Semicarbazone – a versatile therapeutic pharmacophore for fragment based anticonvulsant drug design

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During the last fifteen years, semicarbazones have been extensively investigated for their anticonvulsant properties. 4-(4-Flurophenoxy) benzaldehyde semicarbazone (C0102862, V102862) was discovered as a lead molecule and is being developed as a potent antiepileptic drug, with maximal electroshock (MES) ED_{50} of *i.p.* 12.9 mg kg^{-1}. In MES (oral screen), this compound has a protective index ($PI = TD_{50}/ED_{50} > 315$) higher than carbamazepine (*PI* 101), phenytoin ($PI > 21.6$) and valproate (*PI* 2.17). The compound is a potent sodium channel blocker. Other semicarbazones have demonstrated activity in various chemoshock screens, like subcutaneous pentylenetetrazole, subcutaneous strychnine, subcutaneous picrotoxin and subcutaneous bicculine. Semicarbazones are also GABA-transaminase inhibitors. Extensive structure--activity relationship has demonstrated that F, Cl, Br and NO_2 substituents in the arylhydrophobic pocket and a hydrogen bonding domain (HBD) are generally found in active anticonvulsant agents.

Keywords: semicarbazone, anticonvulsant, Na^+ channel blocker

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Epilepsy is a brain disorder that causes people to have recurring seizures. Epilepsy affects 50 million people worldwide, and 50 % of them live in the developing world (1, 2).

Many options are available, from different chemical classes such as hydantoins (3) barbiturates (4), benzodiazepines (5), gamma-aminobutyric acid (GABA) analogs (6), dibenzepines (7) and carbamates (8). All of these compounds are used in the treatment of epilepsy. All these medications suffer from having many side effects. Therefore, it has become necessary to discover new chemical pharmacophores with a broad spectrum of activity and less neurotoxicity.

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Many new pharmacophores have been developed over the last twenty years. Functionalized amino acids and alpha-amino amides are two classes of antiepileptic drugs (AEDs) that exhibit pronounced anticonvulsant activity (9). Lacosamide (10) and safinamide (11) are two recently launched AEDs resulting from this approach. Enaminones have been extensively investigated as anticonvulsants (12). In this review, advances made in the application of semicarbazones as a versatile pharmacophore model for the design of new anticonvulsant drugs are updated. Some reviews on the biological activity of semicarbazones and thiosemicarbazones (13) and their metal complexes (14) are mentioned.

Evolution of the concept of semicarbazones as anticonvulsants

The semicarbazone moiety is made up of several smaller functional groups exhibiting anticonvulsant activity (Fig. 1).

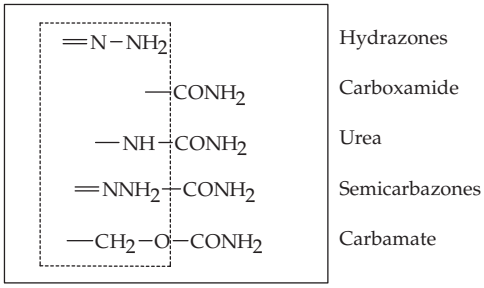


Fig. 1. Concept of semicarbazones as anticonvulsants.

Carboxamides as anticonvulsants

Several carboxamides have been launched on the market. The early drug carbamazepine (15) is the drug of choice for the treatment of grandmal epilepsy and is effective against temporal lobe and generalized seizures. Modification of the drug has resulted in oxacarbazepine (16) and eslicarbamazepine (17), the two most clinically effective drugs for the treatment of epilepsy (Fig. 2).

Progabide (18) is the first GABA agonist that is effective in all the three types of epilepsy, generalized tonic-clonic, myoclonic, and partial seizures in both children and adults.

Hydrazones as anticonvulsants

A series of 3-aryloxy/arylthiooxyacetylhydrazono-3,2-indolines revealed varying degrees of activity against subcutaneous pentylenetetrazole (ScPTZ) induced seizures (19). Anticonvulsant activity of hydrazones, Schiff bases and Mannich bases of isatine were recorded (20). Indole-3-carboxaldehyde hydrazones exhibited low levels of anticonvulsant activity (21). Recently, (±)-3-menthone aryl acid hydrazones afforded signifi-

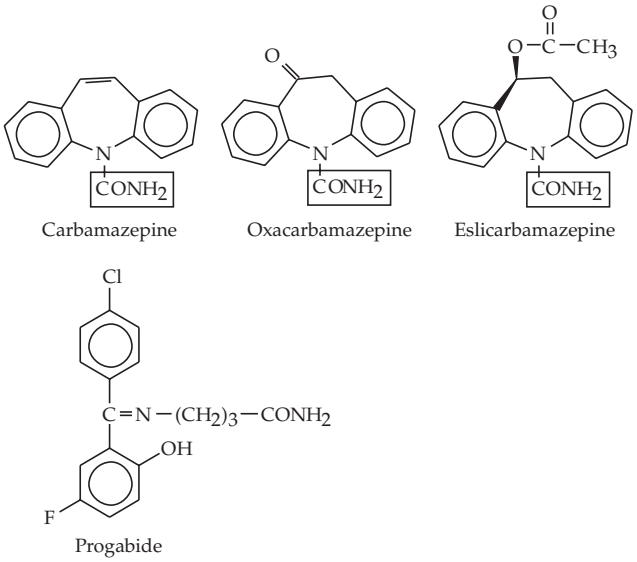


Fig. 2. Carboxamide anticonvulsants.

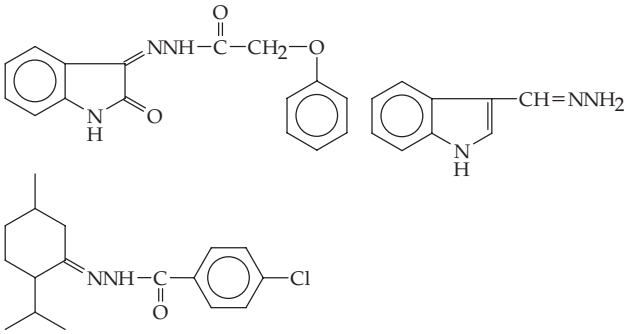


Fig. 3. Hydrazone anticonvulsants.

cant protection in the maximal clonic seizure screen at 6 Hz. 4-Chloro-*N*-(2-isopropyl-5-methylcyclohexylidene) benzohydrazide was active in maximal electroshock seizure (MES) ED_{50} of 16.1 mg kg^{-1} and protective index ($PI = TD_{50}/ED_{50}$) greater than 20 (22) (Fig. 3).

Urea derivatives as anticonvulsant acyclic/cyclic derivatives

In the early days, acyclic ureas and cyclic ureides demonstrated potent anticonvulsant activity. Many of them are still preferred drugs for the treatment of epilepsy (23). Phenacemide (24), hydantoin derivatives, phenytoin (23) and its water soluble prodrug fosphenytoin (25) are used in hospitals for the treatment of epileptic seizures. A succin-

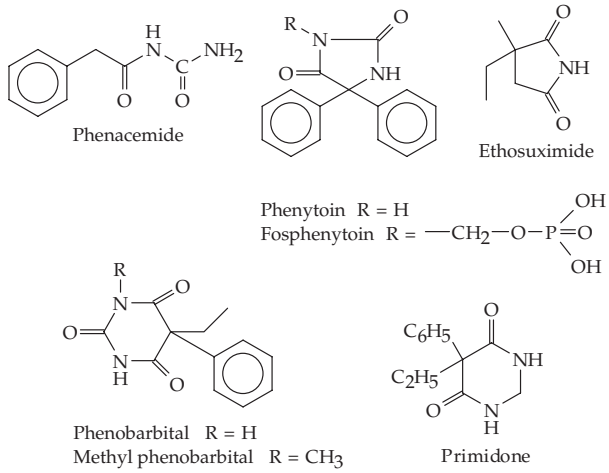


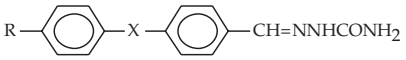
Fig. 4. Acyclic and cyclic ureides.

imide derivative ethosuximide (26) is considered the first choice drug for treating absence seizures. Phenobarbital (27) is a barbiturate and is the most widely used anticonvulsant worldwide. Its N-CH_3 analog, methylphenobarbital, is used as an anticonvulsant. Primidone is used for generalized tonic-clonic and complex seizures (Fig. 4).

Dimmock's early work on semicarbazones

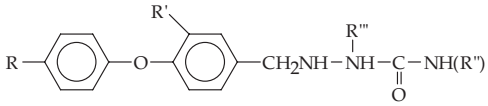
A major achievement of Dimmock (28) was the identification of 4-(4′-fluorophenoxy) benzaldehyde semicarbazone as a lead molecule. Derivatives of this molecule were highly potent and were patented (29). The anticonvulsant activity of some compounds is presented in Table I. The majority of compounds demonstrated no neurotoxicity upto

Table I. Anticonvulsant activity of substituted phenoxybenzaldehyde semicarbazones



R	X	$ED_{(50)}$	Ref.
H	O	1.5	30
H	S	1.5	30
F	O	2.5	30
F	S	2.5	30
Cl	O	1.0	30
Cl	S	1.0	30
Br	O	2.0	30
Br	S	1.5	30

ED_{50}: MES (rat, oral)



R = H, F, Cl, Br, OCH_3, CF_3, CH_3, NO_2, *t*-butyl, C_3H_7, *s*-butyl, cyclohexyl, cycloheptyl, 3-methyl 3,4-methylene dioxy, 5-indanyl, 3,5-diF, 3,4-diF

R′ = F; R‴ = CH_3

R″ = CH_3

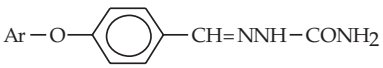
Fig. 5. Aryloxyphenyl semicarbazides.

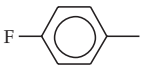
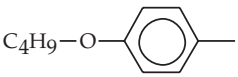
doses of 500 mg kg^{-1}. Among the phenoxybenzaldehyde analogs, halobenzosubstituted derivatives were the most active ones. Further exploring the structural changes, various heterocyclic, carbocyclic and fused rings were introduced in the molecule in place of the aryloxy group (31).

The heterocycles included thiophene, pyrrole, furan, imidazole, pyridine, pyrazine, pyrimidine, phenothiazine, quinoline, indole, benzoxazole and benzimidazole. The carbocyclic groups included cyclohexyl and cycloheptyl. 4-(3,4-Methyleneoxyphenoxy) benzaldehyde semicarbazone had MES (mice, *p.o.*) ED_{50} of 5.3 mg kg^{-1}. Several other substituents showed promising activity and ability to inhibit human skeletal muscles. Na^+ subchannel subunit stable expression in HEK-293 cells was studied (Table II) (29).

Since 4-(4-fluorophenoxy) benzaldehyde semicarbazone metabolizes to the corresponding semicarbazide, some novel substituted semicarbazides were prepared (Fig. 5) and found active (32). Semicarbazide is a base due to the presence of basic N-1 nitrogen; semicarbazone is not a base but the NH group on N-2 nitrogen is slightly acidic. The C=N bond in semicarbazone makes it a relatively rigid structure while the –C-N- single bond in semicarbazide is relatively non-rigid and affects the molecule bioactivity.

Table II. Na^+channel binding of semicarbazones



Ar	ED_{50} MES (*i.p.*) (mg kg^{-1})	*KI*(M) mg kg^{-1}	Ref.
		1.1	29
5-indanyl	0.04	1.7	29
cycloheptoxy	0.25	3.2	29
	0.2	1.6	31
	6	14.9	31

ED_{50} (MES *i.p.* ranged from 0.13 to 7.5 mg kg^{-1}) and *KI*(M) from 0.9–3.4 mg kg^{-1}.

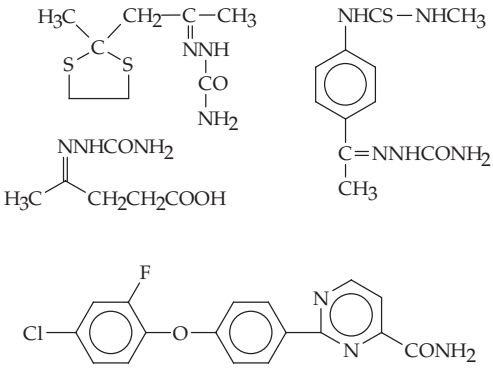


Fig. 6. Thioureido and levulinic acid semicarbazones, pyrimidine carboxamide and 1,3-dithiolane semicarbazones.

Pandeya *et al.* (33) synthesized thiouriedo derivatives of acetophenone semicarbazone. Compound 4-(*N'*-methylthioureido)acetophenone had MES (*i.p.*) ED_{50} 23.5 mg kg^{-1} compared to phenytoin with ED_{50} of 23.2 mg kg^{-1}. This compound has a better protective index ($PI = TD_{50}/ED_{50}$) than sodium valproate (2.55 *vs.* 2.17) and was also active in the subcutaneous pentylenetetrazole (ScPTZ) test (Fig. 6).

A rigid analog of semicarbazone linker was prepared. 2-[4-(4-Chlorophenyl-2-fluorophenoxy)phenyl]-pyrimidine-4-carboxamide was found to be a potent, broad spectrum state-dependent sodium channel blocker for treating pain states. This compound was approximately 1000 times more potent, had 2000-fold faster binding kinetics and 10-fold higher levels of state dependence than carbamazepine and lamotrigine. It had ED_{50} at least 1–3 mg kg^{-1} (*p.o.*) in partial sciatic nerve ligation (34) (Fig. 6).

Pandeya's modifications of semicarbazone scaffold

Dimmock (35) attempted a structural modification of the primary amino group of anticonvulsant arylsemicarbazones and found that the primary amino group was not essential. However, its replacement by an aryl ring generally abolished activity, while a terminal phenyl amino function was better tolerated. Thus, both the size of the group and its hydrogen bonding capabilities appear to influence bioactivity. Alteration of the oxygen atom of semicarbazones by isosteres did not enhance anticonvulsant properties.

Considering the observation of Dimmock of the necessity of the terminal carboxamide group to be essential for bioactivity through its involvement in hydrogen bonding at the putative receptor site, Pandeya *et al.* (36) modified this terminal carboxamide function by substituting it with a *p*-NO_2 phenyl group. This preliminary modification showed anticonvulsant activity at a dose of 30 mg kg^{-1} and ED_{50} of 83 mg kg^{-1} in the MES test. This change was further strengthened by the preparation of a series of *p*-NO_2 substituted semicarbazones. 4-(4'-Chlorophenyl)-*o*-nitrobenzaldehyde was found to be the most active anticonvulsant agent against MES, ScPTZ and subcutaneous strychnine (ScSTY) induced seizures. These compounds showed longer duration of action, upto 4.25 h (Fig. 7).

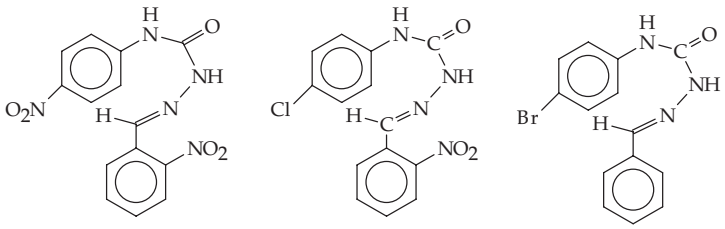
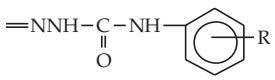


Fig. 7. Pandeya's modification.

It appeared at that point of investigation that an aryl ring with an electron withdrawing substituent was beneficial for the anticonvulsant activity. Therefore, *p*-chlorophenyl group was selected for further modification, because this group is present in diazepam, a drug used to treat *status epilepticus*. A series of *p*-chlorophenyl substituted arylsemicarbazones were synthesized and were found active in MES, ScPTZ and ScSTY tests (37). The majority of compounds showed anticonvulsant activity in all the tests. In this series, 4-(4'-chlorophenyl)-*o*-nitrobenzaldehyde semicarbazone was most active. In this study, the methoxy substituted derivative 4-(4'-chlorophenyl)-3,4-dimethoxybenzaldehyde semicarbazone was found orally active in the MES test at a dose of 30 mg kg^{-1}, with no neurotoxicity at that dose. Quantification studies have revealed that 4-(4'-chlorophenyl)-2-methoxybenzaldehyde semicarbazone has MES (mice *i.p.*) ED_{50} 123.25 mg kg^{-1}; MES (rat, *p.o.*) ED_{50} 18.55 mg kg^{-1} and 6 Hz (mice, *i.p.*) ED_{50} 83.93 mg kg^{-1}.

Bioisosteric replacement of the chloro atom in *N*'-(4-chlorophenyl)-N^4-2-hydroxybenzaldehyde semicarbazone with bromine with higher π values resulted in potent anticonvulsants. These compounds exerted anticonvulsant activity in MES, ScPTZ and ScSTY tests. *N*-(4-bromophenyl) acetophenone semicarbazone protected mice at a dose of 100 mg kg^{-1} in MES and ScSTY tests. It also protected mice at a dose of 300 mg kg^{-1} in the ScPTZ screen. *N*-(4-bromophenyl) acetophenone semicarbazone was not neurotoxic

Table III. Arylsemicarbazones: substitutions at carboxamide nitrogen



R	Ref.
4-F, 4-CH_3, 4-Br, 4-Cl, 2-Br, 3-Br, 3-Cl, 5-CH_3	39–41
2F, 4-Br, 4-F, 4-Cl, 2-Cl	42–44
4-SO_2NH_2, 4-NO_2, 4-Br	38, 41, 45, 46
2, 4-OCH_3, 3-Cl-2-CH_3, -OC_2H_5	47–49
4-NO_2, 4-Cl, 4-SO_2NH_2	37, 50–52
4-Br, 3-CH_3, 2,5-diCH_3, 2F, 5-CH_3	36, 37, 50, 53, 54
2,6-dimethyl	55
N'-(naphtha[1,2-*d*]thiazol-2-yl)	56
benzothiazol-2-yl	57
3-methyl pyridine-2-yl	58

at a dose of 300 mg kg^{-1} either. Further, it was orally active at a dose of 30 mg kg^{-1} upto 4 h of drug administration. *N*-(4-bromophenyl) acetophenone semicarbazone was non--sedating either, a property required for a potential anticonvulsant (38).

Encouraged by these results, various other researchers, like Yogeeswari *et al.* (39–42), introduced several substituents to find out the structure activity relationship between semicarbazone anticonvulsants (Table III).

Some other researchers have prepared semicarbazones as well; 4-substituted semicarbazones of levulinic acid showed anticonvulsant activity (59) (Fig. 6). New α,β and γ-semicarbazones derived from 1,3-dithiolones showed anticonvulsant activity (60) and one compound (Fig. 6) exhibited agonist activity with regard to PTZ at 250 mg kg^{-1}.

Heterocyclic semicarbazones

Siddiqui *et al.* (57) replaced the phenyl ring of *p*-chlorophenyl semicarbazones with a 6-substituted benzothiazole ring to determine the size of the hydrophobic domain.

Rajak *et al.* (61) introduced the phenyl substituted thiadiazole nucleus in N^1-(4-phenyl-1,3,4-thiadiazole-5-benzaldehyde semicarbazone.

Siddiqui *et al.* (62) synthesized coumarin derived thiazolyl semicarbazones. 4-Bromophenyl (1*E*)-1-(4-bromophenyl-1-one-*N*-[4-(2-oxo-2*H*-chromen-2-yl)-1,3-thiazol-2-yl) semicarbazone was most potent at a dose of 30 mg kg^{-1} up to 4 h in the MES test. It was also active against ScPTZ at a dose of 100 mg kg^{-1}. However, it was neurotoxic at a dose of 100 mg kg^{-1} equivalent to phenytoin. Novel quinazolinone semicarbazones displayed anticonvulsant activity in MES and ScSTY tests at a dose of 30 mg kg^{-1} (63) (Fig. 8).

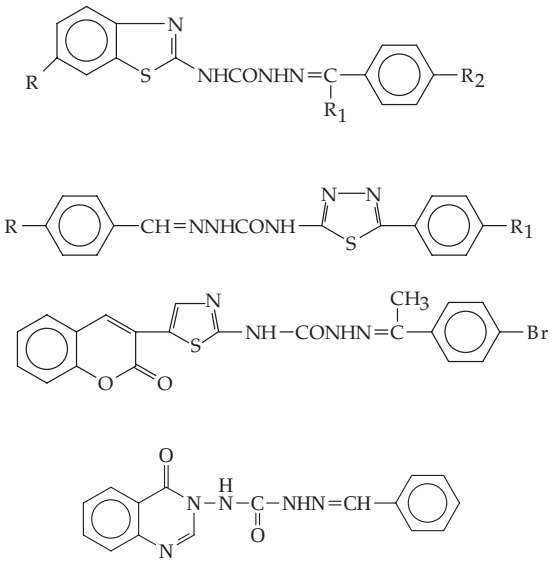


Fig. 8. Heterocyclic semicarbazones.

Modifications in the distal aryl ring

The hydrazono terminal has been substituted by a wide spectrum of aldehydes and ketones having aliphatic, aromatic, alicyclic and heterocyclic moieties (Table IV). From these studies, three compounds have emerged as the most potent anticonvulsants, which were investigated in various phases of drug development, 4-fluorophenoxy benzaldehyde semicarbazone, 4-bromobenzaldehyde semicarbazone and 3,4-dimethoxy benzaldehyde-N^4-(*p*-chlorophenyl) semicarbazone.

4-Fluorophenoxy benzaldehyde semicarbazone displayed MES ED_{50} (*i.p.*) 12.9 mg kg^{-1}; ScPTZ > 54 mg kg^{-1}, with MES, *PI* (protective index) of 3.09. This compound was orally active with very high *PI* (MES) > 315. The oral ED_{50} was 1.59 mg kg^{-1}. It was more potent compared to clinically effective drugs such as phenytoin (*PI* > 21.6), carbamazepine (*PI* 101) and Na-valproate (*PI* 2.17) (28).

Dimmock *et al.* (77) isolated the major inactive urinary metabolite, 4-fluorophenoxy phenylcarboxy semicarbazide (Fig. 9) from 4-(4-fluorophenoxy) benzaldehyde semicarbazone after oral dosing to rats.

On the other hand, Ramu *et al.* (78) studied the pharmacokinetics of this compound (C0102862) in rats. Its half-life was 14 days and renal excretion was 74 %. The main metabolite was the corresponding carboxylic acid. They also developed a HPLC method for the determination of pharmacokinetics of C0102862 in mouse, rat, monkey and dog plasma (79).

Lam (80) patented a large number of substituted phenoxybenzaldehyde semicarbazones as anticonvulsants and sodium channel blockers (Fig. 10). Micale *et al.* (81) studied the anticonvulsant property of 2-[(4-alkyl semicarbazono-(4-aminophenyl) methyl-4,5-methylenedioxy phenylacetic acid alkyl esters.

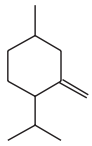
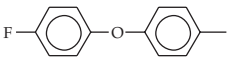
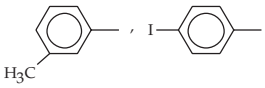
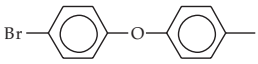
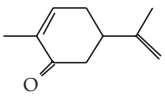
Modification in the semicarbazone linker

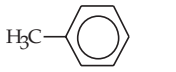
The semicarbazones linker provides two essential requirements for anticonvulsant activity. The carboxamide group is implicated in hydrogen bonding. Pandeya *et al.* (45) replaced the CONH-moiety with non-hydrogen bonding –O-CH_2– moiety. Whereas compounds with –CONH– were active in both the MES and ScPTZ tests, compounds with the –O-CH_2– moiety were completely devoid of any anticonvulsant activity, clearly demonstrating the hydrogen bonding characteristic of the semicarbazono linker (45). Substitution of the carboxamido hydrogen with ethyl group (68) produced inactive compounds. Continuing the role of –CONH– in hydrogen bonding, however, substitution by a methyl group produced active compounds, compared to diazepam with a desmethyl active metabolite.

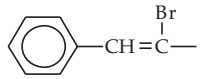
In another study, phenacylhydrazones lacking the hydrogen bonding characteristic exhibited no anticonvulsant activity (65) (Fig. 11).

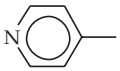
Semicarbazono linker was replaced with a rigid pyrimidine ring to give 2-[4-(4-chloro-2-fluorophenoxy)phenyl]-pyrimidine-4-carboxamide (34). This compound was approximately 1000 times more potent, and had 2000-fold faster binding kinetics than carbamazepine and lamotrigine tested on recombinant rat Na(v) 1.2 channels and native Na(+) currents in cultured rat dorsal root ganglion neuron (ED_{50} 1–3 mg kg^{-1} *p.o.* in partial nerve ligation).

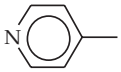
Table IV. Substituents at the hydrazone terminal

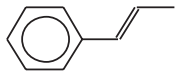
Alkyl/aryl/heteroaryl	R	Ref.
C_6H_5–	CH_3	46
2-NO_2-C_6H_4	H	38
4-Br-C_6H_4	H	64
3,4-dimethoxy	–C_6H_3	37
4-amino C_6H_4	CH_3	33
4-methoxy C_6H_4	H	65
4-C_6H_5, -CH_2-O-C_6H_4	H	66
N-methyl-3-isatine	–	67
4-methoxyphenyl	CH_3	68
1-[2,5-dihydroxyphenyl)-3-	(4-methoxyphenyl)	43
6-chloroisatine	–	69
1,4-benzoquinone	–	45
C_2H_5	CH_3	70
citral, *R*(-) carvone		71, 72
CH_2CH_2COOH	CH_3	59
menthone		44, 41
	H	28
C_6H_4-CH=CH-	H	73
	H	74
	H	55
	CH_3	75
	–	72











	CH_3	58
	H	76
	H	51
	CH_3	51
		44
CH_3	CH_3	47

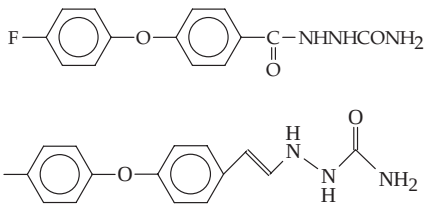
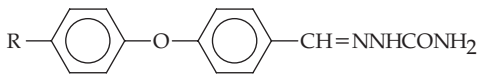


Fig. 9. Metabolites of 4-fluorophenoxy benzaldehyde semicarbazone.



R = H, F, Cl, Br, 3,4-diF, 4-Cl, 2F, CF_3, NO_2, CH_3, OCH_3, 3-CH_3, 3-CH_3, 4-C_3H_7, 5-C_4H_9, t-C_4H_9, 3,4-CH-O-O$^-$ cC_6H_{11}, C_7H_{13}, 5-indanyloxy, 6-quinolyoxy.

Fig. 10. Substituted phenoxy/alicyclic/heteroaryl oxybenzaldehyde semicarbazones.

Siddiqui *et al.* (82) synthesized a rigid oxadiazole analog, which was active in the MES test (*i.p.*) at 30 mg kg^{-1} up to 0.5 h. Mehta *et al.* (83) cyclized the semicarbazone template of an arylsemicarbazone to 4,5-diphenyl-2*H*-1,2,4-triazole-3(4*H*)-one. Compound 4-(4-fluorophenyl)-5-(4-nitrophenyl)-2*H*-1,2,4-triazole-3(4*H*)-one was active in MES (10 mg kg^{-1}) (*i.p.*) and ScPTZ (300 mg kg^{-1}) screens. This indicates a broad spectrum of anticonvulsant activity of cyclized derivatives (83) (Fig. 12).

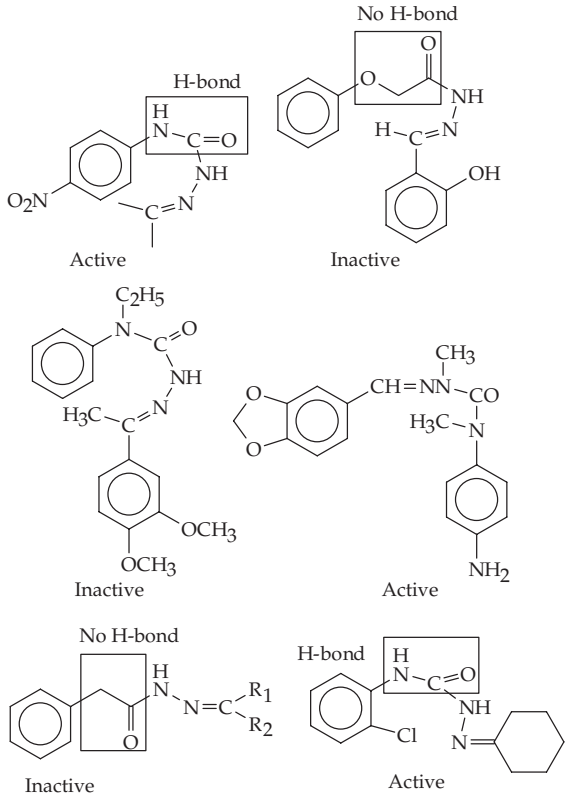


Fig. 11. Modifications in the semicarbazone linker.

General mechanism of action of anticonvulsants

Most antiepileptic agents possess more than one mechanism of action (84). Antiepileptic drugs can be classified according to the mechanism of action as given below.

Blockade of voltage-dependent sodium or calcium channels. – Phenytoin, carbamazepine, lamotrigine, oxacarbazepine, topiramate and valproate belong to this group. These drugs are effective against generalized tonic-clonic and partial seizures.

GABA-mediated anticonvulsants. – Benzodiazepines, gabapentin, tiagabine, vigabatrin, topiramate are in this group. Tiagabine inhibits neuronal and glial uptake of GABA, whilst vigabatrin increases the synaptic concentrations of GABA by inhibiting GABA aminotransferase. Gabapentin was shown to increase brain synaptic GABA.

Modification of T-type calcium channels. – This class includes only one drug, ethosuximide, which is active against seizure absences. The mechanism of action of ethosuximide is based on reducing the current in T-type calcium channels found in thalamic nuclei.

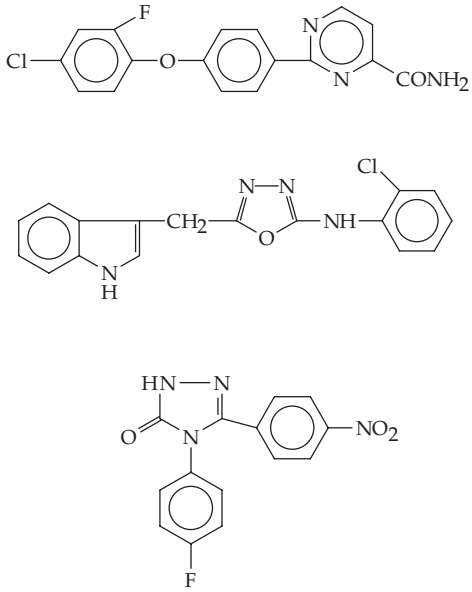


Fig. 12. Rigid analogs of semicarbazones.

Spike-and-wave patterns during petitmal seizures are thought to be initiated in thalamocortical relays by activation of these channels. Agents protecting the ScPTZ induced seizures act by this mechanism.

Mechanism of action of semicarbazone anticonvulsants

Various researchers have studied the mechanism of action of semicarbazones as anticonvulsants. Ilynin *et al.* (85) found 4-(4-fluorophenoxy) benzaldehyde semicarbazone (V102862; C0102862) a potent, broad-spectrum blocker of mammalian voltage-gated sodium channels. V102862 blocked Na^+ currents in acutely dissociated cultured rat hippocampal neurons. V102862 was a potent state dependent blocker of r Na 1, 1.2 channels with a *KI* (ligand/receptor association constant) of ~ 0.4 μmol $L^{-1}$and KR [binding of the ligand for resting state (R) of the receptor] ~30 μmol L^{-1}. V102862 shifted the steady-state availability curve in the hyperpolarizing direction and significantly retarded recovery of Na^+ channels from inactivation. Thus, inhibition of voltage-gated Na^+ channels is the major mechanism underlying the anticonvulsant property of V102862. This agent also displays ~80 fold higher affinity for inactivated Na^+ channels compared to channels in the resting state.

Yogeeswari *et al.* (55) studied the GABA level in different parts of the brain. N^1-(2,6-dimethylphenyl)-N^4-(2-hydroxybenzaldehyde) semicarbazone increased the GABA level by 118 % and inhibited the GABA transaminase enzyme both *in vitro* and *in vivo*.

N-(4-ethoxyphenyl)-N^4-(2-hydroxyacetophenone) semicarbazone increased the GABA level of the control only in the medulla oblongata region (49) (Fig. 13).

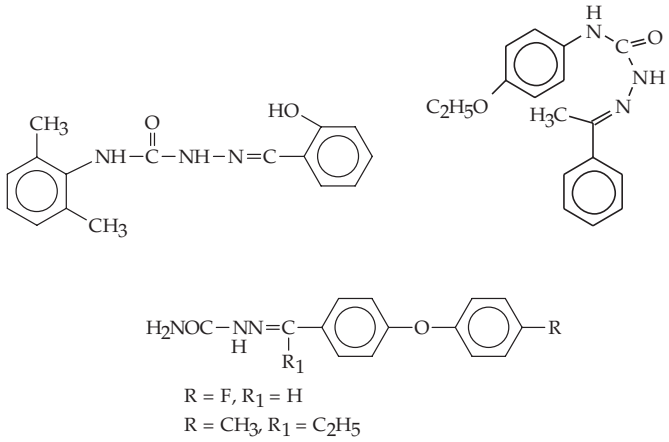


Fig. 13. GABA-T inhibitors.

Cyclized semicarbazones such as 4-(2,4-dimethylphenyl)-5-(4-nitrophenyl)-2*H*-1,2,4--triazole also increased the GABA level more than 10 times compared to the control (83). Some aryl-semicarbazones were shown to act through GABA mediation (86) (Fig. 13).

Apart from experimental evidence in favor of Na^+ channel blockers and the GABA mediated mechanism of action, other indirect evidences are also available. Arylsemicarbazones have been shown to protect against seizures induced by ScPTZ. ScPTZ tests reveal drugs likely to be active against absences, acting possibly as T-type calcium channel blockers; ScSTY test indicates the compound is active through glycine receptors. PTZ or picrotoxin (PIC) do not act through GABA-mediated inhibition (87, 88). They are non--competitive channel blockers. Ethosuxinimide, which is used in absence, reduces low threshold (T-type) calcium channels. Ethosuxinimide protects ScPTZ induced seizures (89). Among the large number of semicarbazones screened for channel activity, only two compounds, 4-fluorophenoxy propiophenone semicarbazone(75) and 4-methylphenoxy-acetophenone semicarbazone (76), were found activein the ScPTZ test, with ED_{50} values of 12.8 and 19.2 mg kg^{-1}, respectively. This indicates that arylsemicarbazones will be more beneficial for grandmal epilepsy. Similarly, only few compounds were active in ScSTY and ScPTZ tests (Fig. 14).

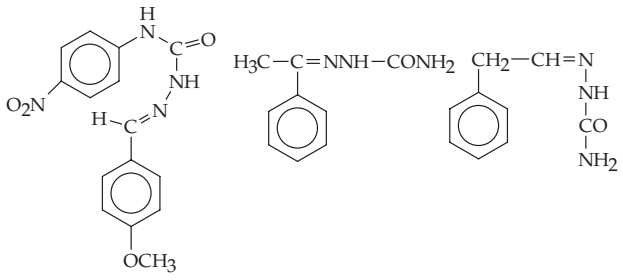


Fig. 14. Anticonvulsants active against ScPTZ, ScBIC and ScSTY.

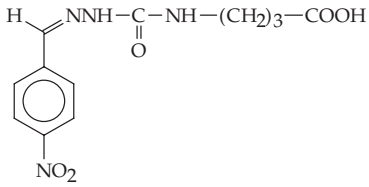


Fig. 15. 4-({[2-(4-Nitrobenzylidene)hydrazine]carboxyl}mino)-butanoic acid.

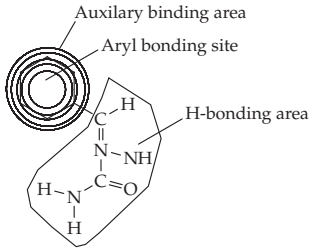


Fig. 16. Dimmock's first model (75).

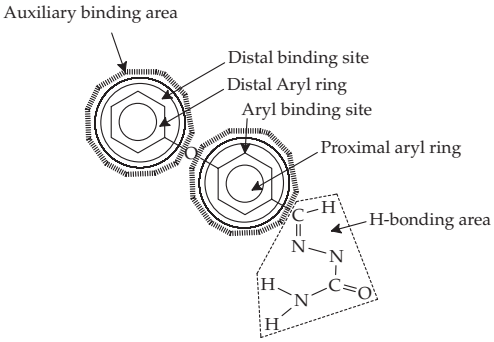


Fig. 17. Dimmock's revised model (75).

In the series of *N*-(2,6-dimethylphenyl) substituted semicarbazones, a large number of compounds were found active at a dose of 30 mg kg^{-1} in ScSTY tests. Therefore, these compounds could be assumed to act through glycine receptors (55). A few compounds (50) with *p*-nitrophenyl substitution also showed activity in ScSTY tests. Acetophenone semicarbazone (73) and phenyl acetaldehyde semicarbazone (73) protected against seizures induced by ScPTZ (ED_{50} 60.75 mg kg^{-1}) and subcutaneous bicuculline (ScBIC) (ED_{50} 57.63 mg kg^{-1}) (Fig. 14).

Compound 4-({[2-(4-nitrobenzylidene)hydrazine]carbonyl}amino)-butanoic acid (Fig. 15) was active in both ScSTY and ScPTZ tests at a dose of 30 mg kg^{-1} (90).

Arylsemicarbazones can be predominantly used to treat grandmal epilepsy because they are active against MES and have been shown to act through Na^+ channel blocking.

Pharmacophore model (91)

Based on the two schools of semicarbazone research, two models have been proposed. In his initial work on semicarbazones, Dimmock (75) proposed a model with (*i*) aryl binding site surrounded by an auxiliary binding area; (*ii*) hydrogen binding area represented by a semicarbazono handle (Fig. 16). Based on new findings of aryl(oxy) arylsemicarbazones as anticonvulsants (75), he modified the earlier model (Fig. 17) as having: (*i*) aryl binding site (proximal aryl ring); (*ii*) distal aryl ring (distal binding site); (*iii*) auxiliary binding area; (*iv*) semicarbazono handle as H-bonding area. It is important to note that proximal rings are nearly coplanar with the ureido group (necessary for H-bonding) (74).

Pandeya's versatile model

Pandeya's work (45, 50) mainly concentrated on the introduction of aryl/alkyl/alicyclic moieties in the carboxamide amino function (38). This created another binding site, distinct from Dimmock's. The anticonvulsant activity of *p*-chlorophenyl/*p*-nitrophenyl/*p*-bromophenyl substituted semicarbazones was compared with active metabolites of diazepam (92), nitrazepam and bromazepam (67) and clonazepam (Fig. 18).

Dimmock proposed the following structural features of an anticonvulsant: (*i*) aryl binding site responsible for hydrophobic interaction (HPB site); (*ii*) two-electron donor system (C=N); and most importantly (*iii*) a hydrogen bonding area as represented by carboxamide $-CONH_2$ function (HBD).

This model can explain a number of AEDs such as safinamide, ezogabine and gabapentin (Fig. 19). However, the model was not able to explain the AEDs having an aryl/alkyl substituent (3, 18) in close proximity to the two-electron donor system, like pro-

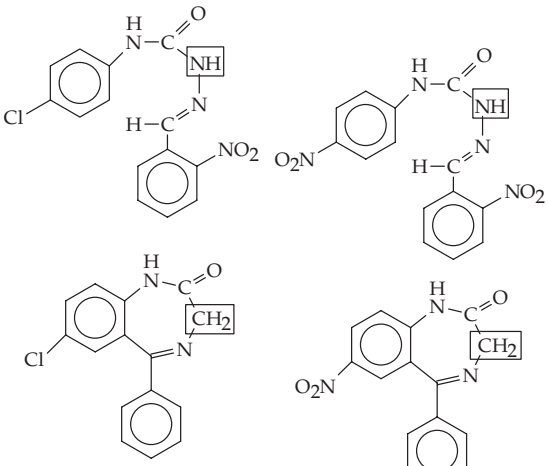


Fig. 18. Structural comparison of semicarbazones with benzodiazepines.

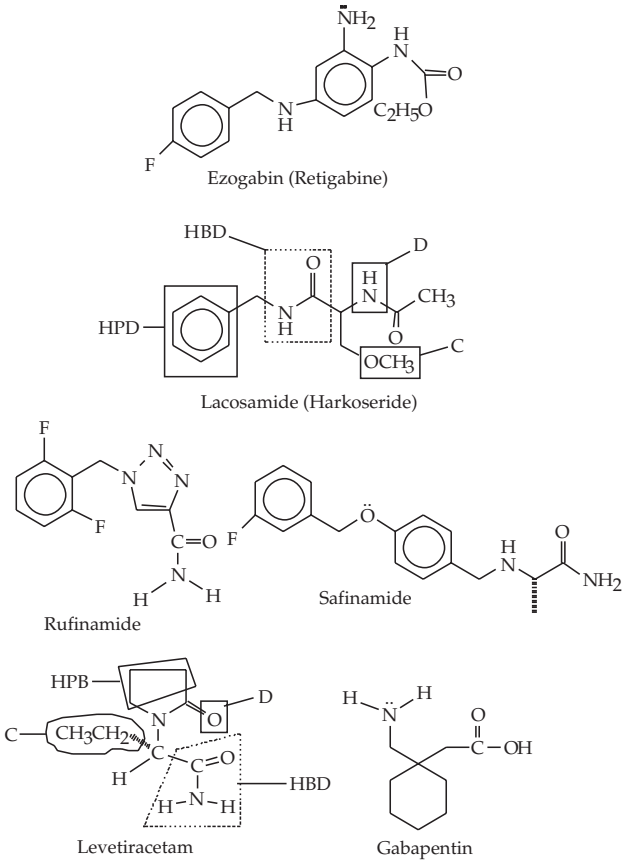


Fig. 19. Structural similarity of different clinically effective AEDs.

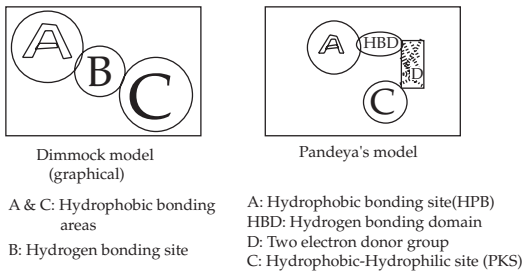


Fig. 20. Dimmock's (91) *vs.* Pandeya's (69) model.

gabide, phenytoin, remacemide, levetiracetam, and arylsemicarbazones having substitution in the carboxamide amino function. Therefore, Pandeya (69) proposed a versatile model to explain the anticonvulsant activity of a large number of AEDs. In addition to

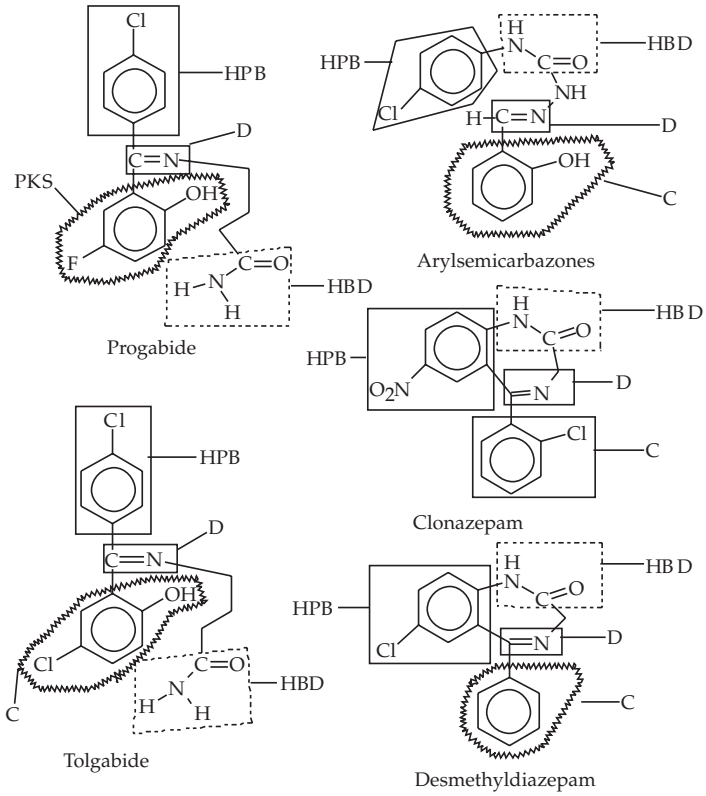


Fig. 21. Pandeya's model compared with different AEDs (55).

the above mentioned three sites, an additional aryl/alkyl site was proposed as pharmacokinetic site. This site was responsible for the pharmacokinetic properties of the molecule and included a phenyl ring with or without *ortho* substitution like benzodiazepines. A comparison of the two models is given in Fig. 20.

Pandeya's model can be thus adopted to design novel anticonvulsants having the structural components of the proposed pharmacophore. It has also explained the pharmacophore similarity of arylsemicarbazones to desmethyldiazepam. Semicarbazones can be considered bioisosteric acyclic analogs of desmethyl diazepam (Fig. 21). The –NH– of semicarbazones is bioisosteric with $–CH_2–$ of benzodiazepines. Also, semicarbazones can be considered acyclic analogs of cyclic benzodiazepines.

CONCLUSIONS

Semicarbazones have been developed as versatile anticonvulsant pharmacophores. Two compounds, 4-(4-fluorophenoxy)benzaldehyde semicarbazone (FPBS) and *N'*-(4--chlorophenyl)-N^4-(2-nitrobenzaldehyde) semicarbazone, have been identified as lead

molecules and are at various stages of development: FPBS is a sodium channel blocker while the others are GABA transaminase inhibitors. Other mechanisms of action, like glycine receptors and non-competitive channel blockers, have been proposed. A versatile pharmacophore model has been suggested for future drug design and development of anticonvulsants.

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S A Ž E T A K

Semikarbazon – svestrani farmakofor u dizajniranju antikonvulziva

SURENDRA NATH PANDEYA

Tijekom posljednjih petnaest godina intenzivno su istraživana antikonvulzivna svojstva semikarbazona. 4-(4-Flurofenoksi)benzaldehid semikarbazon (C0102862, V102862) otkriven je kao vodeći spoj iz kojeg je razvijen antiepileptik s maksimalnom elektrošok aktivnošću (MES) ED_{50} 12,9 mg kg^{-1} *(i.p.)* i zaštitnim indeksom ($PI = TD_{50}/ED_{50} > 315$) većim od karbamazepina (*PI* 101), fenitoina (*PI* > 21,6) i valproata (*PI* 2,17). Spoj je snažni blokator natrijevih kanala. Drugi su se semikarbazoni pokazali učinkovitima u različitim kemo-šok testovima, kao što su supkutana primjena pentilentetrazola, strihnina, pikrotoksina i bikukulina. Semikarbazoni su također inhibitori GABA-transaminaze. Opširne studije odnosa strukture i djelovanja pokazale su da je za antikonvulzivno djelovanje bitna prisutnost F, Cl, Br i NO_2 supstituenata u arilhidrofobnom džepu i domena za vezanje vodikovim vezama (HBD).

Ključne riječi: semikarbazon, antikonvulziv, blokator Na^+ kanala

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