Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(3):302-311

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Benzoxazole: The molecule of diverse biological activities

Priyanka Lokwani[1]*, B.P. Nagori[2], Nikhil Batra[2], Anju Goyal[3], Stuti Gupta[1]and Nisha Singh[4]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur
[2]Lachoo Memorial College of Science and Technology, Pharmacy Wing, Jodhpur
[3]B.N Girls College of Pharmacy, Udaipur
[4]Rameesh Institute of Vocational & Technical Education, Greater Noida

---

ABSTRACT

A series of analogue and derivatives of heterocyclic bearing nitrogen, oxygen and oxazole moieties constitutes the core structure of a several biological active compounds. Oxazole containing heterocyclic compounds plays an important role in medicinal chemistry and exhibit wide range of biological activities. Benzoxazole Nucleus have been reported various types of biological activities such as Antidepressant, Antibacterial, Antifungal, Antiinflammatory, Analgesic and Anticancer.

Keywords: Benzoxazole, antimicrobial, CNS activities, analgesic and antiinflammatory, antihyperglycaemic, anticancer, melatoninergic.

INTRODUCTION

The small and simple benzoxazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like antimicrobial, CNS activities, antihyperglycemic potentiating activity, analgesic and anti-inflammatory activity. Benzoxazole is used primarily in industry and research, and has no household use. Being a heterocyclic compound, benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Benzoxazoles can be considered as structural isosteres of the naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems.

Chemistry of benzoxazole nucleus

Benzoxazole is an aromatic organic compound having benzene fused oxazole ring structure with a molecular formula C_7H_5NO, molar mass 119.12 g/mol, and an odor similar to pyridine with IUPAC name 1-Oxa-3-aza-1H-indene, Insoluble in water and melting point 27-30^{O} C.

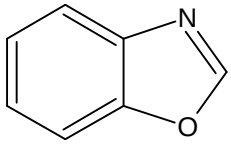
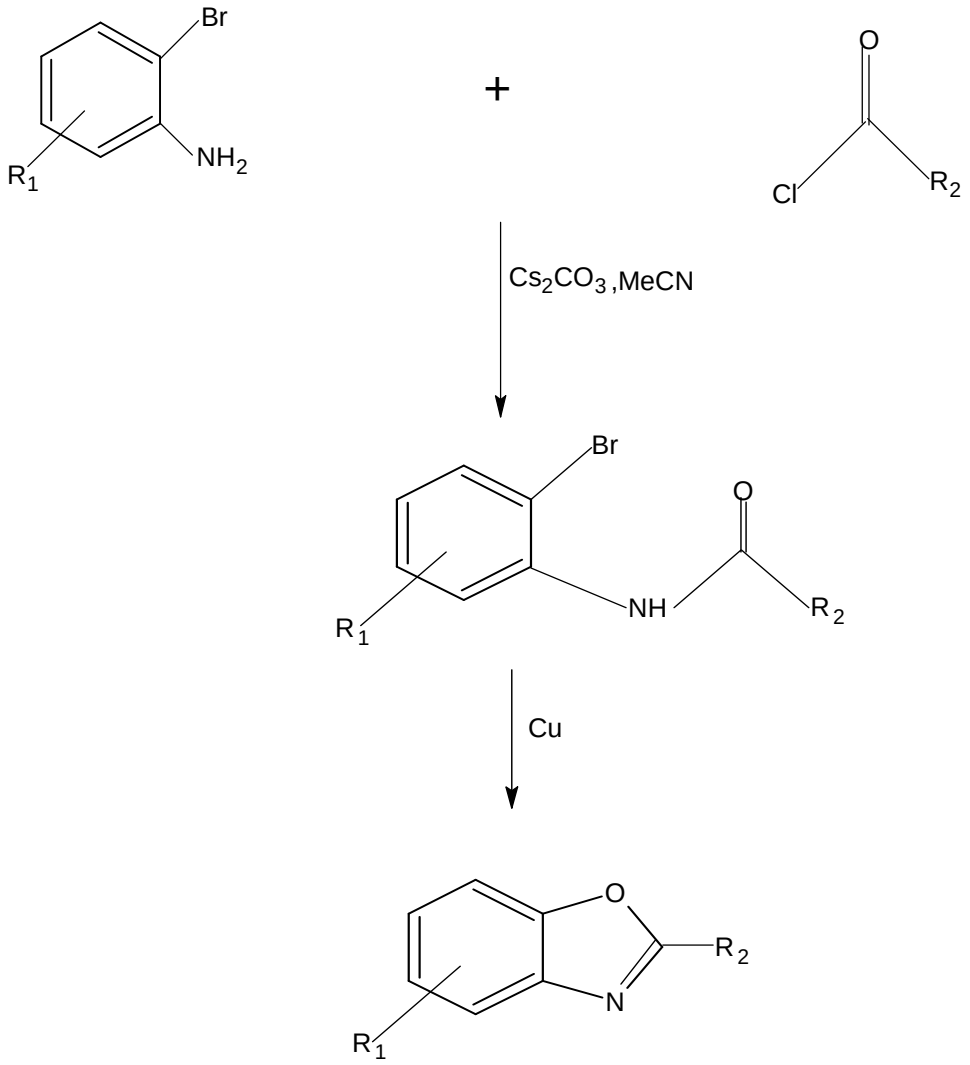


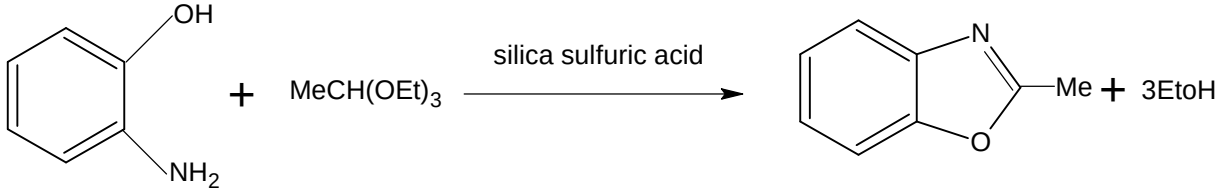
Fig.1. Benzoxazole

Synthesis of benzoxazole nucleus

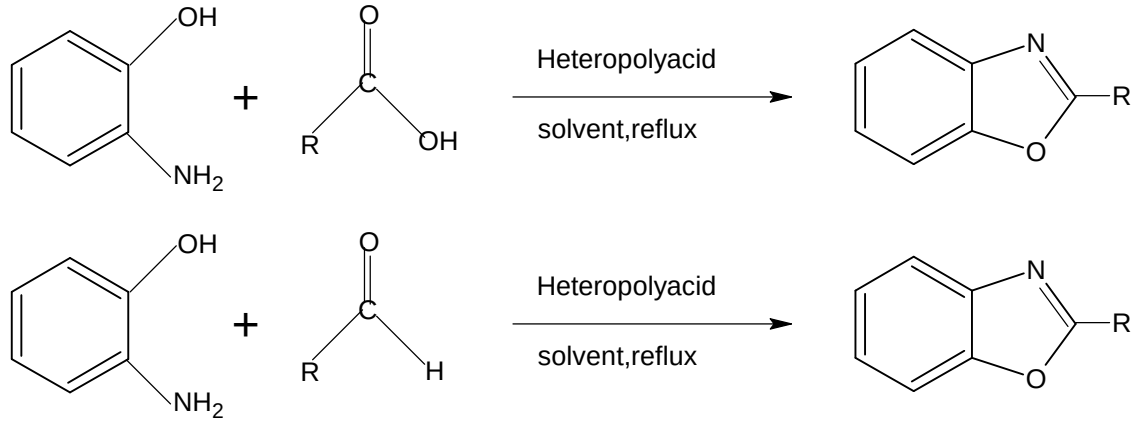
Batley [1] carried out a copper catalyzed one-pot synthesis of benzoxazoles using bromoanilines and acyl halides in the presence of a base and a solvent giving intermediates which finally gave pure benzoxazoles (21–97%) isolated yields, exhibiting a broad range of biological activities. They can also be used as precursors in the synthesis of drugs.



Benzoxazole may be prepared by the reaction of orthoesters with o-aminophenols in the presence of silica sulphuric acid under heterogenous and solvent–free conditions [2].



Benzoxazole derivatives may be synthesized from reaction of 2-aminophenol with benzoic acid and benzaldehyde using catalytic amount of three different Keggin types of HPAs including $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$ and $H_3[PMo_{12}O_{40}]$ as the catalysts. [3-5]

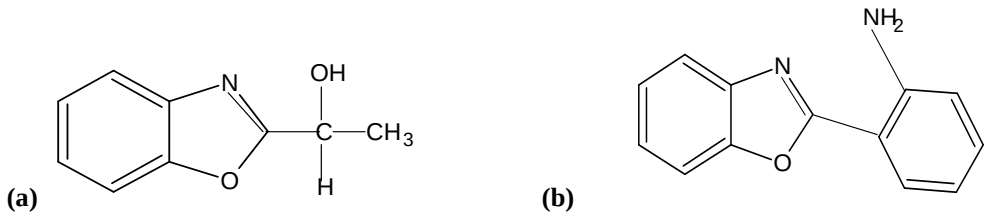


Medicinal importance of benzoxazole nucleus

During recent years there have been some interesting developments in the biological activities of benzoxazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities.

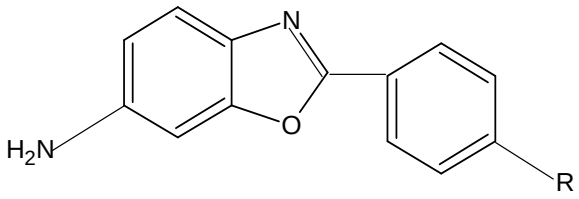
Benzoxazole with antimicrobial activity:

Elamin I Elnima et al [6] studied the in vitro antibacterial[2] and antifungal activities of six benzimidazole and benzoxazole derivatives. They were tested against standard strains and 59 clinical isolates. Of the six compounds, only two compounds (both benzoxazoles) were active, whereas the rest were devoid of any activity. Considerable growth inhibition of all of the standard strains, including fungi and gram-positive and gram-negative bacteria, resulted when they were treated with these compounds. Fifty-nine clinical isolates of *Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus* were tested for susceptibility to the two compounds. The most susceptible were the *S. aureus* isolates. The two compounds were of comparable activity against all of the isolates, with compound (b) showing a slightly higher activity than compound (a). Their respective minimal inhibitory concentrations for 90% inhibition of *S. aureus* were 25 and 50 µg/ml. The gram negative bacteria were resistant to the two compounds and required minimal inhibitory concentrations of 200 µg/ml for a similar degree of inhibition .



(a) **(b)**

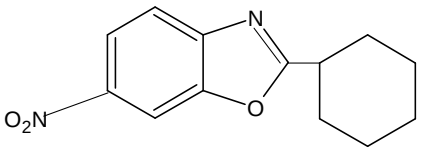
Esin Sener et al [7] synthesized 5-amino -2-(p-substituted-phenyl) Benzoxazole derivatives. They were synthesized by heating 2, 4-diaminophenol with the appropriate carboxylic acids in the presence of polyphosphoric acid. 2-substituted benzoxazoles[3] were prominently studied trusting that this position is decisive for the biological activity whereas position 5 prevailing the intensity of activity. Benzoxazoprofen and zoxazolamin are also the kind of benzoxazole derivatives which are substituted at both 2 and 5 positions.



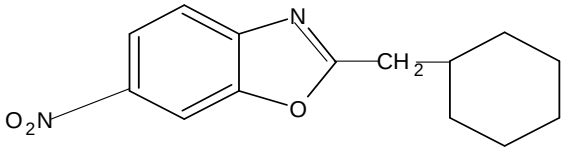
5-Amino-2-(p-Substituted-Phenyl) Benzoxazole Derivatives

R	**Acid used as starting compound**
H	Benzoic acid
C_2H_5	p-Ethyl benzoic acid
Br	p-Bromo benzoic acid
F	p-Fluorobenzoic acid
$N(CH_3)_3$	p-Dimethylaminobenzoic acid
NO_2	p-Nitrobenzoic acid

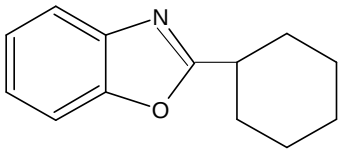
Ahmet Akin et al [8] synthesized 2, 5 – disubstituted benzoxazoles and benzimidazoles in order to determine their antimicrobial[5] activities and feasible structure activity relationship.The synthesized compounds were tested in vitro against 3 gram positive, 3 gram negative, bacteria and a fungus *Candida albicans* .



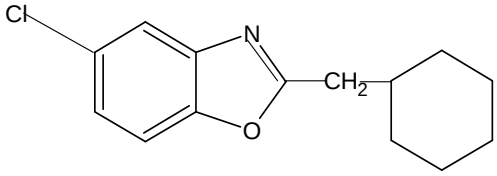
(a) 5-nitro-2-cyclohexyl Benzoxazole



(b) 5-nitro-2- cyclohexylmethyl Benzoxazole



(c) 2-cyclohexyl Benzoxazole

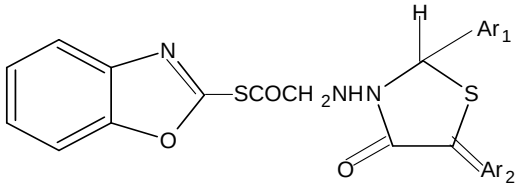


(d) 5-chloro 2-cyclohexylmethyl Benzoxazole

(a) and (b) were found most active than the others against *Bacillus subtilis* at MIC value of 3.12 µg/ml and the compound (b) indicated significant antibacterial activity against the enterobacter *Pseudomonas aeruginosae*. The compound (a), (c), (d) also exhibit antimycotic activity against *C.albicans*.

P.Kohli et al [9] synthesized Arylidenes of thiazolidines[7] with Mercaptobenzoxazole, namely [(aryl-4-oxo-1,3-thiazolidin)-hydrazinoacetyl-mercaptobenxazole];(5-arylidene)-2-aryl-4-oxo-1,3-thiazoliden hydrazinoacetyl-mercaptobenxazole. Thiazolidinone moiety is well known for biological and pharmacological activities such as CNS stimulant , anthelmintic, antibacterial, antifungal, hypnotic, amoebicidal,mosquito repellent, analgesic, diurinals, antiinflammatory, anticonvulsant, nematocidal, antitubercular,etc. 2-Mercaptobenzoxazole is also reported as a good medicinal as well as a biological agent. It has been found that thiazolidinon-arylidenes and 2-mercaptobenzoxazole when incorporated in one framework enhance the biological activity. Antimicrobial evaluation was done by agar dilution method against three pathogenic bacteria viz. *Bacillus subtilis, Escherichia coli and Klebsiella pneumoniae* and three pathogenic fungi viz. *Aspergillus niger, Candida albicans and Fusarium oxysporum*. Among new derivatives

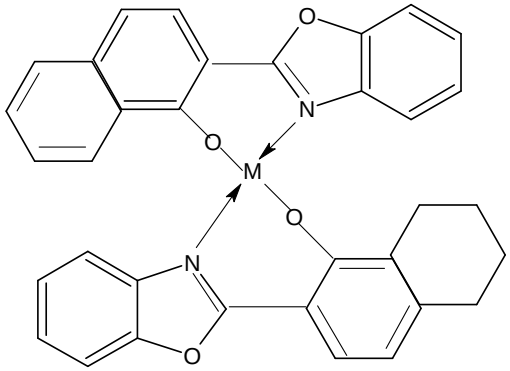
evaluated, the chloro derivatives exhibited higher potency as compared to the standard drugs streptomycin (for bacteria) and griseofulvin (for fungi) against the tested organisms.



Ar_1 = -C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4
Ar_2 = -C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4

Jarmila Vinsova et al (10) synthesized A series of lipophilic 2-substituted 5, 7-di-tert-butylbenzoxazoles by the reaction of 3, 5-di-tert-butyl-1, 2-benzoquinone with amino acids and dipeptides bearing N-terminal glycine. Dipeptides having other N-terminal amino acids undergo oxidative deamination. 5, 7-Di-tert-butylbenzoxazoles have shown activity against Mycobacterium tuberculosis and some nontuberculous strains where isoniazid has been inactive.

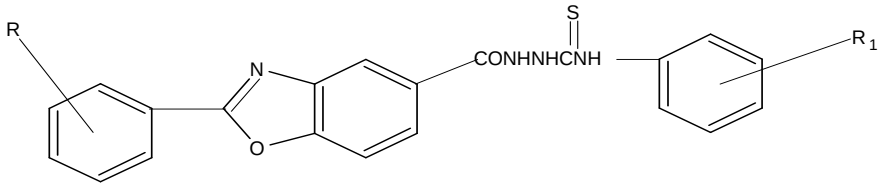
Anil Kumar et al (11) Synthesized new metal [Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II)] complexes from 2-(1'/2'-hydroxynaphthyl)benzoxazoles[8] and evaluate them for antimicrobial activity.



Where M=Fe, Co, Ni, Mg, Zn, Cd.

Benzoxazole with CNS activity:

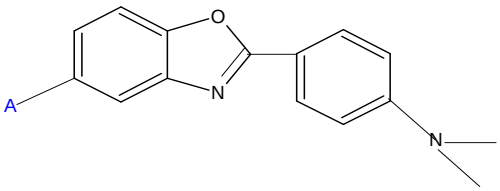
Nadeem Siddiqui et al (12) synthesized a series of 5-Carbomethoxybenzoxazole Derivatives[9] by using methyl-p-hydroxybenzoate and evaluate for anticonvulsant activity and Neurotoxicity. The identity of the compounds was confirmed on the basis of their elemental analysis and spectral data.



R= H,2-Cl,4-Cl
R= H,2-OCH_3,2-CH_3,3-CH_3,4-CH_3

Young Shin Chun et al (13) synthesized Functionalized benzoxazole derivatives[11] based on the structural features of PIB and FDDNP, which show excellent binding affinities to aggregated Aβ42 fibrils. All the synthesized compounds were evaluated by competitive binding assay against aggregated Aβ42 fibrils using [125I]TZDM and displayed good in vitro binding affinities with Ki values (0.47-15.3 nM) from subnanomolar to nanomolar range. Among them, two

benzoxazoles having malononitrile and ester moieties at C-6 exhibited superior binding affinities (Ki = 0.47 and 0.61 nM, respectively) to PIB (Ki = 0.77 nM).



Where A= Malononitrile, Ethyl acetate or ester moiety.

Sarangapani and Reddy (14) synthesized isatin N-(2-alkyl-benzoxazole-5-carbonyl) hydrazones and screened them for analgesic, antidepressent[23] and H1-antihistaminic activities.

Benzoxazole with antihyperglycemic potentiating activity:

Raok Jeon et al (15-18) synthesized Benzoxazole Containing Thiazolidinedione Derivatives.5-[4-[2-(Benzoxazol-2-yl-alkylamino) ethoxy] benzyl] thiazolidine-2, 4-diones have been prepared by Mitsunobu reaction of benzoxazolylalkylaminoethanol and hydroxybenzylthiazolidinedione.

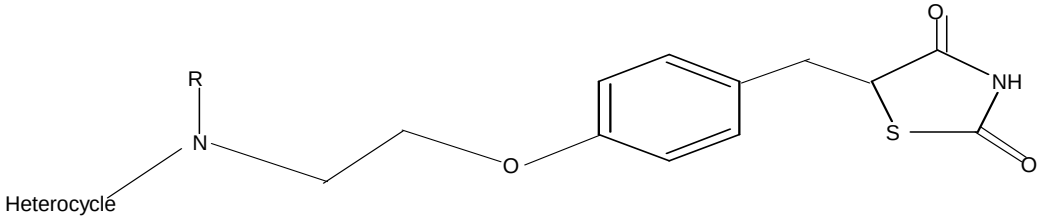
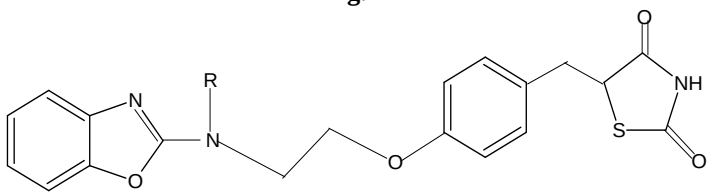


Fig.2



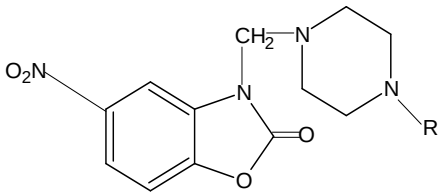
R= Me, BRL 48432

Fig .3

Many of the [[(heterocycloamino) alkoxy] benzyl]-2, 4-thiazolidinediones represented in Fig.2 have been already reported as potent antihyperglycemic agents. Of these Compounds, benzoxazole derivatives such as BRL 48482 (Fig.3) have been reported to have potent agonism to PPAR-γ comparable to the well known antihyperglycemic agent, rosiglitazone.

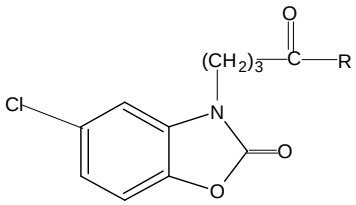
Benzoxazole with analgesic and anti-inflammatory activity:

Hakki Erdogan et al (19) synthesized a novel series of Mannich bases[14] of 5-nitro-3-substituted piperazinomethyl-2-benzoxazolinones. The compounds were examined for their in vivo antiinflammatory and analgesic activities in two different bioassays, namely, carrageenan-induced hind paw edema and p-benzoquinone-induced abdominal constriction tests in mice, respectively. In addition, the ulcerogenic effects of the compounds were determined. Among the tested derivatives most promising results were obtained for the compounds bearing electron-withdrawing substituents (F, Cl, $COCH_3$) in the ortho/para position of the phenyl nucleus on the piperazine ring at 3 position of benzoxazolinone moiety (a, b, c, d, e). The analgesic activities of all compounds are higher than their antiinflammatory activities.

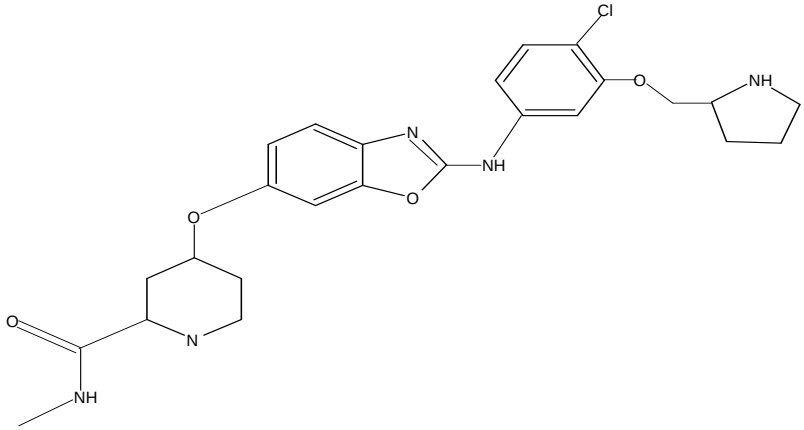


5-nitro-3-piperazinomethyl-2-benzoxazolinones
R= 4-C_6H_5F, 2-C_6H_5F, 4-C_6H_5Cl,2- C_6H_5Cl, 4-$C_6H_5COCH_3$

H. Ozan Gulcan et al (20) synthesized 4-(5-chloro-2-oxo-3H-benzoxazol-3-yl) butanamide derivatives and were screened for their analgesic and anti-inflammatory activities[15] as well as gastric ulceration potential in tested animals. 2-Oxo-3H-benzoxazole derivatives exhibit a broad range of biological properties including analgesic and anti-inflammatory activity. Among them, especially 3-substituted-2-oxo-3H-benzoxazoles are known to exhibit analgesic and anti-inflammatory properties. It has also been reported that mannich bases of 6-acyl-2-oxo-3H-benzoxazoles resulted in compounds with potent analgesic activity. Additional studies with some 3-aminoalkyl-2-oxo-3H-benzoxazole derivatives also demonstrated potent analgesic and anti-inflammatory Activity, and showed that these compounds exerted their in vivo activity by inhibiting the synthesis of prostaglandin E72. It was also demonstrated that the 6-acyl function attached to the benzene portion of 2-oxo-3H-benzoxazole ring was favourable for analgesic activity in these derivatives, and that (6-acyl-2-oxo-3H-benzoxazol-3-yl) alkanoic acids possessed potent analgesic and anti-inflammatory activity with reduced gastric toxicity. In general, most of the research on this class of compounds included substitutions on positions 3 and 6 of the 2-oxo-3H-benzoxazole nucleus. As a result, 2-oxo-3H-benzoxazoles bearing N-alkyl, N-acyl, N-diaminoalkyl and 6-acyl substituents were reported to have higher analgesic and anti-inflammatory activity.



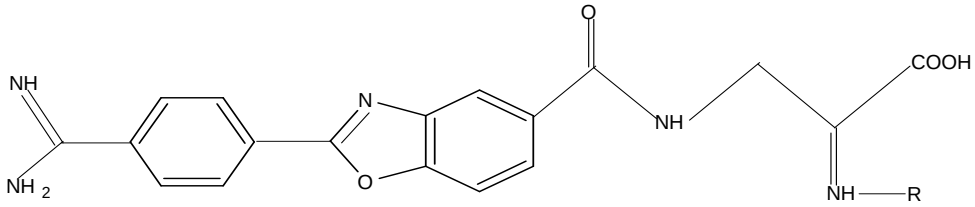
Benzoxazoles as vascular endothelial growth factor-2 receptor tyrosine kinase inhibitors:
Michele H. Potashman et al (21) synthesised a series of 2-aminobenzimidazoles and benzoxazoles, culminating in the identification of benzoxazole **22** as a potent and selective VEGFR-2 inhibitor displaying a good pharmacokinetic profile. Compound **22** demonstrated efficacy in both the murine matrigel model for vascular permeability (79% inhibition observed at 100 mg/kg) and the rat corneal angiogenesis model (ED_{50} = 16.3 mg/kg).



Benzoxazole 22

Benzoxazole as glycoprotein IIb/IIIa inhibitors:

Chu-Biao Xue et al (22-24) synthesized a potent series of benzoxazole GPIIb/IIIa inhibitors[17]. The high potency of this series of compounds in the inhibition of platelet aggregation requires a benzamidine as the basic moiety and an α-carbamate or sulfonamide substituted β-alanine as the acidic moeity.



Benzoxazole derivatives as novel melatoninergic ligands:

Sun LQ et al (25) A novel series of benzoxazole derivatives was synthesized and evaluated as melatoninergic ligands[20]. The binding affinity of these compounds for human MT (1) and MT (2) receptors was determined using 2-[(125) I]-iodomelatonin as the radioligand. This work also established the benzoxazole nucleus as a melatoninergic pharmacophore**.**

Benzoxazole with anticancer activity:

Kumar D et al (26) report the activity of UK-1 (structurally unique bis (benzoxazole) natural product isolated from a strain of *Streptomyces*) against a wide range of human cancer cell lines. UK-1 displays a wide spectrum of potent anticancer activity[21] against leukemia, lymphoma, and certain solid tumor-derived cell lines, with IC (50) values as low as 20 nM, but is inactive against *Staphylococcus aureus*, a methicillin-resistant strain of *S. aureus*, or *Pseudomonas aeruginosa*. A series of analogues of the bis (benzoxazole) natural product UK-1 in which the carbomethoxy-substituted benzoxazole ring of the natural product was modified were prepared and evaluated for their anticancer and antibacterial properties. An analogue of UK-1 in which the carbomethoxy-substituted benzoxazole ring was replaced with a carbomethoxy-substituted benzimidazole ring was inactive against human cancer cell lines and the two strains of *S. aureus*. In contrast, a simplified analogue in which the carbomethoxy-substituted benzoxazole ring was replaced with a carbomethoxy group was almost as active as UK-1 against the four cancer cell lines examined but lacked activity against *S. aureus*. Metal ion binding studies of these analogues demonstrate that they both bind Zn (2+) and Ca (2+) ions about as well as UK-1. The non-cytotoxic benzimidazole UK-1 analogue binds Mg (2+) ions 50-fold weaker than UK-1, whereas the simple benzoxazole analogue binds Mg (2+) ions nearly as well as UK-1. These results support a role of Mg (2+) ion binding in the selective cytotoxicity of UK-1 and provide a minimal pharmacophore for the selective cytotoxic activity of the natural product.

Benzoxazole with antitubercular activity:

Klimesova V et al (27) synthesized a set of 2-benzylsulfanyl derivatives of benzoxazole and evaluated for their in vitro antimycobacterial[22] activity against Mycobacterium tuberculosis, non-tuberculous mycobacteria and multidrug-resistant M. tuberculosis.. The lead compounds in the set, dinitro derivatives exhibited significant activity against both sensitive and resistant strains of *M. tuberculosis* and also against non-tuberculous mycobacteria. It was established that lower lipophilicity has significant contribution to activity. Dinitrobenzylsulfanyl derivative of benzoxazole represents the promising small-molecule synthetic antimycobacterials.

CONCLUSION

Modifications on the benzoxazole nucleus have resulted in a large number of compounds having diverse pharmacological activities. The synthesis, structures and biological activities of

benzoxazole derivatives have long been focused of research interest in the field of medicine, due to potential activities exhibited by them. The biological profiles of these new generations of benzoxazoles represent much progress with regards to older compounds. Looking into the medicinal importance of benzoxazole moiety, it will be worthwhile to synthesize certain newer derivatives of benzoxazole and screen them for their biological activities.

REFERENCES

[1] M.Gupta, S.Paul and R.Gupta, *Acta Chim. Slov*.,**2009,** 56:749–764.
[2] M.Moghadama, S.Tangestaninejada, V.Mirkhania, M.A Zolfigolb, et. Al, *Iran. Chem. Soc*., **2007**, 5, S65-S70.
[3] M. Heravi, S.Sadjadi, A.Hossein, R. Shoar, et al. *journal of the Chinese chemical society*, **2008**, 55,890-895.
[4]T. P. Sycheva, Z. A. Pankina and M. N. Shchukina. *Chemistry of Heterocyclic Compounds*, 2, **2007**,250-252
[5] M.S Singh, Pallavi Singh and Shweta Singh, *Indian Journal of Chemistry*,**2007**, 46B,1666-1671.
[6] I. Elamin , M. Uppal Zubair, and A. Al-Badr Abdullah, *Antimicrobial Agents and Chemotherapy*.**1981**, 19, .29-32.
[7] E. Sener, I.Yalcin, S. Ozden, and T. Ozden, *IL Farmaco*, **2007**, 52(2),99- 103.
[8] Akin Ahmet and Nejat Ucarturk . *IL Farmaco* , **1997,**52(2), 92-96.
[9] P.Kohli, S.D Srivastava and S. K Srivastava. *Journal of the Chinese Chemical Society*, **2007**, 54, 1003-1010.
[10] Jarmila Vinsova, Vaclav Horak, Vladimir Buchta, and Jarmila Kaustova, *Molecules*, **2005**, 10, 783-793.
[11]Anil Kumar and Devinder Kumar, *Arkivoc* , **2007** (xiv) 117-125.
[12] N Siddiqui, M Sarafroz , M. Alam Mumtaz and Waquar Ahsan, *Acta Poloniae Pharmaceutica and Drug Research*, **2008,**Vol. 65 No. 4, 449-455.
[13] Y.S Chun, S .J Lim, S Jun and D.H Moon, *Bioorg Med Chem Lett.*, **2004**,14(5):1197-2000.
[14] M. Sarangapani and V. M. Reddy, *Indian. J. Pharm. Sci*. **1997,** 59, 105–109.
[15] R. Jeon and S.Y Park, *Arch Pharm Res*, **2004** Vol 27, No 11, 1099-1105.
[16] S.Aronoff , S. Rosenblatt , S. Braithwaite et al, *Diabetes Care*, **2000**, 23, 1605-1611
[17] J. Berger, and D. E Moller, *Ann. Rev. Med*., **2002**,53, 409-435
[18] B. C. Cantello , M. A.Cawthorne, Cottam, G. P. And Duff, P. T., **(1994)**; *J. Med. Chem*., 37, 3977-3985.
[19] M. Koksal, N. Gokhan, E. Kupeli and H. Erdogan, *Arch Pharm Res* , **2007,** Vol 30, No 4, , 419-424.
[20] H. Gulcan, S. Unlu , E. Banoglu and M. Fethi Sahin, *Turk J Chem*. **2003,** 27, 467 -476.
[21]M. Potashman, J. Bready, A. Coxon and T. DeMelfi, *J. Med. Chem*., **2007**, Vol.50 (18), 4351–4373.
[22]C. Xue, M. Rafalski, J. Roderick and C. Eyermann, Design, synthesis and in vitro activities of a series of benzimidazole/benzoxazole glycoprotein IIb/IIIa inhibitors, The DuPont Merck Pharmaceutical Co., Experimental Station, Wilmington, DE. **1980**, Vol.20,435-462.
[23]W .Calhoun, R.P Carlson, R.P Crossley and L.J. Datko, *J. Med. Chem*., **1995**,38, 1473-1481.
[24]G. Dannhardt and W. Kiefer, *Eur. J. Med. Chem*., **2001** 36 , 109-126.
[25]LQ Sun , J. Chen , K. Takaki and G. Johnson , Bi*oorg Med Chem Lett*., **2004**, Mar 8; 14(5):1197-**2000**.
[26]Jacob MR Kumar, MB Reynolds and SM Kerwin, *Bioorg Med Chem*. **2002**, Dec;10(12):3997-4004.

[27]V.Klimesova , J.K Koci , J. Waisser , And U. Kaustova , *Eur. J Med Chem.*, **2009**, Vol 44(5):2286-93. Desai, P. S.; Desai, H. R.**(1994)** ; *J. Indian Chem. Soc*., 71,155-157.