Review Article

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

Rituparna Palit *, Nikita Saraswat, Jagannath Sahoo
Department of Pharmacy, Shri Ram Murti Smarak College of Engineering and Technology, Bareilly, U.P, India
*Corresponding Author Email: rituparna.palit32@gmail.com

Article Received on: 11/12/15 Revised on: 04/01/16 Approved for publication: 14/01/16

DOI: 10.7897/2230-8407.07212

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. 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. The five membered oxadiazole nucleus present in heterocyclic compounds is majorly responsible for the diversified useful biological effects.

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 C3H2ONa, this reduces the aromaticity of the ring (oxadiazole) to an extent that they now reflect the characteristics of a conjugate diene. 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.

1,2,3-oxadiazole 1,2,4-oxadiazole

1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is quiet unstable and reverts in the form of diazoketone tautomer. The stable oxadiazoles appear in a many pharmaceutical drugs which include raltegravir, fasilpon, butalamine, oxolamine, pleconaril and Nesapil. Oxadiazole have occupied a unique place in the field of medicinal chemistry due to its wide range of activities like antimicrobial, anti-inflammatory, anti-tubercular, anti-convulsant, analgesic, herbicidal, anti-oxidant, anti-tumour and anti-hepatitis B viral activities.

1,2,5-oxadiazole 1,3,4-oxadiazole

BIOLOGICAL ACTIVITIES

It is an important challenging task for medicinal chemists to develop new anti-microbial, anti-inflammatory, analgesic, anti-tumor, anti-convulsant, antihelmintic, 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 bacteria should have 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.
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, 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 screened for their anti-bacterial and anti-fungal activities against Gram negative bacteria [Escherichia 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

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 Escherichia coli, Pseudomonas picketti, Bacillus subtilis and Staphylococcus aureusby and Micrococcus luteus by agar well diffusion method and anti-fungal activity against Trichphytonlongifusus, Candida albicans, Aspergillus flavus, Micosporumcanis, Fusarium solani and Candida glabratausing agar plate technique. Compounds 4d exhibit moderate activity (60%) against Aspergillus flavus and Trichphytonlongifusus respectively.23

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
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.

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.

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 ulcerogenic activity.
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

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

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-NO2 showed moderate to good activity against selected cell line.27

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

<table>
<thead>
<tr>
<th>Compound(14)</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4-chloro</td>
</tr>
<tr>
<td>b</td>
<td>3-chloro</td>
</tr>
<tr>
<td>c</td>
<td>4-flouro</td>
</tr>
<tr>
<td>d</td>
<td>4-methoxy</td>
</tr>
<tr>
<td>e</td>
<td>1-naphyl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound(15)</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=</td>
<td>CH3-O</td>
</tr>
<tr>
<td>R’=</td>
<td>H, 2-Cl, 4-NH2, 4-NO2, 3,5-diNO2</td>
</tr>
</tbody>
</table>
Anti-Convulsant Activity

1,3,4-oxadiazole when substituted with an amino group at 5th position have good anti-convulsant activity.\textsuperscript{28}

Afschin Zarghi et al \textit{(2008)} synthesized 2-Amino-5-(2-halo-2-benzyloxyphenyl)-1,3,4-oxadiazoles \textit{16}, 5-(2-Halo-2-benzyloxyphenyl)-2-mercapto-1,3,4-oxadiazole \textit{17}, 2-Alkylthio-5-(2-halo-2-benzyloxyphenyl)-1,3,4-oxadiazole \textit{18} and 2-Anilino-5-(2-halo-2-benzyloxyphenyl)-1,3,4-oxadiazole \textit{19}, newly synthesized compounds were investigated for anti-convulsant evaluations by qualitative assays using MES (maximal electroshock) and PTZ (pentylentetrazole) 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 \textit{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.\textsuperscript{29}

Sadaf Jamal Gilani et al \textit{(2009)} synthesized 1-(2-(2-substitutedphenyl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone \textit{20a-h}, newly synthesized compounds were investigated for anti-convulsant activity by PTZ and MES models, a 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 \textit{20a}, \textit{20c}, \textit{20f} & \textit{20g} after 0.5h interval of time. These compounds have shown protection after 4h but at a higher dose of 100mg/kg.

The compound \textit{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 \textit{20a}, \textit{20c} & \textit{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 \textit{20f} has shown the same activity at a dose 100mg/kg at 0.5h time interval. These compounds have also shown protection at a higher dose of 300mg/kg after 4h interval. The rest compounds \textit{20b}, \textit{20d} & \textit{20e} have shown the activity at both time intervals but at a dose of 300mg/kg.\textsuperscript{30}

Ali Almasirad et al \textit{(2004)} synthesized new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles \textit{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.\textsuperscript{31}
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.21

REFERENCES


32. Dr. Murthy MS, Dr. Sudhakar M, Raja reddy A*, Dr. Rao VU. Different Pharmacological Activities of 2,5-Disubstituted 1,3,4-Oxadiazoles. Scholars Academic Journal of Pharmacy 2013;2(4):333-339.

Cite this article as:

Source of support: Nil, Conflict of interest: None Declared

Disclaimer: IRJP is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publish quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. IRJP cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of IRJP editor or editorial board members.