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Review Article

A BRIEF REVIEW ON OXAZOLIDINONE

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ABSTRACT

The development of resistance by the antibiotics in the Gram-positive pathogenic bacteria over the last twenty years and continuing today has created a need for new antibiotic classes, which may be unaffected by existing bacterial resistance. The oxazolidin-2-ones represent not only a new class with a novel mechanism of action, but also satisfy the requirement for overcoming the resistance mechanisms. Both linezolid and eperozolid, the first chemical candidates, arose from the piperazine subclass, with the first one being chosen further development because of its enhanced pharmacokinetic properties. The main attractive traits of the oxazolidinone series has encouraged further work in the area, and the patent literature reveals that extensive chemical investigation is currently being made. The unexpected early resistance development emphasizes the need for further exploration of features of the oxazolidinone to eliminate these deficiencies. Recently, several changes, involving the C5 side chain as well the N-phenyl heterocyclic ring, give promise for such improvement. Oxazolidinone antibacterial agents comprise also ketolides, derivatives of macrolides, such as erythromycin A, with a newly formed carbamate cycle, with a largely unexplored potential. The oxazolidinone nucleus does not appear only in the structures of antimicrobial drugs, but a number of biological activities are connected with frameworks including the oxazolidinone ring. A partial list of these activities comprises enzyme inhibitors, agonists and antagonists, with a particular citation for a new generation of selective monoamino oxidase inhibitors (befloxatone).

KEY WORDS: Oxazolidinones, Antibacterial agents, MAO inhibitors.

INTRODUCTION

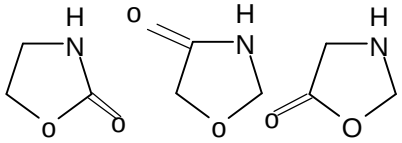
1.1 General Introduction

Heterocyclic compounds are of immense importance due to their wide spectrum of pharmacodyanamic applications. These compounds have attracted the attention of chemists and biologists due to their varied nature of physicochemical and pharmacological activities. An enormous number of biologically active heterocyclic compounds are known in the literature and this number has been increased rapidly, accordingly the literature on subject has been very vast. Heterocyclic compounds occur widely in nature and in the variety of non-naturally occurring compounds. A large number of heterocyclic compounds are essential to life. Heterocycles bearing nitrogen atoms constitute the core structure of a number of important physiologically active molecules and play a vital role in the metabolism of living cells. Their practical applications range from extensive clinical use to fields as diverse as agriculture, photography, biocide formulation and polymer science. The range of known compounds is virtually limitless, encompassing a considerable spectrum of physical, chemical and biological properties. The most widely studied application of heterocycles in the preparations of biologically active and medicinally important molecules. Modern drug discovery focuses on the synthesis of specific bimolecular targets, which invariably contain a heterocyclic component. A key challenge in the synthesis of such targets continues to be the development of new pathways

and improvement of existing pathways. As the main study in the thesis centers around on the synthesis of condensed nitrogen and oxygen heterocyclic systems containing oxazolidinone nucleus. Oxazolidinones are perform an important role in the synthesis of several organic molecules including amino acids [1], aminalcohols[2], thiamine [3], amides [4], peptides [5] and polyfunctional compounds [6]. Natural and synthetic oxazolidinone derivatives possess important biological activities; such as anticancer [7], antibacterial [8], antifungal [9], anticonvulsant [10], anti-inflammatory [11], antituberculosis[12], cardiotonic[13], anti-HIV [14], antidiabetic[15], andantihypertensive activity [16]. Oxazolidinones are also important for drug development, especially in the area inhibitors of monoamine oxidase [17]. Oxazolidinone also have potent pharmacological effects as cytokine modulators [18], sigma receptors, phychotropics[19],antiallergy agents [20],antibiotics [21] and intermediates in the synthesis of rennin inhibitors, lactam and macrolide antibiotics, immunosupressants[22] and in various other applications like ability to inhibit protein synthesis by binding to the 50S subunit and preventing the 30S complex from forming the 70S complex, resulting in inhibition of translation.

1.2 Chemical structure of Oxazolidinones

Oxazolidinones are a class of oxazoles which have the carbon between the nitrogen and oxygen which oxidized to a keton, hence oxazolidinone. The C-2 and C-4 positions of thoxazolidinone are crucial for their various biological activities and N-substituted oxazolidinones 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[23].



1.3 Antibacterial and Antimicrobial oxazolidinones

The discovery of a novel classes of antibacterial agents with a novel mechanisaction appeared as a considerable promise for the solution to the problem of bacterial resistance. Starting from the first clinical candidates, Dup-105 and Dup-721 an iterative medicinal chemistry effort culminated in compound PNU-100592, namely eperezolid. Systematic bioisosteric replacement for the piperazine ring led to the identification of the morpholine derivative PNU-100766, which subsequently became known as linezolid. Linezolid has a spectrum of activity against virtually all-important Gram-positive pathogens. The unique mechanism of action of linezolid makes cross-resistance with other antimicrobial agents unlikely. The antimicrobial activity of linezolid versus other commonly used agents, the health economic outcome of the drug *vs* vancomycin and teicoplanin, and safety issues, have been recently reviewed and updated. The many attractive traits of the oxazolidinone series has encouraged further work in the area, and the patent literature reveals that extensive chemical programs exist. [24]

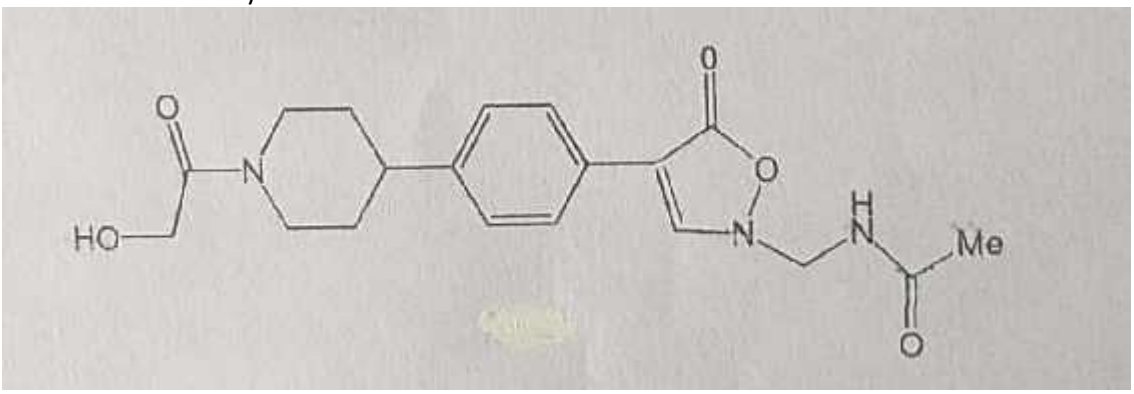
1.4 Structure activity relationship (SAR) of oxazolidinone [25-26]

Oxazolidinones have prompted many pharmaceutical industries and academic institutions to explore the possibilities of expansion of antibacterial spectrum of this class. Investigation of oxazolidinoneantibacterials was leading to the delineation of a series of structure–activity relationships (SAR) and to the synthesis of non-toxic analogues with impressive antibacterial activity, which cumulated in the identification of the lead compounds linezolid and eperezolid. Linezolid bearing an aryl group on the oxazolidinone ring and specific stereochemistry at C-5. The aromatic fluorine substituent improves bioavailability and increases potency. The role of the morpholino group at the para position is to ensure favorable safety profiles. Based on the proven favorable therapeutic potential, the oxazolidinone pharmacophore is indicated in which has been subjected for fine tuning by several researchers. The modifications directed for the different parts of the oxazolidinone template as shown in. The “A” part manifests oxazolidinone ring, which bears aryl system on the 3rd position of the oxazolidinone ring termed as B region and the 4th position of the aryl group is extended by amine functionality that has been termed as C region Oxazolidinone ring, exclusively possess C5 side chain in the (S)-configuration, Which has been optimized for the better efficacy.

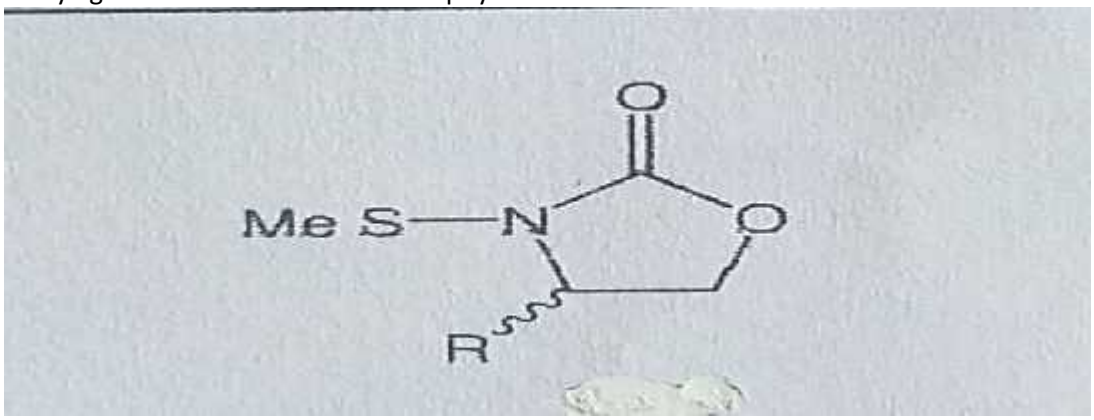
Synthesized derivative of oxazolidinone by modification according SAR

A. Modifications in the region A with C5

Quesnelle et al. have reported isoxazolidinoneagents having various substitutions at the C-region and most of the compounds have been found to be potent against Grampositive strains have shown broadspectrum of antibacterial activity.

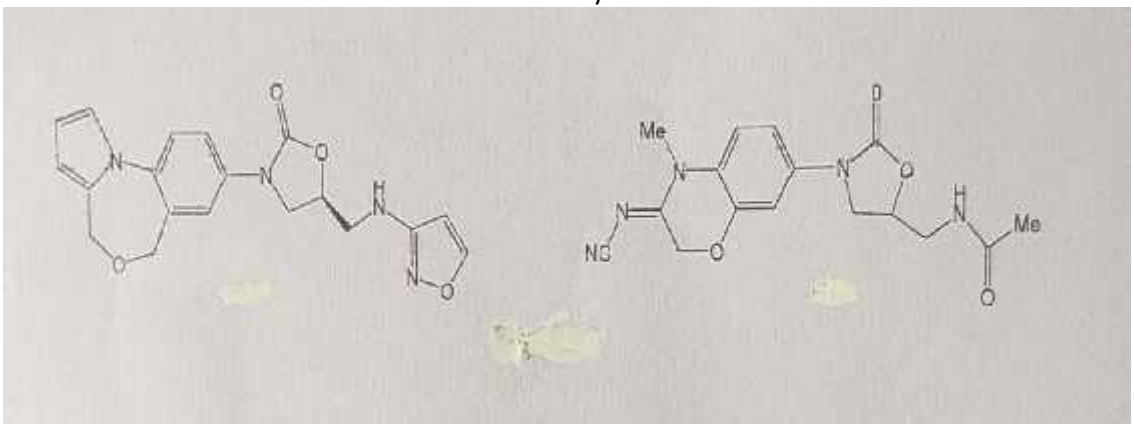


Turos et al. have reported N-thiolated 2-oxazolidinones as a family of antibacterial agents with antibacterial activity against methicillin resistant Staphylococcus aureus and Bacillus anthracis.

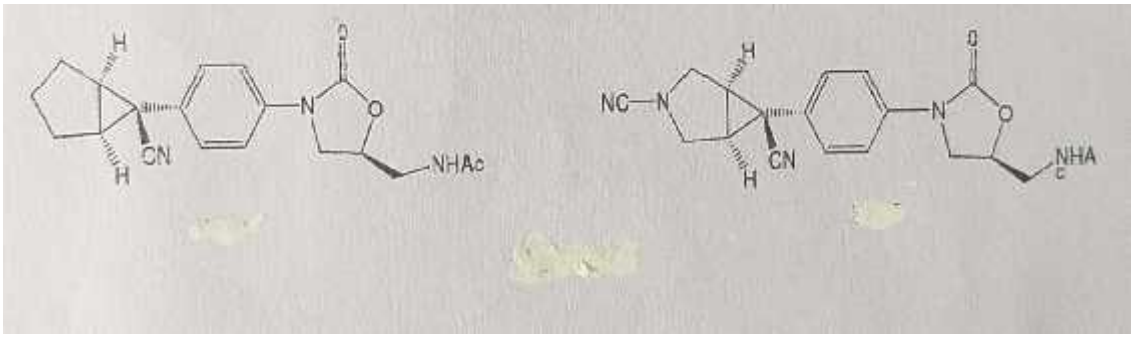


B. Modification in the region B and A at the C5

Bosch et al. have reported convenient synthesis of conformationally constrained analog of linezolid having a tricyclic motification. Pharmacia & Upjohn has described novel amidoxime and amidineoxazolidinone derivatives has shown in vitro antibacterial activity.

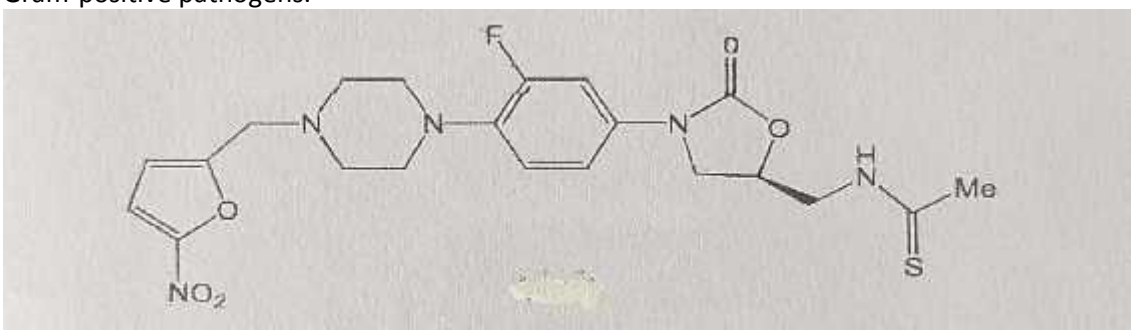


Merck has described novel oxazolidinonederivatives andcyclopropyl moiety which exhibited impressive in vitro antibacterial activities against different strains [38].

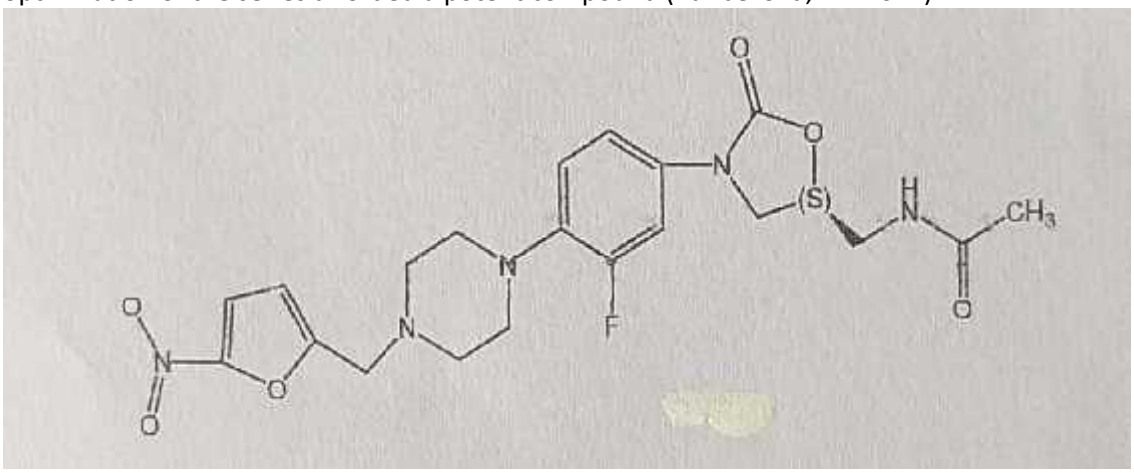


C. Modification in the region C with C5

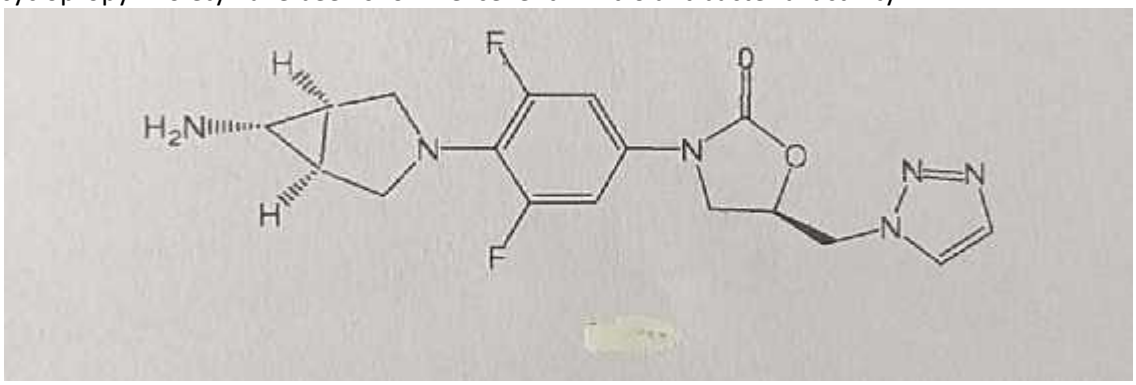
A series of N-phenyl piperazinyl derivatives of oxazolidinonein which the nitrogen atom at 4-position of piperazinyl ring is substituted by different cinnamoyl groups which were found to be active against several Gram-positive pathogens.



Research division of Ranbaxy has reported synthesis of oxazolidinones modified at the C region. The optimization of the series afforded a potent compound (Ranbezolid, RBx7644).



A group of scientists from Merck has published a patent describing novel oxazolidinone derivatives having cyclopropyl moiety have been shown excellent in vitro antibacterial activity.

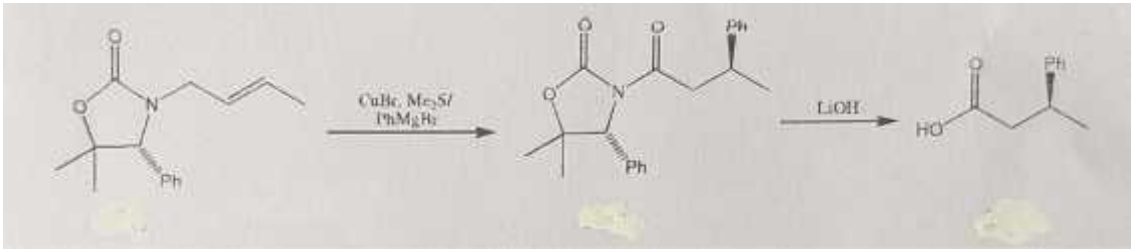


1.5 Reactions of oxazolidinone[27-28]

Oxazolidinones are versatile chiral auxiliaries these are easily recycled under mild conditions, thus enhancing their commercial potential. These offer chiral auxiliaries in research and bulk quantities. A few applications are the synthesis of β-lactams nonproteogenic amino acids aranorosin antibiotics indole-2-acetamide inhibitors and halichomycin and other recent applications are given below;

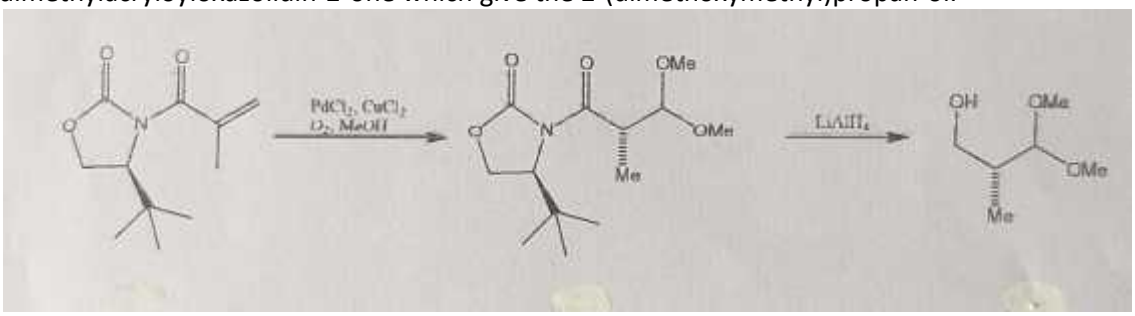
1.5.1 Diastereoselective Michael Additions

Davies S.G., et al. reported that oxazolidinone have the addition of phenyl in the acidic medium and give 3-3henylbutanoyl-5-5dimethylphenyloxazolidin-2-one which give the 4-phenylpentane -2-one in the presence of LiOH.



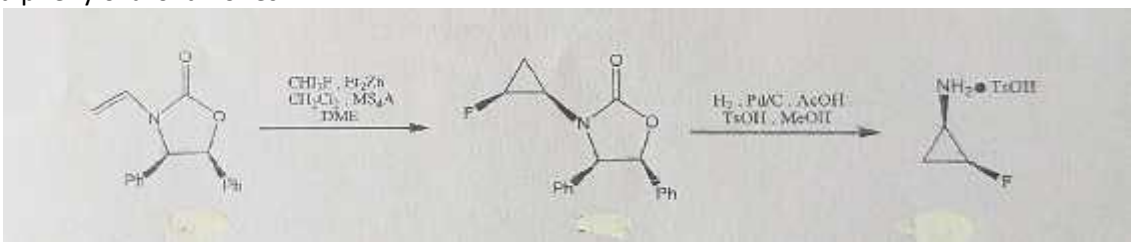
1.5.2 Pd(II)-Catalyzed Acetalization of Alkenes

Hosokawa T., et al. report the acetalization of oxazolidinone in the presence of Pd-catalyzed yield 3,2-dimethylacryloyloxazolidin-2-one which give the 2-(dimethoxymethyl)propan-ol.



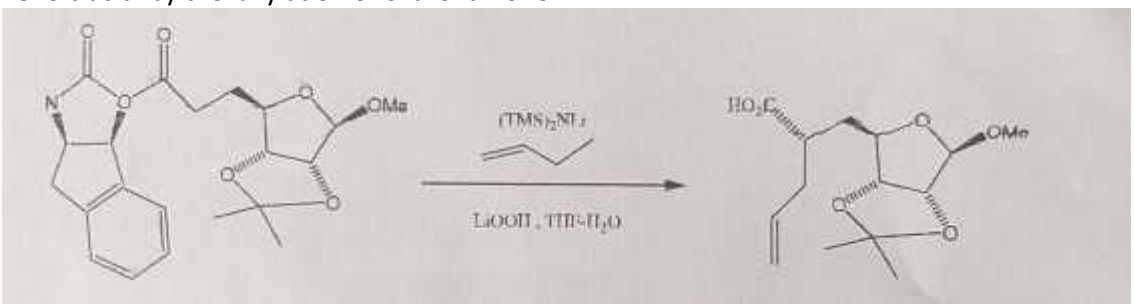
1.5.3 Cyclopropanations

Akiba T., et al. reported 1-fluoro-2-methylcyclopropane by the cyclopropanations of oxazolidinone with diphenyloxazolidinones



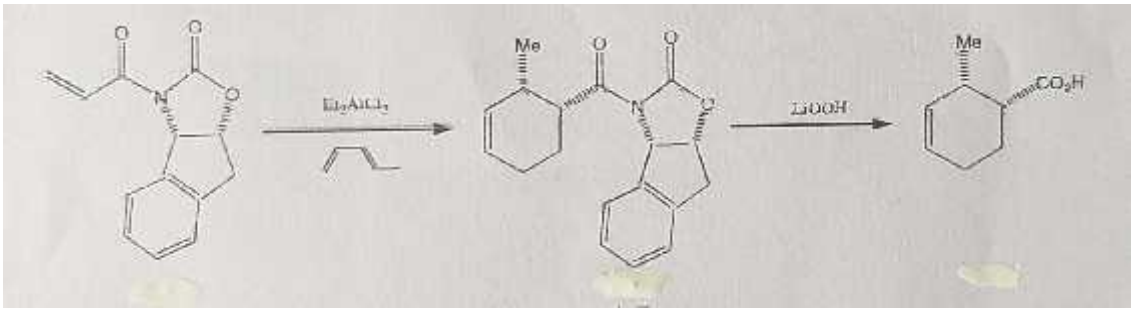
1.5.4 Allylations

Ghosh A.K., et al. reported tetrahydro-4-methoxy-2,2-dimethylfuro(3,4d)(1,3)dioxol-6-yl)methyl)pent-4-enoic acid by the allylation of oxazolidinone



1.5.5 Diels-Alder Reactions

Davies I. W., et al. reported 2-methylcyclohex-2-ene carboxylic acid by the reaction of oxazolidinone with methyl latedindeno-oxazolone.



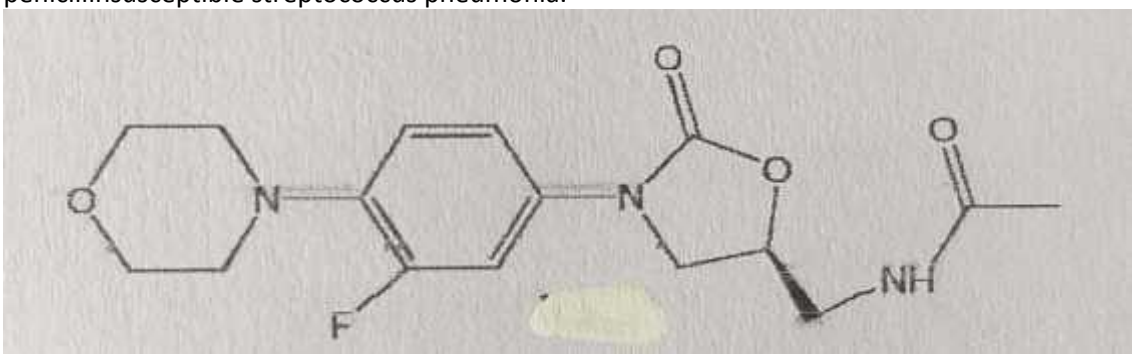
The main goal of this thesis is to synthesize biologically and technically promising oxazolidinone derivatives. In the context of this, it seems necessary to present an overview of the literature methods which have been employed to date for the synthesis of oxazolidinone derivatives and to highlight its biological aspects.

1.6 Biological aspects of oxazolidinone derivatives[29-30]

The development of resistance by the antibiotics in the gram positive pathogenic bacteria over the last twenty years and containing today has created a need for new antibiotic classes, which may be unaffected by existing bacterial resistance. The oxazolidinones represent not only a new class with a novel mechanism of action, but also satisfy the requirement for overcoming the resistance mechanism and its enhanced pharmacokinetic properties. The main attractive traits of the oxazolidinone series has encourage further work in this area and the patent literature reveals that extensive chemical investigation is currently being made. The unexpected early resistance development emphasizes the need for further exploration of features of the oxazolidinone to eliminate these deficiencies. Recently, several changes, involving the C5 side chain as well the N-phenyl heterocyclic ring give promise for such improvement. Various biological activities shown by oxazolidinone derivatives given below;

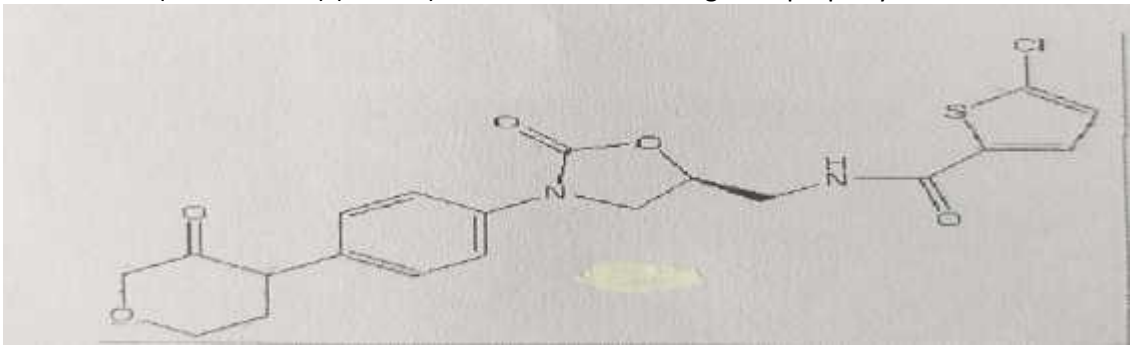
Antibacterial activity

Linezolid and FAD is an oxazolidinone used in the treatment of adults in nosocomial pneumonia, community acquired pneumonia (CAP), skin infections and vancomycin-resistant enterococcus (VRE) infections caused by methicillin-resistant staphylococcus aureus (MRSA), VRE faecium and penicillinsusceptible streptococcus pneumonia.



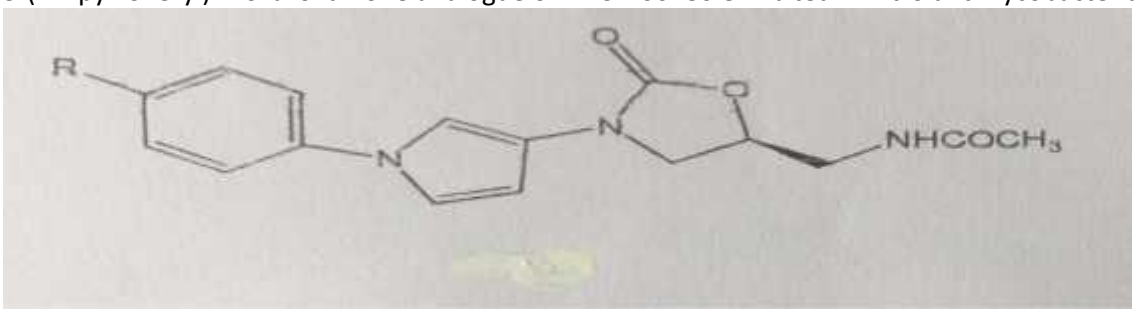
Anticoagulant activity

Rivaroxaban (BAY 59-7939) (Xarelto) found to have anticoagulant property.

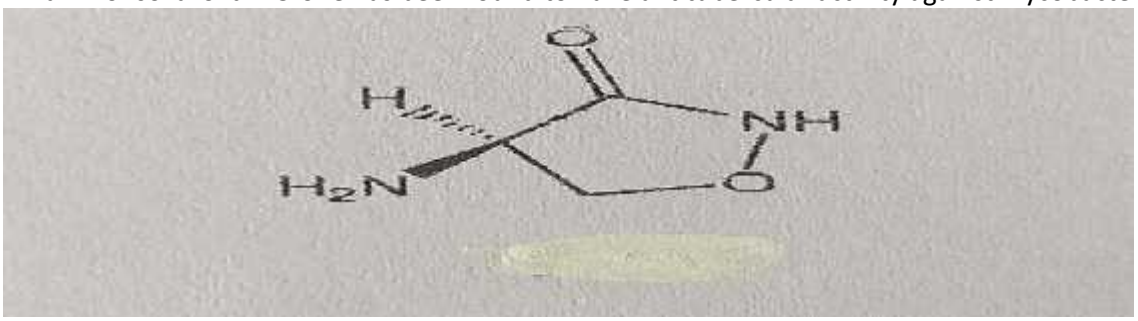


Antitubercular activity

3-(1H-pyrrol-3-yl)-2-oxazolidinone analogue of PNU-100480 exhibited in-vitro antimycobacterial activity.

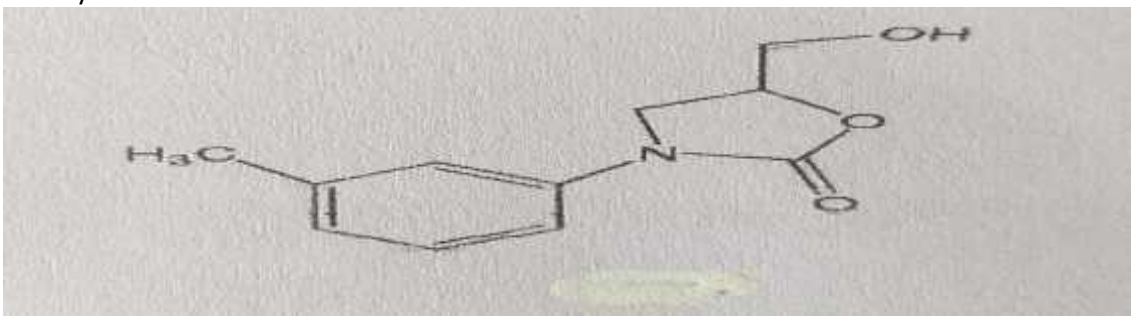


4-amino-isoxazolidin-3-one has been found to have antitubercular activity against mycobacterials.

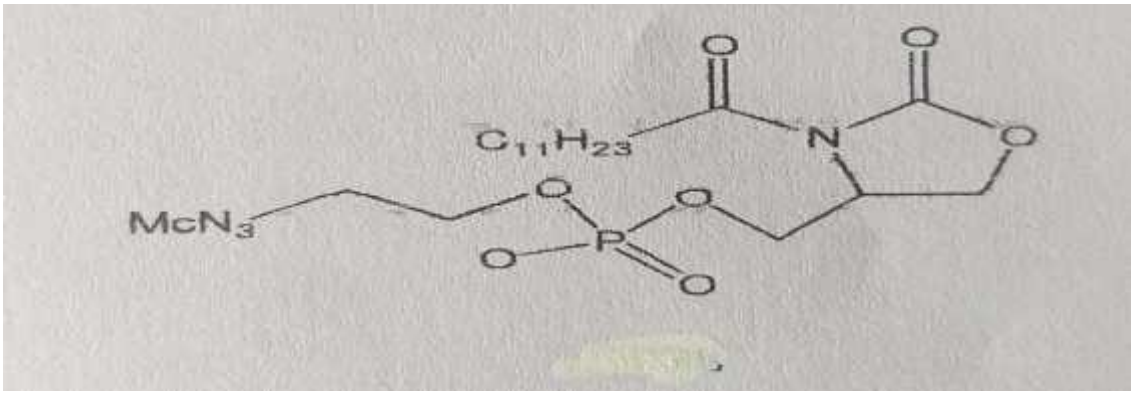


Antidepressant or psychotropic activity

Monoamine oxidase (MAO) inhibitors were developed as antidepressants but many drugs, like oxazolidinone antibacterial agents, share similar molecular properties and have MOA inhibitory activity. 3-(3-methylphenyl)-5hydroxymethyl-2-oxazolidinone (toloxatone) has been found to possess antidepressant activity.



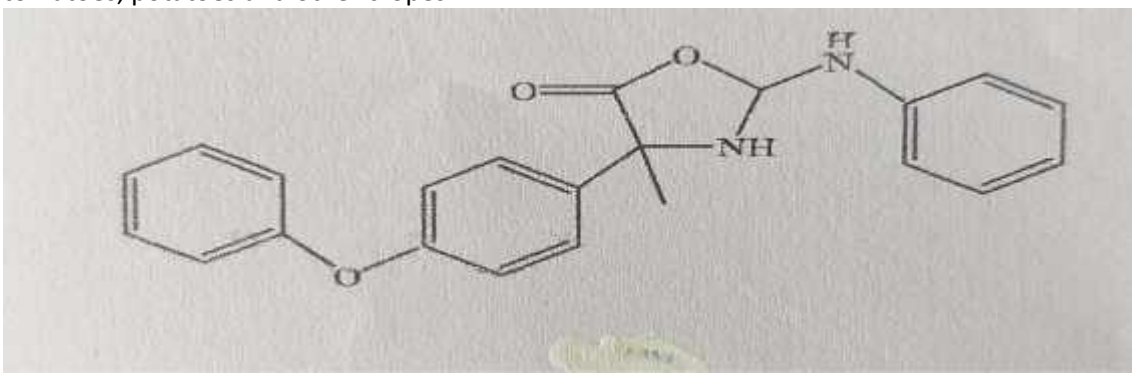
5-morpholinemethyl-3-(4-chlorobenzylideneamino)-2-oxazolidin-2-one (AS8) was found to possesanti depressant activity on the treatment of rat .



Agriculture fungicide

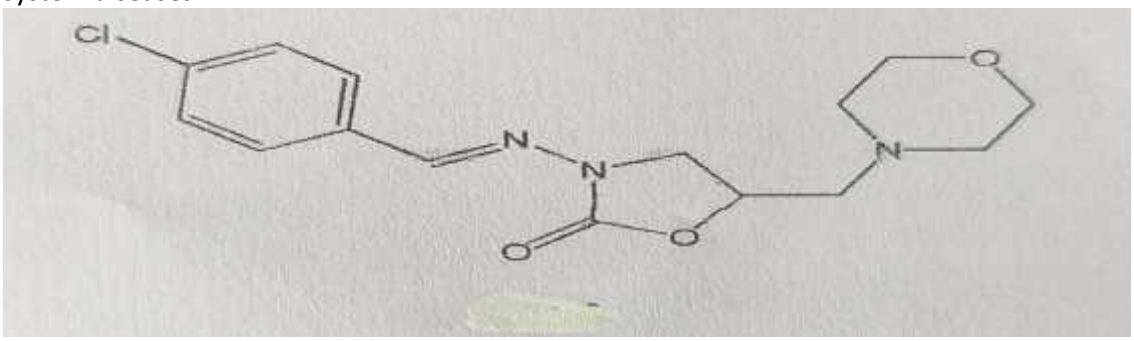
5-methyl-5-(4-phenoxyphenyl)-3-phenylamino-2,4-oxazolidinone (DPXJE874) is a new member of agriculture

fungicide of oxazolidinone under development by DuPont. DPX-JE874 is demonstrate excellent control of plant pathogens in the ascomycete, basidimycete and oomycete classes which infect grapes, cereals tomatoes, potatoes and other cropes.



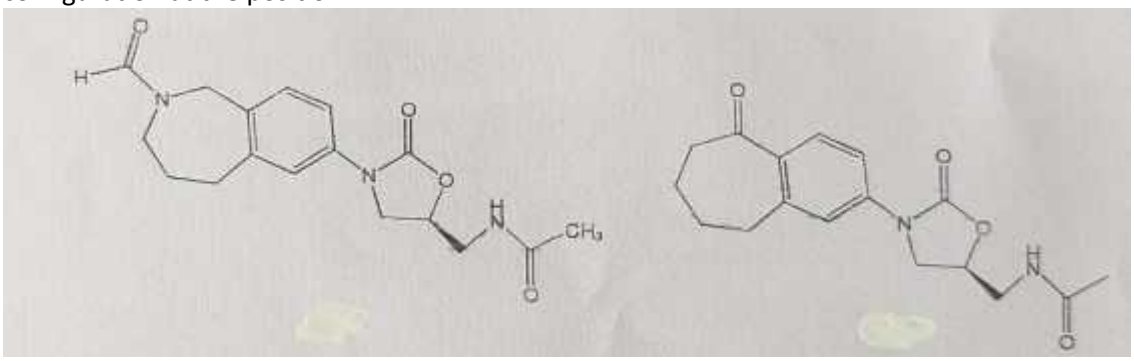
CNS depressant

5-morpholinomethyl-3-(4-chlorobenzylideneamine)-2-oxazolidinone used in the disorder of central nervous system diseases.



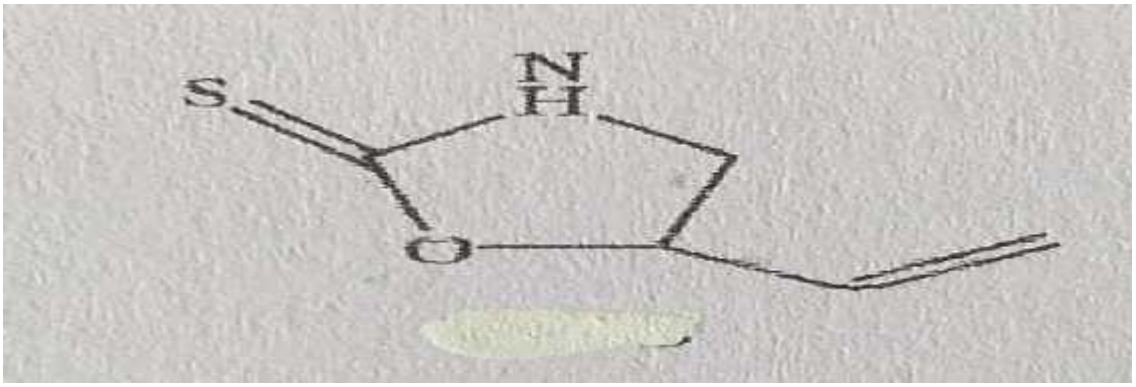
Centrally acting muscle relaxants

(4S, 5R)-4-(2-methylpropyl)-3-[3-(perhydroazepin-1-yl)propyl]-5-phenyl-1,3oxazolidin-2-one and amino alcohol derivative, (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexane-1-ol (MLV-5860) 1.104 act on the brainstem and higher levels of the brain rather than on the spinal cord or the peripheral nervous system to reduce the excessive activities of the nervous system due to the optical isomers with absolute configuration at the position.

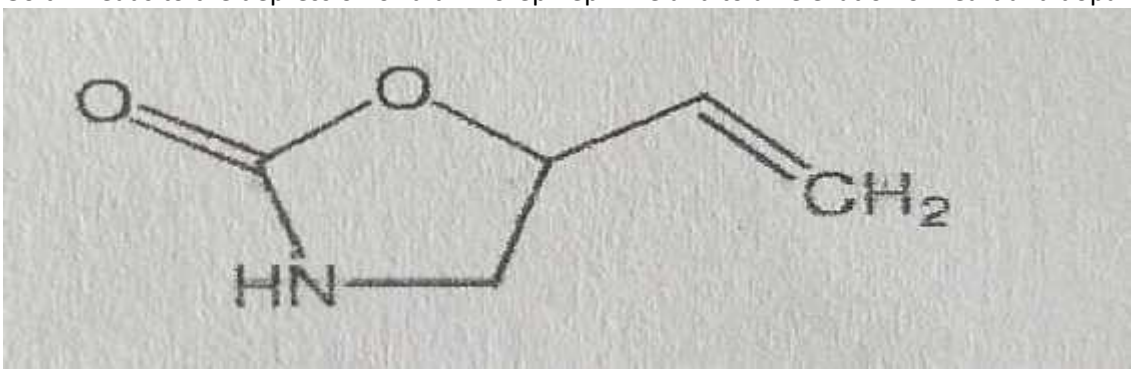


Antithyroid agents

5-vinyloxazolidine-2-thione exhibit antithyroid effects, which are found to be efficiently transferred to the suckling via the milk. In the mothers the exposure to VOT resulted in increased percentage of neutrophils, a decreased percentage of lymphocytes and increased in the weight of liver and thyroid. VOT are the major source of glucosinolates in the human diet.

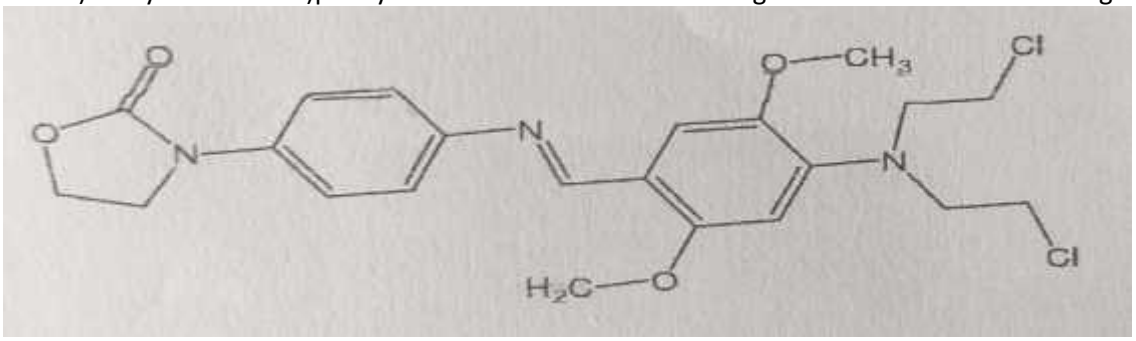


RS-Goitrin (5-vinyloxazolidine-2-one) is a moderate inhibitor of purified bovine dopamine beta-hydroxylase. Goitrin leads to the depression of brain norepinephrine and to an elevation of heart and dopamine.



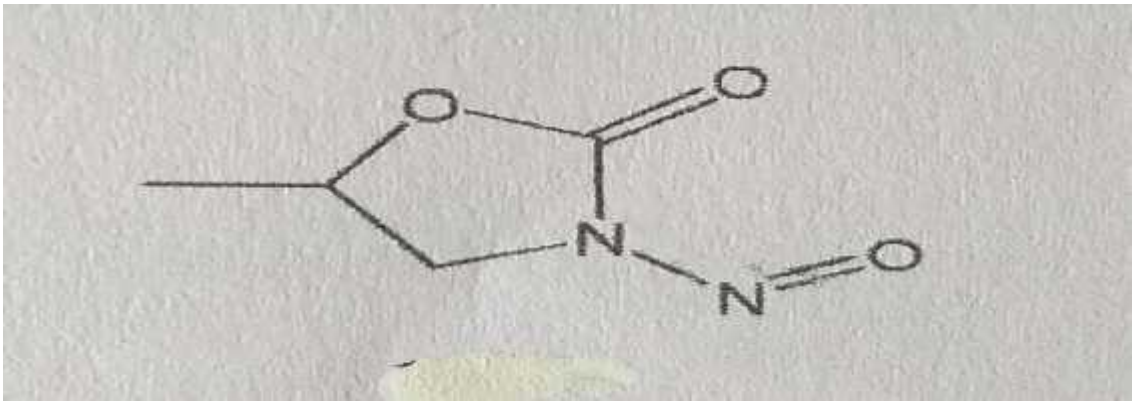
Antiblastic activity in chemotherapy

Antiblastic activity means retardation of growth, 3-p-(2, 5-dimethoxy-4(N,N-bis-(chloroethyl)-amino)benzylideneamino)phenyl-2-oxazolidinone and its analogues are used as antiblastic agent.

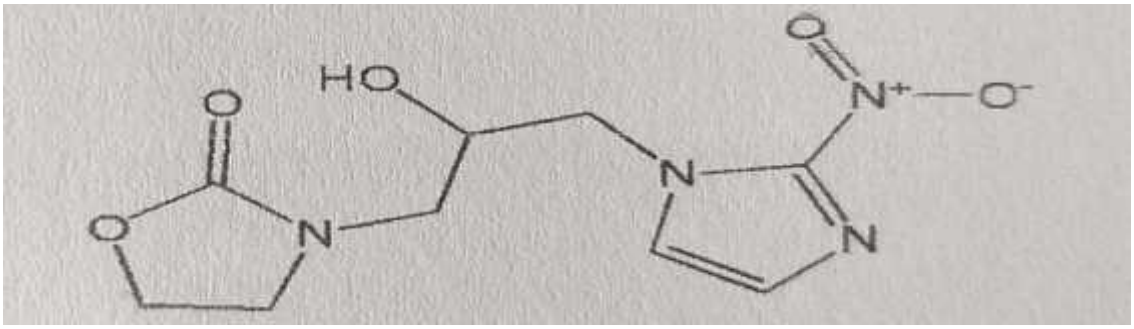


Anticancer activity

3-nitroso-5-methyl-2-oxazolidinone has been found to have anticancer activity.

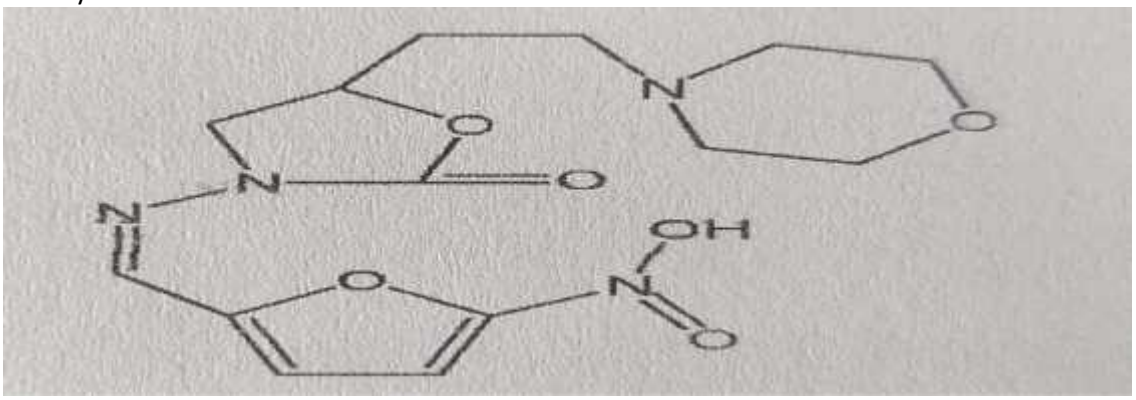


3-(2-hydroxy-3-(2-nitro-1H-imidazol-1-yl) propyl)-2-oxazolidinone exhibit the anticancer ativity.



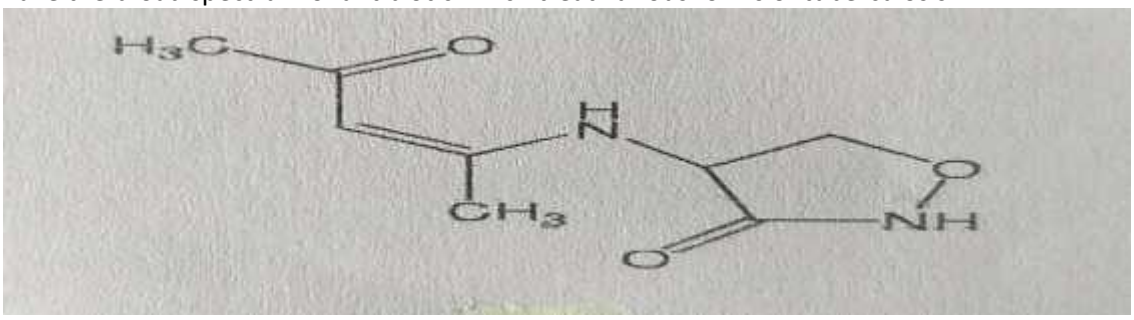
Urinary tract infection

5-morpholinomethyl)-3-(5-nitrofurfurylidene) amino)-2-oxazolidin-5-one (Furaltadone) are used in the urinary tract infection.



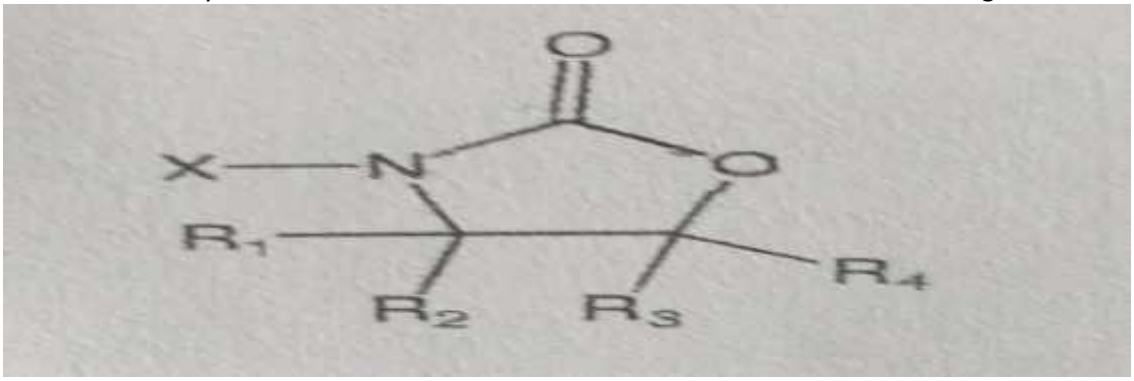
Cycloserine analogues

(R)-4-[(1-methyl-3-oxo-1-buteny) amino] isooxazolidin-3-one (Pentizidone) used as a cycloserine analogues, have the broad spectrum of antibiotic which treat various forms of tuberculosis.



Microcides activity

3-halo-halomethyl-2-oxazolidinone found to have microbicides which control the growth of microorganism.



CONCLUSION

A survey of the literature reveals that a wide variety of oxazolidinone derivatives have been synthesized and tested for their biological activity. The vast commercial success of these medicinal agents and their benefits to

society have led the chemistry of these materials to exponentially in the past few decades causing this subject to command a vast literature. The aim in the present work has been to synthesize oxazolidin-4-one derivatives containing quinolines pharmacophore. The synthesis of above-mentioned series of heterocycles was based on these assumptions that incorporation of more than one, bioactive heterocyclic moiety into a single molecular framework could result heterocycles with enhanced bioactivity.

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