2. LITERATURE REVIEW

The literature review includes study of therapeutic activity and various synthetic pathways of 1,3,4-oxadiazoles. In the literature studies a large number of series of substituted 1,3,4-oxadiazole derivatives were synthesized for their different biological activities.

2.1. BIOLOGICAL ACTIVITIES

2.1.1. Anti-inflammatory activity

Inflammation is a normal and essential response to any noxious stimulus that threatens the host and may vary from a localized response to a generalized response. NSAIDs have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections and fever (Lanza, 1998; Buttgeriet et al., 2001).

The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal upset, irritation, ulceration as the most serious complication of these drugs (Christopher et al., 1998; Deruiter, 2002; Anand, 1979; Abdrabbo, 2005). Some evidences suggest that the oxadiazole moiety present in some compounds possess an anti-inflammatory activity by virtue of dual mechanism i.e., inhibiting both COX/LOX to reduce gastric acid formation (Palomer et al., 2002; Warner and Giuliano, 1999). Aroylpropionic acid belongs to a class of non-steroidal anti-inflammatory agents. Studies suggest that direct tissue contact of these agents plays an important role in the production of side effects and the reported literature confirms that gastrointestinal side
effects of arylpropionic acids and other NSAIDs are due to the presence of a free carboxylic group in the parent drug (Testa and Jenner, 1976; Cioli et al., 1979; Amir and Shikha, 2004; Kalgutkar, 1998). Thus, developing new agents with minimum or without side effects is an extensive research area at present by replacing the terminal free carboxylic function by oxadiazole ring may enhance the anti-inflammatory activity of such compounds with reduced ulcerogenic effects (Khan and Husain, 2002; Husain et al., 2005; Kalgutkar et al., 2000).

Few good examples of substituted 1,3,4-oxadiazole derivatives belonging to series 1-(4-bromo-phenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 1, were synthesized and evaluated for anti-inflammatory activity. 1-(4-Bromo-phenyl)-3-(5-phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 1a, 1-(4-bromo-phenyl)-3-(5-(2-chloro-phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 1b, 1-(4-bromo-phenyl)-3-(5-(4-chloro-phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 1c, and 1-(4-bromo-phenyl)-3-(5-(3,4-dimethoxy-phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 1d, presented better anti-inflammatory activity and shown 40.5, 52.4, 59.5, 61.9 percentage inhibition response of pleurisy at a dose of 20 mg/kg against carrageenan induced rat paw edema (Fig-2) (Husain and Mohammed, 2009).

![Fig-2: 1-(4-Bromo-phenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one](image)

2-(4-Hydroxyphenyl)-5-(napthlene-1-yloxymethyl)-[1,3,4]oxadiazole, 2a and 2-(4-methoxy-phenyl)-5-(napthlene-1-yloxymethyl)-[1,3,4]oxadiazole, 2b, presented significant anti-inflammatory activity and shown 55.93 and 50.84% inhibition in carrageenan induced rat paw edema (Fig-3) (Rajak et al., 2007).
The higher activity of compound 2a may be attributed to the electro negativity of the hydroxyl group, which can withdraw electron more strongly than chloro, nitro and other groups. Among the synthesized oxadiazole 4-hydroxy and 4-methoxy substituted derivatives were showed maximum activity. 2-(4-Hydroxy phenyl)-5-(napthalen-1-yl-oxo-methyl-[1,3,4]oxadiazole, 2a, was showed 55.93, 36.64 and 49.33% protection against carrageenan induced rat paw edema, moist cotton pellet-induced granuloma and dry cotton pellet-induced granuloma respectively. 2-(4-Methoxy phenyl)-5-(napthalen-1-yl-oxo-methyl-[1,3,4]oxadiazole, 2b was showed 50.84, 28.26 and 31.63% protection against carrageenan induced rat paw oedema, moist cotton pellet-induced granuloma and dry cotton pellet-induced granuloma respectively (Fig-3).

3-[5-(Substituted aryl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-ones, 3 were synthesized and tested for their anti-inflammatory activity. The 4-methoxy phenyl and 3,4-dimethoxy phenyl derivatives were showed significant anti-inflammatory activity (Fig-4) (Ausaf et al., 2009).
A novel series of 1-(4-benzylphenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 4, 1-(4-ethylphenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 5 were synthesized and evaluated for anti-inflammatory activity. The 4-methoxy and 3,4-dimethoxy phenyl presented better anti-inflammatory activity and shown 52.6, 56.2 percentage inhibition response against standard drug indomethacin, (61%) in carrageenan induced rat paw edema (Fig-5 and Fig-6) (Husain et al., 2009).

\[ \text{Fig-5: 1-(4-Benzylphenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one} \]

Two novel series of 2-[3-(4-chlorophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole, 6 and 2-[3-(4-ethylphenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole, 7 were synthesized and tested for their anti-inflammatory activity. The 4-methoxy phenyl and 3,4-dimethoxy phenyl derivatives were showed significant anti-inflammatory activity 58.38% and 59.52% respectively against indomethacin (64.28%) (Fig-7 and Fig-8) (Husain et al., 2008).

\[ \text{Fig-6: 1-(4-Ethylphenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one} \]

2-Naptho [2,1-b]furan-2-yl-5-aryl-1,3,4-oxadiazoles, 8, derivatives were shown potent anti-inflammatory activities. The 4-chloro phenyl substituted derivative shown promising activity against carrageenan induced rat paw edema and percentage inhibition
was found to be 71.48 against standard drug ibuprofen (66.54) (Fig-9) (Ravindra et al., 2006).

![Fig-7: 2-[3-(4-Chlorophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole](image)

![Fig-8: 2-[3-(4-Ethylphenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole](image)

2-Substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazoles, 9, were shown potent anti-inflammatory activities. 2,4-dichlorophenyl, 1-(4-isobutylphenyl)ethyl against carrageenan induced rat paw edema and percentage inhibition was found to be 72.72 against standard drug ibuprofen (86.36) (Fig-10) (Amir et al., 2007).

![Fig-9: 2-Naptho [2,1-b]furan-2-yl-5-aryl-1,3,4-oxadiazoles](image)
A new series of 5-methyl-3-\textit{p}-(6'-aryl-2'-thioxo-1',2',5',6'-tetrahydropyrimidin-4'-yl)-phenyl]-3\textit{H}-2-oxo-\Delta^4-1,3,4-oxadiazole, \textbf{10}, derivatives were synthesized and evaluated for anti-inflammatory activity (\textbf{Fig-11}).

The anti-inflammatory activity revealed that the 5-methyl-3-\textit{p}-(6'-phenyl-2'-thioxo-1',2',5',6'-tetrahydropyrimidin-4'-yl)-phenyl]-3\textit{H}-2-oxo-\Delta^4-1,3,4-oxadiazole, \textbf{10a}, showed 55.6% inhibition even more than the standard drug (ibuprofen) in carrageenan-induced paw edema (\textbf{Fig-12}) (Kamble and Sudha, 2006).
2-(1-Adamantyl)-5-substituted-1,3,4-oxadiazoles, 11, derivatives were synthesized and evaluated for anti-inflammatory activity. The best activity was observed with the oxadiazole derivatives 4-ClC₆H₄, 3,4-(OCH₃)₂C₆H₃, 2-thienyl and 1-adamantyl which displayed strong dose-dependent inhibition of carrageenan-induced edema producing >50% inhibition at 60 mg/kg dose (Fig-13) (Kadi et al., 2007).

![Fig-13: 2-(1-Adamantyl)-5-substituted-1,3,4-oxadiazoles](image)

Some new 2-thio-3-(substituted-aminomethyl)-5-(3,5-dinitrophenyl)-1,3,4-oxadiazoles, 12, has been found to possess considerable anti-inflammatory property (Fig-14) (Nigam et al., 1992).

![Fig-14: 2-Thio-3-(substituted-aminomethyl)-5-(3,5-dinitrophenyl)-1,3,4-oxadiazoles](image)

Dual inhibitors of 5-lipoxygenase (LO) and cyclooxygenase (COX) with improved pharmacokinetic properties, a series of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3,4-oxadiazoles 13 and 13a were designed and synthesized (Fig-15) (Mulican et al., 1993).

Most of the compounds of series 5-(6-methyl-2-substituted-4-pyrimidylloxymethyl)-1,3,4-oxadiazole-2-thiones, 14 and their 3-morpholino methyl derivatives exhibited anti-inflammatory activity and moreover some of them were more active than acetylsalicylic acid (Fig-16) (Jakubkiene et al., 2003).
A novel series of 5-(4-pyridyl)-4-(substituted methyl)-1,3,4-oxadiazoline-2-thione hydrochloride, 15 has also been found to possess anti-inflammatory activity (Fig-17) (Singh et al., 1986).

Fig-17: 5-(4-Pyridyl)-4-(substituted methyl)-1,3,4-oxadiazole-2-thione hydrochloride

Fig-18: 3-Pentadecylphenol derivatives containing the 1,3,4-oxadiazole nucleus
Some 3-pentadecylphenol derivatives containing 1,3,4-oxadiazole nucleus, 16 and 16a has been found to have good anti-inflammatory activity (Fig-18) (Ramlingam and Sattur, 1987).

Novel derivatives of 1,3,4-oxadiazole were synthesized and tested for their anti-inflammatory activity, using carrageenan-induced rat paw edema method. They prepared 2,5-disubstituted-1,3,4-oxadiazoles, by the condensation reactions of 4-methoxy benzohydrazide, with different aromatic acids in the presence of phosphoryl chloride. It was found that compound 17 N-{4-[5-(4-methoxy-phenyl)-1,3,4-oxadiazol-2-yl]-phenyl}benzamide exhibited potent anti-inflammatory activity with 50 %, as compared to the standard drug phenylbutazone, with 53.57 % (Fig-19) (Nagalakshmi, 2008).

![Fig-19: N-{4-[5-(4-Methoxy-phenyl)-1,3,4-oxadiazol-2-yl]-phenyl}benzamide](image)

A series of S-substituted phenacetyl 1,3,4-oxadiazoles 18 derived from 2-[2-(2,6-dichloroanilino)phenyl]acetic acid (diclofenac acid) was synthesized. They indicated their better anti-inflammatory activity in the carrageenan induced rat paw edema model, with no GI toxicities, compared to the standard drug diclofenac sodium.
Esterification of 2-[(2,6-dichloroanilino) phenyl]acetic acid (diclofenac acid) followed by treatment with hydrazine hydrate in absolute ethanol, afforded 5-[2-(2,6-dichloroanilino) benzyl] 2-mercapto-1,3,4-oxadiazole (Fig-20) (Bhandari et al., 2008).

![Fig-20](image)

**Fig-20:** 2-(4-Substituted phenyl)-5-(2-aminophenyl)-1,3,4-oxadiazole

A novel series of [5-(4-substituted-phenyl)-[1,3,4]oxadiazol-2-yl]-pyridine 19 and 2-(4-substituted phenyl)-5-(2-aminophenyl)-1,3,4-oxadiazole, 20 was synthesized. The treatment of esters and hydrazine hydrate in the presence of ethanol, via intermediate steps isonicotinic acid hydrazide and 2-amino benzo hydrazide respectively, followed by reaction with phosphorus oxychloride and various aromatic acids, afforded different 1,3,4-oxadiazoles. From all the synthesized compounds, they found that compounds 19 and 20 exhibited significant anti-inflammatory activity (Fig-21 and Fig-22) (Chawla et al., 2010).

![Fig-21](image)

**Fig-21:** [5-(4-Substituted-phenyl)-[1,3,4]oxadiazol-2-yl]-pyridine

A series of 5-(4-hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazoles were synthesized and evaluated them for their biological activity. The treatment of 4-hydroxyphenylacetic acid with hydrazine hydrate in absolute ethanol gave 4-hydroxyphenyl acetic acid hydrazide. Further treatment with various aryl/alkyl isothiocyanates produce \( N\)-[2-(4-hydroxyphenyl)acetyl]\( N\)-aryl/alkyl-3-thiosemicarbazides, which were then and cyclized to form oxadiazole 21 in the presence of iodine and potassium iodide. Of all the synthesized compounds, 5-(4-
hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazole 21 exhibited significant anti-inflammatory activity with 77.77%, due to the presence of a 4-methoxyphenylamino group at the second position of the oxadiazole ring (Fig-23) (Amir et al., 2008).

![Fig-23: 5-(4-Hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazoles](image)

Novel derivatives of ibuprofen 1,3,4-oxadiazoles by cyclization of 2-(4-i-butylphenyl)propionic acid hydrazide and N-[2-(4-i-butylphenyl)-propionyl]-N-alkyl/aryl-thiosemicarbazides were synthesized. All these compounds evaluated for anti-inflammatory activity and less ulcerogenic activity, compared to ibuprofen, through the severity index 0.5 to 0.8, vs. ibuprofen 1.8. They found that compound 22, {5-[1-(4-isobutyl-phenyl)-ethyl]-[1,3,4]oxadiazol-2-yl]-propylamine showed significant anti-inflammatory activity, due to the presence of n-butyl amino group, with yield of 86%, compared to the standard drug ibuprofen, which showed 92 % percentage inhibition (Fig-24) (Amir M, Kumar, 2007).

![Fig-24: 5-(4-Hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazoles](image)

2.1.2. Analgesic activity

1,3,4-Oxadiazole containing compounds were also shown good analgesic activity in acetic acid induced writhing method. A new series of 2-[3-(4-chlorophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole, 6, were shown significant analgesic activity in acetic acid induced writhing method and percentage
protection was found to be 42 to 54 in comparison with standard drug aspirin, whose % protection was found to be 63.4 (Fig-7) (Husain et al., 2008).

1-(4-Bromo-phenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, 1, were shown significant analgesic activity in acetic acid induced writhing method and percentage protection was found to be 57 to 71 in comparison with standard drug aspirin, whose % protection was found to be 63 (Fig-2) (Husain and Mohammed, 2009).

A novel series of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-ones, 23, derivatives showed significant analgesic activity in the acetic acid-induced writhing test. The percentage protection was found to be 38 to 76 in comparison with standard drug indomethacin, whose analgesic activity in terms of % protection was found to be 72.44. The 2-acetoxy phenyl derivative of this series has shown 76% protection in terms of analgesic activity which is higher even than standard drug indomethacin (Fig-25) (Husain et al., 2009).

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-phenoxy phenyl</td>
</tr>
<tr>
<td>b</td>
<td>2-chloro phenyl</td>
</tr>
<tr>
<td>c</td>
<td>4-chloro phenyl</td>
</tr>
<tr>
<td>d</td>
<td>2-acetoxy phenyl</td>
</tr>
<tr>
<td>e</td>
<td>4-nitro phenyl</td>
</tr>
<tr>
<td>f</td>
<td>4-flouro phenyl</td>
</tr>
<tr>
<td>g</td>
<td>4-methyl phenyl</td>
</tr>
<tr>
<td>h</td>
<td>4-methoxy phenyl</td>
</tr>
<tr>
<td>i</td>
<td>3,4-dimethoxy phenyl</td>
</tr>
<tr>
<td>j</td>
<td>benzyl</td>
</tr>
<tr>
<td>k</td>
<td>phenoxy methyl</td>
</tr>
<tr>
<td>l</td>
<td>2-naphthlyoxymethyl</td>
</tr>
</tbody>
</table>

**Fig-25:** 1-(4-Phenoxyphenyl)-3-[5-(substituted aryl) 1,3,4-oxadiazol-2-yl]propan-1-ones

A series of 2′-((benzo[d]thiazol-2-ylthio)methyl)spiro[indoline-3,5′-thiazolo [4,3b][1,3,4]oxadiazol]-2-ones, 24, have been synthesized and screened for their anti-inflammatory, analgesic and antibacterial activities. The most potent anti-inflammatory and antibacterial compound of this series was compound 24d and most potent analgesic compound was compound 24e. Structures of all the compounds were

---

*Faculty of Pharmaceutical Sciences, M.M. University, Mullana, Ambala, Haryana (India)*
established by elemental and spectral (IR and $^1$H NMR) analysis (Fig-26) (Kaur et al., 2010).

![Fig-26: 2'-(Benzo[d]thiazol-2-ylthio)methyl]spiro[indoline-3,5'-thiazolo[4,3b][1,3,4]oxadiazol]-2-ones](image)

### 2.1.3. Antimicrobial activity

The rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists.

BB-83698, 25, is an antibacterial agent. It is an inhibitor of metallo enzyme PDF (Peptide Deformylase).

![Fig-27: BB-83698](image)

PDF is considered as the most promising bacterial targets in the search for novel mode of action of antibiotics that lacks cross-resistance to existing drugs (Fig-27) (Rakesh et al., 2009).
2-[3-(4-Bromophenyl)propan-3-one]-5-(4-fluorophenyl)-1,3,4-oxadiazole, 1, showed very good activity against *S. aureus* (MIC = 12.5 mg mL\(^{-1}\)) and good activity against *E. coli* (MIC = 25 mg mL\(^{-1}\)), whereas 2-[3-(4-bromophenyl)propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole, also showed good activity against *S. aureus* (MIC = 25 mg mL\(^{-1}\)). The reference drug, nitrofurazone, showed MIC of 12.5 mg mL\(^{-1}\) against *S. aureus* and 6.5 mg ml\(^{-1}\) against *E. coli* (Fig-2) (Husain and Mohammed, 2009).

Another series of substituted 5-Indole-1,3,4-oxadiazole, 26, were prepared and evaluated for antimicrobial activity. The antimicrobial activity was observed in compound 5-Indole-1,3,4-oxadiazole (against *B. subtilis* and *P. aeruginosa*), 2-(3-chlorophenyl)-5-indole-1,3,4-oxadiazole (against *S. aureus, E. coli* and *B. subtilis*) and 2-phenyl-5-indole-1, 3, 4-oxadiazole (against *S. aureus*). None of the compounds were found effective against *A. niger*. The compounds which were active against bacterial strains were effective at a much higher concentration as compared to the standard drug, norfloxacin (Fig-28) (Bhardwaj *et al.*, 2009).

![Fig-28: 5-Indole-1,3,4-oxadiazole](image)

Transition metal complexes with a new tridentate ligand, 5-[6-(5-mercapto-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazole-2-thiol, 27, were shown good antimicrobial activity. The antibacterial and antifungal activity of the ligand, transition metal salts and the corresponding complexes were assayed against two
bacteria, *E. coli* and *B. cirroflagellosus* and two fungi, *A. niger* and *C. albicans*, by the cup plate method.

![Diagram](image)

Where M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)

**Fig-29**: 5-[(6-(5-Mercapto-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-1,3,4-oxadiazole-2-thiol

The results were compared against the standards norfloxacin (antibacterial) and griseofulvin (antifungal), which were screened simultaneously. The Cu(II) and Zn(II) complexes were found to be more active, while the Mn(II), Co(II) and Ni(II) complexes were moderately active (Fig-29) (Gudasi *et al*., 2007).

1,3,4-Oxadiazole derivatives bearing 6-bromonaphthalene moiety, 2-[[((6-bromo-2-naphthyl)oxy]methyl]-5-aryl-1,3,4-oxadiazole, **28** and 2-[[((6-bromo-2-naphthyl)oxy]methyl]-5-[[alkyl/aryl]thio]-1,3,4-oxadiazole, **29**, exhibited promising antibacterial and antifungal activity against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumonia*, *A. flavus*, *A. fumigates*, *Penicillium* and *T. mentagrophytes* (Fig-30 and Fig-31) (Mayekar, 2010).

![Diagram](image)

**Fig-30**: 2-[[((6-Bromo-2-naphthyl)oxy]methyl]-5-aryl-1,3,4-oxadiazole

![Diagram](image)

**Fig-31**: 2-[[((6-Bromo-2-naphthyl)oxy]methyl]-5-[[alkyl/aryl]thio]-1,3,4-oxadiazole
A series of new 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanones, 30, was synthesized and evaluated for antibacterial and antifungal activity against cultured strains of *S. aureus*, *P. aeruginosa*, *C. albicans* and *A. flavus* against the standard ampicillin and fluconazole at a concentration of 1 mg/ml.

1-(2-(4-(Dimethylamino)phenyl)-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanone, 30a and 1-(2-(4-chlorophenyl)-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanone, 30b, were found to possess maximum activity against the tested strains of *S. aureus* and *P. aeruginosa* concluded that *para*-substitution enhanced the activity of synthesized oxadiazoles (Fig-32) (Fuloria et al., 2009).

![Figure 32: 1-(2-Aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanones](image)

<table>
<thead>
<tr>
<th>30</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>N(CH₃)phenyl</td>
</tr>
<tr>
<td>b</td>
<td>4-Cl-phenyl</td>
</tr>
</tbody>
</table>

A new series of 2,5-disubstituted-1,3,4-oxadiazoles, 31 compounds were shown *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus*, *B. subtilis*, *B. megaterium*, *E. coli*, *P. aeruginosa*, *S. dysenteriae*, *C. albicans*, *A. niger* and *A. flavus* were compared with the standard antibiotics such as chloramphenicol and griseofulvin.

N-[4-[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl]-2,4-dinitroaniline, 31a and N-[4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl]-2-nitroaniline, 31b, exhibited very good antimicrobial activity (Fig-33 and Fig-34) (Nagalakshmi, 2008).
Chapter 2

Literature Review

Faculty of Pharmaceutical Sciences, M.M. University, Mullana, Ambala, Haryana (India)

Figure 33: N-[4-[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl]-2,4-dinitroaniline

Figure 34: N-[4-[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl]-2-dinitroaniline

2-[5-(Aryl)-[1,3,4]oxadiazole-2-ylsulfanyl]alkanoic acids, 32, were synthesized and screened for antibacterial activity against standard ciprofloxacin which inhibited gram negative bacteria *E. coli* and *P. aeruginosa* at a MIC of 0.01 μg ml⁻¹ and 0.25 μg ml⁻¹, respectively whereas against gram positive bacteria *S. aureus* and *B. subtilis*, MIC was found to be 0.15 μg ml⁻¹ and 0.12 μg ml⁻¹ respectively. Compounds containing 2,4-dichloro moiety were found to be most active (MIC-0.35-0.40 μg ml⁻¹) (Fig-35) (Jain et al., 2009).

Figure 35: 2-[5-(Aryl)-[1,3,4]oxadiazole-2-ylsulfanyl]alkanoic acids

Another series of novel compounds i.e., oxadiazole with pyrimidine, 2-[[2-(morpholino)-3-pyridinyl-5-thio]-2-oxoethyloxadiazolyl]-amino-4-(2,4-dichloro-5-fluorophenyl)-6-(aryl)-pyrimidines, 33, was synthesized and evaluated for in-vitro
antibacterial activity against *S. aureus*, *E. coli*, *S. typhi* and *B. subtilis*. The 4-methoxy and 3,4,5-trimethoxy derivatives were found to be potent against standard drug tetracycline (Fig-36) (Naik and Chikhalia, 2007).

ω-(5-Aryl-1,3,4-oxadiazol-2-thiol)-ω--(1H-1,2,4-triazol-1-yl)acetophenones, 34, were synthesized and preliminary biological test showed that some of them exhibited mild antifungal and plant growth regulative activities (Fig-37) (Chu et al., 1999).

5-Chloro-6-phenyl-2-[(5-phenyl-1,3,4-oxadiazol-2-ylsulfonyl)methyl]pyridazin-3 (2H)-one, 35 was subjected to fungicidal activities *in-vitro* against *G. zeae*, *F. oxysporum* and *C. mandshurica*. The results showed that the synthesized pyridazine compound in combination with oxadiazole nucleus possessed good antifungal activity against the tested fungi (Fig-38) (Wu et al., 2009).
A series of 2-carboxymethylthio-5-substituted phenyl-1,3,4-oxadiazole, 36, were prepared, 2-carboxymethylthio-5-phenyl-1,3,4-oxadiazole, 36a, 2-carboxymethylthio-5-(4-hydroxyphenyl)-1,3,4-oxadiazole, 36b, 2-carboxymethylthio-5-(4-chlorophenyl)-1,3,4-oxadiazole, 36c, 2-carboxymethylthio-5-(4-nitrophenyl)-1,3,4-oxadiazole, 36d were synthesized and evaluated for antimicrobial activity were showed less activity except 4-chloro derivative which showed moderate activity as compared to ofloxacin. 4-Hydroxy, 4-nitro and 4-chloro derivatives have significant activity against C. albicans whereas moderate activity against A. niger as compared to miconazole nitrate (40μg/ml) (Fig-39) (Sengupta et al., 2008).

5-Pyridyl-2-[(N-substituted phenyl)thioacetamido]-1,3,4-oxadiazoles, 37 by conventional and microwave methods and evaluate their antibacterial activities against B. subtilis, S. aureus, E. coli and P. aeruginosa using ampicillin as the standard drug at a concentration of 10 μg ml⁻¹. The compound possessing a dichloro substitution on the phenyl ring has shown promising antibacterial activity against gram positive organism, while the compound possessing chloro substitution on the phenyl ring has shown good antibacterial activity against gram negative organism (Fig-40) (Rajasekaran et al., 2010).
Another series of 5-substituted-3-(4-arylimino)-1-[5-mercapto (1,3,4-oxadiazolyl)]-methyl-indol-2-one, 38, derivatives were evaluated for in-vitro antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, *P. vulgaris* and antifungal activity against *C. albican*, *A. niger*. Remarkable inhibition was observed in compounds bearing R=F, Cl, Br and R\(_1\) = F, CH\(_3\), Br substituents (Fig-41) (Bari et al., 2008).

2-Alkyl-5-phenylsulfanyl-[1,3,4]oxadiazole, 39, can be used as antibacterial agent and (5-alkyl-[1,3,4]-oxadiazol-2-yl)-phenyl-amine, 40 can be used as antibacterial agent against *E. coli* due to its excellent antibacterial activity (Fig-42 and Fig-43) (Toliwal et al., 2009).
Chapter-2

Literature Review

Faculty of Pharmaceutical Sciences, M.M. University, Mullana, Ambala, Haryana (India)

5-Substituted-phenyl-1,3,4-oxadiazol-2-amines, 41, 4-(5-substituted phenyl-1,3,4-oxadiazol 2yl)benzenamines, 42, exhibited very good antimicrobial activity (Fig-44 and Fig-45) (Patel and Patel, 2010).

![Fig-43: 5-Alkyl-[1,3,4]-oxadiazole](image1)

![Fig-44: 5-Substituted-phenyl-1,3,4-oxadiazol-2-amines](image2)

![Fig-45: 4-(5-Substituted phenyl-1,3,4-oxadiazol-2-yl)benzenamines](image3)

2,5-Di-substituted 1,3,4-oxadiazoles, 43, were synthesized and evaluated for antimicrobial activity and 2-chloro phenyl derivative, 43a showed maximum activity against S. aureus. The inhibition was found to be 51.72 % with 50 g/ml and 58.62% with 100g/ml against standard drug ofloxacin (100%) (Fig-46 and Fig-47) (Saini et al., 2009).

![Fig-46: 2, 5-Di-substituted 1,3,4 oxadiazoles](image4)

![Fig-47: 2-Chloro phenyl derivative](image5)
The reaction of hydrazides with substituted aldehydes in the presence of ethanol to yield Schiff bases and further treating with chloramine-T to produce 5-aryl (8-quinolinoxymethyl)-1,3,4-oxadiazoles. The compounds thus obtained were identified by spectral data and screened for their antimicrobial activity. Compounds like 44d showed potent activity while 44b and 44c showed moderate activity against S. aureus. Compounds 44b and 44c showed significant activity and 44d and 44i exhibited similar activity compared to ampicillin against B. subtilis. Compounds like 44e, 44g and 44i showed good activity and compounds like 44e, 44g and 44j showed similar activity compared to standard drug ampicillin against E. coli (Fig-48). Compounds 44i and 44f exhibited significant activity against S. typhi. Compounds like 44e and 44j exhibited potent activity against C. albicans (Fig-48) (Mohammed et al., 2010).

![Image](attachment:image1)

**Fig-48: 5-Aryl (8-quinolinoxymethyl)-1,3,4-oxadiazoles**

New 5-(2-thienyl)-1,3,4-oxadiazoles namely 3-arylaminomethyl-5-(2-thienyl)-1,3,4-oxadiazoline-2-thiones 45, 3-(N-substituted anilinomethyl)-5-(2-thienyl)-1,3,4-oxadiazoline-2-thiones 46 and 3-(4-substituted-1-piperazinylmethyl)-5-(2-thienyl)-1,3,4-oxadiazoline-2-thiones 47, were prepared (Fig-49, Fig-50 and Fig-51). The synthesized compounds were tested for in-vitro activities against certain strains of gram positive and gram negative bacteria and the yeast-like pathogenic fungus C. albicans.
Compound 47a displayed marked broad spectrum antibacterial activity, while compounds 45b, 45c, 45d, 47b, 47c and 47d were highly active against the tested gram positive bacteria. None of the synthesized compounds were proved to be significantly active against *C. albicans* (Al-Omar, 2010).

A series of 5-(4-chlorobenzyl)-N-1,3,4-oxadiazol-2-amines 48(a-g) have been prepared. The compounds were screened against gram positive and gram negative bacteria i.e., *S. aureus* and *E. coli*. Ciprofloxacin was used as a standard drug (Fig-52) (Desai *et al.*, 2008).
All the newly synthesized compounds were compared with the standard drug ciprofloxacin.

Chapter-2

A series of 7-un/substituted-2-spiro-[5-((1-acetyl-5-(substitutedphenyl)amino)-3-(1-acetyloxy-5-(substitutedphenyl))pyazolin-3-yl)-1,3,4-oxadiazol-2-yl]coumarins 49(a-h) (Fig-53) and 7-un/substituted-2-spiro-2-[(5-(substitutedphenyl)amino)-4-(5-(substitutedphenyl))pyazolin-3-yl)-1,3,4-oxadiazol-2-yl]coumarins 50(a-h) (Fig-54) were synthesized. All the newly synthesized compounds were screened for their antibacterial activity against K. pneumoniae, S. aureus, E. coli, B. subtilis and were compared with the standard drug ciprofloxacin. The most potent antibacterial compound of this series was 49g (Kaur et al., 2010).

Fig-52: 5-(4-Chlorobenzyl)-N-1,3,4-oxadiazol-2-amines

Fig-53: 7-Un/substituted-2-spiro-[5-((1-acetyl-5-(substitutedphenyl)amino)-3-(1-acetyloxy-5-(substitutedphenyl)) pyazolin-3-yl)-1,3,4-oxadiazol-2-yl]coumarins

Fig-54: 7-Un/substituted-2-spiro-2-[(5-(substitutedphenyl)amino)-4-(5-(substitutedphenyl))pyazolin-3-yl)-1,3,4-oxadiazol-2-yl]coumarins

Faculty of Pharmaceutical Sciences, M.M. University, Mullana, Ambala, Haryana (India)
2.1.4. Antitumor activity

A novel series of 1-substituted phenyl-3-[3-alkylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]β-carboline derivatives, 51 were found as potent antitumor agents. Among this class, 1-phenyl-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]β-carboline, 51a, 1-(4-N,N-dimethylaminophenyl)-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]β-carboline, 51b, 1-(4-N,N-dimethylaminophenyl)-3-[3-benzylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]β-carboline were the most promising derivatives from this class, exhibiting a broad spectrum antitumor activity.

![Fig-55: 1-Substituted Phenyl-3-[3-alkylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]carboline derivatives](image)

Moreover, 1-phenyl-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]β-carboline, 51a displayed cytotoxic efficacy with LC$_{50}$(MG-MID) value of 60.49 μ mol L$^{-1}$ (Fig-55 and Fig-56).
A potent activity against melanoma (UACC-62) and lung (NCI-460) cell lines, with G1 \textsubscript{50} values of 0.88 and 1.01 \textmu{}mol L\textsuperscript{-1} respectively, was observed for 1-(4-N,N-dimethylaminophenyl)-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]\beta-carboline, \textit{51b} which possess the N,N-dimethylphenyl and isopropylamino(methyl) groups at C-1 and C-3, respectively, of the \beta-carboline nucleus (Fig-57) (Beydoun and Backonja, 2003).

![Fig-57: 1-(4-N,N-Dimethylaminophenyl)-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]carboline](image)

1-(4-N,N-Dimethylaminophenyl)-3-[3-benzylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]\beta-carboline, \textit{51c} also demonstrated a significant activity, with G1 \textsubscript{50} values in the range of 0.38 and 2.98 \textmu{}mol L\textsuperscript{-1} towards four cell lines (melanoma, ovarian resistant, renal and lung) (Fig-58) (Savariz et al., 2010).

![Fig-58: 1-(4-N,N-Dimethylaminophenyl)-3-[3-benzylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]carboline](image)

A new series of combination of adamantanyl-1,3-thiazole and 1,3,4-oxadiazole derivatives i.e., 2-(2-adamantyl-1,3-thiazol-4-yl)-5-(3-substituted phenyl)-1,3,4-oxadiazole, \textit{52} bearing various aryl groups has been synthesized and evaluated for \textit{in-vitro} antiproliferative activity against a large panel of human tumor-derived cell lines (Fig-59) (Zahid et al., 2009).
2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-chlorophenyl)-1,3,4-oxadiazole, \textit{52a}, exhibited activity against human splenic B-lymphoblastoid (WIL-2NS) and human acute B-lymphoblastic leukemia (CCRF-SB) cell lines with $CC_{50} = 68$ and 42 $\mu$M, respectively. 2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(2-bromophenyl)-1,3,4-oxadiazole, \textit{52b}, showed activity against CCRF-SB cell lines with $CC_{50} = 51$ $\mu$M (Fig-59).

Some 3-acetyl-2-substitutedphenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives were synthesized. Among the synthesized compounds \textit{53a, 53b, 53c, 53f, 53l} and \textit{53m} highly active against PC3 cells and \textit{53a, 53c} and \textit{53f} are moderately active against Bcap37 and BGC823 cells (Fig-60) (Jin et al., 2006).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig59.png}
\caption{2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-substituted phenyl)-1,3,4-oxadiazole}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textit{Y} & \textit{52} \\
\hline
3-Cl phenyl & a \\
2-Br phenyl & b \\
\hline
\end{tabular}
\caption{Substituents in 2-(2-Adamantyl-1,3-thiazol-4-yl)-5-(3-substituted phenyl)-1,3,4-oxadiazole}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig60.png}
\caption{3-Acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textit{R} & \textit{53} \\
\hline
3-F & a \\
3-F & b \\
4-F & c \\
2-CF_3 & d \\
4-CF_3 & f \\
3,5-CI & l \\
2,4-OCH_3 & m \\
\hline
\end{tabular}
\caption{Substituents in 3-Acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole}
\end{table}

2.1.5. Anticonvulsant activity

Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES)
test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity.

A series of 3-(4-acetyl-5-methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromene-2-ones, 54 (Fig-61), 3-(4-acetyl-5H-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromene-2-ones, 55, were synthesized and evaluated for anticonvulsant activity and neurotoxicity. 3-(4-Acetyl-5-methyl-5-p-nitrophenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one, 55a (Fig-62), was found to be potent activity at lower dose of 30 mg/kg in MES-test and shown less toxicity as compared with the standard drug phenytoin (Bhat et al., 2008).

![Fig-61: 3-(4-Acetyl-5-methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H chromene-2-ones](image)

A new series of 2-substituted-5-{2-[(2-halobenzyl)thio]phenyl}-1,3,4-oxadiazoles, 56, was designed, synthesized and investigated for anticonvulsant activities. The designed compounds contain the essential pharmacophore for binding to the benzodiazepine receptors. Conformational analysis and superimposition of energy minima conformers of designed molecules on estazolam, a known benzodiazepine receptor agonist, revealed that the main characteristics of the proposed benzodiazepine pharmacophore were well matched. Electroshock and pentylenetetrazole-induced lethal convulsion tests showed 5-{2-[(2-fluorobenzyl)thio]phenyl}-1,3,4-oxadiazol-2-amine, 56a, had significant

---

*Faculty of Pharmaceutical Sciences, M.M. University, Mullana, Ambala, Haryana (India)*
anticonvulsant activity. The structure-activity relationship study of these compounds indicated that the introduction of an amino group at position 2 of 1,3,4-oxadiazole ring and a fluoro substituent at the ortho position of the benzylthio moiety had the best anticonvulsant activity in both PTZ and MES models (Fig-63 and Fig-64) (Zarghi et al., 2008).

Fig-62: 3-(4-Acetyl-5H-5-p-nitro phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2Hchromene-2-ones

Fig-63: 2-Substituted-5-[2-[(2-halobenzyl)thio]phenyl]1,3,4-oxadiazoles

Fig-64: 5-{2-[(2-Fluorobenzyl)thio]phenyl}-1,3,4-oxadiazol-2-amine
Anticonvulsant effect of active compound was antagonized by flumazenil, a benzodiazepine antagonist, which establishes the involvement of benzodiazepine receptors in these effects.

The anticonvulsant activity revealed that the 5-methyl-3-[p-(6′-tolyl-2′-thioxo-1′,2′,5′,6′-tetrahydropyrimidin-4′-yl)-phenyl]-3H-2-oxo-Δ4-1,3,4-oxadiazole 10c and 5-methyl-3-[p-(6′-chlorophenyl-2′-thioxo-1′,2′,5′,6′-tetrahydropyrimidin-4′-yl)-phenyl]-3H-2-oxo-Δ4-1,3,4-oxadiazole, 10d, were found to possess promising anticonvulsant activity, compared to that of standard phenytoin (Kamble and Sudha, 2006).

2.1.6. Anthelmintic activity

A novel series of 1-[(5-substituted-1,3,4-oxadiazol-2-yl)-methyl]-4-propylpiperazines were synthesized and evaluated for anthelmintic activity. Amongst all, the 2-furyl derivative was found to be more potent against earth worms *Eudrilus* species, *M. konkanensis* and *P. corethruses* at a dose of 2mg/ml (Fig-65) (Srinivas and Kumar, 2010). The 2-furyl, 57g, 3-pyridyl, 57f, p-methyl phenoxy, 57h derivatives were found to be more potent against earth worms *Eudrilus* species, *M. konkanensis*, *P. corethruses* at a dose of 2mg/ml.

![Fig-65: 1-[(5-substituted-1,3,4-oxadiazol-2-yl)-methyl]-4-propylpiperazines](image)
2.1.7. Herbicidal activity

Compounds containing 1,3,4-oxadiazole 58 and bis(1,3,4-oxadiazole) derivatives, 59 exhibited no herbicidal activity in the pre-emergence response and low activity (<10%) in the post-emergence response screening when applied to the following species: Soybean (Glycine max), Corn (Zea mays), wheat (T. aestivum), morning glory (Ipomea spp.), velvet leaf (A. theophrasti), barnyard grass (Echinochloa crus-gali), and foxtail green (S. veridis) (Fig-66) (Shaban et al., 1991). The Compound 58, 58a, 59 and 59a showed significant herbicidal activity.

Fig-66: 1,3,4-Oxadiazole derivatives

Oxadazon, 3-[2,4-dichloro-5-(1-methylethoxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one, 60 is a member of the oxadiazole group of herbicide. The herbicide is an inhibitor of protoporphyrinogen oxidase. For weed resistance management, the product is a Group G Herbicide. Some naturally occurring weed biotypes resistant to the herbicide may exist through normal genetic variability in weed population (Fig-67) (Yasuyuki et al., 1994).

The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds will not be controlled by this
product or other oxadiazole group herbicides. Since the occurrence of resistant weeds is difficult to detect prior to use.

![Chemical structure of Oxadiargyl](image)

**Fig-67: 3-[2,4-Dichloro-5-(1-methylethoxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one**

Oxadiargyl (TOPSTAR 80 WP), 3-[2,4-dichloro-5-(2-propynloxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one, **61** is a broad spectrum weed control, similar to oxidiazinon and its potential use on rice, sugarcane, vegetables and tree crops (international registrations approved) (Fig-68) (European Commission Health, 2002).

![Chemical structure of 3-[2,4-Dichloro-5-(2-propynloxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one](image)

**Fig-68: 3-[2,4-Dichloro-5-(2-propynloxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one**

![Chemical structures of 2-Fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadiazoles](image)

**Fig-69: 2-Fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadiazoles**
1,3,4-Oxadiazole is among very few pharmacophore known for its insecticidal activity. A novel series 2-fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadiazoles, 62, 63 and 64 were evaluated for their insecticidal potential (Fig-69) (Shi et al., 2000).

2.1.8. Antimycobacterial activity

Tuberculosis is a serious health problem that causes the death of approximately 2-3 three millions of people every year worldwide. In addition to this, the increase in *M. tuberculosis* strains resistant to front-line antimycobacterial drugs such as rifampin and INH has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of tuberculosis. The World Health Organization estimates that 300,000 cases of multi-drug resistant TB emerge each year, enhanced by the parallel spread of HIV, which weakens the immune system and encourages other diseases. However, powerful new anti-TB drugs with new mechanisms of action have not been developed in the last thirty years. A literature survey also reveals that several 1,3,4-oxadiazole derivatives possess antimycobacterial activity against *M. tuberculosis* H37Rv (Kumar et al., 2007; Konstantinos, 2010)

A series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives, 65, were synthesized and tested for their *in-vitro* antimycobacterial activity. Some compounds showed interesting activity against a strain of *M. tuberculosis* H37Rv. The result of the antimycobacterial activity tests revealed that 2-(2-naphthyloxyethyl)-5-phenoxyethyl-1,3,4-oxadiazole, 65 exhibited > 90% inhibition at MIC ~6.25 using the BACTEC-460 radiometric system. The oxadiazole derivatives having a β-naphthyloxy methyl group at the C-2 position and a phenoxy methyl group at the C-5 position enhances the anti-tubercular activity (Fig-70) (Yar et al., 2007).
Another series of 1,3,4-oxadiazole derivatives, 5-(2-hydroxyphenyl)-2-substituted phenyl-1,3,4-oxadiazole, 66 were evaluated for their \textit{in vitro} antimycobacterial activity. Compounds having substitution with phenyl and 2-hydroxy phenyl system were shown promising antitubercular activity and moderate antitubercular activity respectively (Fig-71) (Pattan \textit{et al.}, 2009).

\textbf{Fig.71: 5 - (2-Hydroxyphenyl)-2-substituted phenyl-1,3,4-oxadiazole}

5-[3'-Oxo-6'-(substitutedphenyl)-2',3',4',5'-tetrahydropyridazin-2'-yl]methyl-2-substituted-1,3,4-oxadiazoles, 67, were synthesized and evaluated for antitubercular activity using the BACTEC 460. All the synthesized compounds screened at 6.25 \mu g/mL showed the percentage inhibition ranging from 48 to 91% (Fig-72).

5-(3'-oxo-6'-phenyl-2',3',4',5'-tetrahydropyridazin-2'-ylmethyl)-2-phenylamino-1,3,4-oxadiazole, 67a, was highly active analogue in this series with 91% inhibition against \textit{M. tuberculosis} H37Rv comparable with that of standard rifampicin and isoniazid (Fig-73) (Siddiqui \textit{et al.}, 2010).

A novel series of 5-substituted-2-thiol-1,3,4-oxadiazoles, 68, have been synthesized. Compounds were screened for antitubercular activity against \textit{M. tuberculosis}.
*tuberculosis* H37Rv strain by broth dilution assay method. Some compounds showed very good antitubercular activities (Fig-74).

![Figure 72](image1)

**Fig-72:** 5-[3'-Oxo-6'-(substituted phenyl)-2',3',4',5'-tetrahydropyridazin-2'-yl]methyl-2-substituted 1,3,4-oxadiazoles

![Figure 73](image2)

**Fig-73:** 5-(3'-Oxo-6'-phenyl 2',3',4',5'-tetrahydropyridazin-2'-ylmethyl)-2-phenylamino-1,3,4-oxadiazole

![Figure 74](image3)

**Fig-74:** 5-Substituted-2-thiol-1,3,4-oxadiazoles

### 2.1.9. Antioxidant activity

1,3,4-oxadiazole nucleus are known to exhibit potential antioxidant activity. The search for antioxidant drugs led to the discovery of several 1,3,4-oxadiazol derivatives having antioxidant activity.

A series of some 5-pyridyl-2-[(N-substituted phenyl)thioacetamido]-1,3,4-oxadiazoles, 37 were synthesized by both conventional and microwave method *in...*
vitro antioxidant activity by 1,1-diphenyl-2,2-picryl hydrazyl free radical (DPPH) method. The compound possessing a 2-chloro substitution on the phenyl ring) has inhibited the DPPH radical at a lower concentration and was found to be a comparatively better than other compounds of the series (Fig-40) (Rajasekaran et al., 2010).

A novel series of 3-acetyl-2-(substituted phenyl)-5-(4-methylcoumarinyl-7-oxymethyl)-2,3-dihydro 1,3,4-oxadiazoles, 69, were prepared and evaluated for antioxidant activity. The derivatives bearing H, CH₃ group showed more than 50% antioxidant activity by the diphenylpicrylhydrazyl (DPPH) assay method. Ascorbic acid was used as the reference compound (Fig-75) (Parameswaran et al., 2009).

![Figure 75](image)

Fig-75: 3-Acetyl-2-(substituted phenyl)-5-(4-methylcoumarinyl-7-oxymethyl)-2,3-dihydro 1,3,4-oxadiazoles

A novel series of 2-((4’-Phenyl-1’H-pyrazol-3’-ylsulfonyl)methyl)-5-substituted phenyl-1,3,4-oxadiazole, 70, derivatives were synthesized and tested for antioxidant property by nitric oxide and 1,1 diphenylpicrylhydrazyl (DPPH) methods.

![Figure 76](image)

Fig-76: 2-((4'-Phenyl-1'H-pyrazol-3'-ylsulfonyl)methyl)-5-substituted phenyl-1,3,4-oxadiazole
The compounds with phenyl and \(p\)-chlorophenyl groups exhibited high antioxidant activity in both nitric oxide and DPPH methods at 100\(\mu\)M concentration (Fig-76) (Venkatapuram et al., 2009).

A series of pyridyl 1,3,4-oxadiazole, 71, derivatives were synthesized by reaction of nicotinoyl chloride with various aromatic aldehydes and further subjected to acetylation. Synthesized compounds were screened for *in-vitro* antioxidant assay and possessed significant activity. Among all the synthesized compounds 1-(2-(4-methoxyphenyl)-5-(pyridine-3-yl)-1,3,4-oxadiazole-3(2H)-yl) ethanone 71e and 1-(2-(4-hydroxy-3-methoxyphenyl)-5-(pyridine-3-yl)-1,3,4-oxadiazole-3(2H)-yl) ethanone, 71h, were found to be potent antioxidant (Fig-77) (Aanandhi et al., 2010).

![Pyridyl 1,3,4-oxadiazole derivatives](image)

**Fig-77: Pyridyl 1,3,4-oxadiazole derivatives**

<table>
<thead>
<tr>
<th></th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>(R_3)</th>
<th>(R_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>(\text{N} (\text{CH}_3))</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>NO(_2)</td>
<td>H</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>OCH(_3)</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>NO(_2)</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>H</td>
<td>NO(_2)</td>
<td>H</td>
</tr>
<tr>
<td>h</td>
<td>H</td>
<td>OH</td>
<td>NO(_2)</td>
<td>H</td>
</tr>
<tr>
<td>i</td>
<td>CH(_3)</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>j</td>
<td>OCH(_3)</td>
<td>OCH(_3)</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

### 2.1.10. Antiviral activity

HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Current treatment regimens are based on the use of two or more drugs that belong to group of inhibitors termed as highly active antiretroviral therapy (HAART).

A new 5-[(naphthalen-5-yloxy)methyl]-1,3,4-oxadiazole, 72 derivatives were synthesized and evaluated for antiviral activity. 2-[[5-[(Naphthalen-5-yloxy)methyl]-1,3,4-oxadiazol-2-ylthio]acetohydrazones were synthesized by the reaction of the
hydrazide with the corresponding monosaccharides. Cyclization of the sugar hydrazones with acetic anhydride afforded the substituted oxadiazoline derivatives. The synthesized compounds were evaluated for their antiviral activity against, the human immunodeficiency virus (HIV-1). Compound 72 showed good antiviral activity (Fig-78) (El-Saysda et al., 2009).

Fig-78: 5-[(Naphthalen-5-yloxy)methyl]-1,3,4-oxadiazole

2.1.11. Hypoglycemic activity

Hyperglycemia or high blood sugar is a condition in which an excessive amount of glucose circulates in the blood plasma. This is generally a glucose level higher than (200 mg/dl. A subject with a consistent range between 100 and 126 (American Diabetes Association guidelines) is considered as hyperglycemic. Chronic levels exceeding (125 mg/dl) can produce organ damage (Giugliano et al., 1997).

2-Phenylamino-5-(2-naphthyloxymethyl)-1,3,4-oxadiazole derivative, 73, has exhibited considerable oral hypoglycemic activity (Fig-79) (Husain et al., 1986).

Fig-79: 2-Phenylamino-5-(2-naphthyloxymethyl)-1,3,4-oxadiazole

2.1.12. Enzyme inhibition activity

An enzyme inhibitor is a molecule which binds to enzymes and decreases their activity. Since blocking an enzyme's activity can kill a pathogen or correct...
a metabolic imbalance. A large number of drugs are available which are used as enzyme inhibitors. They are also used as herbicides and pesticides. Not all molecules that bind to enzymes are inhibitors; enzyme activators bind to enzymes and increase their enzymatic activity, while enzyme substrates bind and are converted to products in the normal catalytic cycle of the enzyme (Shapiro and Vallee, 1991). The monoamine oxidase, pyruvate oxidase and succinate dehydrogenase inhibitory properties were reported in some 3-arylaminoethyl-5-(2-hydroxy-3,5-dibromophenyl)-1,3,4-oxadiazole-2-thiones, 74. (Fig-80) (Soni et al., 1982). The monoamine oxidase inhibitory property were studies in some 5-aryl-3-(2-cyanoalkyl)-1,3,4-oxadiazol-2(3H)-ones, 75 and 5-aryl-3-(2-cyanoethyl)-1,3,4-oxadiazol-2(3H)-thiones, 76 (Fig-81 and Fig-82) (Mazouz et al., 1990; Mazouz et al., 1993).

A series of 5-aryl-2-alkyl-1,3,4-oxadiazoles, 77, were showed good monoamine oxidase inhibitory activity (Fig-83) (Harfenist et al., 1996).
2.1.13. Antiallergic activity

An allergy is a hypersensitivity disorder of the immune system. Allergic reactions occur when a person’s immune system reacts to normally harmless substances in the environment. A substance that causes a reaction is called an allergen. These reactions are acquired, predictable and rapid. Allergy is one of four forms of hypersensitivity and is formally called type-1 (or immediate) hypersensitivity. Allergic reactions are distinctive because of excessive activation of certain white blood cells called mast cells and basophils by immunoglobulin E. This reaction results in an inflammatory response which can range from uncomfortable to dangerous (Kay, 2000).

The in-vitro serotonin-3-antagonist activities were found positive in some new 1,3,4-oxadiazole-2-thione, 78, derivatives (Fig-84) (Pramanik and Mukherjee, 1998).

![Fig-84: 1,3,4-Oxadiazole-2-thione derivatives](image)

The H2-antagonistic activity of N, N'-1,3,4-oxadiazole-2, 5-diamines, 79, has been reported (Fig-85) (Kramer and Schunack, 1986).

![Fig-85: N, N'-1,3,4-Oxadiazole-2, 5-diamines](image)

2.1.14. Antidiarrheal activity

Diarrhoea is the condition of having three or more loose or liquid bowel movements per day. It is a common cause of death in developing countries and the
second most common cause of infant deaths worldwide. The loss of fluids through
diarrhoea can cause dehydration and electrolyte disturbances such as potassium
deficiency or other salt imbalances (Adelstein et al., 1976). A novel series 1-[3,3-
diphenyl-3-(2-alkyl-1,3,4-oxadiazol-5-yl)propyl] cycloalkylamines, 80, were found
to possess antidiarrheal activity (Fig-86).

![Fig-86: 1-[3,3-Diphenyl-3-(2-alkyl-1,3,4-oxadiazol-5-yl)propyl]cycloalkylamines](image)

2.1.15. CNS depressant activity

Central nervous system (CNS) depressants are the drugs that can be used to
slow down brain activity. Most CNS depressants activate a neurotransmitter called
gamma-aminobutyric acid (GABA), which helps in decreasing brain activity.

A series of new 2,5-disubstituted-1,3,4-oxadiazoles, 81 and 82, carrying 1,2-
diarylethyl/aryloxyalkyl moieties at 2-position and phenyl, amino, mercapto,
thioacetic acid or ethyl thioacetate groups at 5 position exhibited CNS depressant
activity in experimental animals (Fig-87) (Ramalingam et al., 1981).

![Fig-87: 2,5-Disubstituted-1,3,4-oxadiazoles](image)
The antidepressant property has also been reported in indolmethyl-1,3,4-oxadiazoles, 83 (Fig-88) (Misra et al., 1996).

![Fig-88: Indolmethyl-1,3,4-oxadiazoles](image)

### 2.2. SYNTHETIC PATHWAYS FOR SUBSTITUTED 1,3,4-OXADIAZOLES

The synthesis of heterocyclic compounds involves multi-structure in a molecule. The cyclization or ring formation occurs by means of condensation reaction. There are two free positions for the substitution in the oxadiazole heterocyclic ring system.

5-Substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles were prepared by both microwave-assisted and conventional method of synthesis. The starting material 2-methyl-4-nitro-imidazole 84, employed in the preparation of hydrazide 86, was obtained commercially. The 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles 87 were prepared by the microwave irradiation of 2-methyl-4-nitro-1-imidazo acetohydrazide, 86, with appropriate carboxylic acids in the presence of phosphorous oxychloride (Fig-89) (Frank et al., 2007). Similarly, the reaction was also carried out by the conventional method by refluxing an intimate mixture of hydrazide 86 with an appropriate carboxylic acid in phosphorous oxychloride in an oil bath.

Reactions of 4-substituted benzoic acid derivatives 88 with (N-isocyanimino)triphenylphosphorane, 89, proceed smoothly at room temperature to lead to the corresponding 2-aryl-1,3,4-oxadiazoles via an intramolecular aza-Wittig reaction. Several synthetic methods have been reported for the preparation of (N-
isocyanimino)triphenylphosphorane, 89. There are several reports for the use of (N-isocyanimino)triphenylphosphorane, 89 in the synthesis of metal complexes. 2-Aryl-1,3,4-oxadiazole derivatives 92 were prepared from 4-substituted benzoic acid derivatives 88 and (N-isocyanimino)triphenylphosphorane, 89 in excellent yields under neutral conditions (Fig-90) (Ramazani and Souldozib, 2008).

Fig-89: Synthesis of 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles
A suspension of salicylic hydrazide/thiosalicylic acid 93 was prepared with toluene and acetic anhydride or with an acid chloride and an equimolar quantity of methanesulfonic acid.

Fig-90: Synthesis of 2-aryl-1,3,4-oxadiazoles
The suspension was refluxed at room temperature to give 1,3,4-oxadiazoles 95. Treatment of salicylic semicarbazides 94, which were readily obtainable by the reaction of 93 with isocyanates, under Appel’s dehydration condition (Ph₃P/CCl₄/Et₃N) smoothly afforded 1,3,4-oxadiazoles 95 via carbodiimide intermediates followed by intramolecular cyclization reaction and hydride shift (Fig-91) (Lee and Cho, 2001).

Some new 2-[5-(aryl)-[1,3,4]oxadiazole-2-ylsulfanyl]alkanoic acids 98 were synthesized from aromatic carboxylic acid hydrazides. Aromatic carboxylic acid hydrazides 96 on refluxing with carbon disulfide and methanolic potassium hydroxide followed by subsequent acidification with hydrochloric acid gave rise to 5-aryl-1,3,4-oxadiazole-2-thiones 97. Further 2-chloro alkanoic acids react with 5-aryl-1,3,4-oxadiazole-2-thiones 97 in alkaline media and on acidification yield the title compounds 98 (Fig-92) (Melo et al., 1989).

![Fig-92: Synthetic pathway of 2-[5-(aryl)-[1,3,4]oxadiazole-2-ylsulfanyl]alkanoic acids](image)

Microwave radiation can be used as alternative method for conventional heating. The use of microwave irradiation has introduced several new concepts in chemistry, as the absorption and transmission of the energy is completely different from the conventional mode of heating.

![Fig-93: Microwave-assisted synthesis of 2,5-disubstituted-1,3,4-oxadiazoles](image)
A number of commercially available hydrazides 99 were treated with different carboxylic acids 100 in the presence of phosphorous oxychloride to afford 2,5-disubstituted-1,3,4-oxadiazoles 101 (Fig-93) (Khan et al., 2004).

Substituted benzoic acids were used for the synthesis of different monomers of 2,5-disubstituted 1,3,4-oxadiazoles. The various substituted benzoic acids 102 were esterified by using ethanol, concentrated H$_2$SO$_4$ and refluxed for 4 hours. These synthesized esters were converted to corresponding hydrazides 104 using hydrazine hydrate and ethanol by refluxing for 4 hours. These hydrazides were cyclized with substituted benzoic acids in the presence of phosphorus oxychloride and toluene by refluxing for 8 hour to get the monomeric units containing oxadiazole nucleus 105. The dimeric 1,3,4-oxadiazoles 105a were prepared from monomeric 1,3,4-oxadiazoles 105 in presence of dichloromethane and DMF by refluxing for 4 hours (Fig-94) (Joyashis et al., 2010).

1-(1,3-Dioxo-1,3-dihydro-2H-isouindol-2-yl)urea 107 was synthesized by reacting phthalic anhydride 106 with semicarbazide. Further it treated with hydrazine hydrate in presence of NaOH under reflux to form N-(1,3-dioxo-1,3-dihydro-2H-
isoindol-2-yl)hydrazinecarboxamide 108. The compound 108 was treated with cyanogen bromide to form cyclized product 2-[(5-amino-1,3,4-oxadiazol-2-yl)amino]-1H isoindole-1,3(2H)-dione 109. The final product 110 was obtained by treating 110 with phenylisothiocyanate (Fig-95) (Bhat et al., 2010).

Treatment of 111 with carbon disulfide and various hydrazides in the presence of sodium hydride (NaH) at room temperature leads to production of corresponding acylthiocarbazate resins 111a. The desired products 113 and 114 are cleaved from the resins 111a by sequential treatment with 3-chloroperbenzoic acid and NaOH in aqueous dioxane (producing the sulfone) and piperidine in 1,4-dioxane at 100 °C (Fig-96) (Hwang et al., 2005).

Six novel 2,5-bis[4-(2-arylvinyl)phenyl]-1,3,4-oxadiazole derivatives 119 were synthesized by introducing 1,3,4-oxadiazole moiety into the stilbene skeleton. This synthetic route included the condensation of toluic acid 115 and hydrazine hydrate in presence of polyphosphoric acid to form 1,3-dibromo-5,5-dimethylhydantoin 116, which further undergo bromination, esterification, and the Wittig-Horner reaction to get the final compounds 119 (Fig-97) (He et al., 2009).
Fig-96: Synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives

2-Oxo-4-aryl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester derivatives 123 were prepared from urea, ethylacetoacetate and aromatic aldehyde in presence of ethanol. In the next step, 2-oxo-4-aryl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid hydrazides 124 were prepared from 123 in presence of hydrazine hydrate and ethanol. 5-(5-Amino-[1,3,4]oxadiazol-2-yl)-4-aryl-3,4-dihydro-1H-pyrimidin-2-one derivatives 125 were prepared by stirring of 125 in absolute ethanol, an aqueous solution of sodium bicarbonate and cyanogen bromide.

Fig-97: Synthesis of 2,5-bis[4-(2-arylviny1)phenyl]-1,3,4-oxadiazoles

Final derivatives of the series, 3-[5-(2-oxo-4-aryl-1,2,3,4-tetrahydro-pyrimidin-5-yl)-[1,3,4]oxadiazol-2-ylimino]-1,3,3a,7a-tetrahydro-indol-2-one 126
were prepared by refluxing 125 with isatin in presence of acetic acid and methanol (Fig-98) (Muthumani et al., 2009).

![Chemical structure of 1,3,4-oxadiazoles and their reaction](image)

Fig-98: Synthesis of 1,3,4-oxadiazoles

Reaction of acetone and cycloalkylbenzoylhydrazones, 127, with phenyl isocyanate, 128, was carried out in chloroform under dry conditions at room temperature to synthesize corresponding 1,3,4-oxadiazole derivative 129 (Fig-99) (Ferwanah, 2005).

![Chemical structure of substituted-2,3-dihydro-1,3,4-oxadiazoles](image)

Fig-99: Synthesis of substituted-2,3-dihydro-1,3,4-oxadiazoles

A novel series of 2-(β-hydroxyalkyl)-1,3,4-oxadiazole derivatives 132 were synthesized in presence of samarium(II) iodide (Kagan reagent). Herein we describe a novel Barbier-type reaction of 2-chloromethyl-1,3,4-oxadiazole with carbonyl compounds promoted by SmI₂. The derivative 132 was prepared by reacting substrate 130 with carbonyl compound 131 in presence of THF containing samarium (II) iodide at room temperature, under inert atmosphere (Fig-100) (Xu et al., 2005).
Figure 100: Synthesis of substituted-1,3,4-oxadiazoles

Synthesis of 5-furan-2-yl[1,3,4]oxadiazole-2-thiol 135 was carried out by the ring closure reaction of furan-2-carboxylic acid hydrazide with carbon disulfide by refluxing in presence of alkaline medium followed by methyl iodide (Fig-101) (Koparir et al., 2005).

2-Amino-1,3,4-oxadiazole 137 was synthesized from 5-nitro-furan-2-carboxylic acid hydrazide 136 in presence of cyanogen bromide (Fig-102). Synthesis of a novel series of disubstituted 1,3,4-oxadiazole derivatives 142 by 4-component condensation of aromatic carboxylic acids 138, bis-aldehydes (isophthalaldehyde and terphthalaldehyde) 139, a secondary amine 140, and N-isocyaniminotriphenylphosphorane 141 in excellent yields under neutral conditions (Fig-103) (Ramazani et al., 2012).
Synthesis of 5-aryl-2-amino-1,3,4-oxadiazole compounds 145 in yields of 62 to 70%. These compounds were used as intermediates for the synthesis of new quinazolinone derivatives (Fig-104) (Patel et al., 2010).

Synthesis of 5-((naphthalen-2-yloxy)methyl)-N-phenyl-1,3,4-oxadiazol-2-amine, 147 in 62% yield, by heating compound 146 in ethanol in the presence of sodium hydroxide and iodine in potassium iodide (Fig-105) (El-Sayed et al., 2012).

A novel series of substituted 1,3,4-oxadiazoles, 149, have been prepared by cyclization reactions of acylthiosemicarbazide, 148, in the presence of 1,3-dibromo-
5,5-dimethylhydantoin, which is an effective oxidizing agent (Fig-106) (Rivera et al., 2006).

Another easy and efficient method to synthesize 5-substituted-2-styryl-1,3,4-oxadiazoles 152 from cinnamic acid hydrazide 150 and commercially available triethyl orthoesters 151.

The method provides the desired products rapidly and in high yields making it a useful addition to the existing synthetic procedures (Fig-107) (Kudelko and Zielinski, 2012).

A new series of 2,5-disubstituted-1,3,4-oxadiazoles, 155 have been synthesized by cyclodehydration of diacylhydrazine 153 using triphenylphosphine oxide and triflic anhydride (Fig-108) (Bostrom et al., 2012).

Another series of substituted oxadiazoles, 157 were prepared by Robinson-Gabriel type reaction of cyclopropane-carboxylic acid N'-substituted-hydrazides, 156 with PPh₃/CX₄ (X = Cl, Br, I) as dehydrating agents (Fig-109) (Yang and Shi, 2005).
A novel series of disubstituted oxadiazoles were synthesized through a one-pot reaction of benzohydrazide, and para substituted aromatic aldehydes in the presence of cerium ammonium nitrate (CAN) and dichloromethane solvent (Fig-110) (Dabiri et al., 2006).

Fig-110: Synthesis of 2,5-diaryl-1,3,4-oxadiazoles

R = H, NO₂, Cl, OCH₃, CH₃