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Advancements in medicinal chemistry: A comprehensive review of antibiotics, sulfonamides, β-lactams, and Azo compounds

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Abstract
This study offers an in-depth examination of the notable advancements in medicinal chemistry, emphasizing the Synthesis and mechanisms of many classes of bioactive chemicals. The discourse underscores the progression of antibiotic drugs, specifically focusing on sulfonamides, β-lactams, and azo compounds. The article elucidates the mechanisms of action, therapeutic applications, and obstacles related to these drugs while also confronting developing issues such as antimicrobial resistance and the necessity for innovative therapeutic tactics. Sulfonamides and β-lactams continue to be essential in the management of bacterial infections, notwithstanding rising resistance, with their intricate modes of action elucidated. Azo compounds are investigated for their diverse applications, including antibacterial and anticancer characteristics. The analysis underscores the necessity of ongoing innovation in medication research to address resistant infections and enhance therapeutic results. This study discusses the significance of these discoveries for future research and clinical applications, rendering it a significant resource for academics and practitioners in medicinal chemistry.

Keywords: Antibiotics, anticancer activity, antimicrobial resistance, Azo compounds, medicinal chemistry, sulfonamides, β-lactams

1. Introduction

Fundamentals of Medicinal Chemistry

Medical chemistry is a discipline classified by IUPAC as a chemistry-based field that encompasses elements of biological and medical sciences. It pertains to the creation, discovery, design, identification, and Synthesis of biologically active compounds, the research of their metabolism, the elucidation of their mode of action, and the development of structure-activity relationships" [Fernandes, 2018] [1].

The active compounds utilized in medical applications are predominantly organic compounds that exhibit enhanced properties, such as reduced side effects. They are complementary in shape and charge to the biomolecular targets with which they interact, thereby facilitating binding [Ekinci, 2012] [2]. Organic compounds were synthesized over a century ago with the objective of developing novel pharmaceuticals. Chloral hydrate (1869) and urethane (1885), as well as the antipyretics phenacetin (1888) and acetylsalicylic acid (1897), are early examples of chemicals with good therapeutic characteristics, as illustrated in Fig. 1 [Klebe, 2013] [3].

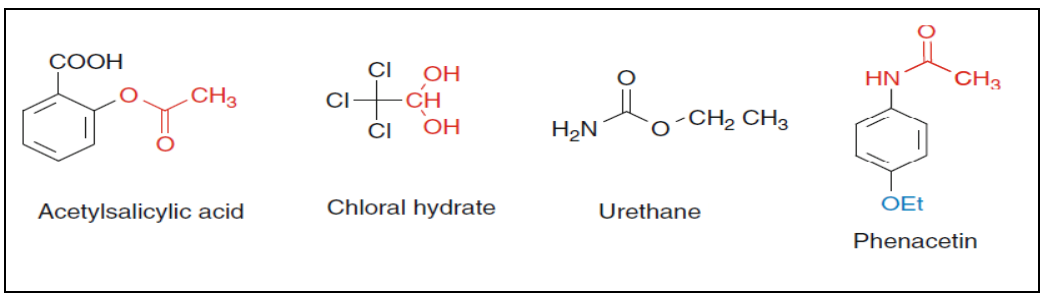


Fig 1: Some bioactive organic compounds

Contemporary drug development involves the identification of screening hits and the optimization of these hits to enhance affinity, selectivity, effectiveness, metabolic stability, and oral bioavailability. Upon identifying a molecule that fulfills all these criteria, the drug development process will commence, leading to clinical trials.

Jian Li and colleagues authored an article titled “Chemical Structure-Related Drug-Like Criteria of Globally Approved Drugs.” They identified significant structure-related criteria pertinent to drug-likeness, specifically: (1) the optimal quantities of aromatic and non-aromatic rings are 2 and 1, respectively; (2) the preferred functional groups for candidate drugs are typically -OH, -COOR, and -COOH, but not -CONHOH, -SH, -CHO, or -SO_3H. The -F functional group is beneficial for central nervous system medications, while the -NH_2 functional group is good for anti-infective and anticancer therapies. [Zhou & Zhong, 2017] [4].

Antibiotic Agents

Antibiotic medications are arguably the most effective class of pharmaceuticals discovered to enhance human health [Martinez, 2009] [5]. This precipitated a profound transformation not only in the treatment of infectious diseases but also in the destiny of humankind [Saga and Yamaguchi, 2009] [6]. The term "antibiotic" was introduced by Selman Waksman, who discovered streptomycin. He defined it as any class of organic molecule that either kills bacteria (bactericidal) or inhibits their growth (bacteriostatic) through specific interactions with a bacterial target. In contrast, "antimicrobial" agents refer to substances that either eliminate or impede the growth of microbes, encompassing antibiotics, antiviral agents, antifungal agents, and antiparasitic drugs [Manageiro, 2011; Hashemi *et al*., 2013] [7, 8].

Antibiotic medications are typically categorized into two types: synthetic antibiotics, such as sulfonamides and quinolones, and natural antibiotics, produced by bacteria, such as aminoglycosides [Gangle, 2005] [9]. Initially, naturally occurring substances were categorized as antibiotics, while synthetically manufactured compounds were designated as chemotherapeutics [McGrane, 2000] [10]. Numerous antibiotic compounds, both natural and semi-synthetic as well as synthetic, are employed in the treatment of infections [Kumar and Singh, 2013] [11].

The inaugural antimicrobial agent was salvarsan, a treatment for syphilis synthesized by Ehrlich in 1910, Fig. 2. In 1935, Domagk and other researchers produced sulfonamides. Penicillin was discovered in 1928 from the fungus Penicillium notatum by Alexander Fleming, with clinical trials first undertaken on humans in 1940 [Russell, 2004; Aminov, 2010; Saga and Yamaguchi, 2009] [12, 13, 6].

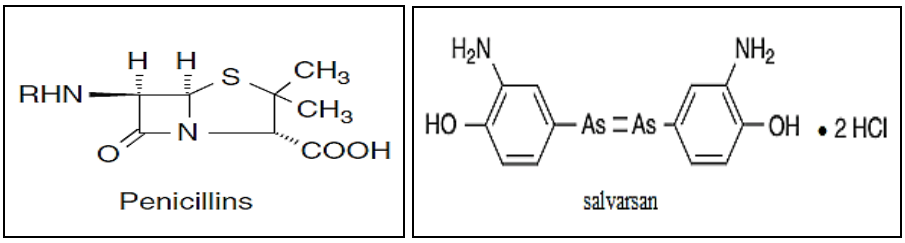


Fig 2: Chemical structures of penicillin and salvarsan

Since the advent of penicillin, antibiotics have emerged as fundamental components of contemporary medicine. Without antibiotics, many currently prevalent medications and medical procedures—such as chemotherapy, organ transplants, joint surgeries, or the care of premature infants—would be unfeasible [Reinitzer *et al*., 2013] [14]. Over the following two decades, novel types of antibacterial drugs were created consecutively. In 1944, streptomycin was extracted from the soil bacteria Streptomyces griseus. Subsequently, chloramphenicol, tetracycline, macrolide, and glycopeptide were isolated from soil microorganisms. The synthesized antibacterial drugs nalidixic acid and quinolone were obtained in 1962, as shown in Fig. 3 [Saga and Yamaguchi, 2009] [6]. Until the 1970s, numerous novel antibacterial agents were created; nevertheless, the final entirely new classes of antibacterial medications were identified during the 1980s [WHO, 2014] [15].

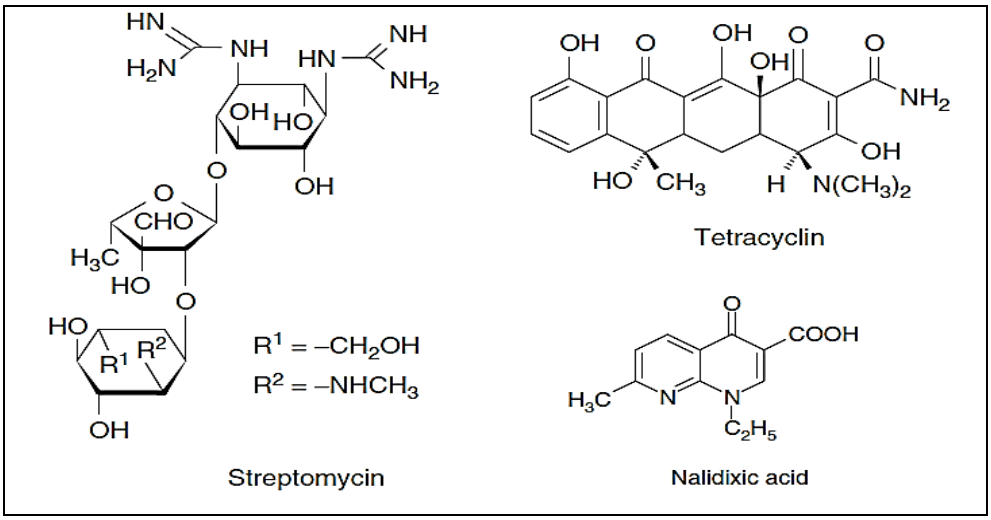


Fig 3: Chemical structures of some antimicrobial drugs

Classification of Antibiotics

The principal kinds of antibiotics can be classified according to their mechanism of antibacterial action, method of administration (injectable, oral, and topical), and spectrum of activity. Antibiotics can generally be categorized into three categories: inhibitors of cell wall synthesis, inhibitors of protein synthesis, and inhibitors of nucleic acid synthesis (Table 1) [Gangle, 2005] [9].

Antibiotics of the same structural class typically exhibit comparable efficacy, toxicity, and potential allergic side effects. Common groups of antibiotics based on chemical structures include beta-lactams, macrolides, tetracyclines, quinolones, aminoglycosides, sulfonamides, glycopeptides, and oxazolidinones [Etebu and Arikekpar, 2016] [16].

Table 1: Major Classes and Examples of Antibiotics [Gangle, 2005].

Inhibitor of	**Cell wall synthesis.'**	**β- lactams (penicillins), Glycopeptides (vancomycin)**
	Protein synthesis'	Aminoglycosides (streptomycin), Macrolides, Tetracyclines
	Nucleic acid synthesis'	Sulfonamides (sulfamethoxazole), Quinolones (ciprofloxacin)

Mechanisms of Action of Antibiotics

Antibiotics suppress or eradicate vulnerable bacteria through five primary mechanisms. Figure 4: 1- Inhibition of cell wall synthesis. 2- Analysis of cell membrane structure or function. 3- Inhibition of the structure and function of nucleic acids. 4- Inhibition of protein synthesis. 5-Obstruction of essential metabolic processes [Kohanski *et al*., 2010] [17].

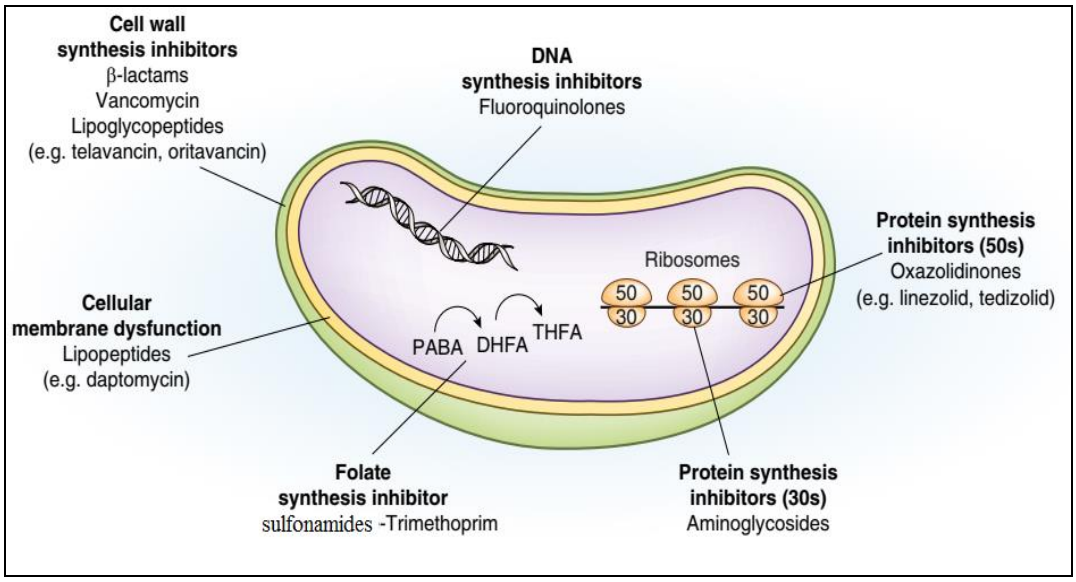


Fig 4: Mechanisms of Antibiotic Classes [Eyler and Shvets, 2019] [18].

1. Inhibition of cell wall synthesis

Most bacterial cells are encased in a hard coating of peptidoglycan (PG), which safeguards the cells from typically harsh environmental conditions. The bacteria synthesize peptidoglycan by the action of trans glycosylases and transpeptidases. These two enzymes add disaccharide pentapeptides to elongate the glycan strands of existing peptidoglycan molecules and also cross-link strands of immature peptidoglycan units. Antibiotics such as penicillins and carbapenems can obstruct the cross-linking of peptidoglycan units by blocking peptide bond formation [Park and Uehara, 2008; Josephine *et al*., 2004] [19, 20].

2. Analysis of cell membrane structure or function

The classes of antibiotics that disrupt bacterial cell membranes are specific to each microbial group, determined by the variations in the types of lipids present in their cell membranes. For instance, polymyxins and daptomycin diffuse past the outer membrane and cell wall of sensitive cells to reach the cytoplasmic membrane. They adhere to the cytoplasmic membrane, causing disruption and weakening. This leads to the cytoplasm leaking from the cell, culminating in cell death [Tenover, 2006] [21].

3. Inhibition of the structure and function of nucleic acids

Disruption of nucleic acid production is detrimental to bacterial cells. Antibiotics disrupt nucleic acid synthesis by impairing replication or inhibiting transcription. DNA replication entails the unwinding of the double helix structure, facilitated by helicase enzymes. The quinolone antibiotics interfere with the helicase enzyme, hence disrupting its role of unwinding DNA [Etebu and Arikekpar, 2016] [16].

4. Inhibition of protein synthesis

Proteins are responsible for structural composition, metabolic and physiological functions, and responses to unfavorable situations. Numerous antibiotics function by attaching to bacterial ribosomes, thereby obstructing the protein synthesis mechanism (translation) within the cell. Antibiotics that bind to the 30S ribosomal subunit include aminoglycosides, tetracyclines, and macrolides [Etebu, 2013; Brodersen *et al*., 2000; Carter *et al*., 2000] [22, 24, 24].

5. Obstruction of essential metabolic processes

The anti-metabolite antibiotics competitively disrupt critical metabolic pathways within the bacterial cell. The principal medications in this category are sulfonamides and trimethoprim. The Synthesis of amino acids and purines in bacteria relies on tetrahydrofolate, a derivative of folic acid. The Synthesis of folic acid is facilitated by two enzymes, dihydrofolate reductase and dihydrofolate synthase, which are blocked by sulfa medications [Walsh, 2000] [25].

Antibiotic Resistance: Antibiotics are regarded as "miracle drugs" that effectively combat bacterial illnesses. However, the extensive use of antibiotics has led to the emergence of antibiotic-resistant pathogenic bacteria, which began to manifest within a few years of their introduction. The prospect of discovering a definitive cure for bacterial diseases has been revealed as a fantasy. In 2004, almost 70% of pathogenic bacteria showed resistance to at least one of the antibiotics in current usage [Penesyan *et al*., 2015; Ashraf and Shah, 2011] [26, 96].

Antimicrobial resistance encompasses the resistance of bacteria, viruses, fungi, and parasites, defined as the capacity of a microbe to endure the presence of an antibiotic [WHO, 2017; Heskett and Keffaber, 2016] [28, 29]. Humans have unknowingly exacerbated resistance through incorrect prescriptions and excessive antibiotic use [Fair and Toi, 2014; Ventola, 2015] [30, 31].

Antimicrobial resistance can be categorized into three groups: intrinsic, mutational, and acquired resistance. Intrinsic resistance refers to an intrinsic resistance that naturally occurs in microorganisms. Mutational resistance arises from a spontaneous chromosomal mutation that generates a genetically modified bacterial population resistant to the treatment. Acquired resistance pertains to the acquisition of a genetic element encoding antibiotic resistance from another bacteria. This process can occur via transduction, which is the mechanism by which exogenous DNA is transferred from one bacterium to another by the intervention of a bacteriophage [Walker, 1996; Kotsiftopoulos, 2017] [32, 33].

The prevalent mechanisms of antibiotic resistance include drug inactivation through hydrolysis (e.g., via β-lactamase) or modification (e.g., aminoglycoside resistance), alteration of intracellular drug targets, rendering them unrecognizable to the antibiotic (e.g., through mutations in DNA gyrase in fluoroquinolone resistance); the establishment of permeation barriers; and active efflux of antibiotics from the cell via membrane-bound efflux transporters. They may either augment the production of the target metabolite [Okonko *et al*., 2008; Nikaido, 1998; Paulsen, 2003] [34, 35, 36].

Sulfonamides: Sulphonamides are the inaugural successful chemotherapeutic medicines employed for bacterial infections in humans. Since their discovery, sulfonamides have been extensively utilized for the prophylaxis and treatment of bacterial infections. Although they are bacteriostatic rather than bactericidal, their significance resides in their capacity to inhibit or prevent growth in wounds or infected organs without considerable toxicity to normal tissues. [Mansour, 2014] [37]. In chemistry, sulphonamide refers to the SO_2NH_2 functional group. Compounds that contain this functional group are referred to as sulphonamides. The general formula of sulphonamides is RSO_2NH_2, as illustrated in Figure (5). The term sulfonamide is typically employed as a generic designation for the derivatives of para-aminobenzene sulfonamide. The nitrogen atom of $-SO_2NH_2$ is designated as 1, and the $-NH_2$ group is designated as 4 [Lavanya, 2017] [38].

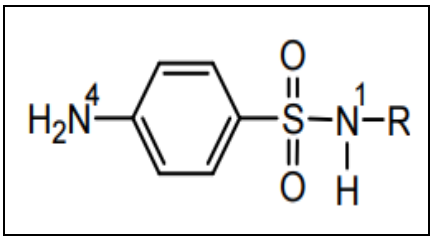
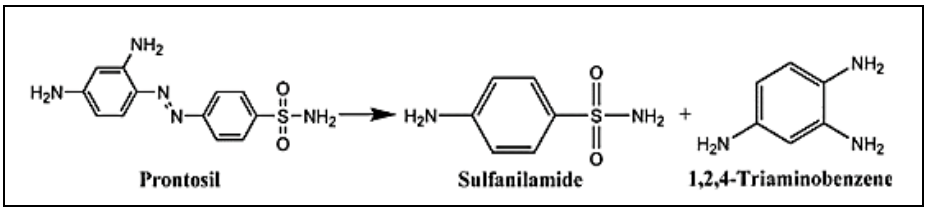


Fig 5: Chemical Structure of sulfonamides

The discovery of the antibacterial properties of prontosil by Gerhard Domagk in the early 1930s signifies the commencement of chemotherapy development. He discovered that "Prontosil" was effective in treating mice inoculated with streptococci. Prontosil is an azo dye characterized by a sulfonamide structure. In the human body, prontosil is metabolized by intestinal bacteria to produce sulfanilamide, the true antibacterial agent, as indicated in equation (1) [Tacic *et al*., 2017] [39]. The inaugural clinical trial of sulfa drugs occurred in 1936, and subsequent clinical evaluations yielded compelling evidence that various sulfa compounds were efficacious in treating puerperal fever, scarlet fever, meningitis, gonorrhea, and erysipelas. Since then, thousands of sulfa drugs have been synthesized and tested [Swarbrick *et al*., 2008] [49].



….. eq. (1)

Sulfanilamide and its derivatives exhibit a broad spectrum of pharmacological activities, including oral hypoglycemic, antileprotic, anti-epileptic, anti-hypertensive, antibacterial, anti-protozoal, antifungal, anti-retroviral, and anti-inflammatory properties. They are utilized as diuretics, and research has indicated that sulfonamides can also inhibit cancerous cells [El-Din, 2000; Ajeet *et al*., 2015] [41, 42].

Classification of Sulfonamides

The majority of currently utilized sulfonamides are N1-derivatives. According to structural differences, sulfonamides can be categorized into three classes as follows:

a. Aryl derivatives (sulfamethoxazole, hydrochlorothiazide, sulfanilamide).
b. Heterocyclic derivatives comprising six-membered rings (e.g., pyridine, pyrimidines).
c. Heterocyclic derivatives with five-membered rings (e.g., thiazole, oxazole, isoxazole) [Sonu *et al*., 2017] [43].

One of the most comprehensive classifications includes absorbable oral sulfonamides, non-absorbable oral sulfonamides, and topical sulfonamides.

Based on the duration of action and half-life, absorbable oral sulfonamides can be categorized into:

Short-acting sulfonamides: possessing a half-life of fewer than 10 hours (e.g., sulfisoxazole and sulfanilamide, utilized for the treatment of urinary tract infections).

- Intermediate-acting sulfonamides possess a half-life ranging from 10 to 24 hours (e.g., sulfamethoxazole, sulfacetamide, and sulfadiazine), utilized for many illnesses, including invasive aspergillosis in AIDS

patients.

- Long-acting sulfonamides, characterized by a half-life exceeding 24 hours (e.g., sulfadimethoxine and sulfadoxine), have been utilized in the treatment of ulcerative colitis [Sonu *et al*., 2017; Shanbhag and Vagdevi, 2016] [43, 44]. The structures of various significant types of sulfonamides are illustrated in Fig. 6.

Distinct sulfonamides exhibit specific effects. Sulfadiazine is extensively distributed throughout the central nervous system. Sulfisoxazole is utilized for the treatment of urinary tract infections and the prophylaxis of rheumatic fever in children with a penicillin allergy. Sulfamethoxazole is frequently utilized alongside trimethoprim for synergistic effects in the treatment of urinary tract infections. Sulfacetamide is applied topically to the eyes for the treatment of conjunctivitis or corneal ulcers. Sulfasalazine is utilized as a therapeutic agent for inflammatory bowel disease. Silver sulfadiazine is available as a topical cream for the treatment of burn patients. [Kester and Vrana, 2012] [45].

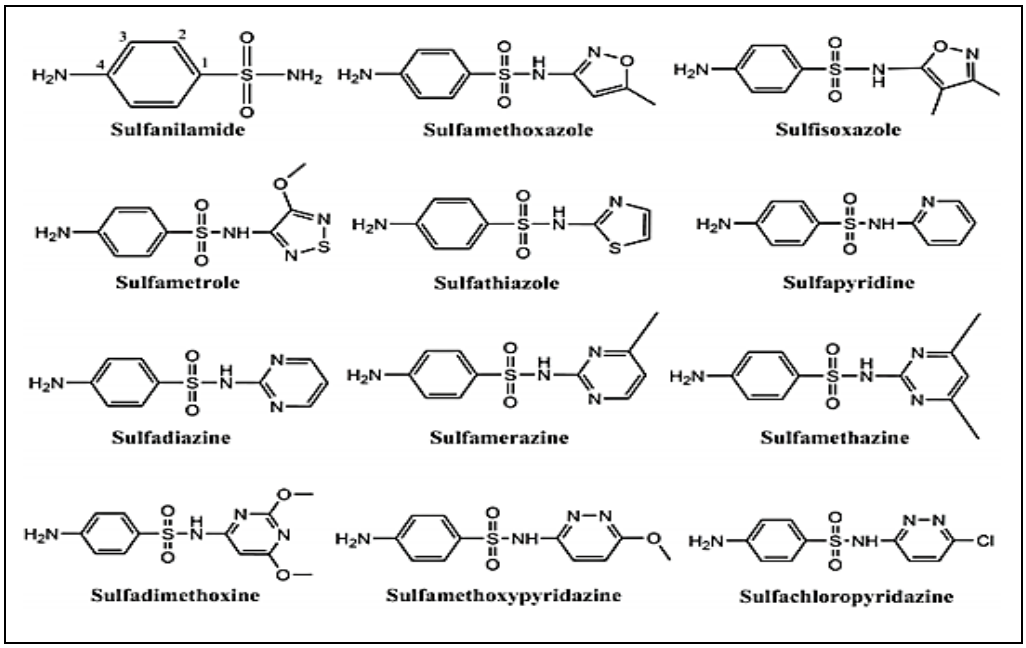


Fig 6: Structures of various sulfa drugs

A limited quantity of 'privileged building blocks', frequently identified in strong pharmacological compounds, includes the SO_2NH_2 moiety. As illustrated in Fig. 7, a minimum of 22 commonly utilized medicines provide this functionality. Compounds 1-3 and 5 are classified as 'drugs' mostly utilized in the treatment of glaucoma, neuromuscular disorders, altitude sickness, and other conditions. Sulthiame 4 is an anti-epileptic medication, whereas 6 and 7 are topically active anti-glaucoma medicines. Zonisamide 8, an aliphatic sulfonamide, is extensively utilized as an anti-epileptic medication. Sulpiride 9 is an antipsychotic agent, as noted by [Carta *et al*., 2012] [46].

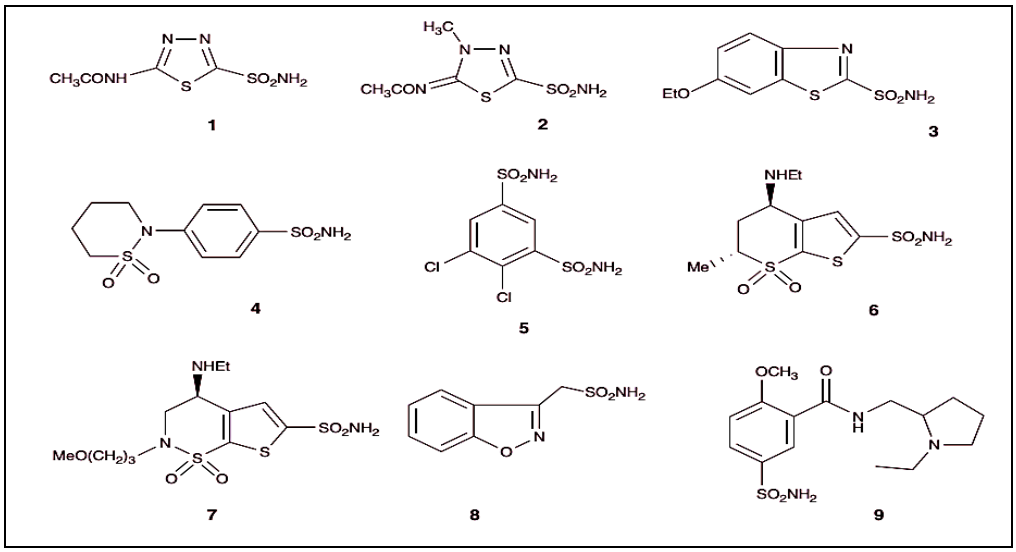


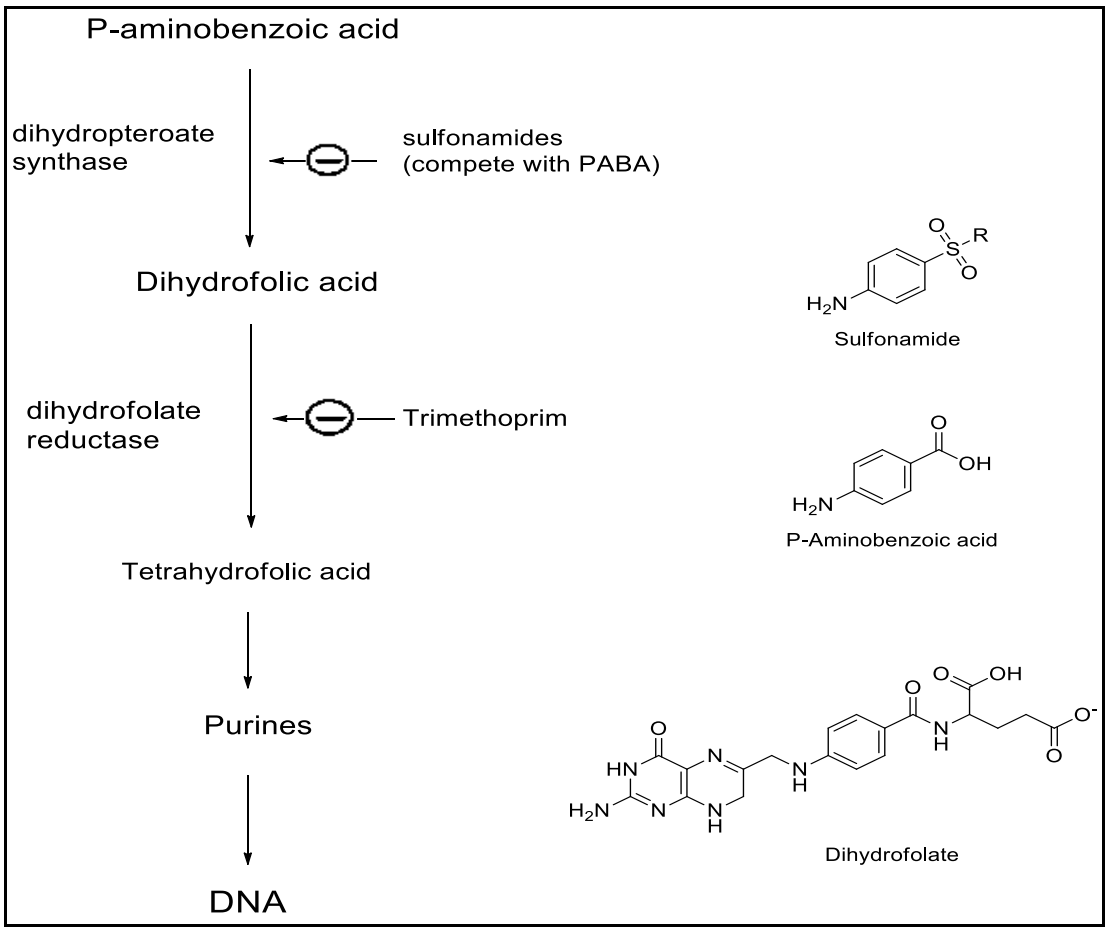
Fig 7: Clinically Used Sulfonamides

Mechanism of Action and Resistance of Sulfonamides

Sulphonamide-sensitive microorganisms require p-Aminobenzoic acid (PABA) for folic acid production, which is crucial for DNA and RNA synthesis. Due to the structural similarity of sulphonamides with PABA, sulphonamides competitively inhibit PABA. This induces folic acid shortage, leading to the cessation of bacterial growth and cell division. Folates are essential for the production of purines and

pyrimidines in humans [Lavanya, 2017; Abdul Qadir *et al*., 2015; Kerns, 2001] [38, 72, 48].

Effective targets for antimicrobials are crucial enzymes present in the bacterium but absent in the host organism. Moreover, it is advantageous for the enzyme to be documented as a therapeutic target [Swarbrick *et al*., 2008] [49]. An examination indicates that bacteria produce folic acid through various enzymes, including dihydropteroate synthetase, which facilitates the binding of p-aminobenzoic acid to a pteridine ring system. Sulfonamides inhibit this enzyme, which is integral to the bacterial folate biosynthetic pathway (Scheme 1). This enzyme is absent in humans, rendering it unaffected by sulfonamides. [Williamson *et al*., 2007] [50].



Scheme 1: Mechanism of Sulfonamides Action

Various mechanisms of drug resistance have developed for sulfonamides, a situation that is not novel for antibiotics in general. Resistance has arisen due to overprescription, insufficient utilization of synergistic drugs, and inadequate patient adherence to medication regimens [Sikarwar *et al*., 2016] [87].

The method of action enables bacteria to circumvent the antibacterial effects of sulfonamides by acquiring folates from their environment, analogous to human acquisition. Resistance may arise from the acquisition of a plasmid-encoded mutant dihydropteroate synthase with diminished affinity for sulfonamides. The chromosomal mutation in genes may induce the substitution of the phenylalanine residue at position 28 with the isoleucine residue, resulting in a decreased affinity of the enzyme for sulfonamides [Skold, 2001; Kerns, 2001] [52, 48].

To combat bacterial resistance to sulfonamides, combinations of certain sulfonamide medicines, such as Sulfadiazine, Sulfamerazine, and Sulfathiazole (Triple sulfa), can be employed [Tacic *et al*., 2017] [39].

Metabolism and Excretion of Sulfonamides

In humans, the metabolic transformation of sulfonamides primarily occurs in the liver through the acetylation of the amino group. The resultant N-acetyl metabolites are inactive and can be eliminated in the urine alongside the unmodified sulfonamides [Davis, 1943] [53]. The rate and method of sulfonamide excretion are contingent upon the specific drug, provided dosage, treated species, and route of administration [Sukul and Spiteller, 2006] [54].

Side Effects of Sulfonamides

Sulfonamides induce adverse effects in 4-6% of the general population and 50-60% of patients with HIV infection. Hypersensitivity (sulfa allergy) is the most prevalent adverse reaction to sulfonamides. Documented side effects encompass fever (in 1-2% of patients), anaphylactic shock, systemic vasculitis, pneumonia, hepatitis, myocarditis, and interstitial nephritis. Patients undergoing treatment with sulfonamides may experience several severe blood diseases, including acute hemolytic anemia, agranulocytosis, and aplastic anemia; nevertheless, these occurrences are exceedingly rare [Gruchalla, 1999; Kerns, 2001] [55, 48].

***β*-Lactam Antibiotics**

β-Lactam antibiotics remain the primary option for treating numerous bacterial infections. The primary classes of beta-lactams include penicillins, monobactams, carbapenems, cephalosporins (cephems), and carbacephems (Table 2) [Ariza *et al*., 2015] [56]. Until 2003, when assessed by sales, over fifty percent of all commercially available antibiotics in use were β-lactam compounds. [Elander, 2003] [57]. β-lactam antibiotics provide a broad spectrum of activity and exhibit

low toxicity due to their mechanism of action, which targets the bacterial cell wall, a structure absent in higher species. They disrupt proteins critical for the production of the bacterial cell wall, thereby either killing or inhibiting their growth. In addition to their significance as antibiotics, β-lactams have garnered substantial interest in chemical synthesis as flexible synthetic intermediates and chiral synthons. This class of antibiotics contains a 3-carbon and 1-nitrogen ring (β-lactam ring) that is extremely reactive. Figure 8. The ring tension of the β-lactam framework promotes ring-opening processes, a unique characteristic that has been utilized for the Synthesis of various pharmacologically active molecules [Heesemann, 1993; Kamath and Ojima, 2012] [5, 59].

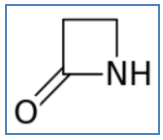
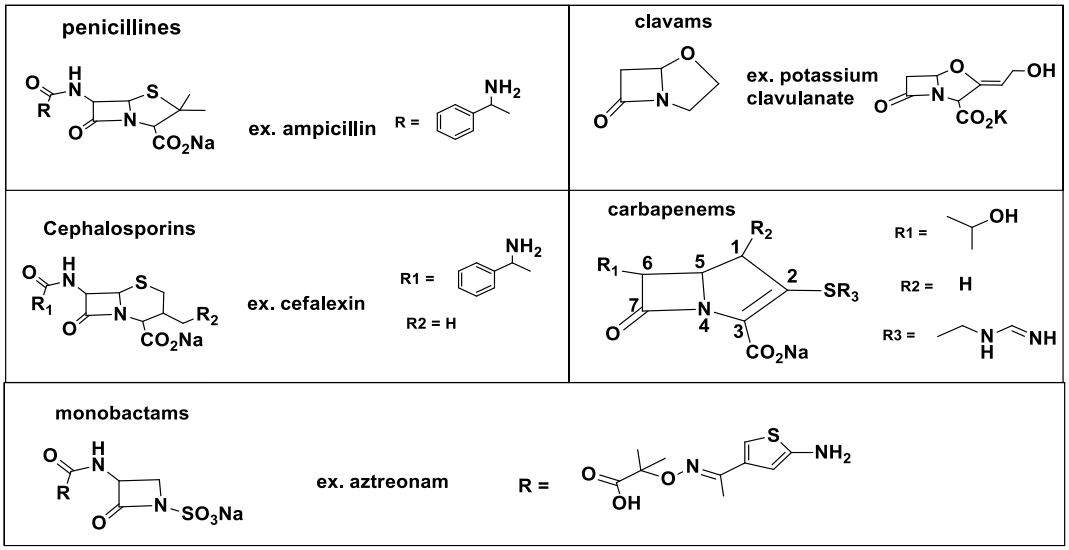


Fig 8: Chemical Structure of a β -Lactam Ring

Carbapenems have a wider spectrum of antibacterial action among β-lactams compared to other groups. Carbapenems have been demonstrated to have greater stability against the activity of several β-lactamases, attributable to their unique stereochemistry at the C5-C6 bond and the presence of the α-hydroxyethyl group (Table 2) [Manageiro, 2011] [7].

Table 2: Chemical Structure of Some β-Lactam Antibiotics



Mechanism of Action and Resistance of β-lactams

β-lactams function as irreversible inhibitors by obstructing the bacterial enzymes transpeptidases and carboxypeptidases, collectively referred to as penicillin-binding proteins (PBPs), which catalyze the processes involved in peptidoglycan production for bacterial cell wall formation. The suppression of cell wall production results in cell lysis. The final stage of cell wall synthesis involves the cross-linking of peptidoglycans between the carboxyl group of D-alanine in one peptidoglycan chain and an amino group in the next chain, a reaction catalyzed by transpeptidase. The cross-linking of contiguous glycan chains induces the stiffness of the cell wall. The binding of penicillin to the transpeptidase enzyme results in the formation of an acyl-enzyme complex through the cleavage of the penicillin β-lactam ring, leading to the inactivation of the transpeptidase enzyme and ultimately causing cell lysis. Figure 9. The efficacy of ß-lactam antibiotics depends on their accessibility to targets, the level of resistance to enzymatic inactivation by β-lactamases, and the ability of β-lactams to inhibit target penicillin-binding proteins (PBPs). Modifying one or a combination of these parameters may result in resistance. [Dowling *et al*., 2017; Jumaa and Karaman, 2015; Essack, 2001] [60, 61, 62].

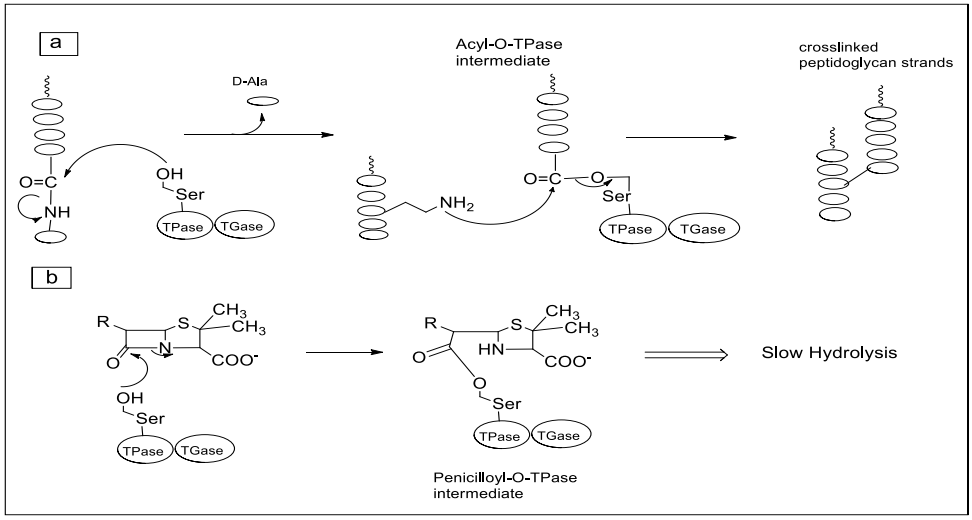


Fig 9: (a) biosynthesis of the cell wall (b) the inhibition of transpeptidase activity by penicillins through the formation of a slowly hydrolyzing covalent acyl-enzyme intermediate [Manageiro, 2011] [7]

Many β-lactams, including penicillin, ampicillin, and amoxicillin, lose their efficacy due to the Synthesis of β-lactamase enzymes, which hydrolyze the amide link in the β-lactam ring [Chandra *et al*. 2017] [63].

Generally, Gram-positive bacteria synthesize a substantial quantity of β-lactamase, which is released extracellularly. In Gram-negative bacteria, β-lactamases are present in relatively low quantities and are situated between the inner and outer cell membranes. These β-lactamases are positioned for optimal protection of the microorganism [Soares *et al*., 2012] [64].

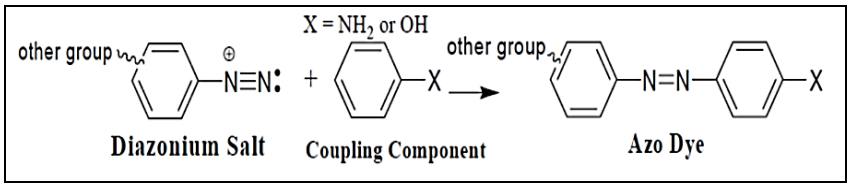
Another mechanism of resistance to β-lactam is the alteration of permeability in the outer membrane. This modification may result from the presence of efflux proteins in the bacterial cell wall and is recognized as a contributing factor to the expulsion of various unrelated substances, including antibiotics, organic solvents, dyes, and detergents [Lewis, 1994] [65].

Azo Compounds

Azo compounds are the most extensive category of organic dyes, first introduced in 1862 by chemist Peter Griess. These compounds are characterized by the presence of the azo moiety (-N=N-) in their structure, conjugated with two aromatic or heteroaromatic systems. Due to their distinct physico-chemical properties and biological activities, they have been employed in various practical applications throughout the pharmaceutical, cosmetic, food, dyeing, textile industries, and analytical chemistry, as illustrated in Fig. (10).

Azo compounds are renowned for their medicinal significance and acknowledged for their applications as antidiabetics, antiseptics, antifungals, anti-inflammatories, antineoplastics, and antibacterials [Weglarz-Tomczak and Gorecki, 2012; Karam and Salman, 2017; Senol, 2017; Patil and Nehete, 2015] [66, 67, 68, 69].

Azo compounds possess numerous advantages over other prevalent compounds: vibrant, high-intensity colors, stability across the entire pH spectrum of foods, heat stability, and resistance to degradation when exposed to light or oxygen. Their most significant advantage is their low cost, attributable to the straightforward manufacturing process involving the coupling of a diazonium compound with a phenol or an aromatic amine (equation 2). [Syhood and Mohammed, 2015; Rasheed, 2011] [70, 71]. Azo dyes are utilized in food products due to their low toxicity, few allergic reactions, and absence of hyperactive effects [Loganathan *et al*., 2015] [72].



….. eq. (2)

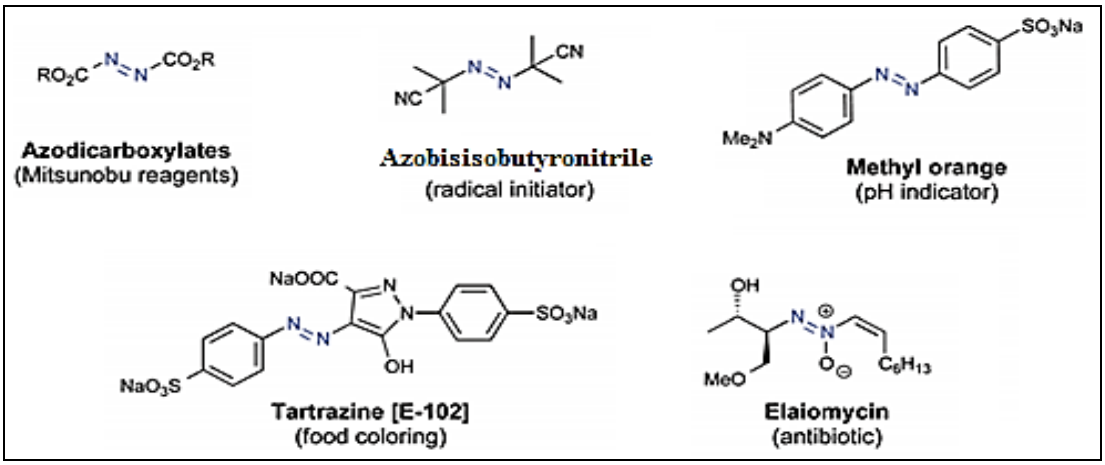


Fig 10: Some Important Azo Compounds [Monge *et al*.,2013] [121]

The inaugural azo dye employed in medicine as an antimicrobial agent is Prontosil (sulfamidochrysoidine), along with Balsalazide, which exclusively releases the active 5-aminosalicylic acid in the colon for the treatment of ulcerative colitis, Fig. (11). Subsequently, a series of azo dyes incorporating the sulfonamide functional group were synthesized as prospective antimicrobial agents. [Al-Rubaie and Mhessn, 2012; Tursi, 2009] [73, 74].

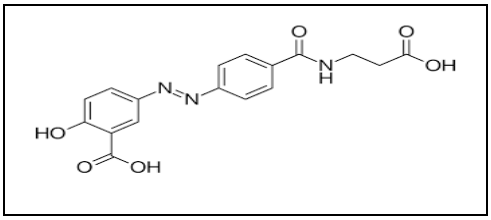


Fig 11. Structure of Balsalazide

Despite the biological efficacy of azo dyes, several of these chemicals pose significant risks to health and the environment due to their carcinogenic properties. Pinheiro *et al*. enumerate many examples of essential amines with carcinogenic effects: Aniline, 4-chloroaniline, toluene-2,4-diamine, 2-naphthylamine, 4,4'-methylenedianiline, and benzidine should be avoided in the manufacture of azo dyes. It is noteworthy that low toxicity has frequently been attained through the incorporation of polar moieties into the dye molecule, which also leads to enhanced aqueous solubility. [Pinheiro *et al*., 2004] [75].

Classification of azo compounds

A) Azo compounds are categorized into two types based on the homogeneity of the rings: homocyclic and heterocyclic azo compounds (fig. 1-12 (a) and (b) [Mahmoud, 2017]) [76].

B) An alternative classification predicated on the quantity of azo groups present in the dye composition: Mono azo, di azo (fig. 1-12 (c)), tri azo, and poly azo dyes [Singh and Singh, 2017] [77].

C) Azo compounds can be categorized based on their origin: natural and synthesized azo compounds.

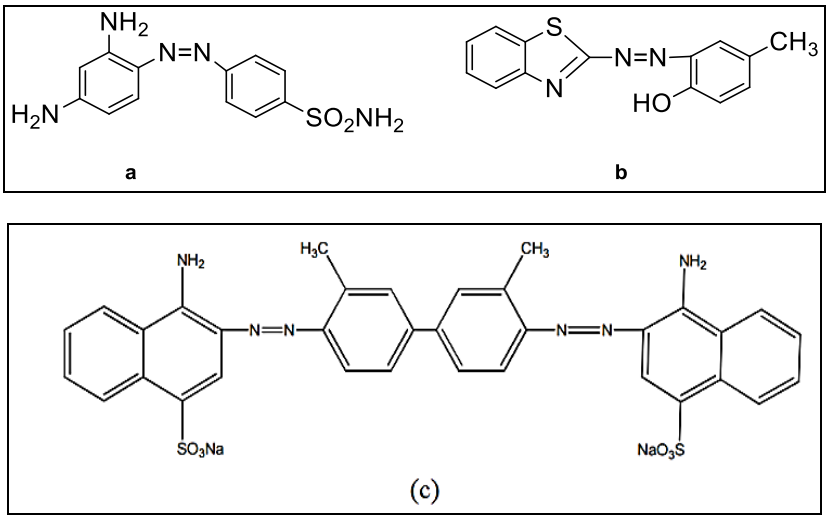


Fig 12: 'Some Types of Azo Compounds'

Natural azo compounds are a rare category of natural chemicals that have been extracted from microbes, fungi, fungal endophytes, lichenized ascomycetes, marine invertebrates, and various plant components, including bark, berries, leaves, roots, and wood. Over 120 biologically active compounds demonstrate verified pharmacological effects, including potent anticancer, antibacterial, antiviral, and other properties (Fig. 13). Natural azo compounds have demonstrated potential as attractive candidates for the creation of novel pharmaceuticals for the treatment of various ailments [Dembitsky, 2017] [78].

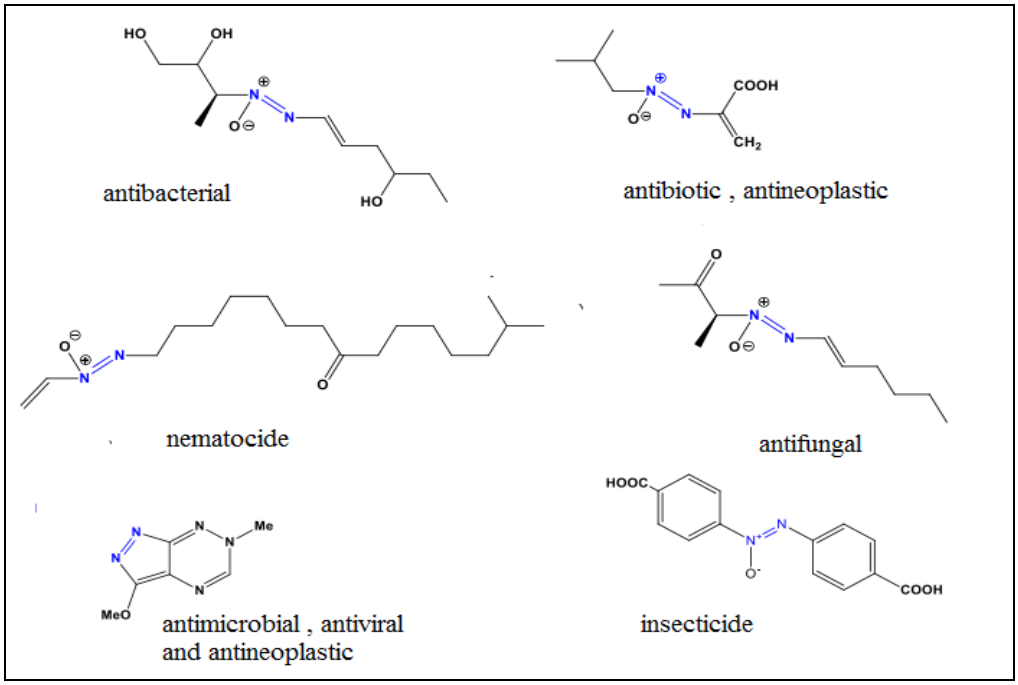
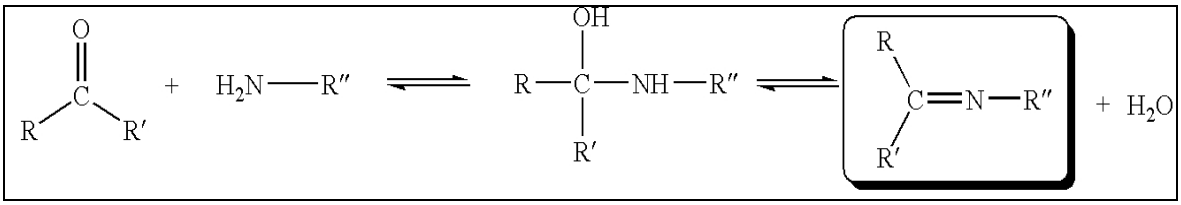


Fig 13: Azo Compounds Derived from Actinomycetes and Fungal Species

Schiff Bases: Schiff bases, a remarkable class of compounds also referred to as anils, imines, or azomethines, consist of the azomethine group (C=N) with the general formula RHC=N-R1, where R and R1 represent alkyl, aryl, cycloalkyl, or heterocyclic groups. Schiff bases were initially synthesized by Hugo Schiff in 1864 through the condensation reaction of primary amines with carbonyl compounds, as illustrated in Scheme 2. Schiff bases comprising diverse donor atoms such as O, N, and S exhibited extensive biological activities [Rayaji and Agadihiremath, 2016; Hussain *et al*., 2014; Kumar *et al*., 2016] [79, 80, 81].

The presence of aryl substituents in Schiff bases typically simplifies their Synthesis and enhances their stability, whereas Schiff bases containing alkyl groups are comparatively unstable. The reactivity of aldehydes is greater than that of ketones, resulting in Schiff bases with a central structure that is less sterically hindered than that of ketones. Schiff bases are important intermediates in the production of certain bioactive chemicals, such as β-lactams [Ejidike, 2016] [82].



Scheme 2: Synthesis of Schiff Base [Abu-Dief and Mohamed, 2015] [83]

Schiff bases have several applications across various fields, including biological chemistry, organic and inorganic chemistry, supramolecular chemistry, and materials science. Schiff bases have gained prominence in the medicinal field due to their extensive array of biological activities, including antibacterial, antifungal, anti-HIV, anti-inflammatory, analgesic, antimicrobial, antispasmodic, anti-tuberculosis, anticancer, antioxidant, anthelmintic, antimalarial, and anti-amoebic properties [Berk *et al*., 2017; Mumtaz *et al*., 2016; Pahontu, 2017] [84, 85, 86]. The imine functional group (HC=N) is thought to be responsible for the biological activity of Schiff base compounds, as intramolecular hydrogen bonding with C=N nitrogen atoms significantly influences several physiological systems. [Sikarwar *et al*., 2016; Pallikkavil *et al*., 2012; Soni *et al*., 2016; Muzammil, 2015] [87, 88, 89, 90]. Azomethine (-C=N) groups are found in numerous natural and synthetic compounds, as illustrated in Fig. (14) [Maihub and El-ajaily, 2018] [91].

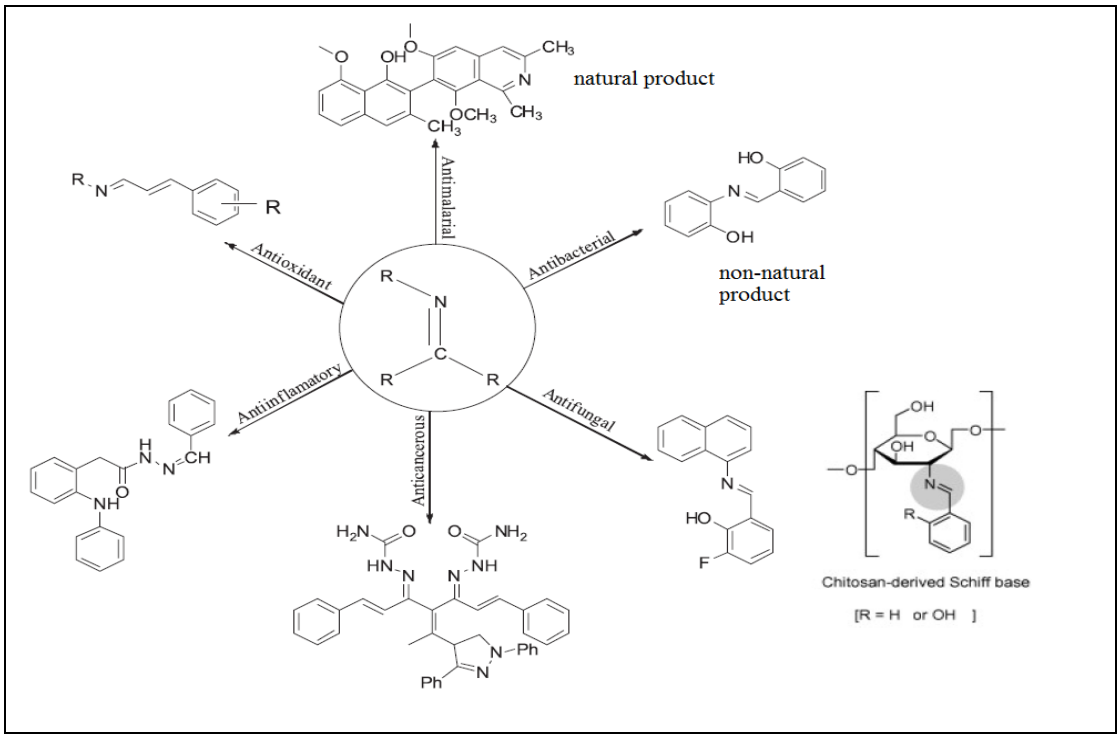


Fig 14: Examples of Bioactive Schiff Bases and Their Uses [Murtaza *et al*., 2014] [92]

Schiff base ligands are acknowledged as "privileged ligands" capable of coordinating with diverse metals. Schiff base metal complexes possess a wide array of applications, including enhancing the aging resistance of natural rubber, exhibiting insecticidal properties, demonstrating antitumor activity, and serving as effective corrosion inhibitors for metal alloys in acidic media [Eissa, 2013; Prakash, 2017] [93, 94].

Madurahydroxylactone Schiff bases are generated from natural ingredients. These chemicals are secondary metabolites synthesized by the plant *Actinomadura rubra* (Fig. 15). These compounds are efficient in the *in vitro* inhibition of B. subtilis, Micrococcus flavus, Sarcina lutea, and S. aureus growth, with MIC values ranging from 0.2 to 3.1 µg/mL [Da Silva *et al*., 2011] [95].

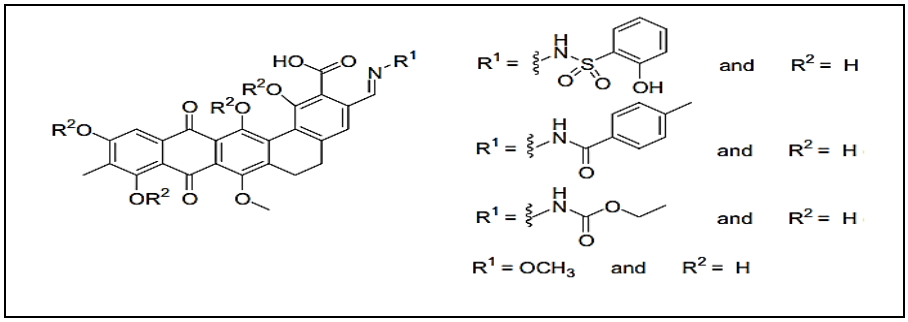


Fig 15: Examples of Antibacterial Schiff Bases Derived from Plant

An imine bond between the aldehyde generated from vitamin A and the protein opsin in the retina of the eye plays a crucial role in the chemistry of vision. Vitamins, commonly referred to as coenzymes, are essential for the functioning of various enzymes, which are big proteins that catalyze chemical transformations within cells. Pyridoxal phosphate, the active form of vitamin B6, exemplifies a physiologically significant aldehyde. Vitamin B6 functions as a coenzyme by creating an imine with an amino acid within an enzyme. The coenzyme, bound to the enzyme, participates in the transamination reaction, which is crucial for the metabolism and biosynthesis of amino acids. In the final stage, enzyme-catalyzed hydrolysis cleaves the imine to pyridoxal and the changed amino acid [Ashraf *et al*., 2011] [96].

A significant quantity of Schiff bases obtained from sulfa medications has been synthesized [Ebrahimi *et al*., 2013] [97]. Numerous investigations have demonstrated that the medicinal effects of sulfonamide compounds improve when converted to Schiff bases [Rana *et al*., 2012] [98]. Sulfonamides and related Schiff base-derived compounds are widely utilized for antibacterial, anticancer, diuretic, anti-carbonic anhydrase, hypoglycemic, anti-thyroid, and protease inhibitor actions [Chohan *et al*., 2012] [99].

Antimicrobial Activity

Antimicrobial therapy is an essential instrument for the treatment of various diseases and is fundamental to contemporary medical practice. Infections caused by pathogenic microbes are a significant concern in various domains, including medical devices, hospital surfaces, surgical equipment, healthcare items, and food packaging and storage. Infections are typically addressed with antimicrobial medicines; however, several bacteria have developed resistance to standard antibiotics, complicating their eradication. As a result, the heightened resistance of bacteria to existing antimicrobials has prompted the assessment of alternative compounds with potential antimicrobial properties [Concilio *et al*., 2017; Ball *et al*., 2004] [100, 101]. Our research detailed the Synthesis and characteristics of several azo-azomethine and β-lactam compounds identified as promising antibacterial agents.

Fungal infections are not often confined to surface tissues; in fact, a rise in life-threatening fungal infections has been documented. The primary cause for this is the rising number of people at risk, including the elderly, those undergoing major surgery, individuals receiving immunosuppressive therapy, patients with acquired immunodeficiency syndrome (AIDS), cancer treatment recipients, and individuals undergoing solid-organ and hematopoietic stem cell transplantation. The exploration and advancement of more efficacious antifungal medicines are essential, and certain Schiff bases are recognized as promising antifungal agents [Sundriyal *et al*., 2006] [102].

Antioxidant Activity

Cellular damage induced by free radicals is thought to be pivotal in the aging process and the advancement of diseases. Antioxidants serve as the primary defence against free radical damage and are essential for sustaining optimal health and well-being. The necessity for antioxidants becomes increasingly vital with heightened exposure to free radicals. Pollution, cigarette smoke, narcotics, disease, stress, and even exercise can elevate exposure to free radicals [Percival, 1998] [103]. The pursuit of novel molecules exhibiting antioxidant properties is a highly active research domain, as they can safeguard the human body from free radicals and impede the progression of various chronic diseases, including vascular disorders, certain cancer types, and oxidative stress, which is responsible for damage to DNA, proteins, and membranes. Reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide, hydroxyl radicals, and nitric oxide radicals, significantly contribute to oxidative stress associated with several critical diseases [Rohini *et al*. 2015] [104].

The term "antioxidant" is becoming increasingly common in contemporary society due to its health benefits. The conventional definition of an antioxidant is "a substance that counteracts oxidation or inhibits reactions induced by oxygen or peroxides', with many of these compounds, such as tocopherols, utilized as preservatives in various products, including oils and food items. An enhanced biologically pertinent definition of antioxidants is "synthetic or natural substances" incorporated into products to avert or postpone their degradation due to the action of atmospheric oxygen. In the realms of biochemistry and medicine, "antioxidants" refer to enzymes or other organic compounds, such as vitamin E or β-carotene, that possess the ability to mitigate the deleterious effects of oxidation in animal tissues. It is noteworthy that numerous anti-inflammatory and anti-necrotic drugs have antioxidant capabilities in addition to their therapeutic qualities [Casas-Grajales and Muriel, 2015; Huang *et al*., 2005] [105, 106].

Antioxidants can be categorized as primary and secondary antioxidants. Primary antioxidants restrict the initiation and propagation of oxidative chain events by neutralizing free radicals, while secondary antioxidants mitigate oxidative damage by preventing radical production [Loganayaki and Manian, 2010] [107].

It has been documented that numerous organic compounds function as effective antioxidants; therefore, it is essential to comprehend their mechanisms of action and efficacy. A substantial number of natural and synthetic antioxidants have been investigated, and their antioxidant capacity has been evaluated using various methodologies [Kumar *et al*. 2017] [108].

Anticancer Action

The term "cancer" encompasses a broad array of disorders characterized by uncontrolled and unwanted cell division. In contrast to other disorders, it can impact all organs of the body, including bones, muscles, brain, blood, liver, and additional organs [Mohamed *et al*., 2013; Saipriya *et al*., 2018] [109, 110].

Breast cancer is the most prevalent type of cancer diagnosed in women, constituting about one-third of all diagnosed cancers. Over twenty-five percent of women infected will ultimately succumb to this disease. The current treatments for breast cancer are chemotherapy, surgery, radiation, and hormone therapy. [Radi *et al*., 2016] [111].

Breast cancer originates in the breast tissue, which comprises glands for milk production known as lobules and the ducts that link the lobules to the nipple. The remaining breast consists of adipose, connective, and lymphatic tissues. Breast cancer is often found either during a screening test before the onset of symptoms or after symptoms have manifested when a woman perceives a lump. The majority of masses identified on a mammogram and most breast lumps are benign, meaning they are non-cancerous, do not proliferate uncontrollably, do not metastasize, and are not life-threatening [Al-Naggar, 2017] [112].

Cancer is a primary cause of mortality worldwide. Significant

efforts have been undertaken in the domain of cancer research during the past few decades; nonetheless, it remains a leading cause of mortality among other diseases. Medicinal chemists are seeking to produce novel chemicals that possess significant anticancer potential in tumor cells without damaging normal cells [Khan *et al*., 2016] [113].

Normal cells generally undergo apoptosis, which regulates cell growth and eliminates abnormal cells; however, in cancer cells, apoptosis is repressed and must be induced, representing a crucial component in the field of anticancer drug research [Faraj *et al*., 2014] [114].

Anti-irritant Efficacy

The skin is the biggest organ in the body, comprising around 15% of total body weight and consisting of three layers: The outermost layer, the epidermis, the dermis, the intermediate layer, and subcutaneous tissue. The skin executes numerous essential activities, including safeguarding against exterior physical, chemical, and biological threats, such as germs, ultraviolet (UV) radiation, allergies, and irritants, in addition to preventing excessive water loss from the body and contributing to thermoregulation. [Kolarsick *et al*., 2011] [115]

Skin illness refers to conditions that affect mainly or predominantly the superficial layers of the skin. Numerous factors contribute to skin illnesses, such as herpes and bacterial infections. Risk factors for prevalent skin illnesses, such as eczema, encompass genetic predisposition and several environmental variables, including exposure to irritants and allergens. Genetic factors may be significant in psoriasis and severe acne. All three forms of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—are associated with excessive sun exposure in individuals with fair skin. The etiology of the majority of uncommon dermatological disorders remains unidentified [Schofield *et al*. 2009] [116].

The skin is the primary organ for exposure to transdermal therapeutic systems since the adherence of these materials to superficial tissues provides a significant route of exposure during the application of such systems [Banerjee *et al*., 2013] [117]. Topical distribution is one of the most preferred methods to address the issues associated with other routes, such as parenteral and oral administration [Nagula and Wairkar, 2019] [118]. The transdermal distribution of pharmaceuticals has long been a promising notion because of its accessibility, extensive surface area, significant exposure to circulatory and lymphatic systems, and the non-invasive nature of the treatment [Jyothi *et al*., 2014] [119].

Irritant and allergic contact dermatitis are prevalent inflammatory skin disorders triggered by recurrent skin exposure to substances known as xenobiotics or haptens. Irritant dermatitis is characterized by damage to the cutaneous integrity, presenting with epidermal lesions of varying degrees of severity and an inflammatory response in the underlying dermis [Nosbaum *et al*., 2009] [102].

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