was added dropwise with continuous stirring under controlled conditions. The reaction mixture was then subjected to microwave irradiation at 300–450 W for 5–10 minutes, with intermittent cooling (every 1–2 minutes) to avoid overheating and excessive pressure build-up. After completion of the reaction (monitored by TLC), distilled water was added to the reaction mixture, and it was further irradiated for 1–2 minutes to ensure complete dissolution of intermediates. The hot reaction mixture was filtered, and the filtrate was allowed to cool to room temperature. The solution was then made alkaline using concentrated ammonium hydroxide, resulting in the precipitation of 2-amino-4-aryl thiazole. The precipitated product was filtered, washed with cold ethanol, and dried over phosphorus pentoxide (P_2O_5).Finally the crude product was recrystallized from ethanol to obtain pure 2-amino-4-aryl thiazole as colorless needle-shaped crystals [6].

Part III (4)



PART II

Synthesis of Schiff's base of 2- amino thiazole

Stir a mixture of 0.01 mole of 2-amino-4-arylthiazole with 18 ml of water & 2.4 ml of conc. NH_3 and add 0.01 mole of aldehyde drop wise with stirring, over a period of 30-60 min. Stir the mixture for further hour. Collect the solid by suction filtration & wash it with water. Recrystallized from 8 ml of rectified spirit [7].

PART III

1) Synthesis of derivatives of thiazolo-triazole using Isoniazide [8,9,10]

Mixture of II (0.01 mole), $FeCl_3.6H_2O$ (0.02 mole) & 0.01 mole of INH was ground by pestle & mortar at room temp. The reaction mixture was digested with water. The resultant solid was filtered, washed with water & the crude material is purified by recrystallization from methanol to afford III.

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2) Synthesis of thiazolo-triazole derivative using pyrazinoic acid hydrazide

Mixture of II (0.01 mole), $FeCl_3.6H_2O$ (0.02 mole) & 0.01 mole of pyrazinoic acid hydrazide was ground by pestle & mortar at room temp. The reaction mixture was digested with water. The resultant solid was filtered, washed with water & the crude material is purified by recrystallization from methanol to afford III **(Table 2)**.

3) Synthesis of thiazolo-triazole derivative using hydrazine hydrate

To the aqueous solution of NaOH (10%) 40 ml was added in 0.01 mole of II. Add 2-3 ml of NH_3 and 0.01 mole of hydrazine hydrate. The reaction mixture was refluxed for 2 hr. The resulting solution was treated with charcoal, cooled & filtered. The filtrate was acidified with 10% HCl, adjust pH 5-6.The solid mass was precipitated, filtered, washed with ice cold water and recrystallized from ethanol **(Table 3).**

4) Synthesis of thiazolo-triazole derivative using cinnamoic acid hydrazide

Mixture of II (0.01 mole), $FeCl_3.6H_2O$ (0.02 mole) & 0.01 mole of cinnamoic acid hydrazide was ground by pestle & mortar at room temp. The reaction mixture was digested with water. The resultant solid was filtered,

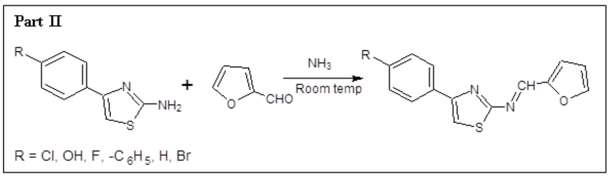
washed with water & the crude material is purified by recrystallization from methanol to afford III **(Table 4)**.

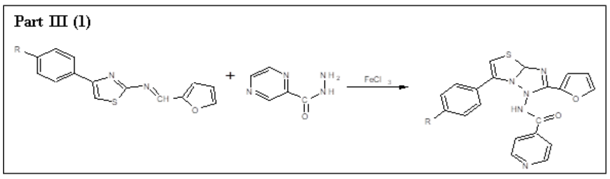
Table 1: Derivatives of thiazolo-triazole using Isoniazide (A_1-A_6)

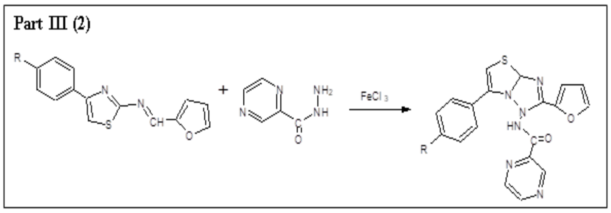
Compound	R
A_1	-Cl
A_2	-OH
A_3	-F
A_4	$-C_6H_5$
A_5	-H
A_6	-Br

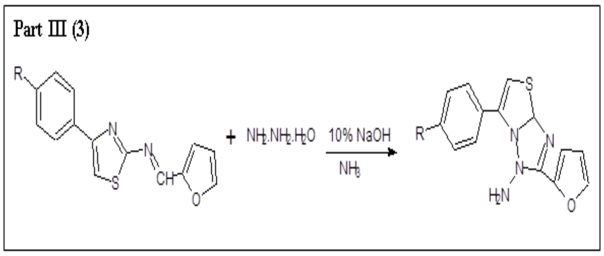
Table 2: Derivative of thiazolo-triazole using pyrazinoic acid hydrazide (A_7 –A_{12})

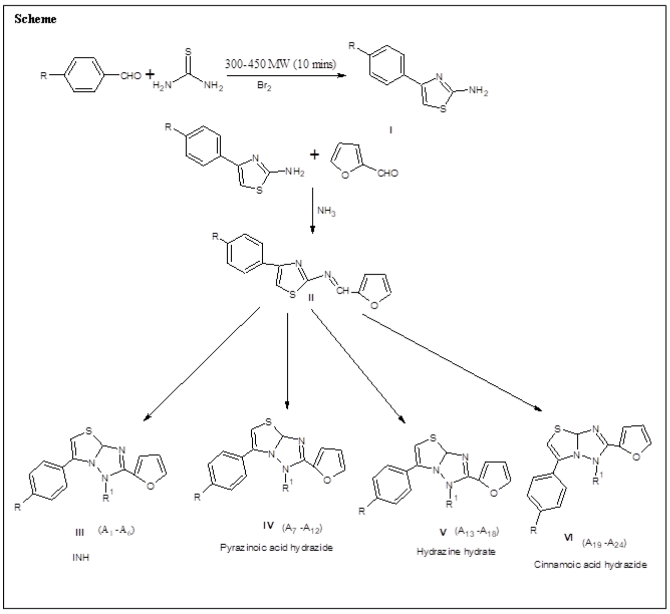
Compound	R
A_7	-Cl
A_8	-OH
A_9	-F
A_{10}	$-C_6H_5$
A_{11}	-H
A_{12}	-Br











SPECTRAL DATA OF INDIVIDUAL COMPOUNDS

Compound A1: IR: 3422 (N–H), 3045 (Ar–CH), 1599 (C=O), 1571 (C=N), 1153 (C–N), 1059 (C–O), 756 (C–S), 690 (C–Cl)**, ^{1}H NMR:** 8.9–9.1 (NH), 8.0–8.1 (pyridine), 7.1–7.4 (phenyl), 6.3–6.5 (furan), 3.7–3.9 (thiazole H)**, MS:** ~380 (M^+)

Compound A2: IR: 3468 (N–H), 3137 (Ar–CH), 1639 (C=O), 1471 (C=N), 1271 (C–N), 1022 (C O), 726 (C–S), 591 (C–Cl)**, ^{1}H NMR:** 8.9–9.1 (s, 1H, NH), 8.0–8.1 (d, 4H, pyridine), 7.1–7.4 (m, 4H, phenyl), 6.3–6.5 (d, 3H, furan), 3.7–3.9 (s, 1H, thiazolo-triazole)**, MS:** ~395 (M^+)

Compound A3: IR: 3468 (N–H), 3212 (Ar–CH), 1471 (C=N), 1271 (C–N), 1077 (C–O), 750 (C–S), 575 (C–Cl)**, ^{1}H NMR:** 8.8–9.0 (NH), 7.0–7.5 (phenyl), 6.2–6.5 (furan)**, MS:** ~360 (M$^+$)

Compound A4: IR: 3475 (N–H), 3272 (O–H), 3122 (Ar–CH), 1648 (C=O), 1474 (C=N), 1292 (C–N), 1053 (C–O), 767 (C–S)**, ^{1}H NMR:** 8.9–9.1 (NH), 8.0–8.1 (pyridine), 7.1–7.4 (phenyl), 6.3–6.5 (furan), 5.0 (OH), 3.7–3.9 (thiazole H)**, MS:** ~400 (M$^+$)

Compound A5: IR: 3455 (N–H), 3345 (O–H), 3101 (Ar–CH), 1640 (C=O), 1471 (C=N), 1272 (C–N), 1077 (C–O), 750 (C–S)**, ^{1}H NMR:** 8.8–9.0 (NH), 7.0–7.5 (phenyl), 5.0 (OH), 3.7–3.9 (thiazole H)**, MS:** ~410 (M$^+$)

Compound A6: IR: 3459 (N–H), 3206 (O–H), 2925 (Ar–CH), 1457 (C=N), 1264 (C–N), 1018 (C–O), 690 (C–S)**, ^{1}H NMR:** 8.7–9.0 (NH), 7.0–7.5 (phenyl)**, MS:** ~370 (M$^+$)

Compound A7: IR: 3402 (N–H), 3126 (Ar–CH), 1635 (C=O), 1499 (C=N), 1236 (C–N), 1013 (C–O), 686 (C–S), 588 (C–F), ^{1}H NMR: 8.9–9.1 (NH), 8.0–8.1 (pyridine), 7.1–7.4 (phenyl), 6.3–6.5 (furan), 3.7–3.9 (thiazole H)**, MS:** ~385 (M$^+$)

Compound A8: IR: 3489 (N–H), 3101 (Ar–CH), 1640 (C=O), 1471 (C=N), 1271 (C–N), 1023 (C–O), 676 (C–S), 591 (C–F)**, ^{1}H NMR:** 8.4–8.6 (pyrazine), 8.0–8.1 (NH), 7.1–7.4 (phenyl), 6.3–6.5 (furan), 3.7–3.9 (thiazole)**, MS:** ~390 (M$^+$)

Compound A9: IR: 3443 (N–H), 3110 (Ar–CH), 1471 (C=N), 1271 (C–N), 1023 (C–O), 750 (C–S), 591 (C–F)**, ^{1}H NMR:** 7.0–7.5 (phenyl)**, MS:** ~360 (M$^+$)

Compound A10: IR: 3490 (N–H), 3122 (Ar–CH), 1648 (C=O), 1474 (C=N), 1292 (C–N), 1029 (C–O), 668 (C–S)**, ^{1}H NMR:** 8.8–9.0 (NH), 7.0–7.5 (phenyl)**, MS:** ~395 (M$^+$)

Compound A11IR: 3550 (N–H), 3140 (Ar–CH), 1673 (C=O), 1457 (C=N), 1264 (C–N), 1018 (C–O), 685 (C–S)**, ^{1}H NMR:** 8.8–9.1 (NH), 7.0–7.5 (phenyl)**, MS:** ~405 (M$^+$)

Compound A12: IR: 3490 (N–H), 3122 (Ar–CH), 1535 (C=N), 1292 (C–N), 1029 (C–O), 683 (C–S)**, ^{1}H NMR:** 7.0–7.5 (phenyl)**, MS:** ~350 (M$^+$)

Compound A13: IR: 3490 (N–H), 3122 (Ar–CH), 1648 (C=O), 1471 (C=N), 1271 (C–N), 1029 (C–O), 668 (C–S)**, ^{1}H NMR:** 8.9–9.1 (NH), 8.0–8.1 (pyridine), 7.1–7.4 (phenyl), 6.3–6.5 (furan), 3.7–3.9 (thiazole H), **MS:** ~400 (M$^+$)

Compound A14: IR: 3474 (N–H), 3140 (Ar–CH), 1673 (C=O), 1457 (C=N), 1264 (C–N), 1076 (C–O), 716 (C–S)**, ^{1}H NMR:** 8.8–9.0 (NH), 7.0–7.5 (phenyl)**, MS: ~410 (M$^+$)**

Compound A15: IR: 3490 (N–H), 3122 (Ar–CH), 1474 (C=N), 1292 (C–N), 1029 (C–O), 683 (C–S)**, ^{1}H NMR:** 7.0–7.5 (phenyl)**, MS:** ~355 (M$^+$)

Compound A16: IR: 3469 (N–H), 3087 (Ar–CH), 1635 (C=O), 1499 (C=N), 1292 (C–N), 1013 (C–O), 746 (C–Br), 624 (C–S)**, ^{1}H NMR:** 8.8–9.0 (NH), 7.0–7.5 (phenyl)**, MS:** ~430 (M$^+$), 432 (M+2)

Compound A17: IR: 3479 (N–H), 3101 (Ar–CH), 1640 (C=O), 1471 (C=N), 1271 (C–N), 1023 (C–O), 750 (C–Br), 712 (C–S)**, ^{1}H NMR:** 8.8–9.0 (NH), 7.0–7.5 (phenyl)**, MS:** ~435 (M$^+$)

Compound A18: IR: 3515 (N–H), 3101 (Ar–CH), 1471 (C=N), 1271 (C–N), 1023 (C–O), 750 (C–Br), 623 (C–S)**, ^{1}H NMR:** 7.0–7.5 (phenyl) **, MS:** ~420 (M$^+$)

Compound A19: IR: 3475 (N–H), 3275 (CH=CH), 3087 (Ar–CH), 1635 (C=O), 1460 (C=N), 1236 (C–N), 1082 (C–O), 686 (C–S), 561 (C–F)**, ^{1}H NMR:** 8.0–8.1 (NH), 7.1–7.4 (phenyl, 9H), 6.3–6.5 (furan), 3.7–3.9 (thiazole)**, MS:** ~410 (M$^+$)

Compound A20: IR: 3402 (N–H), 3275 (CH=CH), 3087 (Ar–CH), 1635 (C=O), 1499 (C=N), 1388 (C–N), 1013 (C–O), 771 (C–Br), 624 (C–S)**, ^{1}H NMR:** 8.0–8.2 (NH), 7.0–7.5 (phenyl)**, MS:** ~430 (M$^+$)

Compound A21: IR: 3515 (N–H), 3479 (CH=CH), 3101 (Ar–CH), 1640 (C=O), 1491 (C=N), 1271 (C–N), 1023 (C–O), 712 (C–S)**, ^{1}H NMR:** 8.0–8.2 (NH), 7.0–7.5 (phenyl)**, MS:** ~400 (M$^+$)

Compound A22: IR: 3516 (N–H), 3475 (O–H), 3272 (CH=CH), 3122 (Ar–CH), 1620 (C=O), 1474 (C=N), 1271 (C–N), 1029 (C–O), 682 (C–S)**, ^{1}H NMR:** 8.0–8.2 (NH), 7.0–7.5 (phenyl), 5.0 (OH)**, MS:** ~420 (M$^+$)

Compound A23: IR: 3520 (N–H), 3320 (CH=CH), 3101 (Ar–CH), 1640 (C=O), 1471 (C=N), 1271 (C–N),

1023 (C–O), 683 (C–S), **¹H NMR:** 8.0–8.2 (NH), 7.0–7.5 (phenyl), **MS:** ~405 (M^+)

Compound A24: IR: 3402 (N–H), 3275 (CH=CH), 3087 (Ar–CH), 1600 (C=O), 1499 (C=N), 1236 (C–N), 1082 (C–O), 686 (C–S), 624 (C–Cl), **¹H NMR:** 8.0–8.2 (NH), 7.0–7.5 (phenyl), **MS:** ~395 (M^+)

ANTITUBERCULAR ACTIVITY

The antitubercular screening was carried out by Middle brook 7H9 agar medium against $H_{37}Rv$ Strain. Middle brook 7H9 agar medium containing different derivatives (**A_1-A_{24}**), standard drug as well as control, Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of $H_{37}Rv$ Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth [3].

Table 6: Antitubercular activity of the synthesized compounds (A_1-A_{24})

SL. No.	Compounds	25 mcg/ml	50mcg/ml	100mcg/ml
1.	A_1	R	**S**	**S**
2.	A_2	R	R	**S**
3.	A_3	R	R	R
4.	A_4	R	R	**S**
5.	A_5	R	R	**S**
6.	A_6	R	R	R
7.	A_7	R	R	**S**
8.	A_8	R	R	**S**
9.	A_9	R	R	R
10.	A_{10}	R	R	**S**
11.	A_{11}	R	R	**S**
12.	A_{12}	R	R	R
13.	A_{13}	R	R	**S**
14.	A_{14}	R	R	**S**
15.	A_{15}	R	R	R
16	A_{16}	R	**S**	**S**
17	A_{17}	R	R	**S**
18	A_{18}	R	R	R
19	A_{19}	R	**S**	**S**
20	A_{20}	R	R	**S**
21	A_{21}	R	R	R
22	A_{22}	R	R	**S**
23	A_{23}	R	R	**S**
24	A_{24}	R	R	R
STD.	**Streptomycin**	**S**	**S**	**S**

R -denotes Resistance and S -denote Sensitive

Compounds **A_{16}** have shown promising antitubercular activity and remaining compounds have shown moderate antitubercular activity. *Mycobacterium tuberculosis* H_{37} Rv strain was used as standard tubercular organism. However the standard drug Streptomycin shows promising antitubercular activity at 25 mcg/ml.

CONCLUSION

The present study successfully demonstrates the design and synthesis of novel sulphur- and nitrogen-containing heterocyclic compounds, specifically thiazolo-triazole derivatives, of significant medicinal interest. A comprehensive literature survey was conducted to understand the chemical and pharmacological relevance of triazole and fused thiazolo-triazole systems, which guided the rational design of target molecules. A total of 24 novel derivatives were synthesized using established synthetic methodologies and standard reagents. All synthesized compounds were subjected to preliminary characterization, including determination of physical constants and thin-layer chromatography (TLC) analysis to confirm purity. Structural elucidation was primarily achieved using IR spectroscopy for all compounds, while selected representative compounds were further characterized by ¹H NMR and CHN analysis, confirming the proposed structures. Biological evaluation revealed that several compounds possess noteworthy antitubercular activity. Among them, compound **A16** exhibited the most promising activity, indicating its potential as a lead molecule and remaining compounds demonstrated moderate activity against

Mycobacterium tuberculosis, suggesting that substitution patterns on the thiazolo-triazole scaffold significantly influence biological efficacy. Overall, the study highlights the potential of thiazolo-triazole derivatives as promising antitubercular agents. The observed biological activity suggests that further structural optimization and detailed pharmacological investigations could lead to the development of more potent and selective therapeutic candidates.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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