

Prospective of thiosemicarbazones as a promising anticonvulsant: A review

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ABSTRACT

Unprovoked seizure or epilepsy has been in existence ever since the advent of the human civilization. However it was perceived as the divine wrath or as a demonic possession. Hippocrates made a pivotal contribution in establishing epilepsy as a brain disorder. Presently available antiepileptic drugs provide only symptomatic relief but are devoid of the ability to cure epileptogenesis, and the associated negative properties limit their use. The thiosemicarbazone nucleus is found to be a promising anticonvulsant. In the recent years a lot of synthetic drugs have been synthesized and found to have prominent anticonvulsant activity. Several compounds including semicarbazones and thiosemicarbazones have been synthesized and evaluated for anticonvulsant activity. This review covers the most active thiosemicarbazone derivatives with considerable anticonvulsant activity which may ignite the future inquisitive minds to undertake molecular modifications for the synthesis of safe and patient compliant antiepileptic drugs.

Keywords: Thiosemicarbazone, Anticonvulsant activity, Maximal Electroshock and Subcutaneous Pentylene tetrazole Seizures.

1. INTRODUCTION

Unprovoked recurrent seizures or epilepsy has been in existence ever since the advent of the human civilization. However it was perceived as the divine wrath or as a demonic possession. Hippocrates (430 BC) made a pivotal contribution in establishing epilepsy as a brain disorder. [1] Epilepsy a common disorder of central nervous system [2] impacts a population of more than 1% throughout the world. [3] World Development Report (1993), projects that epilepsy constitutes 9.3% of the disabilities related to all the mental health problems in the world. [4] Epilepsy accounted for 0.5% of the global burden of disease and 7,307,975 disability adjusted life years (DALYs) in 2005. [5]

As per an estimate there are 55,00,000 epileptics in India, 20,00,000 in USA and 3,00,000 in UK. [6] More than 90% of the epileptic patients are natives of the developing nations. While there are many drugs available for treatment around 30% of the epileptics do not have marked improvement in their condition even with the choicest medications. [7]

Antiepileptic drugs are the first line of treatment employed to allay the symptoms and triggers of epilepsy. They are being manufactured

and increased in exponential terms. The therapeutic regimen has long term effects in the treatment, psycho-social status, quality of life of a patient and requires in-depth consideration of all these factors. [8] Choice of drug depends upon the epileptic syndrome, symptoms, patient history, background, compliance and co-morbidities. [9]

The modern antiepileptic drug discovery can be traced back to the use of bromide (1857), thereafter the researches and the emphasis on drug discovery has led to the flooding of several effective drugs. Many drugs have been approved by regulatory agencies including formulations of Valproates, Carbamazepines, Acetazolamides, Phenytoins, Phenobarbitals, Ethosuximides, Felbamates, Gabapentins, Clonazepam, Lamotrigines, Oxcarbazepines, Pregabalin, Tiagabine, Vigabatrin to name a few. [10]

The antiepileptic drugs at present have a limited scope providing only symptomatic relief yet they fail to address the root cause of epileptogenesis, further more their safety profile and the associated adverse effects narrows the range of usages for the desired benefits and poses severe problems in the management of the disorder. [11]

Poly therapy is required in clinical management of the disorder because of the limitations and insufficiency of the available single antiepileptic drugs. [12] The available antiepileptic drugs possess several side effects which may be acute or chronic in nature. [13] The current scenario, the associated trauma and overall impact on the patients prioritises the requirement of antiepileptic drug discovery. Several compounds are down the pipeline for their role in the design of novel anticonvulsant agents. Semicarbazones, thiosemicarbazones have been demonstrated for their promising anticonvulsant properties by the works of Dimmock and Pandeya. [41-44]

Thiosemicarbazone have been evaluated for their prospective biological properties for more than a century spanning to the early 20th century. The role of thiosemicarbazone against mycobacterium included tuberculosis and leprosy were published in the mid of the last century around fifties. [14, 15]

Sixties saw the discovery of their antiviral properties as a result of the enormous researches on thiosemicarbazones. Methisazone was launched into the market as an agent to treat smallpox along with Marboran. [16] Recently thiosemicarbazones have also been promoted as anticancer drugs and the studies are under clinical trials. [17,18] Thiosemicarbazones are under the scanner for the possible role as an effective therapy in cancer, microbial, protozoal and viral infections. The mechanism of action that is projected involves the interaction of thiosemicarbazones with metal ions. [19, 20, 21]

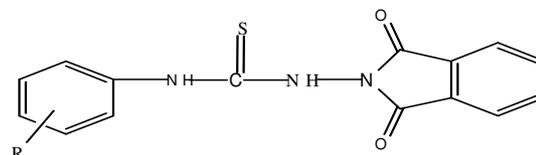
The anticancer activity can be attributed to the inhibition of ribonucleotide reductase, [22] production of reactive oxygen species, [23] inhibition of topoisomerase II, [24] disruption of mitochondria, [25] inhibition of multidrug resistance protein. [26, 27]

The anti-leukemic effect was reported in 1956. [28] Sartorelli *et al.* were able to propose that thiosemicarbazones repressed the incorporation of 3H thymidine into the DNA and inhibited the ribonucleotide reductase. [22, 29, 30] It has also been observed in several studies that the metal ion complexes in particular those of Iron and copper are considerably more active. [31]

Thiosemicarbazone, the versatile bioactive moiety has been employed for diverse therapeutic roles. The current review focuses on therapeutic journey, evolution and development of thiosemicarbazones as a promising candidate for its anticonvulsant potential.

1.1. Anticonvulsant activity of thiosemicarbazones

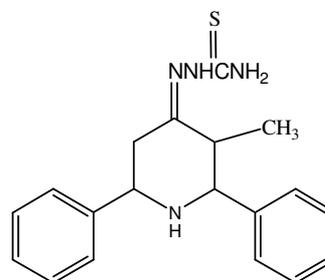
*N*⁴-(4-methyl phthalimido) substituted phenyl (thio) semicarbazide derivatives were synthesised and evaluated for their anticonvulsant activity by Bhushan *et al.* (2011) [32] which revealed four compounds (**1**). The compounds possessed significant anticonvulsant activity which was comparable with that of Phenytoin.



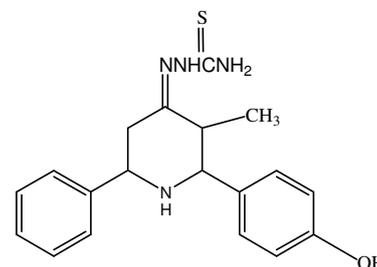
(1)

R=2-OCH₃, 4-CH₃, 4-OCH₃, 4-Cl

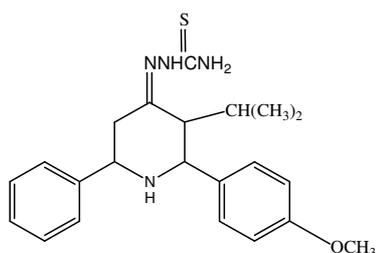
Rastogi *et al.* (2010) [33] using microwave irradiation techniques synthesized the thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones and evaluated them for their anticonvulsant potential by maximal electroshock (MES) method in rats. Three derivatives, 2-[4-(dimethylamino)phenyl]-3-methyl-6-phenyl-piperidin-4thiosemicarbazone (**2**), 2-(4-hydroxyphenyl)-3-methyl-6-phenylpiperidin-4thiosemicarbazone (**3**) and 3-isopropyl-2-(4-methoxyphenyl)-6-phenylpiperidin-4thiosemicarbazone (**4**) showed maximum activity.



(2)

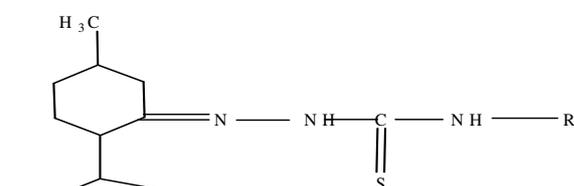


(3)



(4)

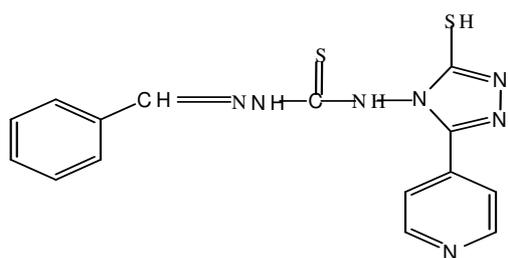
Verma *et al.* (2009)^[34] synthesised the substituted menthone semicarbazone and thiosemicarbazone derivatives and screened them for the possible anticonvulsant effects. Compound (5) exhibited good anticonvulsant activity and least neurotoxicity in MES test at 100 mg/kg body mass.



(5)

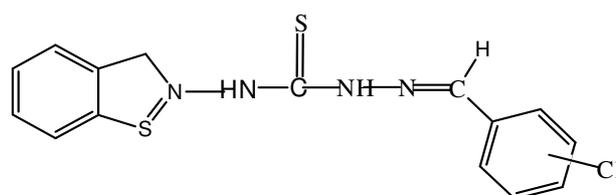
R = p-Br-C₆H₅; p-F-C₆H₅; p-NO₂-C₆H₅; C₅H₄N

Kshirsagar *et al.* (2009)^[35] using microwave irradiation techniques synthesized thiosemicarbazones derivatives and screened them for their biological properties including anticonvulsant activity. Several aryl derivatives of semicarbazones and thiosemicarbazone evolved as novel anticonvulsant agents. Thiosemicarbazone derivatives of 5-mercapto-3-(3'-pyridyl)-4H-1,2,4-triazole (6) showed good antifungal and anticonvulsant activity.



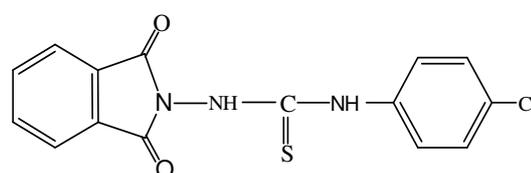
(6)

6-substituted benzothiazolyl-2-thiosemicarbazones were synthesized by Yogeewari *et al.* (2005)^[36] and were examined for their anticonvulsant activity and neurotoxicity. 6-methyl benzothiazolyl-2-thiosemicarbazones and 6-nitro benzothiazolyl thiosemicarbazone derivative (7) showed promising results with lesser or no neurotoxicity when scaled up against phenytoin.



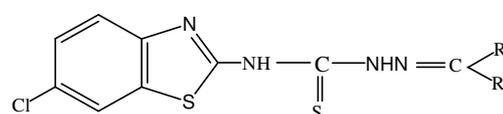
(7)

Yogeewari *et al.* (2003)^[37] synthesized N⁴-phthalimido phenyl (thio) semicarbazides and examined them for their anticonvulsant potential and the associated neurotoxicity. Phthalimido phenyl (thio) semicarbazides presented a diverse degree of anticonvulsant potential. Compound (8) showed promising activity when scaled up with that of phenytoin with none neuronal toxicities up to a dose of 300 mg/kg.



(8)

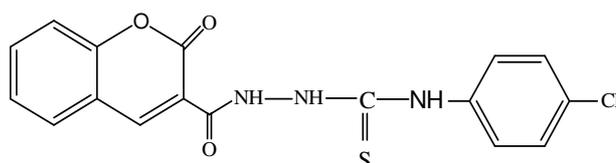
6-chlorobenzothiazolyl-2-thiosemicarbazones were synthesized and evaluated for the associated neurotoxicity by Yogeewari *et al.* (2002)^[38]. ED₅₀ of 17.86 and 6.07 mg/kg in mice i.p. and rat p.o. respectively was observed for Compound (9) 4-(6-chlorobenzothiazol-2-yl)-1-(3-isatinimino) thiosemicarbazone.



CRR' = 3-Isatinyl

(9)

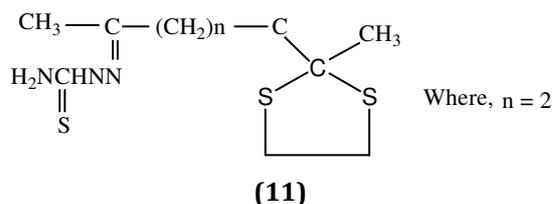
Bhat *et al.* (2002)^[39] synthesized novel thioureido derivatives of sulfonamides and thiosemicarbazido derivatives of coumarin and evaluated them for their anticonvulsant and analgesic potential. Compound 1- [(chromene-2-oxo) carbonyl] -4- (4'- chlorophenyl) -3-thiosemicarbazone (10) showed considerable anticonvulsant activity.



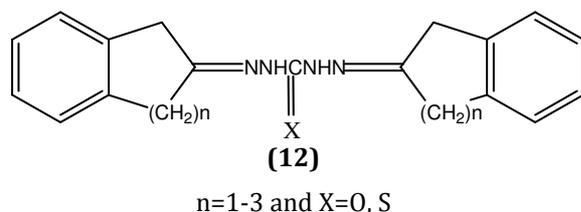
(10)

Synthesis and screening for anticonvulsant activity of some novel semicarbazones and thiosemicarbazone was given by Taroua *et al.* (1996)^[40]. Compound (11) 2-methyl-2-acetyl thiosemicarbazonyl-1,3-

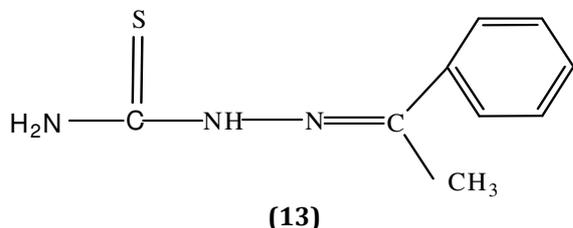
dithiolane displayed significant anticonvulsant activity, with complete safeguard against lethality associated with toxic seizures.



Dimmock *et al.* (1995).^[41] examined aryl alicyclic ketones of semicarbazones, thiosemicarbazones and bis-carbohydrazones for their possible biological activities. When administered intra-peritoneally anticonvulsant potential was exhibited by the compounds **(12)** in both maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screening as compared to the presence of selective activity in the MES screening, on oral administration to rats.

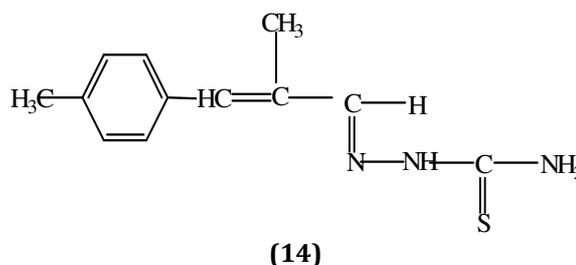


Dimmock *et al.* (1991)^[42] examined some aryl alkyl ketones of thiosemicarbazones for their anticonvulsant properties. This report describes the systematic chemical modification of thiosemicarbazone acetophenone and the activities of these analogues when administered via intra-peritoneal route using maximal electroshock seizure (MES), subcutaneous maximal pentylenetetrazole seizure (scPTZ) and neurotoxicity screening protocols in mice. Many of the tested compounds **(13)** were found active. When administered orally the representative compounds exhibited protection against electroshock seizure only at a dose of 50 mg/kg.

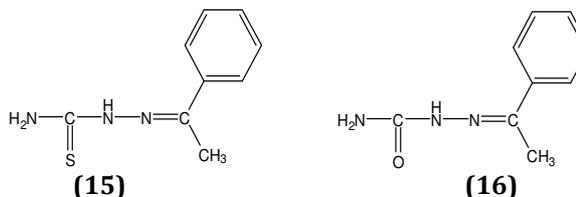


Dimmock *et al.* (1990)^[43] examined the thiosemicarbazone derivatives of arylidene ketones for their anticonvulsant properties. Crystallographic studies of 4-(4-methylphenyl)-3-buten-2-one thiosemicarbazone reveal that the compound possesses *E* configuration with respect to both olefinic and carbimino double bonds. Many compounds exhibited activity in the

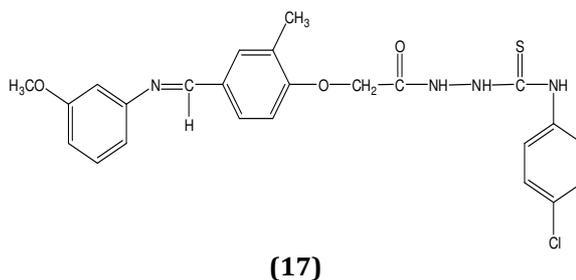
electroshock protocols and/or scMET tests and of particular interest was acetophenone thiosemicarbazone **(14)** which had good activity when administered by the intraperitoneal and oral routes. High resolution ¹H NMR spectroscopy of selected compounds in dimethylsulphoxide revealed that in most cases isomeric equilibrium was pertaining to the carbimino group. The isomeric ratio was dependent on the size of the R group attached to the carbimino function.



Dimmock *et al.*, (1986)^[44] investigated that a number of thiosemicarbazones of arylidene and alkyl ketones and following compounds **(15, 16)** exhibited anticonvulsant activity.



Synthesis and evaluation for anticonvulsant and MAO inhibitory activities of anilino-[3-methoxy-4-(4-arylthiosemicarbazideo-carboxyleneoxy)] benzylidene was done by Dwivedi *et al.* (1974)^[45]. The following compound **(17)** with *p*-chlorophenyl group showed maximum activity in the scMET test



2. DISCUSSION

The unpredictable nature of epilepsy is a psycho-social handicap. The increased morbidity can be attributed to psycho-social variables including lack of support, stigma, social withdrawal and isolation and under-employment and unemployment and lowered rates of academic achievement.^[46]

Though there have been considerable advancements in the knowledge domain and researches in the field of anticonvulsants, yet none of the available drugs promises effective therapy against epilepsy without associated adverse effects of the drugs. The available information and the important demerits of the existing drugs along with advances in the field of drug discovery paves a way for the development to newer Antiepileptic drugs.^[47, 48]

A wide array of compounds are available against a broad spectrum of the epileptic seizures. Several moieties including benzodiazepines, pyrrolidinone, piperidines, isoxazoles, triazines, have been studied and have shown promising anticonvulsant activity.^[49]

Thiosemicarbazones are formed by the condensation of thiosemicarbazide with corresponding aldehydes or ketones where it behaves as bidentate ligands owing to its property to bind with metals via sulphur and nitrogen atoms, however in certain cases they behave as unidentate ligands binding via sulphur atom only. Thiosemicarbazone exhibit a wide array of pharmacological activity against microbes, tumors, cancer, tuberculosis, and viral infections. It has also been proposed that activity may be attributed to the sodium channel blocking potential.^[50]

It is postulated that the thiosemicarbazones possess specific binding sites which determine the type and magnitude of the anticonvulsant activity.^[51]

Thiosemicarbazone is a versatile moiety which can be utilised as a potential lead. We draw a conclusion from the available literature and the interest of various researchers that the derivatives of thiosemicarbazone possess a wide array of pharmacological activities including some potent antiepileptic activity.

Acknowledgements

The authors would like to extend their gratitude to the Department of Pharmaceutical Sciences, Kumaun University Campus, Bhimtal, India for providing access to its resourceful library services to collect and study the various research articles.

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