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Recent Advances in use of Semicarbazones as Anticonvulsant Agents: A Review

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ABSTRACT

Semicarbazone derivatives are most effective anticonvulsant agents. Anticonvulsant effect of numerous semicarbazone derivatives has been demonstrated in a wide range of preclinical anticonvulsant models. Semicarbazones and its analogs are versatile substrates and these have been utilized as constructing unit in synthesis of various heterocyclic compounds. Semicarbazone derivatives have been used in obtaining new products that retains different biological activities. Here, we presented a detailed evaluation of semicarbazone derivatives for their significant anticonvulsant activity along with discussion of recent synthetic advancements in semicarbazones as anticonvulsants.

Keywords: Semicarbazone derivatives, anticonvulsant activity, MES method, ScPTZ screen

INTRODUCTION

Semicarbazones derivatives are obtained by condensation reaction between a ketone or aldehyde and a hydrazine (Semicarbazide) moiety. Semicarbazones and its analogs are versatile substrates as these have been further expanded for the synthesis of various heterocyclic compounds. According to the World Health Organization (WHO), Epilepsy is a most common neurological disorder. Epilepsy is an abrupt and transient disturbance of cerebral functions with or without loss of consciousness and it is characterized by paroxysmal, excessive and hyper synchronous discharges of a large number of neurons.[1] It is a syndrome not a disease affecting a large section (0.5-1%) of the population throughout the world.[2-4] Epilepsy or seizures happens when normal electrical activity in brain goes wrong. Epilepsy can be of two type depending on the which part of brain is affected : partial and generalized epilepsy. The antiepileptic drugs (AEDs) are effective in only 65-75% patients.[5-11] Currently drugs available for the treatment of epilepsy are topiramate, zonisamide, vigabatrin etc. Because of the use of currently available antiepileptic drugs, most of the patients fail to control seizure, and other who experience the control in seizure, have eloquent side effects. The side effects of current drugs limit their use and validate the need for developing new anticonvulsant.[12-18] Previous studies has shown that various amides (-$CONH_2$) and carbamides (NH-CO-NH) containing drugs possesses anticonvulsant properties. The prime requirement to search the combination of both these structures led to the synthesis of semicarbazones as anticonvulsant agent.[19-20] The semicarbazones compounds interact with putative binding site to show their anticonvulsant properties. Semicarbazones are generally derived by the condensation of aldehydes or ketones with semicarbazide [$NH_2NHC(=O)NH_2$], forming a new class of compounds having structure [$R_2C=NNHC(=O)NH_2$]. Semicarbazones have been known for various pharmacological activities like anticonvulsant, antitumor and antimicrobial activity. Semicarbazones are a class of interesting compounds for the researchers looking for new anticonvulsant agents. We here focused on recent synthetic advancement of semicarbazones and their evaluation as anticonvulsant agents in the present review.

CHEMISTRY

According to IUPAC recommendations, semicarbazones are named by adding the class name 'semicarbazone' after the name of condensing aldehyde or ketone.

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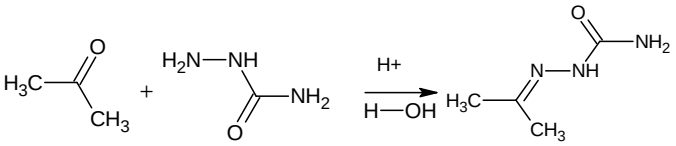


Figure 1. Synthesis of semicarbazone

The semicarbazone also includes derivatives with substituent on the amide nitrogen of semicarbazide. The IUPAC numbering and the basic structure of semicarbazone compounds are shown in figure 2.

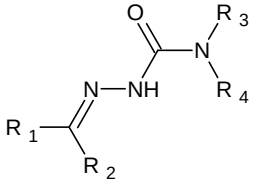


Figure 2. General chemical structure of Semicarbazone.

Semicarbazones are generally obtained when ammonia related compound such as semicarbazide containing nitrogen atom with a lone pair of electrons as a nucleophile which added to the carbonyl group of aldehydes or ketones and forms an unstable intermediate. This intermediate rapidly loses a molecule of water and form a condensation product semicarbazone. In solid state the semicarbazones exist predominantly in the amido form, whereas in solution state, they exhibit a amido-iminol(keto-enol type) tautomerism due to interaction with solvent molecules.

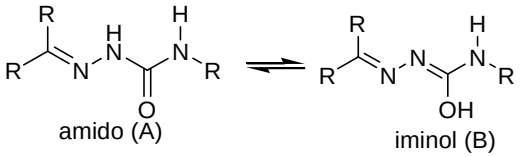
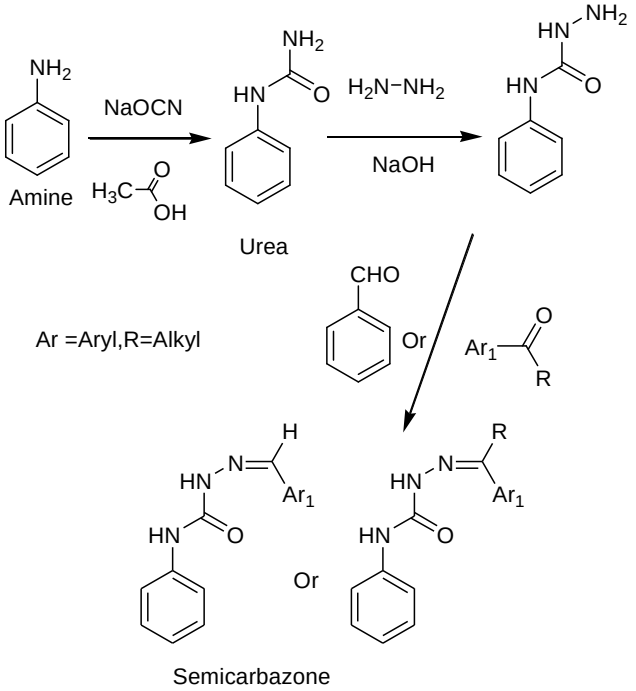


Figure 3. Amido-iminol tautomerism forms of semicarbazone

Amido form acts as a neutral bidentate ligand and the iminol form can deprotonate and serve as monoanionic bidentate ligand in metal complexes. Thus semicarbazones are adaptable ligands in both forms: neutral and anionic; and behave as chelating ligands when reacted with metallic cations and form metal-complexes. Semicarbazone moiety having an efficient electron delocalization with both tautomeric forms and thus the delocalization of electron charge density enhance with the aromatic substitution on the semicarbazone skeleton. A recent review on semicarbazone structures shows that in the solid state free unsubstituted semicarbazones are usually planar with the oxygen atom trans to the azomethine nitrogen atom (configuration E).[20] Trans arrangement places amine (4N) and azomethine (1N) nitrogen atoms at suitable position for formation of intramolecular hydrogen bonding. The coordination possibilities of semicarbazones are further increased when the substituents having additional donor atoms are present on semicarbazones.

General Method for the Synthesis of Semicarbazone

The general procedure for the synthesis of semicarbazone analogues is shown in Scheme 1.



Scheme 1. General route for synthesis of semicarbazones

Evolution of Semicarbazone as Anticonvulsant

The semicarbazone moiety is formed by a number of smaller functional groups which exhibit anticonvulsant activity (Figure 4)

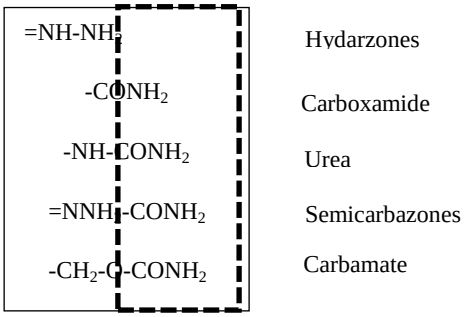


Figure 4. Structural resemblance of various amine moieties of condensation products with aldehydes and ketones. Carboxamide as Anticonvulsant

Many carboxamide drugs have been reported for treatment of epilepsy. The initial drug carbamazepine is a drug of choice for the treatment of grandma epilepsy and it is effective against temporal lobe and generalized seizures.[21] Modification in the drug has resulted in oxacarbazepine[22] and eslicarbamazepine[23] : two clinically most effective drugs for the treatment of epilepsy. The first GABA(Gamma-aminobutyric acid agonist) Progabide is effective in all three types of epilepsies viz generalized tonic-clonic, myoclonic and paratial seizures occurring in both children and adults.[24]

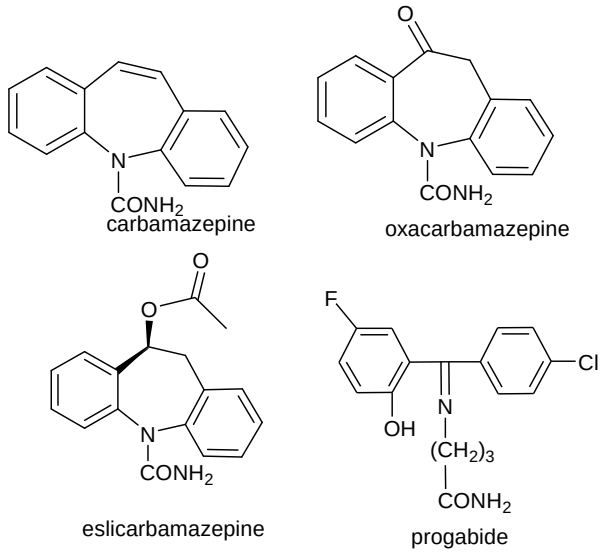


Figure 5. Chemical Structure of Carboxamide anticonvulsants

HYDRAZONE AS ANTICONVULASANT

Anticonvulsant activity in hydrazones, Schiff bases and Mannich bases of isatin have been reported.[25,47] Low anticonvulsant activity is shown by indole-3-carboxaldehyde hydrazones.[26] Recently (±)-3-menthone aryl acid hydrazones has shown significant protection in the maximal clonic seizures and 4-Chloro-*N*-(2-isopropyl-5-methylcyclohexylidene)benzo hydr - azide activated in maximal electroshock seizure (MES) with ED_{50}(Effective dose) of 16.1 mg and protective index (PI = TD_{50}/ED_{50}) greater than 20 TD_{50} (Median toxic dose).

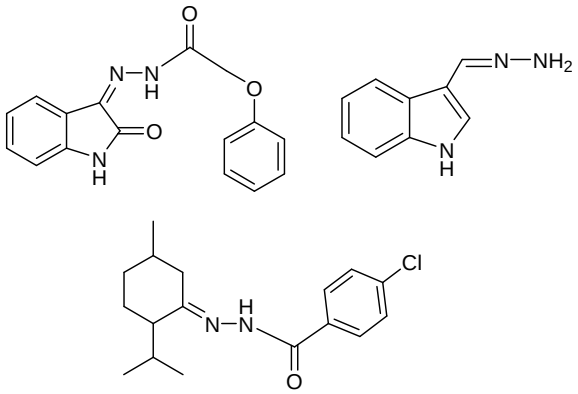


Figure 6. Chemical structure of Hydrazones anticonvulsants

UREA DERIVATIVES AS ANTICONVULSANT

In the earlier days, acyclic urea's and cyclic uredines demonstrated anticonvulsant activity whereas many of these drugs were preferred for the treatment of epilepsy.[26] Currently available drugs used in hospitals for the treatment of epileptic seizures are phenacemide,[27] hydantoin derivatives, phenytoin[28] and its water soluble prodrug fosphenytoin (Figure 7).[29] Ethosuximide, a succinimide derivative is considered as the first drug of choice in treatment of absence seizures.[30] Phenobarbital[31] is a barbiturate and the most extensively used anticonvulsant worldwide. Its N-CH_3 analog methyl Phenobarbital has also been used as an anticonvulsant agent. Primidone is usually used for generalized tonic-clonic and complex seizures.

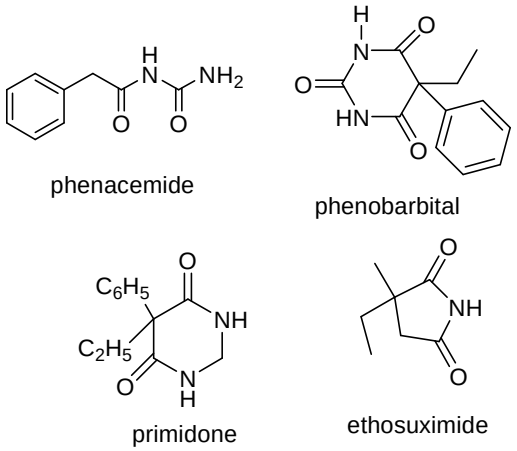


Figure 7. Chemical structure of urea anticonvulsants
Semicarbazones as Anticonvulsant

H. Rajak et al. (2014) Synthesized benzimidazole substituted semicarbazones containing 1, 3,4 –oxadiazole(Figure 8) with antiepileptic activity. The antiepileptic activity was tested by using MEX model by using dose of 50 mg/kg by intra-peritoneal (imp.) injection. Group like nitro, hydroxy on distant phenyl ring showed high antiepileptic activity.[32]

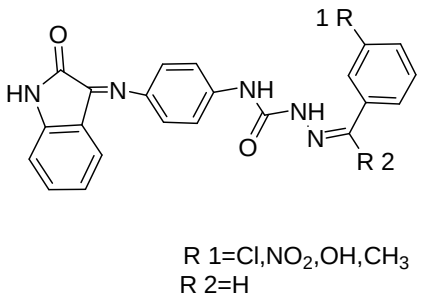


Figure 8. benzimidazole substituted semicarbazones containing 1, 3,4 –oxadiazole

Rajeev et al. (2013) evaluated a series of 5, 7-dibromoisatin semicarbazones for anticonvulsant and CNS depressant activities after intraperitoneal administration to mice by maximal electroshock (MES) induced seizure method. The minimal motor impairment was determined by rotarod test. Compounds (Z)-1-(5,7-dibromo-2-oxoindolin-3-ylidene)-4-(4-chlorophenyl)semicarbazide, (Z)-1-(5,7-dibromo-2-oxoindolin-3-ylidene)-4-(3-chloro4fluorophenyl) semicarbazide and (Z)-1-(5,7-dibromo-1-methyl-2-oxoindolin-3-ylidene)-4-(3-chloro-4-fluorophenyl)semicarbazide exhibited most prominent anticonvulsant effect in the series with little or no neurotoxicity and little CNS depressant effect as compared to standard drug.[33]

Devender et al. (2012) synthesized a series of 4-(3-Chlorophenyl)-1-(substituted acetophenone) semicarbazones and evaluated for their anticonvulsant activity by Maximal Electroshock (MES) method using phenytoin as standard at a

concentration of 30 mg/kg. The anticonvulsant effect of the newly synthesized compounds has been assessed by absence or reduction of hind limb tonic extensor phase. They also reported that among the synthesized derivatives compounds named4-(3-Chlorophenyl)-1-(4'-fluoroacetophenone) Semicarbazone and 1-(2'Chloroacetophenone)-4-(3-chlorophenyl) semicarbazone were most potent compounds in the series.[34]

Rajak et al. (2012) evaluated various semicarbazones containing 1,3,4–thiadiazole and quinazoline ring. The reported derivatives were evaluated for anticonvulsant activity using MES and scPTZ models. In initial screening most of the compounds showed anticonvulsant activity and neurotoxity of compounds as measured by rota rod apparatus. Compounds showed moderate activity as measured by MES screen at doses 100 mg/kg and 300 mg/kg after intraperitoneal administration. Compound(figure 9) N1-{5-(2-methyl-4-oxo quinazolin-3(4*H*)-yl) amino] methyl}-1, 3, 4-thiadiazol-2-yl)}-N4-[1-(4-nitro phenyl) (phenyl) methanone]-semicarbazones were also found active in scPTZ screen at dose 300 mg/kg and were devoid of neurotoxicity in rota rod test.[35]

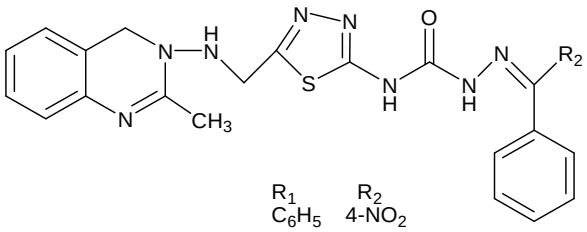


Figure 9. Chemical structure of semicarbazones containing 1, 3, 4-thiadiazole and quinazoline ring

Pandeya et al. (2011) synthesized(figure10) a series of 4-aryl substituted semicarbazones of some terpenes i.e., citral (acyclicterpene), camphor (bicyclic terpene) and menthone (monocyclic terpene) essential for anticonvulsant activity. They also evaluated anticonvulsant and sedative – hypnotic activity of synthesized compounds after intraperitoneal injection to mice as examined by three chemo shock models for a single dose study. These three chemo shock model induced convulsion model. All the compounds were also evaluated for neurotoxicity screening by rota rod test and sedative-hypnotic activity by using pentobarbitone induced narcosis model and these showed anticonvulsant activity in one or more test models. The reported compounds were having anticonvulsant activity with no neurotoxicity and lesser sedative-hypnotic activity.[36]

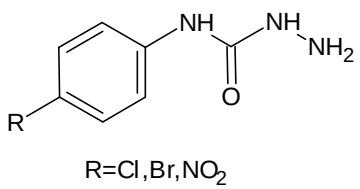


Figure 10. Chemical structure of substituted semicarbazones

Amir et al. (2010) synthesized various 3- chloro- 4- flouro phenyl substituted semicarbazones (figure 11) and evaluated for anticonvulsant activity by using MES test. Initial screening of the compounds are also tested for their neurotoxicity and CNS depressant activity using rotarod test and forced swim pool method respectively. Compound named N1- (3- chloro – 4 – flouro phenyl) – N4- (4- N, N- dimethyl amino benzaldehyde) semicarbazone provided 50 % protection at 30 mg/kg and 100 % protection against seizures at 100 mg/kg after 4.0 h without any sign of neurotoxicity. Compound also performed weak CNS depressant activity as compared to standard drug carbamazepine.[37]

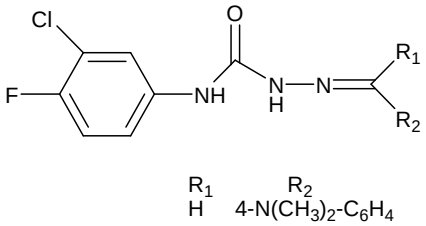


Figure 11. 3-chloro, 4-flouro phenyl substituted semicarbazones

Shaifee et al. (2009) has synthesized a series of 4- (2-phenoxy phenyl) semicarbazones (figure 12) and evaluated for anticonvulsant activity in petylenetetrazole induced kindling model in adult male wistar rats. A compound named that 4- (2-Phenoxy phenyl) -1- [(pyridine-2-yl) methylene] semicarbazide and 4- (2- Phenoxy phenyl) -1- [(pyridine-4-yl) methylene] semicarbazide exhibited greater protection from seizures than sodium valproate at dose of 100 mg/kg on intraperitoneal administration.[38]

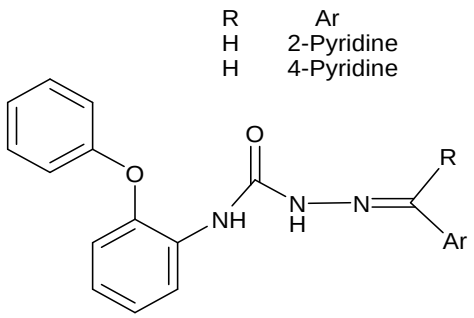
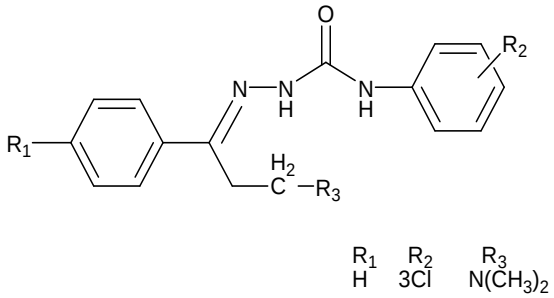


Figure 12. Chemical Structure of 4(2-phenoxy phenyl) semicarbazones

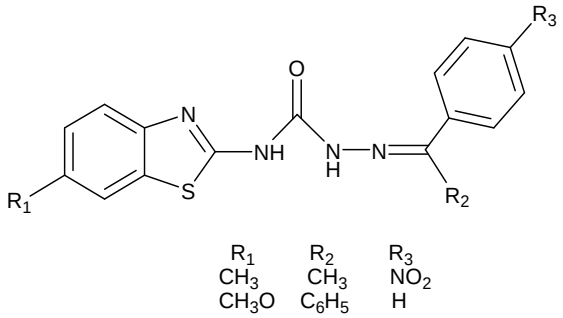
Raja et al. (2007) evaluated various semicarbazones of acetophenone mannich base (figure 13). All of them exhibited anticonvulsant activity MES, scMET and scSTY test models. Initial screening of the synthesized compounds for the anticonvulsant activity was 70%. A compound named 3- chloro phenyl [β – dimethyl amino propiophenone] semicarbazone emerged as most promising anticonvulsant compound which exhibited superior activity than reference compounds phenytoin and carbemazepine in MES and scMET test models at a dose of 300 mg/kg after intraperitoneal administration to mice. The reported compounds were also active in oral MES screen in rats at dose of 30 mg/kg.[39]



R_1	R_2	R_3
H	3Cl	$N(CH_3)_2$

Figure 13. Semicarbazones of acetophenone mannich base

Siddiqui et al. (2007) has developed a series of 1, 3 – benzothiazol – 2- yl semicarbazones (figure 14) and evaluated their anticonvulsant activity using MES test model. The Compound*N*-(6-methyl-1,3-benzothiazol-2-yl)-2-[1-(4-nitrophenyl) ethylidene] hydrazine carboxamide and 2-(diphenyl methylidene)-*N*-(6-methoxy-1,3-benzothiazol-2-yl) hydrazine carboxamide exhibited 100% protection in MES test at 0.5 and 4.0 h after intraperitoneal administration of dose 30 mg/kg without any sign of neurotoxicity.[40]



R_1	R_2	R_3
CH_3	CH_3	NO_2
CH_3O	C_6H_5	H

Figure 14. 1,3-benzothiazol-2yl semicarbazones

Aggarwal et al. (2004) integrated various 4-aryl substituted semicarbazones of levulinic acid (figure 15)and evaluated for anticonvulsant activity using MES and scMET test models. Neurotoxicity of the synthesized compounds has been measured by rotarod apparatus. Most of the compounds showed anticonvulsant activity. They observed that 4-(4'-flouro phenyl) levulinic acid semicarbazone showed most promising activity in both screens with low neurotoxicity. These compounds were also active in oral MES screen in rats at dose of 50 mg/kg without any sign of neurotoxicity.[41]

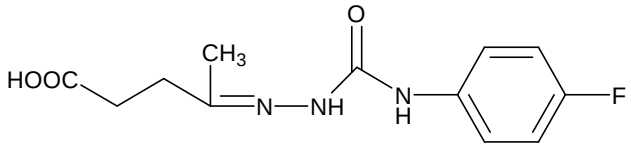


Figure 15. Chemical structure of aryl substituted semicarbazones of levulinic acid

Yogeeswari et al. (2004) reported a series of 3-chloro-2 methyl phenyl substituted semicarbazones (figure-16) and evaluated for anticonvulsant and other CNS activities. Anticonvulsant activity of all compounds tested using MES, scPTZ and scSTY test models after intraperitoneal administration to mice at doses of 30, 100, 300 mg/kg. They found that compounds were active in all the aforementioned screens as well as in oral MES screen in rats named *N*-(3-chloro-4-methylphenyl)-2-(propan-2-ylidene) hydrazinecarboxamide. Weak CNS depressant activity was also found in some compounds when tested in forced swim pool test.[42]

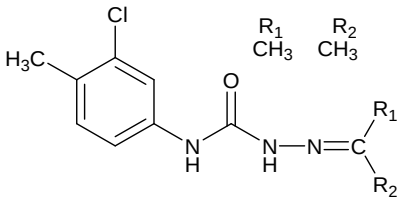


Figure 16. 3-cloro-2-methyl phenyl substituted semicarbazones

Pandeya et al. (2003) synthesized a series of *p*-nitro phenyl substituted semicarbazones and phenoxy/*p*-bromophenoxy acetyl hydrazones and evaluated their anticonvulsant activity by maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and subcutaneous cstrychnine (ScSty) tests. Some compounds with –NHCO– were found to be the most active in all these tests. These compounds were also active in the MES test after oral administration in rats, On the other hand compounds with $–OCH_2–$ were devoid of anticonvulsant activity. The studies revealed that the hydrogen bonding domain in semicarbazones and adjacent to the lipophilic aryl ring which is essential for the anticonvulsant activity.[43]

Pandeya et al. (2000) has synthesized a series of 4-bromo-phenyl substituted aryl semicarbazones (figure 17) and screened for anticonvulsant activities by using MES, scPTZ, scSTY test models. The compound that emerged as most promising anticonvulsant agent was *N*-(4-bromophenyl)-2-(propan-2ylidene)hydrazinecarboxamide as it showed activity shown in all screens employed at doses of 30, 100, 300 mg/kg after intraperitoneal administration to mice. Compounds were also active in oral MES screen in rats at dose of 30 mg/kg.[44]

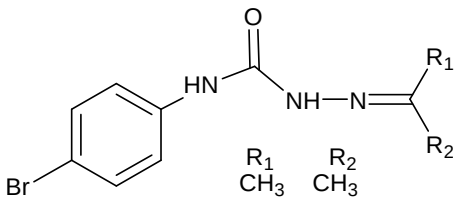


Figure 17. 4-bromophenyl substituted aryl semicarbazones

Puthucode et al. (1998) synthesized a series of aryl, arylidene and aryloxyaryl semicarbazones (figure 18) and evaluated anticonvulsant activity using MES and scPTZ test models after intraperitoneal administration to mice. They reported that compounds 2-[(2*Z*)-2-bromo-3-phenylprop-2-en-1-ylidene] hydrazine carboxamide and 2-{(2*E*)-3-[4-(4-fluorophenoxy) phenyl]prop-2-en1ylidene} hydrazinecarboxamide were found most protective in MES and scPTZ screen after i.p. administration, whereas compounds named 2-[3-(2,6-dimethylphenoxy) benzylidene]hydrazine carboxamide and 2-

{1-[3-(4-methylphenoxy) phenyl] ethylidene} hydrazine carboxamide[45] exhibited highest activity in MES screen after oral administration.

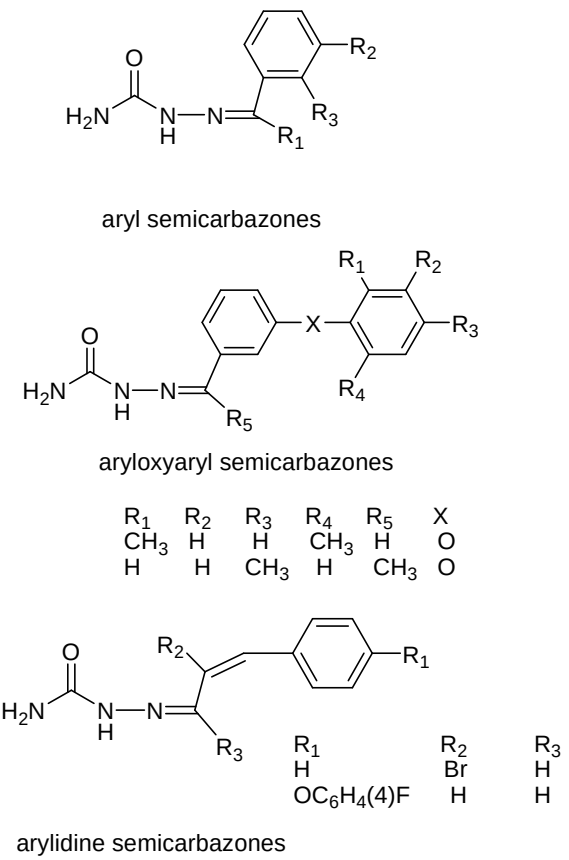


Figure 18. Structure of aryl, arylidine and aryloxyaryl semicarbazones

Dimmock et al. (1995) has been synthesized number of semicarbazone derivatives from resembling aryl alicyclic ketones (figure 19). Anticonvulsant activity has been evaluated using MES and scPTZ test models after intraperitoneal administration to mice. They were found 100% active compound in MES screen while 70% active in scPTZ screen. Some semicarbazones named 2-(2, 3-dihydro-1*H*-inden-1-ylidene) hydrazinecarbox- amide, 2-(3, 4-dihydronaphthalen-1(2*H*)-ylidene) hydrazine carboxamide and 2-(6, 7, 8, 9-tetrahydro-5*H*-benzo [7] annulen-5-ylidene) hydrazinecarboxamide exhibited higher activity in MES screen than valproate.[46]

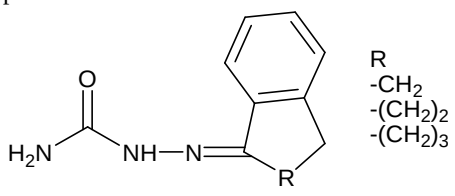


Figure 19. Aryl acyclic semicarbazones

CONCLUSION

Semicarbazone is a lead molecule for designing potential bioactive agents, and its derivatives possess broad-spectrum anticonvulsant, anxiety activities and other biological activities. Semicarbazones are synthetically conversant substrates that can be used for the synthesis of a large variety of heterocyclic compounds and as raw material for drug synthesis. This review highlighted the use of semicarbazone for organic synthesis, biological and pharmacological properties.

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