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# A REVIEW ON BIOLOGICAL ACTIVITIES: 1,3,4- THIADIAZOLE AND ITS DERIVATIVES

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**Abstract:**The chemical features of 1,3,4-thiadiazoles were described in a numerous reviews focusing on the main approaches to the synthesis and modification. Heterocyclic compounds occupy a central position among those molecule that makes life possible. Among of these compounds having 1,3,4,-thiadiazole nucleus are known to exhibit unique antiinflammatory, analgesic, antimicrobial, antitumor, antifungal, antimycobacterial, anticonvulsant, antidiabetic, antiviral, activities. The significant biological activity of thiadiazolederivates promotes the scientists to further investigation of this heterocycle as a building block for medicinal chemistry. The present review highlights the recently synthesized thiadiazole possessing important biological activities.

Keywords: thiadiazole; anticancer activity; cytotoxicity; antimicrobial; anti-diabetic.

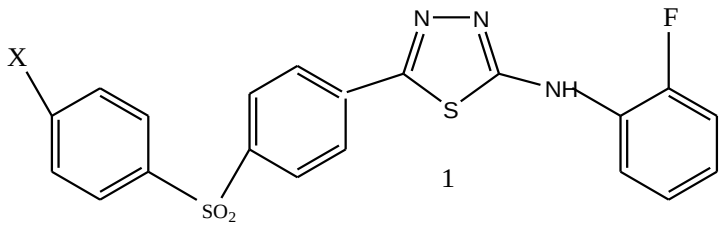
## Introduction

The science of heterocyclic mixtures has been an intriguing field of study for quite a while. Heterocyclic core 1,3,4-thiadiazole is a significant class of mixtures for new medication improvement. The union of novel thiadiazole subsidiaries and examination of their synthetic and organic way of behaving have acquired significance in ongoing many

years. During the new years there has been extraordinary examination of various classes of thiadiazole compounds, large numbers of which have broad pharmacological exercises. During continuous years, little molecules containing five-section heterocyclic moieties have transformed into the subject of great creating interest for arranging new antitumor trained professionals. Thiadiazole subsidiaries have four isomeric structures: 1,3,4-thiadiazole; 1,2,3-thiadiazole; 1,2,4-thiadiazole; and 1,2,5-thiadiazole. In distributed examinations, 1,3,4-thiadiazole subsidiaries will quite often show the main restorative potential [1]. These mixtures had a large number of helpful exercises like antimicrobial [2], antifungal [3], antimycobacterial [4], pain relieving, mitigating [5], antipsychotic [6], stimulant [7], anticonvulsant [8,9], hostile to leishmanial [10] and so on. There are many reports on the natural action of 1,3,4-thiadiazole subordinates. This study is an endeavor to gather the 1,3,4-thiadiazole and its subsidiaries, which can be considered as possible bioactivity, detailed in the writing in light of the mixtures esteem in restorative science.

**1,3,4-thiadiazole**

Babucianu and coworkers reported the new heterocyclic compounds from 1,2 4-triazole and 1,3,4-thiadiazole class having diphenylsulphone and 2-fluorophenyl fragments like 2-amino-1,3,4-thiadiazole) from cyclization of corresponding acylthiosemicarbazides and with the purpose of investigating in the future their possible antimicrobial, analgesic or anti-inflammatory activities [11].




1

Mousa have synthesized new compounds and evaluated for the antibacterial activities. The synthesized molecules have been studied for their antibacterial activity against the S.

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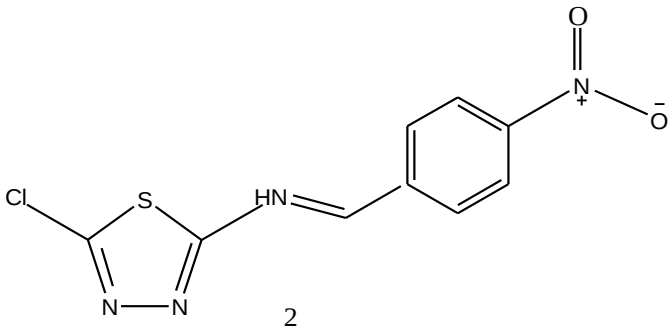
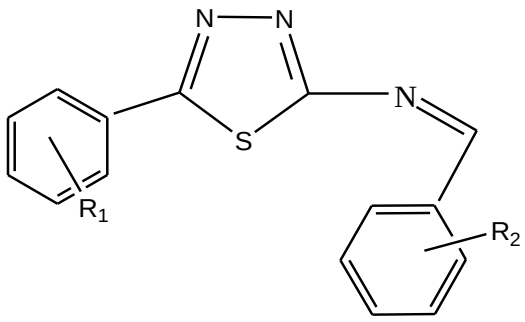
aureus and B. Cereus as gram positive and E. coli and P. Aeroginosa as gram negative bacteria. The prepared compound showed a noticeable antimicrobial activity as compared to standard drug. Compound showed the best antimicrobial activity against the tested bacteria [12].




2

ArunNaskar and coworkers synthesized 2-amino-5-aryl-1,3,4-thiadiazoles by oxidative cyclization of thiosemicarbazones using $FeCl_3$ catalyst and from this Schiff bases were prepared by condensation with aldehyde and synthesized compounds were characterized by IR, NMR, and CHN analysis. Anticancer activity was evaluated using Ehrlich's Ascites carcinoma cells and all the compounds exhibited significant anticancer activity compared to control [13].




3

Brijendra Kumar Soni and coworkers synthesized thiadiazole derivative and evaluated for in vitro antioxidant activity by hydrogen peroxide and nitric oxide scavenging activity and lipid peroxidation inhibitory activity. Some of the compounds showed potent antioxidant activity [14].

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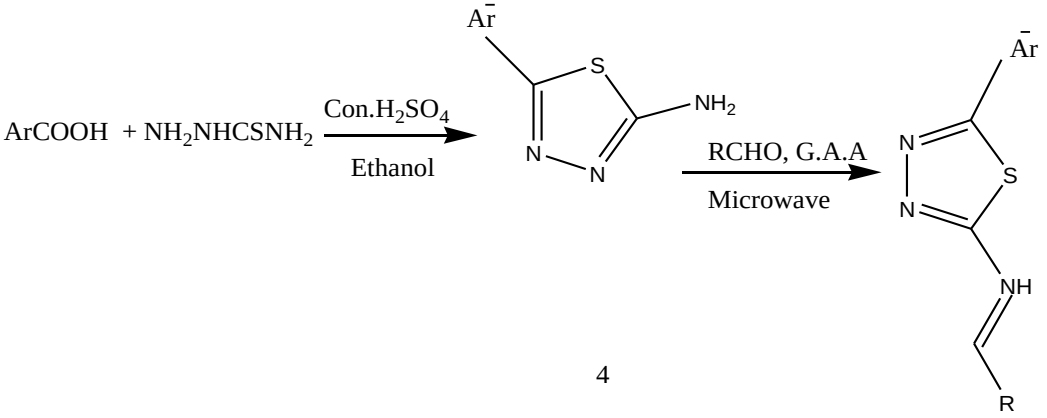
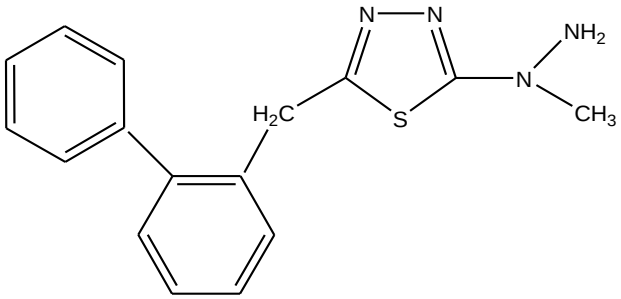



4

Michael Stillings and coworkers synthesized a series of 2-aryl-5-hydrazino-l,3,4-thiadiazole derivatives and evaluated them for anticonvulsant activity. Among them, N-methylhydrazine shown potent anticonvulsant activity in rodent models of grand mal epilepsy and it has neither produced neurotoxicity nor cardiovascular actions occur at anticonvulsant doses. The SAR study of synthesized compounds reveals that the introduction of aromatic substituted in the 2-position tied with alkyl on the hydrazine moiety led to a number of potent compounds lacking sedation, ataxia, or lethality like as 5-(2-Biphenylyl)-2-(1-methylhydrazino)-l,3,4-thiadiazole [15].




5

Ilies and coworkers synthesized a series of aromatic/heterocyclic sulfonamides incorporating adamantyl moieties and evaluated for the anticonvulsant activity using by a MES test in mice. After intraperitoneal injection (30mg $kg^{-1}$), among them compound 5-(Adamantan-1-yl-carboximido)-4-methyl-$\Delta^2$-1,3,4-thidiazoline-2-sulfonamid exhibited a high protection against electrically induced convulsions at a dosage of: 20, 10, 5 and 2.5 mg/kg. (>90%). Their ED50 was 3.5 mg $kg^{-1}$ (Ilies*et al*., 2004)[16].

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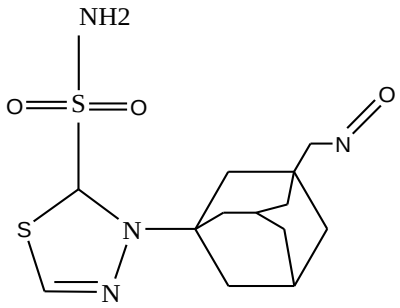
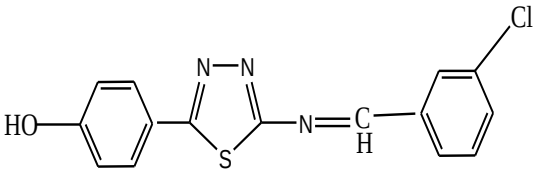



6

Baghel and coworkers had been synthesized a new thiadiazoles and examined the anti-bacterial and antifungal activities for them. The novel prepared thiadiazoles were investigated against Gram positive and gram negative species named Bacillus subtilis, Staphylococcus aureus and Gram negative species Pseudomonas aeruginosa, Escherichia coli addition to fungi Candida albicans and A.niger. Compounds 4-(5-(3-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol [**7**] and 4-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol [**8**] shows potent activities comparing with the examined microbes[17].

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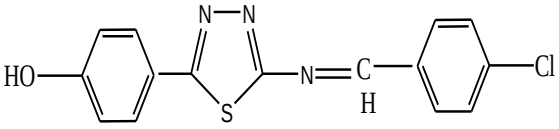


8

Dawood and coworkers synthesized of (Z)-1-(4-(4-chlorophenyl)-5-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)imino)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetaldehyde [**9**] and 4-(4-chlorophenyl)-5-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylimino)-N-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide[10]. The novel synthesized molecules have promising cancer potent against colon [18].

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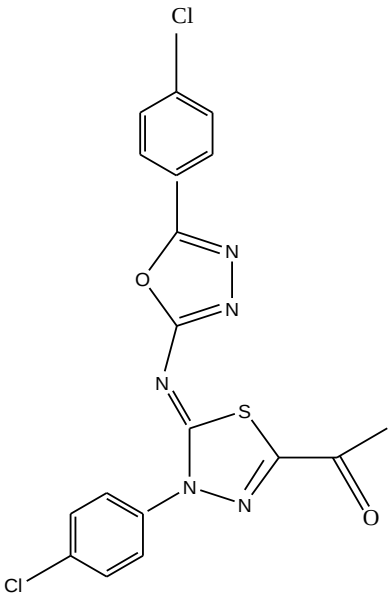

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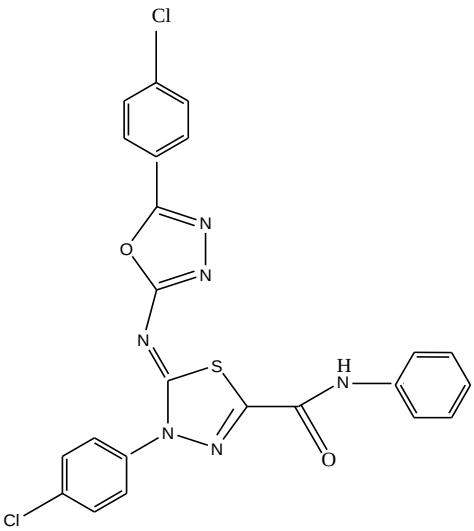
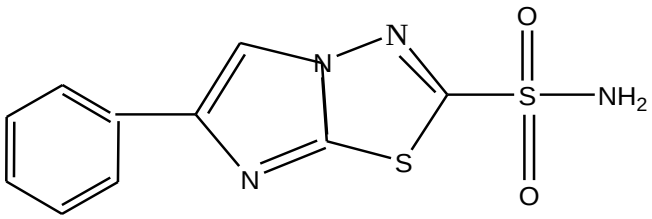


10

Fawzia and coworkers synthesized 6-phenylimidazo[2,1-b][1,3,4]thiadiazole2-sulfonamide [**11**] displayed the antimicrobial activities against the Escherichia coli and staphylococcus aureus in addition to moderate activities against salmonella typhi, pseudomonas aeguginosa and pneumococci [19].



11

Bhandari and coworkers reported thiadiazole with styryl and quinazoline [12] were exhibit wide range of anticonvulsant, sedative, tranquilizer, analgesic, antimicrobial, anesthetic, anticancer, antihypertensive, antiinflammatory, diuretic and muscle relaxant properties [20].

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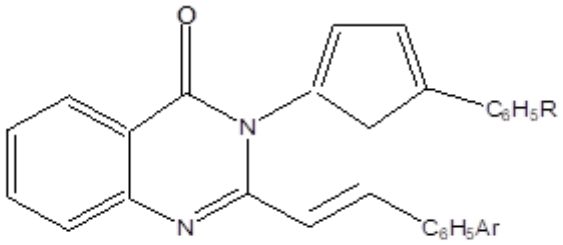
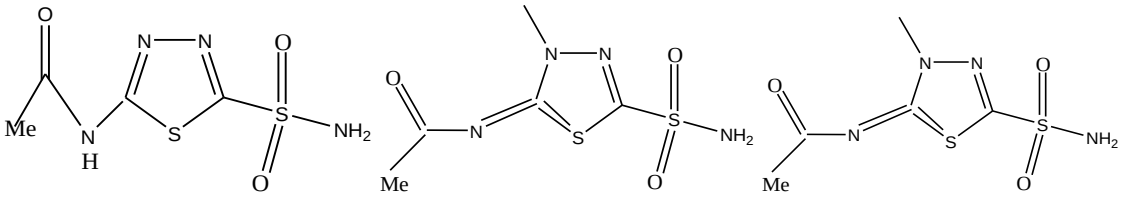



R=$N(CH_3)_3$, p-F, 3-$N_2$, 4-OH; Ar = 3-$NO_2$, $N(CH_3)_3$, 4-Br, 4-$FC_6H_4$

12

Stephanie and co-workers reported the vapoury derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) was one of the best CA I and CA II inhibitor in the series and exhibited very strong anticonvulsant properties in an MES test in mice. In consequence, other 1,3,4-thiadiazolesulfonamide derivatives possessing potent CA inhibitory properties and substituted with different alkyl/ arylcarboxamido/sulfonamido/ureido moieties in the 5 position have been investigated for their anticonvulsant effects in the same animal model. It was observed that some lipophilic derivatives, such as 5-benzoylamido-, 5-toluenesulfonylamido-, 5-adamantylcarboxamido-, and 5-pivaloylamido-1,3,4-thiadiazole-2-sulfonamide, show promising in vivo anticonvulsant properties and that these compounds may be considered as interesting leads for developing anticonvulsant or selective cerebrovasodilator drugs[21].

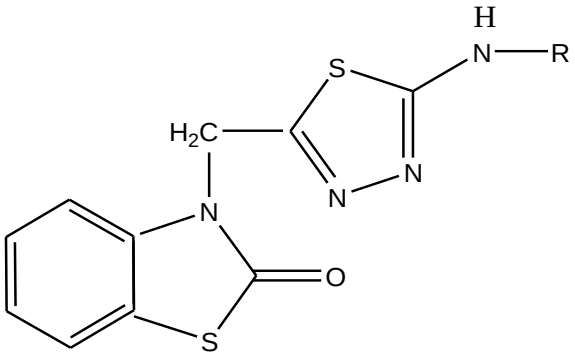



13 14 15

TijenOnkol and coworkers reported ten 2-[(2-oxobenzothiazolin-3-yl)methyl]-5-aminoalkyl/aryl-1,3,4- thiadiazole derivatives. The chemical structures of these compounds were elucidated by their FT-IR and 1H-NMR spectral data, as well as their elemental analyses. The compounds were tested for anti-nociceptive activity. Among these compounds,

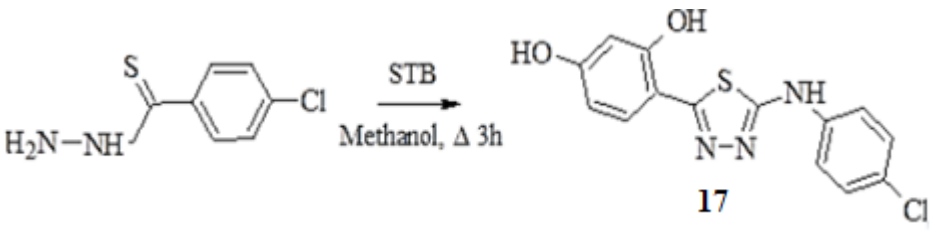
2-[(2-oxobenzothiazolin-3-yl)methyl]-5-aminomethyl-1,3,4-thiadiazole (16a) was found to be significantly more active than the others and the standards in all the tests[22].

2-Oxobenzothiazoline derivatives bearing substituents at position 3 with thiadiazole moiety have reported to exhibit antihistaminic activity [16]. Compounds 16a, 16b, 16d, 16e and 16h were more potent than others and the standards in tail flick test (TijenOnkol*et al.*, 2004 & 2006). 16 a. methyl, 16 b. ethyl, 16 c. allyl, 16 d. cyclohexyl, 16 e. phenethyl, 16 f. phenyl, 16 g. 4-methylphenyl, 16 h. 4-clorophenyl, 16 i. 4-methoxyphenyl, 16 j. 4-nitrophenyl




16

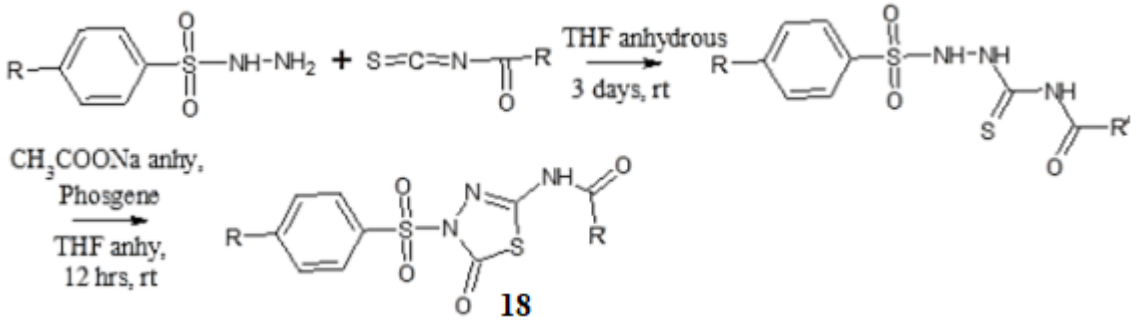
Malgorzata and coworkers synthesized 2-(4-chlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole. The compound was obtained from sulfinylbis (2,4-dihydroxythiobenzoyl) and 4-(3-chlorophenyl)-3-thiosemicarbazide or 4-(4-chlorophenyl)-3-thiosemicarbazide (Lancaster, Germany) via cyclization process [23].



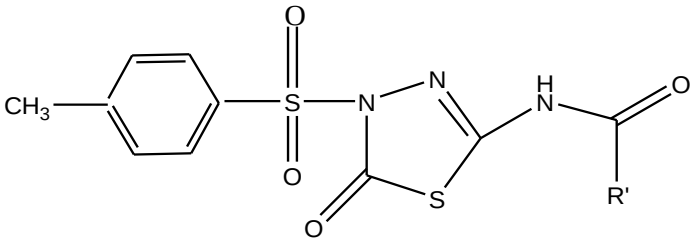

17

Schenone and coworkers synthesized the series of N-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides and tested in vivo for their analgesic and anti-inflammatory activities. All the new synthesized compounds possess 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 [24].



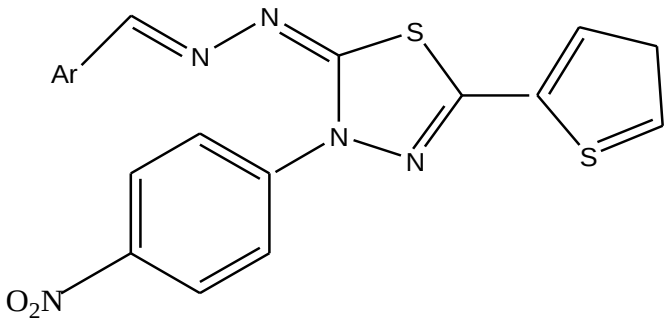

Silvia Schenone and coworkers synthesized the two series of N-[5-oxo4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides and evaluated for in vivo analgesic and anti-inflammatory activities. All the new compounds possess good analgesic action in the acetic acid writhing test and some compounds also showed fair anti-inflammatory activity in the carrageenan rat paw edema test [25].



19

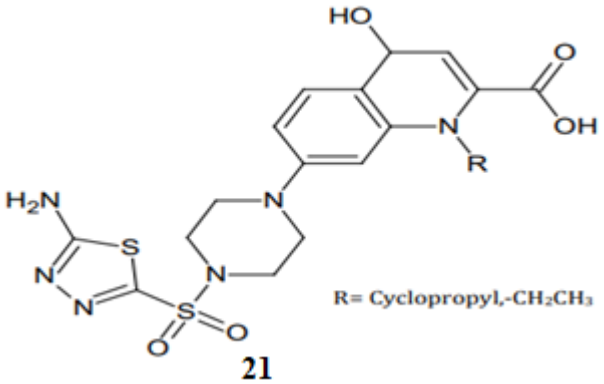
Sobhi M Gomha and coworkers reported a series of new 1,3,4-thiadiazoles were synthesized by heterocyclization of N-(4- nitrophenyl)thiophene-2-carbohydrazonoyl chloride with a variety of hydrazine-carbodithioate derivatives. All the new synthesized compounds were investigated for in vitro activities against human hepatocellular carcinoma (HepG-2) and human lung cancer (A-549) cell lines compared with cisplatin standard anticancer drug. Moreover, molecular docking using MOE 2014.09 software was also carried out for the high potent compound 20b with the binding site of dihydrofolatereductase (DHFR, PDB ID (3NU0)). Compound 20b has promising activities against HepG-2 and A-549 cell

lines ($IC_{50}$ value of 4.37±0.7 and 8.03±0.5 µM, respectively) and the results of molecular docking supported the biological activity with total binding energy equals -1.6 E (Kcal/mol)[26].




20

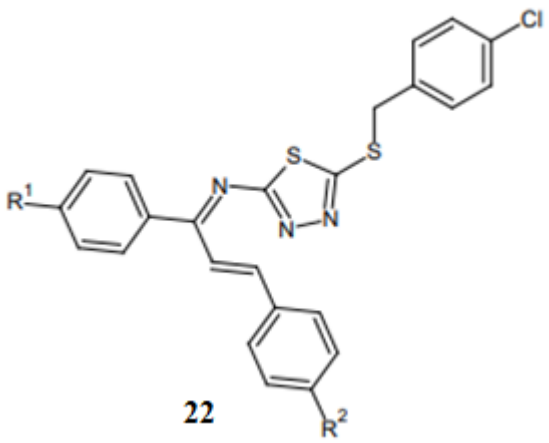
Talath and Gadada synthesized a series of 7-[4-(5-amino-1,3,4-thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives and characterized by IR, $^{1}$H-NMR, $^{13}$C NMR, FAB Mass spectral and elemental analyses. The compounds were evaluated for their preliminary in vitro antibacterial activity against some Grampositive and Gram-negative bacteria and selected compounds were screened for antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method [27].




21

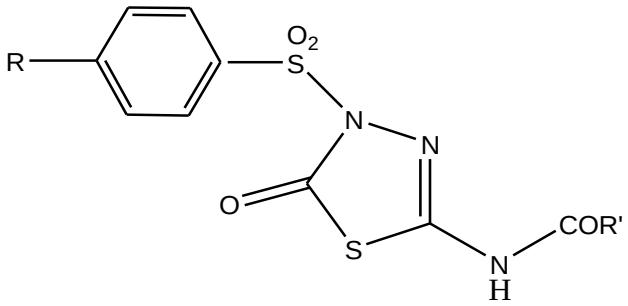
Mohammad Yusuf and coworkers synthesized a number of new imine derivatives of 5-amino-1,3,4-thiadiazole-2-thiol. Two compounds namely 5-{[1-(4-chlorophenyl)-3-(4-methoxy-phenyl)prop-2-en-1-ylidene]-amino}-5-benzylthio-1,3,4–thiadiazole and 5-{[1-(4-

chlorophenyl)-3-(4-dimethylaminophenyl)-prop-2-en-1-ylidene]amino}-5-benzylthio-1,3,4-thiadiazole have shown significant anti-depressant activity [28].




22

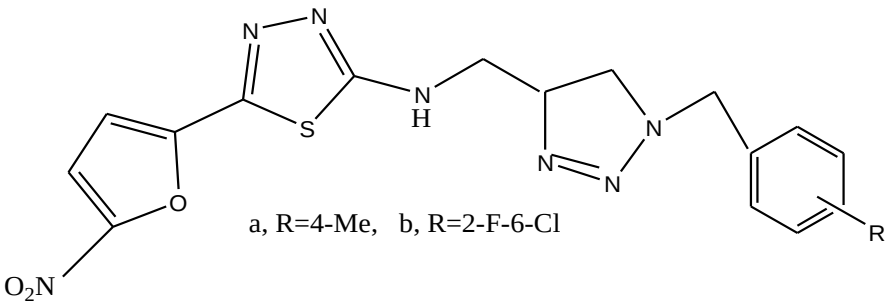
Schenone and coworkers synthesized two series of N-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides **(23)** and tested in vivo for their analgesic and anti-inflammatory activities. All the new compounds possess good analgesic action in the acetic acid writhing test. Ulcerogenic and irritative action on the gastrointestinal mucose, in comparison with indomethacin is low[29].




23

Taghighi and coworkers synthesized a novel series of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines by introducing N-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] moiety as a new functionality on the C-2 amine of thiadiazole ring via click chemistry. The compounds were evaluated for their in vitro anti-leishmanial activity against promostigote form of the Leishmania major. 4-methylbenzyl analog 46 was found to be the most active compound

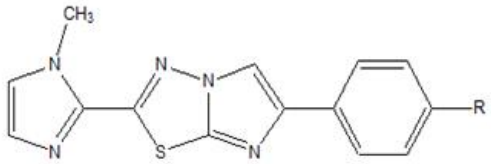
against promostigotes which significantly decreases the number of intracellular amastigotes per macrophage, percentage of macrophage infectivity and infectivity index [30].




a, R=4-Me, b, R=2-F-6-Cl

24

Patel and coworkers synthesized a series of imidazo-[2,1-b][1,3,4]thiadiazole derivatives **5(a–j)** were synthesized and characterized by IR, $^{1}$H NMR, $^{13}$C NMR and mass spectral technique. The compounds were evaluated for their in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain by using micro plate Alamar Blue susceptibility test as part of the TAACF TB screening program under direction of the US National Institutes of Health, the NIAID division. Among the tested compounds, 2-(1-methyl-1H-imidazol-2-yl)-6-(4-nitrophenyl) imidazo-[2,1-b][1,3,4]thiadiazole**(5f)** has shown the highest (98%) inhibitory activity with MIC of 3.14 mg/ml as compared to other tested compounds. Further, some potent compounds were also assessed for their cytotoxic activity against a mammalian Vero cell line using MTT assay. The results reveal that these compounds exhibit anti-tubercular activity at non-cytotoxic concentrations [31].

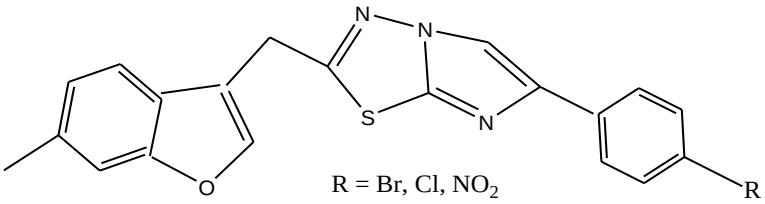



R = **a**) 3-Nitro, **b**) 4-Bromo, **c**) 4-Chloro, **d**) 4-Fluoro, **e**) 2-Hydroxy, **f**) 4-Nitro, **g**) 4-Methyl, **h**) 3-Hydroxy,**i**) 2,4-Dichloro, **j**) 2,4-Dihydroxy

**25**

Jadhav and coworkers evaluated anti-inflammatory and analgesic activities of 6-aryl-2-(6-methyl-benzofuran-3-ylmethyl)imidazo[2,1-b][1,3,4]thiadiazoles and their 5-

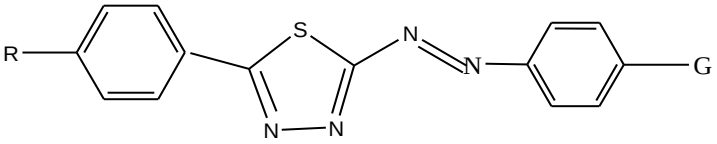
carbaldehyde/(morpholin-4-yl)methyl derivatives. The qualitative SAR studies indicate that the chloro substitution in the imidazole ring and introduction of formyl group at C-5 position of the imidazole ring increased the anti-inflammatory and analgesic activity [32].




R = Br, Cl, $NO_2$

26

AgnieszkaKudelko and coworkers synthesized three series of azo dyes derived from 2-amino-5-aryl-1,3,4-thiadiazoles and aniline, N,N-dimethyl aniline and phenol were synthesized in high yields by a conventional diazotization-coupling sequence. The chemical structures of the prepared compounds were confirmed by $^{1}$H-NMR, $^{13}$C-NMR, IR, UV-Vis spectroscopy, mass spectrometry and elemental analysis. In addition, the X-ray single crystal structure of a representative azo dye was presented. For explicit determination of the influence of a substituent on radiation absorption in UV-Vis range, time-dependent density functional theory calculations were performed[33].

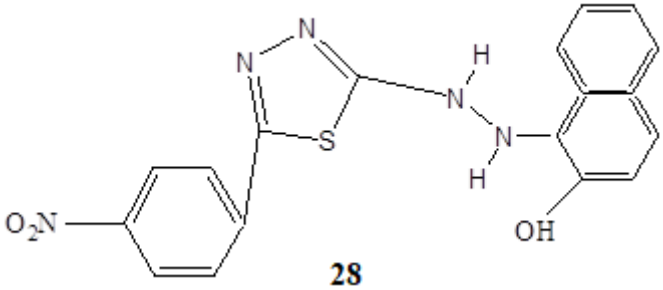



G =$NH_2$, $NMe_2$, OH ； R = H, MeO, $NO_2$, Br, *t*-Bu

27

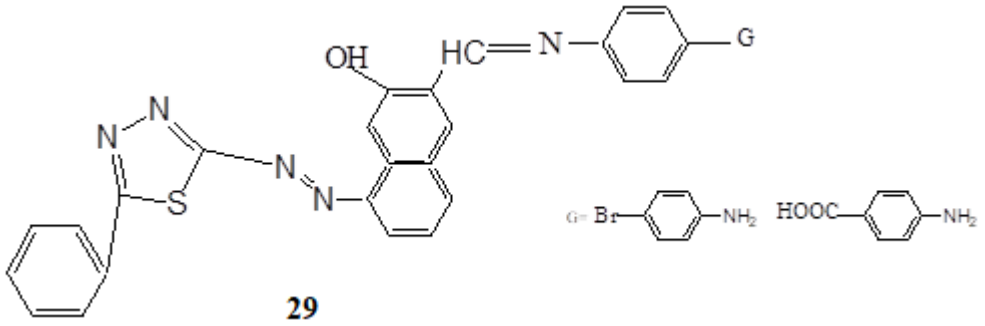
JathiKeshavayya and coworkers reported a series of heterocyclic azo dyes were synthesized by diazotization of 2-Amino-5-(4-nitrophenyl)-1,3,4-thiadiazole by propionic acid and acetic acid in the ratio 2:3, followed by coupling with different coupling components. Synthesized heterocyclic azo dyes were characterized by UV-Vis, IR, $^{1}$HNMR, $^{13}$C-NMR, element analysis and Mass spectral techniques. Electrochemical property of

synthesized thiadiazole substituted azo dyes was studied by cyclic voltammetric technique. Synthesized azo dyes showed two reduction peaks indicating the two step reduction process. Probable mechanism for the reduction of azo dyes was proposed. The synthesized heterocyclic azo dyes were screened for biological activity. The results of these investigations revealed that the newly synthesized compounds are potent antimicrobial agents. Some of the synthesized compounds exhibit significant antimicrobial activity [34].




**28**

SuhierFaaiqHamad and coworkers prepared a series of 1,3,4-thiadiazol derivatives from the benzoic acid reaction with the thiosimicarbazide in the presence of ($POCl_3$) and (KOH) to give compound [I]. The purified product was reacted with o-hydroxynaphthaldehyde to form the azo compounds [II], after that we reacted the compound [II] with different aromatic Amines to give Schiff base compounds [III]. All compounds have been characterized based on FT-IR, and some of them based on $^{1}$H-NMR, $^{13}$C-NMR, MP techniques, and the Biological effectiveness of part of them has been studied [35].




**29**

MahavirChhajed and coworkers synthesizes a series of imines 5-amino-1,3,4-thiadiazol-2-[(N-substituted benzyol)]sulphonamide derivatives were synthesized from

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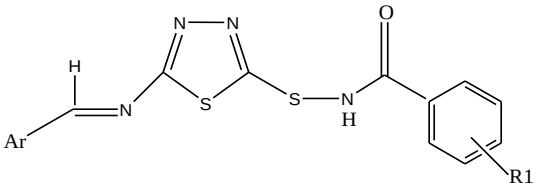
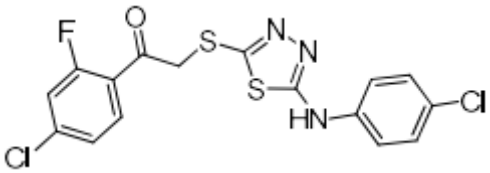
various aromatic aldehydes and substituted with benzoyl acetazolamides under different reaction conditions and were evaluated for their antioxidant and free radical scavenging, antimitotic activity by Allium cepa meristem root model and cytotoxicity activity against HEK 293 (human epidermal kidney cell line), BT474 (breast cancer cell line) and NCI-H226 (lung cancer cell line) by MTT assay [36].




| $R^1$ | Ar |
|---|---|
| H | $C_6H_5$ |
| H | *p*-$ClC_6H_4$ |
| H | *o*-$OCH_3C_6H_4$ |
| H | *p*-$OCH_3$ $C_6H_4$ |
| H | *p*-OH $C_6H_4$ |

30

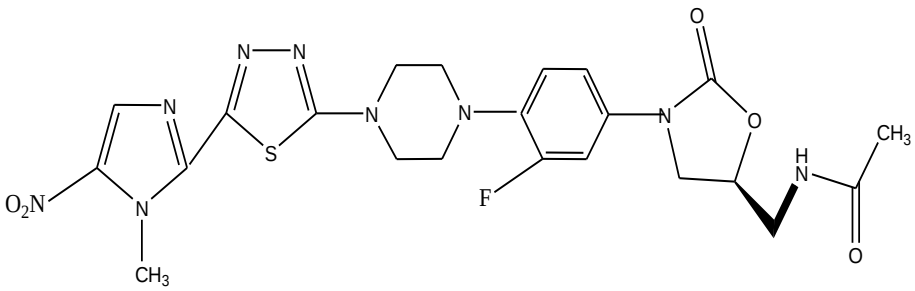
Karaburunet. al., synthesized sequences of novel 1,3,4-thiadiazole derivatives and tested their potential antifungal activities against different fungal strains. Compound 31 showed excellent antifungal activity due to the fluoro and chloro groups at the second position of the phenyl moiety [37].




31

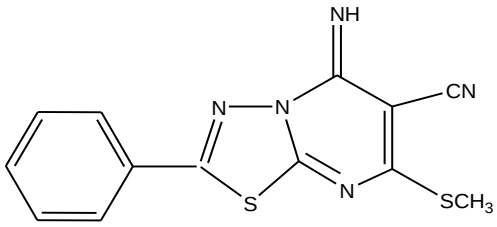
Khalaj and coworkers reported a number of linezolid analogues containing a nitroaryl-1,3,4-thiadiazole moiety, were prepared and evaluated as antibacterial agents against a panel of Gram-positive and Gram-negative bacteria. Among synthesized compounds, nitrofuran analogue exhibited more potent inhibitory activity, with respect to other synthesized compounds and reference drug linezolid. The target compounds were also assessed for their cytotoxic activity against normal mouse fibroblast (NIH/3T3) cells using

MTT assay. The results indicated that compound (32) exhibit potent antibacterial activity against Gram-positive bacteria at non-cytotoxic concentrations[38].



32

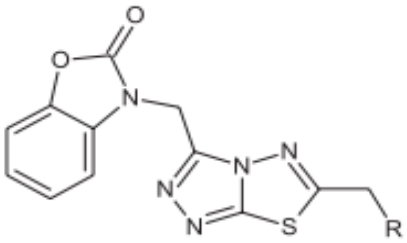
Vijay Bhosale and coworkers synthesized a series of 3-cyano-4-imino-2-methylthio-7-phenyl-4H-pyrimido [2,3-d]-1,3,4-thiadiazole and its 2-substituted derivatives are reported. The newly synthesized compounds were evaluated for their antimicrobial activity (Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Salmonella typhi) and antioxidant activity (2,2-diphenylpicrylhydrazyl and OH model) [39].



33

TijenOnkol and coworkers reported a series of new [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (5a-n, 6a-h) were synthesized under microwave irradiation (MWI). The chemical structures of the compounds were elucidated by their IR, $^{1}$H-NMR, LC-MS, and elemental analysis. The compounds were tested for anti-nociceptive activity by using the tail clip, tail flick, hot plate, and writhing methods in mice. The varying levels of anti-nociceptive activity of the compounds were compared with those of aspirin. Among these compounds, compound 5g and 5j were found to be significantly more active than the other compounds

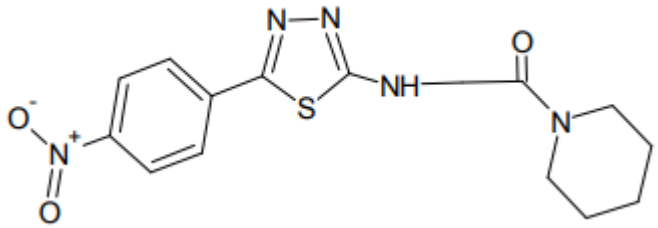
and the standard in the tests. Also, inhibitory effects of the test compounds on COX-1 and COX-2 activities were investigated. DuP-697 for COX-2 and SC-560 for COX-1 were used as reference standards [40].



R (5a-n): H, Cl, F, Br, $OCH_3$, Br, $CH_3$, CN, $C(CH_3)_3$, $SO_2CH_3$, $NO_2$
R (6a-h): H, F, Cl, $CH_3$, $OCH_3$, $CF_3$, $C(CH_3)_3$,$SO_2CH_3$

**34**

Pattan and coworkers have been introduced the synthesis of various compounds and evaluated for anti-diabetic activity. Among of these compound 35(4-$NO_2$) has shown significant anti-diabetic activity and all synthesized compounds in this series have shown moderate anti-diabetic activity [41].



35

Aandanappa and coworkers were showed the series of 2-trifluoromethyl/sulphonamido-5,6-diarylsubtituted imidazo[2,1-b-]-1,3,4-thiadiazole derivatives **36** have been synthesized by the reaction of 2-amino-5-trifluoromethyl/sulphonamido-1,3,4-thiadiazoles and substituted by a-bromo-1,2-(p-substituted)diaryl-1-ethanones and the compound were evaluated by the vitro cyclooxgenage inhibitory activity against COX-2 & COX-1 enzyme [42].

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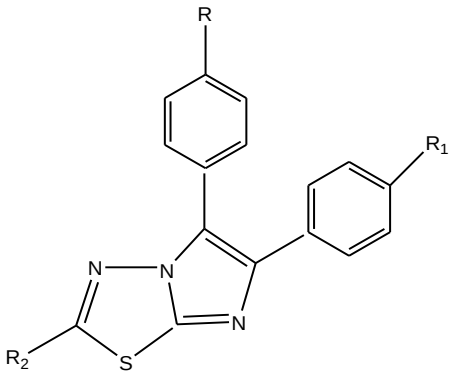
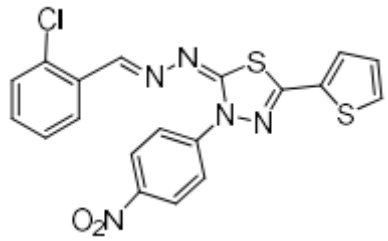


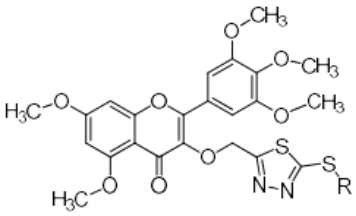

36

M Gomhaet. al. have worked on the preparation of some novel progression of 1,3,4-thiadiazole based compounds. Which to be investigated for their action aligned with human tumor cell lines and human hepatocellular carcinoma cell appearance. The attained compound 37 was reported with the higher potency IC50: 4.37 ± 0.7. When compared with cisplatin IC50 8.03 ± 0.5[43].



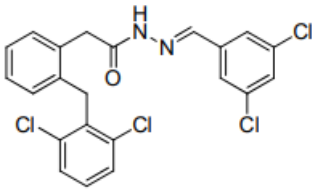

37

Zhonget. al., synthesized a sequence of new myricetin derivatives that have 1,3,4-thiadiazole moiety. The molecules to be tested against antibacterial activities against Xoo and Rs, as well as their antiviral activity against tobacco mosaic virus (TMV) were. Some targeted compounds were showed excellent antibacterial and antiviral activity. Along with, 38a-d shows outstanding curative activity against TMV, by EC50 values of 152.8, 99.7, 127.1, and 167.3 µg/mL, respectively [44].

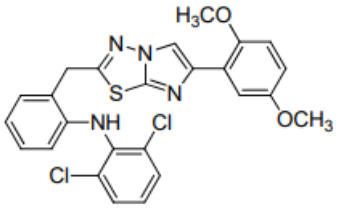


38

Manjula K et. al., have created several new Schiff base and imidazo-(2,1-b)-1,3,4-thiadiazole sequences derived from Diclofenac. The formation of final products will be determined using spectrum data, 1HNMR, and infrared spectral methods. Using the carrageenan-induced rat paw edoema method, all freshly synthesized compounds were tested for anti-inflammatory efficacy. The anti-inflammatory activity of the synthesized molecules indicated that compounds 39 (73.3% and 70.4%) and 46 (71.8% and 70.1%) were the most active when compared to the reference diclofenac [45].



39



40

**Conclusion**

In conclusion, Thiadiazole are significant class f heterocycliccompounds. Among the various isomers ofthiadiazole 1,3,4-thiadiazole is generally examinedcompound in view of its differentpharmacological exercises, for example, anticancer,antitubercular, antimicrobial, antidiabetic,mitigating, anticonvulsant, cancer prevention agentexercises. This audit gives an outline of thewide range of pharmacological exercisesshown by thiadiazole subordinates. Thesignificance of thiadiazole moiety can beamplified via completing further investigations

on itsconceivable replacement and subsequently to blendbetter specialists that can major areas of strength for haveresponsibilities.

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