International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 3(6): November-December 2013

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 25-10-2012; Revised; Accepted: 03-11-2013

CHEMISTRY AND COMMON SYNTHETIC ROUTE OF 1, 3, 4-OXADIAZOLE: AN IMPORTANT HETEROCYCLIC MOIETY IN MEDICINAL CHEMISTRY

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Keywords:

Anticonvulsant, Antitubercular, Antimitotic, Antimicrobial**,** Hypoglyceamic

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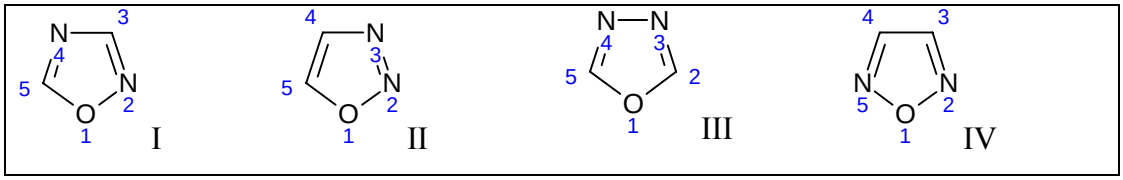
ABSTRACT

These heterocyclic moiety are prepared by different method and have different biological and physiological properties. The widespread use of 1,3, 4 –oxadiazole as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocyclic compounds**.** 1,3, 4 –oxadiazole are also used as pharmacophores due to their favourable metabolic profile and ability to engage in hydrogen bonding. HIV-integrase inhibitor ,raltegravir a nitrofuran antibacterial furamizole , antihypertensive agents tiodazosin , and nesapidil are based on 1,3, 4-oxadiazole moiety. The thermal stability of 1,3,4-oxadiazoles is due to the presence of aryl and perfluoroalkyl groups **.** 1, 3, 4-oxadiazoles is used in medicinal chemistry as ester and amide bioisosteres for a number of biological targets .These compound have biological properties like anticonvulsant, analgesic, antipyretic, antimitotic, antitubercular and antimicrobial etc.

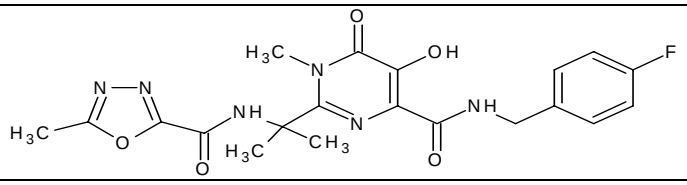
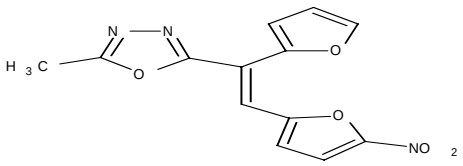
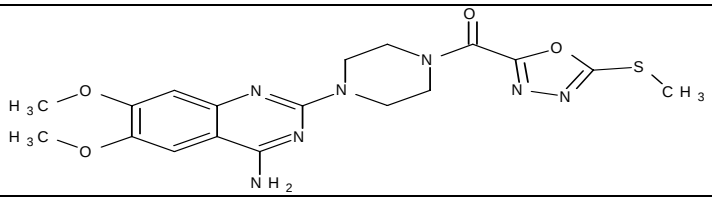
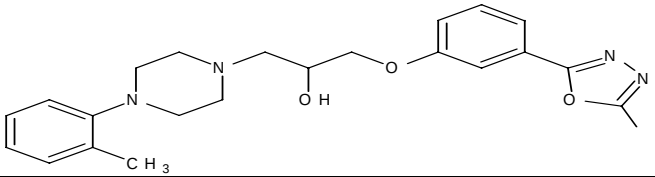
INTRODUCTION

Oxadiazole ring is considered to be derived from furan ring by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=) [1]. There are four possible isomers of oxadiazole **(**I, II, III and IV**)** depending on the position of nitrogen atom in the ring and are numbered as shown in.



Heterocyclic compounds bearing 1, 3, 4-oxadiazole moiety has been used as a π-conjugation relay to prepare a number of donor-acceptor molecules carrying a π-electron rich aromatic ring. Therefore the compounds bearing 1 ,3, 4-oxadiazole moiety may be a good candidate for optical material or biologically active chemicals [2]. 1, 3, 4-oxadiazoles have attracted an interest in medicinal chemistry as ester and amide bioisosteres for a number of biological targets [3, 4].

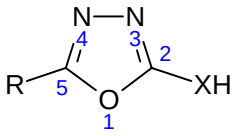
Drugs containing 1, 3, 4-oxadiazole moiety

Sr. no.	Name	Structure
1	Raltegravir	
2	Furamizole	
3	Tiodazosin	
4	Nesapadil	

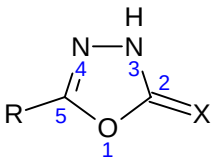
As such their peptidomimetic ability has been explored and reported in the development of Phe-Gly mimetics of dermorphin (Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2) and substance P(Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2) [5].

The widespread use of 1, 3, 4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocycles. These molecules are also used as pharmacophores due to their favourable metabolic profile and ability to engage in hydrogen bonding [6]. 1, 3, 4-oxadiazoles have proved to be useful in material science as probe for their fluorescence and scintillation properties [7]. In addition oxadiazole derivatives have been widely used as electron conducting and hole blocking material in molecules based as well as polymeric light emitting devices [8]. Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutics. Out of its four possible isomers 1, 3, 4-oxadiazole is widely exploited for various applications. A number of therapeutic agents such as HIV-integrase inhibitor,raltegravir[9], anitrofuran antibacterial furamizole [10], antihypertensive agents tiodazosin [11], and nesapidil [12] are based on 1,3, 4-oxadiazole moiety.

Chemistry of oxadiazole:- As 1,3 ,4-oxadiazoles havea relatively low electron density at carbon (position 2 & 5) and a relatively high electron density at nitrogen (position 3 & 4), the major reactions are nucleophilic attack at carbon, generally followed by ring cleavage, and electrophilic attack at nitrogen. This reactivity towards nucleophiles, also catalysed by acid, causes difficulties when carrying out reactions which involves basic or acidic conditions. The ring is more stable when substituted by one or more aryl groups [13].



(a)



(b)

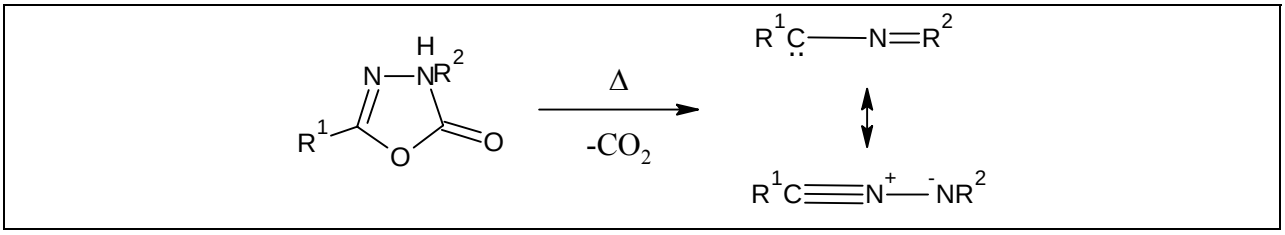
Tautomeric oxadiazoles (a&b) react with electrophiles at ring nitrogen, at the exocyclic heteroatom or at both centres. Reactions in the subsstituent group of alkyl or aryl-1, 3,4-oxadiazoles are possible but they are limited by sensitivity of the ring to the reagent used.

Fully conjugated Rings; Reactivity at Ring Atoms:-

Thermal and photochemical rections, formally involving no other species:-

1,3,4-oxadiazoles are thermally stable compounds and this stability is increased on substitutions, particularly by aryl and perfluoroalkyl groups. Oxadiazolin-5-ones and 5-thiones are somewhat less stable and undergo selective pyrolysis at high temperatures. Oxadiazolinones (1) lose carbon dioxide at high temperature to give nitrilimines (2) which react further. Recrystallization in the

nitrilimine, formed at 210-230˚C from oxadiazolinone (1a), yields a 2-alkoxy-1,3,4-oxadiazole which at the reaction temperature, undergo a further rearrangements to oxadiazolinone (1c). A similar rearrangement occurs on thermolysis of oxadiazolinone (1b). 2,5-diphenyl-1,3,4-oxadiazole is produced on heating oxadiazolinone (1d) at 250˚C. Oxadiazolinones (1e) & (1f) are more stable but undergo flash vacuum pyrolysis at 500˚C to give indazoles. At higher temperature, loss of nitrogen also occurs, and styrene or fluorine respectively is produced in high yield. A variety of hydrocarbons are formed on flash vacuum pyrolysis of oxadiazolinones (1; R^2= alkenyl).



(1) (2)

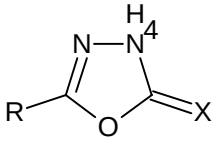
a	R^1	R^2
b	Ph	COOR
c	Ph	COSEt
d	Ph	R
e	Ph	COPh
f	Me	Ph
g	Ph	Ph

Carbon dioxide is lost on thermolysis of 4-ethoxycarbonyl-2-phenyl-Δ^2-1, 3, 4-oxadiazoline-5-thione. Migration of the ethyl group from oxygen to sulfur leads to the product, 5-ethylthio-2-phenyl-1,3,4-oxadiazole.Photolysis of oxadiazolinone (1f) yields a nitrilimine (2f) which, in the presence of alkenes, undergoes cycloaddition to give pyrazoles. Azobenzene is produced on irradiation of 3,4-diphenyl-1,3,4-oxadiazolidine-2,5-dione.

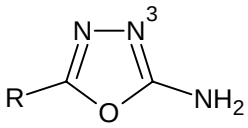
2.1.2. Electrophilic attack at nitrogen:-

Alkyl and aryl-1,3,4-oxadiazoles are neutral compounds and 2-amino derivatives are weak bases. Protonation is believed to occur at ring nitrogen in position 3 which facilitates ring cleavage in aqueous acid. The pk_a (water) value of 2-amino-5-methyl-1, 3, 4-oxadiazole is 2.37 and values in the range 2.3-2.7 have been recorded for 2-amino-5-phenyl- and 2-N-methylamino-5-phenyl-1,3,4-oxadiazole in 50% aqueous ethanol. In the same solvent pk_a values of the more basic imines, 4-methyl-2-phenyl- and 4 N-dimethyl-2-phenyl- Δ^2-1,3,4-oxadiazolin-5-imine, are 6.3 and 6.38 respectively.

Alkylation of oxadiazolines (3) and aminooxadiazole (4) generally result in substitution at ring nitrogen in position 4 or 3 respectively, particularly under neutral conditions. In alkaline medium, alkylation at the exocyclic heteroatom may occur.

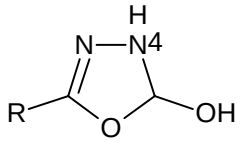


(3)

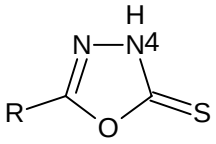


(4)

Oxadiazolinones (3a) and thiones (3b) acylate, for example, with acetic anhydride, benzoyl chloride or alkyl chloroformates at ring nitrogen in position 4.



(3a)



(3b)

2,5-disubstituted 1,3,4-oxadiazoles form double salts with mercuric chloride or with silver nitrate, which in the latter case, are used to purify or characterize the oxadiazole.

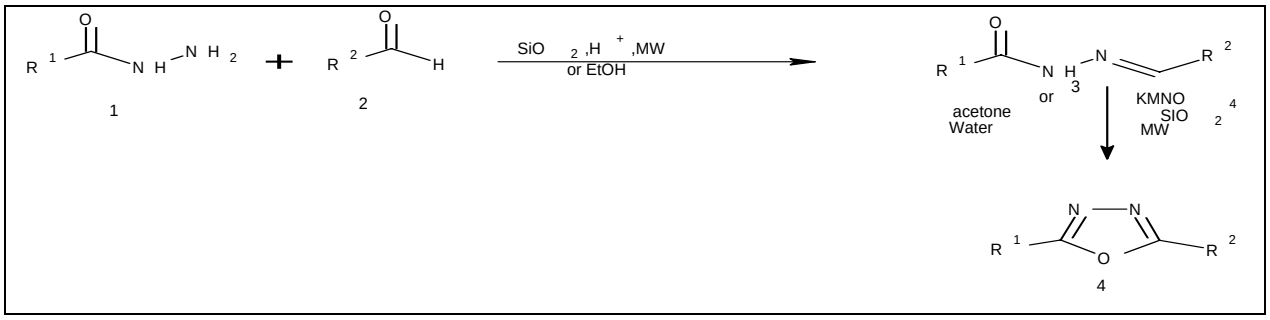
Electrophilic substitution at carbon:-

The relatively low electron density at carbon, coupled with the possibility of Protonation at nitrogen, makes electrophilic substitution at carbon difficult. A further problem is acid catalyzed ring cleavage, particularly with alkyl-oxadiazoles. No example of nitration or sulfonation has been reported.

Synthesis of 1,3,4-oxadiazole backbone:-

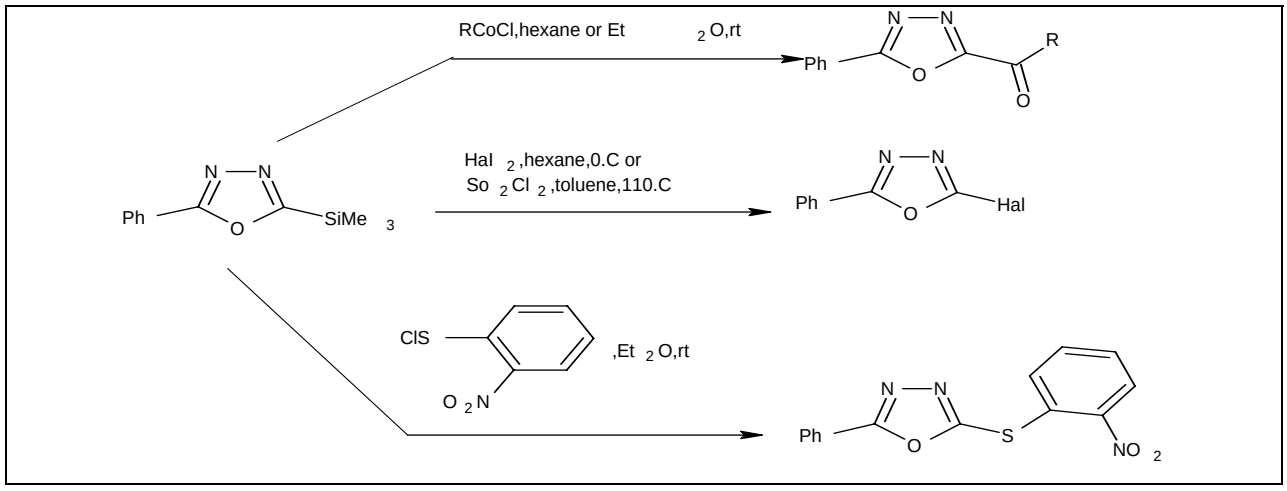
A series of 2,5-disubstituted 1,3,4-oxadiazoles were prepared by oxidation of 1-aroyl-2-arylidine hydrazides with potassium permanganate on the surface of silica gel and also in mixture of acetone and water under microwave irradiation[14].

Scheme 1- synthesis of 2,5-disubstituted 1,3,4-oxadiazoles using microwave



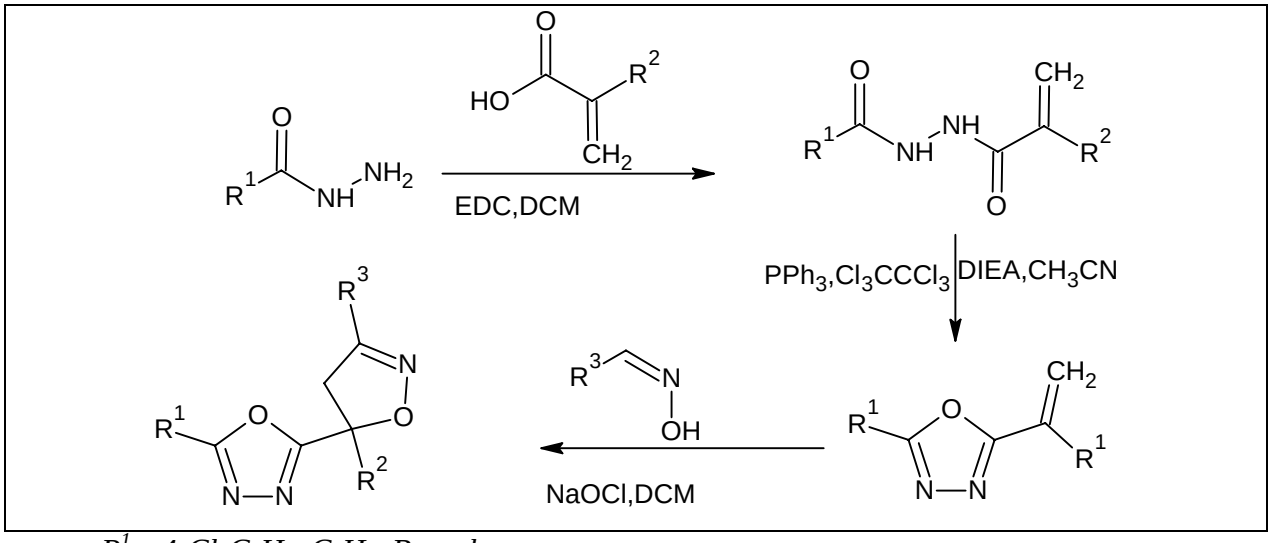
2-phenyl-5-trimethylsilyl-1,3,4-oxadiazole reacted with Cl_2 or Br_2 in hexane at 0□ C for 0.25-1.5 hr affording the corresponding 2-halogen-5-phenyl-1,3,4-oxadiazoles which ppt from the reaction mixture and were isolated in good yield[15,16].

Scheme2 - synthesis of 2,5-disubstituted 1,3,4-oxadiazoles using trimethylsilyl.



Acid hydrazides were coupled with acrylic acid derivatives and cyclodehydration gave 1,3,4-oxadiazoles lastly in situ nitrile oxide formation from aryl oximes treated with sodium hypochlorite, and subsequent 1,3-dipolar cycloaddition to the exomethylene moiety delivered 2-(4,5-dihydroisoxazol-5-yl)-1,3,4-oxadiazoles[17,18].

Scheme 3- synthesis of 2-(4,5-dihydroisoxazol-5-yl)-1,3,4-oxadiazoles



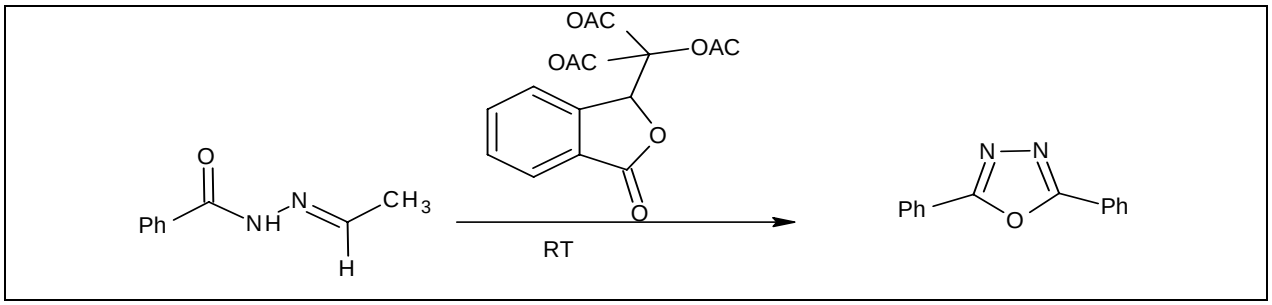
R^1= 4-Cl-C_6H_4, C_6H_5, Benzyl

R^2=CH_3, H

R^3= 4-Pyridyl, 4-F-C_6H_4, 3-Pyridyl

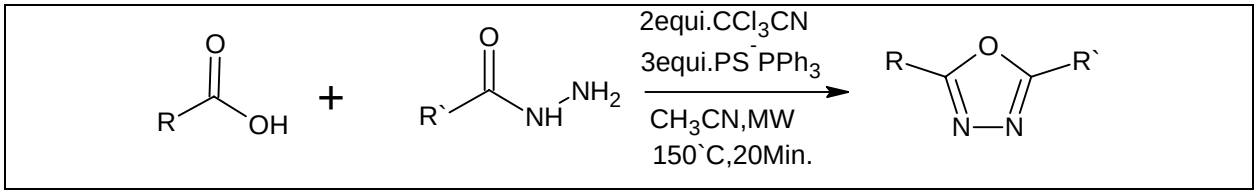
2,5-disubstitutes 1,3,4-oxadiazoles have been conveniently prepared by oxidative cyclization of N-acyl N`aryliden-hydrazines promoted by excess of Dess Martin reagent(1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one[19].

Scheme4- 2,5-disubstituted 1,3,4-oxadiazole from Dess Martin Reagent



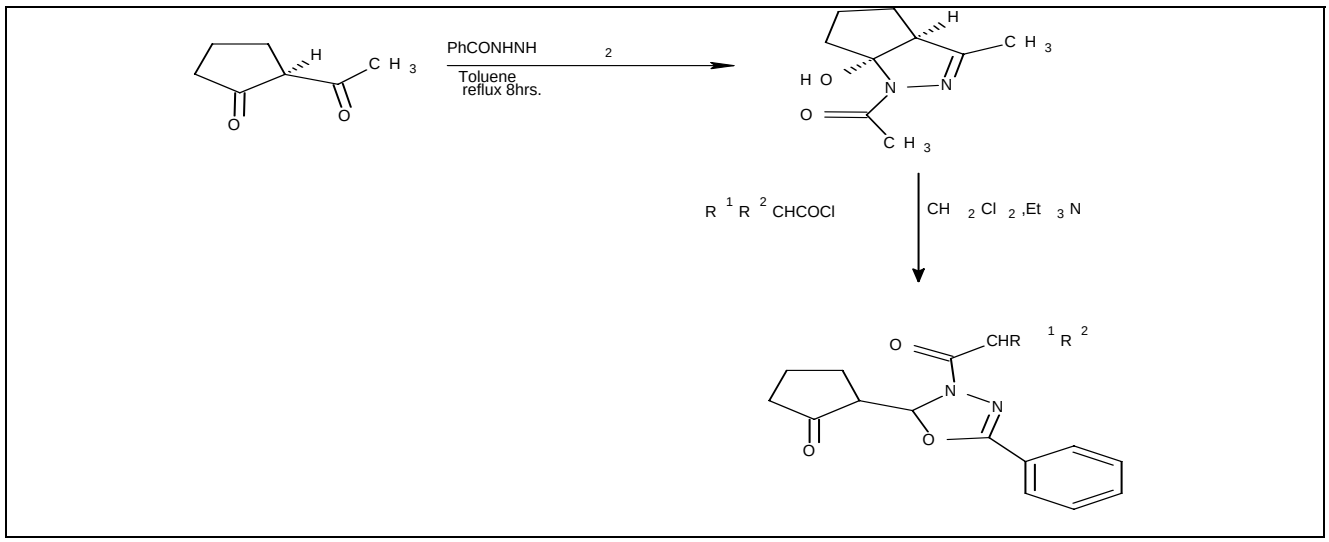
1,3,4-oxadiazoles can be prepared from carboxylic acid and acid hydrazides with PS-PPh3/CCl3CN[20]

Scheme 5 - Formation of 1,3,4-oxadiazoles using PS-PPh3 resin combined with microwave heating.



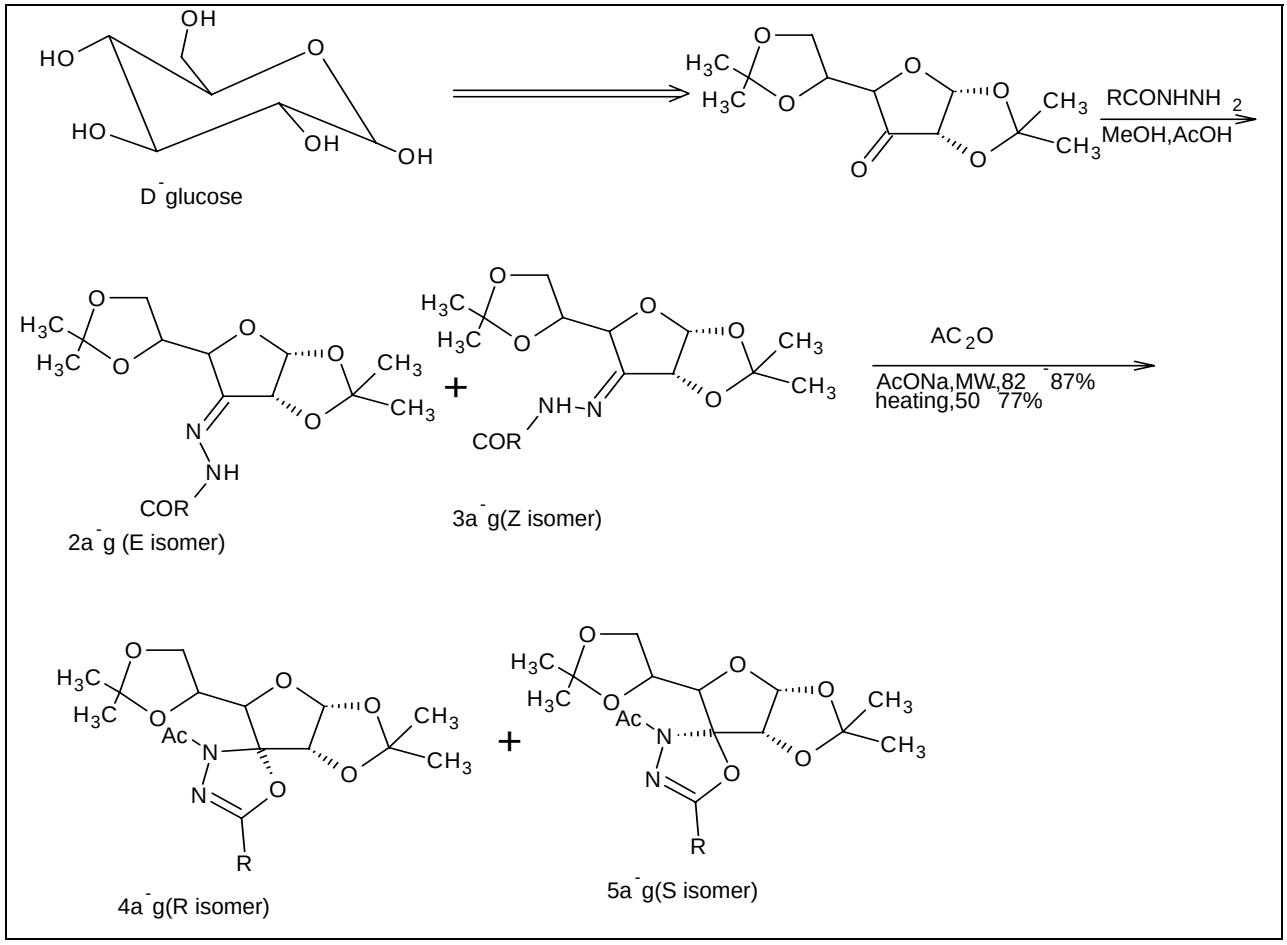
Reaction of 1-benzoyl-5-hydroxy-pyrazoline with ketene, prepared in situ from the corresponding acid chloride and mixed anhydride result in formation of 1,3,4-oxadiazoles [21].

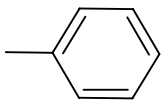
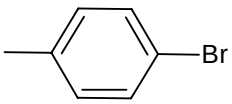
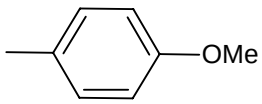
Scheme 6- Formation of 1,3,4-oxadiazoles from reaction of N-aroyl dihydrocyclopenta-pyrazolidinol with ketene



A series of novel glucose based 3-acetyl-5-alkyl-2, 3-dihydro-1,3,4-oxadiazoles withtheassistance of microwave was developed. The effect of different catalysts on the heterocyclization process was investigated and the reaction conditions were optimized with NaOAc emerging as the catalyst of choice. Under the optimized condition a series of novel3-acetyl-5-alkyl-2,3-dihydro-1,3,4-oxadiazole derivatives were successfully synthesized[22].

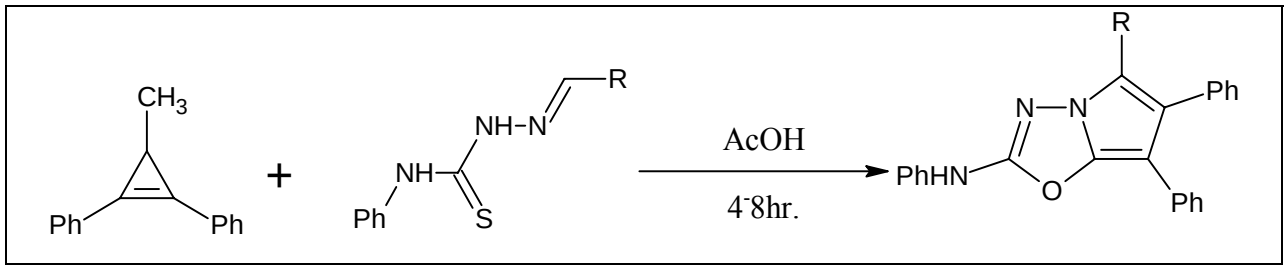
Scheme 7- Microwave assisted synthesis of glucose based 3-acetyl-5-alkyl-2,3-dihydro-1,3,4-oxadiazole derivatives.



A	B	C	D	E	F	G
R	CH_3	n-C_3H_7	n-C_5H_{11}			

The cycloaddition of substituted ylidene-N-phenylhydrazine-carbothioamides with 2,3-diphenylcyclopropenone gave corresponding 1,3,4-oxadiazoles [23].

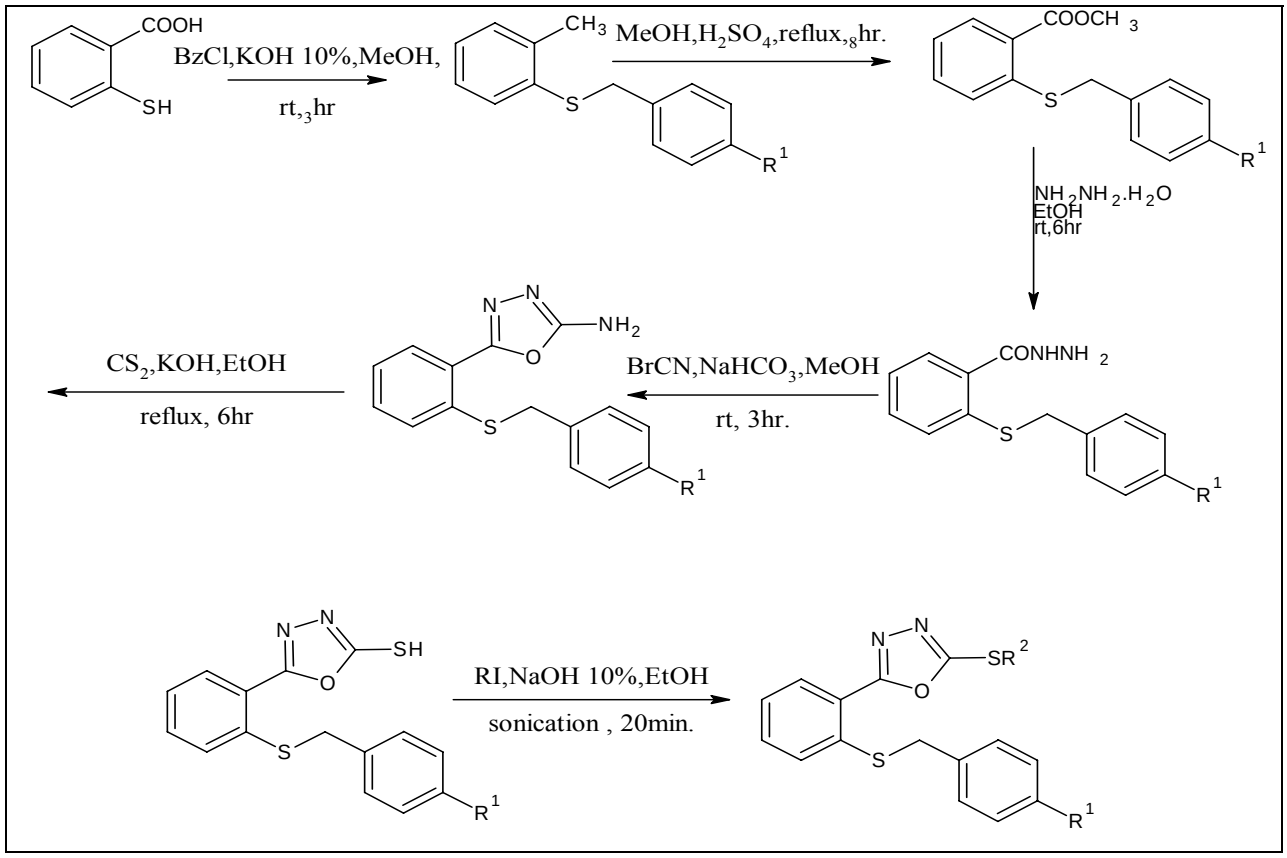
Scheme 8 - Synthesis of some new benzo[b]thiophene as oxadiazoles



R=4-H_3CO-C_6H_4-, 4-OH-C_6H_4-, 4-Cl-C_6H_4, 2-thienyl

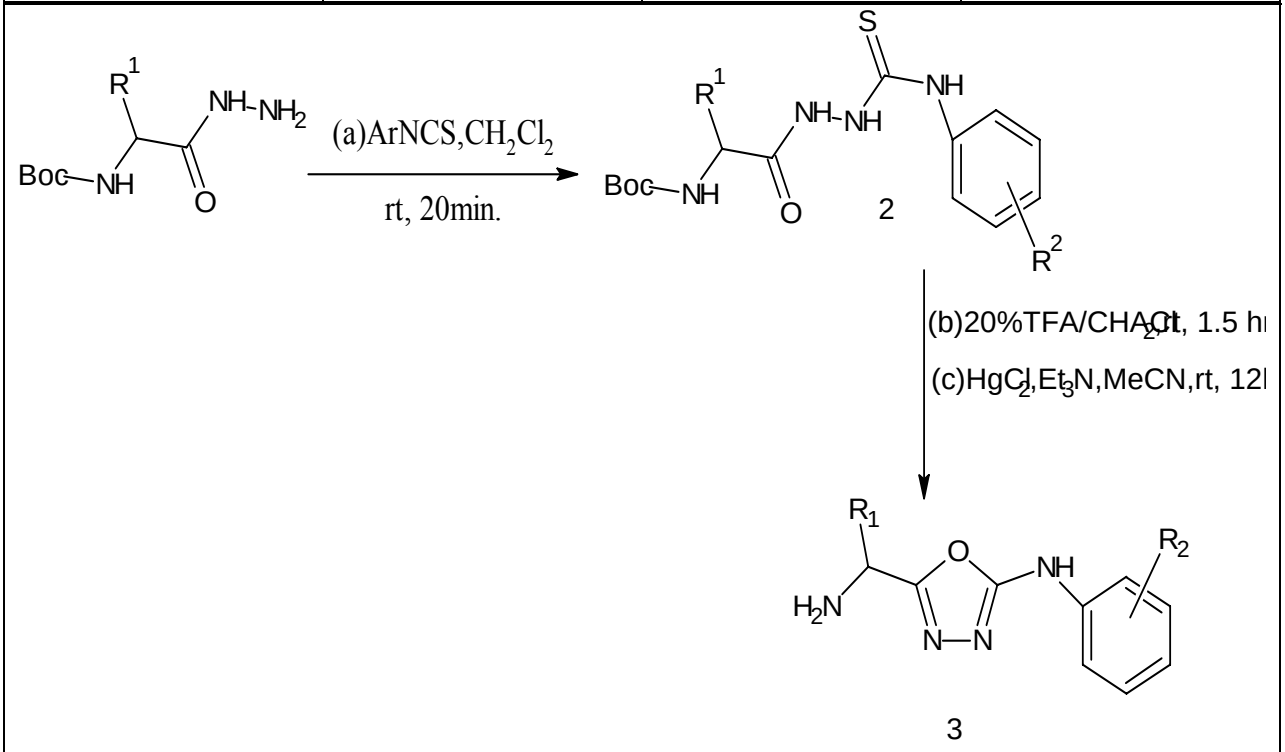
2-amino-5-(2-benzylthiophenyl)-1,3,4-oxadiazoles were prepared by reaction of thiosalicylic acid with appropriate benzyl chloride in alkaline hydromethanolic solution afford 2-benzylthiobenzoic acid, then esterification was done then hydrazides and hydrazides were converted to oxadiazoles[24].

Scheme 9- Synthesis of new 2-substituted -5-(2-benzylthiophenyl)-1,3, 4-oxadiazoles

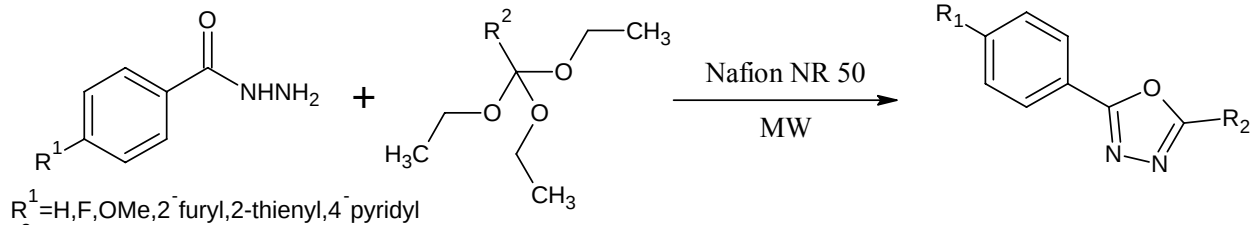


Synthesis of peptidomimetic 2-arylamino-5-5ubstituted 1,3,4-oxadiazoles from BoC-protected α-amino acid derived hydrazides have been reported in a parallel solution phase synthesis[24].

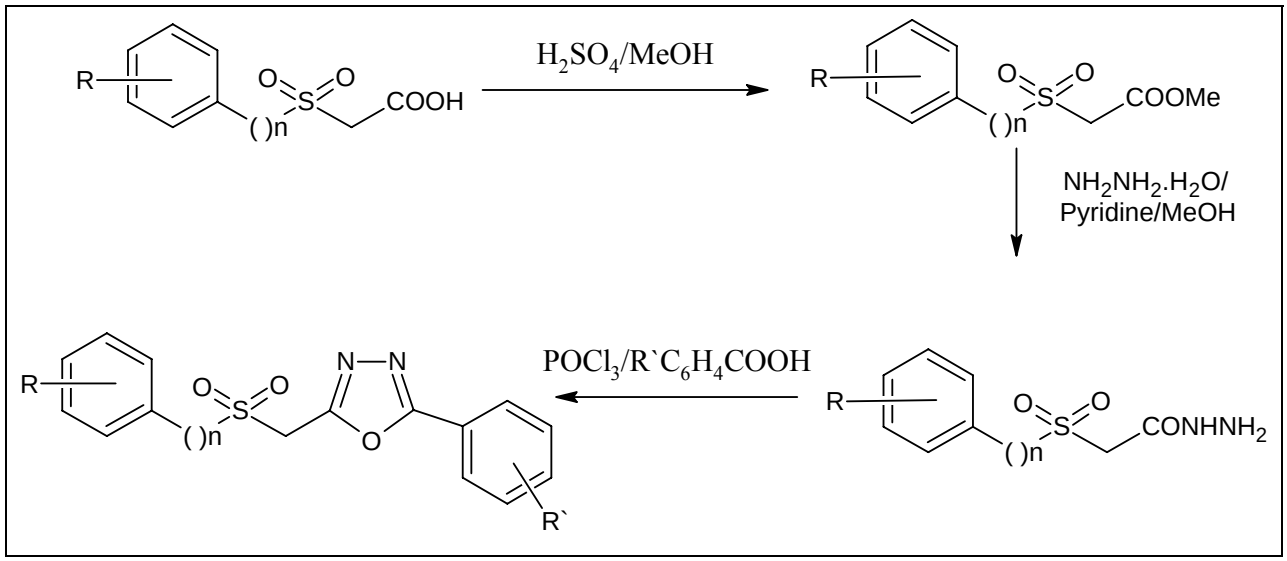
Entry	Products	R^1	R^2
1	2/3a	Me	H
2	2/3b	i-pr	H
3	2/3c	Bn	H
4	2/3d	Bn	4-Me



Scheme10- Parallel solution phase synthesis of a library of amino acid derived 2-arylamino-[1,3,4]-oxadiazoles.



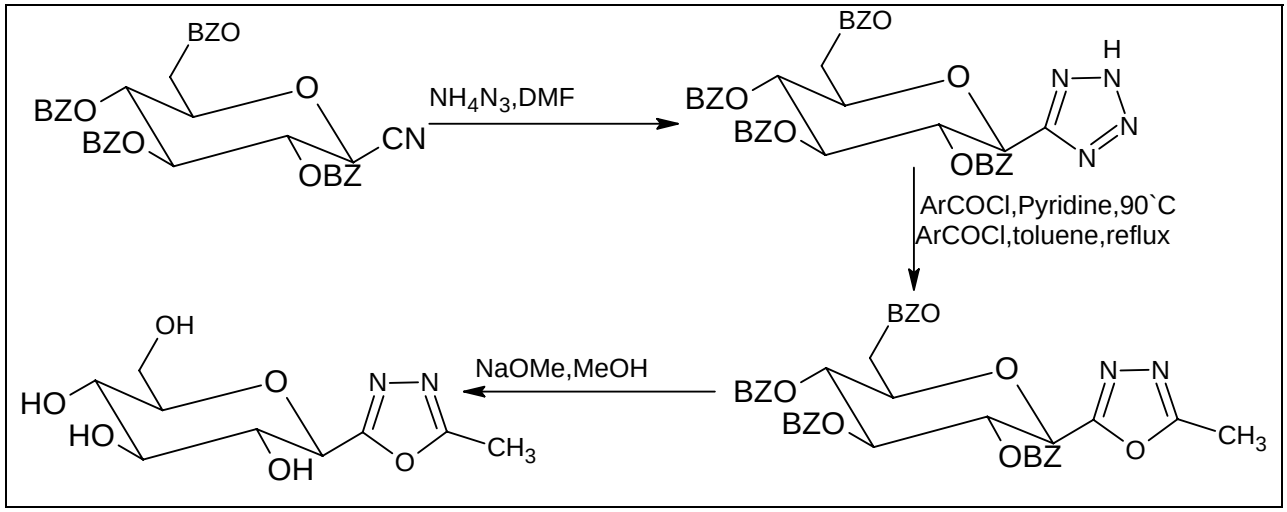
Scheme11- One pot solvent free synthesis of 1,3 ,4-oxadiazole



1,3 ,4-oxadiazoles were prepared from acid hydrazides on treatment with different carboxylic acid in presence of $POCl_3$[26].

Scheme12- Synthesis of 2-mercapto-1,3,4-oxadiazoles

A series of per-o-benzoylated 5-(β-D-glucopyranosyl)-2-substituted-1,3,4-oxadiazoles were prepared by acylation of the corresponding 5-(β-D-glucopyranosyl)tetrazole[27].



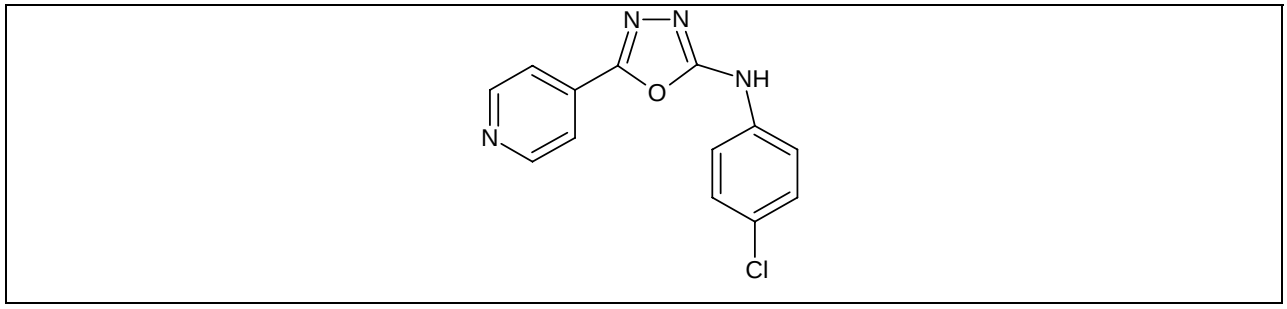
Biological activity:-

Anticonvulsant Activity:-

Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been archieved during the last decade. Furthermore, although for

the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity. The heterocycles profound highly active in epilepsy one heterocycle is 1,3, 4-oxadiazole.

Mohammad et. al. **(2009)** synthesized a series of five membered heterocyclics in reaction between isoniazid and various substituted isothiocyanates and the compounds were tested for their anticonvulsant activity [28].

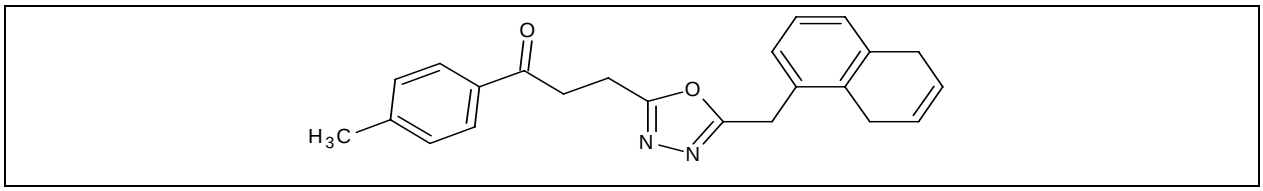


2-(4-chlorophenyl) amino-5-(4-pyridyl)-1, 3,4-oxadiazole

Analgesic, Antiinflammatory and Antiplatelet Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthiritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA_2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. 1,3,4-oxadiazole nucleus found satisfactory role in inflammatory and analgesic.

Akhtar et al. **(2009)** synthesized a series of 2,5-disubstituted-1,3,4-oxadiazoles which are aryolpropanoic acid derivatives. The synthesized compounds were evaluated for anti-inflammatory and analgesic activity [29].

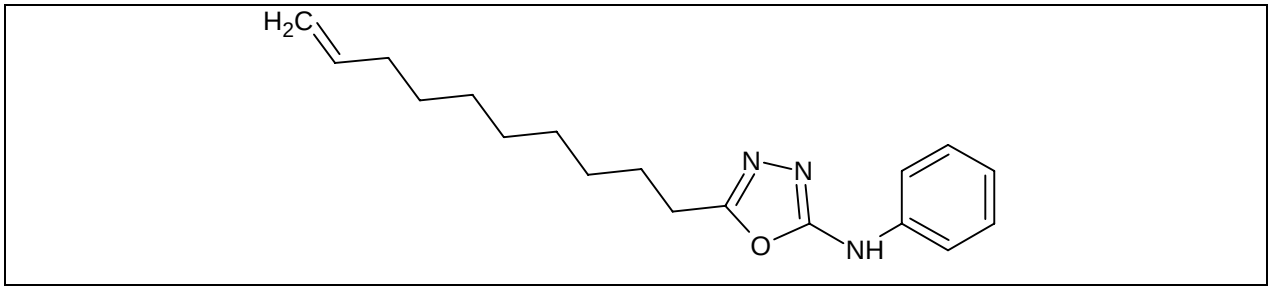


3-[5-(5,8-dihydronaphthalen-1-ylmethyl)-1,3,4-oxadiazol-2-yl]-1-(4-methylphenyl)propan-1-one

Antimicrobial Activity

The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists. Oxadiazoles found highly effective in bacterial and fungal diseases.

Farshori et al. **(2010)** synthesized a series of 5-alkenyl-2-phenylamine-1,3,4-oxadiazoles. The synthesized compounds were investigated for antibacterial and antifungal activities [30].

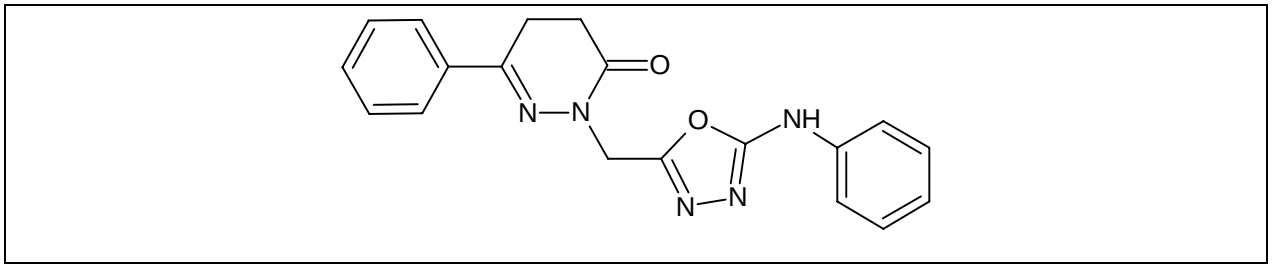


5-(dec-9-en-1-yl)-*N*-phenyl-1,3,4-oxadiazol-2-amine

Antitubercular activity

Tuberculosis is a serious health problem that causes the death of some three million people every year worldwide. In addition to this, the increase in *Mycobacterium tuberculosis* strains resistant to front-line antimycobacterial drugs such as rifampin and isoniazid has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of tuberculosis.

Siddiqui et al. **(2010)** Synthesized a series of 5-{3`-oxo-6`-(substituted aryl)-2`,3`,4`,5`-tetrahydropyridazin-2`ylmethyl}-2-substituted-1,3,4-oxadiazoles. The synthesized compounds were evaluated for their antitubercular activity [31].

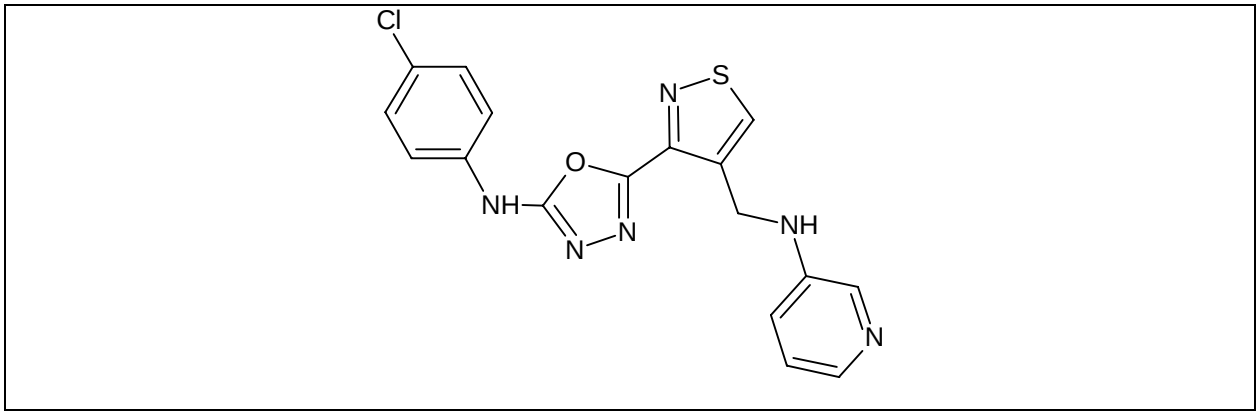


6-phenyl-2-{[5-(phenylamino)-1,3,4-oxadiazol-2-yl]methyl}-4,5-dihydropyridazin- 3(2*H*)- one

Antimitotic Activity

A variety of antitumoral drugs are currently in clinical use. The search for antitumoral drugs led to the discovery of several 1,3,4-oxadiazoles having antitumoral activity.

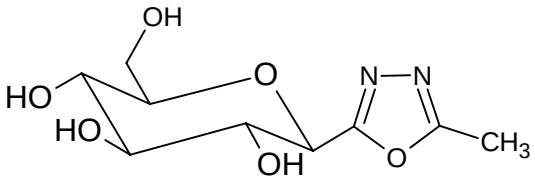
***Kiselyov et al.* (2010)** synthesized a series of 2,5-disubstituted-1,3,4-oxadiazoles. The synthesized compounds were analysed by using the sea urchin embryo test system. The synthesized compounds showed as good as activity as podophyllotoxin [32].



***N*-[(3-{5-[(4-chlorophenyl)amino]-1,3,4-oxadiazol-2-yl}-1,2-thiazol-4-ylmethyl] pyridin-3-amine**

Hypoglycaemic activity:-

***Toth et al*. (2009)** synthesized a series of 5β-D-glucopyranosyl-2-substituted-1,3,4-oxadiazoles. The formed oxadiazoles showed weak inhibitory activity of glycogen phosphorylase [33].

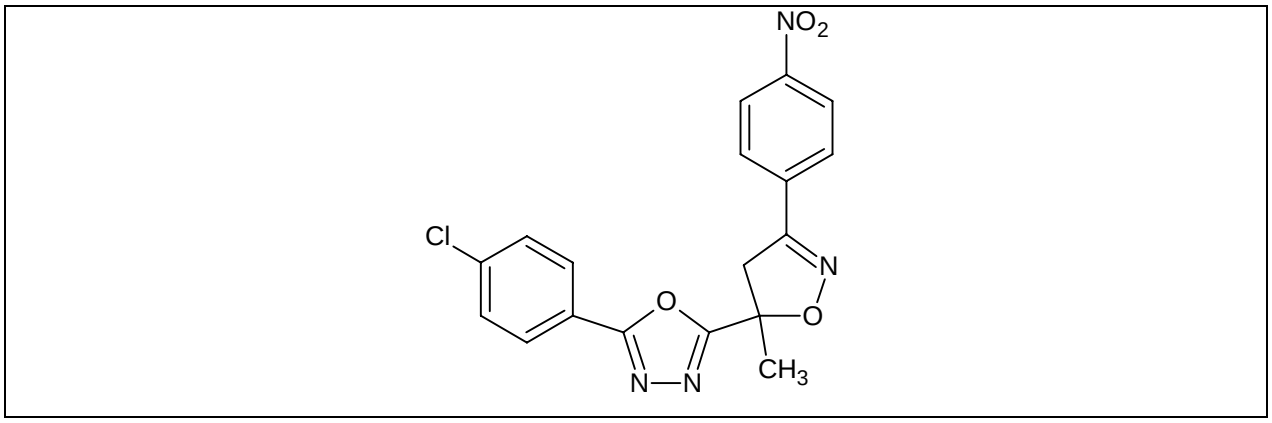


2-(hydroxymethyl)-6-(5-methyl-1,3,4-oxadiazol-2-yl)tetrahydro-2*H*-pyran-3,4,5-triol

Miscellaneous activities:-

Insecticidal Activities:-

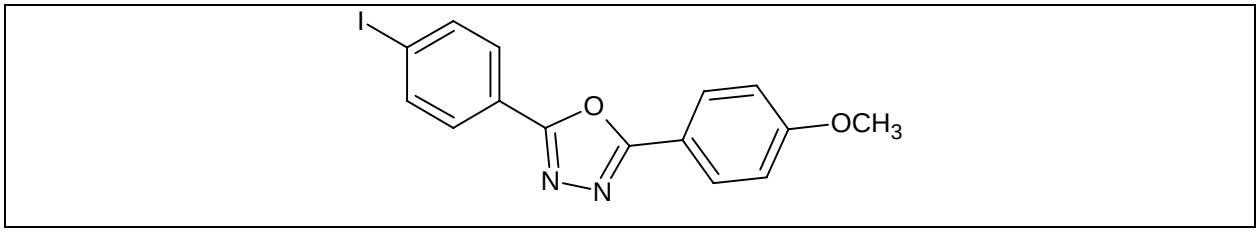
***Milinkevich et al*. (2009)** synthesized a series of 2-(4,5-dihydroisoxazol-5-yl)-1,3,4-oxadiazoles. Several compounds of this series were found active against fungal and pest insects [34].



2-(4-chlorophenyl)-5-[5-methyl-3-(4-nitrophenyl)-4,5-dihydro-1,2-oxazol-5-yl]-1,3,4-oxadiazole

Diagnostic agents

Watanabe et al. **(2009)** synthesized a series of radioiodinated 2,5-diphenyl-1,3,4-oxadiazoles. The synthesized compounds were used for detecting β-amyloid plaques in Alzheimer`s brains [35].

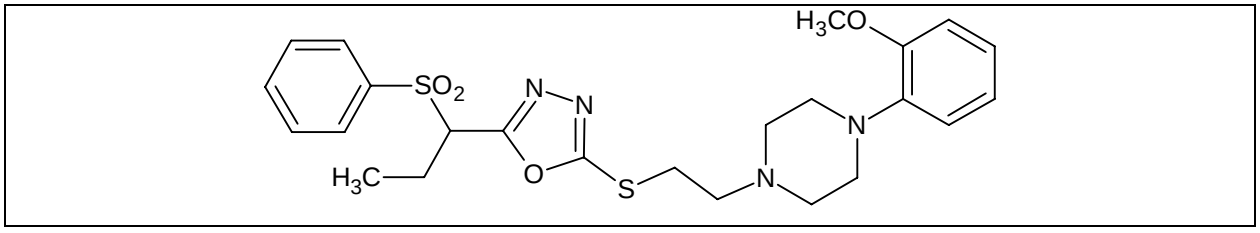


2-(4-iodophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole

Antiviral Activity

HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Current treatment regimens are based on the use of two or more drugs that belong to group of inhibitors termed as highly active antiretroviral therapy (HAART).

Tan et al. **(2006)** synthesized a series of 2-benzenesulfonyl-5-substituted-sulfanyl-[1,3,4]-oxadiazoles. Synthesized compounds were having very good activity against hepatitis virus [36].



1-{2-[5-(1-benzenesulfonyl-propyl)-[1,3, 4]oxadiazol-2-yl-sulfanyl]-ethyl}-4-(2-methoxy-phenyl)-piperazine.

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