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RECENT PROGRESS IN THE PHARMACOLOGICAL APPLICATIONS AND SYNTHETIC STRATEGIES OF ISOXAZOLE DERIVATIVES

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ABSTRACT
Isoxazole and its derivatives have emerged as pharmacologically significant heterocyclic compounds exhibiting a broad spectrum of biological activities. The literature review highlights their diverse therapeutic potential, including antibacterial, anticancer, antiplatelet, analgesic, herbicidal, immunomodulatory, anti-inflammatory, anticonvulsant, and antioxidant properties. These biological effects are often attributed to specific substitutions at various positions on the isoxazole ring, which modulate their interaction with biological targets such as kinases, receptors, and enzymes. Notably, some derivatives demonstrate potent cytotoxicity against cancer cell lines, glycoprotein antagonism for antiplatelet effects, and promising GABA-mediated anticonvulsant action. In addition to pharmacological significance, the review also explores a variety of synthetic strategies for isoxazole derivatives. These include solid-phase synthesis, regiospecific reactions, 1,3-dipolar cycloadditions, metal-catalyzed couplings, and microwave-assisted Michael addition methods. The synthetic approaches offer advantages such as high regioselectivity, mild reaction conditions, good yields, and the use of readily available starting materials. Collectively, the review underscores the considerable potential of isoxazole scaffolds in drug development and agrochemical applications, supported by versatile and efficient synthetic methodologies.

Keywords: *Isoxazole derivatives, Hetero atom drug, Biological significance, Chalcone derivatives, One-pot synthesis, Solid phase synthesis, Regiospecific synthesis, Copper acetylide cycloaddition.*

INTRODUCTION

1.1. ISOXAZOLE

Isoxazole ring systems containing mainly nitrogen and oxygen atom constitute a large class of compounds of biological and medicinal interest[1]. A huge number of heterocyclic systems which include mainly five and six membered compounds represent a diverse group of molecules scaffolds. Several such heterocyclic scaffolds have been successfully incorporated into novel drug leads and therapeutic agents[2]. Example that illustrates the biological[3] importance and therapeutic utility of some heterocyclic derivatives include metronidazole (2-methyl-5-nitroimidazole 1-ethanol), a nitroimidazole derivative used as antimoebic; thaibendazole [2-(4-thaizolyl) benzimidazole], a thaibendazole derivative used as anthelmintic. The study of chemistry and biological importance of heterocyclic compounds has been an interesting area of research for a long time. Recent literature has explored the biological importance of a various structural derivatives of heterocyclic compounds. the condensed product of the aromatic imine and aromatic aldehydes, have been known to possess a wide variety of biological applications like antibacterial, antifungal, antitumor, analgesic, and anti-inflammatory[4] . Nitrogen containing heterocyclic with an oxygen atom is considered as an important class of compounds in medicinal chemistry because of their diversified biological applications. Isoxazole is an azole with an oxygen atom next to nitrogen. Isoxazole rings are found in natural products like ibotonic acid. These are also forming the basis for a number of drugs like cox-2 inhibitor, nitric oxide donor – furaxan. Isoxazolyl is the univalent radical derived from isoxazole. An isoxazolyl group is found in many beta-lactamase-resistant antibiotics such as cloxacillin, dicloxacillin and flucloxacillin[7]. They isolated a liquid base by heating nitroethane with aqueous alkalies to obtain 3,4,5- trimethyl isoxazole. 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. Isoxazole derivatives show hypoglycemic, analgesic, anti-inflammatory, antifungal, anti-bacterial, HIV-inhibitory activities, and antioxidant activities[5-7] and an immunosuppressive disease-modifying antirheumatic drug [DMARD][8].

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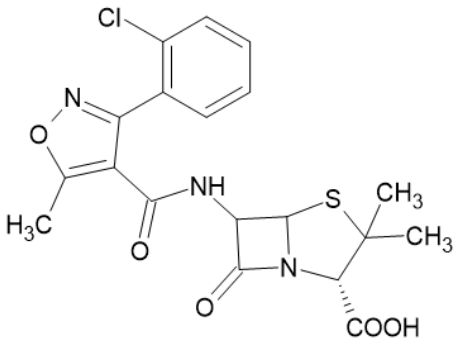
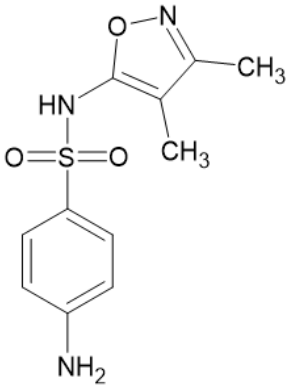


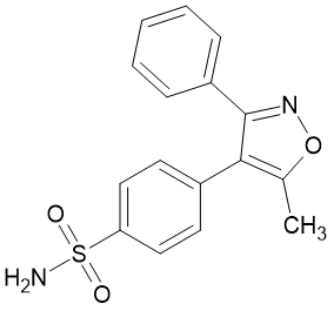
Cloxacillin

Antibacterial



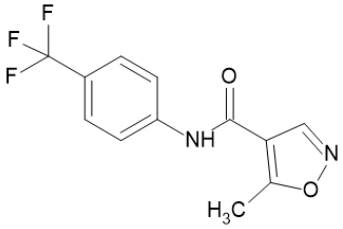
Sulfi-soxazole

Antibacterial



Valdecoxib

Selective COX-II inhibitor



Leflunamide

Immunosuppressive agent

Fig.1. Drugs containing heterocyclic isoxazole moiety

Chemistry of Heterocyclic

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 fused rings, masked aromatic rings and masked aldol and related moieties[13]. 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[9].

1.2. CHALCONE

1.2.1. INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. The name “Chalcones” was given by Kostanecki and Tambor[10]. These compounds are also known as benzal acetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones are -unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. Different methods are available for the preparation of chalcones[11-12]. The most convenient method is the Claisen-Schimdt condensation of equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic alkali[13]. Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles and pyrimidines having different heterocyclic ring systems[14-15].

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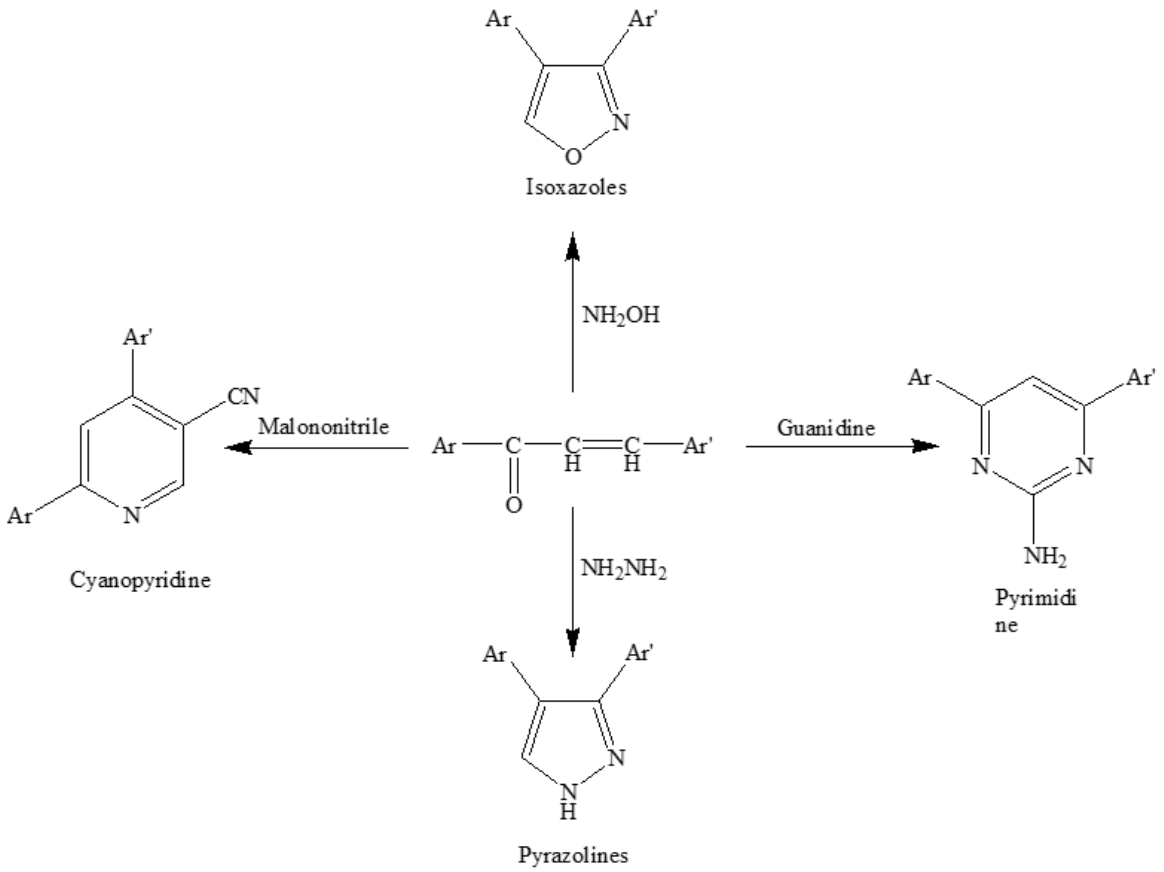
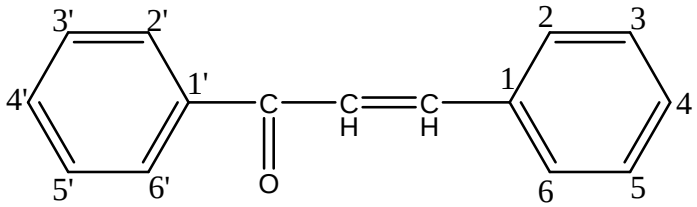


Fig.2. Formation of various rings from chalcone

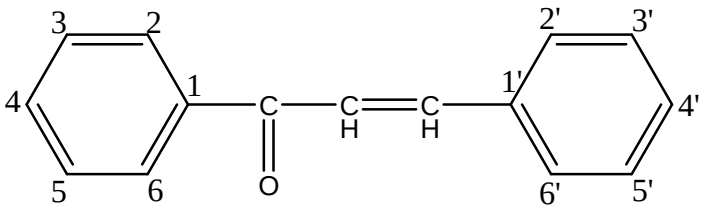
1.2.2. NOMENCLATRURE

Different methods of nomenclatures for chalcone were suggested at different times. The following pattern has been adopted by "Chemical Abstracts" published by American chemical society.



(I)

The British Chemical Abstract and Journal of Chemical Society have followed the following system.



(II)

1.2.3. SYNTHETIC METHODS OF PREPARING CHALCONES

1.2.3.1. CLAISEN-SCHMIDT REACTION

A variety of methods are available for the synthesis of chalcones, the most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali.[16] In the Claisen-Schmidt reaction, the concentration of alkali used, usually ranges between 10 and 60 %[17-18]. The reaction is carried out at about 50°C

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for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizaro reaction also takes place and thereby decreases the yield of the desired product. To avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in place of aldehyde has been recommended[19].

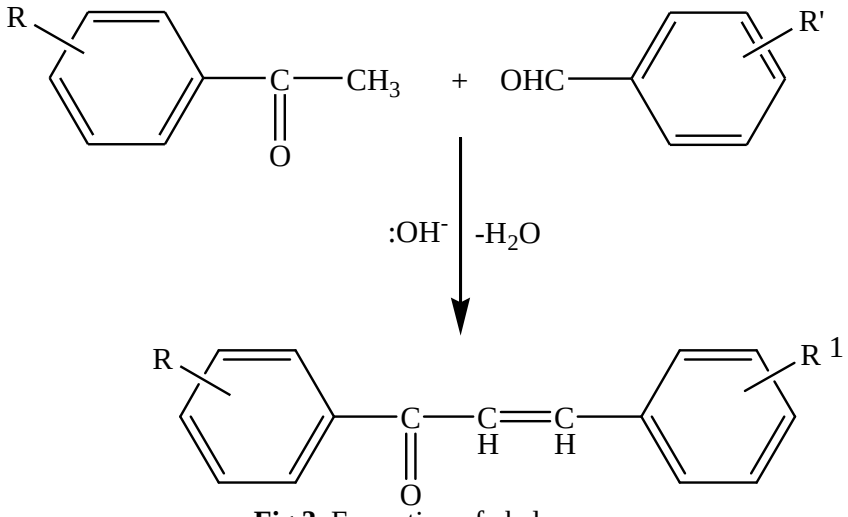

Fig.3. Formation of chalcone

1.2.4. VARIOUS CONDENSING AGENTS USED IN SYNTHESIS OF CHALCONES

[1] Hydrochloric Acid

Dry hydrochloric gas in a suitable solvent like ethyl acetate at 0°C was used as a condensing agent in a few syntheses of chalcones from aromatic ketones. Methanolic solution of dry hydrochloric acid gas at 0°C was also used by Lyle, Paradis and Marathey[20].

[2] Alkali

Alkali has been the most used condensing agents for synthesis of chalcones. It is used as an aqueous solution of suitable concentration viz. 10%, 20 %, 30 % and 50 %.

1.2.5. IMPORTANCE OF CHALCONES

(1) They have close relationship with flavones, aurones, tetralones and aziridines.

(2) Chalcones and their derivatives find application as artificial sweeteners[21], scintillator[22], polymerization catalyst[23-24], fluorescent whitening agent[25], organic brightening agent[26-27], stabilizer against heat, visible light, ultraviolet light and aging[28-31].

(3) 3,2,4,6-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside[32] has been used as synthetic sweetener and is 2200 times sweeter than glucose.

(4) They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g., phenyl hydrazine, 2-amino thiophenol etc.

(5) The chalcones have been found useful in elucidating structure of natural products like hemlock tannin[33], cyanomaclurin[34], ploretin[35], eriodictyol and homo eriodictyol[36], naringenin[37]etc.

LITERATURE REVIEW

2.1. BIOLOGICAL ACTIVITIES (ISOXAZOLE)

2.1.1. Antibacterial Activity[38]

Each Petri dish containing Multer-Hinton agar medium was inoculated with one bacterial culture by spreading the suspension of the organism with a sterile glass rod with a bended tip. In each plate cups of 6mm diameter were made at equal distances using sterile cork borer. One cup was filled with 0.1 ml of standard drug i.e., ampicillin, filled with 0.1 ml of DMF, others were filled with 0.1 ml of synthesized compound's solution in sterile DMF.

All plates were kept in the refrigerator for 30 minutes to allow the diffusion of sample to the surrounding agar medium. The Petri dishes were incubated at 37°C for 24 hrs. Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated. The diameter obtained for the test samples were compared with that produced by standard ampicillin.

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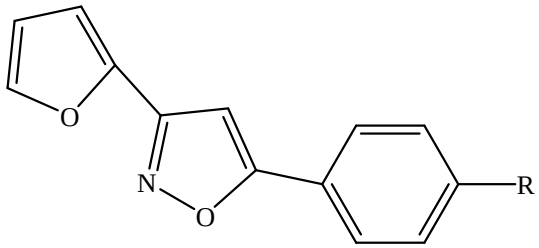
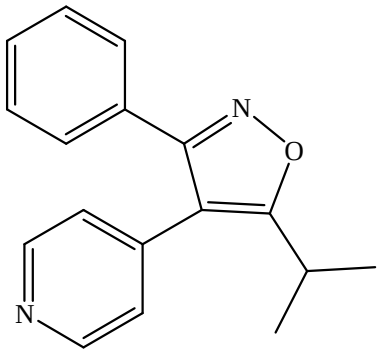


R=NH2, Br, NO2, C, F, CH_3

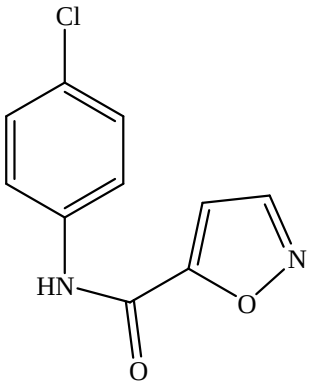
2.1.2. Anticancer activity[39]

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 0.23 μM.

Novel *N*-(phenyl)-5-carboxamidyl isoxazoles synthesized were examined for their anticancer activity *in vitro*. *N*-(4 Chlorophenyl)- 5-carboxamidyl Isoxazole showed promising *in vitro* cytotoxicity and solid tumour 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.



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



Isoxazole-5-carboxylic acid (4-chloro-phenyl)-amide

2.1.3. Antiplatelet Activity[40]

Xue CB, 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.

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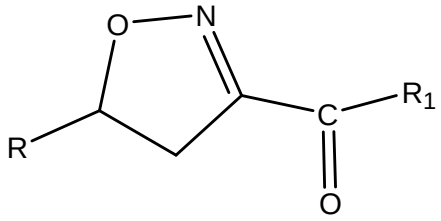
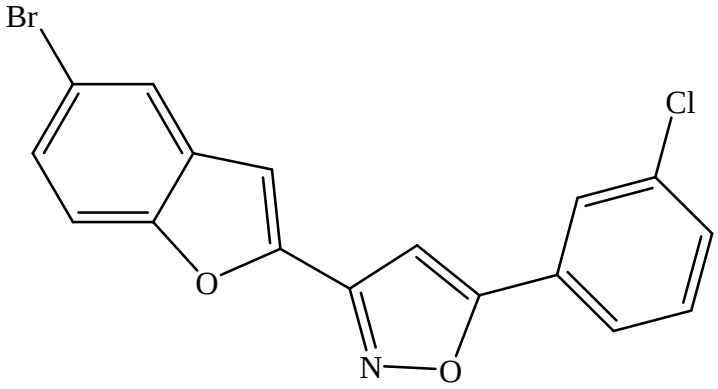


R-Aryl orAlkyl

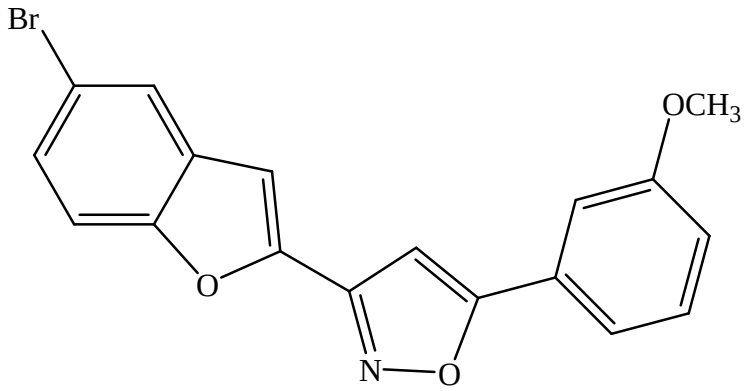
R_1-Alkyl or Benzyl

2.1.4. Analgesic activity[41-44]

All the isoxazole derivatives were evaluated for their analgesic activity employed by Eddy's hot plate method. Ibuprofen was used as a reference standard for comparison. Two compounds possessed maximum activity and this may be due to the presence of 4-methoxyphenyl pharmacophore C-5 position of isoxazole nucleus. Remaining compounds showed remarkable activity.



3-(5-Bromo-benzofuran-2-yl)-5-(3-chloro-phenyl)-isoxazole



3-(5-Bromo-benzofuran-2-yl)-5-(3-methoxy-phenyl)-isoxazole

2.1.5. Herbicidal Activity[45-48]

Yuttanzhou et al synthesized some new three (substituted phenyl) Isoxazole derivatives and subjected them for herbicidal activities which are having property of inhibiting the porphyrinogen oxidase. Many researchers have studied on three compounds having high bioactivities and reported. And some of them have been commercialized such as JU-485 and KPP- 314 which are substituted phenyl isoxazoline derivatives. In this several novel 3(substituted phenyl) Isoxazole derivatives are synthesized and exists herbicidal activities towards various weeds like Echinochloa, Crusgalli, SetariaViridis, Abutilon theoprastil.

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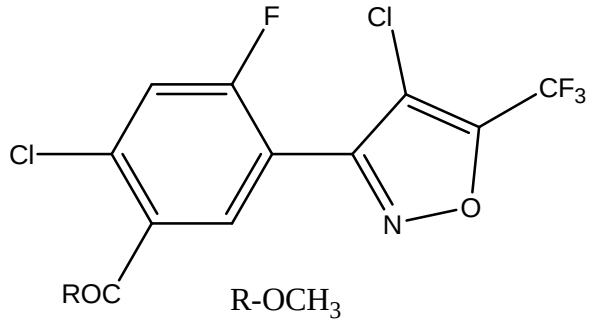
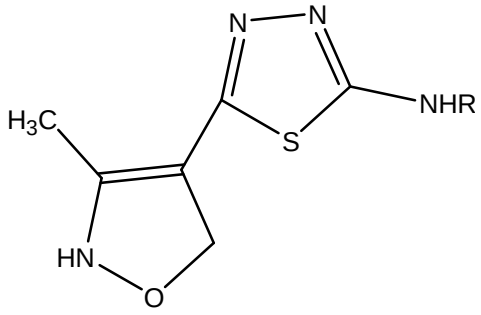


R-OCH_3
-OC_2H_5
-NHC_6H_5
-$N(C_2H_5)_2$

2.1.6. Immunological Activity[49]

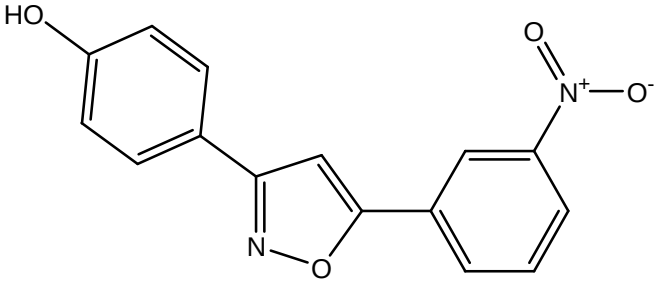
Stanislaw ryng and Michael zimeki synthesized some new derivatives of isoxazoles including 4-substituted 3(5 amino3 methyl 4 isoxazole) 1, 2, 4-triazoline-5-tione and 5-substituted 2(5 amino 3 methyl 4 isoxazole). 1,3,4tridiazole derivatives which shows immune modulatory activity. The compounds were tested for their ability to affect the proliferative response of moulesphlenocytes to conconavalin and secondary humoral immune response of sphlenocytes to sheep red blood cells measured as the number of antibody forming cells and Cyclosporine A served as a reference compound.



R=Aliphatic,Aromatic

2.1.7. Anti-inflammatory Activity[50]

Isoxazole derivatives were screened for their anti-inflammatory activity by *in vivo* method on rats. The action of synthesized compounds 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.



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

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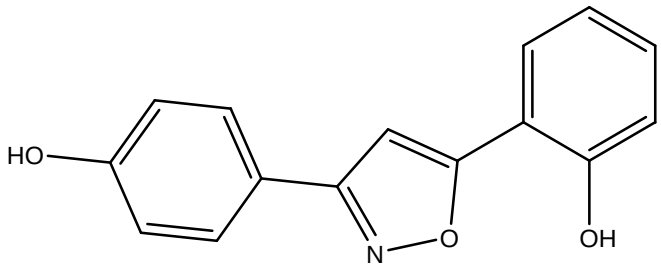
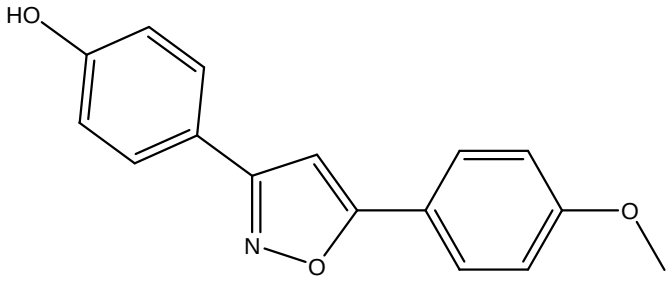
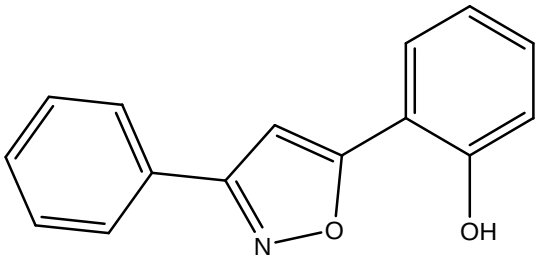


2-[3-(4-hydroxyphenyl) isoxazol-5-yl] phenol



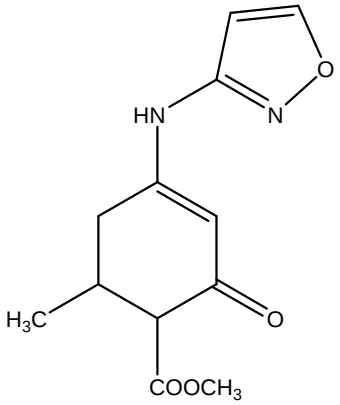
4-[5-(4-methoxyphenyl) isoxazol-3-yl] phenol



2-(3-phenylisoxazol-5-yl)Phenol

2.1.8. Anti-convulsant activity[51-53]

The search 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 as troglial uptake can act as anticonvulsant agents and several isoxazole derivative are synthesized. Second compound is also a synthesized isoxazole derivative which affects the sodium channel to show its activity.



4-(Isoxazol-3-ylamino)-6-methyl-2-oxo-cyclohex-3-enecarboxylic acid methyl ester

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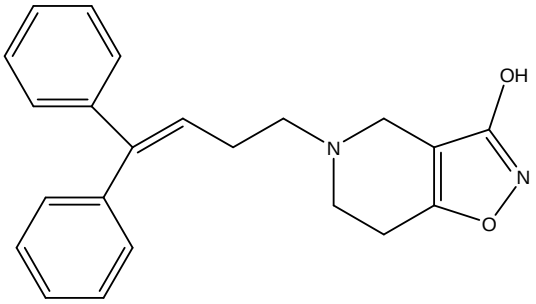
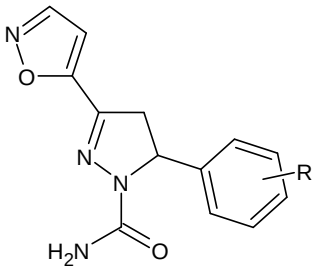


5-(4,4-Diphenyl-but-3-enyl)-4,5,6,7-tetrahydro-isoxazolo[4,5-*c*]pyridin-3-ol

2.1.9. Antioxidant activity[54]

The synthesized of Some Novel Isoxazole Ring Containing Chalcone were evaluated for their potent antioxidant activity.



3-(1,2-oxazol-5-yl)-5-phenyl-substituted-4,5-dihydro-1*H*-pyrazole-1-carboxamide

2.2. METHOD OF PREPARATION OF ISOXAZOLE

2.2.1. Synthesis of isoxazole using solid phase synthesis[55]

Solid phase synthesis of isoxazole derivative from Diaryl 1, 3-diketones can be carried out in presence of Hydroxylamine hydrochloride and Silica gel.

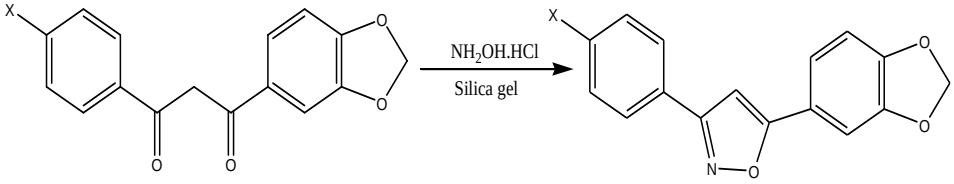


Fig.4. Synthesis of isoxazole using solid phase synthesis

2.2.2. Synthesis of isoxazole using regiospecific synthesis[56]

Regiospecific synthesis of isoxazoles has been reported in excellent yield by acylation of l,4-dilithioximes with amides (DMF) followed by a mineral acid induced cyclization dehydration.

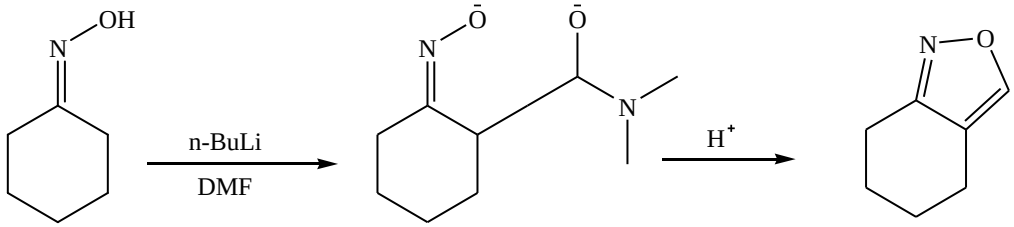


Fig.5. Synthesis of isoxazole using regiospecific synthesis

2.2.3. Synthesis of 3-substituted isoxazole using 1,3-dipolar cycloaddition reaction[57]

A 1,3-dipolar cycloaddition of phenyl vinylic selenide to nitrile oxides and subsequent oxidation-elimination furnished 3-substituted isoxazoles with good yields in a one-pot, twostep transformation.

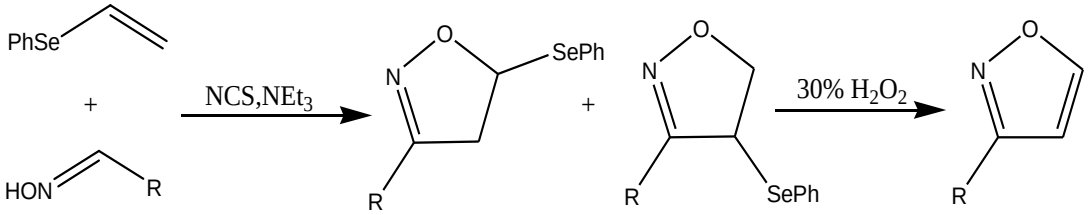


Fig.6. Synthesis of 3-substituted isoxazole using 1,3-dipolar cycloaddition reaction

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2.2.4. Synthesis of 5-silylisoxazoles using silylalkynones[58]

5-Silylisoxazoles have been prepared by condensation of silylalkynones with hydroxylamine hydrochloride.

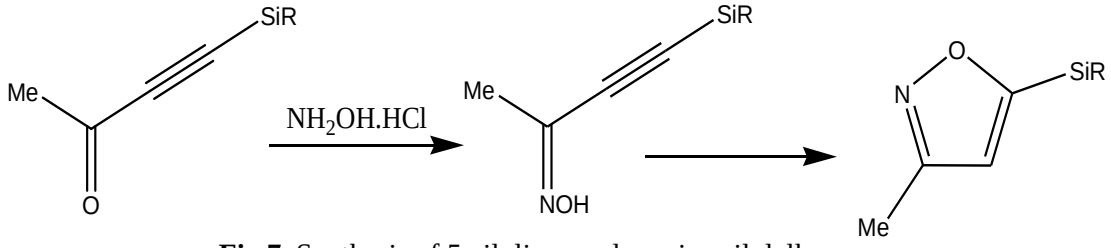

Fig.7. Synthesis of 5-silylisoxazoles using silylalkynones

2.2.5. Synthesis of 3,4,5-trisubstituted 5-(pyrrolidinyl)-4,5-dihydroisoxazoles using Enamine-triggered [3+2]-cycloaddition reactions[59]

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

Subsequent oxidation of the cycloadducts offers a high yielding, regiospecific and metal-free synthetic route for the synthesis of 3,4-disubstituted isoxazoles.

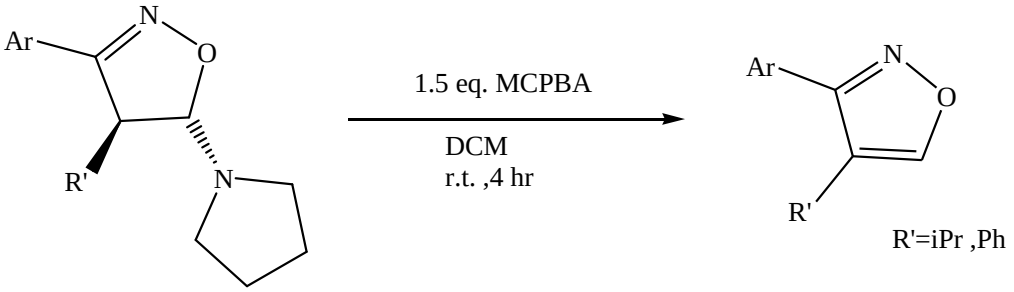

Fig.8. Synthesis of 3,4,5-trisubstituted 5-(pyrrolidinyl)-4,5-dihydroisoxazoles using Enamine-triggered [3+2]-cycloaddition reactions

2.2.6. Synthesis of 3-isoxazole esters using substituted acetophenones[60]

Reaction of various substituted acetophenones with diethyl oxalate in the presence of sodium ethoxide forms resulting 2,4-diketo esters which on treatment with hydroxylamine hydrochloride furnishes substituted 3-isoxazole esters.

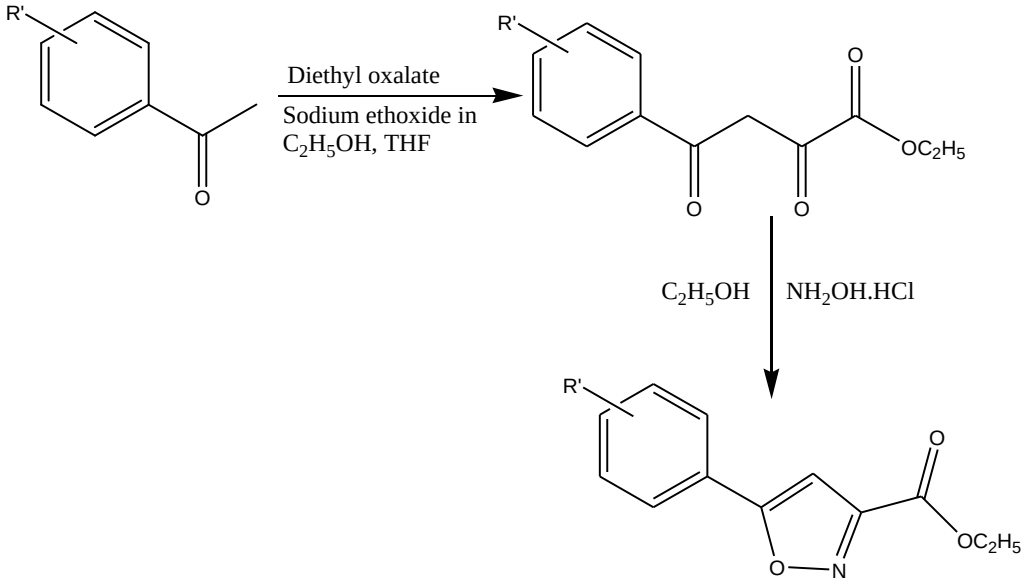

Fig.9. Synthesis of 3-isoxazole esters using substituted acetophenones

2.2.7. Synthesis of isoxazole using nitro compounds[61]

The reaction of activated nitro compounds such as phenyl nitro methane with terminal acetylenes affords isoxazoles derivatives in higher yields compared with those of other methods. However, the reaction is not compatible with nitroalkanes.

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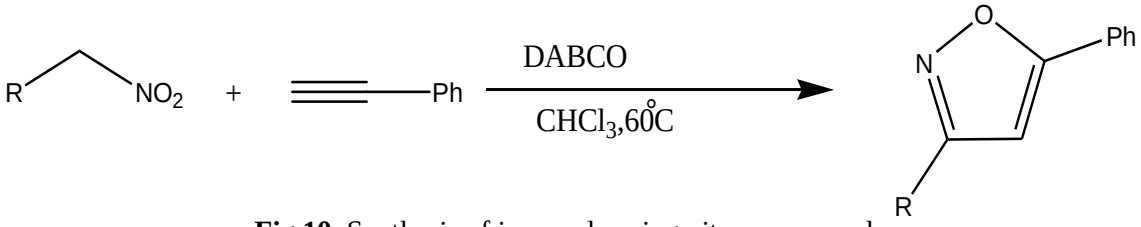

Fig.10. Synthesis of isoxazole using nitro compounds

2.2.8. Synthesis of 3,5-disubstituted 4-halo(seleno) isoxazoles using ICl, I_2, Br_2[62]

The reaction of various 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2, or Ph Se Br provided 3,5-disubstituted 4-halo(seleno) isoxazoles in good to excellent yields under mild reaction conditions.

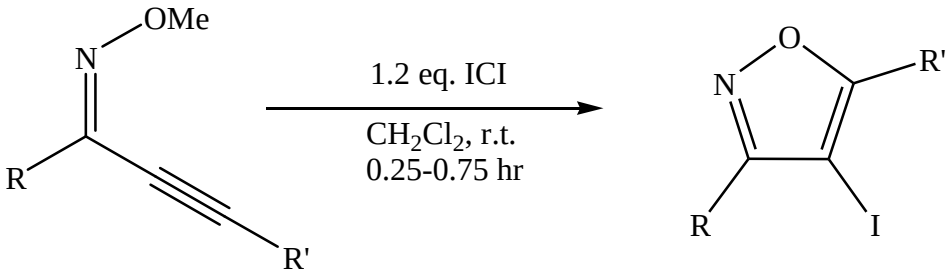

Fig.11. Synthesis of 3,5-disubstituted 4-halo(seleno) isoxazoles using ICl, I2, Br2

2.2.9. Synthesis of isoxazole derivatives using palladium-catalyzed terminal alkyne[63]

Isoxazole derivatives were prepared by a palladium-catalyzed four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide under ambient pressure, and an aryl iodide.

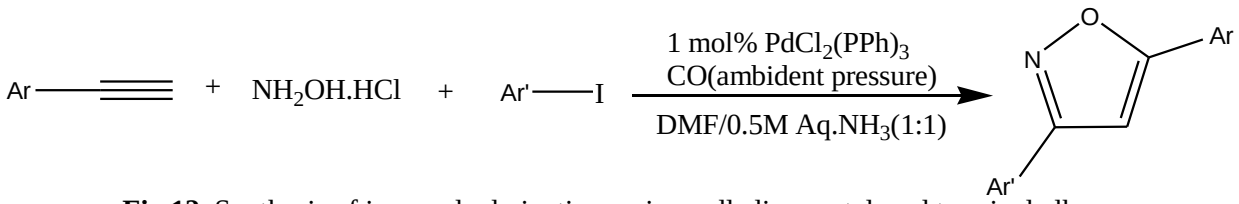

Fig.12. Synthesis of isoxazole derivatives using palladium-catalyzed terminal alkyne

2.2.10. Synthesis of 3-substituted and 3,5-disubstituted isoxazoles using *N*-hydroxyl-4-toluenesulfonamide[64]

Various 3-substituted and 3,5-disubstituted isoxazoles have been efficiently synthesized in good yields by the reaction of *N*-hydroxyl-4-toluenesulfonamide with α,β-unsaturated carbonyl compounds. This strategy is associated with readily available starting materials, mild conditions, high regioselectivity, and wide scope.

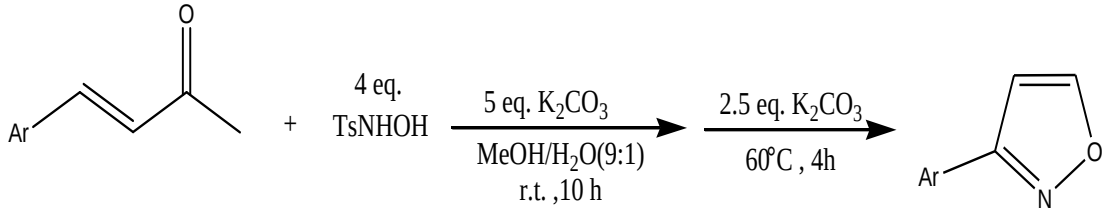

Fig.13. Synthesis of 3-substituted and 3,5-disubstituted isoxazoles using *N*-hydroxyl-4-toluene sulfonamide

2.2.11. Synthesis of 3, 4-disubstituted isoxazoles using copper acetylides[65]

Cycloadditions of copper (I) acetylides to azides and nitrile oxides provide ready access to 1,4-disubstituted 1,2,3-triazoles and 3,4-disubstituted isoxazoles, respectively. The process is highly reliable and exhibits an unusually wide scope with respect to both components. Computational studies revealed a nonconcerted mechanism involving unprecedented metallacycle intermediates.

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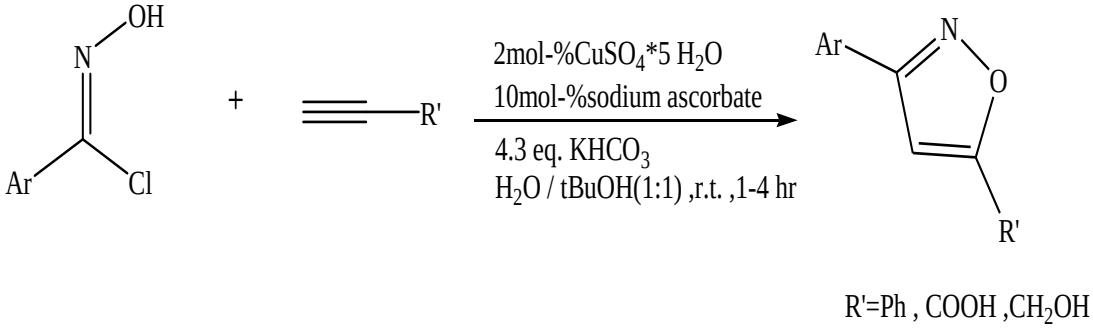

Fig.14. Synthesis of 3,4-disubstituted isoxazoles using copper acetylides

2.2.12. Synthesis of 5-arylisoxazole using Aqueous Media[66-68]

When an equivalent mixture of an 3-(dimethyl amino)-1-arylprop-2-en-1-one derivative and hydroxylamine hydrochloride was stirred at 50 °C in aqueous media, 5-arylisoxazole derivatives were obtained in good yields.

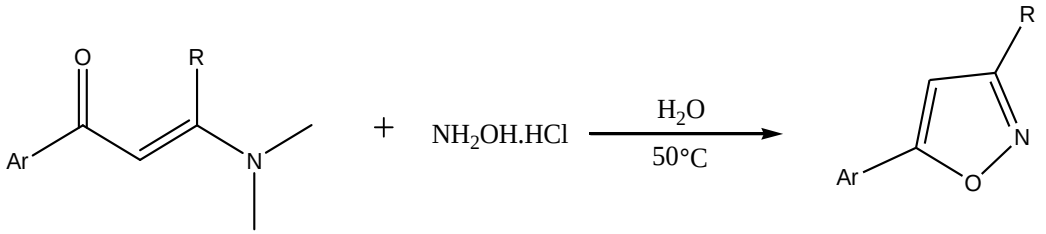

Fig.15. Synthesis of 5-arylisoxazole using aqueous media

2.2.13. Synthesis of isoxazole using solid phase synthesis[69]

Solid phase synthesis of isoxazole derivative from Diaryl 1, 3-diketones can be carried out in presence of Hydroxylamine hydrochloride and Silica gel.

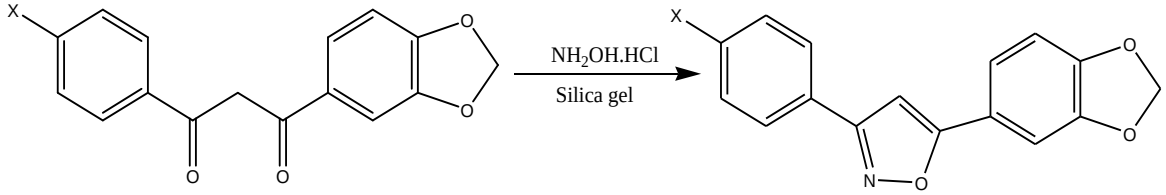

Fig.16. Synthesis of isoxazole using solid phase synthesis

2.2.14. Synthesis of 3,5-diarylisoxazoles using β-diketones[70]

The reaction of asymmetrically substituted β-diketones with hydroxylamine to give 3,5diarylisoxazoles in high yields.

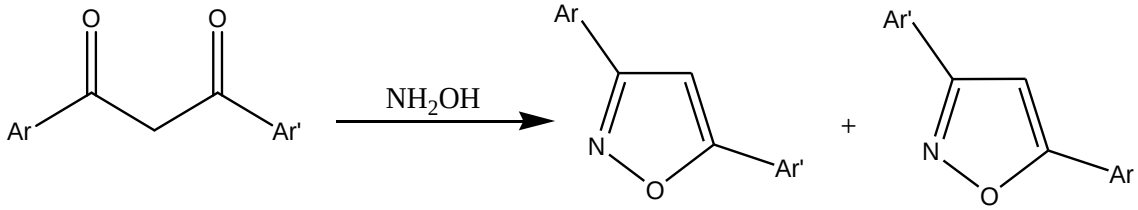

Fig.17. Synthesis of 3,5-diarylisoxazoles using β-diketones

2.2.15. Synthesis of isoxazole derivatives using Michael addition[71]

The synthesis of six isoxazole derivatives via Michael addition of hydroxylamine hydrochloride over chalcones under microwave irradiations using K_2CO_3 as solid support.

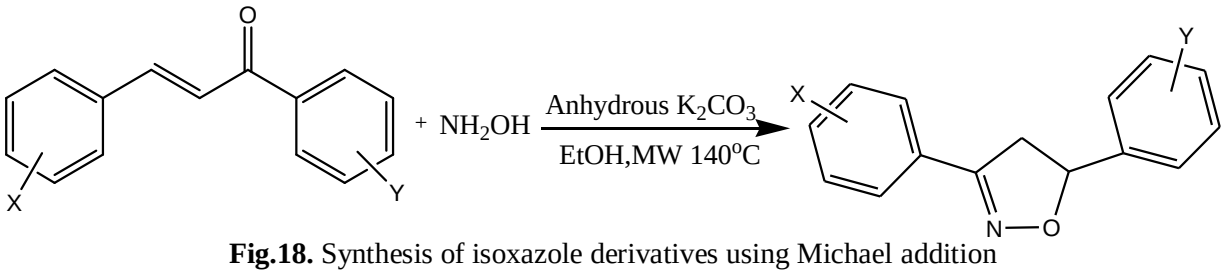

Fig.18. Synthesis of isoxazole derivatives using Michael addition

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CONCLUSION

A promising class of heterocyclic compounds with exceptional pharmacological potential is represented by isoxazole and its derivatives. Their varied pharmacological properties, which include anti-inflammatory, anti-cancer, anticonvulsant, and herbicidal actions, are mostly impacted by structural alterations on the isoxazole ring. The creation of these bioactive compounds with increased efficiency and selectivity has been made easier by developments in synthetic techniques, such as metal-catalyzed couplings, microwave-assisted procedures, and regiospecific reactions. The promise of isoxazole derivatives as useful candidates for upcoming medicinal agents and agrochemical improvements is highlighted by their wide range of biological relevance and adaptable synthetic accessibility.

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