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REVIEW ON SUBSTITUTED 1,2,4-TRIAZOLES AS POTENT ANTI-FUNGAL,ANTI-CANCER AND ANTI-TUBERCULAR AGENTS

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ABSTRACT

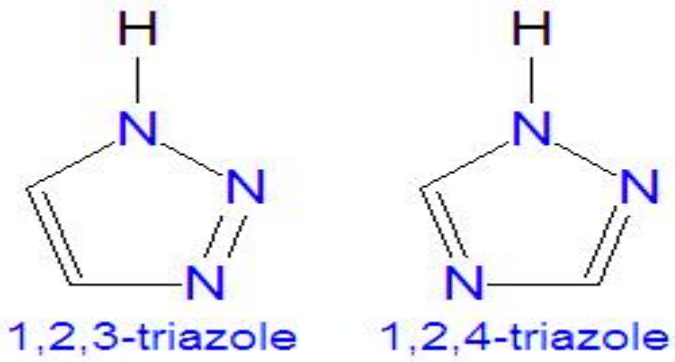
Triazole derivatives are an important class of nitrogen-containing heterocyclic compounds widely studied in medicinal chemistry. These compounds possess a five-membered ring structure containing three nitrogen atoms, which contributes to their remarkable chemical stability and diverse biological activities. Due to their versatile structural properties, triazole derivatives have gained considerable attention in pharmaceutical research and drug development. Many triazole-based compounds exhibit significant pharmacological activities such as antifungal, antibacterial, anticancer, anti-tubercular, anti-inflammatory, and antiviral effects. Several clinically useful drugs, including Fluconazole, Itraconazole, and Voriconazole, contain the triazole ring as a key structural component responsible for their therapeutic action. The presence of nitrogen atoms in the triazole ring enhances their ability to interact with biological targets, improving potency and selectivity. Because of these advantages, triazole scaffolds are frequently used as core structures for designing new bioactive molecules. This review highlights the chemical characteristics of triazole derivatives and summarizes their important pharmacological activities and therapeutic significance in modern medicinal chemistry research.

KEYWORDS: Triazole derivatives, Pharmacological activities, Structure activity relationship (SAR), Antifungal agents, Anticancer, Anti tubercular.

INTRODUCTION

Triazoles are five-membered heterocyclic compounds containing three nitrogen atoms and two carbon atoms within their ring structure. They primarily exist in two isomeric forms, 1,2,3-triazoles and 1,2,4-triazoles, both of which are highly stable and resistant to metabolic degradation. In medicinal chemistry, these rings are prized for their ability to form strong hydrogen bonds and dipole interactions with biological targets, enhancing a drug's therapeutic efficacy. Their versatile nature makes them the core scaffold for numerous essential medications, ranging from systemic antifungals like fluconazole to potent anticancer and antiviral agents. Triazole compunds has various Applications in.

- Chemistry:Triazoles serve as versatile building blocks in organic synthesis,often used in the creation of Pharmaceuticals, Agrochemicals, and Advanced Materials.
- Agriculture:Triazole Fungicides are widely used to protect crops from fungal diseases. They Inhibit Fungal Growth by interfearing with the Biosynthesis of Ergesterol, a important component of Fungal Cell Membranes.
- Pharmaceuticals:Triazole compunds are found in many Pharmaceutical drugs, including Antifungal medications [E.g:Fluconazole] and Anticancer drugs [E.g:Vorozole] and Antituberculosis [E.g:1,2,4-Triazole thione derivatives].



STRUCTURAL CHARACTERISTICS OF TRIAZOLES

Feature	Description	Significance
Molecular Formula	C2H2N3	Defines the basic composition of two carbons and three nitrogens.
Geometry & Architecture	Rigid, planar, five-membered heterocyclic ring.	Ensures a flat, two-dimensional structure that fits into specific biological "pockets."
Hybridization	All carbon and nitrogen atoms are sp^{2} hybridized.	Leads to trigonal planar geometry at every atomic center in the ring.
Aromaticity	Follows Hückel's Rule with a delocalized system of 6π electrons.	Provides high thermal and chemical stability, making them resistant to metabolic breakdown.
Bonding Pattern	Alternating $C=N$ double bonds and $C-C$ single bonds within a resonance hybrid.	Contributes to the molecule's electronic stability and ability to participate in stacking.
Isomeric Forms	Primarily exists as 1,2,3-triazole or 1,2,4-triazole.	The nitrogen arrangement dictates the dipole moment and binding affinity to enzymes.
Functionalization	Hydrogen atoms can be substituted with various alkyl or aryl groups.	Allows medicinal chemists to "fine-tune" lipophilicity, solubility.

STRUCTURAL ACTIVITY RELATIONSHIP OF TRIAZOLES

Structural Feature	1,2,3-Triazoles SAR	1,2,4-Triazoles SAR	Explanation of Activity
Triazole ring nucleus	Essential for anticancer and antimicrobial activity	Essential for antifungal activity	Nitrogen atoms coordinate with biological enzymes and receptors
Aromatic substitution (phenyl ring)	Improves anticancer and antibacterial activity	Improves antifungal potency	Increases lipophilicity and membrane penetration
Halogen substitution (Cl, F, Br)	Enhances antimicrobial activity	Enhances antifungal activity	Electron-withdrawing groups increase enzyme binding
Hydroxyl groups (–OH)	Improve solubility and hydrogen bonding	Improve drug absorption	Helps interaction with biological targets
Alkyl side chains	Increase antibacterial activity	Increase membrane penetration	Improves lipophilicity
Heterocyclic rings attached	Improves anticancer and anti-inflammatory activity	Improves antifungal potency	Provides additional binding sites with enzymes
Long hydrophobic chains	Improve anticancer activity	Increase antifungal activity	Better interaction with lipid membranes

PHARMACOLOGICAL ACTIVITIES OF TRIAZOLES

1. ANTI-FUNGAL ATIVITY

- Fungal infections are increasingly common worldwide, especially in individuals with weakened immune systems such as patients with HIV, cancer, or those receiving long-term antibiotic therapy.
- These infections may range from mild superficial infections of the skin and nails to serious systemic diseases that can affect internal organs.
- The growing incidence of fungal pathogens has created a need for effective and safe antifungal medications.
- Triazoles are an important class of synthetic heterocyclic compounds containing a five-membered ring with three nitrogen atoms.
- Two main types of triazoles exist: 1,2,3-triazoles and 1,2,4-triazoles, with the 1,2,4-triazole derivatives widely used in antifungal therapy.

- Triazole antifungal drugs act by inhibiting the enzyme lanosterol 14-α-demethylase, which is essential for the synthesis of ergosterol in fungal cell membranes.
- Inhibition of ergosterol production disrupts the fungal cell membrane structure, ultimately preventing fungal growth and survival.
- Several clinically used antifungal agents belong to the triazole class, such as Fluconazole, Itraconazole, Voriconazole, and Posaconazole.
- Due to their broad spectrum of activity, improved safety, and good pharmacokinetic properties, triazoles play a major role in modern antifungal therapy and continue to be widely studied in medicinal chemistry.

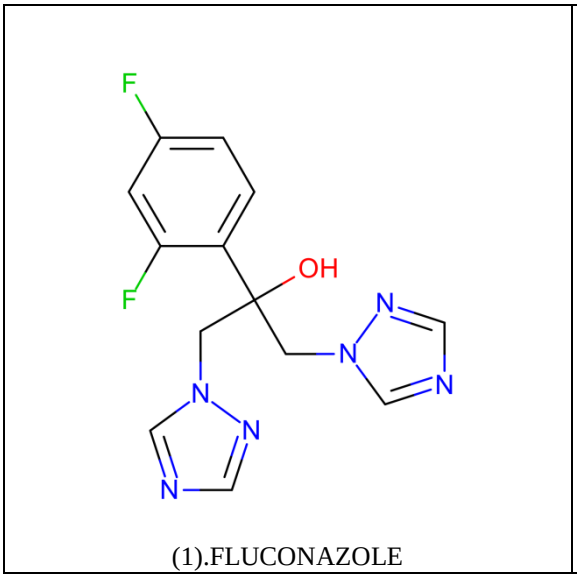
CLASSIFICATION OF TRIAZOLES ANTI-FUNGAL DRUGS

FIRST GENERATION TRIAZOLES

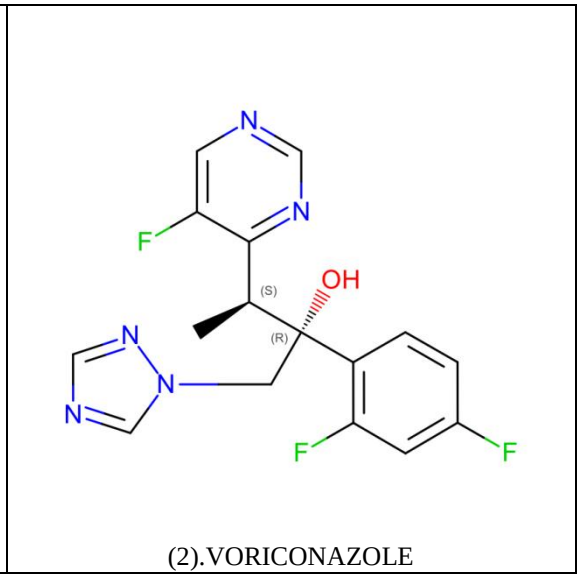
- Fluconazole
- Itriconazole

SECOND GENERATION TRIAZOLES

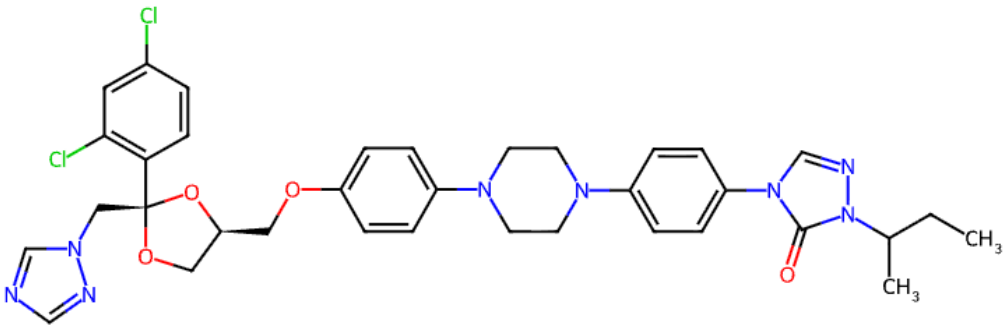
- Voriconazole
- Posaconazole



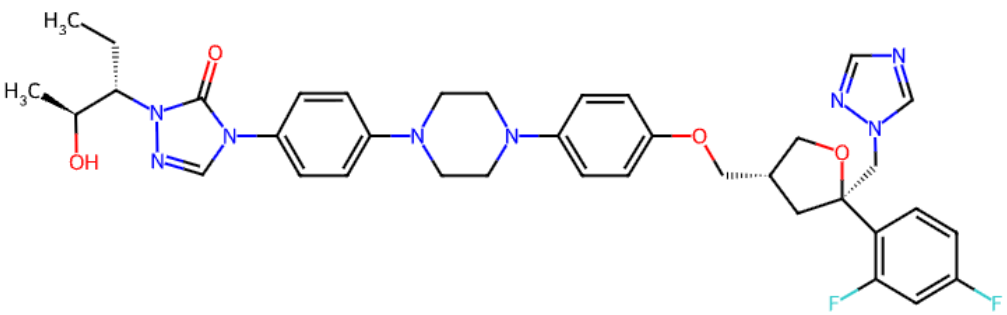
(1).FLUCONAZOLE



(2).VORICONAZOLE

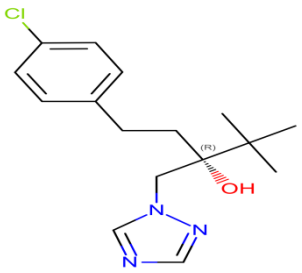
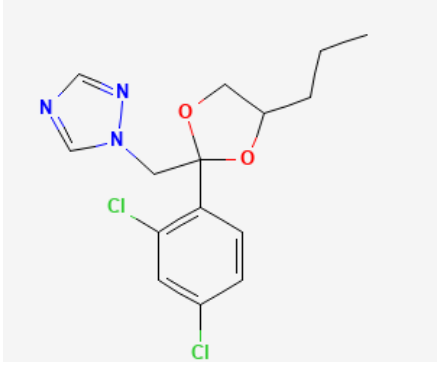
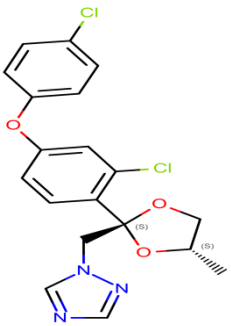
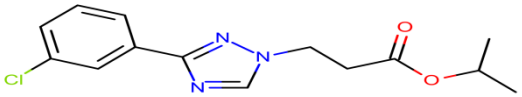


(3). ITRACONAZOLE



(4) . POSACONAZOLE

❖ **ANTIFUNGAL TRIAZOLE DERIVATIVES USED IN AGRICULTURE**

Triazole Fungicide	Molecular Formula	Agricultural Use	Structure
Tebuconazole	$C_{16}H_{22}ClN_3O$	Used to control rusts, leaf spots, and powdery mildew in cereals and vegetables.	 (5)
Propiconazole	$C_{15}H_{17}Cl_2N_3O_2$	Controls fungal diseases in wheat, rice, and turf grass.	 (6)
Difenoconazole	$C_{19}H_{17}Cl_2N_3O_3$	Used for fruit crops, vegetables, and cereals against leaf spot and blight diseases.	 (7)
Triadimefon	$C_{14}H_{16}ClN_3O_2$	Used to control powdery mildew and rust diseases in crops.	 (8)

2. ANTI-CANCER ACTIVITY

- **Chemical Structure:** Triazoles are five-membered heterocyclic compounds containing three nitrogen atoms and two carbon atoms, primarily categorized into **1,2,3-triazole** and **1,2,4-triazole** isomers.
- **Pharmacological Versatility:** They are considered **"privileged scaffolds"** in medicinal chemistry due to their ability to bind with diverse biological targets, making them highly effective in suppressing tumor growth.
- **Aromatase Inhibition:** 1,2,4-triazole derivatives (like Letrozole and Anastrozole) are gold-standard treatments for **hormone-dependent breast cancer** by blocking the enzyme that produces estrogen.

- **Tubulin Interference:** Many synthetic triazoles act as microtubule-disrupting agents, preventing cancer cells from dividing during the **mitosis phase** of the cell cycle.
- **Enzyme Targeting:** These compounds can specifically inhibit key enzymes overexpressed in cancer, such as **Histone Deacetylases (HDACs)** and various protein kinases, which regulate cell signaling.
- **Induction of Apoptosis:** Triazole derivatives often trigger **programmed cell death** (apoptosis) by modulating pro-apoptotic proteins or activating the caspase enzyme cascade within malignant cells.
- **High Metabolic Stability:** Unlike many other organic rings, the triazole moiety is remarkably resistant to metabolic degradation (metabolism), allowing the drug to remain active in the body for longer periods.
- **Bioisosterism:** The triazole ring can act as a **bioisostere** for peptide bonds or other heterocycles, allowing it to mimic natural molecules and fit perfectly into the "pockets" of cancerous proteins.
- **Synthetic Efficiency:** Through **"Click Chemistry,"** 1,2,3-triazoles can be easily synthesized and modified, enabling the rapid development of new, potent anticancer drug candidates with fewer side effects.

CLASSIFICATION OF TRIAZOLES ANTICANCER DRUGS

1. BASED ON RING STRUCTURE

a. 1,2,3-Triazole derivatives
- Triazole-chalcone derivatives
- Triazole-quinoline derivatives
- Triazole-benzimidazole derivatives

b. 1,2,4-Triazole derivative
- Anastrozole
- Letrozole

2. BASED ON STRUCTURAL SUBSTITUTION

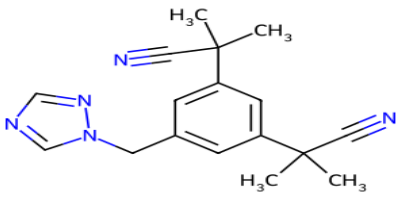
a. Triazole linked heterocylic derivatives;
- Triazoles ring attached to heterocycles like quinoline, indole, or benzimaiazole
- These enchance anti cancer potency

b. Triazole chalcone derivatives :
- Contain both chalcone and triazole moities
- Know for cytotoxic activity adainst tumor cells

TRIAZOLE DERIVATIVES USED IN ANTI-CANCER DRUGS

Triazole Derivative	Type of Triazole	Cancer Type
Anastrozole	1,2,4-Triazole	Breast cancer
Letrozole	1,2,4-Triazole	Hormone-dependent breast cancer
Vorozole	1,2,4-Triazole	Breast cancer (research/clinical studies)
1,2,3-Triazole chalcone derivatives(e.g;Tasisulam)	1,2,3-Triazole	Lung & colon cancer

ANASTROZOLE:



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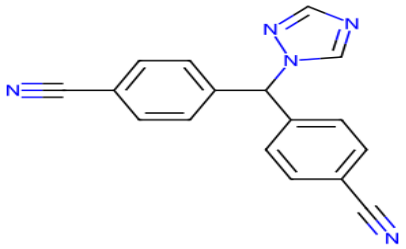
LETROZOLE



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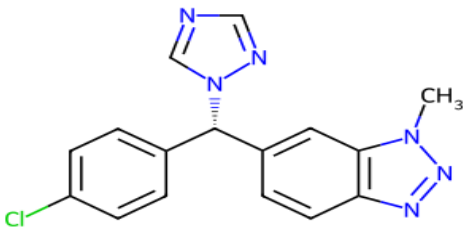
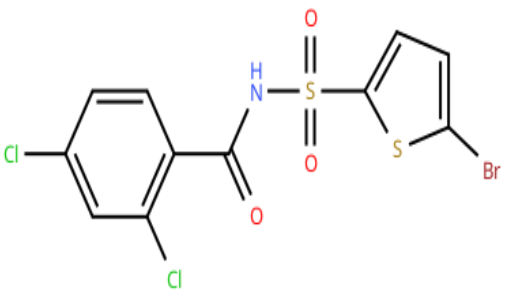


VOROZOLE (11)



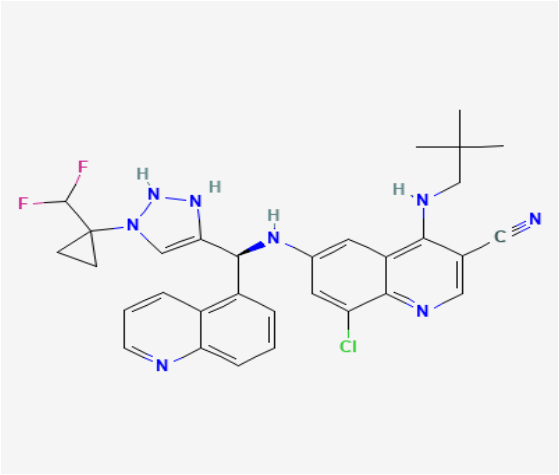
TASIULUM (12)

MECHANISM OF ACTION OF ANTI-CANCER TRIAZOLE DERIVATIVES

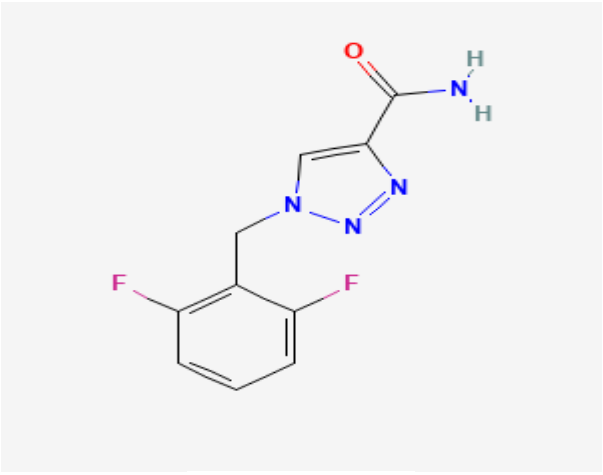
- Enzyme inhibition – Triazole derivatives inhibit key enzymes involved in cancer cell growth. Drugs such as Anastrozole and Letrozole block the aromatase enzyme, reducing estrogen levels and slowing hormone-dependent tumor growth.
- Induction of apoptosis – These compounds can activate programmed cell death in cancer cells, helping eliminate abnormal cells.
- Cell cycle inhibition – Triazole derivatives may stop the progression of the cell cycle, preventing rapid multiplication of cancer cells.
- Inhibition of angiogenesis – Some triazole compounds reduce the formation of new blood vessels that supply nutrients to tumors, thereby limiting tumor development.

3. ANTI-TUBERCULOSIS ACTIVITY

- Triazoles are nitrogen-containing heterocyclic compounds that have gained attention in medicinal chemistry due to their wide range of biological activities, including anti-tuberculosis potential.
- Tuberculosis is caused by the bacterium Tuberculosis and mainly affects the lungs, creating a need for new drugs because of increasing resistance to conventional treatments.
- Triazole derivatives exhibit anti-tubercular activity by interacting with essential enzymes and metabolic pathways of Mycobacterium tuberculosis, thereby inhibiting bacterial growth.
- The presence of nitrogen atoms in the triazole ring enhances binding with biological targets, which improves antimicrobial and anti-tubercular effectiveness.
- Structural modification of triazole derivatives can improve potency, selectivity, and pharmacokinetic properties, making them promising candidates for tuberculosis drug development.
- Due to their chemical stability and ability to form multiple interactions with microbial targets, triazole-based compounds are widely investigated as potential anti-tuberculosis agents in modern drug research.



QUINOLINE 1,2,3-TRIAZOLE (13)



RUFINAMIDE (14)

CONCLUSION

Triazole derivatives play a vital role in modern Medicinal Chemistry because of their versatile chemical structure and broad pharmacological potential. The triazole ring serves as an important pharmacophore that enhances biological activity, stability, and binding interactions with various biological targets.

Several triazole-containing drugs have demonstrated strong therapeutic effects, particularly in the treatment of fungal infections such as Candidiasis and Aspergillosis, while other derivatives have shown promising cytotoxic activity against cancer cells associated with Cancer. In addition, emerging research indicates that triazole derivatives possess significant activity against Tuberculosis by targeting key enzymes and pathways essential for the survival of the pathogen.

Overall, the structural flexibility and wide spectrum of biological activities make triazole derivatives valuable scaffolds for the discovery and development of new therapeutic agents. Continued research and structural modification of triazole compounds may lead to the development of more effective drugs with improved safety profiles for the treatment of infectious diseases, cancer, and other medical conditions.

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