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Microwave assisted synthesis and biological evaluation of a series of 1,5-benzothiazepines as potential cytotoxic and antimicrobial agents

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ABSTRACT

A series of 2,3-dihydro-2-(susbtituted)-4-(1-methyl-1*H*-pyrrol-2-yl)-1,5-benzothiazepines (**4a-v**) have been synthesized evaluated for their *in vitro* cytotoxicity and antimicrobial activities. Among the tested compounds for cytotoxicity using Brine shrimp lethality assay, compound **4q** exhibited significant cytotoxicity at ED_{50} values 3.45±0.15 µg/mL. This level of activity was found comparable to that of the reference drug podophyllotoxin with ED_{50} value 3.61±0.17 µg/mL. Antimicrobial activity was assessed using agar well diffusion assay method against selected Gram-positive, Gram-negative and fungal strains. Among the compounds tested, **4q**, **4r** and **4l** were found to be more active with MIC 16-32 µg/mL against all tested microorganisms.

1. Introduction

1,5-Benzothiazepines are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives, *viz*. 1,4-benzothiazepines, 4,1-benzothiazepines and 1,5-benzothiazepines [1]. The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets [2]. 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, clothiapine and quetiapine [3]. Therefore, the 1,5-benzothiazepines are useful compounds in the drug research that has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations [4]. The common strategy for the construction of the 1,5-benzothiazepine moiety is the reaction of 1,3-diaryl prop-2-enones with *o*-aminothiophenol [5]. The various reported methodologies involve the use of inorganic solid supports such as alumina, silica gel and clay under microwave irradiation, acetic acid or trifluoroacetic acid, hydrochloric acid, piperidine etc. [6].

The importance of the 1,5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents [7]. A number of biological activities have also been associated with it, such as antianginal [8], antihypertensive [9], antiischemic [10], antiarrhythmic [11], platelet aggregation inhibitor [12], vasodilator [13], calcium channel blocker [14], calcium channel antagonist [15] and calcium channel activator [16]. In recent past, under the frame work of "Green Chemistry" microwave-assisted synthesis is one of the non-conventional techniques used in laboratory for the synthesis of organic compounds. This is an eco-friendly technology and helps to prevent pollution [17]. Therefore we are interested in developing a rapid, microwave-assisted protocol towards the preparation of 1,5-benzothiazepines from 2-aminothiophenol and various chalcone derivatives in the presence of catalytic amount of piperidine, acetic acid using DMF as a reaction mediator [18]. The chemical structures of the compounds were proved by analytical and spectral data.

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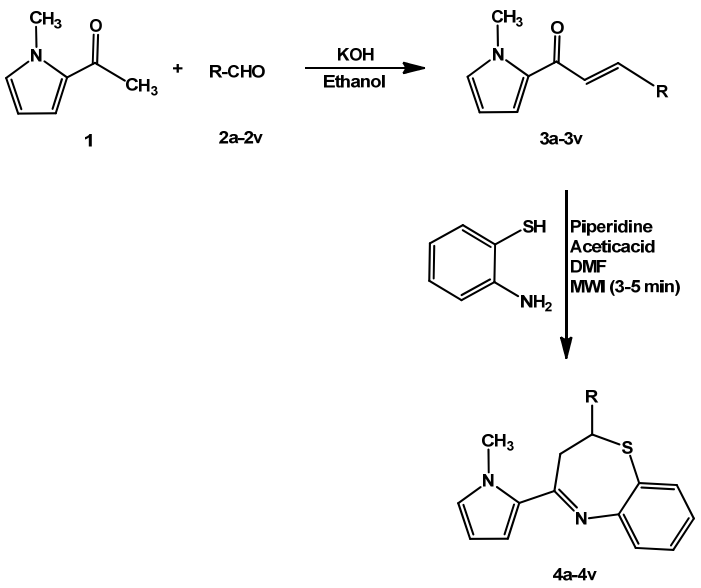

Scheme 1

The newly synthesized compounds, which earlier not reported were evaluated for their *in vitro* cytotoxic and antimicrobial properties.

2. Experimental

2.1. Instrumentation

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The FT-IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a Bruker 400 MHz spectrometer in $CDCl_3$ using TMS as internal standard and chemical shifts are expressed in δ, ppm. The ESI mass spectra were recorded on an Agilent 6100 QQQ spectrometer (positive ion mode). Reactions were carried out in a Catalyst Scientific Microwave Oven, Model: CATA 2R, Range: 140-700 W, Make: Catalyst System, Pune, India.

2.2. General procedure for the synthesis of 1,5-benzo thiazepines (4a-4v)

The reaction order proposed for the preparation of title compounds (**4a**-**v**) is shown in Scheme 1. The principal intermediates in the present study (**3a**-**v**) were prepared by using standard Claisen-Schmidt condensation reaction between 2-acetyl-1-methylpyrrole (**1**) and appropriate aromatic/hetero aromatic aldehydes (**2a**-**v**)in the presence of 100% potassium hydroxide solution in ethanol afforded a series of 1-(1-methyl-1*H*-pyrrol-2-yl)-3-(substituted)-2-propen-1-ones (**3a**-**v**) in good yield. Subsequent condensation reaction of crude chalcone derivatives (**3a**-**v**) and 2-aminothiophenol with catalytic amount of acetic acid and piperidine in dimethyl formamide (DMF) was taken in a conical flask and placed in a microwave oven and irradiated for 3-5 min. Then reaction mixture was cooled to room temperature and treated with cold water. The solid separated was isolated by simple Buchner filtration; final purification was achieved by recrystallization from ethanol to give corresponding 2,3-dihydro-2-(susbtituted)-4-(1-methyl-1*H*-pyrrol-2-yl)-1,5-benzothiazepines (**4a**-**v**) in good yield[19].

2,3-Dihydro-2-(phenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4a**): Colour: Yellow. Yield: 86%. M.p.: 125-127 ^{o}C. FT-IR (KBr, ν_{max}, cm^{-1}): 1596 (C=N), 1510 (C=C), 1365 (C-N), 688 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm):2.50 (3H, s, N-CH_3), 3.36 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.43 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 4.89 (dd,$J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.95-7.60 (7H, m, Ar-H), 7.12 (1H, s, Ar-H), 7.72 (4H, m, Ar-H). ESI-MS (*m/z*): 319 [M+H]$^+$. Anal. calcd. for$C_{20}H_{18}N_2S$: C, 75.44; H, 5.70; N, 8.80. Found: C, 75.41; H, 5.73; N, 8.82%.

2,3-Dihydro-2-(4-methylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4b**): Colour: Yellow. Yield: 89%. M.p.: 141-143 ^{o}C. FT-IR (KBr, ν_{max}, cm^{-1}): 1585 (C=N), 1505 (C=C), 1395 (C-N), 654 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.40 (3H, s, Ar-CH_3), 2.45 (3H, s, N-CH_3), 3.04 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.10-7.33 (6H, m, Ar-H), 7.45 (1H, s, Ar-H), 7.61 (4H, m, Ar-H). ESI-MS (*m/z*): 333 [M+H]$^+$. Anal. calcd. for $C_{21}H_{20}N_2S$: C, 75.87; H, 6.06; N, 8.43. Found: C, 75.85; H, 6.02; N, 8.41%.

2,3-Dihydro-2-(4-dimethylaminophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4c**): Colour: Yellow. Yield: 88%. M.p.: 115-117 ^{o}C. FT-IR (KBr, ν_{max}, cm^{-1}): 1608 (C=N), 1509 (C=C), 1390 (C-N), 679 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.43 (3H, s, N-CH_3), 3.20 (6H, s, N-$(CH_3)_2$, 3.26 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.83 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.2 Hz, 1H, C_3-H-3a), 4.96 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.70-7.20 (4H, m, Ar-H), 7.29 (1H, s, Ar-H), 7.45 (6H, m, Ar-H). ESI-MS (*m/z*): 362 [M+H]$^+$. Anal. calcd. for $C_{22}H_{23}N_3S$: C, 73.09; H, 6.41; N, 11.62. Found: C, 73.04; H, 6.42; N, 11.61%.

2,3-Dihydro-2-(3-methoxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4d**): Colour: Yellow. Yield: 75%. M.p.: 137-139 ^{o}C. FT-IR (KBr, ν_{max}, cm^{-1}): 1612 (C=N), 1501(C=C), 1382 (C-N), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.80 (3H, s, N-CH_3), 2.87 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.36 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 3.82 (3H, s, Ar-OCH_3), 5.31 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.08 (1H, s, Ar-H), 7.30 (3H, m, Ar-H), 6.98-8.12 (7H, m, Ar-H). ESI-MS (*m/z*): 349 [M+H]$^+$. Anal. calcd. for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: C, 72.35; H, 5.75; N, 8.03%.

2,3-Dihydro-2-(3,4-dimethoxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4e**): Colour: Yellow. Yield: 79%. M.p.: 143-145 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1588 (C=N), 1505 (C=C), 1382 (C-N), 1187 (O-CH_3), 656 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.40 (3H, s, N-CH_3), 3.51 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.74 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 3.88 (6H, s, Ar-OCH_3), 4.32 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.09 (1H, s, Ar-H), 7.12 (3H, m, Ar-H), 6.98-8.10 (6H, m, Ar-H). ESI-MS (*m/z*): 379 [M+H]$^+$. Anal. calcd. for $C_{22}H_{22}N_2O_2S$: C, 69.81; H, 5.86; N, 7.40. Found: C, 69.88; H, 5.82; N, 7.41%.

2,3-Dihydro-2-(3,4,5-trimethoxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4f**): Colour: Yellow. Yield: 85%. M.p.: 149-151 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1648 (C=N), 1505 (C=C), 1365 (C-N), 1225 (O-CH_3), 678 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.00 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.45 (3H, s, N-CH_3), 2.83 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 3.06 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.70 (3H, s, Ar-OCH_3), 3.88 (6H, s, 2×Ar-OCH_3), 6.60 (4H, m, Ar-H), 7.22 (1H, s, Ar-H), 7.30-7.50 (4H, m, Ar-H). ESI-MS (*m/z*): 409 [M+H]$^+$. Anal. calcd. for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.65; H, 5.91; N, 6.83%.

2,3-Dihydro-2-(2-hydroxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4g**): Colour: Yellow. Yield: 77%. M.p.: 227-229 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3555 (O-H), 1653 (C=N), 1528 (C-N), 1502 (C=C), 691 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.41 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.68 (3H, s, N-CH_3), 3.34 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.0 Hz, 1H, C_3-H-3a), 3.85 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.85 (1H, s, Ar-OH), 7.25 (1H, s, Ar-H), 7.30 (3H, m, Ar-H), 7.15-7.80 (7H, m, Ar-H). ESI-MS (*m/z*): 335 [M+H]$^+$. Anal. calcd. for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.81; H, 5.45; N, 8.32%.

2,3-Dihydro-2-(4-hydroxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4h**): Colour: Yellow. Yield: 71%. M.p.: 238-240 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3411 (O-H), 1653 (C=N), 1528 (C-N), 1502 (C=C), 697 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.21 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.34 (3H, s, N-CH_3), 3.24 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.0 Hz, 1H, C_3-H-3a), 3.82 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.21 (1H, s, Ar-H), 7.37 (3H, m, Ar-H), 7.11-7.88 (7H, m, Ar-H), 7.99 (1H, s, Ar-OH). ESI-MS (*m/z*): 335 [M+H]$^+$. Anal. calcd. for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.81; H, 5.43; N, 8.39%.

2,3-Dihydro-2-(3-methoxy-4-hydroxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4i**): Colour: Yellow. Yield: 79%. M.p.: 152-154 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3540 (O-H), 1598 (C=N), 1502 (C=C), 1378 (C-N), 1234 (O-CH_3), 688 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.03 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.48 (3H, s, N-CH_3), 2.50 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.4 Hz, 1H, C_3-H-3a), 3.43 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.80 (3H, s, Ar-O-CH_3),6.85 (4H, m, Ar-H), 6.95 (2H, s, Ar-OH), 7.20 (2H, s, Ar-H), 7.35-7.90 (3H, m, Ar-H). ESI-MS (*m/z*): 365 [M+H]$^+$. Anal. calcd. for $C_{21}H_{20}N_2O_2S$: C, 69.20; H, 5.53; N, 7.69. Found: C, 69.24; H, 5.51; N, 7.68%.

2,3-Dihydro-2-(3-nitrophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4j**): Colour: Yellow. Yield: 82%. M.p.: 143-145 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1580 (C=N), 1522 (N=O), 1501 (C=C), 1385 (C-N), 1345 (N=O), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.70 (3H, s, N-CH_3), 2.86 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.38 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 5.42 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.30 (1H, s, Ar-H), 7.80 (3H, m, Ar-H), 7.98-8.60 (7H, m, Ar-H). ESI-MS (*m/z*): 364 [M+H]$^+$. Anal. calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56. Found: C, 66.16; H, 4.74; N, 11.52%.

2,3-Dihydro-2-(4-nitrophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4k**): Colour: Yellow. Yield: 71%. M.p.: 129-131 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1586 (C=N), 1515 (N=O), 1506 (C=C), 1380 (C-N), 1338 (N=O), 713 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.58 (3H, s, N-CH_3), 3.10 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.47 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.7 Hz, 1H, C_3-H-3a), 5.42 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.18 (1H, s, Ar-H), 7.25 (3H, m, Ar-H), 7.65-8.20 (7H, m, Ar-H). ESI-MS (*m/z*): 364 [M+H]$^+$. Anal. calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56. Found: C, 66.12; H, 4.72; N, 11.53%.

2,3-Dihydro-2-(4-fluorophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4l**): Colour: Yellow. Yield: 92%. M.p.: 152-154 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1625 (C=N), 1509 (C=C), 1399 (C-N), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.45 (3H, s, N-CH_3), 2.97 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.50 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 5.27 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.05 (1H, s, Ar-H), 7.19 (3H, m, Ar-H), 7.20-8.09 (7H, m, Ar-H). ESI-MS (*m/z*): 337 [M+H]$^+$. Anal. calcd. for $C_{20}H_{17}FN_2S$: C, 71.40; H, 5.09; N, 8.33. Found: C, 71.41; H, 5.07; N, 8.35%.

2,3-Dihydro-2-(4-chlorophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4m**): Colour: Yellow. Yield: 87%. M.p.: 162-164 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1595 (C=N), 1502 (C=C), 1384 (C-N), 778 (C-Cl), 667 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.40 (3H, s, N-CH_3), 3.39 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.53 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 5.0 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.22-8.08 (7H, m, Ar-H), 7.25 (1H, s, Ar-H), 7.65 (3H, m, Ar-H). ESI-MS (*m/z*): 353 [M+H]$^+$. Anal. calcd. for $C_{20}H_{17}ClN_2S$: C, 68.07; H, 4.86; N, 7.94. Found: C, 68.05; H, 4.81; N, 7.97%.

2,3-Dihydro-2-(2,4-dichlorophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4n**): Colour: Yellow. Yield: 95%. M.p.: 118-120 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1593 (C=N), 1502 (C=C), 1382 (C-N), 805 (C-Cl), 687 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.45 (3H, s, N-CH_3), 2.66 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.27 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 5.10 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.15 (1H, s, Ar-H), 7.20 (3H, m, Ar-H), 7.05-7.95 (6H, m, Ar-H). ESI-MS (*m/z*): 388 [M+H]$^+$. Anal. calcd. for $C_{20}H_{16}Cl_2N_2S$: C, 62.02; H, 4.16; N, 7.23. Found: C, 62.08; H, 4.15; N, 7.21%.

2,3-Dihydro-2-(3-bromophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4o**): Colour: Yellow. Yield: 88%. M.p.: 139-141 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1602 (C=N), 1505 (C=C), 1340 (C-N), 790 (C-Br), 664 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.45 (3H, s, N-CH_3), 2.50 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.42 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.8 Hz, 1H, C_3-H-3a), 4.67 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.20 (2H, s, Ar-H), 7.50 (5H, m, Ar-H), 7.95-8.68 (4H, m, Ar-H). ESI-MS (*m/z*): 398 [M+H]$^+$. Anal. calcd. for $C_{20}H_{17}BrN_2S$: C, 60.46; H, 4.31; N, 7.05. Found: C, 60.45; H, 4.32; N, 7.08%.

2,3-Dihydro-2-(4-bromophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4p**): Colour: Yellow. Yield: 92%. M.p.: 163-165 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1602 (C=N), 1510 (C=C), 1390 (C-N), 777 (C- Br), 668 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.05 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.43 (3H, s, N-CH_3), 3.44 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.4 Hz, 1H, C_3-H-3a), 4.91 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.15 (2H, s, Ar-H), 7.20 (4H, m, Ar-H), 7.90-8.15 (5H, m, Ar-H). ESI-MS (*m/z*): 398 [M+H]$^+$. Anal. calcd. for $C_{20}H_{17}BrN_2S$: C, 60.46; H, 4.31; N, 7.05. Found: C, 60.49; H, 4.32; N, 7.01%.

2,3-Dihydro-2-(2-hydroxy-3-bromo-5-chlorophenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4q**): Colour: Yellow. Yield: 85%. M.p.: 189-191 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3430 (O-H), 1606 (C=N), 1508 (C=C), 1388 (C-N), 802 (C- Cl), 771 (C- Br), 654 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.40 (3H, s, N-CH_3), 3.39 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 4.10 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.2 Hz, 1H, C_3-H-3a), 5.07 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.80 (2H, m, Ar-H),6.90-7.30 (5H, m, Ar-H), 7.10 (2H, s, Ar-H), 7.99 (1H, s, Ar-OH). ESI-MS (*m/z*): 448 [M+H]$^+$. Anal. calcd. for $C_{20}H_{16}BrClN_2OS$: C, 53.65; H, 3.60; N, 6.26. Found: C, 53.62; H, 3.65; N, 6.21%.

2,3-Dihydro-2-(4-allyloxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4r**): Colour: Yellow. Yield: 66%. M.p.: 201-203 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1592 (C=N), 1502 (C=C), 1370 (C-N), 1232 (O-CH_2), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.46 (3H, s, N-CH_3), 3.14 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.1 Hz, 1H, C_3-H-3a), 4.13 (2H, s, -CH_2), 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 5.10 (2H, s, O-CH_2), 7.15 (1H, s, -CH), 7.25-7.85 (11H, m, Ar-H).

Table 1. Cytotoxicity and antimicrobial activity data of 1,5-benzothiazepines (**4a-v**).

Compound	R	Cytotoxicity (Brine shrimp lethality)	Antimicrobial activity [a] (MIC, µg/mL)					
			Gram +ve		Gram -ve		Fungi	
		Effective dose concentration (ED_{50}, µg/mL)	Bs	Bp	Pa	Kp	Ao	Pc
4a	C_6H_5	48.73±0.51	128	128	256	256	256	256
4b	4-MeC_6H_4	45.61±0.23	256	256	512	256	128	128
4c	4-$NMe_2C_6H_4$	54.33±0.12	128	64	128	64	128	256
4d	3-$OMeC_6H_4$	53.67±0.91	64	64	64	64	256	256
4e	3,4-di$OMeC_6H_3$	42.31±0.41	64	32	64	64	32	64
4f	3,4,5-tri$OMeC_6H_2$	18.92±0.33	64	32	32	32	64	64
4g	2-OHC_6H_4	59.67±0.14	64	64	32	64	32	64
4h	4-OHC_6H_4	37.18±0.12	32	32	64	64	64	64
4i	3-OMe,4-OHC_6H_3	24.73±0.81	256	128	128	128	64	32
4j	3-$NO_2C_6H_4$	51.82±0.37	256	128	256	256	512	512
4k	4-$NO_2C_6H_4$	38.64±0.24	128	128	128	128	128	256
4l	4-FC_6H_4	4.17±0.12	16	16	16	16	64	128
4m	4-ClC_6H_4	22.36±0.09	32	32	16	16	128	64
4n	2,4-diClC_6H_3	14.91±0.87	64	64	32	32	32	32
4o	3-BrC_6H_4	3.93±0.42	32	32	64	32	64	32
4p	4-BrC_6H_4	16.32±0.51	64	64	128	256	32	64
4q	2-OH,3-Br,5-ClC_6H_2	3.45±0.15	16	16	16	16	16	16
4r	4-Allyl-OC_6H_4	31.77±0.12	16	16	32	16	64	32
4s	Styren-yl	28.61±0.61	32	64	64	64	128	128
4t	Pyridin-3-yl	33.47±0.23	128	128	256	256	256	256
4u	Indol-3-yl	46.83±0.25	512	512	512	512	512	256
4v	Anthracen-9-yl	39.12±0.12	512	256	512	256	128	256
Standard		3.31±0.15 [b]	16 [c]	16 [c]	16 [c]	16 [c]	16 [d]	16 [d]

[a] Bs: *Bacillus subtilis* (NCIM 2063), Bp: *Bacillus pumilus* (NCIM 2327), Pa: *Pseudomonas aeruginosa* (NCIM 2036), Kp: *Klebsiella pneumonia* (NCIM 5082), Ao: *Aspergillus oryzae* (NCIM 643) and Pc: *Penicillium chrysogenum* (NCIM 738).
[b] Podophyllotoxin.
[c] Chloramphenicol.
[d] Ketoconazole.

ESI-MS (*m/z*): 375 $[M+H]^+$. Anal. calcd. for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.71; H, 5.99; N, 7.45%.

2,3-Dihydro-2-(styren-yl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4s**): Colour: Yellow. Yield: 74%. M.p.: 187-189 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1603 (C=N), 1514 (C=C), 1377 (C-N), 688 (C-S). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.43 (3H, s, N-CH_3), 3.38 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.42 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 4.83 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.78 (1H, d, J = 15.2 Hz, -CH), 7.22 (1H, d, J = 15.2 Hz, -CH), 7.37 (4H, m, Ar-H), 7.69 (1H, d, J = 8 Hz, Ar-H), 7.71-7.98 (6H, m, Ar-H), 8.05 (1H, d, J = 8 Hz, Ar-H). ESI-MS (*m/z*): 345 $[M+H]^+$. Anal. calcd. for $C_{22}H_{20}N_2S$: C, 76.71; H, 5.85; N, 8.13. Found: C, 76.73; H, 5.84; N, 8.17%.

2,3-Dihydro-2-(pyridin-3-yl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4t**): Colour: Yellow. Yield: 73%. M.p.: 119-121 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1599 (C=N), 1506 (C=C), 1382 (C-N), 698 (C-S). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.07 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.40 (3H, s, N-CH_3), 3.37 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.8 Hz, 1H, C_3-H-3a), 4.38 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.25 (2H, s, Ar-H), 7.30 (4H, m, Ar-H), 7.75-8.10 (5H, m, Ar-H). ESI-MS (*m/z*): 320 $[M+H]^+$. Anal. calcd. for $C_{19}H_{17}N_3S$: C, 71.44; H, 5.36; N, 13.15. Found: C, 71.42; H, 5.31; N, 13.17%.

2,3-Dihydro-2-(indol-3-yl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4u**): Colour: Yellow. Yield: 81%. M.p.: 174-176 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3215 (N-H), 1642 (C=N), 1548 (N=O), 1510 (C=C), 1380 (C-N), 1338 (N=O), 668 (C-S). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.40 (3H, s, N-CH_3), 3.51 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.74 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 4.32 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.09 (2H, s, Ar-H), 7.12 (4H, m, Ar-H), 7.98-8.10 (6H, m, Ar-H), 10.5 (1H, s, Ar-H). ESI-MS (*m/z*): 358 $[M+H]^+$. Anal. calcd. for $C_{22}H_{19}N_3S$: C, 73.92; H, 5.36; N, 11.75. Found: C, 73.91; H, 5.35; N, 11.71%.

2,3-Dihydro-2-(anthracen-9-yl)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepine (**4v**): Colour: Yellow. Yield: 66%. M.p.: 201-203 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 1592 (C=N), 1502 (C=C), 1370 (C-N), 2912 (Ar-CH), 689 (C-S). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.46 (3H, s, N-CH_3), 3.14 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.1 Hz, 1H, C_3-H-3a), 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.10 (3H, m, Ar-H), 7.25 (2H, s, Ar-H), 7.40 (6H, m, Ar-H), 7.91-7.85 (5H, m, Ar-H). ESI-MS (*m/z*): 419 $[M+H]^+$. Anal. calcd. for $C_{28}H_{22}N_2S$: C, 80.35; H, 5.30; N, 6.69. Found: C, 80.31; H, 5.32; N, 6.65%.

2.3. Pharmacological activity

2.3.1. Cytotoxicity

The cytotoxicity potential of the synthesized compounds (**4a-v**) was determined by Brine Shrimp Lethality assay as described by Meyer *et al.* [20]. Brine Shrimp (*Artemia salina*) nauplii were hatched in sterile brine solution (prepared using sea water salt 38 g/L and adjusted the pH to 8.5 using 1 N NaOH) under constant aeration for 38 h. After hatching, 10 nauplii were placed in each vial and added various concentrations of drug solutions in a final volume of 5 mL, maintained at 37 °C for 24 h under light of incandescent lamps and surviving larvae were counted. Each experiment was conducted along with control (vehicle treated) at various concentrations of the test substances. The percentage lethality was determined by comparing mean surviving larvae of test and control tubes. The ED_{50} values were obtained using fenny probed analysis software. The result for the test compound was compared with the positive control podophyllotoxin. The results of cytotoxicity study are given in Table 1.

2.3.2. Antimicrobial activity

With respect to the antimicrobial activity, the standard strains were procured from the National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune, India. The antimicrobial activity of the synthesized compounds (**4a-v**) was determined by agar well diffusion method as recommended by the National Committee for Clinical Laboratory Standards, (NCCLS).The compounds were evaluated for antimicrobial activity against selected strains viz. *Bacillus subtilis* (NCIM 2063), *Bacillus pumilus* (NCIM 2327), *Pseudomonas aeruginosa* (NCIM 2036), *Klebsiella pneumonia* (NCIM 5082), *Aspergillus oryzae* (NCIM 643) and *Penicillium chrysogenum* (NCIM 738). Serial solutions of compounds (**4a-v**) were diluted in dimethyl sulfoxide (1%

DMSO) to give a final concentration ranging from 16 to 512 µg/mL used for determining Minimum Inhibitory Concentration (MIC) value. The MIC was defined as the lowest concentration of compound required for a complete inhibition of the bacterial and fungal growth after incubation time. For antibacterial activity nutrient agar was used seeded with 0.1 mL of the respective bacterial culture strains suspension prepared in a sterile saline (0.85%) of 10^5 CFU/mL dilution. For antifungal activity, different fungal spore suspensions in sterile distilled water were adjusted to give a final concentration of 10^6 CFU/mL. An inoculum of 0.1 mL spore suspension of each fungus was spread on Potato-Dextrose- Agar (PDA) plates. The wells of 6 mm diameter were filled with 0.1 mL of each compound having different concentrations separately for each test of bacterial and fungi strain. The DMSO (1%) alone was used as a control. The antibiotic chloramphenicol (16 µg/mL) and ketoconazole (16 µg/mL) are used as reference antibacterial and antifungal agents respectively for comparison. Inoculated plates in triplicate were then incubated at 37±0.5 °C for antibacterial activity for 24 h and 48 h at 28±0.2 °C for antifungal activity. After incubation, the MICs were noted. The results are given in Table 1 [21].

3. Results and discussion

3.1. Synthesis

The titled compound **4a** was analysed for molecular formula $C_{20}H_{18}N_2S$, m.p. 125-127 °C, well supported by a $[M+H]^+$ at *m/z* 319 in its positive mode electron spray ionization mass spectrum. The FT-IR spectrum showed the characteristic bands at 1596 (C=N), 1510 (C=C), 1365 (C-N) and 688 (C-S). The ^{1}H NMR spectrum of compound **4a** showed three characteristic peaks of C_2-H and C_3-CH_2 protons of 1,5-benzothiazepine ring at 4.89 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.43 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a) and 3.36 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b). The spectrum also showed one singlet at δ 2.50 ppm integrating for three protons attributed to the aromatic methyl group. The spectrum also accounted for the other twelve aromatic protons in between δ 7.25-7.95 ppm. 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 **4a** was confirmed as 2,3-dihydro-2-(phenyl)-4-(1-methyl-1*H*-pyrrol-2-yl)-1,5-benzothiazepine. All the compounds synthesized in the present study (**4a**-**4v**) were characterized based on the above mentioned physical and spectroscopic methods.

3.2. Cytotoxicity

The investigation of cytotoxicity screening data (Table 1) of all the synthesized 1,5-benzothiazepines (**4a**-**v**) revealed that the compounds **4q**, **4o** and **4l** demonstrated comparatively the most potent cytotoxicity, with ED_{50} values of 3.45±0.15, 3.93±0.42 and 4.17±0.12 µg/mL respectively, in comparison with the standard drug (Podophyllotoxin, ED_{50} : 3.31 ± 0.17 µg/mL). Structure-Activity Relationship of these compounds clearly revealed the inherent cytotoxicity associated with the basic core consisting of 1-methyl-pyrrole and 1,5-benzothiazepine pharmacophores as displayed in case of the compound **4a** with ED_{50} value of 48.73±0.51 µg/mL, which in some cases was enhanced by the influence of some functional groups and decreased by some other functional groups at position 2 of the 1,5-benzothiazepinering. For example, the compounds **4q** (2-OH, 3-Br, 5-Cl, ED_{50}: 3.45±0.15 µg/mL) > **4o** (3-Br, ED_{50}: 3.93±0.42 µg/mL) > **4l** (4-F, ED_{50}: 4.17±0.12 µg/mL) > **4n** (2,4-di-Cl, ED_{50}: 14.91±0.87 µg/mL) > **4m** (4-Cl, ED_{50}: 22.36±0.09 µg/mL) having halogen substituents either at *ortho* or *meta* or *para* positions significantly enhanced the activity. However, it was revealed that various aromatic/heteroaromatic rings substituted at position 2 of the 1,5-benzothiazepinering system followed its activity order as **4t** (pyridine-3-yl, ED_{50}: 33.47±0.23 µg/mL) > **4v** (anthreacen-9-yl, ED_{50}: 39.12±0.12 µg/mL) > **4u** (indol-3-yl, ED_{50}: 46.83±0.25 µg/mL) moieties, respectively. It is also reported that the cytotoxicity of compounds **4b**-**f** and **4r**, substituted with electron releasing groups was found to be biologically relevant and the activity order was **4f** (3,4,5-tri-OMe, ED_{50}: 18.92±0.33 µg/mL) > **4r** (4-Allyl-O, ED_{50}: 31.77±0.12) > **4e** (3,4-diOMe, ED_{50}: 42.31±0.41 µg/mL) > **4b** (4-Me, ED_{50}: 45.61±0.23 µg/mL) > **4d** (3-OMe, ED_{50}: 53.67 ± 0.91 µg/mL)> **4c** (4-NMe_2, ED_{50}: 54.33 ± 0.12 µg/mL), respectively. It is important that less activity was observed when the hydroxyl groups are substituted at different positions on the phenyl ring as displayed in the case of compounds **4g** and **4h**, the order of activity was **4h** (4-OH, ED_{50}: 37.18±0.12 µg/mL) > **4g** (2-OH, ED_{50}: 59.67±0.14) respectively. It is notable that moderate activity was observed when the nitro groups are introduced on the phenyl ring at position 2 of the 1,5-benzothiazepineringas displayed in the case of compounds **4k** and **4j** with ED_{50} values 38.64±0.24 and 51.82±0.37 µg/mL. The compound **4s** (ED_{50}: 28.61±0.61 µg/mL) having phenylethylidene substitution position 2 of the 1,5-benzothiazepinering is also relevant for enhancing the cytotoxicity [22].

3.3. Antimicrobial activity

The results of antimicrobial activity of the synthesized compounds (**4a**-**v**) against selected Gram-positive, Gram-negative bacteria and fungi are illustrated in Table 1. Among the series tested, compounds **4q**, **4r** and **4l** were found to be more active than other compounds with MIC 16-32 µg/mL against all tested microorganisms. From the results of antibacterial activity, compound **4r** was found to be more active against all Gram-positive bacteria with MIC value 16 µg/mL. Similarly, compound **4l** showed significant inhibition against all Gram-negative bacteria with MIC 16 µg/mL. A broad spectrum of antifungal activity of the compound **4q** was obtained against all the fungi with MIC 16 µg/mL, while other compounds displayed relatively less antifungal activity. From the activity data of compounds **4a**-**4v**, the following conclusions can be made with respect to their structure-activity relationship: the degree of antimicrobial (antibacterial and antifungal) activity may be varied with their corresponding substituents at 2 of the 1,5-benzothiazepinering. A remarkable reduction in the antimicrobial activity was observed when the substituted phenyl ring at position 2 of the 1,5-benzothiazepinering is replaced with other aromatic or heteroaromatic rings as displayed in case of compounds **4a** and **4t**-**v** and its order is phenyl > pyridin-3-yl > anthracene-9-yl > indol-3-yl, respectively. The substituted phenyl ring of the 1,5-benzo thiazepineat position 2further substituted with halogens either at *ortho, meta* or *para* positions correspondingly enhanced the antibacterial activity (**4q** (2-OH, 3-Br, 5-Cl) > **4l** (4-F) > **4o** (3-Br) > **4m** (4-Cl) > **4p** (4-Br)) as displayed in the case of compounds **4l**-**4q**. It is noteworthy that compounds having electron donating substituents (3,4,5-tri-OCH_3 > 3,4-di-OCH_3 > 3-OCH_3 > 4-$N(CH_3)_2$ > 4-CH_3) on the phenyl ring of 1,5-benzothiazepine at *ortho, meta* and *para* positions was found to enhance the antibacterial activity. An increase in the antifungal activity was also observed for the compounds **4l**-**q** having halogen substitution but the degree of activity in most of the cases is found to be less than that of the antibacterial activity. The compounds **4g** and **4h** having hydroxyl group either at *ortho* or *para* position also contributed favourably to the antifungal activity. Similarly, the presence of allyloxy group at the *para* position of the phenyl ring as displayed in case of compound **4r** also enhanced the antibacterial activity. A decrease in the antifungal activity is attributed to the presence of nitro group on the phenyl ring at *ortho* or *meta* or *para*

positions as displayed in the case of compounds **4j** and **4k** [23,24].

4. Conclusion

In conclusion, we have developed a series of some new 2,3-dihydro-2-(susbtituted)-4-(1-methyl-1*H*-pyrrol-2-yl)-1,5-benzothiazepines (**4a**-**v**). In the present study proposed method has advantage over existing conventional method with high yield and shorter reaction time. This procedure represents a convenient, economic and environmentally friendly process. These compounds were screened for cytotoxic and antimicrobial activities. It was observed from the results obtained that most of the tested compounds showed significant cytotoxic and antimicrobial activities and it could be a remarkable preliminary confirmation to develop new leads in fight against cancer and microbial infections. The cytotoxic and antimicrobial activities data revealed that the synergistic nature of 1-methylpyrrole and 1,5-benzothiazepine heterocyclic ring systems which forming part of the basic nucleus. The observed activities may also be due to the substitution at position 2 on the 1,5-benzothiazepine ring.

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