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Synthesis, Mechanism of Action And Characterization of Semicarbazide

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Abstract:

3-Chloro-2-methylphenyl-substituted semicarbazones have shown potential in a variety of therapeutic areas, including anticonvulsant activity. A significant mechanism for the anticonvulsant activity of many compounds is the inhibition of voltage-gated sodium and calcium channels, which play a crucial role in neuronal excitability. Chloro-2-methylphenyl-substituted semicarbazones may possess the ability to block these ion channels, thereby stabilizing the neuronal membrane potential and preventing the excessive firing of neurons that leads to seizures. chloro-2-methylphenyl-substituted semicarbazones may exhibit anticonvulsant activity through modulation of the gamma-aminobutyric acid (GABA) system. GABA is the primary inhibitory neurotransmitter in the brain, and enhancing GABAergic activity can help control excessive neuronal firing that leads to seizures.

Keywords:

Aryl semicarbazones, 3-Chloro-2-methyl substituted phenyl semicarbazones, Anticonvulsants, CNS depressants.

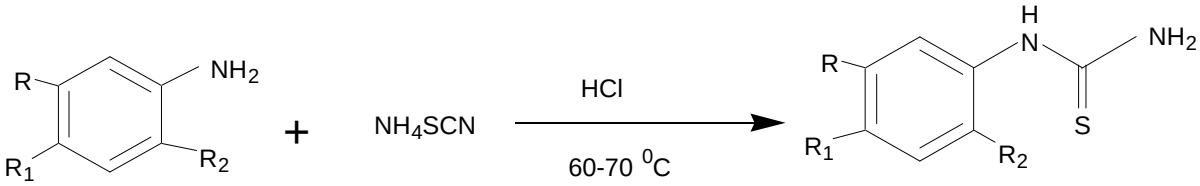
INTRODUCTION:

Epilepsy, one of the most frequent neurological disorders, is a major public health issue, affecting about 4% of individuals over their lifetime .About 20–30% of the patients have seizures that are resistant to the available medical therapies. This fact warrants the search for new anticonvulsant drugs(1).

In recent years, Aryl and heteroaryl semicarbazones and thiosemicarbazones have emerged as structurally novel anticonvulsants. Aryl semicarbazides have also been reported to display excellent anticonvulsant activity in mice and rats. The pharmacophoric elements were thought to be a lipophilic aryl ring and hydrogen bonding semicarbazone moiety. The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the van der Waal's bonding at the binding site and to increase potency have also been reported. Substitutions in the aryl ring by halogens have been found to increase potency in the MES screen and our recent results with 3-bromo substituted phenyl semicarbazones have given an impetus to the present investigation(3). In continuation to our work on aryl semicarbazones, the present work focuses on synthesis and anticonvulsant evaluation of 3-chloro-2-methylphenyl substituted semicarbazones, since substitution in the 2-position of the phenyl ring with electron-donating groups was generally beneficial to activity as reported elsewhere and the importance of the ortho-methyl group for anticonvulsant activity had been depicted in many studies including the recently marketed drug tiagabine(10).

SYNTHESIS OF SEMICARBAZIDE:

Step 1- Synthesis of phenyl thiourea:



1 R=H, R1 = Br, R2=H

2 R=H, R1 = CH3, R2=H

3 R=Cl, R1 = H, R2=Cl

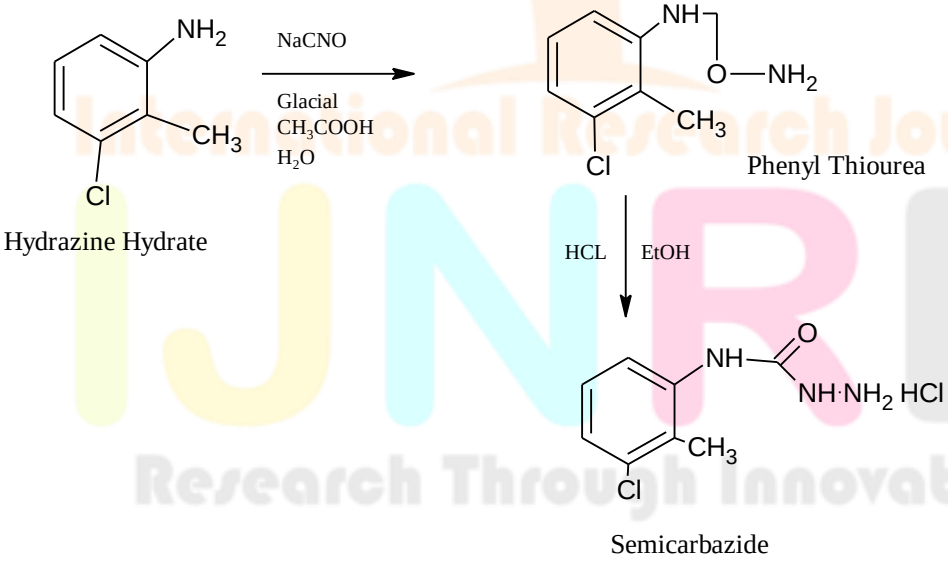
4 R=H, R1 = Cl, R2=H

Reaction no1. Synthesis of phenyl thiourea

Preparation of phenylthiourea:-

Synthesis of substituted phenylthiourea has been prepared from aniline.Take 0.1 mole of aniline add 9ml of HCl and 25 ml of water heat the solution for about 1 hr at about 60-70^{0}C in a round bottom flask. Cool the mixture for about 1 hr and add slowly 0.1 mole ammonium thiocyanate to the solution. Now reflux the solution for about 4hrs. Add 20ml of water to the solution by continuous stirring the crystals form powered solution. Filter the solution and dry it. Finally a powered phenylthiourea is formed(4).

Step 2- Synthesis of Semicarbazide:



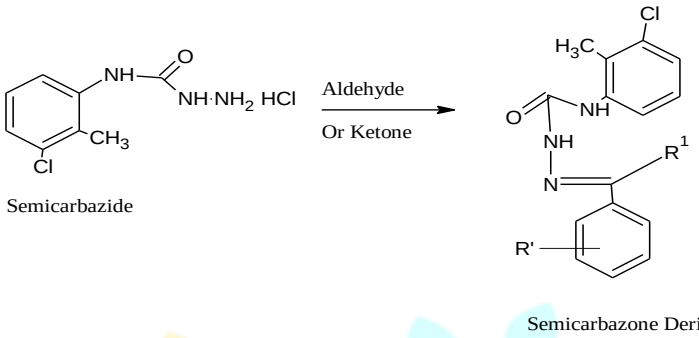
Reaction no2. Synthesis of semicarbazide

Preparation of semicarbazide:-

Equimolar quantities (0.05 mol) of (9.2 g) and hydrazine hydrate (2.5 ml) in ethanol were refluxed for 24 h with stirring. The two-third volume of alcohol was distilled by vacuum distillation unit and then poured into ice. The resultant precipitate was filtered, washed with water and dried. The solid was recrystallized from 50 ml of 90%

alcohol to which 25 ml of concentrated hydrochloric acid was added. The precipitate of semicarbazide, hydrochloride, was filtered by vacuum and dried(1).

Step 3- Synthesis of Semicarbazone Deriative:-



Semicarbazide

Semicarbazone Derivative

Reaction no3. Synthesis of Semicarbazone derivative

Preparation of semicarbazone derivative-

A solution of semicarbazide (0.005 mol, 1.175 g) in 25 ml of water was added sodium acetate (0.005 mol, 0.41 g) in 2 ml water. About 25 ml of ethanol was added to clear turbidity. This solution mixture was added to an equimolar quantity of the appropriate aldehyde or ketone in alcohol. Stirring was done if needed. Immediate precipitation occurred and the solids were filtered, dried and recrystallized from hot ethanol(5).

CHARACTERIZATION OF SEMICARBAZIDE:

Aspect	Details
Structure	Hydrazine and amide groups; forms semicarbazones with carbonyl compounds
Mechanism	Enzyme inhibition (DAO, MAO), metal chelation
Physical/Chemical	Crystalline, water-soluble, reactive with aldehydes/ketones
Pharmacokinetics	Oral absorption, renal excretion, may cross BBB
Drug Interactions	Avoid with MAOIs, SSRIs, histamine-containing foods
Clinical Use	Antimicrobial, Anticonvulsant, Anticancer, Analytical chemistry
Harmfulness	Genotoxic, neurotoxic, teratogenic; possible carcinogen in long-term exposure

RESULT AND DISCUSSION:

The development of semicarbazides was driven by their ability to readily form semicarbazones, compounds that possess potent biological activities. Over time, various synthetic strategies—ranging from classical condensation reactions to green and microwave-assisted approaches—have been employed to generate structurally diverse derivatives. The hydrazine and amide functional groups, along with modifications to the aromatic or heterocyclic core, have been shown to critically influence biological activity, as highlighted in structure-activity relationship (SAR) studies. Semicarbazide derivatives have demonstrated broad therapeutic applications, particularly in antibacterial, antitubercular, anticonvulsant, anticancer, and antiviral domains. Their ability to interfere with key enzymatic pathways, such as metal-dependent enzymes or folate metabolism, underpins their pharmacological action. Some thiosemicarbazone analogs, for instance, inhibit ribonucleotide reductase and disrupt DNA synthesis in cancer cells, while others act as metal chelators in infectious diseases. Mechanistically, semicarbazide compounds can act as enzyme inhibitors, chelating agents, or prodrugs, depending on their structural context. Their therapeutic effects are often attributed to their interaction with biological macromolecules, inhibition of oxidative processes, or disruption of metabolic pathways essential to bacterial or cancer cell survival. In summary, semicarbazide derivatives continue to hold promise in modern medicinal chemistry due to their structural versatility, ease of synthesis, and multi-targeted mechanisms of action. Their historical development and expanding applications

underscore the importance of functional group manipulation and rational design in discovering new drugs. Like sulfanilamide, semicarbazide-based agents stand as a testament to the potential of synthetic chemistry in addressing complex biological challenges, reinforcing their significance in the ongoing pursuit of novel therapeutic agents.

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