



## A REVIEW ON DIVERSE BIOLOGICAL ACTIVITIES OF BENZOXAZOLE MOLECULE

Anusha P.\*<sup>1</sup>, J. Venkateshwar Rao<sup>2</sup> and G. Krishna Mohan<sup>3</sup>

<sup>1</sup>Bojjam Narasimhulu Pharmacy College for Women, Hydreabad, Telangana, India.

<sup>2</sup>Talla Padmavathi College of Pharmacy, Warangal, Telangana, India.

<sup>3</sup>Centre for Pharmaceutical Sciences, JNTU-H, Hyderabad, Telangana, India.

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### \*Corresponding Author

Anusha P.

Bojjam Narasimhulu  
Pharmacy College for  
Women, Hydreabad,  
Telangana, India.

### ABSTRACT

Heterocyclic compounds containing oxazole moiety plays an important role in medicinal chemistry and exhibit wide range of biological activities. Targets containing the benzoxazole moiety either isolated from plants or accessed by total synthesis have remarkable biological activities. Many substituted benzoxazoles have the ability to inhibit the microbial growth, inflammation, and also has activities such as CNS, hypoglycemic, anti tubercular, anticancer, anti fungal, protein kinase inhibition and steroid sulfatase inhibition. The present review focuses on various synthetic derivatives of benzoxazole and their pharmacological activities which may helpful to develop some new

substituted benzoxazoles of medicinal value.

**KEYWORDS:** Benzoxazole, Anti microbial, Anti inflammatory, Antiviral, Antifungal, Hypoglycemic.

### INTRODUCTION

Benzoxazole finds use in research as a starting material for the synthesis of larger bioactive structures. Biologically active benzoxazole derivatives have been known for long time, they are the isosteres of cyclic nucleotides and easily interact with the biopolymers of the organisms.

The substituted benzoxazoles have been shown to exhibit various biological activities<sup>1</sup> like antimicrobial<sup>[2,3]</sup>, anti-inflammatory<sup>[4,5]</sup>, anticancer<sup>[6]</sup>, antihelminthic<sup>[7]</sup>, antifungal<sup>[8]</sup>, cox-2

inhibition<sup>[9]</sup>, antihistaminic<sup>[10]</sup>, antiparasitic<sup>[11]</sup>, herbicidal<sup>[12]</sup>, antitubercular<sup>[13]</sup>, anticonvulsant<sup>[14]</sup>, hypoglycemic activities.<sup>[15]</sup>

The novel antibacterial agent containing benzoxazole system is Boxazomycin B. Benzoxazole ring containing antibiotic calcymicin and the anti inflammatory agent Benzoxaprofen are also obtained by synthetic methods. Zoxazolamine, an  $\alpha$ -amino-5-chlorobenzoxazole is reported to possess muscle relaxant, sedative and uricosuric effect.

### Chemistry Of Benzoxazole

Benzoxazole (m.p 27-30°C, b.p 182°C) is a planar molecule with conjugated  $\pi$  electrons sextets in the cyclic system. It is an aromatic compound having benzene ring fused with oxazole ring with a molecular formula  $C_7H_5NO$ . The lone pair of electrons on nitrogen, which is coplanar with the heterocyclic ring and therefore not involved in delocalization, confers weakly basic properties. Associated with the aromaticity is a degree of stability, but when these are quaternized the resulting azolium species are significantly activated towards nucleophilic attack.

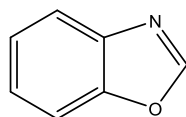
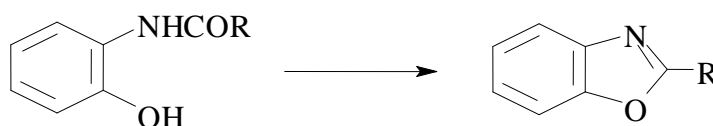


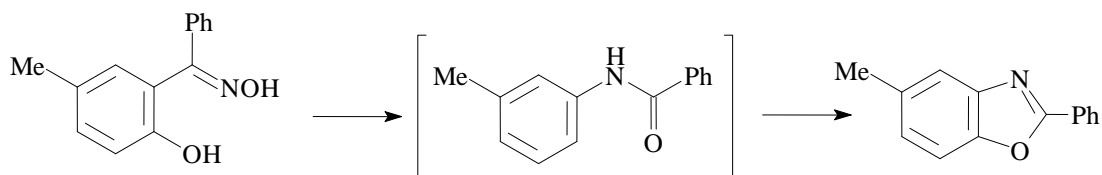
Figure 1: Benzoxazole

### Synthesis Of Benzoxazole

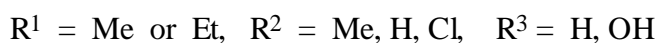
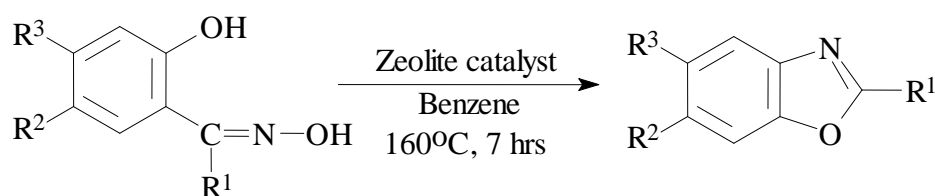
Thermal dehydration of o-(acylamino)phenols is the method of choice for the preparation of benzoxazoles.



The Beckmann rearrangement of oximes of o-hydroxybenzophenones leads directly to benzoxazoles.



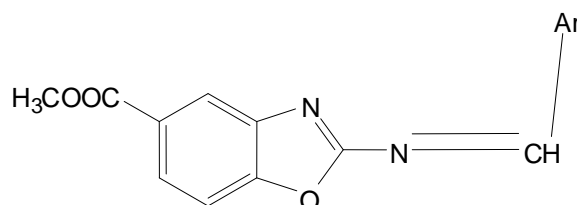
Bhawal *et al.*<sup>[16]</sup>, reported the mild and simple method for the synthesis of benzoxazoles via Beckmann rearrangement of o-acylphenol oximes using zeolite catalyst.



## BIOLOGICAL ACTIVITIES

### 1. Benzoxazoles as Anti Inflammatory Agents

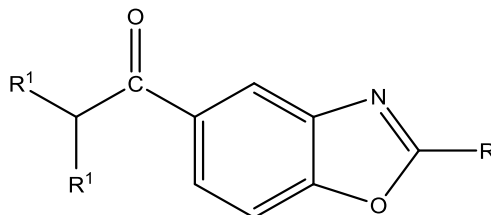
A.Srinivas *et al.*<sup>[17]</sup>, synthesized a new series of Methyl 2-(arylideneamino) benzoxazole-5-carboxylate derivatives (Figure 2) by the reaction of schiff bases of methyl 2-aminobenzoxazole-5-carboxylate with appropriate aromatic aldehydes and were screened for anti-inflammatory activity by using carrageenan-induced paw edema rat model. The synthesized derivatives showed moderate to potent anti-inflammatory activity when compared to standard drug Diclofenac sodium.



**Figure 2: Methyl 2-(arylideneamino) benzoxazole-5- carboxylate derivatives**

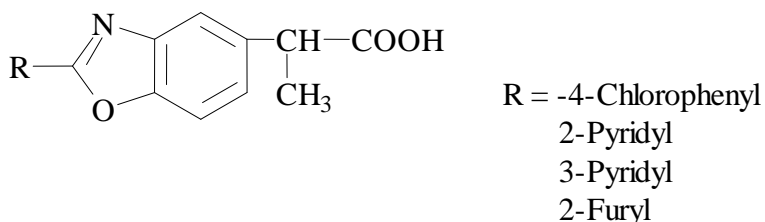
M.Sarangapani *et al.*,<sup>[18,19]</sup> synthesized 2-substituted-[(N,N-disubstituted)-1,3-benzoxazole]-5-carboxamide (Figure 3) by the reaction of 2-(substituted)-5-carboxamethoxy benzoxazole with secondary amines under reflux conditions in the presence of alcohol and were screened

for anti inflammatory activity by using carrageenan induced rat paw edema model. The compounds with 2-substituents were found to be relatively more potent than their unsubstituted analogs.



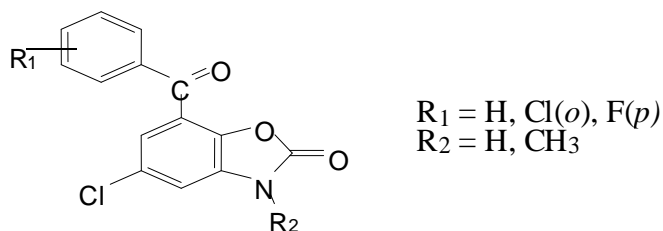
**Figure 3: 2-substituted-[(N,N-disubstituted)-1,3-benzoxazole]-5-carboxamide**

Synthesis and anti-inflammatory activity of 2-heteroaryl- $\alpha$ -methyl-5-benzoxazole acetic acid (fig 4) was studied by David W. Dunwell *et al.*,<sup>[20]</sup> 2-(4-Chlorophenyl)- $\alpha$ -methyl-5-benzoxazole acetic acid, benzoxaprofen (R = 4-chlorophenyl) was shown to be a potent new anti-inflammatory agent. The 2-heteroaryl derivatives (R = 2-pyridyl, 3-pyridyl, 2-furyl) were found to be comparatively less potent in their anti-inflammatory action.



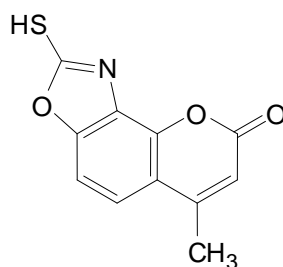
**Figure 4: 2-heteroaryl- $\alpha$ -methyl-5-benzoxazole acetic acid**

Serdar unlu *et al.*,<sup>[21]</sup> reported and synthesized a series of [7-acyl-5-chloro-2-oxo-3H-benzoxazole-3-yl] alkanolic acid derivatives (fig 5) and evaluated for their anti-inflammatory activity. The test results indicated that [7-acyl-2-oxo-3H-benzoxazole-3-yl] alkanolic acids were equally or more potent anti-inflammatory agents than aspirin and indomethacin.



**Figure 5: [7-acyl-5-chloro-2-oxo-3H-benzoxazole-3-yl] alkanolic acid derivatives**

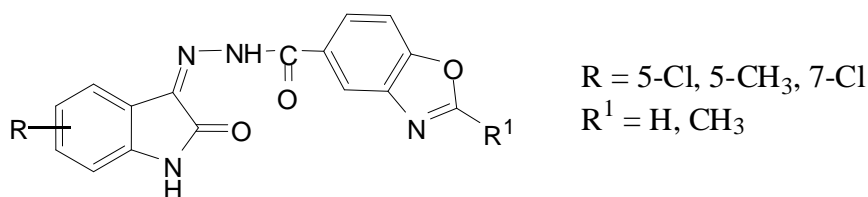
Praveen kumar *et al.*,<sup>[22]</sup> reported a synthesis of an anti-inflammatory activities of various 2-substituted 6-methyl-8H-pyranobenzoxazoles (fig 6).



The above compound was found to show a more potent anti inflammatory activity when compared to Indomethacin.

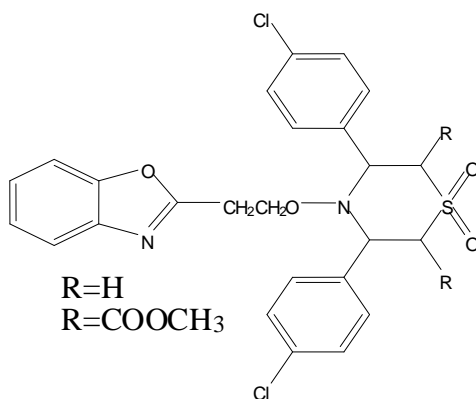
## 2. Benzoxazoles as Antimicrobial Agents

Sarangapani *et al.*,<sup>[23]</sup> investigated some new Isatin-[N-{2-alkylbenoxazol-5-carbonyl}]hydrazones (fig 8) and found them to exhibit a moderate antibacterial activity against *B.subtilis*, *S.aureus*, *E.coli* and *P.vulgaris* and mild antifungal activity against *A.niger* and *C.verticulata*.



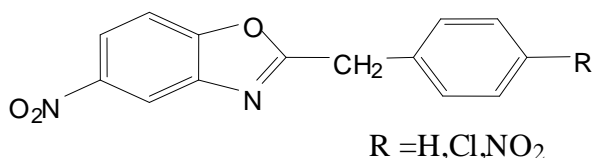
**Figure 8: Isatin-[N-{2-alkylbenoxazol-5- carbonyl}]hydrazones**

V.Sundari and valliappan.,<sup>[24]</sup> synthesized some new 3,5-diaryl-4-{2-ethoxybenzoxazol-2-yl}-tetrahydro-1,4-thiazine-1,1-dioxides and 2,6-dimethoxycarbonyl-3,5-diaryl-4-{2-ethoxybenzoxazol-2-yl}-tetrahydro-1,4-thiazine-1,1-dioxides (fig 9) and they were tested for their antibacterial and antifungal activities. These compounds inhibited the growth of bacteria and fungal at minute concentration of 25µg/ml when compared against the standard Norfloxacin.



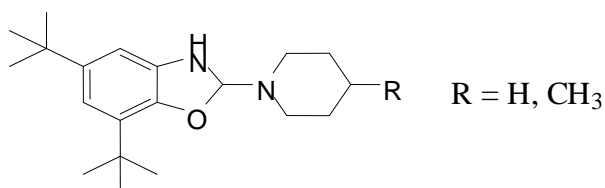
**Figure 9: 2,6-dimethoxycarbonyl/3,5-diaryl-4-{2-ethoxybenzoxazol-2-yl}- tetrahydro-1,4-thiazine-1,1-dioxides**

Aki-sener *et al.*,<sup>[25]</sup> synthesized new antimicrobial active N-(2-hydroxy-4-nitrophenyl)-p-substituted benzamides and phenylacetamide analogues (fig 10) which were prepared by 2-steps procedure from the corresponding carboxylic acid as possible metabolites of benzoxazoles. (R=Cl showed more potency).



**Figure 10: N-(2-hydroxy-4-nitrophenyl)-p-substituted benzamides and phenylacetamide analogues**

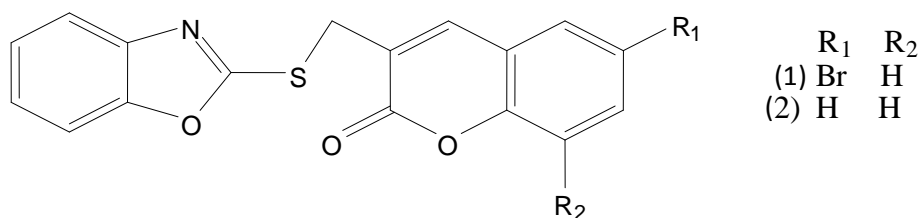
Jermila vinsova *et al.*,<sup>[26]</sup> reported various synthetic pathways of 13 novel 2-substituted 5,7-di-tert-butyl benzoxazoles has no antimicrobial drugs. 5,7-di-tert-butyl-2-(pyridine-4-yl)-benzoxazole (fig 11) was found as the most efficient heterocyclic derivatives of 100% of *M.tuberculosis* growth at 6.25 µg/ml as well as with the best activity also against *M.kansasii* and both strains of *M.avium*.



**Figure 11: 5,7-di-tert-butyl-2-(pyridine-4-yl)- benzoxazole**

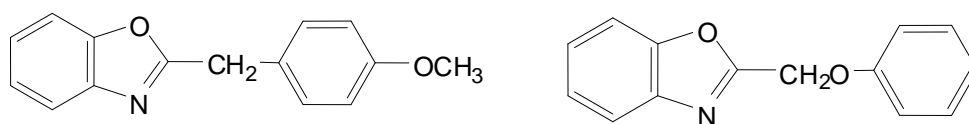
### 3. Benzoxazoles as Antiviral Agents

Johan Neyts *et al.*,<sup>[27]</sup> reported the synthesis of heterobicycle coumarin conjugates and evaluated for Anti *Hepatitis C virus*. Heterobicycle coumarin conjugated compounds with the -SCH<sub>2</sub>- linker were synthesized and found to possess significant antiviral activities. Benzoxazole coumarin (fig 17), which inhibited HCV replication at an EC<sub>50</sub> of 12  $\mu$ M. The heteroatoms in bicycles and the substituent effect on coumarin played essential roles.



**Figure 17: Benzoxazole coumarin**

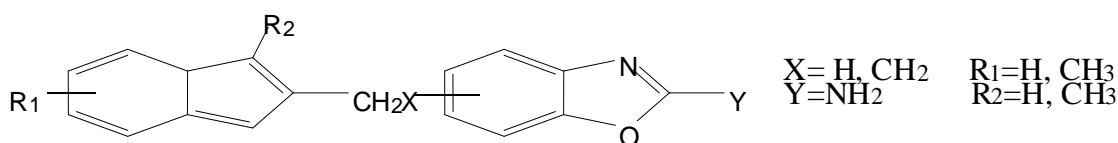
Aysegul akbay *et al.*,<sup>[28]</sup> investigated a synthesis of 2-substituted benzoxazole derivatives and evaluated for *invitro* anti-HIV activity. The following compounds (fig 18) exhibited better inhibiting activity.



**Figure 18: 2-substituted benzoxazole derivatives**

### 4. Benzoxazoles as Antihistaminic Agents

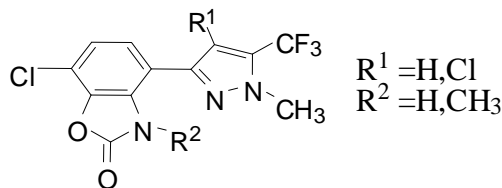
A series of Imidazo[1,2-a]pyridinylalkyl]benzoxazole (fig 19) derivatives was synthesized and tested for histamine H<sub>2</sub>-receptor antagonistic, gastric antisecretory and antiulcer activities. Some of 2-amino-6-[2-(imidazo[1,2-a]pyridin-2-yl)ethyl]benzoxazole and 2-acetamido-6-[2-(7-methylimidazo[1,2-a]pyridin-2-yl)ethyl]benzoxazole showed potent antisecretory and cytoprotective activity.<sup>[29]</sup>



**Figure 19: Imidazo[1,2-a]pyridinylalkyl]benzoxazole**

### 5. Benzoxazoles as Herbicidal Agents

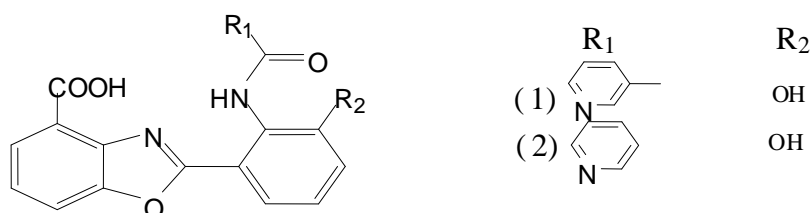
Yuhan Zhou *et al.*,<sup>[30]</sup> reported the synthesis and herbicidal activity of pyrazolyl benzoxazole derivatives (fig 20).



**Figure 20: Pyrazolyl benzoxazole derivatives**

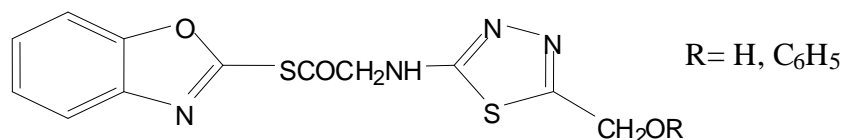
### 6. Benzoxazoles as Antihelminthic Agents

Suresh K. Tipparaju *et al.*,<sup>[31]</sup> reported the synthesis and evaluation of 2-[3-hydroxy-2-[(3-hydroxypyridine-2-carboxylamino)phenyl]benzoxazole-4-carboxylic acid derivatives as Anti-leishmanial chemotypes (fig 21). Chemotype of type (1) was more active against *L. donovani*.



**Figure 21: 2-[3-hydroxy-2-[(3-hydroxypyridine-2-carboxylamino)phenyl]benzoxazole-4-carboxylic acid derivatives**

Saxena *et al.*,<sup>[32]</sup> reported the synthesis of anti-helminthic activity of 2-[aryloxymethyl]-5-[2-mercaptoacetylaminobenzoxazol-2-yl]-1,3,4-thiadiazoles (fig 22).



**Figure 22: 2-[aryloxymethyl]-5-[2-mercaptoacetylaminobenzoxazol-2-yl]-1,3,4-thiadiazoles**

Compounds were tested for their cysticidal activity *invivo* against *H. nana* infection in rats and compound with R=4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 2-NOC<sub>6</sub>H<sub>4</sub> showed the maximum 72.2 and 56.4 to clearance of *H. nana* infection in rats at a dose of 250mg/kg respectively.



### 7. Benzoxazoles as HIV-1-RT Inhibitory Agents

Samia M.Rida *et al.*,<sup>[33]</sup> reported the benzoxazole derivative, 2-[(9N-substituted thio carbamoyl)cyanomethyl]benzoxazoles (fig 23) as an effective non-nucleoside selective HIV-reverse transcriptase inhibitors. Compound R=CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> showed more activity.

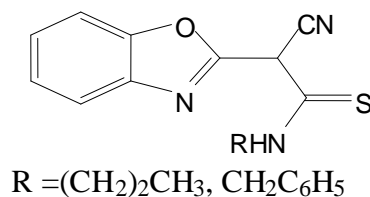


Figure 23: 2-[(9N-substituted thio carbamoyl)cyanomethyl]benzoxazoles

### 8. Benzoxazoles as Anticancer Agents

Mireya L.Mckee *et al.*,<sup>[34]</sup> reported the synthesis of anti cancer activity of 2-(2'-hydroxyphenyl)benzoxazole analogues of UK-1 (fig 24).

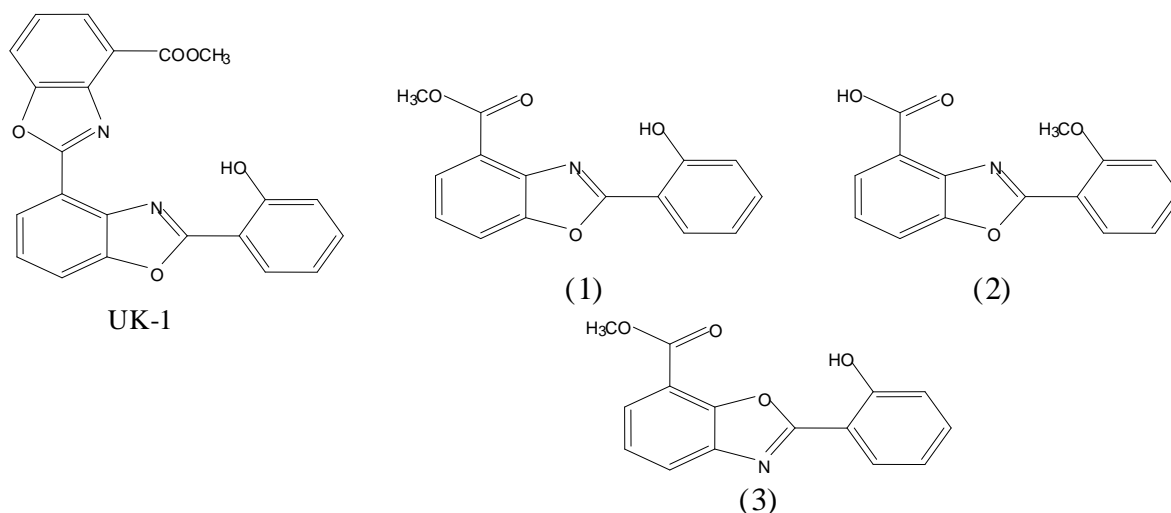
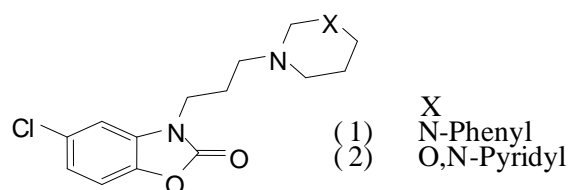


Figure 24: 2-(2'- hydroxyphenyl)benzoxazole analogues of UK-1

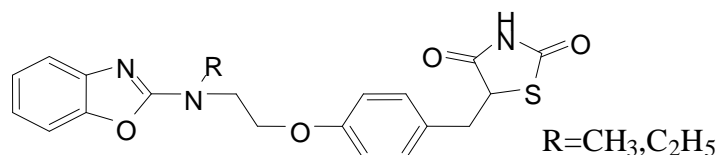
M.S.R.Murty *et al.*,<sup>[35]</sup> reported the synthesis and preliminary evaluation of 2-substituted-1,3-benzoxazole and 3-[(3-substituted)propyl]-1,3-benzoxazol-2(3H)-one derivatives as potent anti cancer agents (fig 25). Compound (2) has shown more potency against cervical and lung cancer cells.



**Figure 25: 2-substituted-1,3- benzoxazole and 3-[(3-substituted)propyl]-1,3-benzoxazol-2(3H)-one derivatives**

### 9. Benzoxazoles as Hypoglycemic Agents

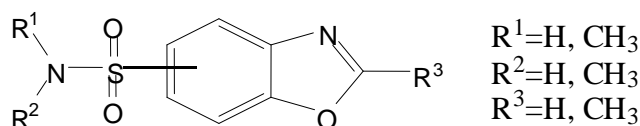
Raok Jeon *et al.*,<sup>[36]</sup> reported the synthesis and biological activity of benzoxazole containing Thiazolidinedione derivatives. 5-[4-[2-(benzoxazol-2-yl-alkylamino)ethoxy]benzyl]thiazolidine-2,4 diones (fig 27) are identified as potent PPAR $\gamma$  agonists. Compound(R=C<sub>2</sub>H<sub>5</sub>) showed more potency.



**Figure 27: 5-[4-[2-(benzoxazol-2-yl-alkylamino)ethoxy]benzyl]thiazolidine-2,4 diones**

### 10. Benzoxazoles as Steroid Sulfatase Inhibitor Agents

Benzoxazoles with the steroid sulfatase inhibitory activity were disclosed by Billich *et al.*,<sup>[37]</sup> 2-Substituted benzoxazoles which carry a sulfamic acid ester group board via oxygen to the Ph part of the ring structure more active (fig 28).

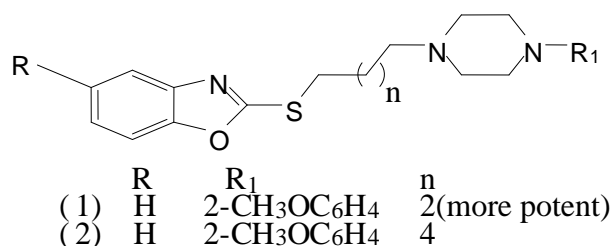


**Figure 28: 2-Substituted benzoxazoles**

They are indicated for use as steroid sulfatase inhibitors in the prevention, treatment of illness, responsive to alopecia, hirsutism, estrogen- and androgen- dependant cancer, inflammatory or autoimmune diseases, skin disorders, or decreased cognitive function.

### 11. Benzoxazoles as 5-HT<sub>1A</sub> Receptor Ligands

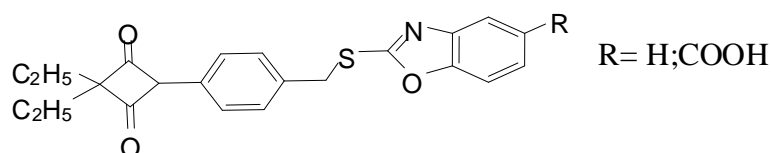
Maria A. Siracusa *et al.*,<sup>[38]</sup> reported the synthesis of new Arylpiperazinyl alkylthiobenzoxazole derivatives (fig 29) as potent and selective 5-HT<sub>1A</sub> serotonin receptor ligands. These were tested in radioligand binding experiments.



**Figure 29: Arylpiperazinyl alkylthiobenzoxazole derivatives**

### 12. Benzoxazoles as Elastase Inhibitor Agents

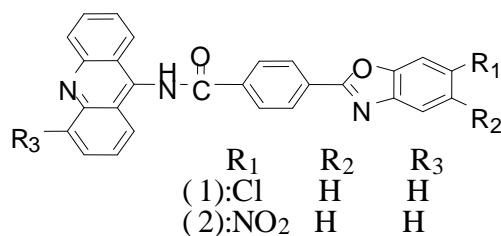
Jalmira Mulchanda *et al.*,<sup>[39]</sup> reported the synthesis and evaluation of 4-oxo- $\beta$ -lactams (Azetidine-2,4-diones) as potent and selective inhibitors of Human leukocyte Elastase. 4-oxo- $\beta$ -lactams containing a hetero arylthiomethyl group on the para position of an N'-aryl moiety (fig 30) afforded highly potent and selective inhibition of HLE, even at a very low inhibitor to enzyme ratio. (R=H is more potent).



**Figure 30: 4-oxo- $\beta$ -lactams (Azetidine-2,4-diones) benzoxazole derivatives**

### 13. Benzoxazoles as Protein Kinase Inhibitor Agents

A series of N-(acridin-9-yl)-4-(benzo[d]imidazoleoxazole-2-yl)benzimidides (fig 31) has been synthesized by Sham M. Sondhi *et al.*,<sup>[40]</sup> by condensation of 9-aminoacrydine derivatives with benzoxazole derivatives. These compounds were screened for kinase (CDK-1, CDK-5, and GSK-3) inhibition activity. Compound (1) showed significant *invitro* activity against CDK-5 and CDK-1 and compound (2) showed moderate CDK-5 inhibitory activity.

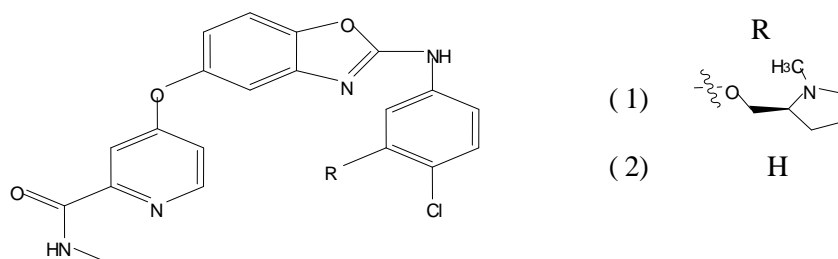


**Figure 31: N-(acridin-9-yl)-4-(benzo[d]imidazoleoxazole-2-yl)benzimidides**

#### 14. Benzoxazoles as Tyrosine Kinase Inhibitor Agents

Michele H.Potashman *et al.*,<sup>[41]</sup> reported the synthesis and evaluation of orally active benzoxazoles as vascular endothelial growth factor-2 receptor tyrosine kinase inhibitor.

Inhibition of the VEGF signaling pathway has become a valuable approach in the treatment of cancers, guided by X-ray crystallography and molecular modeling, a series of 2-aminobenzimidazoles and 2-aminobenzoxazoles were identified as potent inhibitors of VEGFR-2 (KDR) in both enzymatic and HUVEC cellular proliferation assays. Benzoxazole (fig 32) identified as a potent and selective VEGFR-2 inhibitor displaying a good pharmacokinetic profile. Compound(1) has demonstrated efficacy in both the murine matrigel model for vascular permeability (79% inhibition observed at 100 mg/kg) and the rat corneal angiogenesis model(ED50) 16.3 mg/kg.



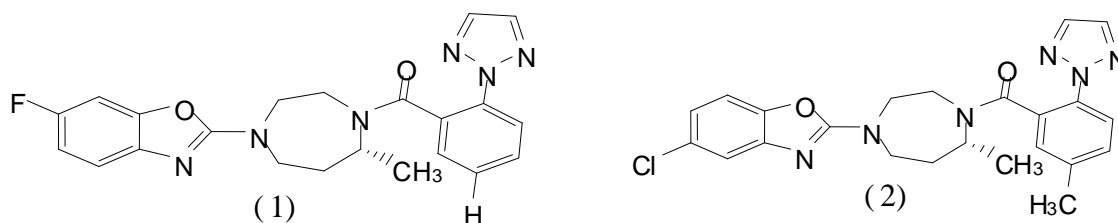
**Figure 32: 2-aminobenzoxazole derivatives**

#### 15. Benzoxazoles as Dual Orexin Receptor Antagonist Agents

Christopher D.Cox *et al.*,<sup>[42]</sup> reported the discovery of the dual orexin receptor antagonist [(7R)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (fig 33) (MK-4305) for the treatment of Insomnia.

Despite increased understanding of the biological basis for sleep control in the brain, few novel mechanisms for the treatment of insomnia have been identified in recent years. One notable exception is inhibition of the excitatory neuropeptides orexins A and B by design of

orexin receptor antagonists. Efforts have done to understand the origin of poor oral pharmacokinetics in a leading HTS derived diazepane orexin receptor antagonist led to the identification of compound (1) with a 7-methyl substitution on the diazepane core. Though 1 displayed good potency, improved pharmacokinetics and excellent *in vivo* efficacy, it formed reactive metabolites in microsomal incubations. A mechanistic hypothesis coupled with an *in vitro* assay to assess bioactivation led to replacement of the fluoroquinazoline ring of (1) with a chlorobenzoxazole to provide **2** (MK-4305), a potent dual orexin receptor antagonist that is currently being tested in phase III clinical trials for the treatment of primary insomnia.



**Figure 33:** antagonist [(7R)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone

## 16. Benzoxazoles as Cyclooxygenase-2 Inhibitor Agents

Srinivas. A *et al*<sup>[43]</sup> had been synthesized methyl-2-[2-(disubstituted amino)acetamido]benzoxazole-5-carboxylates by the reaction of a solution of Methyl 2-(2-chloroacetamido)benzoxazole-5-carboxylate in dry acetone & N,N-dialkylamine. The synthesized compounds showed good to moderate activity.

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