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Review Article

THIADIAZOLE ANALOGS AS POTENTIAL PHARMACOLOGICAL AGENTS: A BRIEF REVIEW

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ABSTRACT

Recently, heterocyclic compounds analogues and their derivatives have attracted strong interest in medicinal chemistry due to their biological and pharmacological properties. The small and simple thiadiazole nucleus possesses numerous biological properties like - antitumor, antimicrobial, anti-inflammatory, anticonvulsant, and antidiabetic activities. These activities are also possessed by its substituted derivatives as well. The present review focuses on pharmacological activities of thiadiazole derivatives

Keywords: Antimicrobial, Antiinflammatory, Anticonvulsant, Antiviral.

INTRODUCTION

Heterocyclic compounds are well known for their pharmacological potential that is exploitable in the synthesis of new bioactive molecules. Moreover, nowadays heterocyclic chemistry becomes more and more advanced in the development of new polyheterocyclic compounds. These compounds are extremely valuable because they possess not only the pharmacological potential owned by the heterocycles themselves, but also a new one due to the reciprocal influence between the contained heterocycles. Azolic derivatives such as thiazole, triazole, oxadiazole and thiadiazole are pharmacologically useful compounds and have been intensely investigated for various biological activities, due to their promising application in the medicinal chemistry.

1,3,4-Thiadiazole and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical and industrial importance. 1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Busch and his coworkers. The advent of sulfur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in this field. 1,3,4-Thiadiazoles were conveniently divided into three subclasses**,** one is Aromatic systems which include the neutral thiadiazole (**1)** and constitute a major part of this review. Second is mesoionic systems (**2)** which is defined as five-membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring. And lastly non aromatic systems such as the 1,3,4-thiadiazolines (**3**,**4)** and the tetrahydo 1,3,4-thiadiazolidines (5) (fig.1) [1].

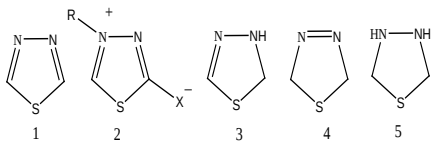


Fig. 1:

The thiadiazole drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings (e.g. Sulphamethazole). They are also choice for the drug as diuretic (e.g. Acetazolamide). Ceftazolene (antibiotic), Atibeprone (anti-depressant) etc [2]**.**

1,3,4-thiadiazoles exhibit a wide spectrum of biological activities, possibly due to the presence of toxophoric **-**N-C-S- moiety. The earliest use of thiadiazoles has been in the field of pharmaceuticals as antibacterials with similar properties to those of sulphonamide drugs. They exhibit a broad spectrum of interesting pharmacological properties like antipanosomal, antibacterial, anticoccoidal, fungicidal, herbicidal, insecticidal, hypoglycemic, diuretic, anti-inflammatory, antiviral, anti acetylcholine, antitubercular, tranquillizer and sedative [3].

Structure and aromatic properties

Bak *et al* recently made a careful analysis of spectra of 1,3,4-thiadiazole. They could determine the structure of molecule with uncertainity of 0.03Å in the coordinates of hydrogen atom and of less than 0.003 Å in the coordinates of other atoms. By an analysis of difference between the measured bond length and covalent radii aromatic character was deduced, as measured by π electron delocalisation decreases in the order:

1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole

Dipole moment

Bak *et al* measured the dipole moment of 1,3,4-thiadiazole and found the value of 3.28±0.03D [4].

Recent approches for the synthesis of 1,3,4-thiadiazoles

The 1,3,4-thiadiazole can be constructed with substituted esters and isothiocyanates. The 1,3,4-thiadiazole bearing substituents at 2 and 5 position have been prepared by using different procedures:

Method 1. 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.

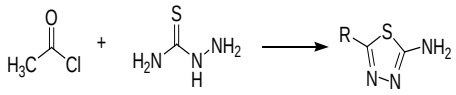


Fig. 2

Method 2. 1,3,4-thiadiazole-2-thiol were prepared by cyclization of arylthiosemicarbazide with carbondisulphide.

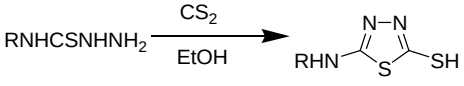


Fig. 3

Method 3. Cyclization of the thiosemicarbazones with acetic anhydride produced 4,5-dihydro-1,3,4-thiadiazolyl Derivatives. Thionation of *N,N'*-acylhydrazines with the use of a fluorous Lawesson's reagent leads to 1,3,4-thiadiazoles in high yields.

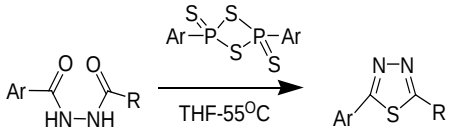


Fig. 4

Method 4. In order 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. Thiourea is introduced as a new reagent for the direct conversion of 2.5-diaryl- 1,3,4-oxadiazole to 2.5-diaryl-1,3,4-thiadiazole. In order to reduce the reaction time and to increase the yield, reaction is carried out in a sealed tube at water bath temperature for 10-15 hr.

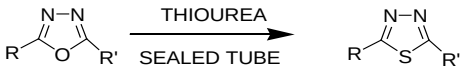


Fig. 5

Method 5. 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.

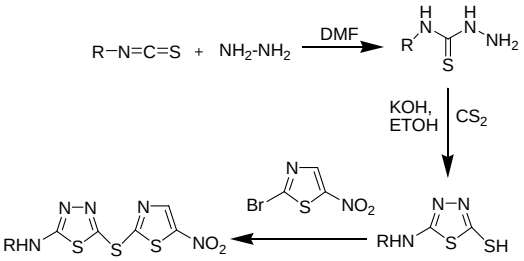


Fig. 6

Method 6. Another method of synthesis of 2-Amino-5-aryl-1,3,4-thiadiazole is by the reaction of thiosemicarbazide, aromatic carboxylic acid in conc. sulphuric acid. Then the compound 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.

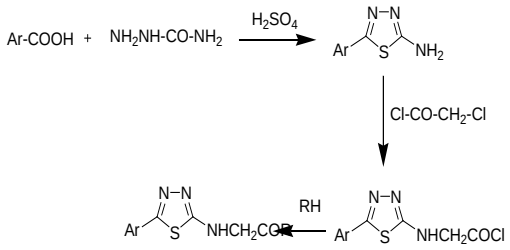


Fig. 7

Method 7. Monothiodiacylhydrazines (prepared from the acylation of thiosemicarbazides or as intermediates in the reactions of thiohydrazides with carboxylic acids and their derivatives) was cyclized through dehydration with sulfuric, polyphosphoric (PPA) or methanesulfonic acids to give 1,3,4-thiadiazoles.

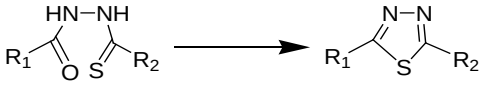


Fig. 8

Method 8. The cyclization of *N*'-imidoylthiohydrazide with bromine in the presence of pyridine gave 2,5-diphenyl-1,3,4- thiadiazole along with the 3,6-diphenyl-4*H*-1,2,4,5-thiatriazine.

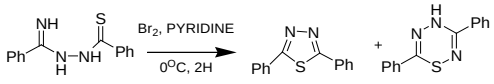


Fig. 9

Method 9. Oxidative cyclization of thioacylhydrazone by common oxidants include bromine, ferric chloride, ammonium ferric sulfate, or potassium permanganate provided 2-amino-5-phenyl-1,3,4-thiadiazole.

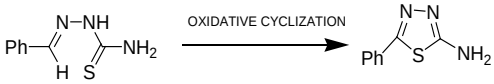


Fig. 10

Method 10. Reaction of acylbithioureas **21** with *p*-tosyl chloride in presence of triethylamine (TEA) provided a 90% yield of the benzoylated thiadiazole **23**, presumably via the intermediate.

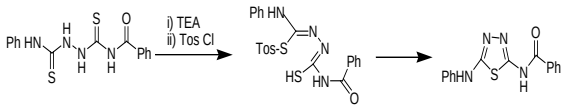
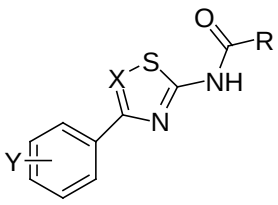


Fig. 11

SAR and QSAR studies of thiadiazole nucleus

Different scientist groups have worked upon QSAR of thiazole/thiadiazole nucleus and obtained interesting results. Bhattacharya *et al* studied binding affinity data of thiazole and thiadiazole derivatives for human adenosine A_3 receptor subtype using quantum chemical and hydrophobicity parameters. The results suggested the A_3 binding affinity increases with decrease of lipophilicity of the compounds (Fig. 12) and in the presence of methyl or ethyl substituent at R position. Furthermore, thiadiazole nucleus is more preferred over thiazole nucleus for the binding [5].



X=CH, in thiazole

X=N, in thiadiazole

Fig. 12

Jung *et al* have identified antagonists for the human adenosine A_3 receptor having sub nanomolar affinity and high selectivity versus other subtype receptors through structure–activity relationship

studies of aminothiazole and aminothiadiazole as the lead templates. An assay of cAMP production also demonstrated functional inhibition by the most potent antagonist, and speculation of a binding mode of thiadiazole isomers was suggested by molecular docking experiments with a human adenosine A_3 receptor model built from homology modeling of the X-ray crystal structure of rhodopsin. The SAR study of thiadiazole derivatives (Fig. 13) will be useful in future to investigate biological significance of adenosine receptors and to develop therapeutics for the treatment of inflammatory disease, such as asthma, and glaucoma [6].

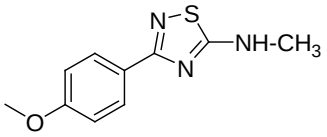


Fig. 13

Recent Advancement in the Therapeutic Potential of 1,3,4 Thiadiazole Derivatives

A brief discription of different activities of thiadiazoles is discussed in the presented article.

Anti-Cancer Activity

Cancer is a leading cause of death throughout the world and Malaysia is of no exception. However, the conventional treatments available for cancer disease, such as chemotherapy or radical surgery, eventually fail to exert control on the disease. Metastatic disease frequently develops even after these treatments and may cause death. Cancer chemoprevention has been an active area of research for several decades. Various efforts were done by different scientists like:

An attempt was made to utilize the concept of bio-isosterism for the synthesis to afford novel fused thiadiazole, thiadiazine compounds by Sivasubramanian ***et al.*** The novel synthesized compounds were characterized by MP, IR, 1H NMR spectra. These synthesized compounds were subjected to anti-microbial and anti cancer studies. All the synthesized compounds in the present study showed significant activity against microbes when compared with that of ampicillin and ketoconazole as standards. Synthesized compounds (Fig. 14) were found to exhibit moderate cytotoxicity activities in all cell lines [7].

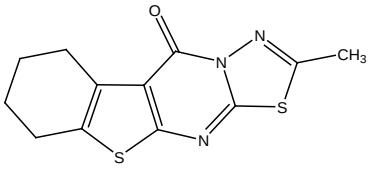


Fig. 14

Several new derivatives of 1,2,4-triazoles and 1,3,4-thiadiazole were synthesized by Mavrova *et al* and investigated for cytotoxic activity by trypan blue exclusion test (Fig. 15). The performed results revealed that some of the compounds showed good cytotoxicity against infected cells [8].

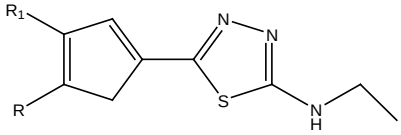


Fig. 15

A series of newly 1,3,4-oxadiazole-2-thioglycoside derivatives were synthesized by Abu Zaied *et al* and were clubbed with different heterocycles like benzothiazole, thiadiazole etc (Fig. 16). Synthesized compounds were screened for anticancer activity. Thiadiazole derivatives showed highly specific and potent activity against cancer cell lines [9].

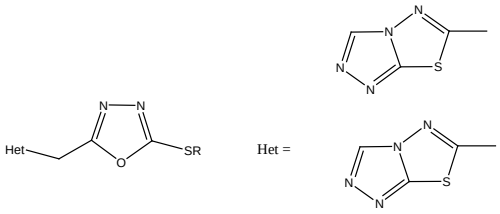


Fig. 16

Three triazolo-thiadiazoles, 6-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-3-[(2-naphthoxy)methyl] [1,2,4]-triazolo [3,4-b] [1,3,4] thiadiazole (CPNT), 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-3-[(2-naphthoxy)-methyl] [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazole (FPNT) and 6-[3-(4-chlororophenyl)-1H-pyrazol-4-yl]-3-[phenoxymethyl] [1,2,4] triazolo [3,4-b][1,3,4]-thiadiazole (CPPT) were synthesized by Dhanya *et al* and tested for their anti-tumor activity in ehrlich ascites carcinoma (EAC) bearing Swiss albino mice (Fig. 17). The effect of thiadiazoles in the mean survival time, body weight, hematological and biochemical parameters in cancer induced mice was studied and it has been found that thiadiazole derivative inhibited angiogenesis and exhibited excellent anticancer activity with minimal toxic effects *in vivo* against EAC cells when compared to the standard drug cisplatin [10].

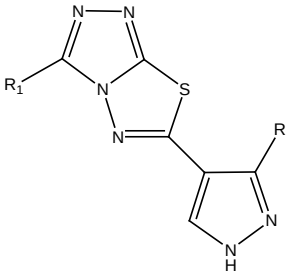


Fig. 17

A facile synthesis of 3,6-disubstituted -1,2,4-triazolo- [3,4-b]-1,3,4-thiadiazoles has been achieved by Ilango *et al*. The compounds were evaluated for *in vitro* cytotoxic activity against four human cancer cell lines. Results showed that some of the tested compounds exhibited significant activity against PA-1 cell lines, which are close to Doxorubin (Fig. 18). Therefore it was concluded that the incorporation of triazolo-thiadiazole moiety in aryl propionic acid group gives rise to enhanced anticancer activity [11].

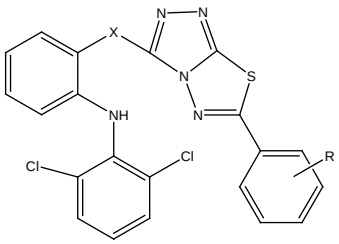


Fig. 18

A series of tetralin-6-yl pyridines and tetralin-6-ylpyrimidines was newly synthesized by Amina *et al* starting from1-(1,2,3,4-tetrahydronaphthalen-6-yl)-ethanone incorporating different five membered nitrogen-containing heterocycles like oxadiazole, triazole, thiadiazole, pyrazoline, thiazolidinone (Fig. 19). The

anticancer activity of some of the prepared compounds was evaluated using two human tumor cell lines, representing liver and breast. The compounds tested were, in most of cases, selective towards liver cancer [12].

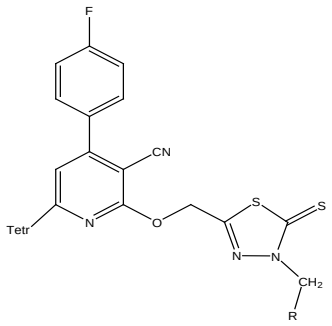


Fig. 19

The title compound *N*1-(1,3,4-thiadiazole-2-yl)-*N*3-*m*-chlorobenzoyl -urea, was prepared by Xia-Juan *et al* and its effect on tumor metastasis was analyzed by Lewis-lung carcinoma model (Fig. 20). The bioassay showed that the title compound significantly reduced the number of lung metastasis [13].

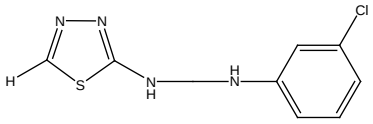


Fig. 20

1,3,4-thiadiazoles are well known compounds with interesting *in vitro* and *in vivo* anti-cancer profiles. With this aim, an *in vitro* evaluation of the anti-cancer activity of a new synthesized amino thiadiazole derivatives (Fig. 21) was conducted by Juszczak *et al.* The effect on tumor cell proliferation, motility and morphology, DNA synthesis as well as the influence on normal cells was assessed. The obtained results confirmed the promising anti-cancer profile of 1,3,4-thiadiazole derivatives [14].

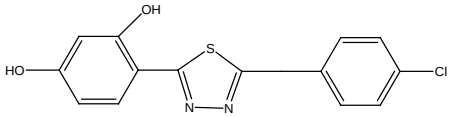


Fig. 21

Some novel derivatives of 1,3,4-thiadiazole-2-sulfonamide were designed by Supuran *et al* as potent sulfonamide inhibitors of the zinc enzyme carbonic anhydrase (Fig. 22), possessing inhibition constants in the range of 10^{-8}–10^{-9} M and were shown to act as efficient *in vitro* tumour cell growth inhibitors typically in the range of 0.1–30 μM against several leukaemia, non-small cell lung cancer, ovarian, melanoma, colon, CNS, renal, prostate and breast cancer cell lines. The mechanism of antitumour action with the new sulfonamides might involve either inhibition of several CA isozymes present predominantly in tumour cell membranes, acidification of the intracellular environment as a consequence of CA inhibition, uncoupling of mitochondria and/or strong CA V inhibition, or a combination of several such mechanisms [15].

A new series of 3,6-disubstituted triazolo-[3,4-b]-thiadiazole derivatives has been synthesized by Ibrahim *et al*. The newly synthesized compounds (Fig. 23) were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines. Many of the compounds demonstrated moderate to high inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5} M level and in some cases at 10^{-7} M concentrations. One Compound exhibited the highest sensitivity against renal, colon and melanoma cancer cell lines, the best results being against Renal cancer cell line with log GI_{50} -7.27 [16].

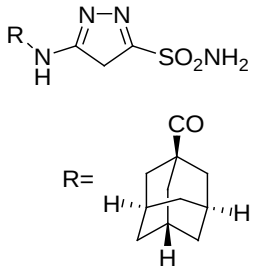
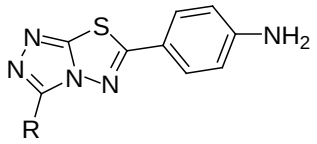


Fig. 22



R=CH_3

R= -CH_2Ph

R= -CH_2O-Ph(p-Cl)

Fig. 23

The action connected with the apoptotic mechanisms and angiogenesis, which is a crucial step in the tumorigenesis, seems to be very promising in anticancer therapy. In order to obtain compounds with better anticancer activities, a variety of novel colchicine derivatives (Fig. 24) were synthesized by combining N-methyl colchiceinamide and differently substituted 1,3,4-thiadiazole moieties by Shen Li Hong *et al* and tested their anticancer activities against a selected panel of human cancer cell lines. The results indicated that most of the derivatives showed significant anticancer activities, particularly, two of the compounds showed more potent cytotoxic activities of all screened cancer cells than colchicines [17].

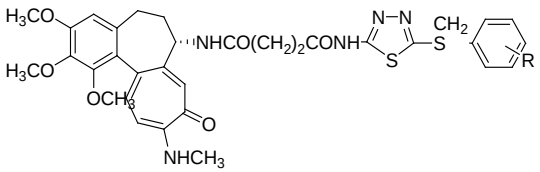
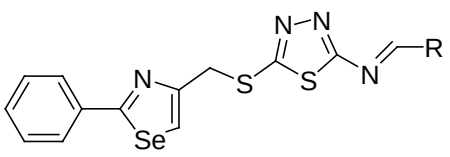


Fig. 24

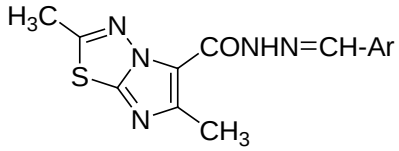
A series of novel 1,3-selenazole-containing 1,3,4-thiadiazole derivatives bearing Schiff base moieties were synthesized and evaluated for their *in vitro* antiproliferative activities by Zhao et al against human breast cancer cell MCF-7 and mouse lymphocyte leukemia cell L1210 (Fig. 25). The majority of the compounds showed better activity against MCF-7 cell, compared with lead compound PCS. In particular, one compound was the most potent compound with IC50 value of 4.02 lM [18].



R= 4-Cl-Ph

Fig. 25

Some novel 2,6-dimethyl-N-substituted phenylmethylene-imidazo [2,1-b][1,3,4]thiadiazole-5-carbohydrazides were synthesized by Terzioglu *et al*. The newly synthesized compounds were evaluated in vitro for primary cytotoxicity assay. Majority of the synthesized compounds (Fig. 26) showed the most favorable cytotoxicity. One compound of the series demonstrated the most marked effects in the human tumor cell line *in vitro* screen on an ovarian cancer cell line (GI_{50} value -5.51) [19].



Ar= 2-OH-Ph

Fig. 26

A facile microwave-assisted procedure for synthesis of novel fluorinated pyrazolo-[3,4 d]-pyrimidine derivatives containing 1,3,4-thiadiazole (Fig. 27) was described by Song *et al*. Their antitumor activities were evaluated against HL-60 by an MTT assay. The preliminary results indicated that some title compounds exhibit more potent antitumor inhibitory activity than doxorubicin (DOX) [20].

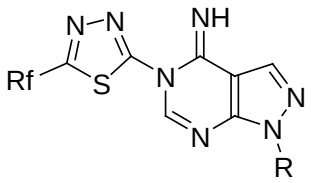


Fig. 27

Anti depressant activity

Mishra *et al* synthesized biologically active indolylmethyl-1,3,4-oxadiazoles, 1,3,4-thiadiazoles-1,3,4-triazoles and 1,2,4-triazines with a view that substitution by heterocyclic moieties, ie, oxadiazole, triazine or triazole, at positions 1 and 3 of the indole nucleus enhances the activities of indole nucleus (Fig. 28).

The compounds were studied for their antiinflammatory properties, CNS activity and acute toxicity. Some compounds were found to potentiate L-Dopa effects and decrease immobility time in the swimming despair test, thus showing anti-depressant activity. Compounds with heterocyclic thiadiazole and triazole moieties, possess greater anti-depressant activity compared to the rest of the compounds [21].

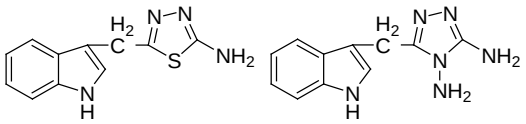


Fig. 28

A number of new imine derivatives of 5-amino-1, 3, 4-thiadiazole-2-thiol have been synthesized (Fig. 29), and their anti-depressant activity was tested using imipramine as reference drug by Yusuf *et al*. Two compounds have shown significant anti-depressant activity, which decreased immobility time by 77.99% and 76.26% compared to the standard imipramine (82%) [22].

Anti Convulsant activity

Epilepsy is the name of brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizure [23]. The current therapy of epilepsy with antiepileptic drugs is associated with side effects, dose related, chronic toxicity and teratogenic effects [24].

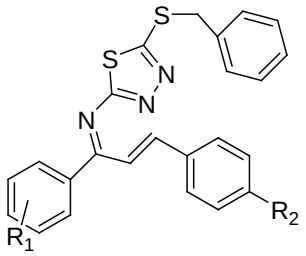


Fig. 29

Several novel 2-amino-5-[4-chloro-2-(2-chlorophenoxy)-phenyl]-1,3,4-thiadiazole derivatives were synthesized by Foroumadi *et al* and their anticonvulsant activity was determined by evaluation of the ability of these compounds (Fig. 30) to protect mice against convulsion induced by a lethal doses of pentylentetrazole (PTZ) and maximal electroshock (MES). The result of anticonvulsant data showed some of the compounds as most active compounds [25].

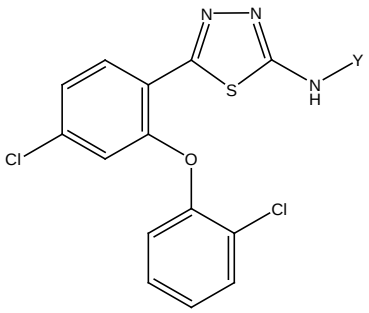


Fig. 30

In view of potential biological activities of thiadiazole novel 2-benzylidenylamino-5-(N-benzotriazolomethyl)-1,3,4-thiadiazole derivatives (Fig. 31) were designed and prepared by Singh *et al*. All the compounds were evaluated for analgesic, antibacterial, anticonvulsant and antitubercular activities. Results showed that synthesized compounds possess significant to excellent analgesic, anticonvulsant and antitubercular activities but none of the derivatives revealed antibacterial activity [26].

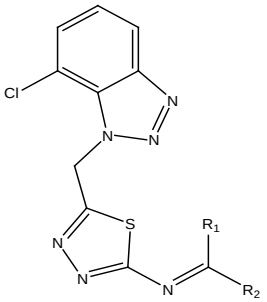


Fig. 31

Thiadiazole with styryl and quinazoline were reported to exhibit wide range of anticonvulsant, sedative, tranquilizer, analgesic, antimicrobial, anesthetic, anticancer, antihypertensive, antiinflammatory, diuretic and muscle relaxant properties. With the intention to develop potent anticonvulsant agents Bhandari *et al* designed, synthesized 3-[5-substituted 1, 3, 4-thiadiazol-yl]-2-styryl quinazolin-4(3H)-ones derivatives. The synthesized derivatives (Fig. 32) were tested *in vivo* for their anticonvulsant activity using MES, PTZ and Actophotometer model. The synthesized compounds, showed significant anticonvulsant activity comparable to the standard phenytoin, diazepam and phenobarbital [27].

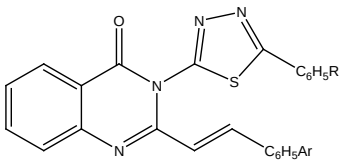


Fig. 32

A series of five membered heterocyclics was synthesized by Shahar Yar *et al* and was tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer. Among the synthesized compounds, 2-(4-chlorophenyl) amino-5- (4-pyridyl) -1,3,4-thia diazole and 2-(4-chlorophenyl)-amino-5-(4-pyridyl)-1, 3, 4-oxadiazole were found promising compounds of the series (Fig. 33) [28].

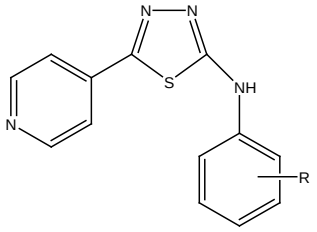


Fig. 33

A series of 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives (Fig. 34) were by Almasirad *et al*. synthesized**.** Compounds were evaluated *in vivo* for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests, respectively. Results depicted that most of the compounds were active in rota rod test and the most effective compound was 5-[2-(phenylthio)-phenyl]-1,3,4-oxadiazole-2(3*H*)-one which had comparable activity with diazepam [29].

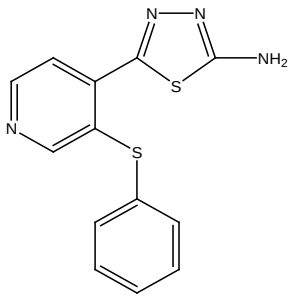


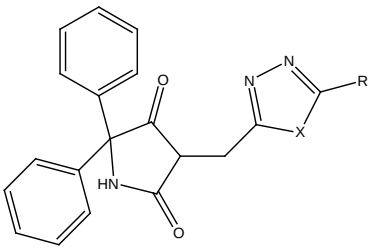
Fig. 34

1,3,4-oxadiazole, 1,3,4-thiadiazole or 1,2,4-triazole were known as hybrids between phenytoin drug and thiosemicarbazides. Some new phenytoin derivatives (Fig. 35) were synthesized by Botros *et al* utilizing these heterocyclic moieties and these were assessed for anticonvulsant activity. Preliminary anticonvulsant screening was performed using standard maximal electroshock (MES) and subcutaneous pentylenetetrazole (sc PTZ) screens in mice.

The neurotoxicity was determined applying the rotarod test. Among tested series, two of the compounds showed the highest protection (80%) in the sc PTZ test at a dose of 100 mg/kg, whereas one compound displayed promising anticonvulsant effect in the MES model [30].

Anti inflammatory activity

The development of an effective therapeutic agent for the treatment of inflammation continues to be a challenging problem in medicinal chemistry research.

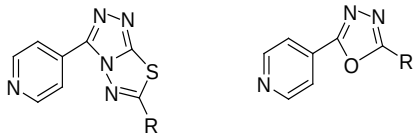


X = O,S

Fig. 35

The therapeutic use of nonsteroidal anti-inflammatory drugs (NSAIDs) is often limited by common side effects, such as gastrointestinal hemorrhage and ulceration. Therefore, a major challenge of the pharmaceutical industry is to develop drugs that have anti-inflammatory activities but lack the toxic side effects associated with currently used NSAIDs [31]**.** Different works reported on anti inflammatory activity are as follows:

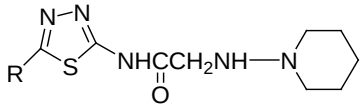
Gilani *et al* studied the significance of introducing isoniazid core into several heterocyclic moieties to explore the possibilities of some altered biological activities. Series of 6-substituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole (3a–g) and 1,3,4-oxadiazole (4a–g and 5) derivatives of isoniazid were synthesized (Fig. 36) in satisfactory yield and pharmacologically evaluated for their anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities by known experimental models. The most potent derivatives of triazolo-thiadiazole and 1,3,4-oxadiazole, respectively, showed potent anti-inflammatory and analgesic activities with reduced ulcerogenicity and lipid peroxidation and were further studied for their hepatotoxic effect in comparison with parent isoniazid and standard ibuprofen drugs [32].



R=4-$C_6H_4NO_2$ R=2,4-$C_6H_3Cl_2$

Fig. 36

Shakya *et al* synthesized Some new N-substituted acetyl derivatives of 2-amino-5-alkyl-1,3,4-thiadiazoles and investigated for antihistaminic and spasmolytic activity on guinea pig ileum. In the studies of the effect of the compounds (Fig. 37) on isolated organs all the compounds showed antihistaminic activity as expected, and all showed competitive antagonism towards histamine. IC_{50} value of all the compounds ranged between 1.20 x 10^{-7} to 4.15 x 10^{-7} mol/l. one of the compound was found to be very potent with IC_{50} value of 5.68 x10^{-8} mol/l. The introduction of 1,3,4-thiadiazoles nucleus in structure -NH-CO-CH,-N< showed anti-inflammatory activity in addition to antihistaminic and spasmolytic activity in a few compounds [33].

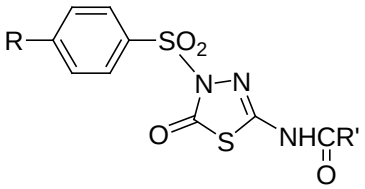


R= C_2H_5

Fig. 37

Two series of N-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides were synthesized by Schenone *et al* and tested *in vivo* for their anti-inflammatory activities. All the new compounds possess good anti-inflammatory activity in the

carrageenan rat paw edema test and some terms of the series showed also fair analgesic action in the acetic acid writhing test. Three of the most active compounds (Fig. 38) were also tested for the irritative and ulcerogenic action on gastric mucosa but were not found to be active [34].



(i) R-H, R'- 4-flourophenyl

(ii) R-H, R'- 4-triflouromethyl phenyl

(iii)R- CH3, R'-4 -triflouromethyl phenyl

Fig. 38

Several 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles were prepared by Mohd. amir *et al*. These compounds (Fig. 39) were investigated for their anti-inflammatory, analgesic, ulcerogenic, lipid peroxidation, antibacterial and antifungal activities. Some of the synthesized compounds showed potent anti-inflammatory activity along with minimal ulcerogenic effect and lipid peroxidation, compared to those of ibuprofen and flurbiprofen [35].

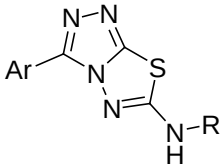


Fig. 39

Toma *et al* synthesized derivatives of 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol, 5-(pyridin-4-yl)-1,3,4-thiadiazole-2-thiol and 5-(pyridin-4-yl)-1,2,4-triazole-3-thiol and evaluated the compounds for anti-inflammatory activity using carrageenan-induced rat paw edema assay (Fig. 40). The oxadiazole, thiadiazole and thiazole rings presented a potent anti-inflammatory activity. The triazole ring presented a non-significant anti-inflammatory activity [36].

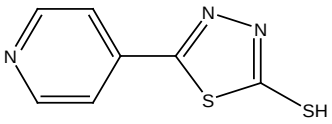


Fig. 40

Singh *et al* synthesized 2,5-Disubstituted-1, 3, 4-thiadiazole derivatives (Fig. 41). All newly synthesized compounds were evaluated by the antimicrobial activity by disc diffusion methods & anti inflammatory method by carreageenan rat paw edema method. Compounds were found to have moderate antibacterial activity and showed significant anti-inflammatory activity compared to Ibuprofen respectively [37].

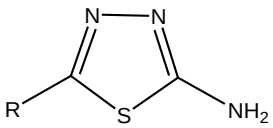


Fig. 41

Fluorobenzothiazole incorporated with 1,3,4-thiadiazole derivatives (Fig. 42) have been synthesized by Vedavathi *et al* and evaluated for their anti-inflammatory activity. Structures of these compounds have been established by IR, ^{1}HNMR data. Significant anti- inflammatory activities were observed for members of this series [38].

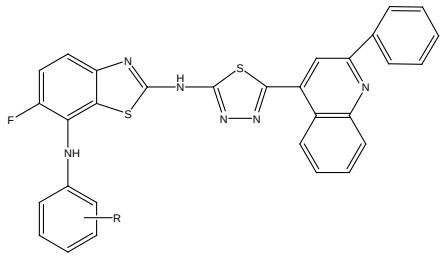


Fig. 42

Shaw *et al* synthesized fluoro substituted benzothiazoles incorporated with 1,3,4-thiadiazoles (Fig.43). They have been screened for their antimicrobial, anti-inflammatory and anticonvulsant activities. Results depicted significant activity for all the synthesized compounds [39].

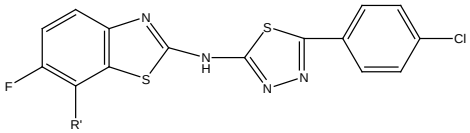


Fig. 43

In order to reduce the ulcerogenic effect of ibuprofen, Amir *et al* converted its carboxylic group into 5-membered heterocyclic rings. Various 1,3,4-oxadiazoles, 1,2,4-triazoles, 1,3,4-thiadiazoles, and 1,2,4-triazine derivatives of ibuprofen were prepared (Fig. 44) and screened for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation properties. All the tested compounds showed a significant reduction in ulcerogenic activity compared to ibuprofen. The results of biological studies showed that oxadiazole derivativeas the lead molecule with maximum anti-inflammatory, analgesic and minimum ulcerogenic and lipid peroxidation activities. The 1,3,4-thiadiazole derivatives of ibuprofen showed anti-inflammatory activity ranging from 75 to 84% [40].

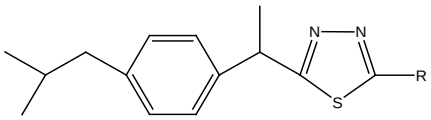


Fig. 44

Anti microbial activity

Several five membered aromatic systems having three hetero atoms at symmetrical Position, 1,3,4-thia/oxa-diazole have been studied because of their interesting physiological properties. It is also well established that various derivatives of 1,2,4-triazole, 1,3,4-thiadiazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal Activities. Novel fluorine-containing triazoles and thiadiazoles (Fig. 45) were synthesized from thiosemicarbazides by Salunkhe *et al***.** These reactions were carried out by green synthesis method such as ultra sonication and microwave technique. Both triazoles and thiadiazoles were screened for their antimicrobial activity. The investigation of antibacterial screening data revealed that all the tested compounds (40 µgms) showed moderate to excellent antibacterial activities against *Bacillus cereus* and *Klebsiella pneumoniae* [41]**.**

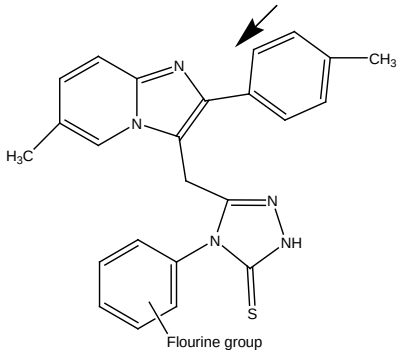


Fig. 45

Jalhan *et al* reviewed the synthesis and different biological activities of some Schiff bases of imidazo-[2, 1b]-1, 3, 4-thiadiazole derivatives (Fig. 46). The substituted derivatives showed moderate biological activity. Further the prepared Schiff bases have been subjected to antimicrobial property. The derivative has shown moderate to good activity when compared with standard antibiotic ampicillin [42].

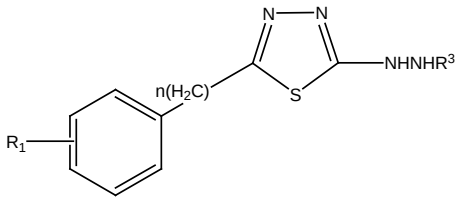


Fig. 46

Swamy *et al* synthesized two series of 4,6-disubstituted 1,2,4-triazolo-1,3,4-thiadiazole of type Fig. 47 and characterized using IR, 1H-NMR, CHNS analysis and by single crystal X-ray crystallographic studies. The title compounds were checked for their efficacy as antimicrobials *in vitro*. Different compounds showed significant inhibition against all the strains tested, when compared to standard drugs [43].

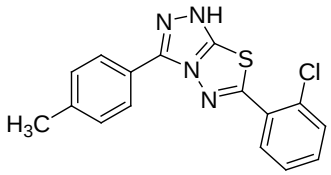


Fig. 47

Thaker *et al* afforded novel thiadiazole derivatives (Fig. 48) by aryl condensation of thiophene with arylisothiocyanate. The pharmacological evaluations have been performed for antimicrobial and anti tubercular activities. The compounds demonstrating more than 90% inhibition in the primary screen have been compared with standard drug Rifampicin at 0.25 µg/ml concentrations and it showed 98% inhibition [44].

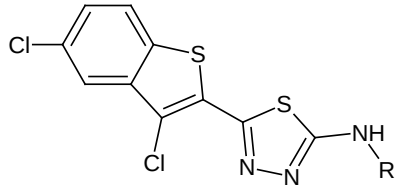


Fig. 48

With a view to obtain better pharmacologically active compounds, Some new Schiff bases containing thiadiazole, sulphonylhydrazide and 4-thiazolidinone moieties (Fig. 49), were synthesized and evaluated for their antimicrobial activity by Sah *et al***.** All the selected strains of the bacteria and fungi namely *S.aureus, E.coli, K.pneumonea, A.niger* and *A.flavus* showed sensitivity to most of the derivatives [45].

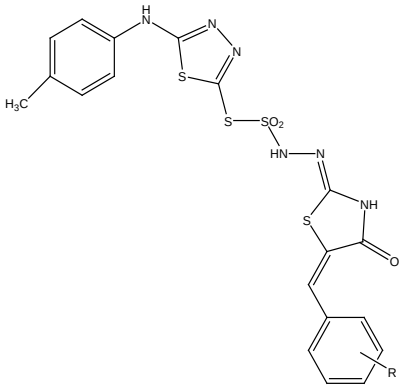


Fig. 49

A total of 20 derivatives of 1,3,4-thiadiazoles (Fig. 50) were synthesized by Ionut *et al* and their antimicrobial activities were assessed *in vitro* against bacterial and fungal strains using gentamicin and ketoconazole as reference drugs. Compounds showed potent bactericidal effects against bacterial strains, with the size of the zone of inhibition ranging between 10 and 20 mm (100 µg compound/well); and most of compounds exhibited antifungal activities, with the size of the zone of inhibition ranging between 12 and 28 mm (100 µg compound/well) [46].

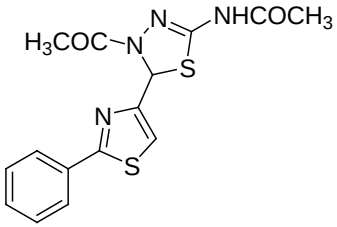


Fig. 50

A new class of 1, 3, 4-thiadiazoles which are incorporating with isoxazolo- thiazole moieties (Fig. 51) were synthesized by Seelam *et al* by the reaction of chalcone derivatives with hydroxylamine hydrochloride. The new synthesized compounds were evaluated for their antimicrobial activity. The final results revealed that some of the compounds were exhibited well antimicrobial activity compared to the standard drugs [47].

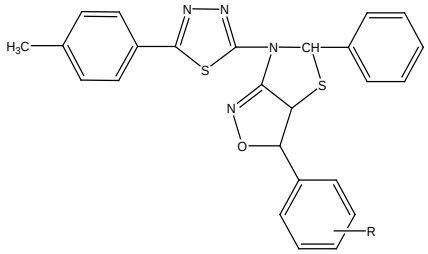


Fig. 51

Abdulrasool *et al* studied the synthesis of new heterocyclic compounds containing 1,2,4- Triazole and 1,3,4-Thiadiazole Rings

by many cyclization reactions. The antibacterial test was performed according to the disc diffusion method. Compounds were assayed for their antimicrobial activity in vitro against four strains of bacteria. From the result it can be concluded that the all compounds revealed good biological activities against these microorganisms with one compound (Fig. 52) showing the highest biological activity against *E.coli* higher than the reference antibiotics (Amoxicillin & ceftriaxone) [48].

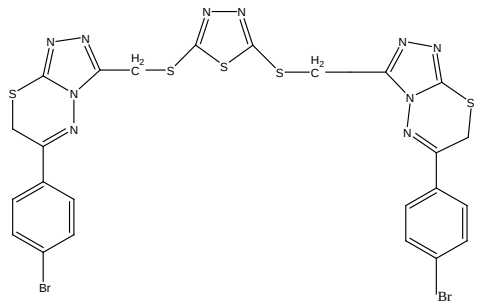


Fig. 52

Novel thiadiazoles were synthesized by Raj *et al.* From these compounds various derivatives of 1,3,4-Thiadiazole derivatives have been synthesized (Fig. 53). These compounds were screened for antibacterial and anti-fungal by paper disc diffusion technique. *In vitro* antibacterial activity data of 1,3,4-Thiadiazole derivatives against tested organisms displayed significant activity with a wide degree of variation [49].

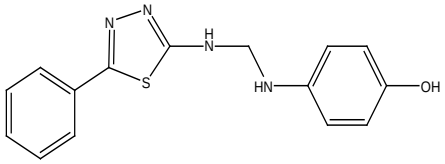


Fig. 53

A series of 6-substituted**-**1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid were synthesized by Gilani *et al* and pharmacologically evaluated for their *in-vitro* antimicrobial activity (Fig. 54). All the synthesized compounds were in good agreement with elemental and spectral data. A majority of the tested compounds showed good to moderate antimicrobial activity against all tested pathogenic bacterial and fungal strains [50].

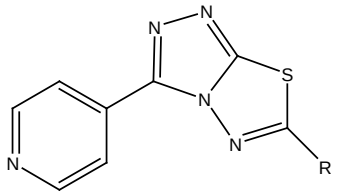


Fig. 54

Pawankar *et al* synthesized a series of α-bromoketones & thiadiazole with various benzimidazoles. Since the title compounds (Fig. 55) are known to possess antimicrobial activity, the compounds were screened for their antibacterial and antifungal activity by cup-plate method. All the benzimidazole substituted thiadiazole derivatives showed significant activities compared to the standards ciprofloxacin for significant activity [51].

Mendhe *et al* synthesized a series of α-bromoketones & thiadiazole derivative. The compounds were confirmed by physical parameters (solubility, melting point), chromatographic methods (TLC) and spectroscopic methods (IR, NMR). The compounds were screened for their antibacterial and antifungal activity by cup-plate method. The 2-amino-1,3,4-thiadiazole derivatives (Fig. 56) showed mild antibacterial activities and significant antifungal activities [52].

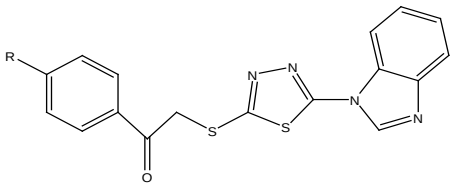


Fig. 55

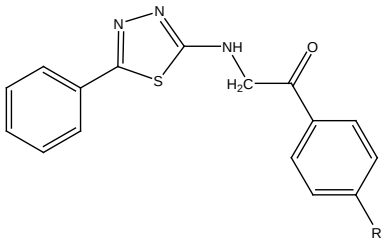


Fig. 56

A series of new 2-amino-1, 3, 4-oxadiazoles and 1, 3, 4-thiadiazoles (Fig. 57) were synthesized followed by condensation with various substituted aldehydes to yield their Schiff bases by Parimi *et al***.** The synthesized compounds were evaluated for their antimicrobial activity against two Gram positive bacteria, two Gram negative bacteria and two fungal species/yeast strains. All the synthesized compounds showed good antimicrobial activity [53].

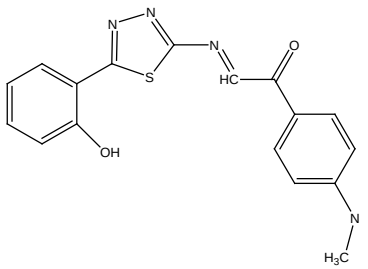


Fig. 57

Various 1,2,4-Triazole and 1,3,4-Thiadiazole Derivatives of 5-Amino-2-Hydroxybenzoic Acid were synthesized by Hussain *et al* and evaluated for their antibacterial and antifungal activity (Fig. 58). The compounds showed significant antibacterial activity against *S. aureus* (gram-positive) and *E.coli* (gram-negative) bacteria and antifungal activity against *A. niger* fungi using cup plate technique [54].

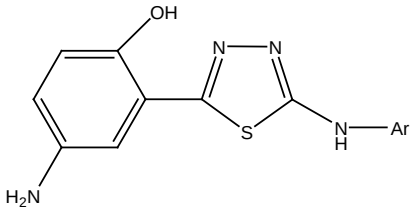


Fig. 58

2-Amino-5-(2-aryl-2*H*-1,2,3-triazol-4-yl)-1,3,4-thiadiazoles have been synthesized by Atta *et al***.** The structure of the above compounds (Fig. 59) was confirmed from their spectral characteristics. Some of these compounds were found to possess

slight to moderate activity against the microorganisms *Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa,* and *Escherichia coli* [55].

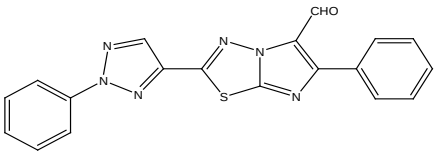


Fig. 59

Anti- tubercular activity

Vasoya *et al* synthesized some new thiosemicarbazide and 1,3,4-thiadiazole heterocycles bearing benzo-[b]-thiophene nucleus (Fig. 60). All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* (H37Rv) and antimicrobial activity against various microorganisms. Some compounds showed higher activity than others [56].

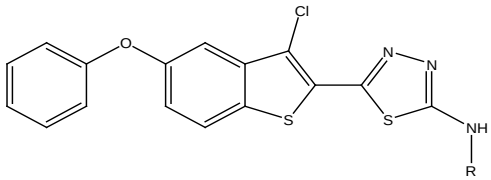


Fig. 60

A series of new Schiff bases were synthesized by Solak *et al* through the condensation reaction of 1,3,4- thiadiazoles containing a aromatic primary amine (Fig. 61). The synthesized compounds screened for antituberculosis activity against *Mycobacterium tuberculosis.* Among the tested compounds, some of them showed the highest inhibitory activity [57].

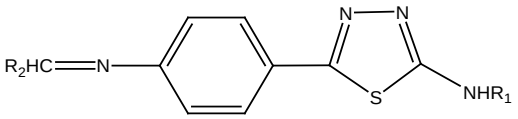
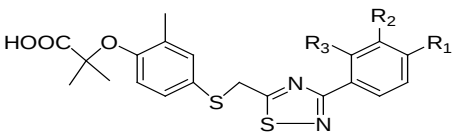


Fig. 61

Miscellaneous activities

The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily and consist of three members, PPARα, PPARβ, and PPARϱ. PPAR α is ex pressed mainly in tissues involved in lipid oxidation such as liver, kidney, adrenal glands, cardiac muscle, and skeletal muscles. PPARα regulates the expression of genes involved in lipid metabolism. Shen *et al* synthesized some [1,2,4]-thiadiazole derivatives (Fig. 62) to give compounds which unexpectedly displayed submicromolar potency as a partial agonist at PPARα in addition to the high potency at PPAR ϱ. A structure–activity relationships study of the compounds resulted in the identification of a potent and selective PPAR α*ϱ* dual agonist [58].



(i) **R_1=CF3,R_2=F,R_3=H**

(ii) **R_1=OCF3,R_2=Cl,R_3=H**

(iii) **R_1= Cl,R_2= Cl,R_3=H**

(iv) **R_1=Cl,R_2=H,R_3=Cl**

(v) **R_1=Me,R_2=Me,R_3=H**

(vi) **R_1=Me,R_2=Cl,R_3=H**

Fig. 62

Ten substituted N-aryl-5-phenyl 1,3,4-thiadiazoles (III) were synthesized by Jayakumar Swamy *et al.* The newly synthesized compounds were characterized by spectroscopic methods (Fig. 63). Further, the synthesized few selected compounds were screened wound healing activity by standard method. Results of the activities revealed that, some compounds exhibited moderate to good selected compounds showed wound healing activity [59].

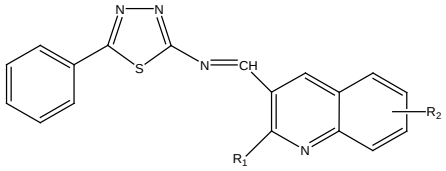


Fig. 63

Karagozoglu *et al* aimed to investigate the antioxidant and antihepatotoxic effect of hydoxyurea derivative 1,3,4-thiadiazoles on serum biochemical parameters (AST, ALT, LDH, urea, creatinine and total bilirubin) and antioxidant parameters (SOD, CAT, GPX, MDA). The levels of all the parameters were determined spectrophotometrically (Fig. 64). From results it can be concluded that pharmacological characteristics can be beneficial in many fields of application asthe hydroxyurea derivative 1,3,4-thiadiazole compounds showed the antioxidant and anti-hepatotoxic activity [60].

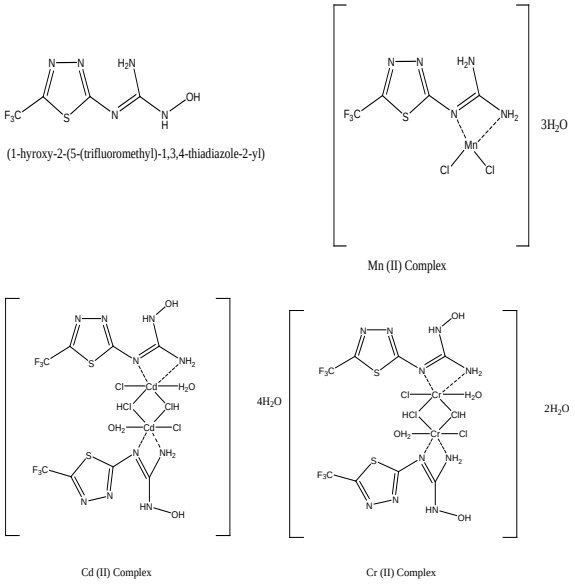


Fig. 64

Starting from the 4-amino-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4,5-dihydro-[1,2,4]-triazole-5(1*H*)-

thione, a series of new [1,3,4]-thiadiazoles and [1,3,4]-thiadiazines (Fig. 65) were prepared by Farghaly *et al.* Also, [1,3,4]-thiadiazepines could be synthesized. Some of the newly prepared compounds were evaluated for their antiviral potential [61].

Banachiewicz *et al* synthesized some new 1,2,4-triazole and 1,3,4-thiadiazole derivatives. The compounds (Fig. 66) were evaluated for their analgesic and anticonvulsant activity. Results revealed that compounds possess weak pharmacological activity in CNS [62].

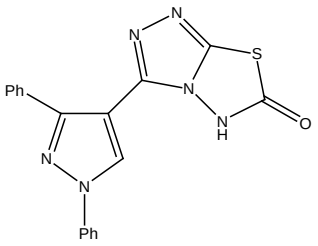


Fig. 65

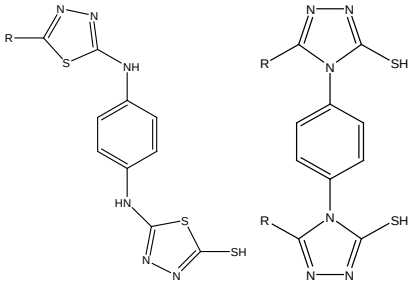


Fig. 66

Some new derivatives of 2,4-diphenyl-5-imino-Δ^2-1,3,4-thiadiazole were prepared by Asif *et al***.** The structures of the compounds (Fig. 67) were elucidated by IR, 1H-NMR and elemental analysis. Antinociceptive activity was evaluated using in vivo tests, by means of the hot plate method and found that all the compounds exerted a lesser antinociceptive effect compared to acetylsalicylic acid [63].

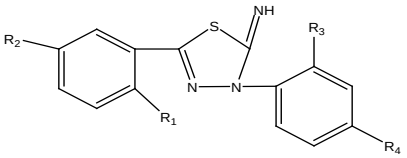


Fig. 67

CONCLUSION

The thiadiazole ring system constitutes a key structural component of pharmaceuticals. Because of its unique pharmaceutical importance, a continous development in the synthesis of new thiadiazole derivatives is a growing area of research. The literature reveals that thiadiazole have diverse biological potential and the easy synthetic routes for synthesis, have taken attention of chemists, pharmacologists and researchers all over the world. Given the advances in synthetic methodology and technology in recent years and the continued interst in the thiadiazole skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the construction of these molecules and even fusion of the thiadiazole nucleus with many heterocyclics ensured that this is an active and pivotal area of research in heterocyclic chemistry.

CONFLICT OF INTERESTS

Declared None

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