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SYNTHESIS, CHARACTERIZATION & SCREENING FOR ANTICONVULSANT ACTIVITY OF BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

Background: Anticonvulsants are commonly used to treat seizure disorders but may also be used to treat other medical conditions, including chronic nerve pain and mental health disorders anti-consulvant Drug are clinically used as anti-consulvant, or antiepileptic agents or anti sizzure but they have the drawbacks of causing poor appetite or fatigue. Recently, benzothiazole derivatives have shown significant and less Aplastic anemia activity. The present study deals with the synthesis and pharmacological assessment of a series of novel benzothiazole derivatives bearing 2-aminobenzothiazole scaffolds as anti-sizzure and anti epilyptic agents. **Methods:** The preparation of the necessary benzothiazole analogues take hold of processes, as shown in **Scheme 1.** The related condensation reaction is produced in the first steps by the reaction of substituted benzaldehyde and substituted aromatic aniline with glacial acetic acid. (**2a-c**). In order to produce the desired compound, oxidative ring bases were given time to react using glacial acetic and ammonium thiocyanate. **(3a-c).**In this investigation Title, synthesize seven new benzothiazole derivatives (**6a-g)** and evaluated them using the maximal electric shock method (maximum electrical shock method) for its anti-convulsion properties. At the beginning, synthesis 2-Aminobenzothiazole at 05 °C using the shiff base technique and bromination followed by an oxidative ring. benzothiazole derivatives were synthesized and characterized by IR, NMR spectroscopy and elemental analysis. **Result:** All elemental analysis, IR, ^{1}H NMR values were found to be prominent. A test for anti-consulvant activity demonstrated that **(7e)** (E)-2-(2,6-dichlorobenzylidene)-1-(4-nitrobenzo[d]thiazol-2-yl)hydrazine, (E)-2-(4-nitrobenzylidene)-1-(4-nitrobenzo[d]thiazol-2-

yl)hydrazine**(7f)**,(E)2(4ethoxybenzylidene)1(4chlorobenzo[d]thiazol2yl)hydrazine**(7g)** exhibited significant anti-consulvant compared to control group. **Conclusion**: A results of the current research show that substitution at substitution benzothiazole derivative products with benzaldehyde scaffolds have potent anticonsulvant activities**.**

KEYWORDS: Schiff base reaction, MES model, anticonvulsant activity.

1. INTRODUCTION

Epilepsy has been thoroughly researched as a human condition.becoming a vibrant study field throughout the past century recently in the area. It outlines conditions characterised by synchronised neurogenesis caused by recurrent seizures firing At estimated 30% of people still experience uncontrolled seizures.even with sufficient antiseizure medication therapy, epilepsies is delivered Various neurological conditions can impact.[1]

The traditional antiepileptic medicines consist of both phenytoin and phenobarbital have been marketed since 1911.carbamazepine, an epileptic drug, was first used in Europe in 1939.valproic acid, and the middle of the 1960s obtainable in a number of European nations since the 1960s There is dose-related toxicity in every antiepileptic medicine now on the market Irregular side effects.[2]

Unique properties from older anticonvulsants Benzothiazole nuclei that have recently been replaced are reportedly have important activities[3-5] there Paroxysmal neurons improve and increase maximal neuronal synthesis, are the hallmark of the status epilepticus spectrum of illnesses, not a single condition. A significant fraction of the global population (0.51 percent) is affected by this basic neurological disease. Only 65.75 percent of patients see any benefit from newly available.[6] A persistent propensity to have epileptic seizures characterizes the neurologic condition epilepsy.[7] Biological activity of benzothiazole and the com pounds derived from it, such as (E)-2-(2,6-dichlorobenzylidene)-1-(4-nitrobenzo[d]thiazol-2yl)hydrazine, (E)-2-(4-nitrobenzylidene)-1-(4-nitrobenzo[d]thiazol-2-yl)hydrazine,(E)-2-(4-ethoxybenzylidene)-1-(4chlorobenzo[d]thiazol-2yl)hydrazine and many chloro-, nitro-, hydroxy-,-methoxy, or ethoxy substituted benzothiazoles have been thorough investigated. Most research has demonstrated a correlation between the metallo-organic and biological activities of molecules with the (H-N) and (C-S) linkage. Most likely, their ability is related to this activity.[8] Due of its diverse applications, the benzothiazole moiety the amazing bioactivity of protein engineering as an

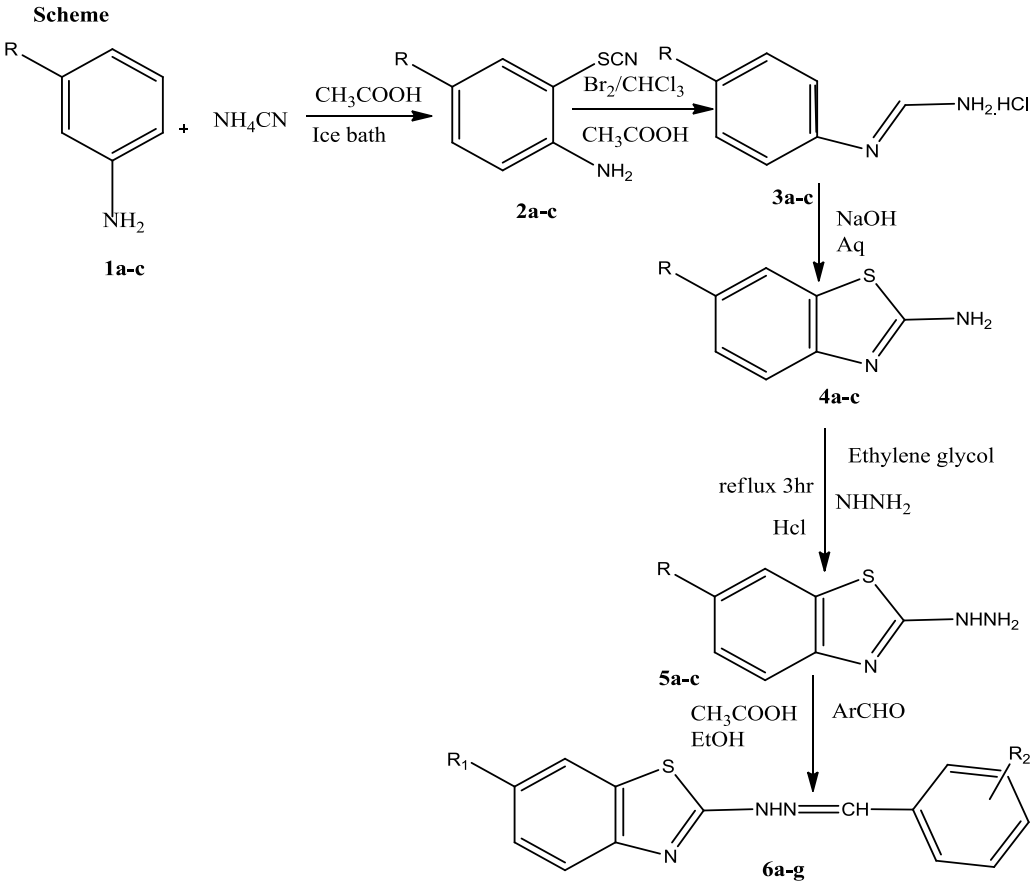
example.[9] Biological activity displaying wide role in the Analgesic activity[10-11], Anti-inflamatory[12], Anti-consulvant[13]

MATERIAL METHODS

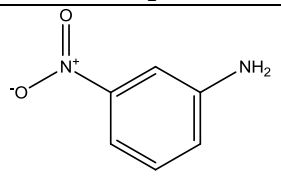
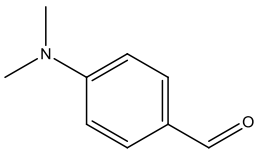
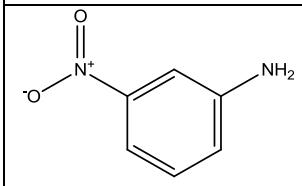
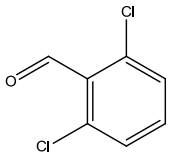
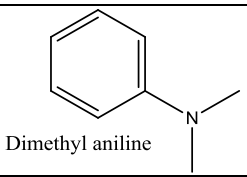
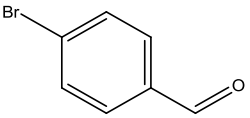
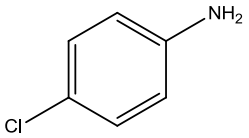
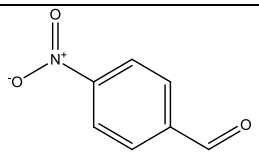
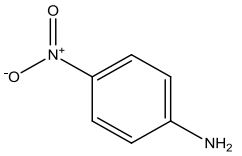
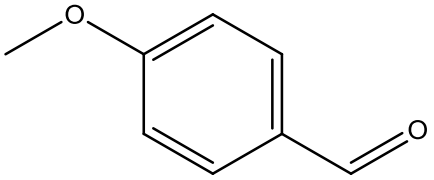
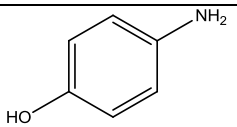
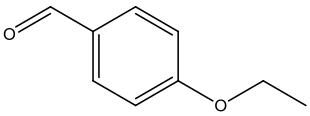
*Chemistry

So all substances needed for synthesis, such as 2-aminobenzenethiazole, Merck Ltd., Sigma-Aldrich, as well as Hi-Media all provided substitution aldehydes that were used commercially without additional preparation. A melting temperature that was mentioned is false and was discovered in a transparent glass tube.

The FT-IR Spectrometer from Shimadzu was used to record the IR spectra. TMS was used as the internal standard to scan the 1H NMR spectra (DMSOd6) using a Bruker Avance II (400MHz) spectrometer, and the chemical shifts are represented in ppm. An analysis of the components was performed on Element Vario EL III Carlo Erba 1108, and the results were all within 0.04 percentage points of the predicted value. Evrey solvents was concentrated and dried used a standard desiccant.



Type of Compound Derivatives

R_1	R_2
 3-Nitro aniline	 p-dimethylaminobenzaldehyde
 3-Nitro aniline	 2,6,dichlorobenzaldehyde
 Dimethyl aniline	 4 Bromobenzeldehyde
 p- chloro aniline	 4 nitrobenzaldehyde
 4-Nitroaniline	 4 methoxybenzaldehyde
 4Hydroxyaniline	 P ethoxy benzaldehyde

Synthesis

General synthetic procedure for Benzo[D]Thiazol-2-amine (4a-c)

A mixture aniline (0.065) mole in glacial acetic acid (20ml) were added ammonium thiocynate (0.208 mole), dissolved in glacial acetic acid (25ml) than the mixture was cooled at 0°C,& bromine (3.5ml) dissolved in glacial acetic acid (25ml) added drop wise in the time of 30 minutes the range of temperature is 0°C-25 °C the mixture was then agitated for five to six hours at a temperature below 25°C. Prolonged storage in the chiller was permitted for the solution's content. The produced residue received 20°C of hot water. The resulting mixture then was heated to temperatures of (85–90°C) and filtrated.[13] Glacial acetic acid (15 ml) was added to the brown precipitate, heated to 90°C in a bottom flask, and then filtration. Its supernatant was then diluted to pH using ammonium hydroxide after chill (6.0-7.0). Bright

brown compound crystals were obtained by collecting a light brown crystal, treating it with charcoal, and washing it with ice water.[15]

General synthetic procedure for 2-Hydrazinyl-3a,7a-dihydrobenzo[*d*]thiazol-7-amine (5a-c)

Dropwise additions were made while stirring at 5–10°C to hydrazine hydrate (99 percent, 6ml) conc (HCl, 6ml). It was then added with portions to Compound 1 (0.03) and Ethylene Glycol (24 ml), and refluxed about three hours. The reaction mixture was added to crushed ice once it had cooled down in order to construct a solid. The chemical was created by filtering and recrystallizing this solid from the ethanol.[15]

General synthetic procedure for synthesis 2-(substituted benzylidene)-1-(4-nitrobenzo[d]thiazol-2-yl)hydrazine (6a-g)

A mixture of 2-aminebenzothiazol (A2) (0.01mol, 1.80g) and para substituted benzaldehydes (0.01mol) was mixed in alcohol (20 ml) with drops of ethanoic acid, and then warm up on a 4 hours of churning in a water bath at 80 °C. following cooling to ambient temperature, the mixture was placed into ice and swirled for 1 hour with a magnetic stirrer. The resulting precipitate was separated before being recrystallized in heated 10% aqueous ethanol.[16]

(E)-3-(3-bromobenzylidene)-1-(benzo[d]thiazol-2-yl)hydrazine (7a)

Yield 84%, mp150-152 ^{0}C; IR (KBr) cm^{-1}: 3029 (N-H), 3012 (C-H), 1619 (C=C), 1602 (C=N), 1166 (C-S), 531(C-Br), ^{1}H NMR (300 MHz, DMSO-d_6): 3.2 (s,1H, benzylic), 3.8 (s, 1H, amino), 7.2-7.4 (m, Ar-H, 8H); Anal. Calcd. For $C_{14}H_{10}BrN_3S$; C, 50.61; H, 3.03; N, 12.65; Found: C, 50.54; H, 3.05; N, 12.63%

(E)-2-(4-methoxybenzylidene)-1-(4-nitrobenzo[d]thiazol-2-yl)hydrazine (7b)

Yeild 78%, mp 160-162 °C; IR (KBr) cm^{-1}: 3032 (C-H), 1658 (C=N), 1622(Ar C=C), 1262(-OCH_3), 1217(C-S), 1204 (Ali C-N). ^{1}H NMR (300 MHz, DMSO-d_6): 3.3 (s, 1H, benzylic), 3.7 (m,2H,O-CH_3), 4.0 (s,1H, N-H), 7.7-7.9 (m, Ar-H, 6H); Anal. Calcd. For $C_{14}H_{10}BrN_4O_3S$ C, 54.87; H, 3.68; N, 17.06; Found: C, 54,82; H, 3.65; N, 17.02 %

(E)-2-(4-ethoxybenzylidene)-1-(benzo[d]thiazol-2-yl)hydrazine (7c)

Yeild 81%, mp 155-157 °C; IR (KBr) cm^{-1}: 3023 (ArC=C), 1657 (C=N), 1643(N-NH), 1325(C-N), 1317(O-C_2H_5) 1204(Ali C=N), 1117(Ali C-S), ^{1}H NMR (300 MHz, DMSO-d_6):

4.21(2H,amino) 7.8-8.2(m,Ar-H, 8H,).Anal. Calcd. For $C_{14}H_{10}N_3OS$ C, 54.87; H, 3.68; N, 17.06; Found: C, 54,82; H, 3.65; N, 17.02 %.

(E)-2-(2-chloronenzylidene)-1-Benzo[D]Thiazol-2-Amine-2-Amine)hydrazine(7d)

Yeild 76%, mp 165-170°C; IR (KBr) cm^{-1}: 2041 (C=N), 1476 (ArC=C), 1342(Ali C-N), 1222(Ali C-S),1075(C-N),776(C-Cl),^{1}H NMR (300 MHz, DMSO-d_6): 3.6(S,1H,benzylic),4.1(S,1H,NH_2),6.8-7.0(m,Ar-H,6H) Anal.Calcd.For $C_{14}H_8Cl_2N_4O_2S$ C,64.38; H,3.51; N,21.05 Found C, 65.31, H,3.29,N,23.08%

(E)-2-(2,6-dichlorobenzylidene)-1-(4-nitrobenzo[d]thiazol-2-yl)hydrazine(7e)

Yeild 79%, m.p 2395-241°C; IR (KBr) cm^{-1}: 1641(N=CH), 1602 (-NO_2), 1455(C=C), 1276 (C-S) 1340 (Ar C-N), 762 (C-Cl).597(C=Br), ^{1}H NMR (300 MHz, DMSO-d_6): 3.6(S,1H,benzylic),4.1(S,1H,NH_2),6.8-7.0(m,Ar-H,6H) Anal. Calcd.For $C_{14}H_8C_{l2}N_4O_2S$ C, 54.40; H, 3.25; N, 17.65 Found C, 55.42; H, 3.29; N,17.67 %

(E)-2-(4-nitrobenzylidene)-1-(4-nitrobenzo[d]thiazol-2-yl)hydrazine (7f)

Yeild 76%,mp 220-222°C; IR (KBr), cm^{-1}: 1600 (C=N), 1492 (NO_2),1468(Ar C=C), 1314(C-N)1242 (C-S), ^{1}H NMR (300 MHz, DMSO-d_6): 3.7(S, 1H,benzylic), 4.2(S,1H,NH_2),7.8-8.0 (m,7H,m). Anal. Calcd.For $C_{14}H_9N_5O_4S$ C, 43.60; H, 2.15; N,17.6 Found C, 42.62; H, 2.14; N,17.668 %

(E)-2-(4-ethoxybenzylidene)-1-(4-chlorobenzo[d]thiazol-2yl)hydrazine (7g)

Yeild 64% m.p 170-180°C; IR KBr, cm^{-1}:, 1605(C=N), 1490 (ArC=C), 1364(C-N), 1313(OC_2H_5), 1240(C-S), ^{1}H NMR (300 MHz, DMSO-d_6): 3.4(S,1H,benzylic) 3.73.8(mAr-H,3H, ethoxy) 4.3(S,1H,amino),7.8-8.0(m,3H,Ar-H)^{1}H NMR δ,ppm3.4(S,1H, benzylic) 3.73.8(mAr-H,5H,ethoxy)4.3(S,1H,amino),7.8-8.0(m,7H,Ar-H)Anal.Calcd.For $C_{16}H_{14}ClN_3OS$ C,47.95, H,2.65;N,20.35Found C,46.88; H,2.60; N,20.40%

Table 1: Physico-chemical parameters of synthesized compounds.

S.No	Comp Code	Molecular formula	Mol.weight	M.P.	R_f	Colour
01	7a	$CH_{10}BrNS$	332	165-162	0.73	Brown crystal
02	7b	$C_{14}H_{10}BrN_{12}N_1S$	626	157-160	0.66	Light yellow needle crystal
03	7c	$C_{16}H10NS$	257	198-200	0.68	Brown brown crystal
04	7d	$C_{16}H_{15}N_3OS$	297	255-260^{o}C	0.54	Yellow needle crystal

05	7e	$C_{14}H_{10}Cl_3S$	287	190-195^{o}C	0.65	Light Brown crystal
06	7f	$C_{14}H_8Cl_2N_4O_2S$	366	200-215	0.75	Yellow crystal
07	7g	$C_{14}H_9N_5O_4$	343	200-230	0.82	Pale yellow

˜Solvent system: *Chloroform: glacial acetic acid (7:3)

~Solvent System: Acetic acid : ethyl acetate: ethanol (6:2:2)

2.3 Parmacological Screening

2.3.1 Animal

Here as test subjects, albino mice (Swiss, 25–30 g) have been divided into six groups. All of the test substances and the reference medication were dissolved in polyethylene glycol (PEG) and given intra peritoneally. Apart from the brief period they were taken out of their cages for testing, the animals were kept on a sufficient diet and given free access to food and drink. The animals were kept at room temperature, which is 25°C.

*Hygia Institute of Pharmaceutical Education & Research, Lucknow, India with no. (88/02/2 022 IPCSEA). Independently housed in polypropylene cage, the animals have been obtained from the CSIR-Indian Institute of Toxicology Research in Lucknow, India, and kept so under recommended conditions of 12-hour light-and-dark cycles at a specific temperature (20 ° C and 35° C relative humidity). Standard pellet diet and unlimited water were given to the animals.

2.3.2 Maximal Electric Shock Method

Upon the anticonvulsant required drugs, the test compounds initial anticonvulsant evaluation was conducted The Seizure Section of developed a program protocol 17,18 that the National Institute of Neurological Disabilities and Stroke National Institutes of Health (NIH) in the USA (NINDS). Each substance was injected intraperitoneal (i.p.) 25mg/kg of body mass was administered through injection, and the measured the anticonvulsant effect at 0.5 and 3 hours.administration. The strongest electroshock seizures were induced. By administerd 60 Hz, 50 mA electrical stimulation to mice for 0. 2.via electrode ear-pinna. The most severe seizure often included of a phase of tonic hind limb extension and a final episode of clonus. blocking the tonic in the lower limb extensor component as a result of medication therapy.[17]

The maximal electroconvulsive method was used to operate anticonvulsant activity (MES). This project approved by the Institutional Animal Ethical Committee at Hygia Institute of Pharmaceutical Education and Research, Lucknow (Ref. No. HIPER/IAEC /88/02/2022).

albino mice of either sex weighing 20-25 g were used. The animals were divided into three groups (control, standard, and test) and each group comprising six mice. test compounds were suspended in 1% aqueous carboxy methyl cellulose (CMC) suspension and were administered p.o. according to their body weight. Phenytoin sodium was used as a standard drug which was given in the dose of 25 mg/kg by i.p. which was observed to protect 100% against the induced convulsions. The control group received only 1% aqueous CMC suspension. The seizures were induced by electro convulsiometer.

The animals were electro shock by delivered by the current of 150 mA through the corneal electrodes for a period of 0.2 s. The animals were observed for convulsive responses. Different stages of convulsions, i.e., the tonic flexion (toward the upper extremities), tonic extensor phase (extension of the lower extremities), clonic convulsions (intermediates jerking of limbs), stupor (unconsciousness), and recovery or death were observed for each animals (**Table 2**). The anticonvulsant effect of new synthesized compounds was assessed by reduction (time) or absence of different phases induced by MES. Each value represents the mean standard error mean of three mice significantly different from standard drug phenytoin.

Compounds 0.5 mg/kg exhibited significant anticonvulsant activity at all-time intervals as compared to control group. In the primary MES screening compounds **7e, 7f,** and **7g** afforded protection against seizures confirm their potential utility as prototypic molecules. The anticonvulsant activity data revealed that all the compounds showed remarkable reduction of hind limb tonic flexion, extensor, clonus, and stupor phase when given in the dose of 25 mg/kg p.o. and compounds **7g** and **7e** were found to be the most potent compounds in the series. Moreover, anticonvulsant activity of the other test compounds was found to be much less effective than phenytoin used as standard anticonvulsant drug. Accordance to the results obtained it seems the presence of ethoxy group and chloro group attached on oxidative ring increase the potency. Almost the derivatives showed good.[18]

Table 2: Anticonsulvant Activity Data of compound 6a-6g.

Compound Code	Flexion [sec] [mean±SEM]	Extension [sec] [mean±SEM)	Convulsion [sec] [mean±SEM]	Stupor [seconds] [mean±SEM]	Recovery/ Death
Control	5.41±0.61	8.80±0.67	4.1±0.64	10.1±0.48	R
7a	5.1±0.54	6.8±0.33	3.9±0.21	7.2±0.41	R
7b	4.4±0.22	6.1±0.34	3.9±0.33	4.6±0.41	R
7c	4.3±0.17	6.3±0.32	3.7±0.41	4.7±0.38	R
7d	4.1±0.68	5.3±0.21	3.8±0.31	6.1±0.33	R

7e**	3.7±0.62	2.3±0.31	3.2±0.33	2.9±0.19	R
7f*	4.1±0.31	4.8±0.21	4.2±0.26	5.1±0.17	R
7g***	3.3±0.64	1.5±0.42	2.4±0.32	2.4±0.31	R
Standard (Phenytoin Sodium)	2.6±0.16	1.2±0.09	1.6±0.25	1.7±0.06	R

Data are expressed as Mean ± SEM for Statistical analysis was performed.

3. RESULT AND DISCUSSION

The titled compounds were synthesized through multistep synthetic route as shown in Scheme. **Scheme 1.**[14] The related condensation reaction is produced in the first steps by the reaction of substituted benzaldehyde and substituted aromatic aniline with glacial acetic acid. (**2a-c**). In order to produce the desired byproducts, oxidative ring bases were given time to react using glacial acetic and ammonium thiocyanate. **(3a-c).** All substituted final benzothiazole derivatives were found(6a-g).

Exhibited a strong, stretching band in the range of cm^1 in their infrared (IR) spectra, which has been caused by the 1342-1266 (C–N) stretching vibration. Because to all the 1610-1670, (N=H) stretching vibration, the IR spectra of the product (6a-g) displayed a strong peak with in range cm^1, which confirm of supports validated the transformation of substrate into the desired products at the substituted benzothiazole ring attached with benzaldehyde group, where C=N is present. ethoxy protons were detected in compounds 7c and7g ^{1}H nuclear magnetic resonance (NMR) spectra of compound approximately showed signal at 7.8-8.01 λ ppm, respectively. All of the additional aromatic and aliphatic protons were observed in the anticipated locations.

CONCLUSION

A through title of the compound reveals that compounds with the benzothiazole nucleus cover a wide range of pharmacologic activities, including anti-hyperglycemic, anti- anti-cancer, convergent anti-hyperlipidemia, anti-obesity, anti-microbial, anti-arthritic, anti-fungal, and cardio tonic effects. In addition to these benzothiazole, there are others that have anti-epileptic action. With good to outstanding yields, we have created a number of new derivatives of 2-aminobenzothiazole 5a-e, which we have characterized using elemental and spectral analyses. Utilizing 1HNMR and FT-IR spectroscopy, the entirety of the substituted-methoxy-2-aminobenzothiazole derivatives along with benzaldehyde Schiff bases created in this work were characterized and verified.

LIST OF ABBREVIATIONS

Ar = Aromatic

FTIR = Fourier transform infrared spectroscopy

NMR = Nuclear magnetic resonance spectroscopy

Str = Stretching

IAEC = Institutional animal ethics committee

IR = Infrared spectroscopy

OECD = Organisation for Economic Co-operation and Development

ppm = Parts per million

SEM = Standard error mean

TLC = Thin layer chromatography

CONFLICT OF INTEREST

None of the author has any conflict of interest in the context of this work.

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