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RECENT ADVANCES IN ISOXAZOLE DERIVATIVES: CHEMISTRY AND BIOLOGICAL ACTIVITIES

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ABSTRACT

Isoxazole derivatives are nitrogen and oxygen containing heterocycles exhibiting diverse pharmacological activities. They represent a significant group of five-membered compounds that have been studied. in medicinal chemistry due to their extensive range of biological activities and beneficial pharmacological characteristics. The adjacency of nitrogen and oxygen atoms within the aromatic structure provides unique electronic properties, allowing for strong interactions with various biological targets. Recent developments in synthetic techniques, including microwave-assisted synthesis, cyclization reactions, multicomponent reactions, and environmentally friendly chemistry methods, have accelerated the rapid creation of structurally varied isoxazole derivatives. Various isoxazole derivatives have demonstrated significant biological activities. Several compounds exhibited potent inhibitory activity against various cancer cell lines such as MCF-7, HeLa, A549 and HepG2.The structure-activity relationship studies revealed that electron-withdrawing substituents including chloro, fluoro and nitro groups generally enhance biological activity. This review highlights recent advancements in both the chemistry and pharmacological uses of isoxazole-based compounds, focusing particularly on their anticancer, antimicrobial, and antifungal properties. Special emphasis is placed on hybrid molecules featuring isoxazole connected to pharmacologically active frameworks such as pyrazole, chalcone, quinoline, and thiazole. These hybrid systems have shown improved biological activity.

KEYWORDS: Isoxazole, Anticancer activity, Antimicrobial activity, Antifungal agents, Drug discovery.

INTRODUCTION

Isoxazole is an important molecule in pharmaceutical chemistry, but many other heterocycles have also been explored for creating significant pharmaceutical compounds. In isoxazole, an oxygen atom is next to a nitrogen atom. The isoxazole ring consists of three carbon atoms and forms an unsaturated aromatic heterocyclic compound. Since the isomer "oxazole" was discovered earlier, Hantzsch was the first researcher to propose isoxazole. The letters "oxa" and "aza" refer to the oxygen and nitrogen atoms, respectively, while "iso" indicates the isomer and "ole" signifies the size of the five-membered ring.

Isoxazole plays an important role in many biological processes. There is considerable variation in the modification of isoxazole structure, which is helpful for developing new treatments with better effectiveness and lower toxicity. The pharmacological actions of isoxazole derivatives include analgesic, anticancer, anti-inflammatory, antibacterial, antihistaminic, anti-tubercular, antiulcer, antiepileptic, 5-HT reuptake inhibitors, antiviral, and anxiolytic properties.[8]

Medications like leflunomide, an antirheumatic drug, and valdecoxib, a COX-2 inhibitor, depend on the isoxazole ring, which shows the pharmacological advantages of using this structure.

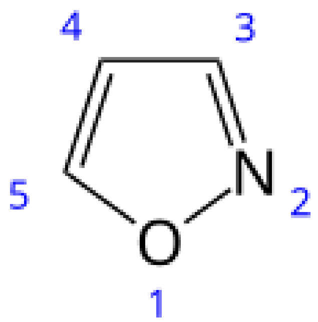

Figure 1: Illustrates the basic structure of isoxazole ring.

ISOXAZOLE BASED DRUGS

These are the examples of currently available marketed drugs that contain isoxazole scaffolds. It has a wide range of pharmacological activities. Therefore used for treatment of many diseases.

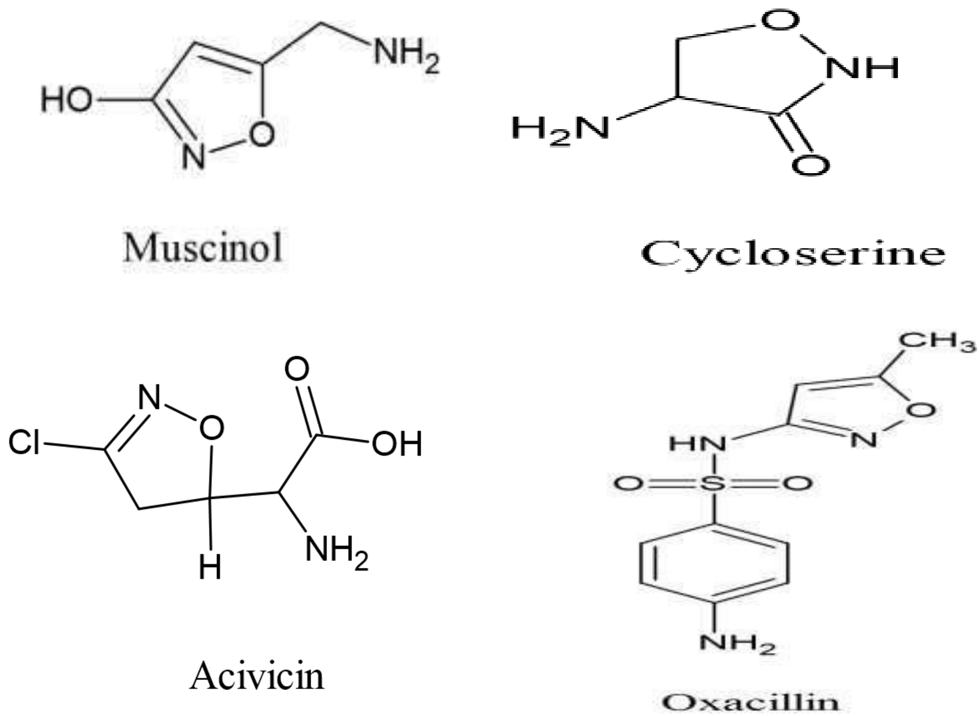

Figure 2: Representative drugs containing the isoxazole scaffold.

Isoxazole-based drugs have gained considerable interest in the field of medicinal chemistry due to their wide-ranging pharmacological effects and therapeutic importance. The addition of the isoxazole ring structure enhances biological interactions and elevates the pharmacological characteristics of a variety of drug compounds. Muscimol is known for its strong neuropharmacological effects as a GABA receptor agonist, while Cycloserine has significant activity against tuberculosis. Likewise, Acivicin shows remarkable anticancer properties through the inhibition of specific enzymes, and Oxacillin is commonly employed for its antibacterial effects against strains of bacteria that are resistant to penicillin. Figure 2 illustrates representative examples of important isoxazole-containing drugs and their respective biological activities.

CHEMISTRY OF ISOXAZOLES

Isoxazoles are five-membered aromatic compounds. They contain one nitrogen and one oxygen atom next to each other, forming a 1,2-oxazole ring system. This ring has six π- electrons, which gives it aromatic properties and a degree of stability. The electronegative heteroatoms create an electron-deficient system that affects how isoxazoles react and interact biologically. Because of this polarity, isoxazoles can form hydrogen bonds and dipole interactions, making them important in medicinal chemistry. Isoxazoles are often made through 1,3-dipolar cycloaddition of nitrile oxides with alkenes or alkynes. This method allows for a variety of substitutions. Another common method involves reacting β-diketones or β-ketoesters with hydroxylamine, which leads to isoxazoles through oxime intermediates. Moreover, chalcones can react with hydroxylamine to produce 3,5-disubstituted isoxazoles.

This reaction is particularly useful for creating hybrid molecules like pyrazolyl-linked isoxazoles. Chemically, isoxazoles face limited electrophilic substitution, mainly at the C-4 and C-5 positions. Nucleophilic attacks typically occur at the C-3 position. Under strong conditions, the ring may break apart. Their flat structure, moderate polarity, and capability to act as hydrogen bond acceptors make isoxazoles valuable in drug design. This allows for the optimization of biological activity through structural changes.

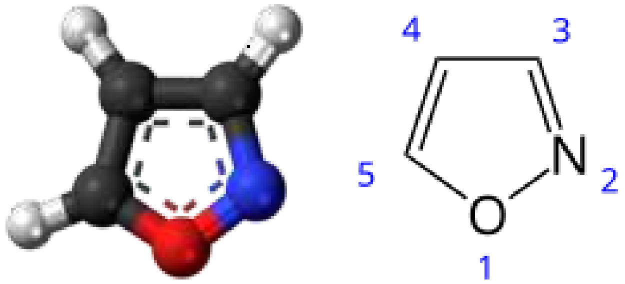

Figure 3: 3D and 2D conformations of isoxazole derivatives.

BIOLOGICAL ACTIVITY OF ISOXAZOLES

Isoxazole is a five-membered ring that contains adjacent nitrogen and oxygen atoms. Its aromatic structure and ability to be substituted at various positions have made isoxazole popular in drug discovery. Many compounds with isoxazole are noted in the literature as biologically active. Some of these compounds are part of clinically useful drugs like Muscimol, Cycloserine, Acivicin, Sulfamethoxazole, Isocarboxazid and Oxacillin.[13]

Antibacterial activity

Isoxazole derivatives have shown strong antibacterial activity against both Gram-positive and Gram-negative bacteria. Structural modifications, especially with electron-withdrawing groups and lipophilic substituents, have improved antibacterial effectiveness. The isoxazole ring is found in key antibacterial drugs like oxacillin, flucloxacillin, dicloxacillin, cloxacillin, sulfamethoxazole, and sulfisoxazole, highlighting its importance in pharmacology.[14]

Antifungal activity

In recent years, a number of new pharmaceutical agents that have been created from derivatives of isoxazoles and similar classes of heterocyclic compounds have emerged as a class of pharmaceutical agents with numerous biological actions, particularly antifungal action. Numerous clinical research studies have demonstrated the selective antifungal activity of isoxazole-derived compounds against various species of pathogenic fungi (such as Candida albicans) and their ability to cause opportunistic infection (e.g., during periods of immunosuppression). Because more and more strains of fungi are developing resistance to traditional antifungal agents such as azoles, researchers have explored new chemical classes such as isoxazoles for their potential as alternative antifungal agents.[15] Eight novel isoxazole-derived compounds (PUB11-PUB18) were synthesized and evaluated for their antifungal activity. Both PUB14 and PUB17 demonstrated a high level of selectivity against Candida albicans as well as minimal effects on the Lactobacillus species and all other normal microflora of humans. This selective toxic effect on pathogenic yeast is a very advantageous property of any compound because typical antifungal agents also affect the normal microflora that can lead to secondary infections and recurrences. In addition, both PUB14 and PUB17 displayed significantly less cytotoxicity against mammalian cells than most antimicrobials used in clinical practice, and therefore may possess a better safety profile for use in clinical therapy.[16]

An additional important attribute of the isoxazole-derived compounds is their ability to inhibit biofilm formation. Biofilms are known to increase antifungal drug resistance and cause persistent infections, and the isoxazole-derived compounds demonstrated significant efficacy against populations of Candida spp. that were used to establish biofilms. Therefore, these newly developed compounds may provide a unique approach to fighting the increasing frequency and severity of fungal infections caused by biofilms.[16,15]

Compound	**Activity**	**Target**	**Key Feature**
PUB14	High antifungal	*C. albicans*	Selective, low toxicity
PUB17	High antifungal	*C. albicans*	Biofilm inhibition

Figure 4: Summarizes key features of antifungal isoxazole derivatives.

Anticancer activity

Isoxazole derivatives have been extensively studied for their anticancer properties against various cell lines, including HeLa, MCF-7, Hep3B, HepG2, PC3, and HT-29. Their anticancer effects are often linked to processes such as inducing apoptosis, cell-cycle arrest, and inhibiting topoisomerase and Hsp90, as well as mechanisms involving microtubules.

Recent literature highlights how isoxazole-containing compounds can serve as promising starting points for developing selective anticancer agents. Isoxazole derivatives show strong anticancer effects through several mechanisms that target cancer cell survival and growth.

One key mechanism triggers apoptosis by changing the expression of apoptotic proteins. This includes increasing Bax levels and decreasing Bcl-2 levels, activating caspases, and releasing mitochondrial cytochrome c. These compounds also stop the cell cycle at the G0/G1 or G2/M phases by controlling cyclin-dependent kinases, which hinders uncontrolled cell division.

Additionally, isoxazole derivatives disrupt important signaling pathways like PI3K/Akt, NF-κB, and ERK/MAPK, leading to slower tumor growth, less cell survival, and reduced metastasis. Some derivatives act as antimitotic agents by blocking tubulin polymerization and interrupting microtubule formation. They also inhibit enzymes such as topoisomerase, histone deacetylase (HDAC), and aromatase. This impairment affects DNA replication and changes gene expression, contributing to anticancer properties. Furthermore, blocking heat shock protein 90 (Hsp90) results in the breakdown of cancer-causing proteins. Isoxazole compounds also have anti-angiogenic properties by preventing VEGF signaling and increasing the production of reactive oxygen species, which leads to oxidative stress and cell death.

In addition, altering immune checkpoints like PD-1/PD-L1 boosts the immune response against tumors. Together, these multiple actions underscore the therapeutic promise of isoxazole derivatives in cancer therapy.

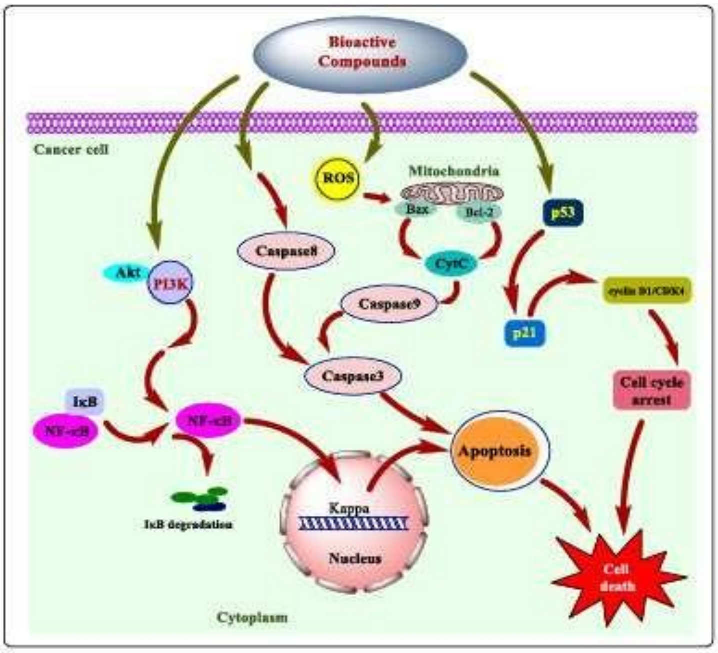

Figure 5: Depicts the proposed mechanisms of anticancer activity.

STRUCTURE ACTIVITY RELATIONSHIP

The Structure–Activity Relationship (SAR) of isoxazole derivatives shows that the isoxazole ring is a five-member heterocycle containing the nitrogen and oxygen atoms and has a critical role in biological activity and the ability to hydrogen bond, dipole interactions and act as bioisostere for functional groups like amides and esters to increase metabolic stability and binding affinity. The structure–activity connection of isoxazole derivatives is depicted in the picture, emphasizing the significance of alterations at the isoxazole ring's third (R1), fourth (R3), and fifth (R5) locations.

Hence, substitution at the 3rd and 5th positions of the isoxazole ring has significant pharmacological importance. The presence of aromatic groups, particularly phenyl rings, at these positions increases anticancer, anti-inflammatory, and other activities. Electron-withdrawing groups such as chloro, nitro and trifluoromethyl tend to increase biological activities by improving receptor binding and inhibiting enzymes, whereas electron-donating groups such as methoxy and methyl are able to improve lipophilicity and membrane permeability, though depending on the biological target, their impact on activities varies. Replacement of phenyl rings with heterocyclic moieties such as pyridine or thiophene often improves selectivity and solubility, leading to better antimicrobial and anticancer properties. Besides, isoxazole use in "hybrid molecules with pyrazolyl chalcone, or quinoline scaffolds connected to each other" results in multi-target activity and better pharmacological properties. The biological activity of isoxazole moieties/or derivatives is very dependent on the type, position, and electronic properties of substituents attached to the ring and their effect on lipophilicity and molecular interactions with biological targets.

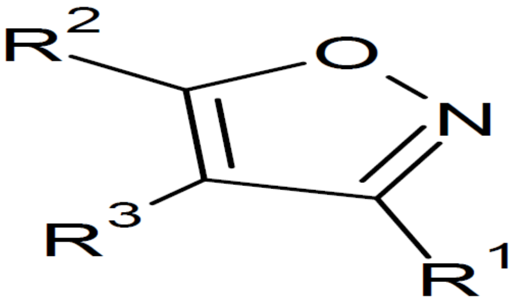

Figure 6: SAR structure of isoxazoles.

Position	Substitution Type	Example Substituents	Biological Activity	Observed Effect
C-3 (R_1)	Aromatic groups	Phenyl, substituted phenyl	Anticancer, antimicrobial	Enhances hydrophobic interaction and potency
C-3 (R_1)	Electron-donating groups	OCH_3, CH_3, OH	Antioxidant, anticancer	Increases lipophilicity and membrane permeability
C-3 (R_1)	Heterocyclic groups	Pyrazole, quinoline, thiophene	Anticancer, antimicrobial	Enhances selectivity and target interaction
C-3 (R_1)	Bulky substituents	tert-Butyl, naphthyl	Anticancer	Excess steric bulk may reduce activity
C-5 (R_2)	Halogen substituents	Cl, Br, F	Anticancer, antimicrobial	Improves metabolic stability and potency
C-5 (R_2)	Phenyl substitution	p-Cl phenyl, p-NO_2 phenyl	Anticancer	Enhances cytotoxic activity
C-5 (R_2)	Heteroaryl groups	Pyridyl, thienyl	Antimicrobial, anticancer	Improves solubility and binding affinity
C-5 (R_2)	Small groups	H, CH_3	Moderate activity	Activity depends on overall scaffold
C-4 (R_3)	Electron-donating groups	OCH_3, OH	Antioxidant, anticancer	Improves electron density and interactions
C-4 (R_3)	Halogens	Cl, F	Antimicrobial, anticancer	Increases potency and selectivity
C-4 (R_3)	Heteroaryl substitution	Pyridyl, furanyl	Anticancer	Better target interaction and solubility
Hybrid molecules	Isoxazole–pyrazole hybrids	Pyrazolyl-isoxazole	Anticancer	Synergistic enhancement of activity
Hybrid molecules	Isoxazole–chalcone hybrids	Chalcone-linked isoxazole	Anticancer	Strong apoptosis-inducing effect
Hybrid molecules	Isoxazole–quinoline hybrids	Quinolinyl-isoxazole	Anticancer, antimicrobial	Multi-target activity and improved binding

FUTURE PERSPECTIVES

The isoxazole scaffold remains a focal point in contemporary medicinal chemistry due to its diverse biological properties and ease of synthesis. Upcoming research is anticipated to emphasize the incorporation of artificial intelligence (AI) and machine learning (ML) into the drug discovery process. These computational methods can forecast biological activity, refine lead compounds, and minimize the time and expenses linked to experimental screenings.Another exciting direction involves the development of multi-target and target-specific medications. Isoxazole derivatives have the capability to engage with several biological targets, making them favorable options for intricate disorders like cancer and tuberculosis. Combining structure–activity relationship (SAR) studies with molecular docking methods will further improve drug optimization.

The progression of green chemistry techniques is also expected to be essential.

Approaches such as microwave-assisted synthesis and solvent-free methods will play a significant part. Furthermore, drug delivery systems based on nanotechnology are rising as a promising approach to amplify the therapeutic effectiveness of isoxazole derivatives.

Nanocarriers like liposomes and polymeric nanoparticles can enhance drug solubility, stability, and targeted delivery, which in turn can decrease side effects.

Future research will also emphasize thorough pharmacokinetic assessments, including absorption, distribution, metabolism, and excretion, and toxicity evaluations. Although these compounds show encouraging biological activities, extensive studies on their pharmacokinetics are crucial for their clinical use. Additionally, there is an anticipation for the advancement of hybrid molecules and fused heterocycles that incorporate isoxazole structures. These compounds frequently demonstrate improved biological activity due to synergistic effects and better binding characteristics. Lastly, the demand for large-scale production and practical industrial use is increasing. Creating cost-effective and scalable synthetic methods will be vital for bridging the gap between laboratory discoveries and real-world applications..

CONCLUSION

Isoxazole derivatives have become an important category of heterocyclic compounds in medicinal chemistry, recognized for their various biological activities and structural diversity.

The distinctive configuration of nitrogen and oxygen atoms within the isoxazole ring facilitates effective interactions with numerous biological targets, which makes it a crucial pharmacophore for drug design. This review highlights that compounds based on isoxazole display a broad spectrum of pharmacological effects, encompassing antifungal, antibacterial, and particularly notable anticancer activities. In particular, the anticancer properties are a prominent focus of research. Isoxazole derivatives have demonstrated strong cytotoxic effects against several cancer cell lines, including HeLa, MCF-7, and HepG2. The mechanisms through which they exert anticancer effects involve initiating apoptosis by modulating essential regulatory proteins, notably by increasing the expression of pro-apoptotic Bax while decreasing the levels of anti-apoptotic Bcl-2 leading to dysfunction in mitochondria and the activation of caspase-dependent pathways. Furthermore, these compounds block essential signaling pathways such as PI3K/Akt and MAPK, disrupt cell cycle progression, and inhibit both tumor growth and metastasis. These multi-faceted effects underline their potential as promising candidates for developing selective and effective anticancer therapies. Simultaneously, the antifungal properties of isoxazole derivatives have drawn interest due to the rising resistance against standard antifungal treatments. Recent research shows that compounds like PUB14 and PUB17 demonstrate potent and selective activity against Candida albicans while maintaining beneficial microbiota. Their capacity to hinder fungal biofilm formation further increases their therapeutic potential in treating persistent infections. Structure–activity relationship (SAR) investigations indicate that biological activity is significantly influenced by modifications at the 3^{rd} and 5^{th} position.

Recent progress in synthetic techniques has enabled the creation of a variety of derivatives that offer enhanced effectiveness and safety features. In summary, isoxazole derivatives are an extremely promising framework for the creation of new therapeutic agents, especially within the fields of anticancer and antifungal drug discovery. Subsequent research aimed at understanding the mechanisms in detail, optimizing pharmacokinetic characteristics, and validating in clinical settings will further amplify their possibilities in contemporary drug development.

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