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Pharmaceutical Sciences **Review Article……!!!**

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A REVIEW ON THE 1, 3, 4 OXADIAZOLE MOIETY

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ABSTRACT

Oxadiazole derivatives have been studied in the past few decades. It is a five member heterocyclic ring that exit in four isomeric forms. Oxadiazole having five member heterocyclic ring which has various pharmacological properties. The present review summarizes the physicochemical properties, various synthetic procedures and the various pharmacological activities of 1, 3, 4 Oxadiazole moiety. Thus by studying all the derivatives showing variety of activities can say that Oxadiazole ring have been explored in past years and is still used for future development of new drugs against many more pathological conditions.

INTRODUCTION

Oxadiazole having a five member heterocyclic ring which has two nitrogen atoms with an oxygen atom are considered to be an important class of compounds in medicinal chemistry because of their interesting diversified biological application.[1] Literature survey revealed that a minor modification in the structure can result in qualitative as well as quantitative changes in the activity, convinced us to begin on the synthesis of various new 1, 3, 4- Oxadiazole derivatives with the aim of having improved activity and lesser toxicity. During the past few years, considerable evidence has been accumulated that demonstrates the efficacy of 1, 3, 4-oxadiazoles having anti-tubercular, and anti-hypoglycemic activity, anti-inflammatory activity, anticancer activity, antibacterial activity. [2]

Oxdiazole is consider to be derived from furan by replacement of two methene (CH=) group by two pyridine type nitrogen (-N=). There are four possible isomers of Oxadiazole

(1, 2, 3, and 4) depending on the position of nitrogen atom in the ring and are numbered as shown. [3]

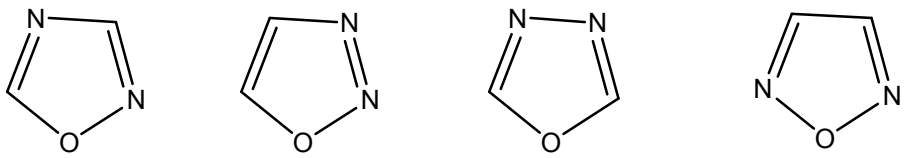


Fig.1

CHEMISTRY

Oxadiazole is a heterocyclic aromatic chemical compound with the molecular formula $C_2H_2N_2O$. There are four isomers of oxadiazole: 1,2,4-Oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unbalanced and reverts to the diazoketone tautomer. The various oxadiazoles moiety involved in variety of drugs including Raltegravir, Butalamine, Fasiplon, Oxolamine, Pleconaril

Fig.2

PHYSICAL PROPERTIES

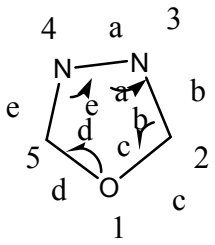


Fig. 3

BOND ANGLE

ANGLE	BOND ANGLE (^{0})
A	105.6
B	113.4
C	102.0
D	113.4
E	105.6

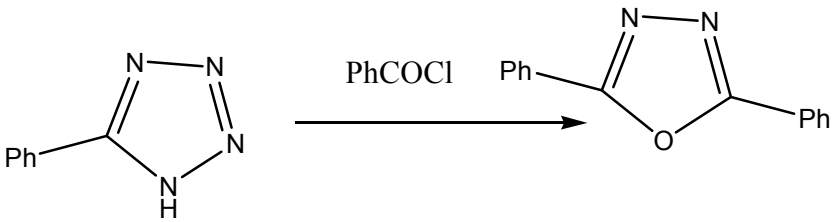
BOND LENTH

BOND	BOND LENTH **(pm)**
A	139.7
B	129.9
C	134.8
D	134.8
E	139.7

CHEMICAL PROPERTIES

1. 1, 3, 4-oxadiazole are much more easily hydrolyzed by acid or alkali than 1, 2, 4 isomer.

2. Loss of Nitrogen: Tetrazoles with acid chlorides (in C_5H_5N at 50°c) give 1, 3, 4-oxadiazole.

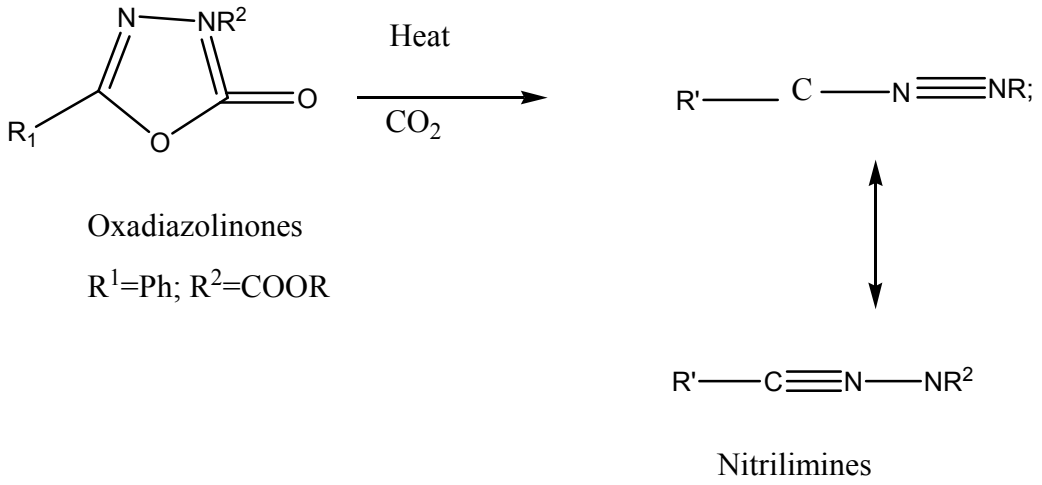


Loss of nitrogen - Fig.4

3. Thermal and photo-chemical reactions (Thermal reaction)

1, 3, 4-oxadiazole is thermally stable and this stability is increased on substitution, particularly by aryl and perfluro alkyl groups.

Oxadiazolinones lose carbon dioxide at high temperature to give nitrelimines. Recyclization in the nitrelimines, formed at 210-230°C from oxadiazolinone yields 2-alkoxy-1, 3, 4-oxadiazole.



Oxadiazolinones

R^1=Ph; R^2=COOR

Nitrilimines

Fig.5

4. Reactivity of 1, 3, 4-oxadiazole: As 1 ,3, 4-oxadiazole have a relatively low electron density at carbon (positions 2 and 5) and a relatively high electron density at nitrogen (positions 3 and 4), the major reactions are neucleophillic attack at carbon, generally followed by ring cleavage and electrophillic attack at nitrogen. This reactivity towards neucleophiles, also catalyzed by acid, causes difficulties when carrying out reactions, which involve basic or acidic conditions. This ring is more stable when substituted by one or more aryl groups. Tautomeric oxadiazole react with electrophile at ring nitrogen at the exocyclic heteroatom or at both center. Reactions in the substituent groups of alkyl or aryl 1,3,4-oxadiazole are possible but they are limited by the sensitivity of the ring to the reagent used substituent groups of alkyl or aryl 1,3,4-oxadiazole are possible but they are limited by the sensitivity of the ring to the reagent used. [4]

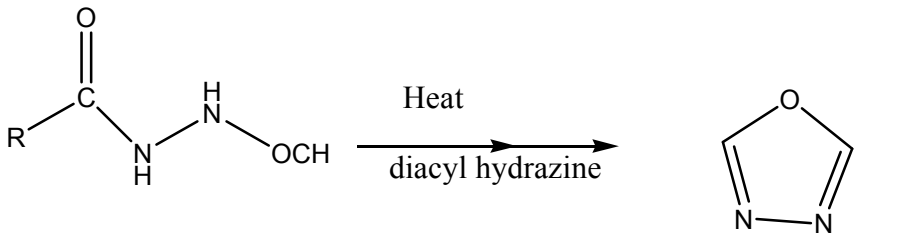
Synthetic procedures for Oxadiazole:-

In generally reported method for the synthesis of 1, 3, 4-Oxadiazole backbone is the reaction between the properly substituted acid hydrazide, carbon disulphide (CS2) and potassium hydroxide (KOH), however the long reaction time is a limiting factor over the high and regular yields obtained with this method. Different other synthetic methods have been reported in literature to overcome this limitation. We are hereby reporting some modification in the synthesis of the supposed nucleus. [5]

1. From Diacyl-hydrazines:

Preparation of 1, 3, 4 Oxadiazole from Diacyl-hydrazines

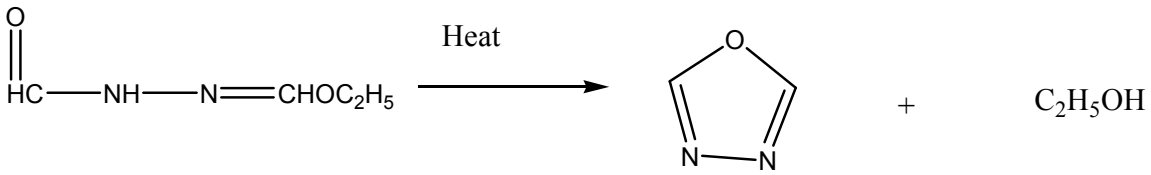
Diacyl-hydrazines yields 1, 3, 4-oxadiazole by heating with SOCl2. [6]



1,3,4 oxadiazole

Fig. 6

Ainsworth prepared 1, 3, 4-Oxadiazole in 1965 by the thermolysis of ethylformate formally hydrazine at atmospheric pressure. [7]



Synthesis of 1,3,4 oxadiazole

Fig 7

Compounds having a five member ring containing one oxygen and two nitrogen are called oxadiazole or in the older literature furadiazole name for Oxadiazole ring such as 'Azoxime' (1, 2, 4 oxadiazole), 'Furazan' for (1, 2, 5 oxadiazole) has gain acceptance, as a effect the literature is complete of diversity of name for this molecule. Amongst these or "Oxybiazole", "Diazoxole" "Furo (bb′) diazole and "Biozole". The systematic name of 1, 3, 4-oxadiazole has gradually become prevalent and is used exclusively.

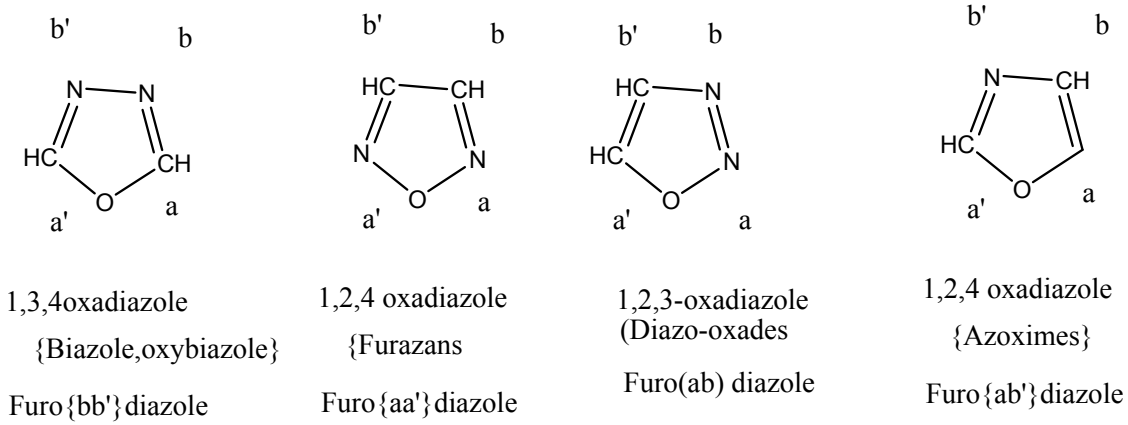


Fig. 8

2. From isothiazole:

Synthesis of 1, 3, 4-Oxadiazole from Isothiazole

Kiselyov *et al.* reported the synthesis of oxadiazole by refluxing isothiazole derivative with orderly hydrazine hydrate for 4 hrs. The hydrazide so obtained can be further reacted with isothiocynates followed by *in situ* cyclization of the intermediate Synthesis of 1, 3, 4-Oxadiazole from Isothiazole thiosemicarbazides with DCC to afford the key molecules.[8]

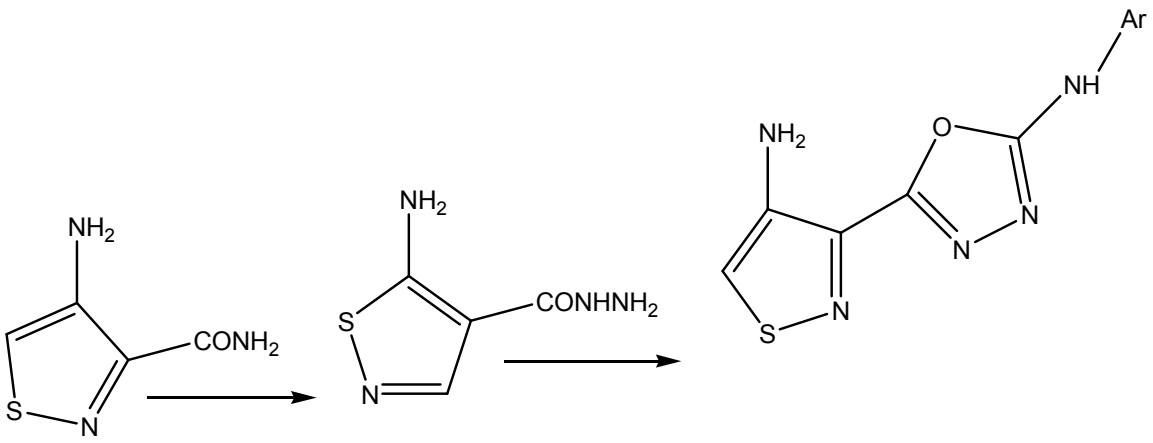


Fig. 9

3. From thiosemicarbazide:

Synthesis of Oxadiazole from Thiosemicarbazide

Barbuceanu *et al* reported synthesis of oxadiazole by reacting N_1-[4-(4-bromophenylsulfonyl) benzoyl]-N_4-(4-flourophenyl)-thiosemicarbazide with Mercuric Oxide (HgO) in ethanol media (b) I_2/KI in NaOH solution media. [9]

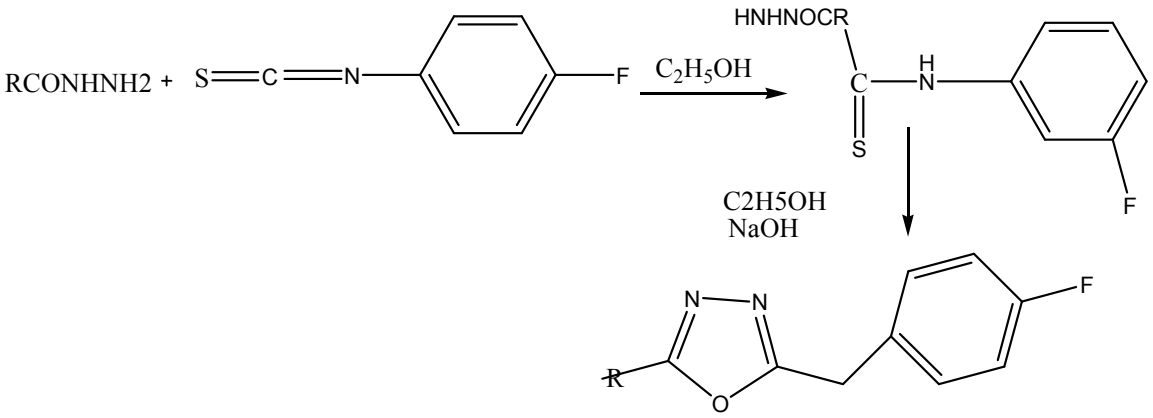


Fig. 10

4. From N-acyl hydrazones:

Synthesis of Oxadiazole from N-acyl hydrazones

Prakash *et al* synthesized of a series of novel 2, 5-disubstituted 1, 3, 4- oxadiazoles by oxidative cyclization of pyrazolylaldehyde N-acyl hydrazones promoted by iodobenzene diacetate under mild conditions shown compound. [10]

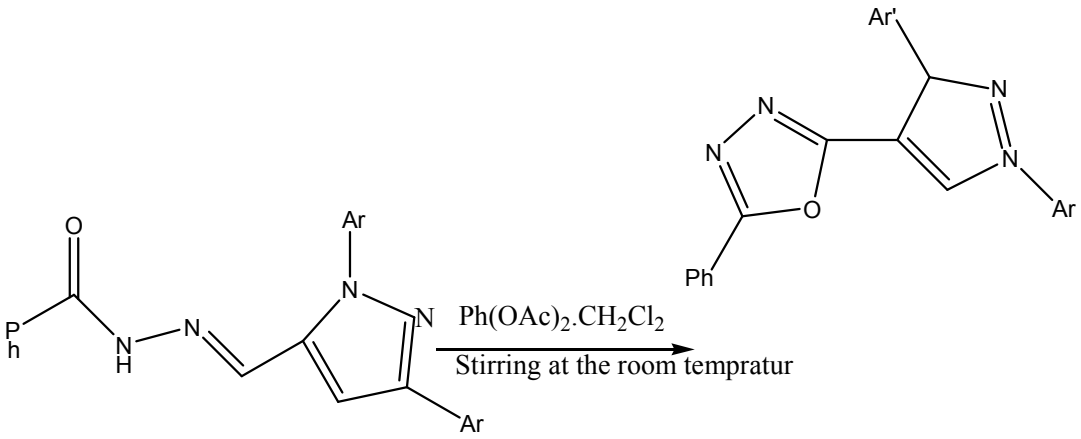


Fig .11

5. From acetic acid hydrazide:

Synthesis from acetic acid hydrazide

Kumar *et al* synthesized 5-[(biphenyl-4-yloxy)-methyl]-2-substituted- 1, 3, 4-oxadiazoles by treatment of 2-(biphenyl-4-yloxy) acetic acid hydrazide with appropriate aromatic acid in presence of phosphorous oxychloride. [11]

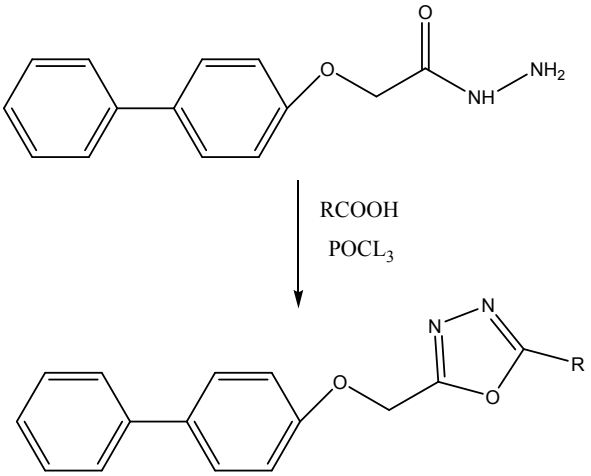


Fig .12

Synthesis of Oxadiazole using phosphorus oxychloride

Husain *et al.* the synthesis of 1, 3, 4-Oxadiazole by reacting 4-oxo- 4(biphenyl-4-yl) botanic acid (fenbufen) with aryl acid hydrazides in phosphorous oxychloride. [12]

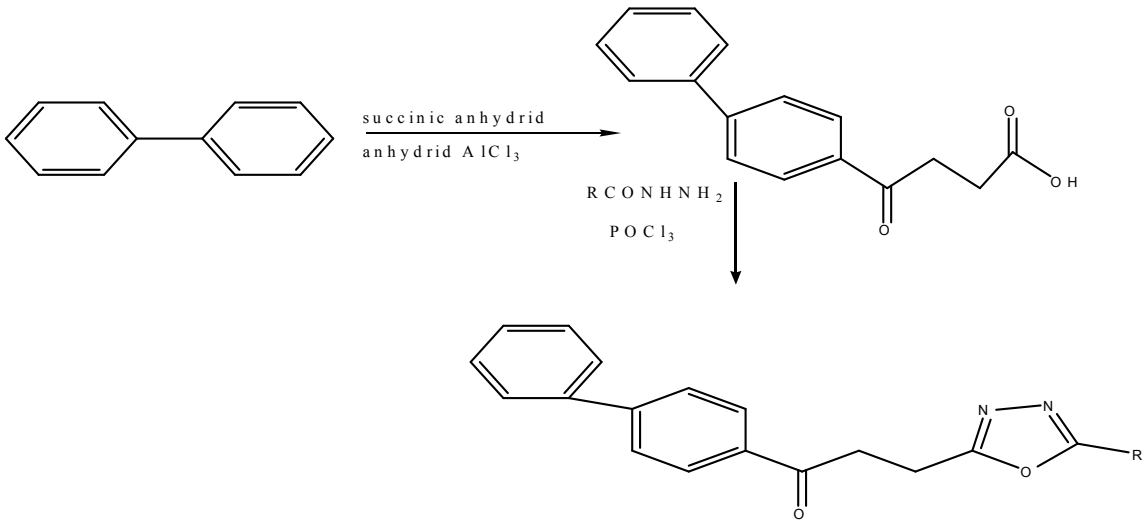


Fig .13

6. From Chalcones:

Synthesis of Oxadiazole from Sydnones

Kamble *et al* reported 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 cyclisation with hydrazine hydrate using Polyethylene glycol (PEG 200) and formic acid as solvents. The Compound step two on bromination and heating with acetic anhydride afforded the Oxadiazole derivatives. [13]

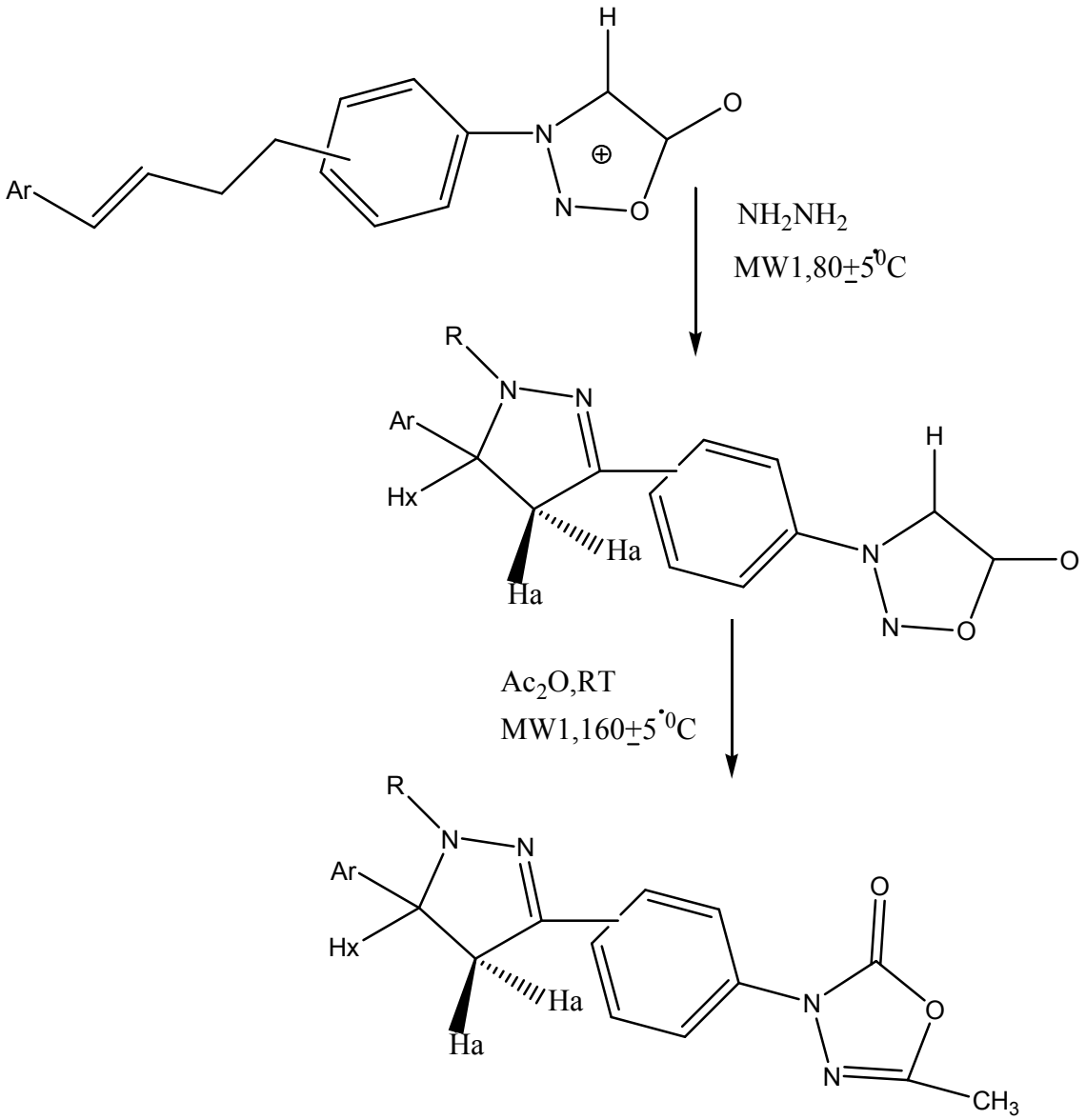


Fig .14

7. From carboxylation of aromatic heterocylces:

Synthesis of 1, 3, 4 oxadiazole from carboxylation of aromatic heterocylces

Xile Hue *et al* prepared Oxadiazole by carboxylation of aromatic heterocyclic such as using the CO_2 as the C1 source requires no metal catalyst and only CS_2CO_3 as the base. [14]

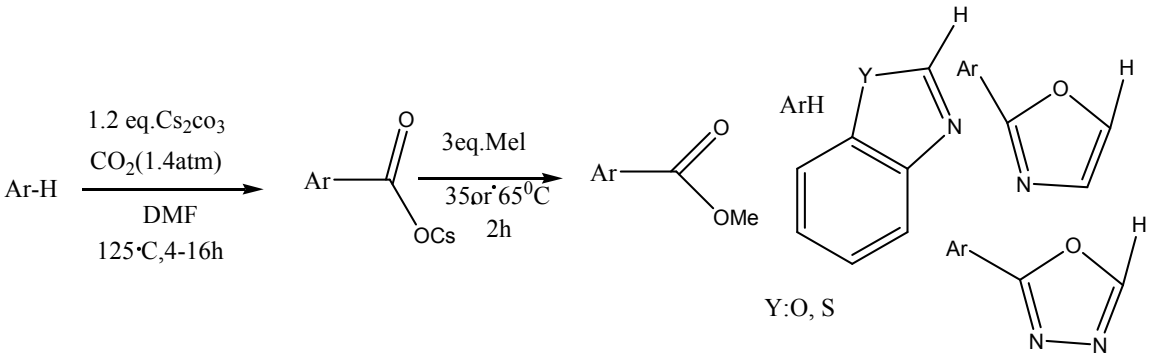


Fig .15

8. From cyclization of thiosemicarbazides:

Synthesis of 1, 3, 4 oxadiazole from cyclization of thiosemicarbazides

Sarah J. Dolman *et al* synthesized 2-amino-1, 3, 4-oxadiazoles relies on a tosyl chloride/pyridine-mediated cyclization of thiosemicarbazides that consistently performs the equivalent semicarbazide cyclizations. Various 5-alkyl- and 5-aryl-2-amino-1, 3, 4-oxadiazoles have been prepared in good yields. [15]

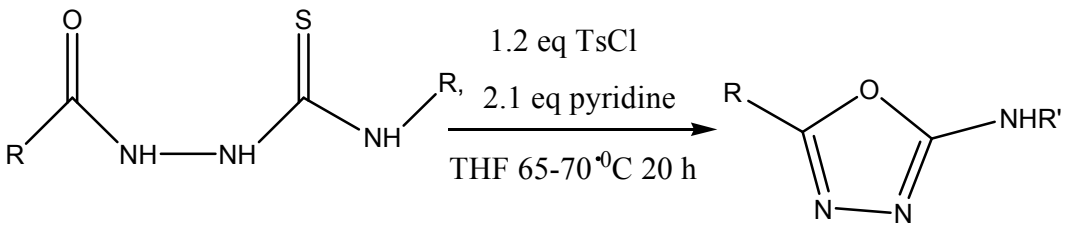


Fig.16

9. From benzoic acids:

Synthesis of 1, 3, 4 oxadiazole from benzoic acids

Mehdi Adib *et al* synthesized **N**-Isocyaniminotriphenylphosphorane, aldehydes, and benzoic acids undergo a one-pot, three-component reaction under mild conditions to afford 2-aryl-5-hydroxyalkyl-1, 3, 4-oxadiazoles in good yields. [16]

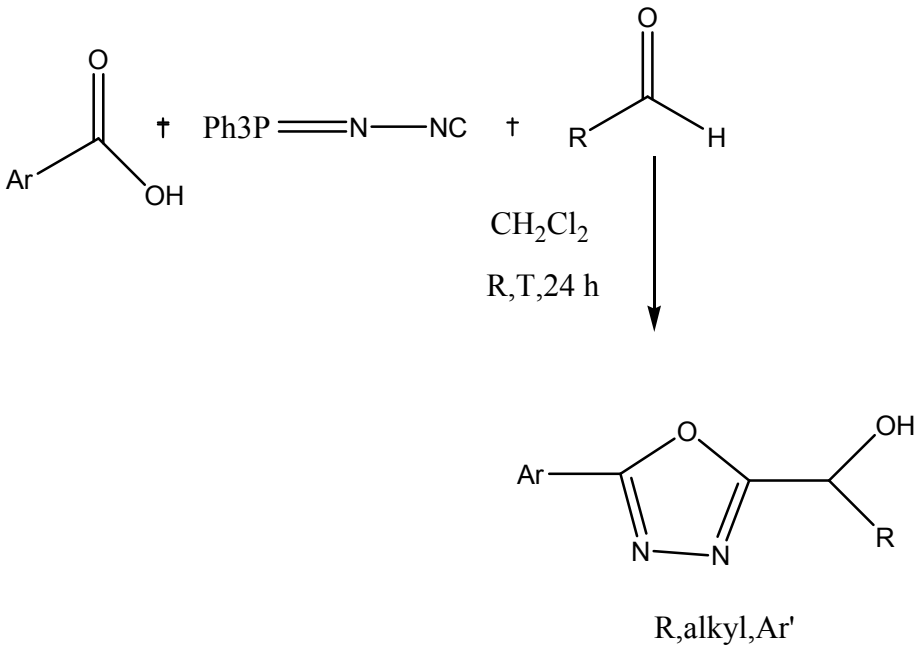


Fig .17

10. From 2-acyl-4, 5-dichloropyridazin-3-ones:

Synthesis of 1, 3, 4 oxadiazole from 2-acyl-4, 5-dichloropyridazin-3-ones

Yong-Jin Yoon *et al.* In general preparation of 1, 3, 4-oxadiazoles were synthesized *in situ* from hydrazine hydrate and the corresponding 2-acyl-4, 5-dichloropyridazin-3-ones as acylating agents in polyphosphoric acid (PPA) in excellent yields. [17]

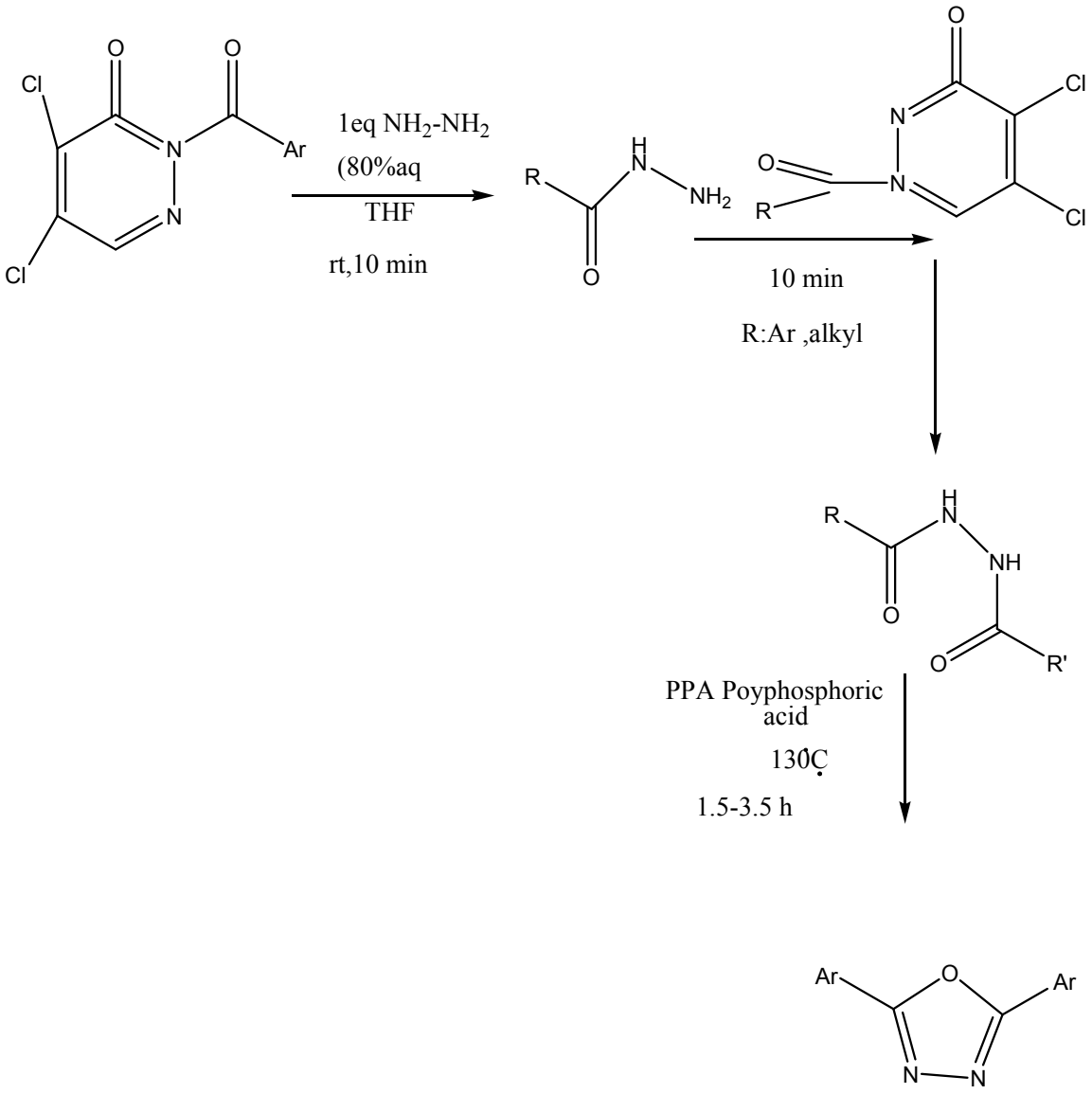


Fig.18

Various biological screening for Oxadiazole activity:-

- **Anti-diabetic activity**

Streptozotocin (STZ) induced diabetic Rats

The acclimatized animals will kept fasting for 24 hrs with water *ad libitum* and *Streptozotocin* (45 mg/Kg) with normal saline was administered. After one hour of Streptozotocin administration, *ad libitum* will *give to animals*. 5% dextrose solutions were given in feeding bottle for a day to overcome the early hypoglycemic phase. The blood glucose regulator was monitored after Streptozotocination by withdrawing a drop of blood from the tail vein by Tail tipping method. The blood will drop on the dextrostrix reagent Pad. The strip will insert into microprocessor digital Blood Lactometer and readings will noted. After 72 hrs rats having blood glucose level beyond 150-mg/dl of blood will be selected for the study and divided into 6 groups. The quantity of thiazolidinone derivatives equivalent to average human intake 200 mg/ kg at a time will calculated for single dose 36 mg/kg (for acute study). The test compounds will be administered orally by mixing with CMC (0.25 %) solution. The blood glucose level will monitor at different times 0hr, 1hr, 3hrs, and 6hrs respectively. The anti-diabetic activities of the synthesized compounds were determined. [18]

- **Anti-inflammatory activity**

Carrageenan induced rat paws edema method [Bhakta` *et al.* 1999]

Weigh and number the rats. The rat was divided into thirteen groups of six animals each. Freshly prepared aqueous suspension of carrageenan (1% m/v, 0.1mL) were inject in the right hind paw of each rat. One group was kept as a control and the animal so further groups were be pretreated with test drugs (20mg/kg) given orally 30 minutes before carrageenan injection. The foot volume was measured before and after carrageenan injection with a Plethysmograph. The mean increase in the paw volume in each group was calculated. Indomethacin used as standard drugs for comparison. [19]

- **Antimicrobial activity**

Cup-plate diffusion method

Antimicrobial activity will be tested by cup-plate diffusion method. The organisms were selected for anti-bacterial activity *Bacillus subtilis, Staphylococcus aureus and Escherichia coli*. The anti-fungal activity was be carried out by using *Aspergillus's Niger* and *Candida albicans*. Dimethyl sulphoxide (1%, DMSO) used as control. The culture strains of bacteria maintained on nutrient agar at 37^{o}C ± 0.5^{o}C for 24 hrs. The anti-

bacterial activity was evaluated, using nutrient agar with 0.1ml of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10^5 CFU/ml dilutions. The agar well of 6 mm diameter was filled with 0.1 ml of compound solution at concentration 25µg/ml of test drug. All the plates will incubated at 37°C± 0.5°C for 24 hrs. Then measure the zone of inhibition. For anti-fungal activity, spore of strains will transferred in a 5 ml of sterile distilled water containing 1% tween-80 (to suspend the spore properly) and agar plate was seeded with 0.1 ml of fungal suspension spread on each plate and it will incubated at 27 °C ± 0.2°C for 12 hrs. After incubation agar gel well prepared using sterile cork borer and each agar well filled with 0.1 ml of compound solution at concentration 25µg/ml. The plates will be then incubated for 24-28 hrs.After incubation, zone of inhibition was measured. Trimethoprim and Voriconazole was be use as standard drugs for anti-bacterial and anti-fungal activity respectively. The plates will be prepared as per the standard methods. [20]

- **Antioxidant activity**

DPPH free radical scavenging method [Lee *et al.*1998]

- The monitoring the DPPH free radical scavenging activity
- DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical was extensively used to evaluate antioxidant activities in less time.
- DPPH is a stable free radical that can accept an electron or hydrogen radical and thus be converted in to a stable, diamagnetic molecule.
  DPPH has an odd electron and so has a strong absorption band at 517 nm.
- When this electron becomes paired off, the absorption decreases.
- Such a change in the absorbance produced in this reaction has been widely applied to test the capacity of numerous molecules to act as free radical scavengers.
- The assay was carried out in triplicate and the percentage of inhibition will calculated using the following formula:

$$\% \text{ Inhibition} = \frac{AB-AA}{AB} \times 100$$

Where AB = Absorption of blank, AA = Absorption of test. [21]

CONCLUSION

Oxadiazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions. In present work an attempt has been made to discuss various aspects such as physicochemical properties, chemical properties and varies type synthetic method of 1, 3, 4 Oxadiazole derivatives

preparation and discovering for potent drugs. The present review highlighted that although a number of methods are available for the synthesis of oxadiazole the most common method is condensation of various alkyl hydrazides with substituted acids using various cyclodehydrogenating agents like phosphorus oxycloride. Thus by studying all the derivatives showing variety of activities can say that oxadiazole ring have been explored in past years and is still used for future development of new drugs against many more pathological conditions.

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