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Antibacterial and Antitubercular Activity of Novel Benzothiazole-Aryl Amine Derivatives Tethered through Acetamide Functionality

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A novel series of substituted benzothiazole-*N*-phenyl acetamides were synthesized through a feasible scheme and characterized by IR, ^{1}H NMR and mass spectral methods. All the synthesized compounds were screened for antibacterial activity against two, Gram-positive strains: *Staphylococcus aureus*, *Bacillus subtilis*; four, Gram-negative strains: *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*; and antitubercular activity against mycobacterial strain: *Mycobacterium tuberculosis*. Among the 15 compounds (**6a-o**) tested, three compounds **6e**, **6l** and **6m** have demonstrated high potency with MIC values ranges from 6.25-12.5 µg/mL against both Gram-positive and Gram-negative strains. Compounds **6e** and **6l** displayed remarkable antitubercular activity with MIC value of 25 µg/mL.

Keywords: Benzothiazole, Acetamide, Antibacterial activity, Antitubercular activity.

INTRODUCTION

Efficacy of the therapeutic antibiotics is in absolute peril due to the unrestrained ascendency of the resistant pathogens. The ability of these resistant strains to the effectiveness of the currently available antibiotics poses serious threat to the lives of patients. The major concern is the emergence of multi-drug resistant *Mycobacterium* strains, methicillin resistant strains of *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), fluoroquinolone-resistant *Enterococcus. faecalis* (QREF) and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP), results in increased rate of mortality. This drug resistance phenomenon creating a major concern to discover the novel targets and drugs in the area of chemotherapy. Designing and developing chemical entities that are structurally distinct from the clinically established drugs represents an effective strategy as they may deliver the novel biomolecular targets for antimicrobial action [1-3].

Owing to their intrinsic nature of vital and diversified biological profile against a plethora of ailments from a simple bacterial infection to life threatening diseases, fused heterocycles' contribution in the well-being of mankind is exceptional. Majority of the drugs in the current market possess these fused heterocycles as a central part for drug action. Many research groups around the globe are making efforts to explore the novel applications of the fused heterocycles in the treatment of different diseases [4]. A review of the recent literature revealed that many effective antimicrobial agents show a heterocyclic moiety within their structure, in particular, substituted benzothiazole and benzimidazole derivatives received special attention as they belong to a class of compounds with proven utility in clinical medicine [5]. In this scenario, benzothiazole moiety represent an important bicyclic scaffold among the family of fused heterocyclic molecules. Benzothiazole is a representative class of sulphur-containing heterocycles and involves a benzene ring fused to a thiazole ring system. Numerous marine and terrestrial natural compounds possess benzothiazole moiety, which are widely premediated as antioxidants, plant growth regulators, enzyme inhibitors, imaging reagents, fluorescence materials and vulcanization accelerators [6,7].

Especially in the field of therapeutics and medicinal chemistry, benzothiazoles play an important role and render an extensive range of biological activities including anticancer [8,9], antibacterial [10,11], antituberculosis [12,13], antidiabetic [14], anthelmintic [15], antitumour [16-18], antiviral [19,20], antioxidant [21], anti-inflammatory [22,23], antiglutamate and

antiparkinsonism [24], anticonvulsant [25], muscle relaxant activities [26], neuroprotective [27], inhibitors of several enzymes [28], *etc*.

Amides, RCONHR' moiety are acknowledged to take part an essential role in molecular recognition, being important constituent in supramolecular chemical anion sensor technology [29-31]. Additionally, in nature, positional alignment of the amide hydrogen bonds are key players in the selective binding with anion substrates such as DNA. Numerous researches specified that the incidence of hydrogen bonding domain *e.g.*, amide appears to be valuable in the structures of antimicrobials [32]. Patel *et al.* [33] identified an agent encompasses of benzothiazole-acetamide system, which plays an indispensable role to provide promising antimicrobial activities. Hence, our attention is focused on the synthesis of benzothiazole-acetamide system containing chemical entities due to their significant biological activities and remarkable pharmaceutical values.

EXPERIMENTAL

All the chemicals and solvents used in this work were of synthetic grade and purchased from Sigma-Aldrich and used without purification. Merck-precoated aluminum TLC plates of silica gel 60 F_{254} were employed for the reaction monitoring and the spots visualized with iodine vapours and in UV chamber. Melting points were determined by Remi electronic melting point apparatus. IR spectra were recorded on Agilent FTIR by KBr pellet method. ^{1}H NMR recorded on BRUKER DRX–400 MHz. Mass spectra were recorded on BRUKER ESI-IT MS. The bacterial strains were obtained from the Department of Microbiology, Osmania University, Hyderabad, India. The samples were sub-cultured and preserved at 4 ºC.

Synthesis of 2-(2-chloroethyl)benzo[*d*]thiazole (3): To a solution of 2-aminothiophenol (**1**) (6.25 g, 50 mmol) in toluene (30 mL), 3-chloropropanoyl chloride (**2**) (6.34 g, 50 mmol) was added dropwise with continuous stirring over a 15 min resulting in the formation of an off-white precipitate. Then the mixture was stirred at room temperature overnight. Reaction progress was monitored using TLC with ethyl acetate/hexane (1:9). After the completion reaction mixture partitioned twice between water (100 mL) and ethyl acetate (200 mL). Two parts of organic layers were collected, combined and washed with a brine solution, dried over sodium sulphate and concentrated in vacuum. The crude product was purified by column chromatography using EtOAc/hexane (1:9) to obtain 2-(2-chloroethyl)-benzo[*d*]thiazole (**3**) as an oily liquid (5 g, 55.5%) [34].

Synthesis of 2-(benzo[*d*]thiazol-2-yl)ethan-1-ol (4): 2-(2-Chloroethyl)benzo[*d*]thiazole (3.96 g, 20 mmol) dissolved in 5 mL of ethanol was added dropwise in 10% NaOH solution (15 mL) and stirred the reaction mixture at room temperature. Reaction progress was monitored using TLC with ethyl acetate/hexane (1:9 v/v). After reaction completion, the unreacted base was quenched by the acid work up with acetic acid solution. Then the crude reaction mass was partition in water (20 mL) and ethyl acetate (40 mL). The organic layer was washed with brine solution and dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography using EtOAc/hexane (1:9) to obtain 2-(benzo[*d*]thiazol-2-yl)-ethan-1-ol (**4**) as off-white solid.

Synthesis of 2-(benzo[*d*]thiazol-2-yl) acetic acid (5): 2-(Benzo[*d*]thiazol-2-yl) ethan-1-ol (**4**, 1.8 g, 10 mmol) dissolved in DMF (10 mL) was treated with pyridinium dichromate (PDC, 3.76 g, 10 mmol) at room temperature. Reaction progress was monitored using TLC with ethyl acetate/hexane (2:8v/v). Reaction mixture was worked up twice by pouring into 7-10 volume of water and subsequent extraction with ether [34]. The ethereal layer was washed with brine solution and dried over anhydrous silica gel and concentrated under vacuum. The crude product was purified by column chromatography using EtOAc/hexane (2:8 v/v) to obtain 2-(benzo[*d*]thiazol-2-yl)-acetic acid (**5**) as off-white solid.

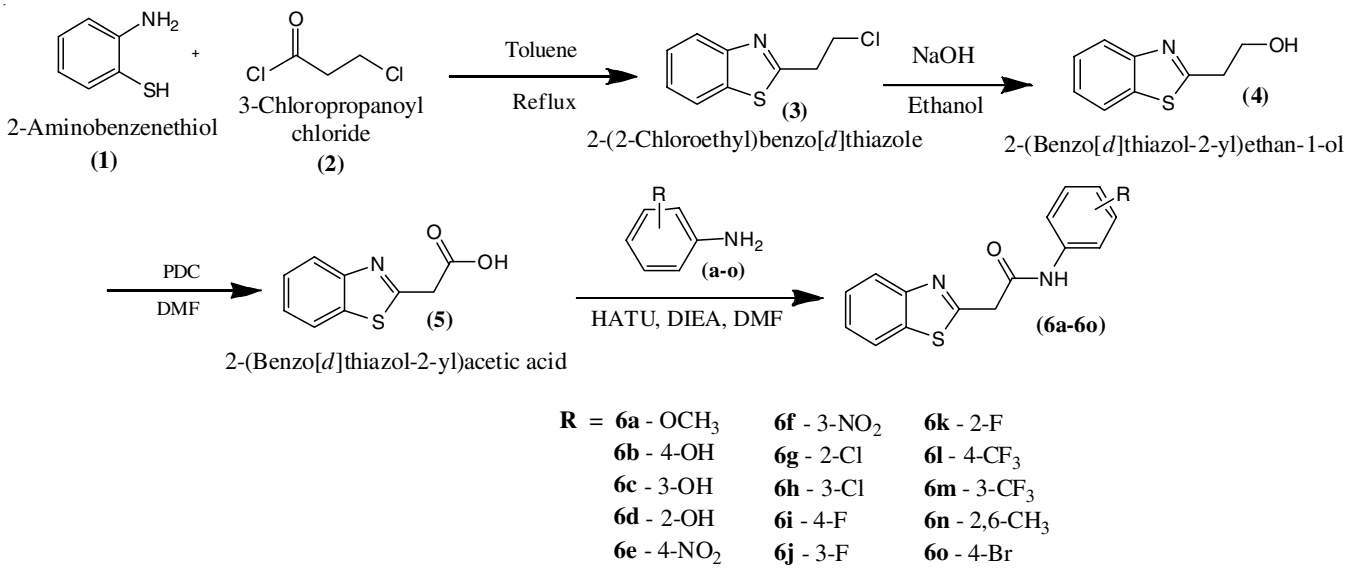
Synthesis of benzothiazole-*N*-phenyl acetamide derivatives (6a-o): A mixture of 2-(benzo[*d*]thiazol-2-yl)acetic acid (**5**) (0.96 g, 5 mmol, 1 equiv.), aryl amines (**a-o**) (5 mmol, 1 equiv.), DIEA (2.8 mL, 15 mmol, 3 equiv.) and HATU (1.9 g, 5 mmol, 1 equiv.) in 30 mL DMF was stirred at room temperature overnight and monitoring the progress with TLC [35]. The reaction mixture was partitioned between dichloromethane and water. The organic layer was dried over sodium sulphate and concentrated *in vacuo*. Then resulting crude material was purified by column chromatography with ethyl acetate/hexane (1:9 v/v) to obtain the final product **6a-o** (**Scheme-I**).

2-(Benzo[*d*]thiazol-2-yl)-*N*-(4-methoxyphenyl)acetamide (6a): Off white crystals, yield: 87%; m.p.: 212-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3280.1 (NH), 3060.3 (=C–H), 1645.5 (C=O), 1605.5 (C=N), 1540.3 (C=C), 1290.5 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 3.75 (3H, s), 4.25 (2H, s), 5.41 (1H, s), 6.60 (2H, ddd, *J* = 8.8, 2.7, 0.5 Hz), 7.24-7.43 (4H, 7.29 (ddd, *J* = 8.8, 1.7, 0.5 Hz), 7.30 (td, *J* = 7.5, 1.5 Hz), 7.37 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.71 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.80 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{16}H_{14}N_2O_2S$ ([M + H]$^+$): 298.36, found 299.25.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(4-hydroxyphenyl)acetamide (6b): Off white crystals, yield: 81%; m.p.: 147-176 ºC; IR (KBr, ν_{max}, cm^{-1}): 3627.3 (O–H), 3282.1 (NH), 3049.5 (=C–H), 1294.5 (C-N), 1646.5 (C=O), 1607.5 (C=N), 1531.3 (C=C), ; ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.38 (1H, s), 9.31 (1H, s), 6.67 (2H, ddd, *J* = 8.8, 2.3, 0.5 Hz), 7.24-7.43 (4H, 7.27 (ddd, *J* = 8.8, 1.7, 0.5 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 9.31 (1H, s). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{12}N_2O_2S$ ([M + H]$^+$): 284.33, found 285.30.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(3-hydroxyphenyl)acetamide (6c): Off white crystals, yield: 76%; m.p.: 179-181 ºC; IR (KBr, ν_{max}, cm^{-1}): 3629.4 (O–H), 3282.1 (NH), 3049.5 (=C–H), 1646.5 (C=O), 1607.5 (C=N), 1531.3 (C=C), 1294.5 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.38 (1H, s), 6.67 (2H, ddd, *J* = 8.8, 2.3, 0.5 Hz), 7.24-7.43 (4H, 7.27 (ddd, *J* = 8.8, 1.7, 0.5 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 9.34 (1H, s). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{12}N_2O_2S$ ([M + H]$^+$): 284.33, found 285.30.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(2-hydroxyphenyl)acetamide (6d): Off white crystals, yield: 80%; m.p.: 186-188 ºC;



R = **6a** - OCH_3 **6b** - 4-OH **6c** - 3-OH **6d** - 2-OH **6e** - 4-NO_2 **6f** - 3-NO_2 **6g** - 2-Cl **6h** - 3-Cl **6i** - 4-F **6j** - 3-F **6k** - 2-F **6l** - 4-CF_3 **6m** - 3-CF_3 **6n** - 2,6-CH_3 **6o** - 4-Br

Scheme-I: Synthesis for the proposed benzothiazole acetamide derivatives

IR (KBr, ν_{max}, cm^{-1}): 3628.9 (O–H), 3282.1 (NH), 3049.5 (=C–H), 1646.5 (C=O), 1607.5 (C=N), 1531.3 (C=C), 1294.5 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.35 (1H, s), 9.31 (1H, s), 6.68 (1H, ddd, *J* = 8.5, 1.3, 0.5 Hz), 7.03 (1H, ddd, *J* = 8.5, 7.5, 1.2 Hz), 7.14 (1H, ddd, *J* = 8.3, 7.5, 1.3 Hz), 7.28-7.43 (3H, 7.35 (ddd, *J* = 8.3, 1.2, 0.5 Hz), 7.35 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 9.38 (1H, s). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{12}N_2O_2S$ ([M + H]$^+$): 284.33, found 285.30.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(4-nitrophenyl)acetamide (6e): Light brown crystals, yield: 64%; m.p.: 192-194 ºC; IR (KBr, ν_{max}, cm^{-1}): 3284.2 (NH), 3051.6 (=C–H), 1644.5 (C=O), 1606.5 (C=N), 1511.7 (-NO_2), 1284.6 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ: 4.31 (2H, s), 5.29 (1H, s), 7.28-7.43 (4H, 7.35 (ddd, *J* = 8.6, 2.2, 0.4 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 8.13 (2H, ddd, *J* = 8.6, 1.8, 0.4 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ([M + H]$^+$): 313.30, found 314.25.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(3-nitrophenyl)acetamide (6f): Light brown crystals, yield: 61%; m.p.: 176-178 ºC; IR (KBr, ν_{max}, cm^{-1}): 3287.7 (NH), 3048.2 (=C–H), 1646.1 (C=O), 1606.5 (C=N), 1513.1 (-NO_2), 1287.8 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.29 (1H, s), 7.28-7.49 (5H, 7.41 (ddd, *J* = 8.2, 1.6, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.45 (ddd, *J* = 8.4, 8.2, 0.5 Hz), 7.44 (ddd, *J* = 8.4, 1.7, 1.6 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 7.99 (1H, ddd, *J* = 1.7, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ([M + H]$^+$): 313.30; found: 314.25.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(2-chlorophenyl)acetamide (6g): Off white crystals, yield: 74%; m.p.: 159-161 ºC; IR (KBr, ν_{max}, cm^{-1}): 3287.5 (-NH), 3050.5 (=C–H), 1646.5 (C=O), 1607.4 (C=N), 1285.5 (C-N), 671.5 (C-Cl); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.30 (2H, s), 7.16-7.43 (4H, 7.21 (ddd, *J* = 8.0, 7.7, 1.4 Hz), 7.29 (ddd, *J* = 8.0, 7.7, 1.6 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.46 (1H, ddd, *J* = 8.0, 1.6, 0.5 Hz), 7.69-7.85 (3H, 7.82 (ddd, *J* = 8.1, 1.5, 0.5 Hz), 7.77 (ddd, *J* = 8.0, 1.4, 0.5 Hz), 7.72 (ddd, *J* = 7.5, 1.8, 0.5 Hz), 9.95 (1H, s). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}ClN_2OS$ ([M + H]$^+$): 302.82, found 303.70.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(3-chlorophenyl)acetamide (6h): Off white crystals, yield: 68%; m.p.: 164-166 ºC; IR (KBr, ν_{max}, cm^{-1}): 3287.5 (-NH), 3050.5 (=C–H), 1646.5 (C=O), 1607.4 (C=N), 1285.5 (C-N), 671.5 (C-Cl); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.40 (1H, s), 7.15 (1H, ddd, *J* = 8.1, 1.7, 1.6 Hz), 7.28-7.43 (3H, 7.35 (ddd, *J* = 8.2, 8.1, 0.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.58 (1H, dt, *J* = 8.2, 1.6 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.77 (1H, td, *J* = 1.7, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}ClN_2OS$ ([M + H]$^+$): 302.82, found 303.70.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(4-fluorophenyl)acetamide (6i): Off white crystals, yield: 62%; m.p.: 147-149 ºC; IR (KBr, ν_{max}, cm^{-1}): 3283.3 (-NH), 3052.9 (=C–H), 1644.8 (C=O), 1602.4 (C=N), 1308.1 (C-F), 1288.2 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.30 (1H, s), 7.02 (2H, ddd, *J* = 8.6, 1.6, 0.6 Hz), 7.28-7.43 (2H, 7.32 (td, *J* = 7.5, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.69-7.76 (3H, 7.73 (ddd, *J* = 8.6, 1.9, 0.6 Hz), 7.72 (ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ([M + H]$^+$): 286.32, found 286.15.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(3-fluorophenyl)acetamide (6j): Off white crystals, yield: 60%; m.p.: 151-153 ºC; IR (KBr, ν_{max}, cm^{-1}): 3282.8 (-NH), 3052.9 (=C–H), 1644.1 (C=O), 1601.9 (C=N), 1303.2 (C-F), 1284.8 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.30 (1H, s), 7.01 (1H, ddd, *J* = 8.4, 1.7, 1.4 Hz), 7.28-7.43 (3H, 7.34 (ddd, *J* = 8.4, 8.2, 0.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.53 (1H, ddd, *J* = 8.2, 1.7, 1.4 Hz), 7.69-7.75 (2H, 7.72 (ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.71 (td, *J* = 1.7, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ([M + H]$^+$): 286.32, found 286.15.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(2-fluorophenyl)acetamide (6k): Off white crystals, yield: 64%; m.p.: 161-163 ºC; IR (KBr, ν_{max}, cm^{-1}): 3287.1 (-NH), 3051.4 (=C–H), 1645.9 (C=O), 1602.9 (C=N), 1308.1 (C-F), 1289.3 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 6.99-7.09 (2H, 7.04 (ddd, *J* = 8.3, 7.7, 1.4 Hz), 7.03 (ddd, *J* = 8.3, 1.6, 0.5 Hz), 7.19-7.43 (3H, 7.24 (ddd, *J* = 7.9, 7.7, 1.6 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 8.33 (1H, ddd, *J* = 7.9, 1.4, 0.5 Hz), 10.10 (1H, s). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ($[M + H]^+$): 286.32, found 286.15.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(4-(trifluoromethyl)phenyl)-acetamide (6l): Off white crystals, yield: 68%; m.p.: 191-193 ºC; IR (KBr, ν_{max}, cm^{-1}): 3280.1 (-NH), 3052.5 (=C–H), 1649.1 (C=O), 1608.2 (C=N), 1310.5 (C-F), 1284.5 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.40 (1H, s), 7.22-7.43 (4H, 7.25 (ddd, *J* = 8.2, 1.4, 0.5 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.57 (2H, ddd, *J* = 8.2, 1.8, 0.5 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ($[M + H]^+$): 336.36, found 337.30.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(3-(trifluoromethyl)phenyl)-acetamide (6m): Off white crystals, yield: 63%; m.p.: 187-189 ºC; IR (KBr, ν_{max}, cm^{-1}): 3285.2 (-NH), 3050.8 (=C–H), 1649.39 (C=O), 1603.4 (C=N), 1309.5 (C-F), 1285.8 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.40 (1H, s), 7.28-7.48 (4H, 7.43 (ddd, *J* = 7.9, 7.7, 0.5 Hz), 7.38 (ddd, *J* = 7.7, 1.8, 1.4 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.51 (1H, ddd, *J* = 1.8, 1.5, 0.5 Hz), 7.56 (1H, ddd, *J* = 7.9, 1.5, 1.4 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ($[M + H]^+$): 336.36, found 337.30.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(2,6-dimethylphenyl)acetamide (6n): Off white crystals, yield: 79%; m.p.: 203-205 ºC; IR (KBr, ν_{max}, cm^{-1}): 3282.2 (-NH), 3052.5 (=C–H), 1644.5 (C=O), 1604.5 (C=N), 1531.2 (C=C), 1293.0 (C-N); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 2.27 (6H, s), 4.29 (2H, s), 6.84 (1H, t, *J* = 7.9 Hz), 6.99 (2H, dd, *J* = 7.9, 2.4 Hz), 7.28-7.43 (2H, 7.32 (td, *J* = 7.5, 1.5 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.72 (1H, ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz), 9.90 (1H, s). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ($[M + H]^+$): 296.39, found 297.35.

2-(Benzo[*d*]thiazol-2-yl)-*N*-(4-bromophenyl)acetamide (6o): Pale yellow crystals, yield: 74%; m.p.: 227-229 ºC; IR (KBr, ν_{max}, cm^{-1}): 3284.2 (-NH), 3051.5 (=C–H), 1642.7 (C=O), 1605.8 (C=N), 1286.5 (C-N), 695.6 (C-Br); ^{1}H NMR (400 MHz, $CHCl_3$-d_6) δ ppm: 4.29 (2H, s), 5.35 (1H, s), 7.28-7.43 (4H, 7.37 (ddd, *J* = 8.4, 1.5, 0.6 Hz), 7.38 (ddd, *J* = 8.1, 7.5, 1.8 Hz), 7.32 (td, *J* = 7.5, 1.5 Hz), 7.69-7.75 (3H, 7.72 (ddd, *J* = 8.4, 1.5, 0.6 Hz), 7.72 (ddd, *J* = 7.5, 1.8, 0.5 Hz), 7.82 (1H, ddd, *J* = 8.1, 1.5, 0.5 Hz). ESI-MS: *m/z* Anal. calcd. for $C_{15}H_{11}N_3O_3S$ ($[M + H]^+$): 347.23, found 348.20.

Pharmacological evaluation

***in vitro* Antibacterial assay:** Agar disc diffusion method was employed for the evaluation of antibacterial activity of the synthesized compounds (**6a-o**) by following standard guidelines of Clinical and Laboratory Standards Institute [36]. The following bacterial strains were used in this study: two Gram-positive strains, *Staphylococcus aureus* (ATCC 25323), *Bacillus subtilis* (ATCC 6051) and four Gram-negative strains, *Escherichia coli* (ATCC 35218), *Salmonella typhi* (MTCC 3216), *Pseudomonas aeruginosa* (ATCC 27893) and *Klebsiella pneumonia* (ATCC 31488).

A stock solution of 20 mg of each synthetic compound dissolved in 1 mL of DMSO as solvent was prepared. Bacterial cultures, collected from the source were sub-cultured to isolate pure colonies and the pure isolates were transferred into sterile normal saline solution and vortexed to form bacterial homogenous suspensions. The turbidity was then adjusted to 0.5 McFarland standard units and the suspensions were poured over Mueller-Hinton agar (MHA) plates. Sterile filter paper disks (Whatman No. 3 chromatography paper) with a diameter of 6 mm were placed over these plates. The sterile disks were impregnated with 20 µL (400 µg in strength) of the tested compounds (20 mg/mL dissolved in DMSO). Ciprofloxacin was used as reference standard (positive control) and sterile distilled water was selected as negative control. Finally, the plates were incubated at 37 ºC for 24 h and the inhibition zones were measured in millimetres.

The minimum inhibitory concentration (MIC) of the synthesized compounds against the tested bacterial strains was determined by the broth dilution method. The pure bacterial culture of each microorganism was adjusted to 0.5 McFarland standards in Mueller-Hinton broth (MHB). Two-fold serial dilution method was followed according to the guidelines of Clinical and Laboratory Standards Institute [37]. The stock solutions of the tested compounds were prepared in DMSO and diluted in sterile water. Concentrations of the tested compounds ranged from 0.8 to 400 µg/mL. The minimal inhibitory concentrations (MICs) were defined as the lowest concentration of the compound that prevents visible growth of the microorganism. Ciprofloxacin used as positive control and sterile distilled water selected as negative control.

***in vitro* Antitubercular assay**

Preparation of inoculum: *Mycobacterium tuberculosis* MTB H37Rv (ATCC 27294) strains, which are susceptible to isoniazid were employed for the evaluation of antitubercular activity of the synthesized compounds. The bacterial strains were sub-cultured to have a fresh batch for the study, supplied with Muller Hinton broth at 37 ºC for two weeks. Bacterial suspensions with 0.5 McFarland standard turbidity, equivalents to 10^8 CFU was prepared by diluting it with normal saline solution. The mixture was vortexed for 30 s in a glass vessel and the particles were allowed to settle [38]. The microbial suspension (100 µL) was used for the inoculation.

Preparation of test samples and determination of MIC: The stock solutions of 400 µg/mL of synthesized compounds were prepared in DMSO. In order to determine the minimum inhibitory concentration of title compounds, serial dilution of compounds with varying strengths from 200 µg/mL to 0.8 µg/mL were prepared from the respective stock solutions.

Middlebrook 7H11 agar medium was used for growing the mycobacterium, supplemented with oleic albumin dextrose

catalase (OADC), after sterilization under moist heat using autoclave at 121 ºC for 15 min. Then medium was diluted with various strengths (200, 100, 50, 25, 12.5, 6.25, 3.12, 1.6 and 0.8 µg/mL) of synthesized (**6a-o**) compounds in appropriate volumes. Using aseptic technique, 5 mL of middle brook 7H11 agar medium was dispensed into each labelled quadrants of sterile quad-plates and allowed to solidify under laminar airflow with lids slightly opened. After solidification, bacterial suspension from the culture broth was inoculated aseptically through a loop (3 mm internal diameter) and incubated for 21 days at 37 ºC. The minimum inhibitory concentration (MIC) was determined by counting the colonies formed on the medium by comparing with the controls. DMSO and isoniazid were served as negative and positive controls, respectively [39].

RESULTS AND DISCUSSION

The compounds were synthesized from 2-aminobenzenethiol **(1)** and a dihalide linker, 3-chloropropanoyl chloride (**2**) in a condensation reaction to 2-(2-chloroethyl)benzo[*d*]-thiazole (**3**), which then converted to an alcohol derivative, 2-(benzo[*d*]thiazol-2-yl)ethan-1-ol (**4**) using base hydrolysis by employing 10% NaOH solution. Subsequently, the intermediate (**4**) was oxidized to a carboxylic acid, 2-(benzo[*d*]thiazol-2-yl)acetic acid (**5**) using PDC in DMF under mild conditions. Ultimately, the targeted benzothiazole-acetamide derivatives were synthesized in an amide coupling reaction between the intermediate, 2-(benzo[*d*]thiazol-2-yl)acetic acid (**5**) and various substituted anilines in the presence of amide coupling catalysts *e.g.* HATU and DIEA in DMF at room temperature.

All the synthesized compounds **6a-o** were resulted in the competitive yields. The synthesized compounds were confirmed by ^{1}H NMR and mass spectral data, which are in accordance with respect to the structure compounds. The C–H peak of the acetamide methylene group's chemical shift value (δ) was observed around 3.30 to 3.45 ppm as a singlet and the N–H peak of the amide group was observed around 5.6 ppm as a singlet in all the compounds. Further, the chemical shift values of the aromatic protons and their splitting patterns provided the confirmation of the structures of synthesized compounds.

The electron donating group substituted anilines delivered, respective benzothiazole-acetamide derivatives, in high yields in the final amide coupling reaction, over the electron withdrawing group substituted anilines. Highest yield (87%) was obtained with 4-OCH_3 substituted aniline, followed by -OH, -CH_3 substituted anilines.

Antibacterial activity: The antibacterial activity of the synthesized compounds (**6a-o**) were evaluated against two Gram-positive strains: *Staphylococcus aureus* (ATCC 25323), *Bacillus subtilis* (ATCC 6051); four Gram-negative strains: *Escherichia coli* (ATCC 35218), *Salmonella typhi* (MTCC 3216), *Pseudomonas aeruginosa* (ATCC 27893) and *Klebsiella pneumonia* (ATCC 31488); and one mycobacterial strain: *Mycobacterium tuberculosis* MTB H37Rv (ATCC 27294). The methods include the agar disc-diffusion method and broth dilution method for MIC determination in accordance with CLSI. The results of the antibacterial assay and antitubercular assay are reported in Tables 1 and 2.

It is evident that the all the synthesized benzothiazole-acetamide derivatives (**6a-o**) possess good to moderate antibacterial activity against the tested bacterial strains with reference to the standard drug ciprofloxacin. Among the tested compounds, compounds **6l, 6e, 6m** and **6i** have displayed higher zone of inhibition against all bacterial strains. Compound **6l** displayed the highest inhibition capacity (23-31mm) against all the bacterial strains. Moreover, all the benzothiazole- acetamide derivatives disclosed a tendency of being highly active against the Gram-positive strains in comaparison to the Gram-negative strains.

The results of MIC study also revealed that most of the compounds possess good to moderate antibacterial activity with MIC values ranging between 6.25 and 200 µg/mL. Out of the 15 compounds tested, compounds **6l**, **6e** and **6m** displayed a broad-spectrum antimicrobial activity and high potency against all the tested bacterial strains with MIC values of 6.25

TABLE-1
RESULTS OF AGAR DISK DIFFUSION STUDY

Compd. No.	R	Gram-positive		Gram-negative			
		S. aureus	*B. subtilis*	*E. coli*	*S. typhi*	*P. aeruginosa*	*K. pneumonia*
6a	4-OCH_3	21	18	19	20	16	18
6b	4-OH	22	23	21	19	20	22
6c	3-OH	20	21	18	16	19	21
6d	2-OH	21	19	18	15	17	19
6e	4-NO_2	29	26	23	21	24	25
6f	3-NO_2	22	22	20	18	21	19
6g	2-Cl	20	19	23	21	23	20
6h	3-Cl	20	20	21	20	24	21
6i	4-F	27	24	23	20	22	22
6j	3-F	25	23	22	21	24	23
6k	2-F	23	21	20	20	19	21
6l	4-CF_3	31	28	25	23	25	27
6m	3-CF_3	28	26	21	24	22	26
6n	2,6-CH_3	15	17	16	14	19	15
6o	4-Br	20	22	18	20	17	18
Ciprofloxacin		33	30	34	33	29	35

The value of each compound consisted of 'zone of inhibition range' of 03 replicates.

TABLE-2
RESULTS OF MIC DETERMINATION OF COMPOUNDS IN BROTH DILUTION STUDY

Compd. No.	R	Minimum inhibitory concentration (µg/mL)						
		Gram-positive		Gram-negative				*M. tuberculosis*
		S. aureus	*B. subtilis*	*E. coli*	*S. typhi*	*P. aeruginosa*	*K. pneumonia*	
6a	4-OCH_3	≥ 50	≥ 50	≥ 50	≥ 50	≥ 50	≥ 50	≥ 200
6b	4-OH	≥ 12.5	≥ 12.5	≥ 25	≥ 25	≥ 25	≥ 25	≥ 200
6c	3-OH	≥ 25	≥ 25	≥ 50	≥ 50	≥ 50	≥ 50	≥ 200
6d	2-OH	≥ 100	≥ 100	≥ 100	≥ 100	≥ 100	≥ 100	≥ 200
6e	4-NO_2	≥ 6.25	≥ 6.25	≥ 6.25	≥ 12.5	≥ 6.25	≥ 6.25	≥ 50
6f	3-NO_2	≥ 12.5	≥ 12.5	≥ 25	≥ 50	≥ 25	≥ 25	≥ 50
6g	2-Cl	≥ 25	≥ 25	≥ 25	≥ 25	≥ 25	≥ 25	≥ 100
6h	3-Cl	≥ 25	≥ 25	≥ 25	≥ 25	≥ 25	≥ 12.5	≥ 100
6i	4-F	≥ 6.25	≥ 6.25	≥ 6.25	≥ 12.5	≥ 6.25	≥ 6.25	≥ 50
6j	3-F	≥ 6.25	≥ 6.25	≥ 12.5	≥ 12.5	≥ 12.5	≥ 12.5	≥ 100
6k	2-F	≥ 12.5	≥ 12.5	≥ 25	≥ 25	≥ 25	≥ 25	≥ 200
6l	4-CF3	≥ 6.25	≥ 6.25	≥ 6.25	≥ 12.5	≥ 6.25	≥ 6.25	≥ 25
6m	3-CF3	≥ 6.25	≥ 6.25	≥ 12.5	≥ 6.25	≥ 12.5	≥ 12.5	≥ 25
6n	2,6-CH_3	≥ 100	≥ 100	≥ 100	≥ 100	≥ 100	≥ 100	≥ 200
6o	4-Br	≥ 50	≥ 25	≥ 50	≥ 50	≥ 50	≥ 50	≥ 200
Ciprofloxacin		≥ 3.12	≥ 3.12	≥ 3.12	≥ 3.12	≥ 3.12	≥ 3.12	NA
Isoniazid		NA	NA	NA	NA	NA	NA	≥ 6.25

The value of each compound consisted of MIC of 03 replicates; Level of significance $p < 0.05$.

-12.5 µg/mL. Compounds **6e** and **6l** exhibited potent MIC of 6.25 µg/mL against all Gram-positive and Gram-negative strains except for *Salmonella typhi* which is 12.5 µg/mL.

It is apparent that the electron withdrawing groups containing compounds displayed high potency over the electron donating group containing compounds. The potent compounds **6e**, **6l** and **6m** possess trifluoromethyl (-CF_3), nitro (-NO_2) and fluorine (-F) group substituents on the phenyl ring that involved in the amide bond formation. Compound **6n** contains 2,6-dimethyl group on the phenyl ring, displayed lowest antibacterial activity against all the bacterial strains. This further supports the importance of electron withdrawing substituents on the synthesized benzothiazole acetamide derivatives.

Antitubercular activity: Antitubercular activity of the synthesized compounds was tested against the *Mycobacterium tuberculosis* MTB H37Rv (ATCC 27294) strain. The MIC results of the antitubercular assay are given in Table-1. The activity of the synthesized derivatives was measured with the reference compound isoniazid. Among the all derivatives tested, compounds **6l** and **6m** exhibited MIC value of 25 µg/mL, followed by the compounds **6e**, **6f** and **6i** which exhibit 50 µg/mL. With respect to the MIC value of standard isoniazid (6.25 µg/mL), compounds **6l**, **6m** displayed good potency, while **6e**, **6f** and **6i** exhibited moderate potency against the MTB H37Rv strain.

Conclusion

The targeted benzothiazole scaffold and various substituted aryl-amines tethered through the acetamide linkage were synthesized *via* a multistep reactions. The synthesized benzothiazole-acetamide derivatives (**6a-o**) were characterized by spectral analysis and also evaluated for their antibacterial activity against Gram-negative and Gram-positive bacterial strains. Further antitubercular activity of these synthesized derivatives also evaluated against MTB H37Rv strain. Compounds **6e**, **6l** and **6m** displayed broad spectrum antibacterial activity and potency among the tested benzothiazole acetamide derivatives. However, to understand the exact mechanism of the antimicrobial property at the molecular level, further investigations are required to develop the potent antimicrobial agents in order to eradicate the pathogenic diseases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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