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*Review Article*

# 4-Thiadiazole: The Biological Activities

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**ABSTRACT**
4-Thiadiazole (1,3,4-thiadiazole) nucleus displayed noteworthy industrial efficiencies and has shown various biological activities, especially as a cancer chemo preventive agent. 4-Thiadiazole has been categorized as a member of family of azole that consist of thiadiazole ring. 4-Thiadiazole is chemical entity which has being synthesized in the past many forms of its derivatives; the entity provides the principal origin of motivating to numerous chemist to investigate its diverse medical efforts especially with regards to the antimicrobial, ant tubercular, anticancer, anti-inflammatory. Current survey supply a wide vision of the antibacterial activity possessed by molecules having a 4-thiadiazole moieties.

**Key words:** 4-thiadiazole, Anti-tubercular, Antimicrobial activity, Medical efforts, Anti-inflammatory.

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## INTRODUCTION

Heterocyclic compounds may found in considerable number of organic molecules that exhibit antimicrobial efficiencies. The antimicrobial efficiencies of these molecules have is fundamentally contingent by structures of these molecules.[1] Thiadiazoles are quite motivating molecules because of the significant utilizations in considerable pharmaceuticals and medicinal domain.[2,3] Thiadiazole [4] have ring of unsaturated structures with moiety formula C2H3N3S having 2 atoms of carbon, Sulphur atom and 3 nitrogen atoms. Thiadiazoles have been utilized for medicinal activity like anti-viral, anti-microbial and anti-tubercular. Thiadiazoles were familiar also to displayed anti-inflammatory, antidepressant and analgesic activities, the latest existence generally investigated through the forced swim investigation.[5,6] Amid the medical profiles of thiadiazoles, their antibacterial and antifungal characteristics appear to be the superior notarized. The ring moiety of thiadiazole was the most significant nuclei, as a well-known whole characteristics of diversity of natural medicinal agents. As essence structural, thiadiazoles are show in configuration of drugs category.[7,8] Thiazoles show a wide range of pharmacological activities and were found in numerous effective pharmacologically active compounds such as anti-neoplastic drugs.[9] However, thiadiazoles especially recognized for their anti-cancer [10,11] activities. In continuation of previous studies on coumarins as heterocyclic compounds,[12-34] herein we are reporting a review for such recent derivatives of heterocyclic compound namely 4-thiadiazole with pharmacological activities.

## CHEMISTRY

Thiadiazoles were compounds with heterocyclic ring having nitrogen and sulfur atoms as part of the aromatic ring. Thiadiazoles with 2 nitrogens and 1 sulfur atoms were named 4-thiadiazole. Thiadiazoles exist in nature in 4 forms as 1,2,3-thiadiazole;1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole (a, b, c and d) respectively. 1, 3, 4-thiadiazole were significant becdue to the biological actions.

(a) (b) (c) (d)

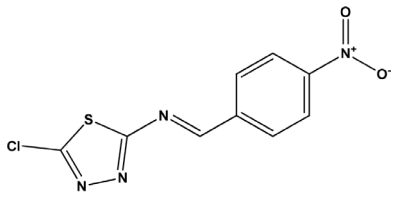
## BIOLOGICAL APPLICATIONS

Thiadiazoles were known to displayed various of pharmacological activity. Thiadiazoles were utilized as antibacterial, antifungal and anti-cancer activities in addition to and anti-inflammatory activities.

### Anti-Microbial Activity

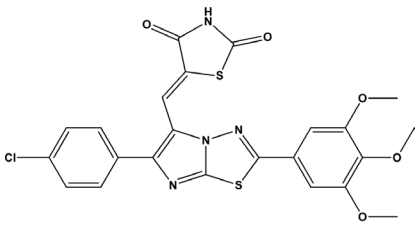
Nowadays research reviews have been shown that thiadiazoles have wide spectrum of biological activities exclusively effective anti-bacterial and anti-fungal activities that were displayed below in this review:

**Mousa** synthesis of thiadiazoles. The preparation compounds were evaluated for the antibacterial activities. The synthesized molecules have been studied for their antibacterial activity against the *S. 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 [1] showed the best antimicrobial activity against the tested bacteria.[35]



[1]

**Alagawadi K. R**. *et al*., have prepared series of novel thiazolidinones [2,3]. These molecules have been examined *the* anti-bacterial activities versus the Gram-positive *and* Gram-negative *bacteria named Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa bacteria in addition to fungi named* and *Candida albicans*, *Aspergillus flavus*, *Aspergillus niger*. They were found that some of the synthesized compounds *named p*-chlorophenyl and 6-*p*-bromophenyl displayed highest antimicrobial activities.[36]



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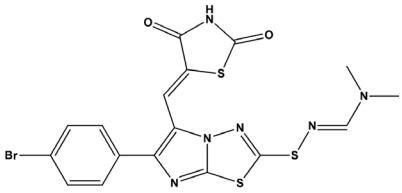
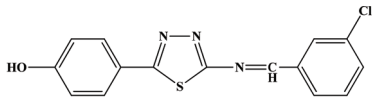
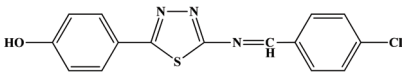


[3]

**Baghel U. S. *et al*** 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 [4] and 4-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol [5] shows potent activities comparing with the examined microbes.[37]

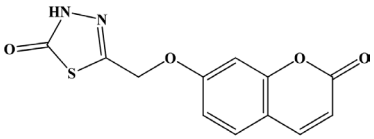


[4]



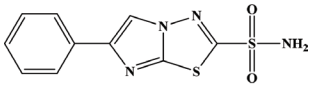
[5]

Al-Amiery *et al* had been synthesized new thiadiazoles that have coumarin moieties [6] and tested for their antimicrobial activity. *In vitro* anti-bacterial and anti-fungal investigations various microbes named (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa* with *Aspergillus niger* and *Candida albicans*).[38]



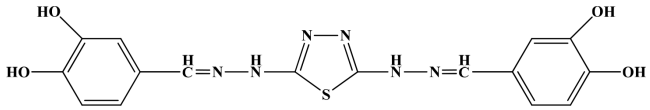
[6]

**Fawzia *et al*** synthesized 6-phenylimidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide [7] displayed the antimicrobial activities vs the *Escherichia coli* and *staphylococcus aureus* in addition to moderate activities vs *salmonella typhi*, *pseudomonas aeguginosa* and *pneumococci*.[39]



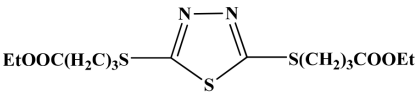
[7]

**Al-Mosowy was** synthesized compound named 4,4'-(2,2'-(4-thiadiazole-2,5-diyl)bi(hydrazin-2-yl-1-ylidene))bi(methan-1-yl-1-ylidene) di-benzene-1,2-diol [8] and investigated for the *in vitro* anti-microbial activities vs the Gram negative bacteria named *Escherichia coli* and Gram positive bacteria named *Staphylococcus aureus*. The synthesized compound showed highest efficiencies vs selected bacteria *Staphylococcus aureus and Escherichia coli.*[40]



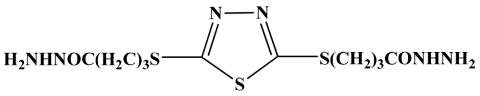
[8]

**Nadjet R. *et al*.**, synthesized diethyl4,4′- [(1,3,4-thiadiazol- 2,5 diyl)bis (sulfa nediyl)]dibutanoate [9] and 4,4'- (1,3,4- thiadiazole-2, 5-diyl)bis (sulfa nediyl)dibutanehydrazide [10]. Compounds [9] and [10] showed a high degree of antibacterial activities vs bacterial species Gram-positive and Gram-negative in addition to fungi.[41]



diethyl 4,4'-((1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl))dibutanoate

[9]

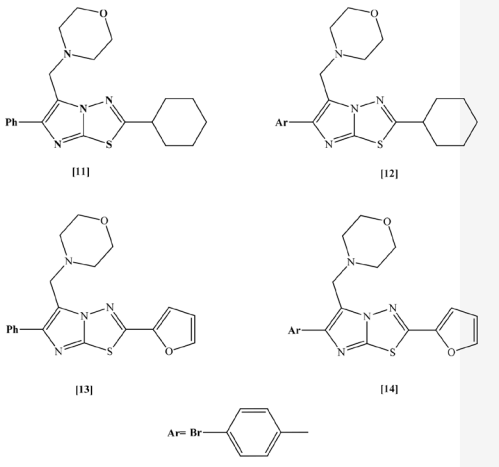


[10]

## Anti-Tubercular Activity

Nowadays there were potent studies on thiadiazoles, some of them that were known to possess considerable medicinal characteristics such as anti-bacterial, anti-fungal, anti-tubercular, anti-inflammatory, anti-convulsing and anti-hypertension activities.

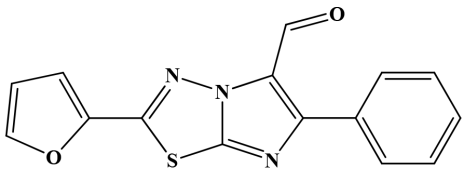
**Onkol T *et al*** synthesized of 4-((2-cyclohexyl-6-phenylimidazo[2,1-b][1,3,4] thiadiazol-5-yl)methyl)morpholine [11], 4-((6-(4-bromophenyl)-2-cyclohexylimidazo [2,1-b][1,3,4] thiadiazol-5yl) methyl)morpholine [12], 4-((2-(furan-2yl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl) methyl)morpholine [13] and 4-((6-(4-bromophenyl)-2-(furan-2-yl) imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methyl)morpholine [14]. The synthesis compounds show excellent activities vs Mycobacterium *tuberculosis.*[42]



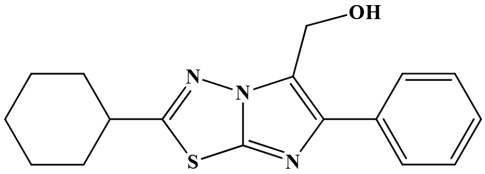
[11] [12] [13] [14]

**Kolavi G. *et al*.**, were prepared substituted thiadiazoles that have imidazole moiety and were investigated for their anti-tubercular activities vs *Mycobacterium tuberculosis* H37Rv utilizing the BACTEC 460 radiometric system. Two of the investigated compounds [15 and 16] were exhibit the

highest inhibition efficiencies.[43]



[15]

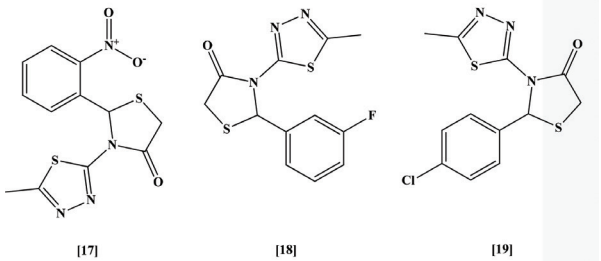


[16]

## Anti-Cancer Activity

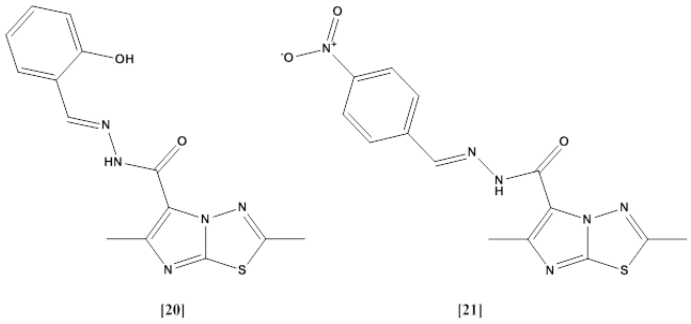
4-Thiadiazole that have Amino group were have inhibition activities against many trans-planted tumors.

**Joseph A. *et al*** were prepares new thiadiazoles having thiazolidin-4-ones moieties and *in vitro* anti-proliferative activity were examined on human breast adenocarcinoma cells (MCF-7) by MTT assay. Among the investigated compounds, 3-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(2-nitrophenyl)-4-oxothiazolidin [17], 2-(3-fluorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-4-oxothiazolidin [18], and 2-(4-chlorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-4-oxothiazolidin [19] were have the highest potent with $IC_{50}$ values of (46.34, 66.84 and 60.71) µmol/L respectively.[44]



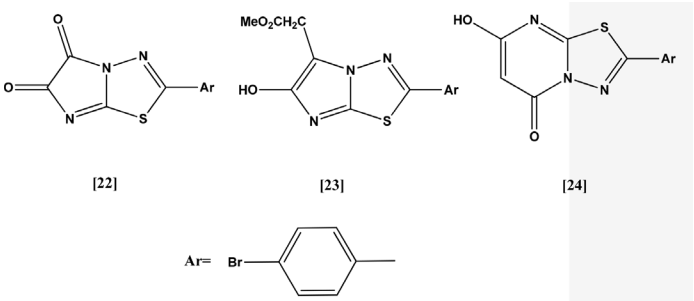
[17] [18] [19]

**Terzioglu N. *et al.*** were prepared new 4-thiadiazole substituted with carbohydrazides. (E)-N'-(2-hydroxybenzylidene)-2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide [20] and (E)-2,6-dimethyl-N'-(4-nitrobenzylidene)imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide [21] were passed the criteria for activities in the assay (20-29% growth percentages) and were automatically scheduled for investigation vs the full panel of 60 human tumor cell lines at minimum concentrations at 10-fold dilutions.[45]



[20] [21]

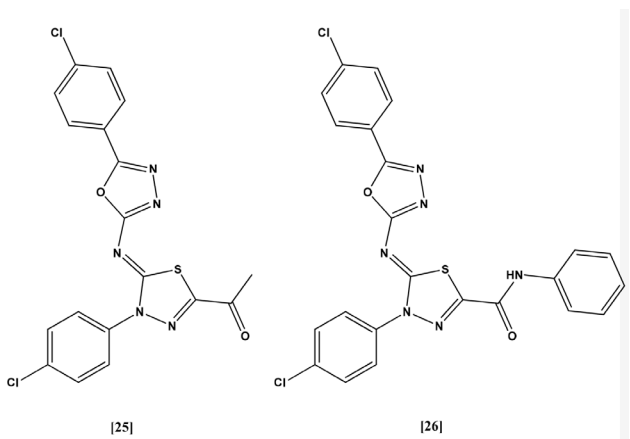
**Doaa E. Abdel Rahman and Khaled O. Mohamed** synthesized substituted imidazo-4-thiadiazoles. All the synthesized compounds have been investigated for their cytotoxic activities vs tumor cell line A549 (Non-Small Cell Lung Cancer Cell Line) utilizing Sulfo-Rodamine B (SRB) technique. The investigated molecules showed potent cytotoxicity especially compounds 2-(4-bromophenyl)imidazo[2,1-b][1,3,4]-5,6-dioxothiadiazole [22], Methyl 2-[2-(4-bromophenyl)-6-hydroxyimidazo[2,1-*b*]-1,3,4-thiadiazol-5-yl]acetate [23], 2-(4-bromophenyl)-5-hydroxy-7*H*-1,3,4 thiadiazolo[3,2-*a*]-7-oxopyrimidin [24] ($IC_{50}$ 2.58-6.47 µM).[46]



[22] [23] [24]

Ar= Br

**Dawood and Gomha,** 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 [25] 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 [26]. The novel synthesized molecules have promising cancer potent against colon.[47]



[25] [26]

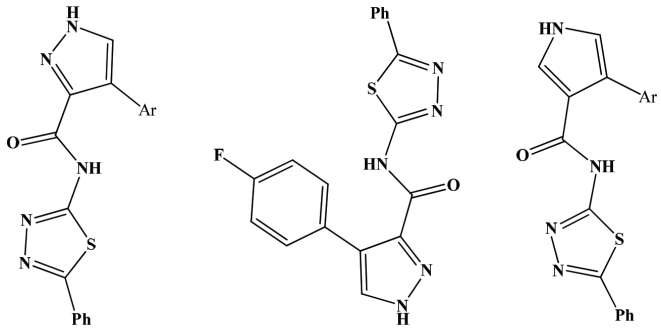
## Anti-Inflammatory Activity

**Maddila S. *et al.***, synthesized of 4-(4-Nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-

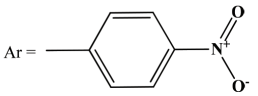
1H-pyrazole-3-carboxamide [27], 4-(4-Fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-

1H-pyrazole-3-carboxamide [28] and 4-(4-Nitrophenyl)-N-(5-phenyl-

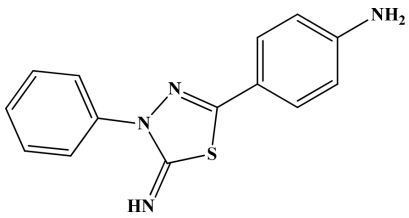
1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide [29]. The new compounds have been tested for their anti-inflammatory activities. Compounds were displayed important anti-inflammatory activities with high percentage inhibition in paw edema, compared with indomethacin as standard drug.[48]




[27] [28] [29]




**Asif M. and Asthana C.** were synthesized thiadiazoles with imino moiety. The synthesized compound named 4-(5-imino-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)aniline [30] have been examined for in vivo anti-inflammatory activities by using of carrageenan induced paw oedema technique and compared with Diclofenac as standard drug.[49]




[30]

## CONCLUSION

Generally, thiadiazoles are extreme effective heterocyclic that have electron-deficient carbon atoms, with nitrogen and sulfur atoms in addition to an electron pair. these compounds have electron deficient nature and high stability, and due to these characteristics, they could react hardly. On the basis of new scientific research concerning a various medicinal activity of new thiadiazoles that have been provided in this review, it could be concluded that thiadiazoles have a considerable property for the lethal microbial infections therapy. Thus, the presented survey could give a another hope and considerable various technique to the chemists to try drug design and evolution of better and safer antimicrobial compounds for future.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATION USED

**IC50:** half maximal inhibitory concentration; **µ:** micro; **MTT assay:** 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide; **MCF-7:** Michigan Cancer Foundation-7.

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