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Microwave Assisted Synthesis, Characterization and Evaluation for Antimicrobial Activity of Novel 1, 5-Benzothiazepines

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: 1,5-benzothiazepine ring is privileged aromatic heterocycles of interest to organic and medicinal chemists because of its ease of synthesis and biological activities. This study aims to synthesize new series of 1, 5-benzothiazepine by direct and efficient microwave assistance and to evaluate for antimicrobial activity by MIC method.
Place and Duration of Study: The study was conducted at Department of Pharmaceutical Chemistry, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur-19, A. P. from January, 2019 to October, 2021.
Methodology: 1, 5-benzothiazepines (BT-21 to BT-40) were synthesized by microwave irradiation. The structures of the products were established by elemental analysis, FTIR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic studies. The synthesized compounds were also evaluated for their Antimicrobial activity by MIC method.
Results: The microwave assisted synthetic procedure adopted yielded the 1,5-benzothiazepine derivatives BT-21 to BT-40 in good amounts and at a lesser time span. The synthesized 1, 5-benzothiazepine derivatives showed good to moderate antibacterial and antifungal activities.BT-25 having a dihydroxy-methyl-phenyl moiety proved to be more potent against all selected bacterial

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strains, *B. subtilis*, *S. aureus*, *E. coli and P. aeruginosa* with a MIC value of 64 µg/ml. BT-33 having fluorophenyl moiety, BT-35 having hydroxyl-nitrophenyl moiety and BT-40having dibromophenyl moiety proved to be more potent against all selected fungal strains, *A. niger and C. tropicalis* with a MIC value of 16 µg/ml.

Conclusion: These results showed that the synthesized 1, 5-benzothiazepine derivatives have better scope for further development as antimicrobial agents.

Keywords: 1, 5-benzothiazepines; 1H-NMR; antibacterial; antifungal.

1. INTRODUCTION

The design and synthesis of heterocyclic hybrids have received greater attention due to their ease of synthesis and improved biological properties [1]. The structures that evolve from such conjugation are usually rigid frameworks that can show the appended rings in a well-defined fashion that is necessary for molecular recognition of the biological target. Usually, the variable nature of these functionalities defines the selectivity on a privileged core for a particular target.1, 5-Benzothiazepines (1 and 2) are seven-membered heterocyclic compounds containing nitrogen and sulphur as hetero atoms with diverse bioactivities [2-6]. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine (3) and one of the three possible benzo-condensed derivatives, viz. 1,4-**(4)**, 4,1- **(5)** and 1,5-benzothiazepines [6-10]. 1,5-benzothiazepine ring is privileged aromatic heterocycles of interest to organic and medicinal chemists because of its ease of synthesis and biological activities.

1, 5-Benzothiazepine scaffold is prominent in a variety of drugs used in the treatment of different complications. The first molecule of 1,5-benzothiazepine used clinically was Diltiazem, followed by Clentiazem, for their cardiovascular action. Some of the 1,5- benzothiazepine derivatives were also used clinically for CNS disorders which includes Thiazesim and Quetiapine fumarate. Moreover, 1,5-benzothiazepine moiety is a privileged class of pharmacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities such as anticonvulsant, Ca+2 channel antagonist, antianginal, anti HIV, squalene synthetase inhibitor, V2 arginine vasopressin receptor antagonist, and HIV-1 reverse transcriptase inhibitor [11-19]. Therefore, the 1, 5-benzothiazepines are useful compounds in the drug research which has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations [20-34]. In the present study, new series of 1,5-benzothiazepine derivatives has been synthesized by a direct and efficient microwave assistance and evaluated for antimicrobial activity by MIC method.

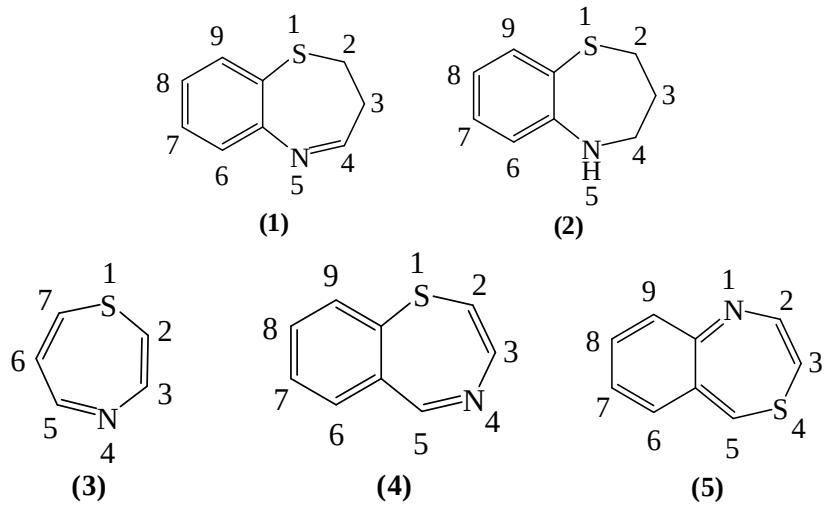


Image 1. 1, 5-Benzothiazepine scaffold is prominent in a variety of drugs used in the treatment of different complications

2. MATERIALS AND METHODS

All the reactions were carried out under specified laboratory conditions. All the synthetic work was done by procuring laboratory grade reagents and analytical grade solvents. Pre-coated silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC) and the spots on the TLC plates were visualized by UV lamp (254 nm). The products were purified by recrystallization using suitable solvents. Melting points were determined by Digital melting point apparatus and were uncorrected.FT-IR spectra were recorded on Bruker Vertex 80v spectrometer using potassium bromide discs and the absorption band values are given in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 400 NMR spectrophotometer using Tetramethyl silane (TMS) as internal standard and the chemical shift values are given in parts per million (ppm) relative to TMS. Mass spectra (MS) were recorded on Agilent 6100 QQQ ESI mass spectrophotometer by electron spray ionization technique.

2.1 General Procedure for Synthesis of 1, 3-substituted-prop-2-ene-1-ones [C-21 to C-40]

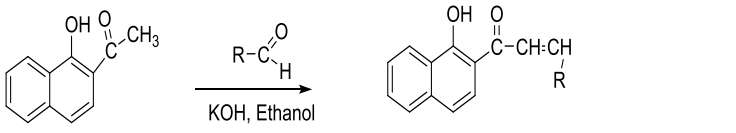
In this method, acetylated α-naphthol (0.01 mol), aromatic aldehyde (0.011mol) were taken in 5ml of ethanol and poured in 100ml Erlenmeyer borosil flask. To this reaction mixture, 4ml basic alumina was added. The reaction mixture was thoroughly mixed and irradiated inside a microwave for 2-3 minutes at medium level 600W. After completion of reaction, mixture was cooled and the product was extracted with ethanol (Fig. 1).

2.2 General Procedure for Synthesis of 2,3-dihydro-2-substituted-4(naphthalene-2-ol)-yl--1,5-Benzothiazepines (BT-21 to BT-40)

A mixture of (0.01 mol) 1,3-substituted-prop-2-en-1-one and (0.01 mol, 1.25ml) 2-aminothiophenol and pinch of potassium acetate as catalyst were thoroughly mixed and taken in a clean borosil beaker. The solvent- free reaction mixture was then subjected to microwave irradiation for 2-3 minutes at 80-85^{o}C. The reaction mixture was then allowed to cool to room temperature and then poured cold water in the mixture and stirred vigorously. Products were washed with water to remove the catalyst, filtered, dried and recrystallized by ethanol (Fig. 2).

2.3 Antimicrobial Activity

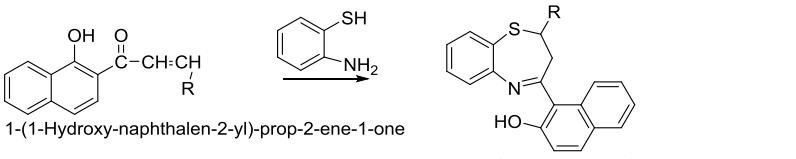
The antimicrobial (antibacterial and antifungal) activities of the novel benzothiazepines was evaluated against selected bacterial and fungal strains using standard experimental procedures as described in the literature [35]. The standard strains were procured from the American Type Culture Collection (ATCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The bacterial strains selected for the study were *Bacillus subtilis* (ATCC-60511), *Staphylococcus aureus* (ATCC-11632), *Escherichia coli* (ATCC-10536), *and Pseudomonas aeruginosa* (ATCC-10145) whereas the fungal strains include *Aspergillus niger* (ATCC-6275) and *Candida tropicalis* (ATCC-1369). Ampicillin was used as positive control for antibacterial activity and fluconazole for antifungal activity.



1-(1-Hydroxy-naphthalen-2-yl)-ethanone

1-(1-Hydroxy-naphthalen-2-yl)-prop-2-ene-1-one

Fig. 1. Scheme for the synthesis of 1, 3-substituted-prop-2-ene-1-ones [C-21 to C-40]



1-(1-Hydroxy-naphthalen-2-yl)-prop-2-ene-1-one

2,4-substituted-1,5-benzothiazepine

Fig. 2. Scheme for the synthesis of 2, 3-dihydro-2-substituted-4(naphthalene-2-ol)-yl--1, 5-benzothiazepines (BT-21 to BT-40)

Antibacterial activity was performed using nutrient agar medium whereas Potato Dextrose-Agar medium was used for antifungal testing. 2.048 mg of each test compound was taken in vials separately. Then 2 ml of methanol was added. Thus, a solution with a concentration of 1.024 mg/ml was obtained. All the experiments were carried out in triplicate and the results are presented as the mean of three independent experiments. The microbial strains were grown at 37 °C in their respective nutrient medium and diluted in sterile nutrient broth medium to get a suspension containing 10^7 cells/ml and this suspension was used as the inoculum. All the test tubes were incubated for 18 h at 37 °C. A similar experiment with inoculum, medium and methanol without compound was furthermore performed to confirm that there is no inhibitory effect of methanol used for the dilutions. The test tube number in which the first sign of the growth of the organism observed was noted using a spectrophotometer. The MIC was determined for all the compounds by taking that concentration used in the test tube number just before the test tube number where the first sign of growth observed [36].

3. RESULTS AND DISCUSSION

3.1 Characterization of Synthesized Compounds BT-21 to BT-40

1,5-benzothiazepines (BT-21 to BT-40) described here were synthesized following the synthetic routes outlined in Scheme. In the Step-1, to synthesize1, 3-substituted-prop-2-ene-1-ones (C-21 to C-40), α-naphthol was irradiated with substituted aromatic and hetero aromatic aldehydes.Compound C-21, analysed for molecular formula $C_{19}H_{13}BrO_2$, m.p. 144-146^oC, exhibited [M^+], at *m/z*353 and also a satellite peak[M + 2] at *m*/*z* 355 with 1:1 intensity in its positive ion mode electron spray ionization mass spectrum. The I.R (cm^{-1}) spectrum showed the characteristic absorption bands at 3455 (-O-H), 1655 (C=O), 1602 (C=C of Ar) and 795 (C-Br).The ^{1}H NMR spectrum showed the characteristic signals of CO-CH= and =CH-Ar at δ 6.65 and 7.42 as doublets (*J* =15.58HZ) respectively confirming the *trans* geometry at the ethylenic double bond of the molecule. The spectrum also showed peaks in between 7.47-8.2 δ integrated for ten protons must be the aromatic protons.The ^{13}C NMR (δ ppm) spectrum exhibited the characteristic signals at δ 119.3 (1C, s), 119.5 (1C, s), 121.2 (1C, s), 122.2 (1C, s), 122.3 (1C, s), 124.8 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 127.1 (1C, s), 127.7 (1C, s), 127.9 (2C, s), 130.3 (1C, s), 131.7 (2C, s), 134.5 (1C, s), 144.1 (1C, s), 162.4 (1C, s), 191.9 (1C, s). The values are consistent with the proposed structure for the compound. The results of elemental analysis were also in close agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the compound C-21 was confirmed as (E)-3-(4-bromophenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one.By adopting the above synthetic procedure, compounds C-22 to C-40 were also synthesized. [M+], 351.15, [M + 2].

In the Step-2, to synthesize 2, 3-dihydro-2-substituted-4(naphthalene-2-ol)-yl--1, 5-benzothiazepines (BT-21 to BT-40), a mixture of 1, 3-substituted-prop-2-en-1-one and 2-aminothiophenol and pinch of potassium acetate as catalyst were thoroughly mixed and then subjected to microwave irradiation. The compound BT-21was analysed for molecular formula $C_{25}H_{18}BrNOS$, m.p. 154-156^{0}C, well supported by a [M^+] at *m/z*463 and also a satellite peak[M + 2] at *m*/*z* 465 with 1:1 intensity in its positive mode electron spray ionization mass spectrum. The IR spectrum (cm^{-1}) showed the characteristic bands at at 3355 (-O-H), 1505 (C=C of Ar), 790 (C-Br) 1595 (C=N), 1390 (C-N) and 665 (C-S).The ^{1}H NMR spectrum of compound BT-21 showed characteristic signals of C_2-H protonsat δ 5.2 as doublet (*J*=9.76HZ),C_3-H-3a protons at δ 3.09 as doublet(*J*=15.79ZH) and C_3-H-3b at δ 3.04 as doublet (*J*=15.79ZH). The spectrum also accounted for the other twelve aromatic protons in between δ 6.939 to 8.02.The ^{13}C NMR spectrum of compound BT-21 accounted for all the carbons whose resonances appeared at the following δ values: 29.2 (1C, s), 46.3 (1C, s), 118.4 (1C, s), 122.3 (1C, s), 122.5 (1C, s), 124.7 (1C, s), 125.3 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 126.7 (2C, s), 127.5 (1C, s), 127.7 (1C, s), 128.0 (1C, s), 128.2 (1C, s), 128.5 (1C, s), 129.4 (1C, s), 130.6 (1C, s), 131.7 (2C, s), 133.4 (1C, s), 135.8 (1C, s), 148.9 (1C, s), 160.0 (1C, s), 173.5 (1C, s).The results of elemental analysis were also in agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the compound BT-21 was confirmed as 1-((E)-2-(4-bromophenyl)-2, 3-dihydrobenzo[b][1,4] thiazepin-4-yl)naphthalen-2-ol. By adopting the above synthetic procedure of BT-21, compounds BT-22 to BT-40 were also synthesized.

3.1.1 1-(-2-(4-bromophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-21)

FT-IR (KBr): 3355 (-O-H), 1505 (C=C of Ar), 790 (C-Br), 1595 (C=N), 1390 (C-N) and 665 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.93-3.11 (2H, 3.01 (dd, *J* = 15.8, 9.8 Hz), 3.04 (dd, *J* = 15.8, 1.6 Hz)), 5.20 (1H, dd, *J* = 9.8, 1.6 Hz), 6.88-7.06 (2H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.68 (9H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.36 (ddd, *J* = 8.3, 1.4, 0.5 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.47 (ddd, *J* = 8.3, 1.9, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)); ^{13}C NMR (100 MHz, CDCl3):δ 29.2 (1C, s), 46.3 (1C, s), 118.4 (1C, s), 122.3 (1C, s), 122.5 (1C, s), 124.7 (1C, s), 125.3 (1C, s), 126.4-126.5 (2C, 126.4 (s), 126.4 (s)), 126.7 (2C, s), 127.5 (1C, s), 127.7 (1C, s), 128.0 (1C, s), 128.2 (1C, s), 128.5 (1C, s), 129.4 (1C, s), 130.6 (1C, s), 131.7 (2C, s), 133.4 (1C, s), 135.8 (1C, s), 148.9 (1C, s), 160.0 (1C, s), 173.5 (1C, s); MS (m/z): [M^{+}], 463, [M + 2], 465.

3.1.2 4-(-2,3-dihydro-4-(2-hydroxynaphthalen-1-yl)benzo[b][1,4]thiazepin-2-yl)benzene-1,2,3-triol (BT-22)

FT-IR (KBr): 3370 (-O-H), 1525 (C=C of Ar), 1580 (C=N) and 680 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.77-3.01 (2H, 2.85 (dd, *J* = 15.7, 9.8 Hz), 2.93 (dd, *J* = 15.7, 1.6 Hz)), 4.92 (1H, dd, *J* = 9.8, 1.6 Hz), 6.53 (1H, d, *J* = 8.6 Hz), 6.88-7.06 (3H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.96 (d, *J* = 8.6 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.68 (5H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.3 1-(-2-(2,3-dichlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-23)

FT-IR (KBr): 3375 (-O-H), 1515 (C=C of Ar), 590 (C-Cl), 1595 (C=N) and 690 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.97-3.24 (2H, 3.05 (dd, *J* = 15.8, 9.8 Hz), 3.17 (dd, *J* = 15.8, 1.6 Hz)), 5.27 (1H, dd, *J* = 9.8, 1.6 Hz), 6.97-7.68 (10H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.29 (dd, *J* = 8.1, 1.1 Hz), 7.37 (dd, *J* = 8.1, 7.8 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.54 (dd, *J* = 7.8, 1.1 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.4 2-(-2,3-dihydro-4-(2-hydroxynaphthalen-1-yl)benzo[b][1,4]thiazepin-2-yl)benzene-1,3,5-triol (BT-24)

FT-IR (KBr): 3340 (-O-H), 1530 (C=C of Ar), 1590 (C=N) and 690 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.72-2.90 (2H, 2.79 (dd, *J* = 15.1, 1.6 Hz), 2.82 (dd, *J* = 15.1, 9.8 Hz)), 5.01 (1H, dd, *J* = 9.8, 1.6 Hz), 6.15 (2H, d, *J* = 2.5 Hz), 6.88-7.06 (2H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.68 (5H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.5 4-(-2,3-dihydro-4-(2-hydroxynaphthalen-1-yl)benzo[b][1,4]thiazepin-2-yl)-5-methylbenzene-1,3-diol (BT-25)

FT-IR (KBr): 3345 (-O-H), 1505 (C=C of Ar), 1595 (C=N) and 679 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.38 (3H, s), 2.79-2.95 (2H, 2.87 (dd, *J* = 15.7, 9.8 Hz), 2.87 (dd, *J* = 15.7, 1.6 Hz)), 5.10 (1H, dd, *J* = 9.8, 1.6 Hz), 6.32 (1H, d, *J* = 2.7 Hz), 6.63 (1H, d, *J* = 2.7 Hz), 6.97-7.68 (7H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.6 4-(-2,3-dihydro-4-(2-hydroxynaphthalen-1-yl)benzo[b][1,4]thiazepin-2-yl)benzene-1,3-diol (BT-26)

FT-IR (KBr): 3355 (-O-H), 1515 (C=C of Ar), 1605 (C=N) and 695 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.77-3.00 (2H, 2.85 (dd, *J* = 15.7, 9.8 Hz), 2.93 (dd, *J* = 15.7, 1.6 Hz)), 5.05 (1H, dd, *J* = 9.8, 1.6 Hz), 6.44-6.60 (2H, 6.50 (dd, *J* = 7.7, 2.8 Hz), 6.55 (dd, *J* = 2.8, 0.4 Hz)), 6.88-

7.06 (2H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.16-7.68 (6H, 7.22 (dd, *J* = 7.7, 0.4 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.7 1-(-2,3-dihydro-2-(2,4,6-trimethoxyphenyl)benzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-27)

FT-IR (KBr): 3360 (-O-H), 1530 (C=C of Ar), 1594 (C=N) and 690 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.70-2.96 (2H, 2.77 (dd, *J* = 14.4, 1.6 Hz), 2.88 (dd, *J* = 14.4, 9.8 Hz)), 3.69-3.82 (9H, 3.74 (s), 3.77 (s)), 4.93 (1H, dd, *J* = 9.8, 1.6 Hz), 6.16 (2H, d, *J* = 2.0 Hz), 6.97-7.68 (7H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.8 1-(-2,3-dihydro-2-(2,4-dimethoxyphenyl)benzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-28)

FT-IR (KBr): 3410 (-O-H), 1495 (C=C of Ar), 1590 (C=N) and 685 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.72-2.95 (2H, 2.80 (dd, *J* = 15.7, 9.8 Hz), 2.88 (dd, *J* = 15.7, 1.6 Hz)), 3.68-3.81 (6H, 3.73 (s), 3.76 (s)), 5.02 (1H, dd, *J* = 9.8, 1.6 Hz), 6.55-6.75 (2H, 6.60 (dd, *J* = 2.6, 0.5 Hz), 6.68 (dd, *J* = 7.7, 2.6 Hz)), 6.94 (1H, dd, *J* = 8.8, 0.5 Hz), 7.08-7.68 (7H, 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.20 (dd, *J* = 7.7, 0.5 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.9 2-(2,3-dihydro-4-(2-hydroxynaphthalen-1-yl)benzo[b][1,4]thiazepin-2-yl)benzene-1,4-diol (BT-29)

FT-IR (KBr): 3390 (-O-H), 1505 (C=C of Ar), 1569 (C=N) and 695 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.92-3.21 (2H, 3.00 (dd, *J* = 15.8, 9.8 Hz), 3.14 (dd, *J* = 15.8, 1.6 Hz)), 5.13 (1H, dd, *J* = 9.8, 1.6 Hz), 6.39 (1H, dd, *J* = 2.8, 0.5 Hz), 6.68 (1H, dd, *J* = 8.6, 0.5 Hz), 6.81 (1H, dd, *J* = 8.6, 2.8 Hz), 6.88-7.06 (2H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.68 (5H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.10 1-(-2,3-dihydro-2-(2,5-dimethoxyphenyl)benzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-30)

FT-IR (KBr): 3365 (-O-H), 1515 (C=C of Ar), 1585 (C=N) and 690 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.95 (1H, dd, *J* = 15.8, 9.8 Hz), 3.17 (1H, dd, *J* = 15.8, 1.6 Hz), 3.72-3.85 (6H, 3.77 (s), 3.80 (s)), 5.10 (1H, dd, *J* = 9.8, 1.6 Hz), 6.50-6.84 (3H, 6.55 (dd, *J* = 2.8, 0.5 Hz), 6.66 (dd, *J* = 8.6, 0.5 Hz), 6.78 (dd, *J* = 8.6, 2.8 Hz)), 6.97-7.68 (7H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.11 1-(2-(2,6-dichlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-31)

FT-IR (KBr): 3340 (-O-H), 1505 (C=C of Ar), 610 (C-Cl), 1605 (C=N) and 695 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 3.01-3.29 (2H, 3.10 (dd, *J* = 15.8, 9.8 Hz), 3.22 (dd, *J* = 15.8, 1.6 Hz)), 5.33 (1H, dd, *J* = 9.8, 1.6 Hz), 6.97-7.68 (10H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.39 (dd, *J* = 8.1, 1.8 Hz), 7.40 (t, *J* = 8.1 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dddt, *J* = 7.9, 1.9, 1.6, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.6, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.12 1-(2-(2-bromophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-32)

FT-IR (KBr): 3365 (-O-H), 1520 (C=C of Ar), 805 (C-Br), 1600 (C=N) and 695 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.96-3.21 (2H, 3.04 (dd, *J* = 15.8, 9.8 Hz), 3.14 (dd, *J* = 15.8, 1.6 Hz)), 5.25 (1H, dd, *J* = 9.8, 1.6 Hz), 6.91-7.68 (11H, 6.97

(ddd, *J* = 8.0, 1.5, 0.5 Hz), 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.10 (ddd, *J* = 8.0, 7.5, 1.6 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.28 (ddd, *J* = 8.0, 7.5, 1.5 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.47 (ddd, *J* = 8.0, 1.6, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.13 1-(2-(2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-33)

FT-IR (KBr): 3350 (-O-H), 1515 (C=C of Ar), 1570 (C=N), 915 (C-F and 695 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.95-3.23 (2H, 3.03 (dd, *J* = 15.8, 9.8 Hz), 3.16 (dd, *J* = 15.8, 1.6 Hz)), 5.20 (1H, dd, *J* = 9.8, 1.6 Hz), 6.88-7.68 (11H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.5, 1.2 Hz), 7.07 (ddd, *J* = 8.3, 1.5, 0.5 Hz), 7.11 (ddd, *J* = 8.0, 1.2, 0.5 Hz), 7.17 (ddd, *J* = 8.0, 7.5, 1.5 Hz), 7.29 (ddd, *J* = 8.1, 7.5, 1.4 Hz), 7.38 (ddd, *J* = 8.3, 7.5, 1.2 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.14 1-(2-(2-ethoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-34)

FT-IR (KBr): 3360 (-O-H), 1525 (C=C of Ar), 1585 (C=N) and 675 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 1.28 (3H, t, *J* = 7.0 Hz), 2.95 (1H, dd, *J* = 15.8, 9.8 Hz), 3.17 (1H, dd, *J* = 15.8, 1.6 Hz), 3.95-4.07 (2H, 4.01 (q, *J* = 7.0 Hz), 4.01 (q, *J* = 7.0 Hz)), 5.20 (1H, dd, *J* = 9.8, 1.6 Hz), 6.84-7.00 (2H, 6.91 (ddd, *J* = 8.0, 7.6, 1.3 Hz), 6.94 (dd, *J* = 8.8, 0.5 Hz)), 7.00-7.68 (9H, 7.07 (ddd, *J* = 8.0, 1.3, 0.6 Hz), 7.09 (ddd, *J* = 8.5, 1.3, 0.6 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.24 (ddd, *J* = 8.5, 7.6, 1.3 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.15 1-(2,3-dihydro-2-(2-hydroxy-3-nitrophenyl)benzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-35)

FT-IR (KBr): 3365 (-O-H), 1515 (C=C of Ar), 1570 (C=N) and 690 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.99 (1H, dd, *J* = 15.8, 9.8 Hz), 3.19 (1H, dd, *J* = 15.8, 1.6 Hz), 5.35 (1H, dd, *J* = 9.8, 1.6 Hz), 6.88-7.06 (2H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.79 (7H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.42 (dd, *J* = 7.8, 7.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz), 7.73 (dd, *J* = 7.5, 1.9 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)), 8.15 (1H, dd, *J* = 7.8, 1.9 Hz).

3.1.16 1-(2,3-dihydro-2-(2-hydroxy-3-methoxyphenyl)benzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-36)

FT-IR (KBr): 3375(-O-H), 1511(C=C of Ar), 1570 (C=N) and 690 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.94-3.22 (2H, 3.02 (dd, *J* = 15.8, 9.8 Hz), 3.15 (dd, *J* = 15.8, 1.6 Hz)), 3.79 (3H, s), 5.00 (1H, dd, *J* = 9.8, 1.6 Hz), 6.59-6.82 (2H, 6.66 (dd, *J* = 8.6, 2.6 Hz), 6.76 (dd, *J* = 8.0, 2.6 Hz)), 6.88-7.14 (3H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.07 (dd, *J* = 8.6, 8.0 Hz)), 7.22-7.68 (5H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.17 1-(2,3-dihydro-2-(2-hydroxy-5-methoxyphenyl)benzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-37)

FT-IR (KBr): 3380 (-O-H), 1515 (C=C of Ar), 1575 (C=N) and 685 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.94-3.22 (2H, 3.02 (dd, *J* = 15.8, 9.8 Hz), 3.15 (dd, *J* = 15.8, 1.6 Hz)), 3.76 (3H, s), 4.99 (1H, dd, *J* = 9.8, 1.6 Hz), 6.50-6.85 (3H, 6.56 (dd, *J* = 2.8, 0.5 Hz), 6.67 (dd, *J* = 8.6, 0.5 Hz), 6.79 (dd, *J* = 8.6, 2.8 Hz)), 6.88-7.06 (2H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.68 (5H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.18 1-(2-(3,4-dichlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-38)

FT-IR (KBr): 3355 (-O-H), 1507 (C=C of Ar), 580 (C-Cl), 1590 (C=N) and 690 (C-S); ^{1}H NMR (400

MHz, CDCl3):δ 2.93-3.22 (2H, 3.02 (dd, *J* = 15.8, 9.8 Hz), 3.15 (dd, *J* = 15.8, 1.6 Hz)), 5.28 (1H, dd, *J* = 9.8, 1.6 Hz), 6.97-7.68 (10H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.28 (dd, *J* = 8.2, 1.3 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.46 (dd, *J* = 8.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.47 (dd, *J* = 1.3, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

3.1.19 4-(2,3-dihydro-4-(2-hydroxynaphthalen-1-yl)benzo[b][1,4]thiazepin-2-yl)benzene-1,2-diol (BT-39)

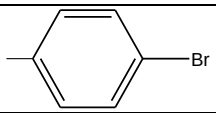
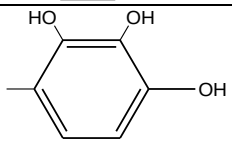
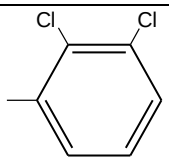
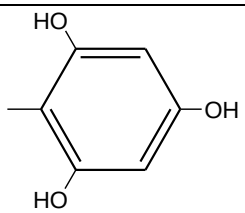
FT-IR (KBr): 3350 (-O-H), 1520 (C=C of Ar), 1575 (C=N) and 680 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.86-3.14 (2H, 2.94 (dd, *J* = 15.8, 9.8 Hz), 3.07 (dd, *J* = 15.8, 1.6 Hz)), 5.09 (1H, dd, *J* = 9.8, 1.6 Hz), 6.66-6.79 (2H, 6.72 (dd, *J* = 8.5, 2.6 Hz), 6.73 (dd, *J* = 8.5, 0.5 Hz)), 6.88-7.06 (3H, 6.94 (dd, *J* = 8.8, 0.5 Hz), 6.95 (dd, *J* = 2.6, 0.5 Hz), 6.99 (ddd, *J* = 7.8, 7.6, 1.2 Hz)), 7.22-7.68 (5H, 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0. 5 Hz)).

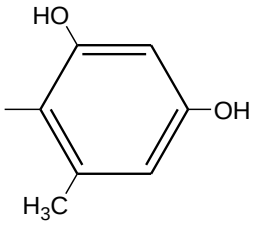
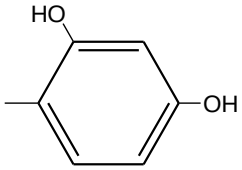
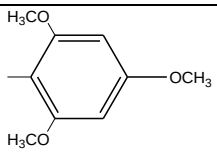
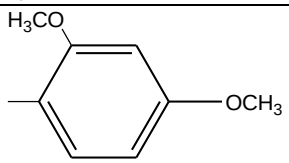
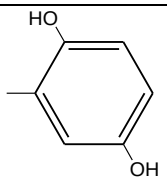
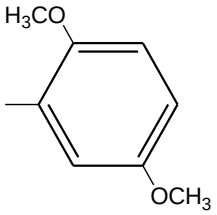
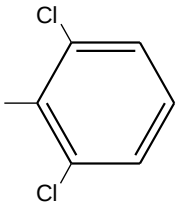
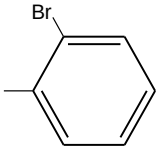
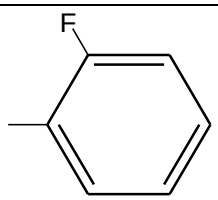
3.1.20 1-(2-(3,4-dibromophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)naphthalen-2-ol (BT-40)

FT-IR (KBr): 3360 (-O-H), 1515 (C=C of Ar), 810 (C-Br) 1585 (C=N) and 670 (C-S); ^{1}H NMR (400 MHz, CDCl3):δ 2.94-3.22 (2H, 3.02 (dd, *J* = 15.8, 9.8 Hz), 3.15 (dd, *J* = 15.8, 1.6 Hz)), 5.23 (1H, dd, *J* = 9.8, 1.6 Hz), 6.97-7.68 (10H, 7.03 (dd, *J* = 8.8, 0.5 Hz), 7.15 (ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.20 (dd, *J* = 8.1, 1.5 Hz), 7.29 (ddd, *J* = 8.1, 7.6, 1.4 Hz), 7.40 (ddd, *J* = 8.1, 1.2, 0.5 Hz), 7.41 (dd, *J* = 1.5, 0.5 Hz), 7.47 (ddd, *J* = 7.8, 1.4, 0.5 Hz), 7.49 (dd, *J* = 8.1, 0.5 Hz), 7.57 (ddd, *J* = 8.6, 7.3, 1.9 Hz), 7.61 (dddd, *J* = 7.9, 7.3, 1.4, 0.5 Hz)), 7.80-8.08 (3H, 7.86 (dtt, *J* = 7.9, 1.9, 0.5 Hz), 7.98 (ddt, *J* = 8.8, 1.9, 0.5 Hz), 8.02 (ddt, *J* = 8.6, 1.4, 0.5 Hz)).

Physical characterization and Elemental Analysis data of 1, 5-benzothiazepines were represented in Table1 and Table 2.

Table 1. Physical characterization data of 2,3-dihydro-2-substituted-4(naphthalene-2-ol)-yl--1,5-benzothiazepines (BT-21 to BT-40)

Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (^{o}C)	Yield %	Rf value
BT-21		$C_{25}H_{18}BrNOS$	460.39	152-154	76	0.6
BT-22		$C_{25}H_{19}NO_4S$	420.49	160-162	78	0.4
BT-23		$C_{25}H_{17}Cl_2NOS$	450.38	138-140	82	0.7
BT-24		$C_{25}H_{19}NO_4S$	420.49	168-170	80	0.5

Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (°C)	Yield %	Rf value
BT-25		$C_{26}H_{21}NO_3S$	427.51	166-168	75	0.6
BT-26		$C_{25}H_{19}NO_3S$	413.19	160-162	83	0.7
BT-27		$C_{27}H_{24}N_2OS$	471.57	172-174	72	0.8
BT-28		$C_{27}H_{23}NO_3S$	441.53	154-156	82	0.6
BT-29		$C_{25}H_{19}NO_3S$	413.19	158-160	77	0.5
BT-30		$C_{27}H_{23}NO_3S$	441.53	170-172	81	0.8
BT-31		$C_{25}H_{17}Cl_2NOS$	450.38	166168	79	0.5
BT-32		$C_{25}H_{18}BrNOS$	460.39	180-182	84	0.5
BT-33		$C_{25}H_{18}FNOS$	399.48	174-176	81	0.6

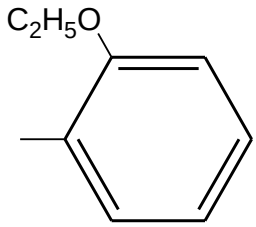
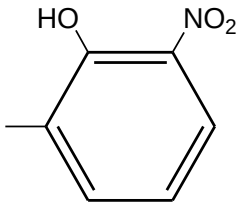
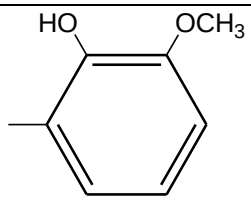
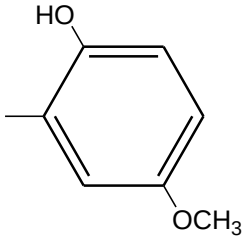
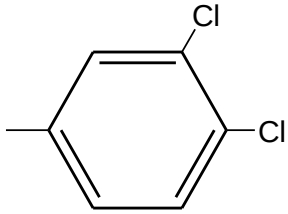
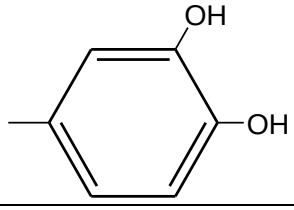
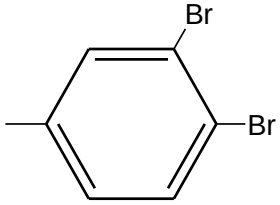
Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (^{o}C)	Yield %	Rf value
BT-34		$C_{27}H_{23}NO_2S$	425.54	164-166	82	0.6
BT-35		$C_{25}H_{18}N_2O_4S$	442.59	170-172	78	0.8
BT-36		$C_{26}H_{21}NO_3S$	427.51	178-180	80	0.6
BT-37		$C_{26}H_{21}NO_3S$	427.51	166-168	84	0.5
BT-38		$C_{25}H_{17}Cl_2NOS$	450.38	160-162	79	0.6
BT-39		$C_{25}H_{19}NO_3S$	413.19	172-174	86	0.7
BT-40		$C_{25}H_{17}Br_2NOS$	539.28	180-182	74	0.8

Table 2. Elemental Analysis data of 2, 3-dihydro-2-substituted-4(naphthalene-2-ol)-yl--1,5-benzothiazepines (BT-21 to BT-40)

Compound	% Calculated			%Found		
	C	H	N	C	H	N
BT-21	65.22	3.94	3.04	65.20	3.96	3.06
BT-22	69.91	4.46	3.26	69.82	4.52	3.34
BT-23	66.67	3.8	3.11	66.76	3.72	66.67
BT-24	69.91	4.46	3.26	66.83	4.51	66.85
BT-25	73.04	4.95	3.8	73.12	4.91	3.79
BT-26	72.62	4.63	3.39	72.71	4.67	3.34
BT-27	71.32	5.34	2.97	71.36	5.37	2.89
BT-28	73.44	5.25	3.17	73.51	5.32	3.15
BT-29	72.62	4.63	3.39	72.66	3.41	3.44
BT-30	73.44	5.25	3.17	73.51	5.22	3.19
BT-31	66.67	3.8	3.11	66.72	3.91	3.16
BT-32	65.22	3.94	3.04	65.26	3.89	3.09
BT-33	75.16	4.54	3.51	75.21	4.59	3.46
BT-34	76.21	5.45	3.29	76.24	5.49	3.33
BT-35	67.86	4.1	6.33	67.86	4.09	6.31
BT-36	73.04	4.95	3.8	73.11	4.91	3.77
BT-37	73.04	4.95	3.8	73.12	4.91	3.81
BT-38	66.67	3.8	3.11	66.64	3.82	3.09
BT-39	72.62	4.63	3.39	72.58	4.61	3.40
BT-40	55.68	3.18	2.6	55.64	2.58	2.58

Table 3. Antibacterial activity of Benzothiazepines (BT-21to BT-40): (Expressed as MIC in µg/ml)

Compound	*B.subtilis*	*S.aureus*	*E.coli*	*P.vulgaris*
BT-21	256	128	256	128
BT-22	64	128	128	128
BT-23	64	128	64	128
BT-24	128	64	128	64
BT-25	64	64	64	64
BT-26	64	128	64	128
BT-27	128	64	128	128
BT-28	256	128	128	256
BT-29	64	128	128	64
BT-30	128	128	128	128
BT-31	64	128	64	128
BT-32	128	64	64	128
BT-33	256	64	128	256
BT-34	128	128	128	128
BT-35	64	128	64	128
BT-36	128	256	256	128
BT-37	256	256	512	256
BT-38	64	128	64	128
BT-39	64	128	128	64
BT-40	128	64	64	64
Standard (Ampicillin)	< 1	< 1	< 1	< 1

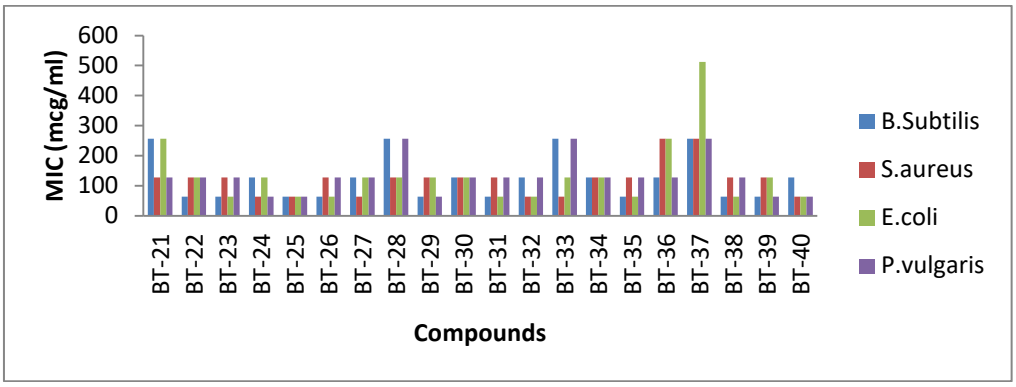


Fig. 3. Antibacterial activity of Benzothiazepines (BT-21to BT-40): (Expressed as MIC in µg/ml)

Table 4. Antifungal activity of Benzothiazepines (BT-21to BT-40): (Expressed as MIC in µg/ml)

Compound	*Aspergillus*niger	*Candida tropicalis*
BT-21	16	32
BT-22	32	64
BT-23	32	34
BT-24	32	64
BT-25	32	32
BT-26	32	32
BT-27	64	32
BT-28	32	64
BT-29	32	64
BT-30	64	32
BT-31	32	64
BT-32	16	32
BT-33	16	16
BT-34	64	128
BT-35	16	16
BT-36	32	64
BT-37	32	64
BT-38	16	32
BT-39	32	32
BT-40	16	16
Standard (Fluconazole)	< 2	< 2

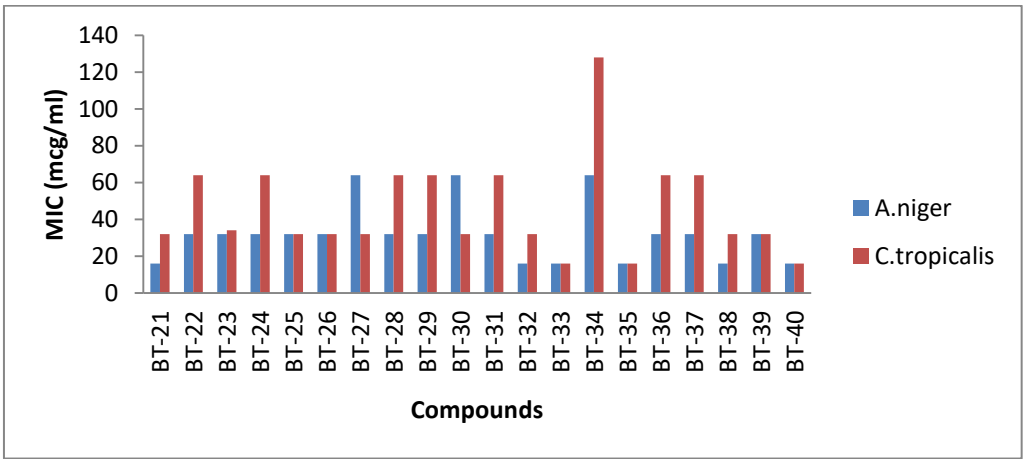


Fig. 4. Antifungal activity of Benzothiazepines (BT-21to BT-40) : (Expressed as MIC in µg/ml)

3.2 Antibacterial Activity

The antibacterial activity of the novel benzothiazepines was evaluated against selected bacterial strains using Ampicillin as positive control by MIC method. From the results (Table 3 & Fig. 3), it is evident that most of the 1,5-benzothiazepines synthesized showed antibacterial activity with different MIC values against the tested organisms, but not comparable with that of the standard. Among the compounds tested, BT-25 having a dihydroxy-methyl-phenyl moiety proved to be more potent against all selected bacterial strains *B.subtilis*, *S.aureus*, *E.coli and P.aeruginosa* with a MIC value of 64 µg/ml. BT-40 having dibromophenyl moiety proved to be more potent against three selected bacterial strains *S.aureus*, *E.coli and P.aeruginosa* with a MIC value of 64 µg/ml. These results suggested that, the electron releasing groups present on phenyl moiety of the BT-25 compound affects the charge distribution, which confers significant improvement in biological effect. The enhanced inhibition observed is more likely due to its interaction with some intracellular target [37]. The presence of a strong electron-withdrawing groups in the compound BT-40 alter the nature of the compound in such a way as to promote binding to the target(s) [38].

3.3 Antifungal Activity

The antifungal activity of the novel benzothiazepines was evaluated against selected fungal strains using Fluconazole as positive control by MIC method. From the results (Table 4 & Fig. 4), it is evident that most of the 1, 5-benzothiazepines synthesized showed antifungal activity with different MIC values against the tested organisms, but not comparable with that of the standard. Among the compounds tested, BT-33 having fluorophenyl moiety, BT-35 having hydroxyl-nitrophenyl moiety and BT-40having dibromophenyl moiety proved to be more potent against all selected fungal strains, *A.niger and C.tropicalis* with a MIC value of 16 µg/ml. BT-25 having dihydroxy-methylphenyl moiety and BT-26 having dihydroxyphenyl moiety proved to be more potent against all selected fungal strains, *A.niger and C.tropicalis* with a MIC value of 32 µg/ml. The presence of substituents containing an electron withdrawing group that is surrounded by high electron density might be the reason for the high antifungal activity of the benzyl tested compounds [39].

4. CONCLUSION

The microwave assisted synthetic procedure adopted was afforded the 1, 5-benzothiazepine derivatives BT-21 to BT-40 in good yield at the cost of shorter reaction time. The synthesized 1, 5-benzothiazepine derivatives showed good to moderate antibacterial and antifungal activities.Out of the synthesized compounds, molecules bearing electron releasing group showed good antibacterial activity and molecules bearing electron withdrawing groups showed good antifungal activity.The compounds BT-25, BT-33 and BT-35 are the promising molecules with antimicrobial properties and have better scope for further development as antimicrobial agents and potency of these compounds is required to be confirmed further by in-vivo screening.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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