A systematic review of semicarbazones as an anticonvulsant agent

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ABSTRACT

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. The use of current antiepileptic drugs has been questioned due to the non-selectivity of the drugs and the undesirable side effects posed by them. This lead to the search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. Semicarbazones are compounds which are synthesized by the condensation of semicarbazide and aldehydes/ketones. The literature survey revealed that semicarbazones had been emerged as a compound with broad range of activities including anticonvulsant, antitubercular, anticancer and antimicrobial activity. In this review chemistry and anticonvulsant activity of semicarbazone analogues are discussed.

Table 1: Major side effects of commonly used anticonvulsants [6]

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Dizziness, lethargy, hypotension, apnea, megaloblastic anemia, Liver damage and so on.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Nausea, skin rashes blood dyscrasias, hyperglycemia cardiac arrhythmias and so on.</td>
</tr>
<tr>
<td>Trimethadone</td>
<td>Drowsiness, G.I.distress, vertigo, diplopia, epistaxis, alopecia, nephrosis, foetal malformation and so on.</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>G.I. distress, euphoria, confusion, myopia, urticaria, vaginal bleeding and so on.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Dizziness, ataxia, drowsiness, hallucinations, dermatologic sweating, genitourinary albuminaria, hypotension, liver dysfunction and so on.</td>
</tr>
<tr>
<td>Primidone</td>
<td>Lethargy, ataxia, vertigo, irritability, severe skin rashes, lymphadenopathy, impotence, visual disturbances, lupus like reactions and so on.</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Nausea, vomiting, indigestion, sedation, abdominal cramps, fetal hepatic failure, alopecia, irregular menses, acute pancreases, blood dyscrasias and so on.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Dizziness, ataxia, blurred vision, vomiting, skin rashes, Stevens Johnson syndrome, disseminated intravascular coagulation</td>
</tr>
</tbody>
</table>

The structural requirements in the semicarbazone series are: a lipophilic aryl ring, a distal aryl ring, a hydrogen-bonding domain (HBD) and an electron donor acceptor system (Fig 1. ). The lipophilic aryl ring with chloro, bromo or nitro groups has been found to be essential for anticonvulsant activity.

Fig 1. Proposed pharmacophore model for anticonvulsant activity: (A) hydrophobic aryl ring; (HBD) hydrogen-bonding domain; (C) distal aryl ring; (D) electron donor acceptor group
Semicarbazones

Chemistry of Semicarbazones

Semicarbazones are among the most relevant nitrogen-oxygen donor ligands (Figure 2.).

Fig. 2. General Structure of semicarbazone analogues

Semicarbazones are the Schiff bases, usually obtained by the condensation of semicarbazide with suitable aldehydes and ketones (Scheme 1.).

Scheme 1. Method of Synthesis of semicarbazone

According to IUPAC recommendations, semicarbazones may be named by adding the class name ‘semicarbazone’ after the name of the condensed aldehyde or ketone. It is usual also to include in this class derivatives with substituents on the amide nitrogen. The numbering scheme shown in the Figure 3. is in accordance with IUPAC system.

Fig. 3. Numbering scheme of the semicarbazone.

An interesting attribute of the semicarbazones is that in the solid state, they predominantly exist in the keto form, whereas in solution state, they exhibit a keto-enol tautomerism (Figure 4.). Keto form acts as a neutral bidentate ligand and the enol form can deprotonate and serve as monoanionic bidentate ligand in metal complexes. Thus semicarbazones are versatile ligands in both neutral and anionic forms.

Fig. 4. Keto-enol tautomerism of semicarbazones

General method for the synthesis of semicarbazone analogues

The general method for the synthesis of semicarbazone analogues is presented in Scheme 2.

Scheme 2. General method for the synthesis of semicarbazone analogues.

Spectral studies on semicarbazones

Infrared

The carbonyl stretching C=O vibration [12, 13] is expected in the region 1715-1680 cm⁻¹ in the IR spectrum. The δ C=O in-plane deformation and the out-of-plane deformation γ C=O are expected in the regions 625 ± 70 and 540 ± 80 cm⁻¹ respectively [12]. According to Socrates [14], the C=N for semicarbazones is expected in the region 1655-1640 cm⁻¹ in IR spectrum. A perusal through literature shows that C=O and C=N stretching modes are reported at 1668, 1671 and 1613, 1602, 1719, 1600 [15, 16], 1669, 1618 [17], 1680, 1586 [18], and at 1682, 1574 cm⁻¹ for semicarbazone derivatives [19]. The NH stretching vibration [12] appears as a strong and broad band in the region 3390 ± 60 cm⁻¹. The C-N stretching vibration [12] coupled with the δNH, is active in the region 1275 ± 55 cm⁻¹. The vibrations of the CH₂ group, the asymmetric stretch, νsCH₂, symmetric stretch νasCH₂, scissoring vibration δCH₂ and wagging vibration νoCH₂ appear in the regions 3000 ± 50, 2965 ± 30, 1455 ± 55 and 1350 ± 85 cm⁻¹, respectively [12, 20]. The rocking mode [12] is expected in the range 895 ± 85 cm⁻¹. The NH₂ asymmetric stretching vibrations [12] give rise to a strong band in the region 3390 ± 60 cm⁻¹ and the symmetric NH₂ stretching in the region 3210 ± 60 cm⁻¹ with a somewhat weaker intensity.

Geometrical parameters

The NN bond lengths are reported as 1.3782-1.389 [21], 1.3867 [22], 1.3894 [23], 1.3966 [24], 1.3796 [25], 1.3675 [26], 1.367 [27], 1.36 [28], and 1.369 Å [29].

¹H NMR

Dimmock et al. [30] studied the ¹H NMR spectra of 1-(4-fluorophenyl)ethanone semicarbazone in DMSO-d₆; the chemical shift and spin coupling constants are given. The ¹H NMR spectra of 1-(4-fluorophenyl)ethanone semicarbazone (Figure 5.) have five characteristic peaks in the NMR spectrum, H(2',5'-H, Aromatic) appears as a triplet at δ 7.18, H(3',5'-H, Aromatic) appears as a triplet at 7.90 ppm, H(CH₃) appears as a singlet at δ 2.20, (H)NH appears as a singlet at δ 9.39 and (H)NH₂ appears as a singlet at δ 6.54.

Fig. 5. Representative ¹H NMR data of 1-(4-fluorophenyl)ethanone semicarbazone.

¹³C NMR

Dimmock et al. [30] studied the ¹³C NMR spectra of 1-(4-fluorophenyl)ethanone semicarbazone in DMSO-d₆; the chemical shift and spin coupling constants are given in the Figure 6.

Fig. 6. Representative ¹³C NMR data of 1-(4-fluorophenyl)ethanone semicarbazone.
Mass spectral studies

Berdyshev [31] reported the mass spectra of fatty aldehyde semicarbazone derivatives (Figure 7).

Fig. 7. Positive product ion mass spectra of fatty aldehyde semicarbazone derivatives. (A) (2E)-Hexadecenal semicarbazone product ions. (B) cis-11-Hexadecenal semicarbazone product ions. (C) Hexadecanal semicarbazone product ions. (D) Proposed pathways for product ion formation during (2E)-hexadecenal semicarbazone CID. cps, counts per second.

Molecular structure studies

Trzesowska [25] reported the molecular structure of p-dimethylaminobenzaldehyde semicarbazone (Figure 8.).

Fig. 8. The molecular structure of p-dimethylaminobenzaldehyde semicarbazone. The displacement ellipsoids are drawn at 50% probability level.

Anticonvulsant activity of Semicarbazones:

Pandeya et al. [10] synthesized a number of 4-bromophenyl semicarbazones (1, 2) and evaluated for anticonvulsant activity. After intraperitoneal injection to mice, the semicarbazone derivatives were examined in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY) and neurotoxicity (NT) screens. All the compounds showed anticonvulsant activity in one or more test models. A compound 2a showed greatest activity, being active in all the screens with very low neurotoxicity. All the compounds except 1g had lower neurotoxicity compared to phenytoin.

Yogeeswari et al. [32] synthesized a series of 4-sulphamoylphenyl semicarbazone derivatives (3, 4) starting from sulphamidine and screened for anticonvulsant activity. The results indicated that greater protection was obtained in the maximal electroshock screen (MES) and subcutaneous strychnine (scSTY) than the subcutaneous pentylenetetrazole (scPTZ) tests. All the compounds showed low neurotoxicity when compared to the clinically used drugs. Compounds with substituted acetophenone (3h-3k) showed good activity in the rat oral MES screen. Seven compounds (3f, 3h-3j, 3l, 4b and 4c) exhibited anticonvulsant activity greater than sodium valproate. Compound 3j emerged as the most active compound as indicated by its protection in the MES and scSTY screens and with low neurotoxicity.
Aggarwal et al. [33] designed a series of 4-aryl substituted semicarbazones of levulinic acid (5) and synthesized to meet the structural requirements essential for anticonvulsant activity. All the compounds were evaluated for anticonvulsant activity. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and subcutaneous metrazole (ScMet) induced seizure methods and minimal motor impairment was determined by rotorod test. A majority of the compounds exhibited significant anticonvulsant activity after intraperitoneal administration. 4-(4′-fluoro phenyl) levulinic acid semicarbazone emerged as the most active molecule, showing broad spectrum of activity with low neurotoxicity.

Siddiqui et al. [34] synthesized a series of 1,3-benzothiazole-2-yl-semicarbazones (6) and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. Majority of the compounds were active in MES screens.

Yogeeswari et al. [35] synthesized a series of 4-ethoxyphenyl semicarbazones (7a), (7b) and evaluated against MES and ScPTZ induced seizure in mice. Among, the compound tested with substituent showed protection from seizure in both animal models.

Pandeya et al. [37] synthesized a series of p-nitrophenyl substituted semicarbazones (11a-c) and phenoxy/p-bromophenoxy acetyl hydrazones (12a-q) were synthesized and their anticonvulsant activity was screened against maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and subcutaneous strychnine (ScSty) tests. Compounds 11a-c with –NHCO– were found to be the most active in all these tests. These compounds were also active in the MES test after oral administration in rats.

Siddiqui et al. [36] synthesized several heteroaryl semicarbazone by the reaction of heteroaryl hydrazine carboxamide with aryl aldehyde or ketone. Compounds were tested for anticonvulsant activity utilising PTZ and MES tests at 30, 100 and 300 mg/kg dose levels and found that (1E)-1-arylalkane-1-one-N-[4-(2-oxo-2H-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazone (8, 9, and 10) exhibited significant anticonvulsant activity at 30 mg/kg dose level comparable to the standard drug taken as phenytoin.
Raja et al. [38] designed and synthesized several semicarbazones of acetophenone and p-chloroacetophenone Mannich bases to meet the pharmacophore requirements essential for anticonvulsant activity. Mannich bases of acetophenone and p-chloroacetophenone were prepared by reacting formaldehyde with various secondary amines and then condensed with several aryl semicarbazides to yield the corresponding semicarbazones. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES) and by subcutaneous metrazole (ScMet) and strychnine (ScSty) induced seizure methods, and their neurotoxic effects were determined using the rotorod test and found that 3-[3-chlorophenyl(β-dimethylaminopropiophenone)semicarbazone] (13) has excellent anticonvulsant activity in MES, ScSty, and ScMet tests.

Srivastava et al. [39] prepared several indole derivatives (14, 15) by the reaction between indole-3-carboxaldehyde and various p-substituted phenylsemicarbazides, in the presence of glacial acetic acid. Later Mannich bases of indole derivatives were prepared by using formaldehyde & various secondary amines. The anticonvulsant activity of the synthesized compounds was evaluated by intraperitoneal administration in three seizure model which include isoniazid, thiosemicarbazide & 4-aminopyridine induced seizure. Most of the compounds exhibit protection in all three seizure model in which N1-(2,4-dimethoxyphenyl)-N4-(propan-2-one) semicarbazone (16) found to be most active with no neurotoxicity. The compound was also found to elevate γ-amino butyric acid (GABA) level in the mid brain and medulla oblongata region.

Singh et al. [41] synthesized a series of 4-(4-substituted aryl) semicarbazones from substituted anilines and evaluated for their anticonvulsant activities. The anticonvulsant activities were established by the anticonvulsant drug development (ADD) programme NIH, USA and screened against electroshock seizure, subcutaneous metrazole and minimal neurotoxicity tests. Compound 17 was found equipotent to carbamazepine in both MES and ScPTZ tests. This study has highlighted the importance of distal alkyl chain which influences the anticonvulsant activity.

Alam et al. [42] synthesized a series of N-(4,6-substituted diphenylpyrimidin-2-yl) semicarbazones and tested for their anticonvulsant activity against the two seizure models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Most of the compounds displayed good anticonvulsant activity with lesser neurotoxicity. The most active compound of the series was N1-[4-(4-Chlorophenyl)-6-(3,4-dimethoxyphenyl)-pyrimidin-2-yl]-N4-(4-nitrobenzaldehyde) semicarbazone (18) devoid of any neurotoxicity.
Pandeya et al. [43] synthesized a series of substituted isatin semicarbazones (19, 20) and all compounds were evaluated for their anticonvulsant activity by maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and subcutaneous strychnine (ScSty) induced seizure models. A number of isatin semicarbazones exhibited significant protection after i.p. administration at the dose of 100 and 300 mg/kg. Some of them showed good anticonvulsant activity in MES test in rats after per oral administration at the dose of 30 mg/kg.

Rajak et al. [44] carried out synthesis of three novel series of semicarbazones containing 1,3,4-thiadiazole and quinazoline ring (21). The anticonvulsant activities of the synthesized compound were evaluated by intraperitoneal administration in seizure model which include MES and ScPTZ induced seizure. The majority of the compounds were found active in the biological screening.

Rajak et al. [45] synthesized a novel series of N1-[(1H-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl]-N4-[(4-substituted phenyl) (phenyl) methanone]-semicarbazones and evaluated for their anticonvulsant potential using maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) models. N1-[(1H-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl]-N4-[(4-hydroxyphenyl) (phenyl) methanone]-semicarbazone 22 come out as the most active compound, showing considerable activity in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0 h) and subcutaneous pentylenetetrazole model (at 300 mg/kg after 4.0 h) without any neurotoxicity (up to 300 mg/kg after 4.0 h).

Khan et al. [46] synthesized a series of 4-aryl substituted semicarbazones of some terpenes i.e., citral (acyclic terpene), camphor (bicyclic terpene) and menthone (monocyclic terpene) from substituted anilines, to meet the structural requirements essential for anticonvulsant activity. The synthesized semicarbazone derivatives were evaluated for anticonvulsant activity by Isoniazid (INH) induced convulsion model, Thiosemicarbazide (TSC) induced convulsion model and 4-aminopyridine (4-AMP) induced convulsion model. All the compounds showed anticonvulsant activity in one or more test models. Compounds (23, 24 and 25) were found to be most active against INH screen at a dose of 30 mg kg\(^{-1}\) showed prolonged duration of action for 4 hours. Compound 25 showed prolong activity at a dose of 30 mg kg\(^{-1}\) against TSC screen. Compound 24 was found to be most potent anticonvulsant that showed activity in all screens with no neurotoxicity.
Compounds showed significant anticonvulsant activity. The results revealed that protection was obtained in all the screens i.e., Maximal electroshock, (MES) subcutaneous pentylene tetrazole (scPTZ) and subcutaneous strychnine (scSTY) screens. Among all the compounds compound with \(	ext{R} = \text{H}, \text{R}' = \text{COCH}_3, X = \text{4-Cl}\); \(\text{R} = \text{H}, \text{R}' = \text{COCH}_3, X = \text{4-NO}_2\); and \(\text{R} = 5-\text{Br}, \text{R}' = \text{COCH}_3, X = \text{4-SO}_2\text{NH}_2\) emerged as broad-spectrum compounds as indicated by their protection in MES, scSTY and scPTZ screens.

Verma et al. [48] synthesized a series of menthone derivative and characterized by their spectral data and evaluated for anticonvulsant activity. Compounds showed significant anticonvulsant activity.

Amir et al. [50] synthesized several 3-chloro-4-florophenyl substituted semicarbazones. Some selected compounds have been evaluated for anticonvulsant activity by using maximal electroshock induced seizures (MES) test. \(\text{N}^1-(3\text{-chloro-4-florophenyl})-\text{N}^2-(4\text{-N,N-dimethylamino-benzaldehyde})\) semicarbazone (29) is found most active of the series without neurotoxicity.

Aggarwal et al. [51] synthesized a series of 4-aryl substituted semicarbazones of pyridyl carboxaldehyde and pyridyl methyl ketone. All the compounds were evaluated for anticonvulsant activity and neurotoxicity. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and subcutaneous metrazol (ScMet) induced seizure methods and minimal motor impairment was determined by rotorod test. Majority of compounds exhibited significant anticonvulsant activity after intraperitoneal administration. (Methyl-4-pyridyl) ketone-N\(\text{H}^2\)-(p-chloro phenyl) substituted semicarbazone (30) emerged as most active derivative showing activity at 100 mg/kg in both the test with prolonged duration of action.

Yogeeswari et al. [52] synthesized a series of substituted \(\text{N}-(3\text{-methylpyridin-2-yl})\) semicarbazones. All the compounds were evaluated for their anticonvulsant activity by maximal electroshock seizures (MES) test, subcutaneous pentylenetetrazole (scPTZ) screen, subcutaneous strychnine (scSTY) pattern test and subcutaneous picrotoxin (scPIC) seizure threshold test along with the behavioral, and neurotoxicity evaluation. A number of \(\text{N}^1-(3\text{-methylpyridin-2-yl})\) semicarbazone derivatives exhibited significant protection after intraperitoneal administration at the dose of 100 and 300 mg/kg. Compound \(\text{N}^1-(3\text{-methylpyridin-2-yl})-\text{N}^2-(\text{isatin})\) semicarbazone (32) emerged as the most active analogue of the series, being more effective in most of the test models than ethosuximide and sodium valporate.
Yogeeswari et al. [53] synthesized various N\(^2\)-(2,6-dimethylphenyl) semicarbazones. All of the compounds exhibited anticonvulsant activity in the maximal electroshock test when administered by both intraperitoneal and oral routes. Compound \(N\(^4\)-(2,6-dimethylphenyl)-N\(^5\)-(2-hydroxybenzaldehyde) semicarbazone (33) emerged as a prototype with wide spectrum anticonvulsant agent active in five models of seizure with no neurotoxicity and hepatotoxicity. Compound 33 increased the 4-aminobutyric acid (GABA) level by 118% and inhibited the GABA transaminase enzyme both in vitro and ex vivo.

![Diagram](image)

Conclusion:
The article has outlined the chemistry and anticonvulsant activity of the semicarbazones. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives. The high degree of protection against seizures can be positive signs for further investigation of semicarbazones as anticonvulsants. Semicarbazones are found to be a better target for the development of more and more anticonvulsant.

References:
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