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Exploring Benzimidazole Analogues: Structural Modifications and Their Impact on Antimicrobial Activity

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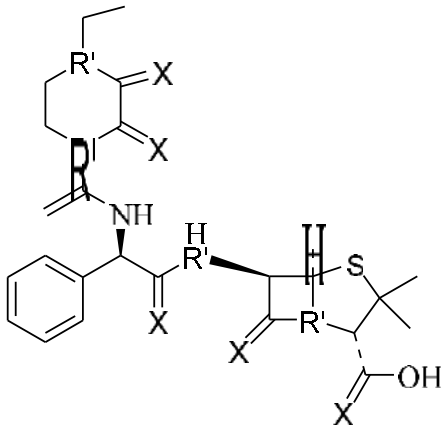
Abstract:
Benzimidazole and its derivatives are well-recognized for their extensive biological activities, including antimicrobial, antifungal, antitumor, anti-inflammatory, and antiviral properties. Their biological efficacy stems from their structural resemblance to purines, which allows them to interact with enzymes and receptors in biological systems. The benzimidazole nucleus functions as a core scaffold in many clinically approved drugs, such as albendazole and mebendazole, which are used as anthelmintic agents. The present study extensively reviewed the biological evaluation of benzimidazole derivatives, focusing on their antimicrobial potential. Various substitutions on the benzimidazole ring significantly influenced the bioactivity of the compounds, highlighting the importance of strategic modifications in enhancing efficacy.
Keywords: Benzimidazole, anti-inflammatory, antimicrobial, antifungal, biological

Introduction

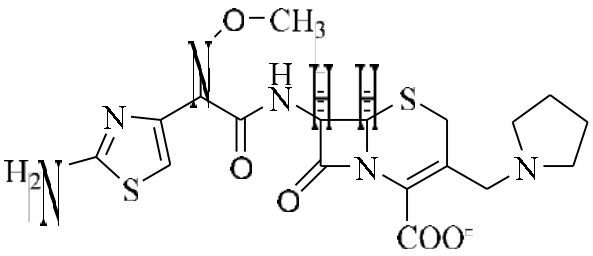
Antimicrobial agents

Antimicrobials are substances that are used to kill or inhibit the growth of bacteria, fungi and protozoa which are produced from microorganism. Penicillin is an antibiotic exuded from *penicillium notatum* in the existence of correct substrate and used for large scale. In order to accomplish probable broad-spectrum activity of compounds which could be adapted by chemical methods or mutagenesis. The mechanism of action involves target one of the actions like cell wall synthesis, DNA synthesis, RNA synthesis, protein synthesis and intermediary metabolism which are required for cell survival. The antimicrobial compounds can also be synthesized chemically like quinolones, sulphonamides, and trimethoprim.

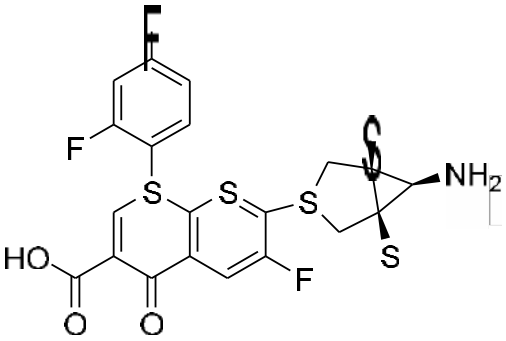
Antimicrobial agents may be bacteriostatic agents or bactericidal agents. An antibacterial is an agent that interferes with the growth and reproduction of bacteria.



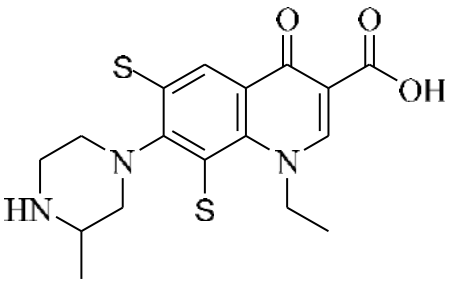
Piperacillin



Cefepime



Trovafloxacin



Lomefloxacin

Common Antimicrobial Agents and Site of Action.

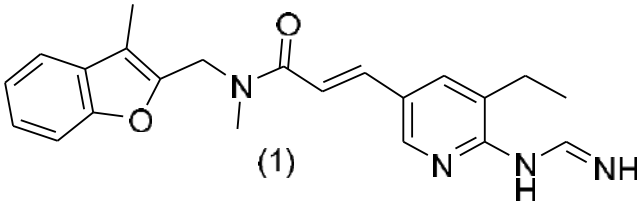
Table -1: Mode of action of antimicrobials

Mode of action	Antimicrobial Agents
Resistant of cell wall synthesis	Penicillin, Cephalosphorin, Cefepime Imipenem, Meropenem, Aztreonam, Vancomycin, Cethromycin, Lymecycline
Resistant of bacterial protein synthesis	Aminoglycosides, Piperacillin Chloramphenicol,Macrolides, Tetracycline, Streptogrmins, Linezolid
Resistant of Nucleic Acid Synthesis	Fluoroquinolones, Rifampin, Sparfloxin, Trovafloxacin, Lomifloxacin
Resistant of Folic Acid Synthesis	Sulfonamides, Trimethoprim, Pyrimethamine

Future Antimicrobial agents in pipeline: Inhibitors of New Targets

Fab I inhibition

In bacterial fatty acid biosynthesis, bacterial enoyl-acyl transporter protein (enoyl-ACP) reductase (FabI) is a basic enzyme which catalyzes the decrease of trans-2-enoyl-ACP to acyl-ACP in the last step of each elongation rotation of bacteria which could be the best target for antibacterial therapy. ACP-1252 (1) and CG400462 (2) are potent FabI inhibitors.



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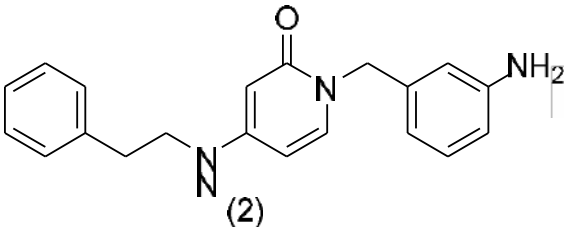

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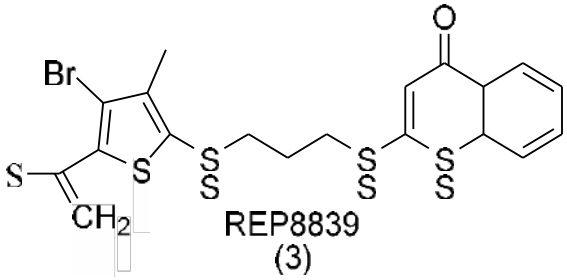
Methionyl-tRNA

Methionyl-tRNA synthetase is an fundamental target that is preserved in Gram-positive bacteria. A high throughput screening and medicinal chemistry endeavor against this target yielded a potent inhibitor: REP8839 (3). REP8839 has no Gram-negative activity but has strong bacteriostatic activity against significant skin pathogens *S. aureus* and *S. pyogens*, together with MRSA and mupirocin and vancomycin-resistant phenotypes with MICs ranging from ≤0.008 to 0.12 µg/ml.

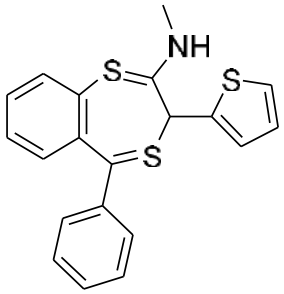


REP8839

(3)

Cell wall biosynthesis inhibition

A high throughput transmission effort going to at glutamate racemase (MurI), a fundamental enzyme in the peptidoglycan biosynthesis pathway from *H. Pylori,* afforded the 2-methylamino-benzodiazepine. In this sequence compound (4) and (5) with aryl (thiophene) group at C-3 and the amino methyl moiety at C-2 were initiate to be important for MurI activity during optimization. These inhibitors join to an allosteric site and are >200-fold discriminating for *H. pylori* over MurI secluded from other Gram positive or Gram-negative sources.



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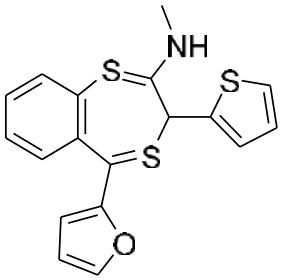

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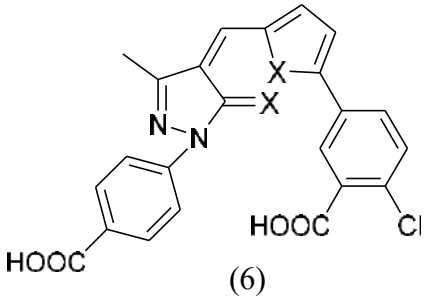
Antivirulence

Unbeaten resistance of virulence in bacteria might have the possible to eradicate antibiotic resistance by eliminating the antibiotic. In result, antivirulence agent would hold back bacteria in their ability to dynamically infect the human host, but might or else leave them undamaged, and harmless. WaaC is a glycosyl transferase that is necessary for inner core lipopolysaccharide (LPS) biosynthesis and that is sealed in Gram-negative bacteria. MUT11931 (6) is a pilot compound within a sequence of diaryl pyrrazolone inhibitors of WaaC. MUT11931 is a possible, reversible inhibitor with IC50 = 3.1 μM. MUT2585 (7) is the pilot compound (IC5071 μM) in a sequence of aryl oxazole inhibitors of RfaE that is undergo lead optimization.



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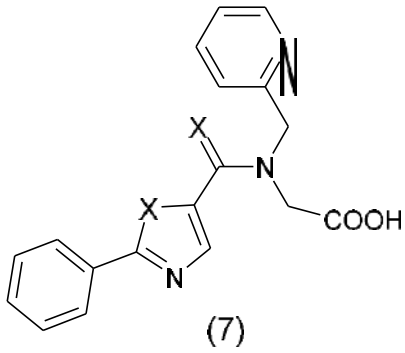

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Antibiotic drugs

Antibiotics are substances or chemicals produced by bacteria that react with and hinder the growth of other microorganisms. Natural antibiotics are often synthetically modified to improve their efficiency. Such antibiotics are called semi-synthetic antibiotics.

- Spectrum of action

Broad spectrum antibiotics

Narrow spectrum antibiotics

- Prerequisite of a good antibiotic
  1. Should not alter the normal microbial flora in body and should not produce drug resistance.
  2. Should not stimulate an allergic reaction in body.

3. Selectively lethal to pathogenic microorganisms.

Classification of antibiotics

Based on spectrum of action

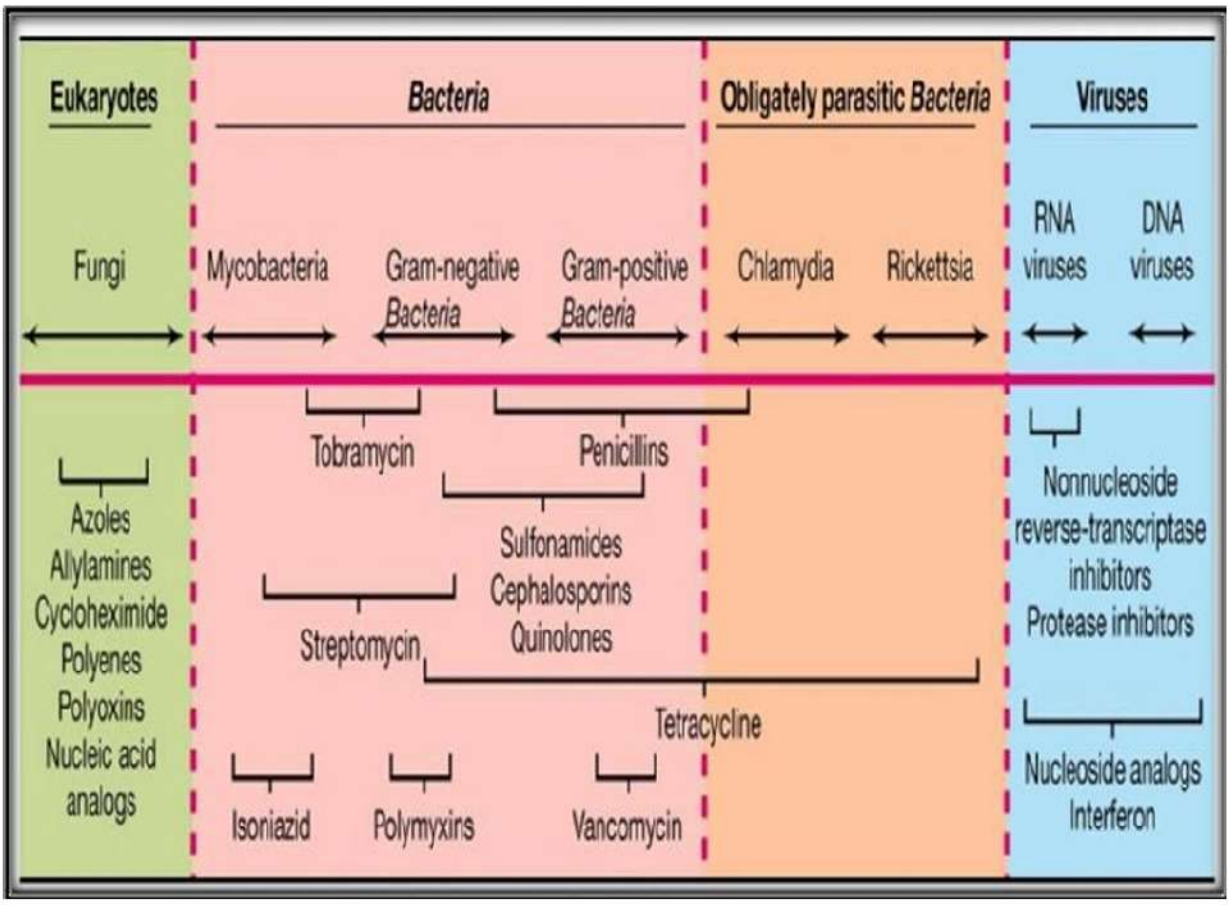
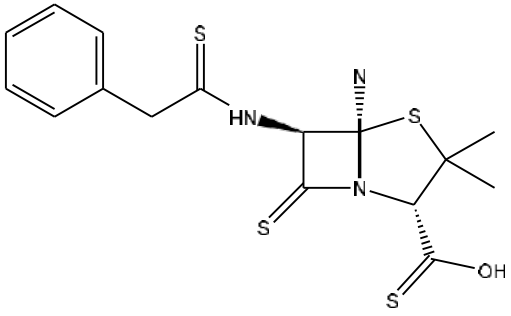


Figure -1: Spectrum of activity

Based on structure

Table -2: Molecular structure of various antibiotics

Antibiotic	Molecular structure
Penicillin G (8) and Cephalosporin N (9)	Beta lactam ring
Aminoglycosides (Streptomycin (10), Neomycin, Amikacin)	Glycosideic linkage contains amino sugars
Macrolides (Erythromycin, Oleandomycin)	Macrocyclic lactone
Tetracyclines (11)	Naphthacene carboxamide
Chloramphenicol	Nitrobenzene derivative of dichloro acetic acid
Peptide antibiotics	Peptide linked D and L amino acids
Antifungal metabolites	Polyenes and non-polyenes
Ansamacrolides (Streptovaricins and Rifamycins)	Naptho and benzoquinone nuclei derivatives
Anthracycline antibiotics (Adriamycin and Duanomycin)	Anthracycline



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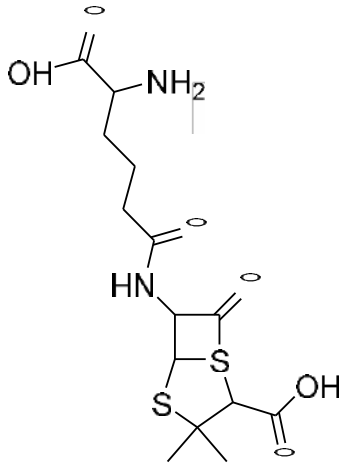

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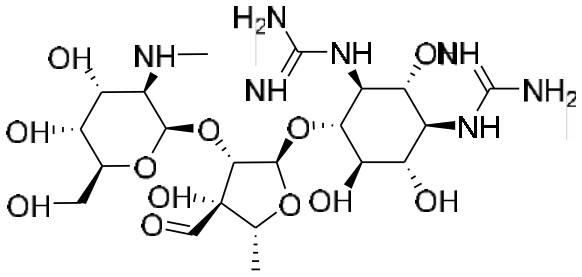

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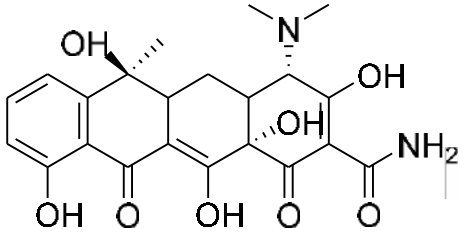

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Based on Mode of action

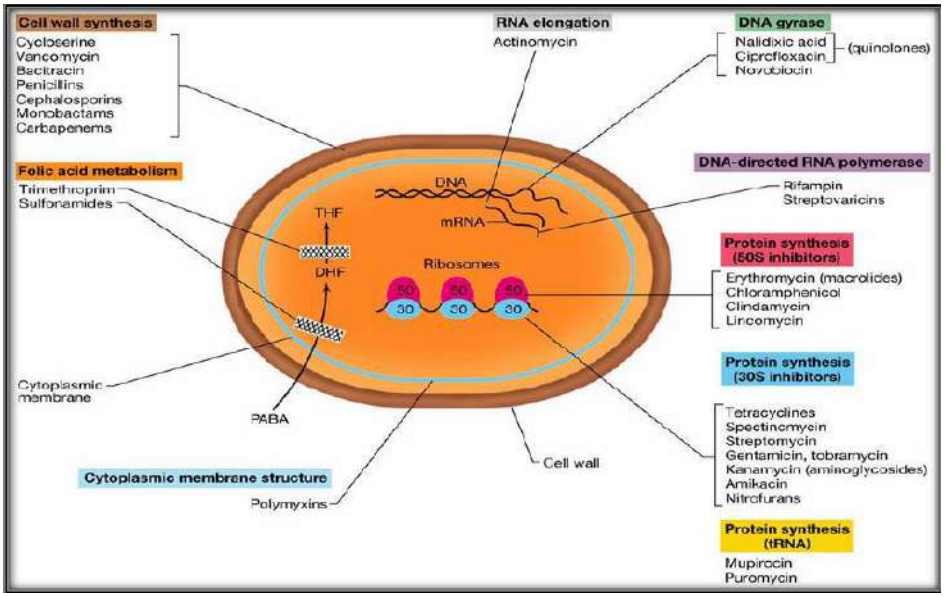


Figure -1: Mechanism of antibiotic agents

Drug	Mechanism of Action
Cell Wall Synthesis Inhibition	
Penicillin Ampicillin Carbenicillin Methicillin Cephalosporins	Inhibit transpeptidation enzymes involved in the cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan. Activate cell wall lytic enzymes.
Vancomycin	Binds directly to the D-Ala-D-Ala terminus and inhibits transpeptidation.
Bacitracin	Inhibits cell wall synthesis by interfering with action of the lipid carrier that transports wall precursors across the plasma membrane.
Protein Synthesis Inhibition	
Streptomycin Gentamicin	Binds with the 30S subunit of the bacterial ribosome to inhibit protein synthesis and causes misreading of mRNA.
Chloramphenicol	Binds to the 50S ribosomal subunit and blocks peptide bond formation through inhibition of peptidyl transferase.
Tetracyclines	Bind to the 30S ribosomal subunit and interfere with aminoacyl-tRNA binding.
Erythromycin and clindamycin	Bind to the 50S ribosomal subunit and inhibit peptide chain elongation.
Fusidic acid	Binds to EF-G and blocks translocation.
Nucleic Acid Synthesis Inhibition	
Ciprofloxacin and other quinolones	Inhibit bacterial DNA gyrase and thus interfere with DNA replication, transcription, and other activities involving DNA.
Rifampin	Blocks RNA synthesis by binding to and inhibiting the DNA-dependent RNA polymerase.
Cell Membrane Disruption	
Polymyxin B	Binds to the plasma membrane and disrupts its structure and permeability properties.
Metabolic Antagonism	
Sulfonamides	Inhibit folic acid synthesis by competition with *p*-aminobenzoic acid.
Trimethoprim	Blocks tetrahydrofolate synthesis through inhibition of the enzyme dihydrofolate reductase.
Dapsone	Interferes with folic acid synthesis.
Isoniazid	May disrupt pyridoxal or NAD metabolism and functioning. Inhibits the synthesis of the mycolic acid "cord factor."

Figure -2 : Antibacterial agents

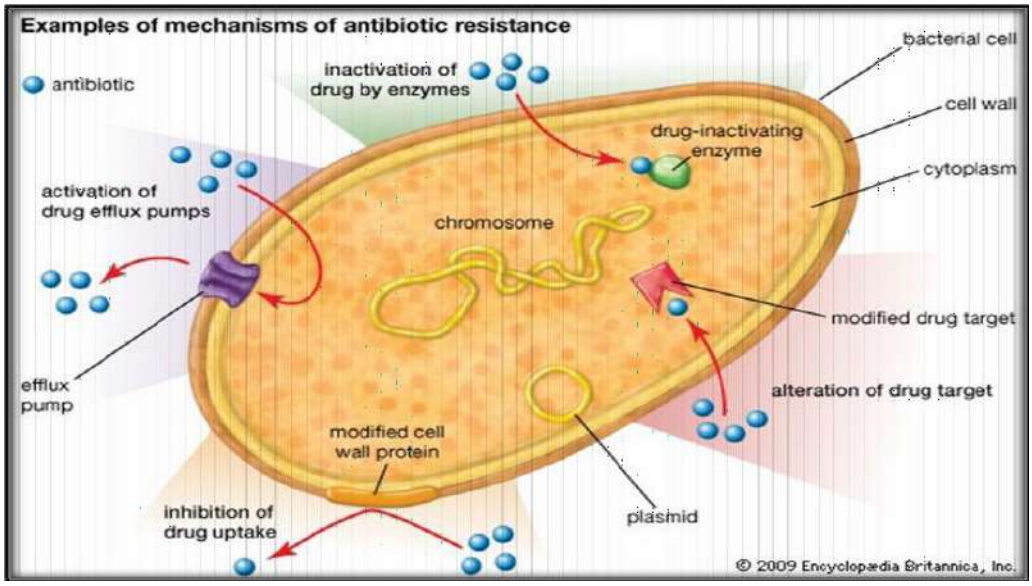


Figure -3: Resistance in bacteria

Antimicrobial drug resistance

Microorganism acquired ability to resist the effects of an antimicrobials to which it is susceptible.

Resistance Mechanisms

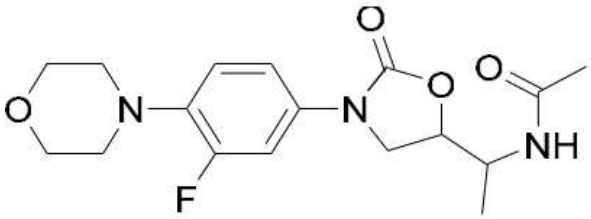
For any of at least five different reasons, some microorganisms are naturally resistant to certain antibiotics.

1. They may be missing in the arrangement of an antibiotic inhibits.
2. Microorganism may be resistant to the antibiotic. For example, Most Gram-negative bacteria are resistant to platensimycin and penicillin-G.
3. Microorganism may be able to make changes in to antibiotic active form to an inactive form.

4. The organism may adapt the target of the antibiotic. In most cases, antibiotic resistance mediated by chromosomal genes arises because of a alteration of the target of antibiotic activity (for example, a ribosome).
5. Through efflux mechanism, organism may be able to force out an antibiotic entering the cell.

Recent advances as antibacterial agents

- Linezolid (12)
- Cefepime (13)
- Sparfloxacin (14)
- Dalbavancin: Phase III trial
- Cethromycin (ABT-773)



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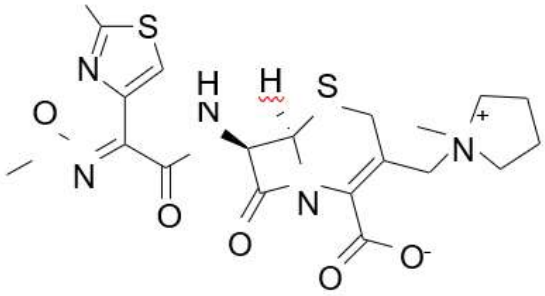

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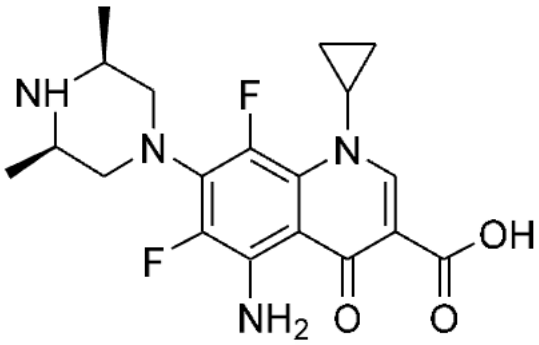

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Antifungal Agents

Fungi

Fungi are large, widespread and diverse group of organisms which includes yeasts, mushrooms and molds. Fungi form a phylogenetic cluster which is nearly correlated to animals but different from other organisms. Their cell walls are mainly contains 80–90% polysaccharide with additionally include lipids, proteins, polyphosphates and inorganic ions. Most fungal cell walls are made up of chitin, a polymer of the glucose derivative *N*-acetylglucosamine.

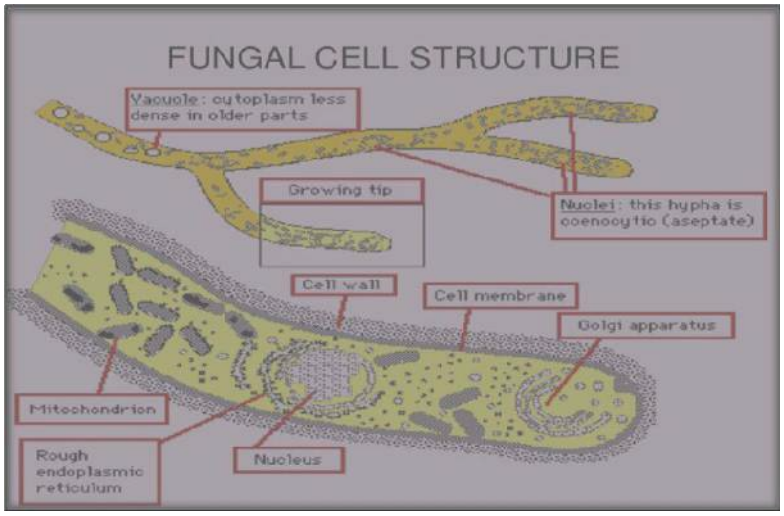


Figure -4: Structure of Fungal cell

Antifungal Drugs

An antifungal drug is medicine used to treat fungal infections such as athlete's foot, ringworm, Kala azar, dermatophytosis, candiasis and severe systemic infections such as *Cryptococcal meningitis*, histoplasmosis, and blastomycosis. Fungi, like viruses, pose special problems for the development of chemotherapy. Because fungi are Eukaryotes and much of their cellular machinery is the similar as that of animals and humans; antifungal agents that act on metabolic pathways in fungi often affect consequent pathways in host cells, making the drugs toxic. As a result, many antifungal drugs can be used only for topical applications.

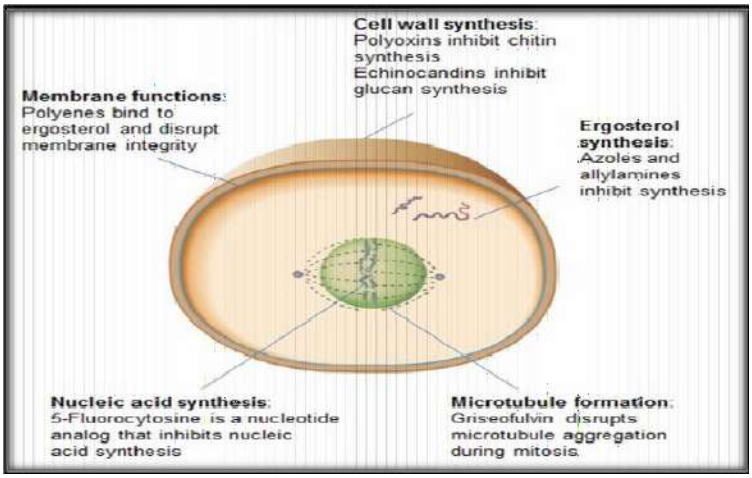


Figure -5: Mechanism of Antifungal drug

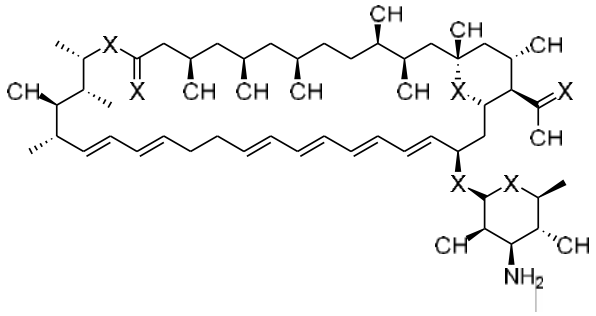
Classification of Antifungal Drugs

1. **Polyene Derivatives**

A polyene is an element having several conjugated double bonds. The polyene antimycotics combine with ergosterols in the fungal cell membrane. Due to changes the transition temperature, cell membrane remain in crystalline state. Thus, the cell's consists monovalent ions like (K^+, Na^+, H^+ and Cl^-)

which leads to leakge of small organic molecules and results in death of cell. Animal cell contains cholesterol instead of ergosterol, so they are much less predisposed.

- Nystatin (15)



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2. **Azole Drugs**

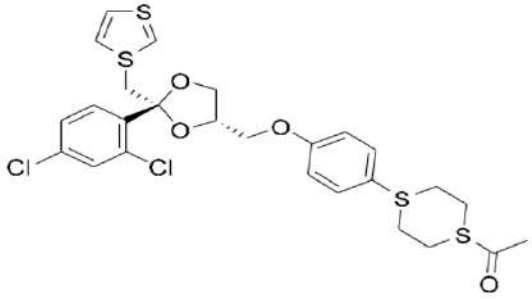
It includes imidazole and triazole derivatives. Azoles decrease the enzyme lanosterol 14 α- demethylase (cytochrome P450), the enzyme essential to ergosterol in fungal membrane breakdown the structure and many functions of fungal membrane leading to resistance of fungal growth. Azole fungicides are also called as demethylase inhibitors.

- Ketoconazole (16)
- Miconazole (17)
- Clotrimazole (18)

Imidazole derivatives

- Fluconazole (19)
- Voriconazole (20)

Triazole derivatives



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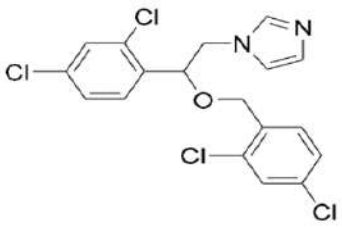

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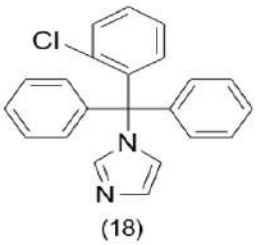

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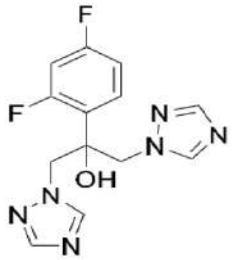

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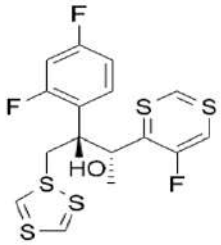

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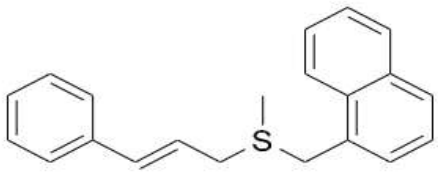
3. **Allylamines**

Allylamines reduce squalene epoxidase, another enzyme required for ergosterol synthesis.

- Naftifine (21)
- Terbinafine (22



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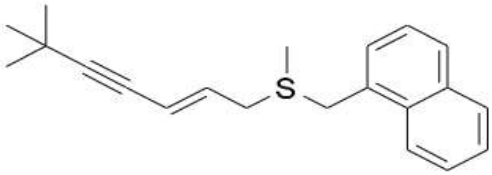

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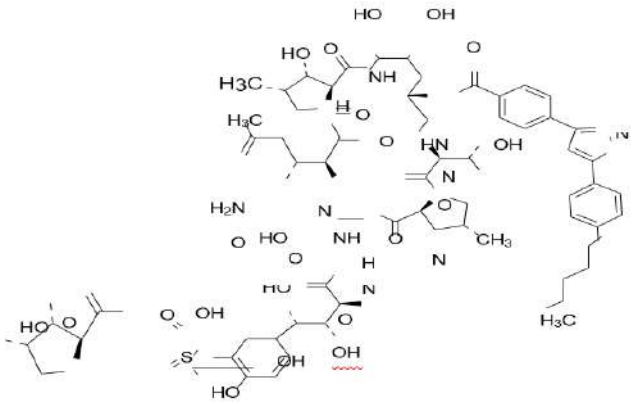
4. **Echinocandins**

The newest class of antifungal permanently inhibits B-1, 3 –D glucan synthase, the enzyme complexes that forms glucan polymers in the fungal cell wall.

- Micafungin (23)



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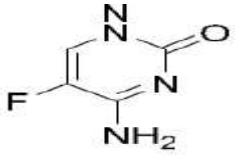
1. **Pyrimidine**



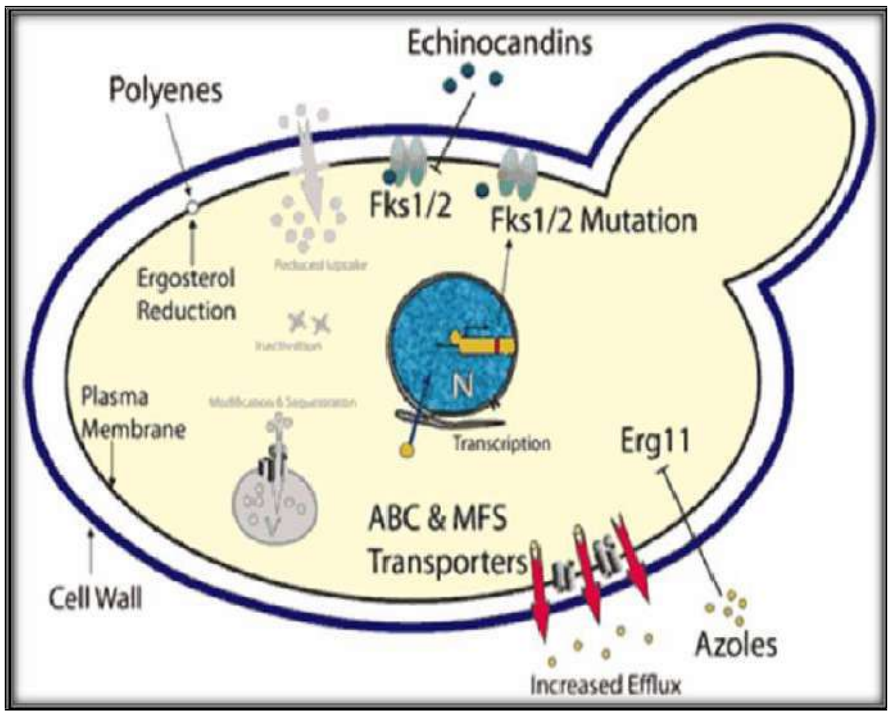
(24)

It inhibits thymidylate synthetase.

- Flucytosin (24)

Fungal Resistance

Antifungal resistance was microbiologic or clinical resistance or as a mixture of the two. Antifungal resistance remains to grow, evolve and difficult patient management which require introduction of new antifungal agents. Antifungal resistance is related with elevated poorer clinical outcomes, breakthrough infections and minimum inhibitory concentrations during antifungal treatment and prophylaxis.



Recent advances in antifungal drug

i. Hydroxypyridinones (25)

ii. Purpuromycin (26)

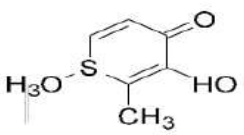
iii. Nikkomycin (27)

iv. Racuconazole (28) - Phase II clinical trial

v. Albaconazole (UR-9825) (29)

vi. Azoxybacillin (30)

Liposomal Nystatin- Phase III clinical trial



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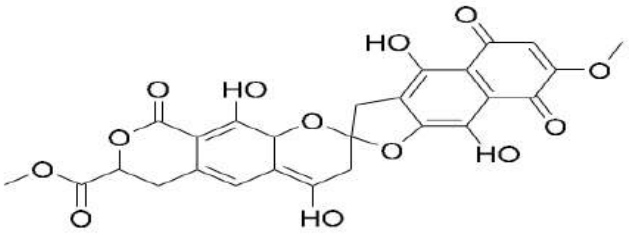
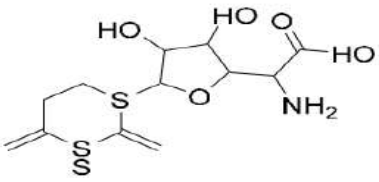
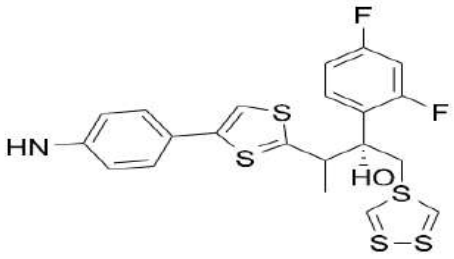


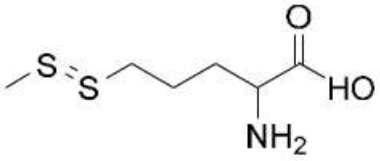
(26)



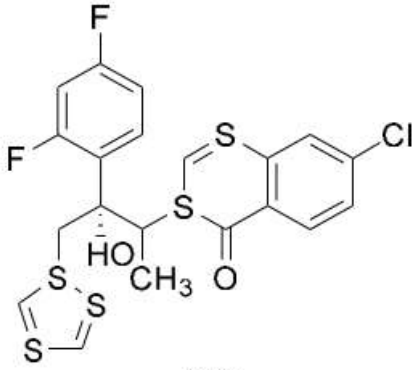
(27)



(28)



(29)



(30)

Future Implications

The study of 1,2-disubstituted benzimidazole derivatives revealed their significant potential as antimicrobial agents. The structural modifications and SAR insights provided a deeper understanding of the factors influencing biological activity. Docking studies complemented the experimental findings, establishing a strong correlation between in silico predictions and in vitro results.

The results emphasize the importance of electron-donating and halogen substituents in enhancing antimicrobial activity. Compounds with optimized substituents can serve as lead molecules for further development and clinical evaluation. The study also highlights the potential of

docking studies as a predictive tool for assessing the activity of newly synthesized compounds.

Conclusion

The present study extensively reviewed the biological evaluation of benzimidazole derivatives, focusing on their antimicrobial potential. Various substitutions on the benzimidazole ring significantly influenced the bioactivity of the compounds, highlighting the importance of strategic modifications in enhancing efficacy.

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