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# SEMICARBAZONE DERIVATIVES AND THEIR PHARMACOLOGICAL ACTIVITIES

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## ABSTRACT

Epilepsy can be devastating to patient's day to day life. Different categories of antiepileptic agents are present in market but they have toxic effects on central nervous system. Aryl and heteroaryl semicarbazone derivatives present a new area of interest as anticonvulsant drugs. Semicarbazones have been widely synthesized for their anticonvulsant properties. Many semicarbazones have shown better activity and low neurotoxicity than already available drugs, therefore they can be used as lead compounds for the synthesis of newer antiepileptics. Various semicarbazones have been synthesized which possess different pharmacological activity in addition to antiepileptic activity.

**KEYWORDS:** antiepileptic, semicarbazones, maximal electroshock seizure (MES), subcutaneous strychnine (scSTY) and subcutaneous penatylenetetrazole (scPTZ), gamma-aminobutyric acid aminotransferase (GABA-AT).

## INTRODUCTION

Semicarbazones show a variety of therapeutic action for example anticonvulsant, antibacterial, antifungal, anticancer activity. Recently 4-aryl substituted semicarbazones have been established as anticonvulsants and can be considered a new class of anticonvulsants with oral activity. Pandeya et al. have recommended a different biophoric model for anticonvusant semicarbazones (Fig 1). They also advocated that the amino end of semicarbazones was not important for activity therefore it could be substituted with a lipophilic aryl ring. The novel pharmacophore model contains four binding sites for interaction with receptor in vivo. These binding sites include: - An aryl or heteroaryl

hydrophobic binding site with electron withdrawing group/groups at para position, two electrons donor systems and hydrogen binding group or groups and hydrophobic-hydrophilic site affecting the pharmacokinetic properties (ADME) of the anticonvulsant compounds.

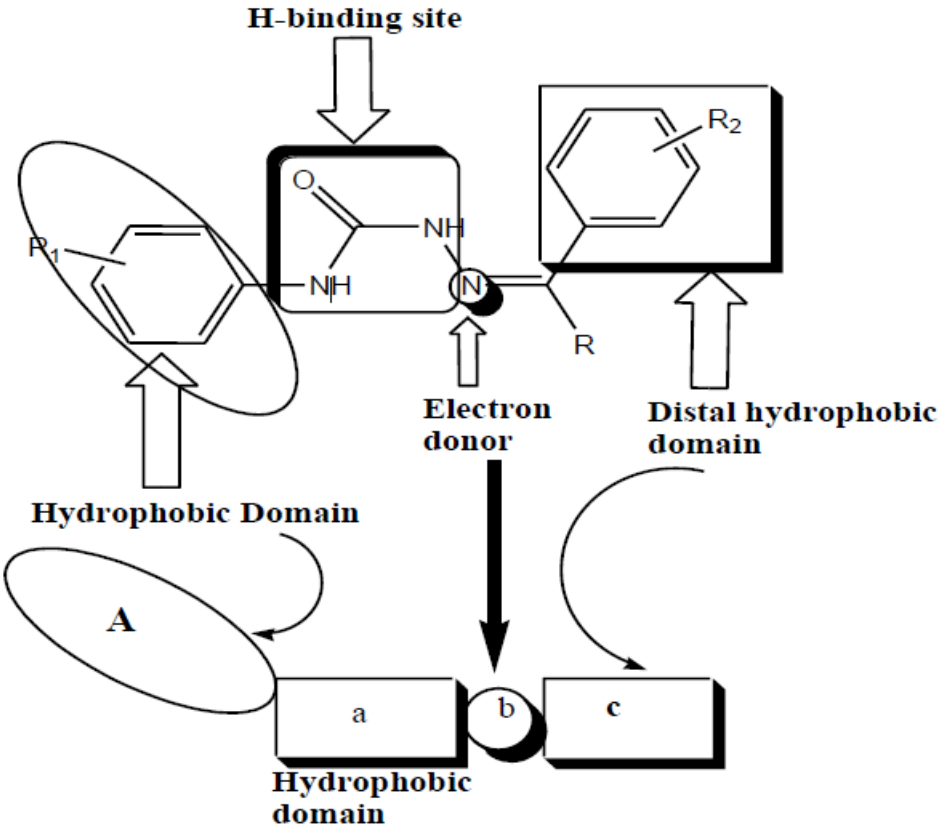


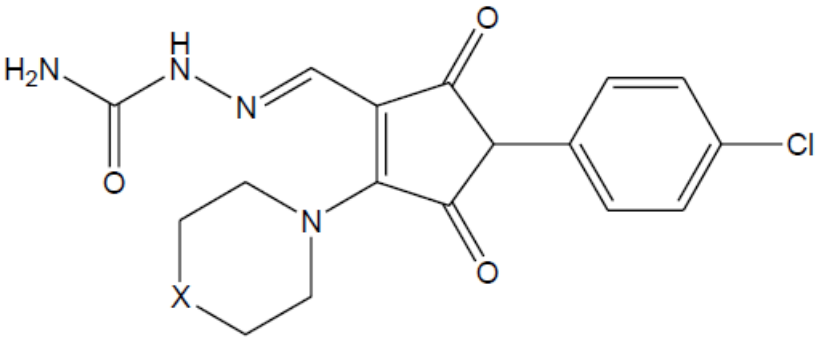

**Fig. 1: Suggested structural features for semicarbazones displaying anticonvulsant activity.**

Semicarbazones have been mainly synthesized as anti-epileptic agents. Epilepsy is the most predominant nervous disorder characterized by recurring epileptic seizures. Seizures result from sudden, abnormal and hyper synchronous discharge of group of neurons within the brain. Epilepsy affects more than 0.5% people worldwide suffer from epilepsy. According to reports 25% of the epileptic population has seizures that remain untreated with presently available antiepileptic drugs. Even though, a variety of antiepileptic drugs are available in market but many patients fail to experience seizure control and others do so only at the cost of significant toxic effects like drowsiness, mental slowing, hepatotoxicity, behavioral changes etc. Currently, available drugs control the seizures in only 50% of patients or decrease incidence in only 75% of patients. Therefore the field of anticonvulsant drugs is highly significant in terms of drug discovery.[1]

**Different Semicarbazones Derivatives**

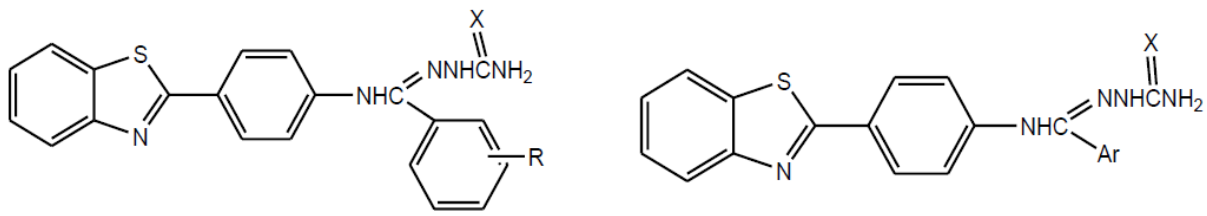
**Disubstituted N-arylmaleimides semicarbazones**

Disubstituted N-arylmaleimides semicarbazones were synthesized from maleimides. Maleimides shows a varied range of pharmacological activities like antibacterial and antifungal, antiprotozoal, antiangiogenic, analgesic, antistress agents, cytotoxic, DNA binding and cell apoptotic inducing activity. Method used for synthesis is different from general method of preparation of semicarbazones. The main advantages are clean, easy operational & simplicity of reaction.[2]



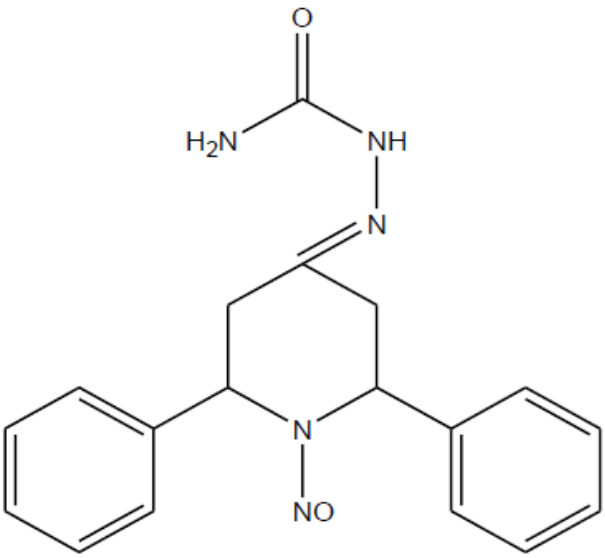

**2-(4-aminophenyl)benzothiazole derivatives of semicarbazone and thiosemicarbazone**

It was determined that the distinction in activity of 2-(4-aminophenyl)benzothiazole derivatives of semicarbazone and thiosemicarbazone can be interrelated with their lipophilic and electronic behavior. The presence of benzothiazole ring with semicarbazone/thiosemicarbazone groups and different R substitutions in compounds improved their electronic and lipophilic nature, thereby increasing their capability to penetrate the microorganisms through the lipid layer of the cell membrane. Benzothiazole–semicarbazone and thiosemicarbazone derivatives showed vivid cell selectivity and killed the bacteria by disrupting the membrane. These compounds have ability to modify the electrophoretic mobility of DNA responsible which may also be responsible for their enhanced potency.[3]



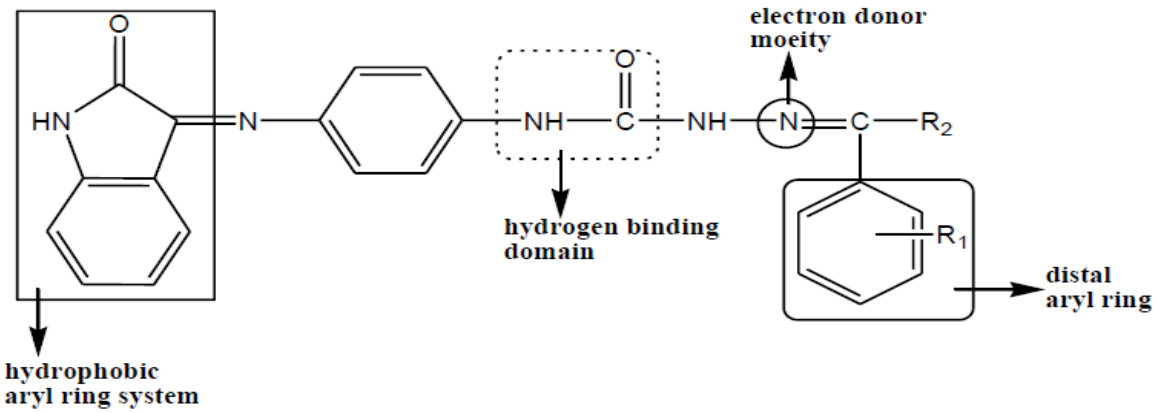

**X = O, S**

**Nitroso semicarbazone:** Nitroso semicarbazone (N-nitroso-2,6-Diphenylpiperidin-4-one) was prepared and evaluated for activity against different bacteria and fungi. This compound has shown substantial antibacterial activity against bacteria Bacillus subtilis (gram-positive), Staphylococcus aureus (gram positive) and Escherichia coli (gram negative). They have also shown activity against fungi Candida albicans.[4]



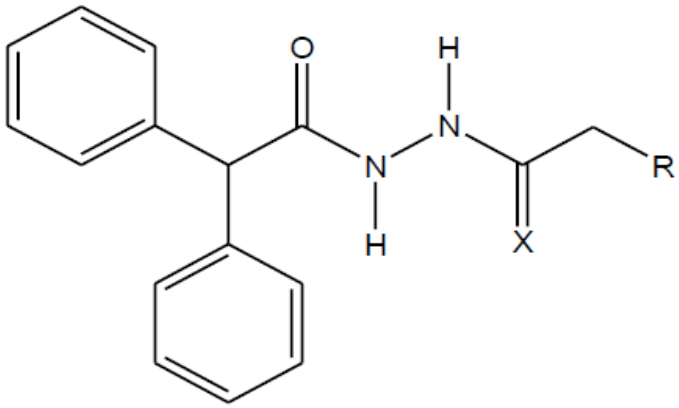

**Benzimidazole derivatives of semicarbazones**

Benzimidazole derivatives of semicarbazones with 1,3,4-oxadiazole nucleus from imesatin were designed and evaluated. According to structure activity relationship study the compounds having groups such as nitro, hydroxy on phenyl ring at hydrazino end have high anticonvulsant potency, while compounds with methyl groups at this position have low anticonvulsant activity. Substitution of the hydrogen on imino group attached to carbon atom by methyl group has resulted in compounds with increased activity.[5]



**4-aryl-1-Diphenylacetylsemicarbazide and thiosemicarbazide**

Six 4-aryl-1-Diphenylacetylsemicarbazide **(series a)** and thiosemicarbazide **(series b)** derivatives were synthesized. Computational chemistry studies were performed for these semicarbazides and they were evaluated for their action on central nervous system. All thiosemicarbazides have shown strong antinociceptive activity, especially 1-diphenylacetyl-4-(4-methylphenyl)thiosemicarbazide possessed maximum analgesic activity. In contrast, significant serotonergic receptor blocking activity was shown by all semicarbazide derivatives especially 1- diphenylacetyl-4-(4-methoxyphenyl)semicarbazide. The computational studies also support the obtained results.[6]

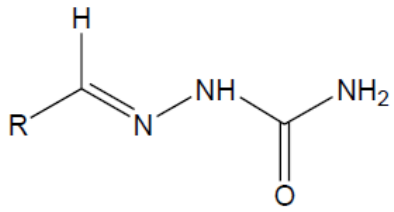



**X= O, S**

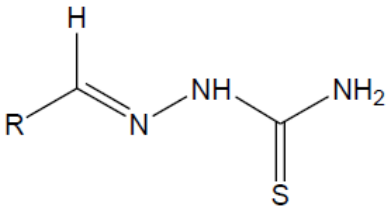
**Series a:** X = O, 1 = 4-$CH_3$Ph, 2 = 4-$OCH_3$, 3 = 4-$OC_2H_5$

**Series b:** X= S, 1 = 4-$CH_3$Ph, 2 = 4-$OCH_3$, 3 = 4-$OC_2H_5$

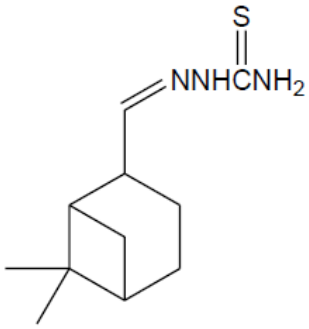
Semicarbazone and thiosemicarbazone derivatives were evaluated for in-vitro antimalarial activity against Plasmodium falciparum. Compound **a, b** produced significant inhibition of Plasmodium falciparum only, while compound c has shown broad spectrum of activity, it was active against P. falciparum in vitro as well as P. berghei in mice and were nontoxic to human peripheral blood mononuclear cell or mice. Therefore, compound **c** can be used as a lead for antimalarial drug synthesis and also thiosemicarbazones from non-synthetic aldehydes and ketones can be synthesized as effective antimalarial compounds.[7]




a




b

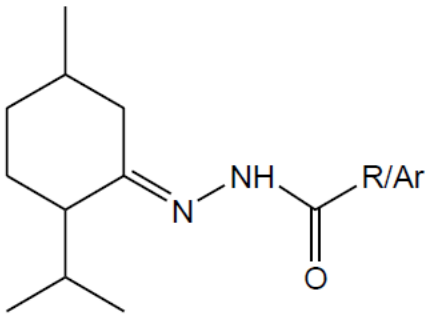



c

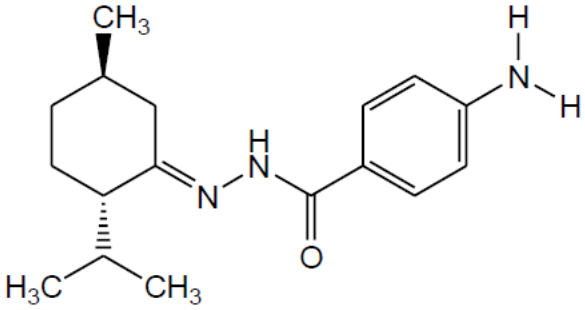
**(±)-3-menthone derivatives of semicarbazone**

In silico pharmacophore validation of anticonvulsant activity of (E) (±)-3-menthone derivatives were performed. Three significant pharmaphoric features of GABA-AT enzyme were recognized and important for activity. They are hydrogen donor site, hydrogen acceptor and aromatic site.

Most compounds produced (5/6) score in docking studies, which was greater than Vigabatrin (GABA-AT inhibitor). According to results it was concluded that, analogues **d** serves as potential lead and compound **e** exhibited excellent binding affinity interaction with LYS329.[8]



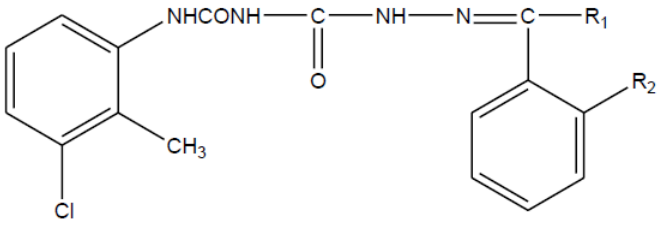

d




e

**3-chloro-2-methylphenyl semicarbazones**

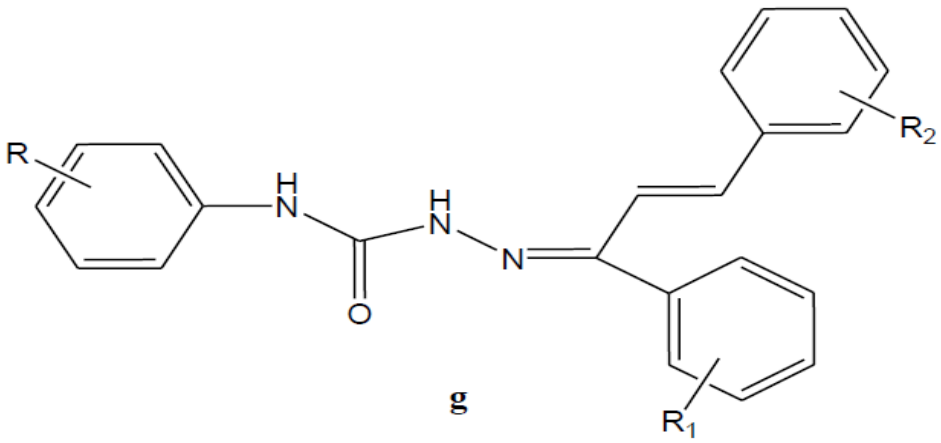
3-chloro-2-methylphenyl semicarbazones were prepared and assessed for anticonvulsant activity. These compounds displayed good activity in scSTY screen and therefore may act on glycine receptors. The anticonvulsant compounds increased immobility time and facilitated depression (dose 30 mg/kg intraperitoneally. Doses for increasing depression are less than the anticonvulsant dose, therefore there is difference in mechanism of anticonvulsant action and in the facilitation of depression.[9]




**R1** = H, $CH_3$; **R2** = 4-$NO_2$, 3-$NO_2$, 4-OH, 2-Cl, 4-$OCH_3$, 4-$CH_3$, H, 2-OH, $CH_3$, $C_2H_5$, 4-Cl, 4-$NH_2$, 4-$NO_2$.

**2-methylphenyl semicarbazones**

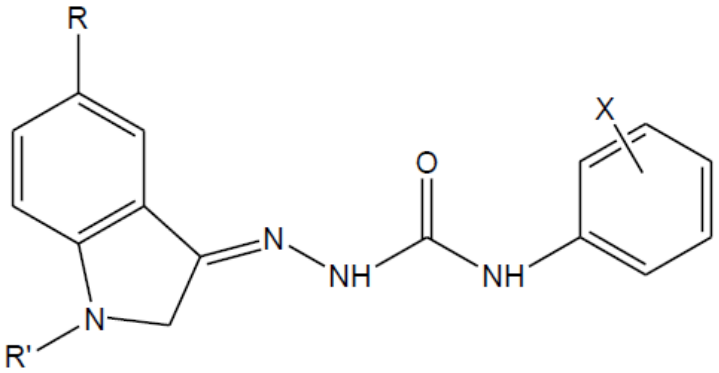
A number of deivatives of 2-methylphenyl semicarbazone were synthesized and evaluated**,** compound **g** was recognized as most active chalcone semicarbazone. The order of decreasing activity regarding substitution on chalconyl group is **OH> OCH3> (CH3)2-N> H**. The replacement of phenyl group adjacent to aldehydic and acetophenic group of chalcone with –OH group increased antipyretic activity when compared to groups like p-dimethyl amino groups**.** It may occur due to increased hydrogen bonding with the receptors.[10]




**g**

**Quinazolinone derivatives of semicarbazones**

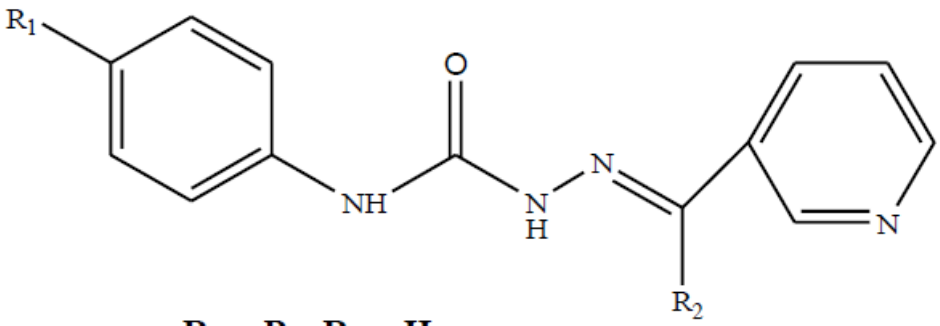
Quinazolinone derivatives of semicarbazones were synthesized and all synthesized compounds displayed potent anticonvulsive activity**.** Most of the semicarbazones showed fast onset and extended duration of action. The semicarbazones **a, b, c** and **d – h** were active at 0.030 g/kg dose in the MES screen and thus may be used in treatment of generalized tonic-clonic in addition to complex partial seizures.[11]




**a**, R = H, R' = $COCH_3$, X = 4-Cl; **b**, R = H, R' = $COCH_3$, X = 4-$NO_2$

**e**, R = Br, R' = $COCH_3$, X= 4-Cl;

**Pyridyl semicabazones:** Pyridyl semicabazones were assessed for their effectiveness against convulsions and deteriorating effect on nervous system. According to studies it was concluded that most of the compounds display neurotoxicity at doses higher than commonly used drugs (phenytoin or carbamazepine). Comparing the results of above studies, compounds **a**, **b** and **c** were most active and least neurotoxic. When hydrogen at the imino group of semicarbazones replaced with methyl substituent, neurotoxicity increases. Pyridyl semicarbazons are also orally active.[12]

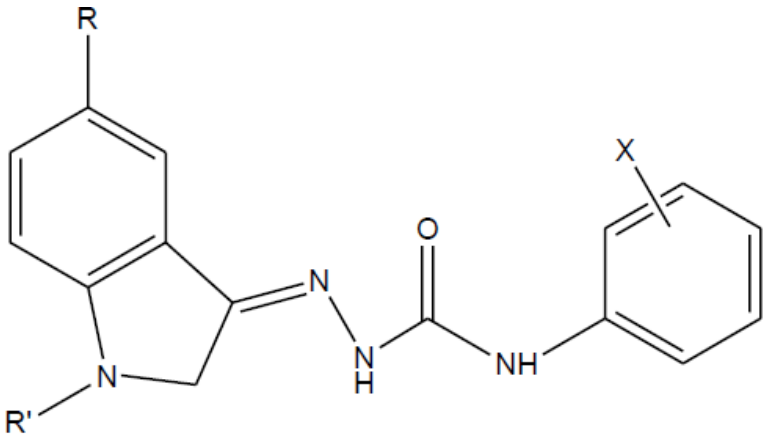



**a:** $R_1$ = Br, $R_2$ = H
**b:** $R_1$ = F, $R_2$ = H
**c:** $R_1$ = Cl $R_2$ = $CH_3$

**N-acetyl/methyl isatin semicarbazone derivatives**

N-acetyl/methyl isatin semicarbazone derivatives were designed and evaluated for activity against convulsions and also for sedative-hypnotic activity (neurotoxicity). Compounds **a, c and e** showed activity in MES screens and their neurotoxicity was less than frequently prescribed drugs. Out of total synthesized semicarbazones, **a, b and e** have wide range of

activity as shown by results of scPTZ, scSTY and MES screens. All the compounds appeared as active sedative-hypnotics only 5b was inactive in this screen.[13]

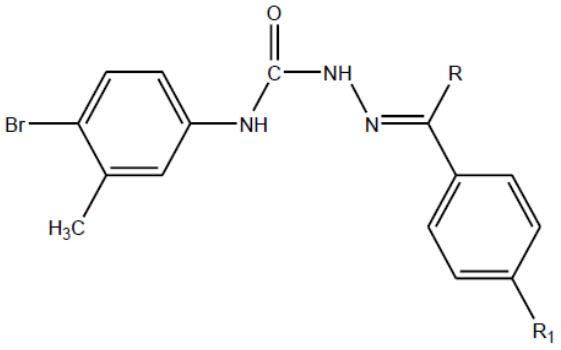


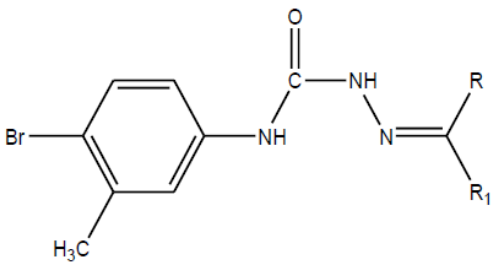

**a:** R = H, R' = $COCH_3$, X = 4-Cl; **b**: R = H, R' = $COCH_3$, X = 4-$NO_2$

**c:** R = Br, R' = $COCH_3$

**N-(4-bromo-3-methylphenyl) semicarbazones**

N-(4-bromo-3-methylphenyl) semicarbazones were prepared by microwave assisted technique. The quantum mechanical (QM) modeling of these compounds revealed that semicarbazones possess broad spectrum antiepileptic activity like other aryl semicarbazone derivatives. These compounds might also act through the GABA or glycine receptors as well as sodium channels. The importance of the 4-point pharmocophore was also confirmed by QM modeling studies.[14]

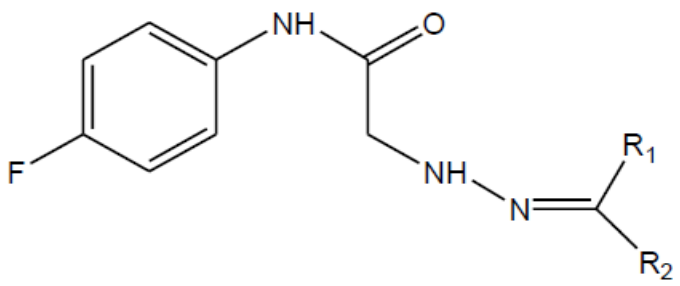



**Substituted 4-aryl semicarbazones**

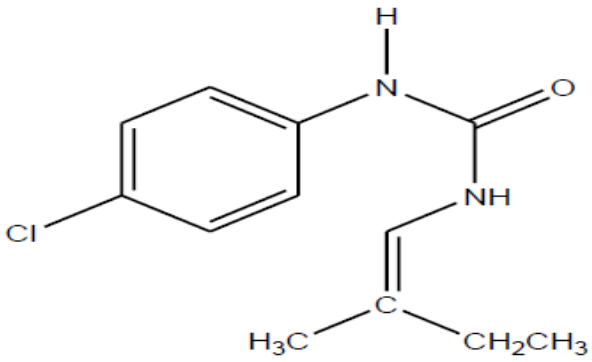
Structure-activity relationship of different substituted aryl semicarbazones revealed that the substitution of groups on the aryl ring and at the terminal imino functions affects their action as anticonvulsants. Order of activity for substitution at aryl ring was 4-Fluoro > 2-Bromo = 3-

Bromo = 4-Chloro > 4-Methyl > 4-Bromo > 3-Chloro > 3-Methyl. At the carbimino terminal the order of activity was methyl or ethyl > phenyl or substituted phenyl > cycloalkyl > heteroaryl. Substitution of carbimino hydrogen with methyl group resulted in greater activity.[15]




**R1 = Alkyl, Aryl, Cyclic, Heteroaryl**

Aryl substituted semicarbazones were designed and synthezed from different substituted anilines and assessed for their capacity to provide protection against convulsions in ScPTZ and MES screens. Compound h appeared as an anticonvulsant equal in potency to carbamazepine in both screens with no neurotoxicity. According to results it was established that distal alkyl chain is important for activity and any change in it impacts the anticonvulsant activity.[16]




**h**

## DISCUSSION

Semicarbazones have been extensively synthesized as anticonvulsants. In addition to anticonvulsant activity, they have shown variety of activities like antimalarial, antipyretic, analgesic and antimicrobial activity. Therefore they may act as a lead for synthesis of different categories of drugs. The anticonvulsant activity of semicarbazones is mainly due to

their interaction with GABA receptor, GABA-AT enzyme, glycine receptors or sodium channels. Substitution of different groups on basic semicarbazone moiety brings about change in activity.

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