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RESEARCH ARTICLE

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 1, 3, 4-OXADIAZOLE DERIVATIVES: A REVIEW OF LITERATURE.

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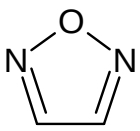
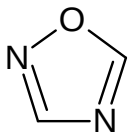
Abstract

A series of derivatives of 1, 3, 4-oxadiazole having verities of biological activities can be synthesised by various methods. The activities include anticancer, antimicrobial, anti- inflammatory, anti-HIV, anti tubercular, anti diabetic, antifungal etc. In this article we have summarized various methods for synthesis of derivatives of 1, 3, 4-oxadiazole nucleus and evaluation of various biological activities.

Introduction:-

Simple five membered heterocycles possessing one oxygen atom and two nitrogen atoms are considered as 1, 3, 4-oxadiazole and its derivatives. 1,3,4-oxadiazole can exist in different isomeric forms, they are 1,2,5-oxadiazole(fig: 1), 1,2,4-oxadiazole(fig: 2), 1,2,3-oxadiazole(fig: 3) and 1,3,4-oxadiazole(fig: 4). Oxygen and nitrogen containing five member heterocyclic nucleus is assessed against various diseases. So they are given importance in medicinal chemistry because of their diverse medicinal potential. Substituted 1, 3, 4-oxadiazole is have broad spectrum of biological activities in pharmaceutical and agrochemical field. [8]


(fig: 1)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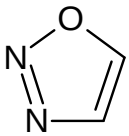
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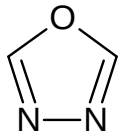
(fig: 4)

1, 3, 4-oxadiazole shows wide variety of activities such as virucidal, CNS depressant, genotoxic, anticonvulsant, insecticidal, anti-tubercular, Anti-HIV, herbicidal, anti-inflammatory. It is also known to exhibit anti malarial, Muscle relaxants, anti tumour, lipid peroxidation inhibitor, antimicrobial, and remarkable analgesic, anti-convulsant, diuretic, hypnotic and sedative properties. There for 1, 3, 4-oxadiazole is commonly used in the area of new drug development. [5]

For the synthesis of 1,3,4-oxadiazole the conventional method used involve the intermolecular condensation of acid hydrazide with carboxylic acid in presence of cyclising agents such as phosphorous oxy chloride, polyphosohoric acid, acetic anhydride. Another reaction involves the condensation with carbon disulfide, potassium hydroxide and ethanol. In this reaction thiol substituted 1, 3, 4-oxadiazole is formed. [10]

This article contains review of the work done by different authors on the synthesis and evaluation of biological activity of 1, 3, 4-oxadiazole.

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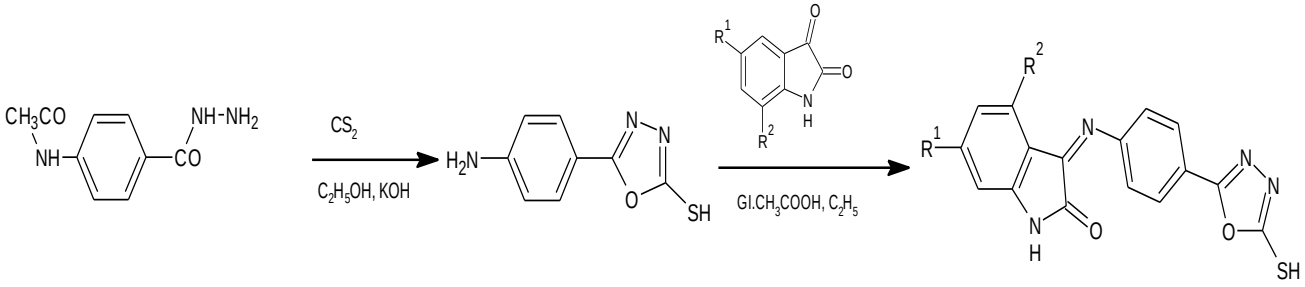
Synthesis and biological activity of 1, 3, 4-oxadiazole:-

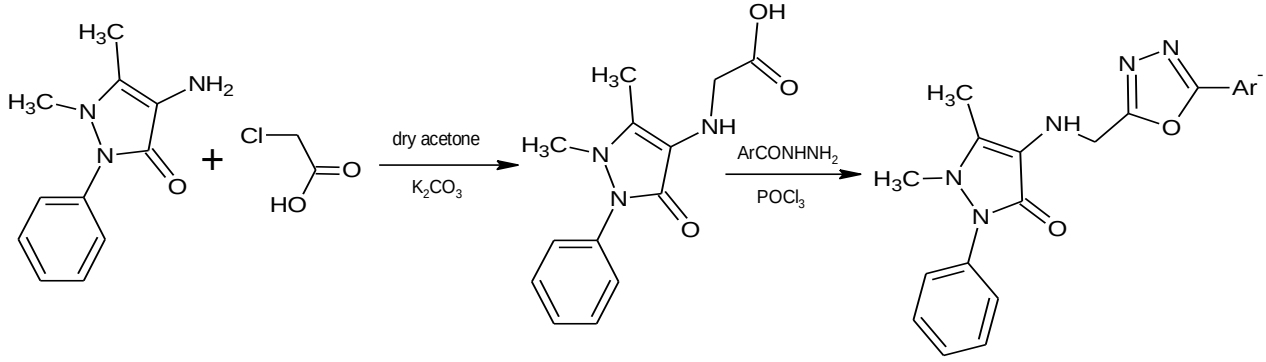
Gudipati R, *et al.,* [4] (2011) were synthesised 5- or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives (scheme: 1) having anticancer activity by treating 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives.



R^1 = H, F, Cl, Br, CH_3, NO_2, COOH
R^2 = H, Cl, NO_2, CH_3, COOH, $COOCH_3$

Scheme 1:-

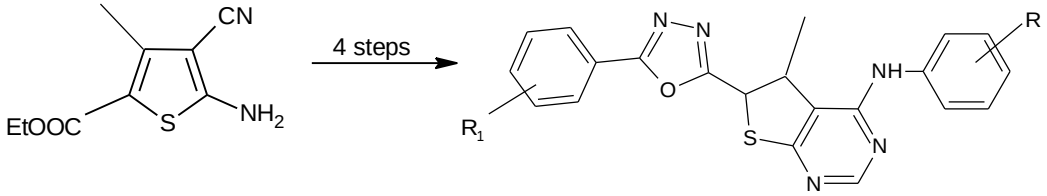
Ahsan MJ, *et al*., [1] (2011) were synthesised a series of 1,5-dimethyl-2-phenyl-4-{[(5-aryl-1,3,4-oxadiazol-2-yl)methyl]amino}-1,2-dihydro-3**H**-pyrazol-3-one derivatives (scheme: 2) having antimicrobial and antitubercular activity.



Ar = 2-chlorophenyl, 4-pyridinyl, 4-aminophenyl, 2-hydroxyphenyl, 4-methyl phenyl benzyl

Scheme 2:-

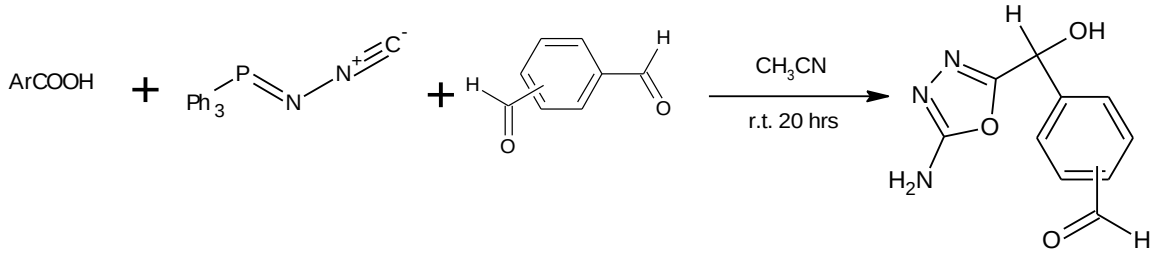
Kotaiah Y, *et al.,* [7] (2012) were synthesised **N**-substituted phenyl-5-methyl-6-(5-(4-substitutedphenyl)-1,3,4-oxadiazol-2-yl) thieno [2,3-**d**]pyrimidin-4-amine derivatives (scheme: 3) and phenylamino-5-methylthieno[2,3-**d**]pyrimidine-6-carboxylic acid derivatives were substituted on it. In this 4 derivatives having antioxidant activity.



R_1	4-Cl	4-Cl	4-F	4-F	3-Cl,4-F	3-Cl,4-F	3-Cl,4-F	2,4-di-F	2,4-di-F
R	4-H	4-Cl	4-Cl	4-NO_2	4-H	4-NO_2	4-Cl	4-Cl	4-NO_2

Scheme 3:-

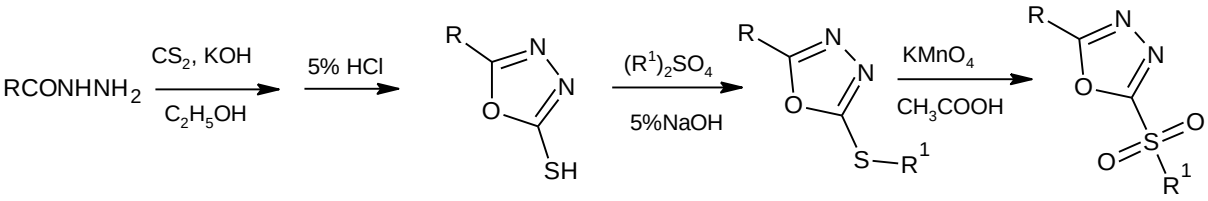
Ramazani A, *et al.,* [14] (2011) were synthesised 1,3,4-oxadiazole derivatives (scheme: 4) by the reaction between (N-isocyanimino) triphenylphosphorane, bis-aldehydes (isophthalaldehyde and terphthalaldehyde) and aromatic (or heteroaromatic) carboxylic acids.



Ar = aromatic carboxylic acids and aromatic bis aldehyde

Scheme 4:-

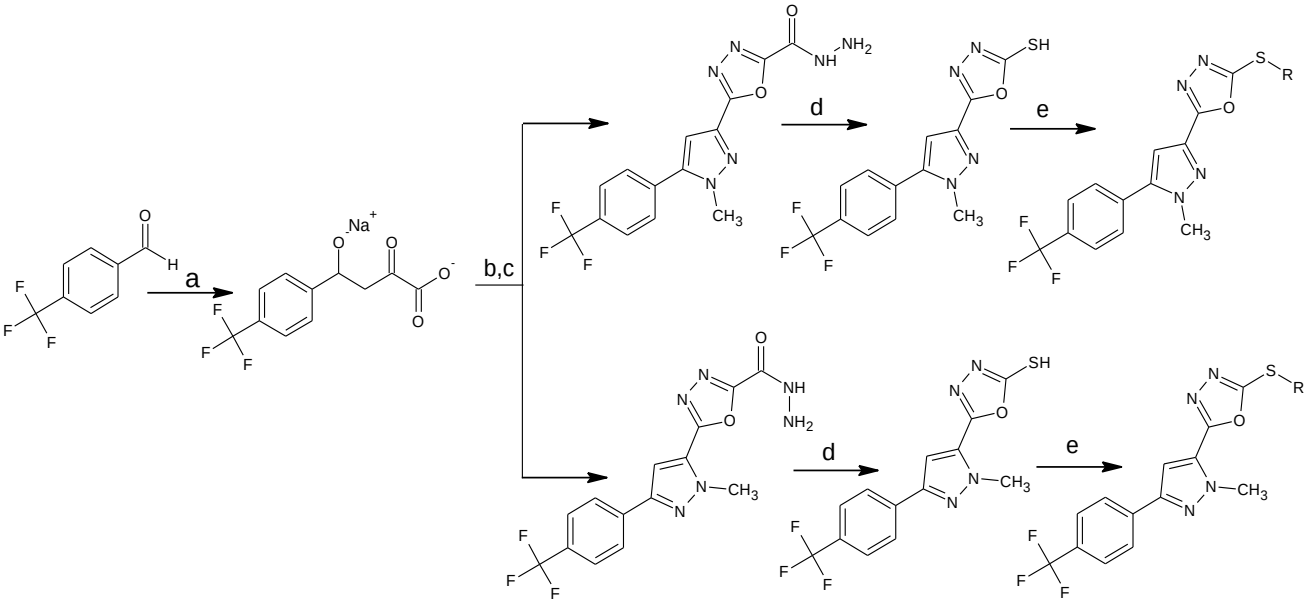
Xu WM, *et al*., [22] (2012) were designed and synthesised 1,3,4-oxadiazole moiety containing sulfone groups (scheme: 5) and were reported to have ability to mycelia growth of *Ralstonia solanacearum* in vitro also having better control effect against tobacco bacterial wilt so sulfone derivatives containing 1,3,4-oxadiazole can be used to develop potential bactericides for plants.



R = benzoic acid, fatty acids, heterocyclic acids $R^1 = CH_3, CH_2CH_3$

Scheme 5:-

Puthiyapurayil P, *et al*., [12] (2012), were synthesised S-substituted-1, 3, 4-oxadiazole bearing N-methyl4 (tri-fluoromethyl)phenyl pyrazole moiety (scheme: 6) and reported to have anticancer activity.

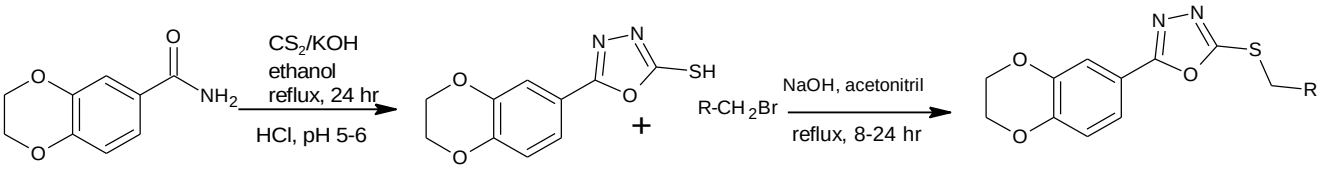


Reagents and conditions: (a) Dimethyl oxalate, NaOMe, MeOH, RT; (b) Methyl hydrazine hydrate, Gla. AcOH, 105 ^{0}C; (c) NH4. H2O, MeOH, 100C; (d) CS_2, KOH, MeOH, Reflux; (e) ReX, K2CO3, DMF, 80 ^{0}C.

R = substituted aryl halides

Scheme 6:-

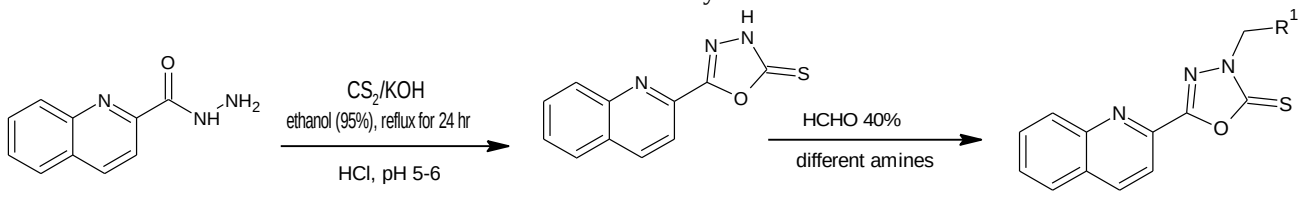
Zhang XM, *et al*., [23] (2011), were synthesised 1, 3, 4-oxadiazole derivative condensed with 1,4-benzodioxan moiety and some of the derivatives (scheme: 7) were having antitumor activity.



R= halogen substituted bromo toluene

Scheme 7:-

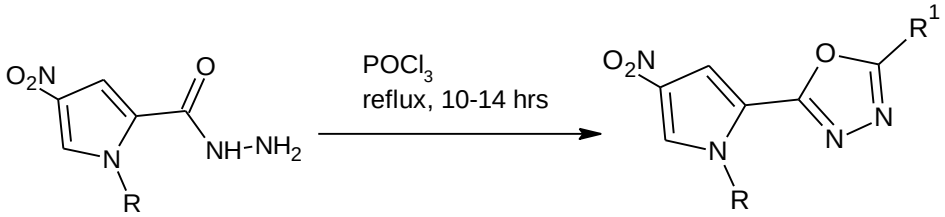
Sun J, *et al*., [19] (2013) were synthesised quinoline derivatives of 1, 3, 4-oxadiazole (scheme: 8) and were having anticancer activity.



R= primary and secondary amines

Scheme 8:-

Rane RA, *et al*., [15] (2013) were synthesised 42 novel 4-nitropyrrole-based 1, 3, 4-oxadiazoles (scheme: 9) and evaluated for anti-bacterial, anti-fungal and anti-tubercular activities.

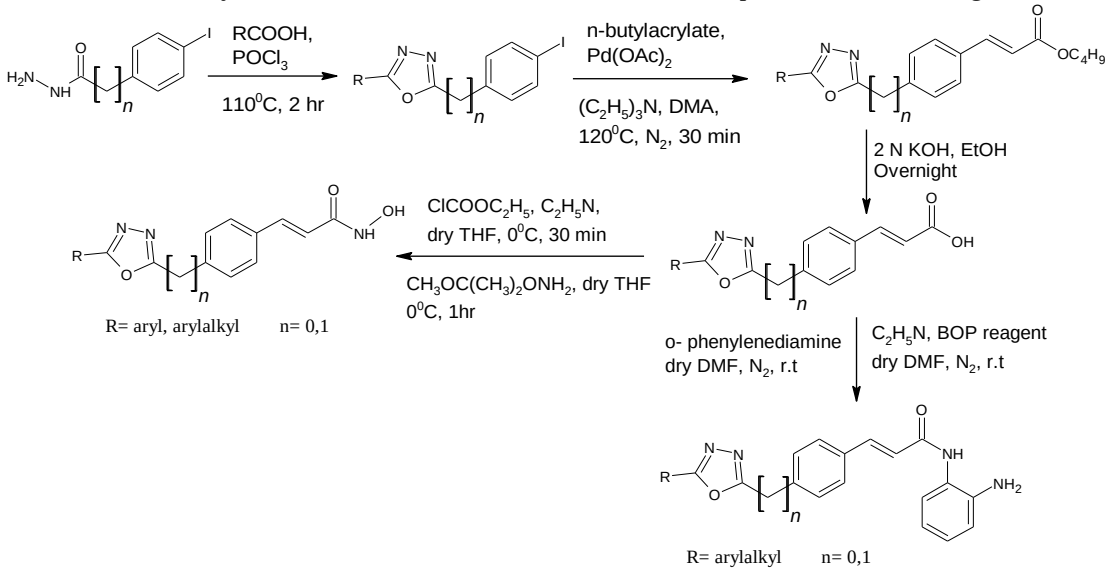


R= H, CH_3

R= aryl, heteroaryl

Scheme 9:-

Valente S, *et al*., [21] (2014) were reported 1, 3, 4-oxadiazole (scheme: 10) containing hydroxamates and 2-aminoanilides as histone deacetylase inhibitors. In this some of them were most potent and selective against HDAC.

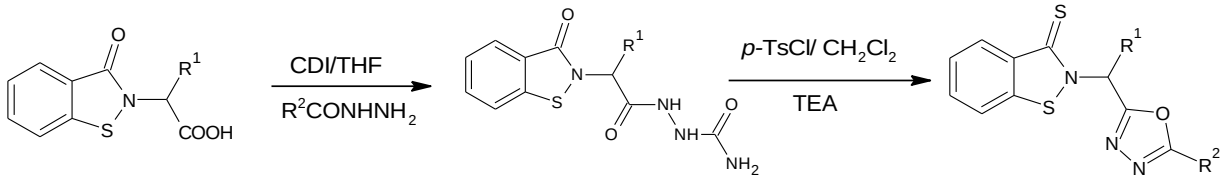


R= aryl, arylalkyl n= 0,1

R= arylalkyl n= 0,1

Scheme 10:-

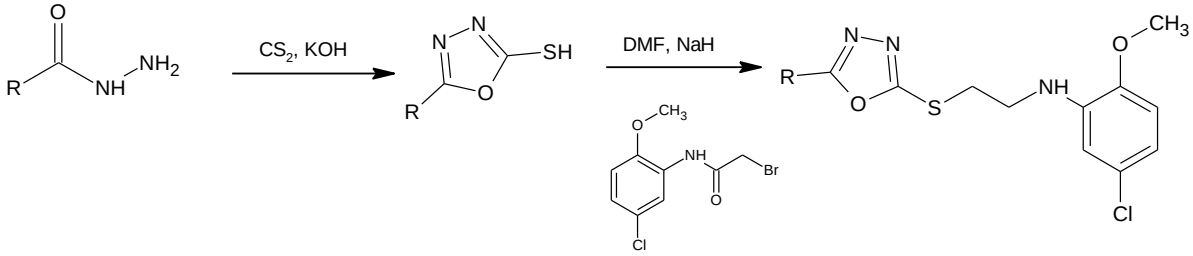
Lai H, *et al*., [9] (2012) were synthesised a series of functionalized 1,2-benzisothiazol-3(2H)-one—1,3,4-oxadiazole hybrid derivatives (scheme: 11) and screened against Dengue and West Nile virus proteases.



R^1= methyl, benzyl, phenethyl, m- flurobenzyl
R^2= substituted phenyl

Scheme 11:-

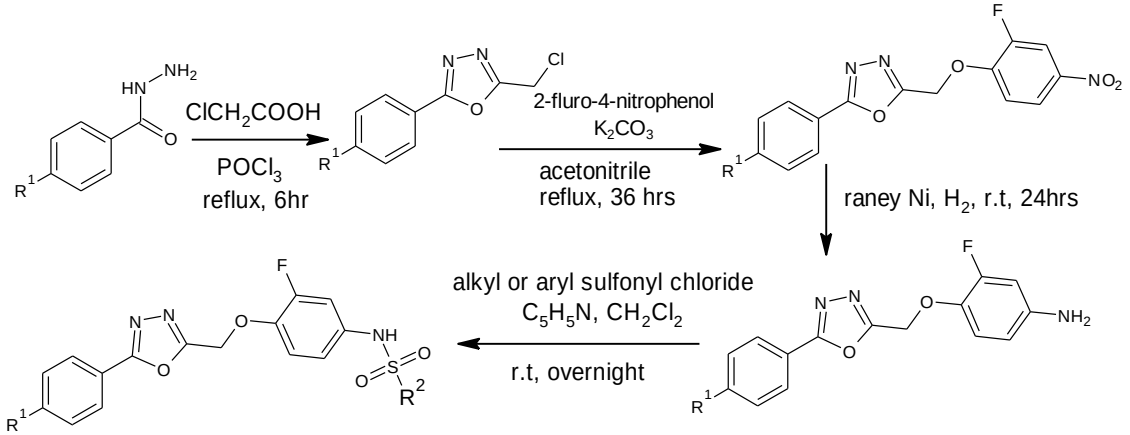
Khan KM, *et al*., [6] (2013) were synthesised, a series of 5-substituted-1,3,4-oxadiazole-2yl-N-(2 methoxy-5-chlorophenyl)-2-sulfanyl acetamide (scheme: 12) and reported their activity against acetyl cholinesterase.



R= substituted aryl, heteroaryl

Scheme 12:-

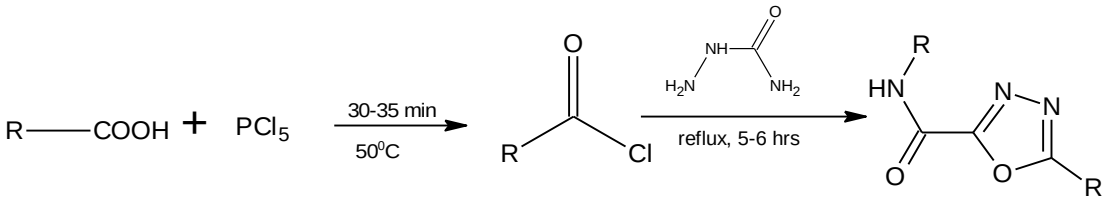
El-Din MM, *et al*., [3] (2014) were reported the synthesis of a new series of 1,3,4-oxadiazole derivatives possessing sulfonamide moiety (scheme: 13) having in vitro antiproliferative activities against NCI-58 human cancer cell lines of nine different cancer types.



R^1= H, Cl, OCH_3
R^2= substituted aniline

Scheme 13:-

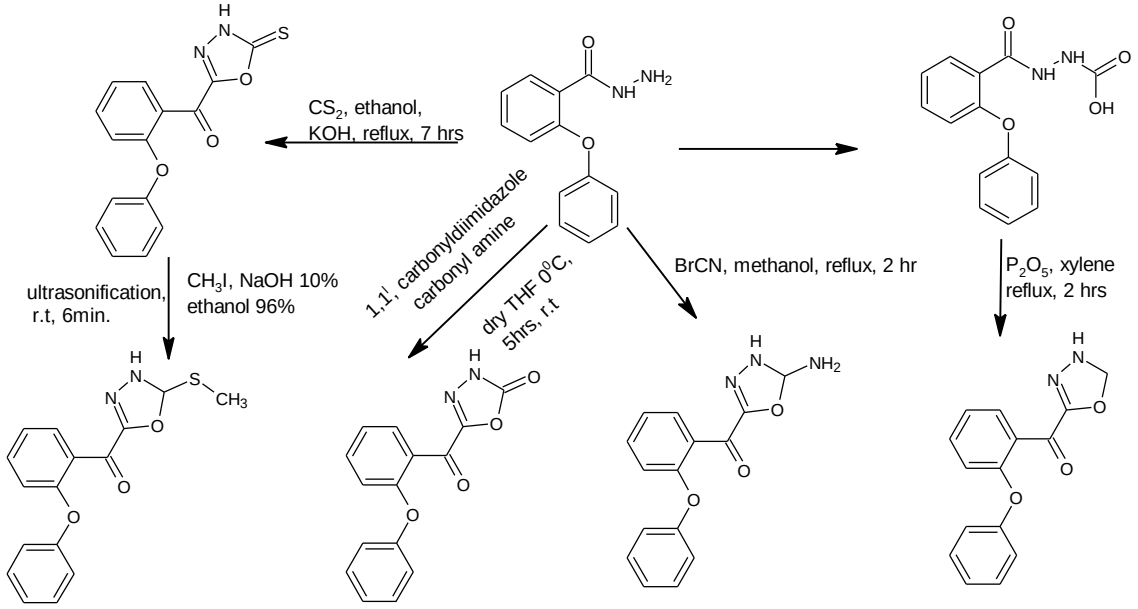
Singh AK, *et al*., [18] (2013) were synthesised a series of 1, 3, 4- oxadiazole derivatives (scheme: 14) and evaluated for anti-inflammatory activity.



R= substituted phenyl

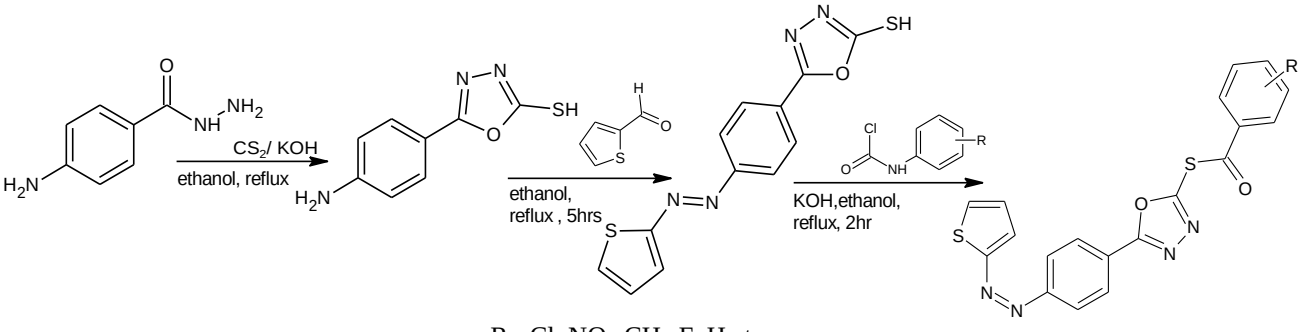
Scheme 14:-

Tabatabai SA, *et al*., [20] (2013) were synthesised some derivatives of 2-(2-Phenoxy) phenyl-1, 3, 4-oxadiazole (scheme: 15) and were reported as benzodiazepine receptor agonists.



Scheme 15:-

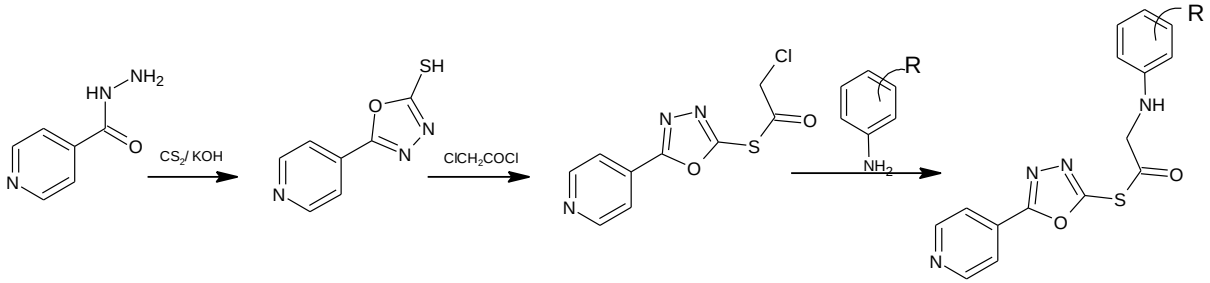
Desai NC, *et al.,* [2] YM (2014) were synthesised novel series of 2-{5-[4-(1-aza-2-(2-thienyl) vinyl) phenyl](1,3,4-oxa-diazol-2-ylthio)}-N-arylacetamides (scheme: 16) and screened for their antibacterial and antifungal activities.



R= Cl, NO_2, CH_3, F, H etc

Scheme 16:-

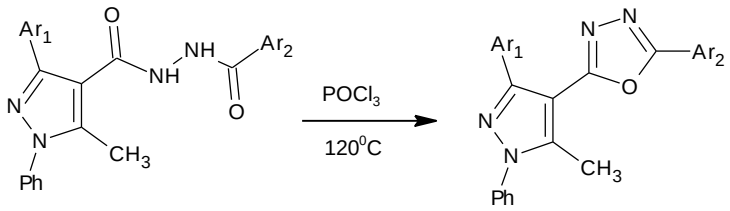
Raval JP, *et al.,* [16] (2011) were synthesised a series of 2(4-pyridyl)-5[(aryl/heteroarylamino)-1-oxoethyl]thio-1,3,4-oxadiazole (scheme: 17) and evaluated for antibacterial activity.



R= H, Cl, NO_2, CH_3 etc

Scheme 17:-

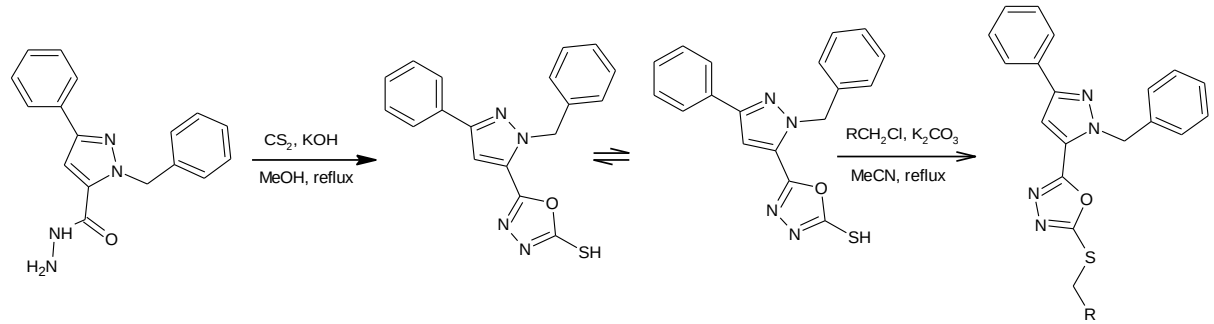
Ningaiah S, *et al.*, [11] (2014) were synthesised a novel series of 2-(5-methyl-1,3-diphenyl-1H-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazoles (scheme: 18) and evaluated for antimicrobial activity.



Ar= aryl halides

Scheme 18:-

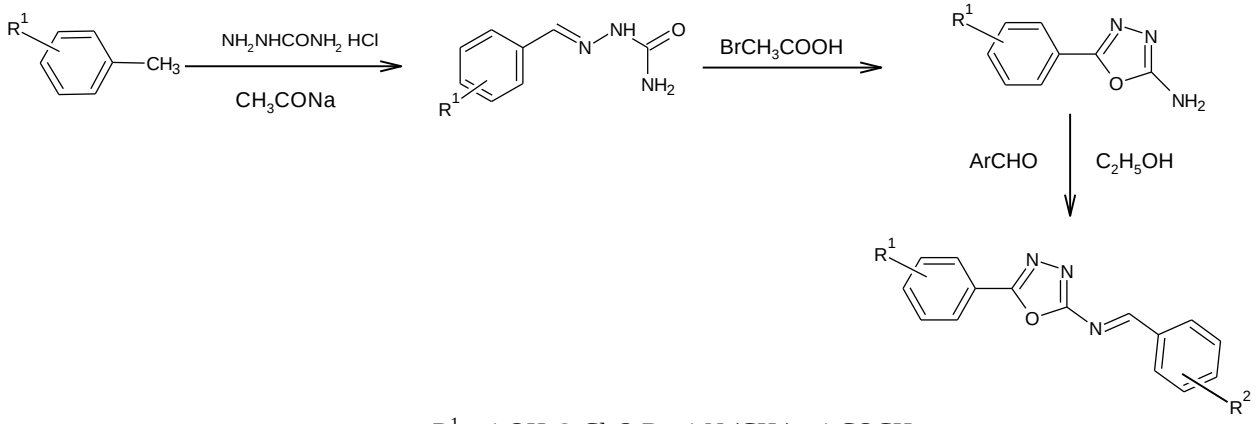
Qi DQ, *et* al., [13] (2015) were designed and synthesised a series of pyrazole-based 1, 3, 4-oxadiazole derivatives (scheme: 19). The fluorescence properties of all the compounds were analysed in dimethyl sulfoxide media and were evaluated for their n vitro inhibitory activity against commercial enzyme xanthine oxidase (XO) by measuring the formation of uric acid from xanthine.



R = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-NO_2 C_6H_4, 4-CNC_6H_4, 4-CH_3 C_6H_4, 3-FC_6H_4, 3-ClC_6H_4, 3-BrC_6H_4, 3-NO_2 C_6H_4, CH $(CH_3)_2$ C_6H_4, $COOCH_2CH_3$ C_6H_4

Scheme 19:-

Roy PP, *et al.*, [17] (2017) were synthesised some novel 2, 5- Disubstituted 1, 3, 4-Oxadiazole derivatives (scheme: 20) using different aromatic benzaldehyde, and evaluated for their anticancer activity against Ehrlich Ascites Carcinoma (EAC) bearing albino mice.



R^1 = 4-OH, 2-Cl, 3-Br, 4-N $(CH_3)_2$, 4-$COCH_3$
R^2 = 4'-OH, 4-Cl, 2-NO_2, 4'-N $(CH_3)_2$

Scheme 20:-

Conclusion:-

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

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