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SYNTHESIS OF NOVEL 1, 5-DIHYDROBENZOTHIAZEPINE DERIVATIVES BY CONVENTIONAL AND MICROWAVE IRRADIATION METHODS AND THEIR PHARMACOLOGICAL ACTIVITIES

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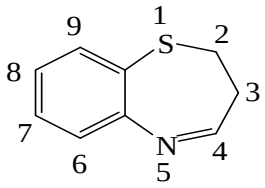
ABSTRACT: 1, 5-Dihydrobenzothiazepines are synthesized by conventional and microwave assisted synthesis methods. By microwave assisted synthesis, a considerable increase in the reaction rate has been observed and that too, with better yields. The compounds have been screened for antimicrobial and cytotoxic activity. 1, 5-Dihydrobenzothiazepines are prepared by the reaction of 1, 3-diarylprop-2-enones with o-aminothiophenol. All the products were tested for purity by tlc and characterized by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies.

INTRODUCTION: The 1, 5-benzothiazepines [1] **(1**and **2)** are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities [2-9].

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 [10-13].



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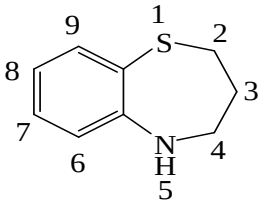

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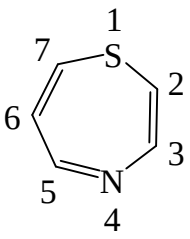
GENERAL STRUCTURES OF 1, 5-BENZOTHIAZEPINE



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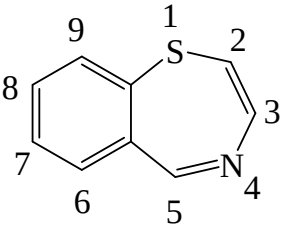

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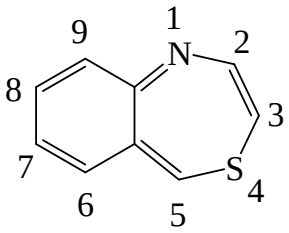


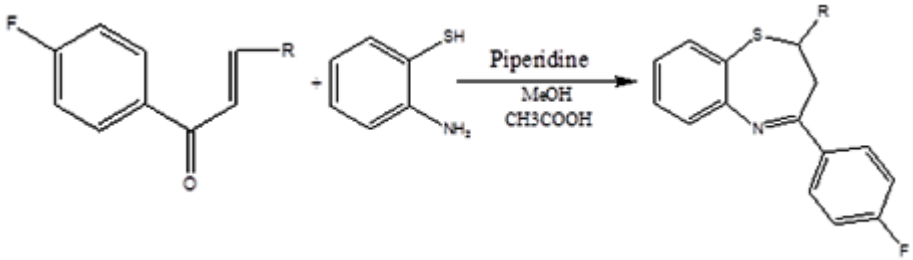
(5)

The 1, 5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets [14-24]. The first molecule of 1, 5-benzothiazepine used clinically was diltiazem **(6)**, followed by clentiazem **(7)**, for their cardiovascular action. Some of the 1, 5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim **(8)**, clothiapine **(9)** and quetiapine **(10)**. Therefore, the 1,5-Dihydrobenzothiazepines 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 [25-45].

Microwave-induced organic reaction enhancement (MORE) chemistry is gaining popularity as a non-conventional technique for rapid organic synthesis. Important features of this technique are easy access to very high temperature, good control over energy input in a reaction; higher yields and rapid synthesis of organic compounds. The synthesized compounds were purified by recrystallization and chromatography. The compounds were characterized by 1H NMR and IR analysis. The compounds were tested for their antimicrobial and cytotoxic activity by standard methods.

MATERIALS AND METHODS: All the chemicals used in the work were of analytical grade and procured from sigma Aldrich, Visakhapatnam.

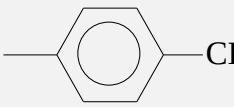
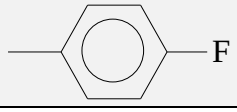
a) **General procedure for synthesis of 1, 5-benzothiazepines (BP-1-20):** To a solution of chalcone derivative in dry acidic methanol acidified by adding few drops of glacial acetic acid to it, 2-aminothiophenol was added. The mixture was then refluxed until a crystalline solid separates out. After cooling, the solid product was collected and washed with diethyl ether and cold methanol. The crude solid was recrystallized from ethanol.

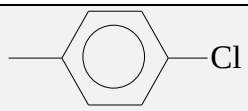
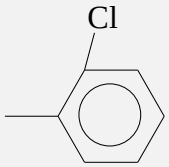
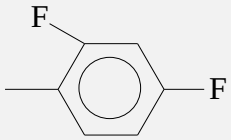
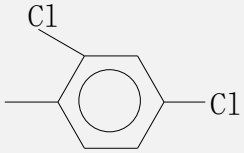
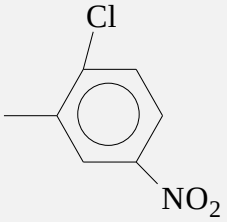
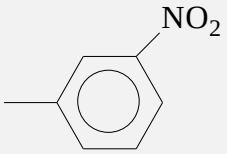
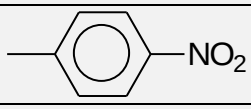
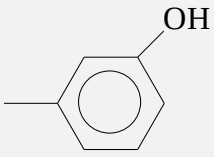
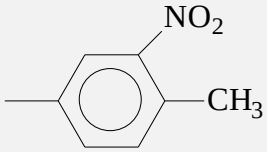
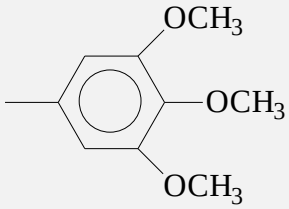
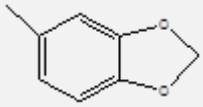
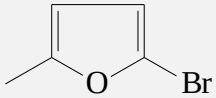


SCHEME-1: (BP-1-20)

b) **General procedure for synthesis of 1, 5-benzothiazepines (BP-1-20) by Microwave irradiation method:** Equimolar quantities (0.001 mol) of chalcone derivatives and 2-aminothiopheno (0.001 mol) were mixed and dissolved in minimum amount (3 ml) of glacial acetic acid l. To this, piperidine (0.003 mol) was added slowly and mixed. The entire reaction mixture was microwave irradiated for about 2–6 min at 180 watts. Physical characterization data and Elemental Analysis data of 1, 5-benzothiazepines were represented in **table1 and 2.**

TABLE 1: PHYSICAL CHARACTERIZATION DATA OF 1, 5-BENZOTHIAZEPINES (BP_1-BP_{20})

Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (^oC)	Yield %
BP_1		$C_{22}H_{18}FNS$	347.45	141-143	89
BP_2		$C_{21}H_{15}F_2NS$	351.41	152-154	89

BP_3		$C_{21}H_{15}ClFNS$	367.87	144-145	93
BP_4		$C_{21}H_{15}ClFNS$	367.87	121-123	71
BP_5		$C_{21}H_{14}F_3NS$	369.40	139-141	75
BP_6		$C_{21}H_{14}Cl_2FNS$	402.31	118-120	86
BP_7		$C_{21}H_{14}ClFN_2O_2S$	412.86	165-167	77
BP_8		$C_{21}H_{15}FN_2O_2S$	378.42	143-145	82
BP_9		$C_{21}H_{15}FN_2O_2S$	378.42	129-131	89
BP_{10}		$C_{21}H_{16}FNOS$	349.42	227-229	84
BP_{11}		$C_{22}H_{17}FN_2O_2S$	392.45	177-179	94
BP_{12}		$C_{24}H_{22}FNO_3S$	423.50	149-151	85
BP_{13}		$C_{22}H_{16}FNO_2S$	377.43	155-157	74
BP_{14}		$C_{19}H_{13}BrFNOS$	402.28	133-135	79

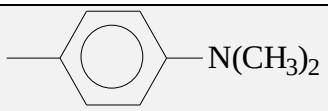
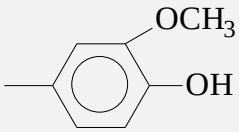
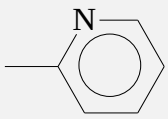
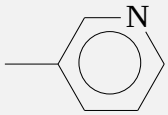
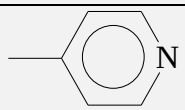
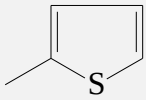
BP_{15}		$C_{23}H_{21}FN_2S$	376.49	115-117	88
BP_{16}		$C_{22}H_{18}FNO_2S$	379.45	152-154	86
BP_{17}		$C_{20}H_{15}FN_2S$	334.41	112-114	78
BP_{18}		$C_{20}H_{15}FN_2S$	334.41	119-121	82
BP_{19}		$C_{20}H_{15}FN_2S$	334.41	109-101	92
BP_{20}		$C_{19}H_{14}FNS_2$	339.45	147-149	86

TABLE 2: ELEMENTAL ANALYSIS DATA OF 1,5-BENZOTHIAZEPINES (BP_1-BP_{20})

Compound	%Calculated			%Found		
	C	H	N	C	H	N
BP_1	76.05	5.22	4.03	76.07	5.17	4.09
BP_2	71.77	4.30	3.99	71.72	4.32	3.91
BP_3	68.56	4.11	3.81	68.46	4.09	3.77
BP_4	68.56	4.11	3.81	68.51	4.10	3.77
BP_5	68.28	3.82	3.79	68.29	3.77	3.69
BP_6	62.69	3.51	3.48	62.72	3.49	3.38
BP_7	62.69	3.51	3.48	62.74	3.46	3.41
BP_8	66.65	4.00	7.40	66.62	4.04	7.43
BP_9	66.65	4.00	7.40	66.67	4.01	7.42
BP_{10}	72.18	4.62	4.01	72.11	4.61	4.07
BP_{11}	67.33	4.37	7.14	67.37	4.31	7.16
BP_{12}	68.07	5.24	3.31	68.11	5.21	3.39
BP_{13}	70.01	4.27	3.71	70.09	4.29	3.69
BP_{14}	56.73	3.26	3.48	56.77	3.20	3.42
BP_{15}	73.37	5.62	7.44	73.33	5.67	7.49
BP_{16}	69.64	4.78	3.69	69.65	4.77	3.61
BP_{17}	71.83	4.52	8.38	71.86	4.54	8.33
BP_{18}	71.83	4.52	8.38	71.81	4.56	8.35
BP_{19}	71.83	4.52	8.38	71.85	4.59	8.33
BP_{20}	67.23	4.16	4.13	67.25	4.12	4.11

Spectral Data for 1, 5-benzothiazepines (BP_1-BP_{20}) are given below:

BP-1:

2,3-Dihydro-2-(4-methylphenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_1): Mol.wt:, 347.45,yield: 89%,mp: 141-143^{0}C ,IR (KBr) (cm^{-1}) : 1585 (C=N), 1505 (C=C), 1395 (C-N), 923 (C-F) and 654 (C-S).^{1}H-NMR ($CDCl_3$) ppm : 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 3.04 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.40 (3H, s, Ar-CH_3), 7.22 (1H, s, Ar-H), 7.61 (3H, m, Ar-H), 7.20-8.10 (8H, Ar-H).

BP-2:

2,3-Dihydro-2-(4-fluorophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_2): Mol. wt: 351.41, Yield: 89%, M.P: 152-154^{0}C, IR (KBr) (cm^{-1}): 1625 (C=N), 1509 (C=C),1399 C-N), 689(C-S), 931 (C-F) , ^{1}H-NMR ($CDCl_3$) ppm : 5.27 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H),3.50 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 2.97 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.05 (1H, s,Ar-H), 7.19 (3H, m, Ar-H), 7.20-8.09 (8H, Ar-H).

BP-3:

2,3-Dihydro-2-(4-chlorophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_3): Mol. wt: 367.87, Yield: 93%, M.P:144-145^{0}C, IR (KBr) (cm^{-1}): 1595 (C=N), 1502 (C=C), 1384 (C-N), 778 (C-Cl), 921 (C-F) and 667 (C-S) ^{1}H-NMR ($CDCl_3$) ppm : 5.0 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.53 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 3.39 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.25 (1H, s, Ar-H), 7.65 (3H, m, Ar-H), 7.22-8.08 (8H, Ar-H).

BP-4:

2,3-Dihydro-2-(2-chlorophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_4): Mol. wt: 367.87, Yield: 71%, M.P:121-123^{0}C, IR (KBr) (cm^{-1}): 1596 (C=N), 1510 (C=C), 1365 (C-N), 688 (C-S), 923 (C-F) and 805 (C-Cl) ^{1}H-NMR ($CDCl_3$) ppm: 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), 3.36 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.12 (1H, s, Ar-H), 7.72 (3H, m, Ar-H), 6.95-7.60 (8H, Ar-H).

BP-5:

2,3-Dihydro-2-(2,4-difluorophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_5): Mol. wt: 369.40,yield:75%,mp:139-141^{0}C.IR (KBr) (cm^{-1}) : 1612 (C=N), 1501 (C=C),1382 (C-N), 689 (C-S), 913 (C-F) and 944 (C-F) ^{1}H-NMR ($CDCl_3$) ppm : 5.31 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.36 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 2.87 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.08 (1H, s, Ar-H), 7.30 (3H, m, Ar-H), 6.98-8.12 (7H, Ar-H).

BP-6:

2,3-Dihydro-2-(2,4-dichlorophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_6): Mol. wt: 402.31,yield:86%,mp:118-120^{0}C. IR (KBr) (cm^{-1}) : 1593 (C=N), 1502 (C=C), 1382 (C-N), 687 (C-S), 925 (C-F) and 805 (C-Cl) ^{1}H-NMR ($CDCl_3$) ppm : 5.10 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.27 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 2.66 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.15 (1H, s, Ar-H), 7.20 (3H, m, Ar-H), 7.05-7.95 (7H, Ar-H).

BP-7:

2,3-Dihydro-2-(2-chloro-5-nitrophenyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_7): Mol. wt: 412.86, Yield: 77%, M.p: 165-167^{0}C,IR (KBr) (cm^{-1}) : 1588 (C=N), 1520 (N=O, asymmetric), 1505 (C=C), 1382 (C-N), 1340 (N=O, symmetric), 656 (C-S), 933 (C-F) and 781 (C-Cl), ^{1}H-NMR ($CDCl_3$) ppm : 4.32 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.74 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 3.51 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.09 (1H, s, Ar-H), 7.12 (3H, m, Ar-H), 6.98-8.10 (7H, Ar-H).

BP-8:

2,3-Dihydro-2-(3-nitrophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_8): Mol. wt: 378.42, Yield: 82%, M.p: 143-145^{0}C,IR (KBr) (cm^{-1}) : 1580 (C=N), 1522 (N=O, asymmetric),1501 (C=C), 1385 (C-N), 1345 (N=O, symmetric), 924 (C-F) and 689 (C-S), ^{1}H-NMR ($CDCl_3$) ppm : 5.42 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.38 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 2.86 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.30 (1H, s, Ar-H), 7.80 (3H, m, Ar-H), 7.48-8.60 (8H, Ar-H).

BP-9:

2,3-Dihydro-2-(4-nitrophenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_9): Mol. wt: 378.42, Yield: 89%, M.p: 129-131^{0}C,IR (KBr) (cm^{-1}) : 1586 (C=N), 1515 (N=O, asymmetric), 1506 (C=C), 1380 (C-N), 1338 (N=O, symmetric), 925 (C-F) and 713 (C-S), ^{1}H-NMR ($CDCl_3$) ppm : 5.42 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.47 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.7 Hz, 1H, C_3-H-3a), 3.10 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.18

(1H, s, Ar-H), 7.25 (3H, m, Ar-H), 7.25-8.20 (8H, Ar-H).

BP-10:

2,3-Dihydro-2-(3-hydroxyphenyl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_{10}): Mol.wt: 349.42, Yield: 84%, M.p: 227-229^{0}C,IR (KBr) (cm^{-1}) : 1653 (C=N), 1528 (C-N), 1502 (C=C), 925 (C-F) and 694 (C-S), ^{1}H-NMR ($CDCl_3$) ppm : 3.85 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.34 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.0 Hz, 1H, C_3-H-3a), 2.41 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.25 (1H, s, Ar-H), 7.30 (3H, m, Ar-H), 7.15-7.80 (8H, Ar-H), 6.85 (1H, s, Ar-OH).

BP-11:

2,3-Dihydro-2-(3-nitro-4-methylphenyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{11}): Mol. wt: 392.45, Yield: 94%, M.p: 177-179^{0}C,IR (KBr) (cm^{-1}) : 1642 (C=N), 1548 (N=O, asymmetric), 1510 (C=C), 1380 (C-N), 1338 (N=O, symmetric), 927 (C-F) and 668 (C-S), ^{1}H-NMR ($CDCl_3$) ppm : 4.16 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.23 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 2.53 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.50 (3H, s, Ar-CH_3), 7.30 (1H, s,Ar-H), 6.70 (3H, m, Ar-H), 7.45-8.78 (7H, Ar-H)

BP-12:

2,3-Dihydro-2-(3,4,5-trimethoxyphenyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{12}): Mol. wt:423.50, Yield:8 %, M.p: 149-151^{0}C, IR (KBr) (cm^{-1}) : 1648 (C=N), 1505 (C=C), 1365 (C-N), 1225 (-O-CH_3), 923 (C-F) and 678 (C-S), ^{1}H-NMR ($CDCl_3$) ppm : 3.06 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 2.83 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 2.0 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.22 (1H, s,Ar-H), 6.60 (3H, m, Ar-H), 7.30-7.50 (6H, Ar-H), 3.70 (3H, s, Ar-OCH_3), 3.88 (6H, s, 2XAr-OCH_3)

BP-13:

2,3-Dihydro-2-(3,4-methelenedioxyphenyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{13}): Mol.wt:377.47, Yield: 74%, M.p: 155-157^{0}C,IR (KBr) (cm^{-1}) : 1592 (C=N), 1502 (C=C), 1370 (C-N),1232 (-O-CH_2-O-), 921 (C-F) and 689 (C-S), ^{1}H-NMR ($CDCl_3$) ppm : 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.1 Hz, 1H, C_3-H-3a), 3.14 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.25 (1H, s,Ar-H), 7.40 (3H, m, Ar-H), 6.10 (2H, s, O-CH_2-O), 7.21-7.85 (7H, Ar-H)

BP-14:

2,3-Dihydro-2-(5-bromofuran-2-yl)-4-(4-fluoro phenyl)-1,5-benzothiazepine (BP_{14}): Mol. wt: 402.28, Yield: 79%, M.p: 133-135^{0}C, IR (KBr) (cm^{-1}): 1602 (C=N), 1505 (C=C), 1340 (C-N), 664 (C-S), 933 (C-F) and 790 (C-Br) , ^{1}H-NMR ($CDCl_3$) ppm : 5.07 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 4.10 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.2 Hz, 1H, C_3-H-3a), 3.39 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.10 (1H, s,Ar-H), 6.80 (3H, m, Ar-H), 6.80-7.30 (6H, Ar-H)

BP-15:

2,3-Dihydro-2-(4-dimethylaminophenyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{15}): Mol. wt: 376.49, Yield: 88%, M.p: 115-117^{0}C, IR (KBr) (cm^{-1}): 1608 (C=N), 1509 (C=C), 1390 (C-N), 1175 (-N-$(CH_3)_2$), 933 (C-F) and 679 (C-S),NMR ($CDCl_3$) ppm : 4.96 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.83 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.2 Hz, 1H, C_3-H-3a), 3.26 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.20 (6H, s, N-$(CH_3)_2$, 7.20 (1H, s,Ar-H), 7.45 (3H, m, Ar-H), 6.70-8.20 (8H, Ar-H)

BP-16:2,3-Dihydro-2-(3-methoxy-4-hydroxy phenyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{16}): Mol.wt:379.45, Yield: 86%, M.p: 152-154^{0}C, , IR (KBr) (cm^{-1}): 3540 (O-H), 1598 (C=N), 1502 (C=C), 1378 (C-N), 1234 (-O-CH_3) 913 (C-F), and 688 (C-S) NMR ($CDCl_3$) ppm : 3.43 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 2.50 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.4 Hz, 1H, C_3-H-3a), 1.03 (t, $J_{3b,3a} = J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.20 (1H, s,Ar-H), 6.85 (3H, m, Ar-H), 7.15-7.90 (7H, Ar-H), 6.95 (1H, s, Ar-OH), 3.80 (3H, s, Ar-O-CH_3)

BP-17:

2,3-Dihydro-2-(2-pyridinyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{17}): Mol.wt:334.41, Yield: 78%, M.p: 112-114^{0}C, 1602 (C=N), 1510 (C=C), 1390 (C-N), 924 (C-F) and 677 (C-S) ,NMR ($CDCl_3$) ppm : 4.91 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$

= 12 Hz, 1H, C_2-H), 3.44 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.4 Hz, 1H, C_3-H-3a), 1.05 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.15 (1H, s,Ar-H), 7.20 (3H, m, Ar-H), 7.10-8.15 (8H, Ar-H)

BP-18:

2,3-Dihydro-2-(3-pyridinyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{18}): Mol.wt:334.41, Yield: 82%, M.p: 119-121^{0}C, IR (KBr) (cm^{-1}):1599 (C=N), 1506 (C=C), 1382 (C-N), 927 (C-F) and 698 (C-S), NMR ($CDCl_3$) ppm : 4.38 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.37 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.8 Hz, 1H, C_3-H-3a), 1.07 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.25 (1H, s,Ar-H), 7.30 (3H, m, Ar-H), 6.75-8.90 (8H, Ar-H)

BP-19:

2,3-Dihydro-2-(4-pyridinyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{19}): Mol.wt:334.41, Yield: 92%, M.p: 109-111^{0}C, IR (KBr) (cm^{-1}):1606 (C=N), 1508 (C=C), 1388 (C-N), 933 (C-F) and 654 (C-S), NMR ($CDCl_3$) ppm : 4.67 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.42 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.8 Hz, 1H, C_3-H-3a), 2.50 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.20 (1H, s,Ar-H), 7.50 (3H, m, Ar-H), 6.95-8.68 (8H, Ar-H)

BP-20:

2,3-Dihydro-2-(2-thienyl)-4-(4-fluorophenyl)-1,5-benzothiazepine (BP_{20}): Mol.wt:339.45, Yield: 86%, M.p: 147-149^{0}C, IR (KBr) (cm^{-1}):1605 (C=N), 1503 (C=C), 1386 (C-N), 928 (C-F) and 644 (C-S), NMR ($CDCl_3$) ppm : 5.50 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 3.53 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.9 Hz, 1H, C_3-H-3a), 2.90 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 7.20 (1H, s,Ar-H), 7.34 (3H, m, Ar-H), 6.60-7.80 (7H, Ar-H)

Antibacterial activity: The antibacterial activity was tested by determining the minimum inhibitory concentration (MIC) for each compound using Standard Serial Tube Dilution Technique. The organisms used are

Gram positive bacteria: *Staphylococcus aureus* (NCIM-2079)**,** *Bacillus subtilis* (NCIM-2063)

Gram negative bacteria: *Escherichia coli* (NCIM-2068), *Proteus vulgaris* (NCIM-2027)

Antifungal activity: The antifungal activity was tested by the same procedure as described in the antibacterial activity, except using Potato-Dextrose-Agar medium.

The organisms used are: *Aspergillus niger* (ATCC-6275), *Candida tropicalis* (ATCC-1369)

The results are presented in **Table 3**.

TABLE 3: ANTIBACTERIAL ACTIVITY OF 1, 5-BENZOTHIAZEPINES (BP_1 TO BP_{12}): (Expressed as MIC in µg/mL)

Compound	R	*B. subtilis*	*S. aureus*	*E. coli*	*P. vulgaris*
BP_1	4"-methylphenyl	256	128	128	128
BP_2	4"-fluorophenyl	128	128	256	128
BP_3	4"-chlorophenyl	64	256	128	128
BP_4	2"-chlorophenyl	128	64	128	128
BP_5	2",4"-difluorophenyl	64	64	32	64
BP_6	2",4-dichlorophenyl	64	128	64	128
BP_7	2"-chloro-5"-nitrophenyl	128	64	128	256
BP_8	3"-nitrophenyl	256	128	128	256
BP_9	4"-nitrophenyl	128	128	64	128
BP_{10}	3"-hydroxyphenyl	64	128	128	64
BP_{11}	3"-nitro-4"-methylphenyl	128	128	256	128
BP_{12}	3",4",5"-trimethoxypheny	128	128	64	128
BP_{13}	3",4"-methylendioxyphenyl	256	512	128	256
BP_{14}	5"-bromofuran-2"-yl	128	64	64	128
BP_{15}	4"-dimethylaminophenyl	64	64	128	64
BP_{16}	3"-methoxy-4"-hydroxyphenyl	128	256	256	128
BP_{17}	2"-pyridinyl	256	256	512	256
BP_{18}	3"-pyridinyl	256	128	256	128
BP_{19}	4"-pyridinyl	128	64	64	128
BP_{20}	2"-thienyl	256	128	128	64
Standard (Ampicillin)		< 1	< 1	< 1	< 1

DISCUSSION ON RESULTS:

Antibacterial activity: From the above results, 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 against *B. subtilis*, the compounds, BP_3 having a chlorophenyl moiety, BP_5 having a difluorophenyl moiety, BP_6 having a dichlorophenyl moiety, BP_{10} having a hydroxyl-lphenyl and BP_{15} having a dimethylaminophenyl moiety proved to be more potent with a MIC value of 64 µg/mL in each case. Against *S.aureus*, BP_4, BP_5, BP_7 (2-chloro-5-nitrophenyl moiety), BP_{14} (bromofuran moiety), BP_{15} and BP_{19} (4-pyridinyl moiety) showed maximum activity with a MIC value of 64 µg/mL in each case. Against *E. coli* BP_5 proved to be the most potent with a MIC value of 32 µg/mL. This is followed by compounds, BP_6, BP_9 (nitrophenyl moiety), BP_{12} (trimethoxyphenyl moiety), BP_{14} and BP_{19} with a MIC value of 64 µg/mL in each case. Against *P. vulgaris*, BP_5, BP_{10}, BP_{15} and BP_{20} (thienyl moiety) showed maximum activity with a MIC value of 64 µg/mL in each case.

Procedure for Antifungal activity: The antifungal activity was tested by the same procedure as described in the antibacterial activity, except using Potato-Dextrose-Agar medium. The results are presented in **Table 4**.

TABLE 4: ANTIFUNGAL ACTIVITY OF 1,5-BENZOTHIAZEPINES (BP_1 TO BP_{12})

Compound	R	*Aspergillus* niger	*Candida tropicalis*
BP_1	4"-methylphenyl	64	32
BP_2	4"-fluorophenyl	32	64
BP_3	4"-chlorophenyl	32	34
BP_4	2"-chlorophenyl	32	64
BP_5	2",4"-difluorophenyl	16	16
BP_6	2",4-dichlorophenyl	16	32
BP_7	2"-chloro-5"-nitrophenyl	16	32
BP_8	3"-nitrophenyl	32	128
BP_9	4"-nitrophenyl	32	64
BP_{10}	3"-hydroxyphenyl	256	128
BP_{11}	3"-nitro-4"-methylphenyl	128	64
BP_{12}	3",4",5"-trimethoxypheny	128	64
BP_{13}	3",4"-methylendioxyphenyl	128	64
BP_{14}	5"-bromofuran-2"-yl	16	32
BP_{15}	4"-dimethylaminophenyl	128	64
BP_{16}	3"-methoxy-4"-hydroxyphenyl	128	64
BP_{17}	2"-pyridinyl	32	64
BP_{18}	3"-pyridinyl	128	64
BP_{19}	4"-pyridinyl	16	32
BP_{20}	2"-thienyl	32	16
Standard (Fluconazole)		< 2	< 2

Antifungal activity: From the above results, It is noticed that the 1, 5-benzothiazepines tested showed more antifungal activity than the antibacterial activity. Among the compounds tested against *A. niger*, the compounds, BP_5 having a difluorophenyl moiety, BP_6 having a dichlorophenyl moiety, BP_7 having a 2-chloro-5-nitrophenyl moiety, BP_{14} having a bromofuran moiety and BP_{19} having a 4-pyridinyl moiety proved to be the most potent compounds with a MIC value of 16 µg/mL in each case. This was followed by the compounds, BP_2 (fluorophenyl moiety), BP_3 and BP_4 (chlorophenyl moieties), BP_8 and BP_9 (nitrophenyl moieties), BP_{17} (2-pyridinyl moiety) and BP_{20} (thienyl moiety) with a MIC value of 32 µg/mL in each case. Against *C. tropicalis*, the compounds, BP_5 and BP_{20}, showed maximum activity with a MIC value of 16 µg/mL in each case.

This was followed by compounds, BP_1 (methylphenyl), BP_6, BP_7 (2-chloro-5-nitrophenyl moiety), BP_{14} and BP_{19} with a MIC value of 32 µg/mL in each case.

Cytotoxicity Studies: The *in vitro* cytotoxicity of the test compounds was evaluated by the MTT assay. HT-29 (colon cancer), MCF-7 (breast cancer) and DU-145 (prostate cancer) cell lines were obtained from ACTREC, Mumbai, India.

Cytotoxicity evaluation: The cells were seeded in 96 well plates at a density of $1x10^4$ (counted by Trypan blue exclusion dye method) per well and were incubated for 24 h to recover. After incubation the medium was replaced with fresh media containing different dilutions of the test compounds. Then the plated were incubated for additional 48 h at 37^0C in DMEM/MEM with 10% FBS medium. Following incubation, the medium was removed and replaced with 90 µl of fresh DMEM without FBS. To the above wells, 10 µl of MTT reagent (5 mg/mL of stock solution in DMEM without FBS) was added and incubated at 37^oC for 3-4 h, there after the above media was replaced by adding 200 µl of DMSO to each well and incubated at 37^0C for 10 min. The absorbance at 570 nm was measured on a spectrophotometer. Methotrexate was used as reference drug for comparison. The results are presented in **Table 5**.

TABLE 5: CYTOTOXICITY OF THE NEW 1,5-BENZOTHIAZEPINES (BP_1 TO BP_{11}): (IC_{50} values in µg/mL)

Compound	R	Cell line		
		HT-29	MCF-7	DU-145
BP_1	4"-methyl phenyl	55 ± 2	62 ± 2	52 ± 1
BP_2	4"-fluorophenyl	42 ± 2	48 ± 1	62 ± 2
BP_3	4"-chlorophenyl	92 ± 2	78 ± 2	65 ± 2
BP_4	2"-chlorophenyl	105 ± 2	168 ± 1	122 ± 2
BP_5	2",4"-difluorophenyl	28 ± 1	42 ± 2	33 ± 2
BP_6	2",4"-dichlorophenyl	42 ± 2	67 ± 1	56 ± 2
BP_7	2"-chloro-5"-nitrophenyl	115 ± 2	NA	NA
BP_8	3"-nitrophenyl	180 ± 2	NA	NA
BP_9	4"-nitrophenyl	155 ± 1	NA	105 ± 2
BP_{10}	3"-hydroxyphenyl	148 ± 2	129 ± 2	155 ± 1
BP_{11}	3"-nitro-4"methylphenyl	64 ± 2	58 ± 1	46 ± 2
BP_{12}	3",4",5"-trimethoxyphenyl	132 ± 2	NA	93 ± 2
BP_{13}	3",4"-methelenedioxyphenyl	NA	NA	75 ± 2
BP_{14}	5"-bromofuran-2"-yl	56 ± 2	27 ± 1	16 ± 1
BP_{15}	4"-dimethylaminophenyl	182 ± 1	106 ± 2	98 ± 2
BP_{16}	3"-methoxy-4"-hydroxyphenyl	123 ± 2	74 ± 1	68 ± 2
BP_{17}	2"-pyridinyl	195 ± 2	140 ± 1	92 ± 2
BP_{18}	3"-pyridinyl	NA	188 ± 2	110 ± 2
BP_{19}	4"-pyridinyl	128 ± 2	NA	148 ± 1
BP_{20}	2"-thienyl	36 ± 2	28 ± 1	16 ± 2
Methotrexate		11 ± 1	9 ± 1	6 ± 1

Data presented as mean ± SD (n=3). All the compounds and the standard dissolved in DMSO, diluted with culture medium containing 0.1% DMSO. The control cells were treated with culture medium containing 0.1% DMSO. NA- No Activity (i.e IC50 > 200 µg/mL)

DISCUSSION ON RESULTS:

Cytotoxic studies: Of all the compounds tested against HT-29 cell lines, the compound BP_5 having a difluorophenyl moiety in its structure showed maximum activity with a IC_{50} value of 28 µg/mL. This is followed by compounds, BP_{20} having a thienyl moiety (IC_{50} 36 µg/mL), BP_2 and BP_6 having fluorophenyl and dichlorophenyl moieties respectively (IC_{50} 42 µg/mL), BP_1 having a methylphenyl moiety (IC_{50} 55 µg/mL) and BP_{14} having a bromofuran moiety (IC_{50} 56 µg/mL). The other compounds also showed activity but at a higher IC_{50} values.

Among the compounds tested for cytotoxicity on MCF-7 cell lines, the compound BP_{14} showed maximum activity (IC_{50} 27 µg/mL). This was followed by compounds, BP_{20} (IC_{50} 28 µg/mL), BP_5 (IC_{50} 42 µg/mL) and BP_2 (IC_{50} 48 µg/mL). All the other compounds showed cytotoxicity at higher values.

Among the compounds tested for cytotoxicity on DU-145 cell lines, the compounds, BP_{14} and BP_{20} showed maximum activity (IC_{50} 16 µg/mL). This was followed by compounds, BP_5 (IC_{50} 33 µg/mL), BP_{11} having a 3-nitro-4-methylphenyl moiety (IC_{50} 46 µg/mL), BP_1 (IC_{50} 52 µg/mL) and BP_6 (IC_{50} 56 µg/mL).

It was also observed that among all the compounds tested on these three cell lines, most of the compounds showed maximum activity on prostate cancer cell lines (DU-145).

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