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REVIEW EMPHASIZING REMEDIAL UTILITY OF OXADIAZOLE FASHIONED DERIVATIVES

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INTRODUCTION: The cyclic organic compounds which comprise of at least one hetero atom, are generally regarded as Heterocyclic compounds [19,29]. The most common heteroatom includes nitrogen, oxygen and Sulphur. There are various known heterocyclics which comprise of some different heteroatoms in their skeleton. These heterocyclics are often regarded as one of the most requisite classes of organic compounds, that are utilized in various biological fields for a numerous number of benefits that they tend to owe. The compounds are entailed too various medicinal aspects **[1,32].** Heterocyclics, which are comprised of Nitrogen, have a special worth in chemistry. Over the past few decades these have attained great attention in applied branches of chemistry due to their significant medicinal and therapeutic benefits **[2,9,10,30].**

These heterocyclics compounds are regarded as an engrossing section of applied chemistry **[3].** In large number of drugs heterocyclics play the most important role**[4,11,12,31].** 1,3,4-oxadiazole are designated as the most reliable moiety with respect to medicinal importance. Oxadiazoles are those compounds which possess five-membered rings which involve one atom of oxygen and two atoms of nitrogen in their structure **[5].** These oxadiazoles are basically obtained by the substitution of two methane groups replacing 2 pyridine types of nitrogen in the structure of furan. Basically, oxadiazole possesses 4 isomers, these differ according to the position of nitrogen atom which is present in the ring. Oxadiazole is regarded as a weak base which is because one extra heteroatom that exhibits inductive effect.

oxadiazole exists in 4 isomeric forms which are represented below:

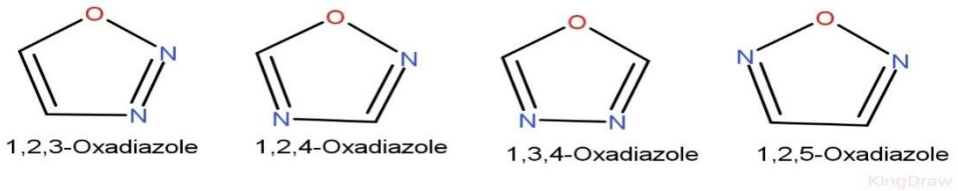


Figure: I

This replacement in the structure of furan by replacing 2 pyridine kinds of nitrogen tends to reduce the probable aromaticity of the emanating ring of oxadiazole which basically depicts the characteristics that a conjugated diene possesses [17]. The oxadiazole ring faces difficulty undergoing substitutions which are electrophilic in nature and occur at the carbon atom which is basically because of extremely low density over the carbon atom because of the withdrawing effect of the nitrogen atom which is like pyridine**[6,13,33]**.

These five membered heterocyclics oxadiazoles; specially comprising of nitrogen and oxygen found to be successful against various diseases and therefore must confer with the special attainment in pharmaceutical chemistry because of its varied medicinal worth. The derivatives of active isomer of oxadiazole are found to owe a broad spectrum of varied therapeutic potency in various sectors such as pharmaceuticals, agrochemicals and several other distinct fields. They tend to owe several properties such as Virucidal potency, as a C.N.S Depressant, Anticonvulsant, Antituberculosis, Anti-malarial, Anti-inflammatory, Insecticidal, Lipid peroxidation inhibitor, and a large no of several other therapeutic importance it tends to owe. An immeasurable amount of scientific research tackles synthesizing these compounds by approaching traditional methods with inculcating new innovative techniques as well as methods to achieve their designated target molecule and its biological evaluation**[7,20,22,34].**

Oxadiazole's chemistry

The nucleus of the oxadiazole moiety is considered as a base which is weak, basically because of the presence of inductive effect which occurs because of 1 extra-heteroatom. This reduction in aromaticity is due to substitution of two –CH= groups of structure like furan by 2 pyridine kind of nitrogen-atoms. The most difficult task considered is the substitutions which is electrophilic

possibly at carbon atom because of relatively low-density which is attributed due to the withdrawal effect[6,14,25,36].

Conventional schemes available for Synthetic procedure of oxadiazoles (1,3,4 isomer):

The conventional approach for synthesis of oxadiazole (1,3,4) inculcates intermolecular-condensation of acid-hydrazides in the presence of cyclizing reagents [16,35], for example it includes phosphorus oxychloride, polyphosphoric acid, acetic anhydride with carboxylic acids **[7,15 21,37].**

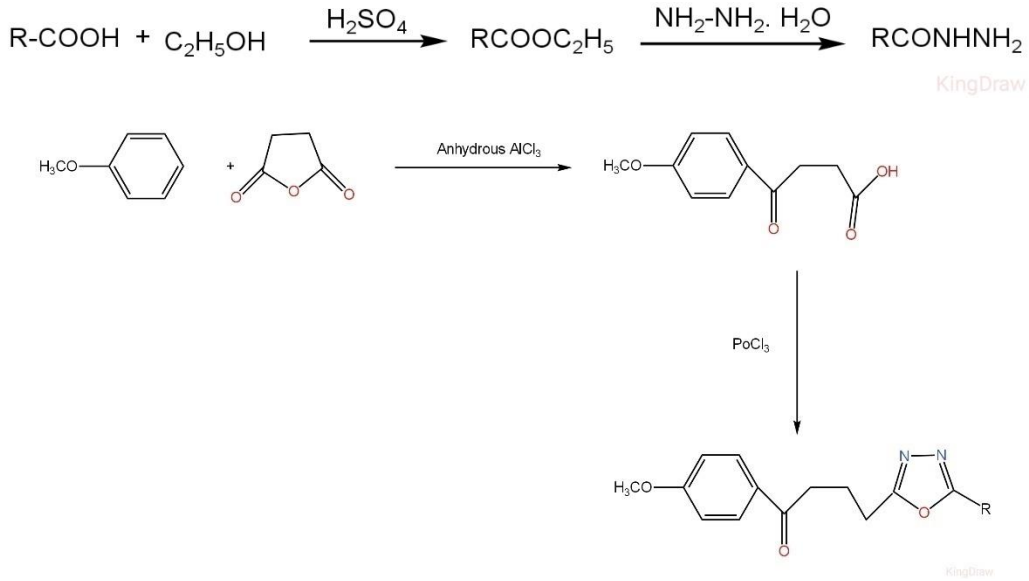


Figure II: Scheme 1

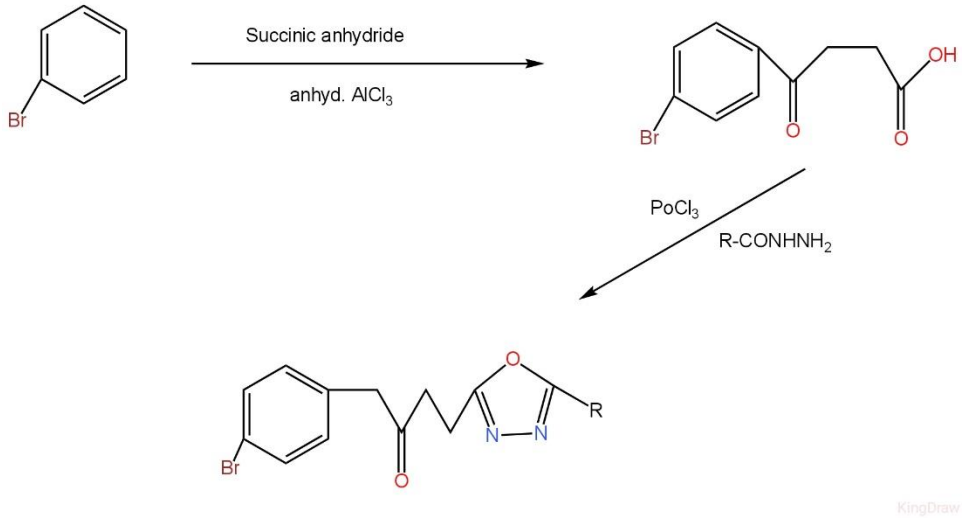


Figure III: Scheme 2

Some of the approaches utilized in the synthetic procedure for oxadiazole-derivatives are discussed below-

1. SM.C Hosur et.al presented the synthetic procedure for the backbone of oxadiazole. His research includes the synthesis which involves [2(mercapto)5aryl],1,3,4-oxadiazole obtained from reaction with acid-hydrazide, which is substituted, this reaction takes place in the presence of KOH, which is depicted in the scheme (1). The scheme is given below-[6]

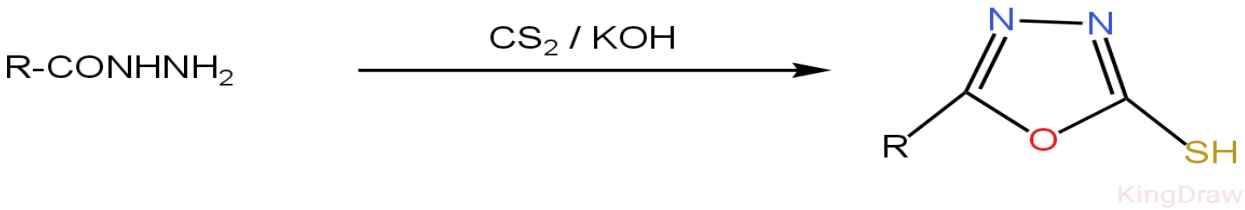


Figure IV: scheme 3

2. The Synthetic scheme for 1, 3, 4-oxadiazole amine by the use of cyanogen bromide is depicted by the following scheme.[6]

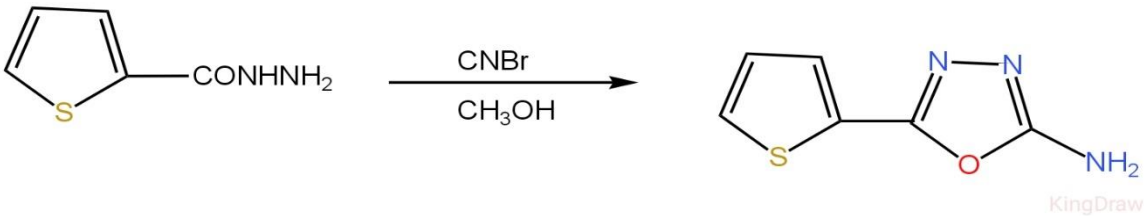


Figure V: Scheme 4

3. Oxidative cyclodesulfurization [8]

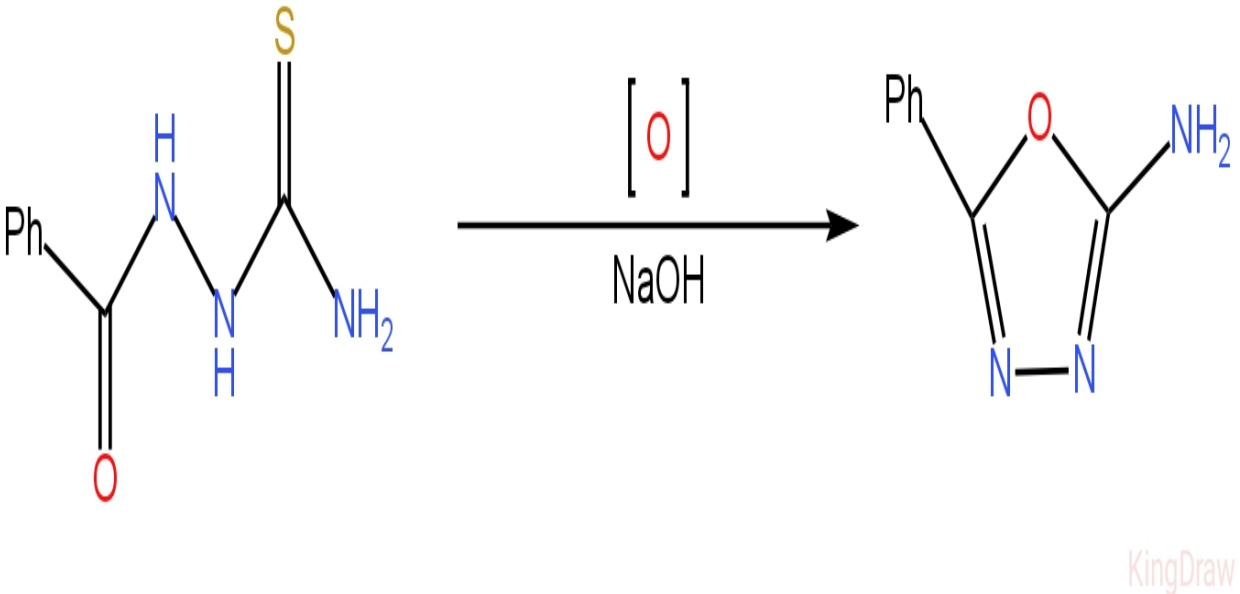


Figure VI: Scheme 5

4. Synthesis methods for 1,3,4-oxadiazoles [18]

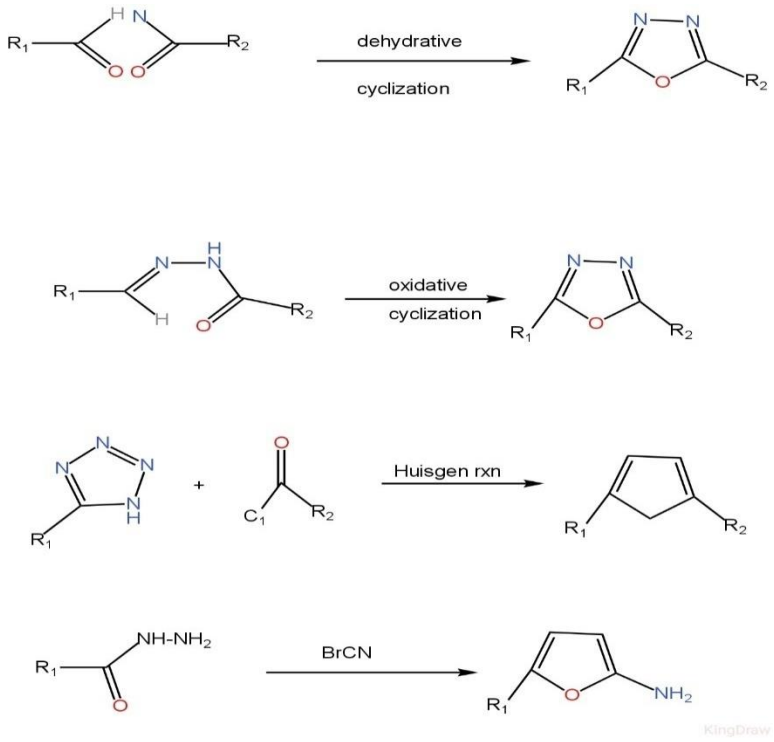


Figure VII: Scheme 6

5. Scheme involving synthetic procedure for oxadiazole which is often named as one-pot synthesis [23,24] :

This synthesis of Oxadiazole is due to the incorporation with a mixture of hydrazine-hydrate to a solution of acid-chloride in dry dioxane with stirring for about 30 minutes, to obtain diacyl hydrazine solution, then the resulting reaction mixture was refluxed for a time of about 1-2.5 hours. The obtained yield is great.

6. Synthesis of Oxadiazole derivatives such as 1-[5{4-chlorophenyl{1,3,4-oxadiazol-2-yl}3] phenylthiourea 3. is depicted in the following scheme: [26,27]

Figure VIII: Scheme 7

7. The reaction catalysed with nafion for the oxadiazoles synthesis [28]
8. The scheme below represents the use of bromine in alkaline media for synthesizing the compounds containing 1,3,4-Oxadiazole nucleus [6].

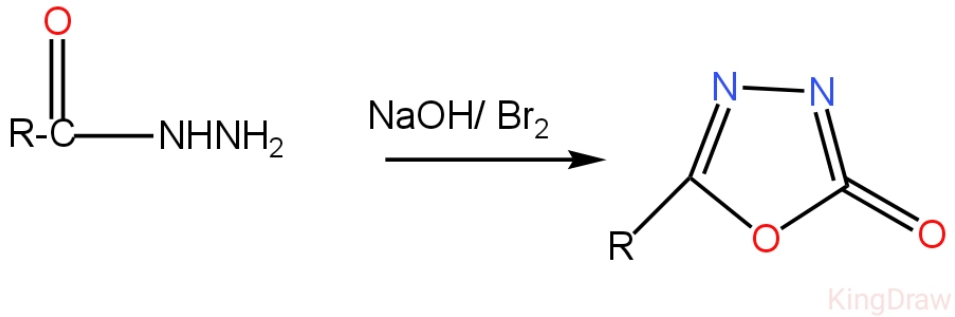


Figure IX: Scheme 8

9. The scheme for Synthesizing [2,5-disubtituted {oxadiazole}] using cyclodehydrogenetion method: The synthesizing procedure for di-substituted Oxadiazole derivatives by using cyclodehydrogenation method, which involves the use of phosphorous oxychloride has been mentioned in several literature available. Basically, it involves the condensation of different alkyl hydrazides in the presence of substituted-aromatic acids. [6]
10. The scheme representing the of Synthesis of oxadiazole-analogues involving the use of hypervalent-iodine

Figure X: Scheme 9

11. The scheme for the synthesis of oxadiazole-analogues by involving LTA

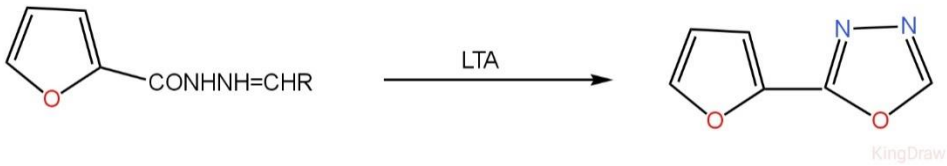


Figure XI: Scheme.10

12. The scheme for the synthetic procedure for substituted-Oxadiazole (1,2,4) [6]

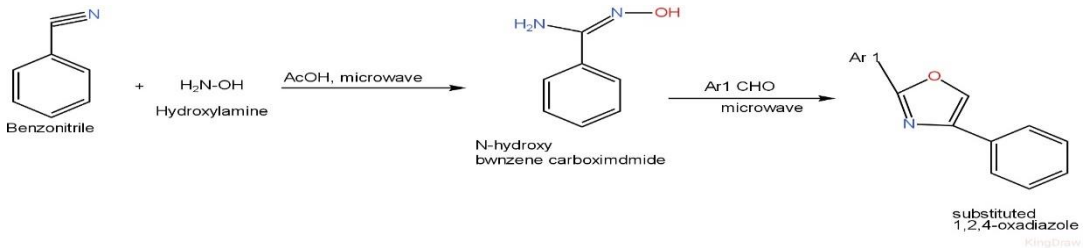
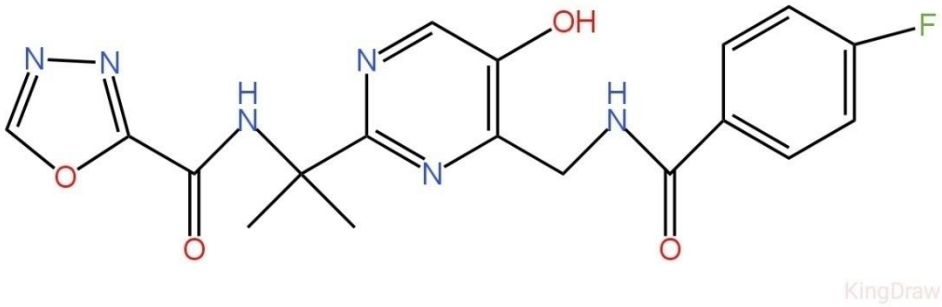


Figure XII: Scheme.11

Biological Activity of 1,3,4 oxadiazole compounds [6]

The nucleus of 1,3,4-Oxadiazole tends to possess a numerous number of chemical reactions, due to which it is often regarded as backbone of medicinal chemistry, working upon which can result in production of number of medicinally important compounds. Some of the therapeutically important compounds owing oxadiazole ring are given below:

The compound A (Raltegravir) discovered by research scholar Merck and Co, is utilized in the treatment of HIV infection. Compound B (Nesapidil) is categorized under class IV category of Anti-arrhythmic drug, it is basically a calcium-channel blocker. Compound C (Furamizole) is a nito-furan derivative, which is found to exhibit Anti-bacterial activity. Compound D (Tiodazosin) is a drug of the Anti-hypertensive category. Compound E (BB-83698) is found to exhibit Anti-bacterial properties.[6]



FigureXIII: Raltegravir

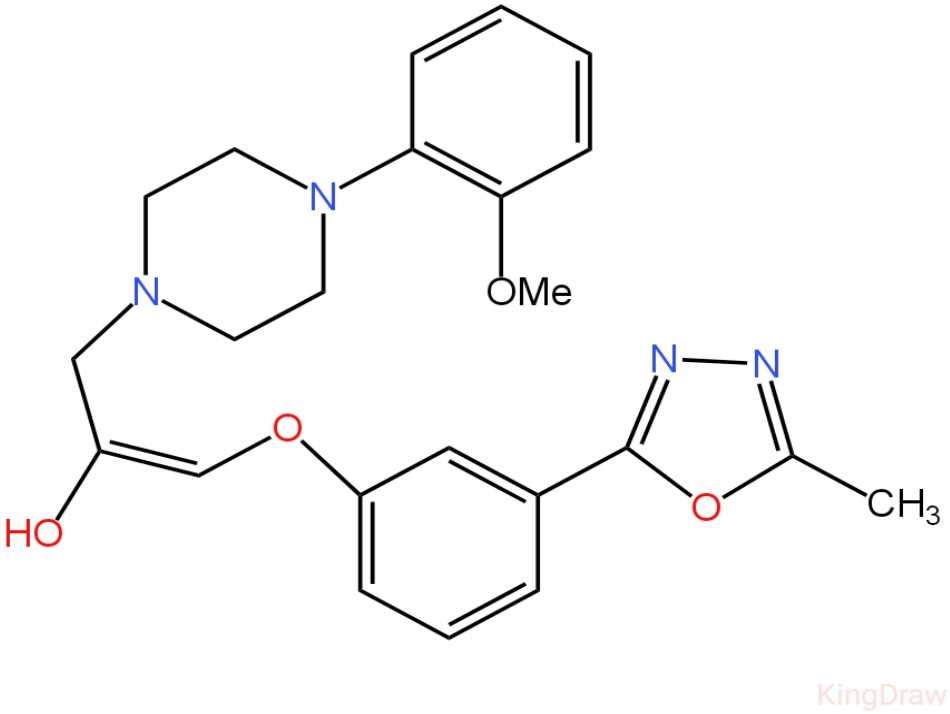


Figure XIV: Nesapidil

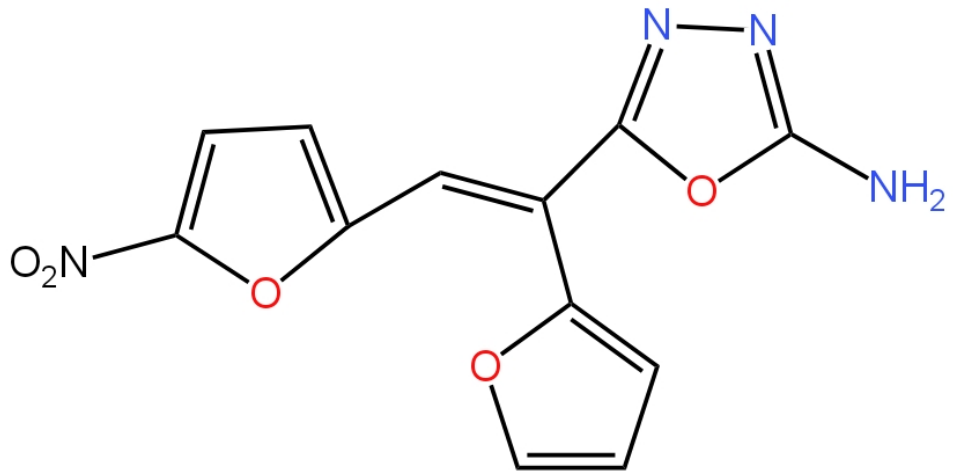


Figure XV: Furamizole

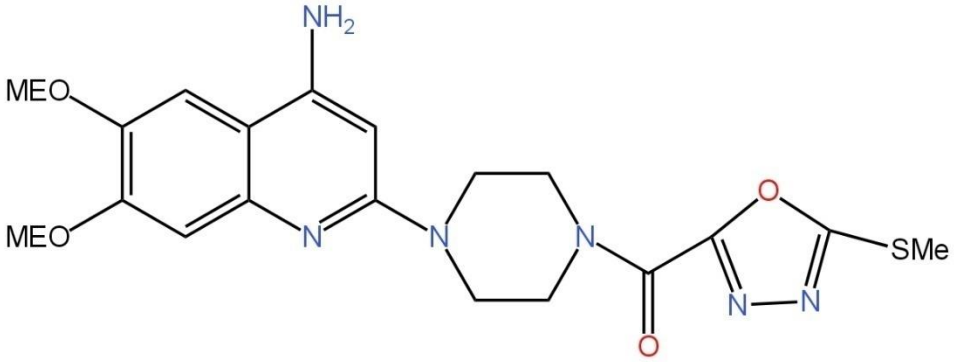


Figure XVI: Tiodazosin

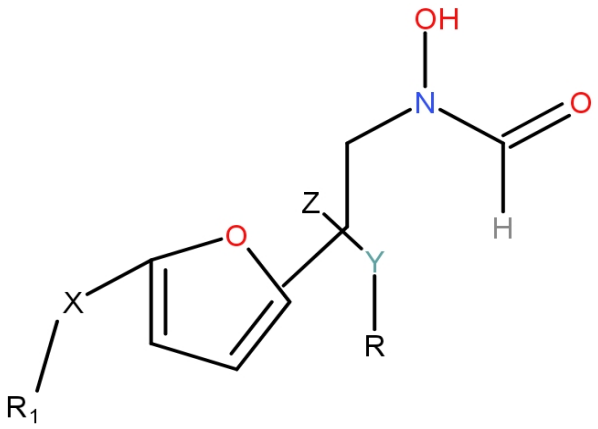


Figure XVII: BB-83698

Analgesic and Anti-inflammatory Activity[2]

The mercaptan substituted bearing 1,3,4Oxadiazole nucleus novel compounds are found to exhibit excellent Anti-inflammatory potential, and if they are added with secondary amines, the level of activity increases. Research scholar Dhansay .et.al., presented their report of the synthesis of [2,5-{di-substituted}1,3,4-Oxadiazole] derivatives. These were investigated for their Analgesic activity by adoption of the CH_3COOH actuate by the involvement of writhing-method utilizing albino mice of Swiss on the other hand the Anti-inflammatory activity was determined by adoption of Carrageenan induced rat paw edema.

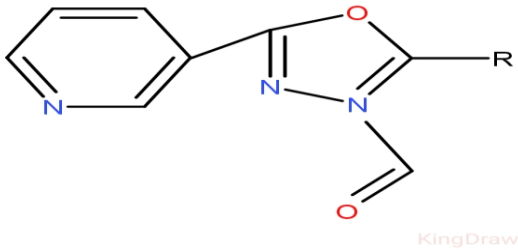


Figure XVIII: Compound 1

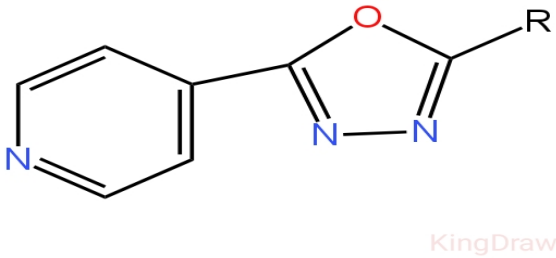


Figure XIX: Compound 2

Antimicrobial Activity[2]

Research scholars' studies show that the compound developed by incorporation of 1,3,4-Oxadiazole nucleus has proven to be effective as an Anti-microbial agent. They are effective against many microbes.

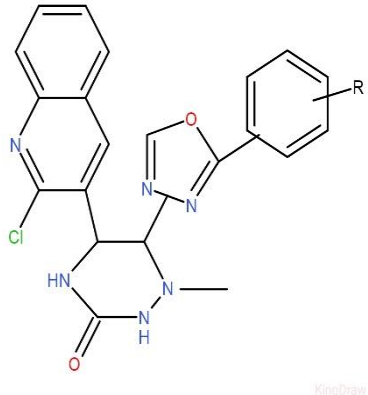


Figure XX: Compound 3

Anti-cancer Activity [2]

Research scholar Polothi and his co-workers in 2019 reported the designing and synthesis of newer hybrids containing the oxadiazole (1,3,4)

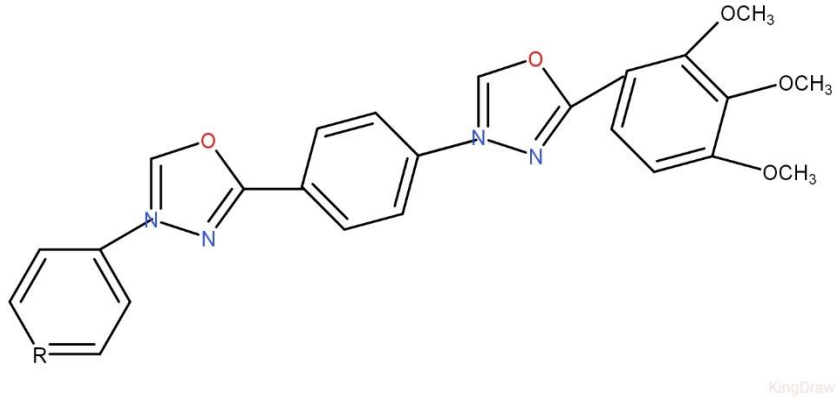


Figure XXI: Compound 4

The research scholar Farshid and his coworkers in 2019 presented the report of their multistep reaction for synthesizing of quinazolinone-Oxadiazole derivatives. Numerous compounds were synthesized which possess the parent nucleus and were found to exhibit a great extent of therapeutic significance.

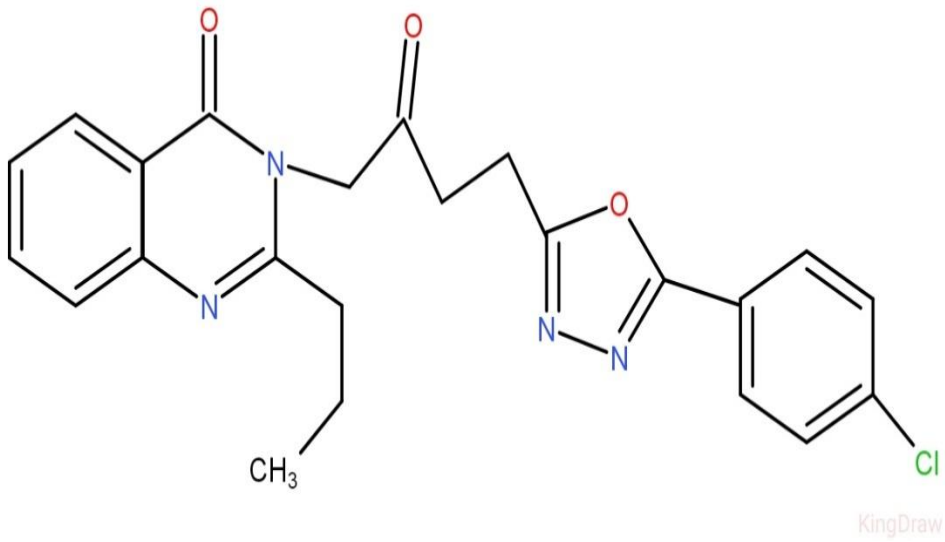


Figure XXII: Compound 5

Antioxidant activity

The research scholar Parveen .et al. presented the report for the synthesis of various 4-arylidene-2-phenyl(4H)-azlactones and calculated and determined their antioxidant potency which decipher that the compound depicted greater extent of antioxidant property. [4]

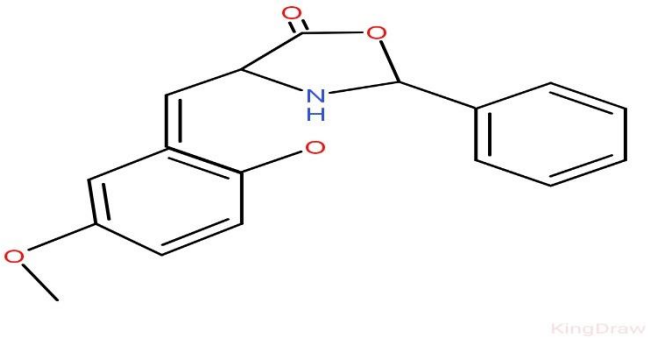


Figure XXIII: Compound 6

Anti progesterone activity

The synthetic report of Jin et al. reported the synthesis of new oxazole nucleus-based analogs which were reported for their antagonist hormonal potency by adopting mifepristone as a standard drug. [4]

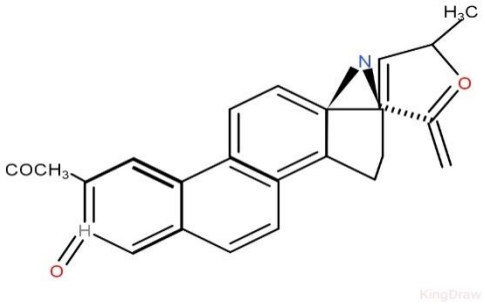


Figure XXIV: Compound 7

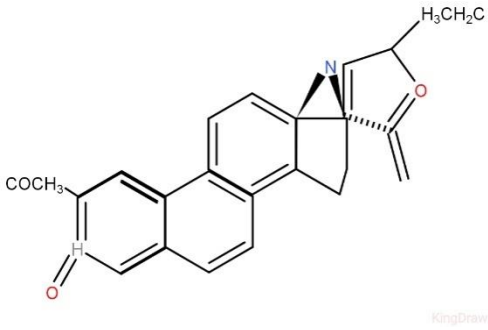


Figure XXV: Compound 8

Some compounds which possess T-type calcium channel blocker potency

Research scholar Lee et al reported the synthetic procedure for the synthesis of derivatives containing oxadiazole nucleus, they substituted it with aryl alkylamines and when they were pharmacologically evaluated, claimed to be act as a T-type calcium channel blocker. [4]

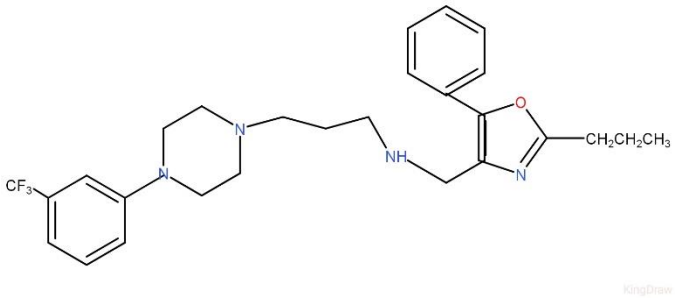


Figure XXVI: Compound 9

Prostacyclin receptor antagonist derivatives

The research scholar Brescia et al. Performed the synthetic procedure for the synthesis of prostacyclin-oxadiazole derivatives and evaluated their biological potency, it tends to present a satisfactory act in the process of inhibition of platelets.[4]

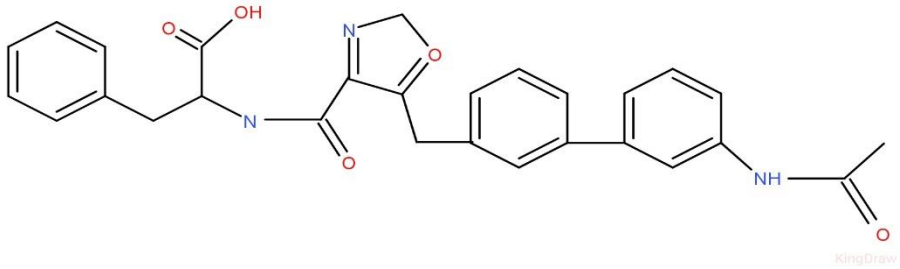


Figure XXVII: Compound 10

Pharmacological activity of Transthyretin (TTR) amyloid fbril inhibitors derivatives

Research scholar Razavi et.al carried out the synthesis of some oxazole-based derivatives which possess transthyretin amyloid fibril inhibitor like activity. The compounds which possess maximum activity are represented below: [4]

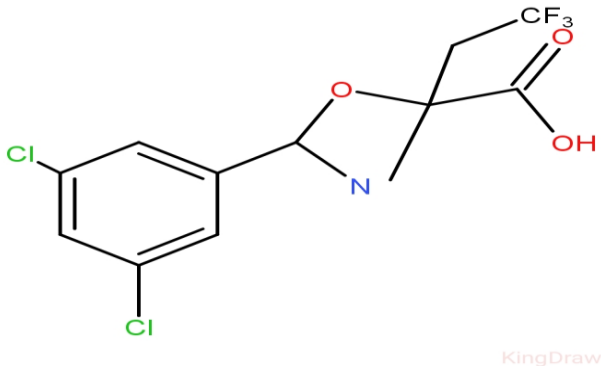


Figure XXVIII: Compound 11

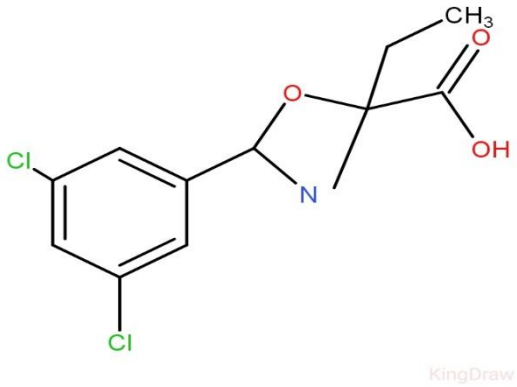


Figure XXIX: Compound 12

CONCLUSION

This review article thus encapsulates several synthetic schemes which were presented by a few research scholars, who worked upon the nucleus of 1,3,4-Oxadiazole as well as establishes a link with their biological significance. It mainly culminates the reactions which it may undergo. It focusses upon the therapeutic potential of such compounds, as well as also provides information about the availability of such drugs which contain oxadiazole ring in their structure. This article may prove to be of greater importance to research scholars who aim to work upon this heterocyclic nucleus.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

'None' declared by the authors.

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