Available online at www.pharmacie-globale.info ISSN 0976-8157

Review Article

PHARMACIE GLOBALE

INTERNATIONAL JOURNAL OF COMPREHENSIVE PHARMACY

STUDIES ON NITROGEN AND OXYGEN CONTAINING HETEROCYCLIC COMPOUND: 1,3,4-OXADIAZOLE

Kratika Shrivastava*[1], Suresh Purohit[2] and Sarita Singhal

[1]Research Scholar, MJRP University, Jaipur, Rajasthan, India.
[2]Department of Pharmacology, Institute of Medical Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
[3]MJRP University, Jaipur, Rajasthan, India.

Received: 3 January 2011; Revised: 21 February 2011; Accepted: 28 February 2011; Available online: 5 March 2011

ABSTRACT

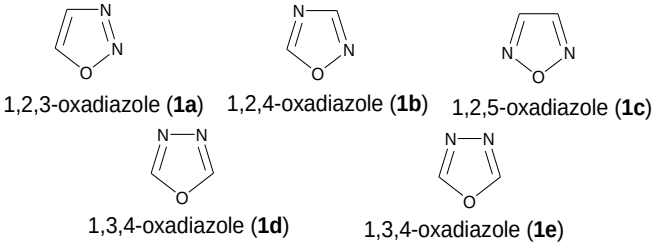
Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules. Out of its four possible isomers, 1, 3, 4-oxadiazole is widely exploited for various applications. The 1, 3, 4-oxadiazole undergoes number of reactions including electrophillic substitution, nucleophilic substitution, thermal and photochemical. The present review attempts to summarize the various routes of synthesis and the reactions of 1, 3, 4-oxadiazole and its derivatives and focus on their biological potential.

Keywords: 1,3,4-Oxadiazole; Antibacterial; Antitubercular; Vasodialatory; antifungal; Cytotoxic; Antiinflammatory; Analgesic; Hypolipidemic; Anticancer; Ulcerogenic activities.

INTRODUCTION

Oxadiazoles belong to an important group of heterocyclic compounds having –N=C–O– linkage. It is well documented that oxadiazole system contains the following members which are numbered by designating the hetero atoms at particular position. There are Four known isomers: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-Oxadiazole (Figure **1a**, **1b**, **1c** and **1d**). 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.[1]

Figure 1. Four isomer of oxadiazole



1,2,3-oxadiazole (**1a**) 1,2,4-oxadiazole (**1b**) 1,2,5-oxadiazole (**1c**)

1,3,4-oxadiazole (**1d**) 1,3,4-oxadiazole (**1e**)

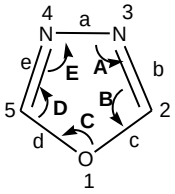
1,3,4-Oxadiazole (Figure **1e**) is a thermally stable aromatic molecule.[2] They have been known for about 80 years, it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas through drug synthesis, dye stuff industry, heat resistant materials, heat resistant polymers and scintillators. Reviews of the relevant literature prior to 1965 are available.[3]

Literature survey reveals that particularly 1, 3, 4-oxadiazole derivatives exhibit wide range of biological activities including Antibacterial[4], Anti-inflammatory[5], fungicidal[6], herbicidal, pesticide[7], anti-leshminasis[8], anticonvulsant[7,8], anti-HIV[9], antibacterial and plant growth regulator activities[10].

***Corresponding Author:**
Kratika Shrivastava
Assistant Professor, Department of Pharmaceutical Chemistry,
Mandsaur Institue of Pharmacy, Mandsaur, Madhya Pradesh, India
Email: shrivastavakratika83@gmail.com

PHYSICAL PROPERTIES OF OXADIAZOLE

Oxadiazole is a five membered heterocycle having two carbons, two nitrogens, one oxygen and two double bonds. The first monosubstituted 1,3,4-Oxadiazoles were reported in 1955 by two independent laboratories.[2,11] Since 1955 other workers have extended this reaction 1,3,4-Oxadiazole boils at 150°C.[12,13] The percentage of C, H, N present in 1,3,4-Oxadiazole is Calculated. (%) for $C_2H_2N_2O$: C; 34.29, H, 2.88; N, 39.99; O, 22.84 Found: C; 34.56, H; 3.19, N; 39.71, O; 22.63.[3,15,16] Its Bond angle and bond length are shown in Table **1** determine with Marvin sketch and Chem Draw.



1,3,4 - Oxadiazole (**4**)

Table 1. Bond angle and Bond length of 1,3,4-Oxadiazole

Bond Angle		Bond Length	
Angle	Bond Angle (°)	Bonds	Bond Length (pm)
A	105.6	a	139.9
B	113.4	b	129. 7
C	102.0	c	134.8
D	113.4	d	134. 8
E	105.6	e	129. 7

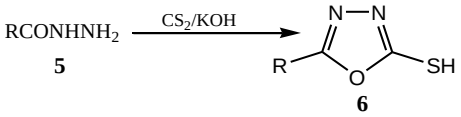
The IR spectra of 1, 3, 4-oxadiazole is characterized by the bonds at 1640-1560 cm-1(C=N) and 1020 cm-1(C=O).[17] The position of both protons of 1, 3, 4-Oxadiazole in 1H-NMR is 1.27. The refractive index $n^{25}D$) of 1,3,4-Oxadiazole is 1.43.[18-20]

CHEMISTRY OF OXADIAZOLE

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom.[21] The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophillic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic *SP*^{2} carbon atom.[22]

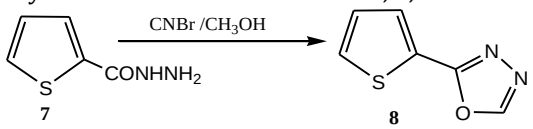
SYNTHETIC ASPECTS OF 1,3,4-OXADIAZOLES

M C Hosur[23] reported synthesis of 2-mercapto-5-aryl-1,3, 4-oxadiazole (**6**) from the properly substituted acid hydrazide (**5**) in presence of CS_2/KOH. This method is very popular since ease in workup and high yields are consistently observed. However, long reaction time is a limiting factor. Number of examples are cited in literature employing this methodology for synthesis of 1,3,4-oxadiazole thione / thiol derivatives.[24]



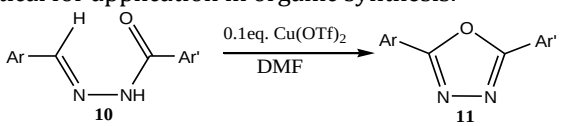
5 6

M A Elborai et al[25] reported synthesis of 2-amino-5-(2'-thienyl)-1, 3, 4-oxadiazole (**8**) by the condensation of 2-thienyl hydrazide (**7**) with CNBr. It is a convenient method of synthesis of amino-1, 3, 4-oxadiazole because of shorter reaction time. More reports are cited in literature, which employed this method to obtain the 1, 3, 4- amines.[26-27]



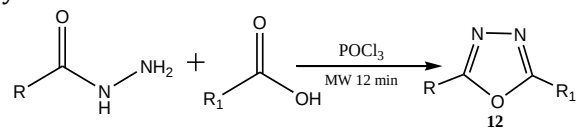
7 8

Guin[28] A direct access to symmetrical and unsymmetrical 2,5-disubstituted [1,3,4]-oxadiazoles (**11**) has been accomplished through an imine C-H functionalization of N-arylidenearoylhydrazide (**10**) using a catalytic quantity of $Cu(OTf)_2$. These reactions can be performed in air atmosphere and moisture making it exceptionally practical for application in organic synthesis.



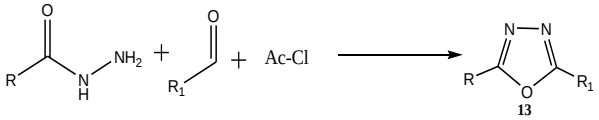
10 11

Yu Yuve have reported microwave assisted synthesis 2,5-disubstituted 1,3,4-oxadiazole (**12**) protocol with 91 % of the yield.[21]



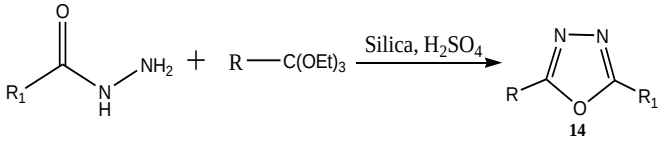
12

L. Somogyi synthesized 1,3,4-oxadiazole (**13**) from several steps, from aryl hydrazide and aryl aldehyde. [22]



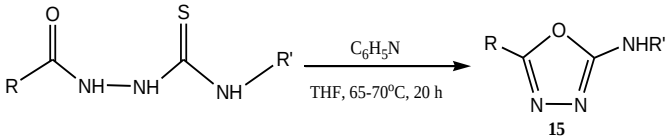
13

Silica sulfuric acid catalyst used for the rapid and ecofriendly synthesis of 1,3,4-oxadiazoles (**14**) at ambient temperature by M Dabiri et al.[23] Green chemistry and one-pot, solvent-free using microwave radiated synthesis of 1,3,4-oxadiazoles (**14**) were reported by V Polshettiwar.[24]



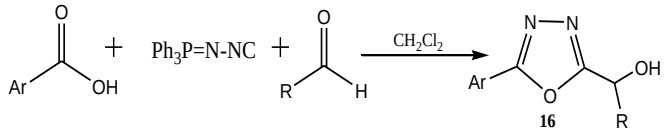
14

Dolman et al A facile and general protocol for the preparation of 2-amino-1,3,4-oxadiazoles relies on a tosyl chloride / pyridine - mediated cyclization of thio-semicarbazides that consistently outperforms the analogous semicarbazide cyclizations. Various 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles (**15**) have been prepared in good yields.[25]



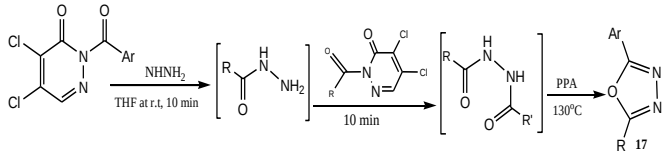
15

Adib et al *N*-Isocyaniminotriphenylphosphorane, aldehydes, and benzoic acids undergo a one-pot, three-component reaction under mild conditions to afford 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles (**16**) in good yields.[26]



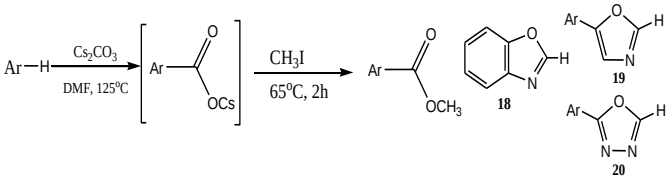
16

Park et al Symmetric and unsymmetric 1,3,4-oxadiazoles (**17**) were synthesized in situ from hydrazine hydrate and the corresponding 2-acyl-4,5-dichloropyridazin-3-ones as acylating agents in polyphosphoric acid (PPA) or $BF_3{\cdot}OEt_2$ in excellent yields.[27]



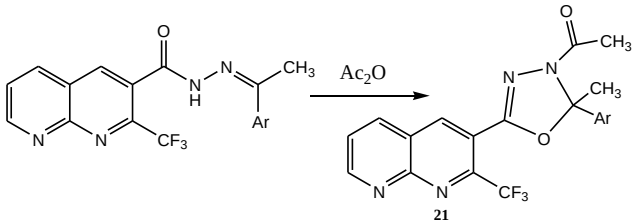
17

Vechorkin et al A simple and straightforward method for the direct carboxylation of aromatic heterocylces such as oxazoles (**18**), thiazoles (**19**), and oxadiazoles (**20**) using CO_2 as the C1 source requires no metal catalyst and only CS_2CO_3 as the base. A good functional group tolerance is achieved. [28]



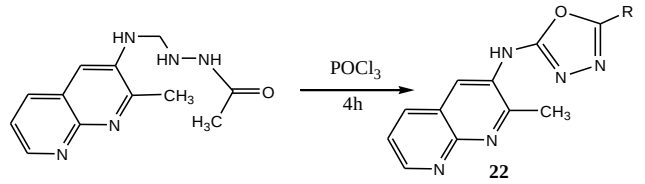
18 19 20

K Mogilaiah and B Sakram[29] have prepared 1,3,4-oxadiazole (**21**) from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.

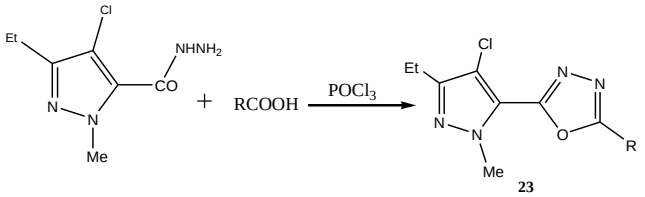


21

D Ramesh and B Sreenivasan[30] have synthesised 1,3,4-oxadiazoles (**22**) from semi-carbazide in presence of $POCl_3$.



Hansong Chen et al[31] have synthesised oxadiazoles (**23**) by the reaction of hydrazide and aromatic acid in presence $POCl_3$.



REACTIONS OF 1, 3, 4-OXADIAZOLE[32-41]

The substituted and unsubstituted 1,3,4-oxadiazole undergoes varieties of organic reactions. Due to very low electron density on the carbon atom, the attack of electrophile preferentially occurs at the position 3 with the formation of 1, 3, 4 -oxadiazolium salts (**24**) (Figure **2**).[32] However, the alkylation of 2-alkoxy-1, 3, 4- oxadiazole with alkyl halides produces labile oxadiazolium salt (**30**) which undergo O-dealkylation to provide 4-alkyl-oxadiazolin-5-ones (**31**) (Figure **3**). 2,5-Diphenyl-1,3,4-oxadiazole can be nitrated or sulfonated by conc. HNO_3 and oleum. This result in to attack on phenyl ring itself.[33]

Figure 2. attack of electrophile (R) at position 3rd.

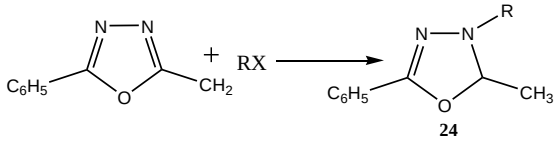
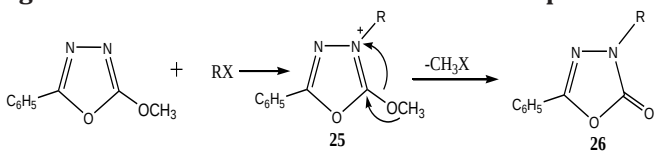
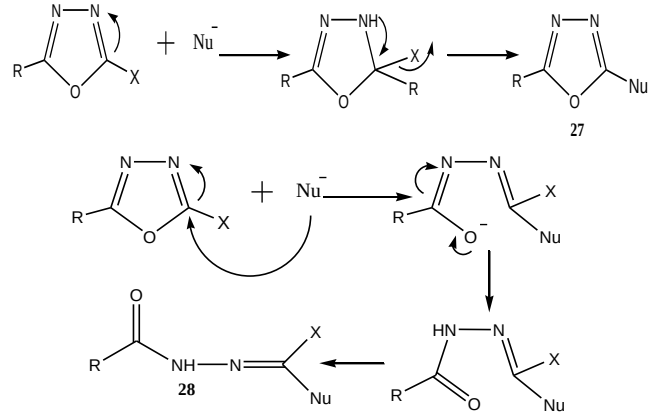


Figure 3. Mechanism of Reaction with electrophiles



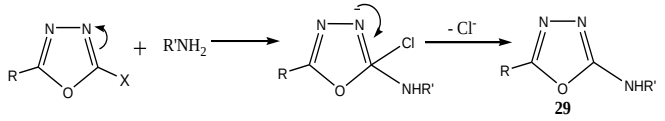
Reactions with nucleophiles are also reported**.** The carbon atoms in 1, 3, 4 -oxadiazole ring are relatively with low π electron density and therefore attack of nucleophiles occurs at this carbon atom. The reaction proceeds either with nucleophilic substitution (**27**) or with ring cleavage (**28**) (Figure **4**). 1,3,4-oxadiazole substituted with halogen or sulfonyl group at the position-2 easily undergo nucleophilic substitution reaction.[34]

Figure 4. Nucleophillic Substitution and Ring Clevage



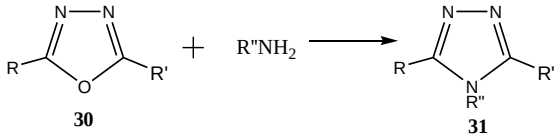
The reaction of 2-chloro-1, 3, 4-oxadizole with nucleophiles such as amines, thiourea or azide proceeds with the substitution of chloro group by nucleophile and result in the corresponding 2-substituted-1, 3, 4-oxadiazoles (**29**) (Figure **5**).[36]

Figure 5. Reaction with amine



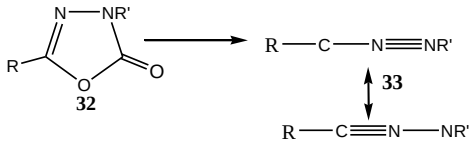
The reaction of alkyl or aryl- 1, 3, 4-oxadiazoles (**30**) with nucleophile involve the cleavage of 1, 3, 4-oxadiazole ring ending to the formation of hydrazine derivative which may recyclize to form 1,2,4-triazoles (**31**) (Figure **6**). Alkyl and aryl-1,3,4-oxadiazole undergo acid or base catalyzed ring opening reaction in aqueous solution with formation of diacylhydrazines. 1, 3, 4 -oxadiazole is thermally stable and the stability of the ring is increased with the substitution of the aryl groups.[37]

Figure 6. Formation of 1,2,4-triazole from 1,3,4-oxadiazole



However, 1,3,4-oxadiazolin-5-one (**32**) undergo thermal and photochemical ring opening reaction with the loss of carbon dioxide to provide nitrilimines (**33**).[38-40] It is well documented that diaryl 1, 3, 4-oxadiazole react with benzothiophene leading to formation of oxadiazepine as a major product. But irradiation of this molecule with benzophenone as sensitizer results in (2+2) cycloadduct product. 2,5-substituted-1,3,4-oxadiazole are greatly affected by strong acid or base. Cleavage of the ring is followed by hydrazine formation. In general aryl derivatives are less sensitive than alkyl substituted derivatives. (Figure **7**)

Figure 7. Formation of nitrilimines



A special type of rearrangement known as 'Dimroth rearrangement' is exhibited by 1,3,4- oxadiazole having a substituents containing heteroatom like O,S,N at position 2 or 5 in presence of strong acid or strong alkali upon long duration heating.[38] If it is intended to carry out the reaction involving heteroatom at position 2 or 5 of 1,3,4-oxadiazole, the reaction should be carried out at lower temperature (<80°C) after mixing the reagent at room temperature. Otherwise, possibility of Dimroth rearrangement always exists which may yield mixture of both.[41]

POSSIBLE REACTION MECHANISM[42-44]

Step 1 In first step carboxylic acid is converted to ester group by Nucleophillic Addition elimination mechanism (Figure **8** & **10**)

Step 2 In this step ester is converted to hydrazide in presence of hydrazine hydrate by nucleophillic substitution mechanism (Figure **9** & **11**)

Step 3 In this step 1,3,4-oxadiazole is prepared by several methods by cyclization mechanism here, three methods are discussing with their reaction mechanism.

Figure 8. Formation of Ester from carboxylic acid

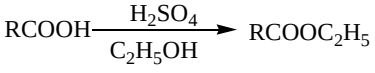


Figure 9. Formation of Hydrazide

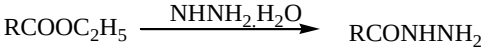


Figure 10. Nucleophillic Addition elimination mechanism for formation of ester

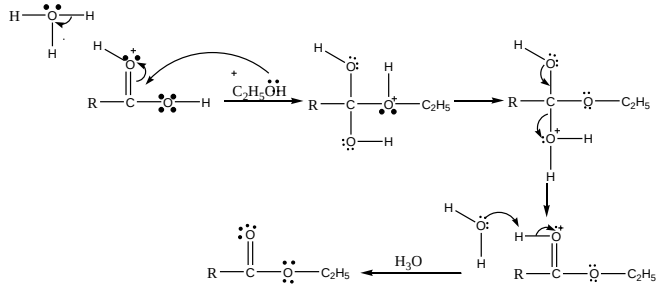
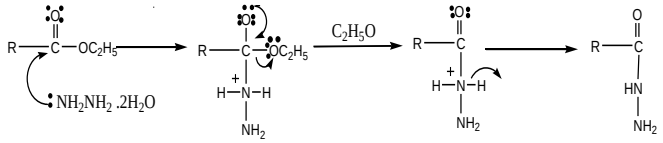
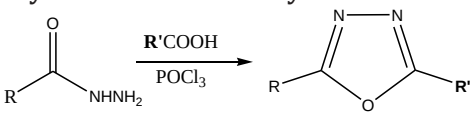


Figure 11. Nucleophillic substitution mechanism for formation of hydrazide



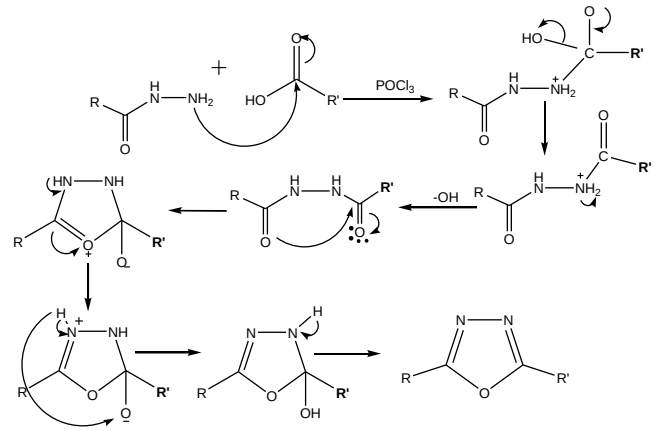
Method A Preparation of 1,3,4-Oxadiazole by using alkyl or aryl substituted carboxylic acid in presence of Phosphorus Trichloride ($POCl_3$) with substituted hydrazide (Figure **12**).

Figure 12. Preparation of 1, 3, 4 - Oxadiazole by using alkyl or aryl substituted carboxylic acid



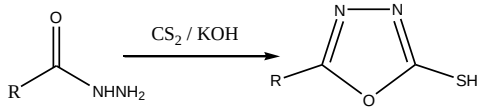
In this Step cyclization take place. (Figure **13**).

Figure 13. Cyclization of substituted hydrazide 2,5-dialkyl or diaryl substituted-1,3,4-oxadiazole derivatives



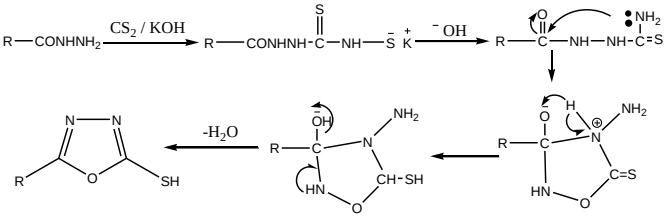
Method B Preparation of 1, 3, 4 - Oxadiazole by using Carbon-di-sulphide and potassium hydroxide with substituted hydrazide (Figure **14** & **15**).

Figure 14. Preparation of 1,3,4-Oxadiazole by using Carbon-di-sulphide and potassium hydroxide



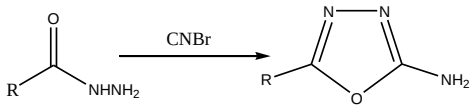
In this method same cyclization occur and hydrazide is converted to potassium thiosemicarbazide salt from which 2,5-disubstitued-1,3,4-oxadiazole-2-thiol is formed (Figure **15**).

Figure 15. Cyclization of substituted hydrazide to form 2, 5-disubstitued-1,3,4-oxadiazole-2-thiol.



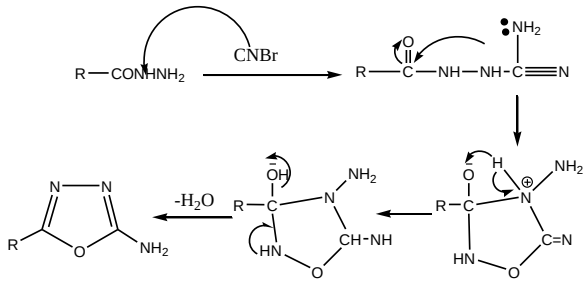
Method C Preparation of 1, 3, 4 - Oxadiazole by using Cyanogen Bromide with substituted hydrazide (Figure **16**).

Figure 16. Preparation of 1, 3, 4 - Oxadiazole by using Cyanogen Bromide with subsituted hydrazide.



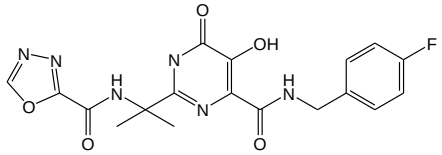
In this method nitrilimines is formed from hydrazide which is converted to 5-substitued-1,3,4-oxadiazol-2-amine. (Figure **17**)

Figure 17. Cyclization of substituted hydrazide to 5-substitued-1,3,4-oxadiazol-2-amine.



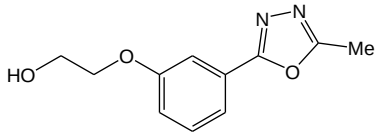
MODE OF ACTION OF 1,3,4-OXADIAZOLE[45-49]

Raltegravir (**34**) an antiretroviral drug by Merck & Co, is used to treat HIV infection. HIV replication involves the conversion of viral RNA into DNA, which is then incorporated into the host cell genome through a process catalyzed by the HIV integrase enzyme. By blocking integrase, raltegravir inhibits HIV replication. [45]



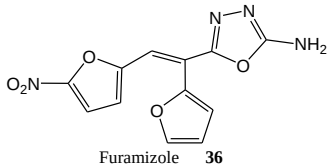
Raltegravir **34**

Nesapidil (**35**) is categorized as a Class IV antiarrhythemic drug. It is calcium channel blocker. Its major effect is to slow down Ca^{+2} channels. The result is a slowing of AV conduction and sinus rate. Nesapidil causes change in the preload, after load, contractility and coronary blood flow.[46]



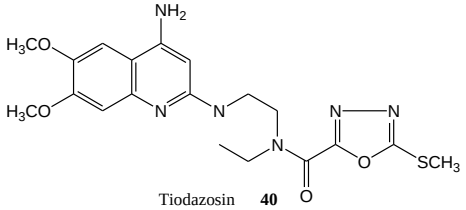
Nesapidil **35**

Furamizole (**36**) a nitrofuran derivative possesses a strong antibacterial activity by inhibiting beta lactamase.[47]



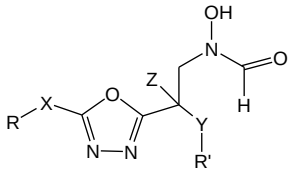
Furamizole **36**

Tiodazosin (**40**) is an antihypertensive drug. Under *in vitro* conditions, tiodazosin produced a noncompetitive antagonism of alpha adrenergic receptors in the portal vein, It did not show marked affinity for presynaptic alpha adrenergic receptors and lacked any measurable direct vasodilator effects (nonreceptor mediated) independent of alpha adrenergic receptor blockade.[48]



Tiodazosin **40**

BB-83698 (**41**) is an antibacterial agent. It is an inhibitor of metallo enzyme PDF (Peptide Deformylase). PDF is considered as the most promising bacterial targets in the search for novel mode of action of antibiotics that lacks cross-resistance to existing drugs.[49]



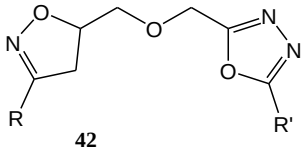
BB-83698 **41**

BIOLOGICAL ACTIVITY

The capacity of 1,3,4-oxadiazole nucleus to undergo variety of chemical reaction have made it medicinal backbone on which number of potential molecules can be constructed. A few therapeutic agents were synthesized possessing of 1,3,4-oxadiazole nucleus are mentioned below.

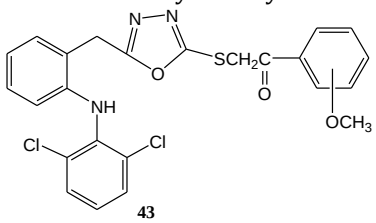
Anti-Inflammatory Activity

B Jayashankar et al[50] synthesized a series of novel ether-linked bis heterocycles (**42**). All the synthesized compounds were screened for anti-inflammatory and analgesic activities. Compound **42** showed excellent activity against ibuprofen and aspirin.



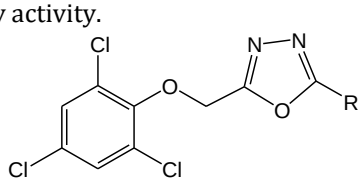
42

Shashikant V Bhandari et al[51] 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 (**43**). 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 (**43**) found to have most prominent and consistent anti-inflammatory activity.



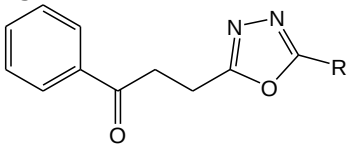
43

Mohd Amir et al[52] synthesized a series of new 1,3,4-oxadiazole derivatives and 1,2,4-triazine- 5-one derivatives (**44**). All the compounds were screened for their Anti-inflammatory activity by using carrageenin-induced rat paw edema method. Compounds **44** among all the synthesized compounds showed maximum anti-inflammatory activity.



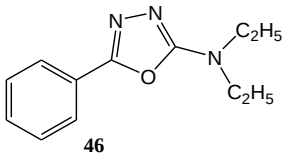
44

Mymoona et al[53] Various derivatives of aryl proponoic acid containing oxadiazole nucleus (**45**) were successfully synthesized and screened for anti-inflammatory, analgesic, ulcerogenic activities and lipid peroxidation studies. Some of the synthesized compounds were very safe with anti-inflammatory and analgesic activities comparable to ibuprofen. The results obtained support the statement that the synthesized compounds may be used as safer anti-inflammatory agents



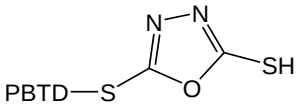
45

Raman et al[54]; The Anti-inflammatory activity of the synthesized Diethyl-(5-phenyl-1,3,4-oxadizol-2-yl)-amine (**46**) were evaluated in vivo by the carrageenan induced paw oedema method in rat. The compounds were tested at an oral dose of 100 mg/kg of body weight, and were compared with the standard drug (Indomethacin) at 1st, 2nd, 3rd and 4th hour of inflammation induction by carrageenan treatment.



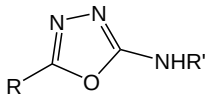
46

Kramer et al[55] Some 1,3,4-oxadiazole DTBP 1,3,4-oxadiazole (**47**) derivatives has found to exert their anti-inflammatory effect via cyclooxygenase and 5-lipoxygenase inhibitory activity.



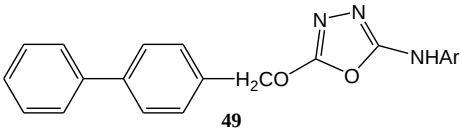
47

Omar et al[56] Anti-inflammatory potential of substituted oxadiazoles i.e. 2-aryl amino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles (**48**) were reflected by their ability to provide 36 to 76% protection in carrageenan induced rat paw edema method.



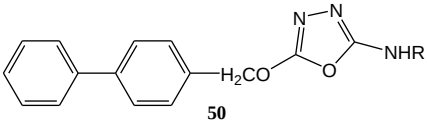
48

Salzman S et al,[57] A series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives were also evaluated for their anti-inflammatory activity.



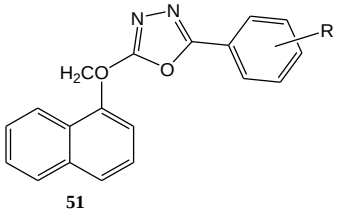
49

Rajak H et al[58], 2-arylamino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles (**50**) on pharmacological screening as anti-inflammatory activity exhibited 10 to 76% protection in carrageenan-induced rat paw edema.



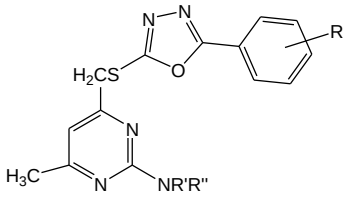
50

Burbuliene M et al,[59] Two novel series of compounds , 1,3,4-oxadiazole (**51**) analogues were synthesized for their potential antiinflammatory activities, using the carrageenan-induced rat paw edema method and cotton pellet-induced granuloma method. Some compounds demonstrated marked antiinflammatory activities.



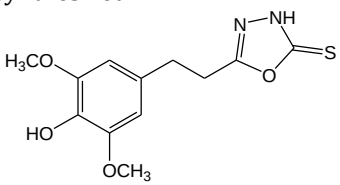
51

Mullican et al,[60] anti-inflammatory evaluation of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones (**52**) found that some of these derivative were much more potent than ibuprofen.



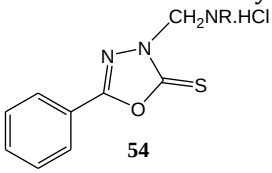
52

Singh et al,[61] With the aim of discovering dual inhibitors of 5-lipoxygenase (LO) and cyclooxygenase (CO) with improved pharmacokinetic properties, a series of 5-(3,5-di--butyl-4-hydroxyphenyl)-1,3,4-oxadiazoles (**53**) were designed and synthesized



53

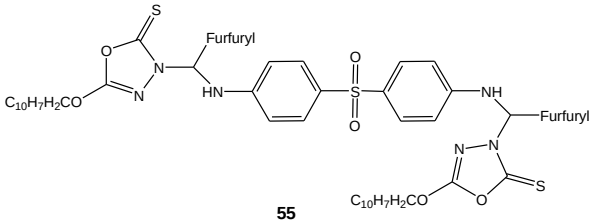
Kumar A et al, Some 5-(4-pyridyl)-4-(substituted methyl)-1,3,4-oxadiazoline-2-thione hydrochloride (**54**) has also been found to possess anti-inflammatory activity [62]



54

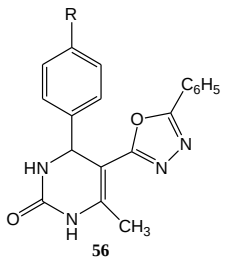
Anti-Microbial Activity

Mohamed Ashraf Ali et al,[63] 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-naphthyl-oxymethyl)- 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 (**55**) from all the synthesized compounds have shown best activity against M. Tuberculosis and isoniazid resistant M. Tuberculosis.



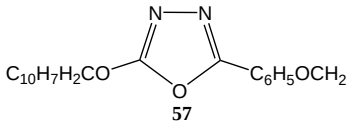
55

Manish Kumar Mishra et al.[64] synthesized 6 – Methyl – 4 – aryl-5- (5-phenyl -1,3,4– oxadiazol-2-yl) -1,2,3,4-tetrahydropyrimidine-2(1*H*)-one (**56**). It has significant effect against Streptococcus *pneumonia* (+ve) and *Escheria coli* (-ve).



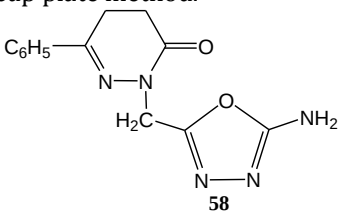
56

M Shahar Yar et al[65] synthesized a series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives and was tested for *in-vitro* Anti-Microbial activity.2-(2-naphthyloxy methyl) -5-phenoxymethyl- 1,3,4-oxadiazole (**57**) exhibited > 90% inhibition among all the synthesized compounds.



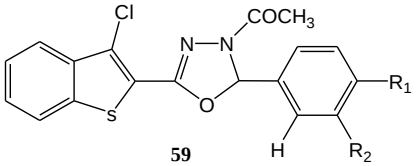
57

Mojahidul Islam et al[66] synthesized a series of 5-{3'-oxo-6'-(substituted aryl)- 2',3',4',5'- tetrahydropyridazin-2i-ylmethyl}-2-substituted 1,3,4-oxadiazole (**58**) and then final compounds were tested for their anti- bacterial activity using cup plate method.



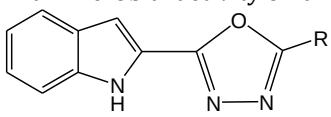
58

Rakesh Chawla et al,[67] synthesized some new 3-acetyl-5-(3-chloro-1 benzo[*b*]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles (**59**) was evaluated for Antimicrobial activity. Compounds (**59**) were found to be most potent than the standard drugs i.e. ciprofloxacin.



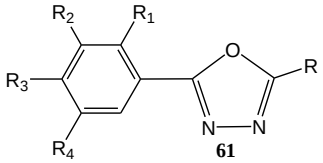
59

Nitin Bhardwaj et al[68] synthesized 2-substiuted-(1,3,4-oxadiazole)-1H-indole (**60**) from different compounds and was tested for Anti- Microbial activity on different strains.



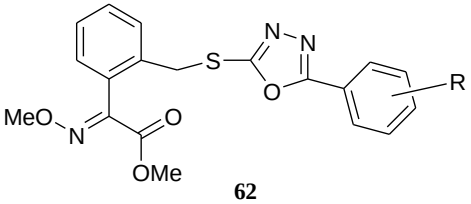
60

B Chandrakantha et al,[69] synthesized a series of new 1,3,4-oxadiazole with 2-fluoro-4-methoxy sustitute 1,3,4-oxadiazole (**61**) moiety and are tested for Anti-Microbial activity. All synthesized compounds showed significant anti-bacterial activity against Escherichia coli and Pseudomonas aeruginosa, and also showed anti-fungal activity against C. Albicans.



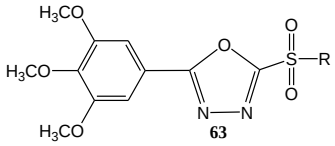
61

Yan Li et al[70] synthesized fifteen novel (E)-a-(methoxyimino)-benzeneacetate derivatives (**62**). Bioassays indicated that compound **62** 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.



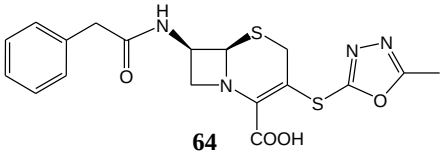
62

Bao-An Song et al[71] synthesized compounds using the key intermediates 5-(3,4,5- trimethoxyphenyl)- 1,3,4-oxadiazole analogue (**63**) and tested for fungicidal activity.



63

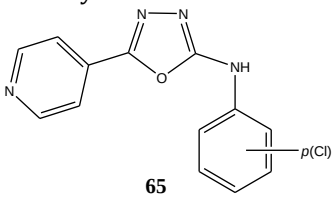
Yoshida et al,[72] described the synthesis and optimization of anti-Helicobacter pylori activity for a new series of cephem derivatives. Compound **64** exhibited anti *Helicobacter pylori* (13001 and FP1757) activity at a minimum inhibitory concentration of 0.1 µg/mL.



64

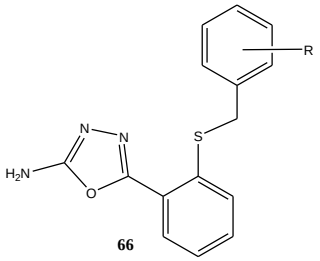
Anti- convulsant Activity

Bhat M A et al[73] synthesized a series of five membered heterocyclics and was tested for convulsion. 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4oxadiazole (**65**) showed potent activity.



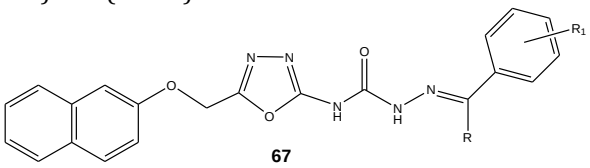
65

Zarghi A et al, A new series of 2-substituted-5-{2-[(2-halobenzyl)thio)phenyl}-1,3,4- oxadiazoles, (**66**) were designed, synthesized and investigated for anticonvulsant activities. The designed compounds contain the main essential pharmacophore for binding to the benzodiazepine receptors. Electroshock and pentyl enetetrazole induced lethal convulsion tests showed 5-{2-[(2-fluorobenzyl) thio] phenyl}-1,3,4- oxadiazol-2-amine had significant anticonvulsant activity in PTZ and MES models.[74]



66

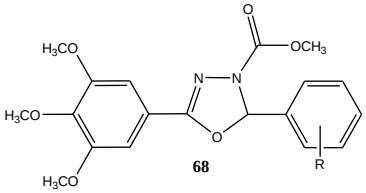
Rajak et al,[75] synthesized and evaluated semicarbazones (**67**) containing the 1,3,4-oxadiazole units for anticonvulsant potential in a three model test (MES), (scPTZ) and (scSTY).



67

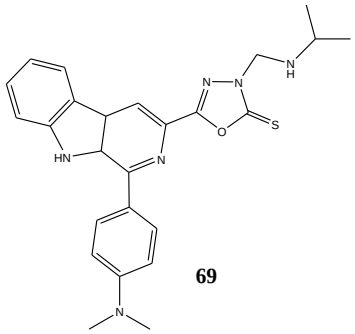
Anti-cancer Activity

Baoan Song et al[76] synthesized some 3-acetyl-2-substituted phenyl-5-(3,4,5- trimethoxyphenyl)-2,3-dihydro-1,3,4- oxadiazole derivatives. Among the synthesized compound (**68**) highly active against PC3 cells and are moderately active against Bcap37 and BGC823 cells.



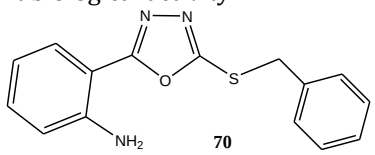
68

Savariz et al,[77] synthesized and evaluated the *in vitro* antitumor activity of new Mannich bases. Among the compounds studied, compound (**69**) showed potent activity against melanoma (UACC-62), and lung (NCI-460) cell lines with GI50 values of 0.88 and 1.01 mmol/L, respectively.



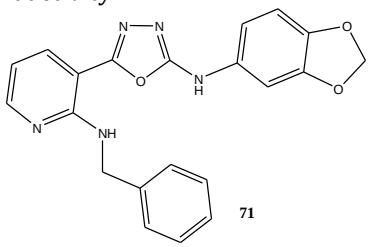
69

Liu et al,[78] synthesized and reported the anti-proliferative and EGFR inhibition properties of a series of 2-(benzylthio)-5-aryloxadiazole derivatives. Compound (**70**) showed potent biological activity



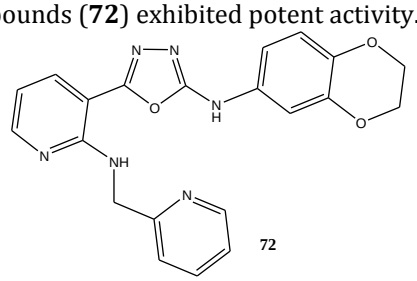
70

Xiaohu Ouyang et al[79] 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, (**71**) showed potent activity.



71

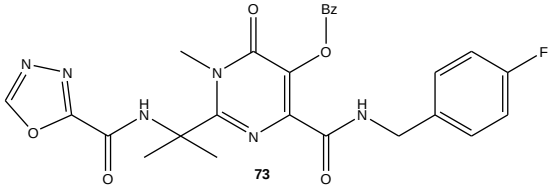
Ouyang et al,[80] Synthesized and evaluated various 1,3,4-oxadiazole derivatives as to their ability to inhibit tubulin polymerization and block the mitotic division of tumor cells. Compounds (**72**) exhibited potent activity.



72

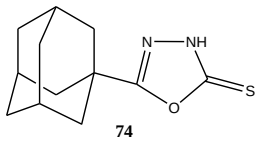
Antiviral Activity

Wang and et al,[81] synthesized a series of raltegravir derivatives by modifying the 5-hydroxyl group of the pyrimidine ring and evaluated them for anti-HIV activity. The 5-hydroxyl modification of raltegravir derivatives significantly increased their activity, which indicates the 5-hydroxyl group's dispensability. Compound (**73**) with a sub-picomol IC50 value was the most potent anti-HIV agent among all of the derivatives synthesized, and thus emerged as a new and potent anti-HIV agent



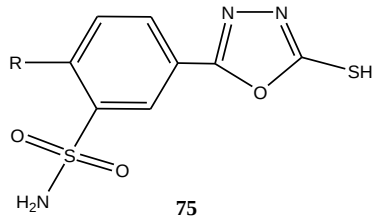
73

El-Emam et al, The inhibitory activity of the compounds **(74)** against the human immunodeficiency virus type 1 (HIV-1) was determined using the XTT assay on MT-4 cells.[82]



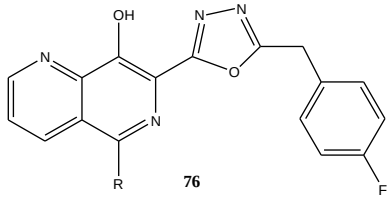
74

Iqbal and et al,[83] reported inhibitory activity for compounds **75** against the human immunodeficiency virus type 1 (HIV-1) which was also determined using the XTT assay on MT-4 cells.



75

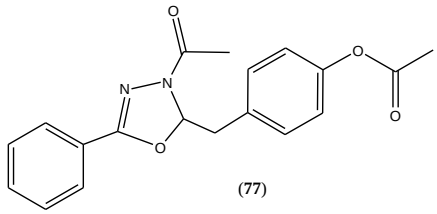
Johns and et al,[84] reported antiviral activity (through inhibition of viral DNA integration) for new derivatives containing the 1,3,4-oxadiazole unit in combination with a ring system of 8-hydroxy-1,6-naphthyridine (**76**).



76

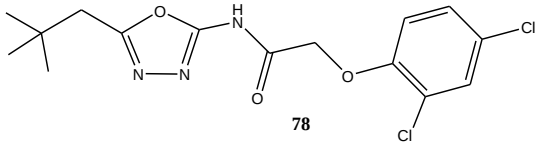
Antihypertensive Activity

Hypertension and cardiovascular disease are major causes of morbidity and mortality worldwide. Bankar and et. al, [85] reported the vasorelaxant effect of compound (**77**)**,** 4-(3-acetyl-5- (pyridin-3-yl)- 2,3-dihydro- 1,3,4-oxadiazol-2-yl)phenyl acetatE, in rat aortic rings by blocking L-type calcium channels.



(77)

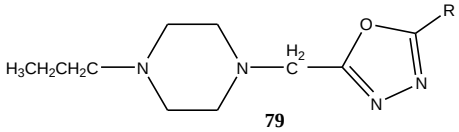
Bankar and et al,[86] also investigated whether the correction of endothelial dysfunction is dependent on high blood pressure normalization; in deoxycorticosterone acetate (DOCA-salt), and NG-nitro-L-arginine (L-NNA) in hypertensive rats. Compound (**78**) is a T type Ca^{+2} channel inhibitor with an IC50 of 810 nM.[86]



78

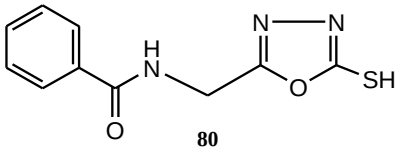
Anthelmintic Activity

A novel series of 1-[(5-substituted-1,3,4-oxadiazol-2-yl)-methyl]-4-propylpiperazines, (**79**) derivatives was synthesized and evaluated for anthelmintic activity.[87]



79

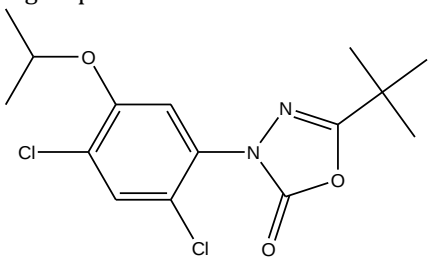
Shrivastava et al, 1,3,4-oxadiazole derivative of hippuric acid, *N*-((5-mercapto-1,3,4- oxadiazol-2-yl) methyl) benzamide (**80**) synthesized and were found to possess potential antihelmentic activity against *Pheretima posthuma*.as compared to albedazole. [88]



80

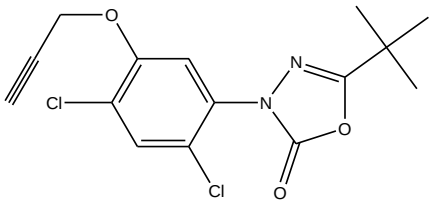
Herbicidal activity

Murakami Y et al, Oxadiazon, 3-[2,4-dichloro-5-(1-methylethoxy) phenyl]-5-(1,1- dimethylethyl)- 1,3,4-oxadiazol -2(3H)-one, **32** is a member of the oxadiazole group of herbicide. For weed resistance management, the product is a group G herbicide.[89]



81

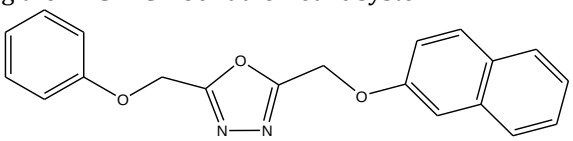
Nandihalli U. B. et. al, Oxadiargyl (TOPSTAR 80 WP), 3-[2,4-dichloro-5-(2- propynyloxy) phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one, **33** is a broad spectrum weed control (international registrations approved).[90]



82

Antimycobacterial Activity

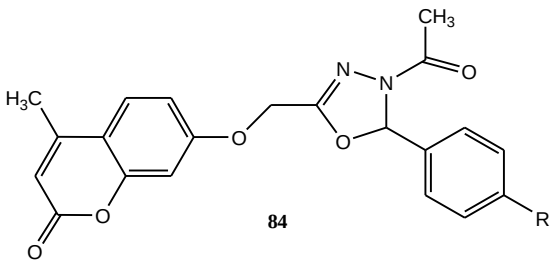
Tuberculosis is a serious health problem that causes the death of approximately 2-3 million of people every year worldwide. A literature survey also reveals that several 1,3,4-oxadiazole derivatives possess antimycobacterial activity against *M tuberculosis* H37Rv. Yar M et al; The result of the antimycobacterial activity tests revealed that 2-(2-naphthyl oxymethyl)- 5-phenoxy methyl-1,3,4-oxadiazole, (**83**) exhibited > 90% inhibition at MIC ~6.25 using the BACTEC-460 radiometric system.[91]



83

Antioxidant Activity

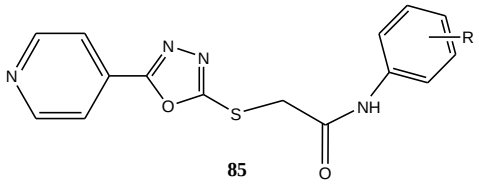
Rajasekaran S et al, 1,3,4-oxadiazole nucleus are known to exhibit potential antioxidant activity. The search for antioxidant drugs led to the discovery of several 1,3,4-oxadiazol derivatives having antioxidant activity. A series of some 5-pyridyl-2- [(N-substituted phenyl) thio-acetamido]-1,3,4- oxadiazoles, (**84**) has inhibited the DPPH radical at a lower concentration.[92]



84

A novel series of 3-acetyl-2-(substituted phenyl)-5-(4-methylcoumarinyl-7 -oxymethyl)- 2,3-dihydro 1,3,4-

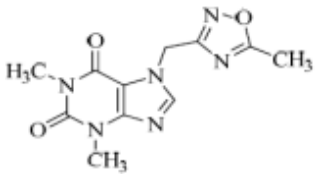
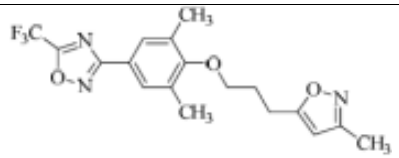
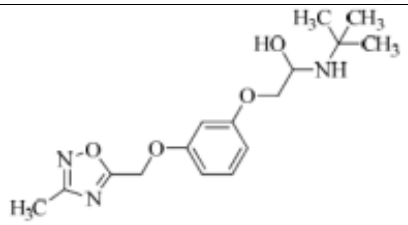
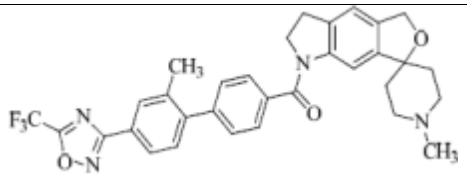
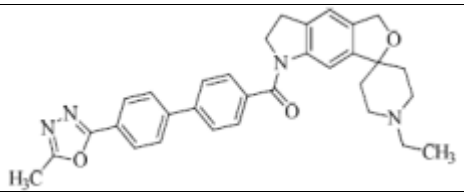
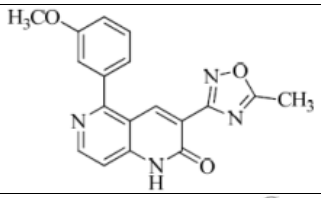
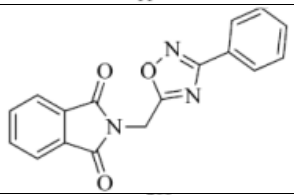
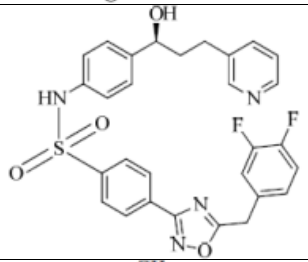
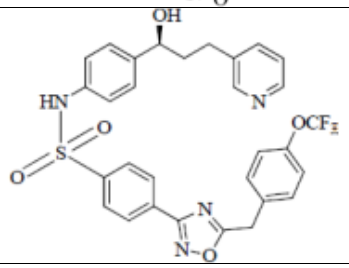
oxadiazoles, (**85**) were evaluated for antioxidant activity. The derivatives bearing H, CH_3 group showed more than 50 % antioxidant activity by the diphenylpicryl hydrazyl assay.[93]

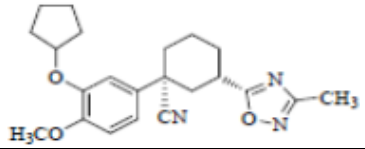
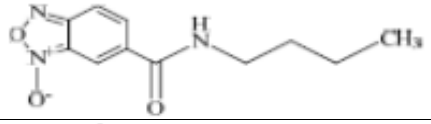
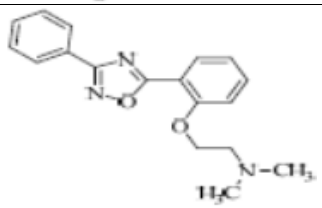


85

Some new oxadiazole drugs & derivatives under Preclinical/Phase clinical trials. (Table **2**)

Table 2. Some new oxadiazole drugs & derivatives under Preclinical/Phase clinical trials.

S.No	Chemical Structure	Activity	Phase	Originator
1		Antitussive, Bronchodilator	Phase-I	Sanofi-Synthlabo
2		Antirhinoviral, Antiviral	Phase-III	Viro pharma
3		Antihypertensive, Antianginal, Antiglaucoma agent, Beta-adrenoceptor antagonist	Phase-II	Center for Chemistry of Drugs
4		Antidepressants, Anxiolytic, 5-HT1D Antagonist	Biological testing	Smithkline Beecham
5		Antidepressants, Anxiolytic, 5-HT1D Inverse agonist	Preclinical	Smithkline Beecham
6		Cognition enhancing drug, GABA(A) receptor modulator, GABA(A) B2 site inverse agonist	Preclinical	Dainoppon pharma
7		Analgesic	Preclinical	Universidade federal pernambuco
8		Antiobesity drug, Antidiabetic drug, Beta3 adrenoce tor agonist	Preclinical	Merck
9		Antiobesity drug, Antidiabetic drug, Beta3 adrenoceptor agonist	Preclinical	Merck

10		Bronchodilator, Phosphodiesterase Inhibitor	Preclinical	Smithkline Beecham
11		Antitrypanosomal	Preclinical	Universidad de lare publica
12		Antiepileptic drug,Neuronal Injury Inhibitor, AMPA antagonist, Sodium channel blocker	Preclinical	Boehringer Ingelaeim

CONCLUSION

This review gives an overview of the various synthetic routes used to form a biologically rich oxadiazole moiety as well as the reactions the molecule undergoes to yield various other important molecules. It also highlights the therapeutic properties of the oxadiazole ring and the availability of varied drugs in the market containing the ring. Thus this paper proves to be significant for further research work on the bioactive oxadiazole ring.

REFERENCES

1. Gupta R R, Kumar M, Gupta V; Five membered heterocycles with more than two heteroatoms. In Heterocyclic Chemistry II, 3rd edition. Springer (India) Pvt. Ltd. 2005; 491-573.
2. Aniswarth C; 1,3,4-Oxadiazole. *J Am Chem Soc*. 1965, 87(24):5800-5801.
3. Hetzheim A and Mockel K; Recent Advances in 1,3,4-Oxadiazole Chemistry. *Adv Heterocycl Chem*. 1966; 7:183-224.
4. Sun X W, Liang H T, Zhang Z Y; Synthesis and antibacterial activity of 4-aryl-l-(1-p-chlorophenyl-5-methyl-1,2,3-triazol-4-carbonyl) thiosemicarbazides and their related heterocyclic derivatives. *Ind J Chem*. 1998; 38B:679-683.
5. Amir M, Shahani S; Synthesis and Antinflammatory activity of new 2-(5-(trifluoromethyl) pyridyl oxymethyl)-1,3,4-oxadiazoles. *Ind J Heterocycl Chem*. 1998; 8:107-110.
6. Nizamudalin M H, Khan A Shafqat; Synthesis and fungicidal activity of some 2-arylamino-1 ,3,4-thiadiazino[6,5-b] indoles and 2-aryl-1 ,3,4-oxadiazolo-[2,3-c]-1,2,4-triazino [5,6-b] indoles. *Ind J Chem*. 1999; 38B:76-82.
7. Nandihalli U B, Duke S O; Synthesis and herbicidal activity and mode of action of IR5790. *Am Chem Soc Symp Ser*. 1993; 524:62-78.
8. Varma R S, Vinita Bajpai and Kapil A; 4-heterocyclic aminomethyl-2-(3'-nitro-4'-benzyloxy phenyl)-1, 3, 4-oxadiazoline-5-thiones and their antileishmanial activity. Indian Journal of Heterocyclic Chemistry 1999; 8.4:281-284.
9. Hazarika J, Kataky J C; Synthesis and Biological Screening of some 2,5-disubstituted-1,3,4-oxadiazoles. *Ind J Heterocycl Chem*. 1998; 8:83-84.
10. Chaudhari B R, Shinde D B & Shingare M S; Synthesis of some 1,4-benzothiazoly thiosemicarbazides, triazoles, Oxadiazoles, thiadiazoles & their antitubercular activities. *Indian J Het Chem*. 1995; 4:187-190.
11. Yar Shahar mohammad, Akhter Wasim Mohd., Acta Poloniae Pharmaceutica Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives. 2009; 66(4):393-397.
12. Almasirad A, Tabatabai S A, Faizi M; Synthesis & anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4- oxadiazole & 1,2,4-triazoles. *Bioorg med Chem Lett*. 2004; 14: 6057-6059.
13. Muller E; Ludsteck D; Untersuchungen an Diazomethanen, Mitteil V. Reaktives Verhalten von Diazomethyllithium Chemische Berichte. 1955; 88:921-923.
14. Nesynov E P and Grekov A P; The Chemistry of 1,3,4-Oxadiazole Derivatives. *Russian Chem Review*. 1964; 33(10):508.
15. Runti C, Sindellari L, C. Nisi. Chem Abstr. 1960; 54:22601.
16. Becker H G O, Witthauer J, Sauder N G; West Relais-Synthesen mit 4-Amino-1.2.4-triazol. VI. Gekoppelte Synthese von 2-substituierten 1.3.4-Oxdiazolen und 3-Phenyl-1.2.4-triazol. Journal für Praktische Chemie. 1969; 311(4):646-655.
17. Jole J A, Mills K, Heterocyclic Chemistry. 4th ed. Blackwell. 2004.
18. Katritzky, Alan Roy et al. eds. Comprehensive Organic Functional Group Transformations: Synthesis: carbon with one heteroatom attached by a single bond. 1995; 2:2. Elsevier.
19. Hosur M C, Talawar M B, Lada U V; Diazoles: Promising and Versatile Class to Design Anti Microbial Agents. *Ind J Heterocycl Chem*. 1994; 3:237-242.
20. Patil R D and Biradar J S; Synthesis and biological activities of new 3, 5-disubstituted-2-(ethyl-5'-thioxo-l',3',4'-oxadiazol-4'- ethylacetate-2'-yl) indoles,-2-(5'-thioxo-1',3',4'-oxadiazol-4'-methyl carboxyhydrazide-2'-yl) indoles and 2-(5'thioxo-1',3',4'-oxadiazol-4'-alkyl-2'-yl) indoles. Indian Journal of Chemistry Section B. 1999; 38:76-82.
21. Tripathi R P, Tewari N, Dwivedi N, Tiwari V K; Fighting tuberculosis: an old disease with new challenges. Medicinal research reviews. 2005; 25(1):93-131.
22. Macaev S F, Rusu G, Gudima A; Synthesis of novel 5-aryl-2-thio-1,3,4-oxadiazoles and the study of their structure–anti-mycobacterial activities. Bio Org Med Chem. 2005; 13(16):4842-4850.
23. Yuye Y; Microwave Synthesis and Biological Activity of

2-Phenyl-5-aryl-1,3,4-oxadiazoles. Asian J Chem. 2007; 19(6):4960-4962.

24. Somogyi L; Synthesis, oxidation and dehydrogenation of cyclic N,O- and N,S-acetals. Part III. Transformation of N,O-acetals: 3-acyl-1,3,4-oxadiazolines. *J Het Chem*. 2007; 44(6):1235-1246.

25. Dabiri M, Salehi P, Baghbanzadeh M, Bahramnejad B; Silica Sulfuric Acid: An Efficient and Versatile Acidic Catalyst for the Rapid and Ecofriendly Synthesis of 1,3,4-Oxadiazoles at Ambient Temperature Synthetic Communication. 2007; 37(7):201-1209.

26. Polshettiwar V, Varma R S; Greener and rapid access to bio-active heterocycles: one-pot solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *Tet Lett*. 2008; 49(5):879-883.

27. Dolman S J, Gosselin F, O'Shea P D, Davies I W;, Superior Reactivity of Thiosemicarbazides in the Synthesis of 2-Amino-1,3,4-oxadiazoles. *J Org Chem*. 2006; 71:9548-9551.

28. Adib M, Kesheh M R, Ansari S, Bijanzadeh H R; Reaction between N-Isocyanimino-triphenyl phosphorane, Aldehydes, and Carboxylic Acids: A One-Pot and Three-Component Synthesis of 2-Aryl-5-hydroxyalkyl-1,3,4-oxadiazoles. Synlett. 2009; 1575-1578.

29. Park Y D, Kim J J, Chung H A, D H Kweon, Cho S D, Lee S G, Yoon Y J; Facile Synthesis of Symmetric and Unsymmetric 1,3,4-Oxadiazoles Using 2-Acyl(or aroyl)pyridazin-3-ones Synthesis. 2003; 560-564.

30. Vechorkin O, Hirt N, Hu X; Carbon Dioxide as the C1 Source for Direct C-H Functionalization of Aromatic Heterocycles. *Org Lett*. 2010; 12:3567-3569.

31. Mogilaiah K and Sakram B; Synthesis and antibacterial activities of 1,3,4-oxadiazole and pyrazoline derivatives containing 1,8-naphthyridine moiety. *Indian J Heterocyclic Chem*. 2004; 13:289-292.

32. Ramesh D & Sreenivasuhi B; Synthesis of 2-methyl-3-(5'-aryl/aryloxymethyl-1',3',4'-oxadiazol-2'-yl) amino-1,8-naphthyridines as possible antimicrobial agents. *Indian J Heterocyclic Chem*. 2003; 13:163-164.

33. Hansong Chen, Zhengming Li and Yufeng Han; Synthesis and Fungicidal Activity against Rhizoctonia solani of 2-Alkyl (Alkylthio)-5-pyrazolyl-1,3,4-oxadiazoles (Thiadiazoles). *J Agric Food Chem*. 2002; 48(11):5312-5315.

34. Hui X P, Chang-Hu C, Zhang Z Y; Synthesis of 1,3,4-thiadiazole, 1,2,4-triazole and 1,3,4-oxadiazole derivatives containing 1-(p-chlorophenyl)-5-methyl-l,2,3-triazol-4-yl moiety. *Ind J Chem*. 2000; 41B:2176-2179.

35. Parekh H, Patel P, Upadhaya P; A novel one-pot synthesis of α-keto-1,3,4-oxadiazole derivatives. *Ind J Chem*. 1996; 35B:1062-1066.

36. Mullican N D, Wilson M W, Connar D T; Design of 5-(3,5-di- tert-butyl-4- hydroxyl phenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, nonulcerogenic antiinflammatory agents. *J Med Chem*. 1993; 1090-1099.

37. Sikder N, Bulakh N R, Mehilal & Sikder A K; Synthesis and characterization of nitroaryl substituted bis-1, 3, 4-oxadiazoles. Indian Journal of Heterocyclic Chemistry. 2002; 12(1):29-32.

38. Zhang Z Y, Sun X W and Liang H T; Synthesis and antibacterial activity of 4-aryl-1-(1-p -chlorophenyl-5-methyl-1,2,3- triazol-4-carbonyl) thiosemicarbazides and their related heterocyclic derivatives. *Indian J Chem*. 1999; 38B:679-683.

39. Dundappa S Donawade, Raghu A V, Muddapur U M & Guru S Gadaginamath; Chemoselective reaction of benz(g)indole based bisheterocycle dicarboxylate towards hydrazine hydrate: Synthesis and antimicrobial activity of new triheterocycles-5-pyrrolylaminocarbonyl/ mercaptooxadiazolyl/4-allyl-5- mercaptotriazolyl methoxy-1-furfuryl-2-methylbenz(g)indoles. Indian Journal of Chemistry. 2005; 44B:1470-1475.

40. Dutta M M, Goswami B N, Kataky J C; Studies on biologically active heterocycles. Part I. Synthesis and antifungal activity of some new aroyl hydrazones and 2,5-disubstituted-1,3,4-oxadiazoles, Journal of Heterocyclic Chemistry. 1986; 23:793.

41. Mogilaiah K, Srinivas K, Rama Sudhakar G; Chloramine-T mediated synthesis of 1,8-naphthyridinyl-1 ,3,4-oxadiazoles. *Indian Journal of Chemistry*. 2004; 43B:2014-2017.

42. March J; Advanced organic chemistry, reaction mechanism and structure. 2007; 4th ed, Wiley sons, Singapore.

43. Solomon G T W, Fryhle B C; Organic Chemistry, reaction mechanism and structure. 2007; 8th ed, Wiley sons, Singapore.

44. Hashlomota M, Ohta M; Studies on Meso-ionic Compounds. XII. Reaction between Acetic Anhydride and Azoles having Carboxymethylmercapto-group. *Bul Chem Soc Japan*. 1960; 33:1394-1399.

45. Madhukar S, Chande and Joshi R M; Synthesis of novel fused ring and spiro heterocyclic compounds. Indian Journal of Chemistry. 1991; 38B:218-220.

46. Kidwai M, Kumar P, Goel Y; Microwave assisted synthesisof 5-methyl- 1,2,4-thiadiazol-2-yl/ thiotetrazol-1-yl substituted pyrazoles, 2-azetidinones, 4-thiazolidinones, benzopyran-2-ones, and 1,3,4-oxadiazoles. Indian Journal of Chemistry. 1997; 36B:175-179.

47. Geoffrey W Stone, Qin Zhang, Rosario Castillo, Ramana Doppalapudi V, Analia R Bueno, Jean Y Lee, Qing Li, Maria Sergeeva, Gody Khambatta and Nafsika H Georgopapadakou; Mechanism of Action of NB2001 and NB2030, Novel Antibacterial Agents Activated by β-Lactamases, Antimicrobial Agents Chemotherapy 2004; 48(2):477-483.

48. Khalid Mohammed Khan, Zia-Ullaha, Mubeen Rania, Shahnaz Perveen, Syed Moazzam Haidera, Muhammad Iqbal Choudharya, Atta-ur-Rahmana and Wolfgang Voelter; Microwave-Assisted Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazoles, Letters in Organic Chemistry. 2004; 1;50-52.

49. Calwell H, Robert J, Burckhatter J H; The synthesis and proof of structure of N-alkylated oxadiazolones. Journal of the American Pharmaceutical Association. 1958; 47:799.

50. Jayashankar B, Lokanath Rai K M, Baskaran N, Sathish H S; Synthesis and pharmacological evaluation of 1,3,4-oxadiazole bearing bis(heterocycle) derivatives as anti-inflammatory and analgesic agents. European Journal of Medicinal Chemistry. 2009; 44:3898-3902.

51. Shashikant V Bhandari, Kailash G Bothara, Mayuresh K Raut, Ajit A Patil, Aniket P Sarkate and Vinod J Mokale;

Design, synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel S-substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives. Bioorganic & Medicinal Chemistry. 2008; 16:1822-1831.

52. Harish Kumar, Sadique A Javed, Suroor A Khan, Mohammad Amir; 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: Synthesis and preliminary evaluation of biological properties. European Journal of Medicinal Chemistry. 2008; 43:2688-2698.

53. Mymoona Akhter, Asif Husain, Bismillah Azad, Mohd Ajmal; Aroylpropionic acid based 2,5- disubstituted-1,3,4-oxadiazoles: Synthesis and their anti-inflammatory and analgesic activities. European Journal of Medicinal Chemistry. 2009; 44:2372–2378.

54. Raman K, Parmar S S and Sulzman S K; Anti-inflammatory activity of substituted 1,3,4-oxadiazoles. *J Pharm Sci*. 1989; 78(12):999-1002.

55. Kramer J B, Boschelli D H, Connor D T, Kostlan C R, Kuipers P J, Kennedy J A, Wright C D, Bornemeier D A and Dyer R D; Cyclooxygenase and 5-lipoxygenase inhibitory activity of 2,6-di-t-butylphenols linked by a sulfur atom to 1,3,4-oxadiazoles. *Bioorg Med Chem Lett*. 1993; 3:2827-2830.

56. Omar F A, Manfouz N M and Rahman M A; Design, synthesis and anti-inflammatory activity of some 1,3,4-oxadiazole derivatives. *Eur J Med Chem*. 1996; 31:819-825.

57. Salzman S K, Raman K, Singh H K, and Parmar S S; Substituted thiosemicarbazides and corresponding cyclized 1,3,4-oxadiazoles and their anti-inflammatory activity. *J Pharm Sci*. 1983; 82:167–169.

58. Rajak H, Kharya M D and Mishra P; Synthesis of some novel oxadiazole and oxadiazoline analogues for their Anti-inflammatory activity. Journal of Pharmaceutical Society of Japan. 2007; 127(10):1757-1764.

59. Burbuliene M M, Jakubkiene V, Mekuskiene G, Udrenaite E, Smicius R and Vainilavicius P; Synthesis and anti-inflammatory activity of derivatives of 5-[(2-disubstituted amino-6-methyl- pyrimidin-4-yl)-sulfanyl methyl]-3H-1,3,4-oxadiazole-2-thiones. Il Farmaco. 2004; 59:767-774.

60. Mullican M D, Wilson M W, Connor D T, Kostlan C R, Schrier D J and Dyer R D; Design of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)- 1,3,4-thiadiazoles, -1,3,4-oxadiazoles and -1,2,4-triazoles as orally-active, nonulcerogenic anti-inflammatory agents. *J Med Chem*. 1993; 36:1090-1099.

61. Singh I P, Saxena A K and Shankar K; Synthesis and anti-inflammatory activity of oxadiazolines thione hydrochlorides. *Eur J Med Chem Chim Ther*. 1986; 21(3):267-269.

62. Kumar A, Singh S, Verma M, Saxena A K and Shankar K; Potent anti-inflammatory, 2-(o-hydroxyphenyl)-5-(p-dimethylaminophenyl)-1,3,4-oxadiazoles. *Indian J Pharm Sci*. 1987; 49(6):201-204.

63. Mohamed Ashraf Ali, Mohammad Shaharyar, Oxadiazole mannich bases: Synthesis and antimycobacterial activity. Bioorganic & Medicinal Chemistry Letters. 2007; 17(12):3314-3316.

64. Manish Kumar Mishra, Gupta A K, Negi S, Bhatt Meenakshi; Synthesis of Some New Oxadiazole with Antimicrobial Activity. International Journal of Pharma Sciences and Research (IJPSR). 2010; 1(3): 172-177.

65. M Shahar Yar, A Ahmad Siddiqui and M Ashraf Ali; Synthesis and Anti Tuberculostatic Activity of Novel 1,3,4-Oxadiazole Derivatives. *Journal of the Chinese Chem Society*. 2007; 54(1):5-8.

66. Mojahidul Islam, Anees Siddiqui, Ramadoss Rajesh, Afroz Bakht and Sunil Goyal, Syntheis and antimicrobial activity of some novel oxadiazole derivatives. *Acta Poloniae Pharmaceutica n Drug Research*. 2008; 65(4):441-447.

67. Rakesh Chawla, Anshu Arora, Manoj Kumar Parameshwaran, Prabodh Chander Sharma, Sukumar Michael, Thengungal Kochupappy Ravi; 2-[3-(4-chloro/ ethyl phenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles: synthesis and biological evaluation, Acta Poloniae Pharmaceutical ñ Drug Research. 2010; 67(3):247-253.

68. Bhardwaj Nitin, Saraf S K, Sharma Pankaj, Kumar Pradeep; Synthesis, Synthesis, Evaluation and Characterization of Some 1, 3, 4-Oxadiazoles as Antimicrobial Agents. E-Journal of Chemistry. 2009; 6(4):1133-1138.

69. Chandrakantha, Prakash Shetty, Vijesh Nambiyar, Nishitha Isloor, Arun M Isloor; Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiet. European Journal of Medicinal Chemistry. 2010; 45:1206-1210.

70. Yan Li, Jie Liu, Hongquan Zhang, Xiangping Yanga and Zhaojie Liu; Stereoselective synthesis and fungicidal activities of (E)-alpha- (methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole ring. Bioorganic & Medicinal Chemistry Letters. 2006; 16:2278-2282.

71. Cai-Jun Chen, Bao-An Song, Song Yang, Guang-Fang Xu, Pinaki S Bhadury, Lin-Hong Jin, De-Yu Hu, Qian-Zhu Li, Fang Liu, Wei Xue, Ping Lu and Zhuo Chen; Synthesis and antifungal activities of 5-(3,4,5-trimethoxy phenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxy phenyl)-2-sulfonyl- 1,3,4-oxadiazole derivatives. Bioorganic & Medicinal Chemistry. 2007; 15:3981-3989.

72. Yoshida, Y, Matsuda K, Sasaki H, Matsumoto Y, Matsumoto S, Tawara S, Takasugi H; Studies on anti-Helicobacter pylori agents. Part 2: New cephem derivatives. *Bioorg Med Chem*. 2000; 8:2317-2335.

73. Bhat M A, Siddiqui N, and Khan S A; synthesis of novel 3-(4-acetyl-5h/ methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2h-chromen-2-ones, as potential anticonvulsant agents. Acta Poloniae Pharmaceutica and Drug Research. 2008; 65(2):235-239.

74. Zarghi A, Hamedi S, Tootooni F, Amini B Sharifi B, faizi M, Tabatabai S A, Shafiee A; Synthesis and pharmacological evaluation of new 2-substituted-5-{2-[(2-halobenzyl) thio) phenyl}-1,3,4-oxadiazoles as anticonvulsant agents. *Sci Pharm*. 2008; 76:185-201.

75. Rajak H, Deshmukh R, Veerasamy R, Sharma A K, Mishra P, Kharya M D; Novel semicarbazones based 2,5-disubstituted-1,3,4-oxadiazoles: One more step towards establishing four binding site pharmacophoric model hypothesis for anticonvulsant activity. *Bioorg Med Chem Lett*. 2010; 20:4168-4172.

76. Linhong Jin, Jiang Chen, Baoan Song, Zhuo Chen, Song Yang, Qianzhu Li, Deyu Hu and Ruiqing Xu, Synthesis, structure, and bioactivity of N′-substituted benzylidene-3,4,5-trimethoxybenzohydrazide and 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxy phenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives. Bioorganic & Medicinal Chemistry Letters. 2006; 16:5036-5040.

77. Xiaohu Ouyang, Evgueni L Piatnitski, Vatee Pattaropong, Xiaoling Chen, Hai-Ying He, Alexander S. Kiselyov, Avdhoot Velankar, Joel Kawakami, Marc Labelle, Leon Smith, II, Julia Lohman, Sui Ping Lee, et al, Synthesis, inhibition of tubulin polymerization, and activity in tumor cell lines. Bioorganic & Medicinal Chemistry Letters. 2006; 16:1191-1196.

78. Savariz F C, Formagio A S N, Barbosa V A, Foglio M A, Carvalho J E, Duarte M C T, Filho B P D, Sarragiotto M H; Synthesis, antitumor and antimicrobial activity of novel 1-substituted phenyl-3-[3-alkyl amino(methyl)-2-thioxo-1,3,4-oxadiazol- 5-yl]-b-carboline derivatives. *J Braz Chem Soc*. 2010; 21:288-298.

79. Liu K, Lu X, Zhang H J, Sun J, Zhu H L; Synthesis, molecular modeling and biologicalevaluation of 2-(benzylthio)-5-aryloxadiazole derivatives as anti-tumor agents. *Eur J MedChem*. 2012; 47:473-478.

80. Ouyang X, Piatnitski E L, Pattaropong V, Chen X, He H Y, Kiselyov A S, Velankar A, Kawakami J, Labelle M, Smith L et al. Oxadiazole derivatives as a novel class of antimitotic agents: Synthesis, inhibition of tubulin polymerization, and activity in tumor cell lines. *Bioorg Med Chem Lett*. 2006; 16:1191-1196.

81. Wang Z, Wang M, Yao X, Li Y, Qiao W, Geng Y, Liu Y, Ang Q; Hydroxyl may not be indispensable for raltegravir: Design, synthesis and SAR studies of raltegravir derivatives as HIV-1 inhibitors. *Eur J Med Chem*. 2012; 50:361-369.

82. El-Emam A A, Al-Deeb O A, Al-Omar M, Lehmann J; Synthesis, antimicrobial, and anti-HIV-1 activity of certain 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones. *Bioorg Med Chem*.2004; 12:5107-5113.

83. Iqbal R, Zareef M, Ahmed S, Zaidi J H, Arfan M, Shafique M, Al-masoudi N A; Synthesis, antimicrobial and anti-HIV activity of some novel benzenesulfonamides bearing 2,5-disubstituted-1,3,4-oxadiazole moiety. *J Chin Chem Soc*. 2006; 53:689-696.

84. Johns B, Weatherhead J G, Allen S H, Thompson J B, Garvey E P, Foster S A, Jeffrey J L, Miller W H; 1,3,4-Oxadiazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 2: SAR of the C5 position. *Bioorg Med Chem Lett*. 2009; 19:1807-1810.

85. Bankar G R, Nandakumar K, Nayak P G, Thakur A, Chamallamudi M R, Nampurath G K; Vasorelaxant effect in rat aortic rings through calcium channel blockage: A preliminary *in-vitro* assessment of a 1,3,4-oxadiazole derivative. *Chem Biol Interact*. 2009; 181; 377-382.

86. Bankar G R, Nampurath G K, Nayak P G, Bhattcharya S; A possible correlation between the correction of endothelial dysfunction and normalization of high blood pressure levels by 1,3,4-oxadiazole derivative, an L-type Ca^{2+} channel blocker in deoxycorticosterone acetate and NG-nitro-l-arginine hypertensive rats. *Chem Biol Interact*. 2010; 183: 327-331.

87. Srinivas K, Kumar K P; Synthesis, antimicrobial and anthelmintic activity of 1-[(5-sustituted-1,3,4-oxadiazol-2-yl) methyl]- 4-propylpiperazines, *International J of Biopharmaceutics*. 2010; 1:14-19.

88. Kratika Shrivastava, Ritesh K Sharma, Vivek Daniel, Swapnil Goyal; Synthesis and Antihelmentic Activity of Some Azole Derivative of Hippuric Acid. International Journal of Pharmaceutical Sciences. 2010; 2(2):502-507.

89. Murakami Y, Nishimune T, Sueki K; Studies on pesticides for a rice plant accumulation of Oxadiazon and its metabolites in processed foods. Toxicological & Environmental Chemistry. 1994; 45:225-235.

90. Nandihalli U B, Duke S O; Synthesis and herbicidal activity and mode of action of IR5790. *Am Chem Soc Symp Ser*.1993; 524:62-78.

91. Yar M S, Siddiqui A and Ali M A; Synthesis and anti tuberculostatic activity of novel 1,3,4- oxadiazole derivatives. Journal of Chinese Chemical Society. 2007; 54:5-8.

92. Rajasekaran S, Rao G K and Vedavathy J; Microwave assisted synthesis of some 5-pyridyl-2-[(nsubstituted phenyl) thioacetamido]- 1,3,4-oxadiazoles as antibacterial and antioxidant agents. *J Chem Pharm Res*. 2010; 2(2):101-106.

93. Manojkumar P, Kochupappy T; Synthesis of coumarin heterocyclic derivatives with antioxidant activity and in vitro cytotoxic activity against tumour cells, Acta Pharm. 2009; 59:159–170.