"SCREENING OF SEMICARBAZONES AS ANTICONVULSANT AGENTS"

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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.

Method- 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.

Result-

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 hyper activity involving essentially all parts of the brain or to hyper activity of only a portion of the brain [1]. Epilepsy is a collective term that includes over 40 different types of human seizures disorders. Approx 1% of world population at any one time (>50 million people worldwide) is afflicted with this serious neurological disorders. Although the current drug provide adequate seizure control in many patients, it is roughly estimated that up to 28-30% of patients are poorly treated with the available anti epileptic drugs (AED's). Moreover, many (AED's) have serious side effects and lifelong medication may be required [2-5]. Conventional antiepileptic drugs (AED's).

Phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepines, are widely used but exhibit and unfavorable side effect profile and failure to adequately control seizures in the recent yearnewdrugs(Oxcarbazepine, Lamotrigine, Topiramate,Gabapentin,Zonisamide,Tigabine,Fosphenitoin,Vigabatrine & felbamate) have been added to the list of therapeutic agents against epilepsy. However there is a significant group of patients (up to 30%) who are resistant to the available antiepileptic drugs. The long established AED's control seizures in 50% of people developing partial seizures and in 60-70% of those developing generalized seizures [6-11].

In the 1960s, research in antiepileptic drug development was stimulated by the creation of the epilepsy Branch and the epilepsy Advisory Committee with in the United states national institute of Neurological and communicative disorders and stroke (NINCDS).These programs were established to collate and review the neuroscience literature pertinent to epilepsy and encouraged to careen large numbers of potentially new anticonvulsants. From this point, the development of new drugs concentrated on different molecular structure, resulting in marketing of carbamazepine (1974), clonazepam (1975) and valproate (1978) [7-10]. It has been estimated that adequate control of seizures could not be obtained in up to 20% of the patients with epilepsy using first generation of antiepileptic drugs (Phenobarbital, phenytoin, carbamzepine, sodiumvalproate, and diazepam). A group of new drugs including felbamate, gabapentin, lamotrigene, oxacarbazepine, topiramate, milacemide, vigabatrine and zonisamide are in to clinical practice .The convulsions of approximately 25% of epileptics are inadequately controlled by current clinically available drugs. Current drug therapy is accompanied by numerous side effects including drowsiness, ataxia, gastrointestinal disturbance, gingival hyperplasia, hirsutism and megaloblastic anemia. [10]

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 urgent need to develop new AEDs. The search f or antiepileptic compounds with a more selective activity and lower toxicity continue to be an area of investigation in medicinal chemistry. A rational drug design process of a new anticonvulsant could be achieved in several ways. 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; hydantoines, iminostillbene, barbiturates, benzodiazepines, valproate, imides, oxazolidine2, 3-diones,

sulfonamides and miscellaneous agents. The efficacy of AED's is due to the main activities which include interaction with ion channels or neurotransmitter systems [12-21].

The new AED's and anticonvulsant agents have been reviewed last few years. The chemical diversity and various mechanism 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, on the basic of seizure type rather than etiology.

These review present new anticonvulsant agents representing various structures for which the precise mechanism of action is still not known. The newer agents include heterocyclic compounds, sulfonamides, amino acids, amides, enaminones and others. The new structural classes of compounds can be useful for the design of future targets and development of new drugs (22-26).

Most recently, a number of new antiepileptic drugs have been approved 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 with novel structures have been 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 (12-15).

Approaches for new antiepileptic drugs:(27-71)

The ideal new antiepileptic drug is one that which will be effective in all seizures disorders in all patients and have no adverse effects. It must be easy to monitor, allowing in frequent clinic visits by the patients, can be administered once or twice daily and is in expensive. In addition, water solubility, a long half life and negligible protein binding properties are preferable.

However, because of the heterogeneity of epilepsy and inter patient, variability in metabolic handling and receptor responses to drug , the possibility of achieving such a drug is at present negligible. Thus current approaches are based on the following target characteristic:

a) As effective as existing therapy
b) Improved therapeutic ratio (i.e. less toxic in proportion to its observed benefit)
c) Simple pharmacokinetics with a half life of 12-24 hours so that once or twice daily administration would be possible.
d) Should not induce or inhibit liver enzymes and consequently have the potential to cause drug interactions.

e) Should not cause tolerance or withdrawal problems.

There are at least three approaches which are currently used for the development of new antiepileptic drugs:

1. Random screening of chemicals of diverse structural categories for anticonvulsant activity,
2. Structural variation of known antiepileptic drugs.
3. Rational drug design.

The efficacy of various antiepileptic drugs (AED's) is due to their activities which include interaction with ion channel or neurotransmitter system. Amongst these classes semicarbazones are of considerable interest because of their better CNS activity especially as anticonvulsants.

The extensive SAR studies of semicarbazones postulate a specific binding site which include.

i) An aryl hydrophobic binding site with halo substituent preferably at the Para position
ii) A hydrogen bonding domain
iii) An electron donor group.
iv) Another hydrophobic –hydrophilic site controlling the pharmacokinetic properties of the anticonvulsant.

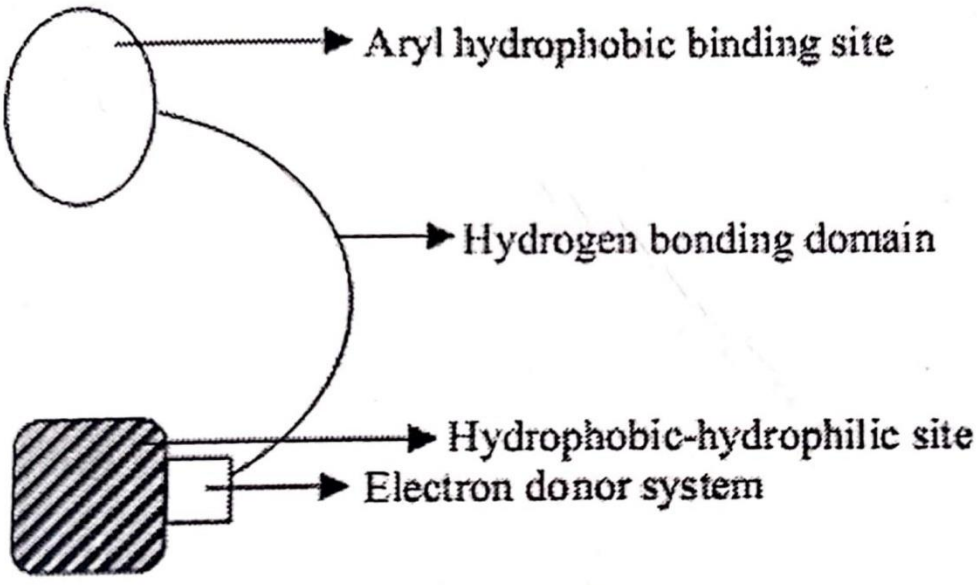


Fig. no. 1- Pharmacophore of the designed Semicarbazone

Structural requirements for the semicarbazones displaying anticonvulsant activity Development of semicarbazones was initially based on the hypothesis of Parmar ***et al.*** [72].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 ,a number of aryl semicarbazones, including series 1, were found to display significant activity (3,4) [73]. These compounds were to interact at two locations on a putative binding site designated a hydrogen bonding area and an aryl binding site (5) .However ,since the aryl group can be replaced by other hydrophobic moieties with retention of anticonvulsant activity (6),the proportion of the binding site with which the aryl group of series [74-75]. The related compounds will be referred to as a hydrophobic bonding area rather than an aryl binding site. The principal objective of the present investigation was the preparation of a number of analogues of with a view to further evaluating the 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.*[15-16] the pharmacophoric elements were thought to be a lipophilic aryl ring 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 have also been reported. Substitutions in the aryl ring by halogens have been found to increase potency in the MES screen. The presence of electron-rich atom or group attached at the Para position of the aryl ring showed increased potency in the MES screen Due to importance of the hetero aryl semicarbazones, we have designed the novel molecules with nucleus of semicarbazones [78]. Based on pharmacophore model as cited in literature review, we design the novel derivative of semicarbazone or thiosemicarbazone. The designed scaffold structure is given in **Figure-2.**

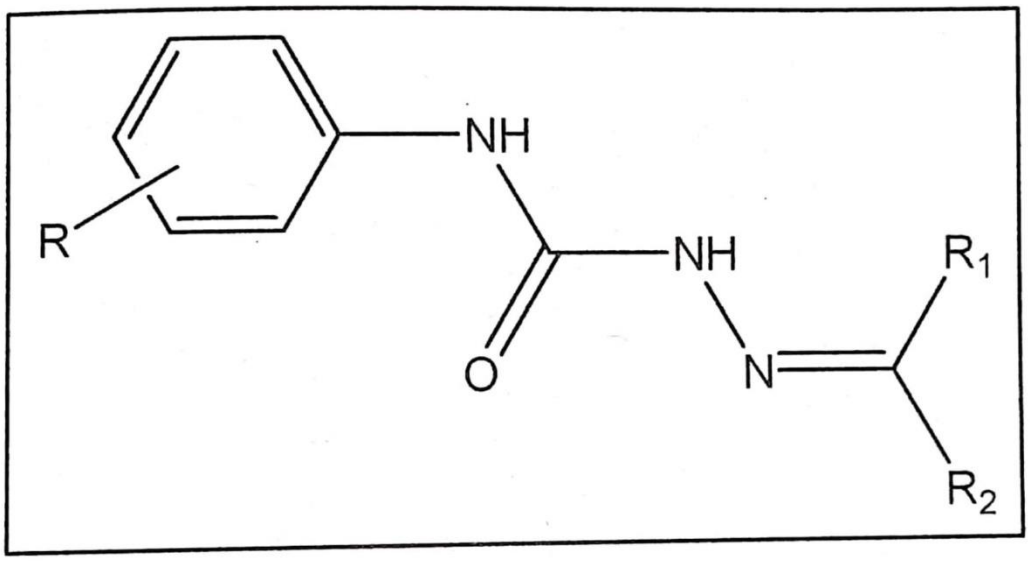


Fig. no. 2 Designed scaffold

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

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 were 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 "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.

The following are the chemicals used for biological testing:

1) Dimethylsulfoxide (A.R.Grade, S.D.Fine Chem.Ltd. Mumbai).

Synthesis of compounds aryl semicarbazones (7a-j)

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

1. ***Cyclohexylidine-4-phenyl semicarbazide(7a)***

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 (7b)***

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}.

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}.

^{1}H 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)

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 animal were excluded because of fact that estrous cycle influences the seizure threshold. Animal were housed in propylene cage with dust free rice husk as bleeding material under laboratory condition with controlled environment of temperature 25 degree ± 2, humidity 60% and before subjecting them to experimentation the animal were given a week of time to acclimatize with laboratory condition . The animals were fasted over night before experiment.

Evolution of Anticonvulsant activity-

An experimental evaluation of Anticonvulsant activity of synthesized semicarbazone compounds done by Maximal Electroshock (MES) induced method.

The by Maximal Electroshock (MES) induced convulsion in animals represent grandma type of epilepsy.

The Maximal Electroshock (MES) convulsion divided in 5- phases.

1. Tonic flexion

2. Tonic Extensor

3. Clonic convulsion

4. Stupor

5. Recovery/ Death

Drug treatment

a) Standard sample: the concentration of phenytoin sodium was prepared in DMSO solution and concentration of final solution was2.5mg/ml and to equate with t of compound synthesized.
b) Test sample: Suspension of synthesized derivatives was prepared in DMSO having concentration of 2.5mg/ml.

Requirements- Test tube, mice, syringes, Needles, Electroconvulsometer, Volumetric flask, Oral feeding needle etc...

Study of Activity-
Weighed and numbered the animals, divided in 12 groups, each group contain 5 animals. One group was used for study the effect of control. One group was used for the study effect of standard drug (Phenytoin Sod.) and another 10 group were used for the study of 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 (weight25-35 gm) with the help of electroconvulsometer by passing current of 60MA for 0.2 sec. using electrode to the cornea of mice. The drug and DMSO were given one hour prior to induction of convulsion .The animal observed for the extensor phase as well its duration. The reduction and abolition of extensor phase (Tonic phase) in drug treated group was taken as criteria for anticonvulsant activity.

RESULT 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 (3) using substituted aniline (1) and potassium cyanate, and then it was hydrolyzed to get substituted phenyl semicarbazide (4), which was directly coupled with ketones (7).

The general scheme utilized for the synthesis of aryl semicarbazone derivatives are outlined below in **Figure-3.**

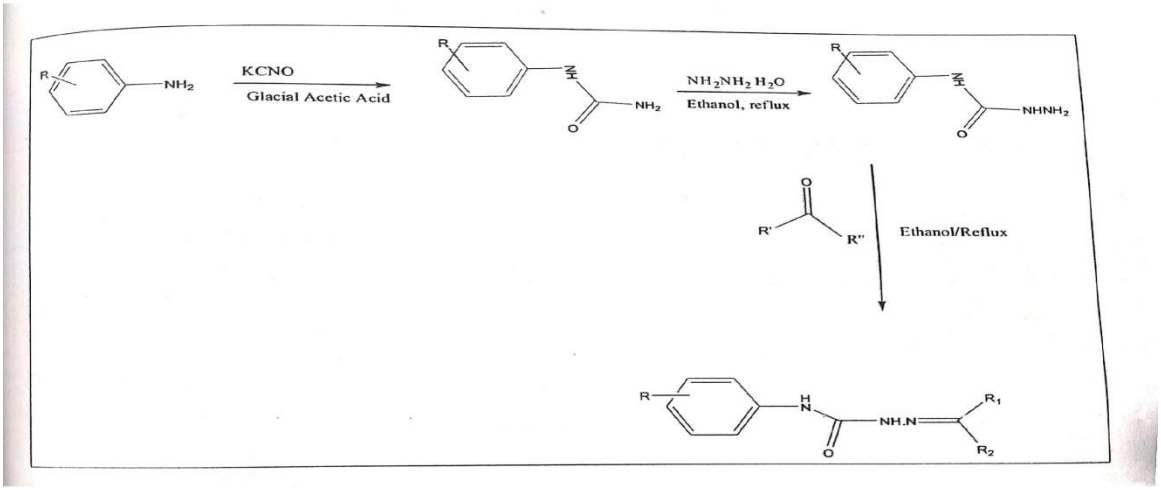
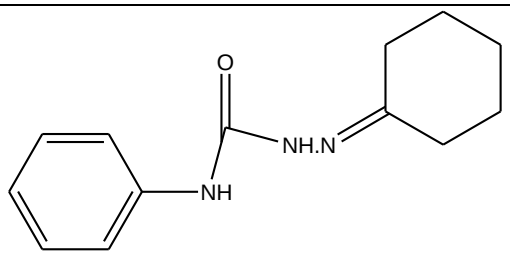
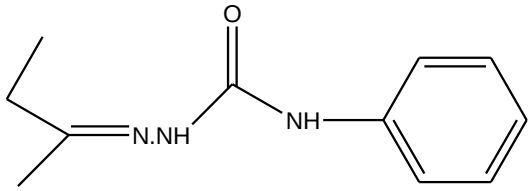
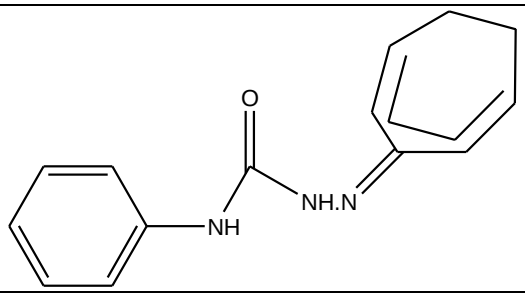
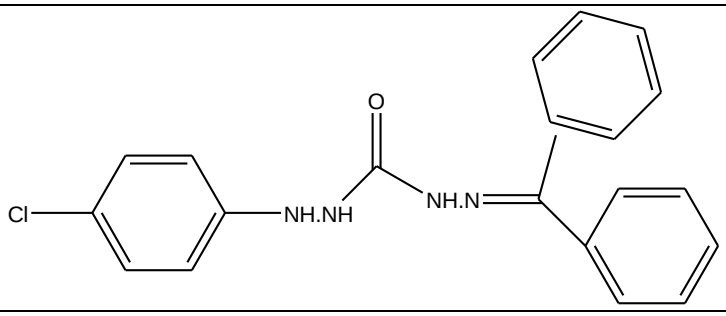
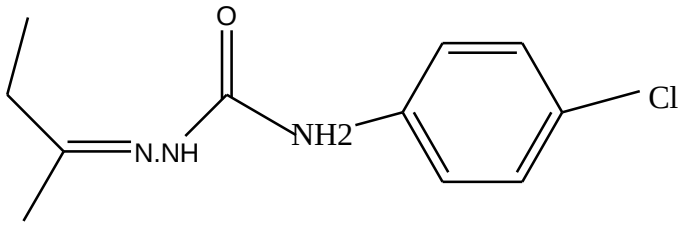
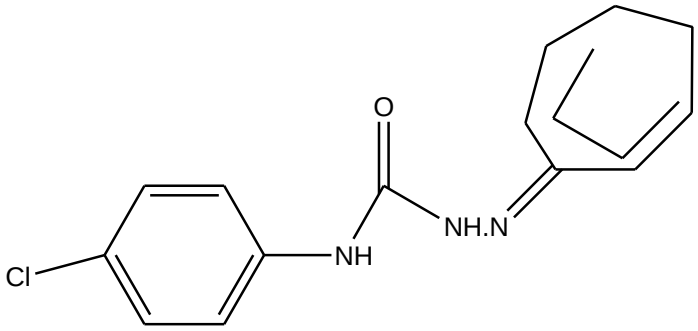
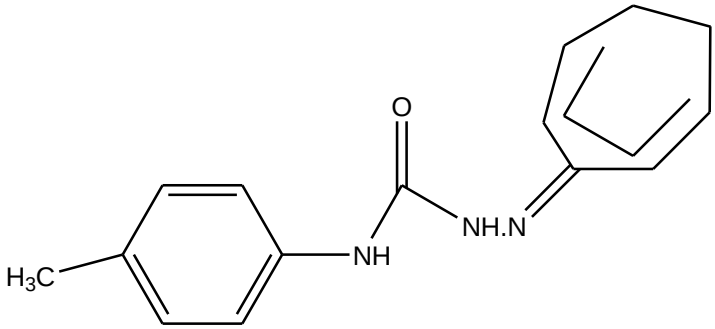
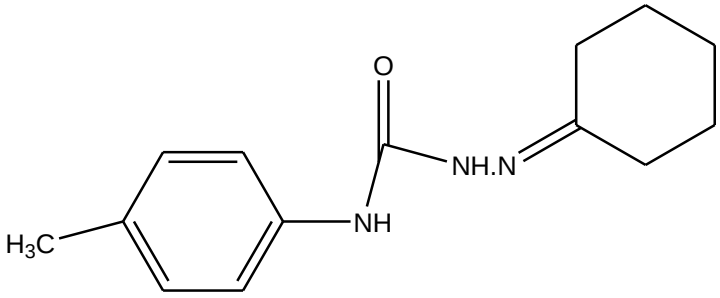
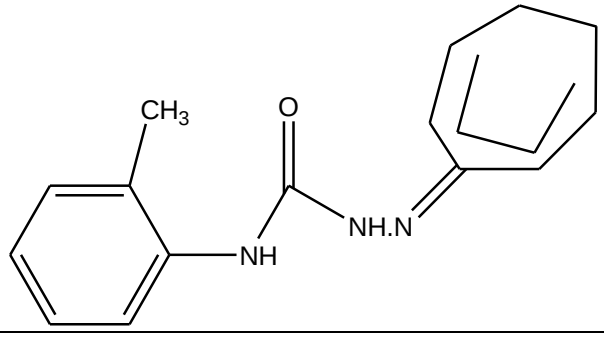
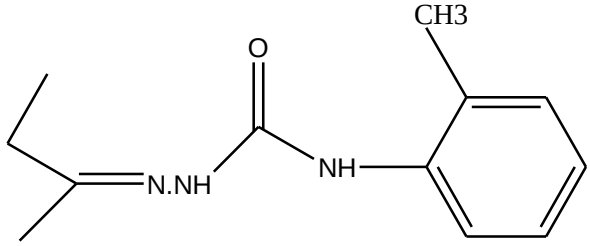


Fig. no. 3- General synthetic scheme for aryl semicarbazone

Table no. 1 List of synthesized molecules-

Sr. No	Mol. ID	Structure
1	7a	
2	7b	
3	7c	
4	7d	

5	7e	
6	7f	
7	7g	
8	7h	
9	7i	
10	7j	

Result of biological evaluation of synthesized molecules:

All the synthesized compounds were screened for their anticonvulsant activity by MES method.

Table -2 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
5	7c	29	0.29	3.57	10.09	24.52	60.59	D
		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
7	7e	31	0.31	4.93	11.99	22.09	32.31	D
		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 no. 3 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.

SUMMARY AND CONCLUSION-

In summary, 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 comparisons to the other molecules.

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