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POTENTIAL ACTIVITIES OF ISOXAZOLE DERIVATIVES

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ABSTRACT

Isoxazole derivatives constitute an important class of heterocycles in drug discovery. They are clinically effective as antibacterial, antifungal, anti-inflammatory, anticancer, anti-tubercular and antineoplastic agnts. Modification in their structure has offered a high degree of diversity that has proven euseful for the development of new therapeutic agents having improved potency and lesser toxicity. Considering the extensive research on isoxazolein the past, it was essential to review the wide spectrum of biological activity of isoxazole. To conclude, this review will be beneficial for new drug discovery of isoxazolemoiety.

KEYWORDS: Isoxazole, Analgesic, Anticancer, Antimicrobial, Anticonvulsant.

INTRODUCTION

The dramatically rising prevalence of multidrug-resistant microbial infection in the past few decades has become a serious health care problem. In order to prevent this serious medical problem, the elaboration of the new types of the previously known drugs is a very actual task. In recent years, the synthesis of novel isoxazole derivatives remains a main focus of medicinal research. Isoxazole is a five membered heterocyclic compound.

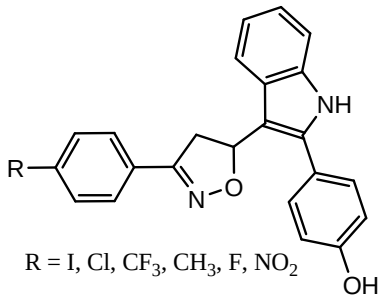
Derivatives of Isoxazole have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores and synthons in the field of organic chemistry. Owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on these nuclei. Isoxazole derivatives exhibit various biological activities such as, Antibacterial.[1] Anticonvulsant.[2] Anticancer.[3]

Anthelmintics.[4] Anti-inflammatory.[5] Adenosine antagonist.[6] Fungicidal.[7] Herbicidal.[8] Hypoglycemic.[9] Muscle relaxant.[10] Nematocidal.[11] Insecticidal.[12] Antiviral[13] and Antimicrobial.[14] Antitubercular.[15] Now days, many drugs are in the world market, while several hundred are in clinical trials. The present review focuses on the Isoxazolewith potential activities that are now in development.

BIOLOGICALLY ACTIVE ISOXAZOLE AND ITS DERIVATIVES

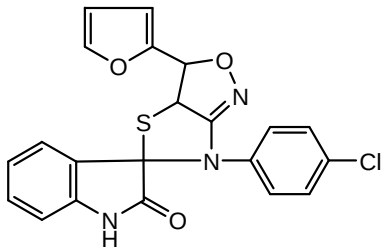
Analgesic and Anti-inflammatory activity

Mastan. M et al synthesized a new series of 4-(3-(3-(4-substituted phenyl)-4, 5-dihydroisoxazol-5-yl)-1H-indol-2-yl) phenol derivatives and observed the Analgesic activity.[16]

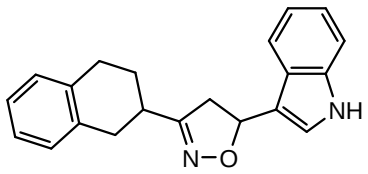


R = I, Cl, CF_3, CH_3, F, NO_2

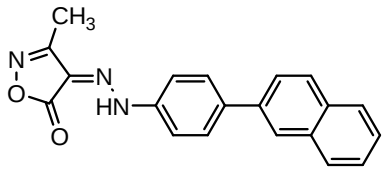
Supriya Mana et.al., Synthesized the Novel Thiazolo-Isoxazole fused Isatin derivatives and evaluated for its possible analgesic and anti-inflammatory activities. These compounds showed the significant activity.[17]



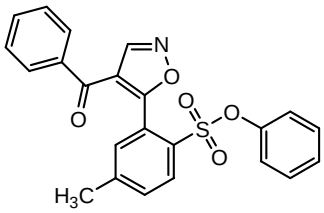
Hamdy and Kamel Synthesized new series of 5,6,7,8-tetrahydronaphthalene derivatives conjugated with chalcone, pyridine, pyrazole and isoxazole functionalities and hoping to circumvent the unwanted ulcerogenic and other side effects of the already used nonsteroidal anti-inflammatory drugs.[18]



S. Subramanyam. et al Synthesised the 1, 8-Napthyridine Nucleus Linked with Pyrazolinone, Pyrazole, Isoxazolinone and Isoxazole Derivatives and the newly synthesized compounds were screened for their anti-inflammatory and analgesics activities.[19]

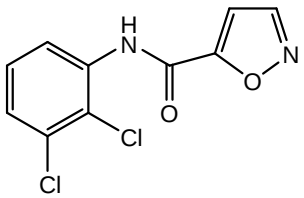


Babasaheb V. Kendre et al, Synthesised some novel pyrazole, isoxazole, benzoxazepine, benzothiazepine and benzodiazepine derivatives bearing an aryl sulfonate moiety. All the synthesized compounds were evaluated for their anti-bacterial and antifungal activities. Some of the selected compounds were also screened for their anti-inflammatory activity.[20]

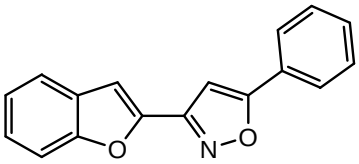


Anti cancer activity

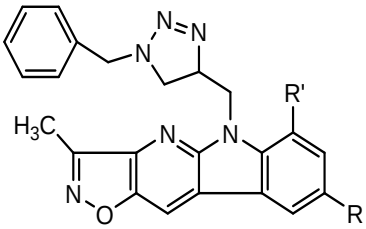
Jiajiu Shaw et al synthesized Novel *N*-phenyl-5-carboxamidyl Isoxazoles and evaluated by the *in vitro* disk-diffusion assay and IC50 cytotoxicity determination. The results showed that one of the derivatives were most active against colon 38 and CT-26 mouse colon tumor cells with an IC50 of 2.5µg/mL for both cell lines.[21]



Rajeshkumar Sahu et al was carried out the studies of 3-(1-Benzofuran-2-yl)-5-(Substituted Aryl) Isoxazole derivatives and evaluated for *in vitro* cytotoxic activity on HeLa cell lines at the minimum seven concentrations at two fold dilutions.[22]

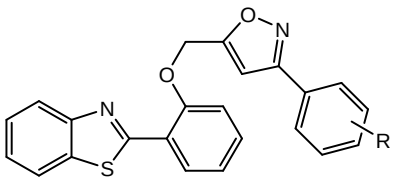


Rajanarendar et al carried out the studies of *In Vitro* Anticancer Activity of Novel 5-[(1-Benzyl-1*H*-1,2,3-Triazol-4-yl)Methyl]-3-methyl-5*H*-isoxazolo[5',4':5,6]pyrido[2,3-*b*]indoles by using MTT assay method. The results indicate that these compounds have considerable *in vitro* anticancer activity.[23]



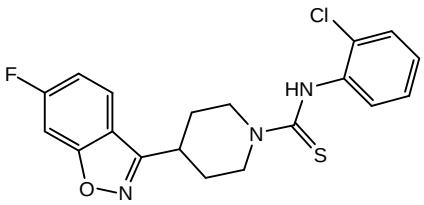
a) R=H, R'=H; b) R=Cl, R'=H; R=Br, R'=H
d) R=CH_3, R'=H; e) R=OCH_3, R'=H; R=H, R'=CH_3

R. M. Kumbhare et al Synthesized the novel triazoles and isoxazoles linked 2-phenyl benzothiazole derivatives. These compounds have been tested for their cytotoxicity against three cancer cell lines. Among the compounds tested, compound 5d showed good cytotoxicity against Colo-205 and A549 cells incomparison to standard control PMX 610(1). Further compound 5d has been tested for its apoptotic activity and its inhibitory activity against caspase and PARP proteins.[24]



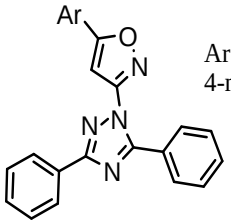
4a: R = 4-CH_3, 4b: R = 4-OCH_3, 4c: R = 2-F,
4d: R = 4-Cl, 4e: R = 4-Br, 4,f: R = 4-OCF_3
4g: R = 3,4,5-OCH_3

Chandra and Mahadimane synthesized the Novel Benzisoxazole Derivatives evaluated Against Ehrlich Ascites Carcinoma Cells in Swiss Albino Mice by in vitro MTT assay, the synthesized molecules have a promising role to play as anticancer agents.[25]



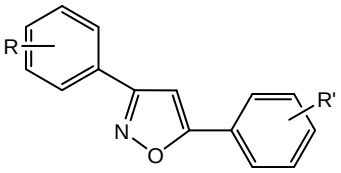
Antitubercular Activity

A new class of isoxazole derivatives containing 1,2,4-triazole moiety were synthesized Khanage et al., All compounds were screened for antibacterial, antimycobacterial and anticancer activity. The *in vitro* antimycobacterial activity of the compounds against Mycobacterium tuberculosis H37Rv was evaluated. The highest inhibition was observed through compound 4f as 76% at >6.25µg/ml.[26]



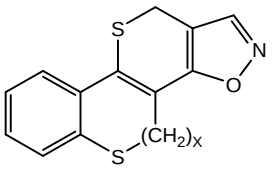
Ar = 4-chlorophenyl, 3-nitrophenyl, 4-(N,N-dimethyl)aniline
4-methoxybenzene, 2-furfuryl, 2-chlorophenyl, phenyl

3,5- substituted isoxazoles, 4-[(3, 5-substituted, 1H-pyrazol-1-yl) carbonyl] pyridines and 4, 6-substituted pyrimidin-2-amines were synthesized by VG. Rajurkar et al and these disubstituted compounds were evaluated for their antimicrobial, antifungal and antitubercular activity.[27]



2a = p-OH, p-H
2b = p-H, m-NO_2
2c = p-OH, p-Cl
2d = p-OH, m-NO_2

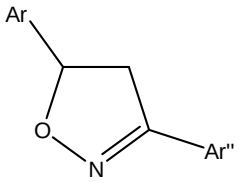
Palanisamy *et al*; Studied the 6,11-Bisthiatetracyclic- and pentacyclic Steroidal Analogues and all these compounds were evaluated for bioactivity against *M. tuberculosis* (H37Rv) with MIC 7.7 and 7.3µM respectively.[28]



X =1, 11
X = 2,12

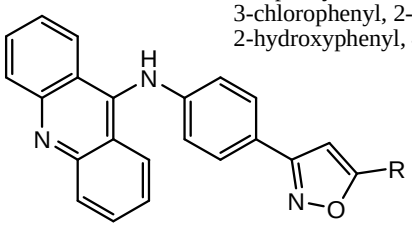
Antioxidant activity

K Madhavi, K Bharathi and KVSRG Prasad were Synthesized a series of 3-methyl-4-nitro-5-(substituted styryl) isoxazole derivatives and evaluated for antioxidant, anti-inflammatory and analgesic activities with a view to evaluate effect of nitro substitution on styrylisoxazoles. Compounds with sterically hindered phenolic groups exhibited good anti-inflammatory activity with better antioxidant properties and are devoid of toxicity as well as ulcerogenic potential.[29]



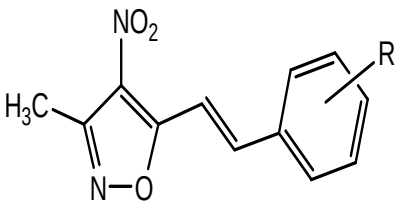
a) Ar = 4-$OCH_3C_6H_4$, Ar'' = 4-FC_6H_4;
b) Ar = 4-$OCH_3C_6H_4$, Ar'' = 4-ClC_6H_4;
c) Ar = 4-$OCH_3C_6H_4$, Ar'' = 2-ClC_6H_4;
d) Ar = 4-$OCH_3C_6H_4$, Ar'' = 4-BrC_6H_4;
e) Ar = 4-$OCH_3C_6H_4$, Ar'' = 4-CNC_6H_4;
f) Ar = 4-$OCH_3C_6H_4$, Ar'' = 4-Cl-2-$NO_2C_6H_3$;
g) Ar = 4-$OCH_3C_6H_4$, Ar'' = C_6H_5;
h) Ar = 4-$OCH_3C_6H_4$, Ar'' = 4-$OCH_3C_6H_4$;
i) Ar = 4-$OCH_3C_6H_4$, Ar'' = 2,4-$(OCH_3)_2C_6H_3$

A convenient synthesis of novel isoxazole-substituted 9-anilinoacridine derivatives was reported by the R. Kalirajan, M. H. Mohammed Rafick, S. Sankar and S. Jubie. The compounds were screened for *in vitro* antioxidant activity by DPPH method, reducing power assay and total antioxidant capacity method. The cytotoxic activity of the compounds was also studied in HEp-2 cell line.[30]



R = phenyl, 4-methoxy phenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 2-hydroxyphenyl, 4-nitrophenyl,2-nitrophenyl

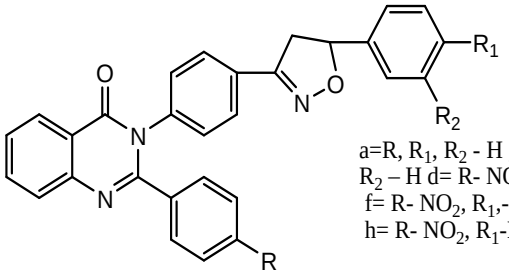
Ajay Kumar Kariyappa et al carried out the studies on the structural impact of 3-aryl-5-(4-methoxyphenyl)-4,5-dihydroisoxazole-4-carbonitriles. The compounds were tested for their antioxidant activity and reducing power ability. Based on the results of an anti-oxidant study, the effect of substitution on the activity and possible structure activity relationship of the compounds for their antioxidant activity is presented.[31]



R = H, 4-Cl, 4-CH3, 4-OCH3, 4-OH
2-OH, 4-dimethylamine, 4-isopropyl,
3,4-dimethoxy, 3,4,5-trimethoxy,

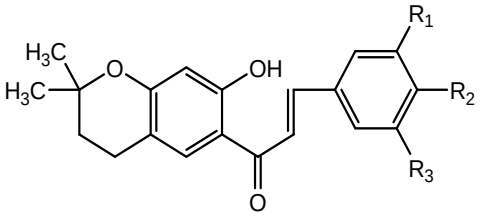
Anti - Microbial Activity

Synthesis of 3-[4-(5-(3,4-disubstituted phenyl)-4,5-dihydro isoxazol-3-yl) phenyl]-2-substutied phenyl Quinolin-4(3H)-one derivatives has been described by Kumar Nallasivan P et al. The synthesized compounds were tested for antibacterial activity against four bacterial strains, of them two are positive strain *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strain *Escherichia coli* and *Pseudomonas aeruginosa*. The compounds were also evaluated for antifungal activity against two fungal strains and *Asperigillus niger* and *Saccharomyces cerevisiae.*[32]



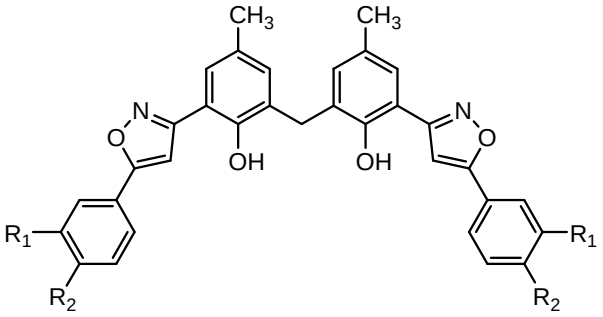
a=R, R_1, R_2 - H , b= R- NO_2, R_1, R_2 –H , c= R- H, R_1, -OCH_3, R_2 – H d= R- NO_2, R_1,-OCH_3, R_2-H; e= R, R_1,-H, R_2 – Cl; f= R- NO_2, R_1,- H, R_2 – Cl g= R, R_1- H, R_2 - NO_2; h= R- NO_2, R_1-H, R_2 - NO_2

Gollapalli Naga Raju et al were synthesized the novel Isoxazole derivatives by the Chalcones were subjected for reaction with hydroxyl amine hydrochloric acid and potassium hydroxide to give isoxazoline derivative of chalcone. All the synthesized compounds were tested for their antibacterial and antifungal activity in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and two fungal strains.[33]

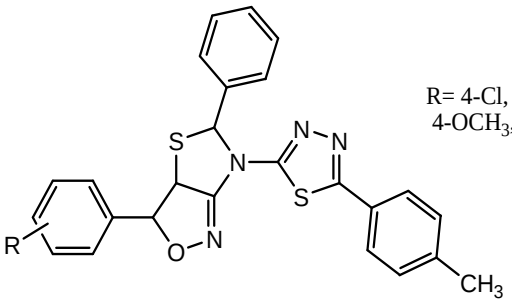


1. R_1 & R_3 = OCH_3; R_3 = H
2. R_1 & R_3 = H; R_2 = N $(CH_3)_2$.
3. R_1 & R_3 = H; R_2 = Cl.
4. R_1 & R_3 = H; R_2 = OCH_3.
5. R_1 & R_3 = H; R_2 = CN.

A series of 1,1-bis [2-hydroxy-3-(5'-aryl-isoxazoline-3-yl)-5-methyl phenyl] methane and 1,1-bis [2-hydroxy-3-(5'-aryl-isoxazol-3-yl)-5-methyl phenyl] methane derivatives were synthesized by Gajbhiye J. M. and Chopade A.U and evaluated for their antimicrobial activity against some selected pathogenic micro-organisms such as Gram-positive bacteria, and Gram-negative bacteria.[34]

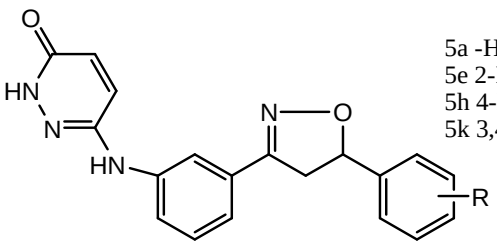


New class of 1, 3, 4-thiadiazoles which are incorporating with isoxazolo-thiazole moieties were synthesized by the Nareshvarma Seelam, Satya P. Shrivastava and Somarouthu Prasanth. The new synthesized compounds were evaluated for their antimicrobial activity. The final results revealed that some of the compounds were exhibited well antimicrobial activity compared to the standard drugs.[35]



R= 4-Cl, 2-Cl, 4-NO_2, 4-N(Me_2), 3-NO_2, 4-OCH_3, 2-OCH_3, 4-CH_3, 3,4,5-$(OCH_3)_3$,4-Br

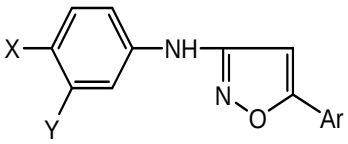
Tupare et al worked on the synthesis and antimicrobial activity of novel isoxazoline derivatives *via* novel chalcones. The synthesized compounds were evaluated for their antimicrobial activity by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and two fungal strains.[36]



5a -H; 5b 3, 4-OCH_3; 5c 4-OH; 5d 2-OH; 5e 2-Br, 3, 4-OCH_3; 5f 3-NO_2; 5g 4-Cl; 5h 4-NO_2; 5i 4-OCH_3; 5j 2-NO_2; 5k 3,4, 5- tri- OCH_3; 5l 2, 6-di-Cl

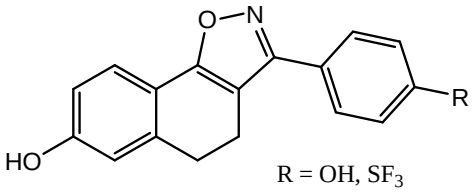
Miscellaneous Activities

Chakka Gopinath et al synthesized a new 3-(4-substituted anilino)-5-(3', 4'-disubstituted aryl)-2-isoxazoles by microwave irradiation (560 w) of 3-phenyl or substituted phenyl -1-anilino or substituted anilino -2- propene -1- ones with hydroxylamine hydrochloride and sodium acetate. These compounds were evaluated for the anthelmintc activity.[37]



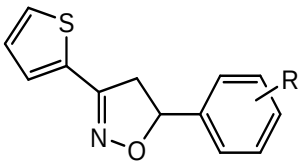
	X	Y	Ar
01.	H	H	C_6H_5
02.	H	H	$C_6H_3(OH)(OCH_3)$
03.	H	H	$C_6H_4N(CH_3)_2$
04.	H	H	$C_6H_4(NO_2)$
05.	H	H	$C_6H_4(NO_2)$
06.	H	H	$C_6H_4(OCH_3)$
07.	H	H	$C_5H_4O_2$
08.	OH	H	C_6H_5
09.	OH	H	$C_6H_3(OH)(OCH_3)$
10.	OH	H	$C_6H_4N(CH_3)_2$

E. Tzanetou et al synthesized a novel isoxazole derivatives and evaluate their angiogenesis inhibition derived anticancer activity. Results indicated that the novel isoxazole derivatives are potent inhibitors of the growth of different types of endothelial cells that play important role in angiogenesis. In addition, they also inhibit the tube formation in human endothelial cells.[38]



R = OH, SF_3

Kumar et al synthesized a series of 5-substituted phenyl-3-(thiophen-2-yl)-4, 5-dihydro-1, 2-oxazoles. All the compounds were evaluated for their antidepressant and antianxiety activities in mice by forced swimming test and elevated plus maze method respectively.[39]



R= 4-Cl, 2-Cl, 4-NO_2, 4-$N(Me_2)$, 3-NO_2, 4-OCH_3, 2-OCH_3, 4-CH_3, 3,4,5-$(OCH_3)_3$,4-Br

CONCLUSION

Isoxazole is a unique template that is associated with several biological activities. Due to the diverse and versatile biological properties of isoxazole derivatives, they are of great interest to the research community. The plethora of research described in this review indicates the wide spectrum of biological activities exhibited by isoxazole derivatives. The biological profiles of these new generations of isoxazoles would represent a fruitful matrix for further development of isoxazole nucleus, which can be a lead nucleus for future developments to get safer and effective therapeutic agents.

ACKNOWLEDGEMENT

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