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Synthesis, Anti-Tubercular and Antimicrobial Screening of 2-aryl/benzyl-2'-Benzyl-4'-Methyl-4,5'-Bithiazole Derivatives

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ABSTRACT

A small focused library of 2-aryl/benzyl-2'-benzyl-4'-methyl-4,5'-bithiazole derivatives, **7a-ag** has been efficiently synthesized. The chemical structure of the newly synthesized compounds was determined by analytical and spectral methods. The title compounds were screened for inhibitory activity against *Mycobacterium smegmatis* MC^2 155 strain while the antimicrobial properties were investigated against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Proteus vulgaris, Saccharomyces cerevisiae* and *Candida albicans.* Most of the synthesized compounds showed moderate antitubercular activity while some compounds showed good antibacterial activity against *B. subtilis.* This study provides valuable directions to our ongoing endeavour of rationally designing more potent antimycobacterial agent.

Keywords: Bisthiazoles, *Mycobacterium Smegmatis*, Antibacterial Activity.

I. INTRODUCTION

Tuberculosis, a contagious disease, is now coexisting with human immunodeficiency virus (HIV) and is responsible for high mortality worldwide [1-2]. The last major clinical advance in tuberculosis chemotherapy was the introduction of Rifampicin in 1968 [3]. The unusual cell wall barrier, ability to remain dormant and emergence of multidrug (MDR) as well as extensively drug resistant (XDR) Mtb strains, demands the development of library of novel entities having various biodynamic heteryl scaffolds and active pharmacophores for treatment of TB [4-5].

Thiazole and its derivatives are important structure in medicinal chemistry that could provide a rich spectrum of biological activities [6-26]. Bithiazoles and directly linked polyazoles containing compounds are the backbone of bioactive natural products and thiopeptide antibiotics [27-28]. Bisthiazoles (cystothiazoles A-F), isolated from the myxobacterium culture broth of *Cystobacter fuscus*, has demonstrated potent antifungal activity against the phytopathogenic fungus *Phytopathora capsici* [29-30]. Large numbers of bisthiazoles have been synthesized by several research groups and screened for their biological activities [31-37].

Bis-1,3-azole scaffolds linked by different chain length and connectivity points between the rings, are present in numerous natural products with broad spectrum of biological activities [38-40]. Representative examples include Bengazoles, containing an uncommon [2,5'] bioxazole system [41-43], Cystothiazole A, with a [2,4']-bithiazole system [44], Largazole containing a [2,4'] thiazoline thiazole system [45], Leucamide A with a [2,4'] oxazole-thiazole system [46] and cyclic peptides containing 1,3-azoles as Venturamide A [47]. 2'-Alkyl/aryl-2-aryl-4-methyl-4',5- bithiazolyls showed anti-inflammatory activity [48] and thiazole linked with other azoles have exhibited anti-tubercular activity [49-50]. We have reported the clubbed 4,5'-bisthiazole derivatives as potential anti-tubercular and antibacterial agent [51]. By considering the importance of bisthiazole derivatives and as part of search for compounds as candidates for antitubercular drugs employing molecular simplification, in this present work we described the synthesis of 2-aryl/benzyl-2'-benzyl-4'-methyl-4,5'-bithiazole derivatives, **7a-ag** as potential antimycobacterial agents.

II. METHODS AND MATERIAL

EXPERIMENTAL

All the reactions were monitored and purity of the products was checked by thin-layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates with visualization by UV light. Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were recorded on Varian mercury XL-300 and BRUKER AVANCE II 400 NMR spectrometer (Bruker Instruments Inc., Billerica, MA, USA) at either 400-MHz (^{1}H NMR) and100-MHz (^{13}C NMR) spectrometer instruments. Chemical shifts are reported from internal tetramethylsilane standard and are given in δ units. Infrared spectra were taken on Shimadzu FTIR (KBr) (Shimadzu Corporation, Kyoto, Japan) – 408 in KBr. The LC-MS spectra were recorded on a Shimadzu 2010 LC-MS. Column chromatography was performed on silica gel (100–200 mesh) supplied by Acme Chemical Co. (Mumbai, Maharashtra, India). The chemicals and solvents used were laboratory grade and were purified as per literature methods.

Synthesis of 3-bromopentane-2,4-dione (2)

A mixture of acetylacetone (10 mmol) and p-toluenesulfonic acid (5 mmol) in DCM (50 mL) was stirred at 0 ºC for 10 minutes, followed by NBS (10 mmol). The reaction mixture was further stirred for 6-8 hour (TLC). The reaction was quenched by sodium bicarbonate solution and stirred for 10 minutes. The aqueous layer was extracted with DCM and combined organic layers was washed with water, dried with sodium sulphate and distilled under vacuum. The product isolated was used for second step without purification.

Synthesis of 1-(2-substitutedbenzyl-4-methylthiazol-5-yl)ethanone (4a):

A mixture of benzylthioamide (6.62 mmol) and of 3-bromopentane-2,4-dione, (6.62 mmol) was refluxed in ethanol. After completion of reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. Organic layer was extracted with sodium bicarbonate and then water. Organic layer was dried over sodium sulphate and distilled under vacuum. The product obtained was purified by column chromatography using hexane: ethyl acetate (9:1) as eluent.

Synthesis of 2-bromo-1-(4-methyl-2-(4-benzyl)thiazol-5yl)ethanone (5a):

A mixture of 1-(4-methyl-2-benzylthiazol-5-yl)ethanone (10 mmol) and pTSA (5 mmol) in DCM (50 mL) was stirred at 0 ºC for 10 minutes, then Br_2 (10 mmol) in DCM (20 mL) was added dropwise in reaction mixture. The reaction mixture was further stirred for further 12 hours at room temperature (TLC). After completion of the reaction, sodium bicarbonate solution was added in reaction mixture and stirred for 10 minutes. The aqueous layer was extracted with DCM and combined organic layer was washed with water, dried with sodium sulphate and distilled under vacuum.

General method for the synthesis 2-aryl/benzyl-2'-benzyl-4'-methyl-4,5'-bithiazole derivatives (7a-ag):

A mixture of 2-bromo-1-(2-(4-phenyl)-4-methyl thiazol-5yl)ethanone (1 mmol) and substituted thioamide (1.1 mmol) was refluxed in dry ethanol (15 mL). The reaction was monitored on TLC. After completion of the reaction; reaction mixture was poured in ice water and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate and water. The solvent was dried over sodium sulphate and removed under vacuum. The product was purified by crystallization from ethanol.

2'-benzyl-4'-methyl-2-phenyl-4,5'-bithiazole (7a):

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.20 (s, 1H, thiazole-H), 7.31-7.44 (m, 8H, Ar-H), 7.92-7.95 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 38.9, 114.3, 126.2, 127.7, 128.5, 129.1, 129.7, 130.4, 130.8, 132.5, 133.8, 147.5, 148.4, 165.1, 168.3; LC-MS, m/z: 349.1 $(M+H)^+$.

2'-benzyl-2-(4-bromophenyl)-4'-methyl-4,5'-bithiazole (7b):

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.12 (s, 1H, thiazole-H), 7.24-7.28 (m, 5H, Ar-H), 7.45 (d, J = 8.00Hz, 2H, Ar-H), 7.72 (d, J=8.00Hz, 2H, Ar-H); ^{13}CNMR(75MHz,$CDCl_3$): δ 17.0, 38.9, 114.3, 123.1, 126.2, 127.7, 128.7, 129.1, 129.7, 132.2, 132.5, 135.4, 147.5, 148.4, 165.1, 168.9; LC-MS, m/z:427.0 $(M+H)^+$, m/z:429.0 $(M+H+2)^+$.

2'-benzyl-2-(3-chlorophenyl)-4'-methyl-4,5'-bithiazole (**7c**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3), 4.35 (s, 2H, CH_2),7.20 (s,1H, thiazole-H), 7.24 -7.28 (m, 5H, Ar-H,), 7.30-7.49 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 39.8, 114.2,124.7, 126.5, 127.5, 128.5, 129.0, 130.2, 131.3, 131.6, 134.7, 135.1, 137.7, 148.6, 148.7, 166.0, 168.6; LC-MS, m/z:383.0 $(M+H)^+$, m/z: 385.0 $(M+H+2)^+$.

2'-benzyl-2-(4-chlorophenyl)-4'-methyl-4,5'-bithiazole (**7d**):
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.22(s,2H, , CH_2)7.21(s, 1H, thiazole-H) 7.24-7.28 (m, 5H, Ar-H,), 7.33 (d, J = 8.00Hz, 2H, Ar-H), 7.42(d, J = 8.00Hz, 2H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 17.3, 39.8, 114.0, 116.1, 126.4, 127.6, 128.5, 129.2, 130.2, 131.8, 136.1, 144.2, 152.4, 163.1, 168.1, 168.9; LC-MS, m/z:383.0 $(M+H)^+$, m/z:385.0 $(M+H+2)^+$.

2-benzyl-5-(2-(3-chloro-4-fluorophenyl)thiazol-4-yl)-4-methylthiazole (**7e**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.12-7.30 (m, 7H, Ar-H, thiazole-H), 7.77-7.80 (m, 1H, Ar-H), 7.99-8.02 (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 39.6, 114.1, 117.0, 122.0, 126.4, 128.3, 129.0, 129.3, 130.3, 130.7, 133.4, 135.4, 148.1, 148.5, 159.4, 164.9, 167.6;LC-MS, m/z: 401.0 $(M+H)^+$,m/z:403.0 $(M+H+2)^+$.

2'-benzyl-2-(4-fluorophenyl)-4'-methyl-4,5'-bithiazole (**7f**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.10 (t, J = 9.0Hz, 2H, Ar-H), 7.17 (s, 1H, thiazole-H) 7.31-7.36 (m, 5H, Ar-H, thiazole-H), 7.90-7.94 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 40.2, 114.0, 115.6, 116.1, 116.8, 125.9, 128.6, 129.1, 129.6, 136.4, 144.2, 152.2, 162.9, 168.2, 168.9; LC-MS, m/z: 367.1 $(M+H)^+$.

2'-benzyl-4'-methyl-2-(p-tolyl)-4,5'-bithiazole (**7g**): ^{1}H NMR (400 MHz, $CDCl_3$):
δ 2.36 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.28 (s, 2H, CH_2),7.10 (s, 1H, thiazole-H) 7.08-7.35 (m, 9 H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$): δ 17.2, 21.5, 39.8, 113.3, 126.5, 127.2, 127.3, 128.8, 129.0, 129.1, 129.6, 130.5, 140.6, 148.1, 148.5, 167.9, 168.2; LC-MS, m/z: 363.1 $(M+H)^+$.

2,2'-dibenzyl-4'-methyl-4,5'-bithiazole (**7h**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.08 (s, 1H, thiazole H),7.28-7.35 (m, 10H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$): δ 17.2, 39.8, 40.4, 114.1, 115.4, 125.4, 125.8, 128.2, 128.6, 129.1, 129.6, 136.2, 136.6, 143.1, 152.2, 167.6, 168.1; LC-MS, m/z: 363.1 $(M+H)^+$.

2'-benzyl-2-(4-chlorobenzyl)-4'-methyl-4,5'-bithiazole (**7i**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 7.10 (s, 1H, thiazole-H), 7.23-7.35 (m, 9H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$): δ 17.1, 39.6, 40.1, 114.1, 115.6, 125.8, 128.4, 128.9, 129.2, 130.6, 134.2, 136.1, 136.8, 143.2, 152.1, 167.8, 168.4; LC-MS, m/z: 397.1 $(M+H)^+$, m/z: 399.1 $(M+H+2)^+$.

2'-benzyl-2-(3-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7j**):
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 4.29 (s, 2H, CH_2), 7.10 (s, 1H, thiazole-H), 6.00-7.14 (m, 9H,Ar-H);^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 39.8, 40.1, 114.1, 115.6, 116.8, 124.4, 127.2, 127.5, 128.8, 129.0, 129.3, 131.2, 137.8, 147.2, 148.4, 161.1, 168.2, 168.9; LC-MS, m/z: 381.1 $(M+H)^+$.

2'-benzyl-2-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7k**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 4.26 (s, 2H, CH_2), 6.99 (t, J = 8.8Hz, 2H, Ar-H), 7.08 (s, 1H, thiazole-H), 7.24-7.38 (m, 7H, Ar-H); ^{13}C NMR (100 MHz,$CDCl_3$): 17.1, 39.8, 40.2, 114.1, 115.2, 115.8, 125.8, 128.8, 129.2, 130.8, 131.8, 136.4, 143.2, 152.2, 160.1, 167.7, 168.2; LC-MS, m/z: 381.1$(M+H)^+$.

2'-(4-chlorobenzyl)-4'-methyl-2-phenyl-4,5'-bithiazole (**7l**):
^{1}H NMR (300 MHz,$CDCl_3$): δ 2.68 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.14-7.31 (m, 6H, Ar-H, thiazole-H), 7.41 (d, J = 7.2Hz, 2H, Ar-H), 7.85-7.90 (m, 2H, Ar-H);^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 38.7, 115.0, 126.2, 128.4, 129.2, 129.8, 130.3, 130.9, 131.2, 133.4, 134.0, 147.7, 148.2, 167.6, 169.1; LC-MS, m/z: 383.0 $(M+H)^+$,m/z: 385.0 $(M+H+2)^+$.

2-(4-bromophenyl)-2'-(4-chlorobenzyl)-4'-methyl-4,5'-bithiazole (**7m**):
^{1}H NMR (300 MHz, $CDCl_3$): 2.69 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.28-7.35 (m, 5H, Ar-H, thiazole-H), 7.57 (d, J = 8Hz, 2H, Ar-H), 7.83 (d, J = 8Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 38.8,114.4, 126.3, 128.5, 129.0, 129.7, 130.2, 130.8, 131.3, 132.9, 135.4, 147.7, 148.0, 166.8, 168.3; LC-MS, m/z: 460.9 $(M+H)^+$, m/z: 462.9 $(M+H+2)^+$.

2'-(4-chlorobenzyl)-2-(3-chlorophenyl)-4'-methyl-4,5'-bithiazole (**7n**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.26-7.50 (m, 7H, Ar-H, thiazole-H), 7.77-7.80 (m, 1H, Ar-H),7.96-7.97 (m, 1H, Ar-H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 17.1, 38.3, 114.2, 115.8, 125.6, 126.9, 128.4, 128.9, 130.2, 130.8, 131.2, 134.2, 134.8, 135.1, 144.0, 151.9, 168.0, 168.8; LC-MS, m/z: 417.0 $(M+H)^+$, m/z: 419.0 $(M+H+2)^+$.

2'-(4-chlorobenzyl)-2-(4-chlorophenyl)-4'-methyl-4,5'-bithiazole (**7o**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.22-7.32 (m, 5H, Ar-H, thiazole-H), 7.41 (d, J = 8Hz, 2H, Ar-H), 7.88 (d, J = 8Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 38.6, 114.0, 116.0, 128.2, 128.8, 129.2, 130.0, 131.2, 131.8, 133.9, 134.4, 144.2, 151.9, 167.9, 168.8; LC-MS, m/z: 417.0 $(M+H)^+$, m/z: 419.0 $(M+H+2)^+$.

2-(3-chloro-4-fluorophenyl)-2'-(4-chlorobenzyl)-4'-methyl-4,5' bisthiazole (**7p**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.16-7.34 (m, 6H, Ar-H, thiazole-H), 7.77-7.80 (m, 1H, Ar-H), 7.99-8.02 (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 39.0, 114.2, 117.3, 122.0, 126.4, 128.3, 129.0, 130.3, 130.7, 132.8, 133.4, 135.4, 148.4, 148.8, 159.5, 165.0, 167.7;LC-MS, m/z: 435.0 $(M+H)^+$,m/z:437.0 $(M+H+2)^+$.

2'-(4-chlorobenzyl)-2-(4-fluorophenyl)-4'-methyl-4,5'-bithiazole (**7q**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 7.10 (t, J = 8.4Hz, 2H, Ar-H), 7.20 (s, 1H, thiazole-H), 7.24-7.41 (m, 4H, Ar-H), 7.91-7.95 (m, 2H, Ar-H);^{13}C NMR (100MHz, $CDCl_3$): δ 17.2, 38.8, 114.0, 116.0, 116.4, 128.6, 129.1, 129.8, 130.6, 131.4, 134.6, 144.0, 152.0, 163.0, 168.2, 168.8; LC-MS, m/z: 401.0 $(M+H)^+$, m/z: 403.0 $(M+H+2)^+$.

2'-(4-chlorobenzyl)-4'-methyl-2-(p-tolyl)-4,5'-bithiazole (**7r**):
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.01 (s, 1H, thiazole-H), 7.00-7.38 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 17.0, 21.5, 38.8, 113.8, 115.8, 127.2, 128.8, 129.6, 130.2, 130.8, 131.6, 133.8, 138.4, 144.2, 152.0, 167.9, 168.8; LC-MS, m/z: 397.1 $(M+H)^+$, m/z: 399.1 $(M+H+2)^+$.

2-benzyl-2'-(4-chlorobenzyl)-4'-methyl-4,5'-bithiazole (**7s**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.01 (s, 1H, thiazole-H), 7.25-7.40 (m, 9H, Ar-H);^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2,39.6, 40.4, 114.4, 115.6, 126.2, 128.1, 128.8, 129.2, 130.3, 131.4, 134.4, 136.2, 143.2, 152.0, 167.9, 168.1; LC-MS, m/z: 397.1 $(M+H)^+$, m/z: 399.1 $(M+H+2)^+$.

2,2'-bis(4-chlorobenzyl)-4'-methyl-4,5'-bithiazole (**7t**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 4.26 (s, 2H, CH_2), 7.11 (s, 1H, thiazole-H),7.22-7.32 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 38.8, 39.0, 114.2, 127.2, 128.3, 128.8, 129.0, 130.4, 133.1, 133.2, 135.9, 136.2, 147.2, 148.5, 136.3, 169.6; LC-MS, m/z: 431.0 $(M+H)^+$, m/z: 433.0 $(M+H+2)^+$.

2'-(4-chlorobenzyl)-2-(3-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7u**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.24 (s, 2H, CH_2),4.30 (s, 2H, CH_2), 7.01 (s, 1H, thiazole-H), 6.77-7.15 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 38.6, 38.8, 112.6, 114.2, 115.4, 116.2, 124.8, 128.8, 130.1, 130.8, 131.4, 134.4, 138.1, 142.9, 152.0, 163.1, 167.9, 168.2; LC-MS, m/z: 415.0 $(M+H)^+$, m/z: 417.0 $(M+H+2)^+$.

2'-(4-chlorobenzyl)-2-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7v**):
^{1}H NMR (400 MHz, $CDCl_3$): 2.58 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 4.27 (s, 2H, CH_2), 6.99-7.04 (m, 2H, Ar-H), 7.11 (s, 1H, thiazole-H), 7.25-7.31 (m, 6H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 32.6, 38.8, 114.2,

115.4, 115.8, 128.8, 130.2, 130.8, 131.1, 131.9, 134.6, 142.9, 152.1, 160.1, 167.6, 168.2; LC-MS, m/z: 415.0 $(M+H)^+$, m/z: 417.0 $(M+H+2)^+$.

2'-(4-fluorobenzyl)-4'-methyl-2-phenyl-4,5'-bithiazole (**7w**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 6.93-6.99 (m, 2H, Ar-H), 7.10-7.43 (m, 6H, Ar-H, thiazole-H), 7.86-7.11 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 38.6, 113.9, 115.7, 126.6, 128.6, 128.9, 130.4, 130.7, 131.4, 133.3, 147.9, 158.6, 162.0, 167.9, 168.4; LC-MS, m/z: 367.1 $(M+H)^+$.

2-(4-bromophenyl)-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7x**):
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 6.94-7.00 (t, J = 9.1Hz, 2H, Ar-H), 7.11-7.42 (m, 5H, Ar-H, thiazole-H), 7.48 (d, J = 8.4Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 38.8, 114.0, 115.8, 126.7, 128.7, 129.1, 129.9, 130.5, 131.2, 132.6, 148.0, 148.2, 162.5, 167.7, 168.6; LC-MS, m/z:445.0 $(M+H)^+$,m/z: 447.0 $(M+H+2)^+$

2-(3-chlorophenyl)-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7y**):
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 7.11-7.22 (t, J = 9.1Hz, 2H, Ar-H), 7.48 (s, 1H, Thiazole-H) 7.73-7.86 (m, 4H, Ar-H), 7.88 (d, J = 8.2Hz, 2H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 17.2, 38.9, 114.0, 115.9, 124.7, 127.1, 128.1, 128.7, 130.7, 132.3, 133.5, 148.4, 148.8, 158.6, 160.8, 163.2, 166.4, 168.2; LC-MS, m/z: 401.0 $(M+H)^+$, m/z: 403.0 $(M+H+2)^+$.

2-(4-chlorophenyl)-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7z**):
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.11 (t, J = 9.1Hz, 2H, Ar-H), 7.41 (s, 1H, thiazole-H), 7.44-7.55 (m, 4H, Ar-H), 7.82 (d, J = 8.4Hz, 2H, Ar-H);^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 38.6, 114.0, 115.2, 116.0, 128.8, 129.6, 130.8, 131.2, 132.0, 134.4, 144.0, 152.0, 159.9, 167.8, 168.6; LC-MS, m/z: 401.0 $(M+H)^+$, m/z: 403.0 $(M+H+2)^+$.

2-(3-chloro-4-fluorophenyl)-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7aa**):
^{1}H NMR (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.10-7.26 (m, 5H, Ar-H, thiazole-H), 7.94- 7.99 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.2, 38.9, 114.1, 115.7, 117.1, 126.7, 128.8, 130.4, 130.7, 132.7, 133.5, 134.2, 148.5, 148.9, 159.5, 160.9, 165.0, 168.2; LC-MS, m/z: 419.0 $(M+H)^+$,m/z: 421.0 $(M+H+2)^+$.

2'-(4-fluorobenzyl)-2-(4-fluorophenyl)-4'-methyl-4,5'-bithiazole (**7ab**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.00-7.05 (m, 2H, Ar-H), 7.11 (t, J = 8.4Hz, 2H, Ar-H), 7.20 (s, 1H, thiazole-H), 7.30-7.33 (m, 2H, Ar-H), 7.91-7.95 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 38.9, 113.6, 115.6, 115.9, 127.1, 128.5, 129.5, 130.6, 133.5, 148.2, 148.7, 160.8, 162.8, 166.4, 168.1; LC-MS, m/z: 385.1 $(M+H)^+$.

2'-(4-fluorobenzyl)-4'-methyl-2-(p-tolyl)-4,5'-bithiazole (**7ac**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.0-7.05 (m, 2H, Ar-H), 7.17 (s, 1H, thiazole-H), 7.22 (d, J = 8.2 Hz, 2H, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 7.84 (d, J = 8.2 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 21.5, 38.9, 113.5, 115.5, 126.5, 127.4, 129.6, 130.2, 130.8, 131.8, 133.6, 148.0, 148.6, 162.0, 167.8, 167.9; LC-MS, m/z: 381.1 $(M+H)^+$.

2-benzyl-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7ad**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 4.33 (s, 2H, CH_2), 7.00-7.20 (m, 6H, Ar-H, thiazole-H), 7.31-7.40 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 38.8, 39.2, 113.8, 114.9, 115.4, 126.0, 128.8, 129.2, 130.6, 132.0, 136.2, 143.2, 151.9, 160.0, 167.6, 168.2; LC-MS, m/z: 381.1 $(M+H)^+$.

2-(4-chlorobenzyl)-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7ae**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 7.08-7.12 (m, 4H, Ar-H), 7.20 (s, 1H, thiazole-H), 7.31-7.40 (m, 4H, Ar-H);^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 39.8, 40.2, 114.2, 115.1, 115.8, 128.6, 129.9, 130.4, 131.1, 132.0, 134.4, 143.0, 152.0, 160.0, 167.8, 168.0; LC-MS, m/z: 415.0 $(M+H)^+$, m/z: 417.0 $(M+H+2)^+$.

2-(3-fluorobenzyl)-2'-(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7af**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 4.47 (s, 2H, CH_2), 7.11-7.24 (m, 5H, Ar-H, thiazole-H), 7.37-7.43 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.1, 32.6, 38.8, 114.2, 115.5, 124.4, 127.2, 128.6, 129.3, 130.6, 131.3, 133.5, 147.1, 148.4, 161.0, 162.2,163.3, 167.9, 169.6; LC-MS, m/z: 399.1 $(M+H)^+$.

2,2'-bis(4-fluorobenzyl)-4'-methyl-4,5'-bithiazole (**7ag**):
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 6.85-7.04 (m, 8H, Ar-H), 7.20 (s, 1H, thiazole-H); ^{13}C NMR (100MHz, DMSO-d_6): δ 17.2, 38.6, 38.8, 114.0, 114.9, 115.2, 115.6, 130.2, 130.6, 131.2,131.6, 142.9, 151.9, 159.9, 160.1, 167.4, 167.9; LC-MS, m/z: 399.1 $(M+H)^+$.

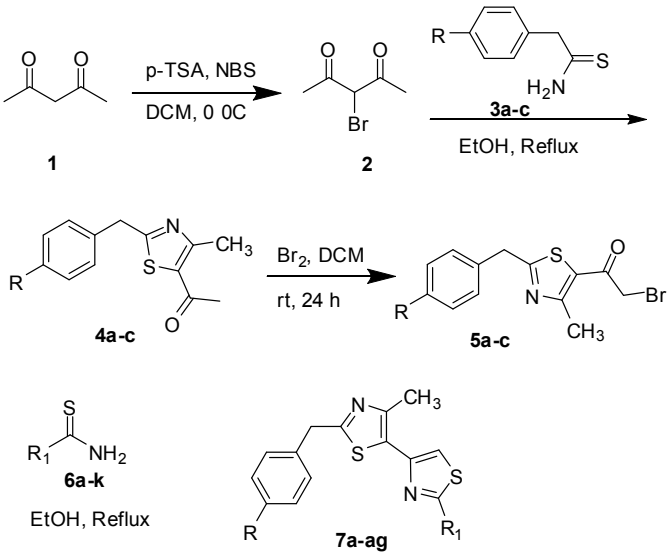
Anti-tubercular activity:
The synthesized compounds were screened for their antitubercular activity against *M. smegmatis* MC^2 155 strain. The series of compounds were obtained in 10 mM stock concentrations. Further, each compound was diluted with the required 100% (v/v) DMSO to achieve a working concentration of 1.5 mM. The inoculum for the assay was prepared by reviving aglycerol stock in Middlebrook 7H9 broth supplemented with 0.1%Tween 80 and 0.5% glycerol. At the time of inoculation, 10% ADS was added to the media and the culture was incubated in ashaker incubator at 37 °C and 200 rpm. The O.D. of the inoculums reached to 0.8-1 approximately, a secondary inoculum was inoculated and subsequently incubated. This was incubated overnight till the O.D. of the inoculum reached 0.4 approx., following which the inoculum was diluted 1:1000 times. In a 96 well microtiter plate, a 2 µL aliquot of the 1.5 mM dilution of compound was added to each well in triplicate, to which 98 µL of inoculum dilution was added, making the final concentration of compound 30 µM. To each plate, a set of controls was added to better ascertain the activity of the compounds. These included DMSO, which was taken as a growth control, and media control (Blank) and Rifampicin and Isoniazid, which were taken as positive controls of inhibition of *M. smegmatis*. After the completion of the period of 32 h, the absorbance of the inoculum in wells was measured at 600 nm using a Multi Mode Reader. Absorbance is considered directly proportional to the increase in growth of bacteria. Thus, it gives a measure of the growth of bacteria in each well. Percentage inhibition was determined against DMSO.

Antimicrobial activity:
The *in vitro* antimicrobial activities of all the synthesized compounds were done by the disc diffusion method [56-57]. All the strains were obtained from National Chemical Laboratory, Pune, India. All cultures were maintained at 4ºC over nutrient agar slants throughout the experiment. The cultures were incubated overnight at 37ºC in nutrient broth before using for antimicrobial activity. Five hundred microliters of overnight old bacterial / fungal suspension was spread over the nutrient agar plates using a sterile cotton swab in order to get a uniform microbial growth. The synthesized compounds were dissolved in DMSO. Under aseptic conditions, empty sterilized discs (Whatman no. 5, 6mm diameter) were impregnated with different concentrations (25µg/disc, 50 µg/disc, 75 µg/disc, 100 µg/disc) of respective synthesized compounds and placed on the agar surface. Paper disc moistened with aqueous DMSO was placed on seeded petri-plates as a vehicle control. The plates were left for 30 min. at room temperature to allow the diffusion of synthesized compounds and then incubated at 37 ºC for 24 h. The antimicrobial activity was evaluated by measuring the zone of inhibition against the test of microorganism. All experiments were carried out in triplicates.

III. RESULTS AND DISCUSSION

A series of 2-aryl/benzyl-2'-benzyl-4'-methyl-4,5'-bisthiazole derivatives, **7a-ag** were synthesized according to Scheme 1. Acetyl acetone **1** on reaction with p-toluene sulphonic acid and NBS in DCM gave 3-bromopentane-2,4-dione, **2** which on cyclocondensation with benzyl thioamide, **3a-c** in dry ethanol gave 1-(2-benzyl-4-methyl-thiazol-5-yl) ethanone, **4a-c**. Compounds **4a-c** on bromination with bromine and p-toluene sulphonic acid as catalyst in DCM at room temperature resulted in the formation of 1-(2-benzyl-4-methyl-thiazol-5-yl)-2-bromo-ethanone, **5a-c** which on

further cyclocondensation with aryl/benzyl thioamide, **6a-k** furnished 2-aryl/benzyl-2'-benzyl-4'- methyl 4,5'-bisthiazole derivatives, **7a-ag**. The physical data and yield of synthesized compounds **7a-ag** are reported in Table 1.



Scheme 1. Synthetic route of compounds**7a-ag**

The structure of the title compounds, **7a-ag** was confirmed by IR, NMR and MS. As a representative analysis of compound **7ac**, the IR (KBr) spectrum showed C=C/C=N absorption bands at 1629-1475 cm^{-1}. The ^{1}H NMR spectrum of compound **7ac** displayed three singlet in aliphatic region at δ 2.39 (CH_3) δ 2.67 (CH_3), δ 4.26 (CH_2) and a singlet in aromatic region at δ 7.17 (thiazole CH). A triplet at δ 7.02 and multiplate at δ 7.29-7.33 were attributed to protons of fluoro substituted phenyl ring, while doublets at δ 7.22 and δ 7.84 corresponds to protons of methyl substituted phenyl ring. The ^{13}C NMR spectrum of compound **7ac** revealed the two signal of methyl carbon at δ 17.1, 21.5 and a signal at δ 38.9 attributed to methylene carbon. Aromatic carbons showed typical fluoro-coupling [$\underline{C}_1$-F, δ 164.0, 160.5 (^{1}J = 250 Hz), $\underline{C}_2$-F δ 115.7, 115.4 (^{2}J = 22 Hz), $\underline{C}_3$-F δ 127.5, 127.4 (^{3}J = 8 Hz)]. Structure of compound **7ac** was further confirmed by molecular ion peak at *m*/*z* 381.1 $(M+H)^{+}$. Structures of all the derivatives were ascertained similarly.

IV. Antitubercular activity

The synthesized compounds (**7a-ag**) were screened for their antitubercular activity against *Mycobacterium smegmatis*, which is a fast growing non-pathogenic strain to assess the activity of the compounds in primary screening. The literature revealed that *M. smegmatis* based screens show 100% specificity and 78% sensitivity in comparison to MDR *Mycobacterium tuberculosis* [52-55]. The percentage inhibition was determined against DMSO. Rifampicin and isoniazid were used as reference drugs. The results of antitubercular activity are reported in **Table 1**.

The *in vitro* antitubercular activity against *M. smegmatis,* revealed that compounds **7d**, **7r**, **7s** and **7ac** exhibited moderate activity at 30 μM concentration. The preliminary structure activity relationship study revealed that replacement of hydrogen atom of phenyl ring A and B (**Figure 1**) by substituent groups like Br, Cl, F and CH_3 affects the antitubercular activity.

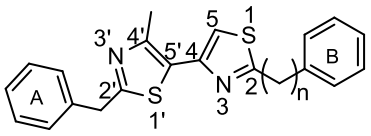


Figure 1

Further it was also noted that among the compounds **7a-g**, with un-substituted benzyl ring A and substituted phenyl ring B, only compound **7d** showed moderate activity. Compounds **7h-k** with substituted benzyl ring B were found to be less active. Among the compounds **7l-r** with 4-chloro substituted benzyl ring A and substituted phenyl ring B, compound **7r** showed moderate activity.

Table 1. Antitubercular activity of synthesized compounds **7a-ag**

Comp.	R	R^1	Yield (%)	MP (°C)	*M.smegmatis*[a]
7a	H	C_6H_5	58	94	13.764
7b	H	4-Br C_6H_4	60	116-118	8.648
7c	H	3-Cl C_6H_4	58	93-94	13.886
7d	H	4-Cl C_6H_4	60	106-108	32.4
7e	H	3-Cl,4-F C_6H_3	62	135-136	-
7f	H	4-F- C_6H_4	60	97-99	16.443
7g	H	4-CH_3-C_6H_4	62	48-50	12.911
7h	H	$C_6H_5CH_2$	60	60-62	7.065
7i	H	4-Cl-$C_6H_4CH_2$	65	82-84	7.552
7j	H	3-F-$C_6H_4CH_2$	62	78-80	-
7k	H	4-F-$C_6H_5CH_2$	62	78-80	4.141

7l	4-Cl	C_6H_5	65	88-90	21.924
7m	4-Cl	4-Br C_6H_4	62	101-103	4.385
7n	4-Cl	3-Cl C_6H_4	65	130-132	-
7o	4-Cl	4-Cl C_6H_4	66	52-54	-
7p	4-Cl	3-Cl,4-F C_6H_3	62	148-150	-
7q	4-Cl	4-F-C_6H_4	65	118-120	-
7r	4-Cl	4-CH_3-C_6H_4	60	136-138	32.034
7s	4-Cl	$C_6H_5CH_2$	70	75-77	38.49
7t	4-Cl	4-Cl-$C_6H_4CH_2$	62	78-80	22.655
7u	4-Cl	3-F-$C_6H_4CH_2$	60	48-50	14.251
7v	4-Cl	4-F-$C_6H_4CH_2$	66	82	11.084
7w	4-F	C_6H_5	60	104	16.797
7x	4-F	4-Br C_6H_4	65	109-110	13.281
7y	4-F	3-Cl C_6H_4	64	116-118	13.281
7z	4-F	4-Cl C_6H_4	66	118-120	8.333
7aa	4-F	3-Cl,4-F C_6H_3	58	104-106	5.078
7ab	4-F	4-F- C_6H_4	60	112-114	13.151
7ac	4-F	4-CH_3-C_6H_4	70	96	38.347
7ad	4-F	$C_6H_5CH_2$	60	98-100	24.609
7ae	4-F	4-Cl-$C_6H_4CH_2$	60	52-54	24.479
7af	4-F	3-F-$C_6H_4CH_2$	65	84	11.719
7ag	4-F	4-F-$C_6H_4CH_2$	66	94-96	13.021
Rifampicin					98
Isoniazid					97

a: % inhibition; - : Not active

Compounds **7s-v** with substituted benzyl ring B, compound **7s** showed moderate activity. Among the compounds **7w-ac**, with 4-fluoro substituted benzyl ring A and substituted phenyl ring B, compound **7ac** exhibited moderate activity. Compounds **7ad-ag** with substituted benzyl ring B, were found less active. It was notable that, chloro or fluoro substituents on ring A and 4-methyl substituted phenyl ring B showed moderate antitubercular activity.

V. Antimicrobial activity

The *in vitro* antimicrobial activity of all the synthesized compounds was done by the disc diffusion method. The antibacterial studies were against the standard Gram-negative bacteria, *Escherichia coli* (NCIM 2576), *Proteus vulgaris* (NCIM 2813) and Gram-positive bacteria, *Bacillus subtilis* (NCIM 2162), *Staphylococcus aureus* (NCIM 2602), while the antifungal activity was against the *Saccharomyces cerevisiae* (NCIM 3045) and *Candida albicans* (NCIM 3100). Amoxycillin and ciprofloxacin served as positive controls for antibacterial whereas fluconazole served as positive control for antifungal activity. The *in vitro* preliminary screening values (zone of inhibition) against microorganisms tested are summarized in **Table 2**.

Careful analysis of the antibacterial results presented in **Table 2**, provides some lead molecules with good antibacterial activity. Among the compounds **7a-ag** tested, it was observed that all the synthesized compounds showed moderate to good activity against *S. aureus* and *B. subtilis*, whereas most of the derivatives showed moderate activity against *E. coli* and *P. vulgaris.*

Table 2. Antimicrobial screening of compounds **7a-ag** (zone of inhibition in mm)

Comp.	Antibacterial activity				Antifungal actiity	
	E. coli	*P. vulgaris*	*S. aureus*	*B. subtilis*	*S. cerevisiae*	*C. albicans*
7a	7	7	10	10	22	16
7b	7	8	7	9	-	7
7c	7	8	7	9	-	7
7d	7	9	7	10	-	8
7e	7	9	11	8	-	-
7f	7	9	8	11	-	7
7g	7	8	7	7	-	7
7h	7	9	7	7	-	8
7i	9	9	10	18	-	9
7j	10	10	11	10	7	8
7k	10	9	11	13	-	7
7l	8	8	10	13	14	8
7m	7	7	7	10	-	9
7n	7	8	7	8	10	9
7o	7	8	7	8	-	10
7p	7	8	7	16	-	8
7q	7	8	7	10	-	7
7r	7	9	8	9	-	7
7s	7	9	9	9	-	10
7t	8	10	10	10	-	7

7u	9	10	10	12	-	-
7v	9	9	9	14	-	7
7w	-	-	8	10	-	-
7x	-	-	7	7	-	7
7y	7	8	8	8	7	7
7z	8	7	7	10	-	10
7aa	7	7	9	8	7	-
7ab	7	7	7	9	-	-
7ac	7	8	7	9	7	8
7ad	-	-	7	8	-	8
7ae	9	10	10	11	-	8
7af	10	11	9	10	-	7
7ag	10	11	10	11	7	-
Amox.	24	40	42	28	NA	NA
Cipro.	27	31	28	26	NA	NA
Fluco.	NA	NA	NA	NA	14	17

Amox: Amoxycillin (100 µg/disc), Cipro: Ciprofloxacin (100 µg/disc), Fluco: Fluconazole (25 µg/disc) were used as reference; synthesized compounds (100 µg/disc);
NA = Not Applicable; (-) = Inactive.

It was worthwhile to note that compounds **7i-k** with un-substituted benzyl ring A and chloro and fluoro substituted benzyl ring B exhibited moderate activity against all the tested strains. The activity was retained for 4-chloro substituted benzyl ring A and chloro and fluoro substituted benzyl ring B as in compounds **7t-u** and 4-fluoro substituted benzyl ring A and chloro and fluoro substituted benzyl ring B as in compounds **7ae-ag**. The results of antifungal activity revealed that most of the synthesized compounds were able to produce moderate inhibitory activity against *C. albicans*. It was noteworthy that un-substituted benzyl ring A and un-substituted phenyl ring B in compound **7a**, showed good activity comparable to the standard drug fluconazole against *S. cerevisiae* and *C. albicans*.

VI. CONCLUSION

In the present study, we have detailed the synthesis and biological screening of bisthiazole derivatives. It can be concluded that, most of the synthesized compounds with Cl and F substituent on benzyl and 4-methyl substituent on phenyl ring showed moderate antitubercular activity. Most of the synthesized compounds exhibited good antimicrobial activity towards most of the tested species. Thus, these results warrant the need for synthesis of similar libraries with other substituents to ascertain the trend described in this work.

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