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Synthesis of Some Novel 1, 5-Benzothiazepine Derivatives Biological Screening for Anticonvulsant Activity

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Abstract: *The presence of recurrent seizures is responsible for epilepsy, further which has been characterized in the era. A seizure can be mention as "an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex" [1]. Epileptic convulsions are expected to have negative consequences on the patient's psychological and social life such as relationships, education and employment. Uncontrolled seizures are associated with physical and psychosocial morbidity, dependent behavior, poor quality of life and an increased risk of sudden unexpected death.*
The heterocyclic compound isa potential compound for the development of chemotherapeutic and pharmacotherapeutic agentscontaining nitrogen and sulphur atoms[2]. Therefore the present investigation was made in direction to the synthesis of some newer 1, 5-benzothiazepine derivatives and their evaluation for anticonvulsant activity. Physicochemical and elemental analysis of all the 1, 5-benzothiazepine (1B-10B)isconfirmedwith a preliminary study like melting point, elemental analysis and hyphenated tool namely IR, NMR and Mass spectroscopy. Firstly Primarily, α,β-unsaturated carbonyl compounds or chalcones were prepared by the well-known Claisen-Schmidt condensation ofacetophenones and substituted aldehyde by using alcoholic KOH (10%) at room temperature.By adding diazonium salt in substituted chalcone ,substituteddiazoniumchalcone was prepared. A yield mixtureand 0.01 mole of substituted mercapto anilines was dissolved in 2-methoxyethanol to get final product 1, 5-benzothiazepine derivatives. These molecules were evaluated for possible anticonvulsant activity.Anti-seizure activities of all synthesized compounds 101B to 110B were explored using MES.The synthesized compounds from (101B to 110B) 108B and 109Bhad shown significant activity against the tonic seizureas compared to the other synthesized compounds.
Keywords: *1, 5-benzothiazepine derivatives; anticonvulsant activity*

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I. Introduction

A seizure can be mention as "an episodic disturbance of movement, feeling, or unconsciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex".Epilepsy, derived from a Greek word epilambanein, which means to attack or seize. Epilepsy is a collective term that includes over 40 different types of human seizure disorders, Approximately 1% of the worldpopulation at any one time (50 million people worldwide) is affected by this neurological disorder which is evoked by unexpected, high-level neuronal discharges in the brain.In fact there are very limited options used in the treatment of epilepsy. Furthermore, the use of some of these options is still a controversial issue[1]. Antiepileptic drugs (AEDs) are the mainstay of epilepsy management.In current drug therapy for epilepsy nearly 95% of clinically drugs are available. Around 60 - 70% of epileptic patients with seizures can be treated successfully with AED therapy. It is roughly estimated that up to 28-30 % epilepsy is inadequately controlled by medication[3].For the treatment of epilepsy currently available anticonvulsant however can minimize the severity and number of seizures in less than 70% of patients. Moreover usage of anticonvulsants is often associated with undesirable and numerous side effects[4].Intolerance,high levels of toxicity and a lack of efficacy also represent further limitations of the current AEDs. With all of this in mind, there is indeeda need for the development of novel AEDs with higher levels of potency and lower levels of toxicity. Hence these facts necessitate the search for the development of a novel anticonvulsant drug with greater efficacy and fewer side effects.

Experimental:

Melting points are confirmed on 'Electronics India 934' Digital apparatus and are accurate. TLC is performed on Silica gel G plates was activated for 40 min. (110º C) and developed using Benzene: Toulene

(7.5:2.5 and 7.0:3.0)as a mobile phase respectively. The spots are visualized by exposure to iodine vapors using a UV cabinet.

Physicochemical and spectroscopical characterization of all the 1, 5-benzothiazepine is confirmed by checking of IR spectra. IR spectra are recorded using KBr discs on 8400-S FTIR (Shimadzu). ^{1}H NMR is recorded on Varian 300MHz spectrometer; chemical shifts are given in ppm units (δ) relative to internal standard Tetramethylsilane (Me4Si) and refer to CDCl3 or DMSO-d6 solutions. Elemental analysis is performed on Vario EL III CHNS serial number 11035060. Data of the elemental analysis was analyzed which corresponds to the calculated values.

Step I - Synthesis of Chalcone (I-X)[5]:

Primarily, α,β-unsaturated carbonyl compounds or chalcones were prepared by the well-known Claisen-Schmidt condensation of acetophenones and substituted aldehyde by using alcoholic KOH (10 %) at room temperature . After the completion of the reaction (30 min) was monitored by TLC and the residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was filtered, collected and washed with distilled water and crystallized from methanol to give corresponding chalcones**I-X**. The precipitate was filtered and purified from hot ethanol by re-crystallization.

Step II - Synthesis of diazonium substituted chalcones[6]

Chalcone (I-X) 7.8gm in 45ml of 10% NaOH solution in a beaker, cool the solution to 5^{o}C by immersion in an ice bath. Stir the chalcone vigorously & add cold diazonium salt very slowly. Red color crystals develop. Allow the mixture to stand in an ice bath for 30 min with occasional stirring. Recrystallized from glacial acetic acid.

Step II - Synthesis of substituted benzothiazepines (101B-110B):

A mixture of different diazoniumsubstituted chalconeand 0.01 mole of substituted mercaptoaniline was dissolved in 10 ml of 2-methoxyethanol. To this 0.001 mmol of piperidine was added to the reaction mixture and refluxed for 10-15 min (TLC). Then the reaction mixture was cooled to room temperature[6]. Solid separated was isolated by simple Buchner filtration; final purification was achieved by crystallization from ethanol to give 101B-110B. The details are depicted in Scheme.

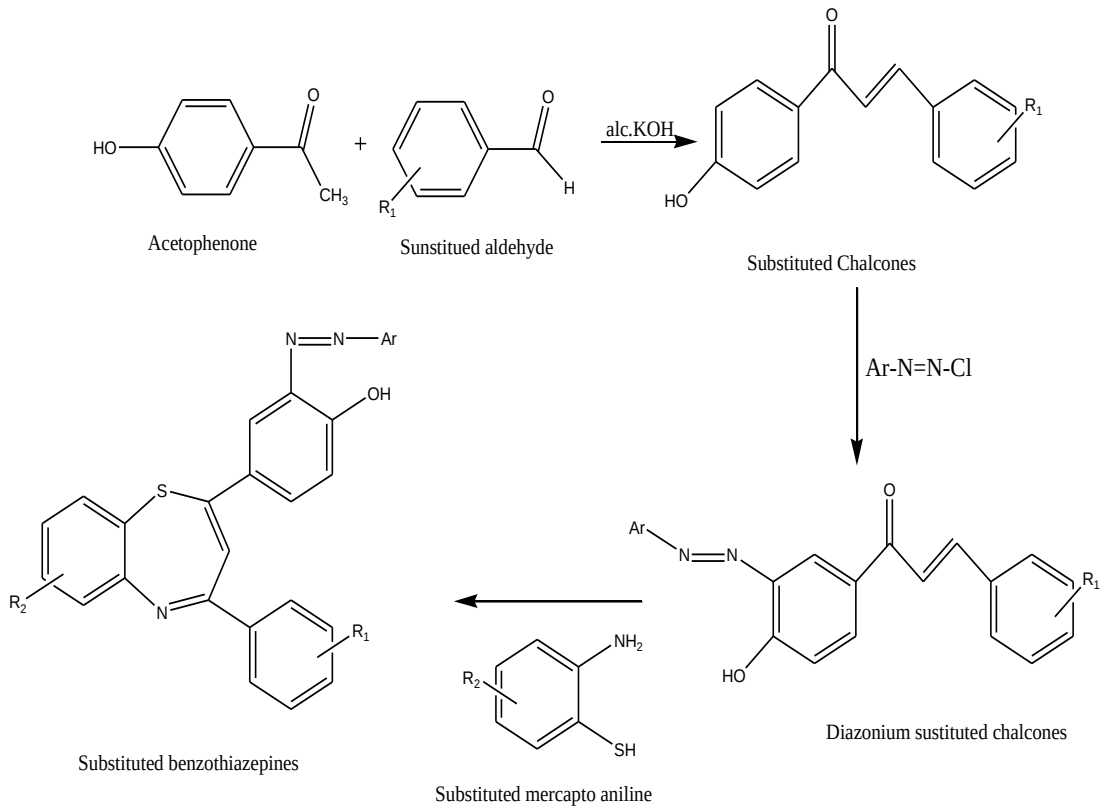

Table No. 1: The structural details of synthesized Benzothiazepine.

Compound Code	R1	R2
101B	-OH	-H
102B	$-OCH_3$	-H
103B	-Cl	-H
104B	-F	-H
105B	$-C_2H_5$	-H
106B	-Br	-H
107B	$-NO_2$	-H
108B	$-NH_2$	-H
109B	$-CH_3$	-H
110B	-I	-H

II. Biological Screening:

Material and Methods

1. Experimental animals:

Albino rats (wistar, 180-200 g) were used in groups as experimental animals. The animals were procured from the central animal house facility of the institute. Animals were provided with standard pelletized feed (Amrut mice feed, Pune India) and water was made available at libitum. Animals were acclimatized to laboratory conditions before commencing with the experimentation. Care was taken to ensure animals' availability in the appropriate size, age, weight and sex for all experiments. The test compounds and standard drugs were suspended in CMC and administered intraperitonially (IP).

All the experimental protocols were performed as per the ethical principles and guidelines, and with permission of the Institutional animal ethical committee (Protocol No. SCOP/IAEC/63/14-15) constituted for the purpose of control and supervision of experimental animal by Ministry of Environment and Forests, Government of India, New Delhi.

2. MES (Maximal Electroshock method):

The preliminary evaluation of the synthesized compounds 101B-110B was evaluated for anticonvulsant activity by the use of predictable animal models.The MES seizure model is an animal seizure models, most widely used in the search for new anticonvulsants.

The anticonvulsant activity was performed on albino rats weighing about 100-120 gms are divided into ten groups of rats. The animals were divided into three groups (control, standard, and test) and each group consisted of six animals. The test compounds 101B-110B at concentration 100mg/kg dose with respect to standard drug phenytoin was administered60 min prior to the start of the experiments by i.p. the route in rats.After 1 hour they were subjected to a shock of 150 mA by convulsiometer through ear electrodes for 0.2 seconds and The latency and incidence of tonic hind limb extension (THLE) and the mortality rate was observed for 15 min. Animals in which extensor response was abolished were taken as protected rats . A value of $P<0.05$ value was considered as statistical significance[7-9]. All the values represent standard error of the mean (SEM) expressed as mean ± SEM.

Table No. 2: Anticonvulsant activity of synthesized compounds (101B- 110B)

Treatment (dose, mg/kg, i.p	Maximal electroshock seizure test		
	Mean duration of tonic hindleg extension (THLE) ± SEM (s)	No. of animals recovered	Protection against mortality (%)
Control	09.39 ± 1.09	3/6	50.00
Phenytoin (20)	Absence of extension	6/6	100.00
B101 (100)	09.13 ± 0.42**	6/6	100.00
B102 (100)	12.09 ± 0.66*	3/6	50.00
B103 (100)	11.14 ± 0.43*	2/6	33.33
B104 (100)	09.86 ± 0.42*	3/6	50.00
B105 (100)	11.63 ± 0.33*	4/6	66.66
B106 (100)	11.97 ± 0.42*	2/6	33.33
B107 (100)	10.11 ± 0.41*	3/6	50.00
B108 (100)	01.09 ± 0.05**	6/6	100.00
B109 (100)	01.12 ± 0.07**	6/6	100.00
B110 (100)	12.32 ± 0.72*	1/6	16.66
The results are shown as the mean values and SEM. * $P<0.05$, ** $P < 0.01$ & *** $P<0.001$ when compared to respective control values by Student's t-test			

III. Result And Discussion:

IR, NMR and Mass spectroscopy of 101B-110B synthesized compounds Physicochemical and elemental analysis of all the 1, 5-benzothiazepine (101B-110B)areconfirmed (Table 2). The IR spectrum also showed reaction progress and completion. At the time of the experiment we have carried out the IR of reactant, reaction mixture and product. Preliminary analysis of IR confirmed the purity and the functional group of the final products. The IR spectrum also showed the reaction progress and the completion. At the time of experiment we have carried out the IR of reactant, reaction mixture and product. Preliminary analysis of IR confirmed the purity and the functional group of the final products. The IR of 101B-110B compound have observed the following functional groups namely C=C str, N=Nstr, C-H str, C-H bend, N-H str, Ar C-N str, O-H stretch, C-H str, O-C, -C-Cl, -C-F, C-Br, -N-Osym, -N-Oasymetc (**Figure 8.25** to **8.34**). The IR spectrum of compound all 10 synthesized compounds showed a broad band at 3040, 3200, 3250, 3100, 3430, 3350, 3210, 3250, 3050 and 3280 cm^{-1}respectively attributed to (OH) group, a characteristic N=Nstr band was assigned at 1575, 1570, 1567, 1560, 1567, 1560, 1666, 1660, 1650 and 1647 cm^{-1} were found to 101B to 110B respectively. 103B, 104B, 106B and 110B halogenated compounds have noted 750, 530, 510 and 501 cm^{-1} sharp peak respectively. Nitro containing compound (107B) was confirmed two peak of symmetry and asymmetry at 1255 and 1291 with strong and sharp edge respectively

Table No. 3: Physiochemical and Elemental Analysis of 101B-110B Compounds

Comp. Code	Molecular Formula	Mol. wt.	M.P. (^{0}C)	Elemental analysis Found (cald.)			% Yield	Rf Value
				C	H	N		
101B	$C_{21}H_{18}ArN_3O_2S$	416.40	256-260^{0}C	71.92	4.59	8.31	71.08	0.58
102B	$C_{22}H_{20}ArN_3O_2S$	430.42	254-256^{0}C	72.14	4.88	9.13	70.45	0.59
103B	$C_{21}H_{17}ArClN_3OS$	434.84	257-260^{0}C	69.01	4.09	8.93	62.25	0.61
104B	$C_{21}H_{17}ArFN_3OS$	418.39	220-222^{0}C	68.22	4.02	8.15	60.15	0.66
105B	$C_{21}H_{17}ArBrN_3OS$	479.29	242-246^{0}C	70.25	4.51	7.71	65.75	0.63
106B	$C_{21}H_{17}ArN_4O_3S$	445.39	232-236^{0}C	70.52	4.25	8.98	64.35	0.57
107B	$C_{23}H_{12}ArN_3OS$	428.45	228-230^{0}C	71.25	4.07	8.51	69.56	0.49
108B	$C_{21}H_{19}ArN_4OS$	415.41	224-226^{0}C	70.23	4.27	10.78	64.35	0.79
109B	$C_{22}H_{20}ArN_3OS$	414.42	224-226^{0}C	68.20	4.21	8.64	62.65	0.65
110B	$C_{21}H_{17}ArIN_3OS$	526.29	278-280^{0}C	71.25	3.99	8.45	67.25	0.49

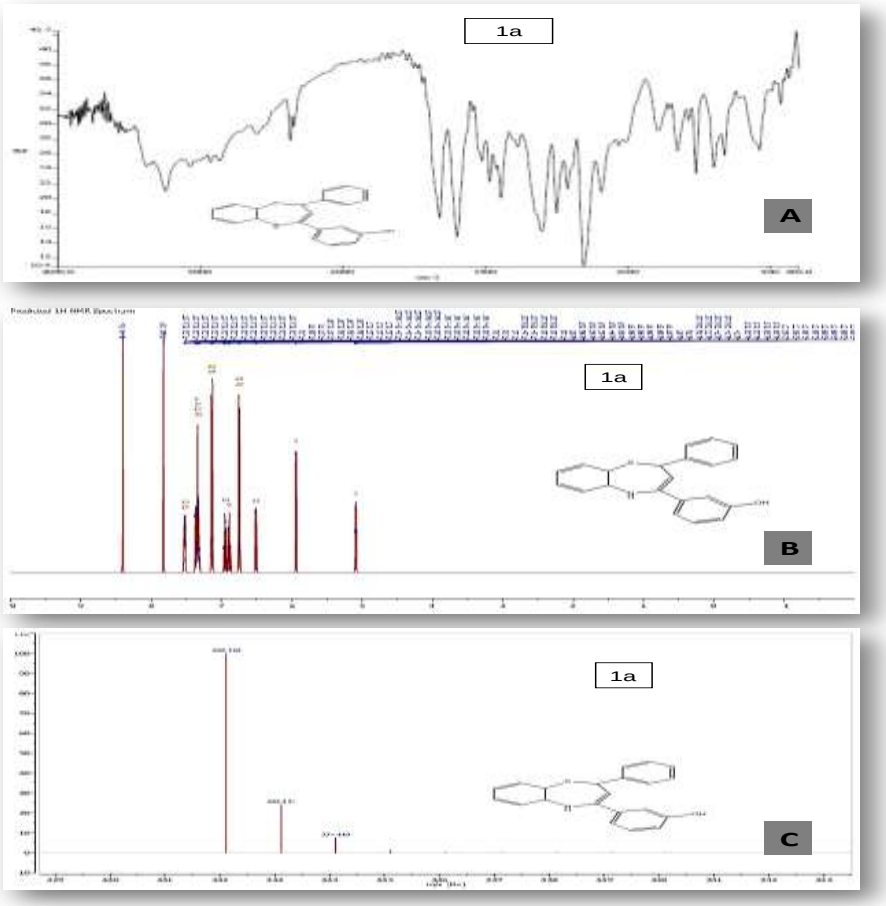

Figure No. 1: Characterization of 101B synthesized compound A) IR B) ^{1}H NMR C) Mass

^{1}H NMR were confirmed the number of hydrogen present in the 101B to 110B compound. The ^{1}H NMR noted the hydrogen namely thiazepine (2H), H-Ar ring, -NH, -OH, -CH_3 (3H) and NH_2 (2H). 101B to 110B compounds were noted the aromatic hydrogen in the range 6.3 to 7.5 ppm with their unique multipletpattern .Thiazepine ring hydrogen was observed in all compounds at 7.7-8.1 and 5.8-6.1 ppm singlet peak. The^{1}H-NMR spectrum of compound 102B and 109B shows signals at 3.8 and 1.5 ppm belongs to the one protons of (-CH_3) attached to the benzyl group respectively. Whereas 107B and 108B compound have –$NH_2$and NO_2 group were conformed with observed singlet 1H peak at 2.0 and 2.5 ppm respectively Mass spectroscopy was confirmed the molecular weight of compound 101B to 103B. The mass spectroscopy noted the fragmentation pattern of the selected synthesized compound. 101B compound was reported the main fragments at 334 with 100%, 257 with 77.03%, 241with 72.20% peak height. This class of compounds has formed a positive ion due to protonation and reported the base peak M+1. The fragmentation pattern was shown in **[Fig. 1]**

IV. Discussion:

The synthesized compounds from series (101B to 110B) 108B and 109Bhad shown significant activity against the tonic seizure with a decreased mean duration of tonic hindleg extension of 1.09 and 1.12respectively as compared to the other synthesized compounds. While evaluating the anticonvulsant activity, it was observed that compounds having an electron withdrawing group on benzothiazole had shown an increasein activity as a comparison to compounds having an electron releasing group. Taking into consideration the newly synthesized compounds of this step, it can be assumed that substitution with the electron withdrawing group on benzothiazole moiety at the 3rd positionof the quinazolineringisbeneficialforanticonvulsantactivity.Synthesized10analogueswere subjectedforIn-vivoanti-convulsantactivity.

Out of 10 analogues, Compound 108B and 109B Quoted above in table showed anticonvulsant activity as compared to standard Phenytoinsodium.

V. Conclusion:

A new series of benzothiazepines based anti-seizure derivatives were designed, synthesized and their activity was investigated by the MES model in mice. These synthesized derivatives displayed a notable protective activity in the utilized convulsing model. 108B and 109B derivatives showed significant anti-seizure activity in the MES model compared to the standard control.

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