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A REVIEW ON THE SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF ISOXAZOLE

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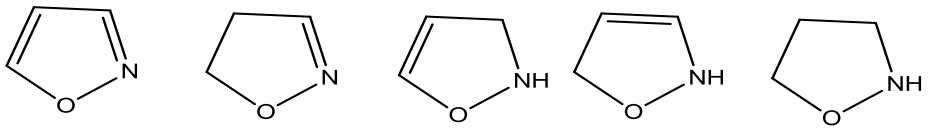
ABSTRACT

This review summarizes the reaction, biological and pharmacological importance and synthetic method of isoxazole, and summarizes some recent development on their derivatives such as chalcone etc., isoxazole is an azole with an oxygen atom next to the nitrogen. The substituted isoxazoles have been reported to exhibit broad range of biological activities such as antimicrobial activity, analgesic activity, anti-inflammatory activity, antioxidant activity, anticancer activity, CNS activity, antitubercular activity, and some miscellaneous activity.

KEYWORDS: Isoxazole, Anti-inflammatory, Anti- microbial, Anti-cancer activity.

INTRODUCTION

Isoxazoles are an important class of heterocyclic compound, displaying a broad spectrum of biological activities. Modification in their structures has offered a high degree of diversity that has proved useful for the development of new therapeutic agents with improved potency and lower toxicity.[1] The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution in the chemistry of heterocycles. Isoxazole **(1a)** is a five membered heterocyclic compound containing oxygen and nitrogen atoms in the 1,2 positions, its partially saturated analogs are called isoxazolines **(1b-d)** and completely saturated analog is isoxazolidine **(1e).**[2]

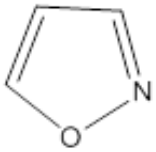


1a **1b** **1c** **1d** **1e**

Isoxazole derivatives display a wide array of pharmacological activities that have been successfully screened for anticancer, anti-inflammatory, antimicrobial, antihistaminic, antitubercular, antiulcer, antiepileptic, dual α2-adrenoreceptor and 5-H Treuptekeinhibitors, antiviral, and anxiolytic acsstivities.The pharmacological profits of employing the isoxazole ring are due to the fact that this structure acts as a key pharmacophore for the biological activity of such drugs as Valdecoxib (COX-2 inhibitor) and Leflunomide (antirheumatic drug)[1]

Structure and Nomenclature of Isoxazole

Isoxazoles are unsaturated aromatic heterocyclic compounds containing a ring with three carbon atoms, one oxygen atom and one nitrogen atom. The trivial name for the title five membered fully unsaturated heterocycles as "isoxazole" was originally proposed by Hantszch as it was the isomer "oxazole"discovered first. The trivial name follows the Hantszch-Widman system of nomenclature: the prefix "iso" represents isomer, "oxa" represents the oxygen atom "aza" represents the nitrogen atom the suffix "ole" denotes the ring size as five-membered; altogether the derived name is "isoxazole". This name has been accepted in IUPAC and has been used in Chemical abstracts. In Chemical Abstracts, the other systematic name 1, 2-azole, is also used.[3]

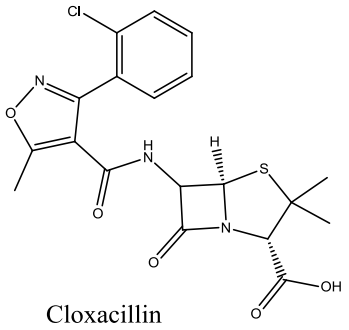


Isoxazole

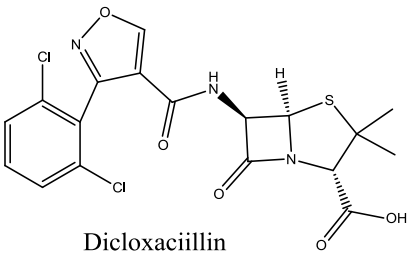
CHEMISTRY OF ISOXAZOLE

The nitrogen hetero atom is more pronounced for electron withdrawing effect, while the oxygen atom is more pronounced for electron donating effect. As neutral

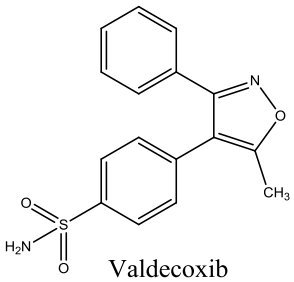
molecules, isoxazoles undergo electrophilic substitution rather more readily at the position 4, than benzene. Effects of substituents can modify their behavior. Substituents at the position-5 apparently have more activating and deactivating effect than substituents at the position- 3. In natural product synthesis, isoxazoles are used as latent synthons, such as masked new heterocyclic rings, masked fusedrings, masked aromatic rings and masked aldol and related moieties.[4] The capability of isoxazole undergoing reaction is diverse: protonation, quaternization, complexation, oxidation, reduction, carbanionic condensations, thermolysis, photolysis, transformations into other heterocyclic ring systems and reaction with electrophiles, nucleophiles and Grignard reagents.[5]



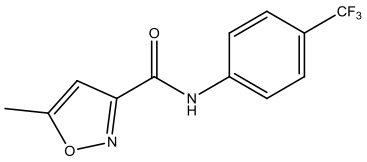
Cloxacillin



Dicloxaciillin



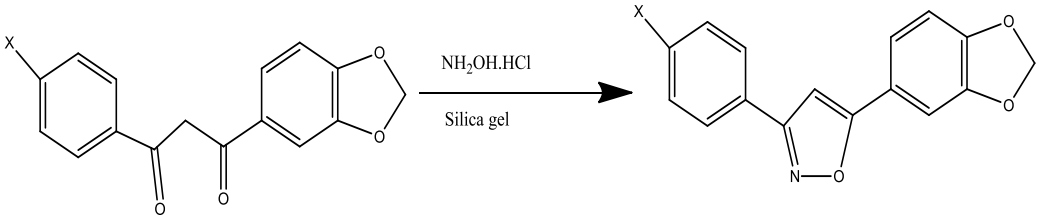
Valdecoxib



Leflunomide

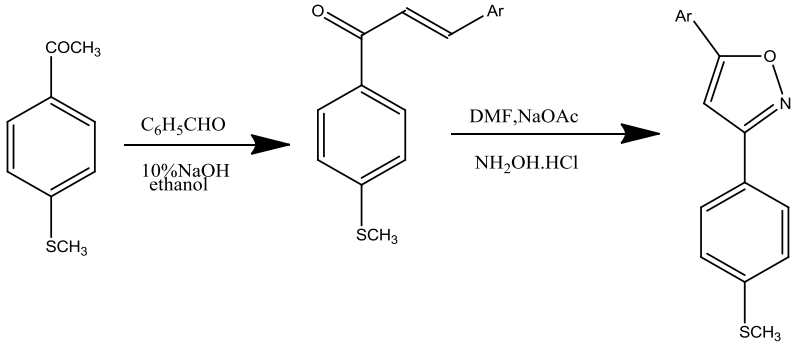
General Methods of Synthesis of Isoxazoles

1. Solid phase synthesis of isoxazole derivative of Diaryl 1,3-diketones can be carried out in presence of hydroxylamine hydrochloride and silica gel.[6]



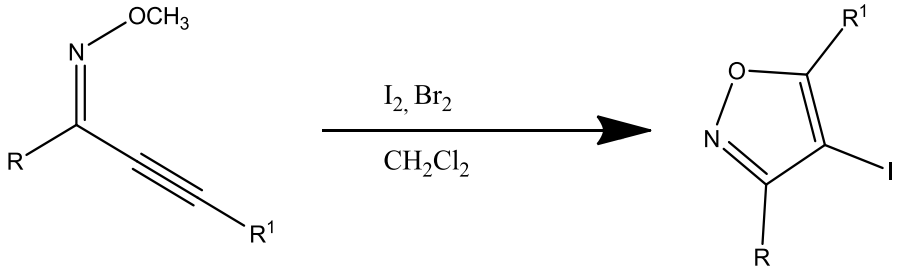
Scheme 1.

2.Synthesis of isoxazole from 4-acetylthioanizole with aryl aldehydes through α, β-unsaturated ketones.[7]



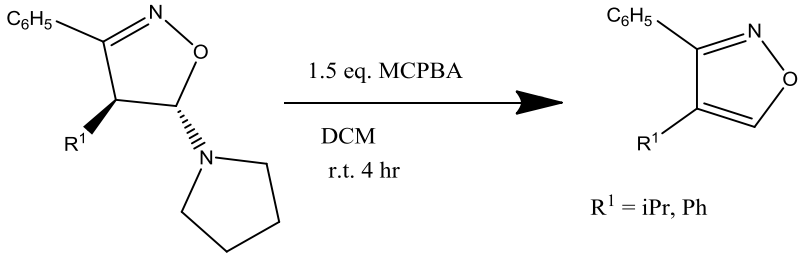
Scheme 2.

3. Synthesis of 3,5-disubstituted 4-hole(seleno) isoxazole from 2-alkyn-1-one *O*-methyl oximes by using ICl, I_2, Br_2.[8]



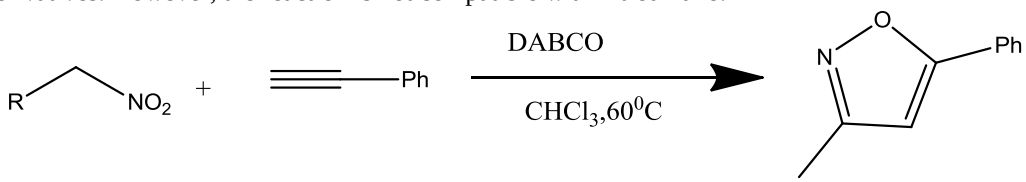
Scheme 3.

4. Synthesis of 3,4,5-trisubstituted 5-(pyrrolidinyl)-4,5-dihydroisoxazoles using Enamine- triggered [3+2]-cycloaddition reactions of aldehydes and *N*-hydroximidoyl chlorides in the presence of triethylamine.[9]



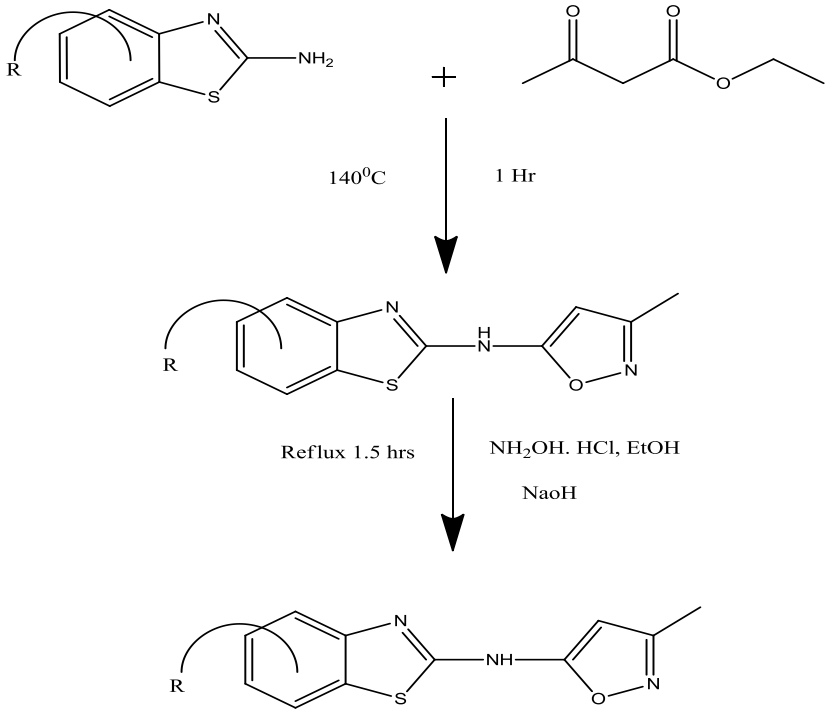
Scheme 4.

5. Synthesis of isoxazole using nitro compounds such as phenyl nitro methane with terminal acetylenes affords isoxazole derivatives. However, the reaction is not compatible with nitroalkane.[10]



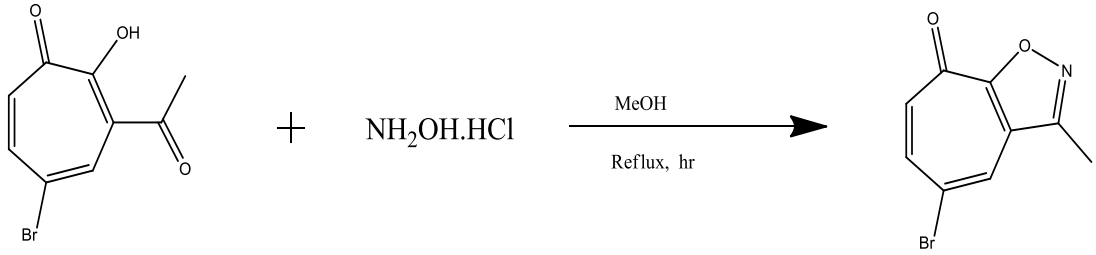
Scheme 5.

6. Synthesis of 3-carboxamideo-(substituted-benzothiazazole-2yl)-propane-2-one from the mixture of 2-amino-benzothiazole and aceto-acetic ester.[11]



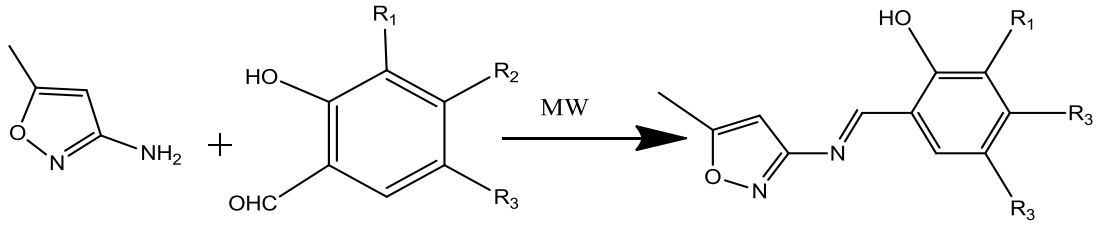
Scheme 6.

7. Synthesis from a mixture of 3-acetyl-5-bromo tropolone and hydroxyl amine hydrochloride in methanol and promoter was reflexed for 10hrs to obtain isoxazole.[12]



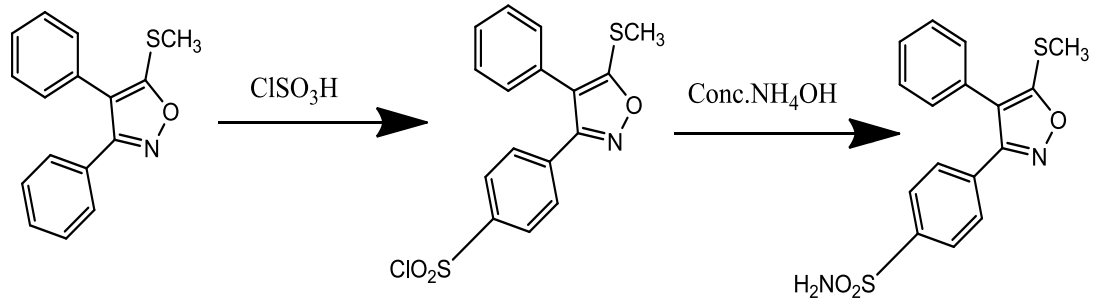
Scheme 7.

8. Synthesis of isoxazole Schiff base from 3-amino-5-methyl isoxazole with substituted salicylaldehyde using microwave assisted method.[13]



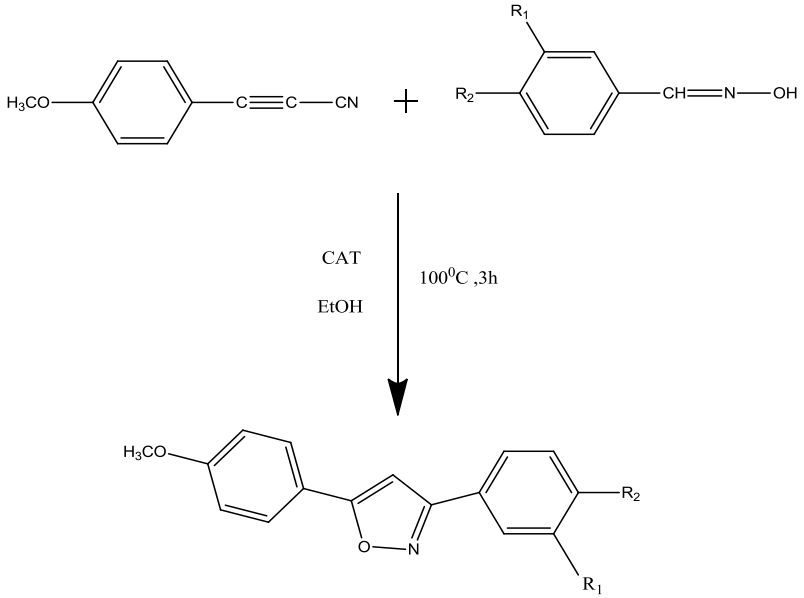
Scheme 8.

9. Synthesis of novel isoxazole by reaction of 5-(methyl thio)-3,4-diphenyl isoxazole with chlorosulfonic acid afforded compound which treated with conc.NH_4OH furnished compound.[14]



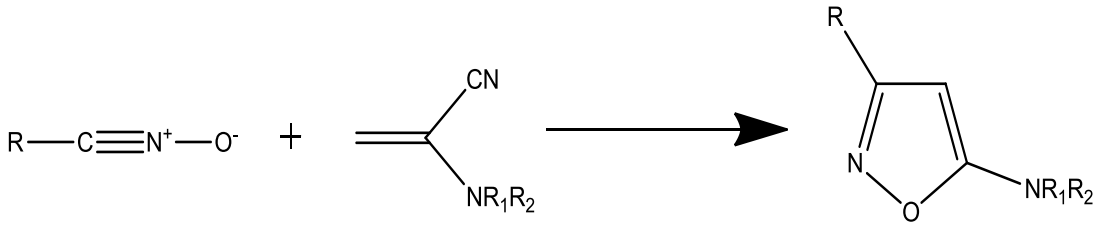
Scheme 9.

10.Synthesis of 3-aryl-5-(4-methoxyphenyl)-isoxazole-4-carbonitriles by the *in situ* generated nitrile oxides obtained by the catalytic oxidation of aldoximes with chloramine-T in alcohol and 3-(4-methoxyphenyl)propiolonitrile.[15]



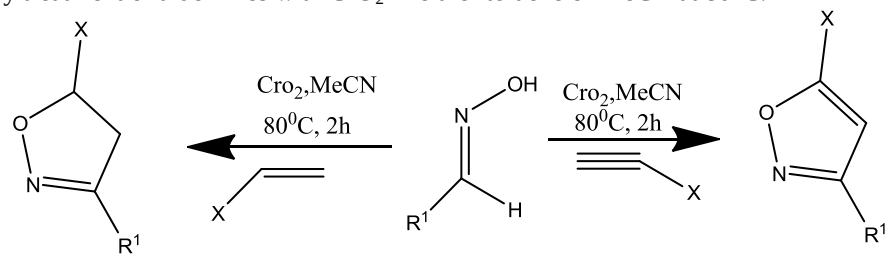
Scheme 10.

11. Regioselective synthesis of 5-aminoisoxazoles in toluene using a 1,3-dipolar cycloaddition reaction between nitrile oxides and captodative α-cyanoenamines.[16]



Scheme 11.

12. Synthesis of isoxazoles and isoxazolines *via* 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides generated *in-situ* by treatment of aldoximes with CrO_2 in either toluene or MeCN at 80°C.[17]



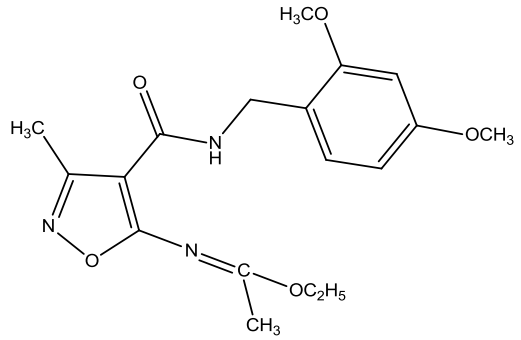
Isoxazoline Isoxazole

Scheme 12.

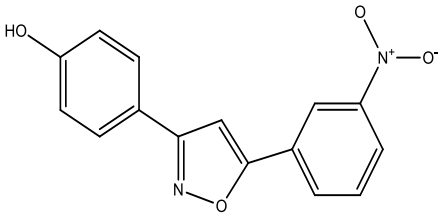
PHARMACOLOGICAL ASPECTS OF ISOXAZOLE

Anti-Inflammatory Activity

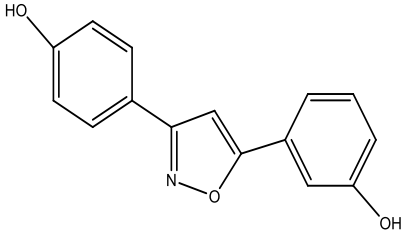
Maczynski *et al*., synthesized a Series of new isoxazole derivatives of expected immunosuppressive activities was synthesized, following *in-vitro* screening in the human cell models, the activity of MZO-2compound (ethyl N-{4-[(2,4-dimethoxybenzyl) carbamoyl]-3-methylisoxazol-5-yl}acetamidate) in mouse *in-vivo* model was evaluated. *In-vitro* tests included evaluation of: peripheral blood mononuclear cells(PBMC) viability, phytohemagglutinin(PHA)-induced PBMC proliferation and lipopolysaccharide (LPS)-induced tumor necrosis factor α (TNF α) production in whole blood cell cultures. MZO-2 was studied in mice for its effects on: humoral immune response to sheep erythrocytes (SRBC), delayed type of hypersensitivity (DTH) to ovalbumin (OVA), contact sensitivity to oxazolone and carrageenan-induced foot pad edema. In addition, the effect of MZO-2 on expression of caspases in Jurkat cells was determined. MZO-2, applied systemically or locally, may serve as a potential drug for amelioration of inflammatory process.[18]



SK Gupta showed isoxazole derivatives were screened for their anti-inflammatory activity by *in vivo* method on rats. The action of synthesized compound was done on paw of Wister albino rats and compared with Diclofenac sodium as a standard. The paw volumes were recorded within one hour interval time duration and the SEM values are calculated by using SPSS software. The study indicated that following compounds exhibited potent anti- inflammatory activity.[19]



4-[5-(3-nitrophenyl) isoxazol-3-yl] phenol

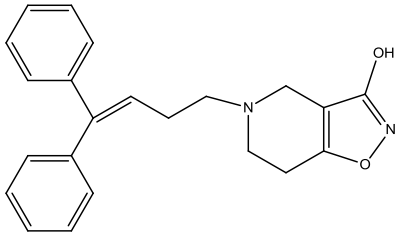


2-[3-(4-hydroxyphenyl) isoxazol-5-yl] phenol

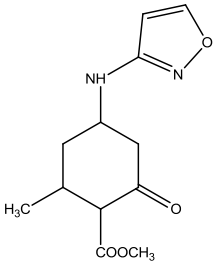
ANTI-CONVULSANT ACTIVITY

Tina Bolvig *et al.*, were searched for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. Many patients with epilepsy fail to experience adequate control of their seizures, despite the optimal use of available antiepileptic drugs. Other patients do so only at the expense of significant toxic side effects. In recent years it has been established that inhibitors of GABA transport and in particular astroglial uptake can act as anticonvulsant agents and several isoxazole derivative synthesized has been proven to be so.[20]

Natalie D. Eddington *et al.*, shows a Compound A and Compound B is also a synthesized isoxazole derivative which affects the sodium channel to show its activity.[21]



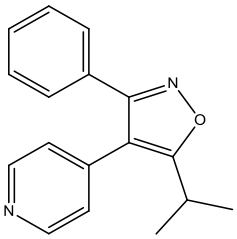
A



B

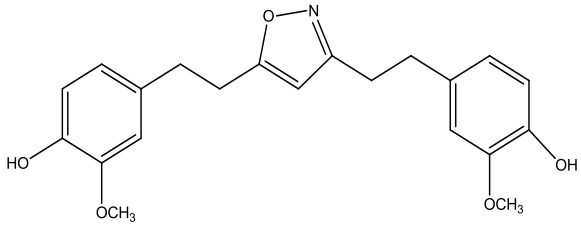
ANTI-CANCER ACTIVITY

Shaw J *et al* ., were designed a Substituted Isoxazole which was originally designed and characterized as ATP competitive p38α mitogen activated protein kinase (MAPK) inhibitors, revealed significant inhibition of casein kinase 1δ (CK1δ) (90% inhibition) in a panel of 78 protein kinases at a concentration of 10μM and also inhibited CK1δ with an IC50 value of 0.23μM. Novel N-(phenyl)-5-carboxamidyl isoxazoles synthesized were examined for their anticancer activity in vitro. N-(4 Chlorophenyl)- 5-carboxamidyl Isoxazole27 showed promising in vitro cytotoxicity and solid tumourselectivity. It exerted most potent cytotoxic activity against both colon-38 and CT-26 mouse colon cancer cell lines. It inhibited the phosphorylation of STAT3, a novel target for chemotherapeutic drugs.[22]

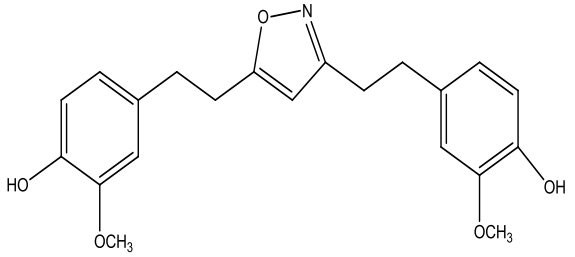


4-(5-Isopropyl-3-phenyl-isoxazole-4-yl)-pyridine

Paola P *et al.*, analysed the effects of curcumin and of its isoxazole analogue in breast cancer cell line and in its multidrug-resistant (MDR) variant were examined. The isoxazole analogue compound has shown more potent antitumor and molecular activities both in parental and in MDR tumour cells. Isoxazole derivatives produce significantly higher direct inhibition of the COX-2 catalytic activity than curcumin. The isoxazole derivatives proved better because of minimum metal chelation when compared to curcumin.[23]



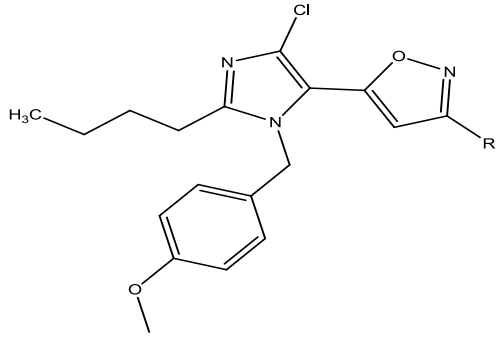
V.H. Bhaskar and P. B Mohite showed the compound has been highly effective against human tumor cell lines especially on renal cancer, CNS cancer cell and ovarian cancer cell lines.[24]



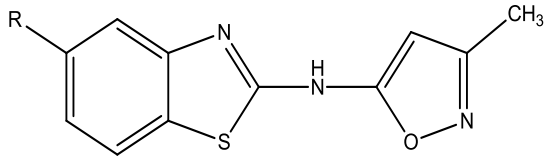
ANTI-MICROBIAL ACTIVITY

Naliapura *et al.*, have showed the antimicrobial activity which were carried out by using the cup-plate agar diffusion method by measuring the zone of inhibition in millimeter. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strain such as *Salmonella typhimurium, Bacillus megaterium, Staphylo coccus aureus, Escherichiacoli* and*Fungi Aspergillus niger* using dimethyl formamide solvent at 50 µg/ml concentration. Standard drugs like ampicillin, chloramphenicol, norfloxacin and greseofulvin were used for Comparison purpose. The screening data indicated that several newly prepared isoxazoles derivatives exhibited significant antibacterial activity against the gram positive (*B.mega or S. typhi*)

andgram negative compounds (*E. coli or S. aureus)* bacterial strains.[25]

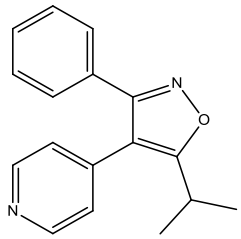


Magar *et al.,* showed the synthesized compounds were tested for their antimicrobial activity by measuring the inhabitation area on agar plates with *Staphylococcus aureus, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Bacillus megatherium* and *Bacillus subtilis* as test germs. The zone of inhibition was compared with standard Chloramphenicol. The result of antibacterial screening indicated the good activity was shown by the compound against the organisms.[11]



ANTI-PLATELET ACTIVITY

Xue CB and Roderick J synthesized the novel isoxazole derivatives which show antiplatelet activity. The Antiplatelet activity of labelled isoxazole derivative is due to glycoprotein 2b/3a antagonistic mechanism. The synthesized Isoxazole derivative show high antiplatelet activity in dogs.[27]



R= Aryl or Alkyl or Benzyl

CONCLUSION

Many procedures are established for the synthesis of isoxazole core, but only few yields better percentage of product. Hence more effort yet to be given to develop new synthetic strategies. Furthermore, pharmacological activity with new dimension need to be explored for isoxazole. Therefore, this review may be helpful for medicinal chemist.

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