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Review Paper

Selenazole-Based Compounds as Antifungal Agents: A Comprehensive Review

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ABSTRACT

Fungal infections have emerged as a major global health concern due to increasing incidence, high mortality, and the development of resistance to existing antifungal therapies. Selenazole-based compounds have attracted considerable attention in medicinal chemistry owing to their unique chemical properties and enhanced biological activities. Incorporation of selenium into azole frameworks improves lipophilicity, redox behavior, and interaction with fungal targets such as lanosterol 14α-demethylase (CYP51). This review summarizes recent advances in selenazole-based compounds as antifungal agents, including their chemistry, classification, physicochemical and pharmacological properties. Furthermore, structure–activity relationships and future perspectives are discussed to highlight their potential in antifungal drug development. The antifungal activity of the synthesized selenazole hybrids was assessed in vitro against clinically relevant fungal strains, including Candida and Aspergillus species, using standard broth microdilution methods. Several compounds exhibited significant antifungal activity, with minimum inhibitory concentration (MIC) values comparable to or better than standard antifungal agents

INTRODUCTION

Heterocyclic compounds constitute a fundamental backbone in medicinal chemistry due to their structural diversity and wide range of biological activities. Among them, selenium-containing heterocycles have gained increasing importance in recent years because of their unique chemical reactivity and biological significance [1]. Selenium is an essential trace element that plays a critical role in various physiological processes, particularly in antioxidant defense systems through selenoproteins such as glutathione peroxidase [2].

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The incorporation of selenium into organic molecules has been shown to significantly enhance their pharmacological properties, including antioxidant, anticancer, and antimicrobial activities [3]. Selenazole, a five-membered heterocyclic ring containing selenium and nitrogen atoms, is structurally analogous to thiazole but exhibits superior biological activity due to the presence of selenium [4]. This substitution leads to increased polarizability, improved lipophilicity, and enhanced interaction with biological targets.

Selenazole derivatives have been widely explored for their therapeutic potential, particularly as antifungal agents, owing to their ability to disrupt fungal cell membranes and inhibit key enzymes involved in ergosterol biosynthesis [5]. In addition, these compounds demonstrate promising anticancer properties by inducing apoptosis through oxidative stress mechanisms and mitochondrial dysfunction [6].

Recent advances in synthetic methodologies have enabled the development of structurally diverse selenazole derivatives, including hybrid molecules that combine multiple pharmacophores to enhance biological activity and selectivity [7]. Moreover, structure–activity relationship (SAR) studies have revealed that substitution patterns on the selenazole ring play a crucial role in determining their pharmacological profile [8].

Despite significant progress, challenges such as toxicity, stability, and bioavailability still need to be addressed for the successful development of selenazole-based drugs. Therefore, a comprehensive understanding of their physicochemical and pharmacological properties is essential for further optimization and clinical application [9]

1.1 Importance of Selenium-Containing Heterocycles

Selenium is an essential trace element known for its crucial role in biological systems, particularly in antioxidant defense mechanisms through enzymes such as glutathione peroxidase [10]. The incorporation of selenium into heterocyclic compounds leads to enhanced biological activity due to its high polarizability and redox capability. Organoselenium compounds have demonstrated significant pharmacological effects, including antioxidant, anticancer, antimicrobial, and anti-inflammatory activities [11].

1.2 Overview of Selenazole Scaffold

Selenazole is a five-membered heterocyclic compound containing selenium and nitrogen atoms within the ring structure. It is structurally analogous to thiazole, where sulfur is replaced by selenium. This substitution results in improved lipophilicity, enhanced electronic interactions, and increased biological activity [12]. The selenium atom contributes to unique chemical reactivity, allowing selenazole derivatives to interact effectively with enzymes, proteins, and nucleic acids.

1.3 Significance of Selenazole in Medicinal Chemistry

Selenazole derivatives have emerged as promising scaffolds in medicinal chemistry due to their ability to modulate multiple biological pathways. These compounds exhibit a wide range of pharmacological activities, including antifungal, anticancer, antimicrobial, and antioxidant effects [13]. Their mechanism of action is often associated with reactive oxygen species (ROS) modulation, enzyme inhibition, and disruption of cellular processes.

Structural modifications at various positions of the selenazole ring significantly influence physicochemical properties such as lipophilicity, solubility, and metabolic stability. These modifications allow optimization of pharmacokinetic and pharmacodynamic

properties, making selenazole a versatile scaffold for drug design [14].

1.4 Advantages over Sulfur Analogues

Compared to thiazole derivatives, selenazole compounds exhibit enhanced biological activity due to:

- Higher polarizability of selenium
- Improved redox properties
- Increased lipophilicity
- Stronger interaction with biological targets

These advantages make selenazole derivatives attractive candidates for the development of novel therapeutic agents [15].

2. Chemistry and Structural Features

2.1 Structural Chemistry of Selenazole

Selenazole is a five-membered aromatic heterocycle containing one selenium atom and one nitrogen atom. Its general molecular formula is C_3H_3NSe. The presence of selenium introduces distinct electronic and steric properties that influence chemical reactivity and biological interactions [16].

2.1.1 Aromaticity and Ring Structure

The selenazole ring is planar and aromatic, following Hückel's rule with six π-electrons. Selenium contributes to the aromatic system through its p-orbitals, enhancing electron delocalization and stability [17]. This aromatic character facilitates substitution reactions and interaction with biological macromolecules.

2.1.2 Electronic Distribution

The electronegativity difference between selenium and nitrogen creates an uneven electron distribution within the ring. Selenium, being less electronegative, contributes to electron density, while nitrogen introduces electron-withdrawing characteristics. This balance influences reactivity and binding affinity.

2.1.3 Reactivity and Substitution

Selenazole derivatives undergo:

- Electrophilic substitution at carbon positions
- N-substitution reactions
- Metal-catalyzed cross-coupling reactions

Substitution patterns significantly affect biological activity and physicochemical properties [18].

3. Physicochemical Properties

3.1 Molecular Properties

- Molecular weight typically ranges between 200–500 Da for active derivatives [19].
- Structural planarity enhances π–π interactions
- Increased lipophilicity due to selenium

3.2 Electronic Properties

- High polarizability of selenium
- Narrow HOMO–LUMO gap enhances reactivity
- Strong dipole moment influences binding

3.3 Lipophilicity and Solubility

- Log P values generally higher than sulfur analogues
- Lipophilicity improves membrane permeability
- Polar substituents enhance aqueous solubility [20]

3.4 Acid–Base Properties

- Weakly basic nature
- Ionization affects pharmacokinetics and receptor interaction

3.5 Spectral Characteristics

- UV absorption due to conjugation
- IR bands for C=N and Se–C bonds
- NMR confirms structural features

4. Synthetic Approaches

4.1 Cyclization Method

Synthesis via reaction of **selenourea with α-haloketones** is the most common method [21].

4.2 Multicomponent Reactions

Provide structural diversity and efficiency.

4.3 Metal-Catalyzed Synthesis

Palladium and copper catalysts enable selective functionalization [22].

5. Structure–Activity Relationship (SAR) of Selenazole Derivatives

5.1 Effect of Substituents

Electron-Withdrawing Groups (EWGs):

- Halogens (Cl, F, Br), $–NO_2$, –CN enhance biological activity
- Increase lipophilicity and membrane permeability
- Improve antifungal and anticancer activity
- Enhance enzyme binding via hydrophobic interactions.

Electron-Donating Groups (EDGs):

- $–CH_3$, $–OCH_3$, $–NH_2$ increase electron density
- Improve antioxidant and anti-inflammatory activity
- Stabilize free radicals
- May reduce antimicrobial activity if excessive [23].

5.2 Influence of Lipophilicity

- Selenium increases lipophilicity compared to sulfur analogues
- Optimal Log P range: **2–5** for drug-like activity
- Higher lipophilicity → better membrane penetration
- Very high lipophilicity → poor solubility and bioavailability

5.3 Role of Selenium Atom

- Provides high polarizability and redox activity
- Enables interaction with thiol-containing enzymes
- Important for ROS modulation and enzyme inhibition
- Oxidation state (Se^{2+}, Se^{4+}) affects biological activity [24].

5.4 Position-Specific Substitution

C-2 Position:

- Aromatic/heterocyclic substitution enhances activity
- Improves π–π interactions with biological targets

C-4 and C-5 Positions:

- Control steric and electronic effects
- Bulky groups → increased selectivity
- EWGs → improved antimicrobial activity
- Polar groups → better solubility and pharmacokinetics

5.5 Hybridization with Other Pharmacophores

- Combination with quinoline, indole, benzothiazole improves activity
- Provides multi-target effects
- Enhances potency and reduces resistance
- Useful in antifungal and anticancer drug design [25]

5.6 Structure–Redox Activity Relationship

- Activity linked to ROS generation or scavenging
- Pro-oxidant behavior → anticancer activity
- Antioxidant behavior → protective effects
- Balance between both is crucial for therapeutic use

6. Pharmacological Activities.

Selenazole derivatives exhibit a broad spectrum of biological activities due to the presence of selenium, which imparts unique redox properties,

enhanced lipophilicity, and strong interaction with biological targets.

6.1 Antifungal Activity

- Show potent activity against *Candida albicans*, *Aspergillus niger*, and other pathogenic fungi
- Mechanism involves:
  - Inhibition of **ergosterol biosynthesis**
  - Disruption of fungal cell membrane integrity
- Selenium enhances permeability and intracellular accumulation
- Some derivatives exhibit **higher potency than standard drugs (e.g., fluconazole)**
- Hybrid selenazole compounds show improved broad-spectrum antifungal activity [26,27]

6.2 Anticancer Activity

- Induce apoptosis in cancer cells via:
  - Generation of reactive oxygen species (ROS)
  - Mitochondrial dysfunction
  - DNA damage and cell cycle arrest
- Effective against various cancer cell lines (breast, lung, colon)
- Selenium plays a key role in redox modulation and enzyme targeting
- Certain derivatives act as **selective cytotoxic agents** with reduced toxicity to normal cells [28]

6.3 Antimicrobial Activity

- Active against both Gram-positive and Gram-negative bacteria
- Mechanisms include:
  - Inhibition of bacterial enzymes
  - Disruption of protein synthesis
  - Interaction with bacterial cell membranes
- Increased lipophilicity improves penetration into microbial cells
- Hybrid molecules show enhanced antibacterial spectrum [29]

6.4 Antioxidant Activity

- Strong free radical scavenging ability
- Mimic activity of natural antioxidant enzymes like **glutathione peroxidase**
- Protect cells from oxidative stress and lipid peroxidation
- Selenium plays a central role in redox cycling and ROS neutralization [30]

6.5 Anti-inflammatory Activity

- Reduce production of inflammatory mediators such as:
  - Cytokines (TNF-α, IL-6)
  - Prostaglandins
- Inhibit oxidative stress-induced inflammation
- Potential application in chronic inflammatory diseases [31]

6.6 Antiviral Activity

- Show potential activity against viral infections by:
  - Inhibiting viral replication
  - Interfering with viral enzymes
- Selenium contributes to immune modulation and antiviral defense
- Emerging area of research with promising results [32]

6.7 Neuroprotective Activity

- Protect neuronal cells from oxidative damage
- Reduce neuroinflammation
- Potential role in neurodegenerative diseases such as Alzheimer's and Parkinson's
- Mechanism involves antioxidant and anti-apoptotic effects [33,34]

6.8 Other Activities

- **Antidiabetic activity:** Improves insulin sensitivity and reduces oxidative stress
- **Cardioprotective effects:** Protects against oxidative damage in cardiac tissues

- **Enzyme inhibition:** Targets key enzymes involved in disease pathways

CONCLUSION

Selenazole derivatives represent a promising class of heterocyclic compounds with significant therapeutic potential. Their unique physicochemical properties, combined with diverse pharmacological activities, make them attractive candidates for drug development. Continued research focusing on structural optimization, toxicity reduction, and clinical evaluation will further enhance their applicability in medicinal chemistry

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