

## SEMICARBAZONES AS ANTICONVULSANTS

BY

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## ABSTRACT

Approximately 25% of epileptics' convulsions are inefficiently controlled by currently available remedies; therefore the preparation of new antiepileptic drugs is of great interest. Aryl semicarbazones can be considered a new class of compounds presenting anticonvulsant activity. In addition, they can be orally administered. Semicarbazones derived from aromatic and unsaturated carbonyl compounds as well as from other precursors are reviewed together with their anticonvulsant profile.

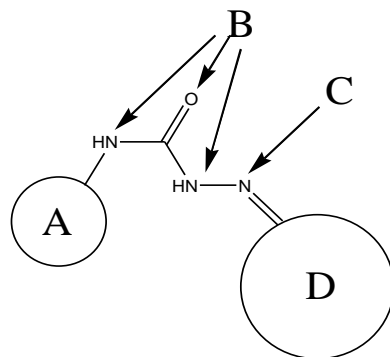
**Key words:** Semicarbazone, Anticonvulsant, pentylenetetrazole (PTZ), maximal electroshock (MES).

## INTRODUCTION:

Aryl semicarbazones have been documented to contribute in the design of novel anticonvulsant agents, due to their excellent activity in the maximal electroshock seizure (MES) in both mice and rats and also against clonic seizures induced by pentylenetetrazole (PTZ) in mice, being more active than some conventional AEDs, beside their low neurotoxicity (**Rajak, et al., 2009**). Semicarbazones have been developed due to their structural dissimilarity from many common monocyclic anticonvulsants containing the dicarboximide function (CONRCO) which may contribute to toxic side effects, so it can be assumed that such novel compounds would not have the side effects seen with many of the currently available anticonvulsant medications (**Kadaba 1984**).

A pharmacophoric model has been put forward for antiepileptic activity owing to conformational investigations on prevailing anticonvulsant drugs such as phenytoin, carbamazepine, lamotrigine and phenobarbitone (**Pandeya, et al., 1999**). This semicarbazones based pharmacophoric model comprises the following four essential binding sites (**Dimmock, et al., 2000; Pandeya, et al., 2002**):

- (A) An aryl hydrophobic binding domain with substituent preferably at para position
- (B) A hydrogen bonding site
- (C) An electron donor moiety
- (D) Another hydrophobic-hydrophilic domain (distal hydrophobic domain) regulating the pharmacokinetic properties of the anticonvulsant (**Fig. 1**).

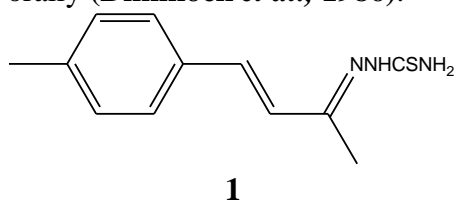


**Fig. 1:** Semicarbazone based pharmacophoric model and its vital structural features (Dimmock, *et al.*, 2000; Pandeya 2002).

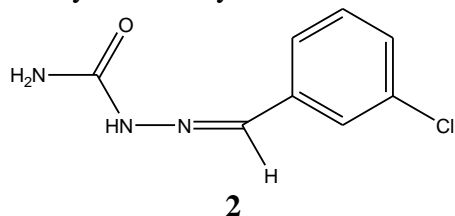
#### Bioactive semicarbazones:

In the last 25 years, in addition to the patented data (Dimmock 1994; Dimmock and Puthucode 1996; Wang *et al.*, 1998; Kadaba *et al.*, 1999; Schann 2008), a series of publications reporting on the anticonvulsant activity of semicarbazones derived from aromatic and unsaturated carbonyl compounds as well as from other precursors has been launched. The following survey comprises most of these publications.

A series of thiosemicarbazones and semicarbazones of arylidene methyl ketones have been prepared and evaluated in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens. Compound **1** had an ED<sub>50</sub> of 6.96 mg/kg in the scPTZ test when administered by intraperitoneal route (i.p.) to mice, and a protection index of 10.37 when given orally (Dimmock *et al.*, 1986).

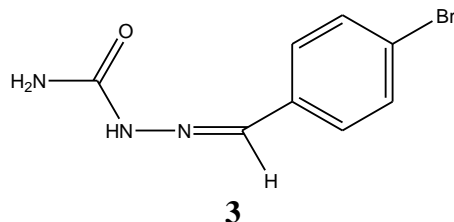


New study (Dimmock *et al.*, 1993) with particular goal of finding compounds with oral activity has been designed with the exclusion of thiosemicarbazones due to its neurotoxicity and lethality (Dimmock *et al.*, 1990; 1991). Most of the synthesized compounds displayed anticonvulsant activity in MES and scPTZ screens when given to mice by i.p. route. Compound **2** showed the best activity in both models (PI > 5.53 MES and > 2.82 scPTZ). Oral administration of the compounds to rats led to excellent potency in the MES screen while virtually no activity in the scPTZ test was displayed.

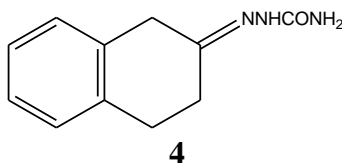


As a continuation of the former work, a molecular modeling study has been performed by Dimmock *et al.* (1995) to develop structure-activity relationship (SAR) of the previously synthesized series of anticonvulsants. Compound **3** was designated the lead compound based on detailed evaluation of its anticonvulsant properties (Dimmock and Baker 1994). The study revealed that the presence of a large hydrophobic group in

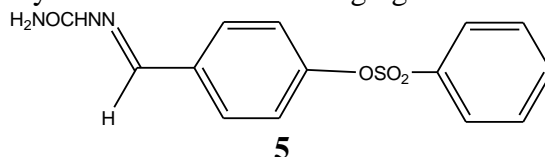
close proximity to at least two electron-donor atoms is required for MES activity while, for scPTZ a smaller less hydrophobic group should be present near to a minimum of two electron-donor atoms.



In order to examine the effect of structure restriction on the anticonvulsant activity, new semicarbazone derivatives of 1-indanone, 1-tetralone, 1-benzosuberone, 2-indanone and 2-tetralone, as frozen analogues of the previously synthesized semicarbazones, have been synthesized and tested for its activity by **Dimmock *et al.* (1995)**. The potency of compound **4** was 2.98 times that of the acyclic analogue and greater activity than both phenytoin and valproate with a PI of approximately 40.

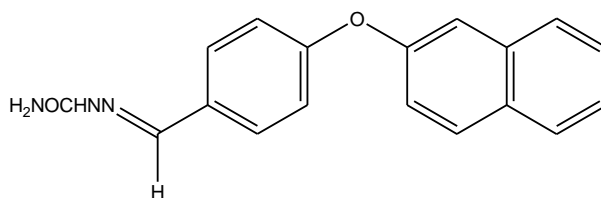


For more understanding of the putative binding site two studies have been performed by **Dimmock *et al.* (1996)** and **(2000)**. The first study has been aimed at investigation of the role of the aryl moiety in anticonvulsant activity, thus a new series of 95 (aryloxy)aryl semicarbazones and related compounds has been synthesized, biologically evaluated and many quantitative structure-activity relationships (QSAR) and X-ray crystallographic studies have been performed. Compound **5** was the most active candidate showing activity in both models at 30 mg/kg.



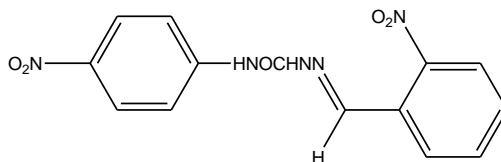
The second study has been particularly oriented towards the hydrogen bonding area. Several compounds have been synthesized following sequential changes in the terminal electron-rich group. It has been revealed that terminal electron-rich groups enhanced the hydrogen bonding capabilities and anticonvulsant properties.

As a part of Dimmocks' research group, **Puthucode *et al.* (1998)** have used Dimmocks' compounds **1** and **5** as prototypic molecules for subsequent molecular modification. The study has identified a number of highly promising anticonvulsant semicarbazones derived from aryl, arylidene and aryloxyaryl ketones and aldehydes. Attachment of a 2-naphthyloxy group (compound **6**) gave high activity in the rat oral MES screen ( $ED_{50} = 26.8$ ,  $PI = 18.7$ ).



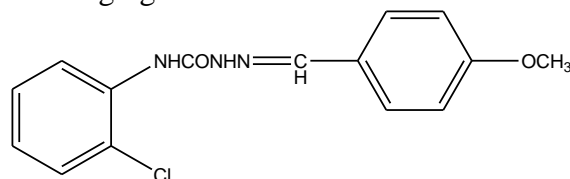
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More efforts have been done in the semicarbazone research field by **Pandeya *et al.* (1999)**. They have adopted a new concept by attaching another lipophilic moiety at the terminal primary amino function. This modification realized that the terminal primary amino ( $\text{NH}_2$ ) group is not essential for anticonvulsant activity and substituting one proton will enhance or at least retain the activity. Investigations in this aspect were started in 1999 through synthesizing a series of 2-nitrobenzaldehyde semicarbazones. The anticonvulsant activity was screened against MES, scPTZ tests in addition to scSTY seizures test which throws light for the interaction with glycine receptors. Compound **7** was the most active in all tests (100 mg/kg MES, 300 mg/kg scPTZ and 30 mg/kg scSTY).



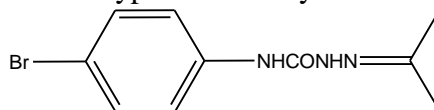
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In the same vein, **Pandeya *et al.* (2001)** studied the effect of using different substituted benzaldehydes at the distal hydrophobic domain and different substituted phenyl moieties at the primary amino functionality of semicarbazones. Many compounds provided significant protection against MES and scSTY where compound **8** displayed the best activity at a dose of 30 mg/kg in scSTY test.



8

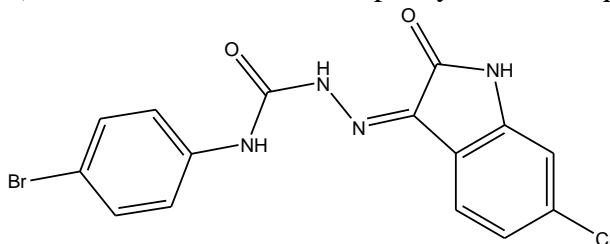
Another study has been performed by **Pandeya *et al.* (2000)** utilizing the reported importance of 4-bromophenyl moiety in biologically active compounds as anticonvulsants (**Unverferth *et al.*, 1998**). They prepared a series of 4-bromophenyl semicarbazones of aliphatic aldehydes. The semicarbazone derivatives were examined in MES, scPTZ and scSTY screens. Semicarbazone **9** showed the greatest activity, being active in all screens (300 mg/kg for MES and scSTY, 100 mg/kg for scPTZ) with very low neurotoxicity and no sedative-hypnotic activity.



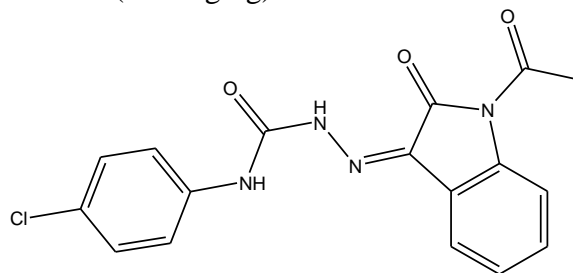
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For activity enhancement, **Pandeya *et al.* (2002)** have combined the 4-bromophenyl moiety with the versatile heterocyclic hydrophobic isatin molecule which has preliminary anticonvulsant activity (**Sareen *et al.*, 1962**). Thus, a series of substituted

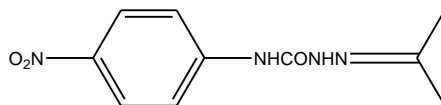
isatin semicarbazones has been prepared. Compound **10** has emerged as the most active analog showing good activity in all the three tests (100 mg/kg MES, 30 mg/kg scPTZ, and 300 mg/kg scSTY) and was more active than phenytoin and valproic acid.

**10**

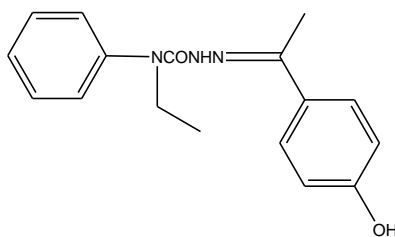
Additional structural modifications of isatin containing semicarbazones have been achieved by **Smitha et al. (2008)**. They have prepared a series of *N*-methyl/acetyl 5-(un)-substituted isatin-3-semicarbazones which were subjected to several pharmacological screens (MES, scPTZ, and scSTY). Among the prepared compounds, compound **11** showed broad-spectrum anticonvulsant activity as indicated by its protection in scSTY (300 mg/kg), MES and scPTZ (100 mg/kg) screens.

**11**

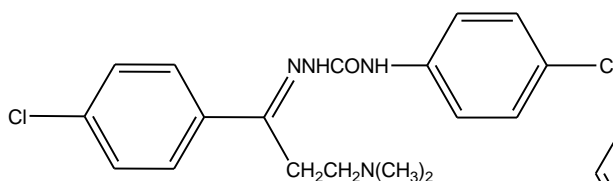
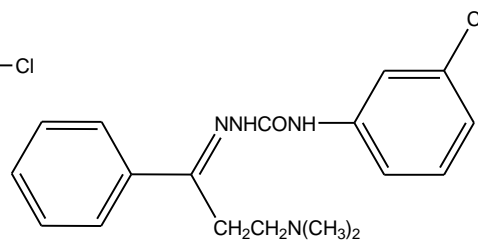
**Pandeya et al. (2003)** performed another study in order to confirm the essentiality of the hydrogen bonding domain (HBD) and the influence of its isosteric modifications. Therefore, the  $\text{-NHCO-}$  pharmacophore has been replaced by  $\text{-OCH}_2\text{-}$  group. Compounds with  $\text{-NHCO-}$  were found to be the most active in MES, scPTZ and scSTY tests. These compounds were also active in the MES test after oral administration in rats. Compound **12** was found to be the most active in all tests (300 mg/kg in MES, 100 mg/kg in scPTZ and scSTY). On the other hand, compounds with  $\text{-OCH}_2\text{-}$  isostere were devoid of anticonvulsant activity. This study revealed that the hydrogen bonding domain in semicarbazones, adjacent to the lipophilic aryl ring, is essential for the anticonvulsant activity.

**12**

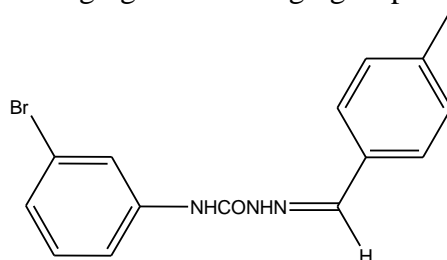
Later on **Pandeya et al. (2003)** have synthesized a series of semicarbazones aiming at testing the effect of increasing the lipophilicity on the anticonvulsant activity. The study has shown that introduction of ethyl at the terminal amino group led to increased activity and decreased toxicity. Compound **13** displayed 100% protection at 300 mg/kg in MES and scPTZ screens.

**13**

In another approach to increase the lipophilicity [50], Pandeya *et al.* have prepared several semicarbazones of *p*-chloroacetophenone Mannich bases where compound **14** was the most active candidate. In a related study in 2007 (Raja *et al.*, 2007), have synthesized new series of acetophenone and *p*-chloroacetophenone Mannich bases semicarbazones. It is established that compound **15** has excellent anticonvulsant activity in MES (300mg/kg i.p in mice and 30 mg/kg oral in rat) and scPTZ (300mg/kg) tests. The inclusion of an additional moiety (CH<sub>2</sub>–CH<sub>2</sub>–N<) retained the anticonvulsant activity.

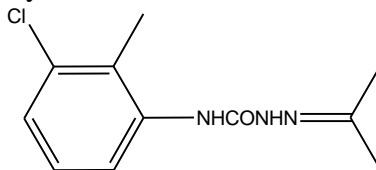
**14****15**

As a continuation of the aforementioned investigations, Yogeeswari and his group started a new intensive work aiming at better understanding of the pharmacophoric binding site and particularly oriented towards the effect of aryl ring substitutions on the activity of semicarbazones as anticonvulsants. Thus, based on the reports stating that substitutions in the proximal aryl ring by halogens, particularly bromide, have been found to increase potency in the MES screen (Pandeya *et al.*, 2000; Pandeya *et al.*, 2001; Pandeya *et al.*, 2002). Yogeeswari *et al.* (2003) have prepared a series of 3-bromophenyl semicarbazone derivatives. Compound **16** showed anticonvulsant activity in MES and scPTZ tests with ED<sub>50</sub> = 32.35 mg/kg and < 45 mg/kg respectively.

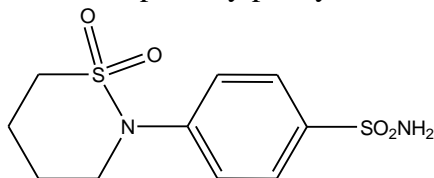
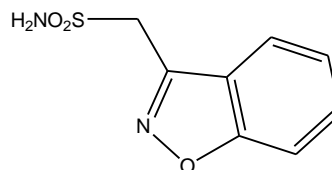
**16**

Motivated by the activity of 3-halo phenyl semicarbazone derivatives (compound **16**) and the reported benefit of 2-methyl substituted phenyl ring on the anticonvulsant activity (Pavia *et al.*, 1990; Bailleux *et al.*, 1994; Moreau *et al.*, 1994), Yogeeswari *et*

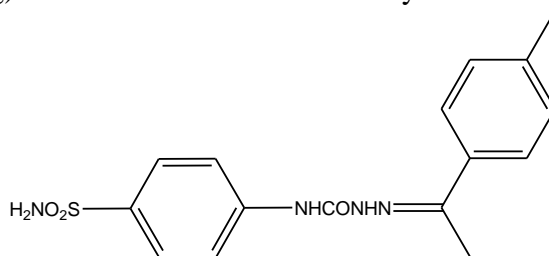
*al.* (2004) have synthesized a series of 3-chloro-2-methylphenyl substituted semicarbazones. The semicarbazone derivatives were examined in MES, scPTZ and scSTY screens. Compound **17** showed the best results by exhibiting anticonvulsant potency against all the three screens (300 mg/kg for MES and scPTZ, 100 mg/kg for scSTY) with lesser neurotoxicity.

**17**

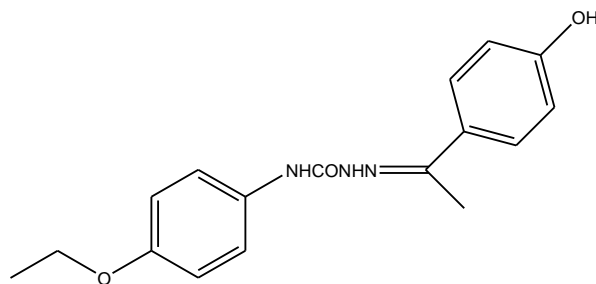
The endowed anticonvulsant properties of semicarbazones substituted in the proximal aryl ring by electron withdrawing atom/group and the anticonvulsant activity of sulphonamide derivatives, (Sulthiame (**18**) Ospolot<sup>®</sup>) (Tanimukai *et al.*, 1965), (Zonisamide (**19**) Zonegran<sup>®</sup>) (Masuda *et al.*, 1980) and other compounds (Hamor and Reavlin 1967; Oles *et al.*, 1989), act as an impetus for Yogeeswari *et al.* (2004) to prepare a series of 4-sulphamoylphenyl semicarbazone derivatives.

**18****19**

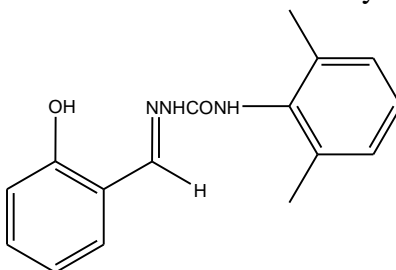
Among the new evaluated derivatives, 4-methyl acetophenone derivative **20** emerged as the most active compound as indicated by its protection in MES (100 mg/kg) and scSTY (300 mg/kg) screens with low neurotoxicity.

**20**

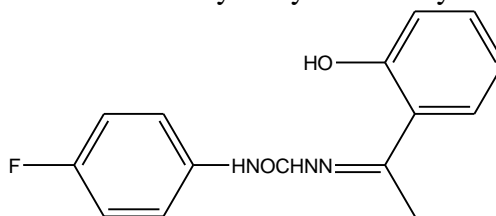
In a further study, Yogeeswari *et al.* 2005 have prepared a series of 4-ethoxyphenyl semicarbazones aiming to evaluate their biological activity and estimate the spatial compatibility of the arylsemicarbazones with the general pharmacophore model of the anticonvulsant activity (two aromatic rings or their equivalent in a favored orientation and a third region containing a number of hydrogen bonding forming functional groups). Most of the tested compounds showed protection from seizures in MES and scPTZ screens. Compound **21** was the most active derivative responding in both models at 100 mg/kg. The study revealed that arylsemicarbazones fulfill the essential demands of previously mentioned pharmacophoric model of anticonvulsant and suggested that the anticonvulsant activity was exerted through GABA-mediated mechanism.

**21**

The successful  $N^4$ -(substituted phenyl) semicarbazones profile as anticonvulsant along with the reported potent activity against MES seizures of some 2,6-dimethylphenyl derivatives (**Clark *et al.*, 1986**; **Vamecq *et al.*, 2000**) advocated **Yogeeswari *et al.* (2005)** to prepare a series of 2,6-dimethylphenyl semicarbazones to find a superior compound that would exhibit a broad spectrum of anticonvulsant activity with less or no toxicity. The 2-hydroxybenzaldehyde derivative **22** emerged as a prototype wide spectrum anticonvulsant agent active in five models (MES 100 mg/kg, scPTZ 300 mg/kg, scSTY 30 mg/kg, scPIC 30mg/kg and the kindling model of seizure 100mg/kg) with no neurotoxicity and hepatotoxicity. As well, it increased the 4-aminobutyric acid (GABA) level by 118% and inhibited the GABA transaminase enzyme.

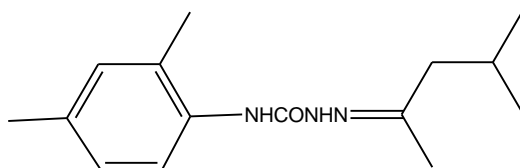
**22**

In a different study by **Yogeeswari *et al.* (2006)** and as further improvement of **22** anticonvulsant activity, compound **23** exhibited a potent anticonvulsant activity in both MES and scPTZ screens in a series of 2-hydroxybenzaldehyde semicarbazones.

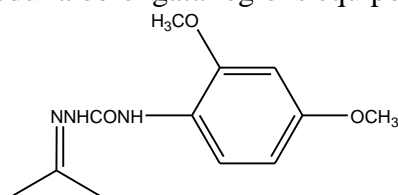
**23**

Further investigations of the  $N^4$ -(substituted phenyl) semicarbazones activity have been performed by **Yogeeswari *et al.* (2006)** through preparation of several 2,4-dimethylphenyl substituted semicarbazones. The synthesized semicarbazones were effective in MES, scPTZ and scSTY models and additional evidents were found realizing the GABA-mediated mechanism. Compound **24** revealed as the most potent derivative in this series with activity against all tested models (100 mg/kg for MES and scPTZ and 300 mg for scSTY).

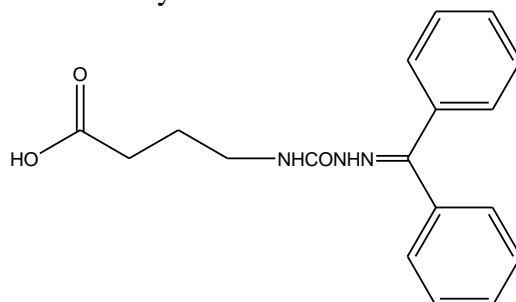


**24**

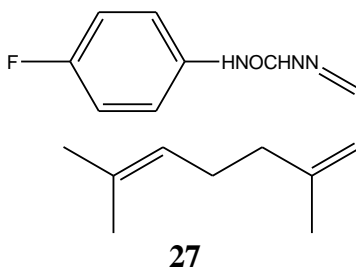
In a closely related study within Yogeeswari group in 2006 (**Thirumurugan *et al.*, 2006**), have prepared a series of 2,4-dimethoxyphenyl semicarbazones. Among which the propan-2-one derivative **25** was the most active compound (100 mg/kg for MES and scSTY and 300 mg for scPTZ) with no neurotoxicity. In addition, it elevated GABA levels in the midbrain and medulla oblongata regions equipotent to clobazam.

**25**

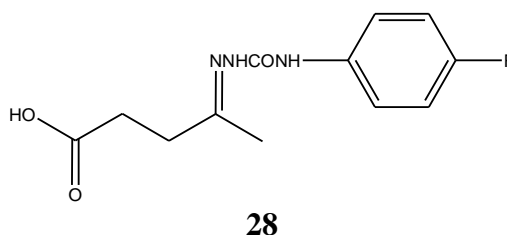
In a hybrid pharmacophoric approach towards CNS depressant candidates, **Yogeeswari *et al.* (2007)** have synthesized a series of newer  $\gamma$ -aminobutyric acid (GABA) aryl semicarbazones. The synthesized derivatives of the inhibitory neurotransmitter GABA exert CNS depressant activity (including anticonvulsant activity) through expected enhancement of peripheral GABAergic neurotransmission. Compound **26** revealed as potent anticonvulsant showing protection against MES, scPIC, and scSTY at 300 mg/kg and lower neurotoxicity.

**26**

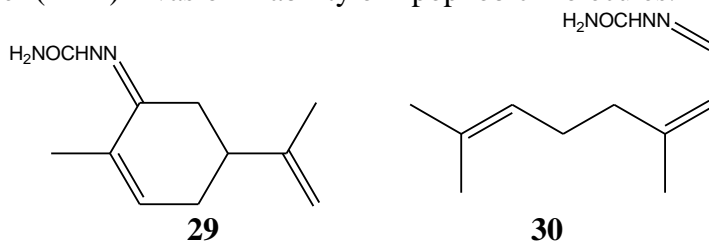
Further series of contributions have been introduced by **Aggarwal *et al.*** to explore the size and the functional requirements of the distal hydrophilic-hydrophobic site of semicarbazones to exert their anticonvulsant activity. Thus, two terpenes namely, citral and *R*-(-)-carvone, have been used for synthesis of a series of 4-substituted aryl semicarbazones by **Aggarwal and Mishra (2004)**. All synthesized compounds exhibited significant protection after i.p. administration in MES test while 72 % exhibited protection in scPTZ test. The results showed that terpenes fulfill the structural requirements for anticonvulsant activity in MES as well as scPTZ test. The 4-F-phenyl semicarbazone **27** emerged as the most active analog (100 mg/kg MES and 300 mg/kg scPTZ).



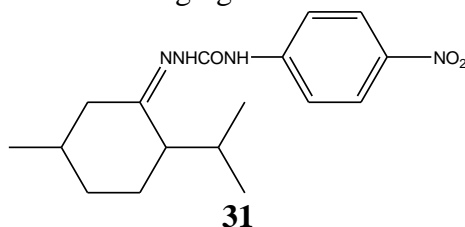
Utilizing the fact that many anticonvulsants have carboxylate group in their structure and as further investigation of the distal hydrophilic-hydrophobic site, **Aggarwal and Mishra (2005)** have synthesized a series of 4-substituted aryl semicarbazones of levulinic acid (4-oxo-pentanoic acid). 4-Fluorophenyl semicarbazone of levulinic acid **28** emerged as the most active congener showing a broad spectrum of anticonvulsant activity (MES 100 mg/kg, scPTZ 300 mg/kg) with low neurotoxicity. Whereas,  $N^4$ - unsubstituted levulinic acid semicarbazone was found to be inactive in all screens.



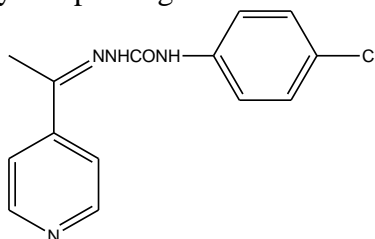
In a further investigations on  $N^4$ - unsubstituted semicarbazones, Aggarwal *et al.* have prepared the unsubstituted semicarbazones of citral, carvone and levulinic acid (**Aggarwal *et al.*, 2008**). Results revealed that the anticonvulsant activity will be retained when lipophilic distal aryl ring replaced with non-cyclic lipophilic groups (carvone (**29**) 300 mg/kg for both models and citral (**30**) 100 mg/kg for MES and 300 mg/kg for scPTZ) but not with hydrophilic substituents (levulinic acid). It could be explained through the blood brain barrier (BBB) invasion inability of lipophobic molecules.



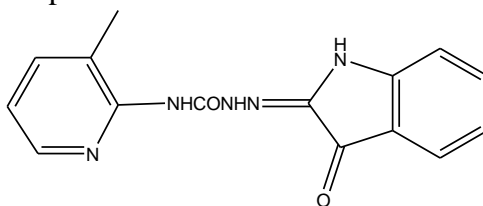
In another study on terpenes by **Verma *et al.* (2009)**, a series of menthone semicarbazones has been prepared. The anticonvulsant potential of the compounds was investigated using MES and scPTZ models. Based on the pharmacological investigations compound **31** has evolved to be the most active compound among the series showing protection against both models at 100 mg/kg.



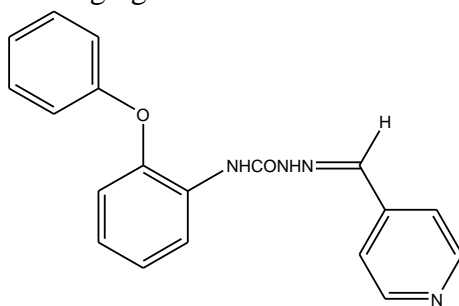
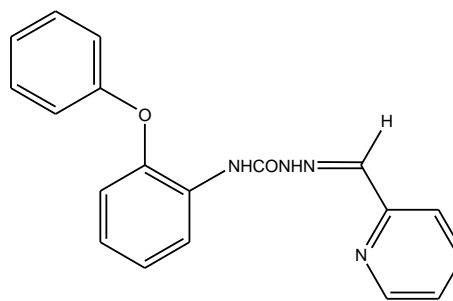
As an isostere of phenyl ring, pyridyl carbaldehydes and methyl ketones have been indulged in a semicarbazone structures by **Aggarwal *et al.* (2009)** to afford a series of 4-aryl substituted pyridine semicarbazones. In this study compound **32** emerged as the most active derivative showing activity at 100 mg/kg in MES and scPTZ tests with prolonged duration of action. In the light of above results the semicarbazones of pyridyl containing carbonyl compounds emerge as lead molecules, showing broad spectrum of activity with low neurotoxicity and prolong duration of action on oral administration.

**32**

In a related study, Mehta *et al.* have synthesized a series of substituted (3-methylpyridin-2-yl) semicarbazones (**Mehta *et al.*, 2006**). The synthesized compounds were evaluated for their anticonvulsant activity by MES, scPTZ, scSTY, and scPIC. The isatin semicarbazone **33** was the most active analog of the series (100 mg/kg in MES and scSTY, and 300 mg/kg scPIC), being more efficacious in most of the tested models than ethosuximide and sodium valporate.

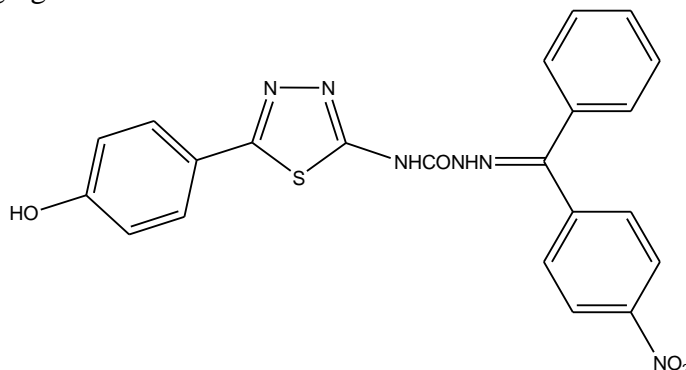
**33**

More pyridyl semicarbazones have been introduced by **Shafiee *et al.* (2009)**. They have synthesized a new series of 4-(2-phenoxyphenyl)pyridyl semicarbazones as potential anticonvulsant agents. All the prepared compounds were evaluated for their anticonvulsant activity in PTZ-induced kindling model. The results showed that two compounds (**34** and **35**) showed greater protection from seizure than sodium valproate at dose of 100 mg/kg.

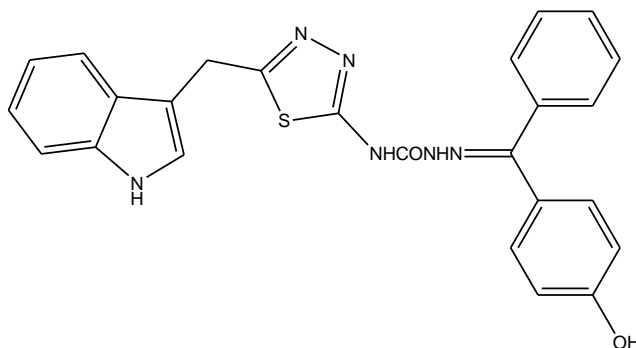
**34****35**

In a series of studies aiming to validate the semicarbazone based pharmacophoric model, **Rajak *et al.* (2009)** have prepared a series of 2,5-disubstituted 1,3,4-thiadiazole semicarbazones as a hybrid structure of 1,3,4-thiadiazole moiety as anticonvulsant pharmacophore (**Dogan *et al.*, 2002; Jatav *et al.*, 2008**) and semicarbazone functionality.

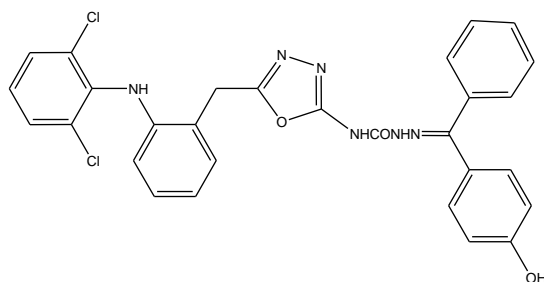
The anticonvulsant potential of the synthesized compounds was investigated using MES and scPTZ models. Compound **36** was found to possess significant anticonvulsant activity at 100 mg/kg in both the models.

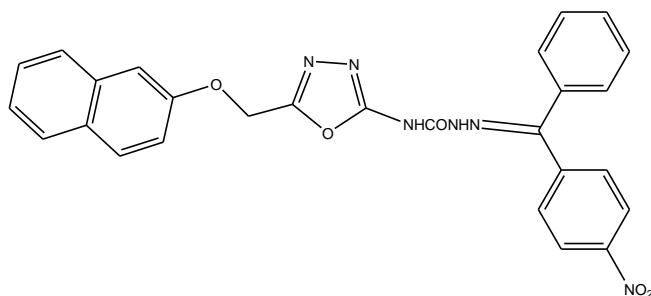
**36**

Further investigation of 1,3,4-thiadiazole semicarbazones by **Rajak *et al.* (2010)** has been performed through substituting indolyl group at position 5. the new compounds have been evaluated for their anticonvulsant potential using MES and scPTZ screens. Compound **37** came out as the most active compound showing activity in both MES (100 mg/kg) and scPTZ (300 mg/kg) without neurotoxicity.

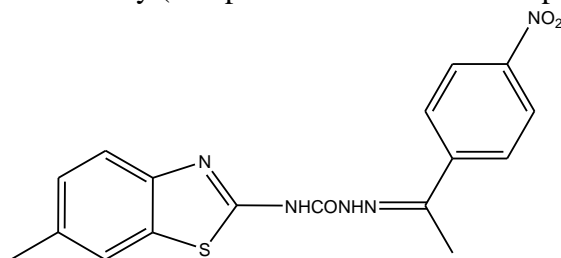
**37**

The oxygen isostere of 1,3,4-thiadiazole semicarbazones, 1,3,4-oxadiazole, has been prepared by the same group in 2009 and 2010. A series of 2,5-disubstituted-1,3,4-oxadiazole semicarbazones has been synthesized and evaluated for its anticonvulsant activity. Compound in the first study **38** showed considerable activity in MES at 100 mg/kg and scPTZ at 300 mg/kg without any neurotoxicity. While in the second study, compound **39** displayed broad spectrum anticonvulsant activity (100 mg/kg for MES and scPTZ and 300 mg/kg for scSTY) and absence of neurotoxicity (**Rajak 2009; 2010**).

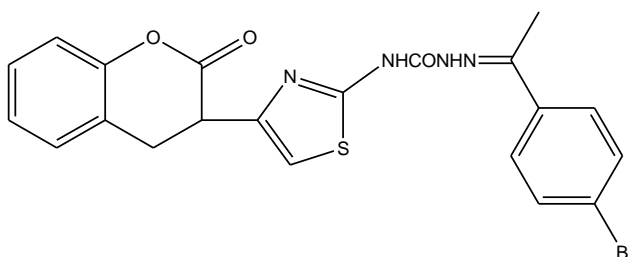
**38**

**39**

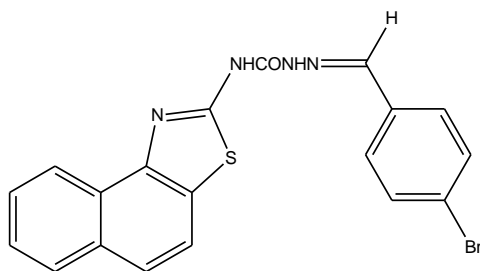
New hybrid pharmacophoric approach has been introduced by **Siddiqui *et al.* (2007)** through combining the anticonvulsant benzothiazole moiety with semicarbazone group. A series of 1,3-benzothiazol-2-yl semicarbazones has been synthesized and screened for MES activity. Compounds with 4-Cl and 4-alkyl substituted phenyl ring of benzothiazole moiety showed the best results and substitution with NO<sub>2</sub> at the distal aryl ring showed favored MES activity (compound **40** showed 100% protection at 30 mg/kg).

**40**

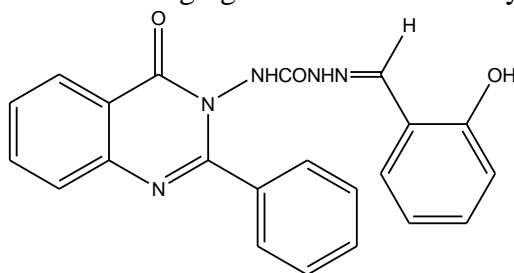
In a further work, **Siddiqui *et al.* (2009)** have synthesized a series of coumarin-thiazole incorporated semicarbazones. The synthesized compounds were tested for anticonvulsant activity utilizing PTZ and MES tests. Compound **41** exhibited significant anticonvulsant activity in all models (30 mg/kg MES and 100 mg/kg scPTZ) with out toxicity.

**41**

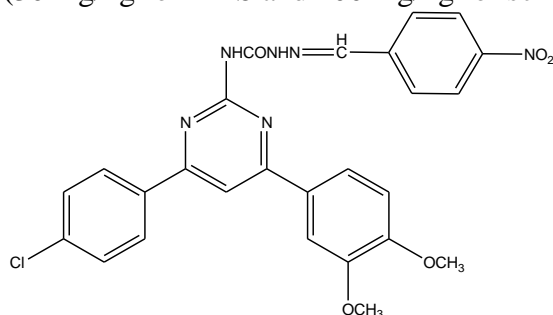
Another series of thiazole semicarbazones has been introduced by **Azam *et al.* (2009)**. Thus, a series of (naphtha[1,2-d]thiazol-2-yl) semicarbazones has been prepared and examined against MES and PTZ in mice and rats. Compound **42** was revealed as the most active compound in all performed pharmacological screens at 100 mg/kg.

**42**

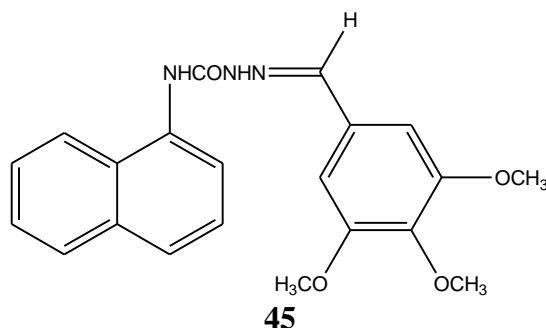
Utilizing the anticonvulsant activity of quinazolinone (Georgey *et al.*, 2008; Ilangovan *et al.*, 2010) have synthesized a series of substituted quinazolinone semicarbazones. The newly synthesized compounds were evaluated intraperitoneally into the mice in MES and scSTY screens. Almost all the synthesized analogues were equipotent to phenytoin with very low neurotoxicity profile. Compound **43** showed the best protection in both models at 30 mg/kg without neurotoxicity.

**43**

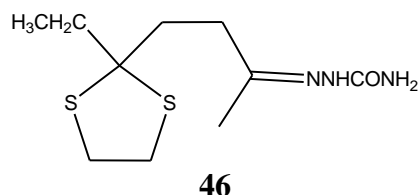
Another hybrid series of the prominent anticonvulsant pyrimidine moiety (Santagati *et al.*, 1996) and semicarbazone has been introduced by Alam *et al.* (2010). They have synthesized a number of (4,6-substituteddiphenylpyrimidin-2-yl) semicarbazones. The new compounds have been tested for their anticonvulsant activity against MES and scPTZ. Among these compounds, **44** was found to be remarkably active in both seizure models (30 mg/kg for MES and 100 mg/kg for scPTZ).

**44**

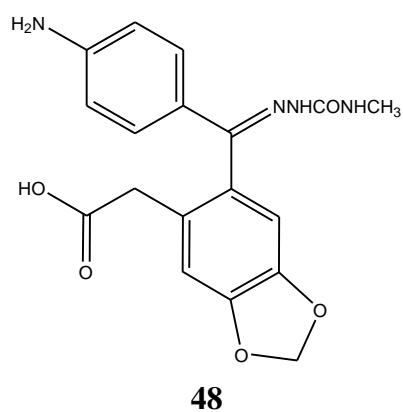
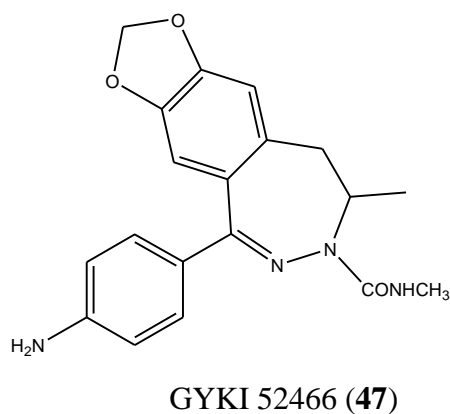
Azam *et al.* (2010) have prepared a series of 1-(substituted benzylidene/ethylidene)-4-(naphthalen-1-yl) semicarbazones. The anticonvulsant activities were evaluated by both MES and PTZ tests. Compound **45** possessed the highest protection profile at 100 mg/kg against MES and PTZ tests that was coinciding with the computational study.



Applications of semicarbazones in radio-induced convulsions have been reported firstly by **Taroua *et al.* (1996)**. They have utilized the radio-protective activity of dithiolane (**Lawa, *et al.*, 1994**) to prepare a series of  $\alpha$ ,  $\beta$  and  $\gamma$ -keto-1,3-dithiolane semicarbazones as protective agents against radio-induced convulsions. Some of the synthesized compounds showed radio-protective effect over 90 min. compound **46** was the most active with respect to duration and number of survivals (90% over 90 min at 400 mg/kg).



In the same vein, contribution has been made by **Micale *et al.* (2005)**. A series of 2-semicarbazonomethyl-4,5-methylenedioxyphenylacetic acid has been synthesized as anticonvulsant against sound-induced seizures. The newly synthesized compounds showed a comparable activity to the potent anticonvulsant 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (**47** GYKI 52466) (**Sólyom and Tarnawa 2002**). Compound **48** was the most active derivative (PI = 3.6).



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## السيميكاربازونات كمركبات ذات تأثير مضاد للصرع

### للسادة الدكتورة

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### ممن

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يعتبر الصرع من أكثر الأمراض المزمنة انتشارا حيث يعاني منه أكثر من 1% من البشر بالإضافة إلى انه حوالي 25% ممن يعانون الصرع لا يستجيبون للأدوية المتاحة و لذلك فان البحث عن أدوية جديدة لعلاج الصرع يعتبر من أولويات البحوث الدوائية. انطلاقا من أهمية السيميكاربازونات الحلقية كفئة جديدة من المركبات ذات التأثير المضاد للصرع تم في هذا العمل مسح مرجعي لمعظم المركبات المحتوية على سيميكاربازون بهدف اختبارها كمضادات للتشنجات.