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DESIGN, SYNTHESIS PHARMACOLOGICAL EVALUATION OF 2-ARYL BENZOTHIAZOLE DERIVATIVES FOR ANTITUBERCULAR ACTIVITY

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ABSTRACT:
A number of novel 2-aryl substituted benzothiazoles were created for the current investigation, and their ability to suppress the growth of Mycobacterium TB H37Rv strain of the bacteria was assessed. FTIR and NMR spectral analysis were used to characterise the structures of the newly synthesised substances. The majority of the synthetic molecules exhibited good to moderate anti-tubercular efficacy. According to the findings, three compounds—3a, 3d, 3f, and 3g—have antitubercular activity that is either superior to or equal to that of ordinary streptomycin and pyrazinamide. Benzothiazoles should be given further thought as potential antitubercular drugs based on future research.

Keywords: Benzothiazoles, H37Rv strain, Anti-mycobacterial activity

INTRODUCTION

Mycobacterium tuberculosis (Mtb) and other species, including M. microti, M. caprae, M. africanum, M. pinipedii, and M. bovis, are the ubiquitous organisms that cause tuberculosis, a chronic necrotizing bacterial illness. (1) First, it infects the lungs (pulmonary TB), then spreads to secondary locations such as the bones, joints, liver, and spleen (extra pulmonary TB) through the lymphatic and circulatory systems. (2) The WHO has listed tuberculosis as one of the three diseases that require the greatest attention in terms of medication research and development due to the severe rise in both mortality and morbidity. (3) 10.5 million individuals contracted tuberculosis in 2022, and 1.7 million of them lost their lives to the illness, according to the WHO. 140,000 children perished from tuberculosis, and an estimated 1 million youngsters were infected. (4) Every year there are around 2-2.5 million cases of TB in India, which thus brings us into the category of the most TB vulnerable nation in the world. (5)

Isoniazid, pyrazinamide, ethambutol, and streptomycin are first-line treatments for tuberculosis; second-line treatments include PAS, ethionamide, cycloserine, amikacin, and kanamycin. (6) In an effort to counteract tuberculosis's worldwide hegemony, the World Health Organisation has initiated an empirical treatment programme known as Directly Observed Therapy Short-course, or DOTS. This programme consists of an initial 2-month dose regimen of isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA), followed by intermittent therapy of INH & RIF for an additional 4–7 months. (7) Inadequate patient adherence resulting from extended treatment regimens, in addition to the co-occurring HIV infection, has led to the rise of both multi- and extreme-drug resistant tuberculosis (MDR-& XDR-TB). Additionally, it was stated that 20% of patients who had previously received treatment and 3.6% of new patients had MDR-TB. (8,9) Mtb bacteria in MDR-TB are resistant to INH and RIF, while strains in XDR-TB are resistant to fluoroquinolones and injectable second-line medications. With the deadly diagnosis of totally-drug resistant tuberculosis (TDR-TB), in which the Mtb strains are resistant to all first- and second-line medications, this situation is become even more dire. (7) The World Health Organisation (WHO) created the "stop TB strategy" in 2006, which called for a reduction in the worldwide TB burden by 2015. The goal is to eradicate tuberculosis as a public health issue by 2050, and it has bolstered the development of innovative and potent methods to protect vulnerable populations against the disease. (10)

Numerous heterocyclic compounds containing nitrogen have been thoroughly investigated in an effort to discover medicines of significant medicinal value. Their wide range of pharmacological activities has made them an important player in the drug discovery process. Potential anti-TB medications are looked for in this group since the majority of provided anti-TB medications have nitrogen in their heterocyclic moiety. The well-known pharmacophore benzothiazole has been significant in the theoretical advancement of organic synthesis and heterocyclic chemistry. It possess multifarious bioactivities as antifungal (11), an appetite suppressant (12), anti-tubercular (13), analgesics (14), anti-malarial (15), antitumor (16), antiviral effects (17), anti-bacterial (18), anti-inflammatory (19), anti-convulsant (20), anthelmintics (21), blood sugar control(22)and antihistamine agents (23). According to the literature survey, benzothiazole derivatives are reported as potent anti-TB agents, due to their have narrow antitubercular spectrum, low bioavailability and faced the problem of drug resistance (24).Hence we have synthesized a series of 2-aryl benzothiazole derivatives and evaluated for their anti-tubercular activity.

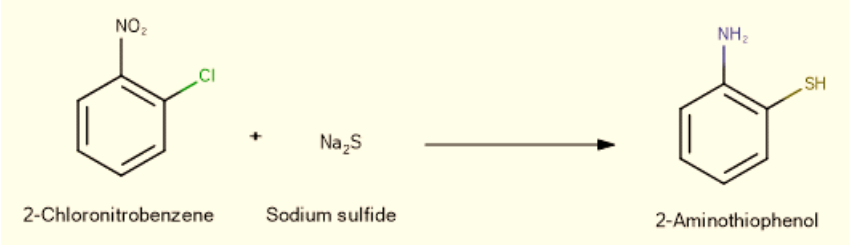
MATERIALS AND METHODS

Experimental: All chemicals and solvents were supplied by Sigma Aldrich, Merck, and CDH under certificate of purity. The melting range of the synthesized compounds was measured by Scientech-2211 digital auto melting/boiling point apparatus. Proton magnetic

resonance (1HNMR) spectra were recorded on Bruker 400 MHz NMR spectrometer using CDCl3 as solvent. Chemical shifts were reported in parts per million relative to internal standard tetramethylsilane (TMS). IR spectra were recorded on Bruker- Alpha 1005151/06 ATIR spectrophotometer.Reaction progress was checked by TLC using Merck Silica gel 60 F-254 coated glass plates. The solvent system used was n-Hexane: Ethyl acetate in the ratio of 4:6.

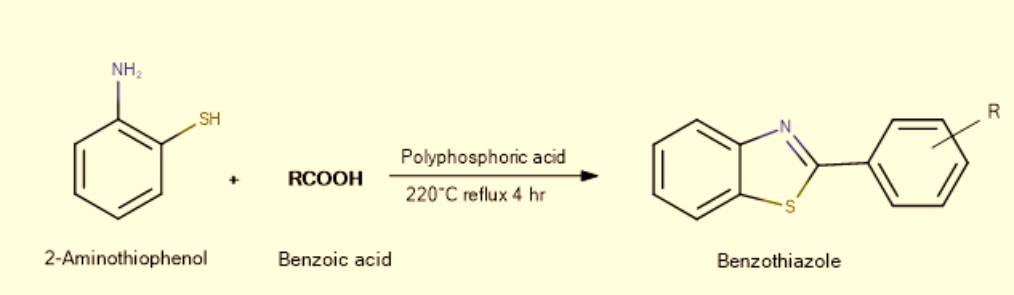
Synthesis

Step I: For synthesis of 2-aminothiophenol-A transparent sodium sulphide nonahydrate solution (4.8g, 0.02M) was made with 20 millilitres of water. It received a single amount of 1.28g of 2-chloronitrobenzene (0.008M), and the mixture refluxed for eight hours. A tiny amount of yellow-colored oil formed in the reaction mixture after 4 hours as a result of the by-product, 2-chloroaniline. After 8 hours, the reaction mixture was cooled, and 2-chloroaniline was subsequently extracted using ether. Glacial acetic acid was used to acidify the aqueous layer containing the sodium salt of 2-aminothiophenol after it had been saturated with sodium chloride. Care must be used when adding acetic acid in order to maximise the production of 2-aminothiophenol. (25)



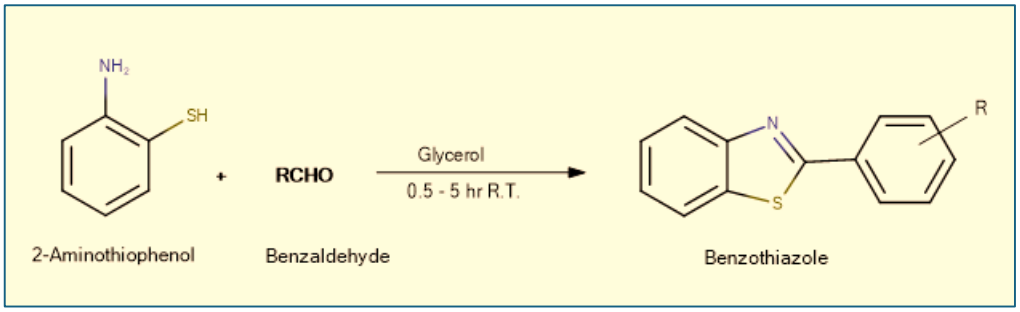
Step II: For synthesis of benzothiazoles

Using 2-aminothiophenol and benzoic acid (Scheme I)-Equimolar amounts of substituted benzoic acid and 2-aminothiophenol were combined with 15g of polyphosphoric acid, and the mixture was refluxed for four hours at 220˚C.After cooling, the reaction mixture was added to a huge amount of quickly agitated ice-cold water. 50% sodium hydroxide solution was added to the slurry to make it alkaline. TLC was used to track the reaction's development, with n-Hexane:Ethyl acetate in a 2:3 ratio serving as the mobile phase. Ice was introduced during the basification process to stop the temperature from rising too high. The reaction mixture was extracted using toluene, and the solvent was then evaporated in a rotary vacuum evaporator before the crude product was recrystallized from ethanol. (26)



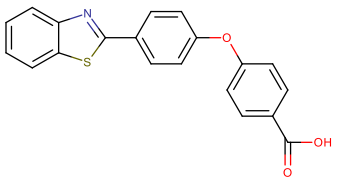
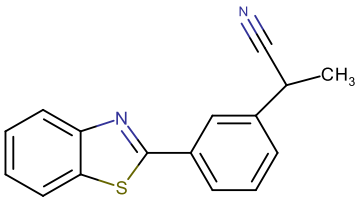
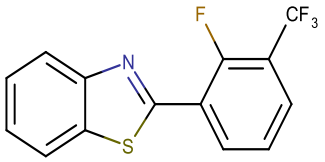
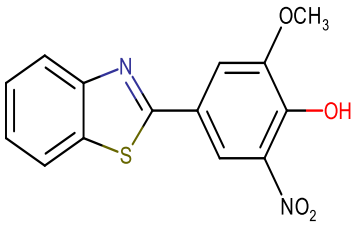
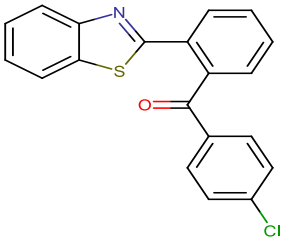
Scheme-1

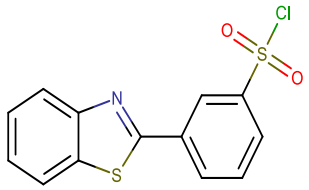
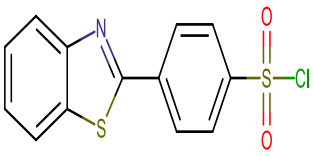
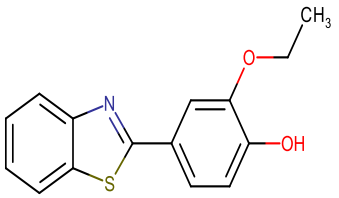
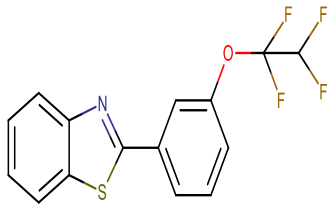
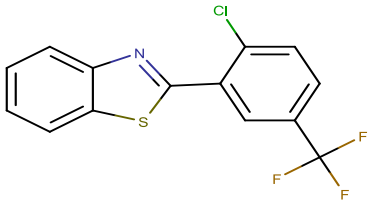
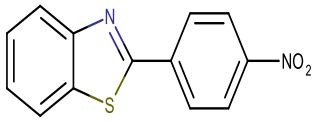
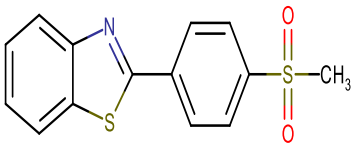
Using 2-aminothiophenol and benzaldehyde- After heating to a clear solution, equimolar amounts of 2-aminothiophenol (1.25 g, 10 mmol) and the corresponding aldehyde (10 mmol) in glycerol (10 ml) were allowed to cool for 0.5–5 hours (TLC control). To obtain the final compounds, the reaction mixture was quenched with water, and the solid product that was produced was filtered, dried, and recrystallized from ethanol. (27)



Scheme-2

Table 1: List of synthesized compounds

Derivatives	**IUPAC name**	**Structure**
3a	4-[4-(1,3-benzothiazol-2-yl) phenoxy] benzoic acid	
3b	2-[3-(1,3-benzothiazol-2-yl) phenyl] propanenitrile	
3c	2-[2-fluoro-3-(trifluoromethyl) phenyl]-1,3-benzothiazole	
3d	4-(benzothiazol-2-yl)-2-methoxy-6-nitrophenol	
3e	2-[2-(4-chlorobenzoyl) phenyl]-1,3-benzothiazole	

3f	3-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride	
3g	4-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride	
3h	4-(1,3-benzothiazol-2-yl)-2-ethoxyphenol	
3i	2-[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-1,3-benzothiazole	
3j	2-[2-chloro-5-(trifluoromethyl) phenyl]-1,3-benzothiazole	
3j	2-(4-nitrophenyl) benzothiazole	
3k	2-(4-methanesulfonyl phenyl)-1,3-benzothiazole	

Anti-Tubercular Activity: In vitro antitubercular activity of compounds (3a-l) was assessed against Mycobacterium tuberculosis $H_{37}Rv$ strain (Table 4). Anti-mycobacterial activity when compared to standard drugs like Pyrazinamide and Streptomycin. (28-29)

RESULTS AND DISCUSSION

Table 2: Physical data of synthesized compounds

Derivative	Molecular formula	Molecular weight (g)	Yield (%)
3a	$C_{20}H_{13}NO_3S$	347.39	62
3b	$C_{16}H_{12}N_2S$	264.34	71
3c	$C_{14}H_7F_4NS$	298	74
3d	$C_{14}H_{10}N_2O_4S$	303.31	56
3e	$C_{20}H_{12}ClNOS$	349.83	82
3f	$C_{13}H_{18}ClNO_2S_2$	309.79	65
3g	$C_{13}H_{18}ClNO_2S_2$	309.79	83
3h	$C_{15}H_{13}NO_2S$	271.22	70
3i	$C_{15}H_8F_4NOS$	327.3	56
3j	$C_{14}H_7ClF_3NS$	313.73	70
3k	$C_{13}H_8N_2O_2S$	256.28	54
3l	$C_{14}H_{11}NO_2S_2$	289.37	69

Table 3: Solubility and TLC data of synthesized compound

Derivative	Rf Value	Solubility
3a	0.56	Ether, acetone, Ethanol, Methanol
3b	0.68	Ether, acetone, Ethanol, Methanol
3c	0.61	Ether, acetone, Ethanol, Methanol
3d	0.41	Ether, acetone, Ethanol, Methanol
3e	0.52	Ether, acetone, Ethanol, Methanol
3f	0.47	Ether, acetone, Ethanol, Methanol
3g	0.52	Ether, acetone, Ethanol, Methanol
3h	0.56	Ether, acetone, Ethanol, Methanol
3i	0.61	Ether, acetone, Ethanol, Methanol
3j	0.49	Ether, acetone, Ethanol, Methanol
3k	0.55	Ether, acetone, Ethanol, Methanol
3l	0.48	Ether, acetone, Ethanol, Methanol

Spectral analysis of synthesized compounds:

4-[4-(1,3-benzothiazol-2-yl) phenoxy] benzoic acid-IR spectra data:1710.98ν (C=O), 1690.08 ν (C=N), 1515.41 ν (C-C), 1411.45ν (C=C), 1058.96 ν (C-O-C), 754.78 ν (Ar C-H), 686.54 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$): δ11.0 (s, 1H, COOH), 8.32-8.00 (m, 4H, Ar-H), 7.55 (t, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.13 (d, 2H, Ar-H), 6.72 (d, 2H, Ar-H)

2-[3-(1,3-benzothiazol-2-yl) phenyl] propanenitrile- IR spectra data:2303.91 ν (C≡N),1665.11 ν (C=N), 1585.15 ν (C-C), 1431.68 ν (C=C), 759.19 ν (Ar C-H), 645.11 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$) : δ 8.20-8.05 (d, 2H, Ar-H), 7.52 (t, 2H, Ar-H), 7.33-6.99 (m, 4H, Ar-H), 3.46 (m, 1H, CH), 1.57 (d, 3H, CH_3)

2-[2-fluoro-3-(trifluoromethyl) phenyl]-1,3-benzothiazole- IR spectra data:1607.75 ν (C=N), 1515.50 ν (C-C), 1465.28 ν (C=C), 1050.58 ν (C-F), 745.14 ν (Ar C-H), 692.81 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$): δ 8.25-8.12 (d, 2H, Ar-H), 7.56 (t, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H), 7.02 (t, 1H, Ar-H)

4-(benzothiazol-2-yl)-2-methoxy-6-nitrophenol-IR spectra data:3376.99 ν (OH), 1615.35 ν (C=N), 1549.28 ν (C-C), 1468.13 ν (C=C), 1318.19 ν (C-N), 1041.48 ν (C-O-C), 799.98 ν (Ar C-H), 672.07 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$): δ 8.32-8.00 (d, 2H, Ar-H), 7.88 (s, 1H, Ar-H), 7.52 (t, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 5.08 (s, 1H, OH), 3.99 (s, 3H, CH3)

2-[2-(4-chlorobenzoyl) phenyl]-1,3-benzothiazole-IR spectra data:1801.85 ν (C=O), 1650.31 ν (C=N), 1515.40 ν (C-C), 1435.28 ν (C=C), 756.63 ν (Ar C-H), 722.64 ν (C-Cl), 692.40 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$): δ 8.03-8.00 (d, 2H, Ar-H), 7.85 (d, 1H, Ar-H), 7.70 (d, 2H, Ar-H), 7.59-7.32 (m, 7H, Ar-H)

3-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride-IR spectra data:1610.16 ν (C=N), 1544.62 ν (C-C), 1409.12 ν (C=C), 1199.10 ν (SO_2Cl), 796.71 ν (Ar C-H), 679.41 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$): δ 8.32-8.05 (m, 3H, Ar-H), 7.72 (d, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.55 (m, 3H, Ar-H)

4-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride- IR spectra data:1605.61ν (C=N), 1506.82 ν (C-C), 1439.52 ν (C=C), 1204.16 ν (SO_2Cl), 754.50 ν (Ar C-H), 670.11 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$): δ 8.15 (d, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.99 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.54 (t, 2H, Ar-H)

4-(1,3-benzothiazol-2-yl)-2-ethoxyphenol- IR spectra data:3367.45 ν (OH), 1601.01 ν (C=N), 1508.41 ν (C-C), 1437.38 ν (C=C), 1039.98 ν (C-O-C), 750.17 ν (Ar C-H), 655 ν (C-S); ^{1}HNMR spectra data: ($CDCl_3$)δ 8.59-8.05 (d, 2H, Ar-H), 7.49 (d, 2H, Ar-H), 6.97-6.68 (m, 3H, Ar-H), 4.65 (s, 1H, OH), 3.97 (m, 2H, CH_2), 1.53 (t, 3H, CH_3)

2-[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-1,3-benzothiazole-IR spectra data:1728.86 ν (C=N), 1596.70 ν (C-C), 1439.12 ν (C=C), 1192.42 ν (C-F), 832.32 ν (Ar C-H), 722.53 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$)δ 8.25 (d, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.56 (t, 2H, Ar-H), 7.21 (t, 1H, Ar-H), 7.04- 6.73 (m, 3H, Ar-H)

2-[2-chloro-5-(trifluoromethyl) phenyl]-1,3-benzothiazole- IR spectra data:1698.40 ν (C=N), 1515.09 ν (C-C), 1404.36 ν (C=C), 1077.57 ν (C-F), 789.28 ν (C-Cl), 742.04 ν (Ar C-H), 641.72 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$)δ 8.32- 8.00 (d, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.55 (t, 2H, Ar-H), 7.40 (d, 1H, Ar-H), 6.72 (d, 1H, Ar-H)

2-(4-nitrophenyl) benzothiazole: IR spectra data:1669.26 ν (C=N), 1586.48 ν (NO_2), 1516.91 ν (C-C), 1417.09 ν (C=C), 752.05 ν (Ar C-H), 657.15 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$)δ 8.28- 8.04 (m, 4H, Ar-H), 7.73 (d, 2H, Ar-H), 7.51 (t, 2H, Ar-H)

2-(4-methanesulfonyl phenyl)-1,3-benzothiazole-IR spectra data:1647.80 ν (C=N), 1523.76 ν (C-C), 1440.49 ν (C=C), 1022.14 (S=O), 802.37 ν (Ar C-H), 690.53 ν (C-S); ^{1}HNMR spectra data ($CDCl_3$)δ 8.31- 8.09 (d, 2H, Ar-H), 7.97 (d, 2H, Ar-H), 7.68(d, 2H, Ar-H) 7.55 (t, 2H, Ar-H), 2.41 (s, 3H, CH_3)

Sodium sulphide and ortho chloronitrobenzoene, two inexpensive ingredients, were used to create the benzothiazole derivatives. Every chemical was produced with a notable yield. ATR IR and 1HNMR spectrophotometry were used to establish the structures of the synthesised compounds. It was discovered that the spectral analysis result matched the information published in the literature (26). The primary peaks were measured at 1728-1605 cm-1 for the C=N group, 1365-1305 cm-1, and 722-640 cm-1 for the C-S group. The corresponding derivatives also showed absorption peaks for other functional groups. 1HNMR: The NMR peak for aromatic hydrogens (Ar-H) was identified in the range δ6.99-8.32ppm, while for the CH3group, it was found at δ1.53-3.99ppm.

With a minimum inhibitory concentration (MIC) of 6.25 µg/ml, four of the twelve compounds—compounds 3a, 3f, 3g, and 3d—exhibited good Mtb inhibitory activity, according to the results. These substances were discovered to exhibit comparable anti-tuberculosis efficacy to that of the common medication streptomycin, and they were regarded as the most effective analogues against mycobacterium. When compared to common medications like streptomycin and pyrazinamide, compounds 3b, 3c, 3e, 3h, and 3k shown moderate action with a MIC of 12.5µg/ml, whereas compounds 3i, 3j, and 3l demonstrated the least anti-mycobacterial activity.

Table 4: Anti-tubercular activity of the synthesized compounds

Sr. No	Compound	MIC(µg/ml)
1	3a	6.25
2	3b	12.5
3	3c	12.5
4	3d	6.25
5	3e	12.5
6	3f	6.25
7	3g	6.25
8	3h	12.5
9	3i	25
10	3j	25
11	3k	12.5
12	3l	25
15	Pyrazinamide	3.125
16	Streptomycin	6.25

CONCLUSION

Every synthesised chemical (3a–3l) was assessed for its ability to inhibit the growth of mould. The FTIR, NMR, and mass spectroscopy techniques were utilised to elucidate the structure of the synthesised molecules. Using the Microplate Almar Blue Assay (MABA) technique, the target compounds' inhibitory efficacy against the Mycobacterium TB H37Rv strain was assessed. Compounds 9a, 9d, 9f, and 9g showed good anti-tubercular activity (MIC-6.25µg/ml) out of all the investigated compounds. The phenyl ring of the 2-Aryl benzothiazole nucleus is most likely responsible for the action of these FOUR compounds. In light of this, additional research can be conducted to create more 2-aryl based benzothiazole derivatives in order to create more effective medications against mycobacteria.

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