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SYNTHESIS, CHARACTERIZATION AND ANTI OXIDANT ACTIVITY OF NOVEL 1,5 BENZOTHIAZEPINES FROM CHALCONES OF 1-(2,4-DIFLUOROPHENYL) ETHANONE PRECURSOR

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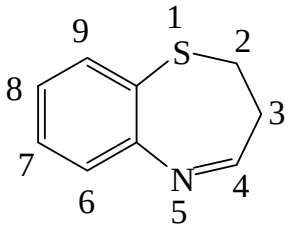
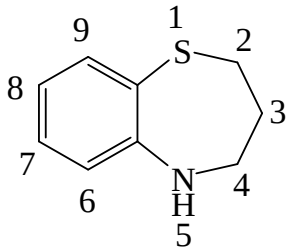
ABSTRACT
1,5 benzothaizepines heterocyclic ring system having the diverse pharmacological activities. The present work focus on synthesis of novel benzothaizepines molecules by condensation of 1-(2',4'-difluorophenyl)-3-(4''-methylphenyl)-2-propen-1-one derivatives and O-amino thiophenol in the presence piperidine and glacial acetic acid. The structures of compounds were confirmed by spectral analysis using IR, 1HNMR and Mass analysis. The biological evolution of compounds were performed for anti oxidant activity by using DPPH reagent method using standard ascorbic acid.

KEYWORDS: Chalcones, 1,5 benzothiazepines, DPPH reagent, anti oxidant activity.

INTRODUCTION
The benzothiazepines[1,6] **(1**and **2)** are important nitrogen and sulfur-containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities.[7,14] 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.[15,18]



(1)



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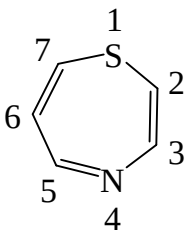
General structures of 1,5-benzothiazepine



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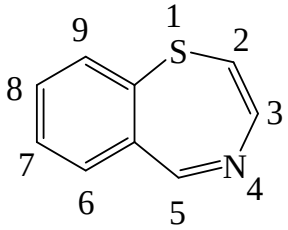

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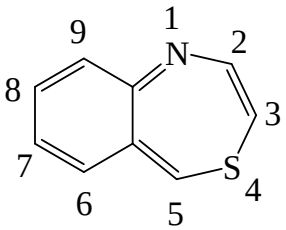
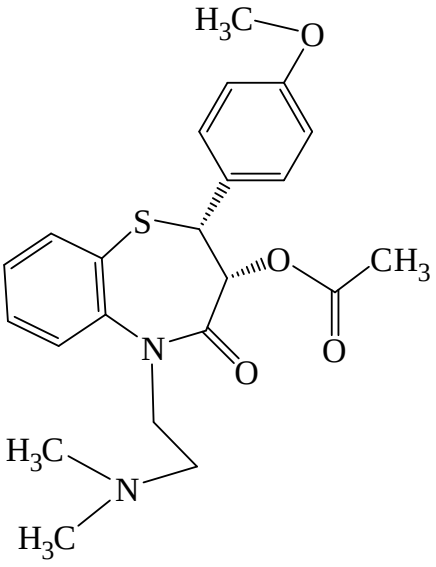


(5)

The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets.[19,24] 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 **(8)**, clothiapine **(9)** and quetiapine **(10)**. Therefore, the 1,5-benzothiazepines are useful compounds in the drug research which has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations.[25,45]



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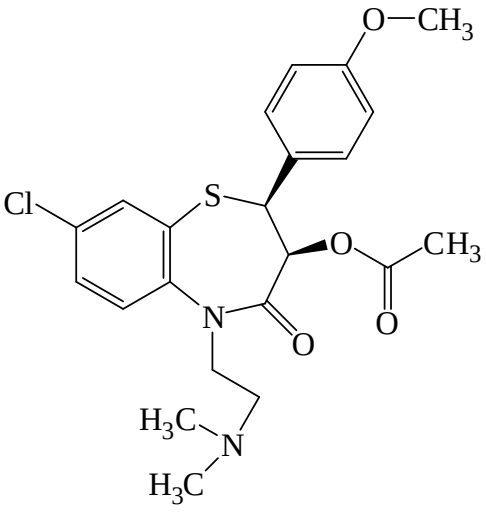

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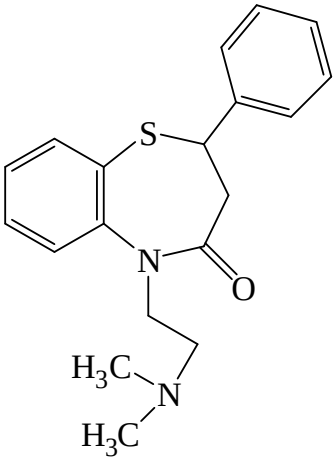

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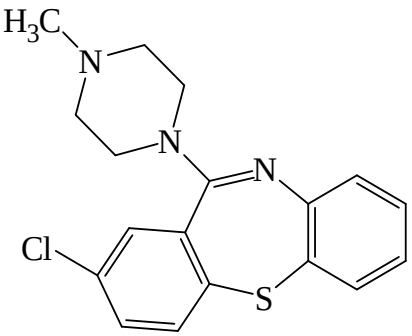

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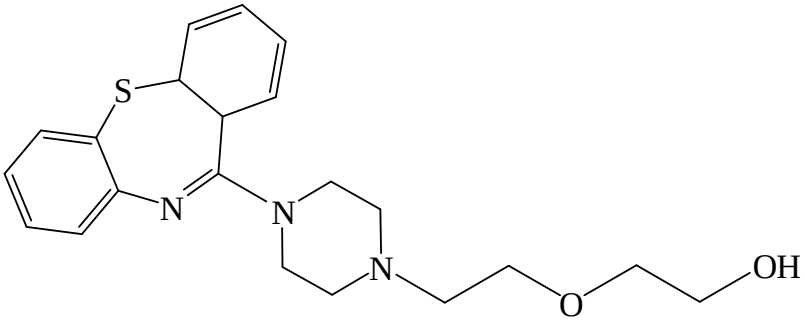


(10)

The importance of the l,5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents.[46] A number of biological activities have been associated with it, such as antifeedant[47], coronary vasodilatory[48], tranquilizer[49], antidepressant[50], CNS stimulant[51], antihypertensive[52], calcium channel blocker[53], antiulcer[54], calcium

antagonist[55], antimicrobial[56] and anticonvulsant agents.[57] l,5-Benzothiazepine molecules have been found to be useful in mucosal blood flow, as antiulcer and gastric secretion inhibitor. Recently, anticancer activities[58], hemodynamic effects[59] and spasmolytic activities[60] have also been reported.

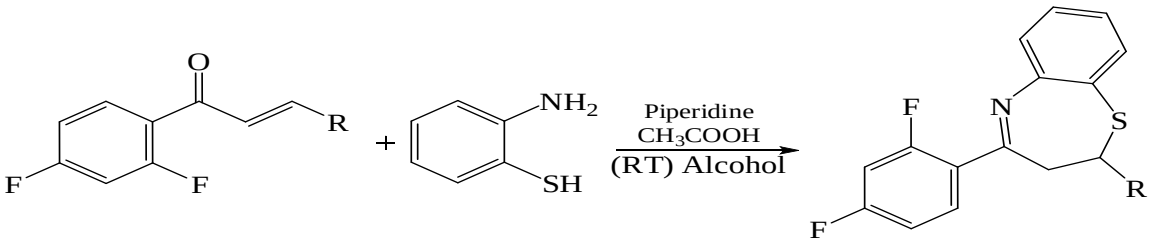
Keeping this broad spectrum of biological activities in mind, in the present investigation it has been considered worthwhile to synthesize benzothiazepines from chalcones derivatives. The compounds were characterized by H^1 NMR and IR analysis. The compounds were tested for their antimicrobial activity by standard protocols.

Experimental work[61,62]

SCHEME OF SYNTHESIS

Synthesis of benzothiazepines from chalcones obtained from 2,4-difluoroacetophenone (Scheme- 12).

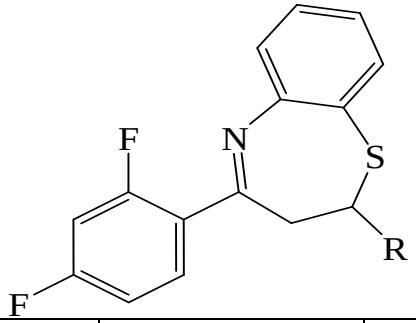
Chemical Reaction

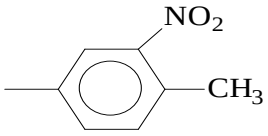
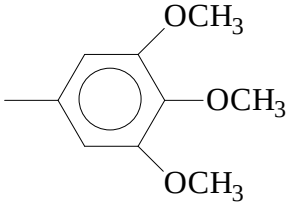


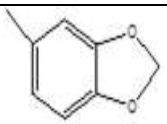
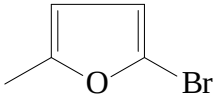
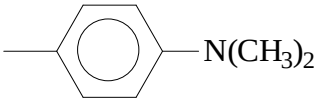
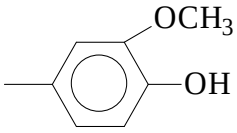
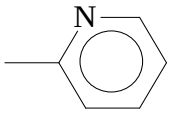
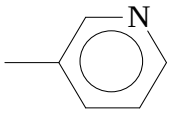
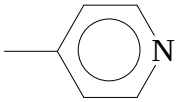
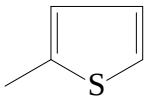
Chalcone derivative **2-Aminothiophenol** **Benzothiazepine derivative**

Scheme- 12

Table-1 Physical characterization data of benzothiazepines (BP_1-BP_6)



Compound	R	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (^oC)	Yield %
BP_1		$C_{22}H_{16}F_2N_2O_2S$	410	176-179	94
BP_2		$C_{24}H_{21}F_2NO_3S$	441	148-151	85

BP_3		$C_{22}H_{15}F_2NO_2S$	395	156-157	74
BP_4		$C_{19}H_{12}BrF_2NOS$	420	132-135	79
BP_5		$C_{23}H_{20}F_2N_2S$	394	114-117	88
BP_6		$C_{22}H_{17}F_2NO_2S$	397	151-154	86
BP_7		$C_{20}H_{14}F_2N_2S$	352	111-114	78
BP_8		$C_{20}H_{14}F_2N_2S$	352	120-121	82
BP_9		$C_{20}H_{14}F_2N_2S$	352	110-101	92
BP_{10}		$C_{19}H_{13}F_2NS_2$	357	146-149	86

Spectral data for synthesised 1,5 benzothiazepines: B_1-B_{10}

2,3-Dihydro-2-(3-nitro-4-methylphenyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{11})

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 (6, Ar-H).

2,3-Dihydro-2-(3,4,5-trimethoxyphenyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{12})

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 (5H, Ar-H), 3.70 (3H, s, Ar-OCH_3), 3.88 (6H, s, 2Ar-OCH_3).

2,3-Dihydro-2-(3,4-methelenedioxyphenyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{13})

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 (6H, Ar-H).

2,3-Dihydro-2-(5-bromofuran-2-yl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{14})

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 (5H, Ar-H).

2,3-Dihydro-2-(4-dimethylaminophenyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{15})

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), ^{1}H-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 (7H, Ar-H).

2,3-Dihydro-2-(3-methoxy-4-hydroxyphenyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{16})

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) ^{1}H-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 (6H, Ar-H), 6.95 (1H, s, Ar-OH), 3.80 (3H, s, Ar-O-CH_3).

2,3-Dihydro-2-(2-pyridinyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{17})

IR (KBr) (cm^{-1}): 1602 (C=N), 1510 (C=C), 1390 (C-N), 924 (C-F) and 677 (C-S), ^{1}H-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 (7H, Ar-H).

2,3-Dihydro-2-(3-pyridinyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{18})

IR (KBr) (cm^{-1}): 1599 (C=N), 1506 (C=C), 1382 (C-N), 927 (C-F) and 698 (C-S); ^{1}H-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 (7H, Ar-H).

2,3-Dihydro-2-(4-pyridinyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{19})

IR (KBr) (cm^{-1}): 1606 (C=N), 1508 (C=C), 1388 (C-N), 933 (C-F) and 654 (C-S);^{1}H-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 (7H, Ar-H).

2,3-Dihydro-2-(2-thienyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine (BP_{20})

IR (KBr) (cm^{-1}): 1605 (C=N), 1503 (C=C), 1386 (C-N), 928 (C-F) and 644 (C-S);^{1}H-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 (6H, Ar-H).

Biological evolution 62

Antioxidant activity by DPPH method (8)

Antioxidant behavior of these chalcones and pyrimidines derivatives were measured *in vitro* by the inhibition of generated stable 2,2-diphenyl- 1-picrylhydrazyl (DPPH) free radical. Methods vary greatly as to the generated radical, the reproducibility of the generation process and the end point that is used for the determination. The DPPH solution was prepared by dissolving accurately weighed 22 mg of DPPH in 100 ml of ethanol. From this stock solution, 18 ml was diluted to 100 ml with ethanol to obtain 100 µM DPPH solutions. The sample solution was prepared by accurately weighed 2.1 mg of each of the compounds and dissolved in 1 ml of freshly distilled DMSO separately to obtain solutions of 2.1 mg/ml concentration and the standard solution of was prepared by accurately weighed 10.5 mg of α-Tocopherol and dissolved in 1 ml of freshly distilled DMSO to get 10.5 mg/ml concentration.

A solution of test compound in ethanol (500 µl) was added to the ethanolic solution of DPPH radical. The reaction mixture was vortexed thoroughly and left in the dark at room temperature for 30 min. The absorbance of the mixture was measured spectrophotometrically at 517 nm against the corresponding blank solution. The final concentration of the samples and standard Ascorbic acid solutions used is 100 µg/ml. The percentage scavenging DPPH radical inhibitions were calculated by using the following formula:

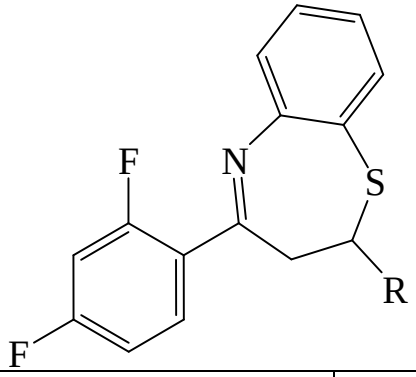
$$\text{DPPH radical scavenging activity (\%)} = \frac{(\text{Abs control} - \text{Abs sample})}{\text{Abs control}} \times 100$$

Where, Abs control was the absorbance of DPPH radical and ethanol, Abs sample was the absorbance of DPPH radical and sample/standard.

The scavenging activity was expressed in terms of IC50, the concentration of the samples required to give a 50% reduction in the intensity of the signal of the DPPH radical. The results were done at least in triplicate.

RESULTS AND DISCUSSION

Table 2. Antibacterial activity of synthesised compounds ($BP_1$to BP_{10}): (Expressed as MIC in µg/mL)



Compound	R	Antioxidant activity (%inhibition)
B_1	3"-nitro-4"-methylphenyl	64
B_2	**3",4",5"-trimethoxypheny**	**52**
B_3	3",4"-methylendioxyphenyl	66
B_4	5"-bromofuran-2"-yl	88
B_5	4"-dimethylaminophenyl	**62**
B_6	3"-methoxy-4"-hydroxyphenyl	58
B_7	2"-pyridinyl	73
B_8	3"-pyridinyl	81
B_9	4"-pyridinyl	83
B_{10}	2"-thienyl	**84**
Standard (Ascorbic acid)		**48**

DISCUSSION

1,5 benzothiaepines were designed synthesized by the condensation 1,3-diphenyl-2-propene-1-one with 2-aminothiophenol in presence of glacial acetic acid to from cyclic product. The obtained compound structures were characterized by its IR and ^{1}H NMR spectral data. Based on the values the compounds 1,5 benzothiaepines were shows better activity Here the compound contains the electron with drawing along the electron releasing groups maximum anti oxidant activity than the other molecule here compound B_2 (2,3-Dihydro-2-(3,4,5-trimethoxyphenyl)-4-(2,4-difluorophenyl)-1,5-benzothiazepine) show activity along with standard ascorbic acid.

CONCLUSION

From the above results it is evident that synthesized chalcone derivatives and di hydro 1,5 benzothiaepines derivatives showed significant in vitro anti oxidant activity. In particularly, compounds containing the electron releasing groups (like OCH_3, OH) show the maximal antioxidant activity compare with standard compound ascorbic acid.

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