Isoxazolines: An insight to their synthesis and diverse applications

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ABSTRACT

The five membered heterocycles isoxazolines are considered as important class of compounds in bioorganic and medicinal chemistry. They were treated as useful intermediates for transforming to large number of bioactive molecules. These classes of compounds were known to have varied biological activities. In this review, critical discussion has been made on synthetic methodologies developed, utility as building blocks for the synthesis of bioactive molecules and medicinal applications of isoxazoline systems.

Key words: Isoxazoles, antioxidant, antimicrobial, analgesic, anti-platelet, anti-HIV.
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INTRODUCTION

The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution in the chemistry of heterocycles. Heterocycles containing nitrogen and oxygen atom are considered as useful scaffolds for the synthesis of biologically active molecules. Among such classes of compounds isoxazolines occupies a prime position in bioorganic chemistry for their diverse biological applications.

Isoxazoles (**1a**) are five membered heterocycles that contains oxygen and nitrogen atoms at adjacent positions. The partially saturated analogs of isoxazoles are termed isoxazolines (**1b-d**) and completely saturated analog is isoxazolidine (**1e**) [1].
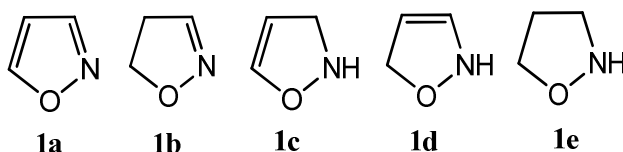

Isoxazolines are considered as versatile synthons in organic synthesis, which have been extensively and efficiently transformed in to various classes of medicinally important molecules. The isoxazolines widely used in pharmaceuticals and therapeutics because of their diverse applications. They were known to exhibit insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic properties. Isoxazoline analogues are used in the market as COX-2 inhibitor and anti-inflammatory drugs.

SYNTHESIS AND REACTIONS OF ISOXAZOLINES:
A significant contribution to the development of isoxazole chemistry was from Quilico's studies on the synthesis of ring system from nitrile oxides and unsaturated compounds [2]. The larger intensity of biological potency exhibited

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by isoxazoline moiety stimulated the researchers work in this area to develop new novel synthetic approaches for their synthesis and study their activity. The recent review articles reported on Huisgen cycloaddition and nitrile oxides describes the method of synthesizing isoxazolines by 1,3-dipolar cycloaddition reactions [3-4]. For example, 1,3-dipolar cycloaddition of alkenes with nitrile oxides generated *in situ* by treatment of aldoximes with Magtrieve (CrO$_2$) in either toluene or MeCN at 80^{0}C afforded isoxazolines in moderate yields (Scheme-1). It was observed that the formation of minor amount of de-oximination product along with isoxazoles and isoxazolines during the cycloaddition. The methodology found to be equally versatile for intramolecular nitrile oxide cycloaddition (INOC) reactions [5].
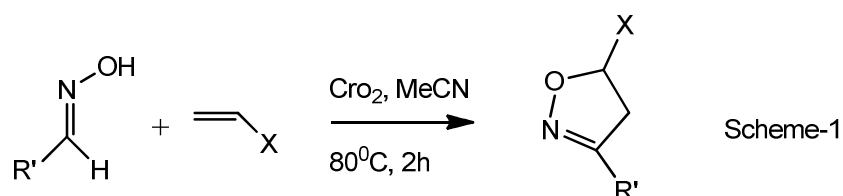

The nitrile oxides generated *in situ* by the oxidative dehydrogenation of aldoximes with chloramine-T reacted with an α, β-unsaturated ketone to afford ethyl 3,5-diarylisoxazole-4-carboxylates. It was observed that the products were formed with unusual elimination of HCN from their expected cycloadduct isoxazolines under reaction conditions (Scheme-2) [6].
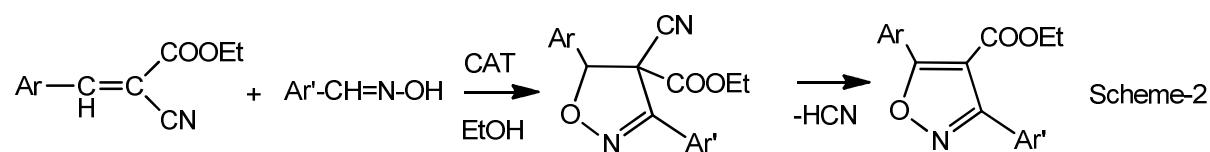
Rai et al [7] reported the synthesis of series 3-Aryl-5*N*-aryl-4,6-dioxo-pyrrolo[3,4-*d*]-7,8-dihydroisooxazolines via 1,3-dipolar cycloaddition of *in situ* generated nitrile oxides with *N*-aryl maleimides (Scheme-3). Later they demonstrated the use of nitrile oxide as a dipolarophile in 1,3-dipolar cycloaddition with acetyl acetone and obtained the substituted isoxazolines in good yield. Here the nitrile oxide gets added to enolic double bond of acetyl acetone (Scheme-3) [8].
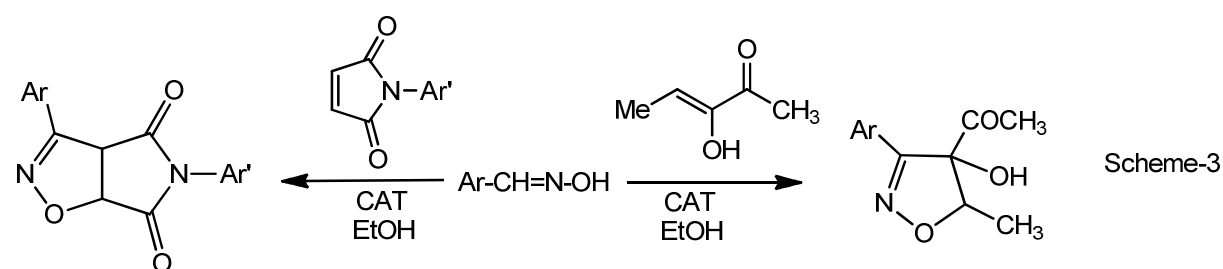

4-Arylidene-3-phenylisoxazol-5-ones were synthesized by three-component condensation of ethyl benzoylacetate, hydroxylamine and aromatic aldehydes in ethanol using DABCO as base under reflux condition (Scheme-4) [9]. It was observed that the good yields were obtained with faster reaction rate with the aldehydes bearing electron-donating groups when compared to aldehydes with electron-withdrawing groups.
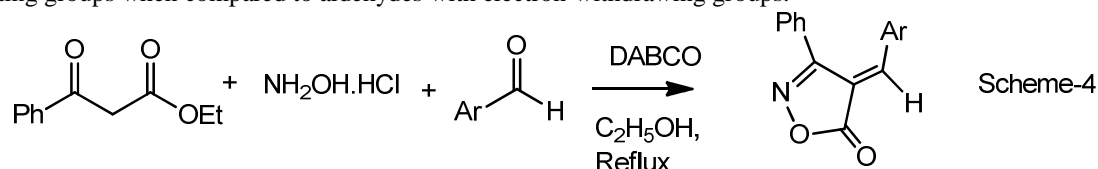

Fluorinated isoxazoline were synthesized in one pot by the reaction of fluorinated chalcones and hydroxylamine in acetic acid medium under reflux conditions (Scheme-5) [10]. The products have been evaluated for their

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antibacterial activities. By introducing fluorine atom into specific position of organic molecule may cause significant changes in the stability, lipophilicity and biological activities of the resulting molecules. This is due to the high electro negativity of halogen, the strong C-F bond and the similar size of halogen and hydrogen atoms.
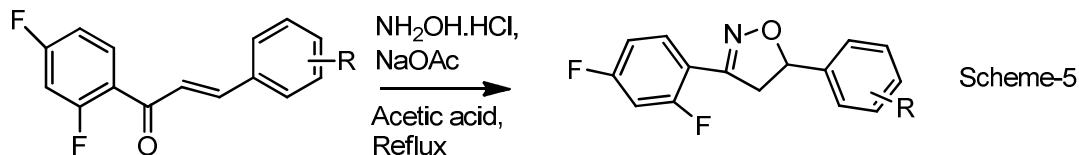
Wei Ming et al synthesized 3,5-disubstituted isoxazolines by mild deselenenylation reaction of isoxazolinyl substituted phenyl selenide, which on treatment with the organic base 1,5-diazabicyclo[5,4,0]-undec-5-ene (DBU) or NaCN afford 5-methyl-3-substituted isoxazole (Scheme-6) [11].
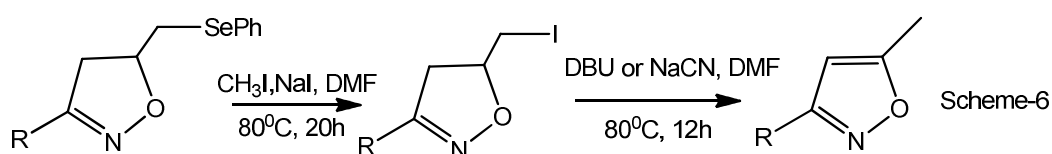
Amar Saad et al [12] reported a simple one step regioselective synthesis of 5-Aminoisoxazoles in toluene using a 1,3-dipolar cycloaddition reaction between nitrile oxides and captodative α-cyanoenamines (Scheme-7). It is a very efficient and simple method for the preparation of 5-aminoisoxazoles.
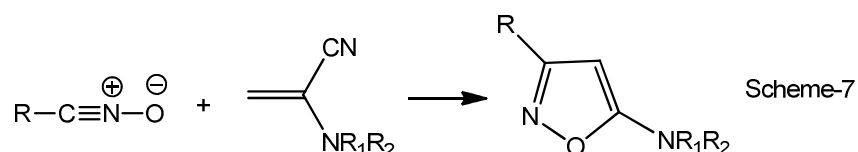
1,3-Dipolar cycloaddition reaction of nitrile oxides generated *in situ* from aldoximes with 4-methoxy cinnamonitrile afforded series of isoxazolines in good yield [13]. The dehydration of primary nitro compounds can be performed by bases in the presence of dipolarophiles. Among the organic bases examined, DABCO gave the best results. The reaction is applicable to activated nitro compounds and to phenylnitromethane and affords isoxazoline derivatives in higher yields compared with those of other methods (Scheme-8). The reaction, however, is not compatible with nitroalkanes [14].
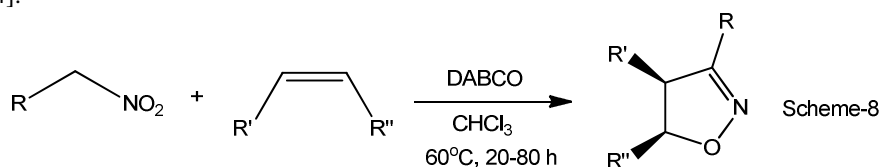
A series of isoxazolines derivatives were synthesised by the reaction of chalcones with hydroxylamine hydrochloride in presence of sodium hydroxide. Then they were transformed into Mannich bases by their reaction with substituted primary amines and formaldehyde for 6-10 h under reflux conditions [15]. A series of 1*H*-3-(4'-substituted phenyl)-5-(6''-methoxynapthaline)-2-isoxazolines were synthesized by reacting 1-(4'-substituted phenyl)-3-(6''-methoxynapthaline)-2-propene-1-one with hydroxylamine hydrochloride (Scheme-9). The synthesised products exhibited significant to moderate antimicrobial activity [16].

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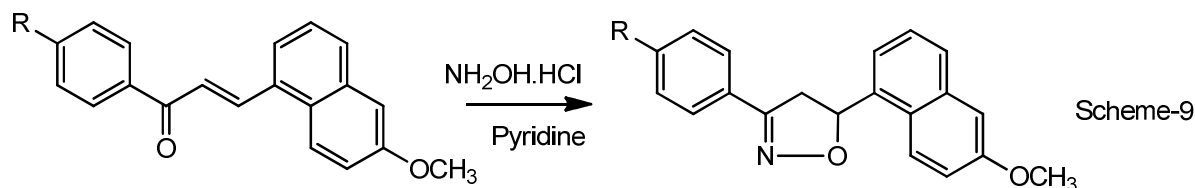
An environmentally benign microwave assisted one pot approach for the synthesis of some 3,5-diaryl-□²-isoxazolines from substituted chalcones with hydroxylamine hydrochloride using basic alumina for its catalytic role as well as energy transfer medium was described. The reaction rate is brought down from hours to minutes along with improved yield as compared to conventional heating [17]. □⁴-Isoxazoline derivatives were synthesized in excellent yields via the titanium tetrachloride–catalyzed 1,3-dipolar cycloaddition reaction of nitrones with α,β-unsaturated compounds under neat conditions at room temperatures in very short reaction time (Scheme-10) [18].


Scheme-10

1-(2-Thienyl)-3-(substituted phenyl)-2-propen-1-one reacts with hydroxylamine hydrochloride and aqueous KOH in presence of ethanol medium to give 3-(2'-thienyl)-5-(substituted phenyl)-2-isoxazoline [19]. 1-Butyl-3-methylimidazolium-based ionic liquids are found to accelerate significantly the intermolecular 1,3-dipolar cycloaddition of *N*-benzyl-fluoro nitrone derived *in situ* from 2,6-difluoro benzaldehyde and *N*-benzylhydroxylamine, with activated alkenes and electron deficient alkynes to afford enhanced rates and improved yields of novel isoxazolines [20].

The reaction of 1,5-diarylpent-1-yne-3, 5-diones or 2,6-diaryl-4H-pyran-4-ones with hydroxylamine in ethanol led to the formation of 5-hydroxisoxazolines as well as isoxazoles as minor products. The isoxazolines could be converted into the latter isoxazoles on prolonged heating in xylene [21]. *tert*-Butyl hypoiodite (*t*-BuOI), generated *in situ* from *t*-BuOCl and NaI, is a powerful reagent for the cycloaddition of oximes to alkenes or alkynes, leading to various isoxazolines or isoxazoles under mild conditions (Scheme-11) [22].


Scheme-11
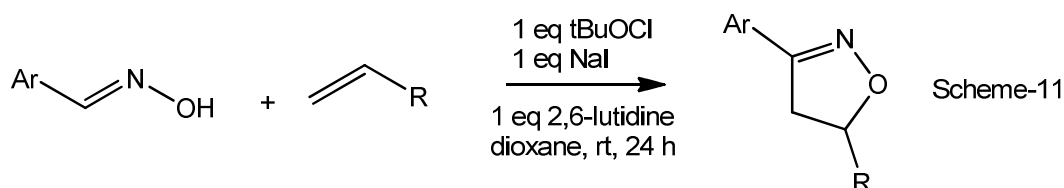
The reaction of substituted 1-(1*H*-indol-3-yl)-3-(substituted aryl)-prop-1-en-3-ones with hydroxylamine hydrochloride under solvent free conditions and microwave irradiation was led to new isoxazoline derivatives. This approach has advantages such as short reaction time, moderate to excellent yield, over the conventional synthesis [23]. 3-Phenylamino-5-(substituted phenyl)isoxazolines (**2**) were prepared by reacting a mixture of purified N-phenyl-3-(substituted phenyl)propenamides, hydroxylamine hydrochloride and a solution of NaOH in dry ethanol by refluxing for 6 h on a water bath [24].

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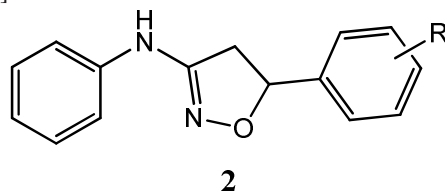
An efficient and simple procedure has been developed for the oxidation of 1,3,5-trisubstituted 4,5-dihydro-isoxazoles to their corresponding aromatic derivatives promoted by bis-bromine-1,4-diazabicyclo[2.2.2]octane complex (DABCO-Br₂) in acetic acid at room temperature. The products 2-pyrazoles and isoxazoles were produced in good to excellent 87-95 % and 78-95 % yields respectively [25]. Iodobenzene diacetate efficiently oxidizes aldoximes to nitrile oxides in MeOH containing a catalytic amount of TFA. Nitrile oxides may be trapped in situ with olefins in a bimolecular or an intramolecular mode. Tandem oxidative dearomatization of

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phenols/intramolecular nitrile oxide cycloaddition sequences lead to useful synthetic intermediates (Scheme-12) [26].

Scheme-12
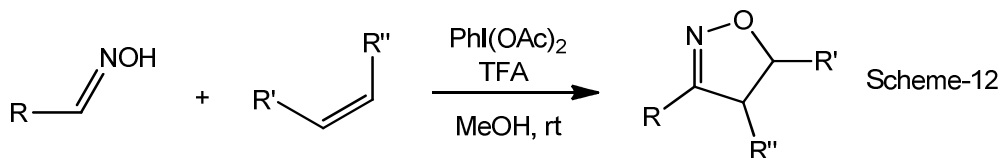
Biologically active isoxazoline derivatives were efficiently synthesized in excellent yields and in smaller reaction times using mild, effective and environmentally friendly butylmethylimidazolium bromide as the solvent and catalyst. By use of this catalyst, isoxazoline derivatives were produced *via* cyclization reaction of a chalcone and hydroxylamine hydrochloride in the ionic liquid media. The separation of the product was facile and the catalyst could be separated and recycled. The method is very rapid, safe and avoids the use of hazardous and expensive reagents and solvents [27]. Unprotected *O*-propargylic hydroxylamines undergo cyclisations when exposed briefly to silver nitrate adsorbed onto silica gel to give 4,5-dihydroisoxazoles [2-isoxazolines] in very good yields, while N-acetyl derivatives give the corresponding 2,5-dihydroisoxazoles [3-isoxazolines] in similar yields (Scheme-13) [28].

Scheme-13
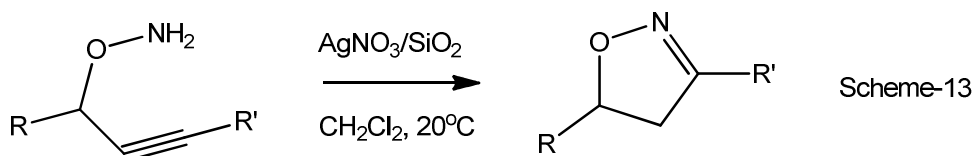
3-Alkylpropargyl or 3-arylpropargyl hydroxylamines hydrochlorides were converted to 2-isoxazolines in good yields in refluxing methanol in the presence of K_2CO_3. Methods for 3-unsubstituted compounds and the direct transformation of *O*-propargyl phthalimide into 2-isoxazolines have been developed [29]. A mild and efficient copper-catalyzed trifluoromethylation reaction which involves the cyclization of oximes has been developed. The method provides a convenient access to a variety of useful CF_3-containing 4,5-dihydroisoxazoles by constructing a C–CF_3 bond and a C–O bond in one step (Scheme-14)[30].

Scheme-14
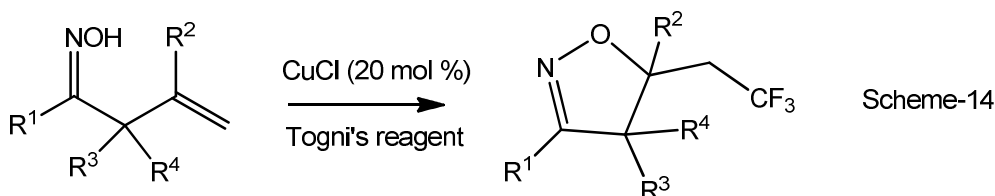
3-Acylisoxazoles were synthesized by the reaction of alkenes or alkynes with ketones (acetone or acetophenone), as both a reagent and the solvent, by three methods: iron(III) nitrate under reflux, iron(III) salt-nitrogen dioxide (NO_2) at room temperature, and iron(III) nitrate under microwave irradiation [31]. The sequential reaction of ketones with arylacetylenes and hydroxylamine in the presence of $KOBu^t$/DMSO followed by the treatment of the reaction mixture with H_2O and KOH leads to Δ^2-isoxazolines in up to 88% yield (Scheme-15) [32].

Scheme-15
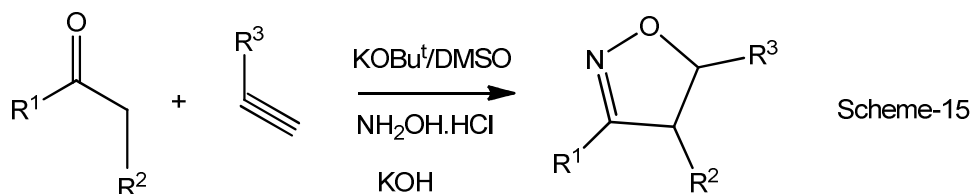
A series of 7-(substituted benzylidene)-3-(substituted phenyl)-3, 3a, 4, 5, 6, 7-hexahydrobenzo[c] isoxazole derivatives were also obtained in quantitative yields by cyclocondensation of substituted α, β-unsaturated cyclohexanone with hydroxylamine hydrochloride under microwave irradiation. The synthesized compounds have shown excellent activity against some Multi Drug Resistant bacteria [33]. Functionalized 3-trifluoromethyl-2-

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isoxazolines and 3-trifluoromethylisoxazoles were easily prepared from trifluoromethyl aldoxime under mild conditions by using DIB as oxidant. Theoretical studies of the reactivity of trifluoroacetonitrile oxide toward olefins and alkynes were carried out. The 3-trifluoromethyl-2-isoxazolines were ring-opened with $NaBH_4$ and $NiCl_2$ to yield the corresponding trifluoromethylated γ-amino alcohols [34].

BIOLOGICAL APPLICATIONS OF ISOXAZOLINES:

Glycosyl nitrile oxides, generated in situ by reaction of glycosyl oximes with N-chlorosuccinimide and DBU, on 1,3-dipolar cycloaddition with substituted alkenes resulted in glycosyl isoxazolines in diastereoselective manner. The extent of diastereoselection varies with the nature of substituents both in sugar and alkenes. The compounds synthesized were screened in vitro against many fungi wherein two of the compounds showed significant inhibition against Sporothrix schenckii, Trychophyton mentagrophytes, and Cryptococcus neoformans with MIC of 12.5 and 6.25mg/mL, respectively [35].

4,5-Diphenyl-4-isoxazolines possessing a variety of substituents (H, F, MeS, MeSO2) at the para position of one of the phenyl rings were synthesized for evaluation as analgesic and selective cyclooxygenase-2 (COX-2) inhibitory antiinflammatory (AI) agents. Although the 4,5-phenyl-4-isoxazolines, which do not have a C-3 Me substituent, exhibited potent analgesic and AI activities. In contrast, 2,3-dimethyl-5-(4-methylsulfonylphenyl)-4-phenyl-4-isoxazoline exhibited excellent analgesic and AI activities, and it was a potent and selective COX-2 inhibitor (36). Isoxazoline derivatives (**3**) were prepared from commercially available 2-hydroxy-aceto-naphthanone were exhibited antibacterial activity against four pathogenic bacteria, two Gram negative bacteria and two Gram positive bacteria. Majority of the isoxazoline analogues exhibited antibacterial activity comparable to ampicillin as reference drug [37].


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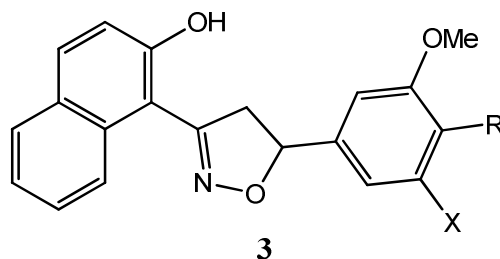
3-Aryl-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitriles (**4**) [38] and 5-Acetyl-3-aryl-4-(2-furanoyl)-4,5-dihydroisoxazoles (**5**) [39] synthesized have been screened for their antibacterial and antifungal activity. Some compounds of the series exhibited promising antibacterial and antifungal activity compared to standard drugs. The substitution of fluoro, chloro, bromo and cyano group C_3-substituted benzene ring of isoxazole ring resulted with potent antimicrobial activities. The compounds also exhibited remarkable antioxidant activity and reducing power ability. A series of 2-(5-phenyl-4,5-dihydroisoxazol-3-yl)benzoic acids (**6**) [40] synthesized were evaluated for their *in vitro* protein denaturation activity. The results of the study showed that all these compounds possess significant anti-arthritic and anti-inflammatory action.

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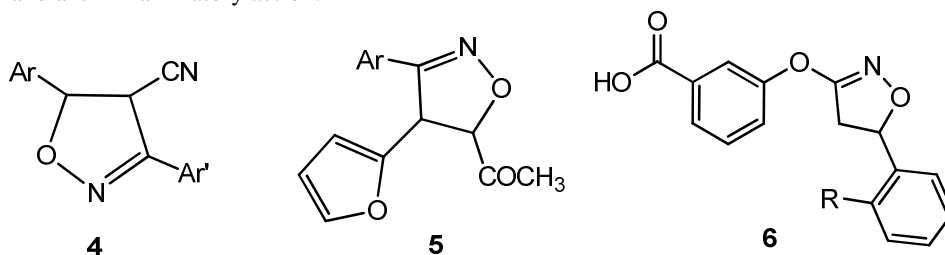
A series of isoxazolines synthesised by 1,3-dipolar cycloaddition exhibited promising antifungal and antibacterial activities [41]. Curcumin-derived isoxazoles (**7**) [42] synthesized were minimize the metal chelation properties of curcumin. Replacement of the 1,3-dicarbonyl moiety with isosteric heterocycles turned curcumin analogue isoxazoles into potent ligands of fibrillar $A\beta_{42}$ aggregates. Curcumin-derived isoxazoles inhibit Aβ secretion, bind to or inhibit the formation of fibrillar $A\beta_{42}$ and tau aggregates. The enhancement in potency in comparison with curcumin is 10-100-fold. It is apparent from these data that curcumin-derived isoxazoles have multiple targets in

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Alzheimer's disease. The multifunctional curcumin–isoxazole 1 displayed interesting properties as an Aβ - modulating agent in primary neuronal cultures.

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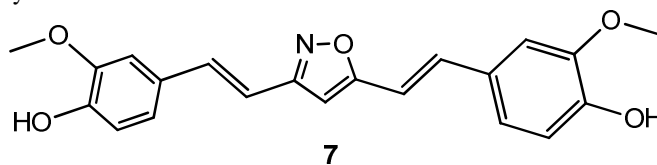
A series of 3-[3-(2,4-dichloro-5-fluorophenyl)-5-(2-furyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-5-(substituted phenyl/2-thienyl)isoxazolines prepared were screened for their *in vitro* antibacterial activity using gram-positive bacteria and gram-negative bacteria [43]. A series of novel 4-(5′-substituted-aryl-4′,5′-dihydro-isoxazole-3′-yl-amino) phenols (**8**) [44] synthesized were investigated for their analgesic and antimicrobial activities. The molecular modification might result in detection of new potential antimicrobial and analgesic drugs were observed. The substitution appeared to be most important for high order of activity in the greatest number of test was the *p*-choloroaryl group. The substitution of *p*-nitrophenyl and *p*-hydroxyphenyl group at 5-position of isoxazoline ring resulted with potent analgesic and antimicrobial activities.

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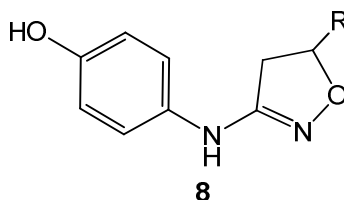
A series of tetracyclic nitrofuran isoxazoline anti-tuberculosis agents were designed to improve the pharmacokinetic properties of an initial lead compound, which had potent anti-tuberculosis activity but suffered from poor solubility, high protein binding and rapid metabolism. The structural modifications were carried on the outer phenyl and piperidine rings to introduce solubilizing and metabolically blocking functional groups. The compounds generated were evaluated for their in vitro antitubercular activity, bacterial spectrum of activity, solubility, permeability, microsomal stability and protein binding. Compounds with phenyl morpholine and pyridylmorpholine outer rings were found to be the most potent anti-tuberculosis agents. These compounds retained a narrow antibacterial spectrum of activity, with weak anti-Gram positive and no Gram negative activity, as well as good activity against non-replicating Mycobacterium tuberculosis in a low oxygen model. The addition of solubilizing and metabolically blocked outer rings did improve solubility and decrease protein binding as designed [45].

A novel class of activators for chloride conductance in the cystic fibrosis transmembrane conductance regulator (CFTR) protein has been identified. These 3-(2-benzyloxyphenyl)isoxazolines were synthesized employing the 1,3-dipolar cycloaddition of nitrile oxides with various alkene dipolarophiles. Utilizing a fluorescence cell-based assay of halide transport, the best compounds increased CFTR-dependent chloride transport with half-maximal stimulation at 20-50 microM [46].

CONCLUSION

The isoxazoline moiety is an important pharmacophore in modern drug discovery. This review gives an overview of the synthetic strategies developed to obtain biologically potential molecules, pharmacological studies carried out and medicinal applications of isoxazolines, appears to be useful for further research work on the bioactive isoxazoline systems.

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