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Review Article

REVIEW ON SUBSTITUTED 1,3,4-OXADIAZOLE AND ITS BIOLOGICAL ACTIVITIES

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ABSTRACT

Oxadiazole or furadiazole is a five membered heterocyclic nucleus and is considered to be derived from furan by replacement of two methane (-CH=) group by pyridine type nitrogen. Oxadiazole is a versatile lead compound for designing potent bioactive agents. The derivative of oxadiazole nuclei (1,3,4-oxadiazole) showed diverse biological activities such as anti-microbial, anti-inflammatory, anti-tubercular, anti-convulsant, anti-cancer, anti-HIV, hypoglycemic and genotoxic. In this article, we have tried to compile some of the major researches carried out for the compound 1,3,4-oxadiazole.

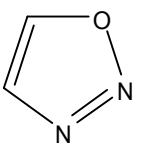
Keywords: Oxadiazole, anti-microbial, anti-inflammatory, analgesic, anti-cancer and anti-convulsant activity.

INTRODUCTION

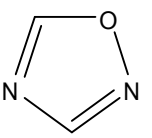
The heterocyclic compounds have always been an interesting area of study in the field of chemistry. The carbon atoms are not the major components in heterocyclic compounds. Nitrogen, oxygen & sulphur are some heteroatoms are present in the rings replacing carbon.[1] Substitutions on the heterocyclic drugs gives them more potent and diverse functionalization. The important compounds present in vitamin- B complex, dyes, enzyme, antibiotics, alkaloids, amino acid and drugs are heterocyclic compounds which are having therapeutics use.[2] The five membered oxadiazole nucleus present in heterocyclic compounds is majorly responsible for the diversified useful biological effects.[3]

When two methane (-CH=) groups present in the furan ring are replaced by two pyridine type nitrogen (-N=) then oxadiazole is derived with the general formula of C_2H_2ONa,[4] this reduces the aromaticity of the ring (oxadiazole) to an extent that they now reflect the characteristics of a conjugate diene.[3]

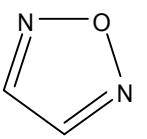
The electrophilic substitution reactions are not possible in oxadiazole because of low density of electrons on carbon atom which causes the electron withdrawal effect of pyridine type nitrogen when any electron releasing group was added to it. The oxadiazole ring is found to be resistant to nucleophilic substitutions. Whereas the halogen substituted oxadiazole can undergo these substitutions by replacing halogen atom by nucleophiles. Four isomers of oxadiazole are present.[3]



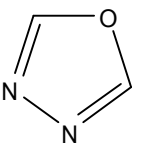
1,2,3-oxadiazole



1,2,4-oxadiazole



1,2,5-oxadiazole



1,3,4-oxadiazole

1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole are known,[5] but the 1,2,3-isomer is quiet unstable and reverts in the form of diazoketone tautomer.[6] The stable oxadiazoles appear in a many pharmaceutical drugs which include raltegravir, fasiplon, butalamine, oxolamine, pleconaril[4] and Nesapidil.[7]

Oxadiazole have occupied a unique place in the field of medicinal chemistry due to its wide range of activities like anti-microbial[8,3], anti-inflammatory,[9,10] anti-fungal,[11] anti-tubercular[12,13], anti-convulsant[14], anthelmintic, herbicidal, anti-oxidant, analgesic,[15,16] anti-tumour[17,18,19] and anti-hepatitis B viral activities.[20]

BIOLOGICAL ACTIVITIES

It is an important challenging task for medicinal chemists to develop new anti-microbial, anti-inflammatory, analgesic, anti-tumor, anti-convulsant, anthelmintic, herbicidal, anti-mycobacterial and anti-oxidant agents. There are two basic approaches for development of new drugs:

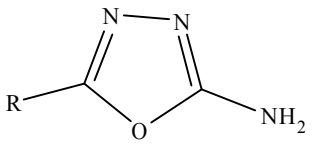
(a) Synthesis of analogous and their modifications as well as derivatization gives novel substituted compounds for better and improved treatment and
(b) Searching and synthesis of novel compounds, that the bacterias and diseases has never been presented before.

For this purpose, substituted 1,3,4-oxadiazoles are already being used as potent anti-microbial, anti-inflammatory, analgesic, anti-tumor and anti-convulsant, documented as well as patented.[21]

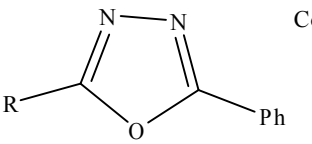
Antimicrobial Activity

Researches on 1,3,4-oxadiazole and their derivatives have shown that they are having very prominent anti-microbial activity against a wide range of microbes. Specially 2, 5-disubstituted 1,3,4-oxadiazole has gained the attention of the medicinal chemists.[22]

Mudasir R. Banday *et al* (2010) synthesized 5-(alkenyl)- 2-amino-1,3,4-oxadiazoles **1a-d** and 2-(alkenyl)-5-phenyl-1,3,4-oxadiazole **2a-d,** newly synthesized compounds were investigated for their anti-bacterial and anti-fungal activities against Gram negative bacteria [*Escherchia coli* and *Salmonella typhimurium*] and Gram positive bacteria [Staphylococcus aureus and *Bacillus subtilis*]. The investigation of the anti-microbial activity of compounds **1a–d** and **2a–d** revealed that all the synthesized compounds showed moderate to good anti-bacterial activity against E. coli. Compound **1d** was active against all the bacteria where as **1c** was active against *E. coli*, *S. typhimurium* and *B. subtilis*. Compounds **2a, 2c** and **2d** also showed promising results against *E. coli*.[21]



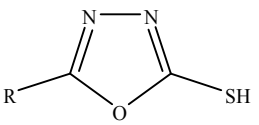
(1)



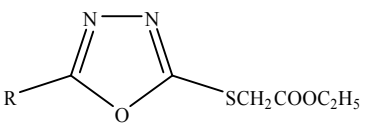
(2)

Compounds	R
1a, 2a	$CH_2=CH(CH_2)_8$
1b, 2b	$CH_3(CH_2)_7CH=CH(CH_2)_7$
1c, 2c	$CH_3(CH_2)_5CHOH\text{-}CH_2CH=CH(CH_2)_7$
1d, 2d	$CH_3(CH_2)_4CH=CH(CH_2)_2CHOH(CH_2)_7$

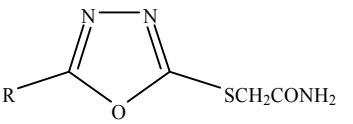
Muhammad Zareef *et al* (2008) synthesized 5-substituted-2-mercapto-1,3,4-oxadiazoles **3a-g**, their corresponding S-esters **4a-g**, and amides **5a-g,** newly synthesized compounds were screened for their anti-microbial activity against *Escherchia coli, Pseudomonas picketti, Bacillus subtilis* and *Staphylococcus aureus*by and *Micrococcus luteus* by agar well diffusion method and anti-fungal activity against *Trichphytonlongifusus, Candida albicans, Aspergillus flavus, Microsporrumcanis, Fusarium solani* and *Candida glabrata*using agar plate technique. Compounds **4d** exhibit moderate activity (60%) against *Aspergillus flavus and Trichphytonlongifusus respectively*.[23]



(3)



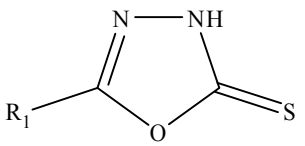
(4)



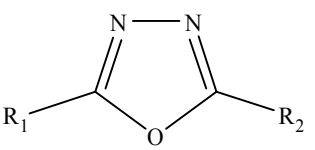
(5)

3-5	R
a	$-C_6H_5$
b	$-C_6H_4CH_3(4)$
c	$-C_6H_4OCH_3(4)$
d	$-C_6H_4Cl(3)$
e	$-C_6H_4Cl(4)$
f	$-C_6H_4Cl(5)$
g	$-C_5H_4N(4)$

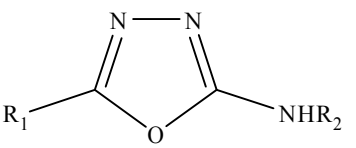
Shaharyar *et al* (2007) synthesized Novel 1,3,4-Oxadiazole Derivatives **6a-g, 7a-g** and **8a-g**, newly synthesized compounds were screened for their anti-microbial activity against *Mycobacterium tuberculosis* using the BACTEC-460 radiometric system. The compound 2-(2-naphthyloxy methyl)-5-phenoxymethyl-1,3,4-oxadiazole **7d** produced the highest efficacy.[24]



(6)



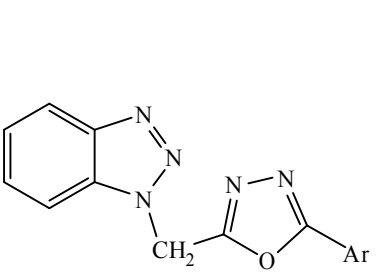
(7)



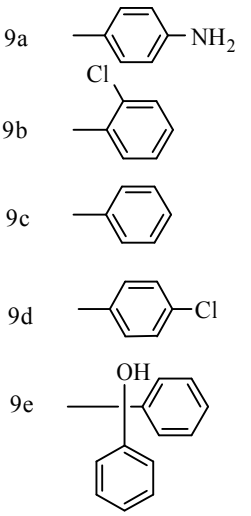
(8)

6-8	R_1	R_2
a	$-C_6H_5$	
b	$-4NO_2C_6H_5$	
c	$-C_6H_5NHC_6H_5$	
d	$-betaC_{10}H_7OCH_2$	
e	$-alphaC_{10}H_7OCH_2$	
f	$-C_6H_5OCH_2$	7(a-g) $C_6H_5OCH_2$
g	$-C_6H_5CH_2$	8(a-g) $3ClC_6H_4$

Rakesh Saini *et al* (2009) synthesized 2, 5 Di-substituted 1, 3, 4 oxadiazoles derivatives **9**, newly synthesized compounds were investigated for their antibacterial activity against *S. aureus* and *E.coli***.** Maximum activity was found in compound **9b** against *S.aureus***.**[25]



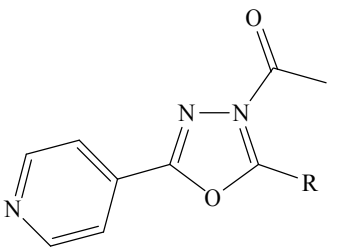
(9)



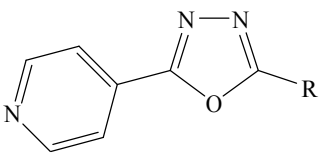
Analgesic and Anti-inflammatory activity

The novel mercapto substituted 1,3,4-oxadiazole bears good anti-inflammatory activity and if secondary amines are added to this scaffold then the activity increases.[26]

Dhansay Dewangan *et al* (2010) synthesized 2, 5- Disubstituted 1, 3, 4-Oxadiazole derivatives **10** and **11**, newly synthesized compounds were investigated for their analgesic activity by Acetic acid induced writhing method using Swiss albino mice (25-35g) and anti-inflammatory activity by carrageenan induced rat paw edema and were determined according to mercury displacement method by using plethysmograph on adult albino rats (150-180g). So compound **10b, 11f** and **11j** were shown significant analgesic activity whereas compound **10c, 11g** and **11j** were shows good anti- inflammatory activity.[15]



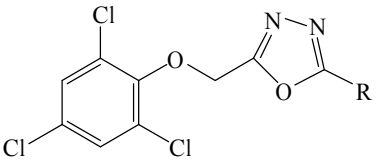
(10)



(11)

Compound 10, 11	R
a	2-OH-C_6H_4
b	4-OCH_3-C_6H_4
c	3-OCH_{3-4}-OH-C_6H_4
d	2-C_4H_3O
e	-C_6H_5
f	-C_8H_8
g	-C_5H_4N
h	2-NH_2-C_6H_4
i	4-NH_2-C_6H_4
j	2-COOH-C_6H_4

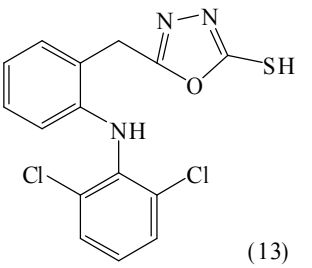
Mohd Amir *et al* (2007) synthesized derivatives of 2-substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazole **12**, newly synthesized compounds were investigated for their anti-inflammatory effect by carrageenan induced paw edema model using male wistar rats (100–120 g) and ulcerogenicity by pylorus ligation method using adult male wistar rats (100–120 g). The compounds **12d** and **2j** showed maximum anti-inflammatory activity. Rest of the compounds showed moderate activity whereas compound **12l** showed maximum reduction in ulcerogenicactivity.[9]



(12)

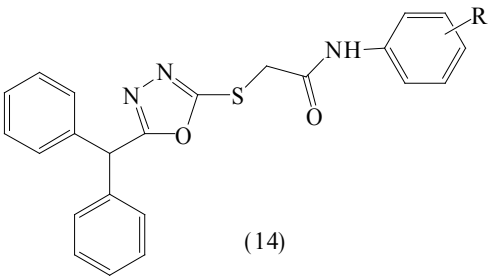
Compound(12)	R
a	Phenyl
b	2-chlorophenyl
c	4-chlorophenyl
d	2,4-dichlorophenyl
e	2,4-dichlorophenoxymethyl
f	4-aminophenyl
g	2-aminophenyl
h	4-nitrophenyl
i	2-acetoxyphenyl
j	1-(4-isobutylphenyl)ethyl
k	1-(2-flouro-4-biphenylyl)ethyl
l	1-(6-methoxynaphth-2-yl)ethyl
m	naphth-2-yl methyl
n	2-(2,6-dichloroanilino)benzyl

Shashikant V. Bhandari *et al* (2008) synthesized 5-[2-(2,6-dichloroanilino)benzyl]2-mercapto-1,3,4-oxadiazole **13**, newly synthesized compounds were investigated for their anti-inflammatory effect by carrageenan induced paw edema model using wistar rats (100–120 g), analgesic activities of the compounds were studied by using acetic acid induced writhing test in mice (25-30g) and acute ulcerogenicity studies by pylorus ligation method using albino rats of wistar strain of either sex, weighing (100–120 g).[16]



(13)

Mohammad Amir et al (2011), synthesized 2-[(5-diphenylmethyl-1,3,4-oxadiazole-2-yl)sulfanyl]-*N*-(substitutedphenyl)-acetamides **14a-e,** newly synthesized compounds were investigated for their anti-inflammatory effect by carrageenan induced paw edema model using wistar rats (180-200g), analgesic activities of the compounds were studied by tail immersion method using albino mice (25-30g). The compounds **14a, 14b** and **14c** showed significant anti-inflammatory activity.[10]



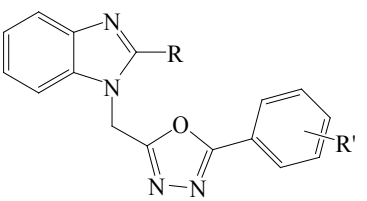
(14)

Compound(14)	R
a	4-chloro
b	3-chloro
c	4-flouro
d	4-methoxy
e	1-napthyl

Anti-Tumor Activity

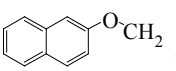
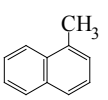
There is a wide scope of novel substituted 1,3,4-oxadiazole as chemotherapeutic agents against breast cancers,[19] leukemia, lung cancers etc

Salahuddin *et al* (2014) synthesized 2-(Naphthalen-2-yloxymethyl)-1-(5-substituted phenyl [1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole **15,** newly synthesized compounds were properly examined for anticancer activity in melanoma, leukemia, ling, colon, breast, ovarian, prostate cancer cell lines in vitro. The anti-cancer screening was carried out according to the NCI US protocol. Compound substituted with 4-NO_2 showed moderate to good activity against selected cell line.[27]



(15)

Compound(15)

R=  , 

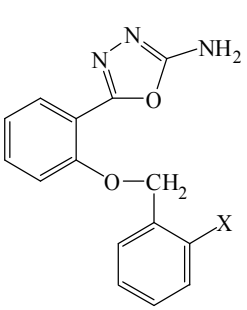
R'= H, 2-Cl, 4-NH_2, 4-NO_2, 3,5-diNO_2

Anti-Convulsant Activity

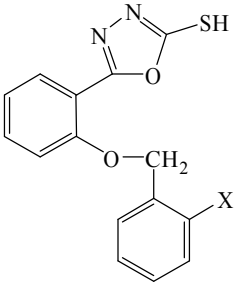
1,3,4-oxadiazole when substituted with an amino group at 5th position have good anti-convulsant activity.[28]

Afshin Zarghi *et al* (2008) synthesized 2-Amino-5-(2-halo-2-benzyloxyphenyl)- 1,3,4-oxadiazoles **16,** 5-(2-Halo-2-benzyloxyphenyl)- 2-mercapto-1,3,4-oxadiazole **17**, 2-Alkylthio-5-(2-halo-2-benzyloxyphenyl)- 1,3,4-oxadiazole **18** and 2-Anilino-5-(2-halo-2-benzyloxyphenyl)- 1,3,4-oxadiazole **19,** newly synthesized compounds were investigated for anti-convulsant evaluations by qualitative assays using MES (maximal electroshock) and PTZ (pentylenetetrazole) tests.

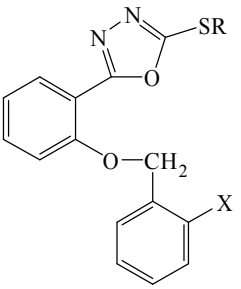
The first assay is related to the induction of seizure electrically and the second induction of seizure is made chemically using adult male albino mice (25-30g). The compound **16** which has amino group on 2 position of oxadiazole ring and fluoro substituent at the ortho position of benzyloxy group has shown best anticonvulsant activity in PTZ and MES models.[29]



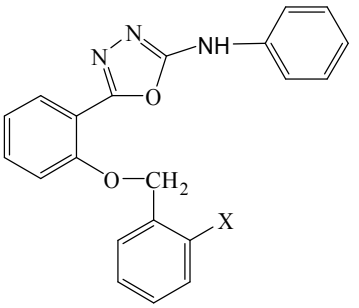
(16)



(17)



(18)



(19)

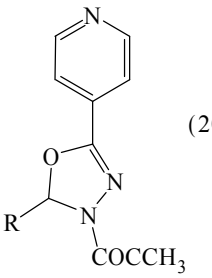
X= F, Cl
R= Me, Et, Bz

Sadaf Jamal Gilani *et al* (2009) synthesized 1-(2-(2-substitutedphenyl)-5-(pyridine-4-yl)-1,3,4- oxadiazol-3(2H)-yl)ethanone **20a-h,** newly synthesized compounds were investigated for anti-convulsant evaluations by qualitative assays using MES (maximal electroshock) and scPTZ (subcutaneous pentylenetetrazole) tests using adult male albino mice (25-30 g).

A 30mg/kg dose was given to mice during MES test which showed protection in half tested mice were **20a, 20c, 20f & 20g** after 0.5h interval of time. These compounds have shown protection after 4h but at a higher dose of 100mg/kg. The compounds **20b, 20d & 20e** have shown protection at a dose of 100mg/kg after duration of 0.5h. These compounds have also shown protection effect but after a duration of 4 hours and also at a higher dose of 300mg/kg.

The compound **20h** has shown protection in the MES test at a dose of 300mg/kg at 0.5 hr as well as 4 hr.

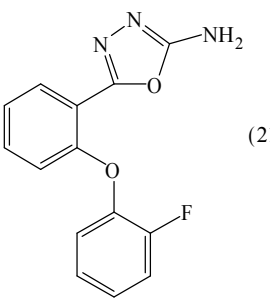
In the scPTZ the compounds **20a, 20c & 20g** have shown the activity at a dose level of 30mg/kg dose level after an interval of 0.5h and 100mg/kg levels after an interval of 4hr but compound **20f** has shown the same activity at a dose 100mg/kg at 0.5 h time interval. These compounds have also shown protection at a higher dose of 300mg/kg after 4 h interval. The rest compounds **20b, 20e &20h** have shown the activity at both time intervals but at a dose of 300mg/kg.[30]



(20)

R
a=*o*-C_6H_5Cl
b=*p*-C_6H_5Cl
c=*o*-C_6H_5OH
d=*m*-C_6H_5OH
e=*p*-$C_6H_5OCH_3$
f=*p*-C_6H_5F
g=*o*-$C_6H_5NO_2$
h=*p*-$C_6H_5N(CH_3)_2$

Ali Almasirad *et al* (2004) synthesized new 2-substituted-5- [2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles **21**, newly synthesized compound was screened for the anti-convulsant activity by PTZ and MES models, and the compound found to have good anti-convulsant activity.[31]



(21)

CONCLUSION

The review has concluded with the key therapeutic activities of the 1,3,4-oxadiazole. This compound has shown a wide range of therapeutic importance. This paper comprises of all the major pharmacological activity of 1,3,4-oxadiazole and it can be used for further researches. The major activities of 1,3,4-oxadiazole are anti-microbial, anti-inflammatory, analgesic, anti-tumour, anti-convulsant, anthelmintic, herbicidal, antioxidant and anti-hepatitis B viral activities.[32]

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