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Review Article

A Short Review on Synthesis and Pharmacological Activity of Isoxazole

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ABSTRACT

In recent year heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. Isoxazole derivatives play vital role in biological field such as antiplatelet, Herbicidal, anticonvulsant, anti-inflammatory and anticancer activity.

Keywords:- Isoxazole , synthesis methods, anticonvulsant activity, antiplatelet activity

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INTRODUCTION

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 forms 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, dicloxacillinand flucloxacillin. Isoxazole 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].

STRUCTURE

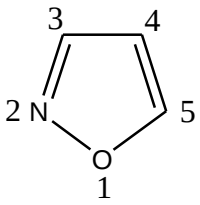


Fig.1

Isoxazole (Fig.1) are unsaturated aromatic heterocyclic compounds containing a ring with three carbon atoms, one oxygen atom and one nitrogen atom. The trivial name for the title five-membered fully unsaturated heterocycles as "Isoxazole" was originally proposed by Hantszch[3].

CHEMISTRY

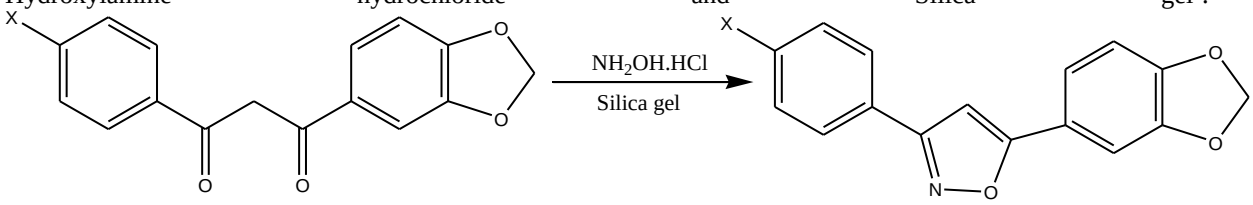
The nitrogen hetero atom is more pronounced for electron withdrawing effect, while the oxygen atom is more pronounced for electron donating effect. As neutral molecules, isoxazoles undergo electrophilic substitution rather more readily at the position 4, than benzene. Effects of substituents can modify their behaviour. 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 maskedaldol and related moieties[4]. The capability of isoxazole undergoing reaction is diverse: protonation, quaternization, complexation, oxidation, reduction, carbanionic condensations, thermolysis, photolysis, transformations into other heterocyclic ring systems and reaction with electrophiles, nucleophiles and Grignard reagents[5].

GENERAL METHOD OF SYNTHESIS

Scheme-1

Synthesis of isoxazole using solid phase synthesis

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

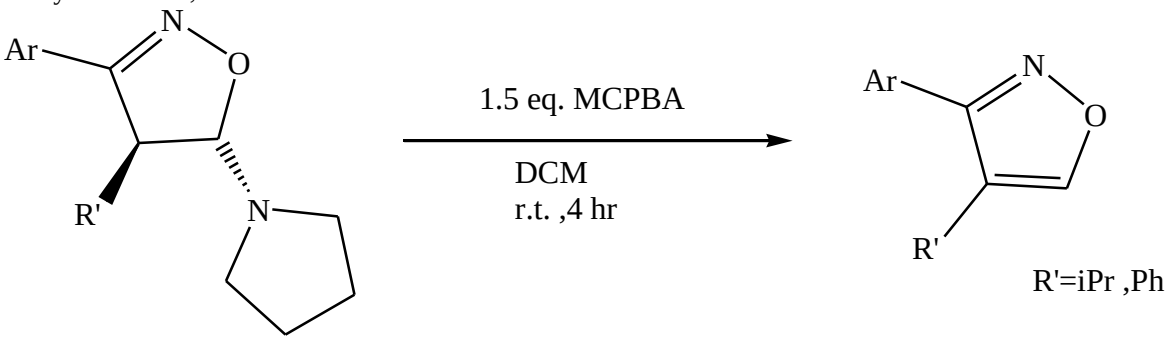


Scheme-2

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

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.

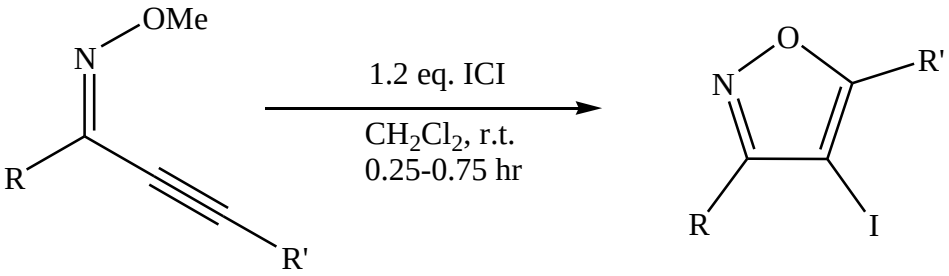
Subsequent oxidation of the cycloadducts offers a high yielding, regiospecific and metal-free synthetic route for the synthesis of 3,4-disubstituted isoxazoles[7].



Scheme-3

Synthesis of 3,5-disubstituted 4-halo(seleno) isoxazoles using ICl, I_2, Br_2

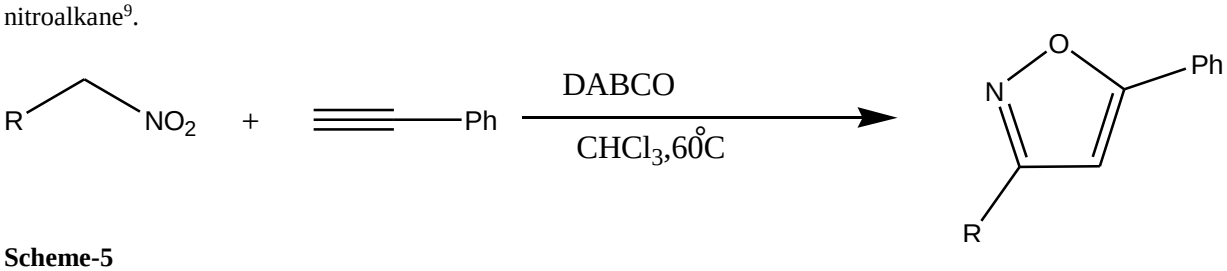
The reaction of various 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2, or PhSeBr provided 3,5-disubstituted 4-halo(seleno)isoxazoles in good to excellent yields under mild reaction conditions[8].



Scheme-4

Synthesis of isoxazole using nitro compounds

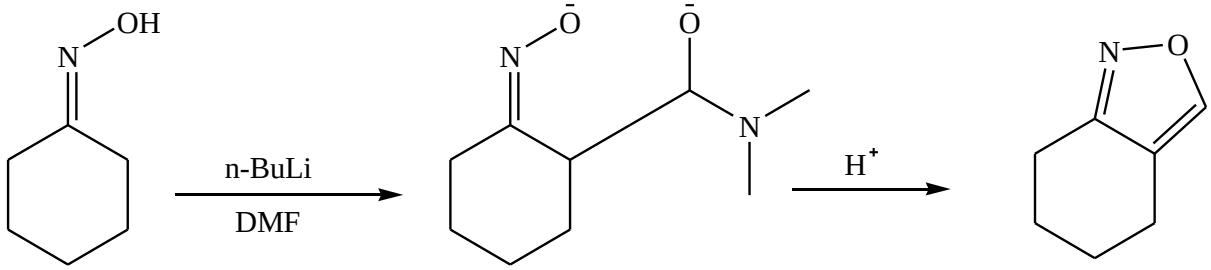
The reaction of activated nitro compounds such as phenyl nitro methane with terminal acetylenes affords isoxazoles derivatives in higher yields compared with those of other methods. However, the reaction is not compatible with nitroalkane[9].



Scheme-5

Synthesis of isoxazole using regiospecific synthesis

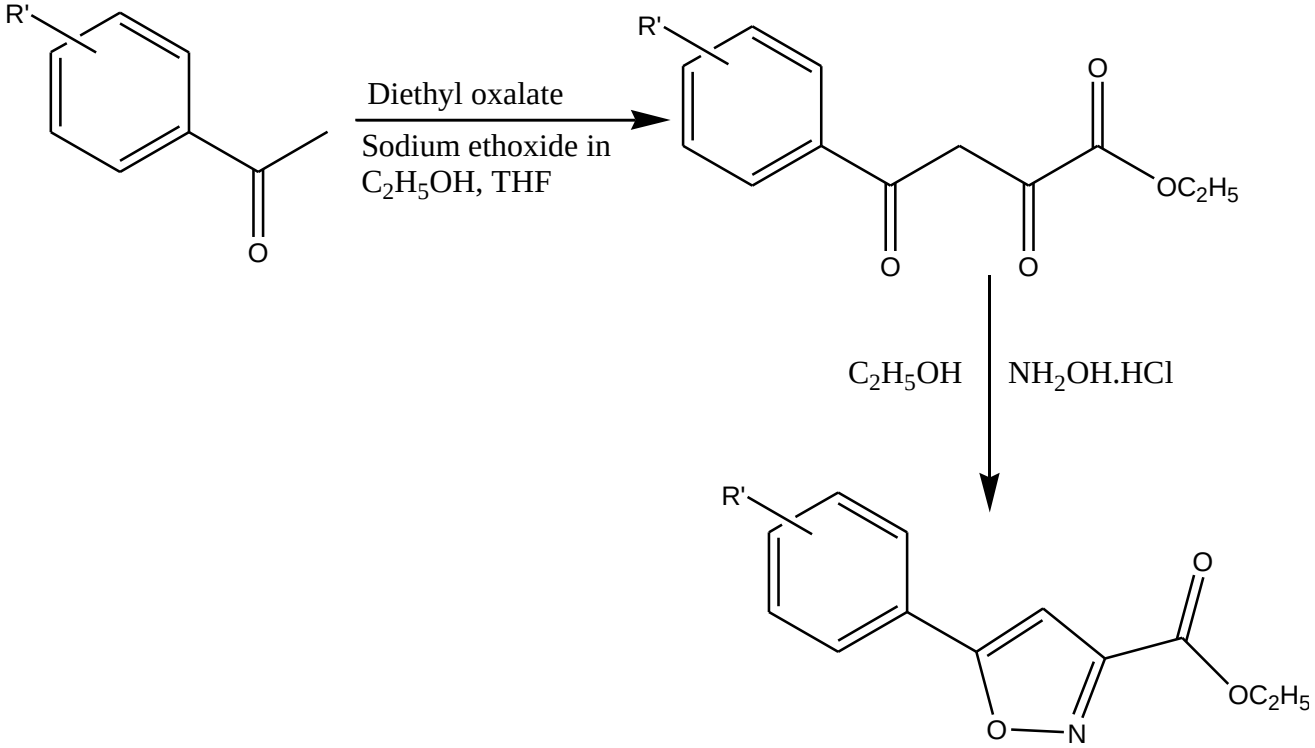
Regiospecific synthesis of isoxazoles has been reported in excellent yield by acylation of syn-l,4-dilithio oximes with amides (DMF) followed by a mineral acid induced cyclizationdehydration[10].



Scheme-6

Synthesis of 3-isoxazole esters using substituted acetophenones

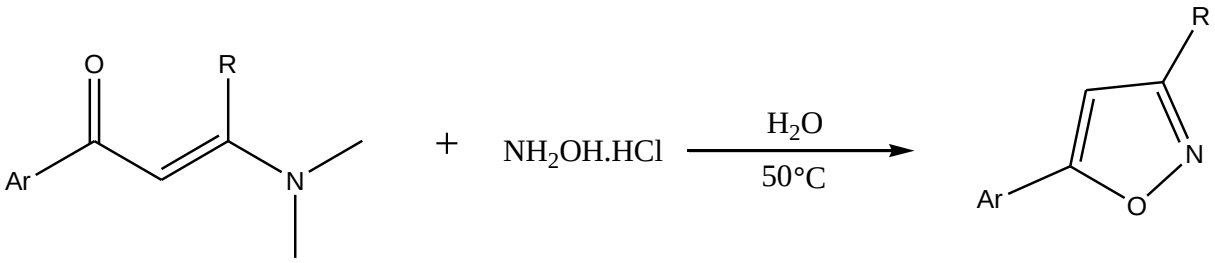
Reaction of various substituted acetophenones with diethyl oxalate in the presence of sodium ethoxide forms resulting 2,4-diketo esters which on treatment with hydroxylamine hydrochloride furnishes substituted 3-isoxazole esters[11].



Scheme-7

Synthesis of 5-arylisoxazole using aqueous media

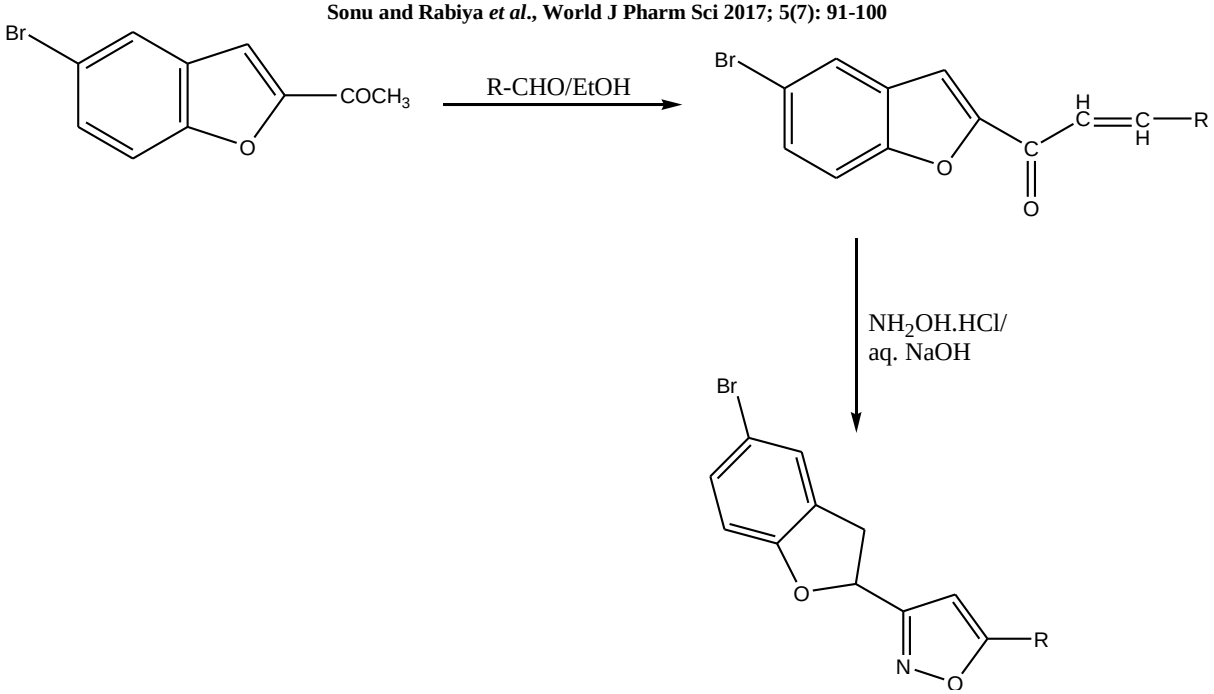
When an equivalent mixture of an 3-(dimethyl amino)-1-arylprop-2-en-1-one derivative and hydroxylamine hydrochloride was stirred at 50 °C in aqueous media, 5-arylisoxazole derivatives were obtained in good yields[12-14].



Scheme-8

Synthesis of isoxazole using 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one

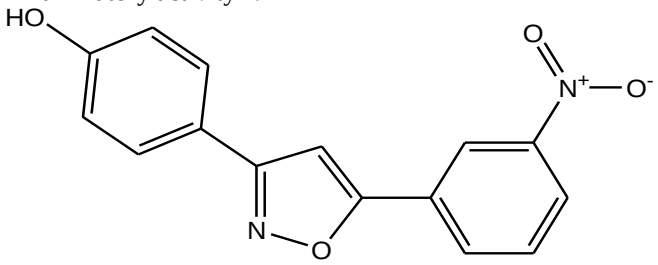
To a solution of 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one (0.01mol) and hydroxylamine hydrochloride (0.01mol) in anhydrous ethanol (50 mL) to this add aqueous sodium hydroxide (10%, 6 mL), the reaction mixture was refluxed for 5hrs and poured into ice cold water the product obtained was filtered[15].



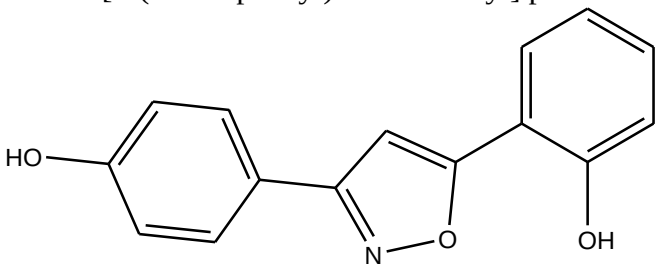
BIOLOGICAL ACTIVITIES

Anti-inflammatory activity

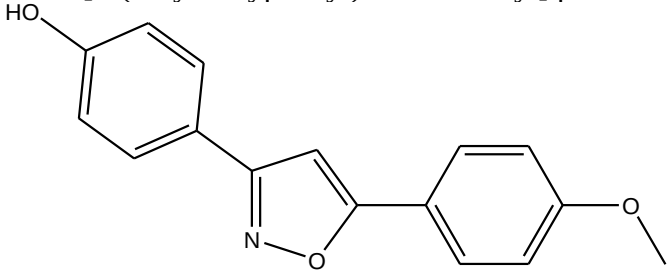
Isoxazole derivatives were screened for their anti-inflammatory activity by *in vivo* method on rats. The action of synthesized compounds was done on paw of Wister albino rats and compared with Diclofenac sodium as a standard. The paw volumes were recorded within one hour interval time duration and the SEM values are calculated by using SPSS software. The study indicated that following compounds exhibited potent anti-inflammatory activity[16].



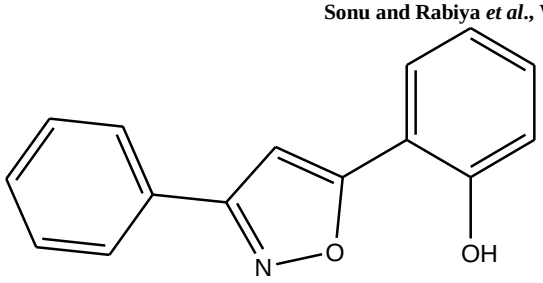
4-[5-(3-nitrophenyl) isoxazol-3-yl] phenol



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



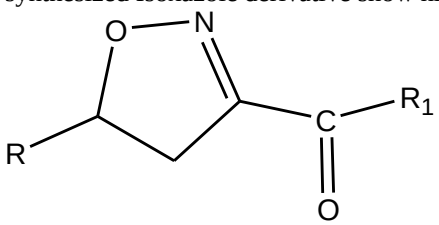
4-[5-(4-methoxyphenyl) isoxazol-3-yl] phenol



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

Antiplatelet Activity

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[17].

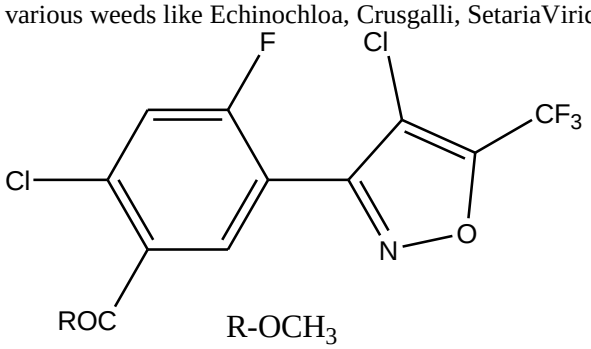


R-Aryl orAlkyl

R_1-Alkyl or Benzyl

Herbicidal Activity

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[18-21].

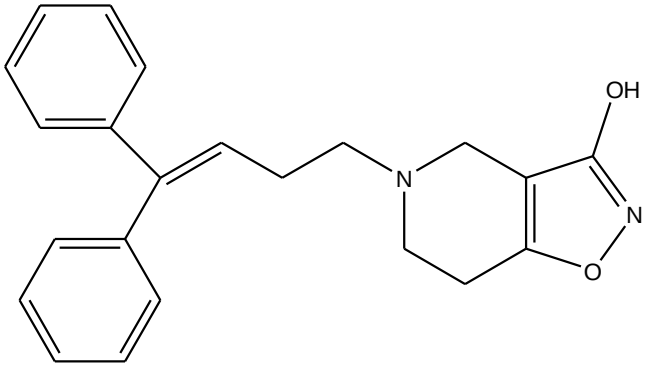


R-OCH_3
-OC_2H_5
-NHC_6H_5
-$N(C_2H_5)_2$

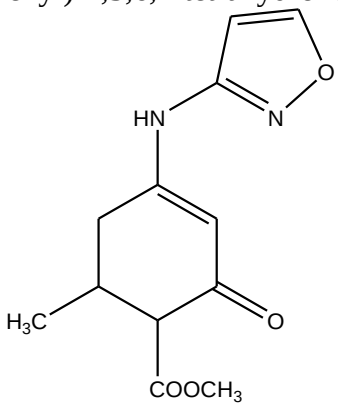
Anti-convulsant activity

The search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry[22]. Many patients with epilepsy fail to experience adequate control of their seizures, despite the optimal use of available antiepileptic drugs. Other patients do so only at the expense of significant toxic side effects. In recent years it has been established that inhibitors of GABA transport and in particular astroglial uptake can act as anticonvulsant agents and several isoxazole derivative are synthesized.

Second compound is also a synthesized isoxazole derivative which affects the sodium channel to show its activity[23-25].



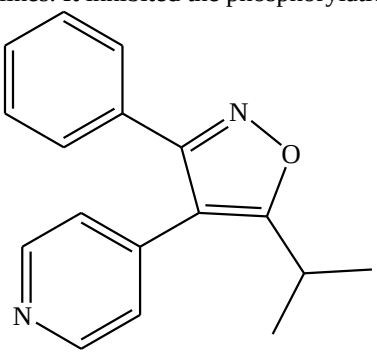
5-(4,4-Diphenyl-but-3-enyl)-4,5,6,7-tetrahydro-isoxazolo[4,5-*c*]pyridin-3-ol



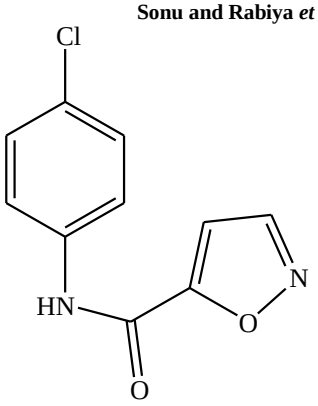
4-(Isoxazol-3-ylamino)-6-methyl-2-oxo-cyclohex-3-enecarboxylic acid methyl ester

Anticancer activity

Substituted Isoxazole[26]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[27] showed promising *in vitro* cytotoxicity and solid tumourselectivity. It exerted most potent cytotoxic activity against both colon-38 and CT-26 mouse colon cancer cell lines. It inhibited the phosphorylation of STAT3, a novel target for chemotherapeutic drugs.



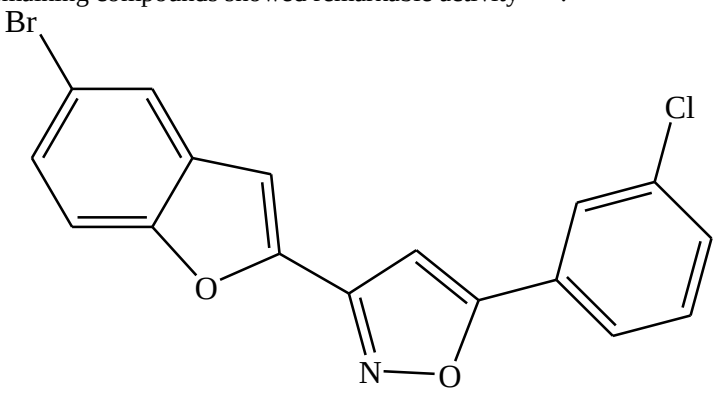
4-(5-Isopropyl-3-phenyl-isoxazol-4-yl)-pyridine



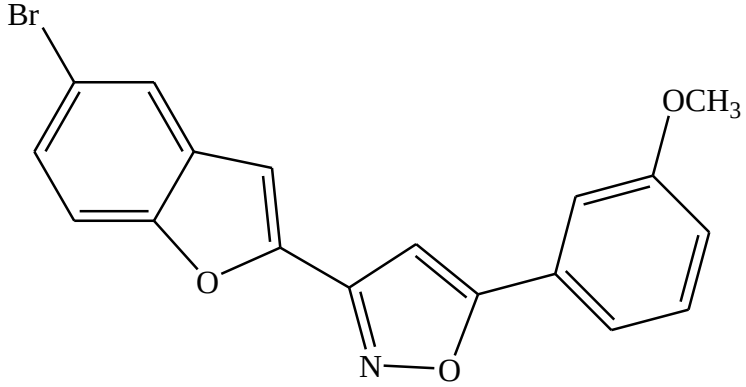
Isoxazole-5-carboxylic acid (4-chloro-phenyl)-amide

Analgesic activity

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 compoundspossessed maximum activity and this may be due to the presence of 4-methoxyphenyl pharmacophoreC-5 position of isoxazole nucleus. Remaining compounds showed remarkable activity[28-30].



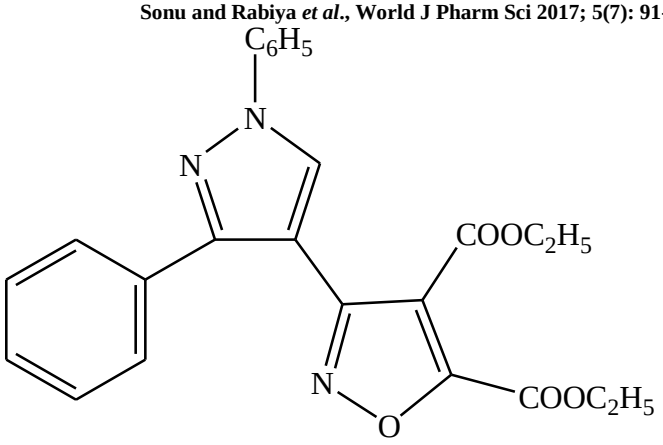
3-(5-Bromo-benzofuran-2-yl)-5-(3-chloro-phenyl)-isoxazole



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

Anti-Nociceptive Activity

K.Karthikeyan, T.veenuseelan et.al was developed a systematic procedure for the synthesis of pyrazolyl isoxazole and they performed the activity of anti-nociceptive action by using various animal tissues. The lead molecule was synthesized by using 1,3dipolar cycloaddition of pyrazole derived nitric oxide with various dipolarophiles such as N-substituted maleimide, diethyl acetylene dicarboxylate and phenyl acetylene. The given structure of synthesized pyrazolylisoxazoles shows maximum anti nociceptive activity[31-33].



3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-isoxazole-4,5-dicarboxylic acid diethyl ester

CONCLUSION

New synthetic strategies. Furthermore biological activity with new dimension need to be explored for isoxazole. Therefore this review may be helpful for medicinal chemist.

ACKNOWLEDGEMENT

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