



## SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF 1,3,4-OXADIAZOLE DERIVATIVES: A REVIEW

**Rajwant Kaur\* and Parminder Kaur**

University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Mohali.

**\*Corresponding Author: Rajwant Kaur**

University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Mohali.

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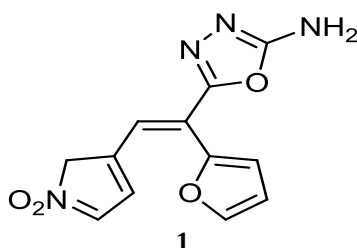
### ABSTRACT

Among different five member heterocyclic systems Pyrrole, Oxadiazole, Thiadiazole, Triazole and their derivatives have gained importance as they constitute the structural features of many bioactive compounds. Among them 1,3,4-oxadiazole are of significant interest in medicinal chemistry. 1,3,4-oxadiazole is a highly privileged structure and its derivatives exhibit a wide range of biological activities including antibacterial, anti-tubercular, vaso-dilatory, antifungal, cytotoxic, anti-inflammatory and analgesic, hypo-lipidemic, anti-cancer and ulcero-genic activities. Furamizole is a compound which is based upon 1,3,4-oxadiazole ring and has strong Antibacterial Activity.

**KEYWORDS:** 1,3,4-oxadiazole, 1,2,4-oxadiazole, Heterocyclic Chemistry, Pharmacological activities.

### INTRODUCTION

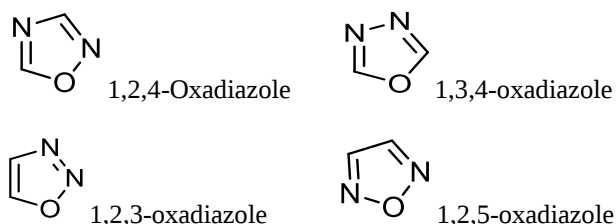
Heterocyclic compound contributes to the major percentage of privileged structures for the designing of new drugs is a very effective approach. Oxadiazole is a five member heterocyclic having two nitrogen, one oxygen and two double bonds. Oxadiazole moiety and its various derivatives studied frequently in the past few decades and found potent in various pharmacological and pathological conditions.<sup>[1]</sup> Among different five members heterocyclic systems pyrrole, oxadiazole, thiadiazole, triazole and their derivatives have gained importance as they constitute the structural features of many bioactive compounds. Among them 1,3,4-oxadiazoles are of significant interest in medicinal chemistry. Literature reveals that 1,3,4-oxadiazole is a highly privileged structure and its derivatives exhibit a wide range of biological activities including antibacterial, anti-tubercular, vasodilatory, antifungal, cytotoxic, anti-inflammatory and analgesic, hypolipidemic, anti-cancer and ulcerogenic activities. Furamizole is a compound which is based upon 1,3,4-oxadiazole ring and has strong antibacterial activity.<sup>[2]</sup>



Oxadiazole derivatives have been found to Posses broad spectrum antimicrobial activity and therefore are useful substructure for further molecular exploration.<sup>[3]</sup>

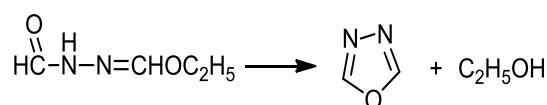
### Isomeres of oxadiazole

Oxadiazole exist in four isomeric forms depending on the position of nitrogen atom in the ring as shown below.<sup>[3]</sup>



### Chemistry of Oxadiazole

Ainsworth prepared 1,3,4-oxadiazole in 1965 by the thermo-lysis of ethyl formate formly hydrazine at atmospheric pressure.<sup>[4]</sup>



### Chemical Reactivity of 1,3,4-Oxadiazole

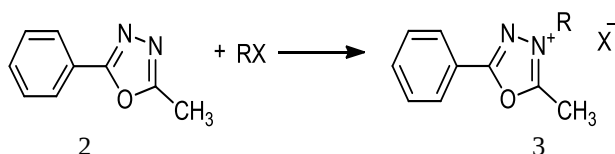
#### Electrophilic substitution reaction

Due to low electron density on the carbon atom, Electrophilic attack is favorable at 3<sup>rd</sup> position and results

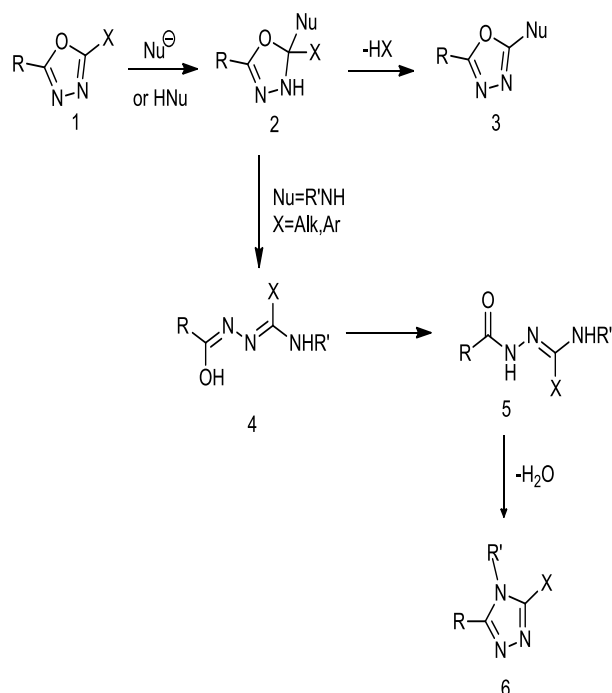
in the formation of 1,3,4-oxadiazolium salts as shown in figure 1.

### Nucleophilic substitution reaction

Nucleophilic attack at ring carbon is a major reaction mode of 1,3,4-oxadiazole. Such reaction lead to Nucleophilic products 3 or to the ring cleavage with the formation of intermediates 4 and 5, which, in case of Nucleophilies, frequently recycle into 1,2,4-triazole as shown in figure 2.<sup>[3]</sup>



**Figure 1: Electrophilic substitution reaction of 1,3,4-oxadiazole**

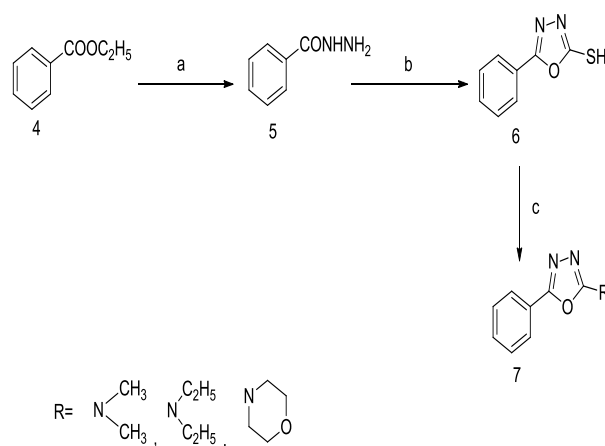


**Figure 2: Nucleophilic substitution reaction of 1,3,4-oxadiazole**

### Methods for the synthesis of 1,3,4-oxadiazole derivatives

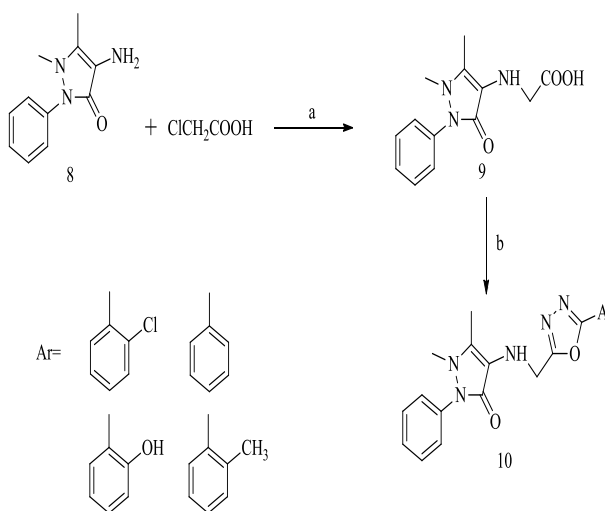
The most popular reported method for the synthesis 1,3,4-oxadiazole backbone is the reaction between the properly substituted acid hydrazide, carbon disulphide (CS<sub>2</sub>) and potassium hydroxide (KOH).

**Sahoo *et al* (2014)** reported synthesis, characterization and biological evaluation of novel oxadiazole derivatives. New 5-phenyl-1,3,4-oxadiazole-2-thiol derivative was synthesized by the ring closure reactions of benzohydrazides with carbon disulphide in presence of ethanolic KOH followed by substitution with secondary amines.<sup>[5]</sup>



**Reagents and conditions:** (a) Hydrazine hydrate, ethanol, stir, 5 h (b) CS<sub>2</sub>/KOH, ethanol, reflux (c) secondary amines, ethanol, 8 h

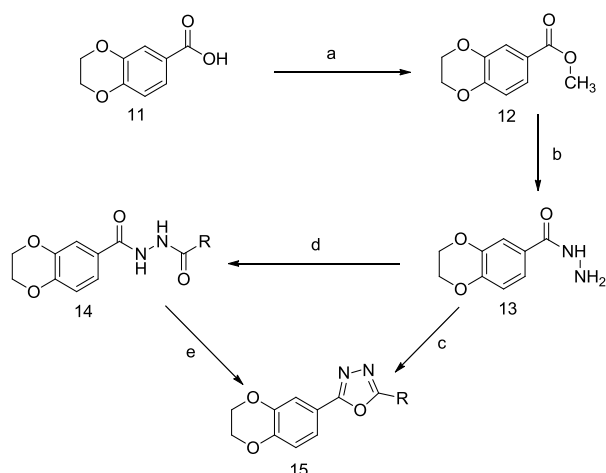
**Ahsan *et al* (2011)** predicted molecular properties and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and anti-tubercular agents. In the initial step 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one and chloroacetic acid in dry acetone and potassium carbonate refluxed for 8 h giving [(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) amino] acetic acid. In the subsequent step [(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) amino] acetic acid was treated with appropriate hydrazide in 5 ml phosphorus oxychloride to furnish the titled compound.<sup>[6]</sup>



**Reagents and conditions:** (a) Potassium carbonate, dry acetone, reflux, 8 h (b) semicarbazide, phosphorus oxychloride, reflux, 5 h.

**Sun *et al* (2011)** reported synthesis of oxadiazole derivatives containing 1,4-benzodioxan as potential immunosuppressive agents against RAW264.7 cells. Compound synthesized by refluxing 2,3-dihydrobenzo [b][1,4]dioxine-6-carboxylic acid in methanol containing concentrated H<sub>2</sub>SO<sub>4</sub>. Water was added, the organic

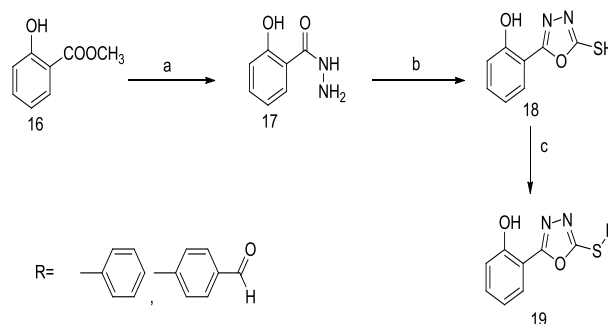
phases were washed with saturated NaCl and dried over  $\text{Na}_2\text{SO}_4$ , and the solvents were evaporated. In the subsequent step compound was dissolved in dry ethanol and hydrazine hydrate was added and the mixture was refluxed for 8-10 h to give compound. Then a stirred solution of in  $\text{CH}_2\text{Cl}_2$  was treated with the appropriate substituted phenyl acetic acid or benzoic acid, EDC.HCl, HOBt with substituted carboxylic acid in phosphoryl chloride or in phosphoryl chloride was refluxed for 5-7 h. Then reaction mixture was cooled, poured into ice-cold water and neutralized with 20%  $\text{NaHCO}_3$  solution. The resultant solid was filtered, washed with water and recrystallized from ethanol to give the title compound.<sup>[7]</sup>



Where R= phenyl, 2-chlorophenyl, 5-bromopyridin-3-yl, 4-nitrophenyl.

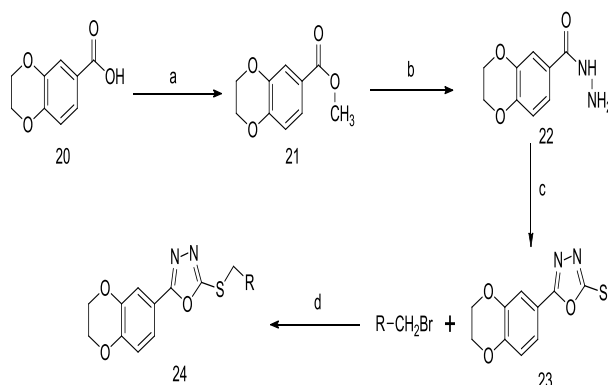
**Reagents and conditions:** (a) conc. sulphuric acid, methanol, reflux,  $90^\circ\text{C}$  (b) Hydrazine hydrate, Ethanol, Reflux,  $90^\circ\text{C}$  (c) Aliphatic or Aromatic carboxylic acids,  $\text{POCl}_3$ ,  $110^\circ\text{C}$  (d) EDC. HCl, HOBt, dichloromethane, Room Temperature (e)  $\text{POCl}_3$ ,  $100^\circ\text{C}$ .

**Parikh *et al* (2011)** reported synthesis of 1,3,4-oxadiazole derivatives by refluxing methyl salicylate with hydrazine hydrate for 16-17 h. The hydrazide so obtained can be further reacted with carbon disulphide and potassium hydroxide to yield. A mixture of 2-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-phenol and different aryl halides were refluxed in pyridine solution for 3.5 hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol to furnish the final compound.<sup>[8]</sup>



**Reagents and conditions:** (a) Hydrazine hydrate, Ethanol, Reflux, 16-17 h (b)  $\text{CS}_2/\text{KOH}$ , ethanol, reflux, 12-12.5 h (c) R-Cl, pyridine, reflux, 4-5 h.

**Zhang *et al* (2011)** reported synthesis, biological evaluation, and molecular docking studies of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan moiety as potential anticancer agents. To a stirred solution of and sodium hydroxide in Acetonitrile was added drop wise Acetonitrile containing halogen substituted compounds. The resulting mixture was heated under reflux for 10-24 h and the reaction was monitored by TLC. Afterwards the solution was cooled to room temperature and the organic solvent was removed in vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with saturated brine. Then the organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and removed in vacuum. The purification of the residue by recrystallization from Acetonitrile yielded the desired compound.<sup>[9]</sup>

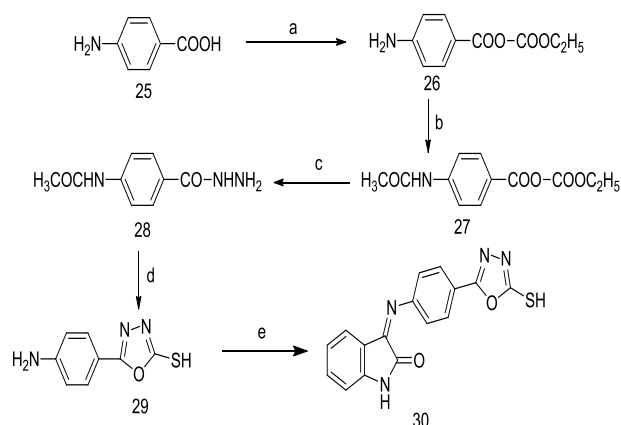


Where R phenyl, 4-fluorophenyl, 4-nitrophenyl, 4-chlorophenyl.

**Reagents and conditions:** (a) Concentrated sulfuric acid, methanol, reflux, 8-12 h (b) Hydrazine hydrate (85%), Ethanol, Reflux, 8-12 h (c)  $\text{CS}_2/\text{KOH}$ , ethanol (95%), reflux, 24 h (d) NaOH, acetonitrile, reflux, 8-24 h.

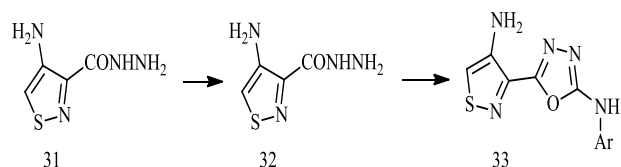
**Gudipati *et al* (2011)** reported synthesis, characterization and anti-cancer activity of certain 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives. Compound 29 and Isatin were refluxed in 20 ml of ethanol in the presence of a catalytic

amount of glacial acetic acid (2–3 drops) for 5–6 h and cooled. The solid separated was filtered and washed with cold alcohol and the product obtained was recrystallized from methanol to yield final compound 30. <sup>[10]</sup>



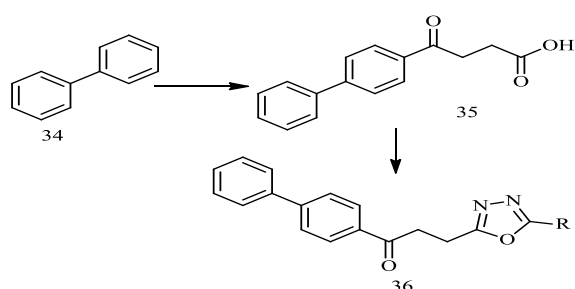
**Reagents and conditions:** (a) Dry acetone, Ethanol, reflux, 6 h (b) Ac<sub>2</sub>O, Reflux (c) Hydrazine Hydrate, Ethanol, Reflux, 8 h (d) CS<sub>2</sub>/KOH, Ethanol, Reflux, 12 h (e) Isatin, glacial acetic acid, ethanol, 5–6 h.

**Kiselyov *et al* (2010)** reported the synthesis of oxadiazole by refluxing isothiazole derivative with neat hydrazine hydrate for 4 h. The hydrazide so obtained can be further reacted with isothiocyanate followed by in situ cyclization of the intermediate thiosemicarbazide with DCC to afford the key molecules. The formation of 1,3,4-oxadiazole via condensation of various alkyl hydrazide with substituted acids using various cycloderhydrogenation agents are reported in literature. A few of them are mentioned below. <sup>[11]</sup>



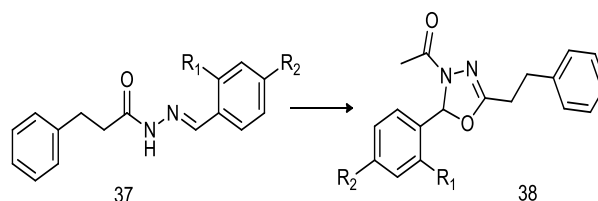
**Reagents and conditions:** (a) NHNH<sub>2</sub>, (b) Isothiocyanate (c) Thiosemicarbazide reflux, 4–6 h

**Husain *et al* (2010)** reported the synthesis of 1,3,4-oxadiazole by reacting 4-oxo-4-(biphenyl-4-yl) butanoic acid (Fenbufen) <sup>[12]</sup> with aryl acid hydrazide in phosphorous oxychloride.



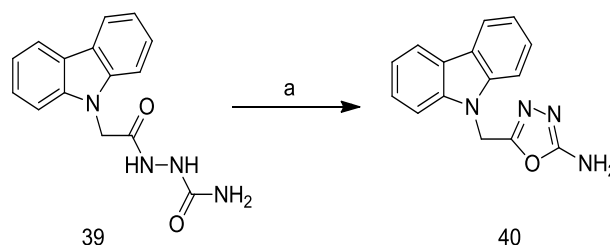
**Reagents and conditions** - (a) Succinic Acid, Anhy. AlCl<sub>3</sub> (b) POCl<sub>3</sub>, RCONHNH<sub>2</sub>

**Fuloria *et al* (2010)** reported the synthesis of 1-(2-ary1-5-phenethyl-1,3,4-oxadiazole-3(2H)-yl)-ethanones by reacting N-(substituted benzylidene)-3-phenyl propionohydrazides with acetic anhydride. <sup>[13]</sup>



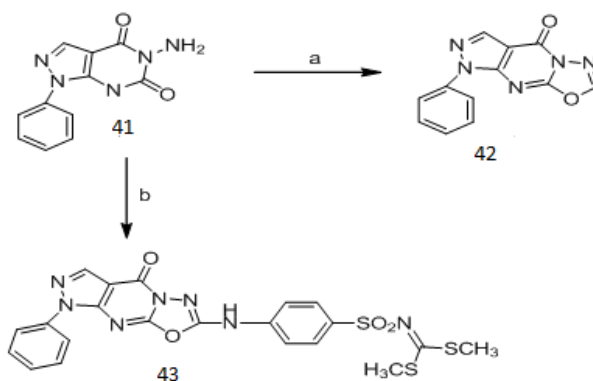
**Reagents and conditions-** (a) Acetic Anhydride

**Kaur *et al* (2012)** reported synthesis of 1,3,4-oxadiazoles by reacting semicarbazide with conc. H<sub>2</sub>SO<sub>4</sub> and then it is kept overnight and then pour it into the ice-cold water. Then it is neutralized with ammonia and extracted with ether. <sup>[14]</sup>



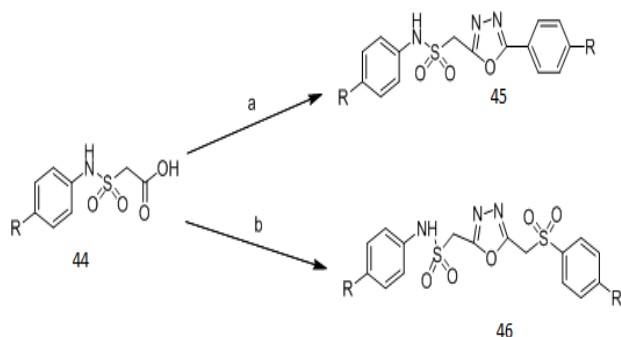
**Reagents and conditions:** (a) Conc. Sulphuric acid, Ammonia, kept overnight.

**Kumar *et al* (2010)** reported synthesis of 1,3,4-oxadiazolopyrazolopyrimidine 43 derivative via reaction of 5-amino derivative with methyl-4-(N-(bis (methylthio) methylene) sulfamoyl) phenyl carbamodithioate in dimethylformamide in presence of triethylamine and 1,3,4-oxadiazolopyrazolo pyrimidinone was obtained via reaction of 5-amino derivative with triethylorthoformate as one carbon cyclizing agent. <sup>[15]</sup>



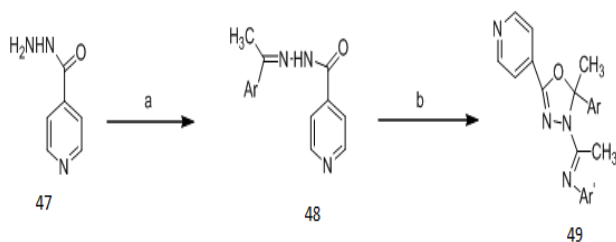
**Reagents and conditions:** (a) Triethylorthoformate, reflux, 8 h (b) Methyl 4-(*N*-(bis(methylthio)methylene)sulfamoyl)phenylcarbamodithioate, triethylamine, DMF, reflux, 5 h.

**Padmavathi *et al* (2009)** reported synthesis of aminosulfonyl-1,3,4-oxadiazoles by reacting an equimolar mixture of arylaminosulfonylacetic acid, aryl acid hydrazide and benzoic acid in POCl<sub>3</sub> and refluxed for 5-8 h.<sup>[16]</sup>



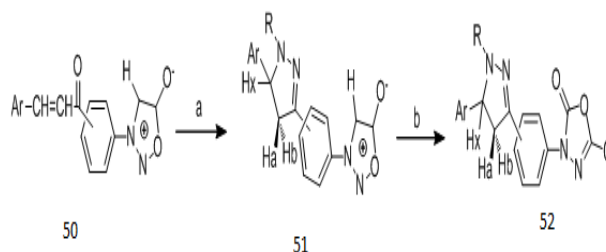
Where R=H, Me, Cl **Reagents and conditions:** (a) R-C<sub>6</sub>H<sub>4</sub>CONHNH<sub>2</sub>/POCl<sub>3</sub> (70-75%) (b) R-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>CH<sub>2</sub>CONHNH<sub>2</sub>/POCl<sub>3</sub>

**Shirote *et al* (2010)** reported synthesis of some 1,3,4-oxadiazoles. Isoniazid was reacted with appropriate acetophenones in methanol with drop of glacial acetic acid and the resulting compound was then treated with acetic anhydride to get the desired 1,3,4-oxadiazoles.<sup>[17]</sup>



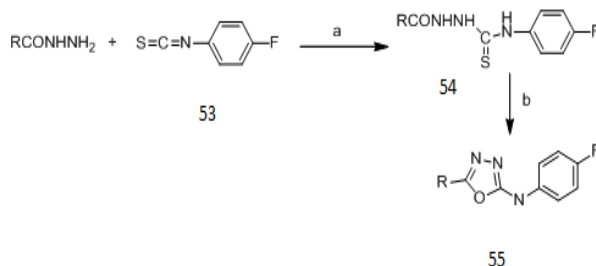
**Reagents and conditions:** (a) Acetophenones, methanol, reflux, 2 h (b) acetic anhydride, reflux, 2 h; aromatic amines, ethanol, 5-6 h.

**Kamble *et al* (2008)** reported the microwave assisted synthesis of 1,3,4-oxadiazole from Chalcones. This microwave assisted synthesis lead to the cleaner reactions as well as afforded high yields and shorter reaction times. The Chalcones underwent a rapid cyclization with hydrazine hydrate using Polyethylene glycol (PEG 200) and formic acid as solvents. Further on bromination and heating with acetic anhydride it resulted in the formation of oxadiazole derivatives.<sup>[18]</sup>



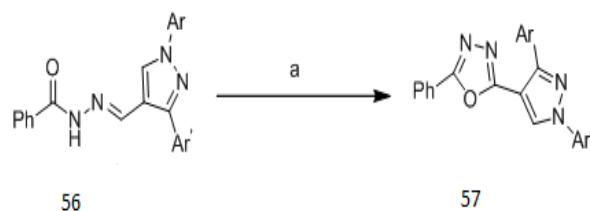
**Reagents and conditions:** (a) Hydrazine, ethanol, reflux, 5-6 h (b) Br<sub>2</sub>/Ac<sub>2</sub>O, RT, MWI

**Barbuceanu *et al* (2010)** reported synthesis of oxadiazole by reacting N<sup>1</sup>-[4-(4-bromophenylsulfonyl)benzoyl]-N<sup>4</sup>-(4-fluorophenyl)-thiosemicarbazide with (a) Mercuric Oxide (HgO) in ethanol (b) I<sub>2</sub>/KI in NaOH solution.<sup>[19]</sup>



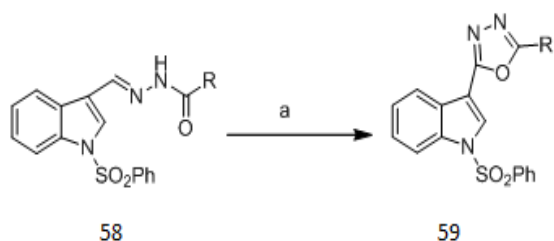
**Reagents and conditions:** (a) Ethanol, reflux, 10 h (b) thiosemicarbazide, yellow mercuric oxide, ethanol, reflux, 8 h.

**Prakash *et al* (2010)** reported synthesis of a series of novel 2,5-disubstituted 1,3,4-oxadiazole by oxidative cyclization of pyrazolylaldehyde *N*-acyl hydrazones promoted by iodobenzene diacetate under mild conditions.<sup>[20]</sup>



**Reagents and conditions:** (a) PhI (OAc)<sub>2</sub>, dichloromethane, stir, RT

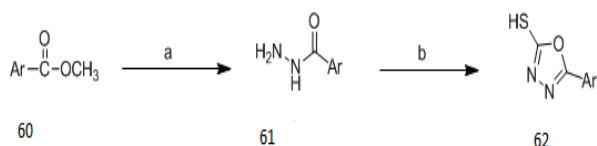
**Kumar *et al* (2008)** reported synthesis of novel indolyl-1,3,4-oxadiazoles by a neat grinding of indolyl-3-aldehyde-*N*-acyl hydrazone with BTI for 10 min at room temperature.<sup>[54]</sup>



Where R=C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 4-pyridyl, 3-pyridyl

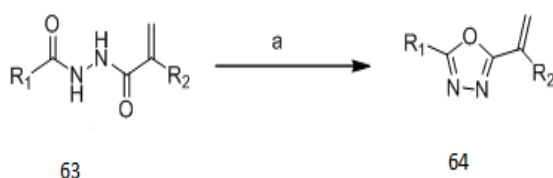
**Reagents and conditions:** (a) CH<sub>3</sub>I, KOH, DMSO, stirring, RT.

**Saitoh *et al* (2009)** reported synthesis of 1,3,4-oxadiazoles by the treatment of aryl acetate with hydrazine hydrate which results in the formation of hydrazide and then treated with carbon disulphide and potassium hydroxide or Et<sub>3</sub>N to yield oxadiazolethiols.<sup>[22]</sup>



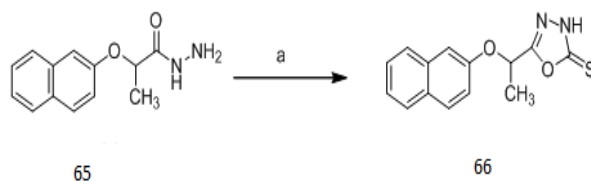
**Reagents and conditions:** (a) Hydrazine hydrate, methanol, reflux, 6 h (b) CS<sub>2</sub>/KOH, ethanol (95%), reflux, 8 h.

**Milinkevich *et al* (2009)** reported synthesis of 1,3,4-oxadiazole exomethylene by diacyl hydrazide as a starting material. Due to the presence of alkenes functionality in the hydrazide a dehydrating reagent was used.<sup>[23]</sup>



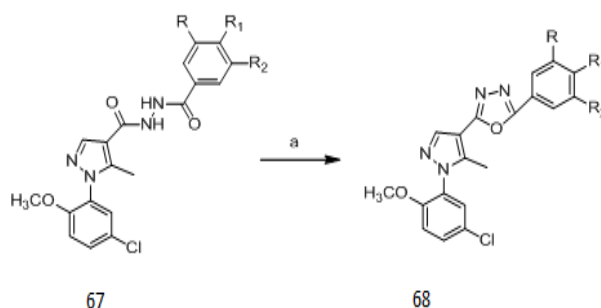
**Reagents and conditions:** (a) PPh<sub>3</sub>, Cl<sub>3</sub>CCl<sub>3</sub>, DIEA, CH<sub>3</sub>CN

**Idrees *et al* (2009)** reported synthesis of 5-[1-(naphthalen-2-yloxy) ethyl]-3H-1,3,4-oxadiazole-2-thione via cyclization of the hydrazide with carbon disulphide in refluxing ethanol.<sup>[24]</sup>



**Reagents and conditions:** (a) CS<sub>2</sub>/KOH, ethanol, reflux, 6 h.

**Rai *et al* (2009)** reported synthesis of 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substituted-phenyl)-[1,3,4]oxadiazoles by reacting substituted pyrazole-4-carbo hydrazide with POCl<sub>3</sub> at 120°C overnight.<sup>[25]</sup>

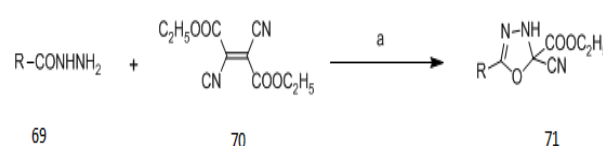


**Where 92a:** R = H, R<sub>1</sub> = Cl, R<sub>2</sub> = H

**92b:** R = H, R<sub>1</sub> = F, R<sub>2</sub> = H

**Reagents and conditions:** (a) POCl<sub>3</sub>, heat, 120<sup>0</sup>C

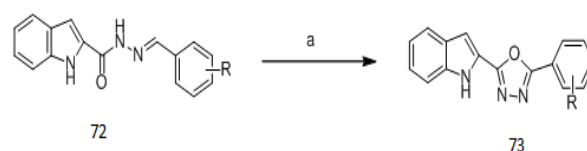
**Abdel-Aziz *et al* (2009)** reported synthesis of some 1,3,4-oxadiazoles by reacting 1-acylhydrazines with diethyl-2,3-dicyanofumarate in ethyl acetate and refluxed it for a required period of time.<sup>[26]</sup>



**Where R=C<sub>6</sub>H<sub>5</sub>, thiophene**

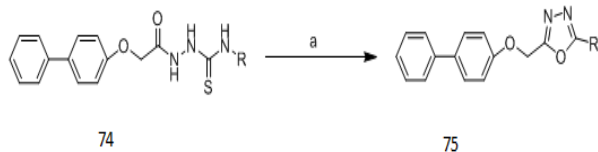
**Reagents and conditions:** (a) Ethyl acetate, heat, 4-18 h

**Bhardwaj *et al* (2009)** reported synthesis of some 1,3,4-oxadiazoles by reacting hydrazones with chloramines-T in ethanol and refluxed for 7 h. Chloramines-T was added as an oxidizing agent.<sup>[27]</sup>



**Reagents and conditions:** (a) chloramine-T

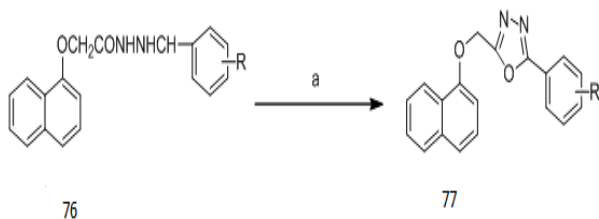
**Kumar *et al* (2009)** reported synthesis of 5-[(biphenyl-4-yloxy)-methyl]-2-alkyl/arylamino-1,3,4-oxadiazole by oxidatively cyclization of thiosemicarbazide and elimination of  $\text{H}_2\text{S}$  using iodine and potassium iodide in ethanolic sodium hydroxide.<sup>[28]</sup>



Where  $\text{R} = \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$

**Reagents and conditions:** (a)  $\text{C}_2\text{H}_5\text{OH}$ ,  $\text{KI/I}_2$ , 5N  $\text{NaOH}$ , reflux

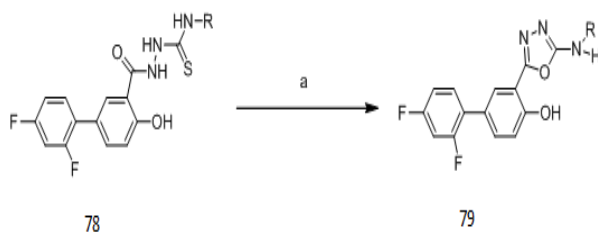
**Rajak *et al* (2007)** reported synthesis of naphthalenoxymethylene oxadiazole from a mixture of respective hydrazide, anhydrous sodium acetate and glacial acetic acid and bromine.<sup>[29]</sup>



Where  $\text{R} = 4\text{-Cl}$ ,  $4\text{-OH}$ ,  $4\text{-CH}_3\text{O}$ ,  $4\text{-NO}_2$

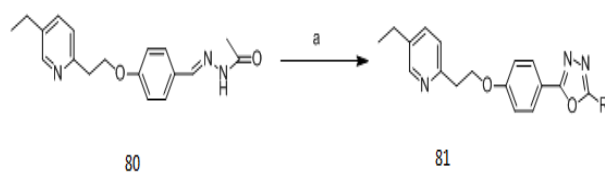
**Reagents and conditions:** (a)  $\text{CH}_3\text{COOH}$  /  $\text{Br}_2$ ,  $\text{CH}_3\text{COONa}$ , glacial acetic acid, stir, 1.5 h

**Kucukguzel *et al* (2006)** reported synthesis of 1,3,4-oxadiazole by reacting an appropriate thiosemicarbazide with ethyl bromoacetate in absolute ethanol in the presence of anhydrous sodium acetate.<sup>[30]</sup>



**Reagents and conditions:** (a)  $\text{Br-CH}_2\text{-COOC}_2\text{H}_5$ , anhyd.  $\text{CH}_3\text{COONa}$ , ethanol, reflux, 4-6 h

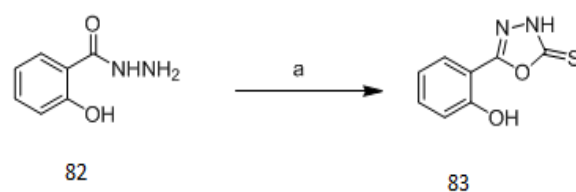
**Gaonkar *et al* (2006)** reported synthesis of a new series 2-{4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl}-5-substituted 1,3,4-oxadiazoles from aryl hydrazones and chloramine-T.  $3\text{H}_2\text{O}$  in ethanol.<sup>[31]</sup>



Where  $\text{R} = \text{phenyl}$ , 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 4-methoxyphenyl

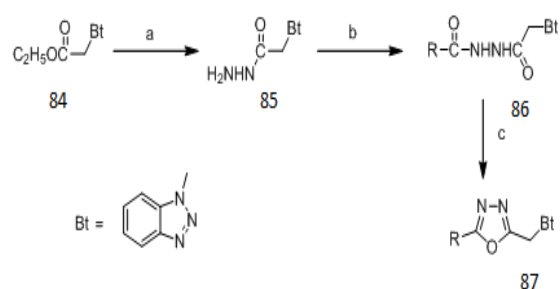
**Reagents and conditions:** (a) chloramine-T, ethanol, reflux, 3 h

**Aboraia *et al* (2006)** reported synthesis of 5-(2-hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione by reaction of salicylic acid hydrazide with  $\text{CS}_2$  in ethanol in the presence of  $\text{KOH}$ .<sup>[64]</sup>



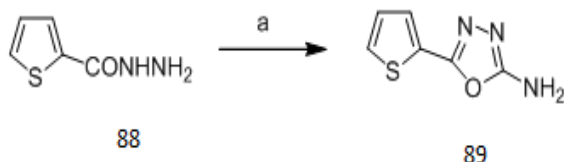
**Reagents and conditions:** (a)  $\text{CS}_2/\text{KOH}$ ,  $\text{HCl}$ , ethanol, reflux, 8 h

**Katritzky *et al* (2001)** reported synthesis of 1-(1,3,4-oxadiazol-2-yl methyl)-1H-benzotriazoles. Reaction of the ester with hydrazine resulted in the formation of hydrazides and then hydrazides are reacted with acyl chloride in pyridine and then finally reacted with phosphorous oxychloride.<sup>[32]</sup>



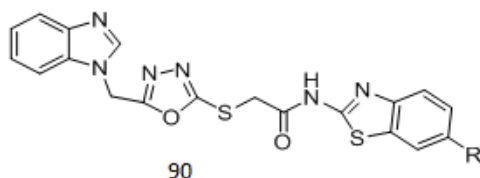
**Reagents and conditions:** (a) hydrazine hydrate, ethanol, stir, RT (b)  $\text{RCOCl}$ , pyridine, reflux, 4 h (c)  $\text{POCl}_3$ , reflux, 5-6 h.

**Elborai *et al* (1993)** reported synthesis of 2-amino-5-(2-thienyl)-1,3,4-oxadiazole by the condensation of 2-thienyl hydrazide with  $\text{CNBr}$ . It is a convenient method of synthesis of amino-1,3,4-oxadiazole because of shorter reaction time.<sup>[33]</sup>



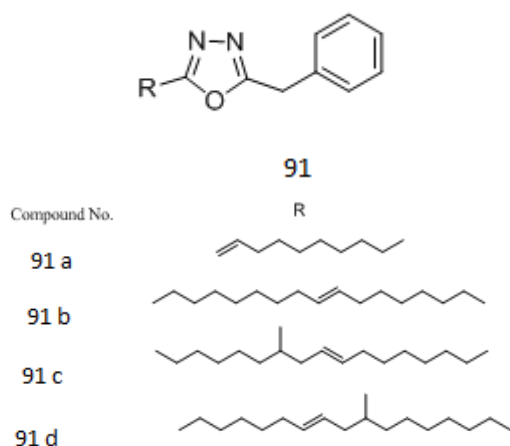
**Reagents and conditions:** (a) CNBr, CH<sub>3</sub>OH, reflux, 3-4 h

**Patel et al (2010)** reported synthesis of benzimidazolyl-1,3,4-oxadiazol-2-ylthio-*N*-phenyl (benzothiazolyl)acetamides as antibacterial, antifungal and anti-tuberculosis agents. 1,3,4-oxadiazoles were synthesized and assessed *in vitro* for their efficacy as antimicrobial agents against eight bacteria *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Proteus vulgaris*, *Shigella flexneri*. Compound with bromine and with fluorine on benzothiazole ring appeared with potential inhibitory efficacy against *Staphylococcus aureus*.<sup>[34]</sup>



Where R is H, NO<sub>2</sub>, CN, Br, I, OC<sub>2</sub>H<sub>5</sub>, CH<sub>3</sub>

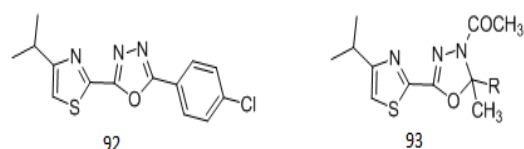
**Farshori et al (2011)** synthesized 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-oxadiazoles and tested for *in vitro* antimicrobial activities by disc diffusion method.



Among the synthesised compounds, compound 91b was found to be more active against fungal strain *i.e.* *Penicillium marneffe* and was compared with Greseofulvin as standard drug. 91c, 91d were found to be more active against bacterial strains *i.e.* *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*,

*Streptococcus pyogenes*, *Klebsiella pneumoniae* and was compared with Chloramphenicol as standard drug.<sup>[35]</sup>

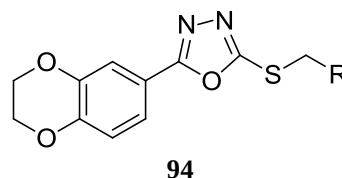
**Parkash et al (2010)** synthesised some novel 2-substituted-5-[isopropylthiazole] clubbed 1,3,4-oxadiazoles (92 and 93) and tested for antimicrobial activity by broth microdilution method. Among the various synthesised compounds, compound 92 showed improved antibacterial activity against tested Gram-positive bacteria *i.e.* *Staphylococcus aureus*, *Staphylococcus faecalis*, *Bacillus subtilis* and compound 92b having *p*-methoxy substitution showed excellent antifungal activity against *Saccharomyces cerevisiae*, *Candida tropicalis*, *Aspergillus Niger*. Compound 92a exhibited good inhibition against Gram-positive bacteria. These tested compounds were compared with standard drugs *i.e.* Ciprofloxacin, Norfloxacin, Flucanazole.<sup>[36]</sup>



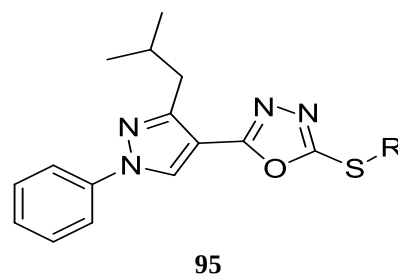
| Compound No. | R                                 | Compound No. | R                                                              |
|--------------|-----------------------------------|--------------|----------------------------------------------------------------|
| 92 a         | 4-ClC <sub>6</sub> H <sub>5</sub> | 93 a         | 4-OC <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>5</sub> |

**Zhang et al (2006)** reported the synthesis, biological evaluation, and molecular docking studies of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan moiety as potential anticancer agents. All the synthesised 1,3,4-oxadiazole derivatives 94a–94e were evaluated for their anti-proliferative activity. The bioassay tests demonstrated that compounds 94k, 94l, 94m, exhibited broad-spectrum antitumor activity. Among these compounds, compound 94j displayed the most potent anti-tumor activity.<sup>[37]</sup>

| Compound No. | R                                                 | Compound No. | R                                                |
|--------------|---------------------------------------------------|--------------|--------------------------------------------------|
| 94a          | Ph-                                               | 94i          | 4-Cl-C <sub>6</sub> H <sub>4</sub>               |
| 94b          | 3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> - | 94j          | 4-I-C <sub>6</sub> H <sub>4</sub>                |
| 94c          | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  | 94k          | 2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> |
| 94d          | 2-F-C <sub>6</sub> H <sub>4</sub>                 | 94l          | 2-Br-C <sub>6</sub> H <sub>4</sub>               |
| 94e          | 2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>  | 94m          | 3-Br-C <sub>6</sub> H <sub>4</sub>               |

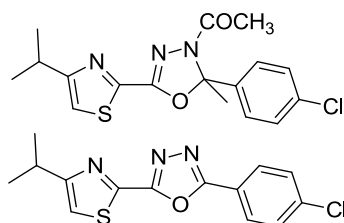


**Abu-Zaied *et al* (2011)** synthesized new oxadiazole thioglycosides and tested for *in vitro* anti-tumor activity. The two cell lines used in the present investigation are MCF-7 (breast) and HEPG2 (liver). From the tested compounds, it was observed that oxadiazole carrying two substituents (95b and 95c) especially when contain thioglycosidic linkage at C<sub>2</sub> are more active than those carrying one substituent (95a). Compound 95b and 95c showed very good anticancer activity in terms of growth inhibitory effect on both cancer cell lines. Standard drug used for breast cancer was tamoxifen and standard drug for liver cancer was 5-fluorouracil.<sup>[38]</sup>

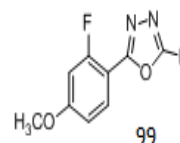


| Compound No. | R | Compound No. | R | Compound No. | R                                    |
|--------------|---|--------------|---|--------------|--------------------------------------|
| 95a          | H | 95b          |   | 95c          | CH <sub>3</sub> -S-CH <sub>2</sub> - |

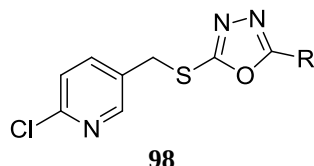
**Kumar *et al* (2010)** synthesized some novel 2-substituted-5-[isopropylthiazole] clubbed 1,3,4-oxadiazole (96 and 97) and tested for anti-tubercular activity. The MIC of each drug was determined by broth dilution assay. From the tested compounds, compound 96 and 97 showed excellent activity against *M. tuberculosis*. Standard drug was Isoniazid.<sup>[39]</sup>

**97**

**Chandrakantha *et al* (2010)** synthesized some novel 1,3,4-oxadiazole bearing 2-fluoro-4-methoxy phenyl moiety and tested for antimicrobial activity by serial dilution method. Among the various synthesized compounds, compound 99a, 99b showed excellent antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* and 99c, 99d showed excellent antifungal activity against *Candida albicans*. Compounds tested for antibacterial activity was compared with standard drug Furacin and for antifungal activity standard drug was Flucanazole.<sup>[41]</sup>



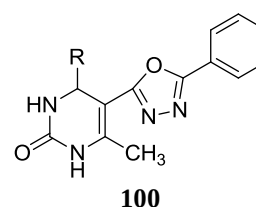
**Zheng *et al* (2010)** synthesized 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety and tested for anti-tumor activity. Anti-proliferative assay results indicated that compound 98a and 98b exhibited the most potent activity against gastric cancer cell SGC-7901. Compound 98a exhibited significant telomerase inhibitory activity which was comparable to the positive control ethidium bromide. 5-Fluorouracil was used as a positive control.<sup>[40]</sup>



| Compound No. | R                                                       | Compound No. | R          |
|--------------|---------------------------------------------------------|--------------|------------|
| 98a          | 2-OH-4OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> - | 98b          | Napthalene |

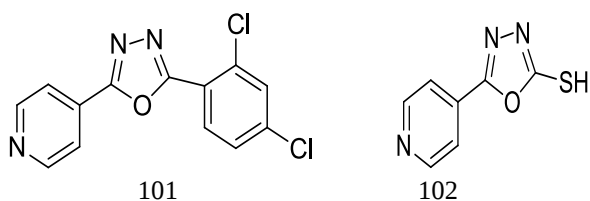
| Compound No. | R                                                    | Compound No. | R                                                  |
|--------------|------------------------------------------------------|--------------|----------------------------------------------------|
| 99a          | 2-CH <sub>3</sub> -3-BrC <sub>6</sub> H <sub>3</sub> | 99b          | 2,3,4-F <sub>3</sub> C <sub>6</sub> H <sub>3</sub> |
| 99c          | 2-Br-5-ClC <sub>6</sub> H <sub>3</sub>               | 99d          | 5-methylisoxazole                                  |

**Mishra *et al* (2010)** synthesized a series of oxadiazole and then final compounds were tested for their antimicrobial activity by cup and plate method. Among the tested compound, compound 100a showed promising antibacterial activity against Gram +ve bacteria *i.e.* *Streptococcus pneumonia* and compound 100b showed promising anti-bacterial activity against Gram-ve bacteria *i.e.* *Escherichia coli* as compared to standard drugs Ofloxacin and Levofloxacin.<sup>[42]</sup>

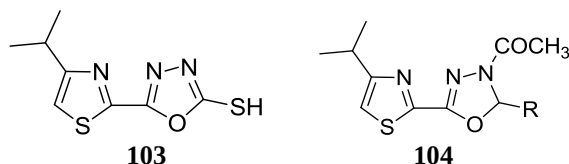


100a: R= 4-OCH<sub>3</sub>C<sub>6</sub>H<sub>5</sub>      100b: R= 4-NO<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

**Gilani *et al* (2010)** synthesized 1,3,4-oxadiazole derivatives of Isoniazid (101 and 102) and tested for anti-inflammatory and analgesic activity. From the tested compounds, compound 101 having 2,4-dichlorophenyl group at second position have highest anti-inflammatory and analgesic activity. When the phenyl group was replaced by mercapto group (102) the activity was found to be moderate. Ibuprofen was used as a standards drug.<sup>[43]</sup>



**Mallikarjuna *et al* (2009)** synthesized oxadiazole derivatives (103 and 104) and tested for their anti-tubercular activity. From the tested compounds, compound 103, 104a, 104b, 104c, 104d show better activity against *M. tuberculosis*. Standard drug was Isoniazid.<sup>[44]</sup>

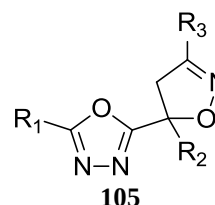


| Compound No. | R                                                                 | Compound No. | R                                                                     |
|--------------|-------------------------------------------------------------------|--------------|-----------------------------------------------------------------------|
| 104a         | C <sub>6</sub> H <sub>5</sub>                                     | 104b         | 3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> |
| 104c         | 4-N(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | 104d         | 4-OH-C <sub>6</sub> H <sub>4</sub>                                    |

**Milinkevich *et al* (2009)** synthesized 2-(4,5-dihydroisoxazol-5-yl)-1,3,4-oxadiazoles (105). Sixteen compounds were synthesized and screened broadly for herbicidal, fungicidal and insecticidal activity. This set of

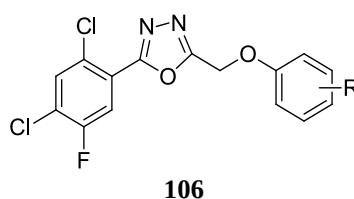
compounds was screened against *Helianthus annuus* and *Digitaria sanguinalis* as a measure of herbicidal activity and *Pyricularia oryzae*, *Septoria tritici* for fungicidal activity. While none of the compound show good herbicidal and fungicidal activity. Standard for fungicidal activity was Azoxystrobin. From the sixteen compounds, compound 105a, 105b, 105c, 105d passed the HTS insect screens against larvae of *Spodoptera exigue*. However further testing of the four compounds in secondary assays against larvae of *Spodoptera exigua* and *Helicoverpa Zea* showed no activity when compared to the insecticidal standard Spinosad.<sup>[45]</sup>

| Compound No. | R <sub>1</sub>                     | R <sub>2</sub>  | R <sub>3</sub>                          |
|--------------|------------------------------------|-----------------|-----------------------------------------|
| 105a         | 3-Cl-C <sub>6</sub> H <sub>4</sub> | CH <sub>3</sub> | 4-Cl-C <sub>6</sub> H <sub>4</sub>      |
| 105b         | 3-Cl-C <sub>6</sub> H <sub>4</sub> | CH <sub>3</sub> | 3-Cl-C <sub>6</sub> H <sub>4</sub>      |
| 105c         | 3-Cl-C <sub>6</sub> H <sub>4</sub> | CH <sub>3</sub> | 2,6-Di-Cl-C <sub>6</sub> H <sub>3</sub> |
| 105d         | 4-Cl-C <sub>6</sub> H <sub>4</sub> | CH <sub>3</sub> | 3-Cl-C <sub>6</sub> H <sub>4</sub>      |

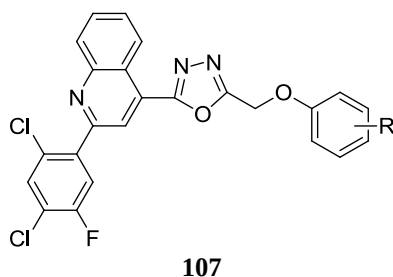


**Karthikeyan *et al* (2008)** synthesized 2,4-dichloro-5-fluorophenyl containing oxadiazoles (106 and 107) and then final compounds were tested for their antimicrobial activity. Among the tested compounds, compound 106a, 106b, 106c, 106a, 106b and 106c showed good inhibition against *Staphylococcus aureus*, *Escherichia coli*. Compounds 107a, 107b, 107c, 107b and 107c exhibited good antibacterial activity almost equal to the standard i.e Ciprofloxacin. Compound 124c showed good bactericidal activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* bacterial strains. Compound 106a, 106c, 106c showed good inhibition against all the fungal strains. Compound 106c showed good fungicidal activity against *Candida albicans*, *Aspergillus fumigatus* and *Penicillium marneffeii* fungal strains and compared with standard drug Greseofluvin.<sup>[46]</sup>

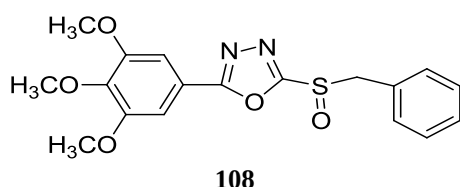
| Compound No. | R                 | Compound No. | R                 | Compound No. | R                      |
|--------------|-------------------|--------------|-------------------|--------------|------------------------|
| 106a         | 4-CH <sub>3</sub> | 106b         | 2-CH <sub>3</sub> | 106c         | 4-Cl-2-CH <sub>3</sub> |



| Compound No. | R    | Compound No. | R    | Compound No. | R                   |
|--------------|------|--------------|------|--------------|---------------------|
| 107a         | 2-Cl | 107b         | 4-Cl | 107c         | 2,4-Cl <sub>2</sub> |



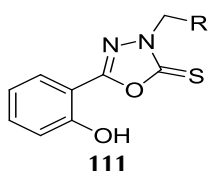
**Liu *et al* (2008)** synthesized sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-oxadiazole moiety (108) and tested for their antifungal activity. From the data it was obtained that introduction of 1,3,4-oxadiazole in sulfoxide might improve their antifungal activities. Among the tested compounds, compound 126 was found to be more active against *G. zeae*, *F. oxysporum* and *C. mandshurica* than other ones. Hymexazol was used as standard drug.<sup>[47]</sup>



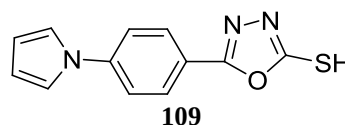
| Compound No. | R                                                 | Compound No. | R                                               |
|--------------|---------------------------------------------------|--------------|-------------------------------------------------|
| 110a         | 2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | 110b         | 4-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> |
| 110c         | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>   | 110d         | 1-(4-isobutylphenyl)ethyl                       |

**Hussain *et al* (2006)** synthesized novel 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazol-2-thione derivatives and tested against cancer cells. From the tested compounds, compound 111a, 111b, 111c, 111d, 111e, 111f, 111g showed non-selective broad spectrum and promising activity against all cell lines. Compound 111b and 111c proved to be the most promising derivatives and also have less toxicity and ease of synthesis makes them promising lead compounds for cancer chemotherapy.<sup>[50]</sup>

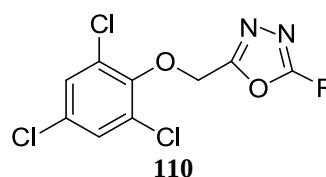
| Compound No. | R                                                        |
|--------------|----------------------------------------------------------|
| 111a         | -NH-C <sub>6</sub> H <sub>4</sub> (2-Cl)                 |
| 111b         | -NH-C <sub>6</sub> H <sub>4</sub> (3-Cl)                 |
| 111c         | -NH-C <sub>6</sub> H <sub>4</sub> (4-Cl)                 |
| 111d         | -NH-C <sub>6</sub> H <sub>4</sub> (2-COOH)               |
| 111e         | -NH-C <sub>6</sub> H <sub>4</sub> (4-COOH)               |
| 111f         | -NH-C <sub>6</sub> H <sub>4</sub> (4-COCH <sub>3</sub> ) |
| 111g         | -NH-C <sub>6</sub> H <sub>3</sub> (2-OH-4-COOH)          |



**Joshi *et al* (2008)** synthesized some oxadiazole derivatives (109) and tested for antitubercular activity. The MIC of each drug was determined by broth dilution assay. From the tested compounds, compound 109 showed highest activity. Standard drug was Isoniazid.<sup>[48]</sup>



**Amir *et al* (2007)** synthesized some 1,3,4-oxadiazole derivatives (110) and tested for its anti-inflammatory activity by carrageenan-induced hind paw edema method. From the tested compounds, compound 110a and 110d showed maximum anti-inflammatory activity. Compound 110b and 110c were found with minimum activity. These compounds were compared with the standard drug Ibuprofen.<sup>[49]</sup>



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