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DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SUBSTITUTED AMINE AND BENZOTHIAZOLE-BASED CYCLOPROPANE CARBOXAMIDES

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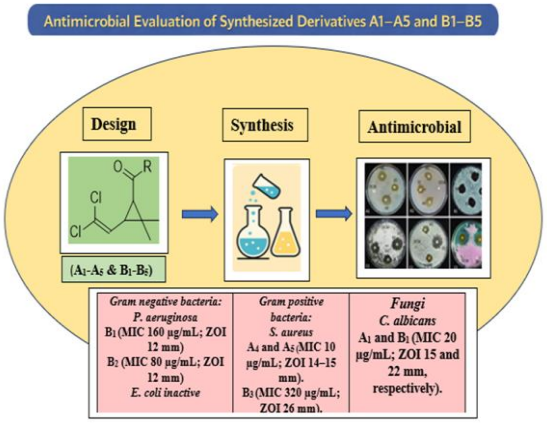
ABSTRACT
The antimicrobial potential of synthesized derivatives A1–A5 and B1–B5 was evaluated against Gram-negative bacteria (*P. aeruginosa*, *E. coli*), Gram-positive bacteria (*S. aureus*, *B. subtilis*), and *C. albicans* using minimum inhibitory concentration (MIC, µg/mL) and zone of inhibition (ZOI, mm) assays. Among Gram-negative strains, B2 exhibited the best activity against *P. aeruginosa* (MIC 80 µg/mL; ZOI 12 mm), followed by B_1 (MIC 160 µg/mL; ZOI 12 mm), whereas all compounds were inactive against *E. coli* (MIC ≥320 µg/mL; ZOI 10 mm). Significant Gram-positive activity was observed for A4 and A5 against *S. aureus* (MIC 10 µg/mL; ZOI 14–15 mm). A4 also showed potent activity against *B. subtilis* (MIC 10 µg/mL; ZOI 12 mm), while B3 demonstrated notable inhibition (MIC 320 µg/mL; ZOI 26 mm). In antifungal screening, A1 and B1 displayed promising activity against *C. albicans* (MIC 20 µg/mL; ZOI 15 and 22 mm, respectively). These findings indicate selective and moderate antimicrobial efficacy among the tested derivatives.

KEY WORDS: Benzothiazole, Cypermethric acid chloride, antibacterial and antifungal.

GRAPHICAL ABSTRACT
Substituted amine (A1–A5) and benzothiazole (B1–B5) cyclopropane carboxamides were screened for antimicrobial and antifungal activity. Most derivatives showed weak activity against Gram-negative bacteria, while *E. coli* remained resistant. Compounds A4 and A5 exhibited strong inhibition against *S. aureus* (ZOI 14–15 mm; MIC 10 µg). Moderate activity was observed against *B. subtilis* (ZOI 20–26 mm). A1 and B1 demonstrated notable antifungal activity against *C. albicans* (ZOI 15–22 mm; MIC 20 µg).

KEYWORDS: Benzothiazole; cyclopropane carboxamides; antibacterial; antifungal.



1. INTRODUCTION

Benzothiazole is a well-recognized heterocyclic scaffold that continues to draw attention in medicinal chemistry due to its wide range of biological activities, including antimicrobial[1,2],[3] anticancer[4, 5], anticonvulsant[6, 7] antiviral[8,9], antimalarial[10,11] anthelmintic[12,13], antitubercular[14,15], analgesic[16,17] and anti-inflammatory[18,19] effects The presence of sulfur and nitrogen atoms in its fused aromatic ring system facilitates strong interactions with microbial enzymes and cellular targets, making benzothiazole derivatives promising candidates for new antimicrobial agents.[20,21] Several studies have shown that appropriate substitutions on the benzothiazole nucleus can significantly improve antibacterial and antifungal activity against both Gram-positive and Gram-negative microorganisms, including resistant strains.[22,23] Furthermore, hybrid molecules combining benzothiazole with other active moieties such as thiazoles, triazoles, pyrimidines, and thiazolidinones have demonstrated enhanced antimicrobial potency, favorable structure–activity relationships, and low minimum inhibitory concentrations.[24-27] Cyclopropane-containing compounds derived from synthetic pyrethroids have also gained attention due to their rigid structure, lipophilicity, and biological relevance. Cypermethric acid derivatives, which contain a dichlorovinyl-substituted cyclopropane ring, are known for strong interactions with biological membranes and cellular systems.[28] Cypermethric acid chloride, 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carbonyl chloride, is an important reactive intermediate used in the synthesis of amide and ester derivatives in agrochemical and pharmaceutical research.[29] Although primarily a synthetic precursor, pyrethroid-based structures have been reported to influence microbial growth, enzyme activity, and membrane permeability, highlighting their relevance in antimicrobial scaffold design. [Molecular hybridization, which integrates two biologically active moieties into a single framework, has emerged as a strategy to enhance antimicrobial activity and overcome microbial resistance.[30] Linking benzothiazole with a cypermethric acid-derived cyclopropane carboxamide via CMAC is expected to generate hybrid compounds with synergistic biological properties. Accordingly, the present study focuses on the synthesis of such hybrids and their in-vitro antimicrobial evaluation against selected bacterial and fungal strains.

2. MATERIALS AND METHODS

The melting points of all synthesized compounds were measured using the open capillary method and are uncorrected. Reactions were monitored by thin-layer chromatography on silica gel plates, which were visualized under ultraviolet light or with iodine. Infrared spectra were obtained using Fourier-transform infrared spectroscopy with a PerkinElmer Infrared Spectrophotometer Model RZX and an Agilent Resolution Pro FT-IR spectrometer, employing potassium bromide pellets. The frequencies are reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker advance II 400 spectrometer (400 MHz FT-NMR) using tetramethyl silane as an internal standard in $CDCl_3$ and dimethyl sulfoxide-d_6. Chemical shifts are reported in δ (ppm). All reagents were used without purification, and solvents were of laboratory reagent and analytical reagent grades.

2.1 Experimental

2.2. Chemistry

General preparation of final compounds amide (A_1- A_5) and (B_1- B_5) [31]

A solution of substituted amines and substituted benzothiazole (1.0 mmol) in acetone (50 mL) was added to cypermethric acid chloride (1.0 mmol) at room temperature, and the reaction mixture was stirred for 15 min. The mixture was then heated to 50°C and maintained at this temperature for 7–8 h with continuous stirring. Reaction progress was monitored by TLC using ethyl acetate–hexane (7:3) as the mobile phase. Upon completion, the reaction mixture was poured into cold water, resulting in the formation of a solid. The precipitated product was collected by filtration and purified by recrystallization from ethanol.

<Scheme-1>

2.3 Spectral characterization

3-(2, 2-dichloroethenyl)-2, 2-dimethyl-*N*-(pyridin-3-yl) cyclopropane carboxamide (A_1): IR (KBr) ν cm^{-1}: 3236.67cm^{-1} N–H stretching, 3031.25 cm^{-1} (aromatic stretching C-H), 2952.81 cm^{-1} aliphatic C–H stretching1677.54 cm^{-1} (C=O stretching), 1584.82 (C=N stretching pyridine ring), 1229.39 cm^{-1} (C–N stretching (amide)), 1048.46 cm^{-1} (C–Cl stretching); **^{1}H NMR (400 MHz DMSO-d_6) δ (ppm):** 10.48 (s, 1H, NH), 7.3–8.7 (m, 4H, aromatic), 0.97 (s, 6H CH_3), 1.9-2.01 (m, 1H cyclopropane) 5.9 (s, 1H terminal -Cl -H); **^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):** 180.70 (C=O), 128.39 (C-CH), 122.19 (C-Cl), 146.20, 143.60, 140.45, 126.69, 117.79, (aromatic) 34.09, 29.80, 28.54 (CH_2-cyclopropane), 22.81- 22.03 (terminal C-CH_3); **ESI–MS:** $[M+H]^+$ 285.7 Solid, yellow color, m.p 108°C-110°C Yield 82%.

3-(2, 2-dichloroethenyl)-2, 2-dimethyl-*N*-(pyridin-4-yl) cyclopropane carboxamide (A_2): IR (KBr) ν cm^{-1}: 3235.67cm^{-1} N–H stretching, 3033.55 cm^{-1} (aromatic stretching C-H), 2955.71cm^{-1} aliphatic C–H stretching1677.54 cm^{-1} (C=O stretching), 1584.82 (C=N stretching pyridine ring), 1229.39 cm^{-1} (C–N stretching (amide)), 1048.46 cm^{-1} (C–Cl stretching); **^{1}H NMR (400 MHz DMSO-d_6) δ (ppm):** 10.48 (s, 1H, NH), 7.3–8.7 (m, 4H, aromatic), 0.97 (s, 6H CH_3), 1.9-2.01 (m, 1H cyclopropane) 5.9 (s, 1H terminal -Cl -H); **^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):** 180.70 (C=O), 128.39 (C-CH), 122.19 (C-Cl), 146.20, 143.60, 140.45, 126.69, 117.79, (aromatic) 34.09, 29.80, 28.54 (CH_2-cyclopropane), 22.81- 22.03 (terminal C-CH_3); **ESI–MS:** $[M+H]^+$ 284.8 Solid, light yellow color, m.p 115°C-117°C Yield 85%

***N*-(3-bromophenyl)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclo propane carboxamide (A_3): IR (KBr) ν cm^{-1}:** 3250 cm^{-1} N–H stretching, 3036.90 cm^{-1} (aromatic C-H stretching), 1677.50 cm^{-1} (C=O stretching), 1345.16 cm^{-1} (C-N stretching), 645.55 cm^{-1} (C-Br stretching); **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 10.05 (s, 1H, NH), 7.33 – 7.89 (m, 4H, aromatic), 0.97 (s, 6H CH_3), 1.80- 2.5 (m, 1H cyclopropane) 5.45 (s, 1H); **^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):):** 180.70 (C=O), 128.39 (C-CH), 122.19 (C-Cl), 123.30(C-Br), 140.20, 130.60, 127.45, 120.60, 120.60, (aromatic) 34.09, 29.80, 28.54 (CH_2- cyclopropane), 22.81- 22.81 (terminal C-CH_3); **ESI–MS:** $[M+H]^+$ 363.07 Solid, brownish color, m.p 135°C-137°C Yield 85%.

***N*-(3-chlorophenyl)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxamide(A_4)**
IR (KBr) ν cm^{-1}: 3249 cm^{-1} N–H stretching, 3035.89 cm^{-1} (aromatic C-H stretching), 1675.50 cm^{-1} (C=O stretching), 1348.15 cm^{-1} (C-N stretching), 695.99 cm^{-1} (C-Cl stretching); **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 10.05 (s, 1H, NH), 7.33 – 7.89 (m, 4H, aromatic), 0.97 (s, 6H CH_3), 1.80- 2.5 (m, 1H cyclopropane) 5.45 (s, 1H); **^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):):** 180.70 (C=O), 128.39 (C-CH), 122.19 (C-Cl), 134.30(C-Cl aromatic), 139.90, 130.60, 127.45, 120.60, 120.60, (aromatic) 34.09, 29.80, 28.54 (CH_2- cyclopropane), 22.81- 22.81 (terminal C-CH_3); **ESI–MS:** $[M+H]^+$ 363.07 Solid, yellow color, m.p 128°C-130°C Yield 87%.

***3*-(2,2-dichlorovinyl)-2,2-dimethyl-*N*-(m-tolyl) cyclopropane-1-carboxamide(A5)**
IR (KBr) ν cm^{-1}: 3359 cm^{-1} N–H stretching, 3055.89 cm^{-1} (aromatic C-H stretching), 1695.50 cm^{-1} (C=O stretching), 1348.15 cm^{-1} (C-N stretching), 695.99 cm^{-1} (C-Cl stretching); **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 10.05 (s, 1H, NH), 7.33 – 7.89 (m, 4H, aromatic), 0.97 (s, 6H CH_3), 1.80- 2.5 (m, 1H cyclopropane) 5.45 (s, 1H); **^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):** 180.70 (C=O), 128.39 (C-CH), 122.19 (C-Cl), 21.3(C-CH_3 aromatic), 139.90, 130.60, 127.45, 120.60, 120.60, (aromatic) 34.09, 29.80, 28.54 (CH_2- cyclopropane), 22.81- 22.81 (terminal C-CH_3); **ESI–MS:** $[M+H]^+$ 298.21 Solid, yellow color, m.p 138°C-140°C Yield 68%.

***N*-(benzo[d]thiazol-2-yl)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxamide(B_1) IR (KBr) ν cm^{-1}:** 3273.91 cm^{-1} (N–H stretching), 3064.07 cm^{-1} (aromatic C–H stretching), 2924. 28 cm^{-1} (aliphatic C–H stretching), 1683.24 cm^{-1}C=O stretching cm^{-1}1594.87 cm^{-1} (C=N stretching), 1235.28 cm^{-1} (C–N stretching), **^{1}H NMR (400 MHz DMSO-d_6) δ (ppm):** 10.48 (s, 1H, NH), 7.01– 8.12 (m, 4H, aromatic), 1.20-1.20 (s, 6H CH_3), 1.08-2.11(m, 1Hcyclopropane) 5.94 (s, 1H terminal -Cl -H); **^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):** 169.89 (C=O), 166.53 (C-NH), 150.4 128.05,126.76, 126.5, 123.0,119.65 (aromatic), 128.50, (C=CH-Cl), 34.59, 29.83, 28.52 (CH_2-CH_2 cyclopropane carbon), 22.80 (terminal carbon -CH_3). **ESI–MS:** $[M+H]^+$ 341.1Solid, yellow color, m.p 192°C-194°C Yield 80%.

***N*-(7-chloro-1, 3-benzothiazol-2-yl)-3-(2, 2-dichloroethenyl)-2, 2-dimethylcyclo propane carboxamide (B_2): IR (KBr) *ν* cm^{-1}:** 3273.91 cm^{-1} (N–H stretching), 3064.07 cm^{-1} (aromatic C–H stretching), 2924. 28 cm^{-1} (aliphatic C–H stretching), 1683.24 cm^{-1}C=O stretching cm^{-1}1594.87 cm^{-1} (C=N stretching), 1235.28 cm^{-1} (C–N stretching), 1110.08 cm^{-1} (C-Cl). **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 3.7(s, 1H, NH), 7.01– 7.90 (m, 3H, aromatic), 1.20-1.20 (s, 6H CH_3), 2.06-2.11(m, 1Hcyclopropane) 6.04 (s, 1H terminal -Cl -H);**^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):** 169.89 (C=O), 166.53 (C-NH), 174.50,153.40, 128.05,126.76, 126.5, 121.0,118.65 (aromatic), 128.48, (C=CH-Cl), 34.59, 29.83, 29.80 (CH_2-CH_2 cyclopropane carbon), 22.80 (terminal carbon -CH_3). **ESI–MS:** $[M+H]^+$ 375.1 Solid, yellow color, m.p 198°C-200°C Yield 82%.

***N*-(5-chloro-1, 3-benzothiazol-2-yl)-3-(2, 2-dichloroethenyl)-2, 2-dimethylcyclo propane carboxamide (B_3): IR (KBr) *ν* cm^{-1}:** 3273.91 cm^{-1} (N–H stretching), 3064.07 cm^{-1} (aromatic C–H stretching), 2924. 28 cm^{-1} (aliphatic C–H stretching), 1683.24 cm^{-1}C=O stretching cm^{-1}1594.87 cm^{-1} (C=N stretching), 1235.28 cm^{-1} (C–N stretching), 1110.08 cm^{-1} (C-Cl). **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 10.50 (s, 1H, NH), 7.01– 7.90 (m, 3H, aromatic), 1.20-1.20 (s, 6H CH_3), 2.06-2.11(m, 1Hcyclopropane) 6.04 (s, 1H terminal -Cl -H);**^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):** 169.89 (C=O), 166.53 (C-NH), 174.50,153.40, 128.05,126.76, 126.5, 121.0,118.65 (aromatic), 128.48, (C=CH-Cl), 34.59, 29.83, 29.80 (CH_2-CH_2 cyclopropane carbon), 22.80 (terminal carbon -CH_3). **ESI–MS:** $[M+H]^+$ 375.69 Solid, light-yellow color, m.p 201°C-203°C Yield 80%.

***3*- (2,2-dichlorovinyl) -2, 2-dimethyl-*N*- (6-nitrobenzo[d]thiazol-2-yl) cyclopropane-1-carboxamide (B_4) IR (KBr) *ν* cm^{-1}:** 3273.91 cm^{-1} (N–H stretching), 3064.07 cm^{-1} (aromatic C–H stretching), 2924. 28 cm^{-1} (aliphatic C–H stretching), 1683.24 cm^{-1}C=O stretching cm^{-1}1594.87 cm^{-1} (C=N stretching), 1385.50 cm^{-1} (NO_2 symmetric stretching)1245.28 cm^{-1} (C–N stretching), 1130.05 cm^{-1} (C-Cl). **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.48 (s, 1H, NH), 7.01– 7.90 (m, 3H, aromatic), 1.20-1.20 (s, 6H CH_3), 2.06-2.11(m, 1Hcyclopropane) 6.04 (s, 1H terminal -Cl -H);**^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):** 169.89 (C=O), 166.53 (C-NH), 174.50,159.40, 128.05,144.3,131.76, 121.5, 119.0,117.65 (aromatic), 128.48, (C=CH-Cl), 34.59, 29.83, 29.80 (CH_2-CH_2 cyclopropane carbon), 22.80,22.80 (terminal carbon -CH_3). **ESI–MS:** $[M+H]^+$ 386.25 Solid, dark yellow color, m.p 218°C-220°C Yield 77%.

***N*-(4-bromobenzo[d]thiazol-2-yl)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxamide (B_5) IR (KBr) *ν* cm^{-1}:** 3277.95 cm^{-1} (N–H stretching), 3065.33 cm^{-1} (aromatic C–H stretching), 2925. 25 cm^{-1} (aliphatic

C–H stretching), 1683.24 cm^{-1}C=O stretching cm^{-1}1594.87 cm^{-1} (C=N stretching), 645.50 cm^{-1} (Br stretching)1245.28 cm^{-1} (C–N stretching), 1130.05 cm^{-1} (C-Cl). **^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.48 (s, 1H, NH), 7.01– 7.90 (m, 3H, aromatic), 1.20-1.20 (s, 6H CH_3), 2.06-2.11(m, 1Hcyclopropane) 6.04 (s, 1H terminal -Cl -H);**^{13}C NMR (100MHz, DMSO-d_6) δ(ppm):** 180.89 (C=O), 166.53 (C-NH), 174.50, 151.05,128.3,128.76, 126.5, 120.0,116.65 (aromatic), 128.48, (C=CH-Cl), 34.30, 29.83, 29.80 (CH_2-CH_2 cyclopropane carbon), 22.80,22.80 (terminal carbon -CH_3). **ESI–MS:** $[M+H]^+$ 420.15 Solid, light brown color, m.p 215°C-217°C Yield 81%.

2.4 Biological evaluation methodology

Antimicrobial activity was evaluated using a dilution–diffusion (agar well diffusion/E-test principle) method to determine the zone of inhibition (ZOI) and minimum inhibitory concentration (MIC).[32,33] Mueller–Hinton agar was prepared from a commercial dehydrated medium, sterilized, and poured to a uniform depth of approximately 4 mm. Microbial inocula were prepared from fresh cultures and adjusted to a 0.5 McFarland turbidity standard. The standardized inoculum was evenly spread over the agar surface, and wells of 10 mm diameter were aseptically punched. Increasing concentrations of test compounds were added to the wells, and plates were incubated at 37 °C for 16–18 h. ZOI values were measured in millimeters, and the MIC was defined as the lowest concentration producing a clear zone of complete growth inhibition.[34,35] Ciprofloxacin and fluconazole were used as standard antibacterial and antifungal agents, respectively.

3. RESULT AND DISCUSSION

3.1 Chemistry

The synthetic strategy adopted in this study is based on the high reactivity of acid chlorides toward nucleophilic amines, enabling efficient amide bond formation under mild conditions. Initially, 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid was converted into the corresponding acid chloride using thionyl chloride in the presence of a catalytic amount of DMF and toluene as solvent at 60–65°C. The resulting 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carbonyl chloride served as a versatile intermediate for subsequent coupling reactions. In the next step, the acid chloride was reacted with a variety of substituted amines to give a series of 3-(2,2-dichloroethenyl)-2,2-dimethyl-N-(substituted amine) cyclopropane carboxamides(A_1–A_5). The reactions proceeded via nucleophilic attack of the amine nitrogen on the electrophilic carbonyl carbon of the acid chloride, followed by elimination of hydrogen chloride. Similarly, coupling of the acid chloride with substituted benzothiazole-2-amines to give 3-(2,2-dichloroethenyl)-N-(substituted benzothiazol-2-yl)-2,2-dimethylcyclopropane carboxamides(B_1–B_5). The reactions were typically carried out in acetone under controlled heating, resulting in efficient conversion and good yields.

Formation of the amide linkage was confirmed by spectroscopic analysis, including the appearance of characteristic amide carbonyl stretching bands in the IR spectra and diagnostic signals in the NMR spectra. The crude products were isolated by precipitation in cold water and further purified by recrystallization from ethanol. The synthesized benzothiazole intermediates and cyclopropane carboxamide derivatives were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and ESI-MS. The IR spectra showed N–H stretching at 3273.91 cm^{-1}, C=O stretching at 1683.24 cm^{-1}, aromatic C–H stretching at 3064.07 cm^{-1}, C=N stretching at 1594.87 cm^{-1}, and C–Cl stretching at 1110.08 cm^{-1}, confirming the presence of amino, amide, aromatic, heteroaromatic, and halogen functionalities. In the additional bands corresponding to C–N, C–Cl, C–Br, and NO_2 groups further supported the proposed substitutions. The ^{1}H NMR spectra displayed a downfield amide NH singlet at δ 10.05–12.48 ppm, aromatic proton multiplets at δ 7.01–8.70 ppm, and characteristic gem-dimethyl singlets at δ 0.97 or 1.20 ppm (6H). The cyclopropane methine proton resonated at δ 1.80–2.50 ppm, while the dichlorovinyl proton appeared as a singlet at δ 5.45–6.04 ppm. In the ^{13}C NMR spectra, the amide carbonyl carbon was observed at δ 169.89–180.89 ppm, aromatic and heteroaromatic carbons appeared between δ 116.65–159.40 ppm, and cyclopropane carbons were detected at δ 28.52–34.59 ppm. These spectral features confirm the successful synthesis of the target compounds.

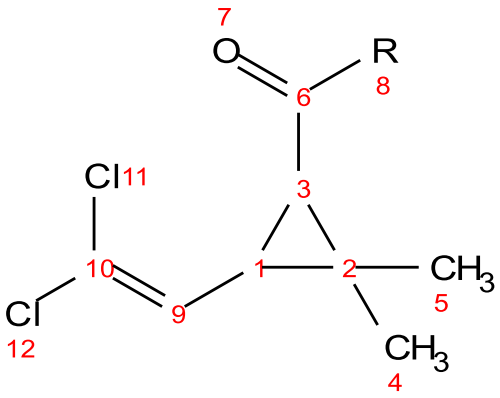
3.2 Biology

The synthesized compounds A_1–A_5 and B_1–B_5 were evaluated for their in-vitro antimicrobial activity against Gram-negative bacteria (*P. aeruginosa* and *E. coli*), Gram-positive bacteria (*S. aureus* and *B. subtilis*), and the fungal strain *C. albicans*, using the agar well diffusion method. Minimum inhibitory concentration values were determined and compared with standard antibacterial (ciprofloxacin) and antifungal (fluconazole) agents. Compound A_1 (pyridin-3-yl) showed moderate antibacterial activity against *P. aeruginosa* (MIC 320 µg, ZOI 15 mm), which was much weaker than the standard drug ciprofloxacin (MIC 10 µg). However, A_1 exhibited good antifungal activity against *C. albicans* (MIC 20 µg, ZOI 15 mm), which was close to that of fluconazole (MIC 16 µg), indicating its promising antifungal nature. Compound A_2 (pyridin-4-yl) displayed only weak activity against *P. aeruginosa* (MIC 320 µg, ZOI 13 mm) and was inactive against fungi, making it clearly less effective than both standard drugs. Compound A_3 (meta-bromo phenyl) showed selective antibacterial activity against Gram-positive bacteria, inhibiting *S. aureus* and *B. subtilis* with MIC values of 80 µg; although this activity was lower than ciprofloxacin, it indicates moderate antibacterial potential. Compound A_4 (meta-chlorophenyl) was one of the most active derivatives, showing strong inhibition of *S. aureus* with an MIC of 10 µg, which is comparable to ciprofloxacin, though with smaller inhibition zones, suggesting potent but selective antibacterial action. Compound A_5 (meta-methylphenyl)

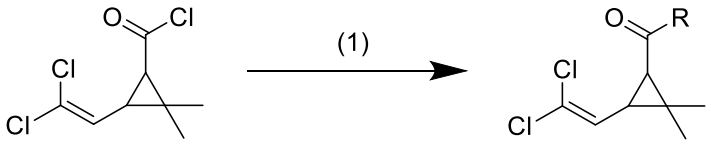
also exhibited strong activity against *S. aureus* (MIC 10 µg) and moderate activity against *B. subtilis* (MIC 160 µg), further confirming the beneficial effect of meta substitution on antibacterial activity. Among the benzothiazole derivatives, compound B_1 showed moderate activity against *P. aeruginosa* (MIC 160 µg) when compared to ciprofloxacin, but demonstrated strong antifungal activity against *C. albicans* (MIC 20 µg, ZOI 22 mm), which was close to that of fluconazole, indicating its potential as an antifungal lead compound. Compound B_2 (ortho-chloro) exhibited improved antibacterial activity against *P. aeruginosa* (MIC 80 µg) and moderate inhibition of *S. aureus* (MIC 320 µg), though it remained less potent than ciprofloxacin. Compound B_3 (para-chloro) showed selective and strong inhibition of *B. subtilis*, producing a large zone of inhibition (26 mm), which was comparable to ciprofloxacin at higher doses despite having a higher MIC value. Compound B_4 (para-nitro) displayed moderate antibacterial activity against Gram-positive bacteria and antifungal activity against *C. albicans* (MIC 320 µg), showing broader activity but lower potency than the standard drugs. Compound B_5 (ortho-bromo) exhibited moderate antibacterial activity against *S. aureus* and *B. subtilis*, along with notable antifungal activity (ZOI 29 mm), although its MIC values were higher than fluconazole, indicating partial effectiveness compared to the standard.

3.3 Structure activity relationship

Structure–activity relationship analysis revealed that antimicrobial potency was strongly influenced by the nature and position of aromatic and heteroaromatic substituents. Pyridyl-containing derivatives showed limited antibacterial activity; however, A_1 bearing a pyridin-3-yl group (γ-position) exhibited enhanced antifungal activity against *C. albicans* (MIC 20 µg) compared to the pyridin-4-yl analogue A_2, highlighting the critical role of nitrogen positioning in biological response. Among phenyl-substituted derivatives, meta-substitution markedly enhanced Gram-positive antibacterial activity, with A_4 (meta-chloro) and A_5 (meta-methyl) displaying the lowest MIC values (10 µg) against *S. aureus*, while A_3 (meta-bromo) showed moderate activity, suggesting that both electron-withdrawing and weak electron-donating groups at the meta position favor antibacterial potency. These compounds were largely inactive against Gram-negative bacteria, reflecting the permeability barrier imposed by the Gram-negative outer membrane. Incorporation of the benzothiazole scaffold significantly improved antimicrobial activity, as observed for B_1 against *P. aeruginosa* and *C. albicans*, indicating that the fused heterocyclic system plays an important role in enhancing efficacy. Further modulation was achieved through position-dependent substitution on the benzothiazole phenyl ring, where ortho-chloro substitution (B_2) enhanced *P. aeruginosa* inhibition, para-chloro substitution (B_3) selectively improved activity against *B. subtilis*, and ortho-bromo (B_5) and para-nitro (B_4) substitutions increased antifungal activity. In comparison, the standard antibacterial drug ciprofloxacin exhibited potent and broad-spectrum activity against both Gram-negative and Gram-positive bacteria with low MIC values (5–15 µg), while the standard antifungal agent fluconazole showed selective activity against *C. albicans* (MIC 16 µg), serving as reliable benchmarks. Overall, the SAR indicates that meta-substituted phenyl rings favor Gram-positive antibacterial activity, whereas benzothiazole incorporation and strategically positioned electron-withdrawing substituents enhance antifungal and selective antibacterial effects, providing a rational framework for further structural optimization.



Scheme-1.



(1) R= Substituted amines, substituted benzothiazole, acetone, 50°C & 7-10 h. (A_1-A_5 & B_1-B_5)

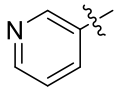
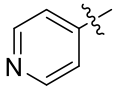
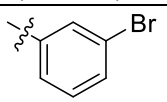
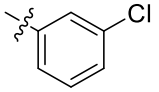
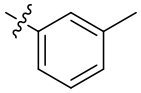
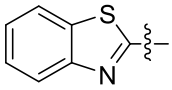
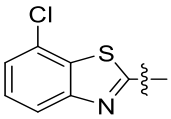
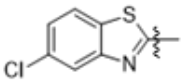
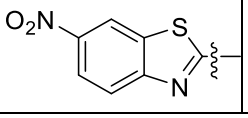
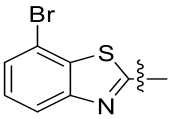
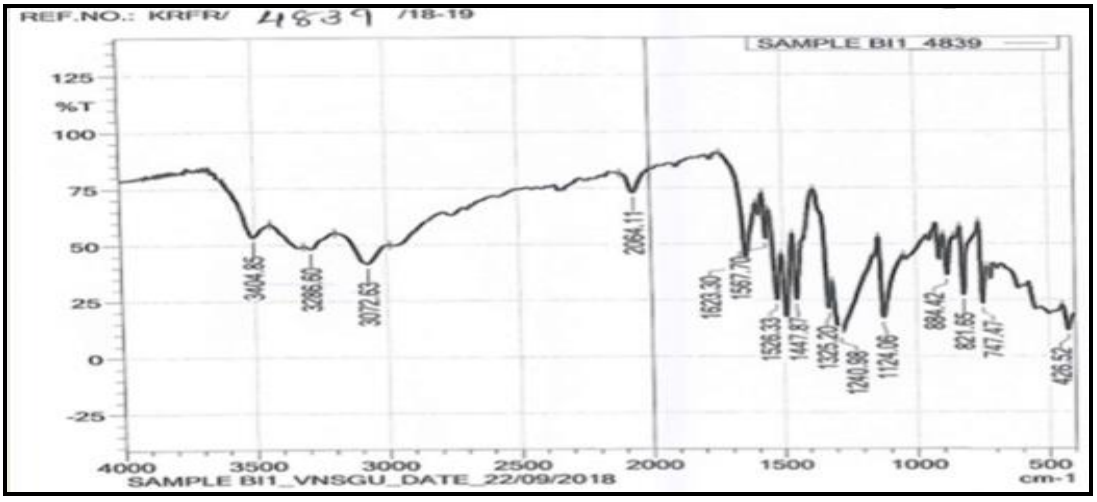
A 1		A 2		A 3		A 4		A 5	
B 1		B 2		B 3		B 4		B 5	

Table 1.

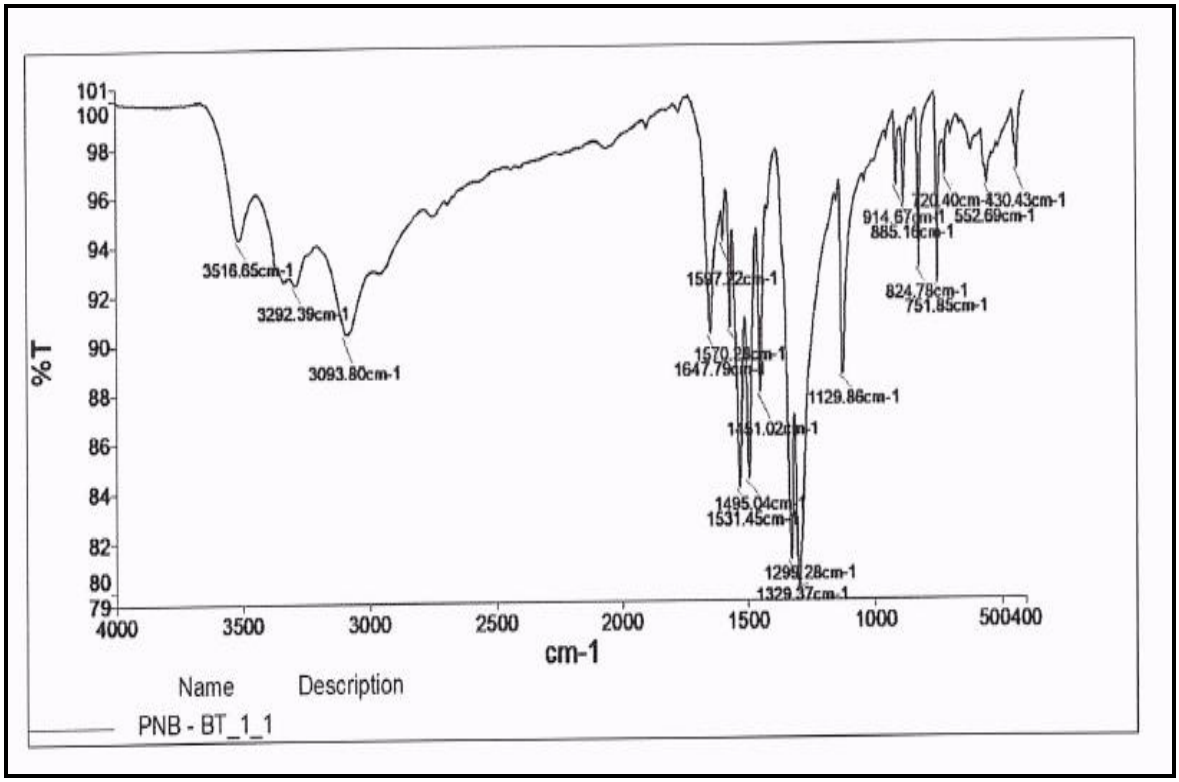
Comp. Code	Time (h)	Yield %	Melting point °C
A_1	8	82	108-110
A_2	8.5	85	115-117
A_3	9	85	135-137
A_4	9	87	128-130
A_5	7	68	138-140
B_1	9	80	192-194
B_2	9.5	82	198-200
B_3	9	80	201-203
B_4	10	77	218-220
B_5	10	81	215-217

Table 2.

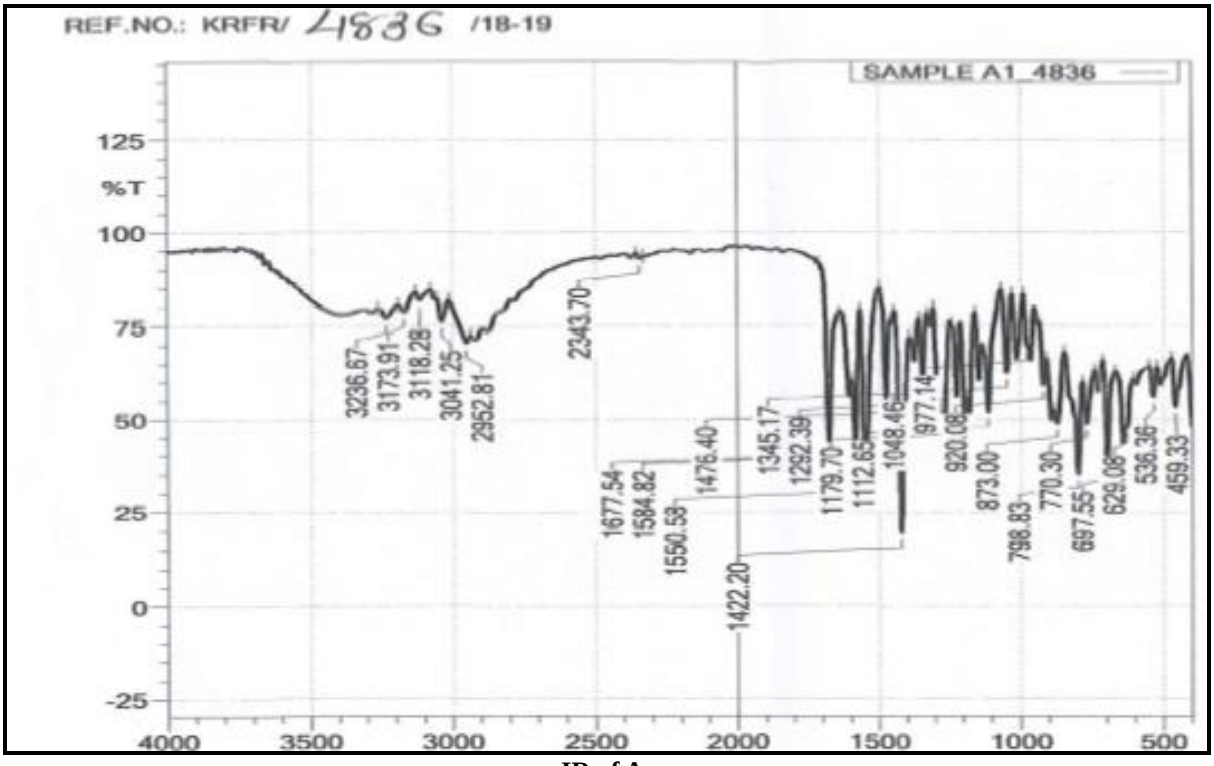
Comp	*Gram negative bacteria*				*Gram positive bacteria*				*Fungi*	
	P. aeruginosa		*E. coli*		*S. aureus*		*B. subtilis*		*C. albicans*	
	MIC µg	**ZOI mm**	**MIC µg**	**ZOI mm**	**MIC µg**	**ZOI mm**	**MIC µg**	**ZOI mm**	**MIC µg**	**ZOI mm**
A_1	320	15	>320	10	>320	10	>320	10	**20**	**15**
A_2	320	13	>320	10	>320	10	>320	10	>320	10
A_3	>320	10	>320	10	80	15	80	13	>320	10
A_4	>320	10	>320	10	**10**	**14**	**10**	**12**	>320	10
A_5	>320	10	>320	10	**10**	**15**	160	14	>320	10
B_1	160	12	>320	10	>320	10	>320	10	**20**	**22**
B_2	**80**	**12**	>320	10	320	18	>320	10	>320	10
B_3	>320	10	>320	10	>320	10	320	26	>320	10
B_4	>320	10	>320	10	320	13	320	20	320	23
B_5	>320	10	>320	10	320	15	320	23	320	29
Ciprofloxacin	10	12	15	12	15	12	5	12	-	-
Fluconazole	-	-	-	-	-	-	-	-	16	15



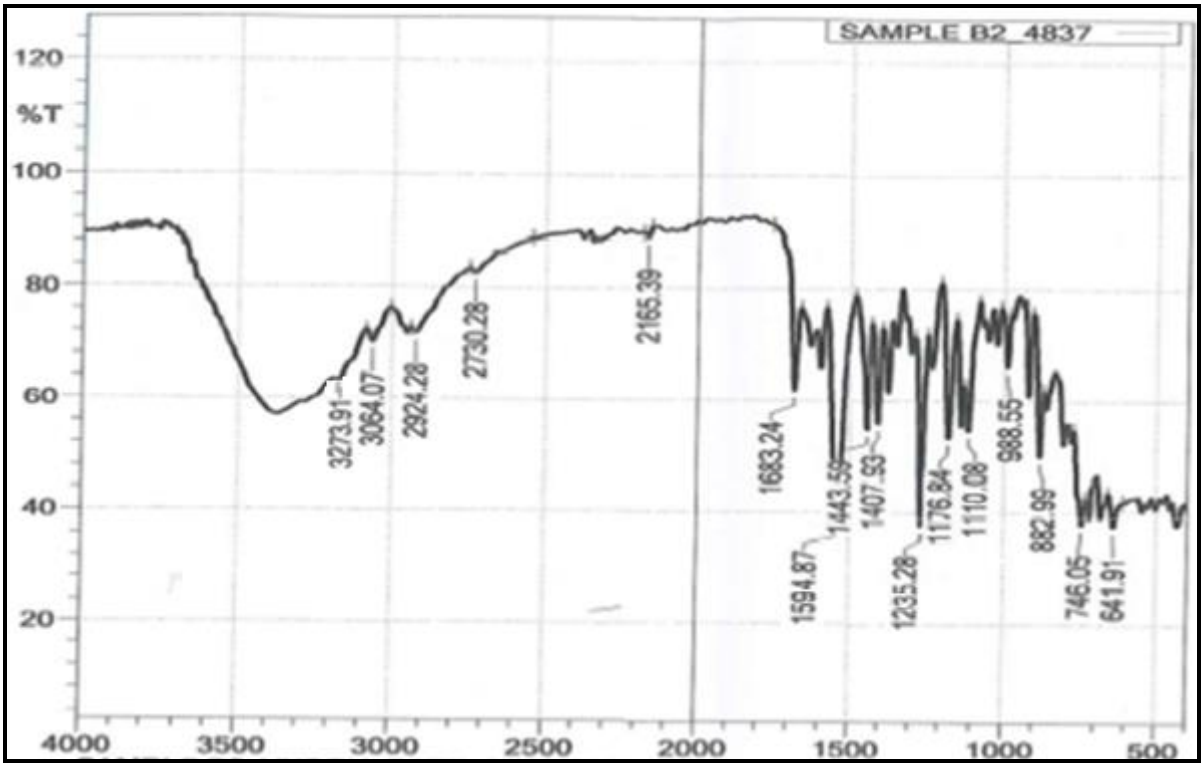
IR of Benzothiazole



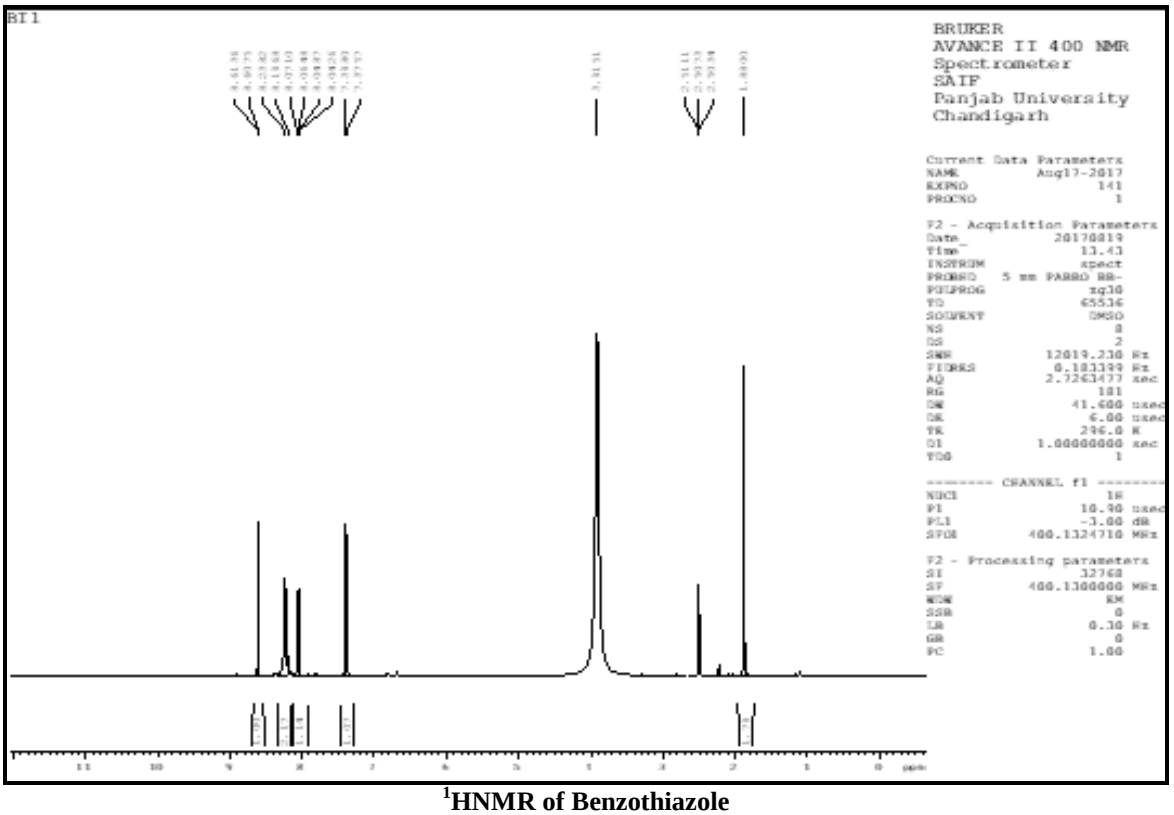
IR of 6-nitrobenzo[*d*]thiazole-2-amine



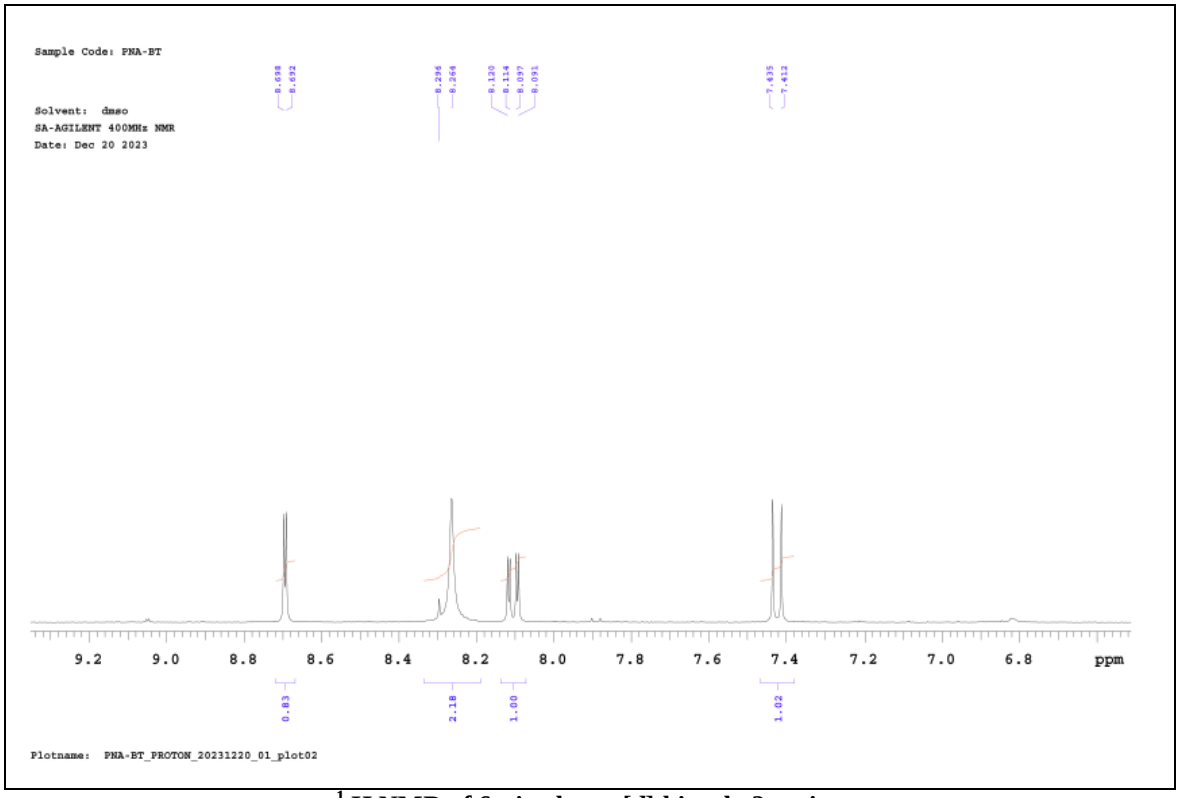
IR of A_1



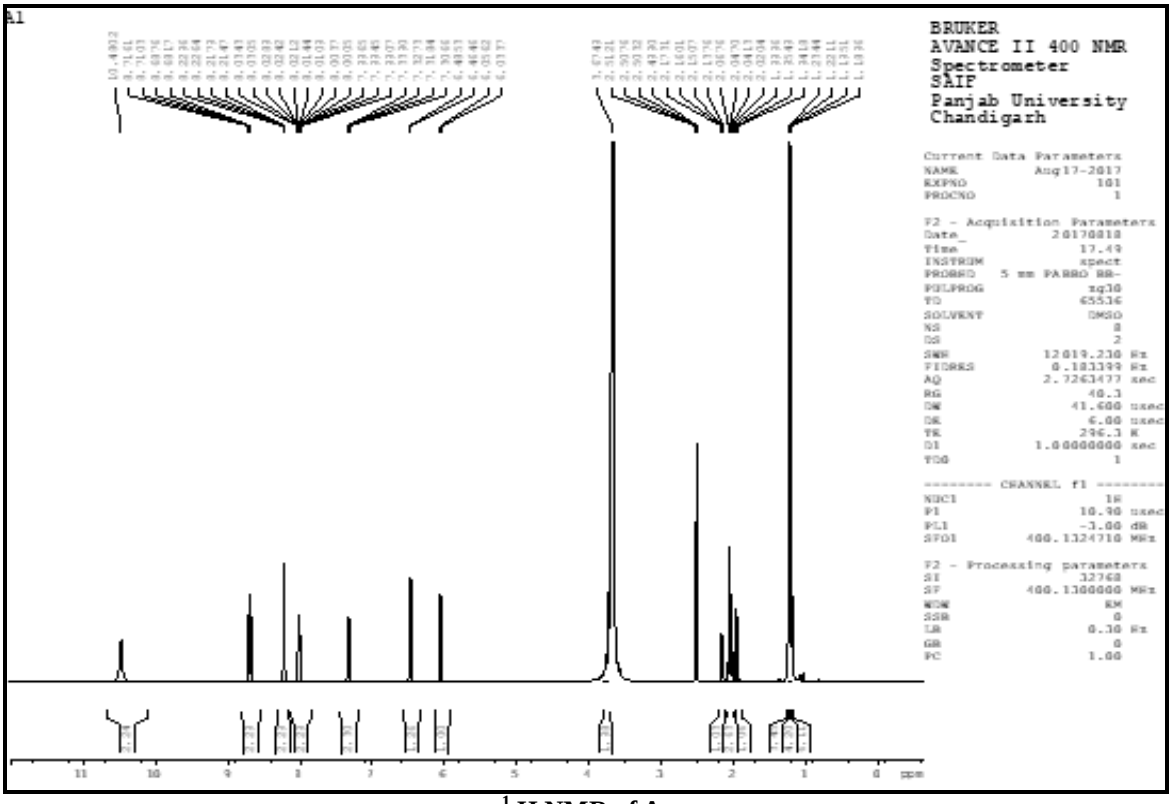
IR of B_2



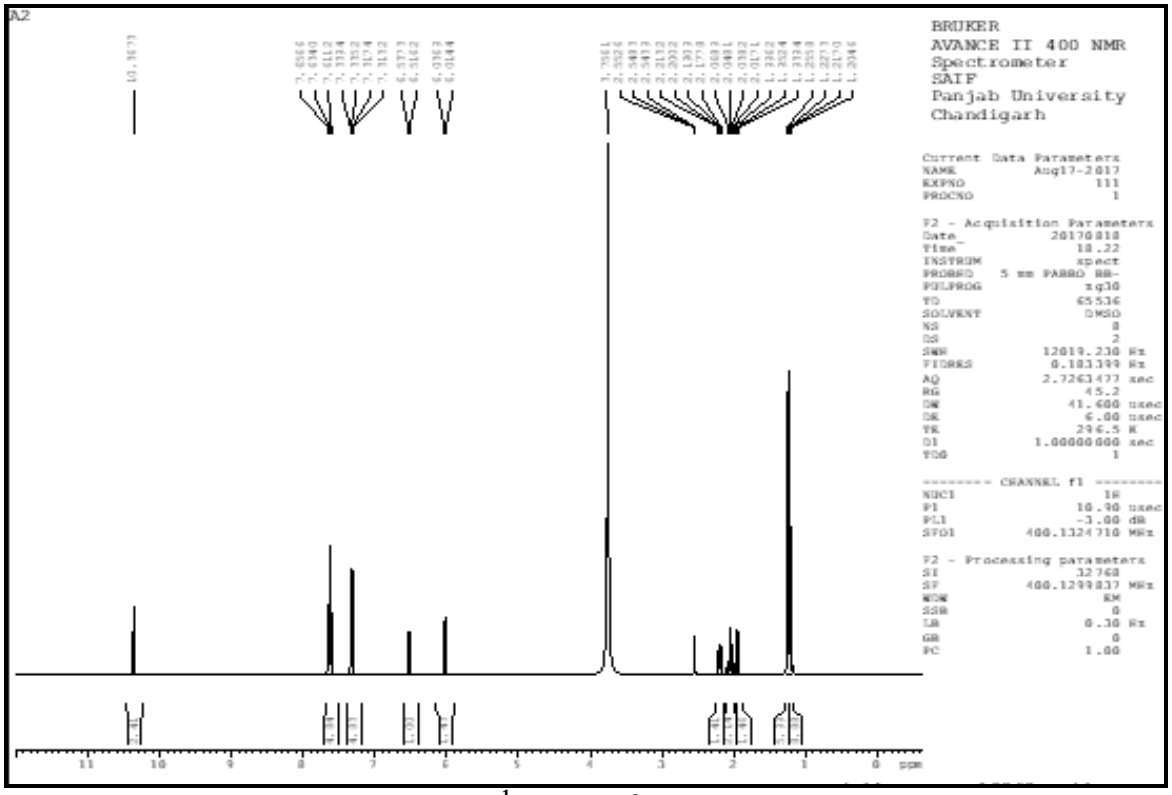
^{1}HNMR of Benzothiazole



^{1} H NMR of 6-nitrobenzo[*d*]thiazole-2-amine



^{1} H NMR of A_1



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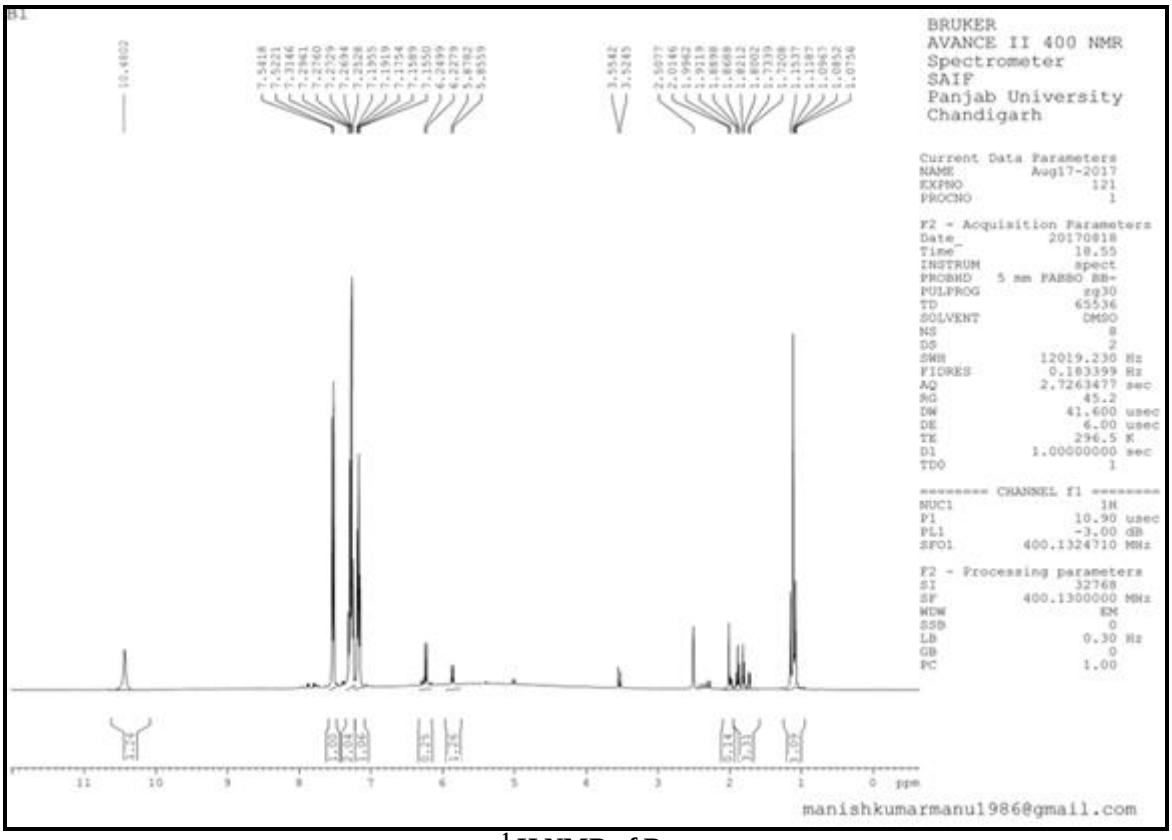

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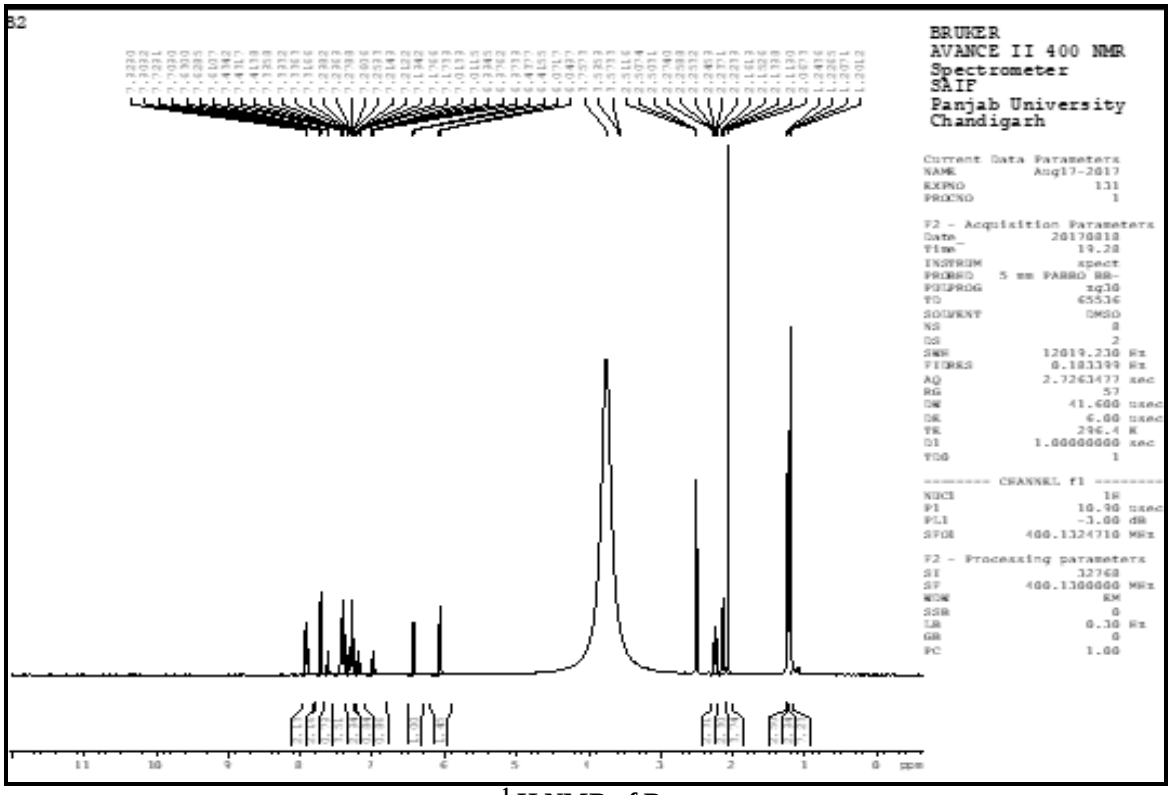

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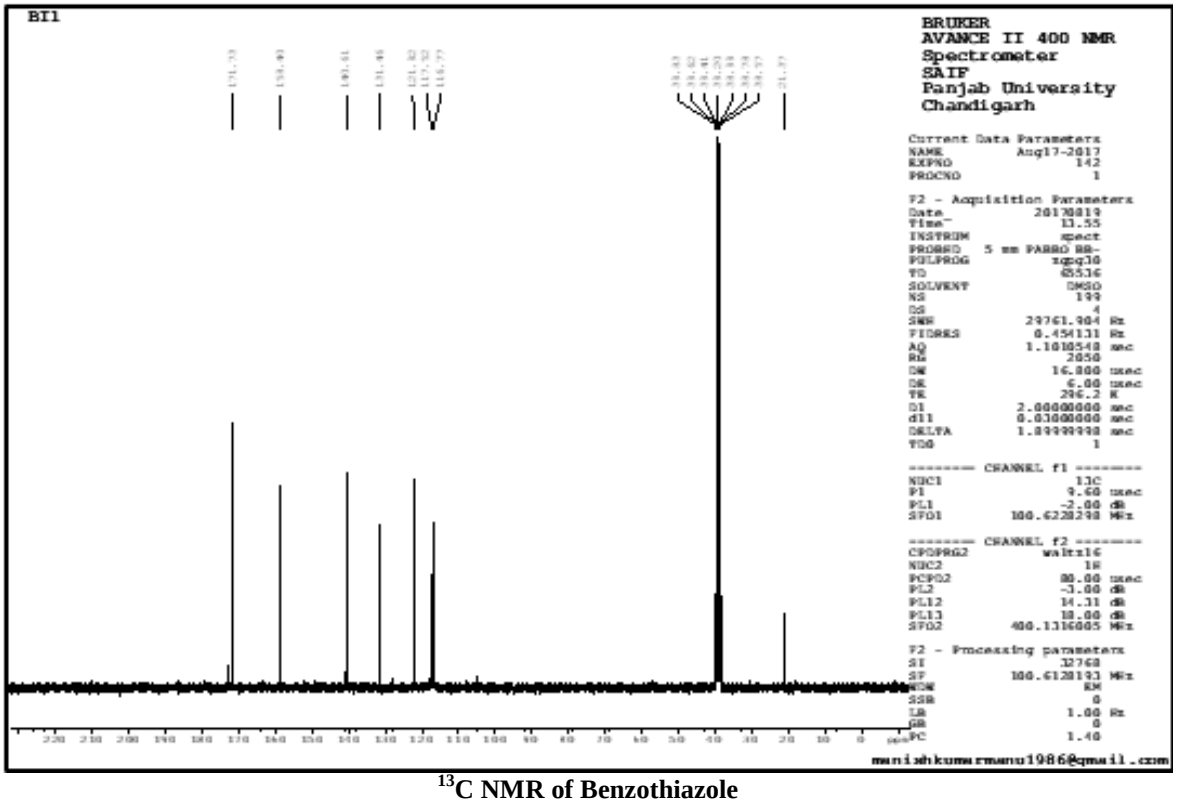
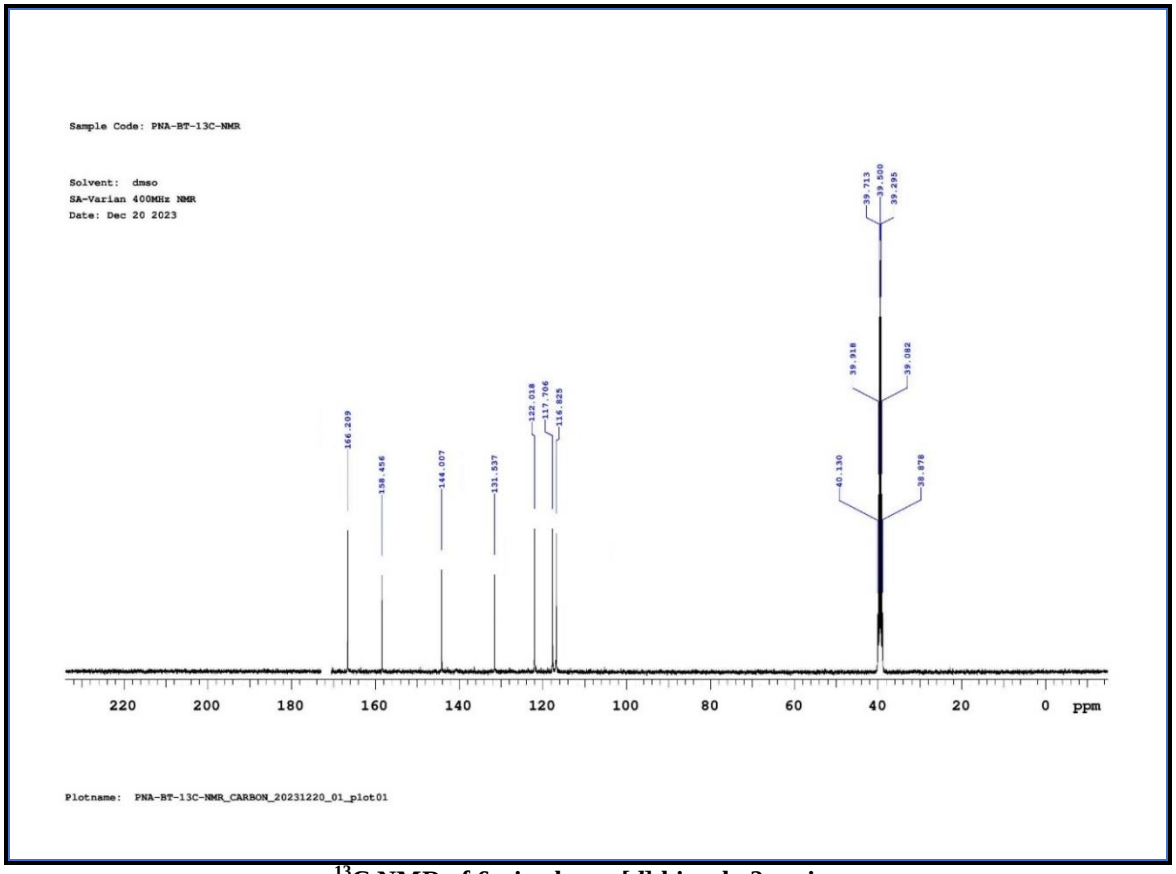
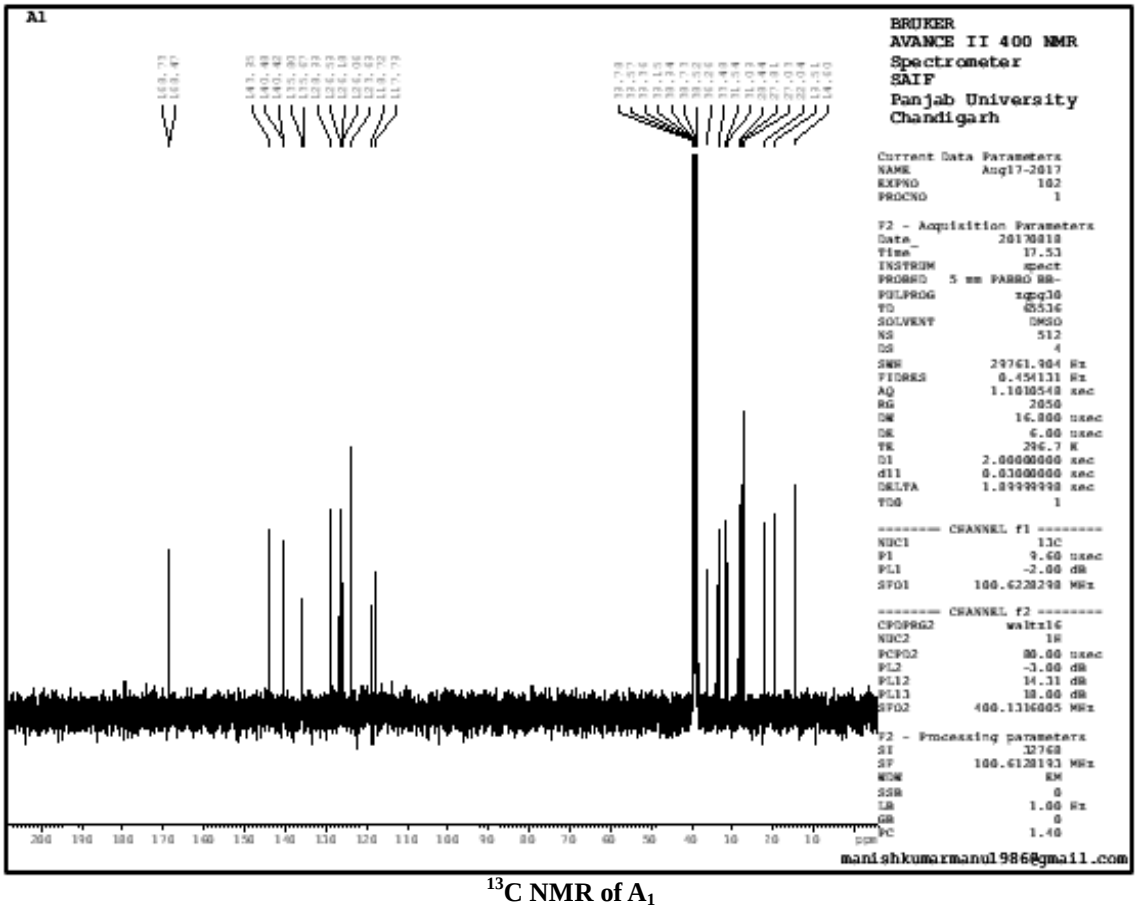


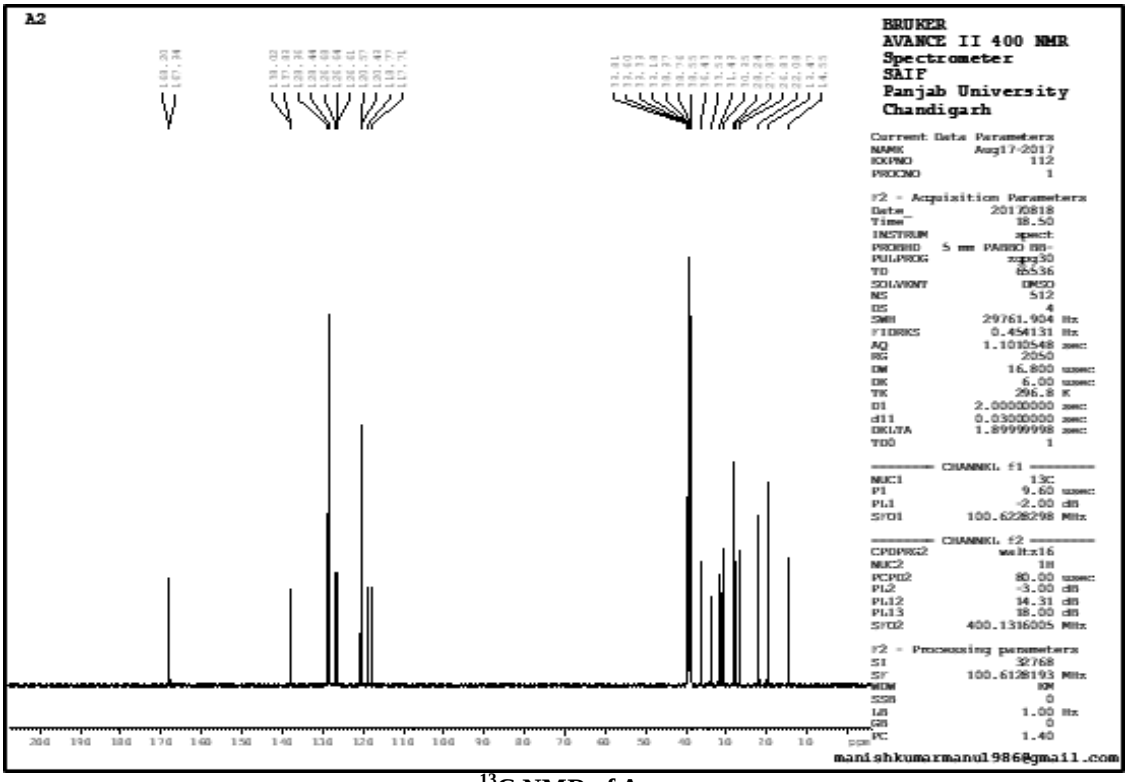
[13]C NMR of Benzothiazole



^{13}C NMR of 6-nitrobenzo[*d*]thiazole-2-amine



^{13}C NMR of A_1



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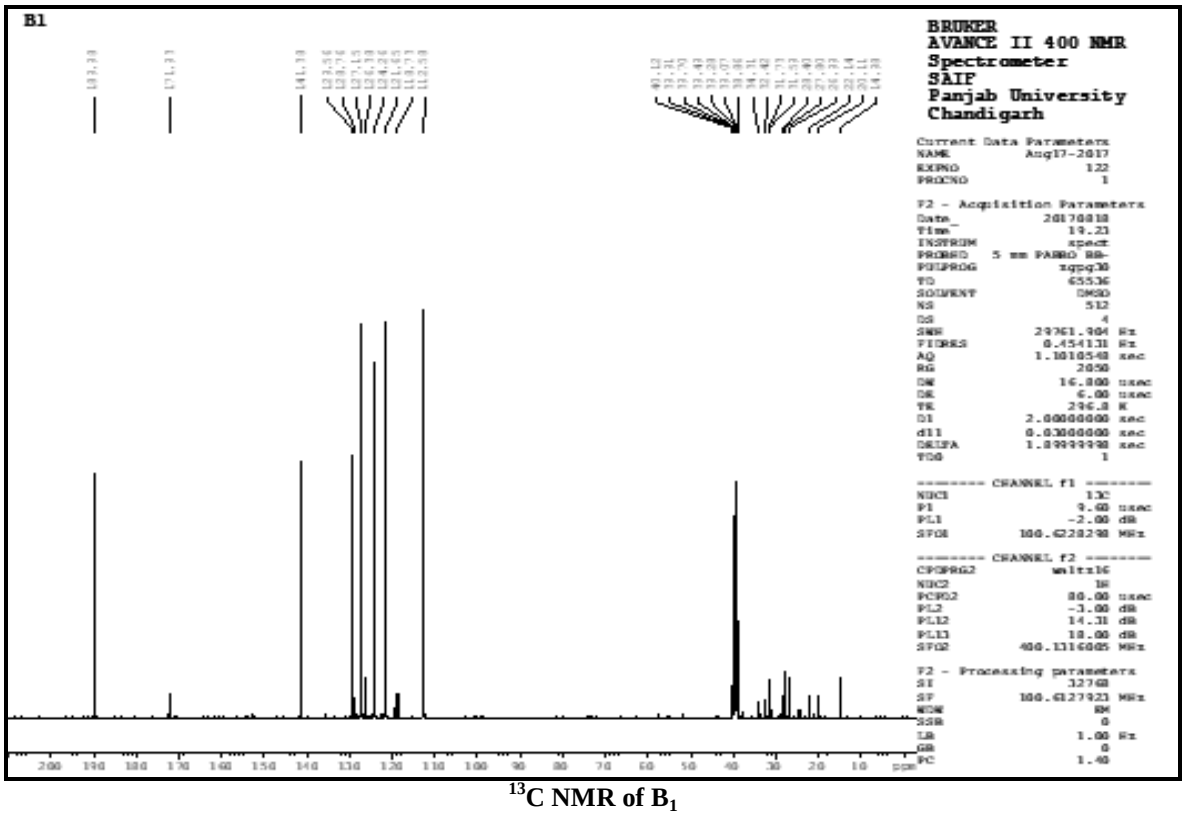

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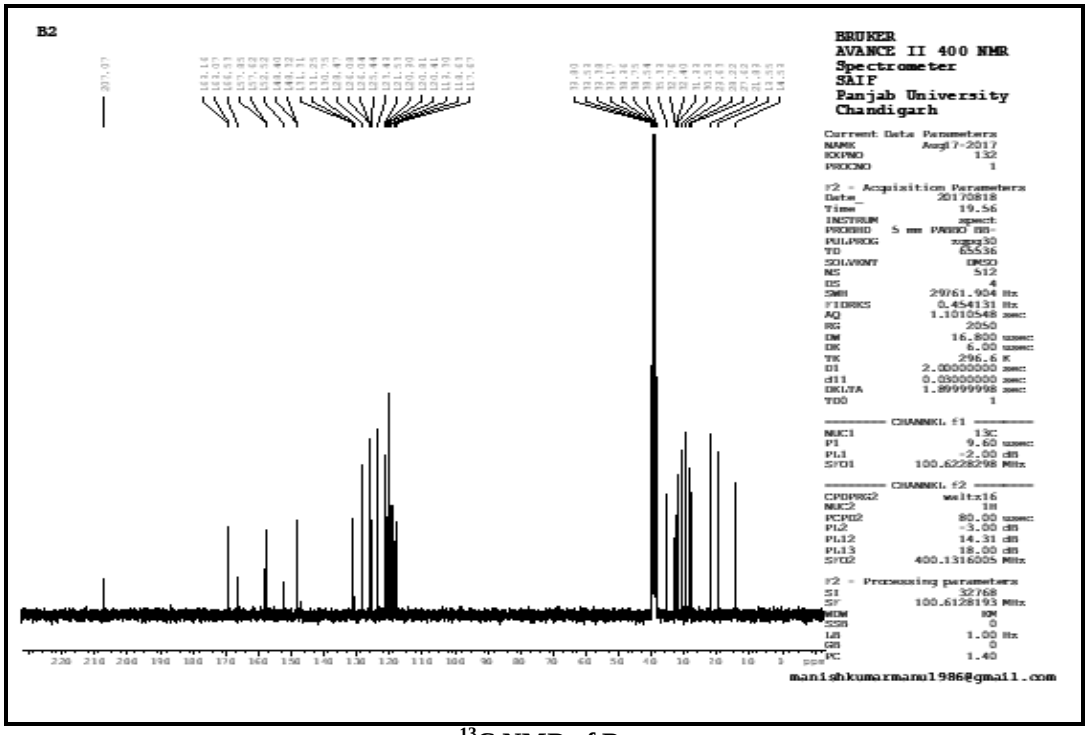
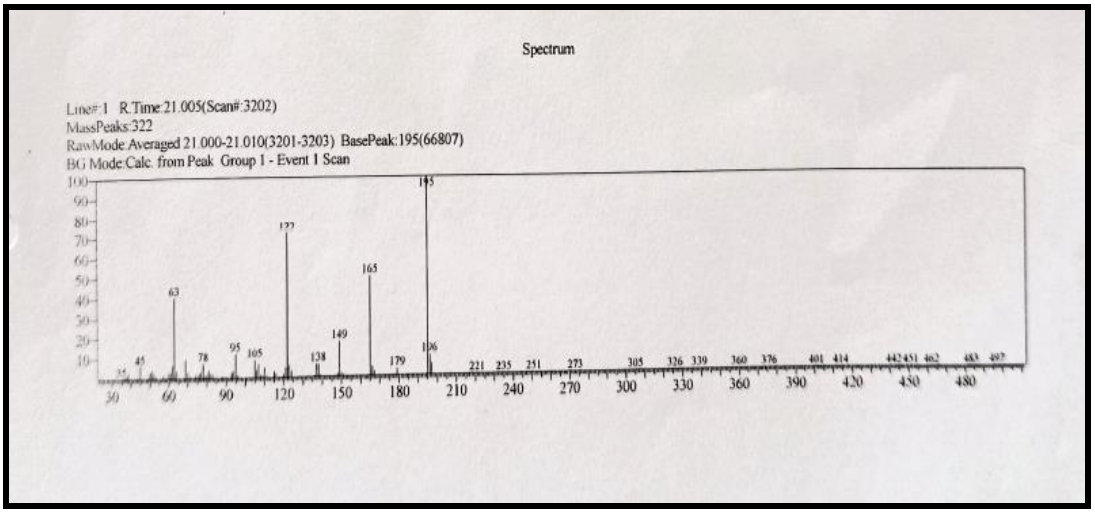
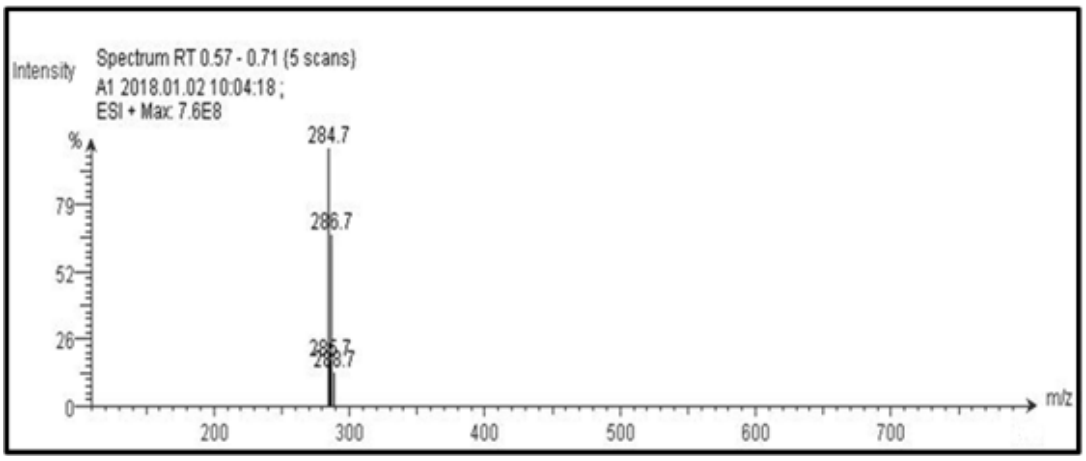


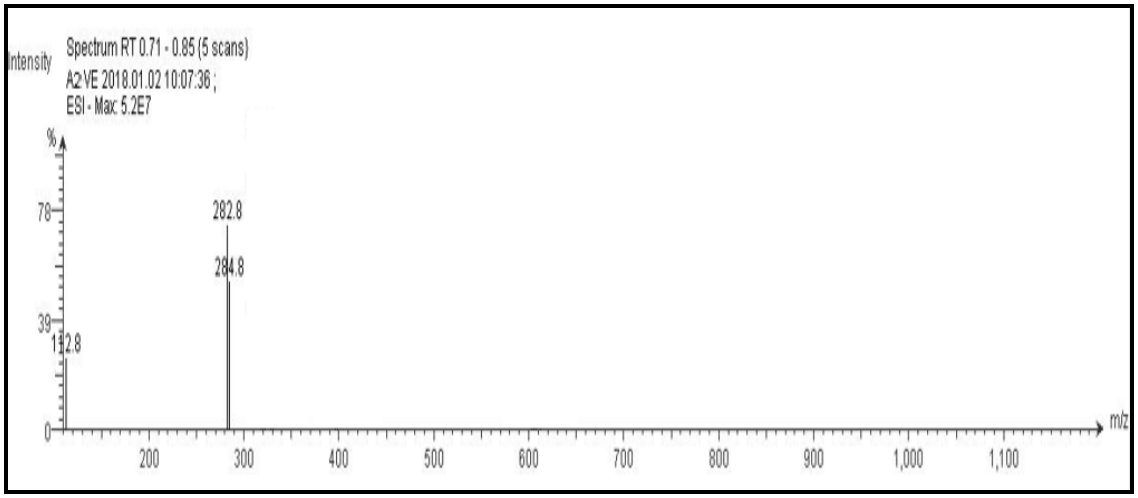
^{13}C NMR of B_2



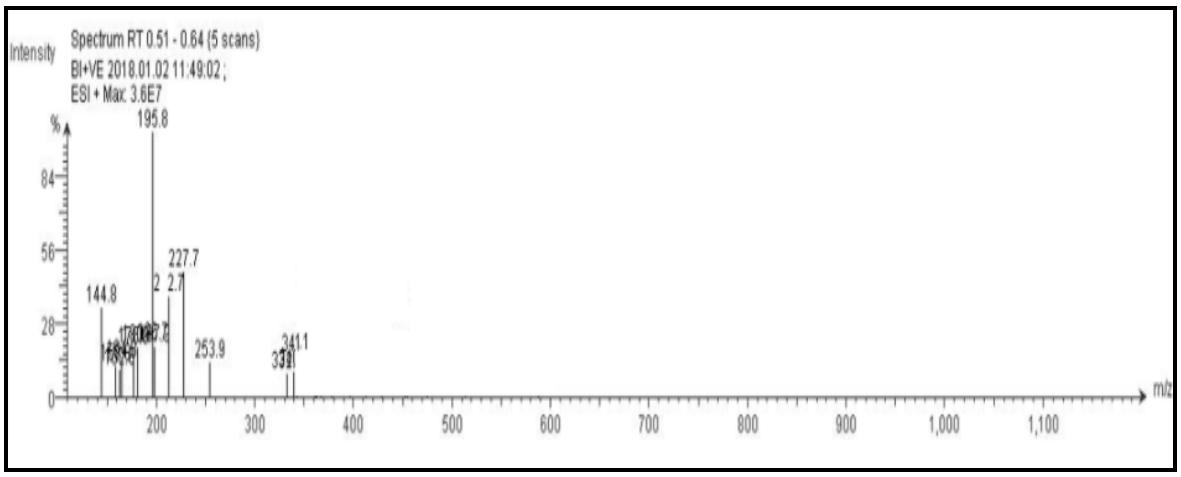
ESI-MS of 6-nitrobenzo[*d*]thiazole-2-amine



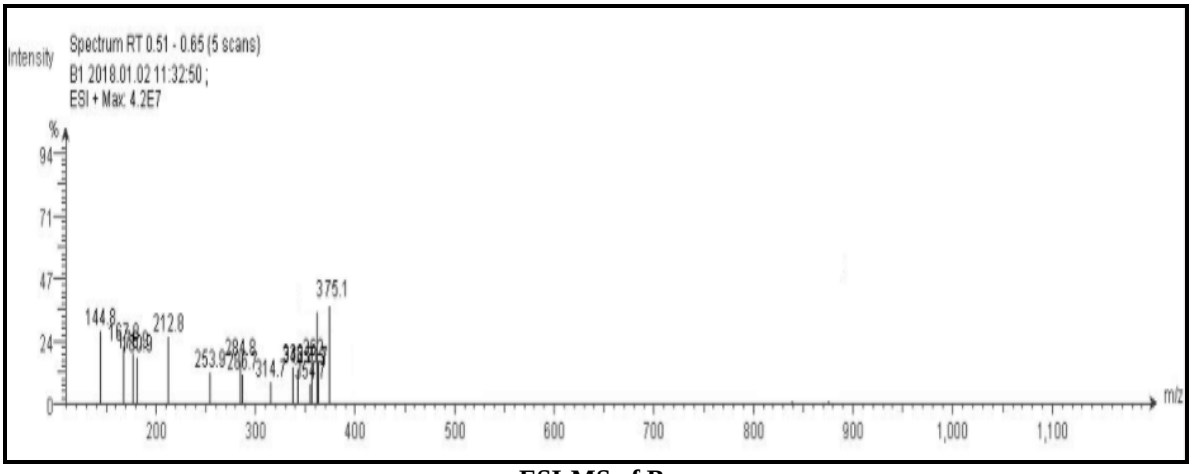
ESI-MS of A_1



ESI-MS of A_2



ESI-MS of B_1



ESI-MS of B_2

4. CONCLUSION

The antimicrobial evaluation of compounds A_1–A_5 and B_1–B_5 demonstrated that both substituent type and positional variation significantly influence biological activity. The synthesized compounds showed generally stronger activity against Gram-positive bacteria than Gram-negative strains, with selected derivatives also exhibiting promising antifungal potential. Meta-substituted phenyl derivatives, particularly A_4 (meta-chloro) and A_5 (meta-methyl), emerged as the most potent antibacterial agents against *S. aureus*, with MIC values comparable to ciprofloxacin, highlighting the beneficial role of meta substitution. Among the heteroaryl derivatives, A_1 (pyridin-3-yl) and B_1 (benzothiazole) showed significant antifungal activity against *C. albicans*, approaching that of fluconazole, and

can be considered promising antifungal leads. Overall, the results underline the importance of structure–activity relationships in guiding antimicrobial efficacy and identify A_4, A_5, A_1, and B_1 as suitable candidates for further structural optimization and mechanistic studies toward the development of new antimicrobial agents.

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Author's Contriobution
Chetankumar D. Bulsara: Writing- Original draft preparation, Faiyazalam Shaikh: Review, writing and editing draft, Hetal I. Soni: Formal Analysis, Vatsal M Patel: Supervision, Review, writing and editing draft, Navin B. Patel: Conceptualization.

Conflict of Interest
The authors declare there is no conflict of interest.

Data availability statement
The datasets used and analyzed during the current study are available on request.

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