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An Updated Review on Synthesis and Biological Activities of 1, 3, 4-Oxadiazole Derivatives

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Abstract: ***Many varieties of biological activities can be synthesized by various methods by the series of derivatives of 1, 3, 4-oxadiazole having. These biological activities include anti-microbial, anti-cancer, anti-inflammatory, anti-HIV, anti-tubercular, anti-diabetic, anti-fungal etc. In this updated review article we have reviewed various synthesis methods of derivatives of1,3, 4-oxadiazole nucleus and evaluation of various biological activities.***

Keywords: 1, 3, 4oxadiazole, derivatives, synthesis, biological activity

1. Introduction

The oxadiazole chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically, which comprise oxadiazole moiety in association with various heterocyclic rings. Oxadiazole is a cyclic compound containing one oxygen and two nitrogen atoms in a five membered ring. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring. The capacity of 1, 3, 4-oxadiazole nucleus to undergo variety of chemical reactions including electrophillic substitution, nucleophilic substitution, thermal and photochemical which made it medicinal backbone on which a number of potential molecules can be constructed. Oxadiazoleis the parent compound for a vastclass of heterocyclic compounds.

These are azoles with oxygen and nitrogen. Oxadiazole moiety and its various derivatives studied frequently in the past few decades and found potent in various pharmacological and pathological conditions. Oxadiazole derivatives have been found to possess broad spectrum antimicrobial activity and therefore are useful substructures for further molecularexploration.

The first monosubstituted 1,3,4-Oxadiazoles were reported in 1955 by two independent laboratories. Since 1955 other workers have extended this reaction 1, 3, 4-Oxadiazole boils at 150° C. Oxadiazole exist in four isomeric forms as shown in Figure 1.

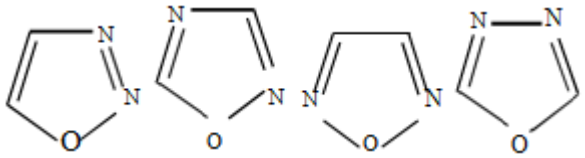

Figure 1: Isomer Structure

Oxadiazole is important heterocyclic ring present in a large number of biologically active molecules of different pharmacological classes. Oxadiazole derivatives have been the subject of numerous reports highlighting their chemistry and use in the recent past. Oxadiazole ring has been shown to impart anti-inflammatory properties in compounds designed as orally-active nonulcerogenic agents or in products formulated as analogs of fenamates for the inhibition of cyclooxygenase and 5-lipooxygenase. Oxadiazole are the major compound of heterocyclic nucleus for the development of new drugs and the drugs of oxadiazole were the first effective chemotherapeutic agent to be employed systemically for the prevention & cure of bacterial infection. Some oxadiazoles with different substituents, especially with a 4-hydroxyphenyl moiety at different locations on the five-membered heterocyclic ring produced fungicidal and bactericidal agents of various potencies

About1, 3, 4-Oxadiazole

Thewidespreaduseof1, 3, 4-oxadiazolesasascaffoldin medicinal chemistry renders this moiety as an important bioactive class of heterocycles. These molecules are also utilized as pharmacophores due to their favorable metabolic profile and ability to engage in hydrogen bonding. Inparticular, marketed antihypertensive agents such as tiodazosin and nesapidil, as well as antibiotics such as furamizole contain the oxadiazole nucleus. They are also useful as HIV integrase inhibitors and the angiogenesis inhibitors. Moreover, 1, 3, 4-oxadiazole derivatives are among the most widely employed electron-transporting andhole-blocking materials in the development of organic light emitting diodes (OLEDs), which are used in energy efficient, full-color and fiat-panel displays. From the literature survey, 1, 3, 4-oxadiazole nucleus has been found to possess diverse pharmacological activities such as antibacterial, anti-inflammatory, analgesic, anti-tubercular, anthelmintic anticonvulsant, muscle relaxant activity and anticancer activity.

Oxadiazole derivatives have been found to possess broad spectrum antimicrobial activity and therefore are useful substructures for further molecular exploration. Furamizole (Figure 1.2) is a compound which is based upon 1,3,4-oxadiazole ring and has strong antibacterial activity.

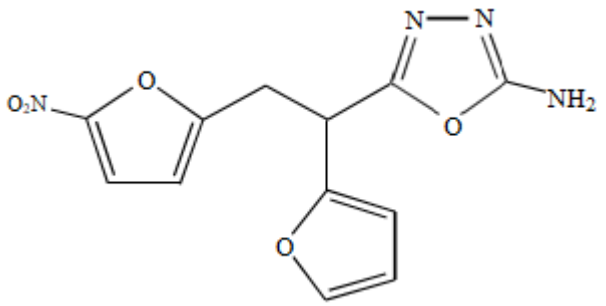

Figure 2: Furamizole

Applications of 1,3,4-Oxadiazole

1, 3, 4-oxadiazoles are biologically active, synthetically useful and important heterocyclic compounds for these reasons the chemistry of 1,3,4-oxadiazoles have been the subject of many investigations. Cerric ammonium nitrate has received considerable attention as an inexpensive and easily available catalyst for various organic reactions such as Oxidation, Oxidative addition, Nitration, Photo-oxidation, Polymerization etc. Some material applications of 1,3,4-oxadiazole derivatives lie in the field of liquid crystals and photosensitizer. Many seed oils, fatty acids and their derivatives are known for their pesticidal, antimicrobial and antifungal activities. Thus fatty acids on derivatization to the heterocyclic compounds can be used as valuable oleo-chemicals.

Versatile Biological Behaviour

1) Basant Kumar, et al,(2016): Heterocyclic compounds have been an interesting area for the study of synthesis and biological activity of novel oxadiazole derivatives for a long time. Heterocyclic compounds possess diverse biological properties that have led to intense study and research of these compounds. One of these compounds 1,3,4- Oxadiazole is a versatile heterocyclic nucleus is a novel molecule which attract the medicinal chemist to search a new therapeutic molecule. 1,3,4-oxadizole exhibited a wide range of biological activities which includes antimicrobial activity, anti- tubercular, anticonvulsant, antidiabetic, anti-allergic, enzyme inhibitors, anti-HIV activity, antipyretic activity, Immunosuppressive activity, Spasmolytic Activity, antioxidant activity, Anti-Alzheimer's activity cardiovascular acivity, anti- inflammatory, anti-tumor activity, insecticidal activity, CGRP receptor antagonists, anti-anthelmintic activities. Results of various derivatives of different oxadiazole and their substitutions with diversebiological activities are reviewed in present article.
2) Musmade Deepak S., et al, (2014) 1,3,4-Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. It is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogens (-N=) [1, 2]. There are three known isomers: 1,2,4-oxadiazole (2), 1,2,3- oxadiazole (3) and 1,2,5- oxadiazole (4). However, 1,3,4-oxadiazole and 1,2,4- oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important construction motif for the development of new drugs. Compounds containing 1, 3, 4-oxadiazole cores have a broad biological activity spectrum including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and anti-diabetic properties. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids, esters and carboxamides. The ability of 1,3,4-oxadiazoleheterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential. The several examples of compounds containing the 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir®, an antiretroviral drug [3] and Zibotentan® an anticancer agent. Oxadiazole nucleus is present in antihypertensive drugs such as tiodazosin and nesapidil and antibiotics such asfuramizole.

2. Antimicrobial Activity

1. Ravitas Deshmukh,et al,(2011) synthesized a series of 5H-[1,3,4]oxadiazolo[3, 2-a] [1,3,5] triazine-5-thione. The newly synthesized compounds were evaluated for their antibacterial activity. [Deshmukh Ravitas, et al, 2011]

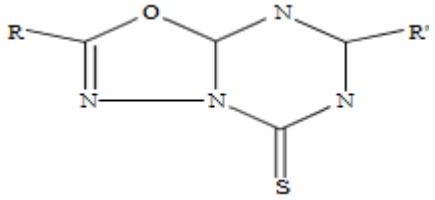

Figure 3: Structure of 5H-[1, 3, 4]oxadiazolo[3,2-a][1,3,5]triazine-5-thione

2. Manish Srivastava, et al, (2010) synthesized a novel series of 2-Amino-5-(4 Nitro)phenyl-1,3,4-Oxadiazole derivatives All the six compounds were tested in vitro for their antibacterial activity against two Gram-positive bacteria namely Staphylococcus aureus, Bacillus subtilis and two Gram-negative bacteria namely Escherichia coli and Pseudomonas aeruginosa. All the compounds of the tested series possessed good antimicrobial activity. Two of these compounds 3a and 3b exhibited good antibacterial activity against both Gram-positive and Gram negative bacteria. [Srivastava Manish, et al, 2010]

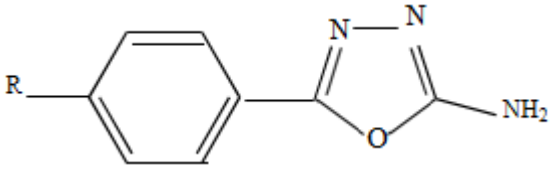

Figure 4: Structure of 2-Amino-5-(4 Nitro)phenyl-1,3,4-Oxadiazole

3. Selvakumar Kanthiah, et al, (2011) synthesized a series of 5-(2-aminophenyl)-1,3,4- oxadiazole-2(3H)-thione derivatives by mannich reaction. In vitro anti-microbial activity was evaluated by disc diffusion method against gram +ve organisms such as Staphylococcus aureus, Streptococcus pyogenes, gram –ve organisms such as Escherichia coli, Klebsiellaaerogenes and fungus such as

Candida albicans. Compounds 1a, 1b, 1c and 1d showed moderate antibacterial and antifungal activities.[Kanthiah Selvakumar, et al,2011]

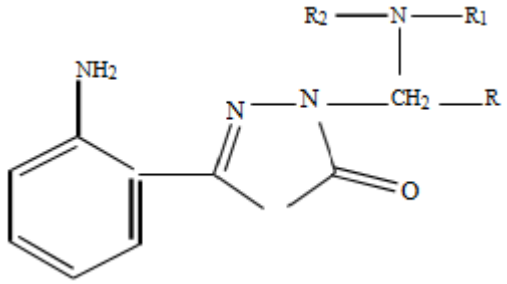

Figure 5: Structure of 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3H)-thione

4. Rakesh Chawla, et al, (2010) synthesized some new 2-(3-chloro-1 benzo[b]thiophen- 2-yl)-5-substituted phenyl-1,3,4-oxadiazoles The compounds exhibited significant antibacterial and moderate antifungal activities. Compounds 4c and 4e were found to be most potent with activities, even better than standard drug ciprofloxacin against S.aureus and B. subtilis.

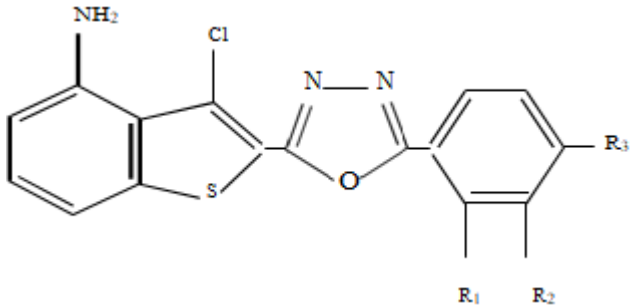

Figure 6: Structure of 2-(3-chloro-1benzo[b]thiophen-2-yl)-5-substitutedphenyl-1,3,4-oxadiazole

5. N. Jain, et al, (2009) synthesized some new 2-[5-(aryl)-[1,3,4]oxadiazole-2 ylsulfanyl]alkanoic acids and studied for their antibacterial activity. All the compounds were evaluated for their in vitro antibacterial activity against two Gram negative strains (Escherichia coli and Pseudomonas aeruginosa) and two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and their minimum inhibitory concentration (MIC) were determined.

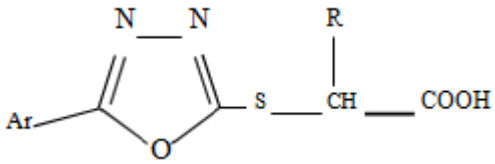

Figure 7: Structure of 2-[5-(aryl)-[1,3,4]oxadiazole-2 ylsulfanyl]alkanoic acids

6. Rakesh Saini , et al, (2009) synthesized 5 – (Benztriazole 1 – yl– methyl) – 2 – (aryl)-1, 3, 4 – oxadiazole derivatives. The Antimicrobial activity of the synthesized compounds was evaluated, on Streptococcus aureus and E. coli. The present investigation deals with the synthesized compounds possessing good antimicrobial activity.

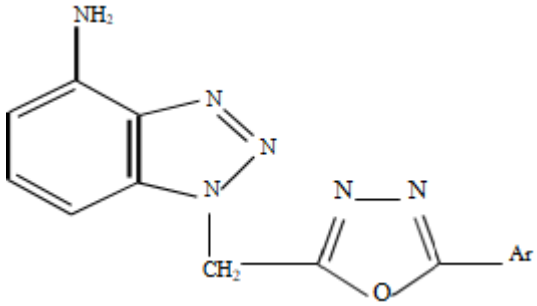

Figure 8: Structure of 5 – (Benztriazole 1 – yl – methyl) – 2 – (aryl)-1, 3, 4 –oxadiazole

7. L. Srikanth, et al, (2010) synthesized a novel series of 3-(5-phenylamino- [1, 3, 4] oxadiazol-2yl methyl)-3H-Benzooxazol-2-one. All the synthesized compounds were screened for antibacterial activity. The compounds were found to have good activity against gram-positive bacteria than gram-negative bacteria. Among all the active compounds thiadiazole and oxadiazole derivatives showed good activity.

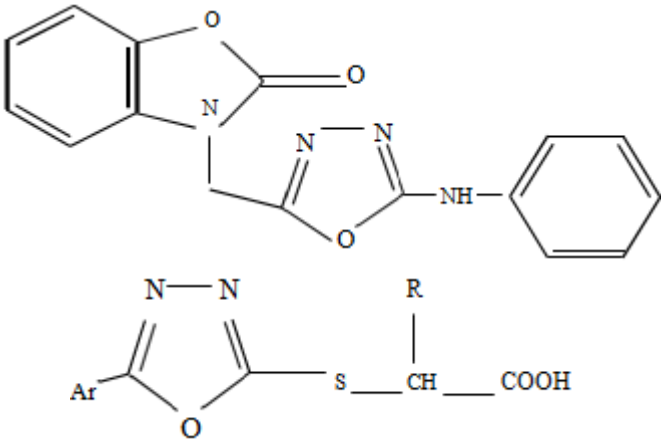

Figure 9: Structure of 2-[5-(aryl)-[1, 3, 4] oxadiazole-2 ylsulfanyl] alkanoic acids

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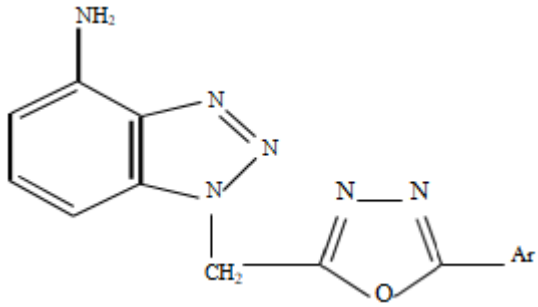

Figure 10: Structure of 5 – (Benztriazole 1 – yl – methyl) – 2 – (aryl)-1, 3, 4 –oxadiazole

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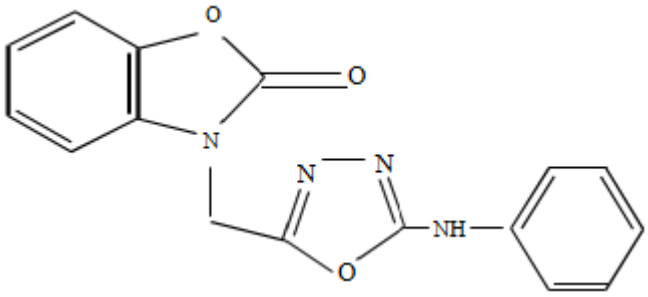

Figure 11: 3-(5-phenylamino- [1, 3, 4] oxadiazol-2yl methyl)-3H- Benzooxazol-2-one

10. B. Rajeeva , et al, (2009) described some new 2-(5-substituted-1,3,4-oxadiazole-2-yl)- 1,3- benzothiazole (3a-j) were synthesized by refluxing benzothiazolylcarboxyhydrazide with different aryl acids in phosphoryl chloride. Structures of the synthesized compounds were established on the basis of 1H NMR and Mass spectral data. The antimicrobial activity of the synthesized compounds was evaluated by disc diffusion method.

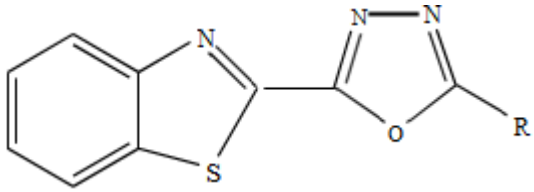

Figure 12: Structure of 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3- benzothiazole

11. ZuhainMuhi-eldeen, et al, (2008) synthesized alkyl, alkenyl, sulfonyl, thiocarbamates and Mannich derivatives and characterized through IR, NMR, and Elemental analysis. It is of interest to report the isomerization rearrangement of propynyl to allene group in Mannich reaction under basic condition. The most promising compound as antibacterial agent was 5-(pyridyl)-1, 3, 4- oxadiazole-2-benzylthiocarbamates. The MIC for the synthesized compounds indicates that the conversion of sulfhydryl group in 1,3,4- oxidazole into alkyl 3, allene 8, sulfonyl 13 derivatives and mannich product 19 showed a weak antimicrobial activity. However, thiocarbamates 16 and 17 were effective against Gram positive and Gram negative bacteria with less activity activity against fungi.

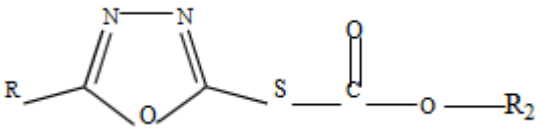

Figure 13: Structure of 5-substituted-1,3,4-oxadiazolyl–2– thiocarbamates

12. Anil N. Mayekar, et al, (2010) described a series of new 1,3,4-oxadiazole derivatives having 6-bromonaphthalene moiety. 2-[(6-bromo-2-naphthyl) oxy] acetohydrazide was treated with various substituted aromatic acids in presence of POCl3 to give 2-{[(6-bromo- 2-naphthyl) oxy]methyl}-5-aryl-1,3,4-oxadiazole. Also the hydrazide on treating with CS2/KOH gave 5-{[(6-bromo-2-naphthyl) oxy]methyl}1,3,4-oxadiazole-2(3H)-thione, which was subjected to Mannich reaction to get a series of Mannich bases and with alkyl/aryl halide to give 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5 [(alkyl/aryl)thio]-1,3,4- oxadiazole. The newly synthesized compounds were characterized by analytical and spectral data. Antimicrobial activities of these compounds were carried out and some of them have exhibited good activity.

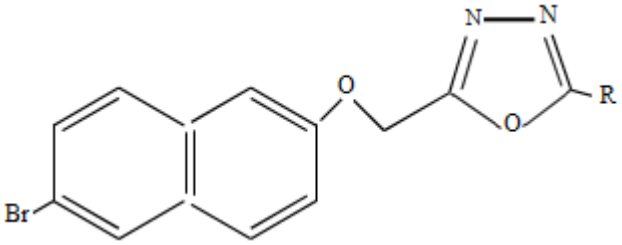

Figure 14: Structure of 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-aryl-1,3,4-oxadiazole

3. Anti-inflammatory Activity

1. Biswa Mohan Sahoo, et al, (2011) synthesized a new 5-phenyl- 1, 3, 4- oxadiazole- 2- thiol derivative by the ring closure reactions of benzohydrazides with carbon disulphide in presence of ethanolic KOH followed by substitution with secondary amines at 2nd position. All the newly synthesized compounds were characterized by IR, NMR and LC- MASS spectral data. Most of them were tested for their anti-inflammatory and antibacterial activity.

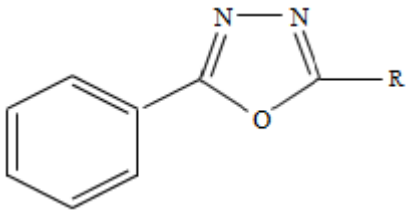

Figure 15: Structure of 5- phenyl (2-substituted) - 1, 3, 4- oxadiazole

Sudhir Bhardwaj, et al, (2011) described a reaction of isonicotinohydrazide with different aromatic aldehydes under the microwave irradiation gives Schiff's bases. These Schiff's bases were converted into 1, 3, 4-oxadiazole derivatives by treating with acetic anhydride under the microwave irradiation. The structures of the compounds were confirmed by elemental analysis, IR, 1H NMR and Mass spectral data .The synthesized compounds were screened for antimicrobial, analgesic and anti-inflammatory activities.

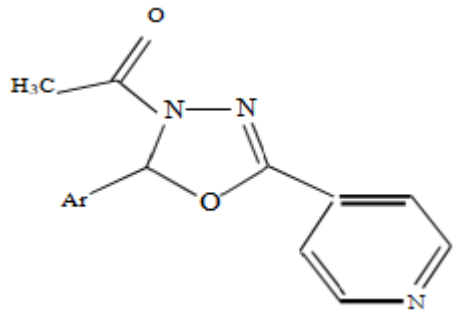

Figure 16: Structure of 1-(2-(substituted-phenyl)-5-(pyridin-4-yl)-1,3,4oxadiazol3(2h) yl) ethanone

2. Adnan A. Kadi, et al, (2007) described a reaction of 1-adamantanecarbonyl chloride with certain carboxylic acid hydrazides in pyridine yielded the corresponding N-acyl adamantane- 1-carbohydrazide derivatives 3aej, which were cyclized to the corresponding 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles 4aej via heating with phosphorus oxychloride. Compounds 4aej, 7aeg, and 8aeg were tested for in vitro activities against a panel of bacteria and the yeast-like pathogenic fungus Candida albicans Meanwhile, compounds 4i and 8g displayed marked antifungal activity against C. albicans. In addition, the in vivo anti-inflammatory activity of the synthesized compounds was determined using the carrageenin-induced paw oedema method in rats. The oxadiazole derivatives 4c, 4g, 4i and 4j produced good dose dependent anti inflammatory activity.

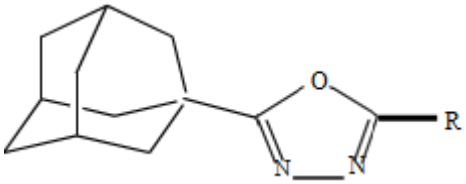

Figure 17: Structure of2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles

3. Mohd Amir, et al, (2007) described the synthesis of some new 1,3,4-oxadiazole derivatives and 1,2,4-triazine-5-one has been described. IR, 1H NMR and mass spectral data support the structures of newly synthesized compounds. All the compounds have been tested in vivo for their anti-inflammatory activity by carrageenin-induced rat paw edema method.

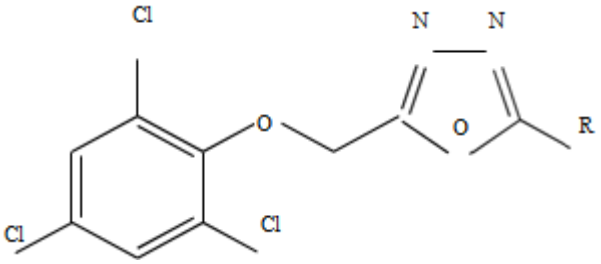

Figure 18: Structure of 2-substituted aryl-5-(2,4,6-trichloro-phenoxymethyl)-1,3,4- oxadiazole

4. Anticonvulsants

1. AfshinZarghi, et al, (2008) synthesized a new series of 2-substituted-5-{2-[(2- halobenzyl) thio) phenyl}-1,3,4-oxadiazoles and investigated for anticonvulsant activities Electroshock and pentylenetetrazole-induced lethal convulsion tests showed that some of the synthesized compounds had significant anticonvulsant activity. The structure-activity relationship study of these compounds indicated that the introduction of an amino group at position 2 of 1,3,4-oxadiazole ring and a fluoro substituent at the ortho position of the benzylthio moiety had the best anticonvulsant activity.

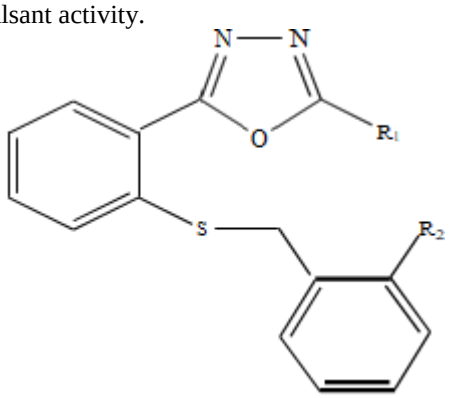

Figure 19: Structure of 2-substituted-5-{2-[(2-halobenzyl)thio)phenyl}-1,3,4-oxadiazoles

2. Ali Almasirad, et al, (2007) synthesized a series of 5-[2-(phenylthio)phenyl]-1,3,4- oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives. Compounds were evaluated in vivo for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests, respectively. Only compound 3-amino-5-[2-(phenylthio) phenyl]-4H-1,2,4-triazole (5) showed weak anticonvulsant activity. However, most of the compounds were active in rotarod test and the most effective compound was5-[2-(phenylthio)phenyl]-1,3,4 oxadiazole-2(3H)-one (13) which had comparable activity with diazepam.

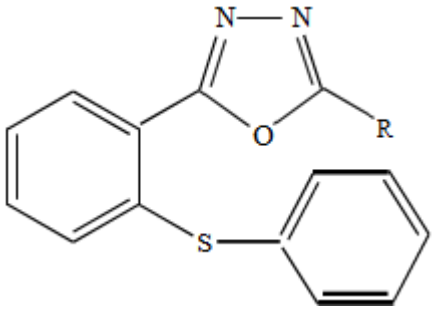

Figure 19: Structure of 5-[2-(phenylthio) phenyl]-1, 3, 4-oxadiazole

5. Antioxidant Activity

1. Sonia George, et al, (2008) Reaction of ethyl-6-methyl–2-oxo-4-aryl-1, 2, 3, 4- tetrahydropyrimidin-5-carboxylates (1a-i) with hydrazine hydrate yielded 6-methyl-2-oxo- 4-aryl-1,2,3,4-tetrahydropyrimidin-5-carbohydrazides (2a-i). These products, on reaction with cyanogen bromide, gave 5-(5-amino-1,3,4--oxadiazol-2-yl)-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones (3a-i). The resultant aminooxadiazolylpyrimidinones were condensed with isatin to obtain various3-5-(6-methyl-4-aryl-2-oxo-1, 2, 3, 4 tetra hydropyrimidin--5-yl)-1, 3, 4-oxadiazol-2-yl-imino-1,3-dihydro-2H-indol--2-ones (4a-i). These products were characterizedbyIR, 1HNMR, mass spectra and elemental analysis. Products (4a-i) revealed promising antibacterial, antifungal and antioxidant activity.

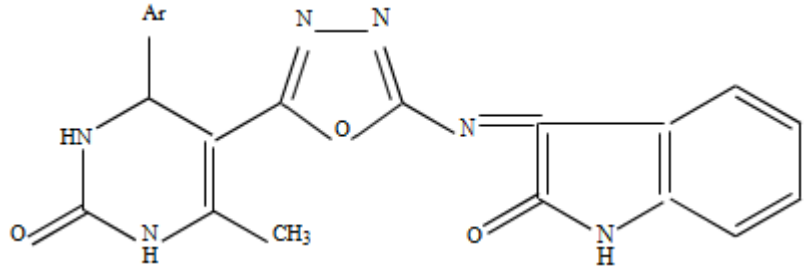

Figure 20: Structure of 3-5-(6-methyl-4-aryl-2-oxo-1,2,3,4tetrahydropyrimidin--5-yl)- 1,3,4-oxadiazol-2-yl-imino-1,3-dihydro-2H-indol--2-ones

2. M VijeyAanandhi, et al, (2010) described a series of substituted pyridinyl 1, 3, 4 oxadiazole derivatives were synthesized from Schiff bases of nicotinic acid derivatives through chlorination followed by reaction with hydrazine hydrate and with the use various aldehydes. The synthesized compounds were characterized by elemental analysis, IR, 1H NMR and Mass Spectra. All the compounds were screened for in vitro antioxidant activity by DPPH and Nitric oxide scavenging assay. Compounds substituted with electron donating groups like methoxy and hydroxyl showed higher antioxidant activity.

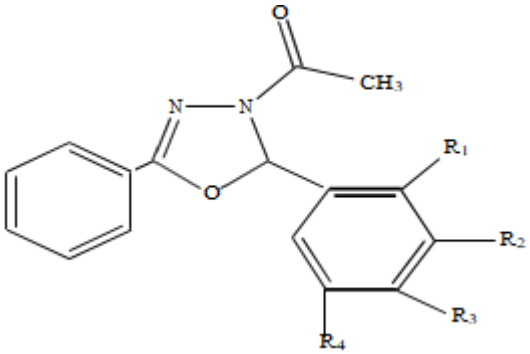

Figure 21: Structure of 1-(2-(2-substituted)-5-(pyridine-3-yl)-1, 3, 4-oxadiazole-3(2H)-yl) ethanone

6. Other Activity

1. Kantham Srinivas, et al, (2010) described the synthesis of 1-[(5-sustituted-1,3,4- oxadiazol-2-yl) methyl]-4-benzylpiperazines was carried out by refluxing the 1-benzylpiperazine II with ethylchloroacetate III in dry acetone in the presence of potassium carbonate and subsequent hydrazinolysis with hydrazine hydrate. Finally 2-(4- benzylpiperazin-1-yl)aceto- hydrazide V was treated with appropriate carboxylic acids in the presence of phosphorous oxy chloride to produce title compounds. All the title compounds (VIa-j) were screened for anticancer activity using HBL-100 cell lines by MTT method and anti bacterial activity against B.subtiliis, S.aureus, E.coli and P.vulgaris.

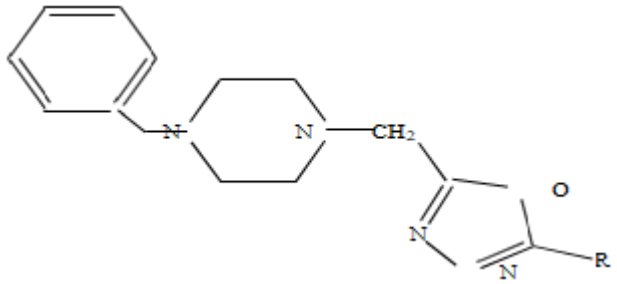

Figure 22: Structure of 1-[(5-sustituted-1,3,4-oxadiazol-2-yl)methyl]4benzylpiperazines

2. A. H. Shridhar, et al, (2011) described a series of 2, 2'-(5-nitrobenzene-1, 3-diyl) bis (5-alkyl-1, 3, 4-oxadiazole) (2a-e) 5,5'-(5-nitrobenzene-1,3-diyl)bis(1,3,4-oxadiazole-2-thiol) (3) and 5,5'-(5-nitrobenzene-1,3-diyl)bis(4-amino-4H-1,2,4-triazole-3-thiol(5) were obtained via reaction of 5-nitro iso-phthalicdihydrazide (1). All these newly synthesized compounds were characterized by IR, NMR and Mass, spectral studies. Newly synthesized compound displayed potent antibacterial and antinociceptive activity.

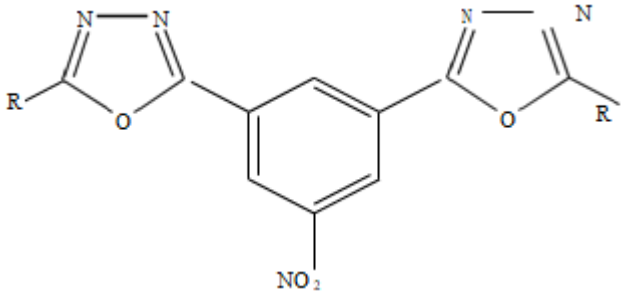

Figure 23: Structure of 2, 2'-(5-nitrobenzene-1, 3-diyl) bis (5-alkyl-1, 3, 4-oxadiazole)

3. Rakesh R. Somani, et al, (2011) described synthesis of some new 2, 5-diaryl-1, 3, 4- oxadiazole derivatives starting from Isoniazide (INH). The target compounds11-20were obtained by treating INH with various aromatic aldehydes and monosaccharides to give corresponding Schiff 's bases, which upon subsequent oxidation, by using either method A, B or C, yielded desired compounds. They were purified and characterized by spectroscopic techniques and elemental analyses. These compounds were evaluated for antibacterial, antifungal and antiviral activities. Compounds 11, 16 and 17 exhibited good antibacterial and antifungal activity, however, none of the compounds were enough active against various strains of virus.

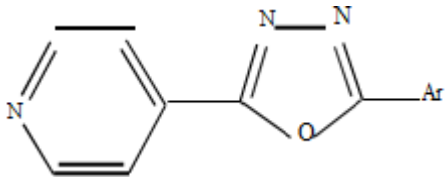

Figure 24: Structure of 2, 5-Diaryl-1, 3, 4-oxadiazole

7. Conclusion

This article summarizes the synthesis and biological activities of 1, 3, 4-oxadiazole derivatives. From this it is found that this five member heterocyclic molecule can be synthesized by various methods and those derivatives are having verities of activities. Such as anticancer, antimicrobial, anti- inflammatory, anti- HIV, anti-tubercular, anti-diabetic, anti-fungal etc. So study on this molecule is useful to the mankind.

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