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REVIEW ARTICLE

A COMPREHENSIVE REVIEW ON CHEMISTRY OF OXAZOLE DERIVATIVES: CURRENT TO FUTURE THERAPEUTIC PROSPECTIVE

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ABSTRACT

The compound oxazole and its derivatives are crucial to the field of medical chemistry. The oxazole nucleus is a heterocyclic five-membered ring that has been explored in an effort to develop new molecules with advantageous biological properties. In recent years, the use of oxazole as intermediates in the synthesis of novel chemical entities in medical chemistry has risen. Oxazole has sporadically been used as a functional lead molecule in contemporary pharmaceutical chemistry. Massive oxazole candidates or medications are being created often for the treatment of diseased condition, increasing their potential as therapeutic agents. Oxazoles five-membered aromatic ring contains nitrogen and oxygen atoms. These rings swiftly interact physiologically with various enzymes and receptors via a variety of non-covalent connections, leading to a range of biological functions. This review makes a rational effort to promote oxazole chemistry research and development. The significant data in this publication will serve as inspiration for fresh ideas in the quest for the rational creation of more physiologically active and less toxic derivatives of oxazoles as pharmaceutical agents.

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INTRODUCTION

Heterocyclic compounds are widely employed in pharmaceutical industry, fields of research studies, and healthcare. In medicinal chemistry, heterocycles with nitrogen and oxygen atoms constitute a key family of molecules. Researchers have been interested in the biology and chemistry of heterocyclic compounds for many years, and in recent years, the oxazole moiety has gained popularity due to its growing importance in the field of medicinal chemistry. A carbon atom supports an oxygen atom at position 1 and a nitrogen atom at position 3 in the five-membered ring of oxazole, which has two unsaturation[1]. Oxazole derivatives have the potential to be used in the fields of agriculture, biotechnology, medicine, chemical engineering, and materials science because of the structure's diverse weak interactions, including the hydrophobic effect, Vander Waals force, hydrogen bonds, coordination bonds, ion-dipole bonds, and pi-pi bonds. The clinical characteristics of a huge number of drugs generated from oxazoles is shown in Figure 1. This review article demonstrates to launch an examination into the body of literature on the chemistry of oxazoles, their therapeutic uses, and the link between structure and activity in oxazole derivatives.

Chemistry of oxazole: The oxazole compound was first created in 1962, although its chemistry had already been known. Novel and potent 2-methyl oxazole derivative was synthesized in the year 1876. Oxazole became well-known during the start of World War I when the antibiotic penicillin was developed. Oxazole chemistry will begin again with the development of dienes in the Diels-Alder reaction. Three carbons, one nitrogen, and one oxygen atoms make up oxazole nucleus. All of them are planar and sp2 hybridised[2]. Additionally, the atoms have an unhybridized p orbital that is parallel to the plane of the bonds. There are a total of six non-bonding electrons, of which three are carbon-based, one is nitrogen-based, and two are oxygen-based, as shown in Figure 2. Because the oxygen atom is so electro-negative, delocalization is not very effective[3]. The structure of additional heterocycles containing nitrogen and oxygen is similar to that of oxazoles.

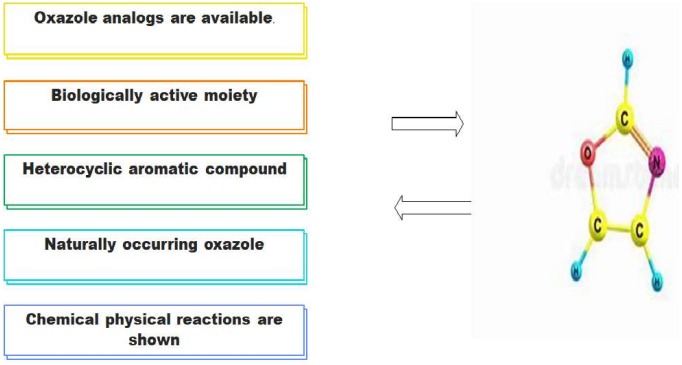

Figure 1. Oxazole derived medicinal agents

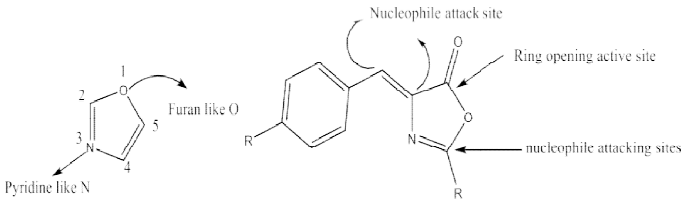

Figure 2. Chemical structure with numbering of oxazole and activesite

The oxygen and nitrogen found in furan and pyridine are structurally similar to the heteroatoms found in oxazoles. The investigations demonstrate that oxazole's nature also interacts with furan and pyridine. Oxazole is a basic chemical that has certain characteristics with pyridine 4. They have less resistance to oxidation and higher resistance to acids as compared to pyridine, but they also exhibit some instability similar to that of furans. The oxazoles, unlike highly volatile liquids, are thermally stable entities and do not decompose at high boiling temperatures. Dienophile is created when an exocyclic double bond is present, and the N-substituted oxazole exhibits the Diels-Alder reaction. These oxazolone rings exhibit highly electrophilic nucleophile attack reaction centre. Oxazole hydrogen atoms become less acidic from C2 to C5 to C4, in that sequence. Hydrogen was found to have a pka 20 acidity and a pkb 1.17 acidity at C25.

Structure Activity Relationship: The SAR investigations in demonstrate the adaptability of the oxazole moiety due to chemical link between a molecule's three-dimensional structure and its biological activity. The pharmacophore that is present in the compounds and necessary for their pharmacological action was discovered using SAR investigations. The significant pharmacophores and their therapeutic action are shown in Table 1.

and strategies used in synthetic methods. Though several recent, effective catalysts have been discussed, a new oxazole derivative has recently been synthesized by applying certain innovative techniques6. In 2017, Mahadavi and colleagues published a study on the synthesis of 1,3-oxazoles utilising trimethylamine as the starting material, water as the solvent, and cyclodextrin (CD) as the catalyst. In 2019, Yasaei and associates created 5-(2-chloroquiolin-3yl) oxazole. In the presence of Pd-catalyzed amidation, 2-chloroquinoline-3-carbaldehyde and TosMIC are synthesized by a Van Leusen route. By condensation of substituted acetophenone with urea and thiourea in the presence of natural red, white, and black clay as a biocatalyst, Supriya and Kamble created new 2,4-disubstituted oxazoles.These reactions provide a high yield of products and are carried out in green medium. In order to create oxazolone in 2019, Phalke and colleagues synthesized 2,4-disubstituted acetyl glycine, aldehyde, acetic anhydrides, and sodium acetate. To create new fused oxazole derivatives, these, unsaturated derivatives react with different nucleophilic reagents. In 2018, Venkata and team produced oxazole as a catalyst by reacting 4-substituted oxazole with aryl bromide in the presence of KOH, CuI, and Pd(PPh3) in DME. By directly arylating 4-aryl/alkyl oxazole, these chemicals were produced in excellent quantities.

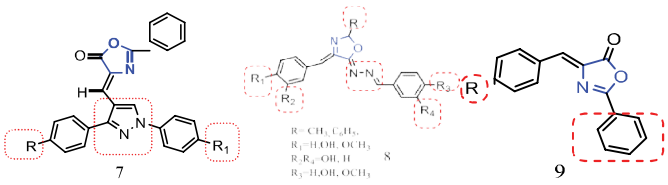

Figure 3. Chemical compounds having active pharmacophores that are antibacterial oxazole derivatives

Table 1. SAR of different oxazole derivatives with biological activity

Biological Activity	SAR
Antibacterial	R1 = C6H5, R2 = 4-substituted-phenyl-1 H-pyrazole-4-carbaldehyde R1 = CH3,C6H5, R2 = CH2-C6H5, R3 = -N-N = CH3- C6H5 R1 = C6H5, R2 = CH2-C6H5
Antioxidant	R1 = glycine substituted hydroxyl cinnamic acid derivatives, R2 = COOCH3, R3 = H R = admantane (CH)4(CH2)6 R = OMe, F, R2 = H,OMe, R3 = 4-methylbenzyl,3,4-dimethylbenzyl,6-methoxychroman,4- methoxybenzyl
Antidiabetic	R1 = Phenyl Toludine, Anisidine, Methyl n-butyl amine, n-Octylamine, R2 = naphthalene R1 = C6H5COCH3, R2 = CH2-C6H5-R, R3 = C = O R = R' = H,Me,Cl
Anticancer	R1 = R-C6H5, R2 = CH-C6H5-R',R" Amidosulfonamido methane linked bis oxazole 2-aryl oxazole sulfonamide derivatives R = CH3, R1,R3 = H, R2 = SCH3, R = CH3,R1,R3 = H, R2 = SOCH3
Anti-inflammatory	R1 = CH2CH2CONHCOOCH3, R2, R3 = C6H5 R1 = 4-F, Ph,R2 = 4-SO2MePh,R3 = 5-Cl-2-pyridine R1 = 4-F, Ph,R2 = pyridine-2-propanol, R3 = 5-Cl-2-pyridine
Antimalarial	R, R' = H, CH3 R =trifluoromethyl,trifluoromethoxy,dichlorodiphenyl,methylthiodiphenyl
Pesticidal activity	R1 = C6H5, CH3, R2 = C6H5 R1 = isobutyl, n-pentyl, benzyl, n-propyl, R3 = indole
Anthelmintic	R1 = C6H5-OH,OCH3,CH3R2 = NH-C6H5NO2
Anti-neuropathic	R1 = Furan, R = H,4-CH3,2-Cl, 4-Cl, 4-Br, 4-F, 4-OH, 4-NH2, R2 = Piperizine, R3 = R-C6H5 Imidazopyridine derivative of oxazole Substitution of pyrimidine, piprezine, pyridine R1 = C6H5, piperazine, diphenyl, bromobenzene, chlorobenzene
Antiparasitic	2-amino-4-phenyl oxazole derivatives R = H,OH,OCH3,CH3,COOH, COOCH3, N(CH3)3 R3 = substituted Thiazole, furan, isoxazole, imidazole
Antiviral	Quinoline substituted oxazole at C-2 position R = thiophene, nitrofuran, pyridine, fluorobenzene X1 = H,Cl,OMe, X2,X3 = H,Cl,OMe,
Antifungal	R = H,OCH3,OCH3 Y = CH,N, X = Cl,Br,alkyl,acyl R2 = CH(CH3)2, CH2CH(CH3)2,substitution of furan, isooxazole, Thiazole

Chemical synthesis of oxazole: The literature has reported conventional synthesis of the oxazole nucleus using various techniques. For example, cyclo isomerization of propargyl amides, Bredereck reaction, Robinson-Gabriel synthesis, Fisher oxazole synthesis, oxidation of oxazolines, Erlenmeyer Plochl reaction, Davidson reaction, organometallic reactions, Williams' reaction, and Van Leusen oxazole synthesis are some of the different starting points

Davidson synthesis was performed by Alexander and other researchers. Ammonium acetate and the starting ingredients are mixed in GAA at a ratio of 1:10 each. At that moment, add haloketone and a few drops of aliquot 336 to the dry toluene. The addition of a purine derivative in acetic acid7. With high yield, it will produce a purine-substituted oxazole derivative. 2019 saw 2,4-disubstituted oxazole compounds produced by para substituted 2-

bromoacetophenone and urea in DMF under MW irradiation at 138°C for 20 min. Singh and other researchers investigated a unique method of producing biphenyl substituted oxazole derivatives using substituted phenyl boronic acid as a catalyst in the Suzuki reaction of 4-(4-bromophenyl)-2,5- dimethyloxazole.

synthesis is utilised to create a balsoxin analogue8. In 2015, Delia Hernandex and colleagues demonstrated a coupling procedure for the synthesis of concatenated oxazoles that was mediated by sp2- sp2 transition metals, namely Pd9. Boron was used to catalyze the arylthiooxygination of N-allyl amide by Emdor and his team, as well

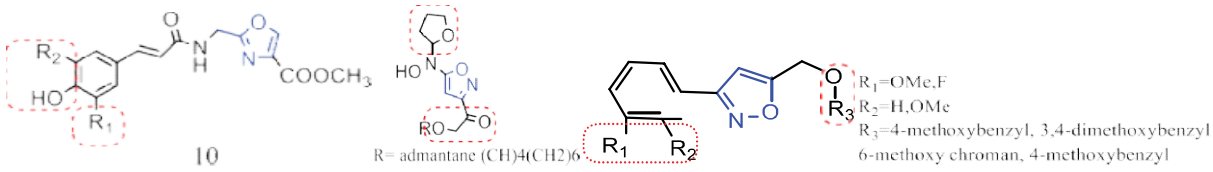

Figure 4. Oxazole derivatives that are active pharmacophores with antioxidant capabilities

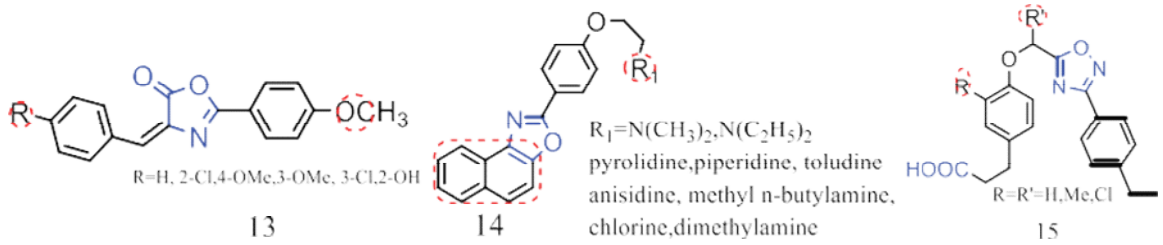

Figure 5. Chemical structures of oxazole derivatives with antidiabetic effect together with active pharmacophores

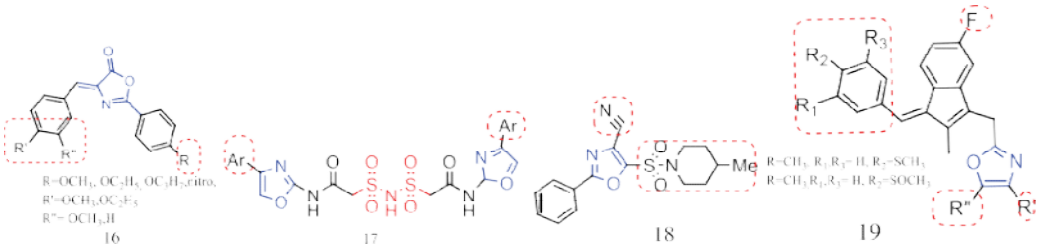

Figure 6. Active pharmacophore oxazole derivatives with anticancer activity

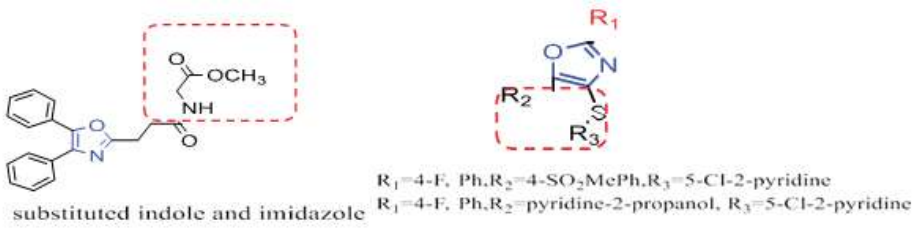

Figure 7. Anti-inflammatory active pharmacophores found in oxazole derivatives

Figure 8. Oxazole compounds with antimalarial pharmacophores that are active[10]

Kobei Yamada developed in 2017 A novel method for making 2,4,5-tri substituted oxazoles is the Suzuki-Miyaura coupling process in a single pot. A novel method for making 2,4,5-tri substituted oxazoles is the Suzuki-Miyaura coupling process in a single pot. This reaction involves a dehydration condensing agent, an amino acid, and a carboxylic acid in the presence of a Ni-catalyst and boronic acid. Ramana Reddy and colleagues provided a method for the synthesis of 2,4-disubstituted oxazole derivatives. Diazoketones and amides are combined when a catalyst called copper (II) triflate is present. The as the creation of arylsulfanyl-oxazolines 8. In 2011, Cano and other researchers created polysubstituted oxazole derivatives by combining 1-alkynes with acyl azides with copper as a catalyst and moderate oxidative cyclization. This resulted in 2,5-disubstituted oxazoles10.

Oxazole in natural products: Oxazole organisms, which include plants, microorganisms11, and marine organisms, are widely found in nature. Oxazole moiety is also found in several marine invertebrate species, including Echinodermata, Porifera, Mollusca, Cnidaria,

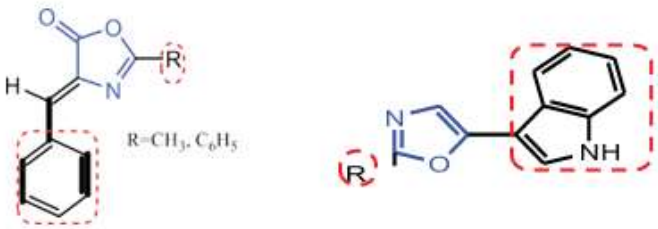

Figure 9. Pesticide-like active pharmacophores found in oxazole derivatives

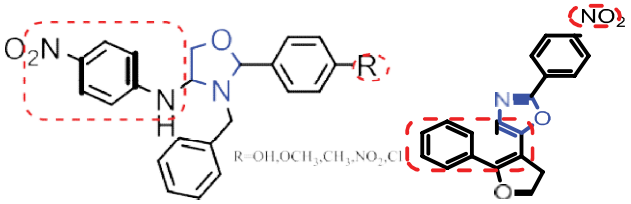

Figure 10. Oxazole derivatives with Antitubercular activity with active pharmacophores

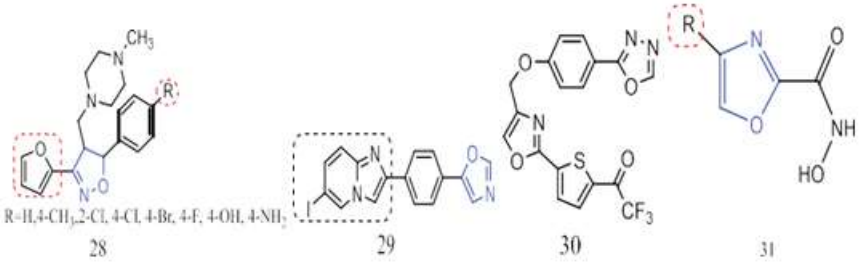

Figure 11. Oxazole derivatives with anti-neuropathic effect with active pharmacophores

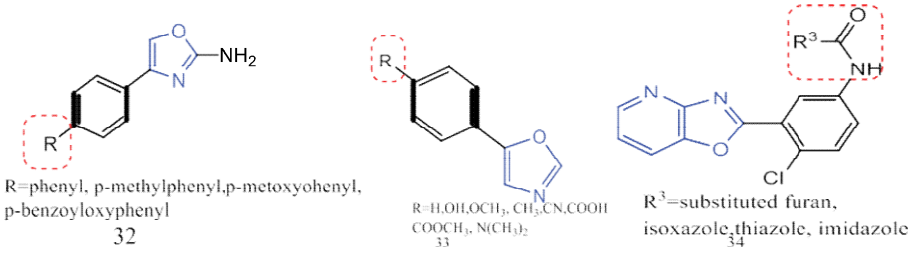

Figure 12. Oxazole derivatives with antiparasitic activity include active pharmacophores

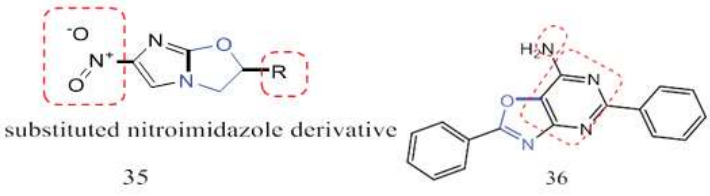

Figure 13. Oxazole derivatives with active plant growth hormone and antileishmanial pharmacophores

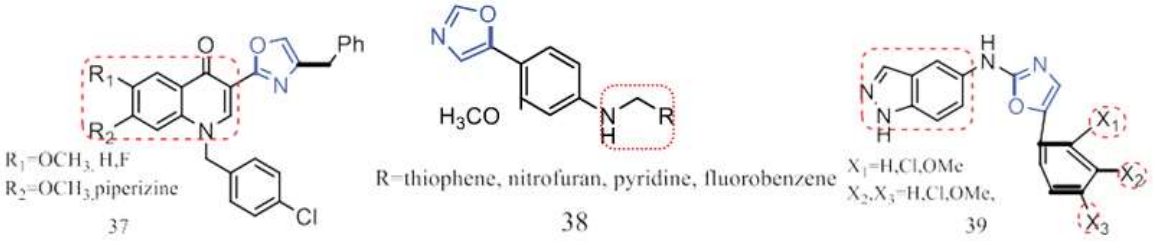

Figure 14. Antiviral oxazole derivatives with active pharmacophores

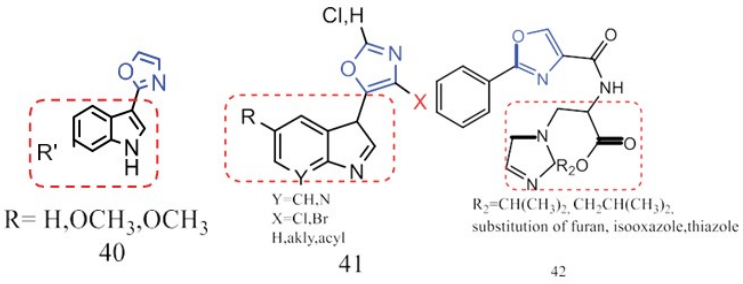

Figure 15. Active pharmacophores that exhibit antifungal effects that are found in oxazole derivatives

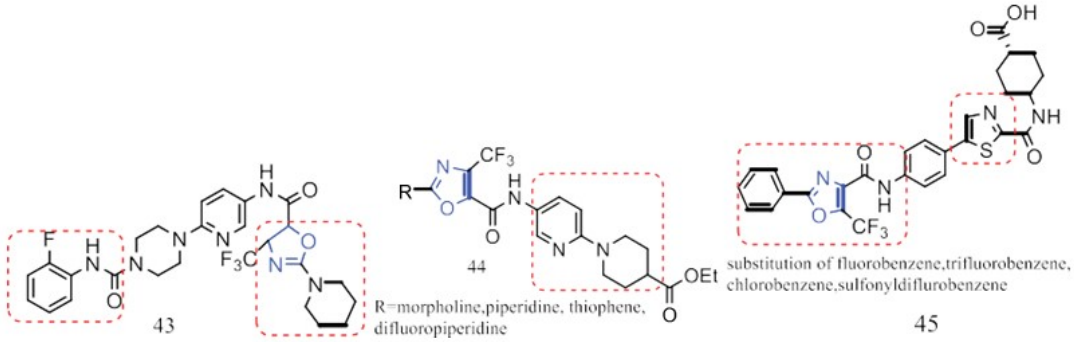

Figure 16. Oxazole derivatives with anti-obesity effect include active

Anthozoa, and Bryozoa. Due to their symbiotic relationship with marine life, these vital bioactive chemicals are only obtained in trace amounts from marine organisms12. Several natural products containing oxazoles in them are produced by terrestrial and marine microbes; Oxazole compounds have a wide range of pharmacological effects, including antimicrobial, antidiabetic, anthelmintic, antifungal, antibacterial, anticonvulsant, antidepressant, and Antitubercular action 13.

CONCLUSION

This groundbreaking discussion highlights the significance of oxazole as a conversant nucleus that has great potential for the creation of potent novel chemical compounds with anti-inflammatory, antiviral, antibacterial, anticancer, analgesic, and antihypertensive activities, among other features. Studies on the link between structure and activity identified the significant groups that were substituted in the oxazole moiety and its pharmacological action. They conducted a thorough investigation into the use of functional groups that are advantageous for boosting the physiochemical characteristics and interaction with the target locations that boost therapeutic activity. Some natural compounds with important medicinal properties also include oxazole moieties. Later, these studies recognize a sizable number of patents that mimic how the development of oxazole derivatives draws researchers, pharmaceutical companies, and academic institutions to create functional molecules by making numerous modifications to the primary scaffold in various places. Additionally, it is thought that researchers are analyzing and finding more clinically relevant oxazole derivatives that actively affect human health and quality of life thanks to the development of novel synthetic techniques and screening procedures. In conclusion, the goal of the current study is to evaluate the research on the chemistry of oxazole derivatives that are important for medical applications in the new century. Oxazole derivatives exhibit an extensive array of biological potentials, including anti-bacterial, analgesic, anti-inflammatory, antidepressant, anticancer, antimicrobial, antidiabetic, antiobesity, antioxidant, adrenergic receptor ligand, antiprogesterone activity, prostacyclin receptor antagonist, T-type calcium channel blocker, and transthyretin amyloid fibril inhibitory properties. Since the heterocyclic moiety is so versatile in nature and gives the medicinal chemist the opportunity to learn more about it in the medicinal sector, the information offered in this article will be very helpful to prospective researchers working in this field for future study of this scaffold. The oxazole moiety is a significant heterocyclic molecule since it is a crucial component of several commercially available medicines. Oxazoles have a tremendous amount of potential to be researched for innovative therapeutic action due to their wide range of biological activities.

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