

REVIEW ON BIOACTIVE ISOXAZOLINES***Vasudeva Rao Avupati**

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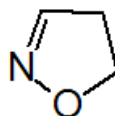
ABSTRACT

In this review we provided an overview of general introduction, synthetic methods, spectral properties and biological activity profiles of some substituted isoxazolines.

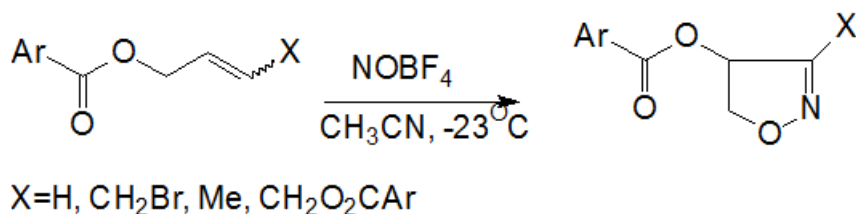
KEYWORDS: Isoxazolines.**INTRODUCTION**

Isoxazole is a π -excessive five membered ring containing two different heteroatoms, oxygen and nitrogen in adjacent positions. Isoxazoline or dihydro isoxazole, like other cyclic systems, show cis-trans isomerism. Four stereoisomers are possible for isoxazolines. These are the two cis and two trans forms. A lot of modifications have been done during the last few years on 2-isoxazoline (1) nucleus and these 2-isoxazoline derivatives have been studied extensively for their chemical and

biological activities.

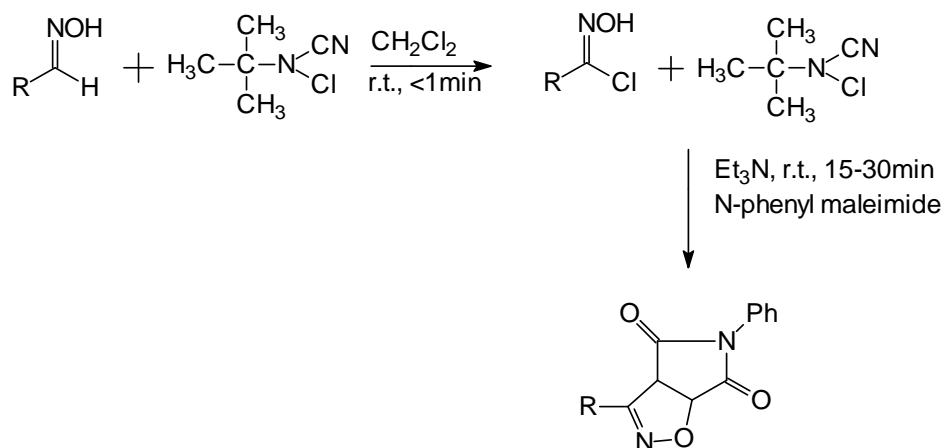
**(1)****General Methods of Synthesis**

1. Treatment of allylic esters such as allyl benzoate, allyl phenyl acetate, 1,4-bis (aroyloxy)-2-butenes with NOBF_4 in CH_3CN at -23°C gives 2-isoxazolines^[1] and substituted 2-isoxazoline derivatives depending upon allyl esters (Scheme 1).



Scheme 1

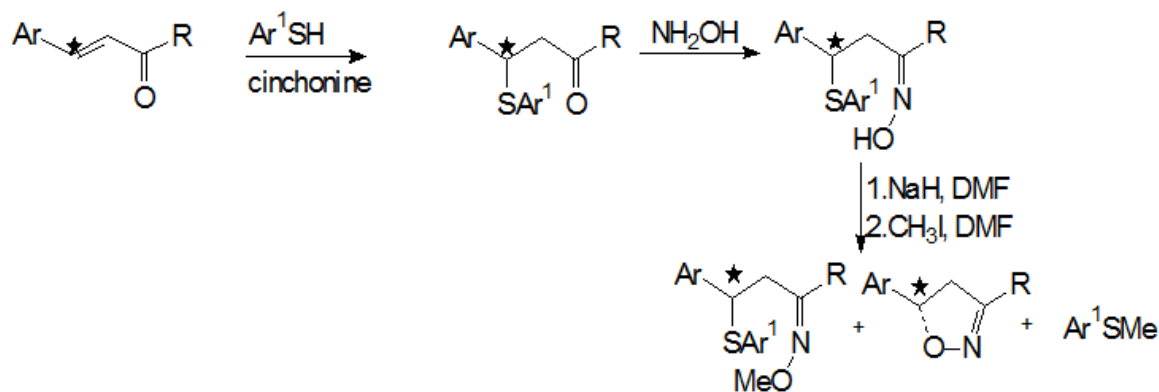
2. Treatment of aldoximes with N-tert-butyl-N-chlorocyanamide gives hydroximoyl chlorides in quantitative yields in less than a minute, which on Heisgen's dehydro halogenation in the presence of triethyl amine gives, the corresponding nitrile oxides. The nitrile oxides gives 2-isoxazolines^[2,3] in excellent yields under mild conditions (Scheme 2).



Scheme 2.

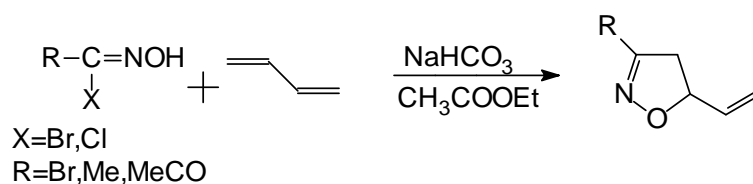
1. Stereospecific synthesis of 4,5-dihydro isoxazoles.^[4]

A simple and new method for the stereo specific synthesis of 3,5-disubstituted-4,5-dihydro isoxazoles was reported from readily available oximes of chiral Michael adducts of thiophenol to chalcones. The key step is the ring-closure reaction, which occurs by stereo specific intramolecular nucleophilic substitution of thiophenoxide (Scheme 3).



Scheme 3

4. 1,3-dipolar cycloaddition of halogen oximes to an excess of butadiene in the presence of sodium bicarbonate to yield Δ^2 -isoxazoles^[5] (Scheme 4).



Scheme 4

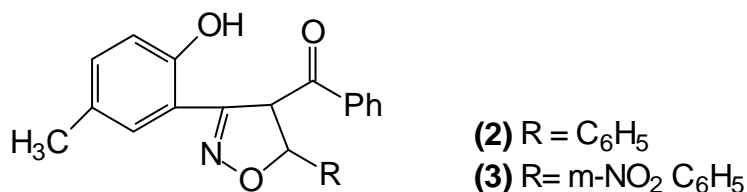
Therapeutic Potential of 2-Isioxazolines

A highly appreciable number of five membered heterocycles, containing nitrogen and oxygen atoms, obtained by laboratory synthesis have turned out to be potential chemotherapeutic and pharmacotherapeutic agents. Various useful synthetic analogs with improved therapeutic properties can be obtained from a single lead compound by structural modifications. The same principle is applicable to the group of 2-isioxazoline. A survey of literature revealed that 2-isioxazoline derivatives possess different types of potential biological activities that include antimicrobial, anti-inflammatory, factor Xa inhibitory, fibrinogen receptor and glycoprotein IIb/3a receptor antagonistic, anticancer, anti HIV, caspase inhibitory and antidepressant activity. Given below is a brief account of various modifications reported on 2-isioxazoline nucleus, which showed a variety of biological activities.

Antimicrobial activity

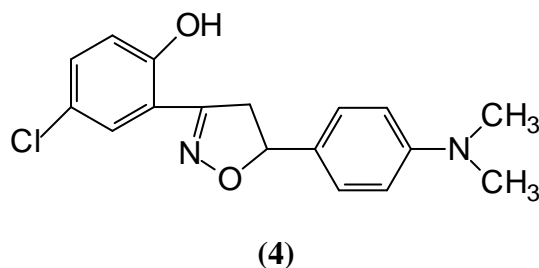
Dighade *et al.*^[6] synthesized some new 3-(2-hydroxy-5-methylphenyl)-4-aryl-5-aryl Isoxazolines (2,3) and subjected them for antimicrobial activity against *E. coli*, *S. aureus*, *P. vulgaris*, *C. guilliermondii*, *C. albicans*, *C. tropicalis* and *C. crusei*. Compounds with R=C₆H₅

and R= m-NO₂C₆H₄ showed highest activity against bacteria and fungi respectively. Other compounds were moderately active.



Various 2-isoxazolines with many substituents are reported by Kaur *et al.*^[7] These compounds showed significant fungicidal activity against *Dreschslera tetramera*, *Alternaria alternata* and *Fusarium oxysporum*. Naik *et al.*^[8] reported some substituted isoxazolines having good inhibitory activity against *E. coli* and *S. aureus*. Some 3,5-diaryl Isoxazolines were prepared by Tayde and Jamode^[9], which showed good activity against *S. aureus* and *Salmonella typhi*. This activity was clearly enhanced by the presence of methoxy group.

Kedar *et al.*^[10] prepared novel isoxazolines and screened them for antibacterial activity against *K. pneumoniae*, *E. coli*, *S. aureus*, *P. mirabilis*, *S. dysenteriae* and *S. typhi*. The compound (4) obtained from 2-hydroxy-5-chloro-4-(dimethylamino) chalcone showed maximum activity.



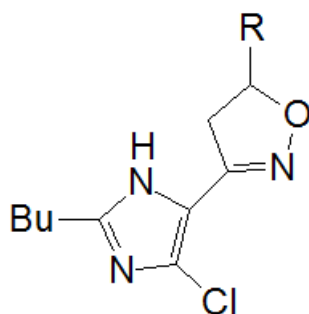
Some 3-methyl-4-(2'-triazoloanilido)-5-aryl isoxazolines are reported as good antimicrobials by Vikani *et al.*^[11] The substituted compounds, such as 3-methyl-4-substituted anilido-5-aryl isoxazolines have been reported as fungicides by Tiwari *et al.*^[12] All the compounds showed remarkably good activity against *Cephalosporium sacchari* and *Helminthosporium oryzae*. The compounds also showed remarkable antifungal activity against two species of aquatic fungi viz. *Saprolegnia parasitica* and *Achlya orion* responsible for fish mycoses. Barot^[13] has also reported synthesis of some isoxazolines using 2-hydroxy chalcones having antimicrobial activity. Many 3-(2'-hydroxy-3'-bromo/nitro-5'-methyl-phen-1'-yl)-5-aryl isoxazolines as antibacterial have been reported by Desai *et al.*^[14] These compounds were not as effective as

tetracycline or gentamycin against *E. coli* and *S. aureus*. Some 2-isoxazolines as antimicrobials have also been reported by Shinde *et al.*^[15], Barot *et al.*^[16] and Otsuji *et al.*^[17]

Rangappa *et al.*^[18] synthesized some new C-(anthranyl and biphenyl)-5-substituted- δ -isoxazolines and evaluated for their antimicrobial activity against different stains such as *B. subtilis*, *E. coli*, *P. fluorescens*, *X. campestris pus*, *X. oryzae*, *A. niger*, *A. flavus*, *F. oxysporum*, *Trichoderma species* and *F. monaliforme*. Some of the compounds showed significant inhibitory activity. Nyati *et al.*^[19] prepared some new 3-benzimidazolyl -5-aryl-2-isoxazolines using microwave irradiation from corresponding chalcones and hydroxylamine hydrochloride in presence of pyridine. Synthesized isoxazolines were screened for their antimicrobial activity and some of the compounds showed activity.

Singhal *et al.*^[20] synthesized some new 3-(4'-(4''-nitrophenoxy)-phenyl)-5-substituted phenyl-2-isoxazolines and reported as antibacterial and herbicidal. Vashi *et al.*^[21] reported the synthesis and antibacterial activity of some 3-(2-hydroxy-3-chloro-5-ethyl phenyl)-5-aryl-2-isoxazolines. All these compounds exhibited mild to moderate antibacterial activity against *S. aureus* and *E. coli*. Gahlot *et al.*^[22] synthesized some new 3-(3',5'-dibromo/diiodo-4'-hydroxy substituted phenyl)-5-substituted phenyl-2-isoxazolines. Some of these Isoxazolines were found to exhibit excellent antibacterial activity.

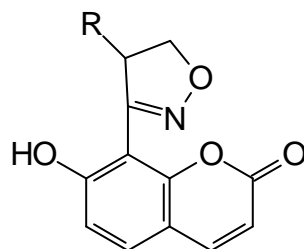
Agarkar *et al.*^[23] synthesized some 3-(2'-hydroxy-3-chloro-5-hydroxy methyl phenyl)-5-aryl-2-isoxazolines and screened them for their antibacterial activities of which some are found to have remarkable activity. Rangappa *et al.*^[24] reported solution phase synthesis and antifungal activities of novel 3-(2-butyl-4-chloro-1H-imidazolyl)-substituted δ 2-isoxazolines (5). The synthesized compounds represent a novel class of potent antifungal agents.



(5) R= Cyano, Ph, COOPh, COOEt,
CH₂COOMe, CH₂OH, COOMe

4.2. Anti-inflammatory activity

Khan and Bawa^[25] synthesized 5-substituted 3-(7'-hydroxy-2H-1-benzopyran-2'-one-8'-yl) isoxazolines as good antiinflammatory agents. Compound (6) and compound (7) showed very good anti-inflammatory activity.

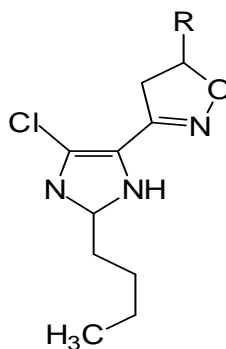


(6) R= 4'-OCH₃C₆H₄

(7) R= 3', 4'- (OCH₃)₂ C₆H₄

Prednisolone derivatives with an isoxazoline fusion at the 16- and 17-carbons and an alkyl carboxylate at 16 α -position as new steroidal anti-inflammatory agents with improved activity has been reported by Lee *et al.*^[26] Shivkumar and Nargund^[27] reported the synthesis of various 3-(4'-fluorophenyl)-5-substituted phenyl isoxazolines having moderate anti-inflammatory activity. Some isoxazoline derivatives showing good anti-inflammatory activity and useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis and other inflammatory conditions have been reported by Kleninman *et al.*^[28]

Rangappa *et al.*^[29] synthesized some novel δ 2-isoxazolines (8) and these, when subjected to phospholipase A2 (PLA2) enzyme inhibitory activity against snake venom source, exerted a significant activity against group II PLA2. These isoxazolines showed comparable *in vivo* anti-inflammatory activity against the standard ursolic acid.



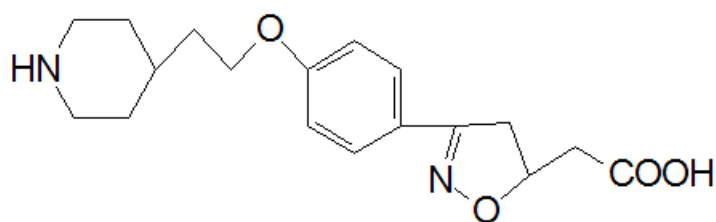
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Factor Xa Inhibitors

Thrombosis is a major cause of mortality in the world. Therefore prevention of blood coagulation has become a major target for new therapeutic agents. One attractive approach is the inhibition of factor Xa, the enzyme directly responsible for prothrombin activation. A series of benzamidine isoxazoline derivatives were evaluated for their inhibitory potency against purified human factor Xa for their antithrombotic activity by Wong *et al.*^[30] Similarly 3,4,5-trisubstituted isoxazolines were evaluated by Pruitt *et al.*^[31] for their antithrombotic activity. Quan *et al.*^[32-34] synthesized isoxazoline derivatives as factor Xa inhibitors. These compounds showed good selectivity for factor Xa compared to thrombin and trypsin.

Fibrinogen receptor and Glycoprotein IIb/3a (GP IIb/3a) receptor antagonists

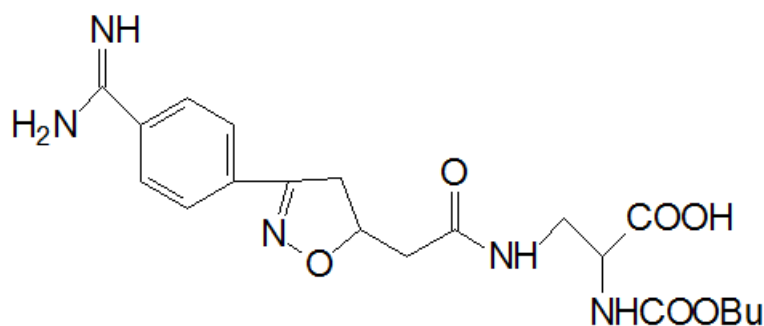
A lot of work has been carried out to discover and develop fibrinogen receptor and glycoprotein IIb/3a receptor antagonists, which can be used safely for the treatment of thromboembolic disorders. Smalheer *et al.*^[35] have prepared isoxazoline derivatives which have IC₅₀ of <50 μM against platelet aggregation. In another report compound (9) has been reported^[36] to inhibit aggregation of human platelets *in vitro* using a variety of agonists with IC₅₀ of <10 μM.



(9)

Wityak *et al.*^[37,38] prepared novel isoxazolines as fibrinogen receptor antagonists with good potential for treating rheumatoid arthritis, asthma, allergies, organ transplantation rejection, septic shock, psoriasis, contact dermatitis, osteoarthritis, tumour metastasis, diabetic retinopathy and inflammatory conditions. GP IIb/3a receptor antagonist XR-299, a 3,5-disubstituted isoxazoline, was investigated^[39] as potential inhibitor of platelet aggregation and platelet adhesion. An α-sulfonamide isoxazoline analog, DMP-802, a novel oral antiplatelet agent with high affinity, relatively slow dissociation rate and specificity for human platelet GP IIb/3a receptor has been reported by Mousa and coworkers.^[40,41] Xue *et al.*^[42] have also reported an orally active series of isoxazoline GP IIb/3a antagonists. Compound (10) in this

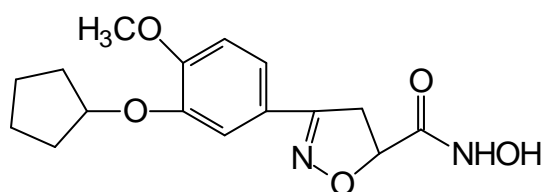
series showed maximum activity. Orally active isoxazoline GP IIb/3a antagonists with extended duration of action have been reported by Olson *et al.*^[4] Olson *et al.*^[44] also reported the synthesis of some isoxazoliny acetamides as potent GP IIb/3a antagonists and also established the structure activity relationships leading to the identification of orally active antiplatelet agents with extended duration of action.



(10)

Anticancer activity

Isoxazoline compounds as inhibitors of tumour necrosis factor (TNF) release, which are useful in the treatment or alleviation of inflammatory conditions or diseases, tuberculosis, graft Vs. host disease and Cachexia associated with AIDS or cancer have been reported by Cohan and Kleinman.^[45,46] Compound (11) showed very good activity in this regard.



(11)

A new type of cyclolignan with an isoxazoline ring fused to hecyclo lignan core were prepared by Del coral *et al.*^[47] and these compounds showed good cytotoxic activity. Simoni *et al.*^[48] studied the effect of several newly synthesized isoxazoline analogs of retinoids on induction of terminal differentiation and *in vitro* growth of tumor cell lines. Some of the tested compounds exhibited (a) ability to induce adipogenic conversion of Ha-ras-1 transformed FHO6T1-1 Chinese hamster fibroblasts (b) antiproliferative activity towards tumour cell lines, including the erythroleukemic K-562 and FL-cell lines and the FHO6T1-1

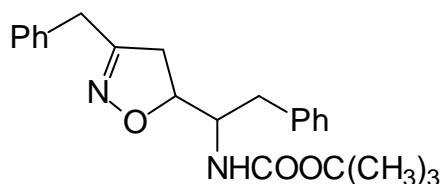
cell lines. This data could be of interest in identifying drugs of possible application in experimental anticancer therapy.

Caspase inhibitors

Kim *et al.*^[49] and Park *et al.*^[50] have reported isoxazoline derivatives as caspase inhibitors for pharmaceutical use. According to this invention, these isoxazoline derivatives can be used for the treatment of diseases related to caspase, such as, diseases in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injury by hepatitis, sepsis, organ transplantation rejection reaction and inflammation.

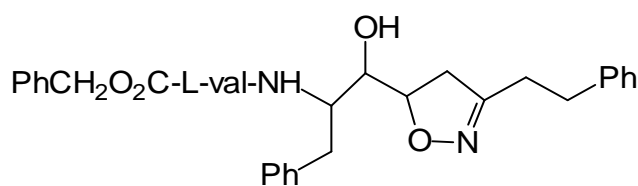
AntiHIV activity

Srivastava *et al.*^[51] synthesized several compounds belonging to 2-isoxazolines with spermicidal and anti HIV activity. Most of these compounds exhibited moderate anti HIV activity. 2-isoxazoline derivatives similar to compound 12 have been prepared by Murai *et al.*^[52] as anti HIV agents. They have also reported that these compounds can also serve as intermediates for preparing medicines such as retrovirus protease inhibitors including human immuno deficiency virus (HIV) protease inhibitors.

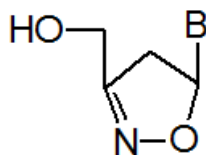


(12)

Synthesis and HIV-1 protease inhibiting activity of 2-isoxazoline derivatives has also been reported by Chung *et al.*^[5] These synthetic compounds were evaluated *in vitro* for the HIV-1 protease inhibition, but inhibitory activity of these compounds was not high enough to be compared with known potent inhibitors. Compound (13) had the best inhibitory activity among them. Biological tests have revealed moderate anti HIV activity for compound (14) that belongs to the class of isoxazoline nucleoside.^[54]



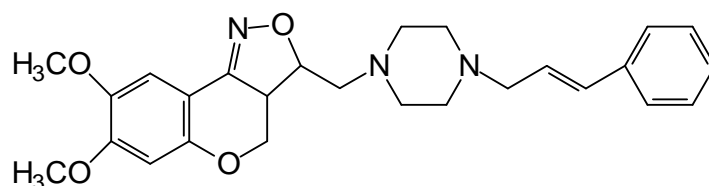
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(14) B= Purine / Pyrimidine base.

Miscellaneous activities

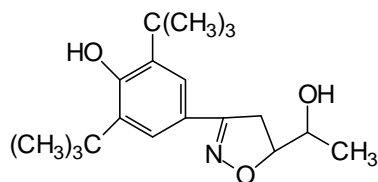
Andres Gil *et al.*^[55] have reported preparation of substituted isoxazolines as antidepressants. Compound (15) has shown serotonin (5-HT) reuptake inhibitory activity in combination with additional α_2 -adrenoceptor antagonist activity and showed a strong antidepressant activity without being sedative.



(15)

Preparation of isoxazoline derivatives as antihelmintic and nematocide is reported by Chalquest *et al.*^[56] The compounds prepared are said to be used in conjunction with other nematocides, such as free fatty acids, fatty acids salts, avermectins and milbemycin. De Amici *et al.*^[57] have reported synthesis and structure activity relationship for a set of new isoxazolines having antimuscarinic activity. The new derivatives were tested *in vitro* for antimuscarinic activity. Most of the derivatives under study behaved as highly potent non-selective muscarinic antagonists.

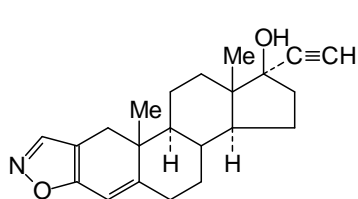
Synthesis of vasodilating, antithrombotic and cardioprotective activity of pyridyl substituted 5-silyl (germyl)-isoxazolines was reported by Lukevics *et al.*^[58] The most active compound of this series, 3-(5-triethylgermyl-3-isoxazoliny) pyridine hydrochloride, protects the heart from rhythm disturbances and lethality during ischemia reperfusion. Preparation of 3-(4-hydroxy-3,5-dibutylphenyl)-2-isoxazolines as noncyclooxygenase inhibiting antirheumatics has been reported by Schwad *et al.*^[59] Compound (16) gave 85% inhibition of adjuvant induced swelling in rats. Dirnens *et al.*^[60] synthesized some silyl 2-isoxazolines, the pharmacological properties including anti-amnesic and memory-stimulating activity of 4-(5-trimethylsilyl-4,5-dihydroisoxazol-3-yl) pyridinium chloride have been studied.



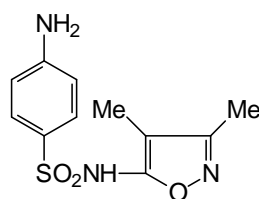
(16)

Therapeutically important drugs^[61,62] containing isoxazole or isoxazoline moiety along with their structures are given below.

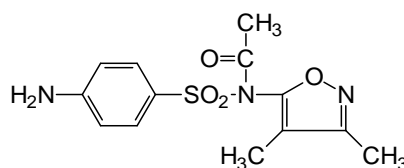
Drug	Activity
Danazol (17)	Anabolic and androgenic activity
Sulfisoxazole (18)	Anti-bacterial
Sulfisoxazole acetyl (19)	Anti-bacterial
Sulfisoxazole diolamine (20)	Anti-bacterial
Oxacillin (21)	Antibiotic
Cloxacillin Sodium (22)	Antibiotic
Dicloxacillin Sodium (23)	Antibiotic
Avicin (24)	Antineoplastic antibiotic
Cycloserine (25)	Anti-tubercular antibiotic
Zonisamide (26)	Anticonvulsant
Risperidone (27)	Hallucinogenic activity
Parecoxib (28)	Rheumatoid arthritis
Valdecoxib (29)	Rheumatoid arthritis



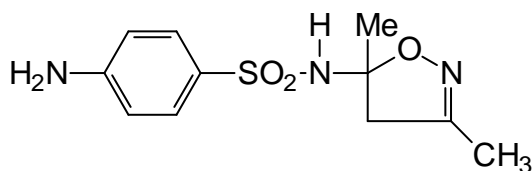
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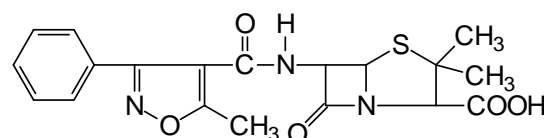
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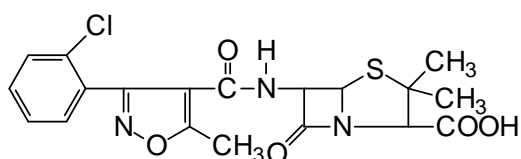
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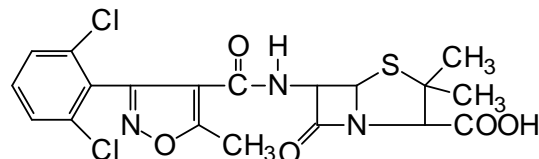
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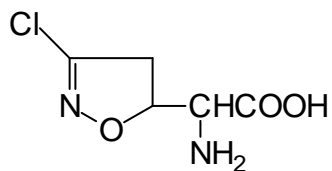
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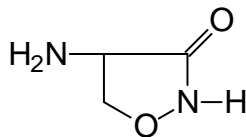
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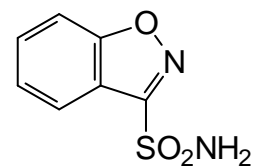
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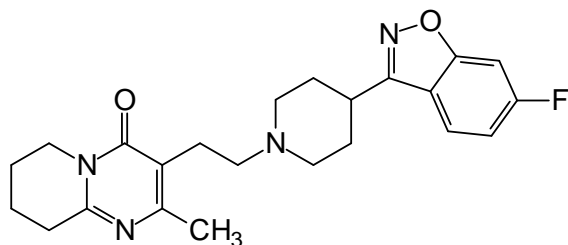
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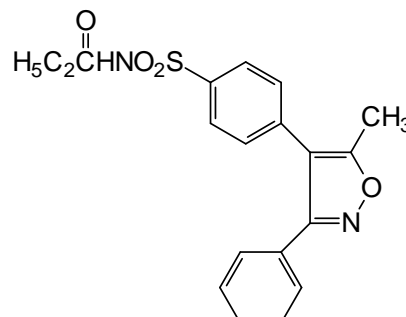
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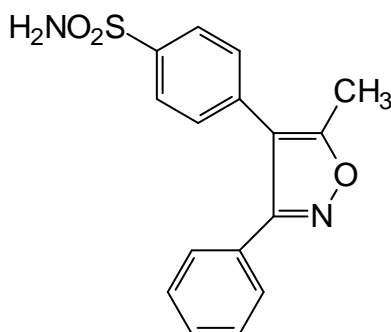
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