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Design, Synthesis And Antitubercular Activity Assessment Of Some 5-Methoxypyrazine-2-Carboxamide Derivatives

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Abstract:
Seven new compounds having 5-methoxypyrazine-2-carboxamide nucleus were synthesized. The chemical structures of the newly synthesized 5-methoxypyrazine-2-carboxamide derivatives were verified by analytical data. Additionally, the resazurin assay was used to assess the antitubercular activity of all the newly synthesized compounds against M. tuberculosis H37RV. The obtained results were compared with Rifampicin, Isoniazid and Pyrazinamide. On M. tuberculosis H37RV, the plurality of the tested compounds displayed impressive antitubercular efficacy. Two of these compounds, S7-13 and S7-26, showed stronger antitubercular activity than pyrazinamide (MIC 12.5 micrograms per milliliter), their MIC values were found 1.6 and 6.25 micrograms per millilitre, respectively.
Keywords: *Antitubercular action, M. tuberculosis H37RV, MABA, and pyrazine*

1. INTRODUCTION

The instrumental agent of the tuberculosis (TB) is Mycobacterium tuberculosis (Mtb), which continues to be a foremost cause of death universally. Annually, around 10 million individuals get TB, and since 2021, the number has been increasing. The total 10.8 million people falling ill with TB, 10.4 million in 2021 and 10.1 million in 2020, a minor increase from 10.7 million in 2022, but still a significant increase in 2023. The TB incident cases (incidence rate) increased by 0.2% 2023 compared with 2022 and 1.25 million fatalities around the globe in the year 2023. India accounted for total 26% of the global TB burden in 2023. Mtb strains with resistance to the effective antibiotics isoniazid and rifampin are the causative agents of multidrug-resistant tuberculosis (MDR-TB). In 2023, 10.8 million people received the diagnosis of tuberculosis, and 175923 new cases of MDR-TB and rifampicin-resistant TB were reported.[1] Since the occurrence of the COVID-19 pandemic, there has been a manifest escalate in the number of Multi Drug Resistance –TB incidents. This troubling drift has been compounded by continuing conflicts in different parts of the world, which hamper timely and efficient health care provision.[2] Traditionally, therapeutic programs for drug-resistant tuberculosis have been plagued with problems, being risky, costly, and long-lasting—driving up to 18 to 24 months. These long treatment regimens negatively impact the patients' quality of life and cause serious medical and financial burdens.[3] The optimization of treatment duration for rifampin-resistant TB and MDR-TB has the potential to enhance the quality of life, treatment course, and drug compliance of patients. Mycobacterium tuberculosis (Mtb), the pathogen for tuberculosis (TB), is known to be an insidious enemy. The integrity of its thick, lipid-containing cell wall makes it a formidable barrier to penetration by pharmacological agents, hindering their entrance into the target molecular entities.[4] In addition, Mtb utilizes a repertoire of drug-resistance strategies, such as the presence of efflux pumps.[5]

Pyrazine and its derivatives have drawn significant academic interest as future building blocks for hybrid pharmacological compounds due to their varied pharmacological characteristics.[6] Pyrazinamide is the key pharmacotherapeutic agent in the treatment scenario of TB and often used together with other anti-TB drugs. Its clear-cut activity against TB is of vital importance for minimizing the duration of tuberculosis therapy.[7] Several pyrazinamide modifications have been studied as effective antitubercular drugs.[8] Bioisosteric replacements of derivatives with the pyrazinamide moiety have resulted in potent antitubercular medicines.[9] Pyrazolopyridones represent a new family of inhibitors of decaprenylphosphoryl-β-D-ribose-2'-epimerase with remarkable antitubercular potency.[10] Zhou and his co-workers have explained the antitubercular activity of carboxamide-substituted pyrazines.[11] Kumar et al. have reported some pyrazine derivatives that show promise as inhibitors of decaprenylphosphoryl-β-D-ribose-2'-epimerase for the therapeutic treatment of tuberculosis.[12] Pyrazines show unique structure–activity relationships (SAR) with respect to their anti-TB potency. The presence of electron-withdrawing groups in pyrazine derivatives has been linked with improved activity.[13] The search for the creation of new chemical scaffolds that are novel and useful as antitubercular drugs is of utmost concern, especially

in view of the high toxicity, heavy burden of treatment, and prolonged duration of standard therapies, as well as the development of drug resistance.[14] Therefore, to overcome the current challenges presented by drug resistance, further research is essential to develop and synthesize novel anti-TB agents with unique mechanisms of action, thus broadening the range of treatment options.

We have designed and synthesized 5-methoxypyrazine-2-carboxamide derivatives. Design of new substituted molecules of different types by ring modification of pyrazine, aiming to evaluate the efficiency of the compounds against tuberculosis and inspect their interaction using virtual screening methods based on pharmacophore modeling and docking approaches. In view of biological information of above mentioned moieties and continuous efforts, a series of 5-methoxypyrazine-2-carboxamide derivatives were synthesized. The chemical structures of the newly synthesized 5-methoxypyrazine-2-carboxamide derivatives were verified by analytical data. Additionally, the resazurin assay [Microplate Alamar Blue Assay (MABA)] method was used to assess the antitubercular activity of all the newly synthesized compounds against M. tuberculosis H37RV.

2. MATERIALS AND METHODS

2.1 Instruments

Each synthesized compound's melting point was ascertained using a melting point device. Thin-layer chromatography (TLC) was conducted on aluminium sheet which was layered with silica gel 60 F254, acquired from Merck. The visualization of the chromatographic spots was accomplished through exposure to iodine vapor. Infrared (IR) spectra of all compounds were recorded employing a Fourier-transform infrared (FTIR) spectrophotometer from Agilent, utilizing potassium bromide (KBr) as the matrix material. Hydrogen-1 nuclear magnetic resonance (1H NMR) spectrum of all the produced compounds were recorded using Avance III HD 500 MHz, Bruker in deuterated Dimethyl Sulfoxide (DMSO). Mass spectrometry data were obtained through the use of an electrospray ionization mass spectrometer (ESI-MS), using Direct Injection Mass (HRMS) Model: 6540ba Qtof - Infinity 1290, Agilent Technologies.

2.2 Chemicals & Apparatus

The reagents utilized for the experimental endeavors were acquired from BLD Pharmatech (India) Pvt Ltd and Sigma-Aldrich. All reagents employed in the experimental methodologies were classified as laboratory reagent (LR) and analytical reagent (AR) grade. The glassware utilized in the reactions was constructed from borosilicate material. All glassware underwent a thorough cleansing process employing chromic acid and was subsequently dried prior to utilization.

2.3 Designing of Pyazine derivatives

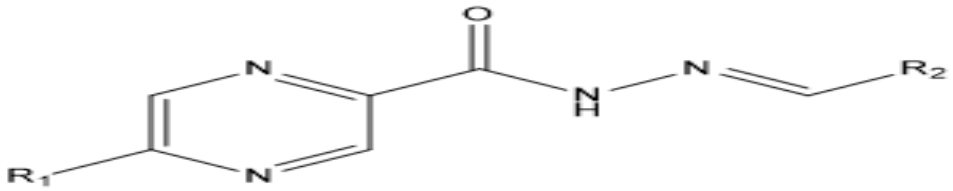

Figure 1: General structure of Designed Compounds

A library of 274 Pyrazine derivatives with various substituted phenoxy, methoxy, and chloro groups at the R1 and various substituted aromatics at the R2.Structure-based pharmacophore model for the protein Fatty Acid Synthase-I in Mycobacterium TB was created. Hypo1 was chosen from ten other Hypothesis of generated pharmacophores. A virtual screening of 274 designed compounds using selected pharmacophore model gave 18 hits. The LibDock methodology on DS docked 18 hits—which were obtained by imposing different constraints—on the active sites of the Mycobacterium TB Fatty Acid Synthase-I protein (PDB ID: 6GJC). The standard 5Cl-PZA ligand was used to compare the docking scores and their interactions with the active site residues to all 18 hit compounds. Under the TOPKAT initiative, all 18 compounds underwent toxicity evaluation and ADMET investigations. Compound No. 13, 17 18, 19, 25, 26, and 28 of S7 series were selected for synthesis on the basis of computational study.

2.4 Synthesis of 5-methoxypyrazine-2-carboxamide derivatives

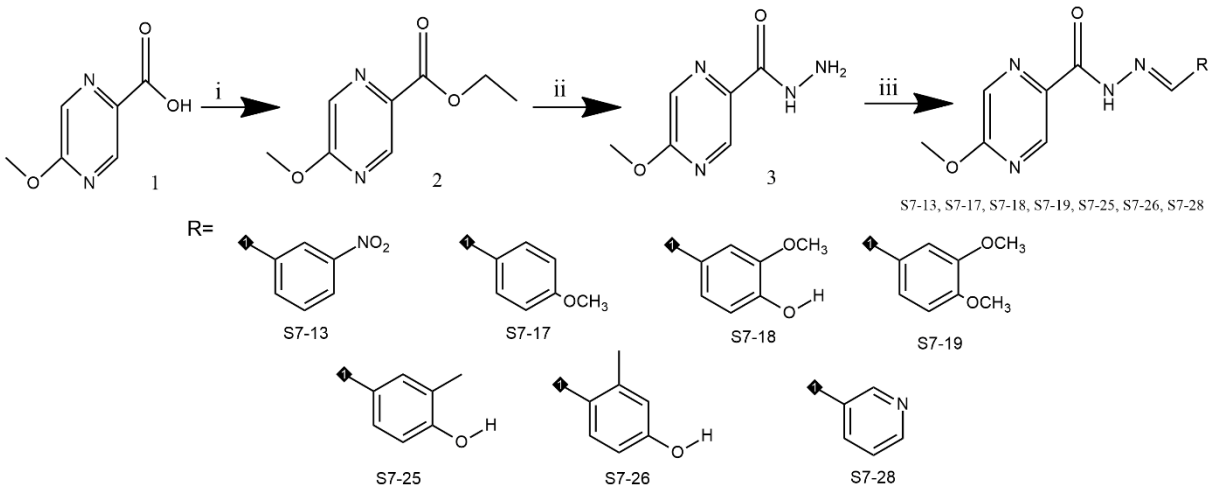

Figure 2: Scheme I. Synthetic pathways for compounds S7-13, S7-17, S7-18, S7-19, S7-25, S7-26 and S7-28. Reagents and conditions: (i) C2H5OH, H2SO4, Reflux, 10 h (ii) C2H5OH, NH2NH2.H2O, Reflux, 4 h (iii) C2H5OH, R-CHO, Reflux, 12 h.

2.4.1 Common procedure of Synthesis of 5-methoxypyrazine-2-carboxylicacidhydrazide:

The scheme for the producing the desired compounds is outlined in Figure 2. By esterifying and then hydrolysis of 5-methoxypyrazine-2-carboxylic acid (1), the core intermediate 5-methoxypyrazine-2-carboxylicacidhydrazide (3) was synthesized. Stir the mixture of 5 ml ethanol and 10 mmol 5-methoxypyrazine-2-carboxylic then Sulphuric acid in catalytic amount (0.5 ml) was added and refluxed for 10 hours. After 10 hours, 10 mmol of Hydrazine hydrate was added and further refluxed for 4 hours. Solutions were cooled to room temperature and then evaporated. Ethanol was used to recrystallize remaining solid mass to give the product 5-methoxypyrazine-2-carboxylicacidhydrazide.[15]

2.4.2 Common procedure for synthesis of the 5-methoxypyrazine-2-carboxylicacidhydrazide derivatives

To a solution containing 5-methoxypyrazine-2-carboxylicacidhydrazide (2 mmol) in 5 ml ethanol corresponding aldehydes (2 mmol) was refluxed for an approximate duration of 12 hours. Cooled the resultant mixture after 12 hours and then filtered to collect the solid. Collected solid then rinsed with distilled water. Dry solid was crystallized from ethanol to obtain compounds.[15]

2.4.2.1 5-methoxy-N-[(E)-(3-nitrophenyl)methyleneamino]pyrazine-2-carboxamide S713. Melting point: 229-231°C. White powder. Yield: 82%. IR (KBr) (ν, cm^{-1}): 3117.92(NH); 3011.73(CH_{arom}); 2931.55, 2838.37 (CH_{aliph}), 1630.71($C=O_{amide}$), 1541.25, 1507.71, 1442.48($C=C_{arom}$), 1321.34(N=O), 1278.48, 1087.88, 1026.88, 995.20 (C=N; Pyrazine), 937.43, 890.83, 820.01, 739.88($C=C_{arom}$). 1H NMR: δ 9.24(s, 1H, NH), 8.90(s, 1H, pyrazine-C2-H), 8.28-8.32(m, 1H, pyrazine-C5-H), 8.25(s, 1H, imine), 7.63-7.66(m, 2H, phenyl), 7.57-7.61(m, 2H, phenyl), 3.87(s, 3H, OCH3), ESI-MS $[M+H]^+$: 302.1142

2.4.2.2 5-methoxy-N-[(E)-(4-methoxyphenyl)methyleneamino]pyrazine-2-carboxamide S717. Melting point: 206-208°C. Yellow powder. Yield: 78%. IR (KBr) (ν, cm^{-1}): 3371.45(NH), 3084.45(CH_{arom}), 2920.35, 2847.67 (CH_{aliph}), 1600.89($C=O_{amide}$), 1507.71, 1459.25, 1420.12 ($C=C_{arom}$), 1248.66, 1164.79, 1108.88, 1023.15 (C=N; Pyrazine), 970.97, 866.61, 829.33, 780.87($C=C_{arom}$). 1H NMR: δ 12.20 (s, 1H, NH), 9.29 (s, 1H, pyrazine-C2-H), 8.70 (s, 1H, pyrazine-C5-H), 8.25 (s, 1H, imine), 7.86-7.98 (m, 2H, phenyl), 7.26-7.38 (m, 2H, phenyl), 3.45, 3.86 (s, 3H, OCH3). ESI-MS $[M+H]^+$: 287.1143

2.4.2.3 N-[(E)-(4-hydroxy-3-methoxy-phenyl)methyleneamino]-5-methoxy-pyrazine-2-carboxamide S718. Melting point: 193-195°C. Yellow solid. Yield: 85%. IR (KBr) (ν, cm^{-1}): 3529.83 (Ar-OH), 3317.33(NH), 3047.10, 3002.37(CH_{arom}), 2946.46, 2881.23(CH_{aliph}), 1604.62($C=O_{amide}$), 1533.80($C=C_{arom}$), 1295.25, 1243.07, 1095.84, 1025.02(C=N; Pyrazine), 972.84, 892.70, 861.02, 792.06($C=C_{arom}$). 1H NMR: δ 12.54(s, 1H, NH), 8.72 (s, 1H, pyrazine-C5-H), 8.25 (s, 1H, pyrazine-C2-H), 8.15 (s, 1H, imine), 7.11-7.15 (m, 1H, phenyl), 6.81-6.87 (m, 1H, phenyl), 3.15&3.26 (s, 3H, OCH3). ESI-MS $[M+H]^+$: 303.1096

2.4.2.4 N-[(E)-(3,4-dimethoxyphenyl)methyleneamino]-5-methoxy-pyrazine-2-carboxamide S719. Melting point: 178-180°C. Yellow solid. Yield: 75%.. IR (KBr) (ν, cm^{-1}): 3373.25(NH), 3000.21(CH_{arom}), 2961.37, 2927.82, 2838.37(CH_{aliph}), 1621.39($C=O_{amide}$), 1578.53, 1505.84, 1461.12, 1418.25($C=C_{arom}$), 1343.71, 1235.61, 1136.84, 1013.84(C=N; Pyrazine), 956.06, 866.61, 810.70, 752.92($C=C_{arom}$). 1H NMR: δ 12.08(s, 1H, NH), 8.79-8.99(m, 1H, pyrazine-C2-H), 8.48-8.58(m, 1H, pyrazine-C5-H), 8.05-8.09(m, 1H, imine), 6.98-7.38(m, 3H, phenyl), 3.19, 3.52, 3.88(s, 3H, OCH3). ESI-MS $[M+H]^+$: 317.1251

2.4.2.5 N-[(E)-(4-hydroxy-3-methyl-phenyl)methyleneamino]-5-methoxy-pyrazine-2-carboxamide S725. Melting point: 202-204°C. White solid. Yield: 86%. IR (KBr) (ν, cm^{-1}): 3520.56 (Ar-OH), 3386.29(NH), 3035.92, 2905.46(CH_{arom}), 1684.76 ($C=O_{amide}$), 1593.44, 1500.25, 1418.25($C=C_{arom}$), 1261.70, 1194.61, 1115.47, 1116.34(C=N; Pyrazine), 969.11, 814.42, 765.97($C=C_{arom}$). 1H NMR: δ 10.54(s, 1H, NH), 9.08-9.12(m, 1H, pyrazine-C2-H), 8.55-8.59(m, 1H, pyrazine-C5-H), 8.10(s, 1H, imine), 6.80-7.97(m, 3H, phenyl), 3.87(s, 3H, OCH3), 2.10(s, 3H, CH_3). ESI-MS $[M+H]^+$: 287.1142

2.4.2.6 N-[(E)-(4-hydroxy-2-methyl-phenyl)methyleneamino]-5-methoxy-pyrazine-2-carboxamide S726. Melting point: 207-209°C. White solid. Yield: 82%. IR (KBr) (ν, cm^{-1}): 3526.15(Ar-OH), 3313.60(NH), 3047.10, 3006.10, 2948.32, 2886.82(CH_{arom}), 1675.44($C=O_{amide}$), 1634.44, 1600.89, 1559.89, 1522.62($C=C_{arom}$), 1384.71, 1291.52, 1245.66, 1023.15(C=N; Pyrazine), 957.93, 792.06, 723.10($C=C_{arom}$). 1H NMR: δ 12.44(s, 1H, NH), 9.58-9.78(m, 1H, pyrazine-C2-H), 8.55-8.59(m, 1H, pyrazine-C5-H), 8.02(s, 1H, imine), 6.15-7.45(m, 3H, phenyl), 3.87(s, 3H, OCH3), 2.20(s, 3H, CH_3). ESI-MS $[M+H]^+$: 287.1138

2.4.2.7 5-methoxy-N-[(E)-3-pyridylmethyleneamino]pyrazine-2-carboxamide S728. Melting point: 218-220°C. White solid. Yield: 83%. IR (KBr) (ν, cm^{-1}): 3371.46(NH), 3121.65, 3039.64, 2875.64(CH_{arom}), 1653.07($C=O_{amide}$), 1585.98, 1418.25($C=C_{arom}$), 1304.57, 1248.66, 1175.98, 1133.11, 1084.66, 1038.06(C=N; Pyrazine), 976.56, 862.88, 803.24, 728.69($C=C_{arom}$). 1H NMR: δ 12.65 (s, 1H, NH), 9.06-9.10 (m, 1H, pyrazine-C2-H), 8.68-8.72 (m, 1H, pyridine-C2-H), 8.46-8.50 (m, 1H, pyridine-C4-H), 8.25-8.29 (m, 1H, pyrazine-C5-H), 8.20 (s, 1H, imine), 8.15-8.18 (m, 1H, pyridine-C6-H), 7.51-7.57 (m, 1H, pyridine-C5-H), 3.35 (s, 3H, OCH3). ESI-MS $[M+H]^+$: 258.0991

2.5 Biological Evaluation

Anti-tubercular screening of all the synthesized compounds were carried out by Microplate Alamar Blue Assay in Middle Brook 7H9 broth media and DMSO solvent using H37Rv strain of Mycobacterium tuberculosis. The compounds were screened for anti-tubercular activity at 0.2-100µg/mL concentration. Rifampin, Isoniazid and Pyrazinamide are used as reference standard drug. A 96-well microliter plate with a U-shaped bottom was used for the assay (sterile). One row of 12 wells was used for each sample. Wells 1-10 for sample dilution and wells 11 and 12 wells as controls. Each row labeled with the sample code. In the each row of all 12 wells, 7H9 broth was added. Solution of the working concentration of 2mg/ml of test compound prepared. In the first well of the each row test compound added (100 µl), mixed well and transferred 100 µl to the 2nd well. This procedure repeated up to well no. 10. 100 µl of appropriately diluted Culture suspension of M tb added to the well numbers 1 - 11. The well no 12 was filled with 100 µl of the test compound. The test compound was serially diluted in wells 1-10. Well no. 11 contains broth + organisms (No drug) and well no 12 contains broth + test compounds (No organisms). The plate covered with lid and incubated in a humidified chamber at 37°C for 7 days. The plate was checked every day for possible contamination. Working solution of resazurin was prepared as mentioned above, 35µl of the dye added to each well than incubated at 37°C overnight and the colour of the dye in the inoculated wells recorded.

3. RESULTS AND DISCUSSION

3.1 5-methoxypyrazine-2-carboxamide derivatives synthesis

Seven different 5-methoxypyrazine-2-carboxamide derivatives 13, 17, 18, 19, 25, 26 and 28 belonging to series 7 (S7) were synthesized using the described synthetic methods as illustrated in Schemes 1. Spectral studies, including FTIR, Hydrogen-1 NMR and mass spectrometry were used to characterize the produced analogues. The FTIR spectrum of all the compounds were performed using potassium bromide (Merck) on Agilent Cary 630 FTIR spectrometer, Agilent Technologies, The 1HNMR spectra of all the compounds were recorded using Avance III HD 500 MHz, Bruker and Mass spectroscopy analysis of all compounds were performed using Direct Injection Mass (HRMS) Model: 6540ba Qtof - Infinity 1290, Agilent Technologies. Spectra were recorded using Agilent MicroLab software. The synthesized compounds' FTIR measurements showed distinctive bands at particular wavenumbers, such as 3100-3400 (N-H), 2800-3100 (aromatic C-H), 1600-1700 (C=O amide), 1400-1600 (C=C), 1000-1400 (C=N of pyrazine) cm-1, respectively. Every synthetic compound's 1H NMR spectrum showed that the protons were signals between 3 and 4 ppm for OCH3, 6 and 8 ppm for phenyl, 8 and 9 ppm for C=N of imine and pyrazine, and 10 and 13 ppm for NH. The newly synthesized compound' mass spectra were as per their molecular weight.

3.1 Biological Evaluation

The outcomes are displayed as the minimal inhibitory concentration (MIC), where growth is indicated by pink and no growth by blue. [16] Figure 3 shows the synthesized compounds' MIC values. Compound S7-13 was found to be the most active of all the 5-methoxypyrazine-2-carboxamide derivatives, with a MIC of 1.6 micrograms per milliliter. In contrast, compounds S7-26, S7-18, S7-28, S7-17, and S7-19 had MIC values of 6.25, 12.5, 25, and 25 6 micrograms per milliliter, respectively. S7-13 and S7-26 showed reasonable antitubercular activity that was superior to Pyrazinamide (MIC 12.5 micrograms per milliliter) when matched to the criterions.

Figure 3: Biological assay plates

S. No.	Compound Name	(MIC) µg/mL
1	Rifampin	0.4
2	Isoniazid	0.8
3	Pyrazinamide	12.5
4	S7-13	1.6
5	S7-17	25
6	S7-18	12.5
7	S7-19	25
8	S7-25	25
9	S7-26	6.25
10	S7-28	12.5

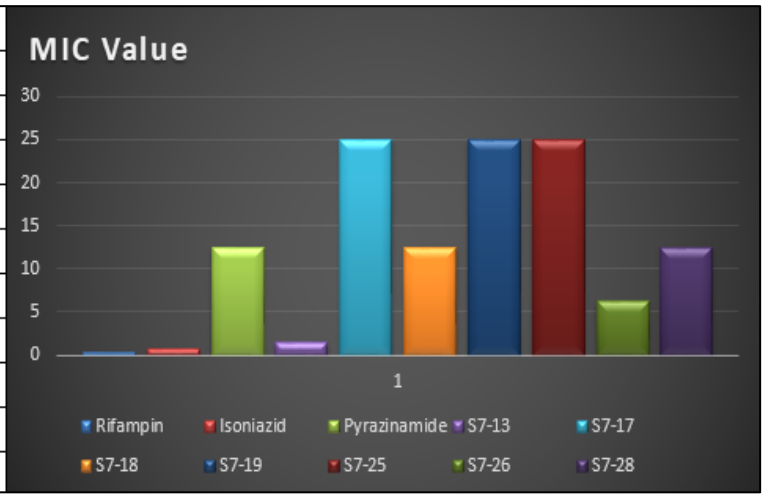

Figure 4: MIC value of in vitro anti-tubercular screening of synthesized compounds against H37Rv strain of M. tuberculosis

4. CONCLUSION

On the basis of detailed literature review pyrazine derivatives has been designed for antitubercular activity. The designed analogs were further subjected to virtual screening and molecular docking studies prior to synthesis. Further physicochemical characterization and spectral analysis was performed to assure the structure of synthesized analogs. The resazurin assay was used to assess the synthesized compounds' in vitro antitubercular activity alongside the Mycobacterium TB H37Rv strain. With minimum inhibitory concentrations (MIC) ranging from 1.6 to 25 µg/mL, the synthesized compounds showed considerable antitubercular action against the H37RV strain of Mycobacterium tuberculosis, suggesting their potential as potent anti-TB medicines. Among the tested compounds S7-13 exhibited potent antitubercular activity at MIC 1.62 µg/ml. The study's findings suggest that these compounds could serve as a foundation for further structural modifications to enhance their efficacy.

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