



**A REVIEW ON 1, 3, 4-THIADIAZOLE AS A SINGLE REMEDY FOR THOUSANDS OF PRESCRIPTION**

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**ARTICLE INFO**

**ABSTRACT**

**Key Words**

Thiadiazole  
Antitubercular  
anti cancer



1, 3, 4- Thiadiazole represent a key motif nucleus in heterocyclic chemistry and a privileged structure in medicinal chemistry due to its broad-range pharmacological activity. Despite the progress in medicine over the past century, cancer and tuberculosis (TB) still remain the leading causes of death in the world and it makes essential needs to synthesize the compounds with thiadiazole as the core nucleus. This review article is focused on different synthetic routes of thiadiazole nucleus containing compounds. The review article also highlights different biological activities such as antitubercular, anticancer, antibacterial, anti-inflammatory, anti-HIV and enzyme inhibition activities.

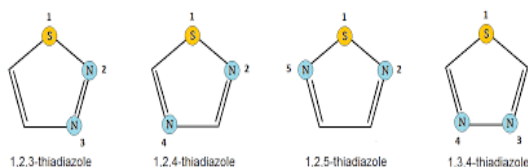
**INTRODUCTION**

A large number of organo-sulfur compounds occur in living and non-living objects. They belong to open chain, alicyclic, aromatic and heterocyclic types of compounds containing sulfur atom or atoms as a part of chain/ring or both in the structure. Isolation, identification and applications of these organo-sulfur compounds are useful in scientific, technical and pharmaceutical industrial growth<sup>(1)</sup>. During last three decades organo-sulphur chemistry developed at a much faster pace than any other branches of organic chemistry. Among the sulphur containing heterocyclic compounds, a lot of research in the field of thiadiazoles has been reported<sup>(2)</sup>. The 1,3,4-thiadiazole nucleus is one of the most important and well known heterocyclic, which is a common and integral feature of a variety of natural products and medicinal agents.

Thiadiazole belongs to the triheterocycle templet which composed of two electron-deficient carbon atoms these are interconnected with nitrogen atoms, and a sulfur atom with lone electron pairs. Thiadiazole is a 5-membered planar aromatic motif comprising a sulfur atom, which improves the lipid solubility of thiadiazole derivatives and hence their pharmacokinetics. The two-electron donor nitrogen system (N=C-S) and hydrogen-binding domain enhance the ability of thiadiazole molecules for binding with receptors<sup>(3,4,5)</sup>. Literature reveals that compounds having thiadiazole nucleus have wide spectrum of pharmacological activities such as antimicrobial, antitubercular, ulcerogenic, anti-inflammatory, analgesic, CNS depressant, anticonvulsant, anticancer, antioxidant, antiviral, antiepileptic properties etc.

Research in this area is still unexplored and is directed towards the synthesis of compounds with enhanced biological activity. (6-13)

**TYPES OF THIADIAZOLE:** Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. It acts as “hydrogen binding domain” and “twoelectron donor system” with a constrained pharmacophore which contains the five membered unsaturated ring structure composed of two nitrogen atoms and one sulfur atom. There are four isomeric types: 1,2,3-thiadiazole(1), 1,2,4-thiadiazole(2), 1,2,5-thiadiazole(3), 1,3,4-thiadiazole(4). (14)

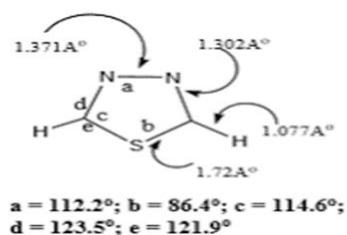


**CHEMISTRY:** Of the four possible thiadiazoles (I, II, III, IV) the chemistry of 1,3,4- thiadiazole (I) has attracted maximum attention since its discovery by Emil Fischer in 1882 on account of its compounds finding applications in agriculture, drugs, dyes and photographic materials.

- The ring system is less aromatic than benzene, thiophene, pyridine and the aromatic character is measured by  $\pi$  electron delocalization.
- The electron withdrawing nature of the nitrogen atoms ensures that electrophilic attack at carbon is very rare and nucleophilic substitution reactions are common.
- Electrophilic attack at the sulphur atom has been observed.
- 1, 3, 4 – thiadiazoles are weak base due to the inductive effects of extra hetero atoms and are readily alkylated and acylated at  $N_3$ .
- The ring is relatively stable in aqueous acid solutions but the ring gets cleaved in aqueous basic solutions.
- 1, 3, 4-thiadiazole core skeletons are subjected to various substitution

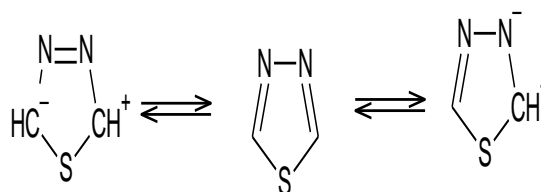
reactions with alkyl halides, acid chlorides, and sulfonyl chlorides to afford various drug like 2-amino-substituted 1, 3, 4- thiadiazole derivatives.

- When substituents are introduced into 2' or 5' position of this ring, the ring is highly reactive and forms different derivatives of thiadiazole easily.



### Molecular geometry figure for 1, 3, 4- thiadiazole

The canonical forms of 1,3,4-thiadiazole are given below of which I with dienic behavior is the maximum contributing structure. (5)



### CHEMICAL REACTIVITY OF 1, 3, 4- THIADIAZOLE (4,5)

1, 3, 4-thiadiazole undergoes following types of chemical reactions.

#### 1) Electrophilic substitution reactions:

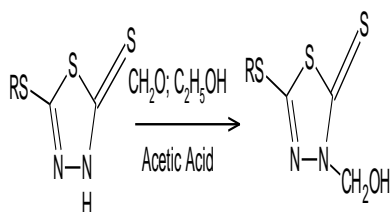
Electrophilic substitution reactions are chemical reactions in which an electrophile displaces a functional group in a compound and these are the characteristic reactions of aromatic compounds.

#### a) Electrophilic attack at nitrogen:

- The ring nitrogen react with electrophiles to form 1,3,4-thiadiazolium salts or 1,3,4-thiadiazol-2(3H)-ones depending on the tautomeris ability of the

substituents at the C-2 or C-5 positions.

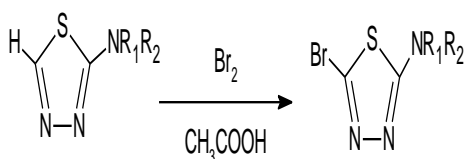
- *N*-alkylation is the most common electrophilic reaction of 1,3,4-thiadiazole, reactions with acyl and cyanogen halides as well as Mannich salts have also been reported. When treated with formaldehyde in the presence of ethanol and acetic acid forms hydroxyl methyl derivatives.



### b) Electrophilic attack at carbon:

- The reactions such as nitration, sulphonation, acetylation, halogenations normally do not take due to the low electron density of carbon atom in 1,3,4-thiadiazole.
- C-Acylation can be accomplished via rearrangement of intermediate *N*-acylthiadiazolium salts while radical halogenation can give chlorinated or brominated 2-halo-5-substituted thiadiazole.

2-amino substituted 1,3, 4-thiadiazoles react with bromine in acetic acid to give the 5-bromo derivatives.



### 2) Nucleophilic Substitution reactions:

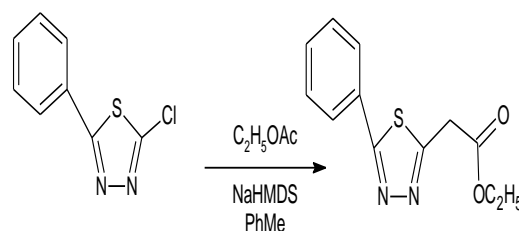
Nucleophilic substitution is a fundamental class of reactions in which an electron rich [nucleophile](#) selectively bonds with or attacks the positive or partially positive charge of an atom or a group of atoms to replace a [leaving group](#).

#### a) Nucleophilic attack at carbon:

Nucleophilic reactions at the carbon atoms of 1, 3, 4-thiadiazoles occur readily owing to

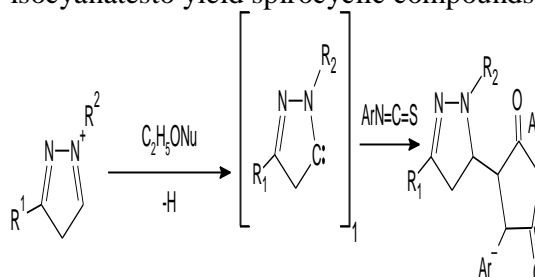
the electron deficient nature of the ring. Halo-substituted thiadiazoles are therefore highly activated and react with a wide range of nucleophiles.

When 2-chlorothiadiazole was treated with ethyl acetate in the presence of sodium hexamethyl disilazane (NaHMDS), the 5-phenyl-1,3,4-thiadiazol-2-ylacetic ester was obtained.

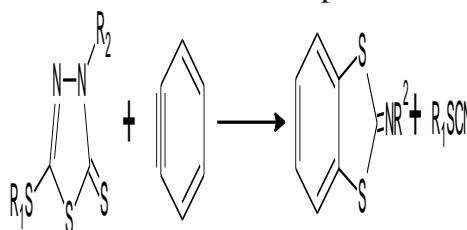


#### b) Nucleophilic attack at hydrogen attached to carbon:

Reaction of various alkylating agents with unsubstituted and 5-substituted thiadiazoles yield 3-alkyl-1,3,4-thiadiazolium salts. These salts were deprotonated with ethoxide to produce carbenes which were trapped with aromatic isocyanate to yield spirocyclic compounds.



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



### PROPERTIES

By the studies on the chemical reactivity's and the spectral features of 1,3,4-thiadiazoles we can summarize their properties as below.

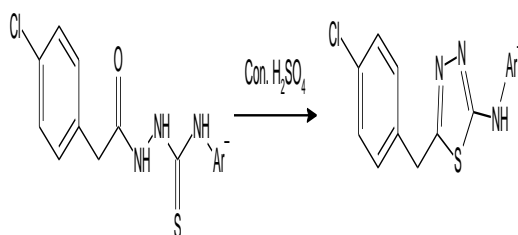
- 1,3,4-thiadiazole is a typical pseudo-aromatic molecule with dipole moment value of 3.25D.
- It is stable to acids but affected by strong bases leading to ring cleavage.
- It resists electrophilic substitution reactions. Facile nucleophilic attack takes place at 2- and 5- positions.
- Groups like  $-\text{CH}_3$ , Halogen,  $-\text{NH}_2$ ,  $-\text{COOH}$  present in this position are reactive and exhibits their typical reactions.
- 2-hydroxy-, mercapto- and amino derivatives display tautomeric behavior.
- It is susceptible to reduction and oxidation in acids/alkali.
- It forms stable mesoionic betaine type compounds.

#### Synthetic methods of thiadiazoles<sup>(4,5,6)</sup>

The different methods like conventional or ultrasound were used to synthesis the thiadiazole from many thiosemicarbazide or hydrazide by using catalyst like  $\text{H}_2\text{SO}_4$ ,  $\text{POCl}_3$ ,  $\text{CS}_2$ , polyphosphoric acid and  $\text{HCl}$ .

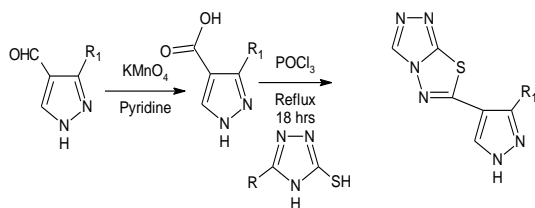
##### 1) From Thiosemicarbazides

The cyclization of thiosemicarbazide through sulphuric acid is the method used to prepare thiadiazole.



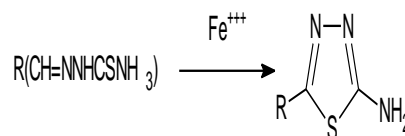
##### By using phosphorous oxychloride

Thiadiazole can be prepared by cyclization through  $\text{POCl}_3$ .



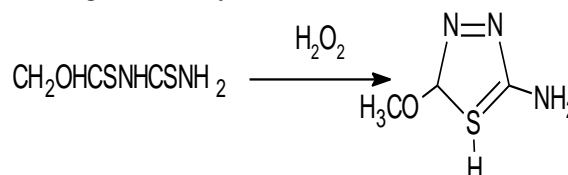
##### 3) From Thiosemicarbazone

Oxidative cyclization of thiosemicarbazones with ferric chloride found 1,3,4-thiadiazole.

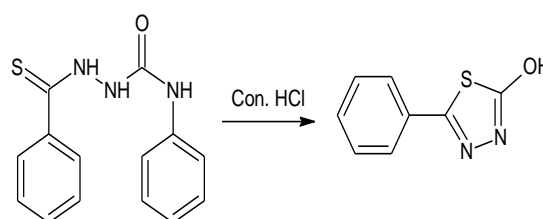


$\text{R} = \text{Ar}, \text{ArCO}, \text{CH}_3\text{CO}, \text{EtCO}$

**4) From Hydrazine:** 3-Thiocarbamoyl thione methyl carbonate on oxidation with  $\text{H}_2\text{O}_2$  gave alkoxythiadiazole.



**From Semicarbazide:** When 4-phenyl-1-(thiobenzole)semicarbazide reacts in the presence of concentrated  $\text{HCl}$  giving 2-hydroxyl-5-phenyl-1,3,4-thiadiazole.



#### SYNTHETIC METHODOLOGY

The different types of schematic representations were used to synthesis the derivatives of thiadiazole<sup>(9-19)</sup>.

**SCHEME-I:** N-phenyl thiosemicarbazide from aromatic amine by refluxing with  $\text{CS}_2$  and hydrazine hydrate in ethanol and from phenyl isothiocyanate by reacting with hydrazine hydrate in ethanol.

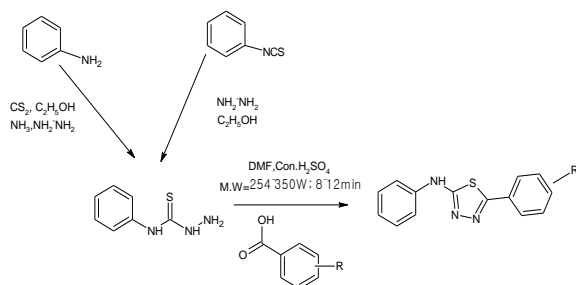
##### STEP 1: Synthesis of N-phenyl thiosemicarbazide

**From aromatic amines:** Aniline (0.01mol) was dissolved in ethanol and ammonia (25ml). Carbon disulfide (0.01mol) was added drop wise and stirred for 30 minutes. To this mixture, hydrazine hydrate (0.01mol) was added, Reaction mixture was refluxed on water bath for 9-12 hrs. Completion of reaction was checked by TLC. After reaction,

reaction mixture was allowed to cool to room temperature, kept overnight in freezing condition to get solid product. Separated solid product was filtered and dried. Recrystallized from ethanol-water mixture (4:1 ratio) to yield white shining crystals. Yield: 62.33% W/W.

**From phenylisothiocyanate:** Phenylisothiocyanate (0.01mol), hydrazine hydrate (0.01mol) in ethyl alcohol (25ml) were taken and subjected to microwave irradiation for 12 minutes at 245-350W power. In between, the completion of reaction was checked by TLC. After that reaction mixture was slowly poured into crushed ice and kept overnight. Separated solid was filtered, washed with water and dried. Solid was then purified by recrystallization from ethanol-water mixture (4:1 ratio) to yield desired compound.

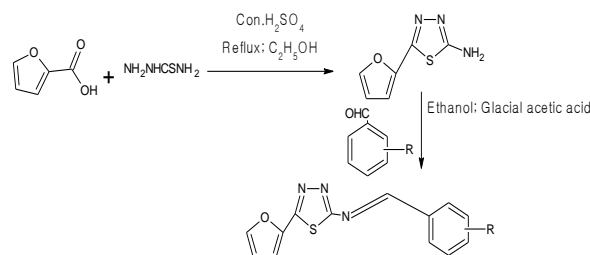
**STEP 2: Synthesis of 5-aryl-N-phenyl-1,3,4-thiadiazole-2-amine:** N-phenyl thiosemicarbazide (0.01mol), aromatic acid (0.01mol) and Sulphuric acid in DMF (25ml) were taken and subjected to microwave irradiation for 6-12 minutes at 245-350W power. In between, the completion of reaction was checked by TLC. After that reaction, mixture was slowly poured into crushed ice and kept overnight. Separated solid was filtered, washed with water and dried. Solid was then purified by recrystallisation from ethanol-water mixture (4:1 ratio) to yield desired compounds.



The compounds were screened for anti-inflammatory activity by carrageenan induced rat paw edema method and the compounds exhibited significant to moderate anti-inflammatory activity.

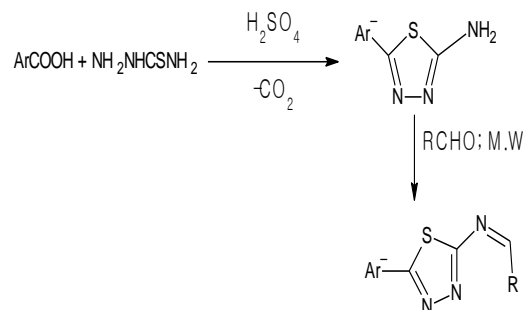
## SCHEME-II

- Thiadiazole derivatives with new amino group were synthesized by refluxing furan-2-carboxylic acid with thiosemicarbazide in presence of conc. H<sub>2</sub>SO<sub>4</sub>.
- Then different Schiff bases were prepared by reacting with various substituted aldehydes in presence of few drops of glacial acetic acid.



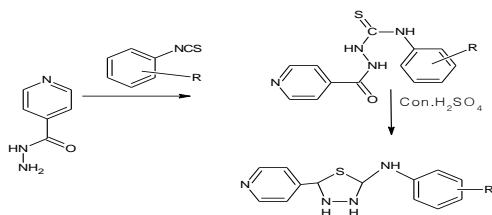
The synthesized derivatives were shown potent cytotoxicity.

**SCHEME-III:** Cyclization between aromatic acid and thiosemicarbazide using conc. H<sub>2</sub>SO<sub>4</sub> and condensing the product with aldehyde in presence by microwave irradiation.



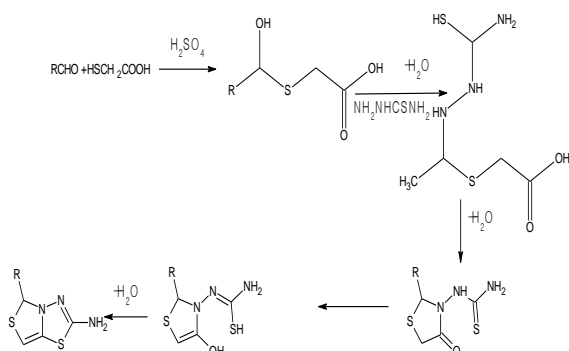
The compounds were subjected to antidiabetic activity by in vitro  $\alpha$  amylase inhibitory method and in vivo method in alloxan induced diabetes rat model.

**SCHEME-IV:** The reaction between isoniazid and various substituted isothiocyanates and was tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electro convulsometer comparing with standard drug phenytoin sodium.



SCHEME-V

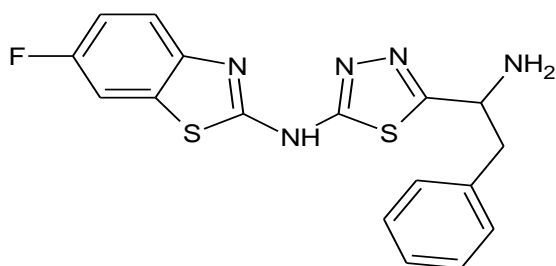
- Equimolar mixture of aromatic aldehydes, thioglycolic acid and thiosemicarbazide in  $H_2SO_4$ . The structures of all the synthesized compounds were confirmed by FTIR.
- NMR and Mass spectral data and their antitubercular activity studied against *Mycobacterium tuberculosis* using microplate alamar blue assay (MABA). All the synthesized compounds showed good anti-tubercular activity.



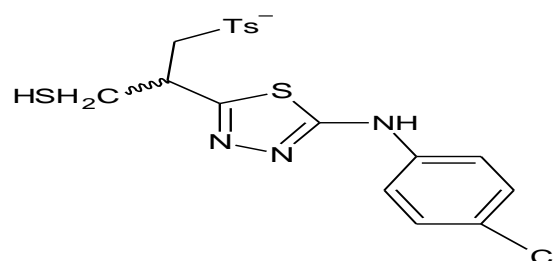
### BIOLOGICAL ACTIVITIES

#### 1. ANTI-TUBERCULAR ACTIVITY

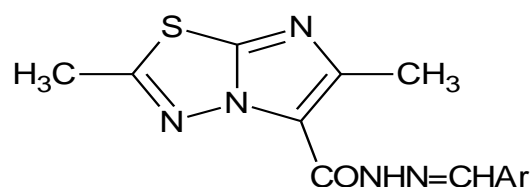
Sathe SB et al reported the synthesis of N-[5-(1-amino-2-phenylethyl)-1,3,4-thiazol-2-yl]-6-fluoro-7-substituted-1,3-benzothiazol-2-amine. The anti-tubercular activity of synthesized compounds was assessed against *Mycobacterium tuberculosis* H37Rv in BACTEC medium and shown good anti-tubercular activity<sup>(22)</sup>.



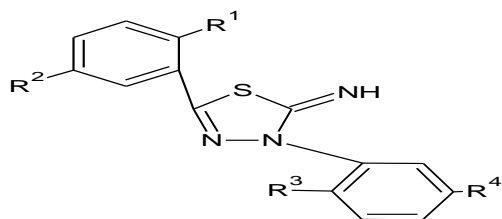
**2. ANTI-HIV ACTIVITY:** Akhtar T et al reported the synthesis and anti-HIV activity of 2-substituted 5-(4-chlorophenylamino)-1,3,4-thiadiazoles. The synthesized compounds were assayed against HIV-1 and HIV-2 strains in human T-lymphocytes MT-4 cells and shown potent activity<sup>(23)</sup>.



**3. ANTI-CANCER ACTIVITY:** Terzioglu N et al reported the synthesis of novel 2,6-dimethyl-N'-substituted phenyl methyleneimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazides. The newly synthesized compounds were evaluated in the National Cancer Institute's 3-cell line, one dose in vitro primary cytotoxicity assay. Some compounds passed the criteria for activity in this assay (20-29% growth percentage) and were scheduled automatically for evaluation against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10-fold dilutions<sup>(24)</sup>.



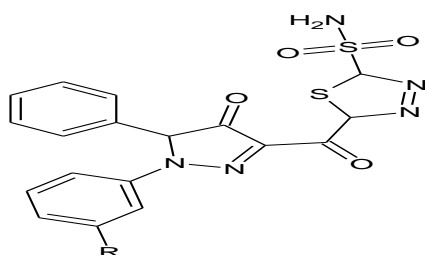
**4. ANTI-INFLAMMATORY ACTIVITY:** Asif M et al (2009) synthesized 2,4-diphenyl-5-imino-1,3,4-thiadiazole derivatives by reaction of benzoyl chloride and phenyl hydrazines. Formed phenyl hydrazone derivatives heated with phosphorous pentachloride and then cyclized with potassium thiocyanate yields the target compound. The newly synthesized compounds were screened for their in-vitro anti-inflammatory activity by using Carrageenan induced rat paw method.<sup>(25)</sup>



## 5. ENZYME INHIBITION ACTIVITY

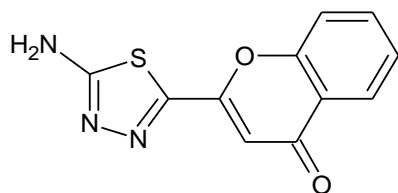
### Carbonic Anhydrase Inhibitor Activity:

Kasimogullari R et al reported the synthesis anti-glaucoma activity of the novel pyrazole derivatives of 5-amino-1, 3, 4-thiadiazole-2-sulfonamide. The inhibitory effects of the synthesized compounds on hydratase and esterase activities of carbonic anhydrase isoenzymes (hCA-1 and Hca-11) have been studied in vitro. Some compounds had more inhibitory effect than the standard compound<sup>(26)</sup>.



### ❖ Pteridine Reductase-1 Inhibitors

Scientific works in the field of antiparasitic therapy has demonstrated that inhibition of enzymes. Involved in the parasites life cycle, such as dihydrofolate reductase (DHFR), thymidylate synthase (TS) And pteridine reductase (PTR1) should provide effective treatment. Even if DHFR inhibitors (antifolates) can severely affect DNA replication resulting in cell death, they are not currently used In the antiparasitic therapy mainly because of the PTR1 activity of the target organisms.



**MARKETTED FORMULATIONS** <sup>(3)</sup>: The list of thiadiazole containing clinically used drugs or drug candidates includes Acetazolamide, Zibotentan, Sulfamethizole,

Methazolamide, Megazol, and Globucid are available. Different mechanisms of the antitumor activity of 1,3,4-thiadiazoles have been reported, including specific inhibition of DNA and RNA syntheses without appreciable impact on protein synthesis, inhibition of carbonic anhydrase, phosphodiesterase-7 (PDE), and histonedeacetylase, or adenosine A3 receptor antagonism.

### 1. Acetazolamide

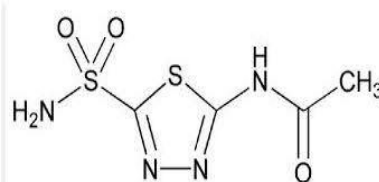
- DIAMOX Tablets are for oral administration.
- Acetazolamide is an enzyme inhibitor which acts specifically on carbonic anhydrase.
- It is indicated in the treatment of:

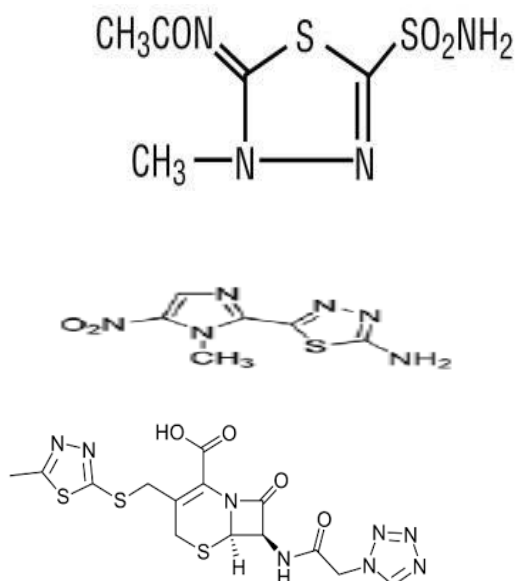
*Glaucoma:* DIAMOX Tablets is useful in glaucoma (chronic simple (open angle) glaucoma, secondary glaucoma, and perioperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure) because it acts on inflow, decreasing the amount of aqueous secretion.

*Abnormal retention of fluids:* DIAMOX Tablets is a diuretic whose effect is due to the effect on the reversible hydration of carbon dioxide and dehydration of carbonic acid reaction in the kidney. The result is renal loss of  $\text{HCO}_3^-$  ion which carries out sodium, water and potassium.

*Epilepsy:* In conjunction with other anticonvulsants best results with DIAMOX Tablets have been seen in petit mal in children. Good results, however, have been seen in patients, both children and adults, with other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk patterns etc.

**Methazolamide:** A carbonic anhydrase inhibitor that is used as a diuretic and in the treatment of glaucoma.





**3. Megazol:** Megazol is a nitroimidazole based drug that cures some protozoan infections.

**4. Cephazoline:** Cefazolin, also known as cefazoline and cephazolin, is an antibiotic used for the treatment of a number of bacterial infections

**Further developments:** Both the sonication and classical condition methods are used to synthesize novel substituted 1,3,4-thiadiazoles. Generally, improvements in rates and yield of reactions were observed when reactions were carried out under sonication compared with classical condition.

**FUTURE SCOPE OF THE STUDY:** The Synthesized compounds should have significant anti-tubercular activity in MABA assay method. Hence the anti-tubercular study would deserve for further investigations of *in-vivo* toxicity and *in-vivo* anti-tubercular studies.

#### CONCLUSION:

1, 3, 4-thiadiazole are one of the most important chemical classes of compounds having a common integral feature of a variety of medicinal agents. 1,3,4-Thiadiazole and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical and industrial importance

and it is surprising that the synthetic publication far outweighs in numbers those relating to all other. Literature review reveals that the compounds containing 1, 3, 4-thiadiazole nucleus and its complexes exhibited diverse biological activities, and have very simple synthetic process. During the recent years, that has been found there are number of thiadiazole which contain the nitrogen in different position as 1,3,4-thiadiazole & 1,2,3-thiadiazole & 1,2,4-thiadiazole, & 1,2,5-thiadiazole etc. & the basic ring 1,3,4-thiadiazole are the fused heterocyclic ring compound have many biological activities as antimicrobial activity, anti-inflammatory, anti-fungal, antibiotic, diuretic, anti-depressant etc. It was found that among the important pharmacophores responsible for various activities. In general, 1,3,4-thiadiazole derivatives are prepared by appropriate intra- or intermolecular ring closure reactions and the substituents are then modified as required. 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. The thiadiazole containing various marketed formulations are available with different mechanism of action. Both the sonication and classical condition methods are used to synthesize novel substituted 1, 3, 4-thiadiazoles and have more scope in the develop of various compounds with wide pharmacological activities.

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