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Thiadiazoles: Molecules Of Diverse Applications -A Review

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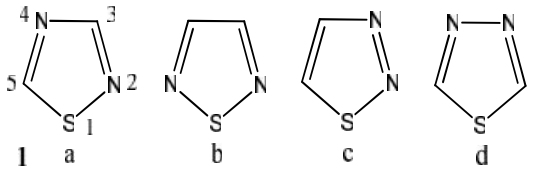
Abstract: Thiadiazoles are an important class of heterocyclic compounds that exhibit diverse applications in organic synthesis, pharmaceutical and biological applications. They also known to useful as oxidation inhibitors, cyanine dyes, metal chelating agents, anti-corrosion agents. Attracted by their broad spectrum of applications; researchers across the globe are working on this moiety and consequently have been instrumental in the advancement of thiadiazole chemistry. This review article provides up to date information about developments, exploration of new methods, synthetic strategies, techniques adopted for the synthesis of thiadiazoles and their diverse pharmaceutical activities, structure-activity relationship of the most potent compounds and physical properties. This article can act as an important tool for organic and medicinal chemists to develop newer compounds possessing thiadiazole moiety that could be better agents in terms of efficacy and safety.
Key words: Semicarbazide, thiadiazoles, antitumour, antioxidant, antiinflammatory.

INTRODUCTION

The five-member heterocyclic compounds; particularly nitrogen and sulphur heterocycles; thiadiazoles have been successfully tested against several diseases and therefore received special attention in pharmaceutical and medicinal chemistry due to their diverse potential applications. Thiadiazoles and their derivatives can be considered as simple five membered heterocycles possessing one oxygen and two nitrogen atoms. The oxadiazoles exist in different isomeric forms such as 1,2,4-, 1,2,5-, 1,2,3- and 1,3,4-thiadiazoles (**1a-d**)[1-2]. Thiadiazoles are numbered by designating heteroatoms as shown below (Scheme-1). Among the different thiadiazoles; more information about the synthesis and applications of 1,3,4-thiadiazoles is available in the literature, relatively less about 1,2,5-thiadiazoles. But there is a scanty of information is there about 1,2,3-thiadiazoles and 1,2,4-thiadiazoles.



1 a b c d

Scheme-1

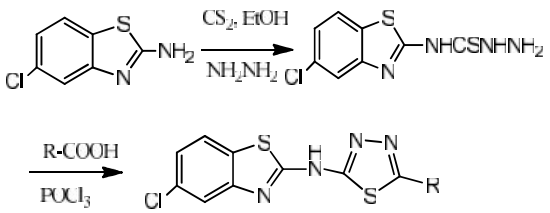
The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the thrust areas of research today. Thiadiazoles continuously draws interest for development of newer drug moiety. Researchers have demonstrated a broad spectrum of biological properties of thiadiazoles in both pharmaceutical and agrochemical fields. Literature reveals that compounds having thiadiazole nucleus have wide spectrum of pharmacological activities such as antimcirobial, antitubercular, antileishmanial, anti-inflammatory, analgesic, CNS depressant, anticonvulsant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic, analgesic properties. For instances, 1,3,4-

thiadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They have known to exhibit diverse biological activities such as in vitro inhibition of cyclooxygenase and 5-lipoxygenase activities[3]. New acylated 5-thio-beta-D-glucopyranosylimino-disusbstituted 1,3,4-thiadiazoles prepared by cycloaddition of the glycosyl isothiocyanate with the reactive intermediates 1-aza-2-azoniaallene hexachloroantimonates, and have been tested in vitro antiviral activity against HIV-1, HIV-2, human cytomegallovirus (HMCV)[4].

Apart from the pharmacological applications, thiadiazoles and their derivatives have been known to exhibit varied physical properties such as exhibit anticorrosion, liquid crystal, optical brightening and fluorescent properties which were discussed in this review article.

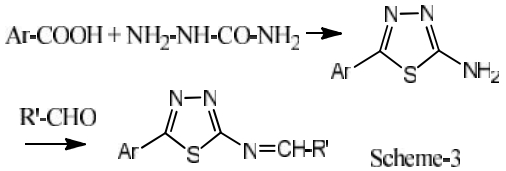
Synthesis of 1,3,4-thiadiazoles:

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



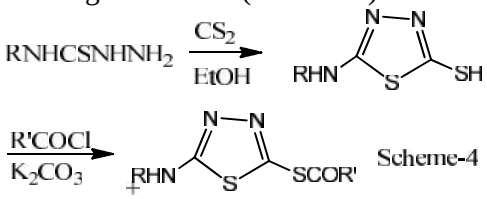
Scheme-2

A series of *N*-(5-phenyl)-1,3,4-thiadiazole-2-yl-benzamide derivatives synthesized from thiosemicarbazide and benzoyl chloride in phosphorous penta chloride. The synthesized compounds have been evaluated for their analgesic activity with each colony standard bred albino mice; the study revealed that all the animals receive 0.6%v of 10ml/kg body weight of acetic acid intraperitonially and number of writhing was recorded after 10 min upto next 15 min. the same groups animals were used next day for evaluating analgesic activity[6]. 2-Amino-5-aryl-1,3,4-oxadiazoles were prepared by heating a mixture of aromatic carboxylic acids, thiosemicarbazine and conc. sulphuric acid, then these were converted to schiffs bases by irradiating a mixture of 2-amino-5-aryl-1,3,4-oxadiazoles and aldehydes for 3 min at 40% power. The products showed promising antidiabetic activity (Scheme-3)[7].



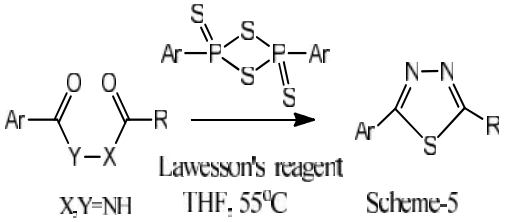
Scheme-3

A series of *S*-[5-(phenylamino)-1,3,4-thiadiazole-2-yl] benzenecarbothioate and *S*-[5-(phenyl amino)-1,3,4-thiadiazole-2-yl] ethanethioate were prepared by refluxing benzoyl chloride and acetyl chloride in presence of potassium carbonate with 5-(phenyl amino)-1,3,4-thiadiazole-2-thiol. 5-(Phenyl amino)-1,3,4-thiadiazole-2-thiol were prepared by cyclization of arylthiosemicarbazide with carbondisulphide. Some of these thiadiazole derivatives exhibited significant antibacterial and antifungal activities (Scheme-4)[8].



Scheme-4

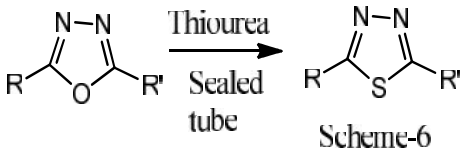
Cyclization of the thiosemicarbazones with acetic anhydride produced 4,5-dihydro-1,3,4-thiadiazolyl derivatives. These compounds were evaluated for inhibitory effect on tyronase enzyme and results indicated some of these thiadiazole derivatives possess moderate inhibitory effect on tyronase enzyme[9]. Thionation of *N,N'*-acylhydrazines with the use of a fluorous Lawesson's reagent leads to 1,3,4-thiadiazoles in high yields. The isolation of the final products is achieved in most cases by a simple filtration (Scheme-5)[10].



Scheme-5

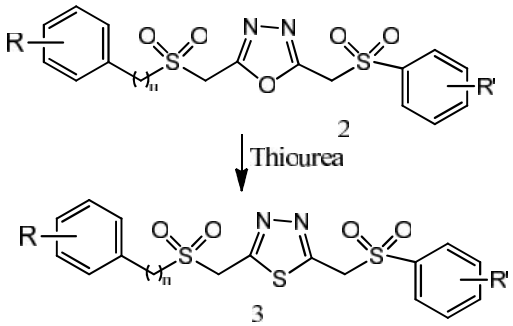
In order to to improve the yield and purity of the products, easy isolation or work up; researchers developed the new synthetic strategies, innovative

methods, new reagents for the synthesis of thiadiazoles. For instance, Rai and co-workers introduced thiourea as a new reagent for the direct conversion of 2.5-diaryl- 1,3,4-oxadiazole to 2.5-diaryl-1,3,4-thiadiazole. They observed that, when the reaction of 1,3,4-oxadiazoles with thiourea was carried out at retlux temperature for 3 to 4 days, only 2 to 5% of oxadiazoles gets converted to thiadiazoles. In order to reduce the reaction time and to increase the yield, they carried out in a sealed tube at water bath temperature for 10-15 hr and obtained the yield in 65-72% (Scheme-6)[11].



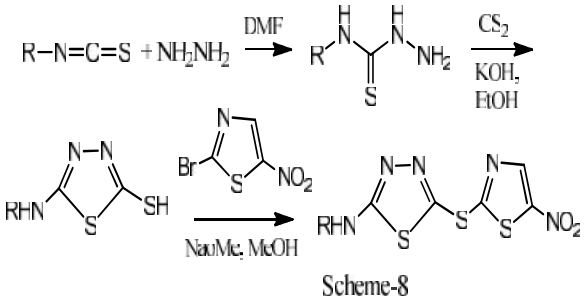
Scheme-6

Rai and coworkers method of using thiourea as thionating agent for the transformation of oxadiazoles to thiadiazoles has been widely accepted and implemented. For instance, the unsymmetrical 1,3,4-oxadiazole (**2**) when treated with two fold excess thiourea in tetrahydrofuran produced 2-(benzylsulfonylmethyl)-5-(arylsulfonylmethyl)-1,3,4-thiadiazole (**3**) (Scheme-7)[12].



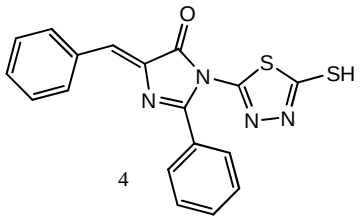
Scheme-7

A series of fluorine-containing thiadiazoles were synthesized from thiosemicarbazides by conventional method by heating mixture of thiosemicarbazide and 2N sodium hydroxide, by green synthesis such as ultrasonification and microwave irradiation. The ultrasonication method, the reaction mixture was subjected to ultrasonic irradiated for 30-35 min at room temperature. The microwave irradiation technique involved the irradiation of the reaction mixture inside a microwave oven for 1 to 2.5 min at an output of 300W power, with short interruption of 15 sec. The products obtainned in all the three methods were compared, and the study reports that the green synthesis yielded more percentage of yield. Other than this these methods are environment friendly and economically cheaper. The thiadiazoles synthesized have exhibited antimicrobial activity[13]. A series of thiadiazole derivatives synthesized found potential allosteric, substrate competitive inhibitors of the protein kinase JNK. The study showed that these compounds are potent and selective JNK inhibitors targeting its JIP-1 docking site (Scheme-8)[14].



Scheme-8

In the past decade Microwave irradiation has gained popularity as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. The MW irradiation provide enhanced reaction rate and improved product field in chemical synthesis and has been extending to modern drug discovery in complex multi-step synthesis and it is proving quite successful in the formation of a variety of carbon-heteroatom bonds. For instance, using this MW irradiation technique; 4-(Substituted benzylidene)-1-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-phenyl-1*H*-imidazol-5(4*H*)-one (**4**) was prepared by the condensation reaction of 4-arylidene-2-phenyloxazol-5(4*H*)-one and 5-amino-1,3,4-thiadiazole-2-thiol[15].



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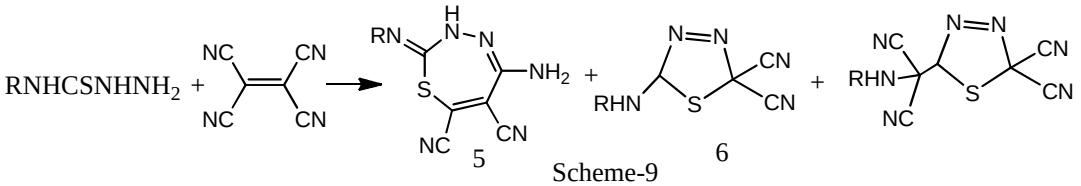
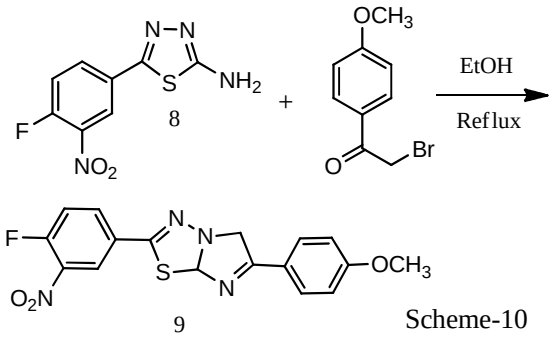
Thiosemicarbazides reacted with tetracyanoethene in ethyl acetate with admission of air to form the 7-amino-2-organylimino-2,3-dihydro-1,3,4-thiadi azepine-5,6-dicarbonitriles**5**), 7-amino-1-organyl imino-3-oxopyrazolo[1,2-c]-1,3,4-thiadiazole-5,5,6-tricarbonitriles (**6**), 7-amino-1-organyl-imino pyra zolo[1,2-c]-1,3,4-thiadiazole-3,3,5,5,6-pentacarbo nitriles (**7**) in moderate yields. Rationales for the observed conversations are presented (Scheme-9)[16].



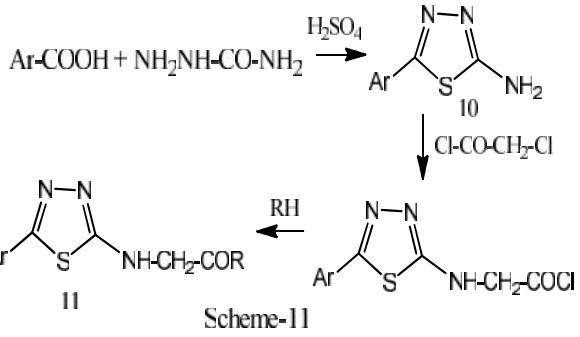
Scheme-9

5-(4-Fluoro-3-nitrophenyl)-1,3,4-thiadiazol-2-ylamine (**8**), on reflux with 4-methoxyphenacyl bromide in ethanol as solvent yielded 2-(4-fluoro-3-nitrophenyl)-6-(4-methoxyphenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole (**9**) (Scheme-10)[17].



Scheme-10

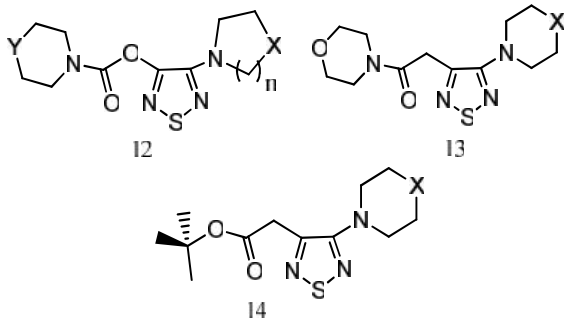
Diabetes mellitus is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly. The underlying causes of diabetes are the defective production or action of insulin, a hormone that controls carbohydrate, fat and protein metabolism. Symptoms of diabetes include frequent urination, lethargy, excessive thirst, and hunger. A large number of 1,3,4-thiadiazoles have been reported to exhibit antidiabetic properties. For instance; 2-Amino-5-aryl-1,3,4-thiadiazole (**10**) synthesized by the reaction of thiosemicarbazide, aromatic carboxylic acid in conc. sulphuric acid. Then the compound (**10**) was converted to chloroacetyl derivative by its reaction with chloroacetyl chloride in the presence of sodium acetate in acetic acid. Finally it was transformed in to *N*-(5-(4-aminophenyl)-1,3,4-thiadiazole-2-yl)-2-chloroacetamide (**11**) (Scheme-11)[18]. The compounds synthesized were evaluated for their antidiabetic activity using wistor albino rats by Alloxan induced tail tipping method. The results of the study revealed that the synthesized compounds exhibited significant antidiabetic activities.



Scheme-11

Pharmacological applications of thiadiazoles:

Niemann-Pick type C (NPC) disease is a lysosomal storage disorder characterized at the cellular level by abnormal accumulation of cholesterol and other lipids in lysosomal storage organelles. Lysosomal acid lipase (LAL) has been identified as a potential therapeutic target for NPC. LAL can be specifically inhibited by a variety of 3,4-disubstituted thiadiazole carbamates. Various thiadiazole carbamates (**12**), amides (**13**), and esters (**14**) synthesised exhibited inhibition of LAL. The comparative studies on the inhibition effect with a diverse selection of commercially available non-thiadiazole carbamates revealed that only thiadiazole carbamates are effective inhibitors of LAL. The mechanism for LAL inhibition by these compounds whereby LAL transiently carbamoylates the enzyme inhibition of acetylcholinesterase by rivastigmine and other carbamates as well as acylation of various lipases by orlistat[19].



Regulation of tissue-specific glucocorticoid action by inhibiting 11β-HSD1 activity is regarded as a potential viable treatment for metabolic and cardiovascular diseases. The effort to find an

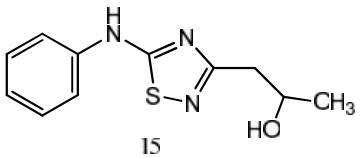
alternative to the highly favoured adamantyl moiety found in many potent 11β-HSD1 inhibitors led to the synthesis and SAR study of a series of phenyl ethanone thiadiazole derivatives. The synthesized thiadiazoles found potential with IC_{50} values in the range 100-300 nM on an HEK293 cell line stably transfected with the human HSD11B1 gene, and are selective with no activity against human 11β-HSD2. An SAR study revealed the favoured combination of phenyl substitution and the linker system being *m*-methoxy with a sulphide linker or a *p*-trifluoromethyl with sulphoxide linker. Docking of thiadiazoles into a crystal structure of the enzyme showed how the substituted phenyl group might mimic the adamantane motif[20].

Aminopeptidase N (APN) is a zinc-dependent ectopeptidase which plays an important role in the invasion of metastatic tumors. A series of 1,3,4-thiadiazoles synthesised were tested in vitro for enzyme inhibition, the report reveals that the compounds have potent inhibitory activities toward APN with IC_{50} values in the micromolar range[21].

Nitroheteroaryl-1,3,4-thiadiazole derivatives have potent activity against *Leishmania* sp. The analogues investigated against infected BALB/c mice, the results revealed that some of these compounds significantly decreased lesion size and progression of infection in the liver and spleen, and were associated with granuloma formation, which correlates with disease regression in the liver of murine hosts. Moreover, the analogues had immunomodulatory effects, stimulating interferon-γ expression and suppressing interleukin-10 and interleukin-5 production, favouring type-1 immune responses and resolution of the parasitic infection[22].

N-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides synthesized were tested *in vivo* for their analgesic and anti-inflammatory activities. The compounds exhibited good antalgic action in the acetic acid writhing test and some terms of the series showed also fair anti-inflammatory activity in the carrageenan rat paw edema test. Ulcerogenic and irritative action on the gastrointestinal mucose, in comparison with indomethacin is low[23]. 1,3,4-thiadiazole-5-fluorouracil acetamides derivatives synthesized were tested for their insecticidal activities against Tetranychus cinnabarinus and Aphis craccivora. The bioassay tests showed that most of these synthesised compounds possessed a good combination of stomach toxicity as well as contact toxicity against Tetranychus cinnabarinus and Aphis craccivora. In particular, the insecticidal activity against Aphis craccivora was better than the commercialized thiacloprid and was also comparable to another commercialized product, imidacloprid. It was observed that the introduction of fluorines to meta and para-position of the benzene ring was essential for high bioactivity[24].

Novel 1,2,4-thiadizole derivatives (**15**) synthesized were found as potent neuroprotectors, their ability to inhibit the glutamate stimulated calcium uptake, permeation on the phospholipid membranes was measured. The partition coefficients in n-octanol/buffer and n-hexane/buffer imminscible phases were determined[25].



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2-(4-(2,4-dibromophenyl)-1,2,3-thiadiazol-5-ylthio)acetamide derivatives synthsised have been tested for their anti-HIV activity. The study indicated that most of these compounds showed good activities against HIV-1, inhibiting HIV-1 replication in MT-4 cells more effectively than NVP (by sevenfold) and DLV (by eightfold)[26].

Unregulated or overexpressed matrix metalloproteinases (MMPs), including stromelysin, collagenase, and gelatinase have been implicated in several pathological conditions including arthritis and cancer. Thiadiazole derivatives interact with stromelysin in a manner distinct from other classes of inhibitors. The inhibitors coordinate the catalytic zinc atom through their exocyclic sulfur atom, with the remainder of the ligand extending into the S_1-S_3 side of the active site. Binding interactions observed for the thiadiazole class of ligands have implications for the design of matrix metalloproteinase inhibitors[27].

The binding of 5-substituted-1,3,4-thiadiazole-2-thione inhibitors to the matrix metalloproteinase stromelysin have been characterized by protein crystallography. Both inhibitors coordinated to the catalytic zinc cation via exocyclic sulfur and lay in an unusual position across the unprimed side of the proteinase active site. Nitrogen atoms in the thiadiazole moiety make specific hydrogen bond interactions with enzyme structural elements that are conserved across all enzymes in the matrix metalloproteinase class. Strong hydrophobic interactions between the inhibitors and the side chain of tyrosine-155 appear to be responsible for the very high selectivity of these inhibitors for stromelysin. A conformational rearrangement of the catalytic domain occurs that revealed an inherent flexibility of the substrate binding region leading to speculation about a possible mechanism for modulation of stromelysin activity and selectivity[28].

In order to understand the pharmacology of carbonic anhydrase inhibitors in reduction of aqueous

secretion, studies were conducted with 2-substituted-1,3,4-thiadiazole-5-sulfonamides for their inhibition of carbonic anhydrase II, electrical measurements of the isolated ciliary body, and intraocular pressure of living animals. The inhibitors of carbonic anhydrase employed were 2-amino-1,3,4-thiadiazole-5-sulfonamide; 2-methylamino-1,3,4-thiadiazole-5-sulfonamide; 2-formylamino-1,3,4-thiadiazole-5-sulfonamide; 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; and 2-propionylamino-1,3,4-thiadiazole-5-sulfonamide. All of these compounds showed significant inhibitory activity to carbonic anhydrase II, which exists in the ciliary epithelium, but their potencies of inhibition varied relative to one another. The effects of the compounds on electrical phenomena were observed using isolated rabbit ciliary body. The study revealed that these compounds decreased the negative electrical potential of the tissue by 10-33%, and this effect was proportional to its inhibitory activity to carbonic anhydrase II. The compounds also showed decreased intraocular pressure 7-32%, this effect was proportional to the inhibitory activity to the enzyme. Correlation between the two effects implies that both effects have a common basis which relates to the physiological role of carbonic anhydrase[29].

Chemoprevention is an approach to decrease cancer morbidity and mortality through inhibition of carcinogenesis and prevention of disease progression. Although the trans- stilbene derivative resveratrol has chemopreventive properties, its action is compromised by weak non-specific effects on many biological targets. Replacement of the stilbene ethylenic bridge of resveratrol with a 1,2,4-thiadiazole heterocycle and modification of the substituents on the two aromatic rings afforded potential chemopreventive agents with enhanced potencies and selectivities[30].

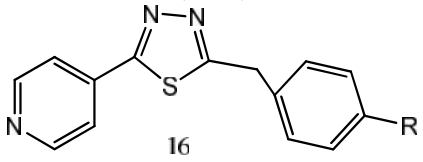
The compounds 5-phenyl-1,3,4-thiadiazole, 2-amino-5-phenyl-1,3,4-thiadiazole and 2-amino-5-(2'-thienyl)-1,3,4-thiadiazole have been evaluated for their antimuscular relaxant properties. The results indicated that these compounds have paralysing effects in mice, rats, cats, and dogs. They block the tonic component of maximal electroshock seizures and protect against strychnine. The other centrally acting paralysing drugs, depress spinal polysynaptic transmission in doses which leave monosynaptic transmission relatively unaffected. The compounds do not induce synchronization in epidural electroencephalogram recordings. In doses not greatly affecting muscular tone and spontaneous activity, they prolong the hypnotic effects of pentobarbitone and other barbiturates in mice. The substituted thiadiazoles and 2-amino-benzothiazoles confirmed the hypothesis that pharmacological equivalence may result either from condensing heterocyclic nuclei with aromatic nuclei or from introducing aryl substituents into them[31].

5-Phenyl-4,5-dihydro-1,3,4-thiadiazoles synthesized by condensation of thiosemicarbazide with substituted benzaldehydes, followed by cyclization with acetic anhydrides were examined for their cytotoxicity against four human cancer cell lines; lung cancer (A549), ovarian cancer (SK-OV-3), skin cancer (SK-MEL-2), and colon cancer (HCT15). The results revealed that most of these compounds exhibited significant suppressive activity against the growth of all of the cancer cell lines. The 4-hydroxy-5-phenyl-4,5-dihydro-1,3,4-thiadiazole was most active in the inhibition of growth of the SK-MEL-2 cell line. The compounds bearing 3-methoxy-4-hydroxy-, 4-hydroxy- and 4-methyl substituents in the C-5 phenyl ring respectively, exhibited the highest activity against the SK-OV-3, HCT15 and A549 cell lines respectively. A structure-activity relationship was evolved that an optimal electron density on the C-5 phenyl ring of 1,3,4-thiadiazoles is crucial for their cytotoxic activity[32].

A three-dimensional quantitative structure-activity relationship (3D-QSAR) study of 1,3,4-thiadiazole derivatives on anticonvulsant activity was demonstrated by employing self-organizing molecular field analysis (SOMFA) techniques to investigate the structural requirements for the design of novel anticonvulsant. Physicochemical determinants of binding, such as steric and electrostatic properties, were mapped onto the molecular structures of 1,3,4-thiadiazole; the study was a guideline for design of novel anticonvulsants[33]. Many thiadiazole derivatives synthesized are found highly potent inhibitors of human immunodeficiency virus type 1 (HIV-1) replication. These compounds belong to the family of nonnucleoside reverse transcriptase inhibitors. The results of the study indicated that these compounds are worth for the treatment of HIV-1 infections[34].

The simultaneous determination of ascorbic acid (AA), dopamine (DA) and uric acid (UA) in 0.20 M phosphate buffer solution (pH 5.0) using electropolymerized ultrathin film of 5-amino-2-mercapto-1,3,4-thiadiazole (AMT) on glassy carbon (GC) electrode. The electropolymerized AMT (p-AMT) modified GC electrode not only resolved the voltammetric signals of AA, DA and UA but also dramatically enhanced their oxidation peak currents when compared to bare GC electrode. The enhanced oxidation currents for AA, DA and UA at p-AMT modified electrode are due to the electrostatic interactions between them and the polymer film. The practical application of the modified electrode was demonstrated by the determination of DA in dopamine hydrochloride injection[35].

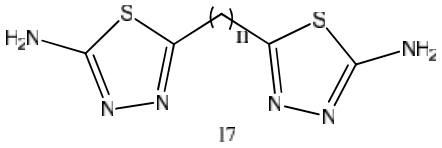
A series of thiadiazole derivative synthesized by the reaction of isoniazid and various substituted isothiocyanates were evaluated for their effect in monocyte and lymphocyte cells. The results of the study indicated that the synthesized compounds (**16**) exhibited significant immune effects in WBCs differential count. Liver enzymes, glutamic oxaloacetic acid transaminase (GOT) and glutamic pyruvic acid transaminase (GPT) were chosen to assess liver function. The administration of thiadiazole derivatives significantly declined the activity of GOT, GPT and urea in comparison with control. These results indicated that effectively increases of immune system in the animals. The exposure of 1,3,4-thiadiazole drivativies caused decreasing the activity of glutamic oxaloacetic acid transaminase (GOT), glutamic pyruvic acid transaaminase (GPT), and urea[36].



16

The enzymatic inhibition of histone deacetylase activity has come out as a novel and effectual means for the treatment of cancer. Two novel series of 2-[5-(4-substitutedphenyl)-[1,3,4]-oxadiazol/thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid (tetrahydro-pyran-2-yloxy)-amides were synthesized as novel hydroxamic acid based histone deacetylase inhibitors. The antiproliferative activities of the compounds were investigated *in vitro* using histone deacetylase inhibitory assay and MTT assay, they also tested for their antitumor activity against Ehrlich ascites carcinoma cells in Swiss albino mice. The results of the study indicated that 2,5-disubstituted-1,3,4-oxadiazole/thiadiazole as promising surface recognition moiety for development of newer hydroxamic acid based histone deacetylase inhibitor[37].

A series of 1,3,4-thiadiazole derivatives (**17**)[38] synthesized have been evaluated *in vitro* for their antifungal and antibacterial activities against different organisms and were found to exhibit appreciable activities. Holla and co-workers[39] reported the synthesis and antimicrobial activity of 1,2,4-triazolo thiadiazoles bearing 2,3,5-trichlorophenyl moiety. Their study on the antimicrobial activity of the synthesized compounds (**18**) showed moderate to good antibacterial and antifungal activities against pathogenic strains. SAR of the compounds showed that presence of 2,3,5-trichloro, -OCH_3, 2,3-dichloro, 4-hydroxy-3-amido, 4-chloro, -SCH_3 groups attached to phenyl ring as well as pyridyl, and bromopyridyl groups attached to the thiadiazole ring of the the compounds are responsible for good antimicrobial activity.



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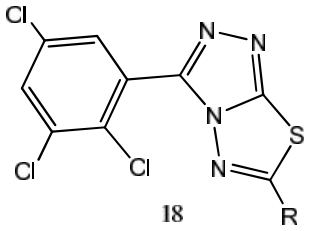
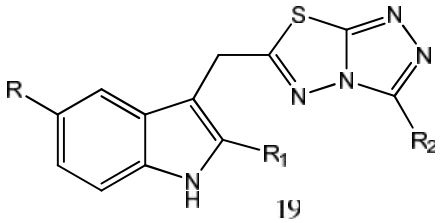


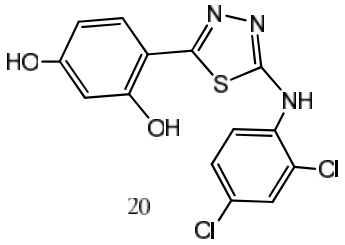
18

Vaidya *et al*[40] reported the synthesis of series of 3,6-disubstituted-1,2,4-triazolo [3,4-b]-1,3,4- thiadi zoles (**19**), they evaluated the synthesized compounds for their anti-inflammatory activity. The result of their study revealed that maximum anti-inflammatory activity was shown in the tested compounds having indole ring at the sixth position of the triazolothiadiazole system.



19

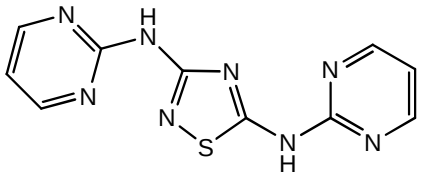
A number of *N*-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles (**20**)[41] were synthesized and evaluated for their antiproliferative activity. The synthesized compounds evaluated for their cytotoxicity *in vitro* against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung) and T47D (breast) was determined. The results indicated that alkyl and morphinoalkyl derivatives exhibited significantly lower effect than phenyl ones. The highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**20**), with ID50 two times lower than for cisplatin studied comparatively as the control compound.



20

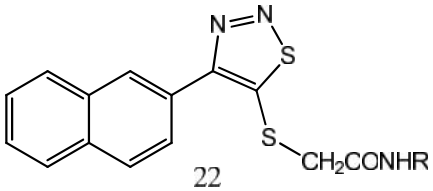
Gupta *et al*[42] reported the synthesis of series of substituted 1,2,4-thiadiazoles (**21**) and their anticonvulsant activity. Their study indicated that all the compounds showed protection against MES (maximal electroshock-induced seizures) screen after 0.5 h and was concluded that the synthesized compounds were potent against MES-induced

seizures than ScPTZ induced and showed low potency as sedative-hypnotic agent which is advantageous.



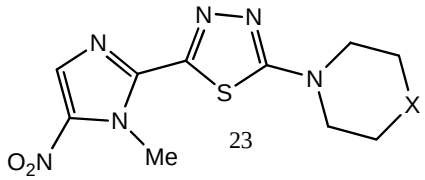
21

A series of 2-(4-(naphthalen-2-yl)-1,2,3-thiadiazol-5-ylthio)acetamide (TTA) derivatives were synthesized and evaluated as potent inhibitors of HIV-1. Amongst the tested compounds, (22) were the most potent inhibitors of HIV-1 replication of the series (EC50=0.17±0.02, 0.36±0.19 and 0.39±0.05 mM, respectively)[43].



22

A series of 2-(1-methyl-5-nitroimidazol-2-yl)-5-(1-piperazinyl, 1-piperidinyl and 1-morpholinyl)-1,3,4-thiadiazoles (**23**) synthesized were evaluated for *in vitro* for their leishmanicidal activity against Leishmania major promastigotes[44]. The leishmanicidal data revealed that the compounds had strong and much better leishmanicidal activity than the reference drug pentostam, piperazine analog was the most active one.

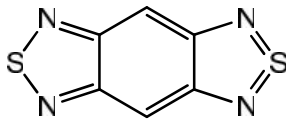


23

Singh et al[45] review article provides a brief acount the pharmacological applications of 1,3,4-thiadiazoles.

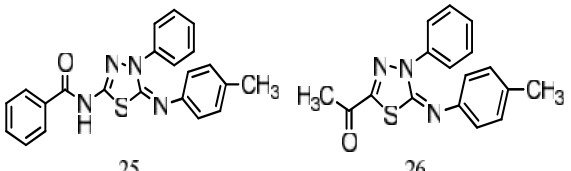
Physico-Chemical applications of thiadiazoles:

Many of the polymers containing thiadiazole moiety exhibited electron donor-acceptor properties, band gap and ambipolar characteristics[46]. The electron accepting properties of these nonclassical heterocycles have shown high reduction potentials. Benzo[1,2-*c*:4,5-*c*′]bis([1,2,5]thiadiazole) containing a hypervalent sulfur atom has a low LUMO energy. Introduction of electron-donating groups into the electron-withdrawing heterocycles (**24**) afforded novel donor-acceptor compounds. Their cyclic voltammograms showed that they are easily both oxidized and reduced[47].

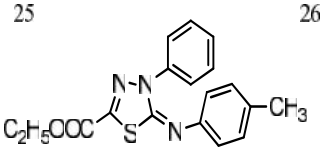


24

Thiadiazole derivative are known to inhibit the corrosion of copper in 3.5% NaCl solutions Weight loss measurement gave an inhibition efficiency of about 99.07% with 100mg/L thiadiazole derivative present. Potentiodynamic polarzation measurements showed that the thiadiazole derivative in 3.5%NaCl solutions decrease corrosion currents and slightly shifts the corrosion potional in a positive direction. From the results it was concluded that the corrosion resistance of copper with inhibitors under alkaline conditions is better than that under near neutral or acidic conditions[48]. The compounds *N*-[4-phenyl-5-(*p*-tolylimino)-4,5-dihydro-1,3,4-thiadiazole-2-yl]benzamide (**25**), 2-acetyl-4-phenyl-5-(p-tolylimino)-4,5-dihydro-1,3,4-thiadiazole (**26**), and Ethyl-4-phenyl-5-(*p*-tolylimino)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**27**) synthesized were used as additives to protect grade 1018 carbon steel from corrosion in naturally aerated 0.5 M NaCl solution[49].



25 26



27

The inhibitive effect of some substituted thiadiazoles, 2-amino-1,3,4-thiadiazoles (AT), 2-amino-5-methyl-1,3,4-thiadiazoles (AMT), 2-amino-5-ethyl-1,3,4-thiadiazoles (AET) and 2-amino-5-propyl-1,3,4-thiadiazoles (APT) against the corrosion of mild steel in formic and acetic acid is studied theoretically using DFT at the B3LYP/6-31G(d) level in order to elucidate the different inhibition efficiencies and reactive sites of these compounds as corrosion inhibitors[50]. The polymers containing thiadiazole moiety prepared were exhibited improved circuit voltages. These polymers are having good power conversion efficiencies with PCE values of 4.22 and 4.12% respectively[51]. Novel OFET materials showing high mobility and good air-stability were developed using benzobis(thiadiazole) (BBT) unit and the high FET performance was attributed to the low LUMO level and the film morphology[52].

CONCLUSION

The detailed research associated with thiadiazoles presented in this review article indicates a broad spectrum of pharmacological activities and physic-chemical properties of different thiadiazoles. The review article will be fruitful base for further development of better medicinal agents for the researchers across the world.

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