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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME NOVEL BENZOTRIAZOLE DERIVATIVES

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ABSTRACT: The vast investigations on the derivatives of 1, 2, 3-benzotriazole explore wide applicability for tagging and delivering a number of other heterocyclic nuclei with benzotriazole. In the present work, several derivatives of 1-(substituted)-5- [(N-benzotriazolo-methyl)-1, 3, 4-thiadiazolyl]- imidazole-2-thione have been synthesized and are evaluated for their anticonvulsant activity. The anticonvulsant activities of the synthesized derivatives were assessed by the maximal electroshock (MES) method. Electric shock (50 mA for 0.2 sec) was delivered with the help of a corneal electrode to induce hind limb tonic extension. The synthesized derivatives X2, X3 and X6 exhibited significant anticonvulsant effect against MES-induced seizure model as an indication for compounds which are effective in grand mal epilepsy.

INTRODUCTION: 1, 2, 3-benzotriazoles were reported to have potential fungicidal [1] and antibacterial activity [2]. Similarly, 1, 3, 4-thiadiazole derivatives were also reported to possess fungicidal, herbicidal, bactericidal [3], pesticidal, insecticidal, antihistaminic, anti-amoebic [4], CNS depressant, antihypertensive, anticonvulsant, hypnotic, analgesic [5], anti-inflammatory [6] and agonist for 5-Ht receptor [7]. 4-thiazolidinone nucleus has also occupied a unique place in the field of medicinal chemistry due to its wide range of biological activities like antibacterial, anticancer [8], Respiratory, syncytial, virus Inhibitor [9], anticonvulsant [10], sciatic nerve blocking, local anaesthetic, inhibitors of human (CK2) protein kinase [11], hypnotic, fungicidal, cysticidal, anti-leukemic and antioxidant activity. In view of potential biological activities of benzotriazole, thiadiazole and imidazole an attempt was made to unite these nuclei together and synthesize some new derivatives of benzotriazole (X1-X6) to screen out some derivatives for significant anticonvulsant activity. The procedure of synthesis has been outlined in Scheme 1.

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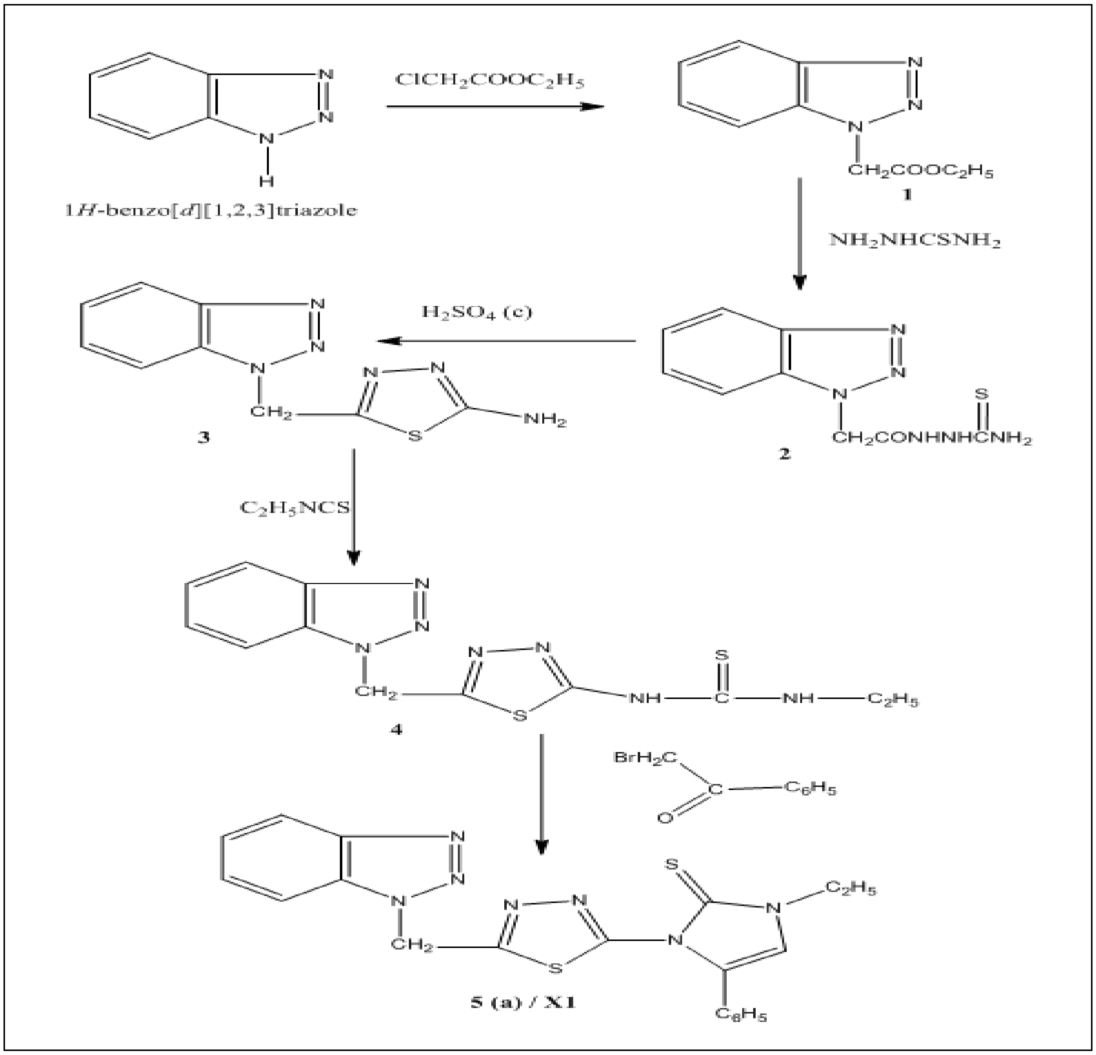
In India, dissemination of epilepsy was reported to be 5.5–7.9 per 1,000 persons which are around 1/18th of the total population of India [12]. The most common anticonvulsant drugs used for the treatments of epilepsy are phenytoin, valproate, carbamazepine, phenobarbital, primidone, and lamotrigine. The currently available drugs, if used judiciously and continuously, abolish seizures completely in 60%–80% of the patients and reduce their frequency in another 10%-20% of the patient. Despite their effectiveness, most of them produce many side effects like drowsiness, nausea, mental dullness, ataxia, teratogenesis, hematological changes, weight gain, paresthesia, hirsutism, congenital malformations and hypertrophy of gums. For these reasons, there is a need for developments of new anticonvulsant drugs to improve epilepsy control and reduce its harmful effects [13].



SCHEME 1: SYNTHESIS OF 1-(SUBSTITUTED)-5-[(N-BENZOTRIAZOLOMETHYL)-1, 3, 4-THIADIAZOLYL]-IMIDAZOLE-2-THIONE DERIVATIVES

MATERIALS AND METHODS: The chemicals and reagents used in this were of AR and LR grade. They were procured from CDH, Hi-Media, Merck, Sigma Aldrich, and Ranbaxy and the standard drug phenytoin were procured as a gift sample from Royal Research Center, Navsari, Gujarat, The melting points of the synthesized compounds were determined by using Thiel's melting point apparatus (open capillary tube method) and all the compounds gave sharp melting points and are uncorrected. The purity of the compounds was ascertained by thin-layer chromatography using silica gel-G as stationary phase and appropriate mixtures of the following solvents as mobile phase: n-butanol, glacial acetic acid and water. The spots resolved were visualized using the iodine chamber. The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrophotometer (Perkin Elimer BX-II) in the range of 400-4000 using diffuse reflectance system and values of peaks (υ) are reported in cm-1. 1H NMR spectra were recorded on Bruker Av- II 400 MHz NMR spectrometer and chemical shifts (δ) are reported in ppm downfield from internal reference Tetramethylsilane (TMS). Mass spectra were recorded on Shimadzu LC-MS model 2010A.

Elemental analysis of the newly synthesized compounds was carried out using Euro - E 3000 series elemental analyzer. 1-(substituted)-5-[(N-benzotriazolomethyl)-1, 3, 4-thiadiazolyl] imidazole-2-thione were prepared as per the method described in the literature [14-16]. The synthetic procedure involved the following six steps as stated below.

Experimental Section:

Ethyl N1-benzotriazoloacetate, 1: A mixture of benzotriazole (0.1 mole), ethyl chloroacetate (0.1 mole) and K_2CO_3 (3 g) in acetone (60 ml) was stirred for 8 h. The solvent was then removed under reduced pressure and the solid mass obtained are subjected to extraction with petroleum ether. The solvent was removed under reduced pressure to yield needle shaped brown crystals of compound 1; yield 90%, m.p. 39-40 ºC. Elemental analysis: Found C, 58.6%; H, 5.4%; N, 20.4% Calc. for $C_{10}H_{11}N_3O_2$; C, 58.5%; H, 5.4%; N, 20.5%; IR: 1740 (C=O); 1232, 1462 ($N-CH_2$); 1HNMR (D_2O): 3.75 (s, 2H, $N-CH_2$), 4.25 (q, 2H, $COOCH_2$), 1.30 (t, 3H, CH_3) and 6.90-7.91 (m, 4H, ArH); MS: m/z 205 (M+).

1-(N1-benzotriazoloacetyl)-thiosemicarbazide, 2: Compound 1 (0.07 mole) and thiosemicarbazide (0.07 mole) in ethanol (50 ml) was stirred for 5 h and then refluxed on steam bath for 2 h. The excess of solvent was removed under reduced pressure and recrystallised from chloroform-hexane (2:1 v/v) to yield pale yellow crystals of product 2; yield 86%, m.p. 103-104 ºC. Elemental analysis: Found C, 43.3%; H, 4.1%; N, 33.5% Calc. for $C_9H_{10}N_6OS$; C, 43.2%; H, 4.1%; N, 33.6%; IR: 3340 ($-NH_2$); 1670 (-CONH-); 1130 (C=S); 1HNMR ($CDCl_3$): 3.80 (s, 2H, $N-CH_2$), 8.30 (m, 4H, NH-NH-CS-NH_2), and 6.45-7.21 (m, 4H, ArH); MS: m/z 250 (M^+)

2-amino-5-(N1- benzotriazolomethyl)- 1, 3, 4 – thiadiazole, 3: The thiosemicarbazide 2 (0.05 mole) together with conc. H_2SO_4 (10 ml) was kept overnight at room temperature, neutralized with ammonia and extracted with ether. The ether was distilled off and the product so obtained was crystallised from 80% ethanol to get yellowish leaflet of compound 3; yield 85%, m.p. 120-121 ºC (d). Elemental analysis: Found C, 46.5%; H, 3.4%; N, 36.0% Calc. for $C_9H_8N_6S$; C, 46.6%; H, 3.4%; N, 36.1%; IR: 3350 ($-NH_2$); 1600 (-C=N-); 690 (C-S-C); 1HNMR ($CDCl_3$): 3.80 (s, 2H, $N-CH_2$), 4.40 (s, 2H, $-NH_2$), and 6.95-7.81 (m, 4H, ArH); MS: m/z 232 (M^+).

1-(5-((1H-benzo[d][1,2,3]triazole-1-yl)methyl)-1, 3, 4-thiadiazole-2-yl) -3-ethyl thiourea, 4: Compound 3 (20 m mole) and ethyl isothiocyanate (20 m mole) in dioxane (5 ml) was heated under reflux for 6 h, concentrated and the residue was recrystallised from dioxane to give 4; yield 84%, m.p. 123-124 ºC. Elemental analysis: Found C, 45.10%; H, 4.1%; N, 30.73% Calc. for $C_{12}H_{13}N_7S_2$; C, 45.13%; H, 4.10%; N, 30.70%; IR: 3210, 3300 (-NH-); 1610 (-C=N-); 1155 (C=S); 1HNMR ($CDCl_3$): 4.90 (s, 2H, $N-CH_2$), 8.4, 8.2 (2s, 2H, 2NH), 7.25-8.0 (m, 4H, ArH), 4.43 (q, 2H, $-CH_2-$) and 1.29 (t, 3H, $-CH_3$); MS: m/z 319 (M^+)

3-(-5-((1H-benzo[d][1, 2, 3]triazole-1-yl)methyl)-1, 3, 4-thiadiazole-2-yl)-1-ethyl -4-phenyl-1,3-dihydro -2H-imidazole-2-thione, 5 (a) / X1: To a stirred solution of compound 4 (10 m mole) and phenacyl bromide, in glacial acetic acid (50 ml) was heated under reflux for 12 h. The obtained solid was recrystallised from acetic acid to give 5 (a); yield 72%, m.p. 130-131 ºC. Elemental analysis: Found C, 57.21%; H, 4.0%; N, 23.33% Calc. for $C_{20}H_{17}N_7S_2$; C, 57.26%; H, 4.0%; N, 23.37%; IR: 3100 (CH-Ar); 2930 (CH-aliphatic); 1320 (N=N); 1HNMR ($CDCl_3$): 4.90 (s, 2H, N-CH_2), 6.8 (s, 1H,=CH), 7.36-8.0 (m, 9H, ArH), 4.21 (q, 2H, $-CH_2-$) and 1.26 (t, 3H, $-CH_3$); MS: m/z 419 (M^+) Other compounds 5(b-f) were synthesized similarly using various isothiocyanate in place of ethyl isothiocyanate. Characterization data are present in **Table 1** and **Table 3**.

Determination of Anticonvulsant Activity Methods: Preparation of DMF (Dimethyl-formamide) suspension of synthesized compounds: All synthesized compounds were dissolved in DMF and used as a suspension in physiological saline containing 2 drops of tween 80 and produce a final conc. of 1.0 mg/ml. The standard drug used for this study was phenytoin. Drugs were administered intraperitoneally (i.p.) 30 min before applying electric shock.

Animals: Swiss-albino mice of either sex weighing 25-35 g obtained from our animal house. The animals were housed at 24 ± 2 ºC with 12:12 h light and dark cycle with free access to water and food. The animals were acclimatized for a period of 7 days before the study.

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Institute of Pharmacy, Bundelkhand University, Jhansi (U.P.) India. The animals were used according to the CPCSEA guidelines for the use and care of experimental animals.

Experimental Design: On the day of the experiment, the animals were divided randomly into control, standard and experimental groups (n = 6) with each having 6 animals of either sex and were fasted overnight with water *ad libitum*. Group 1 received the vehicle, normal saline (10 ml/kg, orally) and served as the control group, group 2 received the standard drug Phenytoin (25 mg/kg, i.p.) and group 3 to 8 received DMF suspension of synthesized compounds X1 to X6 **Table 2**. Drugs were administered to the animals 30 min before applying electric shock.

Evaluation of Anticonvulsant Activity:

Maximal Electro Shock (MES) Induced Seizures: MES model was used for the evaluation of the anticonvulsant effect of synthesized derivatives (X1 to X6). Electro Convulsiometer (Model No EC-02) was used for delivering an electric shock (50 mA for 0.2 sec) with the help of a corneal electrode to induce hind limb tonic extension (HLTE) in mice [17-18]. The total duration of HLTE, onset of convulsions, and incidence of mortality in all groups of animals were recorded. The animals which did not exhibit HLTE were considered protected.

Statistical Analysis: All results were expressed as mean ± standard error means (SEM) and analyzed by one-way ANOVA. Post-hoc comparisons were performed by applying Dunnet’s test. P <0.05 was considered statistically significant.

RESULTS:

TABLE 1: CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS (5A TO 5F)

Compound (X)	R	R’	Yield (%)	m.p. (^{0}C)	Mol. Formula*
X1 : (5a)	$-C_2H_5$	$-C_6H_5$	70	130-131	$C_{20}H_{17}N_7S_2$
X2 : (5b)	$-CH_2CH_2CH_3$	$-C_6H_5$	87	104-105	$C_{21}H_{19}N_7S_2$
X3 : (5c)	$-CH(CH_3)_2$	$-C_6H_5$	80	152-153	$C_{21}H_{19}N_7S_2$
X4 : (5d)	$-CH_2(CH_2)_2CH_3$	$-C_6H_5$	85	166-167	$C_{22}H_{21}N_7S_2$
X5 : (5e)	$-C(CH_3)_3$	$-C_6H_5$	23	148-149	$C_{22}H_{21}N_7S_2$
X6 : (5f)	$-C_6H_5$	$-C_6H_5$	65	132-133	$C_{24}H_{17}N_7S_2$

TABLE 2: EXPERIMENTAL DESIGN

Groups	Treatment	Dose
I	Normal Saline	10 ml/kg, orally
II	Phenytoin	25 mg/kg, intraperitoneally
III	Compound X_1	50 mg/kg, orally
IV	Compound X_2	50 mg/kg, orally
V	Compound X_3	50 mg/kg, orally
VI	Compound X_4	50 mg/kg, orally
VII	Compound X_5	50 mg/kg, orally

TABLE 3: SPECTRAL DATA OF 2-(SUBSTITUTED)-5- [(N-BENZOTRIAZOLOMETHYL)-1, 3, 4-THIADIAZOLYL]-IMIDAZOLE-2- THIONE DERIVATIVES

A. INTERPRETATION OF IR SPECTRA:

Type	Associated Vibration	Frequency (in cm^{-1})
Imidazole-2-thione ring	>C=S str.	1250, 1560 (interaction between C-S and C-N)
	C-N str.	1333
	C=N str.	1670
Thiadiazole ring	N-N str.	1626.7
	C=N str.	1670
	C-S str.	641
Benzotriazole ring	C-N str.	1271.39
	C=C str.	1536.15
	Ar-H str.	3044.19
	N=N str.	1382

B. INTERPRETATION OF 1H-NMR SPECTRA:

Signal position	Relative no. of protons	Inference
7.68-8.0	9H	Ar-H
4.98	2H	$-CH_2$ link between benzotriazole and thiadiazole
6.8	1H	-CH of imidazole
4.2	2H	$>N-CH_2-$ of imidazole
1.26	3H	$>N-CH_2-CH_3$ of imidazole

TABLE 4: MES INDUCED SEIZURES IN MICE

Groups	Number of animals convulsed	Number of animals used	Animals protected against seizures (%)	Duration of HLTE (in seconds)
Control (10 ml / kg, orally)	6	6	0	15.02 ± 0.10
Phenytoin (25 mg/kg, i.p.)	0	6	100	4.00 ± 0.07**
X_1 (50 mg/kg, orally)	5	6	16	12.96 ± 0.17**
X_2 (50 mg/kg, orally)	3	6	50	7.34 ± 0.16**
X_3 (50 mg/kg, orally)	3	6	50	7.34 ± 0.16**
X_4 (50 mg/kg, orally)	5	6	16	12.90 ± 0.17**
X_5 (50 mg/kg, orally)	5	6	16	11.94 ± 0.17**
X_6 (50 mg/kg, orally)	1	6	83	5.56 ± 0.13**

Values are expressed as Mean ± S.E.M., $*p < 0.05$, $**p < 0.01$ Compared with control. HLTE: hind limb tonic extension.

MES-Induced Seizures: Treatment with the derivatives of synthesized compounds X2, X3 and X6 showed significant protection of animals in MES-induced convulsion exhibited protection against HLTE-induced electric shock with maximum protection (83 %) by X6. The compounds X2 and X3 also showed a significant reduction in latency time of convulsion when compared with control, wherein the maximum reduction in tonic seizures duration was exhibited with X6 (83%). Standard drug phenytoin also exhibited protection (100%) against HLTE **Table 4**.

DISCUSSION: The aim of the present study was to investigate the protective effects of synthesized compounds (X1 to X6) on experimental models of convulsions. The MES-induced seizure model is used primarily as an indication for compounds that are effective in grand mal epilepsy [19-20]. The present study revealed that the compounds X2, X3 and X6 attenuated the MES-induced tonic seizures indicating that the compounds possess anticonvulsant effects. In the MES induced convulsions, the synthesized compounds X2, X3 and X6 significantly reduced the latency and showed good protection. The effect was comparable with the standard anticonvulsant drug, phenytoin in their respective model of convulsion.

It is difficult to elucidate the exact mechanism responsible for the anticonvulsant action of these synthesized compounds. Most of the anticonvulsant drugs like phenytoin inhibit voltage-dependent Na^+ channels and prevent tonic extension in MES-induced convulsion [21-24]. Hence, it is possible that synthesized compounds X2, X3 and X6 may have an influence on voltage-gated Na^+ channels. It was observed that the alkyl group in the synthesized derivatives at N-1 position of imidazolo-thione ring must contain a chain of three carbons (n-propyl or isopropyl) as in X2 and X3 respectively, to produce anticonvulsant activity while replacement of open chain with an aromatic substituent, at this place (X6), potentiate anticonvulsant property.

CONCLUSION: The derivatives of benzotriazole (X1 to X6) were synthesized with the objective to develop better anticonvulsant agents with a maximum percentage of yield and optimal anticonvulsant activity. The results of the present study suggest that the synthesized compounds X2, X3 and X6 have produced a significant ($P < 0.01$) delay in onset of seizures in the MES model on oral administration (50 mg/kg, orally) which is comparable to Phenytoin (25 mg/kg, i.p.) and showed good protection against MES induced seizures (50%, 50% and 83%).

Further, investigations with appropriate structural modification of title compound as well as dose-dependent study may result in therapeutically useful products. Further studies are required to elucidate the possible mechanism of anxiolytic activity and its usefulness in human beings.

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