

Review Article

Anticonvulsant potential of Hydrazone derivatives: A Review

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Abstract: The search for antiepileptic compounds with more selective activity and lower toxicity remains an area of intensive investigation in medicinal chemistry. Hydrazone derivatives are significant because of their versatile biological actions. Hydrazone derivatives play an important role in development of various research activities such as anticonvulsant, vasodilator, antimycobacterial, antiviral, antitumoral, antimalarial, analgesic, antiinflammatory, antiplatelet, antidepressant, antimicrobial and antischistosomiasis activities. Numerous biochemical and pharmacological studies have confirmed that these molecules are effective as anticonvulsants. This review describes the Hydrazone derivatives possessing anticonvulsant activities.

Keywords: Anticonvulsant, Hydrazone, Seizure

INTRODUCTION

Epilepsy is a neurological condition which is characterised by unprovoked seizures resulting from abnormal discharge of cerebral neurons and affecting 0.5–1% of the population. There is continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with existing antiepileptic drugs [1,2]. Many options are available, from different chemical classes such as hydantoin, barbiturates, benzodiazepines, gamma-aminobutyric acid (GABA) analogs, dibenzepines and carbamates. All these medications suffer from having lots of side effects. The current therapy of epilepsy is associated with a number of side effects including neurotoxicity, sedation and hypnosis so newer improved molecules are highly desirable [3]. Hydrazones possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. Various researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations have been guiding for the advance of new hydrazones that possess varied biological activities. Hydrazone derivatives play an important role in development of various research activities such as

anticonvulsant, vasodilator, antimycobacterial, antiviral, antitumoral, antimalarial, analgesic, antiinflammatory, antiplatelet, antidepressant, antimicrobial and antischistosomiasis activities. [4,5]. The present review describes the Hydrazone derivatives possessing anticonvulsant activities.

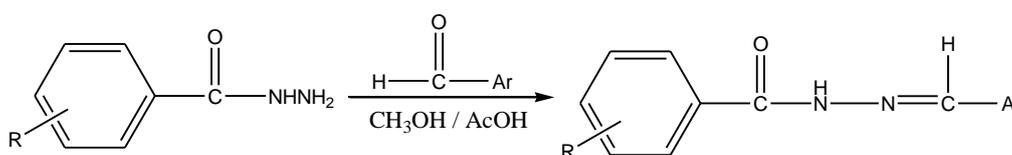
SYNTHESIS

Hydrazones are synthesized by heating the appropriate substituted hydrazines/hydrazides with aldehydes and ketones in solvents like ethanol, methanol, glacial acetic acid, butanol, tetrahydrofuran [5]. Synthesis of some hydrazones has been reported by Rajput et al. 2009 showed in Scheme 1 [6].

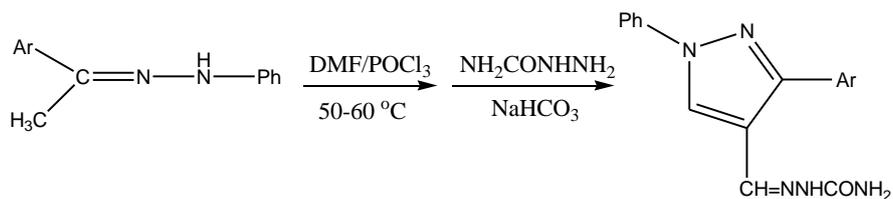
REACTIONS

Hydrazones are very effective organic compounds, but they are also used as intermediates to prepare some biological active compounds by using the active hydrogen component of CONHN=CH-azometine group [5, 7].

Pundeer et al., synthesized some pyrazole derivatives form hydrazones (Scheme 1) [8].



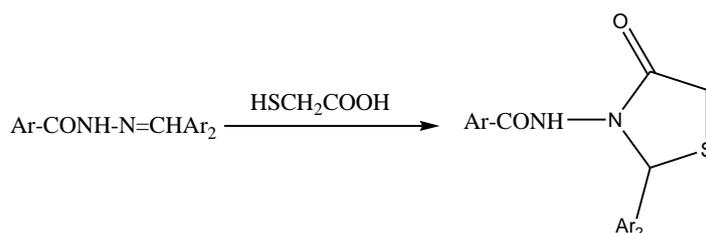
Scheme 1 Synthesis of Hydrazones



Scheme 1

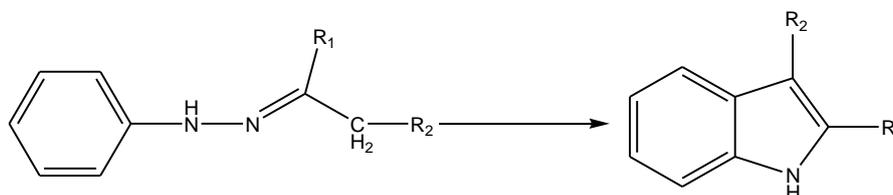
Some new biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides have

been synthesized from hydrazones and evaluated for anti-inflammatory activity shown in Scheme 2[9].



Scheme 2

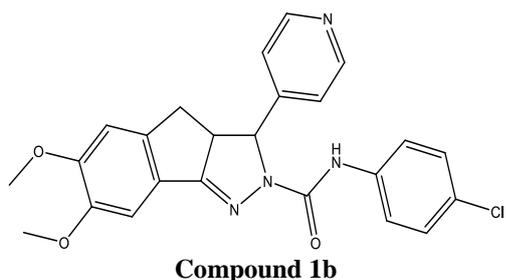
Indole derivatives were synthesized from hydrazone derivative according to the Fischer reaction (Scheme 3) [10].



Scheme 3

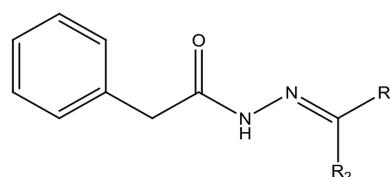
ANTICONSULSANT ACTIVITY

3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide (**1a-c**) were synthesized and screened for anticonvulsant activity and neuroprotection assay. The compound **1b** showed protection against maximal electroshock induced seizure (MES) and subcutaneous metrazole (scMET) induced seizure at 300 mg/kg dose at 0.5 and 4 h, and 100% (4/4, 0.25 h), 75% (3/4, 1.0 h) and 50% (2/4, 0.5 h) protection in 6 Hz psychomotor seizure test devoid of any neurotoxicity or toxicity[11].



Compound 1b

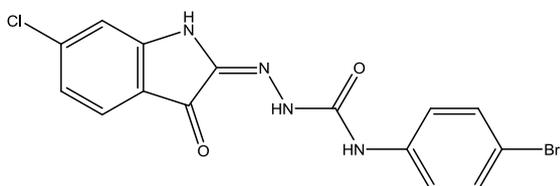
Schiff's bases of 2-phenylacetohydrazide (**2a-2j**) were synthesized by reaction of 2-phenylacetohydrazide with appropriate benzaldehyde/Aromatic ketone and screened for *in vivo* anticonvulsant activity by maximal electric shock method using phenytoin sodium as reference drug. The results showed that substitution with electron withdrawing moiety favors significant reduction in the seizures [12].



Compound 2a-2j

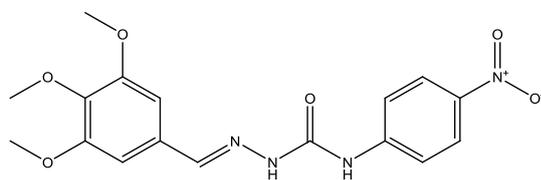
A series of substituted isatin semicarbazones and related bioisosteric hydrazones were designed and synthesized to meet the structural requirements essential for anticonvulsant properties. All compounds were evaluated for their anticonvulsant activity by maximal

electroshock (MES), subcutaneous metrazol (ScMet) and subcutaneous strychnine (ScSty) induced seizure methods and their neurotoxic effects were determined by rotorod test. Compound 6-chloroisatin-3-(4-bromophenyl)-semicarbazone (**3a**) has emerged as the most active analogue of the series showing good activity in all the three tests and was more active than phenytoin and valproic acid[13].

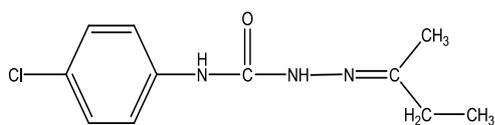


Compound 3a

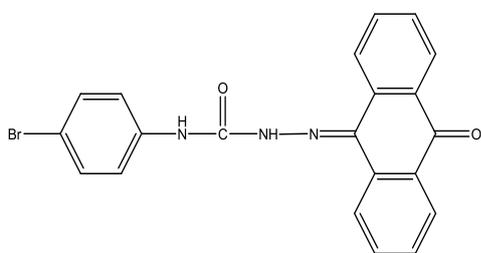
A series of 4-(4-substituted aryl) semicarbazones were synthesized from substituted anilines and subsequently evaluated for their anticonvulsant activities. Compounds were screened for anticonvulsant activity by maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and Minimal neurotoxicity (TOX) test in mice. Minimal neurotoxicity (TOX) was evaluated in rats by examining them for behavioral toxicity using the positional sense test and a gait and stance test. Compounds **4**, **5** and **6** were active in MES test (100 mg/kg). Compound **5** was reported no neurotoxicity at a dose of 30 mg/kg [14].



Compound 4



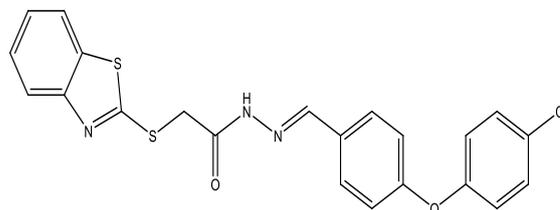
Compound 5



Compound 6

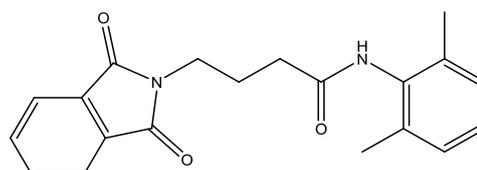
A series of 2-[2-(substituted)hydrazinyl]-1,3-benzothiazole and 2-(1,3-benzothiazol-2-ylsulfanyl)-N'-(substituted)acetohydrazide were synthesized and evaluated for anticonvulsant activity and neurotoxicity. Anticonvulsant activity of the titled compounds was

assessed using the 6 Hz psychomotor seizure test. The most active compound of the series was 2-(1,3-benzothiazol-2-ylsulfanyl)-N'-[4-(4-bromophenoxy)benzylidene] acetohydrazide **7**, which showed 75% protection (3/4, 1.0 h) and 50% protection (2/4, 0.5 h) at a dose of 100 mg/kg in mice [15].

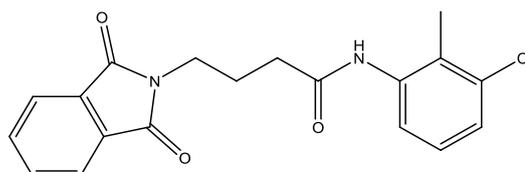


Compound 7

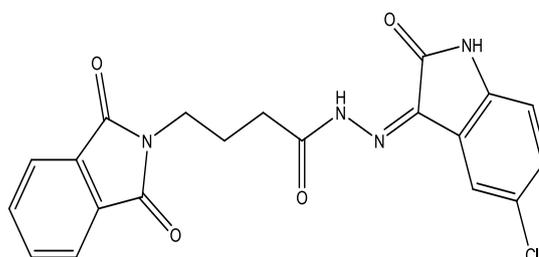
4-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain. Two series of pharmacophoric hybrids of phthalimide GABA anilides/hydrazones synthesized and evaluated for their anticonvulsant and neurotoxic properties. Anticonvulsant screening was performed using intraperitoneal (i.p.) maximal electroshock-induced seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and intraperitoneal picrotoxin (ipPIC)-induced seizure threshold tests. Compounds **8**, **9** and **10** exhibited protection in all the three animal models of seizure, viz. scPTZ, scSTY, and ipPIC [16].



Compound 8



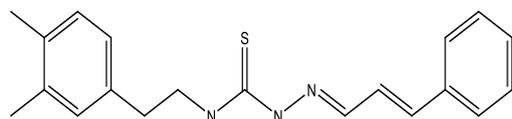
Compound 9



Compound 10

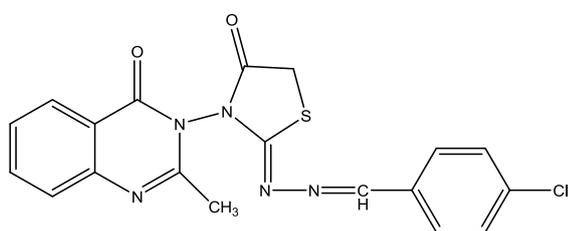
Several 3-(3,4-dimethoxyphenylethyl)-4-oxothiazolin-2-yl substituted hydrazones were synthesized and evaluated for their anticonvulsant activity. Anticonvulsant activity of synthesized

compounds was determined against pentylenetetrazol-induced seizures in mice. Maximum protection was observed with compound **11** [17].



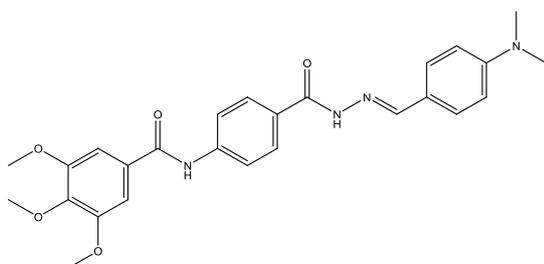
Compound 11

Methyl-4(3*H*)-quinazolinon-3-yl)-1-substituted-3-thiosmicarbazones and 3-(2-methyl-4(3*H*)-quinazolinon-3-yl)-4-oxo-thiazolin-2-yl-substituted hydrazones were synthesized and evaluated for anticonvulsant activity. Compound **12a** was found to be the most active compound [18].



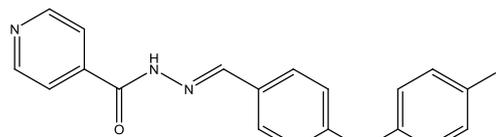
Compound 12a

A series of *N*-[*p*-(substituted benzamido)benzoyl]hydrazones was synthesized by refluxing *N*-[*p*-(substituted benzamido)benzoyl]hydrazines with various araldehyde in ethanol in the presence of a few drops of glacial acetic acid. The maximum protection was exhibited by the compound **13** having 3,4,5-trimethoxy and *p*-*N,N*-dimethylphenyl moiety [19].



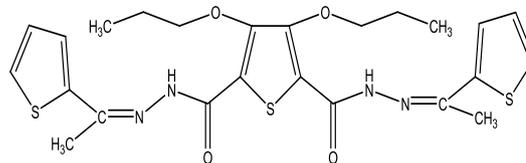
Compound 13

A series of *N*'-[substituted] pyridine-4-carbohydrazides were designed and synthesized taking into consideration the structural requirement of pharmacophore and evaluated for anticonvulsant activity and neurotoxicity. Anticonvulsant activity of the titled compounds was established after intraperitoneal administration in three seizure models, which include MES, scMET and 6 Hz models. The most active compound of the series was *N*'-[4-(4-fluorophenoxy)benzylidene]pyridine-4-carbohydrazide **14**, which showed a MES ED₅₀ value of 128.3 mg/kg and 6 Hz ED₅₀ value of 53.3 mg/kg in mice [4].



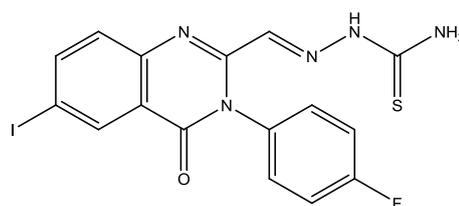
Compound 14

A series of new 3,4-dipropoxy-*N*²,*N*⁵-bis(substituted)thiophene-2,5-dicarbohydrazides was synthesized from ethyl thiodiglycolate and diethyl oxalate. The anticonvulsant activity of all the title compounds was investigated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scMET) models and their neurotoxicity was also evaluated. Compound 3,4-dipropoxy-*N*²,*N*⁵-bis[1-(2-thienyl)ethylidene]thiophene-2,5-dicarbohydrazide (**15**) has emerged as a lead in this series with less neurotoxicity [20].

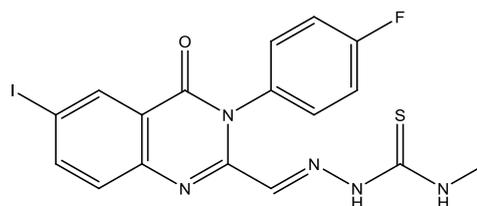


Compound 15

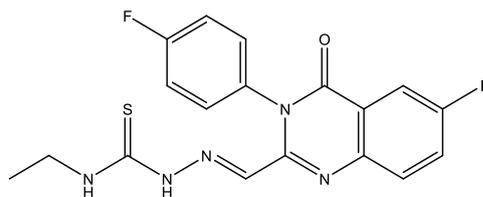
Novel 3-aryl-4(3*H*)-quinazolinone-2-carboxaldehydes, their corresponding Schiff's base and thio-semicarbazone derivatives were synthesized from the starting 5-iodoanthranilic acid. Copper (II), zinc (II) complexes of some thiosemicarbazone derivatives were also synthesized and characterized. Anticonvulsant activity of synthesized compounds was screened by pentylenetetrazole induced seizure method. Compounds **16b**, **16d** and **16f** showed some protection for the animals from developing seizure in comparison with control group [21].



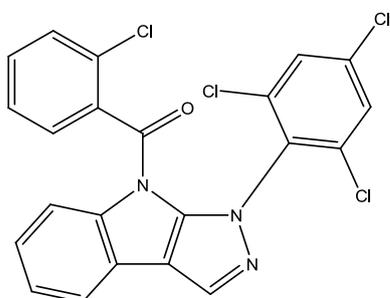
Compound 16b



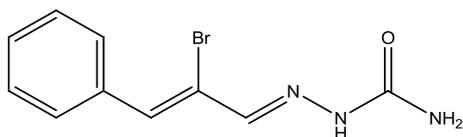
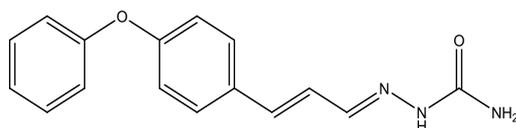
Compound 16d

**Compound 16f**

A series of 1,8-dihydro-1-aryl-8-alkyl pyrazolo(3,4-b)indoles has been synthesized and tested for their anticonvulsant activities. Formation of the pyrazoloindole derivatives was achieved by treating arylhydrazones of N-alkyl indole-3-carboxaldehydes with ten times their mass of polyphosphoric acid as a condensing agent. The newly synthesized compounds were evaluated for their anticonvulsant activity compared diazepam as positive controls. Compound 17 was found to be the most active compound among all the synthesized compounds [22].

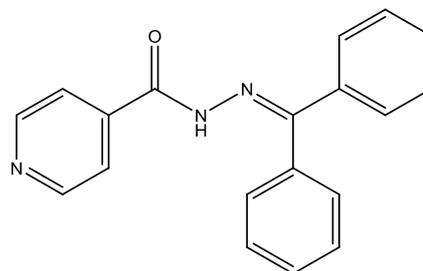
**Compound 17**

A number of aryl, arylidene and aryloxyaryl xemicarbalones were evaluated as candidate anticonvulsants. The semicarbazones were prepared by reaction of the appropriate aldehydes or ketones with semicarbazide. Compounds **18b** and **18c** were considered to be promising anticonvulsant compound in MES and PTZ test [23].

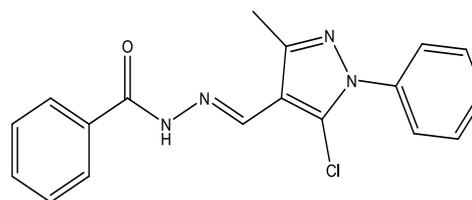
**Compound 18b****Compound 18c**

A series of (*E*)-*N*'-(substituted-benzylidene)isonicotinohydrazide derivatives were synthesized by coupling it with different substituted aldehydes, acetophenone, and benzophenones in presence of absolute ethanol along with catalytic amount of glacial acetic acid. Anticonvulsant evaluations of all the synthesized compounds were

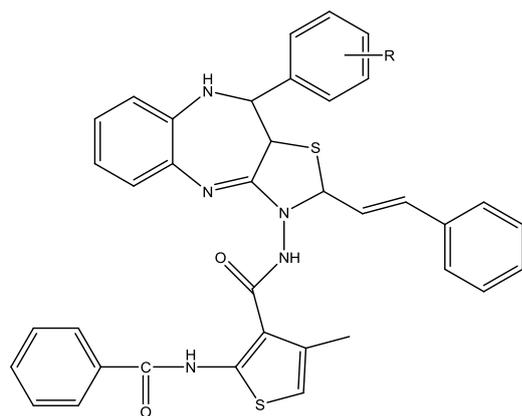
made using various seizures models like maximal electroshock-induced seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Among all synthesized derivatives, analogue **19** was found to exhibit protection in MES and scPTZ seizure models [24].

**Compound 19**

A series of *N*'-[(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene] 2/4-substituted hydrazides were synthesized using appropriate synthetic route. The anticonvulsant activity of some of the synthesized compounds was evaluated against maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazol (scPTZ) induced seizure models in mice. Among the compounds, the aryl derivative **20a** exhibited activity against both the MES and scPTZ models [25].

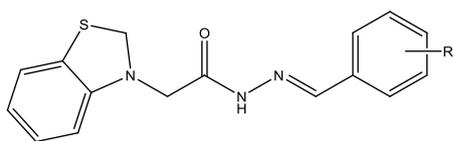
**Compound 20**

A series of 9*H*, 10*H*, 3-[*N*-4 methyl -2-benzamido thiophen 3-yl carbonyl amino [2-(20-phenyl 10-ethylenyl)] 10-(aryl) thiazolidino [4, 5-*b*] 1, 5 benzodiazepine [21a–22h] were designed and synthesized to meet the structural requirements essential for anticonvulsant activity. Anticonvulsant activity was determined after intra-peritoneal administration to mice by supramaximal electroshock seizures model and Isoniazide hydrazone induced seizures model. Among the synthesized compounds, two compounds (21a and 21e) exhibited significant anticonvulsant activity after intra-peritoneal administration [26].



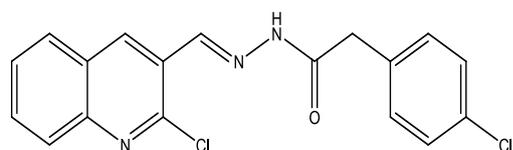
Compound R
21 a *o*-OH
21 e *p*-OCH₃

Fifteen new (2:4-substituted)benzaldehyde (2-oxobenzothiazolin-3-yl)acetohydrazones were synthesized and their anticonvulsant activity was tested by a pentylenetetrazole induced seizure test. Compounds **22e** and **22h** were found to be the most promising among the others [27].



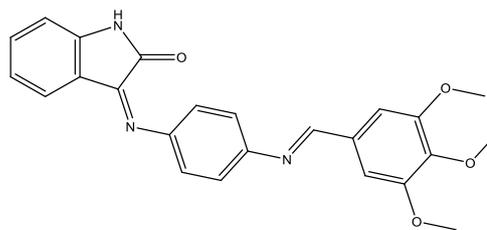
Compound R
22 e *p*-CH₃
22 h *o*-OH

Synthesis and *in vivo* anticonvulsant activity of some new 2-chloroquinoliny-hydrazones (**23a-23n**). The evaluation of anticonvulsant activity was carried out in mice by two models of seizures, viz. Maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ). Compound **23k** showed anti-MES activity at a dose of 300 mg/kg (0.5 h) [28].



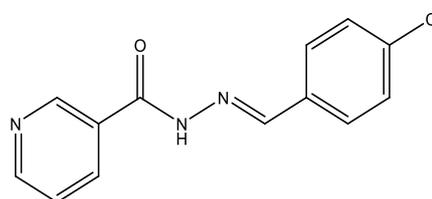
Compound 23k

A series of novel Schiff bases of isatin (**24a-24i**) were synthesized by condensation of imesatin with different aromatic aldehydes. The imesatins were synthesized by reaction of isatin with *p*-phenylenediamine. All the synthesized compounds screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet). Among the compounds synthesized 3-(4-(3, 4, 5-trimethoxy benzylideneamino) phenylimino) indoline-2-one (**24h**) showed excellent anticonvulsant activity with a lower dose in MES as well as in ScMet methods [29].



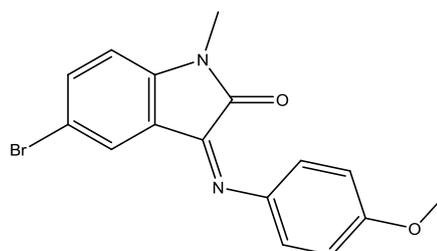
Compound 24h

A series of aryl acid hydrazones of substituted aromatic acid hydrazides were synthesised and evaluated for anticonvulsant activity. Compound **25**, *N*¹-(4-chlorobenzylidene) nicotinohydrazide was found to be the most potent analog with ED₅₀ value of 16.1 mg/kg and protective index (PI = TD₅₀/ED₅₀) value of >20, which was much greater than that of the prototype drug phenytoin (PI = 6.9) [30].



Compound 25

Schiff bases of *N*-methyl and *N*-acetyl isatin derivatives with different aryl amines have been synthesized and screened for anticonvulsant activities against maximal electroshock (MES) and subcutaneous metrazole (ScMet). *N*-methyl-5-bromo-3-(*p*-chlorophenylimino) isatin (**26**) exhibited anticonvulsant activity in MES and ScMet with LD₅₀ > 600 mg kg⁻¹, showing better activity than the standard drugs phenytoin, carbamazepine and valproic acid [31].



Compound 26

CONCLUSION

The present study revealed that all mentioned hydrazone and hydrazide derivatives, under this review, showed promising anticonvulsant activity. These compounds and their modification can be considered as a lead molecule for further investigation and thus to control epileptic seizure in patients.

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