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A COMPREHENSIVE REVIEW ON RECENT ADVANCEMENTS IN THE PHARMACOLOGICAL ACTIVITIES OF 1,3,4-THIADIAZOLE DERIVATIVES

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ABSTRACT

Due to their extensive variety of biological actions, 1,3,4-thiadiazole has been the subject of several investigations. Their antibacterial, anti-inflammatory, anti-cancer, anti-diabetic and anti-convulsant, anti-tubercular actions have been discovered. Several medications on the market include thiadiazole derivatives, including acetazolamide, methazolamide, sulphamethazole, and cefazoline. The creation of new thiadiazoles and the study of their biological and chemical properties have grown in significance. With better efficacy and reduced toxicity, modification of the thiadiazole ring has shown to be quite successful. The newly synthesized thiadiazole with significant biological activity is highlighted in this review study.

Keywords: *1,3,4-Thiadiazole derivatives, Heterocyclic compounds, Microbial activities, Biological activities.*

1. INTRODUCTION

Heterocyclic compounds are special cyclic molecules in which carbon is joined to additional elements in the ring, such as oxygen, nitrogen, and/or sulfur. Two or more fused rings may be present in the heterocyclic compounds [1]. Natural and manufactured substances containing heterocyclic systems are fundamental to all forms of life on Earth [2]. Natural sources, including animals and plants, create a variety of heterocyclic molecules [3-5]. Heterocyclic ring structures are present in various pharmaceutical products [6,7] and found to be anti-fungal, anti-obesity, anti-inflammatory, antibacterial, anti-analgesic, anti-TB, anti-depressant, anti-malarial and anti-cancer [8,9]. They are also present in colours [10] and in lubricants [11,12]. Green chlorophyll and scarlet heme provide colour and vitality to plants and animals. Cinchona bark, which contains the heterocyclic chemical quinine, has been used to cure malaria for hundreds of years [13-15]. The heterocyclic chemicals thiamin, riboflavin and nicotinic acid play crucial roles in metabolism [16].

Heterocyclic compounds are crucial to several biological processes. Among the essential amino acids, tryptophan & histidine are the only ones with a heterocyclic aromatic ring. These amino acids form amide bonds with other amino acids, which aids in protein synthesis. Histamine, a potent vasodilator created by the decarboxylation of histidine, is produced during allergic reactions. It also causes heartburn by increasing gastric acid production. Anti-histamines, which block the effects of histamine, are a popular medication. The amino acid tryptophan is converted into the neurotransmitter serotonin [17-19].

It is becoming more common for pharmaceuticals to have the same biological effect as their natural counterparts. The research and development of novel chemicals to combat any disease require a wide range of heteroaromatic derivatives. Heterocyclic natural products are essential to human and animal health and include antibiotics (penicillin, cephalosporins) alkaloids (vinblastine, reserpine, morphine) and cardiac glycosides [2]. Researchers in the pharmaceutical industry have been motivated by them to develop and create ever-improved medicines [20]. Heterocycles have several modern-day, practical uses, including those in the rubber industry, as well as in the production of rubber, dyeing materials, copolymers, developers, solvents, sensitizers, and cleaning products [21,22].

A compound's molecular structure is a crucial determinant of its biological action. A wide variety of molecules with biological activity include heterocyclic moieties. Thiadiazole, thanks to its N=C-S moiety, is a very adaptable moiety that may be used in a broad range of contexts. Due to their wide range of biological activity, they have emerged as a pivotal class of heterocycles, drawing the attention of scientists throughout the world.

Several pharmaceuticals, including acetazolamide, butazolamide and sulfamethazole have a 1,3,4-thiadiazole nucleus [23,24]. Additionally, various analogues have been discovered and used.

2. THIADIAZOLE

Two nitrogen atoms or one sulfur atom make up the heterocyclic molecule thiadiazole. It is a band with five interlocking parts with one sulphur and two nitrogen molecules [25]. Fischer reported the first 1,3,4-thiadiazole in the year 1882, but Freund & Kuh showed the real structure of the ring system in 1890 for the first time. There are four different isomers of thiadiazole (Figure 1) found in nature: (i) 1,2,3-thiadiazole; (ii) 1,2,5-thiadiazole; (iii) 1,2,4-thiadiazole; and (iv) 1,3,4-thiadiazole [26-28]. 1,3,4-Thiadiazole is significant because of the wide variety of biological functions they provide [29-31]. Compounds containing this moiety are effective anti-microbial and anti-inflammatory effects [32-34], analgesic [35-36], anti-epileptic [36], antibacterial [37,38], anti-tubercular [39], anti-convulsant [40], and anti-cancer [41] activities are only some of the novel effects observed for thiadiazole moieties with various substitutions.

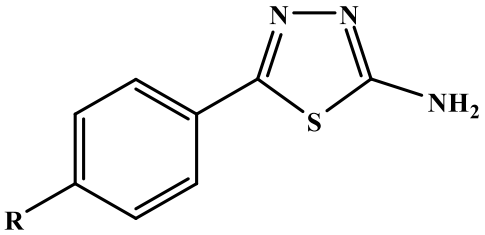
Figure 1: Four different isomers of thiadiazole

3. BIOCHEMICAL FUNCTIONS OF 1,3,4-THIADIAZOLE

1,3,4-Thiadiazole (THZ) is an important molecule as it showcases various applications in agriculture, materials chemistry, and medicine [35], [42-46]. It has diuretic, anti-diabetic, anti-convulsant, anti-tubercular, anti-inflammatory, anti-cancer, anti-oxidant, and anti-microbial characteristics. Some instances in which thiadiazoles are used in biology are shown below.

3.1. Antimicrobial activity

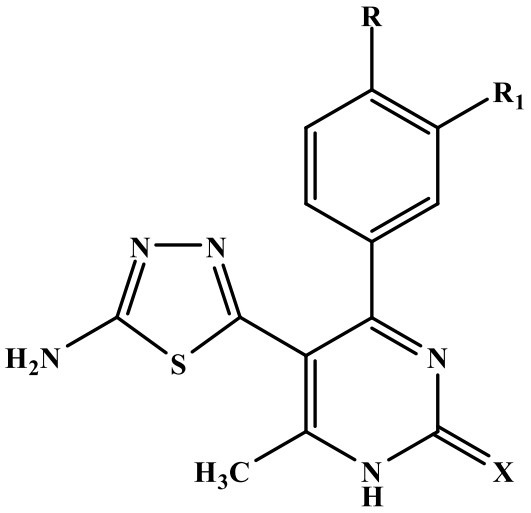
The antibacterial activity of thiadiazole was tested *in vitro* against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa* [47]. The thiadiazole was also tested *in vitro* activity against fungal strain *A. niger, A. flavus, C. albicans, T. cucumeris and G. saubinetii* [48-50]. For 5-(4-substituted phenyl)-1,3,4-thiadiazol-2-amine compounds (here substation can be an atom/ moiety: (a) F, (b) Cl, (c) Br, (d) OH, (e) OCH_3, (f) OC_2H_5 (Figure 2) exhibited significant anti-microbial activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*. The minimum inhibitory concentrations (MIC) observed for fluoro and chloro-substituted products were 20 to 28 µg/ml for *S. aureus* and *B. subtilis.* For fluoro, chloro, bromo and hydroxy-substituted products, the MIC were 24 to 40 µg/ml for *E. coli* and *P. aeruginosa* [51]. The oxygenated substituents at the phenyl ring (MIC 32-42) exhibited activity against the fungal strain *A. niger* and *C. albicans*. The halogen attached to the phenyl-1,3,4-thiadiazol moieties showed antibacterial activity with a bias toward Gram-positive microorganisms, while the oxygenated substituent provides anti-fungal action [51].



R = F, Cl, Br, OH (d), OCH_3, and (e) OC_2H_5

Figure 2: Structure of 5-(4-substituted phenyl)-1,3,4-thiadiazol-2-amine

The *in vitro* antibacterial activity 2-amino-1,3,4-thiadiazole derivatives (Figure 3) was conducted at a concentration of 10 g/ml *via* disk diffusion. For E. coli, however, compounds (Figure 3) where R_1 is NO_2 showed only modest efficacy compared to the gold standard anti-biotic ciprofloxacin. Inhibitory activity against the pathogens *viz. P. aeruginosa, S. aureus*, *and E. coli* ranged from moderate to excellent when tested with hydroxyl derivatives [52].



X = O, SR = OH, R_1 = H, R = H, R_1 = NO_2

Figure 3: Structure of 5-(5-amino-1,3,4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenyl pyrimidin-2(1*H*)-one

The three series of derivatives of imidazole-fused imidazo[2,1-*b*][1,3,4]thiadiazole were produced (Figure 4) and evaluated for their anti-microbial activities [53]. All the prepared compounds exhibited excellent antimicrobial efficacy.

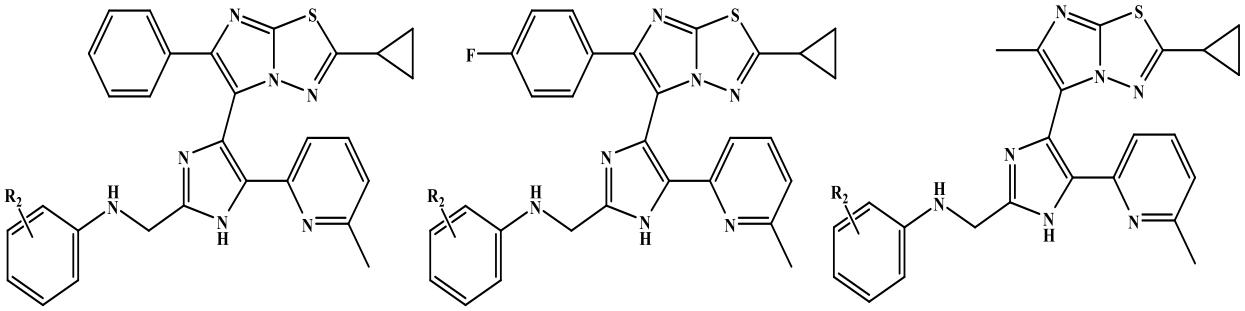


Figure 4: Structure of imidazole-fused imidazo[2,1-*b*][1,3,4]thiadiazole analogues

The imidazo[2,1-*b*]thiadiazole moiety-containing compounds showed an extensive array of antibacterial [54-56], anti-cancer [57-60], anti-tubercular [61-63], analgesic [64], anticonvulsant [65,66], anti-inflammatory [67-69] and anti-fungal [70] properties.

Benzotriazole derivatives (Figure 5) were synthesized by Sen *et al.* [71] by two methods, *viz.* microwave and thermal conventional methods. The anti-microbial properties of studied compounds were also analyzed. The benzotriazole derivatives were found to be potent against *E. coli*, *S. aureus, K. pneumoniae* and *B. substilis* [71].

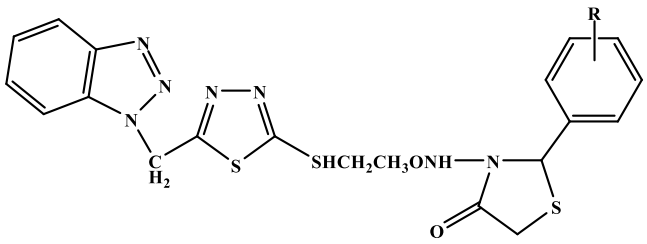


Figure 5: General Structure of 5-[(2’’’-Substituted aryl-1’’’,3’’’-thiazolidine-4’’’-ones)-1’’-(iminothioacetyl)-1-(methylene)-1’,3’,4’-thiadiazoles]-1,2,3-benzotriazoles

Vedavathi *et al*. [72] in year 2010 synthesized fluorobenzothiazole containing THZ derivatives (Figure 6), among which few compounds showed antibacterial and anti-fungal activities. Ahmad *et al*. [73] compiled in a review about the synthetic procedure of THZ derivatives preparation and their important activities in the field of medicine and pharmaceuticals. Six compounds were synthesized with 1,3,4-thiadiazole and Schiff base (Figure 7), which displayed strikingly potent antibacterial activity. The synergistic interaction between the 1,3,4-thiadiazole and Schiff base may be responsible for the activity [74].

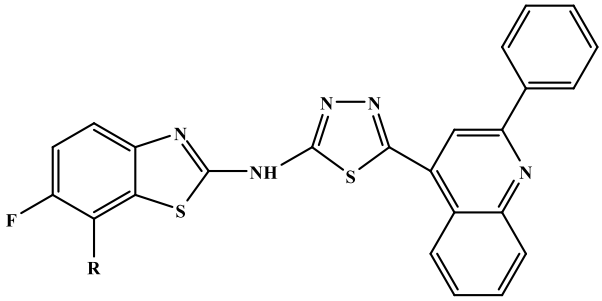


Figure 6: General Structure of fluoro benzothiazole incorporated with 1,3,4-thiadiazole

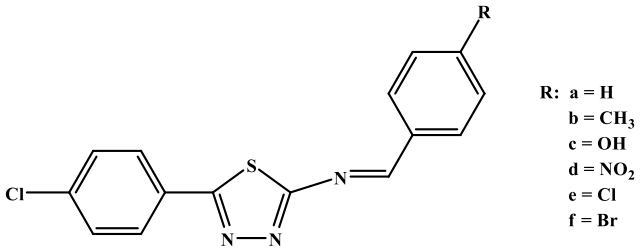


Figure 7: Structure of Schiff base derivatives of 5-p-chlorophenyl-1,3,4-thiadiazole-2-amine

A series of new thiazolidinediones (Figure 8i & ii) were synthesized and assessed for their efficiency against various bacteria and various strains of fungi, and yeasts. The highest antibacterial properties were in two synthesized compounds, *p*-chlorophenyl and 6-*p*-bromophenyl [75].

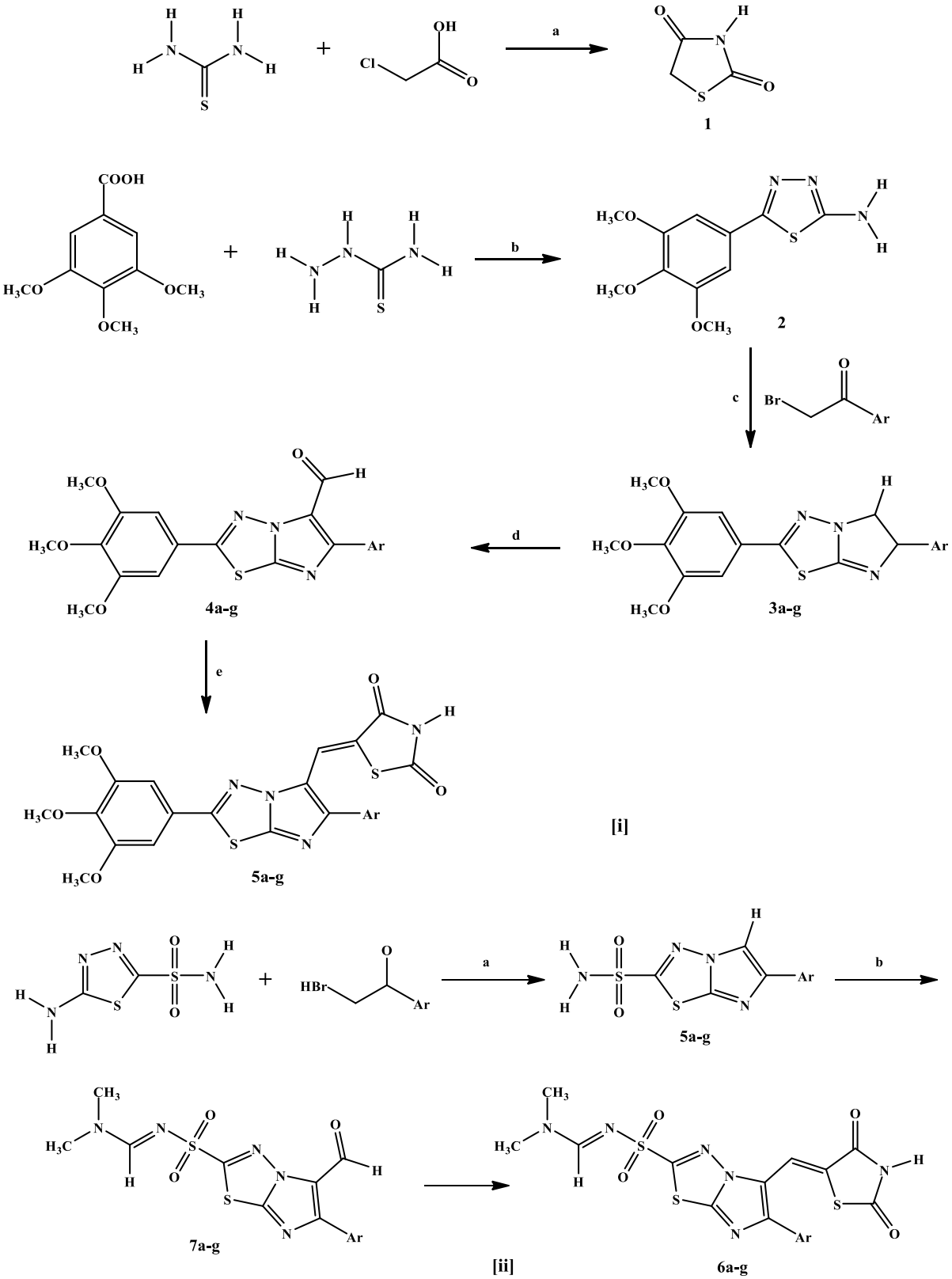


Figure 8: Synthetic route of new 2,4-thiazolidinediones bearing imidazo[2,1-*b*][1,3,4]-thiadiazole moiety [75]

5-((2-Oxo-2*H*-chromen-7-yloxy)methyl)-1,3,4-thiadiazol-2(3H)-one containing coumarin moiety were synthesized by Al-Amiery *et al*. [76]. The *in vitro* antibacterial activity was assessed for a wide range of bacteria and fungi.

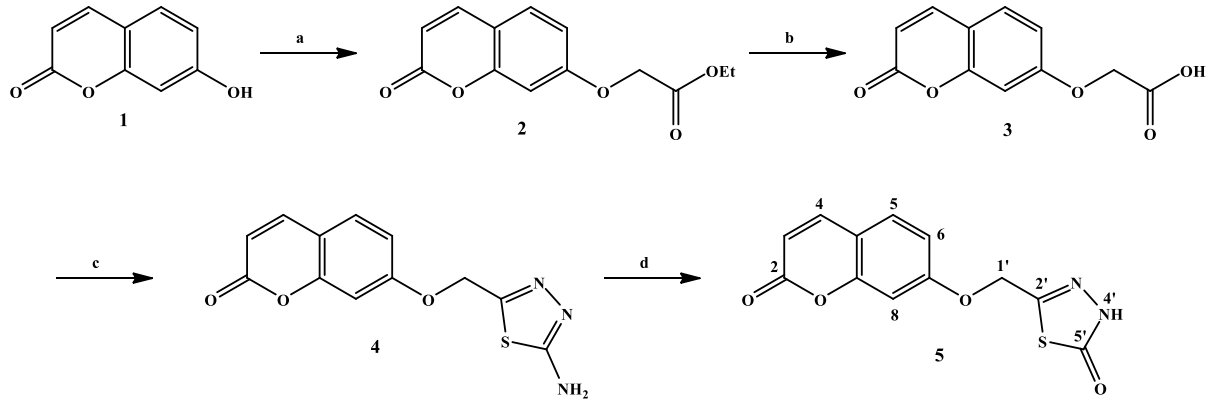


Figure 9: Synthetic route of 5-((2-oxo-2H-chromen-7-yloxy)methyl)-1,3,4-thiadiazol-2(3*H*)-one containing coumarin moiety

Fang *et al*. [77] synthesized sulfoxide derivatives of trimethoxyphenyl substituted THZ (Figure 10). The biological activity of the compounds was also assessed against the fungal strain *S. sclerotiorum*. Rad *et al.* [78] synthesized THZ moiety-containing compounds and observed that the halogenated aryl derivatives and non-substituted ones were the most active against the pathogens *S. typhimurium* and *C. albicans*.

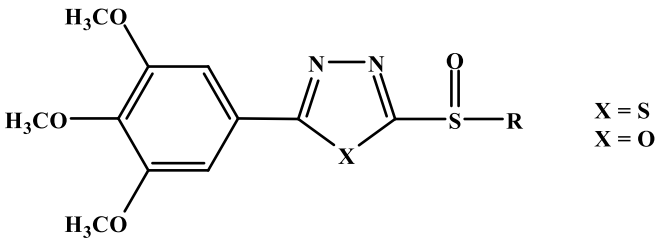


Figure 10: Structure of 2-substituted sulfinyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole (oxadiazole)

Similarly, 2,5-Disubstituted derivatives of THZ were synthesized and characterized by Nadjet *et al.* [79] few of these derivatives exhibited significant anti-microbial activity. The derivatives of thiadiazoles were synthesized by Baghel *et al*. [80] in 2014 (Figure 11) and evaluated their antimicrobial properties. The compounds with phenyl ring substituted with an electron-withdrawing group displayed excellent antimicrobial activity.

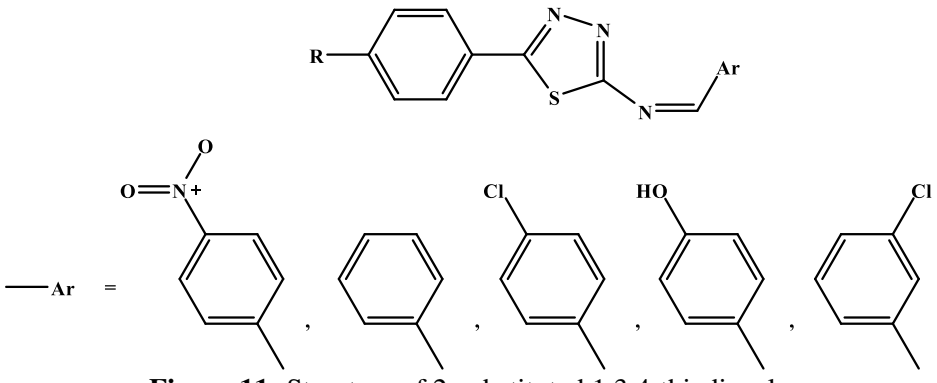


Figure 11: Structure of 2-substituted 1,3,4-thiadiazole

3.2. Anti-Inflammatory Activities

4-(5-imino-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)aniline (Figure 12) was synthesized by Asif & Asthana [81]. The carrageenan-induced paw oedema approach was used for assessing the *in vivo* anti-inflammatory properties and compared to the gold standard NSAID diclofenac.

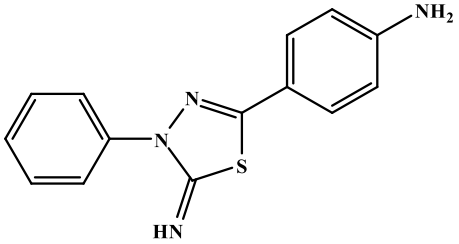
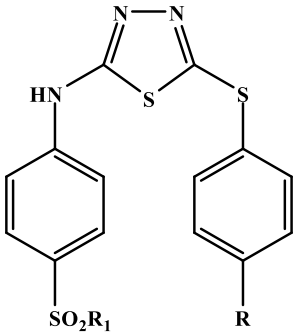


Figure 12: Structure of 4-(5-imino-4-phenyl-4,5- dihydro-1,3,4-thiadiazol-2-yl)aniline

The anti-inflammatory and analgesic tests were performed for 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives (Figure 13), and the results showed promising biological activities [82].



$R_1 = SO_2Cl$, R = CH_3, F, CF_3; $R_1 = SO_2NH_2$, R = Cl, CF_3

Figure 13: Structure of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives

The 4-(4-nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamide (Figure 14(i)), 4-(4-fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamide (Figure 14(ii)) and 4-(4-nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrrole-3-carboxamide (Figure 14(iii)) were also synthesized. The anti-inflammatory activity was investigated and found to inhibit paw oedema to a high degree in comparison to indomethacin [83].

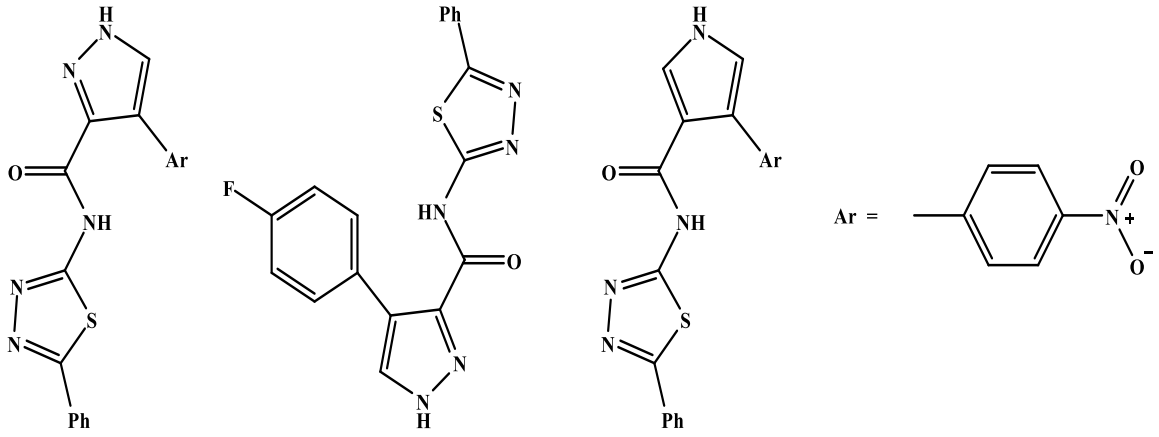


Figure 14: Structure of 4-(4-nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamide (i), 4-(4-fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamide (ii) and 4-(4-nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrrole-3-carboxamide (iii)

5-(*o*-Hydroxy phenyl)-2-[4'-aryl-3'-chloro-2'-azetidinon-1-yl]-1,3,4-thiadiazole (Figure 15) derivatives were also synthesized and characterized. The *in vitro* anti-inflammatory activity of the synthesized derivatives was studied. The obtained results were compared with Ibuprofen. The compounds showed 29.3% to 39.1 % inhibition [84].

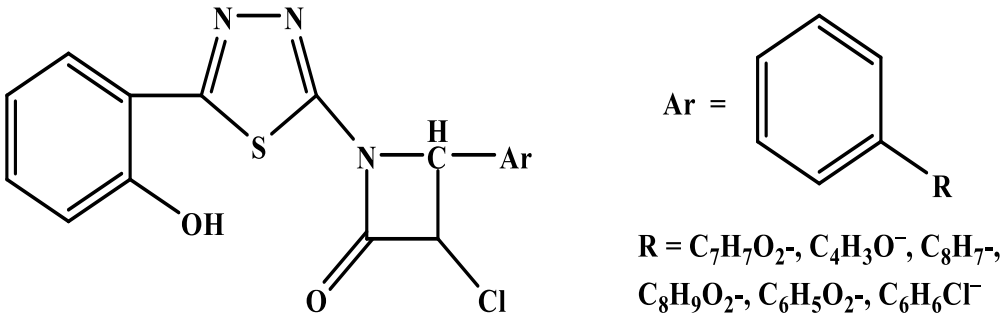


Figure 15: Structure of 5-(*o*-Hydroxy phenyl)-2-[4'-aryl-3'-chloro-2'-azetidinon-1-yl]-1,3,4-thiadiazole

3.3. Anticancer Activity:

The THZ derivatives are capable to disrupt DNA replication tumor/cancer cells [85]. In 1957, anticancer activity THZ derivatives was carried out first time by Shapiro *et al.* [86]. It was found that niacinanalogue2-ethylamino-1,3,4-thiadiazole (EATDA), is the main cause of inhibiting mammary adenocarcinomas. Earlier anticancer activity is prevented by injection of nicotinamide, which favours the evidence that niacin behaves like anantagonist. Additionally, the anticancer efficiency is enhanced by a combination of EATDA, 8-azaguanine, deoxypyridoxine and testosterone [87].

In the literature 1,3,4-thiadiazole-2-sulfonamide derivatives (Figure 16) were documented to show, effectively in vitro tumour activity with GI_{50} varies from 0.1–30 μM against number of human cancer cell lines [88].

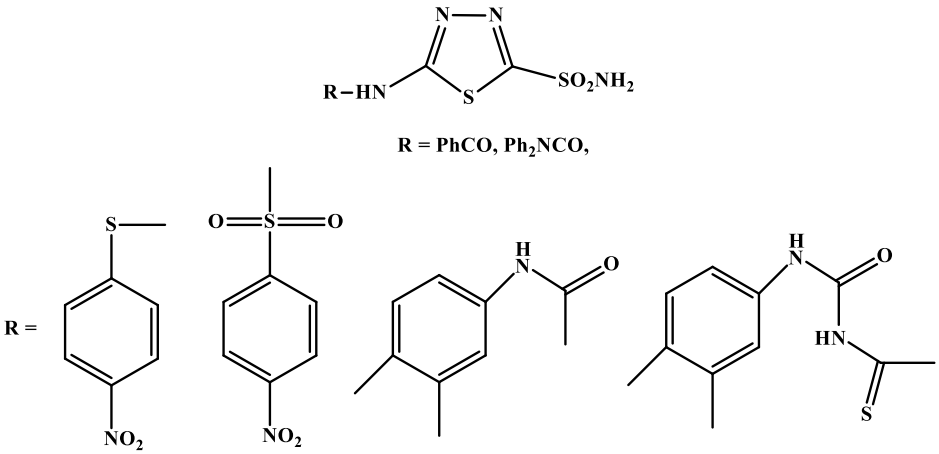


Figure 16: Structure of 1,3,4-thiadiazole-2-sulfonamide derivatives

Morsy and co-workers [89] evaluated a series of 1,3,4-thiadiazole-bis-sulfonamides (Figure 17) for anticancer activity and observed they act as inhibitors of number of carbonic anhydrases. Inhibition of various types of tumour cells was observed in ex vivo with GI_{50} in the range of 0.74–10.0 μg/ml against large intestine, lung, and breast cancer as cell lines *viz*. HCT116, H460, and MCF-7 respectively. Anticancer activity of THZ derivative of dihydrazone with inhibition of growth of CHO, HL60, and L1210 for Chinese hamster ovary, human blood cancer and mouse blood cancer respectively were reported by Zhang and co-workers [90]. El-Ashmawy and co-workers [91]

synthesize and investigated the antitumor activity of a series of THZ derivatives of sulfonamide against mammary cancer cell line (MCF-7) which indicated the inhibition of growth of human breast carcinoma.

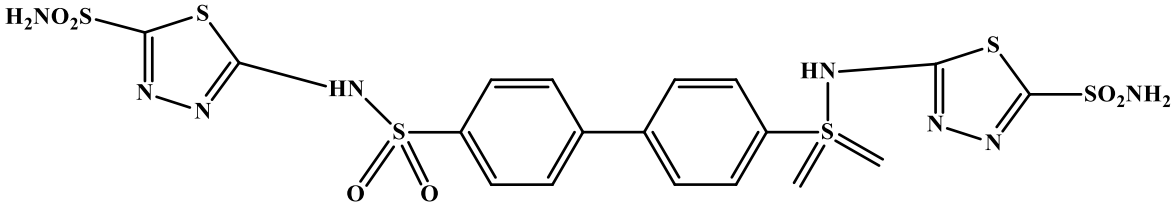


Figure 17: Structure of 1,3,4-thiadiazole-bis-sulfonamide

As reported by Lee *et al.* [92] that lung cancer cell is quite sensitive to glutamine supply. This was evaluated by testing a series of eleven cancer cells for the metabolic dependency for glutamine through regulating fatty acid synthesis, glycolysis, autophagy, etc. The compound bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES) (Figure 18) exhibited anticancer activity by controlling glutamine supply.

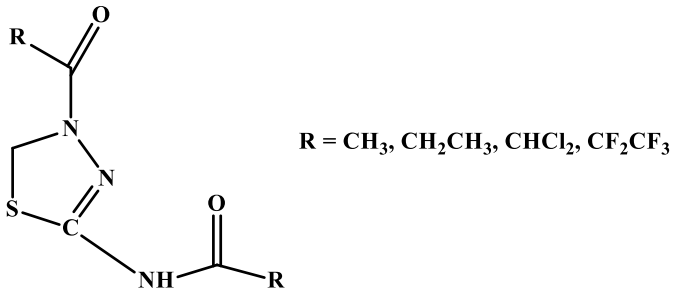
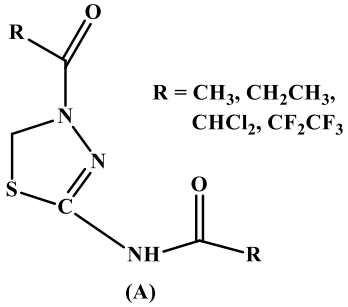


Figure 18: Structure of *bis*-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide

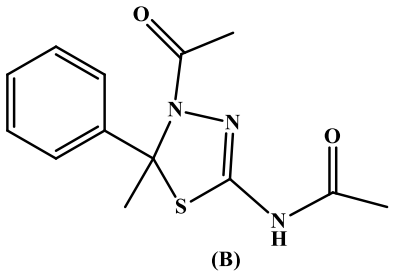
Several scientists evaluated anticancer activity of THZ derivatives against number of human cancer cell lines and found them effective. The THZ derivatives showed effective activity against Hep-2 cell line analysed *via* CCK-8 assay [93], against L929, A549, SMMC-7721, and HeLa.

The *N*-((5-(((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)amino)-1,3,4-thiadiazol-2-yl)methyl)benzamide showed activity against MCF-7 [94]. The *in vivo* antimicrobial, antitumor and dihydrofolate reductase inhibition by 5-(3,5-dinitrophenyl)-1,3,4-thiadiazole derivatives was observed in CCRF-CEM, HCT-15, PC-3, and UACC-257 antitumor activities. 5-Phenyl-substituted 1,3,4-thiadiazole-2-amines derivatives were found to be active against MDA MB-231 [95]. THZ derivatives have significant anticancer activity against MCF-7 and A-549 as reported by Rashdan *et al.* [96].

Mitotic arrest in cancer such as colorectal and ovarian leads to anticancer activity as reported by 1,3,4-thiadiazoline derivatives. For PC3 prostate cancer around 103 compounds were evaluated. The 19(B) compound contains activity against prostate as well as melanoma cell lines [97].



(A)



(B)

Figure 19: Structure of N-((5-(((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)amino)-1,3,4-thiadiazol-2-yl)methyl)benzamide

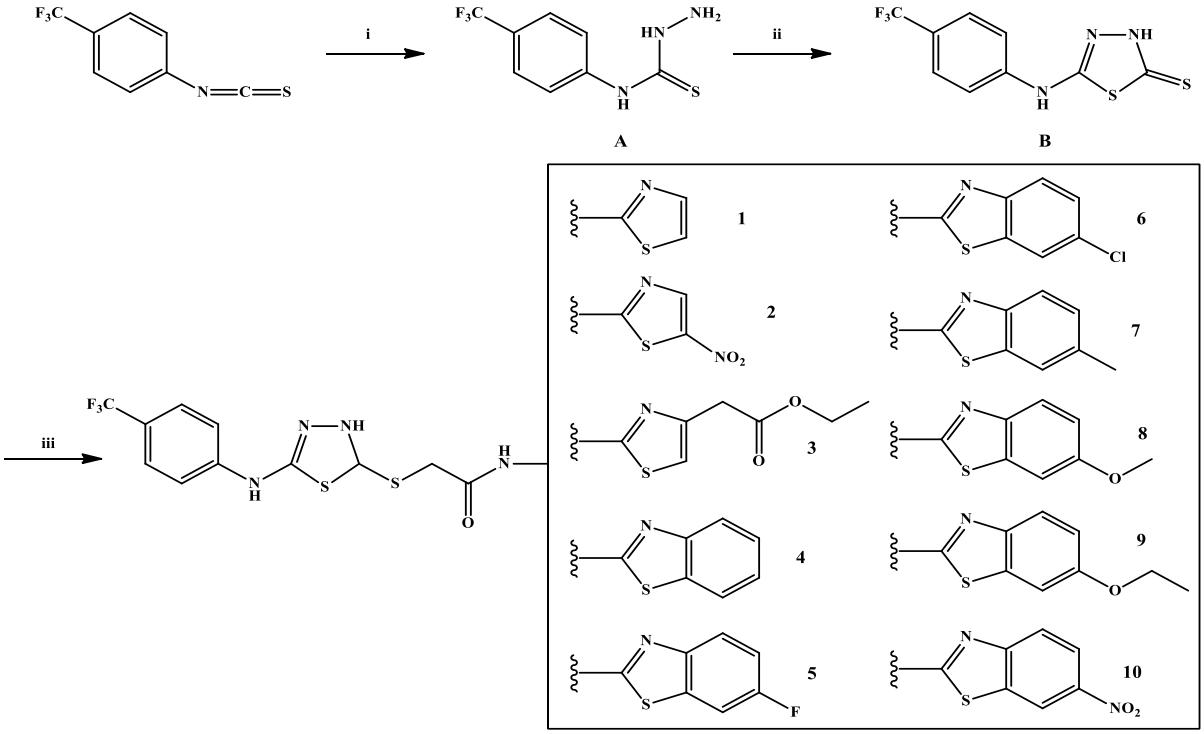


Figure 20: Synthetic route for the preparation of N-(aryl)-2-[(5-((4-(trifluoromethyl)phenyl)amino)-1,3,4-thiadiazol-2-yl)thio]acetamide derivatives

Derivatives of THZ (Figure 20) were evaluated for antiproliferative efficacy on the K562 CML Jurkat. MT-2, and HeLa cell lines. All the compounds exhibited potential anticancer activity against K562 cell line. They found to be kinase inhibitor and shows different profile than imatinib [98].

Synthesis and evaluation of 5-phenyl-4,5-dihydro-1,3,4-thiadiazoles series of anticancer activity was performed by Alam *et al.* [99] and reported inhibitory action against A549, SK-MEL-2,Sk-OV-3,HCT15 cell lines. Similarly, Hosseinzadeh *et al.* [100] evaluated by MTT assay using Doxorubicin as standard the anticancer activity of THZ with trifluoromethyl substituent for PC3, MCF7, and SKNMC and observed better cytotoxicity similarly Aliabadi *et al.* [101] reported an evaluation of series 2-pyridyl moiety containing THZ derivative (Figure 21) for its cytotoxicity against PC3, HT29 and SKNMC cell lines and compared with doxorubicin and observed that the nitro group containing derivatives exhibited better cytotoxicity against PC3 cell line. At the same time the methoxy containing derivatives exhibited adequate cytotoxicity against SKNMC cell line.

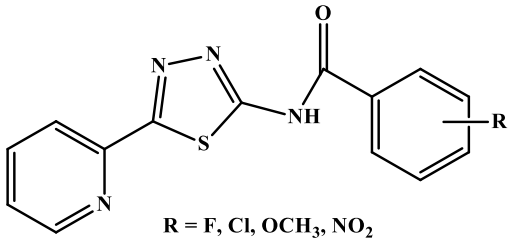


Figure 21: Structure of Substituted N-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)benzamides

The drug ibuprofen and ciprofloxacin derivatives THZ (Figure 22) were prepared and evaluated against cancer cell of human hepatocellular carcinoma (Huh-7) cell line. In the theoretical and as well as in the experimental studies the compounds found to be anticancer in nature [102].

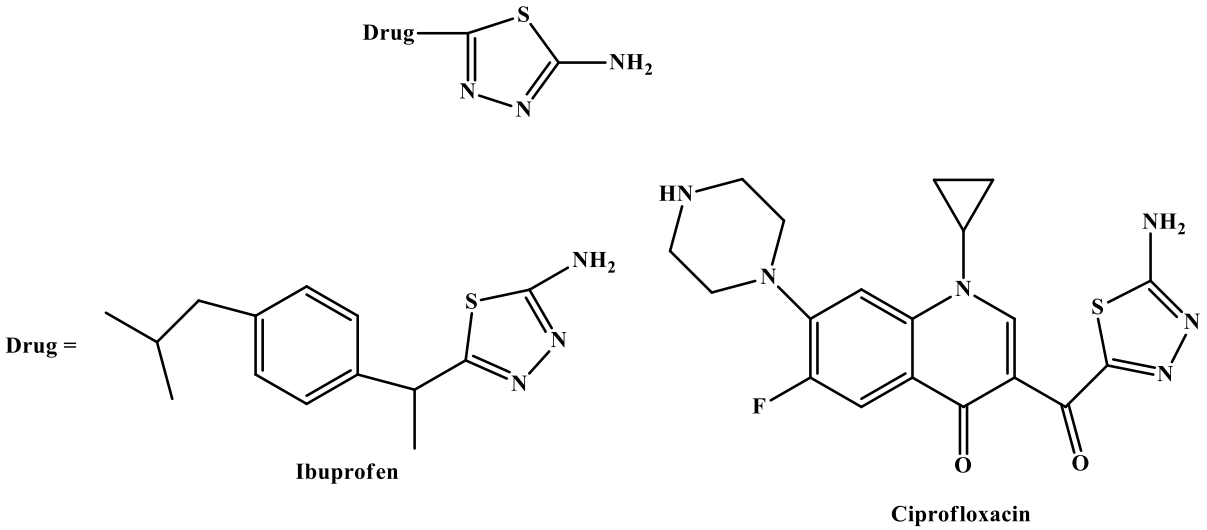


Figure 22: Structure of ibuprofen and ciprofloxacin (drug) derivatives 1,3,4-thiadiazole

Sahem *et al.* [103] synthesized the 5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine (Figure 23) in the presences of $POCl_3$ by picolinic acid and thiosemicarbazide combination by conventional thermal method and also by microwave irradiation method. The compound 5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine were screened for *in-silico* anticancer activity. The compounds found to induce intrinsic dysfunction in mitochondrial membrane leading to cell death. The compound anticancer activity was also found for number of cancer cell lines like Caco, PCL, *in-vitro*.

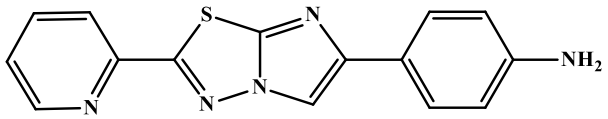


Figure 23: Structures of 5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine

3.2. Antituberculosis

Tuberculosis (TB) is an infectious disease occurred on lungs caused by Mycobacterium tuberculoum. It was reported that one of the three people suffer from latent TB and approximately one-tenth turned out to be active TB [104]. It is a life-threatening disease with 1.3 million deaths globally in 2020 [105]. It is a huge challenge to tackle the disease due to the strains which multidrug resistance and extensively resistant [106-109]. Thus, there is a need for the development of anti-TB drugs which is effective that can make it susceptible to treatment.

Gireesh *et al.* [70] found a novel imidazo[2,1-*b*][1,3,4]thiadiazole derivatives (Figure 24) potent antitubercular in nature. It was observed that compound contains R = *p*-anisyl, R= p-chlorophenyl, and R = *p*-chlorophenyl, R= *p*-chlorophenyl were significantly active against cervical cancer cells (Hela) or Mycobacterium tuberculosis (H37Rv).

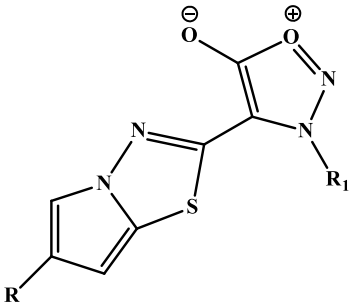


Figure 24: General Structure of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives

The antituberculosis efficacy of 2-(5-nitro-2-furyl) or 2-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-1,3,4-thiadiazole derivatives (Figure 25) was developed and evaluated *in-vitro*. The 16 compounds were tested from two series of 2-(5-nitro-2-furyl)- as 2-(1-methyl-5-nitro-l*H*-imidazol-2-yl)-5-propyl, allyl or propargyl)thio-l,3,4-thiadiazoles or 2-(5-nitro-2-furyl)- and 2-(1-methyl-5-nitro-l*H*-imidazol-2-yl)-5-(nitrobenzyl) [110].

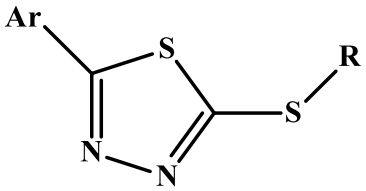


Figure 25: Structure of 2-aryl-5-alkylthio-l,3,4-thiadiazole derivatives

Palkar *et al*. [111] developed an imidazo[2,1-*b*]-1,3,4-thiadiazole derivative family with 2,5,6-diaryl substitutes (Figure 26). The Alamar Blue susceptibility test was used to examine the antitubercular activity *in-vitro* of each drug against *Mycobacterium* TB H37Rv and showed potent anti-tubercular activity.

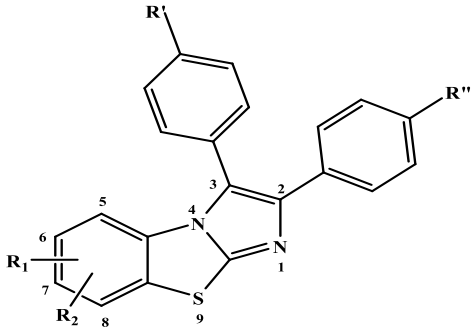


Figure 26: Structure of imidazo[2,1-*b*]-1,3,4-thiadiazole derivative

BACTEC 460 radiometric system was used for the preparation of 2,5-disubstituted-1,3,4-thiadiazoles series (Figure 27) for the antituberculosis activity (*M. tuberculosis* H37Rv). Anti-proliferative efficacy was greatest for compounds 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole screened for antituberculosis activity and found highest inhibitory activity [112].

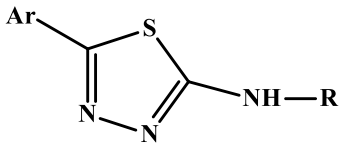


Figure 27: Structure of 2,3-diaryl-substituted imidazo[2,1-*b*]benzothiazoles

Foroumad *et al.* [113] synthesized a novel series of alkyl α-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-ylthio]acetic acid esters against *in vitro* antituberculosis activity (*Mycobacterium tuberculosis* strain $H_{37}Rv$) using the BACTEC 460 radiometric system and BACTEC 12B medium. Methyl, propyl, buthyl and benzyl esters exhibit MIC in the range 0.39-0.78 μg/ml against mycobacterium tuberculosis activity while the ethyl analogue not showed the significant results with MIC > 6.25 μg/ml and % inhibition of 58.

Alkyl α-[5-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-ylthio]- and α-[5-(1-methyl-5-nitro-2 imidazolyl)-1,3,4-thiadiazole-2-ylthio]acetate series were synthesized by Foroumad *et al.*[114]. The compounds exhibited significant antituberculosis activity (6.25 μg/ml) against *Mycobacterium tuberculosis* ($H_{37}Rv$).

2-(1-methyl-5-nitro-2-imidazolyl-1,3,4-thiadiazole-5-alkylsulfides, alkylsulfoxides and alkylsulfone series indicated the active compounds against tuberculosis activity by radiometric BACTEC 460-TB methodology. It was found that compounds contain the alkylthio substitution treat as the significant antituberculosis activity with MIC = 3.13-6.25 μg/ml [115].

A series of quinoline derivatives linked to thiadiazole, using $YbCl_3$ as the catalyst has been synthesized. It was found that compounds gives potent *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) with MIC values 3.2-3.5 μM [116].

N'-substituted-N'-[5-(4-nitrophenyl)-[1,3,4]thiadiazol-2-yl]methanediamines were synthesized and evaluated by Pattan *et al.* [117] (Figure 28) for antitubercular activity. Significant activity has been shown by many of the compounds.

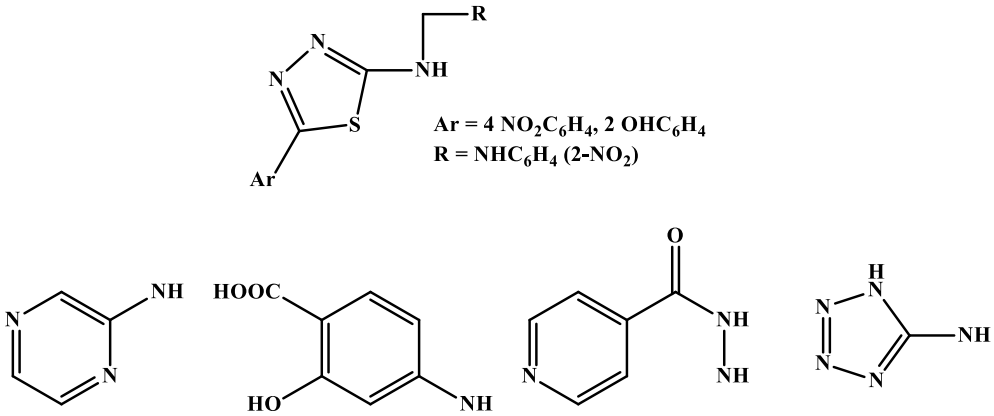
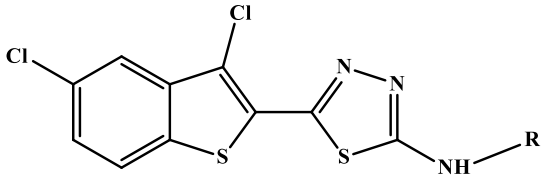


Figure 28: Structure of N'-substituted-N'-[5-(4-nitrophenyl)-[1,3,4]thiadiazol-2-yl]-methanediamines

Joshi & Thaker [118] synthesized 2-(3',5'-dichlorobenzo[*b*]thiophen-2'-yl)-5- arylamino-1,3,4-Thiadiazoles (Figure 29). Compounds having nitro phenyl group contains maximum inhibitionof 98% against *M. tuberculosis* H37Rv among all the compounds screened.



R= C_6H_5, 2 Cl C_6H_4, 3 Cl C_6H_4, 2 Cl 5CH_3 C_6H_3
2,3 $(CH_3)_2$ C_6H_3, 4 OCH_3 C_6H_4,2 $CH_3C_6H_4$
4 CH_3 C_6H_4, 2 NO_2 C_6H_4, 4 NO_2 C_6H_4

Figure 29: Structure of 2-(3',5'-dichlorobenzo[*b*]thiophen-2'-yl)-5-arylamino-1,3,4-thiadiazoles

3.4. Antidiabetic activity

Diabetes is a serious and chronic disorder with multiple aetiologies having acute and chronic consequences [119]. Diabetes is divided into three types [120-124] and its includes different drugs for their treatments.

Synthesis of 2-amino-5-(2-furyl)-1,3,4-thiadiazole (Figure 30) using chromogenic dinitro salicylic acid method with a carbose as standard (α amylase inhibition assay) and their assessment for antidiabetic activity was also performed. The derivatives exhibited significant *in vitro* inhibition [125]. 1,3,4-Thiadiazole contains the nitrogen atom, and it acts as an electron deficient. Nitrogen present in the ring tends to have nucleophilic attack as it have lone pair of electrons whereas carbon can have both electrophilic and nucleophilic attack. The unique structure makes this moiety show anti-diabetic activity [126].

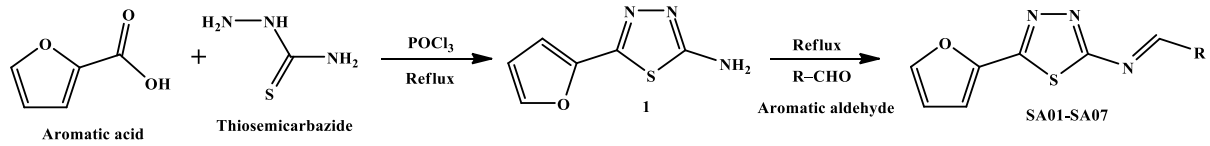


Figure 30: Synthetic route of 2-amino-5-(2-furyl)-1,3,4-thiadiazoles

Docking studies were used in the development of compounds of thiadiazole as an anti-diabetic medication. Conc. H_2SO_4 is used to catalyse the cyclization between aromatic acid and thiosemicarbazide, and then the result is condensed with aldehyde in the presence of microwave radiation to get the desired 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones (Figure 31). Amylase inhibitory test used for *in vitro* while *in vivo* diabetes rat model was

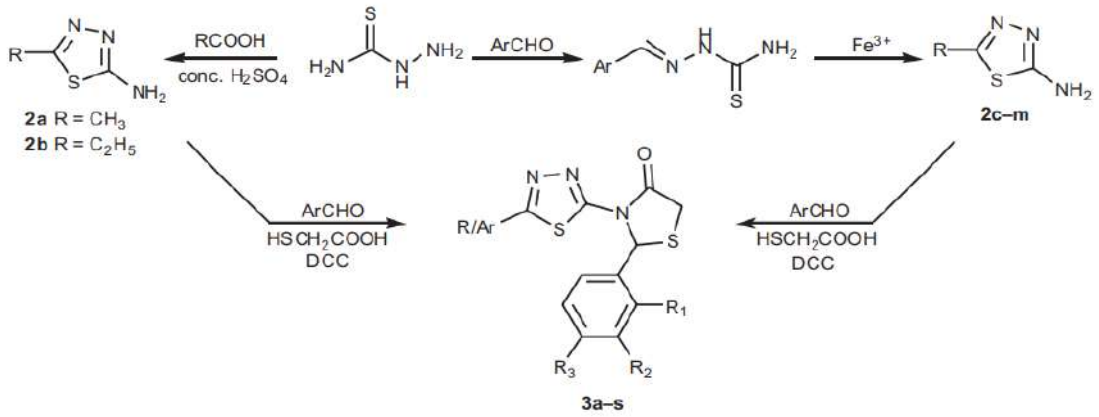


Figure 31: Synthetic route of 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones

used to find the effectiveness of the compounds. The bioactivity of synthesized derivatives was shown to be highly correlated with the proteins they were designed to inhibit in docking tests [127].

Thiadiazole Schiff bases were made by interacting with different aromatic substituted aldehydes. Thiadiazole derivatives (Figure 32) were synthesized by using concentrated sulphuric acid, which can help for the cyclization of aromatic acid and thiosemicarbazide. On the basis of the spectrum, the structures were determined. Most of the substances tested positively for antidiabetic activity when tested using the alloxan-induced tail-tipping technique [128].

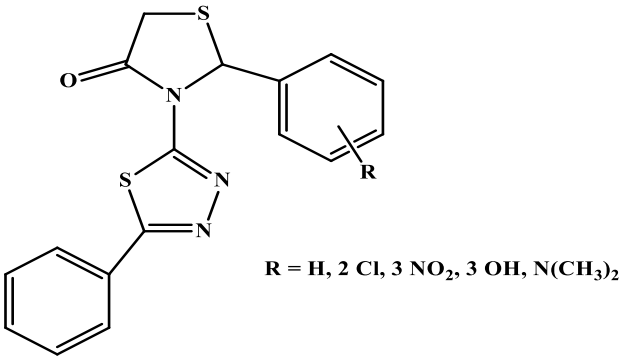


Figure 32: Structure of 2-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one

Figure 33 represent the synthesis of derivatives of 1,3,4-thiadiazol-2-amine, were converted into 2-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2- yl)-1,3- thiazolidin-4-one upon treatment with thioglycolic acid in the presence of $ZnCl_2$. Spectral measurements verified the compound structures. Parameters including blood glucose, serum triglycerides, SGOT, SGPT, or body weight were used in an alloxan-induced rat model to assess the antidiabetic efficacy of the synthesised compounds [129].

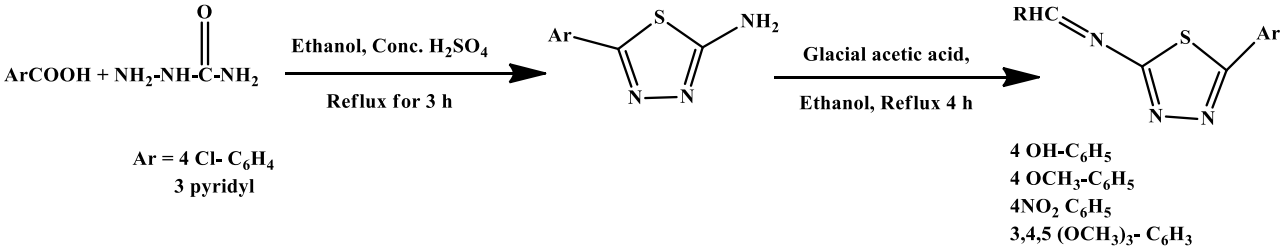


Figure 33: Synthetic route of 2-amino-5-aryl-N-[substituted benzylidene]-1,3,4-thiadiazole

3.6. Anticonvulsant activity

Designed and constructed a novel class of thiadiazole analogues (Figure 34). The effects on the brain and spinal cord were investigated for every chemical. Compound containing R = SO_2NH_2 and R_1 F, Cl, CH_3, CF_3 and SO_2Cl showed potent effects as an antianxiety, anxiolytic, and antiepileptic [130].

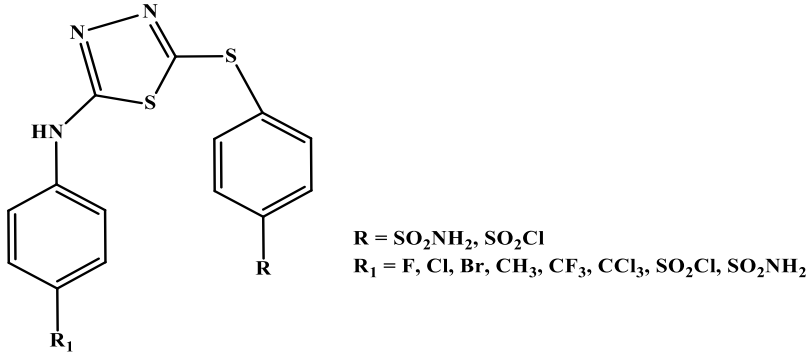
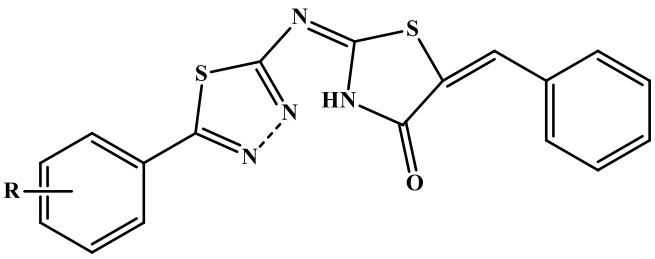


Figure 34: Structure of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives

Developed synthetic thiadiazole compounds and tested them for anticonvulsant efficacy. Differently substituted benzoic acids were used to manufacture a series of thiadiazole derivatives, and these compounds were further cyclized to provide a variety of thiazolidin-4-ones with distinct chemical structures. Compounds **35a** and **35b** (Figure 35a-b) were shown to have promising anticonvulsant efficacy when tested as derivatives of these moieties [131].



R = 1H; 2CH_3; 4CH_3; 2,4-Cl; 2,4-Br; 3,4-NO_2; 2OH; 4-OCH_3

Figure 35a: Structure of 5-benzylidene 2-[5-(substituted phenyl[1,3,4]thiadiazol-2-ylimino)-thiazolidin-4-one

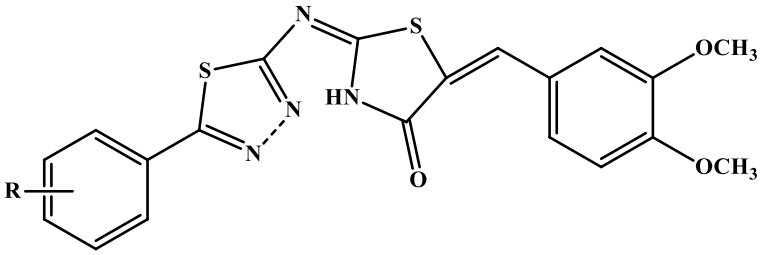


Figure 35b: Structure of 2-[5-(substituted phenyl[1,3,4]thiadiazol-2-ylimino)-5-(3,4-dimethoxy benzylidene)thiazolidin-4-one

Carboxamide moiety derivatives containing substituted THZ (Figure 36) were conceptualised and synthesised. Benzoxaine was condensing by 2,5-disubstituted-1,3,4- thiadiazole for the synthesis of carboxamide moiety derivatives. The molecular structures of the THZ derivatives were identified spectroscopically. Using PTZ model (60mg/kg) or carbamazepine as a benchmark (100mg/kg), the anticonvulsant activity of the afore mentioned drugs was determined. When compared to the gold standard, none of the synthetic chemicals produced any drowsiness (carbamazepine). Their findings suggested that compounds with a bromo group provide substantial protection against pentylenetetrazole-induced convulsions, making them promising prospects for future anti-convulsant studies [132].

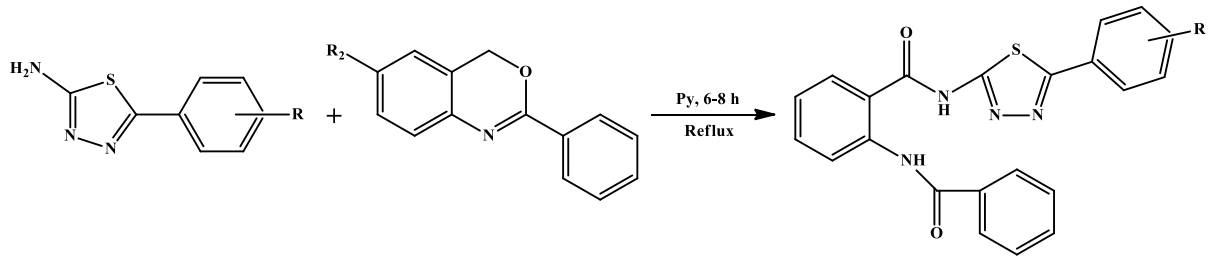


Figure 36: Synthetic route of (2-benzamido-5-substituted-N-(5-substituted phenyl)-1,3,4-thiadiazol-2-yl)benzamide

The anticonvulsant efficacy of certain heterocyclic compounds containing five membered was evaluated by inducing convulsions using an electro convulsometer and comparing the findings to those obtained with the standard gold medication phenytoin sodium. Compound containing R is □H and □Cl (Figure 37) showed very interesting anticonvulsant properties [133].

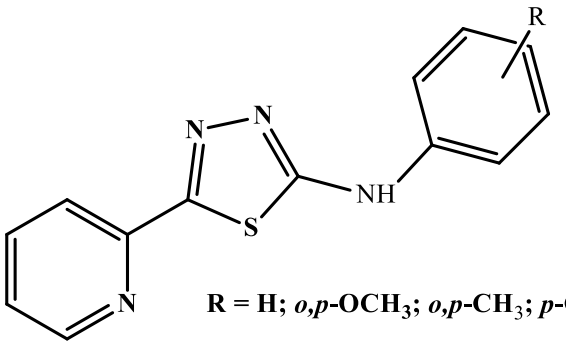


Figure 37: Structure of 2-(substituted phenyl)amino-5-(4-pyridyl)-4*H*-1,3,4-thiadiazoles

Aliyu *et al.* [134] used the glacial acetic acid and ethanol for the synthesis of 5-amino derivative of THZ and studied the anticonvulsant activity (Figure 38). Similarly, series of THZ derivatives were prepared by inserting phenyl isocyanate, and thiosemicarbazide groups at the 2nd and 5th position by Toolabi *et al.* [135] (Figure 39), valproic acid substituted on the amide thiadiazole Malygin *et al.* [136] (Figure 40), and 2-substituted benzoxazin-4-one Bhattacharya *et al.* [137] (Figure 41) were also evaluated and it was found that, all displayed potent anticonvulsant activity.

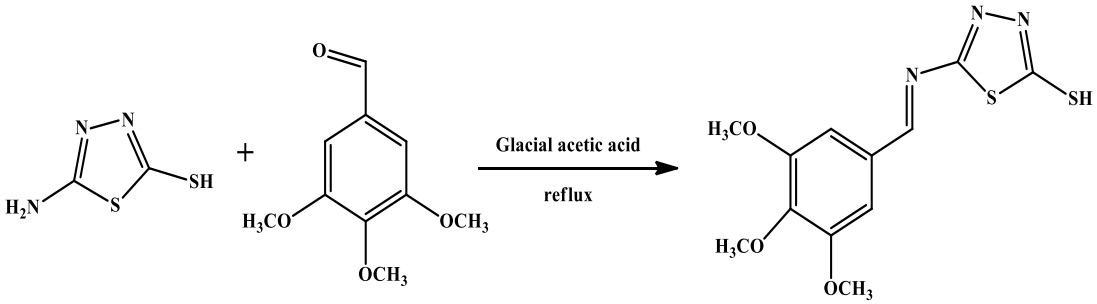


Figure 38: Synthetic route of 5-[(*E*)-(3,4,5-trimethoxybenzylidene)amino]-1,3,4-thiadiazole-2-thiol

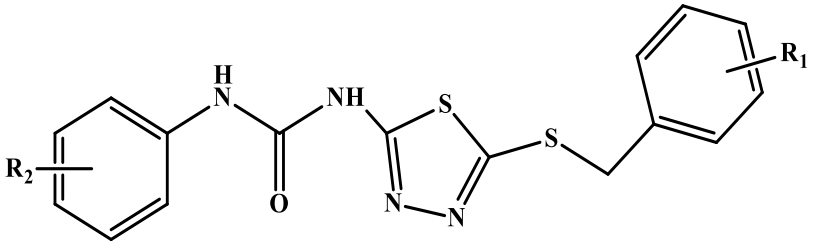


Figure 39: Structure of 1-(5-(benzylthio)-1,3,4-thiadiazol-2-yl)-3-phenylurea derivatives

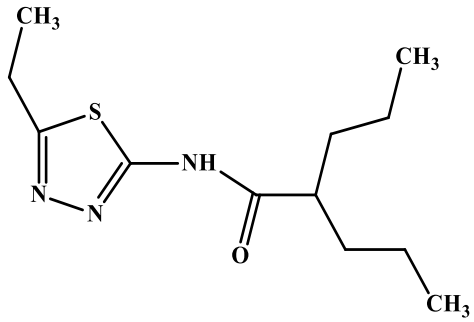
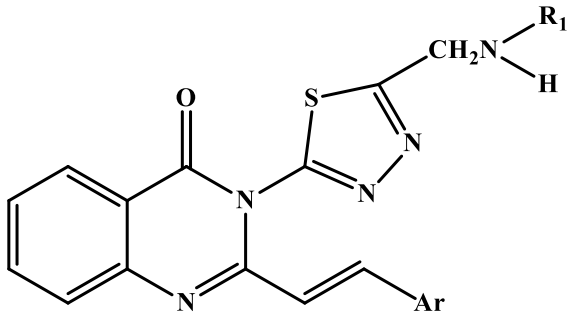


Figure 40: Structure of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentaneamide (valprazolamide)



R = C_6H_5Cl, C_6H_5Br, $C_6H_5NO_2$, C_6H_5F, $C_6H_5CH_3$, $C_6H_5OCH_3$, $C_6H_5C_2H_5$
Ar = C_6H_5, $C_6H_5NO_2$, $C_6H_5CH_3$, C_6H_5Cl, $C_6H_5OCH_3$

Figure 41: Structure of (*E*)-3-(5-(substituted aminomethyl)-1,3,4-thiadiazol-2-yl)-2-styrylquinazolin-4(3*H*)-one

3.7 Antioxidant activity

Antioxidants are the substance which can scavenge, stabilizes or neutralize free radical which may damage the cells. They behave like reducing agents like thiols, ascorbic acids or polyphenols [138]. Cells are protected from free radicals by antioxidant enzymes. The enzymes like catalase, superoxide dismutase, peroxiredoxins, *etc*. are well known for their anti-oxidant nature [139-141]. Lot of literature shares the antioxidant activities properties of THZ containing molecules [142,143].

The reaction of 3-hydrazino-isatin and aryl aldehydes, hetero-aryl aldehydes, and dialdehydes furnished isatin-based Schiff bases. These compounds exhibited antioxidant activity [144].

The derivative 2-amino-5-aryl-1,3,4-thiadiazole aromatic acid/aldehyde (Figure 42) such as 2-amino–5-arylN-[substituted benzylidene]-1,3,4-thiadiazole and (3*E*)-3-[(5-aryl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one was prepared and assessed for the *in vitro* antioxidant activity by measuring the ability to scavenge nitric oxide and hydrogen peroxide. The novel chemicals showed substantial antioxidant activity in certain circumstances [129].

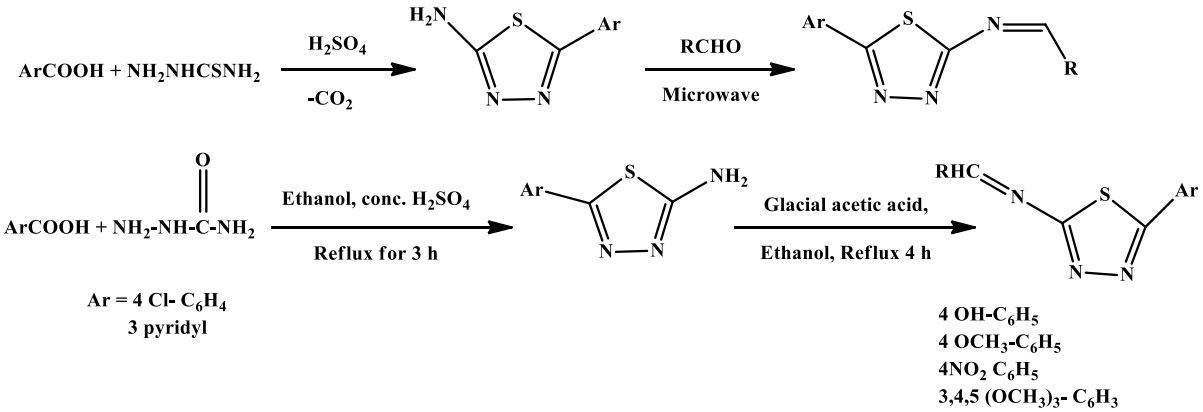


Figure 42: Synthetic route of 2-amino-5-aryl-1,3,4-thiadiazole aromatic acid/aldehyde

Derivative of thiadiazole that was produced and tested for antioxidant activity in vitro by measuring its ability to quench hydrogen peroxide or nitric oxide and prevent lipid peroxidation. Antioxidant activity was shown in several of the compounds to be rather high.

Different amide derivatives (Figure 43) were formed from 2-amino-1,3,4-thiadiazoles along with unlike chlorides of carboxylic acid and tested for antioxidant activity. It was observed that these derivatives shown significant DPPH radical scavenging activity and antiproliferative potential[145].

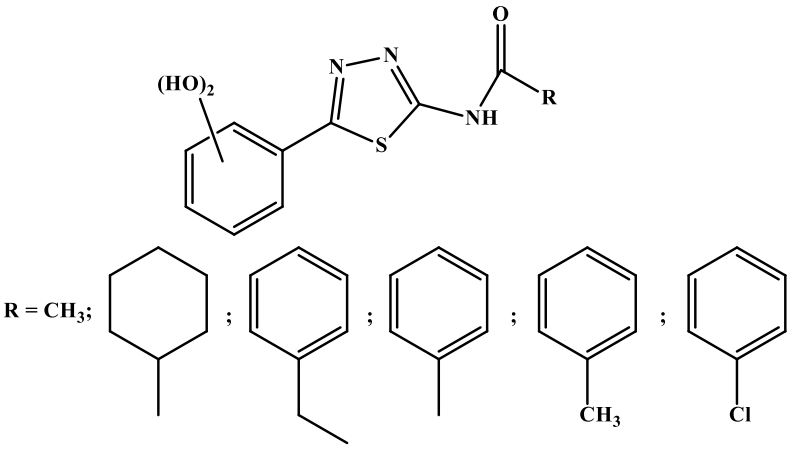
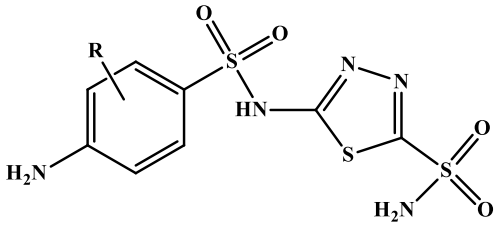


Figure 43: Structure of 2-amino-1,3,4-thiadiazoles containing phenolic hydroxyl groups

Chhajed *et al.* [146] prepared the derivative of 1,3,4-thiadiazol-2-sulphonamides and found that figure 44 showed moderate free radical scavenging activity by DPPH method.



R = H, 5 OCH_3, 2 NO_2

Figure 44: Structure of 1,3,4-thiadiazol-2-sulphonamides

A novel compound 5- [(2,3,5,6-tetrafluorophenoxy)methyl]-N-phenyl-1,3,4-thiadiazol-2-amine was prepared by Randhavane *et al.* [147] and evaluated the antioxidant activity by DPPH method. They found that only some compounds give the moderate antioxidant activity among the synthesized compounds.

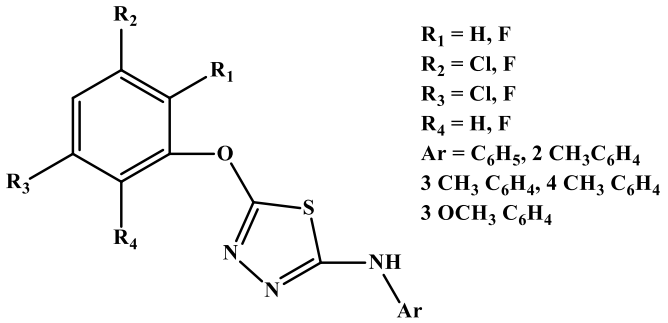


Figure 45: Structure of 5-[(2,3,5,6-tetrafluorophenoxy)methyl]-N-phenyl-1,3,4-thiadiazol-2-amine

Kamotra *et al.* [148] prepared 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-s-triazolo[3,4-*b*][1,3,4]thiadiazoles. The antioxidant properties of the THZ containing compounds were assessed for using Griess reaction by measuring sodium nitroprusside stimulates the production of nitric oxide. They evaluated the significant antioxidant activity on that compound which contains propyl, phenyl, and 4-methylphenyl group.

The *in vitro* antioxidant activity of *N*-aryl-1,3,4-thiadiazole derivatives (obtained by cyclization reaction of benzoic acid and *N*-aryl thiosemicarbazides) was analyzed with DPPH free-radical–trapping process. These molecules were analyzed for structure-activity relationship *via* modifying different substituents [149]. The acid

hydrazide derivatives and ammonium thiocyanate reacted to give THZ derivatives (Figure 46) which also screen for DPPH method and found the good antioxidant activity [150].

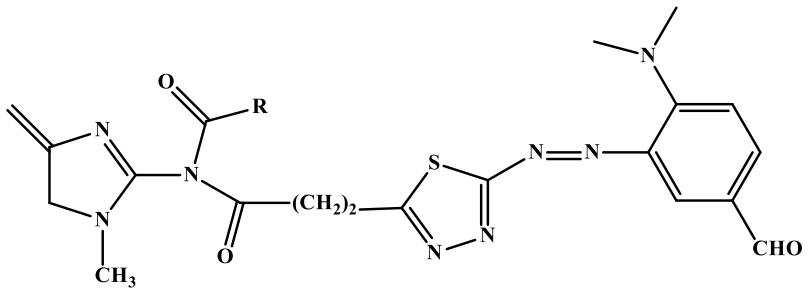


Figure 46: Structure of 1,3,4-thiadiazole containing azo group synthesized from acid hydrazide derivatives

CONCLUSIONS

Lot of research has been done over the thiadiazoles moiety displaying a extensive range of medicinal and pharmacological properties. Thiadiazoles have found to be tremendously good in regrds to stability, they are heterocyclic moieties which have electron- deficient in nature, it also contains nitrogen and sulfur atoms which bear an electron pair. Due to the various biological actions, properties and activities, the 1,3,4-thiadiazole has been the subject of several investigations. Their antibacterial, anti-inflammatory, anti-diabetic, anti-cancer, and anti- tubercular actions have been discovered. Several commercially available medical products contain thiadiazole derivatives, including acetazolamide, methazolamide, sulphamethazole, and cefazoline. The creation of new thiadiazoles and the study of their biological and chemical properties have grown in significance. A slight modification of the thiadiazole to give better efficacy and reduced toxicity is the need of the hour. These newly modified thiadiazoles may provide advanced molecules with better therapeutic abilities.

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