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Review Article

Oxadiazole a nucleus with versatile biological behaviour

Musmade Deepak S.[*1], Pattan Shashikant R.[2] and Manjunath S. Yalgatti[3]

[1]*Department of Pharmaceutical Chemistry, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423603, Jawaharlal Nehru Technological University, Hyderabad, Telgana, India.*
[2]*Department of Pharmaceutical Chemistry, Adv. Abasaheb Kakade's College of Pharmacy, Bodhegaon, Shevgaon, MS, India.*
[3]*Head, Department of Pharmaceutical chemistry, Srikrupa Institute of Pharmaceutical Sciences, Vill: Velkatta, Mdl: Kondapak, Rd: Siddipet, Dist: Medak. 502277 Telangana state.*

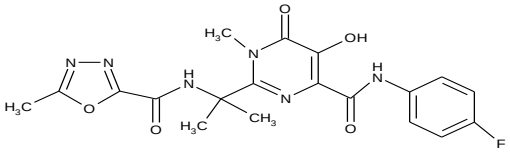
Abstract

The discovery of Oxadiazoles leads to the development of some medicinally important compounds with wide range of biological activities. Oxadiazoles can be synthesized by several methods using carboxylic acid as a starting material. Since Oxadiazoles had been widely investigated, this review is focused on defining the place of oxadiazoles derivatives in biomedical research, highlighting their versatile biological properties, the mode of action and Structure Activity Relationship (SAR) studies for a variety of antimicrobial, anti-tubercular, anti-cancer activity along with some enzyme inhibitory activities.
Keywords: Oxadiazoles, scaffolds, drug discovery, drug development, biological activities

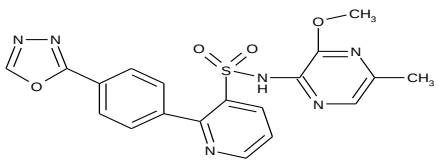
1. Introduction

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 [2]. The ability of 1,3,4-oxadiazole heterocyclic 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 as furamizole.

2. Drugs in market containing oxadiazole as a heterocycle:

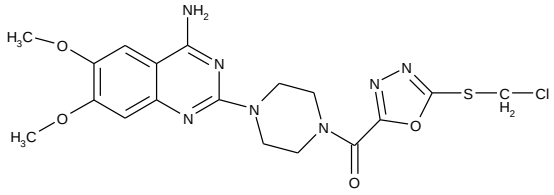


Raltegravir

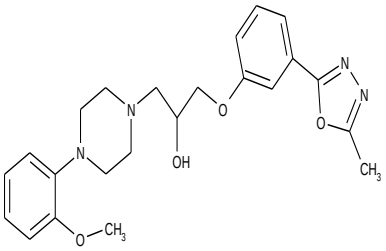


Zibotentan

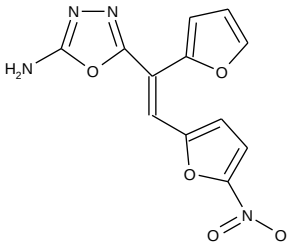
* Correspondence Info
Mr. Musmade Deepak S.
Assistant Professor,
Department of Pharmaceutical chemistry,
SRES's Sanjivani College of Pharmaceutical
Education and Research, Kopargaon, MS, India-423603.
E-mail: deepak.musmade@gmail.com



Tidazosin



Nesapidil



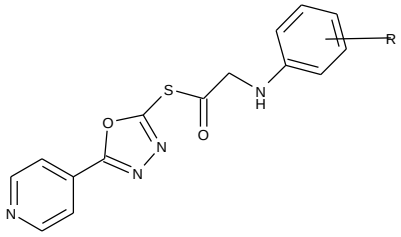
Furamizole

2.1 HIV-1 Integrase and angiogenesis inhibitors

Biologically active molecules containing the oxadiazole motif include the HIV integrase inhibitor and the angiogenesis inhibitor.

2.2 Oxadiazole as an antimicrobial and antiprotozoal agent

Raval *et al* had been reported with synthesis of a series of 2(4-pyridyl)-5[(aryl/heteroarylamino)-1-oxoethyl] thio-1,3,4-oxadiazole and were evaluated for in vitro antibacterial activity. [4]

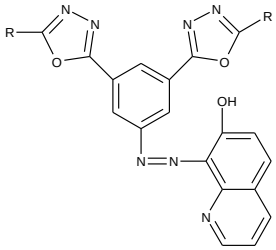


Where

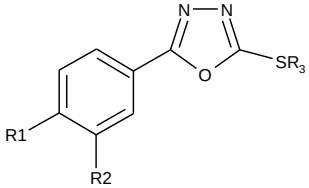
R may be different substituents like –H, -Cl, -CH_3, -OH etc.

Othman *et al* had been reported with the importance of Oxadiazole derivatives as an antibacterial agent.[5]

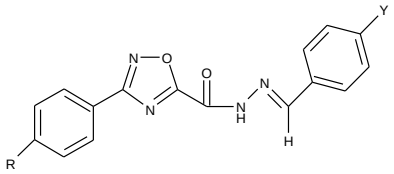
Shridhar *et al* had been reported with synthesis of 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl azo dyes and their evaluation for antibacterial activity.[6]



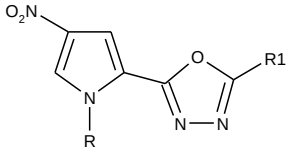
Macaev *et al* had been reported with synthesis of 5-aryl-2-thio-1,3,4-oxadiazole derivatives were screened for their anti-mycobacterial activities against Mycobacterium tuberculosis H37Rv. [7]



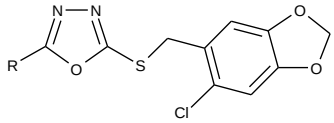
José *et al* had been reported with synthesis and docking studies of 3-(4-substituted-aryl)-1,2,4-oxadiazole scaffold against epimastigote and trypomastigote forms of T. Cruzi.[8]



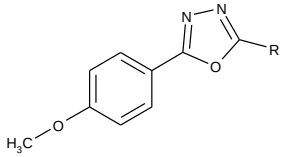
Rane *et al* had been reported with synthesis and antimicrobial evaluation of 42 novel 4-nitropyrrole-based 1,3,4-oxadiazoles. The synthesized molecules were evaluated for anti-bacterial, anti-fungal and anti-tubercular activities. [9]



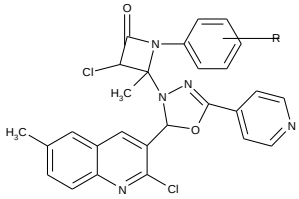
Aziz-ur-Rehman *et al* had been reported with Synthesis of some new 5-substituted-2-((6-chloro- 3,4-methylenedioxyphenyl)methylthio)-1,3,4-Oxadiazole derivatives as suitable antibacterial inhibitors. [10]



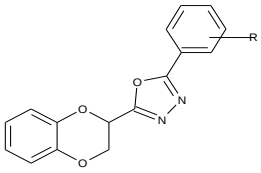
Isloor *et al* had been reported with synthesis of 1,3,4-oxadiazole derivatives containing 2-fluoro-4-methoxy moiety and were evaluated for their anti bacterial activity.[11]



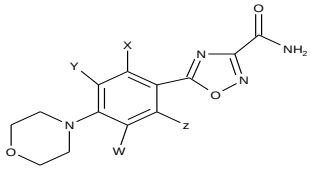
Desai *et al* had been reported with synthesis of 3-chloro-1-(aryl)-4-(2-(2-chloro-6-methylquinolin-3-yl)-5-(pyridin-4-yl)-1,3,4- oxadiazol-3(2H)-yl)-4-ethyl-azetidin-2-ones and were evaluated for their antibacterial activity.[12]



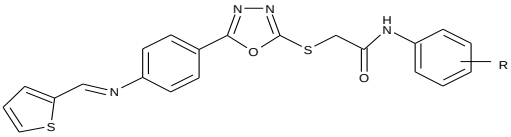
Khalilullah *et al* had been reported with synthesis of 1,3,4-oxadizole derivatives containing 1,4-benzodioxane and evaluation of same for antibacterial activity.[13]



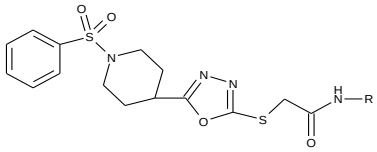
Pace *et al* had been reported with Synthesis and preliminary antibacterial evaluation of Linezolid-like 1,2,4-oxadiazole derivatives. [14]



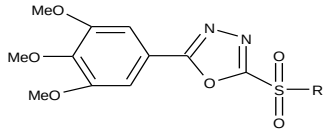
Desai *et al* had been reported with Synthesis and antimicrobial screening of 1,3,4-oxadiazole and clubbed thiophene derivatives. [15]



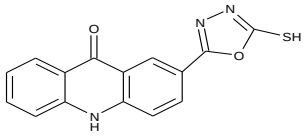
Aziz-ur-Rehman *et al* had been reported with Synthesis, spectral analysis and anti-bacterial study of N-substituted derivatives of 2-(5-(1-(phenylsulfonyl) piperidin-4-yl)-1,3,4-oxadiazol- 2-ylthio)acetamide. [16]



Bao-An Song had been reported with the synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5- (3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. [17]

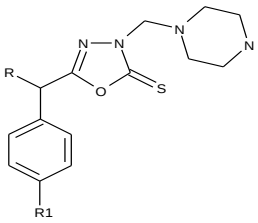


Salimon *et al* had been reported with Synthesis and pharmacological evaluation of 9(10H)-acridone bearing 1,3,4-oxadiazole derivatives as antimicrobial agents. [18]

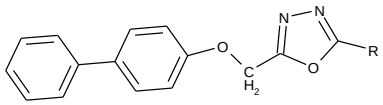


2.3 Anti-inflammatory activity

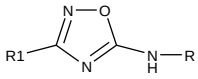
Poojary *et al* had been reported with synthesis of 1,3,4-oxadiazol-2-thiones and were evaluated for their anti-inflammatory activity. [19]



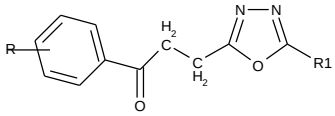
Amir *et al* had been reported with 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid were synthesized in order to obtain new compounds with potential anti-inflammatory activity, analgesic activity and lower ulcerogenic potential.[20]



Fylaktakidou *et al* had been reported with synthesis of 5-amino-substituted 1,2,4-oxadiazoles and were evaluated for in vivo anti-inflammatory activity. [21]

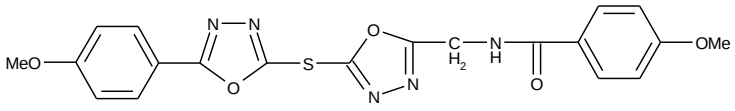


Akhter *et al* had been reported with Aroylpropionic acid based 2,5-disubstituted-1,3,4-oxadiazoles: Synthesis and their anti-inflammatory and analgesic activities.[22]



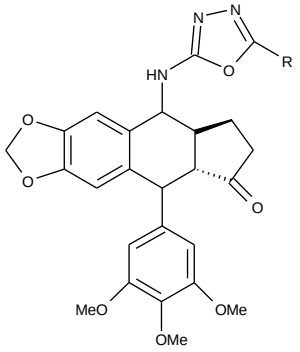
2.4 GOT, GPT AND c-GT inhibitory activity

Tomi *et al* had been reported with synthesis of N-{5-[5-(4-Methoxyphenyl)-1,3,4-oxadiazole-2-yl-sulfanyl]-1,3,4-oxadiazole-2-yl-methyl}-4-methoxybenzamide derivatives and evaluation of same for GOT, GPT and c-GT inhibitory activity.[23]

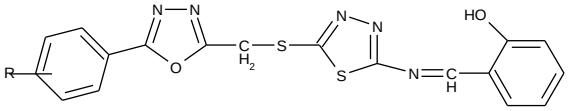


2.5 Anti-cancer activity

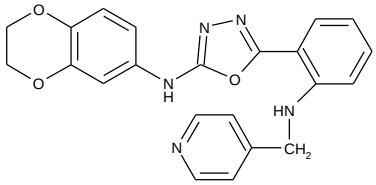
Kun Hu had been reported with synthesis of 4b-(1,3,4-oxadiazole-2-amino)-podophyllotoxin derivatives were designed and synthesized. Their cytotoxicity in vitro against six tumor cell lines (DU-145, SGC-7901, A549, SH-SY5Y, HepG2 and HeLa) were evaluated by standard MTT assay.[24]



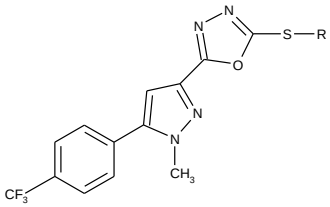
Chen *et al* had been reported with the synthesis of of novel hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing Schiff base moiety were designed, synthesized and evaluated for their in vitro antitumor activities against SMMC-7721, MCF-7 and A549 human tumor cell lines by CCK-8 assay.[25]



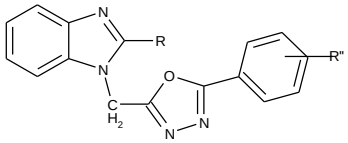
Shafiee *et al* had been reported with One-pot, four-component synthesis of novel cytotoxic agents 1-(5-aryl-1,3,4-oxadiazol-2-yl)-1-(1H-pyrrol-2-yl)methanamines.[26]



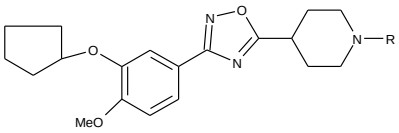
Poojary *et al* had been reported with the Design, synthesis and biological evaluation of a novel series of 1,3,4-oxadiazole bearing N-methyl-4-(trifluoromethyl)phenyl pyrazole moiety as cytotoxic agents. [27]



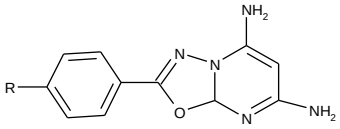
Salahuddin *et al* had been reported with the Synthesis, characterization and anticancer evaluation of 2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1-[5-(substituted phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole. [28]



Shah *et al* had been reported with Synthesis of novel 1, 2, 4-oxadiazoles and analogues as potential anticancer agents.[29]

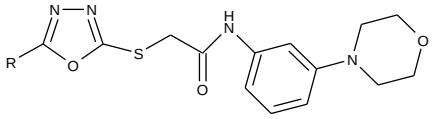


Georgey *et al* had been reported with Novel 1,3,4-heterodiazole analogues: Synthesis and in-vitro antitumor activity. [30]



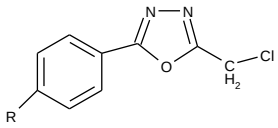
2.6 Haemolytic activity

Aziz-ur-Rehman *et al* had been reported with synthesis of 2-[[5-alkyl/aralkyl-1,3,4-oxadiazol-2-yl]thio]-N-[4-(4-morpholinyl)phenyl]acetamides and were evaluated for their haemolytic activity. [31]



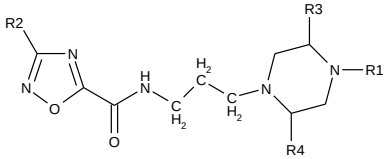
2.7 Antioxidant activity

Padmavathi *et al* had been reported with the synthesis of 2-(Bis((5-aryl-1,3,4-oxadiazol-2-yl)methylthio)methylene)malononitriles and were evaluated for their antioxidant activity. [32]

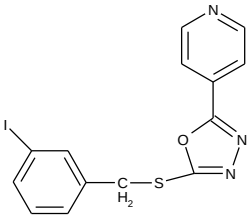


2.8 Inhibitors of GSK-3b Kinase

Ivachtchenko *et al* had been reported with Abstract—Synthesis, biological evaluation, and SAR dependencies for a series of novel aryl and heteroaryl substituted N-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,4-oxadiazole-5-carboxamide inhibitors of GSK-3b kinase. [33]

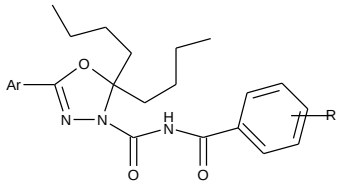


Schmidt *et al* had been reported with Structure-based optimization of oxadiazole-based GSK-3 inhibitors.[34]



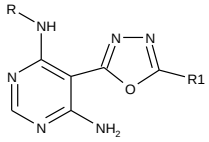
2.9 Monoamine oxidase (MAO) inhibitors

Qian *et al* had been reported with 1,3,4-Oxadiazole-3(2H)-carboxamide derivatives as potential novel class of monoamine oxidase (MAO) inhibitors: Synthesis, evaluation, and role of urea moiety. [35]



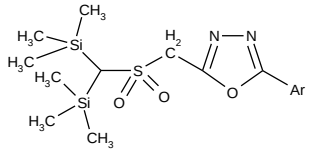
2.10 EGFR/HER2 kinase inhibitory activity

Hughes *et al* had been reported with A novel 5-[1,3,4-oxadiazol-2-yl]-N-aryl-4,6-pyrimidine diamine having dual EGFR/HER2 kinase activity: Design, synthesis, and biological activity. [36]



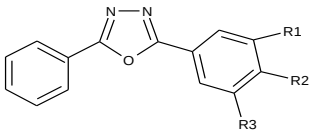
2.11 Anti-allergic activity

Lee *et al* had been reported with Syntheses and anti-allergic activity of 2-((bis(trimethylsilyl) methylthio/methylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazoles. [37]



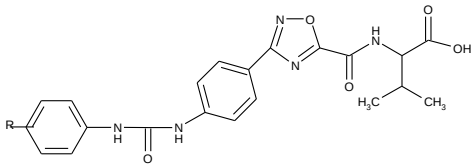
2.12 Aryl hydrocarbon receptor activators

Looper had been reported with the synthesis of 1,2,4-bis-aryloxadiazole that blocks mammary branching morphogenesis through activation of the aryl hydrocarbon receptor (AHR). [38]



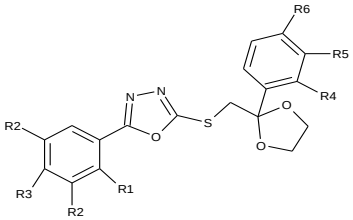
2.13 Diacylglycerol acyltransferase, (DGAT1) inhibitors

Gupte *et al* had been reported with Synthesis and biological evaluation of isoxazole, oxazole, and Oxadiazole containing heteroaryl analogs of biaryl ureas as DGAT1 inhibitors.[39]

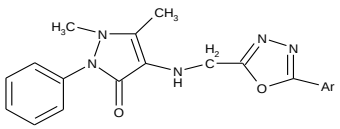


2.14 Anti-tubercular activity

Macaev *et al* had been reported with Synthesis of novel 5-aryl-2-thio-1,3,4-oxadiazoles and the study of their structure–anti-mycobacterial activities. [40]

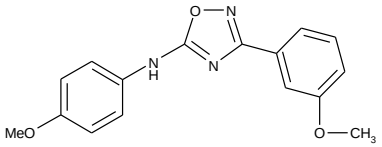


Ahsan *et al* had been reported with Molecular properties prediction and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and antitubercular agents.[41]



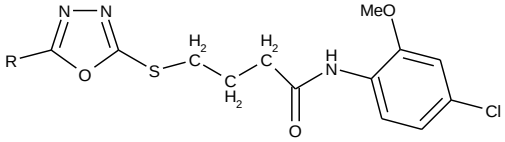
2.15 Tubulin inhibitors

Gakh *et al* had been reported with Identification of diaryl 5-amino-1,2,4-oxadiazoles as tubulin inhibitors: The special case of 3-(2-fluorophenyl)-5- (4-methoxyphenyl)amino-1,2,4-oxadiazole.[42]



2.16 Lipoxygenase inhibitors

Aziz-ur-Rehman *et al* had been reported with Synthesis of new N-(5-chloro-2-methoxyphenyl)-4- (5-substituted-1,3,4-oxadiazol-2-ylthio)butanamide derivatives as suitable lipoxygenase inhibitors. [43]



3. Conclusion

The development of newer drugs in many fields i.e. antibacterials, antivirals, anti cancer etc. Had been started from many years. There is always a need for new pharmaceuticals which have broader spectrum of activities. Along with some novel modes of action to overcome the microbial resistance for currently marketed drugs. Oxadiazoles were identified as a promising class of bioactive heterocycles which exhibit wide range of biological activities. Thus it is considered as a important scaffold for drug discovery and development process. More than 10 possible activities were reported for this nucleus.

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