Review Article

Synthetic Methods, Chemistry, and the Anticonvulsant Activity of Thiadiazoles

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The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Heterocyclic nucleus 1,3,4-thiadiazole constitutes an important class of compounds for new drug development. The synthesis of novel thiadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades. The search for antiepileptic compounds with more selective activity and lower toxicity continues to be an active area of intensive investigation in medicinal chemistry. During the recent years, there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive pharmacological activities, namely, antimicrobial activity, anticonvulsant, antifungal antidiabetic, anti-inflammatory, antioxidant, and antituberculosis activities, and so forth. The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research today. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as “hydrogen binding domain” and “two-electron donor system.” It also acts as a constrained pharmacophore. On the basis of the reported literature, we study here thiadiazole compounds and their synthetic methods chemistry and anticonvulsant activity.

1. Introduction

Epilepsy is the name of a brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures [1, 2]. The current therapy of epilepsy with antiepileptic drugs is associated with side effects, dose-related and chronic toxicity, and teratogenic effects [3, 4]. Epilepsy is not a singular disease entity but a variety of disorders reflecting underlying brain dysfunction that may result from many different causes. Therefore, there is continuing demand for new anticonvulsant agents. So, there is an urgent requirement for the dieovory and development of some novel anticonvulsant agents with more selective activity and lower toxicity for the effective treatment of epilepsy. Several five-membered aromatic systems having three heteroatoms at symmetrical positions such as thiadiazoles have been studied extensively owing to their interesting pharmacological activities. There is a broad variety of heterocyclic compounds which are having medicinal importance, and recently, much attention has been focused on thiadiazole derivatives in view of their broad spectrum activities. Thiadiazole is one such heterocyclic nucleus. There are several isomers of thiadiazole, that is 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole [5], 1,3,4-Thiadiazole is the main isomer of thiadiazole series having versatile pharmacological activities.

2. Thiadiazole

Thiadiazole is a heterocyclic organic compound that has a five-member ring having one sulphur and two nitrogen atoms [6]. 1,3,4-Thiadiazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. Thiadiazoles have become very important
Table 1: Physical properties of 1,3,4-thiadiazole.

<table>
<thead>
<tr>
<th>Bond length</th>
<th>Bonds</th>
<th>Bond angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>A 1.371</td>
<td>α 112.2</td>
</tr>
<tr>
<td>Type</td>
<td>B 1.302</td>
<td>β 114.6</td>
</tr>
<tr>
<td>Type</td>
<td>C 1.721</td>
<td>γ 86.4</td>
</tr>
<tr>
<td>Type</td>
<td>D 1.721</td>
<td>δ 114.6</td>
</tr>
<tr>
<td>Type</td>
<td>E 1.302</td>
<td>ε 112.2</td>
</tr>
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</table>

compounds in medicine, agriculture, and many fields of technology. A large number of 1,3,4-thiadiazoles have been patented in the agricultural field as herbicides and bactericides [7].

X-ray analysis shows the following structure parameter for 1,3,4-thiadiazole ring (see Table 1 and Structure (1)):

3. Chemistry of Thiadiazole

A recent literature survey revealed that the 1,3,4-thiadiazole moiety has been widely used by the medicinal chemist in the past to explore its biological activities. The development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazines and hydrazine in the late nineteenth century. The first 1,3,4-thiadiazole was described by Fischer in 1882, but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh.

Thiadiazole is a five-member heterocyclic compound having one sulphur and two nitrogen atoms. There are several isomers of thiadiazole, that is, 1,2,3-thiadiazole (2), 1,2,5-thiadiazole (4), 1,2,4-thiadiazole (3), and 1,3,4-thiadiazole (5). There are four possible systems in thiadiazole.

4. 1,3,4-Thiadiazoles

1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Bush and his coworkers, but true nature of the ring system was demonstrated first in 1956 by Goerdler et al. [8]. The advent of sulphur drugs and the later discovery of mesoionic compound greatly accelerated the rate of progress in the field of thiadiazole. Thiadiazole carrying mercapto, hydroxyl, and amino substituents can exist in many tautomeric forms. The 1,3,4-thiadiazoles are conveniently divided into three subclasses:

(a) aromatic systems which include the neutral thiadiazoles and constitute a major part of this paper;

(b) mesoionic systems which are defined as five-membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring;

(c) nonaromatic systems such as the 1,3,4-thiadiazoles and the tetrahydro 1,3,4-thiadiazoles. In the partially reduced systems, the position of the double bond is denoted by the prefix Δ, with being a Δ²-1,3,4-thiadiazole (Structures (6), (7), and (8)).

5. Synthetic Procedures of 1,3,4-Thiadiazoles

(a) Formation of One Bond. The most common procedure for the synthesis of 5-substituted 2-amino-thiadiazole
is the acylation of a thiosemicarbazide followed by dehydra-
tion. Sulphuric acid, polyphosphoric acid, and phosphorous
halides are some of the reagents used. The most recent
procedure utilizes 1.5 moles of methane sulphonate as a
dehydrating agent and the thiadiazole obtained in the
high yield and good purity. 5-Alkyl-2-methyl amino-1,3,4-
thiadiazoles are prepared from a suitable carboxylic acid
and methyl thio-semicarbazide in the presence of three parts
of polyphosphoric acid and one part of concentrated sulphuric
acid. 2-alkylamino-1,3,4-thiadiazole n substituted in the 5th
position can be prepared in high yields by the reaction of
4-alkyllhiosemicarbazides with orthoformate esters in the
presence of small amount of concentrated hydrochloric acid
[9] (Scheme 1).

(b) Formation of Two Bonds. This is the most widely used
procedure for the synthesis of thiadiazoles, thiazolidines, and
mesoionic thiadiazoles.

(1) Cyclization. The parent molecule 1,3,4-thiadiazole was
synthesized in 1956 by a four-step reaction sequence start
utilizing hydrazine and from thiosemicarbazide. A second
procedure utilizes hydrazine and potassium dithioformate.
Dehydration of DMF with thionyl chloride or phosgene
gives the formamide chloride which on treatment with
N,N-Diformylhydrazine gives the dihydrochloride of the free
base which is liberated with sodium ethoxide, which then
cyclizes to thiadiazole in the presence of hydrogen sulphide
in an overall yield of 65%. 2-Amino 1,3,4-thiadiazole is also
prepared from thiosemicarbazide and a mixture of formic
and hydrochloric acid in a tedious procedure with an overall
yield of 65% (Scheme 2).

(2) Dipolar Cycloadditions. This procedure has been widely
used during the last decade for both synthetic and mechanistic
reasons.

From Diazo Compounds. The reaction of ary1 sulphonyl-
substituted sulfines with diazomethane gives $\Delta^3$-1,3,4-thia-
diazole 1-oxide which, however, is unstable and rearranged
via an isomerization of the $\Delta^3$ to the $\Delta^2$-thiadiazole oxide.
This is followed by an elimination and readdition of sulfonic
acid and loss of water in a pummerer-type aromatization to
give the rearranged thiadiazole (Scheme 3).

5.1. Method of Synthesis of 1,3,4-Thiadiazole

(a) From Hydrazine. 3-Thiocarbamoyl thione methyl car-
bonate on oxidation with H$_2$O$_2$ gave alkoxythiadiazole [10]
(Scheme 4).

(I) Thiobenzoyl hydrazine cyclized to produce 1,3,4-

(II) Thione carbazate are cyclized by cyanogens chloride
or bromide to give 1,3-thiadiazole [12] (Scheme 6).

(b) From Semicarbazide. When 4-phenyl-1-(thiobenzole)
semicarbazide reacts in the presence of concentrated HCl giv-
ing 2-hydroxy-5-phenyl-1,3,4-thiadiazole [13] (Scheme 7).

(c) From Thiosemicarbazide. Many syntheses of the 1,3,4-
thiadiazole proceed from thiosemicarbazide or substituted
thiosemicarbazide.

Method 1. Gupta et al. have shown that thiosemicarbazide
cyclizes directly to 2-amino-5-diazole with acetyl chloride.
This simple route to 2-amino 5-substituted-1,3,4-thiadiazole
seems to be quite general. In the example shown, R may
be methyl17, nor hydnocarpyl, benzyl, cyclopropyl [14], and
many others (Scheme 8).

(d) From Thiosemicarbazone. 2-Amino-5-substituted thiadi-
zoles are prepared by oxidative cyclization of thiosemicar-
bazones with ferric chloride found 1,3,4-thiadiazole [15]
(Scheme 9).

(e) From Resin. Resin with TMSCI, MCPBA, and R$_2$ R$_3$ NH
gave 1,3,4-S-thiadiazole [16] (Scheme 10).

(f) From Bithioureas. Bithiourea and substituted bithiourease
have been converted to 1,3,4-thiadiazole by several methods.
Method 1. Bithiourea when treated with 3% hydrogen peroxide is cyclized to 2,5-diamino-1,3,4-thiadiazole (Scheme II).

Method 2. Acetic anhydride acts on bithiourea to form a diacetyl derivative of 2,5-diamino-1,3,4-thiadiazole. The acetyl group I is easily removed by hydrolysis to give the parent thiazole [17].

5.2. Chemical Properties

5.2.1. Reactivity. Some of the characteristic reactions of the 1,3,4-thiadiazole nucleus are ring opening by strong base ease of nucleophilic attack and the formation of mesoionic compounds by quaternization. The substituents in the 2 and 5 positions have a large effect in determining the reactivity of the molecule as a whole. Thus, the ambient nucleophilicity of 2-aminothiazoles gives rise to electrophilic attack on both the amino group and the nuclear nitrogen atom. Ring formation between these two nitrogen atoms is also a common reaction. 2-Mercaptothiazoles react similarly to arenethiols while a methyl group on the thiadiazole ring has reactivity similar to that in a picoline. Nucleophiles easily displace halogen atom from the thiadiazole nucleus. This is due to the electronegativity of the two nuclear nitrogen atoms which impart a low electron density to the carbon atom of the nucleus.

5.2.2. Thermal and Photochemical Reactions. Thermal and photochemical fragmentations of 1,3,4-thiadiazole often follow the fragmentation pattern observed in the mass spectrometer. The cis-2,5-di-t-butyl-2,5-dihydro-1,3,4-thiadiazole gives while photolysis yields the kazaetine. The cis 2,5-dihydro-1,3,4-thiadiazole 1,1-dioxide (cis-4) undergoes thermalysis at 50°C to give the azine. The trans isomer (trans-4), however, undergoes thermalysis only above 145°C to give the alkylidine hydrazide plus sulphur monoxide which disproportionate into sulphur dioxide. Compounds were independently prepared from dimethylpropanol, and the hydrazole thermolysis of the isomeric 2,3-dihydro-1,3,4-thiadiol 1,1-thiadiazole 1,1 dioxide also gives rise. The concerted [4 + 1] cycloelimination of sulphur dioxide from the trans isomer cannot take place due to steric hindrance (Scheme 12).

(a) Attack at Ring Nitrogen (Quaternization). Ratio of 3 or 4 substituted product depends on ring substitution, in which nitrogen has high e⁻ density (Scheme 13).

(b) Electrophilic Attack at Carbon. Due to the electron density at the carbon atoms in 1,3,4-thiadiazole, such reaction as nitration, acetylation, sulphonation, halogenations. However, 2-amino-substituted 1,3,4-thiadiazoles (1a–i) heat with bromine in acetic acid to give 5-bromo derivatives (2a–i). Similarly, the thiadiazoles (3b) yield (3d–f) the corresponding 5-bromo derivatives (4b) and (4d–f) (Scheme 14).

(c) Electrophilic Attack at Sulphur. Although direct oxidation at sulphur atom in 1,3,4-thiadiazoles has not been reported, 1,3,4-thiadiazole 1-oxides and 1,1 dioxides can be indirect mean (Scheme 15).

(d) Electrophilic Substitution at Ring. Strong e⁻ donor substituted at ring position 2 activates towards electrophilic agents under drastic condition (conc. H₂SO₄ + fuming HNO₃). Nitration of 2 ammonia 1,3,4-thiadiazoles with fuming nitric acid at 40°C gave 2-amino-1,3,4-thiadiazoles (21A) (Scheme 16).

5.3. Amination. Direct nuclear amination of certain thiadiazoles is possible, illustrating the case of nucleophilic attack. (R=H) react with hydroxylamine in the presence of base to give (R=NH₂) presumably via the imine (Scheme 17).

(III) Nucleophilic Attack. 1,3,4-Thiadiazole ring reacts with strong nucleophiles, treatment of the parent compound with base leading to ring fission. 2-Amino and 2-methylamino 1, 3, 4-thiadiazole rearrange in the presence of methylamine to the triazolinethione (Scheme 18).
(2) **Nucleophilic Substitution.** Due to the electronegativity of the two nitrogen atoms in the ring, the carbon atom has low electron density and gives many possible nucleophilic reactions [18]. Halogenate 1,3,4-thiadiazoles are important intermediates in which the halogen atom is readily replaced by nucleophiles. 5-Chloro-thiadiazole reacts readily with nucleophiles to give a series of 5 substituted-2-aryl-1,3,4-thiadiazoles (Scheme 19).

Amino thiadiazoles are rather weak bases; they are nucleophilic enough to be readily acetylated by acid chlorides or acetic acids (Scheme 20).

Aminothiadiazole forms diazonium salts and shows the coupling activity [19] (Scheme 21).

2-Amino-1,3,4-thiadiazoles and aromatic aldehydes form Schiff bases [20] (Scheme 22).

5.4. **Miscellaneous Reaction.** Direct introduction of mercapto group on 2-phenyl-1,3,4-thiadiazoles is possible by the use of phosphorous pentasulphide [21] (Scheme 23).

5.4.1. **Reduction of Thiadiazole Ring.** 2-Amino-1,3,4-thiadiazoles reduces to benzaldehyde thio semicarbazone [22] (Scheme 24).

5.4.2. **Reaction Involving Formation.** On heating, 2-amino thiadiazole reacts with many dicarbonyl group containing compounds and forms various types of rings attached to thiadiazole (Scheme 25).

5.4.3. **Rearrangement Reaction.** Various 2-chloro and 2-amino substituted thiadiazoles undergo rearrangement by ring opening intermediate formation and again ring closure to form 4N substituted 1,3,4-thiadiazole 5(1)-terione [23,24] (Scheme 26).

(a) **Dimorph Rearrangement.** See Scheme 27.

(b) **Under Same Condition.** See Scheme 28.

(c) **Acid Catalysed.** See Scheme 29.

(d) **Cycloaddition Reaction.** Aminobenzothiadiazoles are produced when 1,3,4-thiadiazoleinethiones (R¹=H, Me, Ac, R²=Me, Ph) are reacted with benzene, most likely by a 1,3-dipolar addition mechanism followed by elimination of RSCN (Scheme 30).

5.4.4. **Reaction of Constituents on Carbon.** Treatment of 2-methyl 1,5 diphenyl-1,3,4-thiadiazole (R=H) with n-butyllithium at −78°C gives the lithio derivative (R=Li)
which, on treatment with methyl iodide, gives the expected 2-ethyl homologue (R=Me); if (R=Li) is allowed to warm from −78°C to 25°C the dimer is formed, which on heating above 150°C converts into starting material. The dimerization proceeds via intermediates and not the ketone amine (Scheme 31).

5.4.5. Sulphur Substituents. The mesoionic 4,5-diphenyl-1,3,4-thiadiazole-2-thiolate reacts with methyl azodicarboxylate to yield the azothiadiazole and not the tetrazine betaine as previously claimed from 2-amino-5-phenyl-1,3,4-thiadiazole and nitrosobenzene (Scheme 32).

5.4.6. Amino Substituents. The reaction of unsubstituted 2-amino-1,3, and 4-thiadiazole with 1,3-dicarbonyl compounds is independent of the nature of the dicarbonyl compounds. The reaction of pentane-2-4-dione gives the 4,6-dimethyl-1,2-thiocyanatepyrimidine. The formation may proceed via the cation. With ethylacetoacetate, however, if a mixture formed also being converted in to on heating.

Biological Activities of 1,3,4-Thiadiazole Derivatives. During the recent years, there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive pharmacological activities. Among of these compounds having 1,3,4-thiadiazole nucleus are known to exhibit unique antimicrobial activity [25–38], Antifungal [39–41], antidiabetic [42], anti-inflammatory [38, 43–54], antileishmanial activity [55–58], antituberculosis activity, [59–61], anticancer activity, [34, 62–68] anti-HIV activity [69, 70], antioxidant/radioprotective Activity [71–73], Carbonic anhydrase inhibitors [74, 75]. Anti-Helicobacter pylori activity [76, 77]. This paper focuses on the therapeutic importance of novel thiadiazole derivatives as anticonvulsant agents for future.

Anticonvulsant Activity of Thiadiazole Derivatives. A series of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazole has been synthesized and screened for anticonvulsant activity. All the synthesized compounds were evaluated against maximal electroshock-induced seizure (MES) and subcutaneous-pentylentetrazole- (ScPTZ-) induced seizure models in mice. Among the compounds tested, all showed protection from MES seizures, whereas only (104) (105) was found to be active in the ScPTZ test. The present results revealed that a number of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazoles exhibit a range of activities in anticonvulsant screen [78].
A series of new substituted 1,2,4-thiadiazoles were synthesized by appropriate route and screened for anticonvulsant, neurotoxic, and sedative-hypnotic activities. The structures of the synthesized compounds were confirmed by IR spectroscopy, C-13 NMR, and elemental (nitrogen and sulphur) analysis. After i.p. injection of the compounds to mice or rats at doses of 30, 100, and 300 mg/kg, body weights were examined in the maximal electroshock-induced seizure (MES) and subcutaneous-pentylenetetrazole- (scPTZ-) induced seizure models after 0.5 and 4 h. All the compounds showed protection against MES screen after 0.5 h. Compounds were active at the doses of 100 mg/kg and 300 mg/kg dose i.p. It may be concluded that the synthesized compounds were potent against MES-induced seizures than ScPTZ-induced seizures [79].

A series of aromatic aldehyde imine derivative of 2-thiobenzyl-1,3,4-thiadiazole were synthesized. These derivatives 109(a–e), 110(ia–ie), 110(iia–iie) show good anticonvulsant activity. Among these compounds, chlorobenzyl substituted compound shows the potent anticonvulsant activity against MES method [81].
A variety of new 3-[5-substituted phenyl-1,3,4-thiadiazol-2-yl]-2-styryl quinazoline-4(3H)-ones were synthesized and evaluated for anticonvulsant activity b. Compounds were examined in the maximal-electroshock- (MES-) induced seizures and subcutaneous-pentylentetrazole- (scPTZ-) induced seizure models. Compounds (111a), (111b), and (111c) showed good anticonvulsant activity in the test models [82].
Several novel 2-amino-5-[4-chloro-2-(2-chlorophenoxy)phenyl]-1,3,4-thiadiazole derivatives 4a–d were synthesized, and their anticonvulsant activity was determined by evaluation of the ability of these compounds to protect mice against convulsion induced by lethal doses of pentylentetrazole (PTZ) and maximal electroshock (MES). The result of anticonvulsant data shows that among the synthesized compounds, 5-[4-chloro-2-(2-chlorophenoxy)phenyl]-N-ethyl-1,3,4-thiadiazol-2-amine (114, 115, 116) was the most active compound in both MES and PTZ tests with an ED50 of 20.11 and 35.33 mg/kg, respectively [85].

3-[(2-Methyl-1H-3-indolyl)methyl]-4-aryl-4, 5-dihydro-1H-1,2,4-triazole-5-thiones and their respective N-[(2-methyl-1H-3-indolyl)methyl]-1,3,4-thiadiazol-2-yl]-N-aryl-amines have been prepared. Behavioral effects, induced by the members of both series, in conjunction with their activity in some specific tests (forced swim, pentetrazol convulsions) on mice, show that these derivatives cross the blood-brain barrier and could develop an antidepressant activity comparable to that of imipramine. Blood-brain barrier penetration is also supported by the lipophilicity data obtained for all analogs [84]. (Structure (113)).
The present study describes the synthesis and anticonvulsant activity evaluation of 6-substituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives and their partially dehydrogenated products 5,6-dihydro-6-substituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives. The bioevaluation demonstrated that most compounds in the series exhibited potent anticonvulsant activity in the maximal electroshock test. Among which, 6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (117) emerged as the most promising candidate on the basis of its favorable ED50 value of 23.7 mg/kg and PI value of 10.8. In addition, the potency of compound 117 against seizures induced by pentylenetetrazole, 3-mercaptopropionic acid, and bicuculline in the chemical-induced seizure tests suggested that compound 117 displayed broad-spectrum activity in several models, and it may exert its anticonvulsant activity through affecting the GABAergic system [86].

Synthesis and pharmacological evaluation of a number of substituted 1,3,4-thiadiazole the first member of the series 2-((aminomethyl)-5-(2-biphenyl)-1,3,4-thiadiazole (118) was found to possess potent anticonvulsant property in rats and mice and compared favourable with the standard anticonvulsant drug phenytoin, Phenobarbital and carbamazepine in a number of test situations. The potency of compound was maintained on alkylation of the side chain nitrogen atom; however, aryl substitution on chain lengthening caused a drop in potency replacement of the two biphenyl group by phenyl or benzyl also lead to inactive compound [87].

Various N-(5-chloro-6-substituted-benzothiazol-2-yl)-N′-(substituted phenyl)-[1,3,4]thiadiazole-2,5-diamines were designed and synthesized starting from substituted acetophenones. Structures of all the compounds were confirmed on the basis of spectral and elemental analyses. All the newly synthesized compounds were screened for their anticonvulsant activity and were compared with the standard drug phenytoin sodium. Interestingly, all the compounds showed protections against seizures in the range 50%–100% indicative of the promising nature of the compounds against seizure spread. Compound 119 showed complete protection against MES-induced seizures [88].
A series of 1,2,4-thiadiazoles (120a–e) were prepared and evaluated for anticonvulsant activity by Siddiqui et al. The compound with para-chloro substitution (120c) showed maximal activity in MES test and blocked strychnine seizures to some extent whereas other compounds of the series were less active [89].

A series of thiadiazole derivatives were synthesized with differently substituted benzoic acids which were cyclized to give differently substituted thiazolidin-4-one. Elemental analysis, IR, HNMR, C NMR, and mass spectral data confirmed the structure of the synthesized compounds. The derivatives of these moieties were evaluated for anticonvulsant activity by MES model and neurotoxicity by rotarod method. The synthesized compounds showed good potential for anticonvulsant activity besides this, and the compounds also showed neurotoxic effect. It was observed that compounds with OCH₃ at 3,4 position of phenyl ring showed less protection against convulsions as compared to compounds having unsubstituted phenyl ring [91].

The synthesis and anticonvulsant activity of a series of 2-aryl-5-hydrazino-1,3,4-thiadiazole are described. The combination of preferred aromatic substituents in the 2-position coupled with alkyl substitution on the hydrazine moiety led to a number of potent compounds lacking sedation, ataxia, or lethality. 5-(2-Biphenylyl)-2-(1-methylhydrazino)-1,3,4-thiadiazole (4m) represents a new class of anticonvulsant agent and compares favorably with the standard drugs phenytoin, phenobarbital, and carbamazepine [92] (Structure (122)).
Scheme 26

\[
\text{Rearranged product}
\]

Scheme 27

Scheme 28

Scheme 29

Scheme 30

Scheme 31
A novel series of NN’-[5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-N4-(4-substituted benzaldehyde) semicarbazones, NI-[5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-N4-[1-(4-substituted phenyl)ethanone]-semicarbazones and NI-[5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-N4-[1-(4-substituted phenyl) (phenyl) methanone]-semicarbazones were synthesized and evaluated for their anticonvulsant potential using maximal electroshock seizure (MES) and subcutaneous pentylentetrtrazole (scPFZ) models. The minimal motor impairment (neurotoxicity) was determined by rotarod test. The results of the present study confirmed the requirements of various structural features of four binding site pharmacophore model for anticonvulsant activity [93].

Treatment of 2-bromoacetylbenzofuran with 1H-benzotriazole afforded 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone which reacted with phenylisothiocyanate to give the corresponding thioacetanilide derivatives. Treatment of the latter ethanone and thioacetanilide derivatives with hydrazonoyl chlorides afforded the corresponding pyrazole and 1,3,4-thiadiazolederivatives. The thioacetanilide derivative reacted with α-haloketones and α-halodiketones to afford thiophene and thiazole derivatives, respectively. The newly synthesized compounds were found to possess anticonvulsant and anti-inflammatory activities with the same mechanism of action of selective COX-2 inhibitors [94].

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