1.2. LITERATURE REVIEW

1.2.1. 1,3,4-OXADIAZOLE

1.2.1.1. INTRODUCTION

Oxadiazole is a five-membered heterocyclic, aromatic chemical compound having two carbons, two nitrogens, and one oxygen atom with two double bonds having general formula C₂H₂ON₂. There are four isomers of oxadiazole- 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer.

Oxadiazole ring is generally resistant to nucleophilic attack (Somani, et al., 2009).
1.2.1.2. SYNTHESIS OF 1,3,4-OXADIAZOLES

Recent reportings about synthesis of 1,3,4-oxadiazole ring via various routes are follows:
A direct access to symmetrical and unsymmetrical 2,5-disubstituted [1,3,4]-oxadiazoles has been accomplished through an imine C-H functionalization of N-arylidenearoylhydrazide using a catalytic quantity of Cu(OTf)$_2$. These reactions can be performed in air atmosphere and moisture making it exceptionally practical for application in organic synthesis (Guin, et al., 2011).

\[
\text{Ar}^2\text{H}_2\text{O} \xrightarrow{\text{Cu(OTf)}_2, \text{Cs}_2\text{CO}_3} \text{DMF, O}_2 \text{ (air), 110 °C, 12-24 h} \quad \text{Ar}^2\text{NHN}^+\text{Ar'}\quad \text{N-Isocyaniminotriphenylphosphorane, aldehydes, and benzoic acids undergo a one-pot, three-component reaction under mild conditions to afford 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles in good yields (Adib, et al., 2009).}
\]

\[
\text{ArOH} + \text{Ph}_3\text{P=N-NC} + R\text{CO} \xrightarrow{\text{CH}_2\text{Cl}_2 \text{ r.t. 24 h}} \text{ArHNN=O} \quad \text{R= alkyl, Ar}
\]

A facile and general protocol for the preparation of 2-amino-1,3,4-oxadiazoles relies on a tosyl chloride/pyridine-mediated cyclization of thiosemicarbazides that consistently outperforms the analogous semicarbazide cyclizations. Various 5-alkyl and 5-aryl-2-amino-1,3,4-oxadiazoles have been prepared in good yields (Dolman, et al., 2006).

\[
R\text{CONH}_2 \xrightarrow{\text{TsCl; Pyridine \text{THF, 65-70 °C, 20h}}} R\text{OHNH}_2\text{R}_1
\]

Reaction of acid hydrazide with aryl acid in the presence of POCl$_3$ as dehydrating agent gives 2,5-disubstituted- 1,3,4-oxadiazole in good yields (Oliveira, et al., 2012a; Amir, et al., 2007).
1.2.1.3. BIOLOGICAL ACTIVITIES OF 1,3,4-OXADIAZOLEs

1.2.1.3.1. Antimicrobial Activity

The recent emergence of drug resistance when treating infectious diseases has underlined the need for new, safer, and more efficient antimicrobial agents. Many researchers have reported excellent antimicrobial activity for compounds containing the 1,3,4-oxadiazole core.

Recently, Oliveira, et al., 2012b; reported synthesis and antistaphylococcal activity of 1,3,4-oxadiazolines against strains of *S. aureus*, resistant to methicillin and amino glycosides, and that encode efflux proteins (multidrug drugs resistant). Compound 1 showed efficient antistaphylococcal activity, being more potent than the standard drug chloramphenicol.

![Image of compound 1]

\[
\begin{align*}
R = \text{H, Me, NO}_2, \text{Cl, OMe} \\
\end{align*}
\]

Bakal, et al., 2012; investigated anti-tubercular activity for a series of 2,5-disubstituted oxadiazoles against *M. tuberculosis* H337Rv. Compound 2 was found with a MIC\(_{50}\) = 0.04 ± 0.01 µM was with isoniazid.

![Image of compound 2]

Patel, et al., 2010; verified the antibacterial activity of a series of derivatives containing the 1,3,4-oxadiazole nucleus against Gram +ve (*S. aureus* and *S. pyogenes*) and Gram -ve bacteria (*E. coli* and *P. aeruginosa*) using ampicillin as the drug standard. The compounds 4-[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzenamine (3), and 3-{[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-{2-[2,6-dichlorophenyl]amino}benzyl]-6-idoquinazolin-4(3H)-one (4) were respectively 2 and 5 times more potent than ampicillin.
Kumar, S., 2010; investigated the antibacterial and antifungal activity of 2-(5-amino-1,3,4-oxadiazol-2-yl)-4-bromophenol (5), and 5-(3,5-dibromophenyl)-1,3,4-oxadiazol-2-amine (6) against two strains of Gram +ve bacteria; *Streptococcus aureus*, *B. subtilis*, two strains of Gram -ve bacterial; *Klebsiella pneumoniae* and *E. coli*, and two fungal species; *A. Niger* and *C. Pannical*. The tests showed activities approximately equal to the standard drugs streptomycin and griseofulvin.

Chandrakantha, *et al.*, 2010; reported that 2-(3-bromo-2-methylphenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (7) and 2-(2-fluoro-4-methoxyphenyl)-5-(2,3,4-trifluorophenyl)-1,3,4-oxadiazole (8) are 2 and 4 fold more potent than furacin when evaluated against *E. coli*, and *P. aeruginosa*. Compounds 2-(2-bromo-5-chlorophenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (9) and 2-(2-fluoro-4-methoxyphenyl)-5-(5-methyl-3-furyl)-1,3,4-oxadiazole (10) were twice as potent as fluconazole against *C. albicans*. 
1.2.1.3.2 Anti-inflammatory Activity

Jayashankar, et al., 2009; synthesized 1,3,4-oxadiazole derivatives and screened them for their anti-inflammatory and analgesic activities. Compound, 2-(((4,5-dihydro-3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl)methoxy)methyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole (11) showed anti-inflammatory (53.1%) and analgesic activity (52.3%) compared with reference drugs ibuprofen (for anti-inflammatory activity, 70.7%) and aspirin (for analgesic activity, 57.3%) at the similar dosages.

![Chemical Structure of Compound 11](image)

Kadi, et al., 2007; synthesized 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazole compounds 12, which displayed strong dose dependent inhibition of carrageenan-induced paw edema with >50% inhibition at dose of 60 mg/kg. The compound with the 3,4-di-OMe substitution was more potent than the standard drug indomethacin.

![Chemical Structure of Compound 12](image)

Burbuliene, et al., 2004; investigated anti-inflammatory activity of 5-[(2-disubstituted diamino-6-methyl-pyrimidin-4-yl)-sulphanyl]methyl]-3H-1,3,4-oxadiazol-2-thione derivatives (13) and found that some were more potent than ibuprofen.

![Chemical Structure of Compound 13](image)
Palaska, et al., 2002; synthesized 2-(2-naphthoxymethyl)-5-substituted-amino-1,3,4-oxadiazoles and evaluated them for anti-inflammatory and ulcerogenic activities. In carrageenan-induced foot paw edema assay, 2-(2-naphthoxymethyl)-5-methylamino-1,3,4-oxadiazole (14) showed an interesting anti-inflammatory activity. In the air-pouch test, these derivatives reduced total number of leukocytes of the exudate that indicates excellent inhibition of prostaglandin production. Side effects of the compounds were examined on gastric mucosa, liver and stomach and none of the compound showed significant side effects when compared with reference nonsteroidal anti-inflammatory drugs.

1.2.1.3.3. Analgesic Activity

Gilani, et al., 2010; reported that the compound (15) containing 2,4-dichlorophenyl group, present at the second position of the oxadiazole ring, showed a maximal analgesic activity (70.37 ± 1.67%), almost equivalent to that of the ibuprofen standard (73.52 ± 1.00%).

Husain, et al., 2009; synthesized 1,3,4-oxadiazole derivatives of fenbufen. Author found that compound 16 substituted with p-fluoro-phenyl ring showed maximal analgesic activity (72.52%) better than diclofenac sodium (70.32%) and fenbufen (54.1%).
Amir, et al., 2007; synthesized a series of 1,3,4-oxadiazole derivatives and among them 5-\((2-(2,6\text{-dichlorophenylamino})\text{benzyl})-N-(4\text{-fluorophenyl})-2\text{-amino}1,3,4\text{-oxadiazole} \) (17) was found to be most potent during evaluation of analgesic activity. It showed 86% activity compared with 81% of diclofenac sodium.

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{F}
\end{align*}
\]

**1.2.1.3.4. Antitumor Activity**

Liu, et al., 2012; synthesized and reported the anti-proliferative properties of a series of 2-\((\text{benzylthio})\)-5-aryl-oxadiazole derivatives. Compound 18 showed potent biological activity \((\text{IC}_{50} = 1.09 \, \mu \text{M})\).

\[
\begin{align*}
\text{N} & \quad \text{S} \\
\text{NH} & \quad \text{2} \\
\text{NH}_2 & \quad \text{S}
\end{align*}
\]

Savariz, et al., 2010; synthesized and evaluated the \textit{in vitro} antitumor activity of new oxadiazole derivatives. Among the compounds studied, compound 19 showed potent activity against melanoma (UACC-62), and lung (NCI-460) cell lines with \(\text{GI}_{50}\) values of 0.88 and 1.01 mmol/L, respectively.

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{NH} & \quad \text{CH}_3 \\
\text{NH} & \quad \text{CH}_3 \\
\text{N} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{NH}_2
\end{align*}
\]
1.2.1.3.5. Anticonvulsant Activity

Zarghi, et al., 2005; designed and synthesized some new 2-substituted-5-[2-(4-substituted-benzyl)-thiophenyl]-1,3,4-oxadiazoles as anticonvulsant agents. The authors found that introduction of an amino group at position 2 of the 1,3,4-oxadiazole ring, and a fluorine substitute at the $p$-position of the benzylthio group, compound (20) improves anticonvulsant activity.

\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{S} \]
\[ \text{O} \]
\[ \text{N} \]
\[ \text{NH} \]
\[ \text{F} \]

1.2.1.3.6. Antiviral Activity

Johns, et al., 2009; reported antiviral activity (through inhibition of viral DNA integration) for new derivatives containing the 1,3,4-oxadiazole unit in combination with a ring system of 8-hydroxy-1,6-naphthyridine (21).

\[ \text{OH} \]
\[ \text{N} \]
\[ \text{R} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{F} \]

Iqbal, et al., 2006; reported the synthesis of various 1,3,4-oxadiazole derivatives and evaluated them for inhibitory activity against the human immunodeficiency virus type 1 (HIV-1). Compound 22 showed the maximum activity (62%) among the compounds tested.

\[ \text{Cl} \]
\[ \text{O} \]
\[ \text{N} \]
\[ \text{SH} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{CH}_3 \]
El-Emam, et al., 2004; synthesized different 1,3,4-oxadiazole derivatives and tested them against the human immunodeficiency virus type 1. Compound 23 was found to be most active among the compounds tested, producing 100%, reduction in viral replication at concentrations of 50 µg/mL.

1.2.1.3.7. Antihypertensive Activity

Bankar, et al., 2009; reported the vasorelaxant effect of compound 24, 4-(3-acetyl-5-(pyridin-3-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl acetate, in rat aortic rings by blocking L-type calcium channels. Compound showed good antihypertensive activity.

1.2.1.3.8. Enzyme Inhibitors

Tomi, et al., 2011; reported a study with a bis-1,3,4-oxadiazole compound 25 containing a glycine unit on the transferase activity of enzymes such as: GOT, GPT and γ-GT in serum. This compound showed activation for GOT and GPT and inhibitory effects on the activity of γ-GT.

Maccioni, et al., 2011; synthesized a set of 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles (compound 26) and tested them as inhibitors of human monoamine oxidase (MAO) A and B
isoforms. None of the tested compounds displayed significant inhibitory ability for MAO-A. However, several derivatives were identified as selective MAO-B inhibitors. Some of the tested compounds exhibited interesting biological properties with an \( IC_{50} \) for the B isoform ranging from micromolar to nanomolar values. The compounds were active as MAO-B inhibitor at nanomolar concentrations.

Leung, et al., 2005; reported the discovery of oleic acid derivatives as a new class of disubstituted oxadiazoles (27) with potent and selective inhibition of fatty acid amide hydrolase.

Khan, et al., 2005; performed studies on inhibition effects on tyrosinase with various 2,5-disubstituted-1,3,4-oxadiazole compounds. The compound 3-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl) pyridine (28) with an \( IC_{50} \) of 2.18 µM was more potent than the standard L-mimosine (\( IC_{50} = 3.68 \) µM).

1.2.1.3.9. Anti-hyperlipidemic Activity

Idrees, et al., 2009; prepared 1,3,4-oxadiazole derivatives of 2-(naphthalen-2-yloxy)propionic acid and evaluated them for hypolipidemic activity in the high cholesterol diet fed hyperlipidemic rat model. Interestingly, 5-[1-(naphthalen-2-yloxy)ethyl]-3H-1,3,4-oxadiazole-2-thione (29) produced striking reduction of serum levels of total cholesterol,
triglycerides, low-density lipoproteins and elevation of serum high-density lipoproteins better than the reference drug gemfibrozil.

\[ \text{Formula 29} \]

### 1.2.1.3.10. Incorporation of Oxadiazole Moiety in Drugs

Manjunatha, *et al.*, 2010; synthesized a series of oxadiazole derivatives (30) of ibuprofen which contains the arylpiperazine unit at position 3 of the oxadiazole ring. Synthesized compounds were investigated for their anti-inflammatory activity using rat paw edema method using diclofenac sodium as the reference. Compounds containing 4-Cl, 4-NO\(_2\), 4-F and 3-Cl substituents were found to be more active than diclofenac sodium.

Husain, *et al.*, 2009; synthesized a series of 3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-y1)propan-1-ones derived from 4-oxo-4-(biphenyl-4-y1)butanoic acid (fenbufen) and tested for their antiinflammatory, analgesic, ulcerogenic and lipid peroxidation actions. A few compounds were found to have very good anti-inflammatory activity in carrageenan induced rat paw edema test, while a fair number of compounds showed significant analgesic activity in acetic acid induced writhing test. The newly synthesized compounds showed very low ulcerogenic action with reduced malondialdehyde content, which is one of the byproducts of lipid peroxidation. Among synthesized compounds, 3-[5-(3,4-dimethoxy phenyl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-y1)propan-1-one, (31a) and 3-[5-(4-
methoxyophenyl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-one (31b) showed most potent anti-inflammatory and analgesic activity with reduced ulcerogenic action.

Bhandari, et al., 2008; synthesized a series of S-substituted phenacyl 1,3,4-oxadiazoles derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid). They replaced the carboxylic group of diclofenac acid with less acidic heterocycle, 1,3,4-oxadiazole, in order to accentuate potency and reduce GI toxicities associated with the parent diclofenac due to its free –COOH group. The free –COOH group is thought to be responsible for the GI toxicity associated with all traditional NSAIDs. These compounds were tested in vivo for their anti-inflammatory activity. The compounds, which showed significant activity (comparable to the standard drug diclofenac sodium), were screened for their analgesic activity and to check their ability to induce ulcers by ulcerogenic studies. Among all the compounds, 5-[2-(2,6-dichloroanilino) benzyl]-S-(3-methoxy-phenacyl)-1,3,4-oxadiazole-2-thiol, (32) showed increased anti-inflammatory activity and reduced ulcerogenic action in comparison of the reference drug diclofenac.

Ali, et al., (2007); synthesized a series of oxadiazole manich bases of dapsone. The synthesized compounds were evaluated for antimycobacterial activity against M. tuberculosis H37Rv and INH resistant M. tuberculosis. Among the synthesized compounds, 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl] methylamino} phenylsulfonyl) anilino] methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-
1,3,4-oxadiazole-2-thione (33) was found to be the most promising compound active against *M. tuberculosis* H37Rv and isoniazid (INH) resistant *M. tuberculosis*. Isoniazid (INH) was used as reference drug.

Indinavir, a protease inhibitor is used as a component of antiretroviral therapy for treating HIV infection and AIDS. Kim, *et al.*, 2004; have synthesized and evaluated the protease inhibitory activity of a series of oxadiazoles (34) of indinavir. All the synthesized compounds inhibited protease activity at picomolar (IC$_{50}$) concentrations (thus being more potent than the indinavir).
1.2.2. 1,2,4-TRIAZOLE

1.2.2.1. INTRODUCTION

Now a days research is concentrated towards the introduction of new and safe therapeutic agents of clinical importance. The heterocycles are enjoying their importance as being the center of activity. As already said the nitrogen containing heterocycles are found in abundance in medicinal compounds. The success of imidazole as an important moiety of number of medicinal agents led to introduction of the triazoles. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazoles are 5-membered ring compounds containing two carbon and three nitrogen atoms. According to the position of nitrogen atoms the triazoles exist in two isomeric forms.

Two structural isomeric triazoles are known, the 1,2,3- or 1,2,5- and the 1,2,4- or 1,3,4-, the former being known as \textit{osotriazole}, and the latter as \textit{triazole}. Each exists in two dissimilar tautomeric forms. The different isomers are characterized by the position of the nascent hydrogen. Thus 1,2,4-triazoles exist in two forms i.e. 1\textit{H} and 4\textit{H}.

1.2.2.2. SYNTHESIS OF 1,2,4-TRIAZOLE

A mild, one-pot cyanoimidation of aldehydes using cyanamide as a nitrogen source and NBS (N-bromo succinimide) as an oxidant was done without the addition of a catalyst. Subsequently, the obtained substituted \textit{N}-cyanobenimidate undergoes a cyclization reaction to give 1,2,4-triazole derivatives in high yields (Yin, \textit{et al.}, 2009).
An effective 1,3-dipolar cycloaddition reaction of oximes with hydrazonoyl hydrochlorides using triethylamine as a base gave the desired 1,3,5-trisubstituted 1,2,4-triazoles in good yields. The reaction was applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates (Wang, et al., 2011).

\[
\text{R}_2\text{NH} \cdot \text{HCl} + \text{NHAr} \cdot \text{HCl} \xrightarrow{\text{Et}_3\text{N}} \text{H}_2\text{C} = \text{N} \left(\text{COOMe}\right) \text{N} \cdot \text{HCl}
\]

3-N,N-Dialkylamino-1,2,4-triazoles can be prepared from S-methylisothioureas and acyl hydrazides in good yields. The reaction conditions are relatively mild and tolerate a broad range of functional groups (Batchelor, et al., 2008).

\[
\text{S} \text{CH}_3 \xrightarrow{\text{TFA}} \text{R}_1\text{N} = \text{N} \xrightarrow{\text{TFA}} \text{R}_2\text{H}_2\text{N} \cdot \text{NH} \cdot \text{R}_3 \xrightarrow{\text{THF; Reflux}} \text{N} \left(\text{R}_1\right) \left(\text{R}_2\right) \left(\text{R}_3\right) \text{N} \left(\text{R}_1\right) \left(\text{R}_2\right) \left(\text{R}_3\right)
\]

A copper-catalyzed reaction under an atmosphere of air provides 1,2,4-triazole derivatives by sequential N-C and N-N bond-forming oxidative coupling reactions. Starting materials and the copper catalyst are readily available and inexpensive. A wide range of functional groups are tolerated (Ueda, et al., 2009).

\[
\text{R}_2\text{NH} \cdot \text{HCl} + \text{CuBr; Cs}_2\text{CO}_3 \xrightarrow{\text{Air; DMSO; 120^\circ C, Reflux, 24 h}} \text{N} \left(\text{R}_1\right) \left(\text{R}_2\right) \left(\text{R}_3\right) \text{N} \left(\text{R}_1\right) \left(\text{R}_2\right) \left(\text{R}_3\right)
\]

1,2,4-Triazole can be prepared from acid hydrazide in presence of carbon disulphide in good yields (Zhang, et al., 2002).
1.2.2.3. BIOLOGICAL ACTIVITIES OF 1,2,4-TRIAZOLES

1.2.2.3.1. Antimicrobial Activity

Bayrak, et al., 2009; synthesized some new 1,2,4-triazole derivatives and evaluated them for their antimicrobial activity against *E. coli*, *Yersinia pseudotuberculosis*, *Pseudomonas aeruginosa*, *E. faecalis*, *S. aureus*, *Bacillus cereus*, *Candida tropicalis* and *C. albicans* using agar-well diffusion method. Compound (35) 2-[(4-phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio]-N’-[pyridin-2-ylmethylene]-aceto- hydrazide was found to be most potent against all the bacterial organisms while compound (36) ethyl-[(4-phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio]acetate was found to be most potent against all the fungal organisms.

![Structural formula of 35 and 36](image)

Demirbas, et al., 2009; synthesized some new 1,2,4-triazole derivatives and investigated for their antimicrobial activities. The study revealed that some compounds showed good activity against a variety of bacterial strains. Compound 37, 2-[[4-amino-3-(4-methylphenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]acetyl]-N-(4-fluorophenyl) hydrazine carbothioamide showed maximum activity among all the tested compounds against bacterial strains.

![Structural formula of 37](image)

Sun, et al., 2007; designed and synthesized a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl]-propan-2-ols. Results of preliminary *in vitro* antifungal tests against eight human pathogenic fungi (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *Cryptococcus neoformans*, *A. fumigatus*, *T. rubrum*, *F. compacta*, and *M. gypseum*) showed that all the title compounds exhibited activity. All the tested
compounds showed higher activity against *C. albicans* than fluconazole while compound 38 showed highest activity among all the tested compounds against all the fungal strains.

![Chemical structure of compound 38](image)

Karnik, *et al.*, 2006; reported syntheses of novel heterocyclic derivatives of 18-nor-equilenin and synthesized compounds were screened for antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*. Among all the tested compounds, 11-bromo-6H-5-oxa-7-thia-8,9,10a-triaza-pentaleno[4,5-a]phenanthrene (39) was found to be most potent against all the organisms except *P. aeruginosa* where the MIC was found out to be 100 µg ml⁻¹.

![Chemical structure of compound 39](image)

Garoufalias, *et al.*, 2002; described the synthesis of a series of substituted triazoles. The new compounds were tested for antimicrobial and antifungal activity. Compound 40, [4-(2,4-dichlorophenyl)-5-(tricyclo[3.3.1.1³⁷]-decan-1-yl)-4H-1,2,4-triazol-3-yl]mercaptoacetic acid cyclobutylidene hydrazide showed moderate activity against *C. albicans*.

![Chemical structure of compound 40](image)

Gunay, *et al.*, 1999; synthesized some novel substituted triazoles derivatives and evaluated for *in vitro* antibacterial and antifungal activity. Compound 41, 1-[3-[[5-(2-furanyl)-4-[(1E)-3,3-dimethylbut-1-enyl]-4H-1,2,4-triazol-3-yl]thio]-2-hydroxypropyl]-2-methyl-5-nitro-1H-imidazole was found to be effective against *S. aureus*. 
1.2.2.3.2. Anti-inflammatory and Analgesic Activity

Kumar, et al., 2008; synthesized a series of 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid in order to obtain new compounds with potential anti-inflammatory, analgesic activity and lower ulcerogenic effect. All the compounds were evaluated for their anti-inflammatory activity by the carrageenan induced rat paw edema test method. Out of all the tested compounds 5-[(biphenyl-4-yloxy)methyl]-4-N-butyl-3-mercapto-(4H)-1,2,4-triazole (42) showed better anti-inflammatory activity (81.81%) than the reference drug flurbiprofen (79.54%), low ulcerogenic action and protective effect on lipid peroxidation.

Amir, et al., 2004; synthesized azole derivatives of 2-[(2,6-dichloroanilino) phenyl] acetic acid. These compounds were tested in vivo for their anti-inflammatory activity. Among all the tested compounds, 5-2-[(2,6-dichlorophenyl)amino]benzyl]-4-(4-methylphenyl)-4H-1,2,4-triazole-3-thiol (43) showed better anti-inflammatory activity (82.69%) than the reference drug diclofenac (80.76%).
Palaska, et al., 2002; prepared 1,2,4-triazole-3-thione derivatives and evaluated them for anti-inflammatory activity. Among all the tested compounds, 5-(2-naphthoxy)methyl-1,2,4-triazole-3-thione (44) showed significant anti-inflammatory activity with reduced side effects, when compared with reference drug naproxen.

1.2.2.3.3. Antitubercular (antimycobacterial) Activity

Kini, et al., 2009; synthesized a novel series of triazole derivatives and determined their activity against H37Rv strain of Mycobacterium. All the compounds inhibited the growth of the H37Rv strain of Mycobacterium at concentration as low as 1 µg/mL. This level of activity was found comparable to the reference drugs rifampicin and isoniazid at the same conc. Among all the compounds, 5-(3-phenoxyphenyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (45) was found to be most potent.

1.2.2.3.4. Anticancer Activity

Li, et al., 2009; synthesized a series of D-glucopyranosyl-1,2,4-triazole-3-thione derivatives by the reaction of 1,2,4-triazole-3-thione Schiff bases with 2,3,4,6-tetra-O-acetyl-s-D-glucopyranosyl bromide. Compound 46 showed cytotoxic activity against human MCF-7 (9.7 µM) and Bel-7402 (8.6 µM) malignant cell lines in comparison to reference drug 5-fluorouracil 4.3 µM and 4.7 µM, respectively.
1.2.2.3.5. Anti-hyperlipidemic Activity

Idrees, et al., 2009; synthesized a series of triazole derivatives and evaluated them for hypolipidemic activity in the high cholesterol diet fed hyperlipidemic rat model. 3-Ethylthio-5-[1-(naphthalen-2-yloxy)ethyl]-4-phenyl-4H-1,2,4-triazole (47) produced striking reduction of serum levels of total cholesterol, triglycerides and low-density lipoproteins and showed elevation of serum high-density lipoproteins better than the reference drug gemfibrozil.

1.2.2.3.6. Anticonvulsant Activity

Rostom, et al., 2009; synthesized 1,2,4-triazole derivatives and tested them for anticonvulsant activity. Synthesized compounds were tested for their preliminary anticonvulsant activity against subcutaneous metrazole and maximal electroshock induced seizures in mice. Compound 48, 5-[(1-(4-chlorophenyl)-2-(5-phenyl-2H-tetrazol-2-yl)ethoxy)methyl]-4-phenyl-4H-1,2,4-triazole-3-thiol showed noticeable anticonvulsant activity in both tests with 33% protection.
1.2.3. 1,3,4-THIADIAZOLE

1.2.3.1. INTRODUCTION

Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. Thiadiazole moiety acts as “hydrogen binding domain” and “two-electron donor system”. It also acts as a constrained pharmacophore. They occur in nature in four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole.

A glance at the standard reference work shows that more work has been carried out on the 1,3,4-thiadiazole than all other isomers combined together. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. The literature review showed that the thiadiazole nucleus has been reported to have antimicrobial, anti-inflammatory, anticancer, anticonvulsant and antidepressant activities.

1.2.3.2. SYNTHESIS OF 1,3,4-THIADIAZOLEs

Thiadiazoles can be synthesized mainly from thiosemicarbazide or hydrazide by conventional method in good yield.

1,3,4-Thiadiazole can be synthesized by cyclization of thiosemicarbazide in presence of sulphuric acid (Desai, et al., 2008).

1,3,4-Thiadiazoles can also be synthesized by refluxing thiosemicarbazones in aqueous ammonium ferric sulfate solution (Forumadi, et al., 2003).
Forumadi also synthesized 1,3,4-thiadiazoles by direct cyclization of an arylcarboxylic acid and thiosemicarbazide in presence of phosphorous oxychloride (Forumadi, et al., 2003).

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\begin{align*}
\text{H}_2\text{N} & \quad \text{NH} \\
\text{NH} & \quad \text{NH}_2 \\
\text{S} & \quad \text{NN} \\
\text{NH}_2 & \quad \text{Ar}\text{-COOH} \\
\text{POCl}_3 & \quad \text{Ar}\text{-COOH}
\end{align*}
\]

1,3,4-Thiadiazole can also be synthesized by direct cyclization of 4-amino-5-aryl-1,2,4-triazole-3-thiol and arylcarboxylic acid in presence of phosphorous oxychloride (Karabasanagouda, et al., 2007).

1.2.3.3. BIOLOGICAL ACTIVITIES OF 1,3,4-THIADIAZOLES

1.2.3.3.1 Antimicrobial Activity

Padmavathi, et al., 2009; synthesized a series of 1,3,4-thiadiazole derivatives and evaluated them for antimicrobial and cytotoxic activities. Among all the tested compounds, 2-(4-chlorobenzylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (49) showed pronounced antimicrobial activity with maximum cytotoxic activity.

Siddiqui, et al., 2009; synthesized a number of new 5-(1H-indol-3-yl methyl)-N-(substituted phenyl)-1,2,4-thiadiazol-2-amine derivatives and evaluated them for their antibacterial and antifungal activities. Compounds 50a and 50b showed 80% and 72% inhibition respectively against S. aureus while compound 50b showed 76% inhibition against E. coli. These two compounds also showed 70% and 85% inhibition respectively against C. albicans.
Palekar, et al., 2009; synthesized a novel series of 1,4-bis(6-(substituted phenyl)-[1,2,4]-triazolo[3,4-b]-1,3,4-thiadiazoles. All the synthesized compounds were screened for their antimicrobial activity against various bacterial and fungal strains. Several of these compounds showed potential antibacterial and antifungal activities. It was observed that compound 51a and 51b having 1,2,4-triazolo[3,4-b]-1,3,4- thiadiazole moiety have comparatively good activity against all the fungal strains.

Mathew, et al., 2007; synthesized several 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues from hetero aromatic acids and hetero aromatic aldehydes, respectively, by microwave-assisted dry media and conventional methods. Compound 6-(2-fluoropyridin-4-yl)-3-(2-methyl-3-furyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (52) showed significant activity against all microbial strains.

1.2.3.3.2. Anti-inflammatory and Analgesic Activity

Salgın-Gökşen, et al., 2007; synthesized some 1,3,4-thiadiazole derivatives. They found that the analgesic effect of compound 53 was better than both morphine and aspirin.
Mathew, et al., 2007; tested some thiazole derivatives and compound 54, 3-[[3-(2-chloro-5-methoxyphenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl][methyl]-1H-indole showed highest anti-inflammatory activity.

Schenone, et al., 2006; synthesized a series of N-[5-oxo-4-(arylsulfonyl)-4, 5-dihydro-1,3,4-thiadiazol-2-yl]-amides (55) and tested them in vivo for their analgesic and anti-inflammatory activities. All the tested compounds showed good analgesic action in the acetic acid writhing test. Few compounds of the series also showed fair anti-inflammatory activity in the carrageenan rat paw edema test. They had reduced ulcerogenic and irritative action on the gastrointestinal mucosa compared to indomethacin.

1.2.3.3. Anticancer Activity

A new series of chiral 1,3,4-thiadiazole derivatives possessing substituted butenolide moiety was synthesized and evaluated for in-vitro anticancer properties by Wei, et al., 2009. All the compounds showed good anticancer activity against Hella cell lines. Out of all the studied compounds, compound 56 exhibited the best inhibitory activity with an IC$_{50}$ of 0.9 µM. The growth inhibition rate of Hella cell lines was 59.2% after being treated with compound 56 (0.1 µg/mL) for 24 h.
Synthesis and biological evaluation of 3,6-disubstituted [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives was reported by Ibrahim, 2009. These compounds demonstrated inhibitory effect on the growth of a wide range of cancer cell lines generally at $10^{-5}\text{M} - 10^{-7}\text{M}$ concentrations. Compounds 57 and 58 demonstrated the highest growth inhibition.

1.2.3.3.4. Anticonvulsant Activity

Jatav, et al., 2008; synthesized a series of new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones and examined them against the maximal electroshock induced seizures and subcutaneous pentylenetetrazole induced seizures in mice model. Compounds 59a and 59b showed significant anticonvulsant activity.

Stillings, et al., 1986; reported the anticonvulsant properties of a number of substituted 2-hydrazino-1,3,4-thiadiazoles. They found that, 2-(aminomethyl)-5-(2-biphenyl)-1,3,4-thiadiazole (60) possess potent anticonvulsant properties.
1.2.3.3.5. Antioxidant Activity

Sunil, et al., 2010; investigated the *in vitro* antioxidant property of two triazolothiadiazole derivatives, 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-3-[(2-naphthyloxy)methyl][1,2,4] triazolo[3,4-b][1,3,4]thiadiazole (61a) and 6-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-3-[(phenyloxy)methyl][1,2,4] triazolo[3,4-b][1,3,4]thiadiazole (61b) by spectrophotometric DPPH and ABTS radical scavenging methods as well as by lipid peroxide assay. The significant antioxidant activity of 61a with low IC$_{50}$ values compared to standard was clearly evident from DPPH, ABTS free radical scavenging and *in vitro* lipid peroxidation assays. The *in vitro* lipid peroxidation assay also proved compound no. 61a to be an excellent antioxidant.