Research Article

Screening of some Semicarbazones as anticonvulsant agent

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Abstract

Objective: The principal objective of the present investigation was the preparation of several analogs to further evaluate the binding site hypothesis. Aryl semicarbazides have also been reported to display excellent anticonvulsant activity in mice and rats. **Matearial and Methods:** In this project, the synthesis of semicarbazone derivatives was carried out. All molecules were synthesized using the common starting material –aniline. In all compounds, an intermediate was first formed by substituted phenyl urea using substituted aniline and potassium cyanate, and then it was hydrolyzed to get substituted phenyl semicarbazide, which was directly coupled with ketones. All the synthesized compounds were biologically screened for their anticonvulsant activity by the MES method. **Results:** Standard error mean was calculated concerning standard and control drug, Phenytoin sodium (25mg/kg.) and DMSO. The synthesized semicarbazone was characterized by using IR Spectroscopy. One another representative molecule compound was characterized using ^{1}H NMR Spectroscopy. **Conclusion:** It can be concluded that designed semicarbazones were synthesized and characterized successfully. After synthesis of designed semicarbazones compounds were evaluated for anticonvulsant activity. Finally, two compounds have shown better activity in comparison to the other molecules.

Keywords: Semicarbazone, MES, SEM, anticonvulsant activity, IR, NMR spectroscopy

Introduction

Epilepsy is a central nervous system (CNS) malfunction that leads either to generalized hyperactivity involving essentially all parts of the brain or to hyperactivity of only a portion of the brain (Guyton, 1976). epilepsy is a collective term that includes over 40 different types of human seizures disorders. Approx 1% of the world population at any one time (>50 million people worldwide) is afflicted with these serious neurological disorders. Although the current drug provides adequate seizure control in many patients, it is roughly estimated that up to 28-30% of patients are poorly treated with the available antiepileptic drugs (AEDs). Moreover, many (AEDs) have serious side effects and lifelong medication may be required. Conventional antiepileptic drugs (AEDs). Phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide, and benzodiazepines, are widely used but exhibit an unfavorable side effect profile and failure to adequately control seizures in the recent year new drugs (Oxcarbazepine, Lamotrigine, Topiramate, Gabapentin, Zonisamide, Tiagabine, Fosphenytoin, Vigabatrine & felbamate) have been added to the list of therapeutic agents against epilepsy (Mccormick and Contreras, 2001). However, there is a significant group of patients (up to 30%) who are resistant to the available anti-epileptic drugs. The long-established AED control seizures in 50% of people developing partial seizures and in 60-70% of those developing generalized seizures (Meador, 2003).

In the 1960s, research in antiepileptic drug development

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was stimulated by the creation of the epilepsy Branch and the epilepsy Advisory Committee in the United States national institute of Neurological and communicative disorders and stroke (NINCDS) (Lima, 2000). These programs were established to collate and review the neuroscience literature pertinent to epilepsy and encouraged to careen large numbers of potential new anticonvulsants. From this point, the development of new drugs concentrated on different molecular structures, resulting in the marketing of carbamazepine (1974), clonazepam (1975), and valproate (1978) (Perucca, 2002). It has been estimated that adequate control of seizures could not be obtained in up to 20% of the patients with epilepsy using the first generation of antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, sodium valproate, and diazepam) (Berk et al., 2001). A group of new drugs including felbamate, gabapentin, lamotrigine, oxacarbazepine, topiramate, milacemide, vigabatrin, and zonisamide are into clinical practice. The convulsions of approximately 25% of epileptics are inadequately controlled by current clinically available drugs (Duncan, 2002). Current drug therapy is accompanied by numerous side effects including drowsiness, ataxia, gastrointestinal disturbance, gingival hyperplasia, hirsutism, and megaloblastic anemia (Eadie, 2001). The long-established AEDs control seizures in 50% of patients developing partial seizures and in 60-70% of those developing generalized seizures. Hence there is an urgent need to develop new AEDs. The search for antiepileptic compounds with a more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. A rational drug design process of a new anticonvulsant could be achieved in several ways (Cosford et al., 2002). The first strategy is the identification of new targets through better understanding of molecular mechanism of epilepsy. Another way is to modify already existing drugs and formulations. AED's belong to many different chemical classes of compounds, including; hydantoins, imino stillbene, barbiturates, benzodiazepines, valproate, imides, oxazolidine2, 3-diones, sulfonamides, and miscellaneous agents. The efficacy of AEDs is due to the main activities which include interaction with ion channels or neurotransmitter systems (Bruno-Blanch, 2003). The new AEDs and anticonvulsant agents have been reviewed last few years. The chemical diversity and various mechanisms of action of anticonvulsants make it difficult to find a common way of identifying new drugs. Novel anticonvulsant is discovered through conventional screening and /or structure modification rather than a mechanism-driven design. Therefore, drug identification is usually conducted via *in-vivo* screening tests, based on seizure type rather than etiology (Malawska, 2003). Most recently, a number of new antiepileptic drugs with novel structures have been or are at the moment awaiting approval in a number of countries and these drugs include vigabetrine (1989), gabapentin (1993), felbamate, oxacarbazepine and zonisamide. In addition, a number of active compounds identified and are at various stages of preclinical and clinical development and these drugs include tigabine, eterobarb, remacemide, stiripentol, flunarizine, topiramate, levetiracetam. However, none of the available drug is ideal as they can be as upon the individual factors like age, sex type of syndrome etc. also in current clinical practice combination therapy is prescribed in significant proportion of patient with epilepsy. Hence there is urgent need to develop new AEDs. The search for antiepileptic compound with a more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry (Isaac, 2005). The efficacy of various antiepileptic drugs (AEDs) is due to their activities which include interaction with ion channels or neurotransmitter systems. Amongst these classes, semicarbazones are of considerable interest because of their better CNS activity, especially as anticonvulsants (Gatti et al., 2000).

Structural requirements for the semicarbazones displaying anticonvulsant activity Development of semicarbazones was initially based on the hypothesis of Parmar et al. (1967), who correlated the MAO inhibiting activity of hydrazine derivatives with anticonvulsant activities specifically subcutaneous metrazol tests (ScMet). in the course of investigations aimed at developing structurally novel anticonvulsants, several aryl semicarbazones, were found to display significant activity (Dimmock and Baker, 1994). These compounds were to interact at two locations on a putative binding site designated a hydrogen bonding area and an aryl binding site. However, since the aryl group can be replaced by other hydrophobic moieties with retention of anticonvulsant activity (Dimmock et al., 1996). The principal objective of the present investigation was the preparation of several analogs to further evaluate the

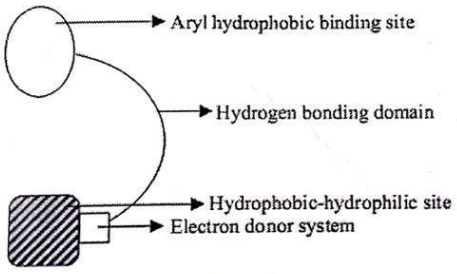

Figure1. Pharmacophore of the designed Semicarbazone

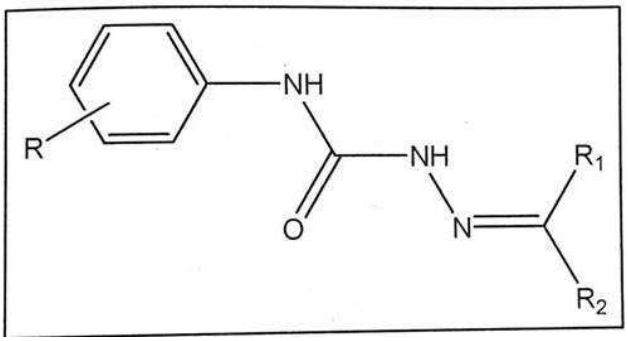

Figure 2. Designed scaffold, Where R=H, 4-Cl, Alkyl and R_1=R_2=H, alkyl, cyclic structure aromatic ring

binding site hypothesis. Aryl semicarbazides have also been reported to display excellent anticonvulsant activity in mice and rats. In terms of interaction at the binding site, as proposed previously by Dimmock et al (2003). The pharmacophoric elements were thought to be lipophilic aryl rings and hydrogen bonding semicarbazone moiety. The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the van der Waals bonding at the binding site and to increase potency has also been reported. Substitutions in the aryl ring by halogens have been found to increase potency in the MES screen. The presence of an electron-rich atom or group attached at the para position of the aryl ring showed increased potency in the MES screen Due to the importance of the heteroaryl semicarbazones, we have designed the novel molecules with the nucleus of semicarbazones. Based on the pharmacophore model as cited in the literature review, we design the novel derivative of semicarbazone or thiosemicarbazone. The designed scaffold structure is given in figure 2.

Materials and methods

The purity of the starting material was confirmed by melting point/ boiling point and thin-layer chromatography. The purity and structures of the synthesized compounds were confirmed by melting point/ boiling point and thin layer chromatography, infrared spectroscopy, and nuclear magnetic spectroscopy.

The melting point of the compound synthesized was uncorrected and recorded by open glass capillary method on '**Janki implex melting point apparatus**" and compared with the reported melting point wherever applicable ^{1}H-NMR spectra and ^{13}CNMR spectra were reported on GEOLAR -300 shifts were expressed in parts per million (ppm). IR spectra were recorded using the "BRUKER ALFA–E infrared spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on pre-coated plates (silica gel G254). For anticonvulsant activity Electroconvulsometer was used.

Synthesis of compounds aryl semicarbazones (a-j)

To a solution of substituted phenyl semicarbazide in ethanol was added an equimolar quantity of the appropriate ketone. The pH of the reaction mixture was adjusted between 5 and 6 by adding glacial acetic acid. The reaction was monitored with TLC. The reaction mixture was refluxed for 1-2 hrs. The product obtained after cooling was filtered and recrystallized from 95% ethanol.

1. Cyclohexylidine-4-phenyl semicarbazide(a)

Yield: 84.0%, m.p.: 140° C, Rf 0.75, Silica gel G; Hexane; Ethyl acetate (1:9)

IR -3749.70, 3648.71, 2360.53, 1636.05, 1540.84, 1418.51, 1361.70, 860.05., 750.18 cm-1

2. (E)-1-(Butan-2-ylidine)-4- phenyl semicarbazide (b)

Yield: 62.0%, m.p.: 155°C, RF 0.50, Silica gel G; Hexane; Ethyl acetate (1:9)

IR -3649.08, 2925.08, 2856.87, 2343.79, 1705.94, 1541.25, 1386.85, 1125.96, 1043.10.747.23 cm-1

3. (E)-1-(7,7-dimethylbicyclo(2,2.1) heptanes-2-ylidine)-4- phenyl semicarbazide (7c)

Yield: 52.0%, m.p.: 178°C, RF 0.50, Silica gel G; Hexane; Ethyl acetate (1:9)

IR -3749.81, 3675.15, 2359.75, 1792.23, 1593.82, 1507.43, 1456.93 cm-1.

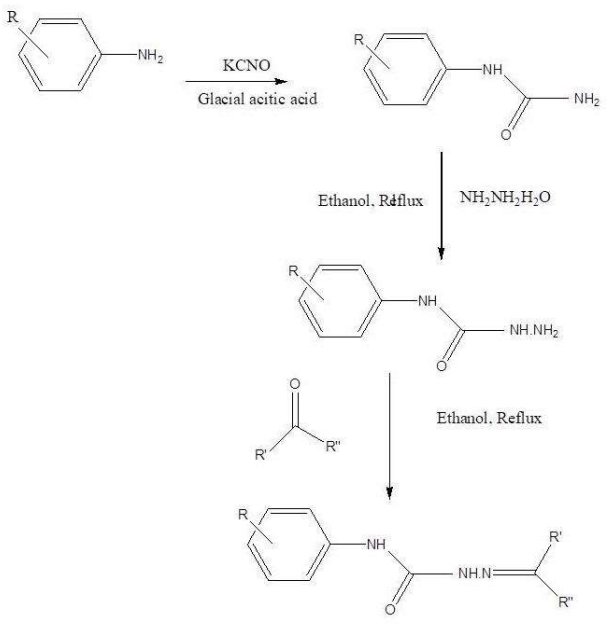

Figure 3. General synthetic scheme for aryl semicarbazone

4.1- benzhydryl-4-(4-chlorophenyl) semi carbazide(7d)

Yield: 48.0%, m.p.: more than250°C, RF 0.50, Silica gel G; Hexane; Ethyl acetate (1:9)

IR -3820.39, 3617.77, 2359.96, 1541.03, 1473.21, 1243.43, 679.07 cm-1.

1H NMR: (s ppm) 6.8-7.6(m, 15H, Ar-H), 6.7(s, 1 H,NH).

5. 1-(butane-2-ylidine)-4-(4-chlorophenyl) semicarbazide (7e)

Yield: 75.0%, m.p.: 160°C, RF 0.50, Silica gel G; Hexane; Ethyl acetate (1:9)

IR-3734.85, 3689.39, 2360.03, 1828.03, 1759.99, 1716.32, 1636.01, 1557.84, 1456.94, 1362.21, 783.12 cm-1

6. (E)-)-4-(4-chlorophenyl)-1-(1,7,7-trimethylbicyclo (2.2.1) heptanes-2-ylidine) semicarbazide (7f)

Yield: 78.0%, m.p.: 149°C, RF 0.56, Silica gel G; Hexane; Ethyl acetate (1:9)

IR – 3750.09, 3617.67, 2360.38, 1828.03, 2342.01, 1748.52, 1541.04, 1146.43, 884.49 cm-1

7. (E)--1-(1,7,7-trimethylbicyclo(2.2.1)heptanes-2- ylidine)-4-p-tolyl-semicarbazide(7g)

Yield: 69.0%, m.p.: 52°C, RF 0.59, Silica gel G; Hexane; Ethyl acetate (1:9)

IR – 3750.19, 3617.77, 3366.46, 2963.53, 2360.41, 1683.46, 1557.69, 1243.56, 1056.02cm-1

8. 1-cyclohylidine-4-p-tolyl semicarbazide (7h)

Yield: 59.0%, m.p.: 55°C, Rf 0.49, Silica gel G; Hexane; Ethyl acetate (1:9)

IR -3735.04, 3628.91, 2360.18, 1652.61, 1521.09, 1339.18, 994.42, 864.20, 810.89 cm-1

9. (E)--1-(1,7,7-trimethylbicyclo(2.2.1)heptanes-2-ylidine)-4-o-tolyl semicarbazide(7i)

Yield: 80.0%, m.p.: 54°C, Rf 0.68, Silica gel G; Hexane; Ethyl acetate (1:9)

IR-3750.18, 3310.58, 2360, 1646.20, 1540.61, 1403.22, 1338.40, 1239.93, 1048.02, 1015.86, 839.27, 798.14cm-1.

10. 1-(butane-2-ylidine)-4-o-tolyl semicarbazide (7j)

Yield: 79.0%, m.p.: 47°C, RF 0.78, Silica gel G; Hexane; Ethyl acetate (1:9)

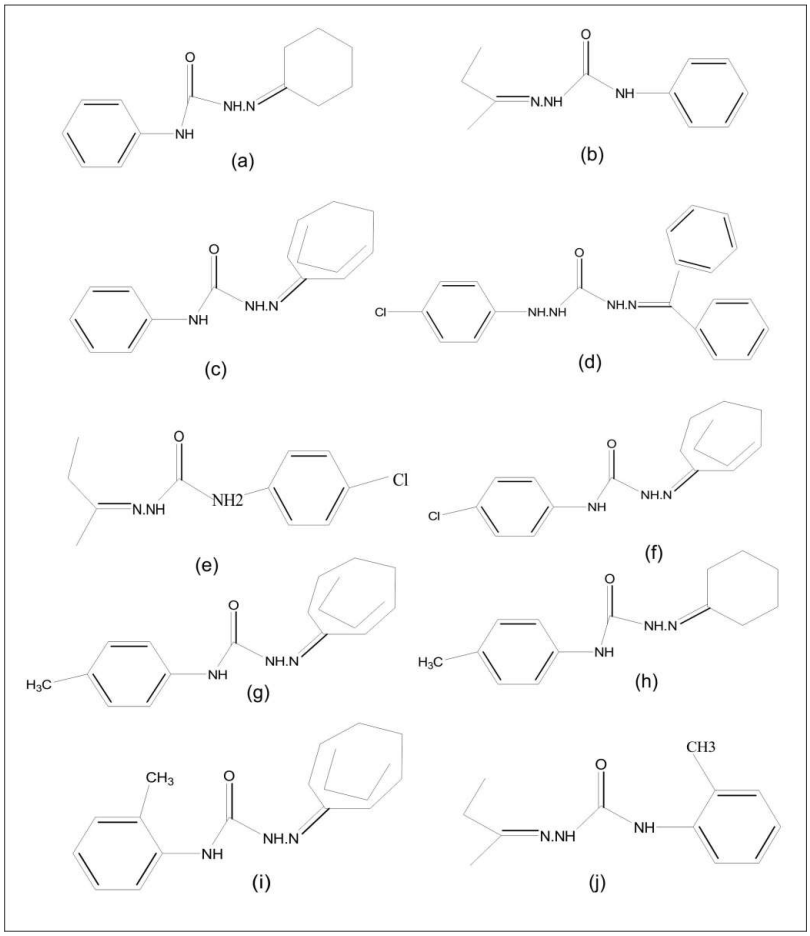

Figure 4. Structures of different synthesized molecules

IR-3749.81, 3595.72, 3421.21, 2360.23, 1908.66, 1646.98, 1521.22, 1435.47, 1254.74, 1073.34, 748.35cm-1.

Animals

Male albino mice weight (25-35 gm) was used to test drug synthesized. Maximal Electro shock-induced seizures. Female animals were excluded because of fact that the estrous cycle influences the seizure threshold. Animals were housed in propylene cage with dust-free rice husk as bleeding material under laboratory condition with the controlled environment of temperature 25 degrees±2, humidity 60%, and before subjecting them to experimentation the animal was given a week to acclimatize with laboratory conditions. The animals fasted overnight before the experiment.

Anticonvulsant activity

An experimental evaluation of Anticonvulsant activity of synthesized semicarbazone compounds done by Maximal Electroshock (MES) induced method. The Maximal Electroshock (MES) induced convulsion in animals to represent grandma type of epilepsy.

The Maximal Electroshock (MES) convulsion divided in 5-phases: Tonic flexion, Tonic Extensor, Clonic convulsion, Stupor and fifth is recovery/ death

Animal protocol and sample preparation

Standard sample: the concentration of phenytoin sodium was

Table 1. Anticonvulsant activities of synthesized compounds

Group (n=3)	Dose (100mg/kg	Body wt.(gm.)	Dose(ml)	Duration (sec) in various phases of convulsion				
				Flaxer	Extensor	Convulsion	Stupor	R/D
1	Control	30	0.30	4.59	15.68	68.29	78.69	D
		29	0.29	4.56	16.20	A	73.00	R
		26	0.26	4.15	14.42	29.28	74.00	D
2	Phenytoin	31	0.31	2.48	3.58	10.40	39.48	R
		23	0.23	2.39	3.39	11.59	35.85	R
		27	0.27	2.19	3.98	11.28	37.85	R
3	7a	31	0.31	4.47	10.01	23.10	23.30	R
		32	0.32	3.07	10.75	24.31	55.52	R
		30	0.30	2.99	10.78	20.99	56.47	D
4	7b	30	0.30	2.25	10.50	21.50	47.42	R
		31	0.31	2.77	9.98	22.80	39.85	R
		30	0.30	2.52	9.95	22.84	37.01	D
	7c	29	0.29	3.57	10.09	24.52	60.59	D
5		32	0.32	3.57	10.98	21.19	56.00	D
		33	0.33	2.69	10.14	22.28	47.10	D
6	7d	31	0.31	4.19	11.99	25.29	50.69	D
		32	0.32	4.40	12.49	24.59	48.48	R
		28	0.28	4.01	12.88	24.90	50.94	D
	7e	31	0.31	4.93	11.99	22.09	32.31	D
7		33	0.33	3.27	11.20	19.34	60.21	R
		27	0.27	3.30	10.50	22.28	48.49	R
8	7f	33	0.33	2.21	9.20	23.49	51.49	R
		32	0.32	1.98	10.01	20.89	27.98	R
		31	0.31	2.57	10.95	22.63	30.26	D
9	7g	31	0.31	2.54	9.80	23.01	44.10	R
		32	0.32	2.16	9.65	22.01	48.49	R
		32	0.32	2.67	9.98	22.86	55.20	D
10	7h	33	0.33	4.61	11.19	22.66	41.00	R
		32	0.32	2.59	11.20	24.64	60.49	R
		31	0.31	4.85	10.99	22.97	55.10	D
11	7i	33	0.33	4.38	11.19	23.82	44.42	D
		33	0.33	4.59	11.99	22.89	41.85	R
		31	0.31	4.19	12.58	22.63	47.59	D
12	7j	28	0.28	3.98	11.37	11.28	33.79	R
		29	0.29	3.39	11.50	11.50	60.28	R
		30	0.30	3.58	10.99	11.22	A	D

Here, R=recovery, D=death, A=absent

Table 2. Anticonvulsant Biological Screening by MES method

S. No.	Dose (25mg/kg)	Flaxer ±SEM	HLTE ±SEM	Convulsion ±SEM	STUPER ±SEM	R/D
1.	**Control**	4.36±0.13	15.66±0.28	29.14±0.69	75.42±0.12	20%
2.	**Phenytoin**	2.31±0.04	3.61±0.04	11.19±0.19	38.20±075	100%
3.	**7a**	3.18±0.38	10.50±0.80	21.55±1.17	50.72±5.00	80%
4.	**7b**	2.49±0.05	10.01±0.29	19.79±2.19	41.80±2.20	60%
5.	**7c**	3.21±0.39	10.66±0.62	21.54±1.29	53.40±6.49	60%
6.	**7d**	4.20±0.20	12.50±0.53	25.54±0.99	50.70±5.53	40%
7.	**7e**	3.39±0.41	11.20±.068	20.55±1.49	49.10±6.10	60%
8.	**7f**	2.22±0.13	9.89±.0.15	21.16±0.71	35.89±6.89	80%
9.	**7g**	2.41±0.11	9.95±0.38	22.51±0.59	53.29±1.69	80%
10.	**7h**	3.65±0.25	11.30±0.38	23.41±0.78	53.26±3.11	60%
11.	**7i**	4.19±0.18	12.00±0.49	23.78±0.65	41.17±2.36	40%
12.	**7j**	3.64±0.16	11.25±0.48	23.73±1.20	51.71±5.81	60%

N=Number of animal, SEM=Standard error mean, Standard drug=Phenytoin sodium (25mg/kg), Control=DMSO (Dimethylsulphoxide), R/D=Recovery/Death

prepared in DMSO solution and the concentration of the final solution was2.5mg/ml to equate with t of a compound synthesized.

Test sample: Suspension of synthesized derivatives was prepared in DMSO having a concentration of 2.5mg/ml.

Weighed and numbered the animals, divided into 12 groups, each group containing 5 animals. One group was used to study the effect of control. One group was used for the study effect of the standard drug (Phenytoin Sod.) and another 10 groups were used for the study of the effect of synthesized final molecules.

MES induced seizures in albino mice

The albino mice were chosen for preliminary screening. Mice with showed extension of hind limb were induced in the study. The seizure was induced by MES in albino mice (weight 25-35 gm) with the help of an electro convulsometer bypassing a current of 60MA for 0.2 sec. using an electrode to the cornea of mice. The drug and DMSO were given one hour before induction of convulsion. The animal has observed for the extensor phase as well its duration. The reduction and abolition of the extensor phase (Tonic phase) in the drug-treated group were taken as criteria for anticonvulsant activity.

Results and discussion

In this project, the synthesis of semicarbazone derivatives was carried out. All molecules were synthesized using the common starting material –aniline. In all compounds, an intermediate was first formed by substituted phenyl urea using substituted aniline and potassium cyanate, and then it was hydrolyzed to get substituted phenyl semicarbazide, which was directly coupled with ketones. The general scheme utilized for the synthesis of aryl semicarbazone derivatives are outlined below in figure 3 .All the synthesized compounds were screened for their anticonvulsant activity by the MES method:

Conclusion

From this present research study, it can be concluded that designed semicarbazones were synthesized and characterized successfully. After synthesis of designed semicarbazones compounds were evaluated for anticonvulsant activity. The electroshock assay in mice is used primarily as an indication for all compounds which are effective in Grand-mal epilepsy. Tonic hind limb extensions are evoked by electric stimuli which are suppressed by synthesized compounds. Finally, Compound 7f & 7g have shown better activity in comparison to the other molecules.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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