INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

ISOXAZOLES: MOLECULES WITH POTENTIAL MEDICINAL PROPERTIES

K. Ajay Kumar and P. Jayaroopa*

Post Graduate Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore-570 005, India.

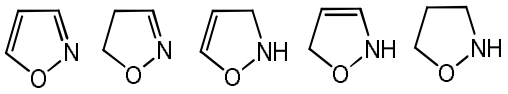
ABSTRACT

Isoxazole is a five membered heterocyclic compound having various pharmacological actions. The great interest associated with isoxazoles and their derivatives is based on their versatility as synthetic building blocks, their latent functionalities as enaminones, 1,3-dicarbonyl compounds, γ-amino alcohols, and β-hydroxy nitriles have been widely exploited for the synthesis of other heterocycles and complex molecules. This review paper comprises of up to date information on isoxazole analogs. More emphasis was given to critical discussion on the synthetic strategy of isoxazole derivative, their utility as building blocks in their transformation to more biologically potent molecules. Results of isoxazole derivatives and their substitutions effect on diverse biological activities also presented.

Keywords: Isoxazoles, antioxidant, antimicrobial, analgesic, anti-platelet, anti-HIV.

INTRODUCTION

Nitrogen containing heterocycles with an oxygen atom are considered as an important class of compounds in medicinal chemistry because of their diversified biological applications. 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**).



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

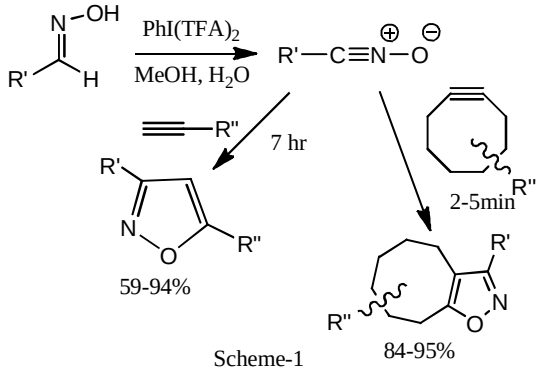
Isoxazoles are an important class of heterocycles, which are largely employed in the area of pharmaceuticals and therapeutics such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic. Isoxazole derivatives are used in the market as COX-2 inhibitor and anti-inflammatory drugs. Isoxazole derivatives such as sulfamethoxazole, sulfisoxazole, oxacillin, cycloserine and acivicin have been in commercial use for many years. Cycloserine is the best known antibiotic drug that possess antitubercular, antibacterial activities and in treatment of leprosy. Acivicin is an antitumour, antileishmania drug, while isoxaflutole is used as herbicidal drug.

Isoxazoles have illustrious history; their chemistry is associated with Ludwig Claisen, who first recognized the cyclic structure of 3-methyl-5-phenylisoxazole in 1888 and was shown to possess typical properties of an aromatic system under certain reaction conditions; particularly in basic media, it is very highly labile. Dunstan and Dymond were the first to synthesize the isoxazole ring[1]. They isolated a liquid base by heating nitroethane with aqueous alkalies to obtain 3,4,5-trimethylisoxazole. A very significant contribution to the development of isoxazole chemistry came between 1930–1946 from Quilico's studies on the synthesis of ring system from nitrile oxides and unsaturated compounds[2].

SYNTHESIS OF FUNCTIONALIZED ISOXAZOLES

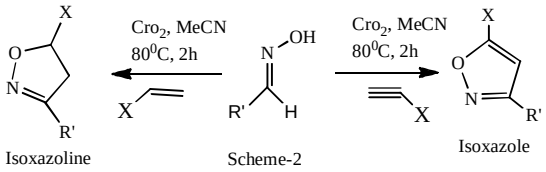
Diverse applications associated with isoxazole moiety led the researchers to develop various novel synthetic approaches for the synthesis of isoxazole ring systems. For instance, recent

review by Ajay Kumar et al[3-5] reports the use of nitrile oxides as versatile intermediates in the synthesis of isoxazole derivatives. Oximes on treatement with $PhI(OCOCF_3)_2$ (hypervalent iodine) leads to rapid formation of nitrile oxides which were trapped *in situ* with terminal and cyclic alkynes efficiently to give 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles in high yield (Scheme-1). The procedure is experimentally convenient, avoids the isolation and handling of potentially harmful and unstable hydroximoyl chlorides[6].



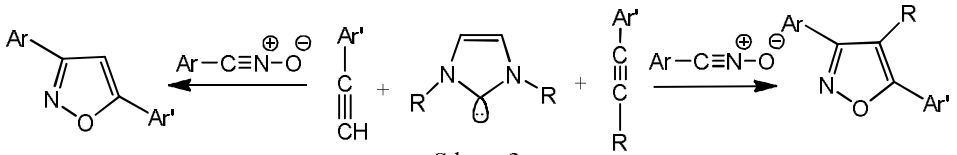
Scheme-1

Sandeep Bhosale et al[7] synthesized isoxazoles and isoxazolines via 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides generated *in situ* by treatment of aldoximes with Magtrieve™ (CrO_2) in either toluene or MeCN at 80°C (Scheme-2). They observed the formation of minor amount of deoximation product along with isoxazoles and isoxazolines. Their methodology has been shown to be equally versatile for intramolecular nitrile oxide cycloaddition (INOC) reactions.



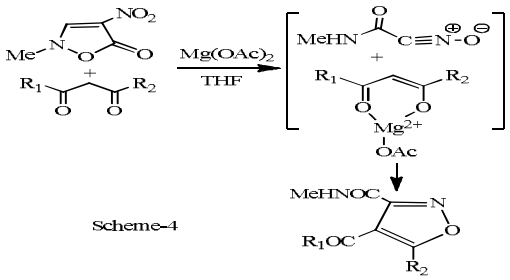
Scheme-2

Shravankumar and co-workers reported a facile catalytic approach to synthesize regioselectively both 3,5-di- and 3,4,5-trisubstiututed isoxazoles in high yields which involve the nucleophilic organo-NHC-catalyzed 1,3-dipolar cycloaddition of nitrile oxide with alkynes. Triethylamine (Et_3N) was employed as an effective base to generate both nitrile oxide and the organo-NHC *in situ* (Scheme-3)[8]. The multinucleus structures like isoindole linked disubstituted isoxazoles and sterically crowded trisubstituted isoxazoles can be accessed easily selectively by this method, which could be useful in biology and material science.



Scheme-3

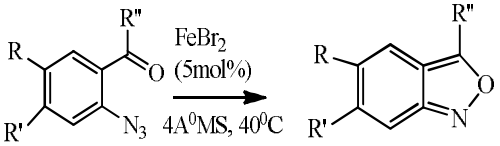
Nagatoshi Nishiwaki et al[9] reported one-step synthesis of different functionalized isoxazoles by cycloaddition of carbamoylnitrile oxide with β-keto esters. Among several salts, magnesium acetate was found to be the most efficient promoter affording isoxazole in 80% yield (Scheme-4). Carbamoylnitrile oxide generated from nitroisoxazolone underwent inverse electron-demand 1,3-dipolar cycloaddition with 1,3-dicarbonyl compounds in the presence of magnesium acetate that formed magnesium enolate *in situ*.



Scheme-4

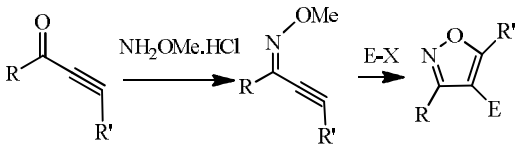
Bhaskar Chakraborty and co-workers[10] reported an aqueous phase cycloaddition reaction. They synthesized and studied the antibacterial activities of some novel isoxazolidine derivatives by 1,3-dipolar cycloaddition reaction of nitrones with different dipolarophiles in water. Significant rate acceleration and high yield of these reactions are observed in water

with remarkable changes in stereo and regioselectivity compared to organic solvents. They have provided a green synthesis avoiding use of organic solvents. Stokes and co-workers[11] reported that iron (II) catalyzes the formation of N-O bonds to transform azides into 2,1-benzisoxazoles under markedly benign conditions (Scheme-5).



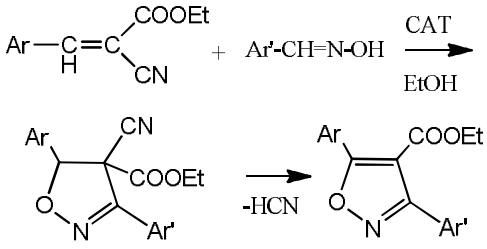
Scheme-5

Highly substituted isoxazoles can be formed in good to excellent yields using mild reaction conditions. For instance, 3,5-disubstituted 4-halo (seleno) isoxazoles have been synthesized by the reaction of various 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2, or PhSeBr (Scheme-6)[12].



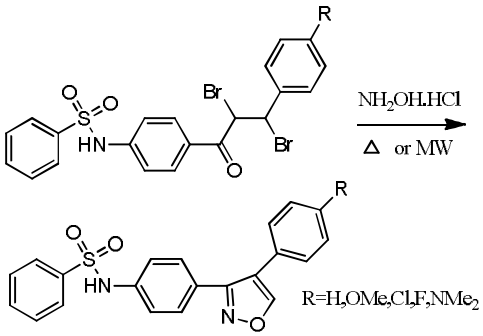
Scheme-6

Rai et al[13] reported that nitrile oxides generated *in situ* by the oxidative dehydrogenation of aldoximes with chloramine-T reacted with α,β-unsaturated compounds to afford ethyl 3,5-diarylisoxazole-4-carboxylates which exhibited remarkable antimicrobial activity. In a typical reaction an equimolar mixture of aldoxime, α,β-unsaturated compounds and chloramine-T trihydrate in ethanol was refluxed on a water bath for 3 hours. After the completion of the reaction, the unusual cycloadducts were obtained in good yield. The products formed with unusual elimination of HCN under reaction conditions (Scheme-7).



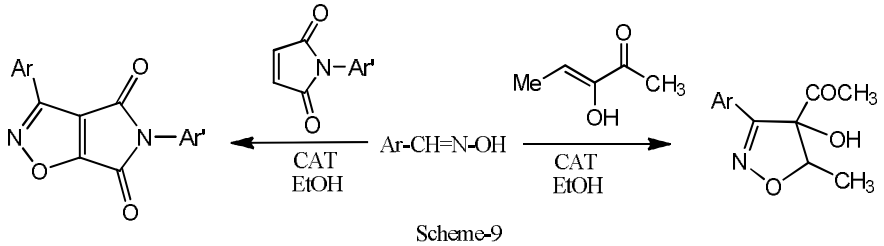
Scheme-7

N-(4-(5-Arylisoxazol-3-yl)phenyl)-benzenesulfonamides were synthesized under conventional heating and microwave irradiation (Scheme-8)[14]. The method was found to be fast, efficient and economical. The reaction proceeded smoothly with better yields under microwave irradiation within 5-6 minutes; while under reflux conditions it required 6-8 hrs.



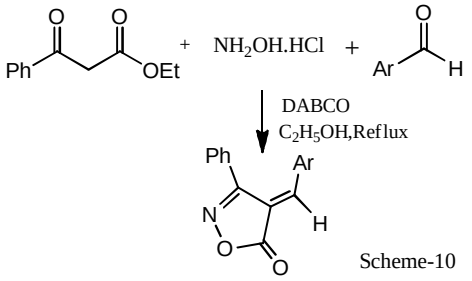
Scheme 8

A series of thirteen cycloadducts 3-Aryl-5*N*-aryl-4,6-dioxo-pyrrolo*[*3,4-*d*]-7,8-dihydroisooxazolines were synthesized by the reaction of *in situ* generated nitrile oxides obtained from the catalytic dehydrogenation of aldoximes with chloramine-T on *N*-aryl maleimides (Scheme-9)[15]. 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-9)[16].



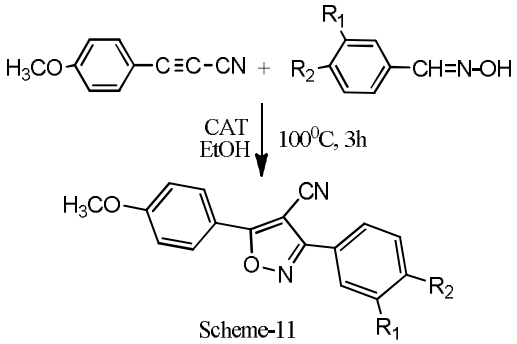
Scheme-9

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-10)[17]. 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.



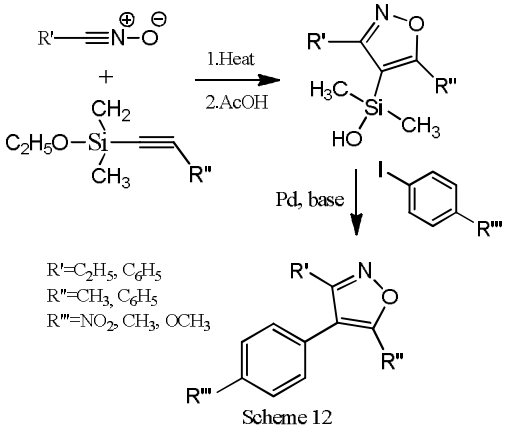
Scheme-10

Recently Vasanth Kumar et al[18] synthesized a series 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 in moderate yield (Scheme-11). The cycloadducts formed were tested for their antibacterial and antifungal activity against different organism.



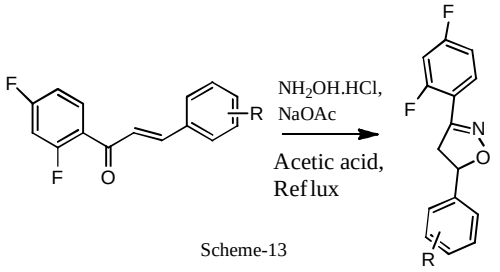
Scheme-11

Scott ED et al[19] developed sequential [3+2]-cycloaddition and cross-coupling reactions for the preparation of 3,4,5-trisubstituted isoxazoles. The reaction between alkynyldimethyl silyl ethers and aryl and alkyl nitrile oxides produce isoxazolylsilanols. The cross-coupling reactions of these heterocyclic silanols with a variety of aryl iodides affords 3,4,5-trisubstituted isoxazoles (Scheme-12). Both alkyl and aryl substituents at the 3- and 5-positions of the isoxazole were selectively incorporated based on the choices of the dipole and dipolarophile. In the development of the cross-coupling reaction conditions, the use of $Cu(OAc)_2$ effected the rate of the cross-coupling reaction; however, in some cases, $Cu(OAc)_2$ also promoted the protodesilylation of the silanol.



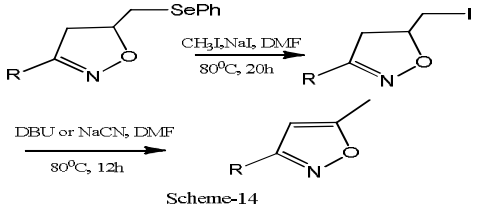
Scheme 12

Fluorinated isoxazoline were synthesized in one pot by the reaction of fluorinated chalcones and hydroxylamine in acetic acid medium under reflux conditions (Scheme-13)[20]. The products have been evaluated for their 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 the halogen, the strong C-F bond and the similar size of the halogen and hydrogen atoms.



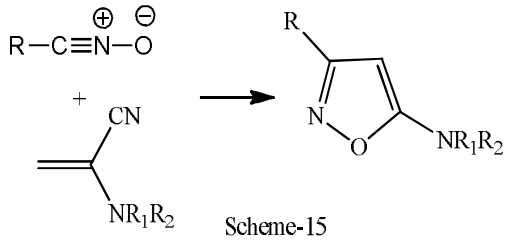
Scheme-13

Wei Ming XU etal 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-14)[21].



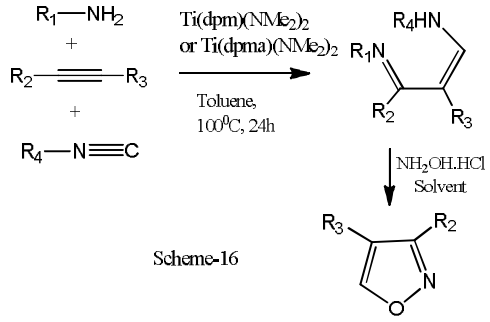
Scheme-14

Amar Saad et al[22] 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-15). It is a very efficient and simple method for the preparation of 5-aminoisoxazoles.



Scheme-15

The regioselective synthesis of 4-substituted isoxazoles from terminal alkynes and 3,4-disubstituted isoxazoles from internal alkynes using one-pot titanium catalyzed 3-component coupling (3CC) reaction in conjunction with hydroxylamine hydrochloride addition (Scheme-16) was reported[23]. The products are easily isolated in pure form after the one pot synthesis.

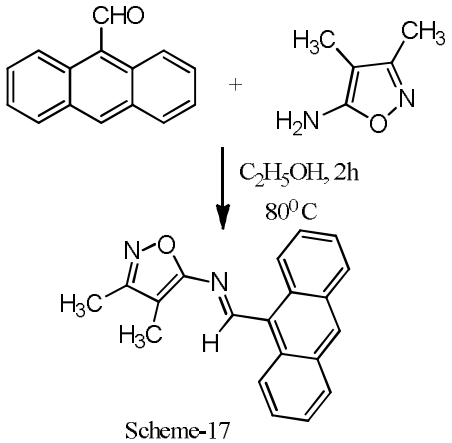


Scheme-16

Ajay Kumar and co-workers[24] reported the synthesis of series of isoxazoles starting from chalcones. The chalcones prepared by the reaction of aromatic aldehydes and acetophenone were converted to dibromo derivatives with bromine-acetic acid and then dibromo derivatives were treated with triethyl amine to get alkyne derivatives. The alkyne derivatives on 1,3-dipolar cycloaddition reaction with nitrile oxides generated in situ from aldoximes afforded isoxazoles in good yield. The isoxazoles were screened and showed promising antimicrobial activities against different organisms. Recently, they successfully transformed 4-methoxy cinnamonitrile to a series of isoxazolines through the Huisgen cycloaddition with nitrile oxides[25].

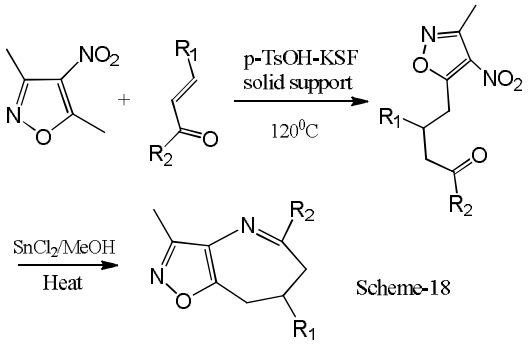
REACTIONS OF ISOXAZOLES

Isoxazoles, isoxazolines and isoxazolidines were considered as useful synthons in organic synthesis. They have been efficiently transformed in to various classes of medicinally important molecules. For instance, Anthracen-9-ylmethylene-(3,4-dimethylisoxazol-5-yl) amine was synthesized in high yield by reaction of anthracene-9-carbaldehyde and 5-amino-3,4-dimethylisoxazole in ethanol (Scheme-17)[26].



Scheme-17

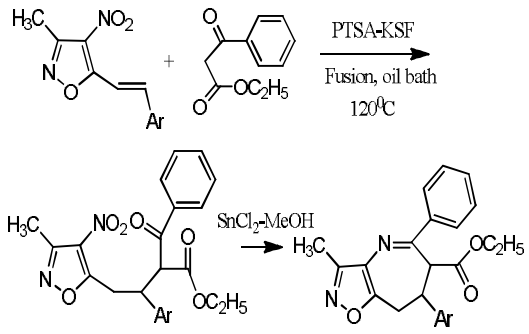
Isoxazoloazepines were synthesized via Michael addition followed by reductive cyclisation. For Michael addition, a convenient and highly efficient protocol was developed by using *p*-TsOH adsorbed on KSF solid support under solvent-free conditions with a variety of Michael donors and acceptors. *p*-TsOH-KSF solid support is found to be a much better alternative to effect the Michael reaction in terms of better yields (85%) and short reaction times (2 hr). The Michael adducts underwent reductive cyclization on treatment with $SnCl_2$-MeOH to afford substituted isoxazolo[4,5-*b*]azepines in high yields (Scheme-18)[27].



Scheme-18

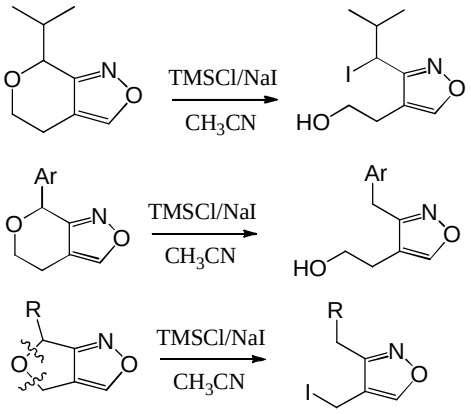
Isoxazoloazepines are also synthesized by conducting Michael reaction in presence of PTSA absorbed on KSF and the resulting Michael

adducts are converted to isoxazoloazepines by reductive cyclization process with $SnCl_2$-MeOH in a one-pot reaction. This procedure offers significant improvement over the existing Michael reactions. All the reactions are clean, high yielding and the method is mild and tolerates several substituents on aromatic ring and devoid of forming any undesired side products (Scheme-19)[28].



Scheme-19

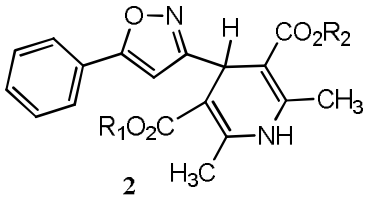
3,4-disubstituted isoxazole derivatives were synthesized from the reductive cleavages of 4,5-dihydro-7H-pyrano[3,4-c]isoxazoles.
Pyrano[3,4-c]isoxazole, upon treatment with TMSCl/NaI in acetonitrile undergoes selective C-O bond cleavage to furnish 3,4-disubstituted isoxazole in high yield without damaging the isoxazole ring whereas furo[3,4-c]isoxazoles with TMSCl/NaI in acetonitrile results in the formation of a reduced iodide and a hydroxyl iodide (Scheme-20)[29].



Scheme-20

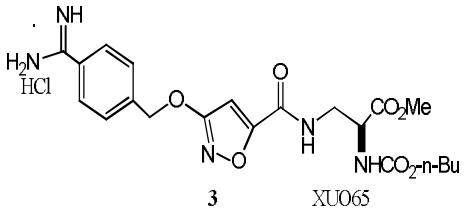
APPLICATIONS OF ISOXAZOLES

A series of dialkyl 1,4-dihydro-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)pyridine-3,5-dicarboxylates (**2**)[30] synthesized have studied for *in vitro* calcium channel antagonist activities. *In vitro* calcium channel antagonist activities (IC_{50}) were evaluated as the molar concentration of the test compounds required to produce 50% inhibition of the high K^+ concentration of guinea-pig ileum longitudinal smooth muscle (GPILSM) assay. These compounds exhibited moderate calcium antagonist activity (IC_{50} = 10^{-7} to 10^{-5} M range) relative to the reference drug nifedipine (IC_{50} = $1.10 \pm 0.40 \times 10^{-8}$ M).



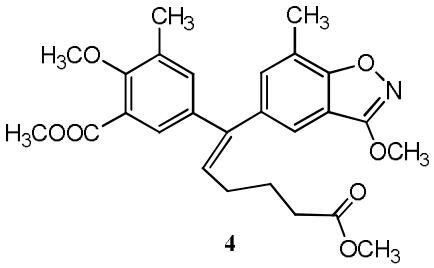
2

Isoxazole series of glycoprotein IIb/IIIa antagonists were synthesized and their antiplatelet effects were studied. The replacement of the benzamide in **XUO57** with an isoxazolecarboxamide afforded **XUO65** (**3**)[31] which showed a significant improvement in in-vivo potency in the inhibition of platelet aggregation. The analogue **XUO65** showed an excellent oral antiplatelet effect in dogs. Following an iv bolus administration of **XUO65** to dogs at a dose of 0.5mg/kg, **XUO65** exhibited a maximum inhibition of ex vivo ADP (100μM) induced platelet aggregation, which was maintained for over 3h.Maximal inhibition of platelet aggregation was achieved and maintained for up to 5h after an oral dose of 1.6mg/kg.



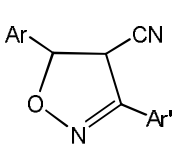
3 XUO65

A series of alkenyldiarylmethanes (ADAMs) with a benzo[*d*]isoxazole and oxazolidine-2-ones synthesized were evaluated for anti-HIV activities and metabolic stabilities. The resulting ADAMs were found to inhibit HIV-1 RT with poly(rC)·oligo(dG) as the template primer. Among these ADAMs, Methyl 5-((*Z*)-5-(methoxycarbonyl)-1-(3-methoxy-7-methylbenzo[d]isoxazole-5-yl) pent-1-enyl-2-methoxy-3-methylbenzoate (**4**)[32] exhibited anti-HIV-1 activity with EC_{50} values in the 20–40 nanomolar range. It also inhibited HIV-1 reverse transcriptase with an IC_{50} of 0.91 μM.

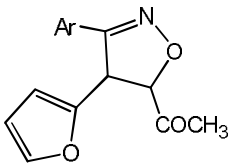


4

3-Aryl-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitriles (**5**)[33] and 5-Acetyl-3-aryl-4-(2-furanoyl)-4,5-dihydroisoxazoles (**6**)[34] 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.

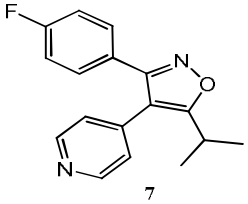


5

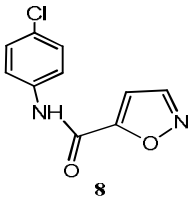


6

Substituted isoxazole (**7**)[35] which was originally designed and characterized as ATP competitive $p^{38\alpha}$ 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 IC_{50} value of 0.23 μM. Novel *N*-(phenyl)-5-carboxamidyl isoxazoles synthesized were examined for their anticancer activity *in vitro*. *N*-(4-Chlorophenyl)-5-carboxamidyl isoxazole (**8**)[36] showed promising *in vitro* cytotoxicity and solid tumor selectivity. 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.

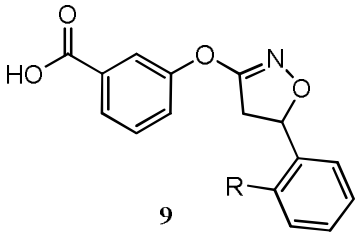


7



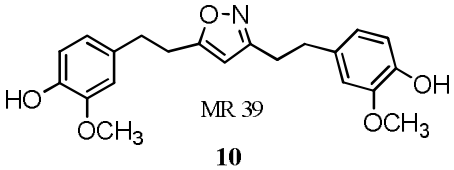
8

A series of 2-(5-phenyl-4,5-dihydroisoxazol-3-yl)benzoic acids (**9**)[37] 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.



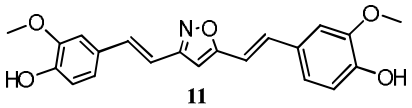
9

The effects of curcumin and of its isoxazole analogue MR 39 (**10**)[38] in the MCF-7 breast cancer cell line and in its multidrug-resistant (MDR) variant MCF-7R were examined. The isoxazole analogue (MR 39) has shown more potent antitumor and molecular activities both in parental and in MDR tumor cells. MR 39 produces significantly higher direct inhibition of the COX-2 catalytic activity than curcumin.

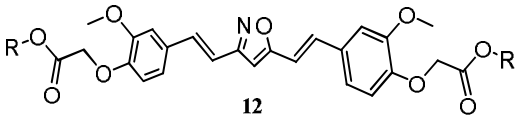


10

Curcumin-derived isoxazoles (**11, 12**)[39] synthesized which 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 Alzheimer's disease. The multifunctional curcumin–isoxazole 1 displayed interesting properties as an Aβ -modulating agent in primary neuronal cultures.

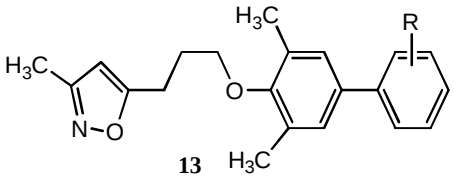


11



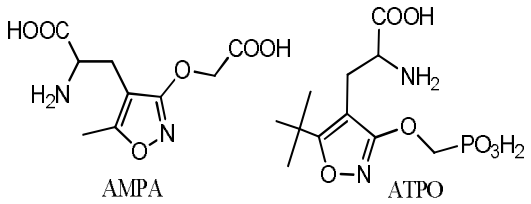
12

[(Biphenyloxy)propyl]isoxazoles (**13**)[40] derivatives of pleconaril with various substituents and substitution patterns at the terminal benzene ring where the oxadiazole ring of pleconaril has been replaced with a substituted phenyl ring synthesized were showed excellent anti-HRV-2 and moderate anticoxsackievirus B3 activity. The antiviral activity of these novel analogues has been determined against pleconaril- resistant as well as pleconaril-susceptible CVB3, HRV-2 and HRV-14. These results indicate that these derivatives are potential inhibitors of HRV-2 and CVB3 replication, and make them promising agents for the specific treatment of these virus infections. These new biphenyl analogues offer the opportunity for the development of highly selective anti-rhinovirus agents.



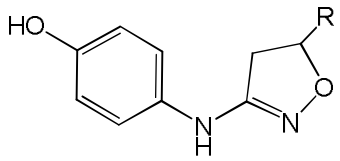
13

((*R,S*)-2-Amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid) AMPA (**14**)[41] and ((*R,S*)-2-Amino-3-[5-*tert*-butyl-3-(phosphonomethoxy)-4-isoxazolyl]propionic acid) ATPO (**15**)[41] were tested for receptor antagonist at recombinant ionotropic glutamate receptors (GluRs) using electrophysiological techniques. The pharmacology of their AMPA receptor antagonist ATPO was described by comparing effects of ATPO on currents through homo- and heterooligomeric AMPA- and KA-preferring GluRs expressed in *Xenopus laevis* oocytes and mammalian cell lines. The results indicate that ATPO has a unique pharmacological profile, being a potent competitive antagonist of AMPA-preferring receptors (GluR1–4) devoid of activity at GluR6 and GluR6/KA2 and with slight agonist activity at GluR5 and GluR5/KA2.



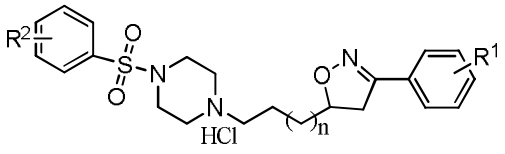
14 **15**

A series of novel 4-(5′-substituted-aryl-4′,5′-dihydro-isoxazole-3′-yl-amino) phenols (**16**)[42] synthesized were investigated for their analgesic and antimicrobial activities. The purpose of the study was to examine whether molecular modification might result in detection of new potential antimicrobial and analgesic drugs. The substitution which 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 isoxazole ring resulted with potent analgesic and antimicrobial activities.

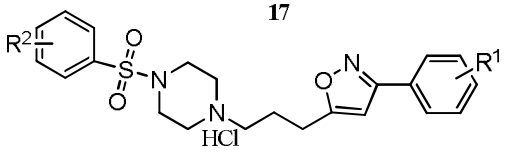


16

Isoxazoline (**17**)[43] and isoxazole derivatives (**18**)[43] synthesized and biologically evaluated in order to find antagonists of 5-HT_{2A} and 5-HT_{2C} receptors, which are known as good targets for the improved treatment of depression [Fig-13]. In particular, an isoxazoline with *o*-Me group as an R^2 substituent and 3, 5-dichloro substituent at R^1 shows the most potent binding affinities to both 5-HT_{2A} and 5-HT_{2C}, of which IC_{50} values were 72 nM and 150 nM, respectively59.



17



18

CONCLUSIONS

The isoxazole ring is an important pharmacophore in modern drug discovery. This review gives an overview of the various synthetic routes used to form a biologically rich isoxazole moiety as well as the reactions the molecule undergoes to yield various other important molecules. This paper proves to be significant for further research work on the bioactive isoxazole ring.

REFERENCES

1. Dunstan WR and Dymond TS. The action of alkalis on the nitro-compounds of the paraffin series. Formation of isoxazoles. J Chem Soc. 1891;59:410-433.
2. a) Quilico A, Stagno d'Alcontres G and Grunanger P. A New Reaction of Ethylenic Double Bonds. Nature. 1950;166: 226-227 : b) Quilico A, Gazz MF. Chim Ital. 1930;60: 172.
3. Ajay Kumar K, Govindaraju M, Jayaroopa P and Vasanth Kumar G. Nitrile oxides: A key intermediate in organic synthesis. Int J Pharma Chem Bio Sci. 2013;3(1):91-101.
4. Ajay Kumar K, Renuka N and Vasanth Kumar G. Thiadiazoles: Molecules of diverse applications-A review. Int J PharmTech Res. 2013;5(1):239-248.
5. Ajay Kumar K, Lokeshwari DM, Pavithra G and Vasanth Kumar G. 1,2,4-Oxadiazoles: A potential pharmacological agents-An overview. Res J Pharm Tech. 2012;5(12):1490-1496.
6. Jawalekar AM, Reubsaet E, Rutjes Floris PJT and van Delft FL. Synthesis of isoxazoles by hypervalent iodine-induced cycloaddition of nitrile oxides to alkynes. Chem Commun. 2011;47:3198-3200.
7. Sandeep B, Santosh K, Uppuleti VP, Venkata PP and Debnath B. Efficient synthesis of isoxazoles and isoxazolines from aldoximes using Magtrieve (CrO_2). Tetrahedron Lett. 2009;50: 3948-3951.
8. Shravankumar K, Ravinder V, Chandra Sekhar V. N-Heterocyclic carbine-catalyzed 1,3-dipolar cycloaddition reactions: a facile synthesis of 3,5-di and 3,4,5-trisubstituted isoxazoles. Org Biomol Chem. 2011;9:7869-7876.
9. Nagatoshi N, Kazuya K, Shotaro H, Jun S, Kazuhiko S, Yumiko I, Maho N and Masahiro A. One-step synthesis of differently bis-functionalized isoxazoles by cycloaddition of carbamoylnitrile oxide with β-keto esters. Org Biomol Chem. 2012;10: 1987-1991.
10. Bhaskar Chakraborty, Manjit Singh Chhetri, Saurav Kafley and Amalesh Samanta. Synthesis and antibacterial activities of some novel isoxazolidine derivatives derived from N-phenyl-α-chloro nitrone in water. Indian J Chemistry. 2010;49B:209-215.
11. Stokes BJ, Vogel CV, Urnezis LK, Pan M and Driver TG. Intramolecular Fe(II)-catalyzed N–O or N–N bond formation from aryl azides. Org Lett. 2010;12(12): 2884-2887.
12. Waldo JP and Larock RC. Synthesis of isoxazoles via electrophilic cyclization. Org Lett. 2005;7:5203-5205.
13. Ajay Kumar K, Lokanatha Rai KM and Umesha K. Synthesis and evaluation of antifungal and antibacterial activity of ethyl 3,5-diarylisoxazole-4-carboxylates. Journal Chem Res (S). 2001;436-438.
14. Hemant S Chandak. Synthesis of Isoxazolyl-benzenesulfonamide derived from N -[4-(2,3-dibromo-3-aryl-propanoyl)-phenyl]benzenesulfonamide. Der Pharma Chem. 2012;4(3):1054-1057.
15. Ajay Kumar K, Lokanatha Rai KM, Umesha KB and Prasad KR. Synthesis of 3-aryl-5N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7,8-dihydroisoxazoles. Ind J Chem. 2001;40B: 269-273.
16. Umesha KB, Lokanatha Rai KM and Ajay Kumar K. Synth Commun. A novel synthesis of isoxazoles via 1,3-dipoar cycloaddition of nitrile oxides to acetyl acetone. 2002;32(12):1841-1846.
17. Maryam M and Gholam HM. Fast and Efficient Synthesis of 4-Arylidene-3-phenylisoxazol-5-ones. E-Journal of Chemistry. 2012;9(1): 425-429.
18. Vasanth Kumar G, Jayaroopa P, Bi Bi Ahmadi Khatoon, Mylarappa BN and Ajay Kumar K. Synthesis of 3,5-diaryl-isoxazole-4-carbonitriles and their efficacy as antimicrobial agents. Der Pharma Chem. 2012;4(6):2283-2287.
19. Scott ED and Jeffrey MK. Synthesis of 3,4,5-trisubstituted isoxazoles via sequential [3+2] cycloaddition/silicon-based cross-coupling reactions. J Org Chem. 2005;70: 2839-2842.
20. Kadnor VA, Pandhare GR, Gadhave AG, Uphade BK. Synthesis and antibacterial activity of some fluorinated isoxazoline. Rasayan J Chem. 2011;4(2):437-441.
21. Xu WM, Wang YG, Chen ZH and Huang X. An efficient deselenenylation reaction to the synthesis of 3, 5-disubstituted isoxazoline and isoxazole. Chin Chem Lett. 2005;16(8):995-996.
22. Amar S, Michel V and Aicha D. One step regioselective synthesis of 5-aminoisoxazoles from nitrile oxides and α-cyanoenamines. Molecules.2004;9(7): 527-534.

23. Amila AD and Aaron LO. Regioselective conversion of alkynes to 4-substituted and 3,4-disubstituted isoxazoles using titanium catalysed multicomponent coupling reactions. Tetrahedron. 2012;68(43):807-812.
24. Ajay Kumar K, Govindaraju M and Vasantha Kumar G. Synthesis of isoxazoles via 1,3-dipolar cycloaddition reactions and their antimicrobial activity. Indian J Heterocycl Chem. 2010;20:183-184.
25. Jayaroopa P, Vasanth Kumar G, Renuka N and Ajay Kumar K. Synthesis of new 3,5-diaryl-4,5-dihydroisoxazole-4-carbonitriles via 1,3-dipolar cycloaddition reaction. IOSR J App Chem. 2012;1(4):20-23.
26. Abdullah MA and Salman AK. Anthracen-9-ylmethylene-(3,4-dimethylisoxazol-5-yl)amine. Molbank. 2011, 2011(3), M736. doi:10.3390/M736.
27. Rajanarendar E, Ramesh P, Kalyan Rao E, Mohan G and Srinivas M. p-TsOH catalysed KSF solid supported Michael addition with substituted isoxazoles and their reductive cyclisation to isoxazolo[4,5-b]azepines. Arkivoc. 2007;(xiv): 266-275.
28. Rajanarendar E, Ramesh P, Firoz PS and Srinivas M. PTSA catalyzed KSF solid supported michael addition onstyrylisoxazoles and their reductive cyclization to azepines. Heterocyclic Lett. 2011;1(1):17-24.
29. Kyong HC, Young JL and Hyung JK. Synthesis of 3,4-disubstituted isoxazoles by reductive leavage of bicyclic isoxazole derivatives with TMSCl/NAI. App Chem. 1998;2(1):417-420.
30. Daryabari N, Akbarzadeh T, Amina M, Miri R, Mirkhani H and Shafiee A. Synthesis and Calcium channel antagonist activities of new derivatives of dialkyl 1,4-dihydro-2,6-dimethyl-4-(5-phenylisoxazol-3-yl)pyridine-3,5-dicarboxylates. J Iran Chem Soc. 2007;4(1):30-36.
31. Xue C-B, Roderick J, Mousa S and Olson RE, DeGrado WF. Synthesis and antiplatelet effects of an isoxazole series of glycoprotein IIb/IIIa antagonists. Bioorg Med Chem Lett. 1998;8(24), 3499-3504.
32. Bo-Liang Deng, Zhao Y, Hartman TL, Watson K, Buckheit Jr. RW, Pannecouque C, De Clercq E and Cushman M. Synthesis of alkenyldiarylmethanes (ADAMs) containing benzo[d]isoxazole and oxazolidin-2-one rings, a new series of potent non-nucleoside HIV-1 reverse transcriptase inhibitors. Eur J Med Chem. 2009;44(3):1210-1214.
33. Jayaroopa P, Vasanth Kumar G, Renuka N, Akshatha KN, Mahadevamurthy S and Ajay Kumar K. Evaluation and studies on the structural impact of 3-aryl-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitriles on their biological activities. Der Pharma Lettre. 2012;4(6):1685-1691.
34. Ajay Kumar K, Lokeshwari DM and Vasanth Kumar G. Evaluation and studies on the structural impact of substituted 4,5-dihydroisoxazoles on their biological activities. Int J Pharm Sci Drug Res. 2012;4(4):236-239.
35. Peifer C, Abadleh M, Bischof J, Hauser D, Schattel V, Hirner H, Uwe K and Stefan L. 3,4-Diaryl-isoxazoles and -imidazoles as potent dual inhibitors of p38alpha mitogen activated protein kinase and casein kinase 1delta. J Med Chem. 2009;52(23):7618-7630.
36. Shaw J, Chen B, Bourgault JP, Jiang H, Narendra K, Jayshree M, Frederick AV, Joe M, Kevin B, Halina P, Matthew E and Peter RA. Synthesis and biological evaluation of novel n-phenyl-5-carboxamidyl isoxazoles as potential chemotherapeutic agents for colon cancer. Am J Biomed Sci. 2012;4(1): 14-25.
37. Banerjee M, Sundeepp Kumar HK, Sahu SK , Das A and Parasar P. Synthesis and in-vitro protein denaturation screening of novel substituted isoxazole/pyrazole derivatives. Rasayan J. Chem, 2011;4(2):413-417.
38. Paola P, Monica N, Manuela L, Annamaria M, Valeria C, Alessandra A, Michele R, Daniele S and D'Alessandro N. The antitumor activities of curcumin and of its isoxazole analogue are not affected by multiple gene expression changes in an MDR model of the MCF-7 breast cancer cell line: analysis of the possible molecular basis. Int j mol med. 2007;20:329-335.
39. Rajeshwar N, Marcus P, Stefanie L, Karlheinz B, Sabine K, Thomas D, Sascha W, Eckhard M and Boris S. Curcumin-derived pyrazoles and isoxazoles: swiss army knives or blunt tools for

alzheimer's disease? ChemMedChem. 2008;3:165-172.

40. Vadim AM, Olga BR, Vladimir GG, Peter W and Michaela S. Novel [(biphenyloxy)propyl]isoxazole derivatives for inhibition of human rhinovirus 2 and coxsackievirus B3 replication. J Antimicrob Chemother. 2005;55: 483-488.
41. Philip W, Charlotte A, Stephen FT, Jan E, Jesper SR, Povl K-L and Ulf M. Antagonist properties of a phosphono isoxazole amino acid at glutamate r1-4 (R,S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid receptor subtypes. Mol Pharmacology. 1998;53: 590-596.
42. Sahu SK, Banerjee M, Sahu D, Behera CC, Pradhan GC and Md. Afzal Azam. Synthesis, analgesic and antimicrobial activities of some novel isoxazole derivatives. Dhaka Univ J Pharm.Sci. 2008;7(2):113-118.
43. Hae SY, Eun JL, Jie EL, Woo-Kyu P, Du-Jong B, Yong SC, Hun YK, Hyunah C and Ae Nim P. Synthesis and biological evaluation of isoxazoline and isoxazole derivatives as 5-HT2A and 5-HT2C Receptor ligands. Bull Korean Chem Soc. 2009;30(8):1873-1876.