Section: Research Paper

A REVIEW OF RECENT SYNTHETIC STRATEGIES AND BIOLOGICAL ACTIVITIES OF ISOXAZOLE

Sonakshi Antal[1]- Associate professor, Atam Institute of Pharmacy, Om sterling global University,Hisar, Haryana
Dinesh Kumar[2] -Assistant professor, Atam Institute of Pharmacy, Om sterling global University, Hisar, Haryana
Kuldeep Saini[3]-Assistant Professor, S.D college of pharmacy and vocational studies Muzaffarnagar, Uttar Pradesh
Poonam[4]-Research Scholar, RUHS University Jaipur,email-vashistapoonam@gmail.com
Shivani Pannu[5]- MM College of Pharmacy, MMDU, Mullana, Ambala, Haryana
Rajni[6]- Assistant professor, Starex University, Guargaon, Haryana
Sumit Kumar[7]-Department of Pharmaceutical Sciences, Central university of Haryana, Jant-Pali, Mahendargarh
Corresponding Authors at-
Dinesh Kumar (Assistant Professor), Atam Institute of Pharmacy, Om sterling global university, Hisar (Haryana)
Email id-dineshpotlia123@gmail.com, Mob no-9992650307

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; pharmacological activity; review.

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 arefound 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 & NOMENCLATURE

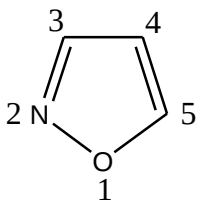


Fig.1

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 as it was the isomer "oxazole" discovered first. The trivial name follows the Hantszch-Widman system of nomenclature: the prefix "iso" represents isomer, "oxa" represents the oxygen atom "aza" represents the nitrogen atom the suffix "ole" denotes the ring size as five-membered; altogether the derived name is "Isoxazole". This name has been accepted in IUPAC and has been used in Chemical abstracts. In Chemical Abstracts, the other systematic name 1, 2-azole, is also used[3].

CHEMISTRY

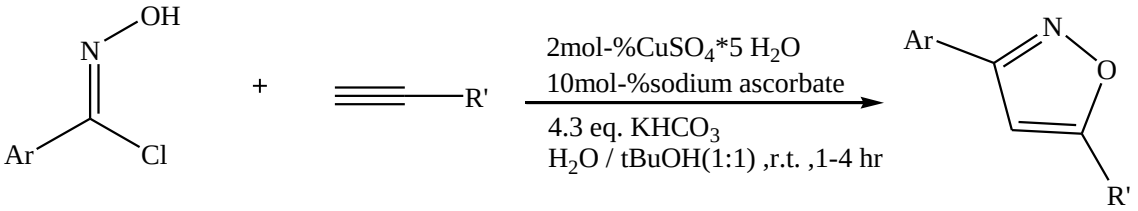
The nitrogen hetero atom is more pronounced for electron withdrawing effect, while the oxygen atom is more pronounced for electron donating effect. As neutral molecules, isoxazoles undergo electrophilic substitution rather more readily at the position 4, than benzene. Effects of substituents can modify 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

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[6].

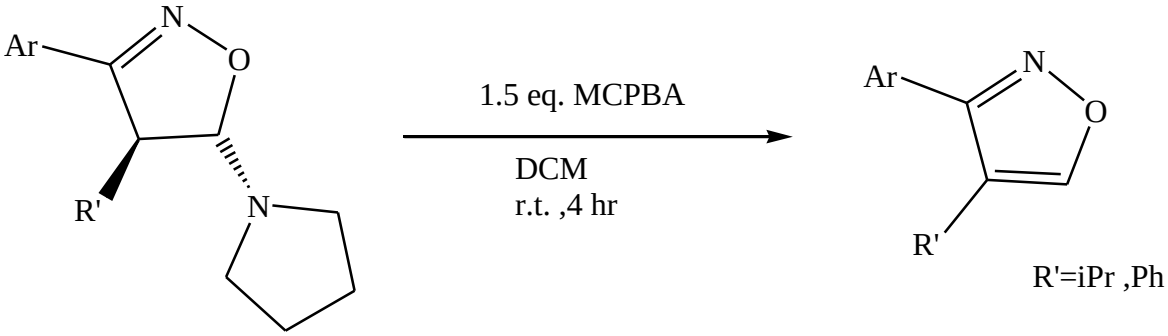


R'=Ph , COOH ,CH_2OH

Scheme-2

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.

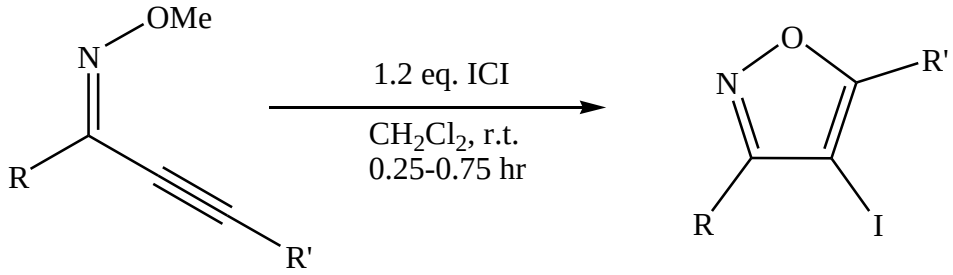
Subsequent oxidation of the cycloadducts offers a high yielding, regiospecific and metal-free synthetic route for the synthesis of 3,4-disubstituted isoxazoles[7].



R'=iPr ,Ph

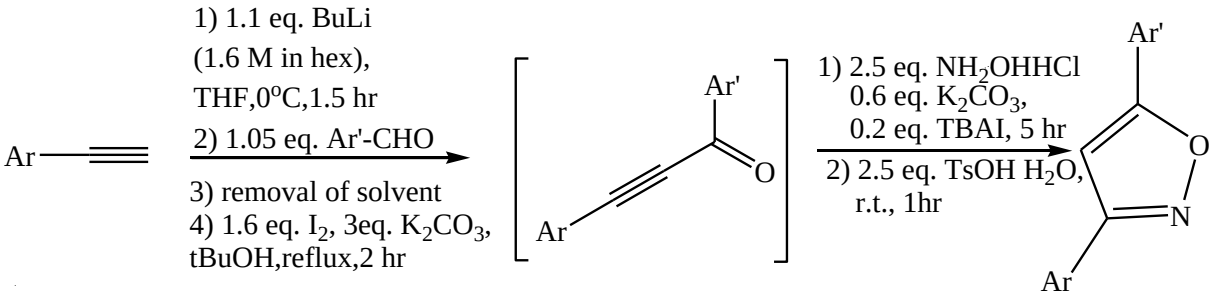
Scheme-3

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].



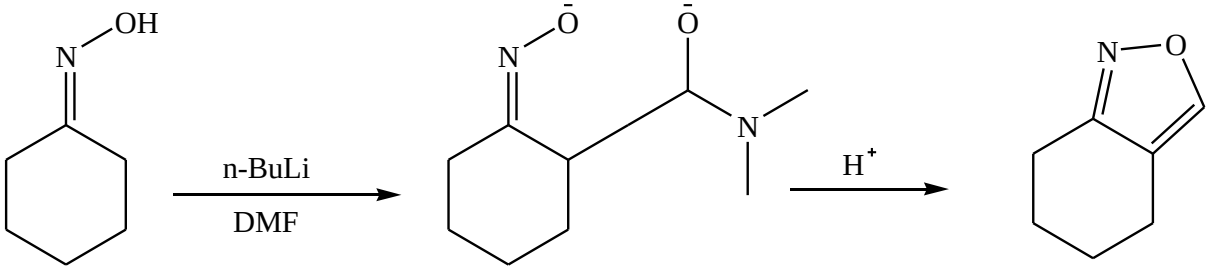
Scheme-4

The reaction of terminal alkynes with *n*-BuLi, and then with aldehydes, followed by the treatment with molecular iodine, and subsequently hydrazines or hydroxylamine provided the corresponding 3,5-disubstituted pyrazoles or isoxazoles in good yields and with high regioselectivity[9].



Scheme-5

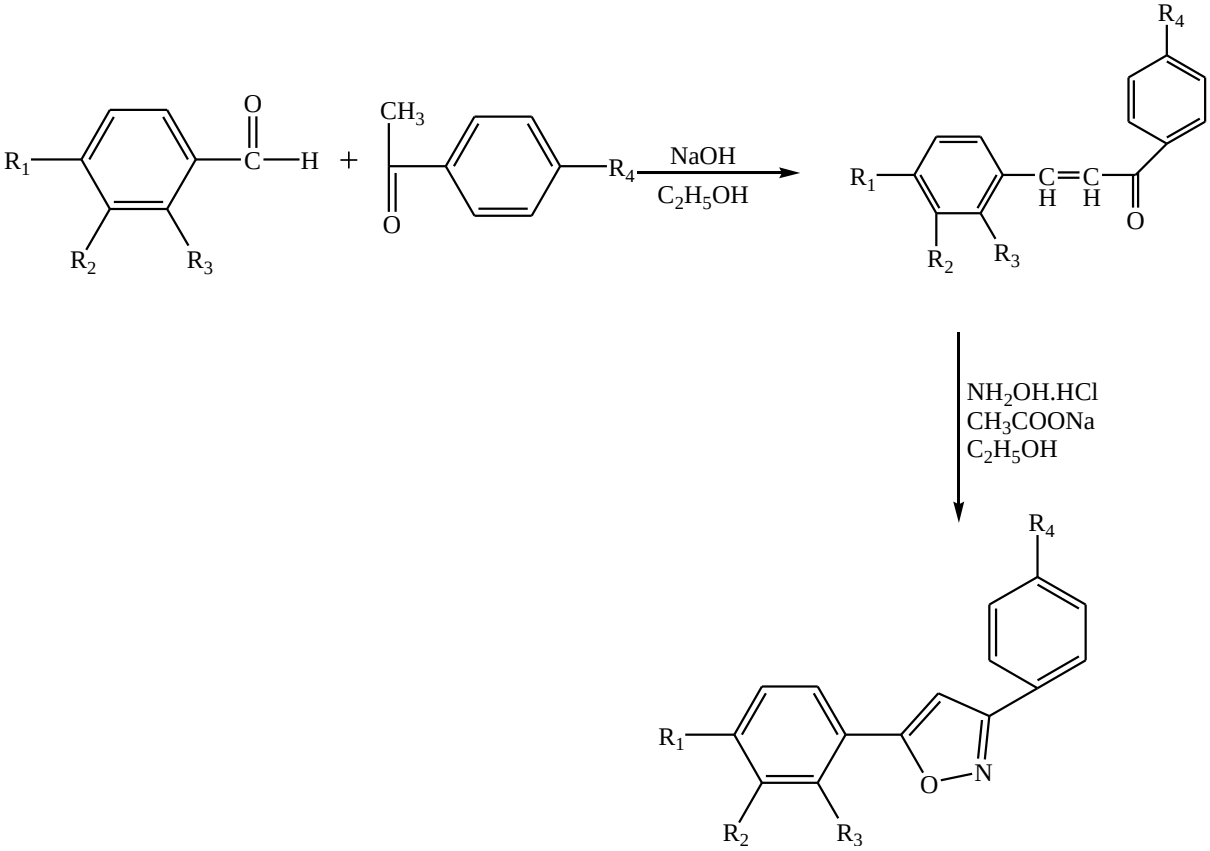
Regiospecific synthesis of isoxazoles has been reported in excellent yield by acylation of syn-l,4-dilithio oximes with amides (DMF) followed by a mineral acid induced cyclizationdehydration[10].



Scheme-6

Equimolar quantities of different substituted aromatic benzaldehydes (0.01 mol) and substituted aromatic acetophenones (0.01mol) were dissolved in 25 mL of alcohol. Sodium hydroxide solution (0.02mol) was added slowly and the mixture stirred for 12 hours until the entire mixture becomes very cloud formed Chalcones.

The formed unstable Chalcones were further cyclised with 0.015 mol of hydroxylamine hydrochloride and sodium acetate 0.015mol in 25 mL of ethanol was refluxed for 6 hours. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice. The precipitate obtained was filtered, washed and recrystallized from acetone[11].

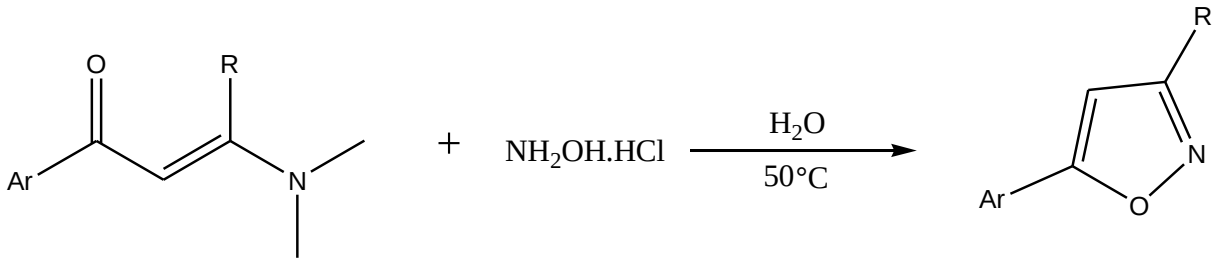


R_1	R_2	R_3	R_4
OH	OCH_3	H	OH
Cl	H	H	OH
H	NO_2	H	OH
H	H	Cl	OH
H	H	OH	OH

OCH_3	H	H	OH
H	H	H	OH
OH	OCH_3	H	H
Cl	H	H	H
H	H	Cl	H
H	H	OH	H
H	H	H	H

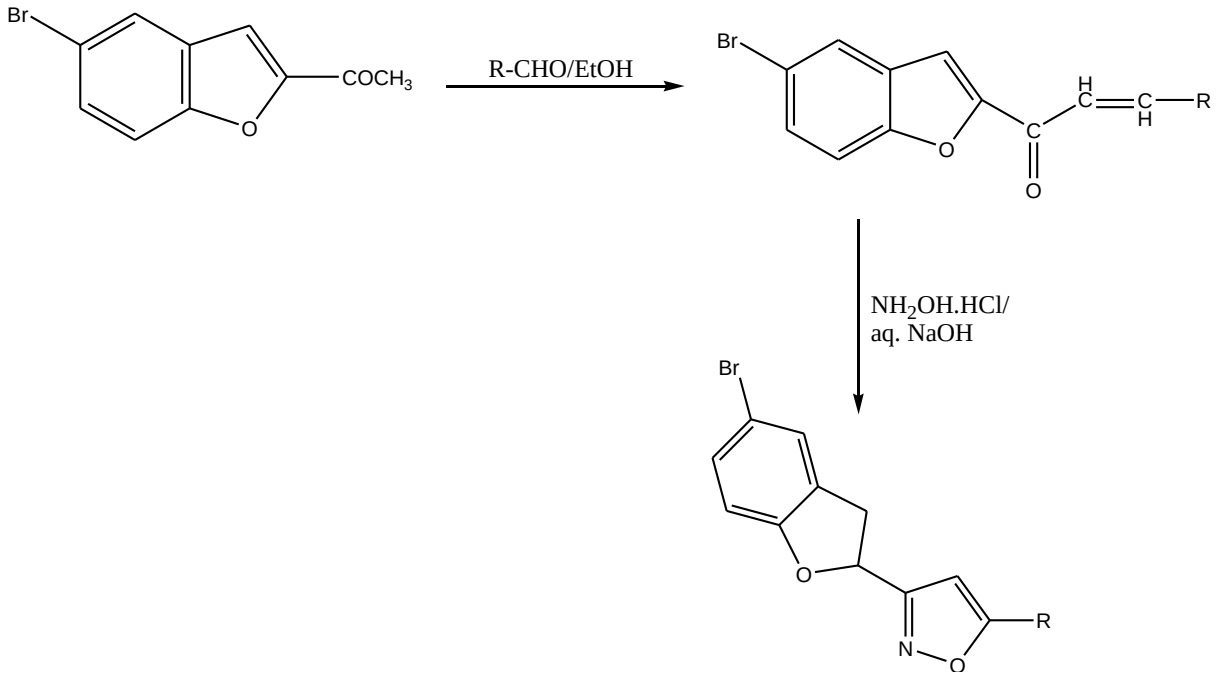
Scheme-7

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

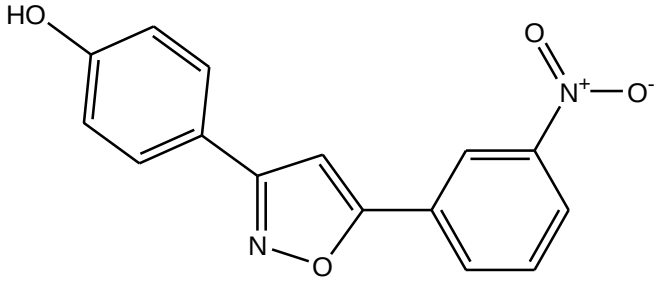
To a solution of 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one (0.01mol) and hydroxylamine hydrochloride (0.01mol) in anhydrous ethanol (50 mL) to this add aqueous sodium hydroxide (10%, 6 mL), the reaction mixture was refluxed for 5hrs and poured into ice cold water the product obtained was filtered, washed with water and crystallized from suitable solvent. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase[15].



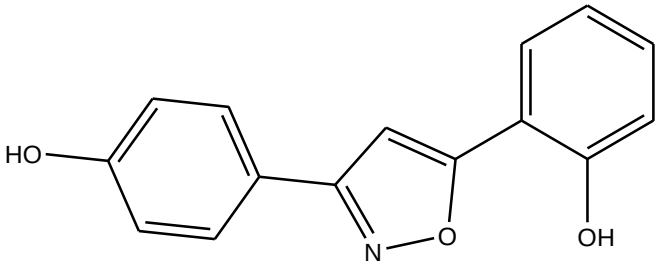
BIOLOGICAL ACTIVITIES

Anti-inflammatory activity

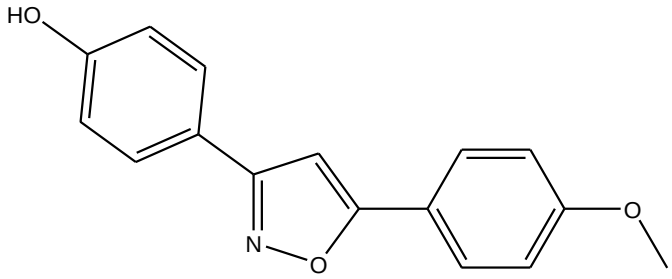
Isoxazole derivatives were screened for their anti-inflammatory activity by *in vivo* method on rats. The action of synthesized compounds was done on paw of Wister albino rats and compared with Diclofenac sodium as a standard. The paw volumes were recorded within one hour interval time duration and the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



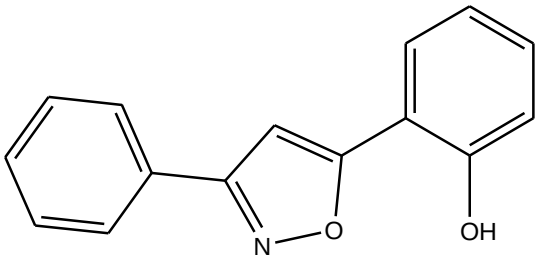
4-[5-(3-nitrophenyl) isoxazol-3-yl] phenol



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



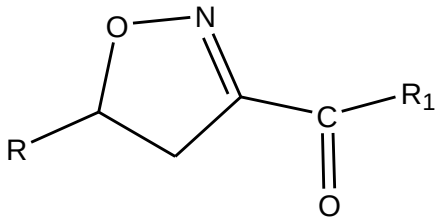
4-[5-(4-methoxyphenyl) isoxazol-3-yl] phenol



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].



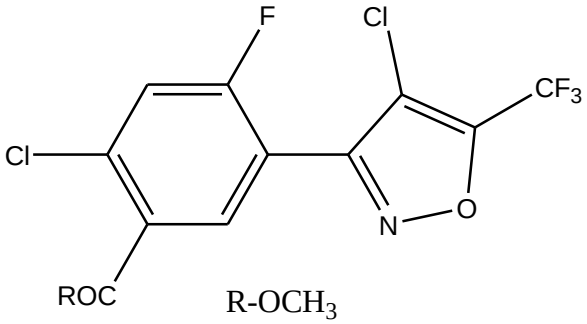
R-Aryl orAlkyl

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

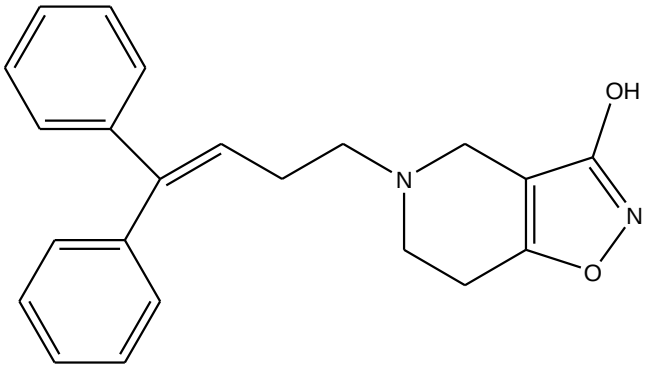
bioactivities and reported. And some of them have been commercialized such as JU-485 and KPP- 314 which are substituted phenyl isoxazoline derivatives. In this several novel-3(substituted phenyl) Isoxazole derivatives are synthesized and exists herbicidal activities towards various weeds like Echinochloa, Crusgalli, SetariaViridis, Abutilon theoprastil[18-21].



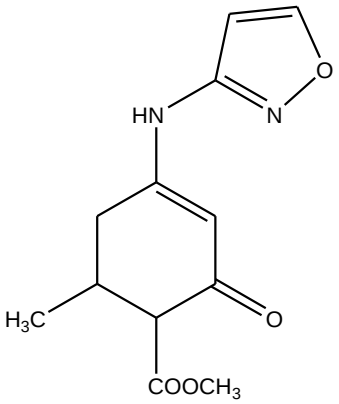
R-OCH_3
-OC_2H_5
-NHC_6H_5
-$N(C_2H_5)_2$

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[23]. Second compound is also a synthesized isoxazole derivative which affects the sodium channel to show its activity[24].



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

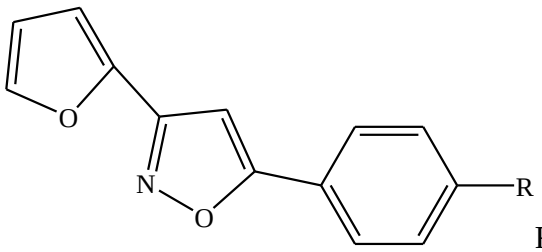


4-(Isoxazol-3-ylamino)-6-methyl-2-oxo-cyclohex-3-enecarboxylic acid methyl ester

Antibacterial Activity

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 370C for 24 hrs. Diameter of the zone of inhibition was measured andthe average diameter for each sample was calculated.The diameter obtained for the test samples were compared with that produced by standard ampicillin.

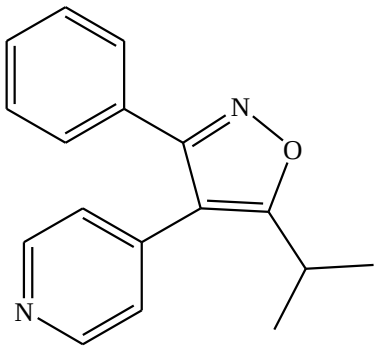


R=NH2, Br, NO2, C, F, CH_{3s}

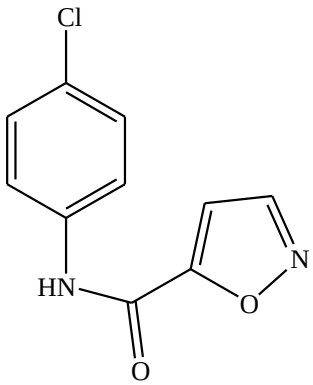
Anticancer activity

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.



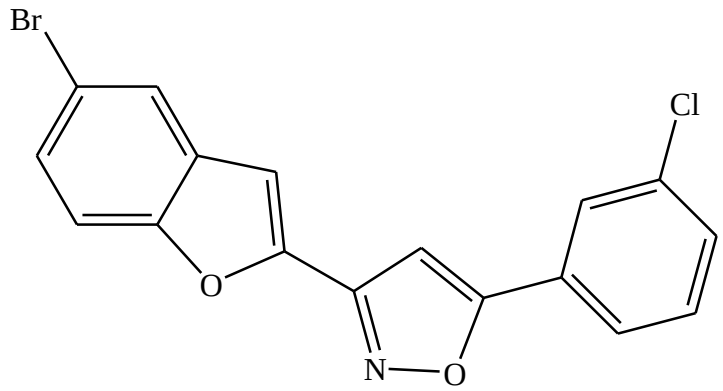
4-(5-Isopropyl-3-phenyl-isoxazol-4-yl)-pyridine



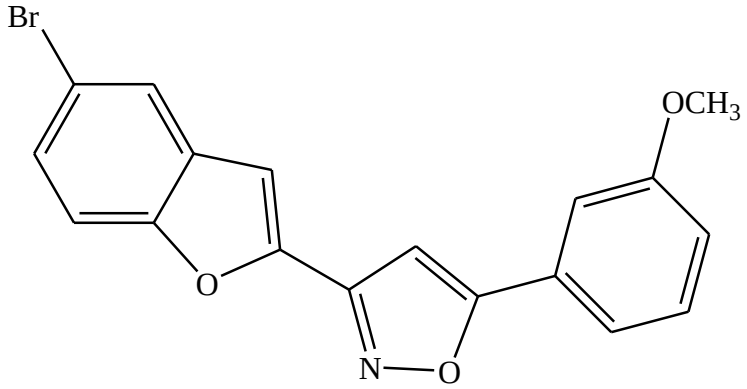
Isoxazole-5-carboxylic acid (4-chloro-phenyl)-amide

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].



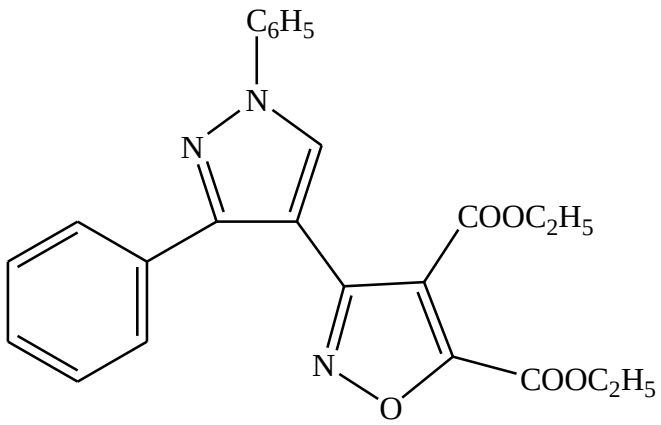
3-(5-Bromo-benzofuran-2-yl)-5-(3-chloro-phenyl)-isoxazole



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

Anti-Nociceptive Activity

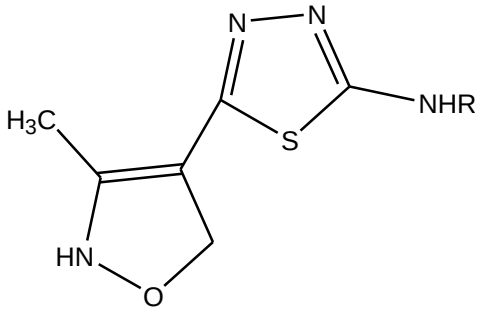
K.Karthikeyan, T.veenuseelan et.al was developed a systematic procedure for the synthesis of pyrazolyl isoxazole and they performed the activity of anti-nociceptive action by using various animal tissues. The lead molecule was synthesized by using 1,3dipolar cycloaddition of pyrazole derived nitric oxide 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

Immunological Activity

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 (A) 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

CONCLUSION

Emerging research interest on isoxazole moiety already has been proven by various search group in the literature. Though many procedures are established for the synthesis of isoxazole core, but very few of them yield isoxazole with better percentage of product. But much more effort yet to be given to develop new synthetic strategies. Furthermore biological activity with new dimension need to be explored for isoxazole. Therefore this review may be helpful for medicinal chemist.

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, Stagnod'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. Rescifina A, Varrica MG, Carnovale C, Romeo G, Chiacchio U. Novel Isoxazole polycyclic aromatic hydrocarbons as DNA-intercalating agents. *Euro. J. Med. Chem.*, 2012, 51:163-173.

4. Fernand Lambein; Yu-HaeyKuo; Roger Van Parijs. Isoxazolin-5-ones, Chemistry and Biology of a New Class of Plant Products, Heterocycles, Vol.4, Issue 3, 1976, Pages 567-593.
5. Kenichi Murai; Shuji Miyazaki; HiromichiFujioka.Reactivityof the ester group attached isoxazoline, benzisoxazole, and isoxazole: a facial preparation of 3-acyl-substituted these heterocycles, Tetrahedron Letters, 2012, Volume 53, Issue 29, Pages 3746–3749.
6. F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.*, 2005, *127*, 210-216.
7. Q.-f. Jia, P. M. S. Benjamin, J. Huang, Z. Du, X. Zheng, K. Zhang, A. H. Conney, J. Wang, *Synlett*, 2013, *24*, 79-84.
8. J. P. Waldo, R. C. Larock, *Org. Lett*, 2005, *7*, 5203-5205.
9. R. Harigae, K. Moriyama, H. Togo, *J. Org. Chem.*, 2014, *79*, 2049-2058.
10. Barber G. and Olofson, R.A. (1978). A useful, regiospecific synthesis of isoxazoles Journal of Organic Chemistry 73: 3015-3021.
11. C Selvam, MJ; Sanjay; T Ramasamy; AK Chakraborti. *Bioorg. Med. Chem. Lett.* 2005, 15, 179.
12. Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. Asymmetric catalytic Strecker reaction of *N*-phosphonyl imines with Et2AlCN using amino alcohols and BINOLs as catalysts. *Chem. Commun*. 2010, *46*, 4330–4332.
13. Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. Asymmetric catalytic *N*-phosphonyl imine chemistry: The use of primary free amino acids and Et2AlCN for asymmetric catalytic Strecker reaction. *J. Org. Chem.* 2010, *75*, 5144–5150.
14. Kaur, P.; Wever, W.; Pindi, S.; Milles, R.; Gu, P.; Shi, M.; Li, G. The GAP chemistry for chiral *N*-phosphonyl imine-based Strecker reaction. *Green Chem*. 2011, *13*, 1288–1292.
15. G. Parmeshwarappa and S.S. Sangapure., *Organic Chemistry An IndianJournal*, 4(5), 2008, 375.
16. SK Gupta. Practical pharmacology, Jaypee Publications, New Delhi, 2007; pp. 480.
17. Fiebig, H. H.; Berger, D. P.; Dengler, W. A.; Wallbrecher, E.; Winterhalter, B. R.Contrib. Oncol. 1992, 42, 321.

18. Y. H. Zhou, W. R. Miao, L. B. Cheng, D. X. Wang, et al. , Chinese J. Pest. Sci., 2002 4 (1), 1.
19. B. C. Hamper, M. K. Mao, W. G. Phillips, US 6,121,458, 2000.
20. H. Kenji, Y. Tomoyuki, Y. Mitsuo, E. Emiko, T. Tomoko, A. Kiyomi., US 5,281,742, 1994.
21. M. Olaf, M. Markus, H. Gerhard, R. Robert, S. Peter, Z. Cyrill, M. Ulf, W. Helmut, 4,654,2001.
22. Lepage F, Tombret F, Cuvier G, Marivain A, Gillardin JM. New Naryl isoxazole carboxamides and N-isoxazolylbenzamides as anticonvulsant agents. *Euro. J. Med.Chem.*, 1992, 27(6):581–593.
23. Bolvig Y, Larsson OM, Pickering DS, Nelson N, Falch E, Krogsgaard- Larsen P, Schousboe A. Action of bicyclic isoxazole GABA analogues on GABA transporters and its relation to anticonvulsant activity. *Euro. J. Pharmacol.*, 1999, 375:367–374.
24. Eddington ND, Cox DS, Roberts RR, Butcher RJ, Edafiogho IO,
1. Stables JP, Cooke N, Goodwin AM, Smith CA, Scott KR. Synthesis and anticonvulsant activity of enaminones. 4. Investigations on isoxazole derivatives. *Euro. J. Med.Chem.*, 2002, 37:635–648.
25. (a) H Schutz. Bezodiazepines. (Springer, Heidelberg), 1982 (b) JK Landquist. in Comprehensive Heterocyclic Chemistry, Vol. 1, Katritzky A R & Rees C W (Pergamon, Oxford), 1984, 166-170. (c) RI Fryer. Bicyclic Diazepines, in Comprehensive Heterocyclic Chemistry edited by Taylor E C, Vol. 50, Chapter II, (Wiley, New York), 1991 (d) LO Randall, B Kappel. in Benzodiazepines, edited by (Raven Press, New York), 1973, 27.
26. 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.
27. 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- carboxamidylisoxazoles as potential chemotherapeutic agents for colon cancer. Am J Biomed Sci. 2012; 4(1): 14-25.
28. P.M. GurubasavarajaSwamy and Y.S. Agasimundin, *RasayanJ.Chem.*, 1, 421 (2008).

29. R.Kalirajan, S.U. Sivakumar, S. Jubie and B.Suresh, *International J Chem Tech Research*,1, 27 (2009).
30. Urmila Gupta, Vineeta Sareen, Vineeta Khatri and Sanjana Chugh, *Indian J.Heterocyclic. Chem*, 13, 351 (2004).
31. Sakem, S.; Sun, H. H. J. Org. Chem. 1991, 56, 4304.
32. Kawasaki, I.; Yamashita, M.; Ohta, S. Chem. Pharm. Bull. 1996, 44, 1831.
33. Gu, X.; Wan, X.; Jiang, B. Bioorg. Med. Chem. Lett. 1999, 9, 569.
34. Fiebig, H. H.; Dengler, W. A.; Roth, T. Contrib. Oncol. 1999, 54, 29.