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Review On Thiadiazol :A Promising Moiety In Medicinal Chemistry

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ABSTRACT

The chemistry of 1,3,4-thiadiazole is one of the most interesting scaffolds for synthesizing new drug Molecules due to their numerous biological activities. Several modifications in the thiadiazole ring have been made, proving it to be more potent and highly effective with a less toxic scaffold for various pharmacological activities.

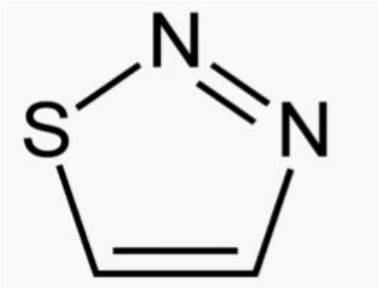
1,3,4-Thiadiazole nucleus exhibited remarkable biological activities. Literature indicates that compounds having 1,3,4 -Thiadiazole nucleus have wide range of pharmacological activities that include antibacterial, antifungal, antiviral, anti-inflammatory, anticonvulsant, anticancer, antioxidant, antidiabetic, antihypertensive, diuretic etc

Keyword- 1,3,4-thiadiazole; scaffolds; Pharmacological activities; Marketed drugs; Synthesized derivatives

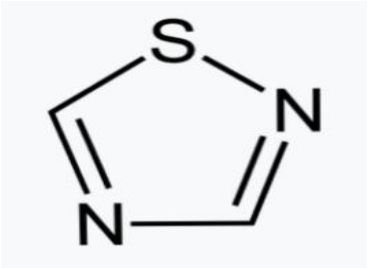
INTRODUCTION

In chemistry thiadiazoles are a sub-family of azole compounds. The name thiadiazole originating from the Hantzsch–Widman nomenclature. They are Aromatic ring by virtue of their two double bonds and the sulfur lone pair. Structurally, they are five-Membered heterocyclic compounds containing one sulfur and two nitrogen atoms. Four possible Structures exist depending on the relative positions of the heteroatoms; these forms do not Interconvert and however are structural isomers and not tautomers

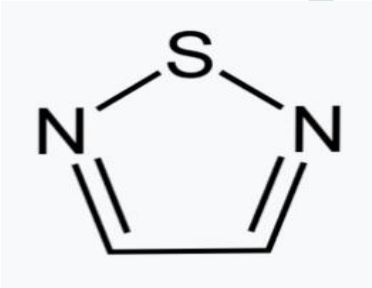
The compounds themselves are rarely synthesized and possess no particular application, However compounds bearing them as a structural motif are fairly common in pharmacology. 1,3,4thiadiazole is the most common, appearing in such medications as cephazolin and Acetazolamide. [1] [2]



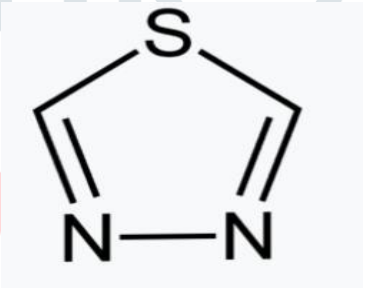
1,2,3-Thiadiazole



1,2,4-Thiadiazole



1,2,5-Thiadiazole

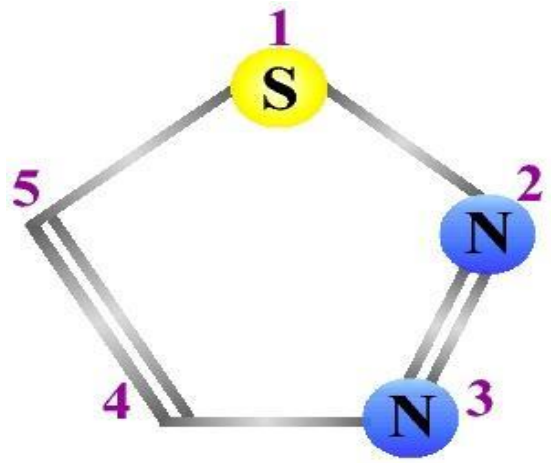


1,3,4-Thiadiazole

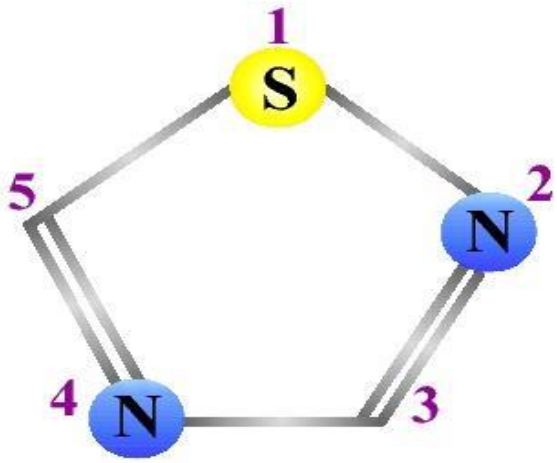
STRUCTURAL CHARACTERISTICS

Thiadiazole are important group of five membrane heterocycle. In which two of the carbon are replaced by nitrogen atom and one carbon with sulphur..

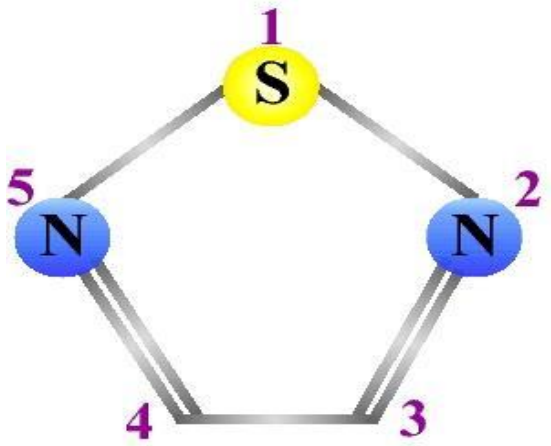
Core structures of the thiadiazole isoforms occurring in nature. Sulphur and nitrogen atoms are marked as yellow or blue circles, respectively[3]



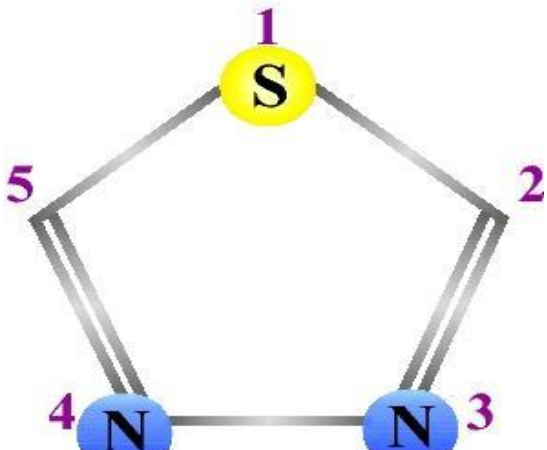
1,2,3-thiadiazole



1,2,4-thiadiazole



1,2,5-thiadiazole



1,3,4-thiadiazole

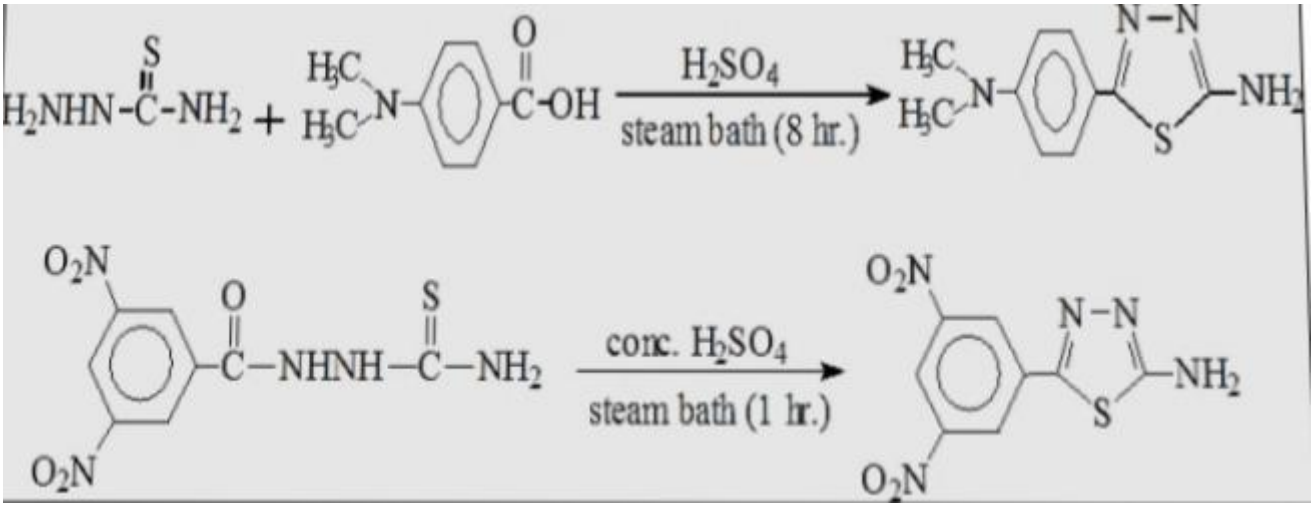
PHYSICAL PROPERTIES

The parent 1,2,3thiadiazole is yellow-colored liquid with a boiling point of 157°C.
It is a thermally stable ,weak base and soluble in water . Most of the organic solvents such as alcohol, ether, DCM, and chloroform.[4]

SYNTHESIS

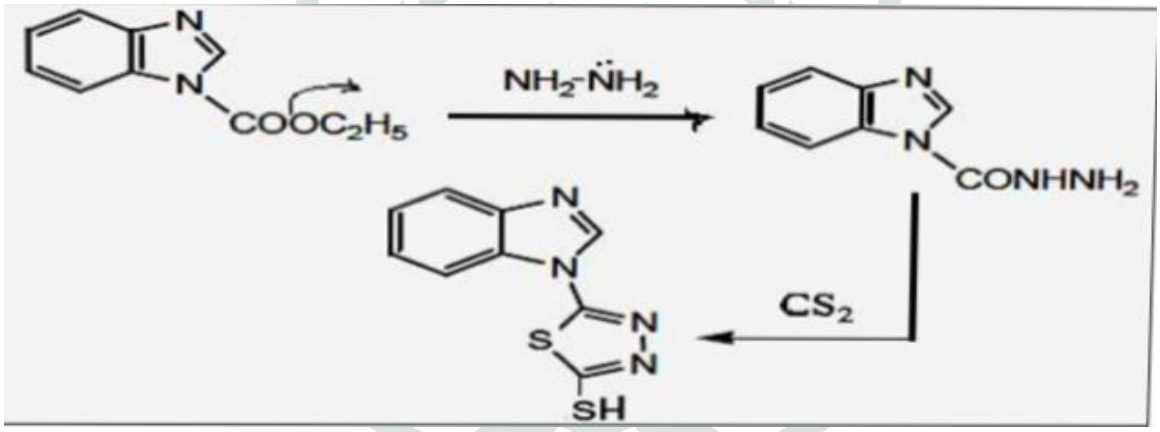
1) From Condensation reaction:

From Condensation of thiosemicarbazide with carbonyl groups like (carboxylic acid, ester, Aldehyde) in presence of sulfuric acid, after condensation reaction, it cyclization with Carboxyl Group (COOH) in acid medium to yield thiadiazole derivatives [5]



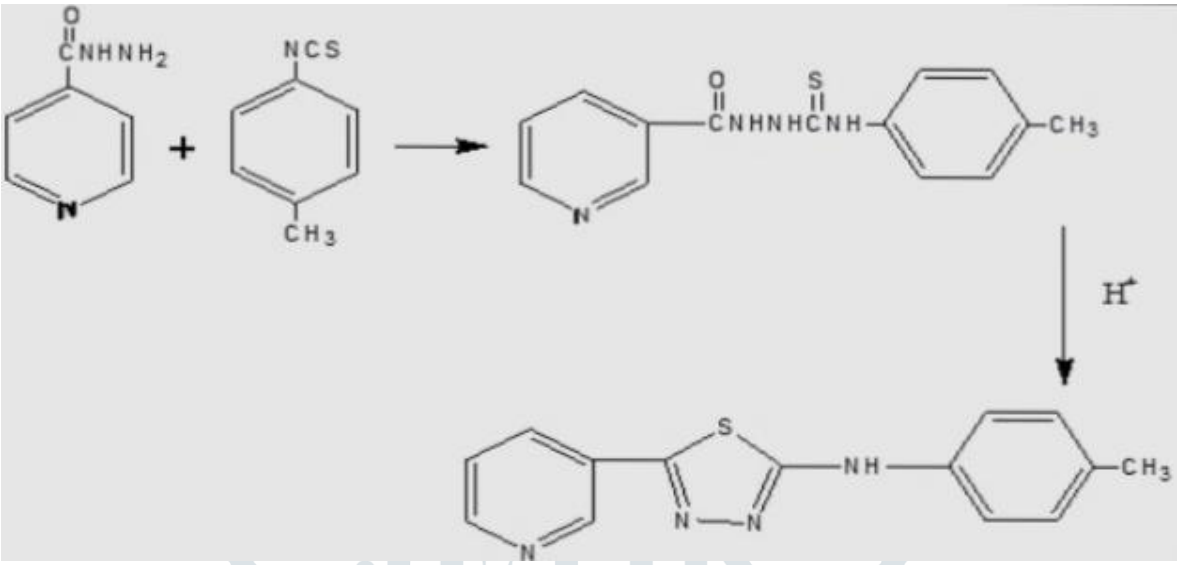
2) Cyclization of Ester with Hydrazine :

Cyclization of carbonyl in ester compound with hydrazine derivatives to yield thiadiazole Compound or can react with any amine derivatives by ring closure step with carbonyl of Carboxylic acid [5]



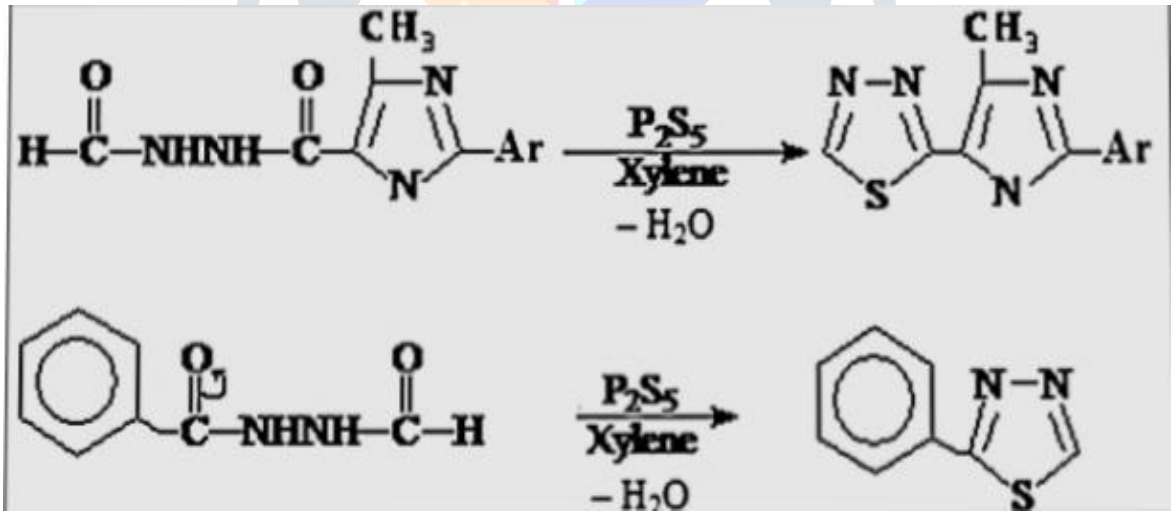
3) From Condensation of Hydrazo with thiocynate derivatives:

Condensation of Hydrazo –derivatives with thiocynate compounds in acid medium to produce thiadiazole Compounds,via ring closure by using conditions and using closure agents for this reaction [5]



4) Cyclization with (P2S5):

Cyclization of Semicarbazide with (P2S3) in xylene as A solvent via substitution of Oxygen atom by sulfur atom (P2S3) through cyclization reaction or ring closure Step, [5]

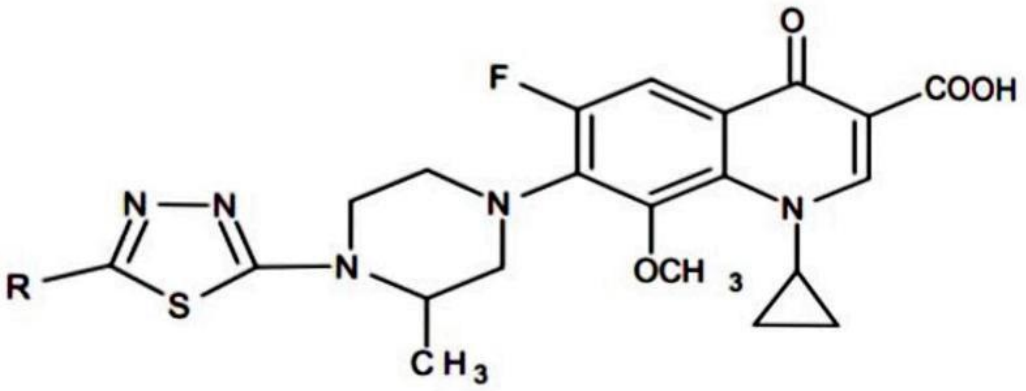


PHARMACOLOGICAL ACTIVITIES

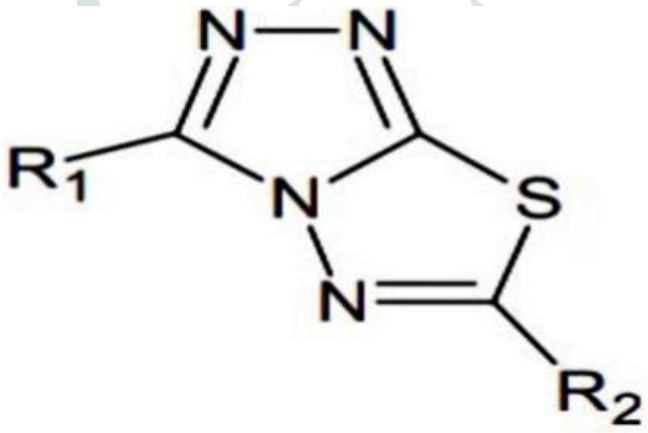
1)Antimicrobial Activity:

Alireza et al [6] synthesized a series of gatifloxacin analogues containing a nitroaryl-1,3,4-Thiadiazole moiety attached to the piperazine ring at C-7 position (1) and tested for In vitro antimicrobial activity against gram positive and gram negative bacteria. Among synthesized compounds, nitrofuran analog exhibited more potent inhibitory activity against gram-positive

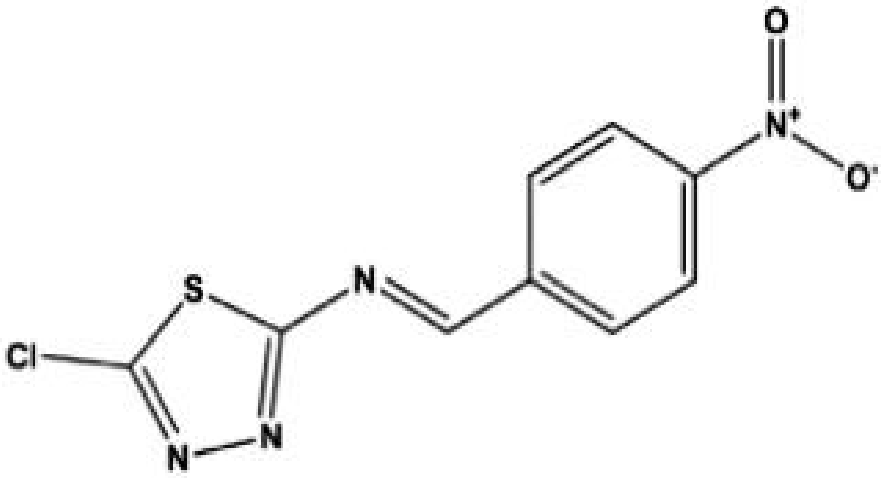
bacteria including Staphylococcus epidermidis, Bacillus subtilis, Enterococcus faecalis and Micrococcus luteus with respect to other synthesized compounds and reference drug Gatifloxacin.



Some of the novel condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-Thiadiazole derivatives (2) synthesized by **Rangappa et al [7]**and checked for their efficacy as antibacterials in vitro. Following compounds showed significant inhibition against all the strains tested, when compared to standard drugs.

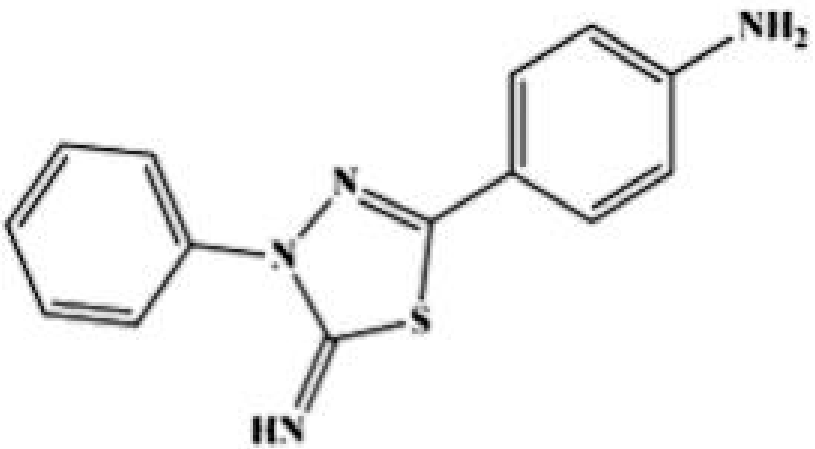


Mousa[8] synthesis of thiadiazoles. The preparation compounds were evaluated for the antibacterial activities. The synthesized molecules have been studied for their antibacterial activity against the S. aureus and B. Cereus as gram positive and E. coli and P. Aeroginosa as Gram negative bacteria. The prepared compound showed a noticeable antimicrobial activity As compared to standard drug. Following compound showed the best antimicrobial activity against the tested bacteria

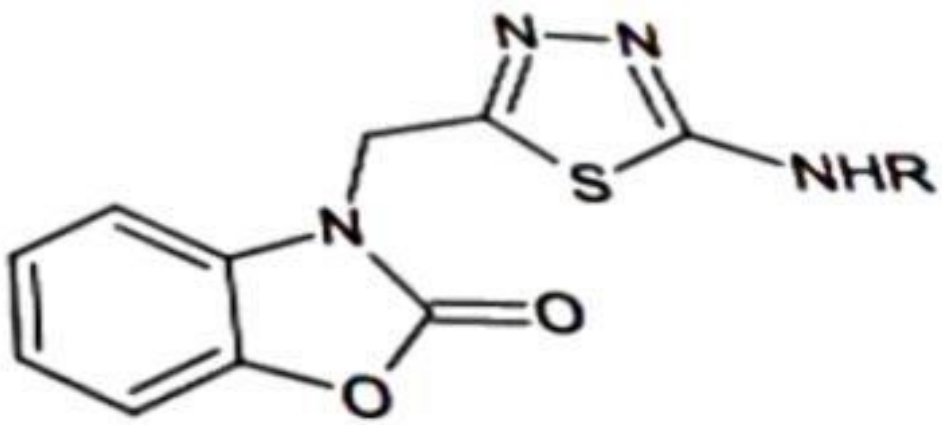


2)Anti-Inflammatory Activity:

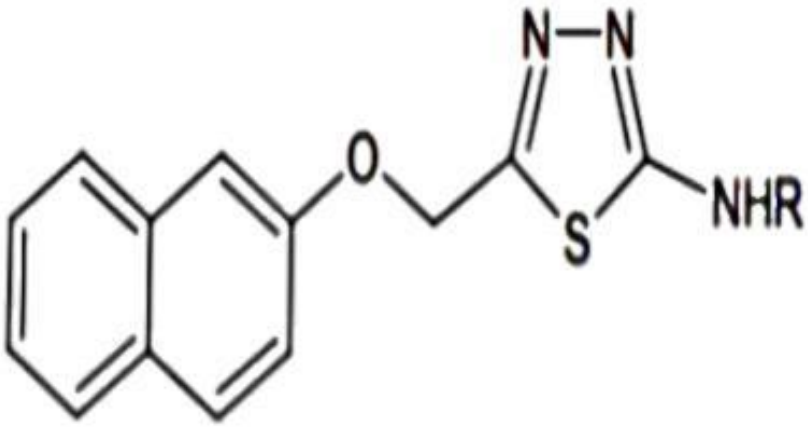
Asif M. and Asthana C[9] were synthesized thiadiazoles with imino moiety. The Synthesized compound named 4-(5-imino-4-phenyl-4,5-Dihydro-1,3,4-thiadiazol-2-Yl)aniline have been examined for in vivo anti-inflammatory activities by using of Carrageenan induced paw oedema technique and compared with Diclofenac as standard Drug.



Various condensed 2-benzoxazolinone and substituted thiadiazoles were synthesized by **Salgin-Goksen et al [10]**and screened for anti-inflammatory activity. Compound with Phenyl Substituent possessed the most prominent and consistent anti-inflammatory Activity. An Increase in the anti-inflammatory activity was observed with replacement of alkyl chain to phenyl ring.

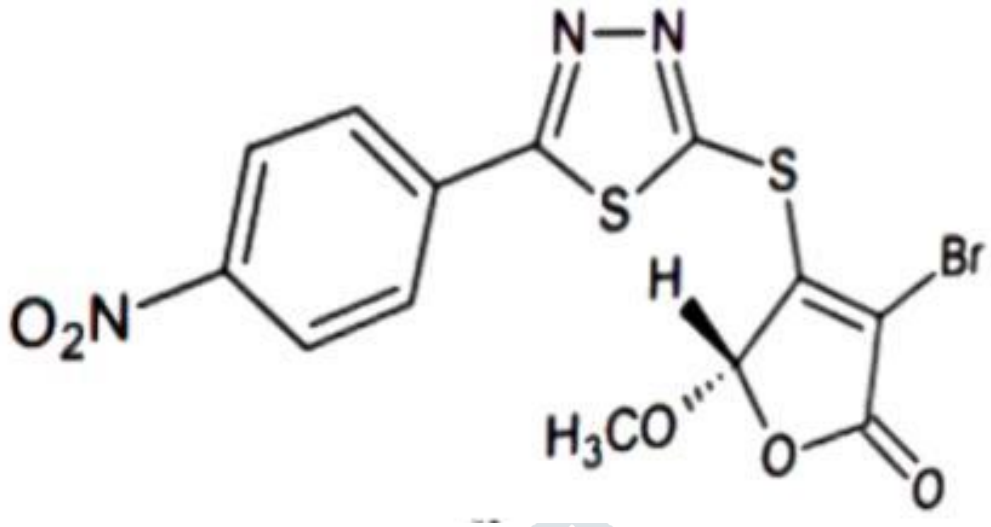


A series of 2-(2-naphthyloxymethyl)-5-substitutedamino-1,3,4-thiadiazole was synthesized by **Erhan et al[11]** and evaluated for their anti-inflammatory activity by Carrageenan hind-paw Edema test. All the compounds were found to exhibit weak anti-Inflammatory activity

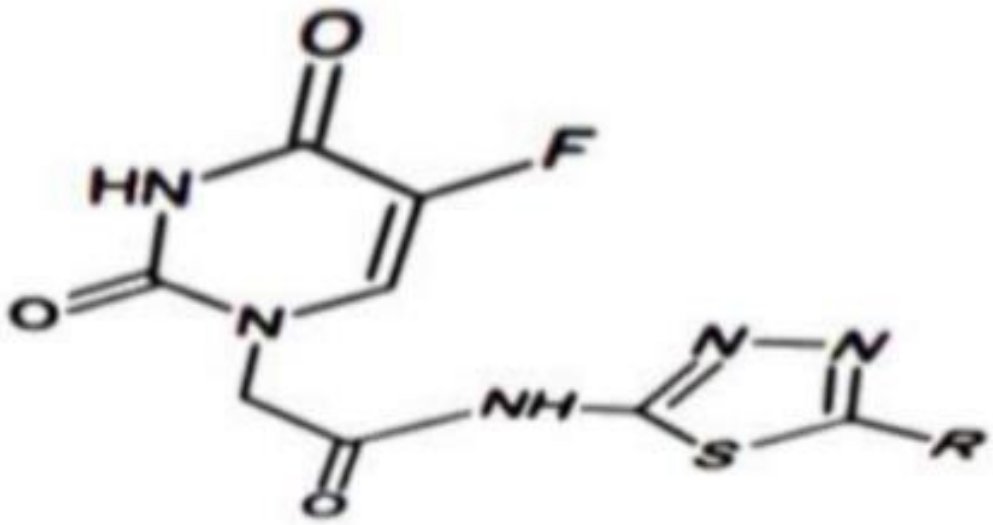


3)Anticancer Activity:

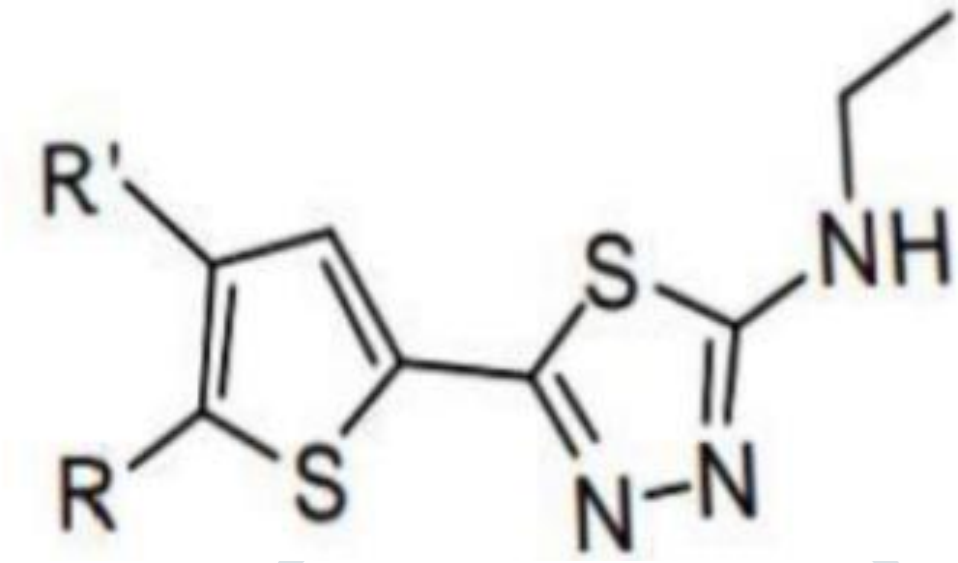
A new series of chiral 1,3,4-thiadiazole derivatives possessing γ-substituted butenolide moiety were synthesized and evaluated for in-vitro anticancer properties by **Wei et Al[12]** All the compounds showed good anticancer activities against Hella cell lines. Of All the studied compound, Following compound exhibited the best inhibitory activity With an IC50 of 0.9 µM. This might have relationship with the hydrophile ability of Nitro group on the benzene ring. After being treated with 0.1 µg/mL compound for 24 h, The growth inhibition rate of Hella cell lines was 59.2%



Synthesis and biological evaluation of N1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5 Fluorouracil derivatives as novel class of potential anti-tumor agents A-549 (human lung cancer Cell), Bcap-37 (human breast cancer cell) done by **Jun et al[13]**. While comparing activity with Standard drug 5-fluorouracil; phenyl, 4-fluorophenyl, 4-Methylphenyl, 3,5-dinitrophenyl Substituted compounds showed higher activity against A-549 and 4-fluorophenyl, 4-methylphenyl, 3,5-dinitrophenyl substituted compounds Showed higher activity against Bcap-3

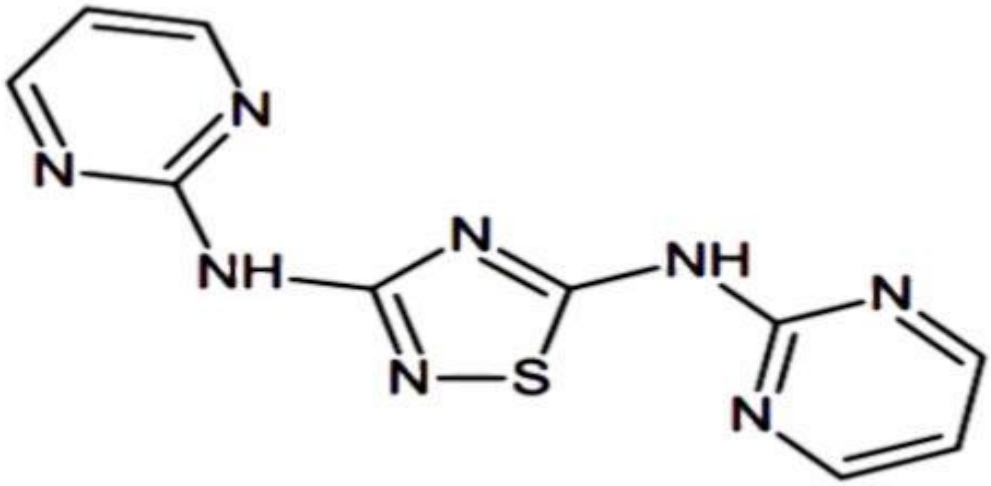


Novel derivatives of 2,5-substituted-1,3,4-thiadiazoles were synthesized and evaluated for their cytotoxicity by **Mavrova et al [14]**. The biological study indicated that n-Ethyl-5-(4,5,6,7-Tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazole-2-amine(24)possessed high cytotoxicity in-Vitro against thymocytes. The corresponding IC50 being 5.2 x 10-6 µM. The derivatives Containing ethyl-amino group at the second position of 1,3,4-thiadiazole cycle resulted in good Activity.

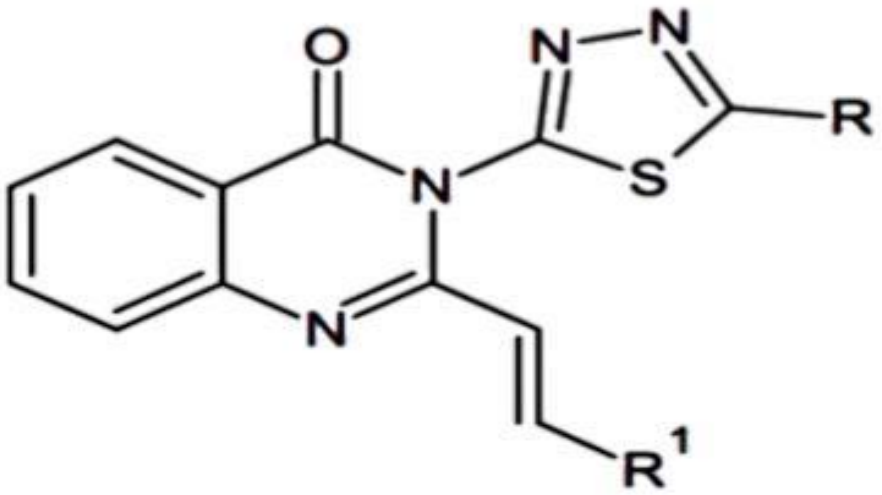


4)Anticonvulsant Activity:

A series of new substituted 1,2,4-thiadiazoles were synthesized and screened for anticonvulsant activity by **Gupta et al [15]**. All the compounds except (26g) showed protection against MES screen after 0.5 h. It may be concluded that the synthesized compounds were potent against MES-induced seizures than scPTZ induced and showed low potency as sedative-hypnotic agent which is advantageous.

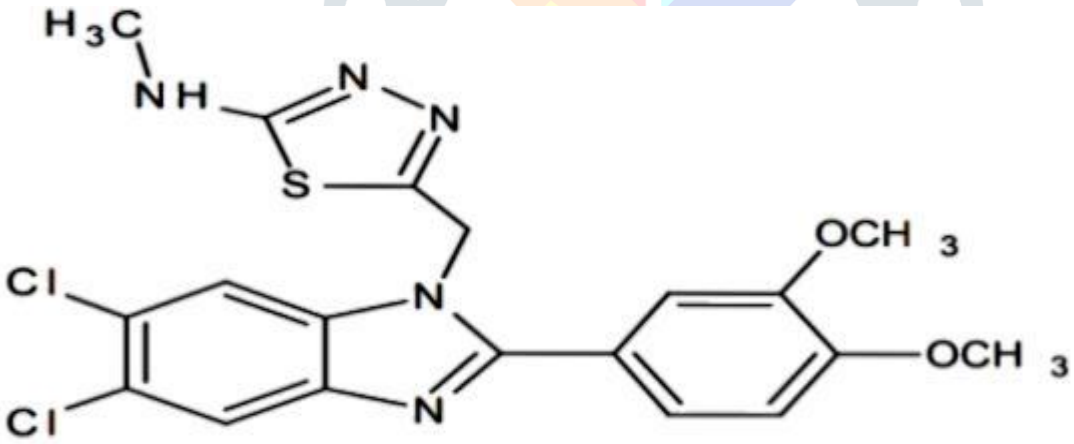


A series of new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-Ones was synthesized by **Sushil et al[16]** and were examined in the maximal Electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) Induced seizure models in mice.



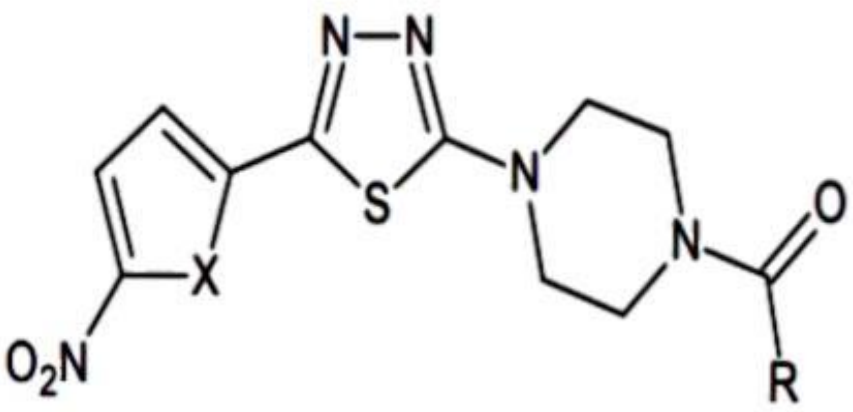
5)Antioxidant Activity:

Some novel 5-[(2-(substituted phenyl)-1H-benzimidazole-1-yl)methyl]-N-methyl-1,3,4- Thiadiazole-2-amines were synthesized and tested for antioxidant properties by **Kus et al [17]** Using various in vitro systems.The following Compound which is the most active derivative Inhibited lipid peroxidation slightly at 10-3 M concentration.

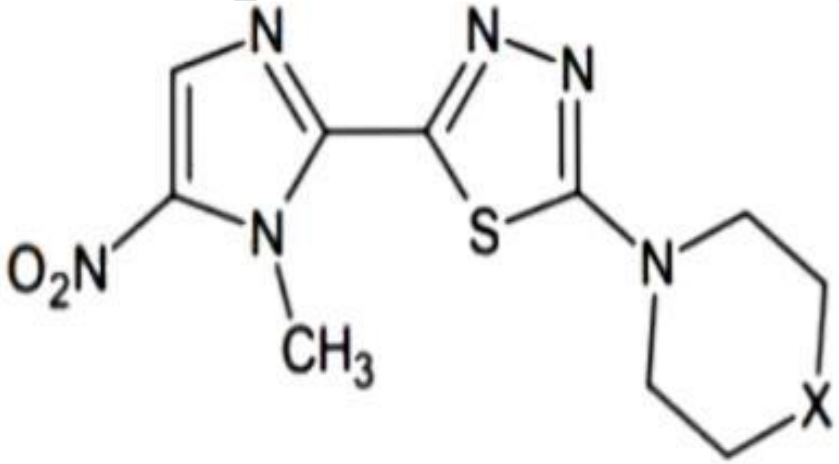


6) Anti-leishmanial activity

A series of 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]- and 1-[5-(5-nitrothiophen-2-Yl)-1,3,4-thiadiazol-2-yl]-4-aroylpiperazines were synthesized and evaluated for in-vitro Leishmanicidal activity against promastigote and amastigote forms of Leishmania major By **Foroumadi et al[18].** From biological results, it was concluded that 5-nitrofuran Derivatives Were more active than the corresponding 5-nitrothiophene analogues.



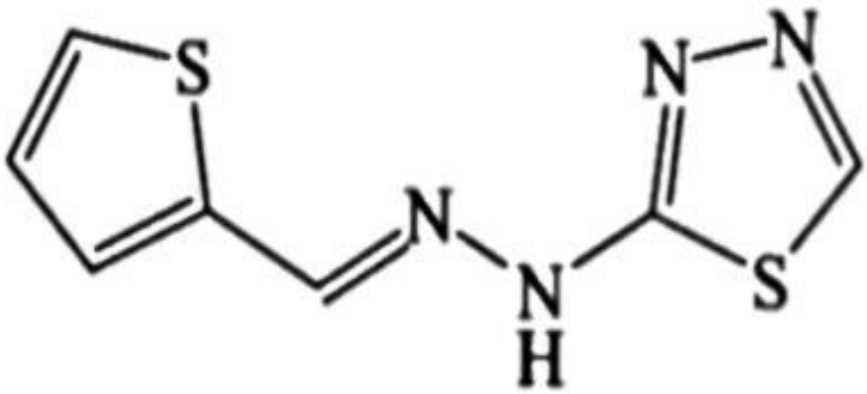
A series of 2-(1-methyl-5-nitroimidazol-2-yl)-5-(1-piperazinyl, 1-piperidinyl and 1-Morpholinyl)-1,3,4-thiadiazoles were synthesized and evaluated for in-vitro Leishmanicidal Activity against Leishmania major promastigotes by **Foroumadi et Al[19]**. The leishmanicidal data revealed that the following compounds had strong and much better leishmanicidal activity than the reference drug following compound (piperazine analog) was the most active one (IC50 = 0.19 μM).



7) Anti-Platelet Activity:

The agents containing hydrazone group in their structure.They are found to be potent anti-platelet agents.

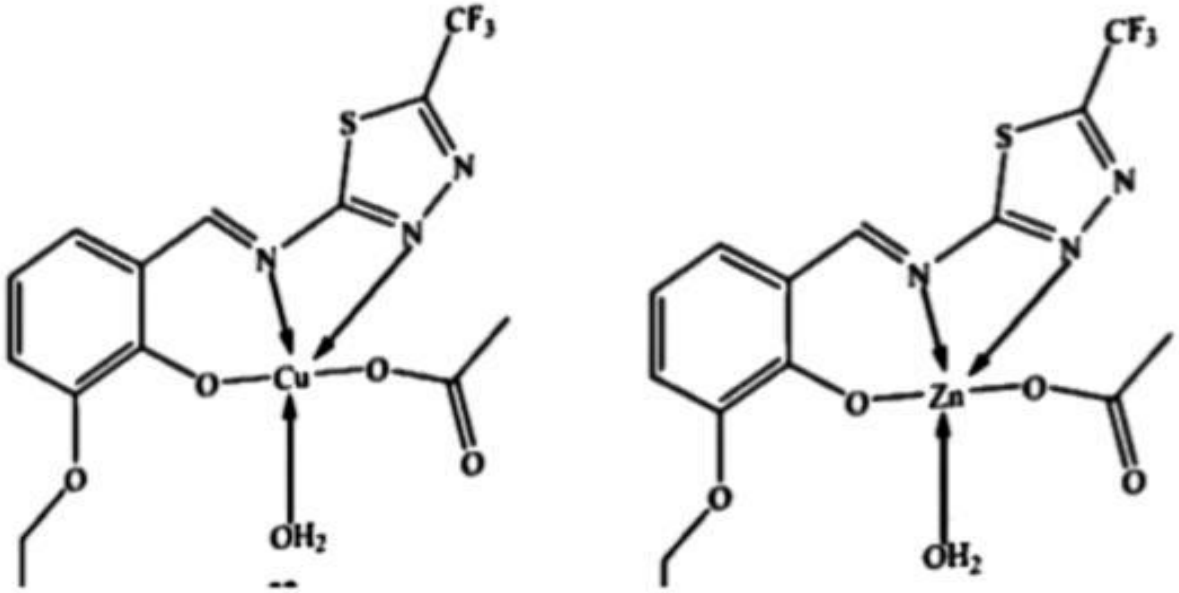
Considering this property of hydrazone **Tehrani E.M.H.K et al.[20]**, designe and synthesized new 2-hydrazinyl-1,3,4-thiadiazole derivatives and after confirming the structure Of the synthesized compounds they were further screened for in-vitro anti-platelet aggregation assay using turbidimetric method and concluded that following compounds showed highest Inhibition Of COX enzyme and hence can be a potent anti-platelet aggregation agent



8) Anti-Diabetic Agents:

Metabolic disorder occurred due to insulin deficiency or inadequate insulin secretion resulting in hyperglycemia is known as diabetes

Deswal Y et al[21] also synthesized some new spchiff base derivatives of thiadiazole and their metal complexes. Furthermore, they performed a comparative in-vitro anti-diabetic assay and molecular docking study of all Synthesized compounds and observed that the Schiff base metal complex derivatives showed high inhibition against α-amylase and α-Glucosidase enzymes in comparison to Schiff base derivative



USES

1) Thiadiazol is most potent therapeutic agent for variety of biological and pharmacological application With little or no side effect
2) Thiadiazol have border application as insecticide synergists, cross linked polymer compound and herbicide
3) Thiadiazol ring are one of the most important class of these hetrocyclic saccffold in medicinal chemistry.
4) Thiadiazol derivative posses a versatile type of biological activity , such as analgesic, antiviral , antifungal and antimicrobial activity[22]

CONCLUSION

1) The 1,3,4-thiadiazole is a heterocyclic moiety that is responsible for various pharmacological activities, such as anticancer, antiinflammatory, anti-microbial, anti viral, antidepressants antiparasitic, anti-obesity, anti-influenza, anti-HIV etc
2) The properties of thiadiazole derivatives are described widely in medical fields, agricultural and materials chemistry
3) Thiadiazole derivatives represent a connecting ring and a raw material for many interactions of synthetic chemistry, chemistry of coordination complexes and reagents, Because of the hybrid atoms they contain within their composition, which gave them extremely important being that they contain atoms characterized by being biological and pharmacological activities and the basic nucleus of many life compounds, vitamins and medicines.
4) It can also be a lead molecule in treating new diseases, e.g., COVID-19 and black fungus.
5) The biological profiles of these new generations of thiadiazoles would represent a fruitful matrix for further development of better medicinal agent

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