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# Utilization of Heterocyclic Moieties for the Development of Anti-Microbial Agent to Combat Resistance

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**KEYWORDS**
AMR; Heterocyclic compounds; Anti-microbial activity

**ABSTRACT:**
Antimicrobial resistance (AMR) poses a significant global health challenge, threatening the effectiveness of current treatment regimens and necessitating the development of novel antimicrobial agents. This review provides a comprehensive overview of AMR, encompassing its mechanisms, epidemiology, and societal impact. We explore the evolution of resistance in major pathogens, emphasizing the urgent need for new therapeutic strategies. Key approaches to combating AMR, including antibiotic stewardship and infection prevention, are discussed alongside promising advancements in antimicrobial drug discovery and development. The role of innovative technologies such as genomics and synthetic biology in accelerating the identification and optimization of novel antimicrobial agents is highlighted. Ultimately, this article underscores the critical importance of collaborative efforts across disciplines to mitigate the AMR crisis and ensure sustainable healthcare practices for future generations. Heterocyclic moieties are often combined with other functional groups or modified to enhance their antimicrobial activity and reduce resistance.

## 1. Introduction

Heterocyclic moieties are structural components of organic compounds where at least one ring in the molecule is composed of atoms from at least two different elements. Typically, these rings include carbon atoms along with elements such as nitrogen, oxygen, sulphur, or other elements, forming rings with diverse electronic and structural properties. Heterocyclic compounds are abundant in nature and play crucial roles in biological processes, pharmaceuticals, agrochemicals, and materials science (Aljamali, 2014). Heterocyclic compounds are the class of cyclic organic compounds those having at least one hetero atom in the cyclic ring system. The most common heteroatoms are nitrogen, oxygen, sulphur. Heterocyclic compounds are frequently abundant in plants and animal products and they are one of the important constituents of almost one half of the natural organic compounds. Heterocyclic compounds can be easily classified based on their electronic structure. Heterocyclic compounds primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties (Shukla *et al.,* 2017). Piperidine and tetrahydrofuran are the conventional amines and ethers of this category. However unsaturated heterocyclic compounds of 5 and 6 member rings have studied extensively because of their unstained nature. The unstrained unsaturated heterocyclic compounds include pyridine, thiophene, pyrrole, furan and benzo fused derivatives. Quinoline, isoquinoline, indole, benzothiophene, benzofuran are some important examples of benzo and fused heterocycles. Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Many heterocyclic compounds are very useful and essential for human life. Various compounds such as hormone, essential amino acids, haemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure (Arora *et al.,* 2012).

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**Common Heterocyclic Structures**

**Pyridine:**

Pyridine is a heterocyclic organic compound with the chemical formula $C_5H_5N$. It's a colorless to yellow liquid with a distinctive, unpleasant fish-like smell. Pyridine is structurally related to benzene, but with a nitrogen atom replacing one methine group (Mahmood and Aljamali, 2020).

Here are some properties and uses of pyridine:

Flammability: Pyridine is highly flammable.

Alkalinity: Pyridine is weakly alkaline.

Solubility: Pyridine is water-miscible.

Solvent: Pyridine is a basic solvent that's used for acylation and dehydrochlorination reactions. It's also used as a solvent for paint, rubber, pharmaceuticals, polycarbonate resins, and textile water repellents.

Denaturant: Pyridine is used as a denaturant for alcohol.

Source: Pyridine occurs in coal tar, but can also be synthesized from acetaldehyde and ammonia.

Parent compound: Pyridine is the parent of many naturally occurring organic compounds.

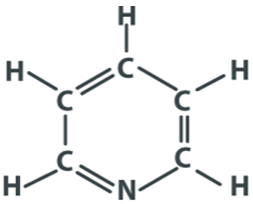

**Fig.1. Example compounds: nicotine, pyridoxine.**

**Furan**

Furan is a heterocyclic organic compound with the chemical formula $C_4H_4O$, made up of a five-membered ring with four carbon atoms and one oxygen atom. It is a colourless, flammable, and highly volatile liquid with a boiling point close to room temperature. Furan has a strong, ethereal odour similar to chloroform (Al Ali, 2023). Furan is toxic and may be carcinogenic in humans. It is also a hepatotoxic agent and a Maillard reaction product. Furan is used as a starting point for other specialty chemicals.

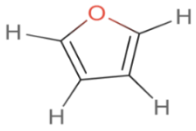

**Fig.2. Example compounds: furfural, certain natural products.**

**Thiophene:**

Thiophene is a heterocyclic compound with a five-membered ring that contains a sulphur atom. It has the chemical formula $C_4H_4S$ and is a colourless liquid with a benzene-like odour (Narayan *et al.*, 2024).

Here are some properties of thiophene:

Reactivity: Thiophene behaves similarly to benzene in many of its reactions.

Stability and electronic properties: Thiophene is used to improve the performance of dye-sensitized solar cells and other electronic devices.

Non-polar solvent: Thiophene acts as a non-polar solvent. Compounds similar to thiophene include furan, selenophene, and pyrrole. The difference between these compounds is the heteroatom in the ring.

**Fig.3. Example compounds: thiophene itself, biologically active compounds.**

**Pyrrole:**

Pyrrole is a heterocyclic, aromatic organic compound with a five-membered ring (Bhardwaj *et al.*, 2015). It has the following properties:

Color: Pyrrole is a colourless, volatile liquid that darkens when exposed to air.

Structure: Pyrrole has a ring with one nitrogen atom and four carbon atoms.

Reactivity: Pyrrole polymerizes easily in air.

Uses: Pyrrole is the parent compound of many biologically important substances, including bile pigments, porphyrins, and chlorophyll. It also forms

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metal complexes that have important functions in nature and in synthetic catalytic systems.

Name: The name pyrrole comes from the Greek word pyrrols, which means "fiery".

Basicity: Pyrrole has lower basicity due to the delocalization of the nitrogen atom's lone pair of electrons.

Acidity: The NH and CH protons in pyrrole are moderately acidic and can be deprotonated with strong bases.

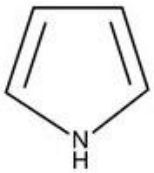

**Fig.4. Example compounds: haemoglobin, chlorophyll.**

**Imidazole**

Imidazole is a heterocyclic organic compound with the formula $C_3N_2H_4$ that has a five-membered ring with two nitrogen atoms and three carbon atoms. It is a white or colorless solid that is soluble in water and produces a mildly alkaline solution. Imidazole is used in pharmaceuticals as an anti-cancer, anti-bacterial, and anti-inflammatory agent (Jabbar *et al.*, 2019).

Here are some properties of imidazole:

Classification: Imidazole is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms in meta-substitution.

Polarity: Imidazole is highly polar.

Properties: Imidazole can exhibit both acidic and basic properties.

Systematic name: The systematic name of this structure is 1,3-diazole, which is rarely used in the chemical literature.

Synthesis: Imidazole is produced by compressing a dicarbonyl chemical such as glyoxal, a-keto aldehyde, or a- diketones in conjunction with an aldehyde in the existence of ammonia.

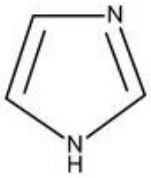

**Fig.5. Example compounds: histidine, antifungal drugs like ketoconazole.**

**Pyrazole:**

Pyrazole is a heterocyclic organic compound that has a five-membered ring with two nitrogen atoms and three carbon atoms. The molecular formula for pyrazole is $C_3H_4N_2$ (Jaiswal, 2019).

Here are some characteristics of pyrazole:

Weak base: Pyrazole is a weak base with a pKb of 11.5.

Nitrogen atoms: The nitrogen atoms in pyrazole are adjacent to each other in the ring structure and are in ortho-substitution.

Pyrrole-like and pyridine-like: The nitrogen atom in the 1-position is pyrrole-like, and the nitrogen atom in the 2-position is pyridine-like.

Pyrazole is a core structure of aromatic compounds with two double bonds. Some drugs that contain a pyrazole ring include celecoxib and stanozolol.

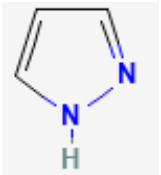

**Fig.6. Example compounds: celecoxib (a COX2 inhibitor), pesticides.**

**2. Medicinally Important Heterocyclic Moieties:**

**Anticancer**

Cancer is a collection of diseases distinguished by irregular or uncontrolled cell growth with the ability to occupy or spread to other parts of the body. This disease is caused by a variety of agents, including chemical compounds and radiant energy. Several medications are used to cure this dis-ease, either by killing cancer cells or altering their growth (Ali *et al.,* 2015). Synthesis of phenanthroindolizidine 1 and phenanthroindolizidine 2

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alkaloids for potential use as anticancer drugs with IC values of 166nM and 2.1nM, respectively. The majority of synthesized compounds exhibited active proliferative action in opposition to BEL-7402and A549 cells. In the primary screening, compound 2 was discovered to have the most potent activity. A mechanistic analysis revealed that compound 2 potently suppressed cell growth and colony formation, which are associated with a delay in S phase advancement via the inhibition of the DNA synthesis (Liu *et al.,* 2017).

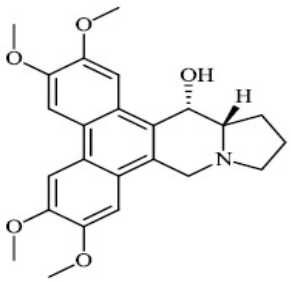


**Fig.7. Phenanthroquinolizidine.**

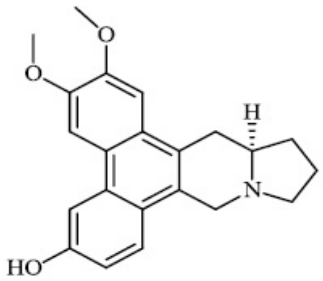


**Fig.8. Phenanthroquinolizidine**

**Antiviral Activity**

A virus is a parasitic organism that cannot replicate on its own. On the other hand, a virus can direct the cell machinery to develop more viruses once it has infected a susceptible cell. The genetic mate-rial in most viruses is either RNA or DNA. The nucleic acid and an outer protein shell make up the whole infectious virus particle, known as a virion. The FDA has approved antiviral agents for the treatment of viral infections. Antiviral drugs mainly target different stages of the viral life cycle. Synthesis of 4, 5, 7, 8-substituted quinazolines 27-30 (EC 0.6±0.1 μM). The synthesized compounds exhibited significant activity against HCMV (Held *et al.* 2017).

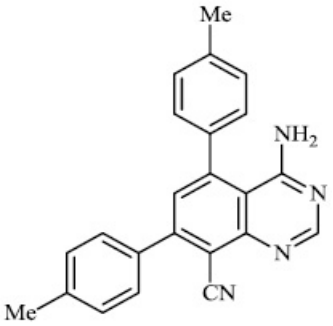


**Fig.9. 4-amino-5, 7-di-p-tolylquinazoline-8-carbonitrile.**

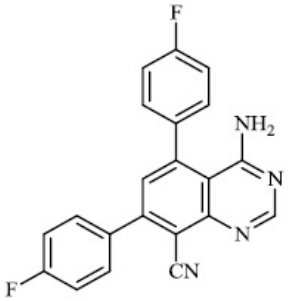


**Fig.10. 4-amino-5, 7-bis (4-flurophenyl) quinazoline-8-carbonitrile.**

**Antibacterial Activity**

Bacteria are single-cell organisms that can be found individually or in groups. Many effective and generally non-toxic medications available to treat bacterial infections pose challenges for medicinal chemists. Antibacterials, often known as antibiotics, are used to prevent or cure bacterial infections by either killing or inhibiting the development of bacteria. Synthesized novel heterocyclic compounds with a sulphonamide moiety, such as amino pyrazole derivatives 47, pyrazolopyrimidine derivative 48, and pyrimidine and thiazine derivatives 49 and 50, and assessed them for their antibacterial efficacy. Most of the synthesized compounds exhibited promising antibacterial properties against Gram-positive and Gram-negative bacteria (Azab *et al.,* 2013).

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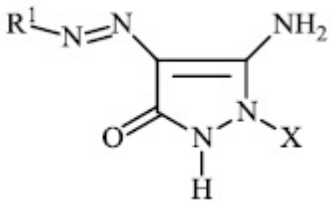

**Fig.11. Amino pyrazole derivatives.**

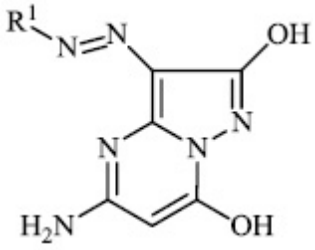

**Fig.12. Pyrazolopyrimidine derivatives.**

**Alzheimer's Disease**

Alzheimer's disease (AD) is the most frequent degenerative brain disorder and is characterized by cognitive impairment. Patients with Alzheimer's disease lose their capacity to code new memories, making life incredibly challenging. In this field, new drugs are being developed at a rapid speed. Synthesized a new class of thiazole-piperazine derivatives 64 and 65 with IC values as 0.0496±0.002μM, 0.0317±0.001μM, and 0.2158±0.010 μM, respectively, to combat Alzheimer's disease. The acetylcholinesterase (AChE) enzyme was significantly inhibited by all the synthesized compounds. On the other hand, none of the substances inhibited the butyrylcholinesterase (BChE) enzyme significantly (Osmaniye *et al.,* 2019)

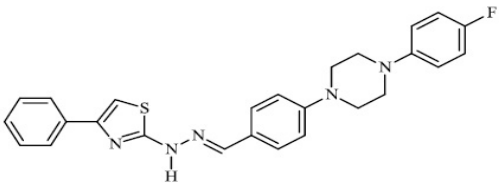

**Fig.13. 4-Phenylthiazole**

**Anti-diabetic Activity**

Diabetes Mellitus is a collection of metabolic disorders defined by a persistently high blood sugar level. The most prevalent symptoms of diabetes include increased appetite, increased thirst, and frequent urination. Diabetes, if left untreated, can lead to several health issues. Cardiovascular dis-ease, nerve damage, stroke, cognitive impairment, eye damage, foot ulcers, and chronic renal dis-ease are all serious long-term consequences of diabetes. Diabetes is caused by either a lack of insulin production by the pancreas or the body cells incapable of responding appropriately to the insulin produced. An enormous number of medications are available to treat diabetes mellitus by lowering the blood glucose level. With the exceptions of insulin, exenatide, and pramlintide, all are ad-ministered orally and are thus called oral hypoglycaemic medications (Hamed *et al.,* 2020). Synthesized benzothiazole derivatives and explored their antidiabetic activity. In diabetic rats, the synthesized compounds 79 caused a greater drop in blood glucose compared to other compounds. The LD values of the synthesized compounds were estimated to be in the range of100-1000 mg/kg, respectively (Prabhat *et al.*, 2013).

**Anti-fungal activity**

Fungi are organisms that do not belong to animal or plant kingdoms. They can be found in the soil, wet places, air, plants, water, decaying organic materials, as well as in animals and humans. Fungi, together with bacteria, perform a crucial function in our environment by reducing organic matter into simpler forms for plant use. They include mushrooms, household yeast, moulds, and many others. Aspergillus, Mucoromycetes, Histoplasma, Candida, Pneumocystis, Cryptococcus are the most prevalent forms of fungi. In general, several forms of fungi do not cause infections in humans, but opportunistic infections, which affect persons with impaired immunity, can cause illness. Diabetes, blood malignancies, iron overdose, trauma, steroids medication, malnourishment, *etc*., are some conditions that reduce our immunity. Mucormycosis, commonly called black fungus, is a deadly but uncommon fungal illness caused by micromycetes, a kind of Mold. Few subgroups are typically involved in the occurrence of this infection, including Rhizomucor, Mucor, and Rhizopus. These fungi are angioinvasive, *i.e.*, they enter and damage the surrounding blood vessels, causing tissue necrosis and death. These infections are extremely deadly, and most people would die if they are not treated. Its associated death rate varies between 25% and 90%. Synthesized *β*-keto-enol pyridine and furan hybrids and screened them for their antifungal activity

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against Gram-positive strains (*B. subtilis* and *M. luteus*) and *F. oxysporum* Compound 90 with an IC value of 12.83 µg mL demonstrated excellent antifungal efficacy against the tested fungal strains (Tighadouini *et al.,* 2020).

**Antibacterial activity**

Bacteria are single-cell organisms that can be found individually or in groups. Many effective and generally non-toxic medications available to treat bacterial infections pose challenges for medicinal chemists. Antibacterials, often known as antibiotics, are used to prevent or cure bacterial infections by either killing or inhibiting the development of bacteria. Synthesized novel heterocyclic compounds with a sulphonamide moiety, such as aminopyrazole derivatives 47 and assessed them for their antibacterial efficacy. Most of the synthesized compounds exhibited promising antibacterial properties against Gram-positive and Gram-negative bacteria (Azab *et al.,* 2013).

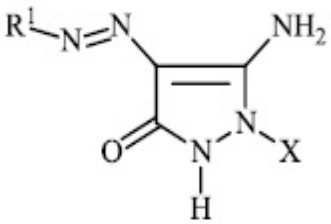


**Fig.14. Aminopyrazole derivative.**

**Anti-microbial Agents**

Antimicrobials are therapeutic substances used to prevent or treat infections. They include antiseptics, antibiotics, antivirals, antifungals and antiparasitic. Disinfectants are antimicrobial agents applied to non-living surfaces. Antimicrobials can kill microorganisms and/or prevent their growth by targeting key steps in cellular metabolism such as the synthesis of biological macromolecules, the activity of cellular enzymes, or cellular structures such as the cell wall, cell membranes (Purssell, 2020). The presence of antimicrobial agents in an ecosystem, whether natural or man-made, always has an ecological impact (Grenni *et al.,* 2018). Antimicrobial agents active against multi-resistant Gram-positive bacteria are considered to be of major commercial potential. Commercially viable agents that have been included in recent successful trials include the streptogramins, novel glycopeptides, oxazolidinones and potent quinolones. Cationic peptides have generated much interest, but their utility as successful drug candidates remain questionable. Novel compound classes for possible exploitation include non-β-lactam β-lactamase inhibitors, inhibitors of lipid a biosynthesis and tRNA synthetase inhibitors.

**3. Bacteria Resistant to Antibiotics**

Some bacteria have developed resistance to antibiotics that were once commonly used to treat them. For example, Staphylococcus aureus (‘golden staph’) and *Neisseria gonorrhoeae* (the cause of gonorrhoea) are now almost always resistant to benzyl penicillin. In the past, these infections were usually controlled by penicillin. Rates of antimicrobial resistance are increasing across the world. Antimicrobial resistance is a major public health problem. The most serious concern is that some bacteria have become resistant to almost all of the readily available antibiotics. This can make infections and diseases more serious and challenging and costly to treat. These bacteria can also spread from person-to-person. Important examples of antimicrobial resistance strains of bacteria are: Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), Multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB), Carbapenemase-producing *Enterobacterales* (CPE).

**Antimicrobial resistant bacteria**

Antibiotic medications are used to treat infections and diseases caused by bacteria. They have made a major contribution to improving human health and life expectancy. Many diseases that once killed people can now be treated effectively with antibiotics. However, some strains of bacteria have become resistant to antibiotics. This is called antimicrobial resistance, also known as antibiotic resistance. Antimicrobial resistant bacteria are bacteria that are not controlled or killed by antibiotics. They are able to survive and even multiply in the presence of an antibiotic. Most infection-causing bacteria can become resistant to at least some antibiotics. Bacteria that are resistant to many antibiotics are known as multi-resistant organisms (MRO).

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**Transmission of antimicrobial resistant bacteria in hospitals**

The common ways in which bacteria can be passed from person to person include: contact with contaminated hands of hospital staff contact with contaminated surfaces such as door handles, over-bed tables and call bells contact with contaminated equipment, such as stethoscopes and blood pressure cuffs.

**Effectiveness Against Resistant Strains**

Here are a few case studies that highlight the effectiveness of heterocyclic agents against resistant strains in various fields:

**Antimicrobial Resistance in Infectious Diseases:**

Example: The development of new imidazole derivatives for antifungal treatment has shown promise against resistant strains of fungi such as Candida spp. and Aspergillus spp. Imidazoles inhibit the biosynthesis of ergosterol, a key component of fungal cell membranes. Their effectiveness against resistant strains underscores their potential in combating fungal infections that are increasingly resistant to conventional therapies.

**Antibiotic Resistance in Bacterial Infections:**

Example: Pyrazole derivatives have demonstrated potent antibacterial activity against multidrug resistant strains of bacteria, including methicillin resistant Staphylococcus aureus (MRSA). These compounds inhibit bacterial DNA synthesis or protein synthesis pathways, thereby circumventing resistance mechanisms such as efflux pumps or altered target sites.

**Resistance in Agricultural Pests and Diseases:**

Example: Triazole fungicides have been effective against agricultural fungal pathogens that have developed resistance to older fungicide classes. Triazoles disrupt ergosterol biosynthesis in fungi, preventing membrane formation and leading to fungal cell death. Their broad-spectrum activity and low risk of resistance development make them valuable tools in crop protection against resistant strains.

**Resistance in Cancer Treatment:**

Example: Pyridine and pyrazole derivatives have been investigated as inhibitors of specific kinase pathways in cancer cells. These compounds show promise in overcoming resistance to conventional chemotherapy drugs by targeting alternative signalling pathways that are active in resistant cancer cells.

**Insecticide Resistance in Vector Control:**

Example: Novel pyrethroid derivatives containing heterocyclic moieties have been developed to combat insecticide resistance in mosquitoes that transmit diseases such as malaria and dengue. These compounds act on voltage gated sodium channels in insect neurons, providing effective control even in regions where resistance to older insecticides is prevalent.

**Role of Heterocyclic Moieties in Antimicrobial Agents:**

Heterocyclic moieties play a crucial role in the development and effectiveness of antimicrobial agents due to their structural diversity and ability to interact with biological targets. Here are key aspects of their role in antimicrobial agents (Rusu *et al.,* 2023):

**Enhanced Bioactivity:** Heterocyclic compounds often exhibit potent antimicrobial activity due to their ability to interact with specific microbial targets, such as enzymes or receptors essential for bacterial growth and survival. The presence of heteroatoms (e.g., nitrogen, oxygen) within the ring structure can impart unique electronic and spatial properties that are conducive to binding and inhibiting microbial targets.

**Broad Spectrum or Selectivity**: Depending on their structure and functional groups, heterocyclic moieties can be tailored to target specific microbial species or have broad spectrum activity against a wide range of pathogens. This versatility allows for the development of antimicrobial agents that can effectively combat different types of bacteria, fungi, viruses, or parasites.

**Resistance Mitigation:** Heterocyclic compounds can help overcome resistance mechanisms in microbes. By targeting essential microbial enzymes or processes that are less prone to mutation or acquired resistance, these agents can circumvent common resistance mechanisms, such as efflux pumps or enzymatic degradation of antibiotics.

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**Structural Modification:** The modular nature of heterocyclic moieties enables medicinal chemists to design and optimize antimicrobial agents through structural modifications. By altering substituents, ring size, or the number and position of heteroatoms, researchers can finetune the pharmacological properties of antimicrobial agents, including potency, spectrum of activity, solubility, and bioavailability.

**Combination Therapy:** Heterocyclic moieties are often integrated into combination therapies with other antimicrobial agents or adjuvants. This approach can synergistically enhance antimicrobial efficacy, delay the emergence of resistance, and reduce the dosage required for effective treatment.

**Examples in Antimicrobial Agents:** Numerous clinically used antimicrobial agents contain heterocyclic moieties. For instance, βlactam antibiotics such as penicillin and cephalosporins contain a β lactam ring, a common heterocyclic structure essential for their antibacterial activity by inhibiting bacterial cell wall synthesis. Fluoroquinolones, another class of antibiotics, feature a heterocyclic ring system that targets bacterial DNA gyrase and topoisomerase IV, crucial enzymes involved in DNA replication and repair. The diverse structural properties and bioactivities of heterocyclic moieties make them indispensable in the development of effective antimicrobial agents. Their ability to interact with microbial targets, mitigate resistance mechanisms, and enable structural optimization positions heterocyclic compounds as key components in combating infectious diseases and addressing the global challenge of antimicrobial resistance.

**Table 1. FDA-approved antibiotics and their essential heterocycles during 1980-2023.**

| FDA Approval Year | Antibiotic Compound | Antibiotic Class (Generation) | Five-Member Heterocycle in the Structure |
|---|---|---|---|
| 1980 | Cefotaxime | Beta-lactam cephalosporin (2nd generation) | 1,3-Thiazole |
| 1981 | Cefoperazone | Beta-lactam cephalosporin (3rd generation) | Tetrazole |
| 1981 | Cefotiam | Beta-lactam cephalosporin (2nd generation) | 1,3-Thiazole, Tetrazole |
| 1982 | Ceftriaxone | Beta-lactam cephalosporin (3rd generation) | 1,3-Thiazole |
| 1982 | Latamoxef/ Moxalactam | Beta-lactam, oxacephem cephalosporin (1st generation) | Tetrazole |
| 1983 | Cefonicid | Beta-lactam cephalosporin (2nd generation) | Tetrazole |
| 1983 | Cefuroxime | Beta-lactam cephalosporin (2nd generation) | Furan |
| 1984 | Ceftazidime | Beta-lactam cephalosporin (2nd generation | 1,3-Thiazole |
| 1986 | Aztreonam | Beta-lactam monobactam | 1,3-Thiazole |
| 1987 | Cefotetan | Beta-lactam cephalosporin (3rd generation) | Tetrazole |
| 1992 | Cefpodoxime proxetil | Beta-lactam cephalosporin (3rd generation) | 1,3-Thiazole |
| 1991 | Cefuroxime axetil | Beta-lactam cephalosporin (3rd generation) | Furan |
| 199 | Ceftibu | Beta-lactam | 1,3- |

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| FDA Approval Year | Antibiotic Compound | Antibiotic Class (Generation) | Five-Member Heterocycle in the Structure |
|---|---|---|---|
| 2 | ten | cephalosporin (3rd generation) | Thiazole |
| 1992 | Tazobactam | Beta-lactamase inhibitor | 1,2,3-Triazole |
| 1993 | Cefixime | Beta-lactam cephalosporin (3rd generation) | 1,3-Thiazole |
| 1996 | Cefepime | Beta-lactam cephalosporin (4th generation) | Pyrrolidine, 1,3-Thiazole |
| 1996 | Meropenem | Beta-lactam carbapenem | Pyrrolidine |
| 1997 | Cefdinir | Beta-lactam cephalosporin (4th generation) | 1,3-Thiazole |
| 2000 | Linezolid | Oxazolidinone | 1,3-Oxazolidine |
| 2001 | Ertapenem | Beta-lactam carbapenem | Pyrrolidine |
| 2001 | Telithromycin | Ketolide macrolide | Imidazole |
| 2003 | Gemifloxacin | Fluoroquinolone | Pyrrolidine |
| 2009 | Ceftobiprole | Beta-lactam cephalosporin (5th generation) | Pyrrolidine |
| 2014 | Doripenem | Beta-lactam carbapenem | Pyrrolidine |
| 2014 | Finafloxacin | Fluoroquinolone | Pyrrole (in a bicycle) |
| 2014 | Tedizolid | Oxazolidinone | 1,3-Oxazolidin-2-one, Tetrazole |
| 2018 | Eravacycline | Tetracycline | Pyrrolidine |
| 2018 | Gemifloxacin | Fluoroquinolone | Pyrrolidine |
| 2019 | Imipenem + Cilastatin + Relebactam | Relebactam: beta-lactamase inhibitor | 2-Imidazolidinone (in an azabicycle) |
| 2019 | Cefidorocol | Beta-lactam cephalosporin (5th generation) | Pyrrolidine, thiazole |
| 2021 | Ceftidoren pivoxil | Beta-lactam cephalosporin (5th generation) | Thiazole (2 groups) |
| 2023 | Sulbactam + durlobactam | Sulbactam: beta-lactam antibacterial and beta-lactamase inhibitor Durlobactam: beta-lactamase inhibitor | Sulbactam: 1,3-Thiazolidine 1,1-dioxide Durlobactam: 2-Imidazolidinone (in an azabicycle) |

**4. Mechanism of Action of Heterocyclic Compounds:**

Heterocyclic compounds exert their biological effects through various mechanisms, depending on their

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specific structure and functional groups (Baranwal, 2023).

**Receptor Binding:** Many heterocyclic compounds act by binding to specific receptors on cell surfaces or within cells. This binding can mimic or block natural ligands, altering cellular signalling pathways. Examples include drugs like nicotine (pyridine derivative) binding to nicotinic acetylcholine receptors.

**Enzyme Inhibition:** Heterocyclic compounds often inhibit enzymes crucial for biochemical processes. For instance, drugs like ketoconazole (imidazole derivative) inhibit fungal cytochrome P450 enzymes, disrupting ergosterol synthesis in fungi.

**DNA/RNA Interaction:** Some heterocyclic compounds interact with nucleic acids (DNA and RNA), altering their structure or inhibiting replication and transcription processes. Examples include drugs like quinolones (such as ciprofloxacin), which inhibit bacterial DNA gyrase.

**Metal Chelation:** Certain heterocyclic compounds can chelate metal ions, affecting their bioavailability or catalytic roles in enzymatic processes. For instance, drugs like EDTA (ethylenediaminetetraacetic acid) chelate metal ions in the bloodstream, preventing them from participating in harmful reactions.

**Allosteric Modulation:** Heterocyclic compounds may bind to allosteric sites on proteins or enzymes, altering their activity without directly competing with substrate binding sites. This modulation can enhance or inhibit enzymatic activity or receptor signalling.

**Ion Channel Modulation:** Some heterocyclic compounds affect ion channels in cell membranes, influencing cellular excitability, neurotransmission, and muscle contraction. Examples include drugs like verapamil (a phenylalkylamine derivative) that block calcium channels in heart muscle cells.

**Heterocycles in Drug Design:**

Incorporating heterocycles into drug design offers several benefits that contribute to the development of effective and safe pharmaceuticals. Here are some key advantages (Broughton and Watson, 2004):

**Bioactivity and Selectivity:** Heterocycles often possess specific structural features that enhance their interaction with biological targets such as receptors, enzymes, or nucleic acids. This can lead to increased potency and selectivity in drug action, reducing side effects by targeting specific pathways or molecules.

**Diversity of Chemical Properties:** Heterocycles vary widely in size, shape, and functional groups, allowing for the design of molecules with diverse chemical properties. This versatility enables drug designers to optimize characteristics like solubility, stability, and bioavailability.

**Pharmacokinetic Properties:** Heterocycles can influence a drug's pharmacokinetic profile, affecting its absorption, distribution, metabolism, and excretion (ADME). Modifications to the heterocyclic core can improve these properties, enhancing drug efficacy and reducing dosing frequency.

**Resistance to Metabolic Degradation:** Some heterocyclic structures exhibit resistance to metabolic degradation compared to aliphatic compounds, leading to longer half-lives and prolonged therapeutic effects. This stability is crucial for maintaining drug concentrations within the therapeutic window.

**Synthetic Accessibility:** Many heterocycles are synthetically accessible through efficient and scalable methods, facilitating the production of large quantities of drugs at reasonable costs. This accessibility is important for pharmaceutical development and commercialization.

**Drug-Drug Interactions:** Incorporating heterocycles can reduce the likelihood of drug-drug interactions by specifically targeting biological pathways or receptors without affecting unrelated systems. This property enhances the safety profile of drugs in combination therapies.

**Recent advance and newly developed heterocyclic agents**

**Pyrimidine containing antimicrobial agents**

Pyrimidines are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities and clinical applications.

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Substituted purines and pyrimidines occur very widely in living organ-isms and were some of the first compounds studied by the organic chemists (Figure 15(a).

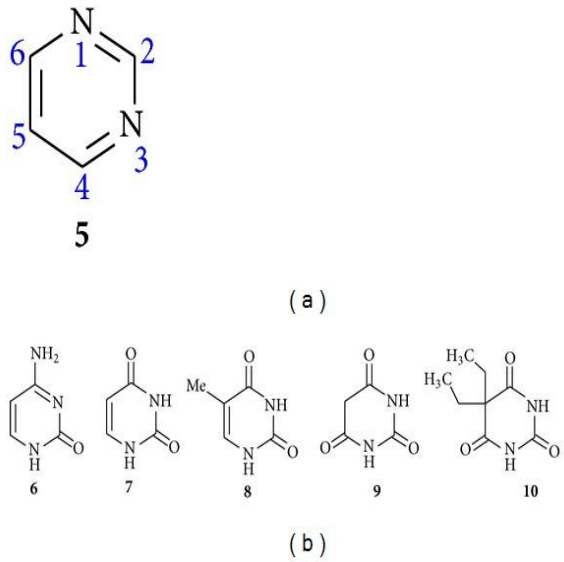


**Fig.15. (a) Pyrimidine. (b) Pyrimidine containing natural and synthetic products.**

Pyrimidines are biologically very important heterocycles and represent by far the most ubiquitous members of the diazine family with uracil and thymine being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine both being present in Figure 2(b). In addition to this, pyrimidines skeleton is also present in many natural products such as vitamin B 1 (thiamine) and many synthetic compounds, such as barbituric acid and Veranal (**10**) which are used as hypnotics (Figure 15(b)).

**5. Medicinal Properties of Pyrimidines**

The presence of pyrimidine base in thymine, cytosine, and uracil, which are the essential building blocks of nucleic acids DNA and RNA, is one possible reason for their widespread therapeutic applications. The pyrimidines represent one of the most active classes of compounds possessing wide spectrum of biological activities like significant *in vitro* activity against unrelated DNA and RNA, viruses including polio herpes viruses, diuretic, antitumour, anti-HIV, and cardiovascular. The literature survey indicated that a wide range of pharmacological activities are exhibited by the compounds encompassing pyrimidines nucleus. In addition to this, various analogs of pyrimidines have been found to possess antibacterial, antifungal, antileishmanial, anti-inflammatory, analgesic, antihypertensive, antipyretic, antiviral, antidiabetic, antiallergic, anticonvulsant, antioxidant, antihistaminic, herbicidal, and anticancer activities and many of pyrimidine's derivatives are reported to possess potential central nervous system (CNS) depressant properties and also act as calcium channel blockers.

**Detailed Examples of Successful Heterocyclic Antimicrobial:**

Heterocyclic compounds have been instrumental in the development of antimicrobial agents, playing crucial roles in combating bacterial, fungal, and parasitic infections. Here are some detailed examples of successful heterocyclic antimicrobials:

**Beta lactams:**

Structure: Beta lactams include penicillin, cephalosporins, and carbapenems, characterized by a beta lactam ring. Mechanism of Action: They inhibit bacterial cell wall synthesis by targeting penicillin binding proteins (PBPs). Examples: Ampicillin, ceftriaxone, and meropenem are widely used beta lactam antibiotics effective against various Gram positive and gram-negative bacteria. They are used for treating infections ranging from pneumonia to skin infections.

**Nitroimidazoles:**

Structure: Nitroimidazoles have a five membered ring containing both a nitro group and an imidazole ring. Mechanism of Action: They disrupt DNA synthesis and damage bacterial and protozoal DNA, leading to cell death. Examples: Metronidazole and tinidazole are commonly used nitroimidazoles effective against anaerobic bacteria and protozoa like Giardia and Trichomonas. These examples demonstrate the diversity and effectiveness of heterocyclic antimicrobials in clinical practice. Their structural versatility and specific mechanisms of action make them invaluable tools in the fight against infectious diseases caused by bacteria, fungi, and parasites.

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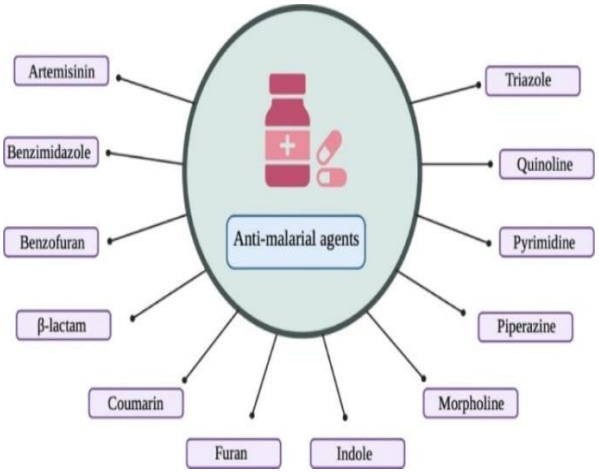
**6. Recent Advances and Newly Developed Heterocyclic Agents:**




Recent advances in heterocyclic agents have seen significant developments across various fields, including pharmaceuticals, materials science, and agrochemicals. Here are some notable examples of newly developed heterocyclic agents:

**Pharmaceuticals:**

Benzimidazoles: Used in the treatment of helminthic infections and as proton pump inhibitors.

Imidazole Derivatives: Act as antifungal agents and are also explored for their potential in cancer therapy.

Pyrazoles: Known for their anti-inflammatory properties and used in drugs targeting conditions like arthritis.

Oxazole's and Thiazoles: These heterocyclic compounds are utilized in the development of antibacterial and antifungal drugs.

**Materials Science:**

Polymeric Materials: Incorporation of heterocyclic units (such as pyrrole, thiophene, furan) in conducting polymers for applications in organic electronics (e.g., OLEDs, solar cells).

Luminescent Materials: Heterocyclic compounds are used to develop fluorescent and phosphorescent materials for sensors and display technologies.

**Agrochemicals:**

Triazoles: Widely used as fungicides to protect crops from fungal infections.

Pyridine and Pyrazole Derivatives: Utilized in the development of insecticides and herbicides due to their biological activity against pests and weeds.

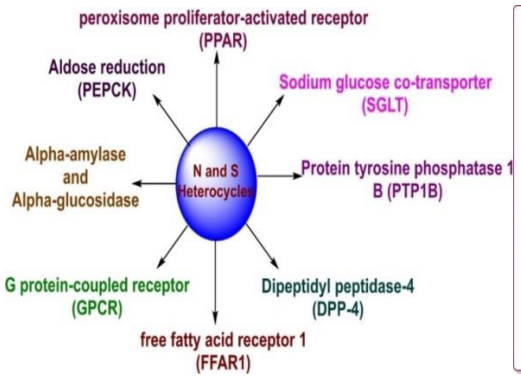
**Catalysis:**

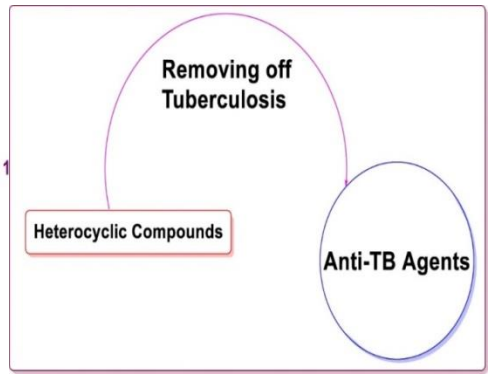
N Heterocyclic Carbenes (NHCs): These compounds have emerged as versatile ligands in organometallic catalysis, enabling efficient transformations in organic synthesis.

**Environmental and Energy Applications:**

Thiophene Derivatives: Incorporated into materials for energy storage devices like lithium-ion batteries due to their electrochemical properties.

Nitrogen Containing Heterocycles: Used in the development of photocatalysts for water splitting and pollutant degradation. These examples highlight the diverse applications of heterocyclic agents in modern science and technology, driven by ongoing research and innovation in the synthesis and functionalization of these compounds.



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**Challenges in antimicrobial drug discovery and the potential of nucleoside antibiotics**

The challenges to antibacterial discovery have kept the output of novel antibacterial drug classes to extraordinarily low levels over the past 25 years, even though discovery programs have been in place at large and small pharmaceutical companies as well as academic laboratories over this period. This review focuses on the scientific challenges to the discovery of novel small-molecule antibacterials rather than on the commercial and regulatory considerations, which are well covered in a number of reviews. Rate-limiting steps to the discovery process are discussed, and some perspective on avenues to address those limitations is offered. An underlying thesis of this review is that the bleak picture of antibacterial discovery is due to an expenditure of effort and resources on non-rate-limiting steps of the process. While it is easy to find compounds that kill bacteria, it is hard to find novel antibacterial classes worthy of development. If new molecular entities with desirable properties and specificity had been discovered commonly throughout the past 25 years, it seems likely that large pharmaceutical companies (Big Pharma) would have viewed the area as productive and continued with antibacterial discovery. Even if unlimited money were poured into discovery and problematic regulatory guidelines were improved and stabilized, then it is probable that novel discovery would still be stymied because scientific obstacles remain to be over.

**7. The Discovery**

Walsh has noted that “no major classes of antibiotics were introduced” between 1962 and 2000 and refers to the interim as an innovation gap. This understates the problem. The latest registered representatives of novel antibacterial classes, linezolid, daptomycin, and the topical agent retapamulin, were indeed introduced in 2000, 2003, and 2007, respectively, but these chemical classes (oxazolidinones, acid lipopeptides, and pleuromutilin) were first reported (or patented) in 1978, 1987, and 1952, respectively. A timeline of dates of discovery of distinct classes of antibacterials (as opposed to dates of introduction) illustrates that there have been no (as yet) successful discoveries of novel agents since 1987. There is a discovery void of unknown extent rather than a gap. While there are a small number of novel compounds in the early clinical phase that might portend the end of this hiatus, in most cases their eventual developmental success is unclear. Is the void due to a lack of innovation? While the simple definition of innovation is the act of introducing something new, the word implies creativity, intent, and experimentation. Almost all the discoveries shown in Fig.19 (with the exception of trimethoprim, monobactams, Fosfomycin, and carbapenems) were serendipitous, made by screening fermentation products or chemicals for inhibition of bacterial growth (empirical screening). Not especially innovative, but it worked. In fact, since those last discoveries in the 1980s, there has been a great deal of creative, rational, technologically cutting-edge screening for and efforts at design of new antibacterials. But so far, little has reached serious development. The problem with the conduct of antibacterial discovery since the early 1980s is not a lack of innovation.

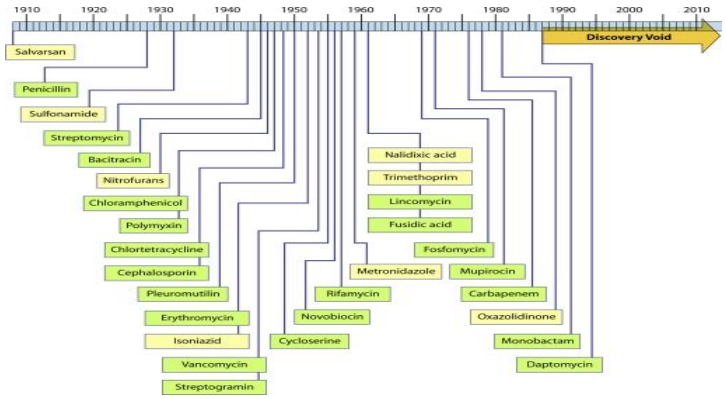


**Fig.16. Illustration of the “discovery void.” Dates indicated are those of reported initial discovery or patent.**

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**Class Modifications versus Novel Classes**

The antibacterial product pipeline has not been emptied during this time but has been filled with improved versions of previously registered classes. Many of these were true improvements, adding bacterial spectrum, safety, simpler dosing regimens, and most importantly, activity insusceptible to specific resistance mechanisms acting on the parent compound. A number of drugs with improved activity against resistant pathogens, such as oritavancin, iclaprim, and ceftobiprole, have reached the FDA but have met with regulatory problems, largely due to inadequacy of trials in proving noninferiority. Telavancin has been approved, and development of ceftaroline continues. Finding a derivative with an exploitable advantage over the original drug is not an easy path but is a process whose starting material has acceptable pharmacological properties and whose modification may be approached rationally. While the same caveats of meeting pharmacological and toxicological standards apply to this effort as to novel drug discovery, the leap is much greater for novel discovery, as it requires that the leads meet a tremendous number of criteria.

**Challenges in Developing Heterocyclic**

These case studies illustrate how the strategic development of heterocyclic agents can address challenges posed by resistant strains across different domains, from infectious diseases and agriculture to cancer treatment and vector control. Continued research and innovation in this area are crucial to staying ahead of evolving resistance mechanisms and ensuring effective therapeutic and agricultural solutions. The issues related to synthesis and scalability of antimicrobials, especially those incorporating heterocyclic structures, are critical considerations in pharmaceutical development. Here are some key challenges and strategies in addressing them:

**Complex Synthesis Routes:**

Challenge: Many heterocyclic antimicrobials require intricate synthetic routes involving multiple steps and specific conditions. This complexity can lead to low yields, high costs, and difficulties in purification.

Strategy: Researchers focus on developing more efficient synthetic methodologies such as catalytic processes, microwave assisted synthesis, or flow chemistry. These approaches aim to streamline reactions, reduce side products, and improve overall yield and purity.

**Raw Material Sourcing:**

Challenge: Heterocyclic antimicrobials often require specialized starting materials, some of which may be expensive or challenging to procure in large quantities.

Strategy: Exploration of alternative starting materials or synthetic routes that utilize more readily available and cost-effective precursors. Green chemistry principles are also considered to minimize environmental impact and optimize resource utilization.

**Scalability of Production:**

Challenge: Transitioning from laboratory scale synthesis to industrial scale production can be hindered by issues such as reactor design, safety considerations, and maintaining product consistency.

Strategy: Process optimization and engineering are crucial. This includes the design of robust synthetic routes that are amenable to scaleup, efficient utilization of resources, and adherence to Good Manufacturing Practices (GMP) to ensure product quality and safety.

**8. Patent and Intellectual Property Issues:**

Challenge: Intellectual property rights and patent protection can impact the accessibility and affordability of new antimicrobials, particularly when novel heterocyclic structures are involved.

Strategy: Collaboration between academia, industry, and regulatory bodies to facilitate technology transfer and ensure fair access to essential medicines. Strategies such as patent pooling or licensing agreements may be explored to balance innovation incentives with public health needs.

**Regulatory Compliance:**

Challenge: Meeting stringent regulatory requirements for quality, safety, and efficacy in antimicrobial development adds complexity and cost.

Strategy: Early engagement with regulatory authorities to understand and navigate the regulatory landscape effectively. Development of robust analytical methods and comprehensive preclinical and clinical studies to

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demonstrate safety and efficacy are essential steps in the regulatory approval process.

Addressing these challenges requires a multidisciplinary approach involving organic chemistry, chemical engineering, pharmacology, and regulatory affairs. Advances in synthetic methodologies, process optimization, and regulatory strategies are pivotal in overcoming barriers to the synthesis and scalability of heterocyclic antimicrobials, ensuring their successful translation from bench to bedside.

**Toxicity and Side Effects Concerns**

Toxicity and side effects are significant concerns in the development of antimicrobial agents, including those based on heterocyclic structures. Here are some key aspects related to toxicity and strategies to address them (Jiang *et al.,* 2005):

**Nonspecific Toxicity:**

Issue: Many antimicrobial agents, especially those with broad spectrum activity, can exhibit nonspecific toxicity to human cells, leading to adverse effects.

Strategy: Structure activity relationship (SAR) studies aim to optimize the molecular structure of heterocyclic antimicrobials to enhance selectivity for microbial targets while minimizing interactions with human cells. This involves modifying functional groups or stereochemistry to improve specificity and reduce toxicity.

**Organ Toxicity:**

Issue: Some antimicrobials, particularly those metabolized in the liver or excreted by the kidneys, can cause organ toxicity with prolonged or high dose use.

Strategy: Preclinical toxicity studies assess the effects of heterocyclic antimicrobials on major organ systems. Understanding and mitigating potential toxicities through dose optimization, drug delivery strategies (such as prodrugs), or development of targeted therapies can minimize adverse effects.

**Drug Interactions:**

Issue: Heterocyclic antimicrobials may interact with other medications, altering their efficacy or increasing toxicity.

Strategy: Comprehensive drug interaction studies are conducted to identify potential interactions. Adjusting dosing regimens or avoiding combinations that may lead to adverse effects is essential in clinical practice.

**Allergic Reactions:**

Issue: Some individuals may experience allergic reactions to antimicrobial agents, ranging from mild skin rashes to severe anaphylaxis.

Strategy: Monitoring and reporting adverse drug reactions (ADR) during clinical trials and post marketing surveillance are critical to identify and manage allergic responses promptly. Developing alternative formulations or chemical modifications may reduce allergenic potential.

**Resistance and Cross Resistance:**

Issue: Prolonged use of antimicrobials can lead to the development of resistance not only to the administered drug but also to structurally related compounds (cross resistance).

Strategy: Implementing stewardship programs to promote judicious use of antimicrobials, combining agents with different mechanisms of action, and continuous surveillance for emerging resistance patterns are essential to mitigate resistance development.

**Chirality and Stereochemistry:**

Chiral Centres: Introducing chiral centres can create stereoisomers with different biological activities. Optimizing the stereochemistry of heterocyclic antimicrobials can enhance potency by improving interactions with target sites while reducing susceptibility to resistance mechanisms based on stereospecific recognition.

**Hybrid Molecules and Scaffold Hopping:**

Hybridization: Combining different pharmacophores or heterocyclic scaffolds with complementary mechanisms of action can create synergistic effects, enhancing potency and reducing the likelihood of resistance.

Scaffold Hopping: Exploring structurally diverse scaffolds while maintaining essential pharmacophores can lead to novel antimicrobial agents with unique mechanisms of action, reducing cross resistance.

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**Modulation of Lipophilicity and Hydrophilicity:**

Hydrophobic Interactions: Adjusting the lipophilicity of heterocyclic antimicrobials can improve membrane permeability and intracellular accumulation, enhancing efficacy against resistant strains that may have altered membrane structures.

Hydrophilic Modifications: Adding hydrophilic groups can enhance solubility, bioavailability, and distribution to infection sites, improving therapeutic outcomes.

**Metal Complexation and Bioconjugation:**

Metal Complexes: Incorporating metal ions into heterocyclic structures can alter physicochemical properties and enhance antimicrobial activity through metal ligand interactions.

Bioconjugation: Conjugating heterocyclic antimicrobials with targeting moieties (e.g., peptides, antibodies) can improve specificity and efficacy against microbial targets while minimizing off target effects. Each of these structural modifications aims to optimize the interaction between heterocyclic antimicrobials and microbial targets, thereby enhancing potency and reducing the likelihood of resistance. Rational drug design approaches, supported by computational modelling and structure activity relationship studies, are essential for guiding these modifications to effectively combat evolving resistance mechanisms in microbial populations and spread of resistance.

**Combination Therapies with Heterocyclic Compounds**

Combination therapies involving heterocyclic compounds offer a promising approach to enhance antimicrobial efficacy, overcome resistance, and minimize side effects. Here are several ways combination therapies with heterocyclic compounds can be effectively utilized across different fields (Basavegowda and Baek, 2022):

**Synergistic Combinations:**

Combining a heterocyclic antibiotic, such as a βlactam derivative targeting bacterial cell wall synthesis, with a βlactamase inhibitor (e.g., clavulanic acid). This combination prevents bacterial resistance mechanisms from degrading the antibiotic, thereby restoring or enhancing its efficacy against resistant strains.

**Dual Targeting Strategies:**

Using a combination of heterocyclic compounds that target different metabolic pathways or cellular processes in pathogens. For instance, combining an inhibitor of DNA replication (e.g., quinolone) with an antimetabolite (e.g., sulphonamide) disrupts multiple essential functions, reducing the likelihood of resistance development.

**Complementary Mechanisms of Action:**

Combining heterocyclic compounds with different modes of action (e.g., targeting cell membrane integrity versus protein synthesis) can enhance antimicrobial efficacy and broaden the spectrum of activity against diverse microbial pathogens.

**Clinical Trial Optimization and Personalized Medicine:**

Clinical Trial Design: AI algorithms optimize clinical trial protocols by predicting patient responses to heterocyclic compounds based on genetic, demographic, and clinical data, improving trial success rates and accelerating drug approval. Personalized Medicine: AI driven approaches tailor treatment regimens based on individual patient characteristics and disease profiles, optimizing therapeutic outcomes with heterocyclic antimicrobial agents. Overall, computational methods and AI technologies are transforming drug discovery and development by accelerating the identification, optimization, and deployment of heterocyclic compounds as effective antimicrobial and therapeutic agents. These approaches complement traditional experimental methods, offering new avenues for innovation in pharmaceutical research.

**9. Future Directions and Research Opportunities**

**Potential of Novel Heterocyclic Scaffolds**

Novel heterocyclic scaffolds hold substantial potential across various domains of drug discovery and development due to their versatility, diverse chemical properties, and potential therapeutic applications. Here are some key aspects highlighting the potential of novel heterocyclic scaffolds:

**Diverse Biological Activities:** Heterocyclic scaffolds offer a wide range of biological activities due to their ability to interact with diverse biological targets such as

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enzymes, receptors, and nucleic acids. This diversity makes them valuable in developing drugs for various therapeutic areas including antimicrobials, anticancer agents, central nervous system (CNS) drugs, and cardiovascular medications.

**Antimicrobial Agents:** Novel heterocyclic scaffolds can be designed or discovered to target specific microbial pathways or enzymes essential for microbial survival. For instance, compounds targeting bacterial cell wall synthesis (e.g., βlactams) or fungal cell membrane integrity (e.g., azoles) demonstrate potent antimicrobial activity. The development of new scaffolds helps combat resistance and broaden the spectrum of antimicrobial agents available.

**Anticancer Agents:** Heterocyclic scaffolds play a crucial role in developing anticancer agents targeting pathways involved in cancer cell proliferation, survival, and metastasis. Examples include Imidazoles, pyrazoles, and indoles, which have shown promising anticancer activities through various mechanisms such as kinase inhibition, DNA intercalation, or disruption of microtubule function.

**Neurological and Psychiatric Disorders:** Heterocyclic compounds are integral in designing drugs for neurological and psychiatric disorders by targeting neurotransmitter receptors, ion channels, or enzymes involved in neurotransmitter metabolism. Examples include benzodiazepines (GABA receptor modulators) and selective serotonin reuptake inhibitors (SSRIs) used in treating anxiety and depression.

**Cardiovascular Drugs:** Novel heterocyclic scaffolds have contributed to the development of cardiovascular drugs targeting ion channels, receptors, or enzymes involved in regulating heart function and vascular tone. Compounds such as calcium channel blockers (e.g., dihydropyridines) and βblockers (e.g., propranolol) exemplify the therapeutic potential of heterocyclic structures in managing cardiovascular diseases.

**Innovative Drug Delivery Systems:** Heterocyclic scaffolds are also explored in developing novel drug delivery systems (DDS) that improve drug solubility, stability, and bioavailability. Nano technology-based DDS incorporating heterocyclic compounds can enhance targeted delivery to specific tissues or cells, reducing systemic side effects and improving therapeutic efficacy.

**Green Chemistry and Sustainability:** Advances in synthetic methodologies allow for the development of heterocyclic scaffolds using sustainable and environmentally friendly approaches. Green chemistry principles promote the use of renewable feedstocks, catalysts, and solvent free conditions, contributing to more sustainable drug manufacturing processes. The potential of novel heterocyclic scaffolds lies in their ability to serve as versatile platforms for developing diverse classes of therapeutic agents. Continued research and innovation in heterocyclic chemistry, coupled with advances in computational modelling and synthetic methodologies, promise to unlock new opportunities in drug discovery and address unmet medical needs across various therapeutic areas.

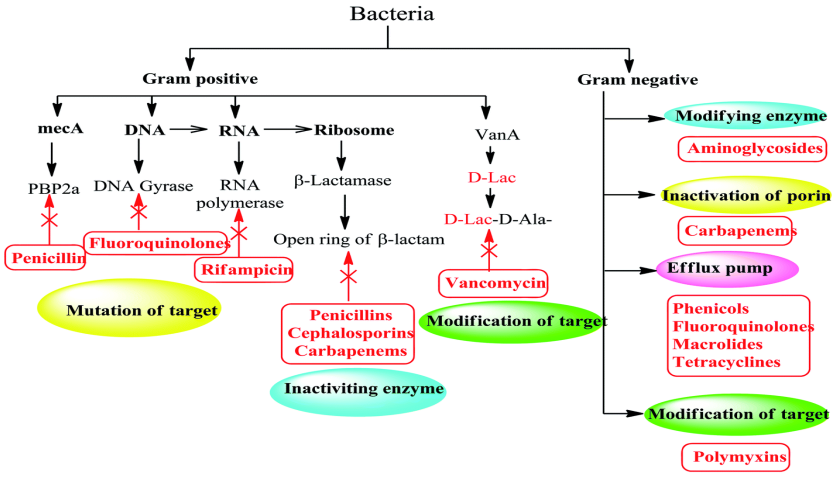


**Fig.17. Different mechanisms of antibiotic resistance in Gram-positive and Gram-negative bacteria**

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**Antibiotic adjuvant**

Therefore, to overcome the emerging of antibiotic resistance, combination therapies of antibiotic with potentiating adjuvants may be used. These adjuvants include drugs that block the mechanisms of resistance for the antibiotics as: (a) efflux pump inhibitors, (b) β-lactamase inhibitors, (c) outer membrane permeability enhancer and (d) anti-virulence compounds. Anti-virulence agents suppress virulence phenotypes without affecting bacterial growth and therefore hance the antibacterial effect of drugs. This method consists of identifying the proteins, genes and other biological macromolecules that cause the virulence of the bacteria, thus, their inhibition will reduce the fitness of the bacteria, making them more vulnerable to the immune system and the use of antibiotics. In fact, such targets have been proposed, although they are not important for survival perse, they are unlikely to produce mutations. Furthermore, to expand drug targets, small molecules that target these "nonessential" genes can be combined with existing antibiotics (González-Bello *et al.*, 2017).

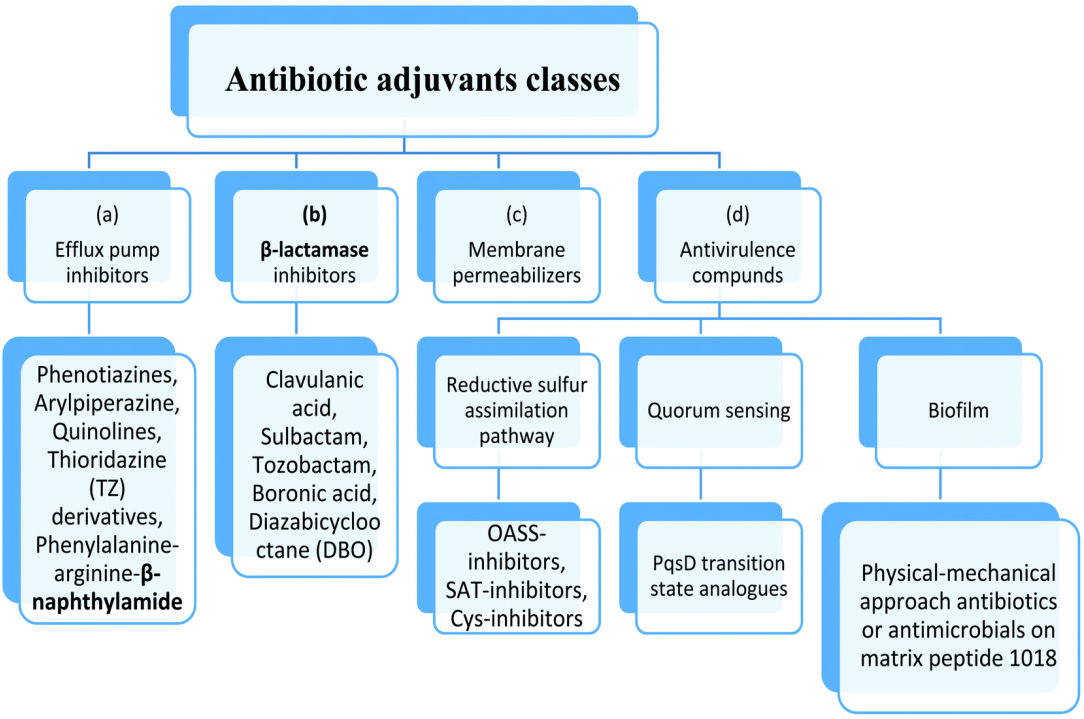


**Fig.18. Antibiotic adjuvants classes.**

**Targeting cysteine biosynthesis**

The rationale behind the exploitation of amino acid biosynthesis as a target for antimicrobial adjuvant development is the observation that some pathogens spend part of their life cycle in extremely harsh conditions, such as macrophages or the gastric mucosa, where survival and proliferation require powerful adaptation mechanisms involving metabolic pathways. In this case, interference with pathogen adaptation strategies can lead to increased sensitivity to antibiotics. Among potential new drugs targets is an enzyme involved in cysteine biosynthesis. It has been observed that the importance of cysteine biosynthesis enzymes differs during the lifecycle of pathogens: their activity can be dispensable during growth in vitro or acute infections but becomes indispensable during the persistence phase. Compared with traditional antibiotics, molecules developed for cysteine biosynthesis and other biosynthetic pathways may have the potential advantage of being more effective against persistence in the host, helping to prevent the development of drug resistance during the clinical incubation period. Many studies on the response of microorganisms to environmental stress (such as lack of nutrients, hypoxia, and oxidative stress) have shown that many genes of the cysteine regulator have a positive regulatory effect. (Starkey *et al.,* 2014).

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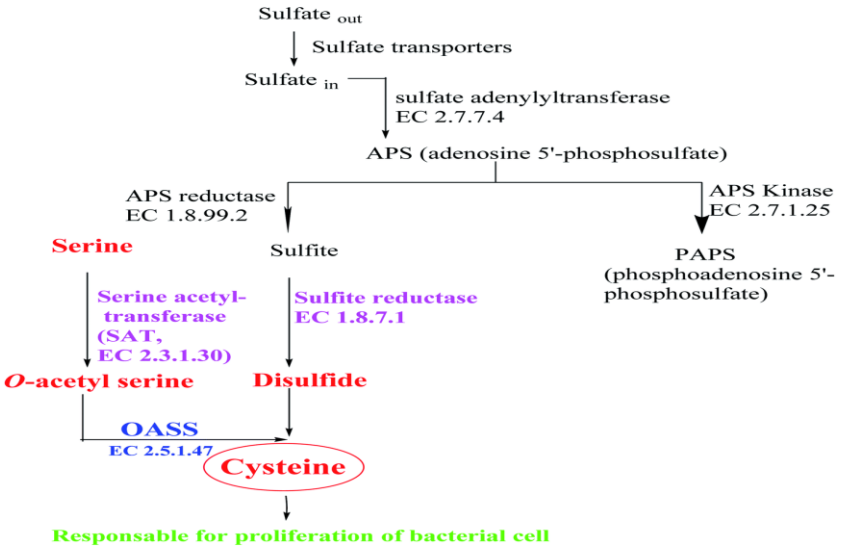


**Fig.19. Overview of sulphur assimilation and related biochemical pathways.**

**Targeting quorum sensing**

In many bacterial pathogens, population growth is controlled by quorum sensing (QS), which is an intercellular communication mechanism that controls phenotypic manifestations (such as virulence).64 Bacteria use this system to communicate with each other in a given population.65 It consists of a signal molecule (called autoinducer) continuously secreted by each type of bacteria, and when the defined concentration of this molecular messenger reaches a threshold, it will activate the QS control process. Several aspects of virulence are affected by QS, so that, the identification of small molecules that can interfere with this cell– cell mechanism is currently a field of great interest (Cooper, 2019).

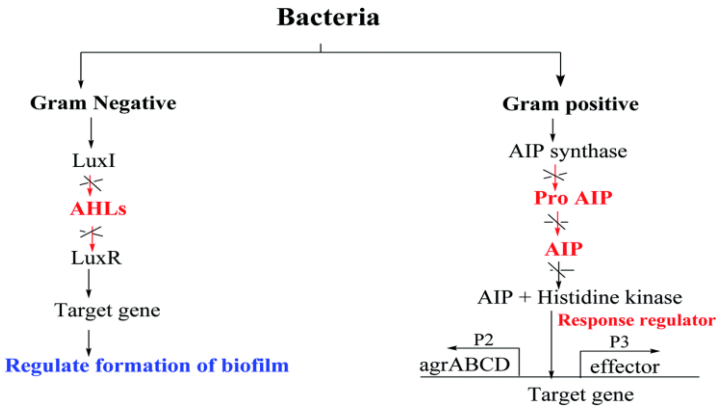


**Fig.20. The mechanisms of QS inhibiting agents in controlling bacterial biofilm formation.**

**10. Conclusion**

Heterocyclic compounds are one of the most significant types of organic molecules in medicinal chemistry and they are used as medications for various diseases. Numerous impressive accomplish-ments have shown that heterocyclic compounds have a wide range of therapeutic drug applications. Heterocyclic compounds are versatile synthetic targets and key structural units in organic synthesis and medicinal chemistry because of their exciting biological activities. The potential applications of heterocycles as anticancer, anti-inflammatory, antifungal, antibacterial, anti-Alzheimer's, antiviral, antidiabetic agents, *etc*., have attracted substantial interest within the pharmaceutical community. Interestingly, an increasing number of

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heterocycles have been identified as potential drug candi-dates in ongoing drug development.

**References**


1. A. Gupta, R. Singh, P. K. Sonar and S. K. (2016). Saraf, Biochem. Res. Int., 8086762.
2. Abushaheen, M. A., Fatani, A. J., Alosaimi, M., Mansy, W., George, M., Acharya, S., Rathod, S., Divakar, D. D., Jhugroo, C., Vellappally, S. and Khan, A. A., (2020). Antimicrobial resistance, mechanisms and its clinical significance. *Disease-a-Month*, 66(6), p.100971.
3. Agarwal N., Raghuwanshi S. K., Upadhyay D. N., Shukla P. K., Ram V. J. Suitably functionalised pyrimidines as potential antimycotic agents. *Bioorganic and Medicinal Chemistry Letters.* 2000,10(8):703–706.
4. Agarwal N., Srivastava P. and Raghuwanshi S. K. (2002). Chloropyrimidines as a new class of antimicrobial agents. *Bioorganic and Medicinal Chemistry.* 10(4):869–874.
5. Al Ali, F. (2023). Investigation of Nocturnal Atmospheric Reactivity of Furan Compounds with $NO_3$ Radicals in Simulation Chambers: Kinetics, Products, Mechanisms, and Secondary Organic Aerosol (SOA) Formation. Université du Littoral Côte d'Opale.
6. Ali, I., Nadeem Lone, M., A Al-Othman, Z., Al-Warthan, A., and Marsin Sanagi, M. (2015). Heterocyclic scaffolds: centrality in anticancer drug development. *Current drug targets*, *16*(7), 711-734.
7. Aljamali, N. M. (2014). Review in cyclic compounds with heteroatom. *Asian Journal of Research in Chemistry*, *7*(11), 975-1006.
8. Alvarez-Builla, J., and Barluenga, J. (2011). Heterocyclic compounds: An introduction. *Modern Heterocyclic Chemistry*, 1-9.
9. Anjaneyulu, B., Rao, G. D., and Nagakalyan, S. (2021). Synthesis and DFT studies of 1, 2-disubstituted benzimidazoles using expeditious and magnetically recoverable CoFe2O4/Cu (OH) 2 nanocomposite under solvent-free condition. Journal of Saudi Chemical Society, 25(12), 101394.
10. Annunziato G. (2019). Strategies to Overcome Antimicrobial Resistance (AMR) Making Use of Non-Essential Target Inhibitors: A Review. Int J Mol Sci. Nov 21,20(23):5844.
11. Arora, P., Arora, V., Lamba, H. S., and Wadhwa, D. (2012). Importance of heterocyclic chemistry: A review. *International Journal of Pharmaceutical Sciences and Research*, *3*(9), 2947.
12. Azab, M. E., Youssef, M. M. and El-Bordany, E. A. (2013). Synthesis and antibacterial evaluation of novel heterocyclic compounds containing a sulfonamido moiety. *Molecules, 18*(1), 832-844.
13. Baranwal, J., Kushwaha, S., Singh, S., and Jyoti, A. (2023). A review on the synthesis and pharmacological activity of heterocyclic compounds. *Current Physical Chemistry*, *13*(1), 2-19.
14. Basavegowda N and Baek K. H. (2022) Combination Strategies of Different Antimicrobials: An Efficient and Alternative Tool for Pathogen Inactivation. Biomedicines. 7,10(9):2219.
15. Bendi, A., Dharma Rao, G. B., Sharma, N., Tomar, R., and Singh, L. (2022). Solvent-Free Synthesis of Glycoside Annulated 1, 2, 3-Triazole Based Dihydropyrimidinones using Copper Ferrite Nanomaterials as Heterogeneous Catalyst and DFT Studies. Chemistry Select, 7(7), e202103910.
16. Bhardwaj, V., Gumber, D., Abbot, V., Dhiman, S., and Sharma, P. (2015). Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics. Rsc Advances, 5(20), 15233-15266.
17. Blakemore, D. C., Castro, L., Churcher, I., Rees, D. C., Thomas, A. W., Wilson, D. M., and Wood, A. (2018). Organic synthesis provides opportunities to transform drug discovery. *Nature chemistry*, *10*(4), 383-394.
18. Boerlin, P. and White, D.G., (2013). Antimicrobial resistance and its epidemiology. *Antimicrobial therapy in veterinary medicine*, pp.21-40.
19. Bonnett, S., Jee, J.A., Chettiar, S., Ovechkina, Y., Korkegian, A., Greve, E., Odingo, J. and Parish, T. (2023). Identification of 2-amino benzothiazoles with bactericidal activity against Mycobacterium tuberculosis. *Microbiology Spectrum*, 11(1), pp.e 04974-22.
20. Botta, M., Artico, M., Massa, S., Gambacorta, A., Marongiu, M. E., Pani, A., & La Colla, P. (1992). Synthesis, antimicrobial and antiviral activities of isotrimethoprim and some related derivatives. European journal of medicinal chemistry, 27(3), 251-257. Broughton, H. B., and Watson, I. A.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2575-2597 | ISSN:2251-6727

(2004). Selection of heterocycles for drug design. *Journal of Molecular Graphics and Modelling*, *23*(1), 51-58.

21. Bird, C. W., & Katritzky, A. R. (Eds.). (1984). Comprehensive heterocyclic chemistry: the structure, reactions, synthesis and uses of heterocyclic compounds, [in 8 volumes]. 4. Pergamon Press. Bruice PY. *Organic Chemistry.* 3rd edition. Singapore: Pearson Education, 2007.
22. Cooper, D. (2019). *Bacterial Attachment and Biofilms in Prosthetic Joint Infections* (Doctoral dissertation, Deakin University).
23. Daluge S.M., Skonezny P., Roth B. and Raukman B. S. (1986) 2,4-Diamino-5-(substituted) pyrimidine, useful as antimicrobials. U.S.Patent 4, 590, 271,.
24. Debono, M., M. Barnhart, C. B. Carrell, J. A. Hoffmann, J. L. Occolowitz, B. J. Abbott, D. S. Fukuda, R. L. Hamill, K. Biemann, and W. C. Herlihy. (1987). A21978C, a complex of new acidic peptide antibiotics: isolation, chemistry, and mass spectral structure elucidation. J. Antibiot. (Tokyo) 40:761-777.
25. DeFronzo R. A. (2010) Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going. *Am J Med* , **123**: S38–S48.
26. Dhingra, S., Rahman, N.A.A., Peile, E., Rahman, M., Sartelli, M., Hassali, M.A., Islam, T., Islam, S. and Haque, M., (2020). Microbial resistance movements: an overview of global public health threats posed by antimicrobial resistance, and how best to counter. *Frontiers in Public Health*, *8*, p.535668.
27. Domínguez, D.C. and Meza-Rodriguez, S.M., (2019). Development of antimicrobial resistance: Future challenges. In *Pharmaceuticals and Personal Care Products: Waste Management and Treatment Technology* (pp. 383-408). Butterworth-Heinemann.
28. Elderfield R. C. (1957) *Heterocyclic Compounds.* Vol. 6. New York, NY, USA: John Wiley and Sons.
29. Fischbach, M. A., and C. T. Walsh. (2009). Antibiotics for emerging pathogens. Science 325:1089-1093.f resistant organisms.
30. Fugitt, R., and R. Luckenbaugh. December (1978). 5-Halomethyl-3-phenylu-2-oxazolidinones. U.S. patent 4,128,654.
31. Gallis, H. A., Drew, R. H., Pickard, W. W. (1990). Amphotericin B: 30 years of clinical experience. *Rev. Infect. Dis.*, *12*(2), 308-329.
32. Gan, B. H., Gaynord, J., Rowe, S. M., Deingruber, T., and Spring, D. R. (2021). The multifaceted nature of antimicrobial peptides: Current synthetic chemistry approaches and future directions. *Chemical Society Reviews*, *50*(13), 7820-7880.
33. González-Bello, C. (2017) Antibiotic adjuvants—A strategy to unlock bacterial resistance to antibiotics. Bioorg. Med. Chem. Lett., 27, 4221–4228.
34. Gootz, T.D., (1990). Discovery and development of new antimicrobial agents. *Clinical microbiology reviews*, *3*(1), pp.13-31.
35. Grenni P., Ancona V. andCaracciolo A. B. (2018). Ecological effects of antibiotics on natural ecosystems: A review. *Microchem J.* , 136:25–39.
36. Hamed, A. A., Abdelhamid, I. A., Saad, G.R., Elkady, N. A. and Elsabee, M. Z. (2020). Synthesis, characterization and antimicrobial activity of a novel chitosan schiff bases based on heterocyclic moieties. *Int. J. Biol. Macromol*, *153*, 492-501.
37. Held, F. E., Guryev, A. A., Fröhlich, T., Hampel, F., Kahnt, A., Hutterer, C., Steingruber, M., Bahsi, H., von Bojničić-Kninski, C., Mattes, D.S., Foertsch, T.C., Nesterov-Mueller, A., Marschall, M.and Tsogoeva, S.B. (2017). Facile access to potent antiviral quinazoline heterocycles with fluorescence properties *via* merging metal-free domino reactions. *Nat. Commun. 8*(1), 15071.
38. Holmes, A. H., Moore, L. S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., Guerin, P. J. and Piddock, L. J. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet, 387*(10014), pp.176-187.
39. Hussain, A., Alajmi, M. F., Lone, M. A., and Wani, W. A. (2023). Therapeutic Rhodium Complexes. Springer.
40. Ito S, Masuda K., Kusano S. (1991) Pyrimidine derivative, process for preparing same and agricultural or horticultural fungicidal composition containing same. U.S. Patent 4, 988, 704.

41. Jabbar, H. S., Al-Edan, A. K., Kadhum, A. A. H., and Sobri, M. (2019). Synthesis and characterization of imidazole derivatives and catalysis using chemical pharmaceutical compounds. J. Adv. Res. Dyn. Control Syst, 11, 1928-1939.
42. Jaiswal, S. (2019). Five and Six Membered Heterocyclic Compound with Antimicrobial Activity. J. Mod. Trends Sci. Technol, 5, 36-39.
43. Japanese Ministry of Health Labour and Welfare. The National Health and Nutrition Survey 2007. Available from URL: http://www.mhlw.go.jp/houdou/2008/12/h1225-5.html. (in Japanese). Accessed 30 November 2011.
44. Jiang, M. and Li, Yongmei and Gu, G. W. (2005). Study on toxicity of nitrogenous heterocyclic compounds to aquatic organisms. Acta Scientiae Circumstantiae. 25. 1253-1258.
45. Kappe CO. (1993). 100 years of the biginelli dihydropyrimidine synthesis. *Tetrahedron.*,49(32):6937–6963.
46. Katz, M. L., L. V. Mueller, M. Polyakov, and S. F. Weinstock. (2006). Where have all the antibiotic patents gone? Nat. Biotechnol. 24:1529-1531.
47. L. Santos and F. Ramos, Int. J. Antimicrob. Agents, 2018, 52(2), 135–143.
48. Liu, Y., Qing, L., Meng, C., Shi, J., Yang, Y., Wang, Z., Han, G.,Wang, Y., Ding, J., Meng, L-H. and Wang, Q. (2017). 6-OHphenanthroquinolizidine alkaloid and Its derivatives exert potent anticancer activity by delaying S phase progression. *J. Med. Chem. 60*(7), 2764-2779.
49. M. Boolchandani, A. W. D`Souza and G. Dantas (2019). Nat. Rev. Genet. 20(6), 356–370.
50. M. S. Saini, A. Kumar, J. Dwivedi, R. Singh (2013). *International Journal of Pharma Sciences and Research*, 4(3), 66–77.
51. Mahmood, R. M. U., and Aljamali, N. M. (2020). Synthesis, spectral investigation, and microbial studying of pyridine-heterocyclic compounds. *Eur. J. Mol. Clin. Med*, *7*(11), 4444-4453.
52. Marquais-Bienewald S., Holzol W., Preuss A. and Mehlin A. (2006). Use of substituted 2,4-bis (alkylamino) pyrimidines. U.S.Patent, 0188453 A1.
53. Mir, R. H., Mohi-ud-din, R., Wani, T. U., Dar, M. O., Shah, A. J., Lone, B., and Masoodi, M. H. (2021). Indole: a privileged heterocyclic moiety in the management of cancer. Current Organic Chemistry, 25(6), 724-736.
54. Mittal, R. K., Aggarwal, M., Khatana, K., and Purohit, P. (2023). Quinoline: Synthesis to application. Medicinal Chemistry, 19(1), 31-46.
55. Murugaiyan, J., Kumar, P. A., Rao, G. S., Iskandar, K., Hawser, S., Hays, J. P. and van Dongen, M. B. (2022). Progress in alternative strategies to combat antimicrobial resistance: Focus on antibiotics. Antibiotics, 11(2), 200.
56. Nakagawa Y., Bobrov S., Semer C.R., Kucharek T.A. and Harmoto M. (2004) Fungicidal pyrimidine derivatives. U.S. Patent 6, 818,631 B1.
57. Narayan, Y., Kumar, A., and Parveen, A. (2024). "Thiophene": A Sulphur Containing Heterocycle as a Privileged Scaffold. Letters in Drug Design and Discovery, 21(11), 1922-1935.
58. Novak, R., and D. M. Shlaes. (2010). The pleuromutilin antibiotics: a new class for human use. Curr. Opin. Invest. Drugs 11:182-191.
59. Osmaniye, D., Sağlık, B.N., Acar Çevik, U., Levent, S., Kaya Çavuşoğlu, B., Özkay, Y., Kaplancıklı, Z.A. and Turan, G. (2019). Synthesis and AChE inhibitory activity of novel thiazolylhydrazone derivatives. *Molecules,* 24(13), 2392.
60. Prakash, H., Ghosh, A. K., Rudramurthy, S. M., Singh, P., Xess, I., Savio, J. and Chakrabarti, A. (2019). A prospective multicenter study on mucormycosis in India: Epidemiology, diagnosis, and treatment. Medical mycology, 57(4), 395-402.
61. Projan, S. J. (2003). Why is big Pharma getting out of antibacterial drug discovery? Current opinion in microbiology, 6(5), 427-430.
62. Puri, S. and Negi, D.S. (2022). Simple to Complex Amide Derivatives as Potent Anti-Tuberculosis Agents: A Literature Survey of the Past Decade. *Chemistry Select*, *7*(43), p.e202202584.
63. Purssell E. (2020). Antimicrobials. In: Hood P, Khan E, editors. *Understanding Pharmacology in Nursing Practice.* Switzerland: Springer Nature. pp. 147–165.
64. Fair, R. J., & Tor, Y. (2014). Antibiotics and bacterial resistance in the 21st century. Perspectives in medicinal chemistry, 6, PMC-S14459.
65. Reis, R.A., Li, H., Johnson, M. and Sobrado, P. (2021). New frontiers in flavin-dependent

monooxygenases. *Archives of Biochemistry and Biophysics*, *699*, p.108765.

66. Spellberg, B., J. H. Powers, E. P. Brass, L. G. Miller, and J. E. Edwards, Jr. (2004). Trends in antimicrobial drug development: implications for the future. Clin. Infect. Dis. 38:1279-1286.
67. Starkey, M., Lepine, F., Maura, D., Bandyopadhaya, A., Lesic, B., He, J., Kitao, T., Righi, V., Milot, S. and Tzika, A. (2014). Identification of Anti-virulence Compounds That Disrupt Quorum-Sensing Regulated Acute and Persistent Pathogenicity. PLoS Pathog. 10, e1004321.
68. Tang, K.C., Maddox, S.M., Backus, K.M. and Raj, M. (2022). Tunable heteroaromatic azoline thioethers (HATs) for cysteine profiling. *Chemical science*, *13*(3), pp.763-774.
69. Tenover, F.C., (2006). Mechanisms of antimicrobial resistance in bacteria. *The American journal of medicine*, *119*(6), pp.S3-S10.
70. Tighadouini, S., Radi, S., Benabbes, R., Youssoufi, M.H., Shityakov, S., El Massaoudi, M., Garcia, Y. (2020). Synthesis, biochemical characterization, and theoretical studies of novel β-keto-enol pyridine and furan derivatives as potent antifungal agents. *ACS Omega, 5*(28), 17743-17752.
71. Tursky, M., Lorentz-Petersen, L. L., Olsen, L. B. and Madsen, R. (2010). Iridium-and ruthenium-catalysed synthesis of 2, 3-disubstituted indoles from anilines and vicinal diols. *Organic and Biomolecular Chemistry*, *8*(24), 5576-5582.
72. Veligeti, D. S. Ramakrishna, R. B. Madhu, J. S. and Anireddy, *J. Fluorine Chem.* 2022, 257–258, 109989.
73. Wilkes, H., Jarling, R., and Schwarzbauer, J. (2020). Hydrocarbons and lipids: an introduction to structure, physicochemical properties, and natural occurrence. Hydrocarbons, Oils and Lipids: Diversity, Origin, Chemistry and Fate, 3-48.
74. Wilson, C., Gardner, J.M.F., Gray, D.W., Baragana, B., Wyatt, P.G., Cookson, A., Thompson, S., Mendoza-Martinez, C., Bodkin, M.J., Gilbert, I.H. and Tarver, G.J. (2023). Design of the Global Health chemical diversity library v2 for screening against infectious diseases. *PLoS neglected tropical diseases*, *17*(12), p.e0011799.