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A Review: Oxadiazole Their Chemistry and Pharmacological Potentials

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ABSTRACT

Oxadiazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. This interesting group of compound has diverse biological activities such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, anticancer, anti-HIV, hypogycemic and genotoxic. Given data represents that oxadiazole being heterocyclic planar five membered ring system have various pharmacological actions. Results of various derivatives of different oxadiazole and their substitutions are reviewed in present article. Various methods for synthesizing oxadiazole are discussed with their pharmacological actions. These derivatives of oxadiazole are analysed here for varying pharmacological activities.

Keywords: Oxadiazole, Antimicrobial, Anti-inflammatory, Anticonvulsant, Anticancer.

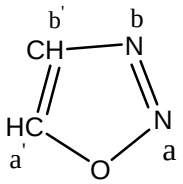
INTRODUCTION

Oxadiazole is important heterocyclic ring present in a large number of biological active molecules of different pharmacological classes [1],[2]. It is known to have fungicidal, bacterial and herbicidal activities.

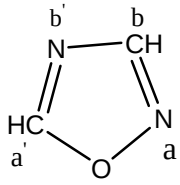
Chemistry of oxadiazole ring

Compounds having a five member ring containing one oxygen and two nitrogen are called oxadiazole or in the older literature furadiazole [3].

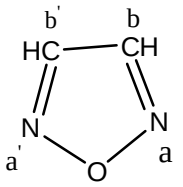
Name for oxadiazole ring such as ‘Azoxime’ (1, 2, 4 oxadiazole), ‘Furazan’ for (1, 2, 5 oxadiazole) has gained acceptance, as a consequence, the literature is full of multiplicity of name for this molecule. Amongst these or “Oxybiazole” , “Diazoxole” , “Furo (bb′) diazole and “Biozole”. The systematic name of 1,3,4-oxadiazole has gradually become prevalent and is used exclusively.



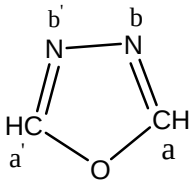
1, 2, 3-oxadiazole
(Diazo-oxides)
Furo (ab) diazole



1, 2, 4-oxadiazole
(Azoximes)
furo (ab′) diazole



1, 2, 5-oxadiazole
(Furazans)
Furo (aa′) diazole



1, 3, 4-oxadiazole
(Biazole, oxybiazole)
furo (bb′) diazole

1,3,4-oxadiazole :

1,3,4-oxadiazole is a liquid, which boils at 150˚c. Ainsworth first prepared it in 1965 by the thermolysis of ethylformate formly hydrazone at atmospheric pressure.

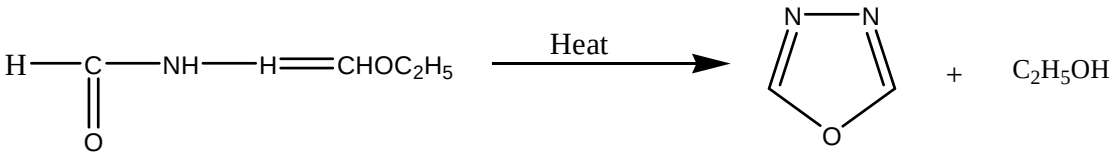
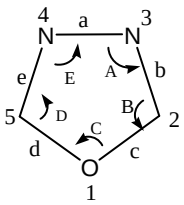


Figure 1: Preperation

1,3,4-oxadiazole is a thermally stable aromatic molecule other aromatic system are 1,3,4-oxadiazolium cation and the exocyclic-conjugated meso ionic-1,3,4-oxadiazole and 1,3,4-oxadizolines. Also known as derivatives of the non-aromatic reduced system, 2,3 dihydro-1,3,4-oxadiazole, 2,5-dihydro-1,3,4-oxadiozole and 2,3,4,5-tetrahydro-1,3,4-oxadiazole.

Physical properties:

Bond angles



Angles	Bond angle (˚)
A	**105.6**
B	**113.4**
C	**102.0**
D	**113.4**
E	**105.6**

Bond lengths

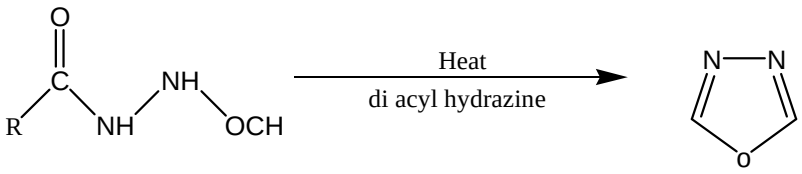
Bonds	Bond length (Pm)
a	**139.9**
B	**129.7**
C	**134.8**
D	**134.8**
E	**129.7**

Infrared spectroscopy:

- The spectra are generally characterized by bonds at 1640-1560 cm^{1}[4],[5],[6] (C=N), 1030-1020 cm^{-1} (C=O).
- The band for C=N stretching is useful in distinguishing between 2 amino-1,3,4-oxadiazole (1640-1610cm^{-1}).
- The molecular ion is the base peak in spectra of 1,3,4-oxadiazole and 2-amino-5-phenyl-1,3,4-oxadiazole.
- Loss of HNCO is significant in the spectrum of 2-amino-5-phenyl-1,3,4-oxadiazole.

Chemical properties:

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



1,3,4-oxadiazole

Figure 2: Preperation of oxadiazole

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

3. **Loss of Nitrogen:** Tetrazoles with acid chlorides (in C5H5N at 50˚c) give 1,3,4-oxadiazole.

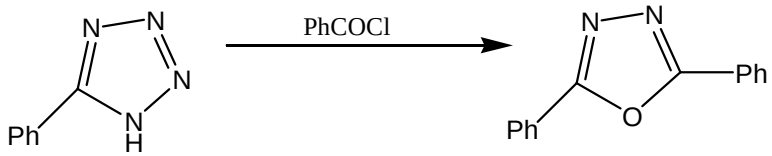
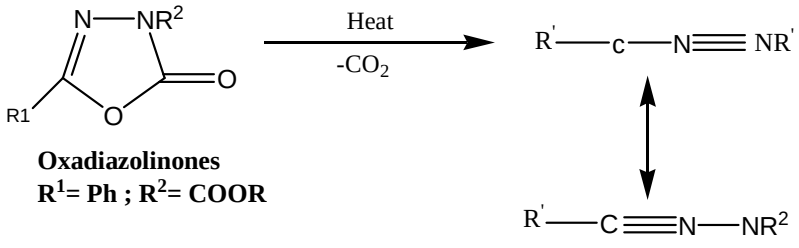


Figure 3: Loss of nitrogen

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 catalysed by acid, causes difficulties when carrying out reactions, which involve basic or acidic conditions. The 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 centres. 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.

5. **Thermal and photo-chemical reactions:** 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

Figure 4: Thermal reaction

Oxadiazole as Anti-Microbial:

Mohamed Ashraf Ali and Mohammad Shaharyar[7] synthesized a series of oxadiazole mannich bases by reaction between oxadiazole derivatives, dapsone, appropriate aldehydes and was evaluated against Mycobacterium Tuberculosis. Compound 3-{2-furyl[4-(4-{2-furyl [5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3 yl] methylamino} phenylsulfonyl) anilino]methyl}-5-(2-naphthyloxymethyl)-

2,3-dihydro-1,3,4-oxadiazole-2-thione from all the synthesized compounds have shown best activity against M. Tuberculosis and isoniazid resistant M. Tuberculosis.

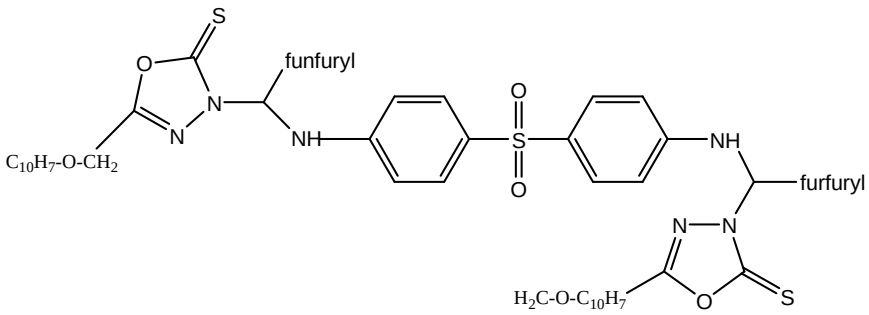
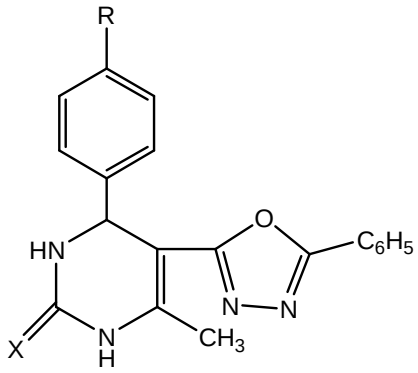


Figure 5: 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazole-3yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione

Manish Kumar Mishra et.al.[8] synthesized 6 – Methyl – 4 – aryl – 5 - (5- phenyl -1, 3, 4 – oxadiazol -2- yl) -1, 2, 3, 4-tetrahydropyrimidine-2(1*H*)-one. Among the derivatives **3e** has significant effect against Streptococcus *pneumonia*(+ve) and **3b** has significant activity effect *Escheria coli* (-ve).



For compounds: 3b- R= OCH_3, X= O
3e- R= NO_2, X= O

Figure 6: compound 3b and 3e

M. Shahar Yar et.al.[9] synthesized a series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives and was tested for in. vitro Anti-Microbial activity. 2-(2 naphthyloxymethyl)-5-phenoxymethyl-1,3,4-oxadiazole exhibited > 90% inhibition among all the synthesized compounds.

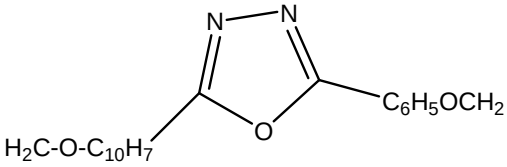


Figure 7: 2-(2naphthyloxymethyl)-5-phenoxymethyl-1,3,4-oxadiazole

Mojahidul Islam et.al.[10] synthesized a series of 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2i-ylmethyl}-2-substituted 1,3,4-oxadiazole and then final compounds were tested for their anti- bacterial activity using cup plate method. Out of all the synthesized compounds **2e and 4e** found to be most potent derivative as compared to the standard drug.

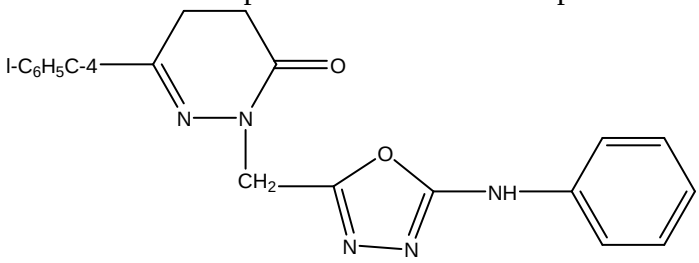


Figure 8: Compound 4

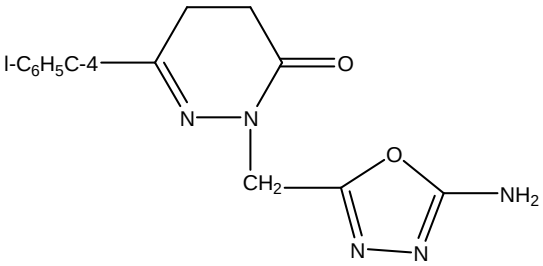
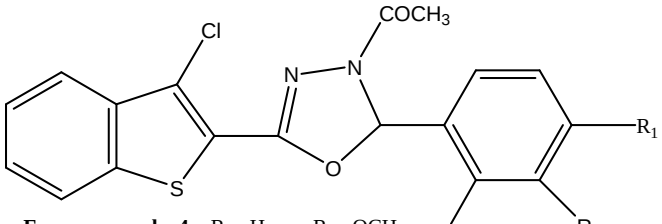


Figure 9: Compound 2e

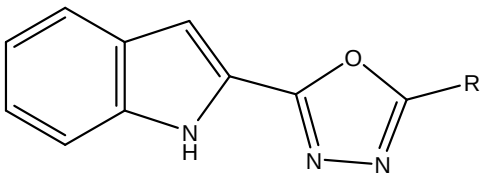
Rakesh Chawla, Anshu Arora[11] synthesized some new 3-acetyl-5-(3-chloro-1 benzo[*b*]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles and 2-(3-chloro-1-benzo[*b*]thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles and was evaluated for Anti-Microbial activity. Compounds **4c and 4e** were found to be most potent against activites, even better than the standard drugs i.e. ciprofloxacin.



For compounds: 4c- R_1= H, R_2= OCH_3
4e- R_1= OCH_3, R_2= H

Figure 10: Compounds 4c and 4e

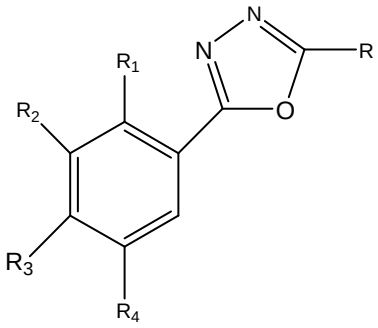
Nitin Bhardwaj et.al.[12] synthesized 1,3,4-oxadiazole from different compounds and was tested for Anti- Microbial activity on different strains. A total of four compounds were synthesized out of those only three found to be effective against bacterial strains and none of the streins were found to be effective against fungal strain.



R= For compound 1= H, 2= 3-ClC_6H_5, 4= 2-ClC_6H_5, 5= C_6H_5

Figure 11: Compounds 1,2,4 and 5

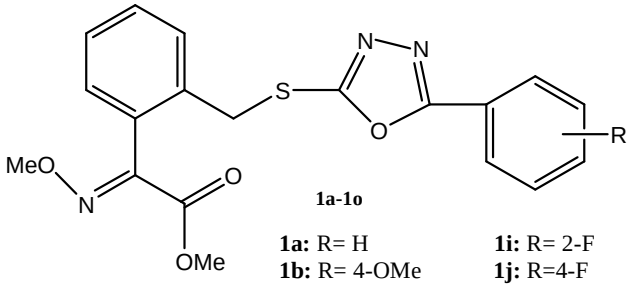
B. Chandrakantha[13] synthesized a series of new 1,3,4-oxadiazole with 2-fluoro-4-methoxy moiety and are tested for Anti-Microbial activity. **4a and 4b** from all synthesized compounds showed significant anti-bacterial activity against Escherichia coli and Pseudomonas aeruginosa, **4i** showed anti-fungal activity against C. Albicans.



For compound 4a: R=2-fluoro-4-methoxyphenyl, R_1=CH_3, R_2= Br, R_3=H, R_4=H
4b: R=2,3,4-trifluorophenyl, R_1=F, R_2=H, R_3=OCH_3, R_4=H
4i: R=2-fluoro-4-methoxyphenyl, R_1=Br, R_2=H, R_3=H, R_4=Cl

Figure 12: Compounds 4a, 4b and 4i

Yan Li et.al.[14] synthesized fifteen novel (E)-a-(methoxyimino)-benzeneacetate derivatives. Bioassays indicated that compound **1a-1o** showed potent fungicidal activity against Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Physalospora piricola and Bipolaris mayclis and 1a-1o showed potent fungicidal activity against R. Solani.

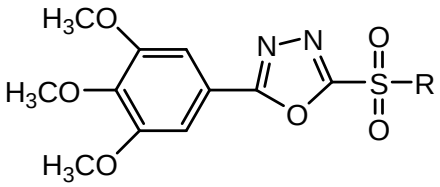


1a-1o

1a: R= H
1b: R= 4-OMe
1c: R= 4-C_6H_5-CH_2O
1d: R= 3-Cl
1e: R= 2,3-Cl_2
1f: R= 2,4-Cl_2
1g:R= 2,5-Cl_2
1h: R= 2,4-Cl_{2-5}-F
1i: R= 2-F
1j: R=4-F
1k: R= 2-F-4-Br
1l: R= 2,3-F_2
1m: R= 4-CF_3
1n: R= 2-I
1o: R= 4-NO_2

Figure 13: Compounds 1a- 1o

Bao-An Song et.al.[15] synthesized compounds using the key intermediates 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol or the oxadiazole analogue and tested for fungicidal activity. From all the synthesized compounds **10i and 10j** can inhibit mycelia growth by approximately 50% *in vitro* against ten kinds of fungus.

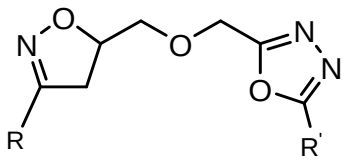


For compounds: 10i - R = CH_3
10j - R = C_2H_5

Figure 14: Compounds 10i and 10j

Oxadiazole as Anti-inflammatory and analgesics:

B. Jayashankar et.al.[16] synthesized a series of novel ether-linked bis(heterocycle)s. All the synthesized compounds were screened for anti-inflammatory and analgesic activities.**7d** and **7g** showed excellent activity against ibuprofen and aspirin.



For copounds **7d:** R,R'= 3-$O_2NC_6H_4$
7g: R,R'= 2,4-$Cl_2C_6H_3$

Figure 15: Compounds 7d and 7g

Shashikant V. Bhandari et.al.[17] synthesized a series of S-substituted phenacryl 1,3,4-

oxadiazole and Schiff bases derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid). Total eighteen compounds were synthesized and out of those only eight were found to have significant anti-inflammatory activity with significant analgesic activity in acetic acid induced writhing models with no ulcerogenic activity. Among those eight active compounds **3k and 4b** found to have most prominent and consistent anti-inflammatory activity.

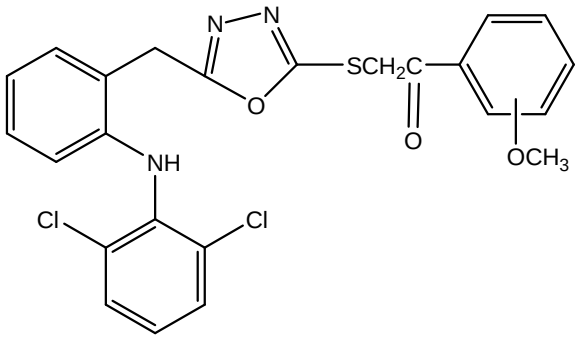


Figure 16: Compound 4b

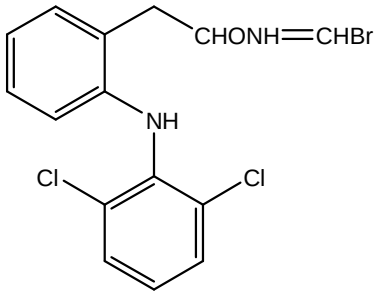


Figure 17: Compound 3k

Mohd Amir et.al.[18] synthesized a series of new 1,3,4-oxadiazole derivatives and 1,2,4-triazine-5-one derivatives. All the compounds were screened for their Anti-inflammatory activity by using carrageenin-induced rat paw edema method. Compounds **2d and 2j** among all the synthesized compounds showed maximum anti-inflammatory activity.

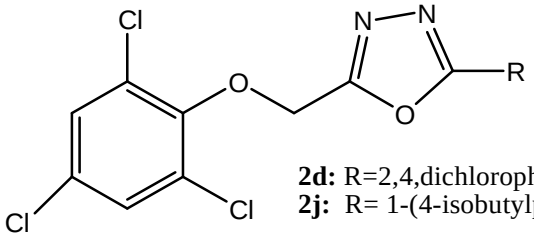
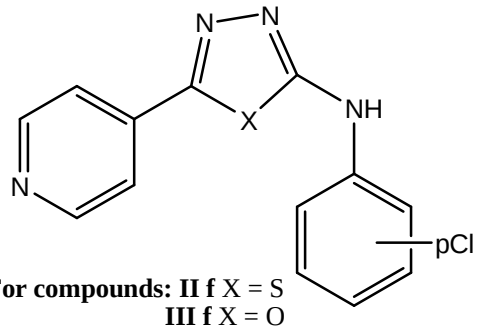


Figure 18: Compounds 2d and 2j

Oxadiazole as Anti- convulsant:

Mohammad Shaharyar et.al.[19] synthesized a series of five membered heterocyclics and was tested for convulsion. From the synthesized compounds **(IIf)** 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole and **(IIIf)** 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4oxadiazole showed potent activity.

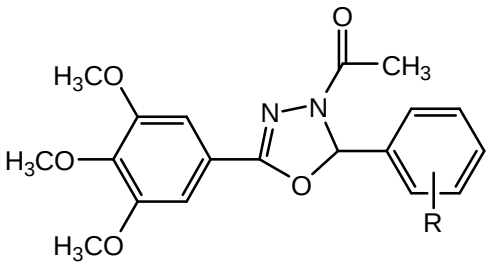


For compounds: II f X = S
III f X = O

Figure 19: Compounds IIf and IIIf

Oxadiazole as Anti-cancer:

Baoan Song et.al.[20] synthesized some 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives. Among the synthesized compounds **2a, 2b, 2c, 2f, 2l and 2m** highly active against PC3 cells and **2a, 2c and 2f** are moderately active against Bcap37 and BGC823 cells.



R= **a:** 2-F; **b:** 3-F; **c:** 4-F; **d:** 2-CF_3; **t:** 4-CF_3;**l:** 3,5-2Cl; **m:** 2,4-3OCH_3

Figure 20: compounds a, b, c, d, f, l and m

Xiaohu Ouyang et.al.[21] synthesized derivatives of oxadiazoles and are evaluated for their ability to inhibit tubulin polymerization and to arrest mitotic division of tumor cells. Among the synthesized compounds, **10** showed potent activity.

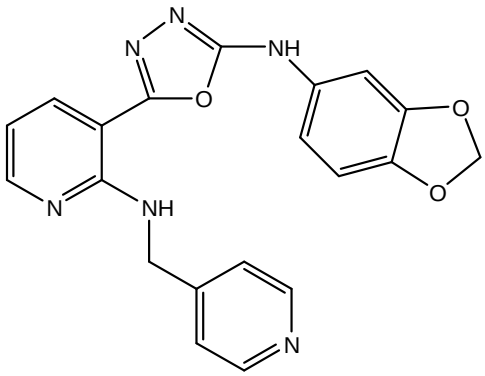


Figure 21: Compound 10

CONCLUSION

Oxadiazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions, which are dicussed in drief in this article. This article mainly focused on the various derivatives of oxadiazole showed various important pharmacological activities, like compound 3-{2-furyl[4-(4-{2-furyl

[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3 yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione have shown best activity against M. Tuberculosis and isoniazid resistant M. Tuberculosis, significant effects of different compounds as antimicrobials like derivatives of 6 – Methyl – 4 – aryl – 5 - (5- phenyl -1, 3, 4 – oxadiazol -2- yl) -1, 2, 3, 4-tetrahydropyrimidine-2(1*H*)-one, 2-(2naphthyloxymethyl)-5-phenoxymethyl-1,3,4-oxadiazole, 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2i-ylmethyl}-2-substituted 1,3,4-oxadiazole etc.

Anti-inflammatory and analgesic activities are also been studied. Compounds that are found to be active are novel ether-linked bis(heterocycle)s, S-substituted phenacryl 1,3,4-oxadiazole, new 1,3,4-oxadiazole and 1,2,4-triazine-5-one derivatives. Various other activities are also been studied like anticonvulsant, anticancer, anti-HIV etc.

Thus by studying all the derivatives showing variety of activities can say that oxadiazole ring have been explored in past years and is still be used for future development of new drugs against many more pathological conditions.

Acknowledgment:

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