ASIAN JOURNAL OF BIOMEDICAL & PHARMACEUTICAL SCIENCES

e-ISSN: 2249-622X

RESEARCH ARTICLE

Design, Synthesis and Anticonvulsant Screening of Newer Benzothiazole-Semicarbazones

Nadeem Siddiqui[1]*, Arpana Rana[1], Suroor A. Khan[1], Ozair Alam[1], Waquar Ahsan[2] , Ruhi Ali[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hamdard University, New Delhi 110 062, India

[2]Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University, P. Box No. 114, Jazan, KSA

Article details:
Received:
15th April 2012
Received in revised form:
27 July 2012
Accepted:
28th July 2012
Available online:
10th Aug 2012

OPEN ACCESS
Online ISSN 2249–622X
http://www.jbiopharm.com

ABSTRACT

Series of 3, 4-disubstituted benzaldehyde-*N*-(6-substituted-1,3-benzothiazol-2-yl)semicarbazones (4a-t) were synthesized by condensation of the *N*-(substituted-1,3-benzothiazol-2-yl)hydrazinecarboxamides with aromatic aldehydes and screened for their anticonvulsant activity using the maximal electroshock seizure (MES) method. The selected compounds were checked for the neurotoxicity by rotorod test method. A distance mapping and matching of the synthesized compounds with the help of given model was also checked. Compounds 4g, 4i, 4k, 4l, 4m, and 4p showed 100% protection in the MES method at the dose level of 30 mg/kg.

KEYWORDS: Benzothiazole; Semicarbazones; Anticonvulsant; Neurotoxicity; Distance mapping

INTRODUCTION

Antiepileptic drug search has come a long way, particularly of the last two decades. With increased understanding of the pathophysiology of epilepsy, the conventional approaches have, to a great extent, been replaced by mechanism based approaches. Several new drugs [1] have been licensed and many others are in various stages of development, e.g. remacemide, lamotrigine, flunarizine, loreclezole and levetiracetam. Although 70-80% of all epileptic patients are significantly benefited by currently available drugs but these often do so at the expense of adverse effects [2]. Drug dose related toxicity and other side effects at times has become a major limitation in their clinical use [3]. Promising new agents may be developing by modification of existing agents or by development of a new class of drugs. In our previous research we have reported [4-7] several benzfused five membered heterocyclic compounds including the benzothiazole moiety and these have shown considerable anticonvulsant activity. The last decade has witnessed the emergence of semicarbazones as potential anticonvulsant agents [8-9].

The aryl semicarbazones, with reference [5, 10] to the earlier reported work believed to interact at locations on the specific binding site designed as a lipophilic aryl ring (or hydrophobic ring), a distal aryl ring, a hydrogen domain (HBD). Furthermore, Pandeya et al [11] have proposed a new pharmacophore model with four binding sites essential for anticonvulsant activity. The MES test is a proven method of generalized tonic-clonic seizures and identifies clinical candidates that prevent seizure spread [12, 13]. The presence of the electron rich atom/group attached at para position of the aryl ring showed increased potency in the MES screen [14-16]. The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the Van der Waal's bonding at the binding site and to increase potency have also been reported [17, 18]. The present work further gives impetus to these observations. In the conformational analysis of the older generation clinically active anticonvulsant drugs such as Phenytoin, Carbamazepine, Lamotrigene, Rufinamide, Remacemide and Phenobarbitone on the basis of molecular dynamics distance estimations, a molecular model was suggested [19, 20]. According to which an electron donor (D) in a distance range of 3.2-5.1 Å to an

*Corresponding author email: nadeems_03@yahoo.co.in

aryl ring or any other hydrophobic unit (R) and of 3.9-5.5 Å to hydrogen bonding domain (HBD). With this background, the present study was set with the aim to prepare the novel agents, which should suppress seizures and have an acceptable limit of unwanted side effects. Our work also highlights the distance mapping and matching of the synthesized compounds with the help of the given model.

MATERIALS AND METHODS:

CHEMISTRY:

The melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. Elemental analysis (C, H, N) performed on the CHNS Elimentor (Analysen systime, GmbH) Germany Vario EL III. FTIR spectra were recorded in KBr pellets on a Jasco FT/IR 410 spectrometer. The ^{1}H NMR spectra were taken on a Bruker model dpx 300 NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) as an internal standard. Splitting patterns are designed as follows: s, singlet; d-doublet; t-triplet; q-quartet; m-multiplet. Mass spectra were measured on a Bruker ion trap (Esquire 3000) mass spectrometer from Regional Research Laboratory (RRL) Jammu, India. The homogeneity of the compounds was checked by TLC on silica gel G by using Toluene: Ethyl acetate: Formic acid (5:4:1) as solvent system. A logarithmic function of R_f value was also calculated; R_m = log ($1/R_f$-1). All the used reagents are commercially available from s.d. fine and Merck. For the molecular mechanics calculations, the ACD/Chemsketch/3-D viewer Freeware version program was used for employing the CHARMM force field [26].

General procedure for the synthesis of 3,4-disubstituted benzaldehyde-*N*-(6-substituted-1,3-benzothiazol-2-yl)semicarbazones (4a-t):

2-Amino-6-substituted benzothiazoles **(1a-e)**

2-Amino-6-substituted benzothiazoles were prepared from the respective aryl amines. A mixture of aryl aniline (0.01 mol) and potassium thiocyanate (0.01 mol) in glacial acetic acid (10%) was cooled and stirred. To this mixture bromine (0.01 mol) was added dropwise at such a rate to keep the rate below 10 °C throughout the addition. Stirring was continued for additional 3 h and the separated hydrochloride salt was filtered, washed with acetic acid and dried. The separated salt was dissolved in hot water and neutralised with aqueous ammonia solution (25%), filtered, washed with water and dried, recrystallized with benzene.

1-(6-Substituted-1,3-benothiazol-2-yl)ureas **(2a-e)**

Compounds (2a-e) were prepared by adding solution of sodium cyanate (0.01 mol) in water (10 mL) to glacial acetic acid (20 mL). This solution was heated with 2-amino-6-substituted benzothiazoles (1a-e, 0.01 mol) in alcohol (30 mL), until the contents of mixture become turbid and volume remained half to the original volume. The contents were then added to ice cold water and the solid obtained was filtered off and dried.

N-(6-substituted-1,3-benzothiazol-2-yl)hydrazinecarboxam -ides (3a-e)

To the warm hydrazine hydrate solution (0.01 mol), a solution of compounds (2a-e, 0.01 mol) in ethanol (30 mL) was added. After the addition of sodium hydroxide (2 g), the reaction mixture refluxed for 4 h. The refluxed reaction mixture poured into crushed ice and solid obtained filtered off and dried.

3,4-Disubstituted benzaldehyde-N-(6-substituted-1,3-benzothiazol-2-yl)semicarbazones **(4a-t)**

Compounds (4a-t) were prepared by refluxing the solution of compounds (3a-e, 0.01 mol) in glacial acetic acid (5 mL) and ethanol (10 mL) with respective aromatic aldehydes (0.12 mol) for 5 h. The refluxed solution was cooled to room temperature and kept overnight. The solid was collected out, washed with methanol, dried, and purified by recrystallization with ethanol.

The spectral data of all the synthesized compound are shown in Table -1.

PHARMACOLOGY:

Maximal Electroshock Seizure test (MES): The test compounds were suspended in Tween 80 (1%). Each compound was administered as an i.p. injection at dose level of 30 mg/kg and the anticonvulsant activity was assessed after 0.5 h and 4 h intervals of administration. Maximal electroshock seizures were elicited in mice by delivering a 60 Hz, 50 mA electrical stimuli for 0.2 s via ear clip electrodes. The maximal seizure typically consists of a short period of tonic extension of the hind limbs and a final clonic episode. Blockade of the hind limbs tonic extensor component due to the drug treatment is taken as the end point. *Rotorod test:* The mice were trained to stay on an accelerating rotorod that rotates at 10 revolutions/min and is 3.2 cm in diameter. Trained mice were given i.p. injection of the test compounds in dose of 30 mg/kg. Unimpaired mice can easily remain on a rod rotating at this speed. Neurological deficit e.g. ataxia, sedation, hyperexcitability

is indicated by the inability of the mice to maintain equilibrium on the rod for at least 1 min in each of three concurrent trails.

RESULTS AND DISCUSSION:

CHEMISTRY:

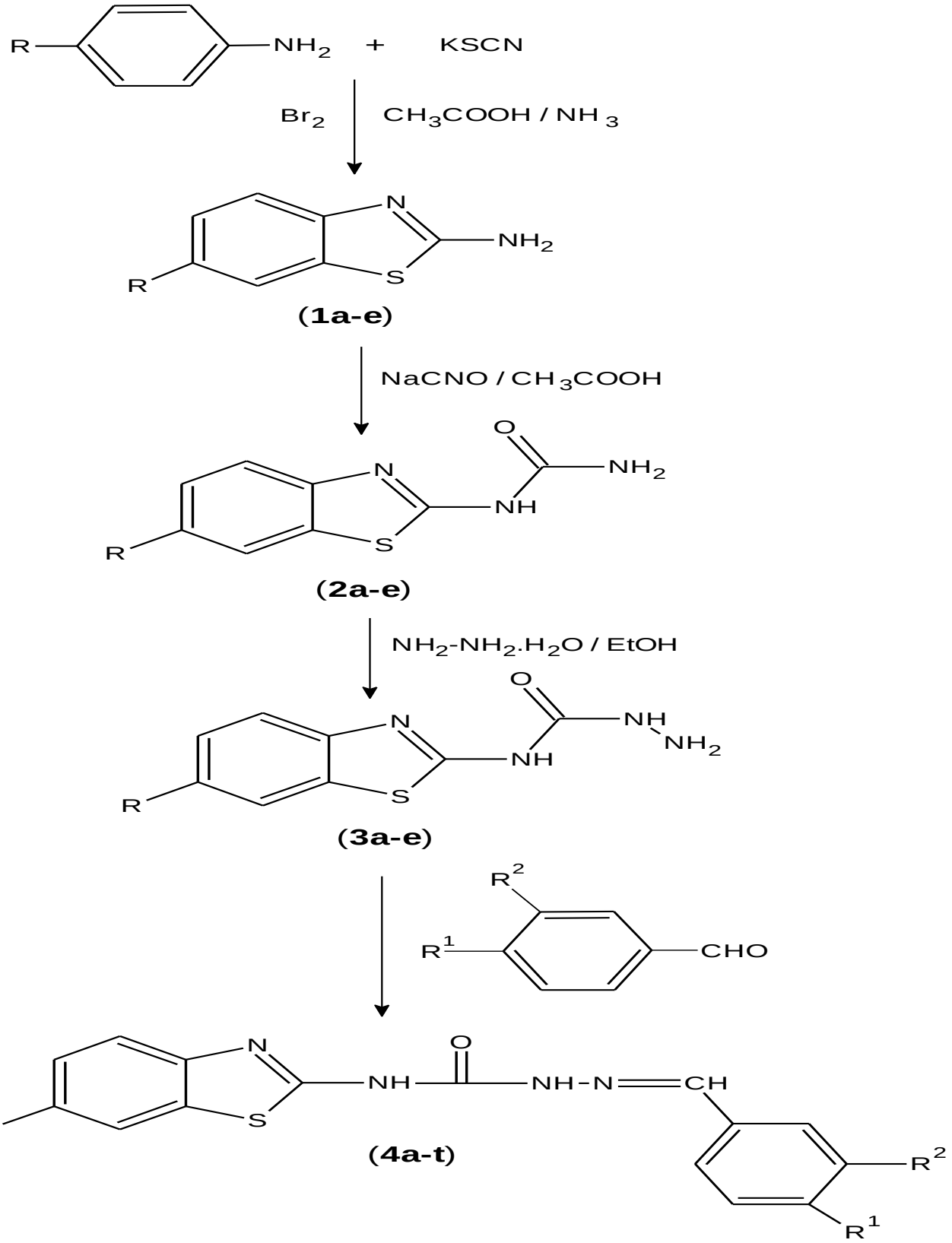
3,4-disubstituted benzaldehyde-*N*-(6-substituted-1,3-benzothiazol-2-yl)semicarbazones (4a-t) were prepared using a multi-step synthetic route. Starting material 2-amino-6-substituted benzothiazoles (1a-e) obtained by reacting aryl amines with potassium thiocyanate in a satisfactory yield according to the procedures reported earlier [21, 22]. The final product (4a-t) obtained by condensing the hydrazine carboxamides (3a-e) with the appropriate aldehydes (Scheme 1). All the synthesized compounds were soluble in methanol, chloroform, and ethyl alcohol but insoluble in benzene and water. The synthesized compounds were characterized by elemental analysis, FTIR, ^{1}H NMR and mass spectra. Elemental and spectral data were in good agreement with the composition of synthesized compounds. Their FTIR spectrum revealed two bands at 3210-3490 and 1520-1583 cm^{-1} due to the NH and C=N respectively. The ^{1}H NMR showed a singlet at 5.80-5.90 ppm due to NH_2 protons (D_2O exchangeable). The benzothiazol-2-yl-ureas (2a-e) were prepared by treating required benzothiazoles (1a-e) with sodium cyanate in presence of glacial acetic acid. The FT-IR bands at 1601-1656 cm^{-1} and 1238-1299 cm^{-1} were assigned to the amide C=O and C-N groups respectively. The benzothiazol-2-yl-ureas (2a-e) were refluxed with hydrazine hydrate to yield hydrazine carboxamides (3a-e). A band at the 936-1127 cm^{-1} confirms the N-N group present. The ^{1}H NMR of (3a-e) showed three singlets at 5.56-5.90, 7.97-12.36 and 9.07-12.71 ppm due to NH_2, NHC=O and NHN protons respectively and all were D_2O exchangeable.

PHARMACOLOGY:

The compounds were tested for anticonvulsant activity by their ability to suppress experimentally induced convulsions in laboratory animals. The test used was the maximal electroshock seizures test (MES), related to electrical induction [23, 24]. The Rotorod test method used to determine the possible neurotoxic effects [25]. Swiss albino mice (25-30 g) of either sex were used as experimental animals. The animals housed in cages, under standard laboratory conditions, at an ambient temperature of 25 $\pm$ 2 °C, food and water were withdrawn 24 h prior to the experiment. Anticonvulsant activity of the compounds evaluated as percentage protection against seizures induced by the MES test method, at the dose level of 30 mg/kg and the results are presented in Table 2. Phenytoin was used as standard for comparison at the same dose as of test compounds. The results from the maximal electroshock model (MES) evaluation are basically equivalent to grand mal seizures in humans. Compounds 4g, 4i, 4k, 4l, 4m and 4p were found to be 100% effective in anti-MES activity, showing their ability to prevent seizure by blockade of neuronal voltage-dependent Na^+ channels. Whereas compounds 4f, 4j and 4r showed 83% protection against the seizures in the MES model without producing any sign of neurotoxicity. The rest of the compounds of the series showed 50-66% protection except the compound 4t, which was devoid of anticonvulsant activity in the MES test. All the compounds were evaluated for the neurotoxicity at the 30 mg/kg dose level; none of the compound had shown the sign of activity.

DISTANCE MAPPING:

Further the present work, involves the comparison of the structures for molecular modeling of well known and structurally different compounds and the synthesized compounds. It is tempting to compare the structure of the aryl semicarbazones and other molecules with anticonvulsant activity to find out the structural elements essential for action. The compounds selected for this comparison have at least one aryl (R) hydrophobic domain, one electron donor (D) and a hydrogen bond acceptor/donor unit (HBD). In an initial study, calculations on the basis of molecular mechanics, with the force field based on CHARMM parameterization were performed to obtain an overview on their minimum conformation for bioactivity, Table 3 shows the distance between the various groups postulated as essential for anticonvulsant action. The synthesized aryl semicarbazones were examined to check whether they reflect the conditions of the derived pharmacophore model. Analyses of the distance relationship showed that synthesized compounds (4a-t) fulfil the essential demands of pharmacophore when compared with other known anticonvulsant drugs. In case of the synthesized aryl semicarbazones the distance R-D is 8.3 Å, which in conformity with the active drugs with distance ranging from 3.9-9.8 Å.



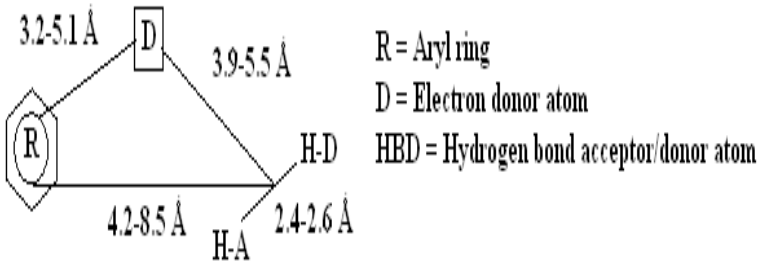
Scheme 1: Synthetic route of the titled compounds (4a-t)

Compd. No.	Yield (%)/Melting pt. (°C)	R_f (R_m)	Elemental analyses Calcd./found	Spectral Analyses
4a	60/200	0.88/-0.86	Cacld: C 54.52, H 3.39, N 17.01; found: C 54.46, H 3.35, N 16.94	IR: ν_{max} (cm^{-1}) 3220, 2930, 1607, 1567, 1263, 936, 805; ^{1}H NMR (DMSO-d_6): (δ, ppm) 7.22-7.77 (m, 8H, Ar-H), 7.93 (s, 1H, CH-Ar), 8.13 (s, 1H, NHC=O, D_2O exchangeable), 12.36 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 183.4, 167.1, 155.6, 138.1-126.4; Mass (EI): m/z: 330 (M^+)
4b	65/117	0.74/-0.45	Cacld: C 52.01, H 3.23, N 16.22; found: C 51.95, H 3.19, N 16.15	IR: ν_{max} (cm^{-1}) 3458, 3130, 3270, 2965, 1630, 1534, 1272, 1093, 811; ^{1}H NMR (DMSO-d_6): (δ, ppm) 6.82-7.59 (m, 7H, Ar-H), 7.77 (s, 1H, CH-Ar), 9.78 (s, 1H, NHC=O, D_2O exchangeable), 9.93 (bs, 1H, NHN=, D_2O exchangeable), 10.61 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 181.6, 166.7, 161.4, 155.3, 135.2-127.3; Mass (EI): m/z: 346 (M^+)
4c	58/119	0.70/-0.36	Cacld: C 51.05, H 3.52, N 14.93; found: C 50.99, H 3.47, N 14.86	IR: ν_{max} (cm^{-1}) 3468, 3133, 3290, 2933, 1626, 1510, 1275, 1245, 1010, 811; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.77 (s, 3H, OCH_3), 6.79-7.53 (m, 6H, Ar-H), 7.71 (s,1H, CH-Ar), 9.48 (s, 1H, NHC=O, D_2O exchangeable), 9.71 (bs, 1H, NHN=, D_2O exchangeable), 10.21 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 182.3, 166.4, 160.8, 154.6, 136.3-126.6, 58.4; Mass (EI): m/z: 376 (M^+)
4d	62/126	0.82/-0.65	Cacld: C 52.30, H 3.90, N 14.93; found: C 52.24, H 3.86, N 14.33	IR: ν_{max} (cm^{-1}) 3422, 2959, 1631, 1510, 1266, 1250, 1020, 809; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.87 (s, 6H, $(OCH_3)_2$), 7.16-7.53 (m, 6H, Ar-H), 7.76 (s,1H, CH-Ar), 9.48 (s, 1H, NHC=O, D_2O exchangeable), 10.32 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 179.8, 163.8, 161.7, 148.1-121.4, 57.6; Mass (EI): m/z: 390 (M^+)
4e	70/235	0.76/-0.50	Cacld: C 57.37, H 3.57, N 17.88; found: C 57.31, H 3.52, N 17.82	IR: ν_{max} (cm^{-1}) 3490, 2924, 1635, 1510, 1255, 1190,1018; ^{1}H NMR (DMSO-d_6): (δ, ppm), 6.81-7.52 (m, 8H, Ar-H), 7.93 (s, 1H, CH-Ar), 8.90 (s, 1H, NHC=O, D_2O exchangeable), 10.45 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 188.6, 168.4, 164.3, 158.5, 133.6-122.6; Mass (EI): m/z: 314 (M^+)
4f	68/215	0.81/-0.62	Cacld: C 54.60, H 3.39, N 17.02; found: C 54.53, H 3.35, N 16.96	IR: ν_{max} (cm^{-1}) 3500, 3310, 2932, 1611, 1512, 1257, 1166, 1096; ^{1}H NMR (DMSO-d_6): (δ, ppm) 6.81-7.53 (m, 7H, Ar-H), 8.01 (s, 1H, CH-Ar), 9.90 (s, 1H, NHC=O, D_2O exchangeable), 10.09 (bs, 1H, NHN=, D_2O exchangeable), 12.09 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 179.1, 163.9, 161.2, 160.5, 156.8, 149.3-119.8; Mass (EI): m/z: 330 (M^+)
4g	60/190	0.80/-0.60	Cacld: C 53.38, H 3.68, N 15.61; found: C 53.32, H 3.63, N 15.54	IR: ν_{max} (cm^{-1}) 3486, 3210, 2923, 1627, 1511, 1272, 1255, 1113, 1032; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.83 (s, 3H, OCH_3), 6.81-7.43 (m, 6H, Ar-H), 7.73 (s,1H, CH-Ar), 7.99 (s, 1H, NHC=O, D_2O exchangeable), 9.51 (bs, 1H, NHN=, D_2O exchangeable), 12.17 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 178.6, 161.4, 158.6, 156.1, 152.4, 150.3-122.3, 59.4; Mass (EI): m/z: 360 (M^+)

4h	72/160	0.85/-0.75	Cacld: C 54.60, H 4.07, N 15.03; found: C 54.53, H 4.03, N 14.96	IR: ν_{max} (cm^{-1}) 3100, 2923, 1623, 1510, 1259, 1238, 1140, 1017; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.82 (s, 6H, $(OCH_3)_2$), 7.06-7.39 (m, 6H, Ar-H), 7.48 (s,1H, CH-Ar), 8.64 (s, 1H, NHC=O, D_2O exchangeable), 9.21 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 183.5, 166.3, 160.5, 156.1, 148.5-127.3, 56.2; Mass (EI): m/z: 330 (M^+)
4i	70/223	0.72/-0.41	Cacld: C 52.85, H 3.28, N 20.57; found: C 52.78, H 3.24, N 20.51	IR: ν_{max} (cm^{-1}) 3470, 2924, 1654, 1533, 1326, 1299, 1122; ^{1}H NMR (DMSO-d_6): (δ, ppm) 7.40-8.12 (m, 8H, Ar-H), 8.25 (s,1H, CH-Ar), 8.67 (s, 1H, NHC=O, D_2O exchangeable), 8.69 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 181.3, 165.3, 155.7, 151.6, 141.1-124.4; Mass (EI): m/z: 341 (M^+)
4j	55/221	0.73/-0.43	Cacld: C 50.48, H 3.14, N 19.64; found: C 50.41, H 3.10, N 19.59	IR: ν_{max} (cm^{-1}) 3452, 3300, 2900, 1608, 1514, 1329, 1286, 1125; ^{1}H NMR (DMSO-d_6): (δ, ppm) 6.84-8.18 (m, 7H, Ar-H), 8.10 (s, 1H, CH-Ar), 8.78 (s, 1H, NHC=O, D_2O exchangeable), 10.01 (bs, 1H, NHN=, D_2O exchangeable), 10.08 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 178.6, 167.2, 159.3, 157.2, 149.4, 133.8-123.1; Mass (EI): m/z: 357 (M^+)
4k	62/220	0.78/-0.54	Cacld: C 49.68, H 3.42, N 18.12; found: C 49.61, H 3.38, N 18.07	IR: ν_{max} (cm^{-1}) 3500, 3220, 2940, 1621, 1510, 1331, 1275, 1263, 1028; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.84 (s, 3H, OCH_3), 6.81-8.15 (m, 6H, Ar-H), 8.10 (s,1H, CH-Ar), 8.79 (s, 1H, NHC=O, D_2O exchangeable), 9.62 (bs, 1H, NHN=, D_2O exchangeable), 9.77 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 184.3, 170.3, 161.9, 158.6, 152.6, 139.7-124.5, 55.8; Mass (EI): m/z: 387 (M^+)
4l	65/205	0.84/-0.72	Cacld: C 50.92, H 3.80, N 17.49; found: C 50.86, H 3.76, N 17.44	IR: ν_{max} (cm^{-1}) 3371, 2925, 1656, 1583, 1326, 1280, 1265, 1011; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.83 (s, 6H, $(OCH_3)_2$), 7.16-8.12 (m, 6H, Ar-H), 8.25 (s,1H, CH-Ar), 8.68 (s, 1H, NHC=O, D_2O exchangeable), 9.84 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 179.6, 169.8, 163.4, 154.3, 135.5-125.1, 57.4; Mass (EI): m/z: 401 (M^+)
4m	68/230	0.77/-0.52	Cacld: C 62.03, H 4.58, N 18.11; found: C 61.96, H 4.54, N 18.05	IR: ν_{max} (cm^{-1}) 3448, 2925, 1601, 1561, 1267, 1024; ^{1}H NMR (DMSO-d_6): (δ, ppm) 1.82 (s, 3H, CH_3), 7.12-7.58 (m, 8H, Ar-H), 7.94 (s, 1H, CH-Ar), 8.08 (s, 1H, NHC=O, D_2O exchangeable), 9.07 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 176.5, 164.2, 160.1, 157.5, 137.4-122.3, 24.2; Mass (EI): m/z: 310 (M^+)
4n	61/217	0.71/-0.38	Cacld: C 58.95, H 4.36, N 17.22; found: C 58.88, H 4.32, N 17.16	IR: ν_{max} (cm^{-1}) 3500, 3310, 2924, 1605, 1526, 1246, 1036; ^{1}H NMR (DMSO-d_6): (δ, ppm) 2.43 (s, 3H, CH_3), 6.88-7.92 (m, 7H, Ar-H), 7.81 (s,1H, CH-Ar), 8.13 (s, 1H, NHC=O, D_2O exchangeable), 8.97 (bs, 1H, NHN=, D_2O exchangeable), 9.77 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 178.3, 168.1, 164.7, 160.8, 158.4, 135.8-123.4, 25.4; Mass (EI): m/z: 326 (M^+)
4o	62/238	0.69/-0.34	Cacld: C 57.35, H 4.57, N 15.78; found: C 57.29, H 4.52, N 15.72	IR: ν_{max} (cm^{-1}) 3510, 3320, 2922, 1605, 1513,1294, 1262, 1086; ^{1}H NMR (DMSO-d_6): (δ, ppm) 2.27 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.91-7.7 (m, 6H, Ar-H), 7.6 (s,1H, CH-Ar), 7.87 (s, 1H, NHC=O, D_2O exchangeable), 8.01 (bs, 1H, NHN=, D_2O exchangeable), 9.83 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 182.1, 171.4, 167.6, 162.4, 154.7, 132.6-125.1, 58.1, 24.8; Mass (EI): m/z: 356 (M^+)

4p	65/140	0.89/-0.90	Cacld: C 58.42, H 4.93, N 15.18; found: C 58.36, H 4.89, N 15.12	IR: ν_{max} (cm^{-1}) 3320, 2940, 1646, 1510, 1276, 1255, 1090; ^{1}H NMR (DMSO-d_6): (δ, ppm) 2.45 (s, 3H, CH_3), 3.89 (s, 6H, $(OCH_3)_2$), 7.06-7.91 (m, 6H, Ar-H), 7.48 (s, 1H, CH-Ar), 8.64 (s, 1H, NHC=O, D_2O exchangeable), 9.84 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 178.8, 168.6, 164.7, 158.4, 137.9-122.6, 57.9, 23.4; Mass (EI): m/z: 370 (M^+)
4q	70/250	0.83/-0.68	Cacld: C 58.94, H 4.37, N 17.21; found: C 58.88, H 4.32, N 17.16	IR: ν_{max} (cm^{-1}) 3412, 2940, 1626, 1510, 1275, 1255, 1102; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.88 (s, 3H, OCH_3), 7.50-7.95 (m, 8H, Ar-H), 7.97 (s, 1H, CH-Ar), 8.99 (s, 1H, NHC=O, D_2O exchangeable), 9.50 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 176.1, 165.4, 161.6, 152.6, 132.7-124.1, 56.4; Mass (EI): m/z: 326 (M^+)
4r	72/258	0.79/-0.57	Calcd: C 56.20, H 4.16, N 16.43; found: C 56.13, H 4.12, N 16.36	IR: ν_{max} (cm^{-1}) 3480, 3280, 2923, 1625, 1514, 1259, 1247, 1102; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.83 (s, 3H, OCH_3), 6.83-7.84 (m, 7H, Ar-H), 7.87 (s,1H, CH-Ar), 8.55 (s, 1H, NHC=O, D_2O exchangeable), 9.53 (bs, 1H, NHN=, D_2O exchangeable), 9.69 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 183.6, 171.1, 166.4, 162.5, 156.1, 134.4-121.6, 55.8; Mass (EI): m/z: 342 (M^+)
4s	65/255	0.75/-0.47	Calcd: C 54.20, H 4.38, N 15.09; found: C 54.13, H 4.33, N 15.04	IR: ν_{max} (cm^{-1}) 3480, 3324, 2923, 1625, 1510, 1285, 1257, 1092; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.82 (s, 6H, $(OCH_3)_2$), 6.83-7.45 (m, 7H, Ar-H), 7.33 (s, 1H, CH-Ar), 8.57 (s, 1H, NHC=O, D_2O exchangeable), 9.53 (bs, 1H, NHN=, D_2O exchangeable), 9.71 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): (δ, ppm): 180.5, 172.6, 163.7, 160.6, 152.6, 132.6-120.4, 56.9; Mass (EI): m/z: 372 (M^+)
4t	60/260	0.68/-0.32	Calcd: C 56.01, H 4.73, N 14.55; found: C 55.94, H 4.69, N 14.49	IR: ν_{max} (cm^{-1}) 3350, 2923, 1624, 1511, 1284, 1257, 1094; ^{1}H NMR (DMSO-d_6): (δ, ppm) 3.82 (s, 9H, $(OCH_3)_3$), 7.06-7.39 (m, 7H, Ar-H), 7.48 (s, 1H, CH-Ar), 8.64 (s, 1H, NHC=O, D_2O exchangeable), 10.53 (bs, 1H, NHN=, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): (δ, ppm): 179.4, 169.1, 160.2, 154.2, 135.1-121.6, 55.4; Mass (EI): m/z: 386 (M^+)

Table No. 1: **Physicochemical and Spectral data of synthesized compounds (**4a-t**)**



Compound	R	R^1	R^2	Intraperitoneal injection in mice[a]			
				MES screen		Neurotoxicity screen	
				0.5 h	4 h	0.5 h	4 h
4a	Cl	H	H	66	66	X	X
4b	Cl	OH	H	50	33	X	X
4c	Cl	OH	OCH_3	50	50	X	X
4d	Cl	OCH_3	OCH_3	66	66	X	X
4e	F	H	H	50	50	X	X
4f	F	OH	H	83	83	X	X
4g	F	OH	OCH_3	100	100	(-)	(-)
4h	F	OCH_3	OCH_3	66	66	X	X
4i	NO_2	H	H	100	100	(-)	(-)
4j	NO_2	OH	H	83	83	(-)	(-)
4k	NO_2	OH	OCH_3	100	100	(-)	(-)
4l	NO_2	OCH_3	OCH_3	100	100	(-)	(-)
4m	CH_3	H	H	100	100	(-)	(-)
4n	CH_3	OH	H	66	66	X	X
4o	CH_3	OH	OCH_3	50	50	X	X
4p	CH_3	OCH_3	OCH_3	100	100	(-)	(-)
4q	OCH_3	H	H	66	66	X	X
4r	OCH_3	OH	H	83	83	(-)	(-)
4s	OCH_3	OH	OCH_3	66	66	X	X
4t	OCH_3	OCH_3	OCH_3	33	33	X	X
Phenytoin	-	-	-	100	100	(-)	(-)

Table No. 2: **Anticonvulsant and Neurotoxicity evaluation of the titled compounds (**4a-t**)**

[a]Dose of 30 mg/kg was administered (n = 6) i.p. The animals were examined 0.5 h and 4 h after administration. The dash (-) indicates an absence of activity and (X) indicates neurotoxicity at 30 mg/kg

Compound	R-HBD[a]	R-D[a]	D-HAD[a]
Carbamazepine	6.517	3.931	5.554
Phenytoin	3.042	3.868	2.497
Lamotrigine	5.807	3.301	4.598
Zonisamide	4.058	5.651	6.729
Rufinamide	2.407	7.474	5.209
Dezinamide	4.481	5.909	2.948
Remacemide	3.211	9.811	6.635
Diazepam	4.793	4.827	1.49
Basic structure of Compounds (4a-t)	5.382	8.336	3.033

Table No. 3: **Distance ranges between the essential structure elements R, D and HBD**

[a]Distance calculated for 3D optimized structures using ACD Freeware 3D Viewer 8.04 version

CONCLUSIONS:

In conclusion, the synthesis of number of 3, 4-disubstituted benzaldehyde-*N*-(6-substituted-1,3-benzothiazol-2-yl)semicarbazones (4a-t) as candidate anticonvulsant and antinociceptive has been reported in this study. The results suggest that minor changes to structure can increase or decrease the activity. The substitution of 6-position with nitro, fluoro, and methyl groups at the terminal benzothiazole ring is beneficial for anticonvulsant activity.

ACKNOWLEDGEMENTS:

This study was financially supported by University Grants Commission (UGC) and Jamia Hamdard University, New Delhi, India.

REFERENCES:

1. Gasior M, Ungard JT, Witkin JM. Preclinical Evaluation of Newly Approved and Potential Antiepileptic Drugs Against Cocaine-Induced Seizures. J Pharmacol Exp Ther. 1999;290:1148-56.

2. Deckers CLP, Genton P, Sills GJ, Schmidt D. Current limitations of antiepileptic drug therapy: a conference review. Epilepsy Res. 2003;53:1-17.

3. Loscher W, Honack D, Fassbender CP, Nolting B. The role of technical, biological and pharmacological factors in the

laboratory evaluation of anticonvulsant drugs. III. Pentylenetetrazole seizure models. Epilepsy Res. 1991;8:171-89.

4. Pandeya SN, Kohli S, Siddiqui N, Stables JP. Synthesis and anticonvulsant activities of 4-*N*-substituted arylsemicarbazones. Polish J Pharmacol. 2003;55:565-71.

5. Siddiqui N, Pandeya SN, Khan SA, Stables JP, Rana A, Alam M, Arshad MF, Bhat MA. Synthesis and anticonvulsant activity of sulfonamide derivatives-hydrophobic domain. Bioorg Med Chem Lett. 2007;17:255-9.

6. Siddiqui N, Rana A, Khan SA, Bhat MA, Haque SE. Synthesis of benzothiazole semicarbazones as novel anticonvulsants-The role of hydrophobic domain. Bioorg Med Chem Lett. 2007;17:4178-82.

7. Rana A, Siddiqui N, Khan SA, Haque SE, Bhat MA. *N*-{[(6-Substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides: Synthesis and pharmacological evaluation. Eur J Med Chem. 2008;43:1114-22.

8. Micale N, Zappala M, Zuccala G, Menniti FS, Ferreri G, De Sarro G, Grasso S. Synthesis of 2-semicarbazonomethyl-4,5-methylenedioxyphenylacetic acids as anticonvulsant agents. Farmaco. 2005;60:231-5.

9. Yogeeswari P, Sriram D, Thirumurugan R, Raghavendran JV, Sudhan K, Pavana RK, Stables JP. Discovery of *N*-(2,6-Dimethylphenyl)-Substituted Semicarbazones as Anticonvulsants: Hybrid Pharmacophore-Based Design. J Med Chem. 2005;48: 6202-11.

10. Puthucode RM, Pugazhenthi U, Quail JW, Stables JP, Dimmock JR. Anticonvulsant activity of various aryl, arylidene and aryloxyaryl semicarbazones. Eur J Med Chem. 1998;33:595-607.

11. Pandeya SN, Raja AS, Stables JP. Synthesis of isatin semicarbazones as novel anticonvulsants - role of hydrogen bonding. J Pharm Pharmaceut Sci. 2002;5:266-71.

12. Stables JP, Kupferberg HJ. Molecular and cellular targets for antiepileptic drugs. In: Avanzini G, Tanganelli P, Avoli M (ed) John Libey, London. 1997, pp 1991.

13. White HS, Woodhead JH, Franklin MR. Antiepileptic drugs. In: Levy RH, Mattson RH, Meldrum BS (ed) 4th ed. Raven, New York. 1995, pp 99.

14. Dimmock JR, Sidhu KK, Tumber SD, Basran SK, Chen M, Quail JW, Yang J, Rozas I, Weaver DF. Some aryl semicarbazones possessing anticonvulsant activity. Eur J Med Chem. 1995;30:287-301.

15. Pandeya SN, Ponnilavarasan I, Pandey A, Lakhan R, Stables JP. Evaluation of *p*-nitrophenyl substituted semicarbazones for anticonvulsant properties. Pharmazie. 1999;54:923-5.

16. Pandeya SN, Yogeeswari P, Stables JP. Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones. Eur J Med Chem. 2000;35:879-86.

16. Yogeeswari P, Sriram D, Suniljit LRJ, Kumar SS, Stables JP. Anticonvulsant and neurotoxicity evaluation of some 6-chlorobenzothiazolyl-2-thiosemicarbazones. Eur J Med Chem. 2002;37:231-6.

17. Pandeya SN, Manjula H, Stables JP. Design of semicarbazones and their bio-isosteric analogues as potential anticonvulsants. Pharmazie. 2001;56:121-4.

18. Wong MG, Dejina JA, Andrews PR. Conformational analysis of clinically active anticonvulsant drugs. J Med Chem. 1986;29:562-72.

19. Yogeeswari P, Sriram D, Veena V, Kavya R, Rakhra K, Ragavendran JV, Mehta S, Thirumurugan R, Stables JP. Synthesis of aryl semicarbazones as potential anticonvulsant agents. Biomed Pharacother. 2005;59:51-5.

20. Kaufmann HP, Oehring W, Clauberg A. Die. Bildung von Thiazol-Derivaten bei der Rhodanierung von. Aminen. Arch Pharm. 1928;266:197-218.

21. Krall RL, Penry JK, White BG, Kupferberg HJ, Swinyard EA. Antiepileptic Drug Development: II. Anticonvulsant Drug Screening. Epilepsia. 1978;19:409-18.

22. Tasso SM, Moon, SC, Bruno-Blanch LE, Estiu GL. Characterization of the anticonvulsant profile of valpromide derivatives. Bioorg Med Chem. 2004;12:3857-69.

23. Yogeeswari P, Sriram D, Saraswat V, Ragavendran JV, Kumar MM, Murugesan S Thirumurugan R, Stables JP. Synthesis and anticonvulsant and neurotoxicity evaluation of N^4-phthalimido phenyl (thio) semicarbazides. Eur J Pharm Sci. 2003;20:341-6.

24. Archana, Srivatava VK, Kumar A. Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3*H*)-ones as potential anticonvulsant agents. Eur J Med Chem. 2002;37:873-82.

25. Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M. CHARMM: A program for macromolecular energy, minimization, and dynamics calculations. J Comput Chem. 1983; 4:187-217.

Conflict of Interest: None Declared

