



**SYNTHESIS AND ANTICONVULSANT STUDIES
OF SOME NEWER BENZOTHIAZEPINE DERIVATIVES**

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ABSTRACT

The 1,5-benzothiazepines are important nitrogen and sulfur-containing seven-membered heterocyclic compounds in drug research because they possess diverse bioactivities. The 1, 5- benzothiazepine derivatives are of particular interest for lead discovery because they have been found to be active against different sites of targets. Benzothiazepine and its derivatives found to exhibit diverse biological activities such as coronary tranquilizer, anticonvulsant activity, antidepressant, antihypertensive, calcium channel blocker. Benzothiazepine derivatives were prepared by using Chalcones in presence of o-aminothiophenol. The synthesized compounds were characterized by using IR –Spectral. Maximal electroshock seizure (MEC) method was used for the pharmacological evaluation of synthesized 1,5- Benzothiazepine derivatives.

KEYWORDS: Benzothiazepine, o-aminothiophenol Maximal electroshock seizure, anticonvulsant activity, antihypertensive.

INTRODUCTION

The benzothiazepines (1 and 2) are important nitrogen and sulfur containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities²⁻⁴. 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

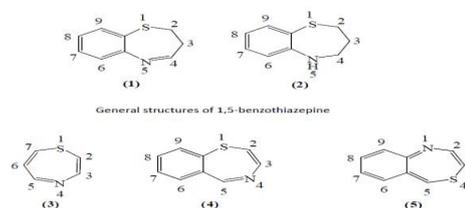
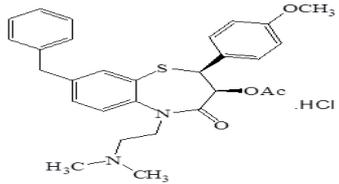
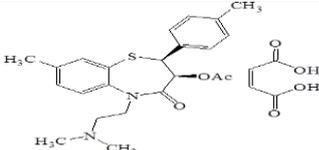
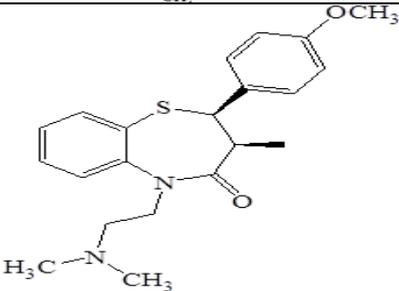


Table 1: Pharmacological profile of benzothiazepines

Compound	Pharmacological profile
	Ca ²⁺ channel antagonistic activity
	+ channel antagonistic activity

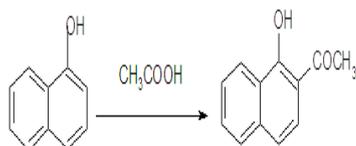
	+ channel antagonistic activity
	+ channel antagonistic activity
	+ channel antagonistic activity

OBJECTIVE:- The main objective behind selecting 1) 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4- thiazepine and one of the three possible benzo-condensed derivatives, namely, 1,4-, 4,1 and 1,5-benzothiazepines
 2) Our aim is to design, synthesize, characterize the novel 1,5-Benzothiazepine analogues which could improve the physiochemical and pharmacological properties of drug.
 3) To evaluate the synthesized compounds for their anticonvulsant activity.

EXPERIMENTAL METHOD

STEP-1: PROCEDURE FOR THE SYNTHESIS OF 2-ACETYL-1-NAPHTHOL

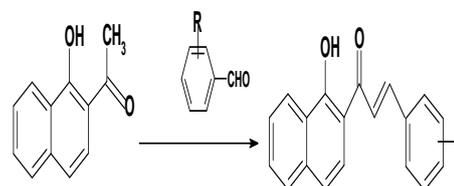
The preparation of benzodiazepines was done in two step process. Initially the 2-acetyl-1-naphthol was prepared in hot glacial acetic acid (20ml), fused ZnCl₂ (25 gm) was added and refluxed until it is dissolved, then powdered 1-naphthol (10gm) was added. The mixture was refluxed for about 8 hours then cooled & poured in acidulated water. The solid obtained was filtered, washed, dried and recrystallized from rectified spirit to obtain 2-acetyl-1-naphthol.



STEP 2: SYNTHESIS OF CHALCONES

2-acetyl-1-naphthol (0.01mole) and aldehydes (0.02 mole) were added in ethanol solvent (20ml). To this mixture KOH (10%, 10ml) solution was added drop wise with constant stirring, the reaction mixture was hydrated overnight. Then the hydrated mixture was passed

through crushed ice & little HCl. The product was filtered and recrystallized from ethanol to obtain the compounds which are mentioned in physical data. The TLC was performed for obtained compounds using mobile phase Ethyl acetate and Hexane.



STEP-03: SYNTHESIS OF 1,5-BENZOTHAZEPINES.

The solution of chalcone derivative in dry acidic ethanol was acidified by adding few drops of glacial acetic acid to it, 2-aminothiophenol was added. The mixture was 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. The TLC was performed for obtained compounds using mobile phase Ethyl acetate and Hexane.

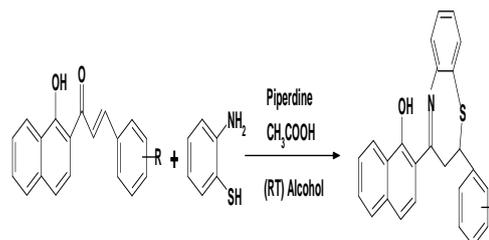


TABLE-2: CHARACTERISATION OF CHALCONES

S.No.	Group(R)	Mol.Formula	Mol.wt	M.pt(⁰ C)	Rf value
01	2-OH	C ₁₉ H ₁₄ O ₃	290	146	0.24
02	4-OH	C ₁₉ H ₁₄ O ₃	290	342	0.56
03	2-Cl	C ₁₉ H ₁₃ O ₂ Cl	308.5	270	0.36
04	4-Cl	C ₁₉ H ₁₃ O ₂ Cl	308.5	200	0.38
05	4-F	C ₁₉ H ₁₃ O ₂ F	292	180	0.42

TABLE-3: CHARACTERISATION OF BENZOTHIAZEPINES

S.No.	Group (R)	Mol.Formula	Mol.wt	M.pt(⁰ C)	Rf value
01	2-OH	C ₂₆ H ₁₉ O ₂ NS	409	112-114	0.55
02	4-OH	C ₂₆ H ₁₉ O ₂ NS	409	152-154	0.57
03	2-Cl	C ₂₆ H ₁₈ ONSCl	427	144-145	0.63
04	4-Cl	C ₂₆ H ₁₈ ONSCl	427	118-120	0.71

IR Interpretation of Benzothiazepines

2-hydroxy benzaldehyde 3377(OH), 2986 (CH), 1625 (C=O), 1596 (C=C), 1152 (C-O)
11043 (C-S), 1314 (C-N)
4-hydroxy benzaldehyde - 3366 (OH), 2936 (CH), 1680 (C=C), 1646 (C-O), 1155 (C-S), 2239(C-N)
2 Chloro benzaldehyde--338 (OH), 2877 (CH), 1519 (C=C), 1234 (C-S), (1309) C-N
4 Chloro benzaldehyde - 3428 (OH), 3153(CH), 1621 (C=C), 1083 (C-O), 748 (C-Cl)
1154 (C-S).

RESULTS AND DISCUSSION**BIOLOGICAL EVALUATION OF SOME NEW NEWER BENZOTHIAZEPINE DERIVATIVES**

We selected the **Electroshock induced convulsions** in order to induce convulsions in the animal. For electroshock induced convulsions we employed **Maximal electroshock seizure (MES)** method in order to evaluate the anticonvulsant activity of newer benzodiazepines.

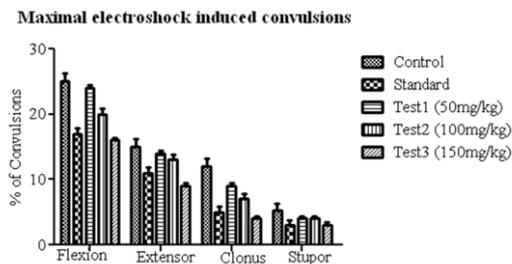
Principle: The MES test, developed by Toman and collaborators, the best validated preclinical test that predicts drugs against the generalized seizure of the tonic-clonic (grand-mal) type of epilepsy. It permits the evaluation of ability of a substance to prevent seizure spread through neural tissue. In MES method, electric shock is applied through the corneal electrodes. The MES convulsions are divided into five phases such as 1. Tonic flexion, 2. Tonic extensor, 3. Clonic convulsions, 4. Stuper, 5. Recovery or Death.

A substance is known to possess anticonvulsant property if it reduces or abolishes the extensor phase of MES convulsions.

Procedure: The animals were divided into two groups, each consists of four mice and group A was regarded as control and group B for drug treatment. For Control 150mA current was applied for 2 seconds on four mice. For testing of a drug a group of four mice were selected and pentazocine was administered intra-peritoneally. After 30 minutes 150mA current was applied to group B animals and reduction in time was noted.

ANTI CONVULSANT ACTIVITY OF NEWER BENZOTHIAZEPINE DERIVATIVES

S.No	Treatment	% of Convulsions (Mean± SEM values)				
		Flexion	Extensor	Clonus	Stupor	Recovery/ Death
1	Control	25±1.41	15±1.41	12±1.41	5±1.19	Recovery
2	Standard (Pentazocine)	17±0.94	11±0.94	5±0.94	3±0.94	Recovery
3	Test-1 (150mg/kg)	24±0.47	14±0.47	14±0.47	4±0.47	Recovery
4	Test-2 (150mg/kg)	20±0.94	13±0.94	7±0.94	4±0.47	Recovery
5	Test-3 (150mg/kg)	16±0.47	9±0.47	4±0.47	3±0.47	Recovery
6	Test-4 (150mg/kg)	14±0.47	9±0.47	3±0.47	2±0.47	Recovery



CONCLUSION

Benzothiazepine derivatives were prepared by using Chalcones in presence Of o-aminothiophenol. The synthesized compounds were characterized by IR – Spectral studies and TLC. Maximal electroshock seizure (MEC) method was used for the pharmacological evaluation of synthesized 1,5-Benzothiazepine derivatives .Test compound 3 was found to be more effective and exhibited significant anticonvulsant activity compared to standard drug, presence of 2-Cl group in aromatic ring is responsible for anticonvulsant activity.

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