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REVIEW ARTICLE **OPEN ACCESS**

A Review on Chemical Synthesis and Biological Activities of Oxazole derivatives

Priyanka[1], Mohd. Shuaib[2], Mr. Pradeep Kumar[1], Ms. Sharma Madhu Suresh Kumar[3], Mr. Shruti Kant Gupta[4], Arbind kumar[5]

[1]Associate Professor, Kalka Institute For Research And Advanced Studies, Meerut
[2]Professor, Kalka Institute For Research And Advanced Studies, Meerut
[3]Assistant Professor, Kalka Institute For Research And Advanced Studies, Meerut
[4]Lecturer, Kalka Institute For Research And Advanced Studies, Meerut
[5]Associate Professor, Kalka Institute For Research And Advanced Studies, Meerut

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***Corresponding Author**
Dr. Priyanka
Associate Professor, Kalka Institute For Research And Advanced Studies, Meerut

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A B S T R A C T

Oxazole is a significant heterocyclic nucleus possessing a wide spectrum of biological activities, which drew the attention of researchers around the globe to synthesize various oxazole derivatives and screen them for their various biological activities. Due to binding with an extensive spectrum of receptors and enzymes easily in biological systems through various non-covalent interactions. Oxazole based compounds as a type of important heterocyclic core, which have been of interest to scientists all over the world, prompting them to synthesize diversified oxazole derivatives.

Keywords: Oxazole derivatives, Antimicrobial, Anticancer, Antitubercular

INTRODUCTION

Oxazoles are quantified as a significant heterocyclic compound class since they are structural building blocks of numerous biologically active natural products and are significant synthetic precursors and drugs. Oxazoles are accompanying with anti-bacterial, antifungal, anti-inflammatory and anti-tumoral activities and may serve as peptide mimetics or enzyme inhibitors. FIGURE 1 [2] One nitrogen and one oxygen atom are present in the oxazole ring, commonly revealed in synthetic and natural molecules. It is regarded as a key skeleton for lead discovery. Due to structural and chemical diversity, oxazole-containing molecules, as a core scaffold, not only facilitate various types of interactions with different receptors and enzymes, exhibiting extensive biological activities, but also hold a central position in medicinal chemistry, exhibiting their vast development potential and they favoured the identification of newer therapeutic agents. [3–7].

Benzoxazoles may be considered structural isosteres of the naturally occurring nucleic bases adenine and guanine, which enable them to interact freely with polymers of living systems.

Chemistry of benzoxazole nucleus

Benzoxazole (FIG1) is a heterocyclic compound made of fused benzene and oxazole, with the molecular formula C7H5NO, molar mass 119.12 g, and an indefinable pyridine-like odor. Soluble in water with a melting point of 27-30 °C, it is also known by its IUPAC name 1-Oxa-3-aza-1H-indene.

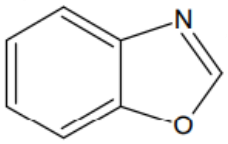
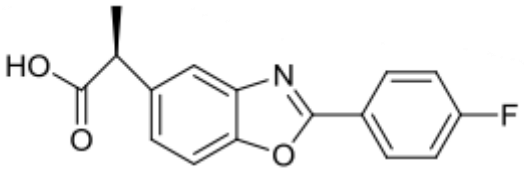


FIGURE 1

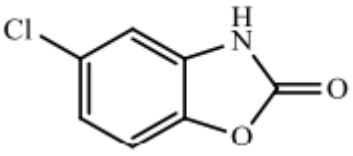
FIGURE 2

Marketed drugs containing benzoxazole

Several marketed drugs (Fig. 3) are present with benzoxazole as central active moiety such as, nonsteroidal anti-infammatory drug (NSAID)— funoxaprofen, benoxaprofen, antibiotic—calcimycin, antibacterial—boxazomycin B, muscle relaxant—chloroxazone.



Flunoxaprofen



Chloroxazole

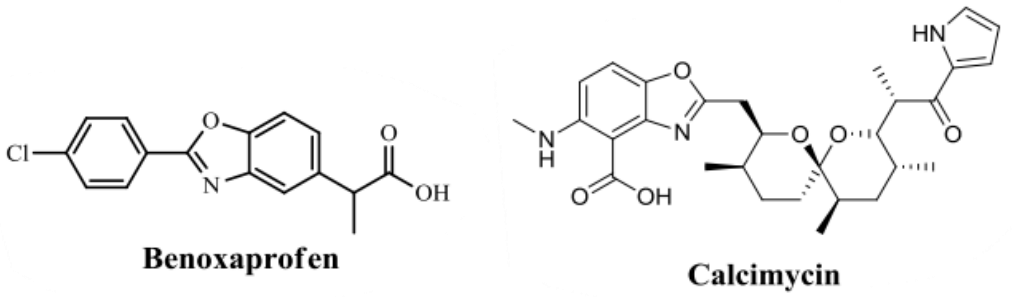
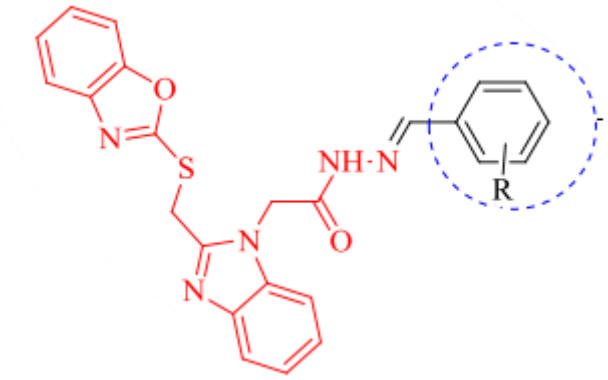


FIG 3

These compounds emphasize the significance of benzoxazole derivatives in drug application because of their extensive biological activities such as anti-inflammatory , antibacterial activity ,anticancancer activities.

SAR (structure activity relationship) studies



Substitution of aromatic aldehydes with dimethoxy and tri-methoxy groups enhanced the anticancer activity of derived derivatives.

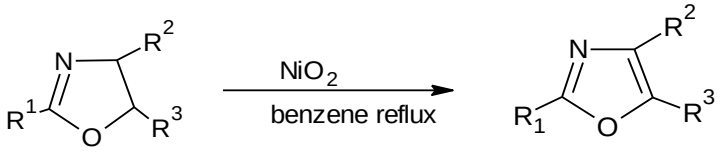
Increased cancer-fighting properties are due to the substitution of the ortho hydroxy group.

The presence of electron-withdrawing groups improved the antimicrobial activity against P. aeruginosa, K. pneumonia, S. typhi and A. niger.

The substitution of thiophene is a five-membered cyclic aldehyde which enhanced the antibactereial properties of benzoxazoles derivatives to E. coli.

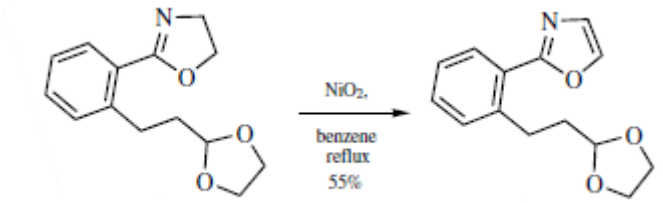
Synthetic Strategies

Although newer procedure for the oxidation of oxazolines have been found in recent times, the procedure using NiO_2 oxidation is one of the most ancient and even a popular one. It was originally described by Meyers and Evans (Scheme 1) [8]



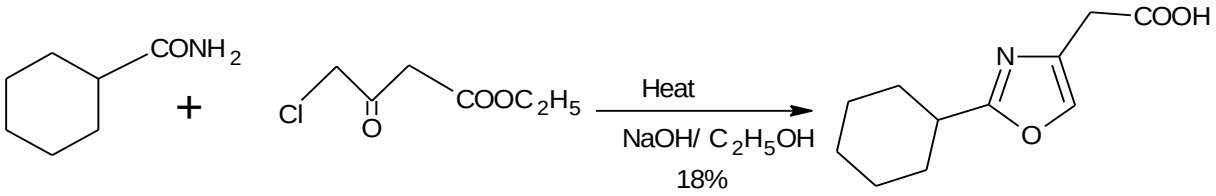
(Scheme 1)

Nickel peroxide [9] is an efficient reagent for the oxidation of activated oxazolines that contain an electron-withdrawing group (R2 or R3 ¼ COOC2H5 or other electron-withdrawing groups), but it is less useful for the oxidation of inactivated oxazolines (R2 or R3 ¼ alkyl, H). The heterogeneous reaction is carriedout by refluxing an excess of NiO2 in benzene, and a radical reaction mechanism has been proposed. The use of NiO2 in the synthesis of eupolauramine [10] is a goodexample of a notable casewhere one of the most important steps is the oxidation of the inactivatedoxazoline to the 2-aryloxazole in 55% yield (Scheme 2).



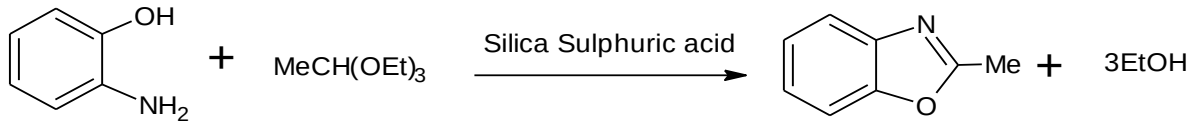
(Scheme 2)

Meguro and co-workers used this method, among others, to prepare a variety of potential antidiabetic agents. For example, cyclization of cyclohexane carboxamide with ethyl 4-chloroacetoacetate gave 2-cyclohexyl-4-oxazoleacetic acid [11], albeit in poor yield (Scheme 3).



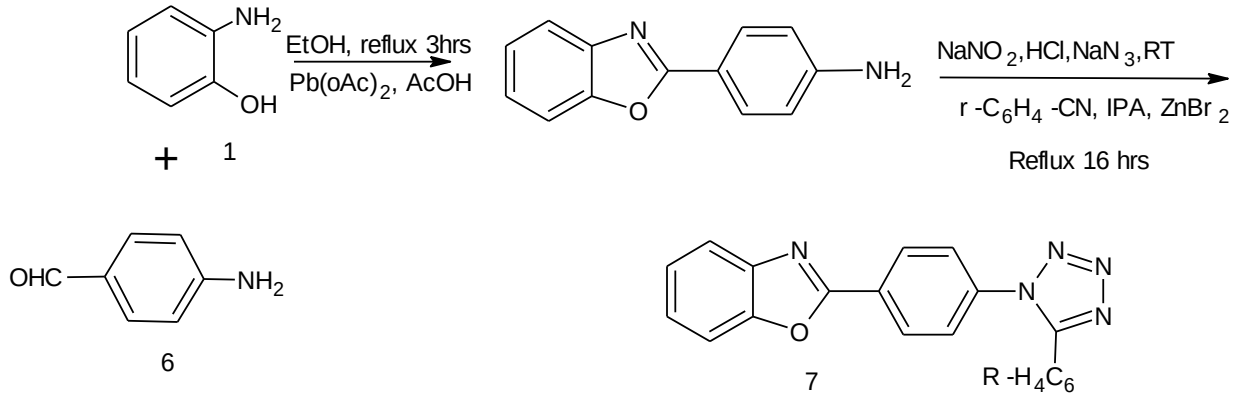
(Scheme 3)

Benzoxazole is prepared by the reaction of orthoesters with o-aminophenols under heterogenous and solvent-free conditions using silica sulphuric acid. (Scheme 4).



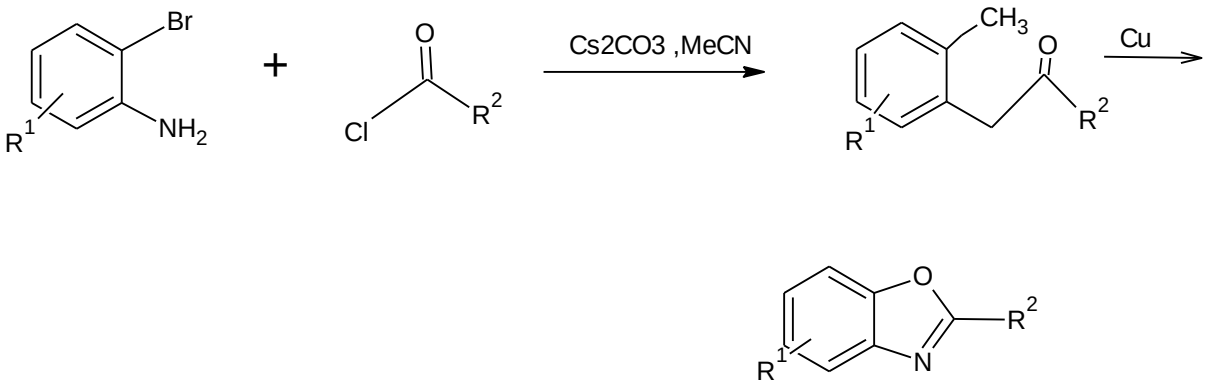
(Scheme 4).

Ravikumar and co-authors [13] prepared tetrazole fused benzoxazole derivatives (7) and then screened for their cytotoxicity against cancer cell lines. The reaction between 2-aminophenol (1) and 4-amino benzaldehyde (6) in ethanol with $Pb(OAc)_4$ in acetic acid under reflux conditions, followed by reactions with HCl, NaNO2, and NaN_3, then additional reaction with aromatic nitriles in isopropanol and in the presence $ZnBr_2$ was employed to get tetrazole fused benzoxazoles and their anticancer activity of the compoundswas evaluated against cancer cell lines such as MCF-7, KB, Hop62, and A-549 (Scheme 5).



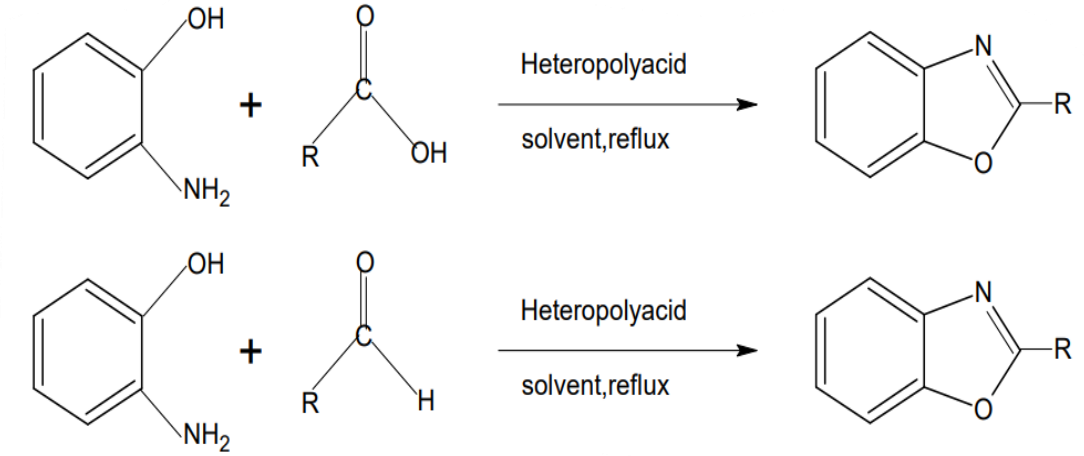
(Scheme 5)

Batley [14] performed a copper catalysed one-pot reaction of bromoanilines and acyl halides in presence of base and a solvent to yield the intermediates which ultimatelydelivered pure benzoxazoles (21–97%) isolated yields, which exhibiteda wide range of biological activities. They can also serve asa precursor in the synthesis of drugs. (Scheme 6).



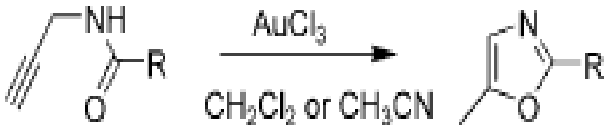
(Scheme 6)

Benzoxazole derivatives may be synthesized from reaction of 2-aminophenol with benzoic acid and benzaldehyde in the presence of catalytic amount of three different Kegginform of HPAs as catalysts i.e; H5 [PMo10V2O40], H 4[PMo11VO40] and H 3[PMo12O40]. [15-17] (Scheme 7)



(Scheme 7)

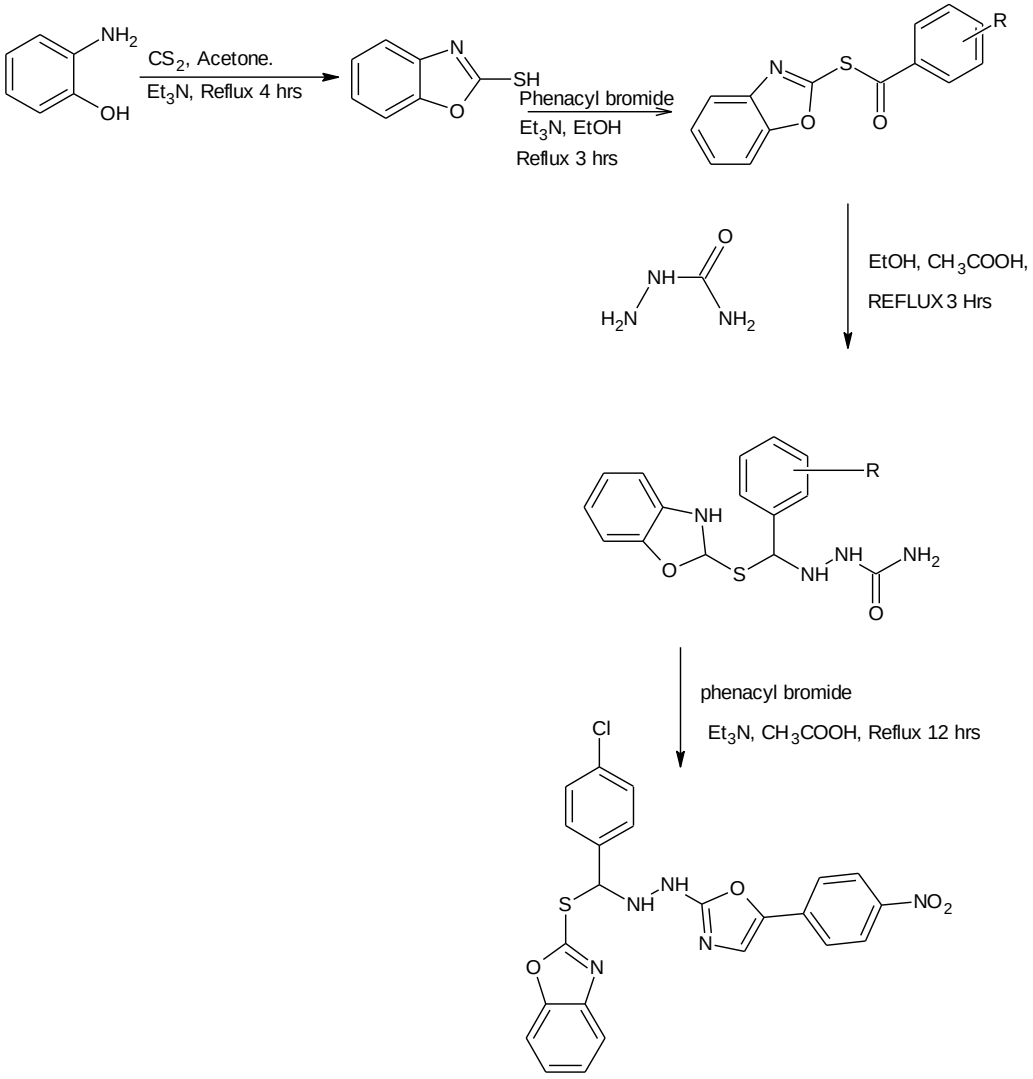
Jan P. Weyrauch et.al [18] wasCyclized of Propargylic Amides: Mild Access to Oxazole Derivatives. Inspired by Arcadi, Cacchi, and co-workers, who published a Pd0-catalyzed coupling–cyclization sequence for the synthesis of disubstituted oxazoles,[5] in 2004 we contributed the gold-catalyzed synthesis of oxazoles 2 formed by a 5- exo-dig cyclization of N-propargyl carboxamides 1 (Scheme 8).



(Scheme 8) Gold-catalyzed oxazole synthesis (R=alkyl, vinyl, aryl).

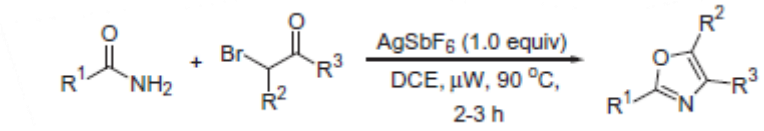
Rafaqat Hussain et.al [19] Synthesized and review in vitro study and molecular docking study of novel benzoxazole-based oxazole derivatives for the treatment of Alzheimer's disease.The synthesis of 2-marcaptobenzoxazole was offered as a substrate by the addition of 2-aminophenol solution and carbon disulphide (CS2) in acetone. The resultant residue was stirred at refluxing temperature for 4 hrs under the catalytic action of triethylamine (Et3N). When the reaction was completed, the solvent was evaporated under decreased pressure and resulting solid residue was further treated with various substituted phenacyl bromide in ethanol (EtOH) and triethylamine (Et3N) to afford substituted benzoxazole substrate which was further redissolved in ethanol followed by addition of semicarbazide in ethanol and glacial acetic acid. Upon completion, the solvent was evaporated under reduced pressure and the resultant substrate underwent

cyclization on refluxing with various substituted phenacyl bromide in ethanol and triethylamine while being stirred for 12hrs at refluxing temperature to afford targeted benzoxazole-based oxazole derivatives (Scheme 9).



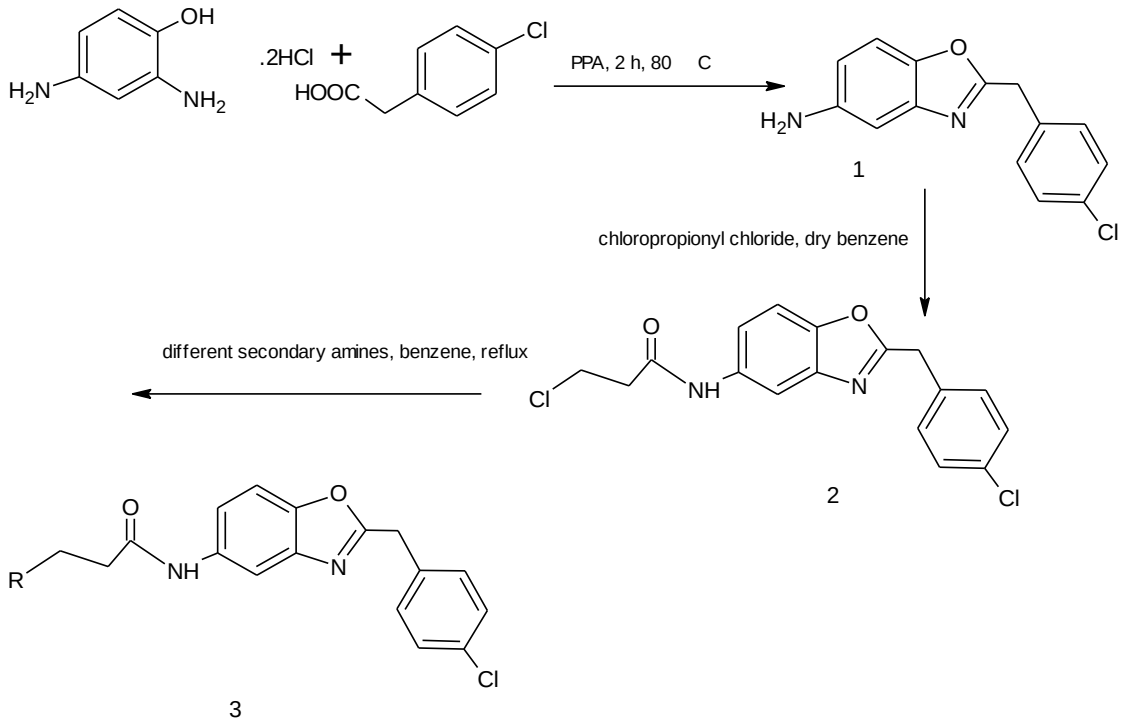
(Scheme 9) Preparation of benzoxazole-bearing 1,3-oxazole derivatives (1–19).

Christian Spiteri et al. [20] reported a one-step synthesis of oxazoles from a-haloketones using silver. The process is effective and simple to follow, producing the necessary oxazoles in good to excellent yields. (Scheme 10).



(Scheme 10)

Ashok K. Shakya et. al [21] were synthesized A series of N-(2-(4-chlorobenzyl) benzo[d]oxazol-5-yl)-3-substituted-propanamide (3a–3n) and screened for their acute and chronic anti-inflammatory activity. Molecular modelling studies indicate that these compounds interact strongly the COX-2 enzyme, which is responsible for the activity. Compound 5-amino-2-(4-chloro benzyl)-benzo[d]oxazole (1) was acetylated with chloropropionyl chloride in dry benzene. The second reaction involved refluxing 3-chloro-N-(2-(4-chloro-benzyl)- benzo-[d]oxazol-5-yl)-propionamide (2) with different secondary amine or heterocyclic compound in dry condition for6 hours yielding final compounds ranging from 30% and 70%. (Scheme 11).



(Scheme 11)

BIOLOGICAL ACTIVITY OF OXAZOLE

Alzheimer'sdisease

Rafaqat Hussain et. al [22] conducted an in vitro analysis and molecular docking investigation on novel benzoxazole-based oxazole derivatives (FIG 4) for the treatment of Alzheimer'sdisease.Hybrid analogues with a 1,3-oxazole moiety based on benzoxazole were designed, developed, and then evaluated for their cholinesterase inhibition. All the novel synthesized analogues exhibitedmoderate to good inhibitory potentials having IC50 values against butyrylcholinesterase enzymes. Among the series, the analogue 11 being the strongest acetylcholinesterase and butyrylcholinesterase inhibitors as compared to standard donepezil drug.

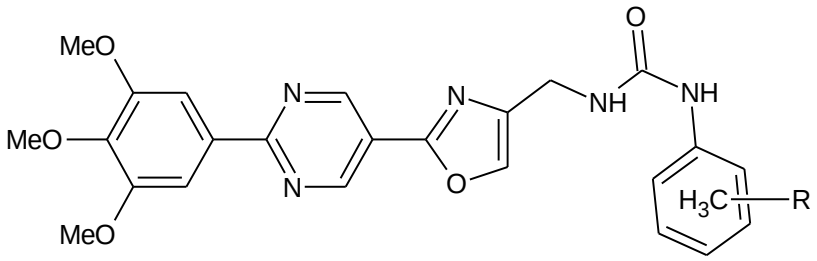
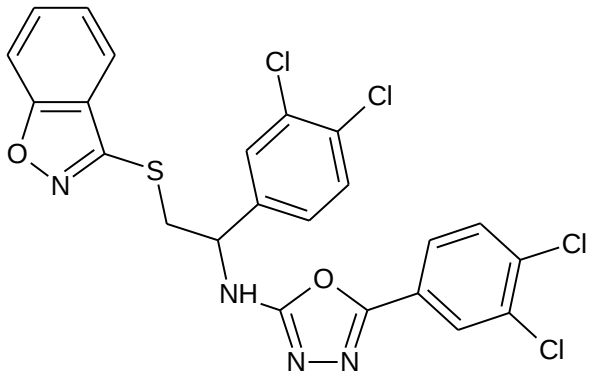


FIGURE 4

Saeed Anwar et. al [23] were focused to synthesize a series of benzoxazole-oxadiazole (FIG 5) and evaluating their anti-Alzheimer properties. These findings demonstrated that benzoxazole-oxadiazole analogues serves as AChE and BuChE inhibitors to develop novel therapeutics for treating Alzheimer's disease and can act as lead molecules in drug discovery as potential anti-Alzheimer agent.



(FIG 5)

ANTICANCER AGENTS

VeeranjaneyuluPattabi et. al [24]were designed, synthesized and evaluated the biological activity of aryl urea derivatives of oxazole-pyrimidine as anticancer agents. A library of aryl urea oxazole-pyrimidine derivatives (FIG 6) has been synthesized and examine their anticancer activity profile against a panel of four human cancer cell lines including breast cancer (MCF-7), lung cancer (A549), colon cancer (Colo-205) and ovarian cancer (A2780) by utilizing of MTT method, the result were compared to etoposide which was used as reference drug candidate. Among the synthesized compounds, seven compounds showed most promising activity than reference drug.

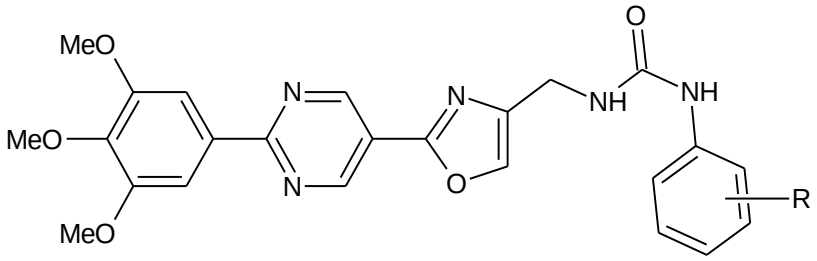


Figure 6

Narendhar Reddy Vanam et.al [25] were synthesized and evaluate their biological activity of aryl amide derivatives of pyridine-imidazo[1,2-a] pyrazine-oxazole FIG 7 as anticancer agents. A nobel series of aryl amide derivatives of pyridine-imidazo[1,2-a] pyrazine-oxazoles (15a-j) was synthesized, designed and tested for their anticancer activity against MCF-7 (human breast cancer), A549 (human lung cancer), Colo-205 (human colon cancer) and A2780 (human ovarian cancer) cell lines by using MTT reduction assay protocol with etoposide (Etoposide) as standard drug. Among the synthesizedderivatives, the compound 15a withtrimethoxy electron donor substituent showed considerable significant anticancer activity against MCF-7, A549, Colo-205, and A2780 cell lines with IC50 values of 0.03 ± 0.0043 μM; 0.02 ± 0.0077 μM; 0.12 ± 0.066 μM; and 0.17 ± 0.059 μM respectively.

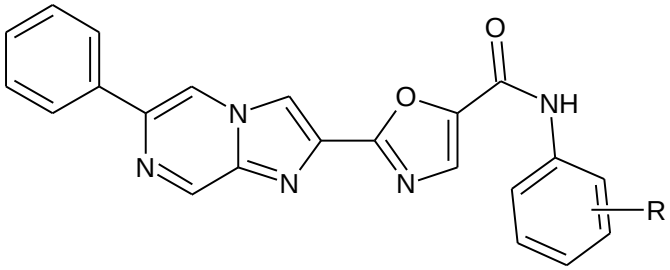
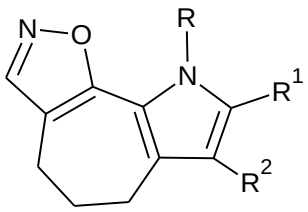


FIG 7

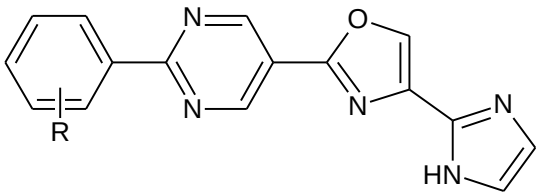
Virginia Spanò et. al [26] describedpyrrolo [2',3':3,4] cyclohepta[1,2-d] [1,2] oxazoles, a novel seriesof antimitotic agents, active against various malignant cell types. Nearly all compounds FIG 8exhibited antiproliferative activity against all human tumor cell linestested,with nM-μM GI50 values.



R=2-OMeBn R_1=COOEt R^2=H

FIG 8

Divya Komirishetti et. al [27] were Synthesized and evaluated biological activity of 4-(1H-imidazol-2-yl)-2-(pyrimidin-5-yl) oxazoles as potent anticancer agents. Among them, five compounds (FIG 9) possessed more potent activity. In which, one compound (9a), showed superior anticancer activity.



9a R= 3,4,5 trimethoxy
9b R= 3,5 trimethoxy
9c R= 4 methoxy
9d R= 4 methyl
9e R= 4 (dimethyl amino)

FIG 9

Anti-microbial activity

Saloni Kakkar et.al [28] was synthesizeda novel series of benzoxazole analogues and tested them for their in vitro antibacterial, antifungal and anticancer activities. The conducted study showed that the FIG 10exhibited highest antimicrobial activity with MIC values equivalent to ofloxacin and fluconazole and FIG 11exhibited best anticancer activity when compared to 5-fuorouracil.

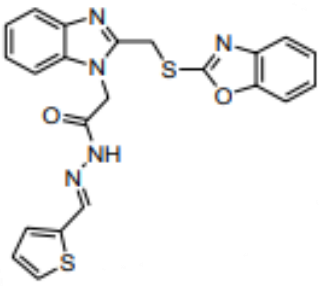


Fig 10

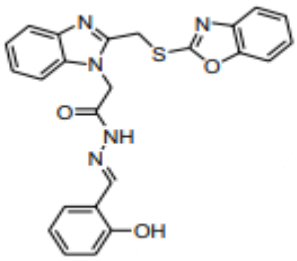
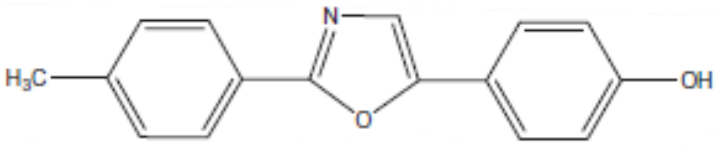


FIG 11

Ivan H.R. Tomi et.al [29] were Synthesized, characterized and comparative study of the microbial activity of some heterocyclic compounds with oxazole (FIG 12) and benzothiazole moieties. The aim of the study was to demonstrate the difference in microbial activity for two classes of five-member heterocyclic rings. The compounds were assessed for antibacterial activity against Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa in nutrient agar medium, and for antifungal activity against Aspergillus Niger and Candida albicans in Sabouraud's dextrose agar medium. The finding indicates that the derivatives with benzothiazole moiety are more active than the derivatives with oxazole moiety.



(FIG 12)

Virendra R. Mishra and colleagues [30] designed and synthesized novel azo-linked substituted derivatives of benzimidazole, benzoxazole, and benzothiazole, evaluating their antimicrobial activity through computational studies. The newly synthesized compounds were tested for in vitro antibacterial activity against Staphylococcus aureus and Escherichia coli strains using the Resazurin microtiter assay method. The azo-linked compound (FIG 13) showed good to moderate or high antibacterial activities in vitro.

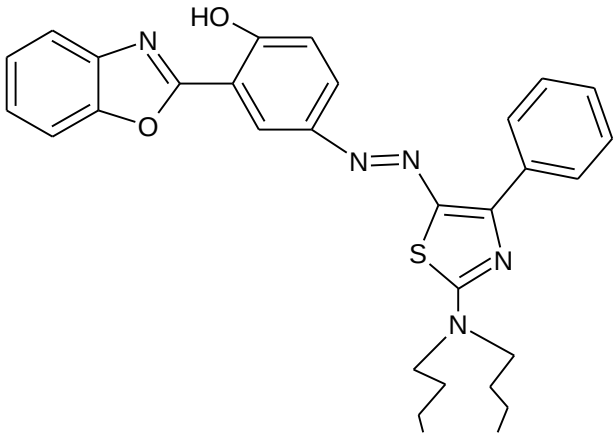
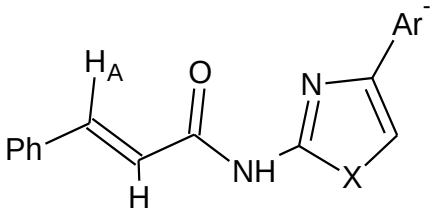


Fig 13

V. Padmavathi et al. [31] synthesized and tested the antimicrobial efficacy of amido-linked pyrrolyl and pyrazolyl oxazoles, thiazoles, and imidazoles. Of these, the chloro substituted imidazolyl cinnamamide (FIG 14) was found to be the best antimicrobial candidate with high antibacterial activity against Bacillus subtilis and antifungal activity against Penicillium chrysogenum..



(Fig 14) X=OAr= 4- Cl Ph

Amol V. Gadakh et al. [32] prepared a group of fluorine-substituted 4-(substituted-2-hydroxybenzoyl) pyrazoles and pyrazolyl benzo[d]oxazoles and studied their antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Bacillus subtilis, and their antifungal activity against Candida albicans. The derivative 1-(3,4-difluorophenyl)-4-(5-fluoro-2-hydroxybenzoyl)-1H-pyrazole (FIG 15) exhibited potent activity against the examined bacterial cultures.

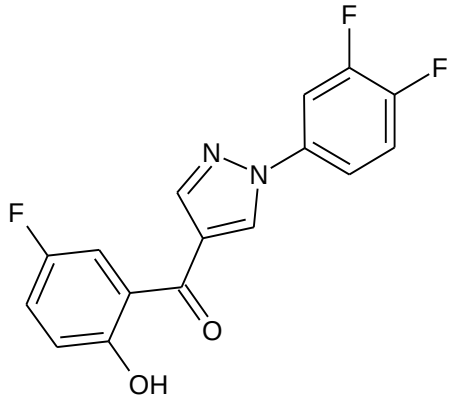


FIG 15

O. Temiz-Arpaci et al. (33) synthesized a series of 2- [4-(4-substituted bbenzamido/phenylacetamido/butanamido) phenyl]-5-ethylsulphonyl-benzoxazole derivatives (FIG16) and evaluated them biologically as potential antimicrobial agents.

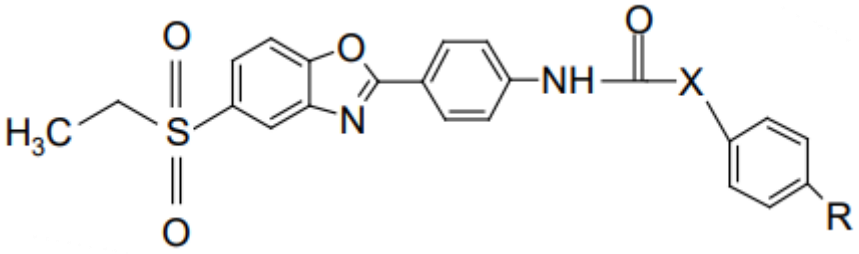
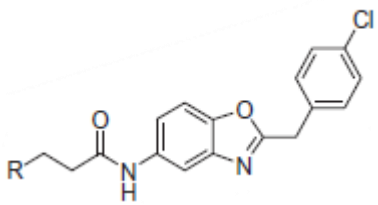


FIG 16

Anti-inflammatory activity

Ashok K. Shakya et al. [34] reported the synthesis of a series of N-(2-(4-chlorobenzyl) benzo[d]oxazol-5-yl)-3-substituted-propanamides (FIG17), which were evaluated for both acute and chronic anti-inflammatory potential. The most active compounds, 17a, 17l, and 17n, were specifically tested for their chronic anti-inflammatory activity using the cotton-pellet-induced granuloma model, as well as for their ulcerogenic effects. These compounds demonstrated 48.4%, 39.3%, and 44.0% protection against granuloma formation induced by cotton pellets, in comparison to diclofenac sodium, which provided 60.2% protection.



R17a=dimethylamino
17i=4-ethyl-1-piperazinyl
17n=4(4 nitrophenyl)-1-piperazinyl. FIGURE 17

Antidiabetic activity

Ramesh S. Gani et.al [35] were Synthesized a series of novel 5-(2,5-bis(2,2,2-trifluoroethoxy) phenyl)-1,3,4-oxadiazole-2-thiol derivatives as potential glucosidase inhibitors. This study has recognized that compounds like(FIG18) may be considered potential candidates for further developing a novel class of antidiabetic agents.

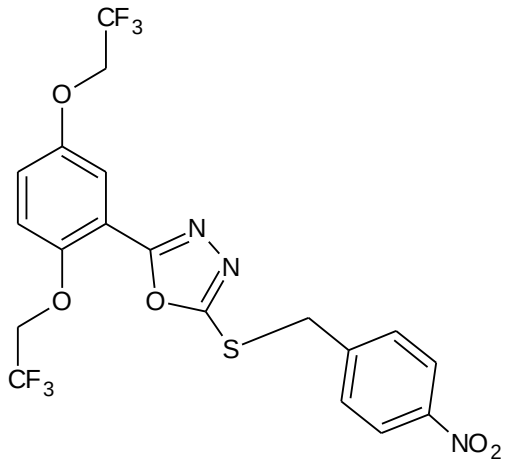
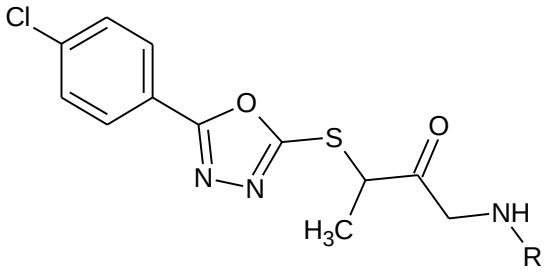


FIG 18 b

Muhammad Iftikharet.al [36] were synthesized a series of new N-aryl/aralkyl derivatives of 2-methyl-2-{5-(4-chlorophenyl) -1,3,4-oxadiazole-2ylthiol} acetamide. All compounds were evaluated for their α-glucosidase inhibitory potential. Compounds 19a found to be promising inhibitors of α-glucosidase.



(FIG 19a) R= $-C_6H_5$

Anti-tubercular agents

Suraj R. Shindeet.al [37] have isolated oxazole-dehydrozingerone based hybrid molecules as effective anti-tubercular agents and docked against Mtb DNA gyrase. Oxazole -dehydrozingerone hybrid molecules and oxazole dehydrozinzerone-thiophene derivatives were synthesized through cyclisation, coupling and aldol condensation reactions. Synthesized compound was tested against Mycobacterium tuberculosis strains. Compound20f exhibited potential activity.

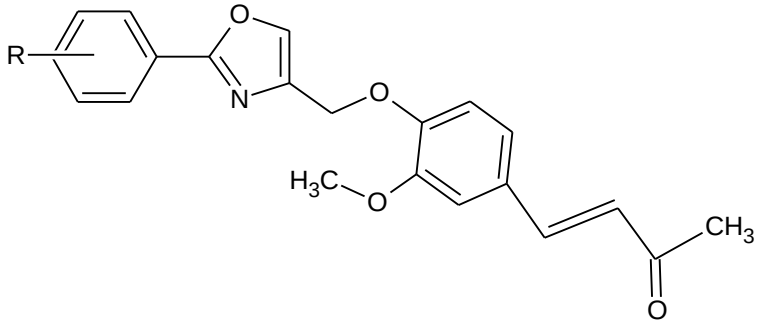
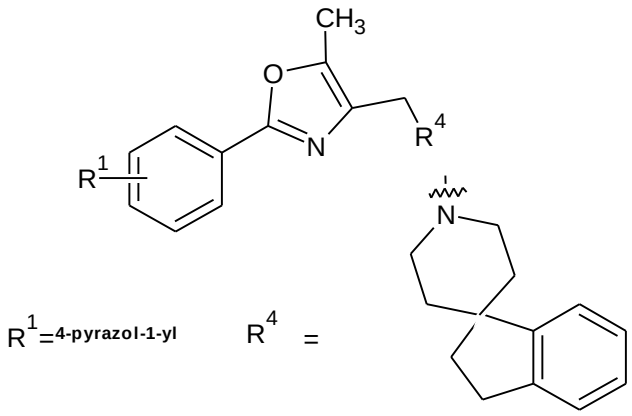


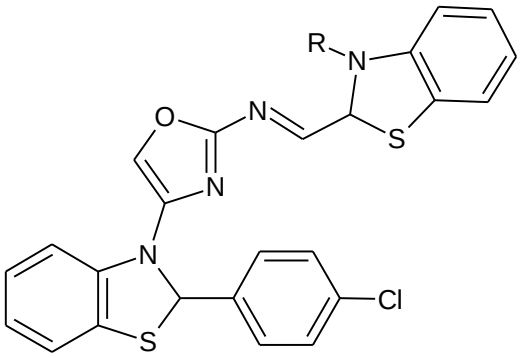
FIG 20f

Young Mi Kim et al [38] presented the development of a phenyl oxazole methyl (POM) core structure with spirocyclic derivatives as part of our efforts to discover innovative anti-tuberculosis agents. Notably, compound (FIG 21c) displayed potent anti-tubercular activity with MIC value of 0.206 μM in culture broth medium.



(FIG 21C)

Gajendra Kumar et. al [39] was synthesized and evaluated anti-inflammatory and analgesic activity of thiazole/oxazole substituted benzothiazole derivatives. Compound 4-(2-(4 chlorophenyl) benzo[d]thiazol-3(2H)-yl)-N-((3-substituted-2-hydrobenzo [d] thiazol-2-yl) methylene) thiazol-2-amine (FIG 22c) was the most active compound than reference drug at a dose of 50 mg/kg p.o.



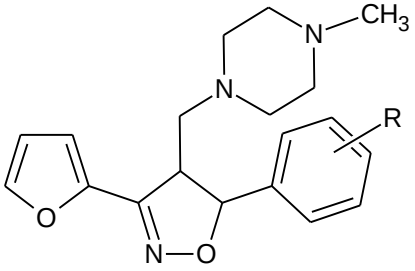
R= H, CH_3, $-C_2H_5$, $-C_6H_5$

22C R=$-C_2H_5$

FIGURE 22

Antianxiety Activity

Jagdish Kumar et. al [40] were synthesized a novel series of 1-{[3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1,2-oxazol-4-yl] methyl}-4-methyl piperazine. Moreover, the antianxiety activity of the newly synthesized compounds was investigated by the plus maze method. Compounds 23a and 23k reduced the duration of immobility times of 152.00–152.33% at10 mg/kg dose level and compounds 23a and 23k have also shown significant antianxiety activity.

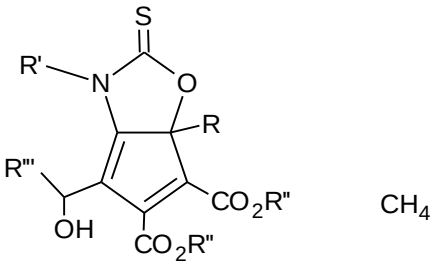


23a R=H ,23k R= 4 - $N(CH_3)_2$

FIGURE 23

Antioxidant Activity

Somayeh Soleimani-Amiriet.al [41] were Synthesized A novel and screened them biological activity of Functionalized [1,3]-Oxazoles Using Fe3O4-Magnetic Nanoparticles. Among investigated compounds, 24a has good power for radical trapping activity.

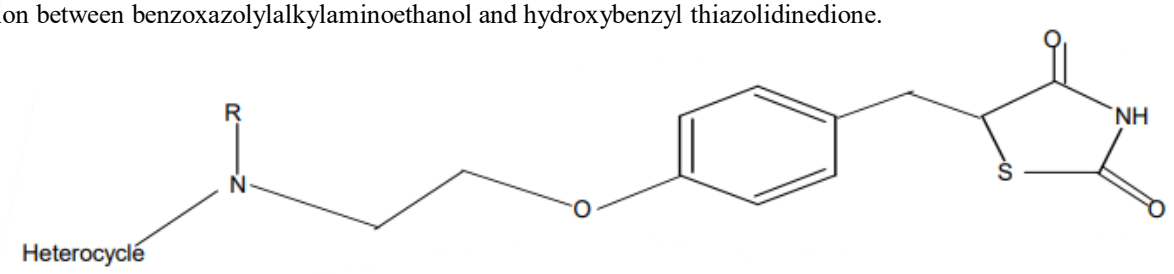


24a R=COOEt ,R'=4MeO C_6H_4 , R"=Me R'"=COOEt

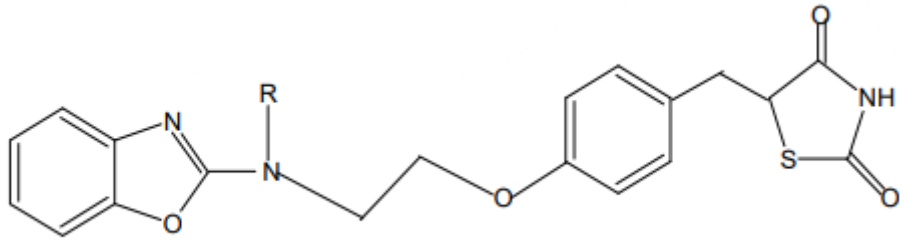
FIGURE 24

Antihyperglycemic activity

Raok Jeon and co-workers (42-45) synthesized benzoxazole-substituted thiazolidinedione derivatives. In particular, the 5-[4-[2-(Benzoxazol-2-yl-alkylamino) ethoxy] benzyl] thiazolidine-2, 4-diones were synthesized via a Mitsunobu reaction between benzoxazolylalkylaminoethanol and hydroxybenzyl thiazolidinedione.



(FIG25)

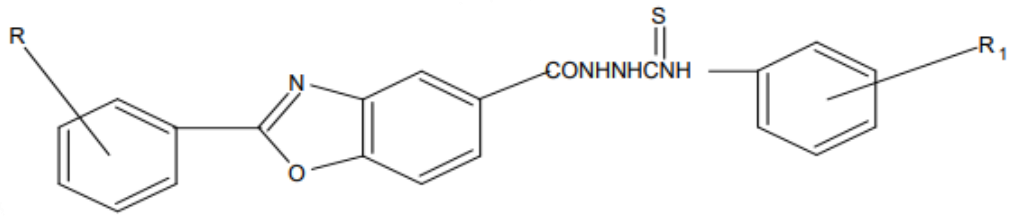


R= Me, BRL 48432

(FIG 26)

A number of derivatives of [(heterocycloamino) alkoxy] benzyl]-2, 4-thiazolidinediones, (FIG 25) have been previously reported as effective antihyperglycemic agents. Among these compounds, benzoxazole derivatives, (FIG 26)e.g., BRL 484482, Figure 3 have been reported to exhibit potent agonistic activity against PPAR-γ, comparable to that of the established antihyperglycemic drug, rosiglitazone.

CNS activity:
Nadeem Siddiqui et al. (46) prepared a set of 5-Carbomethoxybenzoxazoles (FIG 27) from methyl-p-hydroxybenzoate and tested them for anticonvulsant activity and neurotoxicity. The structure of the compounds was established based on 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

(FIG 27)

CONCLUSION
Briefly, the present article is meant to overview the published work on therapeutic potentials of oxazole derivatives of immense worth for medicinal applications in the next millennium. The review article is presented on synthesized oxazole derivatives that have wide spectrum of biological potentials i.e. antibacterial, analgesic, anti-inflammatory, antidepressant, anticancer, antimicrobial, antidiabetic, antioxidant. The biological profile of the newer generations of benzoxazoles demonstrates a considerable improvement over the earlier molecules. Studying the drug importance of benzoxazole moiety, it will be valuable to prepare some newer benzoxazole derivatives and test them for their biological activity, oxazole possesses vast possibilities to be discovered for newer therapeutic possibilities and is a valuable class of lead molecules for the construction of new chemical entities for the treatment of numerous diseases of clinical importance. The reaction is eco -unfriendly and necessitate more environment – friendly and sustainable processes for the field. This review will assist researchers facing new challenges in designing simple, inexpensive, and eco-friendly methods to synthesize benzoxazole derivatives for the benefit of mankind.

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