REVIEW ARTICLE

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Therapeutic Potential of 2-Isoxazolines

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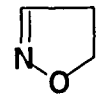
Substituted 2-isoxazolines are well documented in the literature to possess significant biological activities. The 3,5-disubstituted and 3,4,5-trisubstituted 2-Isoxazolines have been reported to exhibit broad range of biological activities such as antimicrobial, antiinflammatory, factor Xa inhibitory, fibrinogen receptor and glycoprotein IIb/IIIa antagonistic, anticancer, antiHIV, caspase inhibitory and as antidepressant. The present review highlights the 2-isoxazoline derivatives with potential biological activities that have been recently reported.

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-isoxazoline (1). Isoxazolines, like other cyclic system, show cis-trans isomerism. Four stereoisomers are possible for isoxazolines containing identical substituents at C_5 and C_6 positions. These are the two cis and two trans forms. A lot of modifications have been done during the last few years on 2-isoxazoline nucleus and these 2-isoxazoline derivatives have been studied extensively for their chemical and biological activities. A survey of literature revealed that 2-isoxazoline derivatives possess different types of potential biological activities that include antimicrobial, antiinflammatory, factor Xa inhibitory, fibrinogen receptor and glycoprotein IIb/IIIa receptor antagonistic, anticancer, antiHIV, caspase inhibitory and antidepressant activity. Given below is a brief account of various modifications reported on 2-isoxazoline nucleus, which resulted in a variety of biological activities.



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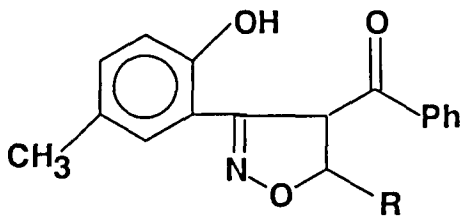
BIOLOGICAL ACTIVITIES OF 2-ISOXAZOLINES

Antimicrobial activity:

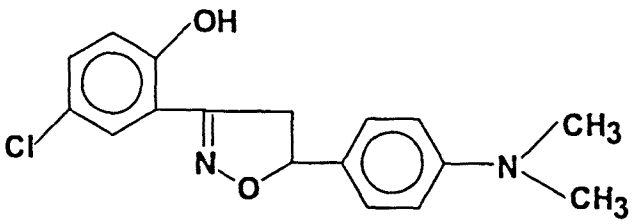
Dighade *et al*[1] synthesized some new 3-(2-hydroxy-5-methylphenyl)-4-aroyl-5-aryl isoxazolines (2, 3) and subjected them for antimicrobial activity against *E. coli, S. aureus, P. vulgaris, C. guillermondii, C. albicans, C. tropicalis* and *C. crusei*. Compounds with R=C_6H_5 and R=m$NO_2C_6H_4$ showed highest activity against bacteria and fungi respectively. Other compounds were moderately active. Various 2-isoxazolines with many substituents are reported by Kaur *et al*[2]. These compounds showed significant fungicidal activity against *Drechslera tetramera, Alternaria alternata* and *Fusarium oxyporum*. Naik and Naik[3] reported some substituted isoxazolines having good activity against *E. coli* and



(2) R= C_6H_5
(3) R= m$NO_2C_6H_4$

S. aureus. Some 3,5-diaryl isoxazolines were prepared by Tayde and Jamode[4], which showed good activity against *S. aureus* and *Salmonella typhi*. This activity was clearly enhanced by the presence of $-OCH_3$ group.

Kedar *et al*[5] prepared novel isoxazolines and screened them for antibacterial activity against *Klebsiella pneumoniae*, *E. coli*, *S. aureus*, *Proteus mirabilis*, *Shigella dysenteriae* and *Salmonella 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*[6]. The substituted compounds, such as 3-methyl-4-substituted anilido-5-aryl isoxazolines have been reported as fungicides by Tiwari *et al*[7]. All the compounds showed remarkably good activity against *Cephalosporium sacchari* and *Helminthosporium oryzae*. Two species of aquatic fungi viz. *Saprolegnia parasitica* and *Achlya orion* responsible for fish mycoses were tested and also found to be remarkably active. Barot[8] has also reported synthesis of some weak antibacterial and antifungal isoxazolines using 2-hydroxy chalcones. Many 3-(2'-hydroxy-3'-bromo/nitro-5'-methylphen-1'-yl)-5-aryl isoxazolines as antibacterial have been reported by Desai and Ankhiwala[9]. These compounds were not as effective as tetracycline or gentamycin against *E. coli* and *S. aureus*. Some 2-isoxazolines as antimicrobial have also been reported by Shinde *et al.*[10], Barot *et al.*[11] and Otsuji and Mizuno[12].



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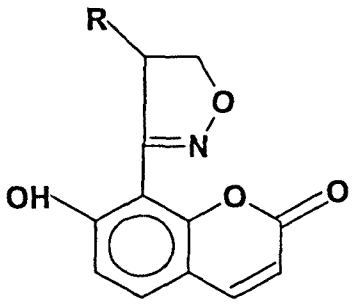
Antiinflammatory activity:

Khan and Bawa[13] synthesized 5-substituted 3-(7'-hydroxy-2H-1-benzopyran-2'-one-8'-yl) isoxazolines as good antiinflammatory agents. Compound (5) and compound (6) showed very good antiinflammatory activity. Prednisolone derivatives with an isoxazoline fusion at the 16- and 17-carbons and an alkyl carboxylate at 16α-position as new steroidal antiinflammatory agents with improved activity has been reported by Lee *et al*[14]. Various 3-(4'-fluorophenyl)-5-substituted phenyl isoxazolines as moderately active antiinflammatory agents are reported by Shivkumar and Nargund[15]. Some isoxazoline derivatives showing good antiinflammatory 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 Kleinman *et al*[16].



(5) R= 4'-$OCH_3C_6H_4$

(6) R= 3', 4'-$(OCH_3)_2C_6H_3$

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*[17]. Similarly 3,4,5-trisubstituted isoxazolines were evaluated by Pruitt *et al*[18] for their antithrombotic activity. Quan *et al*[19-21] 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/IIIa (GP IIb/IIIa) receptor antagonists:

A lot of work has been carried out to discover and develop fibrinogen receptor and glycoprotein IIb/IIIa receptor antagonists, which can be used safely for the treatment of thromboembolic disorders. Smalheer *et al*[22] have prepared isoxazoline derivatives which have IC_{50} of <50 μM against platelet aggregation. In another report compound (7) has been reported[23] to inhibit aggregation of human platelets *in vitro* using a variety of agonists with IC_{50} of <10 μM. Wityak *et al*[24,25] 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/IIIa receptor antagonist XR-299, a 3,5-disubstituted isoxazoline, was investigated[26] 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/IIIa receptor has been reported by Mousa and coworkers[27,28]. Xue *et al.*[29] have also reported an orally active series of isoxazoline GP IIb/IIIa antagonists. In the series reported, compound (8) showed greatest activity. Orally active isoxazoline GP IIb/IIIa antagonists with extended duration of action have been reported by Olson *et al.*[30]. They have also published a review[31] regarding the discovery of isoxazolinyl acetamides as potent GP IIb/IIIa antagonists and the structure activity studies leading to the identification of orally active antiplatelet agents with extended duration of action.

Anticancer activity:

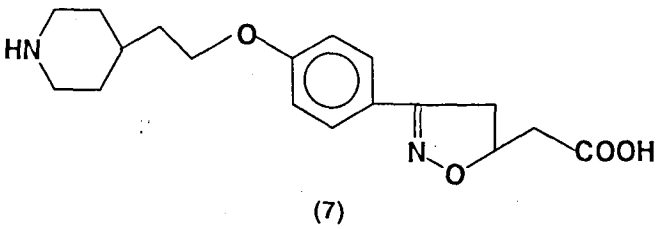
Isoxazoline compounds as inhibitors of tumour necrosis factor (TNF) release which are useful in the treatment or alleviation of inflammatory conditions or diseases, tuberculosis, graft Vs. host disease and Cachexia associated with AIDS or cancer have been reported by Cohan and Kleinman[32,33]. Compound (9) showed very good activity in this regard. A new type of cyclolignan with an isoxazoline ring fused to the cyclolignan core were prepared by Del corral *et al.*[34]. The synthesized compounds were evaluated for their cytotoxic activity with positive results. Simoni *et al.*[35] 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-I 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.*[36] and Park *et al.*[37] 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.*[38] synthesized several compounds belonging to 2-isoxazolines with spermicidal and antiHIV activity. Most of their compounds exhibited moderate antiHIV activity. Preparation of 2-isoxazoline derivatives like (10) has been reported by Murai *et al.*[39] as antiHIV 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



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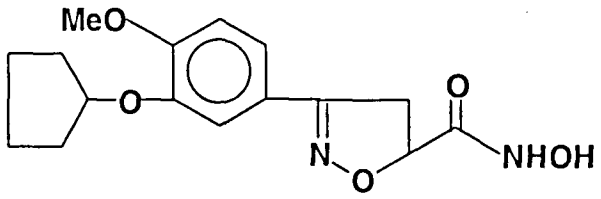

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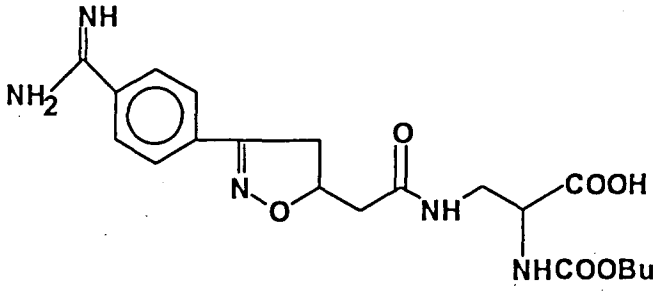

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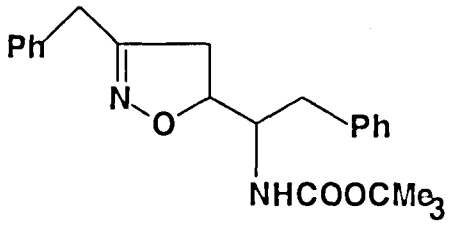

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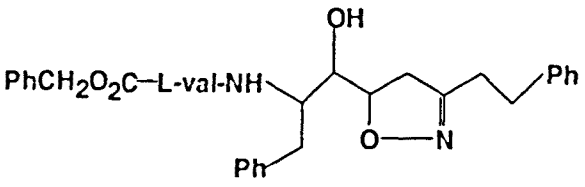
(HIV) protease inhibitors. Synthesis and HIV-1 protease inhibiting activity of 2-isoxazoline derivatives has also been reported by Chung *et al.*[40]. The synthetic compounds were evaluated *in vitro* for the HIV-1 protease inhibition, but inhibitory activity of these compounds was not high enough to be compared with known potent inhibitors. Compound (11) had the best inhibitory activity among them. Biological tests have revealed moderate antiHIV activity for compound (12) that belongs to the class of isoxazoline nucleoside[41].

Miscellaneous activities:

Andres Gil *et al.*[42] have reported preparation of substituted isoxazolines as antidepressants. Compound (13) has shown serotonin (5-HT) reuptake inhibitory activity in combination with additional α2-adrenoceptor antagonist activity and showed a strong antidepressant activity without being sedative. Preparation of isoxazoline derivatives as antihelmintic and nematocide is reported by Chalquest e *al.*[43]. The compounds prepared are said to be used in conjunction with other nematocides, such as free fatty acids, fatty acid salts, avermectins and milbemycin. De Amici *et al.*[44] 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. The major part of derivatives under study behaved as highly potent, though non-selective, muscarinic antagonists.

Synthesis, vasodilating, antithrombotic and cardioprotective activity of pyridyl substituted 5-silyl (germyl)-isoxazolines are reported by Lukevics *et al.*[45]. The most active compound of this series, 3-(5-triethylgermyl-3-isoxazolinyl) pyridine hydrochloride, protects the heart from rhythm disturbances and lethality during ischemia



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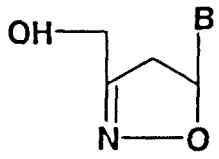
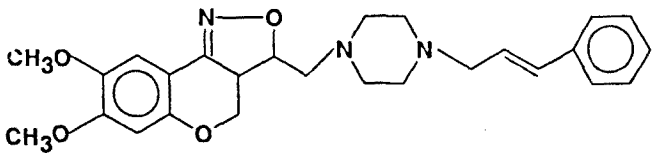


(12) B = Purine/Pyrimidine base

reperfusion. Preparation of 3-(4-hydroxy-3,5-ditert-butylphenyl)-2-isoxazolines as noncyclooxygenase inhibiting antirheumatic have been reported by Schwab *et al*[46]. Compound (14) gave 85% inhibition of adjuvant induced foot swelling in rats.

So far, modifications of the 2-isoxazolines and its derivatives have not proven highly effective. However, modifications that have been made so far do not exhaust the possible changes that can be made to improve potency and efficacy of 2-isoxazolines. It would be interesting to see whether 2-isoxazoline derivatives can be utilized as potent therapeutic agents in the future.



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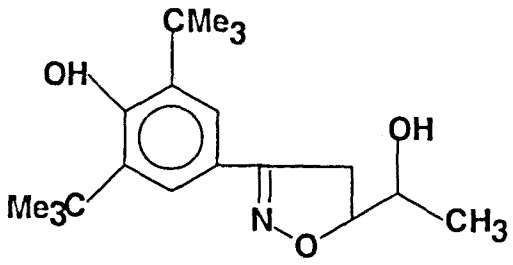

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