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Review Article

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REVIEW ARTICLE ON THIADIAZOLE ANALOGUES

Bhadresh D. R.*, Senthil Kumar G. P., Pramila T. and Chaithra R.

Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Bharathi Nagara, K.M.Doddi, Maddur Taluk, Mandya District, Karnataka, India.

***Corresponding Author: Bhadresh D. R.**
Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Bharathi Nagara, K.M.Doddi, Maddur Taluk, Mandya District, Karnataka, India.

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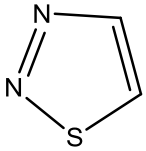
ABSTRACT

This review article presents an outlines of different synthesis and biological activities of 1,2,3 thiadiazole and its derivatives. The scheme of these reaction was discussed and the newly synthesized compounds were possessing different pharmacological activities. 1,2,3 thiadiazole has been studied extensively because of its wide variety of biological activities.

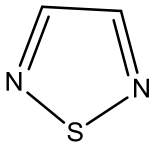
KEYWORDS: 1,2,3 thiadiazole, antimicrobial, antidepressant, anti-tubercular, anticancer.

INTRODUCTION

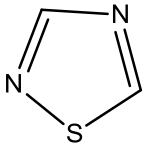
Thiadiazoles are clear to yellowish liquids which are soluble in alcohol, ether and slightly soluble in water; they are starting material for numerous chemical compounds including sulphur drugs. Thiadiazoles are easily metabolized by biochemical reactions and they are non-carcinogenic in nature. Thiadiazoles and their derivatives exhibit wide range of pharmacological activities such as antimicrobial activity, antidepressant, cardiotonic, antibacterial, anti-tubercular, anticonvulsant, antileshmanial, analgesic, anti-inflammtory, anticancer, phosphodiesterase inhibitors and effect on Tyrosinase enzyme. This diversity of biological activity may be due to the presence of -N=C-S moiety. There are four isomers of thiadiazole, among these 1,3,4-thiadiazole is the most thermally stable; which is only isomer doesn´t contain any sulphur- nitrogen bond. 1,3,4-thiadiazole relatively stable in aqueous acid solutions but the nucleus can undergo ring cleavage by aqueous base solutions.



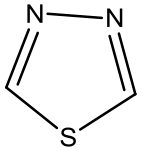
1, 2, 3 Thiadiazole



1,2,5 thiadiazole



1,2,4 thiadiazole

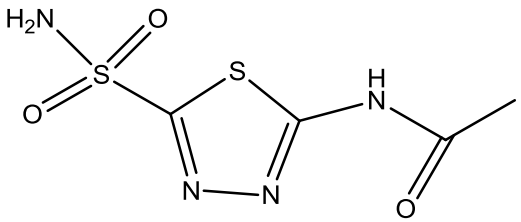


1,3,4 thiadiazole

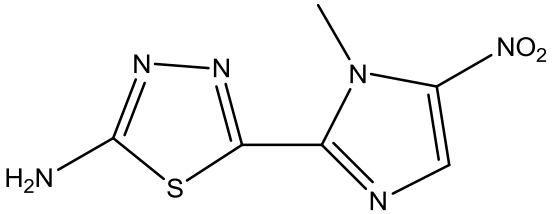
CHEMISTRY OF THIADIAZOLE

Thiadiazole moiety acts as a hydrogen binding domain and two electron donar system. Thiadiazole acts as a bioisosteric replacement of thiazole moiety. Thiadiazole nucleus are ring opening by strong base easy of nucleophilic attack and the formation of mesoionic compound by quaternization. The substituents in the 2,5 position have a large effect in determining the reactivity of the molecules as a whole. Thus, the ambient nucleophillicity of 2-amino thiazoles gives rise to electrophilic attack on both the amino group and the nuclear nitrogen atom. Nucleophilic easily displace halogen atom from the thiadiazole nucleus this is due to the electronegativity of the two nuclear nitrogen atom which impart a low electron density to the carbon atom of the nucleus.

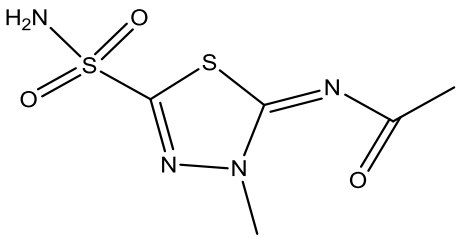
SOME THIADIAZOLE CONTAINING DRUGS



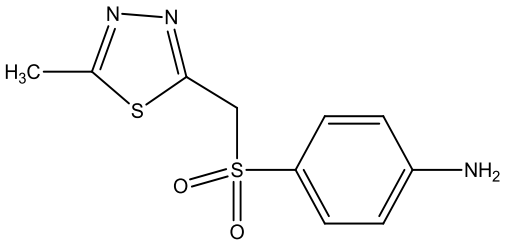
ACETAZOLAMIDE



MEGAZOL



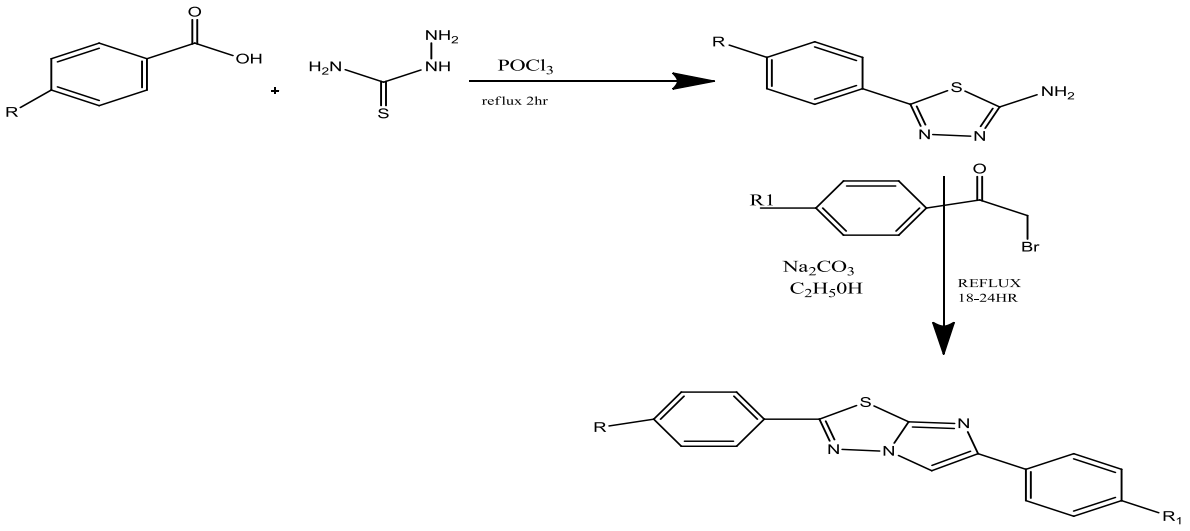
METHAZOLAMIDE



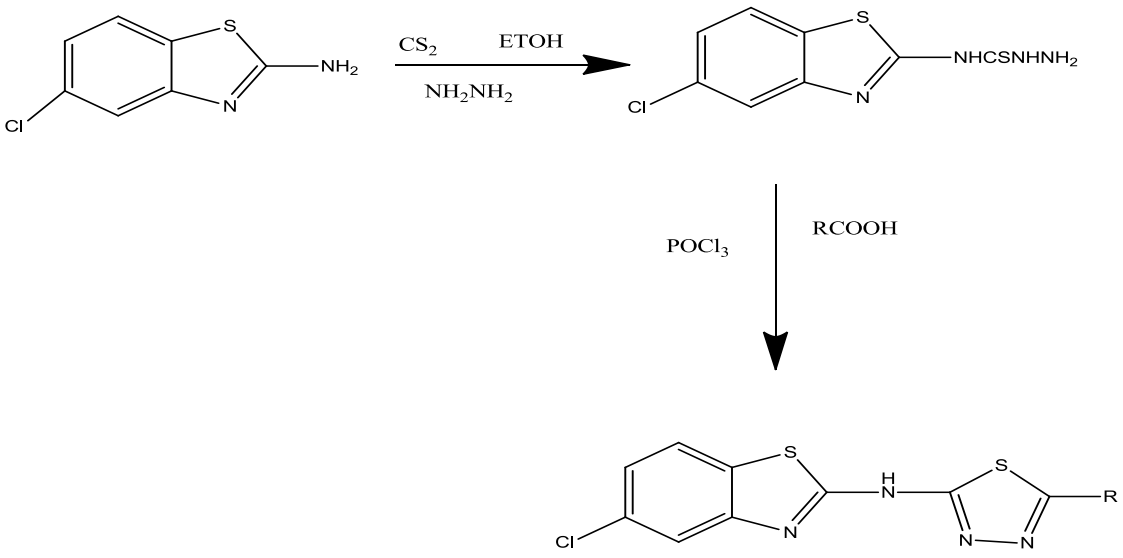
SULFAMETDIZOLE

GENERAL METHODS OF SYNTHESIS OF 1, 2, 4 THIADIAZOLE

Scheme1: Monika Gupta *et al* ; were Synthesis of 5-p-substituted-1,3,4–thiadiazol-2-amine Substituted benzoic acid (6.8 g, 0.05 mol) and thiosemicarbazide (4.5 g, 0.05 mol) in phosphorous oxychloride (30 ml) were refluxed gently for 1-2 hr. The solution was allowed to cooled and then water (90 ml) was added carefully. The separated solid was filtered and suspended in water and basified with aqueous potassium hydroxide. The solid was filtered, washed with water, recrystallized with ethanol.

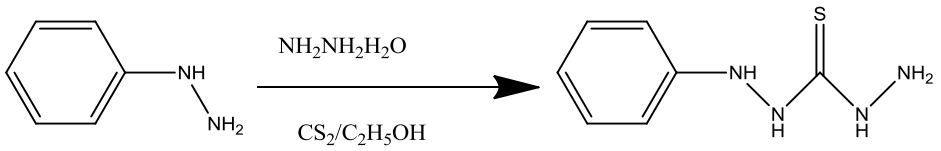


Scheme2: Ajay Kumar *et al*; Synthesis of thiadiazoles involves the condensation of thiosemicarbazides with carboxylic acids or carboxylic acid chlorides or carboxylic acid esters with cyclising or condensing agents such as phosphorus oxychloride, phosphorus pentachloride, acetic anhydride, sulphuric acid *etc*. For instance; The reaction of 6-chloro-1,3-benzothiazol-2-yl semicarbazide, aromatic acid in $POCl_3$ produces 2aryl-5-(6-chloro-1,3-benzothiazol-2-yl-amino-1,3,4 thiadiazoles in good yield.

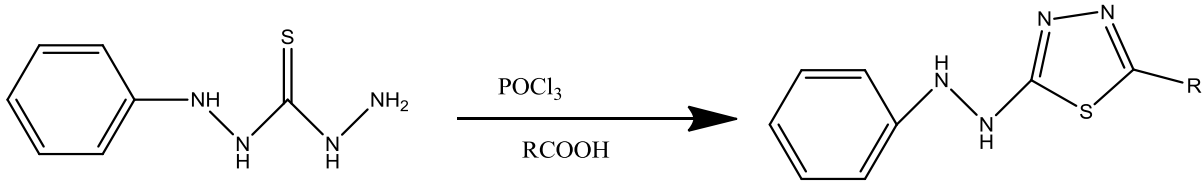


Scheme3: Nitin Deshmukh *et al*

Synthesized the 2-(substituted phenyl)-5-(2-phenylhydrazinyl)-1,3,4-thiadiazole. The N''-phenyl thiocarbono hydrazide phenyl hydrazine (0.1 mol) was dissolve in ethanol (95%, 50ml) and ammonia solution 20 ml then CS_2 (20 ml) was added slowly within 15 min with shaking and solution allow to stand for 1 hr. to it sodium chloroacetate (0.10 mol) and 50% hydrazine hydrate (20 ml)was added. The reaction mixture was warmed gently, filtered and evaporated to half of its volume and kept overnight. The solid thus obtained was filtered and purified by recrystallization from ethanol.

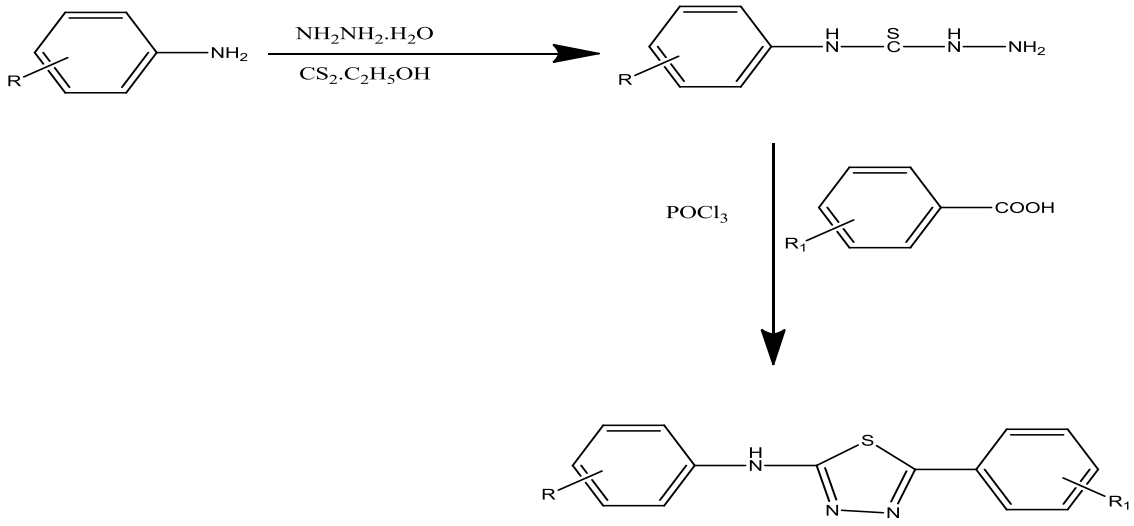


2-(substituted phenyl)-5-(2-phenylhydrazinyl)-1,3,4-thiadiazole: a mixture of N''-phenylthiocarbonohydrazide (0.10 mol), an aromatic acid and phosphorous oxychloride (25 ml) was refluxed for 18-22 hr. after cooling to RT the reaction mixture was poured into the crushed ice and kept overnight. The solid thus separated was filtered, washed with water, dried and purified by recrystallization from methanol.



Scheme4: Himanshu Sharma *et al*

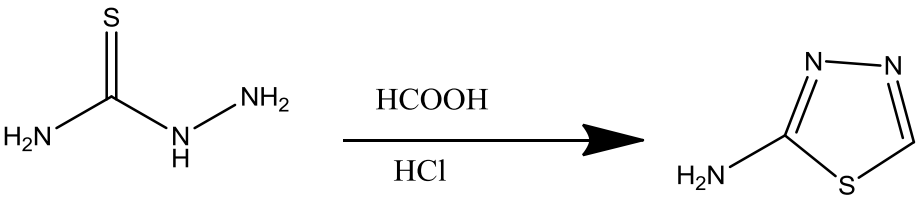
Step 1 Substituted aniline was dissolved in ethanol (95% 50 ml) and ammonia solution (20 ml).Then CS_2 (20 ml) was added slowly within 15 minutes with shaking and the solution was allowed to stand for 1 hr. To it were added sodium chloro acetate (0.1 M) and 50 % hydrazine hydrate (20 ml). The reaction mixture was warmed gently, filtered and evaporated to half of its volume and kept overnight. The solid thus obtained was filtered and purified by recrystallization from ethanol.



Step 2 Take thiosemicarbazide (0.10M), an aromatic acid (0.01 M) and phosphorous oxychloride (25 ml) was reflexed for 18 to 22 hr. After cooling the reaction mixture was slowly poured over crushed ice and kept overnight, The solid thus separated was filtered washed with water, dried and purified by recrystallization from methanol.

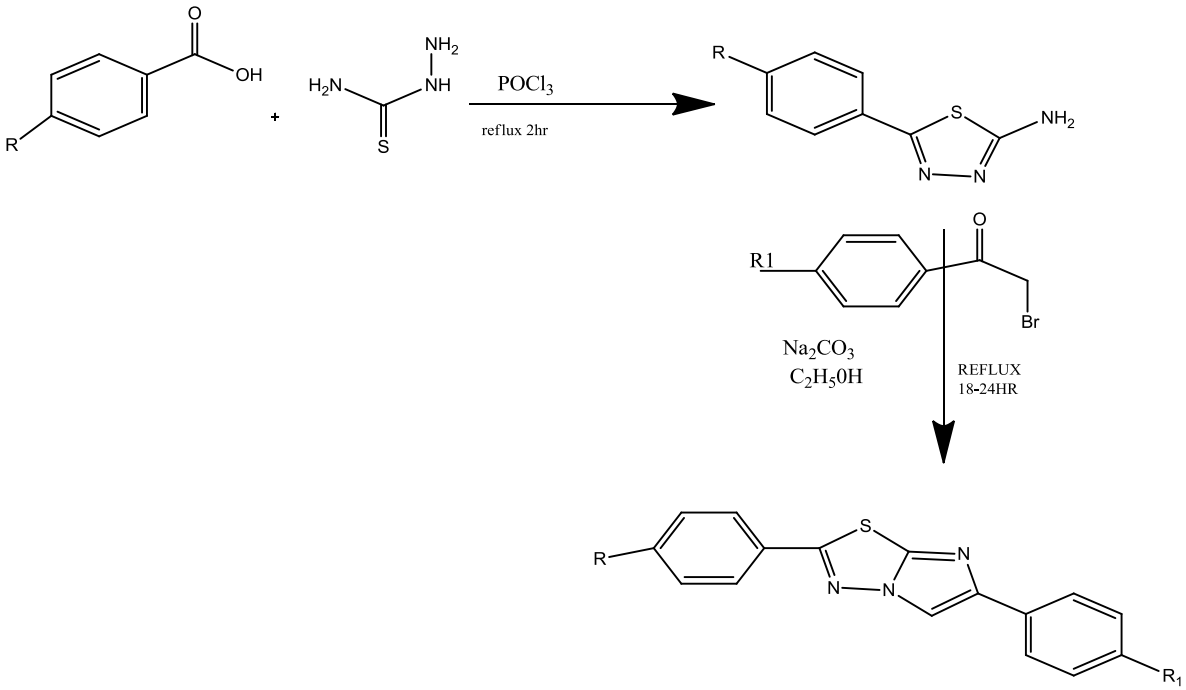
Scheme5: KikkeriP.Harish *et al*

Preparation of 1,3,4-Thiadiazole-2-ylamine (2). Thiosemicarbazide (1, 50.0g, 0.5486mol) was taken in 100ml formic acid and the reaction was stirred at room temperature for 1hr. The reaction was cooled and 100ml conc. hydrochloric acid was added. Reaction completion was monitored by TLC. The reaction was cooled to 0∘C and basified with ammonium hydroxide solution. The solid formed was filtered, washed with water, and dried to yield the above compound as off white solid.



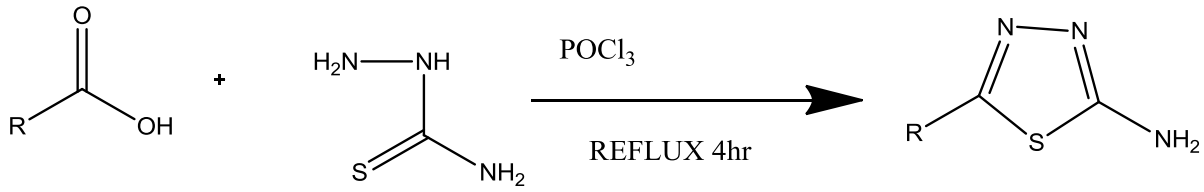
Scheme6: Rabindra Khadka *et al*

Equi-molar concentration of aromatic acid and thiosemicarbazide were mixed in a round bottom flask (100ml).Then about 10 drops of concentrated sulphuric acid &10ml of ethanol was added. It was refluxed for 2hr. The mixture was cooled and kept at room temperature overnight. Next day the excess solvent was distilled off and separated mass were poured into icewater then separated solid was collected by filtration and dried. The crude product was recrystallized in ethanol gave the crystal, pure substances.



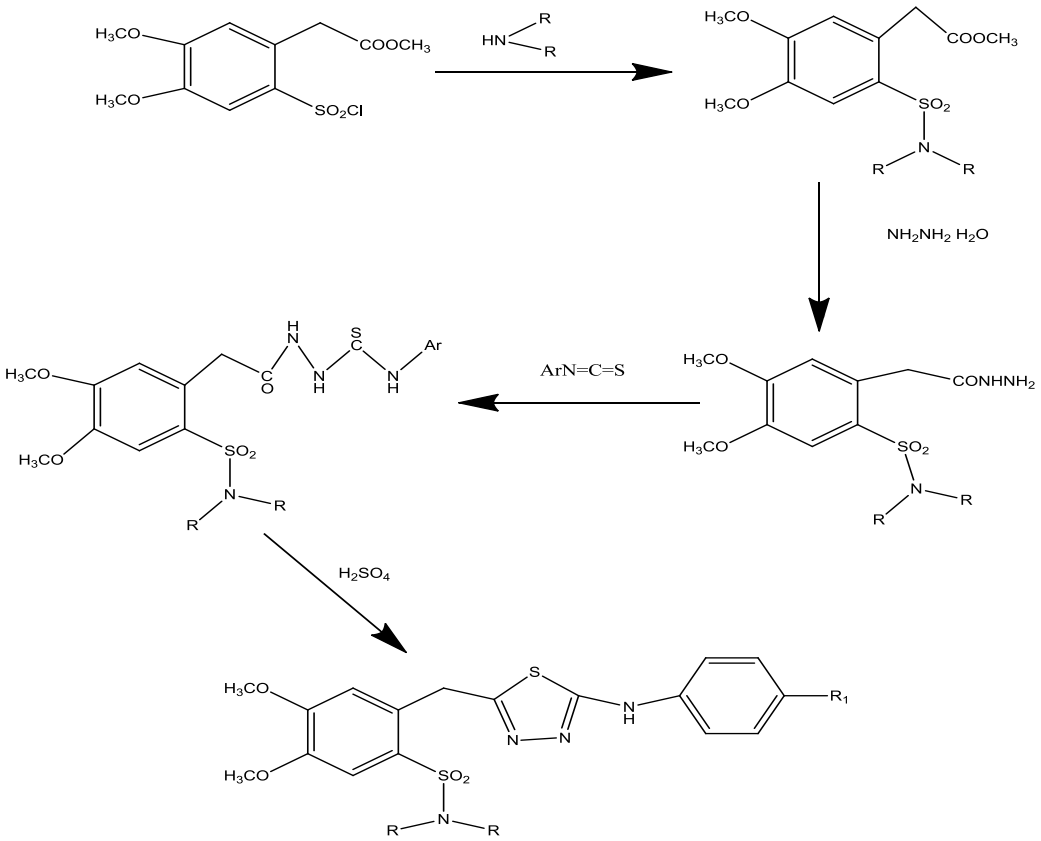
Scheme7: Nawaz khan *et al* ; synthesis of 2-amino-1,3,4-thiadiazole

Thiosemicarbazide and different substituted acids in required ratio in presence of phosphorous oxychloride were refluxed for 4 to 5 hr to yield the corresponding amino thiadiazole. The completion of reaction mixture was monitored by TLC. The resulting reaction mixture was poured into ice cold water, solid separated was filtered.



Scheme8 : camoutsis *et al*

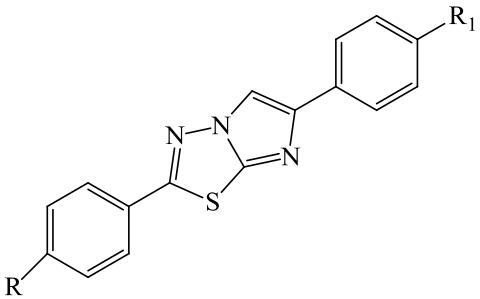
synthesis of N-{5-[2-(N-substituted sulfamoyl)4,5-dimethoxy benzyl]-1,3,4-thiadiazole-2-yl}-N-arylamines Starting from ethyl(2-chlorosulfonyl-4,5-dimethoxyphenyl)acetate (1)17,18) by reaction with secondary aliphatic amines in anhydrous benzene the corresponding sulfonamides (2a—d) were obtained. The latter were converted to the desired 2-(N-substituted sulfamoyl)-4,5-dimethoxyphenylacetylhydrazides (3a—d) by treatment with hydrazine hydrate in xylol. The hitherto unknown 1-[2-(N -substituted sulfamoyl)-4,5-dimethoxy-phenylacetyl]-4-aryl-thiosemicarbazides (4a—m) were obtained upon the reaction of acid hydrazides (3a—d) with suitable aryl isothiocyanates.4) Cyclization of 4a—m with concentrated sulfuric acid in cold resulted to the formation of N-{5-[2-(N-substituted sulfamoyl)4,5-dimethoxy benzyl]-1,3,4-thiadiazole-2-yl}-N-arylamines (5a—m) respectively.



PHARMACOLOGICAL ASPECTS OF THIADIAZOLE

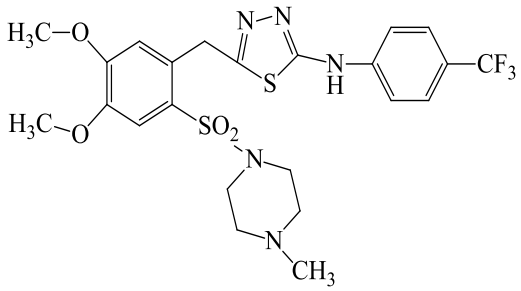
1. ANTIMICROBIAL

- **Gupta *et al.*,** The synthesis and antimicrobial activity of imidazo [2,1-b]-1,3,4-thiadiazole derivatives were reported against Gram +ve bacteria *Bacillus subtilis*, *Staphylococcus aureus*, Gram –ve bacteria *Pseudomonas aeruginosa*, *Escherichia coli*, and fungal strains *Candida albicans*, *Fusarium solani*, *Fusarium oxyporium*. Ciprofloxacin and Fluconazole were used as standard drug for antibacterial and antifungal activity respectively. The synthesized compound had moderate antibacterial activity especially with Gram *-ve; Escherichia coli* had good antibacterial activity.[1]

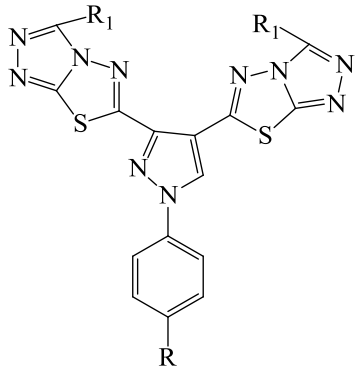


R-F, CH_3 R_1-CH_3,H,NO_2

- **Camoutsis *et al.*,** synthesized the series of sulfonamide-1, 2, 4-thiadiazole derivatives. Performed antifungal and antibacterial effect. The results of antibacterial and antifungal activity of compounds against a panel of selected gram positive, gram negative bacterial and fungal, in order to investigate the antifungal activity of the extracts, a modified microdilution technique was used. All the compounds showed very strong antibacterial and antifungal activity against all the species tested. Compounds 5h, 5k and 5m showed better antibacterial potential with 5h ranking as the more active while compounds 5k and 5m.[2]



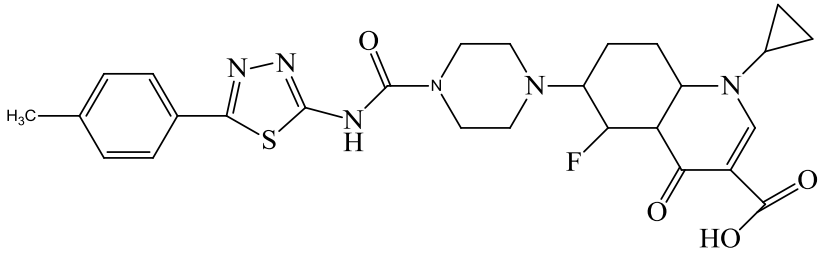
- **Asam *et al* .,** were synthesized a series of novel *bis*-1,2,4-triazole [3,4-b]-1,3,4-thiadiazole derivatives. The newly synthesized compound was studied for their antibacterial, antifungal and antioxidant. Compound 5a showed good activity against bacillus subtilis and compound 5g showed good activity against pseudomonas aeruginosa.[3]



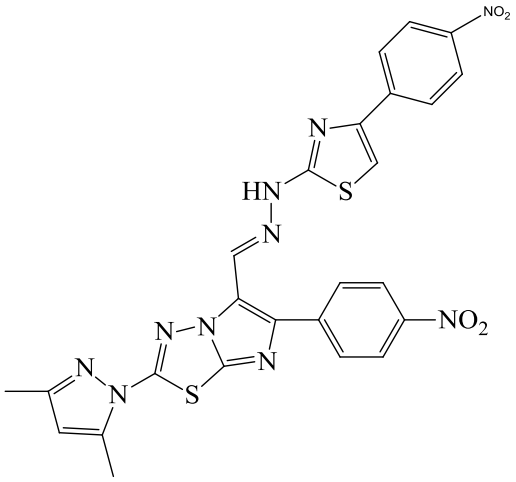
5a R- OCH_3, R_1-CH_3

5g R_1-CH_3,R- CH_3,

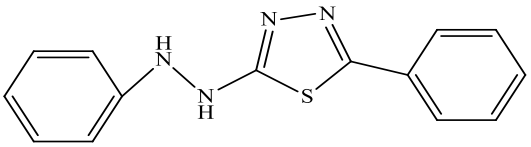
- **Rabindra *et al.,*** synthesized some new 2, 5-disubstituted thiadiazole derivatives. All the synthesized compounds showed moderate activity against gram +ve and gram–ve bacteria antibacterial activity data of all thiadiazole derivatives against tested organisms *(E.coli & S .aureus)* displayed significant activity. It was found that all compounds have shown significant antibacterial activity against these gram positive bacteria and gram negative bacteria. Minimum zone of inhibition (8 mm) was found in case of compound, 3T1 (*E.coli*).[4]



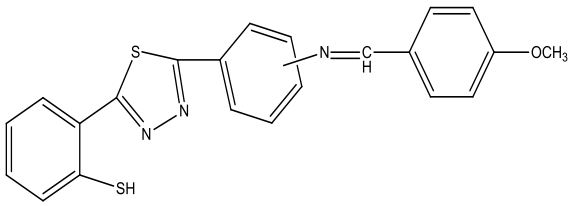
- **Syed *et al.,*** were synthesized imidazo [2, 1-b] [1, 3, 4] thiadiazole derivatives. all synthesized molecules were tested for anti-TB and anti-fungal activity. These derivatives showed a moderate to finest activity against *Mycobacterium tuberculosis* and fungal species. the compounds 6a1, 6a2, 6a3, 6c1, and 6d1 with methoxy/nitro substitution at 4th position of phenyl ring at 4th position of thiazole ring of the condensed imidazo[2,1-b][1,3,4]-thiadiazoles moiety and nitro or chloro or methoxy substitution on the 4th position of the phenyl ring at 6th position of the condensed imidazothiadiazole moiety was shown good anti-tubercular activity (1.6 to 6.25 µg/ml) against *Mycobacterium tuberculosis* H37Rv strain and Streptomycin (6.25 µg/ml), Ciprofloxacin (3.125 µg/ml) along with pyrazinamide (3.25 µg/ml) as standard.[5]



- **Amir *et al.,*** have been synthesized thiosemicarbazide of phenyl hydrazine on cyclization with different aromatic carboxylic acid in $POCl_3$ gives 2-(substituted phenyl)-5(2-phenylhydrazinyl)-1, 3, 4-thiadiazole. Antifungal study of newly synthesized compounds was performed using cup-plate method. The 1,3,4-thiadiazole derivative 1e having 4-aminophenyl group showed maximum inhibition (91.66%) against *A.Niger* whereas 1c having 2,4-dichlorophenyl group showed maximum inhibition (72.72%) against *C.albicans.* Thus it is concluded that 1,3,4-thiadiazole derivative were most effective against all microorganism at the concentration of 50µg/ml.[6]

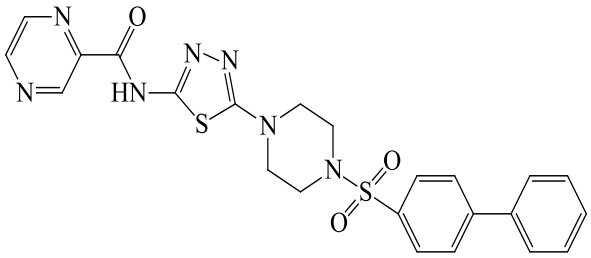


- **Ajit Kumar *et al;*** Synthesis of novel 2, 5disubstituted-1,3,4-thiadiazole derivatives and Biological screening Antibacterial, Antifungal activity. All the synthesized were evaluated for in vitro antibacterial activity against four Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus and Bacillus cereus*) and two Gramnegative bacteria (*Escherichia coli and Pseudomonas aeruginosa*) using the nutrient agar medium and antifungal activity against fungi (*A. niger*) using sabouraud dextrose agar medium. The compound 5-(2-Mercaptophenyl)-2-{N-(4-hydroxy-3-methoxybenzylidene)-4aminophenyl}-1,3,4-thiadiaz -ole 8f was found to exhibit the most potent antimicrobial activity.[7]



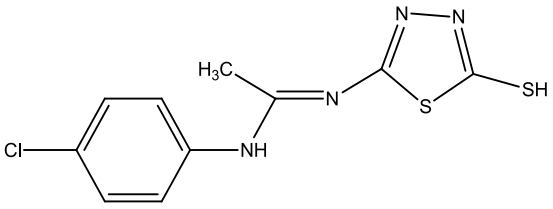
2. ANTICONVULSANT

- **Harish *et al.*,** were synthesized new pyrazine substituted 1, 3, 4-thiadiazole derivatives and carried out the reaction of pyrazine substituted 1, 3, 4 thiadiazoles with various sulfonyl chlorides. The anticonvulsant activity of the synthesized compounds 7(a–o) was evaluated by MES model at the dose of 100mg/kg. Compounds7d and 7g demonstrated significant protective effect on MES induced seizure and the effect of7d and 7g was similar to that of standard (phenytoin).[8]



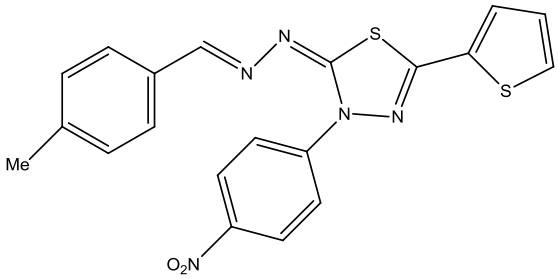
1. ANTI-DIABETIC

2. **Thrilochana *et al.*,** were Synthesis and biological evaluation of new Thiadiazole analogues for anti-diabetic activity against Alloxan induced diabetes. All the synthesised compounds were tested for there Anti Diabetic activity by using alloxan inducing model method taking glibenclamide as standard drug. The fasting blood sugar levels were measured. Especially electron donating compound derivatives at position 5 of thiadiazoles were more potent anti-diabetic activity than electron withdrawing thiadiazole derivatives. Hence, 1(a) = 1(b) = 1(c) can be helpful in the management of Diabetes Mellitus but not alone because of the less potency when it compared to Glibenclamide.[9]

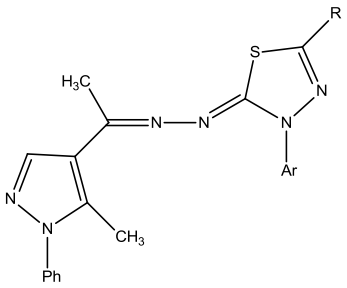


3. ANTICANCER

- **Gomha *et al*.**, synthesis, 5-(Thiophen-2-yl)-1,3,4-thiadiazole derivatives: molecular docking and in vitro cytotoxicity evaluation as potential anticancer agents. The antitumor activity of the products 4, 7, 9, 11, 13, 15, 17, 20a–c, and 23a–c was investigated against 2 carcinoma cell lines, human hepatocellular carcinoma and human lung cancer cell lines, in comparison with cisplatin as anticancer standard drug using colorimetric MTT assay. IC50 (the concentration of test compounds required to kill 50% of cell population) was determined from the dose–response curve. The activity was expressed as IC50 values (μg) ± SD from 3 replicates.[10]

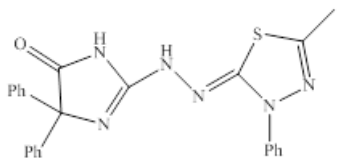


- **Gomha *et al.*,** have synthesized some novel thiadiazoles and thiazoles incorporating pyrazole moiety. The synthesized compounds were tested for *in-vitro* antitumor activity against HCF-7 and could therefore serve as lead chemical entities for further modification to render them clinically useful drug agents.[11]



R-$COCH_3$, COOEt

- **Gomha *et al.*, (2017)**, have synthesis and SAR study of the novel Thiadiazole–imidazole derivatives. The newly synthesized compounds have been evaluated for their anticancer activity against a liver carcinoma cell line HEPG2-1. All the synthesized compounds were evaluated for their anticancer activity against the liver carcinoma cell line. The results revealed that 1,3,4-thiadiazole derivatives 16c, 21c, 10g, 21b and 10h have promising antitumor activities (IC50=0.86, 1.02, 1.08, 1.17, 1.44 μM, respectively) against liver carcinoma cell line and most of the tested compounds showed moderate anticancer activities.[12]



CONCLUSION

Thiadiazole has been and continues to be one of the most active areas of organic chemistry. As a result thiadiazoles have been successfully used as antibacterial, anticancer, hypoglycemic, antihypertensive and anti-inflammatory

agents. In addition, they have also been used in agriculture, plastics, polymers, dyes and textiles. Hence thiadiazole still continues to draw the attention of synthetic organic chemists and is of great scientific interest. Hence it can be concluded that many researches had investigated on substituted thiodiazole compounds having the biological activities.

REFERENCE

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