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Chemistry, synthesis and progress report on biological activities of thiadiazole compounds - a review

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Abstract: Thiadiazoles are an important class of heterocyclic compounds that exhibit diverse applications in organic synthesis, pharmaceutical and biological applications. They are also useful as oxidation inhibitors, cyanine dyes, metal chelating agents, anti-corrosion agents. Researchers across the globe are working on this moiety due to their broad spectrum of applications of thiadiazole chemistry. This article provides information about developments, exploration, synthetic strategies, techniques for the synthesis of thiadiazoles and their diverse biological activities, structure-activity relationship of the compounds and physical properties. This article is an important tool for organic and medicinal chemists to develop newer thiadiazole compounds that could be better agents in terms of efficacy and safety.

Key words: Thiadiazoles, synthesis, biological activities.

Introduction

The five-member heterocyclic compounds; particularly nitrogen and sulphur heterocycles; thiadiazoles have been successfully tested against several diseases and therefore received special attention in pharmaceutical chemistry due to their diverse potential applications [1-2]. Among the different thiadiazoles; more information about the synthesis and applications of 1,3,4-thiadiazoles is available in the literature, relatively less about 1,2,5-thiadiazoles. But there is a scanty of information is there about 1,2,3-thiadiazoles and 1,2,4-thiadiazoles. 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 thrust areas of research today. Thiadiazoles continuously draws interest for development of newer drug moiety. Researchers have demonstrated a broad spectrum of biological properties of thiadiazoles in both pharmaceutical and agrochemical fields. Compounds having thiadiazole nucleus have wide spectrum of pharmacological activities such as antimcirobial, antitubercular, antileishmanial, anti-inflammatory, analgesic, CNS depressant, anticonvulsant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic, analgesic properties. For instances, 1,3,4-thiadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They have known to exhibit diverse biological activities such as in vitro inhibition of cyclooxygenase and 5-lipoxygenase activities [3]. New acylated 5-thio-beta-D-glucopyranosylimino-disusbstituted 1,3,4-thiadiazoles prepared by cycloaddition of the glycosyl isothiocyanate with the reactive intermediates 1-aza-2-azoniaallene hexachloro antimonates, and have been tested in vitro antiviral activity against HIV-1, HIV-2, human cytomegallovirus (HMCV) [1-20].

Thiadiazole compounds show various types of biological activity among them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activity probably virtue of –N=C-S- grouping. Therapeutic importance of these rings prompted us to develop selective molecules in which substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities. Thiadiazoles have occupied an important place in drug industry, 1,3,4-thiadiazoles have wide applications in many fields [5]. 1,3,4-thiadiazole derivatives possess interesting biological activity probably conferred to them due to strong aromaticity of the ring system which leads to great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans when diverse functional group that interact with biological receptor are attached to aromatic ring [6]. Approach to practice of medicinal chemistry has developed from an empirical one involving synthesis of new organic compounds based on modification of chemical compounds of known biological activities could be better explored. It is well established that slight alteration in the structure of certain compounds are

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able to bring drastic changes to yield better drug with less toxicity to the host it observed that chemical modification not only alters physiochemical properties but also pharmacological properties [7].

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. There are several isomers of thiadiazole, that is 1,2,3-Thiadiazole (**1**), 1,2,5-Thiadiazole (**2**), 1,2,4-Thiadiazole (**3**) and 1,3,4-Thiadiazole (**4**). 1,3,4-Thiadiazole is the isomer of thiadiazole series. A glance at the standard reference works shows that more studies have been carried out on the 1,3,4 Thiadiazole than all the other isomers combined. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors, cyanide dyes, metal complexing agents [8-10]. The ending *-azole* designates a five membered ring system with two or more heteroatoms, one of which is Nitrogen. The ending –*ole* is used for other five membered heterocyclic ring without Nitrogen. The numbering of monocyclic azole system begins with the heteroatom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. Hence the numbering of 1,3,4-Thiadiazole (**4**) is done in following manner. This designates that one sulphur group is present in the ring [11,12].
Apart from the pharmacological applications, thiadiazoles and their derivatives have been known to exhibit varied physical properties such as exhibit anticorrosion, liquid crystal, optical brightening and fluorescent properties which were discussed in this review article.

1,2,3-Thiadiazole (**1**) 1, 2,4-Thiadzole (**2**) 1,2,5-Thiadiazole (**3**) 1,3,4-Thiadiazole (**4**)

Chemistry of Thiadiazole

Thiadiazole moiety act as a "hydrogen binding domain" and "two-electron donar system". Thiadiazole act as a bioisosteric replacement of thiazole moiety. So, it acts as third and fourth generation cephalosporin. Thiadiazole is a five membered ring system containing sulphur and nitrogen atom. They occur in four isomeric forms (**1-4**). Its dihydro derivative provides bulk of literature on thiadiazole [13].

Physical properties of -1, 3, 4-thiadiazoles

Structure and Aromatic Properties

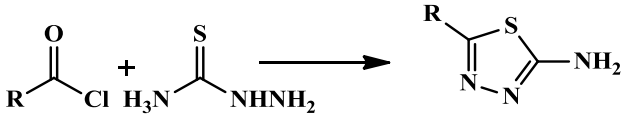
Microwave spectra of 1,3,4-thiadiazole and three isotopically substituted species. They could determine the structure of the molecule with an uncertainty of 0.03 A^o in the coordinates of the hydrogen atom and of less than 0.003 A^o in the coordinates of the other atoms. By an analysis of difference between the measured bond lengths and covalent radii, the author came to the conclusion that the aromatic character, as measured by the π-electron delocalization decreases in the order –1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole [14].

Dipole Moment

The dipole moment of 1,3,4-thiadiazole in the gas phase by microwave technique and found a value of 3.28+-0.03 D. By use of geometry, the π-electron distribution and the bond moment, dipole moment of 3.0 D can be calculated, directed from the sulphur atom towards the center of the nitrogen-nitrogen bond [15-17].

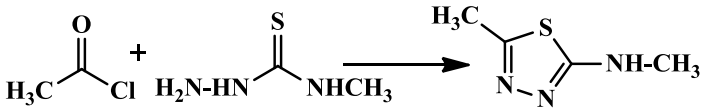
Recent Strategies in the Synthesis of 1, 3, 4-thiadiazoles

Recent strategies on the synthesis of 1,3,4-Thiadiazole derivatives can be summarized in to following points:
Many synthesis of the 1,3,4-Thiadiazole proceed from thiosemicarbazide or substituted thiosemicarbazide.
Thiosemicarbazide cyclizes directly to 2-amino-5-methyl-1,3,4-thiadiazole with acetyl chloride. This simple route to 2-amino 5-substituted-1,3,4-thiadiazole seems to be quite general [18]. In the example shown R may be methyl [18], norhydnocarpyl [19], benzyl [20], cyclopropyl [21] and many others.



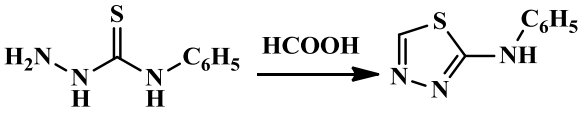
Scheme 1

The acetyl chloride could bring about the cyclization of alkyl- or arylsubstituted thio-semicarbazide. The action of acetyl chloride on 4-methylthiosemicarbazide produces 5-methyl-2-methylamino-1,3,4-thiadiazole [22].



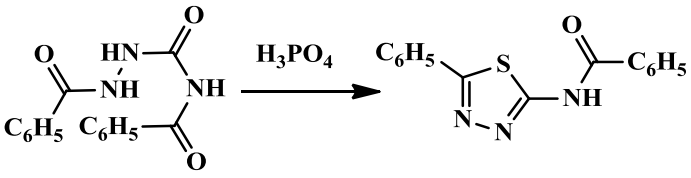
Scheme 2

Formic acid could cyclize the alkanoyl halides by acylation. He found that by heating 4-phenylthiosemicarbazide with formic acid, 2-anilino-1,3,4-thiadiazole was formed [22].



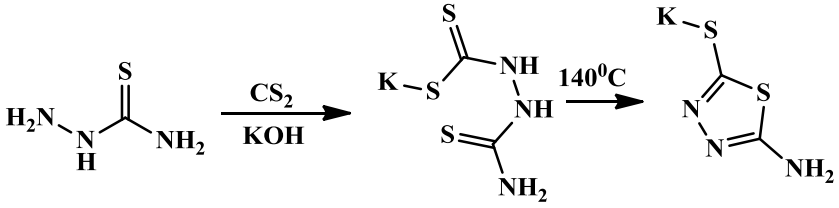
Scheme 3

A number of 2-amino-5-aryl-1,3,4-thiadiazole using phosphoric acid as the dehydrating agents. An example of smooth cyclization in high yield by phosphoric acid is the formation of 2-benzamido-5-phenyl-1,3,4-thiadiazole from 1,4-dibenzoylthio-semicarbazide [23].



Scheme 4

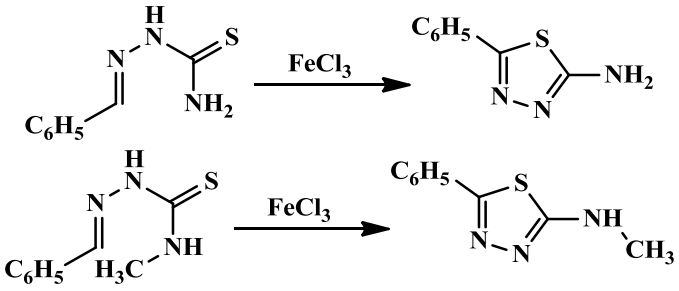
2-amino-5-mercapto-1,3,4-thiadiazole was developed. When thiosemicarbazide is treated with carbon disulphide and potassium hydroxide, the potassium salt of thiosemicarbazide-4-dithiocarboxylic acid is formed. Heating this potassium salt of thiosemicarbazide-4-dithiocarboxylic acid to 140°C causes cyclization to the salt of 2-amino-5-mercapto-1,3,4-thiadiazole [24].



Scheme 5

In certain instances neutral carbon disulphide react directly with thiosemicarbazide to form aminomercaptothiadiazoles. A modification of the carbon disulphide-thiosemicarbazide procedure which results in higher yield of 2-amino-5-marcapto-1,3,4-thiadiazole is carried out in dimethylformamide at 80°, the yield is over 90% [25].

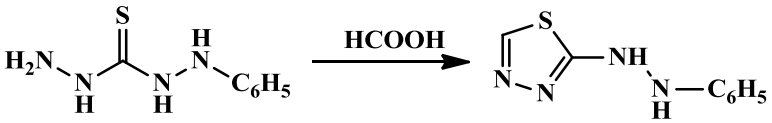
The benzalthiosemicarbazones could be oxidatively cyclize to form 2-amino-5-phenyl-1,3,4-thiadiazole by ferric chloride [25]. A large number of 5-substituted 2-amino-1,3,4-thiadiazole have been prepared by this procedure [26].



Scheme 6

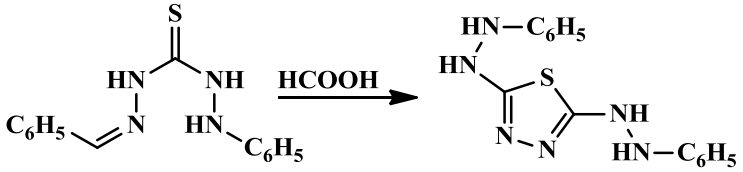
A number of aldose thiosemicarbazones could be converted to thiadiazole derivatives by Young and Eyre method [27].

There are two method by which 1, 3, 4-thiadiazole can be prepared from thiocarbazides.
If 1-phenylthiocarbazide is heated with formic acid, it is converted to 2-phenylhydrazino-1,3,4-thia-diazole [28].



Scheme 7

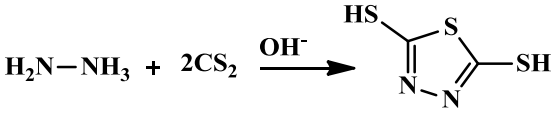
This method is related to the oxidation of 1-phenylbenzalthiocarbazone to 2-phenyl-5-phenyl hydrazino-1,3,4-thiadiazole [29].



Scheme 8

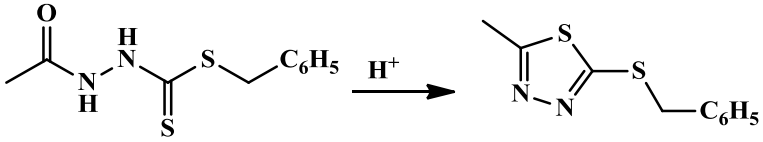
Following methods have been reported for the preparation of 1,3,4-thiadiazole from dithiocarbazates.

Another route to 1,3,4-thiadiazole is via substituted dithiocarbazic acid and their esters. A reaction which belongs in this group is the formation of 2,5-dimercapto-1,3,4-thiadiazole by action of carbon disulphide on hydrazine in basic medium [30,31].

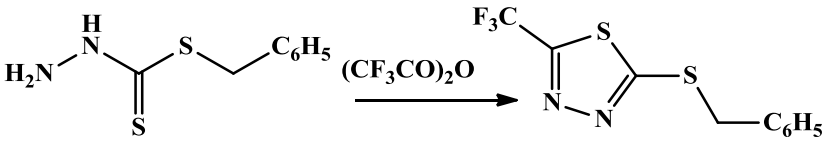


Scheme 9

When 3-acyldithiocarbazic esters are treated with acids, they cyclize to form substituted thiadiazoles. This is a quite general reaction. Both benzyl and methyl 3-acyldithiocarbazates have been employed [32,33].

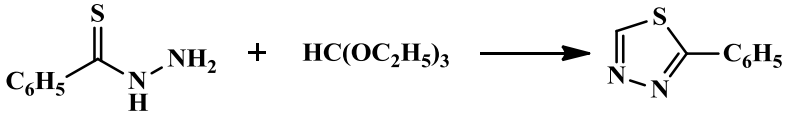


Scheme 10 A



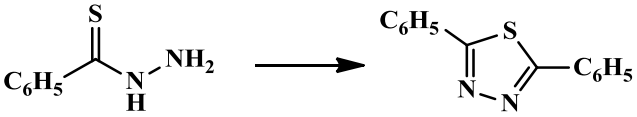
Scheme 10 B

Thioacylhydrazines may often serves as starting materials for the preparation of 1,3,4-thiadiazole. If thiobenzoylhydrazine is heated with ethyl orthoformate, 2-phenyl-1,3,4-thiadiazole is formed. If ethyl orthoacetate is substituted for the orthoformate, 2-methyl-5-phenyl-1, 3, 4-thiadiazole is obtained [34,35].



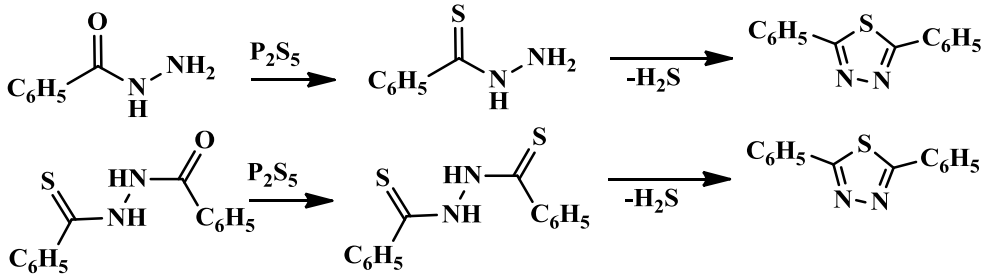
Scheme 11

Thiobezhydrazide is smoothly converted to 2-phenyl-1, 3, 4-thiadiazole by the action of formic acid [27]. Thiobenzhydrazide is form 2, 5-diphenyl-1,3,4-thiadiazole (33) in small amount when warmed in benzene [36].



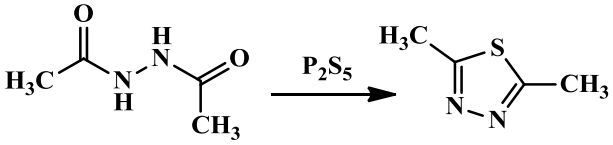
Scheme 12

Stolle obtained 2,5-diphenylthiadiazole (36) by a variety of methods. He found that benzoyl-hydrazine [37] or N,N'-dibenzoylhydrazines [38] react with phosphorus pentasulfide to form 2,5-diphenyl-1,3,4-thiadiazole.



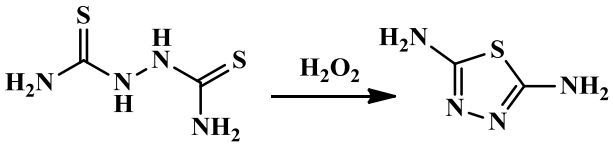
Scheme 13

The reaction of N, N'-diacylhydrazine with phosphorus pentasulfide was used by Stolle and his students for the preparation of a large number of 2,5-disubstituted 1,3,4-thiadiazole [39,40].



Scheme 14

Bithiourea and substituted bithiourease have been converted to 1,3,4-thiadiazole by several methods. Bithiourea, when treated with 3% hydrogen peroxide is cyclized to 2,5-diamino-1,3,4-Thiadiazole [41].

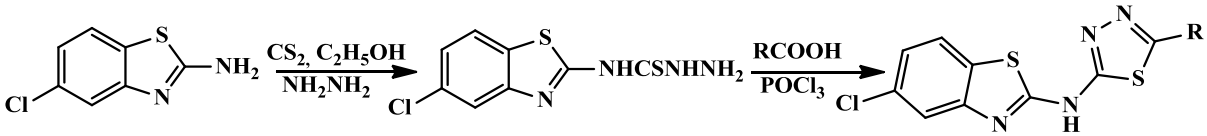


Scheme 15

Acetic anhydride acts on bithiourea to form a diacetyl derivative of 2, 5-diamino-1, 3, 4-Thiadiazole. The acetyl group is easily removed by hydrolysis to give the parent thiadiazole [42].

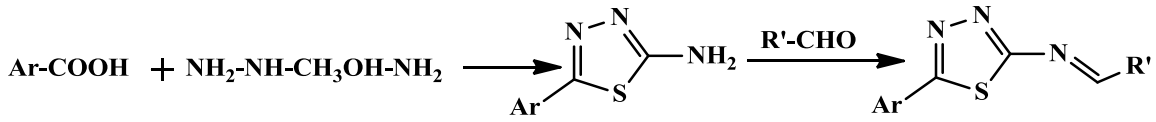
Synthesis of 1,3,4-thiadiazoles

The usual or classical method of synthesis of thiadiazoles involves the condensation of thiosemicarbazides with carboxylic acids or carboxylic acid chlorides or carboxylic acid esters with cyclising or condensing agents such as phosphorus oxychloride, phosphorus pentachloride, acetic anhydride, sulphuric acid etc. For instance; The reaction of 6-chloro-1,3-benzothiazol-2-yl semicarbazide, aromatic acid in $POCl_3$ produces 2-aryl-5-(6-chloro-1,3-benzothiazol-2-yl-amino-1,3,4-thiadiazoles in good yield. The precursor 6-chloro-1,3-benzothiazol-2-yl semicarbazide was obtained by the reaction of 6-Chloro-2-amino benzothiazole, CS_2 and hydrazine hydrate in ethanol and ammonia solution. The synthesized thiadiazoles have showed significant antimicrobial activities [43].



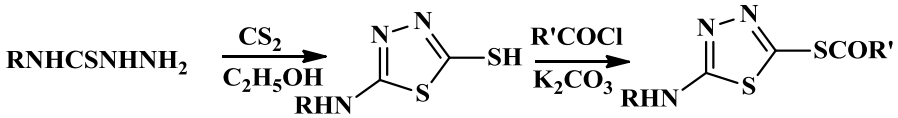
Scheme 16

A series of *N*-(5-phenyl)-1,3,4-thiadiazole-2-ylbenzamide derivatives synthesized from thiosemicarbazide and benzoyl chloride in phosphorous penta chloride. The synthesized compounds have been evaluated for their analgesic activity, study revealed that all the animals receive 0.6%v of 10ml/kg body weight of acetic acid intraperitonially and number of writhing was recorded after 10 min upto next 15 min. the same groups animals were used next day for evaluating analgesic activity [44]. 2-Amino-5-aryl-1,3,4-oxadiazoles were prepared by heating a mixture of aromatic carboxylic acids, thiosemicarbazine and conc. sulphuric acid, then these were converted to schiffs bases by irradiating a mixture of 2-amino-5-aryl-1,3,4-oxadiazoles and aldehydes for 3 min at 40% power. The products showed promising antidiabetic activity [45].



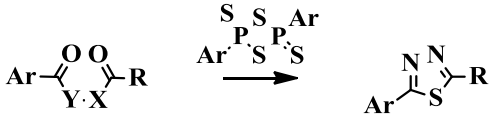
Scheme 17

A series of *S*-[5-(phenylamino)-1,3,4-thiadiazole-2- yl] benzenecarbothioate and *S*-[5-(phenyl amino)-1,3,4-thiadiazole-2-yl] ethanethioate were prepared by refluxing benzoyl chloride and acetyl chloride in presence of potassium carbonate with 5-(phenyl amino)-1,3,4-thiadiazole-2-thiol. 5-(Phenylamino)-1,3,4-thiadiazole-2-thiol were prepared by cyclization of arylthio-semicarbazide with carbondisulphide. Some of these thiadiazole derivatives exhibited significant antibacterial and antifungal activities [46].



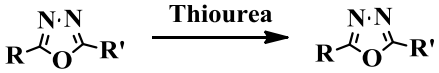
Scheme 18

Cyclization of the thiosemicarbazones with acetic anhydride produced 4,5-dihydro-1,3,4-thiadiazolyl derivatives. These compounds were evaluated for inhibitory effect on tyronase enzyme and results indicated some of these thiadiazole derivatives possess moderate inhibitory effect on tyronase enzyme [47]. Thionation of *N,N'*-acylhydrazines with the use of a fluorous Lawesson's reagent leads to 1,3,4-thiadiazoles in high yields. The isolation of the final products is achieved in most cases by a simple filtration [48].



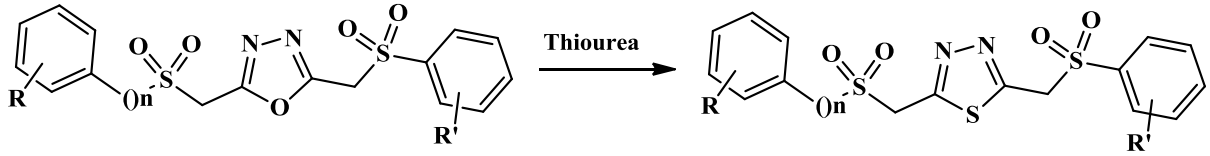
Scheme 19

In order to to improve the yield and purity of the products, easy isolation or work up; researchers developed the new synthetic strategies, innovative methods, new reagents for the synthesis of thiadiazoles. For instance, Rai and co-workers introduced thiourea as a new reagent for the direct conversion of 2.5-diaryl- 1,3,4-oxadiazole to 2.5-diaryl-1,3,4-thiadiazole. They observed that, when the reaction of 1,3,4-oxadiazoles with thiourea was carried out at retlux temperature for 3 to 4 days, only 2 to 5% of oxadiazoles gets converted to thiadiazoles. In order to reduce the reaction time and to increase the yield, they carried out in a sealed tube at water bath temperature for 10-15 hr and obtained the yield in 65-72% [49].



Scheme 20

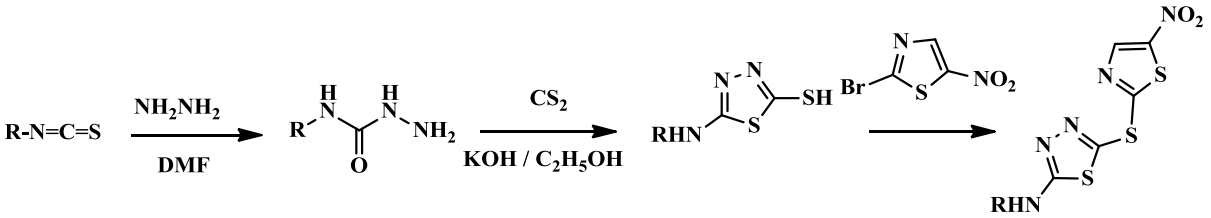
A method of using thiourea as thionating agent for the transformation of oxadiazoles to thiadiazoles has been widely accepted and implemented. For instance, the unsymmetrical 1,3,4-oxadiazole when treated with two fold excess thiourea in tetrahydrofuran produced 2-(benzylsulfonylmethyl)-5-(arylsulfonylmethyl)-1,3,4-thiadiazole [50].



Scheme 21

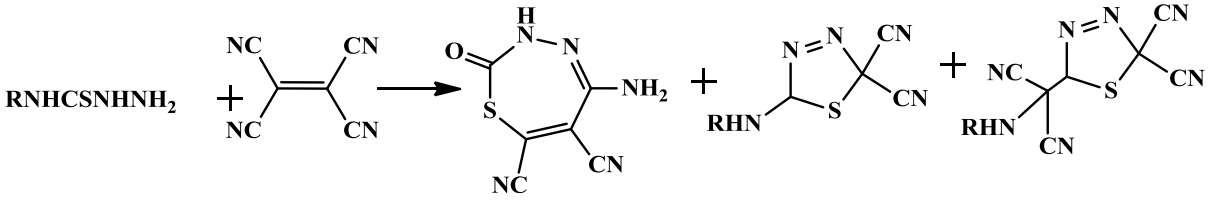
A series of fluorine-containing thiadiazoles were synthesized from thiosemicarbazides by conventional method by heating mixture of thiosemicarbazide and 2N sodium hydroxide, by green synthesis such as ultrasonification and microwave irradiation. The ultrasonication method, the reaction mixture was subjected to ultrasonic irradiated for 30-35 min at room temperature. The products obtainned in all the three methods were compared, and the study reports that the green

synthesis yielded more percentage of yield. Other than this these methods are environment frienadly and economically cheaper. The thiadiazoles synthesized have exhibited antimicrobial activity [51]. A series of thiadiazole derivatives synthesized found potential allosteric, substrate competitive inhibitors of the protein kinase JNK. The study showed that these compounds are potent and selective JNK inhibitors targeting its JIP-1 docking site [52].



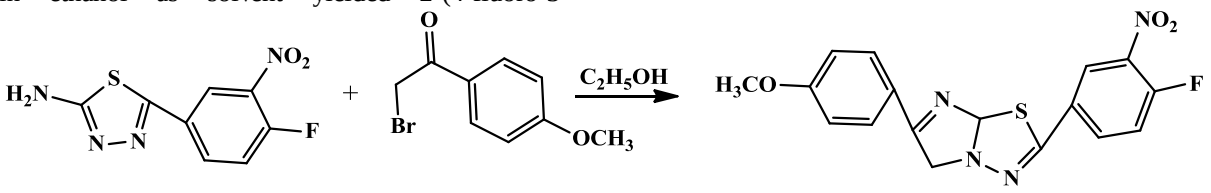
The microwave (MW) irradiation provide enhanced reaction rate and improved product field in chemical synthesis and has been extending to modern drug discovery in complex multi-step synthesis and it is proving quite successful in the formation of a variety of carbon-heteroatom bonds. For instance, using this MW irradiation technique; 4-(Substituted benzylidene)-1-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-phenyl-1*H*-imidazol-5(4*H*)-one was prepared by the condensation reaction of 4-arylidene-2-phenyloxazol-5(4*H*)-one and 5-amino-1,3,4-thiadiazole-2-thiol [53].

Thiosemicarbazides reacted with tetracyano-ethene in ethyl acetate with admission of air to form the 7-amino-2-organylimino-2,3-dihydro-1,3,4-thiadi azepine-5,6-dicarbonitriles), 7-amino-1-organylimino-3-oxo-pyrazolo[1,2-c]-1,3,4-thiadiazole-5,5,6-tricarbonitriles, 7-amino-1-organyl-imino pyra zolo[1,2-c]-1,3,4-thiadiazole-3,3,5,5,6-pentacarbo nitriles in moderate yields. Rationales for the observed conversations are presented [54].



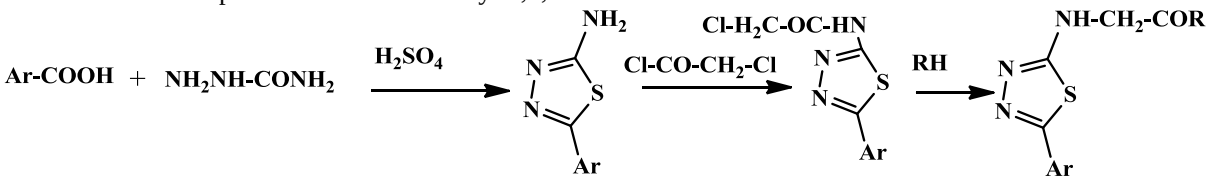
Scheme 22

5-(4-Fluoro-3-nitrophenyl)-1,3,4-thiadiazol-2-ylamine, on reflux with 4-methoxyphenacyl bromide in ethanol as solvent yielded 2-(4-fluoro-3-nitrophenyl)-6-(4-methoxyphenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole [55].



Scheme 23

A large number of 1,3,4-thiadiazoles have been reported to exhibit antidiabetic properties. For instance; 2-Amino-5-aryl-1,3,4-thiadiazole synthesized by the reaction of thiosemicarbazide, aromatic carboxylic acid in conc. sulphuric acid. Then the compound 2-Amino-5-aryl-1,3,4-thiadiazole was converted to chloroacetyl derivative by its reaction with chloroacetyl chloride in the presence of sodium acetate in acetic acid. Finally it was transformed in to *N*-(5-(4-aminophenyl)-1,3,4-thiadiazole-2-yl)-2-chloroacetamide [56].

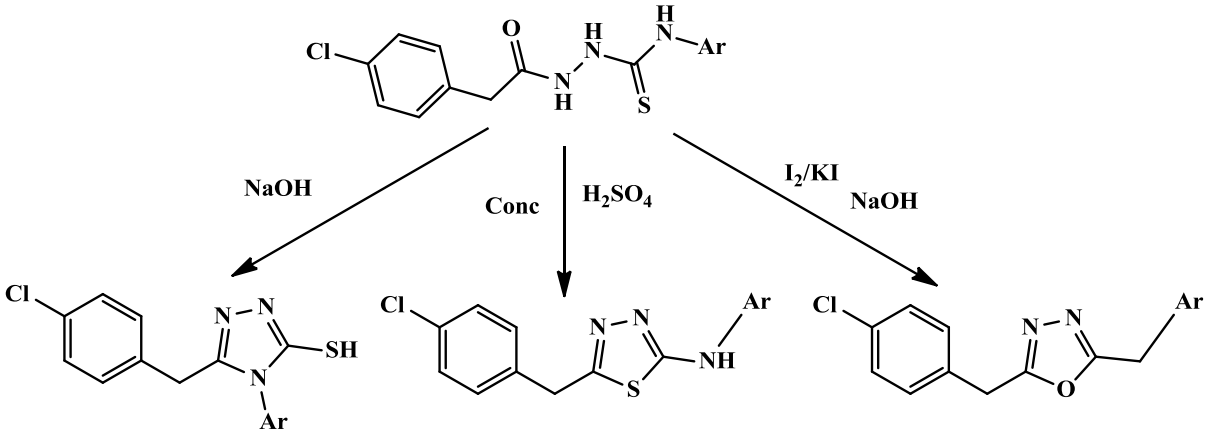


Scheme 24

The compounds synthesized were evaluated for their antidiabetic activity using wistor albino rats by Alloxan induced tail tipping method. The results of the study revealed that the synthesized compounds exhibited significant antidiabetic activities.

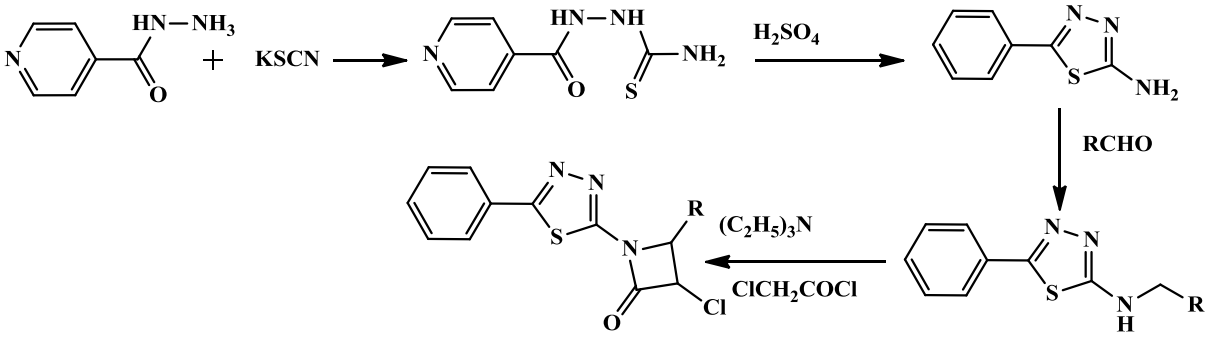
Synthesis of 1.3,4-thiadiazoles

Thiadiazoles can be synthesized from mainly thiosemicarbazide or hydrazide that is thiadiazole can cyclized from thiosemicarbazide or hydrazide by methods like conventional method, ultrasound or microwave using catalyst like H_2SO_4, $POCl_3$, CS_2, polyphosphoric acid and HCl. Important new general routes of 1,3,4-thiadiazole have been reported, The major routes are: 2-(2-(4-chlorophenyl)acetyl)-*N*-aryl hydrazine carbothioamides were prepared by reacting 4-chlorophenyl acetyl hydrazide and aryl isothiocyanate in the presence of ethanol. Various 5-(4-chloro-benzyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols 2,5-(4-chloro benzyl)-N-aryl-1,3,4-thiadiazole-2-amine have been prepared by the cyclization with sodium hydroxide, sulphuric acid and iodine in potassium iodide in presence of sodium hydroxide [57].



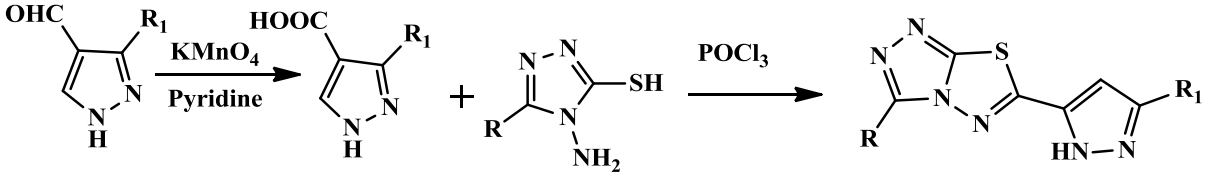
Scheme 25

The 5-(pyridine-4yl)-1,3,4-thiadiazole-2-amine has been synthesized by reacting isonicotino-hydrazide with potassium thiocyanate on further cyclo condensation with concentrated sulphuric acid. The compound reacted with various aromatic aldehydes in the presence ethanol which on further cycloaddition with chloroacetyl chloride and triethylamine in DMF [58].



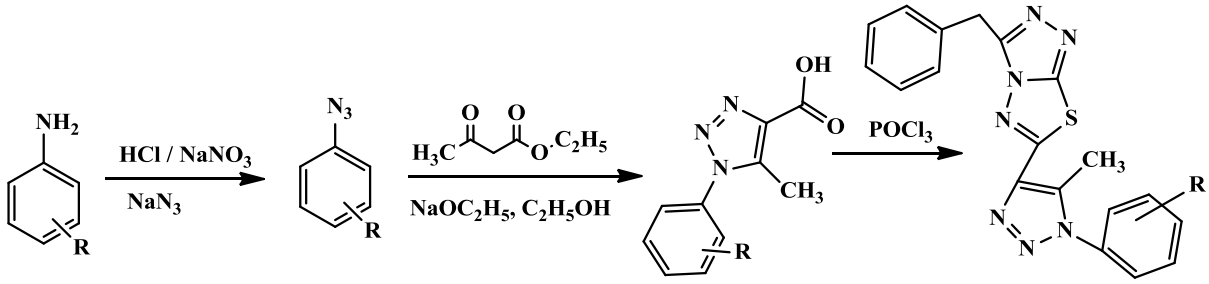
Scheme 26

The 3,6,-disubstituted 1,2,4-triazolo(3,4-b)-1,3,4-thiadiazole from 3-substitued-4-amino-5-mercapto-1,2,4-triazoles and 3-substituted 4-caboxy pyrozoles, naphthyl oxymethyl and flurophenyl group as substituent. Presence of fluorosubstituent and aromatic naphthalene ring was found to enhance activity. The difference in electro negativity between fluorine and carbon created a large dipole moment which contributed to the molecule ability to be engaged in intermolecular interactions [59].



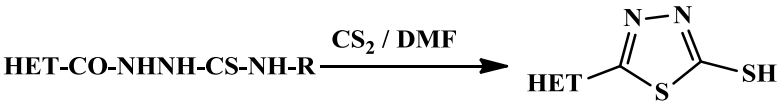
Scheme 27

The 4-amino-5-benzyl-4*H*-1,2,4-triazole-3-thiol with 5- methyl-1-aryl-1*H*-1,2,3-trazole-4-carboxylic acids in phosphorus oxychloride. It was established reaction performed with closuring thiadiazole ring. Thus by the reaction of 4-amino-5-benzyl-4*H*-1,2,4-triazole-3-thiol with 5-methyl-1-aryl-1*H*-1,2,3-triazole-4-carboxylic acid new 3-benzyl-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-yl)(1,2,4)-triazolo(3,4-b)(1,3,4)thiadiazole [60].



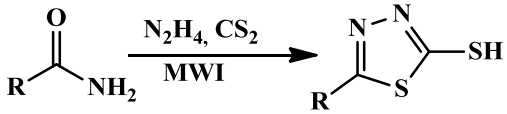
Scheme 28

The thiosemicarbazide with carbon disulphide and DMF under result formation of 5-(3-aryl-1*H*-pyrazole-5-yl)-2-mercapto-1,3,4-thiadiazoles [61].



Scheme 29

The thioamides were treated with hydrazine hydrate followed by carbon disulphide solution. The reaction mixture was irradiated in a microwave oven to yield 5-substituted-2-mercapto-1,3,4-thiadiazoles [62].

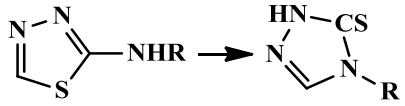


Scheme 30

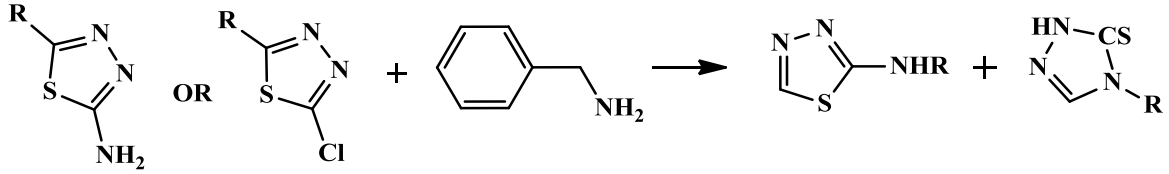
Reactivity of the 1, 3, 4-thiadiazoles

Rearrangements and Ring Opening Reaction

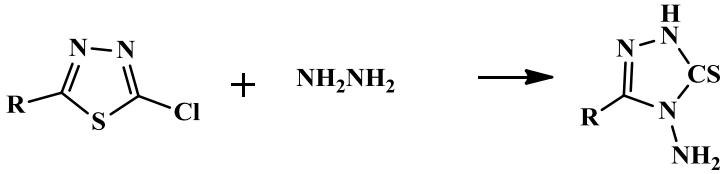
The 1,3,4-thiadiazole ring is rather susceptible to attack by strong neucleophile. Thus the parent compound is stable to acids but is readily cleaved by bases [63]. 2-Amino- and 2-hydrazino-1, 3, 4-thiadiazole can be rearranged to 1,2,4-triazoline-3(2)-thiones. Goerdeler and Galinke43 showed that 2-amino- and 2-methylamino-1, 3, 4-thiadiazole (R=H and CH_3) are rearranged by methylamine in methanol at 150 ^oC to the isomeric triazolinethiones**.**



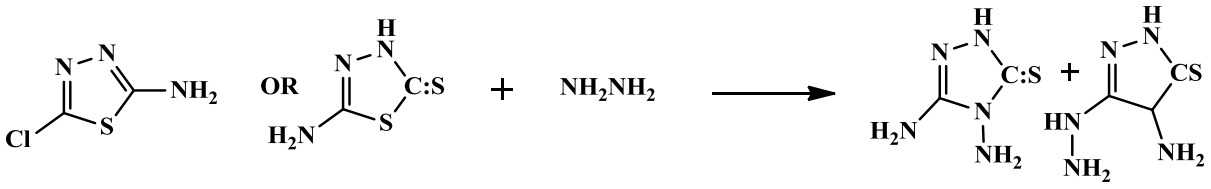
2-Amino-1,3,4-thiadiazole (R=H), when refluxed with benzyl amine in xylene, gave a mixture of about equal amount of 2-benzylamino-1,3,4-thiadiazole (R=CH_2Ph) and 4-benzyl-1,2,4-triazolin-3(2)-thione (R=CH_2Ph). The same two compounds were formed in the reaction between 2-chloro-1, 3, 4-thiadiazole and benzylamine [64,65].



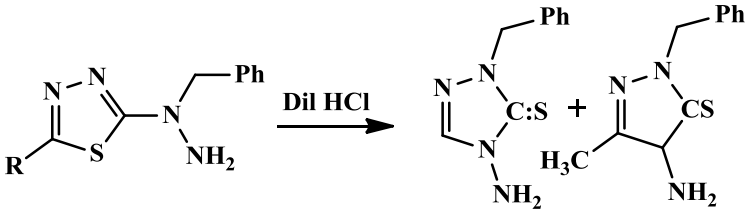
Similarly, 2-alkyl-5-chloro-1,3,4-thiadiazole reacted with a large excess of hydrazine hydrate on heating to give 4-amino-1,2,4-triazolin 4-amino-1,2,4-triazolin-3(2)-thiones**.**



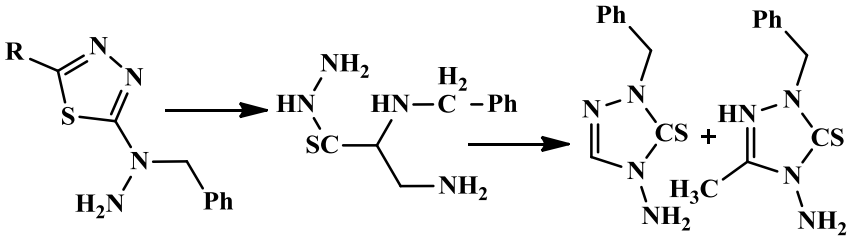
Under the same conditions, 2-amino-5-chloro-1,3,4-thiadiazole and 2-amino-1,3,4-thiadiazolin-5(4)-thione gave a mixture of 3,4-diamino-1,2,4-triazoline-5(1)-thione and 3-hydrazino-4-amino-1,2,4-triazoline-5(1)-thione. 2,5-Dichloro- and 2,5-dimercapto-1,3,4-thiadiazole gave only [66].



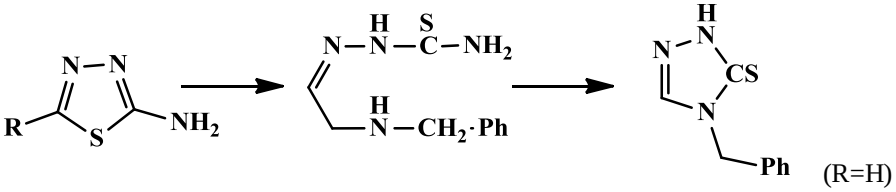
Similar rearrangements can be affected by acids. When 1-benzyl-1-(1,3,4-thiadiazole-2-yl) hydrazine was refluxed with dilute hydrochloric acid, the triazolinethion (R=H) was formed in quantitative yield. When the reaction was performed in the presence of some acetic acid, a mixture of (R=H) and ($R=CH_3$) was formed [67].



In this acid catalyzed rearrangement 2-benzylthiocarbohydrazide is likely an intermediate.



The rearrangement of by benzyl amine probably proceeds with ring opening to an amidrazone followed by recyclization to ($R=CH_2Ph$).



Substitution Reaction

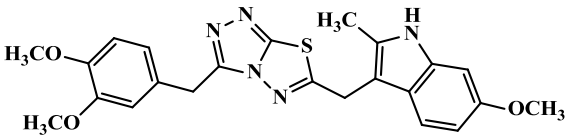
Although the 1,3,4-thiadiazole ring is classed as π-excessive according to Albert [68], the presence of two nitrogen atoms of pyridine type in the ring leaves the carbon atoms with rather low electron density, and consequently no electrophilic substitution in the unsubstituted 1,3,4-thiadiazole ring have been recorded. A bromine adduct of the simple 1,3,4-thiadiazole, but it decomposed and lost bromine in the air. Nitration, even under drastic condition could not be achieved [63]. The 2-phenyl-1, 3, 4-thiadiazole to a mixture of concentrated nitric acid and sulphuric acid at 0 ^oC and obtained a mixture of the three isomeric 2-nitrophenyl-1,3,4-thiadiazole in the ratio *p: m: o* = 2:3:1, but no 2-phenyl-5-nitro-1,3,4-thiadiazole [69]. A 2-amino group does activate the ring towards electrophilic agents,prepared2-amino-5-bromo-1,3,4-thiadiazole by bromination of 2-amino-1,3,4-thiadiazole in 40% hydro-bromic acid. The product was not isolated but was diazotized to give 2,5-dibromo-1,3,4-thia-diazole [70].

Recent advancement in the therapeutic potential of thiadiazole derivatives

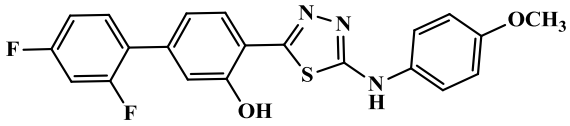
During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial, antituberculosis, anti-inflammatory, anticonvulsants, antihypertensive [71-76], antioxidant, anticancer and antifungal [77-81] activity.

Analgesic and Anti-inflammatory Activity

Several 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole and their dihydro analogues showed anti-inflammatory and analgesic activity. Compounds **1** showed good anti-inflammatory and analgesic activities [72]. The 2-substituted-1,3,4-thiadiazoles, is 5-(2',4'-Difluoro-4-hydroxybiphenyl-5-yl)-4-(4-methoxyphenyl)-1,3,4-thiadiazole (**2**) presented good analgesic activity [82].

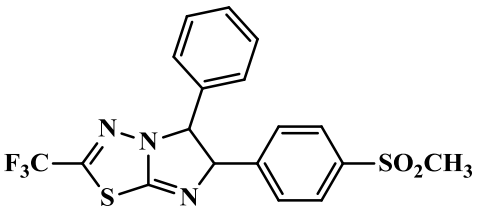


Compound 1

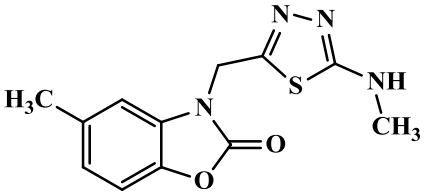


Compound 2

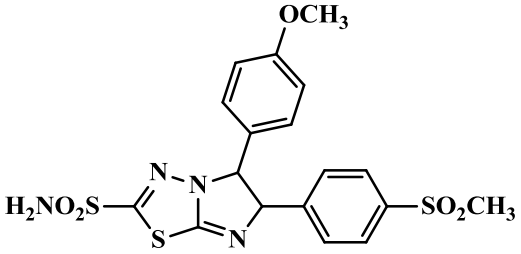
2A series of 2-trifluoromethyl/sulfonamido-5,6-diarylsubstituted imidazo [2,1-b]-1,3,4-thiadiazole derivatives, compounds **3** and **4** showed selective inhibitory activity toward COX-2 over COX-1. These compounds also exhibited significant anti-inflammatory activity, which is comparable to that of celecoxib. Some 1,3,4-thiadiazole derivatives were found as analgesic effects of compound **5** were higher than those of both morphine and aspirin [83-85].



Compound 3

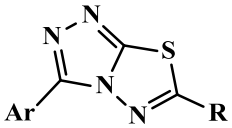


Compound 4

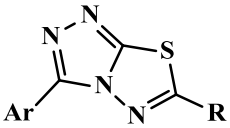


Compound 5

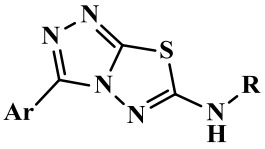
Currently available non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, flurbiprofen, fenbufen and naproxen exhibit gastric toxicity. Modification of the carboxyl function of representative NSAIDs resulted in increased anti-inflammatory activity with reduced ulcerogenic effect [86,87]. Certain compounds bearing 1,2,4-triazole and 1,3,4-thiadiazole nuclei possess significant anti-inflammatory activity with reduced GI toxicity. Replace the carboxylic acid group of 2-(4-isobutylphenyl) propanoic acid and biphenyl-4-yloxy acetic acid by a composite system, which combines both the triazole and the thiadiazole nucleus. Seven cyclized compounds 6a, 6b, 7a, 7b, 8a, 8b and 8c were found to have anti-inflammatory properties comparable to their standard reference drugs ibuprofen and flurbiprofen [88].



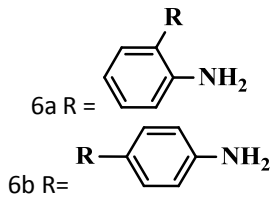
Compound 6

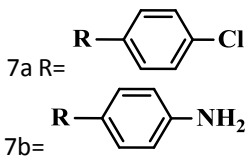


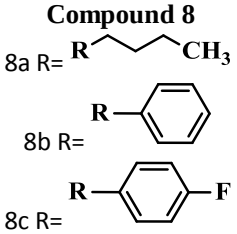
Compound 7



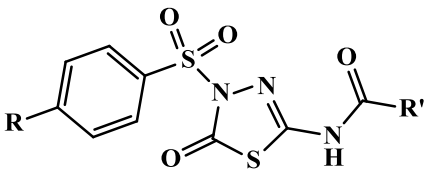
Compound 8



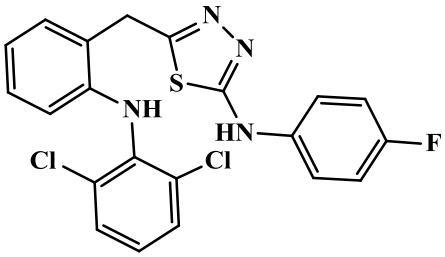




All compounds exhibited moderate to good analgesic activity. These compounds were also showed superior GI safety profile along with reduction in lipid peroxidation as compared with ibuprofen and flurbiprofen. Two series of N-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides (**9**) possess good analgesic activity and also fair anti-inflammatory activity. Ulcerogenic and irritative action on the gastrointestinal mucosa, in comparison with indomethacin is low [89]. The 1,3,4-thiadiazole derivatives of diclofenac showed anti-inflammatory activity from 79.04% to 82.85%. The maximum activity (82.85%) was shown by thiadiazole derivative that is compound **10** having *p*-fluoro phenyl amino group at second position [90].

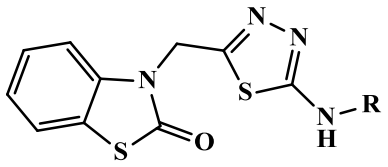


Compound 9



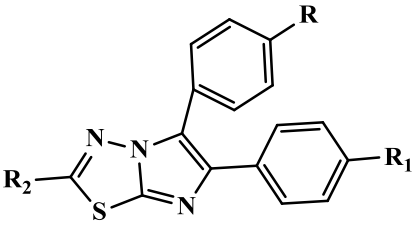
Compound 10

2-(2-oxobenzothiazolin-3-yl)methyl)-5-aminoalkyl/aryl-1,3,4-thiadiazoles (**11**) were showed analgesic and anti-allergic activity [91]. 2-trifluoromethyl/Sulfonamido-5,6-diaryl substituted imidazo(2,1-b)-1,3,4-thiadiazoles (**12**) showed cyclooxygenase-2-inhibitiors activity and used as potential the anti-inflammatory activity using standard drug Celecoxib at concentration 10 mg/kg [92].



11

R=ethyl, methyl, allyl, phenyl,cyclohexyl

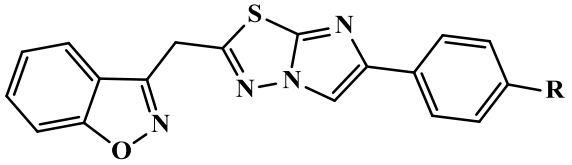


12

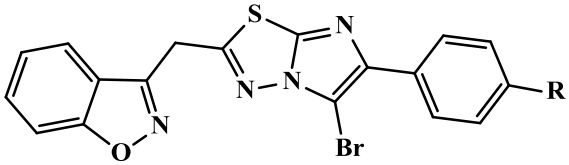
R=H,OCH_3; R_1= SCH_3, SO_2CH_3; R_2=CF_3, SO_2NH_2

Antimicrobial and Antifungal Activity

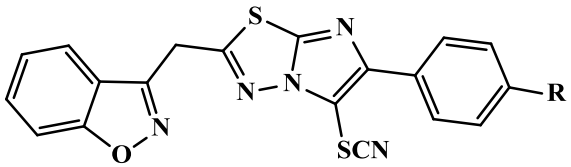
The methylene bridged benzisoxazolyl imidazo [2,1b] [1,3,4]-thiadiazoles were investigated as antibacterial and some compounds showed moderate to good bacterial inhibition. Particularly compounds **13a, 13b, 14a, 14b** and **15a** have shown very good antibacterial activity. Compound **15a** has exhibited highest antibacterial activity. The high activity is attributed to the presence of electron withdrawing chloro- and bromo- functional groups. Antifungal results indicated that compounds **13b, 13c** and **15b** have shown good activity. Compound **13b** showed very good antifungal activity comparable to that of standard [93].



Compound 13a-c
13aR=Cl, 13bR=Br, 13cR=3-coumarinyl

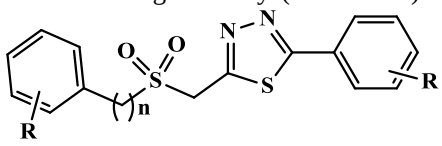


Compound 14a-b
14a R=Cl, 14b, R=NO_2

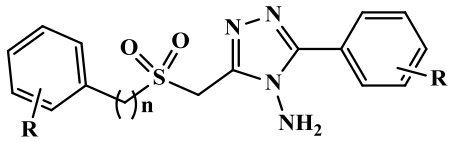


Compound 15a-b 15a, R=Cl, 15b, R=OCH_3

The 2-(arylmethanesulfonylmethyl)-5-aryl-1,3,4-thiadiazoles **16a–d**, 3-(arylmethane-sulfonyl methyl)-5-aryl-4H-1,2,4-triazol-4-amines 71a–d exhibited high activity (22–39 mm) on both Gram (+ve) and Gram (-ve) bacteria. In fact, compounds **16d** and **17d** showed pronounced activity (31–39 mm) towards Gram (+ve) bacteria [94].



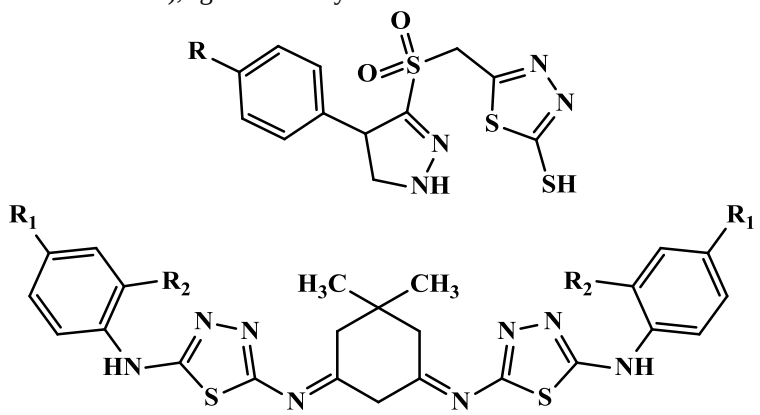
Compound 16a-d



Compound 17a-d

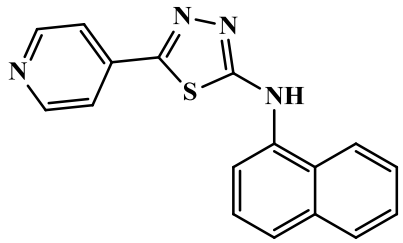
a: R = H, R' = H
b: R = H, R' = 2-Cl
c:R=4-Cl,R'=H
d: R = 4-Cl, R' = 2-Cl
n = 0 (1,3,5,7,9,11)
n = 1 (2,4,6,8,10, 12)

Compounds 2-(4-chlorobenzylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (16d) displayed greater activity against spore germination of tested fungi A. niger, F. solani and C. lunata. Some sulfone-linked bis heterocycles, compounds **19a** showed excellent activity against Gram-positive bacteria (inhibitory zone >25 mm), good activity against Gram-negative bacteria (inhibitory zone >20 mm). The compounds (**19a-c**) showed high inhibitory effect towards tested fungi [95]. Biological studies of *bis* thiadiazole/triazole (**20**) by sonication as potential antibacterial activity using standard drug Ampicillin Trihydrate at concentration 50µg/ml [96].



Compound 19a-c Ra =H, b=CH_3, c=Cl R_1=H, CH_3, Cl, OCH_3; R_2=H, CH_3, Cl,

Antimicrobial activity of some pyridyl and napthyl substituted 1,2,4-triazole and 1,3,4-thiadiazole derivatives (**21**) against *S. aureus* and *E. coli* [97]. Antibacterial activity of some *N,N*-(5-(6-(4-subsitutedphenyl) imidazo(2,1-b) (1,3,4)-thiadiazole-2-yl)-pyrimidine-2,4-diyl) di acetamide derivatives (**22**) against *E. coli*, *Staphylococcus aureus* and *Bacillus subtillis* using cupplate-agar diffusion method using standard drug Methotrexate at concentration 50 µg/ml [98].



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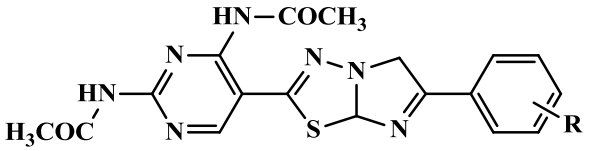
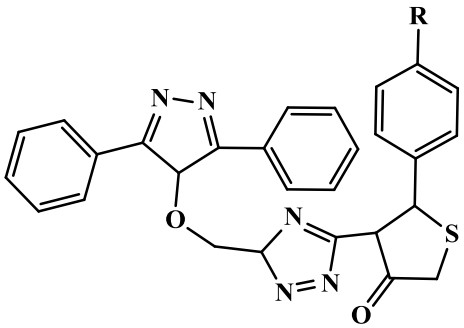


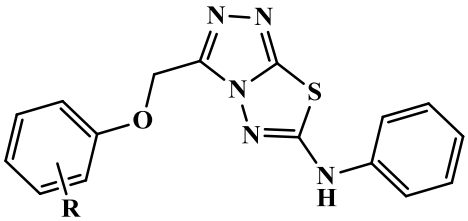
22 R=Br,CH_3, OCH_3, H, NO_2

Antifungal activity

Antifungal activity of 5-(3,5-diphenyl pyrazol-4-yloy methyl)-2-(4-oxo-2-substituted phenyl-3-thiazolidinyl)-1,3,4-oxidiazoles/Thiadiazoles and related compounds (**23**) against *F. oxysporum*, *C. capsicum* and *R. solani* using standard drug Dimethyl formamide at concentration 25 µg/ml [99]. Fungicidal activities of 3-aryloxymethyl-6-substituted- 1,2,4-triazolo(3,4-b)-1,3,4-thiadiazoles (**24**) against species *A. flavus* and *A. niger* using standard drug Dithane at concentration 100 ppm [100].



23 R=OMe, H

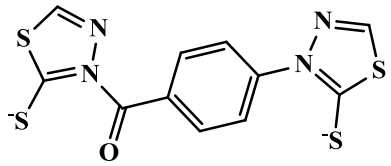


24 R=CH_3, Cl, 2,4-Cl_2, 4-Cl, 3-CH_3, H

Antitubercular activity

The 3-(2-sulphido-1,3,4-thiadiazolium-4-carbonylphenyl) syndones and 4-(4-(2-sulphido-1,3,4-thiadiazolium)benzoyl)-1,3,4-thiadiazolium-2-thiolates from 3-(4/3-(hydrazine carbonyl)phenyl) syndones (**25**), and their antimicrobial and antitubercular (anti-TB) activity against *M. tuberculli* using standard drug Cotrimoxazole and Fluconazoleat concentration 100 µg/ml [101]. Bioactivity of *s*-triazolo

(3,4-b)(1,3,4)thiadiazoles, *s*-triazolo (3,4-b)(1,3,4) thiadiazines and *s*-triazolo(3,4:2,3)-thiadiazino(5,6-b)quinoxaline (**26**) as potential anti-TB activity against *M. tuberculli* using standard drug Rifampicin at concentration 0.03 µg/ml [102].



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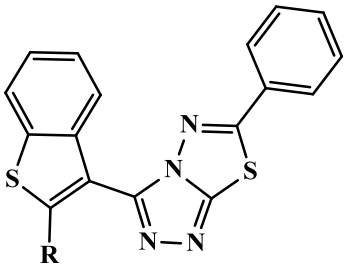
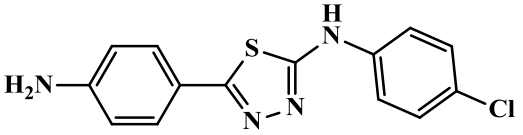
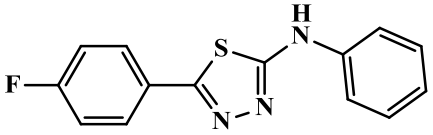
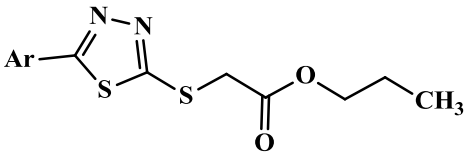


26 R=NHCOCH$_3$

Thiadiazole derivative 2-(4-chlorophenylamino)-5-(4-aminophenyl)-1,3,4-thiadiazole **27a** showed 57% inhibition against *M. tuberculosis*. Further they found that compound **27b** has exhibited the highest inhibitory activity (69%) against in vitro growing *M. tuberculosis* [103,104]. This compound while not active enough to be considered as therapeutics, are definitely lead compounds in the search for novel agents to combat resistance. Two series of 2- and 3-[5-(nitro aryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters and screened for anti-tuberculosis activity against *M. tuberculosis* and found that the compound **28** that is Propyl 3-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio]-propionate was the most active one [105].



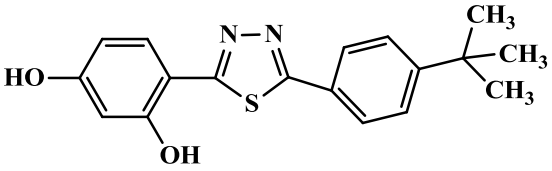


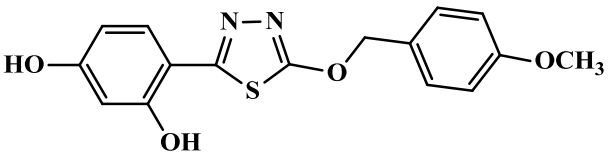


Compound 27a-b **Compound 28 Ar= 5-nitro-2-thienyl**

Anticancer Activity

A series of 5-substituted 2-(2,4-dihydroxy-phenyl)-1,3,4-thiadiazoles were evaluated for their antiproliferative activity against the cells of human cancer lines. Compounds **29** and **30** of different structures prove to be the most active. They exhibited higher inhibitory activity against T47D cells (human breast cancer cells) than cisplatin [106].



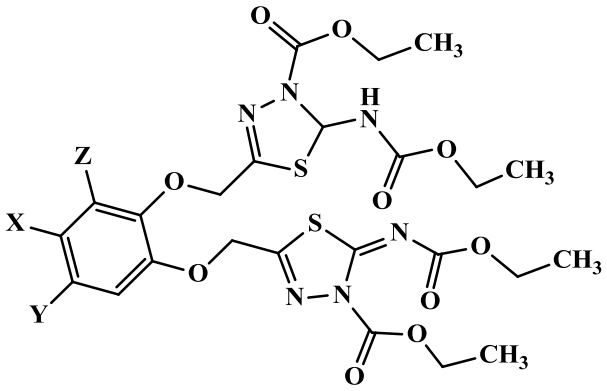


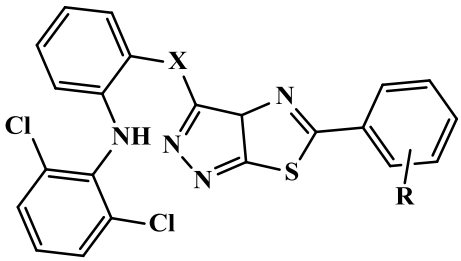
Compound 29 **Compound 30**

Antitumor Activity

2-acylamino 2-aroylamino and ethoxycarbonyl imino-1,3,4-thiadiazoles (**31**) as antitumor agents [107].

Cytotoxic activity of 3,6-disubstituted 1,2,4- triazole-(3,4-b)-1,3,4-thiadiazoles (**32**) as potential antileishmanial activity aganist standard drug Doxorubicin at concentration 10µM [108].

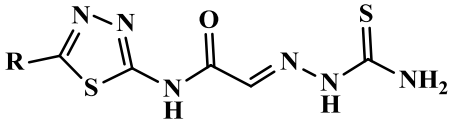




31 X=H, Y=H, Z=H,OCH_3 **32**R=-3-Chloro, -4-Chloro, -4-nitro, -2-methoxy, X= $-CH_2$, $-CH_2COOCH_2$

Antiviral Activity

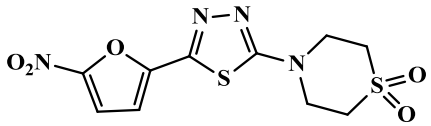
The *N*-(5-Aryl/aryloxymethyl-1,3,4-thiadiazole-2-yl)glyoxylamide thio-semicarbazone (**33**) as potential antiviral and antifungal agents against *Alternaria brassicae* and *Helminthosporium oryzae* using standard drug Bavistin and Dithane at concentration 45µg/ml [109].



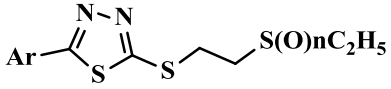
R=aryloxy methyl

Anti-Helicobacter pylori activity

Helicobacter pylori, is a Gram-negative bacterium, causes gastric, duodenal ulcers, and gastric cancer. In vitro anti-*H. pylori* activity of N-[5-(5-nitro-2-heteroaryl)-1,3,4-thiadiazol-2-yl]thiomorpholines and some related compounds. They found that nitrofuran analog (**34**) containing thiomorpholine S, S-dioxide moiety was the most potent compound tested [110]. A series of 5-(nitroaryl)-1,3,4-thiadiazoles bearing certain sulfur containing alkyl side chain similar to pendent residue in tinidazole molecule were evaluated against *H. pylori*. The compound **35** containing 2-[2-(ethylsulfonyl)ethylthio]-side chain from nitrothiophene series was the most potent compound tested against clinical isolates of *H. pylori*, however, nitroimidazoles **35b** and **36c** were found to be more promising compounds because of their respectable anti-*H.pylori* activity [111].



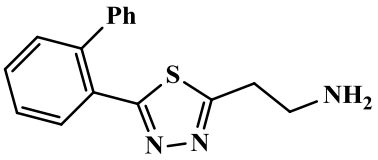
Compound 34



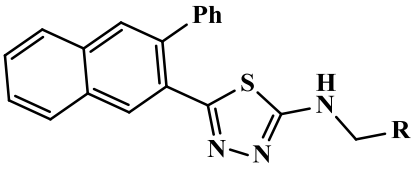
Compound 35a-c **36a,** Ar=5-NO_2-thiophene, n=2; **36b,** Ar=1-Me-5-NO_2-imidazole n=2; **36c,** Ar=1-Me-5-NO_2-imidazole n=0

Anticonvulsants Activity

The anticonvulsants properties of a number of substituted 2-hydrazino-1,3,4-Thiadiazole, compound 2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-Thiadiazole (**37**) possess potent anticonvulsants properties in rat and mice and compared with phenytoin, phenobarbital and carbamazepine in a number of test situations [112]. A number of compounds such as compound **38a** and **38b** showed anticonvulsants activity. These two compounds may be considered promising for the development of new anticonvulsant agents [113].



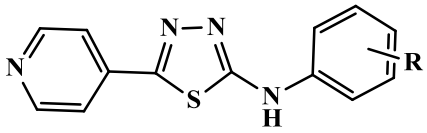
Compound 37



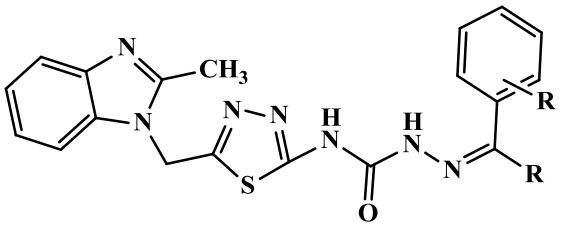
Compound 38a-b: 38aR=Ethyl; 38b: R=*m*-fluorophenyl

Anticonvulsant Activity

Anticonvulsant activity of substituted oxidiazole and thiadiazole derivatives (**39**) using eletro-covulsometer using standard drug Phenytoin Sodium at concentration 25 mg/kg [114]. The 2,5-disubstituted 1,3,4-thiadiazoles (**40**) as potential anticonvulsant activity using standard drug Carbamazepine and Phenytoin at concentration 30 and 100 mg/kg [115].



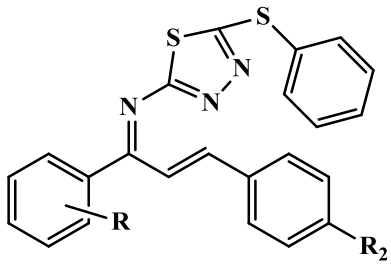
39 R=H, o-CH_3, p-CH_3, p-OCH_3, p-Cl



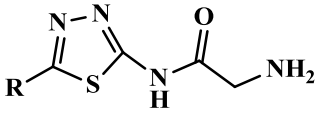
40 R=C_6H_5, R_1=H, 4-OH, 4-NO_2, 4-OCH_3

Antidepressant Activity

A imine derivatives of 5-amino-1, 3, 4-thiadiazole-2-thiol, and their anti-depressant activity. Two compounds namely 5-{[1-(4-chlorophenyl)-3-(4-methoxy-phenyl)prop-2-en-1-ylidene]-amino}-5-benzylthio-1,3,4–thiadiazole (**41a**) and 5-{[1-(4-chlorophenyl)-3-(4-dimethyl-aminophenyl)-prop-2-en-1-ylidene]amino}-5-benzyl thio-1,3,4-thiadiazole (**41b**) have shown significant anti-depressant activity, which decreased immobility time by 77.99% and 76.26% compared to the standard imipramine (82%). These compounds in the series have passed neurotoxicity tests also [116]. Biological activity of 2-substituted ethanamido-5- alkyl-1,3,4-thiadiazoles (**42**) as potential the CNS depressant, spasmolytic activity using standard drug Acetylcholine at concentration 12 to 32 mg/ml [117].



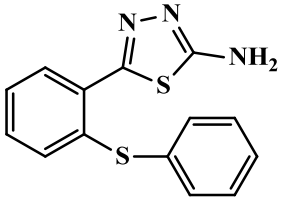
Compound 41a-b
41a R_1= OCH_3, R_2=Cl; 41b, R_1=$(CH_3)_2N$, R_2=Cl



43

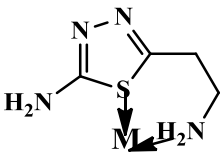
Muscle Relaxant Activites

Anticonvulsant and muscle relaxant activities of substituted 1,3,4-oxidiazole, 1,3,4-thiadiazole and 1,2,4-triazole using standard drug Diazepam at concentration 10ml/kg [118].



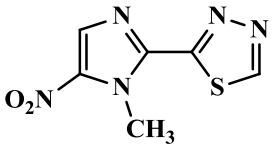
Metal Complexes

Biological activity of metal complexes of 5-(2-aminoethyl)-2-amino-1,3,4-thiadiazole as potential antifungal activity against *Aspergillus* and *Candida spp* using standard drug Clotrimazole at cocentration10µM [119].



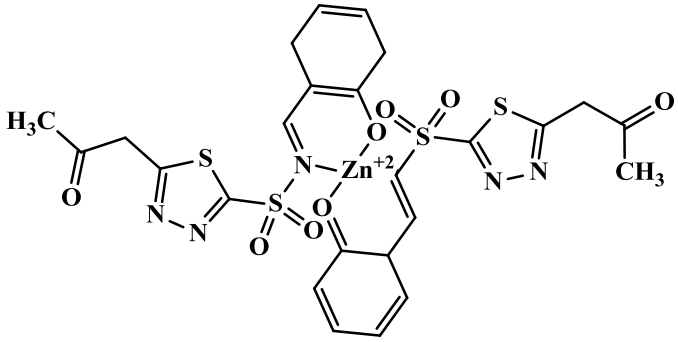
Antiprotozoal Activites

The 1-methyl-2-(1,3,4-thiadiazole-2-yl)-5-nitroimidazole and 1-methyl-2-(1,3,4-oxidiazoles-2-yl)-5-nitro-imidazole as potential antiprotozoal agents [120].



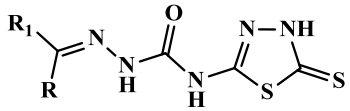
Diuretic Activites

Biological studies of Zn(II) complex of schiff base derived from 5-acetazolamido 1,3,4-thiadiazole-2-sulphonamide as potential diuretic agents using standard drug Acetazolamide [121].



Carbonic anhydrase inhibitor activity

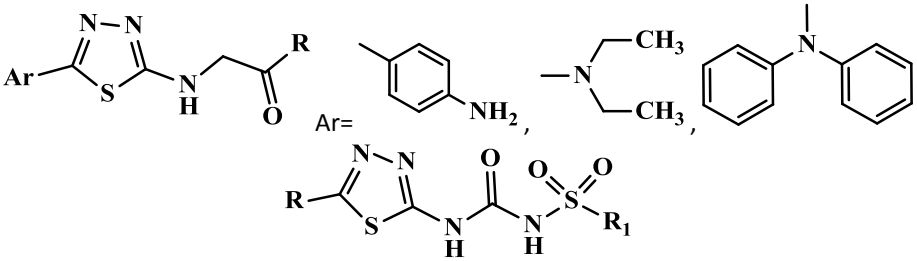
Docking studies of new 1,3,4-thiadiazole-2-thione derivatives with carbonic anhydrase inhibitory agents using standard drug Acetazolamide [122].



R=H, CH_3, C_6H_5, R_1=C_6H_5, 4-(OH)C_6H_4, 3(Br)C_6H_4, 4-(F)C_6H_4, C_6H_5, 3-pyridyl, 2-furyl,

Antidiabetic Activities

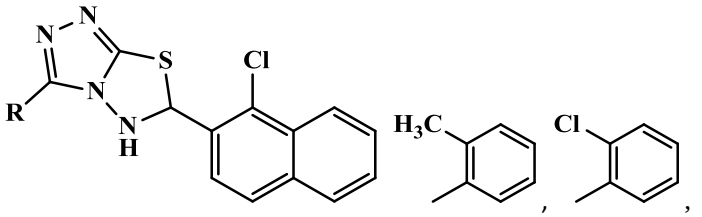
Biological evaluation of some 1,3,4-thiadiazoles as potential the anti-diabetic [123]. Biological activity of sulphanyl urea as potential anti-diabetic agent using standard drug Gliclazide at concentration 200mg/kg [124].



R= phenyl, methyl phenyl, chloro phenyl, methyl R_1= phenyl methyl

Antioxidant Activities

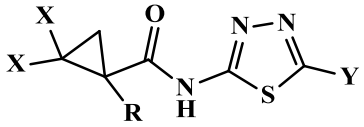
Biological activity of 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-*s*-trizolo (3,4-b) (1,3,4) thiadiazoles as potential the antioxidant and antibacterial agent against *Escherichia coli* and *Staphylococcus aureus* usingstandard drug Sodium Nitroprusside at concentration 5µM [125].



R = Phenyl, CH_3, C_2H_5, $CH_2CH_2CH_3$
R_1=H, OH, Cl, NO_2 R_2=OH, NO_2, Cl, R_3=OH, H, NO_2 R_4=H, OH, OCH_3

Acaricidal Activites

Acaricidal activity of *N*-(1,3,4-thiadiazole-2-yl)cyclo-propane carboxamides against *Tetranychus urticae* [126].



R=H, CH_3, C_2H_5, n-C_3H_7, i-C_3H_7; X=H, Cl, Br; Y=CF_3, CF_2CF_3, H, CH_3, C_2H_5

Discussion: The synthesis of 1,3,4-thiadiazoles that have been illustrates different approaches to the challenge of preparing these bioactive products and allows the synthesis of many novel chemical derivatives [127-132]. The 1,3,4-thiadiazoles are prepared by appropriate rearrangements, ring opening and substitution reaction. The area of the synthesis of 1,3,4-thiadiazole rings continues to grow, and the organic chemistry will provide more and better methods for the synthesis of this interesting heterocycle, allowing the discovery of new drug candidates more active, more specific and safer [133-140]. Thiadiazole are the most important classes of heterocyclic compounds and possess versatile type of biological activities.

Conclusion: The 1,3,4-thiadiazole have advantageous in the medicinal properties. Some 1,3,4- thiadiazole containing drugs having several pharmacological activity. Chemical properties of 1,3,4-thiadiazole have been reviewed in the last few years. This review provides a brief summary of the medicinal chemistry of 1,3,4-thiadiazole system and highlights some examples of 1,3,4-thiadiazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 1,3,4-thiadiazole is presented in sections by generalized synthetic methods.

References

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