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A COMPREHENSIVE REVIEW ON BIOLOGICAL ACTIVITIES AND SCHEME FOR SYNTHESIS OF OXAZOLE DERIVATIVES

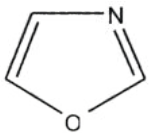
Mr. Amol R. Pund*	Department of Pharmaceutical Chemistry, Mula Education Society's College Of Pharmacy Sonai, Ahmednagar, Newasa, Maharashtra 414105. *Corresponding Author
Dr. V. B. Ghawate	Department of Pharmacognosy, Mula Education Society's College Of Pharmacy Sonai, Ahmednagar, Newasa, Maharashtra 414105.
Dr. P. B. Mohite	Department of Pharmaceutical Chemistry, Mula Education Society's College Of Pharmacy Sonai, Ahmednagar, Newasa, Maharashtra 414105.
Mr. Chetan C. Kedari	Department of Pharmaceutical Chemistry, Mula Education Society's College Of Pharmacy Sonai, Ahmednagar, Newasa, Maharashtra 414105.

ABSTRACT Oxazolone are five member heterocyclic ring containing nitrogen and oxygen as a hetero atom. Oxazolone have been reported to possess diverse biological activities. Oxazolone is a class of small heterocyclic compounds which have acquired more importance in recent years due to their pharmacological activities. Nitrogen, sulphur and oxygen containing five/six member heterocyclic compounds have achieved enormous significance in the field of medicinal chemistry. The C-2 and C-4 positions of the oxazolone are crucial for their various biological activities. N-substituted oxazolones also participated in variety of intermolecular reactions. Considering these properties, various research workers have shown a keen interest in this small heterocyclic moiety as target structure for evaluation of many pharmacological activities. Oxazolone plays very vital role in the manufacturing of various biologically active drug as analgesic, anti-inflammatory, anti-depressant, anti-cancer, anti-microbial, anti-diabetic and anti-obesity.

KEYWORDS : Oxazolone, Anti-bacterial, Anti-fungal and Anti-oxidant, Benzylidene, NCE.

Introduction of Oxazole

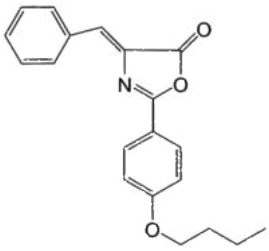
Oxazole is the parent compound for a vast class of heterocyclic compound. These are azoles with an oxygen and a nitrogen separated by one carbon. Oxazole is a weak base its conjugate acid has a PKa of 0.8, compared to 7 for imidazole. Oxazole is a clear colourless liquid. It is polar and wekly basic. Recent activity in the patent litreture indicate that molecule incorporating the oxazole ring are finding increasing utility for example it is used in oil additive and pharmaceutical industry as solvent. Patent activity of oxazole derivative in pharmaceutical industry has been especially notworthy. Oxazole exhibit intresting chemical reactivity. It undergo reaction with electrophile particularly at nitrogen C_2 and C_5 nucleophile also react with oxazole at C_2, C_3 and C_5 position. Oxazole also dinophile in dials alder reaction to prepare substituted pyridines.



IUPAC name:-1, 3-oxazole
Molecular formula:-C_3H_3NO
Molar mass:-69.06 g mol^{-1}
Density:-1.050 gm/cm^3
Boiling point:-69-70 °C
Acidity:- (PKa)0.8

Chemistry of Oxazolone

Substitution of functional group of 4-benzylidene-2-(4-butoxyphenyl) oxazol-5(4H)-one (32) at C-4 and C-2 position plays a vital role in the activity of oxazolone. Substitution of functional group at C-4 and C-2 positions of oxazolone are crucial for tyrosinase inhibitory activity. An extension of conjugation through an aliphatic double bond present at C-4 position of oxazolone moiety and a phenyl ring present at C-2 play a pivotal role in activity .The rate of the oxazolone ring-opening reaction decreased with an increase of the electron donating properties of the substituent of the phenyl ring at C-2 position. Exocyclic double bond can operate as a dienophile and N substituted oxazolone participates in intermolecular Diels–Alder reactions.Lewis acid activation of the carbonyl group of unsaturated oxazolones give electrophilic character to the ß carbon. Mostly they attack the carbonyl group often leading to a ring opening. The positive charge of carbon C-2 increases by m-NO2 group which may be easily attacked by any nucleophile. An alkoxy group at the para position of the phenyl ring decreases the negative effect of the nitro group and the electron withdrawing effect of this group may support the attack of the C=N group. The bond order of the C=N group decreases by the presence of m-NO2 group at the benzylidene ring.



Lespagnol indicated that 2-(3H)-benzoxazolone and some of its derivatives have hypnotic activity, 2(3H)-benzoxazolone nucleus has attracted to researchers for many years. There have been many reports indicating that benzoxazolone derivatives carry various pharmacological activities including hypnotic, analgesic and antibacterial activity among any other biological activites.

Steps for synthesis of oxazolone derivatives

Synthesis of 2- (pyrazine-2-carboxamido) acetic acid from pyrazine 2-carboxamide (2)

Take a Pyrazinamide 1.35 gm (0.11moles) place it in 12ml 10%KOH solution. Then add 10 ml ethanol to above solution to dissolve all Pyrazinamide. Add monochloro acetic acid 0.47gm (0.05moles) side by side in above solution. Stir at room temprature above mixture about three hour continuously on magnetic stirrer, then remove the flask from magnetic stirrer and acidify it with concentrated hydrochloric acid product is precipitated out place this in refrigerator for one hour and filter the product.Recrystalised the product by ethanol. MP: 210-2120C, % yield: 75.64%, TLC mobile phase- Ethyl acetate: Ethanol: Diethyl ether (1:1:1)

Preparation of 4- (Substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4H)-one from 2-(pyrazine-2-carboxamido) acetic acid.

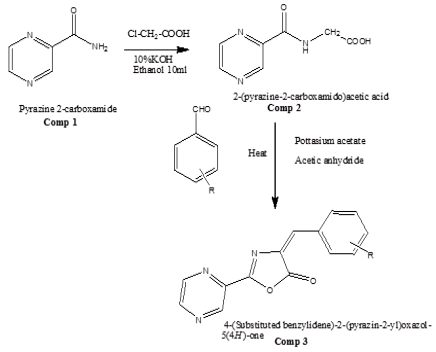
Take 0.01mole of 2-(pyrazine-2-carboxamido) acetic acid then add 0.03 mole of acetic anhydride. Then add 0.01 mole aromatic aldehyde to the above solution mix thoroughly in above solution add 0.01mole of potassium acetate as catalyst liquefy the mixture on heating mental then heat the mixture on water bath for four hour then add 10ml ethanol to reaction mixture the product was precipitated . Then place it overnight in refrigerator then filter and dried in sunlight.

Microbiological screening

Antibacterial Activity

Oxazole containing compounds shows most potent antibacterial

activity. Drug in this class differ from all other in that they are designed to inhibit/kill infecting microorganism .This type therapy are called as chemotherapy, which has come to mean treatment of systemic infection with specific drug that selectively suppress the infecting microorganism without significantly affecting the host. From this they are refferd as bacteriostatic and bactericidal respectively. Broad screening program were instituted to find antibiotics that might be effective in the treatment of infectious diseases that are resistant to existing chemotherapeutic as well as to provide safer and more effective chemotherapy.



Where, R= p-B_r; p-$OH_{,m}$-OCH_3,5-Br(5-Br Vaniline); o,m,p-OH; o,p-Cl; p-Cyno; phenyl; p-CH_3; Furan; p-OCH3; p-OH,m-OCH_3(Vaniline);P-F.

Basis of Antimicrobial Action

Various antimicrobial agents which contain oxazole act by interfering with cell wall synthesis, plasma membrane integrity, nucleic acid synthesis, ribosomal function, and folate synthesis.

Antifungal activity

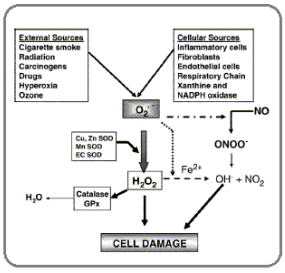
Oxazolone derivatives prepared by various synthetic techniques it shows the potent antifungal activity. Many of fungi that can cause infections live in association with humans as present in the environment but until resently; serious superficial infections were relatively uncommon and systemic infections very uncommon indeed at least in cool and temprate climatic zones. Since the 1970, there has been a steady increase in the incidence of serious secondary systemic fungal infections. One of the factor aiding the spread of fungal disease has been widespread use of broad spectrum antibiotics, which eliminate or decrease the non pathogenic bacterial populations that normally compete with fungi. Fungal infections are termed mycoses and in general, can be divided into superficial infections and systemic infections (affecting deeper tissue and organs).The commonest systemic fungal disease is systemic candidiasis an infection with yeast like organism. Other more serious conditions are cryptococcal meningitis or endocarditis, pulmonary aspergillosis, and rhinocerebral mucormycosis. Superfecial fungal infections can be classified into the dermatomycoses and candidiasis. Dermatomycoses are infections of the skin, hair and nails most commonly caused by Trichophyton, Microsporum and Epidermophyton species. In superficial candidiasis ,the yeast like organism infects the mucous membranes of the mouth(thrush),vagina, or skin.

Antifungal Agents

The number of agents available to treat fungal infections has increased by 30% since the year 2000, yet still only 15 agents are currently approved for clinical use. The greater number of medications now available allows for therapeutic choices however, differences in antifungal spectrum of activity, bioavailability, formulation, drug interactions, and side effects necessitates a detailed knowledge of each drug class.

Antioxidant activity

An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death. When the chain reaction occurs in a purified monomer, it produces a polymer resin, such as a plastic, a synthetic fiber, or an oil paint film. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions.



Inhibition of oxidation

Although oxidation reactions are crucial for life, they can also be damaging; hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases. oxazole containing compound shows promising antioxidant effect.

Hydrogen Peroxide Radical Scavenging Activity

1 ml of (20 - 200µg/ml) test drug/standard (Ascorbic acid) was added to 0.6 ml of hydrogen peroxide solution in phosphate buffer (pH- 7.4). After incubating for 10 minutes at 37oC the absorbance was measured at 230 nm. Corresponding blanks were taken. The experiment was performed in triplicate. The absorbance of hydrogen peroxide in phosphate buffer as control was measured at 230 nm. The scavenging effect (%) was measured using following equation. Hydrogen peroxide produces hydroxyl radicals in cells. Scavenging of these radicals by the test drug is used as a test for antioxidant activity. The reduction of these radicals is seen by the decreased absorbance at 230 nm with increasing concentration of the test drug.

$$\text{Scavenging Effect(\%)} = \frac{\text{Control absorbance- Test absorbance}}{\text{Control ansorbance}} \times 100$$

CONCLUSION

In summary, the present article aims to review the work reported on therapeutic potentials of oxazole derivatives which are valuable for medical applications during new millennium. This review article is based on synthesized oxazole derivatives which display wide spectrum of biological potentials i.e. antibacterial, antimicrobial, antioxidant and antifungal activity. The heterocyclic moiety being so versatile in nature offers the medicinal chemist to explore more about it in medicinal field and the data mentioned in this article will be a great help to prospective researchers working in this area for further study of this scaffold. Oxazole moiety is an important heterocyclic compound as they are being an essential constituent of large number of marketed drugs. Having such diverse spectrum of biological activities, oxazoles has immense potential to be investigated for newer therapeutic possibilities and is an important class of lead compounds for development of new chemical entities (NCE) to treat various diseases of clinical importance.

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