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Newer applications of 1,5-benzothiazepines and their cytotoxic and anticonvulsant activity

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ABSTRACT

1,5-Dihydrobenzothiazepines are synthesized by conventional synthesis method. The compounds have been screened for cytotoxic and anticonvulsant 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 (for carbon, hydrogen and nitrogen), IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies.

Keywords: 4-Fluoroacetophenone, 1, 5-DihydroBenzothiazepine, 2-Aminothiophenol, piperidine

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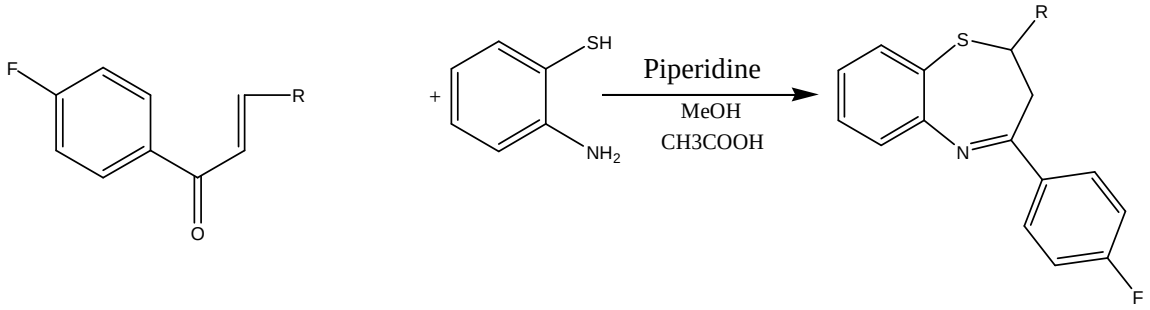
INTRODUCTION

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].

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].

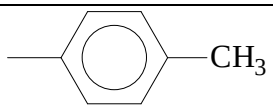
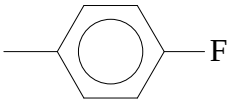
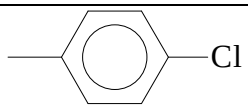
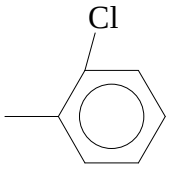
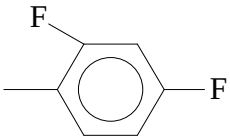
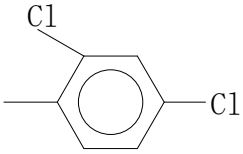
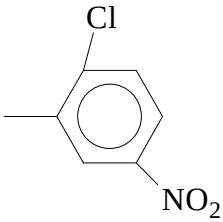
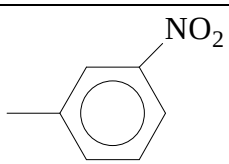
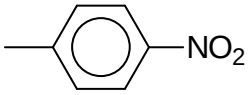
MATERIALS AND METHODS

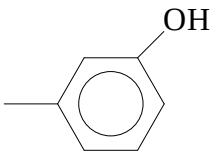
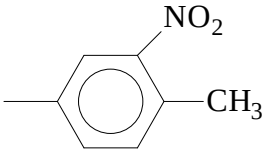
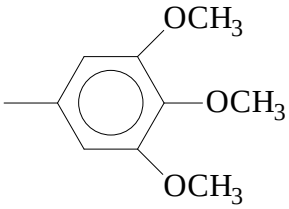
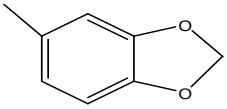
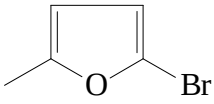
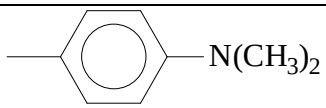
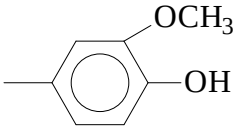
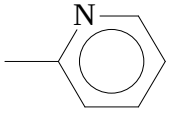
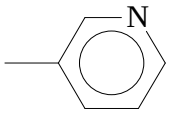
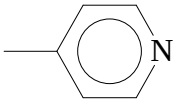
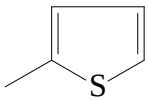
Procedure for Synthesis of 1, 5-Benzothiazepines
Chalcones of P-FluoroAcetophenone (1 mill mole) and O-Amino thiophenol (1 mill mole) was dissolved in 10 ml of boiling methanol the heat was removed and piperidine (2 drops) was added. After the mixture had cooled to room temperature the additional 10 ml of methanol was added and heated until the slurry was dissolved. Then add 1 ml of Glacial acetic acid and allow the mixture at 25^{0}C for overnight. The yellow color crystals benzothiazepine was separated out. This was recrystallised with methanol and filtered. The scheme and physical characterization data will be given below:



SCHEME-1 **BP(1-20)**

Table 1 Physical characterization data of 1, 5-benzothiazepines (BP_1-BP_{20})

Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (°C)	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

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

BP-1: 2,3-Dihydro-2-(4-methylphenyl)-4-(4-fluorophenyl)-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-fluorophenyl)-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)and 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-fluorophenyl)-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-fluorophenyl)-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-fluorophenyl)-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-fluorophenyl)-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-fluorophenyl)-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-fluorophenyl)-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-fluorophenyl)-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: 177-1798^{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)-1,5benzothiazepine (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-fluorophenyl)-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-hydroxyphenyl)-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)

Anticonvulsant activity:
Experimental Animals:
Healthy Swiss albino mice weighing about 25-30 g were used in experiments. Animals were housed in polypropylene cages maintained under standard conditions (12 hours light / dark cycle; 25 ± 3^0 C, 45-65 % humidity) and had free access to standard feed and water.

Drugs and chemicals
Phenytoin, Diazepam and Thiopental sodium were used in this study. The test compounds were dissolved in 1% sodium CMC and subjected for anticonvulsant activity using Electro Convulsiometer. Phenytoin and Diazepam were dissolved in normal saline (0.9% NaCl solution).

Acute toxicity:
The drugs was administered in doses of 500, 1000 and 2000 mg/kg, *i.p.*, to groups of mice, each containing ten animals and mortality was observed after 24 h.

Maximal electroshock seizure test (MES) Maximal seizures were elicited by a 60Hz alternating current of 50mA intensity delivered for 0.2 seconds via corneal electrodes. A drop of 0.9% w/v sodium chloride instilled in each eye prior to application of electrodes assured adequate electrical contact. Test solutions of all the compounds were prepared in 1% sodium CMC and animals were dosed intraperitoneally 30 min prior to testing. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test. Animals were divided into varies groups of six each.

Group I served as control (vehicle treated, i.p.); Group II served as standard (received Phenytoin sodium 25mg/kg body weight, i.p.), Group III was treated with test compound at 200mg/kg body weight, i.p. respectively. The current was delivered after 30 min. of intraperitonial administration of control and standard. The incidence and duration of HLTE was noted.

Statistical analysis
The data are expressed as mean + S.E.M. The data were statistically analyzed using one-way analysis of variance (ANOVA), followed by Duncan's multiple range post test and Chi square test. Values of $p < 0.05$ were considered significant.

Table 2

S. No	Treatment Group [b]	Mean± SE (sec)			Recovery	Mortality
		Flexion	THLE	Clonus		
1	Control (0.9% saline)	3.6	6.2	8.4	Dead	100%
2	BP-1	1.3	3.2	8.5	88	50%
3	BP-2	2	4.8	14.2	76	83.33%
4	BP-3	2.5	2.75	12.5	119.2	**0%**
5	BP-4	1.6	3.2	10.3	94	16.66%
6	BP-5	1.25	2.5	17.5	80.7	**0%**
7	BP-6	1.8	2.8	14	86	16.66%
8	BP-7	1.6	7.3	8	62	33.33%
9	BP-8	1.8	7.6	9	65	33.33%
10	BP-9	2	4.3	15	120	33.33%
11	BP-10	1.8	4.8	16	112	33.33%
12	BP-11	1.5	3	7.7	92.3	16.66%
13	BP-12	2	5	9.5	67	83.33%
14	BP-13	2.6	5.8	10	65	83.33%
15	BP-14	0.85	2.7	6.2	57	**0%**
16	BP-15	1	3.4	6.8	61	**0%**
17	BP-16	1.7	3.2	8.1	69	33.33%
18	BP-17	1.6	3.2	10.3	94	16.66%
19	BP-18	2	5	9.5	67	83.33%
20	BP-19	1.6	3.2	10.3	94	16.66%
21	BP-20	2	5	9.5	67	83.33%
Standard	Phenytoin Sodium[a]	1.2	00	6.75	48.5	0%

[a] 25 mg/kg b.wt, [b] 200 mg/kg b.wt, THLE: Tonic Hind Limb Extension and SE: Standard Error

RESULTS AND DISCUSSION

all the newly synthesized compounds Bp-(1-20) were studied for their anticonvulsant The pharmacological data of all the compounds of this series are reported in table 3. The compounds evaluated for their anticonvulsant activity against maximal electric shock induced seizers at a dose 200mg/kg body wt; ip; and found to exhibit substantive anticonvulsant activity. the compounds Bp(1-20) substituted with different moieties at second and fourth positions of 1,5-benzothiazepine ring. Among the series of compounds tested it was observed that compounds Bp-3(having 4-chloro phenyl group at second position of benzothiazepine ring), Bp-5(having 2, 4-difluoro phenyl group), Bp-14(having 32Bromo furfuryl group) and Bp-15(having 4-dimethylamino phenyl group) exhibit maximum degree of anti convulsant activity with 0% mortality. The remaining results were shown in table 2

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 Tryphan 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 37^0C 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

Table 3. 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 IC_{50} > 200 µg/mL)

RESULTS AND DISCUSSION

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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