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AN INTRODUCTION TO THE SYNTHETIC METHOD AND PHARAMCOLOGICAL ACITVITY OF OXADIAZOLE NUCLEUS: A REVIEW

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ABSTRACT

Oxadiazole contains an oxygen atom at the 1st position and two nitrogen atom at the 3rd and 4th position which is a derivative of furan by substitution of two methylene group (=CH) with two pyridine type nitrogen atom(-N=). Oxadiazole is a heterocyclic compound belonging to the class of diazoles which exhibit a wide variety of pharmacological activities like anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory, anti-cancer, anti-tumor, analgesic, due of the ability of the oxadiazole to undergo various chemical reaction. The activity of the compounds depend upon the substitution being taken place in the oxadiazole ring. The present review article has discussed the oxadiazole chemistry, properties, reactivity, synthetic methods of oxadiazole, marketed drugs containing oxadiazole nucleus and certain pharmacological activities.

KEYWORDS: Oxadiazole, diazoles, pharmacological activities, synthetic methods.

INTRODUCTION

Diazoles

Diazoles are any group of chemical compounds with a 5-membered ring which contains three carbon atoms and two nitrogen atoms and two double bonds. Diazole mainly refers to one

pair of isomeric chemical compound having molecular formula $C_3H_4N_2$. Five membered and two nitrogen containing heterocyclic compounds are:-

- Imidazole
- Benzimidazole
- Pyrazole
- Oxadiazole
- Thiadiazole

All of these possess varieties of biological activities and are collectively called as diazoles.[1]

OXADIAZOLES

Most of the important heterocyclic compounds are those having five and six membered rings that have heteroatom such as O, N, S, B, Si, p etc. heterocyclic compounds have always been in attention of medicinal chemist due to their broad spectrum pharmacological activities. One such heterocyclic compounds is oxadiazole nucleus. Oxadiazole is a heterocyclic compounds with two nitrogen and one oxygen atom.[2] 1, 3, 4 oxadiazole is a heterocyclic compound derived from furan by substitution of two methylene group (=CH) with two pyridine type nitrogen (-N=). The two of its isomers 1, 3, 4-oxadiazole and 1, 2, 4-oxadiazole are known better due to their useful chemical and biological properties. Because of the ability of 1, 3, 4-oxadiazole compounds to undergo various chemical reaction, it has made them very useful for planning of molecule due to its highly privileged structure to have enormous biological potential.[3]

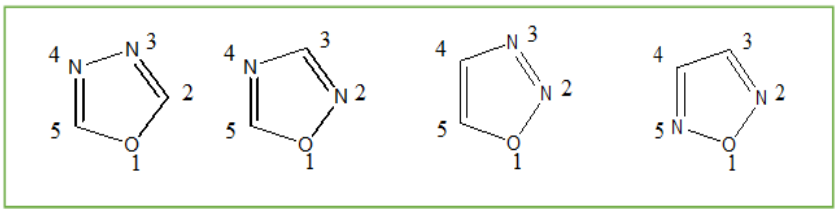


Fig.1: isomers of oxadiazole.

Four possible isomers of oxadiazole are:

CHEMISTRY OF OXADIAZOLE

1. 1, 2, 4-oxadiazole is a molecule which is stable thermally.
2. Due to the inductive effect of extra heteroatom, oxadiazole is a very weak base. 1, 3, 4-oxadiazole undergoes reactions like electrophilic and nucleophilic substitution, thermal and photochemical reactions.

3. In oxadiazole ring, electrophilic substitution is very difficult at carbon atom due to the relatively low electron density on carbon atom, this can be attributed to electron withdrawing effect of nitrogen atom. On substituting electron releasing group at oxadiazole ring, attack to electrophiles occurs at nitrogen atom.
4. The oxadiazole ring is generally resistant to nucleophilic attack. Oxadiazole substituted with halogen undergoes nucleophilic substitution same as at an aliphatic sp^2 carbon atom.[4]
5. Azoxime:-1,2,4-oxadiazole, furazans:-1,2,5-oxadiazole, biazole and oxybiazole:-1,3,4-oxadiazole are the name given to the certain isomers of oxadiazole.
6. According to the literature survey, there are number of reaction as electrophilic, nucleophilic substitution, thermal and photochemical reaction which the oxadiazole undergoes. 1, 3, 4-oxadiazole is a liquid boiling at 150^0C and stable thermally.[5]

PROPERTIES OF OXADIAZOLE

1. 1, 3, 4-oxadiazole is a liquid with a boiling point 150^0C.
2. Its derivative 2, 5-disubstituted -1, 3, 4-oxadiazole are colourless substances.
3. Alkyl derivative which are of lower group are liquids and distil without undergoing decomposition.[2]
4. In 1955, the first mono substituted 1, 3, 4-oxadiazole were reported. The percentage of C, H, N present in 1, 3, 4-oxadiazole is 34.29%, 2.88%, 40.00% respectively.
5. The bond at 1640-1560 cm^{-1}(C=N) and 1020 cm^{-1}(C=O), characterize the IR spectra of 1, 3, 4-oxadiazole. 1.27 in 1H-NMR is the position of both proton of 1, 3, 4-oxadiazole. Molecular ion peak is base as shown by mass spectra.[4]

REACTIVITY OF OXADIAZOLE

1. On replacing the alkyl residues by an aryl radical, the melting and boiling points are raised. The asymmetrical 1, 3, 4-oxadiazole derivatives are supposed to melt and boil at lower temperature than the symmetrical compounds.
2. Oxadiazole solubility in water varies with the variation in the nature of substitutents, e.g**.** 2, 5 dimethyl-1,3,4-oxadiazole is miscible in all proportion with water.
3. Substitution of electrophile occur in aryl substitution. Acylation and alkylation reaction of hydroxyl, thio and amino-1, 3, 4-oxadiazole takes place at ring nitrogen.

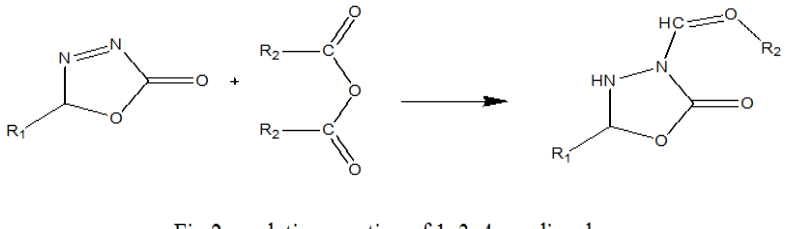


Fig.2: acylation reaction of 1, 3, 4-oxadiazole

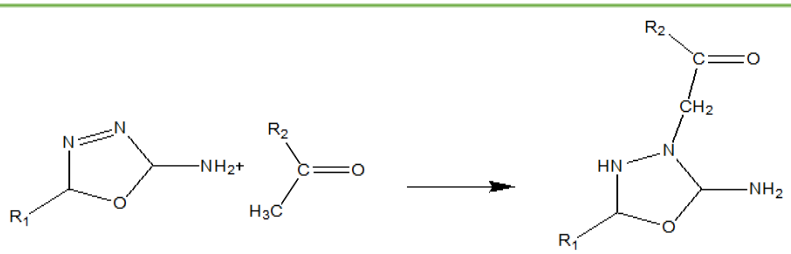


Fig.3: alkylation reaction of 1, 3, 4-oxadiazole.

4. Transformation of 1, 3,4-oxadiazole into other heterocyclic ring can occur, e.g. conversion into triazoles amines in presence of hydrazine hydrate.[2]

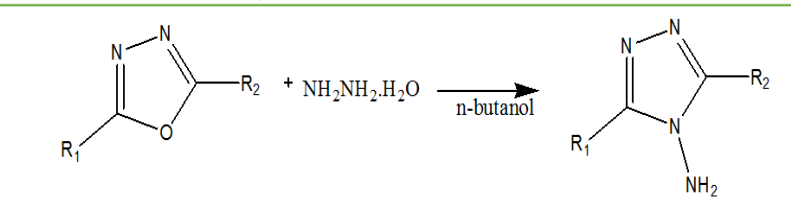
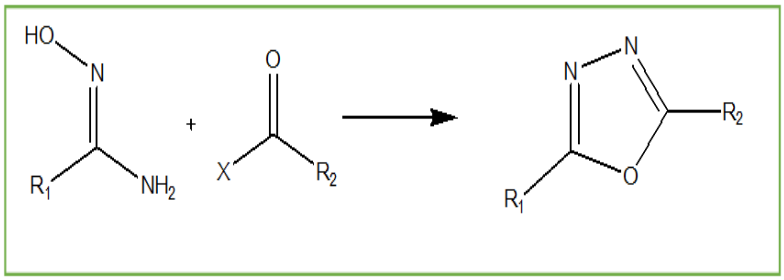


Fig.4: formation of triazole amines

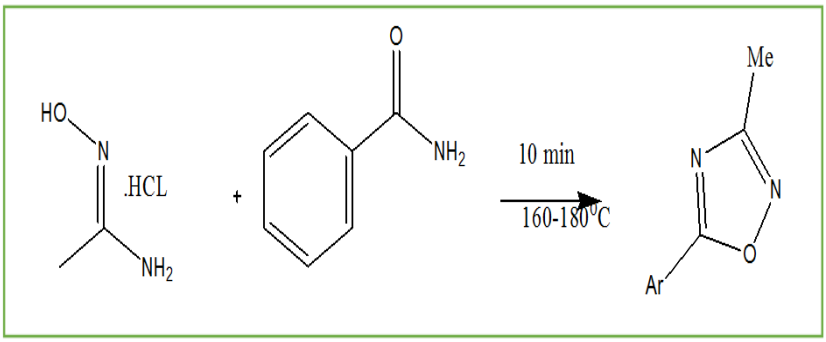
SYNTHETIC METHOD FOR OXADIAZOLES

1. **From amidoxime:** Reaction of amidoxime with a suitably activated acid derivative like ester, acid chloride or anhydride.



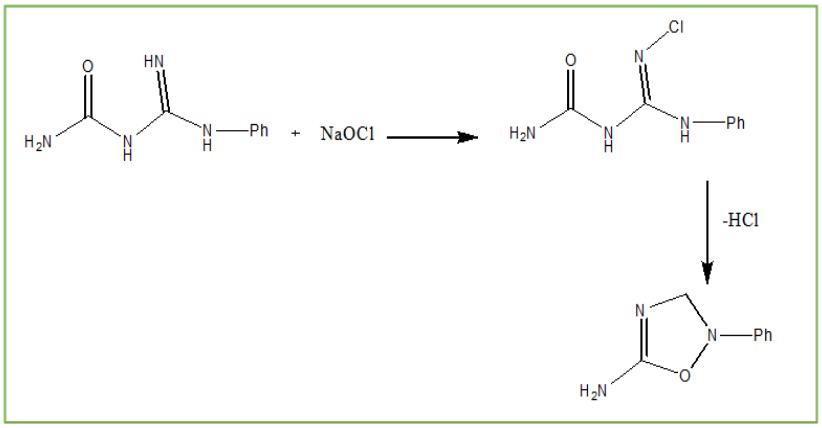
Scheme.1: from amidoxime.

2. **From amide:** On heating the amide with amidoxime salt.



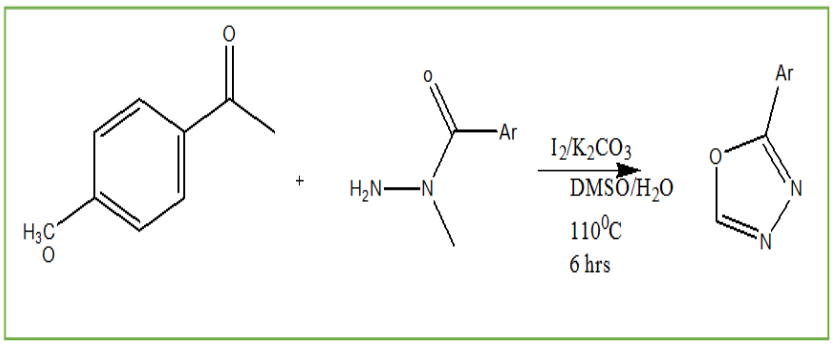
Scheme.2: from amide.

3. **From imines:** By the oxidation of imino group.[6]



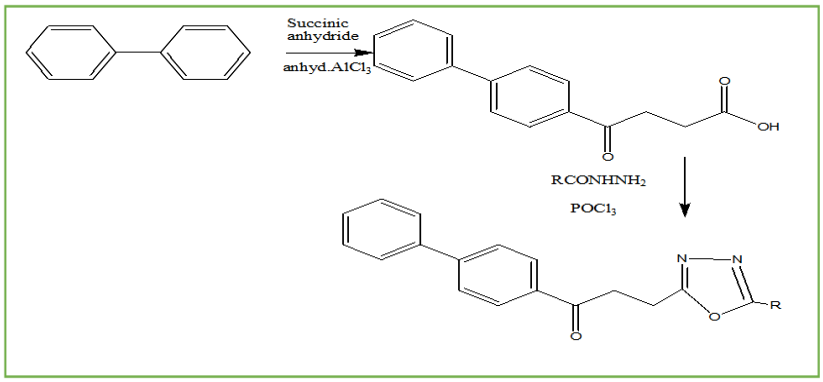
Scheme.3: from imines.

4. Direct annulation of hydrazides with methyl ketones, using K_2CO_3 as a base.[7]



Scheme.4: Annulation of Hydrazides.

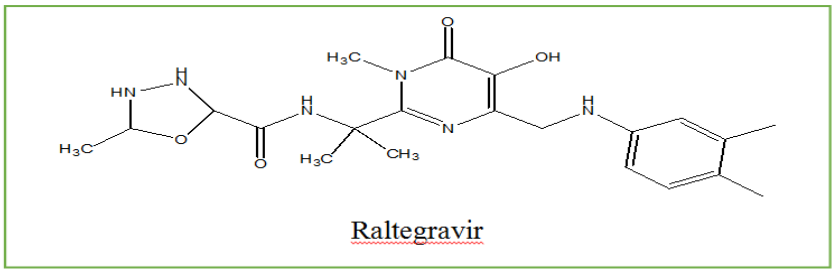
5. **From hydrazide:** Reaction of 4-oxo-4(biphenyl-4-yl)butanoic acid with aryl acid hydrazide in phosphorous oxychloride.[4]



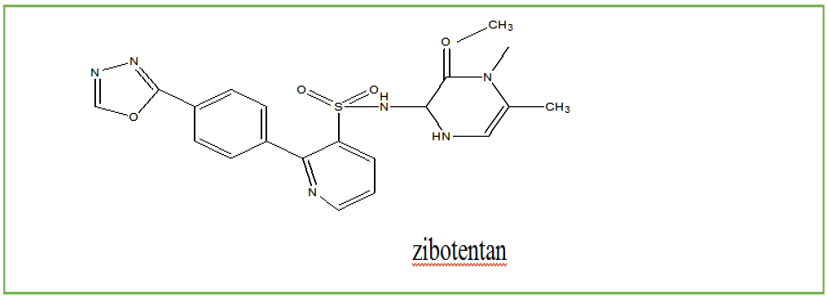
Scheme.5: from hydrazides.

OXADIAZOLE CONTAINING MARKETED DRUGS

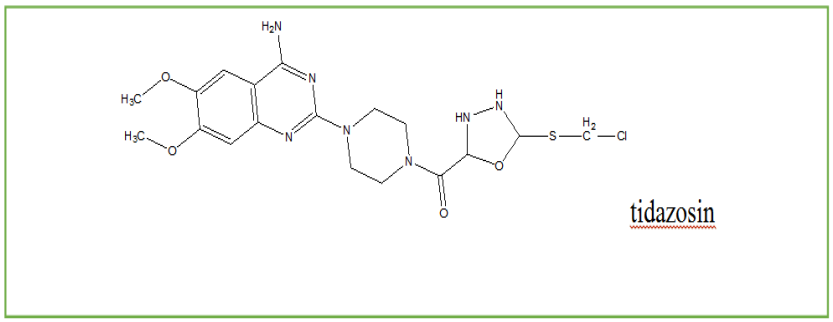
1. **Raltegravir:-** An retroviral drug.



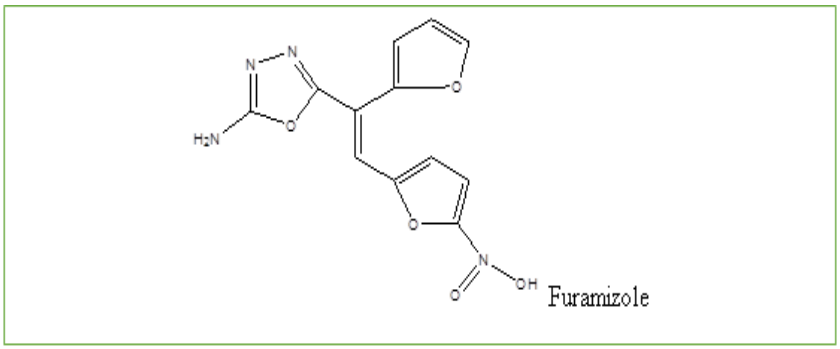
2. **Zibotentan**: Anti-cancer drug.



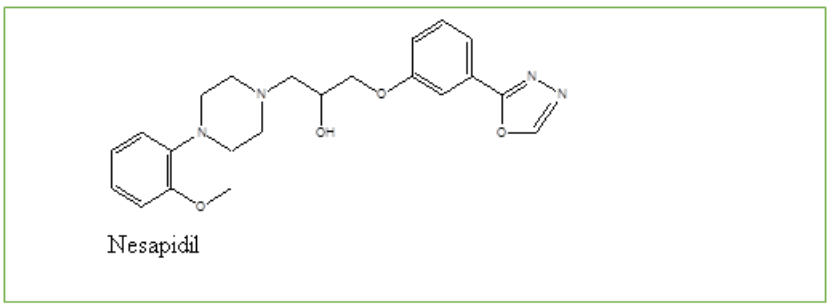
3. **Tidazosin:** Antihypertensive drug.



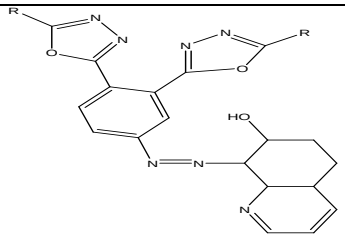
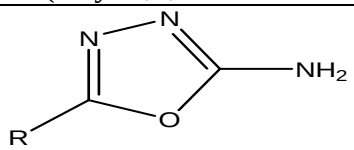
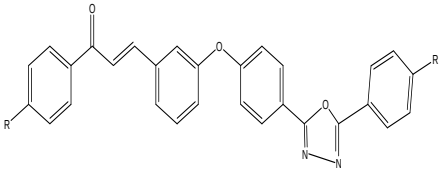
4. **Furamizole:** Antibiotics.[3]

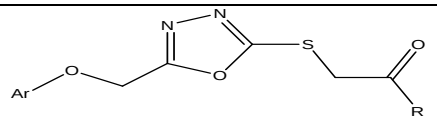
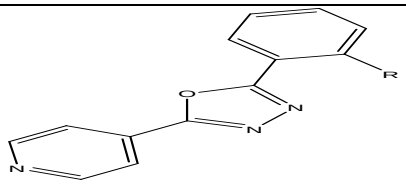
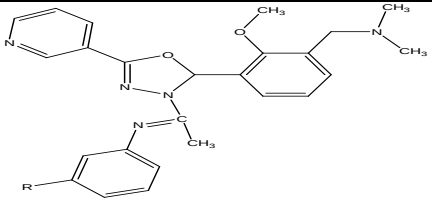
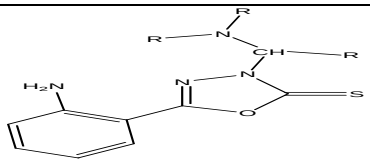
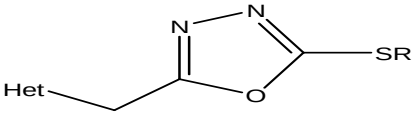
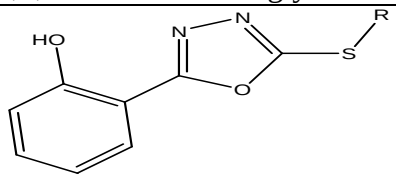
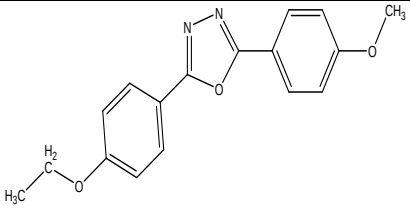


5. **Nesapidil:-** antihypertensive drug.[8]



PHARMACOLOGICAL ACTIVTIY OF OXADIAZOLE

S.No.	Chemical Name/Structure	Activity	Author and Year
1	 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl	Antibacterial	Musmade[3] et al (2015)
2	 2-amino-3-substituted -1,3,4-oxadiazole	Antimicrobial, antioxidant.	Rakesh singh[9] et al(2014)
3	 1-substituted -3-(4-(4-(5-phenyl-1,3,4 oxadiazole-2-yl)phenoxy)phenyl) prop-2-en-1-one.	Anticancer	CK thasneem[10] et al(2014)

4	 1-(substituted)-2-({5-[(naphthalene-1/2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone	Antioxidant.	Priscilla patrao[11] et al (2013)
5	 2-aryl-5-(4-pyridyl)-1,3,4-oxadiazole	Analgesic Anti-inflammatory	C R Biju[12] et al (2012)
6	 (Z)-N-(1-(2-(3-(dimethylamino)methyl)-2-methoxy phenyl)-5-(pyridine-4-yl)-1,3,4-oxadiazole-3(2H)-yl)ethylidene)benzamine derivatives.	Antibacterial	M. Malhotra[13] et al (2012)
7	 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3H)-thione derivative	Analgesic	Selva kumar et al[14] (2012)
8	 1,3,4-oxadiazole thioglycosides	Anticancer	Mamdouh A.Z.Abu-Zaied[15] et al (2012)
9	 2-[5-(substituted sulfanyl)-13,4-oxadiazol-2yl] phenol	Antibacterial Antifungal	P.K. Parikh[16] et al (2011)
10	 2-Aryl-5-(p-ethoxyphenyl)-1,3,4-oxadiazole derivative	Antifungal Antibacterial	Nadia Salih[17] et al (2011)

CONCLUSION

The present study has provided the basic idea regarding the introduction, chemistry, properties, reactivity and synthesis of oxadiazole and its derivatives. The review also provides general concept regarding the use of oxadiazole in various synthesis and the pharmacological activities. In order to form a biologically active oxadiazole moiety, it gives an overview of various synthetic methods which is helpful for the chemist for further novel approaches on oxadiazole ring for a better medicinal compound to increase the efficacy and safety of compound.

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